Novel Synthetic Strategies Towards Ring-Rearrangement, Benzannulation, and Bis-Aryl/Heteroaryl Ketones

A Thesis Submitted for The Degree of

Doctor of Philosophy

By

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17CHPH47



Under the Supervision of

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Declaration

I hereby declare that the matter embedded in the thesis entitled **"Novel Synthetic Strategies Towards Ring-Rearrangement, Benzannulation, and Bis-Aryl/Heteroaryl Ketones"** is a result of the examination carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, India, under the supervision of Prof. Srinivasarao Yaragorla.

In keeping with the general practice of reporting scientific explanations, due acknowledgments have been made on the basis of the contributions of other investigators. Any omission, that might have occurred by oversight or error, is regretted. This research work is free from plagiarism. I hereby agree that my thesis can be deposited in Shodhganga/INFLIBNET. A report on plagiarism statistics from the University Librarian is enclosed.

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Certificate

This is to certify that the thesis entitled **"Novel Synthetic Strategies Towards Ring-Rearrangement, Benzannulation, and Bis-Aryl/Heteroaryl Ketones"** submitted by **Mrs. Tabassum Khan** bearing registration number **17CHPH47** in partial fulfilment of the requirements for the award of Doctor of Philosophy in the School of Chemistry is a bona fide work carried out by her under my supervision and guidance.

This thesis is free from plagiarism and has not been submitted previously in part or in full to this or any other University or Institution for the award of any degree or diploma.

Parts of this thesis have been published in the following three publications:

1. S. Yaragorla, T. Khan, A. Behera. *J. Org. Chem.*, **2023**, *88*, 2103-2112.
2. T. Khan, P. Rajesh, D. Praveen, K. V. J. Jose, S. Yaragorla. *Eur. J. Org. Chem.*, **2020**, 2199-2209.
3. S. Yaragorla, T. Khan. *Org. Biomol. Chem.*, **2018**, *16*, 7920-7925.
4. S. Yaragorla, T. Khan, J. Raoof (Under revision, Manuscript ID-jo-2023-01251e).

Manuscripts for other works in the thesis are communicated.

She has also made presentations at the following conferences:

1. Oral presentation in "***Chemfest 2022***" in-house symposium held at the University of Hyderabad, India (April 22-23, 2022).
2. Oral presentation in National Organic Symposium Trust (***XVII J-NOST 2022***) organized by the University of Hyderabad, Hyderabad, India (January 6-9, 2022).
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4. Poster presentation at an international symposium entitled "***Su***" for Sustainability: Changing Paradigms in Process Innovation held at DRILS, Hyderabad, India (February 24-25, 2020).
5. Poster presentation in "***Chemfest 2020***" an in-house symposium held at the University of Hyderabad, India (February 27-28, 2020).
6. Poster presentation in "***Chemfest 2019***" an in-house symposium held at the University of Hyderabad, India (February 22-23, 2019).

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CY-801	Research proposal	3	Pass
CY-806	Instrumental Methods-B	3	Pass
CY-452	Organic Reactions and Mechanism	3	Pass
CY-573	Stereoselective Organic Synthesis	2	Pass

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Sl. No.	Course No.	Title of the Course	No. of Credits	Grade
1.	CY801	Research Proposal	3	B+
2.	CY806	Instrumental Methods-B	3	B
3.	CY452	Organic Reactions and Mechanisms	3	C
4.	CY573	Stereoselective Organic Synthesis	2	B

Final Result: Passed

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Tabassum Khan

List of Abbreviations

α	alpha
β	beta
γ	gamma
δ	chemical shift
&	and
^{o}C	degree Celsius
µL	Micro litre
ΔE	Energy difference
ν	Wave number
^{13}C{H}	Proton decoupled ^{13}C
A^{o}	angstrom
Ac	acetyl
AcOH	Acetic acid
AcOEt/EtOAc	Ethyl acetate
aq.	aqueous
Ar	aryl
$BF_3.OEt_2$	boron trifluoride etherate
Bn	benzyl
Boc	tertiary butoxycabonyl
bp	boiling point
Br	Bromo
Br_2	bromine
Bu	butyl
BuLi	butyl lithium
Bu_4NPF_6	tetrabutyl ammonium hexafluoro phosphate
$Ca(NTf_2)_2$	Calcium bis(trifluoromethanesulfonimide)
$Ca(OTf)_2$	Calcium trifluoromethanesulfonate
cat.	catalytic
CCDC	Cambridge Crystallographic Data Centre
CDCl3	Deuterated chloroform
CH_3CN	Acetonitrile
Cl	chloro
cm	Centimeter
CN	Nitrile/cyano
CSA	camphorsulphonic acid
CuI	Copper(I)iodide
$Cu(OAc)_2$	Copper(II)acetate
Cu_2O	Copper(I)oxide
$Cu(OTf)_2$	Copper(II)triflate
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene

DCE	1,2-dichloroethane
DCM	dichloromethane
DFT	Discrete Fourier Transform
dig	diagonal
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
EAA	ethyl acetoacetate
ESI-TOF	Electrospray ionization time-of-flight
Et	ethyl
etc.	Et cetra (and so on/and other things)
EtOAc	ethyl acetate
EtOH	ethanol
eq.	equation
equiv.	equivalent
F	fluoro
FDA	Food and Drug Administration
$FeCl_3$	Iron(III)chloride
g	gram (s)
h	hour (s)
HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
$HNTf_2$	Bi(trifluoromethane)sulfonimide
H_2O_2	hydrogenperoxide
HPLC	High performance liquid chromatography
HRMS	high resolution mass spectrum
Hz	hertz
i	iso
I	iodo
I_2	iodine
ICl	Iodine monochloride
i.e.	Id est (that is/in other words)
IR	infrared
J	coupling constant (in NMR spectroscopy)
K	kelvin
KBr	Potassium bromide
K_2CO_3	Potassium carbonate
KO^tBu	Potassium tertiary butoxide
KOH	Potassium hydroxide
LCMS	Liquid chromatography mass spectrometry
LHMDS	lithium bis(trimethylsilyl)amide
M	molar
m	multiplet (In nmr spectra)
m	Meta
Me	methyl

Me_2SO_4	Dimethyl sulfate
MeOH	methanol
mg	milligram
MHz	megahertz
min	minute
mmol	millimoles
mp	melting point
$MeSO_3H$/MsOH	methanesulfonic acid
N_2	nitrogen
NaH	Sodium hydride
$NaHCO_3$	Sodium bicarbonate
Na_2SO_4	Sodium sulfate
NEt_3	triethyl amine
NH_4Cl	Ammonium chloride
NIS	N-iodo succinimide
NO_2	nitro
nm	nanometer
Nu	Nucleophile
NMR	nuclear magnetic resonance
o	ortho
O_2	oxygen
OAc	acetate
OH	hyroxyl
OLED	Organic light emitting diode
OMe	methoxy
OTf	trifluoromethanesulfonate
ORTEP	Oak Ridge Thermal Ellipsoid Plot
p	para
$PdCl_2$	Palladium(II)chloride
$Pd(OAc)_2$	Palladium(II)acetate
Pet ether	hexane
Ph	phenyl
$PhCO_2H$	Benzoic acid
PivOH	Pivalic acid
PPh_3	Triphenyl phosphene
ppm	parts per million
*p*TSA	*p*-toluenesulfonic acid
q	quartet
R_f	Retention factor
rt	room temperature
s	singlet
$Sc(OTf)_3$	Scandium triflate
SeO_2	Selenium dioxide

TBHP	Tertiary-butyl hydroperoxide
TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
tert	tertiary
TFA	Trifluoro Acetic Acid
TfOH	Triflic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	Trimethyl silane
TRR	Thermal ring-rearrangement
Ts	toluenesulfonyl/tosyl
UV	ultraviolet
XRD	X-ray diffraction

Synopsis

The thesis entitled "**Novel Synthetic Strategies Towards Ring Rearrangement, Benzannulation, and bis Aryl/ Heteroaryl Ketones**" consists of four chapters: (1) Brønsted Acid Mediated Ring-Rearrangement of 3H-Benzochromenes, (2) Cu-Catalyzed Intramolecular Etherification *via* C_{sp2}-H Functionalization, (3) KO^{t}Bu Promoted Oxidative Cleavage of C_{sp3}-C_{sp2} and C_{sp3}-H bonds and (4) Cyclizative Strategies Towards Construction of Carbazoles from Indole-Tethered Propargyl Alcohols. The compounds reported in this thesis are characterized using ^{1}H NMR, ^{13}C NMR, IR, MS, and HRMS spectral data. The structures of some representative compounds are unambiguously elucidated by X-ray crystallography.

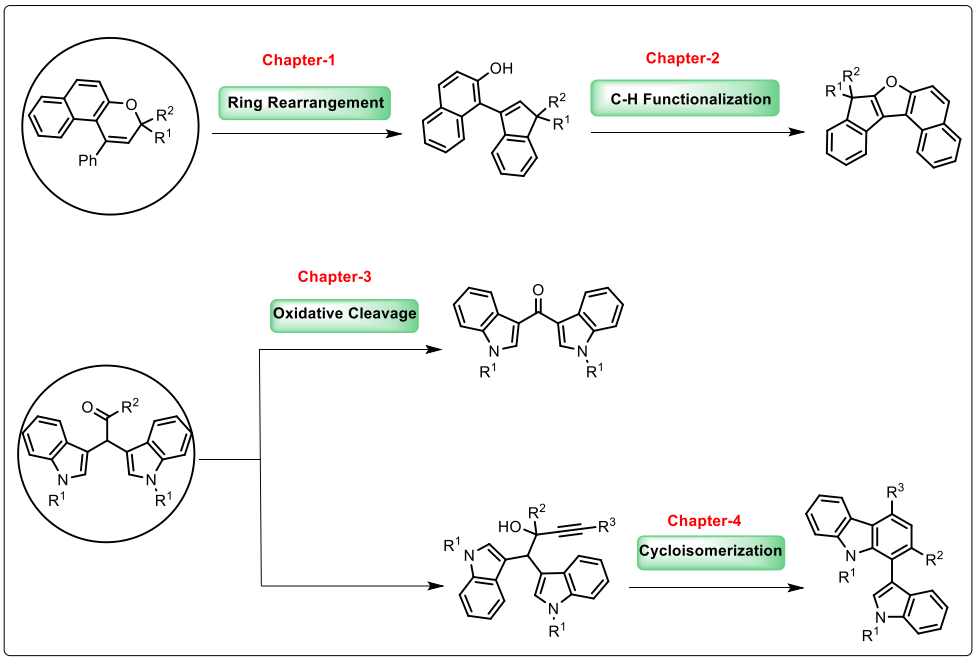


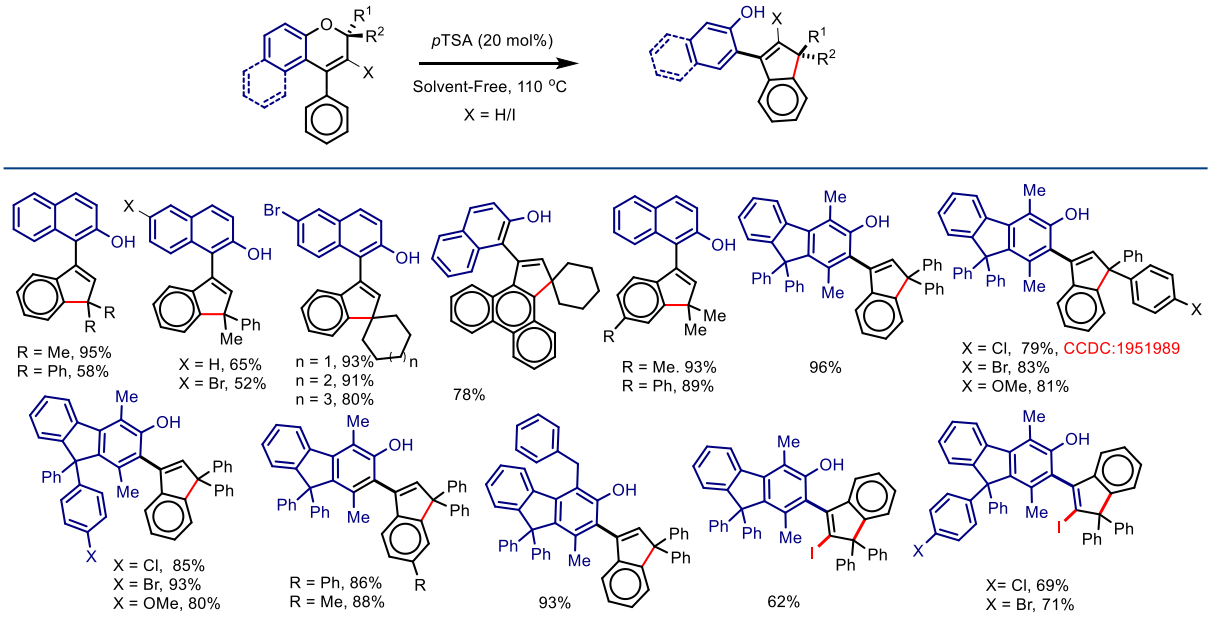
Figure 1: Outline of the thesis

Chapter 1: Brønsted Acid Mediated Ring Rearrangement of 3*H*-Benzochromenes

A rearrangement reaction is a broad class of organic reactions in which an atom, ion, group of atoms, or chemical unit migrates from one atom to another atom in the same or different species, resulting in a structural isomer of the original molecule. Rearrangement reaction mostly involves breaking and/or making of C-C, C-O, or C-N bonds. Benzochromenes are versatile building blocks of natural products and part of many biologically significant molecules. They are known to possess a spectrum of biological activities such as antifungal, anti-inflammatory, anti-hyperglycemic, cytotoxic, and molluscicidal activities. And because of photochromic and acidochromic properties, benzochromenes are known to possess significant material applications.

Thermal ring rearrangement of benzochromenes to indene derivatives promoted by *p*TSA proceeds through the protonation of benzochromenes by the acid catalyst followed by ring-opening and ring-closure by an intramolecular Friedel-Crafts cyclization to provide a new bicyclic framework, inden-3-yl-naphthols bearing a quaternary center, which also exhibited

atropisomerism. This strategy was further extended for the rearrangement of fluorenopyran and 2-iodofluorenopyran to give indenofluorenol and iodoindenofluorenol respectively (Scheme 1). Single point energies of diastereomeric atropisomers were calculated, and DFT calculations were done for the confirmation of the mechanism.

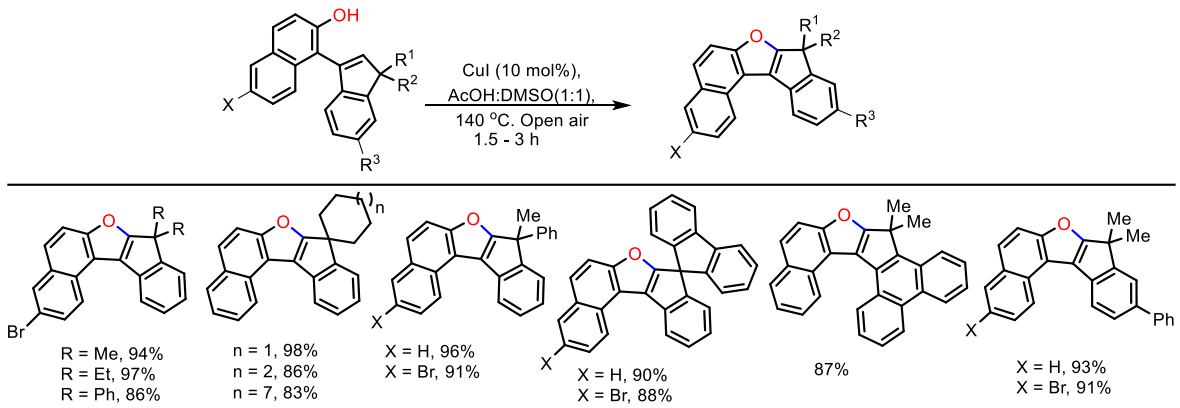


Scheme 1: Ring rearrangement of benzochromene derivatives to indeno-naphthol/fluorenol

Chapter 2: Cu-Catalyzed Intramolecular Etherification *via* C_{sp2}-H Functionalization

C-H functionalization is a type of reaction in which a carbon-hydrogen bond is cleaved and replaced with a C-X bond, where X is usually carbon, oxygen, or nitrogen. The term usually implies that a transition metal is involved in the C-H cleavage process. The potential to eliminate pre-functionalization steps and to streamline synthetic strategies has driven the design and development of reactions and catalyst systems that allow the previously inert C-H bond to replace more conventional functional groups as a reaction partner, and this field has seen explosive growth in recent years.

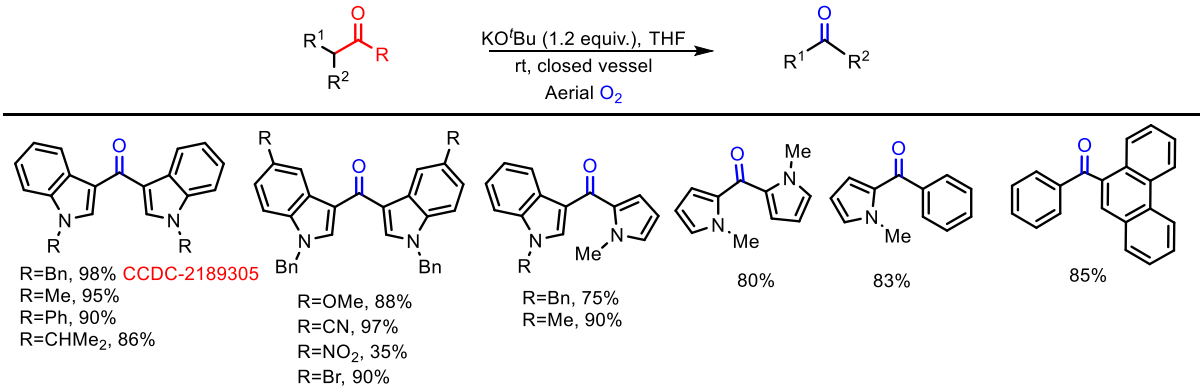
Polycyclic aromatic compounds have attracted interest as promising electronic materials for organic light-emitting diodes, photovoltaic cells, and field-effect transistors. Heteroatom-fused aromatic compounds have been actively investigated because heteroatom doping can induce or enhance the desired electronic and photophysical properties. We achieved intramolecular etherification *via* the C-H functionalization of indenonaphthols after being attracted by the activity of polycyclic compounds and the effectiveness of C-H functionalization in organic synthesis. We propose a method for copper catalysed C-H functionalization to synthesize indenofused naphthofurans that proceed in the presence of acetic acid in DMSO at 140 °C under open-air conditions (Scheme 2).



Scheme 2: Cu-catalyzed intramolecular etherification via C-H functionalization

Chapter 3: KO^{t}Bu Promoted Oxidative Cleavage of C_{sp3}-C_{sp2} and C_{sp3}-H bonds

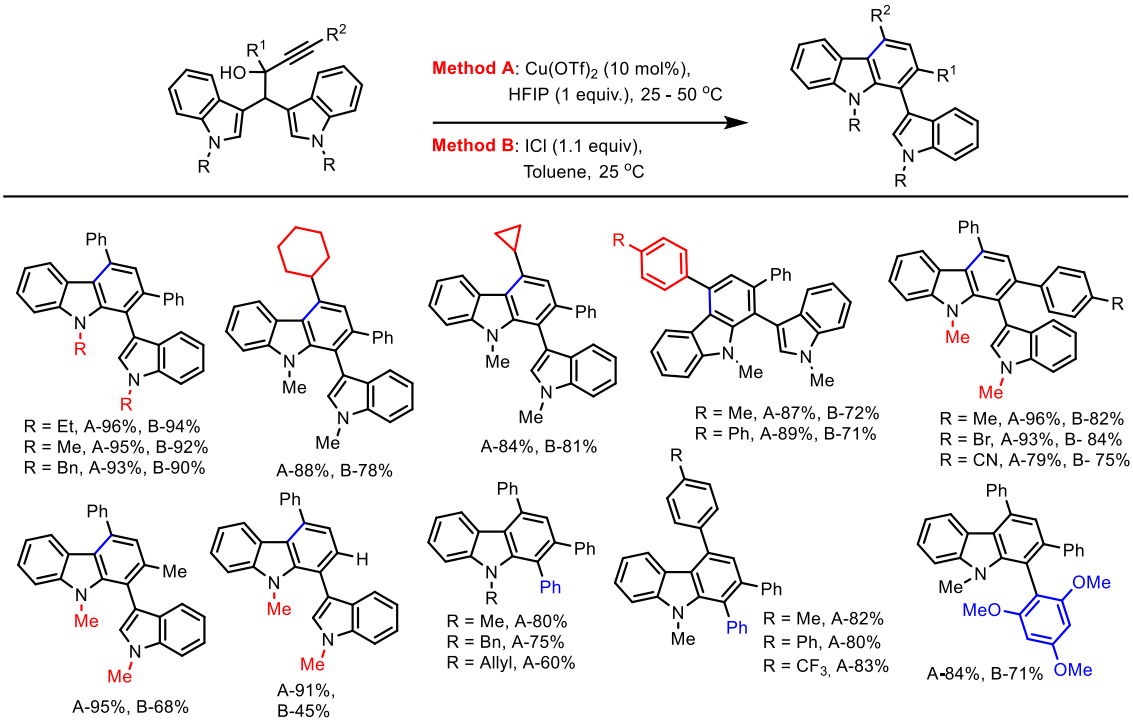
An efficient and practical approach for synthesizing diaryl or heteroaryl ketones from *α*-bisaryl or heteroaryl carbonyl through a simultaneous oxidative cleavage of C-C & C-H bonds is by using KO^{t}Bu. This method makes it possible to easily create a range of symmetrical and unsymmetrical ketones in high yields (Scheme 3). The reaction is initiated by the abstraction of C_{sp3}-H proton of *α*-bisaryl carbonyl by the base, followed by the addition of oxygen to form peroxy ketone. Then intramolecular addition of peroxy anion to carbonyl carbon forms a four-membered 1,2-dioxetan-3-olate. This unstable ring undergoes cleavage to furnish the diaryl ketone. In course of the reaction, we were able to synthesize a huge variety of carbonyl compounds that are otherwise difficult to make. We also demonstrate a total synthesis of a natural product di(1H-indol-3-yl)methanone.



Scheme 3: Selected examples of KO^{t}Bu mediated oxidative cleavage

Chapter 4: Cyclizative Strategies Towards Construction of Carbazoles from Indole-Tethered Propargyl Alcohols

Carbazoles are important heteroaromatic compounds in many biologically active products. Due to their electrical and thermal characteristics, they also serve as building blocks for electroluminescent materials and host materials for triplet emitters in organic light-emitting diodes.



Scheme 4: Selected examples of Cycloisomerization of indole tethered propargyl alcohols

For the cycloisomerization of bisinolyl or aryl-indolyl methane tethered propargyl alcohols to the multi-substituted carbazoles, we report two efficient routes (Scheme 4). Method A is a Cu-catalyzed HFIP-mediated reaction that proceeds through 1,2-alkyl migration of the spirocyclic intermediate generated from the 5-*endo*-spirocyclization. In Method B, we show cycloisomerization without a transition metal using ICl in toluene. Both bisindolyl and aryl-indolyl propargyl alcohol were cycloisomerized to carbazole under Cu-catalysis, whereas ICl-mediated reactions were efficient for cycloisomerization of bisindolyl propargyl alcohol.

Publications which are part of the thesis:

1. KO^{t}Bu Promoted Oxidative Cleavage of C_{sp3}-C_{sp2} and C_{sp3}-H bonds, S. Yaragorla, **T. Khan**, A. Behera *J. Org. Chem.*, **2023**, *88*, 2103-2112.
2. Brønsted acid promoted Thermal-Ring-Rearrangement of Fluorenopyrans to 2-(1H-inden-3-yl)-9H-fluoren-3-ols bearing two all-carbon-quaternary centres. **T Khan**, P Rajesh, D Praveen, K. V. Jovan Jose, S. Yaragorla *Eur. J. Org., Chem.* **2020,** 2199-2209.
3. An unexpected thermal-ring-rearrangement of benzochromenes to inden-3-yl-naphthols with *p*TsOH, S. Yaragorla, **T. Khan**, *Org. Biomol. Chem.*, **2018**, *16*, 7920-7925.
4. Cu-Catalyzed Oxidative C(sp2)-H Cycloetherification of o-Alkenyl Arenols for the Preparation of Fused-Furans, S. Yaragorla, **T. Khan**, J. Raoof *(communicated)*.
5. Cyclizative Strategies Towards Construction of Carbazoles from Indole-Tethered Propargyl Alcohol *(communicated)*.

Chapter-1

Brønsted Acid Mediated Ring-Rearrangement of 3H-Benzochromenes

Org. Biomol. Chem., **2018**, *16*, 7920-7925 & *Eur. J. Org., Chem.* **2020,** 2199-2209

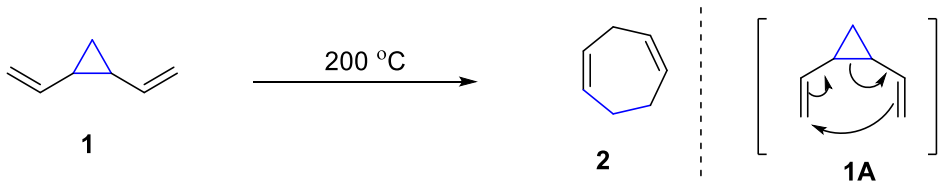
1.1. Introduction

1.1.1. Introduction to Rearrangement Reactions:

Rearrangement reactions are a broad category of organic processes where an atom, an ion, a group of atoms, or a chemical unit moves from one atom to another atom in the same or other species, producing a structural isomer of the original molecule. Usually, C-C, C-O, or C-N bonds are broken or created during rearrangement processes. The rearrangement reactions are often intramolecular because a substituent frequently switches positions between atoms inside the same molecule. Reactions that involve a carbocation intermediate are accompanied by rearrangements, the carbocation intermediate rearranges itself by migrating electron pairs from the C-H to the C-C bond, resulting in the formation of a more stable carbocation. The majority of ring-rearrangement reaction involves only one substrate which on the action of a catalytic amount of acid, base, or metal catalyst or under thermal conditions rearranges itself to a more stable entity. In most of the ring-rearrangement reactions, a singular substrate and catalytic quantity of a metal catalyst, an acid, or a base is used under thermal conditions.[1] These ring rearrangements entail a series of interactions that occur in a single pot with maximal atom economy, and as a result, they are considered green chemical transformations.[2]

Cycloisomerization reactions are a type of rearrangement reaction that involve cyclic substances in reaction variables. The primary positive aspect of cycloisomerization processes is their atom economy, as every atom from the starting material is included in the final product. Transition metals, organocatalysts, and thermal conditions are often used to catalyze these reactions. Since two or more substrate gets involved in ring opening cyclization, it is conceptually different from the ring-rearrangement reactions.[3]

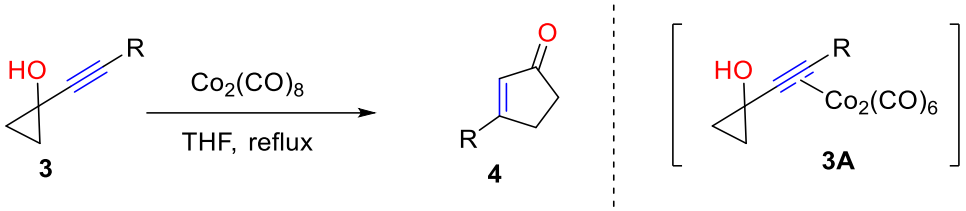
Ring strain becomes one of the major causes of rearrangement in a compound with tiny (3-4 membered) rings, vinyl Cope rearrangement of cyclopropyl vinyl moiety is a significant example of thermal ring-rearrangement. Divinyl cyclopropane **1** rearrangement is a special form of Cope rearrangement which provides access to 1,4-cyclohepatadienes **2** (Scheme 1).[5]



Scheme 1. *Cope rearrangement of divinyl cyclopropane*

Among a huge number of rearrangement reactions on propargyl alcohols, I would like to discuss the rearrangement due to ring strain, wherein a cyclopropyl propargyl alcohol **3** rearranges itself to a stable component as shown in Scheme 2 with $Co_2(CO)_8$. 1n 1993 Iwasawa group reported the hexacarbonyldicobalt complex-

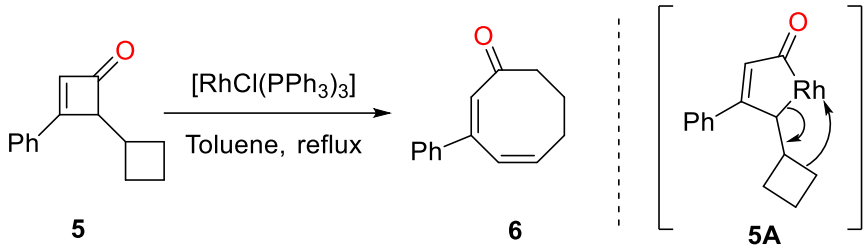
mediated, conformationally regulated regioselective rearrangement of 2-substituted 1-alkynylcyclopropanols to 2-cyclopentene-1-one **4**.[6]



3 **4** **3A**

Scheme 2. *Rearrangement of cyclopropyl propargyl alcohol*

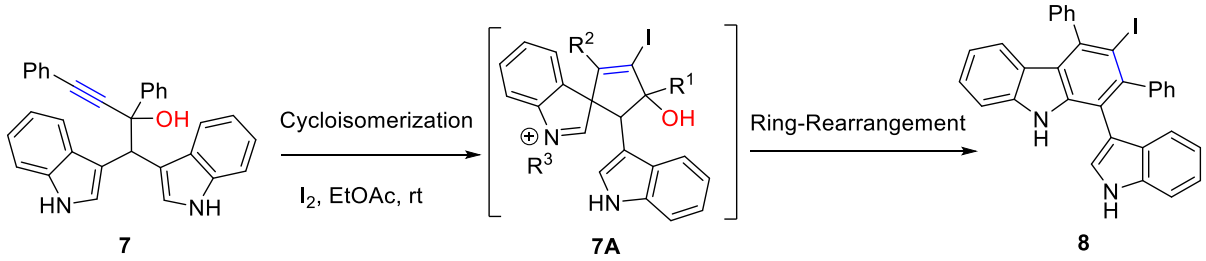
In the case of four-membered strained rings like 4-cyclobutyl-2-cyclobutenone **5**, under Rhodium(I)-catalysis the molecule undergoes intramolecular carbocyclic ring fusion to synthesize large-sized rings like cyclic dieneone **6** (Scheme 3). Similarly, M. Murakami et.al reported consecutive double cleavage of C-C bonds in spiro cyclobutanones.[7,8]



5 **6** **5A**

Scheme 3. *Rearrangement of cyclobutanone systems*

Some indirect examples of transformations involving cycloisomerization of polyunsaturated acyclic substrates are known in literature, these reactions proceed through a reactive spirocyclic intermediate, which further rearranges itself to synthesize stable organic moieties.[9]

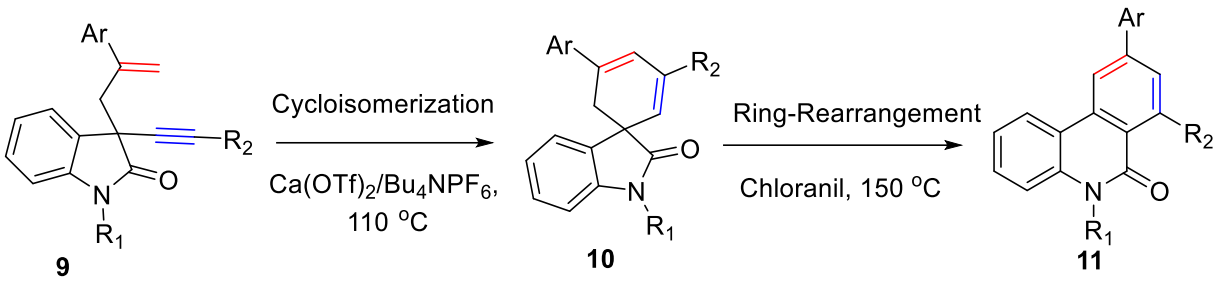


7 **7A** **8**

Scheme 4 *Ring-rearrangement of iodospirane to carbazole*

A ring-rearrangement reaction is generally considered to be the transformation of a substantially stable spirocyclic intermediate into a stable cyclic product *via* cycloisomerization. Our recent report on the cycloisomerization of bis(indolyl)methane tethered propargyl alcohol **7** to a spirane intermediate **7A**, which on 1,2-migration yields stable carbazole **8** (Scheme 4)[10] is an example of a ring

rearrangement reaction. Similarly, chloranil mediated cycloisomerization of spirane intermediate **10** obtained from 1,5-enyne **9**, for synthesis of phenanthridinone **11** (Scheme 5) can also be considered as an example of a ring rearrangement reaction.[10]

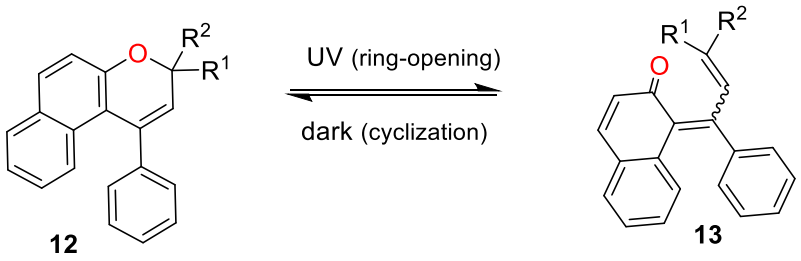


Scheme 5. *Ring-rearrangement of spirane synthesized from 1,5-enyne*

Conventionally, ring-rearrangement reactions proceed under ring strain. However, we were particularly interested in exploring the less prominent ring rearrangement reactions of stable cyclic compounds. To that end, our main focus was to study the rearrangement in chromenes derivatives which were synthesized by our lab.

1.1.2. Chromenes:

Chromenes are a significant group of heterocyclic compounds that include oxygen and have fascinating biological properties. They have a straightforward structure and mild adverse effects. Alkaloids, tocopherols, flavones, and anthocyanins are only a few examples of the numerous chromene compounds that may be found in nature. To find novel therapeutic candidates, the chromene nucleus is a crucial moiety. Chromene derivatives have demonstrated a variety of pharmacological actions, including anticancer, anticholinesterase, anti-inflammatory, antimicrobial, antiproliferative, antitumor, antiviral, EPR-1 (Effector cell Protease Peceptor-1) antagonist, and MAO (Mono-Amine Oxidase) inhibitors.[11] Benzochromenes are fused benzene with chromenes, and these tricyclic heterocycles are significant part of many biologically active molecules and also act as building blocks for many natural products.[11] They possess a wide range of biological properties such as anti-fungal, anti-hyperglycemic, anti-inflammatory, cytotoxic, and molluscidal.[12]



Scheme 6. *Photochromism of Benzochromenes (intramolecular-ring-opening-cyclization)*

Along with these characteristics, benzochromenes exhibit a reversible ring-opening cyclization process (Scheme 6) depending on the presence or absence of light and

thereby illustrate photochromic properties.[13] Whereas when this ring-opening cyclization categorically is driven with the presence of acid-base medium, it is referred to as acidochromism of benzochromenes.[13,14] Because of acidochromic and photochromic properties, benzochromenes are endowed with significant material application.[13-15] Similarly, indenochromenes are also biologically active and have acidochromic properties.

Our group reported that the addition of trifluoroacetic acid (TFA) to **14**, leads to the formation of an intense brick red colour solution which becomes colorless when triethylamine was added. These colour changes can be explained based on the ring opening of **14** with protonation and ring closure with base (NEt_3) as depicted in Figure 1.[16]

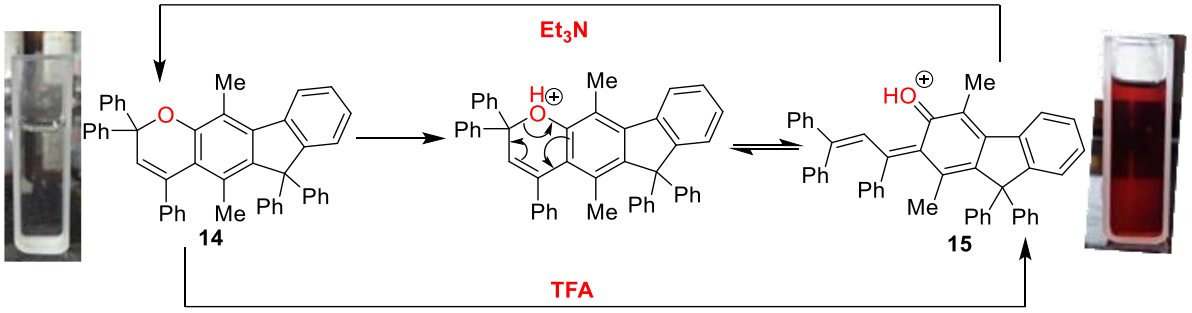
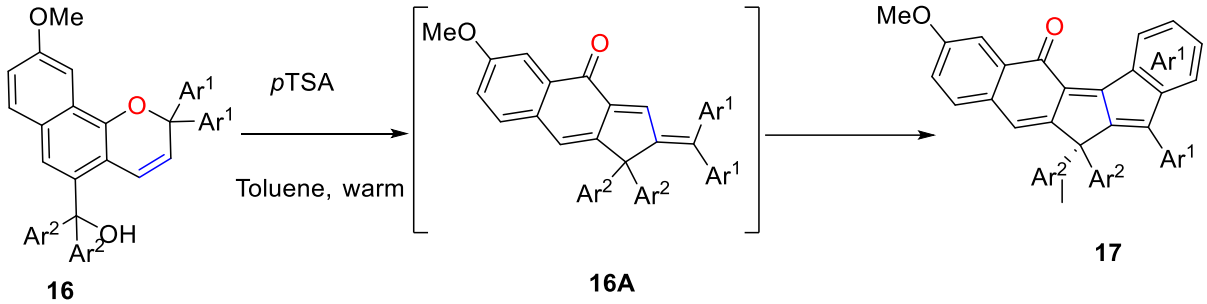


Figure 1. *Acidochrmoic nature of Indenochromene*

These observations and findings of the enormously important chromenes fascinated us to search for the reactivity of chromene in acidic medium.

1.2. Literature Reports

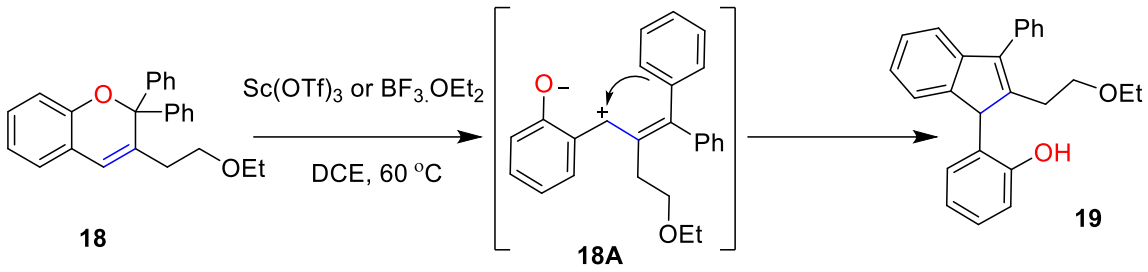
The ring rearrangement reactions of C-2 quaternary center bearing benzochromene derivatives are less known in the literature. For example, when benzochromene/naphthopyran **16** was heated with a catalytic amount of *p*TSA in toluene, irreversible ring-rearrangement took place to give highly coloured turquoise species benzopentalenonaphthalenones **17** (Scheme 7).[17]



Scheme 7. *Rearrangement of Naphthopyran with pTSA*

3-(2-ethoxyethyl)2,2-diphenyl-2H-chromene **18** is reported to undergo ring-rearrangement with scandium triflate at 60 ^{o}C to furnish indenyl-phenol **19**.[18] Heating cycloadduct **18** in the

presence of $Sc(OTF)_3$ or $BF_3.OEt_2$ in DCE at 60 °C leads to product **19** in good yields, suggesting that **18** could be rearranged to **19** upon heating in the presence of Lewis acid (Scheme 8).

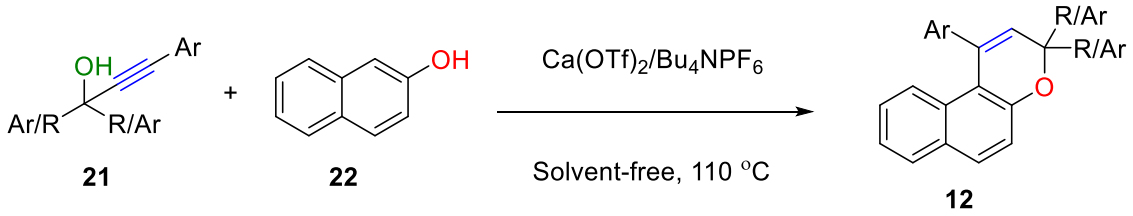


Scheme 8. *Rearrangement of chromene to indenol*

While our group was working on annulation reactions to construct fluorenopyran,[16] acidochromic behaviour of chromene with acid was observed, which motivated us to investigate it with a series of Brønsted acids. Formation of new chemical entity encouraged us to explore the scope, limitation, and mechanistic insights of this reaction.

1.3. Results and Discussion

The precursors for our study were synthesized from propargyl alcohol **21** and naphthol **22** under acid catalysis. S. Ohba, and coworkers in 2000 reported benzochromene synthesis from propargyl alcohol and naphthol using *p*TSA as a catalyst and grinding at room temperature.[19] In the same context, our group in 2017 reported calcium-catalyzed annulation for the synthesis of benzochromene (Scheme 9).[20] Various benzochromenes were synthesized using calcium-catalyzed procedures for our investigation.



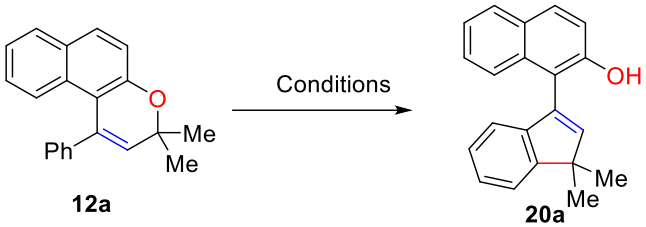
Scheme 9. *Synthesis of Benzochrome*

1.3.1. Optimization of Reaction Condition:

We began our study with simple benzochromene moiety (3,3-dimethyl-1-phenyl-3H-benzo[f]chromene) **12a**. Initially, **12a** was refluxed in toluene with *p*TSA at 120 °C, and 56% of rearranged product naphthoindenol **20a** was formed in 6 hours (entry 1). Following this, several different solvents including 1,2-DCE, EtOH, and CH_3CN were optimized for this rearrangement reaction under reflux temperatures, 78% of the product was formed in 1,2-DCE, whereas EtOH and CH_3CN were inefficient for the rearrangement of **12a** (entries 2-4). Upon heating at 100 °C under solvent-free conditions, 73% of the product was formed (entry

5). The solvent-free system was preferred over such environmentally harmful chlorinated solvent system. Other Brønsted acids, including CSA, benzoic acid, and TFA, were investigated (entries 6-8) but were unable to catalyze the reaction. We attempted to change the reaction condition using Lewis acid catalysts like $Ca(NTf_2)_2$, $Ca(OTf)_2$, and $FeCl_3$ at 100 ^oC for 24 hours; however, it was discovered that there was no effect on the reaction (entries 9-11).

Table 1. Optimization of Reaction Conditions



12a **20a**

S. No.	Reaction Conditions[a]	Yield[b]
1	*p*TSA (10 mol%), Toluene, 120 ^oC, 6 h	56%
2	*p*TSA (10 mol%), 1,2-DCE, 90 ^oC, 8 h	78%
3	*p*TSA (10 mol%), EtOH, 80 ^oC, 24 h	nr
4	*p*TSA (10 mol%), CH_3CN, 90 ^oC, 24 h	nr
5	*p*TSA (10 mol%), Solvent-free, 100 ^oC, 6 h	73%
6	CSA (10 mol%), Solvent-free, 100 ^oC, 24 h	nr
7	$PhCO_2H$ (30 mol%), Solvent-free, 100 ^oC, 24 h	nr
8	TFA (20 mol%), Solvent-free, rt, 24 h	0%
9	$Ca(NTf_2)_2$ (5 mol%), Solvent-free,100 ^oC,24 h	nr
10	$Ca(OTf)_2/Bu_4NPF_6$ (10/10 mol %), Solvent-free, 100 ^oC, 24 h	nr
11	$FeCl_3$ (10 mol%), Solvent-free, 100 ^oC, 24 h	10%
12	*p*TSA (10 mol%), Solvent-free, 110 ^oC, 6 h	91%
13	*p*TSA (10 mol%), Solvent-free, 120 ^oC, 4 h	91%
14	*p*TSA (5 mol%), Solvent-free, 110 ^oC, 4 h	75%
15[c]	*p*TSA (20 mol%), Solvent-free, 110 ^oC, 1.5 h	95%

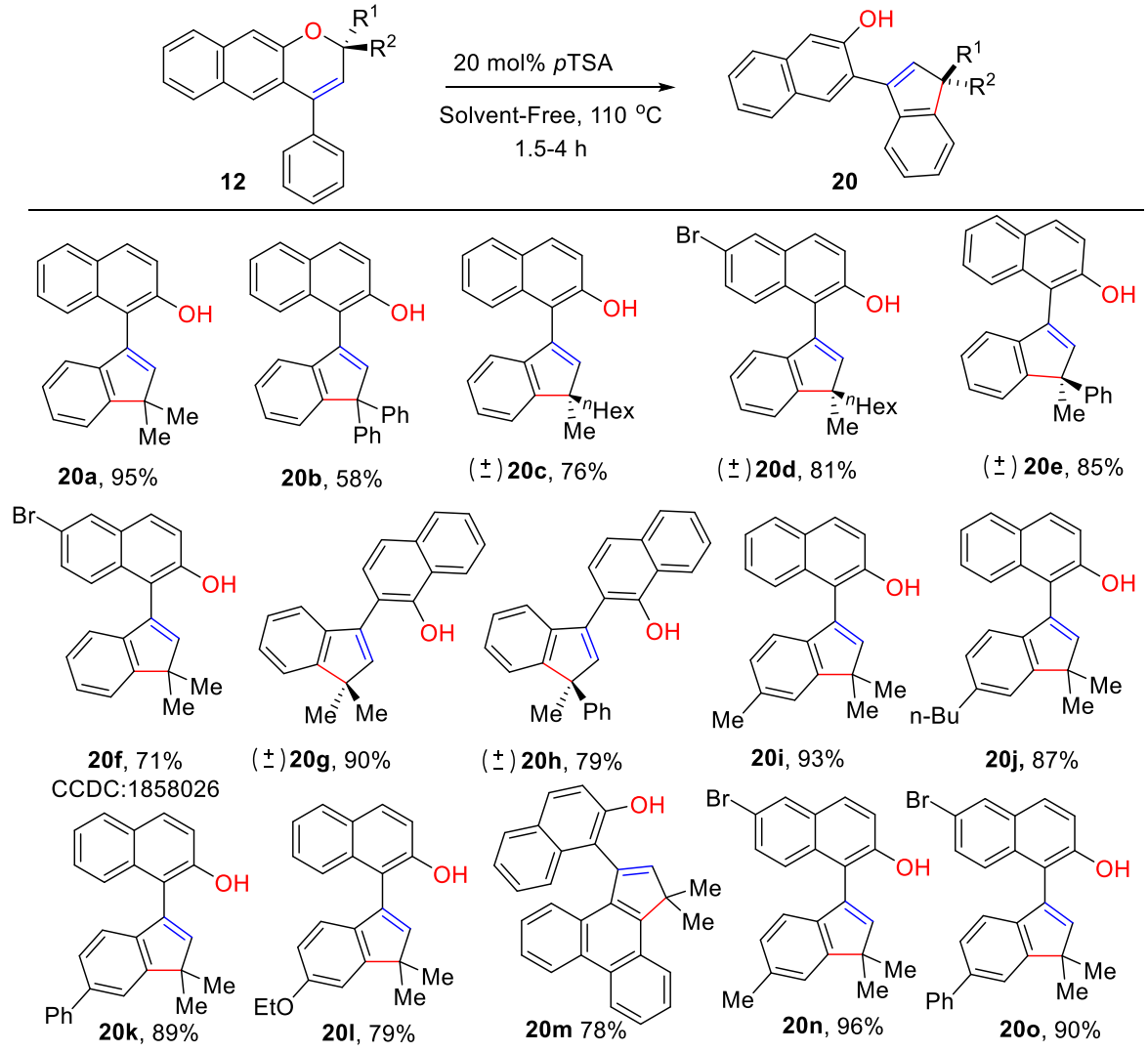
[a] Oil bath temperature. [b] Isolated yield, [c] Optimized condition ; nr: no reaction, *p*TSA: *p*-toluene sulfonic acid, TFA: trifluoroacetic acid, CSA: 10-camphor sulfonic acid, OTf: trifluoromethane sulfonate.

It was advantageous to enhance the yield of **20a** and decrease reaction time by increasing temperature from 100 ^oC to 110 ^oC and 120 ^oC with 10 mol% *p*TSA (entries 12, 13). It is delightful to note that the use of 20 mol% of *p*TSA at 110 ^oC delivered almost quantitative

yield (95%) of the rearranged product in 1.5 hours (entry 15), while it was discovered that 5 mol% of *p*TSA was inefficient (entry 14).

1.3.2. Scope of the reaction:

Soon after analysis of the ideal reaction condition for the ring rearrangement of 3,3-dimethyl-1-phenyl-3H-benzo[f]chromene (**12a**) to 1-(1,1-dimethyl-1H-inden-3-yl)naphthalen-2-ol (**20a**), we were keen to investigate the potential of other benzochromenes to undergo the same ring-rearrangement into indene derivatives. Hence, we synthesized several benzochromenes with different substitutions by treating 3°- propargyl alcohol with naphthol under acidic medium. To begin with, we investigated the role of substitutions at the C3 quaternary center of benzochromene (**12**) during the rearrangement to furnish corresponding indenonaphthols.



Scheme 10. *Substrate scope of Thermal-Ring-Rearrangement*

Aliphatic homo substituted C3 quaternary center bearing benzochromenes and 8-bromo benzochromene underwent rearrangement to produce excellent yields of product. Whereas in the case of aromatic homo substituted benzochromene, a moderate yield of product **20b** was

formed.It is interesting to note that the stereogenic carbon on indene (hereto substituted C3 center) caused the derivatives **20c**- **20e** to be diastereomeric atropisomers. The constrained rotation of the C-C single bond linking the two moieties caused atropisomerism. As the naphthyl and indenyl moieties are perpendicular to one another according to the crystal structure, resembling the structure of a biphenyl system and the presence of chiral carbon makes it easier to identify them as diastereomeric atropisomers. This was further proven by different peaks of diastereomer in ^{1}H and ^{13}C NMR. The compound **20f** synthesized from 8-bromo substituted benzochromene was further confirmed by single crystal XRD. When 2-H-benzochromene derivatives with varied C3 quaternary centers like 2,2-dimethyl-4-phenyl-2H-benzo[h]chromene and 2-methyl-2,4-diphenyl-2H-benzo[h]chromene was treated with the optimal condition, we were able to produce the corresponding indenylnaphthalen-1-ol **20g** and **20h** in good yields (Scheme 10).

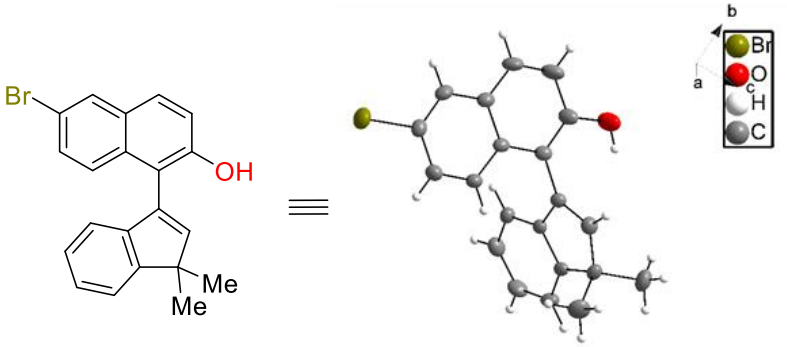
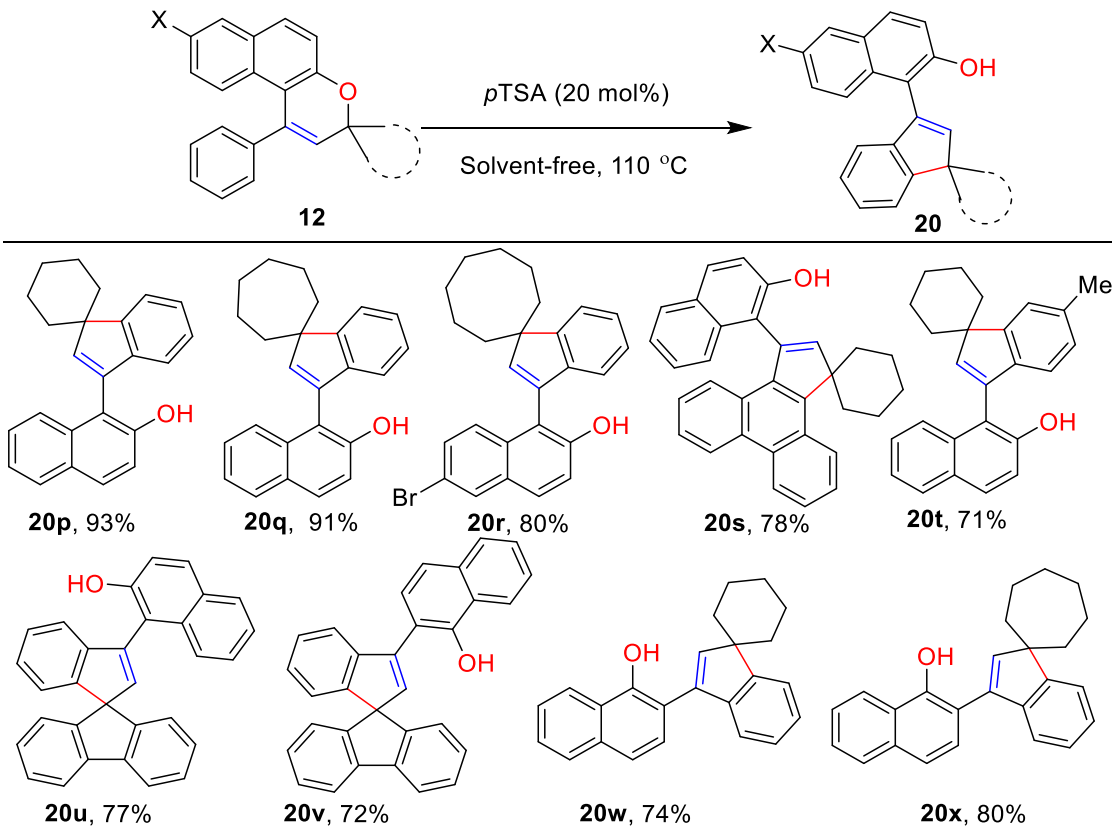


Figure 2. *Single Crystal XRD of* ***20f***

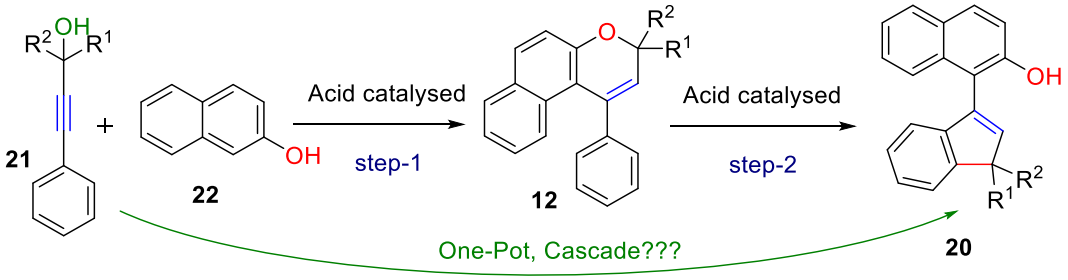
The aryl ring at the C1 position of benzochromene with phenyl, ethoxy, and alkyl substituents such as methyl and n-butyl (**12i**-**12l**) were flexible for the ring-rearrangement to synthesize the corresponding indenenonaphthol derivatives **20i**-**20l** in high yields (Scheme 10). Phenanthrenyl substituted benzochromene when subjected to the optimized condition resulted in 78% of 1-(1,1-dimethyl-1H-cyclopenta[l]phenanthren-3-yl)naphthalen-2-ol (**20m**). 8-bromo benzochromenes with phenyl and methyl substitution on the aryl ring underwent thermal ring rearrangement to get corresponding bromoindenonaphthol **20n** and **20o** (Scheme 10).

In addition, the ring rearrangement of benzochromene bearing the spiro-center at C3 for example 1-phenylspiro[benzo[f]chromene-3-1'-cyclohexane] **12p** on treatment with the optimized condition afforded corelative 1-(spiro[cyclohexane-1-1'-inden]-3'-yl)naphthalen-2-ol **20p** in 93% yield after 3 hours (Scheme 10). Enlightened by the results obtained, we synthesized indenonaphthol moieties containing cyclohexyl (**20p**, **20s**, **20t**, **20w**), cycloheptyl (**20q** and **20x**), cyclooctyl (**20r**) and, fluorenyl (**20u**, **20v**) substitutions at the quaternary carbon (C3-carbon) in distinctive amount from the corresponding benzochromenes (Scheme 11).



Scheme 11. *Substrate scope of spirocyclic benzochromene*

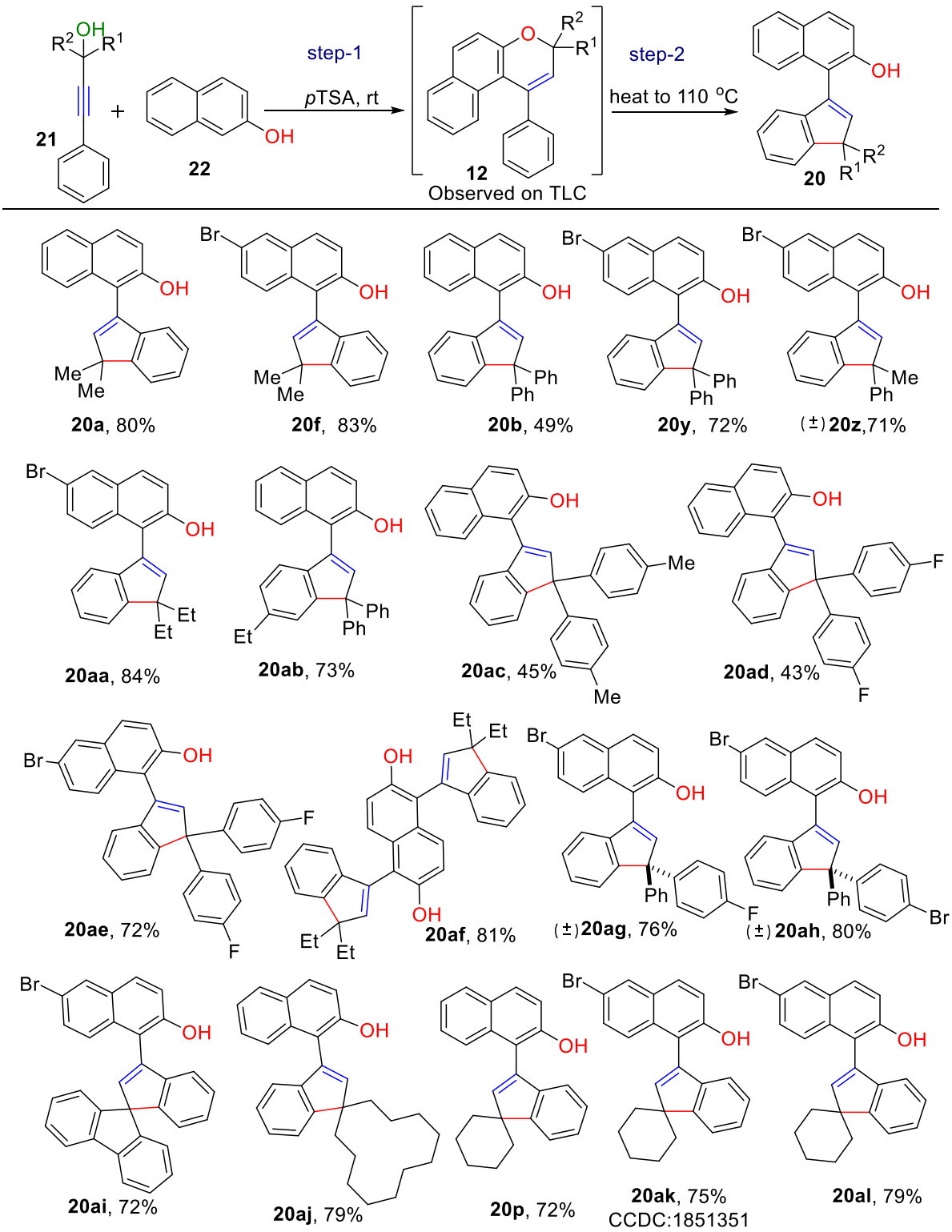
In Scheme 12, synthesis of benzochromene **12** is outlined, benzochromene **12** is known to be synthesized from a tertiary propargyl alcohol **21** and naphthol **22** under acid catalysis particularlt with *p*TSA (step-1),[19] and as our findings suggest the thermal ring rearrangement of benzochromene **12** to indenyl-ol **20** in presence of *p*TSA (step-2), thus, assuming the possibility of a one-pot cascade reaction,[21] and hence develop a reaction in such a manner that tertiary propargyl alcohol **21** and naphthol **22** under the action of *p*TSA will form benzochromene **12**, and then it can undergo a ring-rearrangement to give the indene derivative **20**.



Scheme 12. *Strategy for one-pot approach*

For the implementation of this one-pot reaction, a mixture of 2-methyl-4-phenylbut-3-yn-2-ol **21a**, and 2-naphthol **22** was heated at 100 °C with *p*TSA under solvent-free conditions, and observed the formation of benzochromene **12a** within 20 minutes, further the benzochromene was rearranged to indene **20a** on continuing the reaction for more 1.5 hours (Scheme 13).

Being aware of the importance of a one-pot cascade protocol towards the sustainable synthetic process,[14] we were encouraged to elaborate this method for the synthesis of the inden-3-yl-naphthols with diversity at the quaternary center, bromo substituted naphthol and substituted aryl at akyne terminus of propargyl alcohol was investigated.



Scheme 13. *The substrate scope of benzochromene in one-pot*

Homo-substituted 8-bromo-1,3,3-triphenyl-3H-benzo[f]chromene resulted in 72% of indenonaphthol **20y,** methyl-phenyl (**20z**), and diethyl (**20aa**) substituted bromo indenonaphthol was synthesized in 71% and 84% yield respectively (Scheme 13). **20ab** resulted from the ethyl substituted aryl of propargyl alcohol. Next, we synthesized indenonaphthol bearing homo or hetero substituted C3 center with aryl groups. Compound **2ac**-**2ae** are the outcome of TRR of homo substituted C3 quaternary center with 4-Me-Ph and 4-F-Ph. Compounds **20ag** and **20ah** had a chiral center at C3 as expected these compounds were diastereomeric atropisomers. Using 2,6-naphthalene-diol with 2 mole of propargyl alcohol we synthesized a di-indenyl substituted naphthalendiol **20af**. After synthesizing interesting dimeric substrate 1,5-bis(1,1-diethyl-1H-inden-3-yl)naphthalene-2,6-diol **20af**, spirocyclic system (**20p**, **20ai-20ak**) was synthesized in an excellent comprehensive yields (Scheme 13). Single crystal X-ray data further confirms the structure of **20ak**.

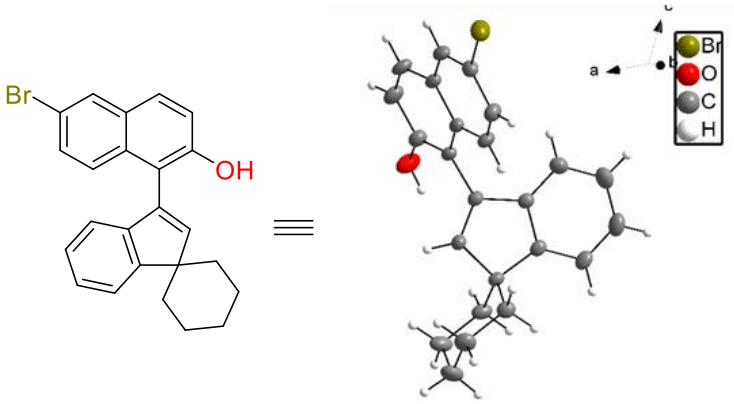
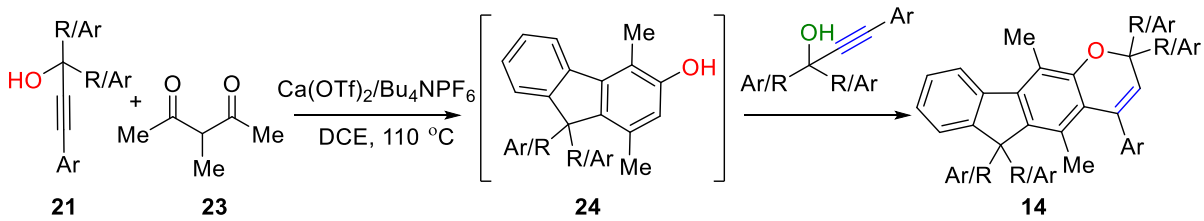


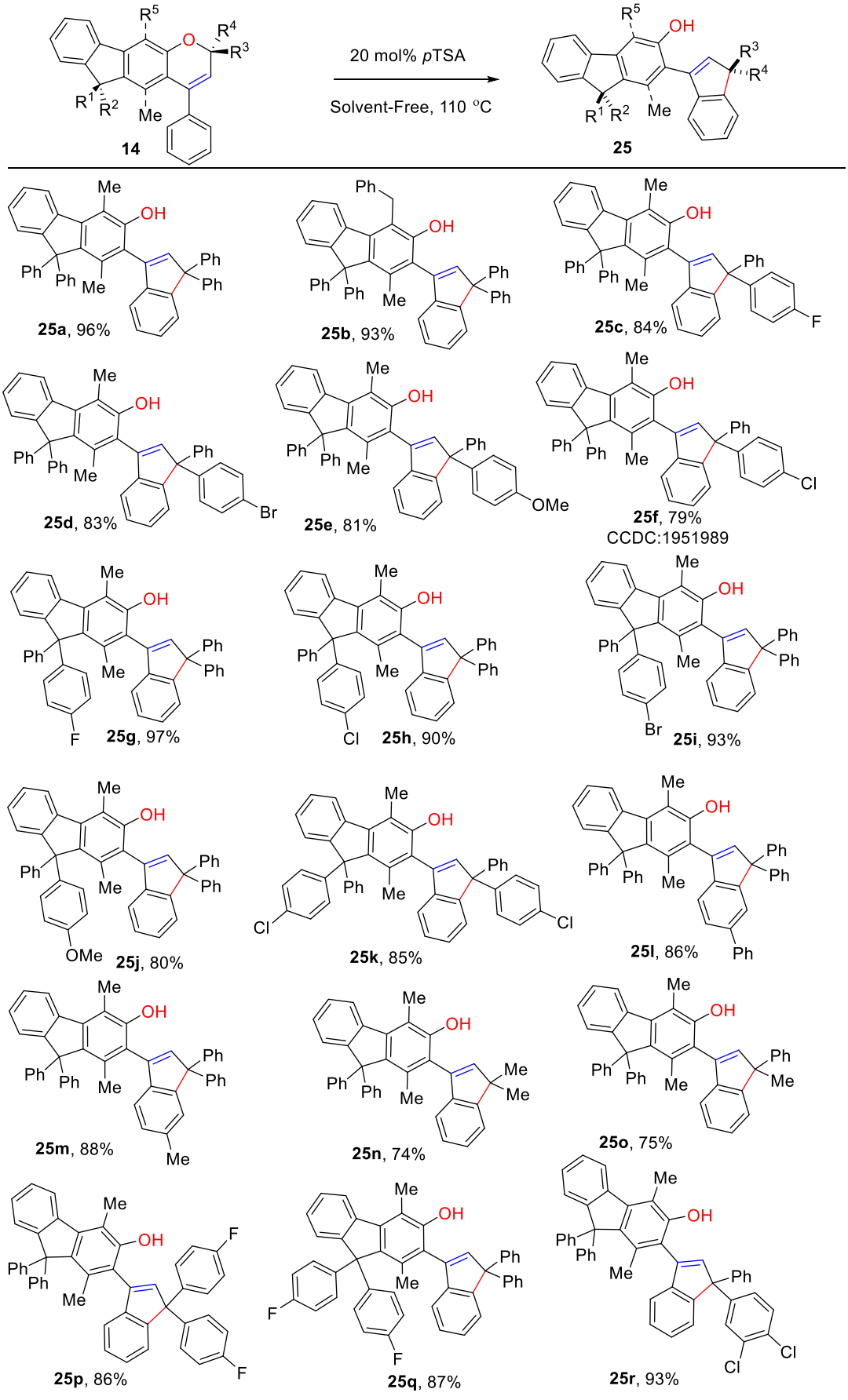
Figure 3. *Single Crystal XRD of* ***20ak***

After success with the rearrangement of benzochromenes, we envisioned to further study on indenochromene/fluorenopyran, hence we selected the model substrate 5,11-dimethyl-2,2,4,6,6-pentaphenyl-2,6-dihydroindeno[2,1-g] chromene **14a**, which was synthesized using a previous approach.[6] The propargyl alcohol was treated with 1,3-diketone which upon nucleophilic addition results in an allene intermediate, this allene intermediate undergoes sequential Allene-Friedel-Crafts cycloisomerization, intramolecular aldol reaction, Claisen rearrangement, and 6-*endo dig* cyclization to get the desired fluorenopyran **14** (Scheme14), this was the first approach for such moiety.



Scheme 14. *Synthesis of Indenochromene*

Under the optimized conditions, compound **14a** underwent an irreversible ring rearrangement to furnish 2-(1,1-diphenyl-1H-inden-3-yl)-1,4-dimethyl-,9-diphenyl-9H-fluoren-3-ol **25a** in near quantitative yield after 90 minutes (Scheme 14). We were encouraged by this result and



Scheme 15. *Substrate scope of Indenochromenes*

decided to use the other fluorenopyrans to test the generality of this approach. When 11-benzyl-5-methyl-2,2,4,6,6-pentaphenyl-2,6-dihydroindeno[2,1- g]chromene was subjected to the optimized condition underwent TRR to synthesize 4-benzyl-2-(1,1-diphenyl-1H-inden-3-yl)-1-methyl-9,9-diphenyl-9H-fluoren-3-ol **25b** in 93% yield.

Fluorenopyrans with stereogenic centres produced diastereomeric atropisomers with constrained rotation of the fluorenyl and indenyl moiety's C-C bond. Substrates bearing stereogenic center at 2-indenyl position obtained diastereomers **25c**, **25d**, **25e** and **25f** in excellent yields (Scheme 15), characterization of these compounds showed that the difference in chemical shift values particularly hydroxyl group is more distinct when compared to diastereomers bearing stereogenic center at fluorene (**25g-25j**), in case of **25j** the methoxy peak δ separation was noticeably more. A single crystal X-ray structure of compound **25f** was obtained to conform its structure without any ambiguity. The stereogenic center at fluorene also resulted in diastereomers **25g-25j** in good yields**.** Diastereomeric atropisomers due to chiral centre at 2-indenyl position were clearly visible on TLC ($R_f \approx 0.48$ and 0.5, mobile phase: 3% EtOAc in hexane), whereas the diastereomers with chiral center at 9-fluorenyl moiety appeared as a single spot on the TLC.

Atropisomers are the stereoisomers that develop because of hindered rotation around a single bond, steric strains lead to energy differences and raise the rotational barrier to a level where isolation of individual conformers is possible.[22] They are significant in pharmacological design and are present naturally. These conformers are enantiomers (atropoenantiomers), indicating axial chirality when the substituents are achiral; they are diastereomers (atropodiastereomers). Separation of the diastereomers on the TLC excited us to separate the diastereomeric mixture, the column chromatography in 100-200 and 230-400 silica mess using pure hexane as the mobile phase could not separate the mixture (compound **25d**), preparative TLC method also fails in our case. We also recorded the High-temperature ^{1}H NMR[23] of compound **25d** in $CDCl_3$ (at 50 ^oC) but it didn't give any conclusion, then we switched the solvent and recorded high-temperature NMR in DMSO-d_6 (at 50 ^oC and 80 ^oC), the -OH peak of the compound merged and shifted slightly towards the upfield region. LCMS separation using a C8 HPLC column shown two peaks in nearly 1:1 ratio on the chromatogram, the corresponding mass spectra of each peak showed the required mass fragment.

9-(4-chlorophenyl)-2-((S)-1-4-chlorophenyl)-1-phenyl-1H-inden-3-yl)1,4-dimethyl-9-phenyl-9H-fluoren-3-ol (**25k**) containing stereocenter at 9-fluorenyl and 2-indenyl position was obtained in 85%, the presence of two pair of diastereomers was supported by NMR. The sustainability of the standard reaction condition was also checked by substituting the electron-releasing group at the *para* position of the aryl ring involved in Friedel Craft's annulation yielded **25l** and **25m**. Different substitution at the quaternary center of 2-indenyl position was explored by replacing the two aryl groups, with the two alkyl groups **25n** and one aryl-one alkyl **25o**. Gem-*p*-fluorophenyl substituted fluorenopyrans (on 6th and 2nd positions respectively) were rearranged to yield **25p** and **25q**. 3,4-dichloro substituted aryl at the quaternary center **25r** was synthesized in 93% yield**.**

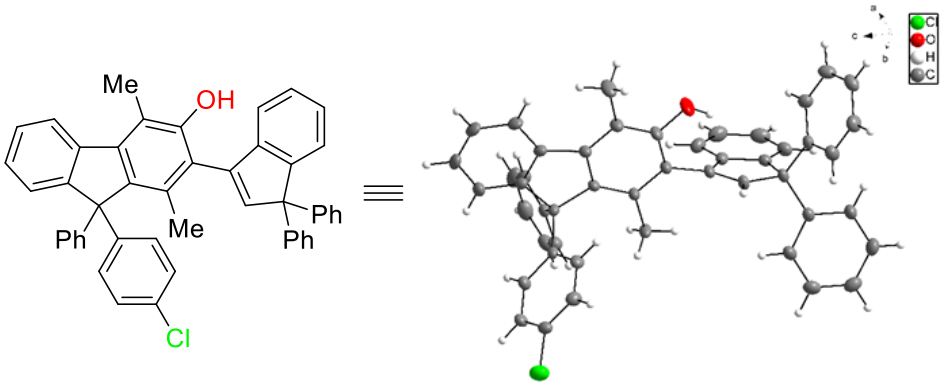


Figure 4. *Single Crystal XRD of* ***25f***

With this success in hand, we further investigated the rearrangement of 3-iodo fluorenochromene, the compounds bearing an iodide substitution at the C3 position. 3-iodo-5,11-dimethyl-2,2,4,6,6-pentaphenyl-2,6-dihydroindeno[2,1-g] chromene **26a** was treated with the optimized condition and it resulted in rearranged product **27a** (Scheme 16). Interestingly there is no report of TRR on any of the iodo/halo-substituted chromene molecules. So, we thought of investigating with this substrate under the standard reaction conditions, presumably, the product (2-(2-iodo-1,1-diphenyl-1H-inden-3-yl)-1,4-dimethyl-9,9-diphenyl-9H-fluoren-3-ol) **27a** was obtained in 62% yield after 2 h. (Scheme 16). Interestingly, iodide functionality was intact with the molecule but on a newly constructed ring. The generality of this reaction was also studied by subjecting several numbers of 3-iodo-fluorenopyrans **26a**-**26g** to ring-rearrangement reaction and obtained the respective products. The stereogenic center at fluorene **27b**-**27d** and stereogenic center at 2-indenyl **27e** was synthesized, the trend of atropisomerism was observed with iodo-substrates also. The structure of these products was unambiguously determined by a single-crystal X-ray structure of **27f**.

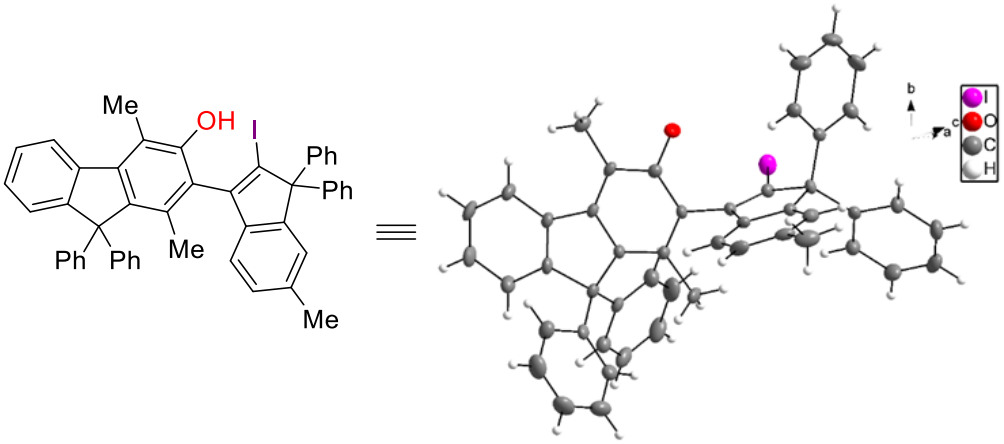
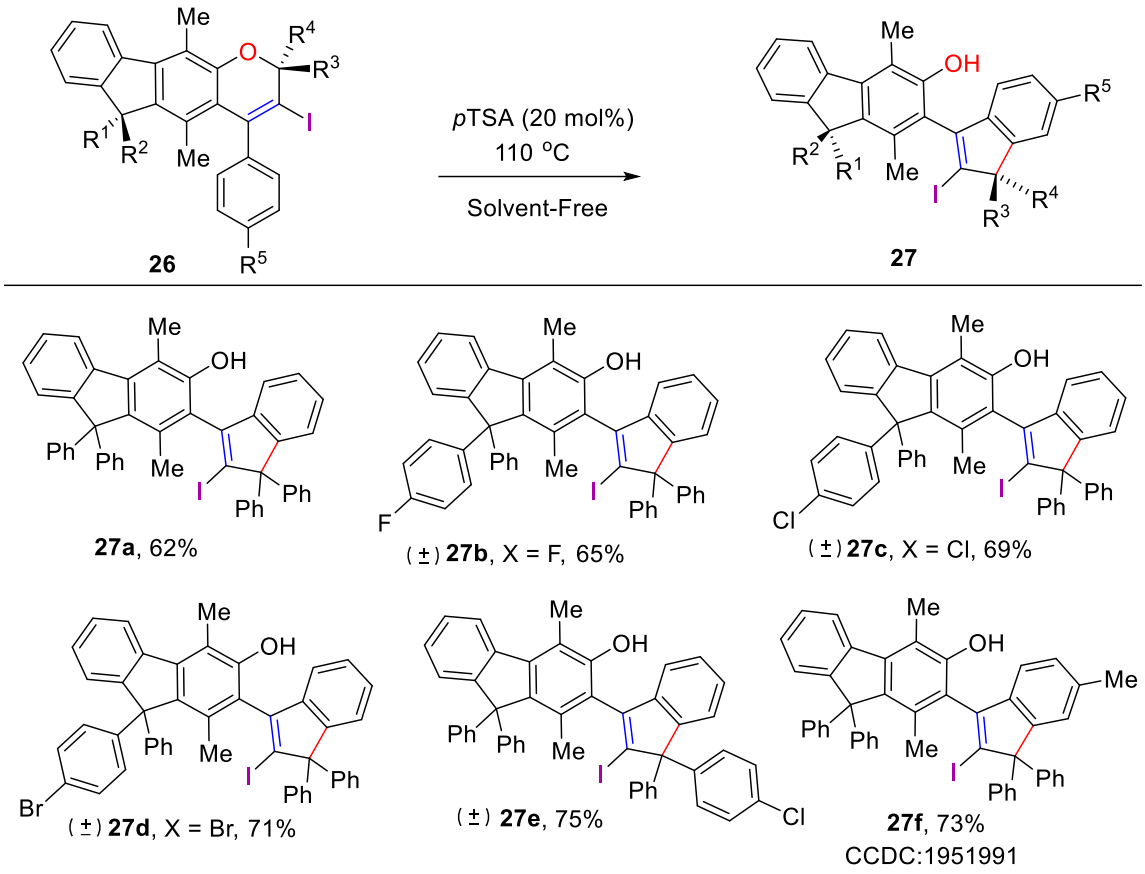


Figure 5. *Single Crystal XRD of* ***27f***



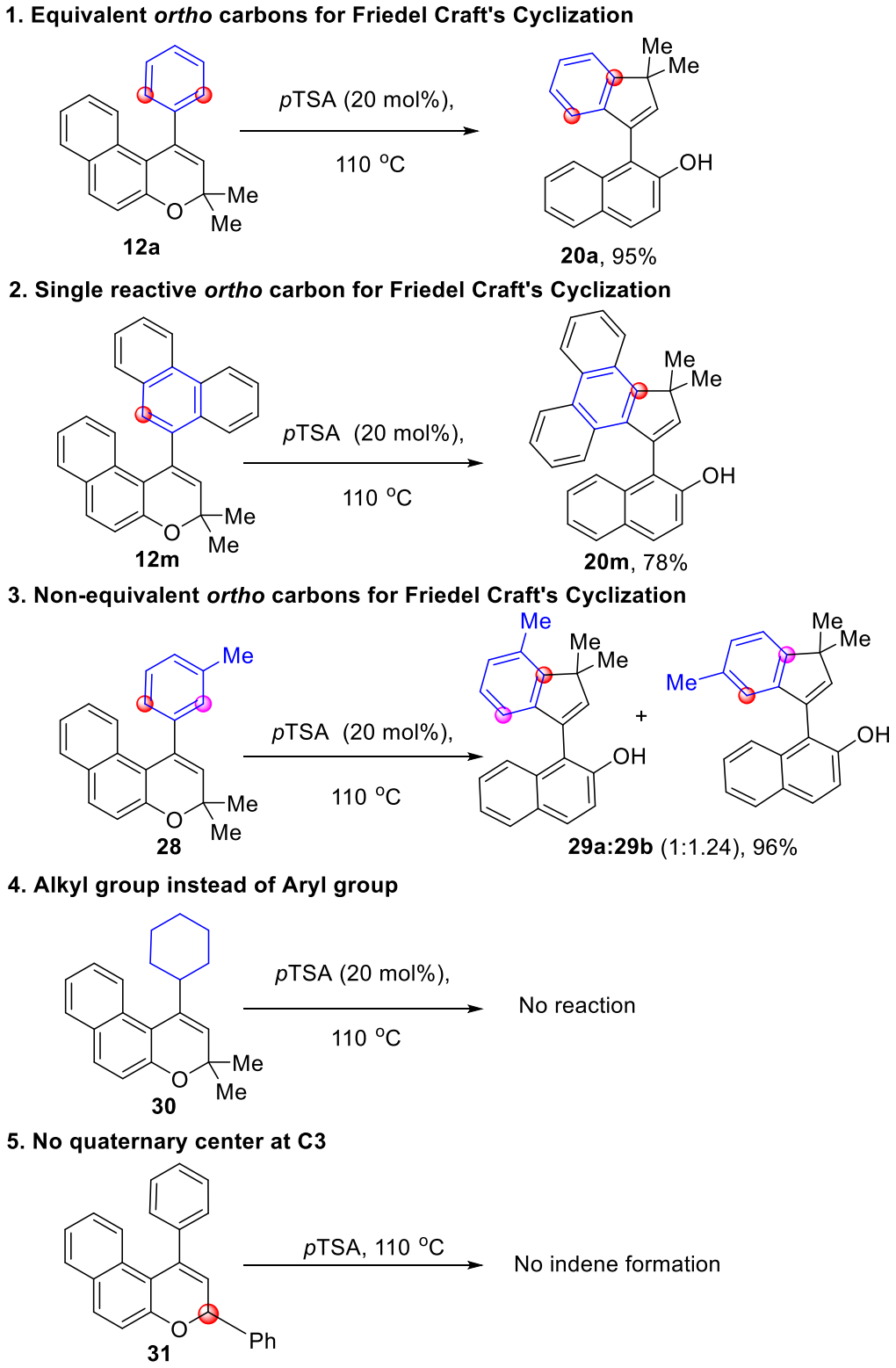
Scheme 16. *The substrate scope of Iodoindenochromenes*

1.3.3. Control Experiments:

After establishing a novel thermal ring rearrangement protocol for the conversion of benzochromene to indenyl-ol derivatives and a one-pot strategy for the rearrangement from propargyl alcohols, we carried out a few control experiments depicted in Scheme fthe C1 and chemically comparable *ortho*-carbons was used in the general experiment to produce product **20a** by thermal ring rearrangement.

When the reaction was performed with a benzochromene with a phenanthrenyl group at C1 (**12m**), having a single reactive *ortho* carbon, the ring rearrangement yielded an indene derivative **20m** in 78% yield. The next experiment commenced with the benzochromene **28** bearing *m*-tolyl group with chemically equivalent *ortho* carbons and obtained the regioisomeric mixture of the two indene derivatives **29a** and **29b** in 1:1.24 ratio with 96% combined yield. Reaction performed with benzochromene **30** bearing a cyclohexyl moiety at C1 under the optimized reaction condition, no change in the starting material was observed. This emphasizes the importance of the aryl group at C1 for the thermal ring rearrangement reaction. The conclusion of all the reactions performed shows the necessity of an aryl group at C1 with at least one reactive *ortho* carbon to carry out the ring rearrangement reaction. A reaction was performed to check the importance of a quaternary center at C3 carbon, for which 1,3-diphenyl-3H-benzo[f]chromene **31** having a phenyl group with a reactive *ortho* carbon

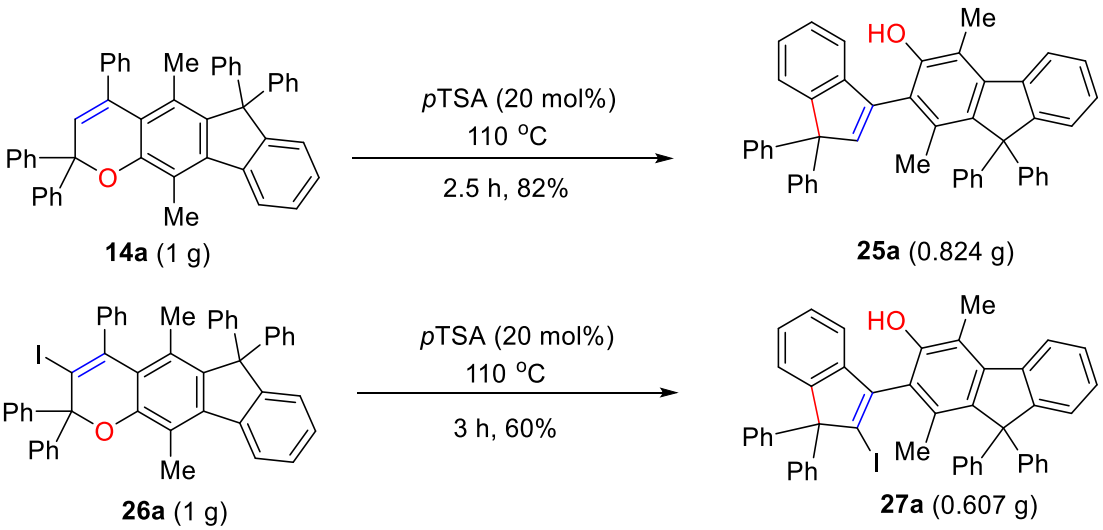
at C1 was subjected to the optimized condition, we found out that the reaction was unable to undergo the rearrangement. According to these experimental findings, the Thermal ring rearrangement occurs when benzochromene has a quaternary centre at C3 and an aryl group with at least one *ortho* carbon at C1.



Scheme 17. *Control experiments*

1.3.4. Gram Scale synthesis and Synthetic Applications

After the establishment of a general protocol for the thermal ring rearrangement of naphthopyrans, fluorenopyrans, and iodofluorenopyrans, we demonstrate the gram scale reaction of **14a**, **26a**, and obtained the corresponding products **25a** in 82% yield and **27a** in 60% yield as shown in the Scheme 18. Good yields obtained in the scaleup reaction suggest the sustainability of the standard reaction condition.

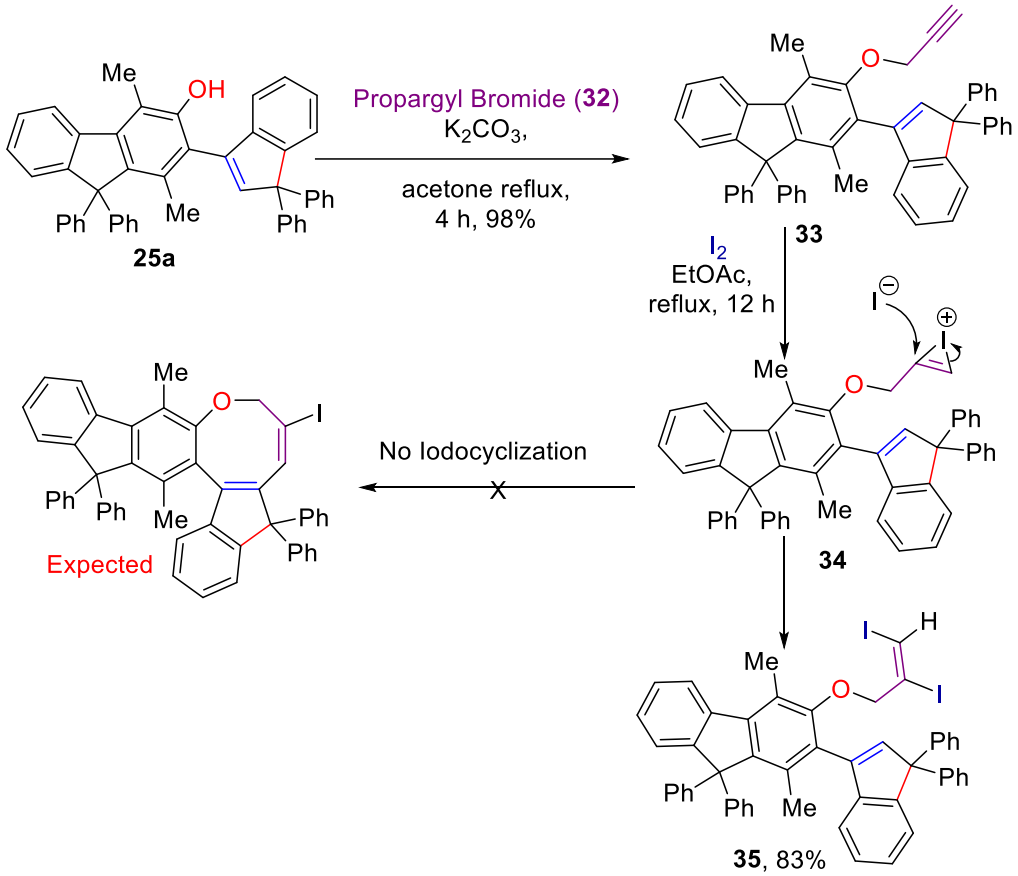


Scheme 18. *Gram scale synthesis of Fuorenoindene and Iodofluorenoindene*

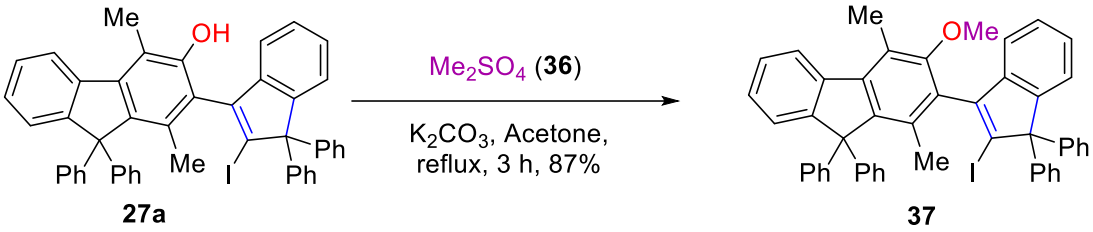
Further, we performed a few synthetic applications, propargylation of **25a** was carried out by refluxing **25a** in acetone with propargyl bromide **32** and potassium carbonate and obtained propargyl ether **33** in 98% yield after 4 hours (Scheme 19).[24] Then we planned an iodocyclization[25] of **33** with iodine, which is supposed to proceed through intermediate **34** *via exo* or *endo* cyclization. Surprisingly, compound **33** did not undergo iodocyclization as expected but electrophilic iodination on the triple bond occurred to give the diiodide **35** (Scheme 19).[25b]

On other hand compound **27a** was subjected to etherification to form methyl ether **37** in 87% yield by refluxing in acetone with dimethyl sulfate **36** and K_2CO_3 for 3 hours (Scheme 20).[26]

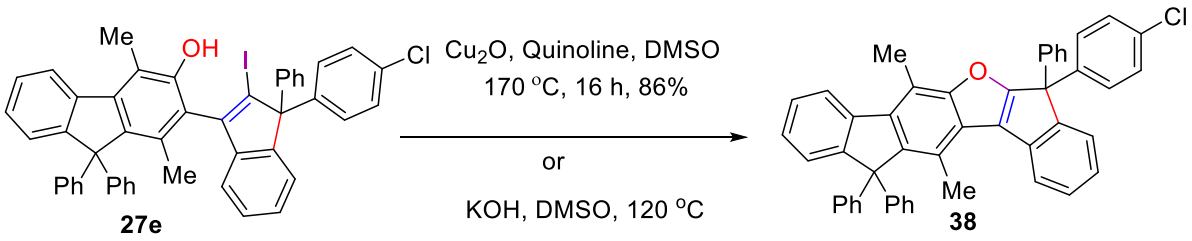
One of the iodinated diastereomeric atropisomer **27e** on being heated with copper (I) oxide in quinoline underwent dehydrohalogenation to give the polycyclic compound **38** in 86% yield (Scheme 21).[27a] It is worth noting that when the dehydrohalogenation of compound **27e** was performed with a base like KOH in DMSO at 120 °C, complete conversion of starting material was not observed even after 48 hours.[27b]



Scheme 19. *Synthetic transformations of* ***25a***



Scheme 20. *Etherification of* ***27a***

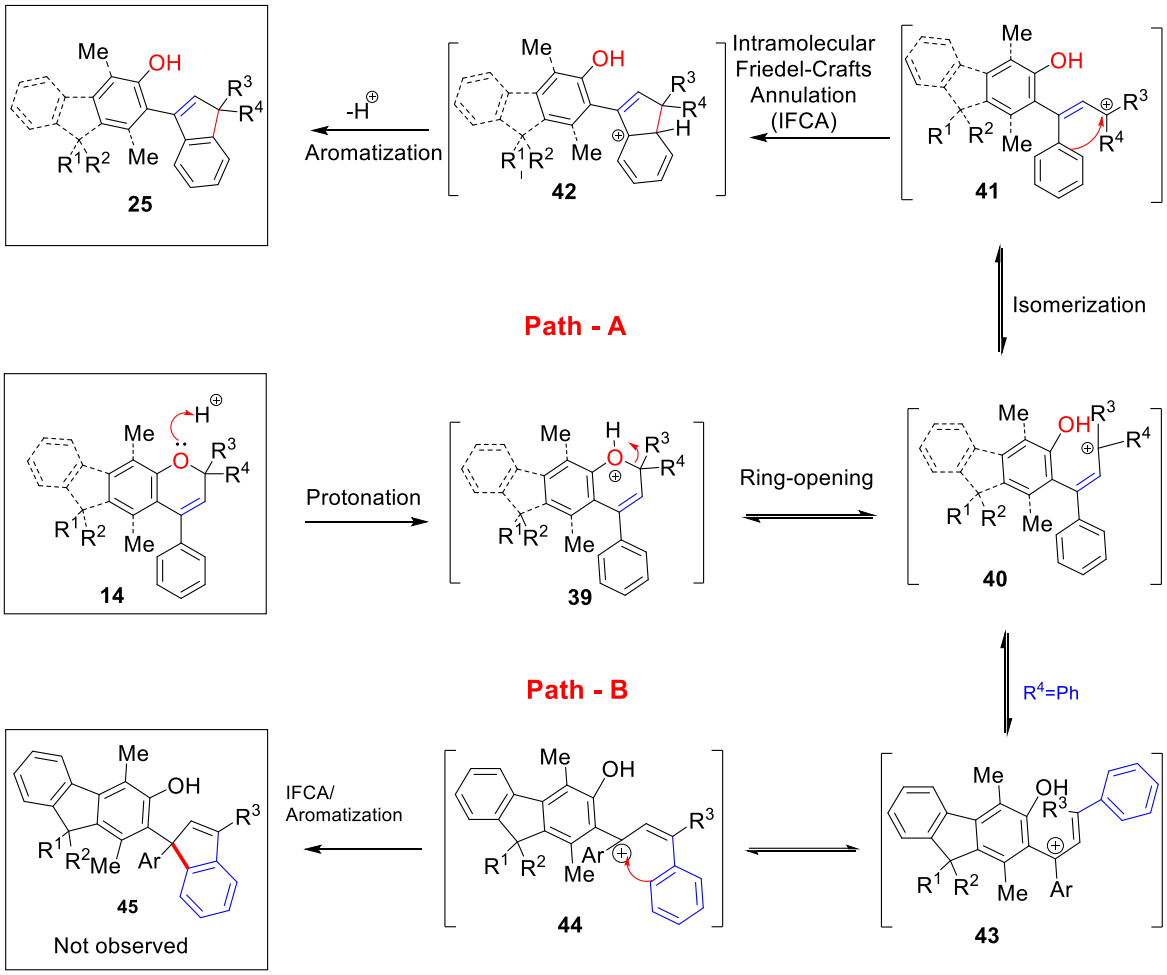


Scheme 21. *Dehydrohalogenation of* ***27e***

1.3.5. Mechanism:

The reaction mechanism of the thermal ring-rearrangement is outlined in Scheme 22 based on the observations of the control experiments. Protonation of chromene

(**12/14/26**) with the Brønsted acid gives oxonium intermediate **39**, the intermediate **39** undergoes ring opening to form a cationic intermediate **40**. Isomerization of **40** followed by an intramolecular Friedel-Crafts annulation gives product **20/25/27** through an intermediate **41**. In the alternate or unfavorable path described in Scheme 23, the cationic intermediate **40** resonate to give **43**, which on isomerization can give **44**, the intramolecular Friedel-Crafts annulation of **44** could give rise to the fluorenoindene **45**.



Scheme 22. *Proposed Mechanism*

1.4. DFT and Single Point Energies of Conformers

The DFT study suggests Path-A as a favorable path without any ambiguity. It is important to note that when we tried thermal ring rearrangement of chromene bearing a C4-alkyl group (instead of an aryl group), it could not give the rearranged product, which of course can be understood that an aryl group is required for the Friedel-Crafts annulation.

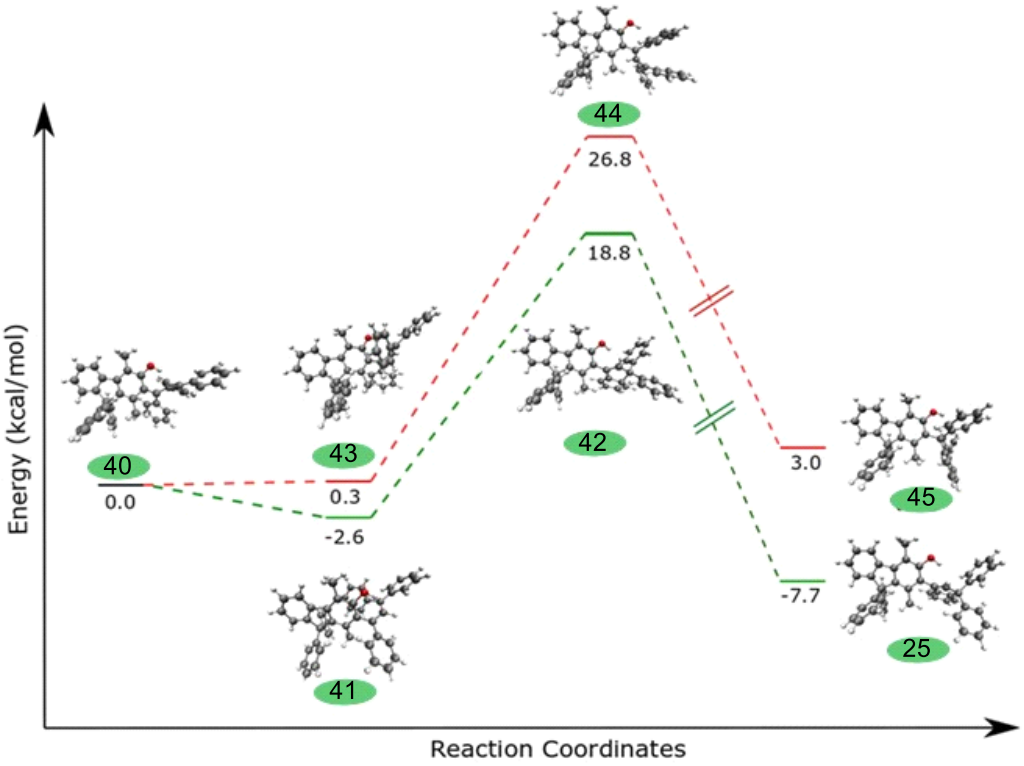


Figure 2. *The energy profile of the reaction mechanism depicted in Schemes 22, the reaction energies are reported in kcal/mol.*

The energy profile of the reaction mechanism is outlined in Schemes 22 is shown in Figure 2. The favorable reaction path is shown in green in the energy profile. The relative energies of the intermediates **41** and **42** are -2.6 and 18.8 kcal/mol respectively, with respect to the common intermediate **40**. The final product **25** is relatively more stable than **40** with an interaction energy of -77 kcal/mol. The unfavorable path is depicted in red, with the intermediate **43** and **44**, and the product **45** with relative energies of 0.3, 26.8, and 3.0 kcal/mol respectively. The relative energies of products **25** and **45** are calculated in accordance with the intermediate **40** as depicted in Figure 2. The final products differ in energy by 10.3 kcal/mol. The energy profile evaluated at M062X/6-31+G(d,p) shows that the proposed reaction mechanism depicted in green colour is preferred over the energy profile shown in red coloured dotted line.

At the DFT level, the M062X functional and 6-31G(d,p) basis functions were used to optimize the geometry and single-point energy.[28-31] Optimized geometries were employed to calculate the ^{1}H-NMR chemical shift at the same level of theory in the presence of solvent. The calculations were performed on selected molecules; it was observed that compounds with achiral indene and fluorenyl center conformers exhibit no energy difference and no difference in ^{1}H-NMR chemical shift values (ppm). Thus, only one peak was observed in **25a**, though the conformer **25h** did not show energy difference in DFT calculation, experimental data show a small difference in the ^{1}H-NMR chemical shift values. However, two of the molecules **25f** and **25k** exhibit energy differences (ΔE) of -1.38 and -1.34 in kcal/mol respectively, as

mentioned in Table 2. Due to the different environments of -OH group located on the naphthyl moiety and the quaternary center of indene, it is expected that the molecular conformers exhibit variation in the energy difference, along with the ^{1}H-NMR chemical shift values. Figure 3 depicts two conformers of molecules **25a**, **25h**, **25f**, and **25k**, the energy difference of the conformers in kcal/mol.

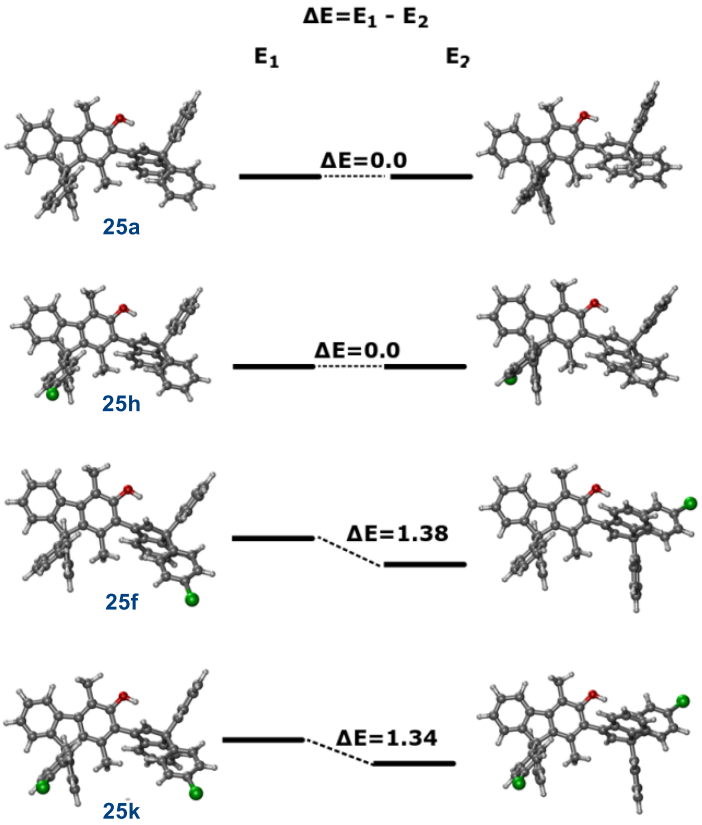


Figure 3. *The energies (E_1 and E_2) and the relative energy differences(ΔE) in kcal/mol, the atom oxygen is depicted in red, the carbon in grey, hydrogen in white and chlorine in green color, respectively*

From the computational results of the selected (**25a**, **25h**, **25k**, **25f**) molecules, it is evident that the conformers with stereogenic center on indene, show differences in the energies and ^{1}H-NMR chemical shifts. Theoretical ^{1}H-NMR chemical shift value corroborates well with the experiment, thus attributing the difference in chemical shifts as a feature of the atropisomerism.

Table 2. depicts single point energies of conformers (designated as E_1 and E_2, respectively) at M062X/6-31+G(d,p), the calculated energies of conformers E_1 and E_2 are represented in Hartree. ΔE represents the energy differences (in kcal/mol) between the two conformers; NMR-1 & NMR-2 are the ^{1}H NMR chemical shift of the -OH functional groups (in ppm) of the conformers, respectively. ΔNMR is the difference in the NMR values (in ppm).

Table 2 Reports of the M062X/6-31 G(d,p) calculations

Molecules	E_1 (Hartree)	E_2 (Hartree)	ΔE (kcal/mol)	NMR-1 (ppm)	NMR-2 (ppm)	ΔNMR (ppm)
25a	-1925.29508	-1925.29508	0.00	5.369	5.369	0.00
25h	-2384.86128	-2384.86128	0.00	5.489	5.489	0.00
25k	-2844.43405	-2844.43191	-1.34	5.309	5.075	0.234
25f	-2384.86444	-2384.86224	-1.38	5.434	5.173	0.262

1.5. Single Crystal XRD

1.5.1. X-ray data of Compound 20f:

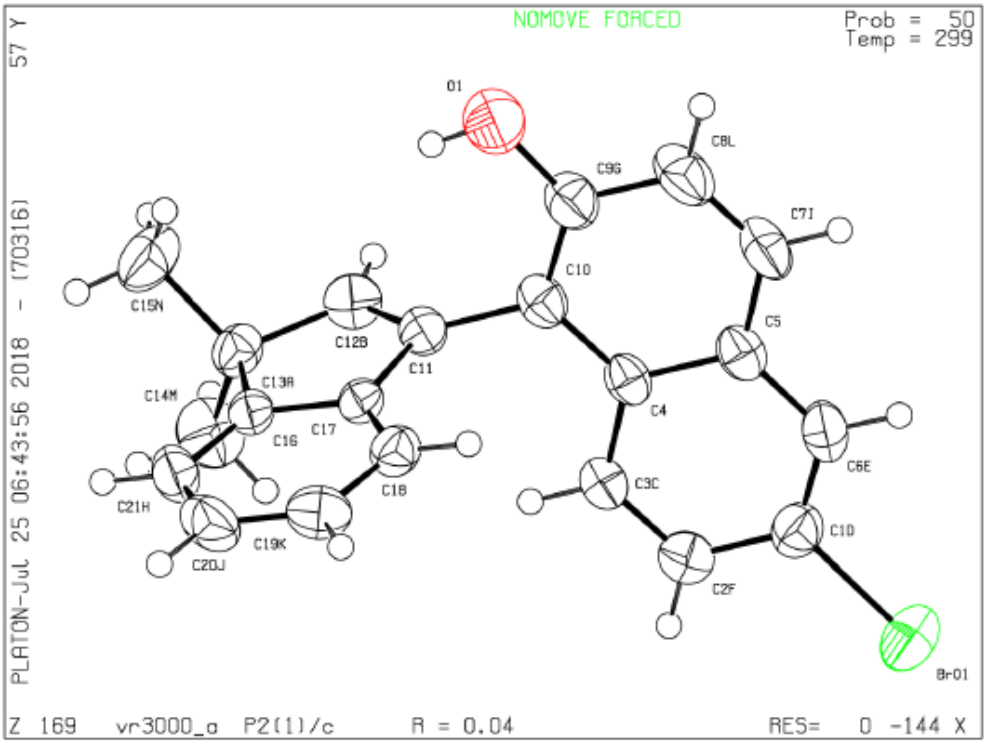


Figure 4. *ORTEP representation of compound* ***20f*** *and thermal ellipsoids are drawn with 50% probability.*

Identification code	shelx-97
Empirical formula	$C_{21}H_{17}BrO$
Formula weight	365.25
Temperature	299 (2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic

Space group	P 21/c	
Unit cell dimensions	a = 12.928 (3) Å	α = 90 °.
	b = 16.007 (4) Å	β = 94.097 (7) °.
	c = 8.3586 (16) Å	γ = 90 °.
Volume	1725.3 (6) $Å^3$	
Z	4	
Density (calculated)	1.406 Mg/m^3	
Absorption coefficient	2.385 mm^{-1}	
F(000)	744	
Crystal size	0.42 x 0.40 x 0.40 mm^3	
Theta range for data collection	2.54 to 27.83 °.	
Index ranges	-16<=h<=16,-20<=k<=20,-10<=l<=10	
Reflections collected	4077	
Independent reflections	2496 [R(int) = 0.0444]	
Max. and min. transmission	0.385 and 0.382	
Refinement method	Full-matrix least-squares on F^2	
restraints / parameters	0 / 210	
Goodness-of-fit on F^2	1.034	
Final R indices [I>2sigma(I)]	R1 = 0.0444, wR2 = 0.0916	
R indices (all data)	R1 = 0.0972, wR2 = 0.1049	
CCDC No.	1858026	

1.5.2. X-ray data of Compound 20ak:

Identification code	shelx-2014/7	
Empirical formula	$C_{24}H_{21}BrO$	
Formula weight	405.32	
Temperature	298 (2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 11.7077 (18) Å	α = 90°.
	b = 9.7297 (13) Å	β = 116.691 (8)°.
	c = 18.751 (2) Å	γ = 90°.
Volume	1908.4 (5) $Å^3$	
Z	4	
Density (calculated)	1.411 Mg/m^3	
Absorption coefficient	2.163 mm^{-1}	
F(000)	832	
Crystal size	0.22 x 0.20 x 0.18 mm^3	
Theta range for data collection	2.334 to 30.562 °.	
Index ranges	-16<=h<=16,-13<=k<=13,-26<=l<=26	
Reflections collected	5813	

Independent reflections	4087 [R(int) = 0.0430]
Max. and min. transmission	0.678 and 0.628
Refinement method	Full-matrix least-squares on F^2
restraints / parameters	1 / 239
Goodness-of-fit on F^2	1.030
Final R indices [I>2sigma(I)]	R1 = 0.0430, wR2 = 0.0904
R indices (all data)	R1 = 0.0748, wR2 = 0.1034
CCDC No.	1851351

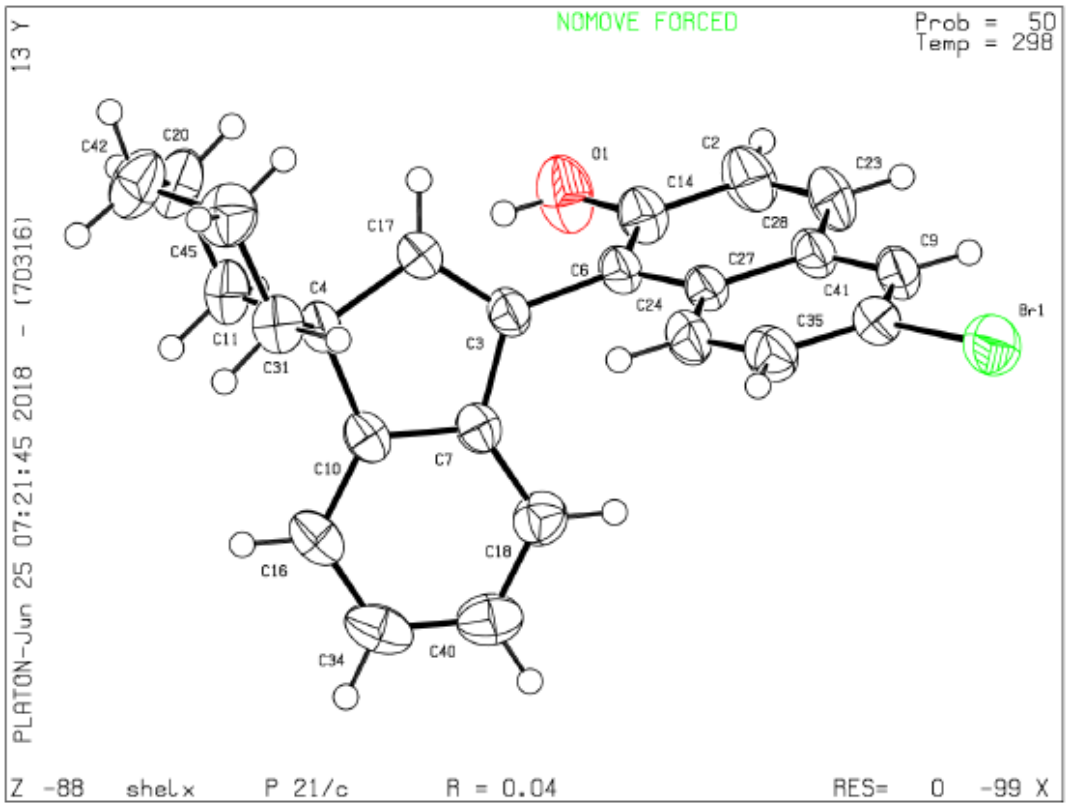


***Figure 5**. ORTEP representation of compound **20ak** and thermal ellipsoids are drawn with 50% probability.*

1.5.3. X-ray data of Compound 25f:

Identification code	shelx-97	
Empirical formula	$C_{48}H_{35}ClO$	
Formula weight	663.21	
Temperature	302 K	
Wavelength	0.71073 Å	
Crystal system	'Triclinic'	
Space group	P-1	
Unit cell dimensions	a = 9.8124 (6) Å	α = 83.207° (4).
	b = 12.0797 (9) Å	β = 75.132 ° (3).
	c = 15.3975 (151) Å	γ = 78.815 ° (3).
Volume	1726.0(2)	

Z	2
Density (calculated)	1.276 g/cm^3
Absorption coefficient	0.149 mm^{-1}
F(000)	696.0
Crystal size	0.38 x 0.32 x 0.28 mm^3
Theta range for data collection	2.28 to 25.00 °.
Index ranges	-11<=h<=11,-14<=k<=14,-18<=l<=18
Reflections collected	6078
Independent reflections	3946 [R(int) = 0.0718]
Refinement method	Full-matrix least-squares on F^2
restraints / parameters	0 / 451
R indices [I>2sigma(I)]	R1 = 0.0718,
R indices	wR2 = 0.2146
CCDC No.	1951989

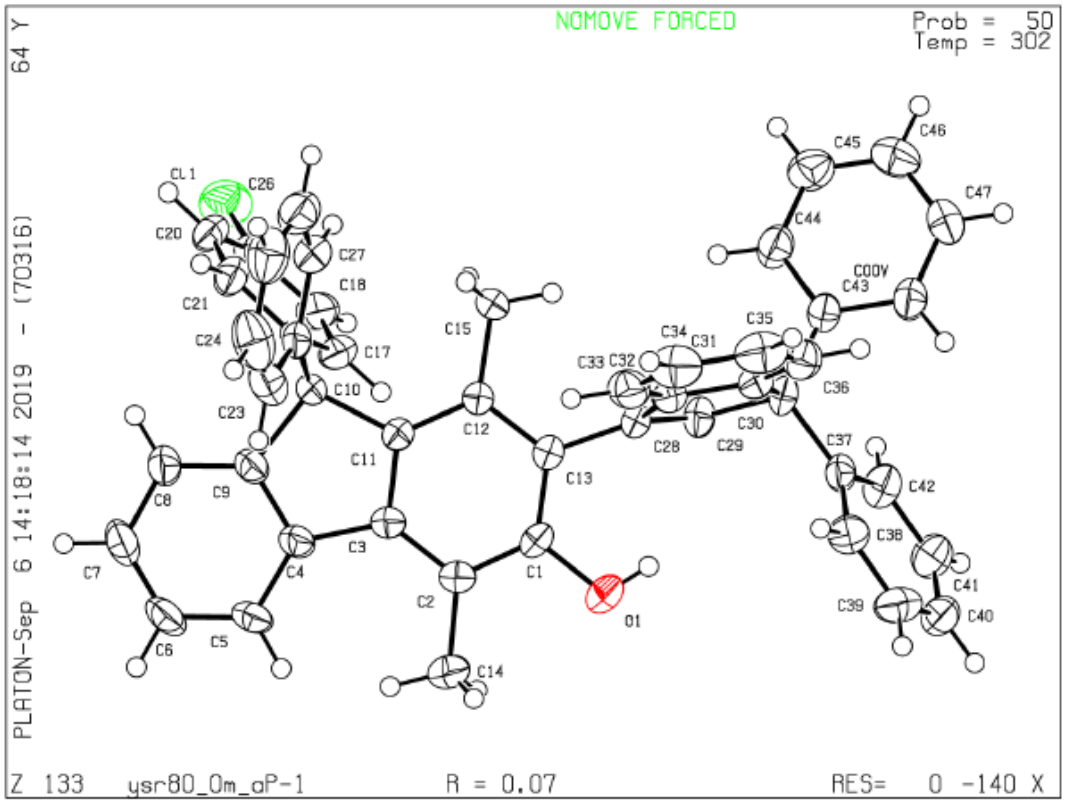


Figure 6. *ORTEP representation of compound* ***25f*** *and thermal ellipsoids are drawn with 30% probability.*

1.5.4. X-ray data of Compound 27f:

Identification code	shelx-97
Empirical formula	$C_{49}H_{37}IO$
Formula weight	768.69
Temperature	299 K
Wavelength	0.71073 Å

Crystal system	'Triclinic'	
Space group	P-1	
Unit cell dimensions	a = 10.5814 (7) Å	α = 79.469° (4).
	b = 12.1084 (8) Å	β = 78.349 ° (4).
	c = 14.9782 (11) Å	γ = 78.229 ° (4).
Volume	1819.8(2)	
Z	2	
Density (calculated)	1.403 g/cm^3	
Absorption coefficient	0.918 mm^{-1}	
F(000)	784.0	
Crystal size	0.38 x 0.32 x 0.27 mm^3	
Theta range for data collection	2.23 to 25.00 °.	
Index ranges	-12<=h<=12,-14<=k<=14,-17<=l<=17	
Reflections collected	6409	
Independent reflections	4163 [R(int) = 0.0496]	
Restraints/parameters	0 / 460	
R indices [I>2sigma(I)]	R1 = 0.0496	
R indices	wR2 = 0.1173	
CCDC No.	19511991	

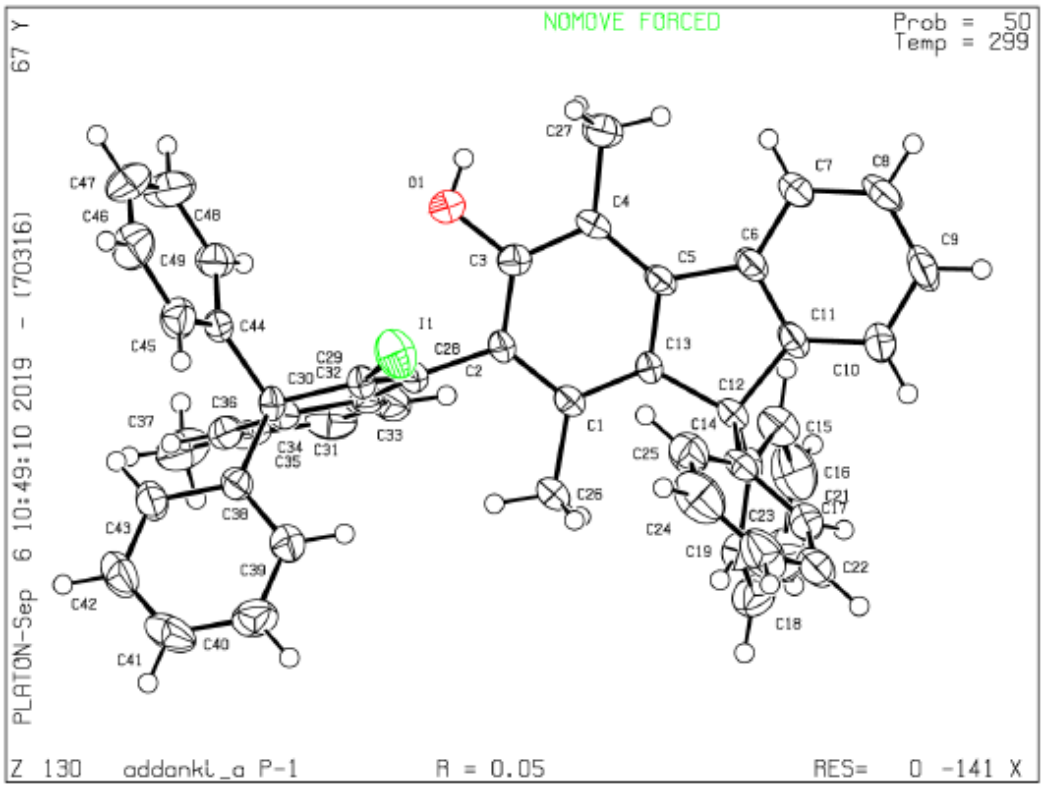


Figure 7*. ORTEP representation of compound* ***27f*** *and thermal ellipsoids are drawn with 30% probability.*

1.6. Conclusion

In conclusion, we have developed a thermal ring rearrangement reaction of naphthopyrans, and fluorenopyrans to indenyl naphthol, and 2-(1H-inden-3-yl)-9H-fluoren-3-ols respectively using *p*TSA under solvent-free conditions for the first time. In addition, we have also extended this thermal ring rearrangement to 3-iodofluorenopyrans (**26**) and obtained the corresponding 2-(2-iodo-1H-inden-3-yl)-1,4-dimethyl-9H-fluoren-3-ols (**27**) bearing all carbon-quaternary centers at C1 and C9 positions. Based on control experiments we confirmed that the presence of an aryl group with at least one reactive *ortho*-carbon at C1 and a quaternary center at C3 is a must for the rearrangement of benzochromenes. The presence of an asymmetric center on indene or fluorene resulted in the formation of diastereomeric atropisomers, which were clearly seen in their NMR spectra, also the two chromatograms in LCMS. DFT calculations agreed with the experimental observations.

1.7. Experimental Section

1.7.1. General information:

Unless otherwise noted, all reagents were used as received from commercial suppliers. *p*TSA, $Ca(OTf)_2$ and Bu_4NPF_6, KO^tBu, 2,4-diones, alkyne, naphthols and ketones were purchased from commercial suppliers such as Sigma-Aldrich, Alfa Aesar, TCI chemicals, and Spectrochem which were used without further purification. Reactions were performed in flame-dried or oven-dried glassware with magnetic stirring. Reactions were monitored by thin-layer chromatography (TLC) using aluminum sheets silica gel 60 F_{254} from Merck. TLC plates were visualized with UV light (254 nm), iodine treatment or using *p*-anisaldehyde or $KMnO_4$ stain. Column chromatography was carried out using silica gel 60-120 mesh as the stationary phase. NMR spectra were recorδed at 500 MHz and 400 MHz (^{1}H) and at 125 MHz and 100 MHz (^{13}C), respectively on Avance Bruker spectrometer. Chemical shifts (δ) are reported in ppm, using the residual solvent peak in $CDCl_3$ (^{1}H: δ = 7.26 and ^{13}C: δ = 77.16 ppm) as internal standard, and coupling constants (*J*) are given in Hz. HRMS were recorded using ESI-TOF techniques. Melting points were measured with the Labindia MEPA melting point apparatus.

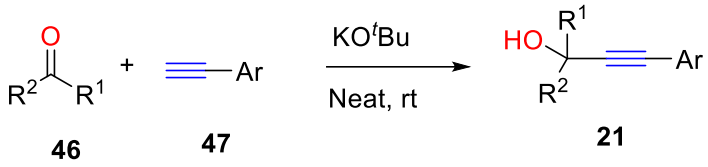
1.7.2. Computational Methods:

The geometry optimization of the structures depicted in Figure 1 is performed at M062X/6-31G (d) using the Gaussian 09 suite of packages.[32] A single point energy calculations were carried out on the optimized structures at M062X[33] density functional, with 6-31G(d,p)[34] basis set for the main group atoms, and the LANL2DZ[35] electron core potential and its associated basis set for the chlorine atom. The ^{1}H-NMR chemical shifts of atropisomer are calculated at the same level of theory with chloroform as the solvent. The NMR chemical shifts reported in Table 3 are calculated relative to the tetramethylsilane (TMS) molecule. The TMS molecule is optimized, and ^{1}H-NMR chemical shift values evaluated at the same level of theory and basis, the same as that for atropisomers. The TMS molecule is optimized, and ^{1}H-NMR chemical shift values are evaluated at the same level of theory and basis, the same

as that for atropisomers. The solvation effect is incorporated using the solvation model based on the density (SMD) implicit solvation model[36] with chloroform as the solvent, as implemented in the Gaussian 09 package.

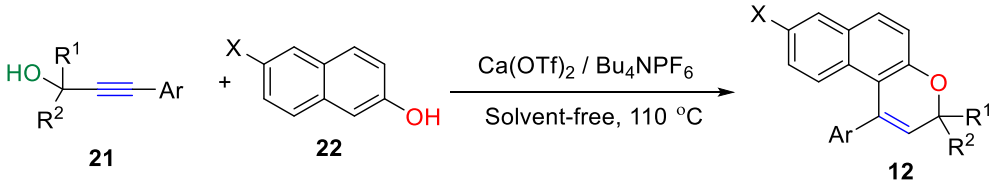
1.7.3. General experimental procedures

1.7.3.1. General experimental procedure for the synthesis of Arylpropargylic alcohol (3):[37] A mixture of aryl alkyne (1.2 equiv.), *t*-BuOK (1.5 equiv.) and respective ketone (1 equiv.) were placed into a reaction flask at room temperature under nitrogen atmosphere and the mixture was stirred for 2-6 hours. After completion of the reaction (monitored by TLC), the resulting mixture was quenched with water and extracted into ethyl acetate (thrice). Combined organic layers were washed with brine solution and dried over anhydrous Na_2SO_4 and the solvent was evaporated to obtain the pure compound **3** in good yield.



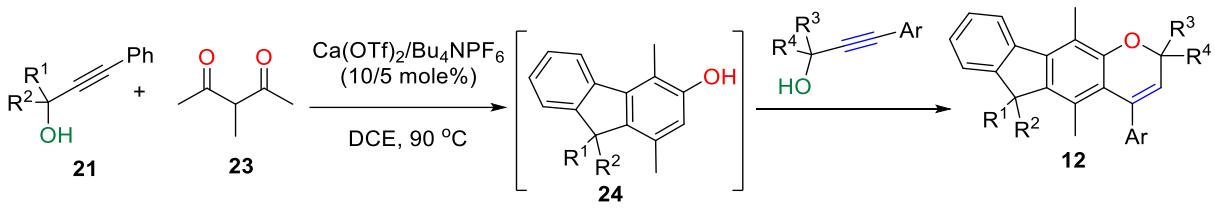
Scheme 23. *Synthesis of propargyl alcohol*

1.7.3.2. General experimental procedure for the synthesis of Benzochromene (1):[20] A mixture of aryl propargylic alcohol **21** (1 equiv.) and respective naphthol **22** (1.2 equiv.) was heated at110 ^oC in the presence of $Ca(OTf)_2$/ Bu_4NPF_6(2 mol%/10 mol%) for 1-2 hours. After completion of the reaction (monitored by TLC), the crude product was purified by silica gel column chromatography (3-5 % EtOAc in pet ether) to obtain the desired product **12** in good yield.



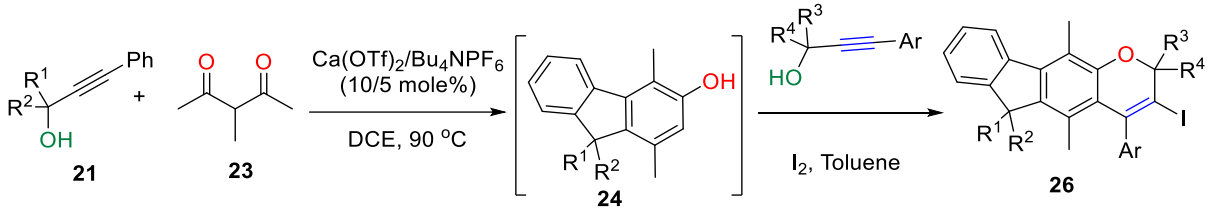
Scheme 24. *Synthesis of Benzochrome*

1.7.3.3. General experimental procedure for the synthesis of Fluorenopyran (12):[16] A mixture of propargyl alcohol **21** (100 mg, 0.35 mmol) and dione **23** (52 mg, 0.45 mmol) were refluxed in 1,2-DCE at 90 ^oC in presence of $Ca(OTf)_2$/Bu_4NPF_6 (10/5 mol%) for 2 hours. Then 0.42 mmol (119 mg) of propargyl alcohol **21** was added to the reaction mixture for the preparation of Fluorenopyran 1**2.** After completion of the reaction, the crude product was purified by silica gel column chromatography (3-5 % EtOAc in pet. ether) to obtain the desired product **12** in moderate to good yield.



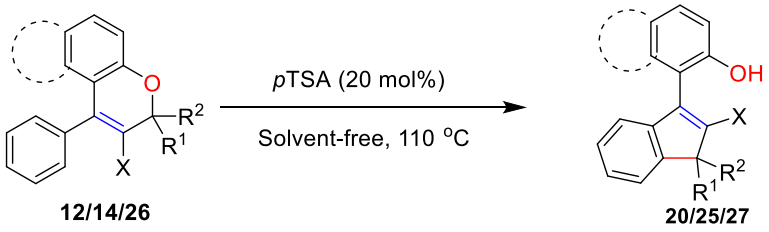
Scheme 25. *Synthesis of Indenochromene*

1.7.3.4. General experimental procedure for the synthesis Iodofluorenopyran (26):[16] A mixture of propargyl alcohol **21** (100 mg, 0.35 mmol) and dione **23** (52 mg, 0.45 mmol) were refluxed in 1,2-DCE at 90 °C in presence of $Ca(OTf)_2/Bu_4NPF_6$ (10/5 mol%) for 2 hours. Then propargyl alcohol **21**, I_2, and toluene were added for the preparation of Iodofluorenopyran **26** and continued till completion of the reaction (monitored by TLC). After completion of the reaction, the crude product was purified by silica gel column chromatography (3-5 % EtOAc in pet. ether) to obtain the desired product **26** in moderate to good yield.



Scheme 26. *Synthesis of Iodoindenochromene*

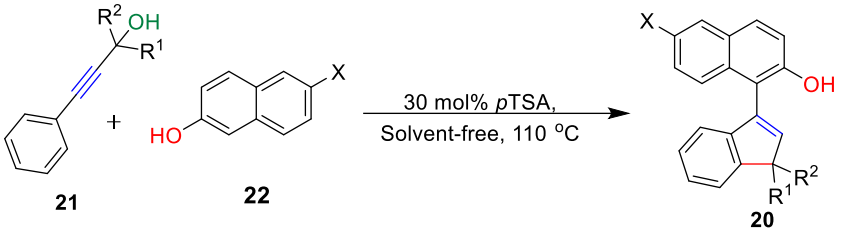
1.7.3.5. General experimental procedure for the synthesis of Indenoarenol (20/25/27): Benzopyran/Fluorenopyrans/Iodofluorenopyrans (1 equiv.) was treated with *p*TSA (20 mol%) at 110 °C in solvent-free condition till completion of the reaction. After completion of the reaction (monitored by TLC), the crude product was purified by silica gel column chromatography (0-5 % EtOAc in pet-ether) to obtain the desired product **20**/**25**/**27** in moderate to good yield.



Scheme 27. *Synthesis of Indenoarenols*

1.7.3.6. General experimental procedure for the synthesis of inden-3-yl-napthols (20) from aryl propargylic alcohol (21) and naphthol (22): A mixture of aryl propargylic alcohol **21** (1 equiv.) and respective naphthol **22** (1.2 equiv.) were heated at 110 °C in presence of *p*TSA (20 mol%) for 3-4 hours. After completion of the reaction (monitored by TLC), the crude product was purified by silica gel column

chromatography (0-5% EtOAc in pet ether) to obtain the desired product **20** in moderate to good yield.



Scheme 28. *One-pot synthesis of Indenylnaphthol*

1.7.3.7. Experimental Procedure for the Synthesis of 2-(1,1-Diphenyl-1H-inden-3-yl)-1,4-dimethyl-9,9-diphenyl-3-(prop-2-yn-1-yloxy)-9H-fluorene (33):

To a stirring solution of 2-(1,1-diphenyl-1Hinden-3-yl)-1,4-dimethyl-9,9-diphenyl-9H-fluoren-3-ol **25a** (100 mg, 0.16 mmol) in anhydrous acetone (5.0 mL), K_2CO_3 (54.9 mg, 0.39 mmol) and propargyl bromide **32** (0.23 mmol) were added. The resulting reaction mixture was heated at 80 °C for 4 h. After completion of the reaction, it was filtered through a short plug of celite, and the filtrate was concentrated in a rotary evaporator and purified by silica-gel column chromatography to afford the propargyl protected compound **33** as a white solid in 98 % yield.

1.7.3.8. Experimental Procedure for the Synthesis of (E)-3-[(2,3-Diiodoallyl)oxy]-2-(1,1-diphenyl-1H-inden-3-yl)-1,4-dimethyl-9,9-diphenyl-9H-fluorene (35):

To the solution of 2-(1,1-diphenyl-1H-inden-3-yl)-1,4-dimethyl-9,9-diphenyl-3-(prop-2-yn-1-yloxy)-9H-fluorene **33** (100 mg, 0.15 mmol) in ethyl acetate (5.0 mL), I_2 (76.0 mg, 0.30 mmol) was added and refluxed for 12 hours. After completion of the reaction, it was quenched with hypo and extracted with ethyl acetate thrice. The organic layer was concentrated in a rotary evaporator and purified by silica gel column chromatography to afford the 3-[(2,3-diiodoallyl)oxy]-2-(1,1-diphenyl-1H-inden-3-yl)-1,4-dimethyl-9,9-diphenyl-9H-fluorene 9 as a white solid in 83 % yield.

1.7.3.9. Experimental Procedure for the Synthesis of 2-(2-Iodo-1,1-diphenyl-1H-inden-3-yl)-3-methoxy-1,4-dimethyl-9,9-diphenyl-9H-fluorene (37):

To a stirring solution of 2-(2-iodo-1,1-diphenyl-1Hinden-3-yl)-1,4-dimethyl-9,9-diphenyl-9H-fluoren-3-ol **25a** (100 mg, 0.13 mmol) in anhydrous acetone (5.0 mL), K_2CO_3 (45.75 mg, 0.33 mmol) and Me_2SO_4 (0.26 mmol) were added. The resulting reaction mixture was heated at 80 °C for 3 hours. After completion of the reaction, it was filtered through a short plug of celite, and the filtrate was concentrated in a rotary evaporator and purified by silica gel column chromatography to afford the methyl-protected compound **37** as a white solid in 87 % yield.

1.7.3.10. Experimental Procedure for the Synthesis of 7-(4-Chloro-phenyl)-5,12-dimethyl-7,13,13-triphenyl-7,13-dihydrofluoreno[3,2-b]indeno[1,2-

d]furan (38): To a stirring solution of 2-[1-(4-chlorophenyl)-2-iodo-1-phenyl-1H-inden-3-yl]-1,4-dimethyl-9,9-di-phenyl-9H-fluoren-3-ol **27e** (100 mg, 0.12 mmol) in DMSO (3.0 mL), Cu_2O (18.0 mg, 0.12 mmol) and quinoline (1 mL) were added. The resulting reaction mixture was heated at 170 °C for 16 hours. After completion purified by silica gel column chromatography to afford the polycyclic compound **38** as a white solid in 86 % yield.

1.7.4. Variable Temperature NMR

Variable temperature NMR was recorded for compound **25d** in DMSO-d_6, it was observed that the hydroxy peak for the two isomers at room temperature was distinct, whereas at the higher temperatures it merged and shifted to the upfield region, hinting the presence of rotamers.

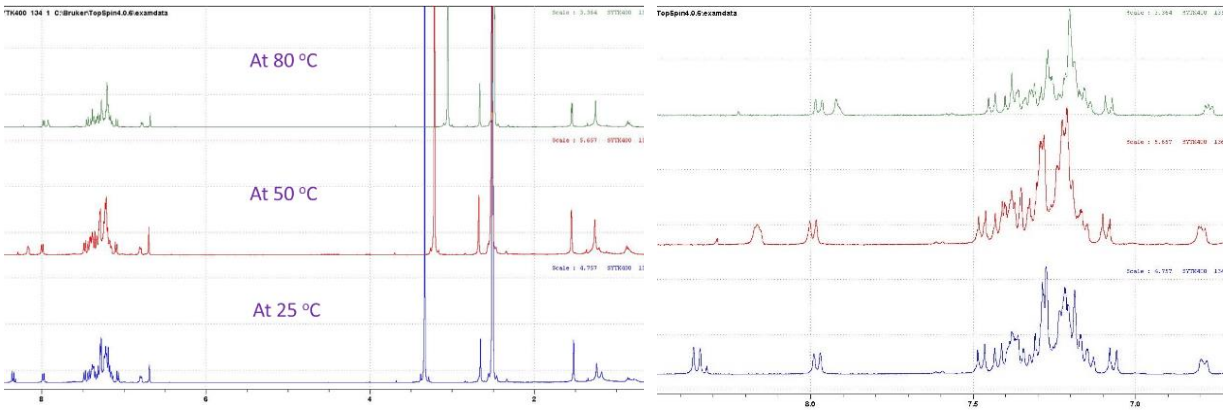
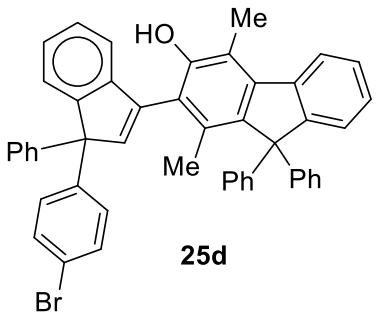


Figure 8 Variable temperature 1H NMR of **25d**

1.7.5. LCMS study of 25d



25d

Chemical Formula: $C_{48}H_{35}BrO$
Exact Mass: 706.1871
Molecular Weight: 707.7110
M^{-2}-705, M-707, M^{+2}-709

Parameters:

Column type	: C 8
Flow rate	: 0.03 ml/min
Concentration of mobile phase	: 80% Methanol: 20% water
The solvent used to dissolve the compound	: Chloroform
Acquisition time	: 30 min
UV wavelength	: 254 nm

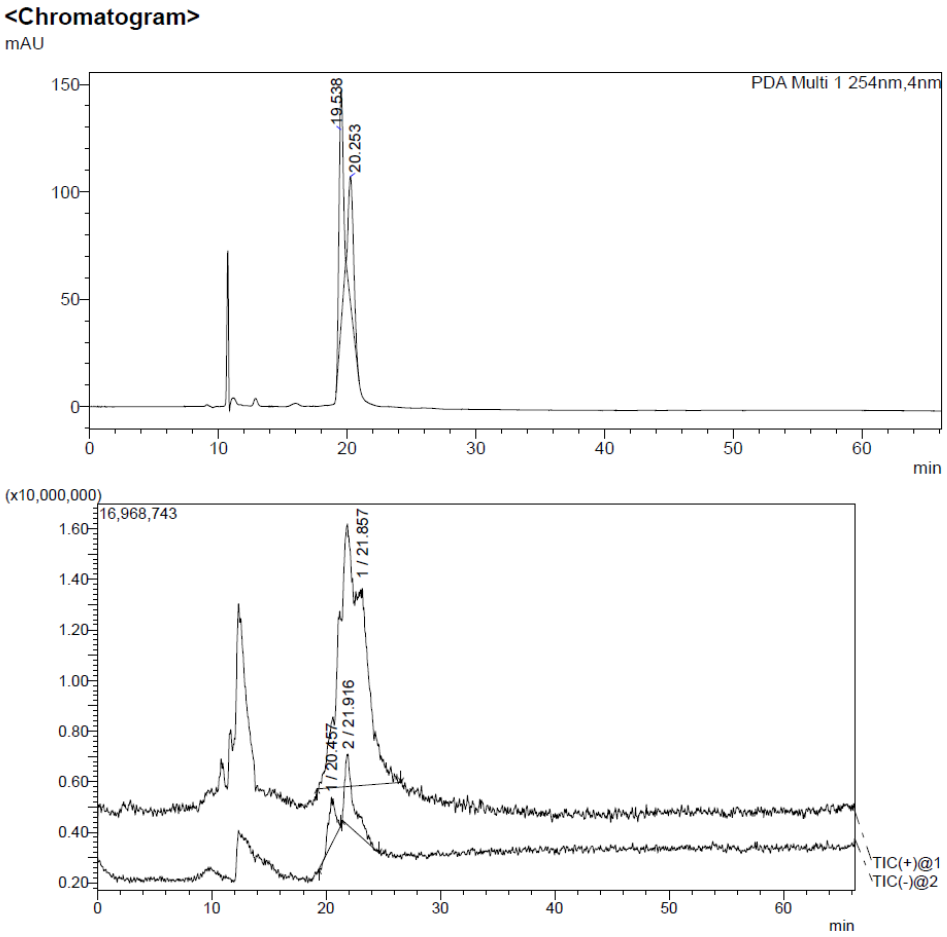


Figure 9 *LCMC chromatogram of* ***25d***

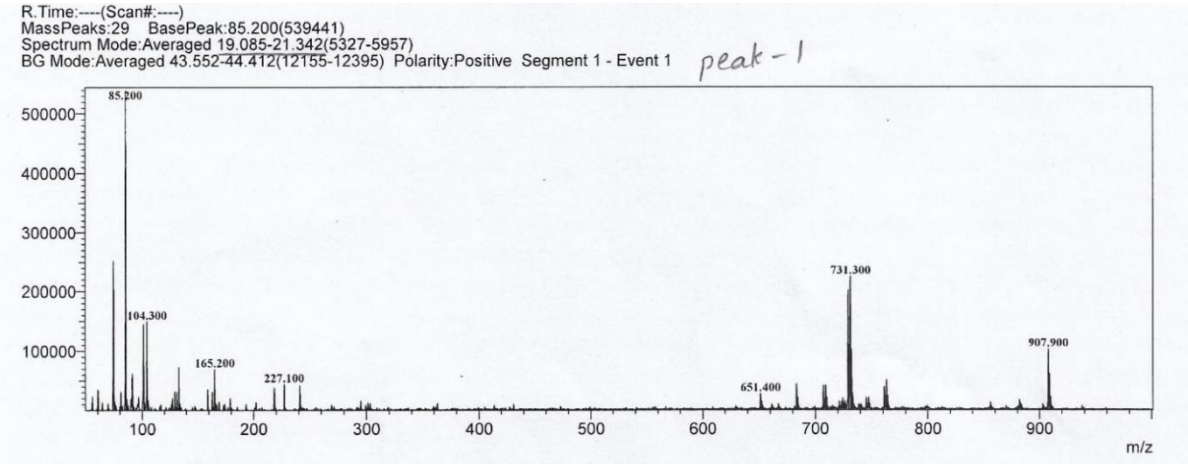


Figure 10 *Mass corresponding to peak 1 at 19.53 minutes in positive polarity*

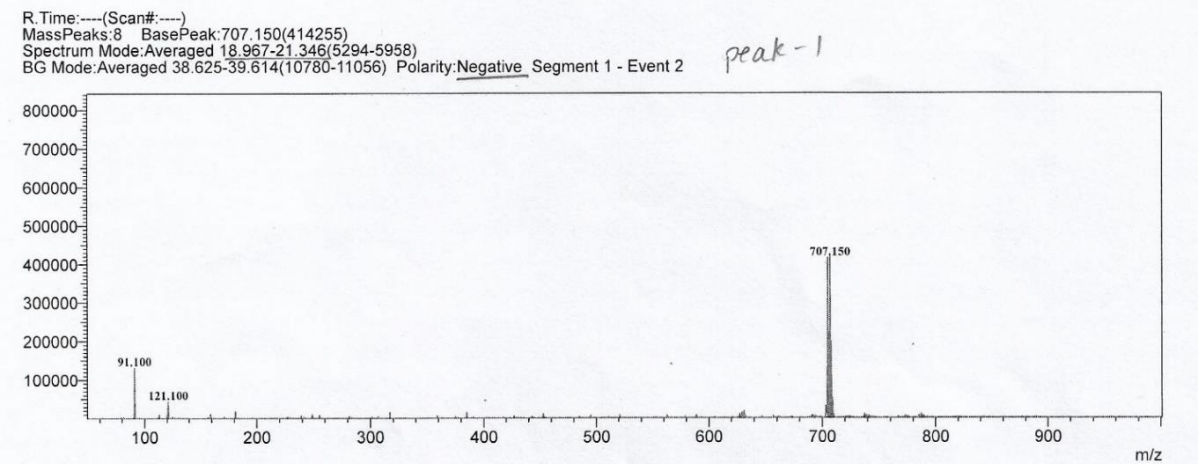


Figure 11 *Mass corresponding to peak 1 at 19.53 minutes in negative polarity*

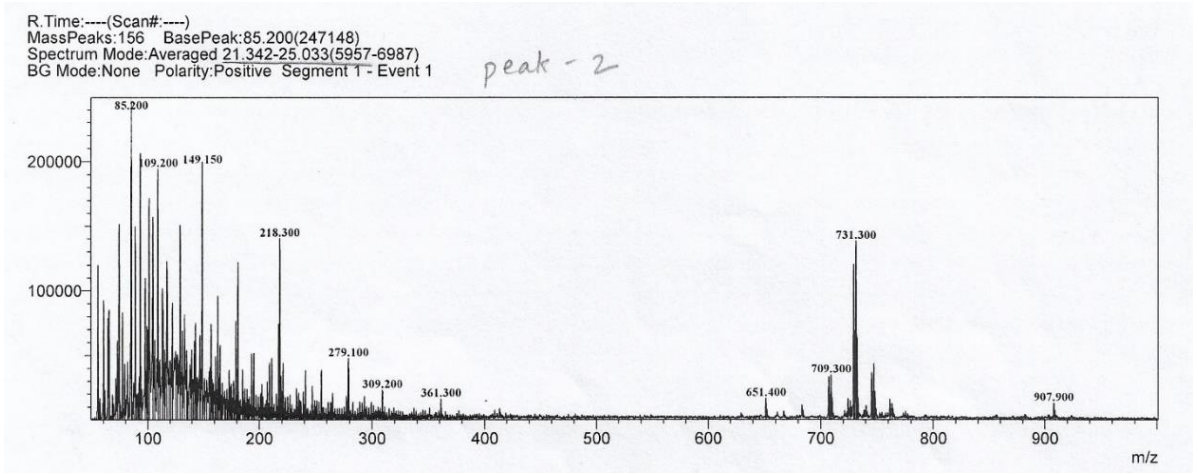


Figure 12 *Mass corresponding to peak 2 at 20.25 minutes in positive polarity*

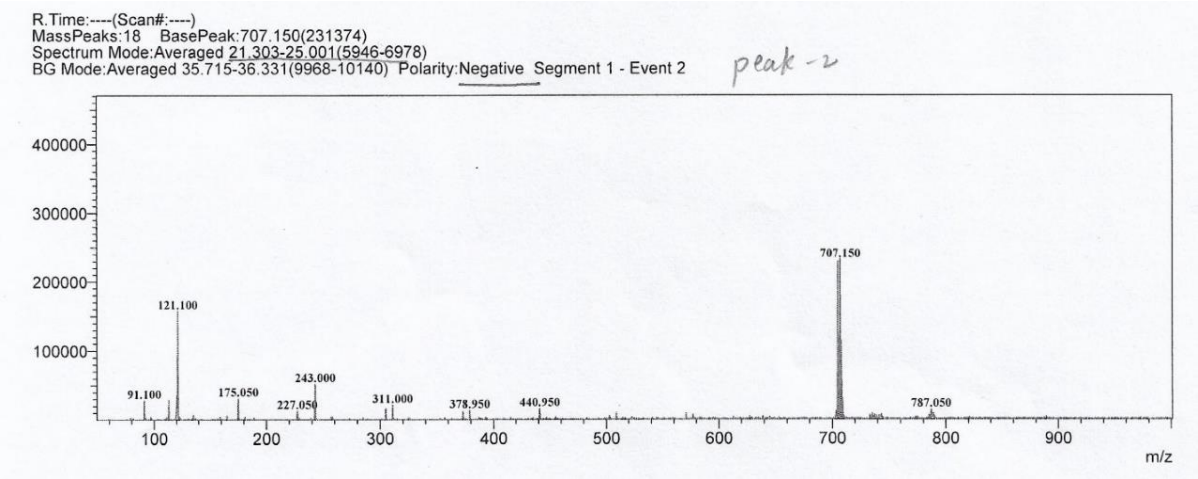


Figure 13 *Mass corresponding to peak 2 at 20.25 minutes in negative polarity*

Separation of diastereomeric atropisomer **25d** was carried out in Shimadzu LCMS spectrometer using C 8 HPLC column with a 0.03 ml/min flow rate of the mobile phase (A: water-20%, B: methanol-80%). The compound was dissolved in chloroform (1M) and with 0.5 µL injection volume LC separation gave two peaks in the chromatogram (Figure 9), the corresponding mass spectra (positive and negative) of the peaks were showing the required mass fragment (Figure 10-13).

1.7.6. Spectral Data

*1-(1,1-dimethyl-1H-inden-3-yl)naphthalen-2-ol (**2oa**).* Isolated as yellow solid, mp: 130-131 ^{o}C; yield: 95% (0.095 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.8 Hz, 2H), 7.54-7.51 (m, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.34-7.26 (m, 4H), 7.15 (t, *J* = 7.2 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.61 (s, 1H), 5.46 (s, 1H), 1.53 (d, *J* = 8.0 Hz, 6H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 153.9, 150.9, 149.1,142.3, 134.5, 133.0, 129.8, 129.0, 128.2, 126.8, 126.5, 126.3, 125.0, 123.4, 121.6, 121.6, 117.4, 114.0, 49.8, 25.0, 24.9 ppm; IR (KBr): ν˜max = 3519, 2956, 1621, 1166, 750 cm^{-1}; HRMS (ESI-TOF): m/z calculated for $C_{21}H_{18}O$ $[M+Na]^+$ 309.1255, found 309.1245.

*1-(1,1-diphenyl-1H-inden-3-yl)naphthalen-2-ol (**20b**).* Isolated as yellow viscous liquid; yield: 53% (0.053 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74-7.72 (m, 2H), 7.48-7.46 (m, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 7.5 Hz, 2H), 7.27-7.24 (m, 3H), 7.24-7.21 (m, 5H), 7.19-7.17 (m, 3H), 7.15 (d, *J* = 7.5 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.93 (s, 1H), 6.83 (d, *J* = 7.5 Hz, 1H), 5.24 (s, 1H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 151.2, 150.9, 147, 143.6, 143.4, 136.2, 133.1, 130.1, 129.1, 128.9, 128.8, 128.4, 127.9, 127.8, 127.6, 127.3, 127.2, 126.9, 126.9, 125.6, 125.1, 123.6, 122.4, 117.5, 113.7, 67.1 ppm; IR (KBr): ν˜max = 3512, 3056, 1514, 1264, 697 cm^{-1}; HRMS (ESI-TOF): m/z calculated for $C_{31}H_{22}O$ $[M+Na]^+$ 433.1568, found 433.1563.

*1-(1-hexyl-1-methyl-1H-inden-3-yl)naphthalen-2-ol (**20c**).* Isolated as white solid, mp: 104-105 ^{o}C; yield: 76% (0.076 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (t, *J* = 7.0 Hz, 4H), 7.55-7.50 (m, 2H), 7.41 (d, *J* = 2.5 Hz, 2H), 7.34-7.31 (m, 4H), 7.29-7.27 (m, 3H), 7.25 (d, *J* = 6.5 Hz, 1H), 7.15 (t, *J* = 7.5 Hz, 2H), 6.85 (d, *J* = 2.5 Hz, 1H), 6.83 (d, *J* = 2.5 Hz, 1H), 6.58 (s, 1H), 6.55 (s, 1H), 5.50 (s, 1H), 5.47 (s, 1H), 1.98-1.89 (m, 4H), 1.55 (s, 2H), 1.51 (d, *J* = 8.0 Hz, 6H), 1.24-1.22 (m, 14H), 0.85-0.83 (m, 6H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 153.0, 152.9, 150.9, 147.7, 147.6, 143.1, 135.6, 135.4, 133.0, 129.8, 129.0, 128.2, 126.8 (2), 126.5, 126.4, 126.2, 125.2, 125.0, 123.8, 121.8, 121.7, 121.6, 121.5, 117.4, 117.3, 114.3, 53.7, 38.9, 38.5, 31.8, 31.7, 29.9, 25.5, 25.4, 24.3, 24.2, 22.7, 22.6, 14.1 ppm; IR (KBr): ν˜max = 3513, 2913, 1594, 1125, 753 cm^{-1}; HRMS (ESI-TOF): m/z calculated for $C_{26}H_{29}O$ $[M+H]^+$ 357.2218, found 357.2218.

*6-bromo-1-(1-hexyl-1-methyl-1H-inden-3-yl)naphthalen-2-ol (**20d**).* Isolated as yellow viscous liquid; yield: 81% (0.081 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 1.6 Hz, 2H), 7.73 (d, *J* = 0.8 Hz, 1H), 7.71 (d, *J* = 0.8 Hz, 1H),7.43-7.36 (m, 7H), 7.31 (d, *J* = 0.8 Hz, 1H), 7.29 (d, *J* = 0.8 Hz, 1H), 7.25 (s, 1H), 7.17-7.13 (m, 2H), 7.81(d, *J* = 2.8 Hz, 1H), 6.80 (d, *J* =

2.8 Hz, 1H), 6.58 (s, 1H), 6.55 (s, 1H), 5.52 (s, 1H), 5.49 (s, 1H), 1.95-1.91 (m, 2H), 1.57 (s, 5H), 1.50 (d, *J* = 5.2 Hz, 5H), 1.22 (t, *J* = 7.5 Hz, 14H), 0.86-0.83 (m, 6H) ppm; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 152.9 (2), 151.2, 148.0, 147.8, 142.8 (20, 135.0, 134.9, 131.5, 130.1, 129.7 (2), 128.8, 127.0, 126.9 (2), 126.8, 126.3, 121.9, 121.8, 121.4, 121.3, 118.5, 117.2, 114.6, 114.5, 53.8, 38.8, 38.4, 31.8, 31.7, 29.9, 25.5, 25.4, 24.2, 24.1, 22.7, 14.2, 14.1 ppm; HRMS (ESI-TOF): m/z calculated for $C_{26}H_{27}BrONa$ $[M+Na]^+$ 457.1142, found 457.1141.

*1-(1-methyl-1-phenyl-1H-inden-3-yl)naphthalen-2-ol (**20e**).* Isolated as green viscous liquid; yield: 85% (0.085 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (t, *J* = 6.4 Hz, 3H), 7.62-7.56 (m, 3H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.38-7.31 (m, 13H), 7.28-7.24 (m, 5H), 7.18 (q, *J* = 3.2 Hz, 2H), 6.97-6.90 (m, 2H), 6.79 (s, 1H), 6.75 (s, 1H), 5.50 (s, 1H), 5.44 (s, 1H), 1.94 (d, *J* = 6.8 Hz, 6H) ppm; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 153.8, 151.1, 151.0, 148.9, 148.5, 142.9, 142.6, 135.7, 135.2, 133, 130.1, 130.0, 129.2, 129.1, 129.0, 128.9, 128.4, 127.2, 127.0 (2), 126.9, 126.8, 126.7, 126.6, 126.3, 126.1, 125.1, 125.0, 123.6, 123.4, 123.3, 122.0, 122.0, 117.5, 117.4, 113.8, 57.2, 57.1, 23.9, 23.5 ppm; HRMS (ESI-TOF): m/z calculated for $C_{26}H_{20}ONa$ $[M+Na]^+$ 371.1412, found 371.1410.

*6-bromo-1-(1,1-dimethyl-1H-inden-3-yl)naphthalen-2-ol (**20f**).* Isolated as yellow solid, mp: 147-148 ^{o}C; yield: 83% (0.083g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.47-7.26 (m, 5H), 7.15 (t, *J* = 7.2 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.60 (s, 1H), 5.47 (s, 1H), 1.52 (d, *J* = 3.6 Hz, 6H) ppm; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 153.9, 151.3, 149.5, 142, 134, 133.4, 131.6, 130.2, 129.8, 128.9, 127, 126.9, 126.5, 121.7, 121.5, 118.6, 117.3, 114.4, 50, 25, 24.9 ppm; HRMS (ESI-TOF): m/z calculated for $C_{21}H_{17}BrONa$ $[M+Na]^+$ 387.0361, found 387.0361.

*2-(1,1-dimethyl-1H-inden-3-yl)naphthalen-1-ol (**20g**).* Isolated as yellow solid, mp: 130-131 ^{o}C; yield: 90% (0.090g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 2.5 Hz, 1H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.33-7.24 (m, 4H), 7.15 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 7.5 Hz, 1H), 6.61 (s, 1H), 5.46 (s, 1H), 1.52 (d, *J* = 6.5 Hz, 6H) ppm; $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 154.0, 150.9, 149.2, 142.3, 134.5, 133.0, 129.8, 129.0, 128.3, 126.9, 126.5, 126.3, 125.0, 123.5, 121.6, 121.6, 117.4, 114.1, 49.9, 25.1, 25.0 ppm; HRMS (ESI-TOF): m/z calculated for $C_{21}H_{18}ONa$ $[M+Na]^+$ 309.1255, found 309.1258.

*2-(1-methyl-1-phenyl-1H-inden-3-yl)naphthalen-1-ol (**20h**).* Isolated as yellow viscous liquid; yield: 79% (0.079g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83-7.80 (m, 3H), 7.62-7.55 (m, 3H), 7.50-7.47 (m, 1H), 7.45-7.41 (m, 3H), 7.37 (s, 1H), 7.35 (t, *J* = 3.6 Hz, 5H), 7.32 (t, *J* = 5.2 Hz, 4H), 7.28 (d, *J* = 2.8 Hz, 1H), 7.27-7.23 (m, 3H), 7.20 (d, *J* = 1.2 Hz, 1H), 7.18-7.14 (m, 3H), 6.92-6.89 (m, 2H), 6.78 (s, 1H), 6.75 (s, 1H), 5.50 (s, 1H), 5.44 (s, 1H), 1.94 (d, *J* = 5.2 Hz, 6H) ppm; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 153.8, 153.7, 151.1, 151.0, 148.8, 148.5, 142.9, 142.6, 142.4, 142.3, 135.7, 135.2, 133.0 (2), 130.1, 130 (2), 129.8, 129.2, 129.1 (2), 128.9, 128.8, 128.3 (2), 128.2, 127.8, 127.2 (2), 127.0, 126.9 (2), 126.8, 126.7 (2), 126.6, 126.3, 126.1, 125.1, 124.9, 123.5, 123.4, 123.3, 123.1, 122.9, 122.2, 122.0, 121.9, 119.5, 118.7, 117.5, 117.4, 113.8 (2), 57.2, 57.1, 23.9, 23.5 ppm; HRMS (ESI-TOF): m/z calculated for $C_{26}H_{20}ONa$ $[M+Na]^+$ 371.1412, found 371.1411.

*1-(1,1,6-trimethyl-1H-inden-3-yl)naphthalen-2-ol (**20i**).* Isolated as white solid, mp: 141-142 ^{o}C; yield: 93% (0.093 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82-7.78 (m, 2H), 7.55-7.52 (m, 1H), 7.33-7.26 (m, 4H), 6.97 (d, *J* = 7.2 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 6.54 (s, 1H), 5.49 (s, 1H), 2.41 (s, 3H), 1.52 (d, *J* = 4.8 Hz, 6H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 154.3, 150.9, 148.3, 139.7, 136.3, 134.4, 133.1, 129.7, 129.09, 128.3, 127.6, 126.5, 125.1, 123.5, 122.6, 121.4, 117.4, 114.3, 49.7, 25.2, 25.2, 21.7 ppm; HRMS (ESI-TOF): m/z calculated for $C_{22}H_{20}ONa$ $[M+Na]^+$ 323.1411, found 323.1411.

*1-(6-butyl-1,1-dimethyl-1H-inden-3-yl)naphthalen-2-ol (**20j**).* Isolated as yellow viscous liquid; yield: 87% (0.087 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (dd, J_1 = 3.0 Hz, J_2 = 9.5 Hz, 2H), 7.56-7.54 (m, 1H), 7.32-7.30 (m, 2H), 7.27 (d, *J* = 8.5 Hz, 2H), 6.96 (d, *J* = 7.5 Hz, 1H), 6.76 (d, *J* = 7.5 Hz, 1H), 6.54 (s, 1H), 5.48 (s, 1H),2.66 (t, *J* = 7.5 Hz, 2H), 1.66-1.60 (m, 2H), 1.52 (d, *J* = 6.0 Hz, 6H), 1.42-1.37 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 154.2, 150.9, 148.3, 141.5, 139.9, 134.4, 133.1, 129.7, 129.1, 128.3, 127, 126.5, 125.1, 123.4, 121.8, 121.3, 117.4, 114.4, 49.7, 36.1, 34.2, 25.3, 25.1, 22.7, 14.1 ppm; HRMS (ESI-TOF): m/z calculated for $C_{25}H_{27}O$ $[M+H]^+$ 343.2061, found 343.2061.

*1-(1,1-dimethyl-6-phenyl-1H-inden-3-yl)naphthalen-2-ol (**20k**).* Isolated as a yellow viscous liquid; yield: 89% (0.089 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 1.2, 1H), 7.53-7.51 (m, 2H), 7.35-7.27 (m, 4H), 7.27-7.18 (m, 4H), 6.82 (d, *J* = 7.6 Hz, 1H), 6.53 (s, 1H), 5.40 (s, 1H), 1.48 (d, *J* = 6.4 Hz, 6H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 154.6, 151, 149.5, 141.5, 141.6, 139.7, 134.3, 133, 129.9, 129.1, 128.9, 128.3, 127.4, 127.3, 126.6, 125, 123.5, 121.9, 120.6, 117.4, 114, 50, 25.2, 25.1 ppm; HRMS (ESI-TOF): m/z calculated for $C_{27}H_{23}O$ $[M+H]^+$ 363.1748, found 363.1748.

*1-(6-ethoxy-1,1-dimethyl-1H-inden-3-yl)naphthalen-2-ol (**20l**).* Isolated as a colorless viscous liquid; yield: 79% (0.079 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81-7.78 (m, 2H), 7.56-7.54 (m, 1H), 7.33-7.31 (m, 2H), 7.26 (t, *J* = 9.0 Hz, 1H), 7.03 (d, *J* = 2.0 Hz, 1H), 6.74 (d, *J* = 8.5 Hz, 1H), 6.67-6.65 (m, 1H), 6.47 (s, 1H), 5.52 (s, 1H), 4.05 (q, *J* = 7.0 Hz, 2H), 1.51 (d, *J* = 7.0 Hz, 6H), 1.42 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 158.6, 156, 150.9, 146.9, 135, 134.2, 133, 129.7, 129.1, 128.3, 126.5, 125.1, 123.4, 122.2, 117.4, 114.3, 112.2, 109.3, 63.9, 49.7, 25.4, 25.3, 15.1 ppm; HRMS (ESI-TOF): m/z calculated for $C_{23}H_{23}O_2$ $[M+H]^+$ 331.1697, found 331.1697.

*1-(1,1-dimethyl-1H-cyclopenta[l]phenanthren-3-yl)naphthalen-2-ol (**20m**).* Isolated as a yellow solid, mp: 168-169 ^{o}C; yield: 78% (0.078 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.73 (d, *J* = 8.4 Hz, 1H), 8.61 (d, *J* = 8.0 Hz, 1H), 8.17 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 9.2 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.65 (t, *J* = 6.8 Hz, 1H), 7.58 (t, *J* = 8.4 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.36 (t, *J* = 8.8 Hz, 1H), 7.30-7.26 (m, 2H), 7.25-7.21 (m, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 6.96 (t, *J* = 8.0 Hz, 1H), 6.72 (s, 1H), 5.44 (s, 1H), 1.72 (s, 3H), 1.68 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 154.1, 150.7, 147.5, 135.5, 133.7, 133.6, 130.7, 130.4, 129.9, 129.0, 128.4, 128.3, 128.2, 126.9, 126.7, 126.6, 125.9, 125.6, 124.9, 124.6, 124.0, 123.9, 123.7, 123.0, 117.5, 117.3, 51.1, 24.1, 24.0 ppm; HRMS (ESI-TOF): m/z calculated for $C_{29}H_{23}O$ $[M+H]^+$ 387.1748, found 387.1749.

*6-bromo-1-(1,1,6-trimethyl-1H-inden-3-yl)naphthalen-2-ol (**20n**).* Isolated as white solid, mp: 177-178 ^{o}C; yield: 96% (0.096g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, *J* = 1.2 Hz, 1H), 7.70 (d, *J* = 9.0 Hz, 1H), 7.41-7.35 (m, 2H), 7.29 (t, *J* = 4.5 Hz, 2H), 6.97 (d, *J* = 7.5 Hz, 1H), 6.71 (d, *J* = 7.5, 1H), 6.53 (s, 1H), 5.50 (s, 1H), 2.42 (s, 3H), 1.51 (d, *J* = 4.5 Hz, 6H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 154.2, 151.2, 148.4, 139.3, 136.4, 133.8, 131.5, 130.1, 129.6, 128.8, 127.6, 126.9, 122.7, 121.2, 118.5, 117.2, 114.5, 49.7, 25.1(2), 21.7 ppm; HRMS (ESI-TOF): m/z calculated for $C_{22}H_{19}BrONa$ $[M+Na]^+$ 401.0516, found 401.0516.

*6-bromo-1-(1,1-dimethyl-6-phenyl-1H-inden-3-yl)naphthalen-2-ol (**20o**).* Isolated as white solid, mp: 177-178 ^{o}C; yield: 90% (0.090g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, *J* = 1.5 Hz, 1H), 7.73-7.68 (m, 2H), 7.61 (d, *J* = 7.0 Hz, 2H), 7.45-7.43 (m, 3H), 7.41-7.38 (m, 2H), 7.35-7.29 (m, 2H), 6.88 (d, *J* = 7.5 Hz, 1H), 6.64 (s, 1H), 5.50 (s, 1H), 1.58 (d, *J* = 5.0 Hz, 6H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 154.6, 151.3, 149.7, 141.6, 141.2, 139.9, 133.8, 131.5, 130.2, 129.8, 128.9(2), 127.4, 127.3, 126.8, 26.2, 121.7, 120.7, 118.6, 117.3, 114.3, 50.1, 25.1(2) ppm; IR (KBr): ν˜max = 3528, 2958, 1585, 1157, 761 cm^{-1}; HRMS (ESI-TOF): m/z calculated for $C_{27}H_{21}BrONa$ $[M+Na]^+$ 441.0853, found 441.0850.

*1-(spiro[cyclohexane-1,1'-inden]-3'-yl)naphthalen-2-ol (**20p**).* Isolated as brown viscous liquid; yield: 93% (0.093 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (t, *J* = 5.5 Hz, 2H), 7.40 (d, *J* = 4.0 Hz, 1H), 7.31 (d, *J* = 7.0 Hz, 1H), 7.16-7.09 (m, 5H), 6.99 (t, *J* = 7.0 Hz, 1H), 6.91 (s, 1H), 6.73 (d, *J* = 7.0 Hz, 1H), 1.88-1.83 (m, 2H), 1.75 (t, *J* = 10.0 Hz, 3H), 1.52-1.47 (m, 3H), 1.42-1.35 (m, 2H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 154, 150.9, 145.2, 142.4, 135.6, 133, 129.8, 129.6, 129, 128.2, 126.9, 126.5, 126.1, 125.0, 123.4, 122.1, 121.6, S9 117.4, 114.3, 54.3, 35.1, 35, 26.1, 24.9, 24.8 ppm; HRMS (ESI-TOF): m/z calculated for $C_{24}H_{22}ONa$ $[M+Na]^+$ 349.1568, found 349.1567.

*1-(spiro[cycloheptane-1,1'-inden]-3'-yl)naphthalen-2-ol (**20q**).* Isolated as green viscous liquid; yield: 91% (0.091 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 7.6 Hz, 2H), 7.25-7.20 (m, 2H), 7.18 -7.12 (m, 2H), 7.06-7.02 (m, 1H), 6.75 (t, *J* = 5.2 Hz, 2H), 5.39 (s, 1H), 2.00-1.94 (m, 2H), 1.85-1.82 (m, 2H), 1.79-1.68 (m, 8H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 155.6, 150.9, 147.9, 142.0, 134.9, 133.1, 129.8, 129.1, 128.3, 126.9, 126.5, 126.3, 125.1, 123.5, 121.9, 121.6, 117.4, 114.3, 57, 37.3, 37.2, 30.1, 30, 25.9, 25.8 ppm; HRMS (ESI-TOF): m/z calculated for $C_{25}H_{24}ONa$ $[M+Na]^+$ 363.1724, found 363.1727.

*6-bromo-1-(spiro[cyclooctane-1,1'-inden]-3'-yl)naphthalen-2-ol (**20r**).* Isolated as yellow viscous liquid; yield: 80% (0.080 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.61 (d, *J* = 8.8, 1H), 7.46 (d, *J* = 8.8, 1H), 7.29 (s, 2H), 7.21-7.15 (m, 3H), 7.09-7.05 (m, 1H), 6.73 (d, *J* = 6.1 Hz, 1H), 5.40 (s, 1H), 1.84 (s, 5H), 1.77-1.63 (m, 9H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 154.3, 151.2, 148.7, 142.2, 133.9, 131.6, 130.2, 129.7, 129.3, 128.8, 128.7, 128.6, 128.4, 127, 126.9, 122.8, 121.6, 118.5, 117.2, 114.5, 56.9, 32.1, 31.9, 28.9, 28.8, 25.5, 25.3, 25.2 ppm; HRMS (ESI-TOF): m/z calculated for $C_{26}H_{26}BrO$ $[M+H]^+$ 433.1166, found 433.1161.

*1-(spiro[cyclohexane-1,1'-cyclopenta[l]phenanthren]-3'-yl)naphthalen-2-ol (**20s**).* Isolated as yellow solid, mp: 193-194 ^{o}C; yield: 78% (0.078 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.72 (d, *J* = 8.0 Hz, 1H), 8.59 (d, *J* = 8.5 Hz, 1H), 8.31 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 9.0 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.63-7.60 (m, 1H), 7.57-7.54 (m, 1H), 7.40-7.38 (m, 1H), 7.35-7.32 (m, 3H), 7.27-7.25 (m, 1H), 7.23-7.19 (m, 1H), 7.14-7.11 (m, 1H), 6.97-6.93 (m, 1H), 5.41 (s, 1H), 2.64-2.58 (m, 2H), 1.92 (d, *J* = 9.5 Hz, 3H), 1.74-1.62 (m, 2H), 1.57-1.42 (m, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 150.7, 150.2, 147.4, 135.6, 134.9, 133.7, 130.7, 130.6, 129.9, 129.0, 128.3, 128.2, 126.9, 126.7, 126.3, 125.9, 125.5, 125.0, 124.6, 124.0 (2), 123.6, 123.0, 117.7, 117.5, 56.1, 33.9, 33.5, 26.1, 25.3, 25.2 ppm; HRMS (ESITOF): m/z calculated for $C_{32}H_{27}O$ $[M+H]^+$ 427.2061, found 427.2065.

*1-(6'-methylspiro[cyclohexane-1,1'-inden]-3'-yl)naphthalen-2-ol (**20t**).* Isolated as yellow viscous liquid; yield: 71% (0.071 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, *J* = 3.0 Hz, 2H), 7.46-7.44 (m, 1H), 7.24-7.21 (m, 3H), 7.20 (t, *J* = 9.0 Hz, 1H), 6.92 (s, 1H), 6.88 (d, *J* = 9.0 Hz, 1H), 6.68 (d, *J* = 9.0 Hz, 1H), 5.42 (s, 1H), 2.33 (s, 3H), 1.94-1.92 (m, 2H), 1.86-1.82 (m, 3H), 1.60-1.52 (m, 2H), 1.45 (d, *J* = 10.5 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 154.4, 150.8, 144.3, 139.9, 136.0, 135.5, 133.0, 129.7, 129.0, 128.2, 126.4, 125.1, 123.4, 123.1, 121.3, 114.5, 54.1, 35.3, 35.2, 26.1, 25.0, 24.9, 21.7 ppm; HRMS (ESI-TOF): m/z calculated for $C_{25}H_{25}O$ $[M+H]^+$ 341.1905, found 341.1907.

*1-(spiro[fluorene-9,1'-inden]-3'-yl)naphthalen-2-ol (**20u**).* Isolated as greenish solid, mp: 114-115 ^{o}C; yield: 77% (0.077 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86-7.80 (m, 5H), 7.47-7.36 (m, 4H), 7.32 (d, *J* = 4.8 Hz, 1H), 7.27-7.16 (m, 4H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.04-6.98 (m, 2H), 6.80 (d, *J* = 7.2 Hz, 1H), 6.47 (s, 1H), 5.65 (s, 1H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 151.0, 148.9, 144.6, 144.6, 144.5, 142.4, 142.3, 142.0, 139.6, 132.8, 130.2, 129.2, 128.5, 128.3, 128.3, 128.1, 128.0, 127.6, 127.2, 126.8, 125.1, 123.9, 123.7, 123.2, 123.1, 121.8, 120.6, 120.5, 117.6, 113.8, 68.0 ppm; IR (KBr): ν˜max = 3504, 3055, 1592, 1196.02, 697 cm^{-1}; HRMS (ESI-TOF): m/z calculated for $C_{31}H_{20}ONa$ $[M+Na]^+$ 431.1411, found 431.1405.

*2-(spiro[fluorene-9,1'-inden]-3'-yl)naphthalen-1-ol (**20v**).* Isolated as a yellow viscous liquid; yield: 72% (0.072 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.4 Hz, 4H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.45-7.38 (m, 4H), 7.32 (d, *J* = 8.8 Hz, 1H), 7.26-7.25 (m, 1H), 7.24 (d, *J* = 1.2 Hz, 1H), 7.19-7.16 (m, 2H), 7.12-7.08 (m, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 7.2 Hz, 1H), 6.48 (s, 1H), 5.66 (s, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 151, 148.9, 144.6, 144.5, 144.4, 142.4, 142.3, 142.0, 139.5, 132.7, 130.2, 129.2, 128.5, 128.3, 128.3, 128.1, 128.0, 127.6, 127.2, 126.8, 125.1, 123.9, 123.7, 123.2, 123.1, 121.8, 120.6, 120.5, 117.6, 113.8, 68.3 ppm; HRMS (ESI-TOF): m/z calculated for $C_{31}H_{20}ONa$ $[M+Na]^+$ 431.1412, found 431.1377.

*2-(spiro[cyclohexane-1,1'-inden]-3'-yl)naphthalen-1-ol (**20w**).* Isolated as a brown viscous liquid; yield: 74% (0.074 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (dd, J_1 = 2.8 Hz, J_2 = 6.4 Hz, 2H), 7.53-7.48 (m, 2H), 7.34-7.23 (m, 4H), 7.15 (td, J_1 = 0.8 Hz, J_2 = 7.6 Hz, 1H), 7.07 (s, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 5.48 (s, 1H), 2.06-1.88 (m, 4H), 1.69- 1.53 (m, 4H), 1.25 (s, 2H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 154.1, 150.8, 145.3, 142.5, 135.6, 133.0,

129.8, 129.0, 128.3, 127.0, 126.5, 126.1, 125.0, 123.5, 122.1, 121.6, 117.3, 114.3, 54.3, 35.2, 35.0, 25.1, 24.9, 24.9 ppm; HRMS (ESI-TOF): m/z calculated for $C_{24}H_{22}ONa$ $[M+Na]^+$ 349.1568, found 349.1558.

2-(spiro[cycloheptane-1,1'-inden]-3'-yl)naphthalen-1-ol ***(20x)***. Isolated as brown viscous liquid; yield: 80% (0.080 g). ^1H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 7.0 Hz, 2H), 7.23-7.12 (m, 5H), 7.05-7.02 (m, 2H), 6.76-6.74 (m, 2H), 5.73 (s, 1H), 1.85 (d, *J* = 8.5 Hz, 2H), 1.78-1.69 (m, 10H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 155.5, 150.9, 147.8, 142.0, 134.9, 133.0, 129.8, 129.0, 128.2, 126.8, 126.5, 126.3, 125.0, 123.4, 121.9, 121.5, 117.3, 114.2, 57.0, 37.3, 37.2, 30.0 (2), 25.8 (2) ppm; HRMS (ESITOF): m/z calculated for $C_{25}H_{24}ONa$ $[M+Na]^+$ 363.1724, found 363.1728.

6-bromo-1-(1,1-diphenyl-1H-inden-3-yl)naphthalen-2-ol ***(20y)***. Isolated as yellow viscous liquid; yield: 52% (0.030 g). ^1H NMR (500 MHz, $CDCl_3$): δ 7.84-7.81 (m, 2H), 7.57-7.55 (m, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), , 7.40 (d, *J* = 7.0 Hz, 2H), S11 7.35-7.32 (m, 2H), 7.31-7.29 (m, 7H), 7.26 (d, *J* = 4.5 Hz, 1H), 7.25 (s, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.02 (s, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 5.31 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 151.1, 150.8, 147.0, 143.6, 143.3, 143.2, 136.1, 133.1, 130.1, 129.1, 128.9, 128.7, 128.3, 127.8 (2), 127.5, 127.3, 127.2, 126.8, 126.7, 125.6, 125.0, 123.6, 122.3, 117.5, 113.6, 67.0 ppm; HRMS (ESI-TOF): m/z calculated for $C_{31}H_{21}BrONa$ $[M+Na]^+$ 511.0673, found 511.0491.

6-bromo-1-(1-methyl-1-phenyl-1H-inden-3-yl)naphthalen-2-ol ***(20z)***. Isolated as a yellow solid, mp: 80-81 °C; yield: 71% (0.036g). ^1H NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 2H), 7.30 (dd, J_1 = 2.8 Hz, J_2 = 8.8 Hz, 2H), 7.47-7.25 (m, 20H), 7.22-7.16 (m, 2H), 6.88 (t, *J* = 1.6 Hz, 1H), 6.86 (d, *J* = 2.8 Hz, 1H), 6.78 (s, 1H), 6.75 (s, 1H), 5.51 (s, 1H), 5.46 (s, 1H), 1.94 (d, *J* = 5.2 Hz, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 153.7(2), 151.4, 149.1, 148.7, 142.6, 142.3, 142.2, 142.1, 135.1, 134.6, 131.5 (2), 130.2, 129.9, 129.8, 129(2), 128.8, 127.3, 127.1, 127.0, 126.9(2), 126.8, 126.2, 126.0, 123.5, 123.4, 121.8, 118.6 (2), 117.3, 114.1, 114.0, 57.3, 57.2, 23.8, 23.4 ppm; IR (KBr): ν˜max = 3504, 3056, 1492, 1138, 696 cm^{-1}; HRMS (ESI-TOF): m/z calculated for $C_{26}H_{19}BrONa$ $[M+Na]^+$ 449.0516, found 449.0518.

1-(1,1-diethyl-1H-inden-3-yl)naphthalen-2-ol ***(20aa)***. Isolated as a yellow viscous compound; yield: 79% (0.131g). ^1H NMR (500 MHz, $CDCl_3$): *δ* (ppm) 7.97 (d, *J* = 2.0 Hz, 1H), 7.72 (d, *J* = 9.0 Hz, 1H), 7.42-7.38 (m, 2H), 7.37-7.36 (m, 1H), 7.30 (d, *J* = 9.0 Hz, 1H), 7.28-7.26 (m, 2H), 7.17-7.13 (m, 1H), 6.79 (d, *J* = 7.5 Hz, 1H), 6.47 (s, 1H), 5.53 (s, 1H), 2.07-1.94 (m, 4H), 0.78 (t, *J* = 7.5 Hz, 3H), 0.74 (t, *J* = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): *δ* (ppm) 151.2, 150.9, 145.7, 144.1, 136.6, 131.5, 130.1, 129.8, 128.8, 126.9(2), 126.3, 122.1, 121.2, 118.4, 117.2, 114.8, 58.8, 30.4, 30.1, 9.5, 9.4; HRMS (ESI-TOF): m/z calculated for $C_{23}H_{23}O$ $[M+H]^+$ 315.1749, found 315.1746.

6-bromo-1-(6-ethyl-1,1-diphenyl-1H-inden-3-yl)naphthalen-2-ol ***(20ab)***. Isolated as yellow viscous compound; yield: 71% (0.117g). ^1H NMR (500 MHz, $CDCl_3$): *δ* (ppm) 7. .97 (d, *J* = 2.0 Hz, 1H), 7.72 (d, *J* = 9.0 Hz, 1H), 7.42 (t, *J* = 9.0 Hz, 2H), 7.39-7.36 (m, 2H), 7.34-7.31 (m, 3H), 7.3-7.29 (m, 5H), 7.28-7.26 (m, 2H), 7.05-7.04 (m, 1H), 6.94 (s, 1H), 6.79 (d, *J* = 7.5 Hz, 1H), 5.36 (s, 1H), 2.69-2.65 (m, 2H), 1.23 (t, *J* = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (100

MHz, $CDCl_3$): δ (ppm) 151.4, 151.0, 146.4, 143.7, 143.5, 143.4, 140.5, 135.3, 131.6, 130.2(2), 129.9, 129.0, 128.8, 128.7, 127.8(2), 127.2(2), 127.1, 126.9, 125.4, 121.9, 118.6, 117.3, 114.1, 66.9, 29.2, 15.9; HRMS (ESI-TOF): m/z calculated for $C_{33}H_{26}BrO$ $[M+H]^+$ 517.1167, found 517.1168.

1-(1,1-di-p-tolyl-1H-inden-3-yl)naphthalen-2-ol ***(20ac)***. Isolated as yellow solid, mp: 121-123 ^oC; yield: 76% (0.094g). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.83-7.81 (m, 2H), 7.57-7.57 (m, 1H), 7.49 (d, J = 7.5 Hz, 1H), 7.36-7.32 (m, 2H), 7.29-7.26 (m, 4H), 7.19-7.16 (m, 3H), 7.10 (t, J = 8.0 Hz, 4H), 6.99 (s, 1H), 6.89 (d, J = 7.5 Hz, 1H), 5.35 (s, 1H), 2.33 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 151.2, 151.1, 147.3, 143.1, 140.6, 140.3, 136.8, 136.7, 135.6, 133.0, 130.0, 129.5, 129.4, 129.0, 128.3, 127.7, 127.6, 127.3, 126.8, 126.7, 125.4, 125.1, 123.5, 122.2, 117.4, 113.7, 66.4, 21.1; HRMS (ESI-TOF): m/z calculated for $C_{33}H_{27}O$ $[M+H]^+$ 439.2062, found 439.2061.

1-(1,1-bis(4-fluorophenyl)-1H-inden-3-yl)naphthalen-2-ol ***(20ad)***. Isolated as yellow solid, mp: 182-184 ^oC; yield: 75% (0.097g). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.84-7.82 (m, 2H) 7.51-7.49 (m, 1H), 7.45 (d, J = 7.5 Hz, 1H), 7.36-7.32 (m, 4H), 7.30-7.29 (m, 1H), 7.28-7.26 (m, 2H), 7.24 (s, 1H), 7.23-7.20 (m, 1H), 7.03-6.97 (m, 4H), 6.95 (s, 1H), 6.93 (d, J = 7.5 Hz, 1H), 5.22 (s, 1H) $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 136.1, 161.1, 151.1, 150.6, 146.4, 142.9, 139.1, 138.8, 136.4, 133.0, 130.2, 129.4, 129.3, 129.2(2), 129.1, 128.4, 127.8, 127.0, 126.8, 125.3, 124.8, 123.7, 122.5, 117.5, 115.8, 115.7(2), 115.6, 113.4, 65.7; HRMS (ESI-TOF): m/z calculated for $C_{31}H_{21}F_2O$ $[M+H]^+$ 447.1560, found 447.1562.

1-(1,1-bis(4-fluorophenyl)-1H-inden-3-yl)-6-bromonaphthalen-2-ol ***(20ae)***. Isolated as yellow solid, mp: 182-184 ^oC; yield: 73% (0.097g). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.98 (d, J = 1.5 Hz, 1H), 7.74 (d, J = 9.0 Hz, 1H), 7.45 (d, J = 7.5 Hz, 1H), 7.41-7.39 (m, 1H), 7.36-7.32 (m, 2H), 7.31-7.30 (m, 2H), 7.28-7.26 (m, 2H), 7.25-7.23 (m, 1H), 7.21-7.20 (m, 1H), 7.03-6.98 (m, 4H), 6.96-6.94 (m, 1H), 6.90-6.89 (m, 1H), 5.25 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 163.1(2), 161.2, 161.1, 151.3, 150.5, 146.7, 142.6, 138.9(2), 138.7(2), 135.8, 131.5, 130.3, 130.2, 130.1, 129.3(3), 129.2, 129.1, 127.9, 127.2, 126.6, 125.4, 122.4, 118.6, 117.4, 115.9, 115.8, 115.7, 115.6, 113.6, 65.7; HRMS (ESI-TOF): m/z calculated for $C_{31}H_{20}BrF_2O$ $[M+H]^+$ 525.0666, found 525.0663.

1,5-bis(1,1-diethyl-1H-inden-3-yl)naphthalene-2,6-diol ***(20af)***. Isolated as brown viscous compound, yield: 68% (0.120g). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.57-7.55 (m, 2H), 7.42-7.40 (m, 2H), 7.33-7.29 (m, 2H), 6.25-6.22 (m, 1H), 7.21-7.19 (m, 1H), 7.18-7.16 (m, 2H), 6.99 (d, J = 7.5 Hz, 1H), 6.89 (d, J = 7.5 Hz, 1H), 6.55 (s, 1H), 6.50 (s, 1H), 5.39 (s, 1H), 5.38 (s, 1H), 2.12-1.99 (m, 8H), 0.88-0.83 (m, 6H), 0.78 (t, J = 7.5 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 150.9, 149.2, 145.5, 144.6, 144.5, 137.4, 128.2, 126.9, 126.8, 126.7(2), 126.1, 122.0, 121.5, 121.4, 117.6, 115.1, 58.8, 58.7, 30.5, 30.1, 9.5; HRMS (ESI-TOF): m/z calculated for $C_{36}H_{37}O$ $[M+H]^+$ 501.2794, found 501.2798.

6-bromo-1-(1-(4-fluorophenyl)-1-phenyl-1H-inden-3-yl)naphthalen-2-ol ***(20ag)***. Isolated as brown viscous compound, yield: 67% (0.080g). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.98 (s, 2H), 7.73 (d, J = 9.0 Hz, 2H), 7.49-7.46 (m, 2H), 7.41-7.37 (m, 4H), 7.36-7.33 (m, 5H),

7.32-7.29 (m, 7H), 7.28-7.26 (m, 6H), 7.24-7.20 (m, 2H), 7.02-6.97 (m, 6H), 6.89 (d, *J* = 7.5 Hz, 2H), 5.30 (s, 1H), 5.28 (s, 1H); 13C{1H} NMR (100 MHz, $CDCl_3$): *δ* (ppm) 151.4, 150.7, 147.0, 143.2, 142.9, 142.7, 138.9, 135.7, 131.6, 130.3, 130.2, 130.1, 129.4, 129.3, 129.2, 129.0, 128.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.1, 126.7, 126.6, 125.6, 122.3, 118.7, 117.4, 115.8, 115.7, 115.6, 115.5, 113.7, 66.4; HRMS (ESI-TOF): m/z calculated for $C_{31}H_{21}BrFO$ $[M+H]^+$ 507.4104, found 507.4107.

*6-bromo-1-(1-(4-bromophenyl)-1-phenyl-1H-inden-3-yl)naphthalen-2-ol (**20ah**).* Isolated as brown viscous compound, yield: 69% (0.120g). ^1H NMR (500 MHz, $CDCl_3$): *δ* (ppm) 7.98 (s, 2H), 7.74 (d, *J* = 8.5 Hz, 2H), 7.48-7.46 (m, 3H), 7.45-7.41 (m, 5H), 7.40-7.37 (m, 4H), 7.36-7.33 (m, 3H), 7.32-7.29 (m, 7H), 7.28 (t, *J* = 2.5 Hz, 3H), 7.23-7.20 (m, 3H), 7.18-7.16 (m, 2H), 6.96 (d, *J* = 3.0 Hz, 2H), 6.89 (d, *J* = 7.5 Hz, 2H), 5.30 (s, 1H), 5.26 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): *δ* (ppm) 146.5, 142.8, 142.6, 136.0, 132.0, 131.9, 131.5, 130.3, 130.1, 129.5, 129.4, 129.3, 129.0, 128.9, 127.8, 127.7, 127.6, 127.2, 126.7, 125.5, 122.3, 118.7, 117.4, 66.6; HRMS (ESI-TOF): m/z calculated for $C_{31}H_{21}Br_2O$ $[M+H]^+$ 566.9959, found 566.9956.

*6-bromo-1-(spiro[naphthal-9,1'-inden]-3'-yl)naphthalene-2-ol (**20ai**).* Isolated as yellow viscous liquid; yield: 72% (0.0415 g). ^1H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, *J* = 2.0 Hz, 1H), 7.79 (d, *J* = 8 Hz, 2H), 7.69 (d, *J* = 9 Hz, 1H), 7.60 (d, *J* = 9 Hz, 1H), 7.45-7.43 (m, 1H), 7.35 (t, *J* = 7.5 H, 2H), 7.26 (d, *J* = 9.0 Hz, 1H), 7.20-7.11 (m, 4H), 7.06-7.02 (m, 2H), 6.95-6.88 (m, 2H), 7.74 (d, *J* = 7.5 Hz, 1H), 6.40 (s, 1H), 5.59 (s, 1H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz,$CDCl_3$): δ 151.3, 148.8, 144.4, 144.3, 144.2, 142.4, 142.3, 142.3, 138.9, 131.3, 130.4, 130.3, 130.1, 128.3, 128.4, 128.4, 128.1, 127.7, 127.4, 126.9, 123.8, 123.3, 123.2, 121.6, 120.7, 120.6, 118.7, 117.5, 114.1, 68.3 ppm; HRMS (ESI-TOF): m/z calculated for $C_{31}H_{19}BrONa$ $[M+Na]^+$ 433.1568, found 433.1563.

*1-(spiro[cyclododecane-1,1'-inden]-3'-yl)naphthalen-2-ol (**20aj**).* Isolated as yellow solid, mp: 126-128 ºC; yield 76% (0.378g). ^1H NMR (500 MHz, $CDCl_3$): *δ* (ppm) 7.83-7.80 (m, 2H), 7.53-7.50 (m, 2H), 7.34-7.31 (m, 2H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.23-7.20 (m, 1H), 7.16-7.13 (m, 1H), 6.86 (d, *J* = 7.5 Hz, 1H), 6.73 (s, 1H), 5.46 (s, 1H), 1.80-1.69 (m, 8H), 1.49-1.41 (m, 14H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): *δ* (ppm) 153.2, 150.9, 147.7, 142.7, 134.6, 133.0, 129.7, 129.0, 128.2, 126.8, 126.5, 125.5, 125.0, 123.5, 123.4, 121.6, 117.3, 114.2, 56.3, 31.3, 31.1, 27.0, 26.2, 23.0, 22.5, 22.0, 21.9; HRMS (ESI-TOF): m/z calculated for $C_{30}H_{35}O$ $[M+H]^+$ 411.2688, found 411.2685.

*6-bromo-1-(spiro[cyclohexane-1,1'-inden]-3'-yl)naphthalen-2-ol (**20ak**).* Isolated as yellow solid, mp: 147-148 ºC; yield: 75% (0.0368 g). ^1H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, *J* = 1.0 Hz, 1H), 7.69 (d, *J* = 9.0 Hz, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.40-7.35 (m, 2H), 7.30-7.26 (m, 2H), 7.16-7.14 (m, 1H), 7.05 (s, 1H), 6.83 (d, *J* = 7.5 Hz, 1H), 5.49 (s, 1H), 2.05-1.98 (m, 2H), 1.95-1.92 (m, 2H), 1.68-1.51 (m, 6H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 154.1, 151.2, 145.6, 142.2, 135.1, 131.6, 130.2 (2), 129.7, 128.9, 127.1, 126.9, 126.3,122.2, 121.5, 118.5, 117.3, 114.6, 54.4, 35.1, 35.1, 26.1, 24.9, 24.8 ppm; IR (KBr): ν˜max = 3496, 2933, 1586,1204, 749 cm^{-1}; HRMS (ESI-TOF): m/z calculated for $C_{24}H_{21}BrONa$ $[M+Na]^+$ 427.0673, found 427.0668.

6-bromo-1-(spiro[cycloheptane-1,1'-inden]-3'-yl)naphthalen-2-ol (**20al**). Isolated as yellow viscous liquid; yield: 79% (0.039 g); ^{1}H NMR (500 MHz, CDCl3,): δ 7.94 (s, 1H), 7.68 (d, *J* = 9 Hz, 1H), 7.51 (d, J = 7.5 Hz, 1H), 7.39−7.34 (m, 2H), 7.28−7.23 (m, 2H), 7.12 (t, J = 7.5 Hz, 1H), 6.83 (s, 1H), 6.78 (d, *J* = 7.5 Hz, 1H), 5.51 (s, 1H), 2.03 (t, *J* = 13.0 Hz, 2H), 1.92 (d, *J* = 5.0 Hz, 2H), 1.84−1.71 (m, 8H) ppm; ^{13}C{H} NMR (125 MHz, CDCl3): δ 155.5, 151.2, 148.1, 141.6, 134.3, 131.5, 130.1, 129.7, 128.8, 126.9, 126.8, 126.4, 122.0, 121.3, 118.5, 117.2, 114.5, 57.0, 37.2, 37.1, 30.1, 30, 25.8, 25.7 ppm; HRMS (ESI-TOF): m/z calculated for $C_{25}H_{23}BrONa$ [M+Na]+ 419.1010, found 419.1010.

*2-(1,1-Diphenyl-1H-inden-3-yl)-1,4-dimethyl-9,9-diphenyl-9Hfluoren-3-ol (**25a**).* Isolated as white solid, mp: 246-248 °C; yield: 96 % (0.096 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.0 Hz, 1H), 7.42-7.40 (m, 1H), 7.39-7.37 (m, 2H), 7.35-7.32 (m, 2H), 7.30-7.28 (m, 4H), 7.27-7.24 (m, 7H), 7.23-7.19 (m, 10H), 6.90 (dd, J_1 = 2.0 Hz, J_2 = 6.5 Hz, 1H), 6.83 (s, 1H), 5.13 (s, 1H), 2.68 (s, 3H), 1.74 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 155.9, 151.2, 150.7, 146.0, 143.5, 142.9, 142.8, 142.7, 142.1, 140.9, 137.9, 132.3, 129.3, 129.0, 128.8, 128.6, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.3, 127.2, 127.0, 126.8, 126.8, 126.5, 126.4, 125.5 (2), 123.4, 121.6, 120.0, 117.2, 66.9, 64.9, 18.0, 12.8 ppm; HRMS (ESI-TOF): m/z calculated for $C_{48}H_{37}O$ $[M + H]^+$ 629.2844, found 629.2845.

*4-Benzyl-2-(1,1-diphenyl-3a,7a-dihydro-1H-inden-3-yl)-1-methyl-9,9-diphenyl-9H-fluoren-3-ol (**25b**).* Isolated as yellow viscous liquid; yield: 93 % (0.093 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 5.6, 1H), 7.42-7.36 (m, 4H), 7.34-7.32 (m, 4H), 7.27-7.26 (m, 8H), 7.24-7.15 (m, 12H), 7.13- 7.11 (m, 3H), 6.90-6.88 (m, 1H), 6.86 (s, 1H), 5.16 (s, 1H), 4.60 (s, 2H), 1.79 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 156.0, 151.9, 150.7, 146.0, 143.5, 143.1, 142.9, 142.8, 142.6, 142.5, 140.7, 140.0, 139.7, 137.7, 133.6, 129.9, 129.4, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 127.3, 127.2, 127.0, 126.8, 126.6, 126.4, 126.1, 125.6, 125.4, 123.3, 121.5, 120.3, 119.0, 67.0, 65.0, 32.1, 18.3 ppm; HRMS (ESI-TOF): m/z calculated for $C_{54}H_{41}O$ $[M + H]^+$ 705.3157, found 705.3122.

*2-[1-(4-Fluorophenyl)-1-phenyl-1H-inden-3-yl]-1,4-dimethyl-9,9-diphenyl-9H-fluoren-3-ol (**25c**).* Isolated as white solid (1:0.91 of diastereomer), mp: 238-240 °C; yield: 84 % (0.084 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ =7.97 (d, *J* = 8.0 Hz, 2H), 7.38-7.32 (m, 10H), 7.31-7.27 (m, 10H), 7.25-7.21 (m, 14H), 7.20-7.19 (m, 8H), 7.17-7.14 (m, 4H), 6.97 (t, *J* = 8.5 Hz, 2H), 6.92-6.88 (m, 4H), 6.79 (s, 2H), 5.10 (s, 1H), 5.08 (s, 1H), 2.68 (s, 6H), 1.73 (s, 3H), 1.72 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 155.9, 151.2, 151.1, 150.6, 145.8, 143.3, 143.1, 142.9, 142.7, 142.6, 142.3, 142.2, 140.9, 140.2, 139.2, 139.0, 138.1, 138.0, 132.3, 132.2, 129.4, 129.3, 129.2 (2), 129.0, 128.9, 128.7, 128.0, 127.9, 127.7, 127.6, 127.5, 127.4, 127.2, 126.9, 126.5, 126.4, 125.5, 125.4, 123.4, 121.7, 119.9, 117.3, 115.7, 115.5 (2), 115.3, 66.3, 65.0, 18.0, 12.8 ppm; HRMS (ESI-TOF): m/z calculated for $C_{48}H_{34}FO$ $[M - H]^+$ 645.2594, found 645.2592.

*2-[1-(4-Bromophenyl)-1-phenyl-1H-inden-3-yl]-1,4-dimethyl-9,9-diphenyl-9H-fluoren-3-ol (**25d**).* Isolated as white solid (1:0.94 of diastrereomer), mp: 274-276 °C; yield: 83 % (0.083 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 7.0 Hz, 2H), 7.41-7.35 (m, 8H), 7.36-7.28

(m, 14H), 7.25-7.23 (m, 10H), 7.21-7.16 (m, 14H), 7.14-7.13 (m, 2H), 7.07-7.06 (m, 2H), 6.93-6.91 (m, 2H), 6.77 (s, 2H), 5.09 (s, 1H), 5.05 (s, 1H), 2.68 (d, *J* = 1.5, 6H), 1.73 (s, 3H), 1.71 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ = 155.9, 151.1, 150.2, 145.4, 142.9, 142.7, 142.6, 142.5, 140.9, 140.2, 138.3, 131.9, 131.7, 129.5, 129.4, 129.3, 129.0, 128.7, 128.0, 127.9, 127.8, 127.6, 127.5 (2), 127.3, 127.2, 127.0, 126.6, 126.4, 125.5, 125.4, 123.4, 121.7, 121.0, 119.8, 117.3, 66.4, 64.9, 18.0, 12.8 ppm; IR: ν˜max = 3514, 2919, 2360, 1487, 748, 699, 577 cm-1; HRMS (ESI-TOF): m/z calculated for $C_{48}H_{35}BrONa$ $[M + Na]^+$ 707.1949, found 707.1917.

2-[1-(4-Methoxyphenyl)-1-phenyl-1H-inden-3-yl]-1,4-dimethyl-9,9-diphenyl-9H-fluoren-3-ol ***(25e)***. Isolated as white solid; mp: 254-256 °C yield: 81 % (0.081 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.90 (d, *J* = 8.0 Hz, 2H), 7.33-7.28 (m, 8H), 7.24-7.19 (m, 12H), 7.17-7.13 (m, 12H), 7.12-7.09 (m, 13H),7.03 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 6.5 Hz, 2H), 6.75-6.73 (m, 3H), 6.66 (s, 1H), 6.65 (s, 1H), 5.08 (s, 2H), 3.70 (s, 3H), 3.65 (s, 3H), 2.61 (s, 6H), 1.67 (s, 3H), 1.65 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ = 158.8, 158.6, 155.9, 151.2, 1561.1, 146.2, 143.7, 143.5, 142.9, 142.7, 142.1, 141.0, 140.1, 137.5, 135.3, 135.0, 132.3, 129.3, 129.0, 128.8, 128.7, 123.3, 121.5, 120.1, 117.2, 114.2, 113.9, 66.2, 65.0, 55.4, 55.3, 29.8, 18.0, 12.8 ppm; IR: ν˜max = 3501, 2953, 1597, 1446, 1294, 775, 699 cm-1; HRMS (ESI-TOF): m/z calculated for $C_{49}H_{39}O_2$ $[M + H]^+$ 659.2950, found 659.2864.

2-[1-(4-Chlorophenyl)-1-phenyl-1H-inden-3-yl]-1,4-dimethyl-9,9-diphenyl-9H-fluoren-3-ol ***(25f)***. Isolated as yellow solid (1:0.92 of diastereomer), mp: 246-248 °C; yield: 79 % (0.079 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 7.6 Hz, 2H), 7.38-7.35 (m, 7H), 7.33-7.26 (m,12H), 7.24-7.23 (m, 12H), 7.21-7.17 (m, 15H), 7.15-7.11 (m, 4H), 6.90-6.91 (m, 2H), 6.78 (s, 2H), 5.09 (s, 1H), 5.06 (s, 1H), 2.68 (s, 6H), 1.73 (s, 3H), 1.70 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ = 155.9, 151.2, 150.4, 145.5, 143.0, 142.9, 142.7, 142.6, 142.2, 142.1, 141.9, 140.9, 140.2, 138.4, 138.3, 133.1, 132.9, 132.3, 132.2, 129.3, 129.1, 129.0, 128.7, 128.0, 127.9, 127.8, 127.6, 127.5 (2), 127.3, 127.2, 126.9, 126.6, 126.4, 125.5, 125.4, 123.4, 121.7, 119.8, 117.3, 66.4, 65.0, 18.0, 12.8 ppm; IR: ν˜max = 3503, 3056, 1445, 748, 696 cm-1; HRMS (ESI-TOF): m/z calculated for $C_{48}H_{35}ClONa$ $[M + Na]^+$ 663.2454, found 663.2411.

2-(1,1-Diphenyl-1H-inden-3-yl)-9-(4-fluorophenyl)-1,4-dimethyl-9-phenyl-9H-fluoren-3-ol ***(25g)***. Isolated as white solid (1:1.02 of diastereomer), mp: 256-258 °C; yield: 97 % (0.097 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 9.5 Hz, 2H), 7.42-7.40 (m, 2H), 7.36-7.33 (m, 4H), 7.32-7.28 (m, 8 H), 7.27-7.24 (m, 15H), 7.23-7.20 (m, 17H), 6.95-6.86 (m, 6H), 6.835 (s, 1H), 6.833 (s, 1H), 5.14 (s, 1H), 5.13 (s, 1H), 2.68 (s, 6H), 1.73 (s, 3H), 1.72 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ = 155.7, 151.3, 150.7, 146.1, 146.0, 143.4, 143.2, 142.7, 142.5, 142.0, 140.8, 140.0, 137.8 (2), 132.2 (2), 130.9 (2), 130.7, 130.6, 129.1, 128.8, 128.6, 128.1, 128.0, 127.7 (2), 127.6, 127.5, 127.3 (2), 127.1, 126.8, 126.7, 126.5, 125.5, 125.3, 123.4, 121.5 (2), 120.1, 117.4, 114.8 (2), 114.6 (2), 66.9, 64.4, 18.0, 12.8 ppm; HRMS (ESI-TOF): m/z calculated for $C_{48}H_{35}FOK$ $[M + K]^+$ 685.2309, found 685.2301.

9-(4-Chlorophenyl)-2-(1,1-diphenyl-1H-inden-3-yl)-1,4-dimethyl-9-phenyl-9H-fluoren-3-ol ***(25h)***. Isolated as yellow viscous liquid (1:1.04 of diastereomer); yield: 90 % (0.090 g). ^{1}H

NMR (500 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 7.5 Hz, 2H), 7.41 (d, *J* = 7.0 Hz, 2H), 7.36-7.29 (m, 11H), 7.26- 7.24 (m, 12H), 7.23-7.22 (m, 6H), 7.21-7.19 (m, 13H), 7.18-7.15 (m, 6H), 6.92-6.89 (m, 2H), 6.83 (s, 2H), 5.16 (s, 1H), 5.15 (s, 1H), 2.68 (s, 6H), 1.73 (s, 6H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 155.4, 151.4, 150.7, 146.2, 146.1, 143.4, 143.3, 142.7, 142.4, 142.2, 141.7(2), 141.5, 140.9, 140.0, 137.8, 137.7, 132.4, 132.2, 130.8, 130.4, 129.1, 128.9, 128.8, 128.6 (2), 128.2, 128.1, 127.7 (2), 127.6, 127.4, 127.3, 127.1, 127.0, 126.9, 126.8, 126.7, 126.6, 125.6, 125.3, 123.5, 121.5, 121.4, 120.2, 117.4, 66.9, 64.5, 18.0, 12.8 ppm; HRMS (ESI-TOF): m/z calculated for $C_{48}H_{36}ClO$ $[M + H]^+$ 663.2455, found 663.2454.

9-(4-Bromophenyl)-2-(1,1-diphenyl-1H-inden-3-yl)-1,4-dimethyl-9-phenyl-9H-fluoren-3-ol ***(25i)***. Isolated as white solid (1:1.02 of diastereomer), mp: 269-271 °C; yield: 93 % (0.093 g). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 7.5 Hz, 2H), 7.42 (d, *J* = 7.0 Hz, 2 H), 7.37-7.33 (m, 7H), 7.32-7.28 (m, 8H), 7.27-7.25 (m, 15H), 7.24-7.23 (m, 4H), 7.21-7.20 (m, 10H), 7.18-7.15 (m, 4H), 6.91-6.87 (m, 2H), 6.836 (s, 1H), 6.832 (s, 1H), 5.15 (s, 1H), 5.14 (s, 1H), 2.68 (s, 6H), 1.72 (s, 6H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 155.3, 151.4, 150.8, 146.2, 146.1, 146.0, 143.4, 142.7, 142.4, 142.3, 142.2, 141.7, 140.9, 140.0, 137.7, 132.2, 131.2, 131.1, 131.0, 130.8, 129.4, 129.2, 129.0, 128.9, 128.6 (2), 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 127.3, 127.1, 126.9, 126.9, 126.8, 126.6, 125.6, 125.3, 123.5, 121.5 (2), 120.5, 120.4, 120.2, 117.5, 67.0, 64.6, 18.0(2), 12.8 ppm; IR: ν˜max = 3505, 3057, 2921, 1445, 748, 697 cm-1; HRMS (ESI-TOF): m/z calculated for $C_{48}H_{36}BrO$ $[M + H]^+$ 707.1950, found 707.1945.

2-(1,1-Diphenyl-1H-inden-3-yl)-9-(4-methoxyphenyl)-1,4-dimethyl-9-phenyl-9H-fluoren-3-ol ***(25j)***. Isolated as white solid (1:0.99 of diastereomer), mp: 268-269 °C; yield: 80 % (0.080 g). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.5 Hz, 2H), 7.42-7.41 (m, 2 H), 7.37 (d, *J* = 7.0 Hz, 2H), 7.34-7.31 (m, 3H), 7.30-7.29 (m, 4H), 7.28-7.27 (m, 9H), 7.26-7.22 (m, 8H), 7.21-7.19 (m, 15H), 7.18-7.15 (m, 3H), 6.93-6.90 (m, 2H), 6.83 (d, *J* = 1.0 Hz, 2H), 6.79-6.74 (m, 4H), 5.14 (s, 1H), 5.13 (s, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 2.68 (s, 6H), 1.74 (s, 3H), 1.74 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 158.2, 158.0, 156.2, 156.1, 151.1, 150.7, 146.0 (2), 143.5, 143.3, 143.2, 143.0, 142.8, 142.3, 140.8, 140.0, 137.9 (2), 134.7, 134.5, 132.3, 130.4, 130.1, 129.3, 128.9, 128.8, 128.6, 128.0, 127.9, 127.7 (2), 127.6, 127.5, 127.2, 127.1, 127.0, 126.8, 126.5, 126.3, 125.5, 125.3, 123.3, 121.6, 120.0, 117.2, 113.3, 113.2, 66.9, 64.3, 18.0, 17.9, 12.8 ppm; HRMS (ESI-TOF): m/z calculated for $C_{49}H_{37}O_2$ $[M - H]^+$ 657.2794, found 657.2822.

9-(4-Chlorophenyl)-2-[1-(4-chlorophenyl)-1-phenyl-1H-inden-3-yl]-1,4-dimethyl-9-phenyl-9H-fluoren-3-ol ***(25k)***. Isolated as white solid (1:1.01 and 1:0.94 of diastereomer), mp: 220-222 °C; yield: 85 % (0.085 g). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.0 Hz, 4H), 7.39-7.37 (m, 4H), 7.36- 7.35 (m, 2H), 7.34-7.33 (m, 4H), 7.32-7.30 (m, 11H), 7.29-7.28 (m, 10H), 7.27-7.25 (m, 18H), 7.24-7.23 (m, 12H), 7.22-7.20 (m, 18H), 7.18-7.15 (m, 12H), 7.14-7.11 (m, 5H), 6.93-6.88 (m, 4H), 6.78 (s, 4H), 5.10 (s, 1H), 5.09 (s, 1H), 5.07, (s, 1H), 5.06 (s, 1H), 2.68 (s, 12H), 1.71 (s, 6H), 1.70 (s, 6H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 155.4, 151.3, 150.3, 145.6, 142.9, 142.8, 142.6, 142.4, 142.1, 142.0, 141.7, 141.6, 141.4, 140.8, 140.1, 138.1, 133.1, 132.9, 132.4, 132.2, 130.8, 130.4, 129.1 (2), 129.0

(2), 128.8, 128.7, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5 (2), 127.4, 127.3, 127.0, 126.8, 126.6, 125.4, 125.3, 123.5, 121.7, 121.6, 119.9, 117.5, 66.4, 64.5, 18.0 (2), 12.8 ppm; HRMS (ESI-TOF): m/z calculated for $C_{48}H_{35}Cl_2O$ $[M + H]^+$ 697.2065, found 697.2021.

1,4-Dimethyl-9,9-diphenyl-2-(1,1,6-triphenyl-1H-inden-3-yl)-9Hfluoren-3-ol ***(25l)***. Isolated as yellow solid, mp: 284-286 °C; yield: 88 % (0.088 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 0.8 Hz, 1H), 7.52 (d, *J* = 7.2 Hz, 2H), 7.45 (dd, J_1 = 1.2 Hz, J_2 = 6.4 Hz, 1H), 7.40-7.36 (m, 5H), 7.34-7.29 (m, 8H), 7.28-7.22 (m, 7H), 7.22-7.17 (m, 6H), 6.97 (d, *J* = 7.6 Hz, 1H), 6.85 (s, 1H), 5.16 (s, 1H), 2.70 (s, 3H), 1.77 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 155.9, 151.4, 151.2, 146.2, 143.4, 143.3, 142.9, 142.7, 142.3, 142.1, 140.2, 140.0, 137.7, 132.4, 129.3, 129.0, 128.9, 128.8, 128.6, 128.0, 127.9, 127.8, 127.7, 127.5, 127.4, 127.3, 127.2, 127.1, 126.8, 126.6, 126.4, 125.5, 124.4, 123.4, 121.8, 120.1, 117.3, 67.1, 65.0, 18.1, 12.8 ppm; HRMS (ESI-TOF): m/z calculated for $C_{54}H_{40}OK$ $[M + K]^+$ 743.2716, found 743.2712.

1,4-Dimethyl-2-(6-methyl-1,1-diphenyl-1H-inden-3-yl)-9,9-diphenyl-9H-fluoren-3-ol ***(25m)***. Isolated as yellow solid; mp: 280-281 °C; yield: 86 % (0.086 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 8.0 Hz, 1H), 7.38-7.33 (m, 3H), 7.31-7.28 (m, 4H), 7.27-7.24 (m, 6H), 7.22-7.16 (m, 11H), 7.02 (d, *J* = 7.0 Hz, 1H), 6.78 (d, *J* = 7.5 Hz, 1H), 6.74 (s, 1H), 5.17 (s, 1H), 2.68 (s, 3H), 2.33 (s, 3H), 1.73 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 155.9, 151.23, 151.0, 145.0, 143.7, 143.5, 142.9, 142.7, 142.1, 141.0, 140.1, 140.0, 137.7, 136.7, 132.3, 129.3, 129.0, 128.8, 128.5, 128.3, 128.0, 127.9, 127.8, 127.7, 127.4, 127.1, 126.9, 126.5, 126.3, 125.4, 123.3, 121.3, 120.2, 117.2, 66.7, 64.9, 21.8, 18.0, 12.8 ppm; IR: ν˜max = 3497, 3052, 1489, 759, 744, 694, 479 cm-1; HRMS (ESI-TOF): m/z calculated for $C_{49}H_{39}O$ $[M + H]^+$ 643.3001, found 643.001.

2-(1,1-Dimethyl-1H-inden-3-yl)-1,4-dimethyl-9,9-diphenyl-9Hfluoren-3-ol ***(25n)***. Isolated as yellowish solid; mp: 217-219 °C; yield: 74 % (0.074 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 8.0 Hz, 1H), 7.40-7.39 (m, 3H), 7.37-7.35 (m, 1H), 7.34-7.31 (m, 3H), 7.27-7.24 (m, 3H), 7.23-7.17 (m, 6H), 6.87 (d, *J* = 7.5 Hz, 1H), 6.44 (s, 1H), 5.36 (s, 1H), 2.74 (s, 3H), 1.69 (s, 3H), 1.48 (s, 3H), 1.38 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 155.9, 153.8, 151.1, 148.2, 143.0, 142.7, 142.0, 141.9, 141.1, 139.8, 136.4, 132.0, 129.4, 129.2, 129.0, 128.0, 127.8, 127.4, 127.1, 126.9, 126.5, 126.3, 126.2, 125.4, 123.3, 121.5, 121.0, 120.5, 117.0, 65.0, 49.6, 24.9, 24.8, 17.8, 12.9 ppm; HRMS (ESI-TOF): m/z calculated for $C_{38}H_{32}ONa$ $[M + Na]^+$ 433.1568, found 433.1563.

1,4-Dimethyl-2-(1-methyl-1-phenyl-1H-inden-3-yl)-9,9-diphenyl-9H-fluoren-3-ol ***(25o)***. Isolated as yellow solid; mp: 206-208 °C; yield: 75 % (0.075 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 7.5 Hz, 1H), 7.39-7.34 (m, 4H), 7.32-7.26 (m, 6H), 7.25-7.23 (m, 3H),7.22-7.17 (m, 8H), 6.90 -6.89 (m, 1H), 6.59 (s, 1H), 5.32 (s, 1H), 2.70 (s, 3H), 1.76 (s, 3H), 1.71 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 155.8, 153.8, 153.5, 151.2, 151.0, 147.8, 147.7, 142.9, 142.8, 142.7 (2), 142.5, 142.4, 142.3, 142.1 (2), 142.0, 141.0, 139.9 (2), 137.0,132.4, 132.2, 129.3 (2), 129.0, 128.9, 128.6, 128.0, 127.9, 127.8, 127.4, 127.2, 127.1, 126.9, 126.8, 126.7, 126.6, 126.5, 126.3, 126.2, 126.0, 125.4, 123.3, 123.2,

121.2 (2), 120.2 (2), 117.1, 64.9, 57.0, 56.9, 23.5, 23.2, 18.1, 17.8, 12.8(2) ppm; HRMS (ESI-TOF): m/z calculated for $C_{43}H_{35}O$ $[M + H]^+$ 567.2688, found 567.2689.

2-[1,1-Bis(4-fluorophenyl)-1H-inden-3-yl]-1,4-dimethyl-9,9-diphenyl-9H-fluoren-3-ol ***(25p)***. Isolated as white solid, mp: 281-283 °C; yield: 86 % (0.086 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 7.5 Hz, 1H), 7.38-7.33 (m, 4H), 7.30-7.28 (m, 3H), 7.25-7.17 (m, 11H), 7.15-7.13 (m, 2H), 7.00-6.95 (m, 2H), 6.93-6.86 (m, 3H), 6.75 (s, 1H), 5.04 (s, 1H), 2.68 (s, 3H), 1.72 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 163.1, 163.0, 161.1, 161.0, 155.9, 151.2, 150.6, 145.6, 142.9, 142.7, 142.6, 142.3, 140.9, 140.3, 139.0 (2), 138.9, 138.8, 138.2, 132.3, 129.4, 129.3, 129.2, 129.1 (2), 129.0, 128.0, 127.9, 127.8, 127.6, 127.2, 127.0, 126.6, 126.4, 125.5, 125.3, 123.4, 121.8, 119.8. 117.4, 115.8, 115.7, 115.6, 115.4, 65.6, 65.0, 18.0, 12.8 ppm; IR: ν˜ max = 3512, 3061, 1501, 1226, 828, 773, 572 cm-1; HRMS (ESI-TOF): m/z calculated for $C_{48}H_{34}F_2ONa$ $[M + Na]^+$ 665.2656, found 665.2653.

2-(1,1-Diphenyl-1H-inden-3-yl)-9,9-bis(4-fluorophenyl)-1,4-dimethyl-9H-fluoren-3-ol ***(25q)***. Isolated as white solid; mp: 186-188 °C; yield: 87 % (0.087 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.0 Hz, 1H), 7.38-7.37 (m, 2H), 7.36- 7.34 (m, 2H), 7.32-7.31 (m, 1H), 7.30-7.28 (m, 2H), 7.26-7.23 (m, 5H), 7.21-7.18 (m, 6H), 7.15-7.13 (m, 2H), 6.98 (t, *J* = 8.5 Hz, 2H), 6.93- 6.91 (m, 1H), 6.88 (t, *J* = 8.5 Hz, 2H), 6.75 (s, 1H), 5.04 (s, 1H), 2.68 (s, 3H), 1.72 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 163.1, 163.0, 161.1, 161.0, 155.9, 151.1, 150.5, 145.6, 142.9, 142.6, 142.6, 142.3, 140.9, 140.3, 139.0 (2), 138.9, 138.8, 138.2, 132.3, 129.4, 129.3, 129.2, 129.1 (2), 129.0, 128.0, 127.9, 127.8, 127.6, 127.2, 127.0, 126.6, 126.4, 125.5, 125.3, 123.4, 121.8, 119.8. 117.4, 115.8, 115.7, 115.6, 115.4, 65.6, 65.0, 18.0, 12.8 ppm; HRMS (ESI-TOF): m/z calculated for $C_{48}H_{34}F_2ONa$ $[M + Na]^+$ 687.9898, found 687.9812.

2-[1-(3,4-Dichlorophenyl)-1-phenyl-1H-inden-3-yl]-1,4-dimethyl-9,9-diphenyl-9H-fluoren-3-ol ***(25r)***. Isolated as white solid (1:0.90 of diastereomer), mp: 256-258 °C; yield: 93 % (0.093 g). ^{1}H NMR (400 MHz,$CDCl_3$): δ = 7.97 (d, *J* = 7.6 Hz, 2H), 7.39-7.36 (m, 9H), 7.34-7.33 (m, 2 H), 7.31-7.28 (m, 10H), 7.27-7.24 (m, 11H), 7.22- 7.20 (m, 8H), 7.197-7.190 (m, 3H), 7.17-7.15 (m, 3H), 7.10-7.08 (m, 1H), 7.03-7.00 (m, 1H), 6.94-6.92 (m, 2H), 6.756 (s, 1H), 6.751 (s, 1H), 5.04 (s, 1H), 5.01 (s, 1H), 2.69 (s, 3H), 2.68 (s, 3H), 1.73 (s, 3H), 1.72 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 155.9, 151.1 (2), 149.8, 149.7, 144.8, 144.7, 144.0, 143.8, 142.8 (2), 142.7, 142.6, 142.4, 142.3, 142.1, 140.8, 138.9 (2), 132.6, 132.3, 132.2, 130.7, 130.5, 129.7, 129.5, 129.3, 129.1, 129.0, 128.8, 128.0, 127.9, 127.7, 127.6, 127.5, 127.2, 127.1, 126.6, 126.4 (2), 125.5, 125.3, 123.4, 121.9, 119.7 (2), 117.4, 66.1, 65.0, 18.0, 12.8 ppm; IR (KBr): ν˜max 3528, 2958, 1585, 1157, 761cm-1; HRMS (ESI-TOF): m/z calculated for $C_{48}H_{34}Cl_2ONa$ $[M + Na]^+$ 697.2065, found 697.2014.

2-(2-Iodo-1,1-diphenyl-1H-inden-3-yl)-1,4-dimethyl-9,9-diphenyl- 9H-fluoren-3-ol ***(27a)***. Isolated as white solid, mp: 130-131 °C; yield: 62 % (0.062 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.0 Hz, 1H), 7.42-7.40 (m, 2H), 7.37 (d, *J* = 7.0 1H), 7.33-7.29 (m, 8H), 7.26-7.25 (m, 4H), 7.23-7.19 (m, 9H), 7.16-7.13 (m, 2H), 6.88-6.87 (m, 1H), 4.76 (s, 1H), 2.72 (s, 3H), 1.68 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 156.0, 152.4, 150.7, 146.4, 143.2, 142.6, 142.3, 142.2, 142.1, 141.7, 140.9, 132.4, 130.7, 129.4, 129.1, 128.8, 128.7,

128.5, 128.4, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.2, 126.9, 126.5, 126.4, 125.5, 125.4, 123.4, 122.0, 121.4, 120.8, 117.7, 80.1, 71.0, 64.9, 17.4, 12.8 ppm; IR: ν˜max = 3534, 3058, 2959, 1597, 1446, 744, 698, 579 cm-1; HRMS (ESI-TOF): m/z calculated for $C_{48}H_{36}IO$ $[M + H]^+$ 755.1811, found 755.1807.

*9-(4-Fluorophenyl)-2-(2-iodo-1,1-diphenyl-1H-inden-3-yl)-1,4-dimethyl-9-phenyl-9H-fluoren-3-ol (**27b**).* Isolated as white solid (1:0.93 of diastereomer), mp: 141-142 °C; yield: 65 % (0.065 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.4 Hz, 2H), 7.41-7.37 (m, 3H), 7.36-7.34 (m, 5H), 7.33-7.29 (m, 14H), 7.28-7.27 (m, 5H), 7.247-7.241 (m, 4H), 7.23-7.22 (m, 3H), 7.20-7.18 (m, 8H), 7.12-7.13 (m, 4H), 6.92-6.87 (m, 6H), 4.77 (s, 1H), 4.76 (s, 1H), 2.72 (s, 6H), 1.67 (s, 6H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 155.7, 151.3, 150.7, 146.1, 143.4, 143.3, 142.7, 142.1, 140.8, 140.0, 137.8, 132.2, 131.7, 130.9 (2), 130.7, 130.6, 129.1, 128.8, 128.6, 128.4, 128.2, 128.1, 128.0, 127.7 (2), 127.6, 127.3, 127.1, 127.0, 126.8, 126.7, 126.5, 125.5, 125.3, 123.4, 123.3, 122.0, 121.5, 120.2, 117.4, 114.8 (2), 114.6 (2), 90.7, 88.5, 66.9, 64.4, 23.6, 18.0, 12.8 ppm; HRMS (ESI-TOF): m/z calculated for $C_{48}H_{35}FIO$ $[M + H]^+$ 755.1811, found 755.1806.

*9-(4-Bromophenyl)-2-(2-iodo-1,1-diphenyl-1H-inden-3-yl)-1,4-dimethyl-9-phenyl-9H-fluoren-3-ol (**27c**).* Isolated as yellow viscous liquid (1:1.08 of diastereomer); yield: 90 % (0.090 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.4 Hz, 2H), 7.40-7.37 (m, 2H), 7.35-7.31 (m, 14H), 7.27-7.25 (m, 4H), 7.24-7.22 (m, 12H), 7.21-7.19 (m, 8H), 7.18-7.16 (m, 6H), 7.15-7.13 (m, 4H), 6.89-6.86 (m, 2H), 4.78 (s, 1H), 4.77 (s, 1H), 2.72 (s, 6H), 1.68 (s, 6H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 155.5, 152.4 (2), 150.9, 146.2, 142.7, 142.1 (2),142.0 (3), 141.7 (2), 141.6, 141.0, 140.8, 140.6, 132.4, 132.3, 132.2, 130.8, 130.5, 129.2, 128.9, 128.7 (2), 128.5, 128.4 (2), 128.2 (2), 128.1, 127.7 (2), 127.5 (2), 127.4, 127.1, 127.0, 126.8, 126.6, 125.4, 125.3, 123.5, 122.2, 122.1, 121.5, 120.7 (2), 117.8, 71.0, 64.4, 17.4, 12.8 ppm; HRMS (ESI-TOF): m/z calculated for $C_{48}H_{35}ClIO$ $[M + H]^+$ 343.2061, found 343.2061.

9-(4-Chlorophenyl)-2-(2-iodo-1,1-diphenyl-1H-inden-3-yl)-1,4-dimethyl-9-phenyl-9H-fluoren-3-ol (27d): Isolated as yellow viscous liquid (1:0.7 of diastereomer); yield: 89 % (0.089 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.5 Hz, 2H), 7.39-7.37 (m, 2H), 7.34-7.30 (m, 19H), 7.29-7.27 (m, 3H), 7.26-7.25 (m, 2H), 7.25-7.23 (m, 6H), 7.22-7.21 (m, 3H), 7.21-7.20 (m, 6H), 7.19-7.17 (m, 4H), 7.16-7.13 (m, 5H), 6.89-6.86 (m, 2H), 4.78 (s, 1H), 4.77 (s, 1H), 2.72 (s, 6H), 1.67 (s, 6H) ppm; ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 155.4, 152.4, 150.9, 146.2, 142.6 (2), 142.1, 142.0 (2), 141.7, 141.6, 140.8, 140.6, 132.3, 131.2, 131.1, 130.9 (2), 129.2, 128.9, 128.8, 128.7, 128.5, 128.4 (2), 128.2, 128.0, 127.8, 127.7, 127.5, 127.4, 127.1, 127.0, 126.8, 126.6, 125.5, 125.3, 123.5, 122.2, 122.1, 121.5, 120.7, 120.3, 117.8, 71.0, 64.5, 17.4, 12.8 ppm; HRMS (ESI-TOF): m/z calculated for $C_{48}H_{35}BrIO$ $[M + H]^+$ 363.1748, found 363.1748.

*2-[1-(4-Chlorophenyl)-2-iodo-1-phenyl-1H-inden-3-yl]-1,4-dimethyl-9,9-diphenyl-9H-fluoren-3-ol (**27e**).* Isolated as yellow viscous liquid (1:1.06 of diastereomer); yield: 53 % (0.053 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.0 Hz, 2H), 7.42-7.37 (m, 6H), 7.33-7.31 (m, 5H), 7.30- 7.28 (m, 8H), 7.25-7.24 (m, 11H), 7.23-7.20 (m, 10H), 7.19-7.18 (m, 4H), 7.16-7.14 (m, 4H), 7.11 (d, *J* = 8.5 Hz, 2H), 6.90-6.88 (m, 2H), 4.74 (s, 1H), 4.69 (s,

1H), 2.72 (s, 6H), 1.68 (s, 3H), 1.65 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ = 156.0, 151.9, 150.6, 143.1, 142.6, 140.8, 130.1, 130.0, 129.4, 129.0, 128.9, 128.6, 128.4, 128.1, 127.8, 127.6, 127.2, 127.1, 126.6, 126.4, 125.4, 125.3, 123.4, 121.2, 120.9, 117.6, 70.4, 64.9, 17.4, 12.8 ppm; HRMS (ESI-TOF): m/z calculated for $C_{48}H_{34}ClIONa$ $[M + Na]^+$ 433.1568, found 433.1563.

*2-(2-Iodo-6-methyl-1,1-diphenyl-1H-inden-3-yl)-1,4-dimethyl-9,9-diphenyl-9H-fluoren-3-ol (**27f**).* Isolated as colorless viscous liquid; mp: 284-285 °C; yield: 79 % (0.079 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 6.6 Hz, 1H), 7.42-7.36 (m, 5H), 7.32-7.29 (m, 7H), 7.26-7.23 (m, 5H), 7.22-7.17 (m, 6H), 7.10 (s, 1H), 6.95 (d, *J* = 6.6 Hz, 1H), 6.79-6.76 (m, 1H), 4.77 (s, 1H), 2.72 (s, 3H), 2.25 (s, 3H), 1.68 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ = 156.0, 152.6, 150.7, 146.2, 143.2, 142.5, 142.4, 142.3, 141.9, 140.9, 140.6, 139.6, 137.1, 132.4, 129.4, 129.1, 128.8, 128.7, 128.6, 128.4, 128.0, 127.8, 127.6, 127.5, 127.4, 127.2, 126.5, 126.4, 126.2, 125.5, 123.4, 121.5, 120.5, 117.6, 76.8, 70.8, 64.9, 21.7, 17.4, 12.8 ppm; IR: ν˜max = 3534, 3056, 2922, 1595, 1445, 741, 696, 642, cm-1; HRMS (ESI-TOF): m/z calculated for $C_{49}H_{38}IO$ $[M + H]^+$ 331.1697, found 331.1697.

*1-(1,1,7-trimethyl-1H-inden-3-yl)naphthalen-2-ol and 1-(1,1,5-trimethyl-1H-inden-3-yl)naphthalen-2-ol (**29a:29b**).* Isolated as browm viscous liquid; yield: 96% (0.096 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82-7.7 (m, 4H), 7.55-7.51 (m, 2H), 7.35-7.26 (m, 7H), 7.10-7.01 (m, 3H), 6.67 (s, 2H), 6.58 (s, 1H), 6.52 (s, 1H), 5.43 (s, 2H), 2.57 (s, 3H), 2.23 (s, 3H), 1.63 (d, *J* = 7.0 Hz, 6H), 1.52 (d, *J* = 9.0 Hz, 6H) ppm; $^{13}C\{^{1}H\}$ NMR (125 MHz,$CDCl_3$): δ 151.2, 150.9, 150.4, 150.3, 149.7, 143.0, 142.5, 136.7, 134.3, 133.8, 133.2, 133.1, 133.0, 129.7, 129.0, 128.7, 128.2, 127.2, 127.0, 126.5, 126.4, 125.0, 123.5, 123.4, 122.1, 121.3, 119.3, 117.3 (2), 114.2 (2), 50.8, 49.5, 25.2, 25.1, 22.5, 22.4, 21.4, 18.9 ppm; HRMS (ESI-TOF): m/z calculated for $C_{22}H_{20}ONa$ $[M+Na]^+$ 323.1411, found 323.1412.

*2-(1,1-Diphenyl-1H-inden-3-yl)-1,4-dimethyl-9,9-diphenyl-3-(prop-2-yn-1-yloxy)-9H-fluorene (**33**).* Isolated as a white solid, mp: 273-275 °C; yield: 98 % (0.110 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.5 Hz, 1H), 7.38-7.34 (m, 6H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.29-7.25 (m, 6H), 7.24-7.21 (m, 3H), 7.20-7.17 (m, 10H), 6.85-6.84 (m, 1H), 6.67 (s, 1H), 4.11-4.10 (m, 2H), 2.79, (s, 3H), 2.35-2.34 (m, 1H), 1.72 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ = 155.7, 154.8, 150.2, 146.4, 144.4, 144.0, 143.8, 142.4, 142.2, 140.7, 140.1, 138.3, 133.5, 129.3, 129.0, 128.5, 128.4 (2), 128.0, 127.9 (2), 127.6, 127.3, 127.2, 126.8, 126.7, 126.6, 126.5, 125.9, 125.5, 125.3, 125.0, 123.3, 121.2, 79.3, 74.9, 66.8, 65.2, 61.1, 17.8, 14.2 ppm; IR: ν˜max = 3276, 1489, 1445, 1078, 756, 747, 699, 652 cm-1; HRMS (ESI-TOF): m/z calculated for $C_{51}H_{38}OK$ $[M + K]^+$ 705.2560, found 705.2586.

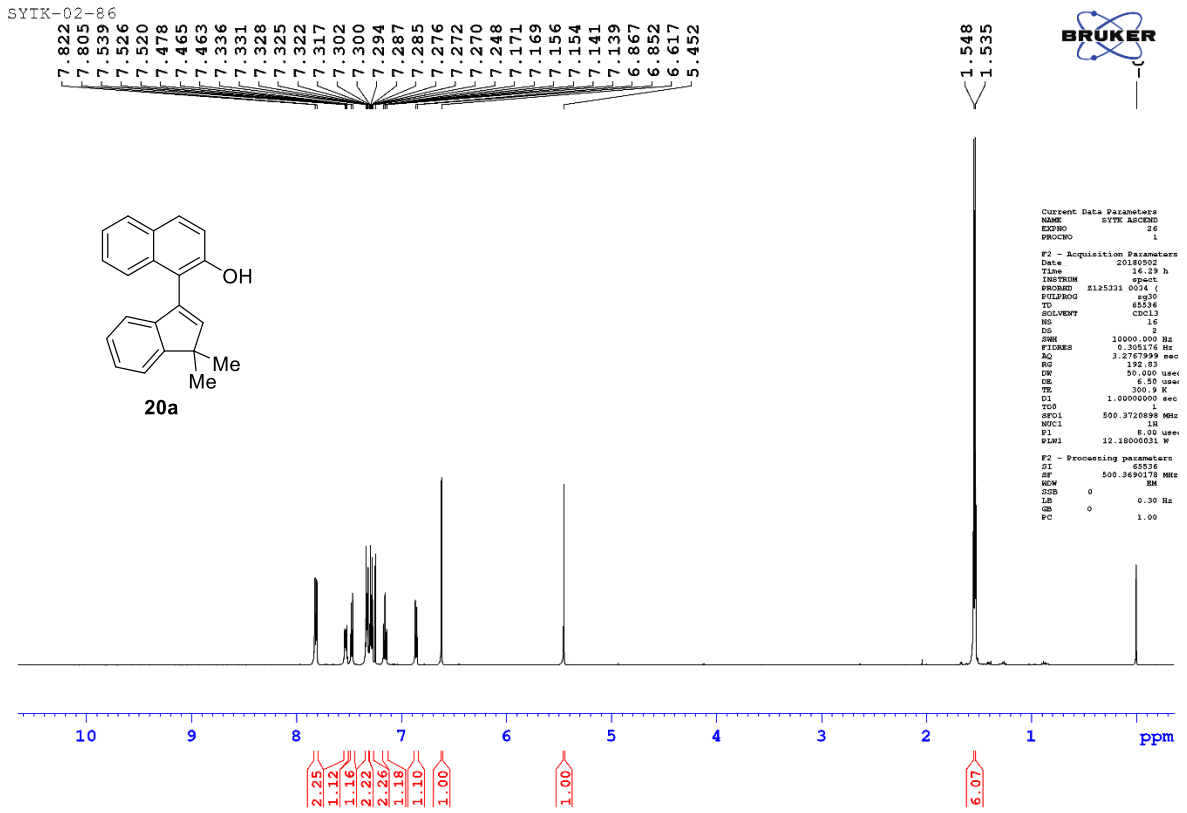
*(E)-3-[(2,3-Diiodoallyl)oxy]-2-(1,1-diphenyl-1H-inden-3-yl)-1,4-dimethyl-9,9-diphenyl-9H-fluorene (**35**).* Isolated as white solid, mp: 295-296 °C; yield: 83 % (0.114 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 7.8 Hz, 1H), 7.39-7.34 (m, 6H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.28-7.23 (m, 6H), 7.22-7.19 (m, 5H), 7.18-7.15 (m, 8H), 6.93 (d, *J* = 7.0 Hz, 1H), 6.86 (s, 1H), 6.70 (s, 1H), 4.19 (d, *J* = 12.5 Hz, 1H), 4.06 (dd, J_1 = 1.0 Hz, J_2 = 11.0 Hz, 1H), 2.80 (s, 3H), 1.72 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ = 155.8, 154.8, 150.3, 146.6, 144.6, 144.2, 143.9, 143.8, 142.4, 142.2, 140.7, 140.1, 138.4, 133.8, 129.3, 129.0, 128.7, 128.3,

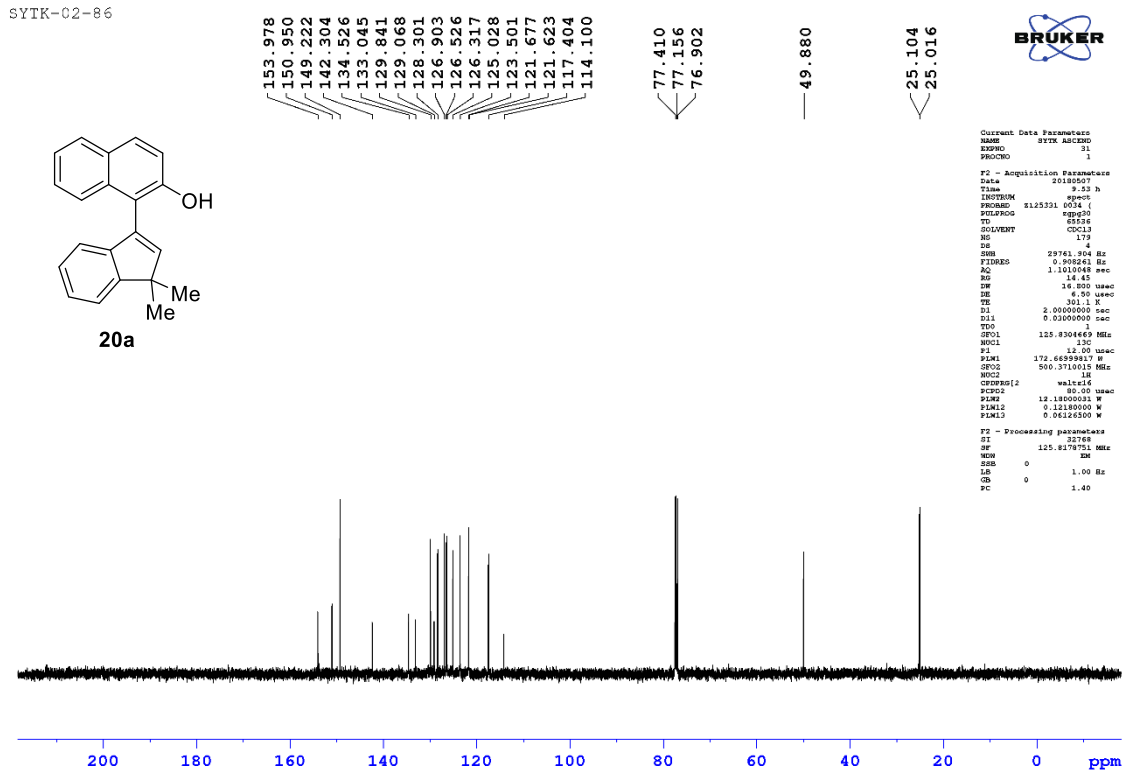
128.0 (2), 127.9, 127.6, 127.4, 127.2, 126.9, 126.7, 126.5, 125.8, 125.5 (2), 124.5, 123.3, 121.5, 98.0, 81.0, 79.1, 66.7, 65.2, 17.8, 14.5 ppm; HRMS (ESI-TOF): m/z calculated for $C_{51}H_{38}I_2OK$ $[M + K]^+$ 959.0649, found 959.0690.

*2-(2-Iodo-1,1-diphenyl-1H-inden-3-yl)-3-methoxy-1,4-dimethyl-9,9-diphenyl-9H-fluorene (**37**).* Isolated as white solid, mp: 268-270 °C; yield: 96 % (0.088 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 7.5 Hz, 1H), 7.42-7.40 (m, 2H), 7.39-7.37 (m, 3H), 7.33-7.29 (m, 6H), 7.27- 7.24 (m, 2H), 7.22-7.21 (m, 6H), 7.21-7.16 (m, 5H), 7.12-7.08 (m, 2H), 6.87-6.85 (m, 1H), 2.89 (s, 3H), 2.75 (s, 3H), 1.72 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 156.6, 155.9, 152.0, 148.1, 146.2, 143.7, 142.9, 142.5, 142.3, 141.9, 140.9, 140.8, 133.4, 129.5, 129.4, 129.1, 129.0 (2), 128.5, 128.4, 128.3, 128.2, 128.1, 127.9 (2), 127.6, 127.4, 127.3, 127.2 (2), 126.6, 126.5, 126.2, 125.5, 125.1, 124.5, 123.3, 120.5, 118.8, 70.7, 65.2, 61.7, 17.2, 13.5 ppm; IR: ν˜max = 3396, 3056, 2923, 1594, 1443, 1029, 743, 724, 646 cm-1; HRMS (ESI-TOF): m/z calculated for $C_{49}H_{38}IO$ $[M + H]^+$ 769.1967, found 769.1927.

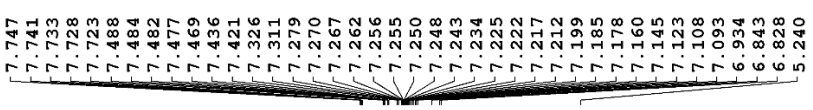
*7-(4-Chlorophenyl)-5,12-dimethyl-7,13,13-triphenyl-7,13-dihydrofluoreno[3,2-b]indeno[1,2-d]furan (**38**).* Isolated as white solid, mp: > 300 °C; yield: 86 % (0.085 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.37-7.36 (m, 2H), 7.35-7.34 (m, 3 H), 7.30-7.24 (m, 7H), 7.23 (d, *J* = 1.2 Hz, 5H), 7.21 (s, 2H), 7.21-7.18 (m, 4H), 7.16-7.12 (m, 2H), 2.88 (s, 3H), 2.49 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 168.9, 159.9, 155.3, 149.9, 145.6, 142.9 (2), 141.8, 141.0, 140.9, 135.9 (2), 133.2, 129.7, 129.1, 128.7 (2), 128.2, 128.0, 127.8, 127.5, 127.3, 127.2, 126.5 (2), 125.5, 125.4, 124.9, 124.3, 122.7, 121.5, 115.8, 64.8, 59.9, 19.6, 13.1 ppm; HRMS (ESI-TOF): m/z calculated for $C_{48}H_{34}ClO$ $[M + H]^+$ 661.2298, found 661.2293.

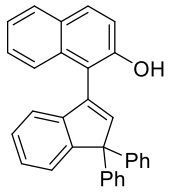
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AQ 3.2767999 sec
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DW 50.000 usec
DE 6.50 usec
TE 300.9 K
D1 1.00000000 sec
TD0 1
SFO1 500.3720898 MHz
NUC1 1H
P1 8.00 usec
PLW1 12.18000031 W
F2 - Processing parameters
SI 65536
SF 500.3690178 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
10
9
8
7
6
5
4
3
2
1
ppm
2.25
1.12
1.16
2.22
2.26
1.18
1.10
1.00
1.00
6.07


SYTK-02-86
153.978
150.950
149.222
142.304
134.526
133.045
129.841
129.068
128.301
126.903
126.526
126.317
125.028
123.501
121.677
121.623
117.404
114.100
77.410
77.156
76.902
49.880
25.104
25.016
BRUKER
OH
Me
Me
20a
Current Data Parameters
NAME SYTK ASCEND
EXPNO 31
PROCNO 1
F2 - Acquisition Parameters
Date 20180507
Time 9.53 h
INSTRUM spect
PROBHD Z125331 0034 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 179
DS 4
SWH 29761.904 Hz
FIDRES 0.908261 Hz
AQ 1.1010048 sec
RG 14.45
DW 16.800 usec
DE 6.50 usec
TE 301.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8304669 MHz
NUC1 13C
P1 12.00 usec
PLW1 172.66999817 W
SFO2 500.3710015 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 12.18000031 W
PLW12 0.12180000 W
PLW13 0.06126500 W
F2 - Processing parameters
SI 32768
SF 125.8178751 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
200
180
160
140
120
100
80
60
40
20
0
ppm

SYTK-02-104 B





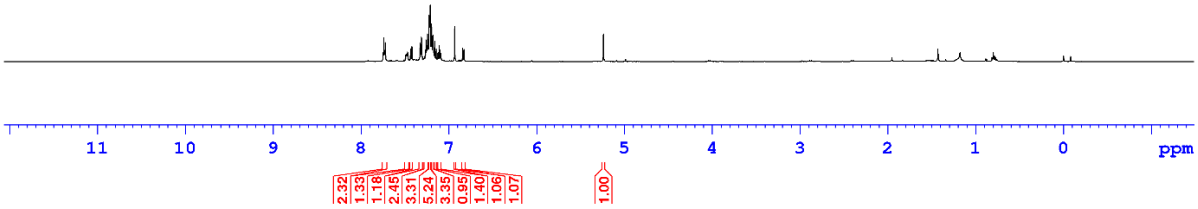
20b

```
Current Data Parameters
NAME                 SYTK500
EXPNO                     40
PROCNO                     1

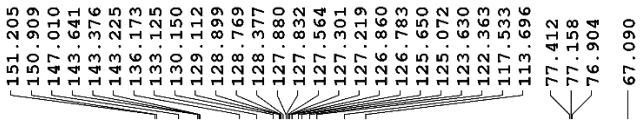
F2 - Acquisition Parameters
Date_              20180529
Time                  15.19
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH               10330.578 Hz
FIDRES                0.157632 Hz
AQ                3.1719425 sec
RG                       128
DW                   48.400 usec
DE                    6.50 usec
TE                   298.5 K
D1                1.00000000 sec
TD0                        1

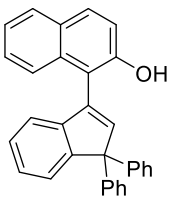
======== CHANNEL f1 ========
NUC1                      1H
P1                    14.90 usec
PL1                    2.00 dB
PL1W             12.85348415 W
SFO1             500.1830888 MHz

F2 - Processing parameters
SI                        32768
SF               500.1800679 MHz
WDW                        EM
SSB                    0
LB                     0.30 Hz
GB                     0
PC                     1.00
```



SYTK-02-104 B





20b

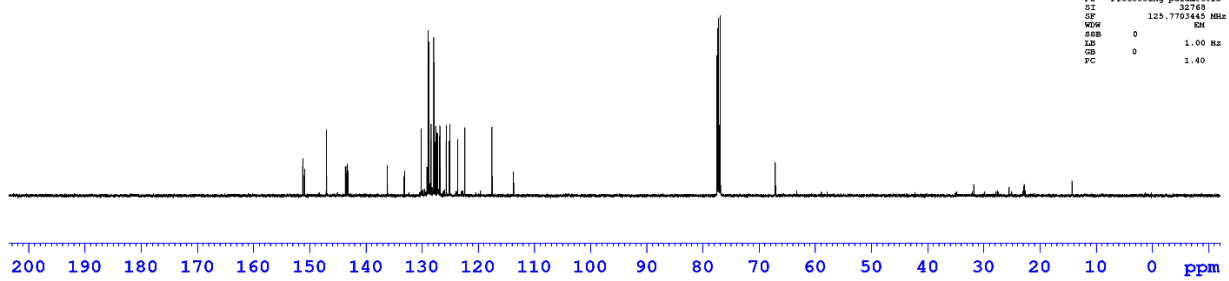
```
Current Data Parameters
NAME                 SYTK500
EXPNO                     42
PROCNO                     1

F2 - Acquisition Parameters
Date              20180529
Time                  15.35
INSTRUM                spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT               CDCl3
NS                      743
DS                        4
SWH               29761.904 Hz
FIDRES                0.454131 Hz
AQ                1.1010048 sec
RG                     2050
DW                   16.800 usec
DE                    6.50 usec
TE                   299.5 K
D1                2.00000000 sec
D11               0.03000000 sec
TD0                        1

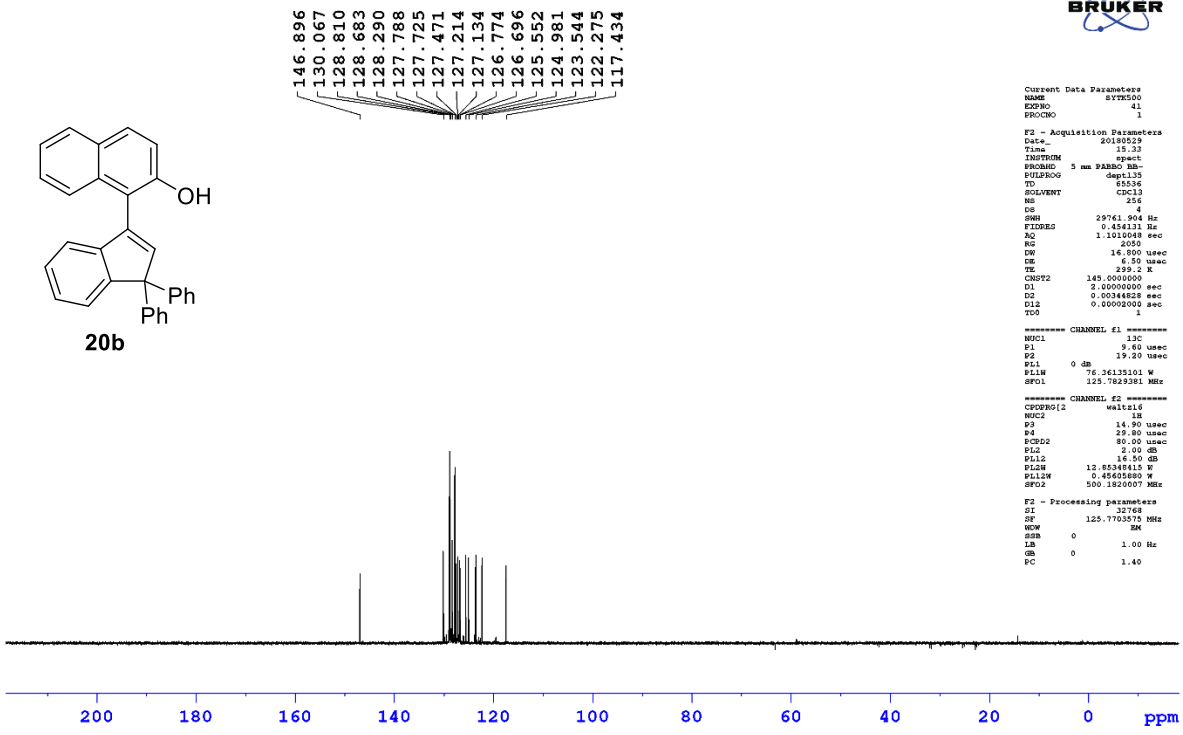
======== CHANNEL f1 ========
NUC1                      13C
P1                    9.60 usec
PL1                    0 dB
PL1W             76.36135101 W
SFO1             125.7829381 MHz

======== CHANNEL f2 ========
CPDPRG[2          waltz16
NUC2                      1H
PCPD2                 80.00 usec
PL2                    2.00 dB
PL12                  16.50 dB
PL13                  16.50 dB
PL2W             12.85348415 W
PL12W             0.45605880 W
PL13W             0.45605880 W
SFO2             500.1820007 MHz

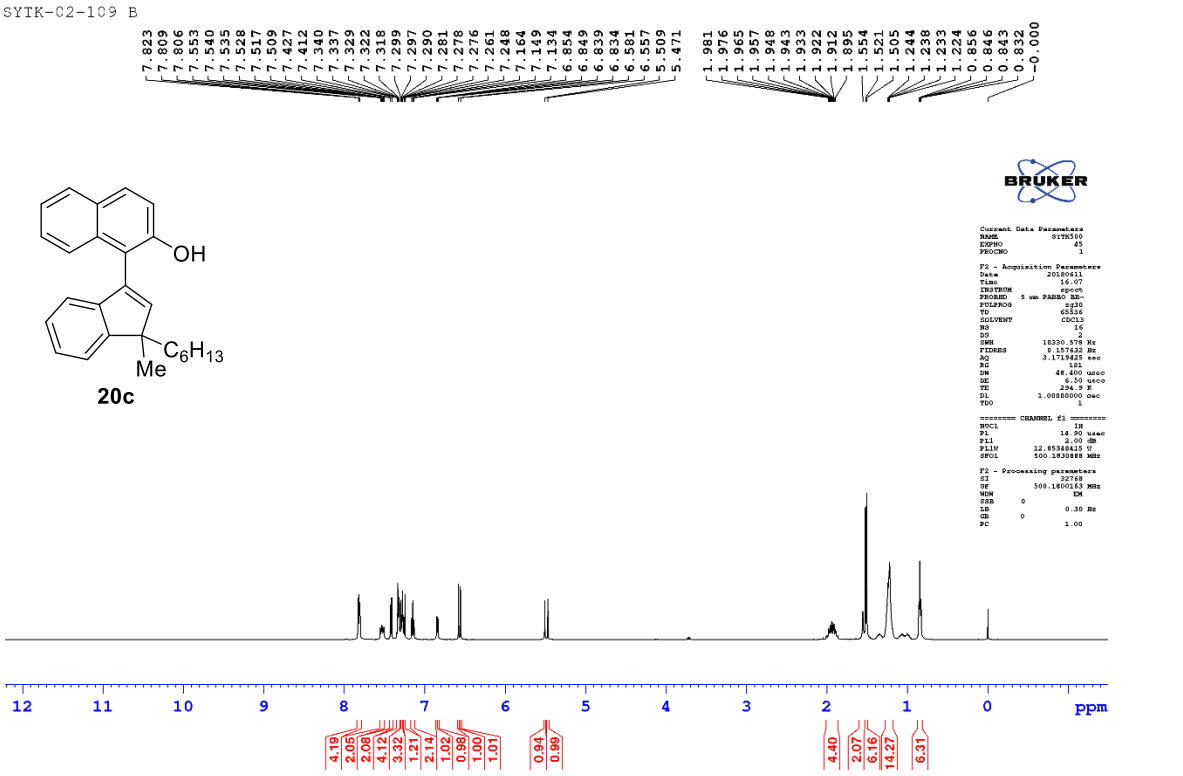
F2 - Processing parameters
SI                        32768
SF               125.7703445 MHz
WDW                        EM
SSB                    0
LB                     1.00 Hz
GB                     0
PC                     1.40
```



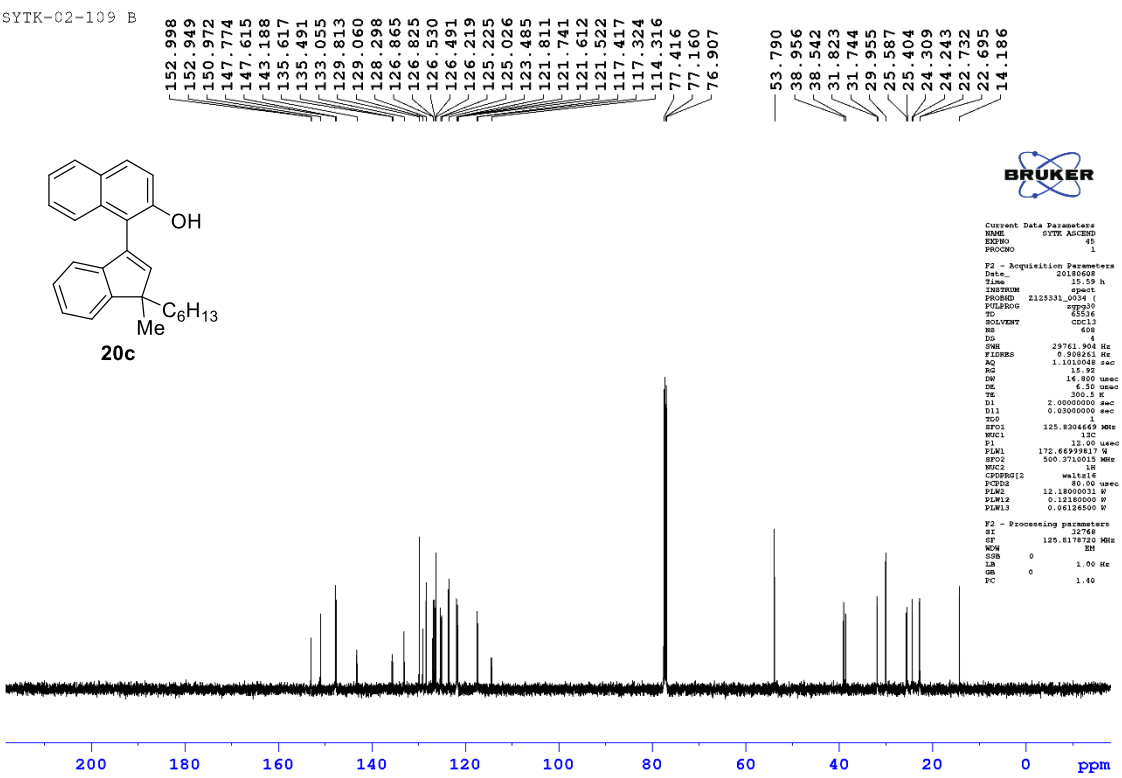
SYTK-02-104 B



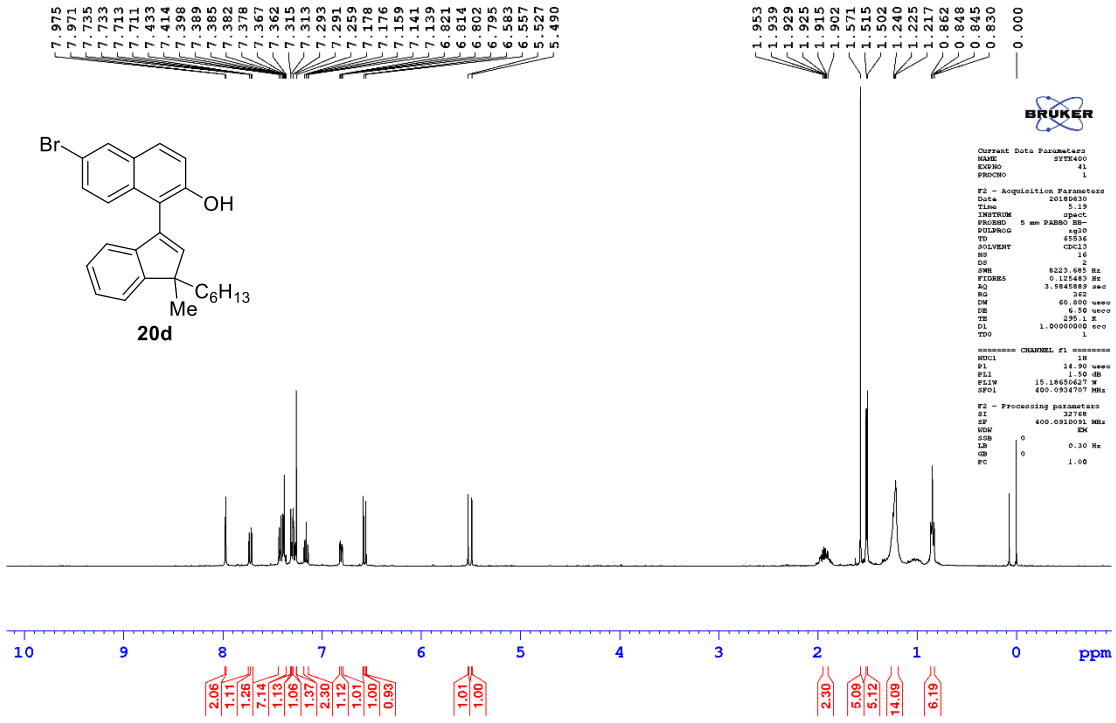
SYTK-02-109 B



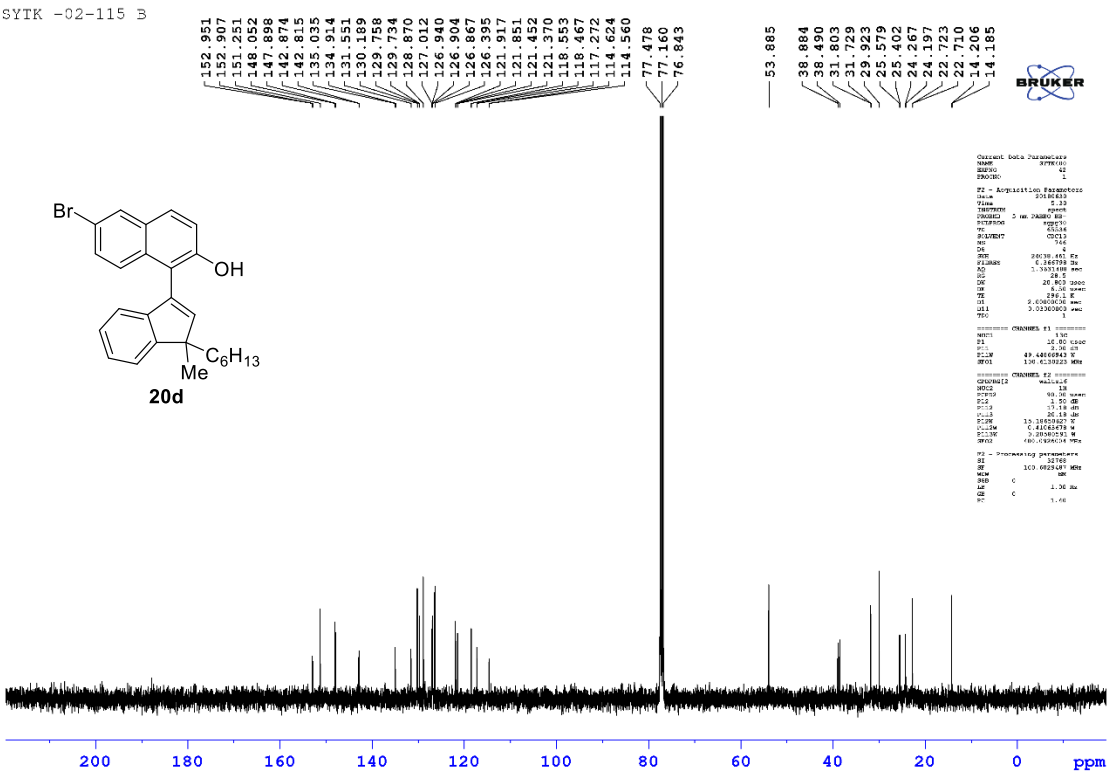
SYTK-02-109 B



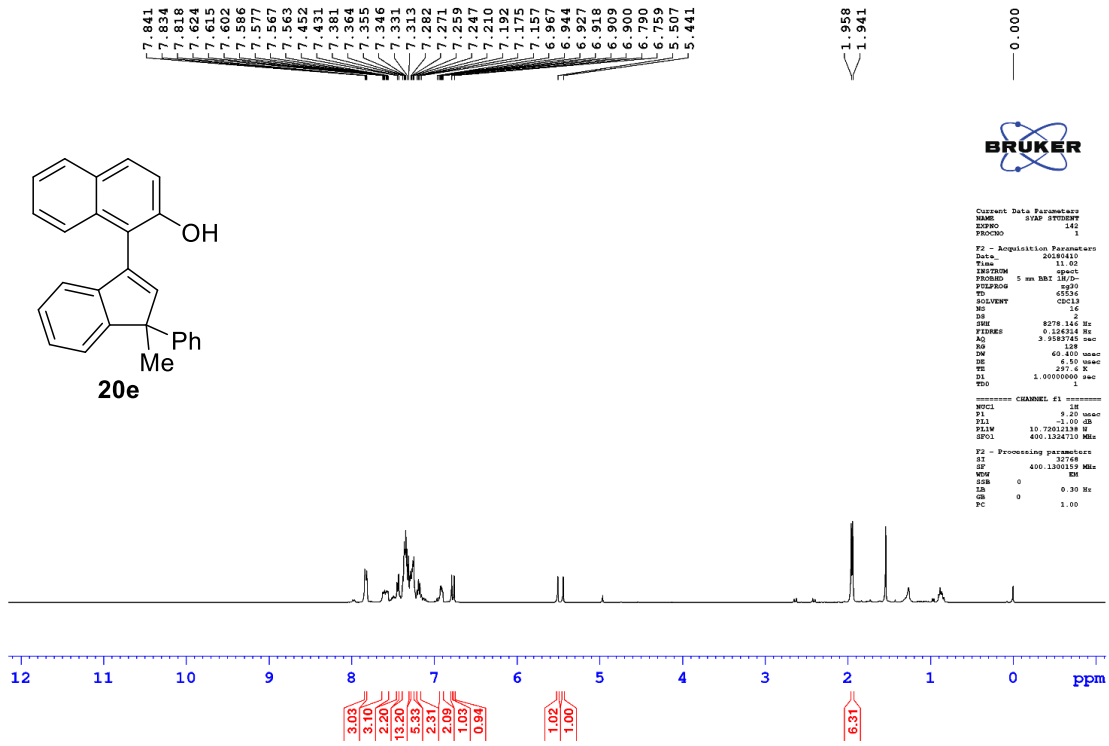
SYTK -02-115 B



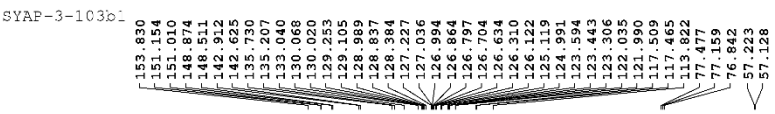
SYTK -02-115 B



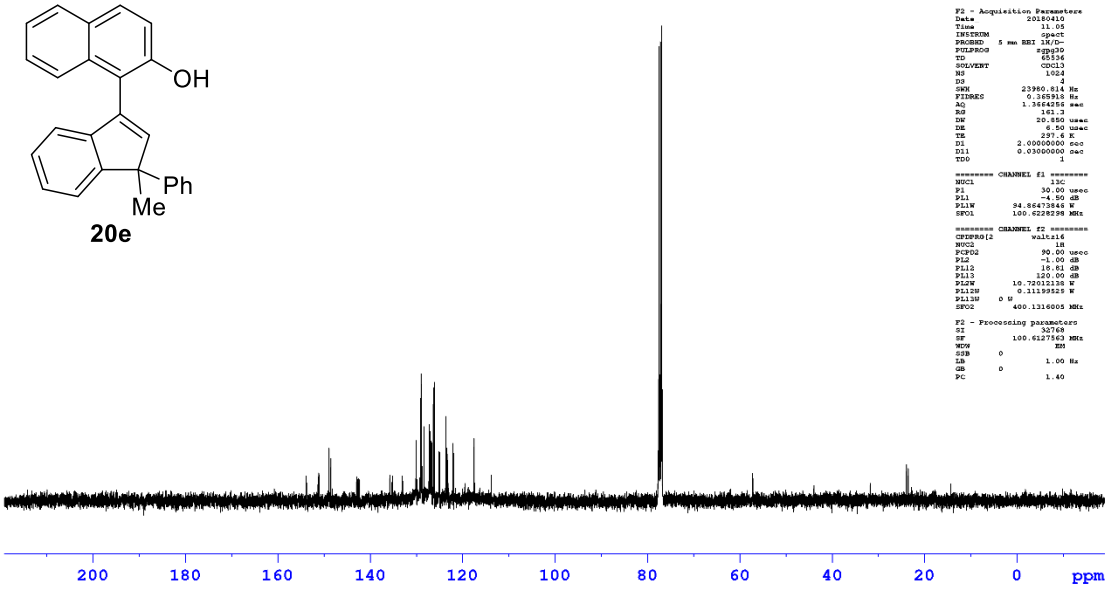
SYAP-3-103b1



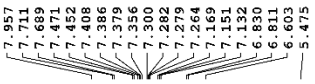
SYAP-3-103b1

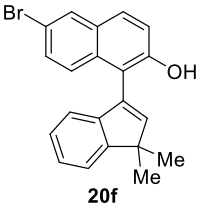


20e



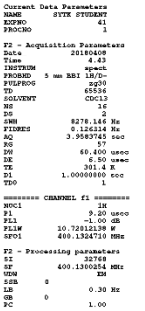
SYTK-02-67

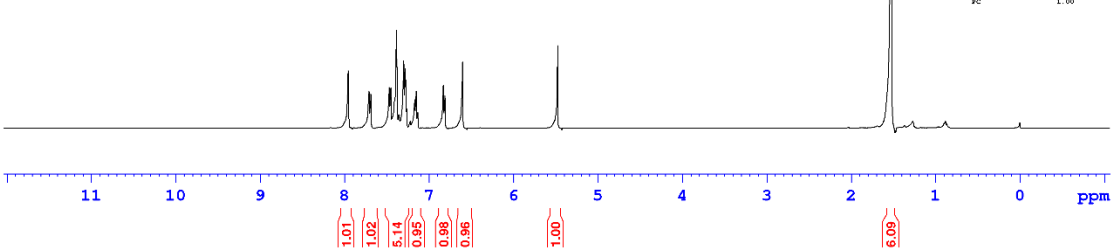




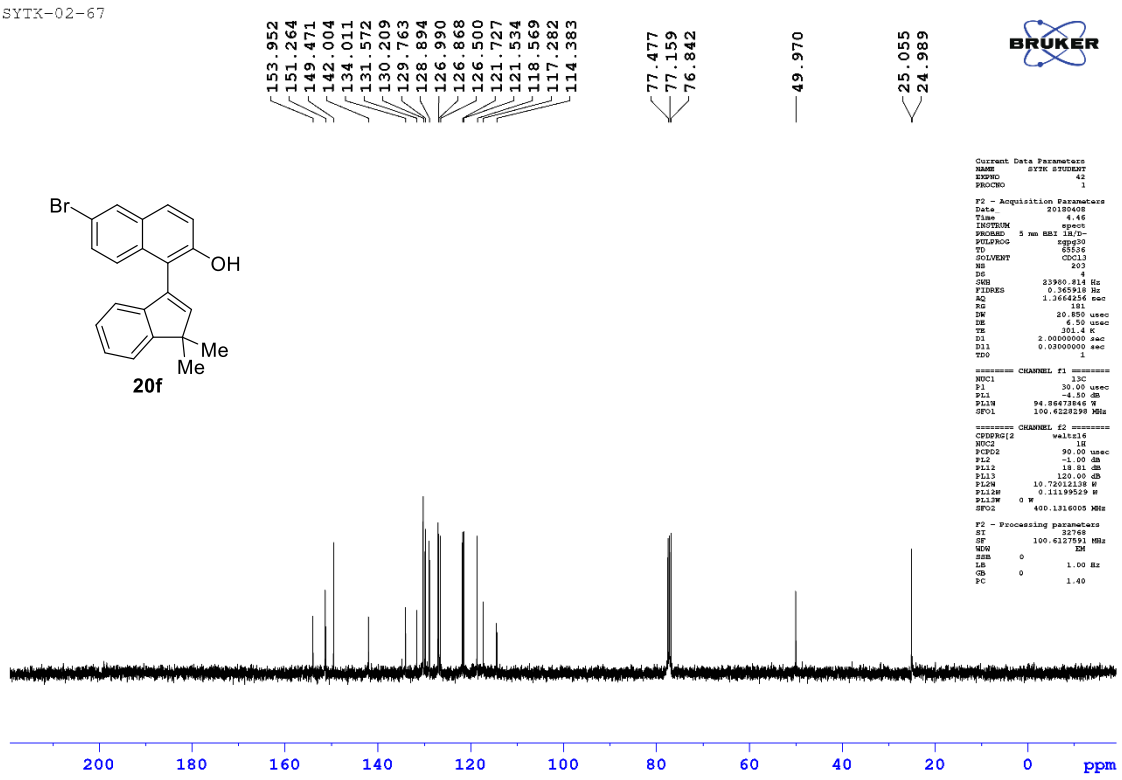
20f



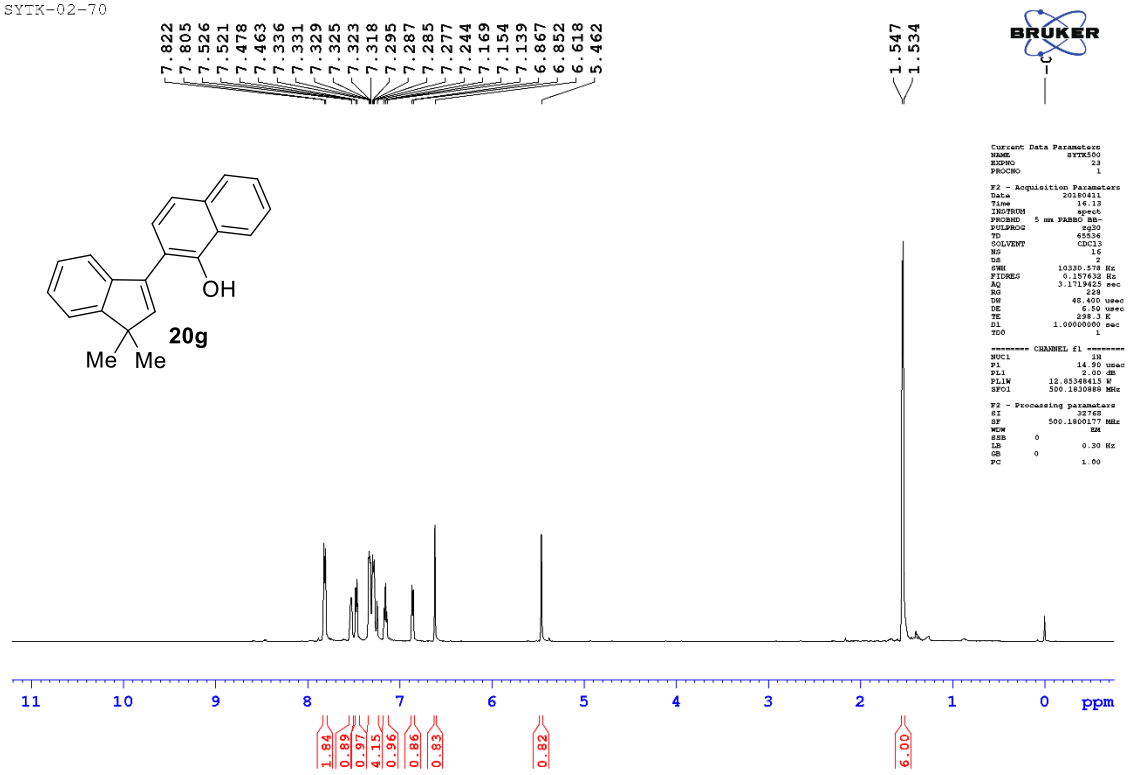


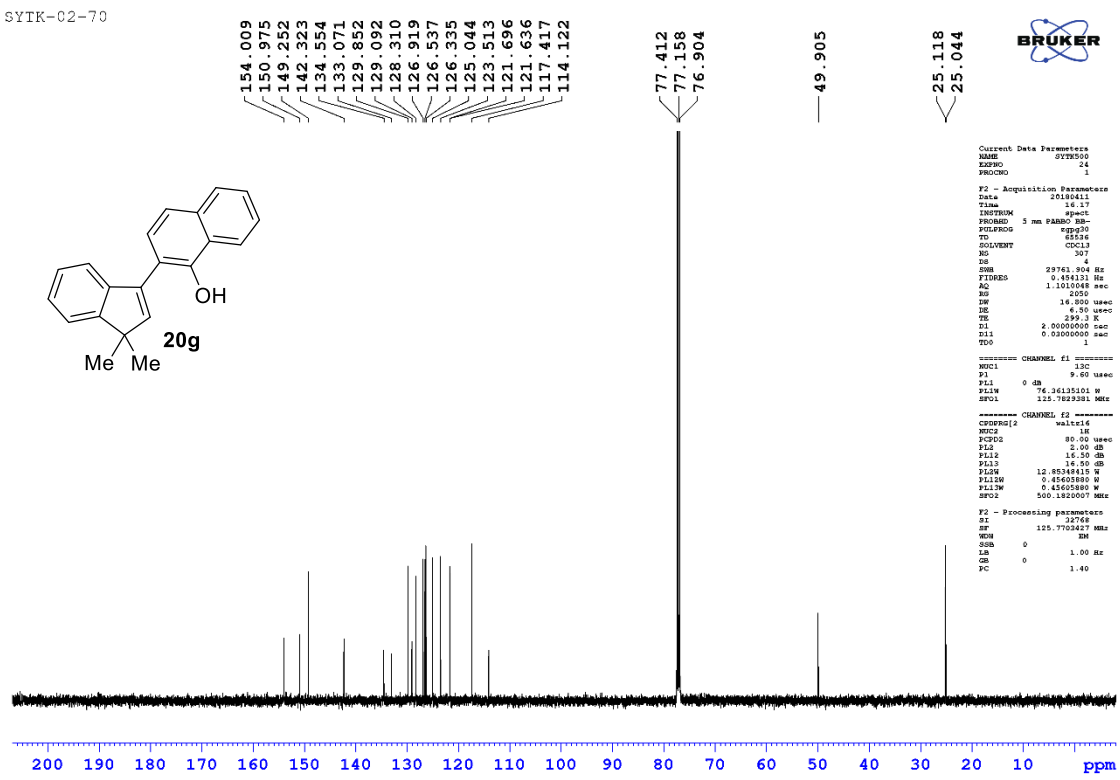


SYTK-02-67

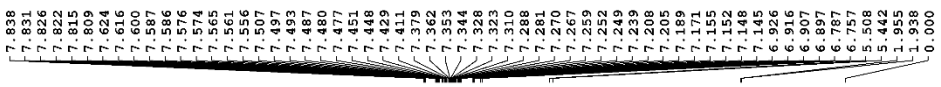


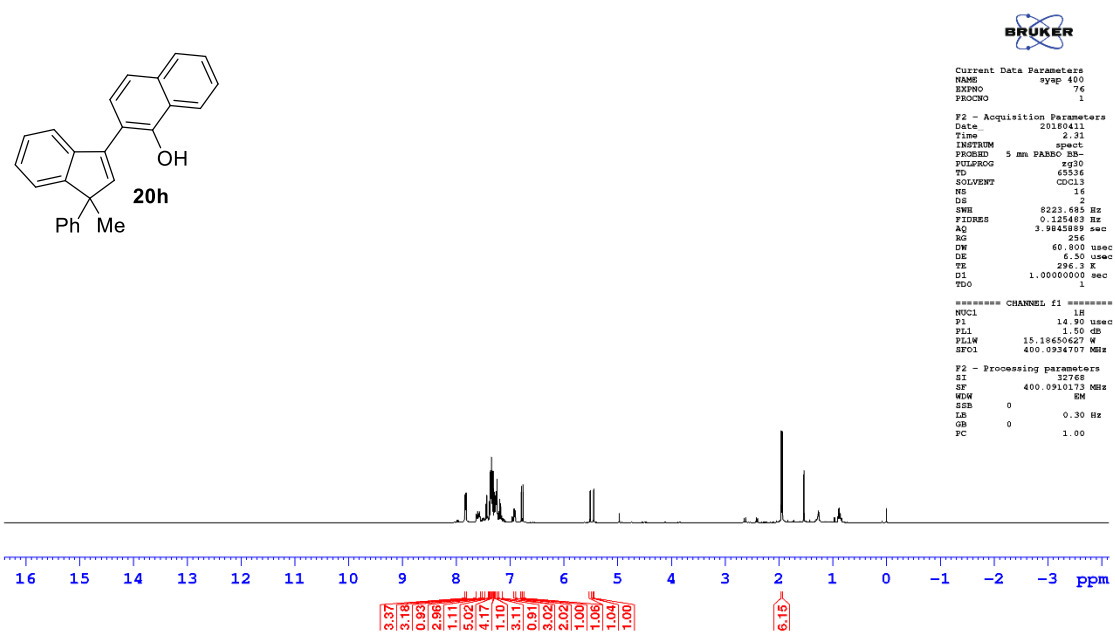
SYTK-02-70



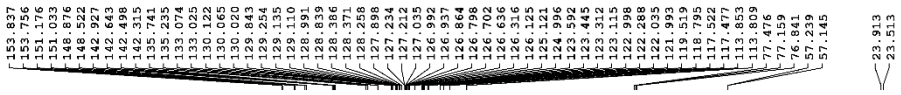

SYTK-02-70
154.009
150.975
149.252
142.323
134.554
133.071
129.852
129.092
128.310
126.919
126.537
126.335
125.044
123.513
121.696
121.636
117.417
114.122
77.412
77.158
76.904
49.905
25.118
25.044
BRUKER
OH
Me Me
20g
Current Data Parameters
NAME SYTK500
EXPNO 24
PROCNO 1
F2 - Acquisition Parameters
Date 20180411
Time 16.17
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 307
DS 4
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010048 sec
RG 2050
DW 16.800 usec
DE 6.50 usec
TE 299.3 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.60 usec
PL1 0 dB
PL1W 76.36135101 W
SFO1 125.7829381 MHz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 16.50 dB
PL13 16.50 dB
PL2W 12.85348415 W
PL12W 0.45605880 W
PL13W 0.45605880 W
SFO2 500.1820007 MHz
F2 - Processing parameters
SI 32768
SF 125.7703427 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

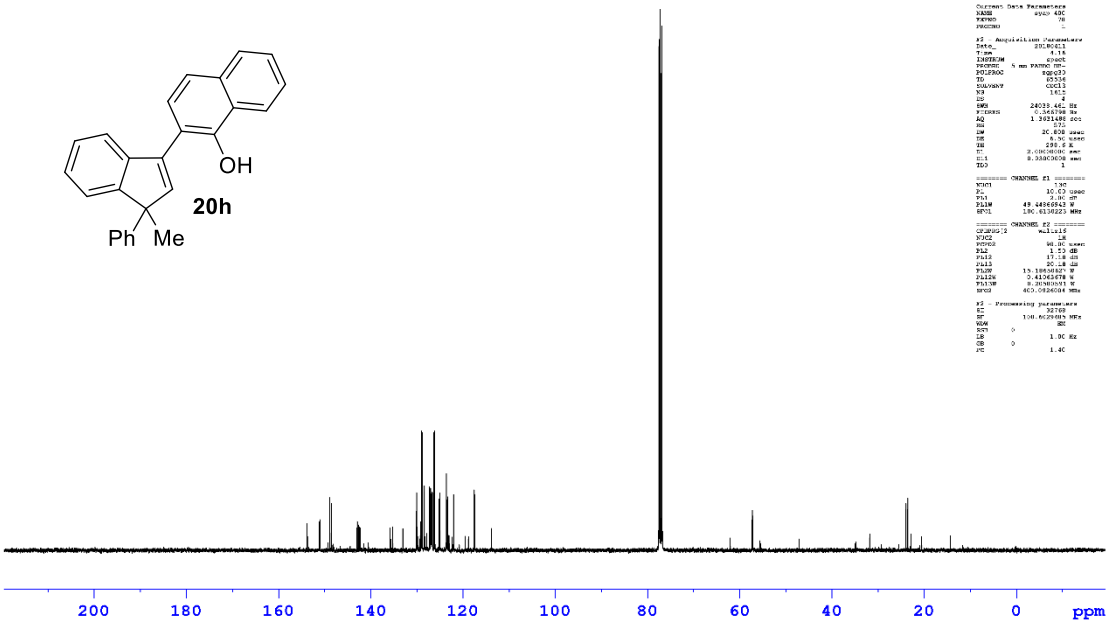
SYAP- 3- 104A1



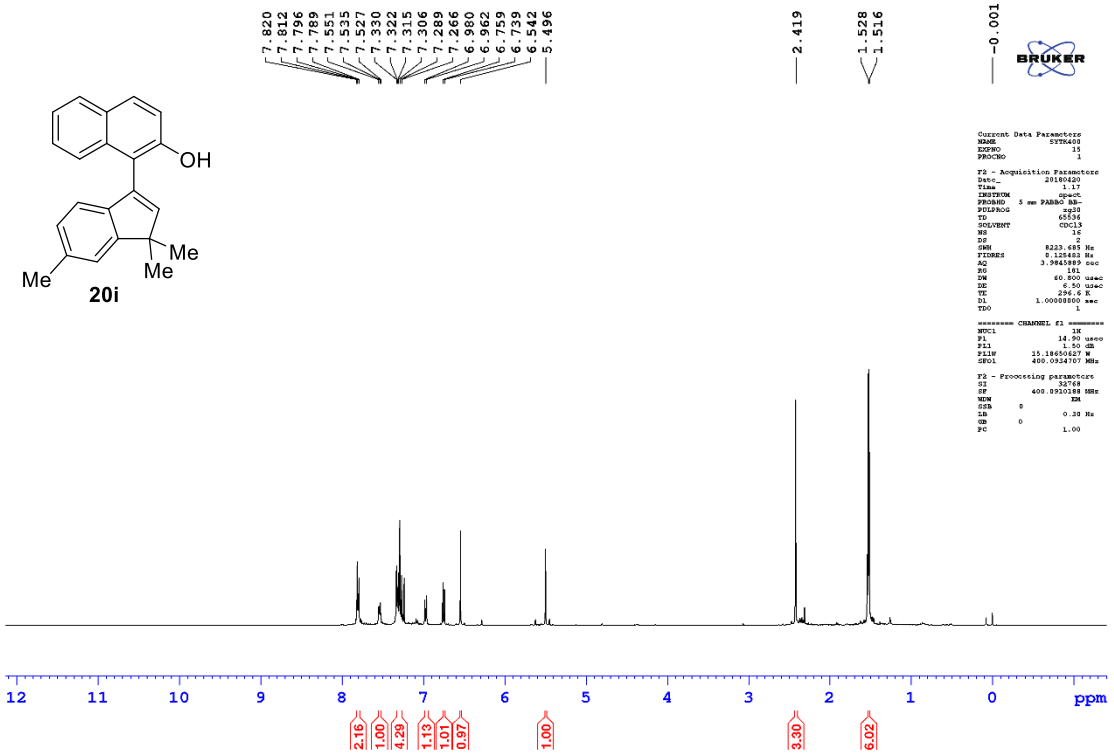


SYAP- 3- 104A1

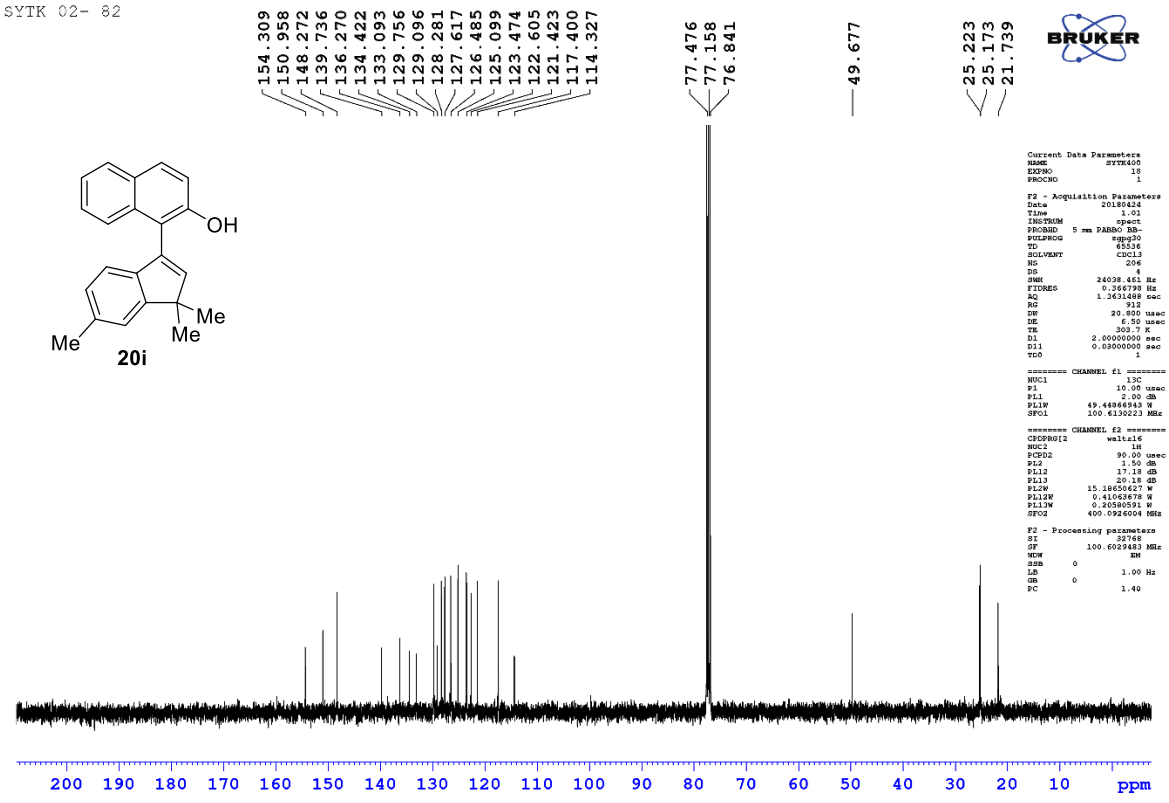




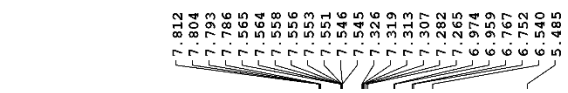
SYTK 02- 82

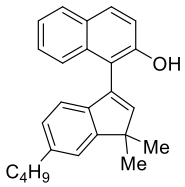


SYTK 02- 82

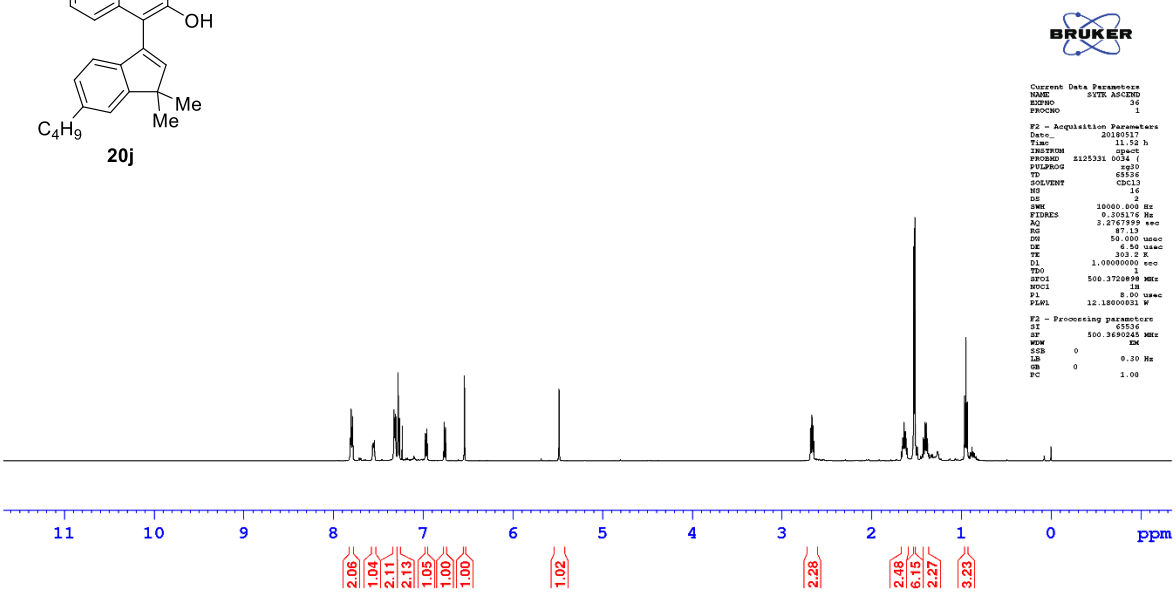


SYTK-02-99 B

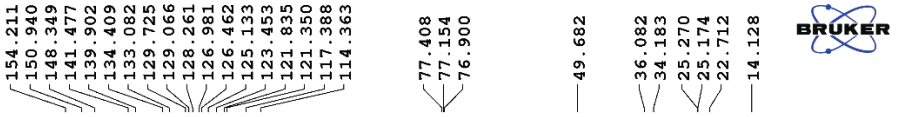


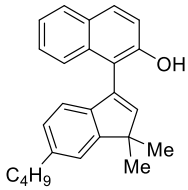


20j

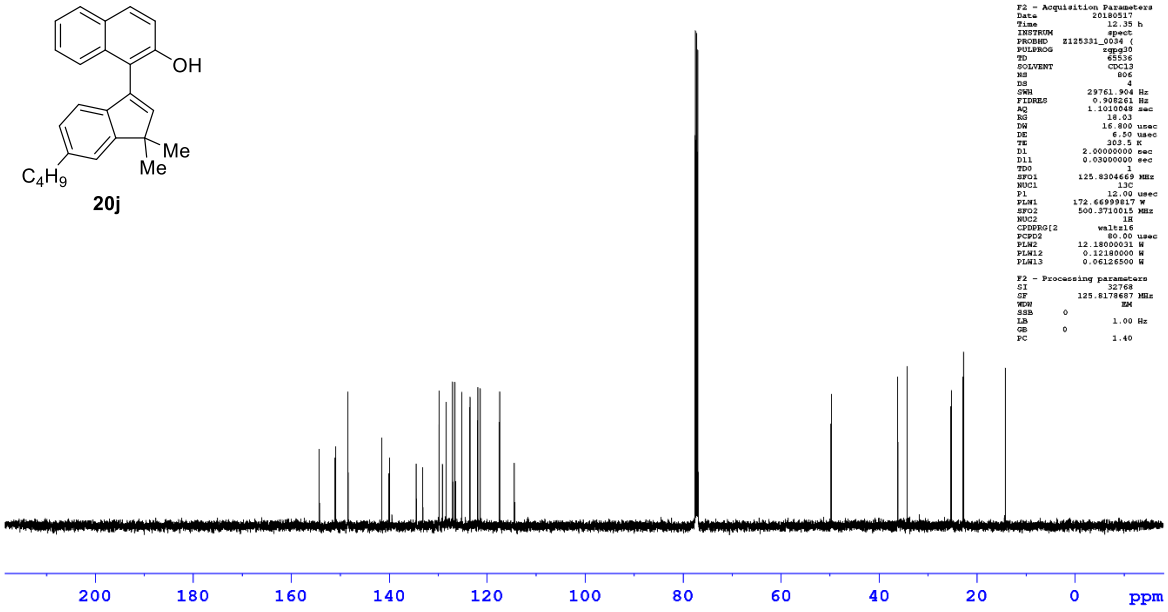


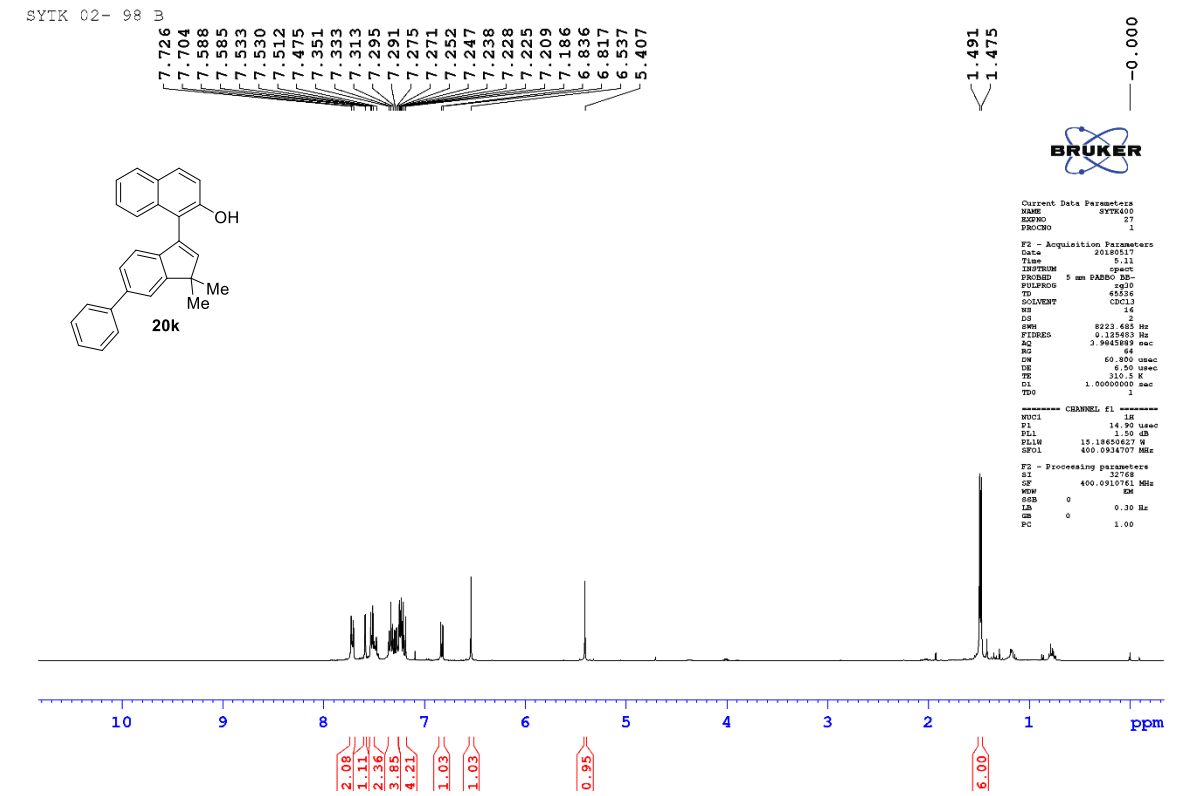
SYTK-02-99 B

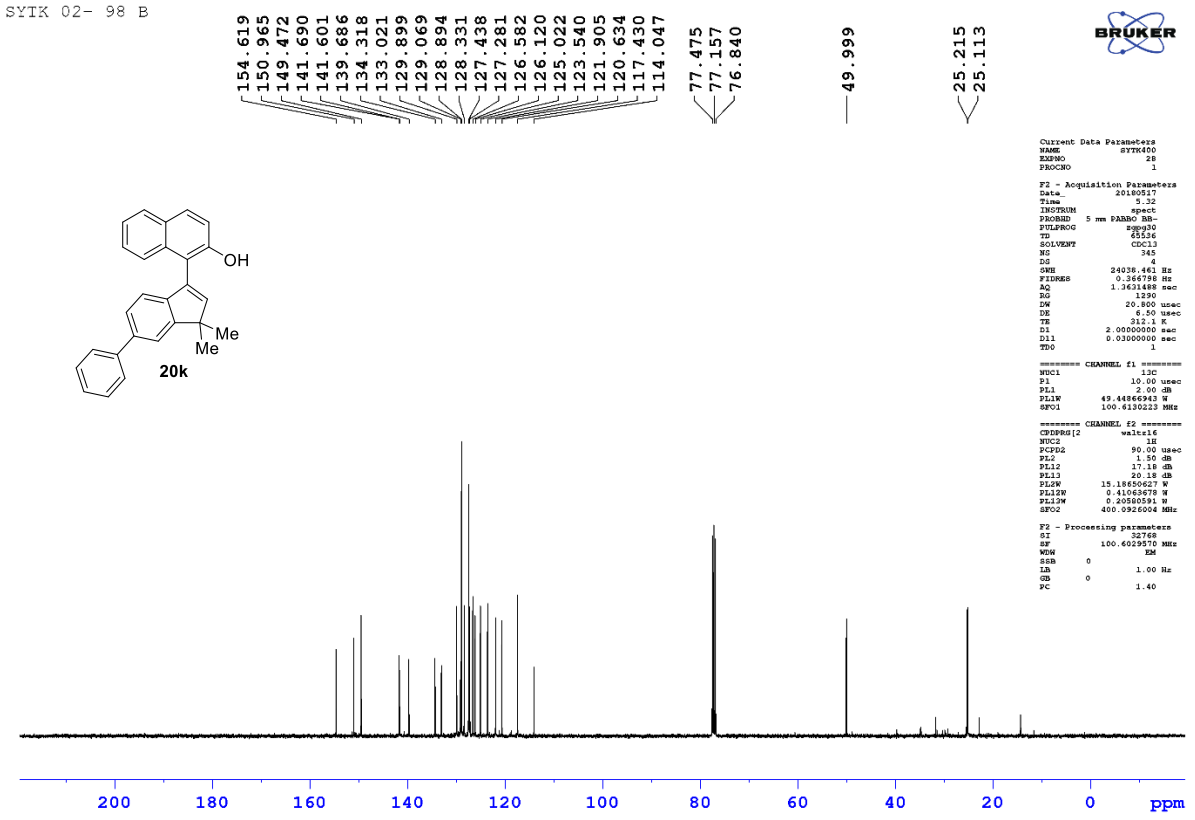




20j

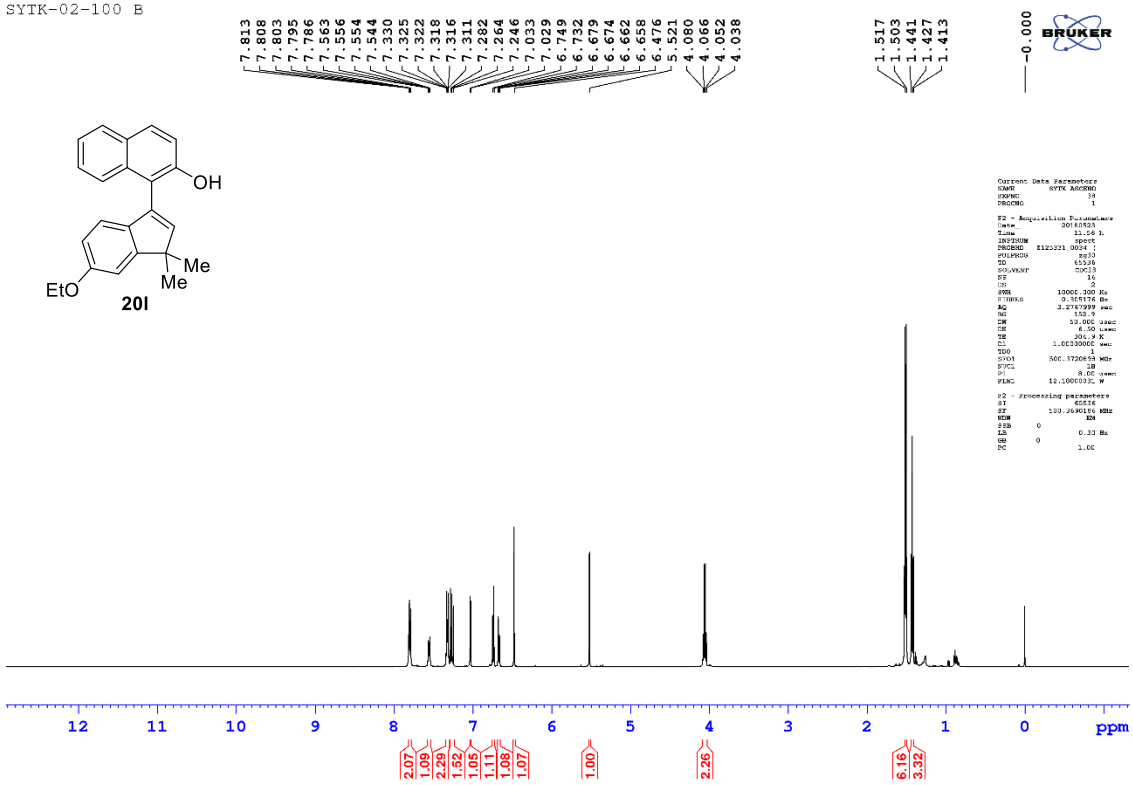



SYTK 02- 98 B
7.726
7.704
7.588
7.585
7.533
7.530
7.512
7.475
7.351
7.333
7.313
7.295
7.291
7.275
7.271
7.252
7.247
7.238
7.228
7.225
7.209
7.186
6.836
6.817
6.537
5.407
1.491
1.475
0.000
BRUKER
OH
Me
Me
20k
Current Data Parameters
NAME SYTK400
EXPNO 27
PROCNO 1
F2 - Acquisition Parameters
Date 20180517
Time 5.11
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg10
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 8223.685 Hz
FIDRES 0.125483 Hz
AQ 3.9845889 sec
RG 64
DW 60.800 usec
DE 6.50 usec
TE 310.5 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.90 usec
PL1 1.50 dB
PL1W 15.18650627 W
SFO1 400.0934707 MHz
F2 - Processing parameters
SI 32768
SF 400.0910761 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
10
9
8
7
6
5
4
3
2
1
ppm
2.08
1.11
2.36
3.85
4.21
1.03
1.03
0.95
6.00


SYTK 02- 98 B
154.619
150.965
149.472
141.690
141.601
139.686
134.318
133.021
129.899
129.069
128.894
128.331
127.438
127.281
126.582
126.120
125.022
123.540
121.905
120.634
117.430
114.047
77.475
77.157
76.840
49.999
25.215
25.113
BRUKER
OH
Me
Me
20k
Current Data Parameters
NAME SYTK400
EXPNO 28
PROCNO 1
F2 - Acquisition Parameters
Date 20180517
Time 5.32
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 345
DS 4
SWH 24038.461 Hz
FIDRES 0.366798 Hz
AQ 1.3631488 sec
RG 1290
DW 20.800 usec
DE 6.50 usec
TE 312.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 10.00 usec
PL1 2.00 dB
PL1W 49.44866943 W
SFO1 100.6130223 MHz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 90.00 usec
PL2 1.50 dB
PL12 17.18 dB
PL13 20.18 dB
PL2W 15.18650627 W
PL12W 0.41063678 W
PL13W 0.20560591 W
SFO2 400.0926004 MHz
F2 - Processing parameters
SI 32768
SF 100.6029570 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
200
180
160
140
120
100
80
60
40
20
0
ppm

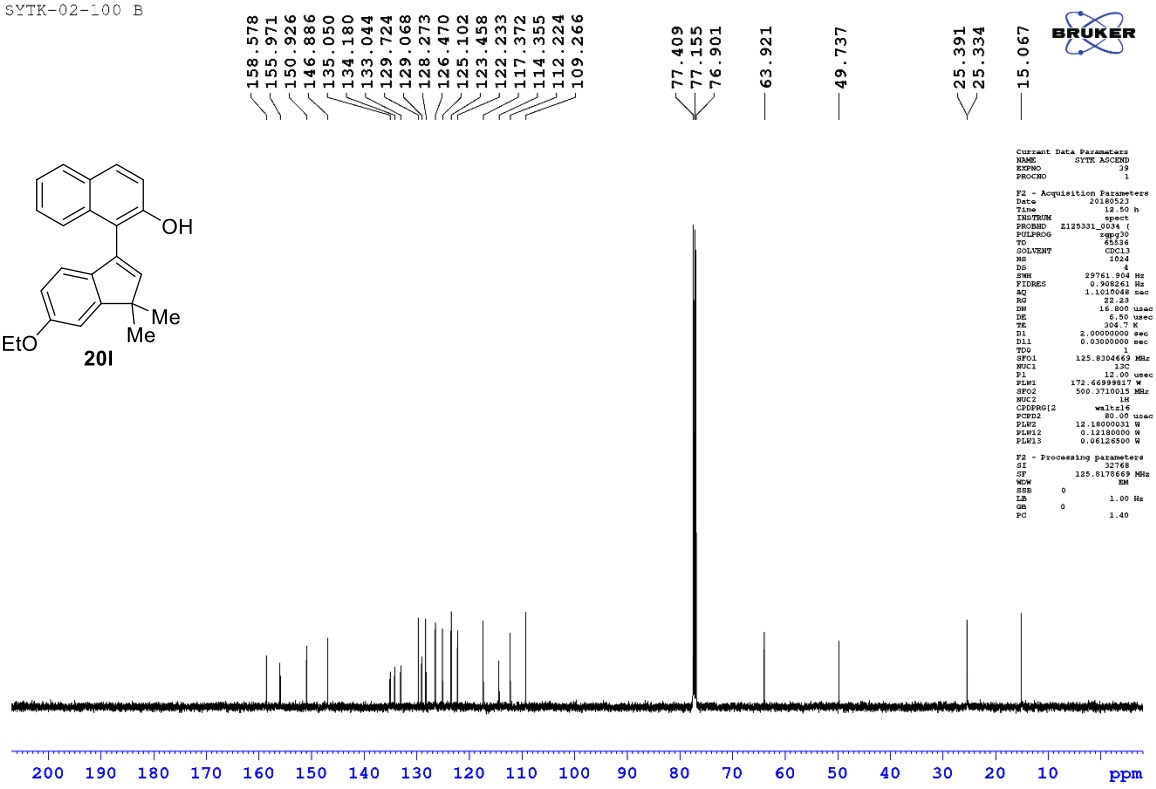
SYTK-02-100 B

20l

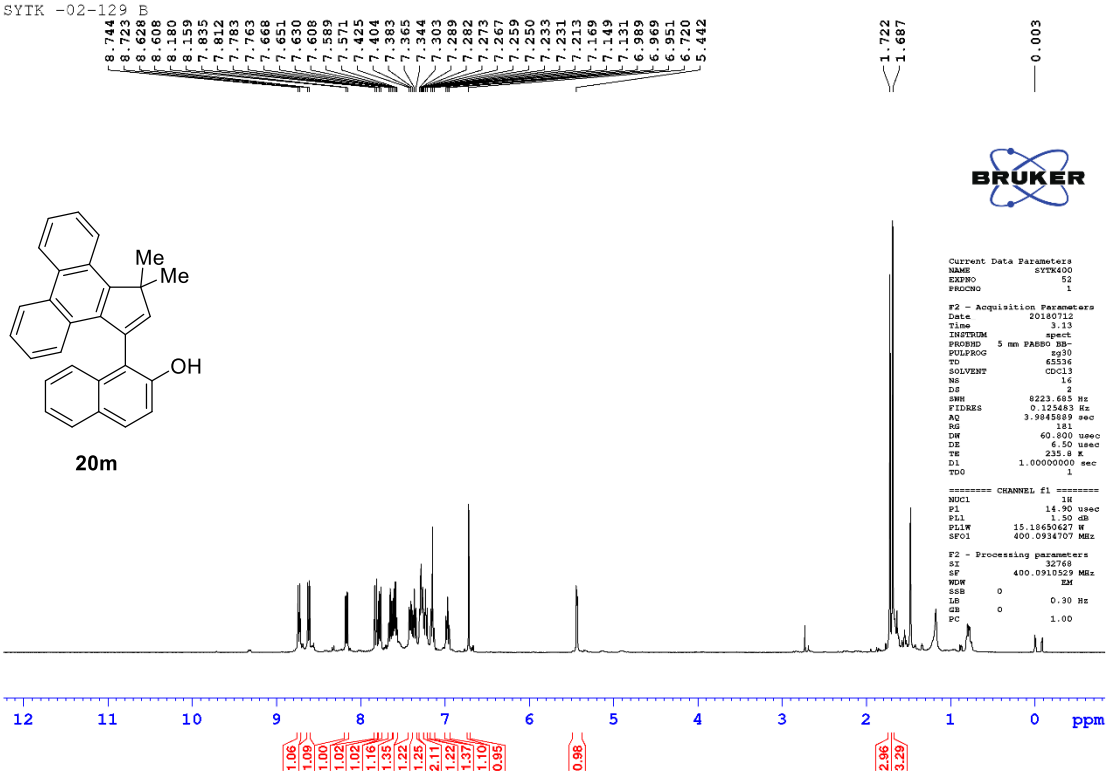


SYTK-02-100 B

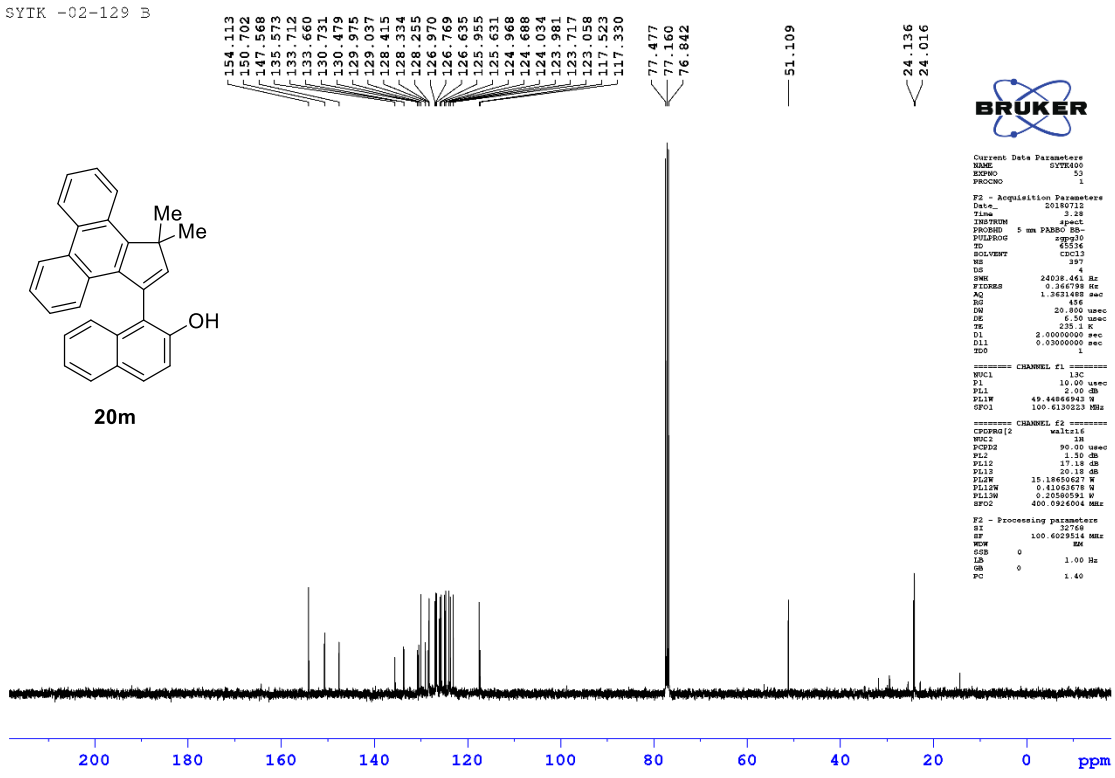
20l



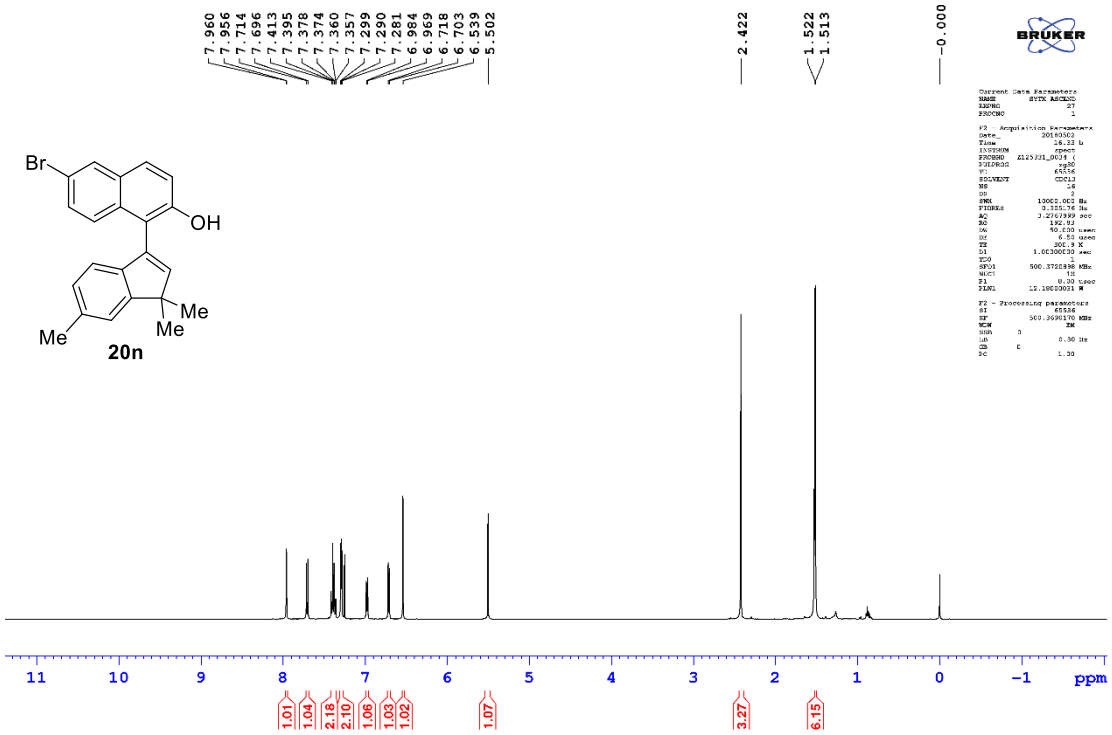
SYTK -02-129 B



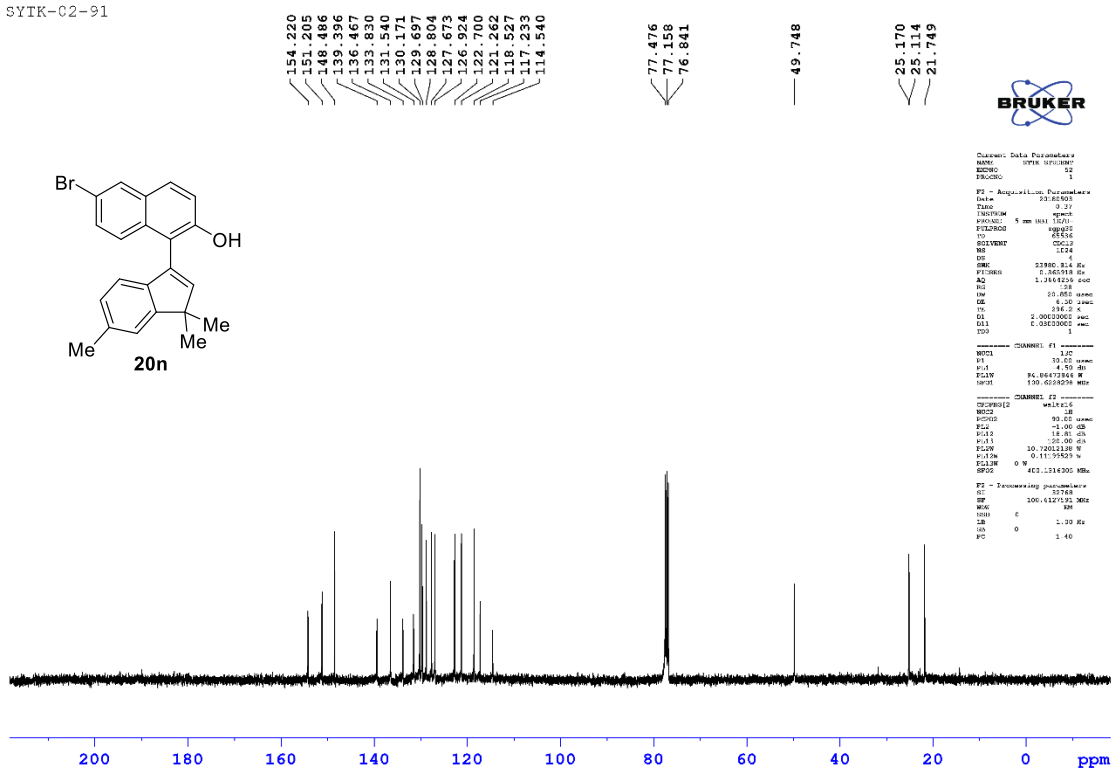
SYTK -02-129 B

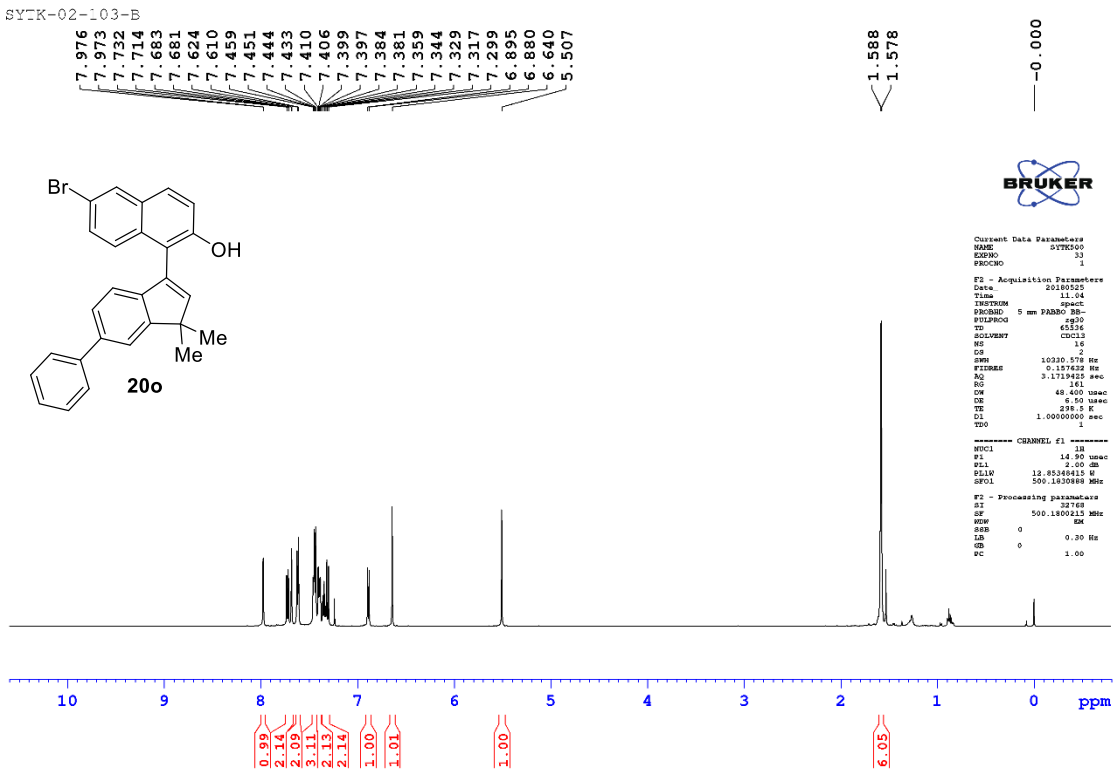


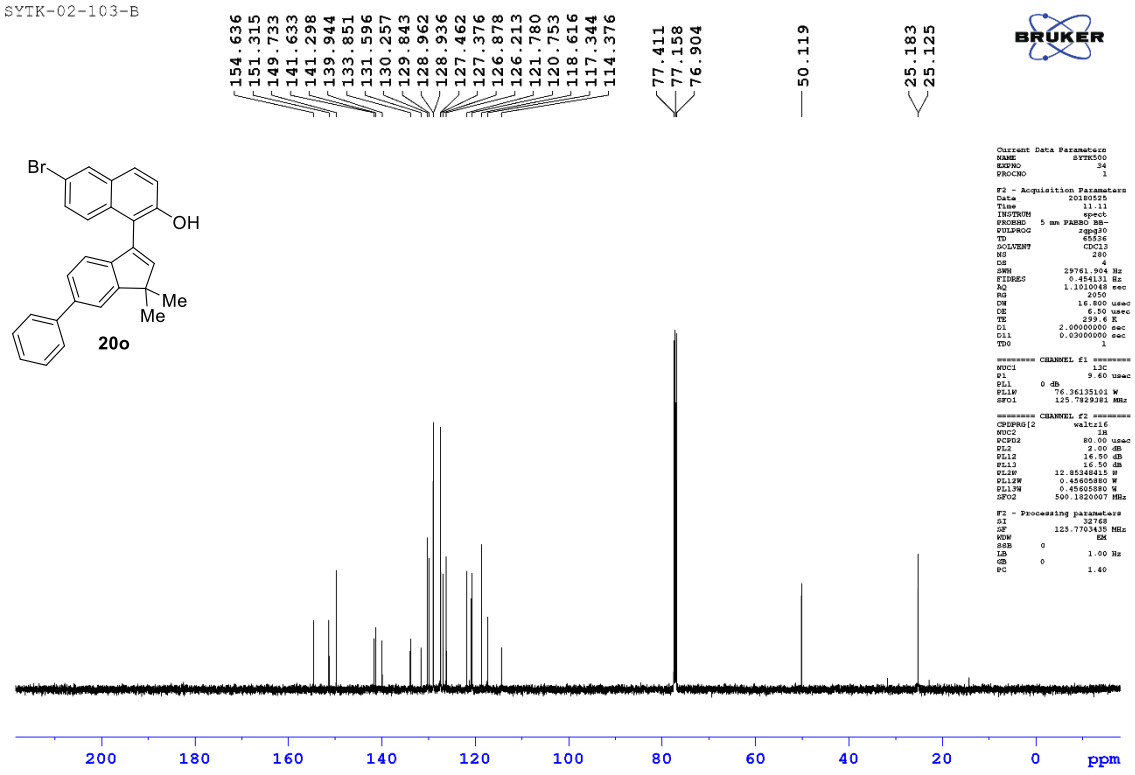
SYTK-02-91



SYTK-02-91

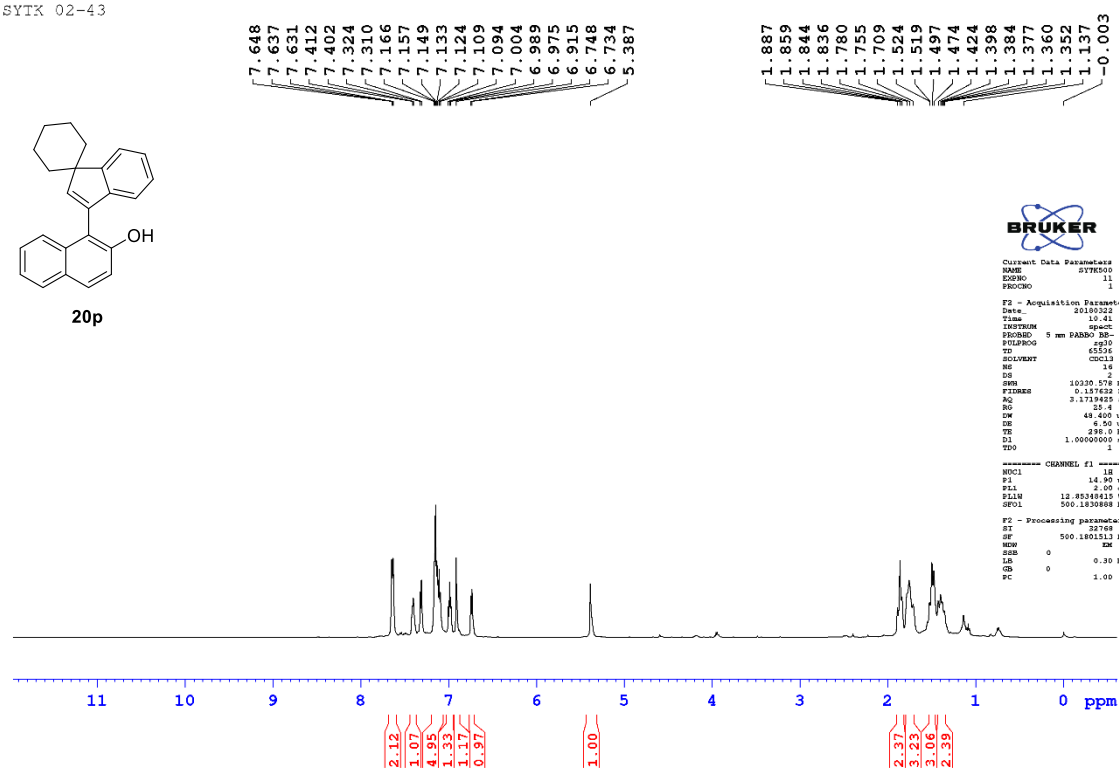



SYTK-02-103-B
7.976
7.973
7.732
7.714
7.683
7.681
7.624
7.610
7.459
7.451
7.444
7.433
7.410
7.406
7.399
7.397
7.384
7.381
7.359
7.344
7.329
7.317
7.299
6.895
6.880
6.640
5.507
1.588
1.578
0.000
Br
OH
Me
Me
20o
BRUKER
Current Data Parameters
NAME 5YTK500
EXPNO 33
PROCNO 1
F2 - Acquisition Parameters
Date 20180525
Time 11.04
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 161
DW 48.400 usec
DE 6.50 usec
TE 298.5 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.90 usec
PL1 2.00 dB
PL1W 13.85346415 W
SFO1 500.1830888 MHz
F2 - Processing parameters
SI 32768
SF 500.1800213 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
10
9
8
7
6
5
4
3
2
1
0
ppm
0.99
2.14
2.09
3.11
2.13
2.14
1.00
1.01
1.00
6.05


SYTK-02-103-B
154.636
151.315
149.733
141.633
141.298
139.944
133.851
131.596
130.257
129.843
128.962
128.936
127.462
127.376
126.878
126.213
121.780
120.753
118.616
117.344
114.376
77.411
77.158
76.904
50.119
25.183
25.125
Br
OH
Me
Me
20o
BRUKER
Current Data Parameters
NAME 5YTK500
EXPNO 34
PROCNO 1
F2 - Acquisition Parameters
Date 20180525
Time 11.11
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 260
DS 4
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010048 sec
RG 2050
DW 16.800 usec
DE 6.50 usec
TE 299.6 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.60 usec
PL1 0 dB
PL1W 76.36135101 W
SFO1 125.7829381 MHz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 16.50 dB
PL13 16.50 dB
PL2W 13.85346415 W
PL12W 0.45605880 W
PL13W 0.45605880 W
SFO2 500.1820007 MHz
F2 - Processing parameters
SI 32768
SF 125.7703435 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
200
180
160
140
120
100
80
60
40
20
0
ppm

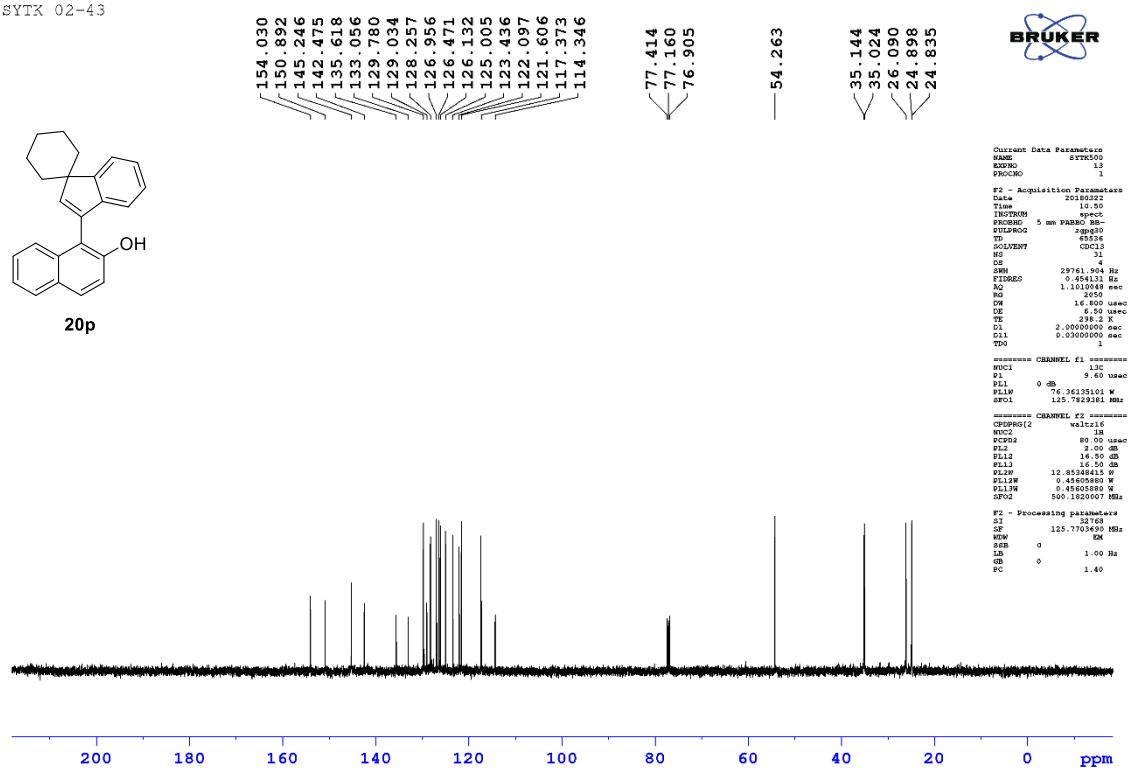
SYTK 02-43

20p



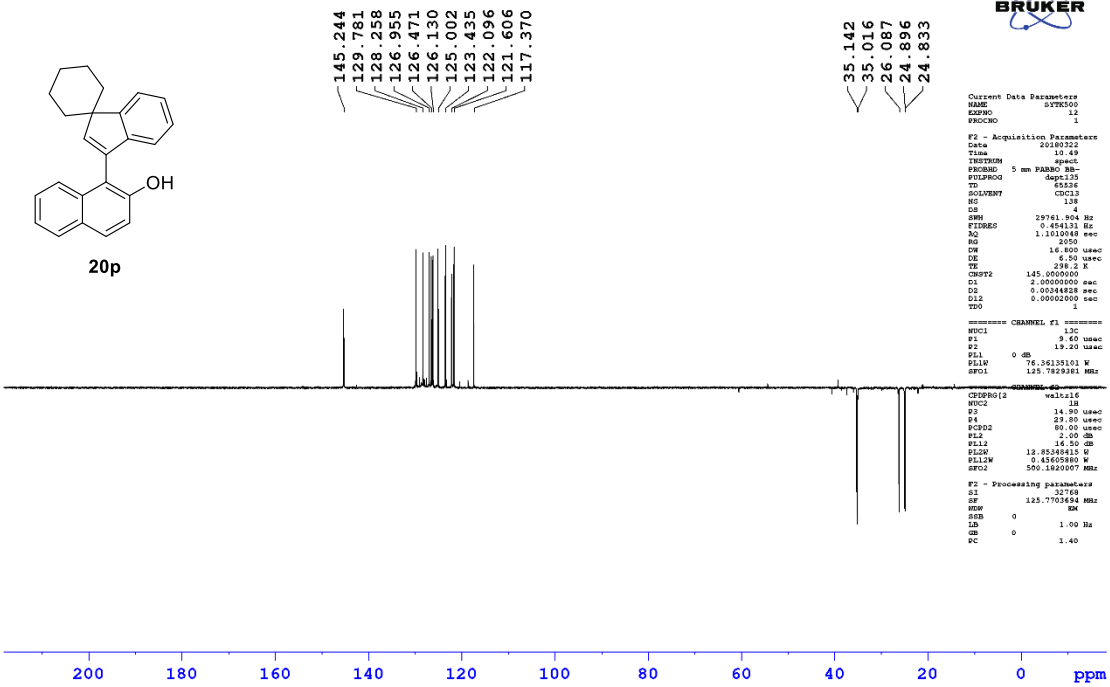
SYTK 02-43

20p



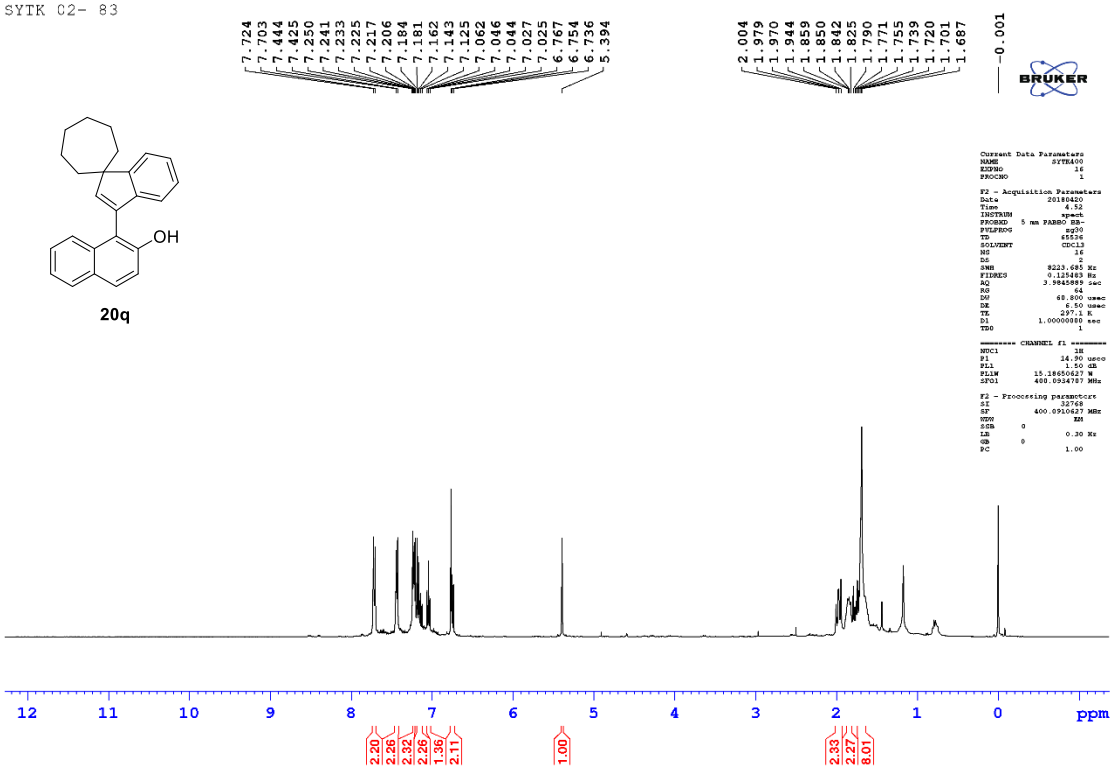
SYTK 02-43

20p

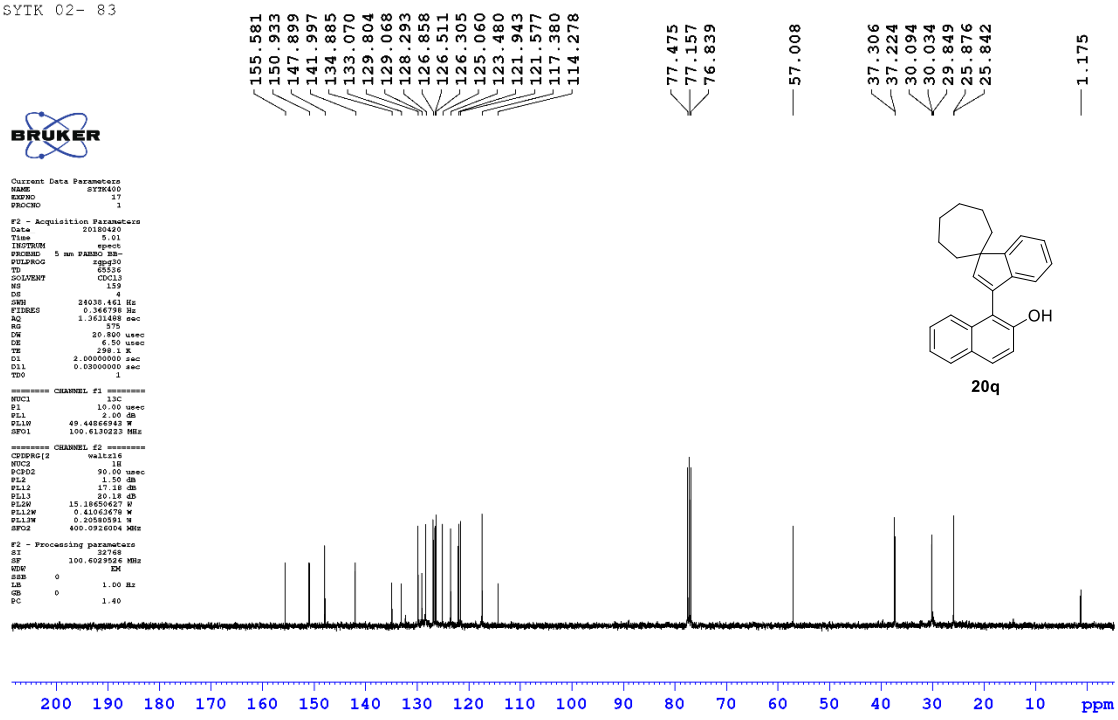


SYTK 02- 83

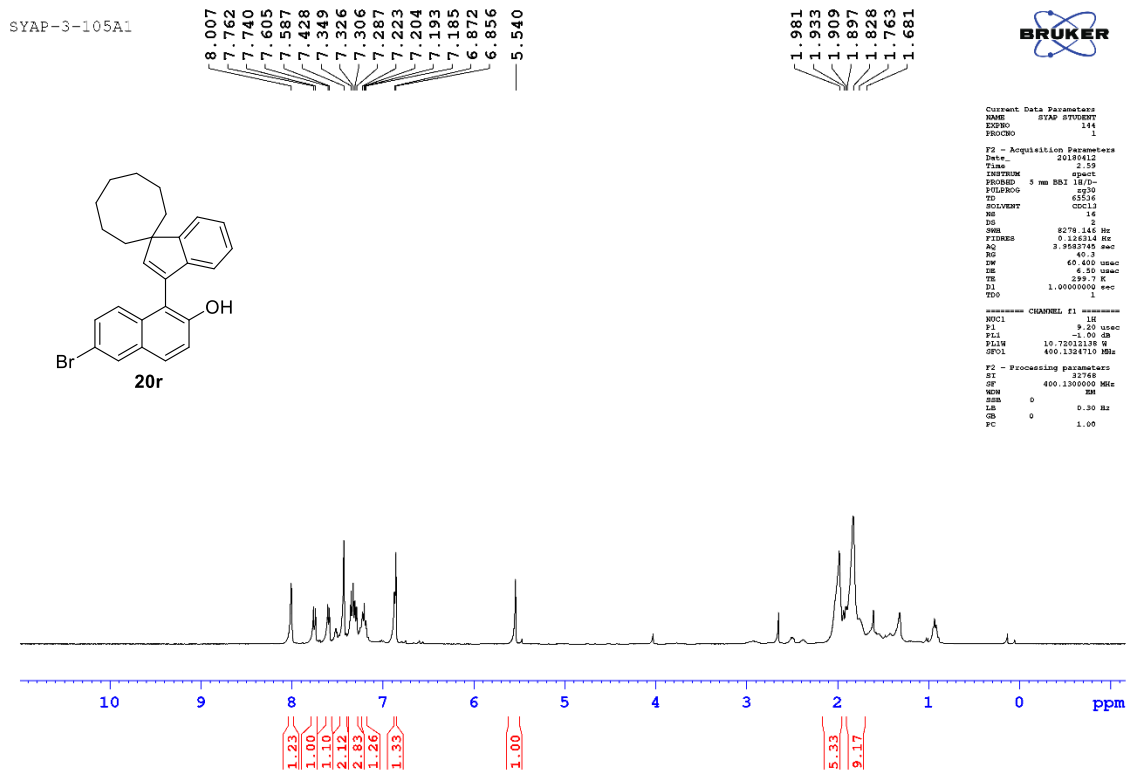
20q



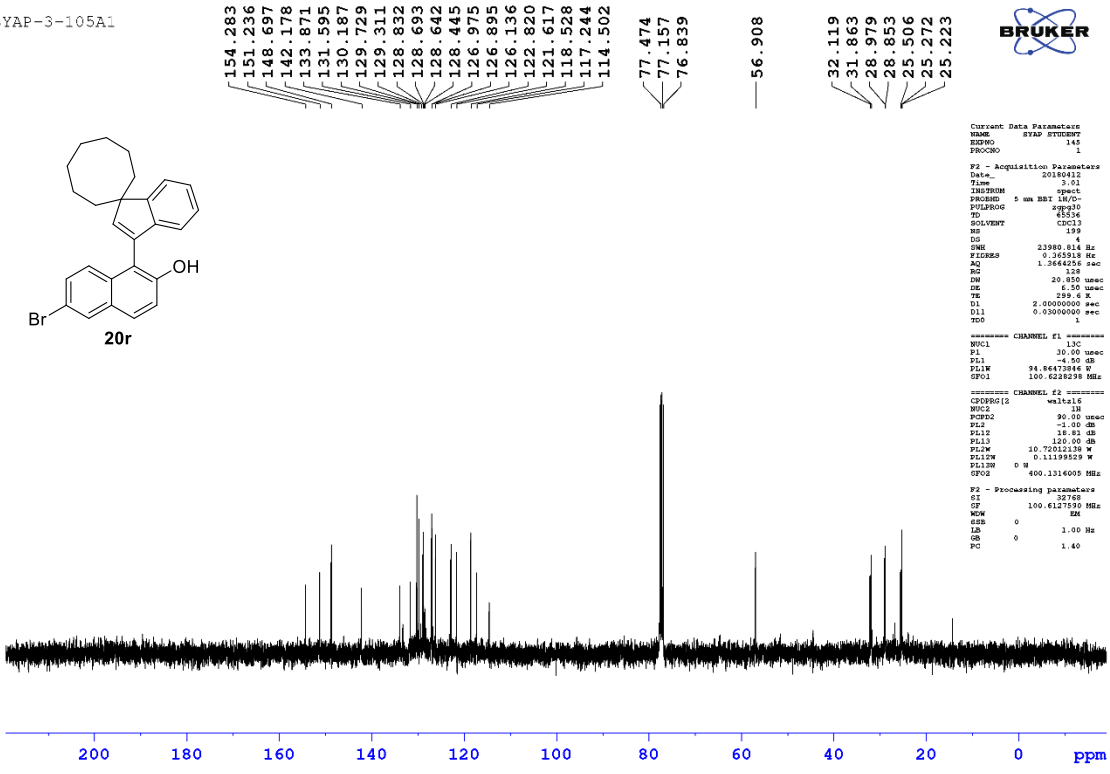
SYTK 02- 83



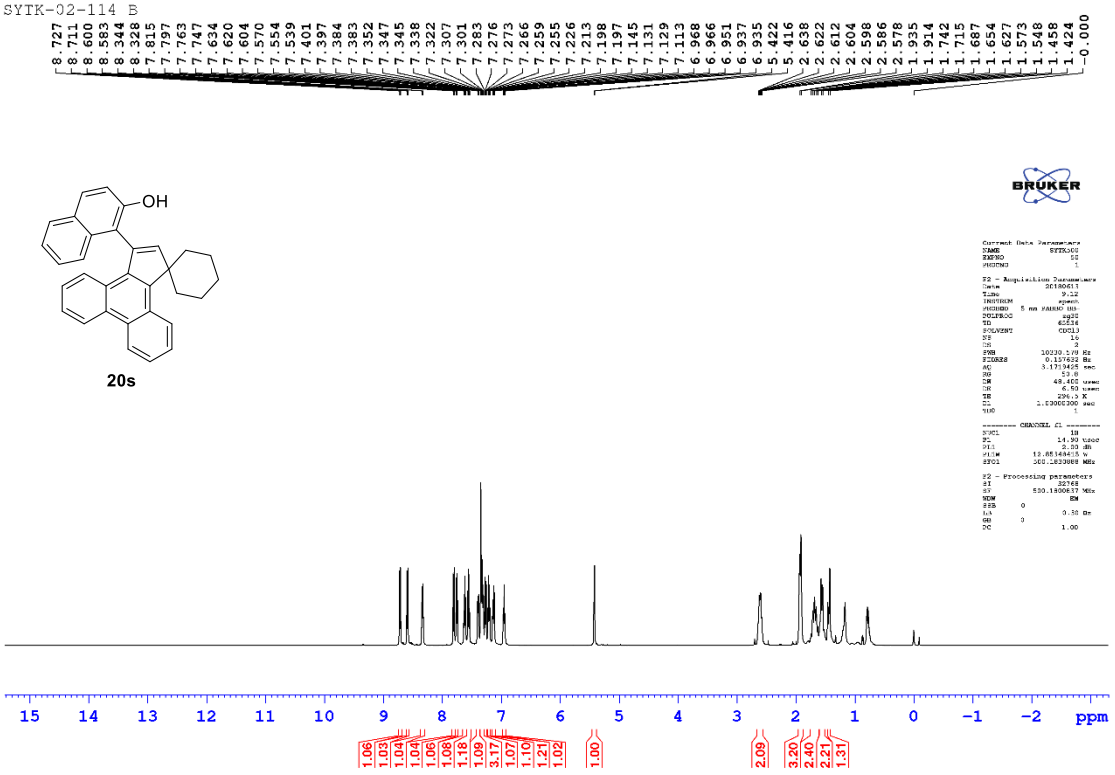
SYAP-3-105A1



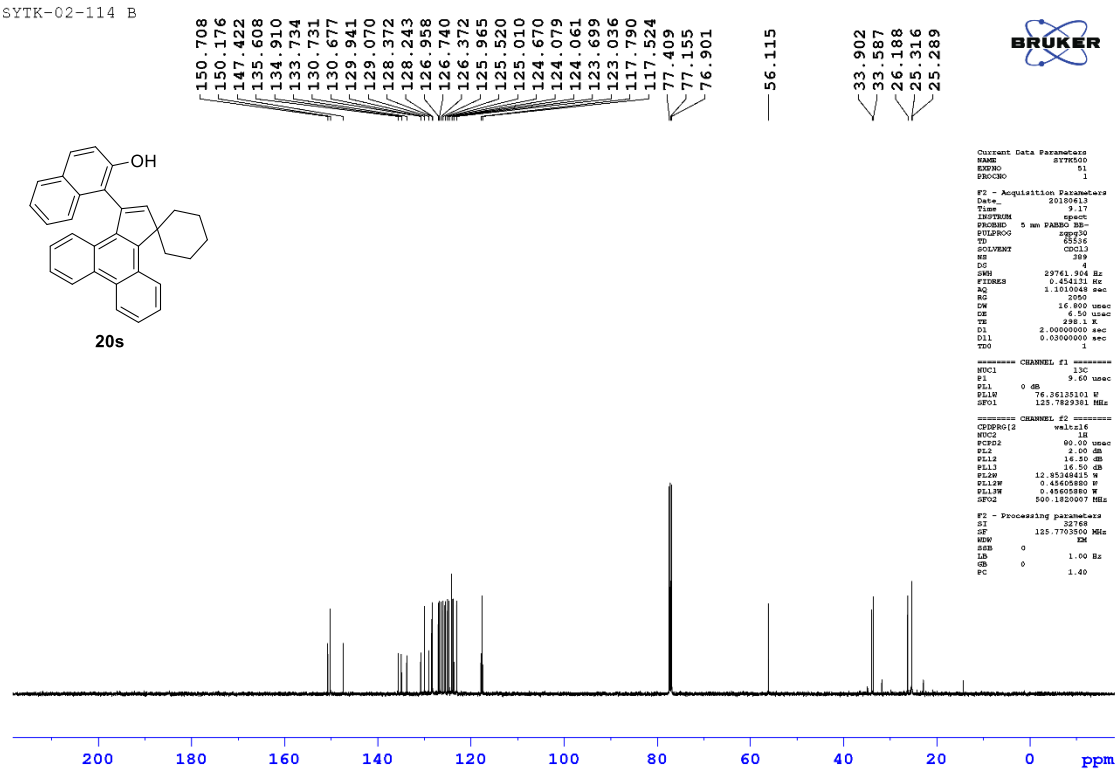
SYAP-3-105A1



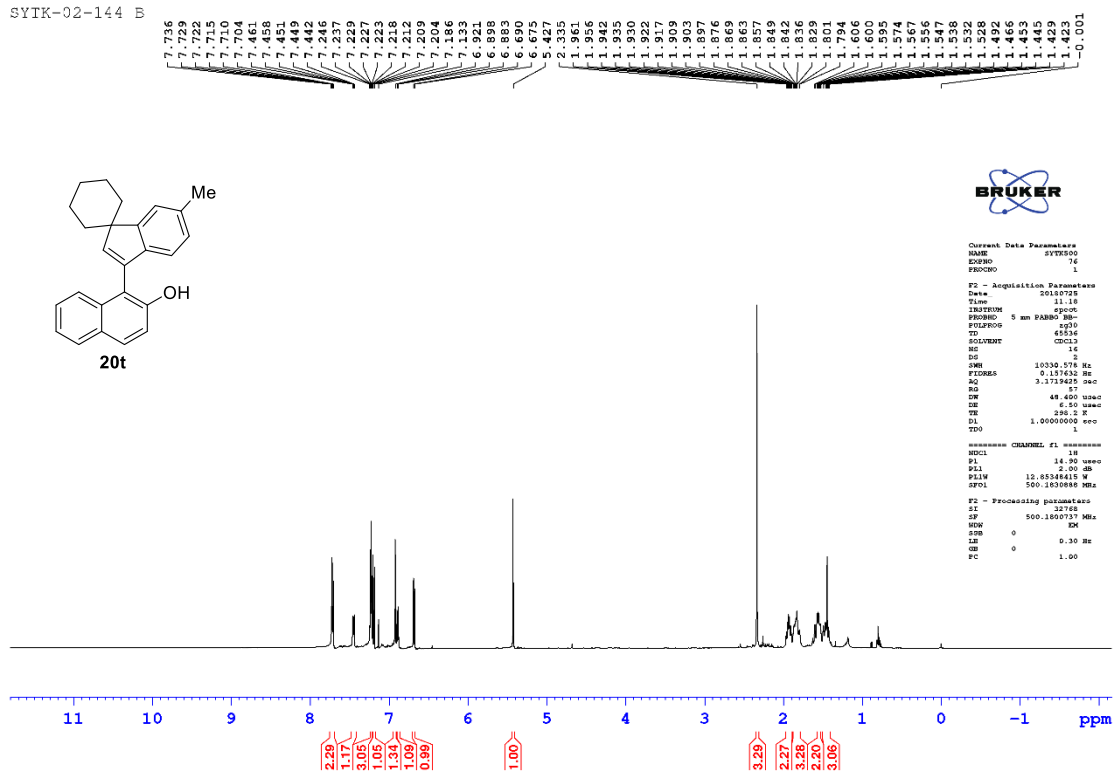
SYTK-02-114 B



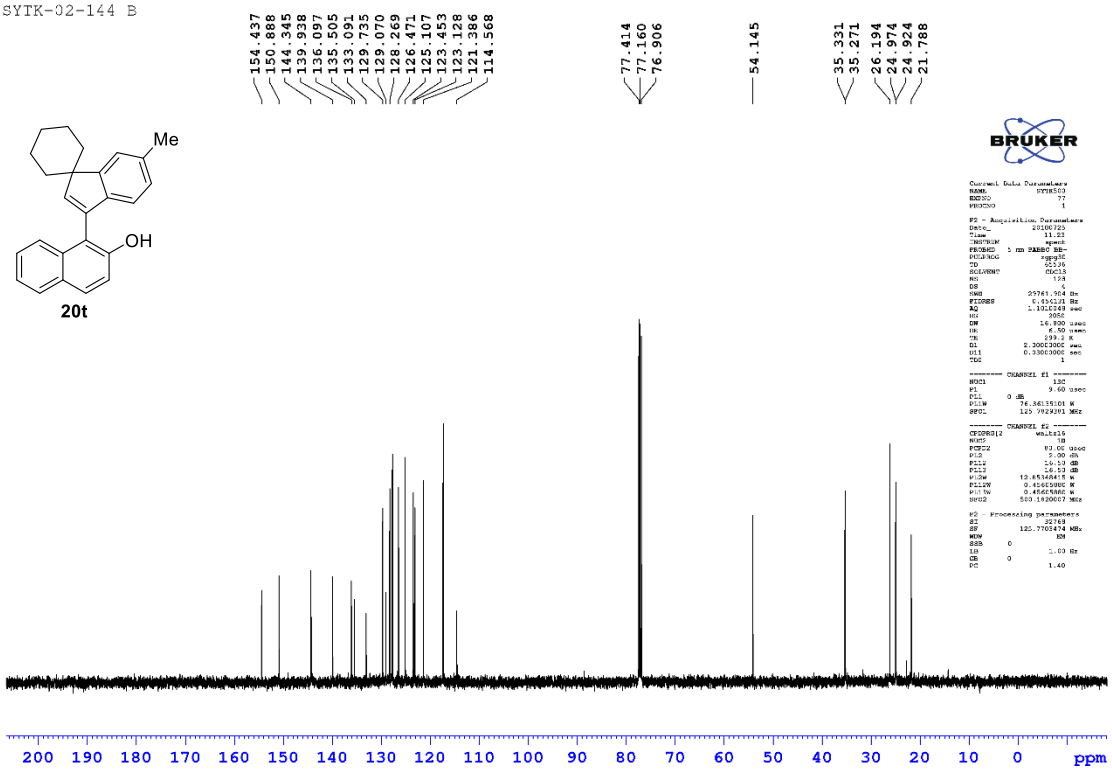
SYTK-02-114 B



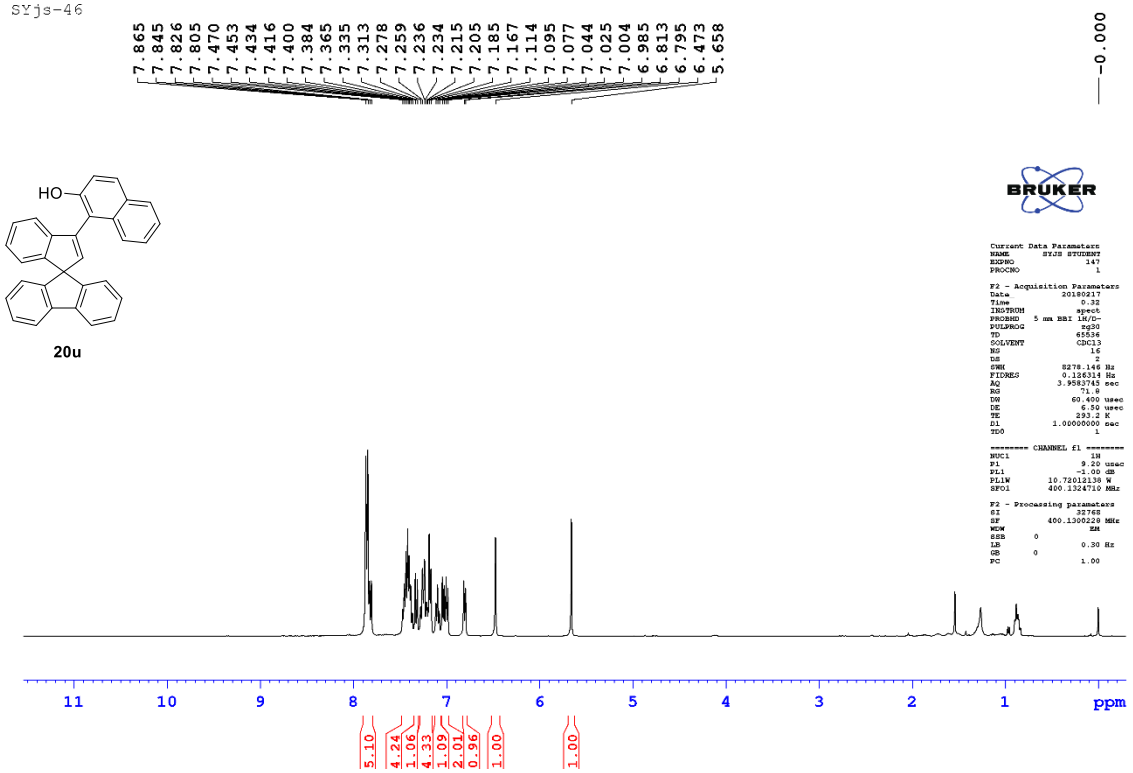
SYTK-02-144 B



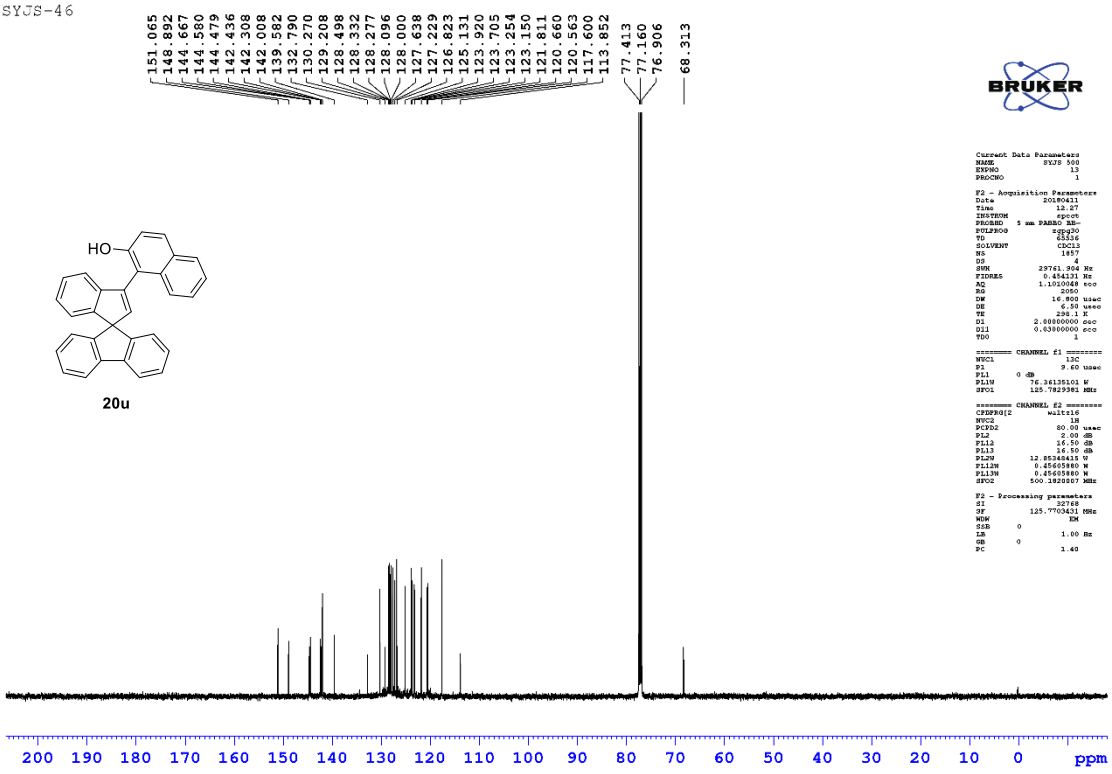
SYIK-02-144 B



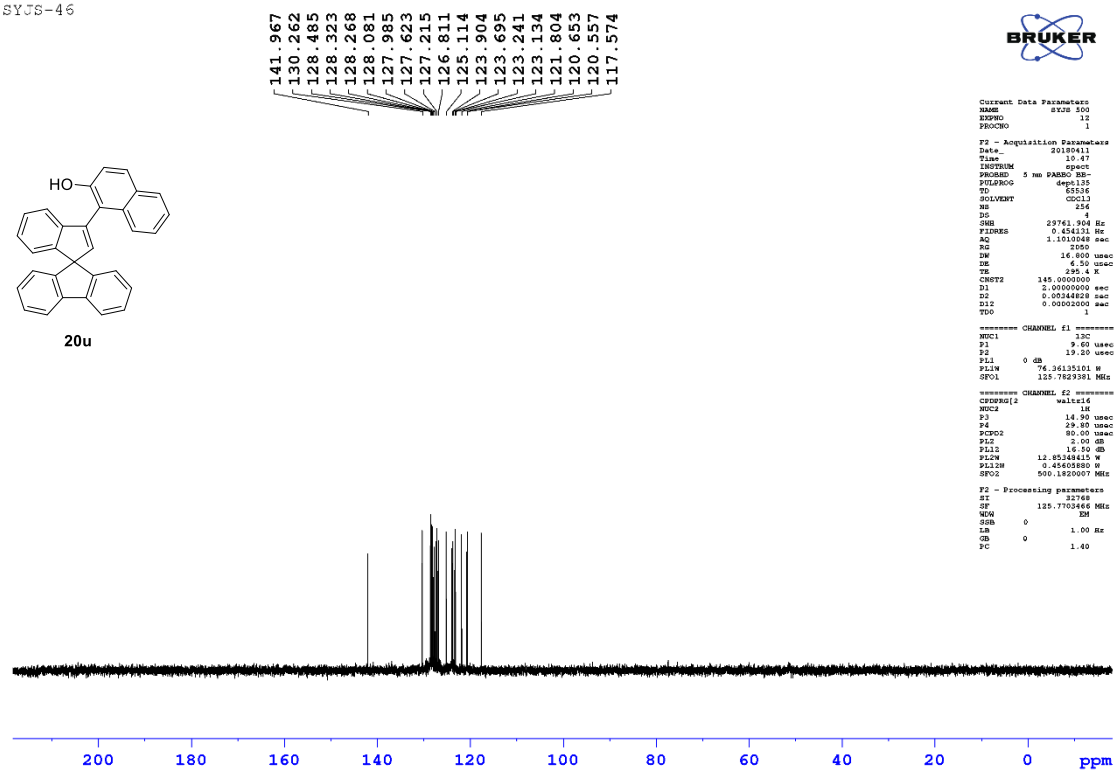
SYjs-46



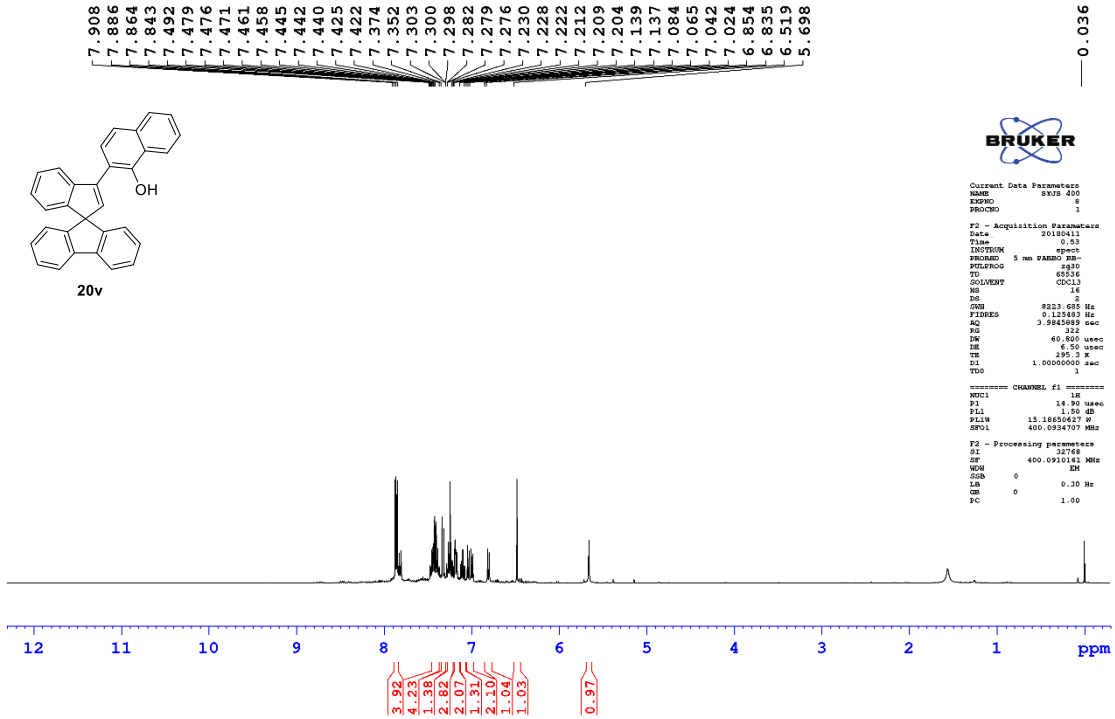
SYJS-46



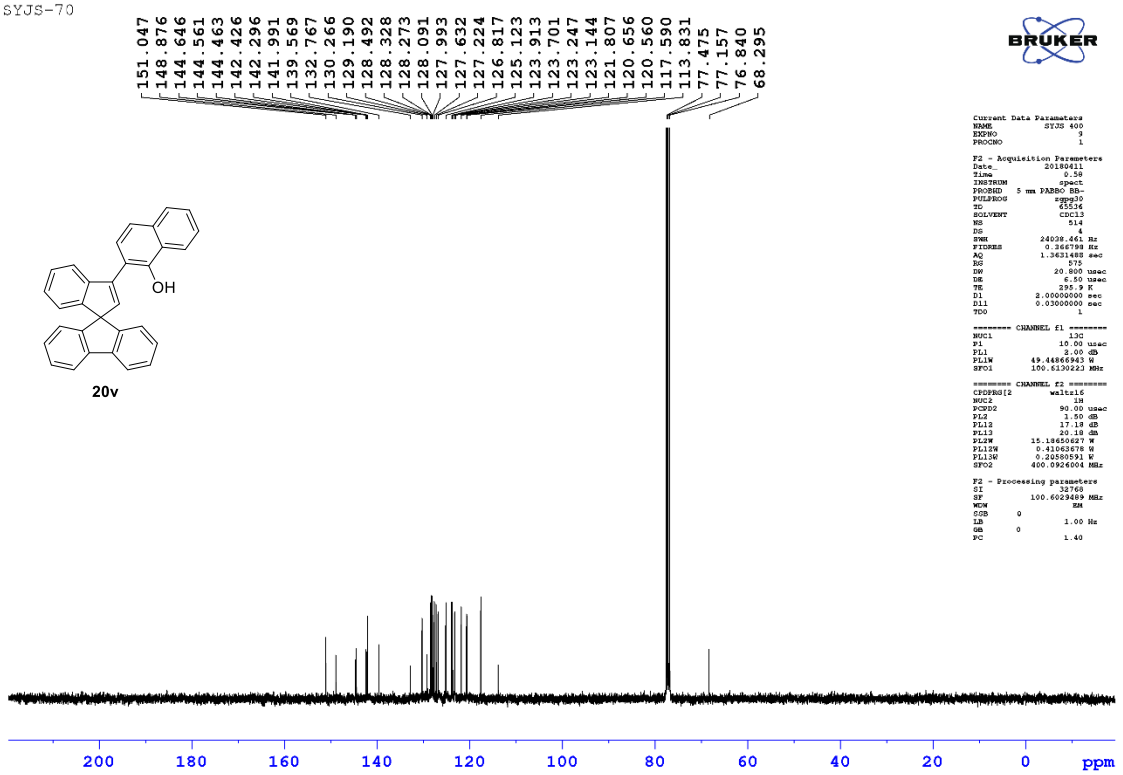
SYJS-46

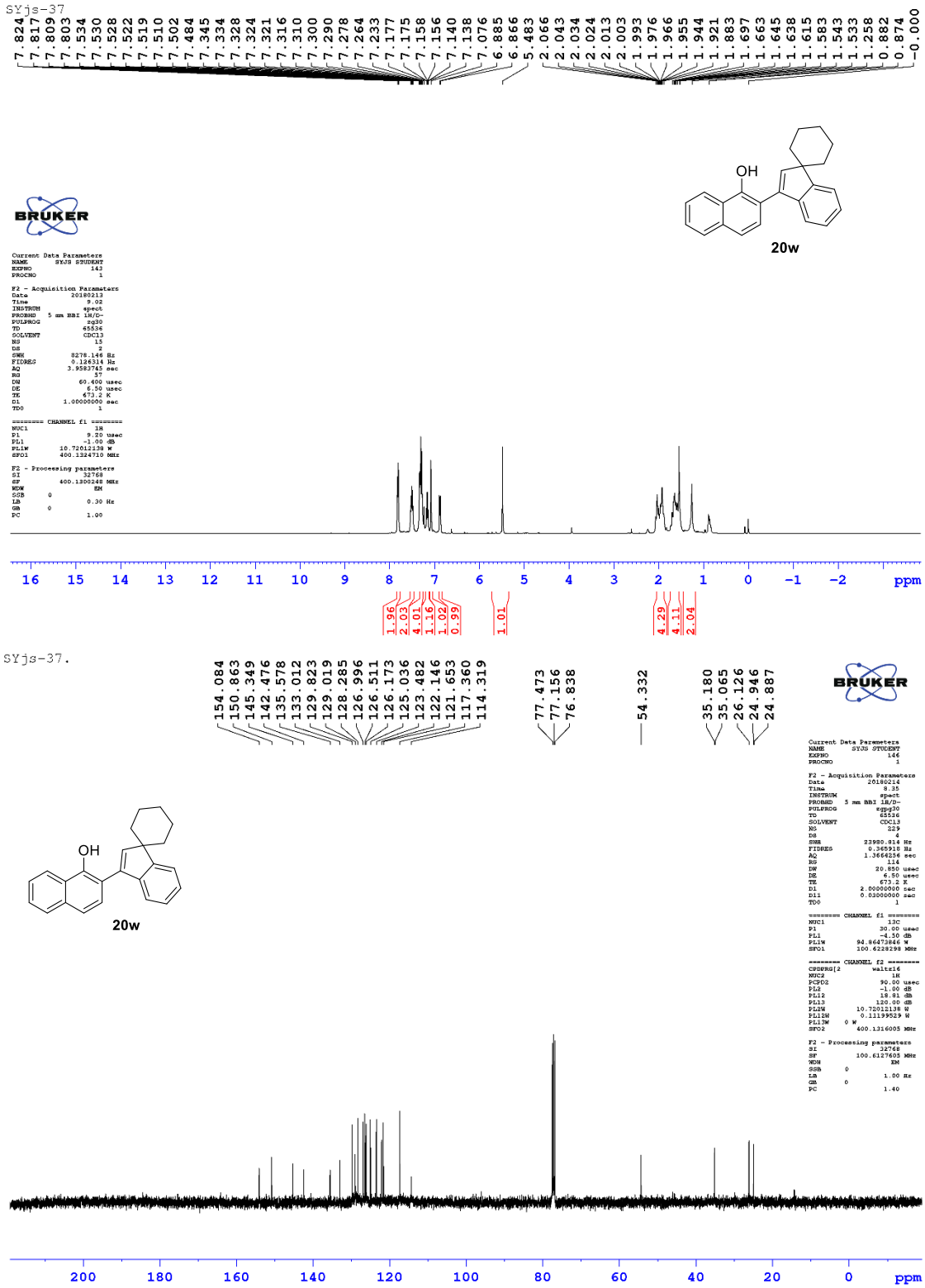


SYJS-70

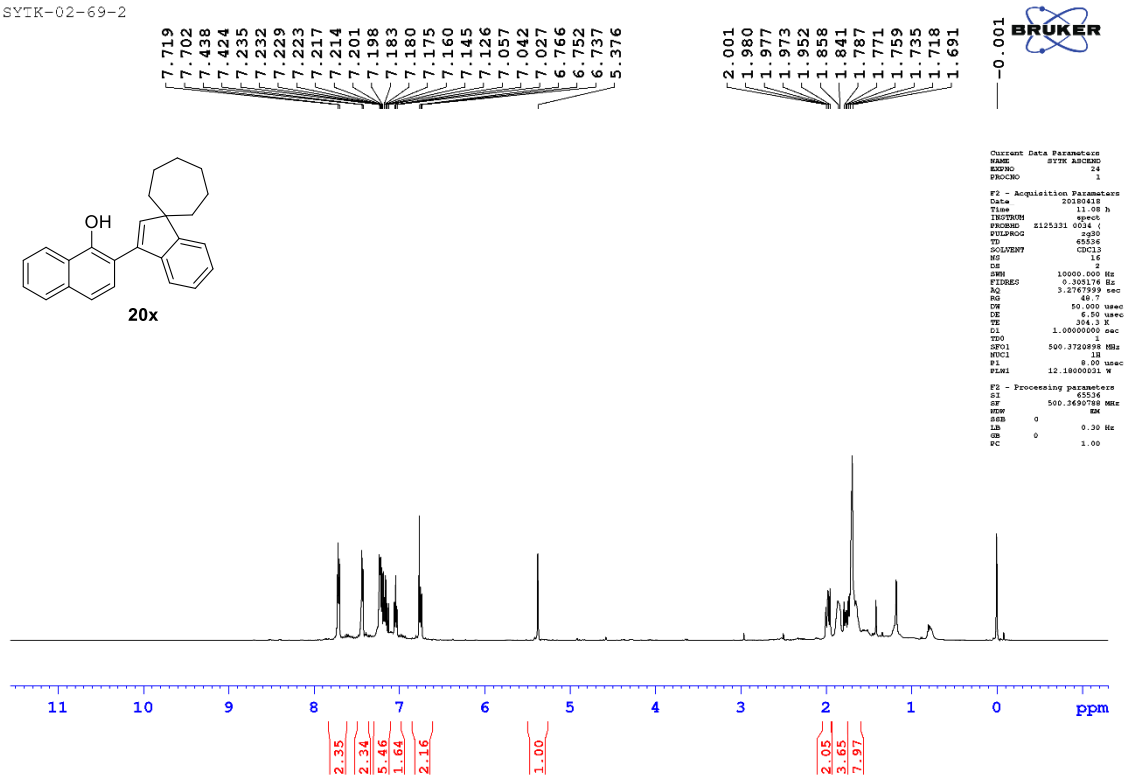


SYJS-70

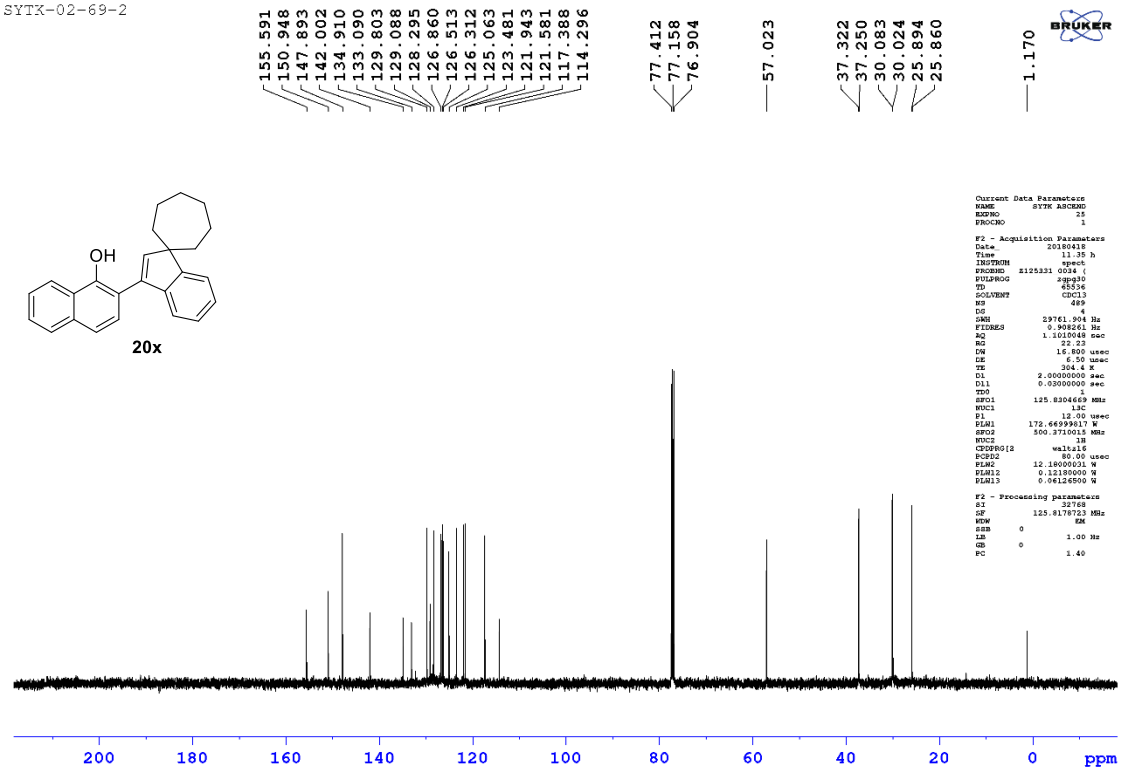


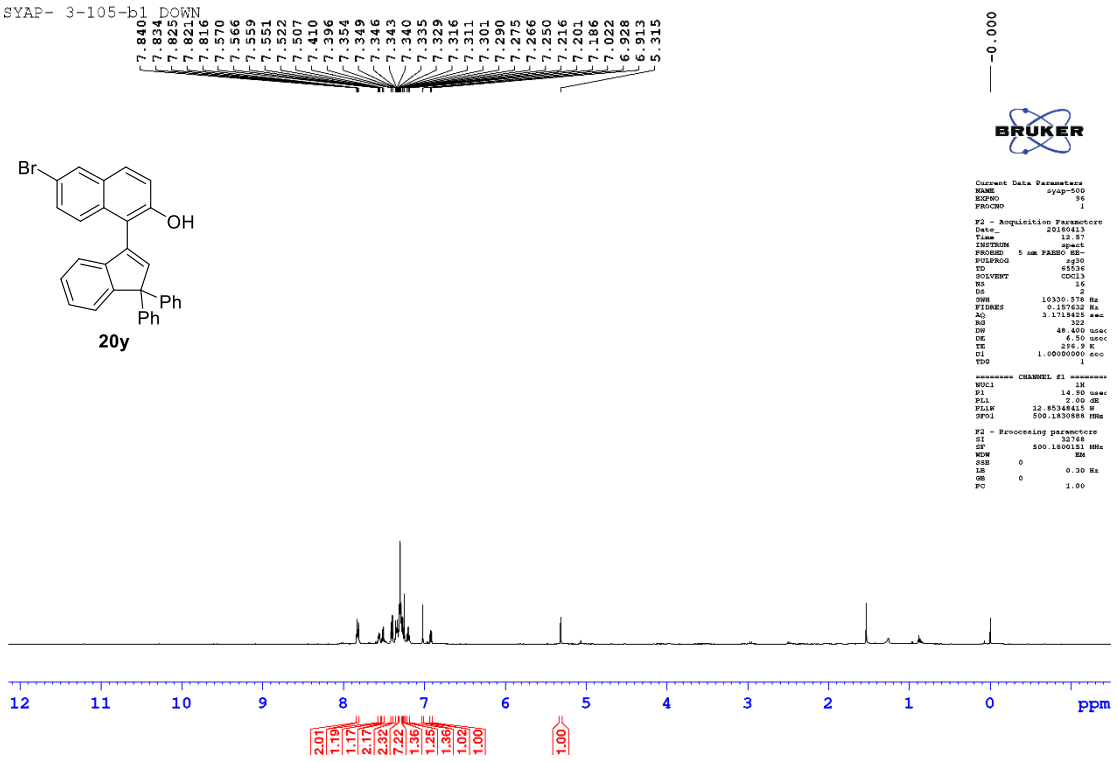

SYjs-37
7.824 7.817 7.809 7.803 7.534 7.530 7.528 7.522 7.519 7.510 7.502 7.484 7.345 7.334 7.328 7.324 7.321 7.316 7.310 7.300 7.290 7.278 7.264 7.233 7.177 7.175 7.158 7.156 7.140 7.138 7.076 6.885 6.866 5.483 2.066 2.043 2.034 2.024 2.013 2.003 1.993 1.976 1.966 1.955 1.944 1.921 1.883 1.697 1.663 1.645 1.638 1.615 1.583 1.543 1.533 1.258 0.882 0.874 -0.000
OH
20w
BRUKER
Current Data Parameters
NAME SYJS STUDENT
EXPNO 143
PROCNO 1
F2 - Acquisition Parameters
Date 20180213
Time 9.02
INSTRUM spect
PROBHD 5 mm BBI 1H/D-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 15
DS 2
SWH 8278.146 Hz
FIDRES 0.126314 Hz
AQ 3.9583745 sec
RG 37
DW 60.400 usec
DE 6.50 usec
TE 673.2 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 9.20 usec
PL1 -1.00 dB
PL1W 10.72012138 W
SFO1 400.1324710 MHz
F2 - Processing parameters
SI 32768
SF 400.1300248 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 ppm
1.96 2.03 4.01 1.16 1.02 0.99 1.01 4.29 4.11 2.04
SYjs-37.
154.084 150.863 145.349 142.476 135.578 133.012 129.823 129.019 128.285 126.996 126.511 126.173 125.036 123.482 122.146 121.653 117.360 114.319
77.473 77.156 76.838
54.332
35.180 35.065 26.126 24.946 24.887
OH
20w
BRUKER
Current Data Parameters
NAME SYJS STUDENT
EXPNO 146
PROCNO 1
F2 - Acquisition Parameters
Date 20180214
Time 8.35
INSTRUM spect
PROBHD 5 mm BBI 1H/D-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 229
DS 4
SWH 23980.814 Hz
FIDRES 0.365915 Hz
AQ 1.3664256 sec
RG 114
DW 20.850 usec
DE 6.50 usec
TE 673.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 30.00 usec
PL1 -4.50 dB
PL1W 94.86473846 W
SFO1 100.6228298 MHz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 90.00 usec
PL2 -1.00 dB
PL12 19.91 dB
PL13 120.00 dB
PL2W 10.72011138 W
PL12W 0.11199529 W
PL13W 0 W
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127605 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
200 180 160 140 120 100 80 60 40 20 0 ppm

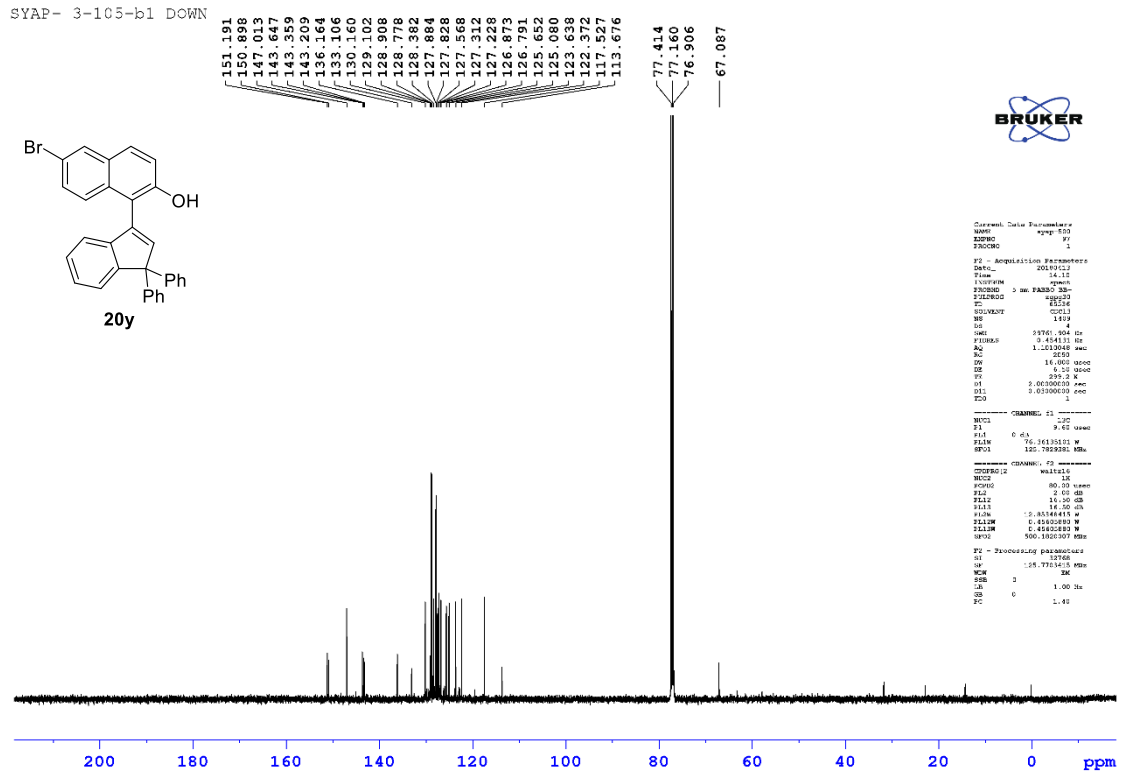
SYTK-02-69-2



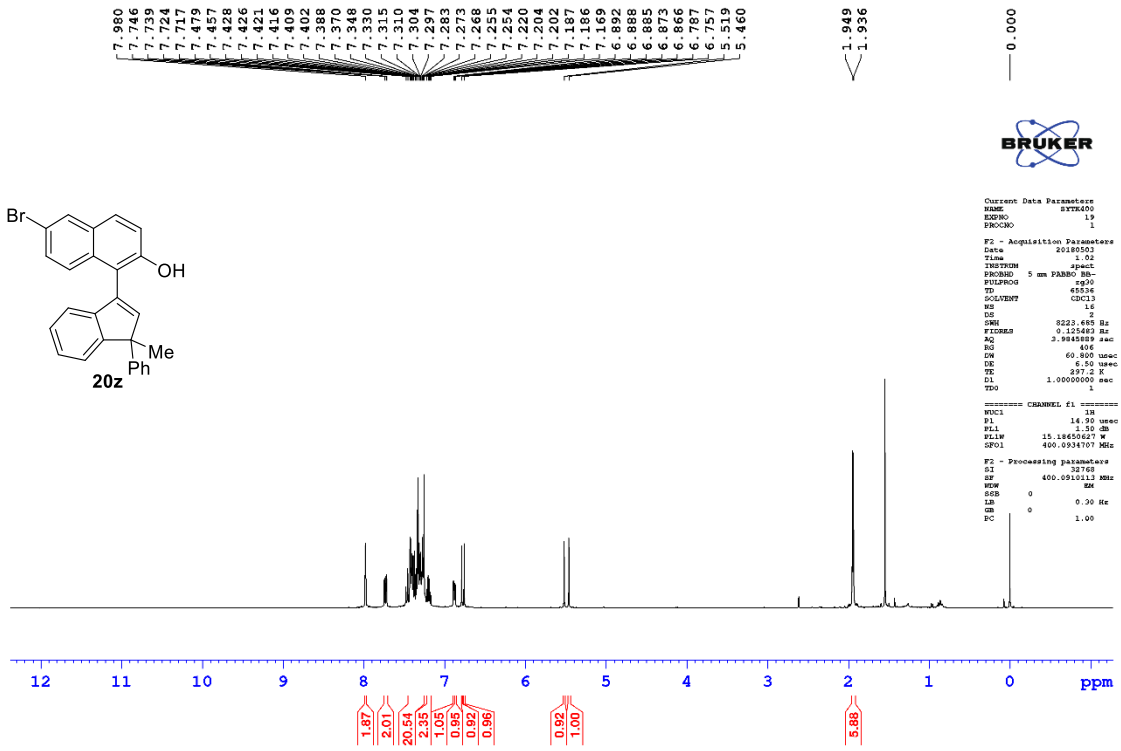
SYTK-02-69-2



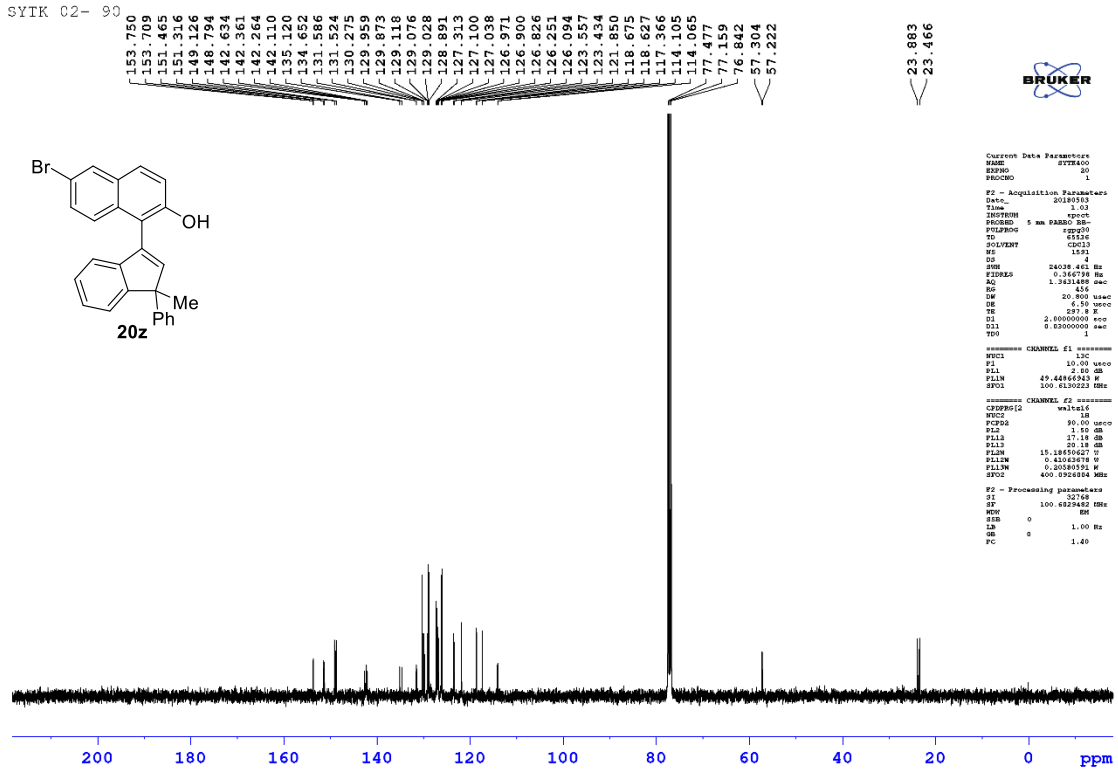

SYAP- 3-105-b1 DOWN
7.840
7.834
7.825
7.821
7.816
7.570
7.566
7.559
7.551
7.522
7.507
7.410
7.396
7.354
7.349
7.346
7.343
7.340
7.335
7.329
7.316
7.311
7.301
7.290
7.275
7.266
7.250
7.216
7.201
7.186
7.022
6.928
6.913
5.315
-0.000
Br
OH
Ph
Ph
20y
BRUKER
Current Data Parameters
NAME syap-500
EXPNO 96
PROCNO 1
F2 - Acquisition Parameters
Date_ 20180413
Time 12.57
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10330.578 Hz
FIDRES 0.157632 Hz
AQ 3.1719425 sec
RG 322
DW 48.400 usec
DE 6.50 usec
TE 296.9 K
D1 1.00000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 14.90 usec
PL1 2.00 dB
PL1W 12.85348415 W
SFO1 500.1330886 MHz
F2 - Processing parameters
SI 32768
SF 500.1800151 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
2.01
1.19
1.17
2.17
2.32
7.22
1.36
1.25
1.36
1.02
1.00
1.00


SYAP- 3-105-b1 DOWN
151.191
150.898
147.013
143.647
143.359
143.209
136.164
133.106
130.160
129.102
128.908
128.778
128.382
127.884
127.828
127.568
127.312
127.228
126.873
126.791
125.652
125.080
123.638
122.372
117.527
113.676
77.414
77.160
76.906
67.087
Br
OH
Ph
Ph
20y
BRUKER
Current Data Parameters
NAME syap-500
EXPNO 97
PROCNO 1
F2 - Acquisition Parameters
Date_ 20180413
Time 14.15
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1409
DS 4
SWH 29761.904 Hz
FIDRES 0.454131 Hz
AQ 1.1010048 sec
RG 2050
DW 16.800 usec
DE 6.50 usec
TE 299.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 13C
P1 9.60 usec
PL1 0 dB
PL1W 76.36135101 W
SFO1 125.7829381 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 80.00 usec
PL2 2.00 dB
PL12 16.30 dB
PL13 16.50 dB
PL2W 12.85346415 W
PL12W 0.45600880 W
PL13W 0.41802880 W
SFO2 500.1820307 MHz
F2 - Processing parameters
SI 32768
SF 125.7734615 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
200
180
160
140
120
100
80
60
40
20
0
ppm

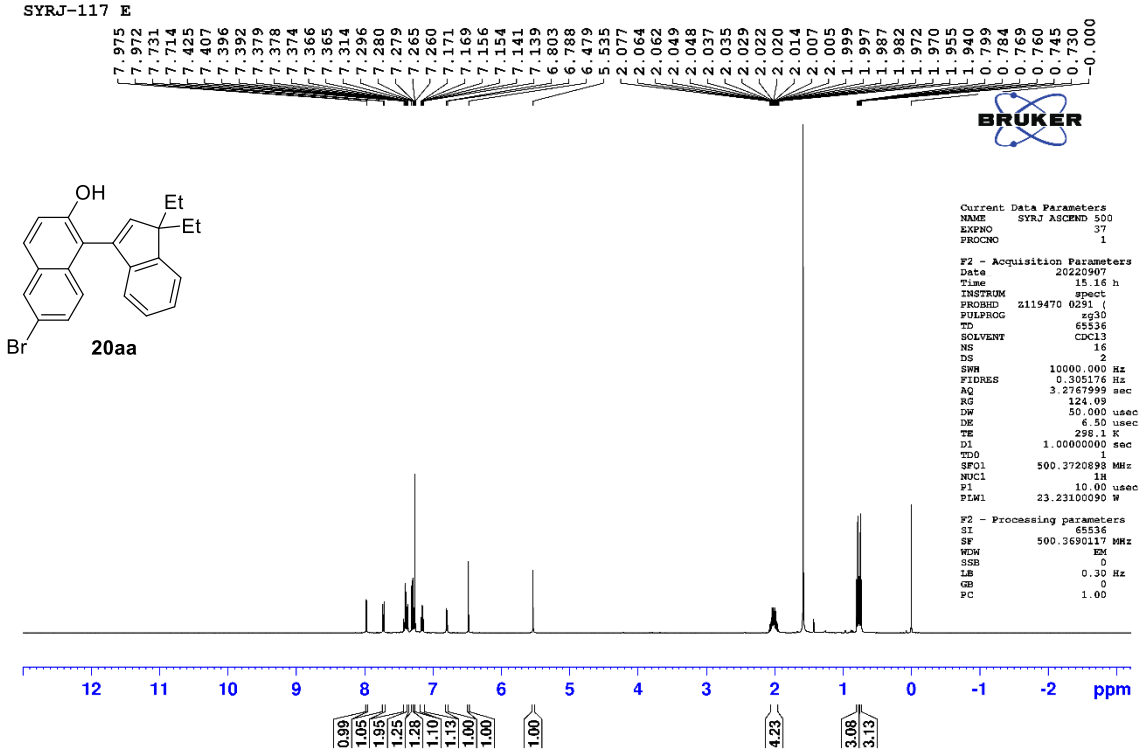
SYTK 02- 90



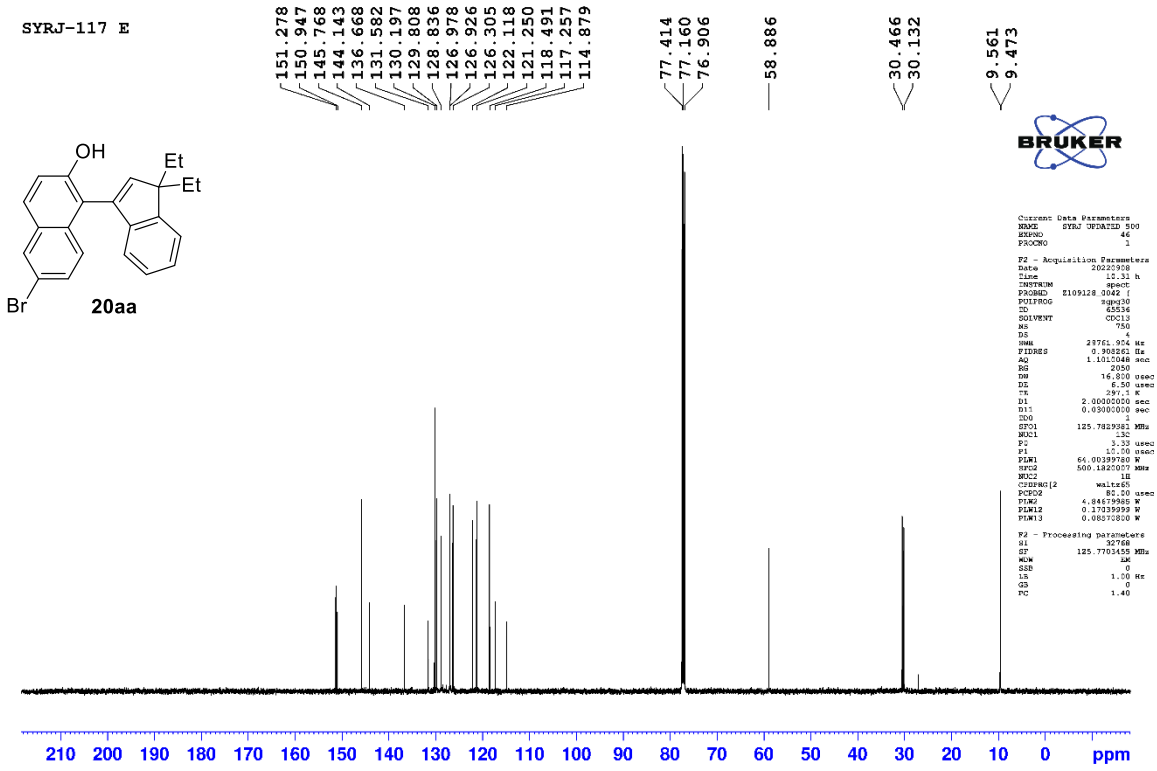
SYTK 02- 90

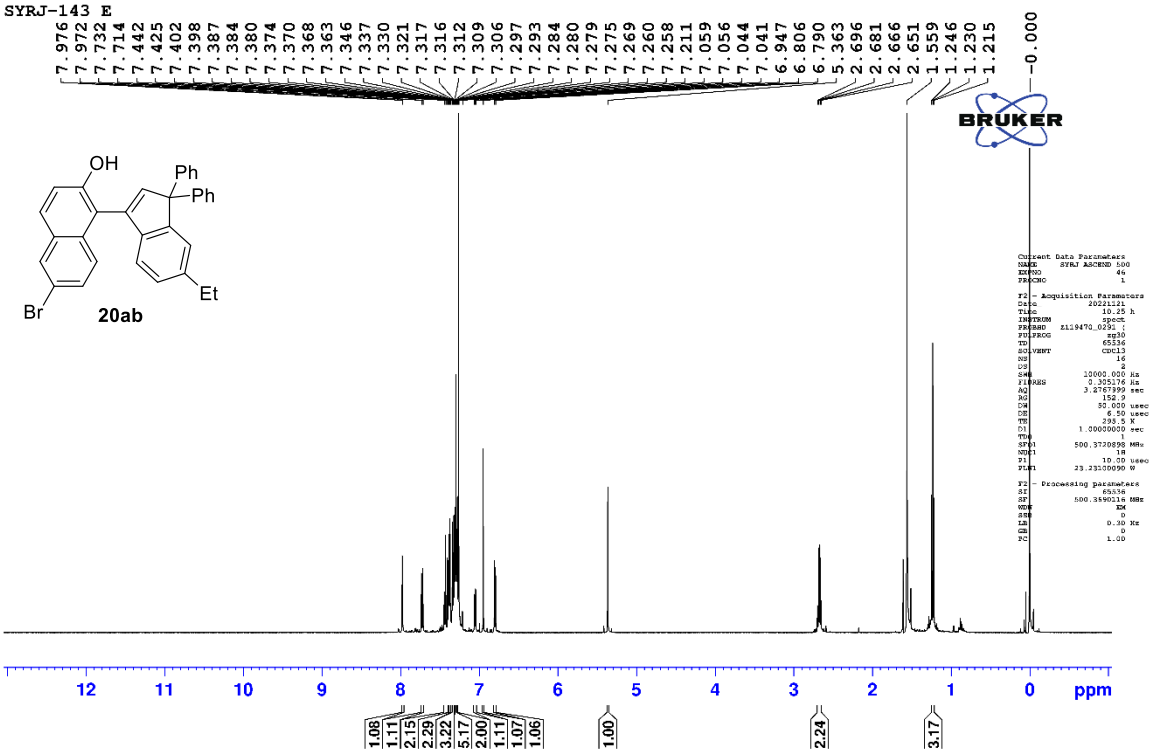


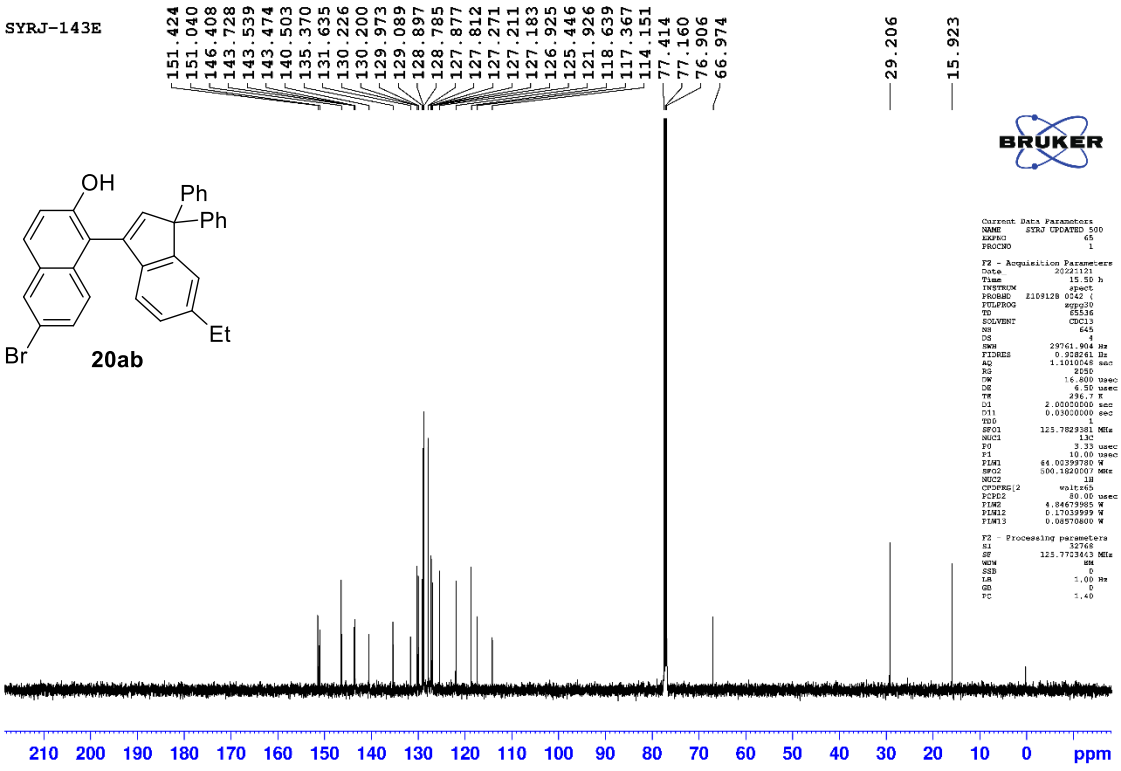
SYRJ-117 E



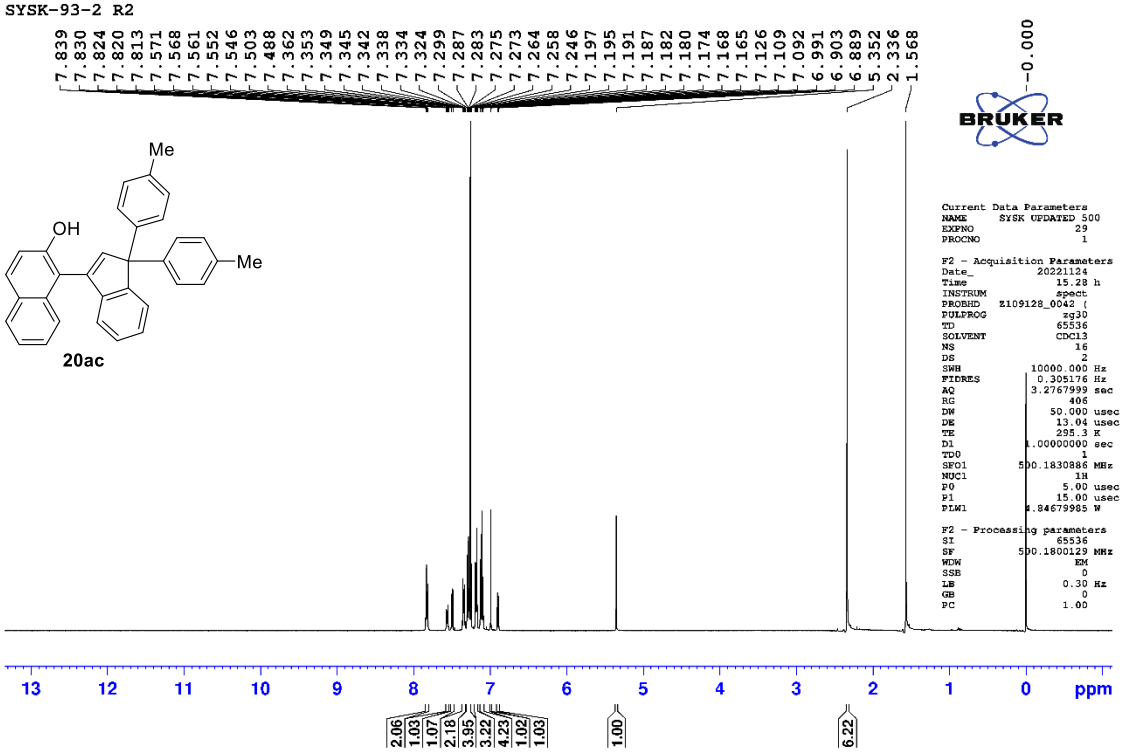
SYRJ-117 E



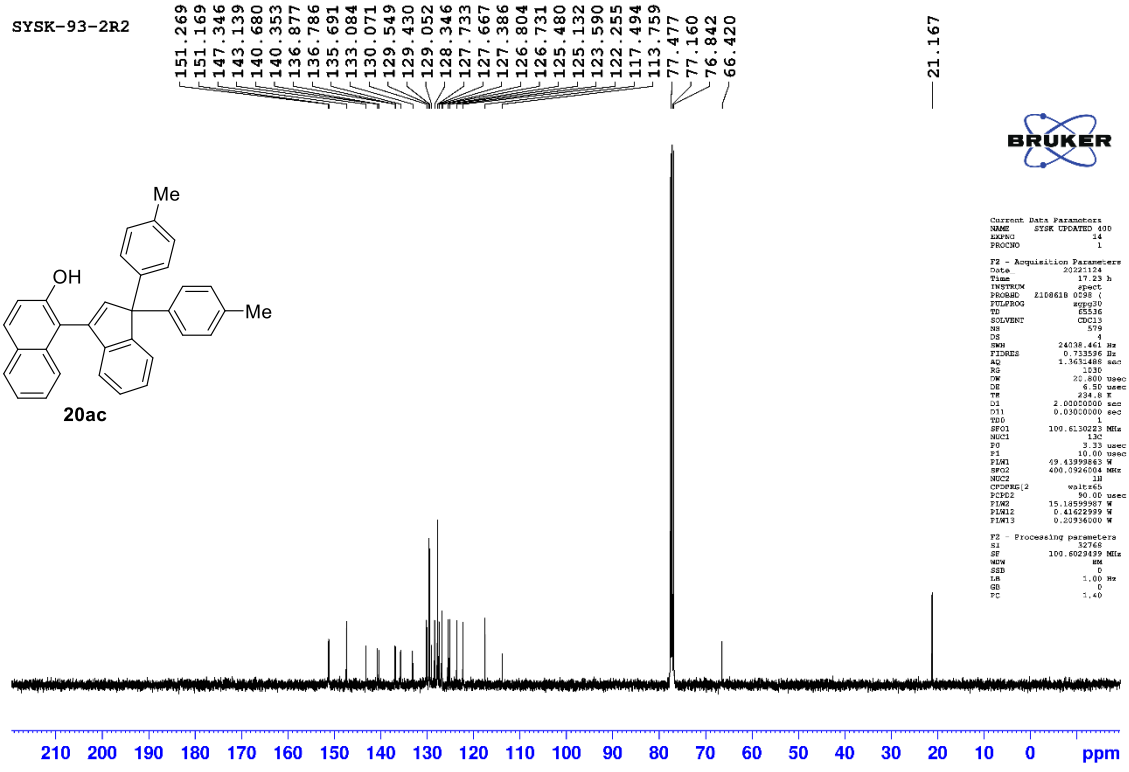

SYRJ-143 E
OH
Ph
Ph
Et
Br
20ab
BRUKER
ppm


SYRJ-143E
OH
Ph
Ph
Et
Br
20ab
BRUKER
ppm

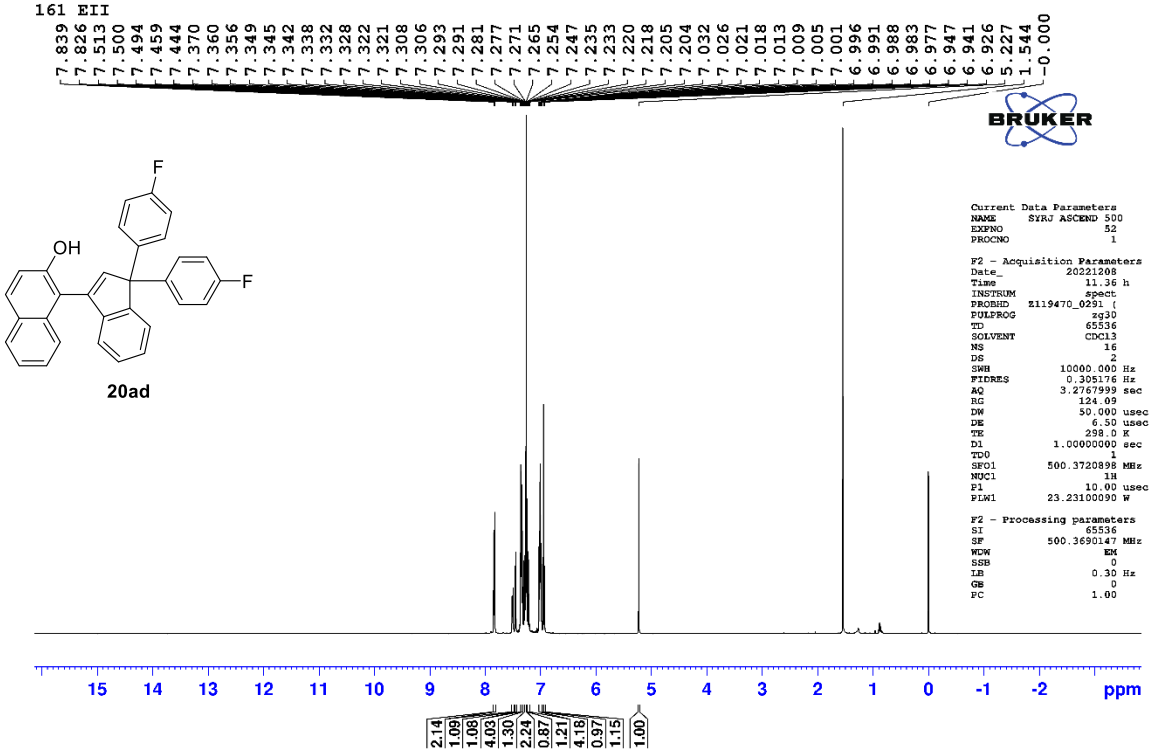
SYSK-93-2 R2



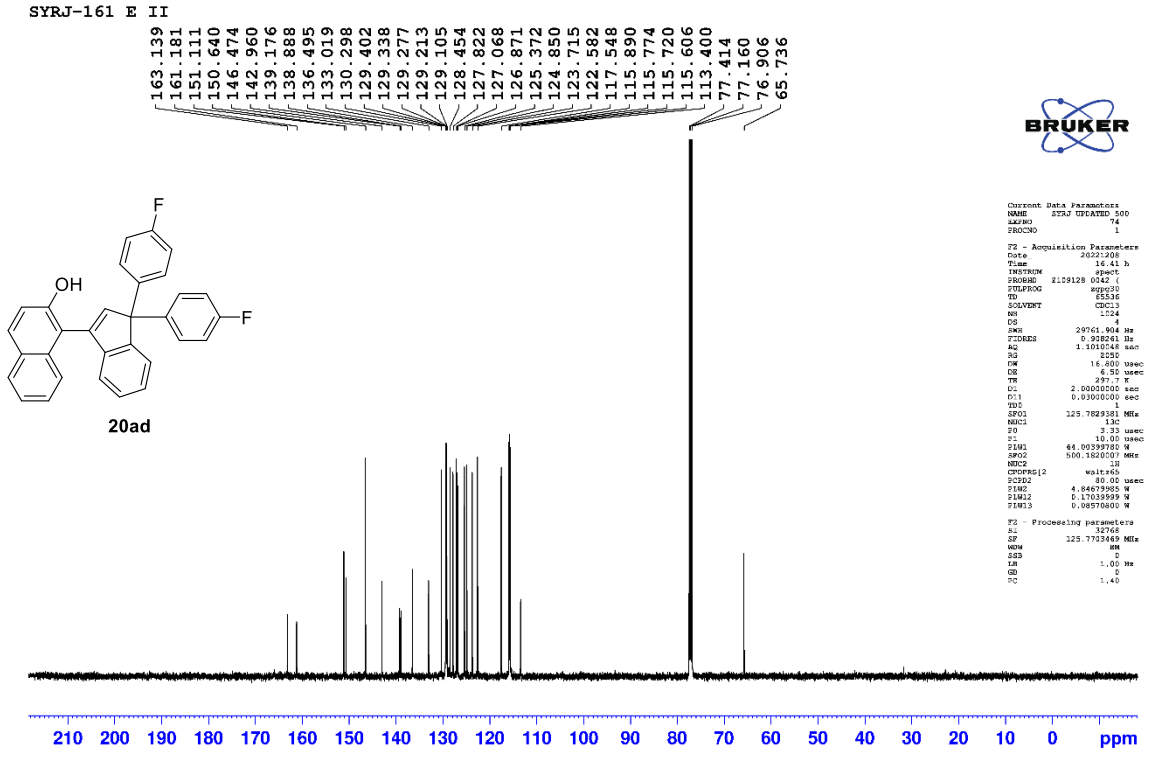
SYSK-93-2R2

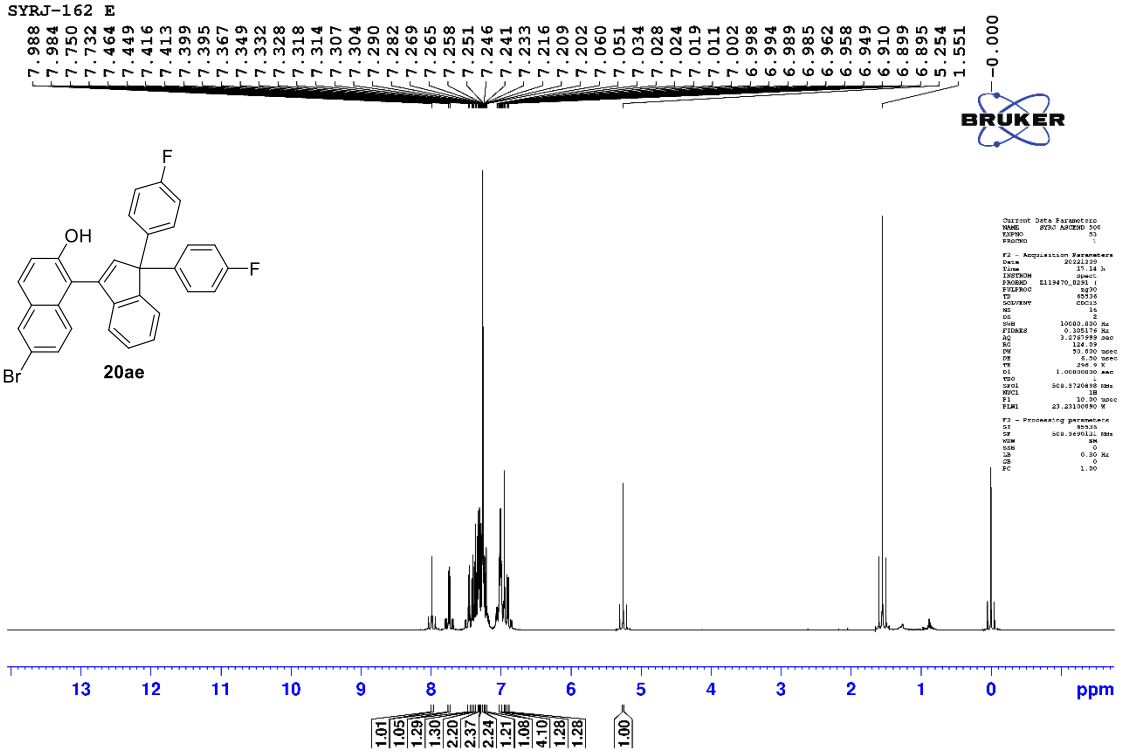


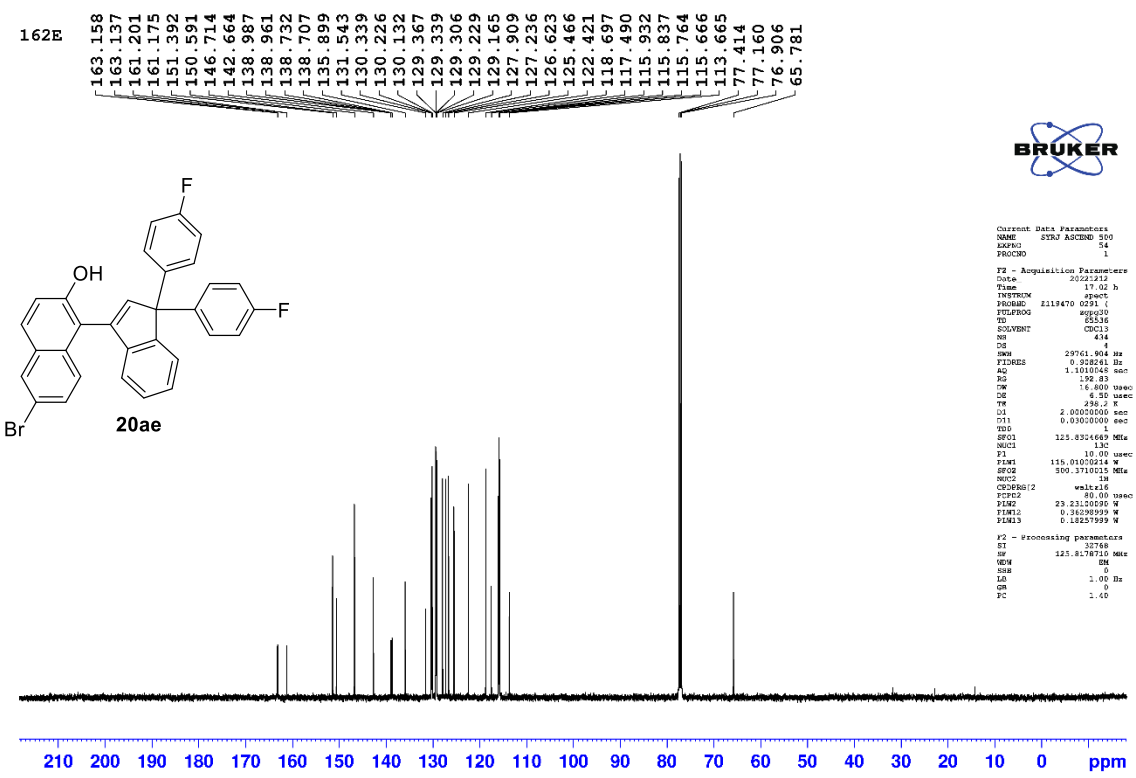
161 EII



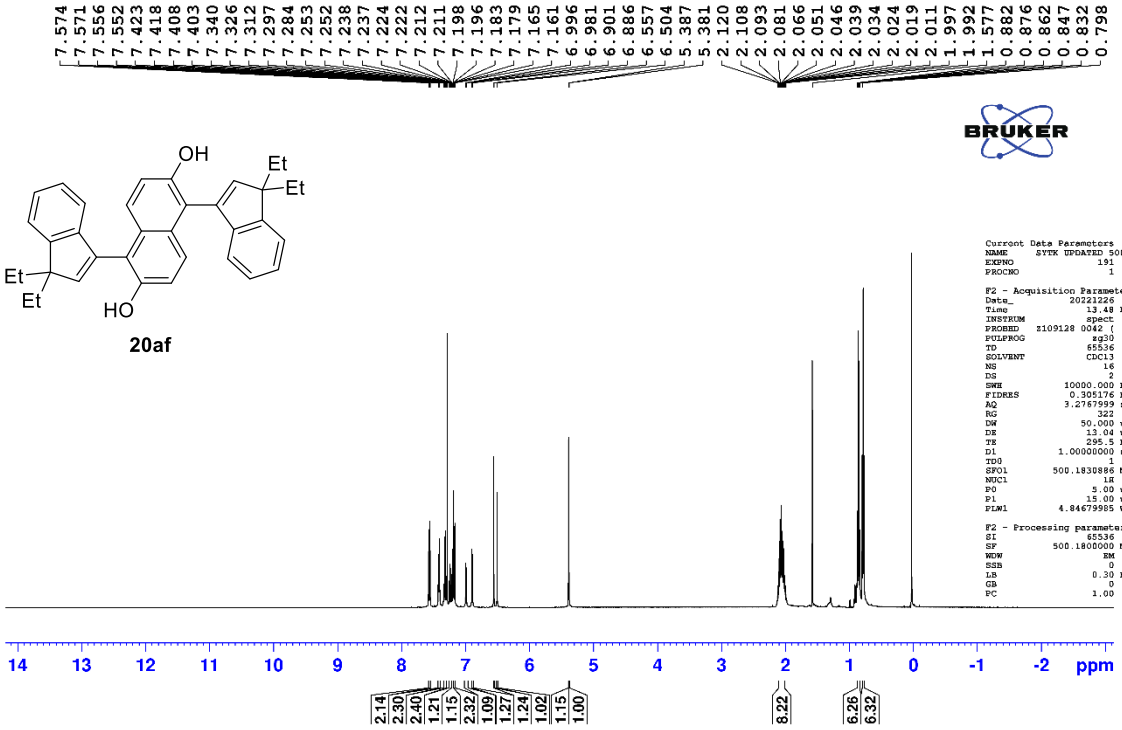
SYRJ-161 E II



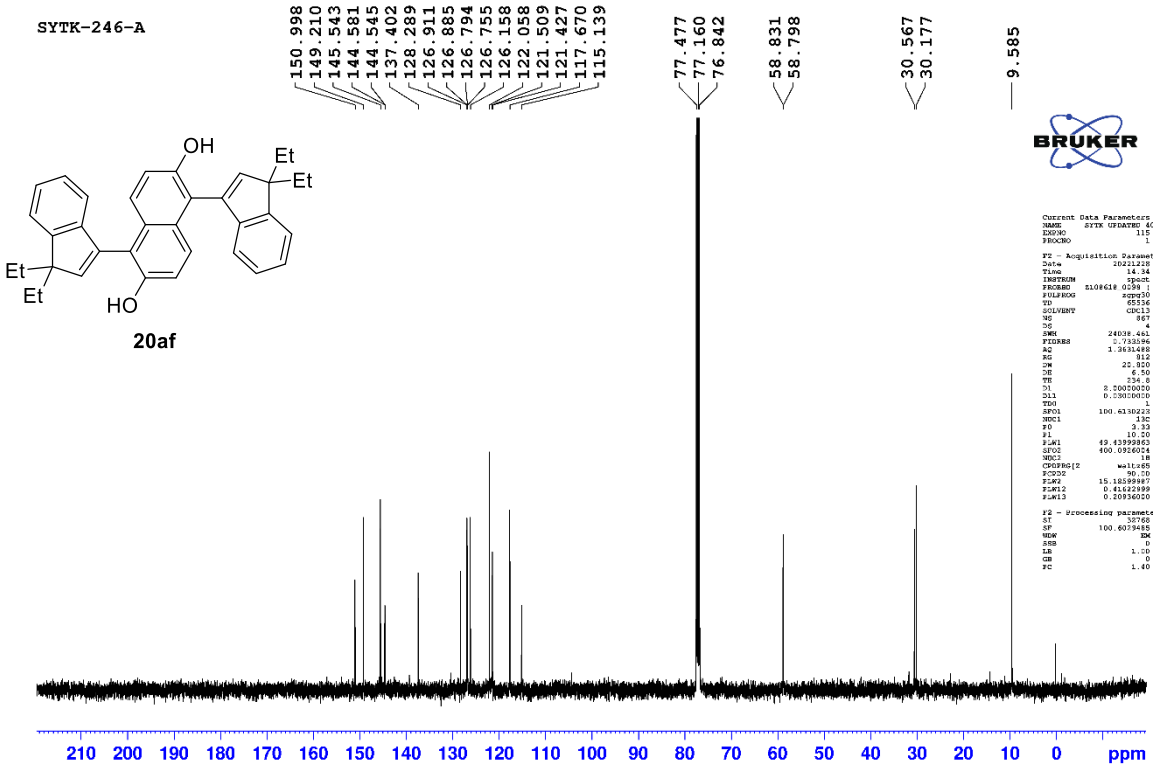

SYRJ-162 E
7.988 7.984 7.750 7.732 7.464 7.449 7.416 7.413 7.399 7.395 7.367 7.349 7.332 7.328 7.318 7.314 7.307 7.304 7.290 7.282 7.269 7.265 7.258 7.251 7.246 7.241 7.233 7.216 7.209 7.202 7.060 7.051 7.034 7.028 7.024 7.019 7.011 7.002 6.998 6.994 6.989 6.985 6.962 6.958 6.949 6.910 6.899 6.895 5.254 1.551 0.000
BRUKER
F
OH
F
Br
20ae
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.01 1.05 1.29 1.30 2.20 2.37 2.24 1.21 1.08 4.10 1.28 1.28 1.00

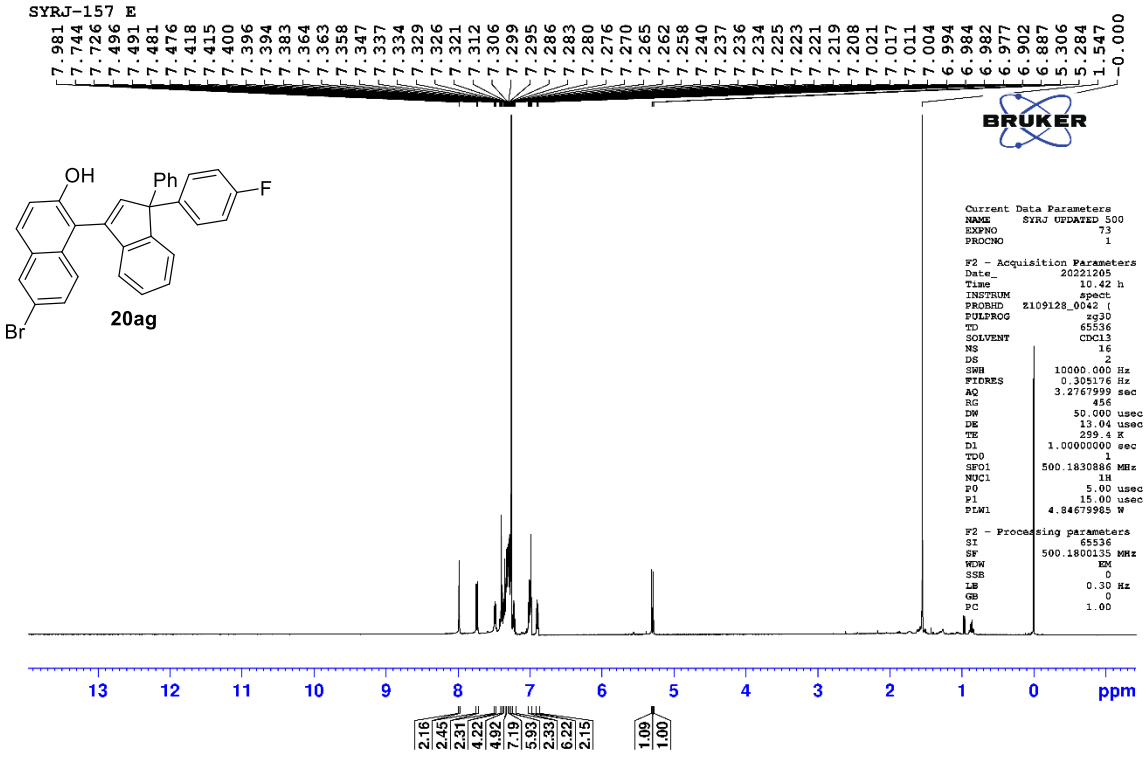

162E
163.158 163.137 161.201 161.175 151.392 150.591 146.714 142.664 138.987 138.961 138.732 138.707 135.899 131.543 130.339 130.226 130.132 129.367 129.339 129.306 129.229 129.165 127.909 127.236 126.623 125.466 122.421 118.697 117.490 115.932 115.837 115.764 115.666 113.665 77.414 77.160 76.906 65.781
BRUKER
F
OH
F
Br
20ae
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

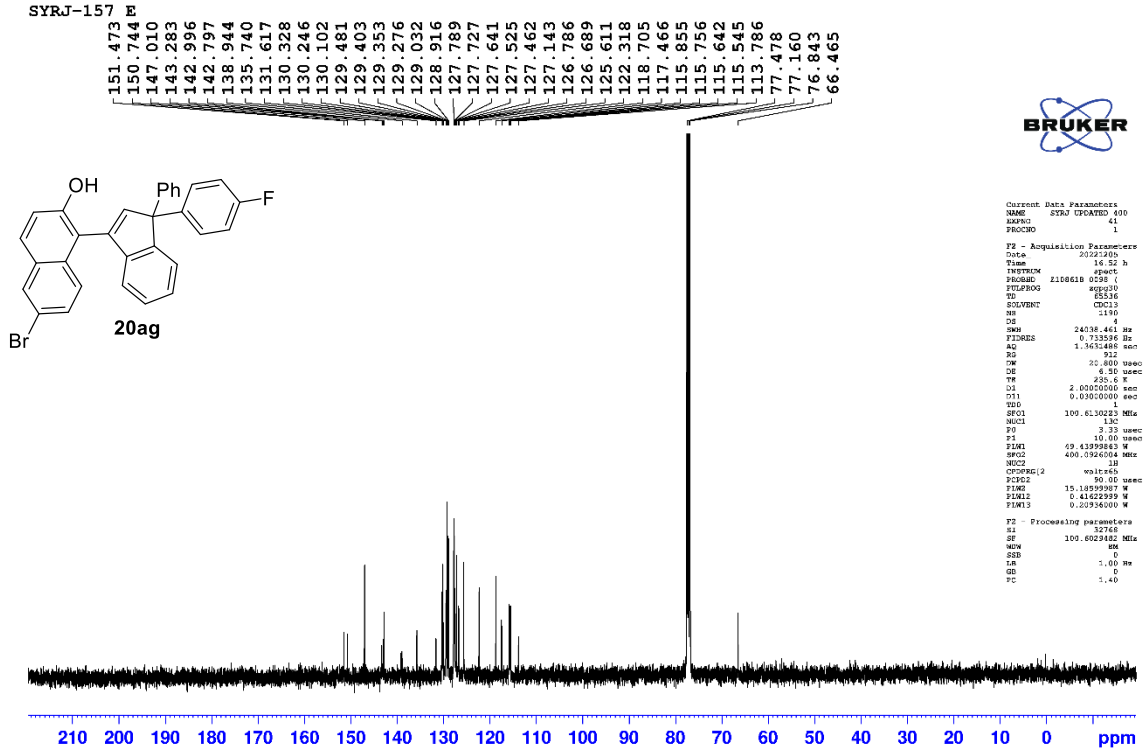
SYTK- 246-A



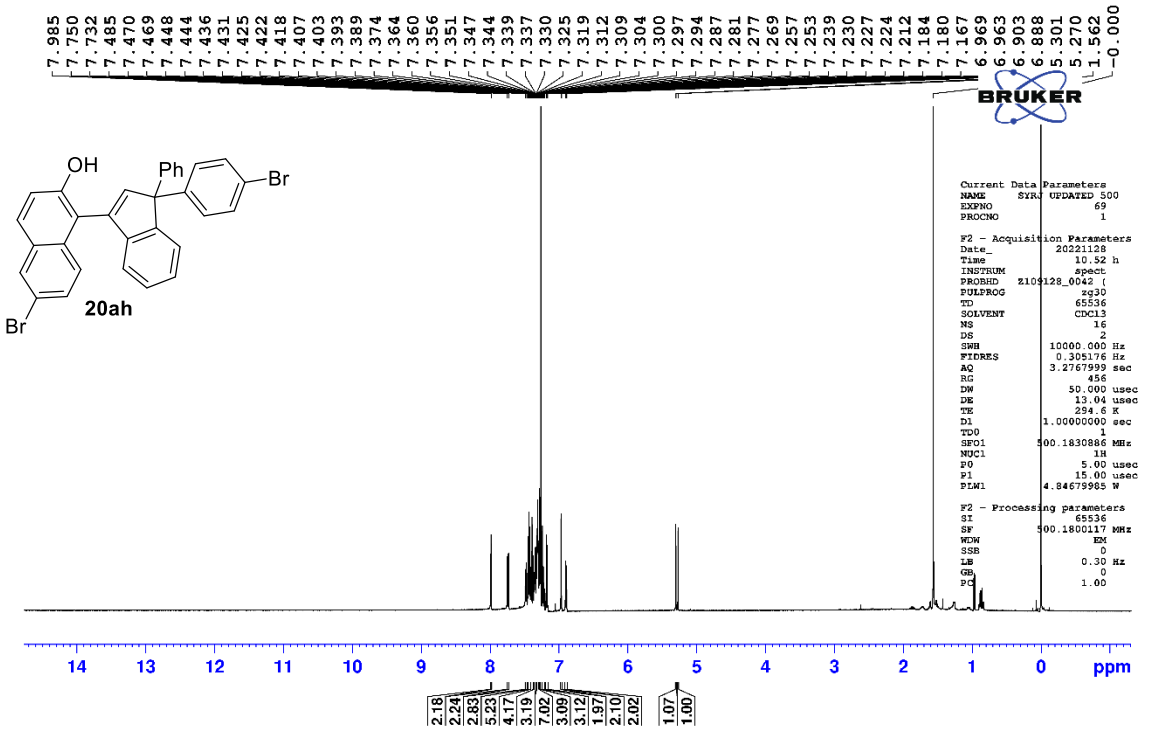
SYTK-246-A



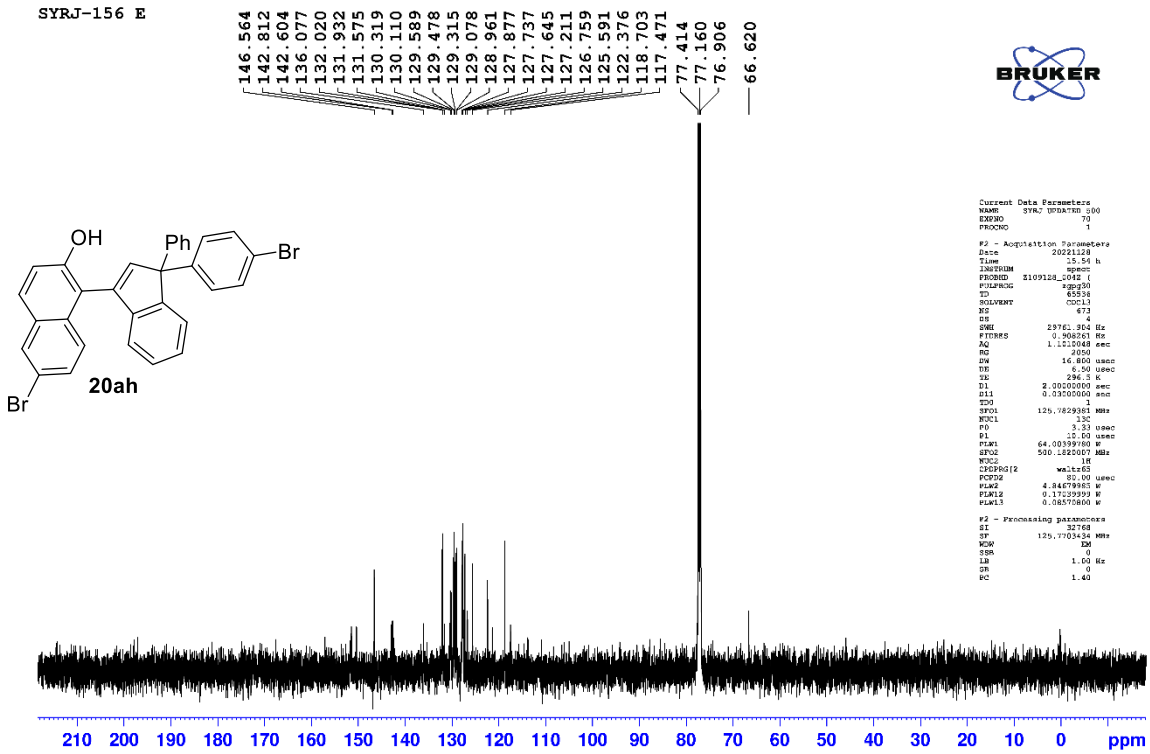

SYRJ-157 E
7.981 7.744 7.726 7.496 7.491 7.481 7.476 7.418 7.415 7.400 7.396 7.394 7.383 7.364 7.363 7.358 7.347 7.337 7.334 7.329 7.326 7.321 7.312 7.306 7.299 7.295 7.286 7.283 7.280 7.276 7.270 7.265 7.262 7.258 7.240 7.237 7.236 7.234 7.225 7.223 7.221 7.219 7.208 7.021 7.017 7.011 7.004 6.994 6.984 6.982 6.977 6.902 6.887 5.306 5.284 1.547 0.000
OH
Ph
F
Br
20ag
BRUKER
Current Data Parameters
NAME SYRJ UPDATED 500
EXPNO 73
PROCNO 1
F2 - Acquisition Parameters
Date_ 20221205
Time 10.42 h
INSTRUM spect
PROBHD Z109128_0042 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 456
DW 50.000 usec
DE 13.04 usec
TE 299.4 K
D1 1.00000000 sec
TD0 1
SFO1 500.1830886 MHz
NUC1 1H
P0 5.00 usec
P1 15.00 usec
PLW1 4.84679985 W
F2 - Processing parameters
SI 65536
SF 500.1800135 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
2.16 2.45 2.31 4.22 4.92 7.19 5.93 2.33 6.22 2.15 1.09 1.00


SYRJ-157 E
151.473 150.744 147.010 143.283 142.996 142.797 138.944 135.740 131.617 130.328 130.246 130.102 129.481 129.403 129.353 129.276 129.032 128.916 127.789 127.727 127.641 127.525 127.462 127.143 126.786 126.689 125.611 122.318 118.705 117.466 115.855 115.756 115.642 115.545 113.786 77.478 77.160 76.843 66.465
OH
Ph
F
Br
20ag
BRUKER
Current Data Parameters
NAME SYRJ UPDATED 400
EXPNO 41
PROCNO 1
F2 - Acquisition Parameters
Date_ 20221205
Time 16.52 h
INSTRUM spect
PROBHD Z108618 0098 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1190
DS 4
SWH 24038.461 Hz
FIDRES 0.733596 Hz
AQ 1.3631488 sec
RG 922
DW 20.800 usec
DE 6.50 usec
TE 295.6 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.6130213 MHz
NUC1 13C
P0 3.33 usec
P1 10.00 usec
PLW1 69.43999863 W
SFO2 400.0924064 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 90.00 usec
PLW2 15.18999987 W
PLW12 0.41629999 W
PLW13 0.20936000 W
F2 - Processing parameters
SI 32768
SF 100.6029482 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

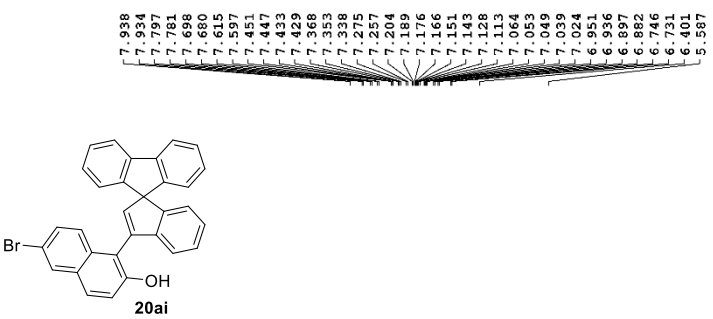
SYRJ-156 E



SYRJ-156 E

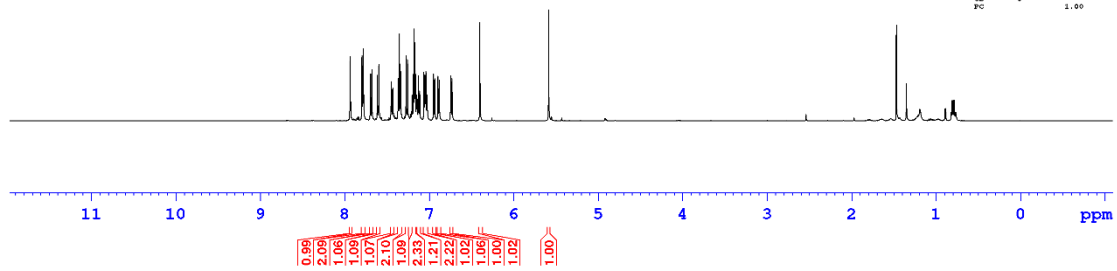


SYAR-120

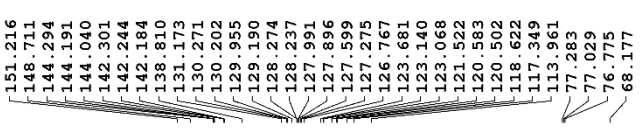


20ai



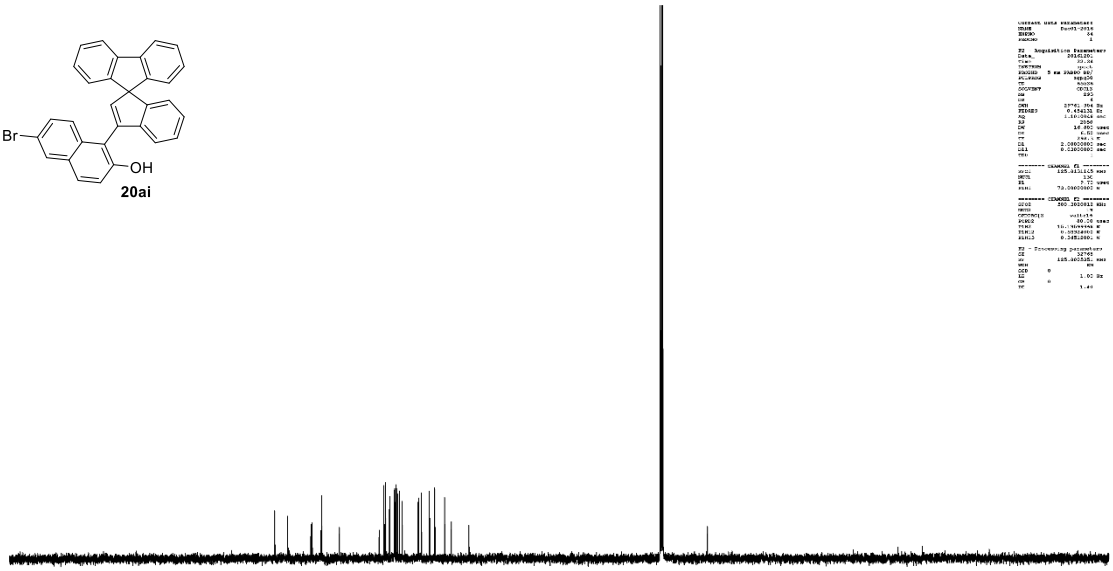


SYAR-120



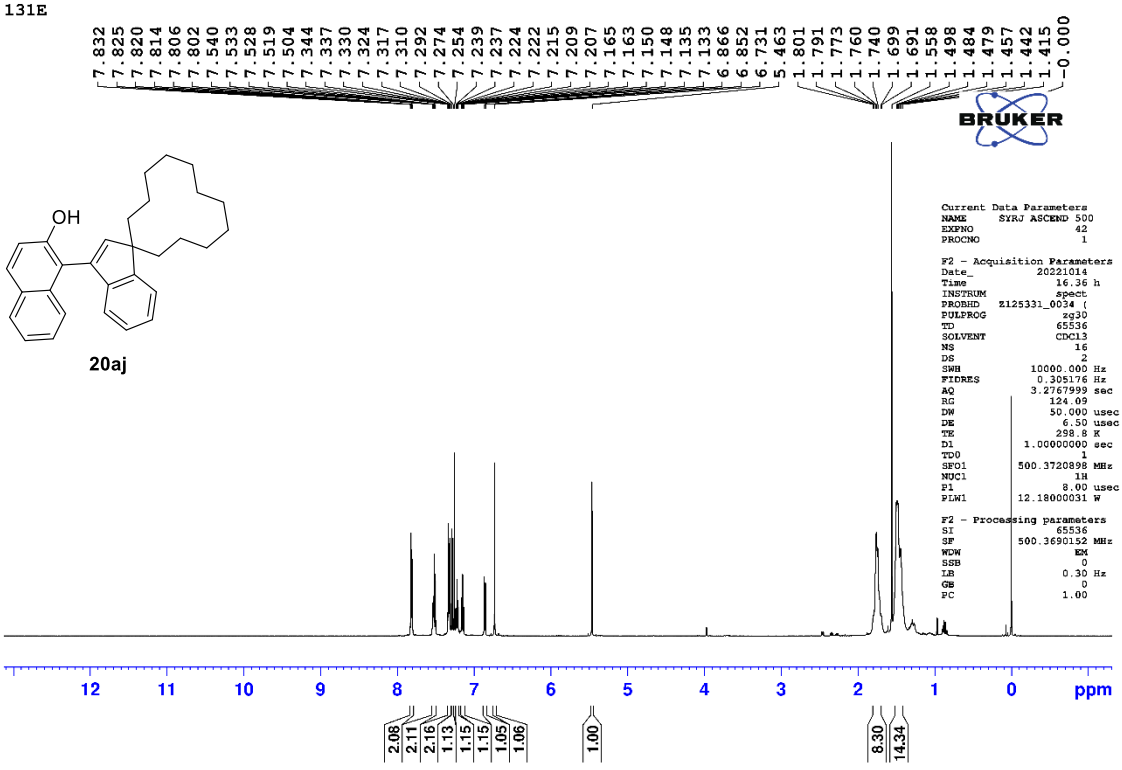
20ai



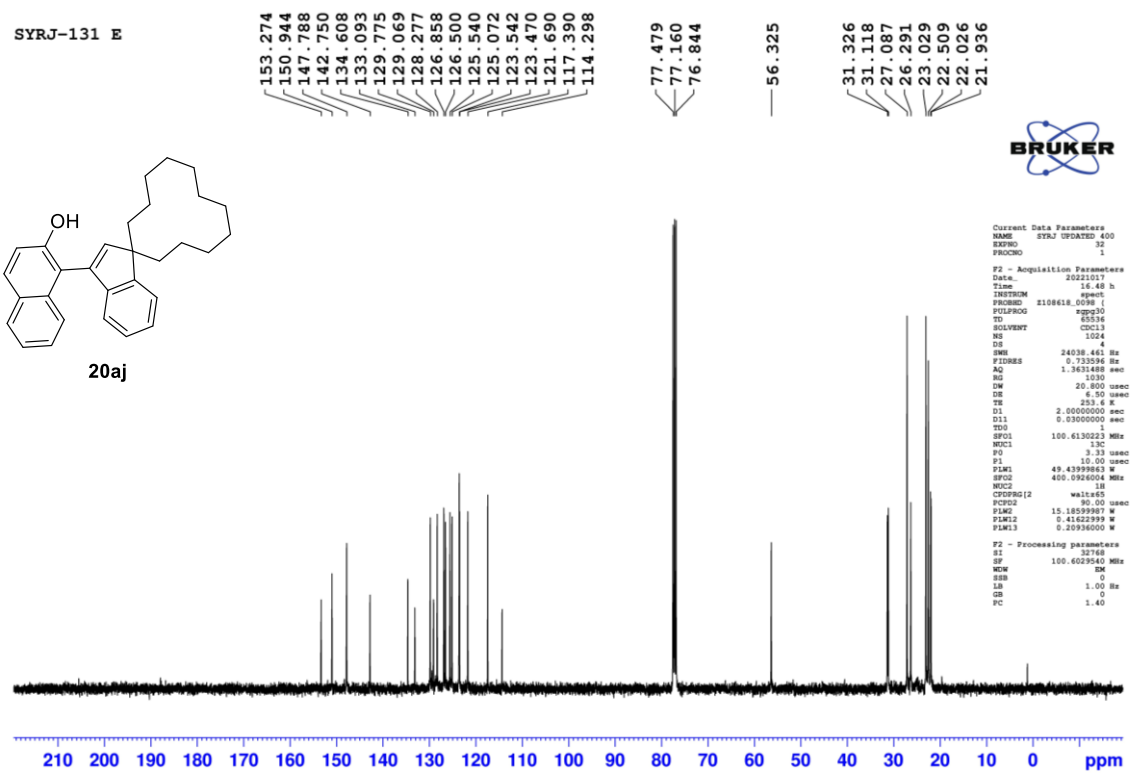




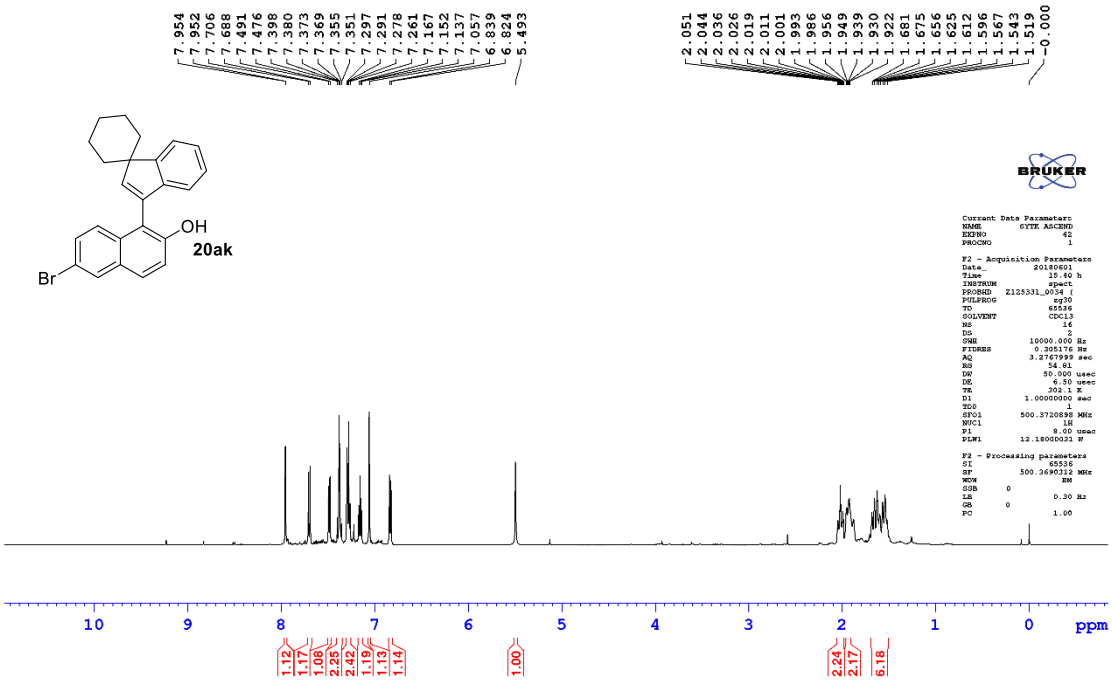
131E



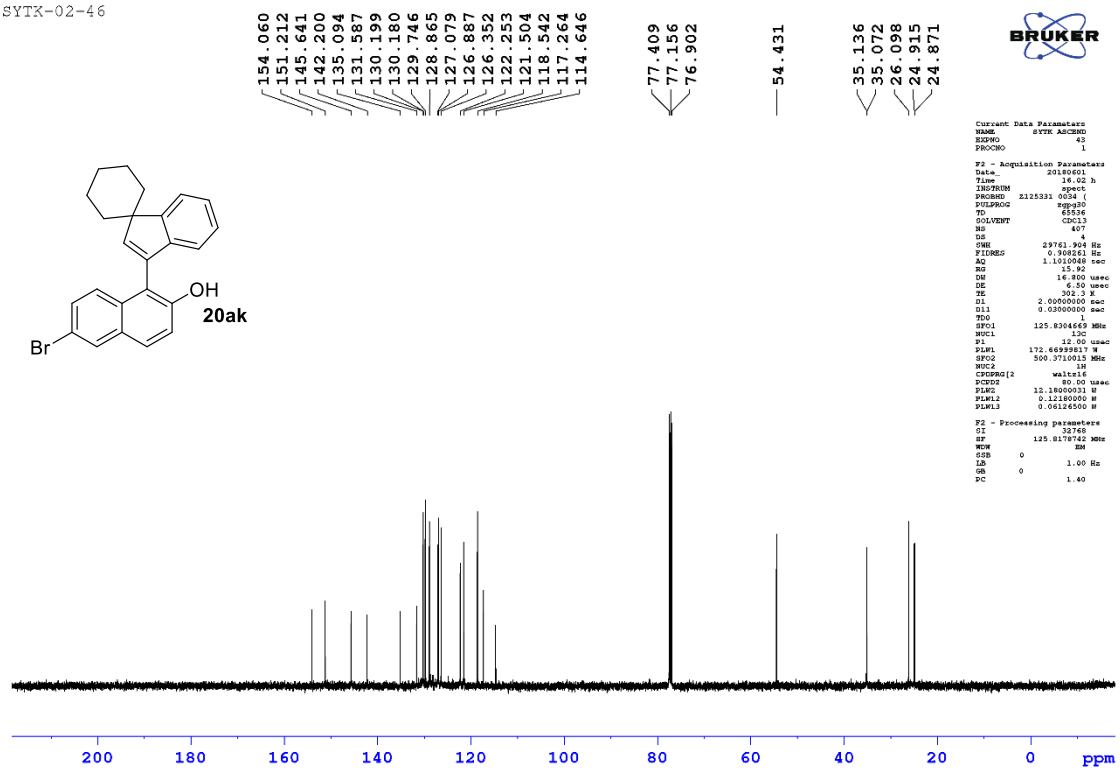
SYRJ-131 E



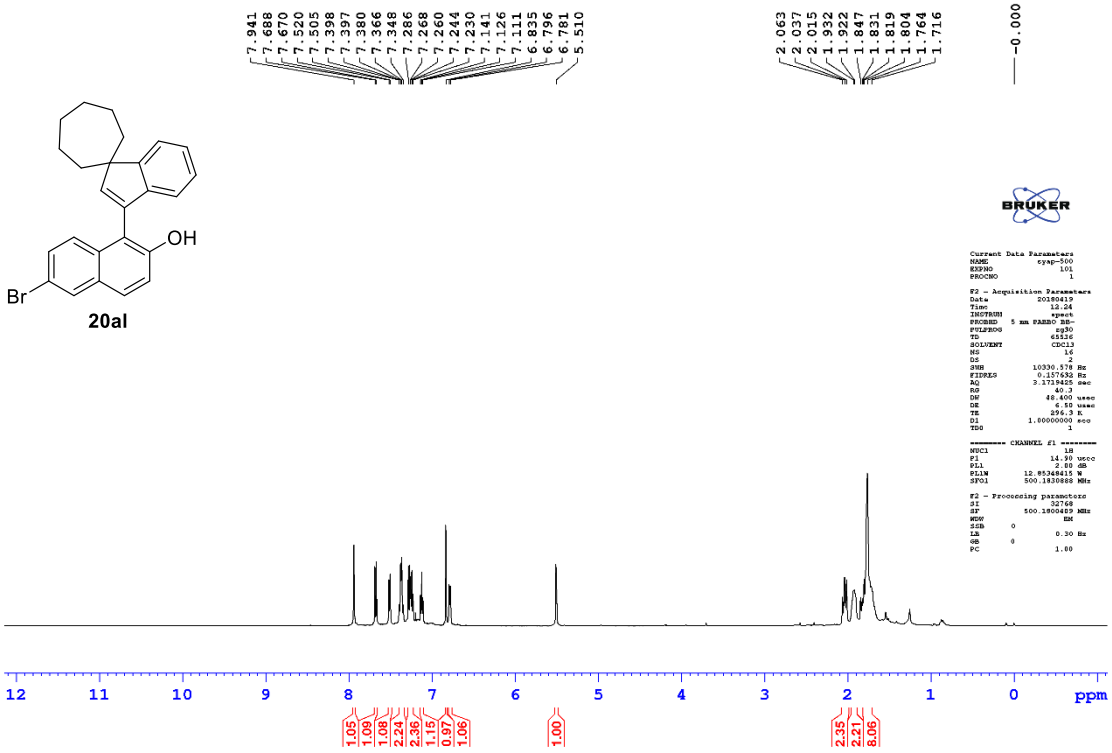
SYTK-02-46



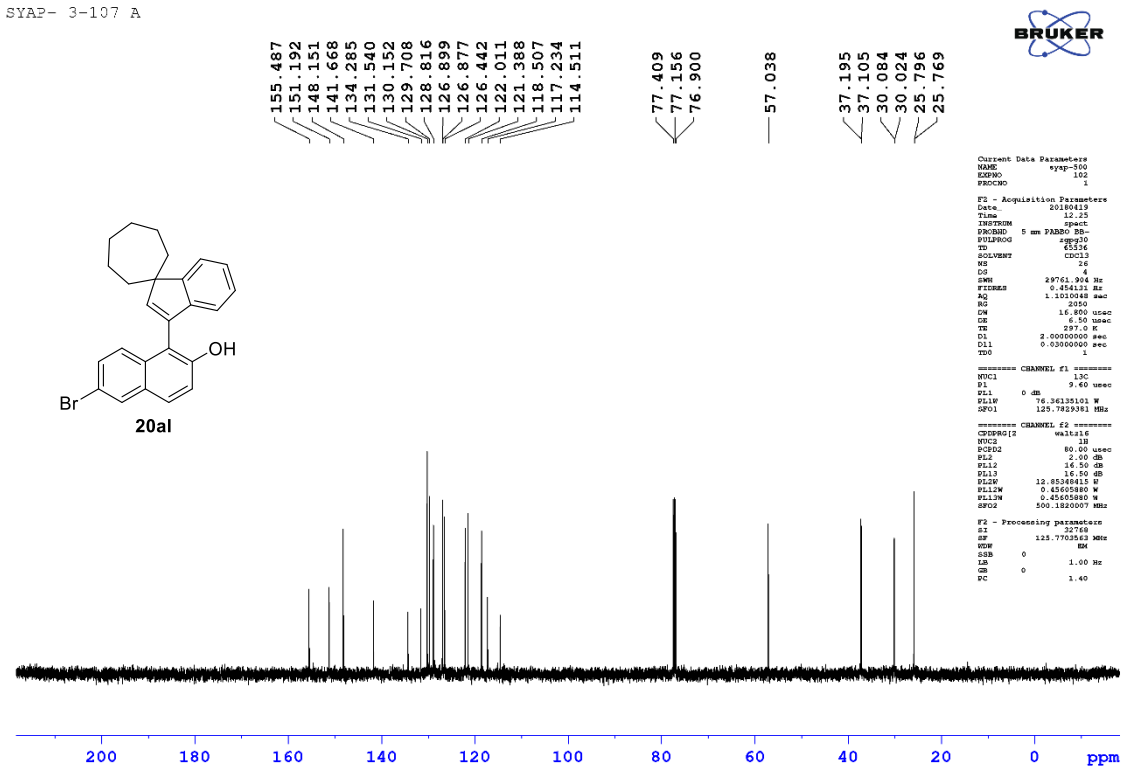
SYTK-02-46



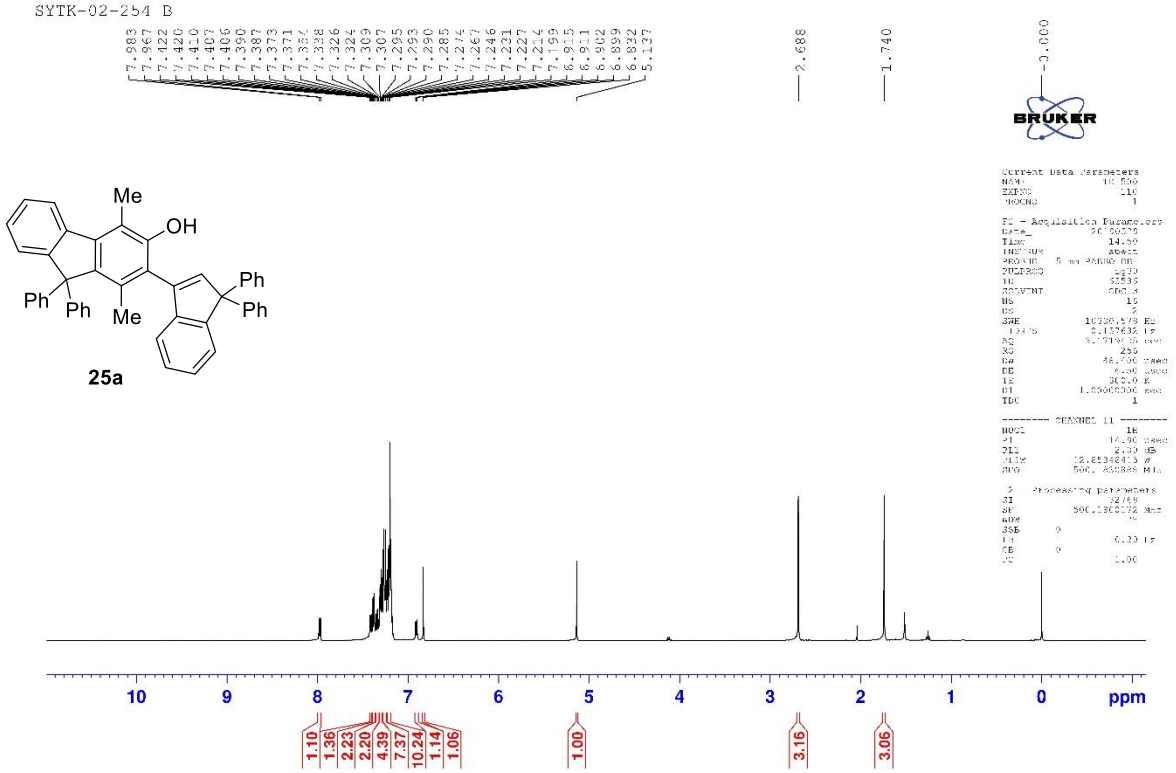
SYAP- 3-107 A



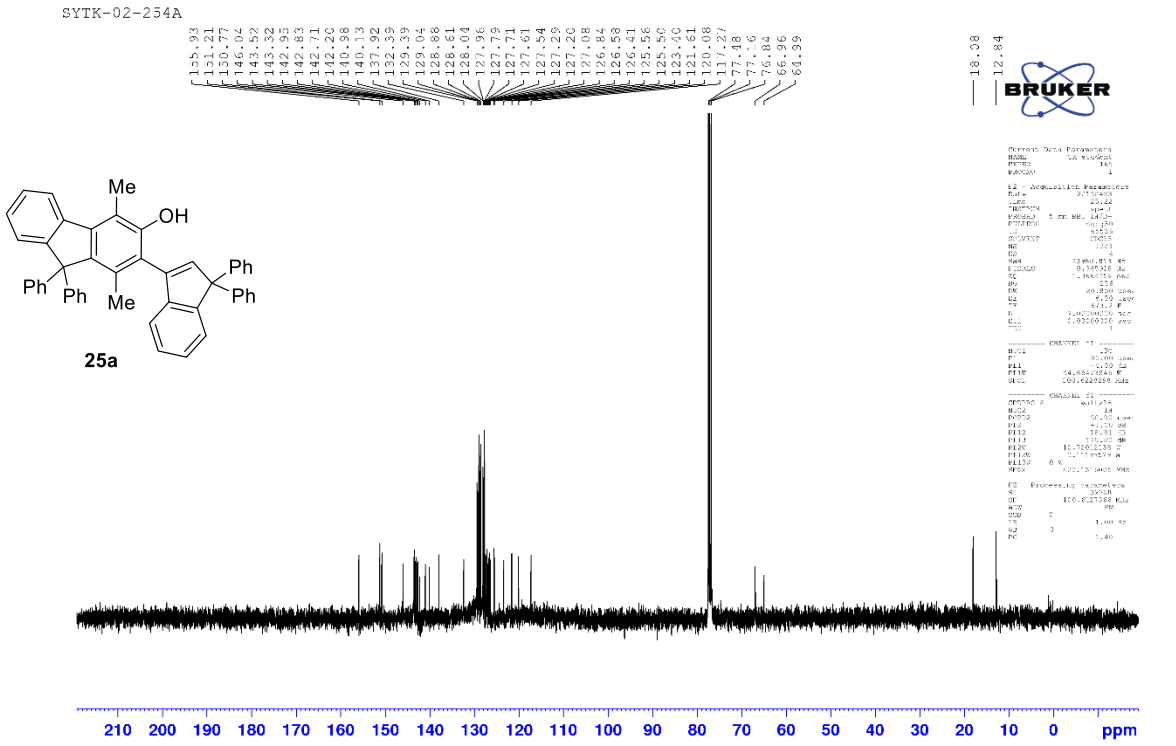
SYAP- 3-107 A



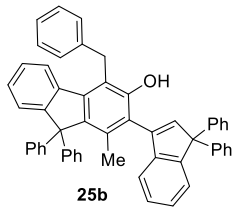
SYTK-02-254 B



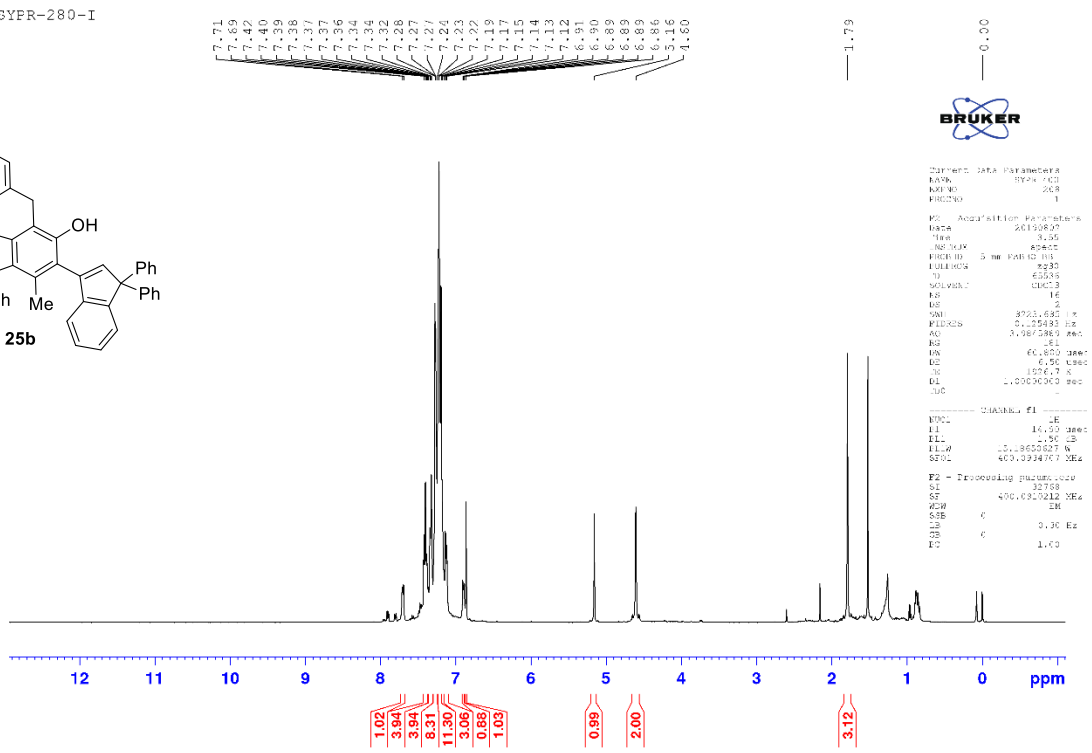
SYTK-02-254A



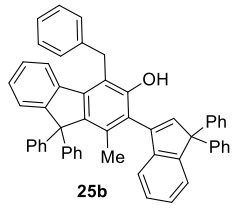
SYPR-280-I



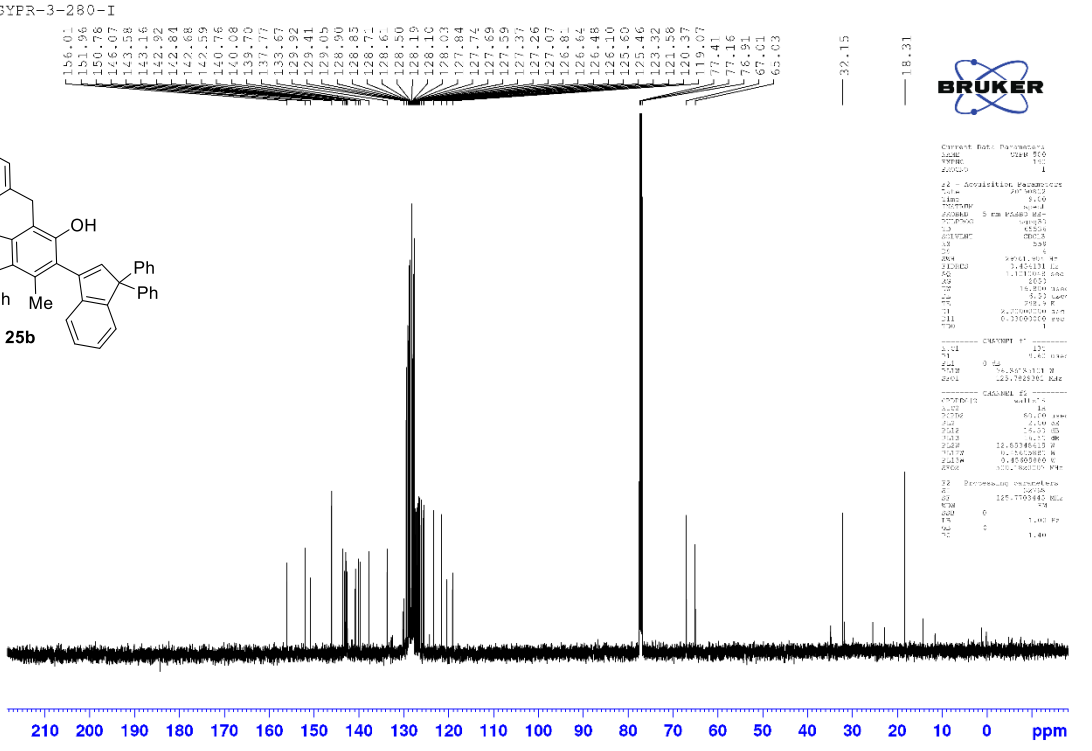
25b

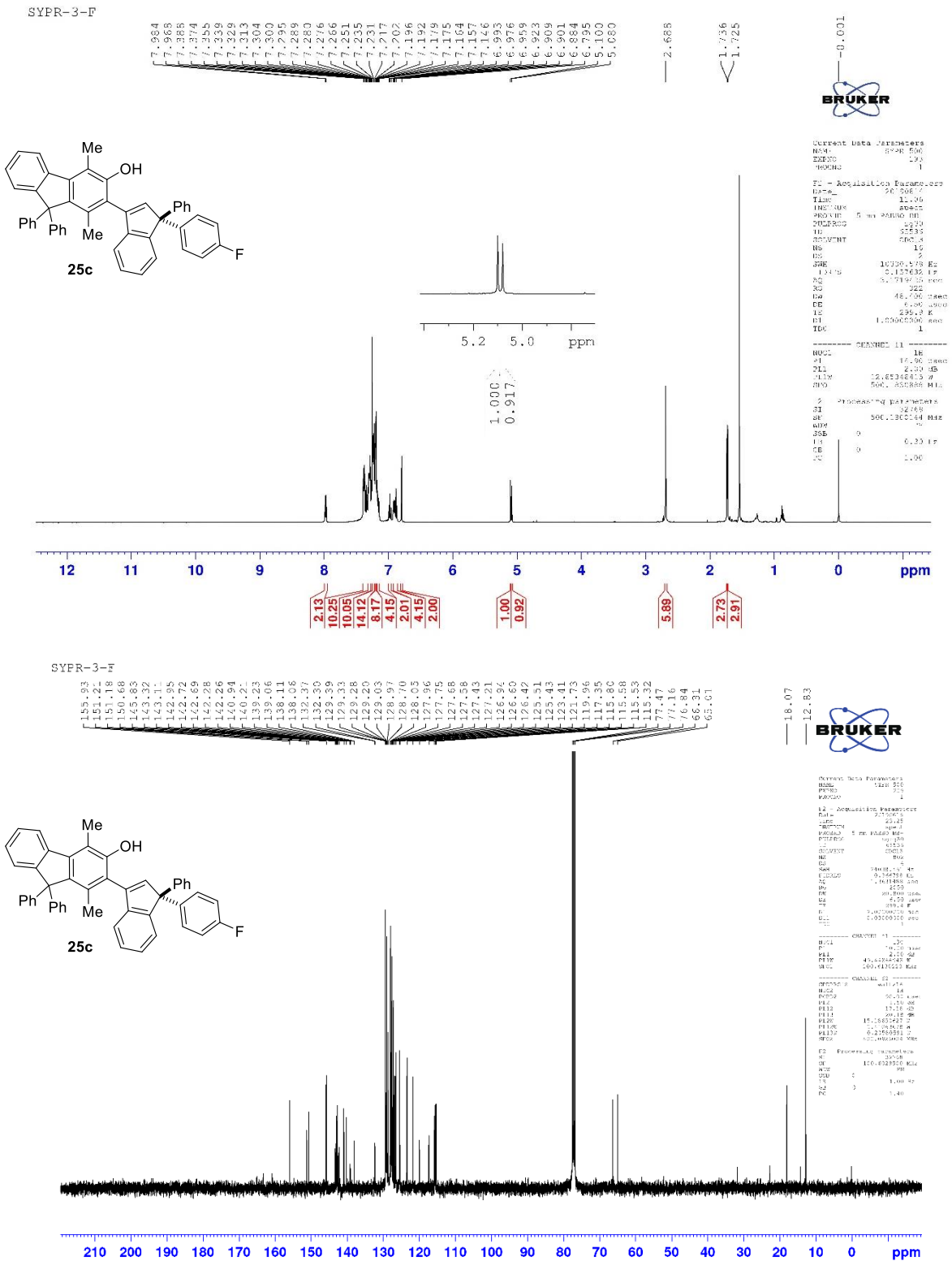


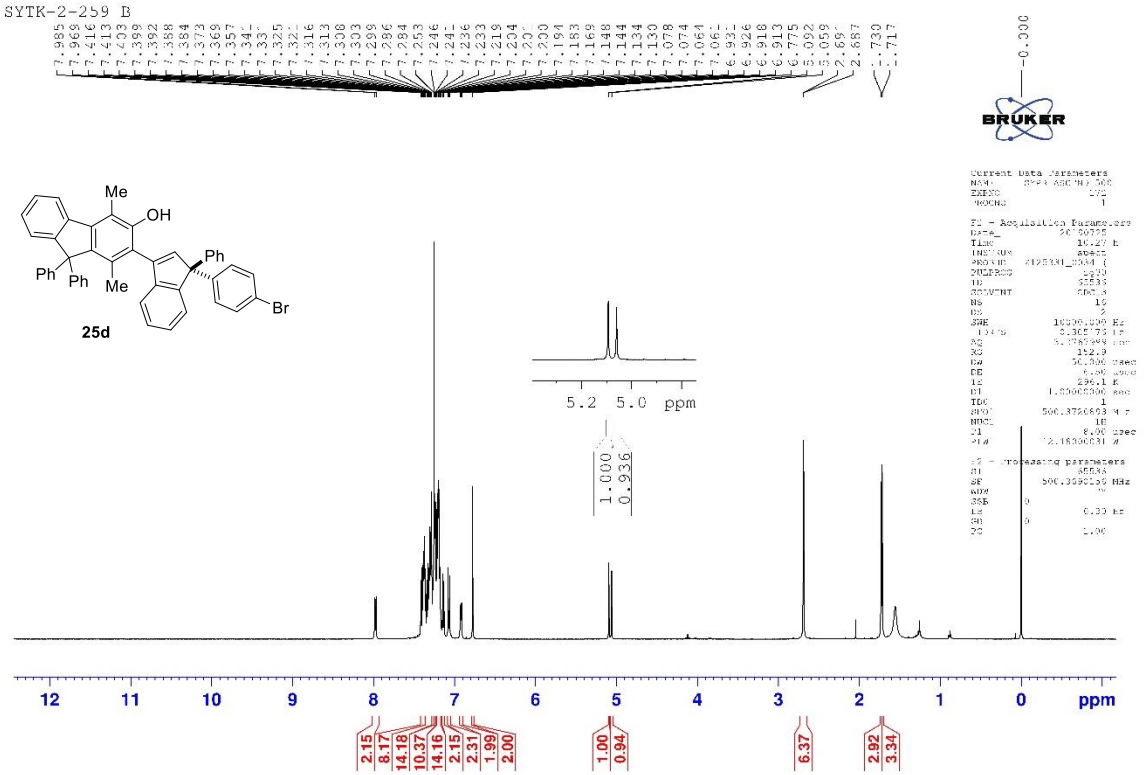
SYPR-3-280-I

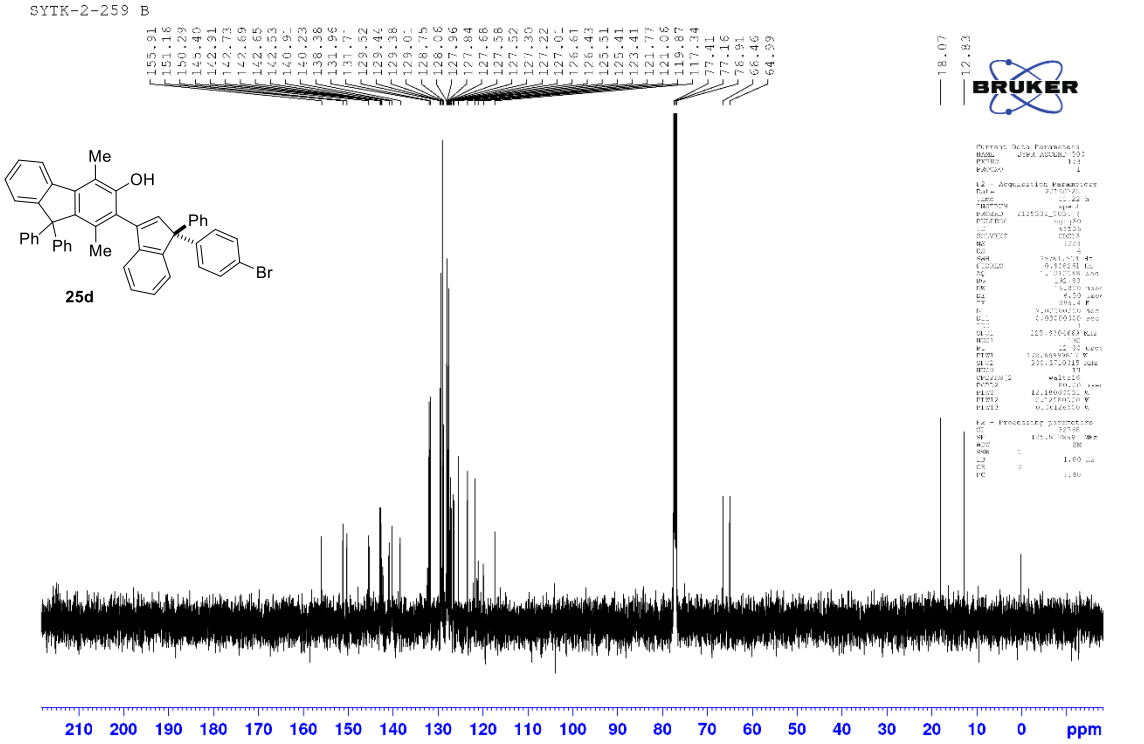


25b

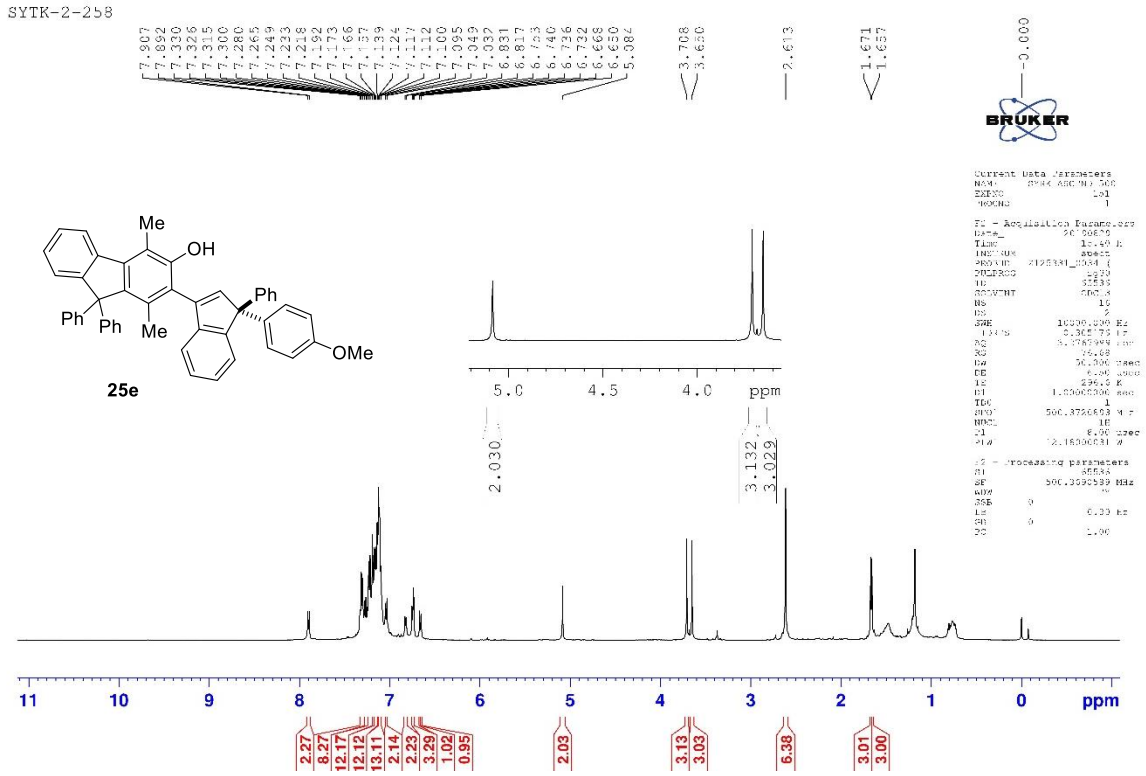



SYPR-3-F
Me
OH
Ph
Ph
Ph
Me
F
25c
5.2
5.0
ppm
1.000
0.917
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
2.13
10.25
10.05
14.12
8.17
4.15
2.01
4.15
2.00
1.00
0.92
5.89
2.73
2.91
SYPR-3-F
Me
OH
Ph
Ph
Ph
Me
F
25c
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

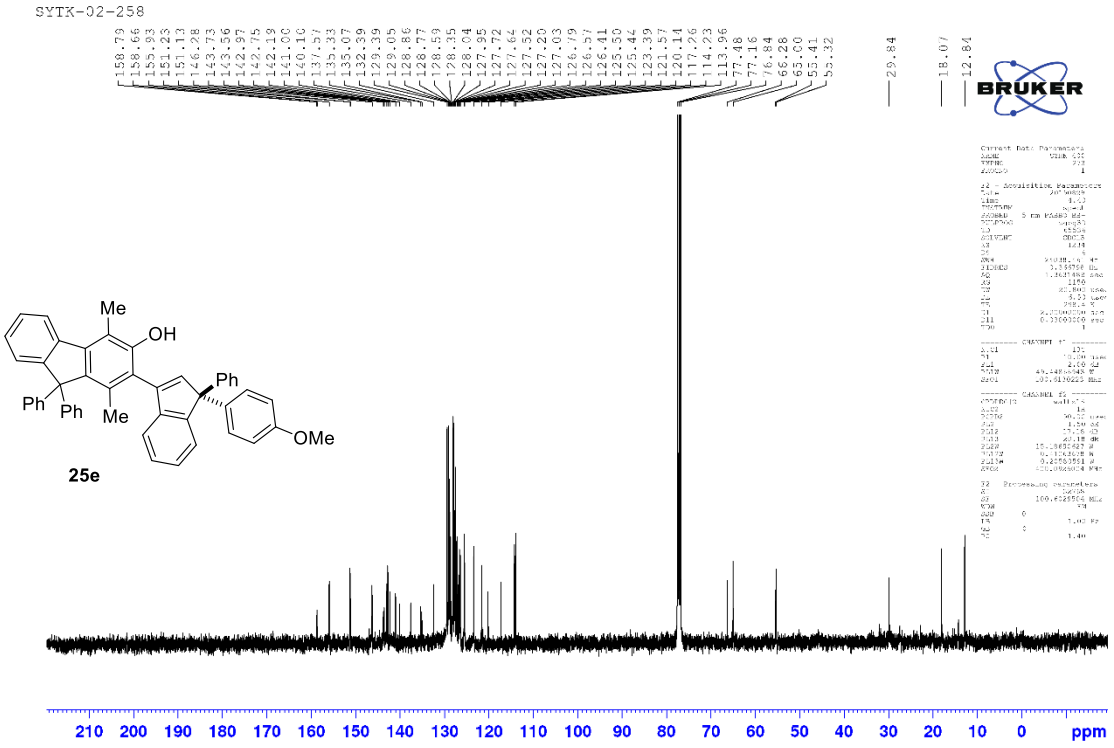

SYTK-2-259 B
Me
OH
Ph
Ph
Ph
Me
Br
25d
5.2 5.0 ppm
1.000
0.936
12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
2.15 8.17 14.18 10.37 14.16 2.15 2.31 1.99 2.00
1.00 0.94
6.37
2.92 3.34

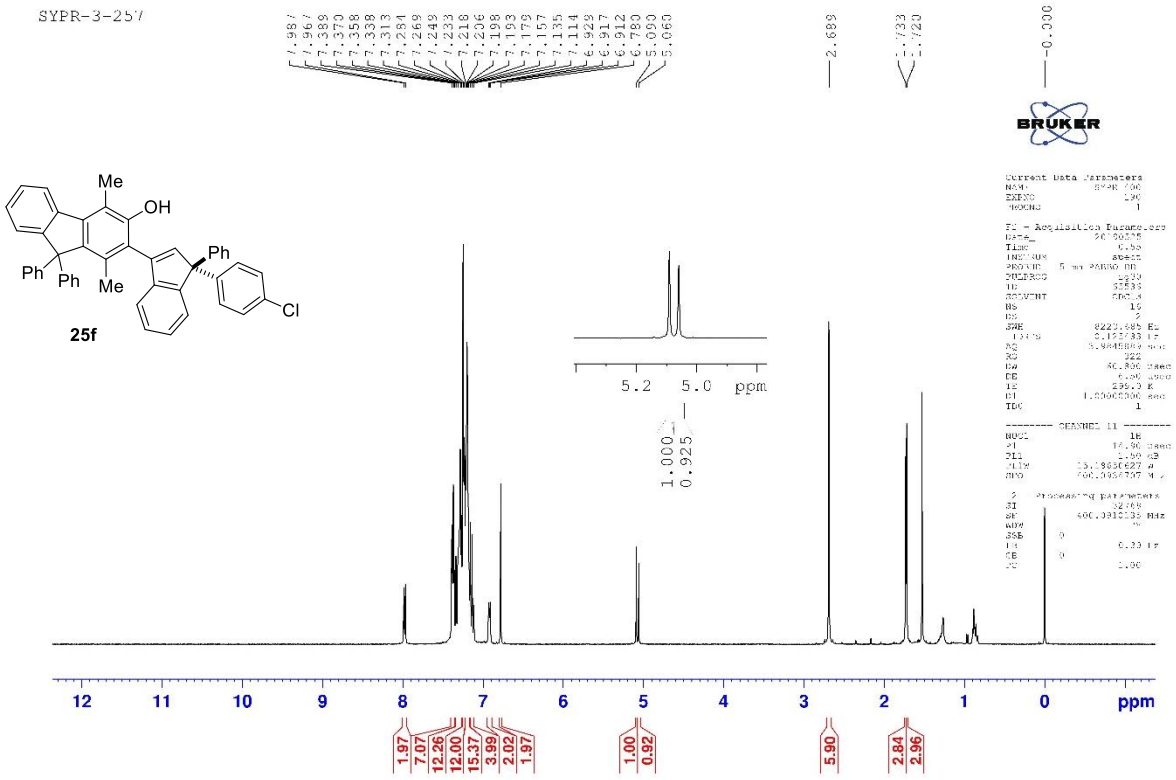

SYTK-2-259 B
Me
OH
Ph
Ph
Ph
Me
Br
25d
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

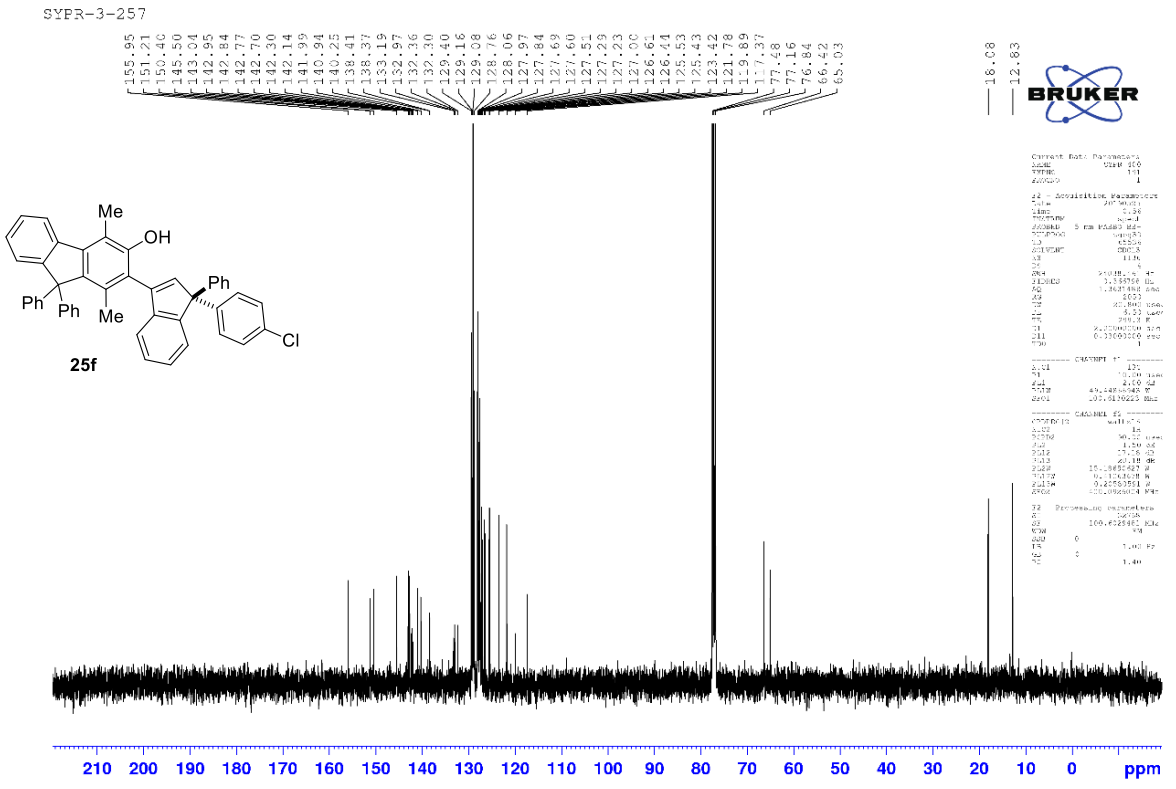
SYTK-2-258

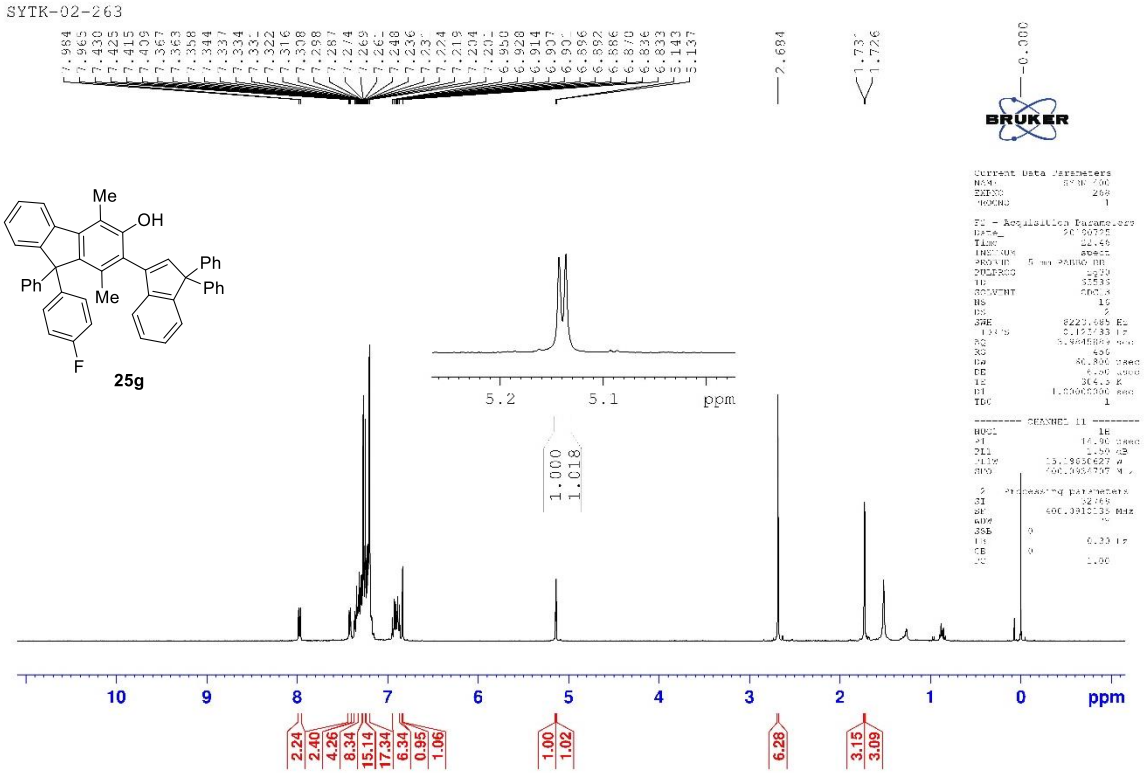


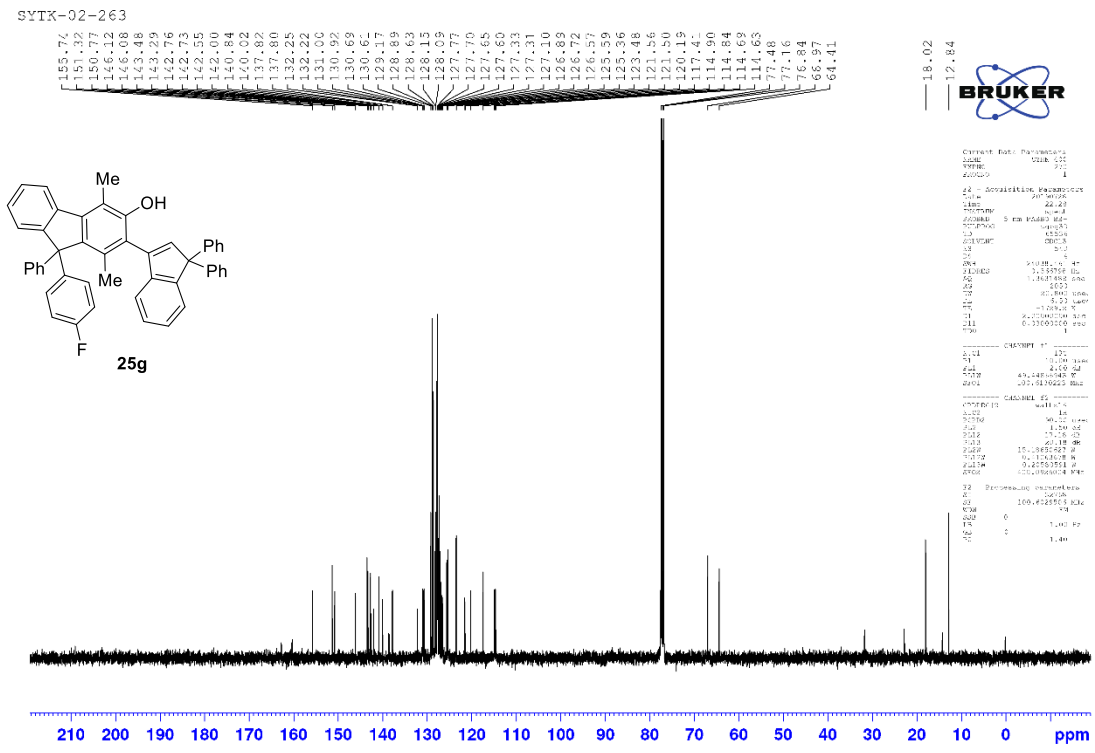
SYTK-02-258

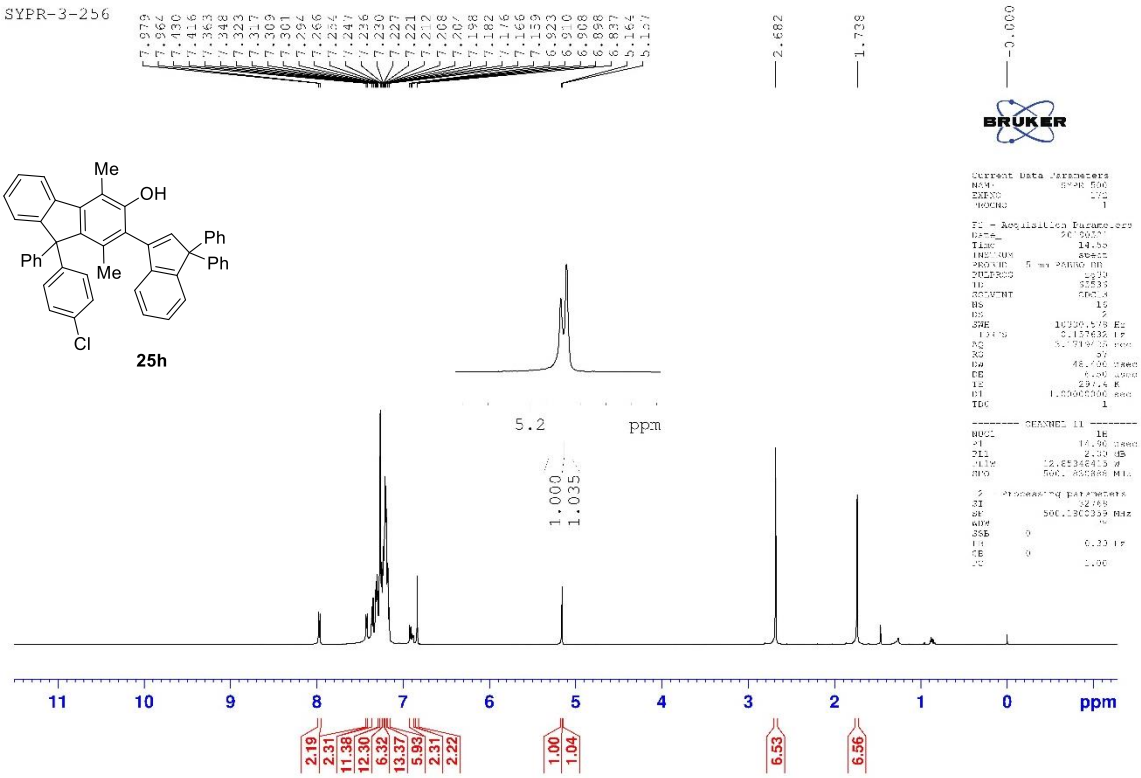


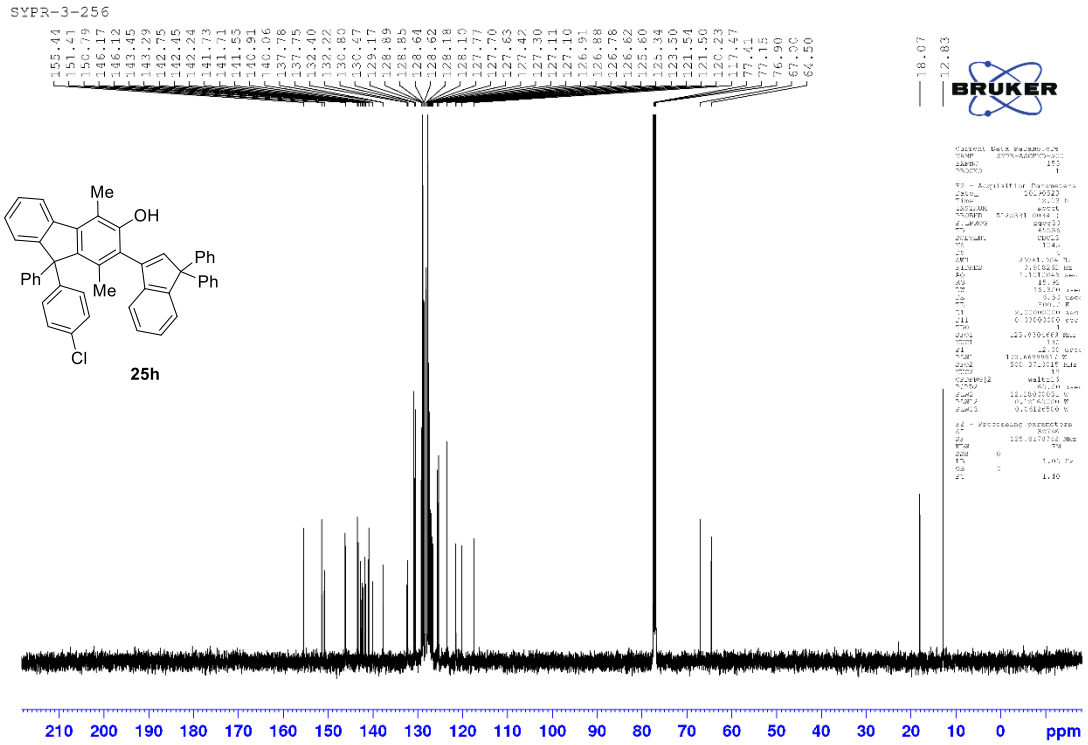

SYPR-3-257
Me
OH
Ph
Ph
Ph
Me
Cl
25f
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm

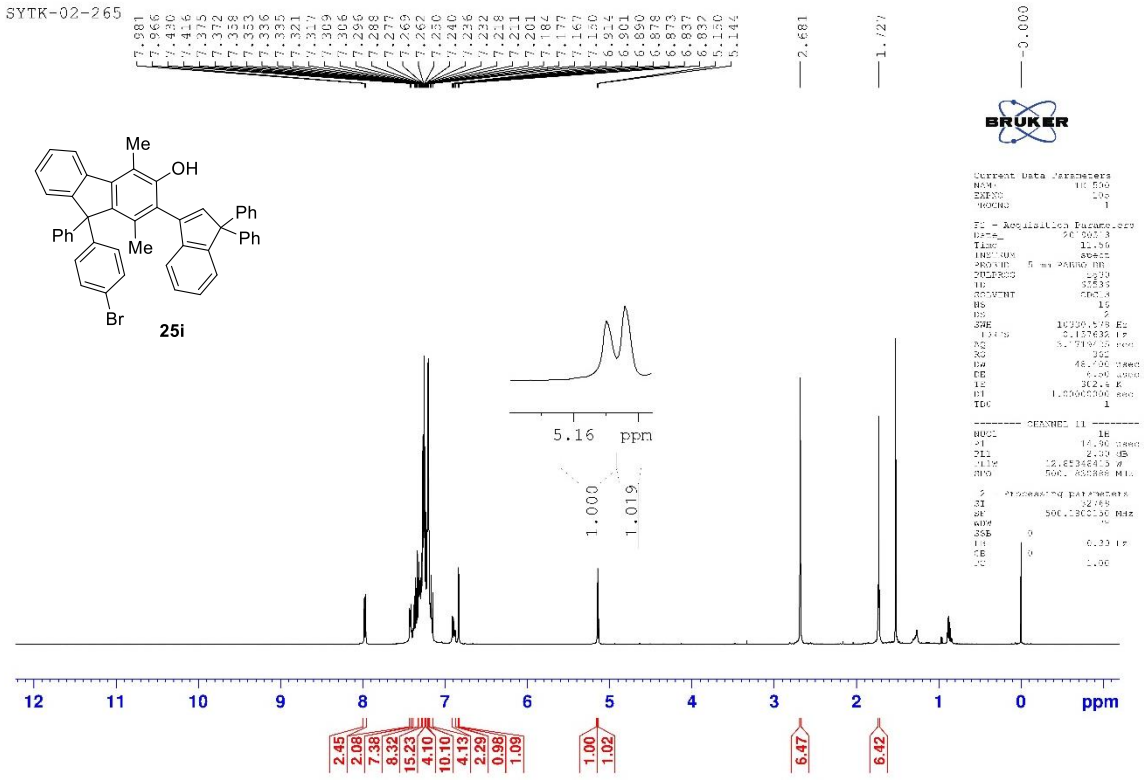

SYPR-3-257
Me
OH
Ph
Ph
Ph
Me
Cl
25f
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

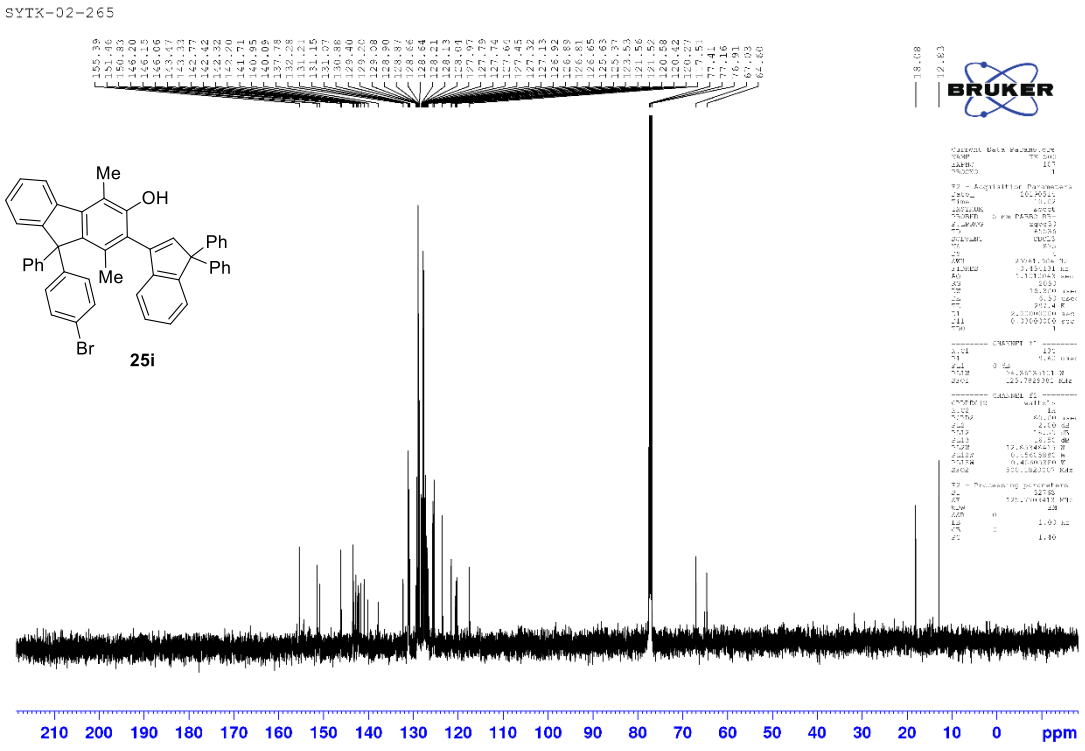

SYTK-02-263
Me
OH
Ph
Ph
Me
Ph
Ph
F
25g
5.2
5.1
ppm
1.000
1.018
10
9
8
7
6
5
4
3
2
1
0
ppm
2.24
2.40
4.26
8.34
15.14
17.34
6.34
0.95
1.06
1.00
1.02
6.28
3.15
3.09


SYTK-02-263
Me
OH
Ph
Ph
Me
Ph
Ph
F
25g
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

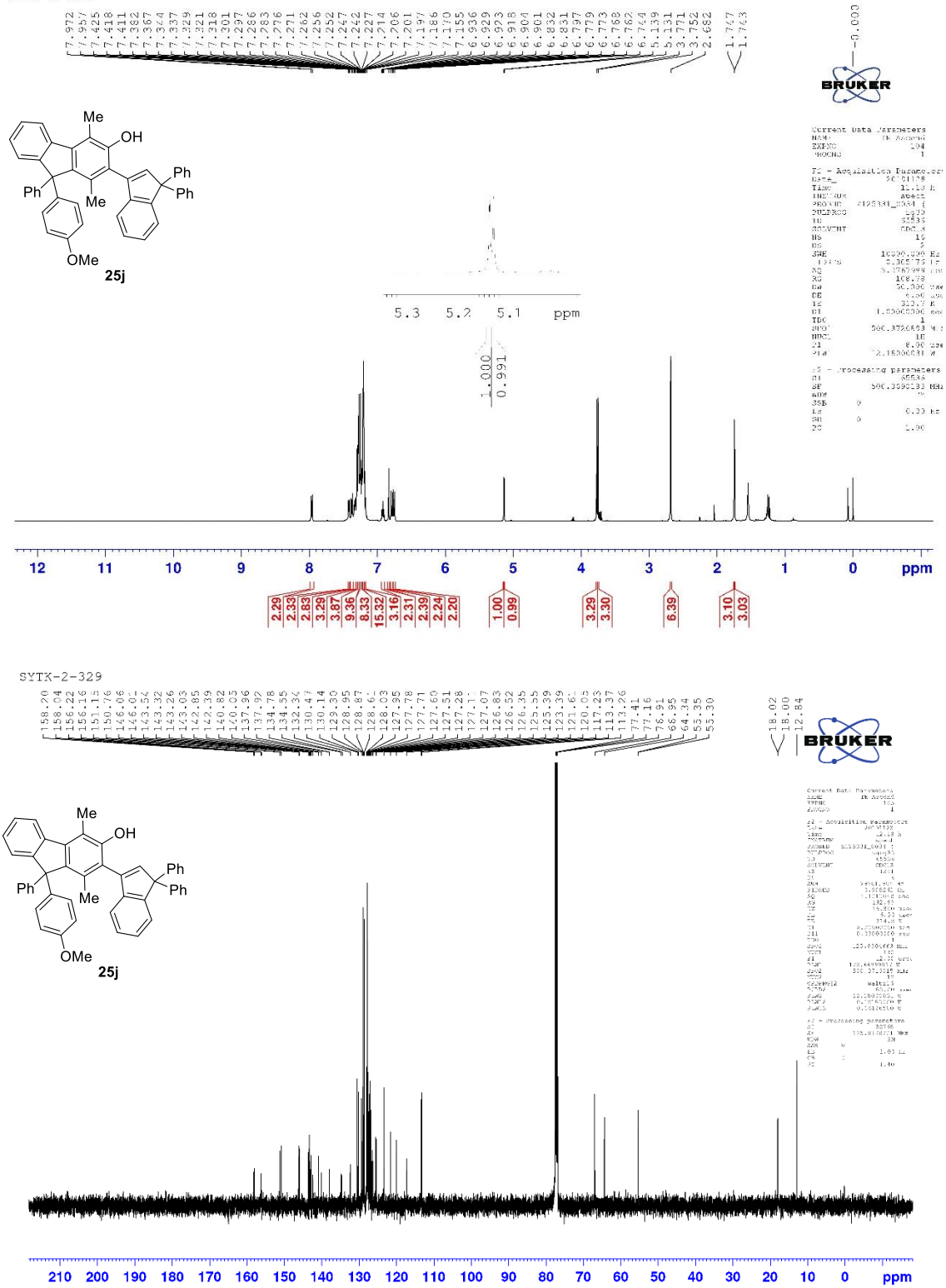

SYPR-3-256
Me
OH
Ph
Ph
Ph
Me
Cl
25h
5.2
ppm
1.000
1.035
11
10
9
8
7
6
5
4
3
2
1
0
ppm
2.19
2.31
11.38
12.30
6.32
13.37
5.93
2.31
2.22
1.00
1.04
6.53
6.56


SYPR-3-256
Me
OH
Ph
Ph
Ph
Me
Cl
25h
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

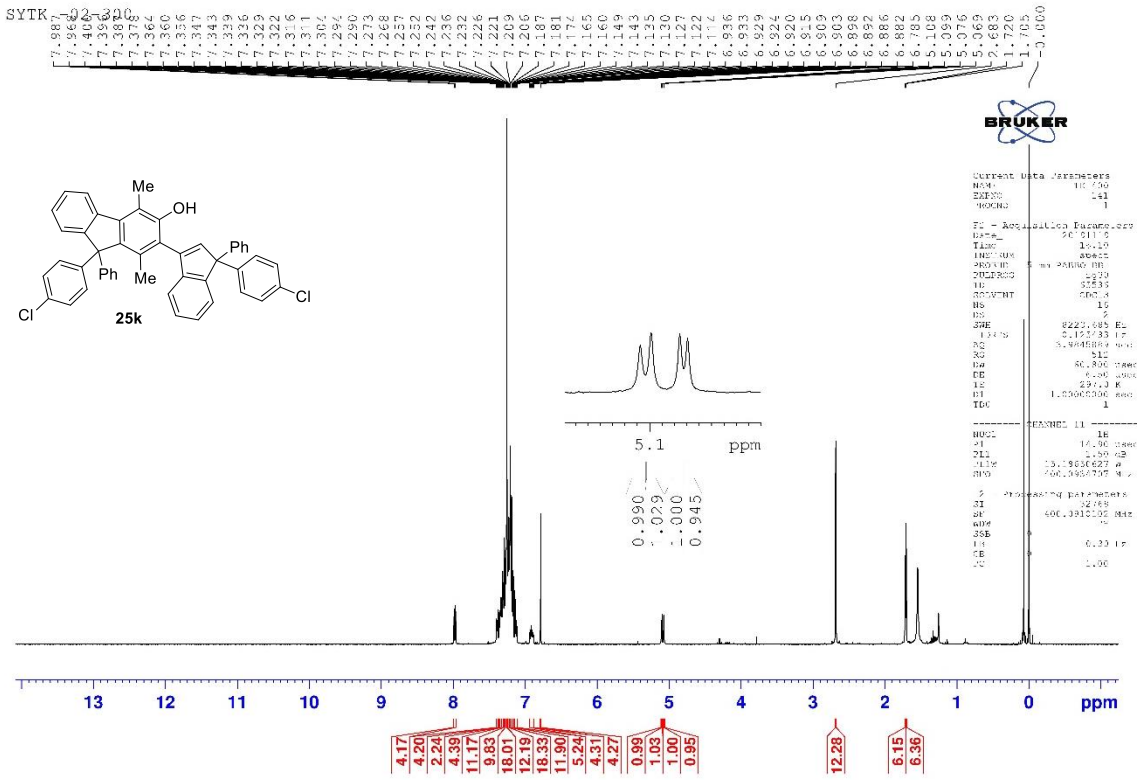

SYTK-02-265
Me
OH
Ph
Ph
Me
Ph
Ph
Me
Br
25i
5.16 ppm
1.000
1.019
2.45
2.08
7.38
8.32
15.23
4.10
10.10
4.13
2.29
0.98
1.09
1.00
1.02
6.47
6.42
12 11 10 9 8 7 6 5 4 3 2 1 0 ppm

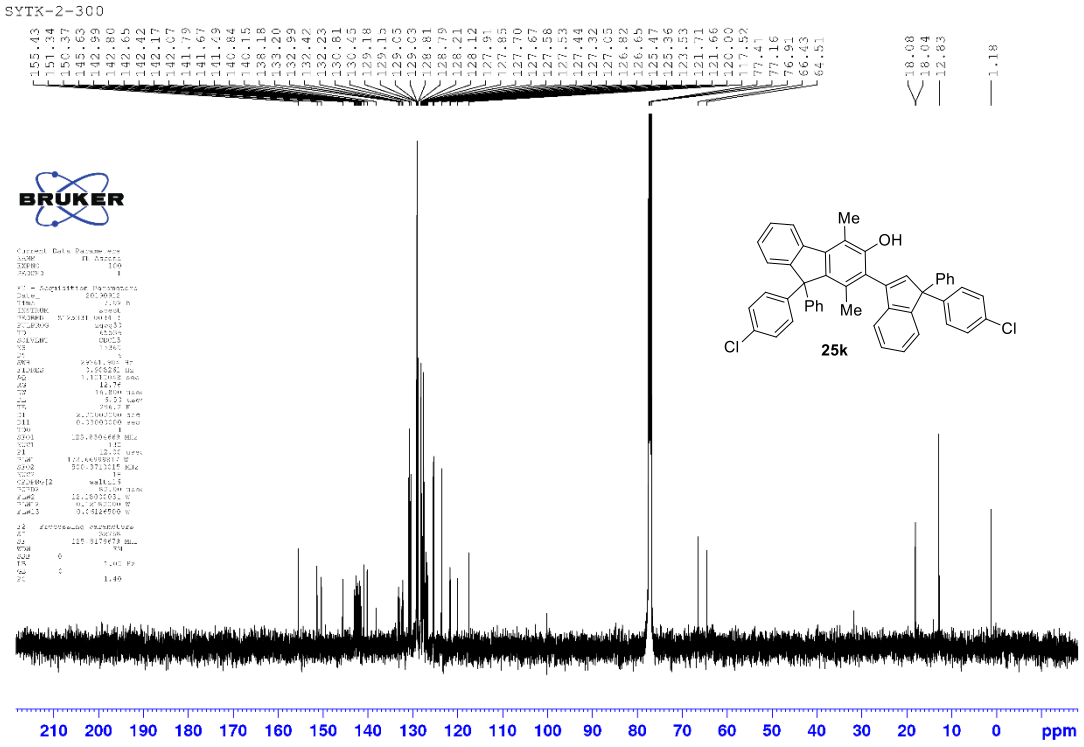

SYTK-02-265
Me
OH
Ph
Ph
Me
Ph
Ph
Me
Br
25i
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

SYTK-2-329

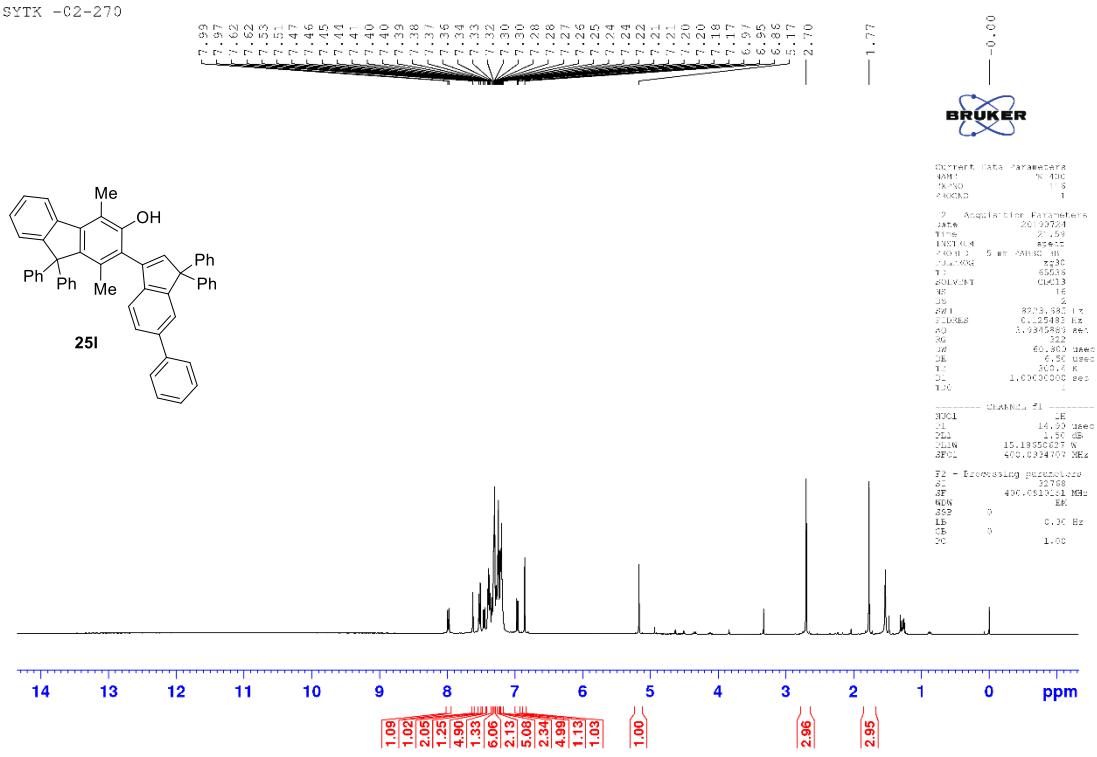


SYTK-2-329

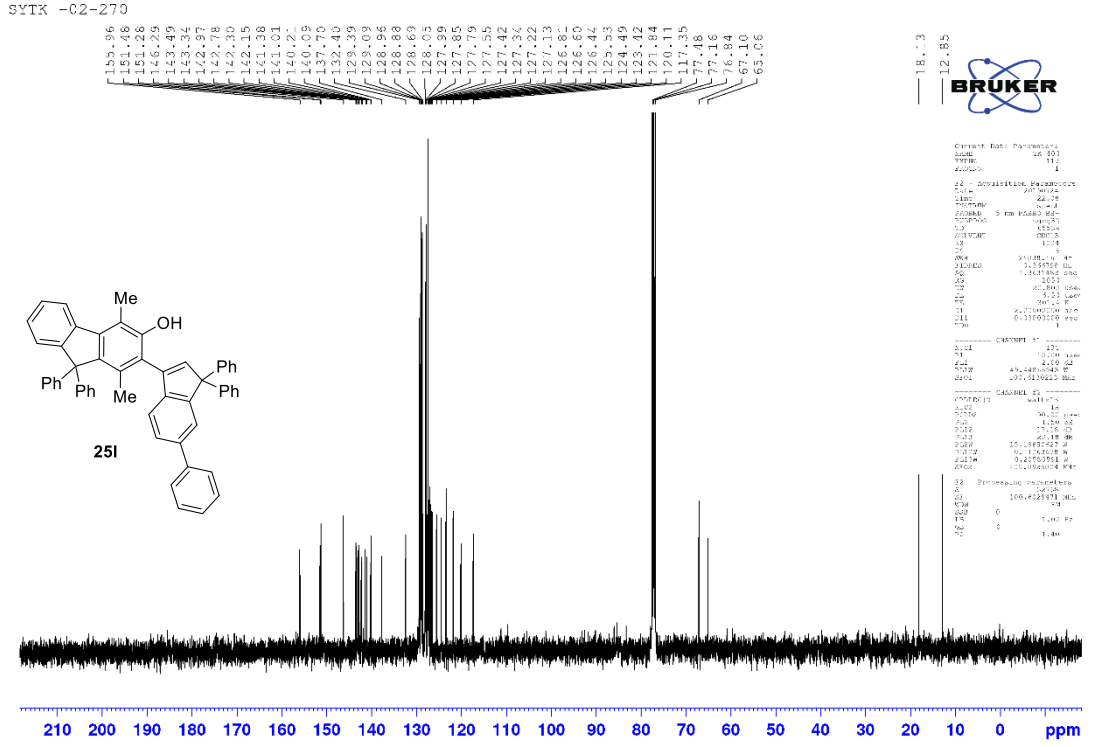

SYTK-02-300
Me
OH
Ph
Ph
Me
Cl
Cl
25k
5.1
ppm
13
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm


SYTK-2-300
Me
OH
Ph
Ph
Me
Cl
Cl
25k
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

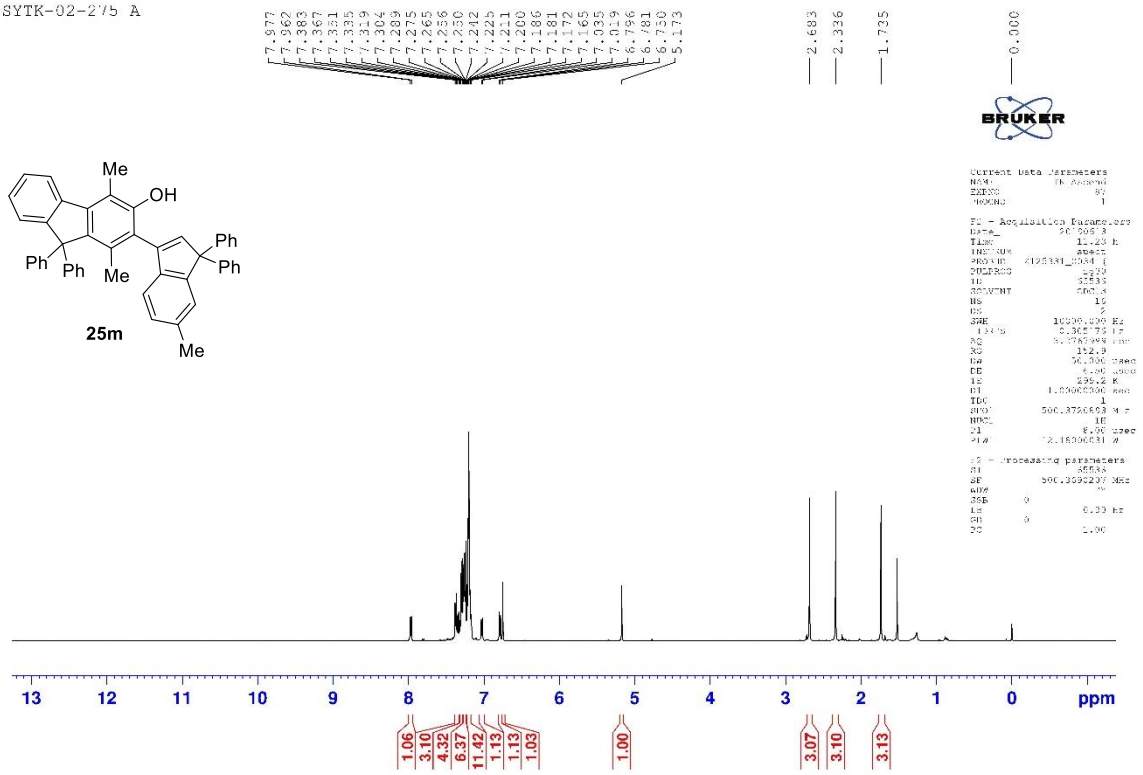
SYTX -02-270



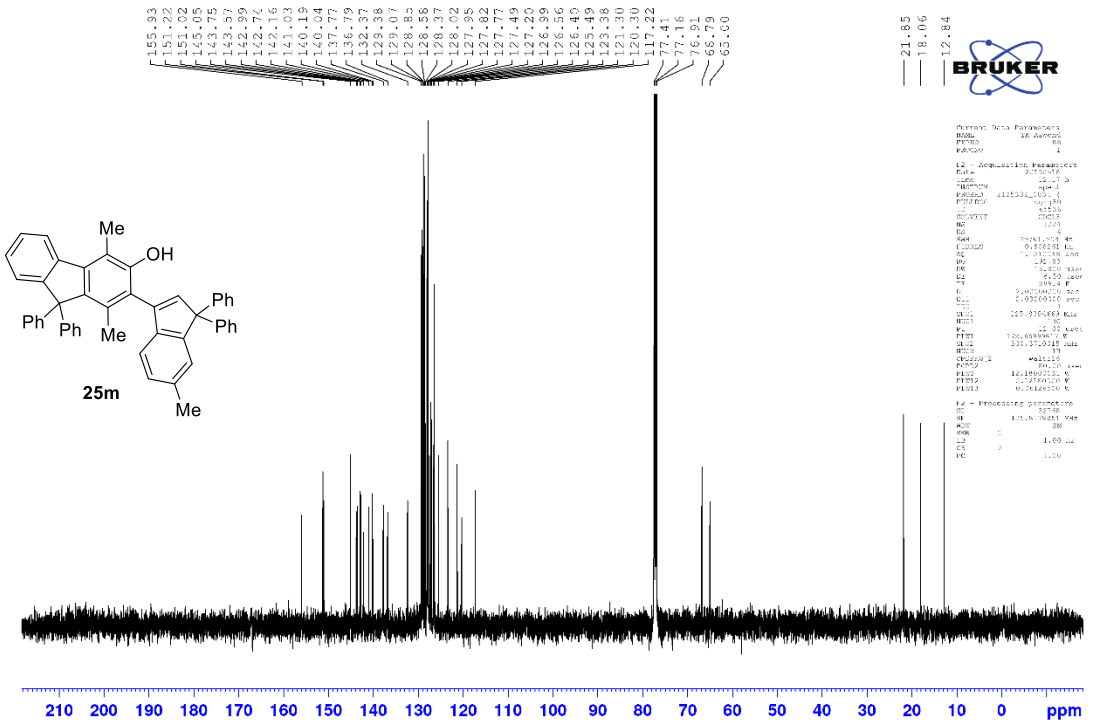
SYTX -02-270



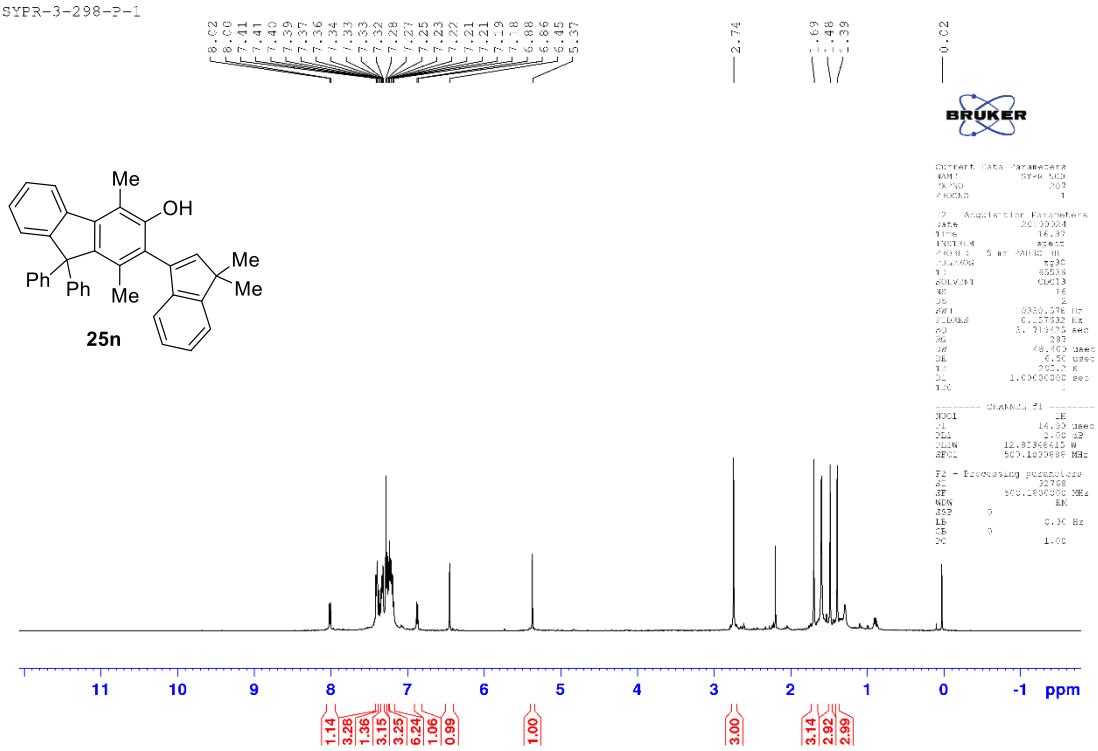
SYTK-02-275 A



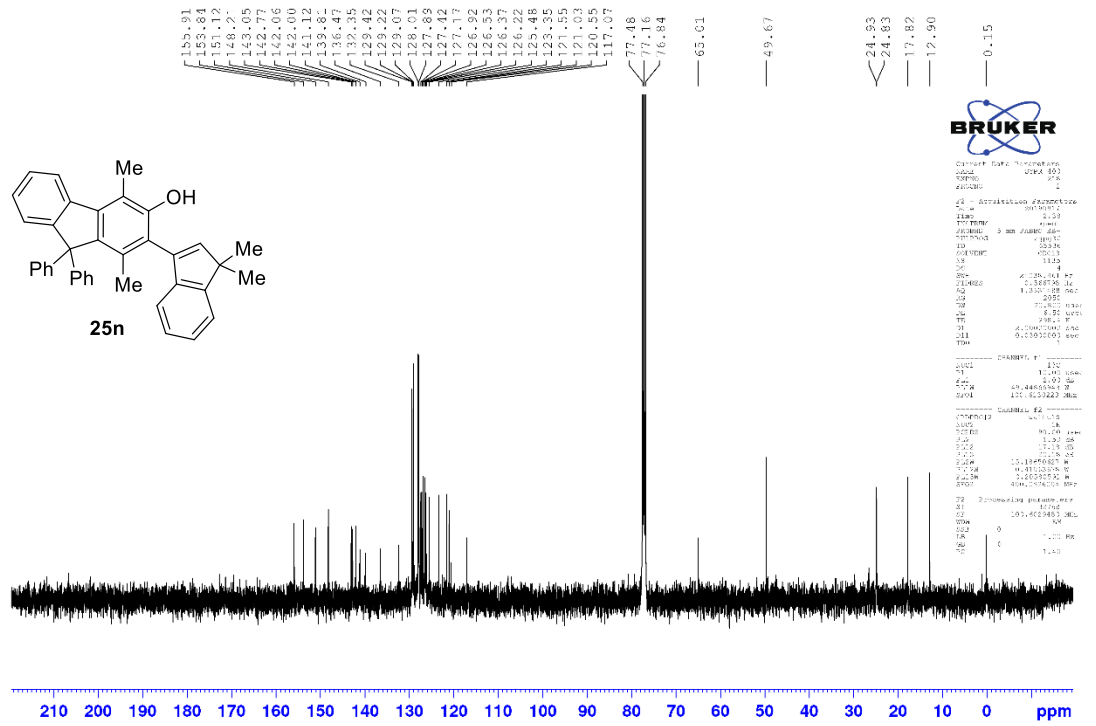
SYTK-02-275 A



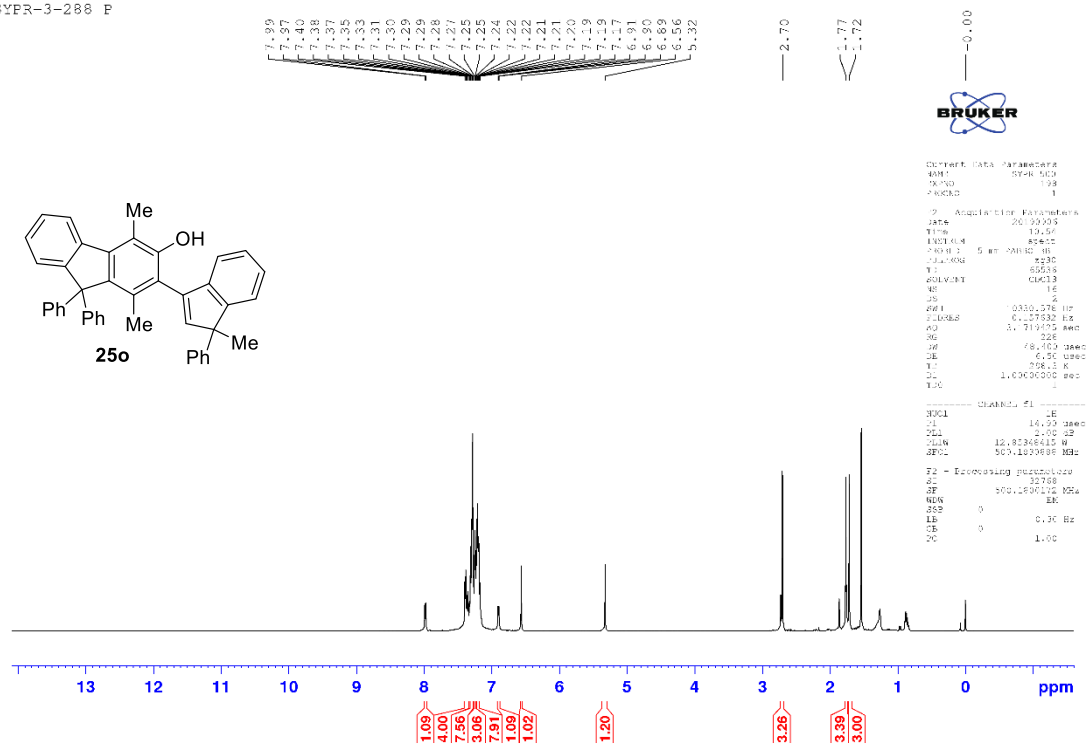
SYPR-3-298-P-1



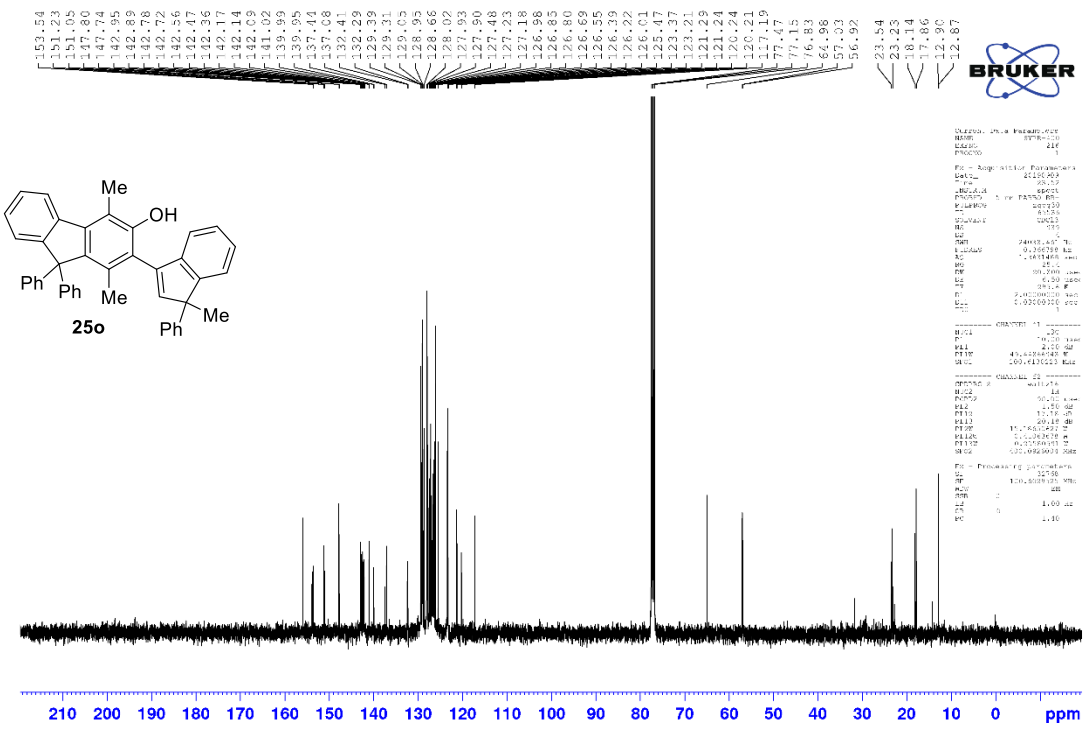
SYPR-3-289P



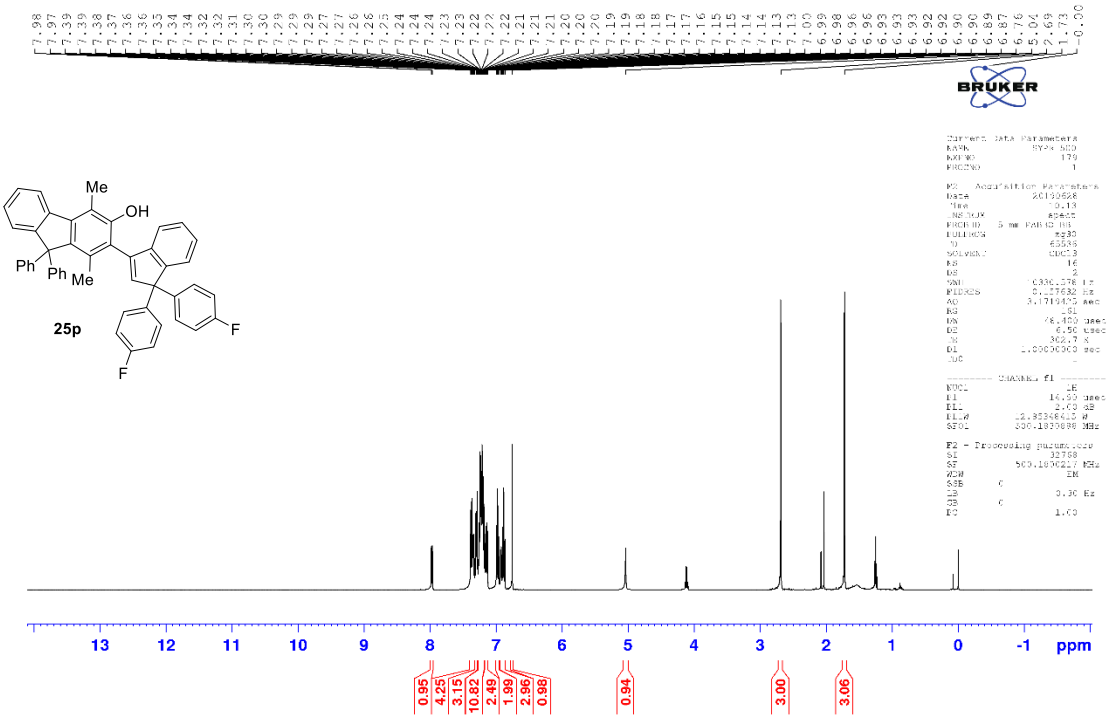
SYPR-3-288 P



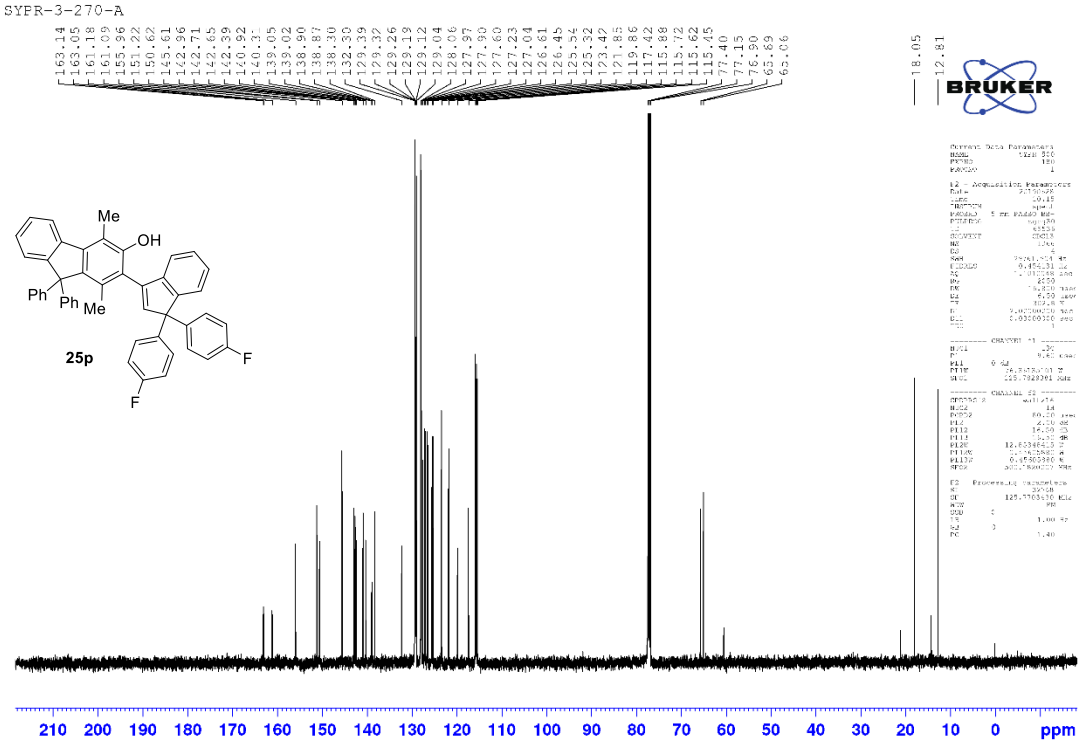
SYPR-3-288P



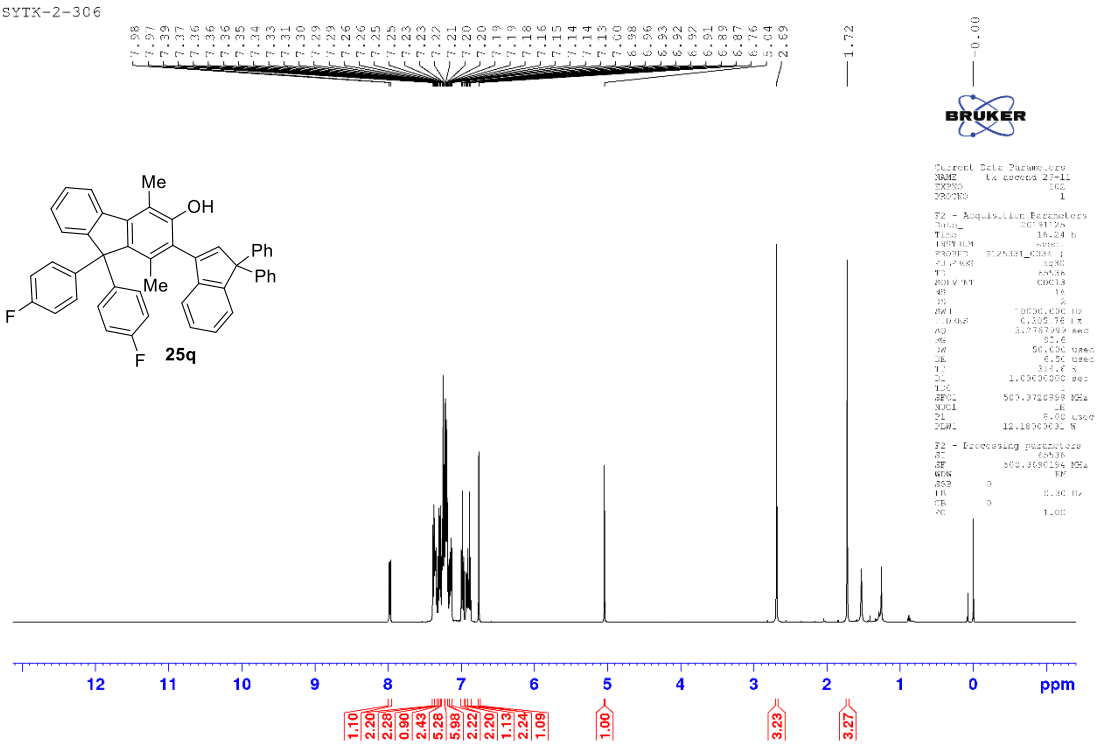
SYPR-3-270-A



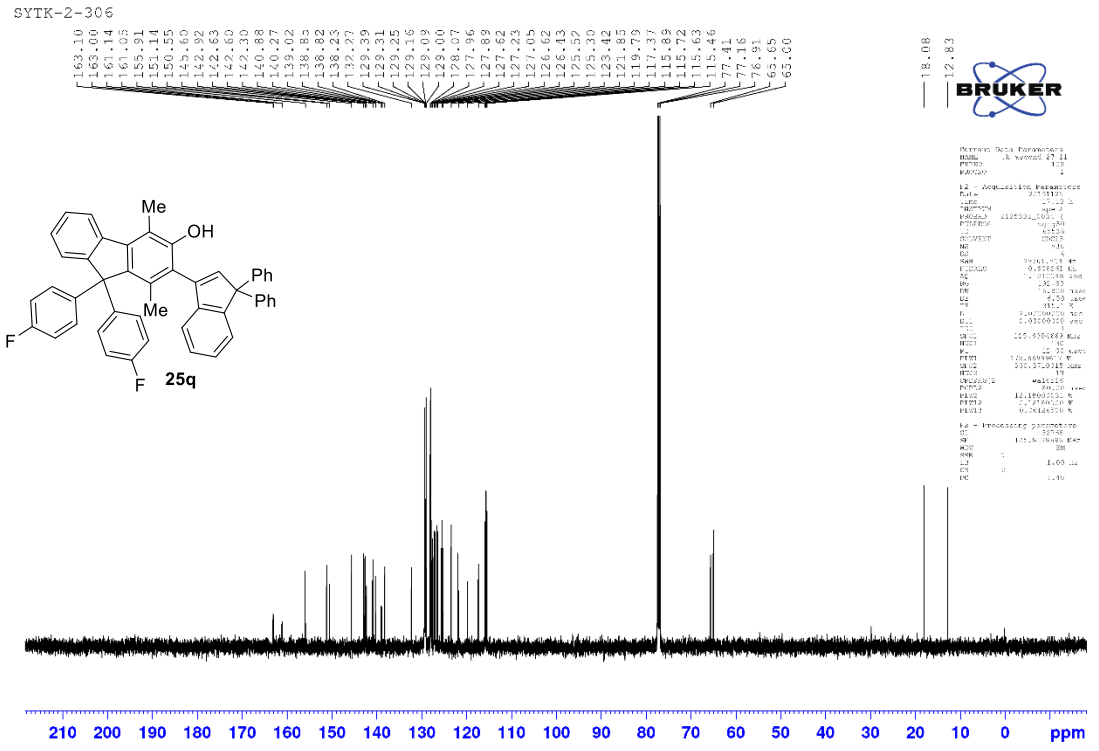
SYPR-3-270-A



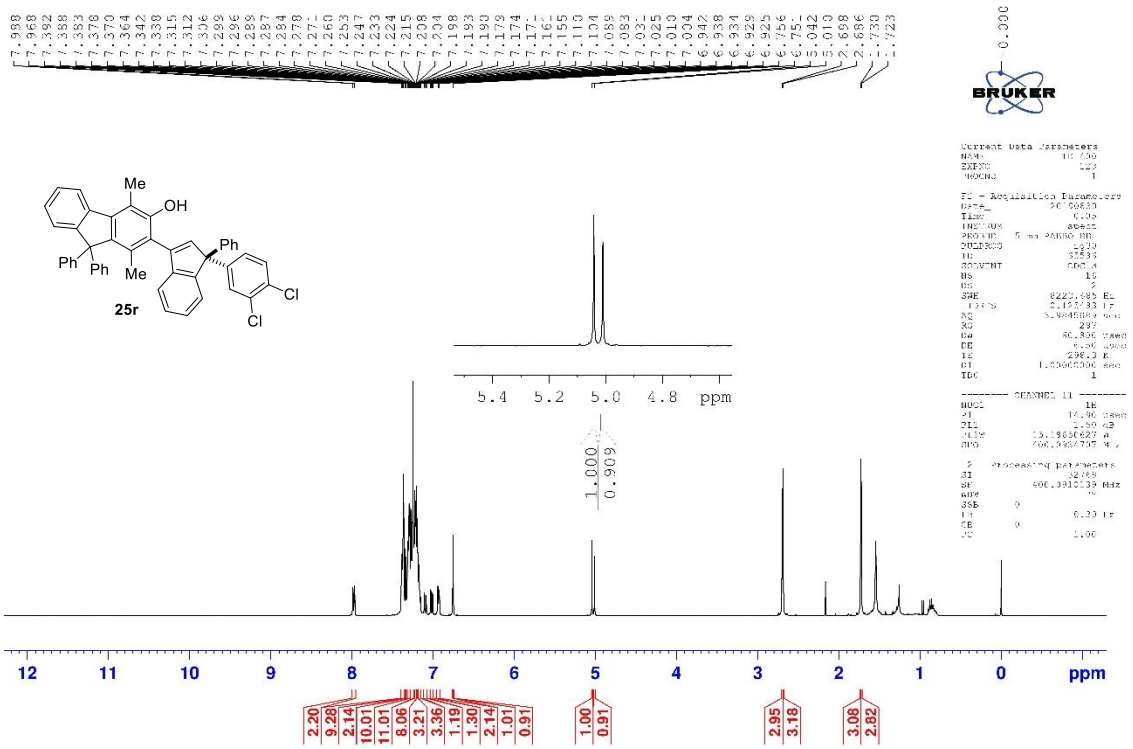
SYTK-2-306



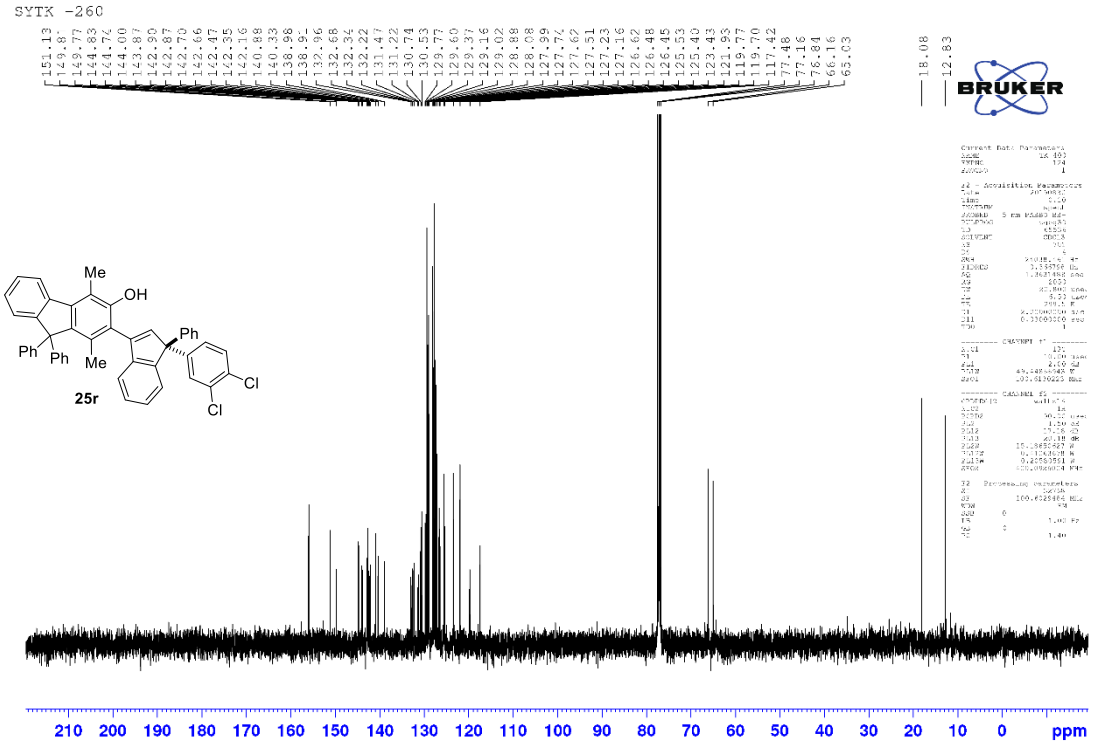
SYTK-2-306



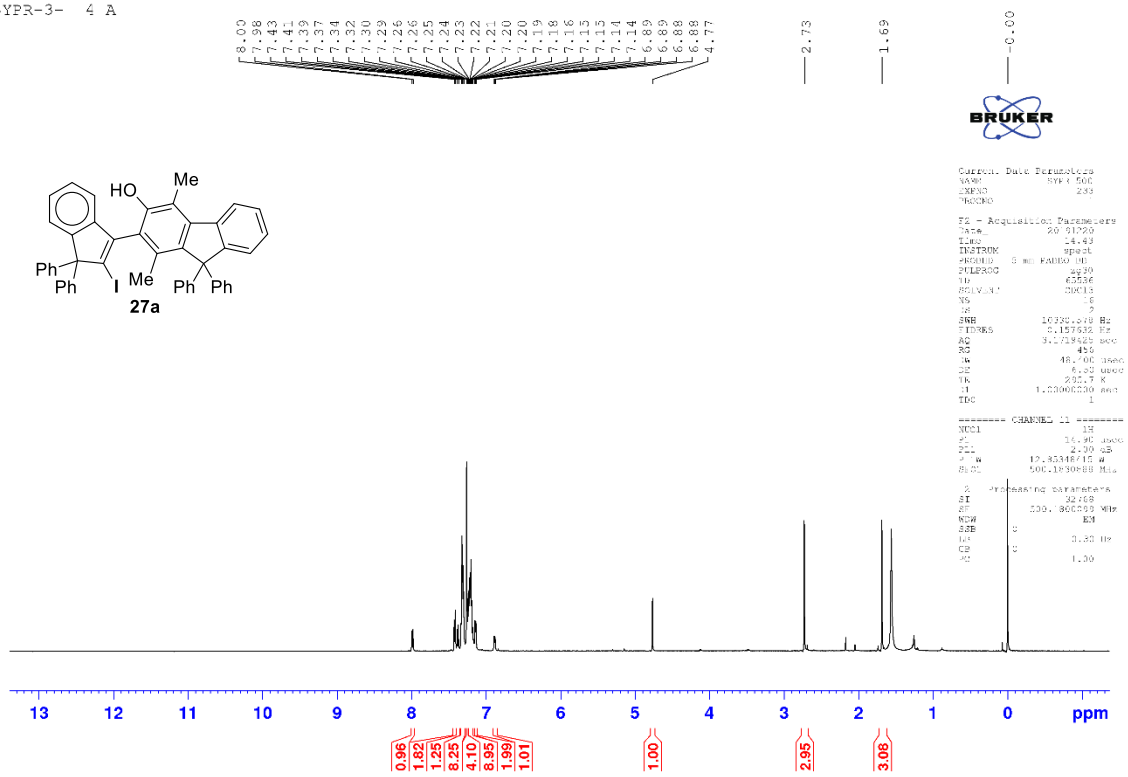
SYTK -260



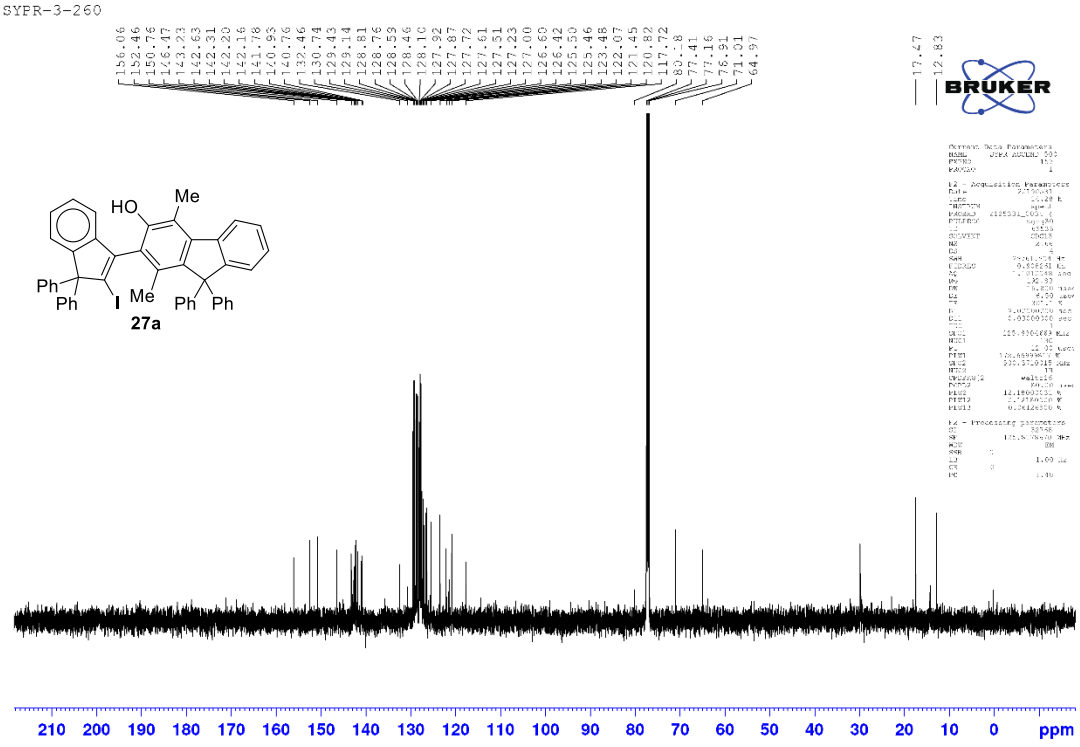
SYTK -260

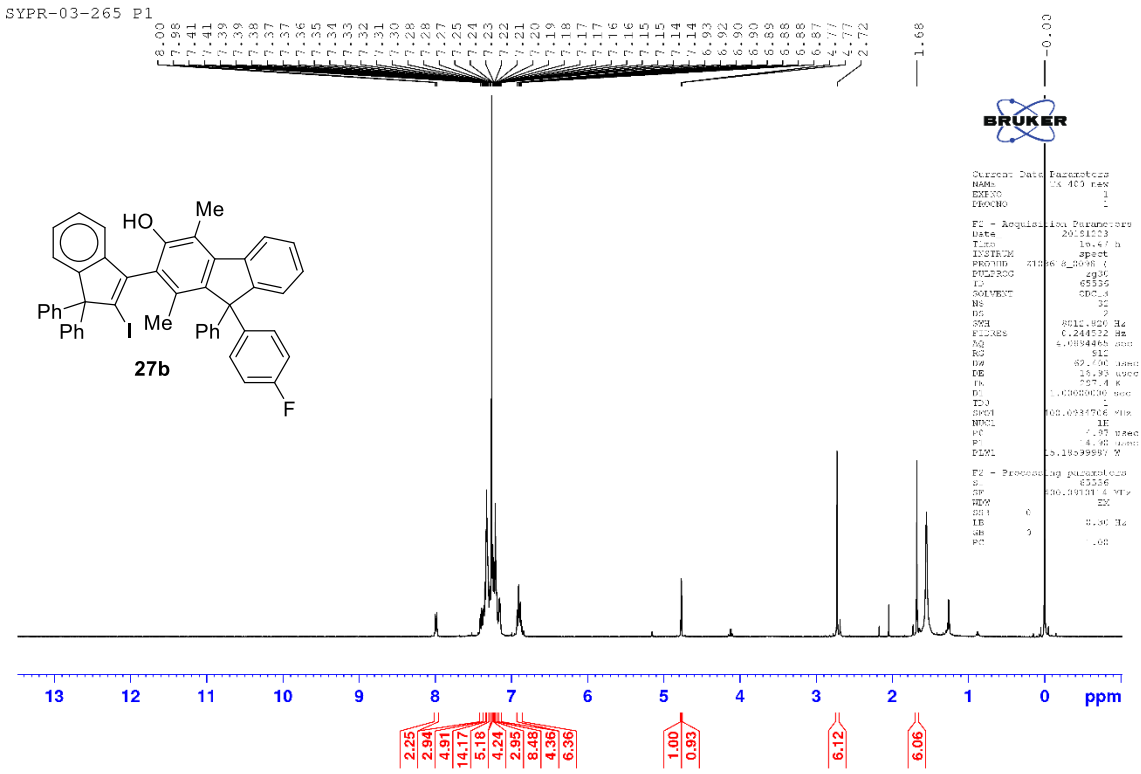


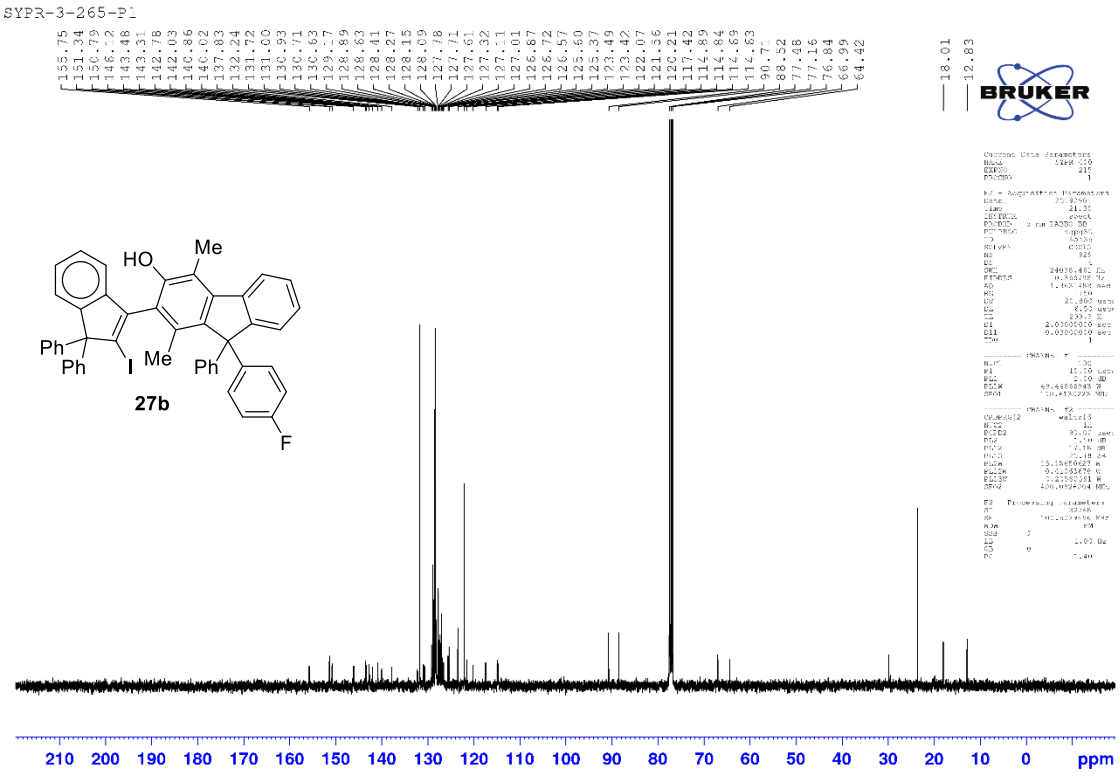
SYPR-3- 4 A

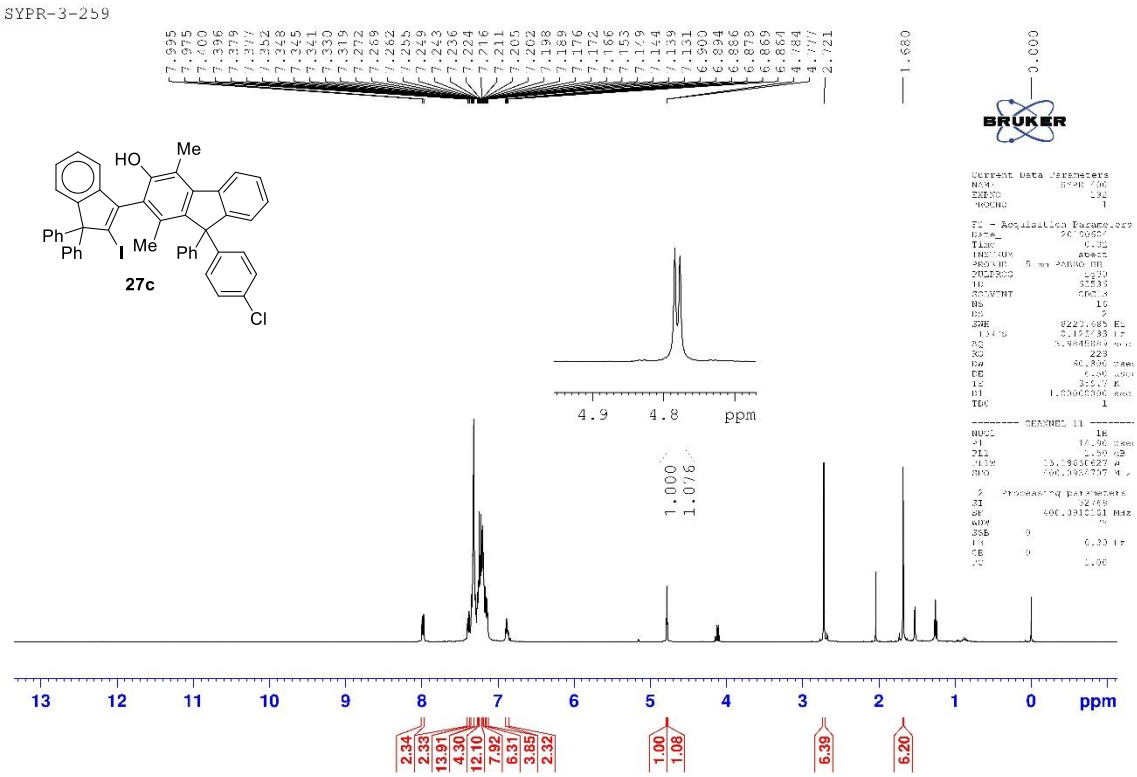


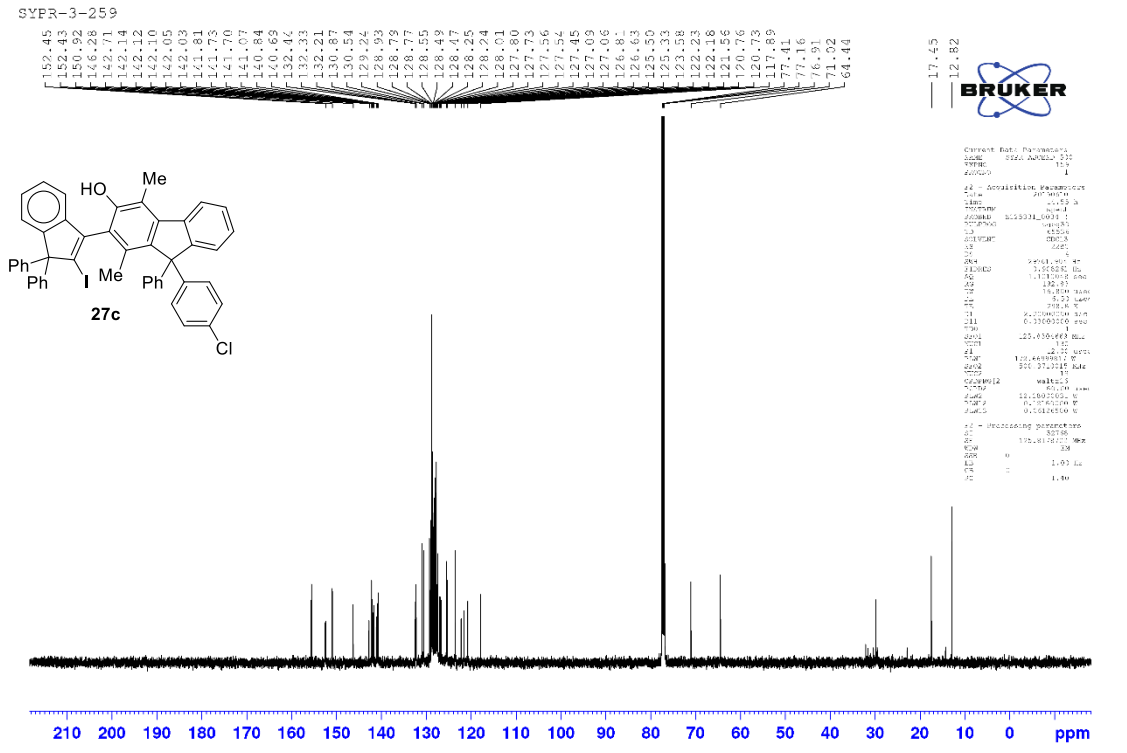
SYPR-3-260

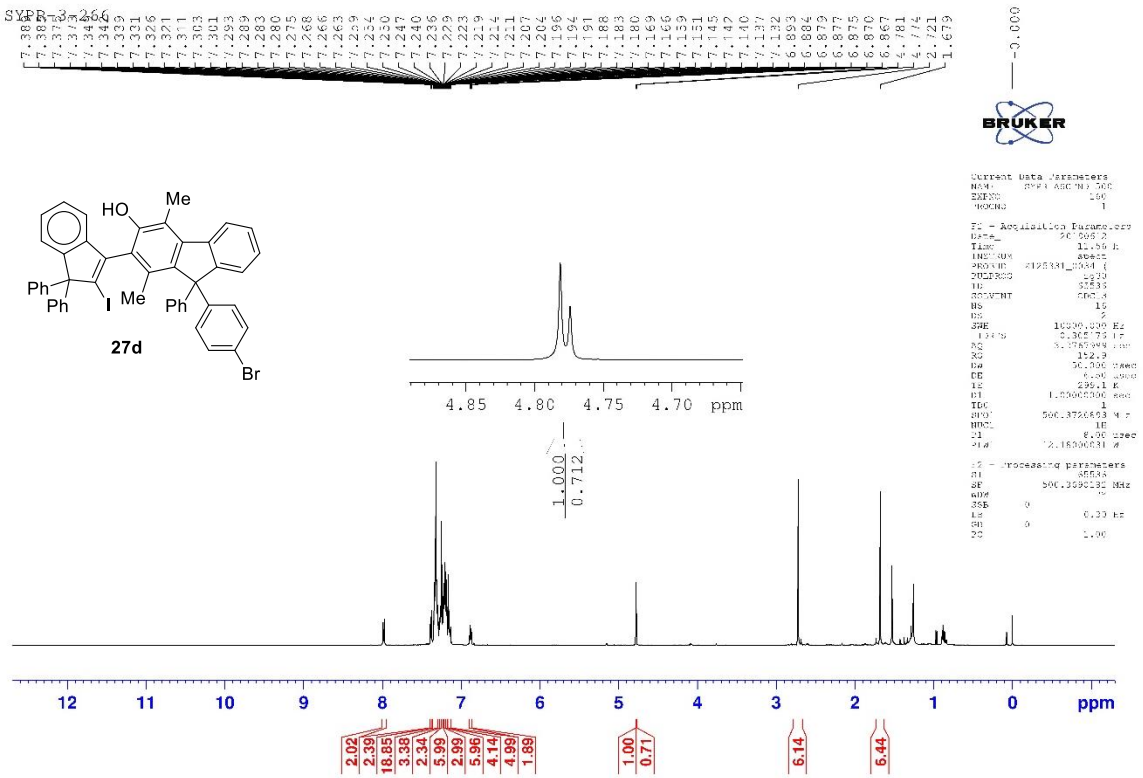


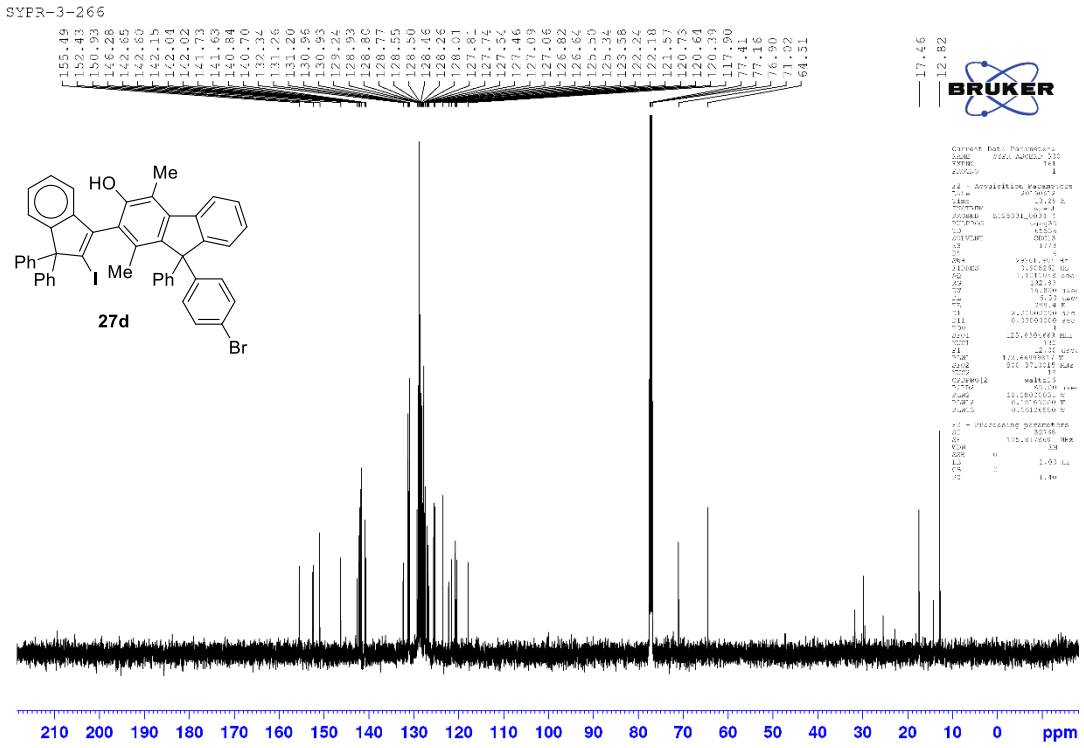

SYPR-03-265 P1
HO
Me
Ph
Ph
Me
Ph
F
27b
BRUKER
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
2.25 2.94 4.91 14.17 5.18 4.24 2.95 8.48 4.36 6.36 1.00 0.93 6.12 6.06


SYPR-3-265-P1
HO
Me
Ph
Ph
Me
Ph
F
27b
BRUKER
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

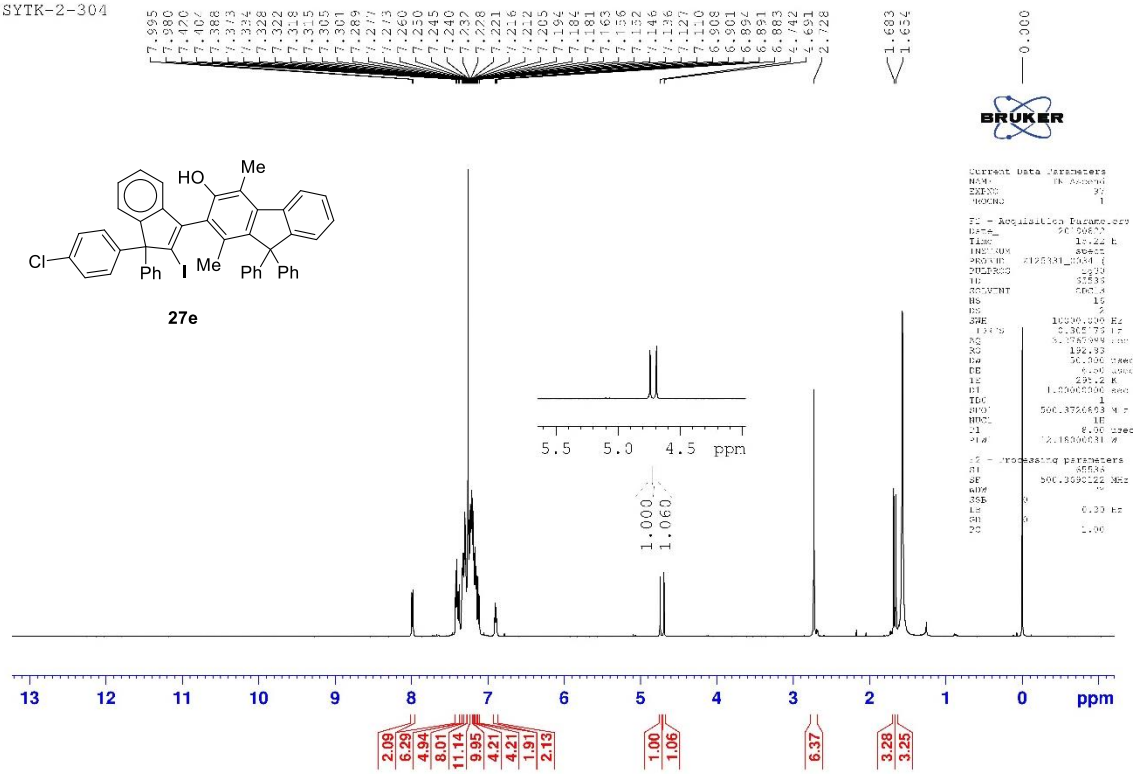

SYPR-3-259
HO
Me
Ph
Ph
Me
Ph
Cl
27c
ppm


SYPR-3-259
HO
Me
Ph
Ph
Me
Ph
Cl
27c
ppm


SYPR-3-266
HO
Me
Ph
Ph
Me
Ph
Br
27d
4.85
4.80
4.75
4.70
ppm
1.000
0.712
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
2.02
2.39
18.85
3.38
2.34
5.99
2.99
5.96
4.14
4.99
1.89
1.00
0.71
6.14
6.44

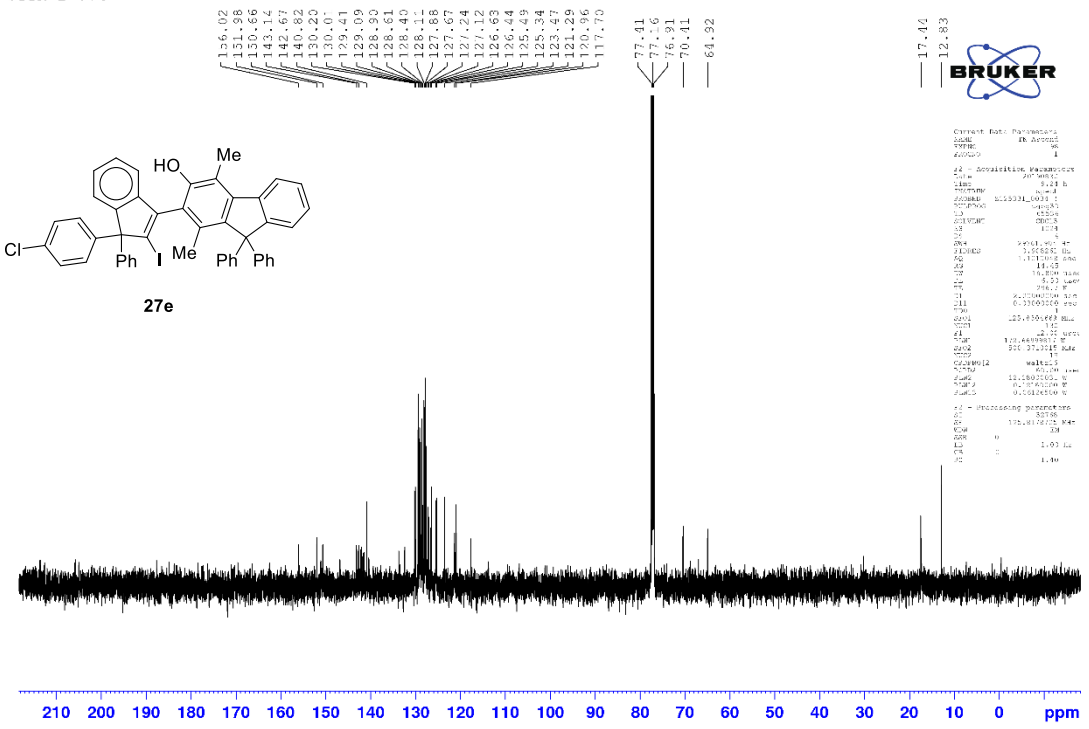

SYPR-3-266
HO
Me
Ph
Ph
Me
Ph
Br
27d
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

SYTK-2-304



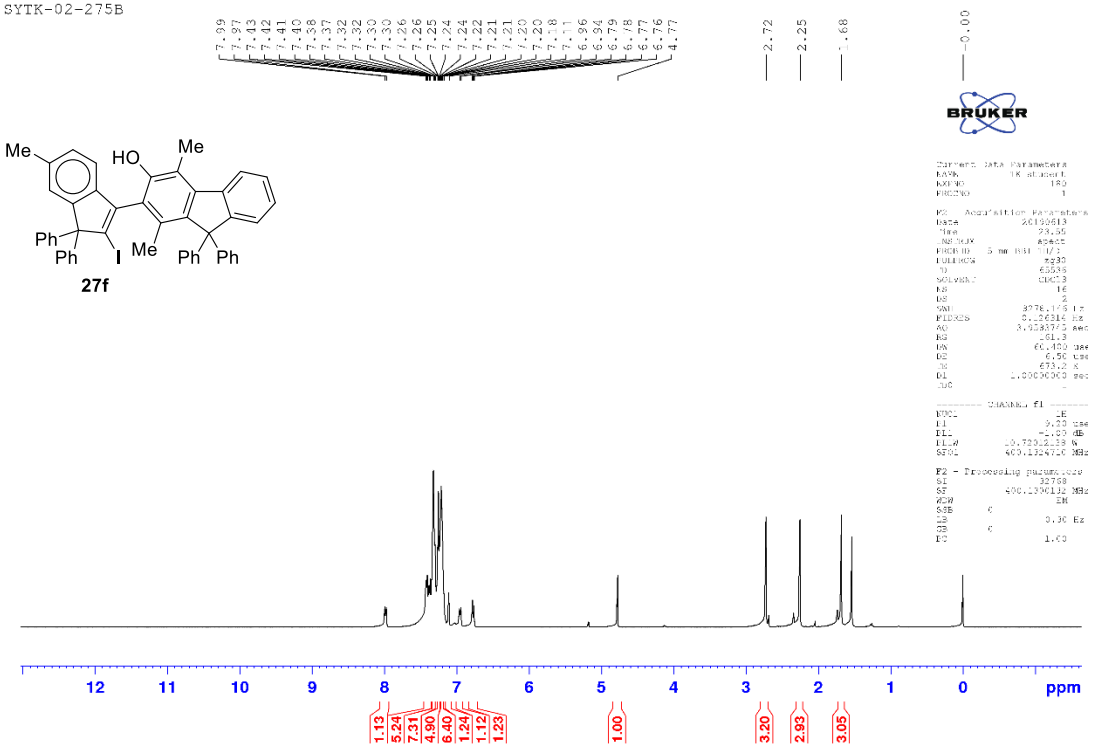
27e

SYTK-2-304

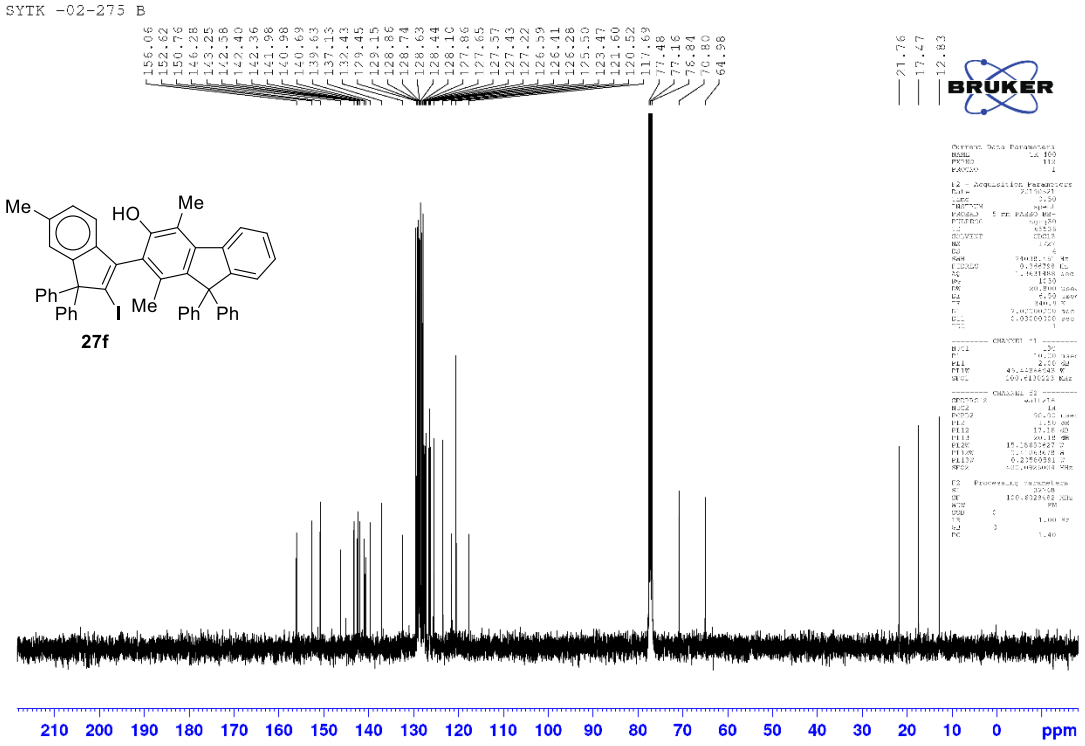


27e

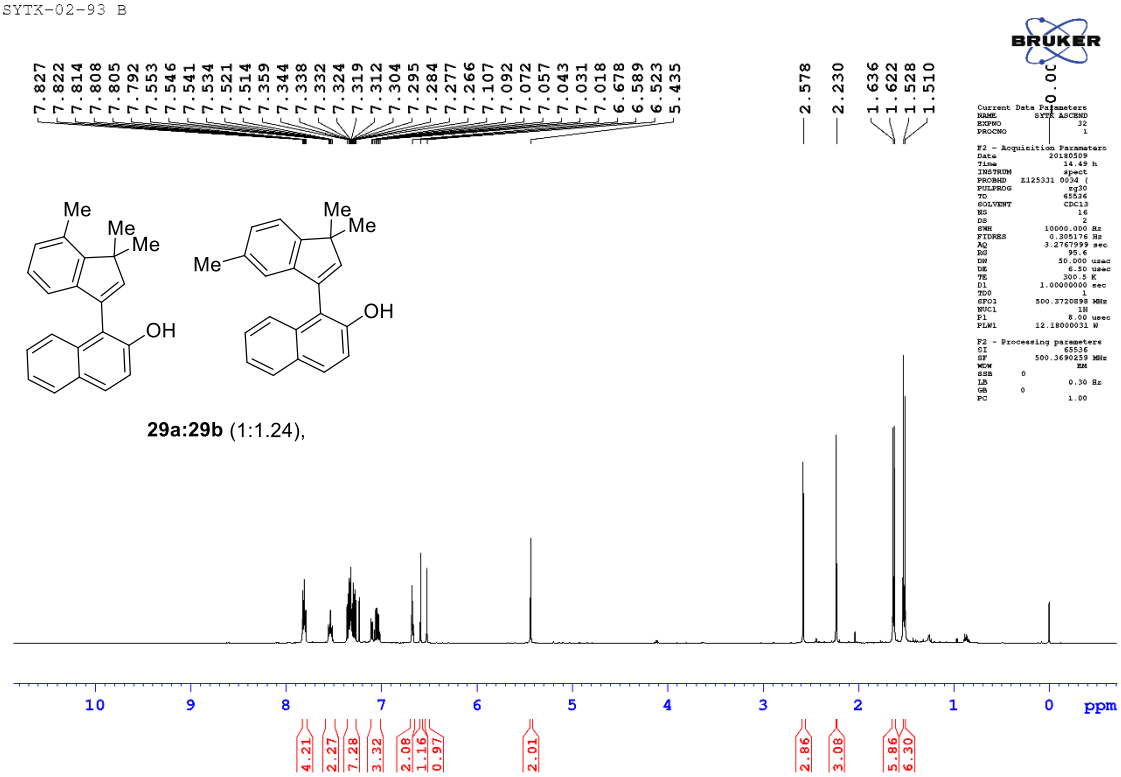
SYTK-02-275B



SYTK -02-275 B

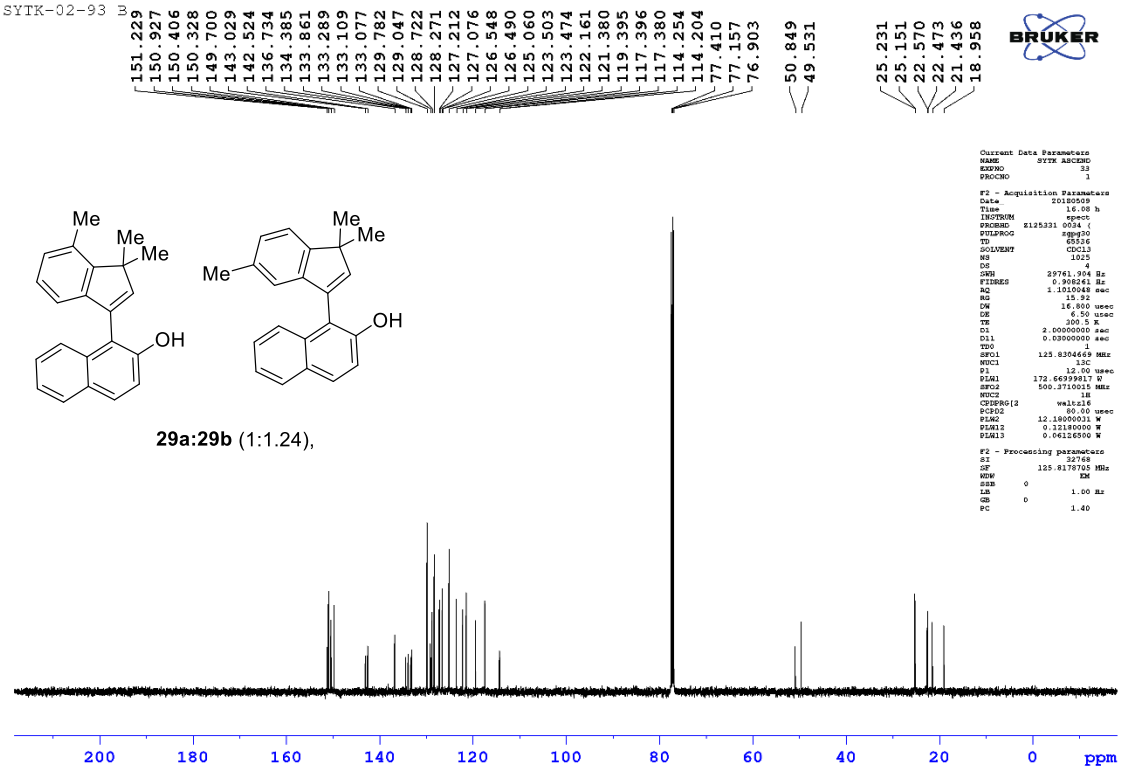


SYTK-02-93 B



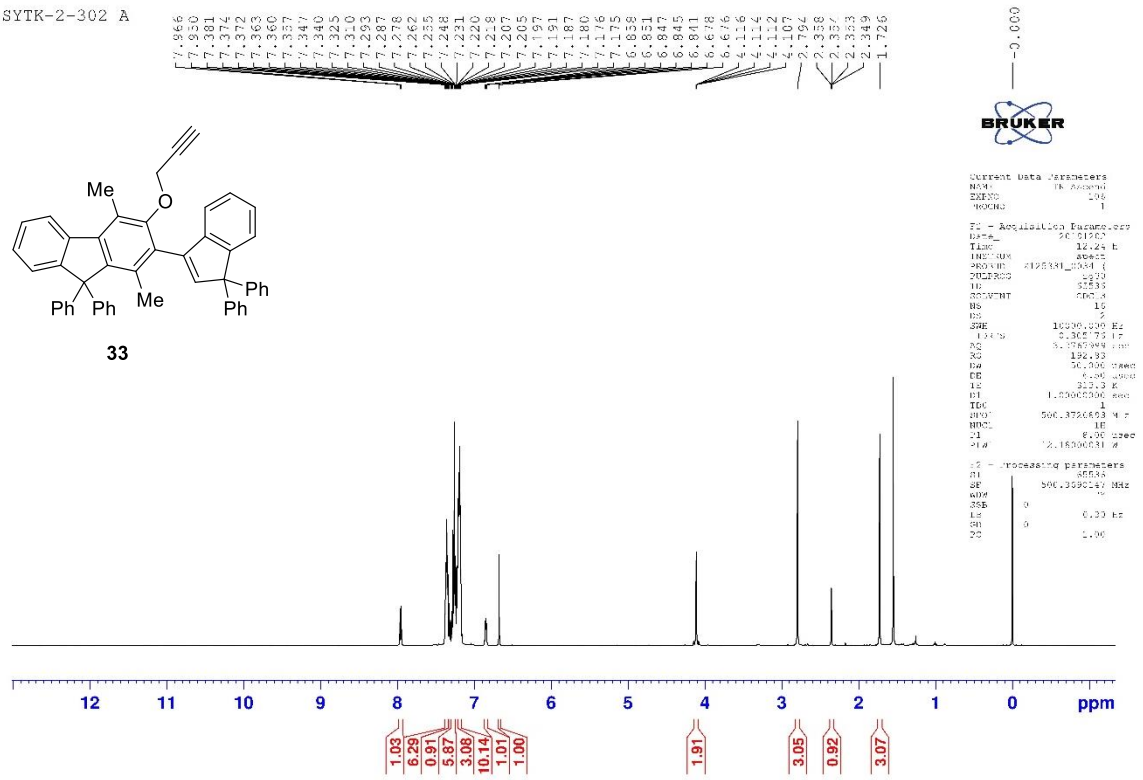
29a:29b (1:1.24),

SYTK-02-93 B

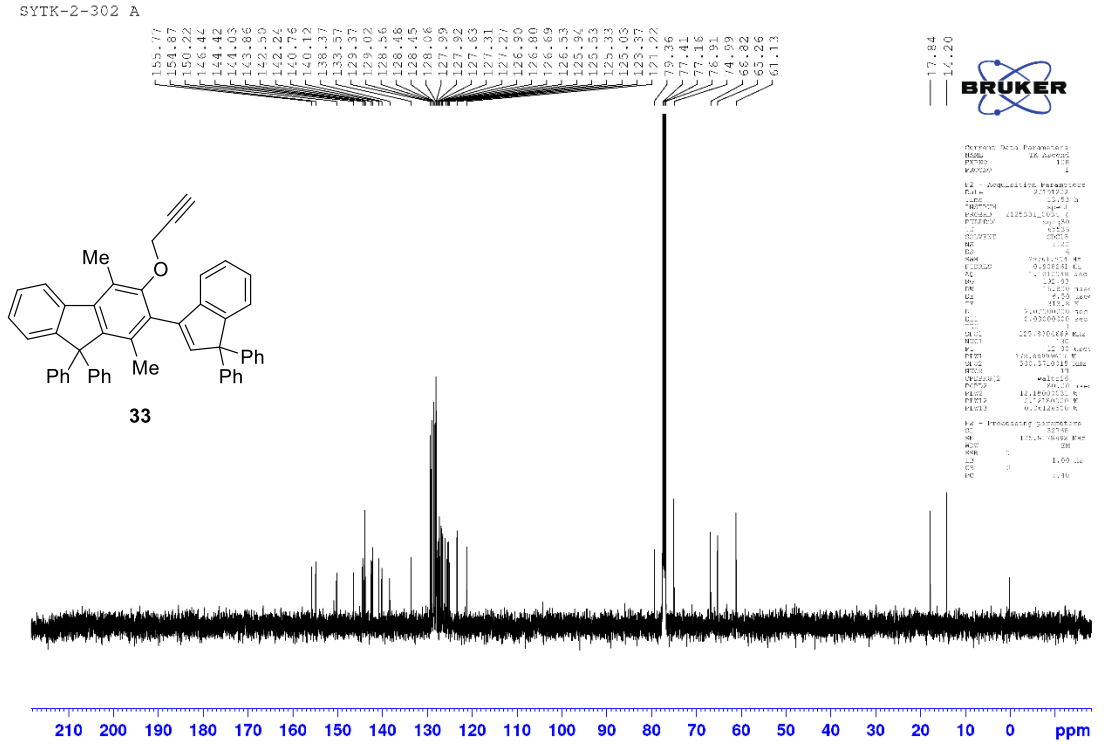


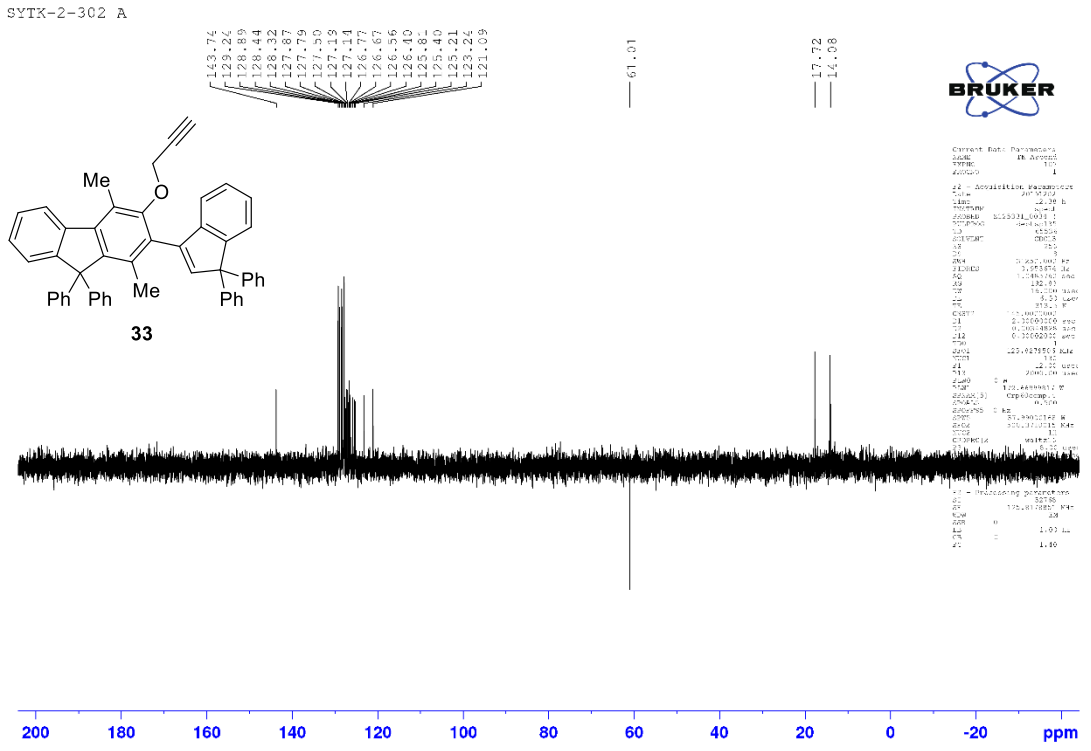
29a:29b (1:1.24),

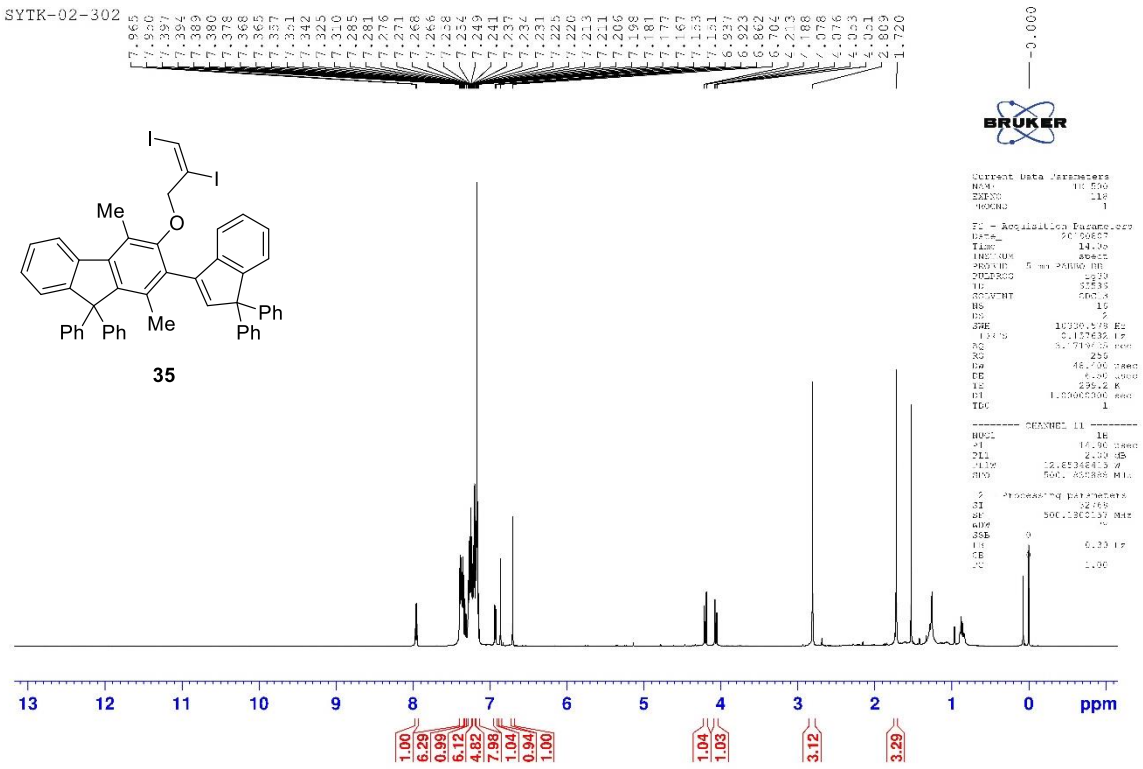
SYTK-2-302 A



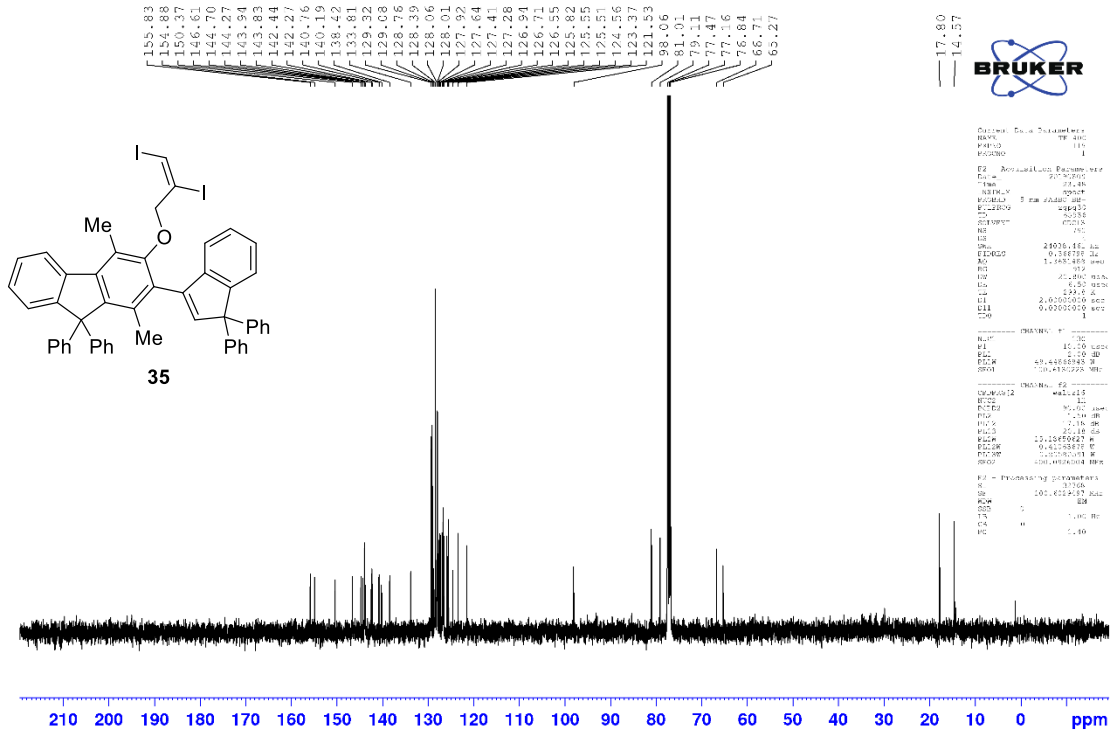
SYTK-2-302 A



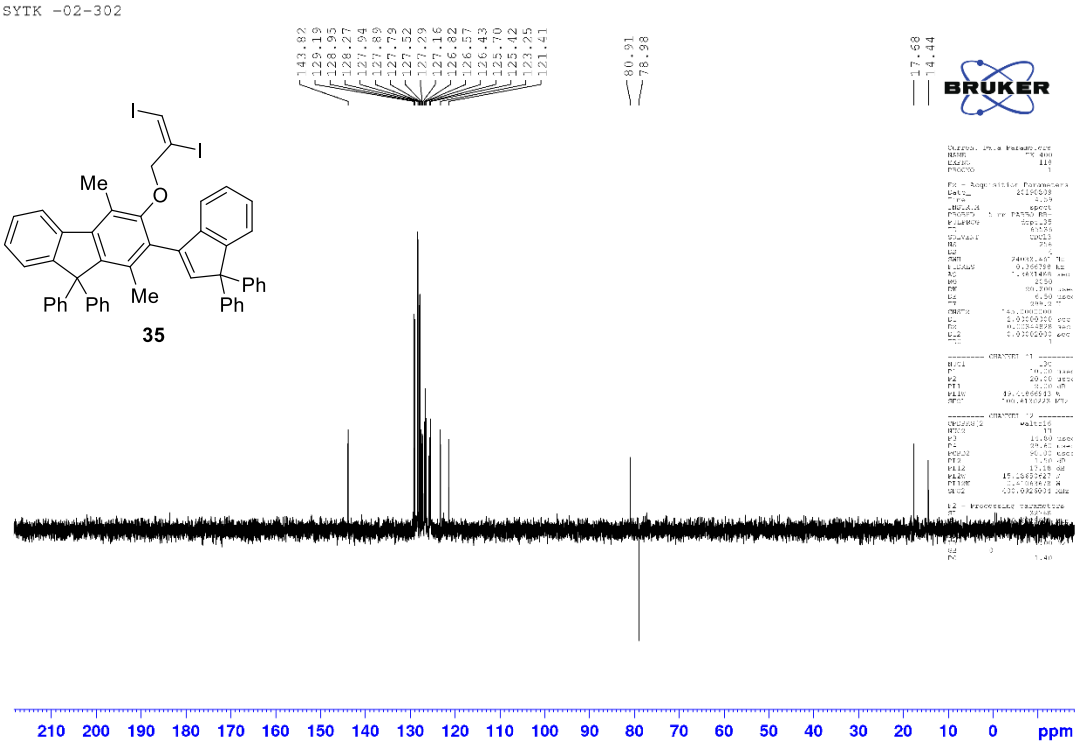

SYTK-2-302 A
Me
O
Ph Ph
Me
Ph
Ph
33
200 180 160 140 120 100 80 60 40 20 0 -20 ppm

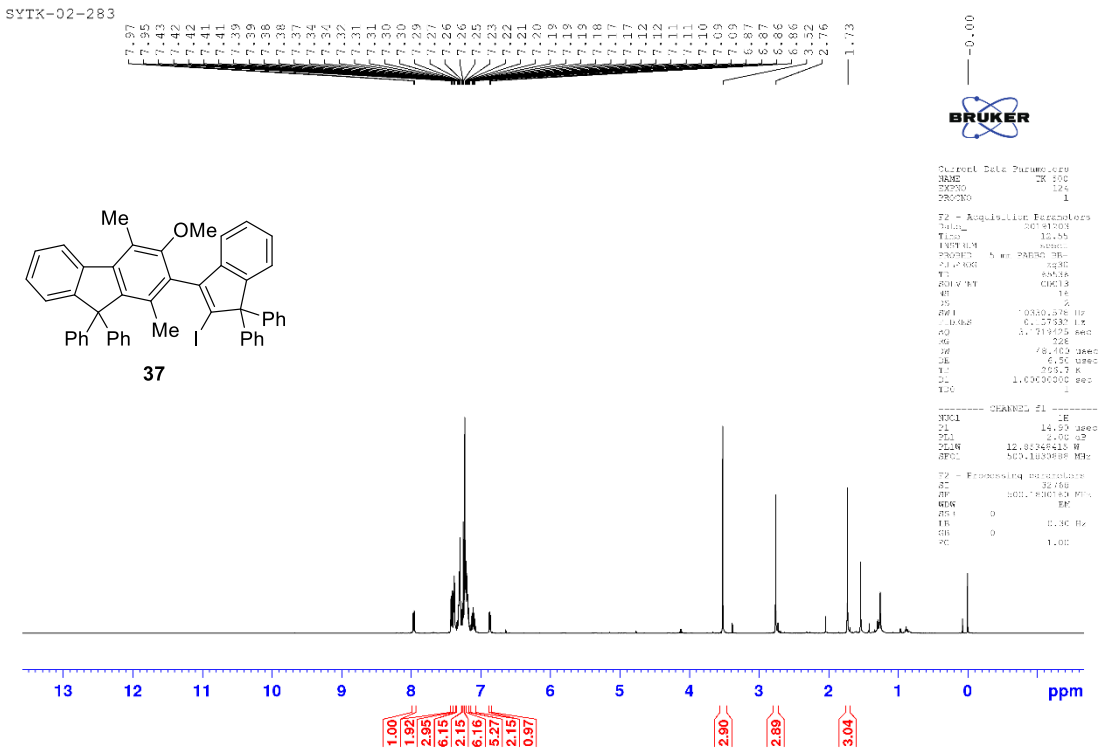

SYTK-02-302
I
I
Me
O
Ph Ph
Me
Ph
Ph
35
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm

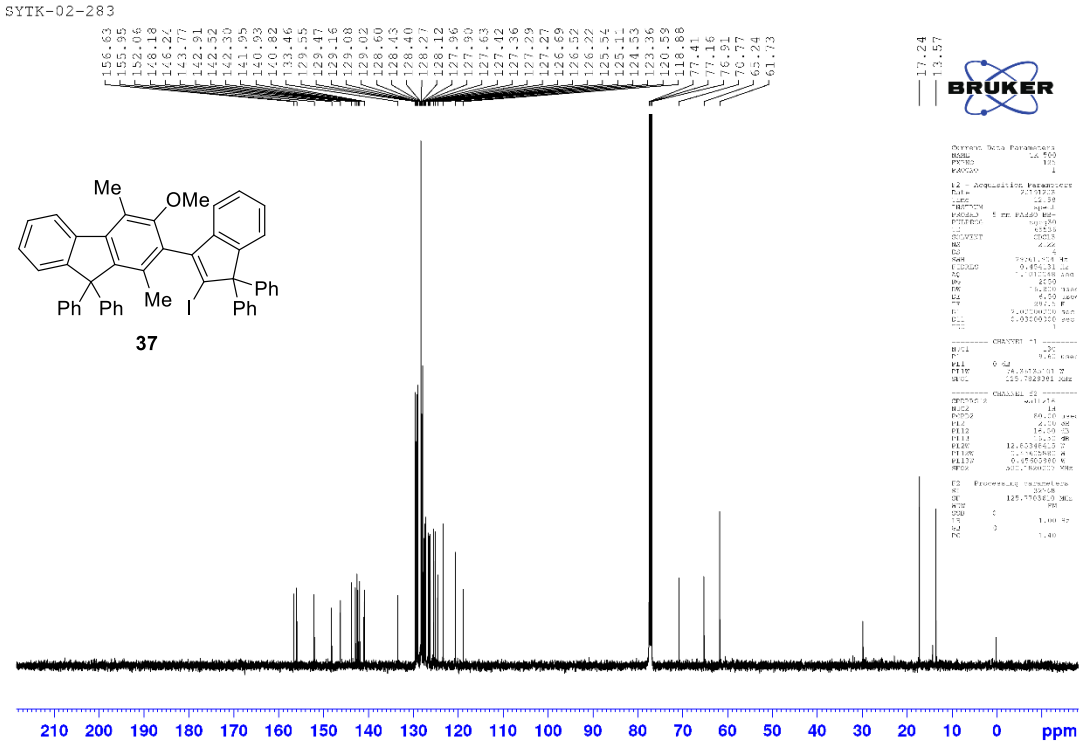
SYTK -02-302



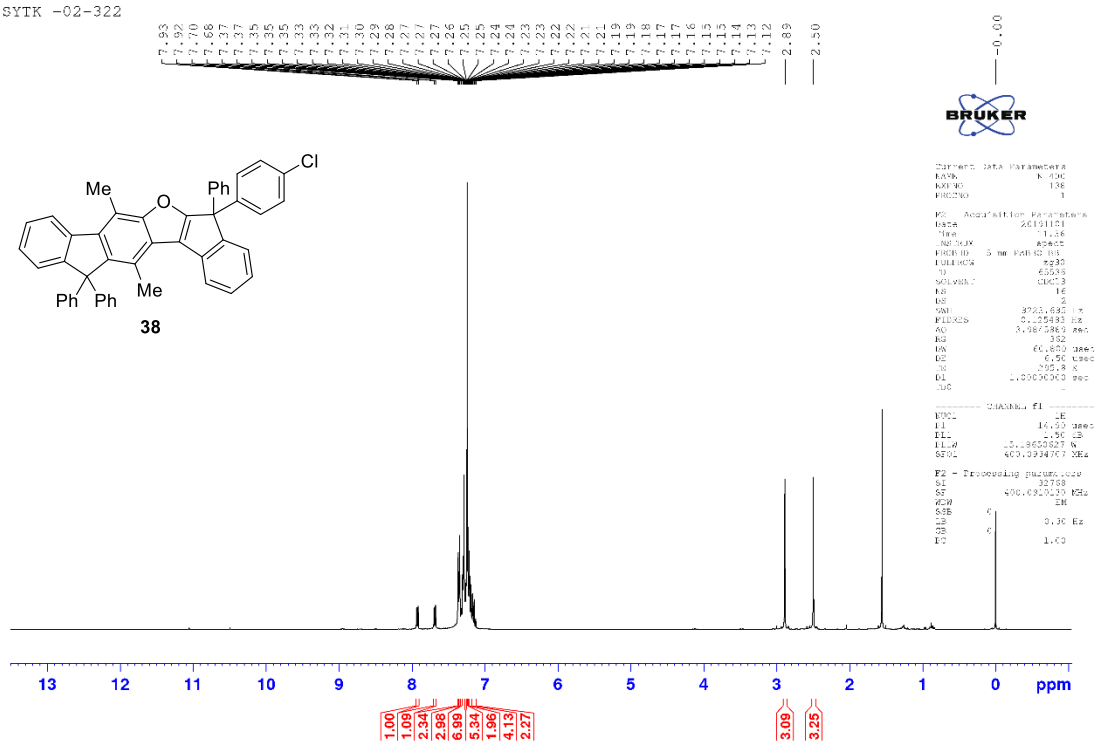
SYTK -02-302



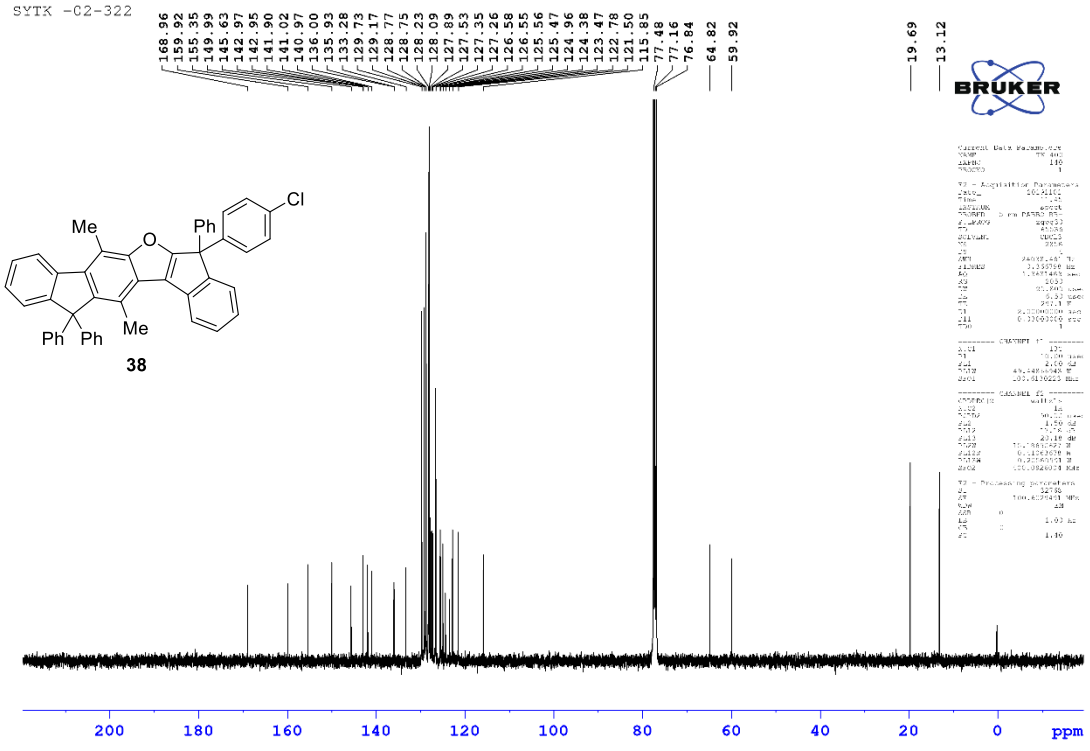

SYTK-02-283
Me
OMe
Ph
Ph
Me
I
Ph
Ph
37
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.00 1.92 2.95 6.15 2.15 6.16 5.27 2.15 0.97 2.90 2.89 3.04

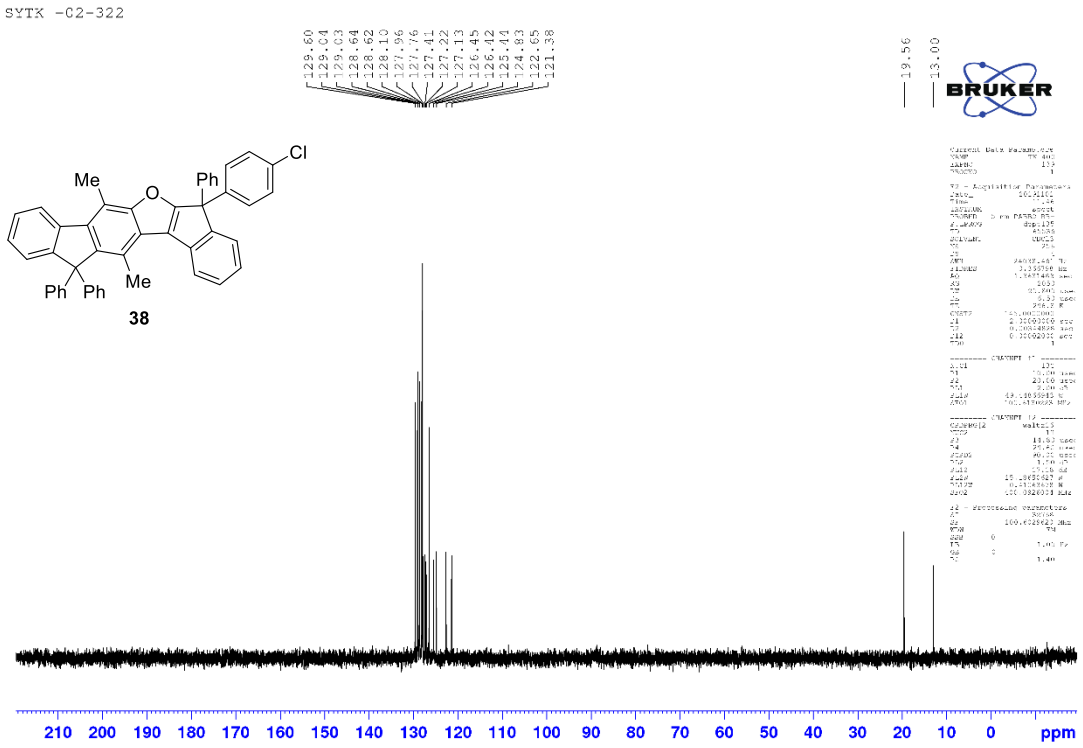

SYTK-02-283
Me
OMe
Ph
Ph
Me
I
Ph
Ph
37
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

SYTK -02-322



SYTK -02-322





1.8. References

(1) (a) De, S.K. Applied organic chemistry: reaction mechanisms and experimental procedures in medicinal chemistry**. 2020**. John Wiley & Sons, ISBN: 978-3-527-34785-8. (b) Yaragorla, S.; Dada, R.; Bag, D. Benzannulation Reaction of Indol-3-yl-but-3-yn-2-ols to Substituted 2-Iodocarbazoles *via* Domino 5-*endo* Spirocyclization/Selective Vinyl Shift and Aromatization. *Eur. J. Org. Chem*. **2019**, 6983-6988. (c) Yaragorla, S.; Pareek, A.; Dada, R. Cycloisomerization of Oxindole-Derived 1, 5-Enynes: A Calcium (II)-Catalyzed One-Pot, Solvent-free Synthesis of Phenanthridinones, 3-(Cyclopentenylidene) indolin-2-ones and 3-Spirocyclic Indolin-2-ones. *Adv. Synth. Catal*. **2017**, *359*, 3068-3075. (d) Hronec, M.; Fulajtarová, K.; Liptaj, T. Effect of catalyst and solvent on the furan ring rearrangement to cyclopentanone. *Appl. Catal. A* **2012**, *437*, 104-111. (e) Donnard, M.; Tschamber, T.; Desrat, S.; Hinsinger, K.; Eustache, J. Ring-rearrangement metathesis of 3, 6-dialkoxy-3, 6-dihydro-2H-pyrans. *Tetrahedron Lett.* **2008**, *49*, 1192-1195. (f) Hergueta, A.R.; Moore, H.W. Rearrangements of cyclobutenones. electrocyclic ring closure and thermal ring expansions of 3-allenyl-and 3-alkynyl-2-dienyl-4, 4-dimethoxycyclobutenones. *J. Org. Chem.* **2002**, *67*, 1388-1391. (g) Scott, L.T.; Roelofs, N.H. Thermal rearrangements of aromatic compounds. 11. benzene ring contractions at high temperatures. evidence from the thermal interconversions of aceanthrylene, acephenanthrylene, and fluoranthene. *J. Am. Chem. Soc.* **1987**, *109*, 5461-5465.

(2) (a) Trost, B.M.; Shi, Y. Cycloisomerization for atom economy. Polycycle construction *via* tandem transition metal catalyzed electrocyclic processes. *J. Am. Chem. Soc.* **1992**, *114*, 791-792. (b) Li, C.J.; Trost, B.M. Green chemistry for chemical synthesis. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 13197-13202. (c) A. Moores. Atom Economy - Principles and Some Examples in Homogeneous Catalysis (Ed.: Robert H. Crabtree, P. Anastas), Pub. Wiley & Sons, 2009, p. 1-15. (d) Marson, C.M. Multicomponent and sequential organocatalytic reactions: diversity with atom-economy and enantiocontrol. *Chem. Soc. Rev.* **2012**, *41*, 7712-7722.

(3) (a) Crespin, L.; Biancalana, L.; Morack, T.; Blakemore, D.C.; Ley, S.V. One-pot acid-catalyzed ring-opening/cyclization/oxidation of aziridines with N-tosylhydrazones: access to 1, 2, 4-triazines. *Org. Lett.*, **2017**, *19*, 1084-1087. (b) Pradhan, S.; Shahi, C.K.; Bhattacharyya, A.; Chauhan, N.; Ghorai, M.K. Syntheses of Tetrahydrobenzoazepinoindoles and Dihydrobenzodiazepinoindoles *via* Ring-Opening Cyclization of Activated Aziridines with 2-(2-Bromophenyl)-1 H-indoles. *Org. Lett*., **2017**, *19*, 3438-3441. (c) Xia, Y.; Lin, L.; Chang, F.; Liao, Y.; Liu, X.; Feng, X. Asymmetric ring opening/cyclization/retro-Mannich reaction of cyclopropyl ketones with aryl 1, 2-diamines for the synthesis of benzimidazole derivatives. *Angew. Chem., Int. Ed*., **2016**, *55*, 12228-12232. (d) Nambu, H.; Fukumoto, M.; Hirota, W.; Yakura, T. Ring-opening cyclization of cyclohexane-1, 3-dione-2-spirocyclopropanes with amines: Rapid access to 2-substituted 4-hydroxyindole. *Org. Lett.*, **2014**, *16*, 4012-4015. (e) Miao, H.; Tallarico, J.A.; Hayakawa, H.; Münger, K.; Duffner, J.L.; Koehler, A.N.; Schreiber, S.L.; Lewis, T.A. Ring-opening and ring-closing reactions of a shikimic acid-derived substrate leading to diverse small molecules. *J. Comb. Chem*., **2007**, *9*, 245-253.

(4) (a) Lloyd-Jones, G.C. Mechanistic aspects of transition metal catalysed 1, 6-diene and 1, 6-enyne cycloisomerisation reactions. *Org. Biomol.Chem*. **2003**, 1, 215-236. (b) Marinetti, A.; Jullien, H.; Voituriez, A.Enantioselective, transition metal catalyzed cycloisomerizations. *Chem. Soc. Rev.*, **2012**, *41*, 4884-4908. (c) Watson, I. D. G.; Toste, F. D. Catalytic enantioselective carbon-carbon bond formation using cycloisomerization reactions. *Chem. Sci.* **2012**, *3*, 2899-2919.

(5) Vogel, E., Kleine kohlenstoff-ringe. *Angew.Chem.* **1960**, *72*, 4-26.

(6) (a) Iwasawa, N. A novel rearrangement of 1-alkynylcyclopropanol to 2-cyclopenten-1-one *via* dicobalt hexacarbonyl complex. *Chem. Lett.* **1992**, *21*, 473-476. (b) Iwasawa, N.; Iwamoto, M. A conformationally controlled regioselective rearrangement of 2-substituted 1-alkynylcyclopropanols to 2-cyclopenten-1-ones *via* hexacarbonyldicobalt complex. *Chem. Lett.* **1993**, *22*, 1257-1260.

(7) Huffman, M.A.; Liebeskind, L.S. Rhodium (I)-catalyzed intramolecular carbocyclic ring fusion: a new approach to medium-sized-ring ketones. *J. Am. Chem. Soc.* **1993**, *115*, 4895-4896.

(8) Murakami, M.; Takahashi, K.; Amii, H.; Ito, Y. Rhodium (I)-Catalyzed Successive Double Cleavage of Carbon- Carbon Bonds of Strained Spiro Cyclobutanones. *J. Am. Chem. Soc.* **1997**, *119*, 9307-9308.

(9) (a) Hashmi, A. S. K. Gold-catalyzed organic reactions. *Chem. Rev*., **2007**, *107*, 3180-3211. (b) Jiménez-Núñez, E.; Echavarren, A.M. Molecular diversity through gold catalysis with alkynes. *Chem. Commun*. **2007**, *0*, 333-346. (c) Hashmi, A.S.K.; Hutchings, G.J. Gold catalysis. *Angew. Chem., Int. Ed.*, **2006**, *45*, 7896-7936. (d) Aubert, C.; Buisine, O.; Malacria, M. The behavior of 1, n-enynes in the presence of transition metals. *Chem. Rev.*, **2002**, *102*, 813-834. (e) Trost, B.M.; Toste, F.D.; Pinkerton, A.B. Non-metathesis ruthenium-catalyzed C- C bond formation. *Chem. Rev*., **2001**, *101*, 2067-2096. (f) Trost, B.M.; Krische, M.J. Transition metal catalyzed cycloisomerizations., *Synlett*, **1998**, *1*, 1-16. (g) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R.J. Transition metal-catalyzed carbocyclizations in organic synthesis. *J. Chem. Rev*., **1996**, *96*, 635-662.

(10) (a) Yaragorla, S.; Bag, D.; Dada, R.; Jose, K.J. Iodo-cycloisomerization of aryl (indol-3-yl) methane-tethered propargyl alcohols to 3-iodocarbazoles *via* selective 1, 2-alkyl migration. *ACS omega* **2018**, *3*, 15024-15034. (b) Yaragorla, S.; Pareek, A.; Dada, R. Cycloisomerization of Oxindole-Derived 1, 5-Enynes: A Calcium (II)-Catalyzed One-Pot, Solvent-free Synthesis of Phenanthridinones, 3-(Cyclopentenylidene) indolin-2-ones and 3-Spirocyclic Indolin-2-ones. *Adv. Synth. Catal*., **2017**, *359*, 3068-3075.

(11) (a) Kumar, D.; Sharma, P.; Singh, H.; Nepali, K.; Gupta, G.K.; Jaina, S.K.; Kang, F.N. The value of pyrans as anticancer scaffolds in medicinal chemistry. *RSC Adv*., **2017**, *7*, 36977-36999. (b) Costa, M.; Dias, T.A.; Brito, A.; Proença, F. Biological importance of structurally diversified chromenes. *Eur. J. Med. Chem*., **2016**, *123*, 487-507. (c) Goel, A.; Kumar, A.; Raghuvanshi, A. Synthesis, stereochemistry, structural classification, and chemical reactivity of natural pterocarpans. *Chem. Rev.*, **2013**, *113*, 1614-1640. (d) Rueping, M.;

Sugiono, E.; Merino, E. Asymmetric organocatalysis: an efficient enantioselective access to benzopyranes and chromenes. *Chem. Eur J.*, **2008**, *14*, 6329-6332. (e) Kidwai, M.; Saxena, S.; Khan, M.K.R.; Thukral, S.S. Aqua mediated synthesis of substituted 2-amino-4H-chromenes and in vitro study as antibacterial agents. *Bioorg. Med. Chem. Lett*., **2005**, *15*, 4295-4298. (f) Simon-Levert, A.; Arrault, A.; Bontemps-Subielos, N.; Canal, C.; Banaigs, B. Meroterpenes from the Ascidian *Aplidium aff. densum*. *J. Nat. Prod*., **2005**, *68*, 1412-1415. (g) Zeni, G.; Larock, R.C. Synthesis of heterocycles *via* palladium π-olefin and π-alkyne chemistry. *Chem Rev*, **2004**, *104*, 2285-2310. (h) Rukachaisirikul, V.; Kamkaew, M.; Sukavisit, D.; Phongpaichit, S.; Sawangchote, P.; Taylor, W.C. Antibacterial xanthones from the leaves of Garcinia nigrolineata. *J. Nat. Prod*., **2003**, *66*, 1531-1535. (i) Salni, D.; Sargent, M.V.; Skelton, B.W.; Soediro, I.; Sutisna, M.; White, A.H.; Yulinah, E. Rhodomyrtone, an antibotic from Rhodomyrtus tomentosa. *Aust. J. Chem*., **2002**, *55*, 229-232. (j) Kashiwada, Y.; Yamazaki, K.; Ikeshiro, Y.; Yamagishi, T.; Fujioka, T.; Mihashi, K.; Mizuki, K.; Cosentino, L.M.; Fowke, K.; Morris-Natschke, S.L.; Lee, K.H. Isolation of rhododaurichromanic acid B and the anti-HIV principles rhododaurichromanic acid A and rhododaurichromenic acid from Rhododendron dauricum. *Tetrahedron*, **2001**, *57*, 1559-1563. (k) Nicolaou, K.C.; Pfefferkorn, J.A.; Roecker, A.J.; Cao, G.Q.; Barluenga, S.; Mitchell, H.J. Natural product-like combinatorial libraries based on privileged structures. 1. General principles and solid-phase synthesis of benzopyrans. *J. Am. Chem. Soc.*, **2000**, *122*, 9939-9953. (l) Nicolaou, K.C.; Pfefferkorn, J.A.; Mitchell, H.J.; Roecker, A.J.; Barluenga, S.; Cao, G.Q.; Affleck, R.L.; Lillig, J.E. Natural product-like combinatorial libraries based on privileged structures. 2. Construction of a 10 000-membered benzopyran library by directed split-and-pool chemistry using NanoKans and optical encoding. *J. Am. Chem. Soc*., **2000**, *122*, 9954-9967.

(12) (a) Raj, T.; Bhatia, R.K.; Sharma, M.; Saxena, A.K.; Ishar, M.P.S. Cytotoxic activity of 3-(5-phenyl-3H-[1, 2, 4] dithiazol-3-yl) chromen-4-ones and 4-oxo-4H-chromene-3-carbothioic acid N-phenylamides. *Eur. J. Med. Chem*., **2010**, *45*, 790-794. (b) Raj, T.; Bhatia, R.K.; Sharma, R.K.; Gupta, V.; Sharma, D.; Ishar, M.P.S. Mechanism of unusual formation of 3-(5-phenyl-3H-[1, 2, 4] dithiazol-3-yl) chromen-4-ones and 4-oxo-4H-chromene-3-carbothioic acid N-phenylamides and their antimicrobial evaluation.*Eur. J. Med. Chem*., **2009**, *44*, 3209-3216. (c) Symeonidis, T.; Fylaktakidou, K.C.; Hadjipavlou-Litina, D.J.; Litinas, K.E. Synthesis and anti-inflammatory evaluation of novel angularly or linearly fused coumarins. *Eur. J. Med. Chem*., **2009**, *44*, 5012-5017. (d) Kumar, A.; Maurya, R.A.; Sharma, S.; Ahmad, P.; Singh, A.B.; Bhatia, G.; Srivastava, A.K. Pyranocoumarins: A new class of anti-hyperglycemic and anti-dyslipidemic agents. *Bioorg. Med. Chem. Lett*., **2009**, *19*, 6447-6451. (e) Abdelrazek, F.M.; Metz, P.; Farrag, E.K. Synthesis and molluscicidal activity of 5-oxo-5, 6, 7, 8-tetrahydro-4H-chromene derivatives. *Arch. Pharm*., **2004**, *337*, 482-485.

(13) (a) Tian, H.; Zhang J. *Industrial Applications and Perspectives. Photochromic Materials: Preparation, Properties and Applications*, Wiley-VCH Verlag GmbH & Co. KGaA, 1st edn, **2016**, 393-415. (b) Bouas-Laurent, H.; Dürr, H. Organic photochromism (IUPAC technical report). *Pure. Appl. Chem.*, **2001**, *73*, 639-665. (c) Becker, R.S.; Michl, J. Photochromism of synthetic and naturally occurring 2H-chromenes and 2H-pyrans. *J. Am. Chem. Soc.*, **1966**, *88*, 5931-5933.

(14) (a) Guo, K.; Chen, Y. A strategy for the design of photochromic naphthopyrans with large optical density at photosteady state and fast fading speed at ambient temperature in the dark. *J. Mater. Chem*., **2010**, *20*, 4193-4197. (b) Glebov, E.M.; Smolentsev, A.B.; Korolev, V.V.; Plyusnin, V.F.; Chebunkova, A.V.; Paramonov, S.V.; Fedorova, O.A.; Lokshin, V.; Samat, A. Synthesis and photochromic properties of crown-containing styryl derivatives of naphthopyrans. *J. Phys. Org. Chem.*, **2009**, *22*, 537-545. (c) Kumar, S.; Hernandez, D.; Hoa, B.; Lee, Y.; Yang, J.S.; McCurdy, A. Synthesis, photochromic properties, and light-controlled metal complexation of a naphthopyran derivative. *Org. Lett.*, **2008**, *10*, 3761-3764. (d) Sriprom, W.; Néel, M.; Gabbutt, C.D.; Heron, B.M.; Perrier, S. Tuning the color switching of naphthopyrans *via* the control of polymeric architectures. *J. Mater. Chem.*, **2007**, ***17***, 1885-1893. (e) Moorthy, J.N.; Venkatakrishnan, P.; Samanta, S.; Kumar, D.K.

Photochromism of arylchromenes: remarkable modification of absorption properties and lifetimes of o-quinonoid intermediates. *Org. Lett*., **2007**, *9*, 919-922.
(15) (a) Taugerbeck, A.; Klasen-Memmer M. Benzochromene derivatives. US 2009/0023802 A1, Jan. 22, **2009**. (b) Hannesschlager, P.; Brun, P. Synthesis and photochromic properties of tricarbonylchromium complexes of 2H-η6-benzochromenes. *Appl. Organometal. Chem*., **2000**, *14*, 371-375.
(16) Yaragorla, S.; Rajesh, P.; Pareek, A.; Kumar, A. Ca (II)-Mediated Regioselective One-pot Sequential Annulation of Acyclic compounds to Polycyclic Fluorenopyrans. Adv. Synth. Catal. **2018**, *360*, 4422-4428.
(17) Gabbutt, C.D.; Heron, B.M.; Kilner, C.; Kolla, S.B. Benzopentalenonaphthalenones from the intramolecular capture of a merocyanine derived from a naphthopyran. *Chem. Commun.* **2010**, *46*, 8481-8483.
(18) Jiang, M.; Shi, M. Lewis acid catalyzed cycloaddition of methylenecyclopropanes with salicylaldehydes. *Org. Lett.* **2010**, *12*, 2606-2609.
(19) Tanaka, K.; Aoki, H.; Hosomi, H.; Ohba, S. One-pot synthesis of photochromic naphthopyrans in the solid state. *Org. Lett.,* **2000,** *2,* 2133-2134.
(20) Yaragorla, S.; Pareek, A.; Dada, R. Regioselective annulation of propargyl alcohols with ambident-enols: A Ca (II)-catalyzed trisubstituted benzochromene synthesis. *Tet. Lett.,* **2017**, *58*, 4642-4647.
(21) (a) Hayashi, Y. Pot economy and one-pot synthesis. *Chem. Sci*., **2016**, *7*, 866-880. (b) Newhouse, T.; Baran, P.S.; Hoffmann, R.W. The economies of synthesis. *Chem. Soc. Rev*., **2009**, *38*, 3010-3021. (c) Ramón, D.J.; Yus, M. Asymmetric multicomponent reactions (AMCRs): the new frontier. *Angew. Chem., Int. Ed*., **2005**, *44*, 1602-1634. (d) Anastas, P.T.; Kirchhoff, M.M. Origins, current status, and future challenges of green chemistry. *Acc. Chem. Res*., **2002**, *35*, 686-694. (e) Tietze, L.F. Domino reactions in organic synthesis. *Chem. Rev.*, **1996**, *96*, 115-136.
(22) (a) Wang, L.; Zhong, J.; Lin, X. Atroposelective phosphoric acid catalyzed three-component cascade reaction: enantioselective synthesis of axially chiral N-arylindoles. *Angew. Chem. Int. Ed.* **2019**, *58*, 15824-15828. (b) Christie, G.H.; Kenner, J. LXXI.-The molecular configurations of polynuclear aromatic compounds. Part I. The resolution of γ-6: 6′-dinitro- and 4: 6: 4′: 6′-tetranitro-diphenic acids into optically active components. *J. Chem. Soc. Trans*. **1922**, *121*, 614-620.
(23) (a) Hu, D.X.; Grice, P.; Ley, S.V. Rotamers or diastereomers? An overlooked NMR solution. *J. Org. Chem.* **2012**, *77*, 5198-5202. (b) Frank, J.H.; Powder-George, Y.L.; Ramsewak, R.S.; Reynolds, W.F. Variable-temperature ^{1}H-NMR studies on two C-glycosylflavones. *Molecules* **2012**, *17*, 7914-7926.
(24) (a) Yaragorla, S.; Rajesh, P. An efficient Benzannulation protocol for the synthesis of 9, 9-Diphenyl-9H-fluorenols using Intramolecular Allene Friedel-Crafts Annulation. *Eur. J. Org. Chem*. **2019**, 5740-5748. (b) Keskin, S.; Balci, M. Intramolecular heterocyclization of O-propargylated aromatic hydroxyaldehydes as an expedient route to substituted chromenopyridines under metal-free conditions. *Org. Lett.* **2015**, *17*, 964-967.
(25) (a) Khan, T.; Yaragorla, S. Iodocyclization of propargyl alcohols: Highly facile approach to hetero/carbocyclic iodides. *Eur. J. Org. Chem.* **2019**, 3989-4012. (b) Timonen, J.M.; Turhanen, P.A. (E)-Di-iodination of Alkynes Using Dried Dowex H^{+}/NaI Approach. *ACS Omega* **2019**, *4*, 14663-14668. (c) Rao, D.S.; Reddy, T.R.; Kashyap, S. Chemoselective and stereospecific iodination of alkynes using sulfonium iodate (i) salt. *Org. Biomol. Chem.* **2018**, *16*, 1508-1518. (d) Yaragorla, S.; Bag, D.; Dada, R.; Jose, K.J. Iodo-cycloisomerization of aryl (indol-3-yl) methane-tethered propargyl alcohols to 3-iodocarbazoles *via* selective 1, 2-alkyl migration. *ACS Omega* **2018**, *3*, 15024-15034.
(26) (a) Singh, S.; Samineni, R.; Pabbaraja, S.; Mehta, G. Nitromethane as a Carbanion Source for Domino Benzoannulation with Ynones: One-Pot Synthesis of Polyfunctional Naphthalenes and a Total Synthesis of Macarpine. *Angew. Chem. Int. Ed.* **2018,** *57*, 16847-16851. (b) Lewis, H.F.; Shaffer, S.; Trieschmann, W.; Cogan, H. Methylation of Phenol by Dimethyl Sulfate. *Ind. Eng. Chem.* **1930**, *22*, 34-36.

(27) (a) Litinas, K.E.; Nicolaides, D.N. Reactions of o-quinones with some bis-phosphonium salts in the presence of lithium ethoxide. *J. Chem. Soc. Trans.1* **1985**, 429-435. (b) Hori, M.; Guo, J.D.; Yanagi, T.; Nogi, K.; Sasamori, T.; Yorimitsu, H. Sigmatropic Rearrangements of Hypervalent-Iodine-Tethered Intermediates for the Synthesis of Biaryls. *Angew. Chem. Int. Ed.*, **2018**, *57*, 4663-4667.
(28) Bringmann, G.; Gulder, T.; Gulder, T.A.; Breuning, M. Atroposelective total synthesis of axially chiral biaryl natural products. *Chem. Rev.* **2011**, *111*, 563-639.
(29) Zhang, K.; Liu, Y.; Shang, Z.; Evans, C.J.; Yang, S. An investigation of atropisomerism in ortho-imide substituted 1, 3-benzoxazine by experimental NMR and DFT calculations. *J. Phys. Org. Chem.* **2019**, *32*, e3926.
(30) Ambrogi, M.; Ciogli, A.; Mancinelli, M.; Ranieri, S.; Mazzanti, A. Atropisomers of arylmaleimides: stereodynamics and absolute configuration. *J. Org. Chem.* **2013**, *78*, 3709-3719.
(31) Smyth, J.E.; Butler, N.M.; Keller, P.A. A twist of nature-the significance of atropisomers in biological systems. *Nat. Prod. Rep.* **2015**, *32*, 1562-1583.
(32) Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G.A.; Nakatsuji, H., Caricato, M.; Li, X.; H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery Jr. J.A.; Peralta, J.E.; Ogliaro, F.; Bearpark, M.; Heyd, J.J.; Brothers, E.; Kudin, K.N.; Staroverov, V.N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J.C.; Iyengar, S.S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J.M.; Klene, M.; Knox, J.E.; Cross, J.B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R.E.; Yazyev, O.; Austin, A.J.; Cammi, R.; Pomelli, C.; Ochterski, J.W.; Martin, R.L.; Morokuma, K.; Zakrzewski, V.G.; Voth, G.A.; Salvador, P.; Dannenberg, J.J.; Dapprich, S.; Daniels, A.D.; Farkas, Ö.; Foresman, J.B.; Ortiz, J.V.; Cioslowski, J.; Fox, D.J. Gaussian 09, Revision E.01, Gaussian, Inc., Wallingford CT, **2009**.
(33) Zhao, Y.; Truhlar, D.G. The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals. *Theor. Chem. Acc.* **2008**, *120*, 215-241.
(34) Ditchfield, R.H.W.J.; Hehre, W.J.; Pople, J.A. Self-consistent molecular-orbital methods. IX. An extended Gaussian-type basis for molecular-orbital studies of organic molecules. *J. Chem. Phys.* **1971**, *54*, 724-728.
(35) Hay, P.J.; Wadt, W.R. *Ab initio* effective core potentials for molecular calculations. Potentials for K to Au including the outermost core orbitals. *J. Chem. Phys.* **1985**, 82, 299-310.
(36) Marenich, A.V.; Cramer, C.J.; Truhlar, D.G. Universal solvation model based on solute electron density and on a continuum model of the solvent defined by the bulk dielectric constant and atomic surface tensions. *J. Phys. Chem. B* **2009**, *113*, 6378-6396.
(37) Chen, S.; Yuan, F.; Zhao, H.; Li, B. Efficient solvent-free synthesis of tertiary propargylic alcohols from arylacetylenes and ketones promoted by tert-BuOK. *Res. Chem. Intermed.*, **2013**, *39*, 2391-2399.

Chapter 2

Cu-Catalyzed Intramolecular Etherification via C_{sp2}-H Functionalization

Manuscript communicated.

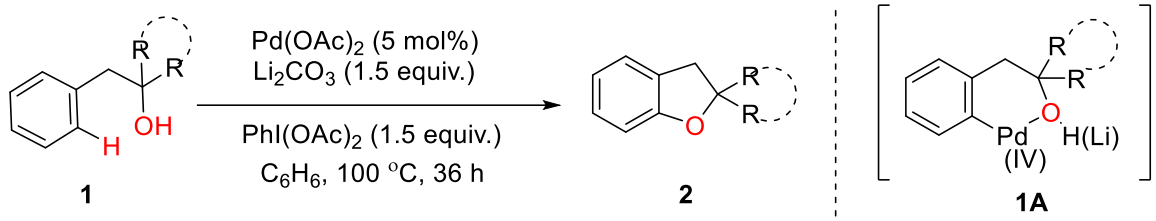
2.1. Introduction

Many of the natural products, biologically active molecules, drugs, etc., are heterocyclic in nature. Among heterocycles, a five-membered aromatic ring with one oxygen atom and four carbon atoms known as furans is reported to be a biologically active and privileged molecule. The fusion of the furan ring to an aromatic system is a viable technique to obtain stable and functional furan derivatives. Multisubstituted benzo[b]furan and polycyclic furans such as benzodifuran, naphthodifurans, and anthrodifuran,[1] and simple furan derivatives like benzofuran and naphthofuran are privileged scaffolds, because of their abundance as the natural product.[2] They demonstrate an ample number of biological activities[3-5] like antidiabetic, antifungal, antiparasitic, and antiviral. Furthermore, these structures were investigated as regulators of the nuclear receptor HNFα,[6] and to design potential anticancer agents. antifungal, antiparasitic, and antiviral activities. Moreover, these structures were used to design potential anticancer agents and studied as regulators of nuclear receptors HNF4α.[6] Fused furans are recognized as thermally and electrochemically stable molecules and thus appropriate for light emitting diodes (OLEDs) and organic field effect transistors (OFETs).[7]

In recent years, catalytic C-H functionalization became an important synthetic strategy for constructing various carbon-heteroatom and carbon-carbon bonds, due to its atom-economical and environmentally benign nature.[8] The intramolecular C-H heterofunctionalization strategy emerged as a pioneering method for the construction of heterocycles.[9] In particular, the intramolecular C-H functionalization is widely employed for the construction of aza-heterocycles, including carbazoles,[10] oxathiazinane,[11] oxazolidinone,[12] indoles,[13] indazoles,[14] benzimidazoles,[15] and Pyrido[1,2-a]benzimidazoles through Cu, Pd, Pt, Rh, or Ru-catalyzed transformations.[16] In contrast, the application of a similar C-H functionalization strategy for the preparation of oxygen containing heterocycle has been less explored. In this connection, a recent study shows the synthesis of cyclic ether or lactone through Pt or Pd-catalyzed C_{sp3}-H functionalization.[17] Another mode to synthesize benzoxazole derivatives by a Cu-catalyzed intramolecular C-O bond construction reaction was developed between aromatic C-H bond and carbonyl oxygen of benzanilide.[18]

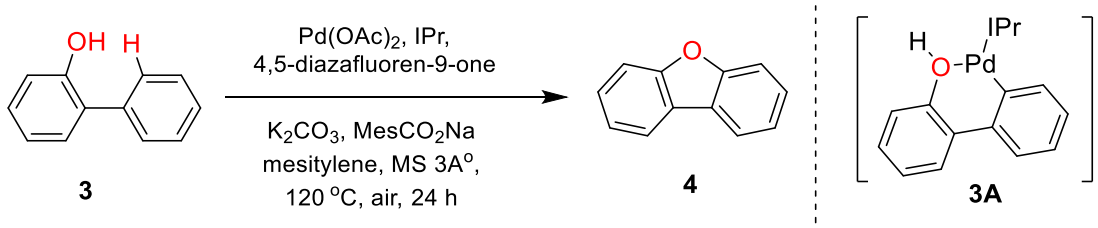
2.2. Literature Reports

In 2010 a cycloetherification process for the dihydrobenzofuran synthesis was reported by Yu et al. describing the involvement of a tertiary aliphatic alcohol catalyzed by $PhI(OAc)_2$ and $Pd(OAc)_2$ as the oxidant.[19] The reaction proceeds by oxidizing Pd(II) to the higher oxidation state to a possible transition state **1A** and then C-O reductive elimination to get the product **2** (Scheme 1).



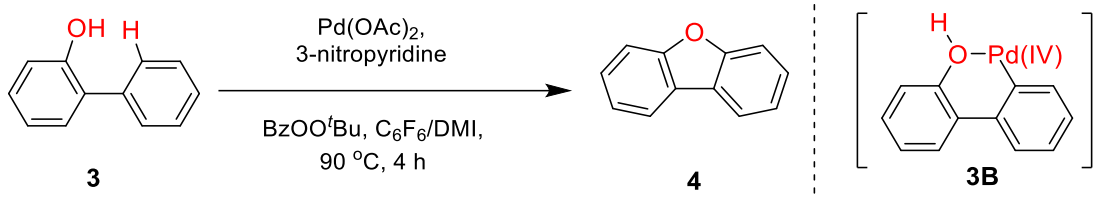
Scheme 1. *Palladium catalyzed synthesis of dihydrobenzofuran*

Despite the effectiveness of the previous studies,[20] it is still difficult to carryout C-H cycloetherification method which employ phenols as nucleophiles because strong oxidants ($PhI(OAc)_2$) can oxidize the phenol, secondly it can undergo homocoupling with transition metals.[21] In 2011 Liu and co-workers reported a pioneering work of dibenzofuran production by palladium-catalyzed cyclization of 2-aryl phenols by a combination of ligands and additives, IPr and 4,5-diazafluoren-9-one as ligands and $MesCO_2Na$ and K_2CO_3 as additives were used in this particular transformation (Scheme 2).[22]



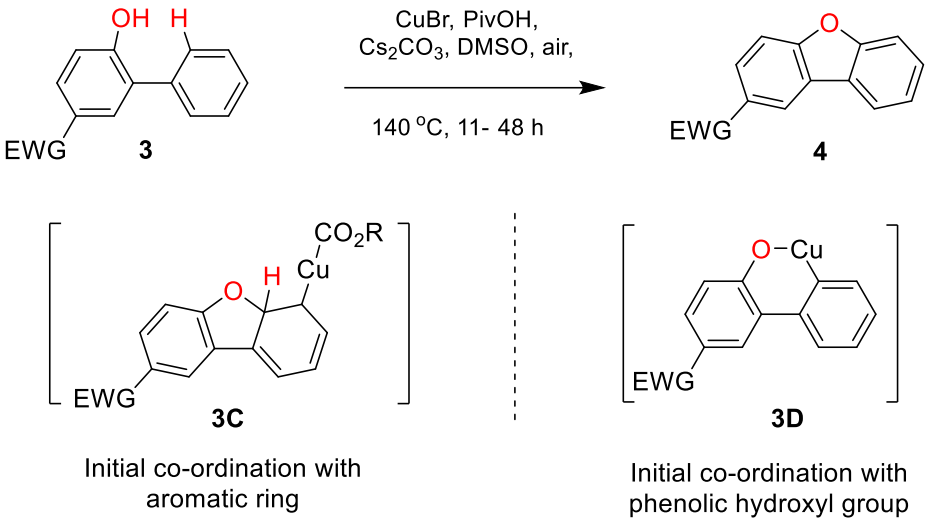
Scheme 2. *Palladium catalyzed synthesis of dibenzofuran with Ipr as ligand*

Simultaneously, Yoshikai's group also reported a similar transformation under palladium catalysis but by use of different ligands and oxidants., 3-nitropyridine as a ligand and tertiary butyl peroxy benzoate ($BzOO^tBu$) as an oxidant were used for the transformation(Scheme 3).[23] This transformation initiates by cleavage of C-H bond because of co-ordination of Pd(II) species, which gets oxidized to Pd(IV) **3B** by the attack of benzoate and then reductive elimination takes place to construct C-O bond.



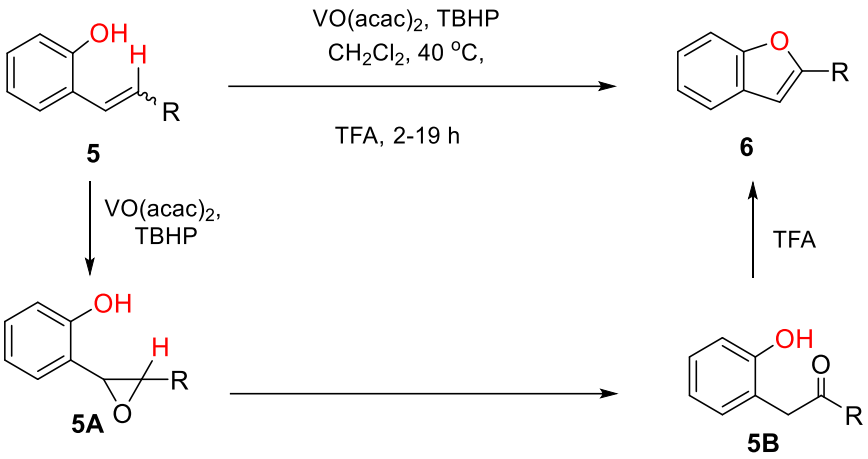
Scheme 3. *Palladium catalyzed synthesis of dibenzofuran with 3-nitropyridine as ligand*

In continuation, Zhu et al. in 2012 demonstrated a copper-catalyzed C_{sp2}-H bond cycloetherification for the preparation of a multi-substituted dibenzofuran from *o*-aryl phenols having a strong *para*-electron-withdrawing substituent (Scheme 4).[24]



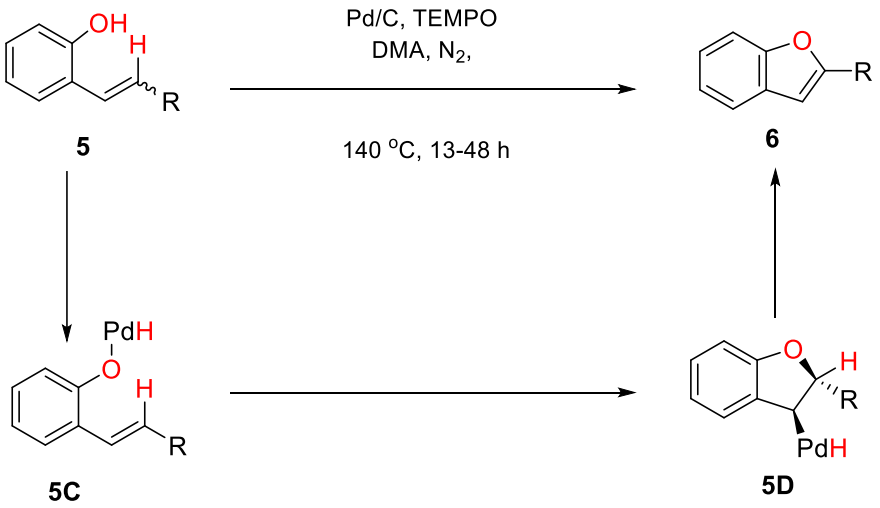
Scheme 4. *Copper catalyzed synthesis of dibenzofuran*

The reaction proceeds through two pathways, one by the initial activation of the aromatic ring followed by phenolic OH group attack from the intermediate **3C**, which then undergoes *cis*-hydride elimination to generate the product. The alternate path suggests initial coordination happens with a phenolic hydroxyl group and then a concerted metalation-deprotonation gives intermediate **3D**, which on reductive elimination results in product **4**.



Scheme 5. *Vanadium catalyzed synthesis of benzofuran*

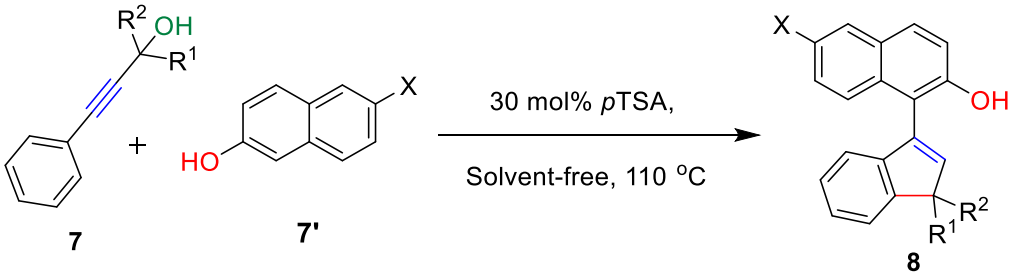
On the other hand, cycloetherification of *ortho*-alkenyl phenol system have not been studied for the synthesis of respective fused furans. Nevertheless, few multi-step approaches are reported.[25] Lattanzi and co-workers reported a $VO(acac)_2$/TBHP promoted oxidation of *o*-alkenyl phenols **5** to *o*-hydroxy benzyl ketones **5B** *via* an epoxy intermediate **5A**, during their study, it was observed that the addition of TFA resulted in the formation of benzofuran (Scheme 5).[26]



Scheme 6. *Palladium catalyzed synthesis of benzofuran*

Later in 2016, R. Liu et al. reported a dehydrogenative oxygenation of C_{sp2}-H bond of *ortho*-alkenyl phenols with intramolecular phenolic hydroxy groups to access benzofurans (Scheme 6).[27] Oxidative addition for insertion of Pd in O-H bond to give intermediate **5C**, and *syn* addition of arene on the Pd-O bond to generate intermediate **5D**, are the key steps in mechanism, the intermediate **5D** then undergo beta-hydride elimination to get benzofuran **4**. TEMPO here is used as polymerization inhibitor.

Looking at this background, we realized that there is no report on cycloetherification of C(sp^2)-H bond of phenols/naphthols having cyclic olefin on the *ortho* position. Developing such a protocol will offer an atom-economical construction of fused furans. Inspired by the recent recognition and advantages of thr inexpensive copper catalyst for the C-H functionalization,[28] we anticipated that the Cu-catalysts could promote the intramolecular C-O cyclization of 2-alkenyl phenols. This prompted us to develop a Cu-catalyzed oxidative C(sp^2)-H cycloetherification of *o*-alkenyl phenols to synthesize fused furans. In this regard, we wanted to investigate the indenyl arenol synthesized by *in-situ* ring-rearrangement of benzochromene or indenochromene generated by regioselective annulation of propargyl alcohol **7** with ambident enols **7'** (Scheme 7).[29]



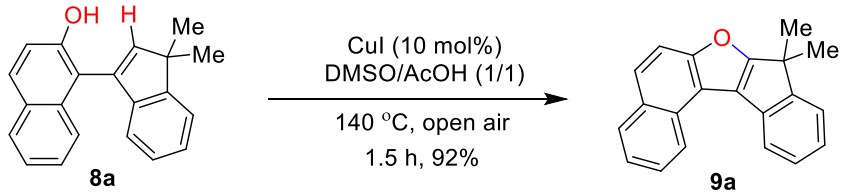
Scheme 7. *Synthesis of Indenyl arenols*

2.3. Results and Discussion

2.3.1. Optimization of Reaction Condition:

We initiated our study by examining the intramolecular C(sp^2)-H oxaclization of 1-(1,1-dimethyl-1H-inden-3-yl)naphthalen-2-ol (**8a**) prepared by thermal ring-reaarangement of benzochrome[29] to 8,8-dimethyl-8H-indeno[2,1-b]naphtho[1,2-d]furan (**9a**).

Table 1. Optimization of Reaction Conditions [a]



8a 9a

Entry	Deviation from the standard condition	result
1	DMF in place of DMSO	78%, 2 h
2	PivOH in place of AcOH	88%, 3 h
3	Reaction temperature 120 °C	85%, 12 h
4	Reaction temperature 100 °C	85%, 12 h
5	Reaction temperature 30 °C	nr
6	Without AcOH	40%, 24 h
7	Without DMSO	60%, 8 h
8	Without CuI	30%, 24 h
9	No CuI, No AcOH	nr, 24 h
10	Under nitrogen atmosphere	70%, 8 h
11	5 mol% CuI	68%, 6 h
12	$Cu(OTf)_2$ instead of CuI	55%, 8 h
13	$Cu(OAc)_2$ instead of CuI	50%, 8 h
14	$PdCl_2$ instead of CuI	35%, 8 h
15	$FeCl_3$ instead of CuI	35%, 8 h
16	*p*TSA instead of CuI	50%, 8 h

[a] Unless mentioned, all the reactions were carried out with **8a** (100 mg, 0.355 mmol) under specified conditions. Oil bath temperatures and Isolated yields are mentioned.

An in-depth analysis of the reaction conditions suggested that heating **8a** in 1:1 DMSO/AcOH at 140 °C with 10 mol% CuI in an open flask accomplished the highest yield of **9a**, 92% (Table 1). The reaction yield was reduced while switching from DMSO to DMF (entry 1). It was found that the yield of **9a** was slightly decreased when pivalic acid was

employed in place of acetic acid (entry 2). Lowering reaction temperature show decreased yield of the product (entries 3 & 4); no reaction occurred at room temperature (entry 5). Additionally, we noticed that low yields were achieved without acetic acid, DMSO, or CuI (entries 6-9). In a similar vein, the nitrogen atmosphere was not in better shape as it produced a moderate yield of **9a** in 8 hours (entry 10). Since 5 mol% CuI was not producing an appreciable yield, 10 mol% of catalyst is justified (entry 11). Moderate yields were observed when we switched the catalyst to other copper salts, such as copper triflate and copper acetate (entries 12,13). Other transition metal halide catalysts, such as palladium chloride and iron chloride, were found to be inadequate (entries 14,15). Similarly, *p*TSA was unreliable as it gave only a 50% yield of **9a** (entry 16). The structure of **9a** was confirmed by NMR and HRMS analysis, and a single crystal XRD was recorded to clear the ambiguity (Figure 1).

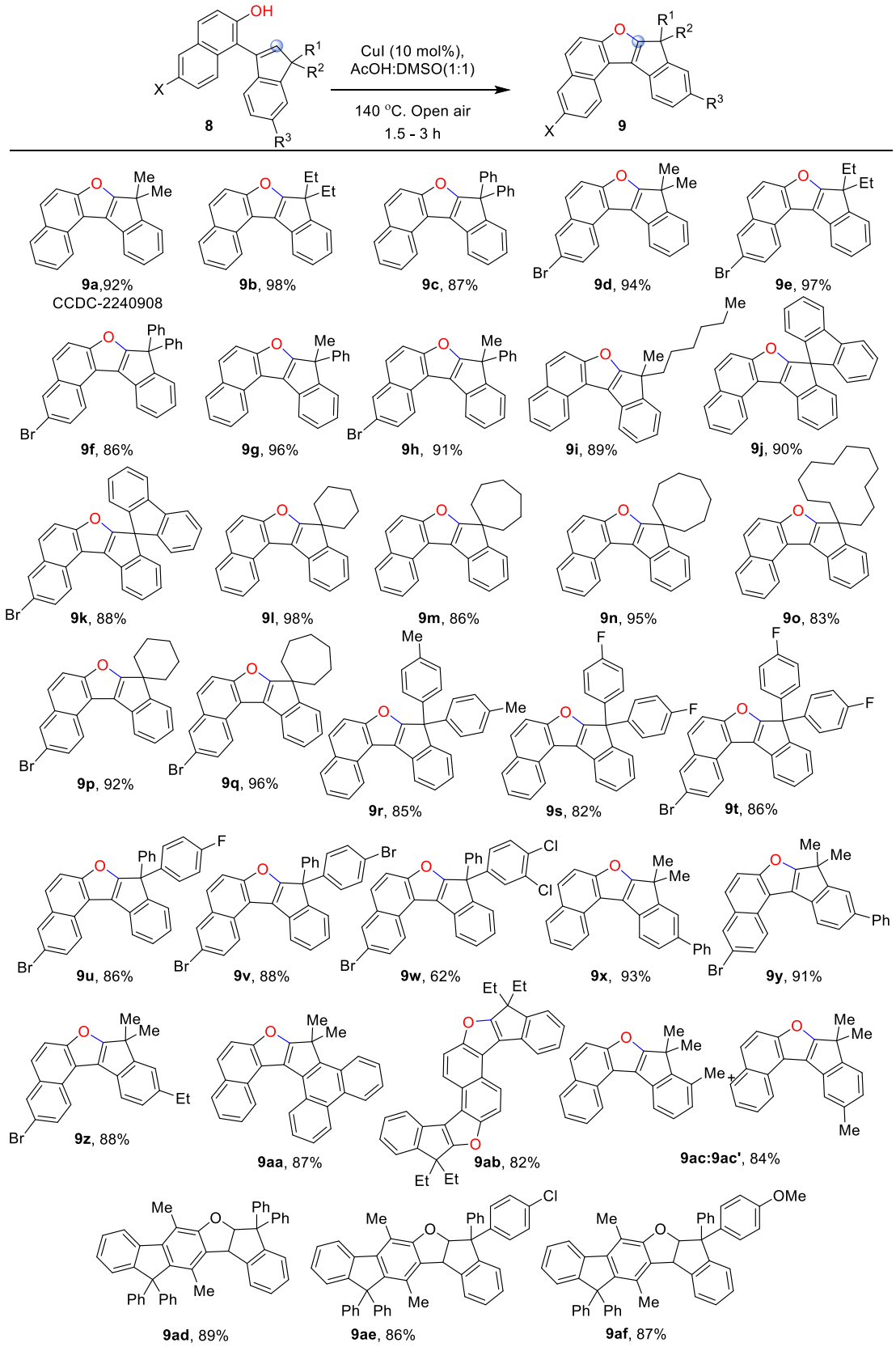
2.3.2. Scope of the Reaction:

After determining the optimal reaction condition, we intended to explore the potential of indenoarenol derivatives for the synthesis of fused furans (Scheme 8). The presence of alkyl substituent on quaternary centre of indene resulted in better yields of product in lesser time (0.5 h to 1.5 h) when compared to the aryl substituents.

Compounds **9a-9f**, represent homosubstituted quaternary carbon with alkyl and aryl groups (methyl, ethyl, and phenyl). Bromo substitution on naphthol did not show any additional effect, nearly identical yields were observed when compared with unsubstituted naphthol. Heterosubstituted quaternary carbon of indene tolerated the optimized condition to produced corresponding fused furans **9g-9i**. Next, we extended our focus to see the influence of cyclic rings (spiranes) on the C1 quaternary centre of indene under standard reaction conditions. Interestingly, the substrates possessing 9-fluorenyl **8j** and **8k**, cyclohexyl **8l** and **8p**, cycloheptyl **8m** and **8q**, cyclooctyl **8n**, and cyclododecyl **8o** on indeneproduced corresponding poly fused furans **9j-9q** through copper-catalyzed cycloetherification in good to excellent yields. Compounds **9r-9w** having diaryl substituent at the quaternary centre were synthesized from respective indenes in good to moderate yields, it is worth noting that the reaction time for these substrates was around 3-4 hours. Indene with dichloro phenyl substitution on the quaternary center showed less yield compared to monosubstitution. Next, we synthesized fused furans with substitution at the C6 position of indene (**9x-7z**) with this protocol.

Cyclopentaphenanthrene attached to 2-naphthol (**8aa**) also showed excellent reactivity for the cycloetherification reaction to furnish 87% of **9aa**. A fascinating substrate **8ab**, which had two indenyl groups on naphthalene-2,6-diol when subjected to the optimized condition resulted in double C(sp^2)-O bond formation to produce eight rings fused into a single molecule (**9ab**), however, the catalyst loading was doubled for this case. Compounds **8ac** and **8ac'** as 1:1 regioisomeric mixture, when subjected to cycloetherification obtained the desired products **9ac:9ac'** as a 1:1 mixture with 84% combined yield. Next, we demonstrated that indene-tethered fluorenol derivatives underwent intramolecular etherification and yielded **9ad** in an adequate yield. Due to the stereogenic centres on the indene moiety, the substrates

8ae and **8af** display diastereoselectivity, also tolerated by the reaction conditions and gave rise to **9ae** and **9af** in excellent yields.



Scheme 8. *Substrate scope of fused furans*

The substrates **8g-8i**, **8u-8w**, **8ae,** and **8af** exhibiting diastereoselectivity due to atropisomerism, when subjected to the standard reaction conditions, obtained corresponding fused furans as single isomers due to the loss of axial chirality in constructing a planar ring.

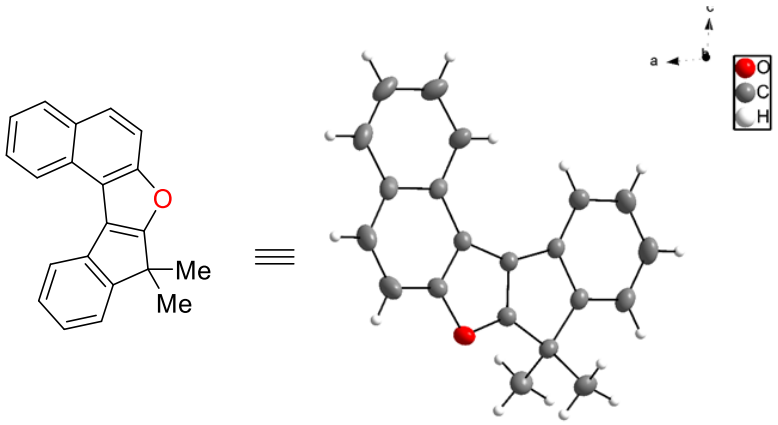
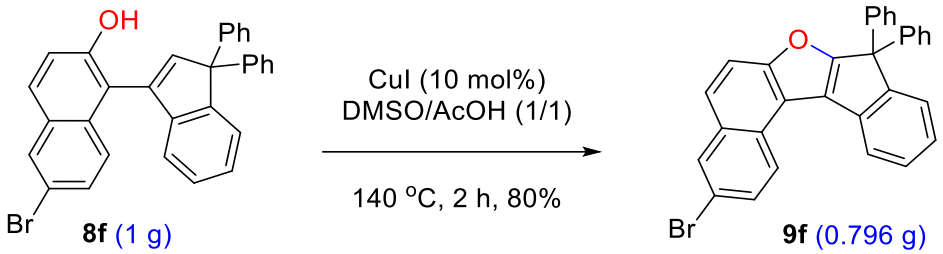


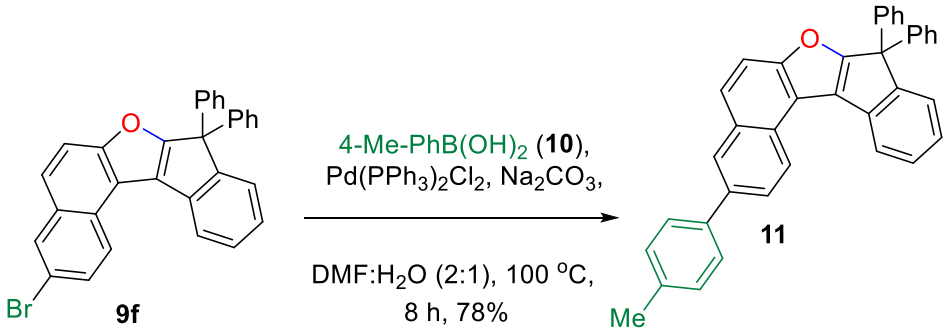
Figure 1. *Single Crystal XRD of* ***9a***

2.3.3. Gram Scale Synthesis and Synthetic Transformation:



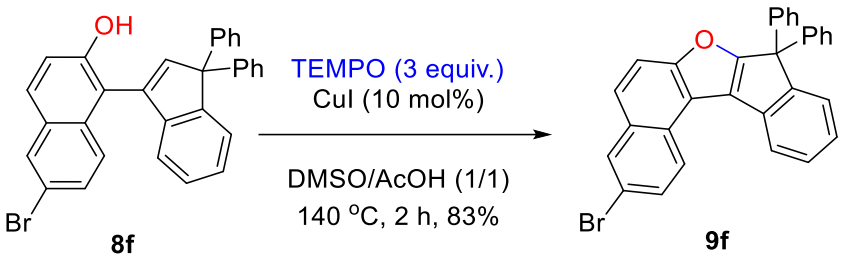
Scheme 9. *Gram Scale Preparation*

Following this achievement, we performed a gram scale reaction of **8f** (1 g) under the standard reaction conditions and isolated **9f** in 80% yield (Scheme 9), and a post-synthetic modification was performed with *p*-tolyl boronic acid **10** under Suzuki cross-coupling reaction conditions to obtain compound **11** in 78% yield (Scheme 10).



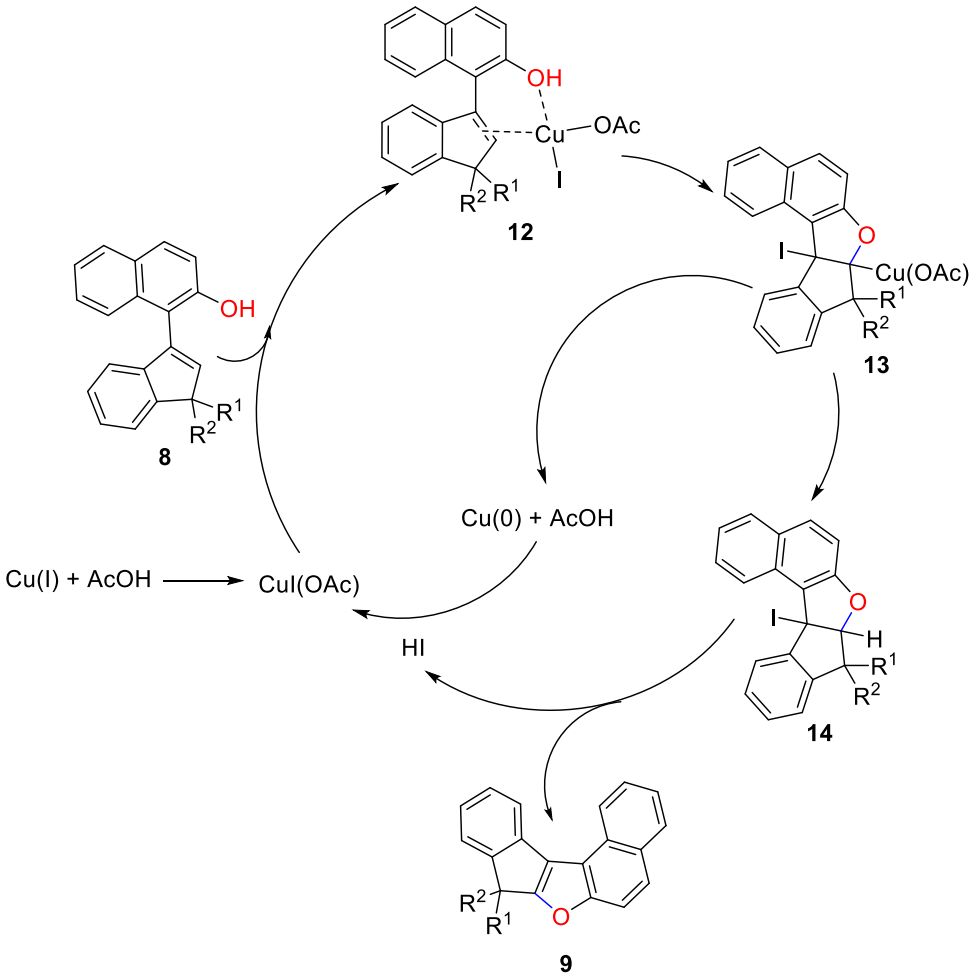
Scheme 10. *Suzuki cross coupling of* ***9f***

Excess of 2,2,6,6-tetramethylpiperidinyl-1-oxy (TEMPO) was employed as a radical scavenger in the reaction along with the reaction with standard reaction conditions, to avoid the uncertainty on the reaction mechanism to be a radical pathway (Scheme 11). It was observed that product **9f** was formed with consistent yield, further, the mass of TEMPO adduct was not detected in the HRMS analysis of the crude reaction mass, this suggested that the radical route may not be followed. Based on these observations and previous reports[23,24,30] we proposed a possible reaction mechanism for the cycloetherification depected in Scheme 12.



Scheme 11. *Employing radical scavenger*

2.3.4. Mechanism:



Scheme 12. *Proposed Mechanism*

We believe that the initial coordination of indene π-bond with Cu(II) takes place to produce intermediate (**12**), which will reorganize to intermediate (**13**). Then cycloetherification, and demetallation take place to produce (**14**). Next, intermediate **14** undergoes a dehydroiodination to produce the desired product **9**. In the presence of HI, air, and acid, Cu(0) is oxidized to Cu(II) (Scheme 12).

2.4. Conclusion

In conclusion, we demonstrate a C_{sp2}-H functionalization strategy for the cycloetherification process with an internal -OH group. CuI was employed in the open flask process with quick reaction times to produce poly fused furans in high yields. The demonstration of synthetic use and gram scale synthesis. Single crystal X-ray data of compound **9a** confirms the structure unambiguously (CCDC No. 2240908). A radical scavenging experiment with TEMPO was performed to rule out the radical reaction path. We believe this copper-catalyzed, atom economically benign transformation is complementary to the existing and related methods for constructing fused furans.

2.5. Single Crystal XRD of 9a

The vapor diffusion crystallization method was used for crystal growth for 9a, where the compound was dissolved in chloroform by heating to make a saturated solution in a small vial which was placed in a closed bottle with another solvent as n-hexane. The crystal data was recorded on Rigaku Oxford Diffractometer.

Identification code	YSR107
Empirical formula	C21H16O
Formula weight	284.36
Temperature	298 K
Wavelength	0.71073 Å
Crystal system	'Monoclinic'
Space group	P 1 21/c 1
Unit cell dimensions	a = 6.0848 (5) Å α = 90. b = 14.5499 (13) Å β = 98.874 (3). c = 17.4078 (15) Å γ = 90.
Volume	1522.7 (2)
Z	4
Density	1.240 g/cm^3
Absorption coefficient	0.075 mm^{-1}
F (000)	600.0
Crystal size	0.15 x 0.17x 0.1 mm^3
Theta (max)	25.96
Theta (min)	2.37
Index ranges	-7<=h<=7, -17<=k<=17, -21<=l<=21
Reflections collected	49894
R (reflection)	0.0432 (2564)

wR2 (reflections)	0.1224(3002)
restraints / parameters	0/201
Goodness-of-fit on F^2	1.1001
Data completeness	0.993
S	1.100
Npar	201
CCDC No.	2240908

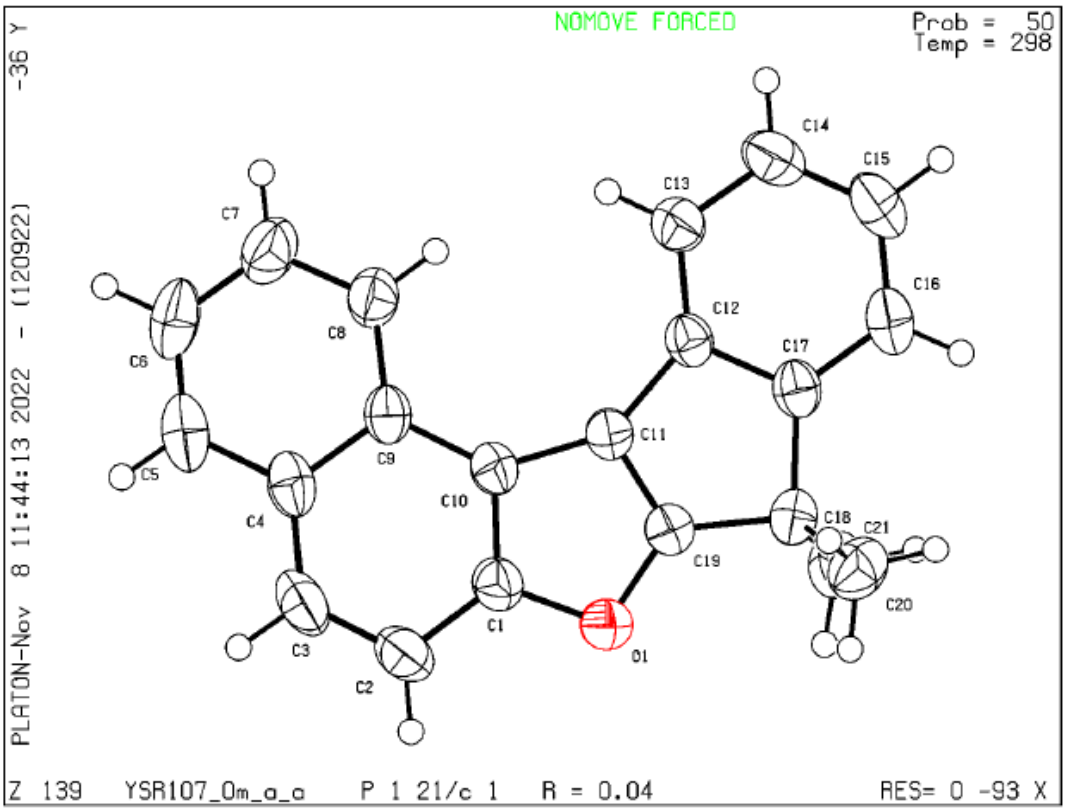


Figure 1. *ORTEP representation of compound* ***9a*** *and thermal ellipsoids are drawn with 50% probability*

2.6. Experimental Section

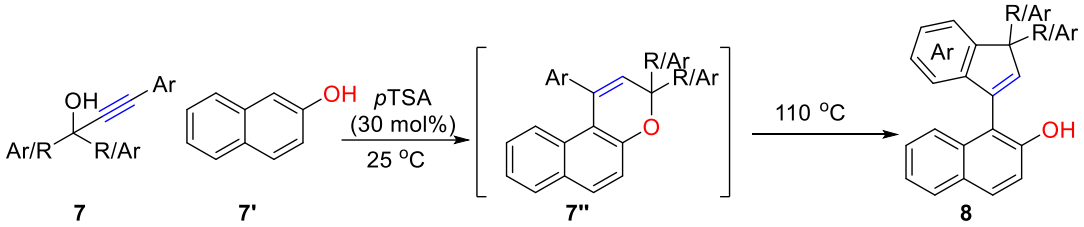
2.6.1. General Information:

Unless otherwise noted, all reagents were used as received from commercial suppliers, and indeno-naphthols were synthesized by following the reported procedures. Reactions were performed in flame-dried or oven-dried glassware with magnetic stirring and were monitored using thin-layer chromatography (TLC) with aluminum sheets of silica gel 60 F_{254} from Merck. TLC plates were visualized with UV light (254 nm), iodine treatment, or using *p*-anisaldehyde or vanillin stain. Column chromatography was carried out using silica gel 60-120 and 100-200 mesh size as stationary phase. NMR spectra were recorded at 500 MHz and 400 MHz (^{1}H) and 125 MHz and 100 MHz (^{13}C{^{1}H}), respectively on the Avance Bruker spectrometer. NMR spectra were solved by using Bruker Topspin software. Chemical shifts (δ) are reported in ppm, using the residual solvent peak in $CDCl_3$ (^{1}H: δ= 7.26 and ^{13}C{^{1}H}: δ

= 77.16 ppm) as internal standard, and coupling constants (*J*) are given in Hz. HRMS were recorded using ESI-TOF techniques. Melting points were measured with the LABINDIA mepa melting apparatus.

2.6.2. General Experimental Procedures:

2.6.2.1. General experimental procedure for synthesis of inden-ols:[29] A mixture of aryl propargylic alcohol **7** (1 equiv.) and naphthol **7'** (1.2 equiv.) and *p*TSA (20 mol%) were stirred at 25 °C till the formation of benzochromenes (monitored by TLC and then the reaction mixture was heated at 110 °C for 3-4 hours. After completion of the reaction (monitored by TLC), the crude product was purified by silica gel column chromatography (5-10 % EtOAc in pet ether) to obtain the desired product **1** in moderate to good yield.



Scheme 13. *Synthesis of Indenyl arenol*

2.6.2.2. General experimental procedure for the preparation of indeno furan (9): To the solution of indenyl naphthalen-2-ol (**8**) in DMSO (0.5 mL), CuI (10 mol%) and acetic acid (0.5 mL) were introduced and heated to 140 °C. The progress of the reaction was monitored by TLC. After the complete consumption of starting materials, the reaction mixture was quenched with water, and the product was extracted with EtOAc (thrice), the combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated to obtain the crude product. The crude was purified by column chromatography using an eluent of ethyl acetate and pet ether (5-7 % ethyl acetate in pet ether) to afford the desired indeno furan in a good to excellent yield.

2.6.2.3. Experimental procedure for the synthesis of 8,8-diphenyl-3-(p-tolyl)-8H-indeno[2,1-b]naphtho[1,2-d]furan (11):[31] 4-Me-PhB$(OH)_2$ **10** (42.18 mg, 0.312 mmol) was added to a solution of 3-bromo-8,8-diphenyl-8H-indeno[2,1-b]naphtho[1,2-d]furan **9f** (100 mg, 0.208 mmol) in DMF/H_2O (2:1; 3.0 mL) that contained Na_2CO_3 (21.8 mg,0.207 mmol), and the resulting mixture was stirred at room temperature for 5 min. $Pd(PPh_3)_2Cl_2$ (5 mol%) was then added, and the flask was flushed with N_2 and sealed. The mixture was stirred at 100 °C for 8 hours and then filtered. The filter cake was washed with diethyl ether, and the combined filtrates were extracted with diethyl ether. The combined organic layers were washed with water and brine and then dried with anhydrous Na_2SO_4. After filtration, the solvent was evaporated under reduced pressure, and the crude residue was purified by column chromatography on silica gel to isolate the pure product in a 78% (79 mg) yield.

2.6.3. Spectral data

8,8-dimethyl-8H-indeno[2,1-b]naphtho[1,2-d]furan ***(9a).*** Isolated as colourless solid, mp: 185-186 ^{o}C; yield 92% (0.091g). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.59 (d, J = 8.0 Hz, 1H), 8.03 (d, J = 7.0 Hz, 1H), 7.97 (d, J = 7.5 Hz, 1H), 7.73-7.66 (m, 3H), 7.51 (t, J = 7.5 Hz, 1H), 7.43-7.40 (m, 2H), 7.26 (t, J = 7.5 Hz, 1H), 1.60 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 172.7, 157.3, 153.6, 135.2, 131.0, 128.9, 127.9, 127.3, 126.2, 125.9, 124.9, 124.6, 124.5, 122.5, 121.1, 121.0, 120.2, 113.3, 42.6, 24.3; HRMS (ESI-TOF): m/z calculated for $C_{21}H_{17}O$ $[M+H]^+$ 285.1279, found 285.1278.

8,8-diethyl-8H-indeno[2,1-b]naphtho[1,2-d]furan ***(9b).*** Isolated as colourless solid, mp: 188-190 ^{o}C; yield: 97% (0.096g). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.61 (d, J = 8.0 Hz, 1H), 8.03 (d, 1H, J = 7.5 Hz), 7.98 (d, 1H, J = 8.0 Hz), 7.73 (s, 2H), 7.71-7.67 (m, 1H), 7.54-7.51 (m, 1H), 7.42 (t, 1H, J = 7.5 Hz),7.31 (d, 1H, J = 7.5 Hz), 7.26 (d, 1H, J = 7.5 Hz), 2.24-2.17 (m, 2H), 2.03-1.96 (m, 2H), 0.56 (t, 6H, J = 7.5 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 170.1, 157.6, 150.4, 137.2, 131.0, 128.9, 127.8, 127.2, 126.2, 126.0, 124.7, 124.6, 124.3, 124.1, 122.7, 120.7, 120.0, 113.4, 52.4, 30.1, 9.0; HRMS (ESI-TOF): m/z calculated for $C_{23}H_{21}O$ $[M+H]^+$ 313.1592, found 313.1595.

8,8-diphenyl-8H-indeno[2,1-b]naphtho[1,2-d]furan ***(9c).*** Isolated as colourless solid, mp: 185-187 ^{o}C; yield: 87% (0.086g). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.62 (d, J = 8.0 Hz, 1H), 8.11 (d, J = 7.5 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.71-7.68 (m, 2H), 7.55-7.52 (m, 1H), 7.48-7.44 (m, 2H), 7.33-7.30 (m, 4H), 7.29-7.28 (m, 1H), 7.27-7.26 (m, 2H), 7.25-7.24 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169.2, 158.1, 151.1, 142.5, 136.1, 131.4, 129.1, 128.6, 128.4, 128.1, 127.9, 127.4, 126.9, 126.4, 125.9, 125.3, 125.1, 124.8, 123.8, 121.7, 120.0, 113.6, 60.8; HRMS (ESI-TOF): m/z calculated for $C_{31}H_{21}O$ $[M+H]^+$ 409.1592, found 409.1594.

3-bromo-8,8-dimethyl-8H-indeno[2,1-b]naphtho[1,2-d]furan ***(9d).*** Isolated as colourless solid, mp: 203-205 ^{o}C; yield: 94% (0.093g). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.42 (d, J = 8.8 Hz, 1H), 8.11 (d, J = 1.6 Hz, 1H), 7.94 (d, J = 7.6 Hz, 1H), 7.73 (t, J = 6.0 Hz, 1H), 7.71 (t, J = 6.0 Hz, 1H),7.61 (d, 1H, J = 8.8 Hz), 7.43-7.40 (m, 2H), 7.27 (t, 1H, J = 6.8 Hz), 1.59 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.3, 157.4, 153.7, 137.6, 134.9, 134.7, 132.4, 131.0, 129.4, 127.5, 127.4, 126.5, 125.1, 123.5, 122.5, 121.0, 120.9, 120.4, 118.4, 114.4, 42.7, 24.3; HRMS (ESI-TOF): m/z calculated for $C_{21}H_{16}BrO$ $[M+H]^+$ 363.0385, found 363.0384.

3-bromo-8,8-diethyl-8H-indeno[2,1-b]naphtho[1,2-d]furan ***(9e).*** Isolated as yellowish solid, mp: 192-194 ^{o}C; yield: 97% (0.096g). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.46 (d, J = 8.0 Hz, 1H), 8.13 (d, J = 2.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.76-7.74 (m, 2H), 7.62 (d, J = 9.0 Hz, 1H), 7.44-7.41 (m, 1H), 7.32 (d, J = 7.0 Hz, 1H), 7.27 (d, J = 7.5 Hz, 1H), 2.24-2.17 (m, 2H), 2.03-1.96 (m, 2H), 0.56 (t, J = 7.5 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 170.7, 157.6, 150.3, 136.8, 132.2, 130.9, 127.6, 127.2, 126.2, 124.9, 123.9, 123.3,

122.8, 120.6, 120.0, 118.2, 114.4, 52.5, 30.1, 9.0; HRMS (ESI-TOF): m/z calculated for $C_{23}H_{20}BrO$ $[M+H]^+$ 391.0698, found 391.0698.

3-bromo-8,8-diphenyl-8H-indeno[2,1-b]naphtho[1,2-d]furan ***(9f):*** Isolated as colourless solid, mp: 217-219 ºC; yield: 85% (0.084g); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.46 (d, J = 8.5 Hz, 1H), 8.12 (d, J = 2.5 Hz, 1H), 8.03 (d, J = 7.5 Hz, 1H), 7.76-7.74 (m, 1H), 7.72 (d, J = 6.0 Hz, 1H), 7.63 (d, J = 8.5 Hz, 1H),7.48-7.44 (m, 2H), 7.31-7.28 (m, 5H), 7.27-7.28 (m, 5H), 7.25 (s, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$): δ (ppm) 169.7, 158.1, 151.1, 142.3, 135.7, 132.6, 131.1, 129.7, 128.7, 128.4, 128.0, 127.6, 127.5, 127.0, 126.6, 125.5, 124.1, 123.6, 121.6, 120.1, 118.6, 114.7, 113.6, 60.9; HRMS (ESI-TOF): m/z calculated for $C_{31}H_{20}BrO$ $[M+H]^+$ 487.0698, found 487.0697.

8-methyl-8-phenyl-8H-indeno[2,1-b]naphtho[1,2-d]furan ***(9g):*** Isolated as colourless solid, mp: 164-166; yield: 96% (0.095g). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.63 (d, J = 8.5 Hz, 1H), 8.09 (d, J = 7.0 Hz, 1H), 7.98 (d, J = 8.5 Hz, 1H), 7.73 (d, J = 9.0 Hz, 1H), 7.71-7.69 (m, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.55-7.52 (m, 1H), 7.45-7.42 (m, 1H), 7.33-7.29 (m, 3H), 7.28-7.25 (m, 2H), 7.24-7.20 (m, 2H), 2.00(s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 171.6, 157.5, 153.7, 141.3, 135.5, 131.1, 129.0, 128.8, 127.9, 127.6, 127.2, 126.5, 126.4, 125.9, 125.3, 124.8, 124.7, 124.2, 122.5, 121.2, 120.0, 113.5, 50.2, 22.8; HRMS (ESI-TOF): m/z calculated for $C_{26}H_{19}O$ $[M+H]^+$ 347.1436, found 347.1437.

3-bromo-8-methyl-8-phenyl-8H-indeno[2,1-b]naphtho[1,2-d]furan ***(9h):*** Isolated as yellowish solid, mp: 193-195 ºC; yield: 91% (0.090g). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.46 (d, 1H, J = 9.0 Hz), 8.14 (d, 1H, J = 2.0 Hz), 8.01 (d, 1H, J = 7.5 Hz), 7.78-7.76 (m, 1H), 7.70 (d, 1H, J = 8.5 Hz), 7.62 (d, 1H, J = 9.0 Hz), 7.46-7.43 (m, 1H), 7.33-7.31 (m, 3H), 7.29-7.26 (m, 2H), 7.25-7.21 (m, 2H), 2.00 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 172.1, 157.5, 153.6, 141.1, 135.1, 132.3, 131.0, 129.5, 128.8, 127.6, 127.5, 127.3, 126.5, 126.3, 125.5, 124.3, 123.8, 122.2, 121.1, 120.1, 118.4, 114.5, 50.3, 22.8; HRMS (ESI-TOF): m/z calculated for $C_{26}H_{18}BrO$ $[M+H]^+$ 425.0541, found 425.0544.

8-hexyl-8-methyl-8H-indeno[2,1-b]naphtho[1,2-d]furan ***(9i):*** Isolated as colourless solid, mp: 195-197 ºC; yield: 89% (0.088g). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.60 (d, J = 8.0 Hz, 1H), 8.03 (d, J = 6.5 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.73 (s, 2H), 7.71-7.66 (m, 1H), 7.50 (t, J = 7.0 Hz, 1H), 7.43-7.40 (m, 1H), 7.35 (d, J = 7.5 Hz, 1H), 7.26-7.23 (m, 1H), 2.14-2.8 (m, 1H), 1.93-1.87 (m, 1H), 1.57 (s, 3H), 1.14-1.10 (m, 6H), 0.97-.96 (m, 2H), 0.77-0.74 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 171.8, 157.4, 152.3, 136.0, 131.0, 128.9, 127.8, 127.2, 126.2, 125.9, 124.8, 124.6, 124.4, 122.5, 122.3, 120.9, 120.1, 113.3, 46.7, 38.4, 31.6, 29.6, 24.7, 23.5, 22.7, 14.1; HRMS (ESI-TOF): m/z calculated for $C_{26}H_{27}O$ $[M+H]^+$ 355.2062, found 355.2060.

spiro[fluorene-9,8'-indeno[2,1-b]naphtho[1,2-d]furan] ***(9j):*** Isolated as colourless solid, mp: 214-216 ºC; yield: 90% (0.089g). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.72 (d, J = 8.5 Hz, 1H), 8.16 (d, J = 7.5 Hz, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.76 (t, J = 7.5 Hz, 2H), 7.97 (d, J = 7.5 Hz, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.59- 7.53 (m, 2H), 7.46-7.40 (m, 3H), 7.15 (t, J = 7.5 Hz, 2H),7.06 (t, J = 7.5 Hz, 1H), 6.91 (d, J = 7.5 Hz, 2H), 6.71 (d, J = 7.5 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 166.2, 157.9, 149.6, 144.4, 142.3, 137.2, 131.1, 129.0,

128.6, 128.1, 128.0, 127.7, 126.5, 126.0, 125.9, 125.7, 125.2, 124.9, 124.0 (2), 121.1, 120.6, 119.9, 113.5, 60.6; HRMS (ESI-TOF): m/z calculated for $C_{31}H_{19}O$ $[M+H]^+$ 407.1436, found 407.1437.

3'-bromospiro[fluorene-9,8'-indeno[2,1-b]naphtho[1,2-d]furan] ***(9k):*** Isolated as colourless solid, mp: 238-240 ^oC; yield: 88% (0.086g). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.57 (d, J = 8.5 Hz, 1H), 8.15 (d, J = 1.5 Hz, 1H), 8.08 (d, J = 7.5 Hz, 1H), 7.89 (d, J = 7.5 Hz, 2H), 7.84-7.82 (m, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.47- 7.41 (m, 3H), 7.18-7.14 (m, 2H), 7.9-7.06 (m, 1H), 6.90 (d, J = 7.5 Hz, 2H),6.72 (d, J = 7.0 Hz, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 166.8, 157.9, 149.5, 144.2, 142.3, 136.8, 132.2, 131.0, 129.6, 128.7, 128.1, 128.0, 127.5, 126.1, 125.9, 125.8, 124.1, 123.9, 121.0, 120.6, 120.0, 118.5, 114.5, 60.6; HRMS (ESI-TOF): m/z calculated for $C_{31}H_{18}BrO$ $[M+H]^+$ 485.0541, found 485.0540.

spiro[cyclohexane-1,8'-indeno[2,1-b]naphtho[1,2-d]furan] ***(9l):*** Isolated as colourless solid, mp: 175-177 ^oC; yield: 98% (0.097g). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.62 (d, J = 8.5 Hz, 1H), 8.05 (d, J = 7.5 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.76-7.72 (m, 2H), 7.70-7.66 (m, 1H), 7.54-7.50 (m, 1H), 7.44-7.40 (m, 2H), 7.28-7.25 (m, 1H), 2.17-2.08 (m, 2H), 2.07-2.01 (m, 3H), 1.92-1.89 (m, 2H), 1.66-1.60 (m, 2H), 1.58-1.52 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 173.4, 157.4, 152.9, 135.2, 131.0, 128.9, 127.9, 127.2, 126.2, 125.9, 124.7, 124.6, 124.4, 122.9, 121.6, 120.9, 119.8, 113.4, 48.1, 34.6, 26.0, 23.6; HRMS (ESI-TOF): m/z calculated for $C_{24}H_{21}O$ $[M+H]^+$ 325.1592, found 325.1590.

spiro[cycloheptane-1,8'-indeno[2,1-b]naphtho[1,2-d]furan] ***(9m):*** Isolated as yellowish solid, mp: 182-184 ^oC; yield: 86% (0.085g). ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.60 (d, J = 8.5 Hz, 1H), 8.03 (d, J = 7.5 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H),7.74 (s, 2H), 7.70-7.66 (m, 1H), 7.54-7.51 (m, 1H), 7.48 (d, J = 7.0 Hz, 1H), 7.43-7.39 (m, 2H), 2.12-2.04 (m, 4H), 1.92-1.90 (m, 6H), 1.86-1.81 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 173.7, 157.3, 155.1, 134.8, 131.0, 128.9, 128.8, 127.9, 127.7, 127.1, 126.2, 125.9, 124.8, 124.6, 124.4, 122.8, 121.2, 120.9, 120.0, 113.4, 50.4, 37.1, 30.0, 24.8; HRMS (ESI-TOF): m/z calculated for $C_{25}H_{23}O$ $[M+H]^+$ 339.1749, found 339.1747.

spiro[cyclooctane-1,8'-indeno[2,1-b]naphtho[1,2-d]furan] ***(9n):*** Isolated as yellowish viscous compound; yield: 95% (0.094g).^1H NMR (500 MHz, $CDCl_3$): δ (ppm); 8.60 (d, 1H, J = 8.0 Hz), 8.05 (d, 1H, J = 7.5 Hz), 7.97 (d, J = 8.0 Hz, 1H), 7.29 (s, 2H), 7.69-7.66 (m, 1H), 7.53-7.50 (m, 1H), 7.49 (d, J = 7.0 Hz, 1H), 7.44-7.40 (m, 1H), 7.25-7.22 (m, 1H), 2.09-2.07 (m, 2H), 2.03-1.97 (m, 4H), 1.94-1.92 (m, 2H), 1.86-1.78 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 174.0, 157.3, 153.9, 134.9, 131.0, 128.9, 127.9, 127.1, 126.2, 125.9, 124.6, 124.5, 124.4, 123.5, 121.0, 120.9, 120.0, 113.4, 50.0, 32.0, 28.8, 25.2, 24.3; HRMS (ESI-TOF): m/z calculated for $C_{26}H_{25}O$ $[M+H]^+$ 353.1905, found 353.1906.

spiro[cyclododecane-1,8'-indeno[2,1-b]naphtho[1,2-d]furan] ***(9o):*** Isolated as yellow viscous compound; yield: 83% (0.082g). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.61 (d, J = 8.5 Hz, 1H), 8.06 (d, J = 7.5 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H),7.73 (s, 2H), 7.71-7.67 (m, 1H), 7.54-7.51 (m, 1H), 7.46-7.41 (m, 2H), 7.24-7.21 (m, 1H), 1.87-1.78 (m, 8H), 1.55-1.42

(m, 14H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 173.4, 157.3, 152.3, 135.3, 131.0, 128.9, 127.9, 127.1, 126.2, 125.9, 124.6, 124.5, 124.4, 124.1, 121.2, 121.0, 120.0, 113.3, 49.3, 30.9, 26.9, 26.2, 23.1, 22.6, 21.1; HRMS (ESI-TOF): m/z calculated for $C_{30}H_{33}O$ $[M+H]^+$ 409.2531, found 409.2530.

3'-bromospiro[cyclohexane-1,8'-indeno[2,1-b]naphtho[1,2-d]furan] ***(9p):*** Isolated as colourless solid, mp: 206-208 ^oC; yield: 92% (0.091g). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.48 (d, *J* = 9.0 Hz, 1H), 8.13 (d, *J* = 1.5 Hz, 1H), 7.97 (d, *J* = 7.5 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.75-7.73 (m, 1H), 7.64 (d, *J* = 9.0 Hz, 1H), 7.44-7.41 (m, 2H), 7.29-7.25 (m, 1H), 2.15-2.02 (m, 6H), 1.92-1.89 (m, 2H), 1.65-1.63 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 173.8, 157.4, 152.8, 134.8, 132.2, 130.9, 129.3, 127.5, 127.2, 126.3, 125.0, 123.3, 123.0, 121.5, 120.8, 119.9, 118.2, 114.4, 48.2, 34.5, 25.9, 23.6; HRMS (ESI-TOF): m/z calculated for $C_{24}H_{20}BrO$ $[M+H]^+$ 403.0698, found 403.0699.

3'-bromospiro[cycloheptane-1,8'-indeno[2,1-b]naphtho[1,2-d]furan] ***(9q):*** Isolated as yellowish solid, mp: 210-212 ^oC; yield: 96% (0.095g). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.61 (d, *J* = 8.0 Hz, 1H), 8.03(d, *J* = 7.5 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H),7.74 (s, 2H), 7.70-7.66 (m, 1H), 7.54-7.51 (m, 1H) 7.48 (d, *J* = 7.0 Hz, 1H), 7.43-7.39 (m, 1H), 2.12-2.04 (m, 4H), 1.92-1.86 (m, 6H), 1.81 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 174.2, 157.3, 155.0, 134.3, 132.2, 130.9, 129.3, 127.5, 127.1, 126.3, 125.0, 123.3, 122.9, 121.0, 120.7, 120.0, 118.2, 114.4, 50.5, 37.0, 30.0, 24.8; HRMS (ESI-TOF): m/z calculated for $C_{25}H_{22}BrO$ $[M+H]^+$ 417.0854, found 417.0853.

8,8-di-p-tolyl-8H-indeno[2,1-b]naphtho[1,2-d]furan ***(9r):*** Isolated as colourless solid, mp: 169-171 ^oC; yield: 85% (0.084g). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.61 (d, *J* = 7.0 Hz, 1H), 8.10 (d, *J* = 7.5 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.74-7.68 (m, 3H), 7.53 (t, *J* = 7.0 Hz, 1H), 7.46-7.42 (m, 2H), 7.27-7.24 (m, 1H), 7.19 (d, *J* = 8.0 Hz, 4H), 7.07 (d, *J* = 8.0 Hz, 4H), 2.29 (s, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 169.3, 157.8, 151.2, 139.4, 137.0, 135.8, 131.1, 129.3, 129.0, 128.1, 127.8, 127.7, 126.6, 126.3, 125.9, 125.2, 124.9, 124.7, 123.3, 121.5, 119.9, 113.6, 59.9, 29.8, 21.1; HRMS (ESI-TOF): m/z calculated for $C_{33}H_{25}O$ $[M+H]^+$ 437.1905, found 437.1907.

3-bromo-8,8-bis(4-fluorophenyl)-8H-indeno[2,1-b]naphtho[1,2-d]furan ***(9s):*** Isolated as yellowish solid, mp: 182-184 ^oC; yield: 82% (0.081g). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.61 (d, *J* = 7.5 Hz, 1H), 8.12 (d, *J* = 7.5 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.77 (d, *J* = 9.0 Hz, 1H), 7.73-7.70 (m, 2H), 7.57-7.53 (m, 1H), 7.50-7.47 (m, 1H), 7.39 (d, *J* = 7.5 Hz, 1H), 7.30-7.26 (m, 5H), 6.99-6.94 (m, 4H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 168.4, 163.4, 161.0, 157.9, 150.7, 137.8, 135.7, 131.1, 129.9, 129.8, 129.1, 128.2, 127.9, 126.5, 125.8, 125.5, 125.4, 124.9, 123.6, 121.8, 119.7, 115.7, 115.5, 113.5, 59.3; HRMS (ESI-TOF): m/z calculated for $C_{31}H_{19}F_2O$ $[M+H]^+$ 445.1404, found 445.1401.

3-bromo-8,8-bis(4-fluorophenyl)-8H-indeno[2,1-b]naphtho[1,2-d]furan ***(9t):*** Isolated as yellowish solid, mp: 212-214 ^oC; yield: 86% (0.085g). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.45 (d, *J* = 9.0 Hz, 1H), 8.14 (d, *J* = 2.0 Hz, 1H), 8.04 (d, *J* = 7.5 Hz, 1H), 7.78-7.76 (m, 1H), 7.73 (d, *J* = 9.0 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.50-7.47 (m, 1H), 7.40 (d, 1H, *J* =

7.0 Hz), 7.31-7.28 (m, 1H), 7.27-7.26 (m, 2H), 7.25-7.23 (m, 2H), 6.99-6.94 (m, 4H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 168.9, 163.5, 161.0, 157.9, 150.6, 137.7, 135.3, 134.9, 132.8, 132.3, 131.1, 129.8, 128.2, 127.4, 126.6, 126.6, 126.3, 125.7, 124.3, 123.4, 121.7, 119.8, 118.6, 115.7, 115.5, 114.6, 114.4 59.3; HRMS (ESI-TOF): m/z calculated for $C_{31}H_{18}BrF_2O$ $[M+H]^+$ 523.0509, found 523.0506.

3-bromo-8-(4-fluorophenyl)-8-phenyl-8H-indeno[2,1-b]naphtho[1,2-d]furan ***(9u)****:* Isolated as colourless solid, mp: 218-220; yield: 86% (0.085g). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.46 (d, *J* = 9.0 Hz, 1H), 8.14 (d, *J* = 2.0 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.78-7.76 (m, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.49-7.46 (m, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.30-7.27 (m, 8H), 6.96 (d, *J* = 8.5 Hz, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 169.1, 163.4, 160.9, 157.9, 150.6, 141.9, 137.8 (2), 137.6, 135.4, 134.8, 132.7, 132.3, 131.0, 129.9, 129.8, 129.6, 128.7, 128.1, 127.6, 127.4, 126.8, 126.6, 126.3, 125.6, 124.2, 124.0, 123.4, 121.6, 119.8, 118.5, 115.6, 115.4, 114.6, 114.4, 59.9; HRMS (ESI-TOF): m/z calculated for $C_{31}H_{19}BrFO$ $[M+H]^+$ 505.0603, found 505.0603.

3-bromo-8-(4-bromophenyl)-8-phenyl-8H-indeno[2,1-b]naphtho[1,2-d]furan ***(9v):*** Isolated as colourless solid, mp: 226-228; yield: 88% (0.087g). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm)) 8.48 (d, *J* = 8.5 Hz, 1H), 8.16 (d, *J* = 2.0 Hz, 1H), 8.07 (d, *J* = 7.5 Hz, 1H), 7.80-7.78 (m, 1H), 7.75 (d, *J* = 9.0 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.52-7.49 (m, 1H), 7.44-7.40 (m, 3H), 7.33-7.31 (m, 6H), 7.21-7.18 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm168.7, 157.9, 150.2, 141.5, 141.3, 137.7, 137.6, 135.4, 134.9, 132.3, 131.8, 131.0, 130.2, 130.0, 129.7, 128.8, 128.2, 128.1, 127.7, 127.4, 126.8, 126.3, 125.6, 124.3, 124.1, 123.6, 121.7, 121.6, 119.8, 118.5, 114.6, 114.4, 60.1; HRMS (ESI-TOF): m/z calculated for $C_{31}H_{18}Br_2NaO$ $[M+Na]^+$ 586.9622, found 586.9621.

8-(3,4-dichlorophenyl)-8-phenyl-8H-indeno[2,1-b]naphtho [1,2-d]furan ***(9w)****:* Isolated as yellow viscous compound; yield: 62% (0.061g). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.60 (d, *J* = 8.5 Hz, 1H), 8.13 (d, *J* = 7.5 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 9.0 Hz, 1H), 7.73-7.70 (m, 2H), 7.57-7.54 (m, 1H), 7.51-7.48 (m, 1H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.37 (d, *J* = 2.0 Hz, 1H), 7.36-7.33 (m, 1H), 7.31-7.27 (m, 6H), 7.17-7.15 (m, 1H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 167.6, 158.0, 149.9, 142.8, 141.2, 135.8, 132.7, 131.6, 131.1, 130.5, 130.0, 129.1, 128.9, 128.3, 128.1, 127.9, 127.8, 126.6, 125.8, 125.6, 125.5, 125.0, 124.0, 121.9, 119.7, 113.5, 59.8; HRMS (ESI-TOF): m/z calculated for $C_{31}H_{19}Cl_2O$ $[M+H]^+$ 477.0813, found 477.0811.

8,8-dimethyl-10-phenyl-8H-indeno[2,1-b]naphtho[1,2-d]furan ***(9x):*** Isolated as colourless solid, mp: 174-176 ^{o}C; yield: 93% (0.092g). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.62 (d, *J* = 8.5 Hz, 1H), 8.09 (d, *J* = 7.5 Hz, 1H), 7.99 (d, *J* = 3.0 Hz, 1H), 7.76-7.74 (m, 2H), 7.73-7.71 (m, 1H), 7.69-7.64 (m, 4H), 7.56-7.53 (m, 1H), 7.50-7.47 (m, 2H), 7.38-7.35 (m, 1H), 1.66 (s, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 172.9, 157.3, 154.3, 141.6, 138.1, 134.4, 131.1, 128.9, 127.9, 127.2, 126.3 (2), 125.9, 124.7, 124.6, 121.4, 121.2, 120.8, 120.1, 113.3, 42.8, 24.4; HRMS (ESI-TOF): m/z calculated for $C_{27}H_{20}NaO$ $[M+Na]^+$ 383.1412, found 383.1414.

3-bromo-8,8-dimethyl-10-phenyl-8H-indeno[2,1-b]naphtho[1,2-d]furan ***(9y):*** Isolated as colourless solid, mp: 188-190 °C, yield: 91% (0.090g). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.47 (d, *J* = 8.5 Hz, 1H), 8.15 (d, *J* = 2.0 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 7.78-7.76 (m, 1H), 7.75 (d, *J* = 5.5 Hz, 1H), 7.69-7.64 (m, 5H), 7.50-7.47 (m, 2H), 7.39-7.36 (m, 1H), 1.66 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.4, 157.3, 154.2, 141.5, 138.3, 134.0, 132.3, 130.9, 129.4, 129.0, 127.5, 127.3, 127.2, 126.3, 123.5, 121.5, 121.1, 120.7, 120.2, 118.3, 114.4, 42.9, 24.4; HRMS (ESI-TOF): m/z calculated for $C_{27}H_{20}BrO$ $[M+H]^+$ 439.0698, found 439.0699.

*3-bromo-10-ethyl-8,8-diphenyl-8H-indeno[2,1-b]naphtho[1,2-d]furan (****9z***): Isolated as a yellowish viscous compound; yield: 88% (0.087g). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.46 (d, *J* = 9.0 Hz, 1H), 8.13 (d, *J* = 2.0 Hz, 1H), 7.94 (d, *J* = 7.5 Hz, 1H), 7.77-7.75 (m, 1H), 7.72 (d, *J* = 9.0 Hz, 1H), 7.63 (d, *J* = 9.0 Hz, 1H),7.31-7.30 (m, 3H), 7.29-7.28 (m, 7H), 7.27-7.26 (m, 2H), 2.70 (q, *J* = 7.5 Hz, 2H), 1.26 (t, *J* = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 169.0, 157.8, 150.8, 142.4, 141.7, 132.8, 132.3, 131.0, 129.5, 128.6, 128.3, 127.5, 127.3, 127.2, 126.7, 126.4, 123.8, 123.3, 121.3, 119.9, 118.4, 114.6, 60.7, 29.1, 15.9; HRMS (ESI-TOF): m/z calculated for $C_{33}H_{24}BrO$ $[M+H]^+$ 515.1011, found 515.1013.

8,8-dimethyl-8H-dibenzo[4,5:6,7]indeno[2,1-b]naphtho[1,2-d]furan ***(9aa):*** Isolated as colourless solid, mp: 193-195 °C; yield: 87% (0.086g). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.85 (d, *J* = 8.0 Hz, 1H), 8.82 (d, *J* = 8.5 Hz, 2H), 8.76 (d, *J* = 8.5 Hz, 1H), 8.20 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 7.5 Hz, 1H), 7.81-7.77 (m, 2H), 7.76-7.72 (m, 1H), 7.71-7.68 (m, 2H), 7.65-7.62 (m, 1H), 7.61-7.58 (m, 1H), 7.55-7.52 (m, 1H), 1.90 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ (ppm) 174.3, 157.2, 143.6, 132.4, 131.6, 130.9, 129.9, 129.1, 128.9, 128.4, 127.9, 127.6, 126.4, 125.6, 125.4, 124.9, 124.8, 124.5, 124.0, 123.5, 123.4, 119.7, 119.6, 113.3, 44.5, 23.9; HRMS (ESI-TOF): m/z calculated for $C_{29}H_{21}O$ $[M+H]^+$ 385.1592, found 385.1593.

Compound ***(9ab):*** Isolated as colourless solid, mp: 187-189 °C; yield: 82% (0.081g). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.54 (d, *J* = 9.0 Hz, 2H), 8.10 (d, *J* = 7.5 Hz, 2H), 7.93 (d, *J* = 9.0 Hz, 2H), 7.45 (t, *J* = 7.0 Hz, 2H), 7.34 (d, *J* = 7.0 Hz, 2H), 7.28 (t, *J* = 7.0 Hz, 2H), 2.27-2.20 (m, 4H), 2.06-1.99 (m, 4H), 0.59 (t, *J* = 7.5 Hz, 12H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 170.5, 156.9, 150.4, 137.3, 127.2, 125.0, 124.7, 124.0, 122.7, 122.0, 121.1, 120.7, 113.0, 52.3, 30.2, 9.0; HRMS (ESI-TOF): m/z calculated for $C_{36}H_{33}O_2$ $[M+H]^+$ 497.2481, found 497.2480.

8,8,9-trimethyl-8H-indeno[2,1-b]naphtho[1,2-d]furan ***(9ac)*** *and 8,8,11-trimethyl-8H-indeno[2,1-b]naphtho[1,2-d]furan* ***(9ac'):*** Isolated as colourless solid in 1:1 ratio, mp: 136-138 °C; yield: 92% (0.091g). ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm); 8.64 (d, *J* = 4.0 Hz, 1H), 8.62 (d, *J* = 4.5 Hz, 1H), 8.02-8.00 (m, 2H), 7.94 (d, *J* = 7.5 Hz, 1H), 7.86 (s, 1H), 7.77-7.75 (m, 4H), 7.49-7.73 (m, 1H), 7.72-69 (m, 1H), 7.58-7.53 (m, 2H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 1H), 2.59 (s, 3H), 2.57 (s, 3H), 1.74 (s, 6H), 1.58 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 173.0, 172.8, 157.2, 157.1, 150.7, 149.8, 136.9, 135.9, 135.3, 134.1, 131.0, 128.9, 128.0, 127.9, 127.7, 127.4, 126.3, 126.2, 126.0, 125.9, 125.3, 124.6 (2), 124.4, 122.2, 122.0, 120.9, 120.4, 120.2,

118.9, 113.3 (2), 43.3, 42.3, 24.4, 22.0, 21.9, 18.9; HRMS (ESI-TOF): m/z calculated for $C_{22}H_{19}O$ $[M+H]^+$ 299.1436, found 299.1436.

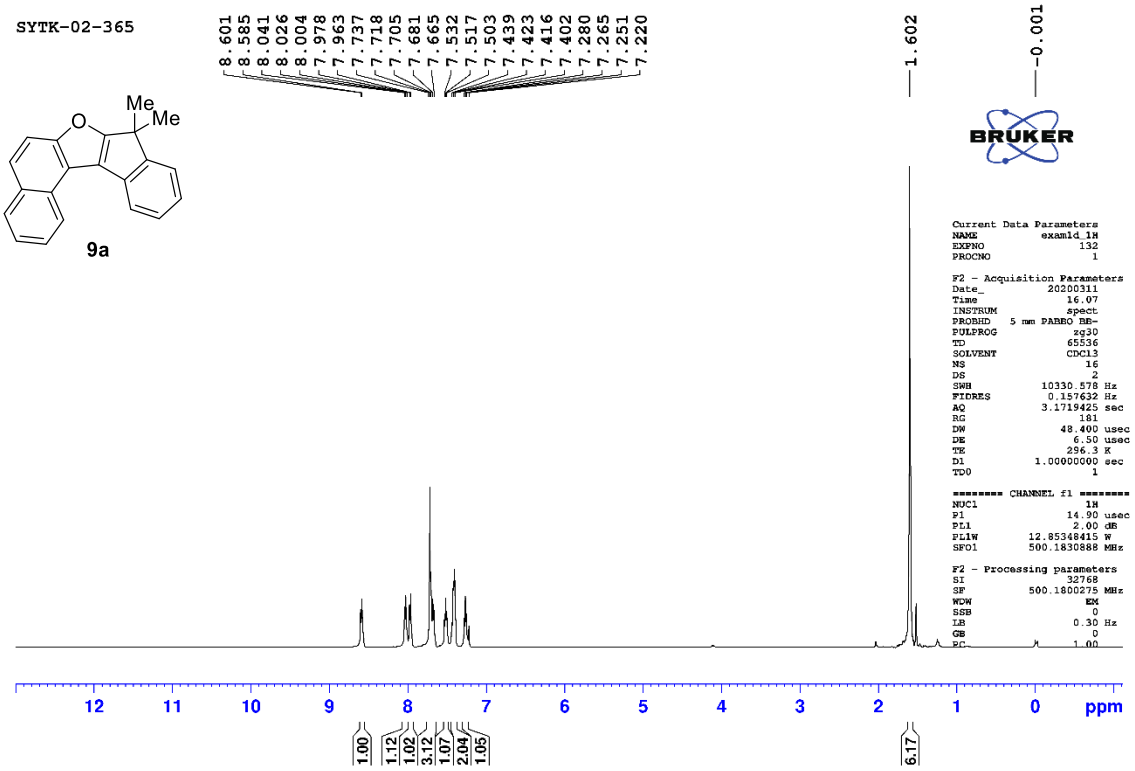
5,12-dimethyl-7,7,13,13-tetraphenyl-7,13-dihydrofluoreno [3,2-b]indeno[1,2-d]furan ***(9ad):*** Isolated as colourless solid, mp: 213-215 ^oC; yield: 89% (0.088g). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.92 (d, J = 7.5 Hz, 1H), 7.68 (d, J = 6.5 Hz, 1H), 7.37-7.34 (m, 5H), 7.32 (s, 2H), 7.30-7.29 (m, 3H), 7.28-7.26 (m, 6H), 7.24 (s, 2H), 7.23 (s, 2H), 7.21-7.19 (m, 3H), 7.18-7.15 (m, 2H), 7.14-7.13 (m, 1H), 2.89 (s, 3H), 2.49 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 169.5, 159.9, 155.3, 150.3, 145.5, 143.0, 142.4, 141.0, 136.0, 135.7, 129.1, 128.6, 128.3, 128.0, 127.6, 127.3, 127.1, 126.7, 126.5, 125.5, 125.4, 124.8, 124.5, 123.3, 122.7, 121.3, 115.8, 64.8, 60.4, 19.6, 13.1; HRMS (ESI-TOF): m/z calculated for $C_{48}H_{35}O$ $[M+H]^+$ 627.2688, found 627.2685.

7-(4-chlorophenyl)-5,12-dimethyl-7,13,13-triphenyl-7,13-dihydrofluoreno[3,2-b]indeno[1,2-d]furan ***(9ae):*** Isolated as yellowish solid, mp: 198-200 ^oC; yield: 86% (0.085g). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.92 (d, J = 7.5 Hz, 1H), 7.68 (d, J = 6.5 Hz, 1H), 7.36-7.35 (m, 5H), 7.32-7.27 (m, 7H), 7.25-7.23 (m, 7H), 7.21-7.18 (m, 4H), 7.16-7.13 (m, 2H), 2.89 (s, 3H), 2.50 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 168.9, 159.9, 155.3, 150.0, 145.6, 142.9, 141.9, 141.0, 140.9, 136.0, 135.9, 133.3, 129.7, 129.1, 128.7, 128.2, 128.0, 127.8, 127.5, 127.3, 127.2, 126.5, 125.6, 125.5, 124.9, 124.4, 123.4, 122.7, 121.5, 115.8, 64.8, 59.9, 19.6, 13.1; HRMS (ESI-TOF): m/z calculated for $C_{48}H_{34}ClO$ $[M+H]^+$ 661.2298, found 661.2298.

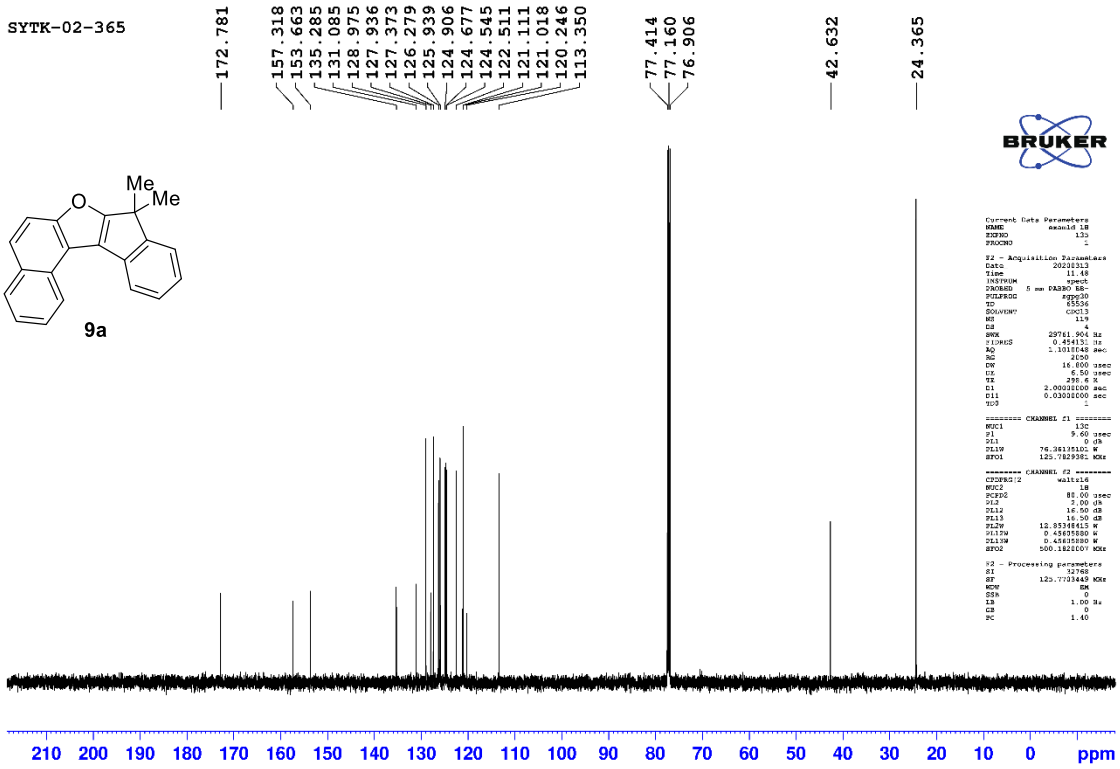
7-(4-methoxyphenyl)-5,12-dimethyl-7,13,13-triphenyl-7,13-dihydrofluoreno[3,2-b]indeno[1,2-d]furan ***(9af):*** Isolated as colourless solid, mp: 195-197 ^oC; yield: 87% (0.086g). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.92 (d, J = 8.0 Hz, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.36-7.34 (m, 5H), 7.32-7.29 (m, 4H), 7.28-7.26 (m, 2H), 7.24-7.22 (m, 5H), 7.21-7.18 (m, 4H), 7.17-7.11 (m, 3H), 6.82-6.80 (m, 2H), 3.76 (s, 3H), 2.88 (s, 3H), 2.49 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 170.2, 160.1, 159.2, 155.6, 151.1, 145.8, 143.3, 142.8, 141.3, 136.3, 134.4, 129.6, 129.3, 128.6, 128.4, 128.1, 127.6, 127.4, 127.3, 127.1, 126.7, 126.6, 125.7, 125.6, 124.8, 123.2, 122.8, 121.4, 115.8, 114.2, 65.1, 60.1, 55.4, 19.7, 12.9; HRMS (ESI-TOF): m/z calculated for $C_{49}H_{37}O_2$ $[M+H]^+$ 657.2794, found 657.2797.

8,8-diphenyl-3-(p-tolyl)-8H-indeno[2,1-b]naphtho[1,2-d]furan ***(11):*** Isolated as colourless solid, mp: 217-219 ^oC; yield: 78% (0.079g). ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.66 (d, J = 8.5 Hz, 1H), 8.16 (d, J = 1.5 Hz, 1H), 8.13 (d, J = 7.5 Hz, 1H), 7.97-7.94 (m, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.72 (d, J = 9.0 Hz, 1H), 7.68 (d, J = 8.0 Hz, 2H), 7.49-7.45 (m, 2H), 7.33-7.32 (m, 6H), 7.29-7.28 (m, 1H), 7.27-7.26 (m, 6H), 2.43 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$): δ (ppm) 169.0, 158.0, 150.8, 142.3, 138.2, 137.5, 137.2, 135.8, 131.4, 129.8, 128.6, 128.3, 127.9, 127.4, 127.3, 126.8, 126.6, 126.3, 125.9, 125.3 (2), 123.6, 121.6, 119.7, 113.9, 60.6, 21.3; HRMS (ESI-TOF): m/z calculated for $C_{38}H_{27}O$ $[M+H]^+$ 499.2062, found 499.2060.

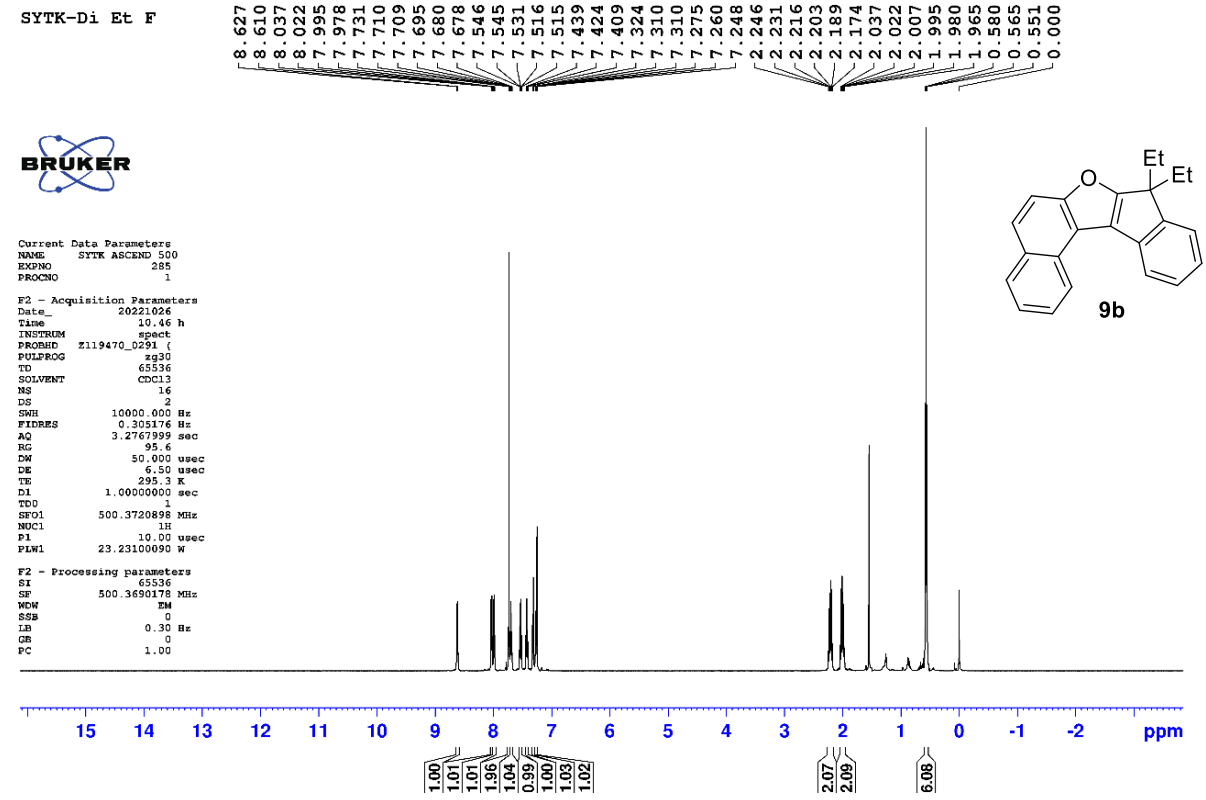
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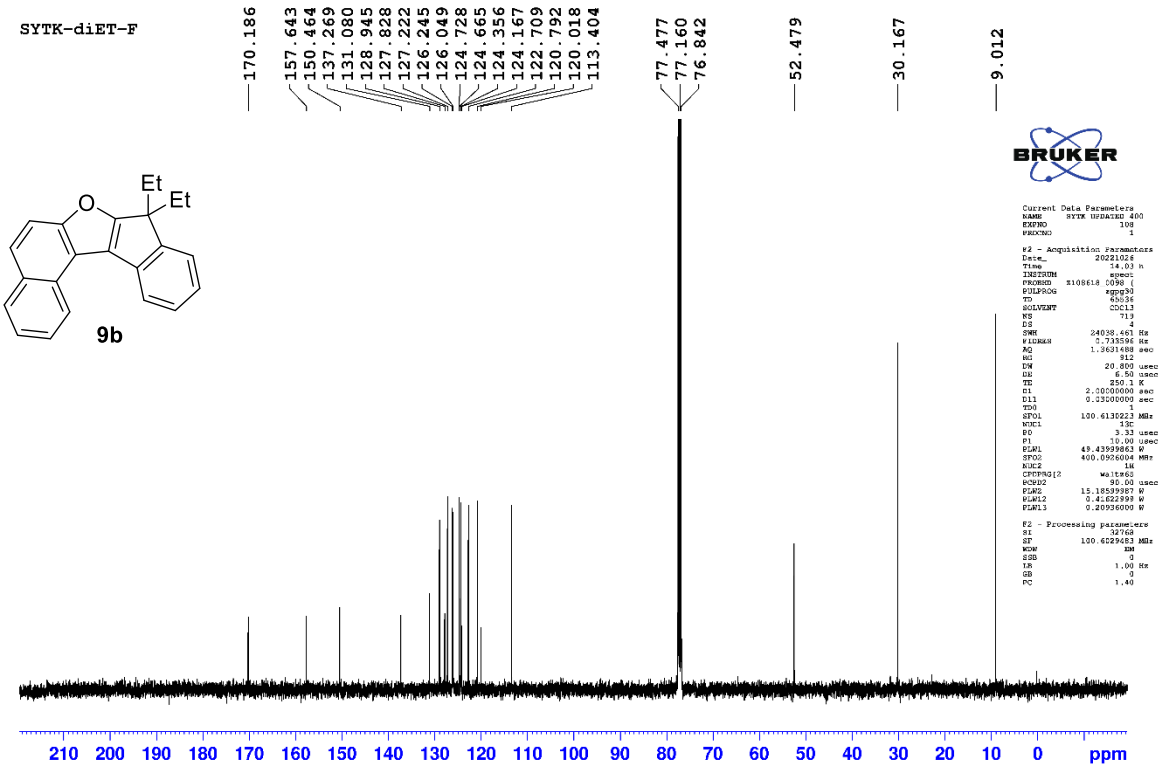


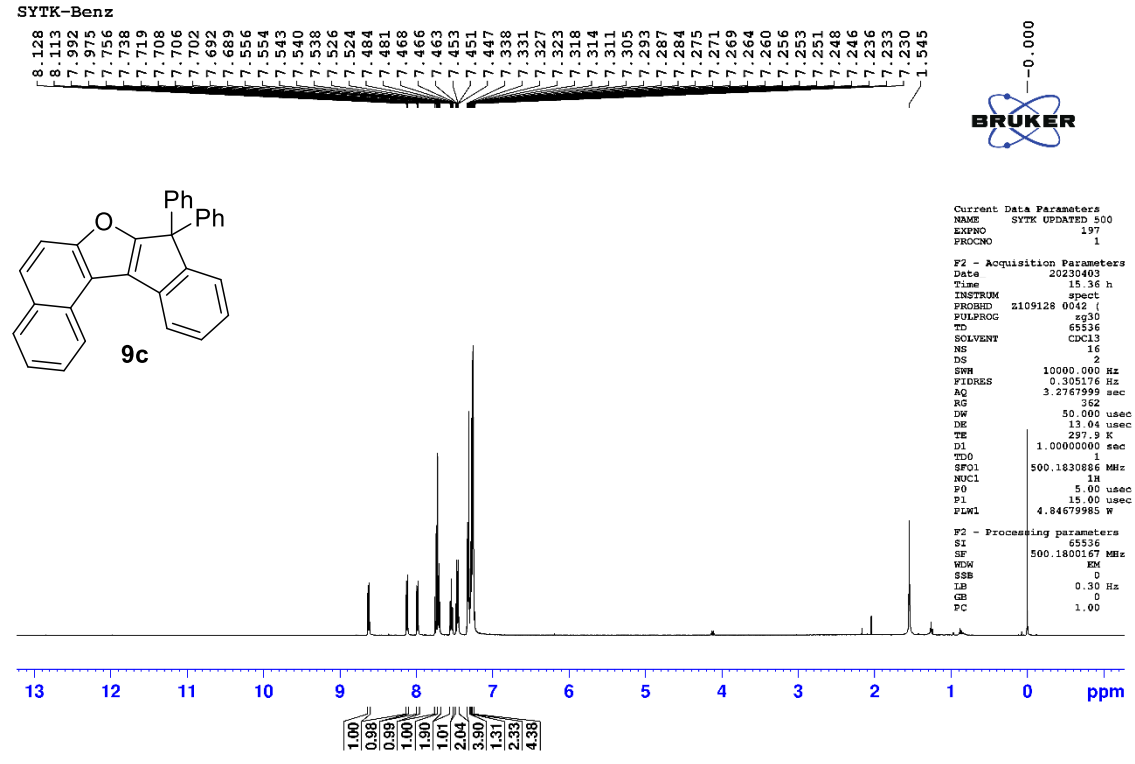
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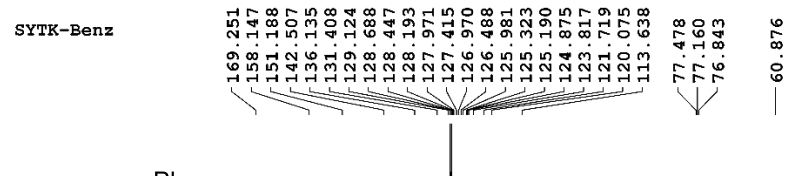
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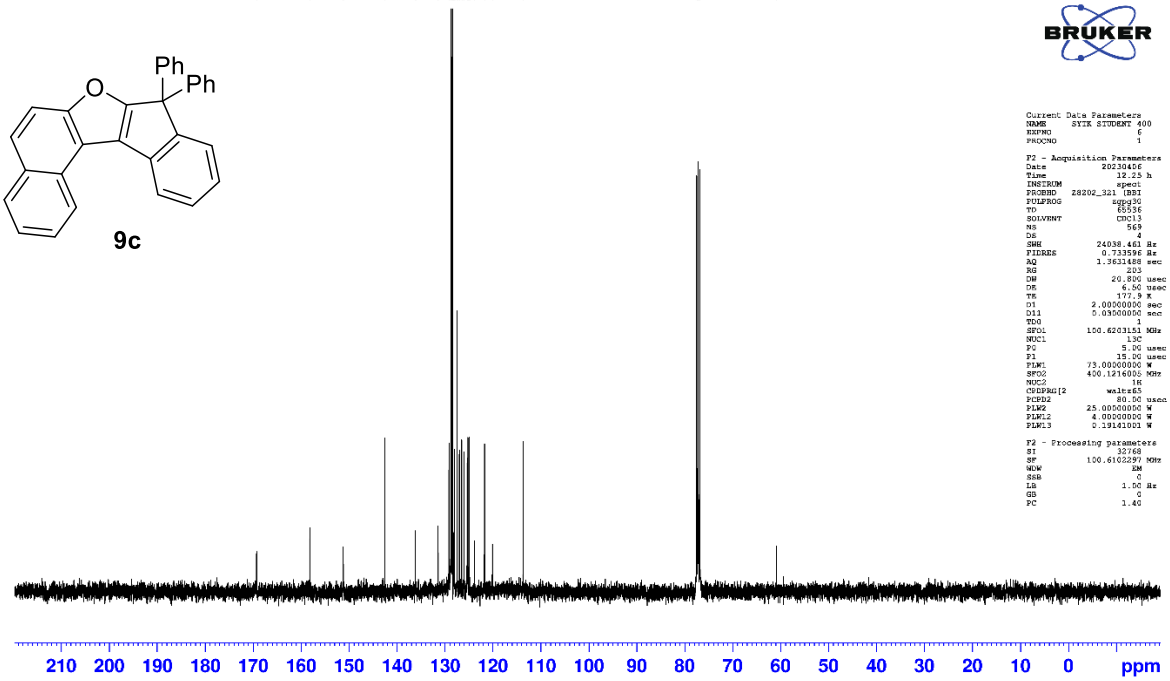

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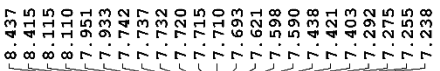
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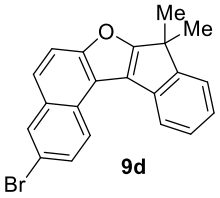


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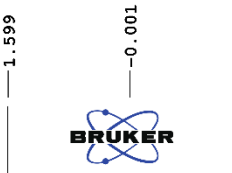


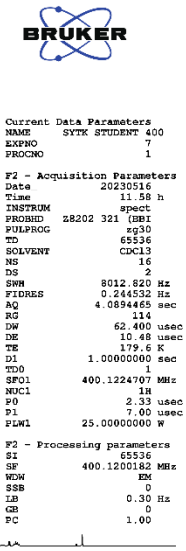
SYTK-2b-F

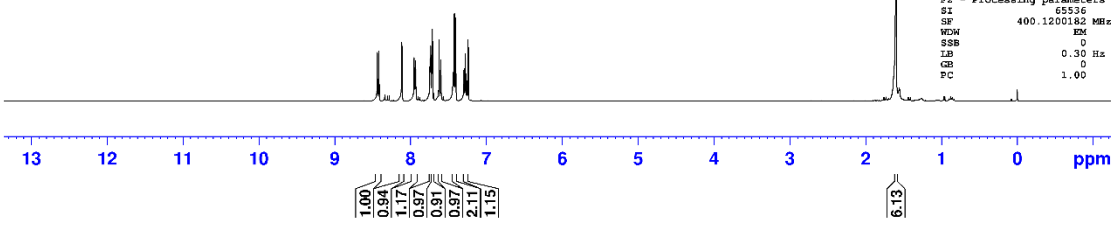




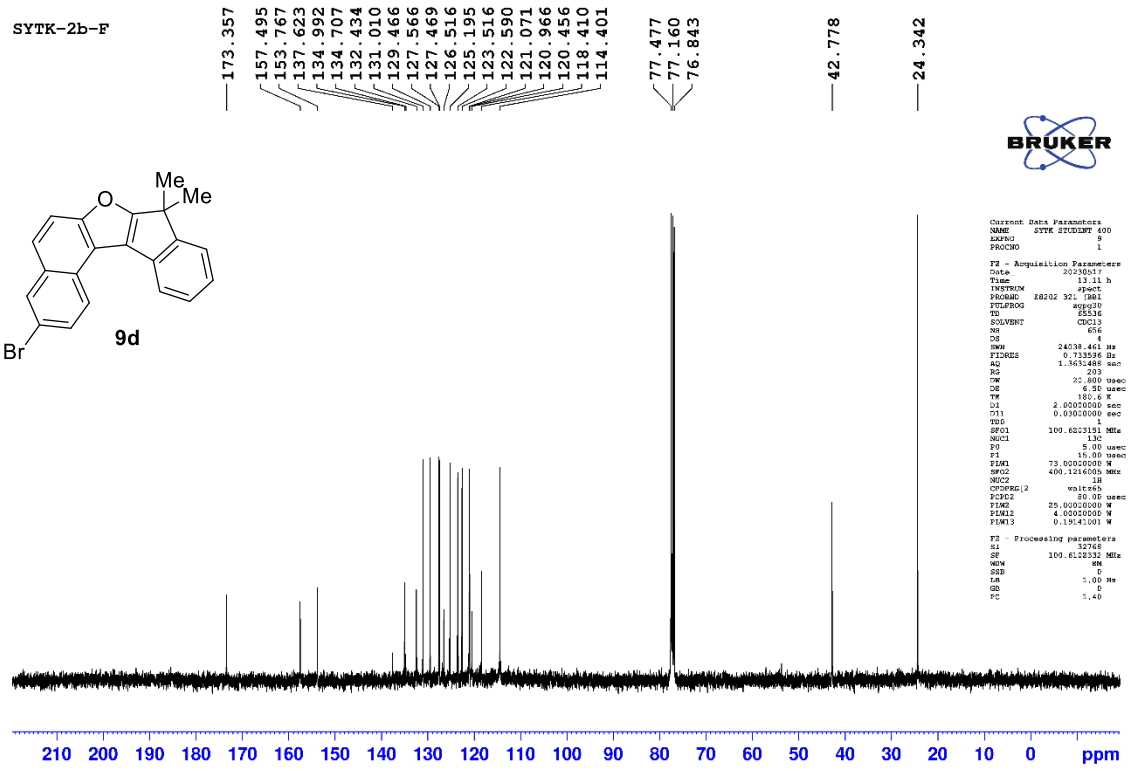
9d



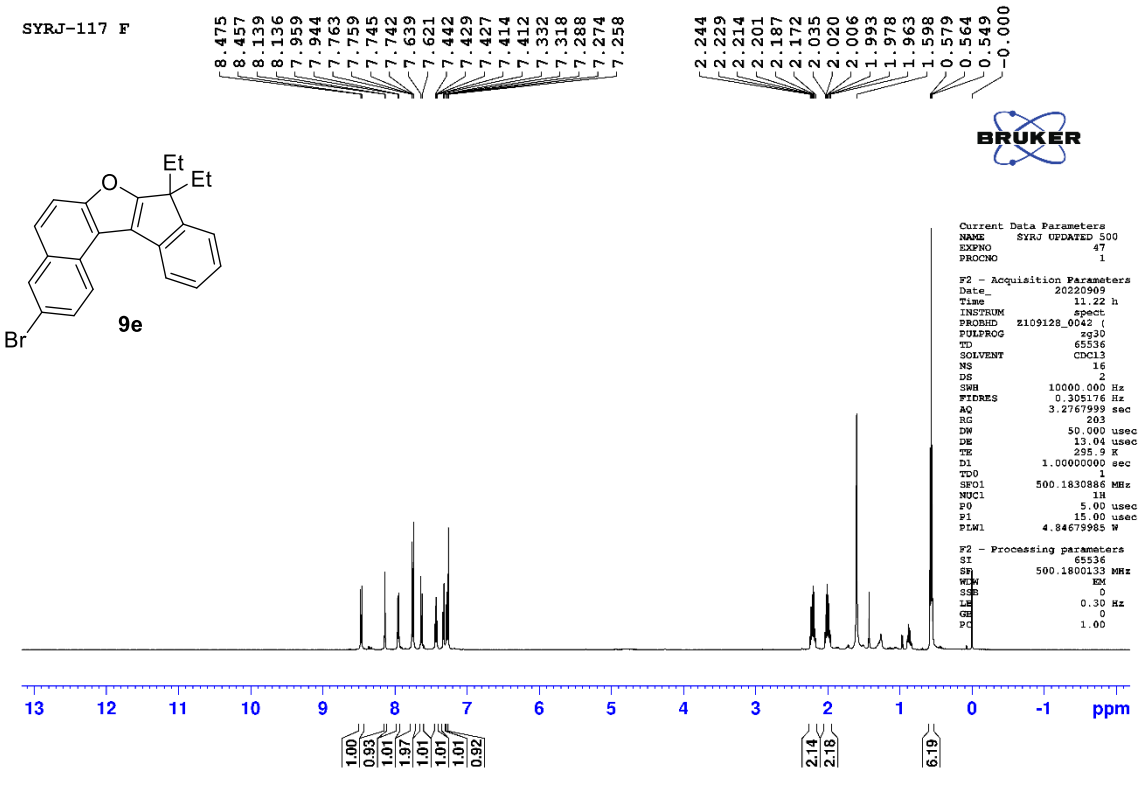




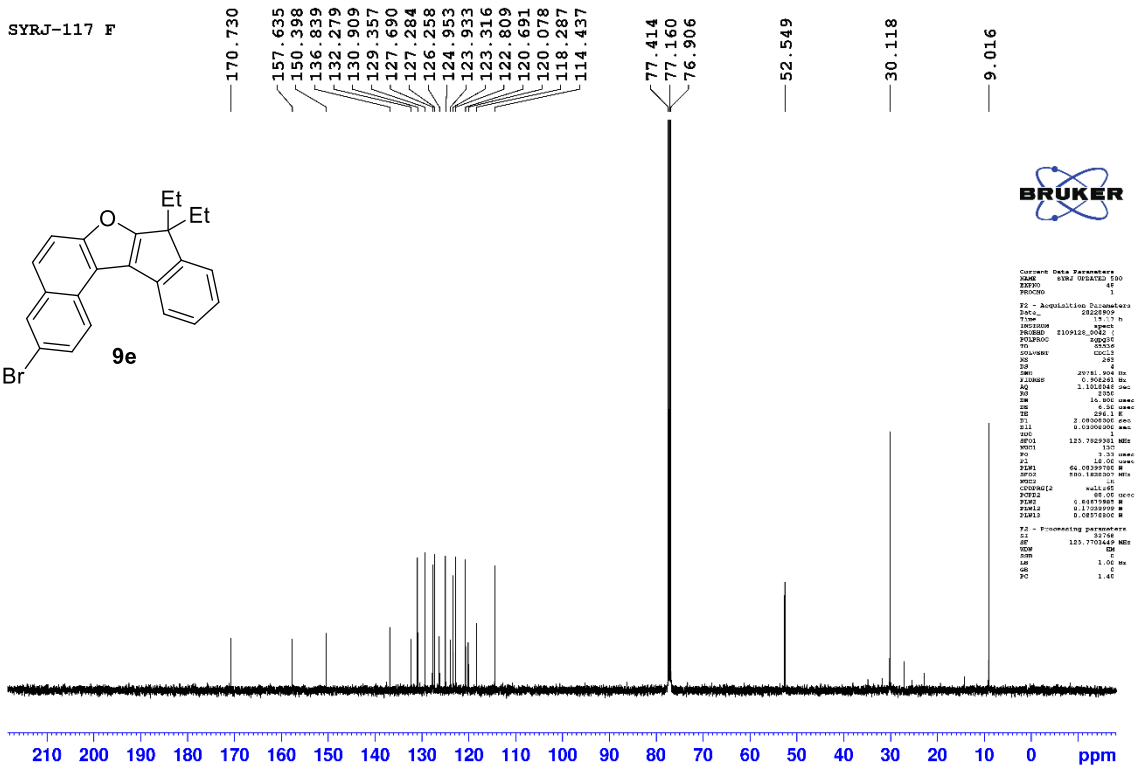
SYTK-2b-F



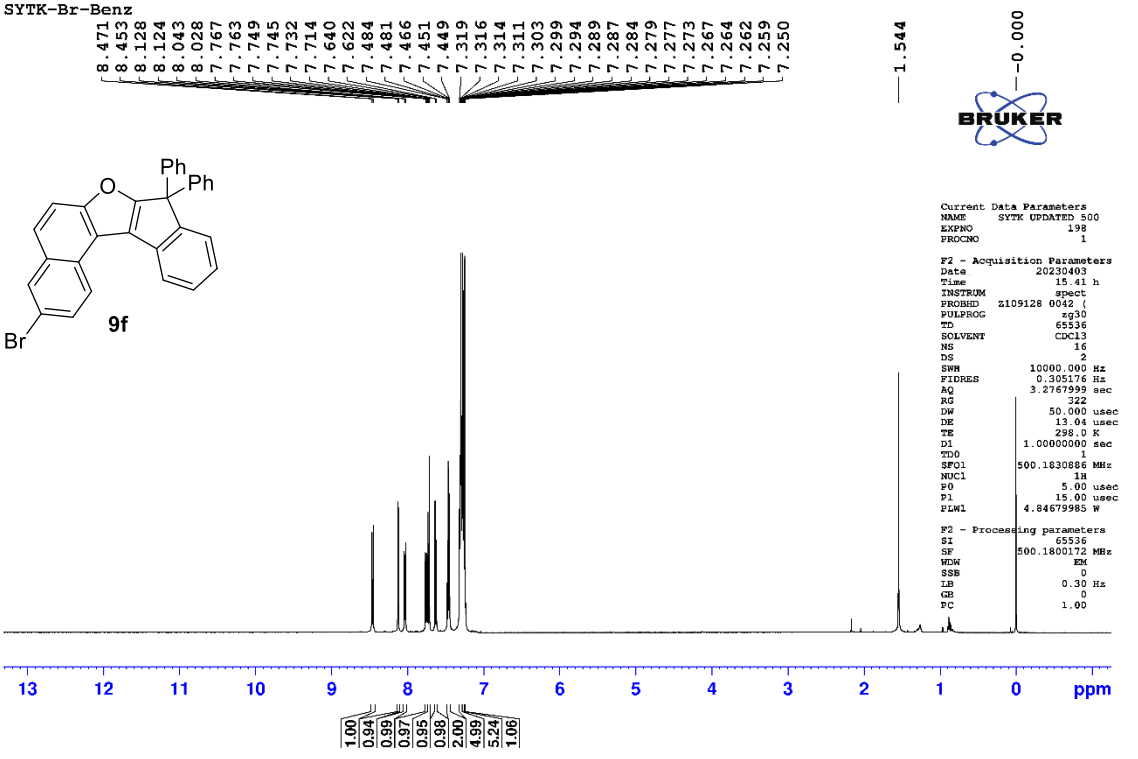
SYRJ-117 F



SYRJ-117 F



SYTK-Br-Benz

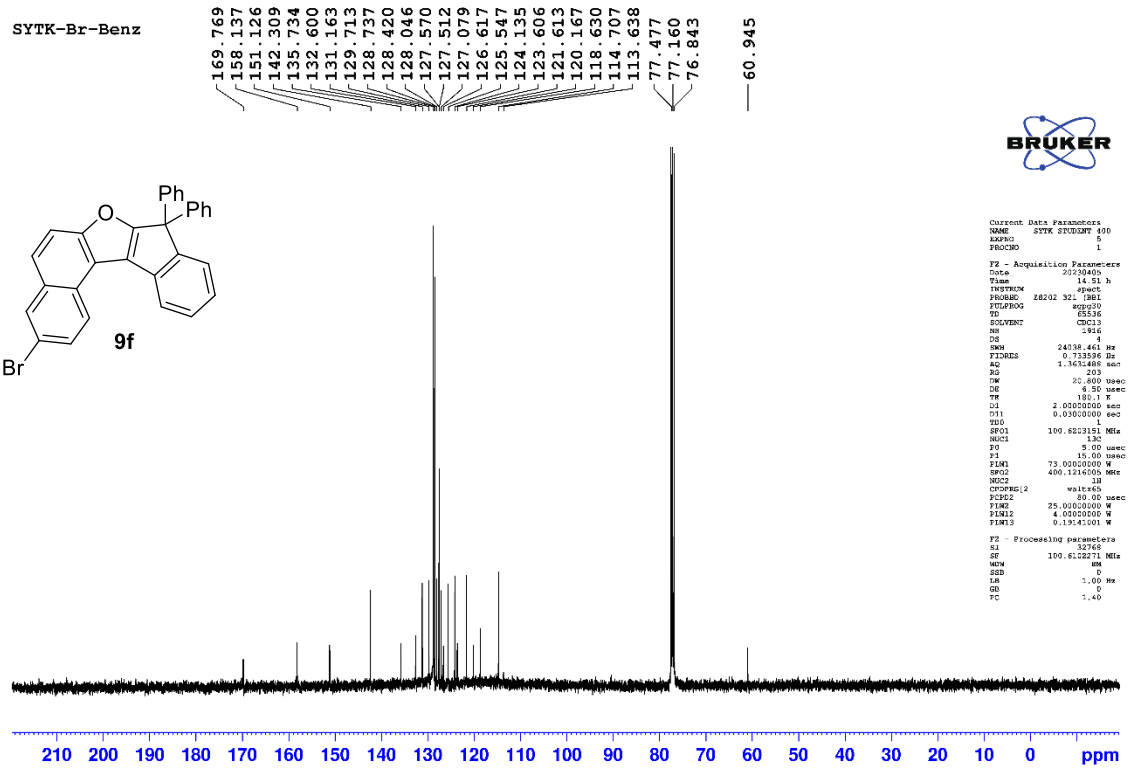


Current Data Parameters
NAME SYTK UPDATED 500
EXPNO 198
PROCNO 1

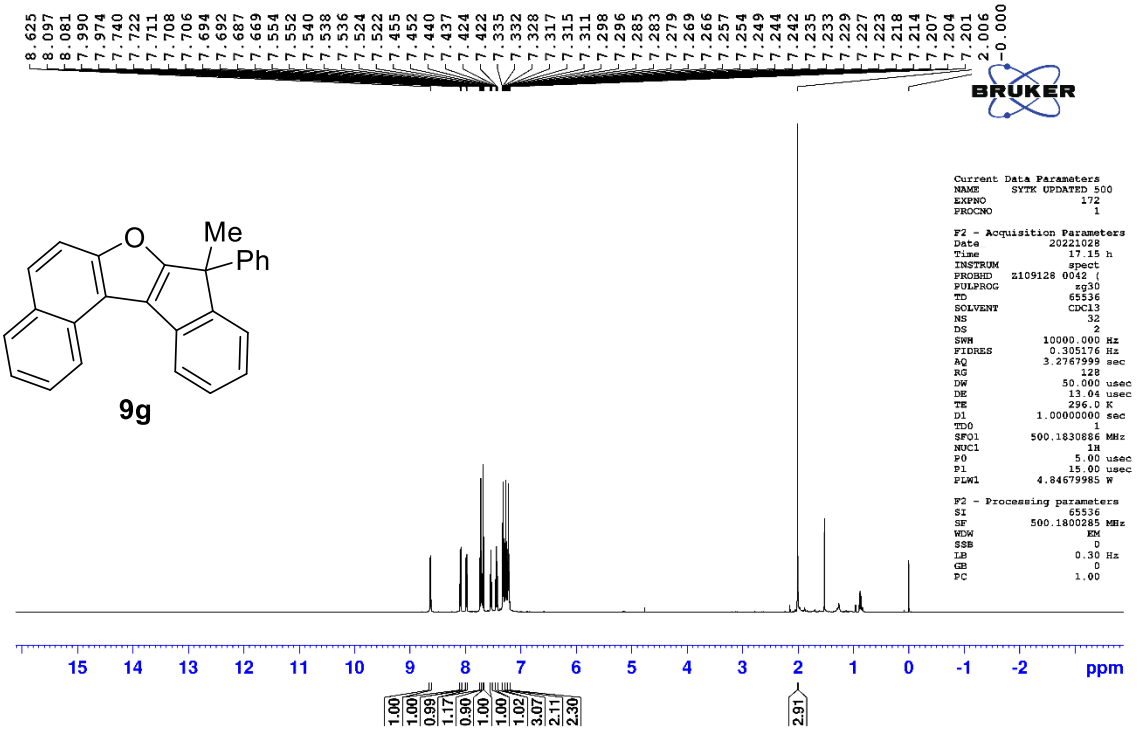
F2 - Acquisition Parameters
Date 20230403
Time 15.41 h
INSTRUM spect
PROBHD Z109128 0042 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 322
DW 50.000 usec
DE 13.04 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
SFO1 500.1830886 MHz
NUC1 1H
P0 5.00 usec
P1 15.00 usec
PLW1 4.84679985 W

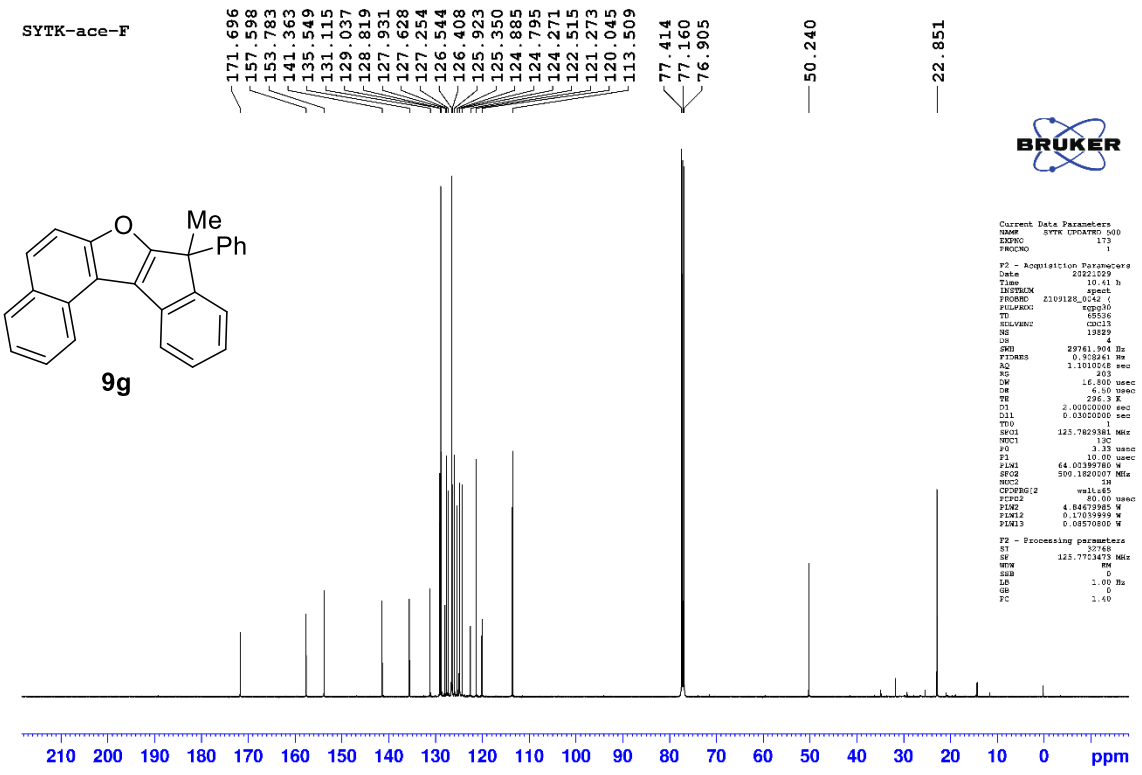
F2 - Processing parameters
SI 65536
SF 500.1800172 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

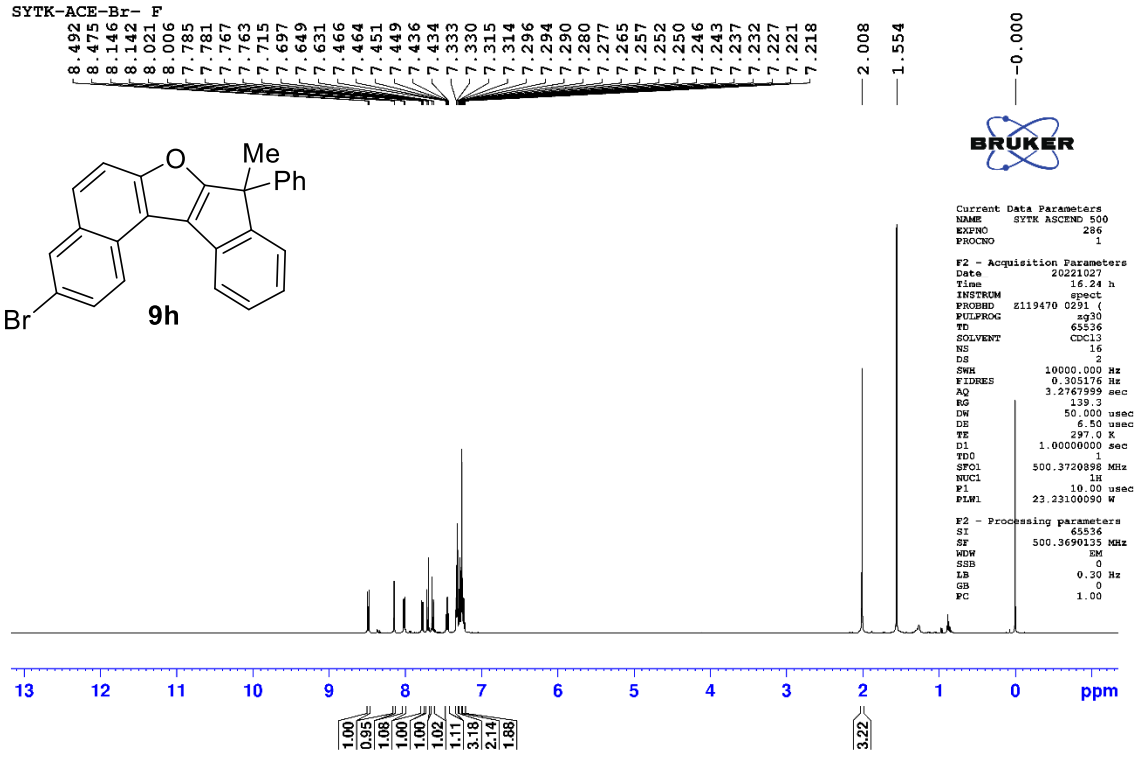
SYTK-Br-Benz

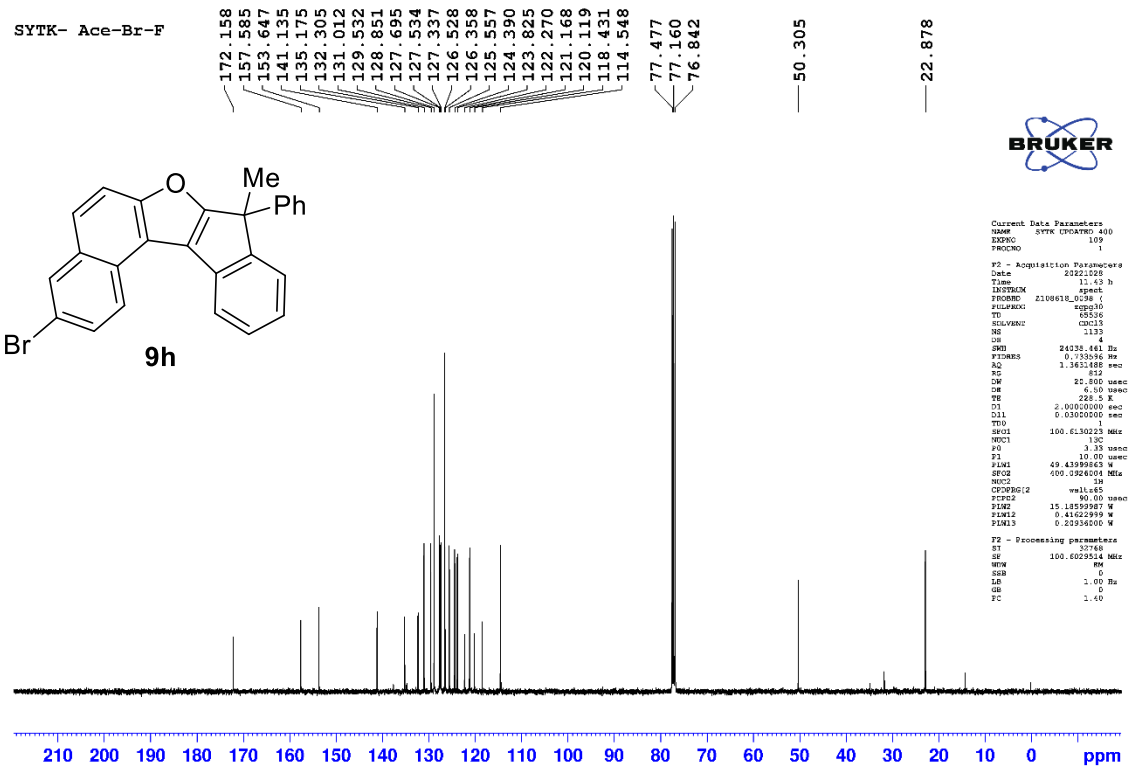


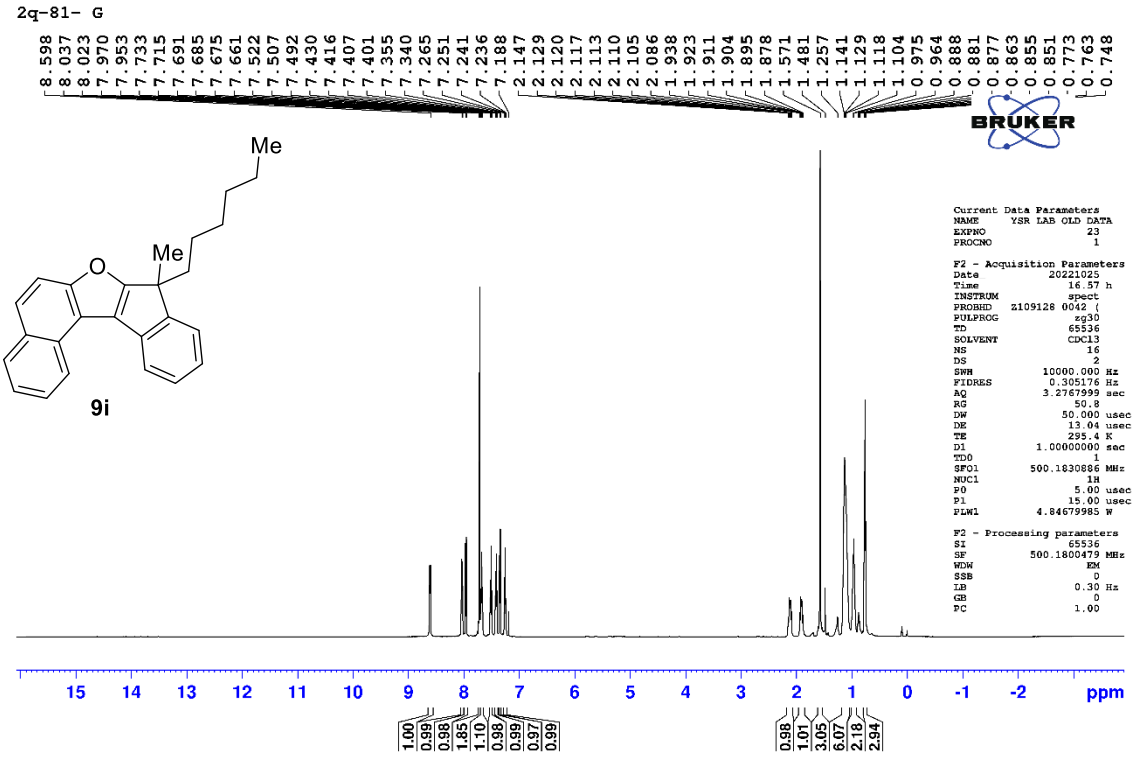
SYTK-ACE-F

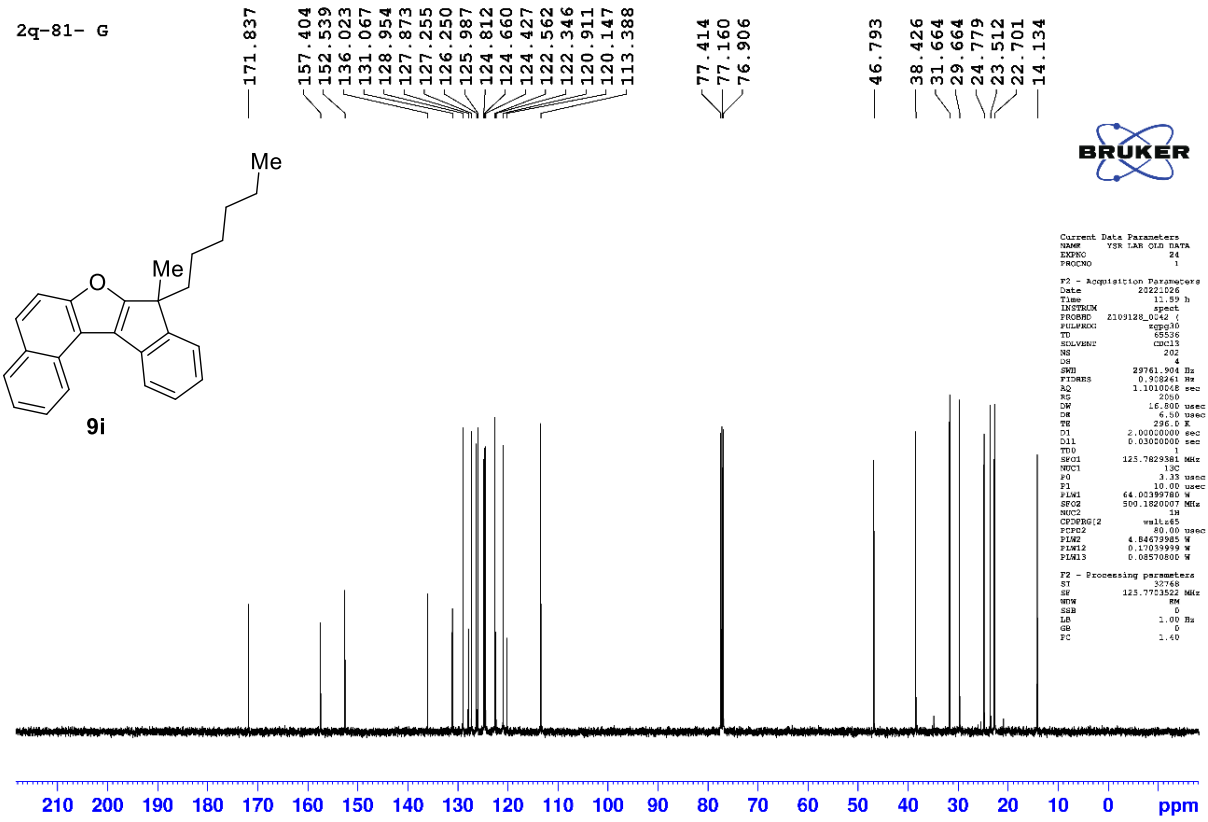


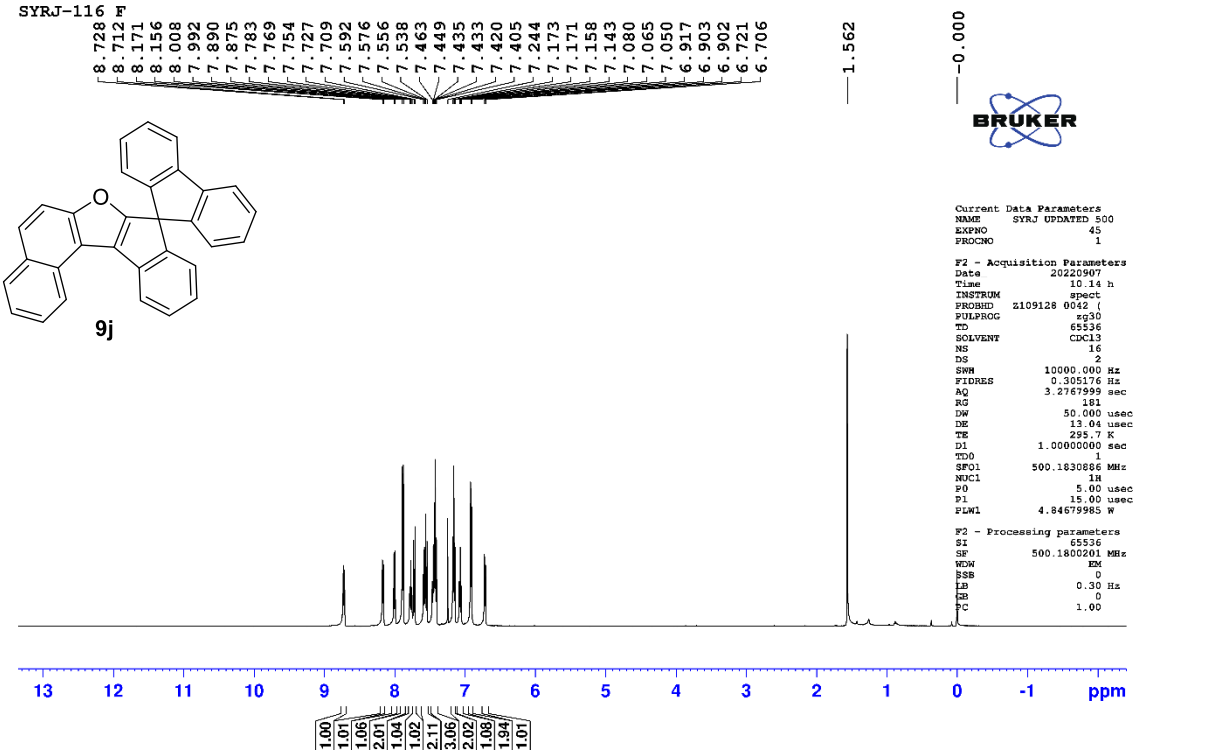

SYTK-ace-F
171.696
157.598
153.783
141.363
135.549
131.115
129.037
128.819
127.931
127.628
127.254
126.544
126.408
125.923
125.350
124.885
124.795
124.271
122.515
121.273
120.045
113.509
77.414
77.160
76.905
50.240
22.851
O
Me
Ph
9g
BRUKER
Current Data Parameters
NAME SYTK UPDATED 500
EXPNO 173
PROCNO 1
F2 - Acquisition Parameters
Date 20221029
Time 10.61 h
INSTRUM spect
PROBHD Z109128_0042 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 19829
DS 4
SWH 29761.904 Hz
FIDRES 0.908261 Hz
AQ 1.1010068 sec
RG 203
DW 16.800 usec
DE 6.50 usec
TE 296.3 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.7829381 MHz
NUC1 13C
P0 3.33 usec
P1 10.00 usec
PLW1 64.00399780 W
SFO2 500.1820007 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 80.00 usec
PLW2 4.84673985 W
PLW12 0.17999999 W
PLW13 0.08570800 W
F2 - Processing parameters
SI 32768
SF 125.7703473 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


SYTK-ACE-Br- F
8.492
8.475
8.146
8.142
8.021
8.006
7.785
7.781
7.767
7.763
7.715
7.697
7.649
7.631
7.466
7.464
7.451
7.449
7.436
7.434
7.333
7.330
7.315
7.314
7.296
7.294
7.290
7.280
7.277
7.265
7.257
7.252
7.250
7.246
7.243
7.237
7.232
7.227
7.221
7.218
2.008
1.554
-0.000
O
Me
Ph
Br
9h
BRUKER
Current Data Parameters
NAME SYTK ASCEND 500
EXPNO 286
PROCNO 1
F2 - Acquisition Parameters
Date 20221027
Time 16.24 h
INSTRUM spect
PROBHD Z119470 0291 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 139.3
DW 50.000 usec
DE 6.50 usec
TE 297.0 K
D1 1.00000000 sec
TD0 1
SFO1 500.3720898 MHz
NUC1 1H
P1 10.00 usec
PLW1 23.23100090 W
F2 - Processing parameters
SI 65536
SF 500.3690135 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.00
0.95
1.08
1.00
1.00
1.02
1.11
3.18
2.14
1.88
3.22


SYTK- Ace-Br-F
172.158
157.585
153.647
141.135
135.175
132.305
131.012
129.532
128.851
127.695
127.534
127.337
126.528
126.358
125.557
124.390
123.825
122.270
121.168
120.119
118.431
114.548
77.477
77.160
76.842
50.305
22.878
BRUKER
O
Me
Ph
Br
9h
Current Data Parameters
NAME SYTK CPDATRD 400
EXPNO 109
PROCNO 1
F2 - Acquisition Parameters
Date 20221028
Time 11.43 h
INSTRUM spect
PROBHD Z108618_0098 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1133
DS 4
SWH 24038.461 Hz
FIDRES 0.733696 Hz
AQ 1.3631488 sec
RG 812
DW 20.800 usec
DE 6.50 usec
TE 228.5 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.6130223 MHz
NUC1 13C
P0 1.35 usec
P1 10.00 usec
PLW1 49.43999863 W
SFO2 400.0926004 MHz
NUC2 1H
CPDPRG2 waltz65
PCPD2 90.00 usec
PLW2 15.18599987 W
PLW12 0.41622999 W
PLW13 0.23936000 W
F2 - Processing parameters
SI 32768
SF 100.6029514 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

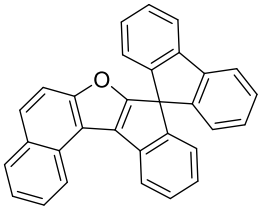

2q-81- G
8.598
8.037
8.023
7.970
7.953
7.733
7.715
7.691
7.685
7.675
7.661
7.522
7.507
7.492
7.430
7.416
7.407
7.401
7.355
7.340
7.265
7.251
7.241
7.236
7.188
2.147
2.129
2.120
2.117
2.113
2.110
2.105
2.086
1.938
1.923
1.911
1.904
1.895
1.878
1.571
1.481
1.257
1.141
1.129
1.118
1.104
0.975
0.964
0.888
0.881
0.877
0.863
0.855
0.851
0.773
0.763
0.748
BRUKER
Me
Me
O
9i
Current Data Parameters
NAME YSR LAB OLD DATA
EXPNO 23
PROCNO 1
F2 - Acquisition Parameters
Date 20221025
Time 16.57 h
INSTRUM spect
PROBHD Z109128 0042 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 50.8
DW 50.000 usec
DE 13.04 usec
TE 295.4 K
D1 1.00000000 sec
TD0 1
SFO1 500.1830886 MHz
NUC1 1H
P0 5.00 usec
P1 15.00 usec
PLW1 4.84679985 W
F2 - Processing parameters
SI 65536
SF 500.1800479 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 ppm
1.00 0.99 0.98 1.85 1.10 0.98 0.99 0.97 0.99
0.98 1.01 3.05 6.07 2.18 2.94


2q-81- G
171.837
157.404
152.539
136.023
131.067
128.954
127.873
127.255
126.250
125.987
124.812
124.660
124.427
122.562
122.346
120.911
120.147
113.388
77.414
77.160
76.906
46.793
38.426
31.664
29.664
24.779
23.512
22.701
14.134
Me
Me
O
9i
BRUKER
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

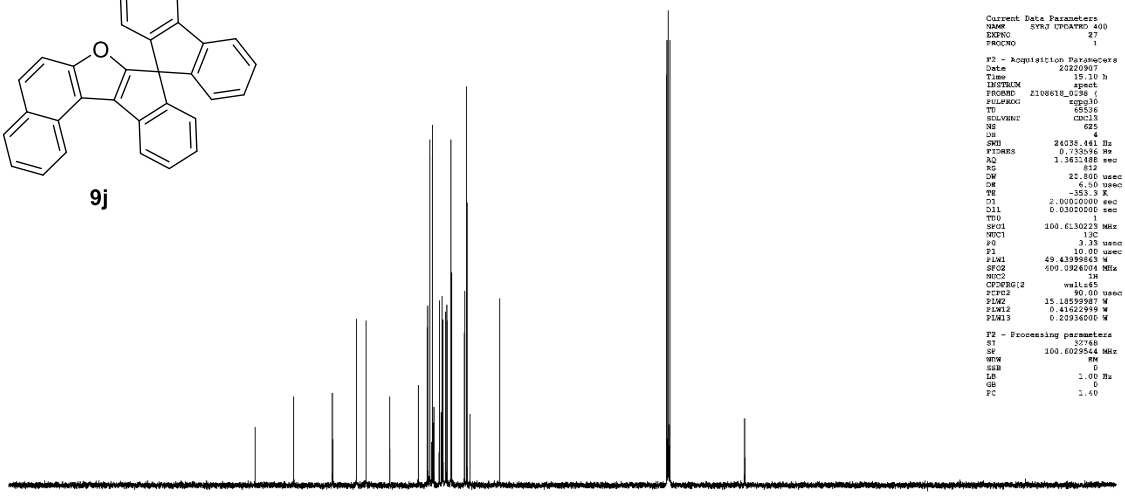

SYRJ-116 F
8.728
8.712
8.171
8.156
8.008
7.992
7.890
7.875
7.783
7.769
7.754
7.727
7.709
7.592
7.576
7.556
7.538
7.463
7.449
7.435
7.433
7.420
7.405
7.244
7.173
7.171
7.158
7.143
7.080
7.065
7.050
6.917
6.903
6.902
6.721
6.706
1.562
0.000
O
9j
BRUKER
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 ppm
1.00
1.01
1.06
2.01
1.04
1.02
2.11
3.06
2.02
1.08
1.94
1.01

SYRJ-116 F

166.266
157.956
149.613
144.444
142.383
137.233
131.112
129.091
128.638
128.108
128.083
127.756
126.580
126.090
125.920
125.743
125.209
124.920
124.064
124.000
121.123
120.620
119.977
113.541
77.478
77.160
76.842
60.694



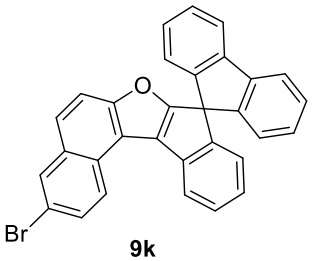
9j



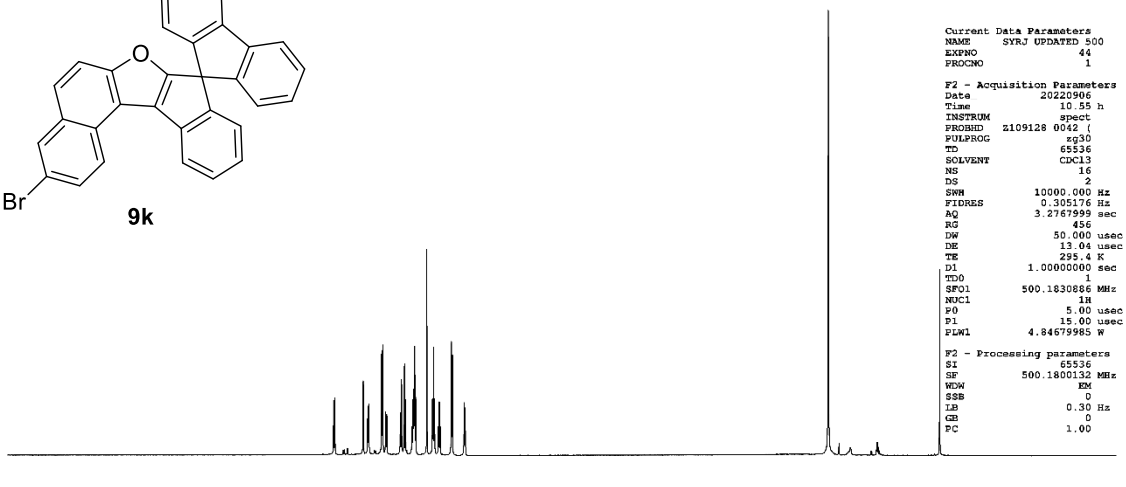


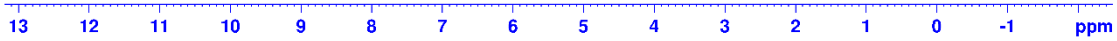
SYRJ-115 F

8.578
8.560
8.160
8.156
8.095
8.080
7.898
7.882
7.842
7.839
7.825
7.821
7.635
7.617
7.576
7.558
7.472
7.470
7.457
7.455
7.446
7.445
7.440
7.431
7.416
7.415
7.258
7.180
7.178
7.165
7.164
7.150
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1.575
0.000

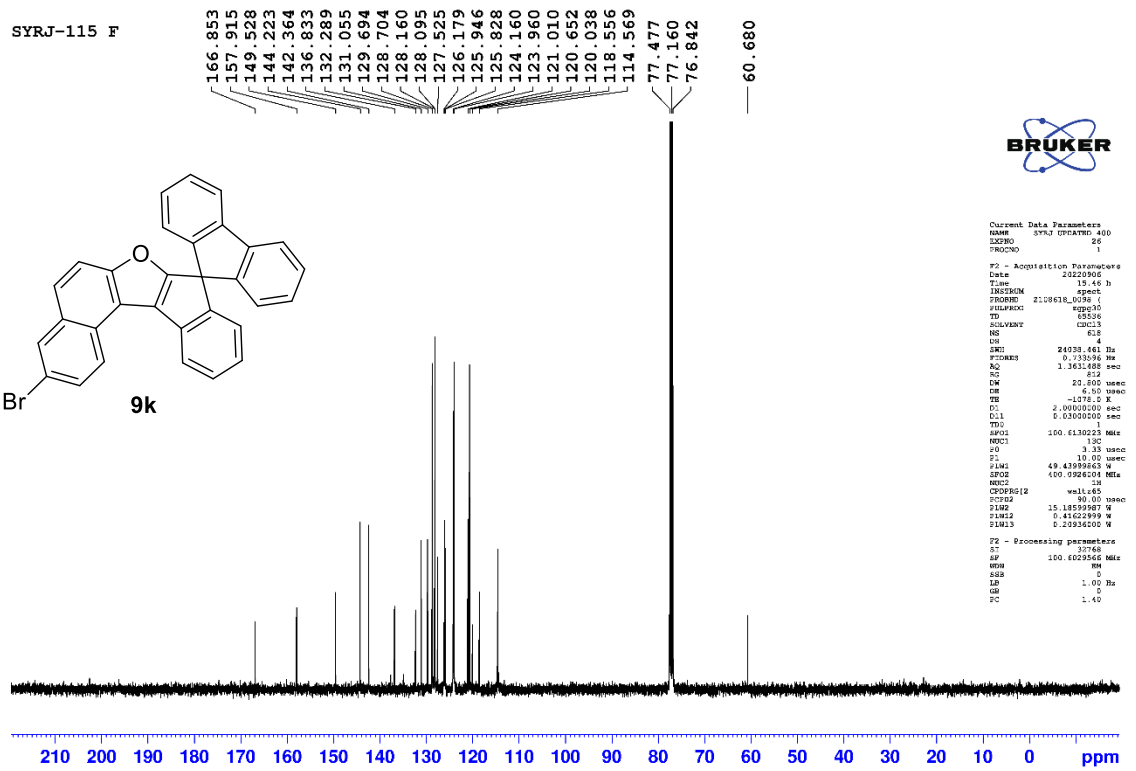


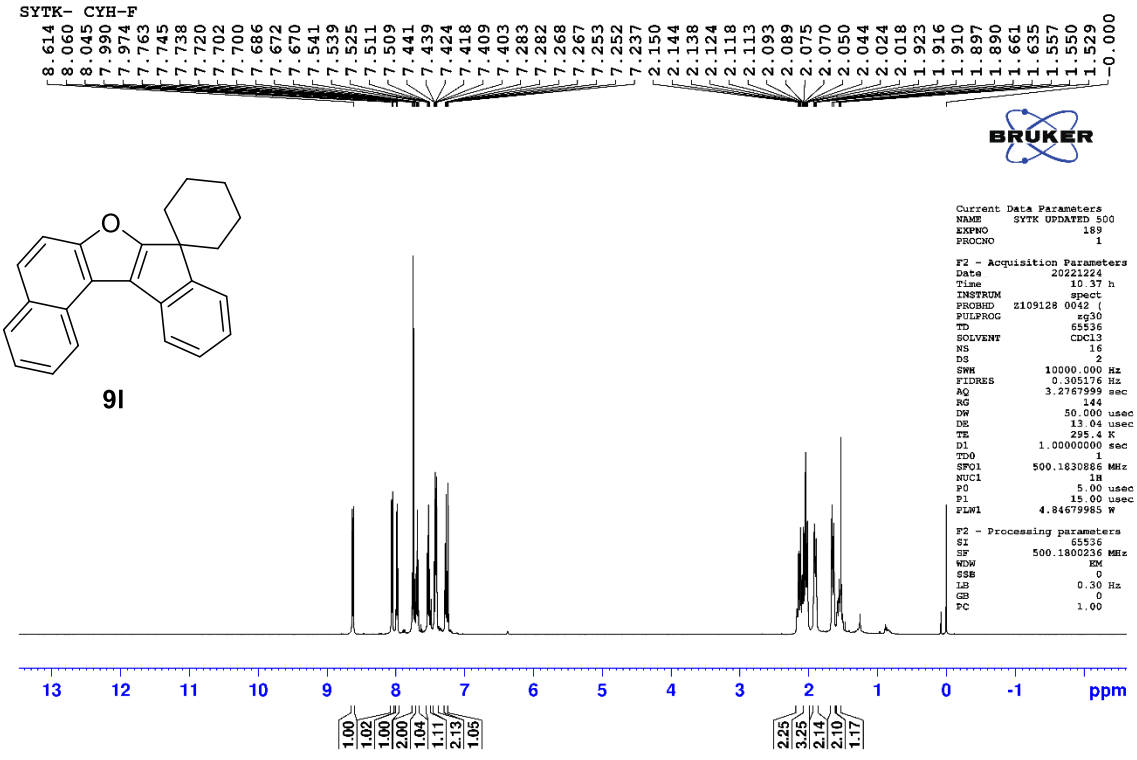
9k

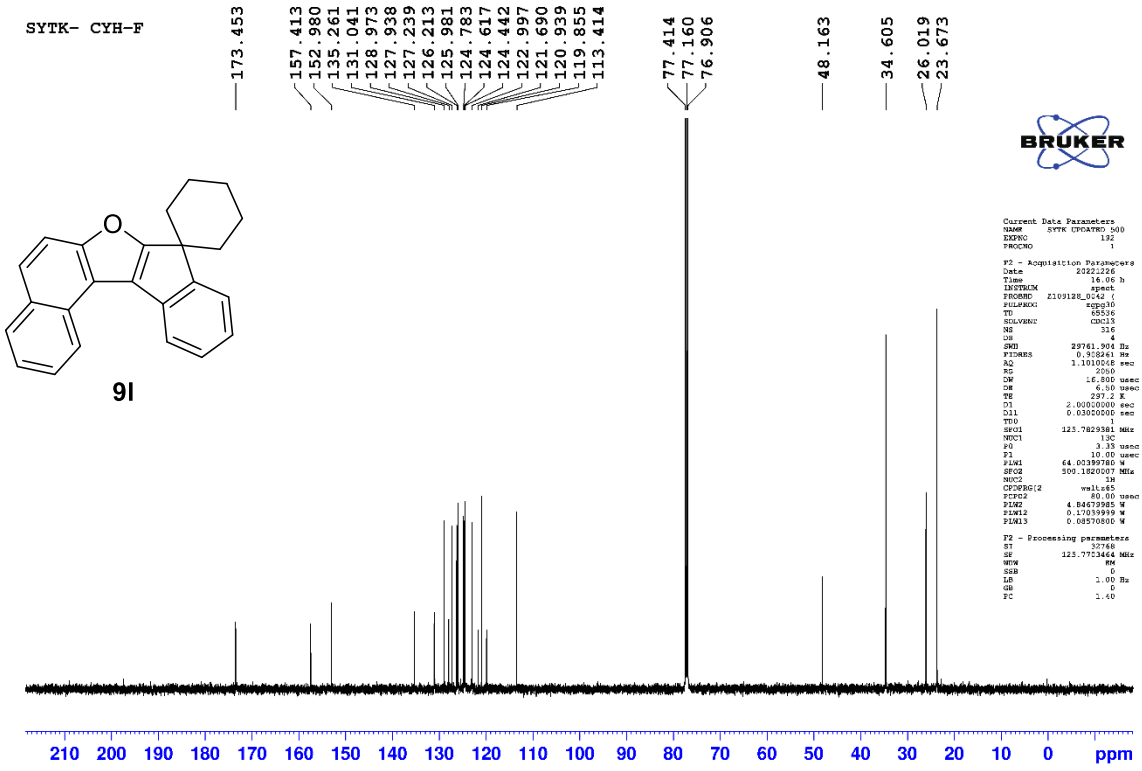


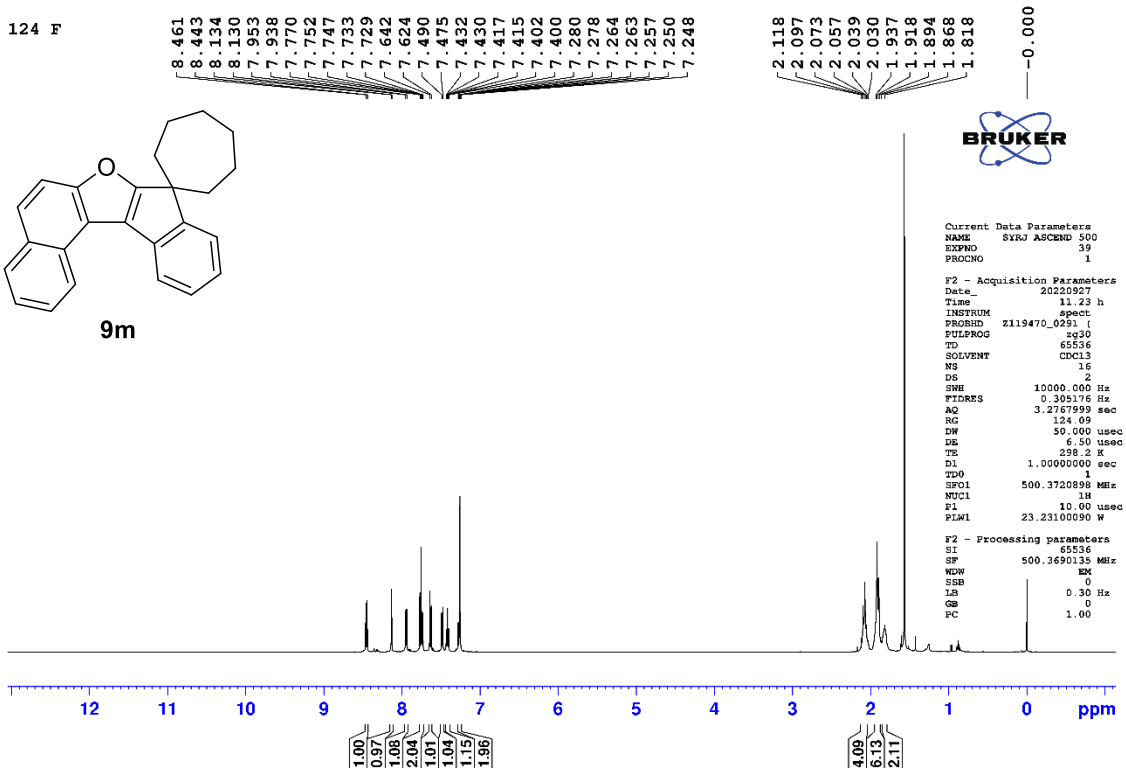


1.00 0.99 1.13 2.13 1.00 1.04 1.09 3.17 2.05 1.02 1.99 0.97

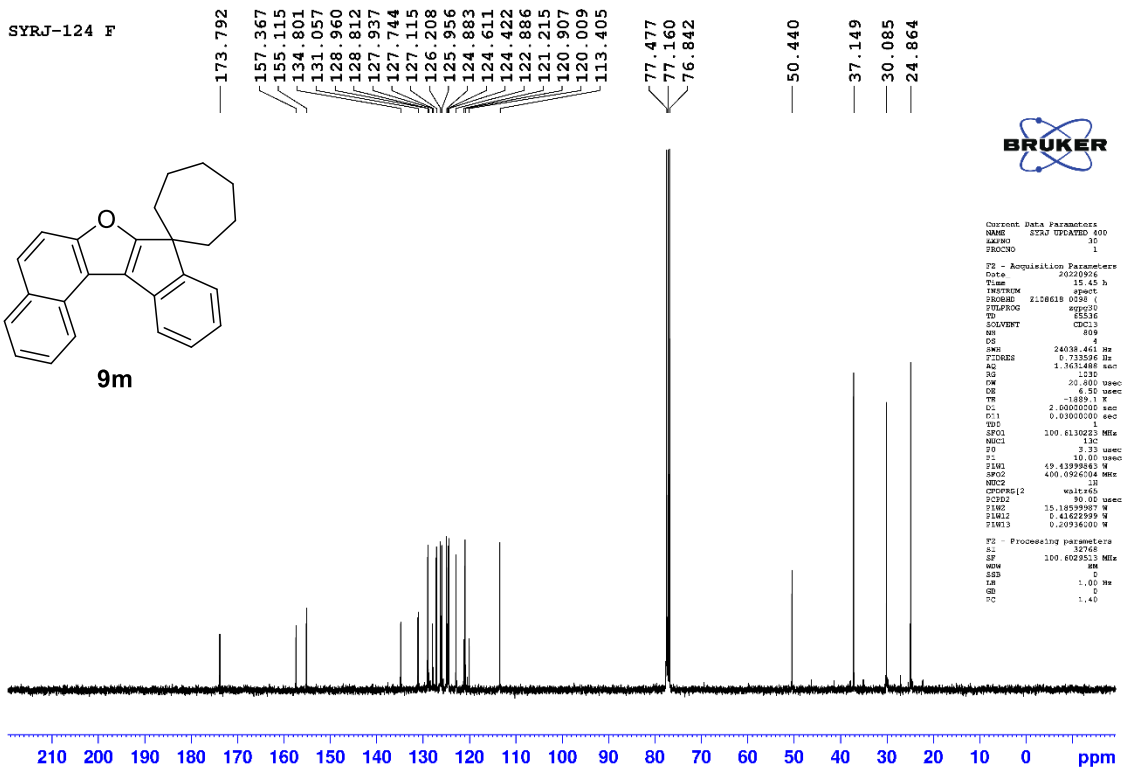

SYRJ-115 F
166.853
157.915
149.528
144.223
142.364
136.833
132.289
131.055
129.694
128.704
128.160
128.095
127.525
126.179
125.946
125.828
124.160
123.960
121.010
120.652
120.038
118.556
114.569
77.477
77.160
76.842
60.680
BRUKER
O
Br
9k
Current Data Parameters
NAME SYRJ UPDATED 400
EXPNO 26
PROCNO 1
F2 - Acquisition Parameters
Date 20220906
Time 15.46 h
INSTRUM spect
PROBHD Z108618_0096 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 618
DS 4
SWH 24038.461 Hz
FIDRES 0.733596 Hz
AQ 1.3631488 sec
RG 812
DW 20.800 usec
DE 6.50 usec
TE -1078.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.6130223 MHz
NUC1 13C
P0 3.33 usec
P1 10.00 usec
PLW1 49.43999863 W
SFO2 400.0926204 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 90.00 usec
PLW2 15.18599987 W
PLW12 0.41622999 W
PLW13 0.23936200 W
F2 - Processing parameters
SI 32768
SF 100.6029566 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


SYTK- CYH-F
8.614
8.060
8.045
7.990
7.974
7.763
7.745
7.738
7.720
7.702
7.700
7.686
7.672
7.670
7.541
7.539
7.525
7.511
7.509
7.441
7.439
7.424
7.418
7.409
7.403
7.283
7.282
7.268
7.267
7.253
7.252
7.237
2.150
2.144
2.138
2.124
2.118
2.113
2.093
2.089
2.075
2.070
2.050
2.044
2.024
2.018
1.923
1.916
1.910
1.897
1.890
1.661
1.635
1.557
1.550
1.529
-0.000
BRUKER
O
9l
Current Data Parameters
NAME SYTK UPDATED 500
EXPNO 189
PROCNO 1
F2 - Acquisition Parameters
Date 20221224
Time 10.37 h
INSTRUM spect
PROBHD Z109128 0042 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 144
DW 50.000 usec
DE 13.04 usec
TE 295.4 K
D1 1.00000000 sec
TD0 1
SFO1 500.1830886 MHz
NUC1 1H
P0 5.00 usec
P1 15.00 usec
PLW1 4.84679985 W
F2 - Processing parameters
SI 65536
SF 500.1800236 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 ppm
1.00
1.02
1.00
2.00
1.04
1.11
2.13
1.05
2.25
3.25
2.14
2.10
1.17

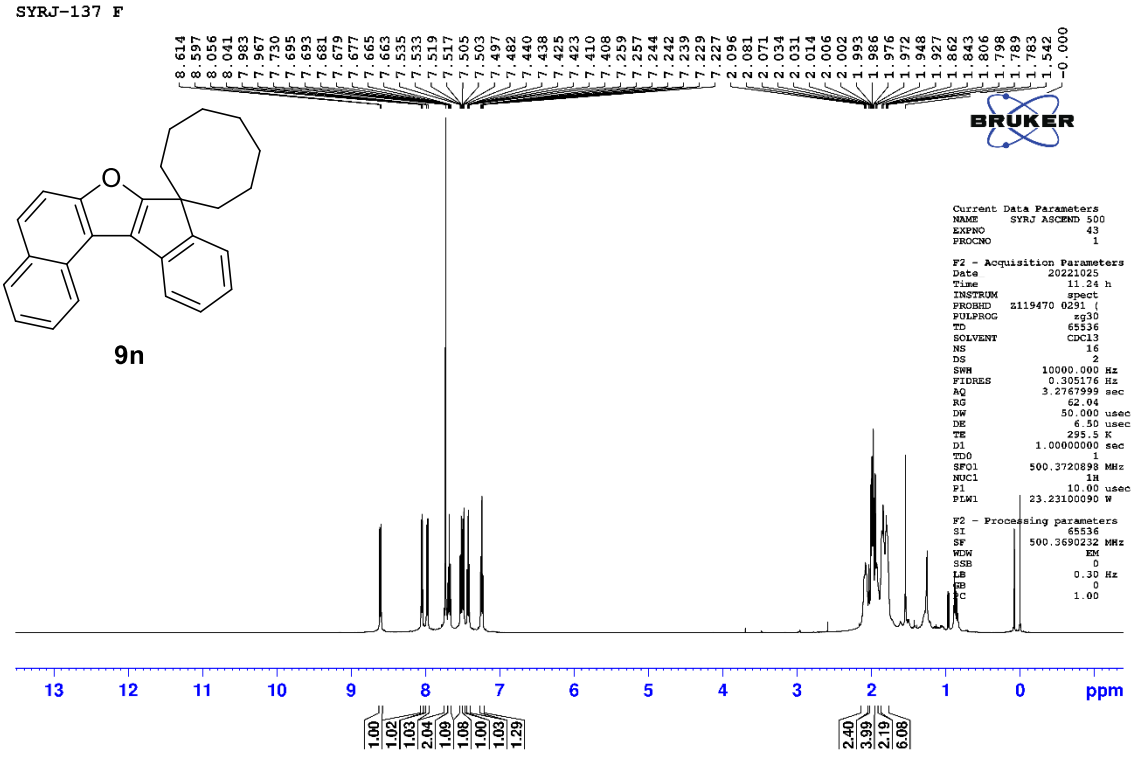

SYTK- CYH-F
173.453
157.413
152.980
135.261
131.041
128.973
127.938
127.239
126.213
125.981
124.783
124.617
124.442
122.997
121.690
120.939
119.855
113.414
77.414
77.160
76.906
48.163
34.605
26.019
23.673
BRUKER
O
9l
Current Data Parameters
NAME SYTK UPDATED.500
EXPNO 192
PROCNO 1
F2 - Acquisition Parameters
Date 20221226
Time 16.06 h
INSTRUM spect
PROBHD Z109128_0242 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 336
DS 4
SWH 29761.904 Hz
FIDRES 0.908261 Hz
AQ 1.1010048 sec
RG 2050
DW 16.800 usec
DE 6.50 usec
TE 297.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.7829381 MHz
NUC1 13C
P0 3.35 usec
P1 10.00 usec
PLW1 64.00399780 W
SFO2 500.1620007 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 80.00 usec
PLW2 4.84673985 W
PLW12 0.17039999 W
PLW13 0.08570800 W
F2 - Processing parameters
SI 32768
SF 125.7753464 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

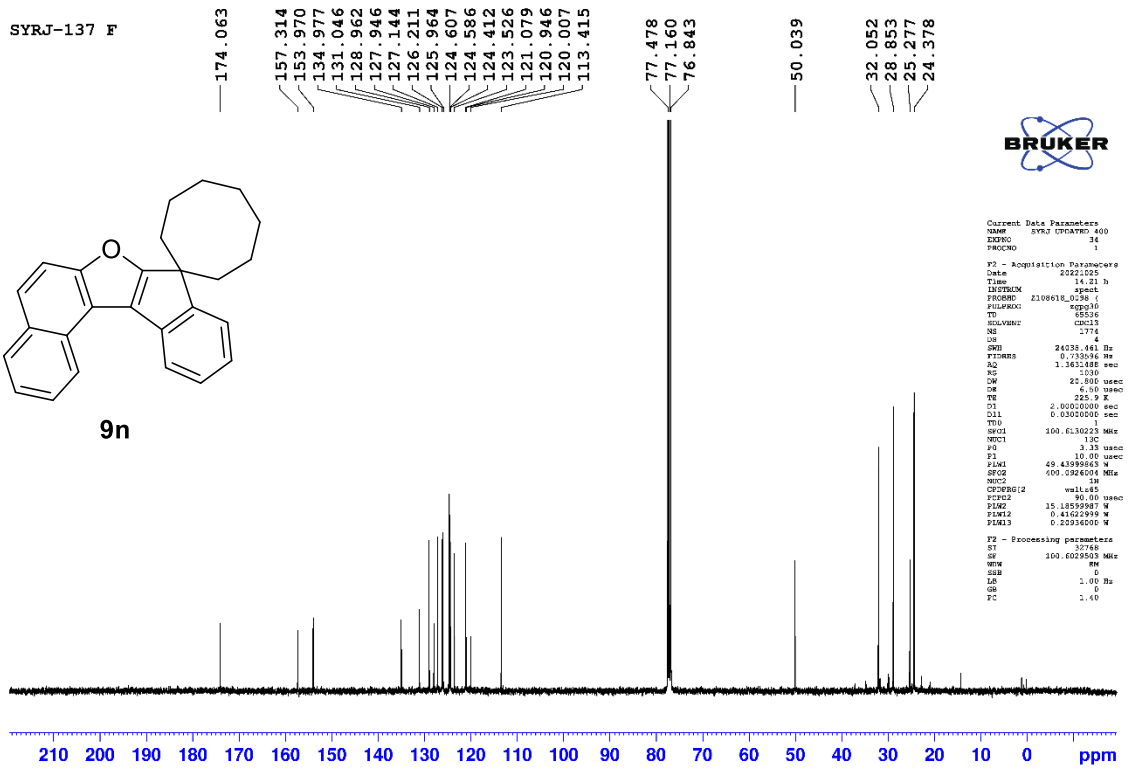

124 F
8.461
8.443
8.134
8.130
7.953
7.938
7.770
7.752
7.747
7.733
7.729
7.642
7.624
7.490
7.475
7.432
7.430
7.417
7.415
7.402
7.400
7.280
7.278
7.264
7.263
7.257
7.250
7.248
2.118
2.097
2.073
2.057
2.039
2.030
1.937
1.918
1.894
1.868
1.818
0.000
BRUKER
O
9m
Current Data Parameters
NAME SYRJ ASCEND 500
EXPNO 39
PROCNO 1
F2 - Acquisition Parameters
Date_ 20220927
Time 11.23 h
INSTRUM spect
PROBHD Z119470_0291 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 124.09
DW 50.000 usec
DE 6.50 usec
TE 298.2 K
D1 1.00000000 sec
TD0 1
SFO1 500.3720898 MHz
NUC1 1H
P1 10.00 usec
PLW1 23.23100090 W
F2 - Processing parameters
SI 65536
SF 500.3690135 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.00 0.97 1.08 2.04 1.01 1.04 1.15 1.96
4.09 6.13 2.11

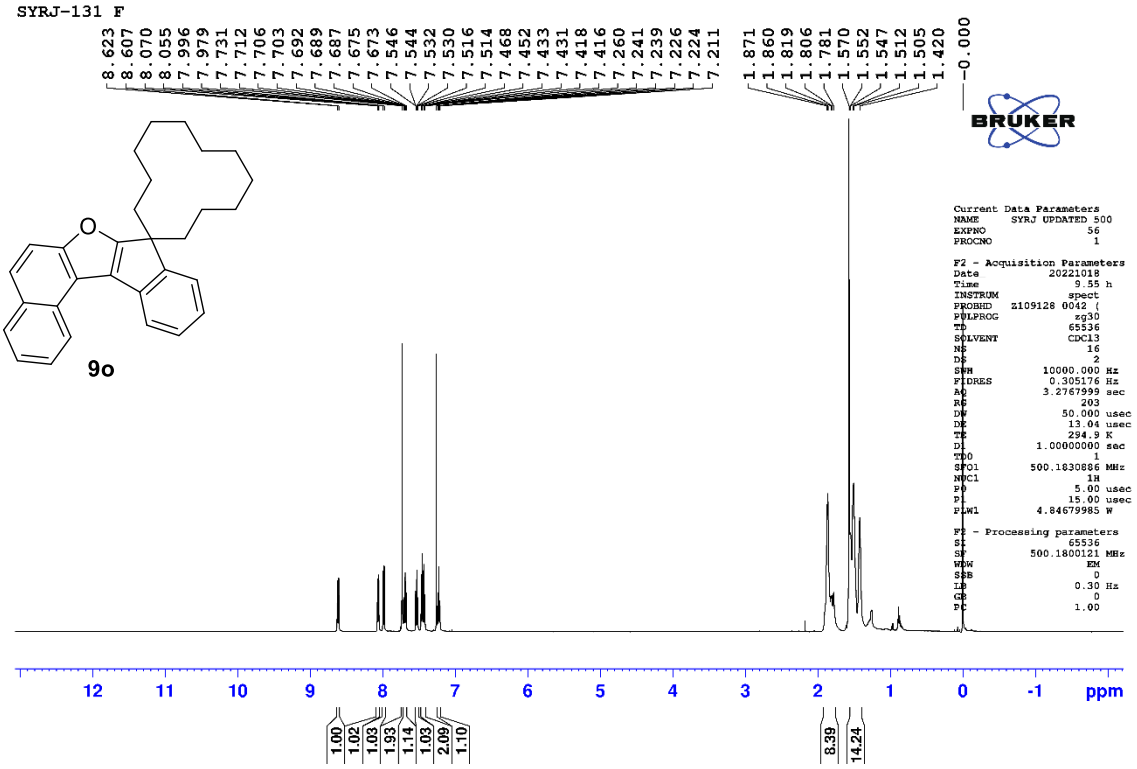
SYRJ-124 F

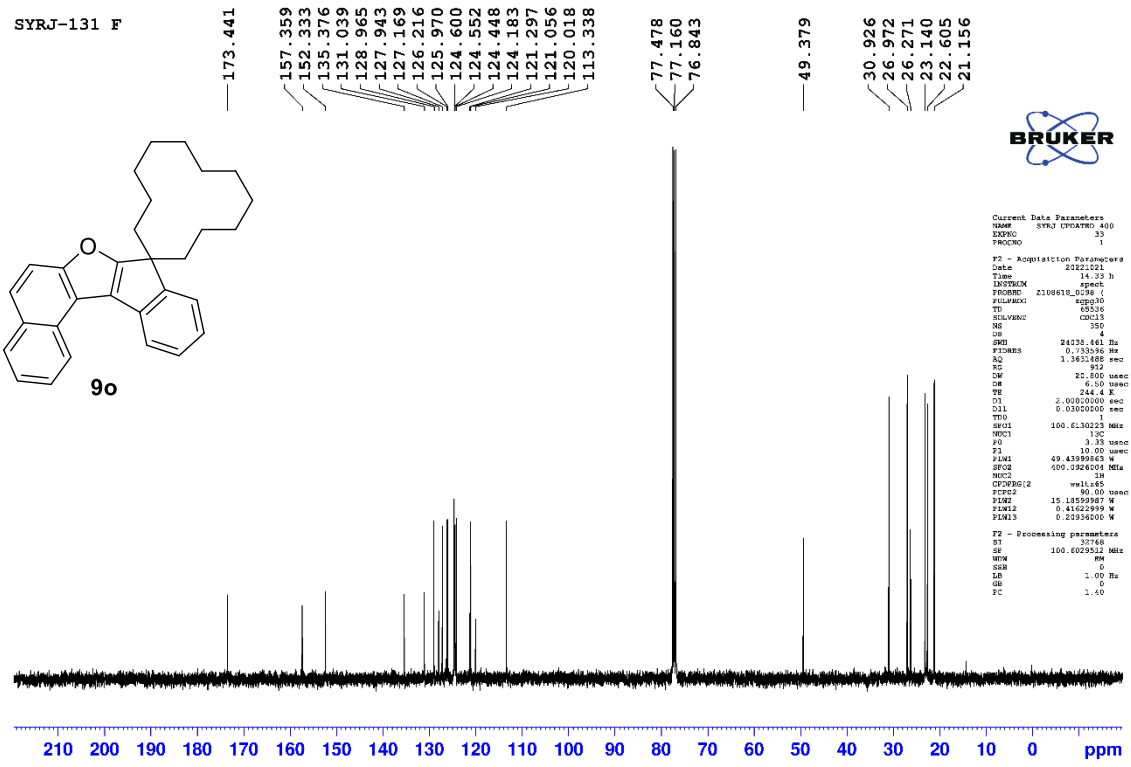


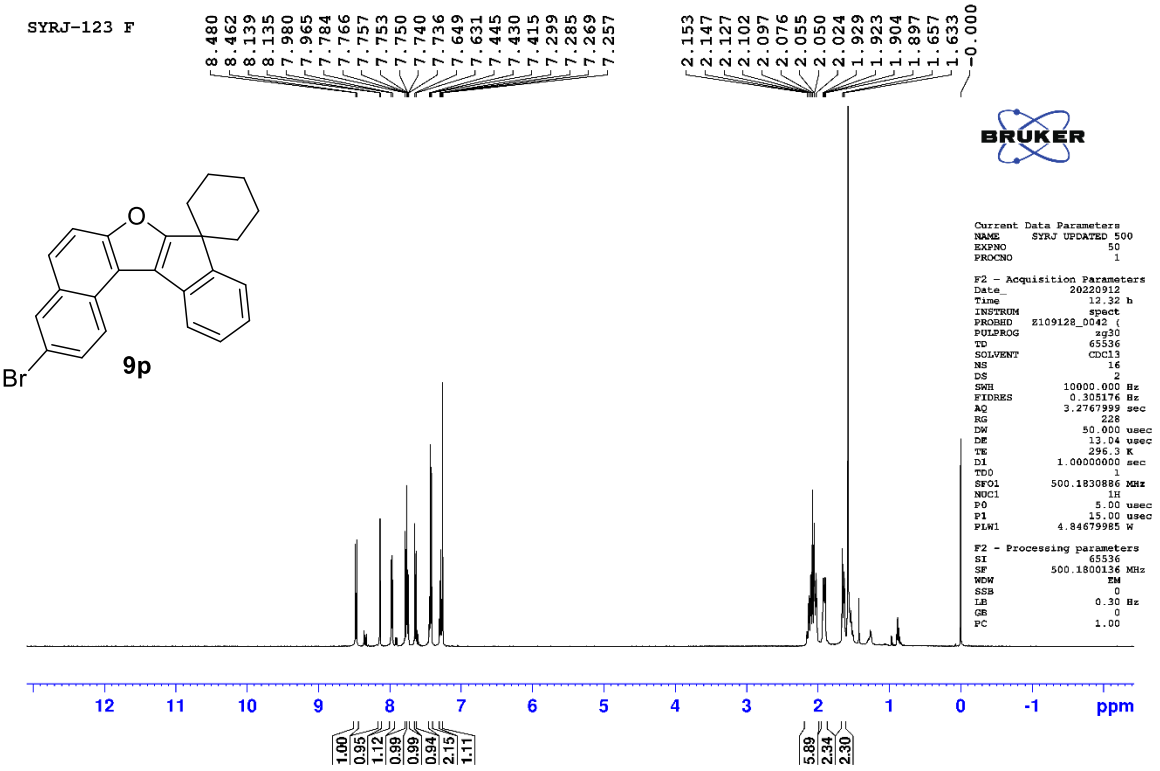
SYRJ-137 F

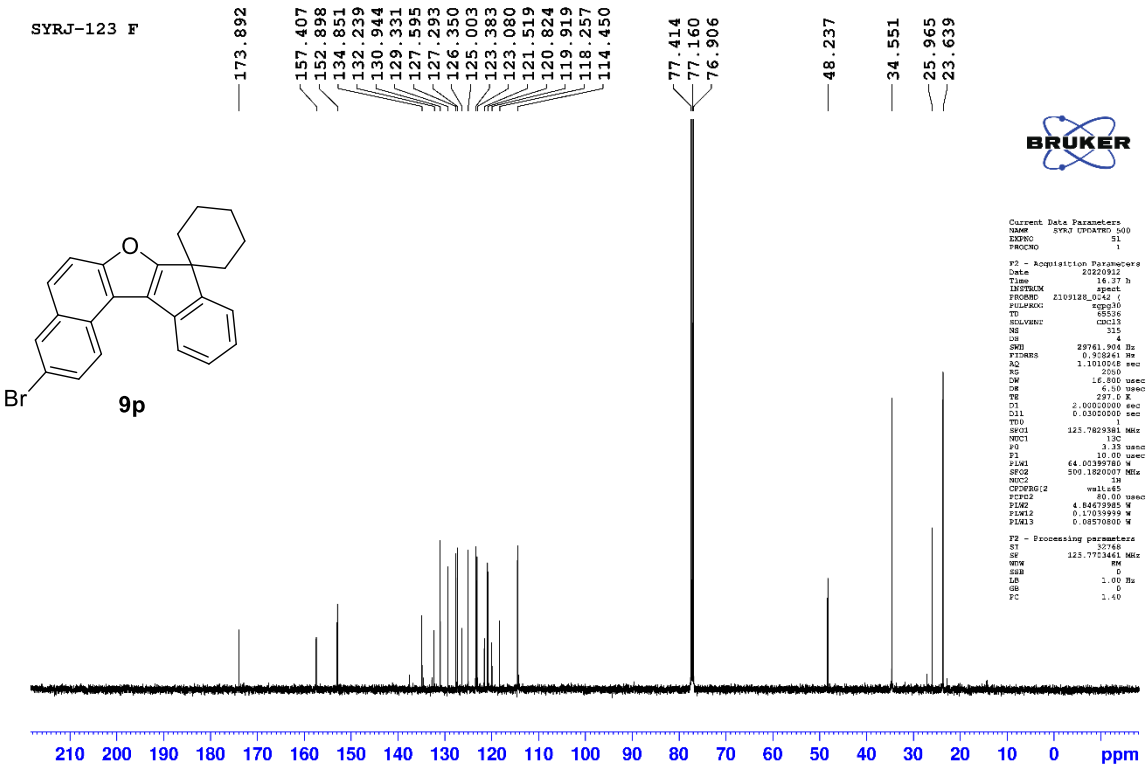


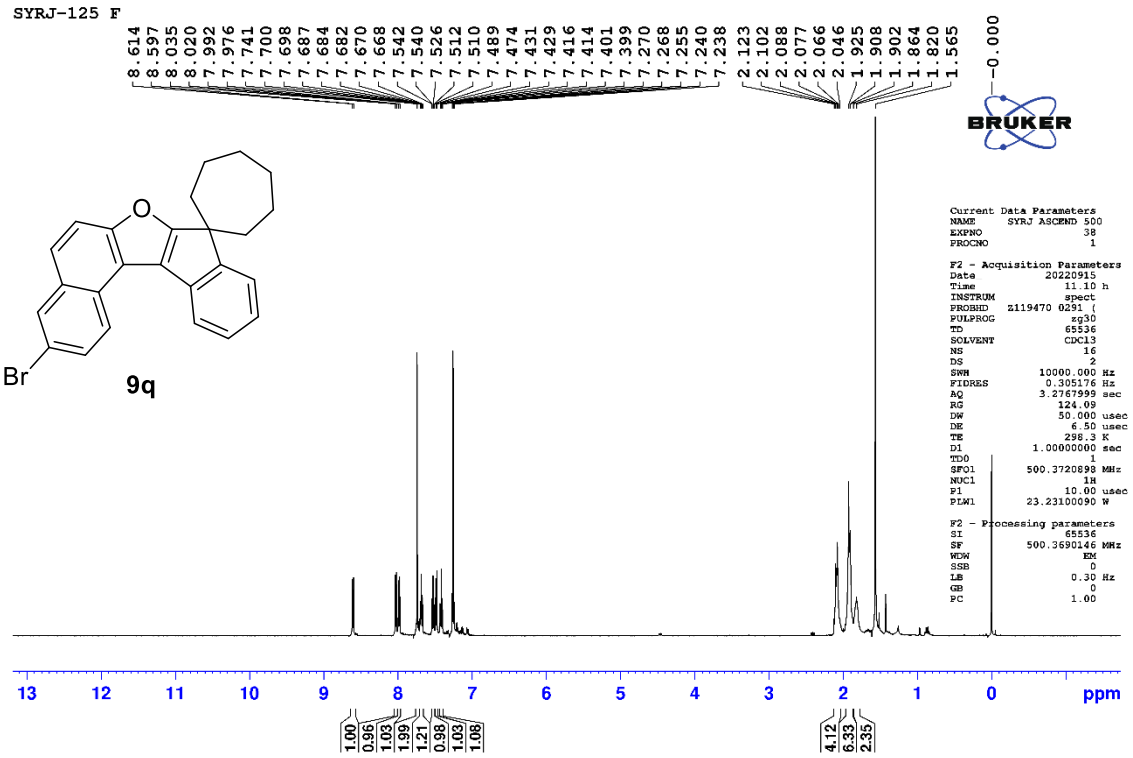

SYRJ-137 F
174.063
157.314
153.970
134.977
131.046
128.962
127.946
127.144
126.211
125.964
124.607
124.586
124.412
123.526
121.079
120.946
120.007
113.415
77.478
77.160
76.843
50.039
32.052
28.853
25.277
24.378
BRUKER
9n
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

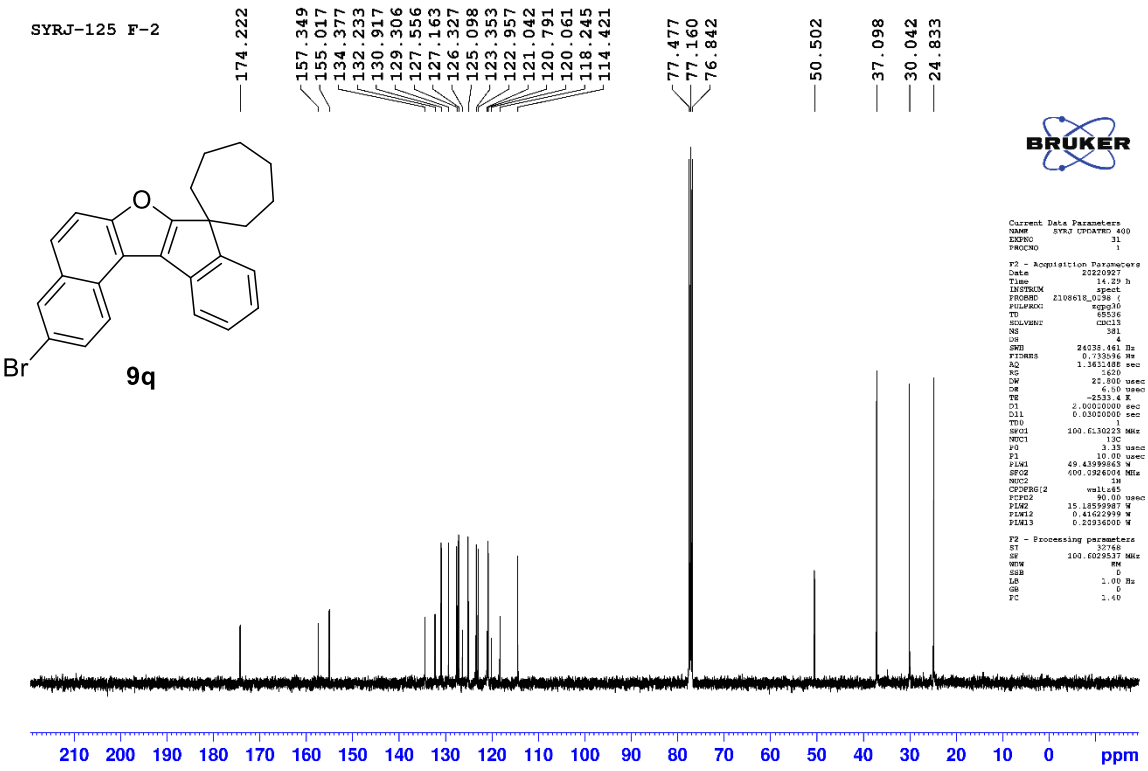

SYRJ-131 F
8.623
8.607
8.070
8.055
7.996
7.979
7.731
7.712
7.706
7.703
7.692
7.689
7.687
7.675
7.673
7.546
7.544
7.532
7.530
7.516
7.514
7.468
7.452
7.433
7.431
7.418
7.416
7.260
7.241
7.239
7.226
7.224
7.211
1.871
1.860
1.819
1.806
1.781
1.570
1.552
1.547
1.512
1.505
1.420
0.000
BRUKER
9o
12 11 10 9 8 7 6 5 4 3 2 1 0 -1 ppm
1.00
1.02
1.03
1.93
1.14
1.03
2.09
1.10
8.39
14.24

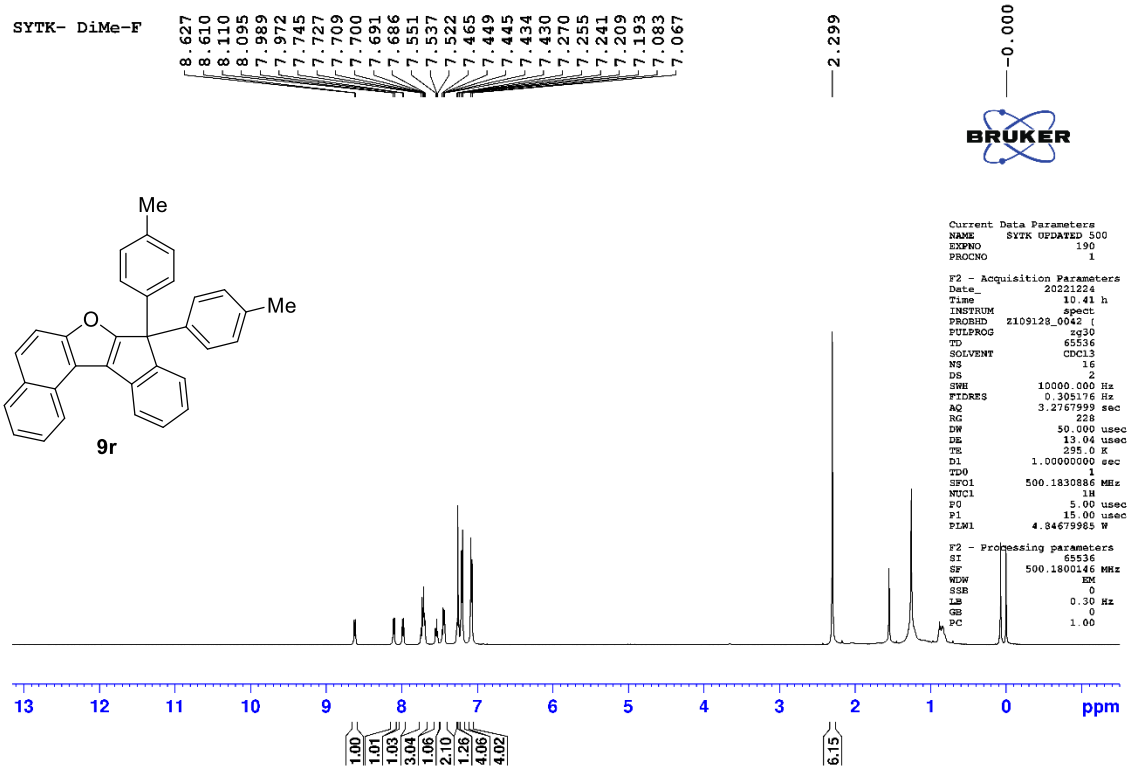

SYRJ-131 F
173.441
157.359
152.333
135.376
131.039
128.965
127.943
127.169
126.216
125.970
124.600
124.552
124.448
124.183
121.297
121.056
120.018
113.338
77.478
77.160
76.843
49.379
30.926
26.972
26.271
23.140
22.605
21.156
BRUKER
O
9o
Current Data Parameters
NAME SYRJ UPDATRO 400
EXPNO 33
PROCNO 1
F2 - Acquisition Parameters
Date 20221021
Time 14.33 h
INSTRUM spect
PROBHD Z108618_0098 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 350
DS 4
SWH 24038.461 Hz
FIDRES 0.733596 Hz
AQ 1.3631488 sec
RG 912
DW 20.800 usec
DE 6.50 usec
TE 244.4 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.6130223 MHz
NUC1 13C
P0 3.35 usec
P1 10.00 usec
PLW1 49.43998563 W
SFO2 400.0926004 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 90.00 usec
PLW2 15.18599987 W
PLW12 0.41622999 W
PLW13 0.22936000 W
F2 - Processing parameters
SI 32768
SF 100.6029512 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

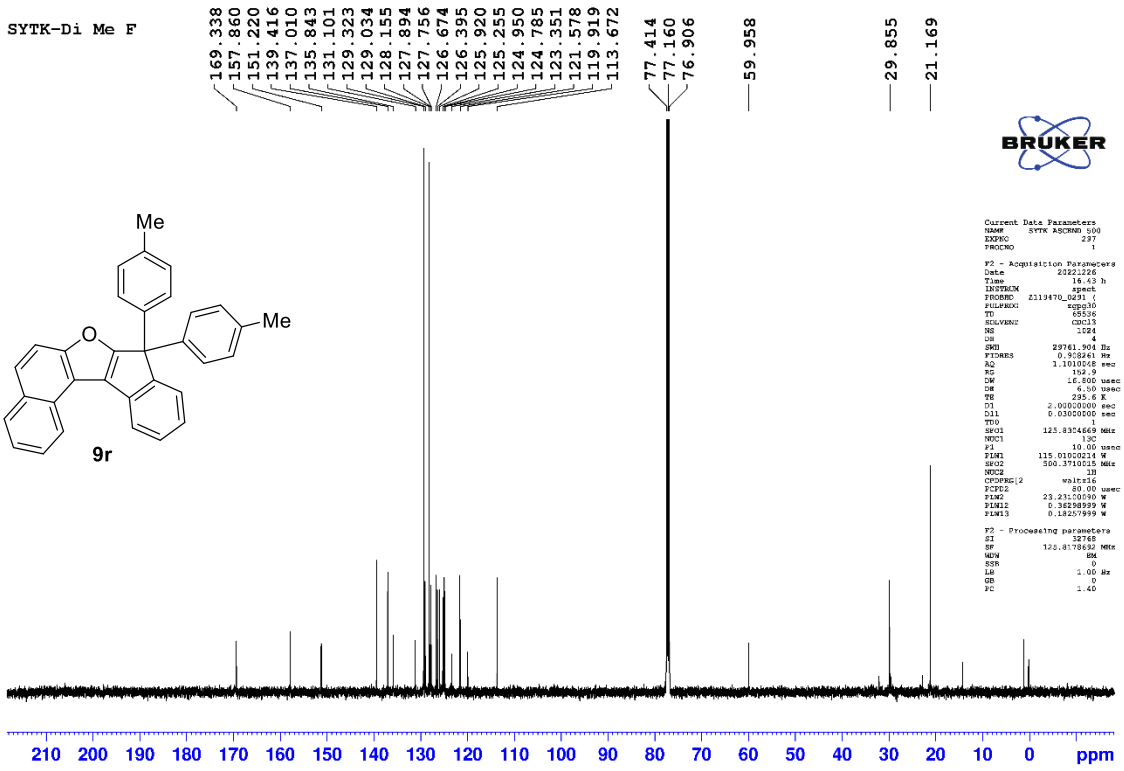

SYRJ-123 F
8.480
8.462
8.139
8.135
7.980
7.965
7.784
7.766
7.757
7.753
7.750
7.740
7.736
7.649
7.631
7.445
7.430
7.415
7.299
7.285
7.269
7.257
2.153
2.147
2.127
2.102
2.097
2.076
2.055
2.050
2.024
1.929
1.923
1.904
1.897
1.657
1.633
-0.000
BRUKER
O
Br
9p
Current Data Parameters
NAME SYRJ UPDATED 500
EXPNO 50
PROCNO 1
F2 - Acquisition Parameters
Date_ 20220912
Time 12.32 h
INSTRUM spect
PROBHD Z109128_0042 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 228
DW 50.000 usec
DE 13.04 usec
TE 296.3 K
D1 1.00000000 sec
TD0 1
SFO1 500.1830886 MHz
NUC1 1H
P0 5.00 usec
P1 15.00 usec
PLW1 4.84679985 W
F2 - Processing parameters
SI 65536
SF 500.1800136 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
12 11 10 9 8 7 6 5 4 3 2 1 0 -1 ppm
1.00
0.95
1.12
0.99
0.99
0.94
2.15
1.11
5.89
2.34
2.30

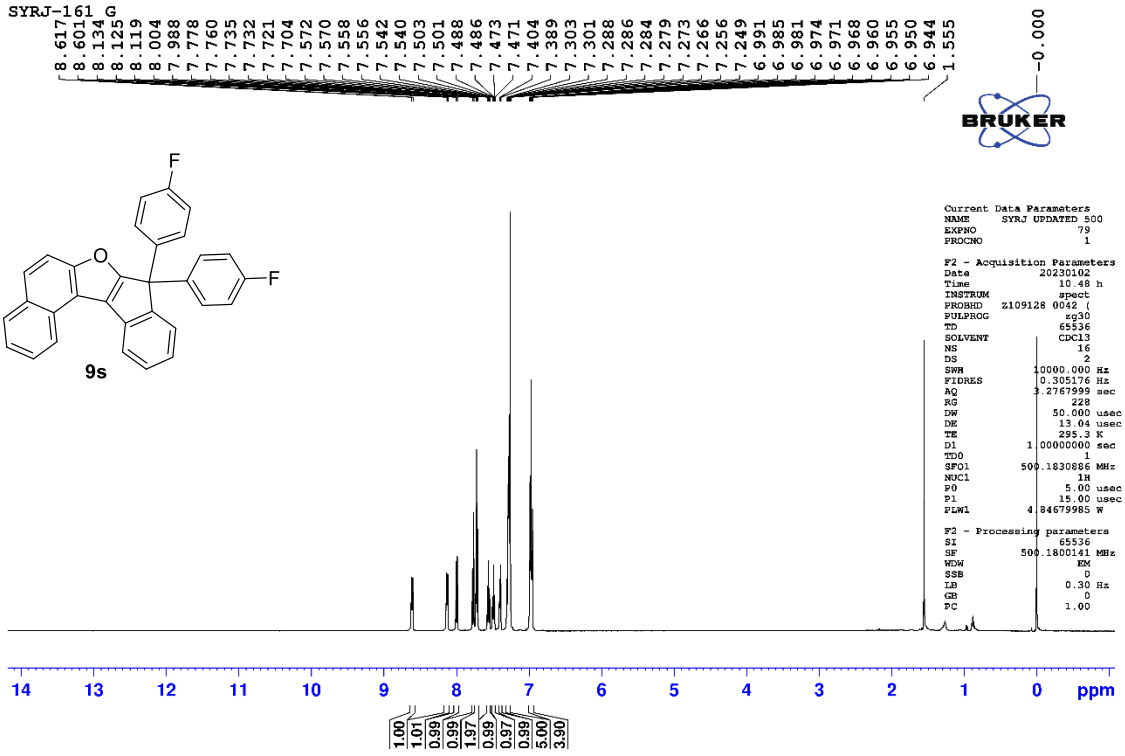

SYRJ-123 F
173.892
157.407
152.898
134.851
132.239
130.944
129.331
127.595
127.293
126.350
125.003
123.383
123.080
121.519
120.824
119.919
118.257
114.450
77.414
77.160
76.906
48.237
34.551
25.965
23.639
BRUKER
O
Br
9p
Current Data Parameters
NAME SYRJ UPDATED 500
EXPNO 51
PROCNO 1
F2 - Acquisition Parameters
Date 20220912
Time 16.37 h
INSTRUM spect
PROBHD Z109128_0242 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 315
DS 4
SWH 29761.904 Hz
FIDRES 0.908261 Hz
AQ 1.1010048 sec
RG 2050
DW 16.800 usec
DE 6.50 usec
TE 297.0 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 123.7829381 MHz
NUC1 13C
P0 3.35 usec
P1 10.00 usec
PLW1 64.00399780 W
SFO2 500.1820007 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 80.00 usec
PLW2 4.84673985 W
PLW12 0.17039999 W
PLW13 0.08570800 W
F2 - Processing parameters
SI 32768
SF 123.7723461 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


SYRJ-125 F
8.614
8.597
8.035
8.020
7.992
7.976
7.741
7.700
7.698
7.687
7.684
7.682
7.670
7.668
7.542
7.540
7.526
7.512
7.510
7.489
7.474
7.431
7.429
7.416
7.414
7.401
7.399
7.270
7.268
7.255
7.240
7.238
2.123
2.102
2.088
2.077
2.066
2.046
1.925
1.908
1.902
1.864
1.820
1.565
0.000
BRUKER
O
Br
9q
Current Data Parameters
NAME SYRJ ASCEND 500
EXPNO 38
PROCNO 1
F2 - Acquisition Parameters
Date 20220915
Time 11.10 h
INSTRUM spect
PROBHD Z119470 0291 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 124.09
DW 50.000 usec
DE 6.50 usec
TE 298.3 K
D1 1.00000000 sec
TD0 1
SFO1 500.3720898 MHz
NUC1 1H
P1 10.00 usec
PLW1 23.23100090 W
F2 - Processing parameters
SI 65536
SF 500.3690146 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.00 0.96 1.03 1.99 1.21 0.98 1.03 1.08
4.12 6.33 2.35

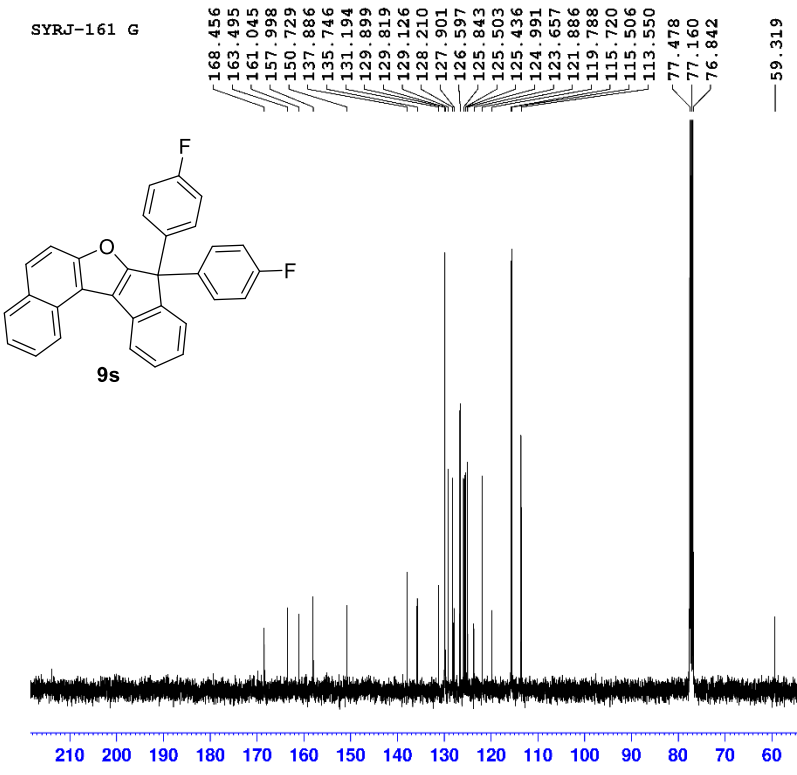

SYRJ-125 F-2
174.222
157.349
155.017
134.377
132.233
130.917
129.306
127.556
127.163
126.327
125.098
123.353
122.957
121.042
120.791
120.061
118.245
114.421
77.477
77.160
76.842
50.502
37.098
30.042
24.833
BRUKER
O
Br
9q
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


SYTK- DiMe-F
8.627
8.610
8.110
8.095
7.989
7.972
7.745
7.727
7.709
7.700
7.691
7.686
7.551
7.537
7.522
7.465
7.449
7.445
7.434
7.430
7.270
7.255
7.241
7.209
7.193
7.083
7.067
2.299
0.000
BRUKER
Me
Me
O
9r
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.00
1.01
1.03
3.04
1.06
2.10
1.26
4.06
4.02
6.15

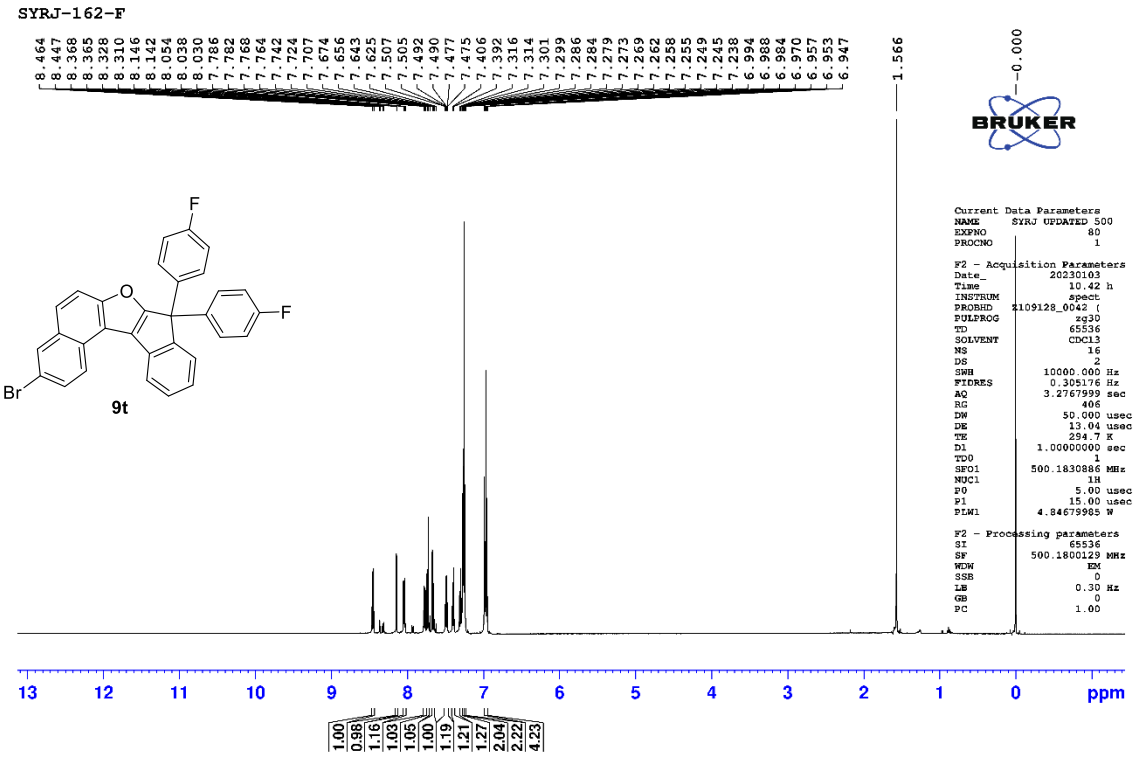

SYTK-Di Me F
169.338
157.860
151.220
139.416
137.010
135.843
131.101
129.323
129.034
128.155
127.894
127.756
126.674
126.395
125.920
125.255
124.950
124.785
123.351
121.578
119.919
113.672
77.414
77.160
76.906
59.958
29.855
21.169
BRUKER
Me
Me
O
9r
Current Data Parameters
NAME SYTK ASCEND 500
EXPNO 297
PROCNO 1
F2 - Acquisition Parameters
Date 20221226
Time 16.43 h
INSTRUM spect
PROBHD Z119470_0291 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 4
SWH 29761.904 Hz
FIDRES 0.908241 Hz
AQ 1.1010548 sec
RG 152.9
DW 16.800 usec
DE 6.50 usec
TE 295.6 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8304669 MHz
NUC1 13C
P1 10.00 usec
PLW1 115.01000214 W
SFO2 500.3710515 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 23.23100590 W
PLW12 0.36298999 W
PLW13 0.18257999 W
F2 - Processing parameters
SI 32768
SF 125.8278692 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

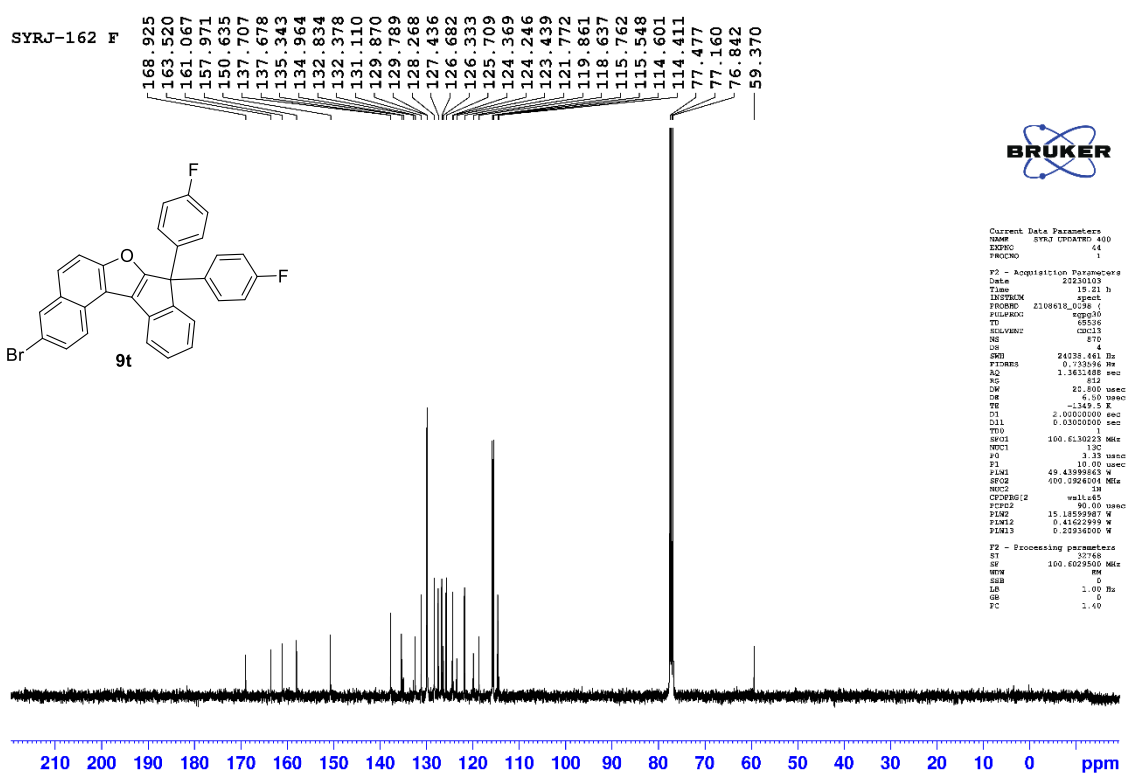

SYRJ-161 G
8.617
8.601
8.134
8.125
8.119
8.004
7.988
7.778
7.760
7.735
7.732
7.721
7.704
7.572
7.570
7.558
7.556
7.542
7.540
7.503
7.501
7.488
7.486
7.473
7.471
7.404
7.389
7.303
7.301
7.288
7.286
7.284
7.279
7.273
7.266
7.256
7.249
6.991
6.985
6.981
6.974
6.971
6.968
6.960
6.955
6.950
6.944
1.555
0.000
BRUKER
F
O
F
9s
Current Data Parameters
NAME SYRJ UPDATED 500
EXPNO 79
PROCNO 1
F2 - Acquisition Parameters
Date 20230102
Time 10.48 h
INSTRUM spect
PROBHD Z109128 0042 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 228
DW 50.000 usec
DE 13.04 usec
TE 295.3 K
D1 1.00000000 sec
TD0 1
SFO1 500.1830886 MHz
NUC1 1H
P0 5.00 usec
P1 15.00 usec
PLW1 4.84679985 W
F2 - Processing parameters
SI 65536
SF 500.1800141 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.00
1.01
0.99
0.99
1.97
0.99
0.97
0.99
5.00
3.90

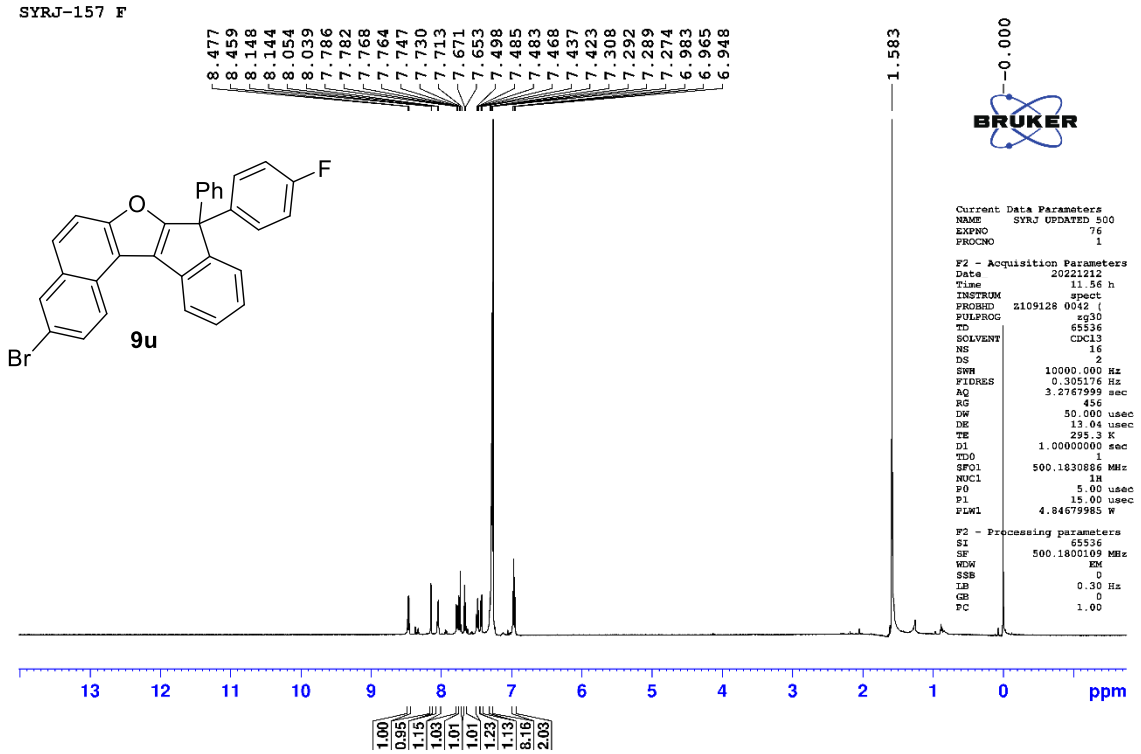
SYRJ-161 G



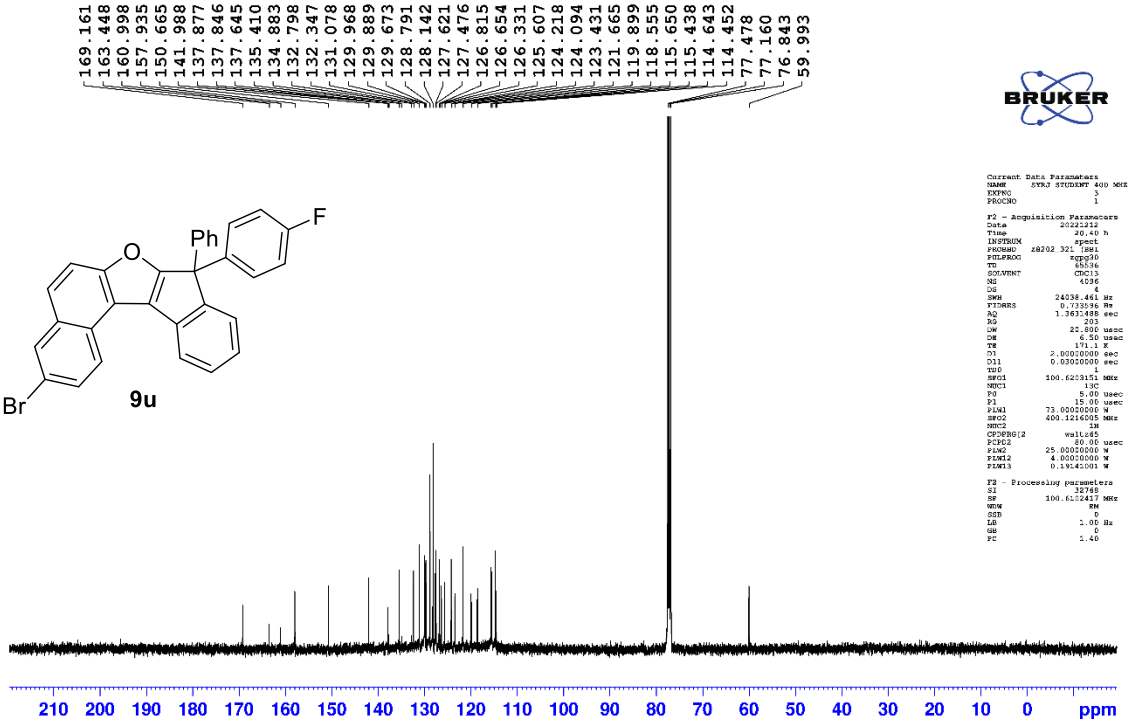
SYRJ-162-F



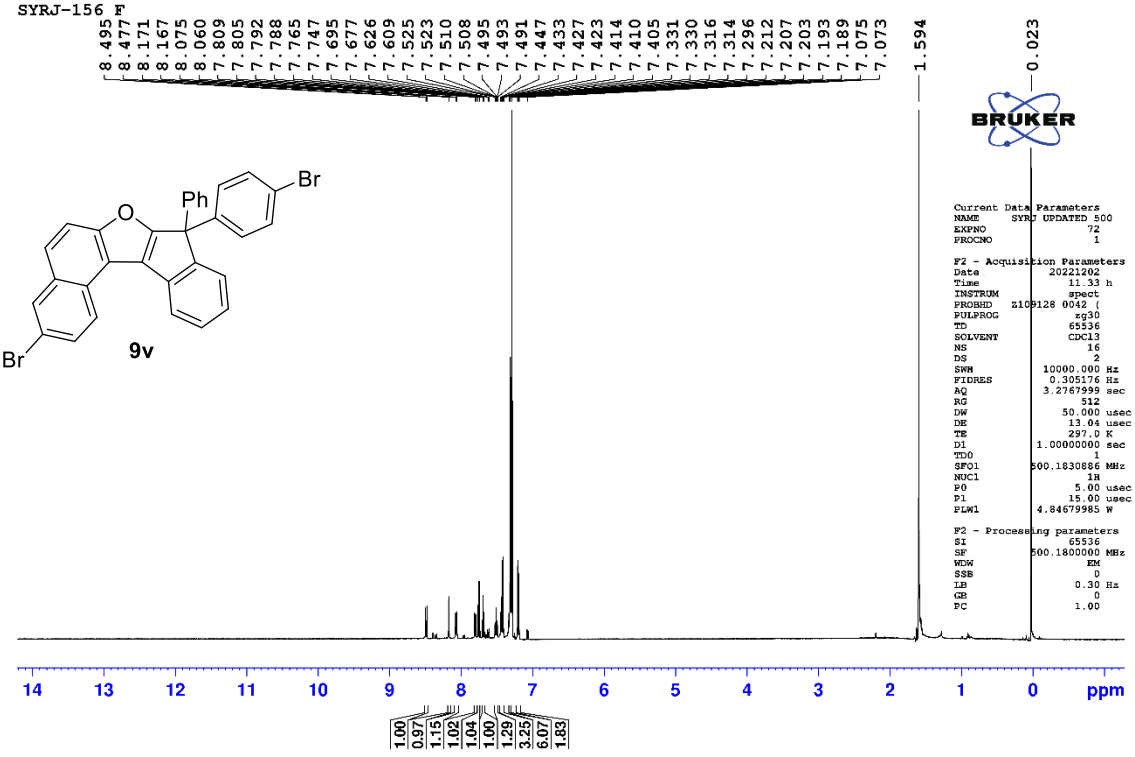

SYRJ-162 F
168.925
163.520
161.067
157.971
150.635
137.707
137.678
135.343
134.964
132.834
132.378
131.110
129.870
129.789
128.268
127.436
126.682
126.333
125.709
124.369
124.246
123.439
121.772
119.861
118.637
115.762
115.548
114.601
114.411
77.477
77.160
76.842
59.370
F
O
F
Br
9t
BRUKER
Current Data Parameters
NAME SYRJ UPDATED 400
EXPNO 44
PROCNO 1
F2 - Acquisition Parameters
Date 20230103
Time 15.21 h
INSTRUM spect
PROBHD Z108618_0196 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 870
DS 4
SWH 24038.461 Hz
FIDRES 0.733596 Hz
AQ 1.3631488 sec
RG 812
DW 20.800 usec
DE 6.50 usec
TE ~349.5 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.6130223 MHz
NUC1 13C
P0 3.33 usec
P1 10.00 usec
PLW1 49.43998863 W
SFO2 400.0926004 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 90.00 usec
PLW2 15.18599987 W
PLW12 0.41622999 W
PLW13 0.22936000 W
F2 - Processing parameters
SI 32768
SF 100.6029500 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


SYRJ-157 F
8.477
8.459
8.148
8.144
8.054
8.039
7.786
7.782
7.768
7.764
7.747
7.730
7.713
7.671
7.653
7.498
7.485
7.483
7.468
7.437
7.423
7.308
7.292
7.289
7.274
6.983
6.965
6.948
1.583
0.000
F
Ph
O
Br
9u
BRUKER
Current Data Parameters
NAME SYRJ UPDATED 500
EXPNO 76
PROCNO 1
F2 - Acquisition Parameters
Date 20221212
Time 11.56 h
INSTRUM spect
PROBHD Z109128 0042 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 456
DW 50.000 usec
DE 13.04 usec
TE 295.3 K
D1 1.00000000 sec
TD0 1
SFO1 500.1830886 MHz
NUC1 1H
P0 5.00 usec
P1 15.00 usec
PLW1 4.84679985 W
F2 - Processing parameters
SI 65536
SF 500.1800109 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.00 0.95 1.15 1.03 1.01 1.01 1.23 1.13 8.16 2.03

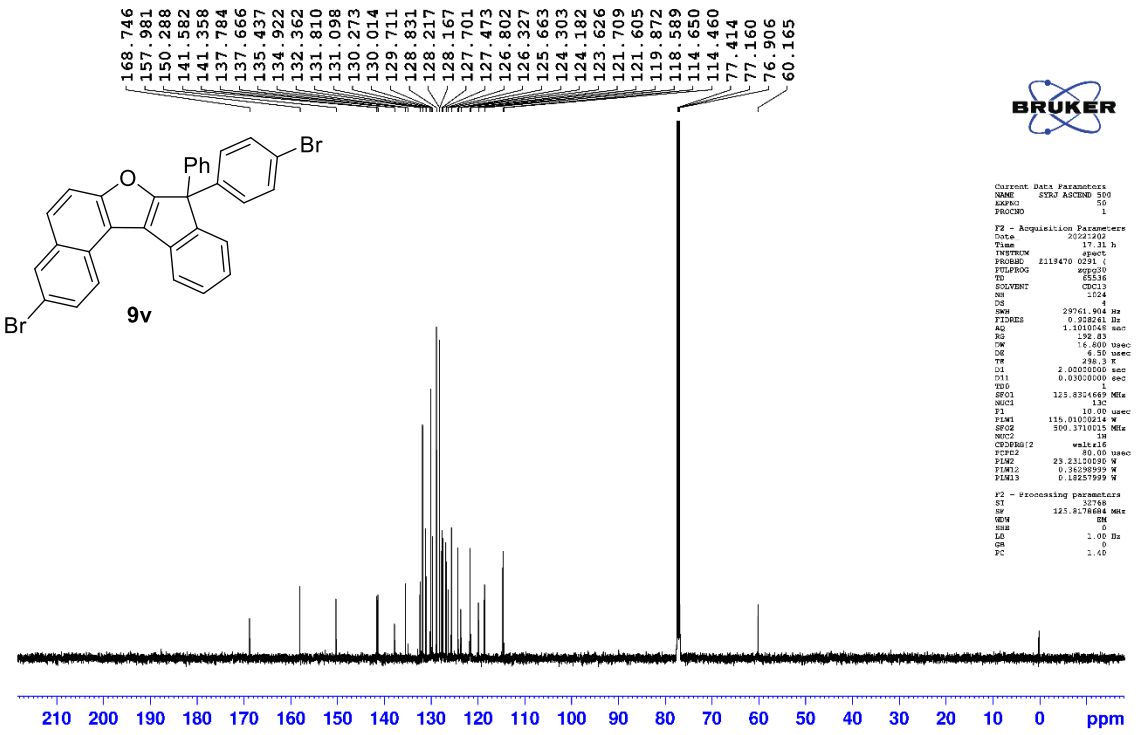
SYRJ-157 F



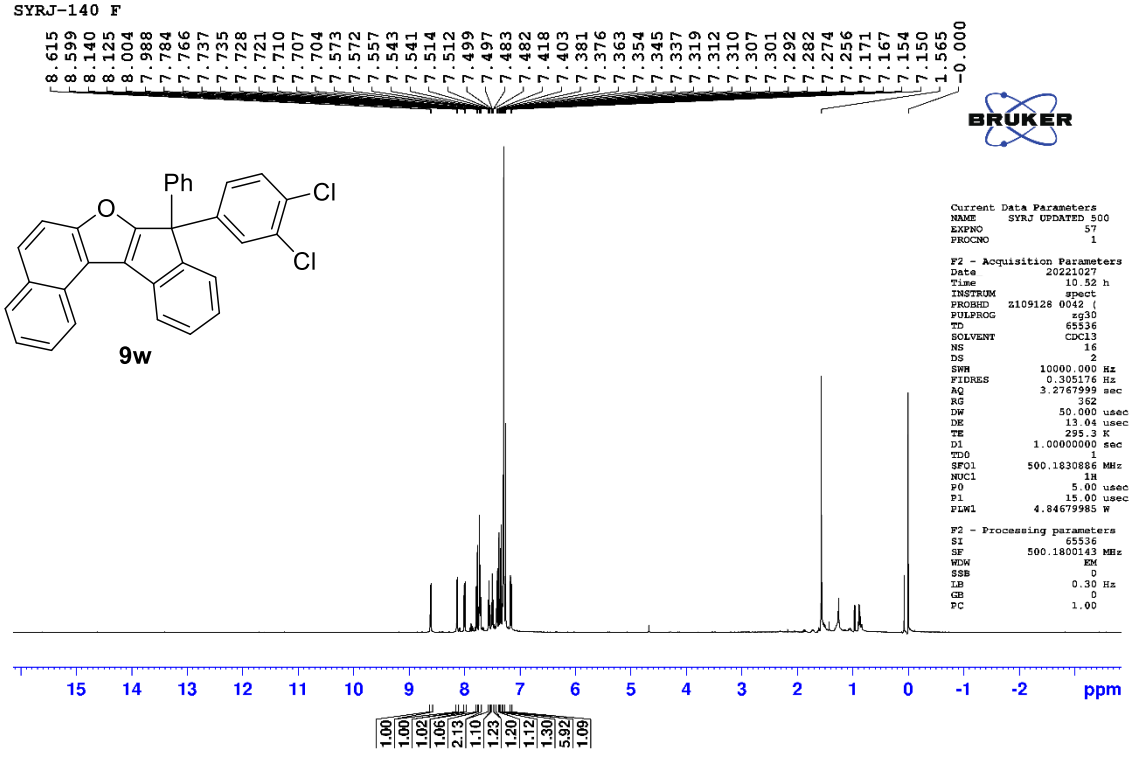
SYRJ-156 F



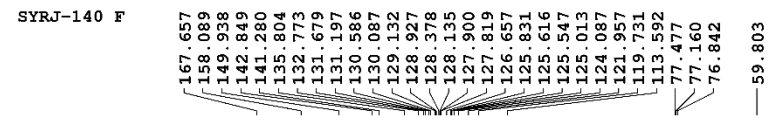
SYRJ-156 F

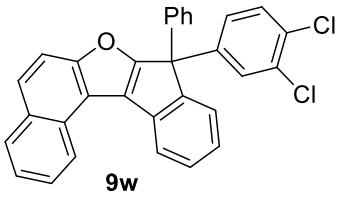


SYRJ-140 F



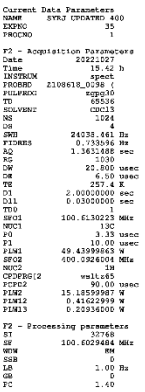
SYRJ-140 F





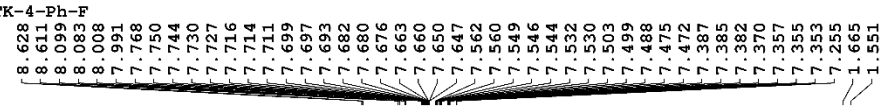
9w

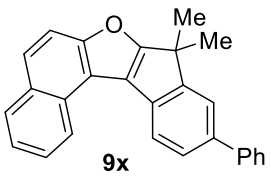






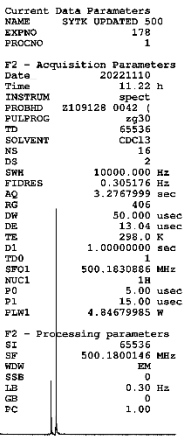
SYTK-4-Ph-F

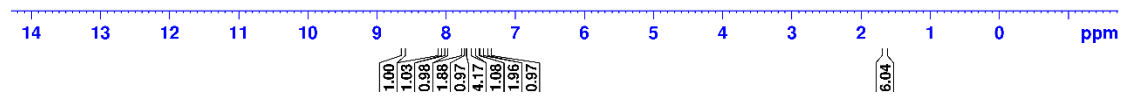


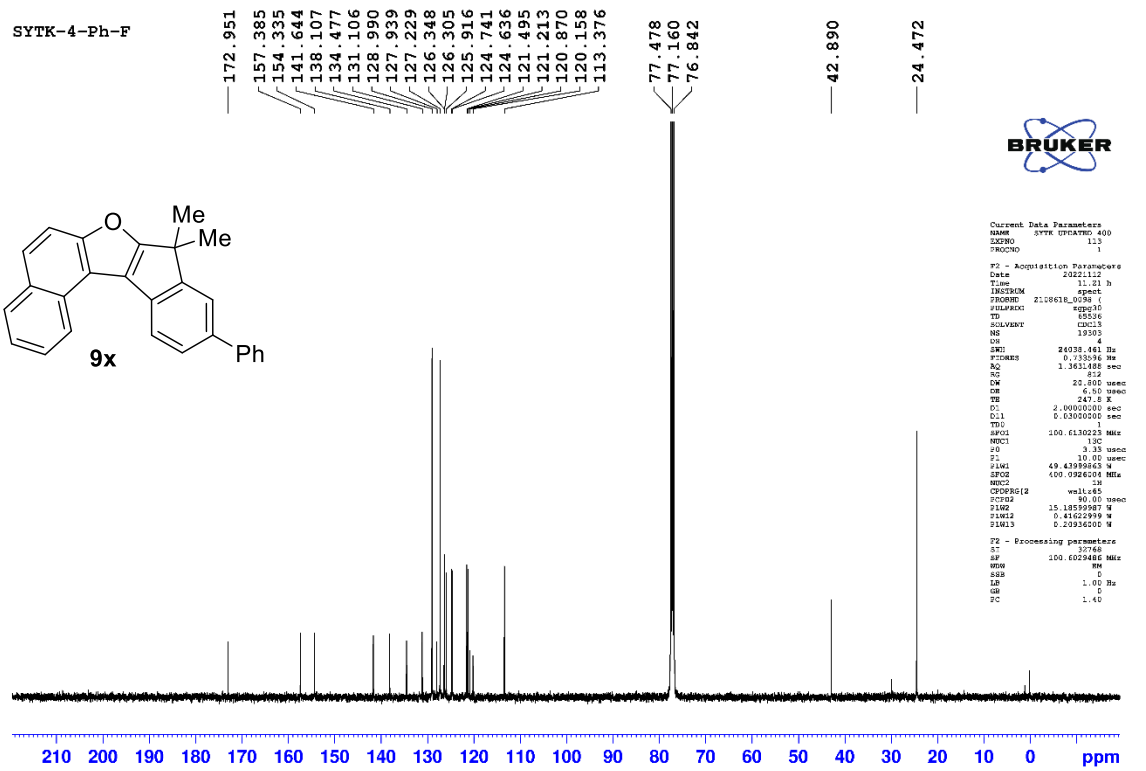


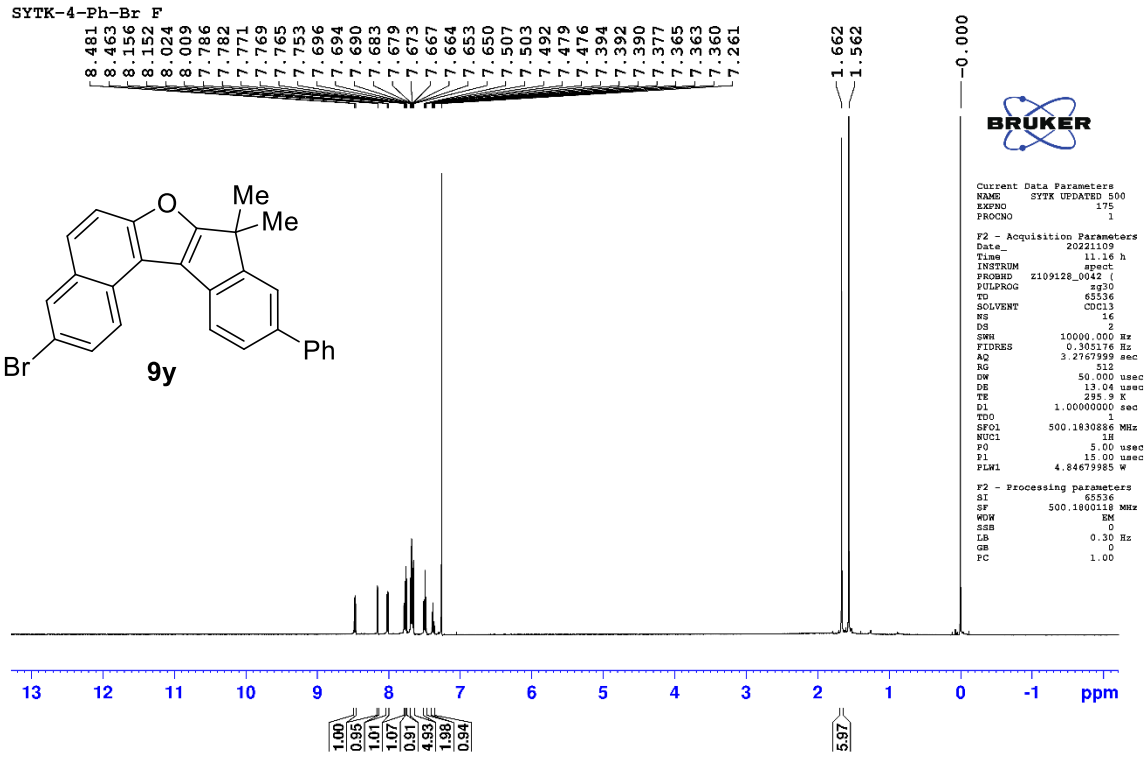
9x

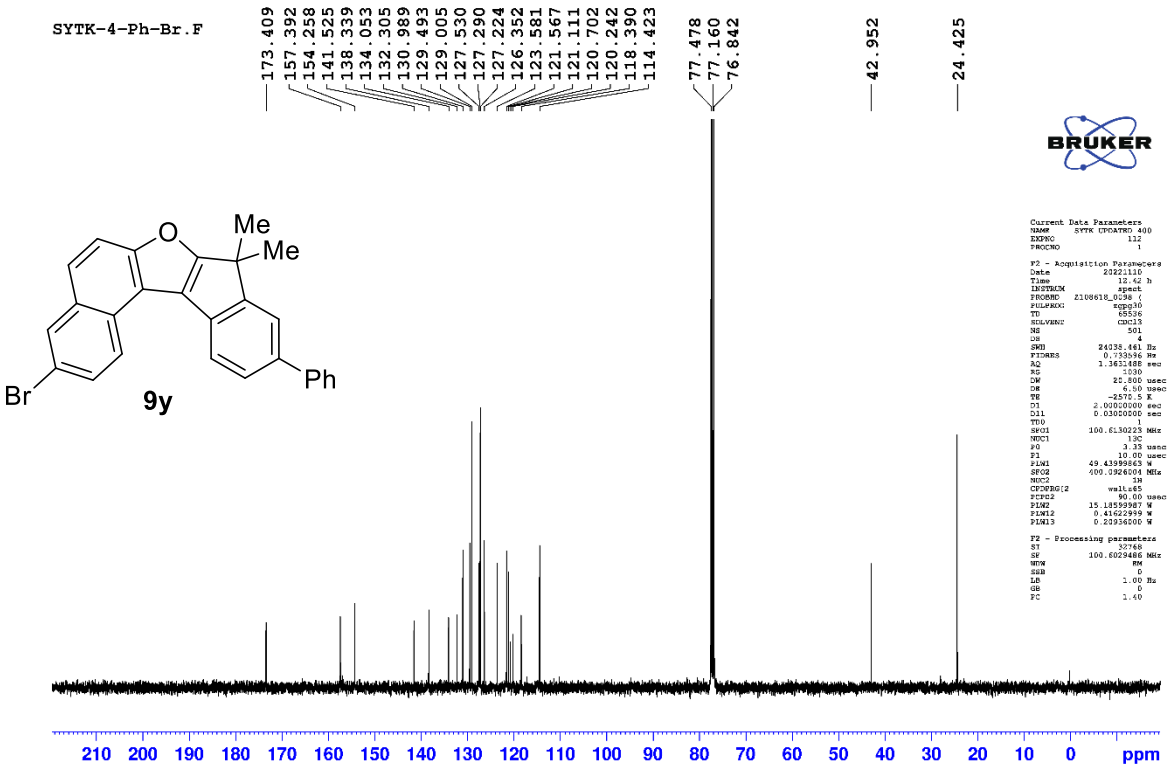


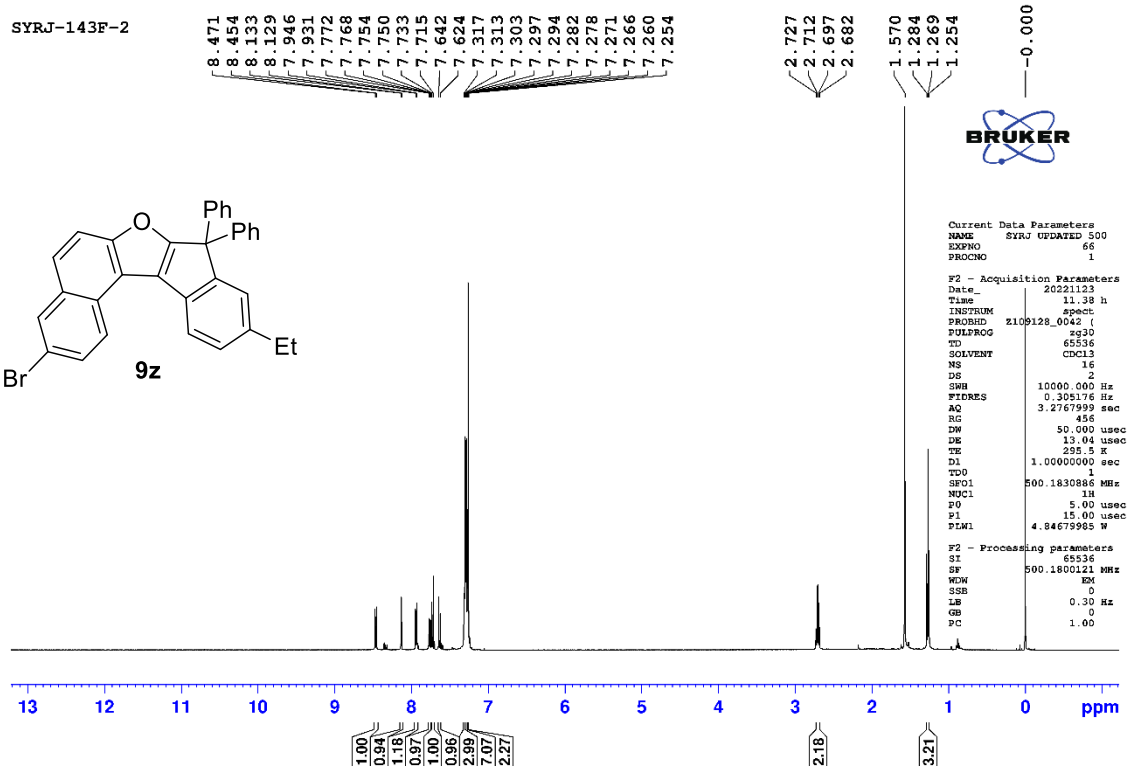




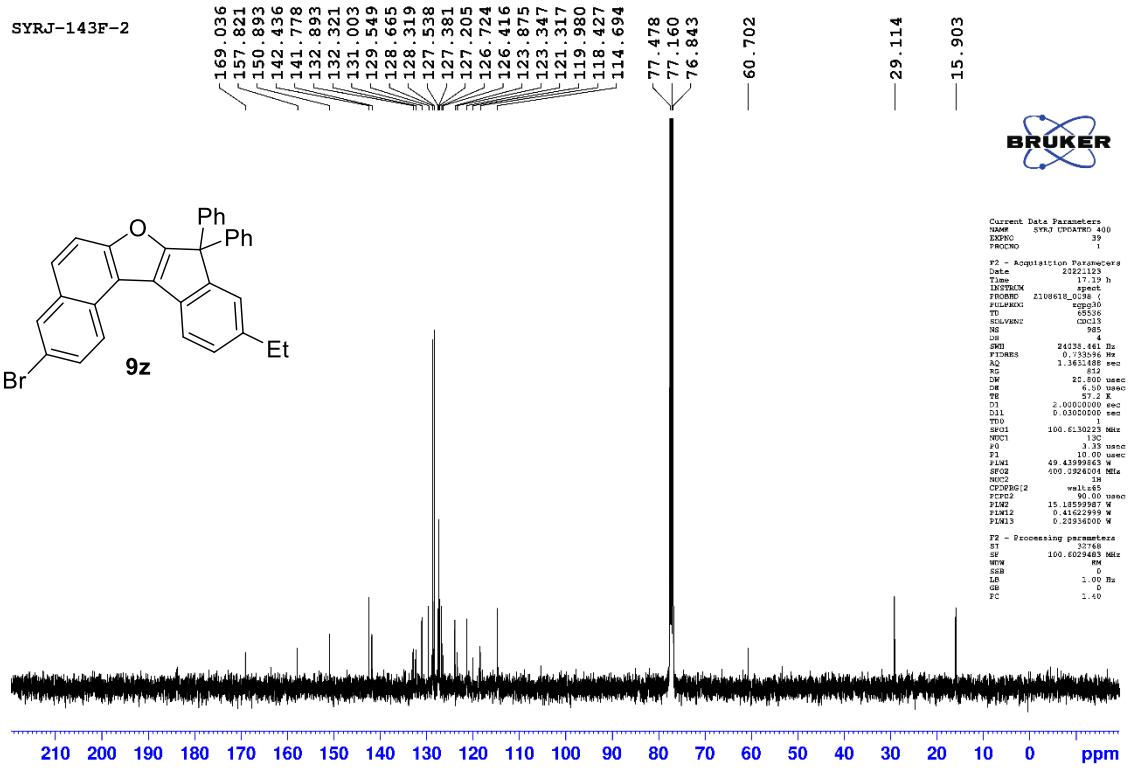

SYTK-4-Ph-F
172.951
157.385
154.335
141.644
138.107
134.477
131.106
128.990
127.939
127.229
126.348
126.305
125.916
124.741
124.636
121.495
121.213
120.870
120.158
113.376
77.478
77.160
76.842
42.890
24.472
BRUKER
O
Me
Me
Ph
9x
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


SYTK-4-Ph-Br F
8.481
8.463
8.156
8.152
8.024
8.009
7.786
7.782
7.771
7.769
7.765
7.753
7.696
7.694
7.690
7.683
7.679
7.673
7.667
7.664
7.653
7.650
7.507
7.503
7.492
7.479
7.476
7.394
7.392
7.390
7.377
7.365
7.363
7.360
7.261
1.662
1.562
0.000
BRUKER
O
Me
Me
Br
Ph
9y
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 ppm
1.00
0.95
1.01
1.07
0.91
4.93
1.98
0.94
5.97

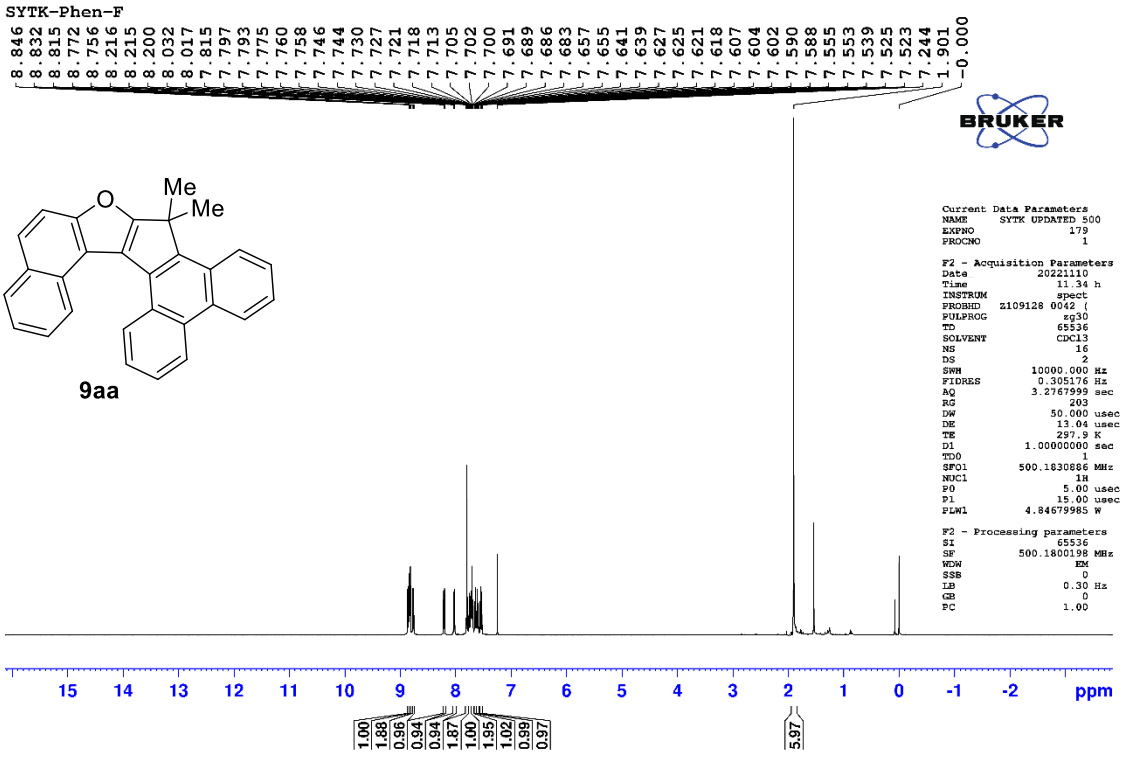

SYTK-4-Ph-Br.F
173.409
157.392
154.258
141.525
138.339
134.053
132.305
130.989
129.493
129.005
127.530
127.290
127.224
126.352
123.581
121.567
121.111
120.702
120.242
118.390
114.423
77.478
77.160
76.842
42.952
24.425
BRUKER
O
Me
Me
Br
Ph
9y
Current Data Parameters
NAME SYTK UPDATED 400
EXPNO 132
PROCNO 1
F2 - Acquisition Parameters
Date 20221110
Time 12.42 h
INSTRUM spect
PROBHD Z108618_0238 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 501
DS 4
SWH 24038.461 Hz
FIDRES 0.733596 Hz
AQ 1.3631488 sec
RG 1030
DW 20.800 usec
DE 6.50 usec
TE 297.5 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.6130223 MHz
NUC1 13C
P0 3.35 usec
P1 10.00 usec
PLW1 49.43999863 W
SFO2 400.0926004 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 90.00 usec
PLW2 15.18599987 W
PLW12 0.41622999 W
PLW13 0.22936000 W
F2 - Processing parameters
SI 32768
SF 100.6029486 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


SYRJ-143F-2
8.471
8.454
8.133
8.129
7.946
7.931
7.772
7.768
7.754
7.750
7.733
7.715
7.642
7.624
7.317
7.313
7.303
7.297
7.294
7.282
7.278
7.271
7.266
7.260
7.254
2.727
2.712
2.697
2.682
1.570
1.284
1.269
1.254
0.000
BRUKER
O
Ph
Ph
Br
Et
9z
Current Data Parameters
NAME SYRJ UPDATED 500
EXPNO 66
PROCNO 1
F2 - Acquisition Parameters
Date_ 20221123
Time 11.38 h
INSTRUM spect
PROBHD Z109128_0042 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 456
DW 50.000 usec
DE 13.04 usec
TE 295.5 K
D1 1.00000000 sec
TD0 1
SFO1 500.1830886 MHz
NUC1 1H
P0 5.00 usec
P1 15.00 usec
PLW1 4.84679985 W
F2 - Processing parameters
SI 65536
SF 500.1800121 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.00
0.94
1.18
0.97
1.00
0.96
2.99
7.07
2.27
2.18
3.21

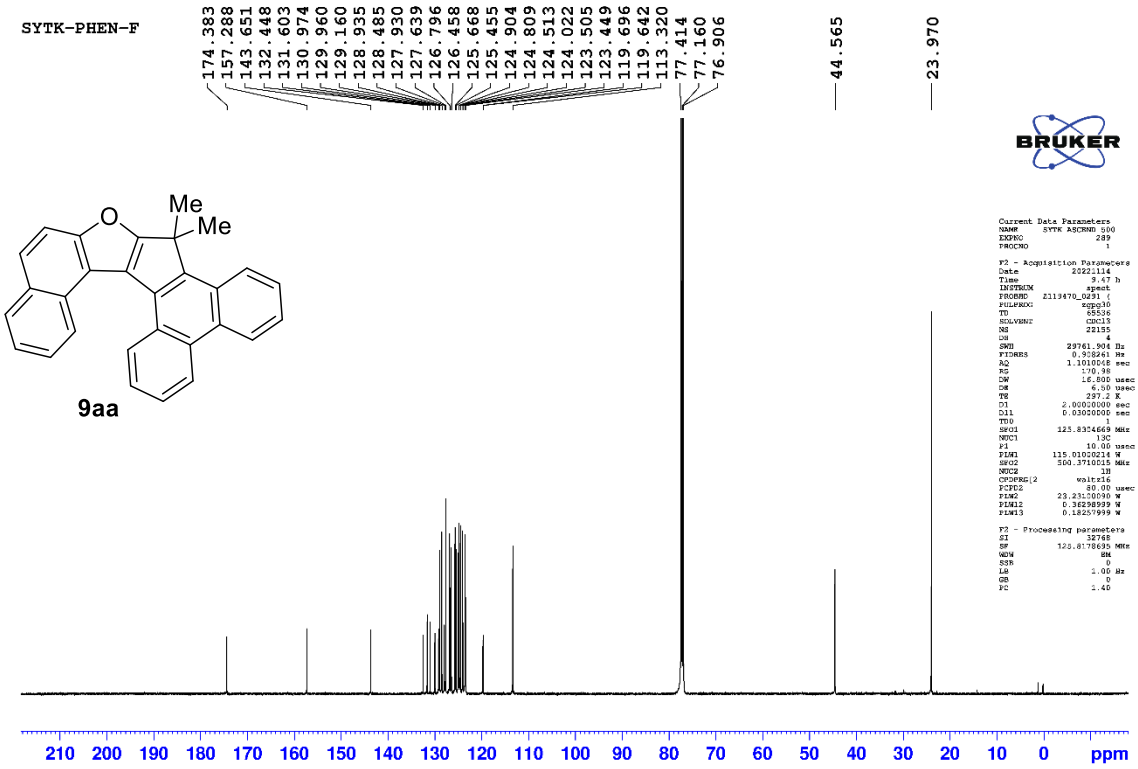
SYRJ-143F-2



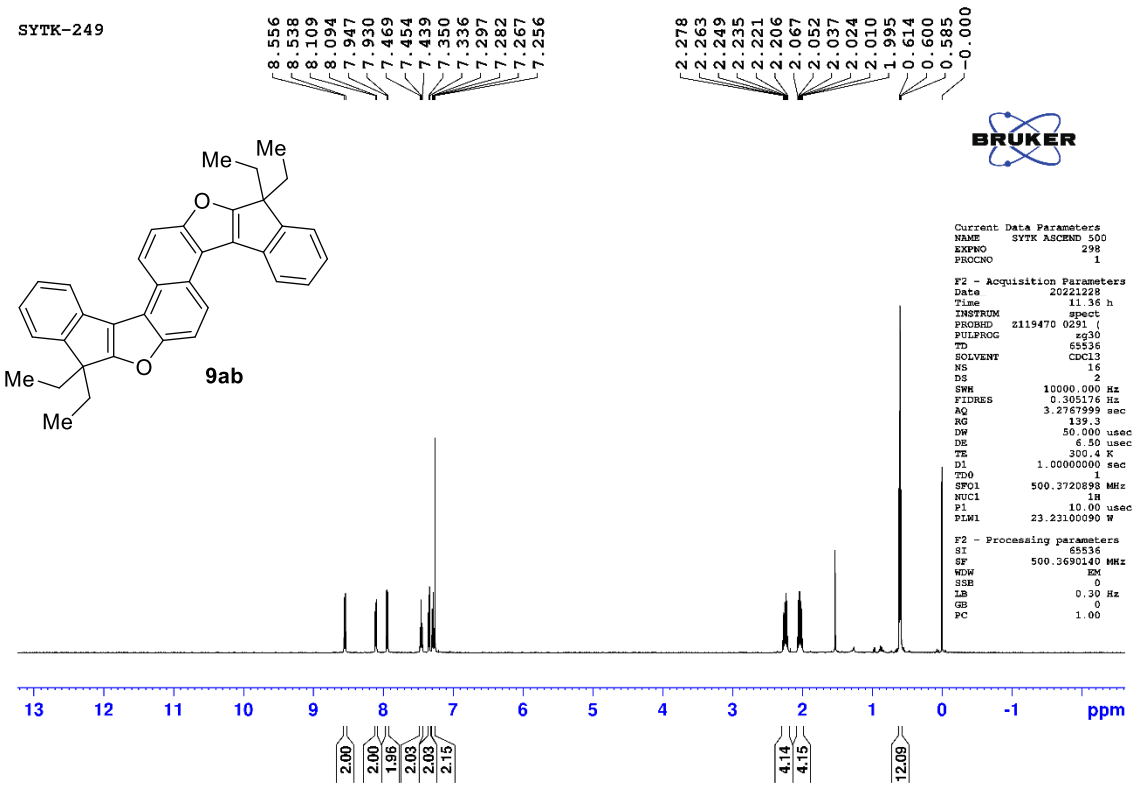
SYTK-Phen-F



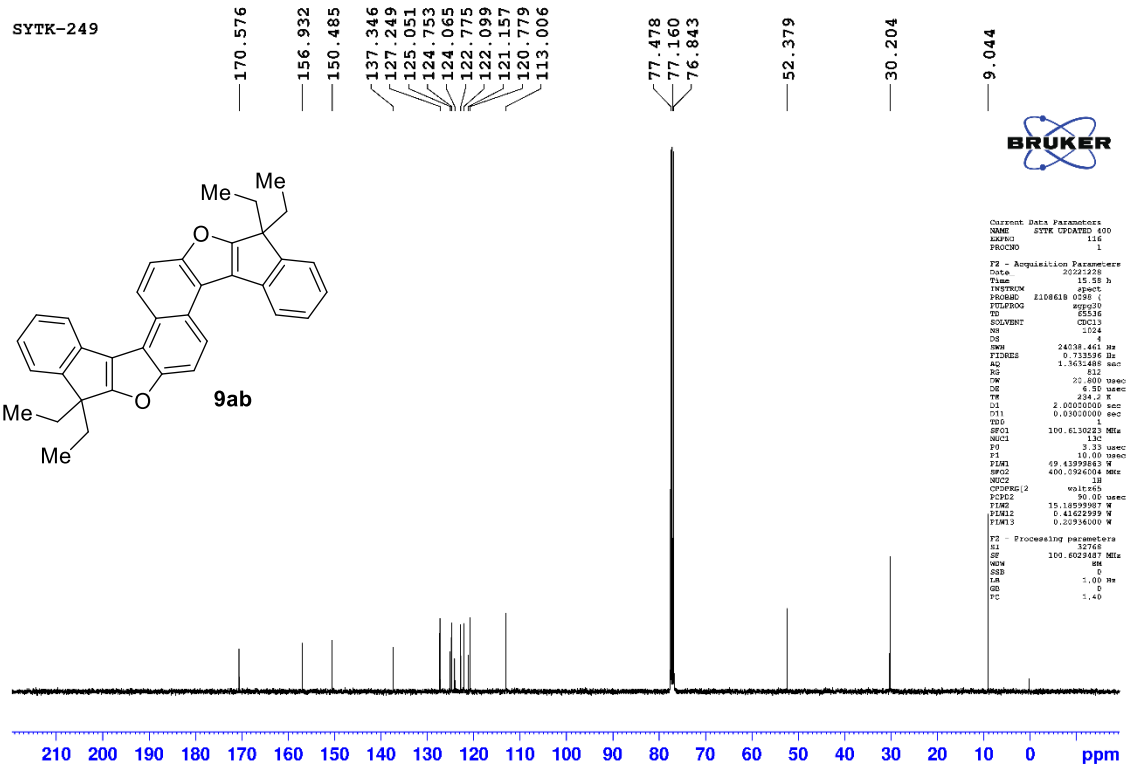
SYTK-PHEN-F



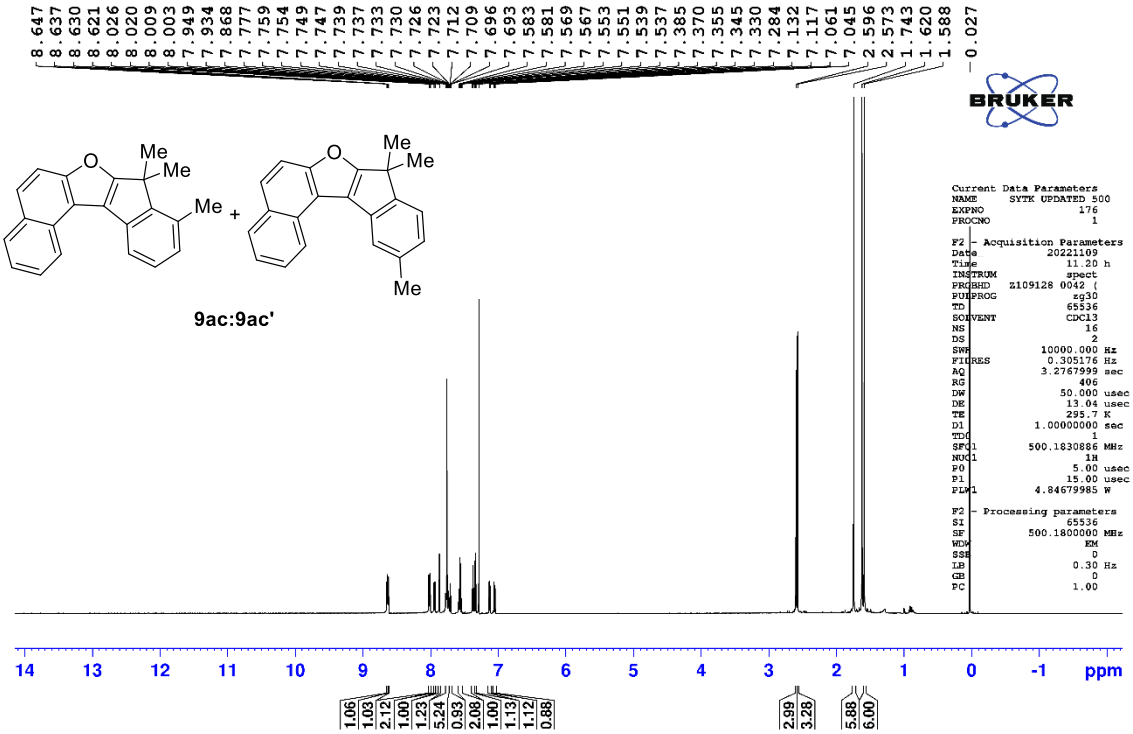
SYTK-249

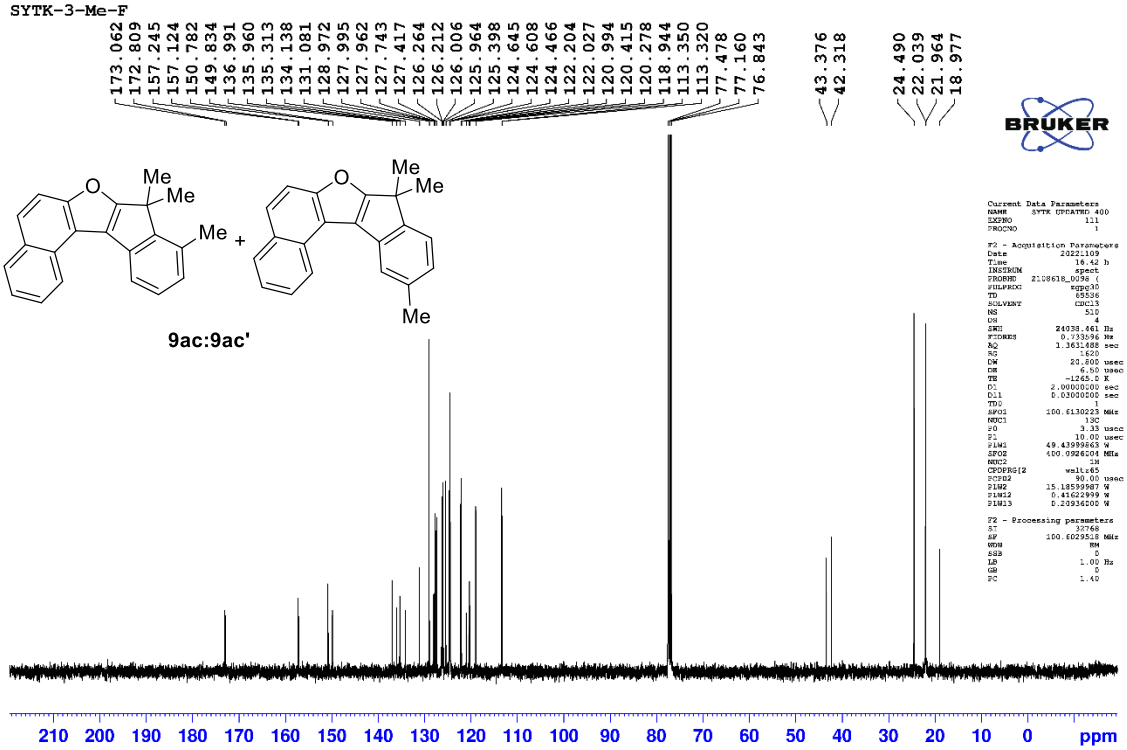


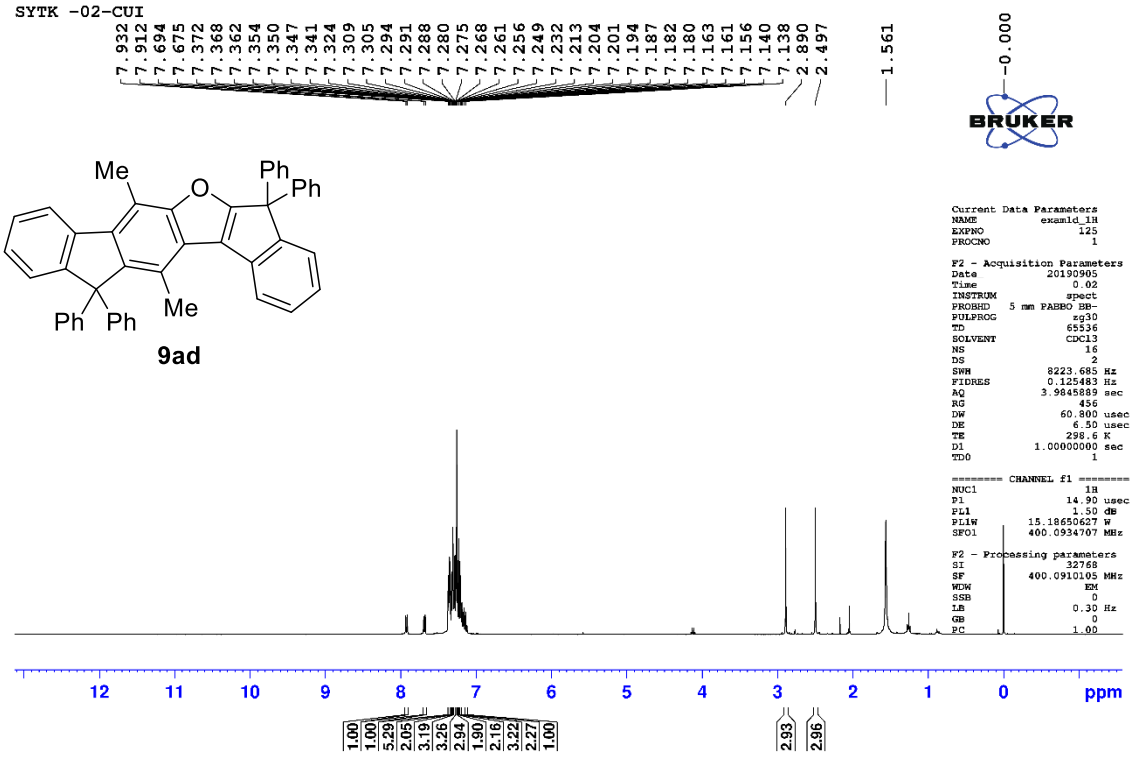
SYTK-249



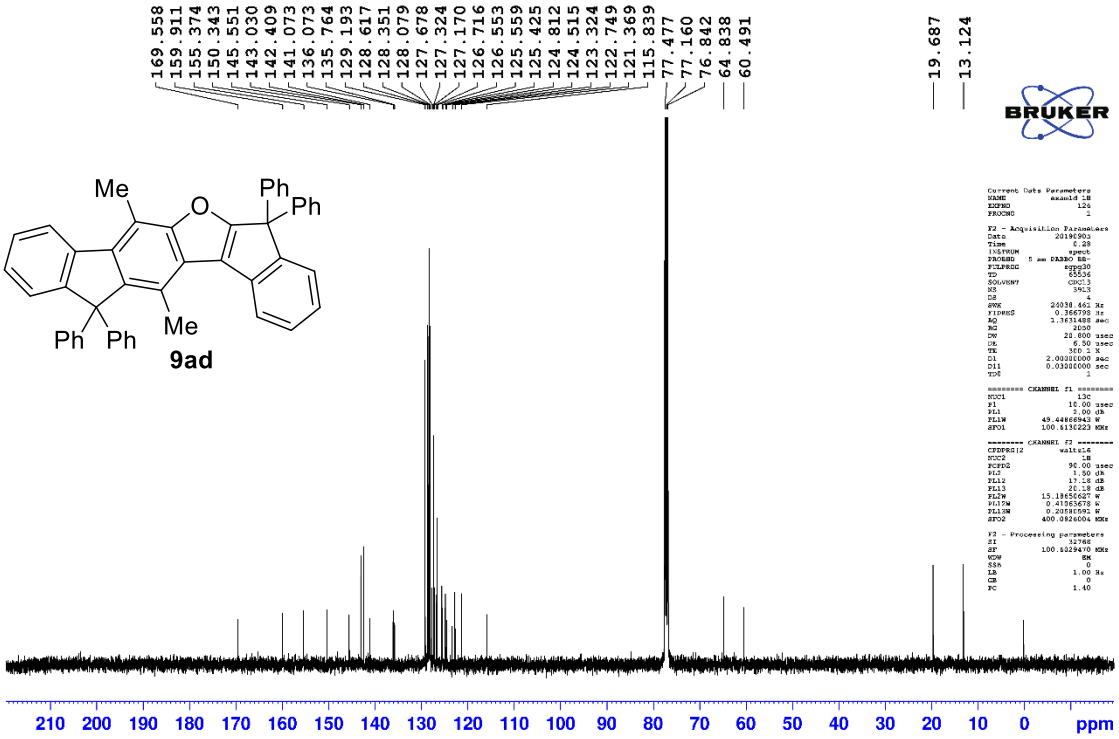
SYTK-3-Me-F



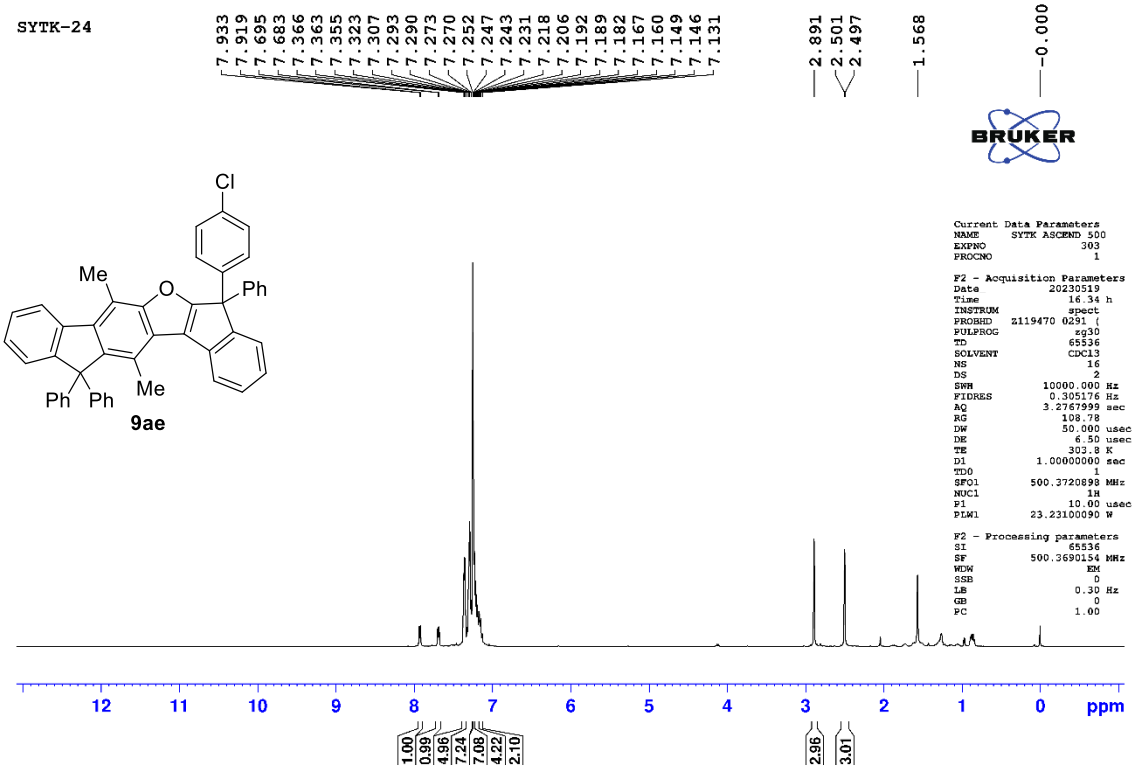

SYTK-3-Me-F
173.062
172.809
157.245
157.124
150.782
149.834
136.991
135.960
135.313
134.138
131.081
128.972
127.995
127.962
127.743
127.417
126.264
126.212
126.006
125.964
125.398
124.645
124.608
124.466
122.204
122.027
120.994
120.415
120.278
118.944
113.350
113.320
77.478
77.160
76.843
43.376
42.318
24.490
22.039
21.964
18.977
BRUKER
Me
Me
Me
+
Me
Me
Me
9ac:9ac'
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

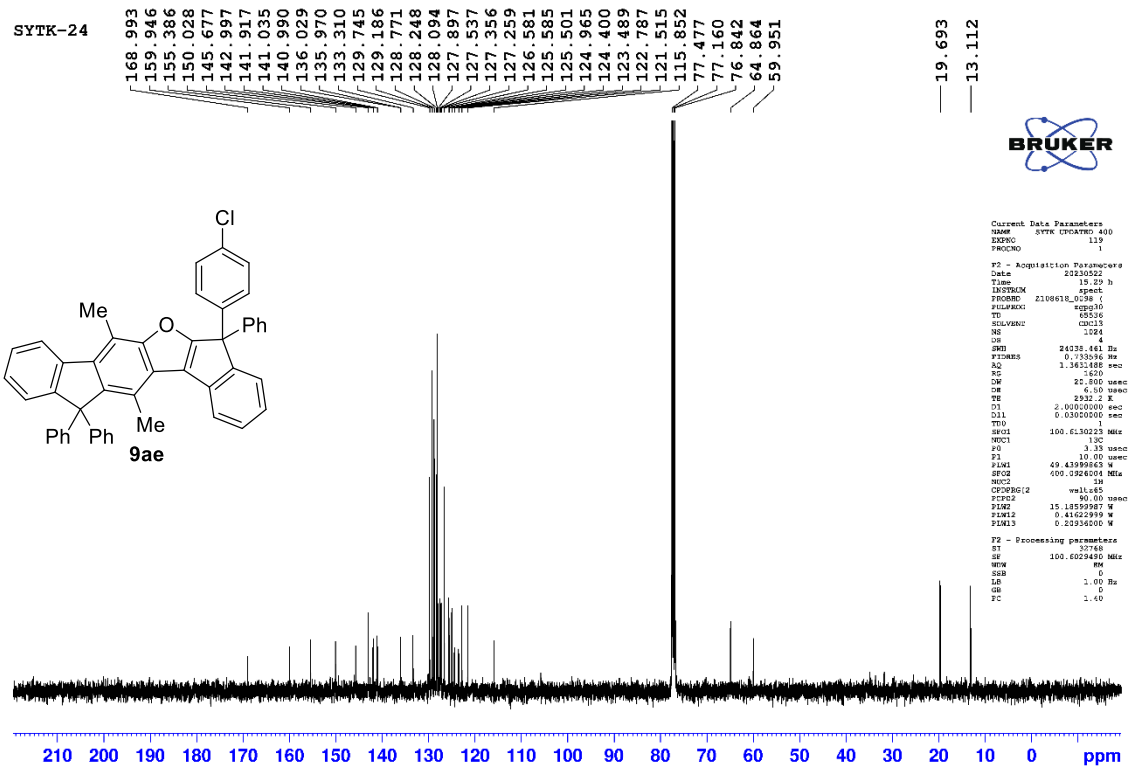

SYTK -02-CUI
7.932
7.912
7.694
7.675
7.372
7.368
7.362
7.354
7.350
7.347
7.341
7.324
7.309
7.305
7.294
7.291
7.288
7.280
7.275
7.268
7.261
7.256
7.249
7.232
7.213
7.204
7.201
7.194
7.187
7.182
7.180
7.163
7.161
7.156
7.140
7.138
2.890
2.497
1.561
0.000
BRUKER
Me
O
Ph
Ph
Ph
Ph
Me
9ad
12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.00
1.00
5.29
2.05
3.19
3.26
2.94
1.90
2.16
3.22
2.27
1.00
2.93
2.96

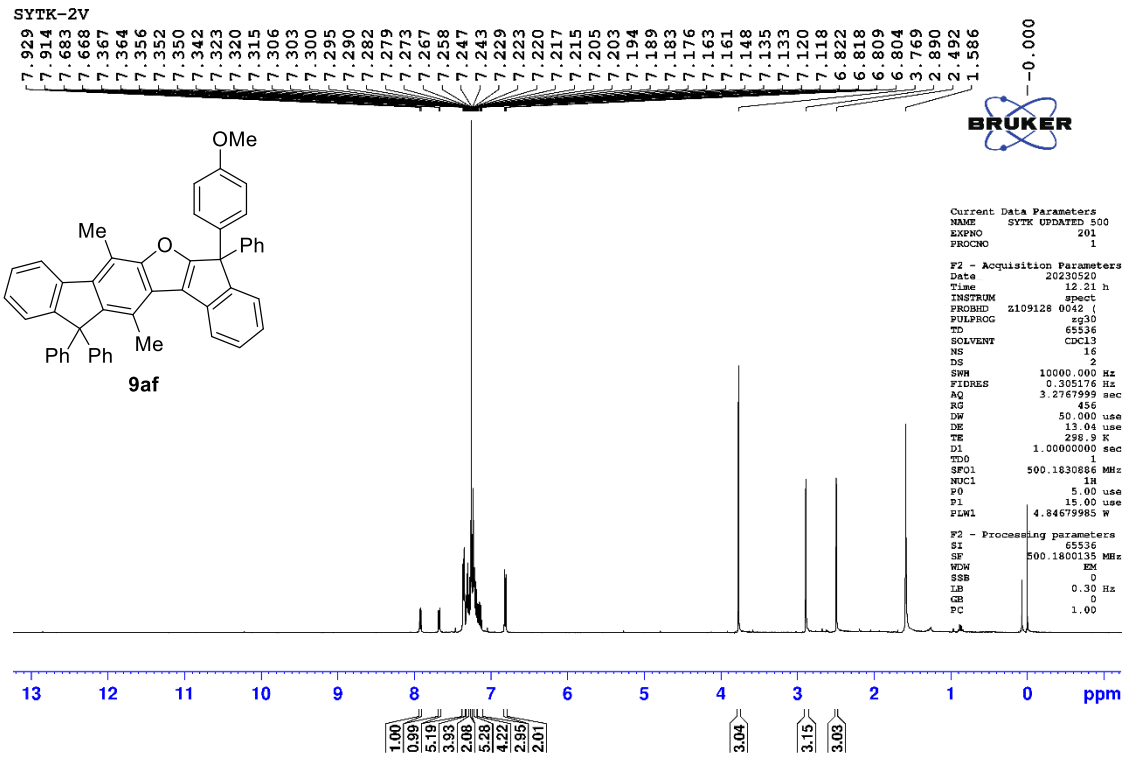
SYTK -02-CUI

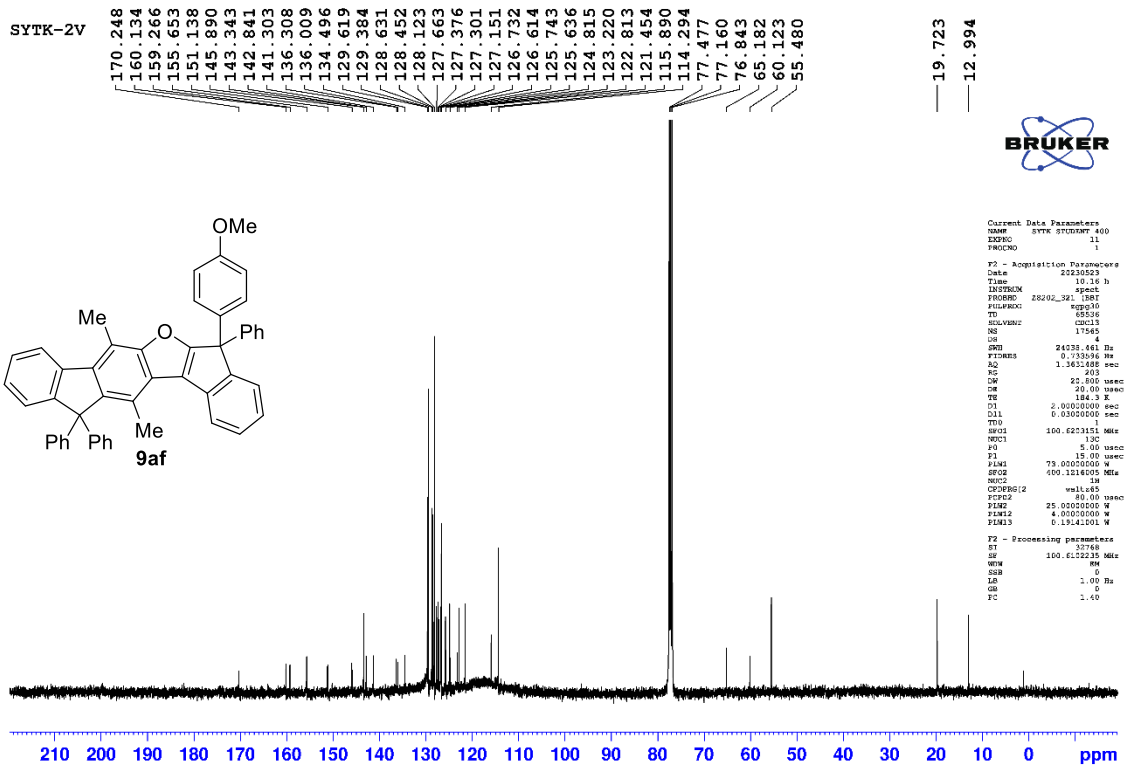


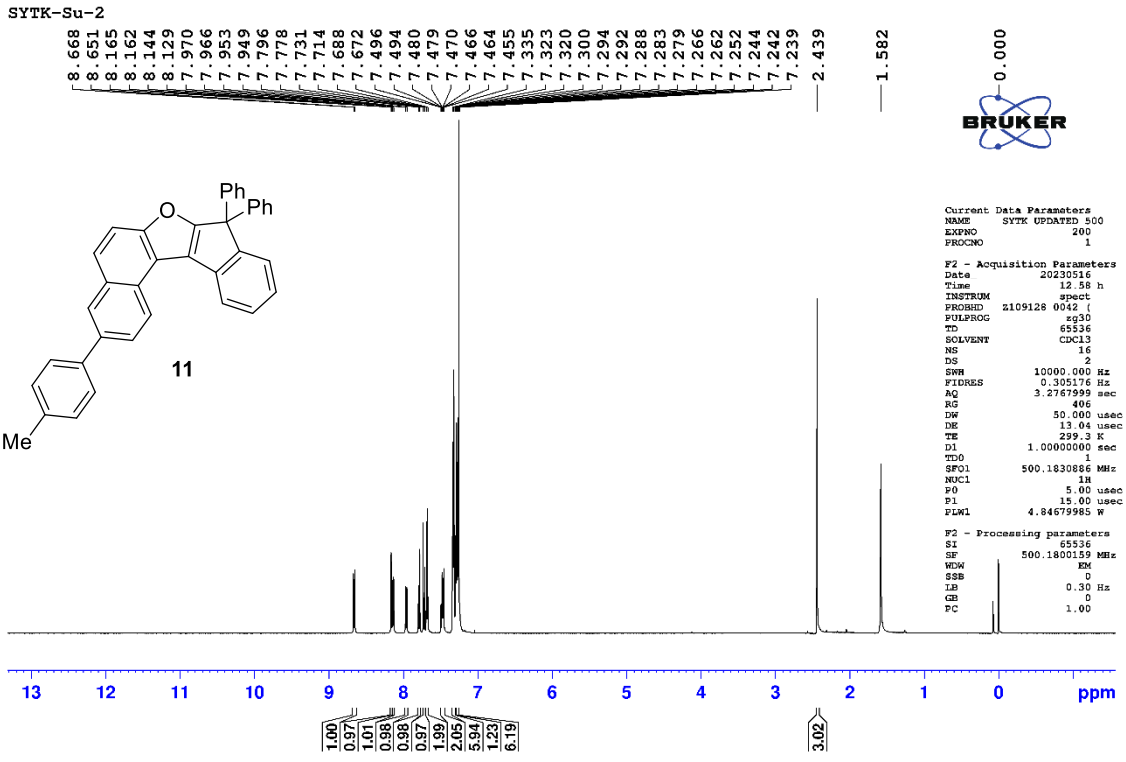
SYTK-24

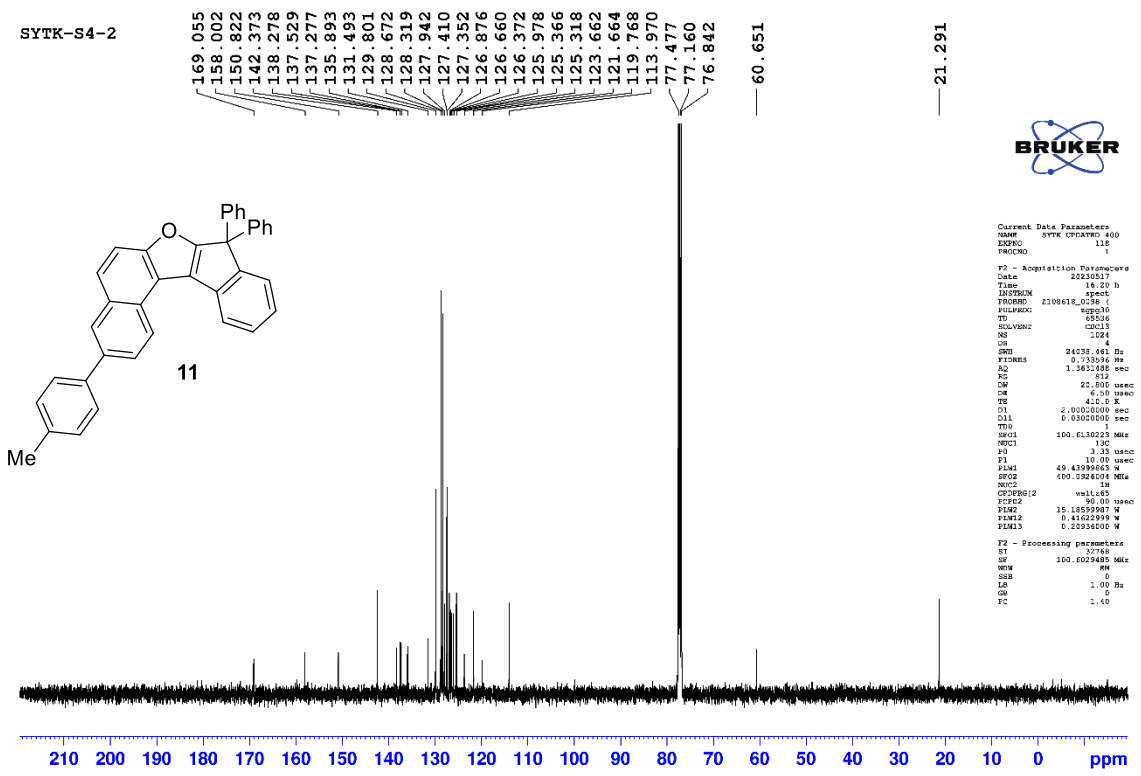



SYTK-24
168.993
159.946
155.386
150.028
145.677
142.997
141.917
141.035
140.990
136.029
135.970
133.310
129.745
129.186
128.771
128.248
128.094
127.897
127.537
127.356
127.259
126.581
125.585
125.501
124.965
124.400
123.489
122.787
121.515
115.852
77.477
77.160
76.842
64.864
59.951
19.693
13.112
Cl
Me
O
Ph
Ph
Ph
Me
9ae
BRUKER
Current Data Parameters
NAME SYTK UPDATED 400
EXPNO 119
PROCNO 1
F2 - Acquisition Parameters
Date 20230522
Time 19.29 h
INSTRUM spect
PROBHD Z108618_0298 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 1024
DS 4
SWH 24038.461 Hz
FIDRES 0.733696 Hz
AQ 1.3651488 sec
RG 1620
DW 22.800 usec
DE 6.50 usec
TE 293.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.6130223 MHz
NUC1 13C
P0 3.33 usec
P1 10.00 usec
PLW1 49.43999863 W
SFO2 400.0926004 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 90.00 usec
PLW2 15.18599987 W
PLW12 0.41622999 W
PLW13 0.29336000 W
F2 - Processing parameters
SI 32768
SF 100.6029490 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


SYTK-2V
7.929
7.914
7.683
7.668
7.367
7.364
7.356
7.352
7.350
7.342
7.323
7.320
7.315
7.306
7.303
7.300
7.295
7.290
7.282
7.279
7.273
7.267
7.258
7.247
7.243
7.229
7.223
7.220
7.217
7.215
7.205
7.203
7.194
7.189
7.183
7.176
7.163
7.161
7.148
7.135
7.133
7.120
7.118
6.822
6.818
6.809
6.804
3.769
2.890
2.492
1.586
0.000
OMe
Me
O
Ph
Ph
Ph
Me
9af
BRUKER
Current Data Parameters
NAME SYTK UPDATED 500
EXPNO 201
PROCNO 1
F2 - Acquisition Parameters
Date 20230520
Time 12.21 h
INSTRUM spect
PROBHD Z109128 0042 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 456
DW 50.000 use
DE 13.04 use
TE 298.9 K
D1 1.00000000 sec
TD0 1
SFO1 500.1830886 MHz
NUC1 1H
P0 5.00 use
P1 15.00 use
PLW1 4.84679985 W
F2 - Processing parameters
SI 65536
SF 500.1800135 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.00
0.99
5.19
3.93
2.08
5.28
4.22
2.95
2.01
3.04
3.15
3.03


SYTK-2V
170.248
160.134
159.266
155.653
151.138
145.890
143.343
142.841
141.303
136.308
136.009
134.496
129.619
129.384
128.631
128.452
128.123
127.663
127.376
127.301
127.151
126.732
126.614
125.743
125.636
124.815
123.220
122.813
121.454
115.890
114.294
77.477
77.160
76.843
65.182
60.123
55.480
19.723
12.994
BRUKER
OMe
Me
O
Ph
Ph
Ph
Me
9af
Current Data Parameters
NAME SYTK STUDENT 400
EXPNO 11
PROCNO 1
F2 - Acquisition Parameters
Date 20230523
Time 10.16 h
INSTRUM spect
PROBHD Z8202_321 (BBI
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 17565
DS 4
SWH 24038.461 Hz
FIDRES 0.733596 Hz
AQ 1.3631488 sec
RG 203
DW 22.800 usec
DE 20.00 usec
TE 184.9 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.6233151 MHz
NUC1 13C
P0 5.00 usec
P1 15.00 usec
PLW1 73.00000000 W
SFO2 400.1316005 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 80.00 usec
PLW2 25.00000000 W
PLW12 4.00000000 W
PLW13 0.19141001 W
F2 - Processing parameters
SI 32768
SF 100.6122235 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


SYTK-Su-2
8.668
8.651
8.165
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2.7. References

1. (a) Lipshutz, B. H. Five-membered heteroaromatic rings as intermediates in organic synthesis. Chem. Rev. **1986**, *86*, 795-819. (b) Wong, H.N.; Yu, P.; Yick, C.Y. The use of furans in natural product syntheses. *Pure Appl. Chem.*, **1999**, *71*, 1041-1044. (b) Srivastava, V.; Negi, A.S.; Kumar, J.K.; Faridi, U.; Sisodia, B.S.; Darokar, M.P.; Luqman, S.; Khanuja, S.P.S. Synthesis of 1-(3′, 4′, 5′-trimethoxy) phenyl naphtho [2, 1b] furan as a novel anticancer agent. *Bioorg. Med. Chem. Lett.*, **2006**, *16*, 911-914.
2. (a) Ochi, M.; Yamada, K.; Kawakami, H.; Tatsukawa, A.; Kotsuki, H.; Shibata, K. Calicogorgins A, B, and C, three bioactive sphinganine derivatives from the gorgonian Calicogorgia sp. Tetrahedron Lett. **1992**, *33*, 7531-7534. (b) Majumdar, K.C.; Chattopadhyay, S.K. Heterocycles in natural product synthesis. John Wiley & Sons. 2011. (c) Craig, R.A.; Stoltz, B.M. Polycyclic furanobutenolide-derived cembranoid and norcembranoid natural products: Biosynthetic connections and synthetic efforts. *Chem. Rev.*, **2017**,*117*,7878 -7909. (h) H. Khanam and Shamsuzzaman. Bioactive Benzofuran derivatives: A review. *Eur. J. Med. Chem.*, **2015**, *97*, 483-504. (a) Loğoğlu, E., Yilmaz, M., Katircioğlu, H., Yakut, M. and Mercan, S. Synthesis and biological activity studies of furan derivatives. *Med. chem. Res.*, **2010**. *19*, 490-497. (b) Spiteller, G. Furan fatty acids: occurrence, synthesis, and reactions. Are furan fatty acids responsible for the cardioprotective effects of a fish diet?. *Lipids*, **2005**, *40*, 755-771. (c) Cadierno, V.; Diez, J.; Gimeno, J.; Nebra, N. Ruthenium/TFA-catalyzed coupling of activated secondary propargylic alcohols with cyclic 1, 3-diones: Furan versus pyran ring formation. *J. Org. Chem.*, **2008**, *73*, 5852-5858. (g) Welsch, M.E.; Snyder, S.A.; Stockwell, B.R. Privileged scaffolds for library design and drug discovery. *Curr. Opin. Chem. Biol*., **2010,** *14*, 347-361.

3. (a) Schulte, G.; Scheuer, P.J.; McConnell, O.J. Two furanosesquiterpene marine metabolites with antifeedant properties. *Helv. Chim. Acta*, **1980**, *63*, 2159-2167. (b) Wohlfarth, C.; Efferth, T. Natural products as promising drug candidates for the treatment of hepatitis B and C. *Acta Pharmacol. Sin.*, **2008**, *30*, 25-30. (c) Ni, G.; Zhang, Q.J.; Zheng, Z.F.; Chen, R.Y.; Yu, D.Q. 2-Arylbenzofuran derivatives from Morus cathayana. *J. Nat. Prod.*, **2009**, *72*, 966-968. (d) Riviere, C.; Pawlus, A.D.; Merillon, J.M. Natural stilbenoids: distribution in the plant kingdom and chemotaxonomic interest in Vitaceae. *Nat. Prod. Rep.*, **2012**, *29*, 1317-1333. (e) Radadiya, A.;Shah, A. Bioactive benzofuran derivatives: An insight on lead developments, radioligands and advances of the last decade. *Eur. J. Med. Chem.*, **2015**, *97*, 356-376.
4. (a) Ito, J.; Takaya, Y.; Oshima, Y.; Niwa, M. New oligostilbenes having a benzofuran from Vitis vinifera 'Kyohou'. Tetrahedron, **1999**, *55*, 2529-2544. (b) Manna, K.; Agrawal, Y.K. Microwave assisted synthesis of new indophenazine 1, 3, 5-trisubstruted pyrazoline derivatives of benzofuran and their antimicrobial activity. *Bioorg. & Med. Chem. Let.*, **2009**, *19*, 2688-2692.
5. (a) Khan, M.W.; Alam, M.J.; Rashid, M.A.; Chowdhury, R. A new structural alternative in benzo [b] furans for antimicrobial activity. *Bioorg. Med. Chem.*, **2005**, *13*, 4796-4805. (b) Zanatta, N.; Alves, S.H.; Coelho, H.S.; Borchhardt, D.M.; Machado, P.; Flores, K.M.; Da Silva, F.M.; Spader, T.B.; Santurio, J.M.; Bonacorso, H.G.; Martins, M.A. Synthesis, antimicrobial activity, and QSAR studies of furan-3-carboxamides. *Bioorg. Med. Chem.*, **2007**, *15*, 1947-1958. (c) Rao, R.R.; Chaturvedi, V.; Babu, K.S.; Reddy, P.P.; Rao, V.R.S.; Sreekanth, P.; Sreedhar, A.S.; Rao, J.M. Synthesis and anticancer effects of pongamol derivatives on mitogen signaling and cell cycle kinases. *Med. Chem. Res.*, **2012**, *21*, 634-641.
6. Le Guével, R.; Oger, F.; Lecorgne, A.; Dudasova, Z.; Chevance, S.; Bondon, A.; Barath, P.; Simonneaux, G.; Salbert, G. Identification of small molecule regulators of the nuclear receptor HNF4α based on naphthofuran scaffolds. *Bioorg. Med. Chem.*, **2009**, *17*, 7021-7030.
7. (a) Xiao, L.; Chen, Z.; Qu, B.; Luo, J.; Kong, S.; Gong, Q.; Kido, J. Recent progresses on materials for electrophosphorescent organic light-emitting devices. *Adv. Mater.* **2011**, **23**, 926-952. (b) S. Beaupré, P.-L. T. Boudreault, M. Leclerc, Adv. Mater. 2010, 22, E6; c) Grimsdale, A.C.; Leok Chan, K.; Martin, R.E.; Jokisz, P.G.; Holmes, A.B. Synthesis of light-emitting conjugated polymers for applications in electroluminescent devices. *Chem. Rev.*, **2009**, *109*, 897-1091; d) Scherf, U.; List, E.J. Semiconducting polyfluorenes - towards reliable structure-property relationships. *Mater.*, **2002**, *14*, 477-487. E) Tsuji, H.; Nakamura, E. Design and functions of semiconducting fused polycyclic furans for optoelectronic applications. *Acc. Chem. Res.*, **2017**, *50*, 396-406.
8. For recent reviews of transition-metal-catalyzed C_H functionalization, see: (a) Daugulis, O.; D, H.-Q.; Shabashov, D. Palladium-and copper-catalyzed arylation of carbon-hydrogen bonds. *Acc. Chem. Res*. **2009**, *42*, 1074-1086. (b) Ackermann, L.; Vicente, R.; Kapdi, A. R. Transition-metal-catalyzed direct arylation of (hetero) arenes by C-H bond cleavage. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792-9826. (c) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. Direct C-H transformation *via* iron catalysis. *Chem. Rev.* 2011, 111, 1293-1314. (d) Lyons, T. W.; Sanford, M. S. Palladium-catalyzed ligand-directed C-H functionalization reactions. *Chem. Rev.* **2010**, *110*, 1147-1169. (e) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. Towards mild metal-catalyzed C-H bond activation. *Chem. Soc. Rev.* **2011**, *40*, 4740-4761. (f) Newhouse, T.; Baran, P.S., 2011. If C-H Bonds Could Talk: Selective C-H Bond Oxidation. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362-3374. (g) Dalton, T.; Faber, T.; Glorius, F. C-H activation: toward sustainability and applications. ACS Cent. Sci. **2021**, *7*, 245-261. (h) Babu, S.A.; Padmavathi, R.; Aggarwal, Y.; Kaur,

R.; Suwasia, S. Pd-Catalyzed C (sp^3) -H Activation by Native Directing Groups. *Handbook of CH-Functionalization*, **2022**, 1-71. (i) Liu, J., Xiao, X., Lai, Y. and Zhang, Z., 2022. Recent advances in transition metal-catalyzed heteroannulative difunctionalization of alkenes *via* CH activation for the synthesis of heterocycles. *Org. Chem. Front*. **2022**, *9*, 2256-2279.

9. For reviews of the synthesis of heterocycles *via* transition-metalcatalyzed C-H functionalization, see: (a) Tansandote, P.; Lautens, M. Thansandote, P.; Lautens, M. Construction of Nitrogen-Containing Heterocycles by C-H Bond Functionalization. *Chem. Eur. J.* **2009**, *15*, 5874-5883. (b) Zhang, M. Construction of Heterocycle Scaffolds *via* Transition Metal-Catalyzed sp2 C-H Functionalization. *Adv. Synth. Catal.* **2009**, *351*, 2243-2270. (c) Stokes, B. J.; Driver, T. G. Transition Metal-Catalyzed Formation of N-Heterocycles *via* Aryl-or Vinyl C-H Bond Amination. *Eur. J. Org. Chem.* **2011**, 4071-4088. (d) Beccalli, E. M.; Broggini, G.; Fasana, A.; Rigamonti, M. Palladium-catalyzed C-N bond formation *via* direct C-H bond functionalization. Recent developments in heterocyclic synthesis. *J. Organomet. Chem*. **2011**, *696*, 277-295. (e) Fathi, V.V.; Seyed, H.M.; Balalaie, S. Ru-Catalyzed One-Pot Synthesis of Heterocyclic Backbones. Catalysts, **2023**, *13*, 87. (f) Beckers, I.; Bugaev, A.; De Vos, D. Dual ligand approach increases functional group tolerance in the Pd-catalysed C-H arylation of N-heterocyclic pharmaceuticals. Chem. Sci. **2023**, *14*, 1176-1183. (g) Josephitis, C.M.; Nguyen, H.M.; McNally, A. Late-Stage C-H Functionalization of Azines. *Chem. Rev.* **2023**, (10.1021/acs.chemrev.2c00881).
10. (a) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. Combined C-H functionalization/C- N bond formation route to carbazoles. *J. Am. Chem. Soc.* **2005**, *127*, 14560-14561. (b) Tsang, W. C. P.; Munday, R. H.; Brasche, G.; Zheng, N.; Buchwald, S. L. A Palladium-Catalyzed Method for the Synthesis of Carbazoles *via* Tandem CH Functionalization and CN Bond Formation. *J. Org. Chem.* **2008**, *73*, 7603-7610. (c) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. Oxidative Pd (II)-catalyzed C-H bond amination to carbazole at ambient temperature. *J. Am. Chem. Soc.* **2008**, *130*, 16184-16186. (d) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. Multiple C-H Activations to Construct Biologically Active Molecules in a Process Completely Free of Organohalogen and Organometallic Components. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115-1118. (e) Youn, S. W.; Bihn, J. H.; Kim, B. S. Pd-catalyzed intramolecular oxidative C-H amination: synthesis of carbazoles. *Org. Lett.* **2011**, *13*, 3738-3741. (f) Cho, S. H.; Yoo, J.; Chang, S. Intramolecular oxidative C-N bond formation for the synthesis of carbazoles: comparison of reactivity between the copper-catalyzed and metal-free conditions. *J. Am. Chem. Soc.* **2011**, *133*, 5996-6005. (g) Liu, X.; Sheng, H.; Zhou, Y.; Song, Q. Palladium-catalyzed C-H bond activation for the assembly of N-aryl carbazoles with aromatic amines as nitrogen sources. Chem. Comm. **2020**, *56*, 1665-1668.
11. (a) Espino, C. G.; Wehn, P. M.; Chow, J.; Bois, J. D. Synthesis of 1, 3-difunctionalized amine derivatives through selective C-H bond oxidation. *J. Am. Chem. Soc.* **2001**, *123*, 6935-6936. (b) Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Che, C.-M. Intramolecular C- N bond formation reactions catalyzed by ruthenium porphyrins: amidation of sulfamate esters and aziridination of unsaturated sulfonamides. *J. Org. Chem.* **2004**, *69*, 3610-3619.
12. Hinman, A.; Bois, J. D. A stereoselective synthesis of (-)-tetrodotoxin. *J. Am. Chem. Soc.* **2003**, *125*, 11510-11511.
13. (a) Tan, Y.; Hartwig, J. F. Palladium-catalyzed amination of aromatic C-H bonds with oxime esters. *J. Am. Chem. Soc.* **2010**, *132*, 3676-3677. (b) Neumann, J.J.; Rakshit, S.; Dröge, T.; Glorius, F. Palladium-Catalyzed Amidation of Unactivated C (sp^3) H Bonds: from Anilines to Indolines. *Angew. Chem., Int. Ed.* **2009**, *48*, 6892-6895. (c) Mei, T. S.; Wang, X.; Yu, J. Q. Pd (II)-catalyzed amination of C-H bonds using single-electron or

two-electron oxidants. *J. Am. Chem. Soc.* **2009**, *131*, 10806-10807. (d) Wasa, M.; Yu, J. Q. Synthesis of β-, γ-, and δ-Lactams *via* Pd (II)-Catalyzed C-H Activation Reactions. *J. Am. Chem. Soc*. **2008**, *130*, 14058-14059.

14. Inamoto, K.; Saito, T.; Katsuno, M.; Sakamoto, T.; Hiroya, K. Palladium-catalyzed C-H activation/intramolecular amination reaction: a new route to 3-aryl/alkylindazoles. *Org. Lett*. **2007**, *9*, 2931-2934.
15. Benzimidazole: (a) Brasche, G.; Buchwald, S. L. C-H Functionalization/C-N Bond Formation: Copper-Catalyzed Synthesis of Benzimidazoles from Amidines. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932-1934. (b) Xiao, Q.; Wang, W.-H.; Liu, G.; Meng, F.-K.; Chen, J.-H.; Yang, Z.; Shi, Z.-J. Direct Imidation to Construct 1H-Benzo [d] imidazole through PdII-Catalyzed C-H Activation Promoted by Thiourea. *Chem. Eur. J.* **2009**, *15*, 7292-7296. (c) Wang, H.; Wang, Y.; Peng, C.; Zhang, J.; Zhu, Q. A direct intramolecular C-H amination reaction cocatalyzed by copper (II) and iron (III) as part of an efficient route for the synthesis of pyrido [1,-2-a] benzimidazoles from N-aryl-2-aminopyridines. *J. Am. Chem. Soc.* **2010**, *132*, 13217-13219.
16. Pyrido[1,2-a]benzimidazole: Master, K. S.; Rauws, T. R. M.; Yadav, A. K.; Herrebout,W. A.; Van der Veken, B.; Maes, B. U. W. On the importance of an acid additive in the synthesis of pyrido [1, 2-a] benzimidazoles by direct copper-catalyzed amination. *Chem. Eur. J*. **2011**, *17*, 6315-6320
17. (a) Mojet, B.L.; Eckert, J.; van Santen, R.A.; Albinati, A.; Lechner, R.E. Evidence for chemisorbed molecular hydrogen in Fe-ZSM5 from inelastic neutron scattering. *J. Am. Chem. Soc.* **2001**, *123*, 8147-8148. (b) Fraunhoffer, K. J.; Prabagaran, N.; Sirois, L. E.; White, M. C. Macrolactonization *via* hydrocarbon oxidation. *J. Am. Chem. Soc.* **2006**, *128*, 9032-9033. (c) Lee, J. M.; Chang, S. Pt-Catalyzed sp^3 C-H bond activation of o-alkyl substituted aromatic carboxylic acid derivatives for the formation of aryl lactones. *Tetrahedron Lett.* **2006**, *47*, 1375-1379. (d) Takenaka, K.; Akita, M.; Tanigaki, Y.; Takizawa, S.; Sasai, H. Enantioselective cyclization of 4-alkenoic acids *via* an oxidative allylic C-H esterification. *Org. Lett.* **2011**, *13*, 3506-3509.
18. (a) Ueda, S.; Nagasawa, H. Synthesis of 2-Arylbenzoxazoles by Copper-Catalyzed Intramolecular Oxidative C-O Coupling of Benzanilides. *Angew. Chem., Int. Ed.* **2008,** *47*, 6411-6413. (b) Ueda, S.; Nagasawa, H. Copper-catalyzed synthesis of benzoxazoles *via* a regioselective C-H functionalization/C- O bond formation under an air atmosphere. *J. Org. Chem.* **2009**, *74*, 4272-4277.
19. Wang, X.; Lu, Y.; Dai, H.-X.; Yu, J.-Q. Pd (II)-catalyzed hydroxyl-directed C-H activation/C-O cyclization: expedient construction of dihydrobenzofurans. *J. Am. Soc. Chem.* **2010**, *132*, 12203-12205.
20. (a) Uyanik, M.; Okamoto, H.; Yasui, T.; Ishihara, K. Quaternary ammonium (hypo) iodite catalysis for enantioselective oxidative cycloetherification. *Science* **2010**, *328*, 1376-1379. (b)Tang, L.; Pang, Y.; Yan, Q.; Shi, L.; Huang, J.; Du, Y.; Zhao, K. Synthesis of coumestan derivatives *via* $FeCl_3$-mediated oxidative ring closure of 4-hydroxy coumarins. *J. Org. Chem.* **2011**, *76*, 2744-2752. (c) Uyanik, M.; Suzuki, D.; Yasui, T.; Ishihara, K. In situ generated (hypo) iodite catalysts for the direct α-oxyacylation of carbonyl compounds with carboxylic acids. *Angew. Chem., Int. Ed.* **2011**, *50*, 5331-5334.
21. For selected examples, see: (a) Smrcina, M.; Polakova, J.; Vyskocil, S.; Kocovsky, P. Synthesis of enantiomerically pure binaphthyl derivatives. Mechanism of the enantioselective, oxidative coupling of naphthols and designing a catalytic cycle. *J. Org. Chem.* **1993**, *58*, 4534-4538. (b) Li, X.; Hewgley, B.; Mulrooney, C. A.; Yang, J.; Kozlowski, M. C. Enantioselective oxidative biaryl coupling reactions catalyzed by 1, 5-diazadecalin metal complexes: Efficient formation of chiral functionalized BINOL derivatives. *J. Org. Chem.* **2003**, *68*, 5500-5511.

22. Xiao, B.; Gong, T.-J.; Liu, Z.-J.; Liu, J.-H.; Luo, D.-F.; Xu, J.; Liu, L. Synthesis of dibenzofurans *via* palladium-catalyzed phenol-directed C-H activation/C-O cyclization. *J. Am. Chem. Soc.* **2011**, *133*, 9250-9253.
23. Wei, Y.; Yoshikai, N. Oxidative cyclization of 2-arylphenols to dibenzofurans under Pd (II)/peroxybenzoate catalysis. *Org. Lett.* **2011**, *13*, 5504-5507
24. Zhao, J.; Wang, Y.; He, Y.; Liu, L.; Zhu, Q. Cu-catalyzed oxidative C (sp2)-H cycloetherification of *o*-arylphenols for the preparation of dibenzofurans. *Org. Lett*, **2012**, *14*, 1078-1081.
25. (a) Cardillo, G.; Cricchio, R.; Merlini, L. Reaction of ortho alkenyl-and alkylphenols with 2, 3-dichloro-5, 6-dicyanobenzoquinone (DDQ): Syntheses of 2, 2-dialkylchromenes. *Tetrahedron* **1971**, *27*, 1875-1883. (b) Nicolaides, D.N.; Fylaktakidou, K.C.; Litinas, K.E.; Adamopoulos, S.G. The synthesis of some pyrano [2, 3-g] chromene-2, 7-diones and furo [2, 3-g] chromen-6-ones. *J. Heterocycl. Chem.* **1998**, *35*, 91-96. (c) Aslam, S.N.; Stevenson, P.C.; Phythian, S.J.; Veitch, N.C.; Hall, D.R. Synthesis of cicerfuran, an antifungal benzofuran, and some related analogues. *Tetrahedron* **2006**, *62*, 4214-4226. (d) Duan, X.F.; Zeng, J.; Zhang, Z.B.; Zi, G.F. A facile two-step synthesis of 2-arylbenzofurans based on the selective cross McMurry couplings. *J. Org. Chem.* **2007**, *72*, 10283-10286.
26. Lattanzi, A.; Senatore, A.; Massa, A.; Scettri, A. Novel highly regioselective VO (acac) 2/TBHP mediated oxidation of o-alkenyl phenols to *o*-hydroxybenzyl ketones. *J. Org. Chem.* **2003**, *68*, 3691-3694
27. Yang, D.; Zhu, Y.; Yang, N.; Jiang, Q.; Liu, R. One-Step Synthesis of Substituted Benzofurans from ortho-Alkenylphenols *via* Palladium-Catalyzed C-H Functionalization. *Adv. Synth. Catal.* **2016**, *358*, 1731-1735
28. Zhang, M. Copper-catalyzed/mediated aromatic C-H bond functionalization. *Appl. Organometal. Chem.* **2010**, *24*, 269-284.
29. (a) Yaragorla, S.; Khan, T. An unexpected thermal-ring-rearrangement of benzochromenes to inden-3-yl-naphthols with *p* TsOH. *Org. & Biomol. Chem.* **2018**, *16*, 7920-7925. (b) Khan, T.; Rajesh, P.; Praveen, D.; Jose, K.J.; Yaragorla, S. Brønsted acid promoted Thermal-Ring-Rearrangement of Fluorenopyrans to 2-(1H-inden-3-yl)-9H-fluoren-3-ols bearing two all-carbon-quaternary centres. *Eur. J. Org. Chem*. **2020**, 2199-2209.
30. Kamei, T.; Uryu, M., Shimada, T. Cu-Catalyzed Aerobic Oxidative C-H/C-O Cyclization of 2,2′-Binaphthols: Practical Synthesis of PXX Derivatives. *Org. Lett*. **2017**, *19*, 2714-2717.
31. Yaragorla, S.; Dada, R.; Bag, D. An Expeditious Benzannulation Reaction of Indol-3-yl-but-3-yn-2-ols to Substituted 2-Iodocarbazoles *via* Domino 5-*endo* Spirocyclization/ Selective Vinyl Shift and Aromatization. *Eur. J. Org. Chem.* **2019**, 6983-6988.

Chapter-3

KO^tBu Promoted Oxidative Cleavage of C_{sp3}-C_{sp2} and C_{sp3}-H bonds

J. Org. Chem., **2023**, *88*, 2103-2112.

3.1. Introduction

Carbon-carbon bonds are core components of synthetic chemistry, and it is the most prevalent and fundamental bond existing in organic compounds. For the synthesis of new organic frameworks, the formation and cleavage of such linkages are essential. C-C bond cleavages are very common in the oil industry for breakdown of the hydrocarbons, and it is also a main aspect in the metabolism of carbohydrates. The cleavage of the C-C bonds remains a challenging goal regardless of the tremendous study that has been done on the construction of carbon-carbon bonds. The inertness of the C-C bond makes it difficult to break, despite reports on the cleavage of C-C single, double, and triple bonds. The disconnection approach for the construction of a new C-C is challenging. Due to the thermodynamic stability of C-C bonds, the viable protocols that must be taken into consideration are the involvement of reactive intermediates and starting materials. For the functionalization of C-C bonds, scientists have created several catalytic systems. Among these, transition-metal catalysts have demonstrated remarkable efficacy in carrying out a variety of intriguing transformations or conversions *via* C-C single, double, and triple bond cleavage. There are numerous applications of C-C bond oxidative cleavage, because of the wide spread of these covalent bonds in organic compounds.[1]

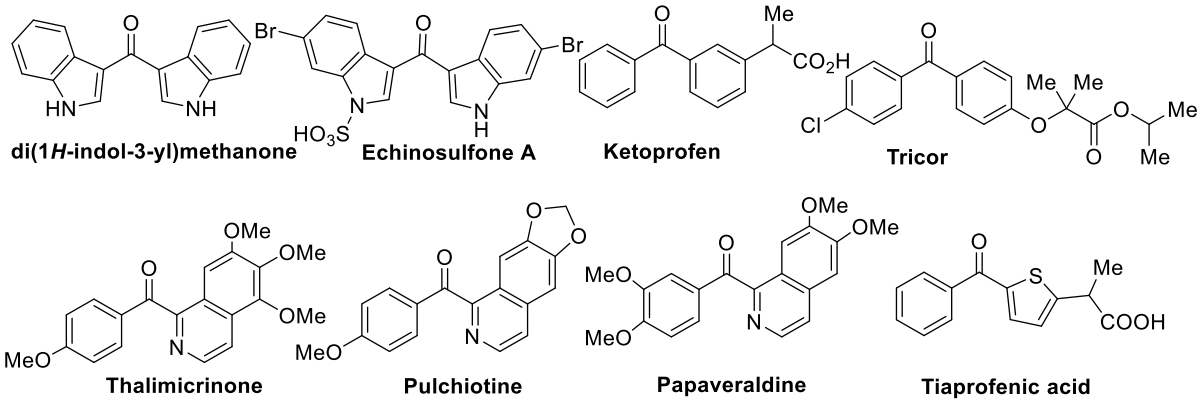


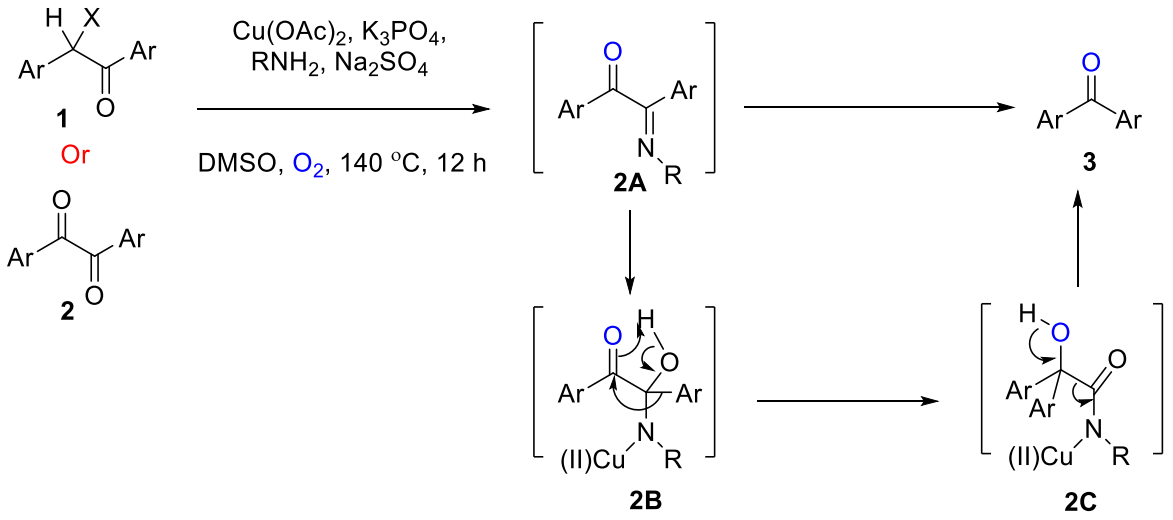
Figure 1. *Representative examples of natural and pharmaceutical diaryl ketones*

In industrial and synthetic organic chemistry, functional group transformations are crucial processes. Since ketone and their derivatives often serve as building blocks and precursors for the synthesis of medicines, physiologically active compounds, polymers and natural products (Figure 1),[2] in recent years the healthcare industry has been fascinated by the oxidation processes that are simultaneously economical yet sustainable and environmentally advantageous.[3] Due to atom economy, C_{sp3}-H oxidation has become one of the more prevalent methods for oxidizing diaryl ketones among the existing oxidation techniques.[3-5] However, the majority of them demand either transition metal catalysts[6] or excessive employment of chemical oxidants such as oxone,[7] peroxides,[8] and PhIO;[9] which must be addressed and resolved. On the other hand, cleavage of C(CO)-C bond under aerobic conditions is used to produce acids,[10] aldehydes, amides,[11] esters,[12] α-keto amides, and α-ketoesters also demands transition metals.[13] Transition metal-catalyzed aerobic oxidation of

C(CO)-C is well documented, which includes Cu, Fe, Mn, Au, Ru, Rh, etc. In addition, several promoters or base-catalyzed transition metal-free strategies have been established in the literature.

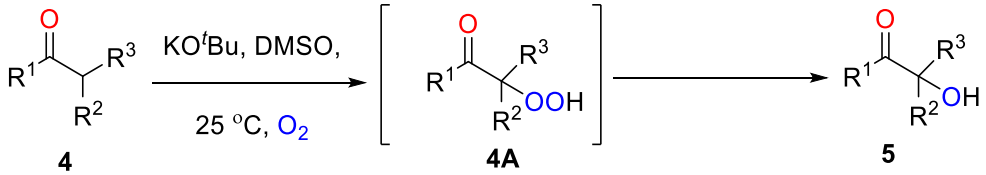
3.2. Literature Reports

Synthesis of diaryl ketones from C(CO)-C *via* C-C bond cleavage or C-H bond oxidation is limited. Maiti and co-workers in 2014 disclosed a Cu-catalyzed procedure for the construction of diaryl ketone **3** (Ar-CO-Ar') by benzylic CH_2, CO, and CXR groups from Ar-CO-CXR-Ar' **1** or benzil derivative **2** which in turn can be synthesized from compound **1**. [14] The transformation creates direct bonding between β-C and carbonyl carbon by elimination of α-C atom and maintaining the bond connectivity intact with the involvement of intermediates **2A**, **2B**, and **2C**.



Scheme 1. *Copper catalyzed C-C bond cleavage*

In addition to serving as a non-nucleophilic base, KO^{t}Bu has emerged as a preferred reagent for oxidation and electron transfer processes.[15] In a few instances, it has been investigated as an environmentally conscious and transition metal-free oxidizing reagent due to its relatively inexpensive nature, easy availability, and ease of handling.[15-17] M. B. Chaudhari et al. reported hydroxylation of α-C(sp^3)-H carbon of compound **4** (ketones and amides) with KO^{t}Bu/DMSO;[16] and air as oxidant at room temperature.

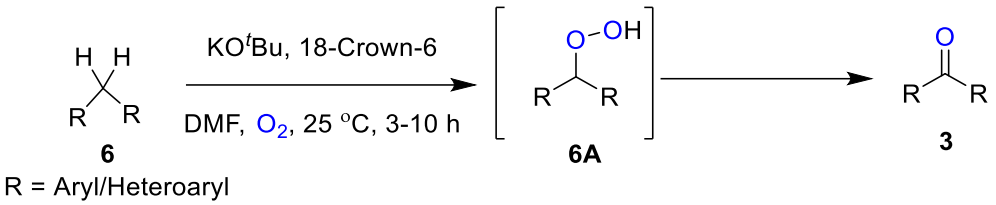


Scheme 2. *KO^{t}Bu catalyzed hydroxylation of carbonyl*

However, this approach does not function with alkyl replacements, rather it works best with the cyclic carbonyls with benzylic substitutions at the *α*-position. Base-mediated deprotonation of **4** generates the enolate ion, which in reaction with O_2 gives a superoxide ion

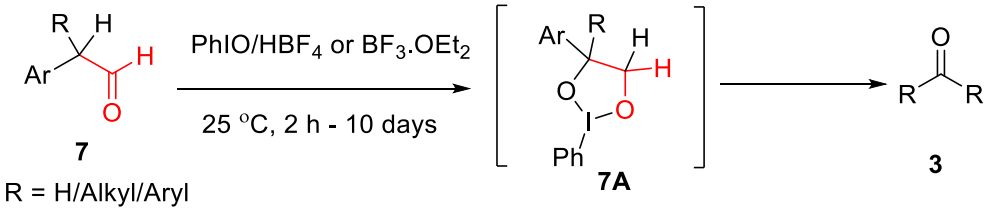
that abstracts a proton from compound **4** to form the intermediate **4A**. The intermediate **4A** is subsequently dissociated by the *in-situ* generated enolate to produce **5**.

Direct benzylic oxidation was reported by Wang et al. using KO^{t}Bu/18-crown-6, O_2 in DMF for the synthesis of diaryl or diheteroaryl ketone **3**.[17a] KO^{t}Bu acts as a promoter, and the reaction proceeds with the use of oxygen as oxidant leading to the formation of hyperoxide intermediate **6A**.



Scheme 3 . *KO^{t}Bu catalyzed direct benzylic oxidation*

C1 elimination from the aldehydic group **7** by oxidative cleavage to give aldehyde or ketone **3** with the use of combined reagent iodosylbenzene and HBF_4 was developed by A. Plattner in the year 2012. The iodosylbenzene attacks compound **7** and forms a five-membered cyclic intermediate **7A**, which after rearrangement generates the product **3**.[17b]



Scheme 4. *Oxidative cleavage of aldehydes*

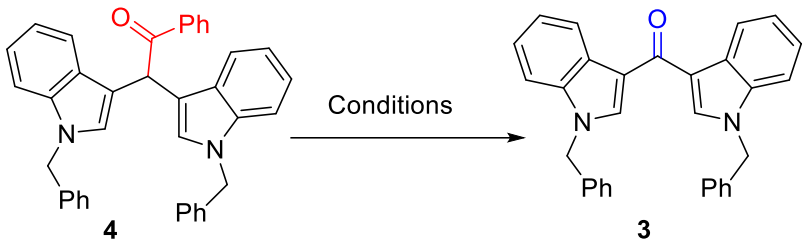
3.3. Results and Discussion

3.3.1. Optimization of the Reaction Conditions:

To gain additional insight into the impact of the base on α-C(sp3) hydrogen of bis-aryl phenylethanone, we subjected 2,2-bis(1-benzyl-1H-indol-3-yl)-1-phenylethan-1-one **4a** with KO^{t}Bu (Table 1) in THF under nitrogen atmosphere at room temperature, progressive production of bis-indolyl ketone **3a** was observed within 2 hours in 76% yield. The nitrogen balloon has been used to prevent the base from being quenched by moisture, and the oxidation occurs with the oxygen present in the reaction flask. As the reaction performed by just capping the reaction tube in the absence of nitrogen resulted in a near quantitative yield of product. NMR, mass, IR, and single crystal X-ray data (CCDC No. 2189305) confirm the structure of **3a** unambiguously. Inspired by the outcome, we concentrated on enhancing the reaction yield by increasing the stoichiometry of KO^{t}Bu and concluded that 1.2 equiv. of KO^{t}Bu is ideal for this oxidative cleavage (entries 2&3). Both lowering and raising the reaction temperature were inappropriate for the conversion (entries 4&5). No improvement in yield was observed by using 18-Crown-6 (entry 6). Solvents like DMF, DMSO, and CH_3CN

were not found suitable (entries 7&8), whereas 95% of **3a** was formed in toluene (entry 9). The reaction carried out in a closed flask without nitrogen provided a quantitative yield of product **3a** in 20 minutes (entry 10), and a trace amount of product was formed in a degassing condition (entry 11). According to these observations, the aerial oxygen present in the reaction flask was sufficient to carry out this oxidative cleavage reaction. The presence of an O_2 balloon led to the formation of product **3a** in quantitative yield within 20 minutes, but a further continuation of the reaction resulted in the oxidation of N-benzylic protons of **3a**, hence slightly lesser yield of **3a** was observed (entry 12). Other bases such as K_2CO_3, DBU, DABCO, and NaH were not suitable for this conversion (entries 13-16). Peroxide reagents such as H_2O_2 or TBHP were not found to be suitable for oxidation (entries 17&18).

Table 1. Optimization of Reaction Conditions[a]



4 **3**

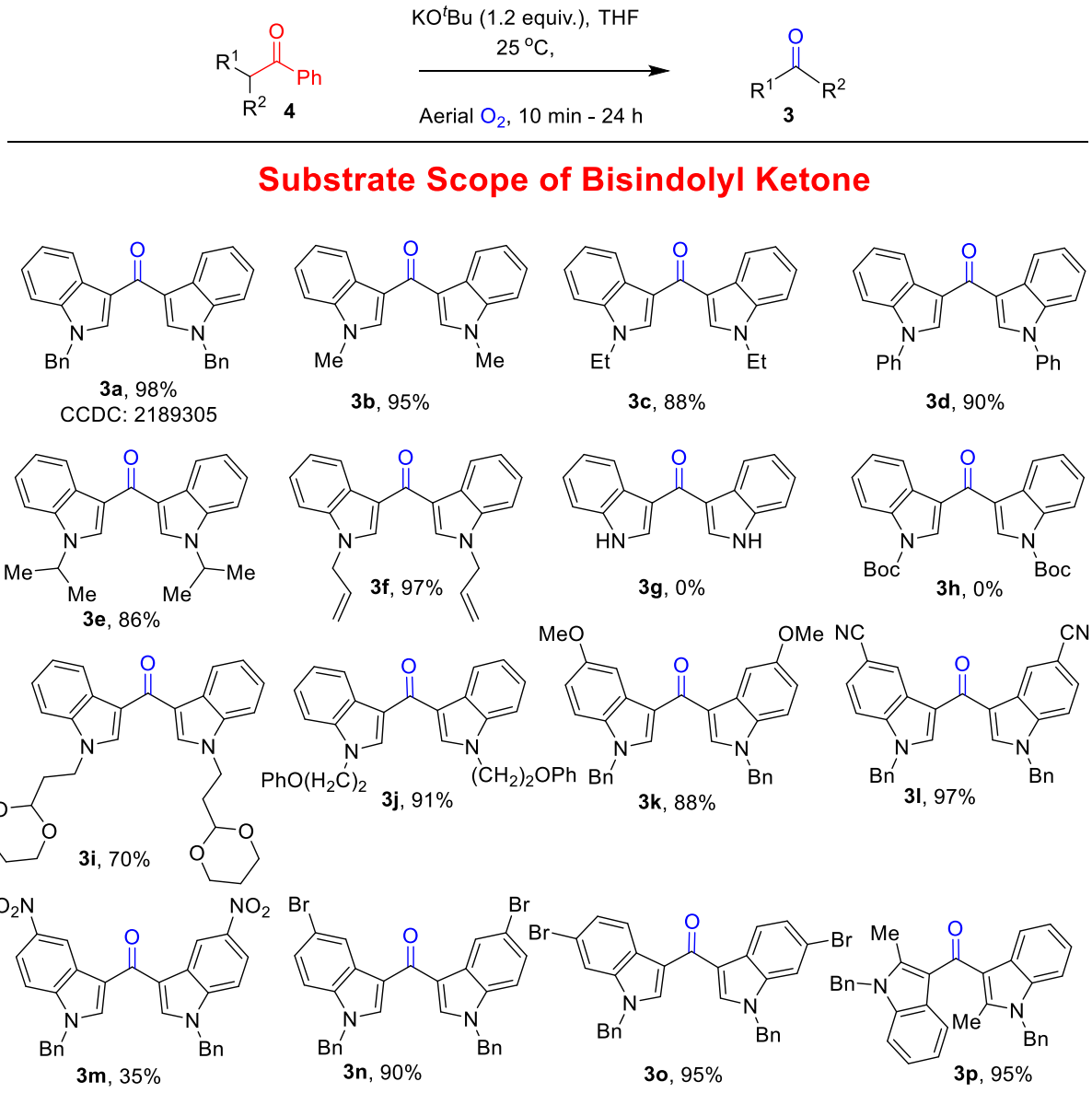
S.No.	Reaction conditions	Yield (%)[b]
1.	KO^{t}Bu (1 equiv.), THF, rt, 2 h	76
2.	KO^{t}Bu (1.2 equiv.), THF, rt, 20 min	81
3.	KO^{t}Bu (1.5 equiv.), THF, rt, 20 min	79
4.	KO^{t}Bu (1.2 equiv.), THF, 0 ^{o}C, 5 h	72
5.	KO^{t}Bu (1.2 equiv.), THF, 60 ^{o}C, 20 min	62
6.	KO^{t}Bu (1.2 equiv.), 18-Crown-6, THF, rt, 1 h	60
7.	KO^{t}Bu (1.2 equiv.), DMSO, rt, 2 h	40
8.	KO^{t}Bu (1.2 equiv.), CH_3CN, rt, 2 h	35
9.	KO^{t}Bu (1.2 equiv.), Toluene, rt, 2 h	95
10.[a]	KO^{t}Bu (1.2 equiv.), THF, rt, closed vessel, 20 min	98
11.	KO^{t}Bu (1.2 equiv.), THF, rt, degas, 24 h	trace
12.	KO^{t}Bu (1.2 equiv.), THF, rt, O_2, 2 h	93
13.	K_2CO_3 (1.2 equiv.), THF, rt, 24 h	nr
14.	DBU (1.2 equiv.), THF, rt, 24 h	05
15.	DABCO (1.2 equiv.), THF, rt, 24 h	05

16.	NaH (1.2 equiv.), THF, rt, 1 h	40
17.	H_2O_2 (1.2 equiv.), THF, rt, 24 h	nr
18.	TBHP (1.2 equiv.), THF, rt, 24 h	nr

[a] all the reactions were carried out with **1a** (100 mg, 0.1884 mmol), at rt (25°C) under specified conditions. Oil bath temperatures were mentioned. [b]Isolated yields. [c]Optimum condition.

3.3.2. Scope of the Reaction

After determining the ideal reaction parameters (entry 10, Table 1), we began examining the extent of the oxidative protocol. This oxidative transformation smoothly converted bisindolyl benzoyl methanes to the respective di(3-indolyl) methanone in substantial amounts.



Scheme 5. *Scope of bisindolyl ketone*

This oxidative protocol allowed a variety of N-substituted bisindolyl benzoyl methanes like benzyl, methyl, ethyl, phenyl, isopropyl, and allyl to convert into the corresponding bisindolyl methanone (**3a**-**3f**). However, N-H and N-Boc substituted indoles did not equip the desire products.

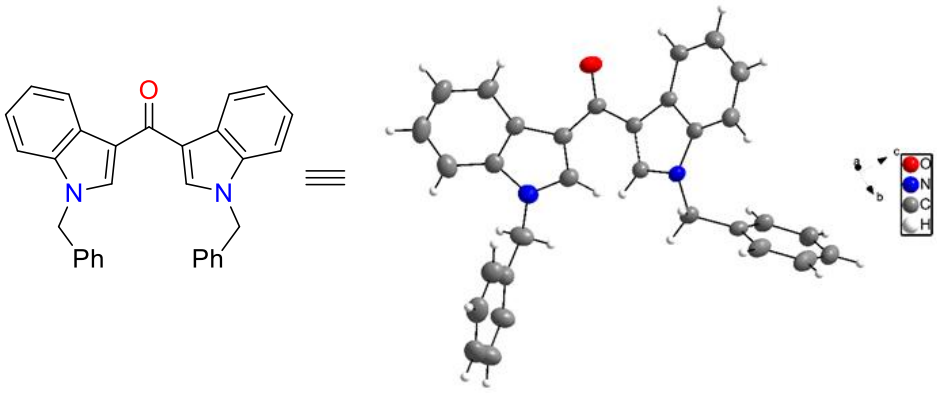


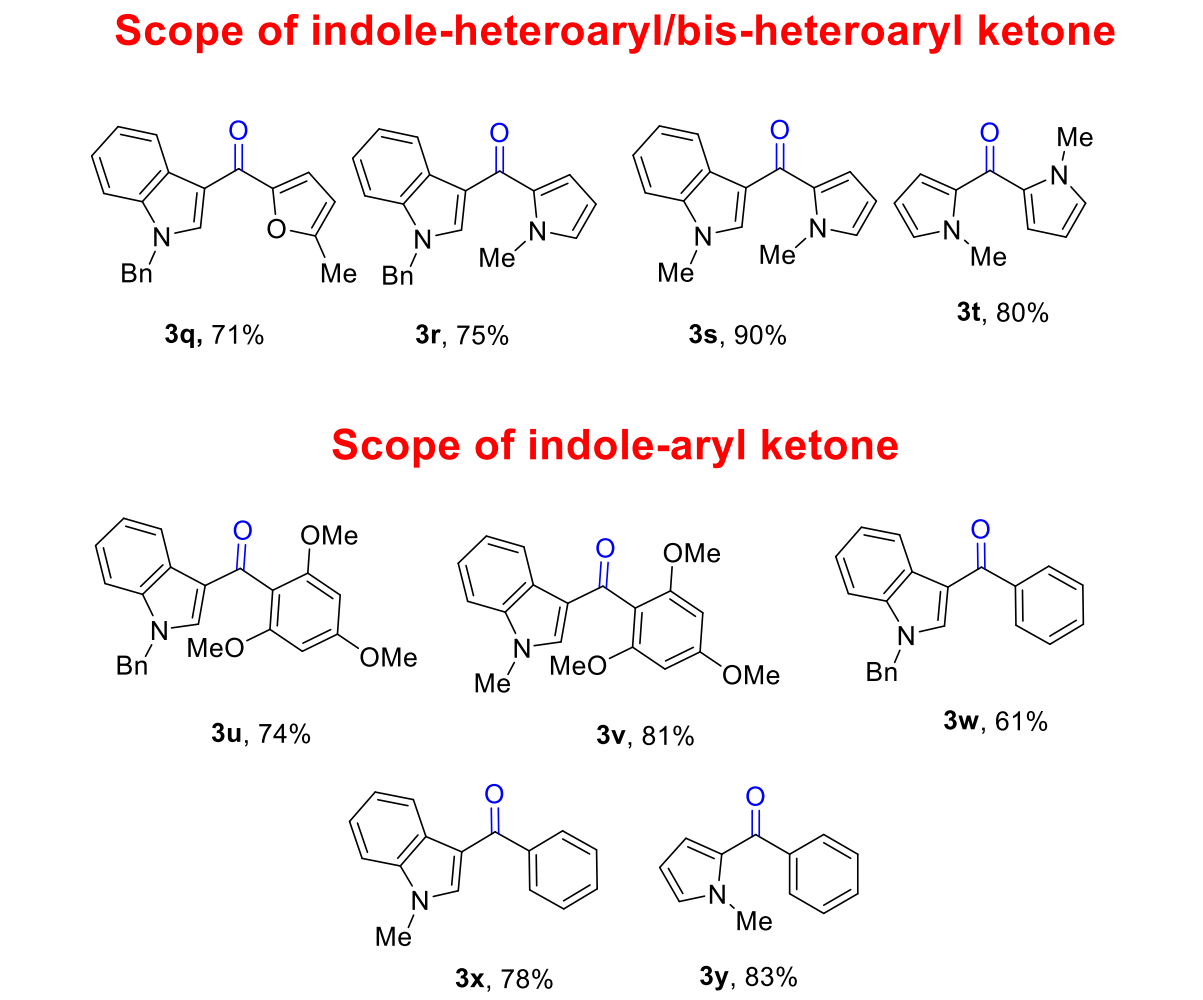
Figure 1. *Single Crystal XRD of* ***3a***

Bisindolyl benzoyl methanes such as 1-(2-(1,3-dioxan-2-yl)ethyl)-1H-indole **4i** and 1-(2-phenoxyethyl)-1H-indole **4j** also tolerated the optimized condition to produce corresponding bisindolyl ketone **3i** and **3j**. Then, we investigated the impact of substitutions on indole, for which we took 5-substituted N-benzyl indoles with OMe, CN, NO_2, and Br. All of them tolerated the reaction condition to furnish the ketones (**3k**-**3n**), in the case of NO_2 substituted indole lesser yield was observed. The compound **3o** C6 of N-benzylated indole was substituted with bromine. Further investigated the reactivity of C2-substituted bisindolyl phenylethane-1-one, which provided the product **3p** in 95% yield.

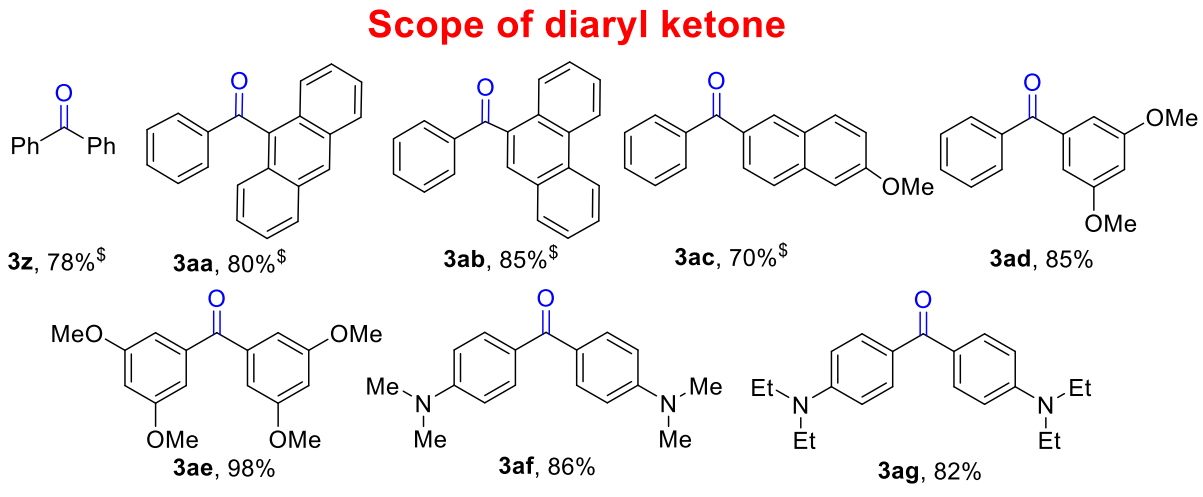
To enhance the use of the oxidative technique, we subsequently examined other typical compounds having benzylic C_{sp3}-H bonds and synthesized unsymmetrical bisheteroaryl and ary-heteroaryl ketones in excellent yields. In this context, we synthesized **3q** (1-benyl-1H-indol-3-yl)-(5-methylfuran-2-yl)methanone containing indole and furan. We also synthesized **3r** and **3s** from this protocol having indole and pyrrole substituent. Indole and aryl substituted benzoyl methanes also tolerated the optimized condition to produce corresponding methanones (**3u**, **3v**, **3w**, and **3x**). Under optimal conditions, it was possible to successfully synthesize pyrrolo-phenyl methanone **3y** and symmetrical bispyrrolyl ketone **3t** in excellent yield.

Following the successful synthesis of bis heteroaryl and aryl-heteroaryl ketones in both symmetrical and unsymmetrical forms, we then started to investigate the scope of oxidation to produce diaryl ketones. Under the optimized conditions, 1,2,2-triphenylethan-1-one was oxidized to benzophenone in 65% yield after 12 hours. Further attempts to enhance the yield of 3z were successful by switching the solvent from THF to toluene, 78% of the product was formed. It was observed that substrate with electron-rich substituent tolerated the optimized condition (THF as solvent) to produce diaryl ketones, whereas for others toluene was required as a solvent to get maximum yields. The use of KO^{t}Bu (1.2 equiv.) in toluene at room temperature produced compounds **3aa**-**3ac** in comparable quantities, however, electron-

rich symmetrical diaryl ketones **3ad**-**3ag** were synthesized in excellent yields in THF. It is worth noting that compound **3af** is a fundamental precursor for an organic dye known as crystal violet.[18]



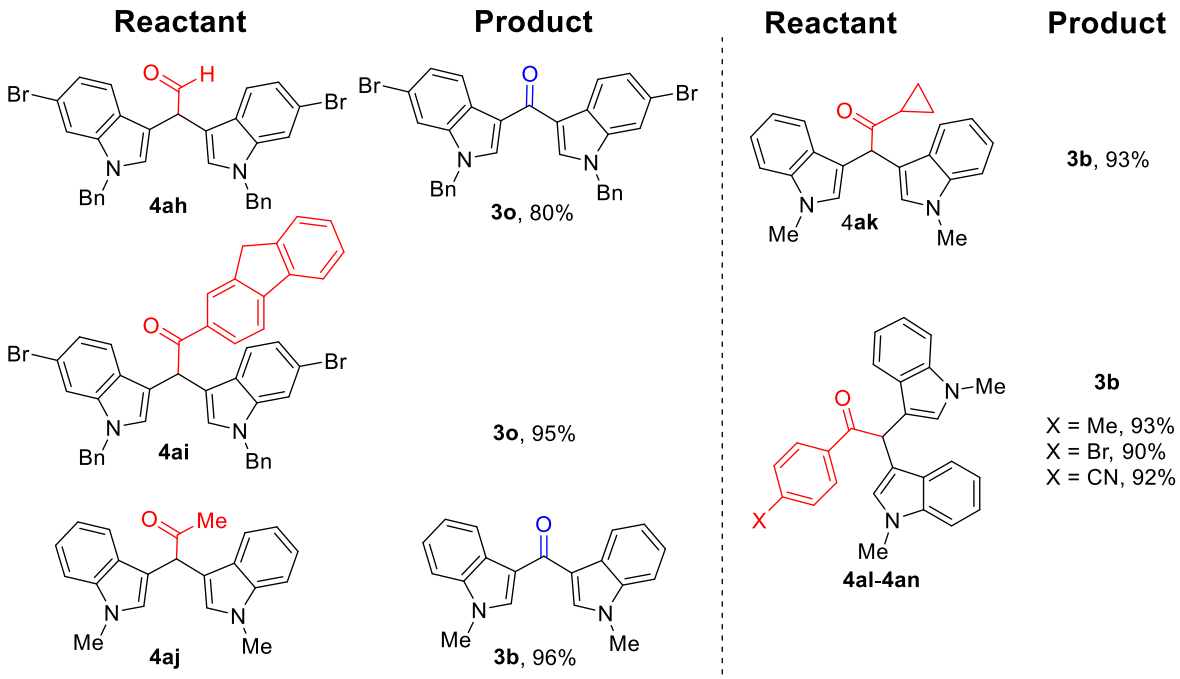
Scheme 6. *Scope of Indole-Aryl/Heteroaryl ketone*



Scheme 7. *Scope of Diaryl ketone*

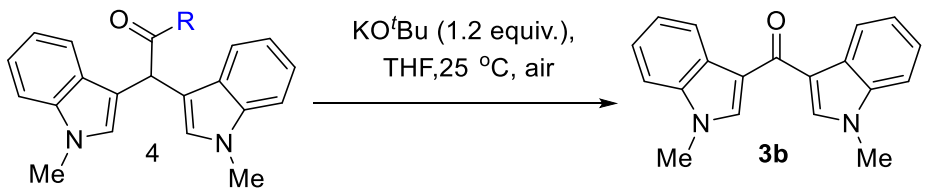
We also investigated whether other types of ketones such as those with aldehyde, cyclopropyl, 2-fluorenyl, methyl, and aryl substitution (**4ah**-**4an**), will undergo the transformation and found out that all these ketones underwent oxidation to deliver the desired bisindolyl ketones in excellent yields.

When Me, Br, and CN were substituted into the aryl group of the bisindolyl aryl ketone, they all tolerated the optimal conditions very well and produced good yields of bisindolyl ketone **3b** with a difference in reaction time. To get more insight into the effect of the substituted aryl and alkyl group on the rate of oxidative cleavage, reactions were carried out with various substrates, and the reaction completion time is summarized in Table 2.



Scheme 8. *Scope of Bisindolyl methanone*

Table 2



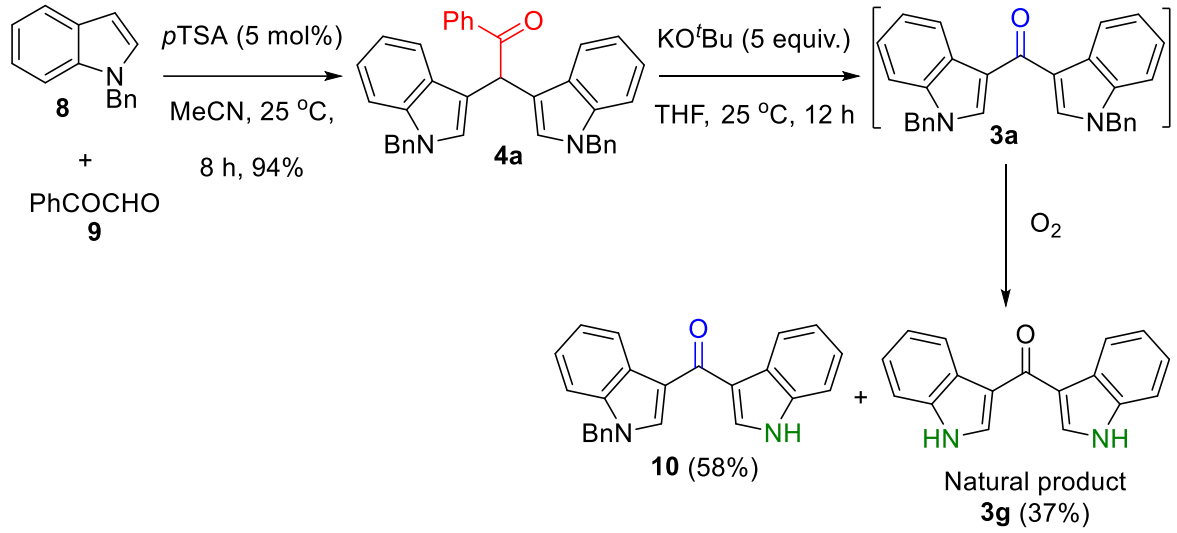
R	Me	cyclopropyl	Ph	4-Me-Ph	4-Br-Ph	4-CN-Ph
Time in minutes	80	30	20	07	12	40

The comparison data shows that alkyl groups were slower in reactivity when compared to the aryl groups. Consistent effects of electronic factors were seen in the case of substituted aryl

groups, the donating group accelerated the reaction whereas the withdrawing group took a bit longer time for the conversion.

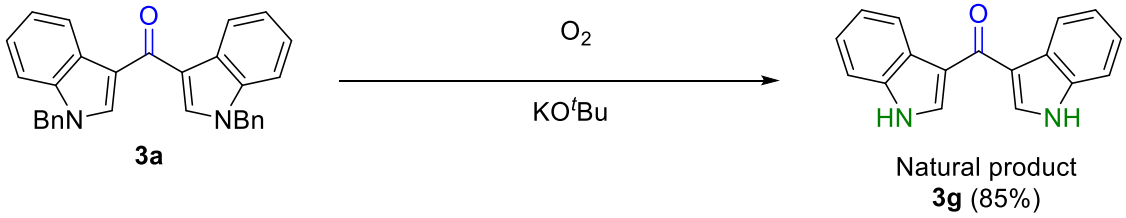
3.3.3. Natural Product Synthesis:

A natural product Di(1H-indol-3-yl)methanone[19] **3g** a precursor for an anti-breast cancer drug Arudine[20] and other natural products was been synthesized to show the potential of the protocol. An established procedure was used to prepare **4a** by the treatment of phenylglyoxal with N-benzylated indole in an acid medium.[21] When **4a** was treated with an excess of KO^{t}Bu in THF yielded **3a** initially, further continuing the reaction under O_2 atmosphere led to the formation of natural product di(1H-indol-30yl)methanone **3g** in 37% yield along with mono N-benzyl derivative **10** (58%) in the duration of 12 hours (Scheme 9).



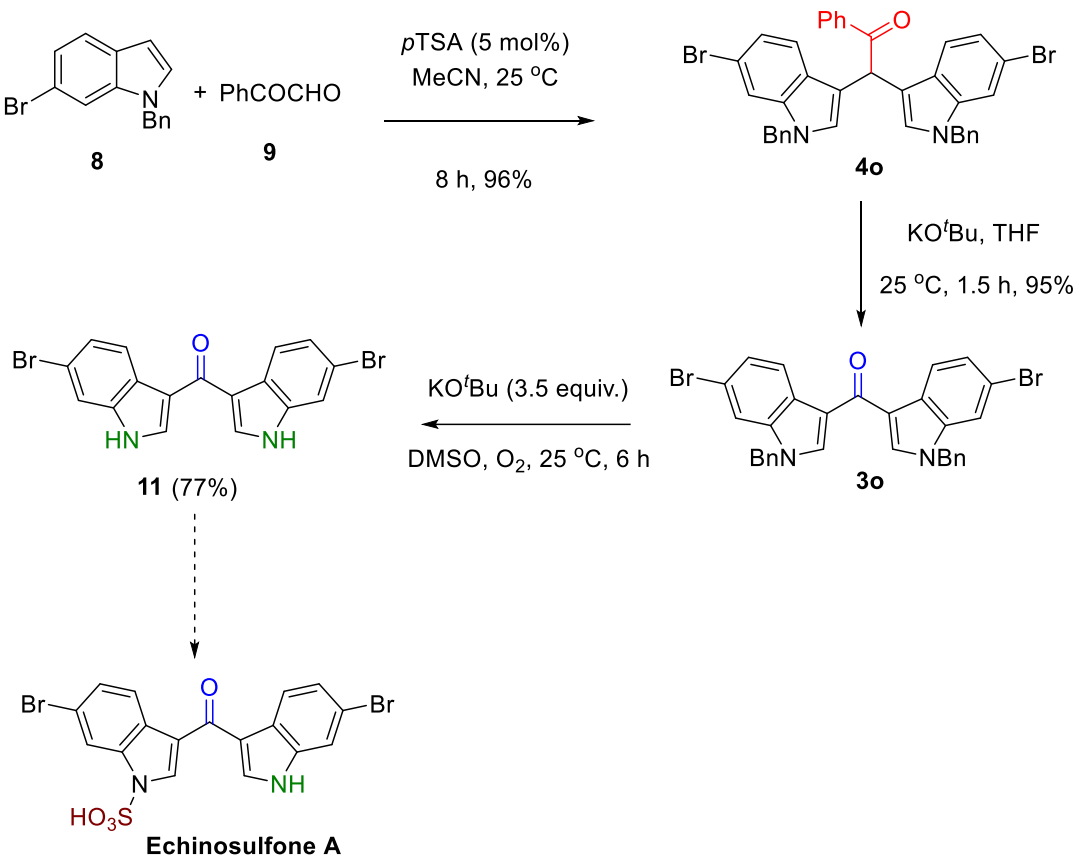
Scheme 9. *One-pot synthesis of natural product **3g***

However, when **3a** was directly subjected to the debenzylation process with KO^{t}Bu in DMSO at room temperature under O_2 atmosphere gave 83% of the natural product **3g** in 5 hours (Scheme 10).[22]



Scheme 10. *Debenzylation for the synthesis of **3g***

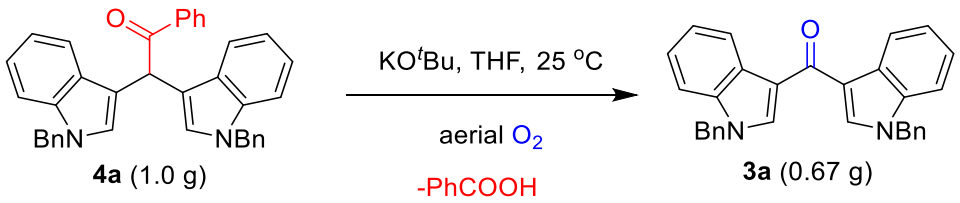
Following this, we have outlined the formal synthesis of Echinosulfone A,[23] from **4o**, which was again synthesized by treating 6-bromo-N-benzyl indole with phenyl glyoxal under acidic medium and then subjected to oxidation for the synthesis of **3o**. The debenzylated product **11** was synthesized in 77% yield by the oxidative debenzylation of **3o**, which can be converted to Echinosulphone A by following a reported method of N-sulfonation.[23]



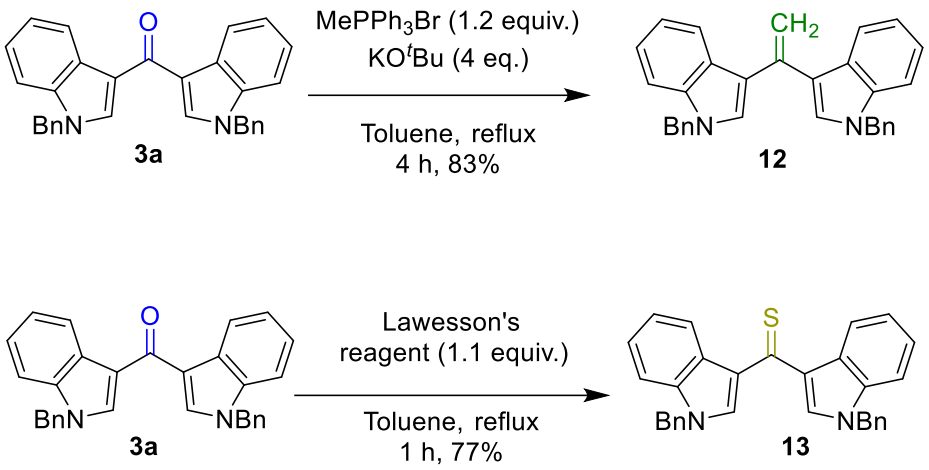
Scheme 11. *Formal Synthesis of Echinosulphone A*

3.3.4. Gram Scale Synthesis and Synthetic Transformations:

The scalability and ease of the process were demonstrated by performing a gram-scale reaction for the synthesis of ketone **3a** (Scheme 12). The synthesized compound **3a** was then used to show the synthetic utility. The compound **3a** when subjected to the C1-Wittig olefination produced alkene **12** in 83% yield, additionally, **3a** also showed excellent reactivity when treated with Lawesson's reagent and gave rise to corresponding thione **13** in 77% yield (Scheme 13).



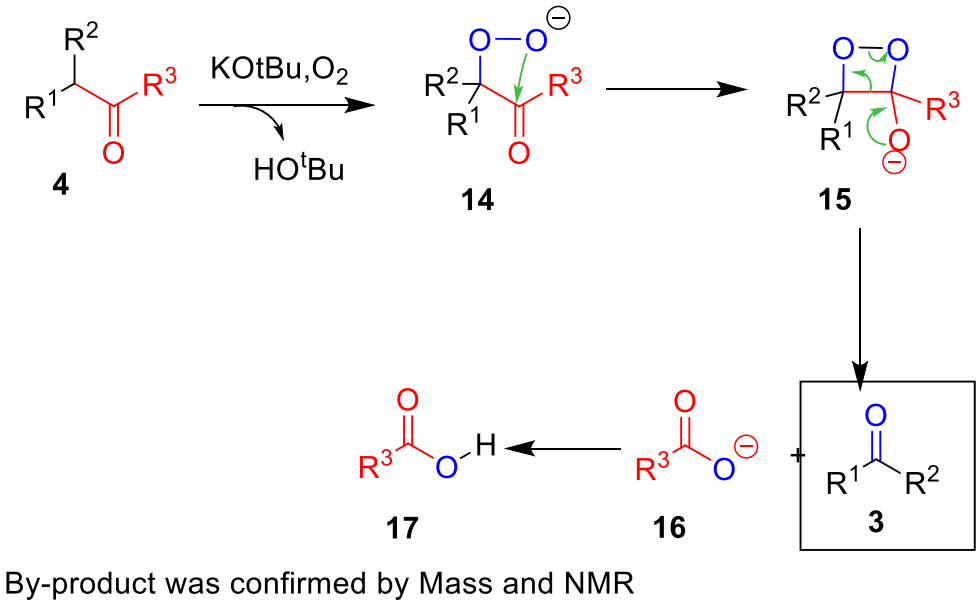
Scheme 12. *Scale-up reaction*



Scheme 13. *Synthetic Transformations*

3.3.5. Mechanism:

To understand the mechanism of this oxidative cleavage reaction, TEMPO was used as a radical scavenger, and the substrate was subjected to the optimized reaction condition, but no apparent alteration was observed in the reaction yield of **3a**. HRMS analysis of the crude reaction mass did not detect the mass of the TEMPO adduct. It was clear from these observations that the reaction is not proceeding *via* a radical path. The possible reaction mechanism is outlined in Scheme 14, by considering these observations as well as previous reports.[16,21]



Scheme 14. *Proposed Mechanism*

The base abstracts the C_{sp3}-H proton of the compound 4, subsequent attack of oxygen forms an anionic peroxy ketone intermediate **14**, which on the intramolecular attack from the peroxy anion to carbonyl carbon forms a four-membered 1,2-dioxetan-3-olate intermediate **15**. Oxidative cleavage of this reactive intermediate furnishes the diaryl ketone **3**. The

byproduct was obtained after neutralization of the aqueous layer of reaction mass after quenching with water.

3.4. Conclusion

Using easily accessible KO^{t}Bu, a straightforward methodology for the synthesis of symmetric and unsymmetric diaryl, diheteroaryl ketones was established. The simultaneous breakage of C-C bonds and oxidation of C-H bonds using potassium *tert*-butoxide in the presence of aerial oxygen was shown to aid in the facile and practical synthesis of diheteroayl and diaryl ketones. With outstanding yields, this method produced various ketones from a wide variety of substrates. The reaction does not appear to proceed through a radical path, according to TEMPO tests, which is why the ionic pathway has been postulated. Using this procedure, a quick synthesis of natural products **3g** and a formal synthesis of Echinosulfone A were accomplished.

3.5. Single Crystal XRD of 3a:

The vapor diffusion crystallization method was used for crystal growth for **3a,** where the compound was dissolved in chloroform by heating to make a saturated solution in a small vial which was placed in a closed bottle with another solvent as *n*-hexane. The crystal data was recorded on Rigaku Oxford Diffractometer.

Identification code	ysr12
Empirical formula	$C_{31}H_{24}N_2O$
Formula weight	440.55
Temperature	297 K
Wavelength	0.71073 Å
Crystal system	'Triclinic'
Space group	P -1
Unit cell dimensions	a = 9.5014 (5) Å α = 78.783 (4).
	b = 10.3744 (5) Å β = 71.877 (4).
	c = 13.6237 (5) Å γ = 63.790 (5).
Volume	1142.49 (11)
Z	2
Density	1.281 g/cm^3
Absorption coefficient	0.078 mm^{-1}
F (000)	464.2
Crystal size	0.2 x 0.15 x 0.1 mm^3
Theta (max)	27.240
Index ranges	-11<=h<=11, -13<=k<=12, -17<=l<=17
Reflections collected	4826
R (reflection)	0.049 (3215)
wR2 (reflections)	0.1437(4826)
restraints / parameters	0/307

Goodness-of-fit on F^2	1.076
Tmin, Tmax	0.986, 0.992
Data completeness	0.944
S	1.089
Npar	307
CCDC No.	2189305

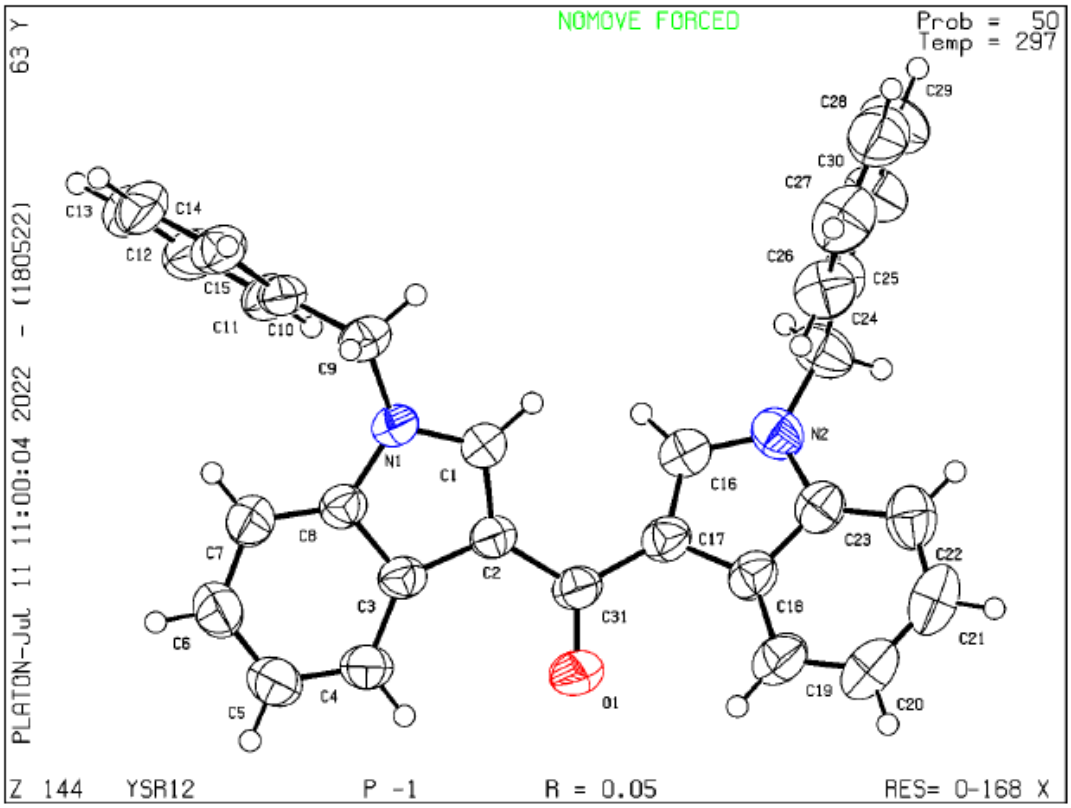


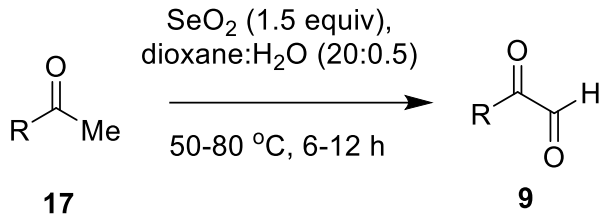
Figure 2*. ORTEP representation of compound* ***3a*** *and thermal ellipsoids are drawn with 50% probability.*

3.6. Experimental section:

3.6.1. General experimental procedures

3.6.1.1.The general experimental procedure for Aryl/Alkyl glyoxal:[24]

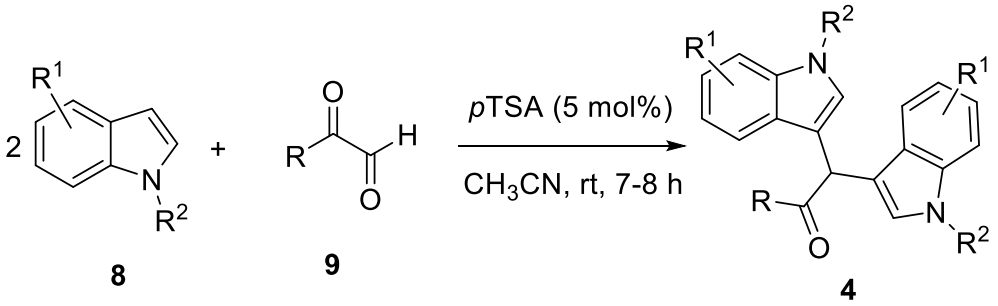
SeO_2 was charged into a two-neck round bottom flask along with dioxane and water in a 20:0.5 ratio, and the mixture was heated until the SeO_2 dissolved. Aryl/alkyl acetate was then added to the reaction mixture, and the heating process was continued using a condenser setup. The reaction was monitored by TLC. After completion, the reaction mass was cooled to room temperature and filtered over a celite bed (washed with DCM). DCM was evaporated under a vacuum; the reaction mass was recrystallized by adding a few drops of water to it and heating then it was filtered in an ice-cold beaker.



Scheme 15. *Synthesis of Aryl and Alkyl glyoxal*

3.6.1.2. General experimental procedure for the synthesis of 2,2-bis(1-alkyl/aryl-1H-indol-3-yl)-1-phenylethanone (4a-4p):[21]

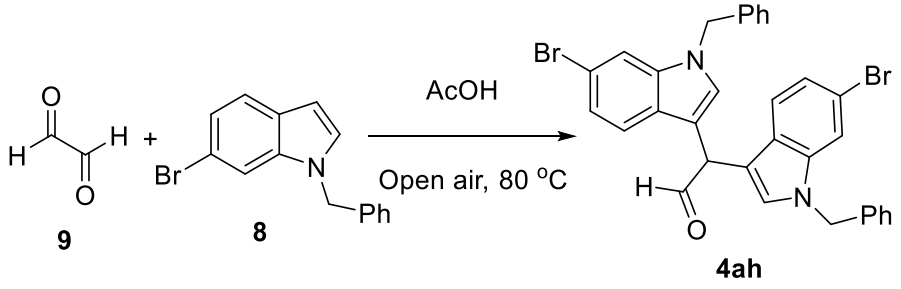
A mixture of phenylglyoxal (1 equiv.), *N*-alkyl/aryl Indole (2 equiv.), *p*TSA (5 mol%), and CH_3CN was stirred at room temperature for 7-8 hours. After completion of the reaction (monitored by TLC), the resulting mixture was quenched with water and extracted into ethyl acetate (thrice). Combined organic layers were washed with $NaHCO_3$ solution and dried over anhydrous Na_2SO_4 and the solvent was evaporated to obtain the crude product. The crude product was purified by column chromatography to obtain pure product **4** in good yield.



Scheme 16. *Synthesis of 2,2-bis(1-alkyl/aryl-1H-indol-3-yl)-1-phenylethanone*

3.6.1.3. General experimental procedure for the synthesis of 2,2-bis(1-benzyl-6-bromo-1H-indol-3-yl)acetaldehyde (4ah):[25]

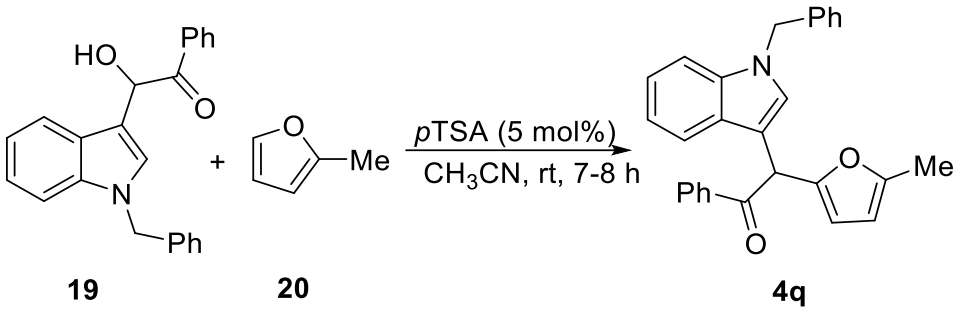
A mixture of glyoxal (40% in water), 6-bromo-*N*-benzyl Indole, acetic acid (2 ml) was heated at 80 °C in the open air. After completion of the reaction (monitored by TLC), the resulting mixture was quenched with water and extracted into ethyl acetate (thrice). Combined organic layers were washed with brine solution and dried over anhydrous Na_2SO_4 and the solvent was evaporated to obtain the crude product. The crude product was purified by column chromatography to obtain the pure product **4ah** in good yield.



Scheme 17. *Synthesis of 2,2-bis(1-benzyl-6-bromo-1H-indol-3-yl)acetaldehyde*

3.6.1.4. General experimental procedure for the synthesis 2-(1-benzyl-1H-indol-3-yl)-2-(5-methylfuran-2-yl)-1-phenylethanone (4q):[26]

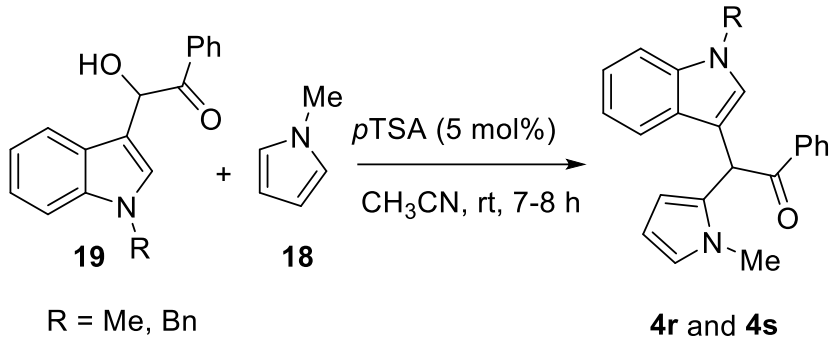
A mixture of 2-(1-benzyl-1H-indol-3-yl)-2-hydroxy-1-phenylethanone (200 mg, 0.5862 mmol), 2-methylfuran (52.90 mg, 0.6451 mmol) *p*TSA (5 mol%) and CH_3CN was stirred at room temperature for 7-8 hours till the consumption of starting material (monitored by TLC). Then the reaction mixture was concentrated under a vacuum and the crude product was purified by using silica gel column chromatography (10-12 % EtOAc in pet ether) to obtain the desired product in good yield.



Scheme 18. *Synthesis of 2-(1-benzyl-1H-indol-3-yl)-2-(5-methylfuran-2-yl)-1-phenylethanone*

3.6.1.5. General experimental procedure for the synthesis 4r and 4s:[26]

A mixture of 2-(1-benzyl-1H-indol-3-yl)-2-hydroxy-1-phenylethanone (200 mg, 0.5862 mmol) or 2-(1-benzyl-1H-indol-3-yl)-2-hydroxy-1-phenylethanone (200 mg, 0.7547 mmol), *N*-methyl pyrrole, *p*TSA (5 mol%) and CH_3CN were stirred at room temperature for 7-8 hours or till the consumption of starting material (monitored by TLC). Then the reaction mixture was concentrated under a vacuum and the crude product was purified by using silica gel column chromatography (10-12 % EtOAc in pet ether) to obtain the desired products in good yields.

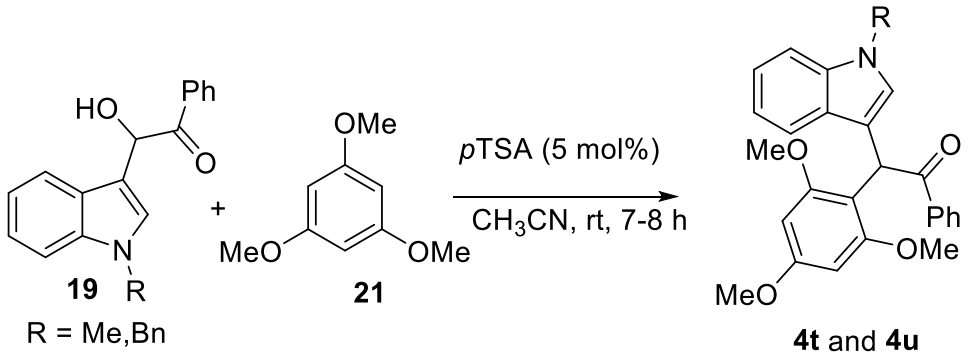


Scheme 19. *Synthesis of unsymmetrical bisheteroaryl phenylethanone*

3.6.1.6. General experimental procedure for the synthesis of 4t and 4u:[26]

A mixture of 2-(1-benzyl-1H-indol-3-yl)-2-hydroxy-1-phenylethanone (200 mg, 0.5862 mmol) or 2-(1-benzyl-1H-indol-3-yl)-2-hydroxy-1-phenylethanone (200 mg, 0.7547 mmol), trimethoxybenzene, *p*TSA (5 mol%) and CH_3CN were stirred at room temperature for 7-8 hours till the consumption of starting material (monitored by TLC). Then the reaction mixture was concentrated under a vacuum and the crude product was purified by using

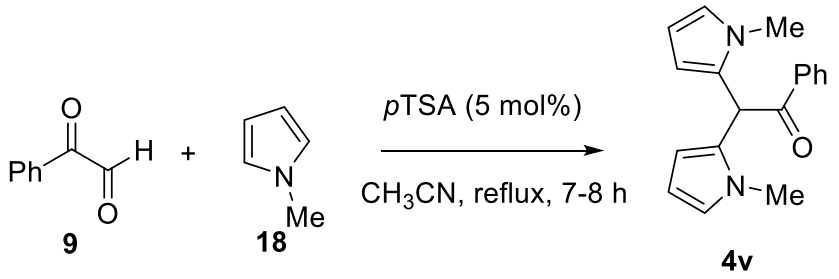
silica gel column chromatography (10-12 % EtOAc in pet ether) to obtain the desired product in good yield.



Scheme 20. *Synthesis of unsymmetrical phenylethanone*

3.6.1.7. General experimental procedure for the synthesis of 2,2-bis(1-methyl-1H-pyrrol-2-yl)-1-phenylethan-1-one (4v):

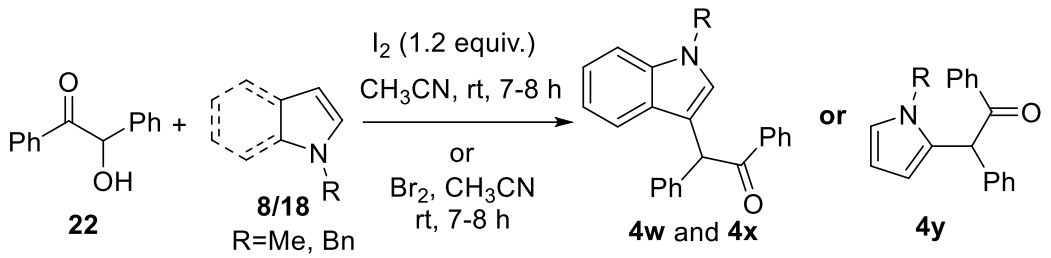
A mixture of phenylglyoxal (250 mg, 1.8656 mmol) and N-methyl Pyrrole (377.79 mg, 4.6641 mmol), *p*TSA (5 mol%), and acetonitrile were charged into an oven-dried round bottom flask and stirred at reflux temperature. The progress of the reaction was monitored by TLC. Then the reaction mass was quenched with water and extracted with ethyl acetate 2 times. The combined organic layer was concentrated, and the crude was purified using column chromatography.



Scheme 21. *Synthesis of 2,2-bis(1-methyl-1H-pyrrol-2-yl)-1-phenylethan-1-one*

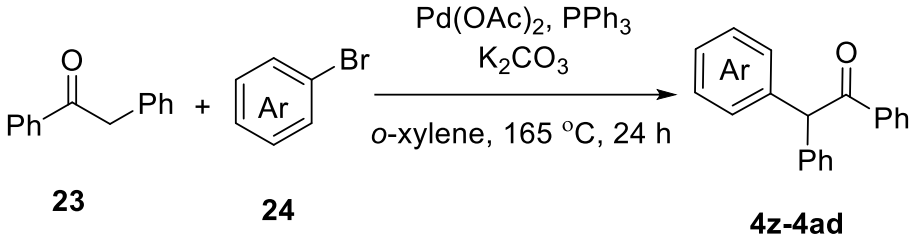
3.6.1.8. General experimental procedure for the synthesis of 4w, 4x, and 4y:[27]

A mixture of 2-hydroxy-1,2-diphenylethanone (1 equiv.) and N-alkyl/aryl Indole (1.2 equiv.), I_2 (1.2 equiv.) and acetonitrile were charged into an oven-dried round bottom flask and stirred at reflux temperature. The progress of the reaction was monitored by TLC. Then the reaction mass was quenched with $Na_2S_2O_3$ solution and extracted with ethyl acetate 2 times. The combined organic layer was concentrated, and crude was purified using column chromatography (60-120 mess size, 15% EtOAc in pet ether).



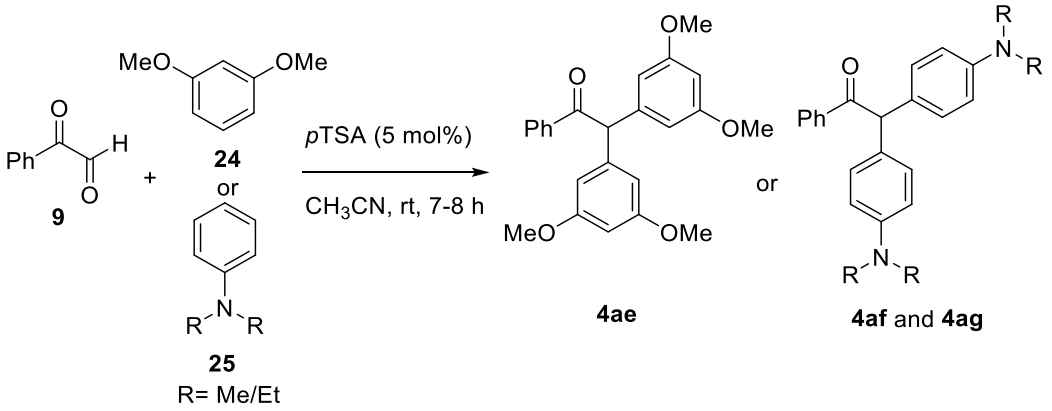
Scheme 22. *Synthesis of heteroaryl substituted diphenylethanone*

3.6.1.9. General experimental procedure for the synthesis of 4-4ad:[28] A mixture of deoxybenzoin (250 mg, 1.2739 mmol), $Pd(OAc)_2$ (1 mol%), PPh_3 (4 mol%), K_2CO_3 (703 mg, 5.0958 mmol), bromoarenes (1.9108 mmol), and o-xylene were taken in a round bottom flask and purged with nitrogen at room temperature and then heated to 165 ^oC under N_2. The reaction was continuously stirred at room temperature under an N_2 atmosphere for 24 hours. The disappearance of deoxybenzoin has been monitored from TLC. The reaction mixture was cooled to room temperature, diluted with ethyl acetate, and washed with ice-cold water. The crude product was purified by using silica gel column chromatography (5-6 % EtOAc in pet ether) to obtain the desired product **3a-3e** in moderate to good yield.



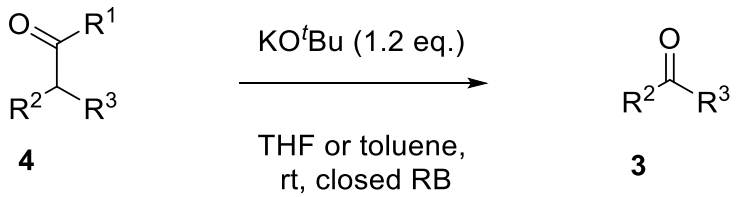
Scheme 23. *Synthesis of Bisaryl phenylethanone* ***4z-4ad***

3.6.1.10. General experimental procedure for the synthesis of 4ae-4ag: A mixture of phenylglyoxal (250 mg, 1.8656 mmol) and 1,3-dimethoxybenzene/N,N-diaryl amine (3.9177 mmol), *p*TSA (5 mol%), and acetonitrile were charged into an oven-dried round bottom flask and stirred at room temperature. The progress of the reaction was monitored by TLC. Then the reaction mass was quenched with water and extracted with ethyl acetate 3 times. The combined organic layer was concentrated to the product **3f-3h** in quantitative yields.



Scheme 24. *Synthesis of bisaryl phenylethanone* ***4ae-4ag***

3.6.1.11. General experimental procedure for the preparation of ketones (3): A round bottom flask was charged with bis-aryl/heteroaryl alky/arylethanone **4** (100 mg) and KO^{t}Bu (1.2 equiv.) and was sealed properly. Then dry THF or dry toluene (0.5 mL) was added to the reaction mixture and allowed to stir at room temperature, and the progress of the reaction was monitored by TLC. After the complete consumption of the starting material, the reaction mixture was distilled. The base was quenched with water and the product was extracted with EtOAc (thrice), the combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated to obtain the crude product The crude was purified by column chromatography using an eluent of ethyl acetate and pet ether (20-30 % ethyl acetate in pet ether) to afford the desired product in a good to excellent yield.



Scheme 25. *Synthesis of Bisheteroaryl and diaryl Ketones*

3.6.2. Spectral data:

*Bis(1-benzyl-1H-indol-3-yl)methanone (**3a**).* Yellow solid (mp: 123-125 ^{o}C), yield 98%; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.40-8.38 (m, 2H), 7.65 (s, 2H), 7.33-7.31 (m, 4H), 7.30-7.28 (m, 5H), 7.26-7.25 (m, 3H), 7.14 (d, 4H, J = 7.0 Hz), 7.35 (s, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 185.0, 137.1, 136.3, 134.0, 129.1, 128.2, 127.5, 127.1, 123.5, 122.6, 122.2, 118.2, 110.1, 50.7; IR (KBr): ν˜max = 3030, 2921, 1686, 1594, 1570, 1517, 1494, 1449, 1389, 1351, 1330, 1302, 1247, 1172, 1079, 1009, 829, 779, 736, 695, 624, 572 cm^{-1}; HRMS (ESI-TOF): m/z calculated for $C_{31}H_{24}N_2O$ $[M+H]^+$ 441.1967, found 441.1965.

*Bis(1-methyl-1H-indol-3-yl)methanone (**3b**).* Yellow solid (mp: 111-113 ^{o}C), yield 95%; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.40-8.38 (m, 2H), 7.50 (s, 2H), 7.30-7.29 (m, 5H), 7.28-7.27 (m, 1H), 3.77 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 184.8, 137.4, 134.5, 127.3, 123.1, 122.4, 121.9, 117.3, 109.5, 33.3; IR (KBr): ν˜max = 3123, 2911, 1667, 1597,

1517, 1466, 1373, 1244, 1210, 1128, 1002, 839, 775, 740, 645, 573 cm^{-1}; HRMS (ESI-TOF): m/z calculated for $C_{19}H_{16}N_2O$ $[M+H]^+$ 289.1341, found 289.1342.

*Bis(1-ethyl-1H-indol-3-yl)methanone (**3c**).* Colourless solid (mp: 285-286 ^oC), yield 88%; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.37 (d, 2H, J = 7.0 Hz), 7.69 (s, 2H), 7.39 (d, 2H, J = 8.0 Hz), 7.32-7.25 (m, 4H), 4.25-4.21 (m, 4H), 1.52 (t, 6H, J = 7.0 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 185.0, 136.5, 133.0, 127.4, 123.0, 122.5, 121.8, 117.6, 109.7, 41.6, 15.4; IR (KBr): ν˜max = 2982, 2886, 1666, 1592, 1514, 1484, 1451, 1391, 1351, 1310, 1233, 1192, 1131, 1081, 1007, 838, 822, 741, 715, 642, 560, 508 cm^{-1}; HRMS (ESI-TOF): m/z calculated for $C_{21}H_{20}N_2O$ $[M+H]^+$ 317.1654, found 317.1655.

*Bis(1-phenyl-1H-indol-3-yl)methanone (**3d**).* Colourless viscous compound, yield 90%; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.51-8.49 (m, 2H), 7.93 (s, 2H), 7.57-7.52 (m, 10H), 7.45-7.42 (m, 2H), 7.38-7.35 (m, 2H), 7.34-7.31 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 185.1, 138.7, 137.0, 133.5, 129.9, 127.8, 127.7, 125.0, 124.0, 122.7, 119.4, 110.8.; IR (KBr): ν˜max = 3103, 3043, 1738, 1589, 1519, 1499, 1480, 1454, 1359, 1297, 1232, 1208, 1184, 1095, 1075, 1030, 947, 829, 777, 743, 717, 689, 661, 579, 533 cm^{-1}; HRMS (ESI-TOF): m/z calculated for $C_{29}H_{20}N_2O$ $[M+H]^+$ 413.1654, found 413.1656.

*Bis(1-isopropyl-1H-indol-3-yl)methanone (**3e**).* Yellow solid (mp: 128-130 ^oC), yield 86%; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.33-8.31 (m, 2H), 7.81 (s, 2H), 7.43 (d, 2H, J = 8.0 Hz), 7.32-7.29 (m, 2H), 7.28-7.25 (m, 2H), 4.76-4.71 (m, 2H), 1.58 (s, 6H), 1.57 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 22.8, 47.7, 109.9, 118.0, 121.8, 122.4, 122.9, 127.4, 130.2, 136.5, 185.2; IR (KBr): ν˜max = 3107, 2974, 2927, 1604, 1582, 1511, 1458, 1397, 1368, 1346, 1302, 1234, 1178, 1130, 1064, 1014, 851, 827, 781, 754, 702, 605, 554, 508 cm^{-1}; HRMS (ESI-TOF): m/z calculated for $C_{23}H_{24}N_2O$ $[M+H]^+$ 345.1967, found 345.1966.

*Bis(1-allyl-1H-indol-3-yl)methanone (**3f**).* Colourless solid (mp: 100-102 ^oC), yield 97%; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.39-8.37 (m, 2H), 7.68 (s, 2H), 7.39-7.35 (m, 2H), 7.33-7.30 (m, 2H), 7.29-7.27(m, 2H), 6.07-6.03 (m, 1H), 6.02-5.99 (m, 1H), 5.28-5.26 (m, 2H), 5.19-5.15 (m, 2H), 4.82-4.81 (m, 2H), 4.80-4.79 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 13.1, 110.5, 118.9, 121.9, 122.3, 122.5, 122.7, 123.9, 124.2, 126.8, 133.2, 137.2, 185.2; IR (KBr): ν˜max = 3049, 2919, 1665, 1602, 1573, 1516, 1482, 1459, 1363, 1312, 1226, 1192, 1047, 932, 833, 779, 743, 564, 530 cm^{-1}; HRMS (ESI-TOF): m/z calculated for $C_{23}H_{20}N_2O$ $[M+H]^+$ 341.1654, found 341.1654.

*Di(1H-indol-3-yl)methanone (**3g**).* Colourless solid (mp 305-307 ^oC), yield 37% incase of onepot reaction from **1a** and 85% from **2a** with KO^tBu/DMSO under O_2; ^1H NMR (500 MHz, $CDCl_3$ and a drops of DMSO-*d6*): δ (ppm) 10.98 (s, 2H), 8.36-8.35 (m, 2H), 7.78-7.77 (m, 2H), 7.47-7.43 (m, 2H), 7.25-7.21 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$ and a drop of DMSO-d_6): δ (ppm) 185.6, 136.5, 131.0, 126.3, 122.5, 121.5, 121.1, 117.7, 111.4; HRMS (ESI-TOF): m/z calculated for $C_{17}H_{12}N_2O$ $[M+H]^+$ 261.1028, found 261.1028.

*Bis(1-(2-(1,3-dioxan-2-yl)ethyl)-1H-indol-3-yl)methanone (**3i**)*. Brown solid (mp 114-116 ^{o}C), yield 70%; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.40 (d, 2H, J = 7.0 Hz), 7.67 (s, 2H), 7.42 (d, 2H, J = 7.5 Hz), 7.33-7.27 (m, 4H), 4.45-4.43 (m, 2H), 4.35-4.32 (m, 4H), 4.10-4.07 (m, 4H), 3.70-3.65 (m, 4H), 2.17-2.12 (m, 4H), 2.11-2.02 (m, 2H), 1.33 (d, 2H, J = 13.5 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 25.8, 35.4, 41.9, 66.9, 99.3, 109.9, 117.9, 122.0, 122.6, 123.3, 127.5, 133.8, 136.8, 185.1; HRMS (ESI-TOF): m/z calculated for $C_{29}H_{32}N_2O_5$ $[M+H]^+$ 489.2389, found 489.2389.

*Bis(1-(2-phenoxyethyl)-1H-indol-3-yl)methanone (**3j**)*. Yellow solid (mp: 128-130 ^{o}C), Yield 91%; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.42 (d, 2H, J = 8.0 Hz), 7.73 (s, 2H), 7.42 (d, 2H, J = 8.0 Hz), 7.34-7.31 (m, 2H), 7.30-7.27 (m, 2H), 7.25-7.21 (m, 4H), 6.94-6.91 (m, 2H), 6.84-6.82 (m, 4H), 4.53-4.51 (m, 4H), 4.31-4.29 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 46.2, 66.3, 109.5, 114.5, 117.9, 121.5, 122.1, 122.7, 123.3, 127.5, 129.7, 134.6, 136.8, 158.1, 185.0; IR (KBr): ν˜max = 2970, 1597, 1517, 1494, 1438, 1382, 1363, 1300, 1235, 1187, 1080, 931, 882, 827, 792, 740, 687, 569, 509 cm^{-1}; HRMS (ESI-TOF): m/z calculated for $C_{33}H_{28}N_2O_3$ $[M+H]^+$ 501.2178, found 501.2180.

*Bis(1-benzyl-5-methoxy-1H-indol-3-yl)methanone (**3k**)*. Colourless solid (mp: 242-244 ^{o}C), yield 88%; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.93 (d, 2H, J = 2.5 Hz), 7.59 (s, 2H), 7.32-7.25 (m, 6H), 7.18 (d, 2H, J = 9.0 Hz), 7.13-7.11 (m, 4H), 6.91-6.89 (m, 2H), 5.31 (s, 4H), 3.88 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 185.3, 156.2, 136.3, 134.1, 132.1, 129.0, 128.3, 128.2, 127.0, 117.6, 114.4, 111.0, 103.4, 55.9, 50.9; HRMS (ESI-TOF): m/z calculated for $C_{33}H_{28}N_2O_3$ $[M+H]^+$ 501.2178, found 501.2173.

*3,3'-Carbonylbis(1-benzyl-1H-indole-5-carbonitrile) (**3l**)*. Brown solid (mp: 208-210 ^{o}C), yield 97%; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.71-8.70 (m, 2H), 7.72 (s, 2H), 7.52 (d, 1H, J = 2.0 Hz), 7.50 (d, 1H, J = 1.5 Hz), 7.41-7.39 (m, 2H), 7.38-7.37 (m, 1H), 7.36 (s, 1H), 7.35-7.34 (m, 2H), 7.33-7.32 (m, 2H), 7.15-7.13 (m, 4H), 5.38 (s, 4H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$ and 2- drops of DMSO-d_6): δ (ppm) 182.5, 137.6, 136.0, 135.9, 134.8, 128.2, 127.4, 126.9, 126.8, 126.4, 126.1, 125.3, 119.2, 116.2, 50.0; HRMS (ESI-TOF): m/z calculated For $C_{33}H_{22}N_4O$ $[M+H]^+$ 491.1872, found 491.1871.

*Bis(1-benzyl-5-nitro-1H-indol-3-yl)methanone (**3m**)*. Yellow solid (mp: 256-258 ^{o}C), yield 35%; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 9.08 (d, 2H, J = 2.0 Hz), 8.07-8.05 (m, 2H), 7.75 (s, 2H), 7.39-7.36 (m, 1H), 7.35-7.33 (m, 4H), 7.30 (d, 3H, J = 9.5 Hz), 7.18-7.17 (m, 4H), 5.40 (s, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$ and a drop of DMSO-d_6): δ (ppm) 182.8, 143.7, 139.7, 136.3, 134.9, 129.4, 128.8, 127.2, 126.6, 119.3, 119.1, 110.4, 51.3; HRMS (ESI-TOF): m/z calculated For $C_{31}H_{22}N_4O_5$ $[M+H]^+$ 531.1668, found 531.1669.

*Bis(1-benzyl-5-bromo-1H-indol-3-yl)methanone (**3n**)*. Brown solid (mp: 208-210 ^{o}C), yield 90%; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.54 (d, 2H, J = 1.5 Hz), 7.59 (s, 2H), 7.34-7.33 (m, 2H), 7.32 (d, 2H, J = 2.5 Hz), 7.31-7.29 (m, 4H), 7.14 (s, 1H), 7.13-7.12 (m, 4H), 7.11 (s, 1H), 5.31 (s, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 183.9, 135.7, 134.5, 129.2, 128.9, 128.4, 127.0, 126.5, 125.1, 117.1, 115.9, 111.6, 51.0; IR (KBr): ν˜max = 1590, 1518,

1458, 1388, 1167, 1054, 821, 789, 744, 728, 699, 638, 599, 562, 495 cm^{-1}; HRMS (ESI-TOF): m/z calculated for $C_{31}H_{22}Br_2N_2O$ $[M+H]^+$ 597.0177, found 597.0166.

*Bis(1-benzyl-6-bromo-1H-indol-3-yl)methanone (**3o**).* Yellow solid (mp: 236-238 ^oC), yield 95%; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.22 (d, 2H, J = 8.5 Hz), 7.55 (s, 2H), 7.46 (d, 2H, J = 1.5 Hz), 7.38 (d, 1H, J = 1.0 Hz), 7.36 (d, 1H, J = 2.0 Hz), 7.35-7.33 (m, 2H), 7.32-7.31 (m, 3H),7.30-7.29 (m, 1H), 7.12-7.10 (m, 4H), 5.27 (s, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 184.2, 137.9, 135.6, 134.2, 129.2, 128.4, 127.0, 126.2, 125.6, 123.8, 117.8, 117.2, 113.1, 50.7; HRMS (ESI-TOF): m/z calculated for $C_{31}H_{22}Br_2N_2O$ $[M+H]^+$ 597.0177, found 597.0176.

*Bis(1-benzyl-2-methyl-1H-indol-3-yl)methanone (**3p**).* Yellow viscous compound, yield 95%; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.56 (d, 2H, J = 8.0 Hz), 7.48-7.45 (m, 1H), 7.31-7.30 (m, 3H), 7.28-7.27 (m, 3H), 7.15-7.12 (m, 3H), 7.04-7.02 (m, 6H), 5.39 (s, 4H), 2.47 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 188.2, 142.2, 136.7, 136.5, 133.7, 130.3, 129.0, 128.6, 127.7, 127.1, 126.1, 122.2, 121.5, 121.0, 117.5, 109.5, 46.7, 12.1;HRMS (ESI-TOF): m/z calculated for $C_{33}H_{28}N_2O$ $[M+H]^+$ 469.2280, found 469.2278.

*(1-Benzyl-1H-indol-3-yl)(furan-2-yl)methanone (**3q**).* Yellow viscous compound, yield 71%; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.54 (d, 1H, J = 8.5 Hz), 8.23 (d, 1H, J= 0.5 Hz), 7.36-7.34 (m, 1H), 7.33-7.31 (m, 3H), 7.30 (s, 1H), 7.28-7.27 (m, 1H), 7.20-7.17 (s, 3H), 6.17 (d, 1H, J = 3.5 Hz), 5.41 (s, 2H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 176.0, 155.7, 153.0, 136.6, 135.8, 129.0, 128.1, 127.8, 127.0, 123.5, 123.0, 122.6, 118.0, 114.7, 110.0, 108.6, 50.8, 14.1; HRMS (ESI-TOF): m/z calculated for $C_{21}H_{17}NO_2$ $[M+H]^+$ 316.1338, found 316.1337.

*(1-Benzyl-1H-indol-3-yl)(1-methyl-1H-pyrrol-2-yl)methanone (**3r**).* Brown solid (mp: 107-109 ^oC), yield 75%; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.41-8.39 (m, 1H), 7.73 (s, 1H), 7.30-7.25 (m, 5H), 7.24-7.21 (m, 1H), 7.11 (d, 2H, J = 7.0 Hz), 6.82 (s, 1H), 6.77-6.76 (m, 1H), 6.12-6.11 (m, 1H), 5.30 (s, 2H), 3.97 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 180.8, 137.0, 136.1, 135.3, 132.2, 129.6, 129.0, 128.1, 127.6, 126.9, 123.5, 122.5, 122.3, 118.7, 117.2, 110.1, 107.6, 50.6, 36.7; IR (KBr): ν˜max = 3005, 1595, 1520, 1460, 1412, 1383, 1306, 1234, 1195, 1168, 1055, 1011, 892, 841, 729, 695, 667, 607, 578 cm^{-1}; HRMS (ESI-TOF): m/z calculated for $C_{21}H_{18}N_2O$ $[M+H]^+$ 315.1497, found 315.1498.

*(1-Methyl-1H-indol-3-yl)(1-methyl-1H-pyrrol-2-yl)methanone (**3s**).* Brown solid (mp: 129-131 ^oC) yield 90%; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.38-8.37 (m, 1H), 7.69 (s, 1H), 7.37-7.35 (m, 1H), 7.34-7.28 (m, 2H), 6.86-6.85 (m, 1H), 6.81-6.80 (m, 1H), 6.16-6.15 (m, 1H), 4.00 (s, 3H), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 180.8, 137.4, 136.0, 132.3, 129.5, 127.4, 123.3, 122.4, 122.1, 118.5, 116.7, 109.6, 107.5, 36.7, 33.4; HRMS (ESI-TOF): m/z calculated for $C_{15}H_{14}N_2O$ $[M+H]^+$ 239.1184, found 239.1185.

*Bis(1-methyl-1H-pyrrol-2-yl)methanone (**3t**).* Browm liquid, yield 80%; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.84 (d, 4H, J = 2.0 Hz), 6.13-6.12 (m, 2H), 3.94 (s, 6H); $^{13}C\{^1H\}$ NMR

(100 MHz, $CDCl_3$): δ (ppm) 176.6, 131.6, 130.2, 120.3, 107.6, 36.8; HRMS (ESI-TOF): m/z calculated for $C_{11}H_{12}N_2O$ $[M+H]^+$ 189.1028, found 189.1028.

*(1-Benzyl-1H-indol-3-yl)(2,4,6-trimethoxyphenyl)methanone (**3u**).* Brown solid (mp: 100-102 ^oC), yield 74%; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.28 (d, 1H, J= 6.5 Hz), 7.49 (s, 1H), 7.30-7.26 (m, 4H), 7.25-7.22 (m, 2H), 7.12-7.10 (m, 2H), 6.17 (s, 2H), 5.29 (s, 2H), 3.85 (s, 3H), 3.69 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 188.6, 161.9, 158.6, 137.7, 137.3, 136.1, 129.0, 128.1, 126.9, 126.7, 123.3, 122.7, 122.6, 119.0, 113.6, 110.2, 90.9, 55.9, 55.5, 50.7; HRMS (ESI-TOF): m/z calculated for $C_{25}H_{23}NO_4$ $[M+H]^+$ 402.1705, found 402.1704.

*(1-Methyl-1H-indol-3-yl)(2,4,6-trimethoxyphenyl)methanone (**3v**).* Yellow solid (mp: 162-164 ^oC), yield 81%; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.29 (d, 1H, J = 4.0 Hz), 7.38 (s, 1H), 7.31-7.30 (m, 2H), 7.29-7.28 (m, 1H), 6.19 (s, 2H), 3.87 (s, 3H), 3.76 (s, 3H), 3.70 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 188.6, 161.8, 158.4, 138.2, 137.8, 126.4, 123.2, 122.6, 122.5, 118.5, 113.6, 109.6, 90.8, 56.0, 55.5, 33.5; HRMS (ESI-TOF): m/z calculated for $C_{19}H_{19}NO_4$ $[M+H]^+$ 326.1392, found 326.1392.

*(1-Benzyl-1H-indol-3-yl)(phenyl)methanone (**3w**).* Yellow solid (mp: 140-142 ^oC), yield 61%; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.44-8.43 (m, 1H), 7.83-7.81 (m, 2H), 7.62 (s, 1H), 7.53-7.52 (m, 1H), 7.48-7.45 (m, 2H), 7.35-7.31 (m, 3H), 7.31-7.29 (m, 3H), 7.14-7.13 (m, 2H), 5.37 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 191.0, 140.9, 137.3, 137.2, 135.9, 131.3, 129.1, 128.8, 128.4, 128.2, 127.5, 126.9, 123.9, 122.9, 116.2, 110.3, 50.9; HRMS (ESI-TOF): m/z calculated for $C_{22}H_{17}NO$ $[M+H]^+$ 312.1388, found 312.1393.

*(1-Methyl-1H-indol-3-yl)(phenyl)methanone (**3x**).* Brown solid (mp: 112-114 ^oC), yield 78%; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.43-8.41 (m, 1H), 7.80 (d, 2H, J = 7.5 Hz), 7.54-7.50 (m, 2H), 7.48-7.45 (m, 2H), 7.35-7.32 (m, 3H), 3.82 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 190.7, 140.7, 137.9, 137.4, 130.9, 128.5, 128.2, 127.0, 123.4, 122.5, 122.4, 115.2, 109.6, 33.3; IR (KBr): $\tilde{\nu}$max = 3046, 2933, 1611, 1572, 1521, 1467, 1391, 1367, 1265, 1230, 1124, 1073, 1007, 927, 872, 840, 790, 772, 715, 693, 666, 607, 572, 539 cm^{-1}; HRMS (ESI-TOF): m/z calculated for $C_{16}H_{13}NO$ $[M+H]^+$ 236.1075, found 236.1075.

*(1-Methyl-1H-pyrrol-2-yl)(phenyl)methanone (**3y**).* Yellow solid (mp: 261-263 ^oC), yield 83%; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.82-7.80 (m, 2H), 7.53-750 (m, 1H), 7.46-7.43 (m, 2H), 7.19-7.18 (m, 1H), 6.69-6.68 (m, 1H), 6.64-6.63 (m, 1H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 190.7, 140.2, 131.3, 129.0, 128.9, 128.2, 124.7, 123.4, 111.2, 36.7; HRMS (ESI-TOF): m/z calculated for $C_{12}H_{11}NO$ $[M+H]^+$ 186.0919, found 186.0918.

*Benzophenone (**3z**).* Colourless solid (mp: 50-52 ^oC), yield 78%; ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.74-7.72 (m, 4H), 7.53-7.50 (m, 2H), 7.42-7.39 (m, 4H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 196.9, 137.7, 132.5, 130.2, 128.4; HRMS (ESI-TOF): m/z calculated for $C_{13}H_{10}O$ $[M+H]^+$ 183.0810, found 183.0815.

*Anthracen-9-yl(phenyl)methanone (**3aa**).* Yellow solid (mp: 101-103 °C), yeld 80%; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.49 (s, 1H), 7.99 (d, 2H, *J* = 8.5 Hz), 7.74 (d, 2H, *J* = 7.5 Hz), 7.65-7.63 (m, 2H), 7.52-7.48 (m, 1H), 7.41-7.38 (m, 2H), 7.34-7.30 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 200.3, 138.2, 134.1, 131.1, 130.2, 128.9, 128.7, 128.5, 126.6, 125.6, 125.4; IR (KBr): ν˜max = 3053, 2921, 2850, 1736, 1662, 1594, 1447, 1347, 1309, 1285, 1264, 1224, 1171, 1049, 1021, 898, 845, 812, 733, 703, 664, 621, 600, 557, 529 cm^{-1}; HRMS (ESI-TOF): m/z calculated for $C_{21}H_{14}O$ $[M+H]^+$ 283.1123, found 283.1121.

*Phenanthren-9-yl(phenyl)methanone (**3ab**).* Yellow solid (mp: 123-125 °C), yield 85%; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.65 (d, 1H, *J* = 8.5 Hz), 8.61 (d, 1H, *J* = 8.0 Hz), 8.01 (d, 1H, *J* = 8.0 Hz), 7.84 (d, 2H, *J* = 8.5 Hz), 7.77 (d, 1H, *J* = 7.0 Hz), 7.74 (s, 1H), 7.64-7.61 (m, 1H), 7.60-7.57 (m, 1H), 7.53-7.47 (m, 3H), 7.37-7.34 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 198.0, 138.3, 135.4, 133.4, 131.4, 130.7, 130.5, 130.1, 129.6, 126.4, 129.2, 128.6, 128.4, 127.3 (2), 126.7, 123.0, 122.8; IR (KBr): ν˜max = 3058, 1736, 1653, 1595, 1577, 1527, 1493, 1447, 1315, 1251, 1210, 1174, 1058, 1023, 881, 844, 745, 720, 700, 671, 615, 579, 506 cm^{-1}; HRMS (ESI-TOF): m/z calculated for $C_{21}H_{14}O$ $[M+H]^+$ 283.1123, found 283.1123.

*(6-Methoxynaphthalen-2-yl)(phenyl)methanone (**3ac**).* Pink solid (mp: 121-123 °C), yield 70%; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.12 (d, 1H, *J* = 1.5 Hz), 7.86-7.84 (m, 1H), 7.76-7.46 (m, 2H), 7.73-7.74 (m, 2H), 7.53-7.50 (m, 1H), 7.44-7.40 (m, 2H), 7.12-7.09 (m, 2H), 3.87 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 196.7, 159.8, 138.3, 137.1, 132.7, 132.2, 132.1, 131.1, 130.0, 128.4, 127.7, 127.1, 126.6, 119.8, 105.8, 55.5; IR (KBr): ν˜max = 3004, 2844, 1646, 1617, 1594, 1476, 1436, 1385, 1304, 1211, 1167, 1078, 1028, 914, 863, 819, 715, 695, 633, 587, 528 cm^{-1}; HRMS (ESI-TOF): m/z calculated for $C_{18}H_{14}O_2$ $[M+H]^+$ 263.1072, found 263.1073.

*(3,5-Dimethoxyphenyl)(phenyl)methanone (**3ad**).* Yellow solid (mp: 133-135 °C), yield 85%; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.73-7.71 (m, 2H), 7.50-7.47 (m, 1H), 7.39-7.36 (m, 2H), 6.83 (d, 2H, *J* = 2.0 Hz), 6.59-6.58 (m, 1H), 3.73 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 196.4, 160.6, 139.5, 137.6, 132.5, 130.1, 128.3, 107.9, 104.8, 55.6; IR (KBr): ν˜max = 2937, 2837, 1657, 1589, 1451, 1424, 1349, 1325, 1297, 1241, 1203, 1152, 1061, 986, 924, 845, 810, 721, 696, 662, 538 cm^{-1}; HRMS (ESI-TOF): m/z calculated for $C_{15}H_{14}O_3$ $[M+H]^+$ 243.1021, found 243.1021.

*Bis(3,5-dimethoxyphenyl)methanone (**3ae**).* Colourless solid (mp: 146-148 °C), yield 98%; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.50-7.48 (m, 2H), 6.50-6.48 (m, 2H), 6.42 (s, 2H), 3.84 (s, 6H), 3.66 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 193.0, 163.4, 160.1, 132.5, 123.8, 104.4, 98.4, 55.6, 55.4; HRMS (ESI-TOF): m/z calculated for $C_{17}H_{18}O_5$ $[M+H]^+$ 303.1323, found 303.1326.

*Bis(4-(dimethylamino)phenyl)methanone (**3af**).* Grey solid (mp: 164-166 °C), yield 86%; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.77-7.75 (m, 4H), 6.70-6.68 (m, 4H), 3.05 (s, 12H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 194.1, 152.8, 132.3, 126.4, 110.7, 40.2; HRMS (ESI-TOF): m/z calculated for $C_{17}H_{20}N_2O$ $[M+H]^+$ 269.1654, found 269.1609.

*Bis(4-(diethylamino)phenyl)methanone (**3ag**).* Brown solid (mp: 177-178 °C), yield 82%; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.76-7.73 (m, 4H), 6.66-6.63 (m, 4H), 3.44-3.40 (m, 8H), 1.21 (t, 12H, J = 8.5 Hz); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 193.6, 150.4, 132.6, 125.7, 110.1, 44.5, 12.7; HRMS (ESI-TOF): m/z calculated for $C_{21}H_{28}N_2O$ $[M+H]^+$ 325.2280, found 325.2282.

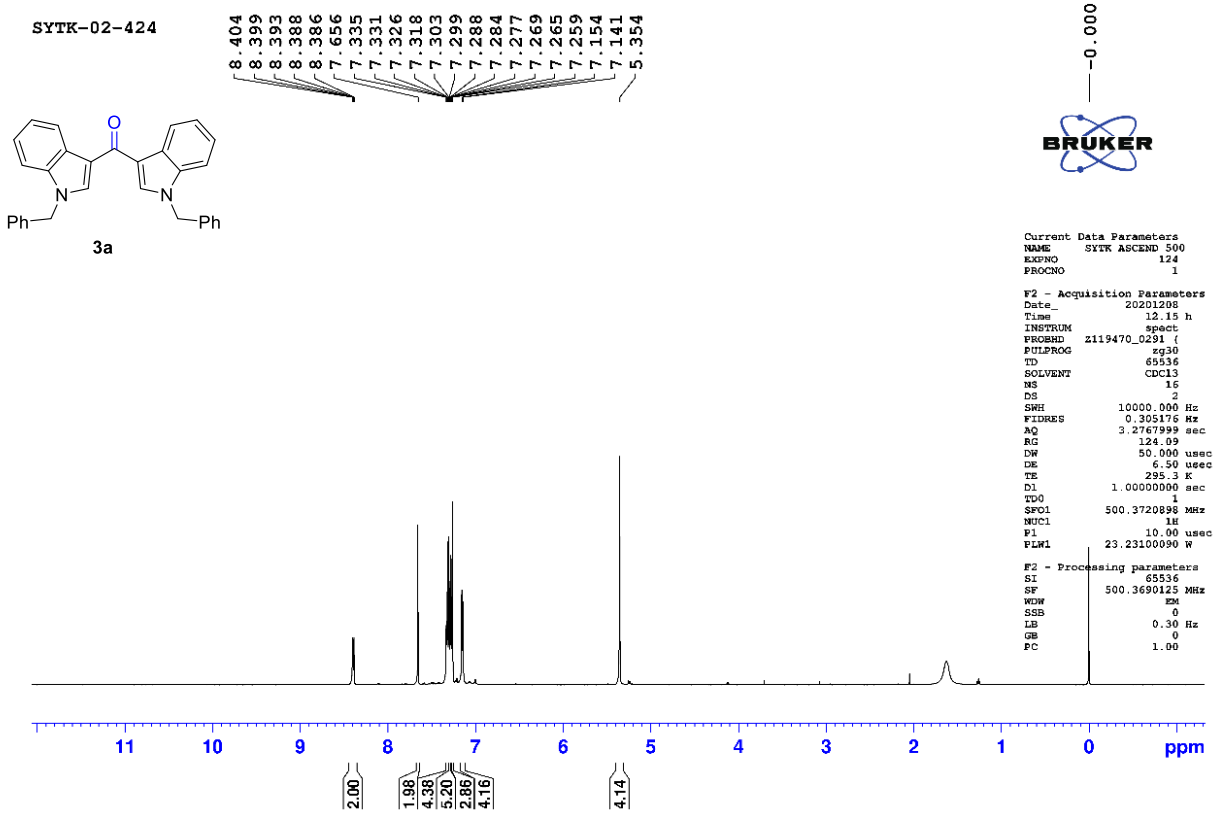
*(1-Benzyl-1H-indol-3-yl)(1H-indol-3-yl)methanone (**10**):* Pinkish solid (mp: 248-150 °C), yield 58%; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 10.91 (s, 1H), 8.41-8.38 (m, 1H), 8.35-8.33 (m, 1H), 7.80-7.78 (m, 2H), 7.47-7.45 (m, 1H), 7.41-7.40 (m, 1H), 7.35-7.29 (m, 3H), 7.28-7.23 (m, 4H), 7.18-7.16 (m, 2H), 5.40 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$ and a drop of DMSO-d_6): δ (ppm) 184.4, 136.1, 135.8, 133.6, 130.7, 128.1, 127.1, 126.7, 126.1, 125.8, 122.4, 122.1, 121.5, 121.0 (2), 120.6, 117.0, 116.8, 111.1, 109.5, 49.7; HRMS (ESI-TOF): m/z calculated for $C_{24}H_{18}N_2O$ $[M+H]^+$ 351.1497, found 351.1496.

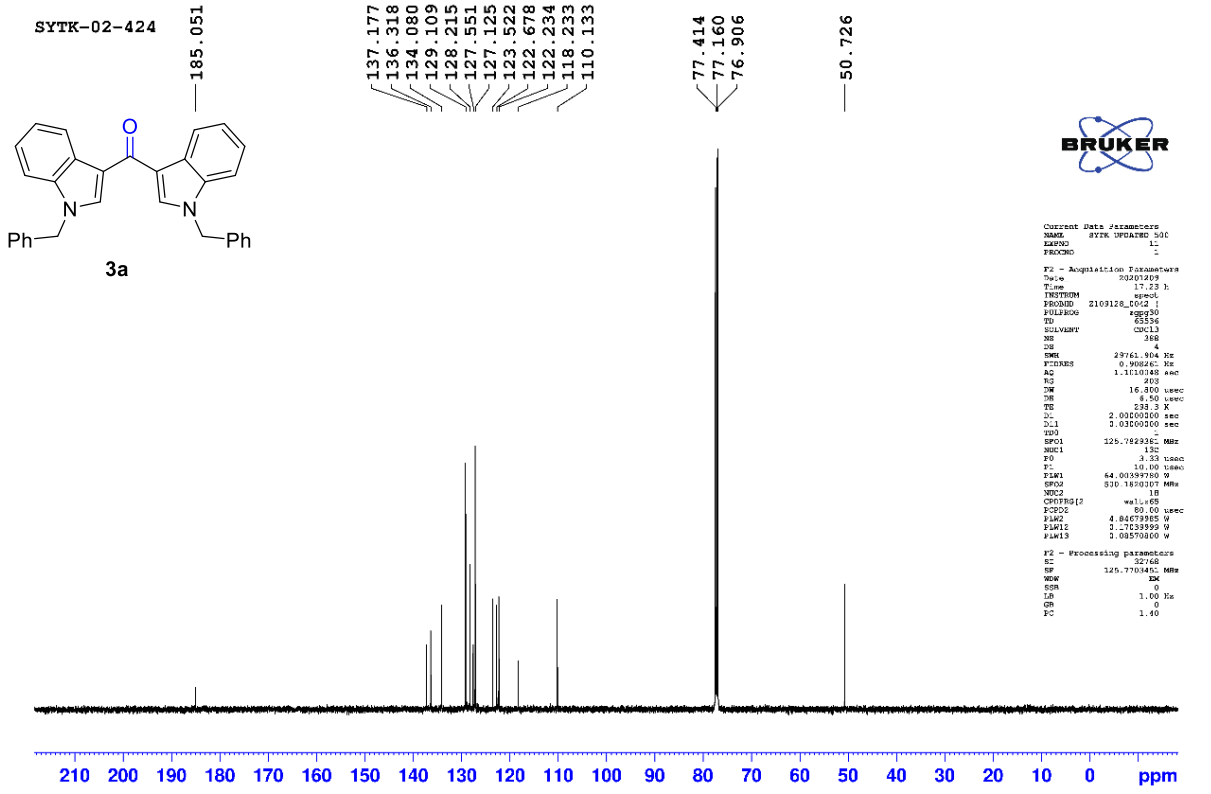
*bis(6-bromo-1H-indol-3-yl)methanone (**11**).* yellow solid (mp 330-332 °C), yield 83%; ^{1}H NMR (500 MHz, DMSO-*d6*): δ (ppm) 11.90 (s, 2H), 8.14 (d, 2H, J = 2.5 Hz), 8.10 (d, 2H, J = 8.5 Hz), 7.60 (d, 2H, J = 1.5 Hz), 7.25-7.23 (m, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6): δ (ppm) 184.0, 137.4, 132.9, 125.5, 124.0, 123.1, 116.5, 115.2, 114.6; HRMS (ESI-TOF): m/z calculated for $C_{17}H_{10}Br_2N_2O$ $[M+H]^+$ 416.9238, found 416.9235.

*3,3'-(Ethene-1,1-diyl)bis(1-benzyl-1H-indole) (**12**).* Colourless solid (mp: 158-160 °C), yield 83%; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.77 (d, 2H, J = 8.0 Hz), 7.30-7.26 (m, 6H), 7.25-7.22 (m, 2H), 7.20-7.16 (m, 4H), 7.14-7.13 (m, 4H), 7.11-7.07 (m, 2H), 5.58 (s, 2H), 5.28 (s, 4H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 137.4, 137.1, 135.7, 128.8, 128.7, 128.4, 127.7, 127.3, 126.9, 126.5, 122.0, 121.1, 119.8, 118.1, 110.0, 109.9, 50.1; HRMS (ESI-TOF): m/z calculated for $C_{32}H_{26}N_2$ $[M+H]^+$ 439.2174, found 439.2172.

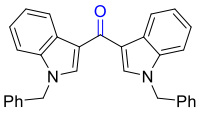
*Bis(1-benzyl-1H-indol-3-yl)methanethione (**13**).* Brown solid (mp: 213-215 °C), yield 97%; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.51-8.49 (m, 2H), 7.61 (s, 2H), 7.35-7.29 (m, 8H), 7.28-7.21 (m, 4H), 7.18-7.16 (m, 4H), 5.29 (s, 4H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 212.0, 137.7, 135.9, 133.6, 129.1, 128.2, 127.9, 127.2, 123.8, 122.7, 122.6, 110.3, 50.7; HRMS (ESI-TOF): m/z calculated for $C_{31}H_{24}N_2S$ $[M+H]^+$ 457.1738, found 457.1735.

3.6.3. Spectral Copies

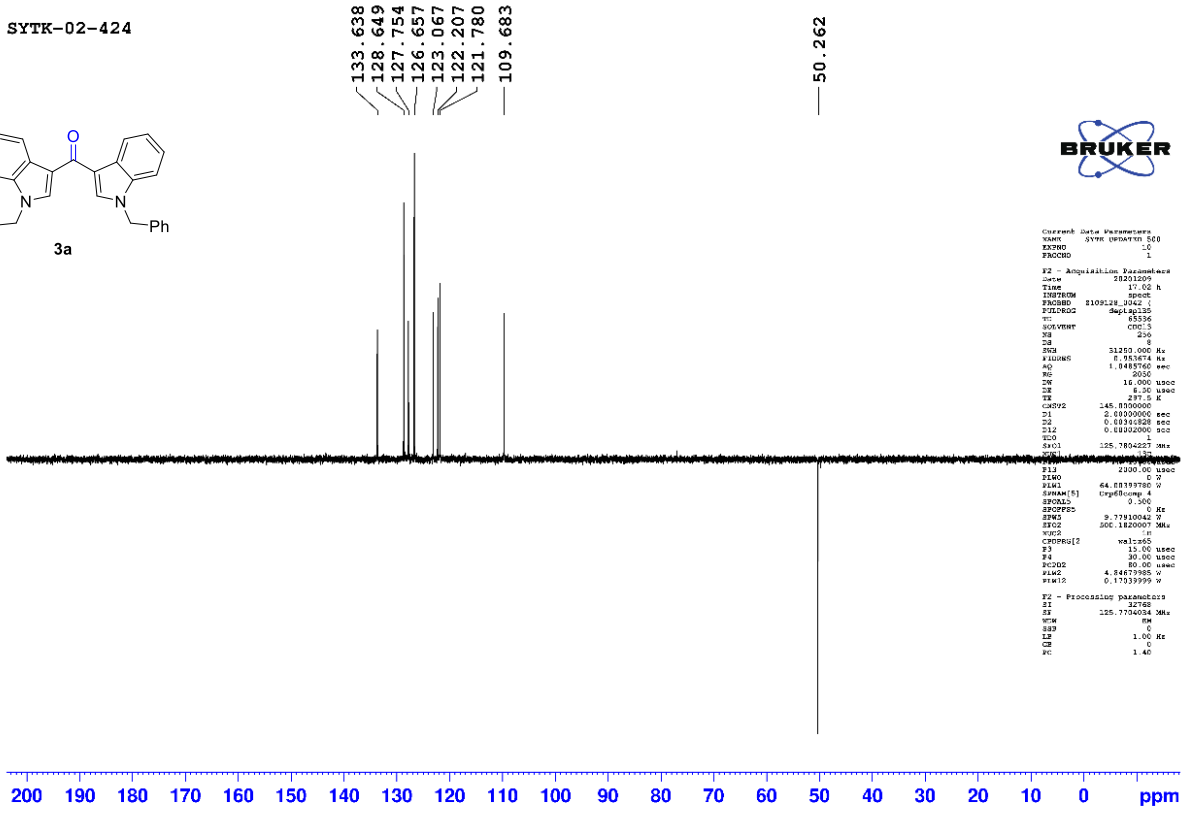




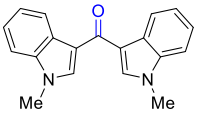
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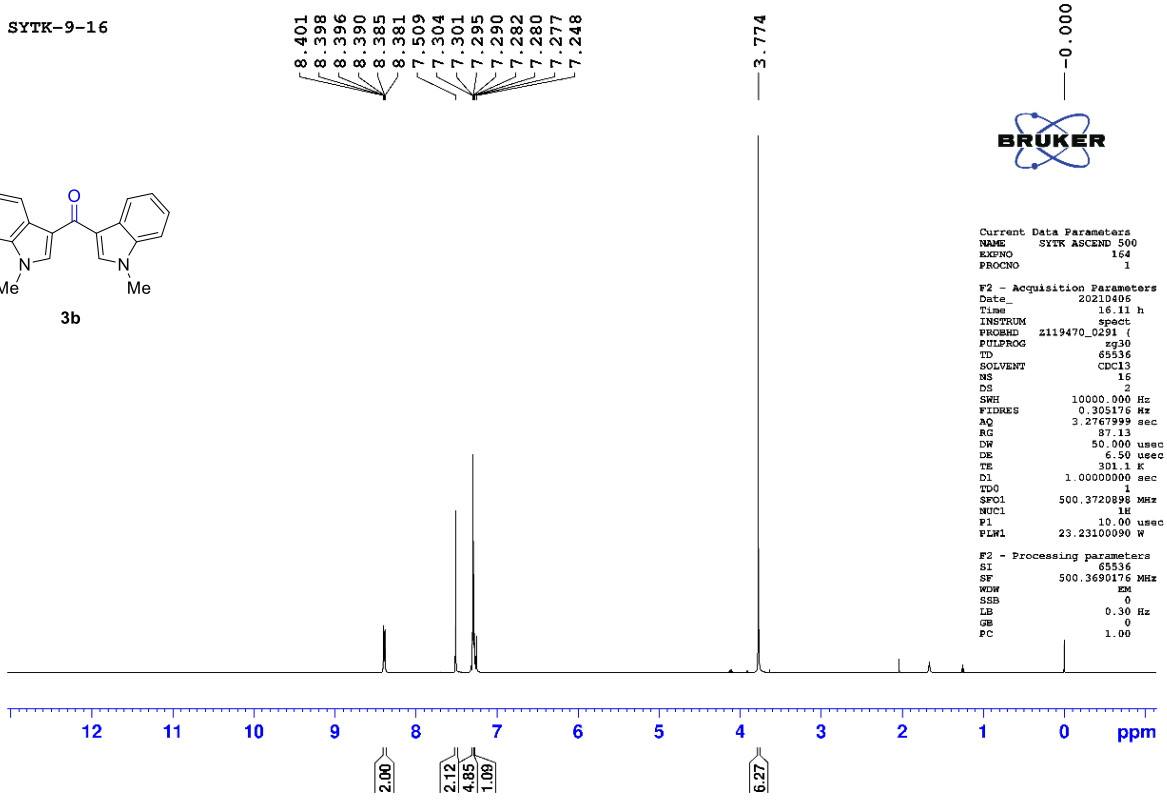
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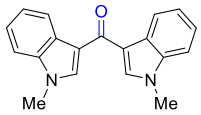


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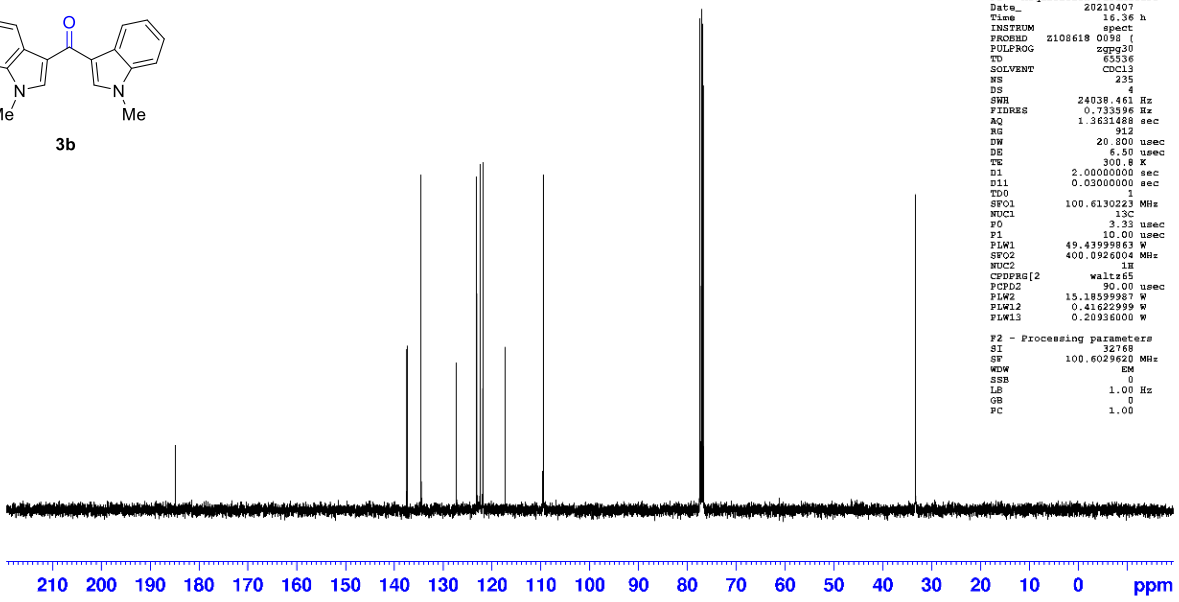


SYTK-9-16

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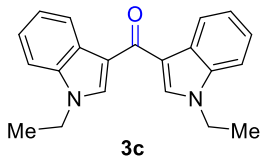

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PLW12        0.41622999 W
PLW13        0.20936000 W

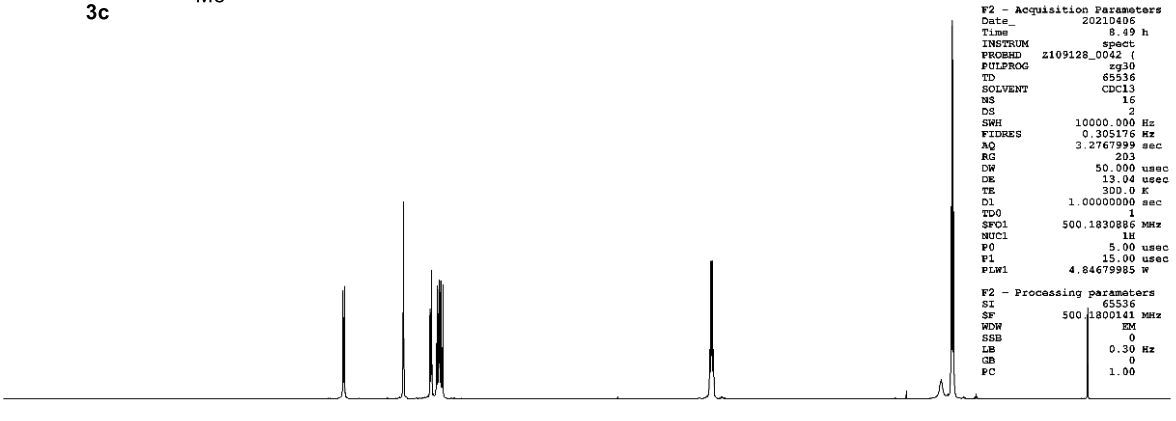
F2 - Processing parameters
SI                 32768
SF          100.6029620 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.00
```

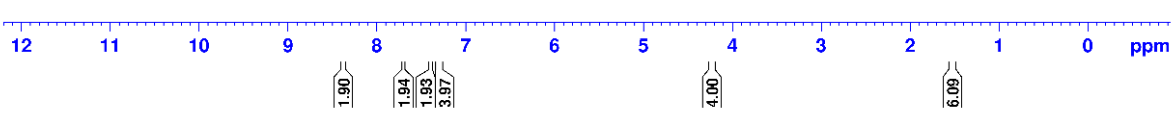
SYAH-Net-184

8.378
8.364
7.699
7.399
7.383
7.330
7.327
7.315
7.313
7.300
7.295
7.292
7.279
7.277
7.265
7.263
7.253
4.252
4.240
4.238
4.225
4.223
4.211
1.536
1.522
1.508
-0.000



3c

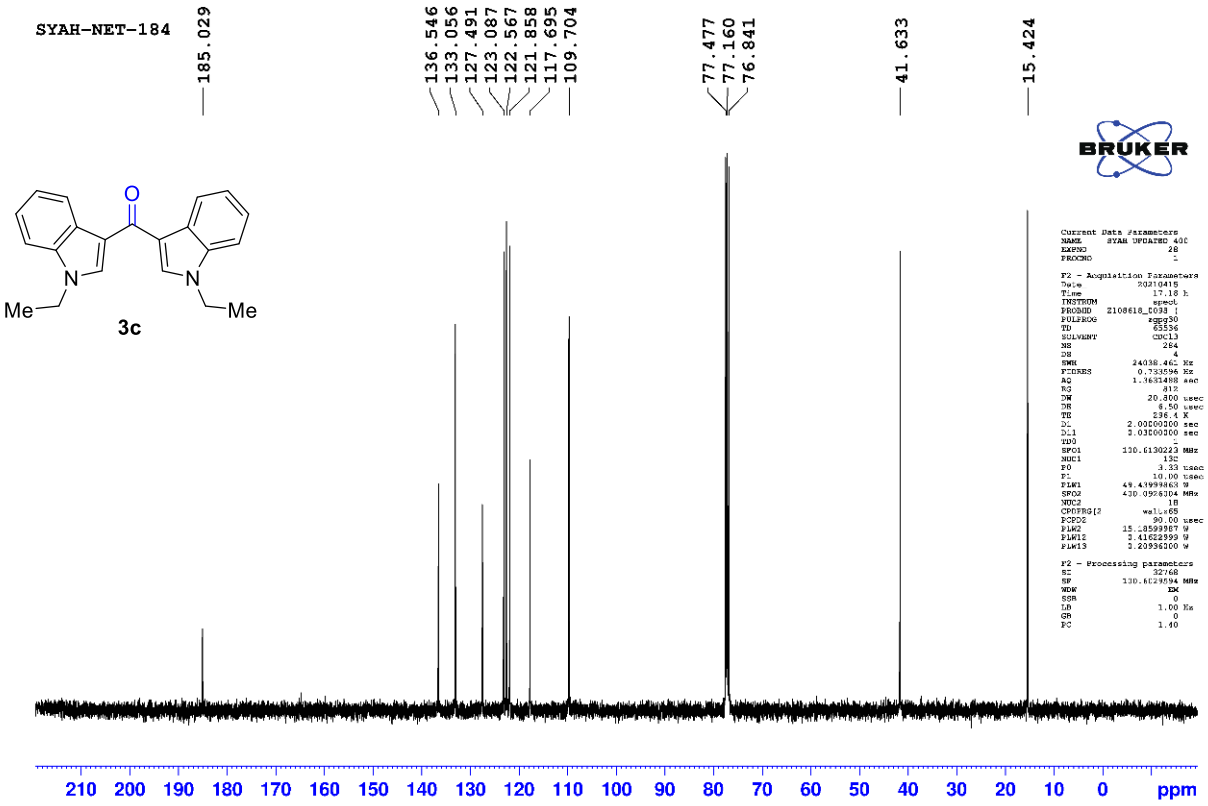


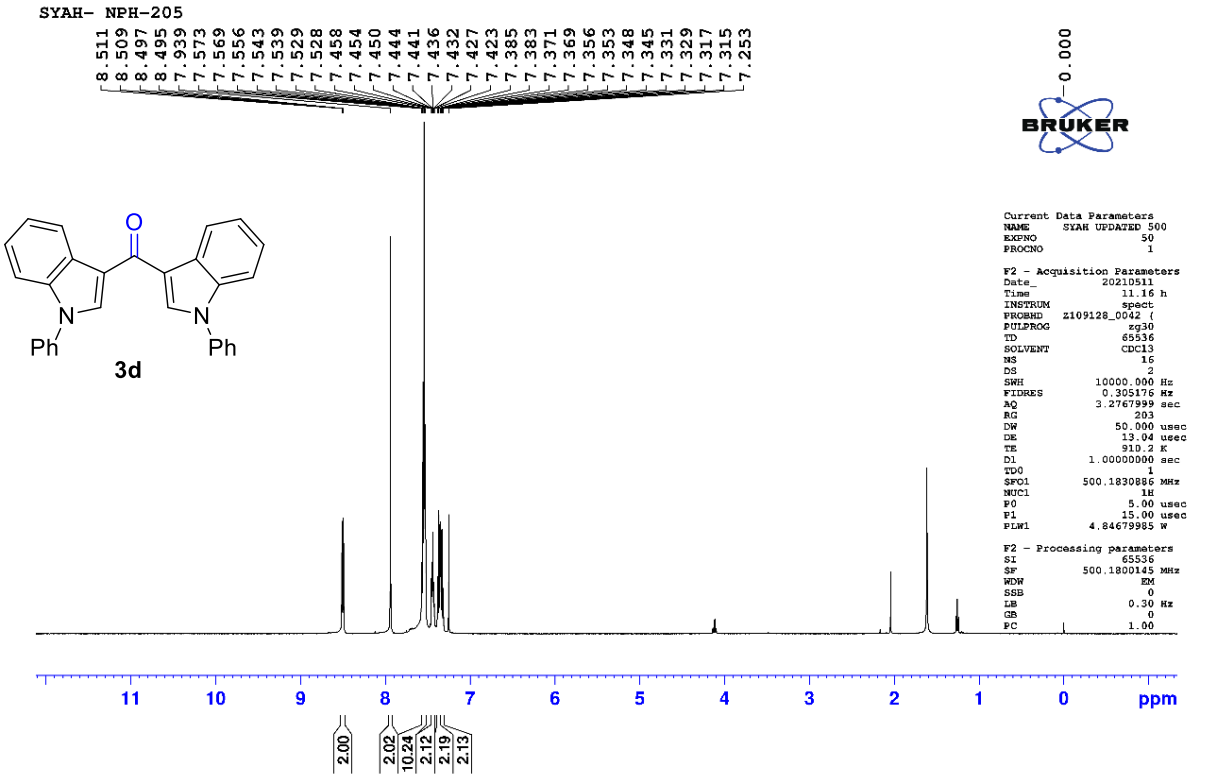


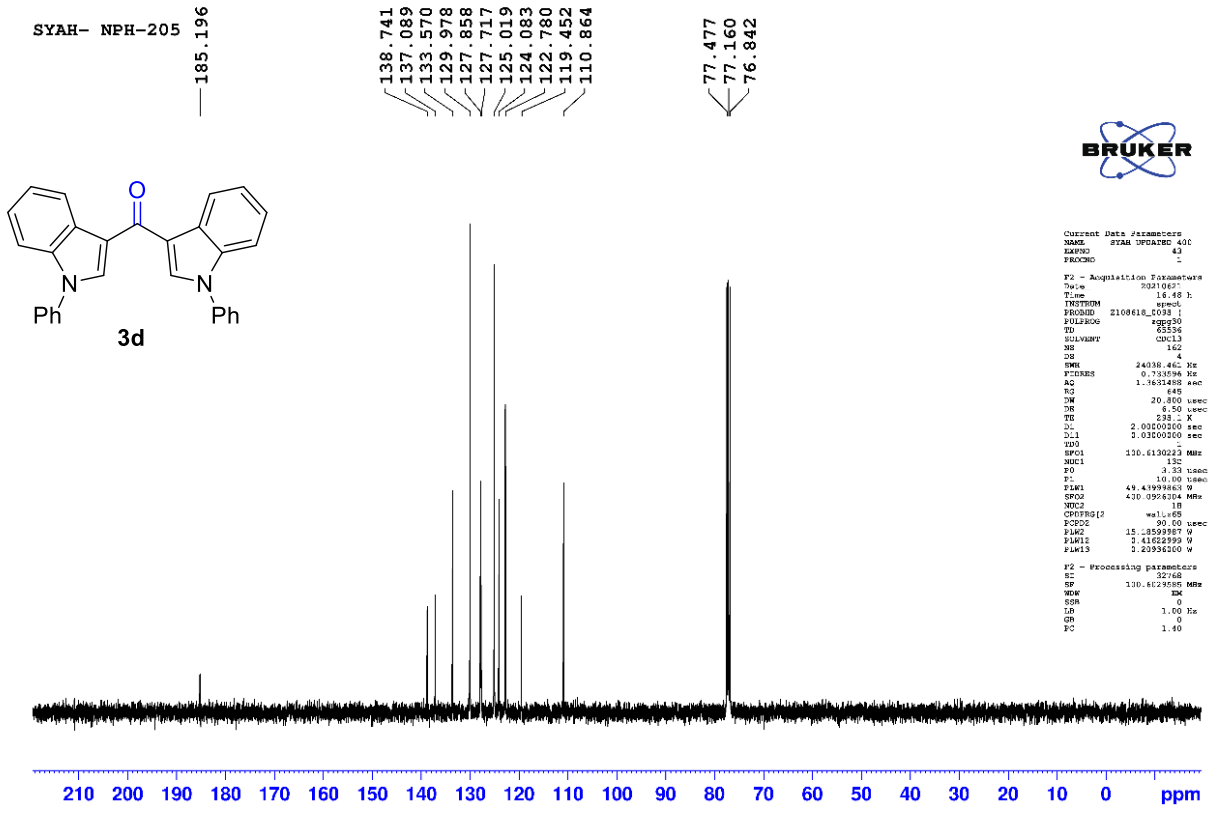

```
Current Data Parameters
NAME      SYAH UPDATED 500
EXPNO                  39
PROCNO                  1

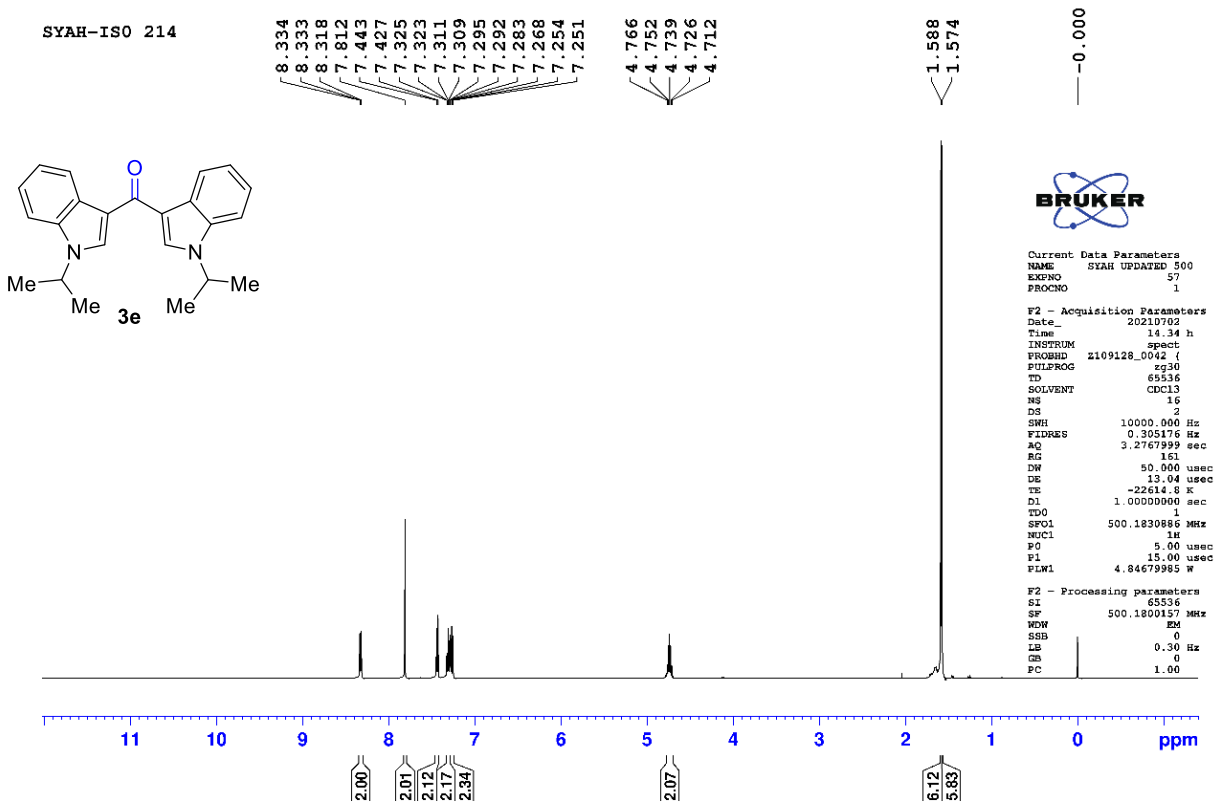
F2 - Acquisition Parameters
Date_           20210406
Time              8.49 h
INSTRUM             spect
PROBHD   Z109128_0042 (
PULPROG             zg30
TD                65536
SOLVENT           CDCl3
NS                   16
DS                    2
SWH          10000.000 Hz
FIDRES        0.305176 Hz
AQ            3.2767999 sec
RG                  203
DW               50.000 usec
DE               13.04 usec
TE               300.0 K
D1           1.00000000 sec
TD0                   1
SFO1        500.1830886 MHz
NUC1                1H
P0                 5.00 usec
P1                15.00 usec
PLW1         4.84679985 W

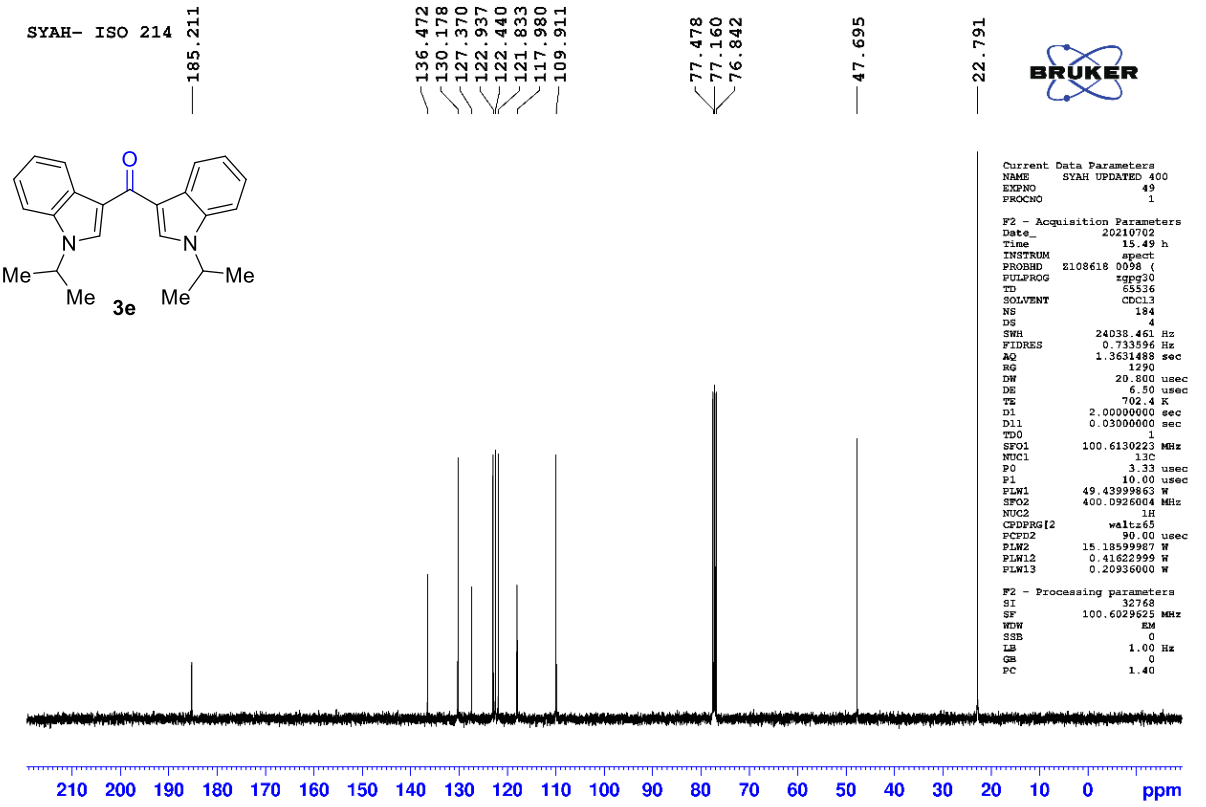
F2 - Processing parameters
SI                 65536
SF          500.1800141 MHz
WDW                   EM
SSB                    0
LB                  0.30 Hz
GB                     0
PC                  1.00
```

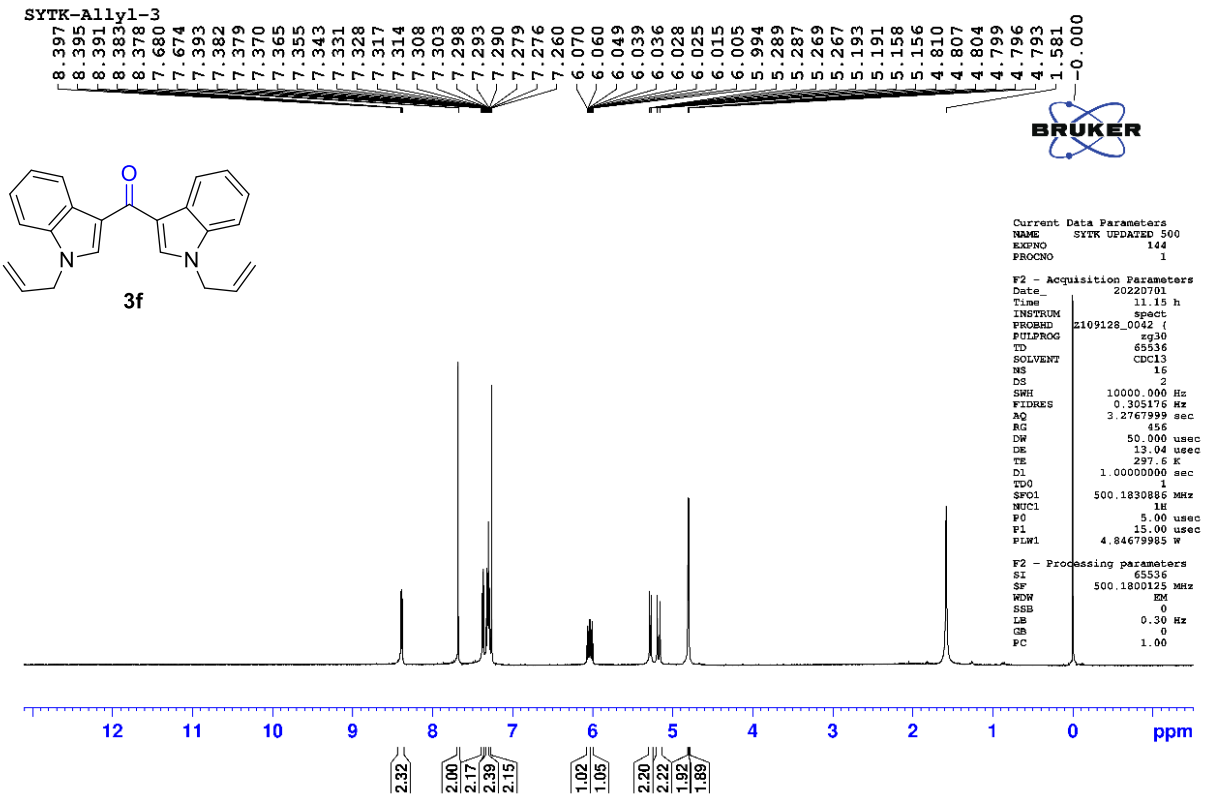

SYAH-NET-184
185.029
136.546
133.056
127.491
123.087
122.567
121.858
117.695
109.704
77.477
77.160
76.841
41.633
15.424
O
N
Me
N
Me
3c
BRUKER
Current Data Parameters
NAME SYAH UPDATED 400
EXPNO 28
PROCNO 1
F2 - Acquisition Parameters
Date_ 20210415
Time 17.18 h
INSTRUM spect
PROBHD Z108618_0093 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 264
DS 4
SWH 24038.461 Hz
FIDRES 0.733596 Hz
AQ 1.3631488 sec
RG 812
DW 20.800 usec
DE 6.50 usec
TE 296.4 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.6130223 MHz
NUC1 13C
P0 3.33 usec
P1 10.00 usec
PLW1 49.43999863 W
SFO2 400.0926304 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 90.00 usec
PLW2 15.28599987 W
PLW12 3.41622999 W
PLW13 1.20936000 W
F2 - Processing parameters
SI 32768
SF 100.6029594 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

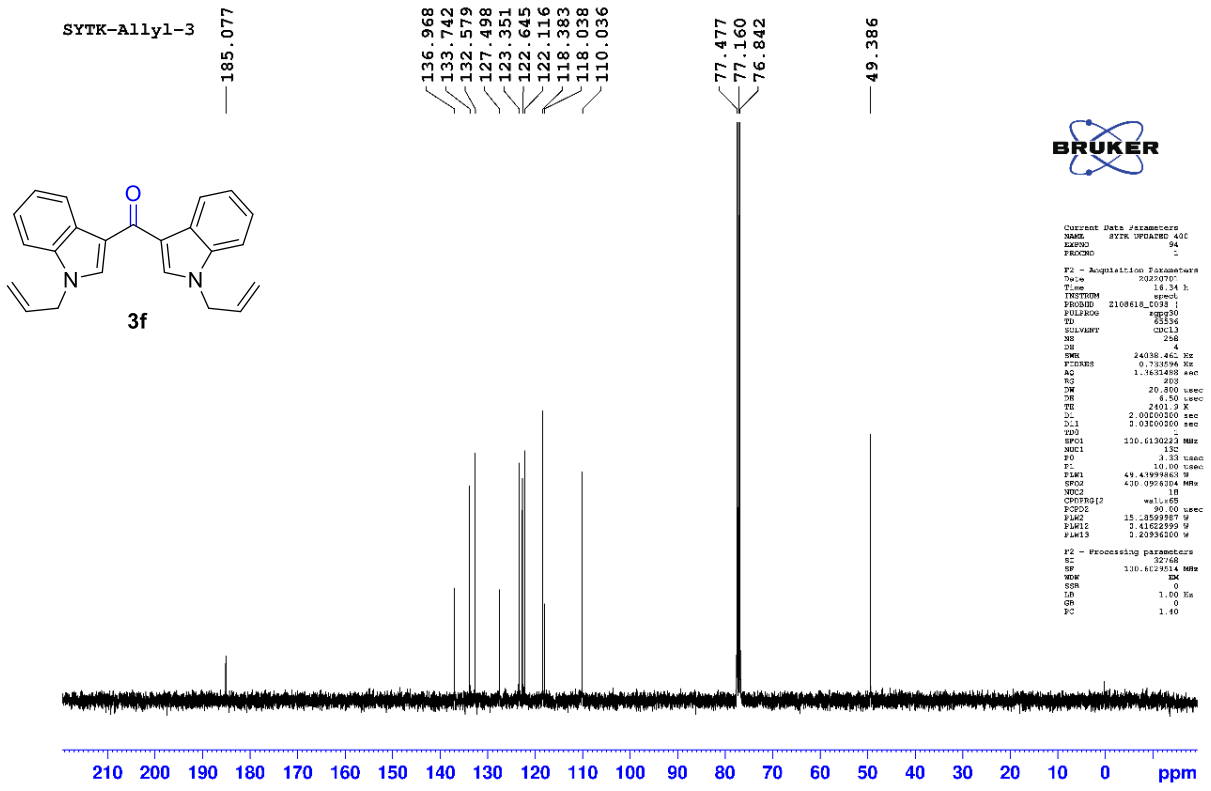

SYAH- NPH-205
8.511
8.509
8.497
8.495
7.939
7.573
7.569
7.556
7.543
7.539
7.529
7.528
7.458
7.454
7.450
7.444
7.441
7.436
7.432
7.427
7.423
7.385
7.383
7.371
7.369
7.356
7.353
7.348
7.345
7.331
7.329
7.317
7.315
7.253
0.000
O
N
Ph
N
Ph
3d
BRUKER
Current Data Parameters
NAME SYAH UPDATED 500
EXPNO 50
PROCNO 1
F2 - Acquisition Parameters
Date_ 20210511
Time 11.16 h
INSTRUM spect
PROBHD Z109128_0042 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 203
DW 50.000 usec
DE 13.04 usec
TE 910.2 K
D1 1.00000000 sec
TD0 1
SFO1 500.1830886 MHz
NUC1 1H
P0 5.00 usec
P1 15.00 usec
PLW1 4.84679985 W
F2 - Processing parameters
SI 65536
SF 500.1800145 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
11 10 9 8 7 6 5 4 3 2 1 0 ppm
2.00
2.02
10.24
2.12
2.19
2.13

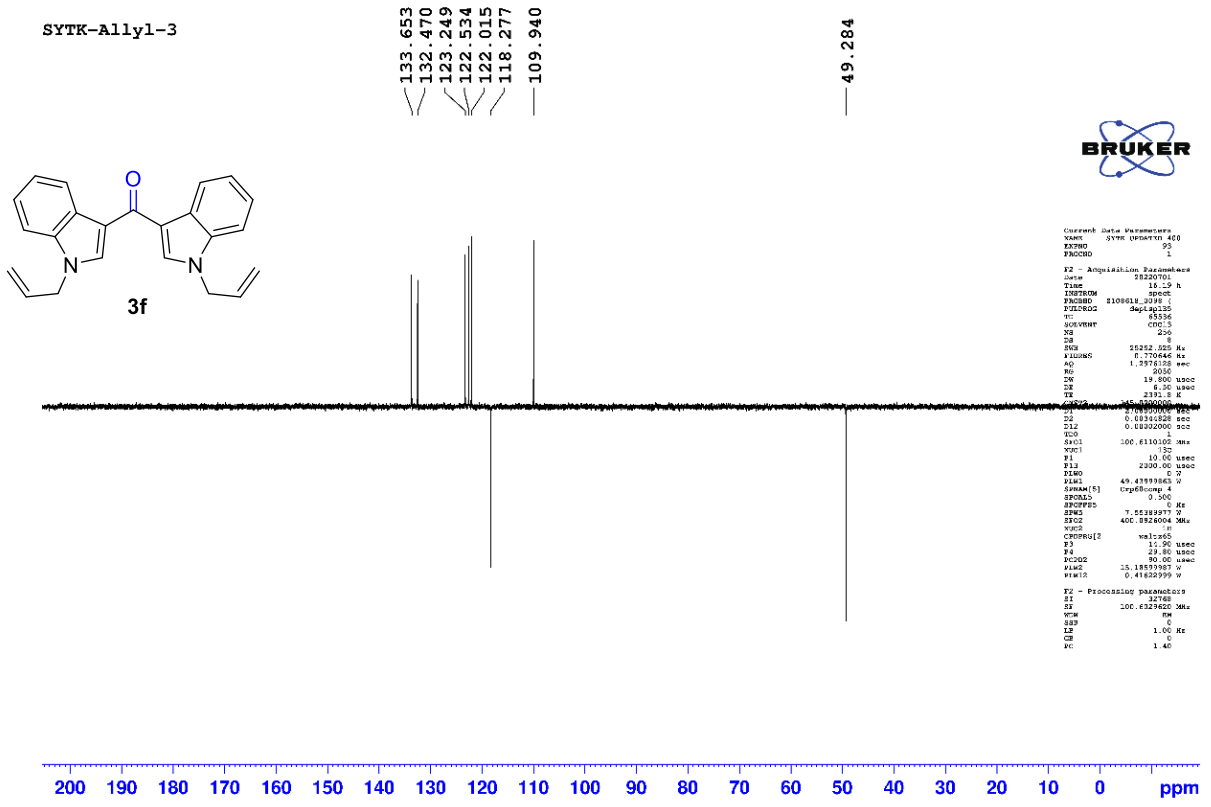

SYAH- NPH-205
185.196
138.741
137.089
133.570
129.978
127.858
127.717
125.019
124.083
122.780
119.452
110.864
77.477
77.160
76.842
O
N
Ph
N
Ph
3d
BRUKER
Current Data Parameters
NAME SYAH UPDATED 400
EXPNO 43
PROCNO 1
F2 - Acquisition Parameters
Date_ 20210627
Time 16.48 h
INSTRUM spect
PROBHD Z108618_0088 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 162
DS 4
SWH 24038.462 Hz
FIDRES 0.733596 Hz
AQ 1.3631488 sec
RG 645
DW 20.800 usec
DE 6.50 usec
TE 298.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.6130223 MHz
NUC1 13C
P0 3.33 usec
P1 10.00 usec
PLW1 49.43999863 W
SFO2 400.0926204 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 90.00 usec
PLW2 15.28599987 W
PLW12 3.41622999 W
PLW13 3.20936000 W
F2 - Processing parameters
SI 32768
SF 100.6029585 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


SYAH-ISO 214
8.334
8.333
8.318
7.812
7.443
7.427
7.325
7.323
7.311
7.309
7.295
7.292
7.283
7.268
7.254
7.251
4.766
4.752
4.739
4.726
4.712
1.588
1.574
0.000
O
N
Me
Me
N
Me
Me
3e
BRUKER
Current Data Parameters
NAME SYAH UPDATED 500
EXPNO 57
PROCNO 1
F2 - Acquisition Parameters
Date_ 20210702
Time 14.34 h
INSTRUM spect
PROBHD Z109128_0042 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 161
DW 50.000 usec
DE 13.04 usec
TE -22614.8 K
D1 1.00000000 sec
TD0 1
SFO1 500.1830886 MHz
NUC1 1H
P0 5.00 usec
P1 15.00 usec
PLW1 4.84679985 W
F2 - Processing parameters
SI 65536
SF 500.1800157 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
11 10 9 8 7 6 5 4 3 2 1 0 ppm
2.00
2.01
2.12
2.17
2.34
2.07
6.12
5.83

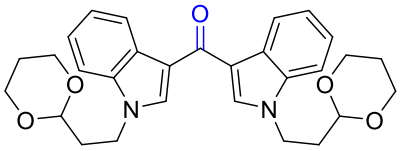

SYAH- ISO 214
185.211
136.472
130.178
127.370
122.937
122.440
121.833
117.980
109.911
77.478
77.160
76.842
47.695
22.791
BRUKER
O
N
N
Me
Me
Me
Me
3e
Current Data Parameters
NAME SYAH UPDATED 400
EXPNO 49
PROCNO 1
F2 - Acquisition Parameters
Date_ 20210702
Time 15.49 h
INSTRUM spect
PROBHD Z108618 0098 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 184
DS 4
SWH 24038.461 Hz
FIDRES 0.733596 Hz
AQ 1.3631488 sec
RG 1290
DW 20.800 usec
DE 6.50 usec
TE 702.4 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.6130223 MHz
NUC1 13C
P0 3.33 usec
P1 10.00 usec
PLW1 49.43999863 W
SFO2 400.0926004 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 90.00 usec
PLW2 15.18599987 W
PLW12 0.41622999 W
PLW13 0.20936000 W
F2 - Processing parameters
SI 32768
SF 100.6029625 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


SYTK-Allyl-3
8.397
8.395
8.391
8.383
8.378
7.680
7.674
7.393
7.382
7.379
7.370
7.365
7.355
7.343
7.331
7.328
7.317
7.314
7.308
7.303
7.298
7.293
7.290
7.279
7.276
7.260
6.070
6.060
6.049
6.039
6.036
6.028
6.025
6.015
6.005
5.994
5.289
5.287
5.269
5.267
5.193
5.191
5.158
5.156
4.810
4.807
4.804
4.799
4.796
4.793
1.581
0.000
BRUKER
O
N
N
3f
Current Data Parameters
NAME SYTK UPDATED 500
EXPNO 144
PROCNO 1
F2 - Acquisition Parameters
Date_ 20220701
Time 11.15 h
INSTRUM spect
PROBHD Z109128_0042 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 456
DW 50.000 usec
DE 13.04 usec
TE 297.6 K
D1 1.00000000 sec
TD0 1
SFO1 500.1830886 MHz
NUC1 1H
P0 5.00 usec
P1 15.00 usec
PLW1 4.84679985 W
F2 - Processing parameters
SI 65536
SF 500.1800125 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
2.32
2.00
2.17
2.39
2.15
1.02
1.05
2.20
2.22
1.92
1.89

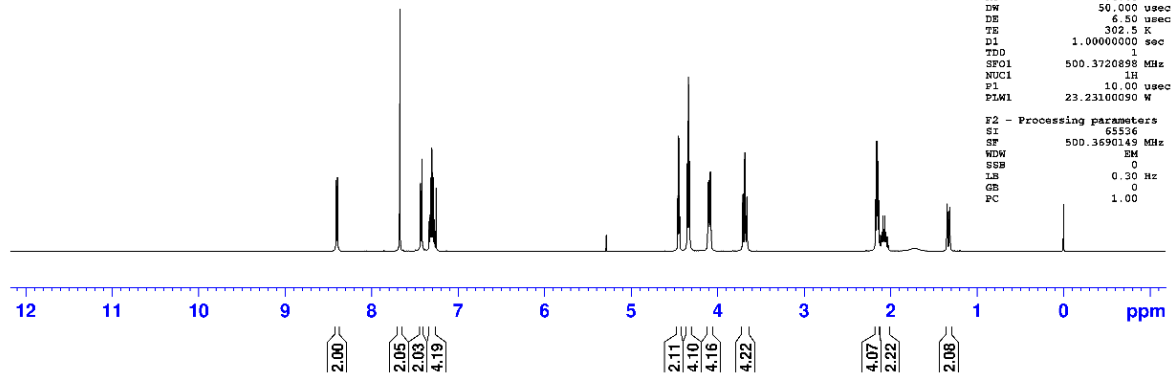

SYTK-Allyl-3
185.077
136.968
133.742
132.579
127.498
123.351
122.645
122.116
118.383
118.038
110.036
77.477
77.160
76.842
49.386
3f
BRUKER
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


SYTK-Allyl-3
133.653
132.470
123.249
122.534
122.015
118.277
109.940
49.284
3f
BRUKER
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

SYAH-DIOX-187

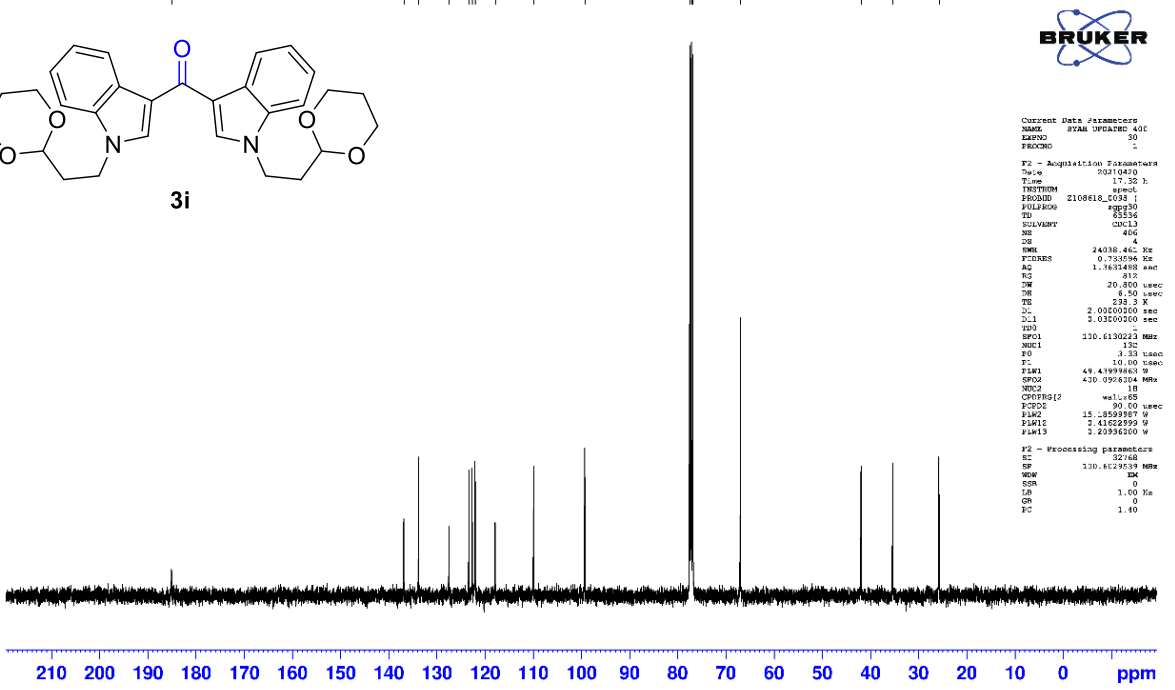


3i

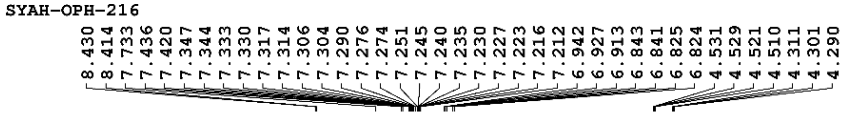


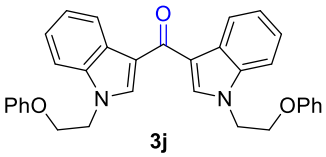
SYAH-DIOX-187

3i

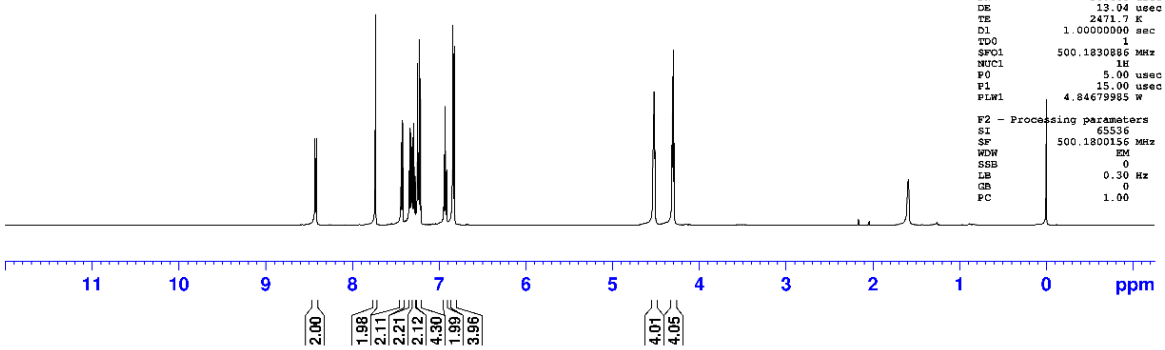


SYAH-OPH-216





3j

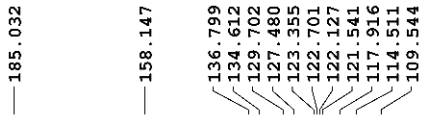


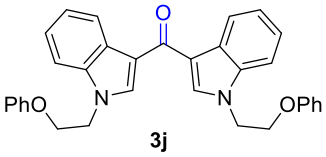
Current Data Parameters
NAME SYAH UPDATED 500
EXPNO 56
PROCNO 1

F2 - Acquisition Parameters
Date_ 20210701
Time 15.47 h
INSTRUM spect
PROBHD Z109128_0042 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 228
DW 50.000 usec
DE 13.04 usec
TE 2471.7 K
D1 1.00000000 sec
TD0 1
SFO1 500.1830886 MHz
NUC1 1H
P0 5.00 usec
P1 15.00 usec
PLW1 4.84679985 W

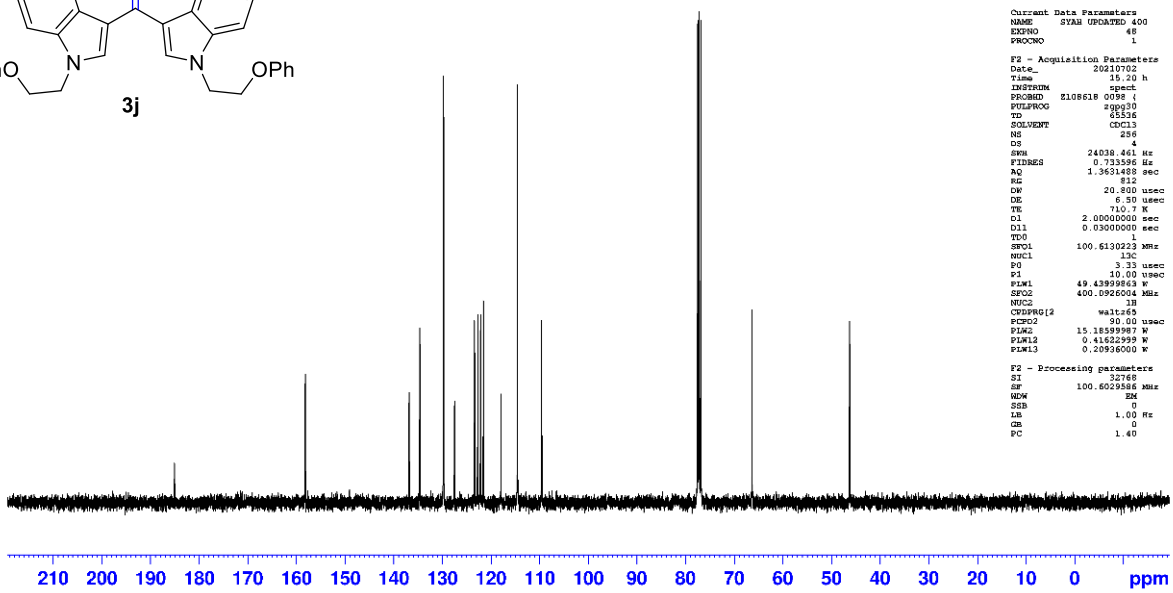
F2 - Processing parameters
SI 65536
SF 500.1800156 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

SYAH- OPH-216





3j

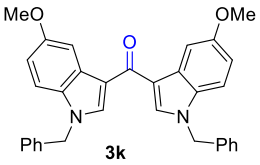


Current Data Parameters
NAME SYAH UPDATED 400
EXPNO 48
PROCNO 1

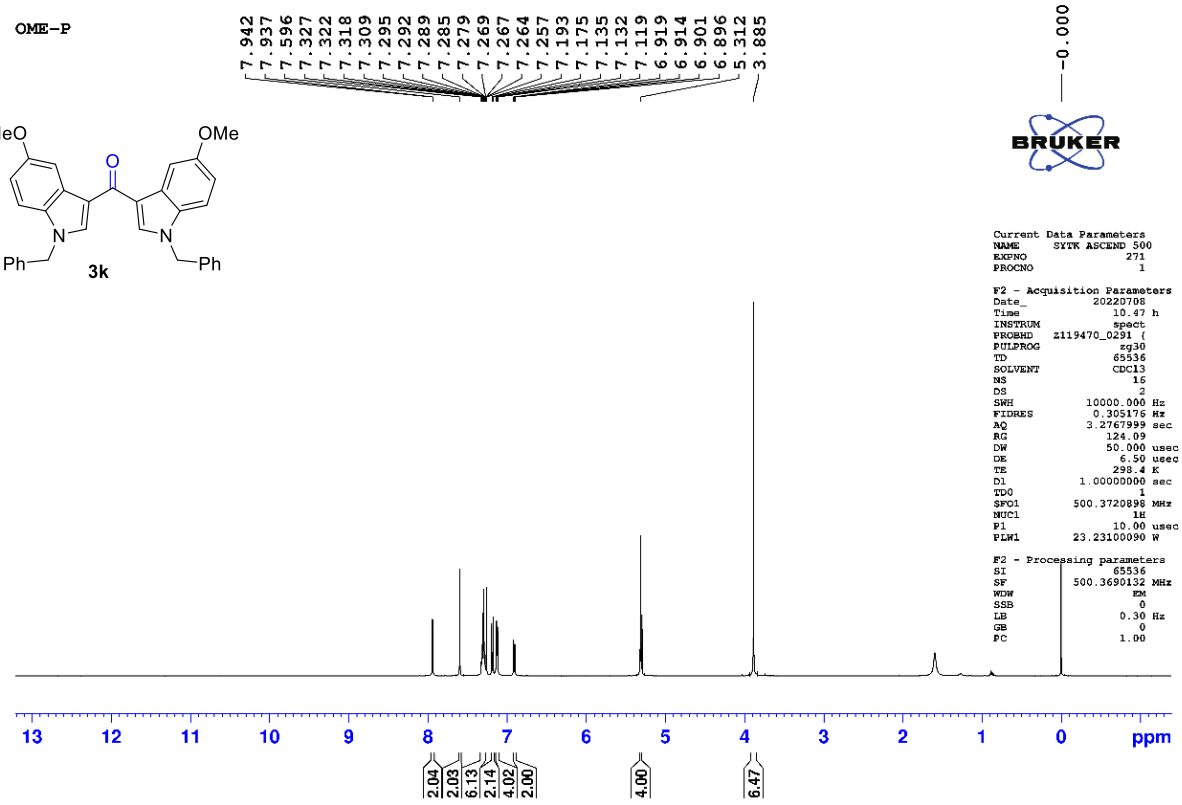
F2 - Acquisition Parameters
Date_ 20210702
Time 15.20 h
INSTRUM spect
PROBHD Z108618 0098 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 256
DS 4
SWH 24038.461 Hz
FIDRES 0.733596 Hz
AQ 1.3631488 sec
RG 812
DW 20.800 usec
DE 6.50 usec
TE 710.7 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.6130223 MHz
NUC1 13C
P0 3.33 usec
P1 10.00 usec
PLW1 49.43999863 W
SFO2 400.0926004 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 90.00 usec
PLW2 15.18599987 W
PLW12 0.41622999 W
PLW13 0.20936000 W

F2 - Processing parameters
SI 32768
SF 100.6029586 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40

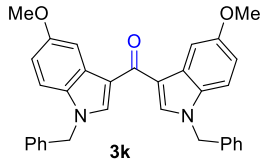
OME-P



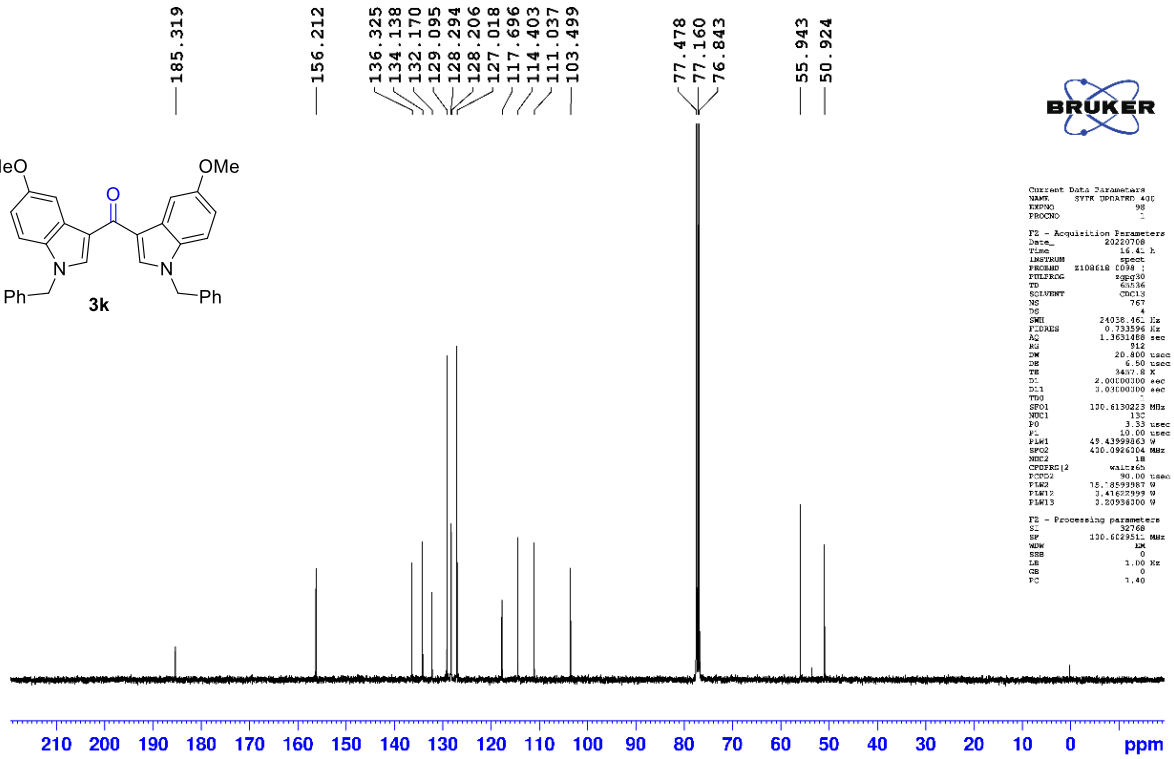
3k

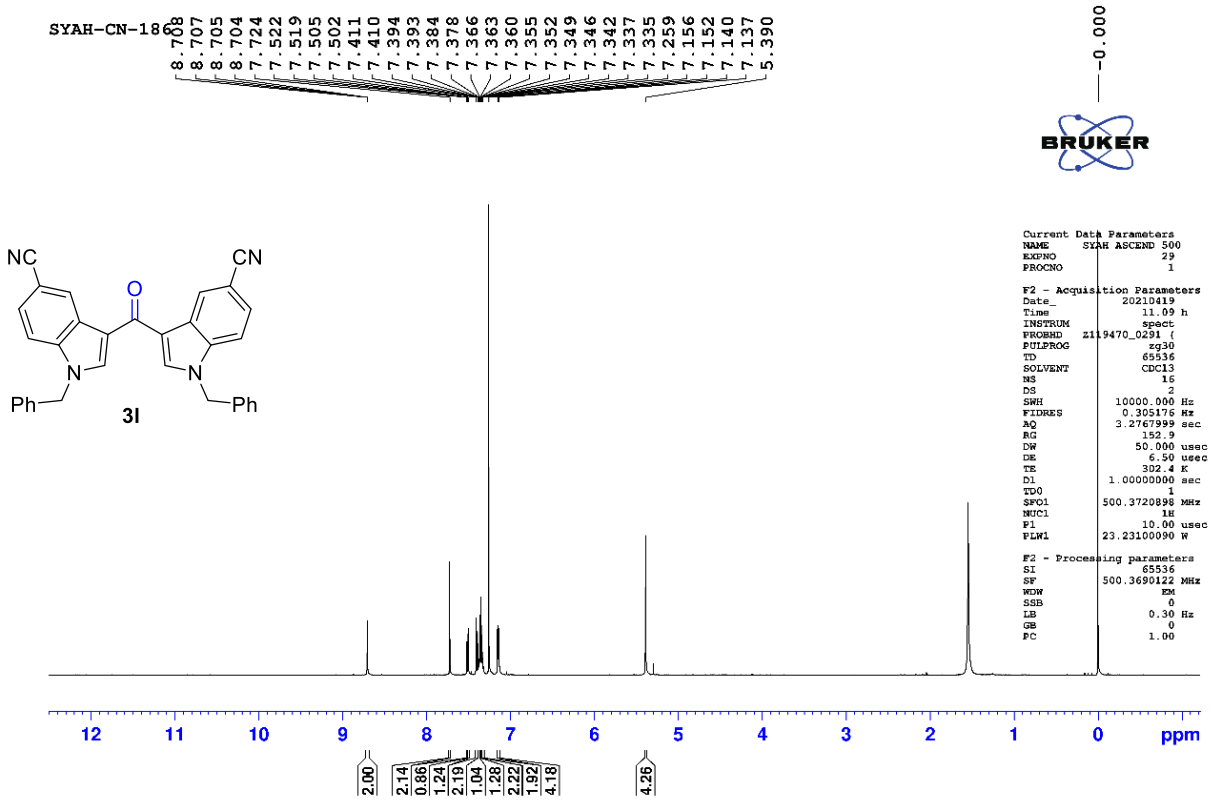


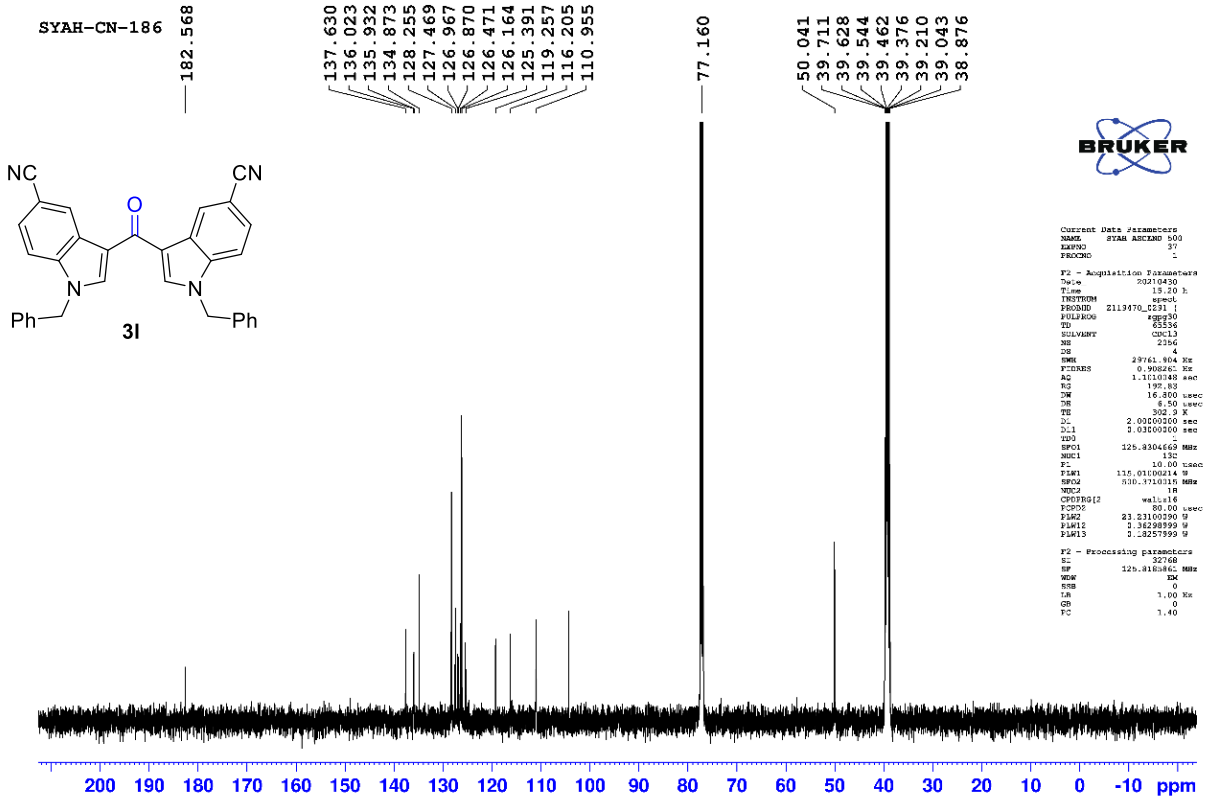
SYTK-Ome-P



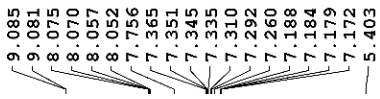
3k

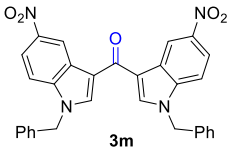



SYAH-CN-186
8.708
8.707
8.705
8.704
7.724
7.522
7.519
7.505
7.502
7.411
7.410
7.394
7.393
7.384
7.378
7.366
7.363
7.360
7.355
7.352
7.349
7.346
7.342
7.337
7.335
7.259
7.156
7.152
7.140
7.137
5.390
0.000
BRUKER
NC
CN
O
N
N
Ph
Ph
3l
Current Data Parameters
NAME SYAH ASCEND 500
EXPNO 29
PROCNO 1
F2 - Acquisition Parameters
Date_ 20210419
Time 11.09 h
INSTRUM spect
PROBHD Z119470_0291 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 152.9
DW 50.000 usec
DE 6.50 usec
TE 302.4 K
D1 1.00000000 sec
TD0 1
SFO1 500.3720898 MHz
NUC1 1H
P1 10.00 usec
PLW1 23.23100090 W
F2 - Processing parameters
SI 65536
SF 500.3690122 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
2.00 2.14 0.86 1.24 2.19 1.04 1.28 2.22 1.92 4.18 4.26

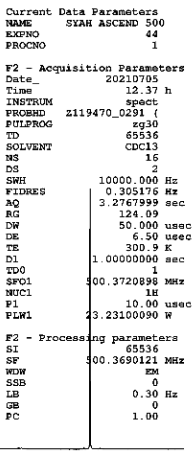

SYAH-CN-186
182.568
137.630
136.023
135.932
134.873
128.255
127.469
126.967
126.870
126.471
126.164
125.391
119.257
116.205
110.955
77.160
50.041
39.711
39.628
39.544
39.462
39.376
39.210
39.043
38.876
BRUKER
NC
CN
O
N
N
Ph
Ph
3l
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 ppm

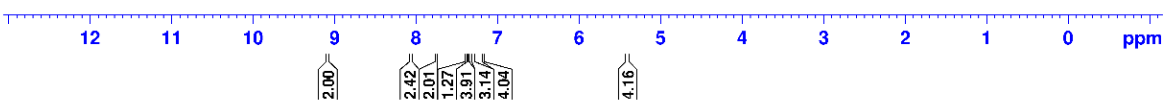
NO2 -215



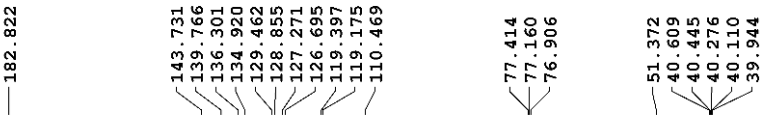


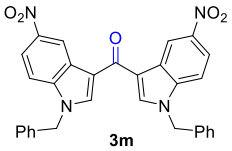
3m



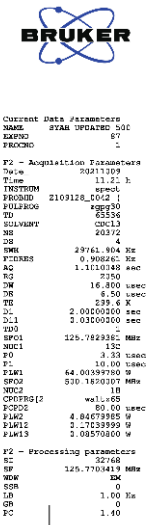


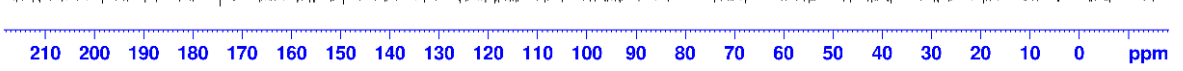
SYAH-No2-215

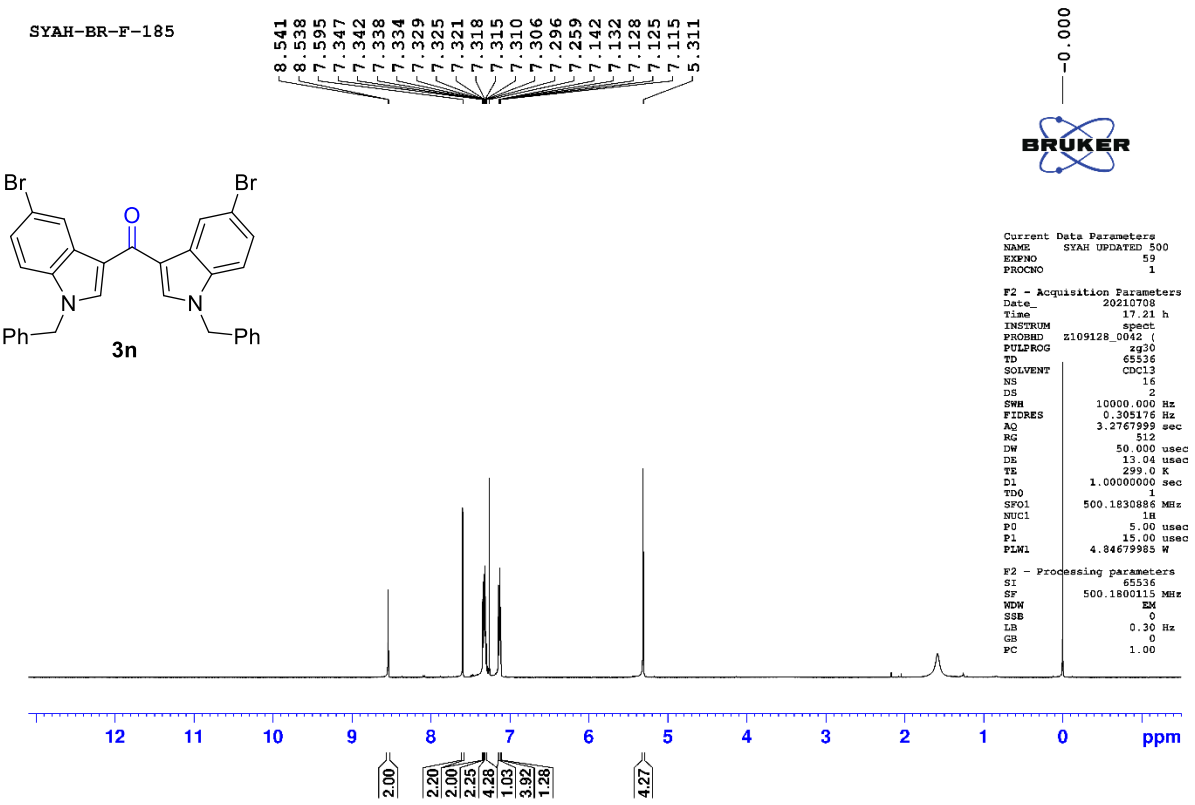


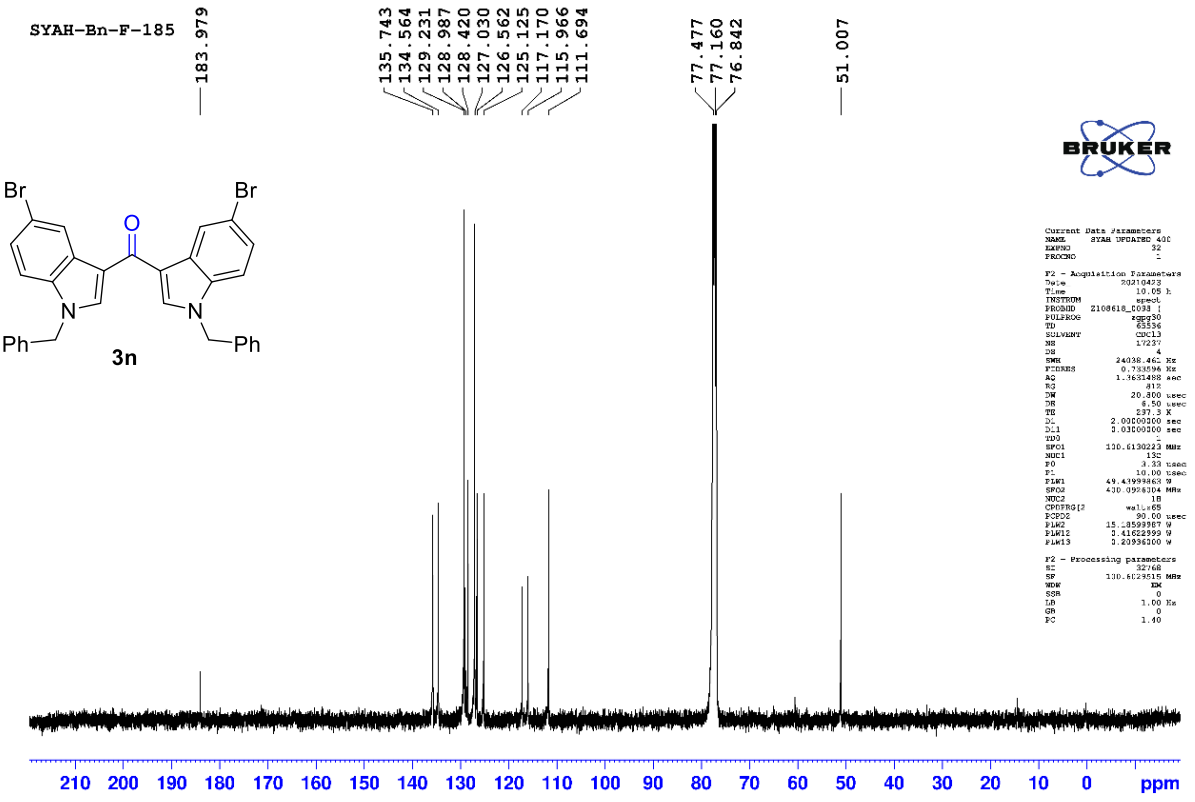


3m

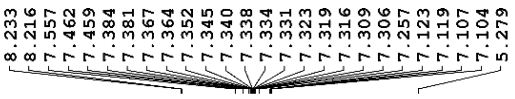


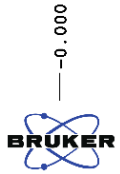


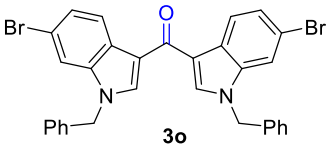

SYAH-BR-F-185
8.541
8.538
7.595
7.347
7.342
7.338
7.334
7.329
7.325
7.321
7.318
7.315
7.310
7.306
7.296
7.259
7.142
7.132
7.128
7.125
7.115
5.311
0.000
BRUKER
Br
Br
O
N
N
Ph
Ph
3n
Current Data Parameters
NAME SYAH UPDATED 500
EXPNO 59
PROCNO 1
F2 - Acquisition Parameters
Date_ 20210708
Time 17.21 h
INSTRUM spect
PROBHD Z109128_0042 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 512
DW 50.000 usec
DE 13.04 usec
TE 299.0 K
D1 1.00000000 sec
TD0 1
SFO1 500.1830886 MHz
NUC1 1H
P0 5.00 usec
P1 15.00 usec
PLW1 4.84679985 W
F2 - Processing parameters
SI 65536
SF 500.1800115 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
2.00
2.20
2.00
2.25
4.28
1.03
3.92
1.28
4.27


SYAH-Bn-F-185
183.979
135.743
134.564
129.231
128.987
128.420
127.030
126.562
125.125
117.170
115.966
111.694
77.477
77.160
76.842
51.007
BRUKER
Br
Br
O
N
N
Ph
Ph
3n
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

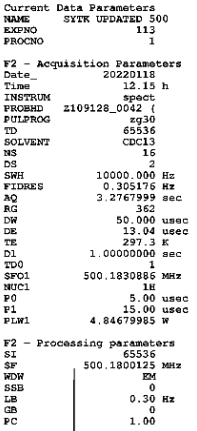
SYTK-125

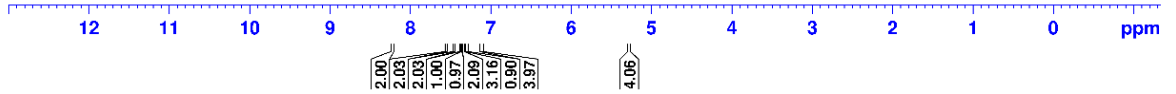






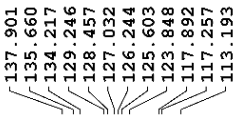
3o

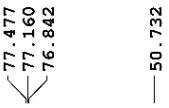




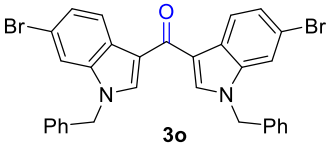
SYTK- 125





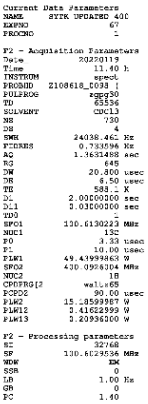


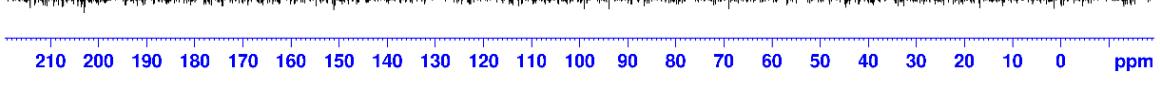


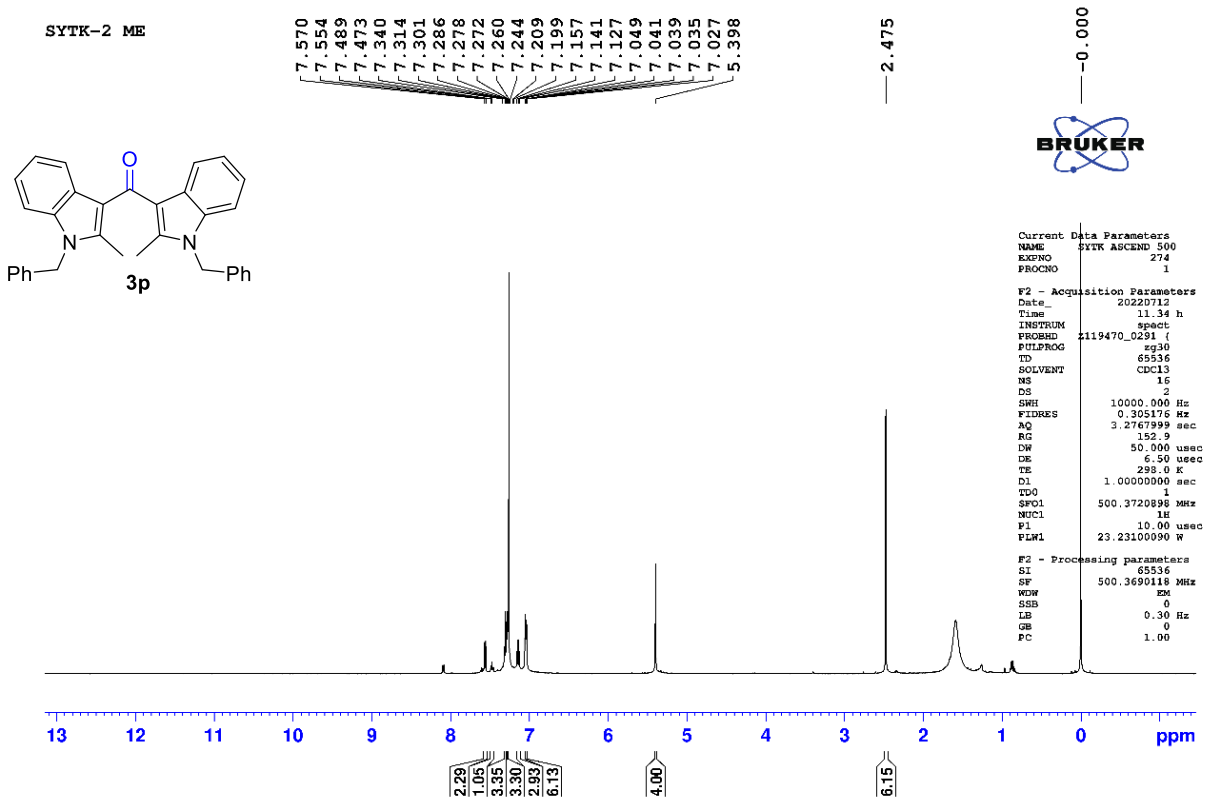


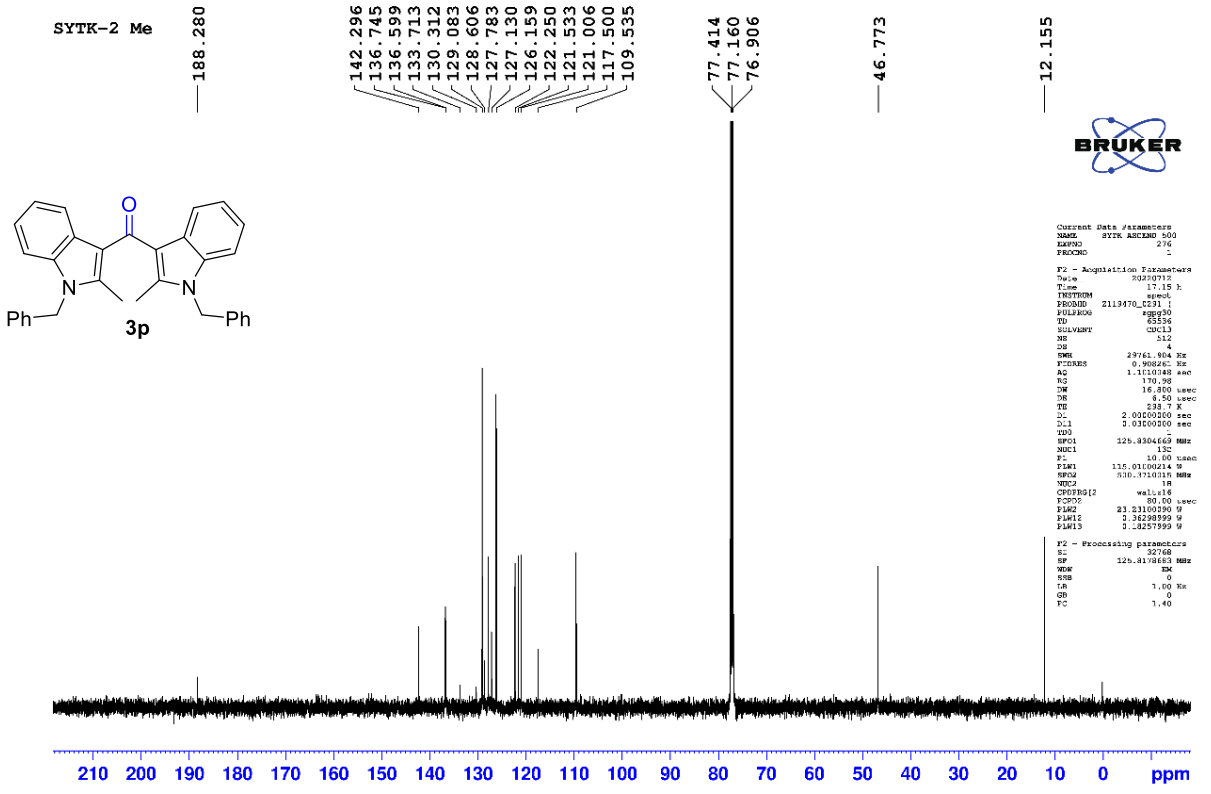
3o



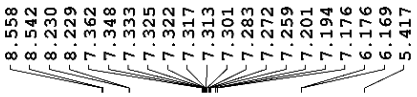


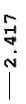



SYTK-2 ME
7.570
7.554
7.489
7.473
7.340
7.314
7.301
7.286
7.278
7.272
7.260
7.244
7.209
7.199
7.157
7.141
7.127
7.049
7.041
7.039
7.035
7.027
5.398
2.475
0.000
BRUKER
Ph
N
O
N
Ph
3p
Current Data Parameters
NAME SYTK ASCEND 500
EXPNO 274
PROCNO 1
F2 - Acquisition Parameters
Date_ 20220712
Time 11.34 h
INSTRUM spect
PROBHD Z119470_0291 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 152.9
DW 50.000 usec
DE 6.50 usec
TE 298.0 K
D1 1.00000000 sec
TD0 1
SFO1 500.3720898 MHz
NUC1 1H
P1 10.00 usec
PLW1 23.23100090 W
F2 - Processing parameters
SI 65536
SF 500.3690118 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
2.29
1.05
3.35
3.30
2.93
6.13
4.00
6.15

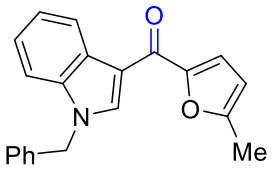

SYTK-2 Me
188.280
142.296
136.745
136.599
133.713
130.312
129.083
128.606
127.783
127.130
126.159
122.250
121.533
121.006
117.500
109.535
77.414
77.160
76.906
46.773
12.155
BRUKER
Ph
N
O
N
Ph
3p
Current Data Parameters
NAME SYTK ASCEND 500
EXPNO 276
PROCNO 1
F2 - Acquisition Parameters
Date_ 20220712
Time 17.15 h
INSTRUM spect
PROBHD Z119470_0291 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 512
DS 4
SWH 29761.904 Hz
FIDRES 0.908267 Hz
AQ 1.1010348 sec
RG 170.98
DW 16.800 usec
DE 6.50 usec
TE 298.7 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.8304669 MHz
NUC1 13C
P1 10.00 usec
PLW1 115.01000214 W
SFO2 500.3710315 MHz
NUC2 1H
CPDPRG[2 waltz16
PCPD2 80.00 usec
PLW2 23.23100090 W
PLW12 0.36298999 W
PLW13 0.18257999 W
F2 - Processing parameters
SI 32768
SF 125.8178683 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

SYAH-FUR-259

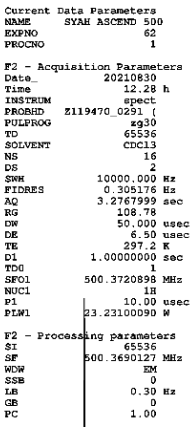


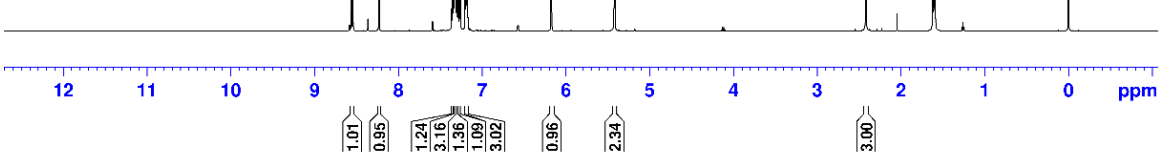




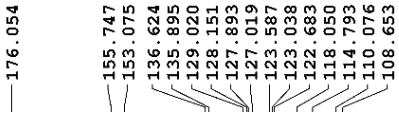


3q

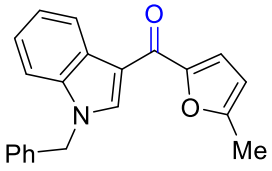




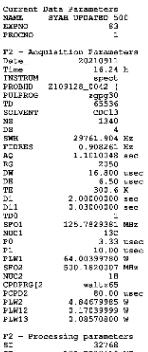
SYAH-FUR-F-259

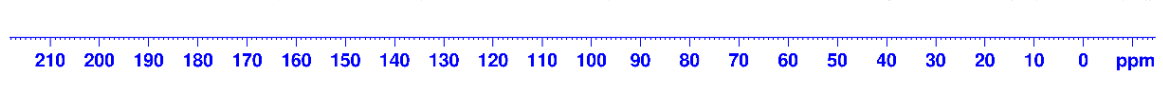


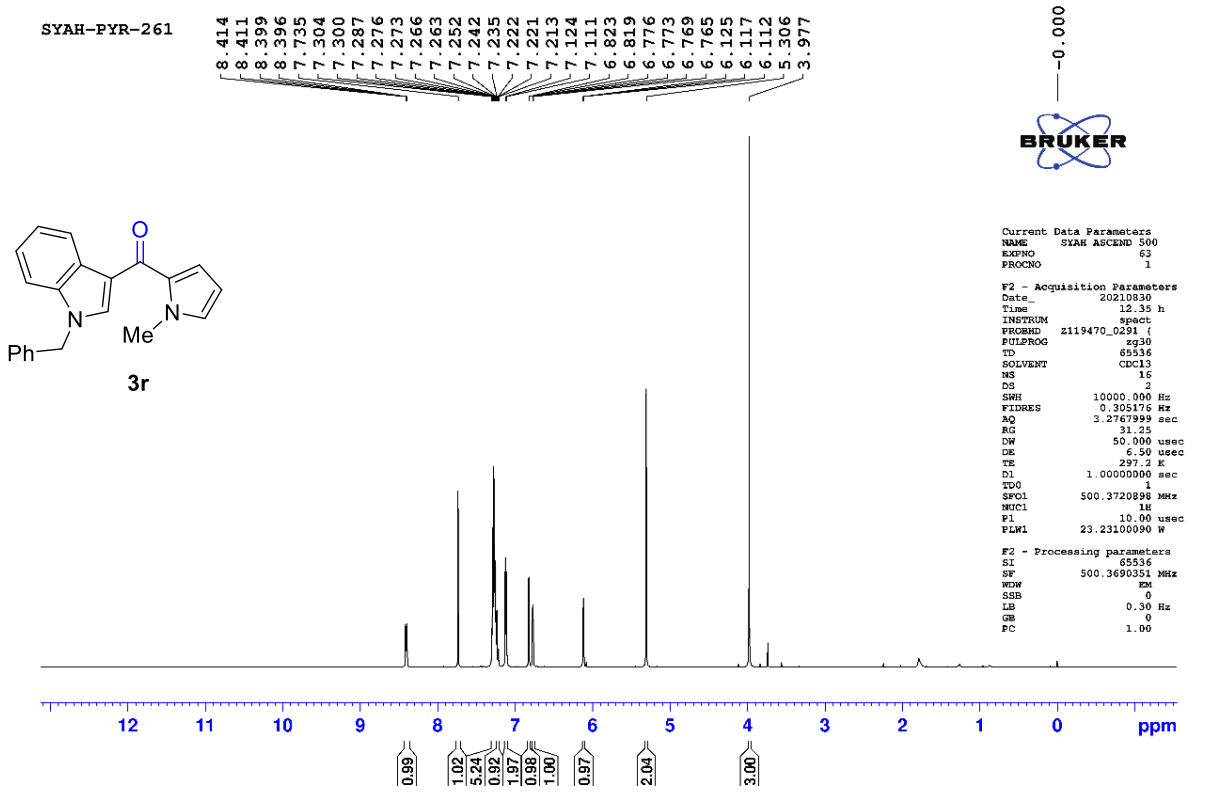


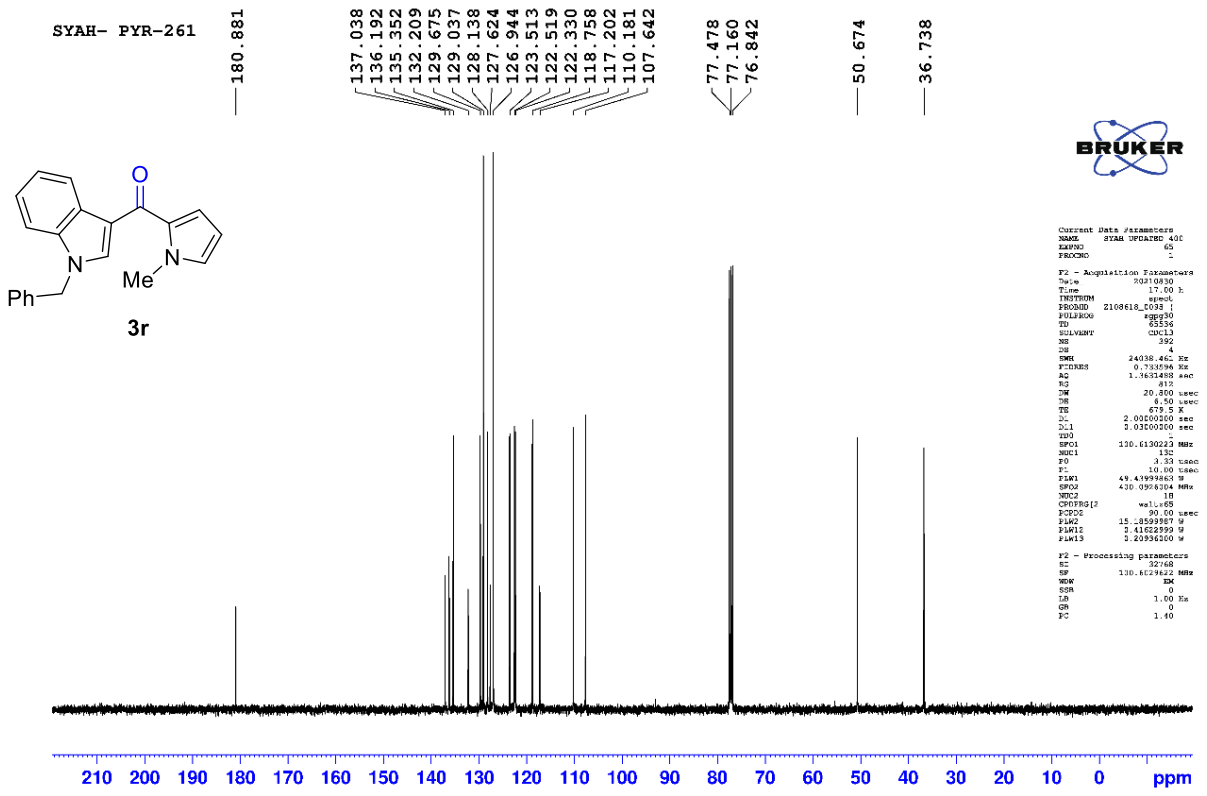


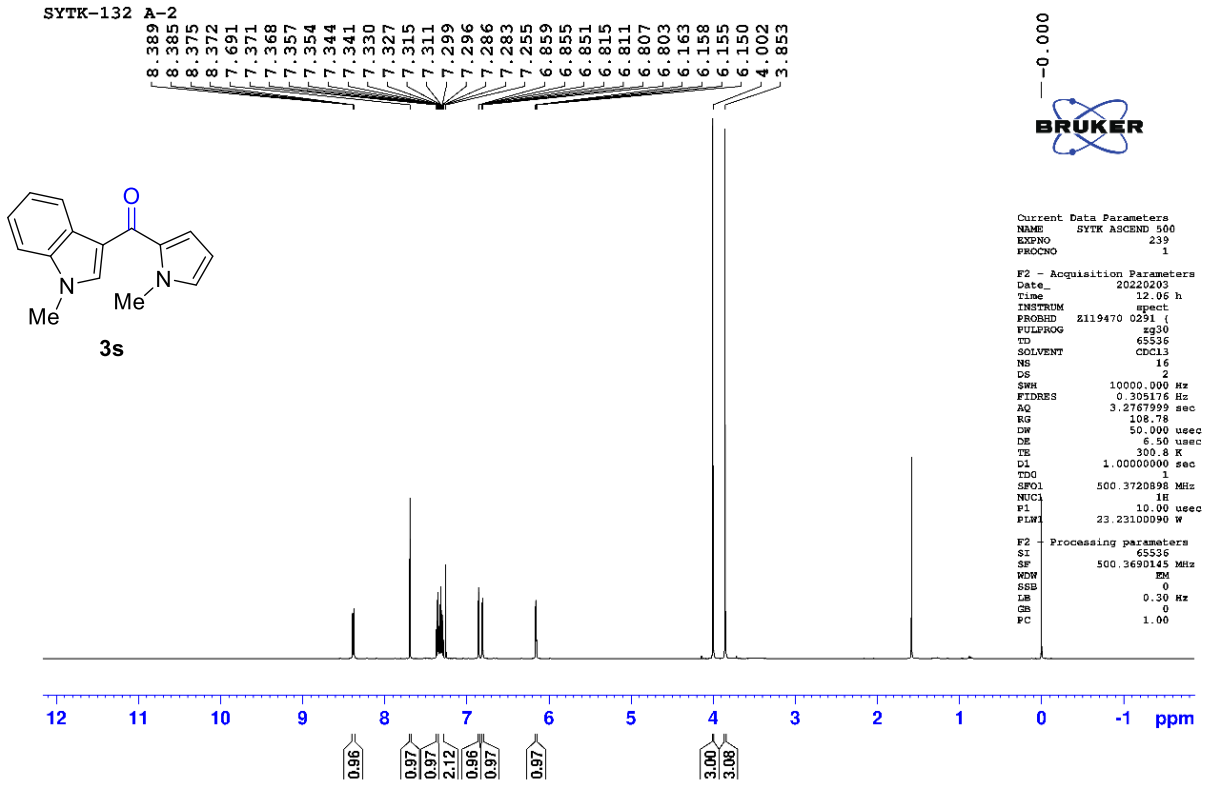
3q

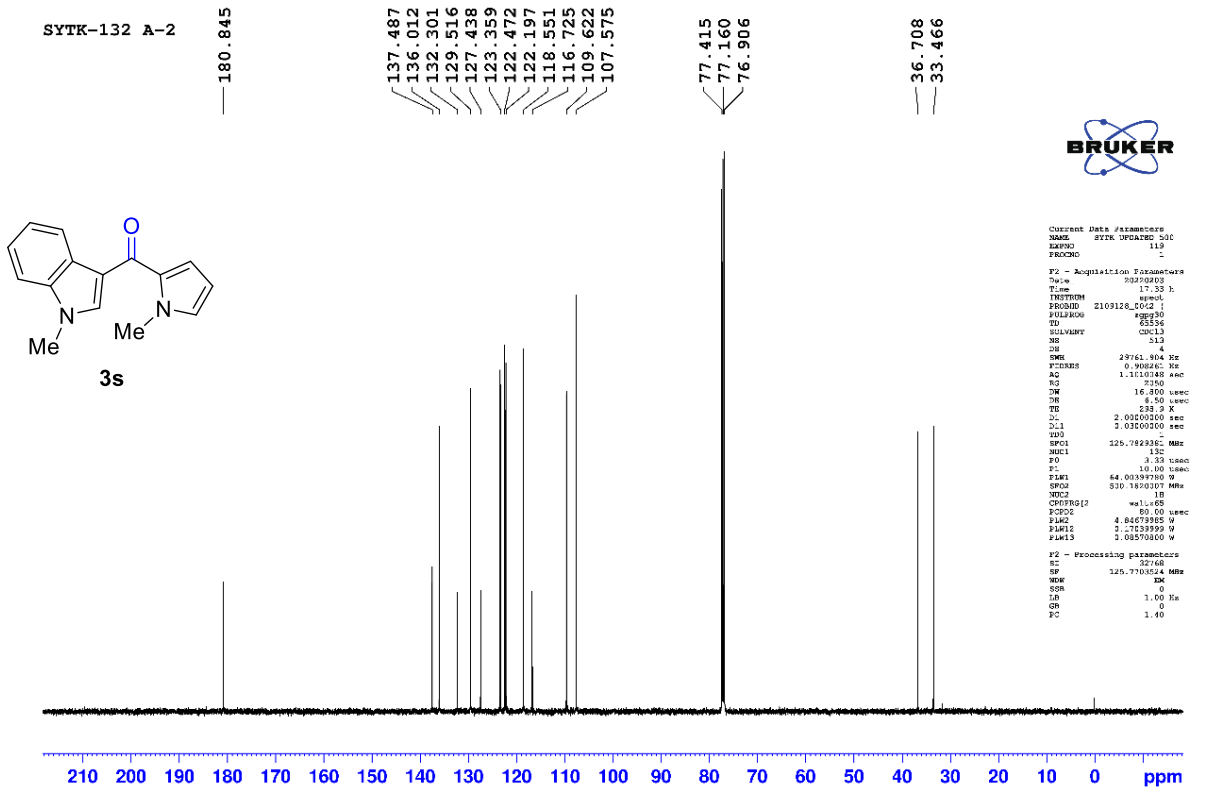




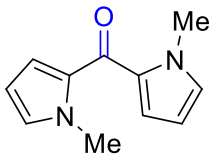

SYAH-PYR-261
8.414
8.411
8.399
8.396
7.735
7.304
7.300
7.287
7.276
7.273
7.266
7.263
7.252
7.242
7.235
7.222
7.221
7.213
7.124
7.111
6.823
6.819
6.776
6.773
6.769
6.765
6.125
6.117
6.112
5.306
3.977
0.000
BRUKER
O
N
Me
N
Ph
3r
Current Data Parameters
NAME SYAH ASCEND 500
EXPNO 63
PROCNO 1
F2 - Acquisition Parameters
Date_ 20210830
Time 12.35 h
INSTRUM spect
PROBHD Z119470_0291 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 31.25
DW 50.000 usec
DE 6.50 usec
TE 297.2 K
D1 1.00000000 sec
TD0 1
SFO1 500.3720898 MHz
NUC1 1H
P1 10.00 usec
PLW1 23.23100090 W
F2 - Processing parameters
SI 65536
SF 500.3690351 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.99
1.02
5.24
0.92
1.97
0.98
1.00
0.97
2.04
3.00


SYAH- PYR-261
180.881
137.038
136.192
135.352
132.209
129.675
129.037
128.138
127.624
126.944
123.513
122.519
122.330
118.758
117.202
110.181
107.642
77.478
77.160
76.842
50.674
36.738
BRUKER
O
N
Me
N
Ph
3r
Current Data Parameters
NAME SYAH UPDATED 400
EXPNO 65
PROCNO 1
F2 - Acquisition Parameters
Date_ 20210830
Time 17.00 h
INSTRUM spect
PROBHD Z108618_0038 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 392
DS 4
SWH 24038.461 Hz
FIDRES 0.733096 Hz
AQ 1.3631488 sec
RG 812
DW 20.800 usec
DE 6.50 usec
TE 679.5 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.6130223 MHz
NUC1 13C
P0 3.33 usec
P1 10.00 usec
PLW1 49.43999863 W
SFO2 400.0908304 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 90.00 usec
PLW2 15.08599987 W
PLW12 3.41622999 W
PLW13 1.20936200 W
F2 - Processing parameters
SI 32768
SF 100.6129622 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

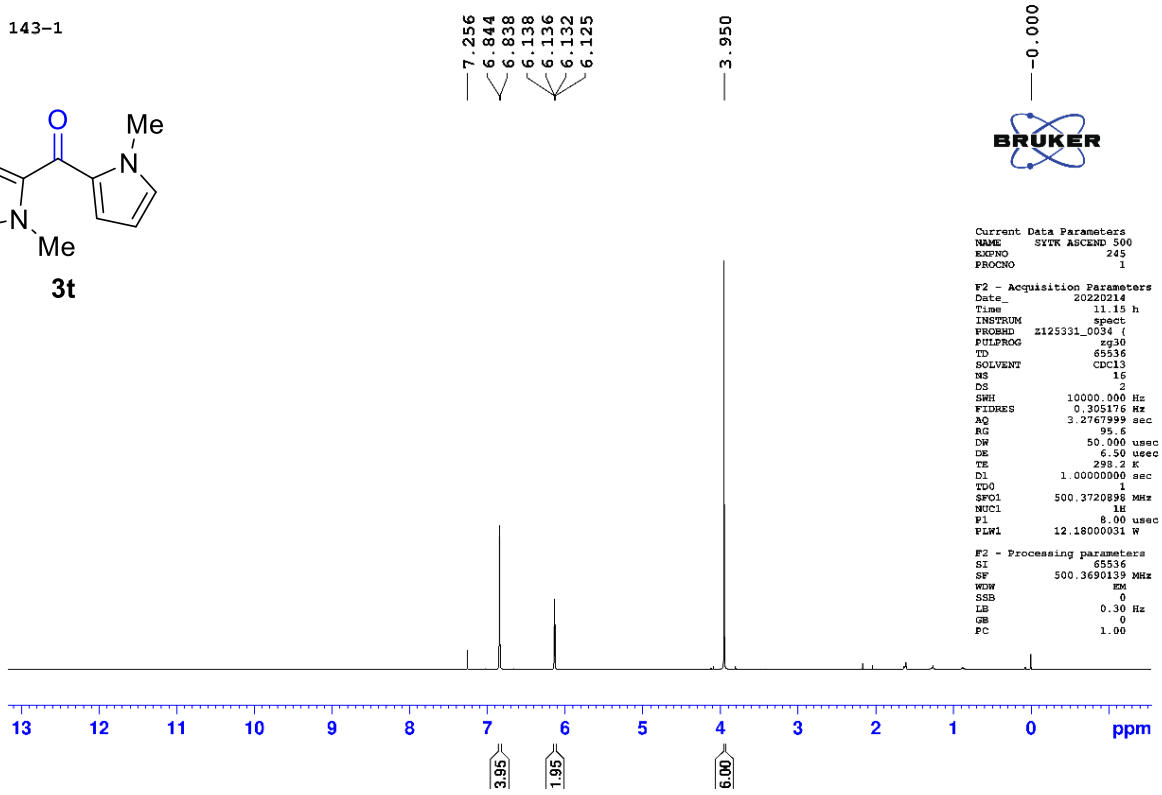

SYTK-132 A-2
8.389
8.385
8.375
8.372
7.691
7.371
7.368
7.357
7.354
7.344
7.341
7.330
7.327
7.315
7.311
7.299
7.296
7.286
7.283
7.255
6.859
6.855
6.851
6.815
6.811
6.807
6.803
6.163
6.158
6.155
6.150
4.002
3.853
-0.000
BRUKER
O
N
Me
N
Me
3s
Current Data Parameters
NAME SYTK ASCEND 500
EXPNO 239
PROCNO 1
F2 - Acquisition Parameters
Date_ 20220203
Time 12.06 h
INSTRUM spect
PROBHD Z119470 0291 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 108.78
DW 50.000 usec
DE 6.50 usec
TE 300.8 K
D1 1.00000000 sec
TD0 1
SFO1 500.3720898 MHz
NUC1 1H
P1 10.00 usec
PLW1 23.23100090 W
F2 - Processing parameters
SI 65536
SF 500.3690145 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
0.96
0.97
0.97
2.12
0.96
0.97
0.97
3.00
3.08


SYTK-132 A-2
180.845
137.487
136.012
132.301
129.516
127.438
123.359
122.472
122.197
118.551
116.725
109.622
107.575
77.415
77.160
76.906
36.708
33.466
BRUKER
O
N
Me
N
Me
3s
Current Data Parameters
NAME SYTK UPDATED 500
EXPNO 119
PROCNO 1
F2 - Acquisition Parameters
Date_ 20220203
Time 17.33 h
INSTRUM spect
PROBHD Z103128_5mm_2
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 513
DS 4
SWH 29761.904 Hz
FIDRES 0.908261 Hz
AQ 1.1010048 sec
RG 7350
DW 16.800 usec
DE 6.50 usec
TE 298.9 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.7823362 MHz
NUC1 13C
P0 3.33 usec
P1 10.00 usec
PLW1 54.00399780 W
SFO2 500.1870207 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 80.00 usec
PLW2 4.84679985 W
PLW12 1.17033999 W
PLW13 1.08570800 W
F2 - Processing parameters
SI 32768
SF 125.7703524 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

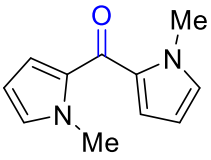
143-1



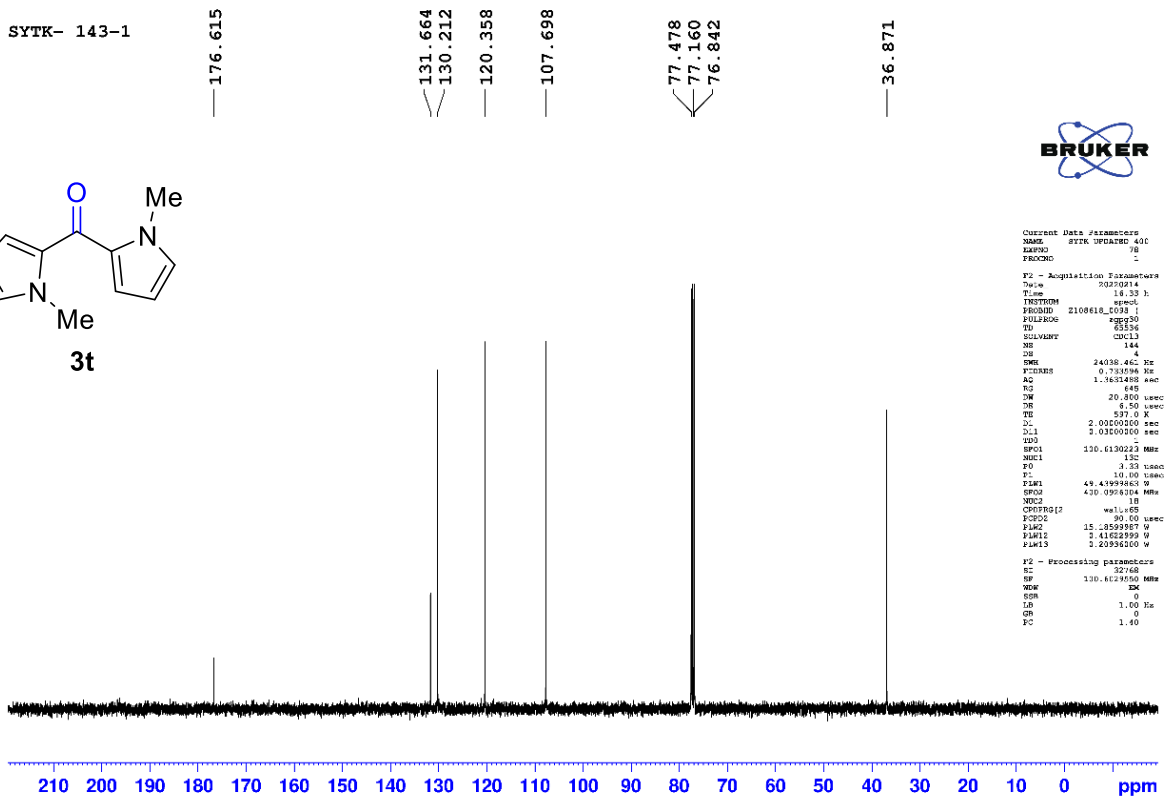
3t

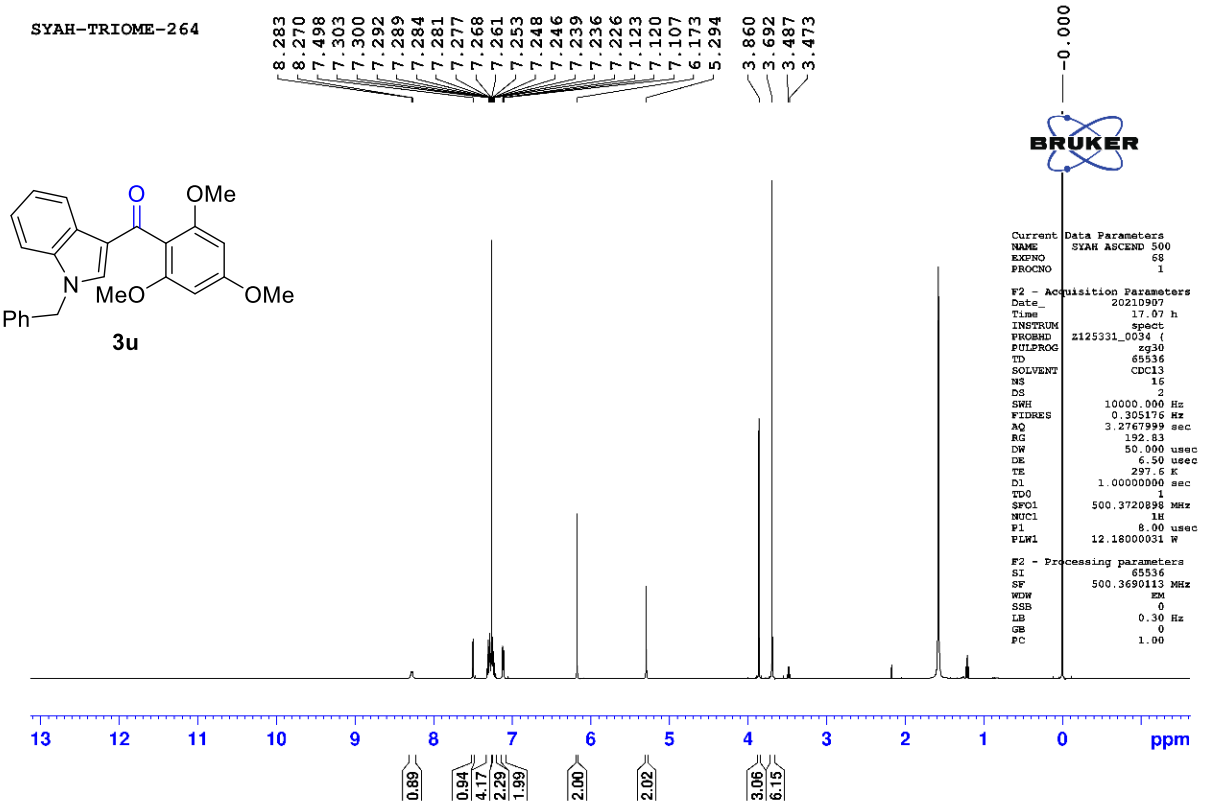


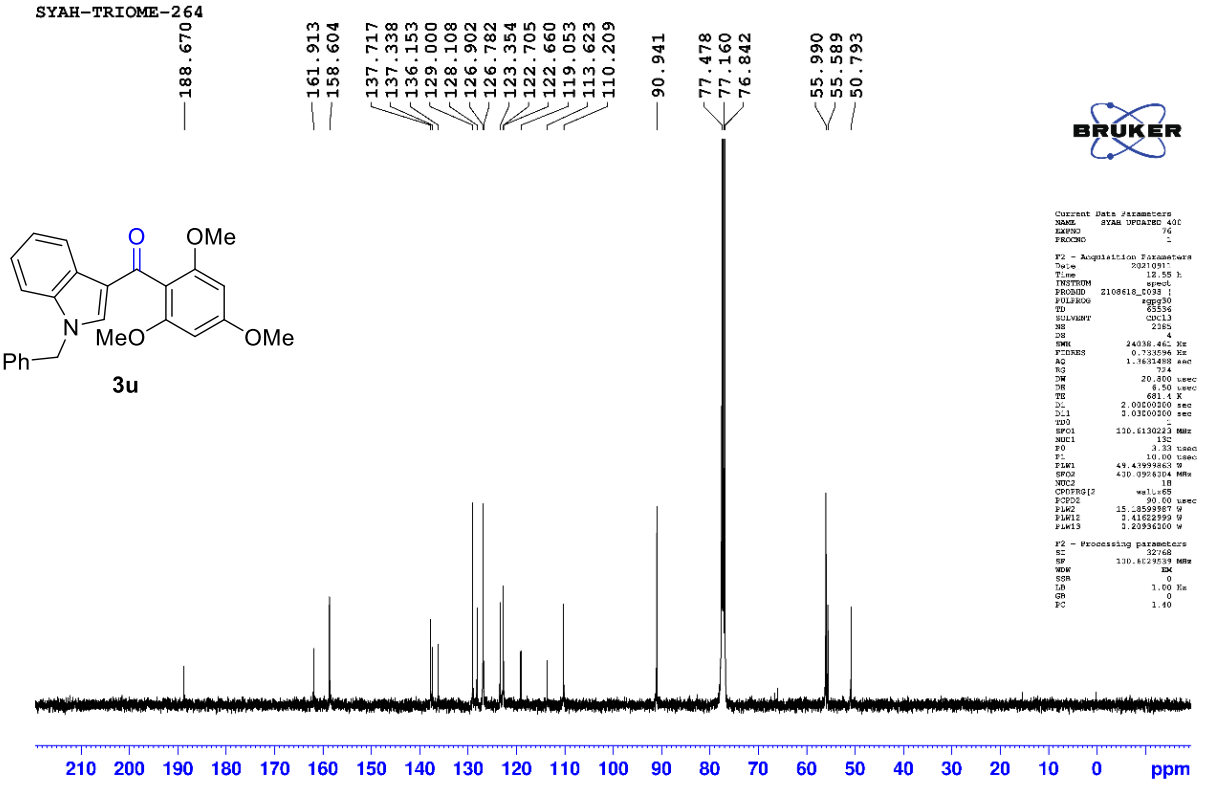
SYTK- 143-1



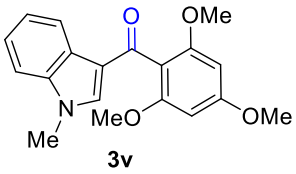
3t



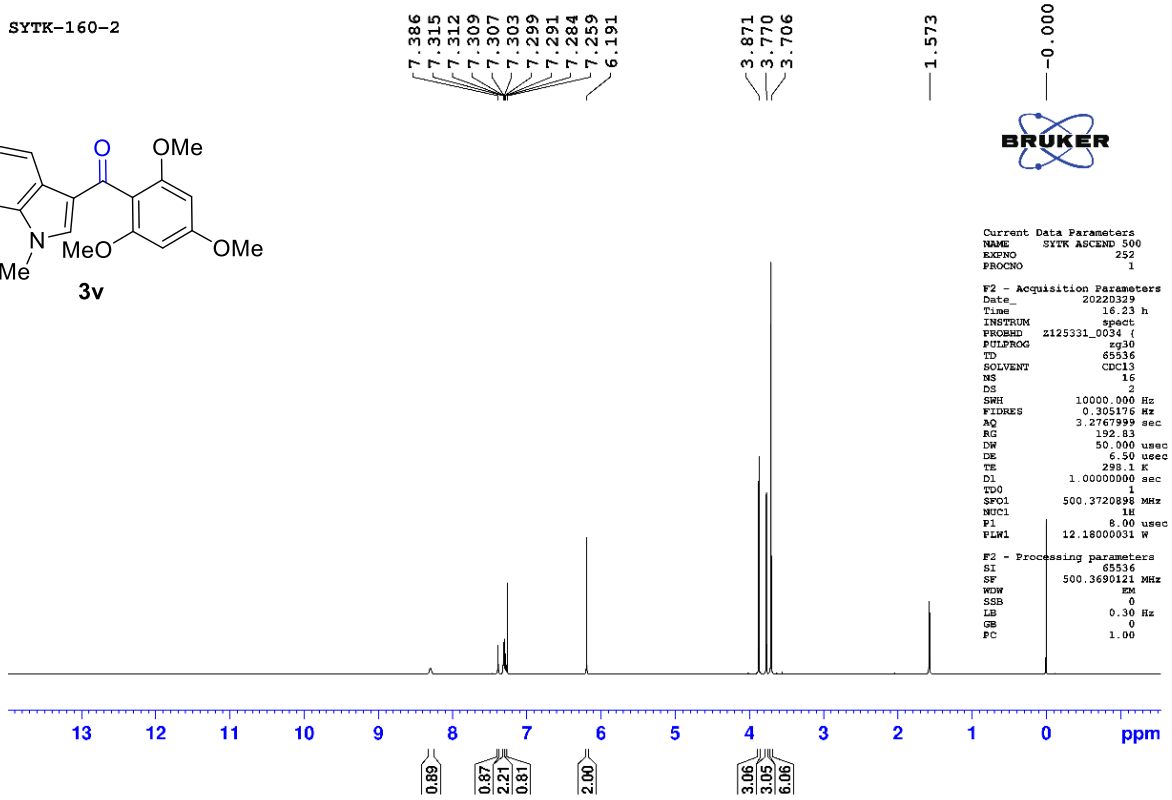

SYAH-TRIOME-264
8.283
8.270
7.498
7.303
7.300
7.292
7.289
7.284
7.281
7.277
7.268
7.261
7.253
7.248
7.246
7.239
7.236
7.226
7.123
7.120
7.107
6.173
5.294
3.860
3.692
3.487
3.473
-0.000
BRUKER
O
OMe
N
MeO
OMe
Ph
3u
Current Data Parameters
NAME SYAH ASCEND 500
EXPNO 68
PROCNO 1
F2 - Acquisition Parameters
Date_ 20210907
Time 17.07 h
INSTRUM spect
PROBHD Z125331_0034 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 192.83
DW 50.000 usec
DE 6.50 usec
TE 297.6 K
D1 1.00000000 sec
TD0 1
SFO1 500.3720898 MHz
NUC1 1H
P1 8.00 usec
PLW1 12.18000031 W
F2 - Processing parameters
SI 65536
SF 500.3690113 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
0.89
0.94
4.17
2.29
1.99
2.00
2.02
3.06
6.15


SYAH-TRIOME-264
188.670
161.913
158.604
137.717
137.338
136.153
129.000
128.108
126.902
126.782
123.354
122.705
122.660
119.053
113.623
110.209
90.941
77.478
77.160
76.842
55.990
55.589
50.793
BRUKER
O
OMe
N
MeO
OMe
Ph
3u
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

SYTK-160-2

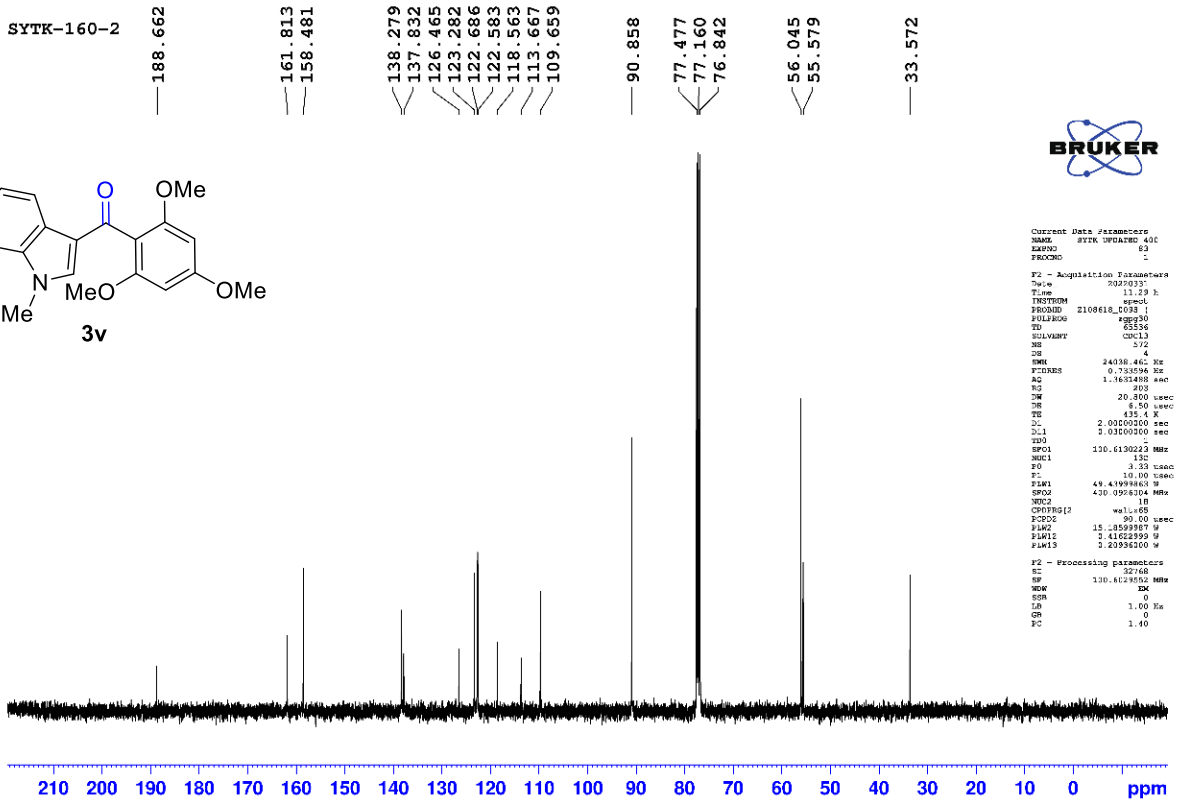


3v

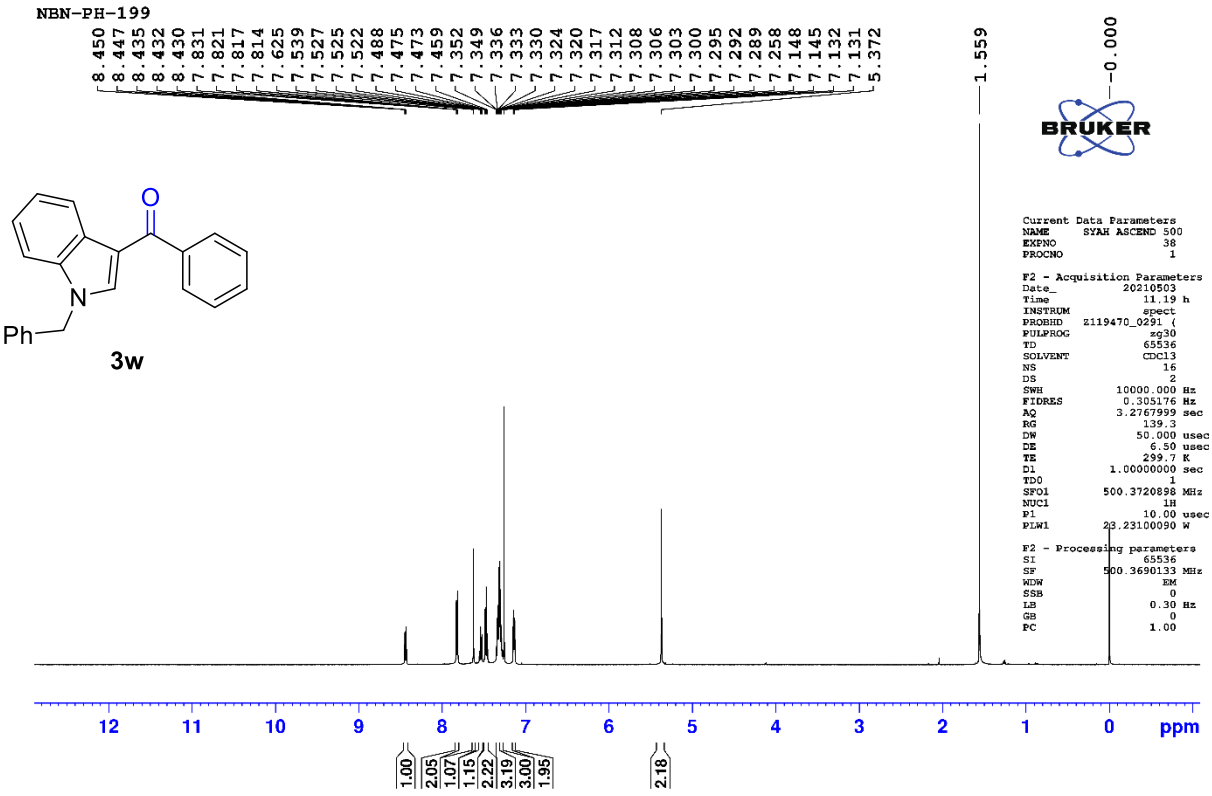


SYTK-160-2

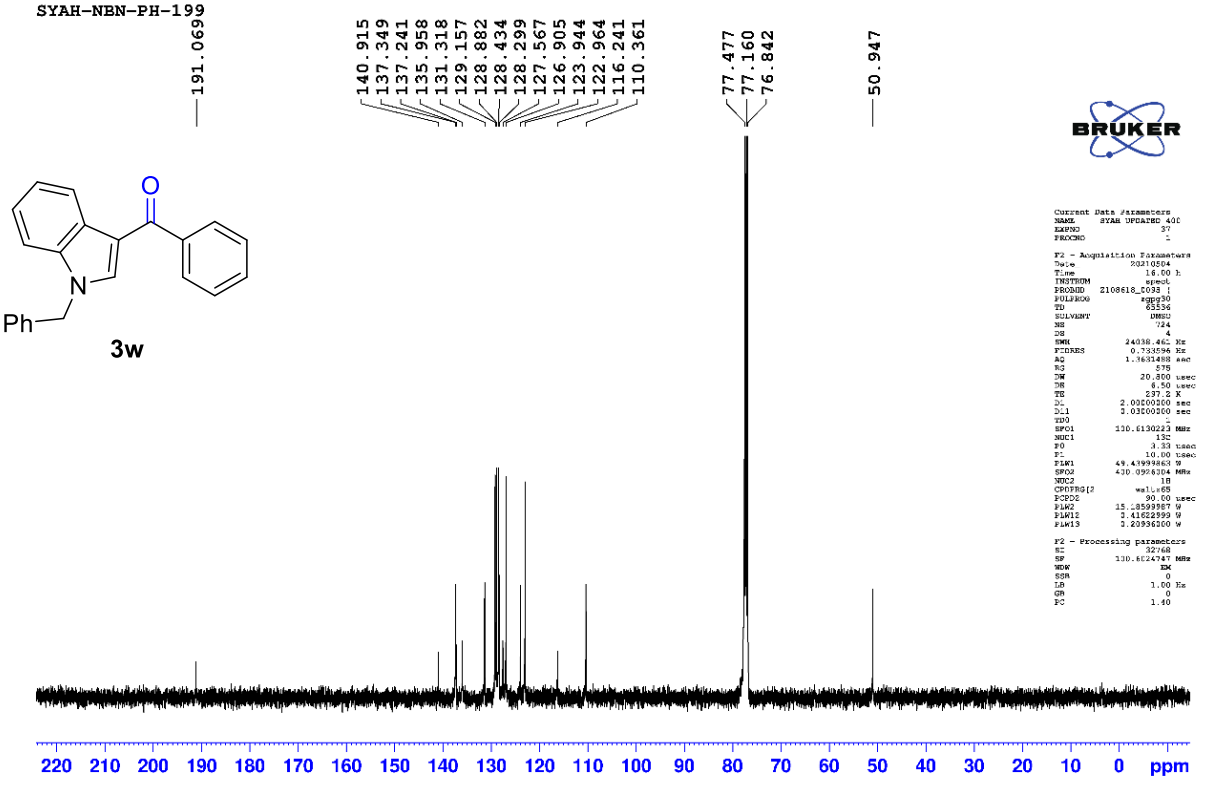
3v



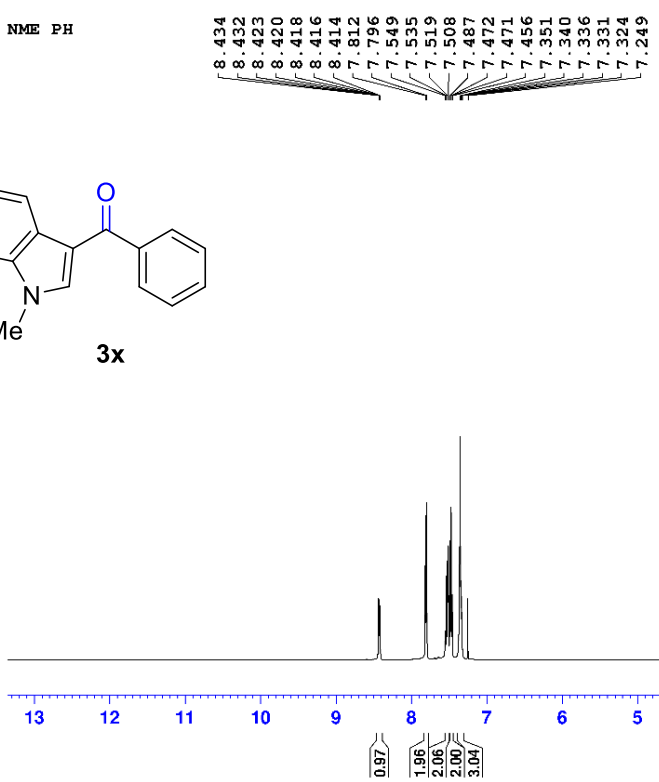
NBN-PH-199



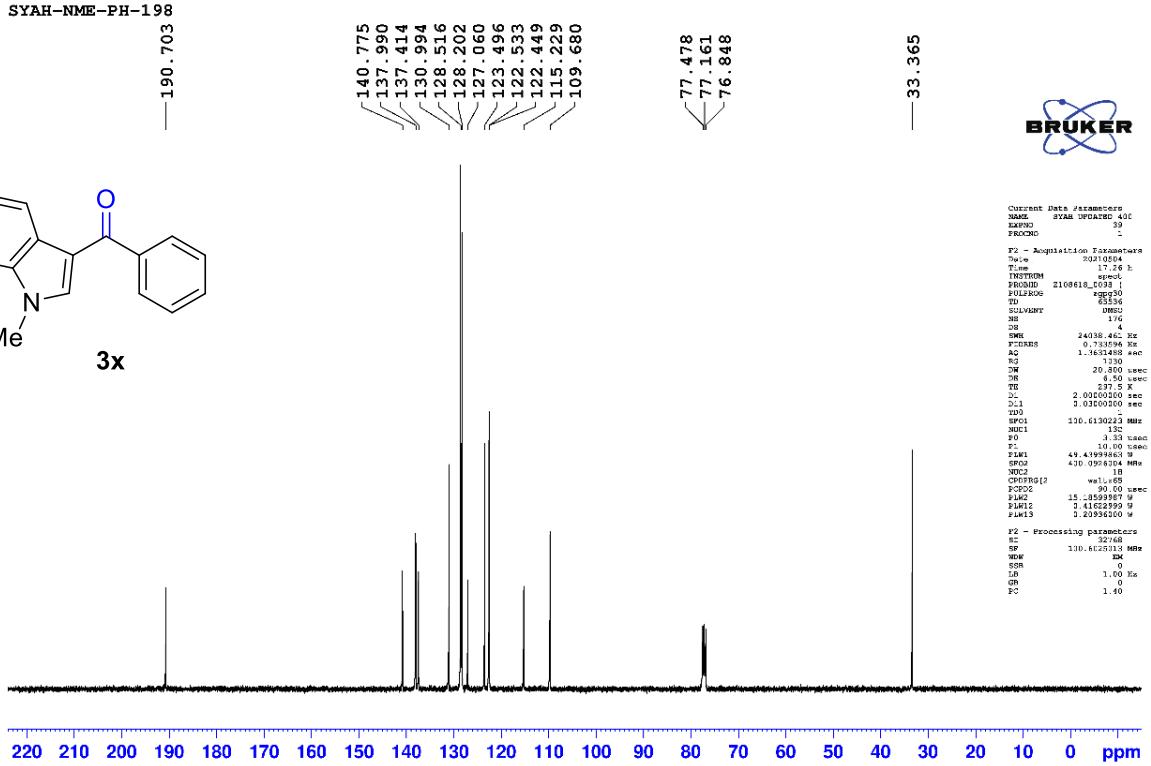
SYAH-NBN-PH-199



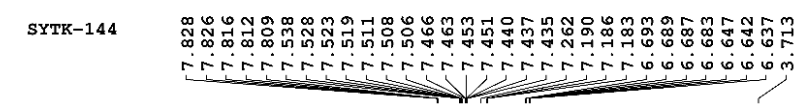
NME PH

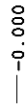


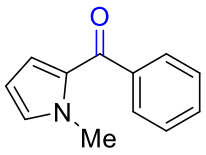
SYAH-NME-PH-198



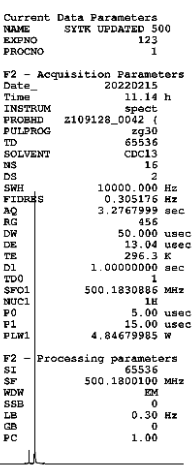
SYTK-144

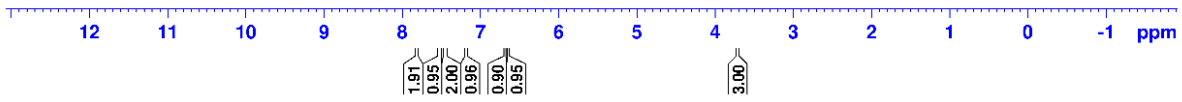




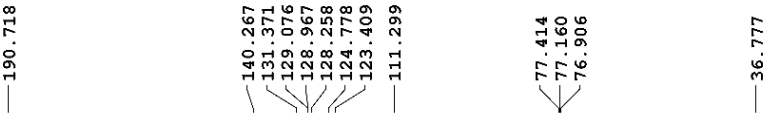


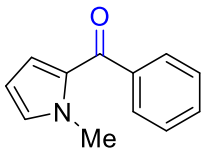
3y



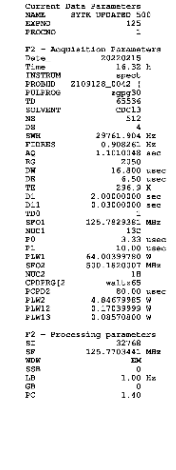


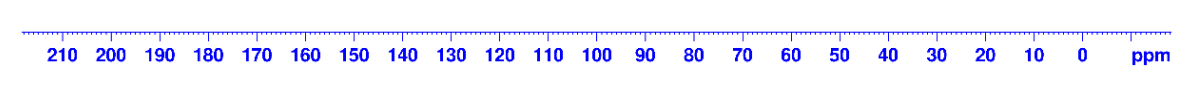
SYTK-144



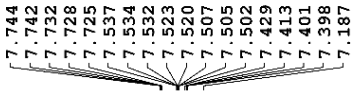


3y

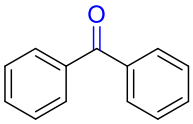




PH-221





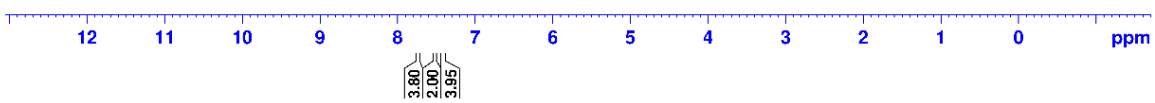


3z

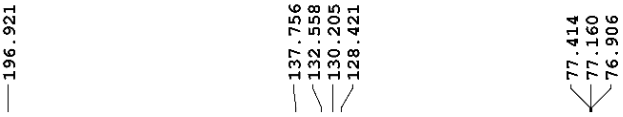
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Current Data Parameters
NAME      SYAH ASCEND 500
EXPNO             47
PROCNO             1

F2 - Acquisition Parameters
Date_          20210729
Time              16.38 h
INSTRUM           spect
PROBHD    Z119470 0291 (
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                16
DS                 2
SWH          10000.000 Hz
FIDRES           0.305176 Hz
AQ            3.2767999 sec
RG              108.78
DW               50.000 usec
DE                6.50 usec
TE              298.3 K
D1           1.00000000 sec
TD0                1
SFO1         500.3720898 MHz
NUC1               1H
P1                10.00 usec
PLW1         23.23100090 W

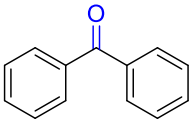
F2 - Processing parameters
SI               65536
SF           500.3690490 MHz
WDW                EM
SSB                0
LB              0.30 Hz
GB                 0
PC              1.00
```



PH-221





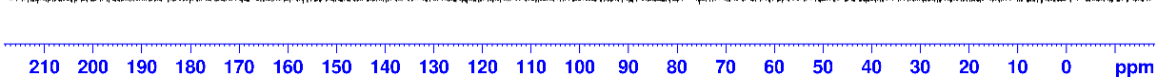


3z

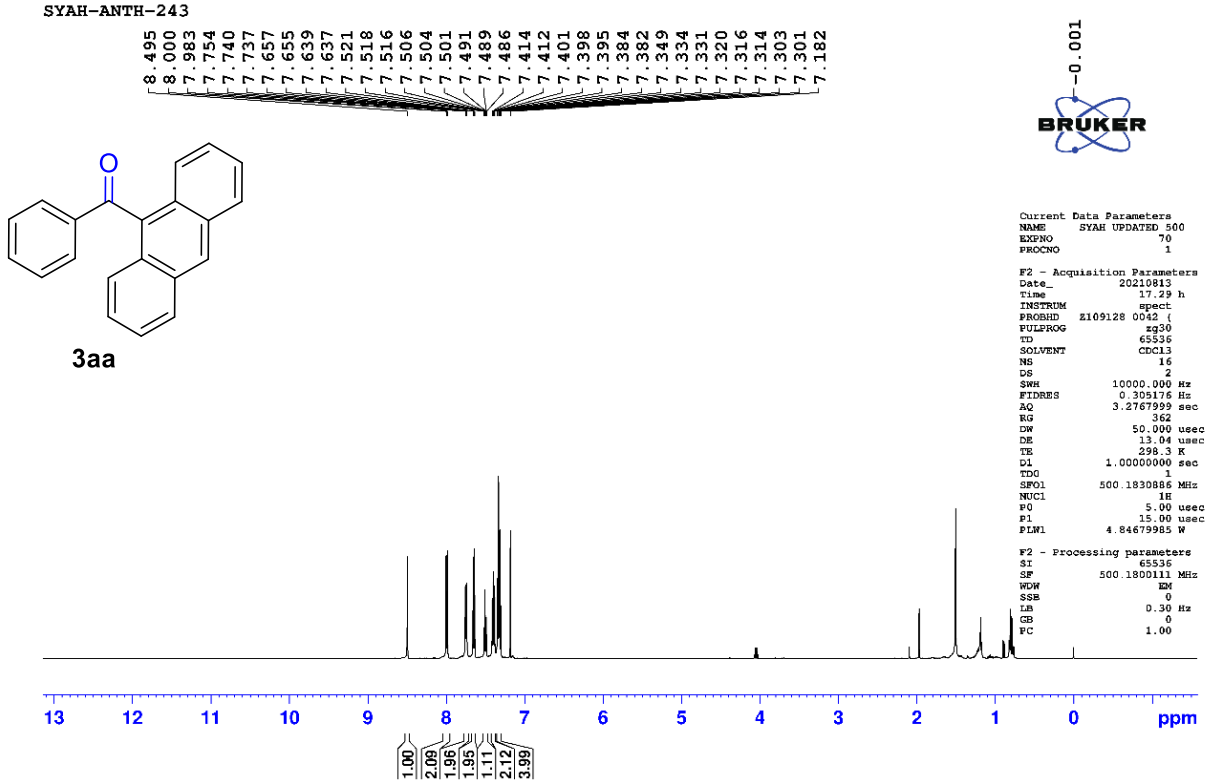
```
Current Data Parameters
NAME      SYAH ASCEND 500
EXPNO             48
PROCNO             1

F2 - Acquisition Parameters
Date_          20210730
Time              19.54 h
INSTRUM           spect
PROBHD    Z119470_0291 (
PULPROG           zgpg30
TD               65536
SOLVENT          CDCl3
NS                140
DS                 4
SWH          29761.904 Hz
FIDRES           0.908262 Hz
AQ            1.1010348 sec
RG              192.9
DW               16.800 usec
DE                6.50 usec
TE              299.2 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                1
SFO1         125.8304669 MHz
NUC1               13C
P1                10.00 usec
PLW1         135.01000214 W
SFO2         500.3710315 MHz
NUC2               1H
CPDPRG[2           waltz16
PCPD2             80.00 usec
PLW2         23.23100090 W
PLW12         3.36298999 W
PLW13         3.28257999 W

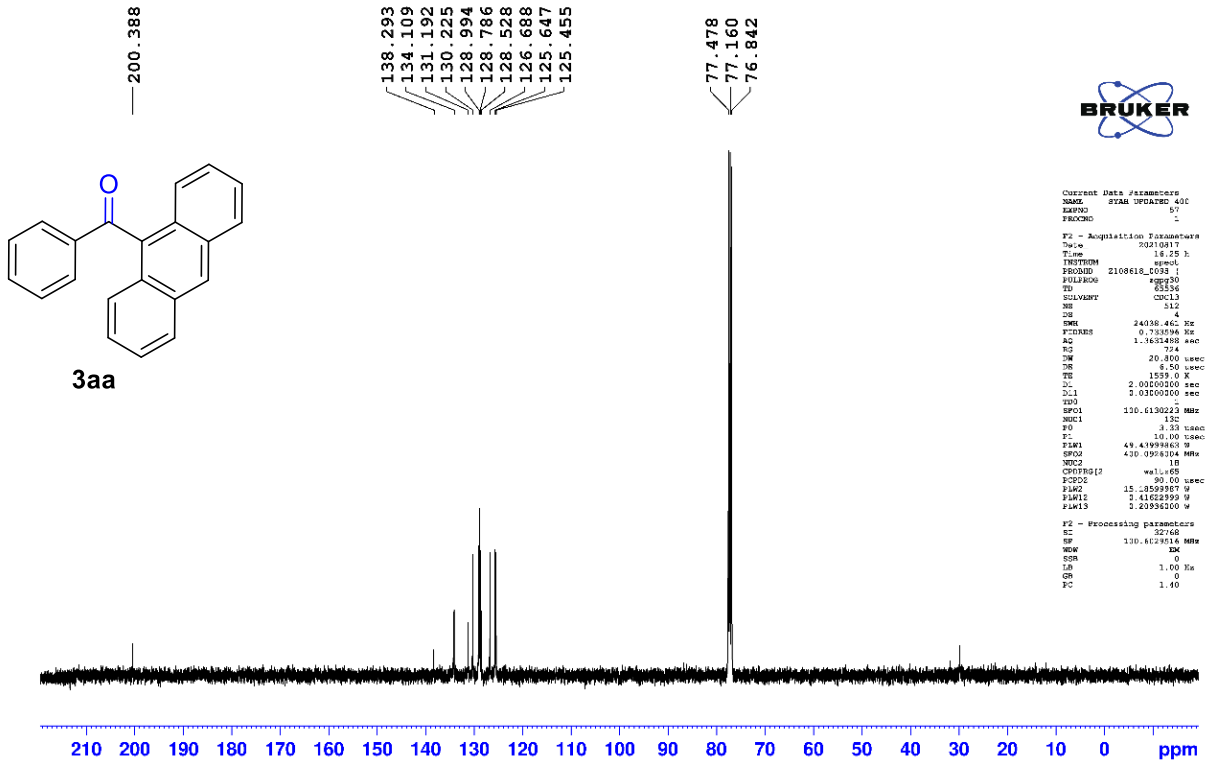
F2 - Processing parameters
SI               32768
SF           125.8178663 MHz
WDW                EM
SSB                0
LB              1.00 Hz
GB                 0
PC              1.40
```



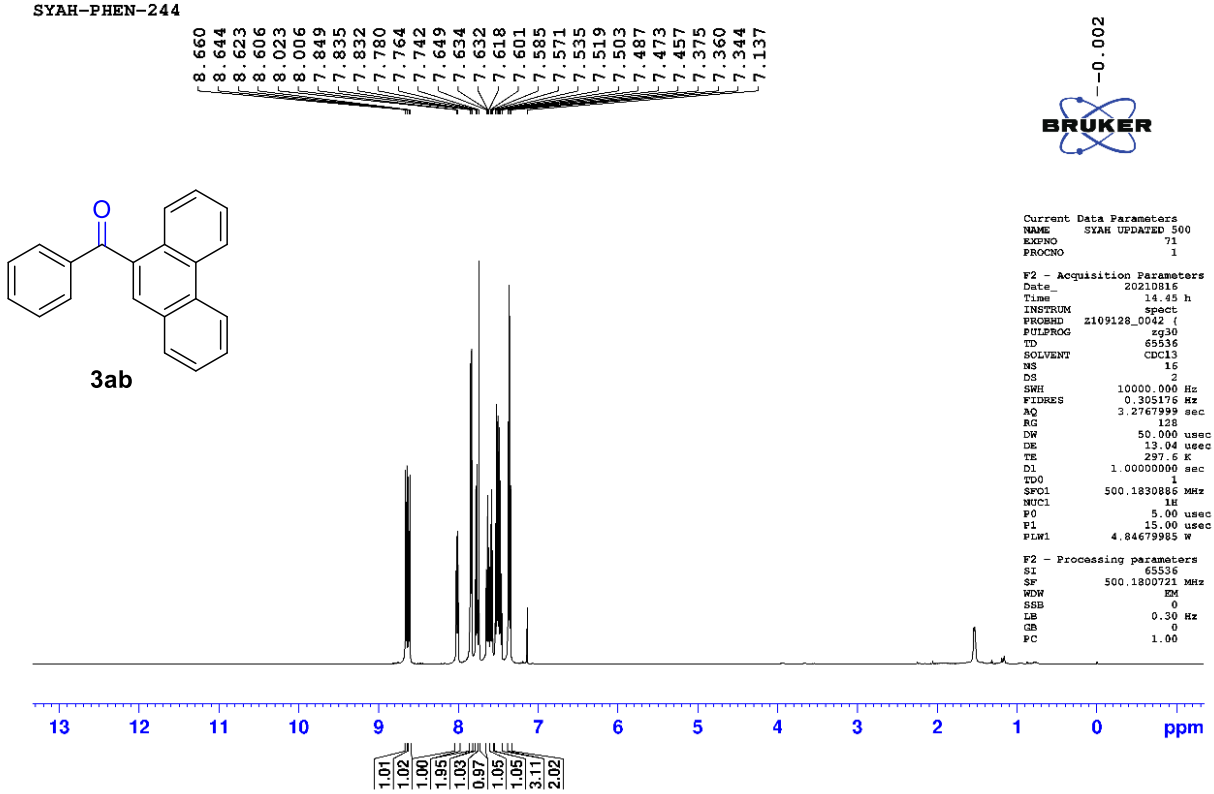
SYAH-ANTH-243



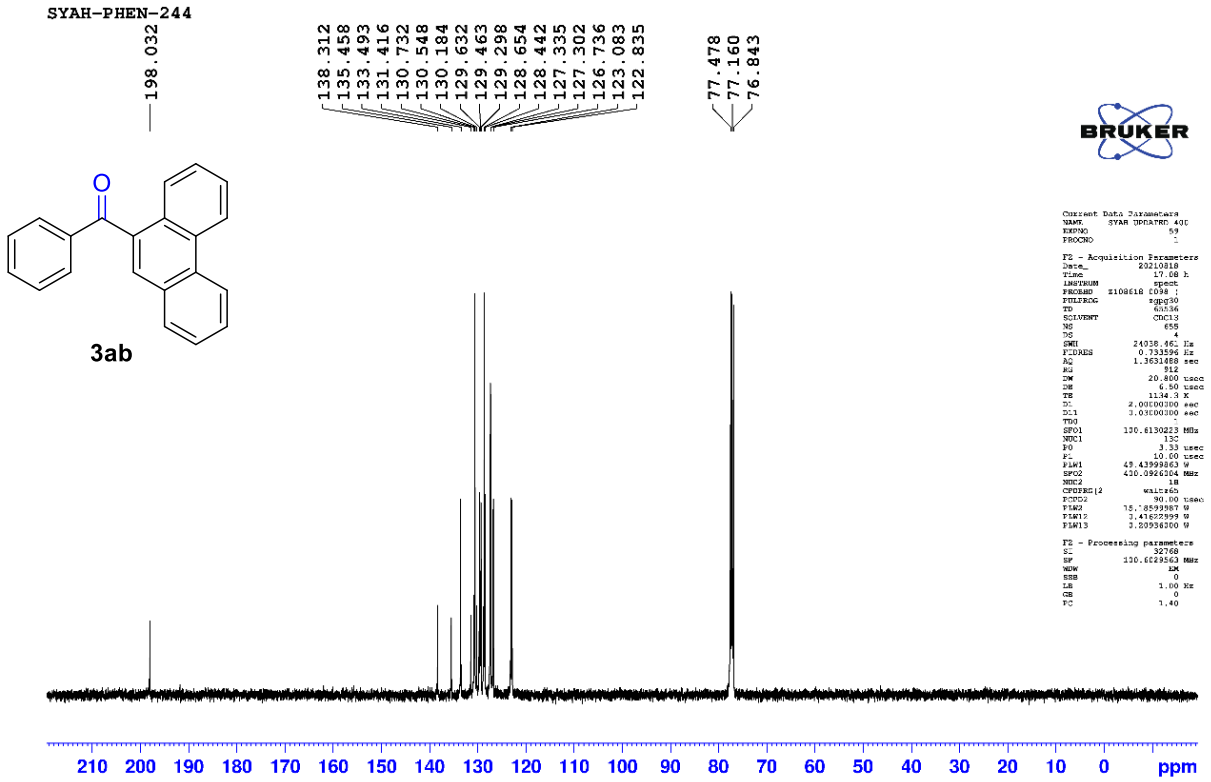
SYAH-ANTH-243



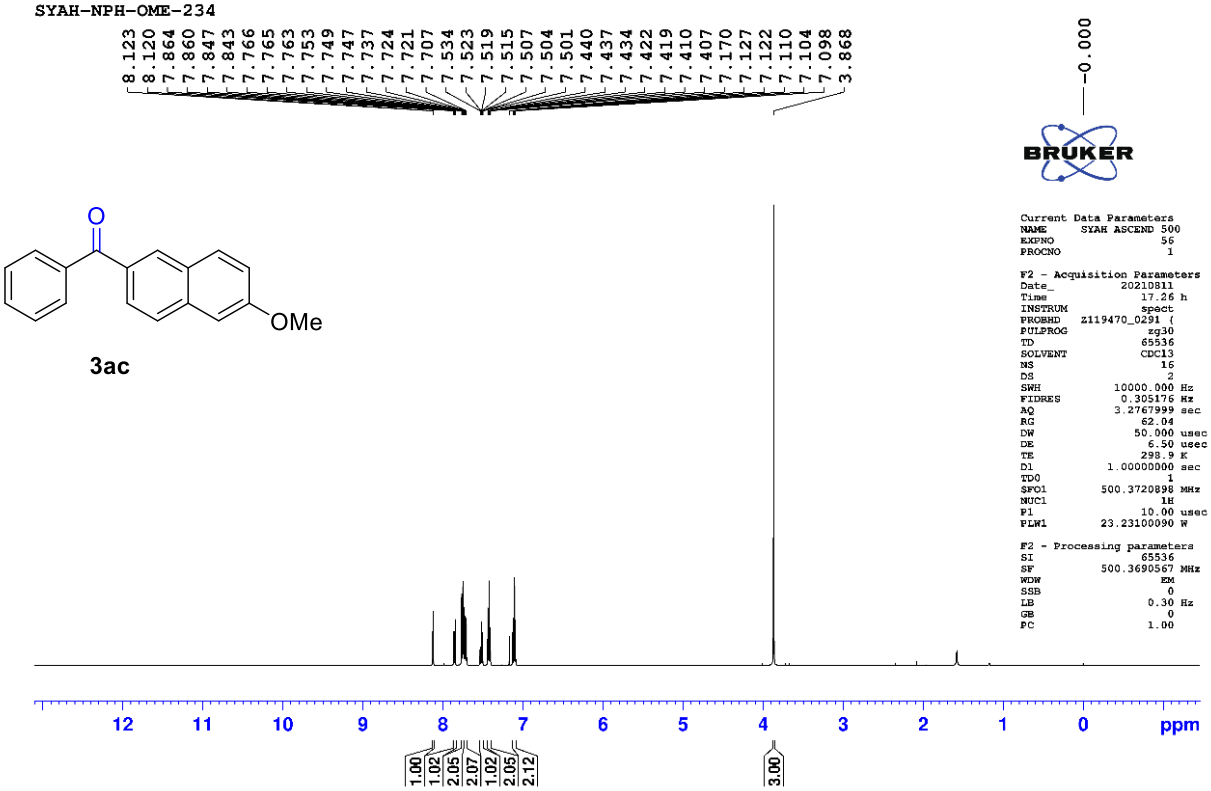
SYAH-PHEN-244



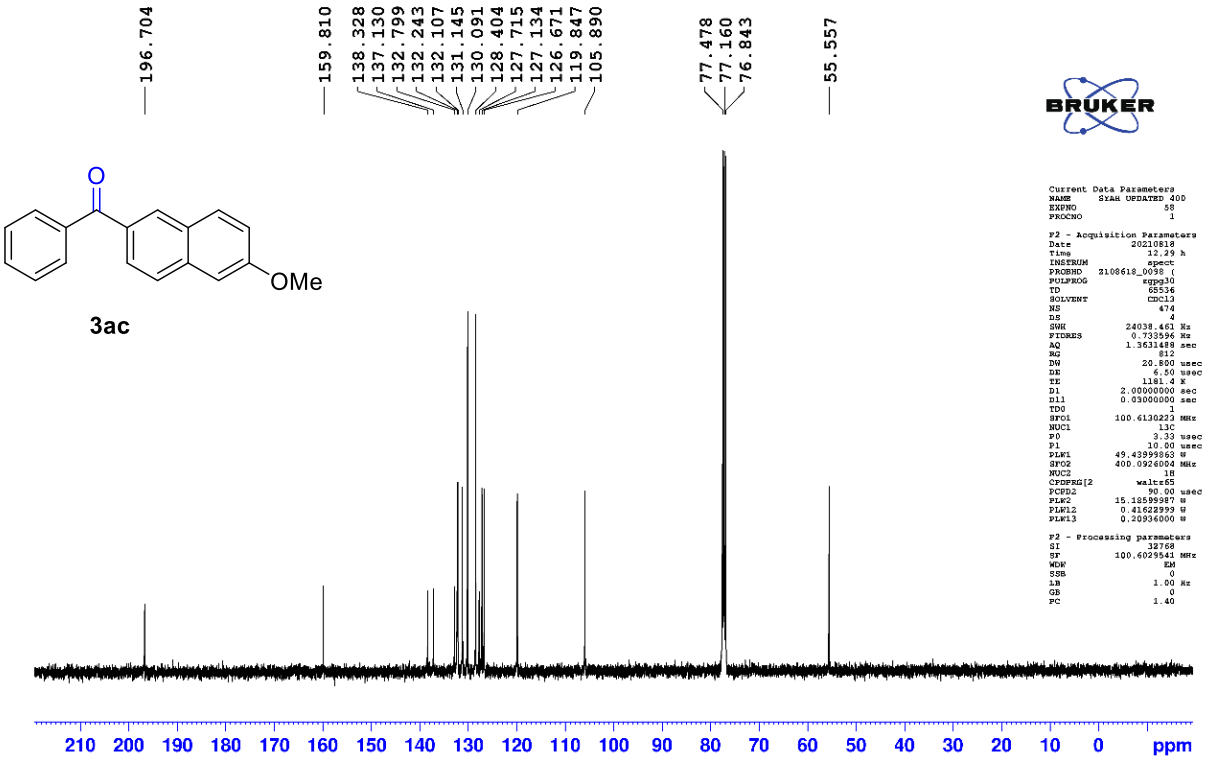
SYAH-PHEN-244

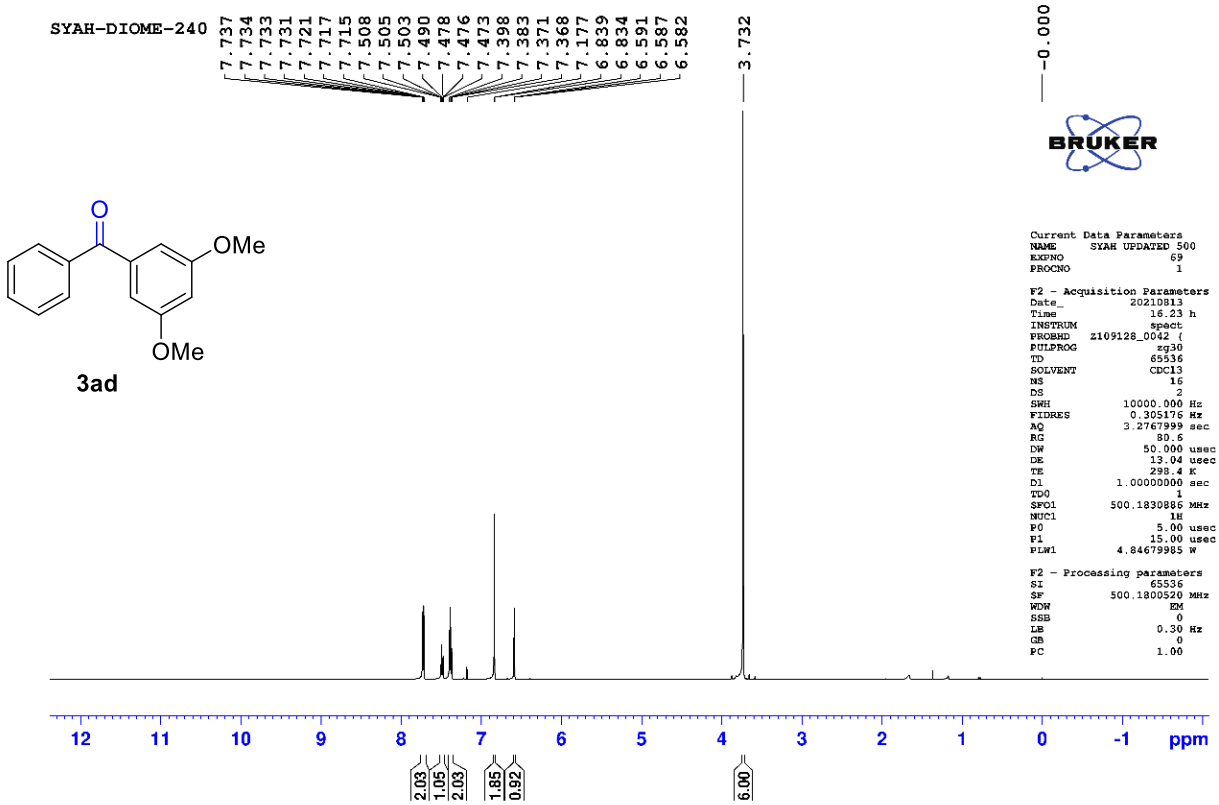


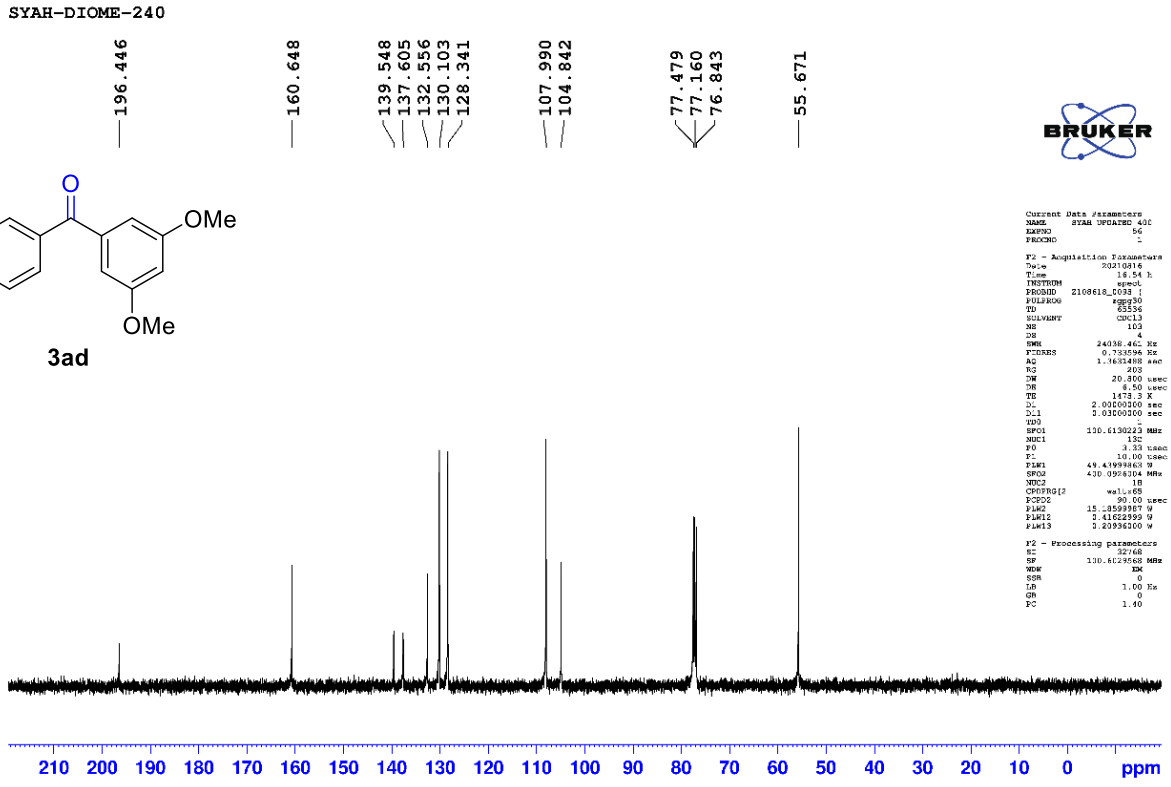
SYAH-NPH-OME-234



SYAH- NPH-OME-234

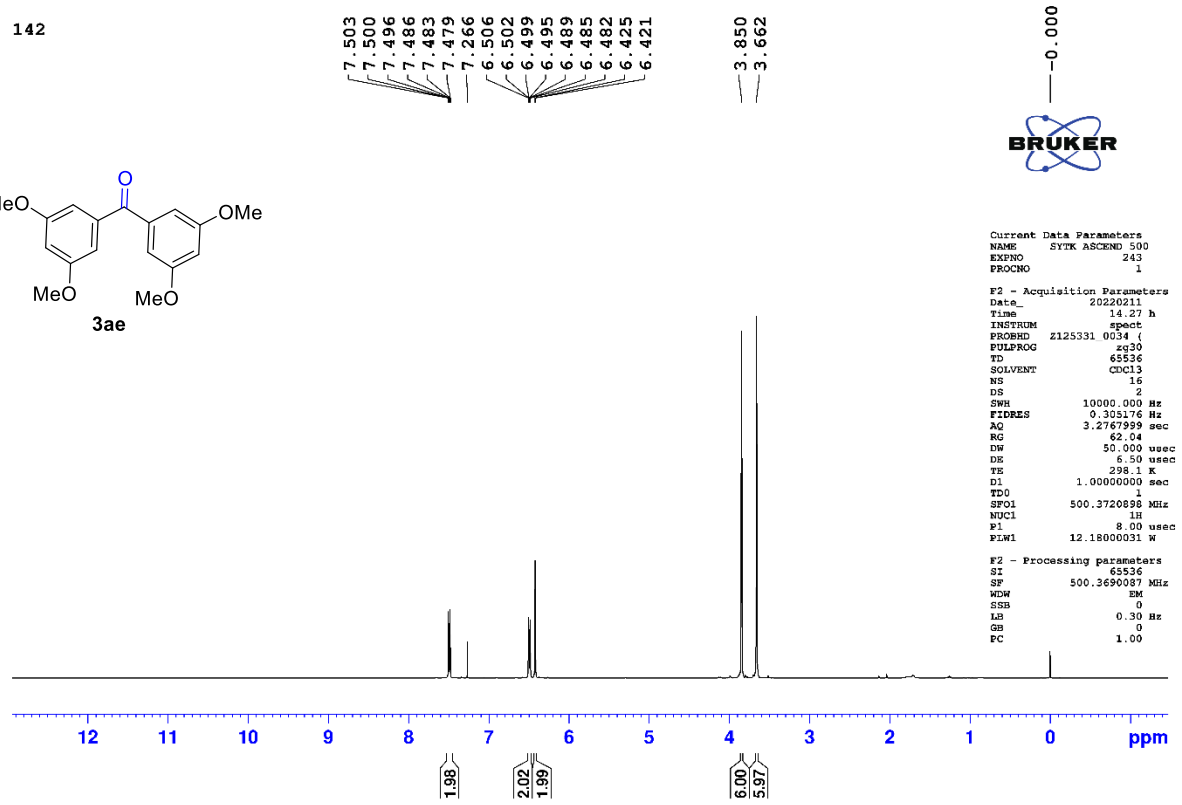



SYAH-DIOME-240
7.737
7.734
7.733
7.731
7.721
7.717
7.715
7.508
7.505
7.503
7.490
7.478
7.476
7.473
7.398
7.383
7.371
7.368
7.177
6.839
6.834
6.591
6.587
6.582
3.732
0.000
OMe
OMe
3ad
Current Data Parameters
NAME SYAH UPDATED 500
EXPNO 69
PROCNO 1
F2 - Acquisition Parameters
Date_ 20210813
Time 16.23 h
INSTRUM spect
PROBHD Z109128_0042 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 80.6
DW 50.000 usec
DE 13.04 usec
TE 298.4 K
D1 1.00000000 sec
TD0 1
SFO1 500.1830886 MHz
NUC1 1H
P0 5.00 usec
P1 15.00 usec
PLW1 4.84679985 W
F2 - Processing parameters
SI 65536
SF 500.1800520 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
12 11 10 9 8 7 6 5 4 3 2 1 0 -1 ppm
2.03 1.05 2.03 1.85 0.92 6.00

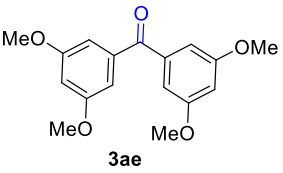

SYAH-DIOME-240
196.446
160.648
139.548
137.605
132.556
130.103
128.341
107.990
104.842
77.479
77.160
76.843
55.671
OMe
OMe
3ad
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

142

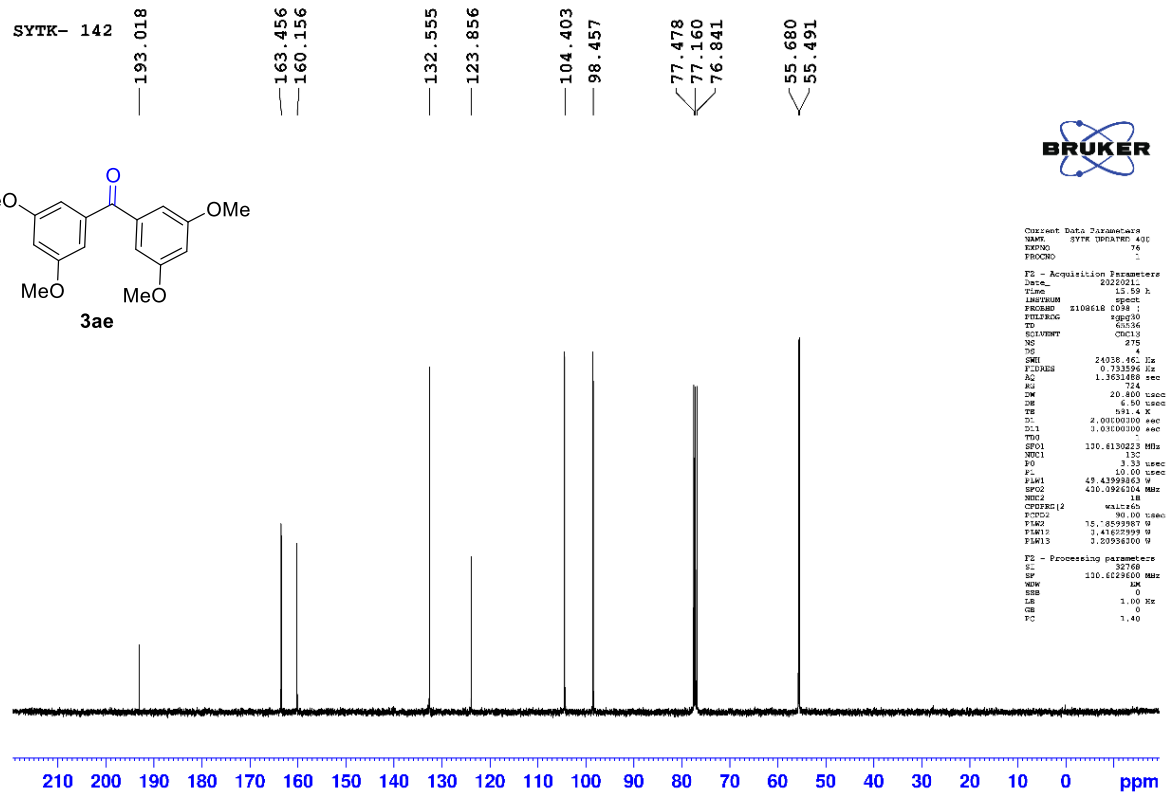
3ae



SYTK- 142

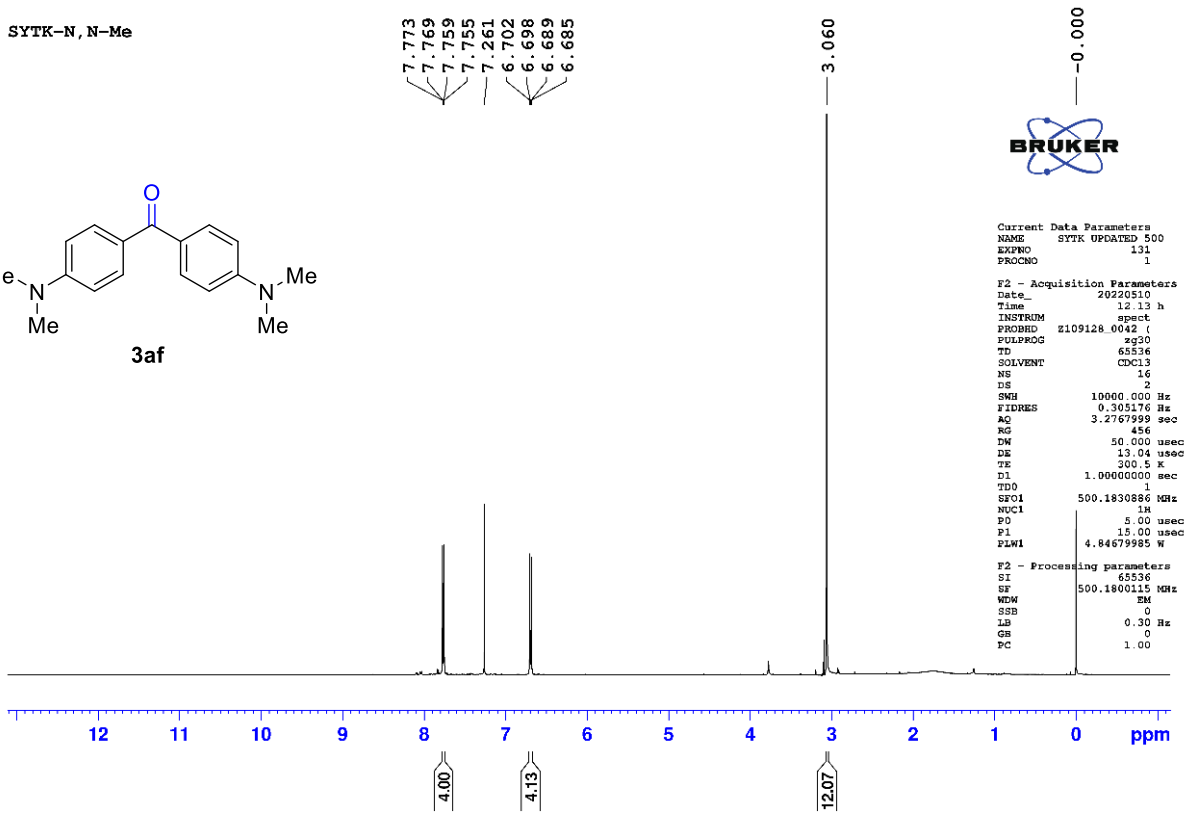


3ae



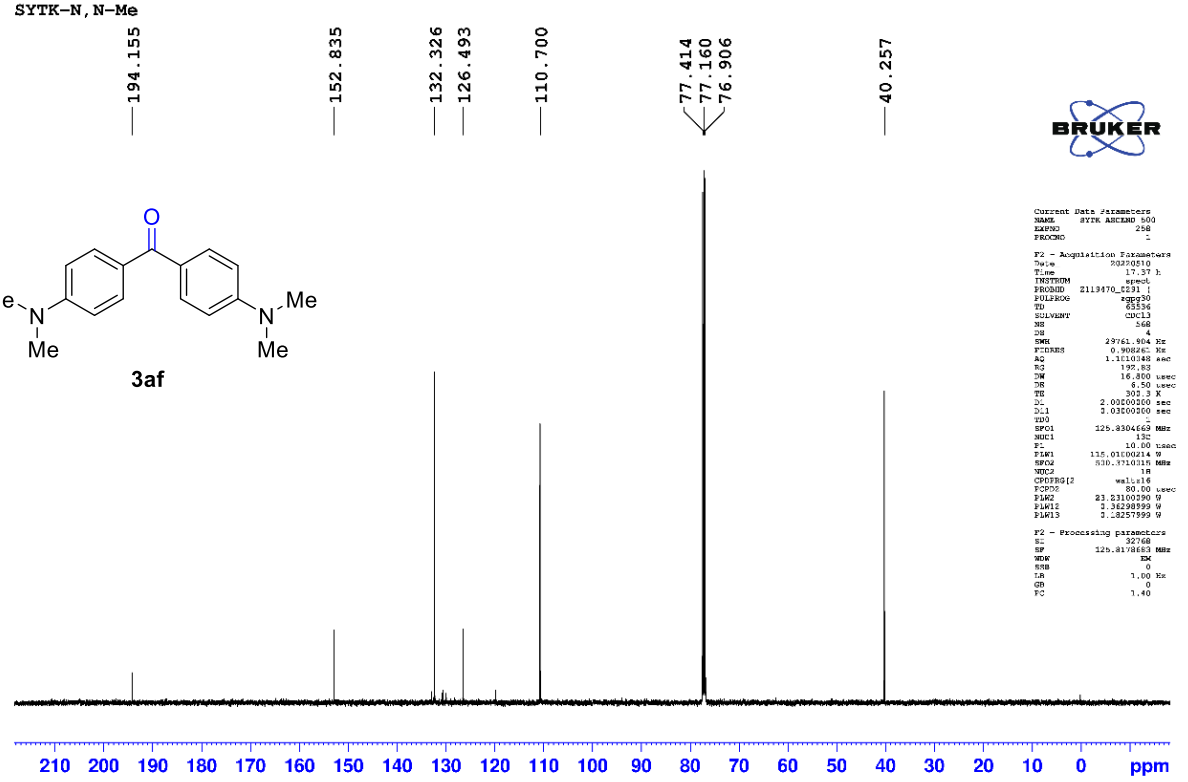
SYTK-N,N-Me

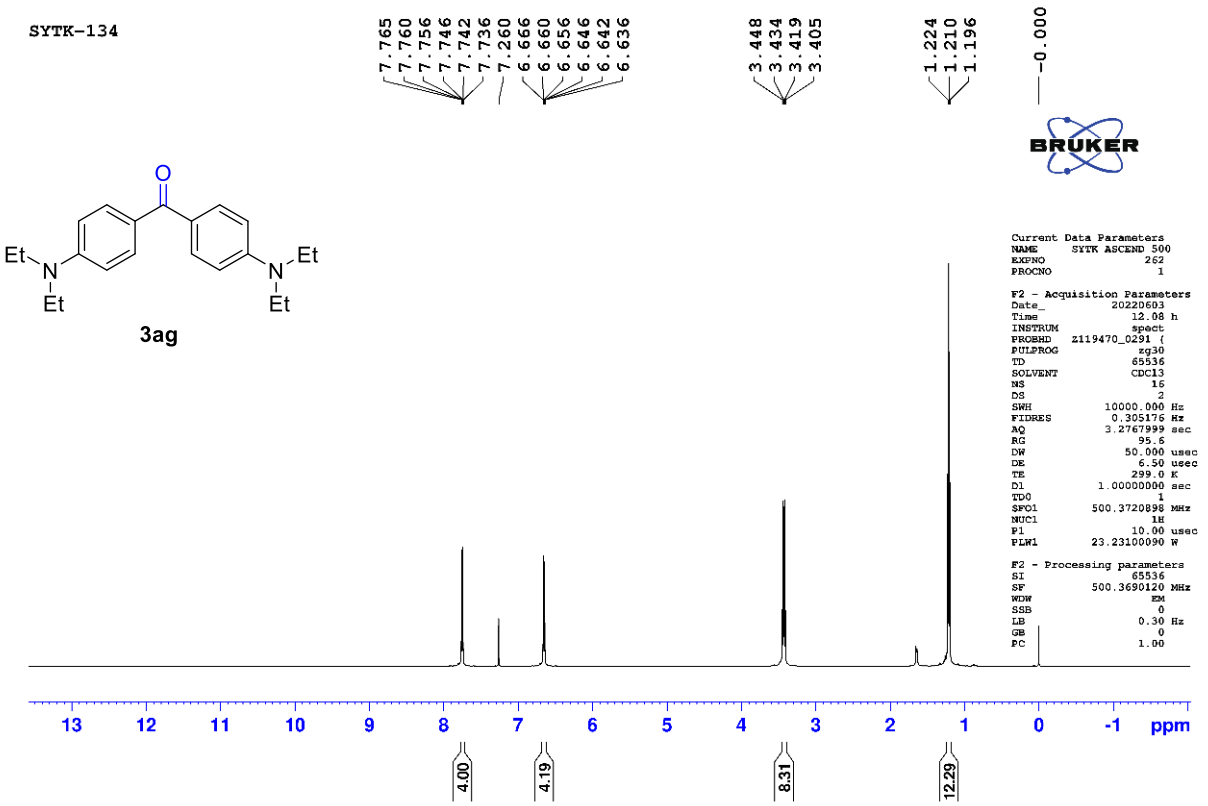
3af

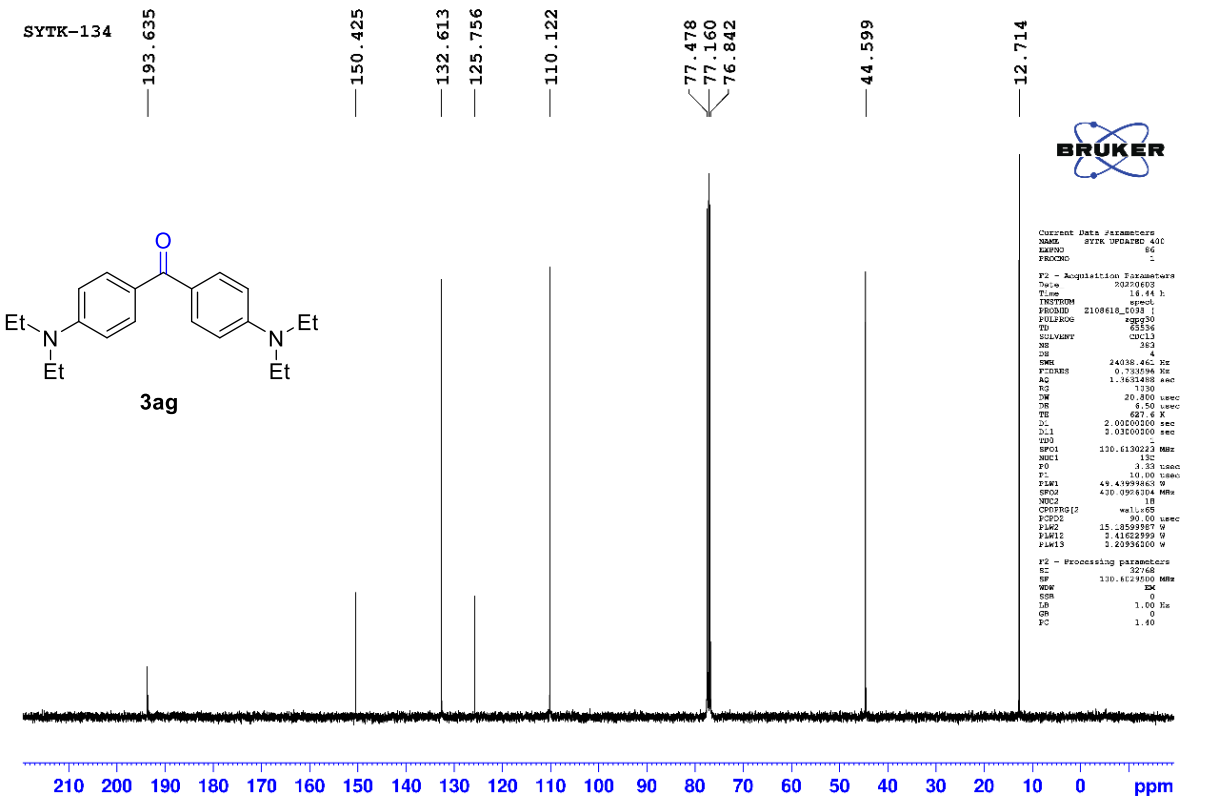


SYTK-N,N-Me

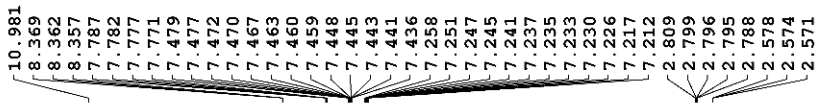
3af

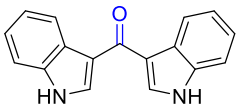



SYTK-134
7.765
7.760
7.756
7.746
7.742
7.736
7.260
6.666
6.660
6.656
6.646
6.642
6.636
3.448
3.434
3.419
3.405
1.224
1.210
1.196
0.000
BRUKER
Et
N
Et
O
N
Et
Et
3ag
Current Data Parameters
NAME SYTK ASCEND 500
EXPNO 262
PROCNO 1
F2 - Acquisition Parameters
Date_ 20220603
Time 12.08 h
INSTRUM spect
PROBHD Z119470_0291 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305175 Hz
AQ 3.2767999 sec
RG 95.6
DW 50.000 usec
DE 6.50 usec
TE 299.0 K
D1 1.00000000 sec
TD0 1
SFO1 500.3720898 MHz
NUC1 1H
P1 10.00 usec
PLW1 23.23100090 W
F2 - Processing parameters
SI 65536
SF 500.3690120 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 ppm
4.00
4.19
8.31
12.29

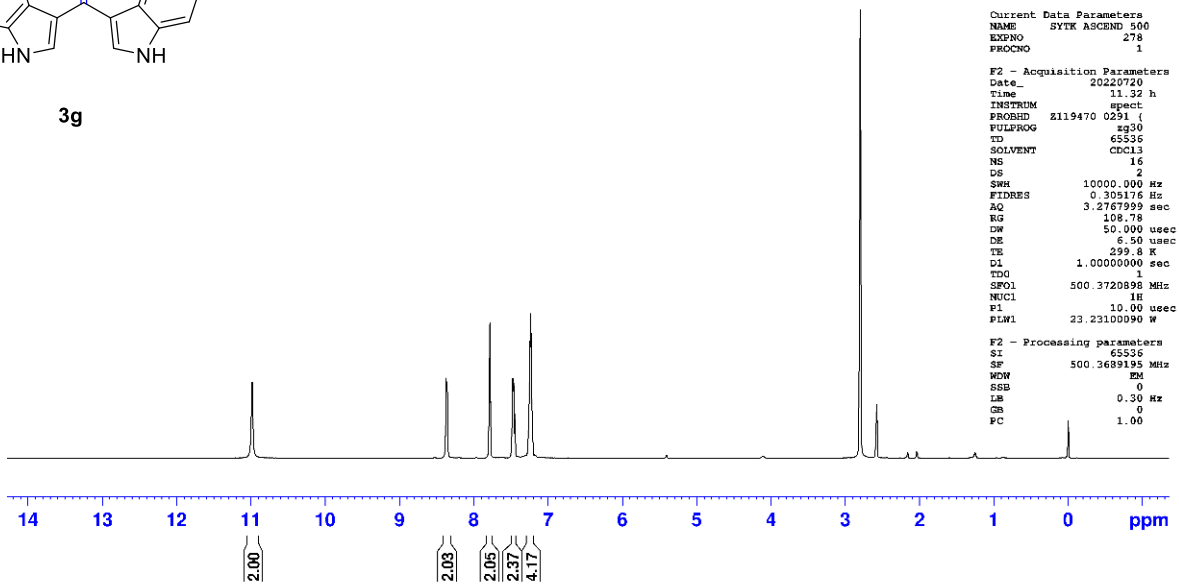

SYTK-134
193.635
150.425
132.613
125.756
110.122
77.478
77.160
76.842
44.599
12.714
BRUKER
Et
N
Et
O
N
Et
Et
3ag
Current Data Parameters
NAME SYTK UPDATED 401
EXPNO 86
PROCNO 1
F2 - Acquisition Parameters
Date_ 20220603
Time 14.44 h
INSTRUM spect
PROBHD Z108618_0098 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 383
DS 4
SWH 24038.461 Hz
FIDRES 0.733094 Hz
AQ 1.3631488 sec
RG 1330
DW 20.800 usec
DE 6.50 usec
TE 627.6 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 130.6130223 MHz
NUC1 13C
P0 3.33 usec
P1 10.00 usec
PLW1 49.43999863 W
SFO2 500.0908304 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 90.00 usec
PLW2 15.85999987 W
PLW12 3.41622999 W
PLW13 3.20936200 W
F2 - Processing parameters
SI 32768
SF 130.6129500 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
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DB-2

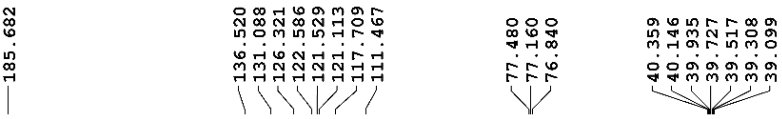


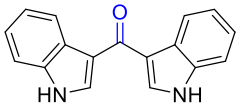


3g

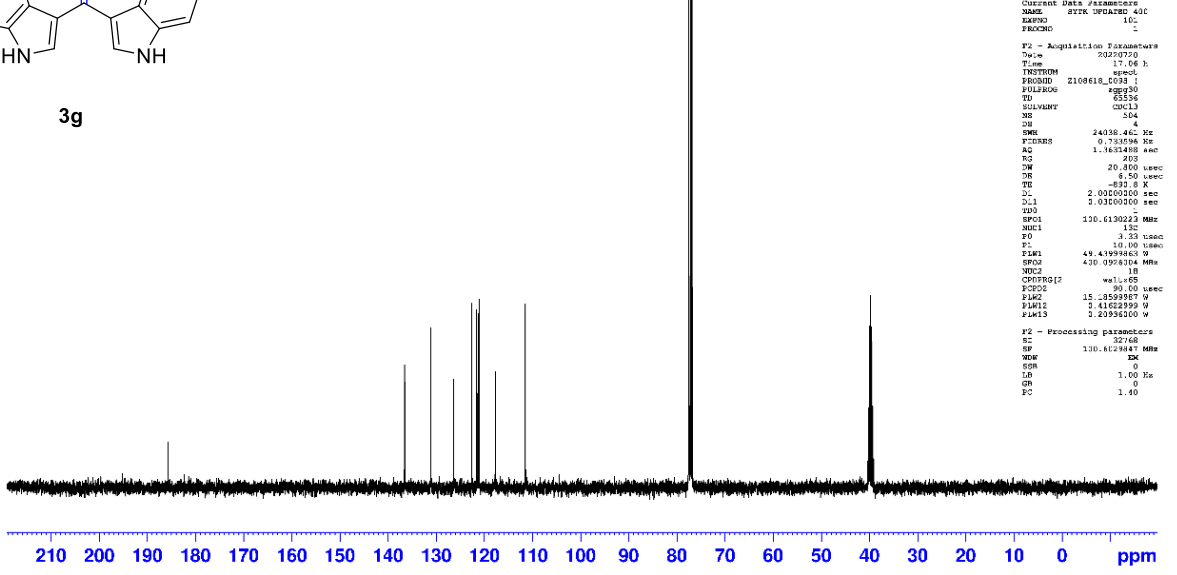


SYTK-DB-2



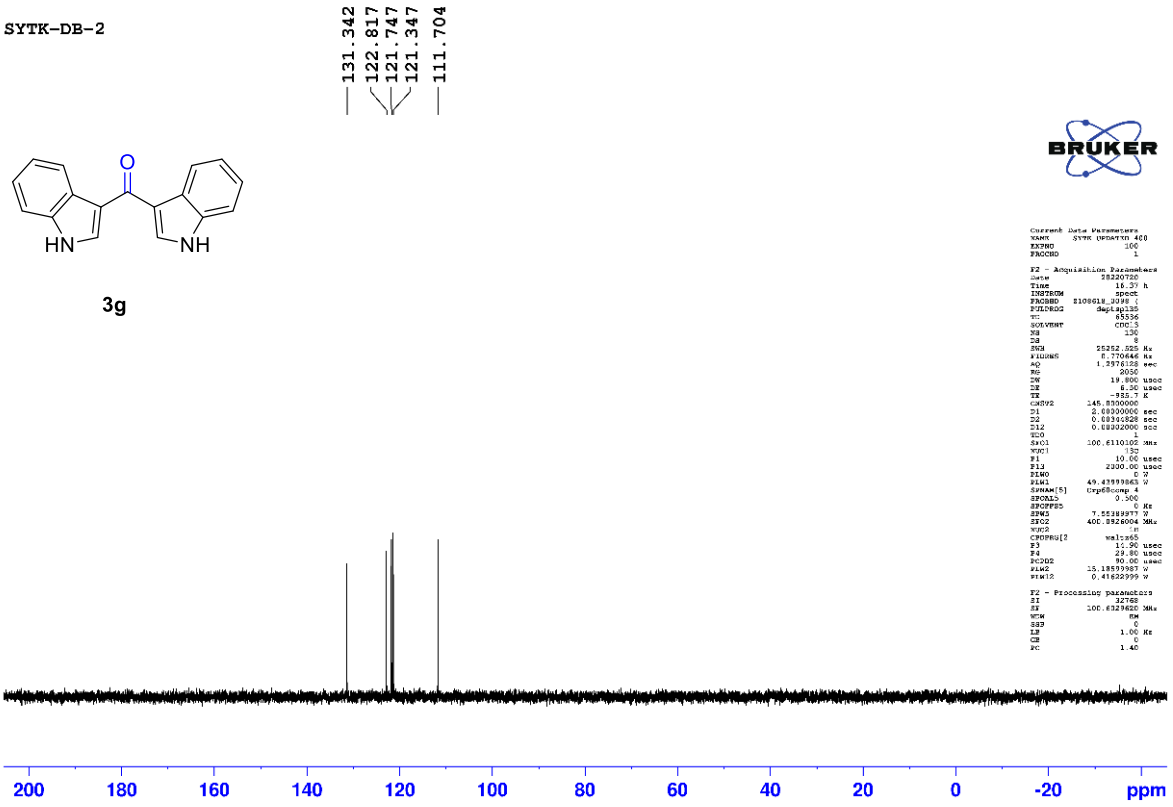


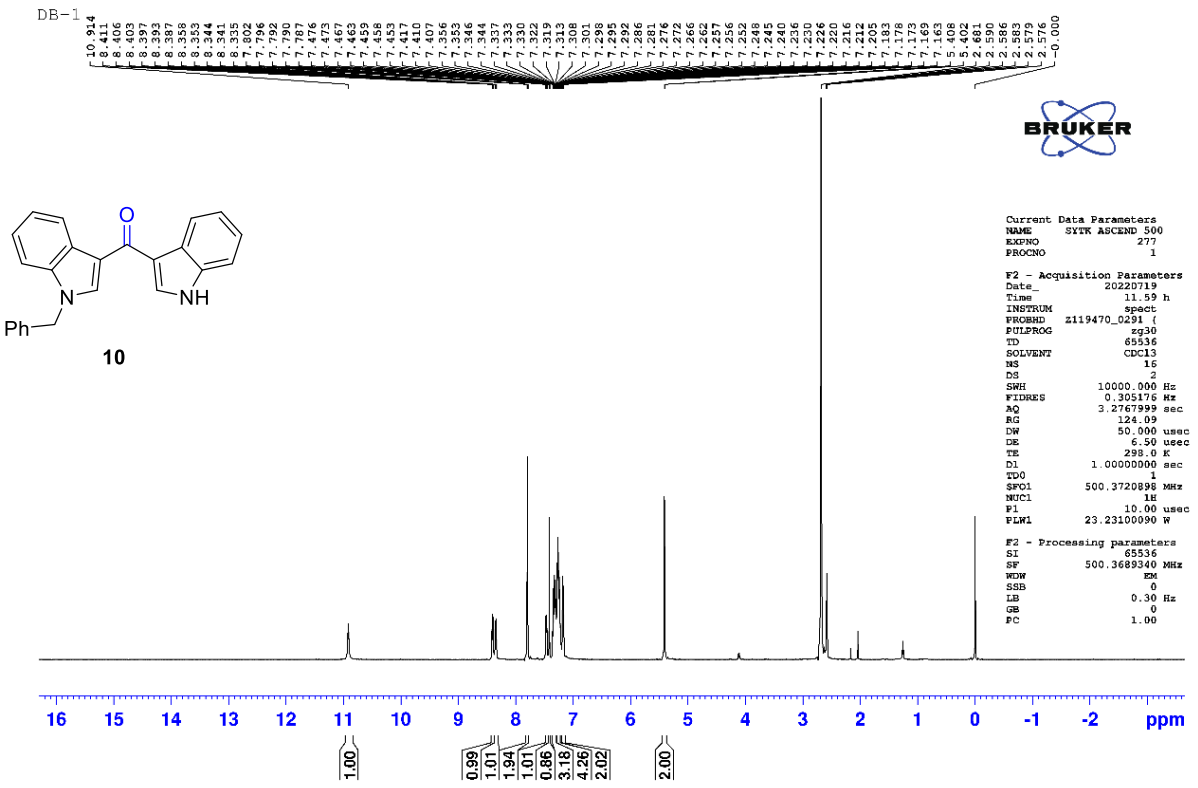
3g



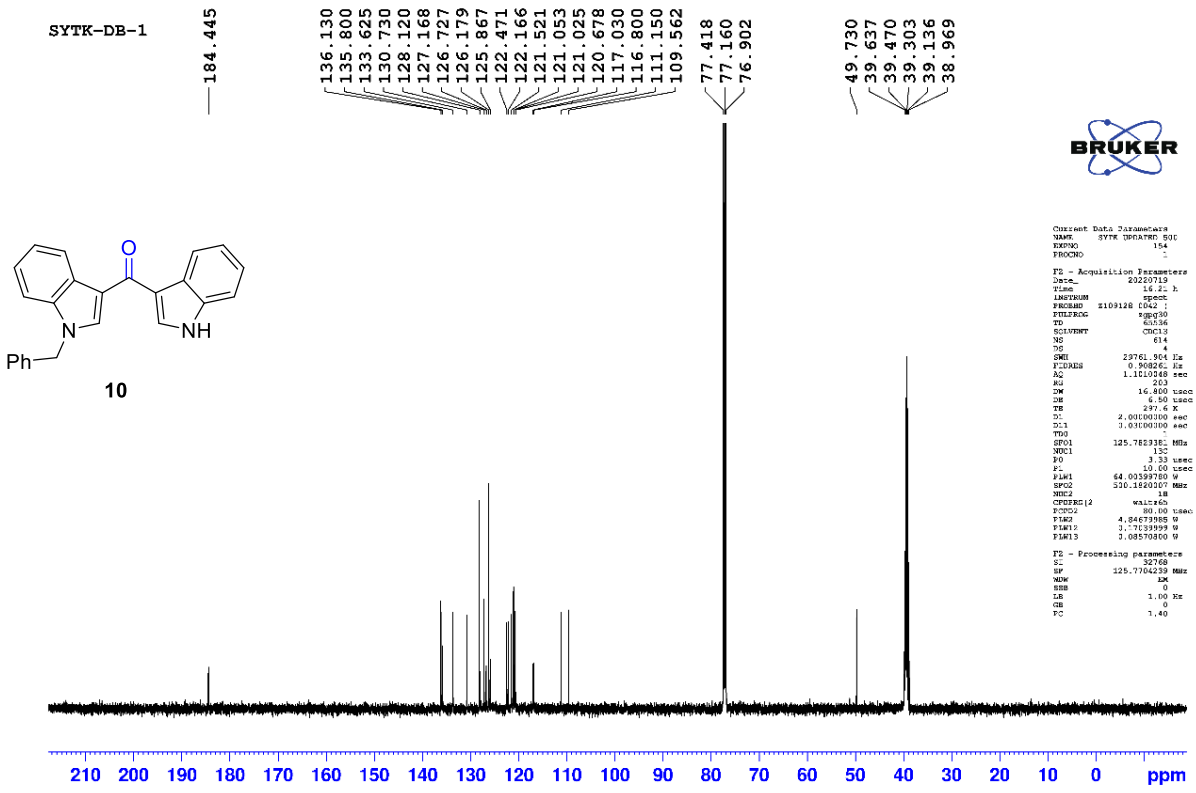
SYTK-DB-2

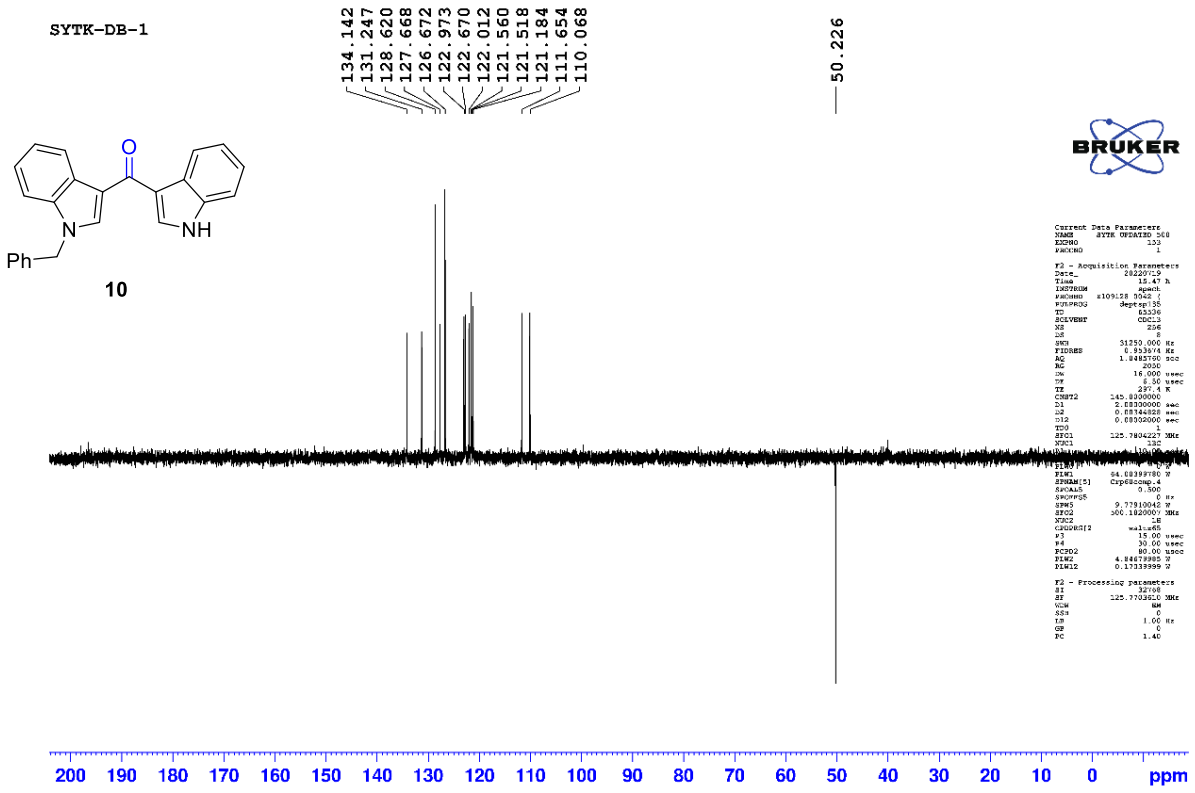
3g

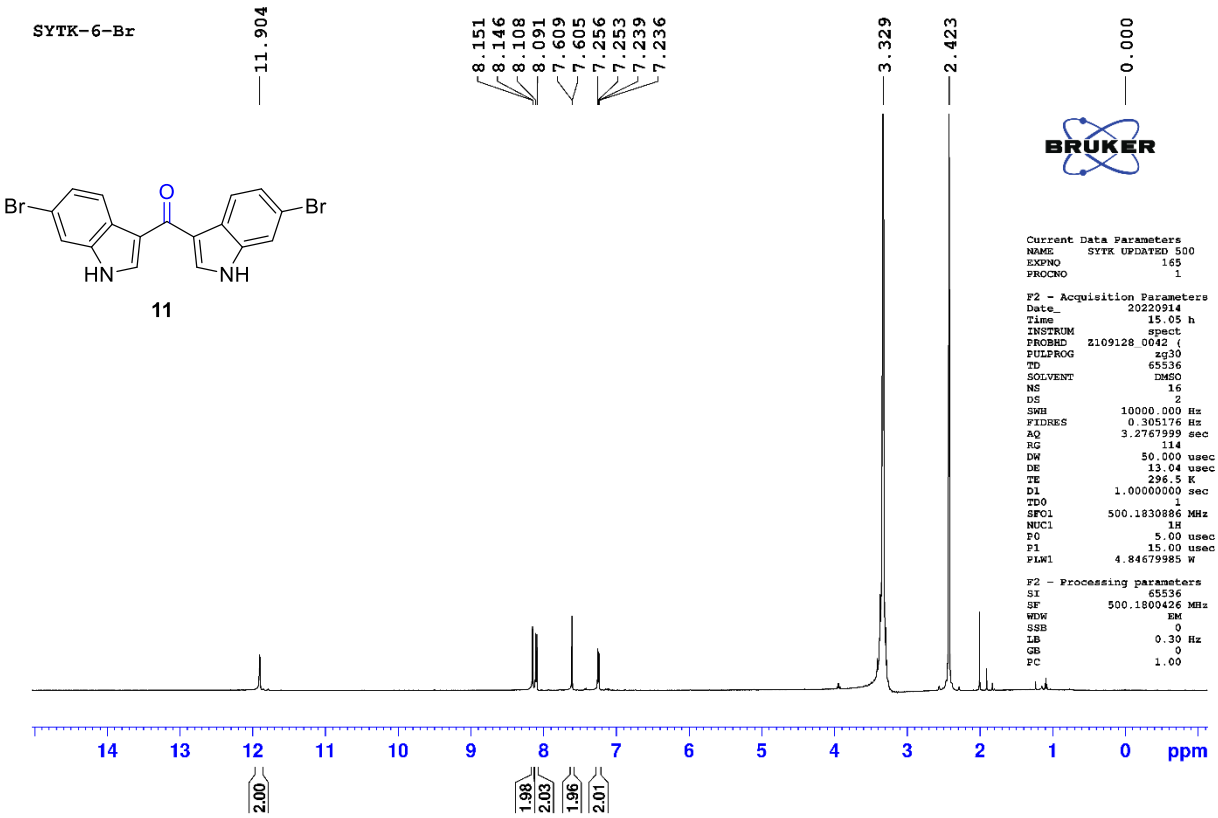


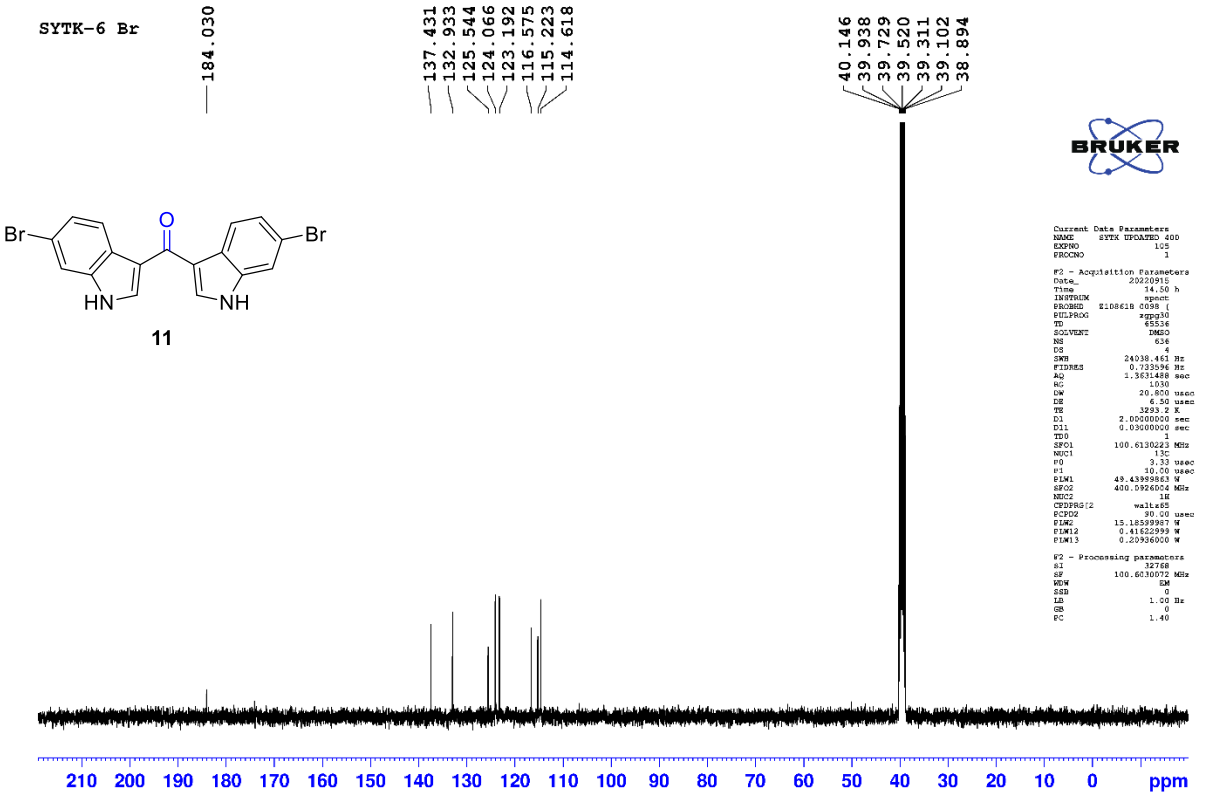


10

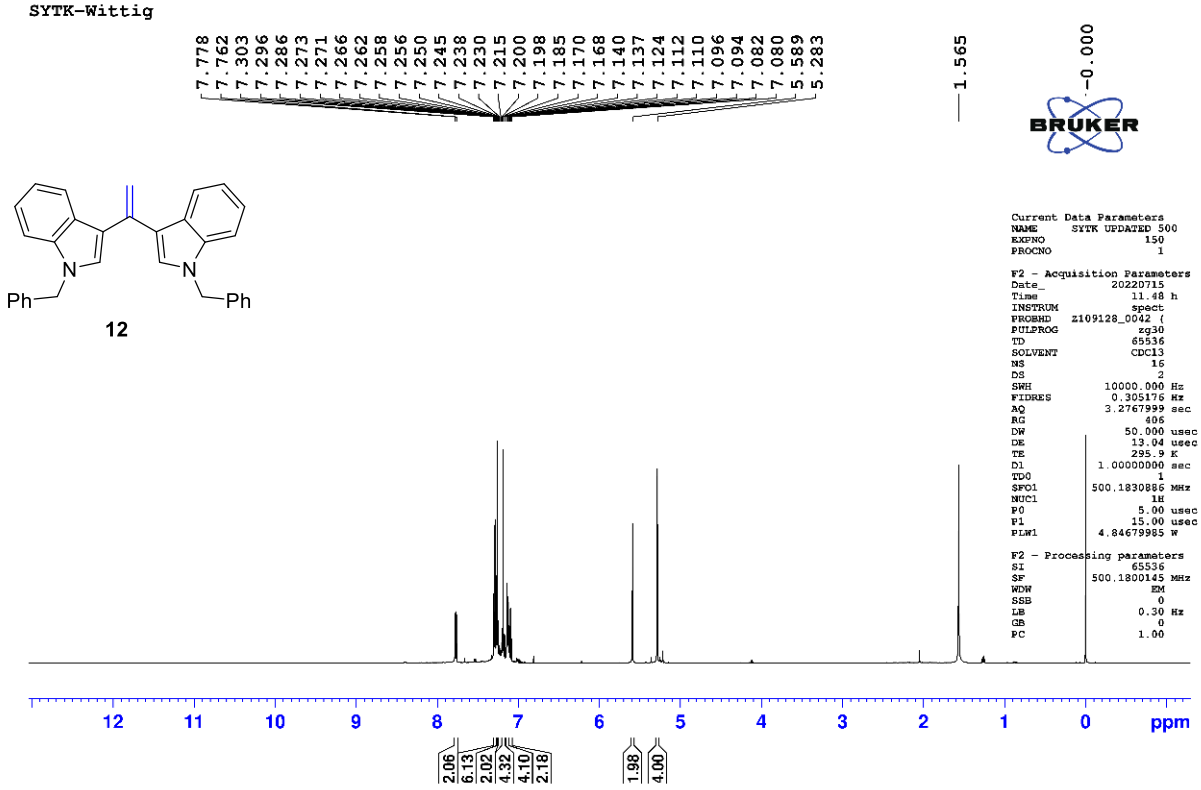

SYTK-DB-1
184.445
136.130
135.800
133.625
130.730
128.120
127.168
126.727
126.179
125.867
122.471
122.166
121.521
121.053
121.025
120.678
117.030
116.800
111.150
109.562
77.418
77.160
76.902
49.730
39.637
39.470
39.303
39.136
38.969
BRUKER
O
N
NH
Ph
10
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


SYTK-DB-1
134.142
131.247
128.620
127.668
126.672
122.973
122.670
122.012
121.560
121.518
121.184
111.654
110.068
50.226
BRUKER
O
N
NH
Ph
10
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

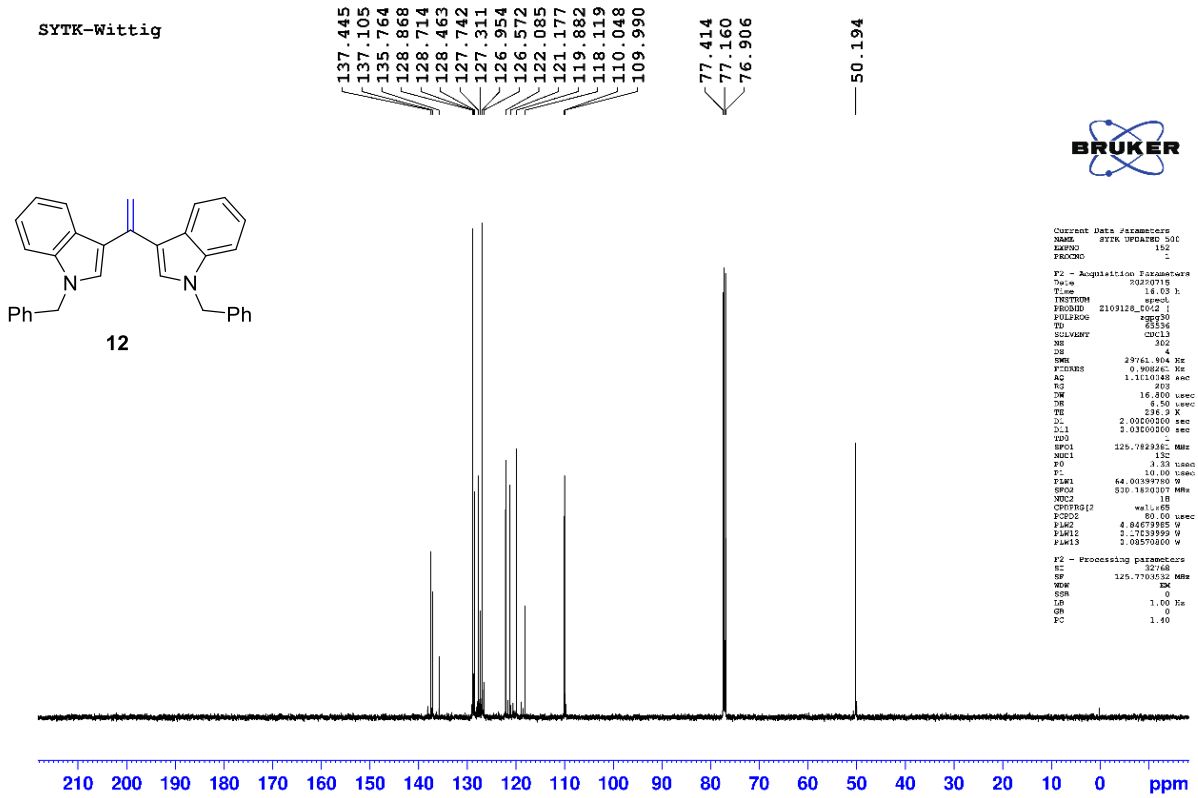

SYTK-6-Br
11.904
8.151
8.146
8.108
8.091
7.609
7.605
7.256
7.253
7.239
7.236
3.329
2.423
0.000
Br
O
Br
HN
NH
11
BRUKER
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PROCNO 1
F2 - Acquisition Parameters
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Time 15.05 h
INSTRUM spect
PROBHD Z109128_0042 (
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 114
DW 50.000 usec
DE 13.04 usec
TE 296.5 K
D1 1.00000000 sec
TD0 1
SFO1 500.1830886 MHz
NUC1 1H
P0 5.00 usec
P1 15.00 usec
PLW1 4.84679985 W
F2 - Processing parameters
SI 65536
SF 500.1800426 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
2.00
1.98
2.03
1.96
2.01


SYTK-6 Br
184.030
137.431
132.933
125.544
124.066
123.192
116.575
115.223
114.618
40.146
39.938
39.729
39.520
39.311
39.102
38.894
Br
O
Br
HN
NH
11
BRUKER
Current Data Parameters
NAME SYTK UPDATED 400
EXPNO 105
PROCNO 1
F2 - Acquisition Parameters
Date_ 20220915
Time 14.50 h
INSTRUM spect
PROBHD Z108618_0098 (
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 634
DS 4
SWH 24038.461 Hz
FIDRES 0.733596 Hz
AQ 1.3631488 sec
RG 1030
DW 20.800 usec
DE 6.50 usec
TE 293.2 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 100.6130233 MHz
NUC1 13C
P0 3.33 usec
P1 10.00 usec
PLW1 48.43999863 W
SFO2 400.0926004 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 90.00 usec
PLW2 15.18599987 W
PLW12 0.41622999 W
PLW13 0.20936000 W
F2 - Processing parameters
SI 32768
SF 100.6030072 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

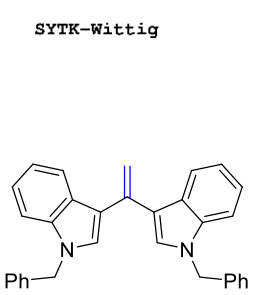
SYTK-Wittig



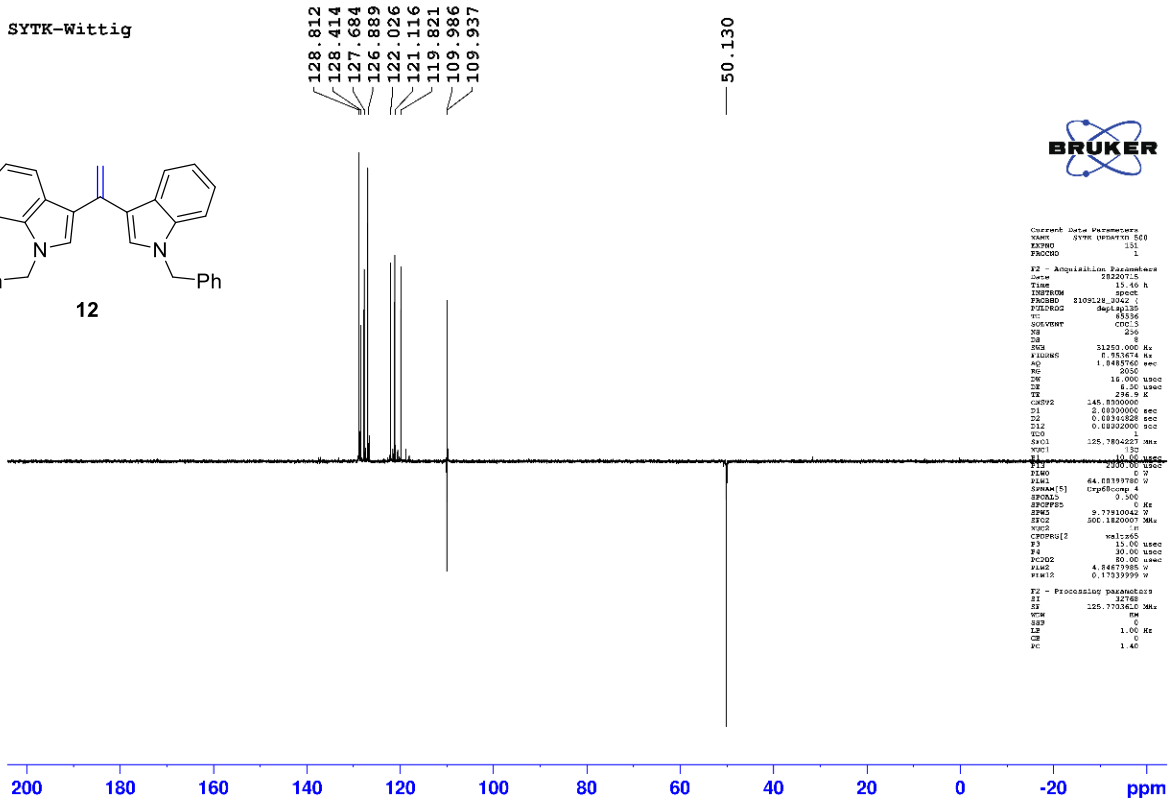
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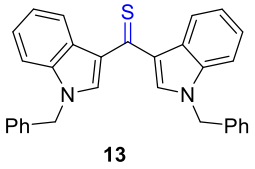
SYTK-Wittig



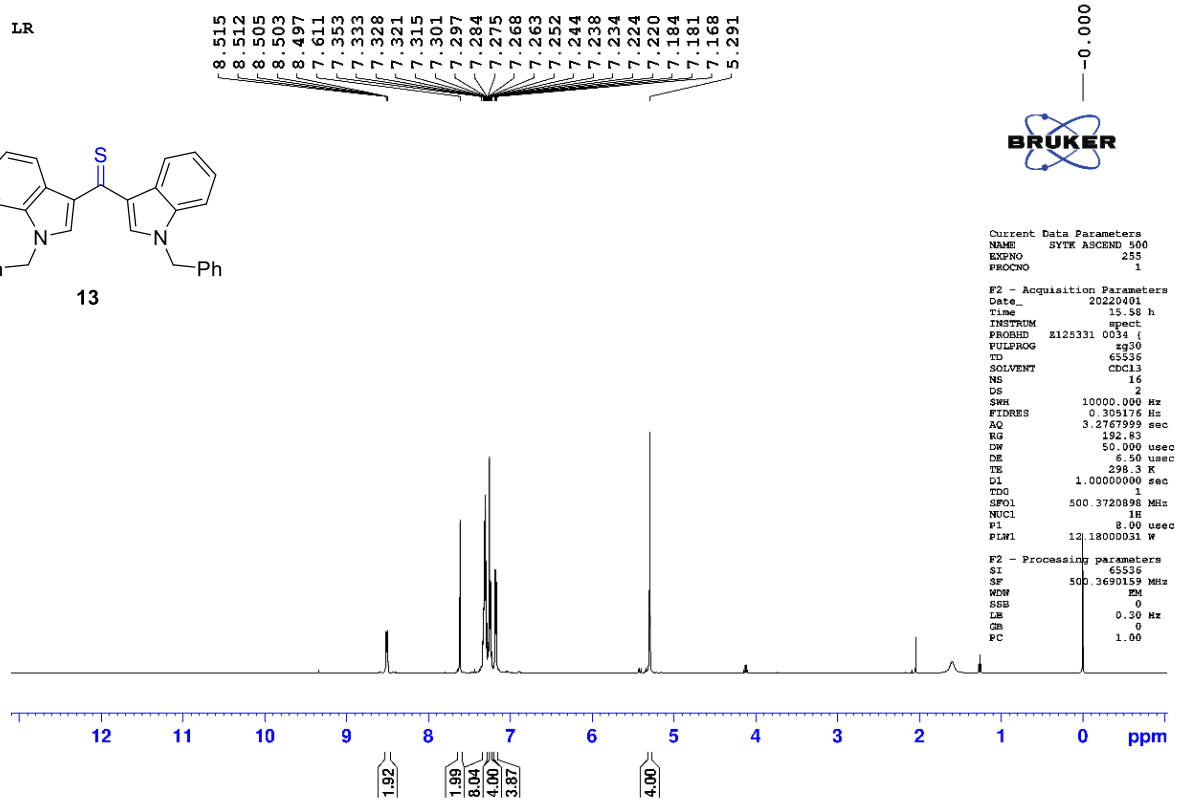
12

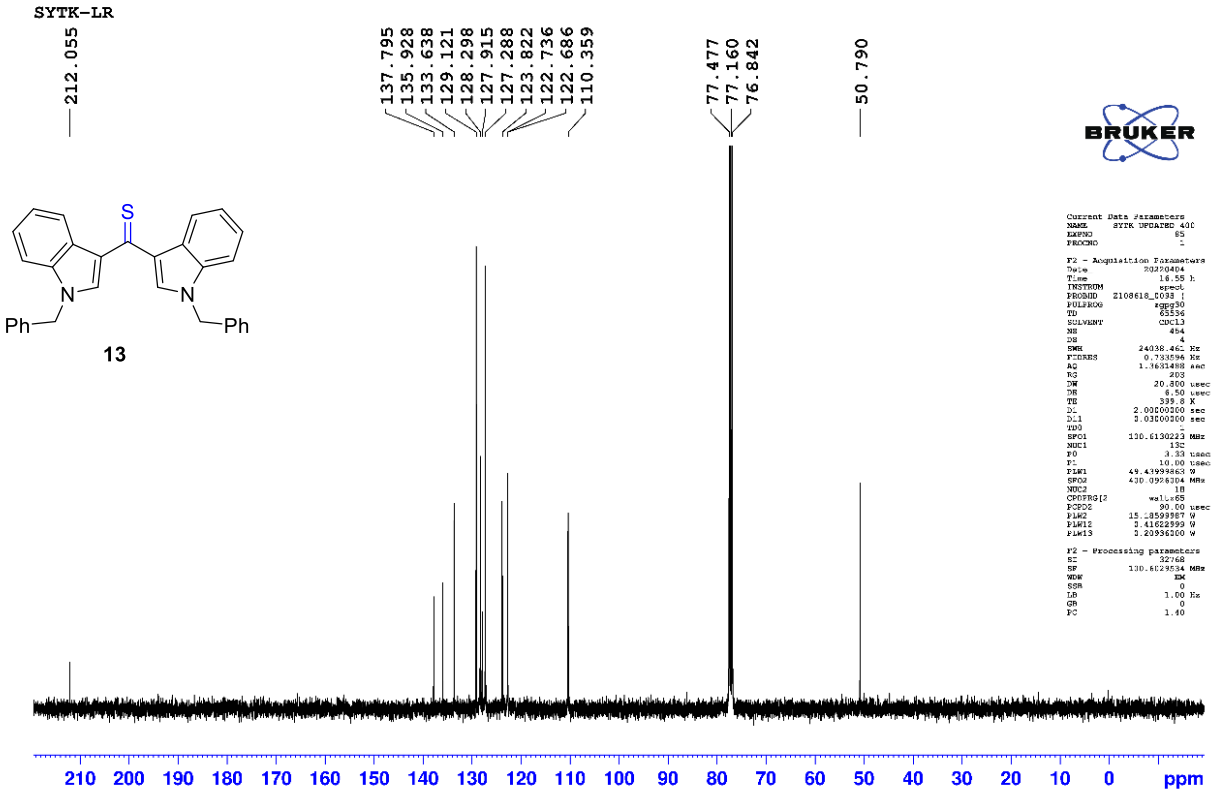


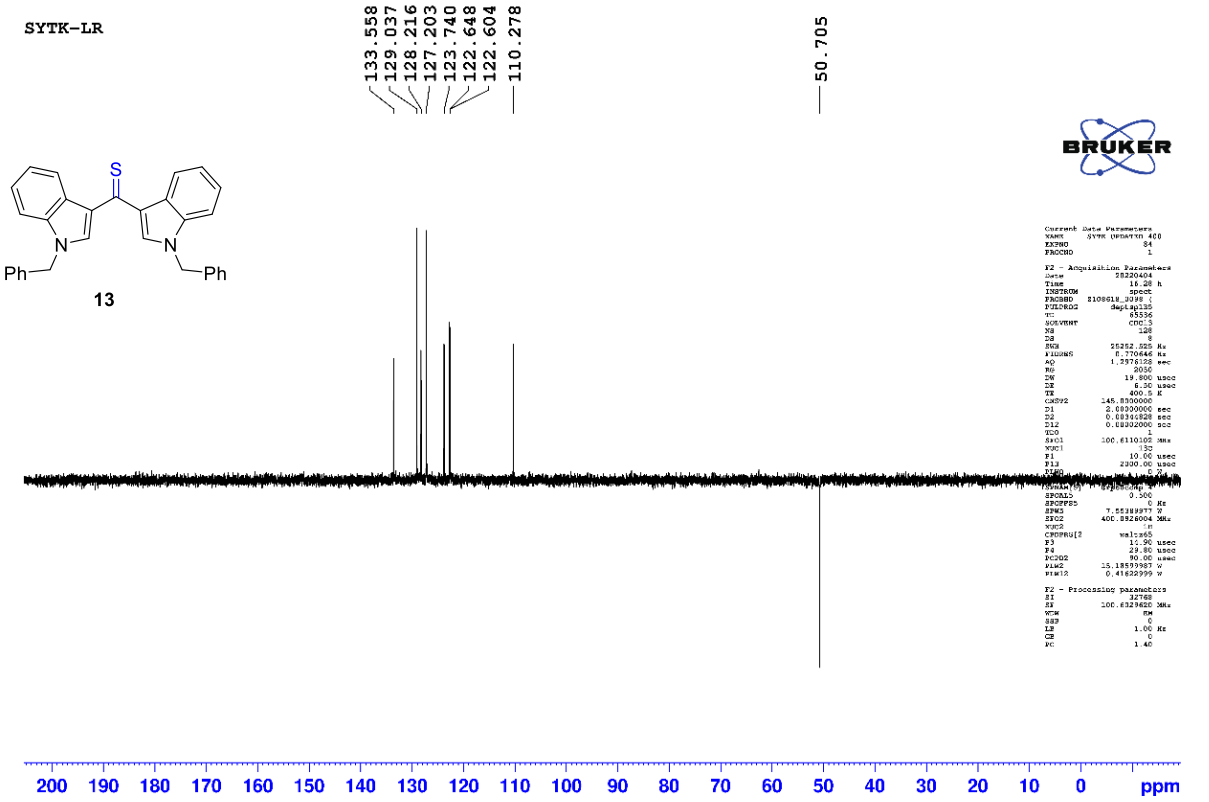
LR

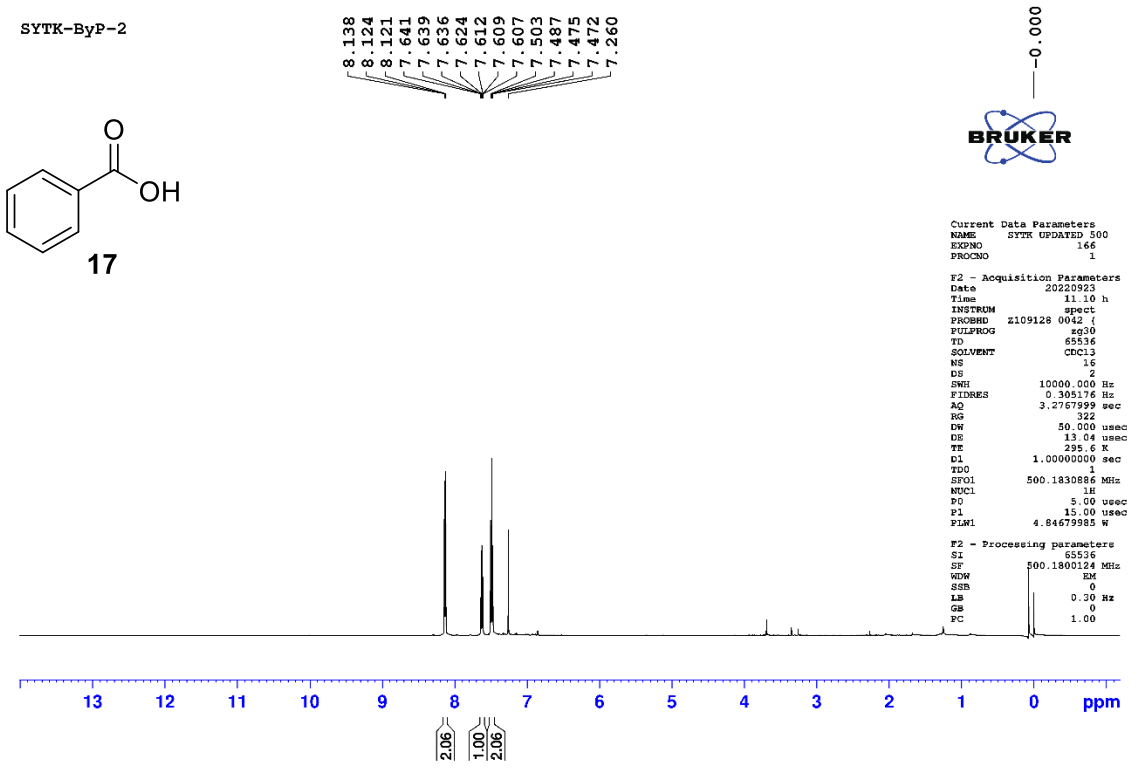


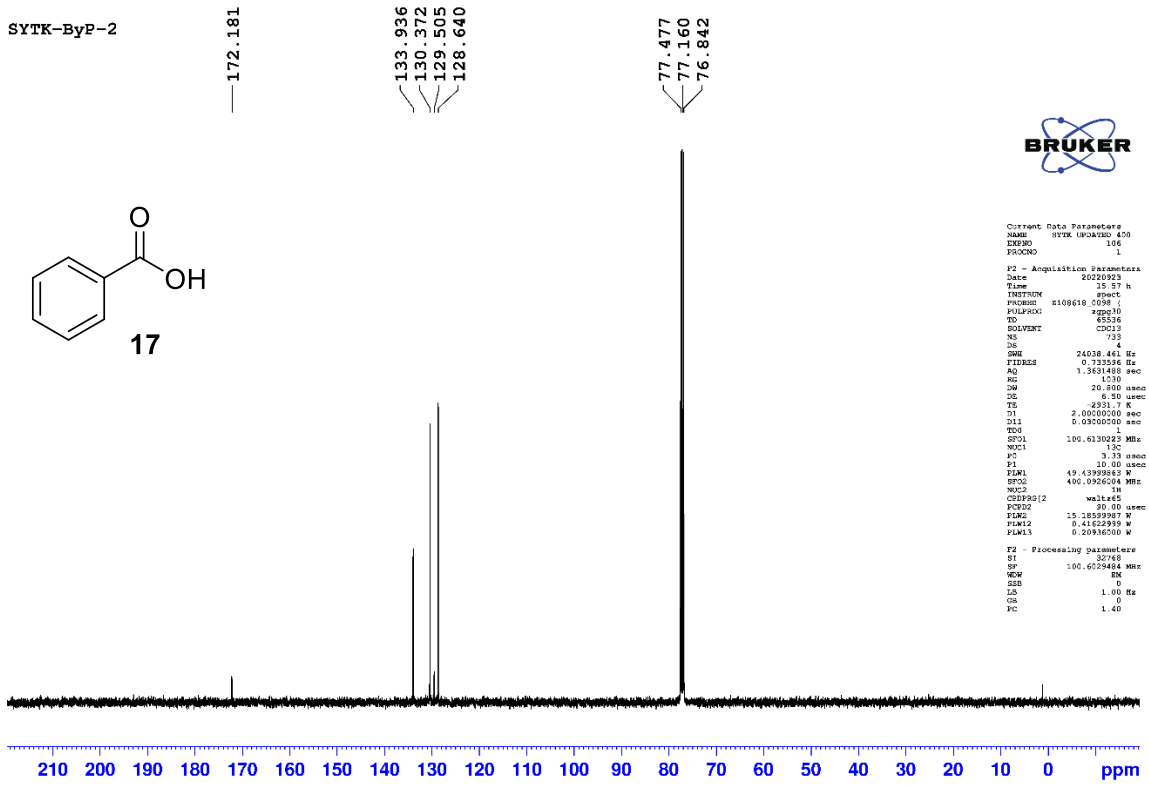
13




SYTK-LR
212.055
137.795
135.928
133.638
129.121
128.298
127.915
127.288
123.822
122.736
122.686
110.359
77.477
77.160
76.842
50.790
BRUKER
S
N
N
Ph
Ph
13
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


SYTK-LR
133.558
129.037
128.216
127.203
123.740
122.648
122.604
110.278
50.705
BRUKER
S
N
N
Ph
Ph
13
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm





M+H calculated: 123.0446, observed:123.0447.

3.7. References

1. (a) Bishop, K.C. Transition metal-catalyzed rearrangements of small ring organic molecules. *Chem. Rev.* **1976**, *76*, 461-486. (b) Watson, P. L.; Parshall, G. W. Organolanthanides in catalysis. Acc. Chem. Res. 1985, 18, 51-56. (c) Crabtree, R. H. The organometallic chemistry of alkanes. *Chem. Rev.* **1985**, *85*, 245-269. (d) Jennings, P. W.; Johnson, L. L. Metallacyclobutane complexes of the group eight transition metals: synthesis, characterizations, and chemistry. *Chem. Rev.* **1994**, *94*, 2241-2290. (e) Rybtchinski, B.; Milstein, D. Metal insertion into C- C bonds in solution. Angew. *Chem. Int. Ed.* **1999**, *38*, 870-883. (f) Murakami, M.; Ito, Y. In Topics in Organometallic Chemistry; Murai, S., Ed.; Springer: Berlin, Germany, **1999**, 97-129 and references therein. (g) Jun, C.-H. Transition metal-catalyzed carbon-carbon bond activation. *Chem. Soc. Rev.* **2004**, *33*, 610-618. (h) Drahl, M.A.; Manpadi, M.; Williams, L.J. C-C Fragmentation: Origins and Recent Applications. *Angew. Chem. Int. Ed*., **2013**, *52*, 11222-11251. (i) Murakami, M.; Ishida, N. Potential of metal-catalyzed C-C single bond cleavage for organic synthesis. *J. Am. Chem. Soc.*, **2016**, *138*, 13759-13769. (j) Sivaguru, P., Wang, Z., Zanoni, G.; Bi, X. Cleavage of carbon-carbon bonds by radical reactions. *Chem. Soc. Rev.*, **2019**, *48*, 2615-2656. (k) Lutz, M.D.; Morandi, B. Metal-catalyzed carbon-carbon bond cleavage of unstrained alcohols. *Chem. Rev.*, **2020**, *121*, 300-326.
2. (a)Hodkova, J.; Vesely, Z.; Koblicova, Z.; Holubek, J.; Trojanek, J. On alkaloids XXV minor alkaloids of poppy capsules. *Lloydia* **1972**, *35*, 61-68. (b) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances*, 4th ed. Georg Thieme: Stuttgart, Germany, **2001**. (c) Nachshon-Kedmi, M.; Yannai, S.; Fares, F. A. Induction of apoptosis in human prostate cancer cell line, PC3, by 3,3′-diindolylmethane through the mitochondrial pathway. *Br. J. Cancer* **2004**, *91*, 1358-1363.
3. Genovino, J.; Lütz, S.; Sames, D.; Touré, B. B. Complementation of Biotransformations with Chemical C-H Oxidation: Copper-Catalyzed Oxidation of Tertiary Amines in Complex Pharmaceuticals. *J. Am. Chem. Soc.* **2013**, *135*, 12346-12352. (b) Cavani F.; Teles, J. H. Sustainability in Catalytic Oxidation: An Alternative Approach or a Structural Evolution? *ChemSusChem.* **2009**, *2*, 508-534.
4. For selected recent reviews, see: (a) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. Recent Advances in Transition Metal Catalyzed Oxidation of Organic Substrates with Molecular Oxygen. *Chem. Rev.* **2005**, *105*, 2329-2364. (b) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. Recent advances in transition-metal catalyzed reactions using molecular oxygen as the oxidant. *Chem. Soc. Rev.* **2012**, *41*, 3381-3430. (c) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. Aerobic Copper-Catalyzed Organic Reactions. *Chem. Rev.* **2013**, *113*, 6234-6458. For selected recent reports, see: (d) Wakaki, T.; Togo, T.; Yoshidome, D.; Kuninobu, Y.; Kanai, M. Palladium-Catalyzed Synthesis of Diaryl Ketones from Aldehydes and (Hetero)Aryl Halides *via* C-H Bond Activation. *ACS Catal.* **2018**, *8*, 3123-3128. (e) Dai, W.; Lv, Y.; Wang, L.; Shang, S.; Chen, B.; Li, G.; Gao, S. Highly efficient oxidation of alcohols catalyzed by a porphyrin-inspired manganese complex. *Chem. Commun.* **2015**, *51*, 11268-11271. (f) Kamijo, S.; Tao, K.; Takao, G.; Tonoda, H.; Murafuji, T. Photoinduced Oxidation of Secondary Alcohols Using 4-Benzoylpyridine as an Oxidant. *Org. Lett.* **2015**, *17*, 3326-3329. (g) Shen, D.; Miao, C.; Xu, D.; Xia, C.; Sun, W. Highly Efficient Oxidation of Secondary Alcohols to Ketones Catalyzed by Manganese Complexes of N4 Ligands with H_2O_2. *Org. Lett.* **2015**, *17*, 54-57. (h) Chebolu, R.; Bahuguna, A.; Sharma, R.; Mishra, V. K.; Ravikumar, P. C. An unusual

chemoselective oxidation strategy by an unprecedented exploration of an electrophilic center of DMSO: a new facet to classical DMSO oxidation. *Chem. Commun*. **2015**, *51*, 15438-15441. (i) Song, H.; Kang B.; Hong, S. H. Fe-Catalyzed Acceptorless Dehydrogenation of Secondary Benzylic Alcohols. *ACS Catal*. **2014**, *4*, 2889-2895.

5. For selected recent reviews, see: (a) Sun, C.-L.; Li, B.-J.; Shi, Z. J. Direct C-H Transformation *via* Iron Catalysis. *Chem. Rev*. **2011**, *111*, 1293-1314. (b) Liu, C.; Zhang, H.; Shi, W.; Lei, A. Bond Formations between Two Nucleophiles: Transition Metal Catalyzed Oxidative Cross-Coupling Reactions. *Chem. Rev*. **2011**, *111*, 1780-1824. (c) Campbell, A. N.; Stahl; S. S. Overcoming the "Oxidant Problem": Strategies to Use O2 as the Oxidant in Organometallic C-H Oxidation Reactions Catalyzed by Pd (and Cu). *Acc. Chem. Res*. **2012**, *45*, 851-863. (d) Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. Oxidative Coupling between Two Hydrocarbons: An Update of Recent C-H Functionalizations. *Chem. Rev*. **2015**, *115*, 12138-12204.
6. (a) Bonvin, Y.; Callens, E.; Larrosa, I.; Henderson, D. A.; Oldham, J.; Burton, A. J.; Barrett, A. G. M. Bismuth-Catalyzed Benzylic Oxidations with tert-Butyl Hydroperoxide. *Org. Lett*. **2005**, *7*, 4549-4552. (b) Nakanishi, M.; Bolm, C. Iron-Catalyzed Benzylic Oxidation with Aqueous tert-Butyl Hydroperoxide. *Adv. Synth. Catal*. **2007**, *349*, 861-864. (c) Kumar, R. A.; Maheswari, C. U.; Ghantasala, S.; Jyothi, C.; Reddy, K. R. Synthesis of 3H-Quinazolin-4-ones and 4H-3,1-Benzoxazin-4-ones *via* Benzylic Oxidation and Oxidative Dehydrogenation using Potassium Iodide-tert-Butyl Hydroperoxide. *Adv. Synth. Catal*. **2011**, *353*, 401-410. (d) Liu, P.; Liu, Y.; Wong, E. L.-M.; Xiang, S.; Che, C.-M. Iron oligopyridine complexes as efficient catalysts for practical oxidation of arenes, alkanes, tertiary amines and N-acyl cyclic amines with Oxone. *Chem. Sci*. **2011**, *2*, 2187-2195. (e) Hruszkewycz, D. P.; Miles, K. C.; Thiel, O. R.; Stahl, S. S. Co/NHPI-mediated aerobic oxygenation of benzylic C-H bonds in pharmaceutically relevant molecules. *Chem. Sci*. **2017**, *8*, 1282-1287; and references cited therein.
7. Moriyama, K.; Takemura, M.; Togo, H. Direct and Selective Benzylic Oxidation of Alkylarenes *via* C-H Abstraction Using Alkali Metal Bromides. *Org. Lett*. **2012**, *14*, 2414-2417.
8. (a) Catino, A. J.; Nichols, J. M.; Choi, H.; Gottipamula, S.; Doyle, M. P. Benzylic Oxidation Catalyzed by Dirhodium(II,III) Caprolactamate. *Org. Lett*. **2005**, *7*, 5167-5170. (b) Zhang, J.; Wang, Z.; Wang, Y.; Wan, C.; Zheng, X.; Wang, Z. A metal-free catalytic system for the oxidation of benzylic methylenes and primary amines under solvent-free conditions. *Green Chem*. **2009**, *11*, 1973-1978. (c) Peng, H.; Lin, A.; Zhang, Y.; Jiang, H.; Zhou, J.; Cheng, Y.; Zhu, C.; Hu, H. Oxidation and Amination of Benzylic sp3 C-H Bond Catalyzed by Rhenium(V) Complexes. *ACS Catal*. **2012**, *2*, 163-167. (d) Shen, D.; Miao, C.; Wang, S.; Xia, C.; Sun, W. Efficient Benzylic and Aliphatic C-H Oxidation with Selectivity for Methylenic Sites Catalyzed by a Bioinspired Manganese Complex. *Org. Lett*. **2014**, *16*, 1108-1111. (e) Prakash, G. K. S.; Shakhmin, A.; Glinton, K. E.; Rao, S.; Mathew, T.; Olah, G. A. Poly(N-vinylpyrrolidone)-H_2O_2 and poly(4-vinylpyridine)-H_2O_2 complexes: solid H_2O_2 equivalents for selective oxidation of sulfides to sulfoxides and ketones to gem-dihydroperoxides. *Green Chem*. **2014**, *16*, 3616-3622. (f) Eliasen, A.; Thedford, R.; Claussen, K.; Yuan, C.; Siegel, D. A Protocol to Generate Phthaloyl Peroxide in Flow for the Hydroxylation of Arenes. *Org. Lett*. **2014**, *16*, 3628-3631.
9. Dohi, T.; Takenaga, N.; Goto, A.; Fujioka H.; Kita, Y. Clean and Efficient Benzylic C-H Oxidation in Water Using a Hypervalent Iodine Reagent: Activation of Polymeric Iodosobenzene with KBr in the Presence of Montmorillonite-K10. *J. Org. Chem*. **2008**, *73*, 7365-7368.

10. (a) Doering, W. E.; Haines, R. M. Alkoxide-catalyzed Autoxidative Cleavage of Ketones and Esters. J. *Am. Chem. Soc*. **1954**, *76*, 482-486. (b) Boisselier, V.; Coin, C.; Postel, M.; Dunach, E. Molecular oxygen oxidative carbon-carbon bond cleavage of α-ketols catalysed by Bi(III) carboxylates. *Tetrahedron* **1995**, *51*, 4991-4996.
11. Zhang, N.; Vozzolo, J. Novel C-C Bond Cleavage under Mild, Neutral Conditions: Conversion of Electron-Deficient Aryl Alkyl Ketones to Aryl Carboxylic Esters. *J. Org. Chem*. **2002**, *67*, 1703- 1704. (b) Paria, S.; Halder, P.; Paine, T. K. Oxidative Carbon-Carbon Bond Cleavage of a α-Hydroxy Ketone by a Functional Model of 2,4′-Dihydroxyacetophenone Dioxygenase. *Angew. Chem. Int. Ed.* **2012**, *51*, 6195-6199. (c) Zhang, C.; Feng, P.; Jiao, N. Cu-Catalyzed Esterification Reaction *via* Aerobic Oxygenation and C-C Bond Cleavage: An Approach to α-Ketoesters. *J. Am. Chem. Soc*. **2013**, *135*, 15257-15262.
12. Becker, J. Y.; Miller, L. L.; Siegel, T. M. Nitrogen-bound and carbon-bound xanthine complexes of ruthenium ammines. *J. Am. Chem. Soc*. **1975**, *97*, 849-853. (b) Ishihara, K.; Yano, T. Synthesis of Carboxamides by LDA-Catalyzed Haller-Bauer and Cannizzaro Reactions. *Org. Lett*. **2004**, *6*, 1983-1986. (c) Kuninobu, Y.; Uesugi, T.; Kawata, A.; Takai, K. Manganese-Catalyzed Cleavage of a Carbon-Carbon Single Bond between Carbonyl Carbon and α-Carbon Atoms of Ketones. *Angew. Chem. Int. Ed*. **2011**, *50*, 10406-10408.
13. Arisawa, M.; Kuwajima, M.; Toriyama, F.; Li, G. Z.; Yamaguchi, M. Rhodium-Catalyzed Acyl-Transfer Reaction between Benzyl Ketones and Thioesters: Synthesis of Unsymmetric Ketones by Ketone CO-C Bond Cleavage and Intermolecular Rearrangement. *Org. Lett*. **2012**, *14*, 3804-3807. (b) Yoshida, H.; Kishida, T.; Watanabe M.; Ohshita, J. Fluorenes as new molecular scaffolds for carbon-carbon σ-bond cleavage reaction: acylfluorenylation of arynes. *Chem. Commun*. **2008**, 5963-5965. (c) Dreis, A. M.; Douglas, C. J. Catalytic Carbon-Carbon σ Bond Activation: An Intramolecular Carbo-Acylation Reaction with Acylquinolines. *J. Am. Chem. Soc*. **2009**, *131*, 412-413. (d) Sakurai, H.; Kamiya, I.; Kitahara, H.; Tsunoyama, H.; Tsukudad, T. Aerobic Oxygenation of Benzylic Ketones Promoted by a Gold Nanocluster Catalyst. *Synlett* **2009,** 245-248.
14. Maji, A.; Rana, S.; Akanksha; Maiti, D.; Synthesis of Bis(heteroaryl) Ketones by Removal of Benzylic CHR and CO Groups. *Angew. Chem. Int. Ed*. **2014**, *53*, 2428-2432.
15. For selected examples of oxidations with KO^{t}Bu, see: (a) Bai, L.-G.; Zhou, Y.; Zhuang, X.; Zhang, L.; Xue, J.; Lin, X.-L.; Cai, T.; Luo, Q.-L. Base-promoted aerobic oxidation of N-alkyl iminium salts derived from isoquinolines and related heterocycles. *Green Chem*. **2020**, *22*, 197-203. (b) Tan, S.; Li, F.; Park S.; Kim, S. Transition metal-free aerobic oxidative cleavage of the C-N bonds of α-amino esters. *Org. Chem. Front*. **2019**, *6*, 3854-3858. (c) Barham, J. P.; Coulthard, G.; Emery, K. J.; Doni, E.; Cumine, F.; Nocera, G.; John, M. P.; Berlouis, L. E. A.; McGuire, T.; Tuttle, T.; Murphy, J. A. KO^{t}Bu: A Privileged Reagent for Electron Transfer Reactions? *J. Am. Chem. Soc*. **2016**, *138*, 7402-7410. (d) Muhammad, I.; Balakrishnan, M. H.; Sasidharan, M.; Mannathan, S. Potassium tert-butoxide mediated aerobic hydroxylation of arylboronic acids: an application towards the synthesis of (E)-phenoxy acrylates. *New J. Chem.* **2019**, *43*, 11065-11068. (e) Wang, Z.; Zhang, J.; Shia, J.; Wang, H. KO^{t}Bu-promoted oxidative dimerizations of 2-methylquinolines to 2-alkenyl bisquinolines with molecular oxygen. *RSC Adv.* **2019**, *9*, 30139-30143.

16. Chaudhari, M. B.; Sutar, Y.; Malpathak, S.; Hazra, A.; Gnanaprakasham, B. Transition-Metal-Free C-H Hydroxylation of Carbonyl Compounds. *Org. Lett.* **2017**, *19*, 3628-3631.
17. Wang, H.; Wang, Z.; Huang, H.; Tan J.; Xu, K. KOtBu-Promoted Oxidation of (Hetero)benzylic Csp3-H to Ketones with Molecular Oxygen. *Org. Lett*. **2016**, *18*, 5680-5683.
18. Gessner, T.; Mayer, U. Ullmann's Encyclopedia of Industrial Chemistry, Wiley-VCH, Weinheim, **2000**.
19. Nguyen, H.-H.; Do, T.-H.; Nguyen, T.-H.-T.; Duong, T.-H.; Vo, H.-C.; Do, V.-M.; Nguyen, T.-P.; Sichaem, J.; Nguyen, N.-H.; Nguyen, H. T. Two new phenolic compounds from Boerhavia erecta collected in Vietnam. *Nat. Prod. Res*. **2022**, DOI: 10.1080/14786419.2022.2086543.
20. Praveen, P. J.; Parameswaran, P. S.; Majik, M. S. Bis(indolyl)methane Alkaloids: Isolation, Bioactivity, and Syntheses. *Synthesis* **2015**, *47,* 1827-1837
21. Sua´rez, A.; Martı´nez, F.; Sua´rez-Pantiga, S.; Sanz, R. PTSA-Catalyzed Reaction of Indoles with 2-Oxoaldehydes: Synthesis of α, α-Bis(indol-3-yl) Ketones. *ChemistrySelect.* **2017**, *2*, 787-790.
22. (a) Haddach, A. A.; Kelleman, A.; Deaton-Rewolinski, M. V. An efficient method for the N-debenzylation of aromatic heterocycles. *Tetrahedron Lett*. **2002**, *43,* 399-402.
23. Holland, D. C.; Kiefel, M. J.; Carroll, A. R. Structure Revisions of the Sponge-Derived Dibrominated Bis-indole Alkaloids, Echinosulfone A and the Echinosulfonic Acids A to D. *J. Org. Chem.* **2020**, *85*, 3490-3496.
24. Riley, H. A.; Gray, A. R. Phenylglyoxal. *Org. Synth.* **1935**, *15*, 67.
25. Nandwana, N. K.; Patel, O. P. S.; Srivathsa, M. R.; Kumar**,** A. Dual Role of Glyoxal in Metal-Free Dicarbonylation Reaction: Synthesis of Symmetrical and Unsymmetrical Dicarbonyl Imidazoheterocycles. *ACS Omega* **2019**, *4*, 10140-10150
26. Suárez, A.; Martínez, F.; Sanz, R. Synthesis of α-functionalized α-indol-3-yl carbonyls through direct S_N reactions of indol-3-yl α-acyloins. *Org. Biomol. Chem.*, **2016**, *14*, 11212-11219.
27. Liang, D.; Li, X.; Li, Y.; Yang, Y.; Gao, S.; Cheng, P. Br_2-Catalyzed regioselective dehydrative coupling of indoles with acyloins: direct synthesis of α-(3-indolyl) ketones. *RSC Adv.* **2016**, *6*, 29020-29025.
28. Satoh, T.; Kametani, Y.; Terao, Y.; Miura, M.; Nomura, M. Palladium-catalyzed multiple arylation of phenyl ketones with aryl bromides. *Tetrahedron Lett*., **1999**, *40*, 5345-5348.

Chapter 4

Cyclizative Strategies Towards Construction of Carbazoles from Indole-Tethered Propargyl Alcohols

Manuscript communicated

4.1. Introduction

Carbazoles are a class of alkaloids, which is a tricyclic structure comprising a nitrogen-containing five-membered ring with a benzene ring fused on either side.[1] Carbazole is a very important type of heterocycle that is widely spread in nature, Graebe and Glazer isolated it from coal tar for the first time in 1872.[2] The isolation of murrayanine from Murraya koenigii species (curry patta or curry-leaves), and its antibacterial activities were published in 1965 by Chakraborty et al.[3,4] Murrayanine was the naturally occurring alkaloid that was isolated for the first time. Numerous chemical substances, drugs, bioactive molecules, and natural products revolve around carbazoles.[5] The electroluminescent[6] nature of the carbazole exists because of its electrical and thermal properties.[7] Carbazole also serves as a host material for triplet emitters in organic light-emitting diodes.[8]

Derivatives of carbazole serve as a precursor for the design of novel drugs and act as an intermediate for the synthesis of many biologically active molecules. The carbazole derivatives are reported to exhibit profound biological and pharmacophoric properties.[9] Numerous carbazole derivatives have been synthesized[10] and are well known for their pharmacological properties.[11-16] These includes benzocarbazole, benzofurano carbazole, furo-carbazole, imidacarbazole, indocarbazole, oxazinocarbazole, pyridocarbazole, pyrrolocarbazole, tetrahydrocarbazole, thiazolocarbazole, and N-substituted carbazole.[10] The pharmacological activities include antibacterial, anti-cancer, anti-epileptic, antifungal, anti-HIV, anti-histaminic, anti-inflammatory, antioxidant, antiprotozoal, anti-tubercular, anti-tumor, anti-viral, hepatoprotective, sedative, and topoisomerase II inhibition.[11]

Several naturally occurring compounds with therapeutic properties, such as carbazomycin and murrayafoline A, contain the carbazole ring and are potential drugs for the treatment of chronic diseases. A non-steroidal drug Caprofen is known to possess anti-inflammatory activity.[12] The FDA has authorized the use of indolocarbazole-mediated drug RYDAPT (midostaurin) for the treatment of acute myeloid leukemia (AML) and FLT3 mutations.[13] A carbazole-based fluorophore SLM showed neuroprotection by binding to the β-amyloid peptides and has emerged as a prospective drug for the treatment of Alzheimer's disease. Clausenol and clausinine[14] demonstrate antibacterial activity, while P7C3[15] and its derivatives have illustrated potential neuroprotective properties for drug development in animal models of Parkinson’s disease, amyotrophic lateral sclerosis, traumatic brain injury, and age-related cognitive decline.[16] Complex alkaloids tubingensin A and B demonstrate anticancer, antiviral, and powerful action against agriculturally important pests.[11] Figure 1 represents some of the carbazoles that are found to be biologically and medicinally important.

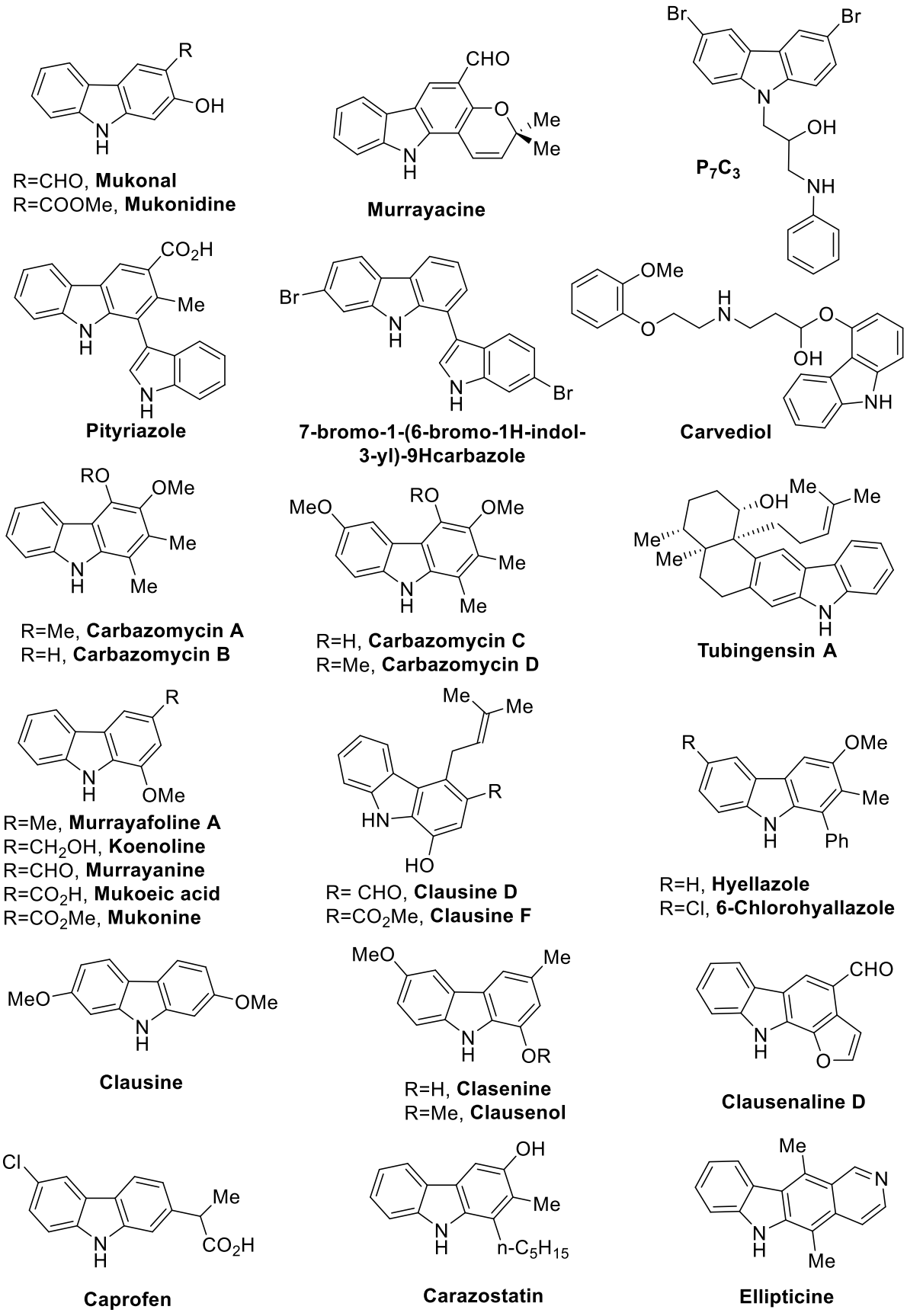


Figure 1. *Representative examples of biologically and medicinally important carbazoles*

Part A: Cu(II)/HFIP Mediated Cycloisomerization of Indole-tethered Propargyl Alcohols to Carbazole

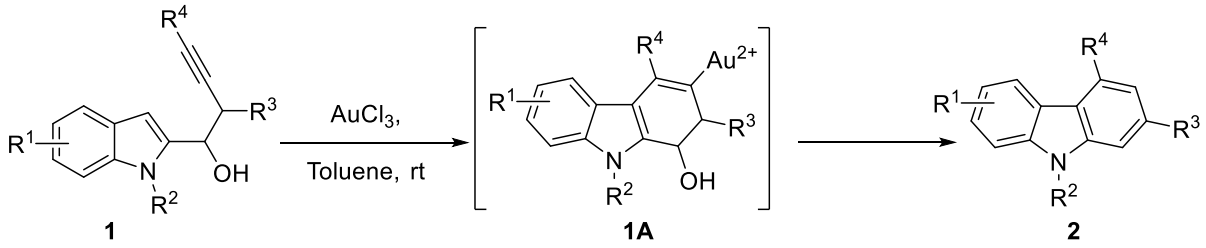
Carbazole scaffolds have attracted a lot of interest throughout time due to their extensive number of medicinal chemistry applications,[11-16] and as a result, simple, rapid, flexible, and adaptable strategies for synthesizing carbazole analogs have emerged.[10,17] Traditionally, carbazole synthesis depended heavily on the nitrene insertion,[18] Fischer indolization,[19], Diels Alder reaction, dehydrogenative cyclization of diarylamines, etc.[20] and Fischer-Borsche, synthesis employing arylhydrazines and cyclohexanones through a series of condensation, cyclization, and dehydrogenation under acidic and oxidative conditions.[21] Naphthols and aryl hydrazines happen to be the initial constituents for the Bucherer carbazole synthesis, a chemical process that produces carbazoles, by employing sodium bisulfite.[22] Recently, research has focused on processes such as ring-closing metathesis, cycloisomerization, benzannulation, Suzuki-Miyaura coupling, and transition metal mediated C-N and C-C bond formations.[17]

4.A.1. Literature Reports

Significant synthetic techniques have been published in the literature, considering the carbazole's rising significance. Electrophilic cyclization of alkyne or allene has become an interesting subject in organic chemistry to construct heterocycles and carbocycles.[23,24] In this regard propargyl alcohol is a potential starting material for creating a wide range of carbo and heterocyclic compounds. In most cases, the activation of a triple bond of the propargyl alcohol with a suitable reagent becomes a demanding and appealing aspect of research due to the ambident reactivity of this substrate. Because of the association of two functional groups, i.e., alkyne and hydroxy group, it gains more emphasis on reactivity, these alcohols undergo various transformations by involving either alkyne or hydroxyl group or both. The chemistry of propargylic alcohols is substantially expanded by chemo and regioselective processes, opening the possibility of appealing synthetic methods for new functionalization.[25] Various synthetic protocols are developed for the synthesis of the carbazole with indole-tethered propargyl alcohol.[26] Transition metal complexes catalyze a number of these methods, currently recognized as a potent tool for the simple synthesis of complex compounds from commonly available starting materials. The behavior of indole derivatives with alkynes bound to the C-2 or C-3 sites has been widely investigated.[27] These are a few examples of indole-tethered alkyne-based carbazole synthesis.

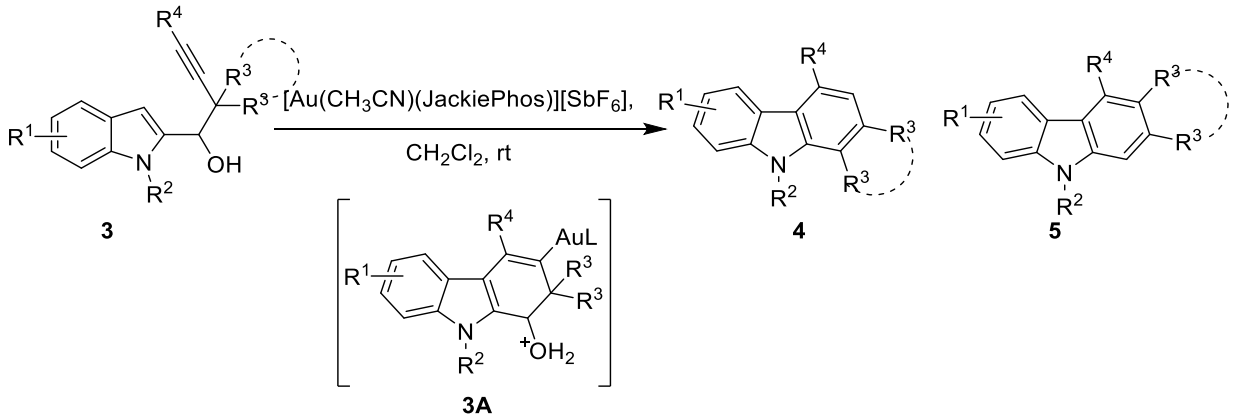
Shengming Ma and coworkers have worked extensively on the cyclization of homopropargylic alcohols to afford the alkaloid carbazole following the expulsion of water to construct the aromatic ring. In 2012, they demonstrated an $AuCl_3$-catalyzed transformation of 1-(indol-2-yl)-3-alkyn-1-ols in toluene solvent media at room temperature to form a series of carbazole derivatives efficiently. Initial coordination of alkyne with Au^{3+} and subsequent

nucleophilic attack from the C3 carbon of indolyl moiety to the electrophilic C-C triple bond results in intermediate **1A**. The intermediate **1A** on demetallation and aromatization give rise to carbazole **2** (Scheme 1).[28]



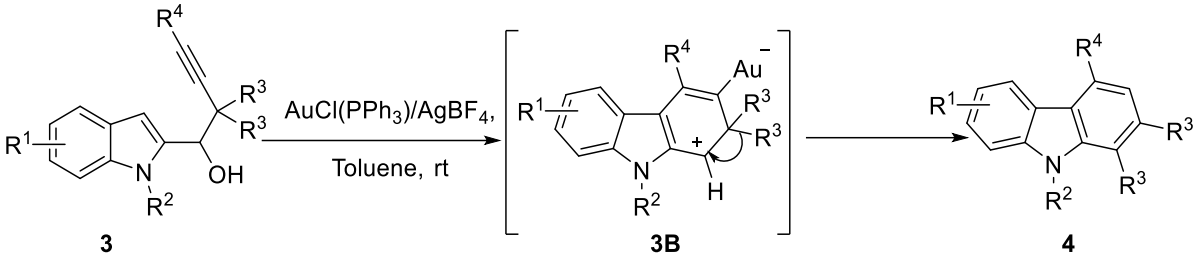
Scheme 1. *Gold catalyzed cyclization of homopropargyl alcohol for the synthesis of carbazole*

In 2013 they reported a diversified gold-catalyzed intramolecular cyclization of 1-(indol-3-yl)-3-alkyn-1-ols, for the synthesis of substituted carbazoles (Scheme 2).[29] This divergent reaction route propped for several types of carbazole synthesis depending on the reaction conditions and substitution pattern. They show the synthesis of cycloalkyl-annulated [a]carbazoles **4** through a Wagner-Meerwein type 1,2-alkyl shift, cycloalkyl-annulated [b]carbazoles **5** by 1,2-alkyl migration to the proximal carbenoid center of the intermediate **3A**, or carbazole ethers by ring-opening the cyclopropyl group through nucleophilic attack of water or alcohol.

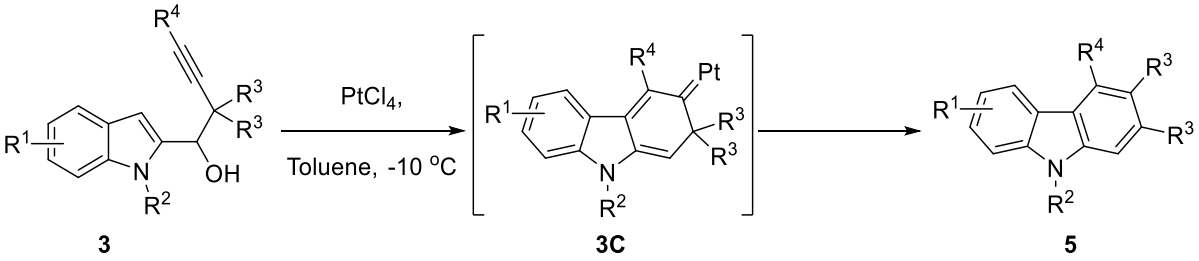


Scheme 2. *Gold catalyzed cyclization for carbazole synthesis*

Similarly, an $AuCl(PPh_3)/AgBF_4$ or $PtCl_4$ catalyzed cyclomerization reaction of 1-(indol-2-yl)-2,2-dialkyl substituted 3-alkyn-1-ols **3**, to synthesize substituted carbazole **4** was reported by the same group in 2014 (Scheme 3). They show that carbazoles **4** was obtained in the presence of $AuCl(PPh_3)/AgBF_4$ *via* a Wagner-Meerwein type of 1,2- alkyl shift of the intermediate **3B** (Scheme 3), whereas in cases of $PtCl_4$ at -10 ^oC afforded carbazoles **5** with inverted regioselectivity because of the involvement of platinum carbene intermediate **3C** (Scheme 4).[30]

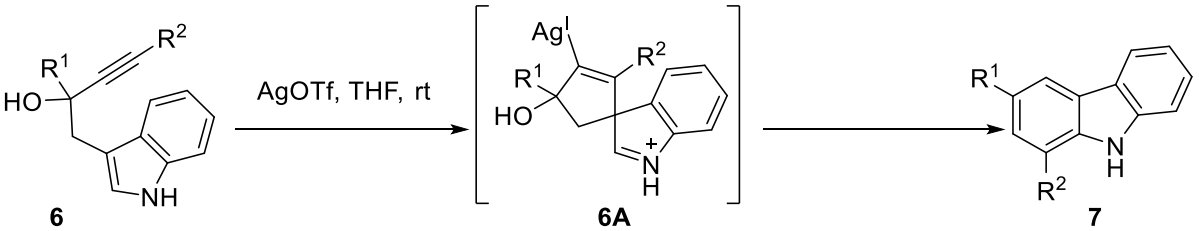


Scheme 3. *Gold catalyzed Carbazole synthesis via 1,2-alkyl shift*



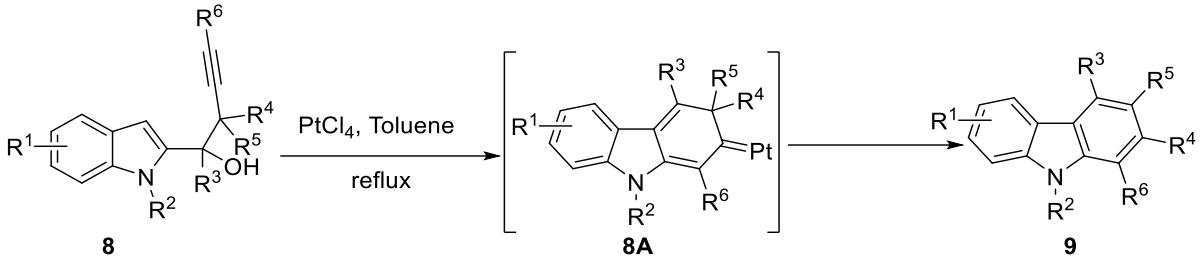
Scheme 4. *Platinum catalyzed carbazole synthesis from homopropargyl alcohol*

In 2015, a novel strategy for the selective synthesis of carbazole from indole-tethered propargyl alcohol **6** was demonstrated in the presence of AgOTf (Scheme 5). Ag(I)-catalyzed spirocyclization was the first step in this reaction, which produced **6A**, subsequent 1,2-migration of vinylic carbon, and elimination/ aromatization produces carbazole **7**.[31]



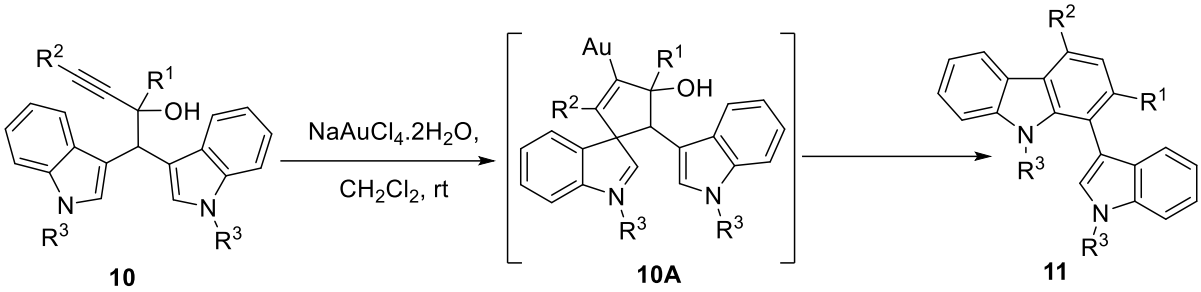
Scheme 5. *Silver catalyzed carbazole synthesis from propargyl alcohol*

Later, in 2017, S. Ma et al. reported a synthesis of tetra-substituted carbazole **9** from indol-2-yl-2,2-dialkyl substituted 3-alkynol **8**, involving rearrangement of the carbon skeleton and 1,2-alkyl migration using $PtCl_4$ in toluene at reflux temperature (Scheme 6). A spirocyclic intermediate formed due to the activation of a triple bond and subsequent nucleophilic attack, followed by selective ring expansion to give platinum-mediated carbene intermediate **8A**. The intermediate **8A** then affords carbazole by migrating the group present at the C3 position to the C2 position.[32]



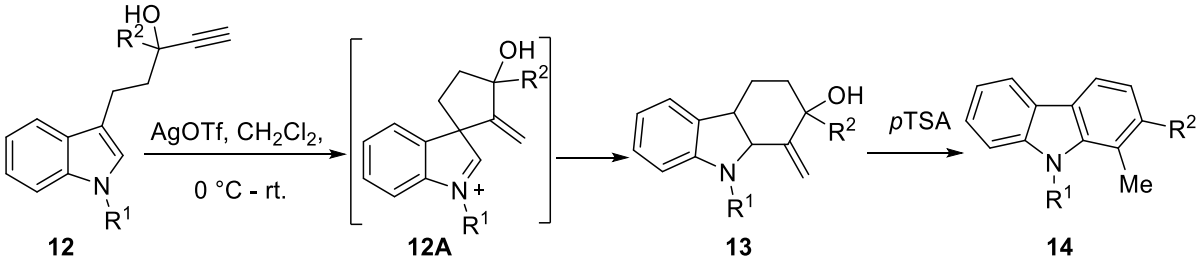
Scheme 6. *Platinum catalyzed carbazole synthesis from 3°-homopropargyl alcohol*

Similarly, the Sanz group reported the selective synthesis of 1-(indol-3-yl)carbazole **11** under gold catalysis from bis(indol-3-yl)methyl alkynol **10**. This transformation proceeds through a selective 1,2-alkyl migration over 1,2-vinyl migration of the intermediate **10A** generated by the 5-*endo* spirocyclization process (Scheme 7). [33]



Scheme 7. *Gold catalyzed cycloisomerization for synthesis of carbazole*

In 2018, Baire and coworkers reported a highly regioselective synthesis of substituted carbazole **14** from (indol-3-yl)-pentyn-3-ols **12** using AgOTf and *p*TSA in cascade manner (Scheme 8). The transformation constitutes regio as well as chemoselective intramolecular cyclization of indolyl and propargyl alcohol parts present within (indol-3-yl)-pentyn-3-ol **12**. AgOTf after coordination with the ynol part and subsequent nucleophilic attack of C3 carbon of indole results in compound **13** with an exocyclic double bond which later transformed to carbazole **14** when treated with *p*TSA. However, direct carbazole (**14**) synthesis took place with a good yield when reactions were exclusively carried out in *p*TSA.[34]

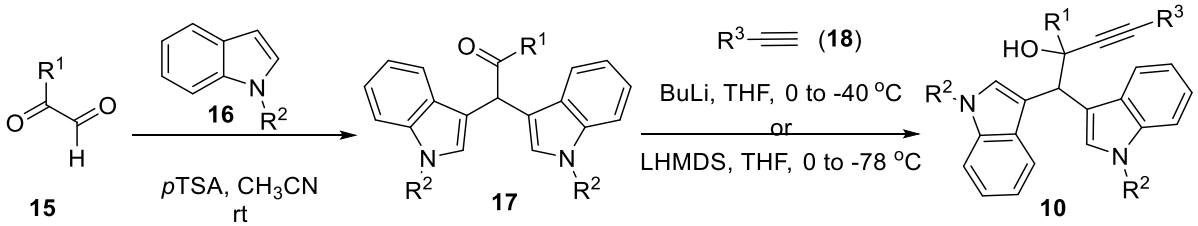


Scheme 8. *Silver and pTSA catalyzed carbazole synthesis*

4.A.2. Results and Discussion

Brønsted and Lewis acid-catalyzed reactions have become increasingly prevalent in modern chemical synthesis because of the distinctive reactivity and selectivity that may be produced under benign circumstances.[35] The exceptional potential of several metal triflates (trifluoromethylsulfonates) stimulates further investigation. Weak nucleophilicity and

coordination of triflate anion, favor the metal counter ion to be more cationic and thus a stronger Lewis acid. Considering the significance of carbazole and the reactivity of Lewis acid, we intended to discover the most practical strategy in terms of accessibility for the synthesis of carbazole.



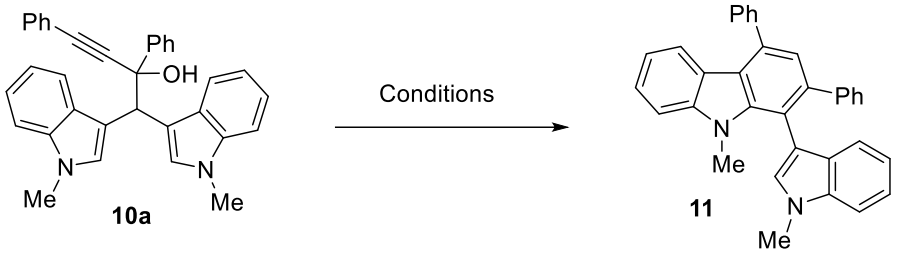
Scheme 9. *Synthesis of bis-indolyl propargyl alcohol*

To begin our investigation in this respect, a bis-indolyl propargyl alcohol was subjected it to several Lewis and brønsted acids. The bis-indolyl propargyl alcohol was prepared as shown in Scheme 9. Glyoxal on reaction with indole undergoes nucleophilic addition to give the bis-indolyl carbonyl,[36] which on reaction with alkynes in the presence of base gives rise to bis-indolyl propargyl alcohol.[33]

4.A.2.1. Optimization of Reaction Condition:

The compound 10a 1,1-bis(1-methyl-1H-indol-3-yl)-2,4diphenylbut-3-yn-2-ol was subjected to various acid catalysts in DCE at room temperature. $Ca(NTf_2)_2$ and $Ca(OTf)_2$ along with additive Bu_4NPF_6, resulted in a low yield of carbazole in 8 hours (12% and 18% respectively). Reaction with *p*TSA yielded only 10% of the product, whereas, the use of $Cu(OTf)_2$ enhanced the yield of carbazole to 43%. It was discovered that several acid catalysts such as triflic acid, methane sulphonic acid, $BF_3.OEt_2$, $Mg(OTf)_2$, Triflamide, and $FeCl_3$ were inefficient for the synthesis of carbazole. Next solvent optimization was carried out using toluene, DMSO, and CH_3CN, but none of them proved to be a superior solvent, despite the fact that in toluene 45% of the product was formed. Owing to the potency of HFIP,[37] next a reaction was performed where HFIP was used as a solvent, surprisingly, 82% of carbazole was formed within 15 minutes. When a stoichiometric amount of HFIP was used, 96% of carbazole was formed in 15 minutes. We also tried to enhance the yield of the product by using a solvent with HFIP, a combination of HFIP and toluene gave 75% of carbazole, on the other hand, HFIP and DCE resulted in 45% of the product. We also checked the necessity of the catalyst by performing a reaction without $Cu(OTf)_2$ in HFIP, the product was not formed in this case. Optimization of the reaction condition suggested that $Cu(OTf)_2$ in a stoichiometric amount of HFIP, was the best condition for this transformation.

Table 1. Optimization of Reaction Conditions



S. No.	Reaction Conditions (mol %)	Yield[b]
1.	$Ca(NTf_2)_2/Bu_4NPF_6$ (10), DCE, 25 ^oC, 8 h	12%
2.	$Ca(OTf)_2/Bu_4PF_6$ (10), DCE, 25 ^oC, 8 h	18%
3.	*p*TSA (10), DCE, 25 ^oC, 24 h	10%
4.	$Cu(OTf)_2$ (10), DCE, 25 ^oC, 4 h	43%
5.	TfOH (10), DCE, 25 ^oC, 4 h	0%
6.	$MeSO_3H$ (10), DCE, 25 ^oC, 4 h	0%
7.	$BF_3.Et_2O$ (10), DCE, 25 ^oC, 4 h	0%
8.	$Mg(OTf)_2$ (10), DCE, 25 ^oC, 24 h	nr
9.	$HNTf_2$ (10), DCE, 25 ^oC, 4 h	0%
10.	$FeCl_3$ (10), DCE, 25 ^oC, 24 h	nr
11.	$Cu(OTf)_2$ (10), Toluene, 25 ^oC, 1 h	45%
12.	$Cu(OTf)_2$ (10), DMSO, 25 ^oC, 24 h	nr
13.	$Cu(OTf)_2$ (10), CH_3CN, 25 ^oC, 2 h	<20%
14.[c]	$Cu(OTf)_2$ (10), HFIP , 25 ^oC, 15 min	82%
15.[d,e]	$Cu(OTf)_2$ (10), HFIP, 25 ^oC, 15 min	96%
16.	HFIP, 25 ^oC, 24 h	nr

[a]all the reactions were carried out with **10a** (100 mg), at rt (25^oC) under specified conditions. [b]Isolated yields, [c]HFIP as a solvent, [d]HFIP in 1 equivalent, [e]Optimum condition.

4.A.2.2. Scope of the Reaction:

To examine the scope and limitation of this copper-catalyzed cycloisomerization, we subjected the developed condition to various bis-indolyl-butynols **10**. Different N-substituted bis-indolyl-butynol shown excellent reactivity toward the formation of 1-indolyl carbazole. N-Me (**11a**), N-Et (**11b**), N-Bn (**11c**), N-allyl (**11d**), and N-isopropyl (**11e**) substituted 1-

indolyl carbazole were synthesized using this protocol in excellent yields. N-H bisindolyl-butynol **10f** also tolerated the optimized condition and resulted in 67% of the product **11f**. Substitution on the alkyne terminus also tolerated the condition, tolyl and biphenyl substituted indolyl carbazoles (**11g** and **11h**) were achieved in 87% and 89% respectively. Alkyl substituents instead of aryl were checked for reactivity, and we were able to synthesize indolyl carbazole with cyclopropyl (confirmed by single crystal XRD) in 84% (**11i**) and cyclohexyl in 88% (**11j**) at C-4 carbon. To check the tolerance of the R^1 group of the bis-indolyl-butynol, different R^1 substituted bis-indolyl-butynol were subjected to the optimized condition. Electronic effects of the aryl group were compared, and it was observed that the Me, F, and Br groups show excellent reactivity and gave the products **11k-11m** in nearly quantitative yield, whereas, in the case of CN slightly lesser yield of the product **11n** was formed. The compound **11k** was further confirmed by single crystal XRD. 91% of indolyl carbazole with naphthyl substituent (**11o**) and 95% with methyl substituent (**11p**) was formed and when R^1 was equal to H, 89% of indolyl carbazole **11q** was formed. Indolyl carbazole **11r** with methoxy C-5 substituted indole was obtained in 87% under the optimized condition.

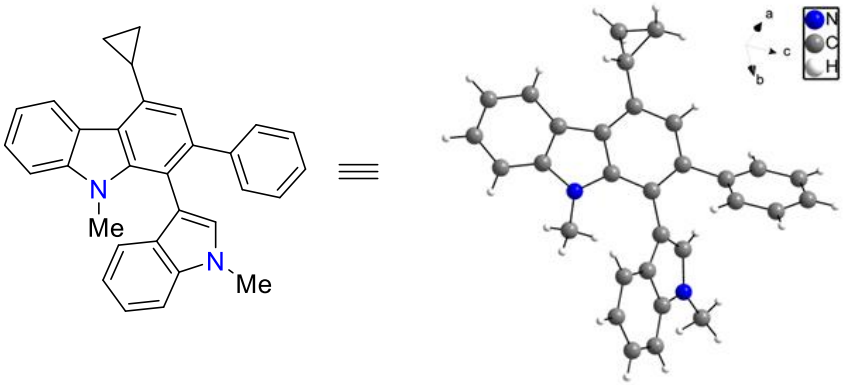


Figure 2. *Single crystal XRD of* ***11i***

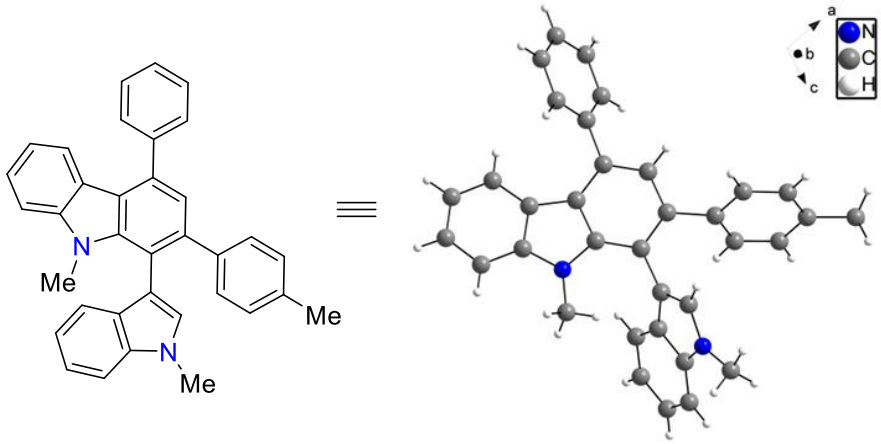
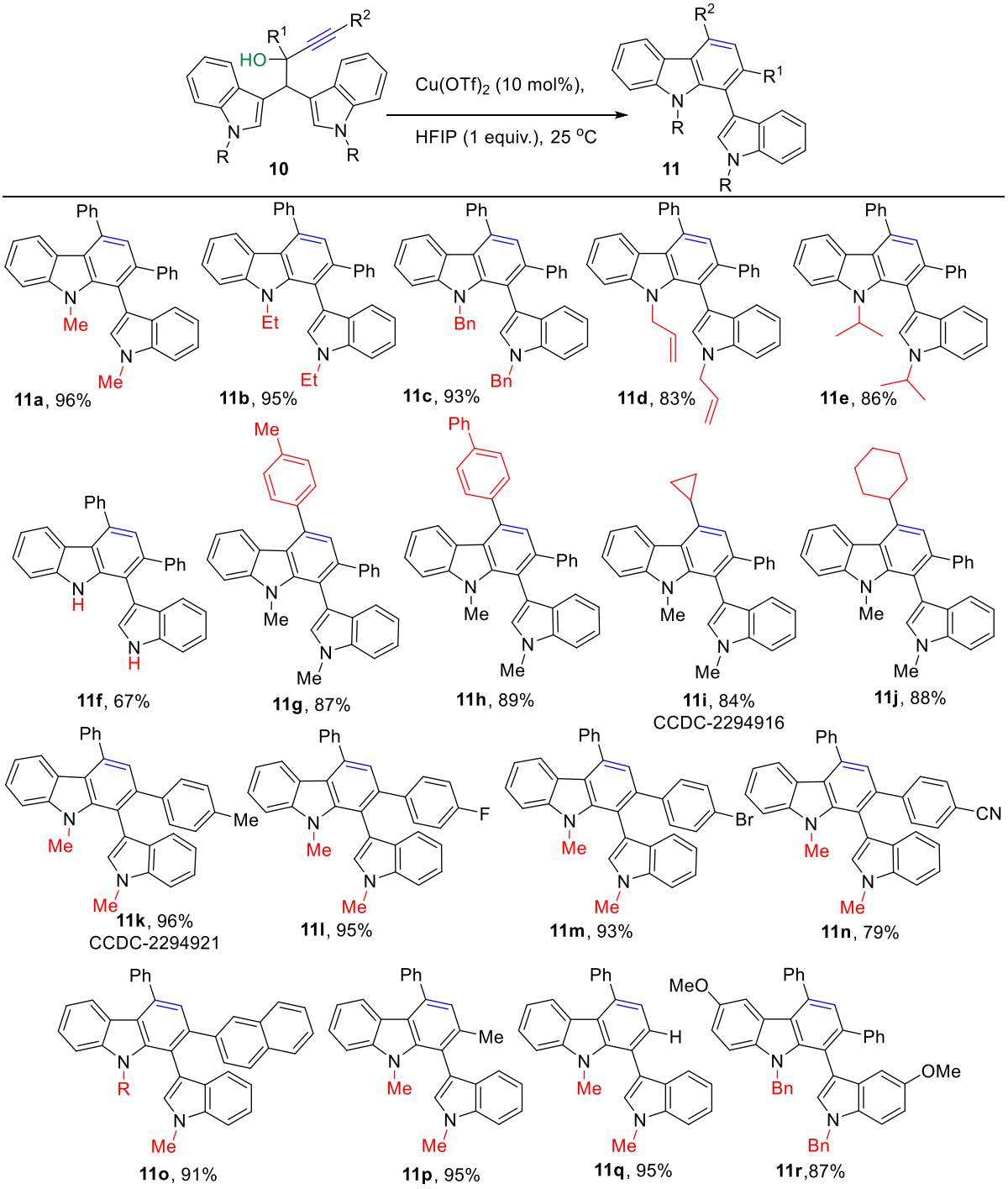


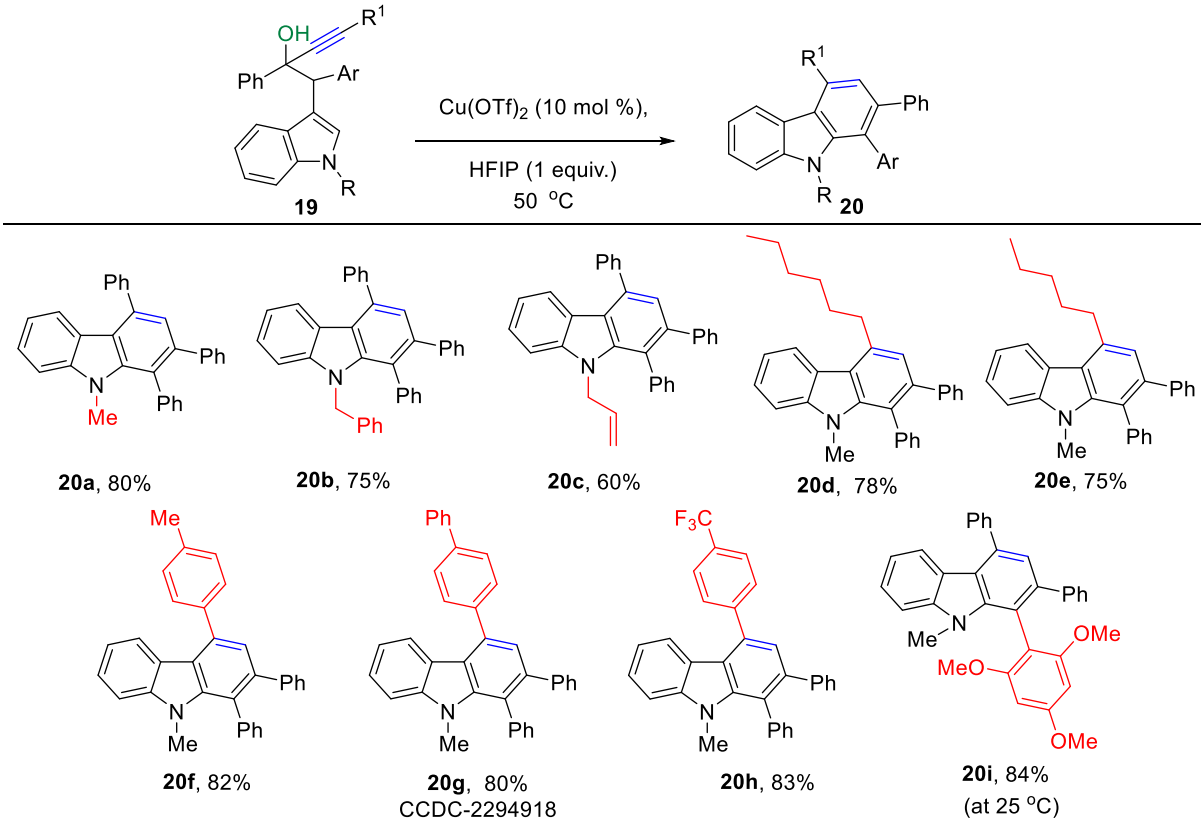
Figure 3. *Single crystal XRD of* ***11k***



Scheme 10. *Scope of indolyl carbazole*

Motivated by this outcome, we intended to substitute one of the indole rings of bis-indolyl-butynol (**10**) with a phenyl group and check the reactivity. Therefore, we subjected 1-(1-methyl-1H-indol-3-yl)-1,2,4-triphenylbut-3-yn-2-ol (**19a**) to the optimized condition, the corresponding product was formed in very low yield, to enhance the yield of the carbazole we elevated the reaction temperature to 50 °C considering the boiling point of HFIP. The attempt was successful and carbazole **20a** was obtained in 80%. After this success, N-Bn and N-allyl substituted indolyl-1,2,4-triphenylbutynols were subjected to the condition and 75% and 60%

of the carbazole respectively (**20b** and **20c**). Changes in the alkyne terminus were feasible for the transformation, alkyl, and aryl groups tolerated the condition.



Scheme 11. *Scope of carbazole*

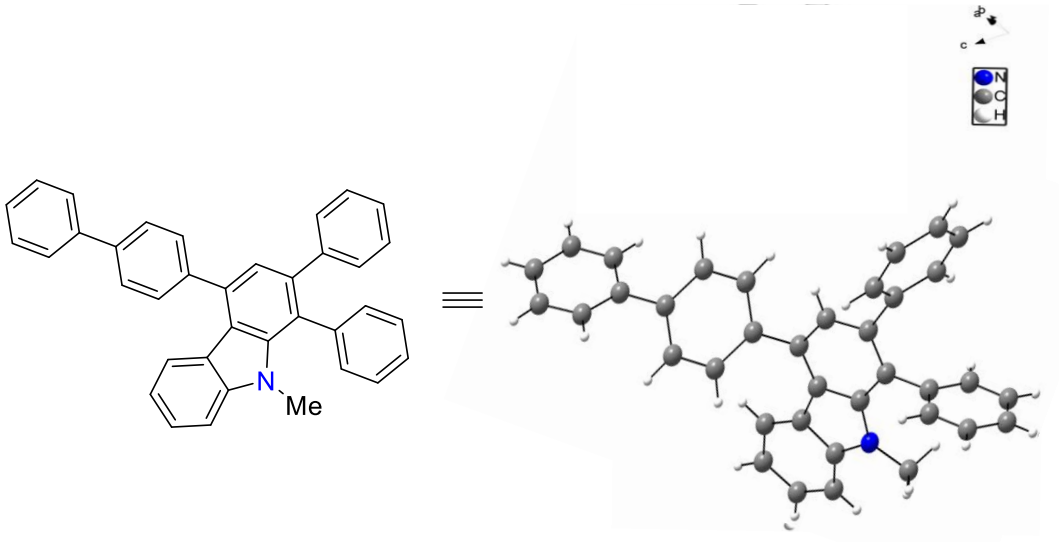
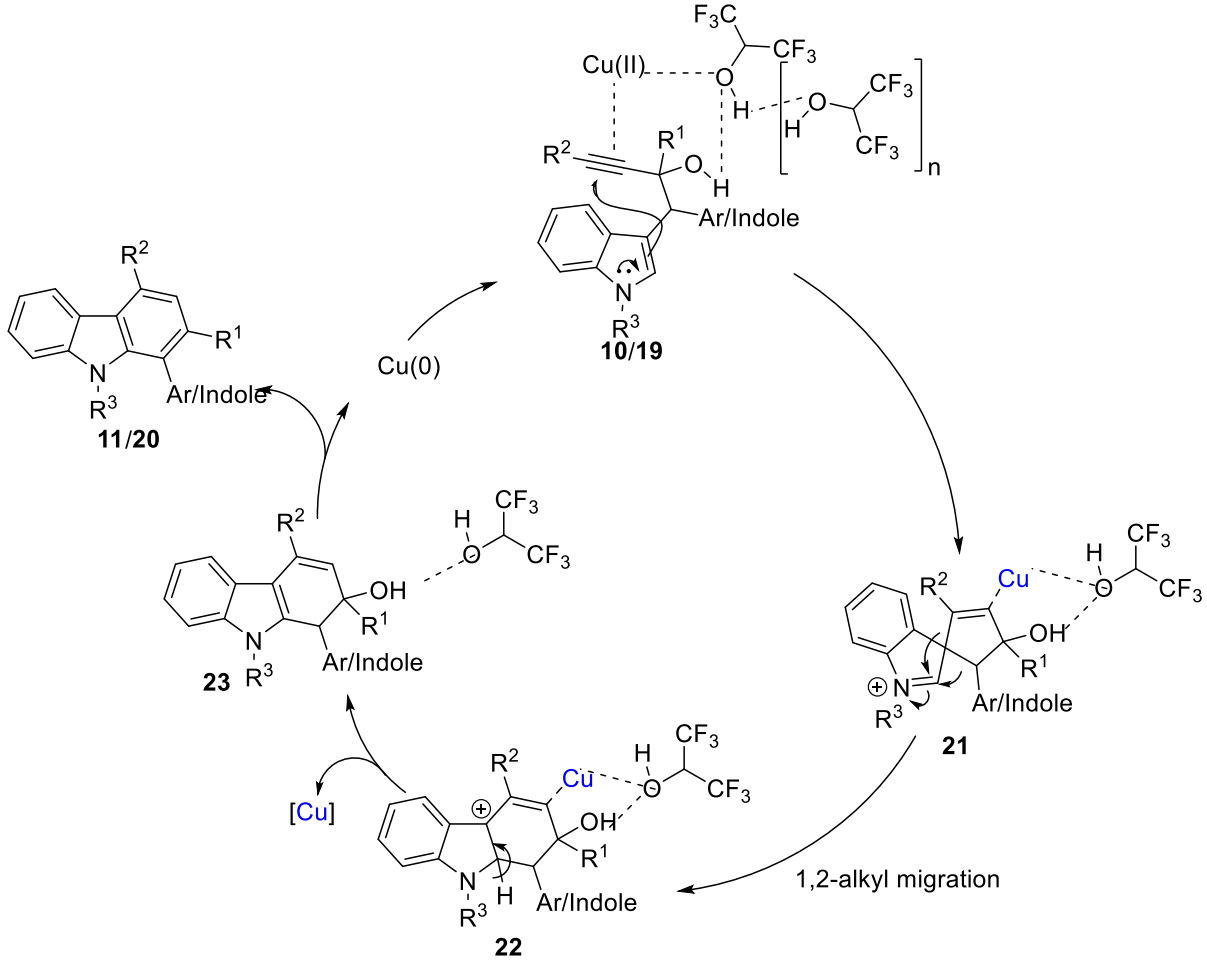


Figure 4. *Single crystal XRD of* ***20g***

During the reaction, we were able to synthesize carbazoles bearing hexyl, pentyl, tolyl, biphenyl, and trifluoromethylphenyl at the C-4 carbon of carbazole (**20d-20h**). Compound **20g** was also confirmed by single crystal X-ray structure, which also support the mechanism to be an 1,2-alkyl migration. 1-(1-met hyl-1H-indol-3-yl)-2,4-diphenyl-1-(2,4,6-

trimethoxyphenyl)but-3-yn-2-ol (**19i**) at room temperature underwent the cycloisomerization to give 9-methyl-2,4-diphenyl-1-(2,4,6-trimethoxyphenyl)-9H-carbazole **20i** in 84%.

4.A.2.3. Mechanism



Scheme 12. *Proposed Mechanism*

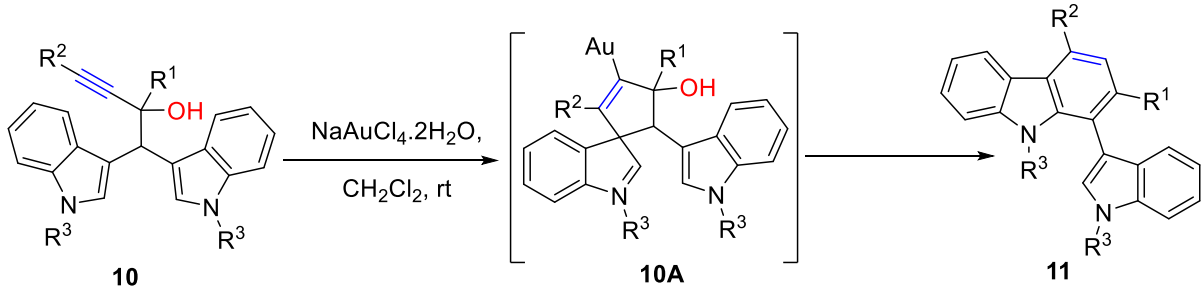
$Cu(OTf)_2$ coordinates with the triple bond of ynol, along with H-bonding with HFIP, the nucleophilic attack from indole leads to the formation of a spirocyclic cationic intermediate **21**. This intermediate brings about two possibilities of migration to stabilize itself, a 1,2-alkyl migration and a 1,2-vinyl migration. The product suggests that it undergoes a 1,2 alkyl migration to form the intermediate **22**. Elimination of proton and subsequent protodemetallation results in dihydrocarbazole **23**, which after dehydration delivers carbazole **11**/**20**.

Part B: Transition Metal-Free Cycloisomerization of Indole-tethered Propargyl Alcohols for Construction of Carbazoles

Although there are other traditional and transition metal-mediated ways to make carbazoles, the benzannulation route from indole has gained popularity recently since there are so many of them that are accessible as discussed in part A of this chapter. Alkenes, alkynes, dicarbonyls, and other compounds have generally been used effectively as diene precursors for the production of carbazoles from indoles using the benzannulation technique.[38] However, some of these methods have limitations such as using precious metal catalysts (Pt, Au, Ag, Pd, etc.), harsh reaction conditions, and limited functional group tolerance. Therefore, it is highly desirable to develop a one-pot, transition metal-free approach for the construction of pre-functionalized carbazoles, particularly iodocarbazoles[39] because these compounds can be easily transformed into desired carbazole materials using suitable reaction conditions, such as cross-coupling reactions.

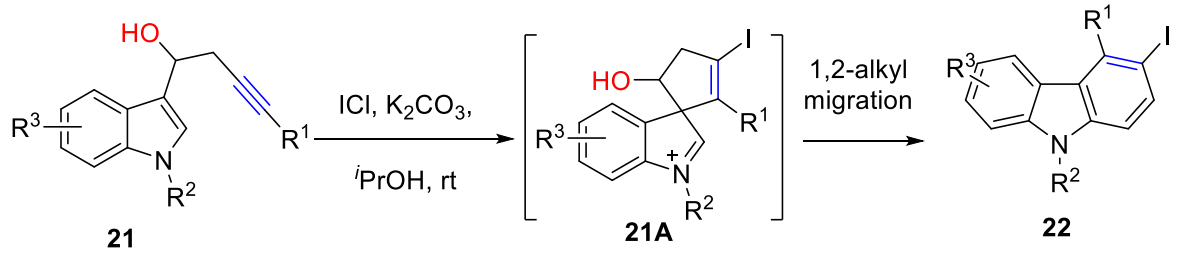
4.B.1. Literature Reports

Sanz group reported the selective synthesis of 1-(indol-3-yl)carbazole **11** under gold catalysis from bis(indol-3-yl)methyl alkynol **10**. This transformation proceeds through a selective 1,2-alkyl migration over 1,2-vinyl migration of the intermediate **10A** generated by the 5-*endo* spirocyclization process. [33]



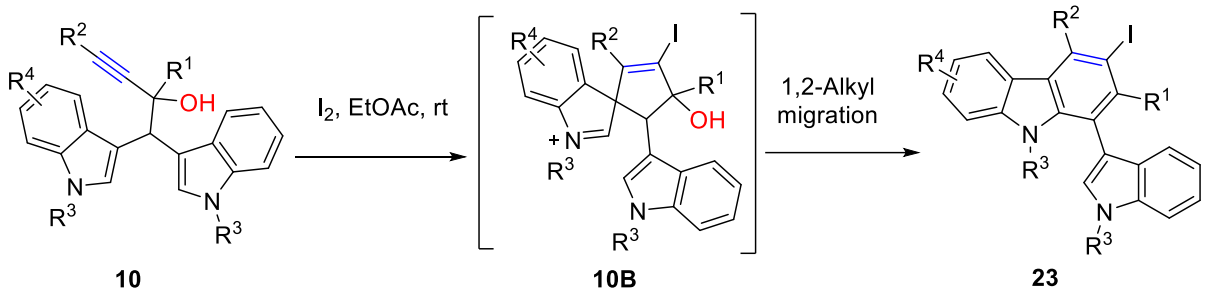
Scheme 13. *Gold catalyzed cycloisomerization for synthesis of carbazole*

In the past few years, iodocyclization of propargylic systems, particularly propargyl alcohols, has been emerging as one of the potential strategies for the construction of various prefunctionalized carbo and heterocyclic compounds. Particularly when we look at the iodocyclization of indole-tethered propargyl alcohol, very few reports appear in the literature. In 2015, Wang et al. reported an iodo-cycloisomerization of homopropargyl alcohol to synthesize 3-iodocarbazole using ICl, K_2CO_3 in isopropanol at room temperature.[40] The reaction proceeds through a spirocyclic intermediate **21A**, which undergoes 1,2-alkyl migration.



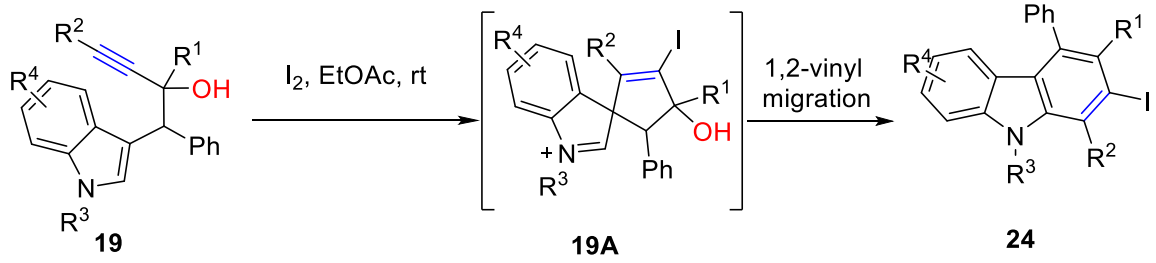
Scheme 14. *Iodocyclisomerization of homopropargyl alcohol*

Our group is also working on the cycloisomerization of indole tethered propargyl alcohol for the construction of carbazole. In 2018 our group demonstrated iodo-cycloisomerization of 1-(indol-3-yl)-1-arylbut-3-yn-2-ols **10** to form 3-iodocarbazoles **23**. The transformation proceeds through a selective 1,2-alkyl migration of a cationic spirocyclic intermediate **10B** formed 5-endo-spirocyclization.[41]



Scheme 5. *Iodocycloisomerization via 1,2-alkyl migration*

Further investigation on these types of ynols, in 2019 our group reported iodo-cycloisomerization for the construction of 2-iodocarbazole **24**. When one of the indoles from bisindolyl-butynol is replaced with a phenyl group, the reaction path is common till the formation of spirocyclic intermediate **19A**. The intermediate undergoes 1,2-vinyl migration instead of 1,2-alkyl migration which was observed in the above cases.[42]



Scheme 66. *Iodocycloisomerization via 1,2-vinyl migration*

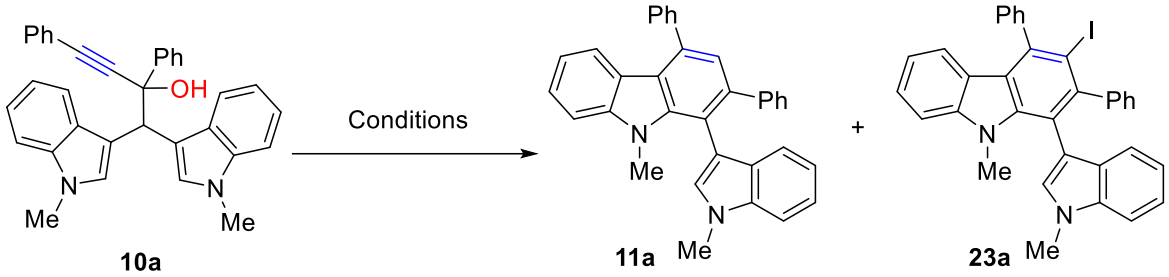
4.B.2. Results and Discussion

4.B.2.1. Optimization of Reaction Conditions

In continuation to our investigation, we witnessed an interesting result when the bisindolyl-butynol was treated with ICl, along with iodocycloisomerized product non-iodocycloisomerized i.e. cycloisomerized product was formed. We found this very

fascinating, and therefore, started investigating the exclusive synthesis of the cycloisomerized product by using a halogenated reagent. Our initial observation reveals that bisindolyl-butynol when reacted with Icl in ethyl acetate at room temperature results in nearly 1:1 ratio of iodocyclized and cycloisomerized product (42% of cycloisomerized and 39% of iodocyclized product). Our intuition to change the solvent for the exclusive cycloisomerized product was successful, by optimizing solvents like DCE, toluene, ethanol, acetonitrile, and THF we found that the required product was obtained in an excellent yield in the case of toluene (92%).

Table 2 Optimization of reaction condition



10a 11a 23a

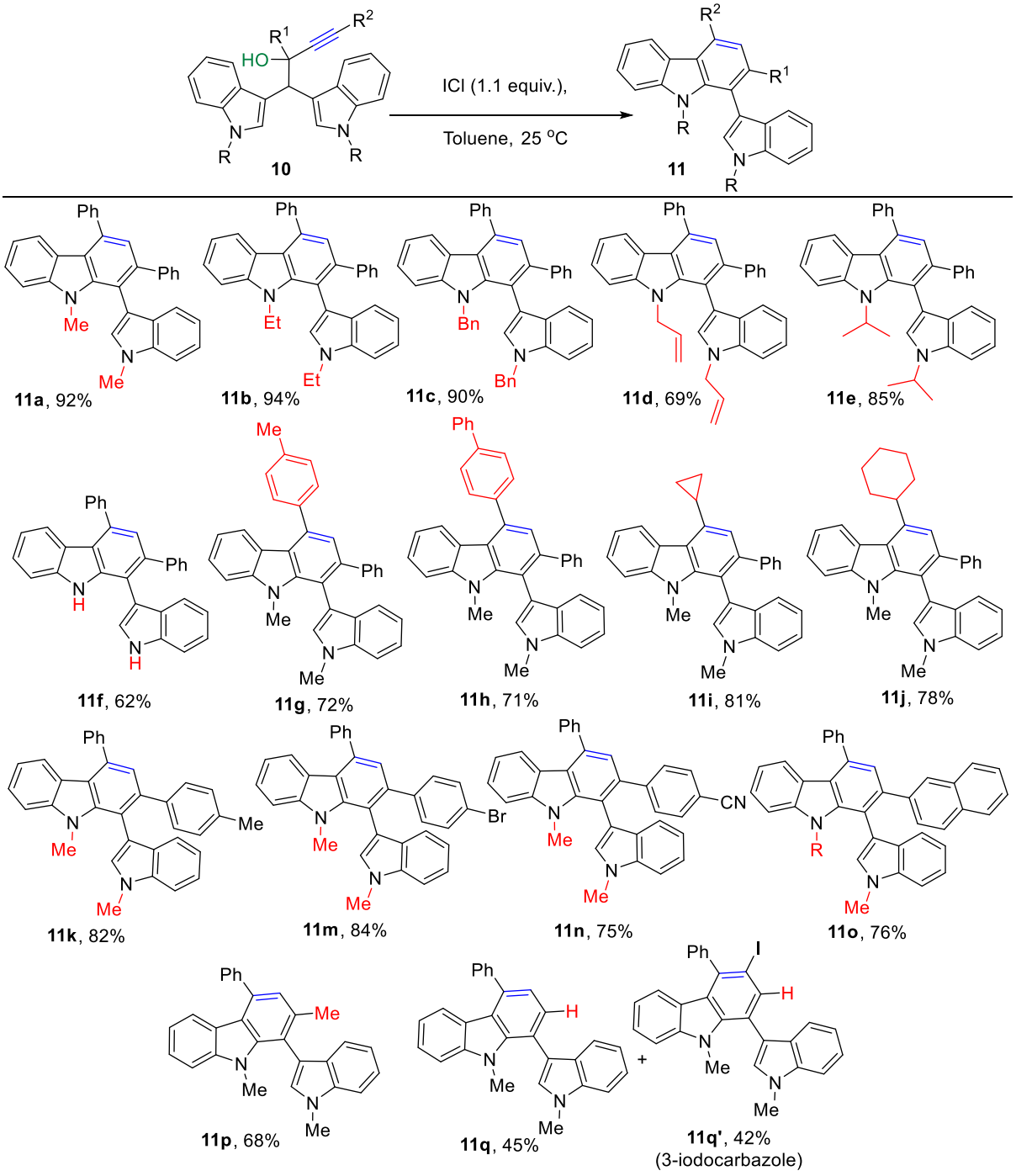
S.No.	Reaction Conditions	Result[b] (11a)	(23a)
1.	ICl (1.1 equiv.), EtOAc, rt, 20 min	42%	39%
2.	ICl (1.1 equiv.), DCE, rt, 20 min	40%	54%
3.[c]	ICl (1.1 equiv.), Toluene, rt, 20 min	92%	Trace
4.	ICl (1.1 equiv.), EtOH, rt, 20 min	48%	20%
5.	ICl (1.1 equiv.), ACN, rt, 20 min	52%	Trace
6.	ICl (1.1 equiv.), THF, rt, 20 min	38%	Trace
7.	I_2 (1.1 equiv.), Toluene, rt, 20 min	0%	28%
8.	NIS (1.1 equiv.), Toluene, rt, 20 min	Complex TLC	
9.	*p*TSA (10 mol%), Toluene, rt, 24 h	Trace	0%
10.	$Ca(NTf_2)_2$ (10 mol%), Toluene, rt, 24 h	12%	0%
11.	$Cu(OTf)_2$ (10 mol%), Toluene, rt, 24 h	45%	0%
12.	$BF_3.OEt_2$ (10 mol%), Toluene, rt, 24 h	0%	0%

[a] all the reactions were carried out with **10a** (100 mg), at rt (25°C) under specified conditions. [b]Isolated yields. [c]Optimum condition.

In DCE nearly 1:1 ratio of iodo and cycloisomerized products was formed, whereas, in other solvents cycloisomerized product was formed as major. I_2 instead of ICl in toluene gave only an iodocyclized product, and NIS lead to the decomposition of bisindolyl-butynol. As there is no role of I^+ in activating the triple bond instead it acted as an acid catalyst, therefore, other

acid catalysts such as *p*TSA, $Ca(NTf_2)_2$, $Cu(OTf)_2$, and $BF_3{\cdot}OEt_2$ in toluene was examined for reactivity but none show better reactivity than the ICl.

4.B.2.2. Scope of the Reaction:



Scheme 17. *Scope of Cycloisomerization*

With the optimized condition, N-substituted indolyl carbazole was synthesized with ease in good yields. The substitutions made to indole included methyl, ethyl, benzyl, allyl, and isopropyl, and the respective carbazoles **11a-11e** were formed in 94%-69% of the yield. Unsubstituted bisindolyl-butynol **10f** tolerated the condition and resulted in 62% of the

product **11f**. Change in the alkyne terminus also supported the protocol and produced the corresponding indolyl carbazole. **11g** and **11h** contain an aryl group on C4 carbon (tolyl and biphenyl respectively) and **11i** and **11j** possess cyclopropyl and cyclohexyl respectively. Tolerance of the R^1 group was also examined, *para*-substituted aryl with Me, Br, and CN groups showed excellent reactivity and gave respective indolyl carbazole **11k**, **11m**, and **11n**. Naphthyl and methyl group successfully resulted in a cycloisomerized product **11o** and **11p**, whereas, when R^1 was equal to H (i.e., secondary propargyl alcohol) both cycloisomerized **11q** and the iodocyclized product **11q'** was formed in 1:1 ratio.

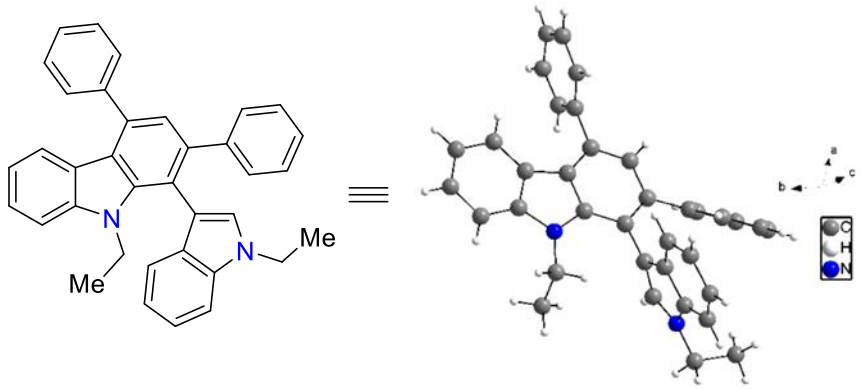
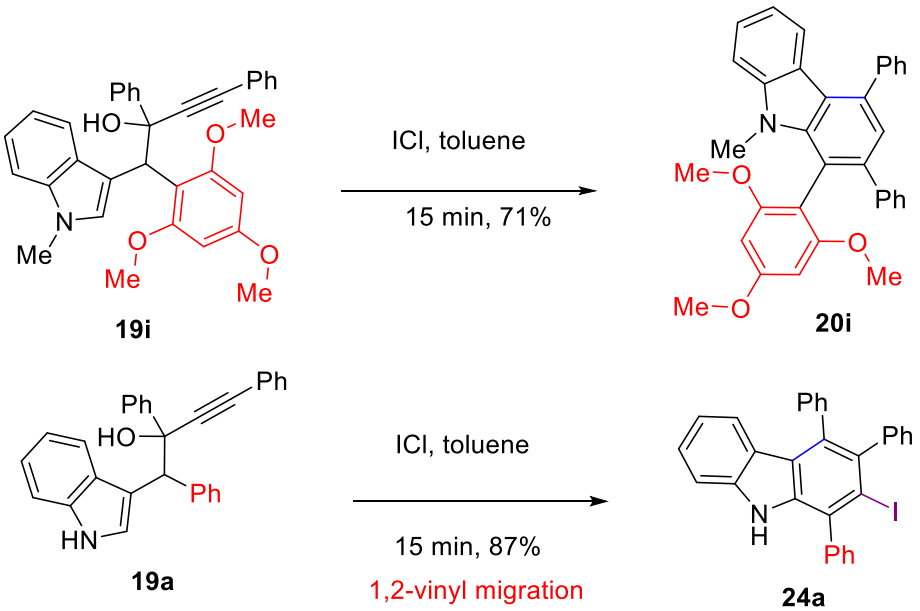


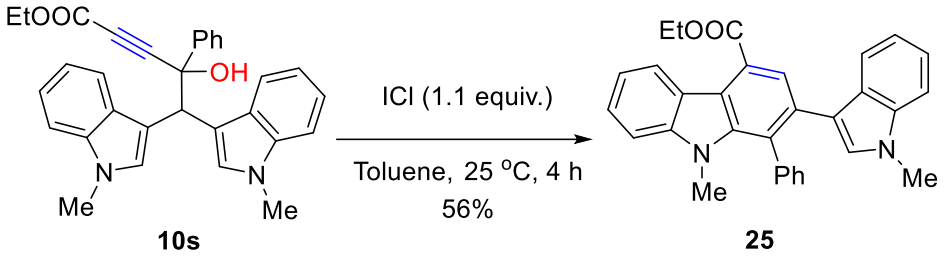
Figure 5. *Single crystal XRD of* ***11b***

Encouraged by the results, we aimed to expand our investigation. Surprisingly, 71% of carbazole **20i** was produced when one of the indoles in bisindolyl-butynol was replaced with an electron-rich trimethoxy benzene group. And when the indole was replaced with a phenyl group iodo-cycloisomerization took place to give 2-iodocarbazole **24a** through 1,2-vinyl migration of spirocyclic intermediate.



Scheme 18. *Scope of Indolyl propargyl alcohol*

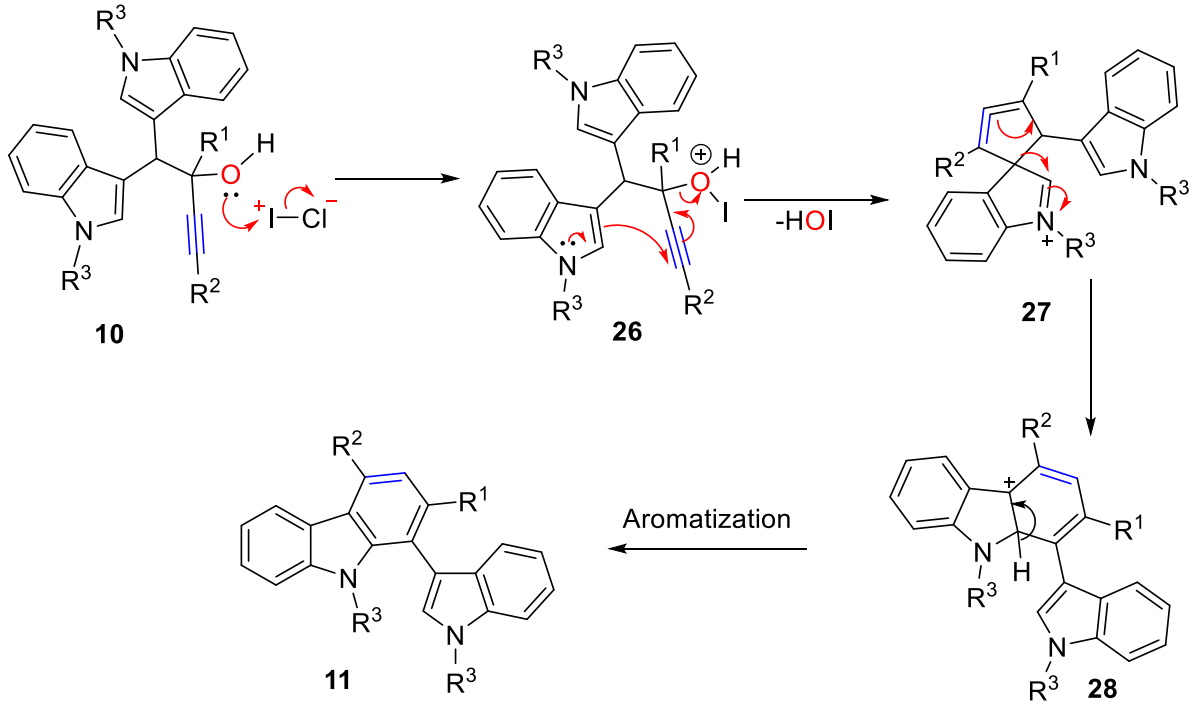
An interesting product was observed when the alkyne terminus was substituted with COOEt group, the alcohol **10s** when subjected to the optimized condition in 4 hours we were able to isolate the carbazole **25** in 56% of yield. Switch of the C1 and C2 carbon substituent was further confirmed by single crystal XRD.



Scheme 19. *Synthesis of carbazole **25***

4.B.2.3. Mechanism

The plausible reaction mechanism is depicted in Scheme 20, ICl acts as Lewis acid and coordinates to the hydroxyl group of bisindolyl propargyl alcohol, the lone pair of oxygen attacks on I^+ by eliminating Cl^- to give the intermediate **26**. Elimination of the HOI group followed by nucleophilic attack from indole gives the cationic spirocyclic allenyl intermediate **27**. The intermediate **27** then undergoes 1,2 alkyl migration promoted by the electron push from the allene carbon, the 1,2-alkyl migration results in hydrocarbazole intermediate **28**, which on aromatization gives the desired carbazole **11**.



Scheme 20. *Proposed Mechanism*

4.2. Conclusion

In conclusion, we were able to develop two easily accessible strategies for the synthesis of carbazole from indole-tethered propargyl alcohols. $Cu(OTF)_2$/HFIP mediated reaction

involves cycloisomerization followed by 1,2-migration to give the indolyl carbazole, this method was also applicable when one of the indoles from bisindolyl propargyl alcohol was replaced with the aryl group. ICl in toluene would be the first of a kind of reaction, which is transition metal-free for the synthesis of carbazole from the propargyl alcohols. Despite undergoing an iodocyclization reaction the combination of ICl in toluene underwent cycloisomerization where the ICl acts as a Lewis acid.

4.3. Single Crystal XRD data

The vapor diffusion crystallization method was used for crystal growth, where the compound was dissolved in chloroform by heating to make a saturated solution in a small vial which was placed in a closed bottle with another solvent as *n*-hexane. The crystal data was recorded on Bruker Apex-II CCD.

4.3.1. X-ray data of Compound 11i:

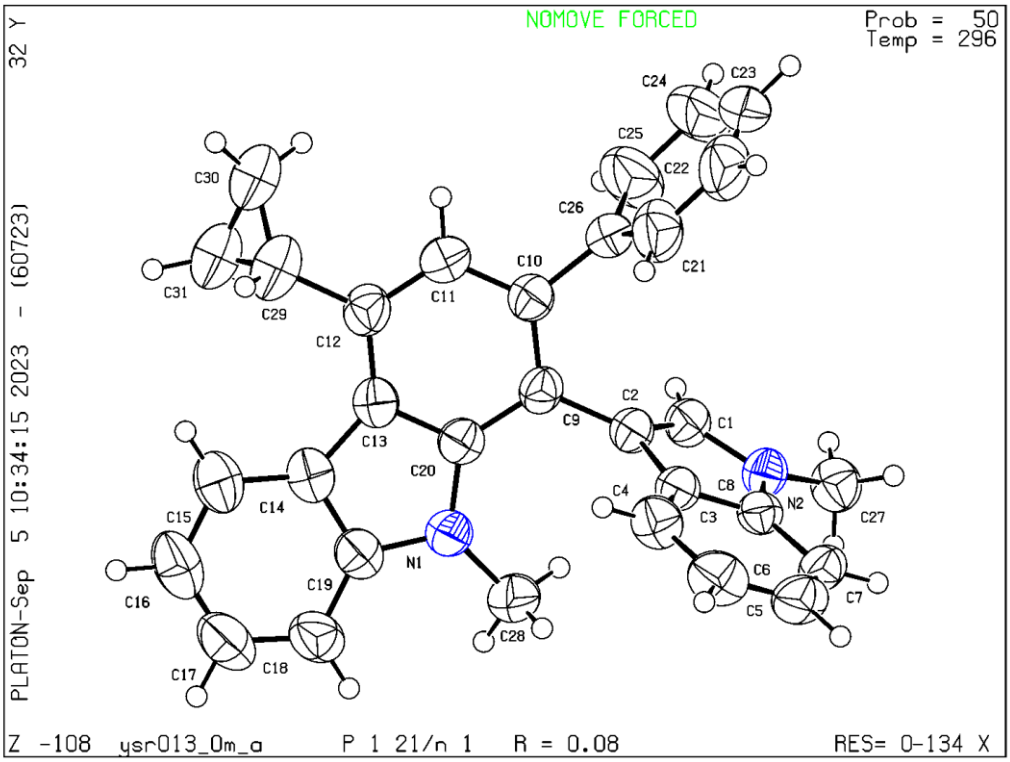


Figure 4. *ORTEP representation of compound* ***11i*** *and thermal ellipsoids are drawn with 50% probability.*

Identification code	ysr013
Empirical formula	$C_{31}H_{26}N_2$
Formula weight	426.54
Temperature	296 K
Wavelength	0.71073 Å
Crystal system	'Monoclinic'
Space group	P1 21/n 1
Unit cell dimensions	a = 13.23 (18) Å α = 90.
	b = 9.3280 (11) Å β = 102.019 (5).

	c = 19.219 (3) Å γ = 90 (5).
Volume	2320.3 (5)
Z	4
Density	1.221 g/cm^3
Absorption coefficient	0.071 mm^{-1}
F (000)	904
Crystal size	0.21 x 0.17 x 0.12 mm^3
Theta (max)	25.35
Index ranges	-15<=h<=15, -11<=k<=11, -23<=l<=23
Reflections collected	54774
R (reflection)	0.049 (3215)
wR2 (reflections)	0.2386(4254)
restraints / parameters	285/288
Goodness-of-fit on F^2	1.034
Tmin, Tmax	0.655, 0.746
Data completeness	1.000
S	1.034
Npar	288
CCDC No.	2249416

4.3.2. X-ray data of Compound 11k:

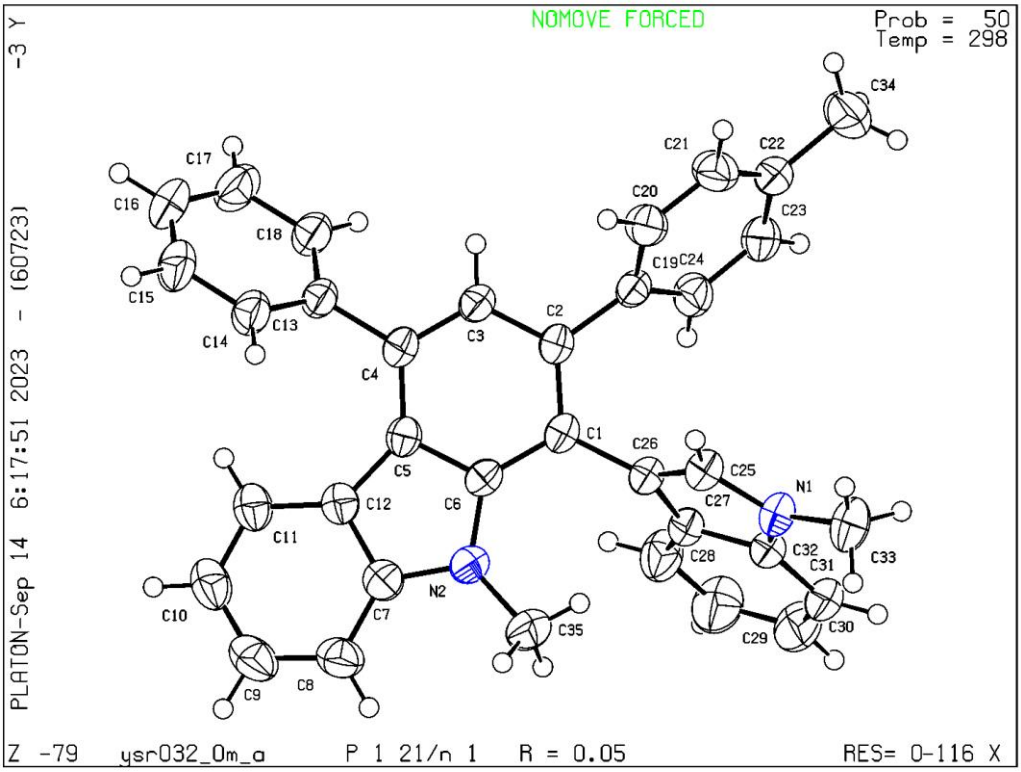


Figure 5. *ORTEP representation of compound* ***11k*** *and thermal ellipsoids are drawn with 50% probability.*

Identification code	ysr032
Empirical formula	$C_{35}H_{28}N_2$

Formula weight	476.59
Temperature	298 K
Wavelength	0.71073 Å
Crystal system	'Monoclinic'
Space group	P 1 21/n 1
Unit cell dimensions	a = 10.7077 (8) Å α = 90.
	b = 9.2729 (7) Å β = 98.298 (3).
	c = 25.954 (2) Å γ = 90.
Volume	2550.0 (3)
Z	4
Density	1.241 g/cm^3
Absorption coefficient	0.072 mm^{-1}
F (000)	1008.0
Crystal size	0.21 x 0.17 x 0.11 mm^3
Theta (max)	27.539
Index ranges	-13<=h<=13, -12<=k<=12, -33<=l<=33
Reflections collected	50346
R (reflection)	0.0514 (4500)
wR2 (reflections)	0.1462 (5871)
restraints / parameters	0/337
Goodness-of-fit on F^2	1.064
Tmin, Tmax	0.502, 0.746
Data completeness	0.999
S	1.064
Npar	337
CCDC No.	2294921

4.3.3. X-ray data of Compound 20g:

Identification code	ysr014
Empirical formula	$C_{37}H_{27}N$
Formula weight	485.59
Temperature	298 K
Wavelength	0.71073 Å
Crystal system	'Triclinic'
Space group	P -1
Unit cell dimensions	a = 9.6614 (12) Å α = 66.465 (4).
b = 12.3016 (5) Å β = 77.764 (5).	
c = 12.4047 (5) Å γ = 82.339 (5).	
Volume	1319.0 (3)
Z	2
Density	1.223 g/cm^3
Absorption coefficient	0.070 mm^{-1}
F (000)	512.0
Crystal size	0.2 x 0.15 x 0.1 mm^3

Theta (max)	25.349
Index ranges	-11<=h<=11, -14<=k<=14, -14<=l<=14
Reflections collected	20603
R (reflection)	0.1040 (2010)
wR2 (reflections)	0.2919 (4319)
restraints / parameters	0/344
Goodness-of-fit on F^2	0.970
Tmin, Tmax	0.609, 0.746
Data completeness	0.892
S	0.970
Npar	344
CCDC No.	2294918

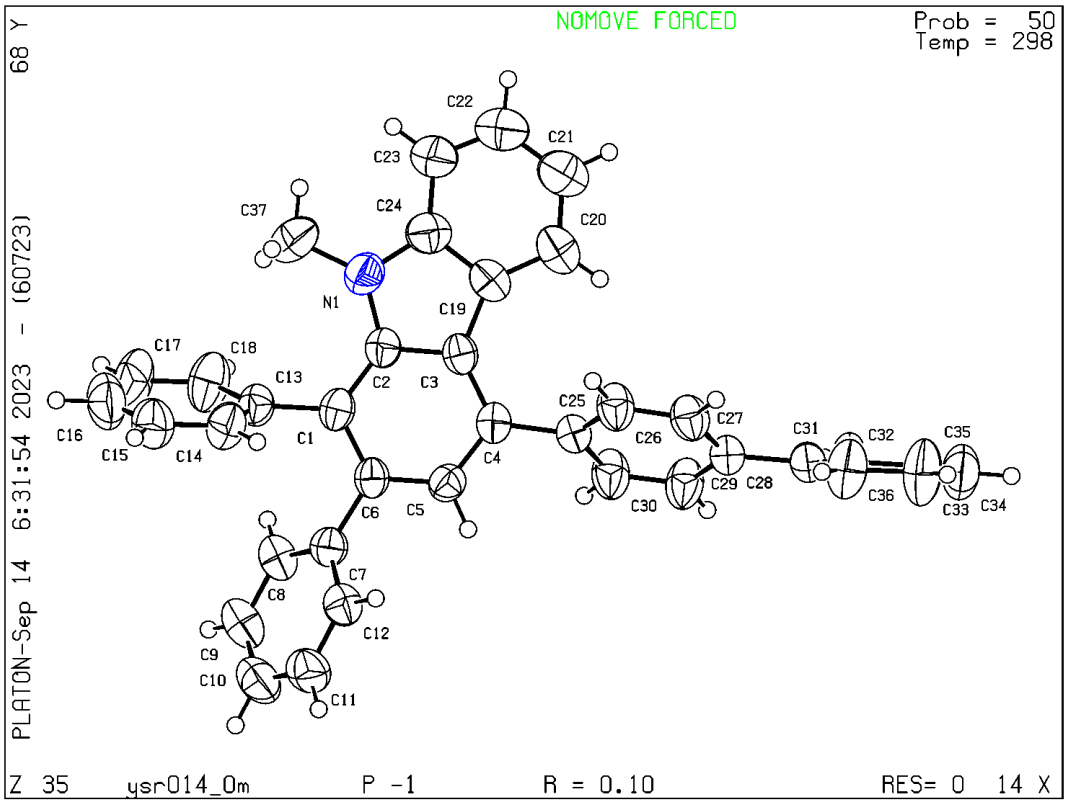


Figure 6. *ORTEP representation of compound* ***20g*** *and thermal ellipsoids are drawn with 50% probability.*

4.3.4. X-ray data of Compound 25:

Identification code	ysr17
Empirical formula	$C_{31}H_{26}N_2O_2$
Formula weight	458.54
Temperature	297 K
Wavelength	0.71073 Å
Crystal system	'Triclinic'
Space group	P -1
Unit cell dimensions	a = 8.5529 (7) Å α = 66.134 (10).

b = 12.8514 (10) Å β = 74.199 (9).
c = 12.8645 (18) Å γ = 76.245 (7).

Volume	1231.1 (2)
Z	2
Density	1.237 g/cm^3
Absorption coefficient	0.077 mm^{-1}
F (000)	484.0
Crystal size	0.131 x 0.112 x 0.101 mm^3
Theta (max)	24.711
Index ranges	-10<=h<=10, -14<=k<=15, -15<=l<=15
Reflections collected	14876
R (reflection)	0.0848 (1262)
wR2 (reflections)	0.2968 (4173)
restraints / parameters	0/319
Goodness-of-fit on F^2	1.008
Tmin, Tmax	0.502, 0.746
Data completeness	0.997
S	1.008
Npar	319

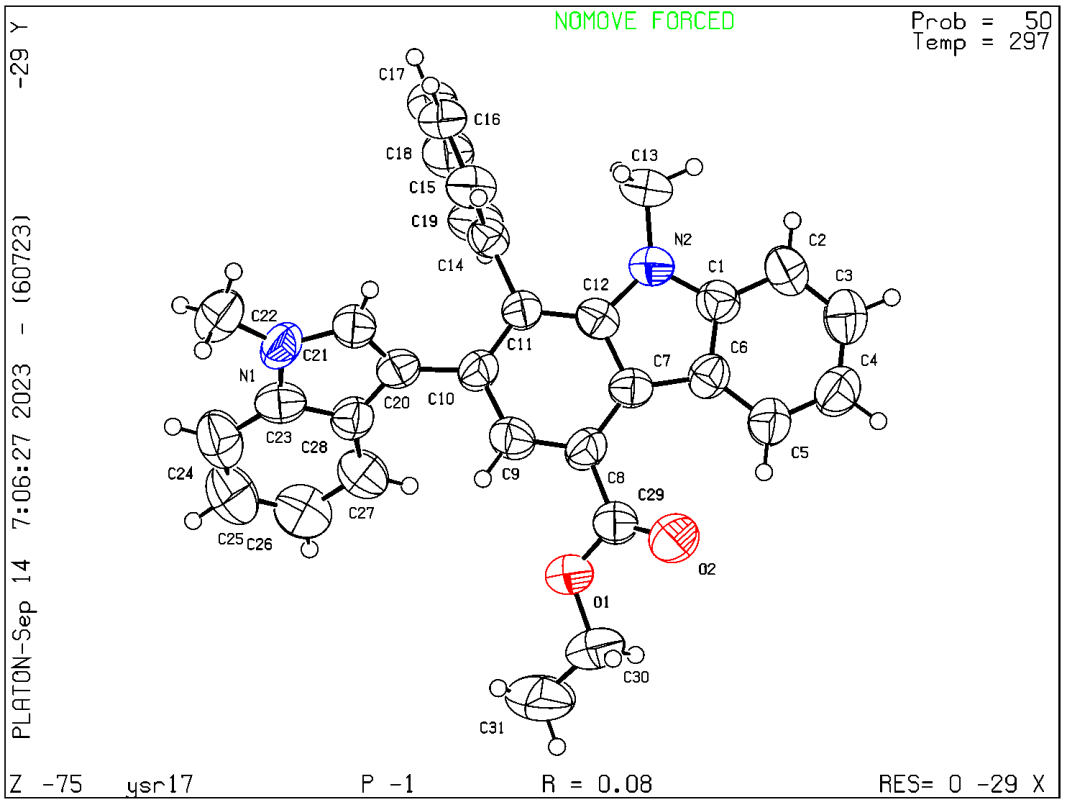
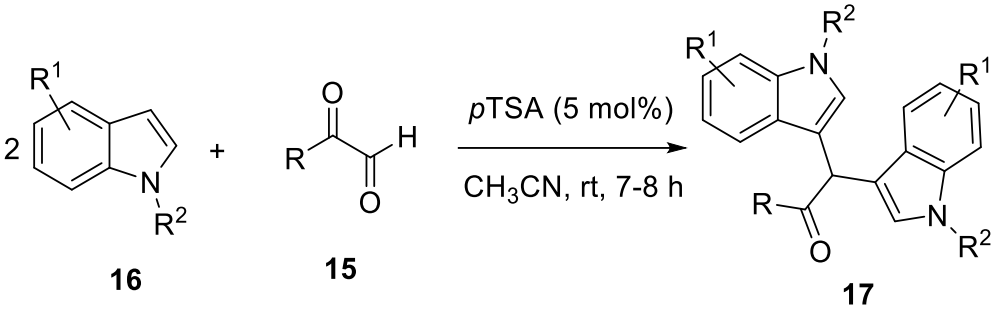


Figure 7. *ORTEP representation of compound* ***25*** *and thermal ellipsoids are drawn with 50% probability.*

4.4. Experimental section

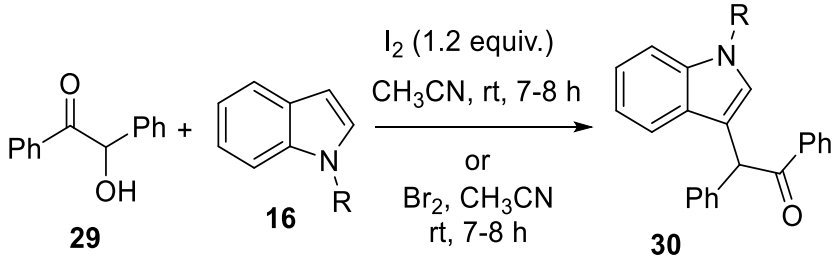
4.4.1. General experimental procedures

4.4.1.1. General experimental procedure for the synthesis of 2,2-bis(1-alkyl/aryl-1H-indol-3-yl)-1-phenylethanone:[36] A mixture of phenylglyoxal (1 equiv.), *N*-alkyl/aryl Indole (2 equiv.), *p*TSA (5 mol%), and CH_3CN was stirred at room temperature for 7-8 hours. After completion of the reaction (monitored by TLC), the resulting mixture was quenched with water and extracted into ethyl acetate (thrice). Combined organic layers were washed with $NaHCO_3$ solution and dried over anhydrous Na_2SO_4 and the solvent was evaporated to obtain the crude product. The crude product was purified by column chromatography to obtain pure product **17** in good yield.



Scheme 21. *Synthesis of 2,2-bis(1-alkyl/aryl-1H-indol-3-yl)-1-phenylethanone*

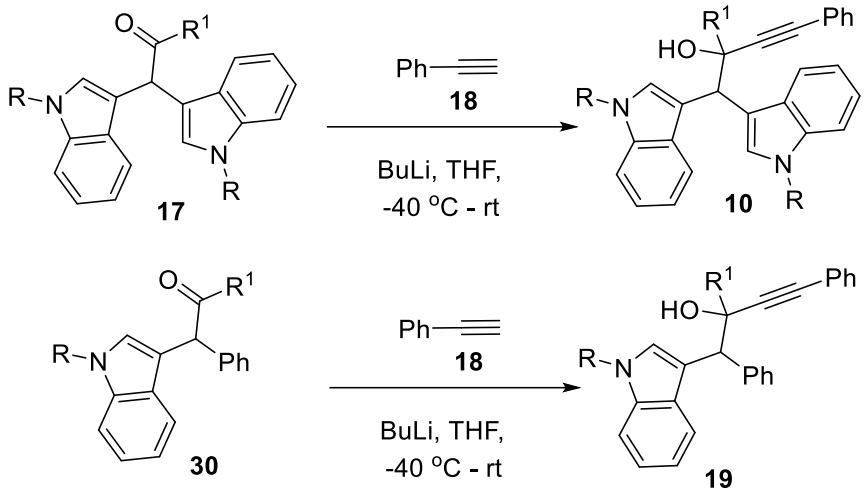
4.4.1.2. General experimental procedure for the synthesis of ketone 30:[36] A mixture of 2-hydroxy-1,2-diphenylethanone (1 equiv.) and N-alkyl/aryl Indole (1.2 equiv.), I_2 (1.2 equiv.) and acetonitrile were charged into an oven-dried round bottom flask and stirred at reflux temperature. The progress of the reaction was monitored by TLC. Then the reaction mass was quenched with $Na_2S_2O_3$ solution and extracted with ethyl acetate 2 times. The combined organic layer was concentrated, and crude was purified using column chromatography (60-120 mess size, 15% EtOAc in pet ether).



Scheme 22. *Synthesis of heteroaryl substituted diphenylethanone*

4.4.1.3. General experimental procedure for the propargyl alcohol 10:[33] To a solution of terminal alkyne (6 mmol) at 0 ºC in THF (10-30 mL), was added 3 equiv., 6 mmol of *n*-BuLi (2 M in hexanes). The solution was stirred at 0 ºC for 20 min, then the appropriate α-(3-indolyl) ketone was added (2 mmol, 1.0 equiv.) at -40ºC. The resulting mixture was stirred at room temperature until the starting ketone was consumed as determined by TLC. The reaction was quenched with a saturated aqueous NH_4Cl solution and extracted with AcOEt (3 × 20 mL). The combined organic layers were dried over

anhydrous Na_2SO_4, filtered and concentrated at reduced pressure. The residue was purified by flash chromatography on silica gel using mixtures of hexane and AcOEt as eluents to obtain the alkynols **10** or **19**.



Scheme 23. *Synthesis of propargyl alcohols*

4.4.1.4. General experimental procedure for the Synthesis of carbazole under copper catalysis: To the suspension of alkynol **10** in 1 equiv. of HFIP, 10 mol% $Cu(OTf)_2$ was added and was allowed to stir at room temperature till completion of reaction or until the starting alkynol was consumed as determined by TLC. The reaction was quenched with a water and extracted with AcOEt (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated at reduced pressure. The residue was purified by column chromatography on silica gel using mixtures of hexane and AcOEt as eluents to obtain the carbazole **11**.

4.4.1.5. General experimental procedure for the Synthesis of carbazole with ICl: To the solution of alkynol **10** in toluene, 1.1 equiv. of ICl was added and was allowed to stir at room temperature till completion of reaction or until the starting alkynol was consumed as determined by TLC. The reaction was quenched with aqueous solution of $Na_2S_2O_3$ and extracted with AcOEt (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated at reduced pressure. The residue was purified by column chromatography on silica gel using mixtures of hexane and AcOEt as eluents to obtain the carbazole **11**.

4.4.2. Spectral data:

9-methyl-1-(1-methyl-1H-indol-3-yl)-2,4-diphenyl-9H-carbazole (**11a**). Isolated as a pale yellow solid; mp: 224-225 °C; ^{1}H NMR (400 MHz, CDCl3): δ 7.71 (d, *J* = 7.0 Hz, 2H), 7.53 (t, *J* = 7.0 Hz, 2H), 7.49-7.46 (m, 2H), 7.38-7.35 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.26-7.22 (m, 2H), 7.19 (s, 1H), 7.15-7.13 (m, 2H), 7.08-7.05 (m, 4H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.70 (s, 1H), 3.72 (s, 3H), 3.25 (s, 3H) ppm; ^{13}C{^{1}H} NMR (125 MHz, CDCl3): δ 142.9, 141.8, 141.5, 140.9, 136.5, 136.3, 131.2, 129.7, 129.5, 129.4, 128.5, 127.6, 127.3, 125.9, 125.5,

123.6, 122.3, 121.8, 120.5, 120.4, 119.8, 118.7, 115.2, 112.0, 109.2, 108.8, 32.9, 31.4 ppm; HRMS (ESI-TOF): m/z calculated for $C_{34}H_{27}N_2$ $[M + H]^+$ 463.2174, found 463.2177.

9-ethyl-1-(1-ethyl-1H-indol-3-yl)-2,4-diphenyl-9H-carbazole (**11b**). Isolated as a pale yellow solid; mp: 181-182 ^oC; ^1H NMR (400 MHz, CDCl3): δ 7.72 (d, *J* = 7.0 Hz, 2H), 7.53 (t, *J* = 7.5 Hz, 2H), 7.48-7.46 (m, 2H), 7.37-7.37 (m, 3H), 7.29 (d, *J* = 7.0 Hz, 1H), 7.23 (t, *J* = 3.5 Hz, 1H), 7.21-7.19 (m, 1H), 7.11-7.10 (m, 2H), 7.06-7.02 (m, 4H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.79 (s, 1H), 4.14-4.03 (m, 2H), 3.93-3.85 (m, 1H), 3.84-3.77 (m, 1H), 1.26 (t, *J* = 7.0 Hz, 3H), 0.86 (t, *J* = 6.5 Hz, 3H) ppm; $^{13}C\{1H\}$ (125 MHz, $CDCl_3$) *δ* 143.0, 142.1, 141.8, 141.5, 139.8, 136.5, 135.1, 131.2, 129.6, 129.5, 128.5, 127.5, 127.4, 127.1, 125.8, 125.4, 123.4, 122.8, 122.5, 121.7, 120.8, 120.5, 119.6, 118.7, 115.2, 112.0, 109.4, 109.1, 40.9, 38.4, 15.8, 14.3 ppm; HRMS (ESI-TOF): m/z calculated for $C_{36}H_{31}N_2$ $[M + H]^+$ 491.2487, found 491.2487.

9-benzyl-1-(1-benzyl-1H-indol-3-yl)-2,4-diphenyl-9H-carbazole (**11c**). Isolated as white solid; mp: 174-176^oC; ^1H NMR (500 MHz, $CDCl_3$): *δ* 7.76 (d, *J* = 7.0 Hz, 2H), 7.56 (t, *J* = 7.0 Hz, 2H), 7.53-7.48 (m, 2H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.32-7.28 (m, 1H), 7.24-7.22 (m,1H), 7.21 (d, *J* = 7.5 Hz, 1H), 7.17-7.15 (m, 3H), 7.14-7.13 (m, 3H), 7.12-7.09 (m, 3H), 7.06-6.97 (m, 6H), 6.61-6.59 (m, 2H), 6.51-6.49 (m, 2H), 6.23 (s, 1H), 5.12-5.02 (m, 3H), 4.69-4.65 (m, 1H) ppm; $^{13}C\{1H\}$(100 MHz, $CDCl_3$) *δ* 176.1, 164.3, 161.8, 151.4, 149.2, 130.9, 129.2, 127.9, 127.8, 127.4, 127.0, 126.6, 124.9, 121.9, 120.0, 116.3, 116.1, 112.6, 49.5, 31.2, 19.4 ppm; HRMS (ESI-TOF): m/z calculated for $C_{46}H_{35}N_2$ $[M + H]^+$ 615.2800, found 615.2790.

9-allyl-1-(1-allyl-1H-indol-3-yl)-2,4-diphenyl-9H-carbazole (**11d**). Isolated as white solid; mp: 162-163 ^oC; ^1H NMR (400 MHz, CDCl3): δ 7.73-7.72 (m, 2H), 7.54 (t, *J* = 7.0 Hz, 2H), 7.48 (t, *J* = 8.0 Hz, 2H), 7.35-7.32 (m, 2H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.25-7.21 (m, 1H), 7.20-7.19 (m, 2H), 7.16-7.14 (m, 2H), 7.05-7.02 (m, 4H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 1.0 Hz, 1H), 5.86-5.79 (m, 1H), 5.50-5.42 (m, 1H), 5.05 (d, *J* = 10.5 Hz, 1H), 4.85 (d, *J* = 10.0 Hz, 1H), 4.72-4.66 (m, 2H), 4.63-4.57 (m, 2H), 4.45-4.35 (m, 2H) ppm; $^{13}C\{1H\}$ NMR (125 MHz, CDCl3): δ 142.8, 142.2, 141.4, 140.1, 136.5, 135.5, 133.7, 133.2, 130.7, 129.6, 129.5, 128.5, 128.4, 127.6, 127.2, 125.9, 125.4, 123.6, 122.6, 122.3, 121.9, 120.6, 119.8, 119.0, 116.6, 115.5, 115.1, 111.8, 48.4, 46.3 ppm.; HRMS (ESI-TOF): m/z calculated for $C_{38}H_{31}N_2$ $[M + H]^+$ 515.2487, found 515.2487.

9-isopropyl-1-(1-isopropyl-1H-indol-3-yl)-2,4-diphenyl-9H-carbazole (**11e**). Isolated as yellowish solid; mp: 199-200 ^oC; ^1H NMR (400 MHz, CDCl3): δ 7.70 (d, *J* = 7.0 Hz, 2H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 7.49-7.45 (m, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.37-7.33 (m, 2H), 7.30-7.27 (m, 1H), 7.21-7.18 (m, 1H), 7.16 (s, 1H), 7.08-7.06 (m, 2H), 7.03-6.99 (m, 4H), 6.94-6.91 (m, 1H), 6.84 (s, 1H), 4.96-4.90 (m, 1H), 4.64-4.59 (m, 1H), 1.46 (d, *J* = 6.5 Hz, 3H), 1.24-1.20 (m, 6H), 1.14 (d, *J* = 7.0 Hz, 3H) ppm; $^{13}C\{1H\}$ NMR (125 MHz, CDCl3): δ 143.2, 142.3, 141.6, 140.4, 140.3, 136.2, 135.3, 130.0, 129.5, 128.5, 127.5, 127.0, 125.7, 124.6, 123.8, 123.3, 122.6, 121.6, 120.9, 120.6, 119.4, 118.3, 115.6, 112.7, 112.6, 109.3, 46.9, 46.5, 22.9, 22.8, 21.0, 20.0 ppm.; HRMS (ESI-TOF): m/z calculated for $C_{38}H_{31}N_2$ $[M + H]^+$ 519.2800, found 519.2805.

1-(1H-indol-3-yl)-2,4-diphenyl-9H-carbazole (**11f**). Isolated as brown viscous compound; ^{1}H NMR (500 MHz, CDCl3): δ 8.23 (s, 1H), 8.13 (s, 1H), 7.77 (d, *J* = 7.0 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 7.0 Hz, 2H), 7.50-7.46 (m, 3H), 7.32-7.27 (m, 6H), 7.17-7.12 (m, 4H), 7.00-6.97 (m, 1H), 6.88 (d, *J* = 2.0 Hz, 1H) ppm; ^{13}C{1H} NMR (125 MHz, CDCl3): δ 142.2, 141.2, 140.2, 140.0, 139.3, 136.5, 136.2, 130.0, 129.4, 128.5, 127.7, 127.6, 127.1, 126.3, 125.6, 124.8, 123.8, 123.2, 122.5, 120.4, 120.2, 119.6, 119.1, 114.9, 112.2, 111.6, 110.6 ppm; HRMS (ESI-TOF): m/z calculated for $C_{32}H_{23}N_2$ $[M + H]^+$ 435.1861, found 435.1867.

9-methyl-1-(1-methyl-1H-indol-3-yl)-2-phenyl-4-(p-tolyl)-9H-carbazole (**11g**). Isolated as white solid; mp: 223-224 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.71 (d, *J* = 7.0 Hz, 2H), 7.53 (t, *J* = 7.5 Hz, 2H), 7.49-7.46 (m, 2H), 7.37-7.34 (m, 3H), 7.27 (s, 1H), 7.24 (s, 1H), 7.17 (s, 1H), 7.09-7.06 (m, 1H), 7.04 (d, *J* = 7.5 Hz, 2H), 6.98-6.95 (m, 1H), 6.87 (d, *J* = 8.0 Hz, 2H), 6.73 (s, 1H), 3.75 (s, 3H), 3.23 (s, 3H), 2.22 (s, 3H) ppm; ^{13}C{1H}(125 MHz, $CDCl_3$) *δ* 176.1, 151.4, 150.4, 132.2, 131.2, 130.1, 129.2 (2), 129.1, 129.0, 125.8 (2), 125.4, 123.6, 120.3, 118.5, 116.7, 113.7, 49.4, 31.2, 19.4 ppm; HRMS (ESI-TOF): m/z calculated for $C_{35}H_{29}N_2$ $[M + H]^+$ 477.2331, found 477.2330.

4-([1,1'-biphenyl]-4-yl)-9-methyl-1-(1-methyl-1H-indol-3-yl)-2-phenyl-9H-carbazole (**11h**). Isolated as white solid; mp: 225-226 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 7.82-7.77 (m, 4H), 7.75 (d, *J* = 7.5 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.40-7.36 (m, 3H), 7.33 (d, *J* = 8.5 Hz, 1H), 7.27-7.23 (m, 3H), 7.16-7.15 (m, 2H), 7.08-7.06 (m, 4H), 7.01-6.98 (m, 1H), 6.71 (s, 1H), 3.72 (s, 3H), 3.27 (s, 3H) ppm; ^{13}C{1H}(100 MHz, $CDCl_3$) *δ* 142.9, 141.9, 141.0, 140.5, 140.3, 136.3, 136.0, 131.2, 129.9, 129.7, 129.4, 128.9, 127.4, 127.3, 127.2 (2), 126.0, 125.5, 123.6, 122.4, 122.3, 121.8, 120.5, 120.3, 119.8, 118.8, 115.3, 112.0, 109.2, 108.8, 32.9, 31.5 ppm; HRMS (ESI-TOF): m/z calculated for $C_{40}H_{31}N_2$ $[M + H]^+$ 539.2487, found 539.2481.

4-cyclopropyl-9-methyl-1-(1-methyl-1H-indol-3-yl)-2-phenyl-9H-carbazole (**11i**). Isolated as yellowish solid; mp: 246-247 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): 8.56 (d, *J* = 7.5 Hz, 1H), 7.48-7.44 (m, 1H), 7.32-7.29 (m, 3H), 7.28-7.26 (m, 1H), 7.23-7.20 (m, 1H), 7.11-7.09 (m, 2H), 7.08-7.05 (m, 4H), 7.04-7.01 (m, 1H), 6.64 (s, 1H), 3.70 (s, 3H), 3.23 (s, 3H), 2.67-2.62 (m, 1H), 1.20-1.17 (m, 2H), 1.00-0.96 (m, 2H) ppm; ^{13}C{1H}(125 MHz, $CDCl_3$) *δ* δ (ppm) 143.3, 142.7, 141.8, 140.6, 136.6, 136.3, 131.2, 129.6, 129.4, 127.2, 125.8, 125.1, 123.1, 123.0, 122.5, 121.7, 120.5, 120.3, 119.7, 119.0, 114.1, 112.1, 109.1, 108.6, 32.9, 31.3, 15.0, 6.9 (2) ppm; HRMS (ESI-TOF): m/z calculated for $C_{31}H_{27}N_2$ $[M + H]^+$ 427.2174, found 427.2175.

4-cyclohexyl-9-methyl-1-(1-methyl-1H-indol-3-yl)-2-phenyl-9H-carbazole (**11j**). Isolated as white solid; mp: 220-221 ºC; ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 8.19 (d, *J* = 7.5 Hz, 1H), 7.45-7.42 (m, 1), 7.31 (d, *J* = 3.5 Hz, 1H), 7.29-7.27 (m, 3H), 7.23-7.20 (m, 1H), 7.19 (s, 1H), 7.13-7.11 (m, 2H), 7.08-7.06 (m, 3H), 7.04-7.01 (m, 1H), 6.64 (s, 1H), 3.70 (s, 3H), 3.66-3.56 (m, 1H), 3.22 (s, 3H), 2.31-2.28 (m, 2H), 1.99 (s, 2H), 1.89 (d, *J* = 7.5 Hz, 1H), 1.72-1.63 (m, 4H), 1.43-1.36 (m, 1H) ppm; ^{13}C{1H}(100 MHz, $CDCl_3$) *δ* 143.6, 142.8, 142.3, 142.1, 140.8, 136.3, 131.2, 129.7, 129.4, 127.2, 125.8, 124.9, 122.7, 122.4, 121.6, 120.6,

120.4, 119.6, 119.1, 118.5, 113.6, 112.3, 109.1, 108.8, 41.0, 33.3, 33.2, 32.9, 31.4, 27.5, 27.4, 26.7 ppm; HRMS (ESI-TOF): m/z calculated for $C_{34}H_{33}N_2$ $[M + H]^+$ 469.2644, found 469.2648.

9-methyl-1-(1-methyl-1H-indol-3-yl)-4-phenyl-2-(p-tolyl)-9H-carbazole (**11k**). Isolated as white solid; mp: 208-209 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 7.5 Hz, 2H), 7.52 (t, J = 7.5 Hz, 2H), 7.47 (d, J = 7.5 Hz, 2H), 7.37-7.32 (m, 3H), 7.25-7.22 (m, 2H), 7.17 (s, 1H), 7.08-7.03 (m, 3H), 6.96 (t, J = 7.5 Hz, 1H), 6.86 (d, J = 7.5 Hz, 2H), 6.71 (s, 1H), 3.72 (s, 3H), 3.22 (s, 3H), 2.21 (s, 3H) ppm; ^{13}C{1H}(100 MHz, $CDCl_3$) δ 142.9, 141.8, 141.5, 141.0, 139.9, 136.4, 136.3, 135.4, 131.3, 129.5, 129.3, 128.5, 128.0, 127.5, 125.4, 123.7, 122.3, 121.7, 120.5, 120.2, 119.8, 118.7, 115.1, 112.1, 109.2, 108.7, 32.9, 31.4, 21.1 ppm; HRMS (ESI-TOF): m/z calculated for $C_{35}H_{29}N_2$ $[M + H]^+$ 477.2331, found 477.2329.

2-(4-fluorophenyl)-9-methyl-1-(1-methyl-1H-indol-3-yl)-4-phenyl-9H-carbazole (**11l**). Isolated as pale yellow solid; mp: 234-235 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72-7.70 (m, 2H), 7.55-7.52 (m, 2H), 7.50-7.45 (m, 2H), 7.38-7.33 (m, 3H), 7.26-7.23 (m, 3H), 7.14 (s, 1H), 7.11-7.05 (m, 3H), 6.99-6.95 (m, 1H), 6.76-6.72 (m, 2H), 6.71 (s, 1H), 3.75 (s, 3H), 3.25 (s, 3H) ppm; ^{13}C{1H}(100 MHz, $CDCl_3$) δ 162.7, 160.2, 142.9, 141.3, 140.9, 140.7, 138.8, 136.5, 136.3, 131.1, 131.0, 129.4, 129.3, 128.5, 127.6, 125.5, 123.4, 122.3, 122.2, 121.9, 120.5, 120.4, 119.9, 118.8, 115.2, 114.2, 114.0, 111.9, 109.3, 108.8, 33.0, 31.4 ppm; HRMS (ESI-TOF): m/z calculated for $C_{34}H_{26}FN_2$ $[M + H]^+$ 481.2080, found 481.2076.

2-(4-bromophenyl)-9-methyl-1-(1-methyl-1H-indol-3-yl)-4-phenyl-9H-carbazole (**11m**). Isolated as white solid; mp: 200-201 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70-7.68 (m, 2H), 7.55-7.52 (m, 2H), 7.50-7.48 (m, 1H), 7.46 (d, J = 8.0 Hz, 1H), 3.84 (s, 3H), 7.38-7.32 (m, 3H), 7.25 (t, J = 9.0 Hz, 2H), 7.18-7.16 (m, 2H), 7.12 (s, 1H), 7.09-7.05 (m, 1H), 7.03-7.00 (m, 2H), 6.98-6.95 (m, 1H), 6.70 (s, 1H), 3.75 (s, 3H), 3.23 (s, 3H) ppm; ^{13}C{1H}(125 MHz, $CDCl_3$) δ 142.9, 141.9, 141.3, 140.9, 140.5, 136.7, 136.3, 131.3, 131.1, 130.4, 129.4, 129.3, 128.5, 127.7, 125.6, 123.2, 122.4, 122.2, 122.0, 120.6, 120.4, 120.2, 120.0, 118.8, 115.1, 111.8, 109.4, 108.8, 33.0, 31.4 ppm; HRMS (ESI-TOF): m/z calculated for $C_{34}H_{26}BrN_2$ $[M + H]^+$ 541.1279, found 541.1274.

4-(9-methyl-1-(1-methyl-1H-indol-3-yl)-4-phenyl-9H-carbazol-2-yl)benzonitrile (**11n**). Isolated as yellowish solid; mp: 300-301 ºC; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.70-7.68 (m, 2H), 7.56-7.53 (m, 2H), 7.51-7.48 (m, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.41-7.39 (m, 1H), 7.37 (d, J = 8.5 Hz 1H), 7.34-7.32 (m, 3H), 7.29-7.26 (m, 2H), 7.25-7.24 (m, 2H), 7.12 (s, 1H), 7.08 (t, J = 7.5 Hz, 1H), 6.99 (t, J = 7.5 Hz 1H), 6.70 (s, 1H), 3.76 (s, 3H), 3.27 (s, 3H) ppm; ^{13}C{1H} NMR ($CDCl_3$, 125 MHz): 148.0, 142.9, 141.0, 140.7, 139.7, 136.8, 136.2, 131.1, 130.8, 130.3, 129.3, 128.6, 127.8, 125.9, 122.7, 122.4, 122.2, 122.0, 121.1, 120.2, 120.1, 119.3, 119.0, 115.0, 111.3, 109.5, 108.8, 33.0, 31.4 ppm; HRMS (ESI-TOF): m/z calculated for $C_{35}H_{26}N_3$ $[M + H]^+$ 488.2127, found 488.2125.

9-methyl-1-(1-methyl-1H-indol-3-yl)-2-(naphthalen-2-yl)-4-phenyl-9H-carbazole (**11o**). Isolated as yellow solid; mp: 291-292 ºC; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.77 (s, 1H), 7.75 (d, J = 6.5 Hz, 2H), 7.70-7.64 (m, 2H), 7.55 (t, J = 7.0 Hz 2H), 7.51-7.47 (m, 2H), 7.46-7.43 (m, 2H), 7.41-7.39 (m, 1H), 7.40-7.35 (m, 3H), 7.33 (d, J = 8.0 Hz, 1H), 7.29 (s, 1H), 7.28-

7.27 (m, 1H), 7.14-7.09 (m, 2H), 7.00-6.97 (m, 1H), 6.68 (s, 1H), 3.65 (s, 3H), 3.28 (s, 3H) ppm; $^{13}C\{1H\}$ NMR ($CDCl_3$, 100 MHz): 143.0, 141.6, 141.5, 141.0, 140.8, 136.6, 136.3, 133.2, 131.9, 131.3, 131.0, 129.6, 129.5, 128.5, 128.4, 128.2, 128.0, 127.6, 127.5, 126.3, 125.6, 125.5, 125.4, 123.9, 122.3, 121.9, 120.5, 119.9, 118.8, 115.4, 112.0, 109.3, 108.8, 32.9, 31.4 ppm; HRMS (ESI-TOF): m/z calculated for $C_{38}H_{29}N_2$ $[M + H]^+$ 513.2331, found 513.2330.

2,9-dimethyl-1-(1-methyl-1H-indol-3-yl)-4-phenyl-9H-carbazole (**11p**). Isolated as white solid; mp: 88-89 ºC; ^1H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, J = 7.0 Hz, 2H), 7.54 (t, J = 8.0 Hz, 2H), 7.49-7.46 (m, 1H), 7.44 (d, J = 9.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.33-7.28 (m, 3H), 7.21 (d, J = 8.0 Hz, 1H), 7.11-7.10 (m, 1H), 7.08 (s, 1H), 7.06 (m, 1H), 6.94-6.91 (m, 1H), 3.94 (s, 3H), 3.21 (s, 3H), 2.26 (s, 3H) ppm; $^{13}C\{1H\}$(100 MHz, $CDCl_3$) δ 142.3, 141.7, 141.2, 137.0, 136.8, 136.4, 129.7, 129.4, 128.4, 127.4, 125.0, 123.1, 122.5, 122.1, 122.0, 120.5, 119.7, 119.2, 118.5, 115.8, 112.5, 109.4, 108.5, 33.1, 31.4, 20.8 ppm; HRMS (ESI-TOF): m/z calculated for $C_{29}H_{25}N_2$ $[M + H]^+$ 401.2018, found 401.2013.

9-methyl-1-(1-methyl-1H-indol-3-yl)-4-phenyl-9H-carbazole (**11q**). Isolated as white solid (232 mg, 73%); mp: 97-98 ºC; ^1H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, J = 2 Hz, 1H), 7.54 (d, J = 6.5 Hz, 2H), 7.50-7.48 (m, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.43-7.41 (m, 2H), 7.39 (s, 1H), 7.38-7.36 (m, 1H), 7.31-7.28 (m, 2H), 7.22 (s, 1H), 7.13-7.09 (m, 2H), 6.98-6.95 (m, 1H), 3.93 (s, 3H), 3.45 (s, 3H) ppm; $^{13}C\{1H\}$(125 MHz, $CDCl_3$) δ 142.5, 141.6, 140.2, 136.7, 136.6, 129.9, 129.6, 129.4, 128.5, 127.9, 127.5, 125.5, 122.7, 122.4, 122.1, 121.4, 120.7, 120.5, 119.9, 118.7, 117.2, 114.9, 109.4, 108.8, 33.1, 31.8 ppm; HRMS (ESI-TOF): m/z calculated for $C_{28}H_{23}N_2$ $[M + H]^+$ calculated 387.1861, found 387.1863.

2-iodo-9-methyl-1-(1-methyl-1H-indol-3-yl)-4-phenyl-9H-carbazole (**11q'**). Isolated as white solid (170 mg, 73%); mp: 229-230 ºC; ^1H NMR (500 MHz, $CDCl_3$): δ 7.90 (s, 1H), 7.61-7.56 (m, 3H), 7.44 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 8.5 Hz, 3H), 7.36-7.32 (m, 1H), 7.31-7.28 (m, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.20 (s, 1H), 7.13-7.10 (m, 1H), 6.91-6.88 (m, 1H), 6.64 (d, J = 8.0 Hz, 1H), 3.90 (s, 3H), 3.41 (s, 3H) ppm; $^{13}C\{1H\}$(100 MHz, $CDCl_3$) δ 143.7, 142.2, 140.1, 139.8, 138.9, 136.6, 129.5, 128.9, 128.1, 128.0, 126.0, 123.4, 122.4, 120.3, 120.1, 119.5, 119.2, 113.4, 109.5, 108.7, 88.5, 33.1, 31.7 ppm; HRMS (ESI-TOF): m/z calculated for $C_{28}H_{22}IN_2$ $[M + H]^+$ 513.0828, found 513.0828.

9-benzyl-1-(1-benzyl-5-methoxy-1H-indol-3-yl)-6-methoxy-2,4-diphenyl-9H-carbazole (**11r**). Isolated as yellowish solid (232 mg, 73%); mp: 185-186 ºC; ^1H NMR (500 MHz, $CDCl_3$): δ 7.77 (d, J = 7.5 Hz, 2H), 7.57 (t, J = 7.0 Hz, 2H), 7.52-7.48 (m, 1H), 7.21 (s, 1H), 7.18-7.12 (m, 6H), 7.11-7.09 (m, 4H), 7.08-7.03 (m, 4H), 7.01-6.99 (m, 1H), 6.98-6.96 (m, 2H), 6.78-6.72 (m, 2H), 6.61 (d, J = 7.0 Hz, 2H), 6.51-6.5 (m, 2H), 6.24 (s, 1H), 5.07 (s, 3H), 4.73-4.60 (m, 1H), 3.69 (s, 3H), 3.61 (s, 3H) ppm; $^{13}C\{1H\}$(125 MHz, $CDCl_3$) δ 154.6, 153.2, 142.8, 142.5, 141.2, 140.8, 139.0, 137.5, 136.6, 131.5, 130.6, 129.7, 129.6, 128.6, 128.4, 128.1, 127.7, 127.3, 127.2, 126.4, 126.2, 125.9, 125.2, 123.1, 122.7, 120.4, 115.3, 114.9, 112.4, 111.0, 110.6, 109.9, 105.3, 101.4, 55.8, 55.6, 49.7, 47.4 ppm; HRMS (ESI-TOF): m/z calculated for $C_{28}H_{23}N_2O_2$ $[M + H]^+$ calculated 675.8520, found 675.8524.

9-methyl-1,2,4-triphenyl-9H-carbazole (**20a**). Isolated as a yellow solid (84 mg, 80%); mp: 179-180 ºC; ^{1}H NMR (400 MHz, CDCl3): δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.50-7.48 (m, 4H), 7.41 (t, *J* = 7.0 Hz, 2H), 7.36-7.33 (m, 2H), 7.32-7.30 (m, 5H), 7.28-7.26 (m, 2H), 7.23 (d, *J* = 8.5 Hz, 1H), 7.14 (t, *J* = 8.5 Hz, 1H), 7.11 (s, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 3.10 (s, 3H) ppm; ^{13}C{1H} NMR (125 MHz, CDCl3): δ 143.0, 140.5, 138.3, 137.2, 136.2, 135.9, 135.7, 133.8, 132.6, 131.8, 131.2, 130.5, 130.3, 129.9, 129.7, 128.5, 128.4, 128.1, 128.0, 127.8, 127.6, 127.2, 126.6, 125.5, 122.2, 121.8, 120.2, 120.1, 110.5, 34.3 ppm; HRMS (ESI-TOF): m/z calculated for $C_{31}H_{24}N$ $[M + H]^+$ 410.1909, found 410.1903.

9-benzyl-1,2,4-triphenyl-9H-carbazole (**20b**). Isolated as a yellow solid (78mg, 75%); mp: 179-180 ºC; ^{1}H NMR (400 MHz, CDCl3): δ 7.74-7.72 (m, 2H), 7.56-7.53 (m, 2H), 7.51-7.48 (m, 2H), 7.31-7.27 (m, 1H), 7.17 (s, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 7.12-7.09 (m, 6H), 7.08-7.06 (m, 3H), 7.04-7.02 (m, 2H), 7.00-6.96 (m, 3H), 6.61-6.59 (m, 2H), 5.01 (s, 2H) ppm; ^{13}C{1H} NMR (125 MHz, CDCl3): δ 142.6, 142.1, 141.2, 140.8, 139.7, 138.1, 137.5, 136.8, 136.1, 135.9, 135.7, 135.2, 134.4, 134.2, 133.2, 131.9, 131.2, 130.5, 129.9, 129.7, 129.5, 129.1, 128.5, 128.4, 128.1, 128.0, 127.8, 127.3, 127.2, 127.0, 126.9, 126.7, 126.6, 126.3, 126.1, 125.4, 122.7, 122.5, 122.0, 121.8, 121.6, 120.5, 120.4, 120.1, 119.8, 111.8, 110.0, 49.9 ppm; HRMS (ESI-TOF): m/z calculated for $C_{37}H_{28}N$ $[M + H]^+$ 486.2222, found 486.2223.

9-allyl-1,2,4-triphenyl-9H-carbazole (**20c**). Isolated as a yellow solid (63 mg, 60%); mp: 179-180 ºC; ^{1}H NMR (400 MHz, CDCl3): δ 7.71-7.69 (m, 2H), 7.53 (t, *J* = 7.5 Hz, 2H), 7.49-7.46 (m, 1H), 7.44 (d, *J* = 8.0 Hz, 1H),7.36-7.33 (m, 1H), 7.30-7.28 (m, 2H), 7.27 (s, 1H), 7.25-7.22 (m, 3H), 7.16-7.10 (m, 6H), 6.97 (t, *J* = 7.0 Hz, 1H), 5.57-5.49 (m, 1H), 4.96 (dd, J_1 = 1.0 Hz, J_2 = 10.5 Hz 1H), 4.65 (dd, J_1 = 1.0 Hz, J_2 = 16.0 Hz 1H), 4.32-4.31 (m, 2H) ppm; ^{13}C{1H} NMR (125 MHz, CDCl3): δ 142.3, 141.2, 139.9, 138.5, 138.1, 136.6, 133.3, 131.7, 130.3, 129.4, 128.5, 127.6, 127.3, 126.0, 125.6, 123.6, 123.2, 122.4, 119.1, 115.8, 109.7, 46.7 ppm; HRMS (ESI-TOF): m/z calculated for $C_{33}H_{26}N$ $[M + H]^+$ 436.2065, found 436.2063.

4-hexyl-9-methyl-1,2-diphenyl-9H-carbazole (**20d**). Isolated as a yellow solid (82 mg, 78%); mp: 179-180 ºC; ^{1}H NMR (400 MHz, CDCl3): δ 8.10 (d, *J* = 7.5 Hz, 1H), 7.40-7.37 (m, 1H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.21-7.19 (m, 1H), 7.18 (s, 1H), 7.17 (s, 4H), 7.08-7.04 (m, 5H), 7.00 (s, 1H), 3.21 (t, *J* = 7.5 Hz, 2H), 3.13 (s, 3H), 1.87-1.81 (m, 2H), 1.54-1.47 (m, 2H), 1.34-1.28 (m, 4H), 0.84 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C{1H} NMR (125 MHz, CDCl3): δ 142.7, 142.4, 139.7, 139.3, 138.7, 132.1, 130.4, 127.5, 127.4, 126.9, 125.9, 125.2, 122.6, 122.4, 121.9, 120.9, 108.8, 34.6, 32.8, 31.9, 29.8, 29.7, 22.8, 14.2 ppm; HRMS (ESI-TOF): m/z calculated for $C_{31}H_{32}N$ $[M + H]^+$ 418.2535, found 418.2537.

9-methyl-4-pentyl-1,2-diphenyl-9H-carbazole (**20e**). Isolated as a yellow solid (62mg, 75%); mp: 179-180 ºC; ^{1}H NMR (400 MHz, CDCl3): δ 8.17 (d, *J* = 7.5 Hz, 1H), 7.48-7.44 (m, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.29-7.27 (m, 1H), 7.26-7.25 (m, 1H), 7.24-7.23 (m, 4H), 7.17-7.10 (m, 5H), 7.07 (s, 1H), 3.28 (t, *J* = 8.0 Hz, 2H), 3.20 (s, 3H), 1.95-1.89 (m, 2H), 1.61-1.53 (m, 2H), 1.49-1.40 (m, 2H), 0.94 (t, *J* = 7.5 Hz, 1H) ppm; ^{13}C{1H} NMR (125 MHz, CDCl3): δ 142.7, 142.4, 139.7, 139.3, 138.6, 137.1, 132.1, 130.3, 127.5, 127.4, 126.9, 125.9,

125.2, 122.6, 122.5, 122.4, 121.9, 120.9, 119.3, 108.8, 34.5, 32.8, 32.3, 29.5, 22.8, 14.3 ppm; HRMS (ESI-TOF): m/z calculated for $C_{30}H_{30}N$ $[M + H]^+$ 404.2378, found 404.2377

9-methyl-1,2-diphenyl-4-(p-tolyl)-9H-carbazole (**20f**). Isolated as a yellow solid (86 mg, 82%); mp: 179-180 ºC; ^{1}H NMR (400 MHz, CDCl3): δ 7.58 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.40-7.36 (m, 2H), 7.34-7.33 (m, 2H), 7.32-7.29 (m, 3H), 7.28-7.26 (m, 2H), 7.24 (s, 1H), 7.16-7.15 (m, 2H), 7.14 (s, 2H), 7.13-7.10 (m, 1H), 7.00-6.97 (m, 1H), 3.23 (s, 3H), 2.49 (s, 3H) ppm; ^{13}C{1H} NMR (125 MHz, CDCl3): δ 142.9, 142.1, 139.6, 139.3, 138.5, 138.2, 137.3, 136.6, 132.0, 130.4, 129.3, 129.2, 127.6, 127.4, 127.1, 126.0, 125.6, 123.5, 123.0, 122.4, 122.2, 120.5, 118.8, 108.7, 32.8, 21.5 ppm; HRMS (ESI-TOF): m/z calculated for $C_{32}H_{26}N$ $[M + H]^+$ 424.2065, found 424.2066.

4-([1,1'-biphenyl]-4-yl)-9-methyl-1,2-diphenyl-9H-carbazole (**20g**). Isolated as a yellow solid (83 mg, 80%); mp: 179-180 ºC; ^{1}H NMR (400 MHz, CDCl3): δ 7.78 (s, 3H), 7.76-7.74 (m, 2H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.41-7.37 (m, 3H), 7.33-7.31 (m, 3H), 7.29-7.27 (m, 3H), 7.20 (s, 1H), 7.17-7.16 (m, 2H), 7.15-7.11 (m, 3H), 7.01-6.98 (m, 1H), 3.25 (s, 3H) ppm; ^{13}C{1H} NMR (125 MHz, CDCl3): δ 142.9, 142.0, 141.0, 140.4, 140.2, 139.7, 139.4, 138.4, 136.1, 132.0, 130.6, 130.4, 129.9, 129.0, 127.6, 127.4, 127.2, 126.1, 125.7, 126.1, 125.7, 123.5, 123.2, 122.4, 122.1, 120.5, 118.9, 108.4, 32.9 ppm; HRMS (ESI-TOF): m/z calculated for $C_{37}H_{28}N$ $[M + H]^+$ 486.2222, found 486.2221.

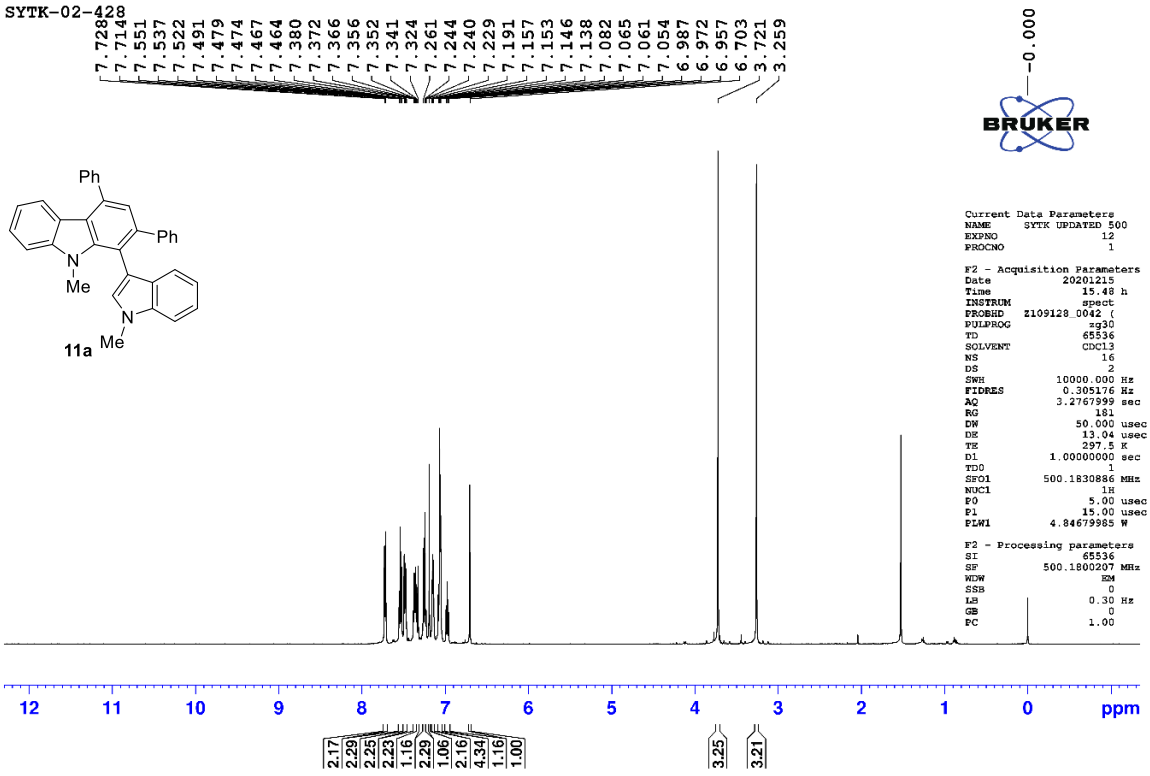
9-methyl-1,2-diphenyl-4-(4-(trifluoromethyl)phenyl)-9H-carbazole (**20h**). Isolated as a yellowsolid (86 mg, 83%); mp: 179-180 ºC; ^{1}H NMR (400 MHz, CDCl3): δ 7.76-7.71 (m, 4H), 7.36-7.32 (m, 2H), 7.26-7.20 (m, 6H), 7.18 (s, 1H), 7.9-7.08 (m, 4H), 7.06 (d, *J* = 3.5 Hz, 1H), 7.05 (s, 1H), 6.95-6.92 (m, 1H), 3.18 (s, 3H) ppm; ^{13}C{1H} NMR (125 MHz, CDCl3): δ 145.0, 143.0, 141.7, 139.8, 139.4, 138.1, 134.9, 131.9, 130.3, 129.9, 127.7, 127.5, 127.3, 126.2, 126.0, 125.5, 123.9, 123.3, 122.1, 121.7, 120.2, 119.1, 109.0, 32.8 ppm; HRMS (ESI-TOF): m/z calculated for $C_{32}H_{23}F_3N$ $[M + H]^+$ 478.1783, found 478.1783.

9-methyl-2,4-diphenyl-1-(2,4,6-trimethoxyphenyl)-9H-carbazole (**20i**). Isolated as a yellow solid; mp: 186-187 ºC; ^{1}H NMR (400 MHz, CDCl3): δ 7.72 (d, *J* = 7.0 Hz, 2H), 7.52-7.50 (m, 2H), 7.49-7.43 (m, 2H), 7.36-7.33 (m, 1H), 7.28 (d, *J* = 8.5 Hz, 1H), 7.19-7.17 (m, 2H), 7.15-7.08(m, 4H), 6.94-6.91 (m, 1H), 6.05 (s, 2H), 3.81 (s, 3H), 3.54 (s, 3H), 3.42 (s, 3H) ppm; ^{13}C{1H} NMR (125 MHz, CDCl3): δ 161.5, 159.4, 143., 142.4, 141.7, 141.1, 140.1, 136.2, 129.6, 129.2, 128.3, 127.3, 127.0, 125.9, 125.1, 123.2, 122.5, 122.2, 120.2, 118.3, 114.6, 108.7, 108.3, 90.1, 55.6, 55.3, 30.6 ppm; HRMS (ESI-TOF): m/z calculated for $C_{34}H_{30}NO_3$ $[M + H]^+$ 500.2226, found 500.2220.

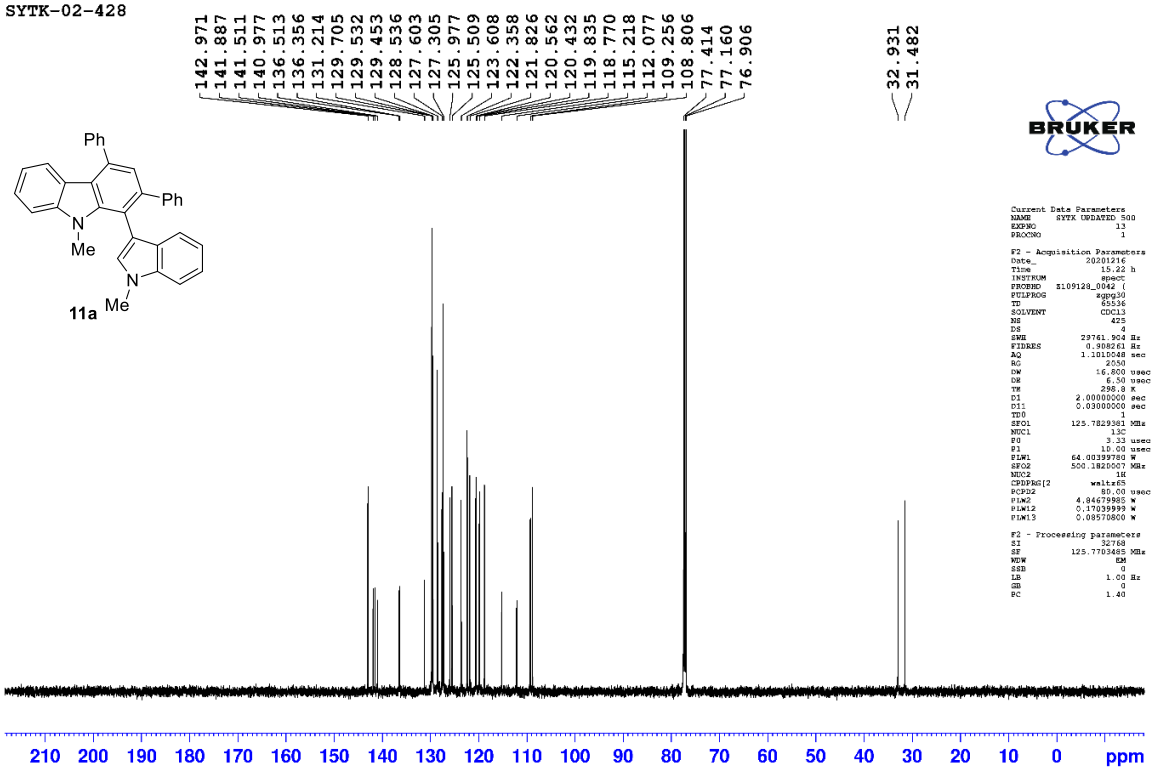
2-iodo-1,3,4-triphenyl-9H-carbazole (**24a**). Isolated as white solid (98 mg, 78%); mp: 227-228 ºC; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.80 (s, 1H), 7.62-7.59 (m, 2H), 7.55-7.52 (m, 3H), 7.32-7.26 (m, 5H), 7.25-7.21 (m, 3H), 7.20-7.19 (m, 2H), 7.17-7.12 (m, 3H), 6.89-6.86 (m, 1H), 6.71 (d, *J* = 8.0 Hz, 1H) ppm; ^{13}C{1H}(125 MHz, $CDCl_3$) *δ* 145.0, 141.7, 140.0, 139.9, 137.8, 137.6, 135.7, 131.4, 130.3, 129.9, 129.3, 129.2, 128.5, 128.1, 127.3, 126.7, 126.3, 123.2, 122.6, 121.8, 119.7, 110.6, 102.7 ppm; HRMS (ESI-TOF): m/z calculated for $C_{30}H_{21}IN$ $[M + H]^+$ 522.0719, found 522.0719.

ethyl 9-methyl-2-(1-methyl-1H-indol-3-yl)-1-phenyl-9H-carbazole-4-carboxylate (**25**). Isolated as white solid (54 mg, 56%); mp-189-190 oC; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (d, J = 8.5 Hz, 1H), 8.11 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.50-7.47 (m, 1H), 7.32-7.29 (m, 5H), 7.28-7.25 (m, 3H), 7.24-7.21 (m, 1Hz), 7.15-7.12 (m, 1H), 6.29 (s, 1H), 4.54 (q, J = 7.0 Hz, 2H), 3.58 (s, 3H), 3.21 (s, 3H), 1.45 (t, J = 7.0 Hz, 3H) ppm; ^{13}C{1H}(125 MHz, $CDCl_3$) δ 168.5, 143.3, 140.4, 139.0, 136.4 131.9, 131.3, 128.9, 128.3, 128.2, 127.8, 127.5, 126.5, 125.0, 124.9, 124.8, 121.7, 121.3, 120.6, 120.0, 119.6, 119.5, 114.5, 109.2, 108.6, 61.2, 32.9, 32.7, 14.5 ppm; HRMS (ESI-TOF): m/z calculated for $C_{31}H_{27}N_2O_2$ $[M + H]^+$ 459.2073, found 459.2074.

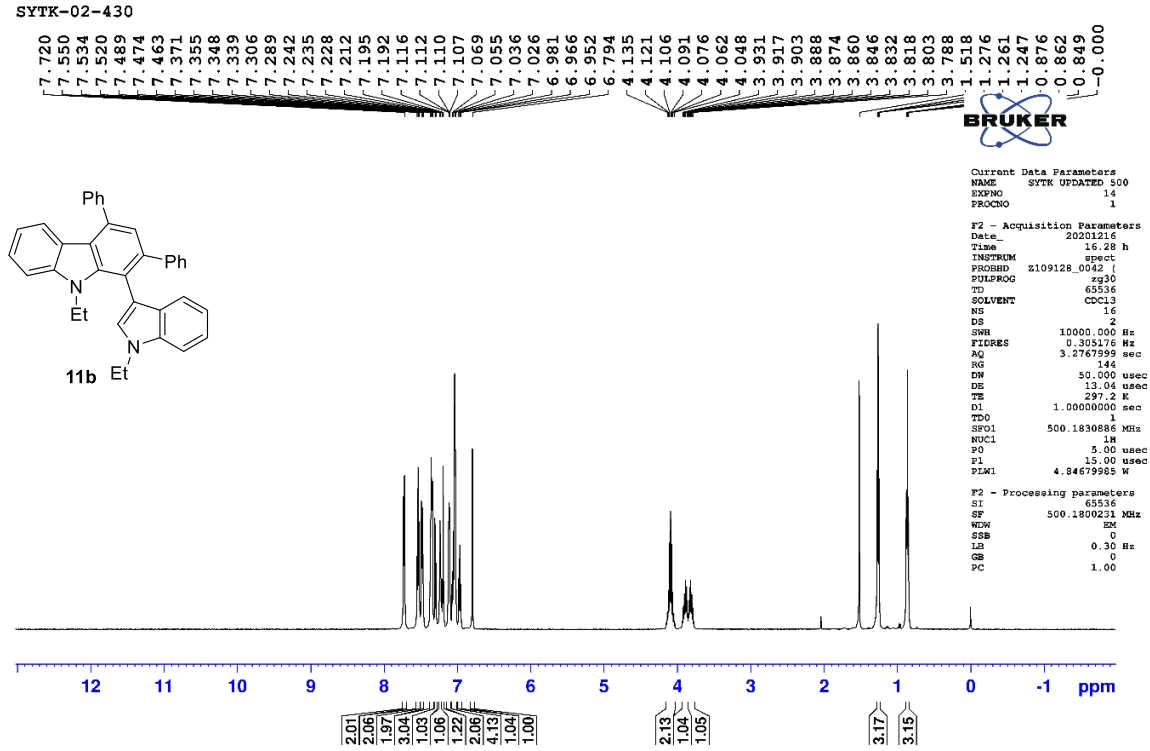
4.4.3. Spectral copies



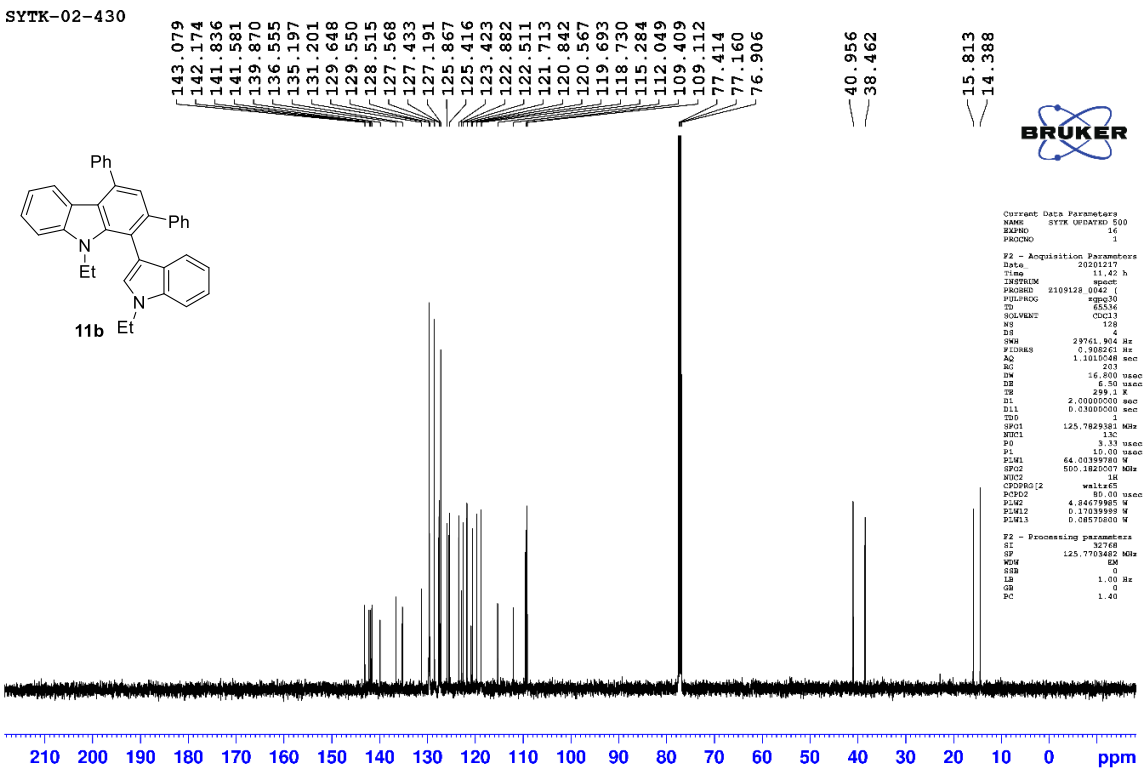
SYTK-02-428



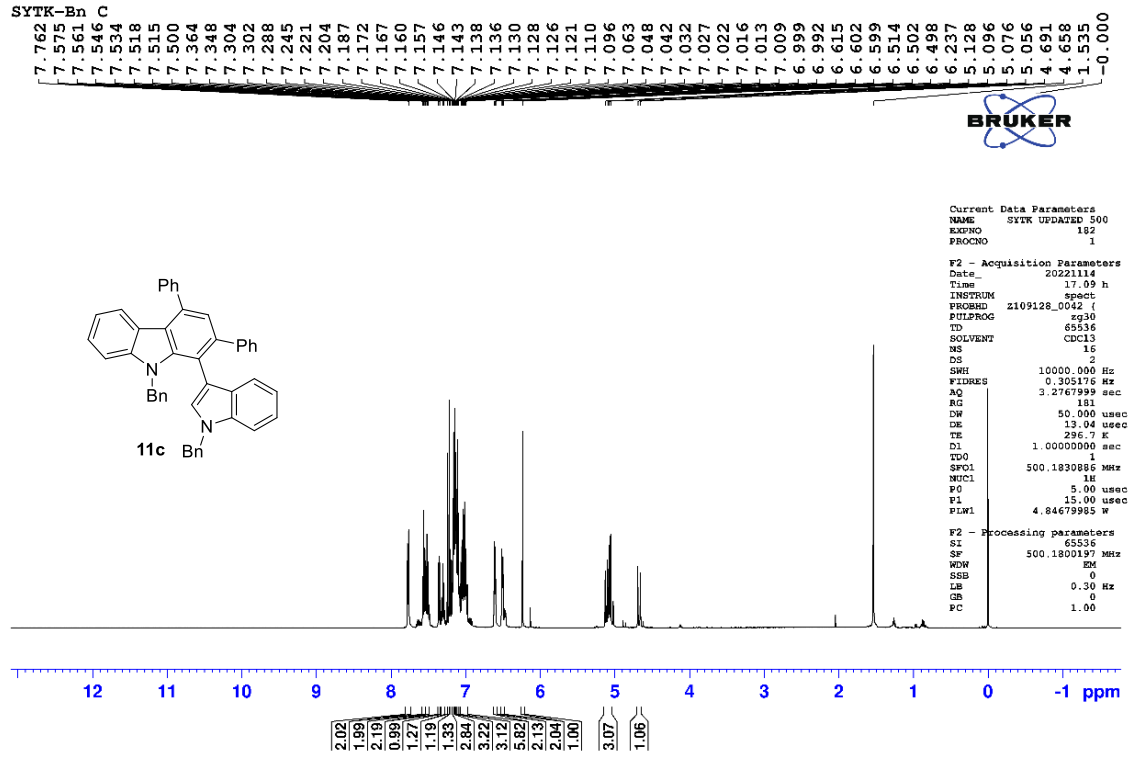
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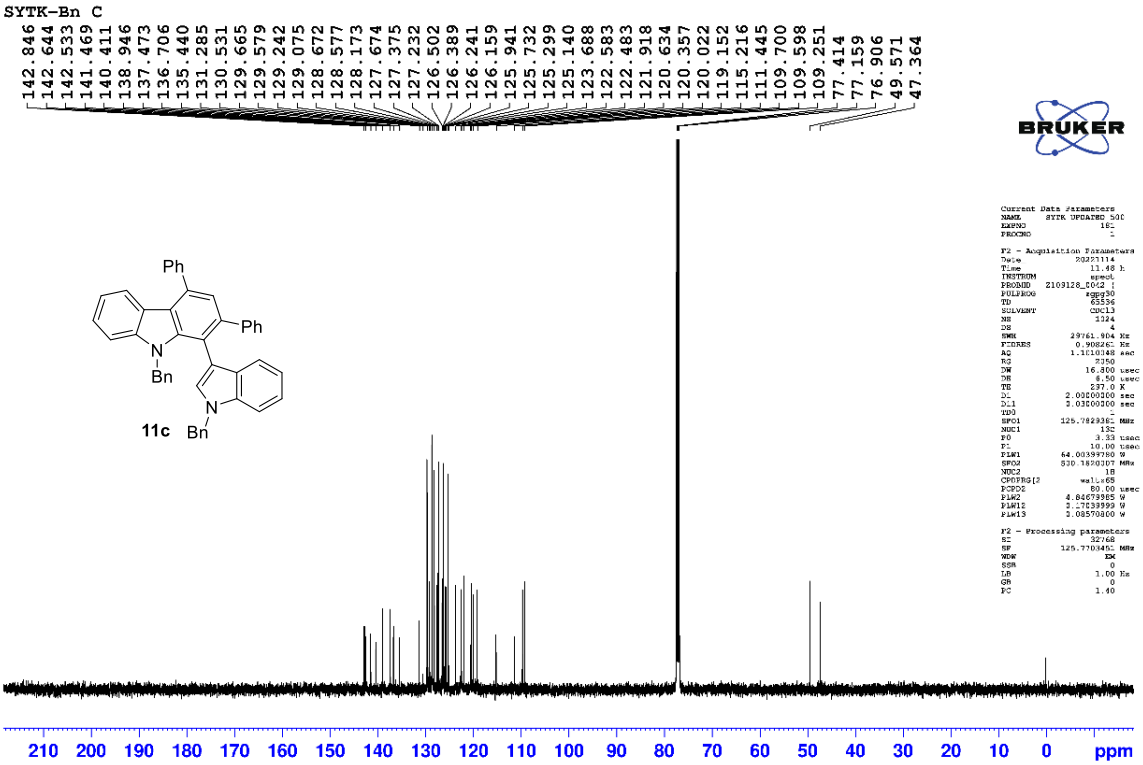
SYTK-02-430



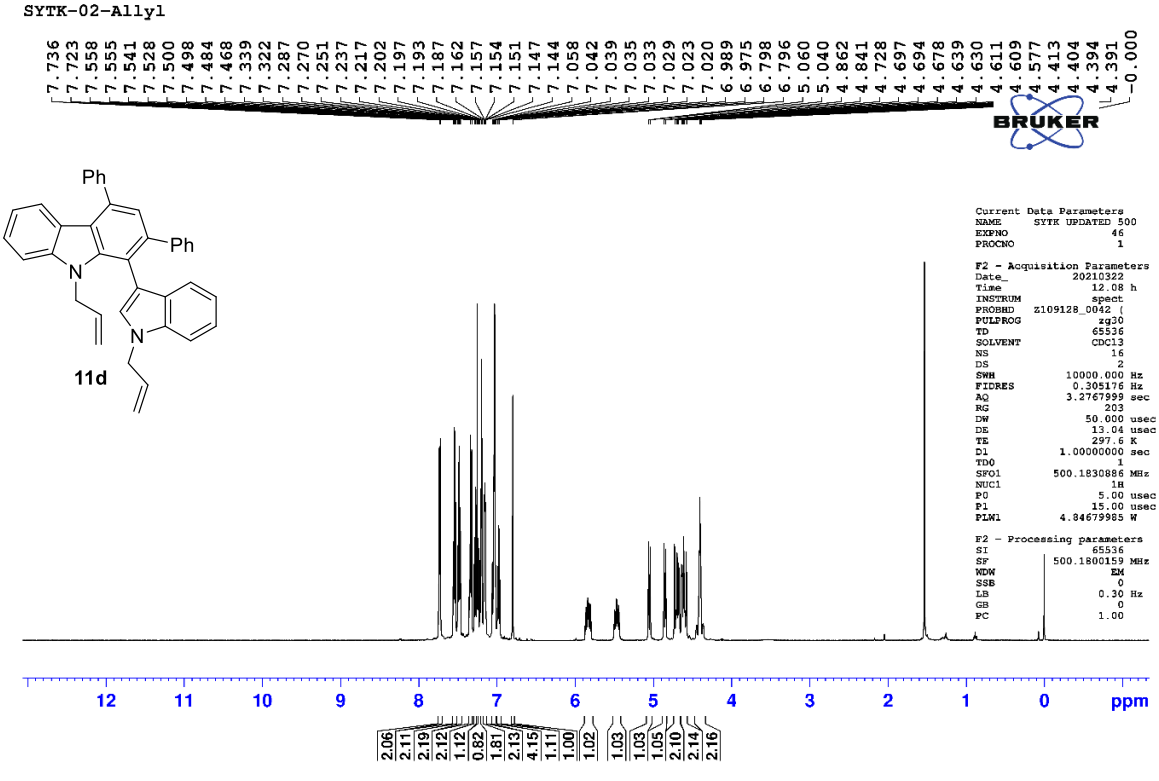
SYTK-Bn C



SYTK-Bn C

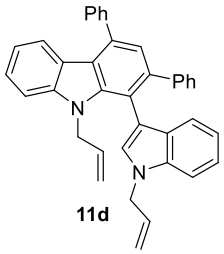


SYTK-02-Allyl



SYTK-02-ALLYL

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11d




```
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PROCNO              1

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PULPROG          zgpg30
TD               65536
SOLVENT          CDCl3
NS                 558
DS                   4
SWH          24038.461 Hz
FIDRES        0.733596 Hz
AQ            1.3631488 sec
RG                 575
DW              20.800 usec
DE               6.50 usec
TE              468.9 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                  1
SFO1        100.6130223 MHz
NUC1               13C
P0               3.33 usec
P1              10.00 usec
PLW1        49.43999863 W
SFO2        400.0926004 MHz
NUC2               1H
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PCPD2            90.00 usec
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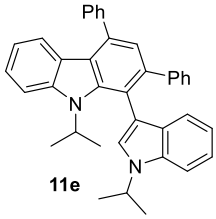
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PC               1.40
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SYTK-49 B

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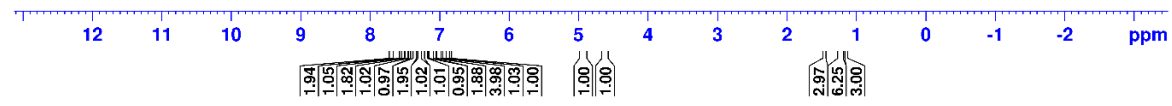


11e

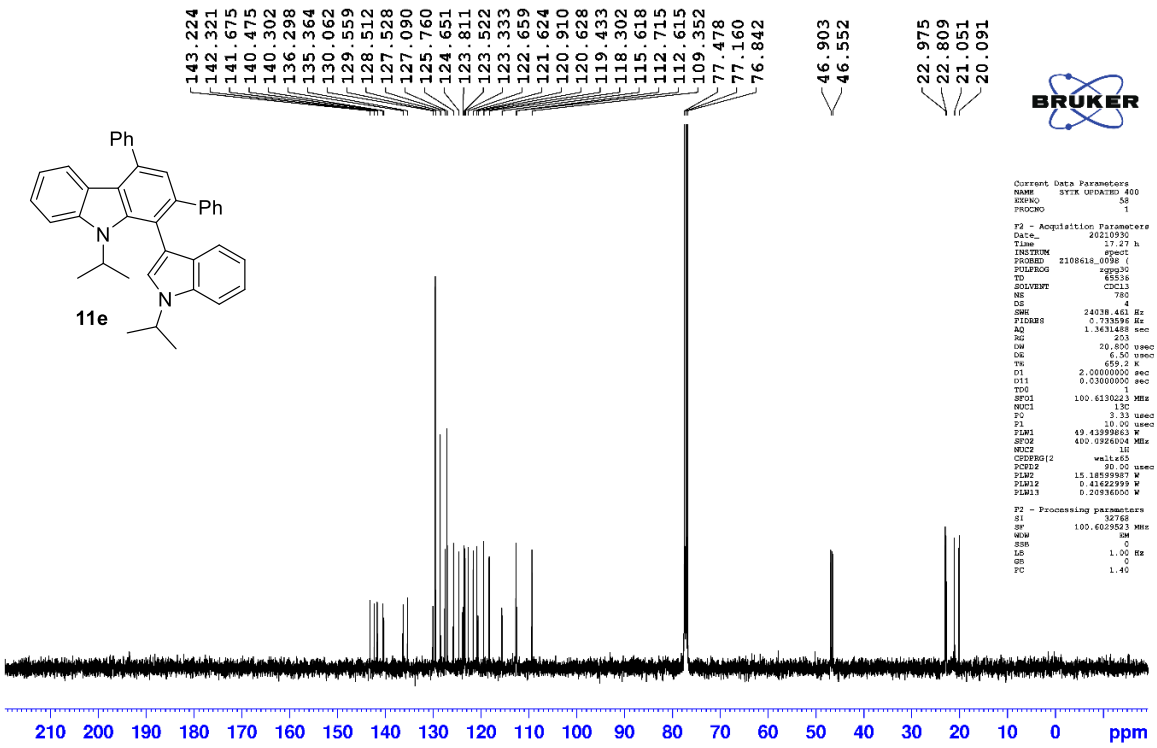
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PROCNO               1

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PULPROG             zg30
TD                 65536
SOLVENT          CDCl3
NS                    16
DS                     2
SWH           10000.000 Hz
FIDRES            0.305176 Hz
AQ            3.2767999 sec
RG                 108.78
DW              50.000 usec
DE               6.50 usec
TE              299.2 K
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TD0                    1
SFO1        500.3720898 MHz
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PLW1        23.23100090 W

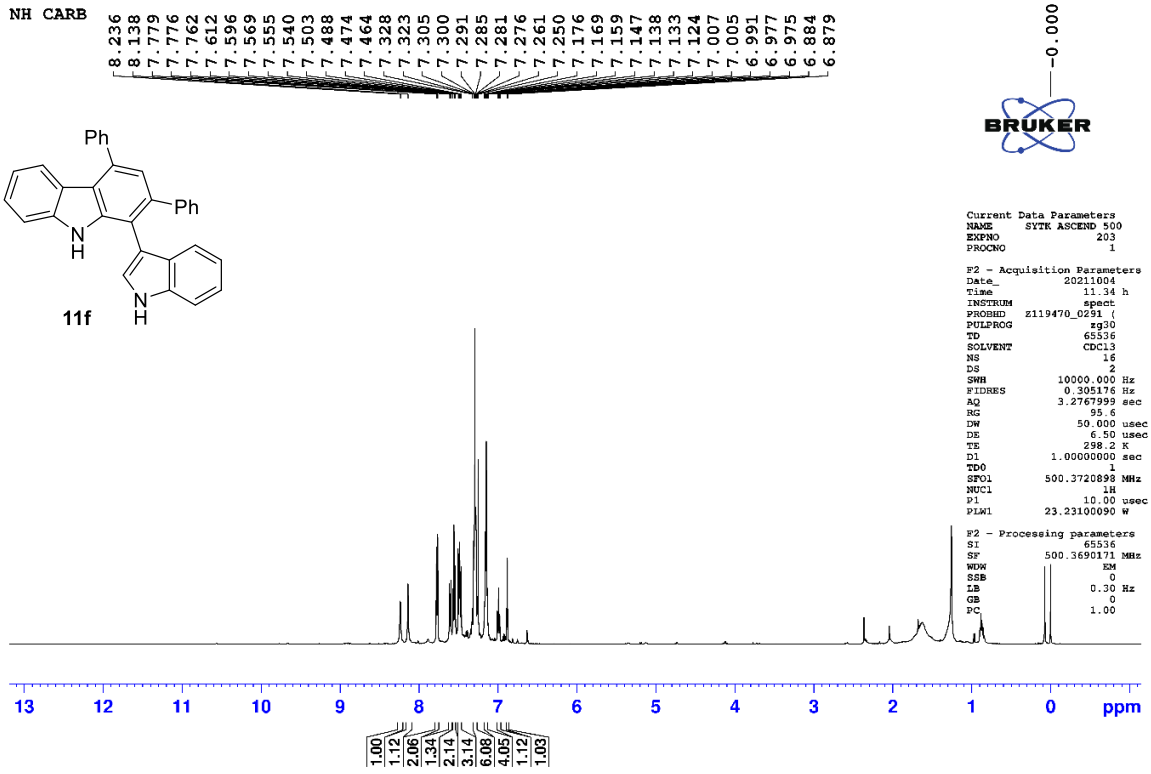
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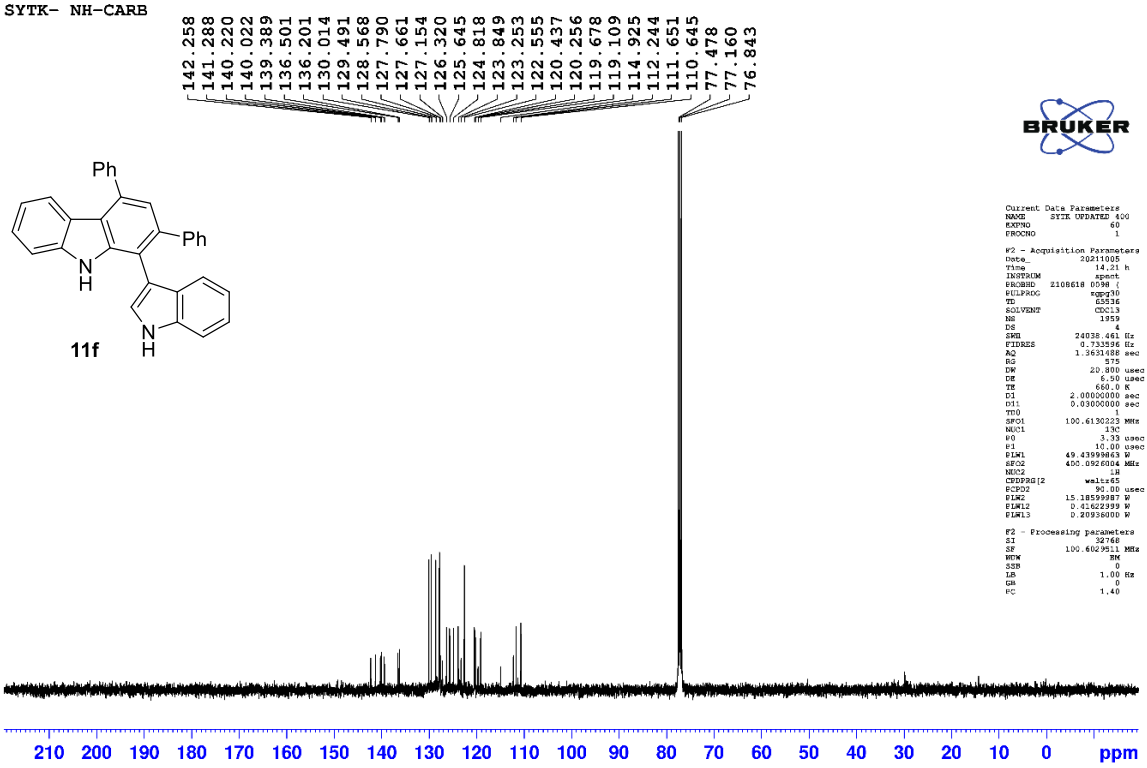
SYTK-49 b



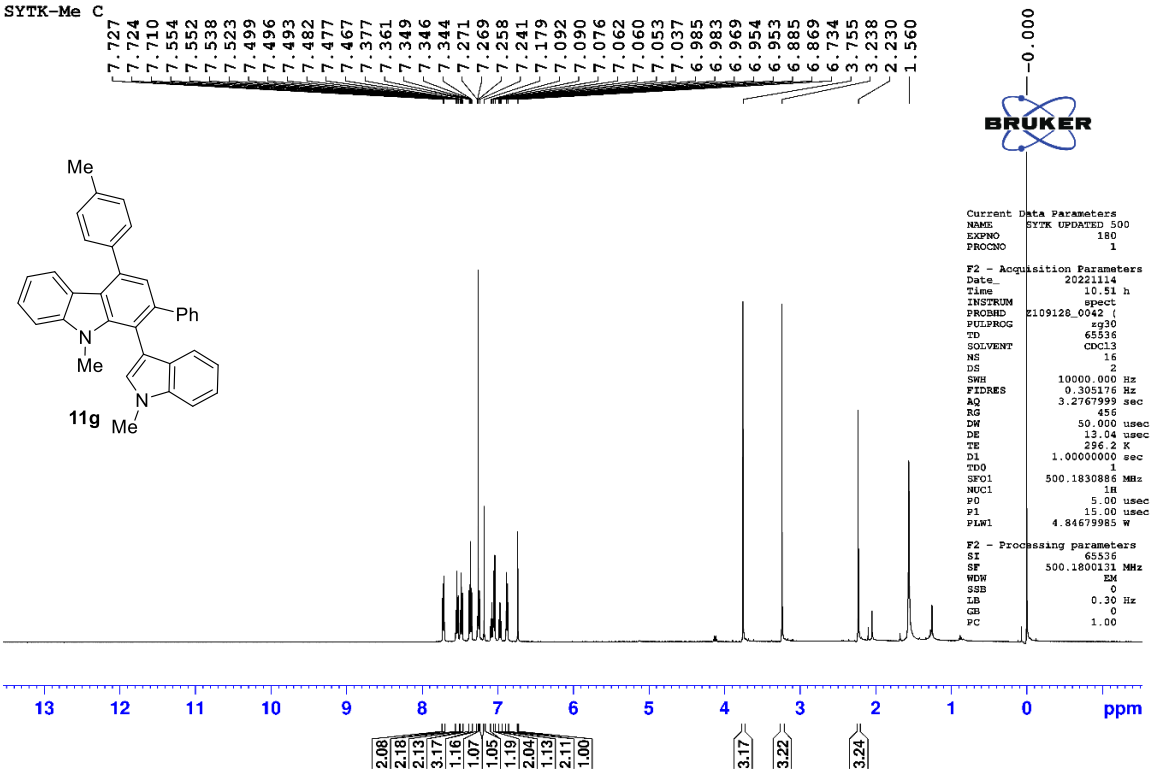
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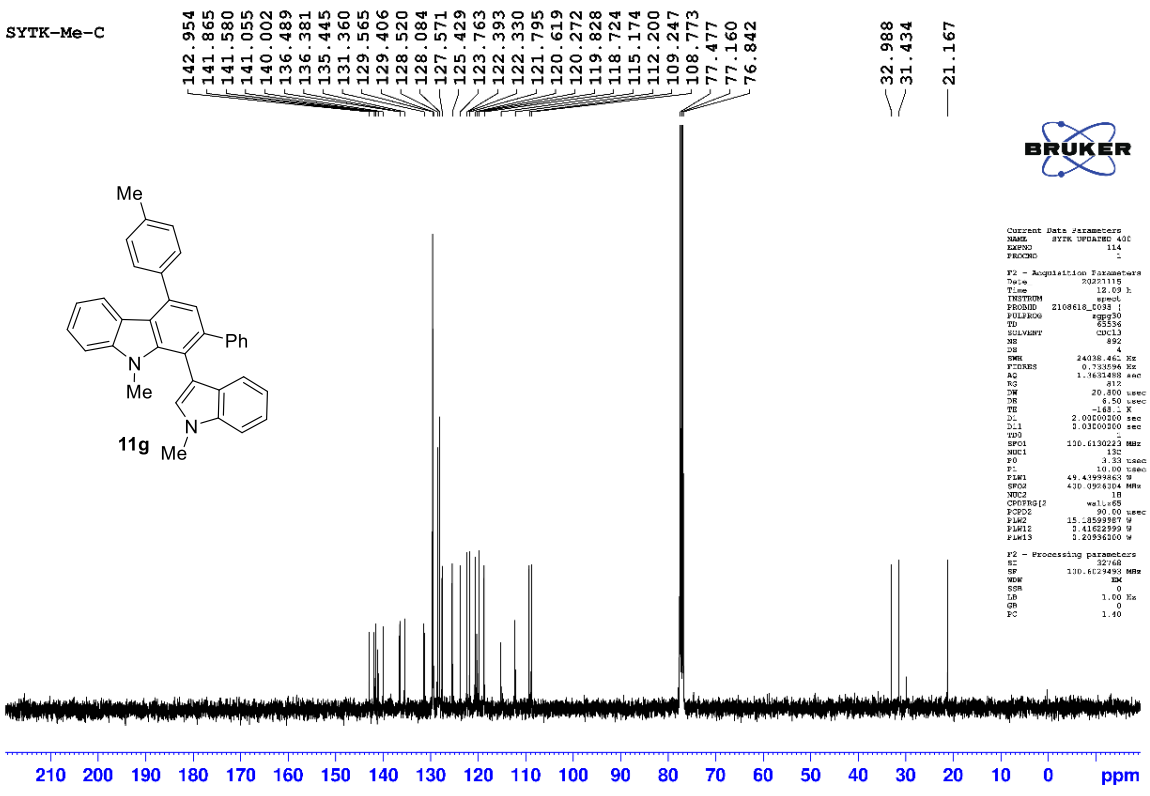


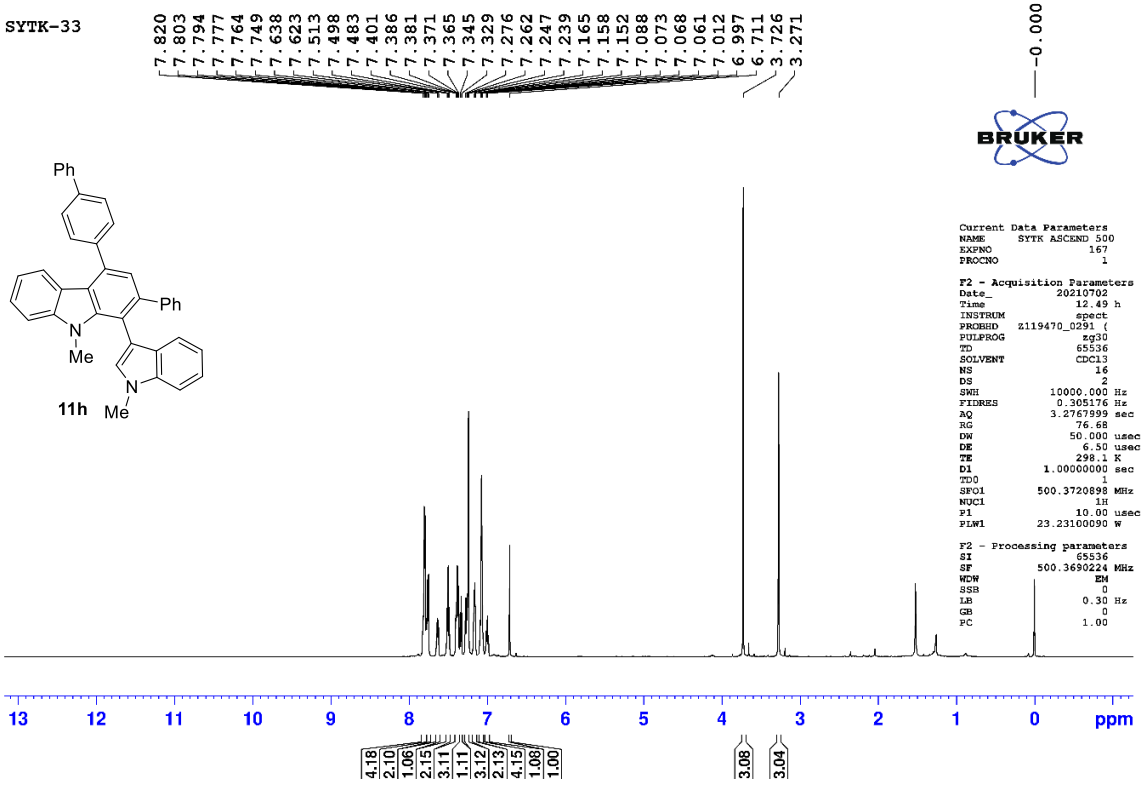
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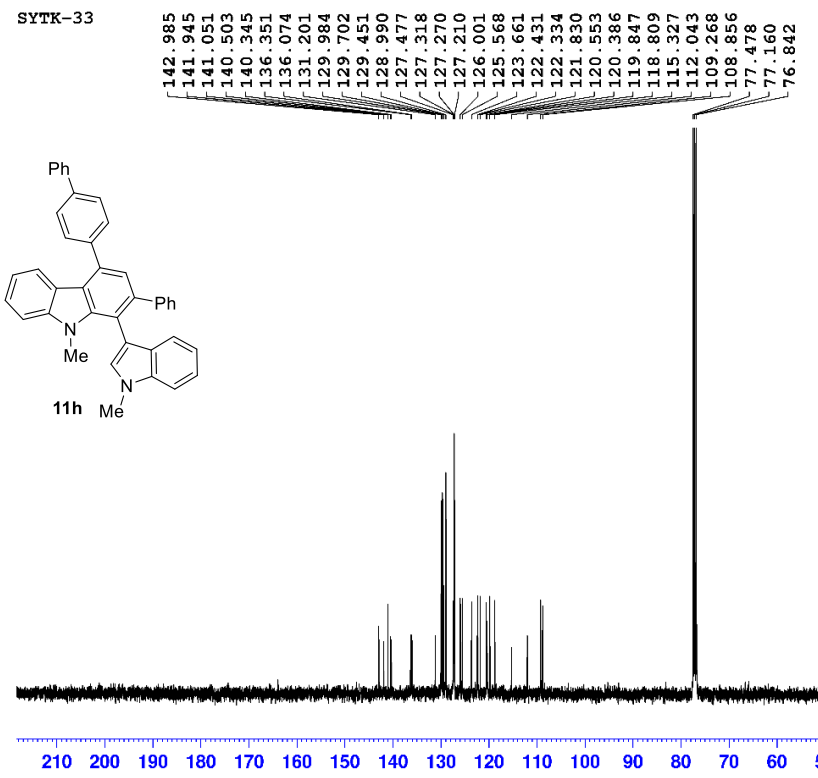
SYTK-Me C



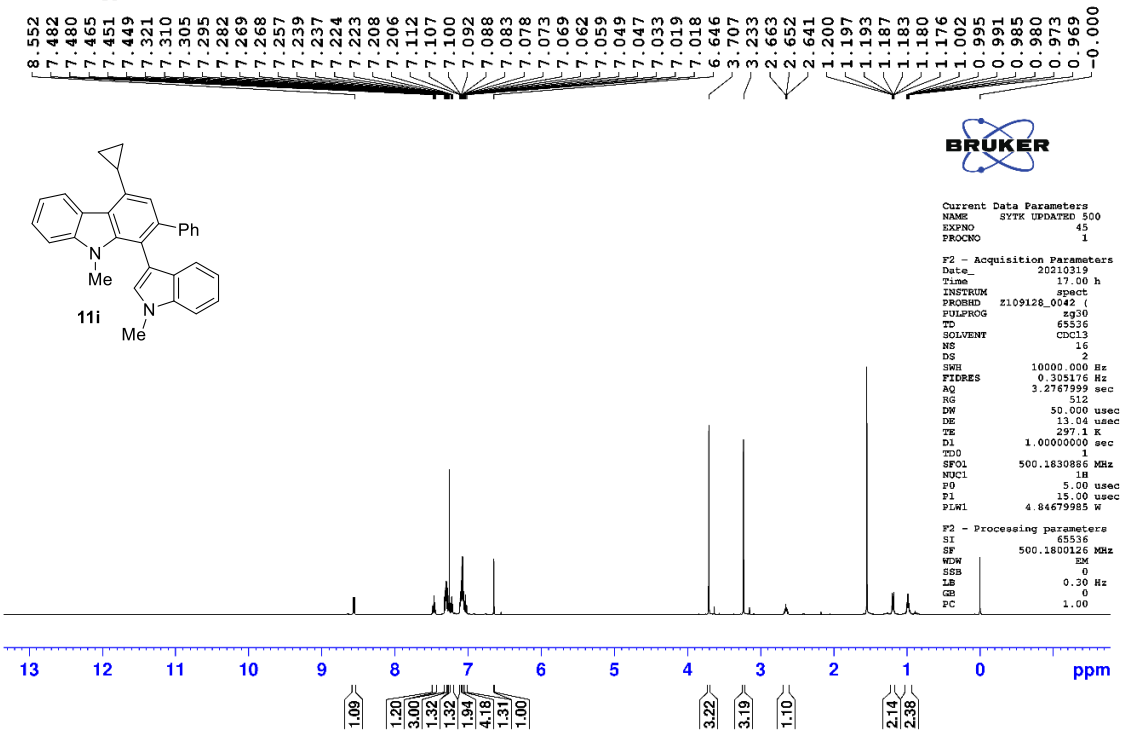

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127.571
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118.724
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112.200
109.247
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77.477
77.160
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31.434
21.167
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Ph
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Me
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11g
BRUKER
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PULPROG zgpg30
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AQ 1.3631488 sec
RG 812
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DE 6.50 usec
TE 298.1 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
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P1 10.00 usec
PLW1 49.43999863 W
SFO2 400.0908304 MHz
NUC2 1H
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PCPD2 90.00 usec
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PLW13 0.20936300 W
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LB 1.00 Hz
GB 0
PC 1.40
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SYTK-33
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7.068
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6.997
6.711
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3.271
0.000
Ph
Ph
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Me
N
Me
11h
BRUKER
Current Data Parameters
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EXPNO 167
PROCNO 1
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PULPROG zg30
TD 65536
SOLVENT CDCl3
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FIDRES 0.305176 Hz
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RG 76.68
DW 50.000 usec
DE 6.50 usec
TE 298.1 K
D1 1.00000000 sec
TD0 1
SFO1 500.3720898 MHz
NUC1 1H
P1 10.00 usec
PLW1 23.23100090 W
F2 - Processing parameters
SI 65536
SF 500.3690224 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
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3.12
2.13
4.15
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3.04

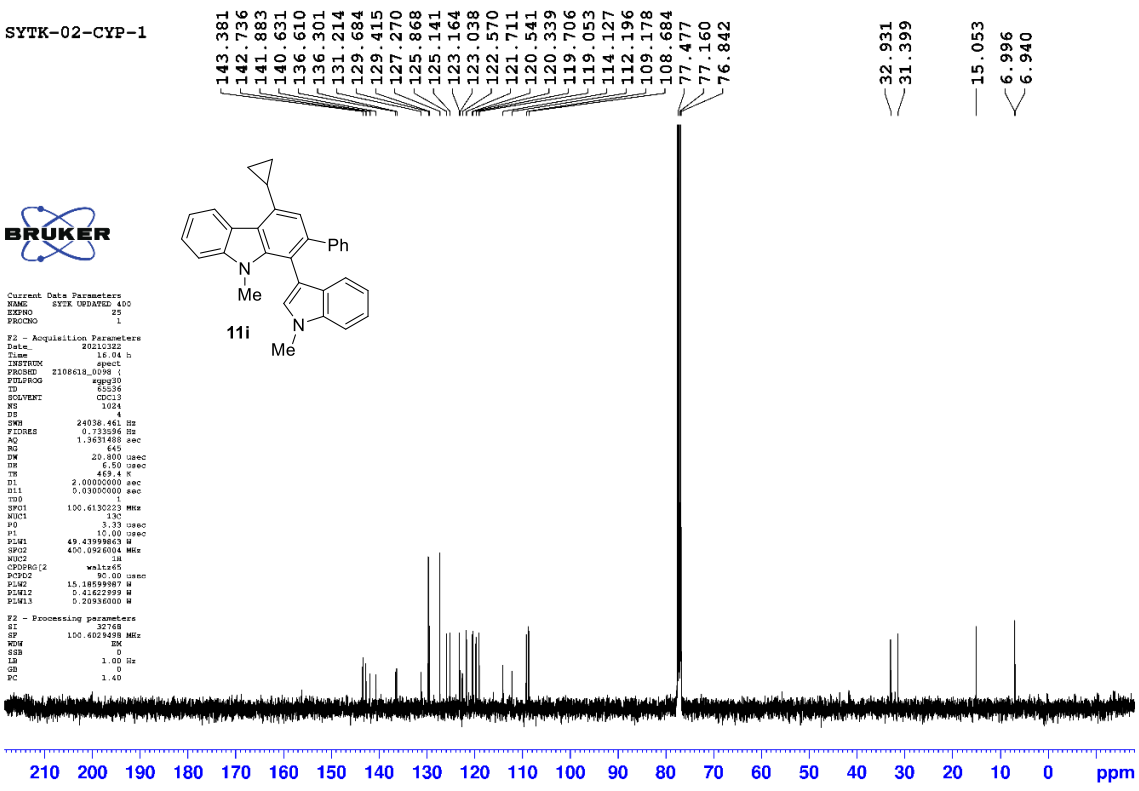
SYTK-33



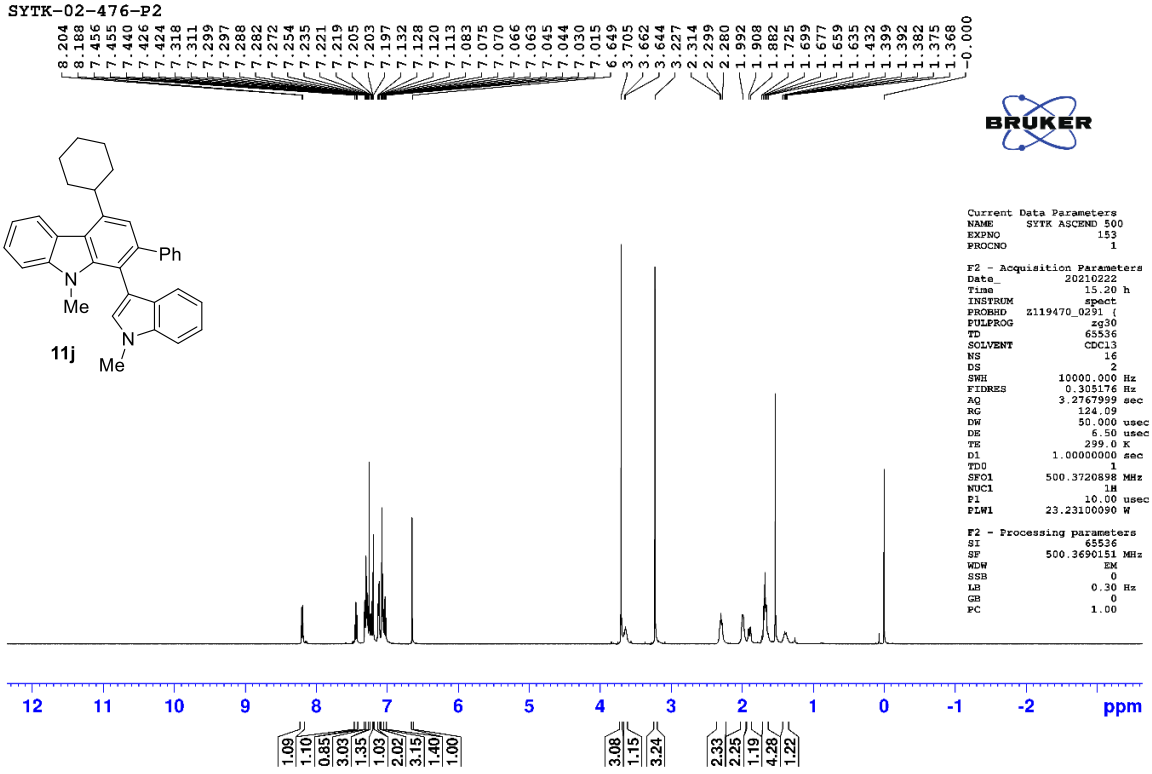
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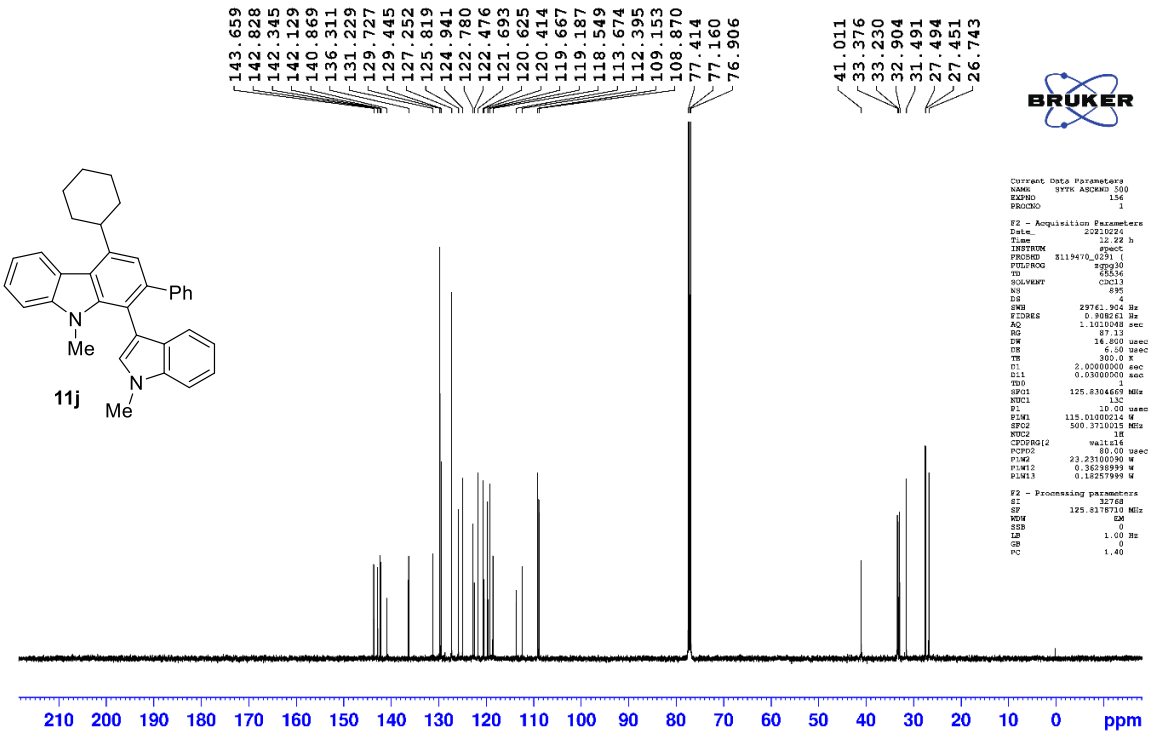
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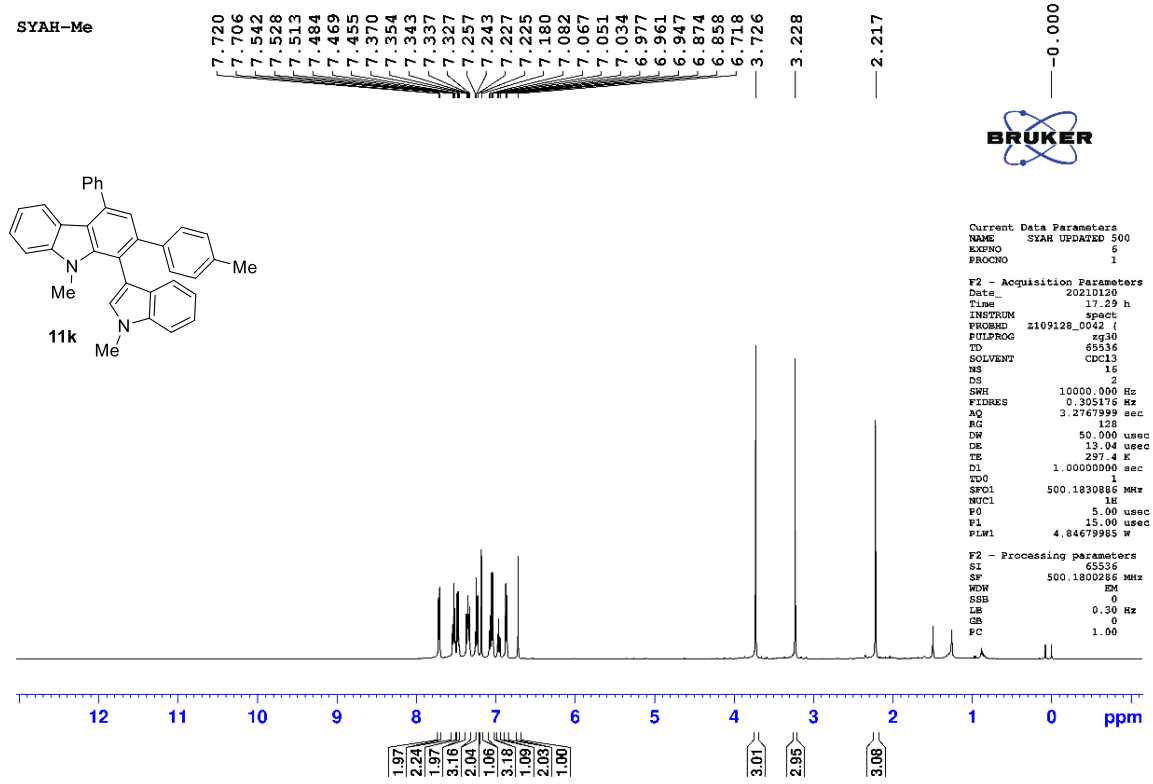
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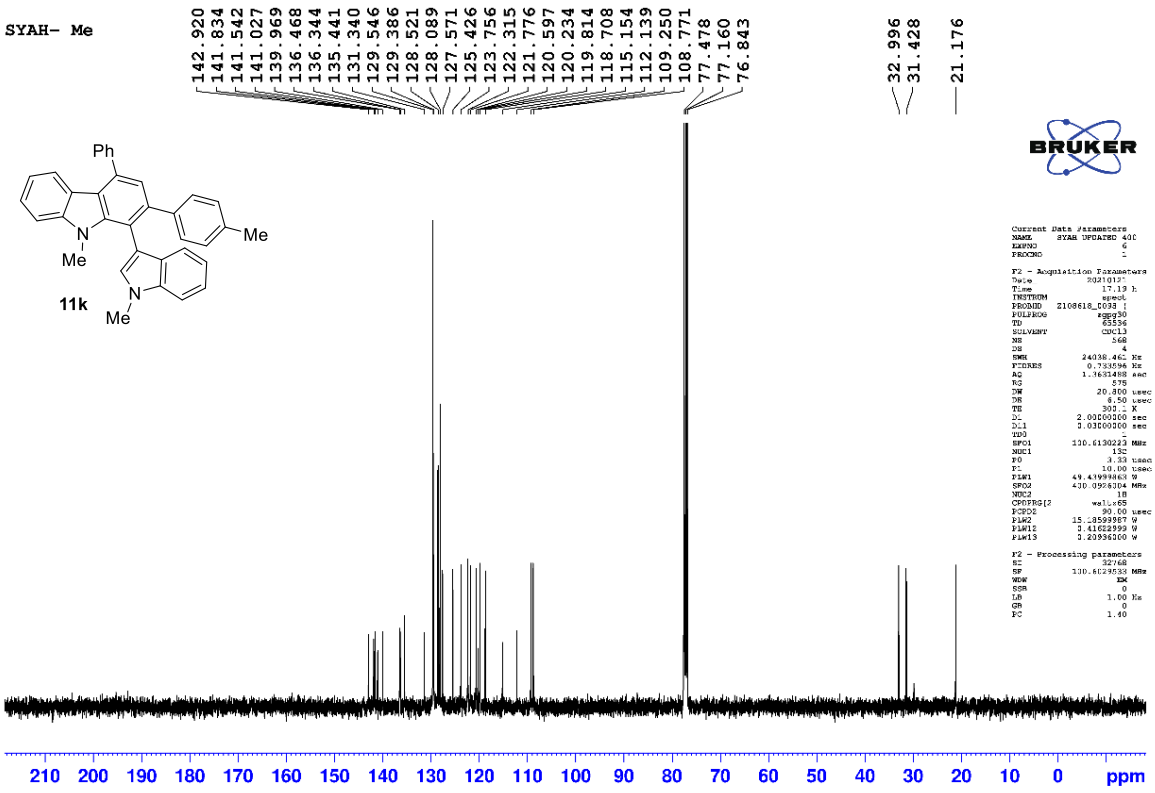
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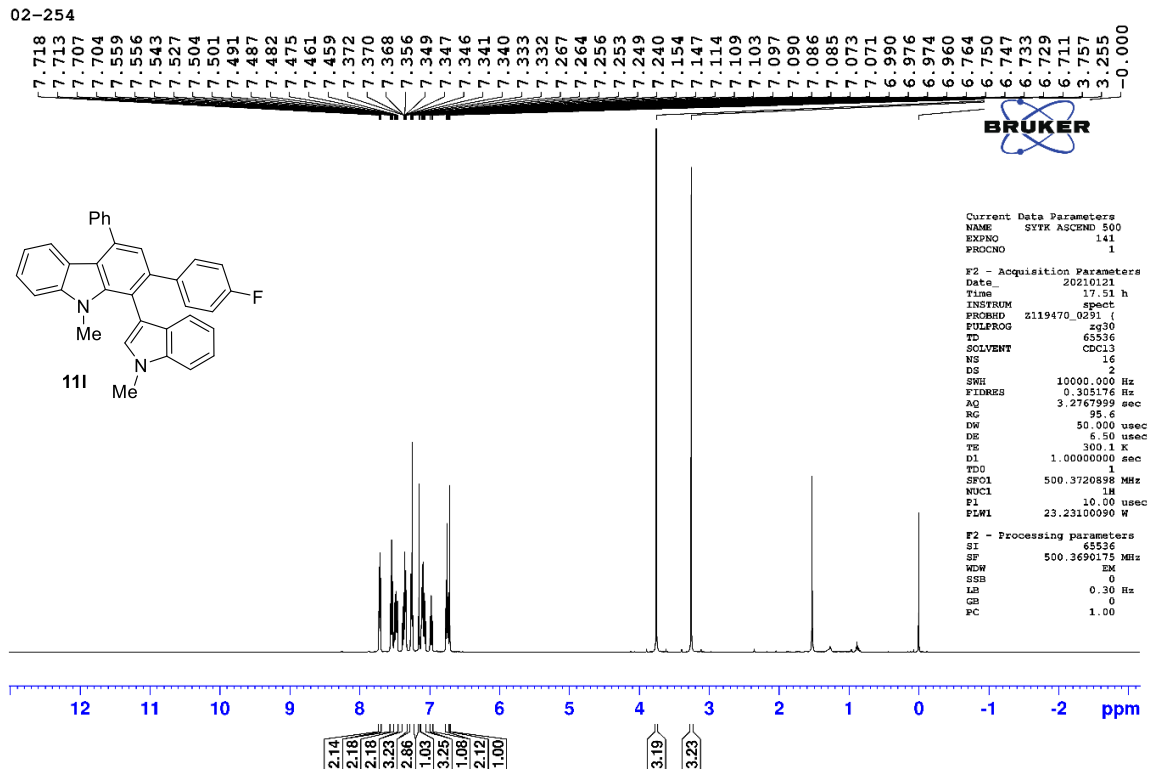
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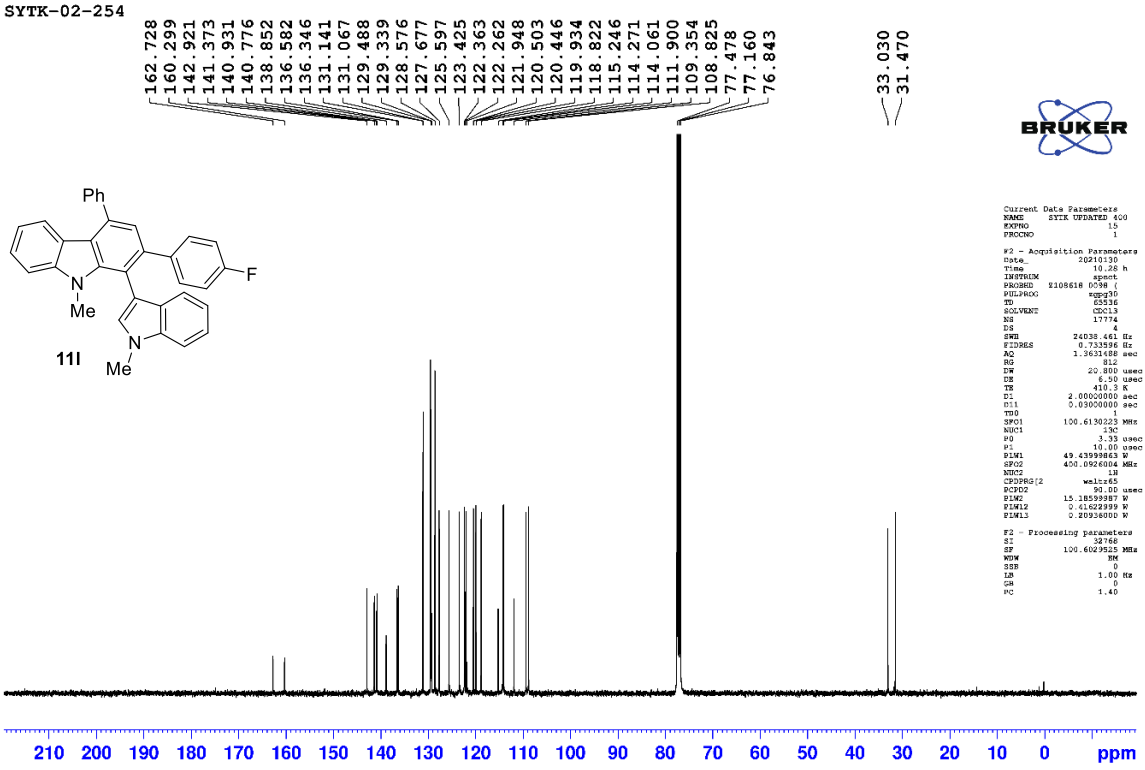
SYAH- Me



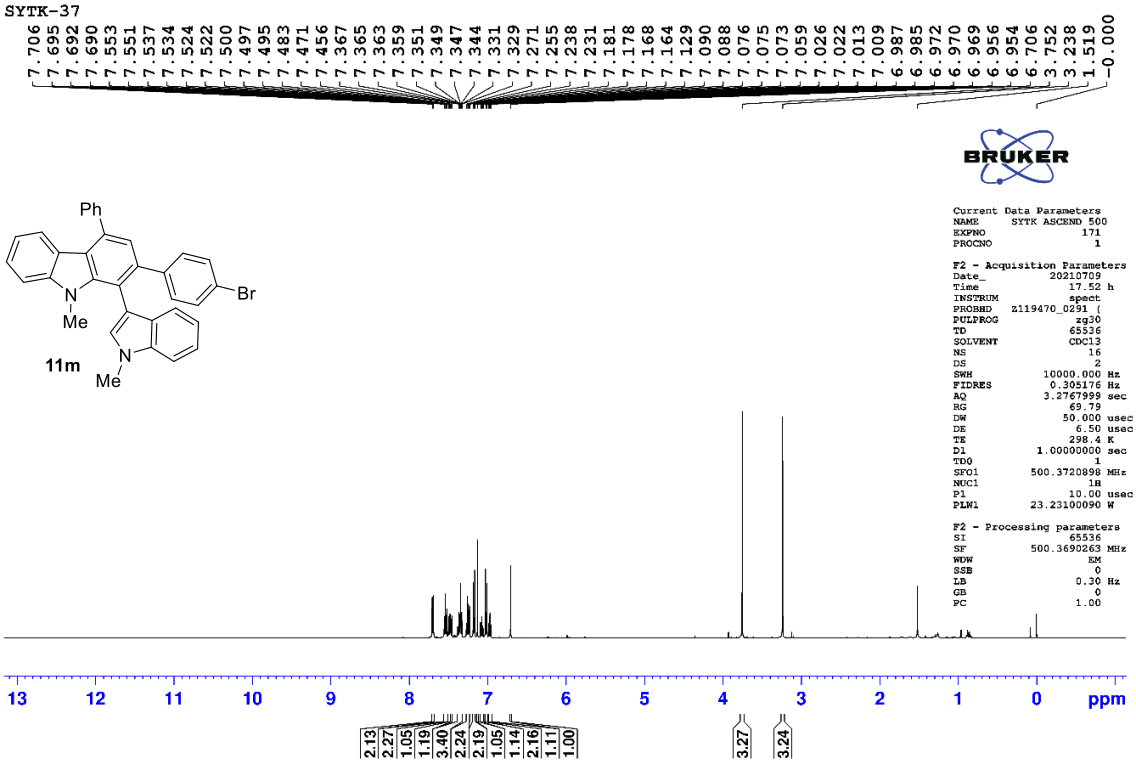
02-254



SYTK-02-254



SYTK-37

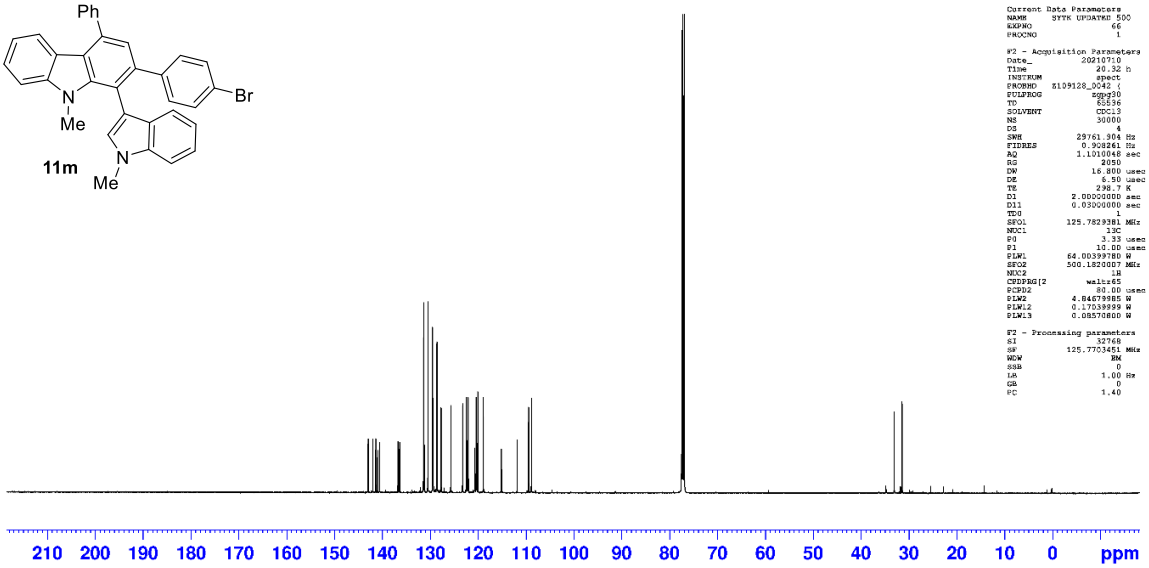


SYTK-37

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123.212
122.410
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120.409
120.251
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77.160
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33.051
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11m

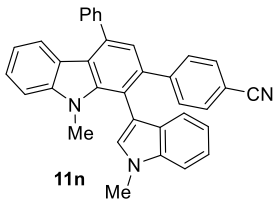


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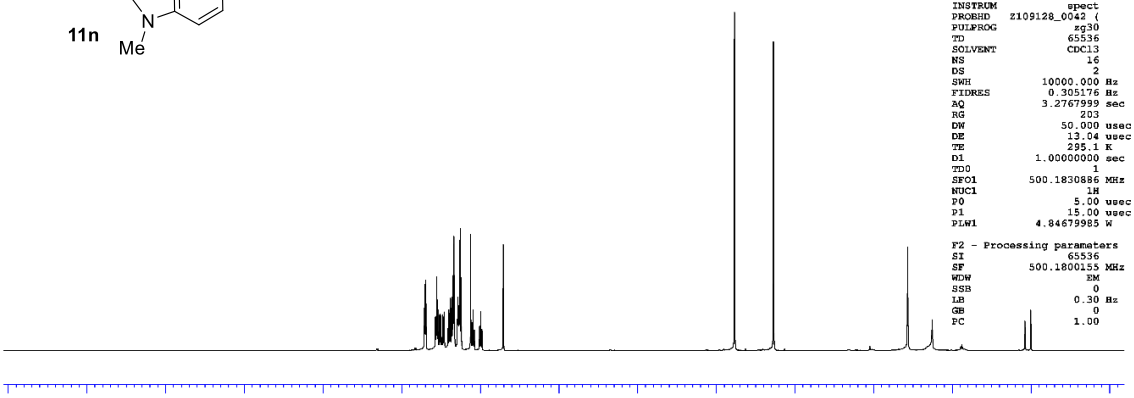
SYAH- CN

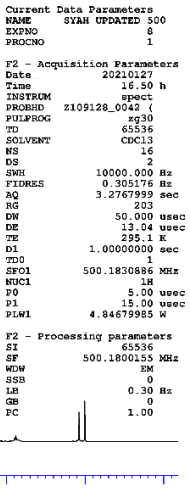
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7.499
7.489
7.473
7.457
7.413
7.411
7.396
7.394
7.378
7.362
7.349
7.346
7.343
7.333
7.327
7.290
7.284
7.276
7.268
7.258
7.251
7.241
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6.706
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0.000



11n



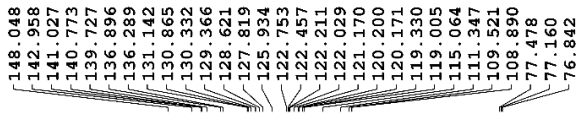


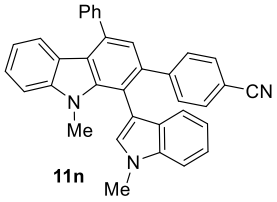
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1.08
1.00

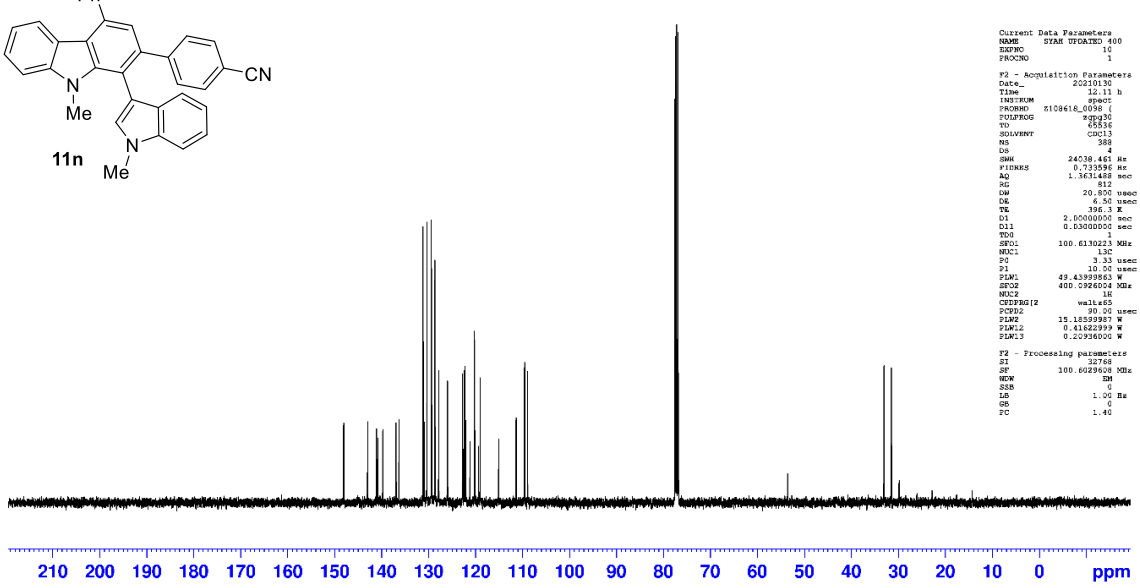
3.28
3.22

SYAH-CN

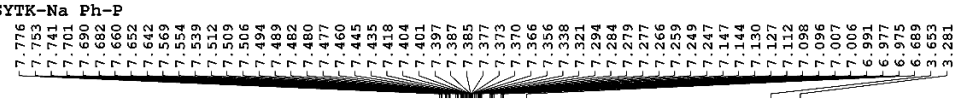




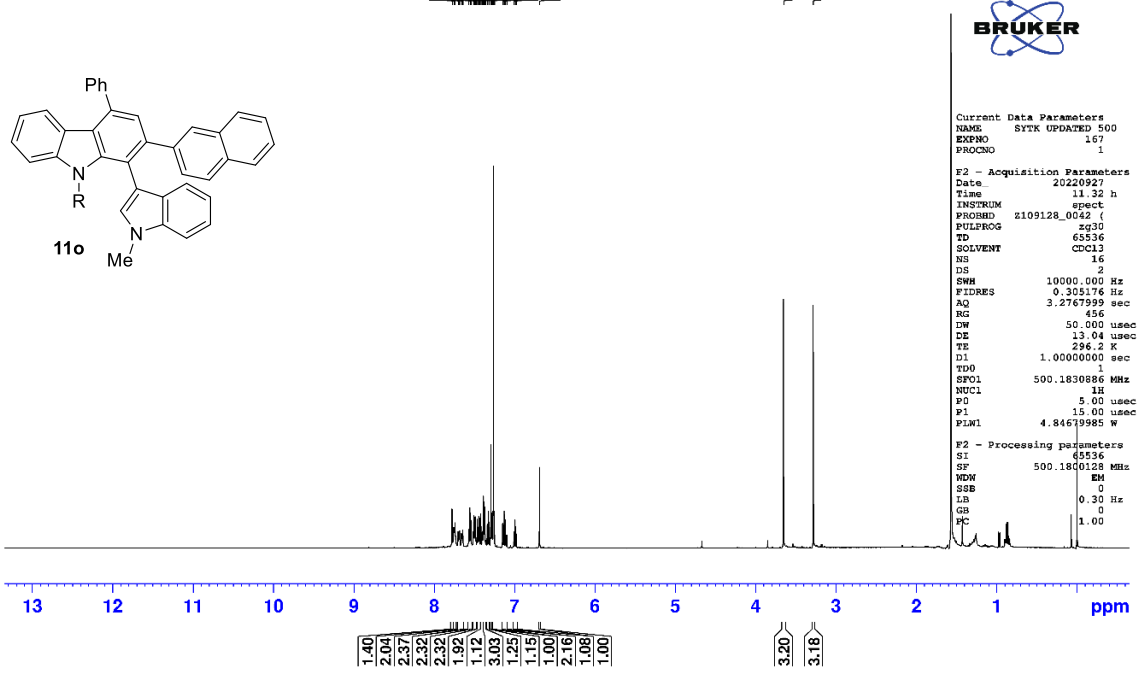
11n



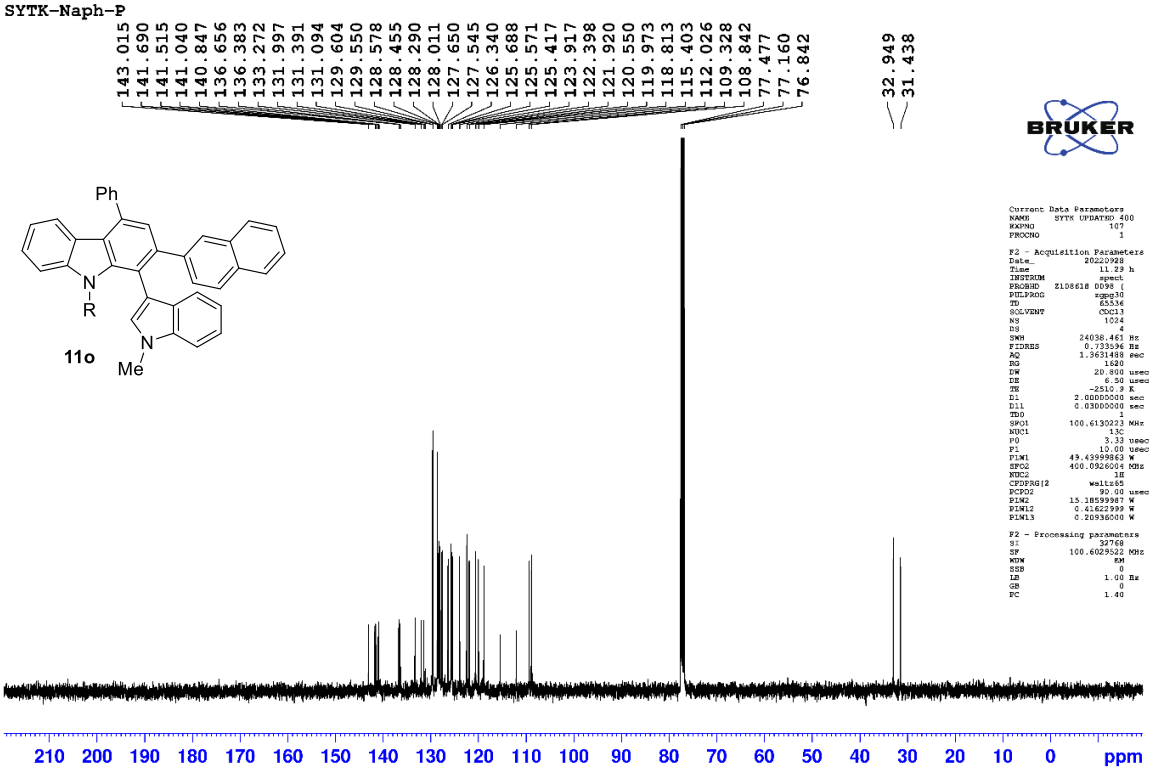
SYTK-Na Ph-P



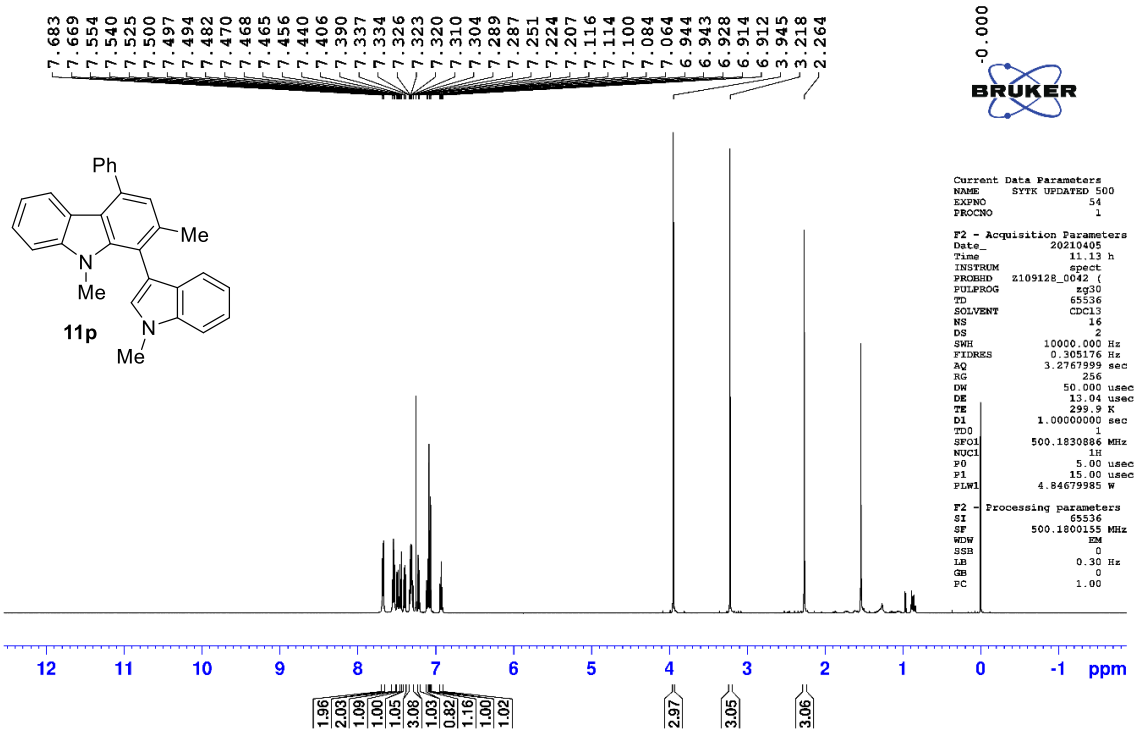
11o



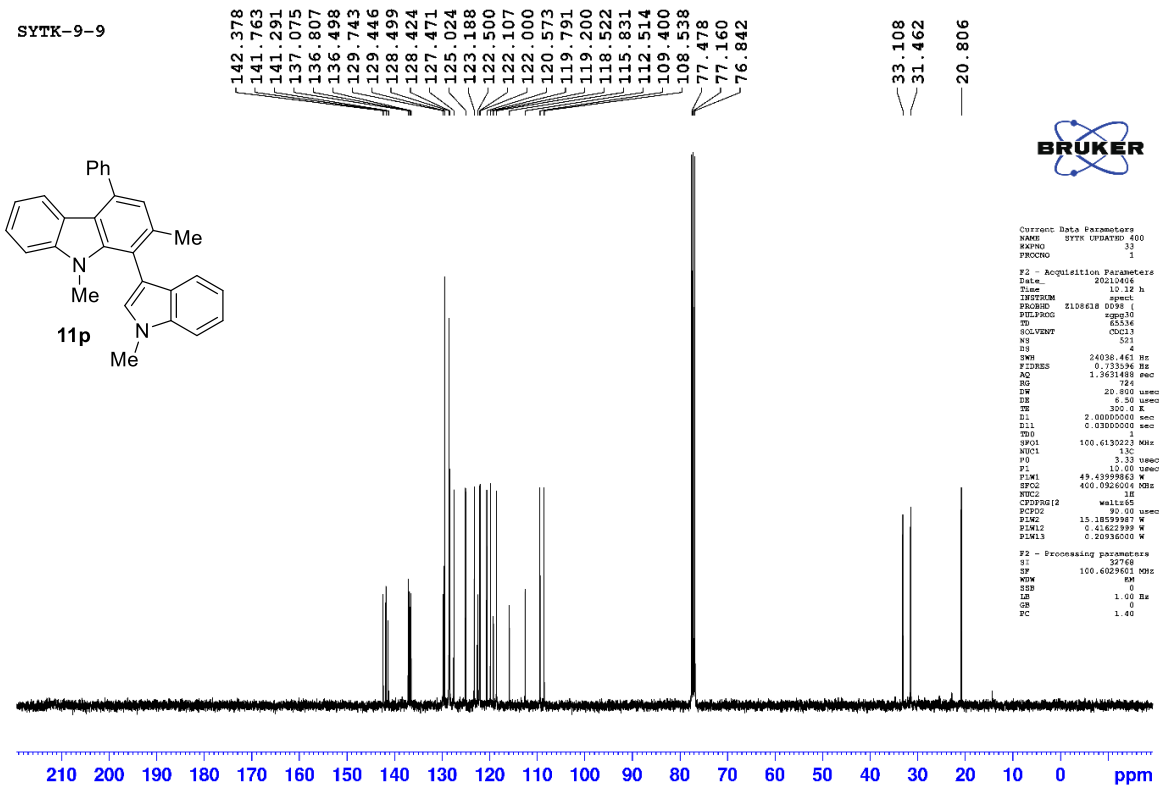
SYTK-Naph-P



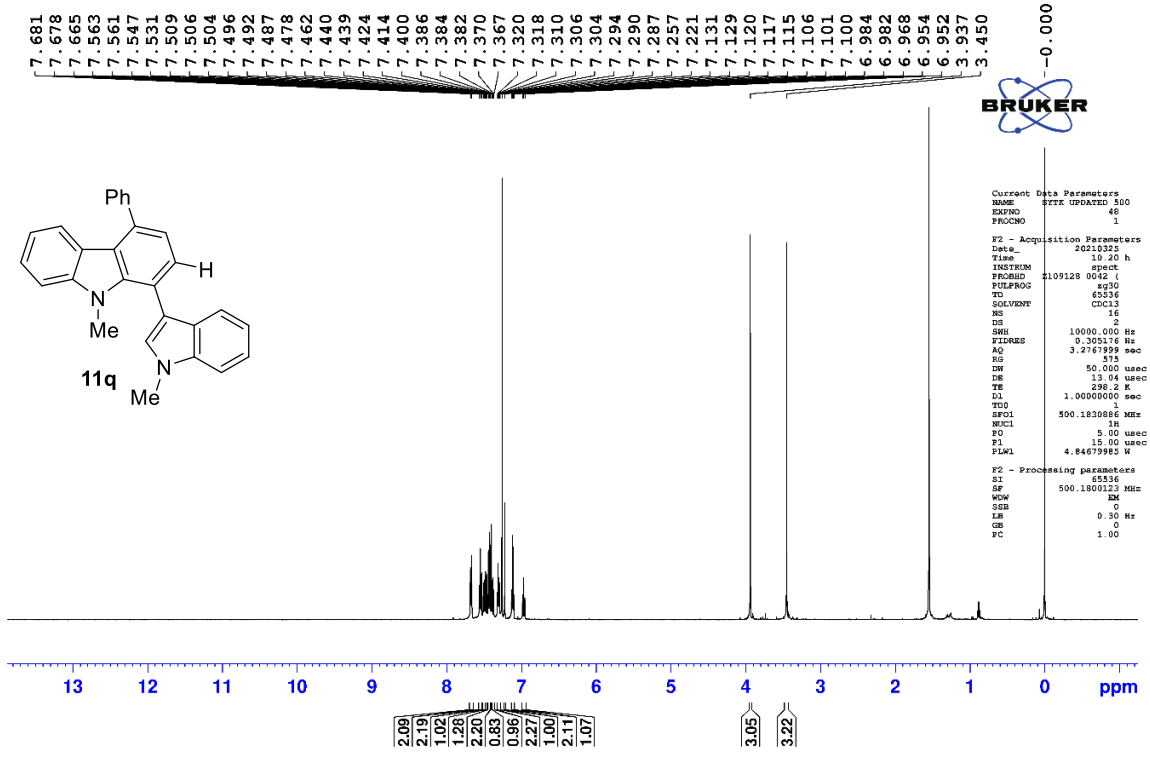
SYTK-9-9



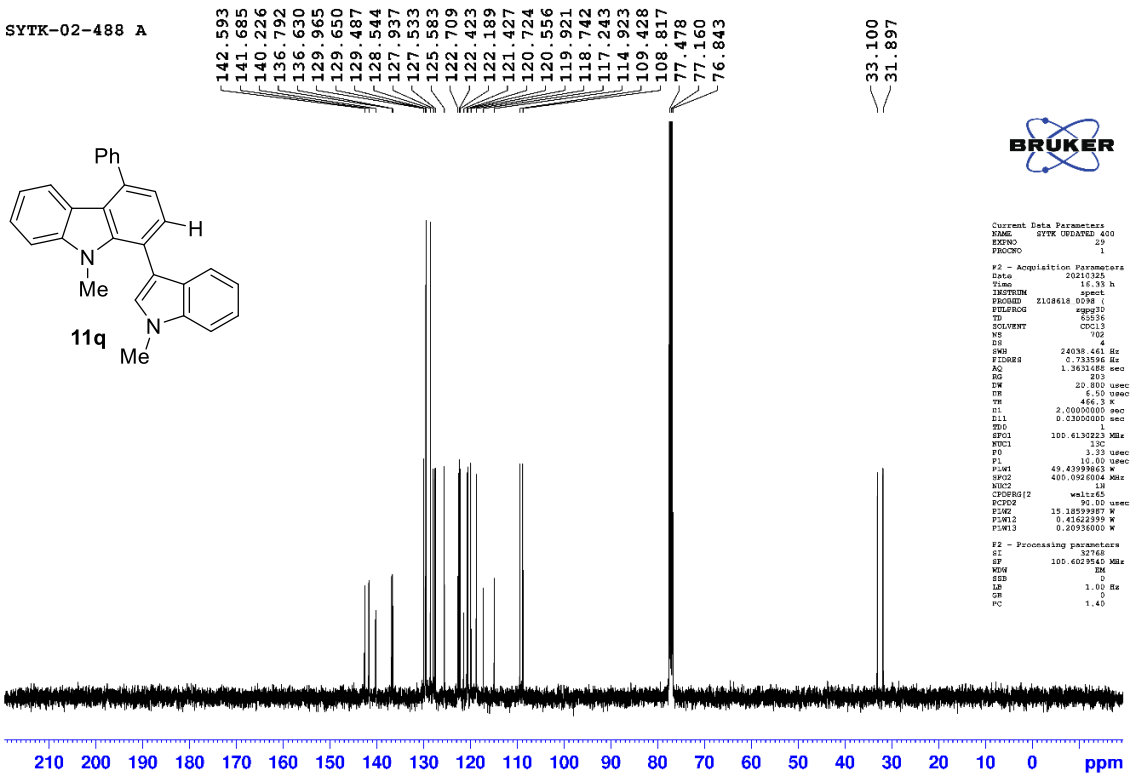
SYTK-9-9



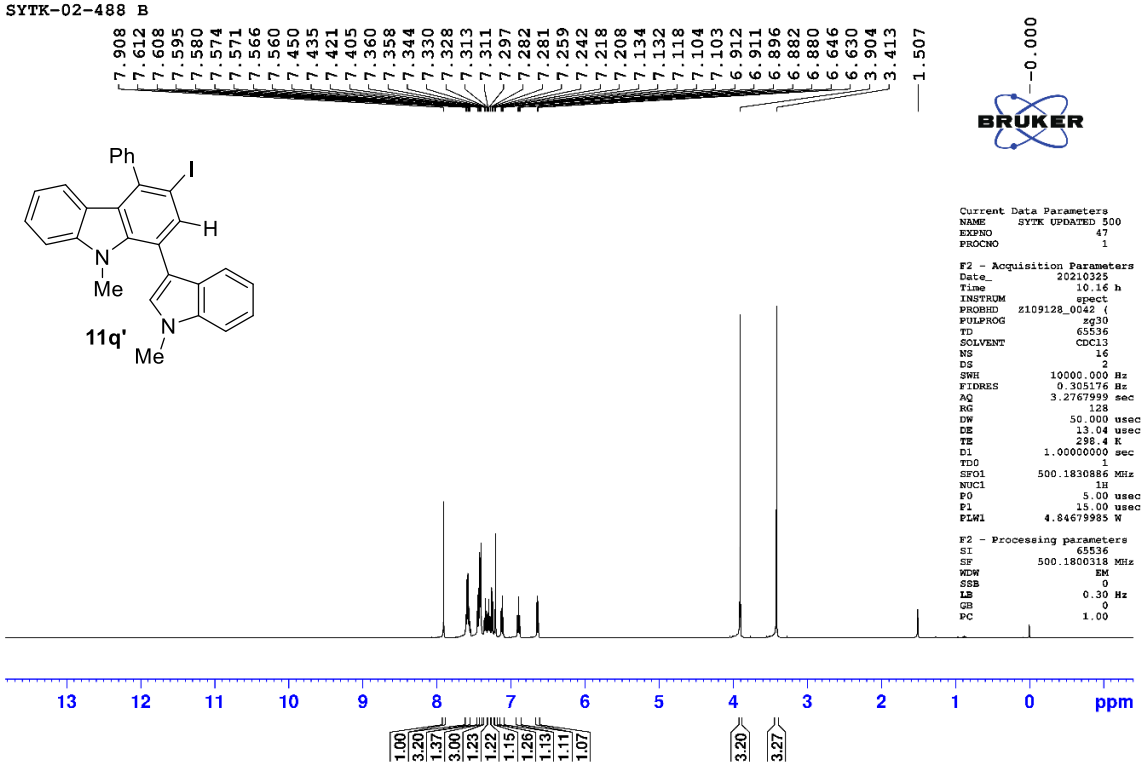
SYTK-02-488 A



SYTK-02-488 A



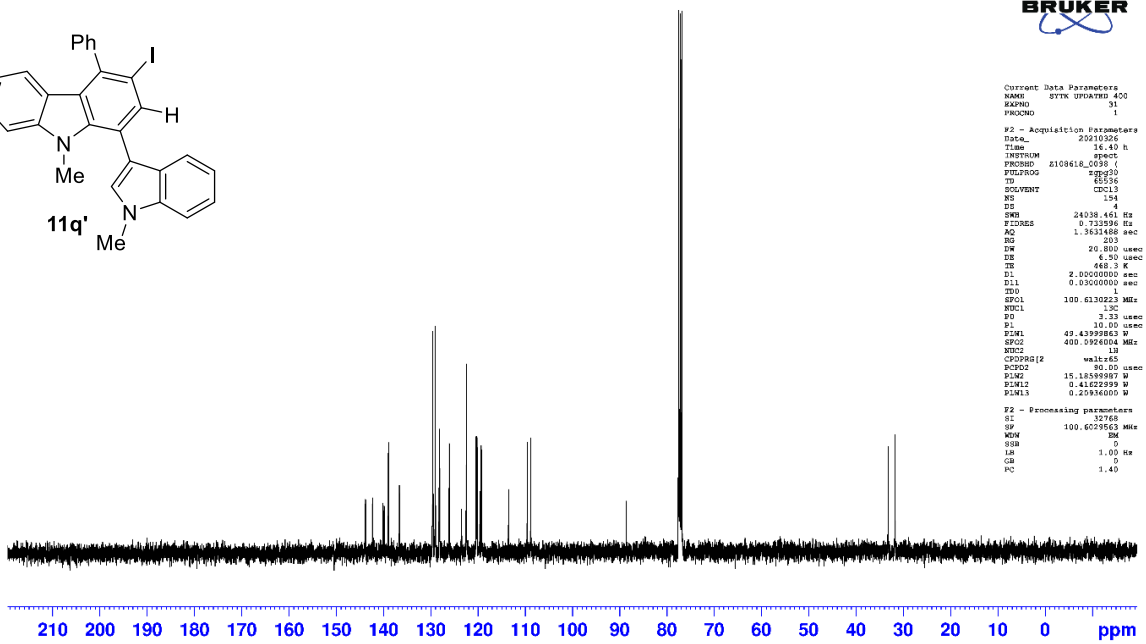
SYTK-02-488 B



SYTK-02-488 B

143.774
142.286
140.108
139.843
138.915
136.601
129.530
128.991
128.167
128.083
126.041
123.438
122.406
120.355
120.157
119.565
119.273
113.471
109.536
108.793
88.544
77.477
77.160
76.842
33.139
31.704

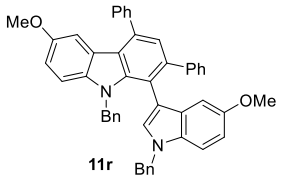
11q'



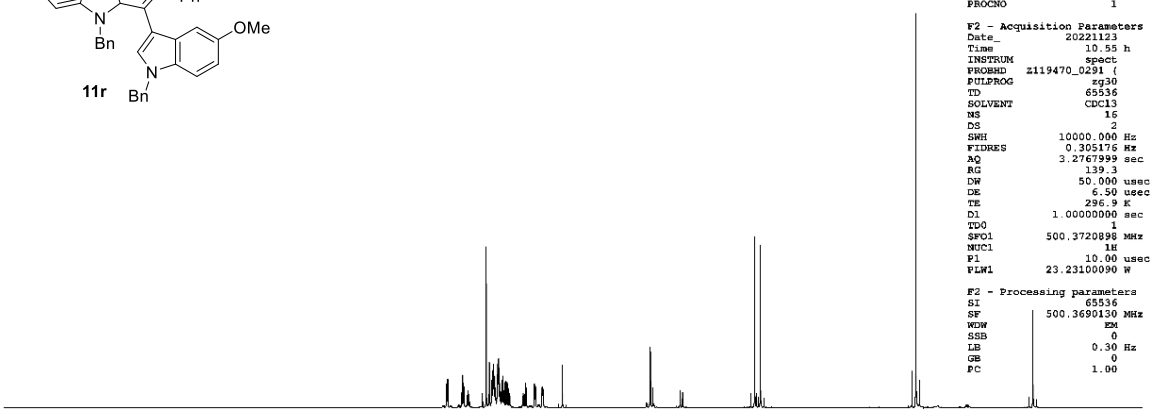


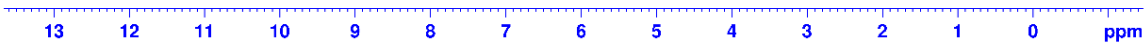
237-B

7.770
7.585
7.570
7.555
7.510
7.495
7.307
7.258
7.217
7.209
7.184
7.174
7.167
7.161
7.145
7.133
7.112
7.106
7.104
7.094
7.081
7.067
7.048
7.033
7.020
7.014
6.996
6.985
6.981
6.967
6.962
6.949
6.944
6.772
6.767
6.749
6.732
6.728
6.618
6.605
6.516
6.504
6.500
6.247
5.080
5.046
4.684
4.651
3.742
3.693
3.667
3.619
1.604
1.555
1.546
1.506
-0.000

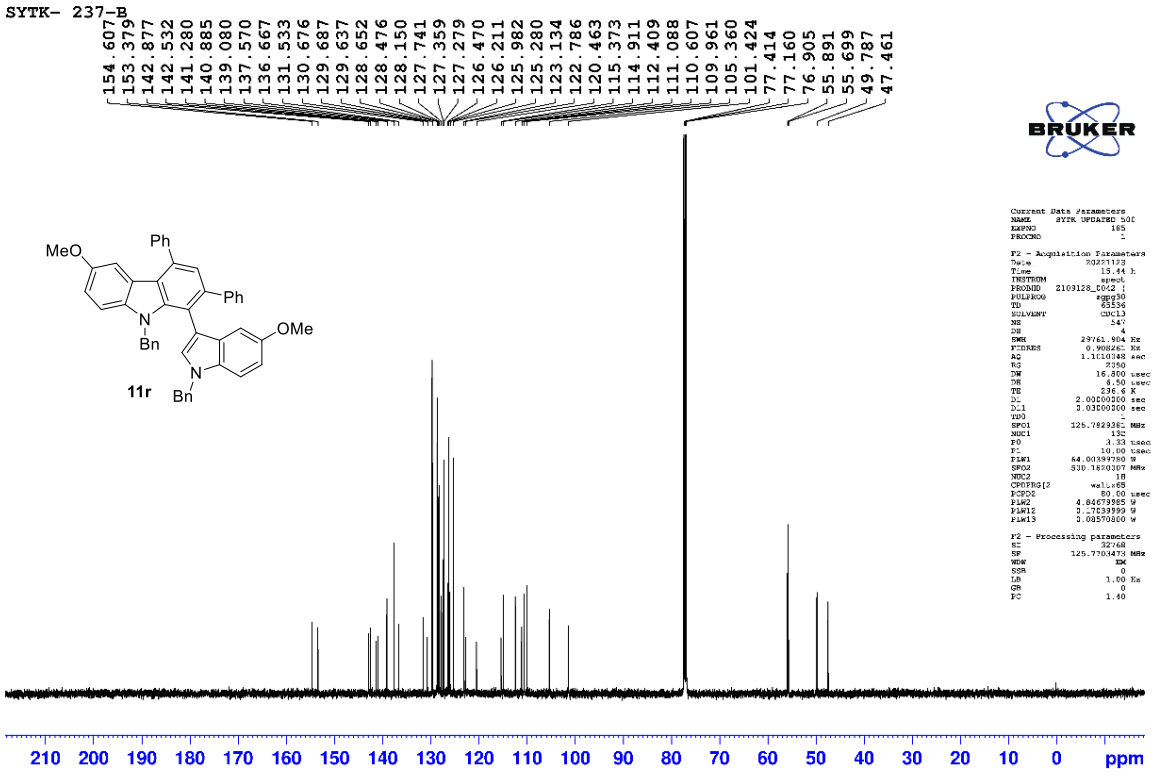


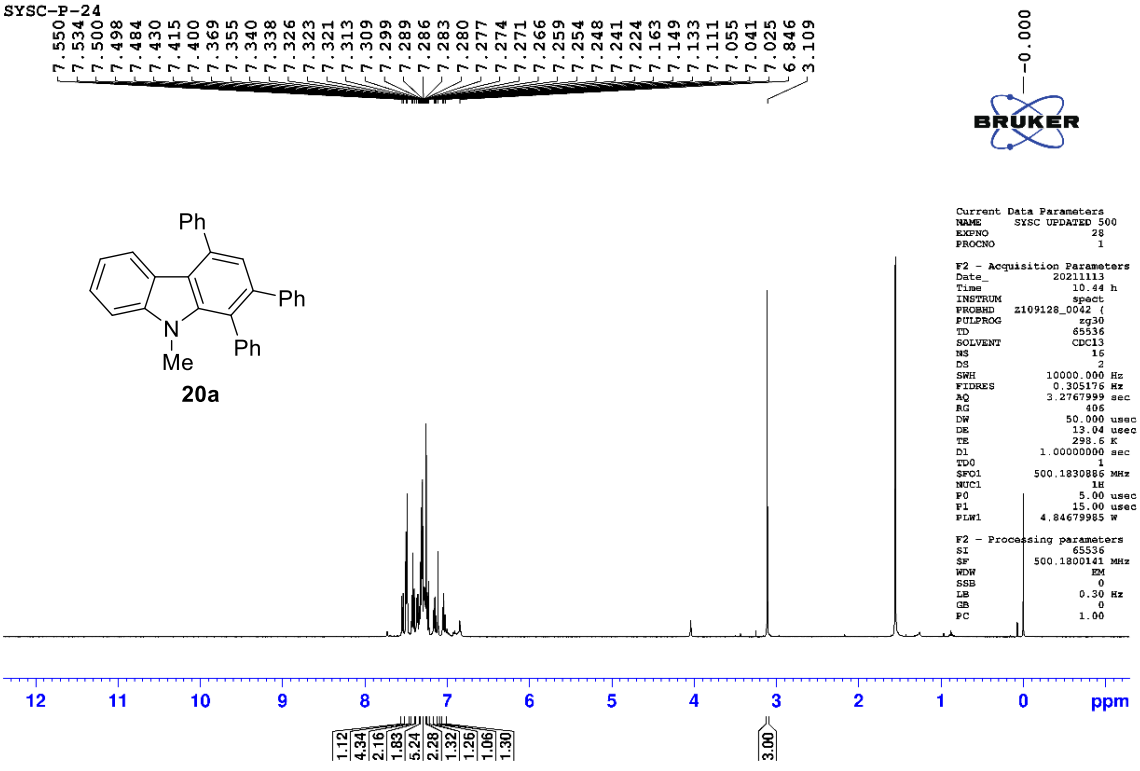
11r



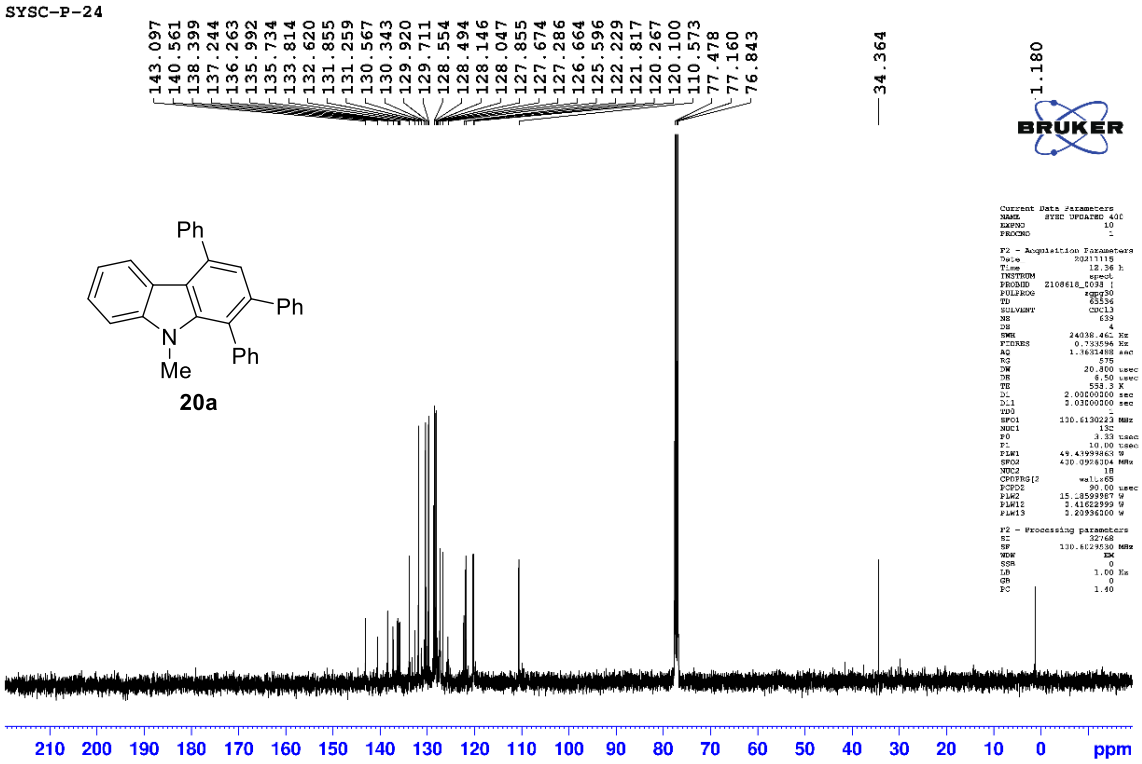




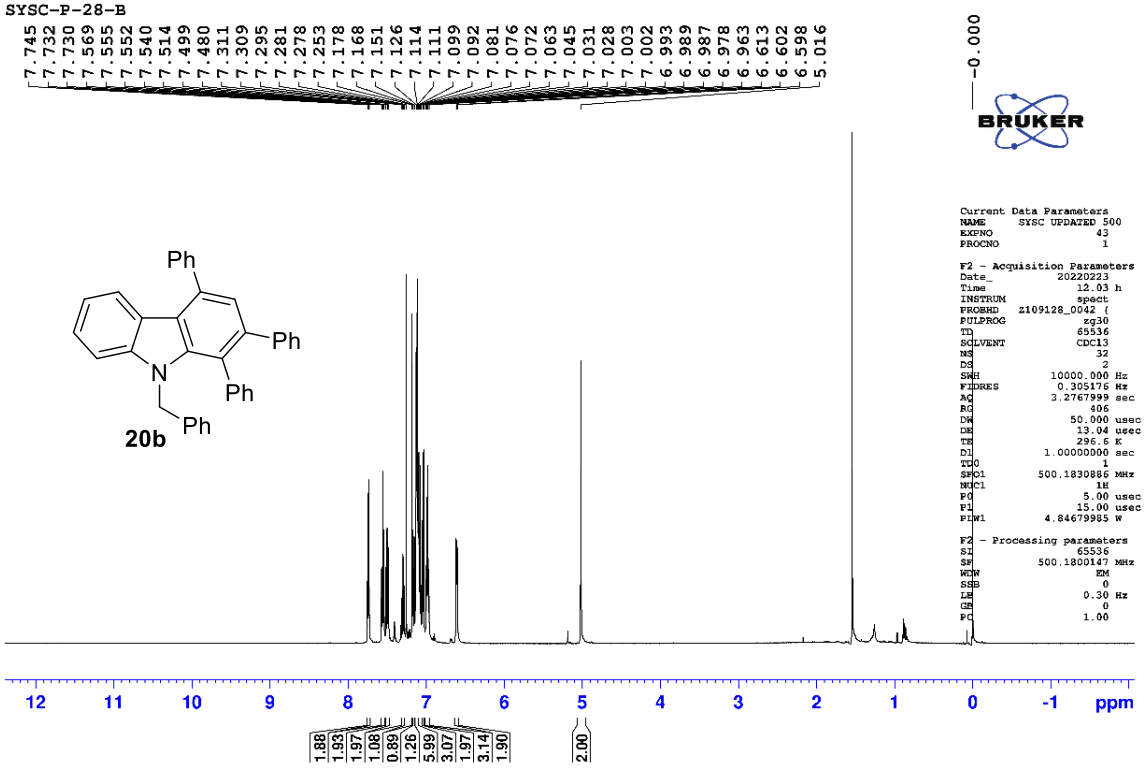

SYTK- 237-B
154.607
153.379
142.877
142.532
141.280
140.885
139.080
137.570
136.667
131.533
130.676
129.687
129.637
128.652
128.476
128.150
127.741
127.359
127.279
126.470
126.211
125.982
125.280
123.134
122.786
120.463
115.373
114.911
112.409
111.088
110.607
109.961
105.360
101.424
77.414
77.160
76.905
55.891
55.699
49.787
47.461
MeO
Ph
Ph
N
Bn
OMe
N
Bn
11r
BRUKER
Current Data Parameters
NAME SYTK UPDATED 500
EXPNO 185
PROCNO 1
F2 - Acquisition Parameters
Date_ 20201123
Time 15.44 h
INSTRUM spect
PROBHD Z109128_0042 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 547
DS 4
SWH 29761.904 Hz
FIDRES 0.908826 Hz
AQ 1.1010240 sec
RG 7350
DW 16.800 usec
DE 6.50 usec
TE 296.6 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 1
SFO1 125.7823961 MHz
NUC1 13C
P0 3.33 usec
P1 10.00 usec
PLW1 64.00397980 W
SFO2 500.1830307 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 80.00 usec
PLW2 4.84679985 W
PLW12 3.37539999 W
PLW13 2.08570800 W
F2 - Processing parameters
SI 32768
SF 125.7703473 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


SYSC-P-24
7.550
7.534
7.500
7.498
7.484
7.430
7.415
7.400
7.369
7.355
7.340
7.338
7.326
7.323
7.321
7.313
7.309
7.299
7.289
7.286
7.283
7.280
7.277
7.274
7.271
7.266
7.259
7.254
7.248
7.241
7.224
7.163
7.149
7.133
7.111
7.055
7.041
7.025
6.846
3.109
-0.000
Ph
Ph
N
Me
Ph
20a
BRUKER
Current Data Parameters
NAME SYSC UPDATED 500
EXPNO 28
PROCNO 1
F2 - Acquisition Parameters
Date_ 20211113
Time 10.44 h
INSTRUM spect
PROBHD Z109128_0042 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 406
DW 50.000 usec
DE 13.04 usec
TE 298.6 K
D1 1.00000000 sec
TD0 1
SFO1 500.1830886 MHz
NUC1 1H
P0 5.00 usec
P1 15.00 usec
PLW1 4.84679985 W
F2 - Processing parameters
SI 65536
SF 500.1800141 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
1.12
4.34
2.16
1.83
5.24
2.28
1.32
1.25
1.06
1.30
3.00

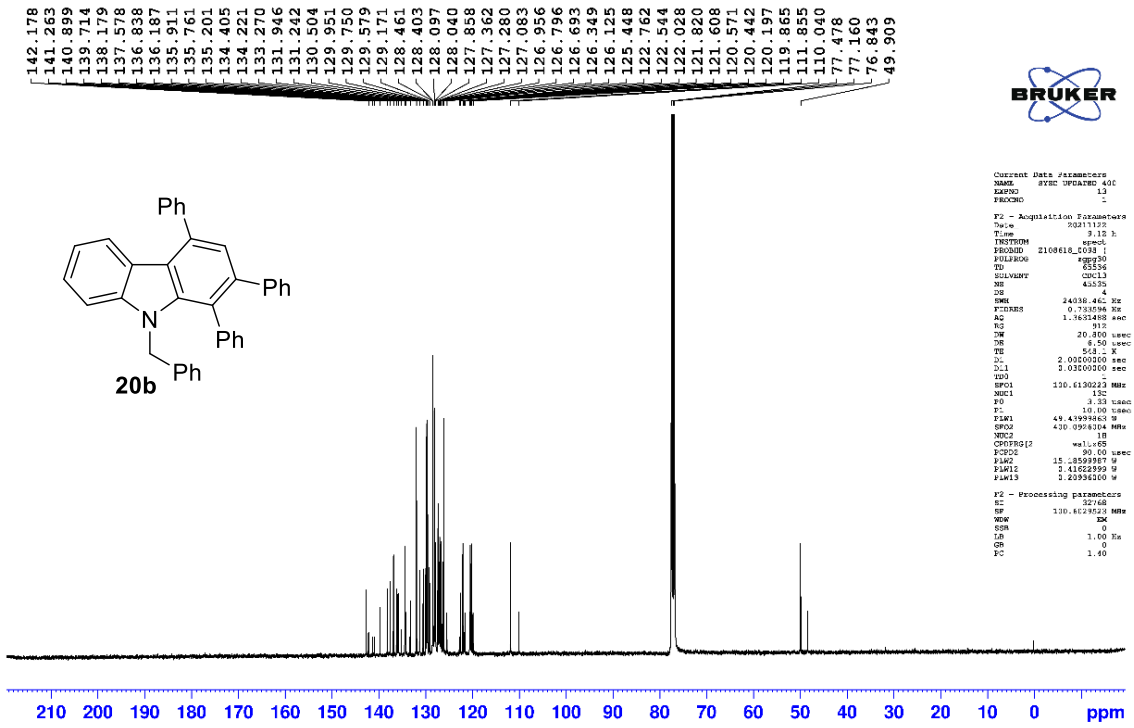
SYSC-P-24



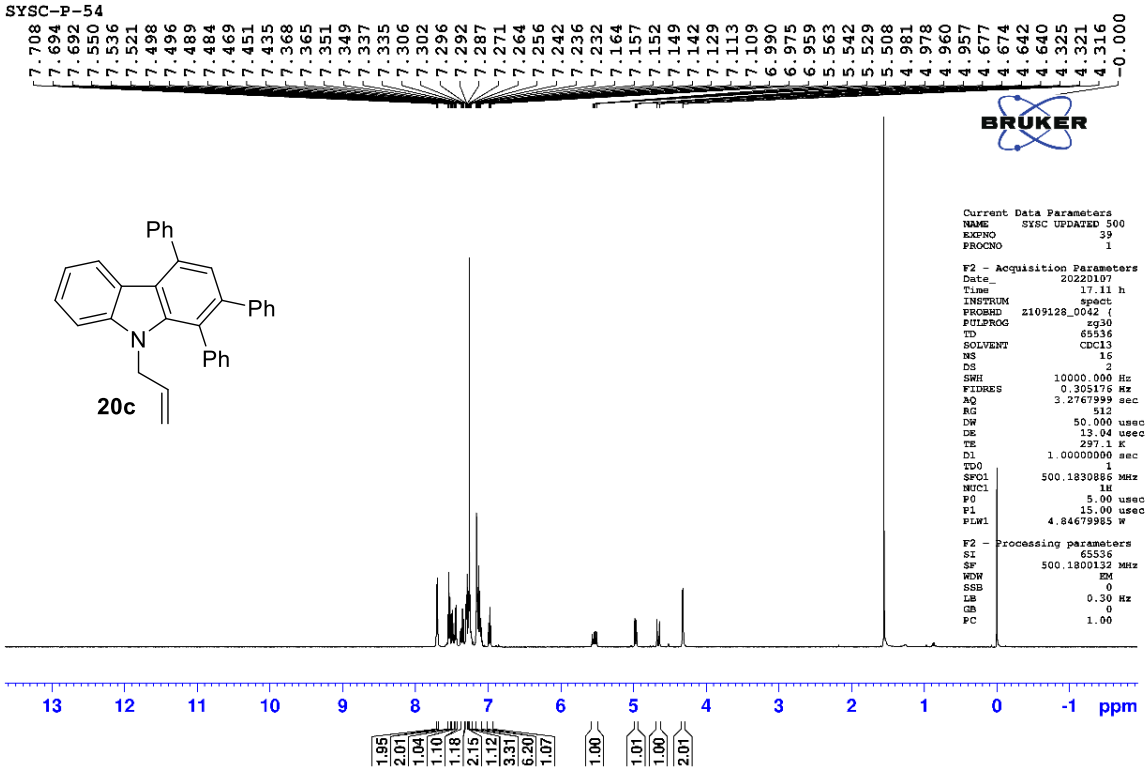
SYSC-P-28-B



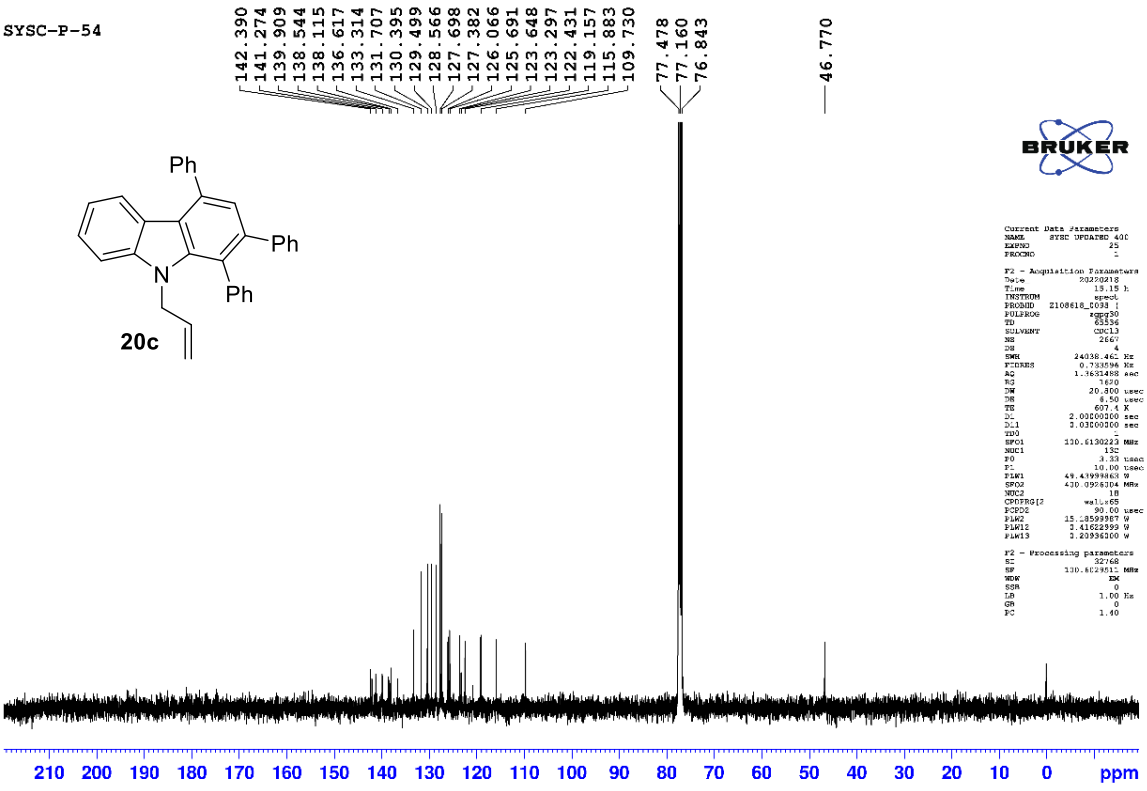
SYSC-P-28-overnight



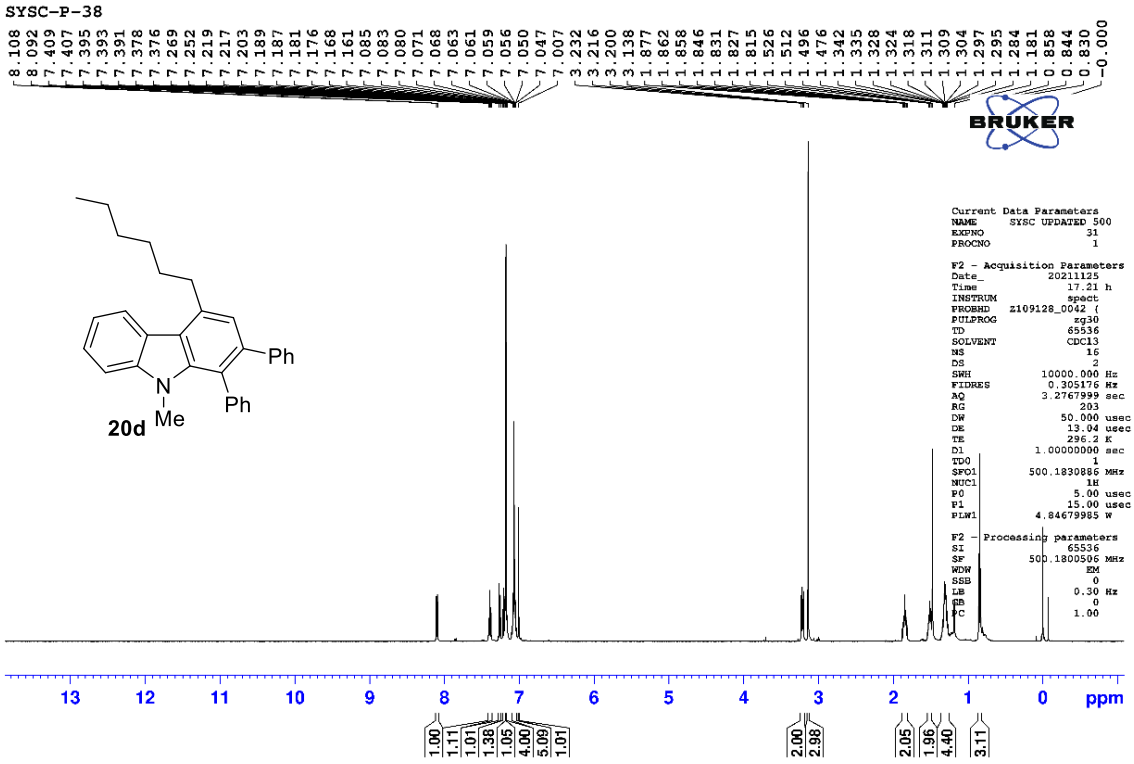
SYSC-P-54

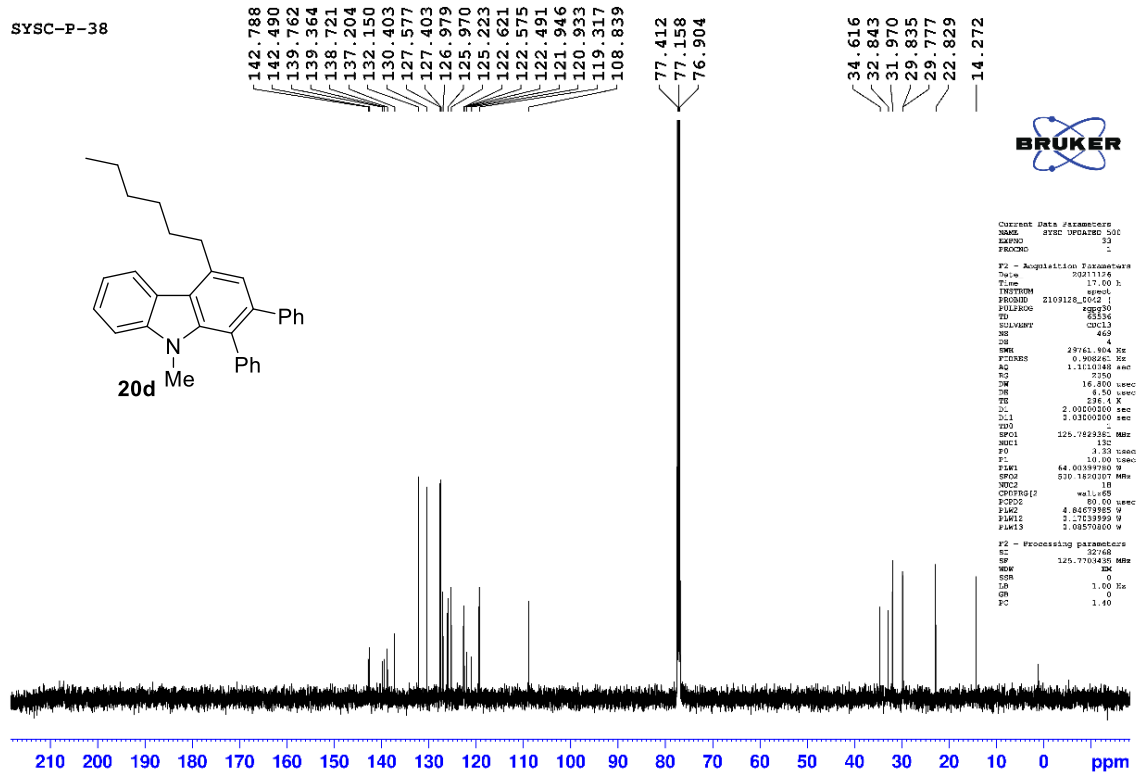


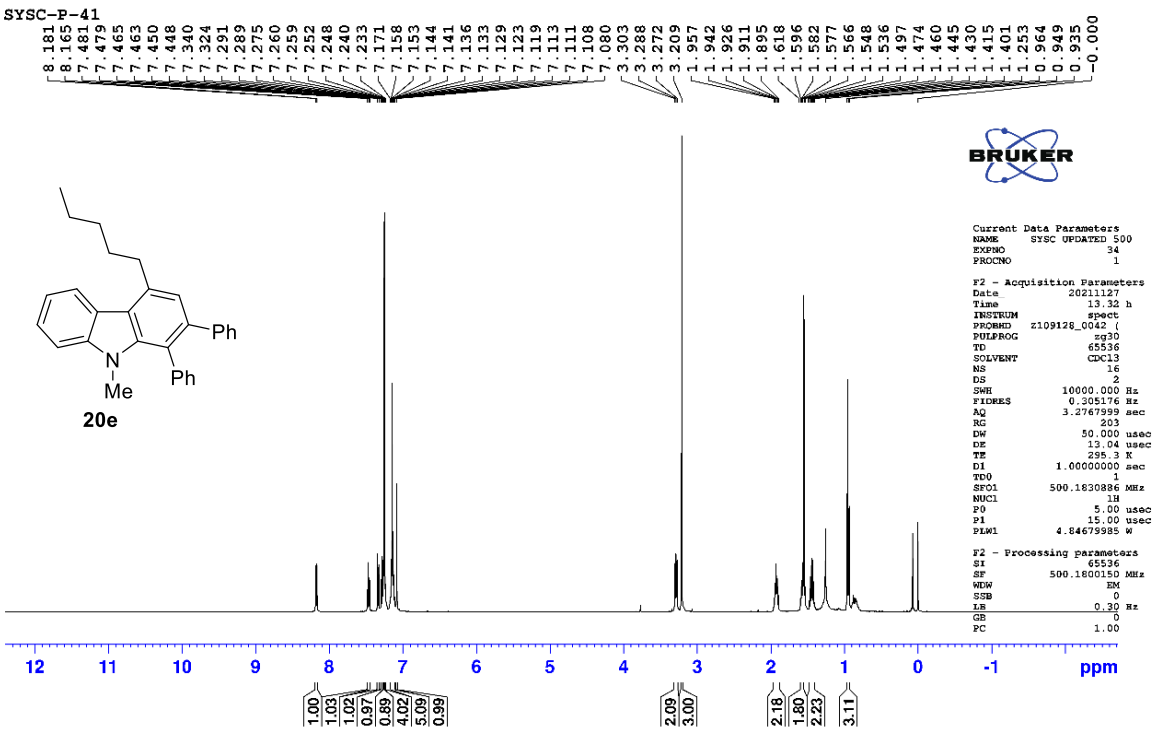
SYSC-P-54



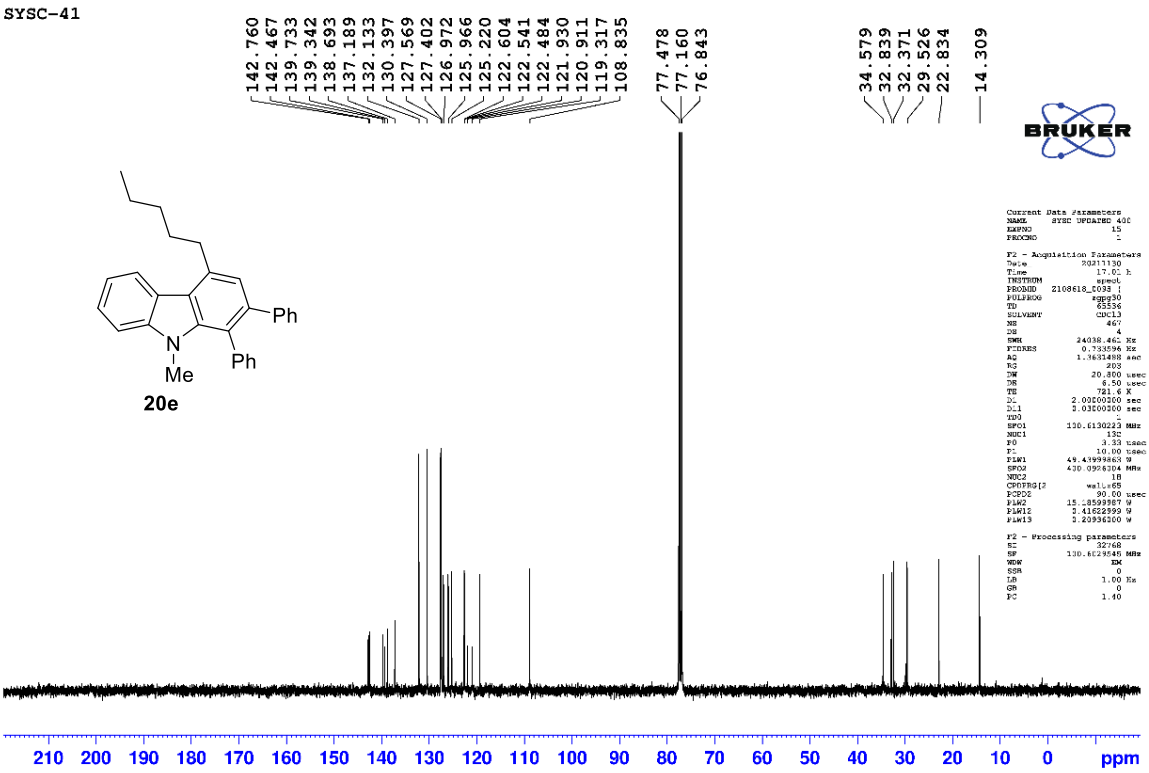
SYSC-P-38



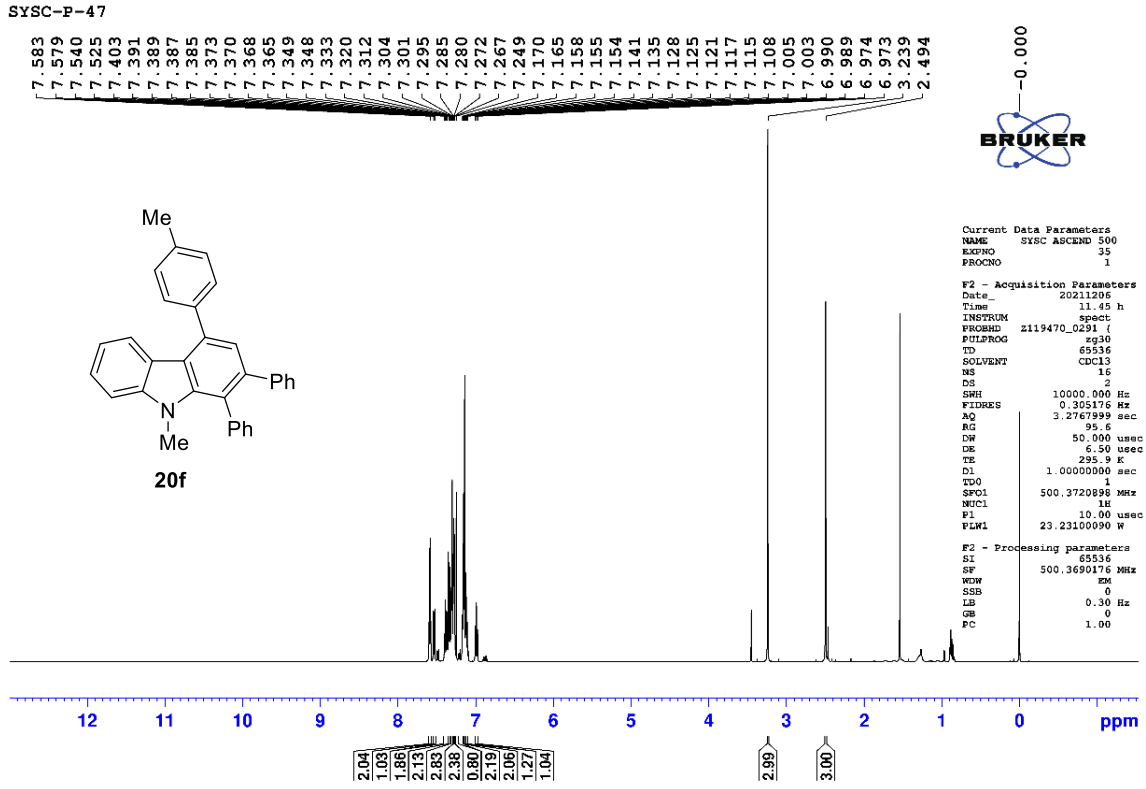

SYSC-P-38
142.788
142.490
139.762
139.364
138.721
137.204
132.150
130.403
127.577
127.403
126.979
125.970
125.223
122.621
122.575
122.491
121.946
120.933
119.317
108.839
77.412
77.158
76.904
34.616
32.843
31.970
29.835
29.777
22.829
14.272
Ph
N
Me
Ph
20d
BRUKER
Current Data Parameters
NAME SYSC UPDATED 500
EXPNO 33
PROCNO 1
F2 - Acquisition Parameters
Date 20211126
Time 17.00 h
INSTRUM spect
PROBHD Z109128_0042 (
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 469
DS 4
SWH 29761.904 Hz
FIDRES 0.908262 Hz
AQ 1.1010348 sec
RG 7150
DW 16.800 usec
DE 6.50 usec
TE 296.4 K
D1 2.00000000 sec
D11 0.03000000 sec
TD0 2
SFO1 125.7829385 MHz
NUC1 13C
P0 3.33 usec
P1 10.00 usec
PLW1 64.00399780 W
SFO2 500.1820007 MHz
NUC2 1H
CPDPRG[2 waltz65
PCPD2 80.00 usec
PLW2 4.84679985 W
PLW12 1.27539999 W
PLW13 1.08570000 W
F2 - Processing parameters
SI 32768
SF 125.7703435 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

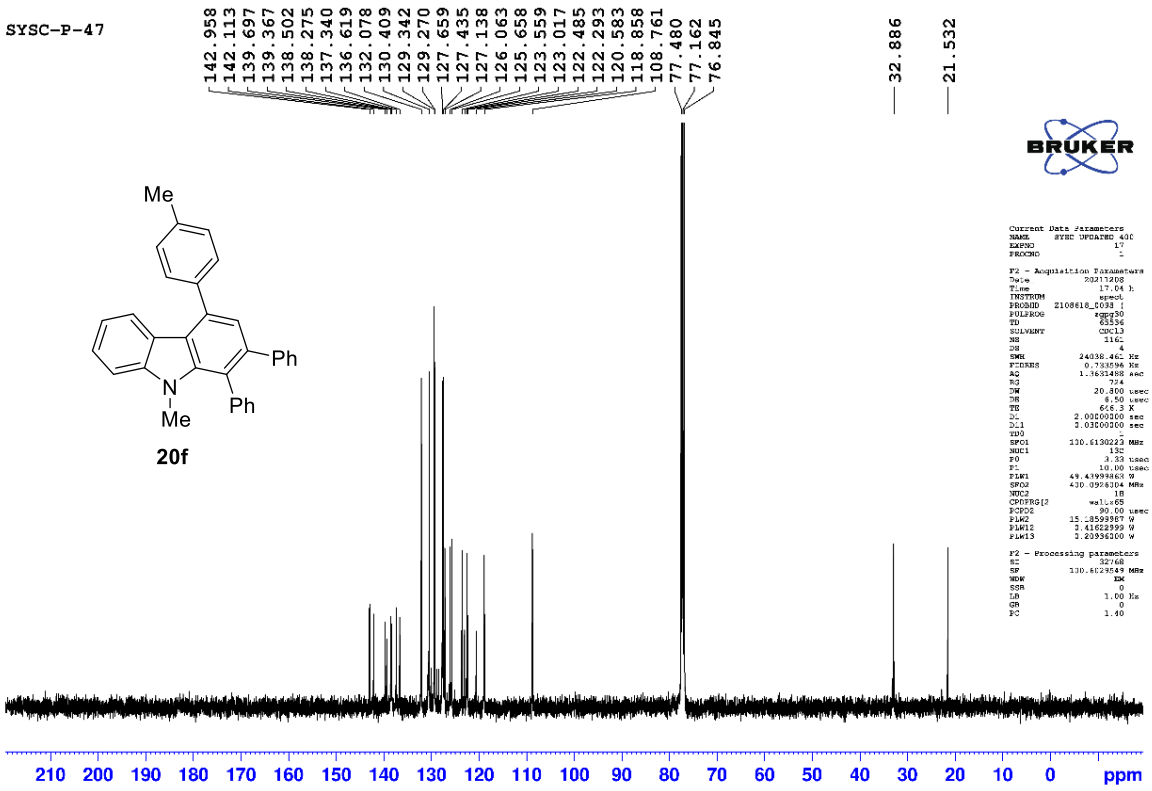

SYSC-P-41
8.181
8.165
7.481
7.479
7.465
7.463
7.450
7.448
7.340
7.324
7.291
7.289
7.275
7.260
7.259
7.252
7.248
7.240
7.233
7.171
7.158
7.153
7.144
7.141
7.136
7.133
7.129
7.123
7.119
7.113
7.111
7.108
7.080
3.303
3.288
3.272
3.209
1.957
1.942
1.926
1.911
1.895
1.618
1.596
1.582
1.577
1.566
1.548
1.536
1.497
1.474
1.460
1.445
1.430
1.415
1.401
1.253
0.964
0.949
0.935
-0.000
Ph
N
Me
Ph
20e
BRUKER
Current Data Parameters
NAME SYSC UPDATED 500
EXPNO 34
PROCNO 1
F2 - Acquisition Parameters
Date 20211127
Time 13.32 h
INSTRUM spect
PROBHD Z109128_0042 (
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 10000.000 Hz
FIDRES 0.305176 Hz
AQ 3.2767999 sec
RG 203
DW 50.000 usec
DE 13.04 usec
TE 295.3 K
D1 1.00000000 sec
TD0 1
SFO1 500.1830886 MHz
NUC1 1H
P0 5.00 usec
P1 15.00 usec
PLW1 4.84679985 W
F2 - Processing parameters
SI 65536
SF 500.1800150 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
12 11 10 9 8 7 6 5 4 3 2 1 0 -1 ppm
1.00
1.03
1.02
0.97
0.89
4.02
5.09
0.99
2.09
3.00
2.18
1.80
2.23
3.11

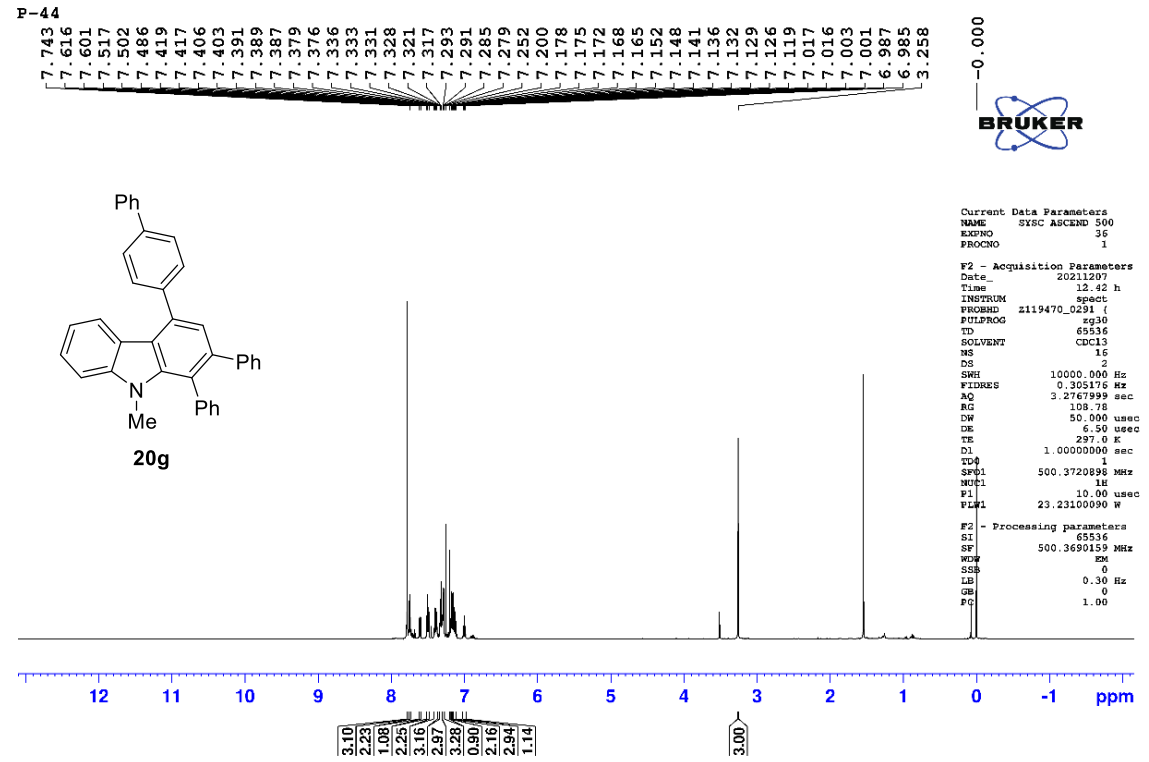
SYSC-41



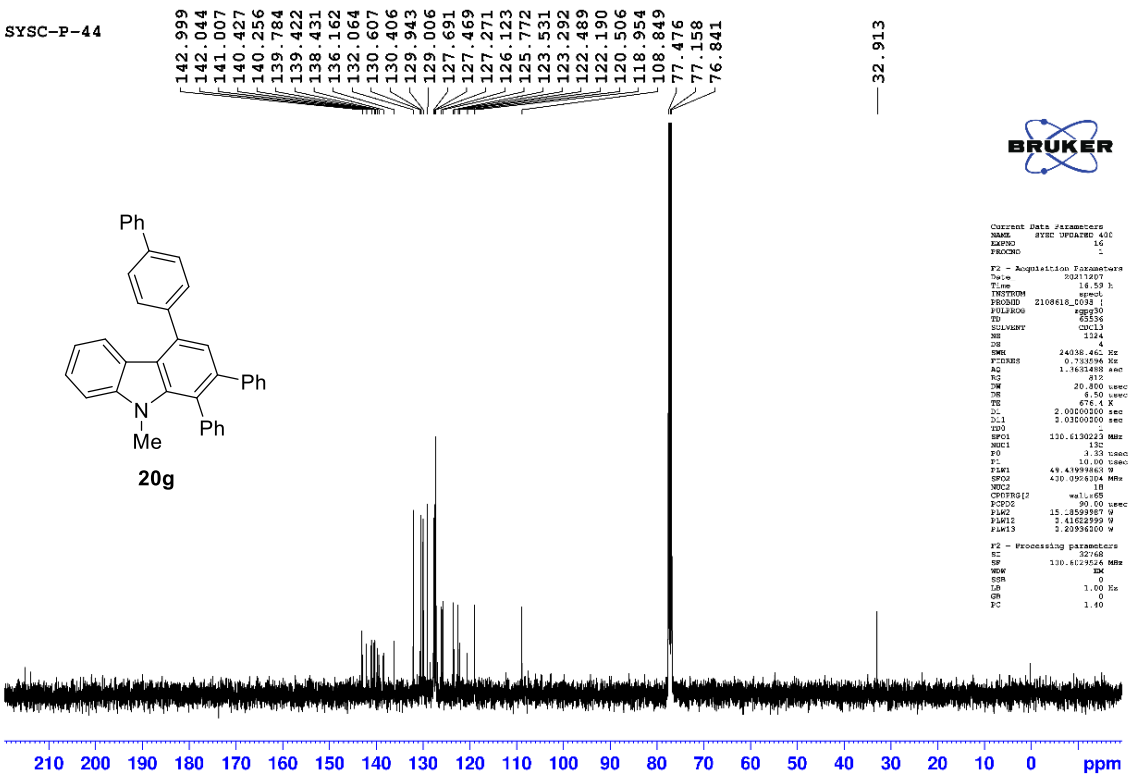
SYSC-P-47




SYSC-P-47
142.958
142.113
139.697
139.367
138.502
138.275
137.340
136.619
132.078
130.409
129.342
129.270
127.659
127.435
127.138
126.063
125.658
123.559
123.017
122.485
122.293
120.583
118.858
108.761
77.480
77.162
76.845
32.886
21.532
Me
Ph
N
Me
Ph
20f
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

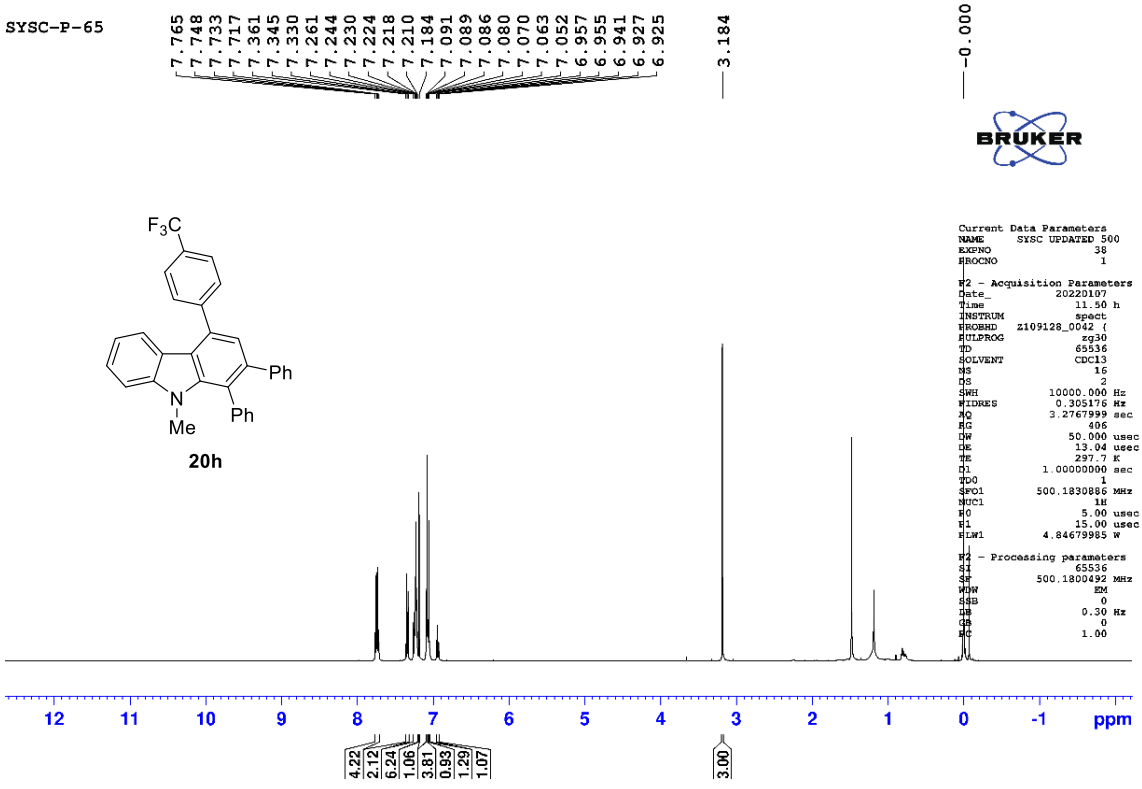

P-44
7.743
7.616
7.601
7.517
7.502
7.486
7.419
7.417
7.406
7.403
7.391
7.389
7.387
7.379
7.376
7.336
7.333
7.331
7.328
7.321
7.317
7.293
7.291
7.285
7.279
7.252
7.200
7.178
7.175
7.172
7.168
7.165
7.152
7.148
7.141
7.136
7.132
7.129
7.126
7.119
7.017
7.016
7.003
7.001
6.987
6.985
3.258
0.000
Ph
Ph
N
Me
Ph
20g
12 11 10 9 8 7 6 5 4 3 2 1 0 -1 ppm
3.10
2.23
1.08
2.25
3.16
2.97
3.28
0.90
2.16
2.94
1.14
3.00

SYSC-P-44



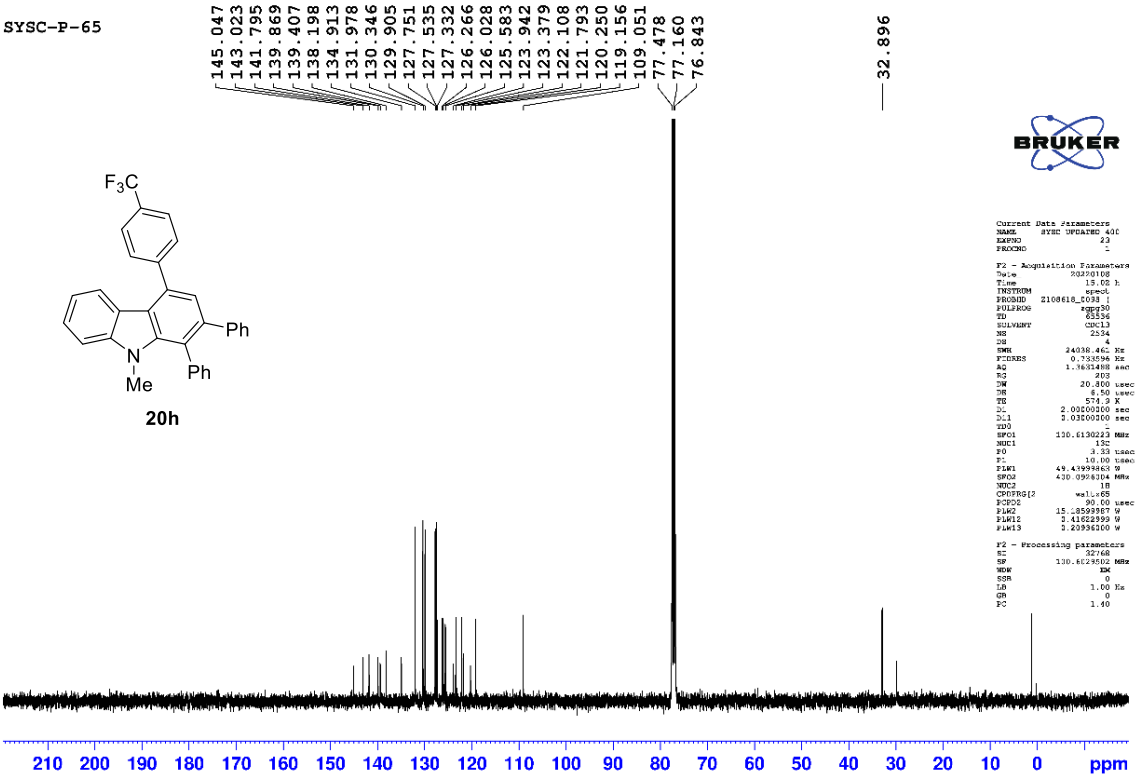
20g

SYSC-P-65

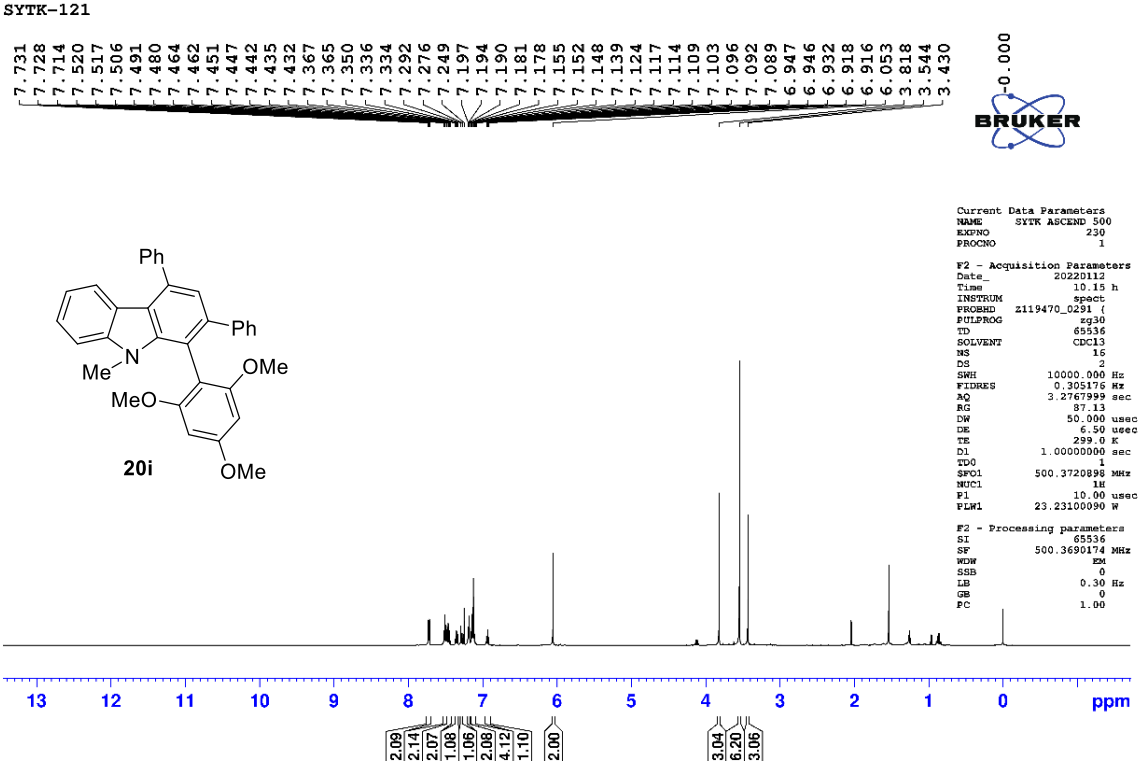


20h

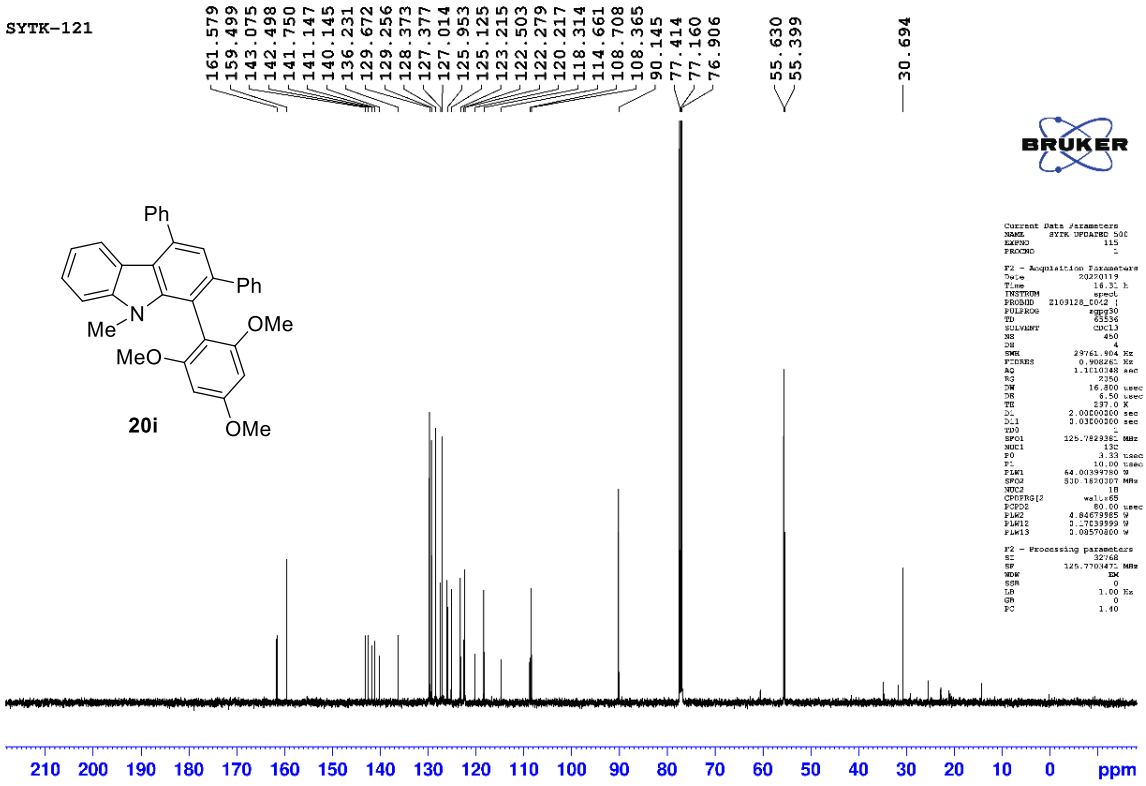
SYSC-P-65



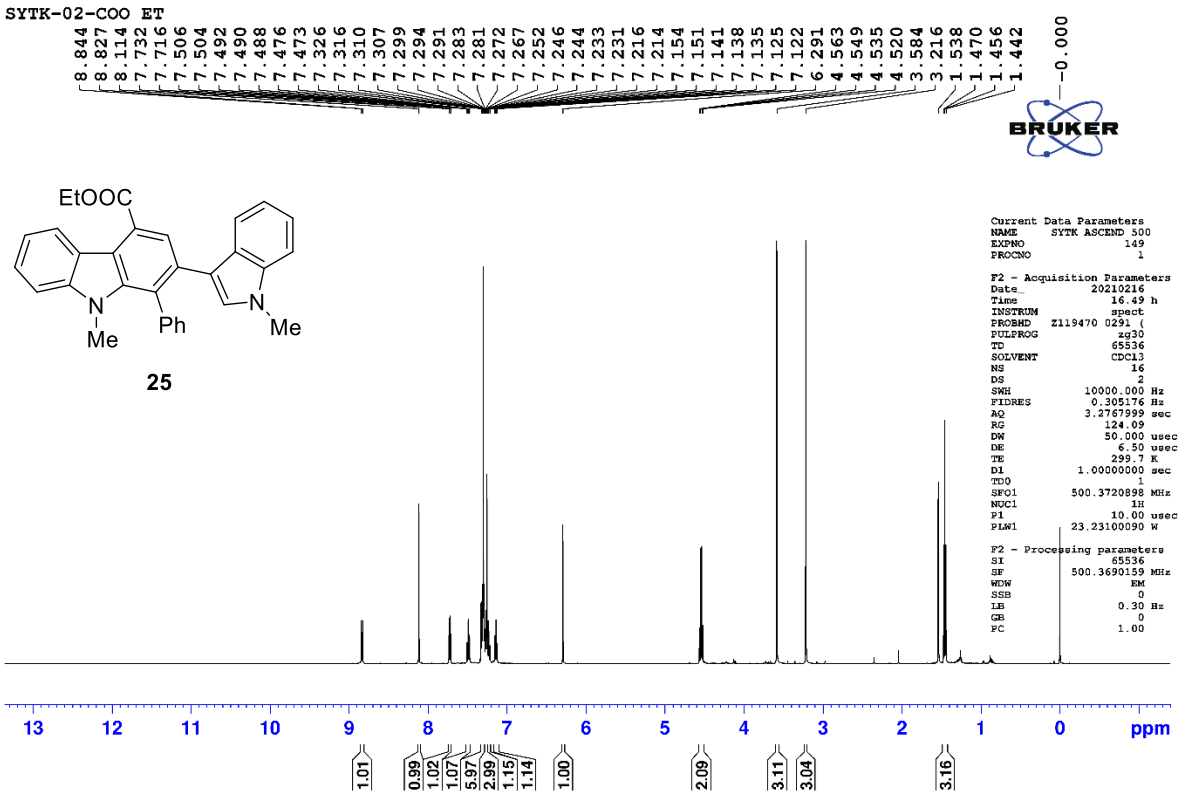
SYTK-121

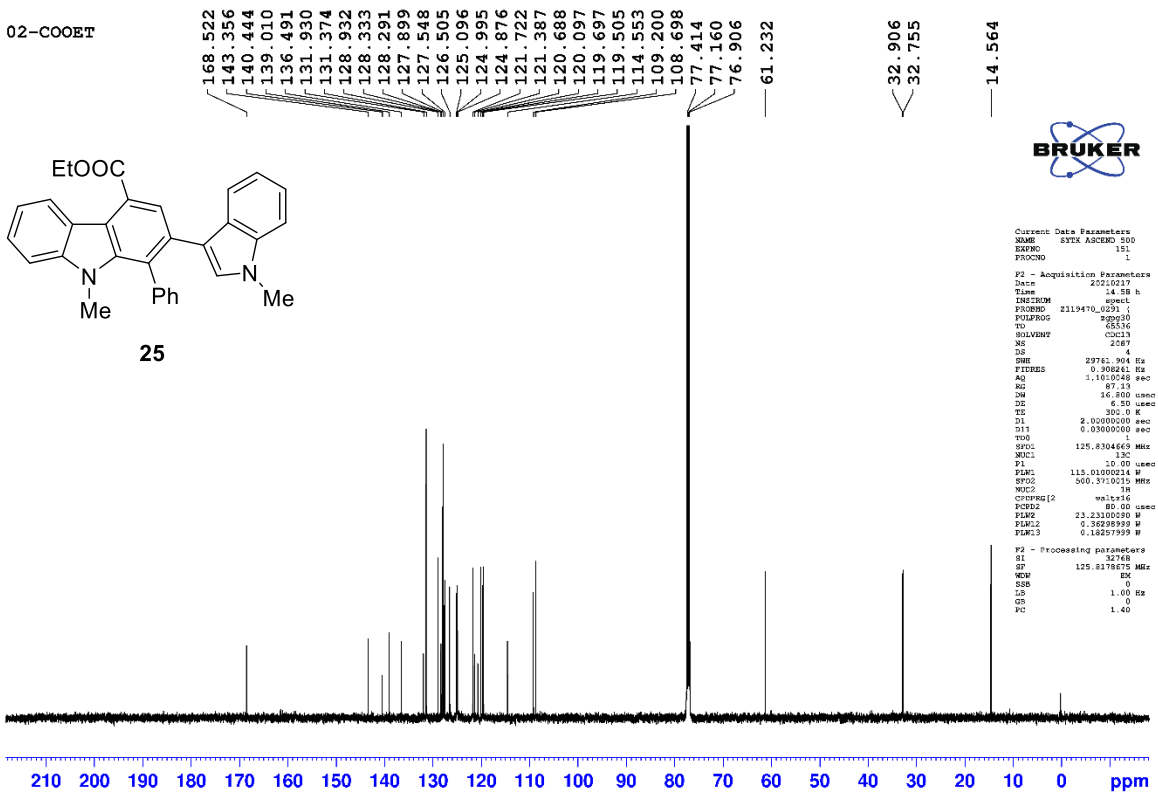


SYTK-121



SYTK-02-COO ET





4.5. References

1. (a) Kapil, R. S. In The Alkaloids; Manske, R. H. F., Ed.; Academic Press: New York, **1971**, *13*, 273. (b) Knölker, H.J.; Reddy, K.R. Isolation and synthesis of biologically active carbazole alkaloids. *Chem. Rev.*, **2002**, *102*, 4303-4428. (c) Knölker, H.J.; Reddy, K.R., Biological and pharmacological activities of carbazole alkaloids. *The alkaloids: chemistry and biology*, **2008**, *65*, 181-193. (d) Schmidt, A.W.; Reddy, K.R.; Knölker, H.J. Occurrence, biogenesis, and synthesis of biologically active carbazole alkaloids. *Chem. Rev.*, **2012**, *112*, 3193-3328.
2. (a) Maneerat, W.; Ritthiwigrom, T.; Cheenpracha, S.; Promgool, T.; Yossathera, K.; Deachathai, S.; Phakhodee, W.; Laphookhieo, S. Bioactive carbazole alkaloids from Clausena wallichii roots. *J. Nat. Prod.*, **2012**, *75*, 741-746. (b) Głuszyńska, A. Biological potential of carbazole derivatives. *Eur. J. Med. Chem.*, **2015**, *94*, 405-426. (c) Kumar, S. A brief review of the biological potential of indole derivatives. *Future J. Pharm.Sci.*, **2020**, *6*, 1-19.
3. Chakraborty, D.P.; Barman, B.K.; Bose, P.K. On the constitution of murrayanine, a carbazole derivative isolated from Murraya koenigii Spreng. *Tetrahedron*, **1965**, *21*, 681-685.
4. Reisch, J.; Goj, O.; Wickramasinghe, A.; Herath, H.B.; Henkel, G. Carbazole alkaloids from seeds of Murraya koenigii. *Phytochemistry*, **1992**, *31*, 2877-2879.
5. (a) Das, K.C.; Chakraborty, D.P.; Bose, P.K. Antifungal activity of some constituents of Murraya koeningii Spreng. *Experientia*, **1965**, *21*, 340. (b) Nandy, B.C.; Gupta, A.K.; Mittal, A.; Vyas, V. Carbazole: It's biological activity. *J. Biomed. Pharm. Res.*, **2014**, *3*, 42-48. (c) Bashir, M.; Bano, A.; Ijaz, A.S.; Chaudhary, B.A. Recent developments and biological activities of N-substituted carbazole derivatives: a review. *Molecules*, **2015**, *20*, 13496-13517.

6. (a) Justin, T.K.R.; Lin, J.T.; Tao, Y.T.; Ko, C.W. Light-emitting carbazole derivatives: potential electroluminescent materials. *J. Am. Chem. Soc.*, **2001**, *123*, 9404-9411. (b) Huang, J.; Niu, Y.; Yang, W.; Mo, Y.; Yuan, M.; Cao, Y. Novel electroluminescent polymers derived from carbazole and benzothiadiazole. *Macromolecules*, **2002**, *35*, 6080-6082.
7. Häussler, M.; Liu, J.; Zheng, R.; Lam, J.W.Y.; Qin, A.; Tang, B.Z. Synthesis, thermal stability, and linear and nonlinear optical properties of hyperbranched polyarylenes containing carbazole and/or fluorene moieties. *Macromolecules*, **2007**, *40*, 1914-1925.
8. (a) Sanda, F.; Nakai, T.; Kobayashi, N.; Masuda, T. Synthesis of polyacetylenes having pendant carbazole groups and their photo and electroluminescence properties. *Macromolecules*, **2004**, *37*, 2703-2708. (b) van Dijken, A.; Bastiaansen, J.J.; Kiggen, N.M.; Langeveld, B.M.; Rothe, C.; Monkman, A.; Bach, I.; Stössel, P.; Brunner, K. Carbazole compounds as host materials for triplet emitters in organic light-emitting diodes: polymer hosts for high-efficiency light-emitting diodes. *J. Am. Chem. Soc.*, **2004**, *126*, 7718-7727. (c) Adhikari, R.M.; Neckers, D.C.; Shah, B.K. Photophysical study of blue, green, and orange-red light-emitting carbazoles. *J. Org. Chem.* **2009**, *74*, 3341-3349.
9. Ito, C.; Itoigawa, M.; Sato, A.; Hasan, C.M.; Rashid, M.A.; Tokuda, H.; Mukainaka, T.; Nishino, H.; Furukawa, H. Chemical Constituents of Glycosmis arborea: Three New Carbazole Alkaloids and Their Biological Activity. *J. Nat. Prod.*, **2004**, *67*, 1488-1491.
10. (a) Knölker, H.J. Synthesis of biologically active carbazole alkaloids using selective transition-metal-catalyzed coupling reactions. *Chem. Lett.*, **2009**, *38*, 8-13. (b) Roy, J.; Jana, A.K.; Mal, D. Recent trends in the synthesis of carbazoles: an update. *Tetrahedron*, **2012**, *68*, 6099-6121. (c) Bauer, I.; Knölker, H.J. Synthesis of pyrrole and carbazole alkaloids. *Alkaloid synthesis*, **2012**, 203-253. (d) Aggarwal, T.; Verma, A.K., Recent advances in the synthesis of carbazoles from indoles. *Org. Biomol. Chem.*, **2019**, *17*, 8330-8342.
11. (a) TePaske, M.R.; Gloer, J.B.; Wicklow, D.T.; Dowd, P.F. The structure of tubingensin B: a cytotoxic carbazole alkaloid from the sclerotia of Aspergillus tubingensis. *Tetrahedron Lett.*, **1989**, *30*, 5965-5968. (b) TePaske, M.R.; Gloer, J.B.; Wicklow, D.T.; Dowd, P.F. Tubingensin A: an antiviral carbazole alkaloid from the sclerotia of Aspergillus tubingensis. *J. Org. Chem.*, **1989**, *54*, 4743-4746. (c) Choi, T.A.; Czerwonka, R.; Fröhner, W.; Krahl, M.P.; Reddy, K.R.; Franzblau, S.G.; Knölker, H.J. Synthesis and activity of carbazole derivatives against Mycobacterium tuberculosis. *ChemMedChem: Chemistry Enabling Drug Discovery*, **2006**, *1*, 812-815. (d) Wang, Y.Q.; Li, X.H.; He, Q.; Chen, Y.; Xie, Y.Y.; Ding, J.; Miao, Z.H.; Yang, C.H. Design, synthesis, and biological evaluation of substituted 11H-benzo [a] carbazole-5-carboxamides as novel antitumor agents. *Eur. J. Med. Chem.*, **2011**, *46*, 5878-5884. (e) Zhu, D.; Chen, M.; Li, M.; Luo, B.; Zhao, Y.; Huang, P.; Xue, F.; Rapposelli, S.; Pi, R.; Wen, S. Discovery of novel N-substituted carbazoles as neuroprotective agents with potent anti-oxidative activity. *Eur. J. Med. Chem.*, **2013**, *68*, 81-88. (f) Börger, C.; Brütting, C.; Julich-Gruner, K.K.; Hesse, R.; Kumar, V.P.; Kutz, S.K.; Rönnefahrt, M.; Thomas, C.; Wan, B.; Franzblau, S.G.; Knölker, H.J. Anti-tuberculosis activity and structure activity relationships of oxygenated tricyclic carbazole alkaloids and synthetic derivatives. *Bio. Med. Chem.*, **2017**, *25*, 6167-6174. (g) You, X.; Zhu, D.; Lu, W.; Sun, Y.; Qiao, S.; Luo, B.; Du, Y.; Pi, R.; Hu, Y.; Huang, P.; Wen, S. Design, synthesis, and biological evaluation of N-arylsulfonyl carbazoles as novel anticancer agents. *RSC Adv.*, **2018**, *8*, 17183-17190.

12. Fox, S.M.; Johnston, S.A. Use of carprofen for the treatment of pain and inflammation in dogs. *J. Am. Vet. Med. Assoc.*, **1997**, *210*, 1493-1498.
13. Levis, M. Midostaurin approved for FLT3-mutated AML. *Blood*, **2017**, *129*, 3403-3406.
14. (a) Chakraborty, A.; Chowdhury, B.K.; Bhattacharyya, P. Clausenol and clausenine two carbazole alkaloids from Clausena anisata. *Phytochemistry*, **1995**, *40*, 295-298. (b) Zhang, A.; Lin, G. The first synthesis of clausenamine-A and cytotoxic activities of three biscarbazole analogues against cancer cells. *Bioorganic Med. Chem. Lett.*, **2000**, *10*, 1021-1023. (c) Kataeva, O.; Krahl, M.P.; Knölker, H.J., First total synthesis of the biologically active 2, 7-dioxygenated tricyclic carbazole alkaloids 7-methoxy-O-methylmukonal, clausine H (clauszoline-C), clausine K (clauszoline-J) and clausine O. *Org. Biomol. Chem.*, **2005**, *3*, 3099-3101. (d) Huang, L.; Zhe-Ling, F.E.N.G.; Yi-Tao, W.A.N.G.; Li-Gen, L.I.N. Anticancer carbazole alkaloids and coumarins from Clausena plants: A review. *Chin. J. Nat. Med.*, **2017**, *15*, 881-888.
15. Pieper, A.A.; McKnight, S.L.; Ready, J.M. P7C3 and an unbiased approach to drug discovery for neurodegenerative diseases. *Chem. Soc. Rev.*, **2014**, *43*, 6716-6726.
16. (a) Börger, C.; Kataeva, O.; Knölker, H.J. Novel approach to biscarbazole alkaloids *via* Ullmann coupling-synthesis of murrastifoline-A and bismurrayafoline-A. *Org. Biomol. Chem.*, **2012**, *10*, 7269-7273. (b) Börger, C.; Krahl, M.P.; Gruner, M.; Kataeva, O.; Knölker, H.J. First total synthesis of the biscarbazole alkaloid oxydimurrayafoline. *Org. Biomol. Chem.*, **2012**, *10*, 5189-5193. (c) Börger, C.; Knölker, H.J. Transition metals in organic synthesis. Part 101: Convergent total synthesis of 1, 6-dioxygenated carbazole alkaloids. *Tetrahedron*, **2012**, *68*, 6727-6736.
17. (a) Roy, J.; Jana, A.K.; Mal, D. Recent trends in the synthesis of carbazoles: an update. *Tetrahedron*, **2012**, *68*, 6099-6121. (b) Georgiade, S. N.; Nicolaou, P. G. Advances in Heterocyclic Chemistry, ed. E. Scriven and C. Ramsden, Elsevier, 1st edn, **2019**, ch. 1, *129*, 6-42. (c) Tian, X.; Song, L.; Hashmi, A.S.K. Synthesis of carbazoles and related heterocycles from sulfilimines by intramolecular C-H aminations. *Angew. Chem., Int. Ed.*, **2020**, *59*, 12342-12346.
18. Miller, R.B.; Dugar, S. A regiospecific total synthesis of ellipticine *via* nitrene insertion. *Tetrahedron lett.* **1989**, *30*, 297-300.
19. Robinson, B. The Fischer Indole Synthesis. *Chem. Rev.*, **1963**, *63*, 373-401.
20. Barrera, E.; Hernández-Benitez, R.I.; González-González, C.A.; Escalante, C.H.; Fuentes-Benítes, A.; González-Romero, C.; Becerra-Martínez, E.; Delgado, F.; Tamariz, J. Synthesis of diarylamines and methyl carbazoles and formal total synthesis of alkaloids ellipticine and olivacine. *Eur. J. Org. Chem.*, **2022**, e202200364.
21. Naykode, M.S.; Humne, V.T.; Lokhande, P.D. A One-pot Direct Iodination of the Fischer-Borsche Ring Using Molecular Iodine and its Utility in the Synthesis of 6-Oxygenated Carbazole Alkaloids. *J. Org. Chem.*, **2015**, *80*, 2392-2396.
22. Drake, N.L. The Bucherer Reaction. *Org. React.*, **2004**, *1*, 63-90.
23. (a) Bedford, R.B.; Betham, M. N-H Carbazole Synthesis from 2-Chloroanilines *via* Consecutive Amination and C-H Activation. *J. Org. Chem.*, **2006**, *71*, 9403-9410. (b) Ackermann, L.; Althammer, A. Domino N-H/C-H Bond Activation: Palladium-Catalyzed Synthesis of Annulated Heterocycles Using Dichloro (hetero) arenes. *Angew. Chem., Int. Ed.*, **2007**, *46*, 1627-1629. (c) Zhou, T.; Li, B.; Wang, B. Rhodium-catalyzed C_2 and C_4 C-H activation/annulation of 3-(1 H-indol-3-yl)-3-oxopropanenitriles with internal alkynes: a facile access to substituted and fused carbazoles. *Chem. Commun.*, **2017**, *53*, 6343-6346.

24. Reddy, C.R.; Valleti, R.R.; Dilipkumar, U. One-Pot Sequential Propargylation/Cycloisomerization: A Facile [4+2] Benzannulation Approach to Carbazoles. *Chem. Eur. J.*, **2016**, *22*, 2501-2506.
25. (a) Yamamoto, M.; Matsubara, S. Carbazole Synthesis by Platinum-catalyzed C-H Functionalizing Reaction Using Water as Reoxidizing Reagent. *Chem. Lett.*, **2007**, *36*, 172-173. (b) Saunthwal, R.K.; Patel, M.; Kumar, S.; Danodia, A.K.; Verma, A.K. Pd (II)-Catalyzed C-H Activation of Styrylindoles: Short, Efficient, and Regioselective Synthesis of Functionalized Carbazoles. *Chem. Eur. J.*, **2015**, *21*, 18601-18605. (c) Saunthwal, R.K.; Patel, M.; Kumar, S.; Danodia, A.K.; Verma, A.K.; Pd (II)-Catalyzed C-H Activation of Styrylindoles: Short, Efficient, and Regioselective Synthesis of Functionalized Carbazoles. *Chem. Eur. J.*, **2015**, *21*, 18601-18605.
26. (a) Liu, Z.; Larock, R.C. Synthesis of carbazoles and dibenzofurans *via* cross-coupling of *o*-iodoanilines and *o*-iodophenols with silylaryl triflates and subsequent Pd-catalyzed cyclization. *Tetrahedron*, **2007**, *63*, 347-355. (b) Roy, J.; Jana, A.K.; Mal, D. Recent trends in the synthesis of carbazoles: an update. *Tetrahedron*, **2012**, *68*, 6099-6121.
27. (a) Sánchez, C.; Méndez, C.; Salas, J.A. Indolocarbazole natural products: occurrence, biosynthesis, and biological activity. *Nat. Prod. Rep.*, **2006**, *23*, 1007-1045. (b) Watanabe, T.; Ueda, S.; Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. One-pot synthesis of carbazoles by palladium-catalyzed N-arylation and oxidative coupling. *Chem. Commun.*, **2007**, *43*, 4516-4518. (c) Mukherjee, R.; Basak, A. Synthesis of 1-Indol-3-yl-carbazoles *via* Garratt-Braverman Cyclization. *Synlett*, **2012**, *23*, 877-880.
28. Qiu, Y.; Kong, W.; Fu, C.; Ma, S. Carbazoles *via* $AuCl_3$-Catalyzed Cyclization of 1-(Indol-2-yl)-3-alkyn-1-ols. *Org. Lett.*, **2012**, *14*, 6198-6201.
29. Zhang, Z.; Tang, X.; Xu, Q.; Shi, M. Gold-Catalyzed Cyclization of 1-(Indol-3-yl)-3-alkyn-1-ols: Facile Synthesis of Diversified Carbazoles. *Chem. Eur. J.*, **2013**, *19*, 10625-10631.
30. Qiu, Y.; Ma, D.; Kong, W.; Fu, C.; Ma, S. Regiocontrolled 1, 2-migration in cyclization of 1-(indol-2-yl)-3-alkyn-1-ols:$(Ph_3P)Au^+$ vs. $PtCl_4$. *Org. Chem. Front.*, **2014**, *1*, 62-67.
31. James, M.J.; Clubley, R.E.; Palate, K.Y.; Procter, T.J.; Wyton, A.C.; O'brien, P.; Taylor, R.J.; Unsworth, W.P. Silver (I)-catalyzed dearomatization of alkyne-tethered indoles: Divergent synthesis of spirocyclic indolenines and carbazoles. *Org. Lett.*, **2015**, *17*, 4372-4375.
32. Zhou, J.; Qiu, Y.; Li, J.; Fu, C.; Zhang, X.; Ma, S. $PtCl_4$-catalyzed skeleton rearrangement-cyclization of tertiary indolyl-3-alkynols. *Chem. Commun.*, **2017**, *53*, 4722-4725.
33. Suárez, A.; Suárez-Pantiga, S.; Nieto-Faza, O.; Sanz, R. Gold-catalyzed synthesis of 1-(indol-3-yl) carbazoles: Selective 1, 2-alkyl *vs* 1, 2-vinyl migration. *Org. Lett.*, **2017**, *19*, 5074-5077.
34. Tharra, P.; Baire, B. Regioselective Cyclization of (Indol-3-yl) pentyn-3-ols as an Approach to (Tetrahydro) carbazoles. *Org. Lett.*, **2018**, *20*, 1118-1121.
35. (a) Corma, A.; Garcia, H. Lewis acids: from conventional homogeneous to green homogeneous and heterogeneous catalysis. *Chem. Rev.*, **2003**, *103*, 4307-4366. (b) Yamamoto, H. From designer Lewis acid to designer Brønsted acid towards more reactive and selective acid catalysis. *Proc. Jpn. Acad. B*, **2008**, *84*, 134-146. (c) Lathem, A.P.; Heiden, Z.M. Quantification of Lewis acid induced Brønsted acidity of protogenic Lewis bases. *Dalton Trans.*, **2017**, *46*, 5976-5985.

36. Sua´rez, A.; Martı´nez, F.; Sua´rez-Pantiga, S.; Sanz, R. *p*TSA-Catalyzed Reaction of Indoles with 2-Oxoaldehydes: Synthesis of α, α-Bis(indol-3-yl) Ketones. *ChemistrySelect.* **2017**, *2*, 787-790.
37. (a) Ignacio, C.; Haughey, M.B.; Donohoe, T.J. Hexafluoroisopropanol as a highly versatile solvent. *Nat. Rev. Chem.*, **2017**, *1*, 0088-0099. (b) Ramos-Villaseñor, J.M., Rodríguez-Cárdenas, E., Díaz, C.E.B. and Frontana-Uribe, B.A., use of 1, 1, 1, 3, 3, 3-hexafluoro-2-propanol (HFIP) Co-solvent mixtures in organic electrosynthesis. *J. Electrochem. Soc.*, **2020**, *167*, 155509. (c) Motiwala, H.F.; Armaly, A.M.; Cacioppo, J.G.; Coombs, T.C.; Koehn, K.R.; Norwood IV, V.M.; Aubé, J. HFIP in organic synthesis. *Chem. Rev.*, **2022**, *122*, 12544-12747.
38. (a) Yamashita, M.; Horiguchi, H.; Hirano, K.; Satoh, T.; Miura, M. Fused ring construction around pyrrole, indole, and related compounds *via* palladium-catalyzed oxidative coupling with alkynes. *J. Org. Chem.*, **2009**, *74*, 7481-7488. (b) Jurberg, I.D.; Odabachian, Y.; Gagosz, F. Hydroalkylation of alkynyl ethers *via* a gold (I)-Catalyzed 1, 5-hydride shift/cyclization sequence. *J. Am. Chem. Soc.*, **2010**, *132*, 3543-3552. (c) Godoi, B.; Schumacher, R.F.; Zeni, G. Synthesis of heterocycles *via* electrophilic cyclization of alkynes containing heteroatom. *Chem. Rev.*, **2011**, *111*, 2937-2980. (d) Guney, T.; Lee, J.J.; Kraus, G.A. First Inverse Electron-Demand Diels-Alder Methodology of 3-Chloroindoles and Methyl Coumalate to Carbazoles. *Org. Lett.*, **2014**, *16*, 1124-1127. (e) Suárez, A.; García-García, P.; Fernández-Rodríguez, M.A.; Sanz, R. Brønsted Acid-Catalyzed Straightforward Synthesis of Benzo [b] carbazoles from 2, 3-Unsubstituted Indoles. *Adv. Synth. Catal.*, **2014**, *356*, 374-382. (f) Yuan, Z.G.; Wang, Q.; Zheng, A.; Zhang, K.; Lu, L.Q.; Tang, Z.; Xiao, W.J. Visible light-photocatalysed carbazole synthesis *via* a formal (4+2) cycloaddition of indole-derived bromides and alkynes. *Chem. Commun.*, **2016**, *52*, 5128-5131.
39. Alcaide, B.; Almendros, P.; Alonso, J.M.; Busto, E.; Fernandez, I.; Ruiz, M.P.; Xiaokaiti, G. Versatile synthesis of polyfunctionalized carbazoles from (3-Iodoindol-2-yl) butynols *via* a gold-catalyzed intramolecular iodine-transfer reaction. *ACS Catal.*, **2015**, *5*, 3417-3421.
40. Wang, J.; Zhu, H.T.; Qiu, Y.F.; Niu, Y.; Chen, S.; Li, Y.X.; Liu, X.Y.; Liang, Y.M. Facile synthesis of carbazoles *via* a tandem iodocyclization with 1, 2-alkyl migration and aromatization. *Org. Lett.*, **2015**, *17*, 3186-3189.
41. Yaragorla, S.; Bag, D.; Dada, R.; Jose, K.J. Iodo-cycloisomerization of aryl (indol-3-yl) methane-tethered propargyl alcohols to 3-iodocarbazoles *via* selective 1, 2-alkyl migration. *ACS omega*, **2018**, *3*, 15024-15034.
42. Yaragorla, S.; Dada, R.; Bag, D. An Expeditious Benzannulation Reaction of Indol-3-yl-but-3-yn-2-ols to Substituted 2-Iodocarbazoles *via* Domino 5-*endo* Spirocyclization/Selective Vinyl Shift and Aromatization. *Eur. J. Org. Chem.*, **2019**, 6983-6988.

List of Publications

1. KO^{t}Bu Promoted Oxidative Cleavage of C_{sp3}-C_{sp2} and C_{sp3}-H bonds, S. Yaragorla, **T. Khan**, A. Behera. *J. Org. Chem.*, **2023**, *88*, 2103-2112.
2. Stereoselective Sulfenylation of Oxindole-derived Propargyl Alcohols: Calcium catalyzed, Solvent-Free Synthesis of Sulfenylated-3-Alkenyloxindoles, **T. Khan**, P. Rajesh, D. Arun, S. Yaragorla. *Org. Biomol. Chem.*, **2021,** *19*, 10201-10209.
3. Brønsted acid promoted Thermal-Ring-Rearrangement of Fluorenopyrans to 2-(1H-inden-3-yl)-9H-fluoren-3-ols bearing two all-carbon-quaternary centres. **T Khan**, P Rajesh, D Praveen, K. V. Jovan Jose, S. Yaragorla. *Eur. J. Org., Chem.* **2020,** 2199-2209.
4. Cyclocarbonylation-Iodination of terminal Alkynes with Ketones and ICl *via* 1,2-Migration, K. M. Kumar, **T. Khan**, A. I. Almansour, N. Arumugam, S. Yaragorla. *Tetrahedron Lett.*, **2020,** *61*, 152374-152377.
5. Iodocyclization of Propargyl Alcohols: Highly Facile Approach to Hetero/Carbocyclic Iodides**, T. Khan,** S. Yaragorla. *Eur. J. Org. Chem.*, **2019**, 3989-4012.
6. An unexpected thermal-ring-rearrangement of benzochromenes to inden-3-yl-naphthols with *p*TsOH, S. Yaragorla, **T. Khan**. *Org. Biomol. Chem.*, **2018**, *16*, 7920-7925.
7. Cu-Catalyzed Oxidative C($_{sp2}$)-H Cycloetherification of o-Alkenyl Arenols for the Preparation of Fused-Furans, S. Yaragorla, **T. Khan**, J. Raoof *(under revision)*.
8. Cyclizative Strategies Towards Construction of Carbazoles from Indole-Tethered Propargyl Alcohol *(communicated)*.

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An unexpected thermal-ring-rearrangement of benzochromenes to inden-3-yl-naphthols with *p*TsOH†

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Described here is the first report of an unexpected thermal-ring rearrangement (TRR) of benzochromenes to indene derivatives promoted by *p*TsOH. This cascade ring-rearrangement proceeds through the protonation of benzochromenes by an acid catalyst followed by ring-opening and ring-closure by an intramolecular Friedel–Crafts cyclization to provide a new bicyclic framework, inden-3-yl-naphthols bearing a quaternary center, which also exhibited atropisomerism. Regioselectivity, broad substrate scope, high yields, solvent-free conditions and atom economy are the additional high points of this ring-rearrangement.

Introduction

Benzochromenes are versatile building blocks of natural products and part of many biologically significant molecules.[1] They are known to possess a spectrum of biological activities such as antifungal, anti-inflammatory, anti-hyperglycemic, cytotoxic and molluscicidal activities.[2] In addition to these features, benzochromenes are known to undergo a reversible ring-opening-cyclization process (Fig. 1) in a thermal/photochemical environment and hence exhibit photochromic properties,[3] and if this ring-opening-cyclization occurs in a specific acid–base medium, it leads to acidochromism.[3,4] As a result of photochromic and acidochromic properties, benzochromenes are known to possess significant material applications.[3–5]

Ring-rearrangement is conceptually different from the known ring-opening-cyclization reactions because at least two substrates are involved in the ring-opening-cyclization reactions,[6] whereas in ring-rearrangement reactions a single substrate is involved and rearranged to a new cyclic compound. Intramolecular ring-opening-cyclization reactions are also known as depicted in Fig. 1, but it is a reversible reaction (no rearrangement). To the best of our knowledge, these kinds of ring-rearrangements (RR) are not extensively investigated. However, there are some indirect examples, such as a cycloisomerization reaction, where the transformation of a polyunsaturated acyclic substrate initially cyclizes it to a less stable cyclic intermediate which further rearranges to a stable product.[7] Therefore in cycloisomerization reactions, the rearrangement of the less stable cyclic intermediate to a final (cyclic) product can be considered as a ring-rearrangement (RR) reaction. A couple of examples of RR are shown in Scheme 1, including our recent report on the cycloisomerization of 1,5-enyne, which proceeded through the formation of a less stable spirane, which then underwent a thermal-ring-rearrangement (TRR) with chloranil to yield the stable phenanthridinone (eqn (i), Scheme 1).[8] Another example is the cycloisomerization of bis(indolyl)methane tethered propargyl alcohol to yield a less stable spirane intermediate, which then underwent ring-rearrangement (RR) through 1,2-migration and yielded a stable carbazole (eqn (ii), Scheme 1).[9] With this background, herein we would like to report our first observation on the *p*TSA catalyzed thermal ring-rearrangement (TRR) of benzochromenes to inden-3yl-naphthols.

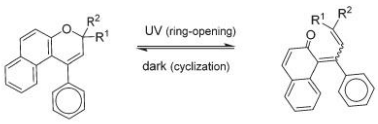


Fig. 1 Photochromism of benzochromenes (intramolecular-ring-opening-cyclization).

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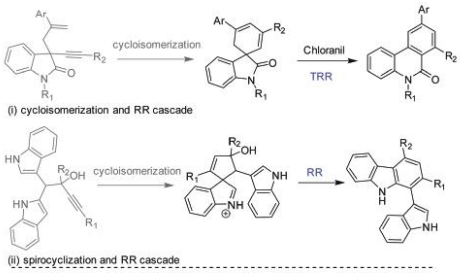
†Electronic supplementary information (ESI) available. CCDC 1858026 and 1851351. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8ob02264j

Results and discussion

We commenced our investigations with 3,3-dimethyl-1-phenyl-3*H*-benzo[*f*]chromene (**1a**), which was synthesized using a

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Scheme 1 Representative examples of ring-rearrangement (RR) reactions in cycloisomerizations.

known procedure.[10] Initially, **1a** was treated with the Lewis acid catalyst, $Ca(OTf)_2$ at 120 °C under solvent-free conditions for 48 h, unfortunately, we found that there was no change in the reaction; considering the solvent effect, the reaction was refluxed in toluene for 48 h, but no initiation of reaction was observed (entries 1 and 2, Table 1). Among the variety of Brønsted acids studied, TFA, CSA and benzoic acids (entries 4–6) were unable to catalyze the reaction, however to our delight PTSA gave 60% of product **2a** at 100 °C under solvent-free conditions after 16 h (entry 3).[11] The increase of temperature from 100 °C to 120 °C with 10 mol% PTSA was beneficial for elevating the yield of **2a** and also lessening the reaction time (entries 7 and 8). Interestingly, the maximum reaction yield (95%) was obtained with 20 mol% PTSA at 110 °C within 1.5 h (entry 9). It is worth mentioning that a further increase of catalyst loading and temperature did not have much influence on the reaction yield and time (entry 10). Among the various solvents screened (1,2-DCE, EtOH, CH_3CN, toluene, and water), it was found that the reaction yield of **2a** was best under solvent-free conditions (entries 11–15, Table 1).

Table 1 Optimization of the reaction conditions[a]



Entry	Catalyst (mol%)	Reaction conditions[a]	Yield[b] (%)
1	$Ca(OTf)_2/Bu_4NPF_6$, (10/10)	Neat, 120 °C, 48 h	nr
2	$Ca(OTf)_2/Bu_4NPF_6$, (10/10)	Toluene, 120 °C,48 h	nr
3	PTSA (10)	Neat, 100 °C, 16 h	60
4	TFA (100)	Neat, rt, 48 h	nr
5	CSA (20)	Neat, 110 °C, 48 h	nr
6	$PhCO_2H$ (30)	Neat, 110 °C, 48 h	nr
7	PTSA (10)	Neat, 110 °C, 6 h	91%
8	PTSA (10)	Neat, 120 °C, 4 h	92%
9	PTSA (20)	Neat, 110 °C, 1.5 h	95%
10	PTSA (40)	Neat, 120 °C, 1.5 h	78%
11	PTSA (20)	1,2-DCE, 90 °C, 14 h	20%
12	PTSA (20)	EtOH, 90 °C, 48 h	10%
13	PTSA (20)	CH_3CN, 90 °C, 48 h	nr
14	PTSA (20)	Toluene, 120 °C, 6 h	10%
15	PTSA (20)	H_2O, 100 °C, 48 h	nr

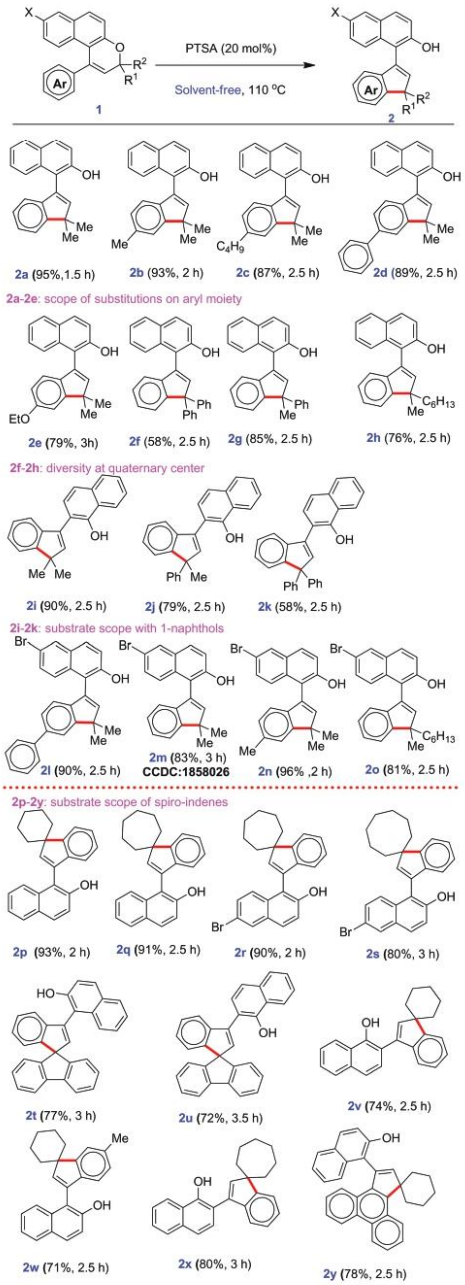
[a] Oil bath temperature. [b] Isolated yield; nr = no reaction, PTSA: *p*-toluene sulfonic acid, TFA: trifluoroacetic acid, CSA = 10-camphor sulfonic acid, OTf – trifluoromethane sulfonate.

Having discovered the optimum conditions for the ring-rearrangement of benzochromene (**1a**) to 1-(1,1-dimethyl-1*H*-inden-3-yl)naphthalen-2-ol (**2a**), we were keen to test the scope of different benzochromenes to rearrange into indene derivatives under the optimum conditions (Scheme 2). Therefore, we prepared several benzochromenes with different substitutions and subjected them to the standard reaction conditions (s.r.c). The ring rearrangement was compatible with alkyl (methyl, *n*-butyl), phenyl and ethoxy substitutions on the aryl ring to produce the corresponding-indene derivatives, **2b**, **2c**, **2d** and **2e** in excellent yields (Scheme 2). Substitutions at the quaternary center (phenyl–phenyl; phenyl–methyl; methyl–hexyl) of benzochromene (**1**) were retained during the TRR reaction to furnish indenes **2f–2h** in good yields. Interestingly, we observed that products **2g** and **2h** appeared as diastereomers in the ^1H and ^{13}C NMR spectra, which is due to the presence of a chiral carbon on the indene.[12] The crystal structure of the product (Fig. 2) shows that naphthyl and indenyl moieties are perpendicular to each other, and this may be analogous to a biphenyl system, so we presume that there could be a restricted rotation existing between the C–C single bond connecting naphthyl and indenyl moieties, which leads them to show atropisomerism. We may need to study this property more deeply to understand this phenomenon; however, our main objective here is to show the RR of benzochromenes.

In the case of TRR with 2-methyl-2,4-diphenyl-2*H*-benzo[*h*]chromene (**1j**) the product 2-(1-methyl-1-phenyl-1*H*-inden-3-yl)naphthalen-1-ol (**2j**) was yielded in 79% as a 1 : 1 mixture of diastereomers. In a similar way, other benzo[*h*]chromenes were also subjected to the standard TRR conditions and the 1-naphthol derivatives of indenes (**2i**, **2k**) were obtained in good yields. Bromonaphthol derivatives **2l–2o** were also formed from the corresponding benzochromenes through the TRR reaction in good to excellent yields. As expected, compound **2o** also exhibited atropisomerism due to the presence of a chiral carbon on the indene. The product 6-bromo-1-(1,1-dimethyl-1*H*-inden-3-yl)naphthalen-2-ol (**2m**) was found as a good crystalline solid, and hence the single crystal X-ray data of **2m** were obtained to confirm its structure (Fig. 2).[13] Furthermore, we examined the TRR of benzochromenes bearing the spiro-centre such as 1-phenylspiro[benzo[*f*]chromene-3,1′-cyclohexane] **1p** under standard reaction conditions and obtained the corresponding 1-(spiro[cyclohexane-1,1′-inden]-3′-yl)naphthalen-2-ol **2p** in 93% yield after 3 h (Scheme 2). Encouraged by this result, we prepared indene derivatives bearing cyclohexane (**2p**, **2v**, **2w**, **2y**), cycloheptane (**2q**, **2r**, **2x**), cyclooctane (**2s**) and fluorenyl (**2t**, **2u**) substitutions at the C1-spiro center in excellent yields from the corresponding spirocyclic-benzochromenes.

As depicted in Scheme 3, the synthesis of benzochromene (**1**) is known to begin from propargyl alcohol **3** and naphthol **4**

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Scheme 2 Substrate scope of TRR reaction.

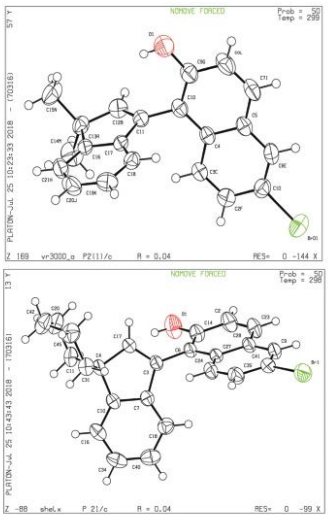
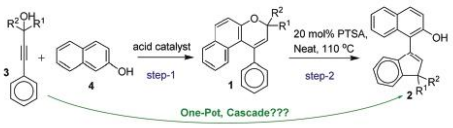


Fig. 2 ORTEP diagram of **2m** (top) and **2ab** (bottom) with 50% probability.



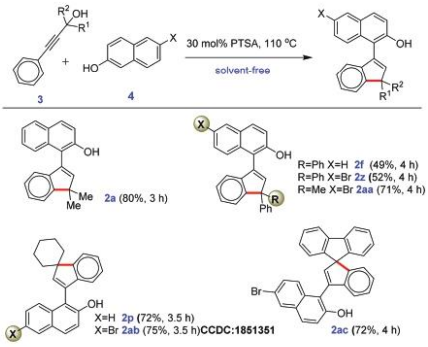
Scheme 3 The rationale for the one-pot cascade protocol.

using acid catalysts (step-1),[10] and here we discovered the TRR of benzochromene (**1**) to indene (**2**) in the presence of an acid catalyst (step-2, Scheme 3). Therefore, presuming that it is possible to develop a one-pot cascade reaction,[14] in such a way that **3** and **4** will form benzochromene **1** with PTSA, and then ring-rearrangement of **1** should give indene derivative **2** (Scheme 3).

To implement this one-pot proposal, a mixture of 2-methyl-4-phenylbut-3-yn-2-ol (**3a**), 2-naphthol and PTSA was heated at 110 °C under solvent-free conditions and the formation of 3,3-dimethyl-1-phenyl-3*H*-benzo[*f*]chromene (**1a**) was observed in 20 min, and delightfully, further continuation of the reaction yielded the indene **2a** in 80% through the ring-rearrangement reaction (Scheme 4). Knowing the importance of a one-pot, cascade protocol towards a sustainable synthetic process,[14] we were encouraged to elaborate this method to synthesize some of the inden-3-yl-naphthols with diversity at the quaternary center (**2f**, **2z** and **2aa**) and with the spirocyclic system (**2p**, **2ab** and **2ac**) in a good overall yield. The structure of **2ab** was further confirmed by using single crystal X-ray data (Fig. 2).[13]

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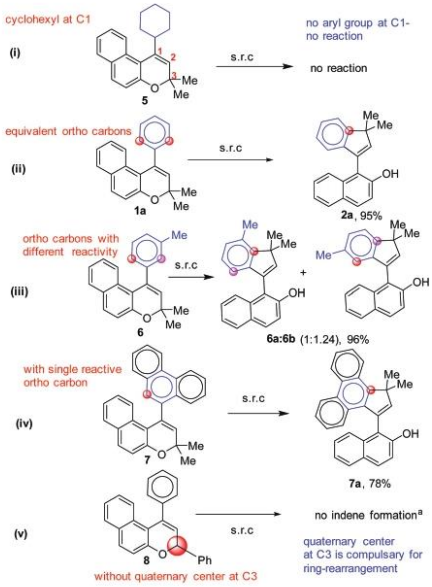
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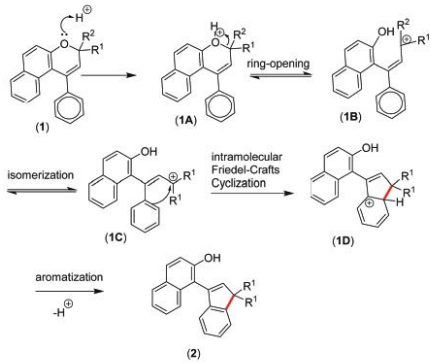
Scheme 4 One-pot synthesis. A mixture of 3 (1 equiv.), 4 (1.2 equiv.) and PTSA (30 mol%) was heated at 110 °C (oil bath temperature) for a specified time.

After developing a new TRR reaction of benzochromenes (Scheme 2) to indene derivatives and the one-pot reaction from propargyl alcohols (Scheme 4), we were interested in checking the scope and limitations of this method by performing control experiments as depicted in Scheme 5. The first reaction was performed with benzochromene **5** bearing a cyclohexyl moiety at C1 under standard reaction conditions (s.r.c) and found that no change in the starting material was observed. This result emphasizes the importance of having an aryl group at C1 to accomplish the TRR reaction (eqn (i), Scheme 5). The second experiment was performed with benzochromene **1a** bearing a phenyl group at C1 with chemically equivalent *ortho*-carbons and accomplished the TRR (eqn (ii), Scheme 5). The third reaction was performed with a benzochromene (**6**) bearing a *meta*-tolyl group (with chemically inequivalent *ortho*-carbons) and a regioisomeric mixture of two indene derivatives (**6a**/**6b**) was obtained in a 1 : 1.24 ratio with 96% combined yield (eqn (iii), Scheme 5).[15] The fourth experiment commenced with the benzochromene **7** bearing a phenanthrenyl group at C1, with a single reactive *ortho*-carbon and accomplished the TRR to yield indene derivative **7a** in 78% yield (eqn (iv), Scheme 5). All these experiments (i–iv) concluded that it is must to have an aryl (phenyl) group at C1 with at least one reactive *ortho*-carbon to accomplish the TRR reaction. Later, we performed another reaction to check the importance of a quaternary center at C3 in TRR. Therefore we chose 1,3-diphenyl-3*H*-benzo[*f*]chromene (**8**), having a phenyl group with a reactive *ortho* carbon at C1 but not a quaternary center at C3 and subjected it to s.r.c., surprisingly, we found that the reaction did not yield the desired product (eqn (v), Scheme 5).[16] This experimental observation as a whole suggests that the TRR works with benzochromenes bearing a C3-quaternary center and aryl group at C1 with at least one reactive *ortho*-carbon.

Based on the observations made through the control experiments the plausible reaction mechanism for the PTSA catalyzed, thermal-ring-rearrangement (TRR) of benzochromene (**1**) to inden-3-yl-naphthol (**2**) is proposed in Scheme 6. Here, the Brønsted acid protonates the benzochromene **1** to form the oxonium **1A**, which then undergoes the ring-opening to yield carbocation intermediate **1B**. Isomerization of **1B** to **1C** followed by an intramolecular Friedel–Crafts cyclization and aromatization cascade provides the indene **2** with a ring rearrangement.



Scheme 5 Control experiments.



Scheme 6 The reaction mechanism for the TRR of benzochromenes.

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Conclusions

In conclusion, we disclose here the first report on PTSA catalyzed, intramolecular thermal-ring-rearrangement (TRR) of benzochromenes to indene derivatives. Based on control experiments we confirmed that the presence of an aryl group with at least one reactive *ortho*-carbon at C1 and a quaternary center at C3 is must for the TRR of benzochromenes. We observed that these compounds exhibit atropisomerism, and in the case of **2g**, **2h**, **2j**, **2o**, and **2aa** we have noticed the formation of diastereomers in the ^{1}H and ^{13}C NMR spectra. Taking advantage of the benzochromene synthesis, from propargyl alcohols and naphthols, we developed further a green synthetic protocol by combining the benzochromene synthesis and their TRR in a one-pot, cascade strategy under solvent-free conditions. Further investigations towards the TRR concepts are in progress.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 (*a*) D. Kumar, P. Sharma, H. Singh, K. Nepali, G. K. Gupta, S. K. Jaina and F. N. Kang, *RSC Adv.*, 2017, **7**, 36977; (*b*) A. Goel, A. Kumar and A. Raghuvanshi, *Chem. Rev.*, 2013, **113**, 1614; (*c*) M. Rueping, E. Sugiono and E. Merino, *Chem. – Eur. J.*, 2008, **14**, 6329; (*d*) F. Shaheen, M. Ahmad, S. N. Khan, S. S. Hussain, S. Anjum, B. Tashkhodjaev, K. Turgunov, M. N. Sultankhodzhaev, M. I. Choudhary and A. Rahman, *Eur. J. Org. Chem.*, 2006, 2371; (*e*) M. Kidwai, S. Saxena, M. K. R. Khan and S. S. Thukral, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 4295; (*f*) A. Simon-Levert, A. Arrault, N. Bontemps-Subielos, C. Canal and B. Banaigs, *J. Nat. Prod.*, 2005, **68**, 1412; (*g*) G. Zeni and R. C. Larock, *Chem. Rev.*, 2004, **104**, 2285; (*h*) V. Rukachaisirikul, M. Kamkaew, D. Sukavisit, S. Phongpaichit, P. Sawangchote and W. C. Taylor, *J. Nat. Prod.*, 2003, **66**, 1531; (*i*) S. Dachriyanus, M. V. Sargent, B. W. Skelton, I. Soediro, M. Sutisna, A. H. White and E. Yulinah, *Aust. J. Chem.*, 2002, **55**, 229; (*j*) Y. Kashiwada, K. Yamazaki, Y. Ikeshiro, T. Yamagishi, T. Fujioka, K. Mihashi, K. Mizuki, L. M. Cosentino, K. Fowke, S. L. Morris and K. H. Lee, *Tetrahedron*, 2001, **57**, 1559; (*k*) K. C. Nicolaou, J. A. Pfefferkorn, A. J. Roecker, G. Q. Cao, S. Barluenga and H. J. Mitchell, *J. Am. Chem. Soc.*, 2000, **122**, 9939; (*l*) K. C. Nicolaou, J. A. Pfefferkorn, H. J. Mitchell, A. J. Roecker, S. Barluenga, G. Q. Cao, R. L. Affleck and J. E. Lillig, *J. Am. Chem. Soc.*, 2000, **122**, 9954.

2 (*a*) T. Raj, R. K. Bhatia, A. Kapur, M. Sharma, A. K. Saxena and M. P. S. Ishar, *Eur. J. Med. Chem.*, 2010, **45**, 790; (*b*) T. Raj, R. K. Bhatia, R. K. Sharma, V. Gupta, D. Sharma and M. P. S. Ishara, *Eur. J. Med. Chem.*, 2009, **44**, 3209; (*c*) T. Symeonidis, K. C. Fylaktakidou, D. J. Hadjipavlou and K. E. Litinas, *Eur. J. Med. Chem.*, 2009, **44**, 5012; (*d*) A. Kumar, R. A. Maurya, S. A. Sharma, P. Ahmad, A. B. Singh, G. Bhatia and A. K. Srivastava, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 6447; (*e*) F. M. Abdelrazek, P. Metz and E. K. Farrag, *Arch. Pharm.*, 2004, **337**, 482.

3 (*a*) H. Tian and J. Zhang in *Photochromic Materials: Preparation, Properties and Applications*, Wiley-VCH Verlag GmbH & Co. KGaA, 1st edn, 2016; (*b*) H. Bouas-Laurent and H. Durr, *Pure Appl. Chem.*, 2001, **73**, 639; (*c*) H. Durr and H. Bouas-Laurent, *Photochromism: Molecules and Systems*, Elsevier, Amsterdam, 1st edn, 1990; (*d*) R. S. Becker and J. Michl, *J. Am. Chem. Soc.*, 1966, **88**, 5931.

4 (*a*) G. Kunpeng and C. Yi, *J. Mater. Chem.*, 2010, **20**, 4193; (*b*) E. M. Glebov, A. B. Smolentsev, V. V. Korolev, V. F. Plyusnin, A. V. Chebunkova, S. V. Paramonov, O. A. Fedorova, V. Kokshin and A. Samat, *J. Phys. Org. Chem.*, 2009, **22**, 537; (*c*) S. Kumar, D. Hernandez, B. Hoa, Y. Lee, J. S. Yang and A. McCurdy, *Org. Lett.*, 2008, **10**, 3761; (*d*) W. Sriprom, M. Neel, C. D. Gabbutt, B. M. Heron and S. Perrier, *J. Mater. Chem.*, 2007, **17**, 1885; (*e*) J. N. Moorthy, P. Venkatakrishnan, S. Samanta and D. K. Kumar, *Org. Lett.*, 2007, **9**, 919; (*f*) B. M. Heron, C. D. Gabbutt, J. D. Hepworth, S. M. Partington, D. A. Clarke and S. N. Corns, *WO*, 2001/12619A1, 2001.

5 (*a*) P. Hannesschlager and P. Brun, *Appl. Organomet. Chem.*, 2000, **14**, 371; (*b*) A. Taugerbeck and M. Klasen-Memmer, *US* 2009/0023802A1, 2009.

6 (*a*) L. Crespin, L. Biancalana, T. Morack, D. C. Blakemore and S. V. Ley, *Org. Lett.*, 2017, **19**, 1084; (*b*) S. Pradhan, C. K. Shahi, A. Bhattacharyya, N. Chauhan and M. K. Ghorai, *Org. Lett.*, 2017, **19**, 3438; (*c*) Y. Xia, L. Lin, F. Chang, Y. Liao, X. Liu and X. Feng, *Angew. Chem., Int. Ed.*, 2016, **55**, 12228; (*d*) H. Nambu, M. Fukumoto, W. Hirota and T. Yakura, *Org. Lett.*, 2014, **16**, 4012; (*e*) H. Miao, J. A. Tallarico, H. Hayakawa, K. Munger, J. L. Duffner, A. N. Koehler, S. L. Schreiber and T. A. Lewis, *J. Comb. Chem.*, 2007, **9**, 245.

7 (*a*) A. S. K. Hashmi, *Chem. Rev.*, 2007, **107**, 3180; (*b*) E. JiménezNúñez and A. M. Echavarren, *Chem. Commun.*, 2007, 333; (*c*) A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2006, **45**, 7896; (*d*) A. Furstner and P. Hannen, *Chem. – Eur. J.*, 2006, **12**, 3006; (*e*) G. C. Lloyd-Jones, *Org. Biomol. Chem.*, 2003, **1**, 215; (*f*) C. Aubert, O. Buisine and M. Malacria, *Chem. Rev.*, 2002, **102**, 813; (*g*) B. M. Trost, F. D. Toste and A. B. Pinkerton, *Chem. Rev.*, 2001, **101**, 2067; (*h*) B. M. Trost and M. J. Krische, *Synlett*, 1998, 1; (*i*) B. M. Trost, *Chem. – Eur. J.*, 1998, **4**, 2405; (*j*) I. Ojima,

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M. Tzamarioudaki, Z. Y. Li and R. Donovan, *Jpn. Chem. Rev.*, 1996, **96**, 635.
8 S. Yaragorla, A. Pareek and R. Dada, *Adv. Synth. Catal.*, 2017, **359**, 3068.
9 A. Suárez, S. Suárez-Pantiga, O. Nieto-Faza and R. Sanz, *Org. Lett.*, 2017, **19**, 5074.
10 (*a*) S. Yaragorla, A. Pareek and R. Dada, *Tetrahedron Lett.*, 2017, **58**, 4642; (*b*) K. Tanaka, H. Aoki, H. Hosomi and S. Ohba, *Org. Lett.*, 2000, **2**, 2133.
11 Refer to the ESI† for the confirmation of the product.
12 ^{1}H and ^{13}C NMR spectra suggested that the rotamers are almost in a 1 : 1 ratio (see the ESI†).
13 Refer to the ESI† for the details of the single crystal X-ray data.
14 (*a*) Y. Hayashi, *Chem. Sci.*, 2016, **7**, 866; (*b*) L. F. Tietze, G. Brasche and K. M. Gericke in *Domino Reactions*, Wiley-VCH, Weinheim, 1st edn, 2014; (*c*) T. Newhouse, P. S. Baran and R. W. Hoffmann, *Chem. Soc. Rev.*, 2009, **38**, 3010; (*d*) C. J. Chapman and C. G. Frost, *Synthesis*, 2007, 1; (*e*) D. J. Ramon and M. Yus, *Angew. Chem., Int. Ed.*, 2005, **44**, 1602; (*f*) J. C. Wasilke, S. J. Obrey, R. T. Baker and G. C. Bazan, *Chem. Rev.*, 2005, **105**, 2001; (*g*) P. T. Anastas and M. M. Kirchhoff, *Acc. Chem. Res.*, 2002, **35**, 686; (*h*) P. T. Anastas and J. C. Warner, *Green Chemistry: Theory and Practice*, Oxford University Press, New York, 1998; (*i*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; (*j*) S. E. Denmark and A. Thorarensen, *Chem. Rev.*, 1996, **96**, 137; (*k*) B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 259; (*l*) B. M. Trost, *Science*, 1991, **254**, 1471; (*m*) R. Robinson, *J. Chem. Soc. Trans.*, 1917, **111**, 762.
15 The ratio of the regioisomeric mixture is calculated based on the ^{1}H NMR spectrum.
16 Benzochromene **8** was consumed and gave a complex mixture but not the desired indene derivative.

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Minireview

Iodocyclization

Iodocyclization of Propargyl Alcohols: Highly Facile Approach to Hetero/Carbocyclic Iodides

Tabassum Khan[a] and Srinivasarao Yaragorla*[a]

Abstract: Iodocyclization of propargyl alcohols is an active area for the construction of hetero/carbocyclic iodides. Ambiphilic reactivity of propargyl alcohols made it more attractive to tune their reactivity towards the development of regioselective synthetic strategies. In general, iodocyclization reactions are atom and step economic, promoted by simple and readily available inexpensive electrophilic iodine reagents at ambient temperature. These compounds find potential applications in pharmaceutical and material sciences, because of the presence of a preinstalled reactive iodide functionality. Therefore, many researchers are actively involved in developing synthetic strategies towards iodocyclizations from propargyl alcohols for various applications. In this mini-review, we emphasize the full list of synthetic endeavors made towards the "iodocyclization of propargyl alcohols, propargyl ethers and homopropargyl alcohols".

1. Introduction

Propargyl alcohols have been emerging as the promising feedstock materials for the construction of a large variety of carbo and heterocyclic molecules.[1] In most of the cases, the activation of unsaturated bonds of propargyl alcohols using suitable reagents and conditions becoming a challenging and exciting area of research due to the "ambident reactivity" of these substrates. Electrophilic iodine mediated π-activation of these propargyl alcohols has been explored as one of the challenging regioselective methods for the synthesis of iodo-substrates using inter or intra-nucleophiles. Generally, hydroxyl, carbonyl oxygen, carboxylate, amino, amido, thio and some carbanions act as the nucleophiles and molecular iodine, ICl, IBr, NIS, IPy_2BF_4, and $I(coll)_2PF_6$ are the sources of electrophilic iodine in these iodocyclization reactions.[2] Though there are some exceptions, the preferred ring size is 5 > 6 > 3 > 4, and this preference and selectivity are usually attributed to the structural and conformational features of the transition state of cyclization. Baldwin has reported a detailed study of these stereo-electronic factors of cyclization, in which he named the cyclizations as *exo* and *endo* further he proposed *tet* (sp^3), *trig* (sp^2) and *dig* (*sp*) nomenclature based on hybridization at the cyclization center.[3] Therefore, iodocyclization of propargyl alcohol is one of the efficient ways of constructing aryl and heteroaryl iodides in a single-step with maximum atom economy. Interestingly, these cyclic iodides are an integral part of a large variety of natural products[8] (Figure 1). Further, these products can be converted

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Srinivasarao Yaragorla was born in Sitharamapuram village in Telangana, India. He obtained master's in chemistry from the University of Hyderabad and then moved to IICT-Hyderabad for Ph D. After completion of Ph D (2008), he moved to the University of Minnesota, USA for Postdoctoral research. Subsequently, he was also a DS Kothari Postdoctoral Fellow at the University of Hyderabad. In 2012, he joined the Central University of Rajasthan as Assistant Professor and moved to the University of Hyderabad in 2017. He is a synthetic organic chemist, working on Allene-cyclizations, rearrangements, cycloadditions, and iodocyclization reactions by exploring the ambiphilic reactivity of propargyl alcohols and β-enaminones. He is also pursuing the total synthesis of natural products.

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into useful organic materials[4] and medicinally important compounds[5] using a cross-coupling[6] (Figure 2) or substitution reactions[7] with the preinstalled iodide functionality.

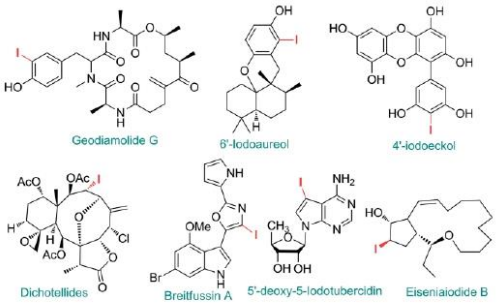


Figure 1. Representative examples of natural products with iodide functionality.

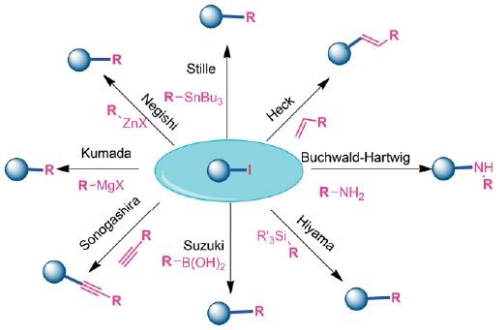


Figure 2. Synthetic transformations of iodo-compounds through cross-coupling reactions.

The general way of iodocyclization of propargyl alcohol (**a**) is depicted in Figure 3. When a bidentate nucleophile reacts with the ambiphilic substrate (**a**), in general one can expect three reaction paths. One is the direct substitution (S_N1) via the carbocation intermediate to give (**b**), then activation by electrophilic iodine gives the intermediate (**c**). Now (**c**) can undergo *exo* cyclization to give (**e**) or *endo* cyclization to give (**d**). Alternatively, an S_N2' can take place between (**a**) and bidentate nucleophile to give allene (**h**). Activation of (**h**) by iodine gives iodonium intermediate (**i**), which can undergo *exo* cyclization to give (**k**), or *endo* cyclization to form (**j**). The third case is that if the propargyl alcohol has a nucleophilic branch at propargylic carbon, then the triple bond can be activated with iodine (**f**) and then cyclizes to give (**g**).

We classified the available literature reports of iodocyclizations into four significant sections based on the nucleophile that reacts with the cyclic iodonium ion.

i. Oxygen-containing heterocycliciodides (includes-furans, benzofurans, pyrans, benzopyrans, benzoxepines, lactones and oxazoles)

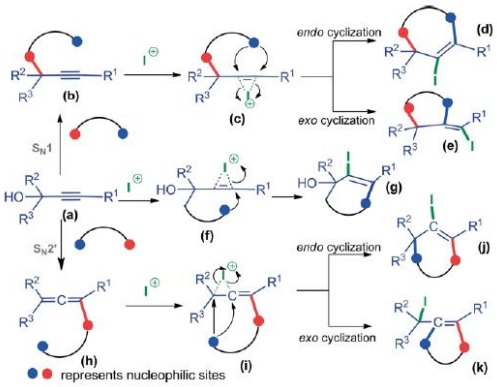


Figure 3. Possible ways of iodocyclizations from propargyl alcohol.

ii. Nitrogen-containing heterocycliciodides (includes pyrroles, indoles, indolizines, quinolines, Oxindoles, carbazoles and lactams)

iii. Sulfur and Selenium-containing heterocyclic iodides (includes thiophenes, benzothiophenes and selenophenes)

iv. Carbocyclic iodides (includes benzenes, indenes, and naphthalenes)

However, we do not include the cross-coupling reactions of these iodides, as a routine practice, many authors have performed cross-coupling reactions to show the synthetic utility of these iodides (briefly as shown in Figure 2).

2. Oxygen-Containing Heterocyclic Iodides

Oxygen-containing heterocycles are naturally abundant as well as biologically active molecules. For example, sugars, vitamins, pigments, antibiotics and hormones are biologically active compounds which belong to this class.[9–13] In this section, we will review the synthetic methods developed to achieve the oxygenated heterocyclic iodides, such as iodofurans(benzo) (Scheme 1–Scheme 11), iodo-pyrans(benzo) (Scheme 12–Scheme 24), bezoxepine-iodides (Scheme 25 and Scheme 26), iodolactones (Scheme 27–Scheme 29) and iodoxazoles (Scheme 30 and Scheme 31).

2.1. Iodofurans and Iodobenzofurans

Furans are five-membered heterocyclic aromatic compounds, considered as a privileged scaffold in medicinal and material science due to their unique properties.[14] Therefore many synthetic methods were developed for the iodofurans, so that they can be conveniently transformed into the desired products. A regioselective iodocyclization of propargyl alcohol **1** (3-alkyne-1,2-diol) through a 5-*endo-dig* manner followed by a dehydration method was developed to achieve the synthesis of 3-iodofurans (**2**) using molecular iodine (Scheme 1).[15] This reaction was performed using 3 equiv. of iodine and 3 equiv. of $NaHCO_3$ in acetonitrile for 2–12 h at ambient temperature. The products

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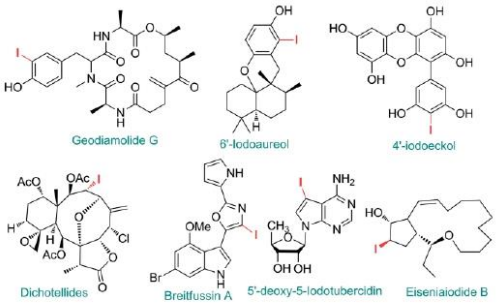


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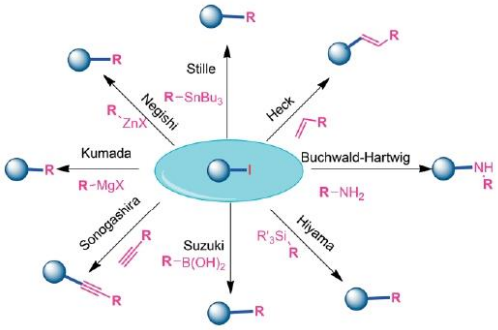


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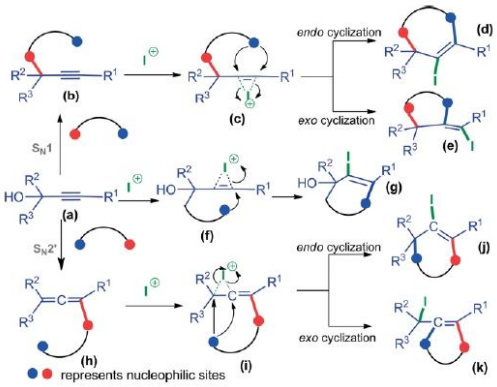


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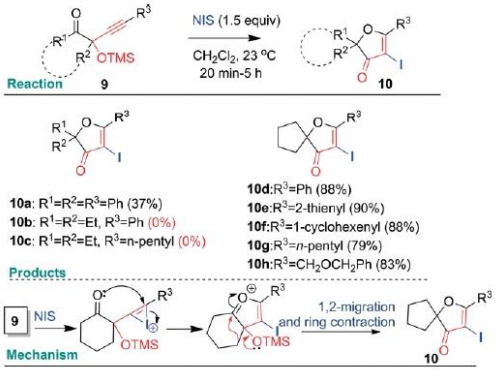
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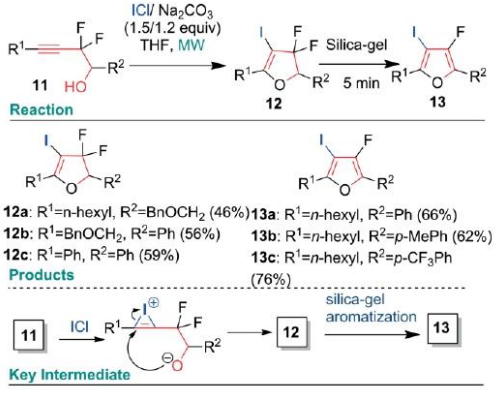
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molecular oxa-nucleophile to open the cyclic iodonium. The next approach is the cyclization through carbonyl-tethered propargyl alcohol (**9**). 2-Alkynyl-2-silyloxy carbonyl compounds (**9**) were treated with *N*-iodo succinimide (NIS, 1.3 equiv.) in DCM at 23 °C gave 4-iodo-2,2,5-triphenylfuran-3(2H)-one **10a** in 37 % yield. The reaction did not produce the desired product when R^1 and R^2 are ethyl groups. If R^1 and R^2 are connected (cyclic structure, see mechanism), then the reaction yielded the spirocyclic compound **10d** with a ring contraction via a 1,2-migration. This iodocyclization through 1,2-migration is highly flexible with the alkyne substitutions (R^3) like 2-thienyl, 1-cyclohexenyl, *n*-pentyl and methoxybenzyl groups (**10e**–**10h**).[18] (Scheme 4).



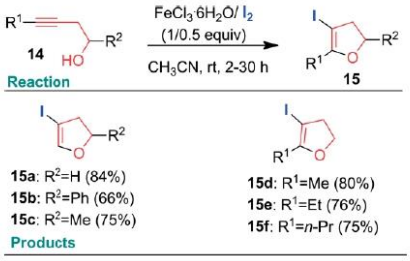
Scheme 4.

The next iodocyclization precursors were homopropargyl alcohols. G. B. Hammond[19] group reported a microwave assisted iodocyclization of gemdifluoro homopropargyl alcohols with ICl to produce the fluorinated iodofuran analogues **12** and **13.** As mentioned in Scheme 5, iodofuran **12** was further aromatized to **13** by stirring in silica gel.



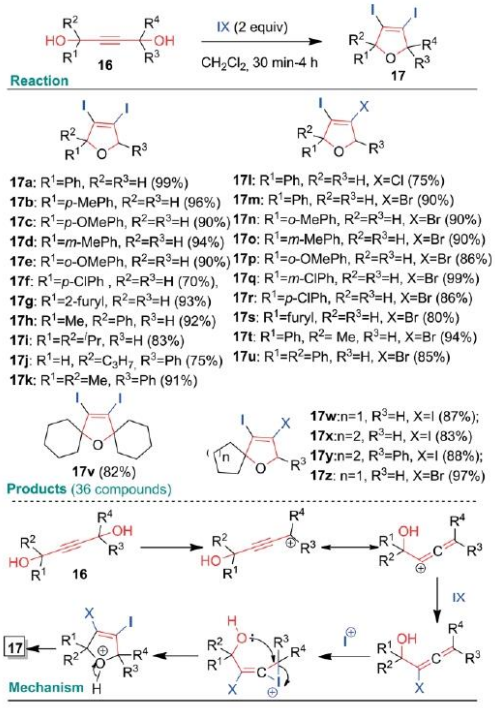
Scheme 5.

Homopropargyl alcohols and higher homologs were subjected to iron-promoted iodocyclization to get cyclic vinyl iodides. The reaction was performed with 30 mol-% $FeCl_3$, and stoichiometric amounts of propargyl alcohol (**14**) and iodine at r.t. in acetonitrile to obtain the reaction yields in the range of 66–80 % (Scheme 6).[20] It is interesting to note that, primary and secondary alcohols (**14**) were good nucleophiles for this 5-*endo* cyclization, but not the tertiary alcohols.



Scheme 6.

Liang[21a,21b] and his co-workers utilized but-2-yne-1,4-diols (**16**) as the iodocyclization precursor to obtain the dihalo-furans (**17**). The reaction was performed at r.t. in DCM and gave good yields of the products. They have used a variety of electrophilic iodine reagents such as I_2, IBr and ICl. It was observed that a trace amount of water (in the form of wet-DCM) is necessary



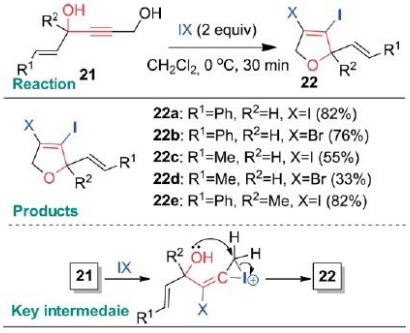
Scheme 7.

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for obtaining better yields. Interestingly, both the halide (anionic and cationic) ions are incorporated in the products (atom economy) and water is the only by-product formed (Scheme 7). In the proposed mechanism, propargyl alcohol **16** yields allenyl cation upon dehydroxylation, which combines with X^- to form allenyl halide. Then the formation of cyclic iodonium takes place, which then regioselectively opened by the nucleophilic alcohol to give the desired products **17.** A year later another publication was appeared using the same protocol for the 3,4-diiodofurans (I_2 (3 equiv.), r.t., 1 h).[21c] However, it is interesting to note that Kruglov[22] and his group reported the first method of diiodofurans from **16** using iodine in chloroform under heating conditions.

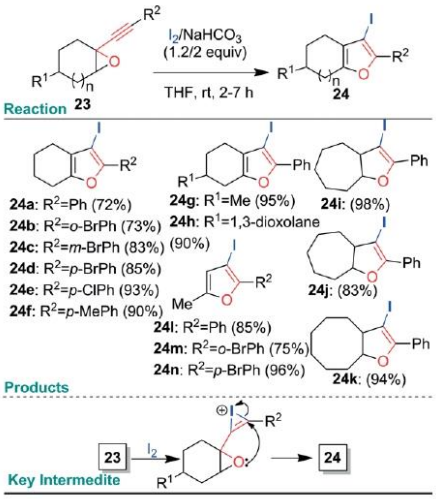
4-Hydroxy-2-but-2-yn-1-ones (**18**) were used as the next iodocyclization precursors to generalize synthetic method for 3,4-dihalofurans (Scheme 8).[23] The optimization studies suggested that the use of methanol as the nucleophilic solvent is crucial for the chemoselective synthesis of the 3,4-dihalofurans. Iodine and IBr were used as the electrophilic reagents, and the reaction was performed at r.t. to obtain the products in moderate to good yields (48–91 %). The reaction mechanism proceeded through the formation of allenyl cation which combines with the nucleophilic halide. Activation of allene with I^+ followed by ring opening gives the desired product **19** or **20**.

Liang group[21b] has explored the propargyl alcohols tethered vinyl groups as the iodocyclization precursors (Scheme 9). The reaction proceeded in wet DCM at 0 °C for iodine and –10 °C for IBr. This reaction proceeded through chemoselective iodination (vinyl verses alkyne) followed by the 5-*endo* cyclization to yield the iodofuran **22**.

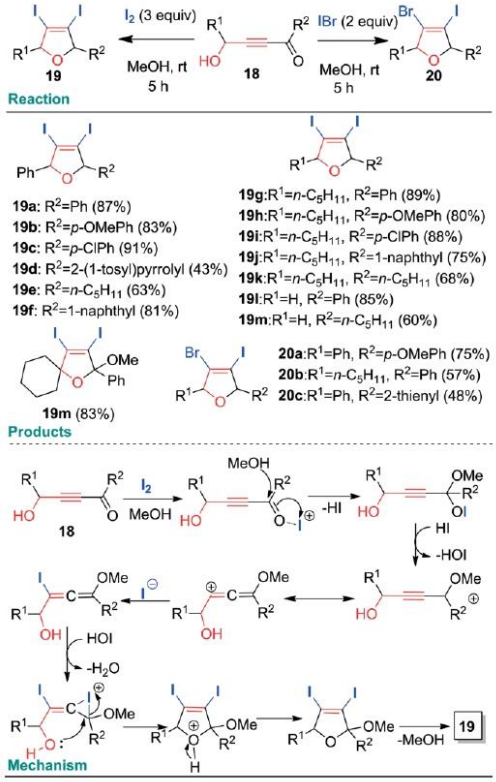


Scheme 9.

In continuation of iodofuran synthesis, now let us look at the literature reports on analogous compounds, iodo-benzofurans. Liu and co-workers reported the iodocyclization of propargyl oxiranes (**23**) using iodine as the electrophilic reagent in THF solvent at r.t.[24] The reaction generally completed in 2–7 h and produced the desired 3-iodobenzofurans (**24**) in excellent yields. In this method, cyclohexane, cycloheptane and cyclooctane fused iodofurans were synthesized without compromising the reaction yields (Scheme 10).



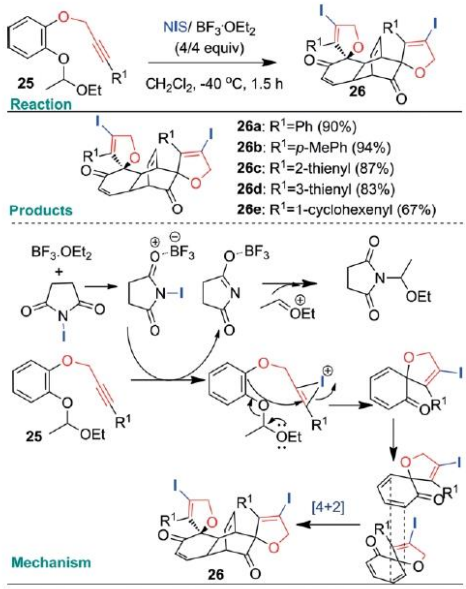
Scheme 10.



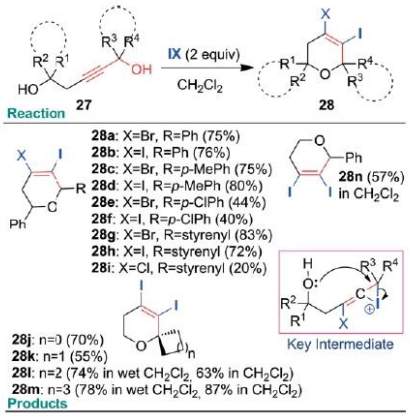
Scheme 8.

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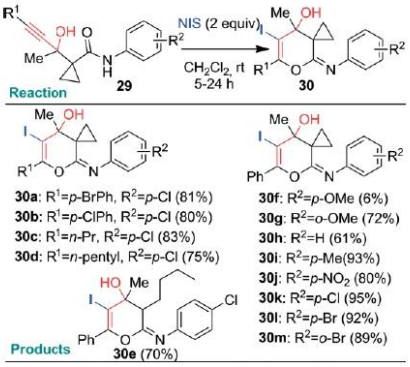
A. Wada[25] reported an efficient synthesis of spiro-furans through *ipso*-iodocyclization strategy from ethoxyethyl ethers to alkynes at the *ortho*-position (**25**). A combination of NIS and BF_3·Et_2O in DCM at –40 °C was found to be the optimum condition for the *ipso* cyclization. Spirofuran thus obtained was further underwent a Diels-Alder cycloaddition to yield the dimer **26** (Scheme 11). The proposed reaction mechanism suggested that activated NIS (with BF_3·Et_2O) reacts with **25** and produce the cyclic iodonium, which further undergoes a cascade spirocyclization and Diels-Alder cycloaddition to give **26**.



Scheme 11.



Scheme 12.

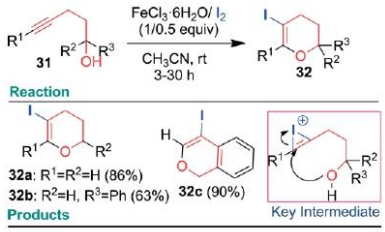


Scheme 13.

2.2. Iodopyrans and Iodobenzopyrans

Pyrans (includes benzo/naphthopyrans) have wide occurrence in numerous natural products and biologically active molecules.[26] Therefore several groups developed the iodocyclization protocol for their synthesis from propargyl alcohols. As an extension to the Scheme 7, Liang[21b] has reported the iodocyclization protocol to synthesize 4,5-dihalogenated 3,6-dihydro-2H-pyran (**28**) from pent-2-yne-1,5-diol derivatives (**27**). Here, propargyl alcohol (**27**) was stirred in wet-DCM with 2 equiv. of IX (X=I, Br, Cl). The reaction yields are generally good with I_2 and IBr but poor with ICl (20 %). The same transformation was also reported by the Yamamoto[21c] in the following year using 3 equiv. of iodine (**28l**, **28m**) as mentioned in Scheme 12. An approach, where amide oxygen acts as an internal nucleophile to open the cyclic iodonium salt to achieve the synthesis of iodopyrans **30** is developed from propargyl alcohols **29** (Scheme 13).[27] Interestingly, the cyclopropane ring is stable under these conditions and retained in the product.

A direct 6-*endo dig* cyclization is reported using a combination of $FeCl_3$·$6H_2O$ and iodine (Scheme 14) from **31**.[20] Here the length of the alkyl chain between triple bond and alcohol (two carbons) is significant for this transformation. Accordingly, propargyl alcohol derivative **31** gave the iodopyrans **32a**, **32b** and **32c** in good yields. By decreasing the carbon length to one

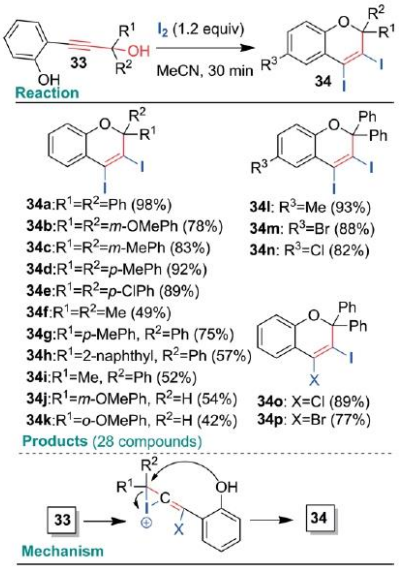


Scheme 14.

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(between triple bond and alcohol), this method yielded the iodofuran as the product (see Scheme 6).

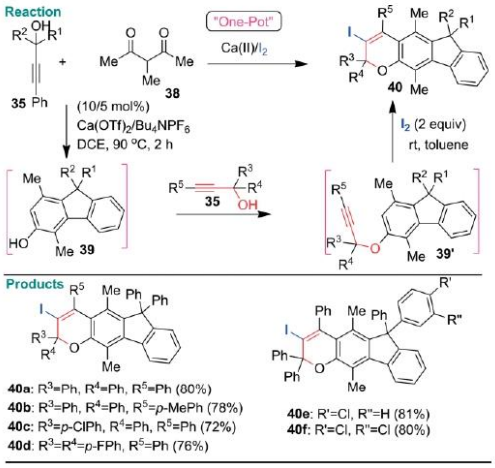
Benzopyrans[28a] are an important group of a natural compound such as flavonoids,[28b] which are abundant in the plant kingdom. 2-(3-Hydroxy-3,3-diphenylprop-1-yn-1-yl)phenols (**33**) was subjected to iodocyclization using I_2 (1.2 equiv.) at r.t. in acetonitrile. The reaction completes in 30 min and yields the 3,4-diiodo benzopyrans **34** in good to excellent yields (Scheme 15).[29] ICl and IBr were also employed for cyclization to obtain **34o** and **34p**. This reaction proceeds through the formation of an allenyl cation that combines with iodide and further iodocyclization gives the product **34**.



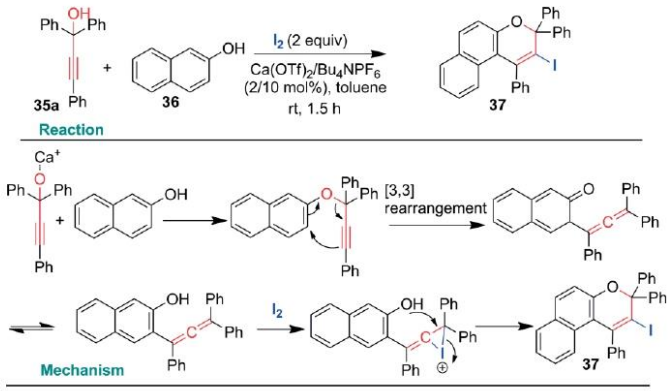
Scheme 15.

Recently, we have developed a two-component protocol for the synthesis of 3- iodochromenes from a *tert*-propargyl alcohol **35** and 2-naphthol (**36**). The combination of $Ca(OTf)_2$ and I_2 were used in toluene at r.t. Initially, Ca(II) produce the ether, which then undergoes 6-*endo* iodocyclization to furnish the iodobenzochromene **37**. (Scheme 16).[30] In this reaction, the ether intermediate was isolated and treated with iodine under the same conditions to obtain the product and thus confirms the mechanism.

Later we extended this concept to make the iodo-derivatives of fluorenopyrans (**40**) starting from **35** and **38** in a one-pot method. In this reaction, initially, propargyl alcohol **35** reacts with diketone **38** to give fluorenol **39** (in situ). Etherification of **39** with **35** gave the iodocyclization precursor **39′**. Electrophilic iodine promoted 6-*endo* cyclization of **39′** gave 3-iodofluorenopyrans **40a**–**40f** in good yields (Scheme 17).[31] Interest-



Scheme 17.

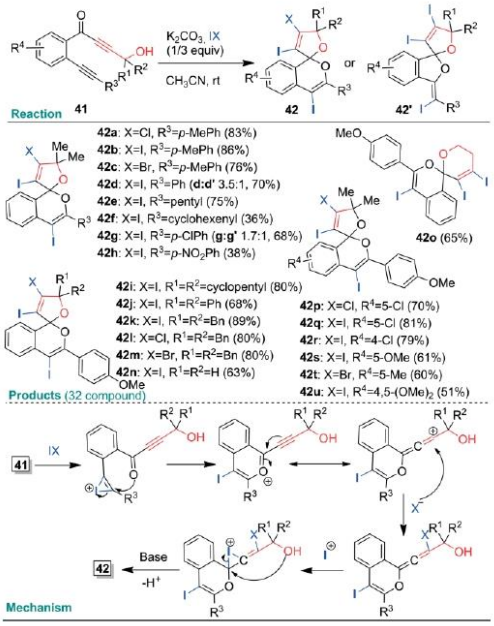


Scheme 16.

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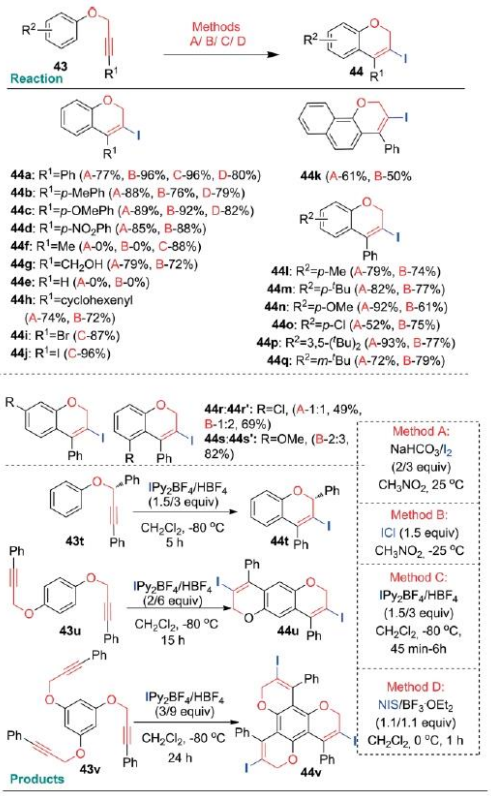
ingly all these reactions were performed in one-pot, and in this protocol 7 new bonds were formed. The proposed fluorenol intermediate **39** was isolated and further treated under iodocyclization conditions to obtain the desired product **40**.

The synthesis of spiroketal compounds (furopyrans) **42** from a tandem iodocyclization of 1-(2-ethynylphenyl)-4-hydroxybut2-yn-1-one derivatives (**41**) is developed under mild reaction conditions using K_2CO_3, IX in CH_3CN, at r.t. The source of I^+ is I_2, ICl and IBr. The substrate scope of the reaction is very general and gave the products in good yields (Scheme 18).[32] The proposed reaction mechanism indicates that initially, simple alkyne moiety was activated with I^+ and then the nucleophilic attack by carbonyl oxygen through *6-endo* fashion gave the iodobenzopyran intermediate, which could resonate with the corresponding allenyl cation. Then a sequential halide attack on allenyl cation folllowed by the activation of allene with I^+ and a spirocyclization gave the product **42** in good yields.



Scheme 18.

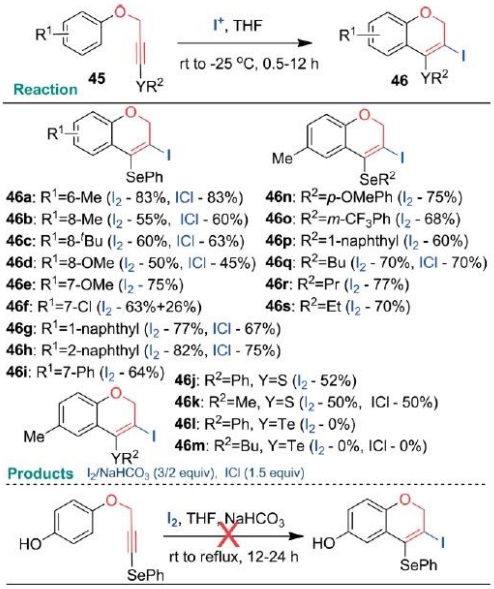
Iododcyclization of propargylic aryl ethers to iodochromenes is extensively studied by various research groups using the following conditions – method-A: I_2/$NaHCO_3$, nitromethane, 25 °C; method-B: ICl, nitromethane, –25 °C; method-C: IPy_2BF_4/HBF_4, DCM, –80 °C, method-D: NIS, BF_3·Et_2O, DCE, 0 °C (Scheme 25).[33] Further, it is demonstrated that the chirality at propargylic carbon (**43t**) retained during the formation of iodopyran **44t**. Next, it is proved that bis and trispropargyl ethers are involved in cyclization to yield fused pyrans **44u** and **44v** in good yields, of course, the catalyst loadings were increased as per the number of pyrans formed (Scheme 19).[33] Organochalcogen propargyl aryl ethers underwent highly selective intramolecular electrophilic cyclizations with I_2 or ICl afforded 3-iodo-4-chalcogen-2H-benzopyrans (Scheme 20).[34] It is observed that the efficiency of the cyclization process was significantly influenced by the steric effects of an aryl ring because the cyclization reaction gave low yields with aromatic rings having an *ortho*-substituent than those having no substituent (Scheme 20). When the aryl ring is bearing a 4-hydroxyl group, the reaction did not proceed. The chalcogen atoms used here are selenium, tellurium and sulfur. The proposed reaction mechanism suggests that initially, diiodo selenium (chalcogen) will form and then the triple bond is activated with I^+ followed by a *6-endo dig* cyclization results the product **46**.



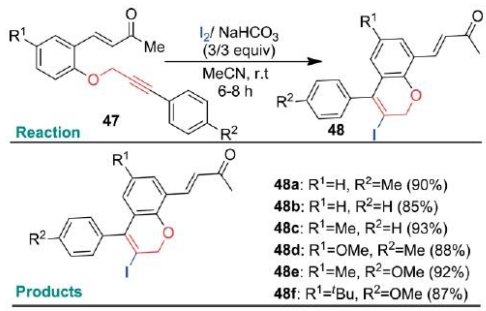
Scheme 19.

Propargyl ether **47** was subjected to iodocyclization using iodine in acetonitrile at r.t. Interestingly, conjugated ester moiety on the *ortho* position was unreactive under these conditions and the propargyl ether cyclized to yield the iodochromene **48** in good yields (Scheme 21) through the other *ortho* carbon attack.[35]

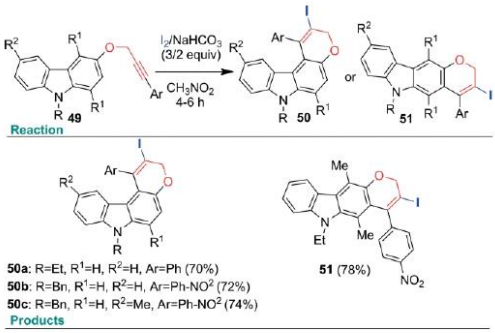
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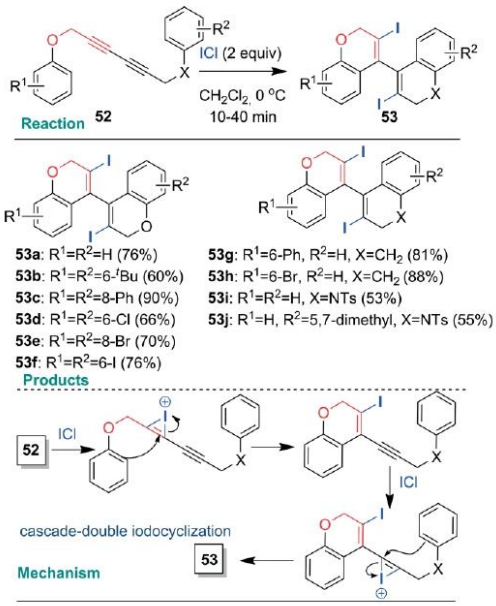
Scheme 20.



Scheme 21.



Scheme 22.



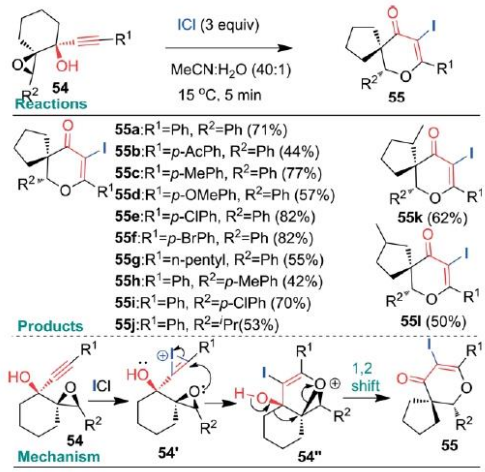
Scheme 23.

R. Nagarajan[36] reported a simple and straightforward iodocyclization of *o*-propargylated carbazoles (**49**) for the synthesis of iodo-pyranocarbazole derivatives **50**, **51** in good yields. In this protocol, the authors used *N*-alkylated carbazoles as the reactants (Scheme 22).

P. H. Lee[37] reported an electrophilic intramolecular two fold iodocyclization from the reaction of diynes and diynyl diethers with ICl under mild conditions (DCE, 0 °C). The reaction produced bis(2H-hydronaphthalene and chromene) and 2H-quinoline bearing an alkenyl iodide moiety in good to excellent yields (Scheme 23). Interestingly, for the second iodocyclization reaction, the cyclic iodonium was opened with *ortho*-carbon (of phenyl ring) to give the respective iodopyrans **53a**–**53j.**

1-Alkynyl-2,3-epoxy alcohols (**54**) were conveniently transformed to construct 2,3-dihydro-5- iodopyran-4-one (**55**) through a domino cyclization/1,2-migration reaction using ICl. Use of wet solvent (acetonitrile) is proved to be essential for this reaction. The reaction rate is fast (5 min) and yielded the products in moderate to good yields (42–82 %). Single crystal X-ray data confirmed the structure of the product. As depicted below (Scheme 24), the proposed reaction mechanism suggests that this reaction proceeds through the formation of intermediate **54′** which cyclizes to oxonium intermediate **54′′** followed by 1,2-shift gives the final product **55**.[38]

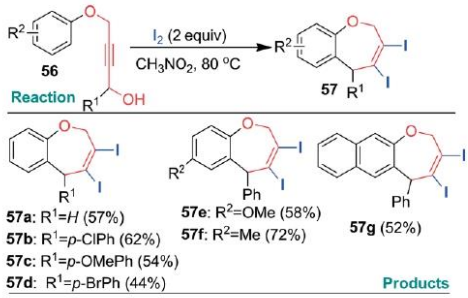
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Scheme 24.

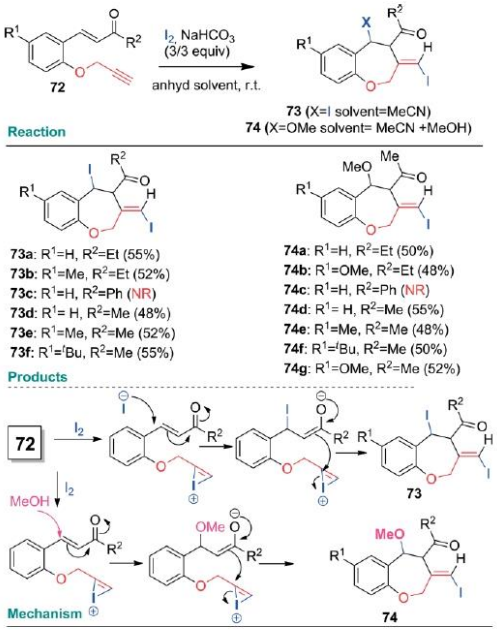
2.3. Iodobenzoxepines

A wide range of natural products possesses seven-membered oxacycle (benzoxepine)[39] in their molecular framework, and these heterocyclic rings are important intermediates for the synthesis of pharmaceuticals and biologically active molecules.[39] Liang[40] reported iodocyclization of 4-aryloxy-but-2-yn-1-ols (**56**) in nitromethane at 80 °C to give 3,4-diiodo benzo[*b*]oxepines (**57**). The reaction proceeds through the formation of allenyl cation, which combines with iodide to give allenyl iodide and the activation of this with I^+ forms the cyclic iodonium ion which is further opened by *ortho*-carbon of phenol gives the final product (**57**) (Scheme 25). In all the cases the benzylic carbon of **57** is a 2°-carbon.



Scheme 25.

Before this report, K. C. Majumdar[35,41] reported the synthesis of benzoxepines (**59** and **60**) from **58** with I_2 (1 equiv.) and $NaHCO_3$ (1 equiv.) in acetonitrile (Scheme 26). In this reaction, solvent played a crucial role in the formation of the product. When acetonitrile is the solvent, iodine acted as both electrophile and nucleophile. Initially, when the reaction was performed without methanol **59** was obtained, by the Michael addition of nucleophilic iodine and the subsequent carbanion opens cyclic iodonium to yield **59**. With excess methanol (20 equiv.) reaction afforded a mixture of **60** and uncyclized iodo derivative, here methanol adds to the conjugate enone in the 1,4-fashion followed by the resulting carbanion attacks on the cyclic iodonium to yield **60**. Surprisingly, when the aryl ketone (**59c**, **60c**) was subjected to iodocyclization, it was observed that the reaction did not occur.



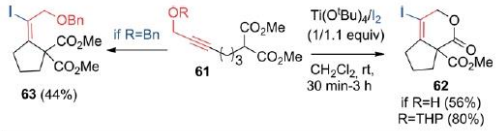
Scheme 26.

2.4. Iodolactones

Lactones are cyclic esters, which widely occurs as building blocks for hormones, enzymes, antibiotics and some anticancer drugs.[42] Iodocarbocyclization reactions of 4-alkynylmalonates (**61**) were developed to synthesize bicyclic-iodolactones (**62**) in good yields. A combination of iodine and $TiCl_4$ was employed as the catalysts for this conversion. When R=H or THP, the reaction proceeded smoothly to yield **62**. However, it failed to yield lactone if R is a benzyl group. The reason being the benzyl group could not deprotect under these conditions to form lactone and hence furnished **63** only (Scheme 27).[43]

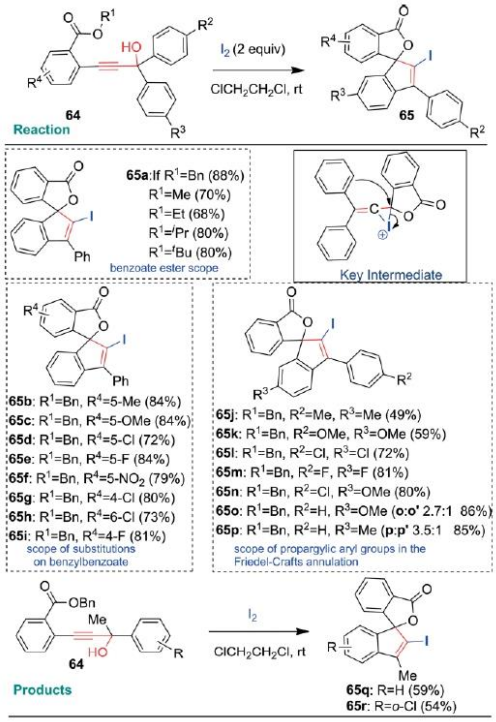
Facile synthetic approach to substituted 2-iodospiro[indene-1,10 -isobenzofuran]-3[l]-ones (**65**) is developed at r.t. via an iodine-promoted cascade cyclization of 2-(3-hydroxy-3,3- diary prop-1-yn-1-yl)benzoates (**64**) in good yields (Scheme 28).[44] Various benzoates such as benzyl, methyl, ethyl, isopropyl and *tert*-butyls are compatible with the protocol (**65a**). The method-

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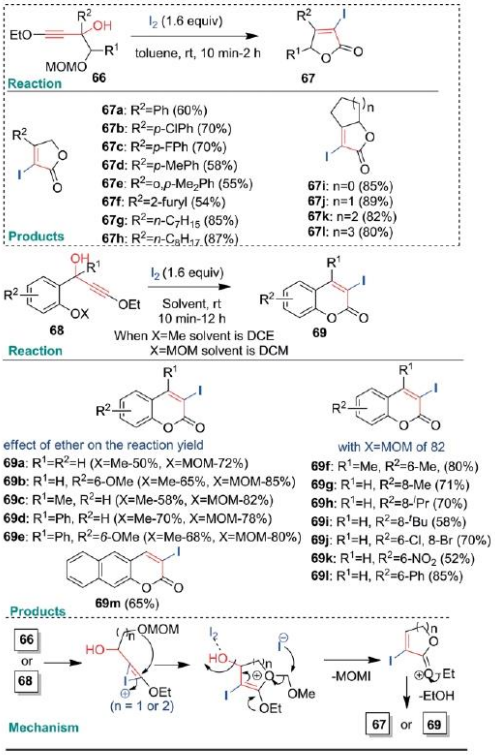
Scheme 27.

ology also tolerated a large variety of substitutions on the benzoate ring. If we look at the proposed reaction mechanism, there is a possibility of cyclization with both the propargylic aryl rings. The authors thoroughly investigated the propensity of cyclization, and the implications suggest that electron-rich aryl ring undergo Friedel-Crafts annulation more rapidly compared to the electron poor aryl rings. If there is an aryl and methyl group at the propargylic position, obvious products are obtained.



Scheme 28.

Another report on the synthesis of 4,5-disubstituted 3-iodobutenolides **67** is developed through a 5-*endo-dig* iodocyclization of 1-alkoxy-4-ethoxy-3-yn-1,2-diol derivatives (**66**). This protocol is further extended to the synthesis of 4-substituted 3-iodocoumarins through 6-*endo-dig* iodocyclization of 3-ethoxy-1-(2-alkoxyphenyl)-2-yn-1-ols.[45] The reaction proceeded under mild conditions using I_2 in CH_2Cl_2 or toluene at room temperature. Hydroxyl groups are protected as methoxy and MOM ethers and used as oxy-nucleophiles for this intramolecular cyclization to obtain the desired products in good to excellent yields (Scheme 29).



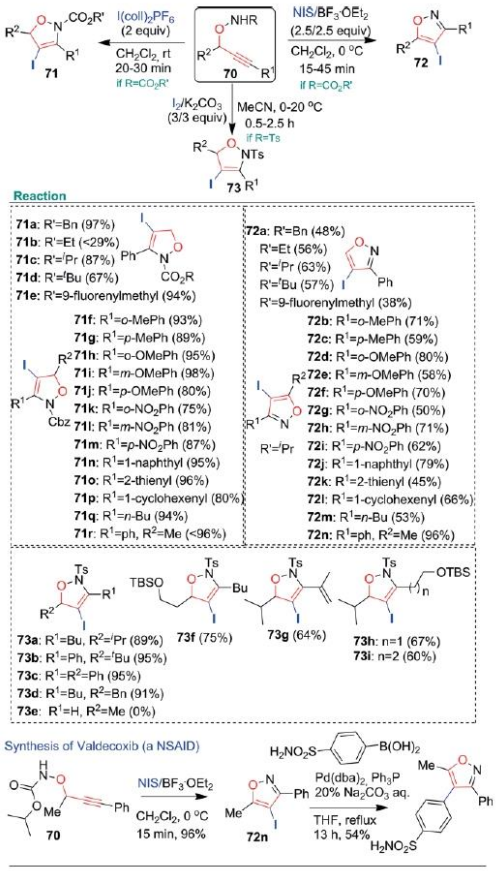
Scheme 29.

2.5. Iodoxazole

Oxazole is a significant class of heterocyclic compounds, various biological activities of these type of heterocycles are well known in the literature.[46] Synthesis of 2,5- dihydroisoxazoles and isoxazoles using iodocyclization of *N*-alkoxycarbonyl o-propargylic hydroxylamines **70** were developed by A. Wada, this method was also used for the preparation of valdecoxib and its 2,5-dihydroxy derivative.[47] Valdecoxib is used as a nonsteroidal anti-inflammatory drug (NSAID) for treatment of rheumatoid, osteoarthritis and painful menstruation. Here iodine act as both an iodinating and an oxidizing agent thus formation of aromatized product (**72**) by oxidative aromatization. When bis(2,4,6-collidine)iodonium(I) hexafluorophosphate $[I(coll)_2PF_6]$ was used as an iodinating reagent, reaction resulted in an excellent yield of 2,5-dihydroisoxazole (**71**), use of $BF_3{\cdot}Et_2O$ with $[I(coll)_2PF_6]$ gave trace amount of aromatized product **72** along with dihydroisoxazole **71**, NIS (without $BF_3{\cdot}Et_2O$) did not result

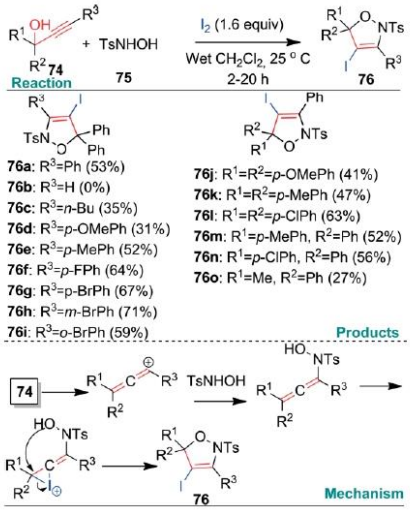
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in the aromatized product (**72**) whereas NIS with BF_3·Et_2O gave moderate to excellent yields of aromatized products. Synthesis of 2,5- dihydroisoxazoles was also reported by D. W. Knight[48] by treating *N*-alkoxycarbonyl *o*-propargylic hydroxylamines (**70**). *N*-tosyl compound (**70**) was treated with I_2 in the presence of K_2CO_3 reaction gave an excellent yield of **73**, however reaction was not observed in case of terminal alkynes (**70e**, R^1=H) (Scheme 30).



Scheme 30.

An efficient synthesis of 4-iodo-2,5-dihydroisoxazoles (**76**) was achieved from propargylic alcohols and *N*-tosyl hydroxylamine using iodine in wet DCM at 25 °C. *N*-sulfonyl allenamide was the key intermediate for this tandem transformation (Scheme 31).[49] Broad range of substrate scope was achieved for this transformation and all the products resulted in moderate to good yields. However, in the case of the terminal alkyne (**74b**, R^3=H) desired product was not formed, and slightly lesser yield was observed in case of 2,4-diphenylbut-3-yn-2-ol (**74o**).



Scheme 31.

3. Nitrogen-Containing Heterocyclic Iodides

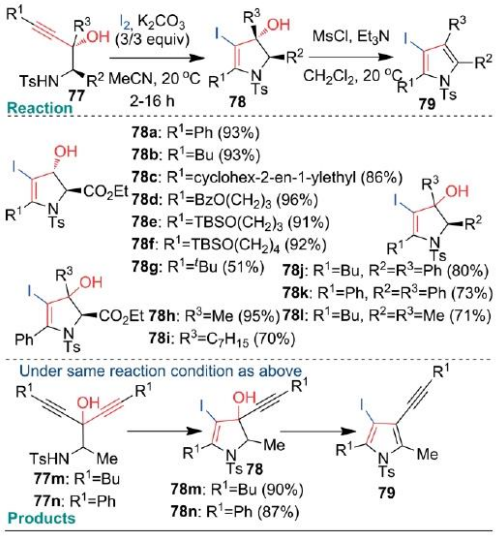
Azaheterocycles are known to show better biological activity than non-nitrogen compounds. Heterocyclic compounds containing nitrogen are key building blocks for the synthesis of biologically and medicinally important molecules. A vast number of nitrogen-containing heterocyclic building blocks have applications in drug discovery,[50] pharmaceutical research, and agriculture science.[51] This section will deal with the synthetic methods developed for the nitrogen-containing heterocyclic iodides, such as iodopyrrole (Scheme 32–Scheme 34), iodoindole (Scheme 35–Scheme 37), iodoindolezine (Scheme 38 and Scheme 39), iodoquinoline (Scheme 40–Scheme 43) and iodoxindole (Scheme 44), iodocarbazole (Scheme 45 and Scheme 46), oxa-fused benzimidazole (Scheme 47) and iodolactam (Scheme 48).

3.1. Iodopyrroles

Pyrroles are known to possess a diverse range of biological activities.[52] David W. Knight[53] reported the facile synthesis of iodopyrroles **79** from 3-hydroxy-2-sulfonylamino-4-alkynes **77** in good to excellent yields by treating with iodine/K_2CO_3 in acetonitrile at 20 °C. Interestingly, they were able to isolate the hydroxyl-dihydropyrrole (**78**) intermediate, which is stable under the reaction conditions. The tertiary alcohols were isolated and treated with triethylamine to get the desired *N*-tosyl pyrrole **79**. The reaction mechanism suggests that the tosylamine opens the cyclic halonium ion in 5-*endo* fashion for yielding hydroxy pyrroles (Scheme 32). When a gem-dialkynyl substituents at propargylic carbon was taken as the precursors (**77m, 77n**), the reaction conditions gave the alkynyl-substituted iodopyrrole **79.** Interestingly, here only one of the alkynes was selec-

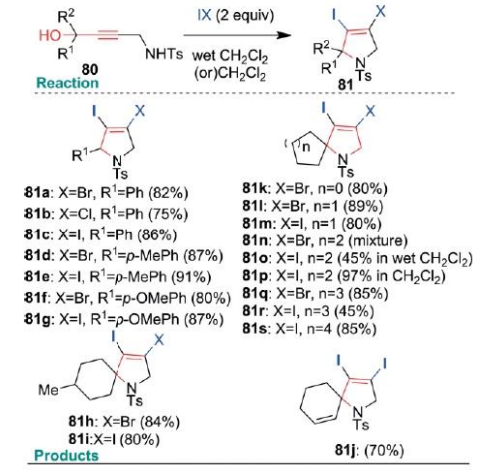
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tively activated with iodine even though the stoichiometry of the reagent is three.



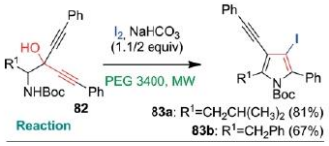
Scheme 32.

Later 4-aminobut-2-yn-1-ol (**80**) was treated with different electrophilic iodine reagents (I_2 and IBr) to obtain *N*-tosyl dihalo pyrrole derivatives **81** in good to excellent yields (Scheme 33).[21b,54] Spiranes (**81k**–**81s**) were also obtained using this protocol, and the ring sizes at pyrrolidine 2-positions varied from 3–7. The proposed reaction mechanism suggests the formation of allenyl cation followed by iodocyclization to furnish the target compounds.



Scheme 33.

Polyethelene glycol (PEG) has been explored as a practical, alternative, a cheap and eco-friendly solvent for organic synthesis.[55] F. Lamaty[17] reported electrophilic iodine mediated cyclization of *N*-Boc alkynyl amino alcohols (**82**) in solid PEG-3400 as the reaction medium under microwave irradiation (50 °C, 10 min). These products are effectively isolated by a simple workup procedure, (avoiding chromatographic purification) in moderate to good yields (Scheme 34). This method was also extended to make the iodofurans using the same strategy starting from alkynyl diols as depicted in Scheme 3.



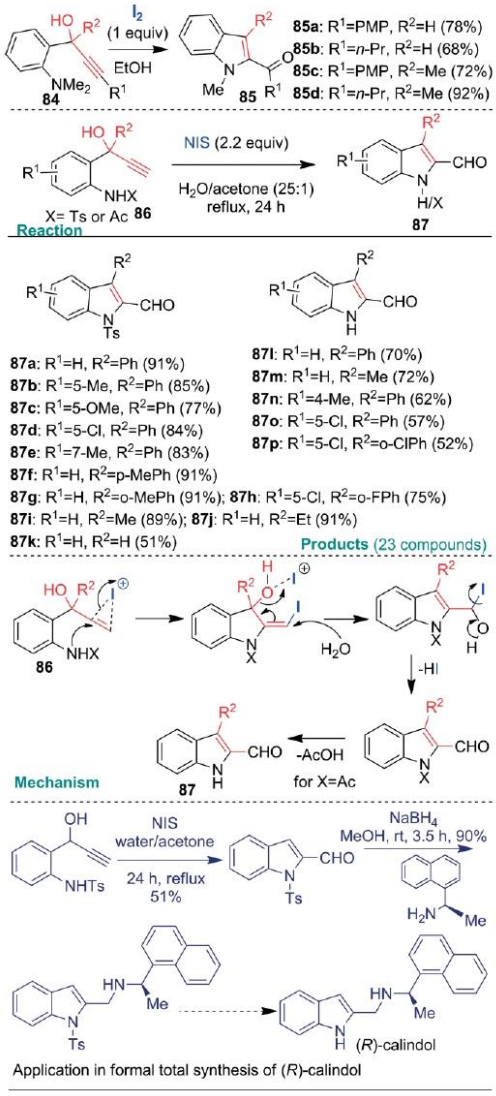
Scheme 34.

3.2. Iodoindole

Indoles[56] or benzopyrroles have a broad range of application in pathophysiological conditions such as cancer, viral and microbial infections, depression, migraine, hypertension, etc. Owing to these important aspects of indoles, several methodologies were developed for the synthesis of iodoindoles. Propargyl alcohol **84** with a dimethylamino functionality were subjected to iodocyclization in protic solvents such as methanol or ethanol to obtain 1-methyl,2-acylindoles **85** in good yields.[57a] The reaction proceeds through a 5-*endo dig* cyclization to give exocyclic vinyl iodide which underwent aromatization and elimination cascade process to yield **85**. It was also observed that the mode of cyclization depends on the nature of the solvent. In case of a polar aprotic solvent (DCM or acetonitrile), the reaction proceeded through a 6-*exo* cyclization to give iodoquinolines. Another report was known for the synthesis of 1H-indole-2-carbaldehydes (**87**) from 1-(2-aminophenyl)-prop-2-yn-1-ols (**86**) using NIS in water. In this report, the arylamines were protected as tosylates and acylates (unlike dimethyl groups in Flynn approach). When the reaction commenced from acylamines, deacetylation was observed in the final products, but in the case of tosylamines, the tosyl group is intact with the products (**87a**–**87k**). In the reaction mechanism, a stable vinyl iodide was obtained through iodocyclization, which was further continued to get indole-2-carbaldehyde. The reaction yields are generally from 48–91 %. A gram scale synthesis was also exemplified, and formal synthesis of (*R*)-calindol was also achieved using this protocol (Scheme 35).[57b]

In another approach (B. L. Flynn)[58] propargyl alcohol **88** was treated with NIS in CH_2Cl_2 to obtain the iodide **89** through a cascade cyclization (Scheme 36). This reaction was also optimized with iodine/K_2CO_3 in wet-acetonitrile. The benzaldehyde imine (R^1=R^2=H, **88**) failed to give the **89b** (with both the NIS and I_2) however the ketone derivative (ketimines) gave 63 % yield of **88a** with NIS. In the case of a 6–5–6 ring fusion (**89c**–**89h**), both the aldimines and ketimines are reactive to produce the product with NIS (Method A). The proposed mechanism has

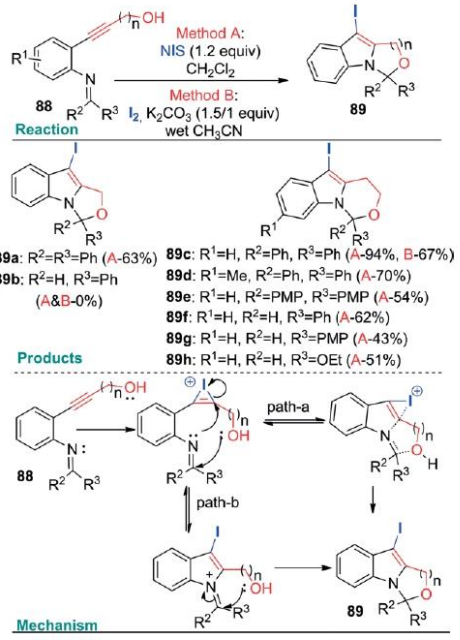
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Scheme 35.

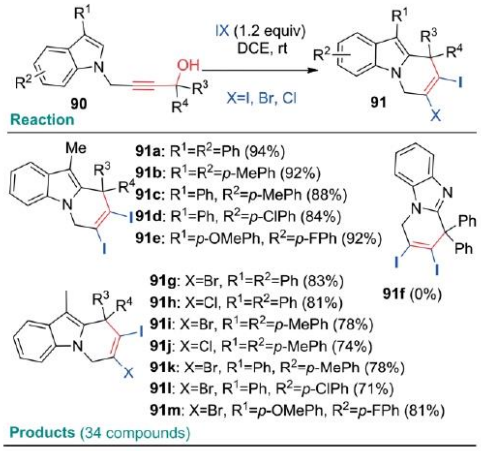
two paths, after the formation of cyclic iodonium ion hydroxy can attack on imine carbon, and a simultaneous attack of nitrogen on iodonium ion can lead to the product **89** (path a). Another path is a stepwise mechanism (Scheme 36).

A strategy for the synthesis of dihalo-6,9-dihydropyrido[1,2-*a*]-indoles (**91**) has been developed through a cascade iodocyclization of 4-(3-methyl-1*H*-indol-1-yl)-1,1-diphenylbut-2-yn-1-ol derivatives (**90**) using electrophilic reagents such as IX (X=I, Br, Cl) at r.t. in DCM. The reaction mechanism proceeds through



Scheme 36.

the formation of allenyl cation which combines with halide ion and follows *6-exo* iodocyclization gave the dihalo-dyhydropyridoindoles in good yields. When the precursor is benzimidazolylpropargyl alcohol, the reaction did not take place (**91f**) (Scheme 37).[59]

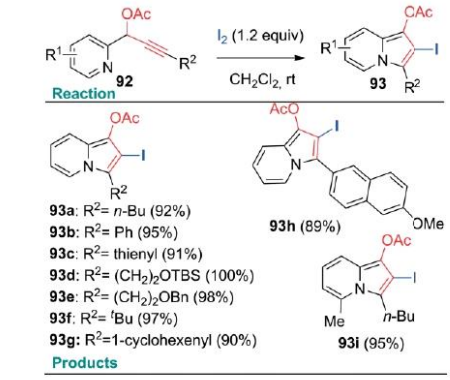


Scheme 37.

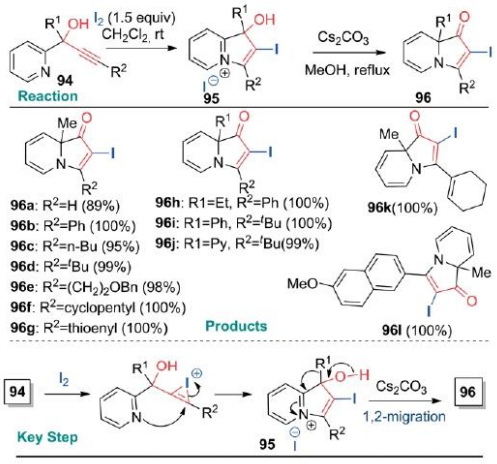
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3.3. Iodo-Indolizines

Aromatic indolizines[60] exhibit interesting biological and fluorescent properties, although these do not seem to occur in nature, studies show indolizines as biologically and medicinally important compounds. Various indolizine derivatives exhibiting different biological activities such as anticancer, antimicrobial, and phosphatase inhibitory actions are reported. Propargylic acetates bearing a 2-pyridyl substitution at propargylic center (**92**) underwent a smooth iodocyclization with iodine at r.t. to give fully substituted iodoindolizines (**93**). In this reaction, pyridine opens the iodonium ion through 5-*endo dig* cyclization followed by aromatization to yield **93** in good yields (Scheme 38).[61] The same group extended this work with *tert*-propargylic system (**94**) and subjected to iodocyclization (I_2, DCM, r.t.) to obtain the corresponding indolizinium salts (**95**) (Scheme 39),[62] which were isolated by a simple filtration method. Further, these salts were refluxed in methanol under basic conditions (Cs_2CO_3) to obtain iodo-indazolinones (**96**) via 1,2-shift.



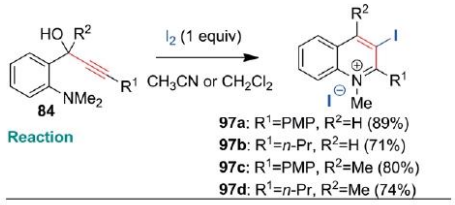
Scheme 38.



Scheme 39.

3.4. Iodoquinolines

The wide occurrence of quinolines and their derivatives in nature and their important biological and pharmacological activities have been attracting chemists for the synthesis of quinolines.[63] In Scheme 41, we have seen that dimethyl amino propargyl alcohol **84** gave indole-2-carbaldehyde with iodine in an ethanol solvent. However, further it is demonstrated that if the solvent changed from ethanol to acetonitrile or DCM, they found that the reaction proceeds through a 6-*endo dig* iodocyclization to give *N*- methylmethylquinolinium salts (**97**) in good yields (Scheme 40). In both the cases (Scheme 35 and Scheme 40)[57a] polar solvents were used, however protic and aprotic nature caused the regioselective cyclization.

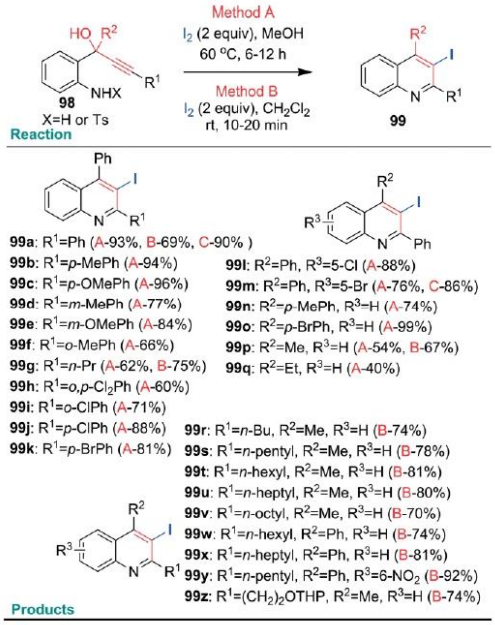


Scheme 40.

Interestingly, when precursor **84** with a tosylamine or the free amine functionality (**98**), iodocyclization went smoothly to yield 3-iodoquinolines (**99**) in good to excellent yields (Scheme 41). Surprisingly, here the protic solvent (MeOH) and aprotic solvent (DCM) gave the same products (Scheme 41).[64a,64b] However, the most important point that we should notice here is the preparation of these starting materials (**84** or **98**), which involves multiple steps with special reagents and conditions (Scheme 42).[64] For example compound **100** was treated with alkynyllithium to get the ketone **101**, and a Grignard addition gave the precursor **84**. In another case, **102** was tosylated (**103**) and treated with alkynylmagnesium bromide to get **98**. The third method is again a Grignard addition to **102** gives **98**. Therefore, we have developed a one-pot synthesis of these iodoquinolines from *o*-amino ketones and alkynes (Scheme 42).[64c] Propargyl alcohol **98** was obtained from **102** and **104** with KO*t*Bu under solvent-free conditions, then added water and iodine to the same pot to obtain the desired products in excellent overall yields. Compared to the previously reported methods, this method is superior in terms of green chemistry aspects, such as step economy, maximum atom economy, the formation of propargyl alcohol is a solvent-free, and no isolation is required, and the solvents for the iodocyclization are a combination of water and ethyl acetate.

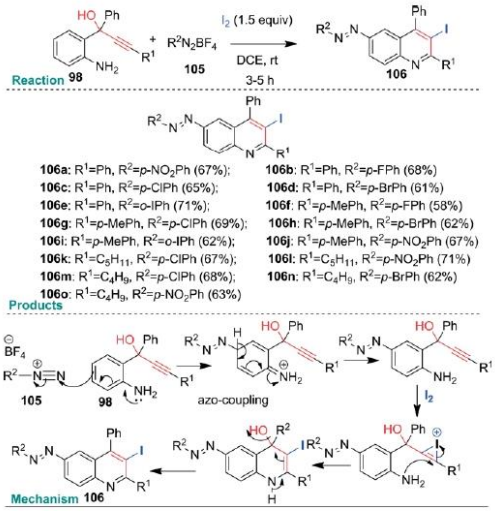
Later, we have extended this green strategy (due to the formation of HI as the by-product, there is always a question about the greener of iodocyclization reactions) to synthesize 3-iodo-6-diazo quinolines **106** (Scheme 43)[65] through a sequential azo-

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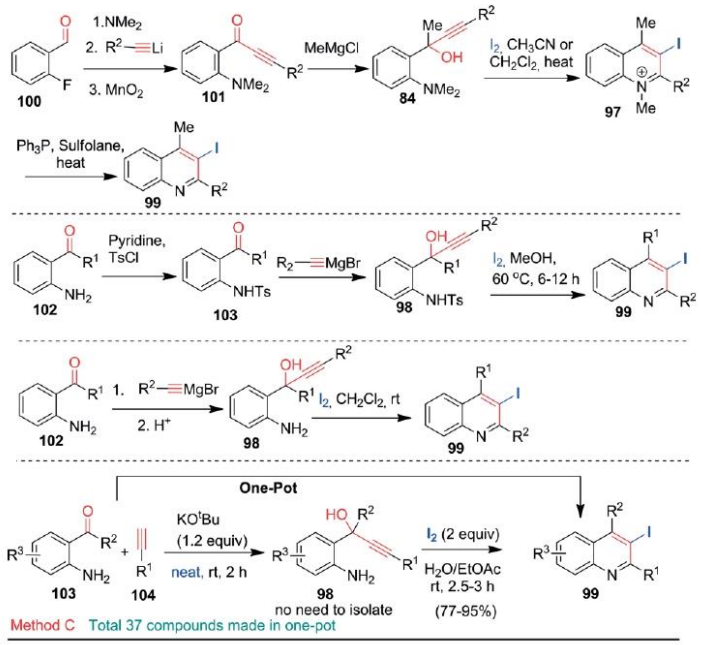


Scheme 41.

coupling and iodocyclization. The obtained products are unique as this is the first approach of such systems and furnished the 2,3,4,6-tetrasubstituted quinolines in good yields.



Scheme 43.

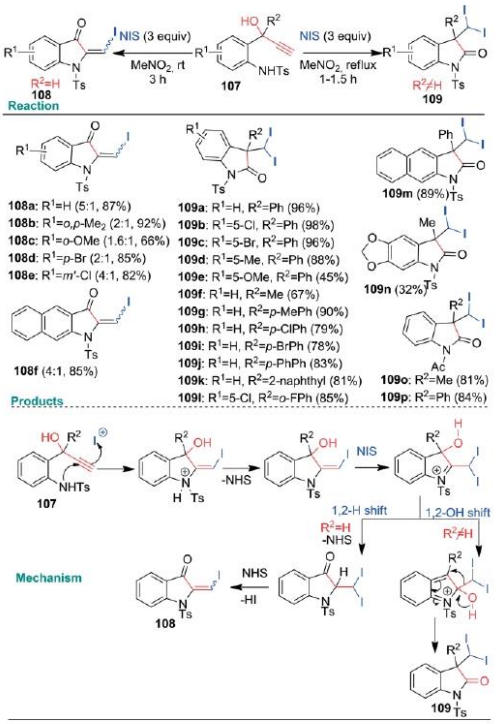


Scheme 42.

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3.5. Iodoxindoles

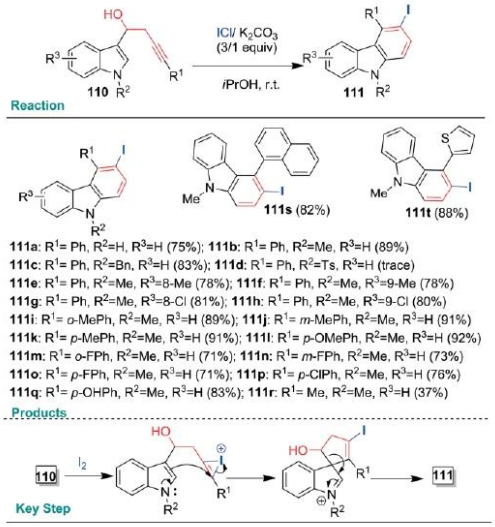
Oxindoles are endogenous aromatic compounds which are found in the body fluids and tissues of mammals, and the natural products of some plants.[66] Oxindoles have a wide range of applications, and they exhibit an extensive range of biological effects which include the antibacterial, anticancer, antifungal, anti-inflammatory, antiviral, antiproliferative and antihypertensive activities. NIS-mediated strategy for the construction of highly functionalized iodo-derivative of 2-oxindole (**109**) and 3-oxindole (**108**) from secondary and tertiary 1-(2′-anilinyl) prop-2-yn-1-ols (**107**), respectively, was developed by Chan et al.[67] This method shows chemoselectivity in product formation by migration of alcohol moiety in tertiary and secondary substrates. 2-Oxindole synthesis is reported to show unique double migratory cascade reaction involving 1,2-OH shift followed by 1,2-alkyl shift (Scheme 44).



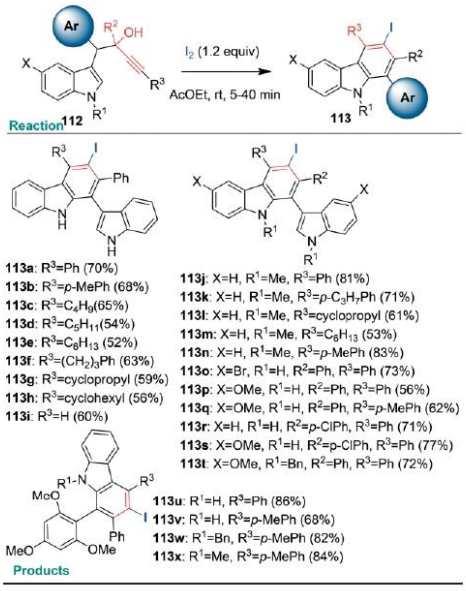
Scheme 44.

3.6. Iodocarbazoles

Carbazoles an important class of heterocyclic compounds, which have a broad range of pharmacological activities, such as antimicrobial, anticancer, and antipsychotic activities. These are also building blocks for potential electroluminescent materials due to their unique electrical, thermal, and optical properties.[68] Owing to the exceptional importance of functionalized carbazoles and their derivatives across many fields, various methods have been developed for the synthesis of carbazoles, particularly iodocarbazoles. Rearrangement and migration reac-



Scheme 45.



Scheme 46.

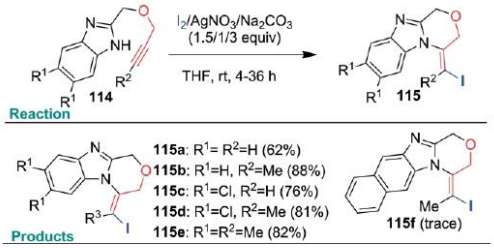
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tions play an essential role in chemical synthesis. When Indole-tethered propargyl alcohols (**110**) were stirred with ICl (3 equiv.) /K_2CO_3 (1 equiv.) at r.t. in 2-propanol, 3-iodocarbazoles (**111**) were obtained in high yields. The reaction proceeds through the formation of the spirocyclic indole through the C3-attack followed by the 1,2-alkyl migration and aromatization cascade gives the desired iodocarbazoles. (Scheme 45).[69]

Recently, our group developed a more detailed study on the iodocycloisomerization reaction of indole-tethered *tert*-propargyl alcohols (**112**) with molecular iodine in ethyl acetate at r.t. In this reaction C3-spirocyclic indole forms through a 5-*endo* spirocyclization, which then undergoes 1,2-alkyl shift with aryl moiety to give 1,2,3,4-tetra substituted carbazole (**113**). The aryl groups used here are indole and trimethoxy phenyl. (Scheme 46).[70]

3.7. Iodo-Oxa-Fused Benzimidazoles

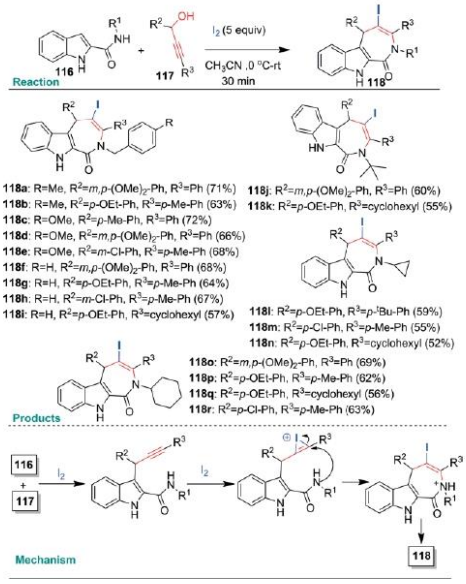
Fused benzimidazoles[71] are important building block in synthetic chemistry. Liu[72] group developed protocol for the synthesis of oxa-fused benzimidazoles **115** using iodine and silver nitrate by an *exo-dig* cyclization pathway at room temperature (Scheme 47). The reaction proceeded through cyclic iodonium intermediate followed by nucleophilic attack of lone pair of nitrogen from benzimidazole moiety. Silver nitrate was used as a crucial additive, it reacts with iodide ion and prevent the formation of bis-diiodo compounds as the by-products and thus improves the yields of **115**.



Scheme 47.

3.8. Iodolactams

Owing to the importance of iodolactam,[73] Iodo-indoloazepinones or iodolactam **118** derivatives were synthesised via a three-component reaction of indole-2-carboxamides (**116**), and 1,3-disubstituted propargyl alcohols (**117**) and I_2. (Scheme 48).[74] The reaction proceeded through iodine mediated C-H functionalization, alkyne activation, intramolecular hydroamination, deprotonation domino sequence to afford 4-iodoindoloazepinones. Reaction mechanism suggests regioselective electrophilic 7-endo-*dig* iodocyclization where a nitrogen nucleophile from the amide moiety preferentially attacks the activated alkyne rather than the oxygen nucleophile. The substrate scope of reaction shows moderate to a good yield of products.



Scheme 48.

4. Sulfur or Selenium Containing Heterocyclic Iodides

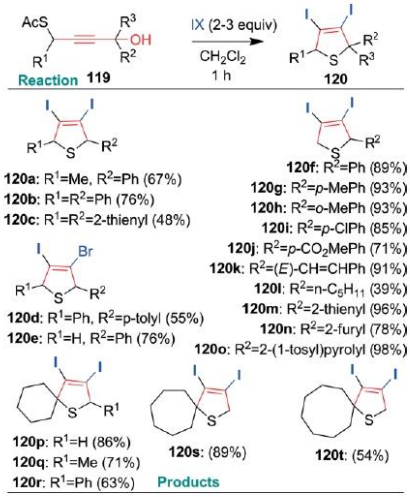
Sulfur and selenium-containing compounds serve as very useful heterocyclic cores for drug leads and biologically active compounds and provide useful properties in the development of novel materials.[75–81] Synthetic methods for the preparation of iodothiophene, iodobenzothiophene (Scheme 49–Scheme 52) and iodoselenophene (Scheme 53) will be discussed in this section.

4.1. Iodothiophenes

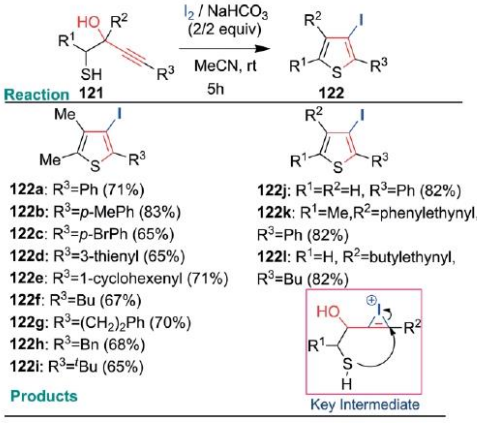
Dihydrothiophenes, thiophenes and benzothiophenes are an important class of heterocycles which are used as versatile intermediates in the synthesis of natural and unnatural molecules with diverse biological activities.[75] A facile synthetic approach for construction of 3,4-diiodo-dihydrothiophenes (**120**) was developed by Yamamoto[76] group via the electrophilic iodocyclization of hydroxy-2-butynyl ethanethioates (**119**), in DCE at room temperature. A detailed study on the substrate scope revealed that heteroaromatic rings (thienyl, pyrrolyl, furanyl) at R^2 position have higher compatibility with this reaction condition, whereas the aryl group at R^2 gave a lower yield of product. Cyclic tertiary alcohols also worked well and gave thiaspirocyclic derivatives. Iodocyclization with IBr instead of I_2 was also reported to give 3-bromo-4-iodo-dihydrothiophenes derivatives in good yields. The reaction proceeded through allene cation intermediate (Scheme 49). In another report, B. Gabriele [77] showed the synthesis of 3- iodothiophene (**122**) from 1-mer-

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capto-3-alkyn-2-ols (**121**) with I_2 in the presence of a base ($NaHCO_3$) at room temperature using MeCN as a solvent. The products are fully substituted and obtained in moderate to good yields as showed in Scheme 50.

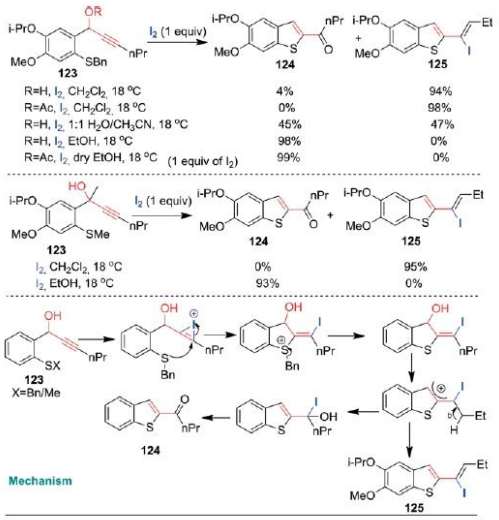


Scheme 49.



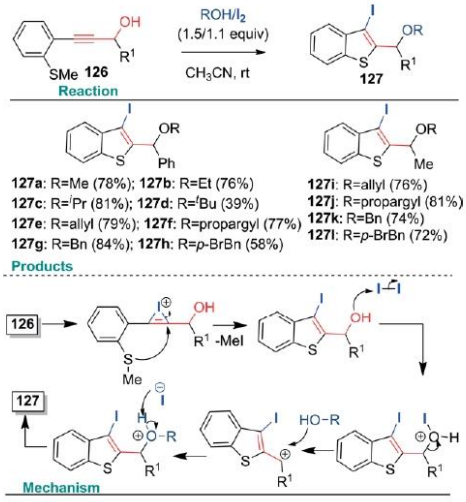
Scheme 50.

Propargyl alcohol (**123**) with a 2-thioxyphenyl substituent selectively underwent 5-*exo*-iodocyclization with iodine. This followed a tandem rearrangement and elimination to give 2-acyl-benzo[b]thiophenes **124**. Moreover, the same precursor, gave 2-(1-iodoalkeny)-benzo[b]thiophene (**125**), through a cascade 5-*exo*-iodocyclization followed by rearrangement and substitution processes. Optimization conditions suggested that free-propargyl alcohol gave 94 % of **125** in DCM, whereas acetylated **123** yielded exclusively **125** (98 %). Ethanol found to be the right solvent to get **124** as the sole product. A thiomethyl ether of **123** gave exclusively **125** (95 %) in DCM solvent, whereas in ethanol it gave exclusively **124** (93 %). This reactive difference due to the change in the solvent can be explained based on the proposed mechanism (Scheme 51).[78]



Scheme 51.

A simple thiomethyl ether **126** was subjected to iodocyclization with iodine and alcohol (ROH) in acetonitrile at r.t. (Scheme 52). In contrast to the above method (Scheme 51), 2-alkoxy-3-iodo-thiophene derivatives (**127a**–**127l**) were ob-



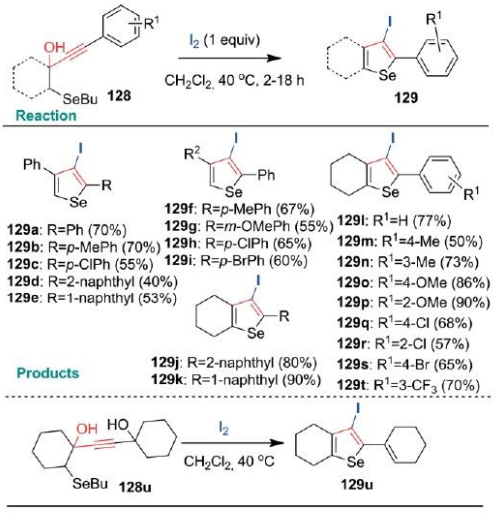
Scheme 52.

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tained here in good yields.[79] Alcohol acted as a nucleophile and substituted the oxonium ion on the 2-position of thiophene and yielded **127**.

4.2. Iodoselenophenes

Selenophenes[80] are also an important class of heterocyclic compounds, recently G. Zeni and co-workers reported the synthesis of 3-Iodoselenophenes (**129**) from butylselenyl propargyl alcohols (**128**) using I_2 (1 equiv.) in DCE at 40 °C (Scheme 53).[81] Reaction time and yields suggest that electronic effects have very little influence than steric factors, as similar yield observed in both electron-withdrawing and electron-donating group substituents. Whereas, in the case of butylselenyl propargyl alcohol **128u**, cyclohexenylselenophene **129u** was obtained instead of the corresponding selenophene derivative (Scheme 53). Further, the scope of butylthio propargyl alcohol and butyltelluro propargyl alcohol was also studied. Iodocyclization of thio derivative proceeded smoothly to give 3-iodothiophene in 65 % yield whereas telluride derivative failed to give 3-iodotellurophene.



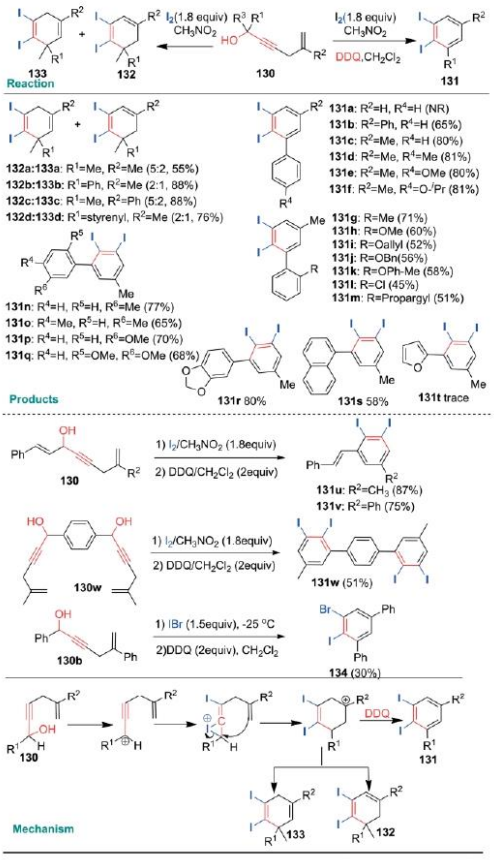
Scheme 53.

5. Carbocyclic Iodides

Carbocyclic compounds[82] are one of the primary class of organic chemistry. These are extremely widespread, and many of them are of great practical importance, carbocyclic compounds are also used in the preparation of synthetic resins and plastics as well. In this section, the synthetic methods developed for the carbocyclic iodides, such as iodobenzenes (Scheme 54), iodoindenes (Scheme 55 and Scheme 56), and iodonaphthalenes (Scheme 57 and Scheme 58) will be discussed.

5.1. Iodobenzene

Benzene is a widely used industrial chemical. It is used to make plastics, resins, synthetic fibers, dyes, detergents, drugs and pesticides. Volcanoes and forest fires naturally produce benzene. Similarly, iodobenzene has wide applications, particularly in cross-coupling reactions. Preparation of diiodocyclohexadienes (**132,133**) and 2,3- diiodobenzenes (**131**), proceeds through the attack of unactivated olefins of hydroxylated [1,5]-enyne **130.** 2,3- diiodobenzene **131** was synthesized using DDQ as oxidant after formation of diiodocyclohexadienes (**132** and **133**).[83] The reaction was also performed by varying substituents at a propargylic position such as benzyl and styrenyl, however, in case of benzyl substitution cyclization did not occur. Whereas, styrenyl substituent gave a good yield of diiodobenzene derivatives. This cyclization reaction was also performed using IBr as I^+ source at –25 °C, and the reaction gave the product **149** but in a low yield (30 %). In the reaction mechanism, it was showed that **130** will give a propargyl cation, which is in resonance with



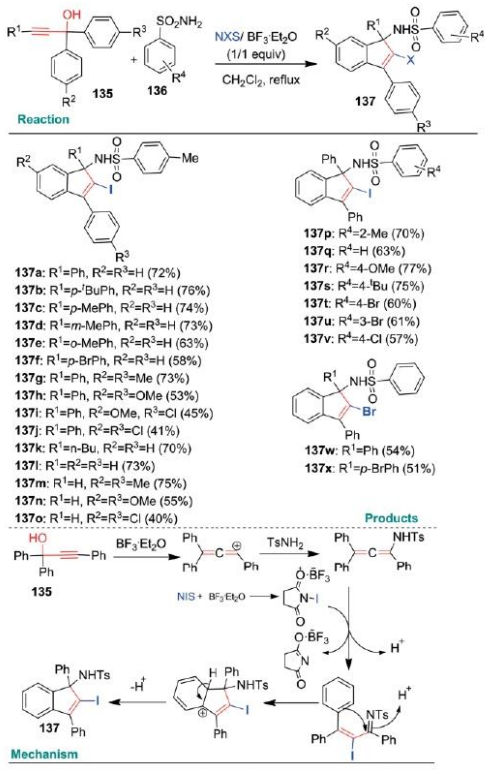
Scheme 54.

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allenyl cation and a subsequent activation with iodine. The π-electron cloud of the double bond acts as a nucleophile and opens the cyclic iodonium to give iodo-cyclohexadiene derivatives (**133** and **132**). This upon oxidation with DDQ gave diiodobenzene **131** in good yields. The vinyl substitution at propargylic carbon was intact in this process (**131u**, **131v**). A two-fold 1,5-enyne cyclization two yield two additional benzene rings were demonstrated from the suitable precursor **130w**. IBr was also used for this purpose, and the product **134** was prepared. However, the reaction yield is 30 % only (Scheme 54).

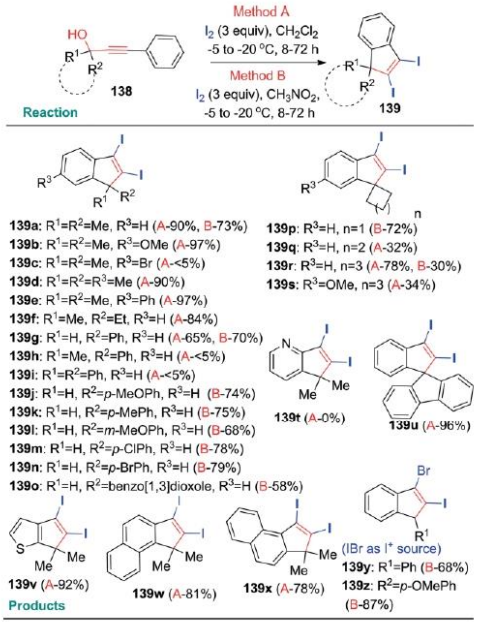
5.2. Iodoindenes

Indenes[84] are an integral part of several natural products of biological importance. Wang[85] group reported the synthesis of *N*-(2-iodoinden-1-yl)-arenesulfonamide **137** from propargylic alcohols (**135**) and sulfonamides (**136**). The reaction was catalyzed by the combination of NIS and BF_3•Et_2O in DCM under reflux conditions. A detailed substrate scope studies show the decreased reactivity in case of halo and methoxy substituted propargyl alcohols (Scheme 55). Allenesulfonamide is the key intermediate, which attacks the cyclic-iodonium species generated by the activation with NIS in BF_3•Et_2O. NBS mediated cyclization was also observed to yield 2-bromoindenes (**137w**, **137x**) but in poor yields.



Scheme 55.

Two independent reports on electrophilic carbocyclization of aryl propargylic alcohols (**138**) using iodine at low temperatures (–5 °C to –20 °C) at longer reaction times have been reported by Liang[40] and Wang[86] groups. Surprisingly, the only difference in these two reports is the solvent, one of the methods uses DCM, and the other is nitromethane. Overall the products (**139**) were formed in good yields with a broad substrate scope (Scheme 56). The reaction proceeded through allenyl intermediate and gave moderate to good yields of 2,3-diiodo indenes (**139**). When aryl was replaced by heteroaryl moiety (pyridyl group) (**139t**), there was no formation of iodoindene whereas thienyl group resulted in an excellent yield of iodoindene (**139v**).

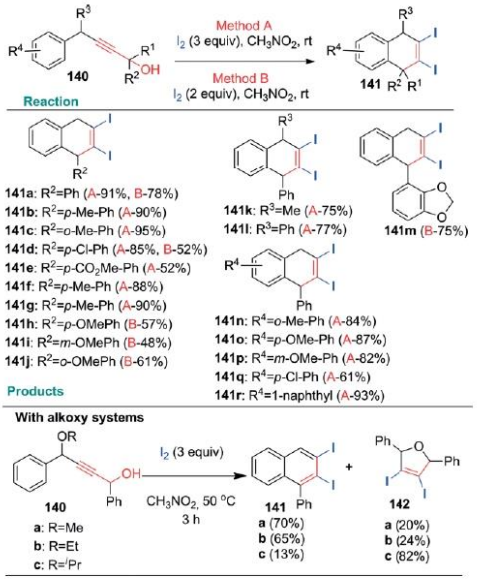


Scheme 56.

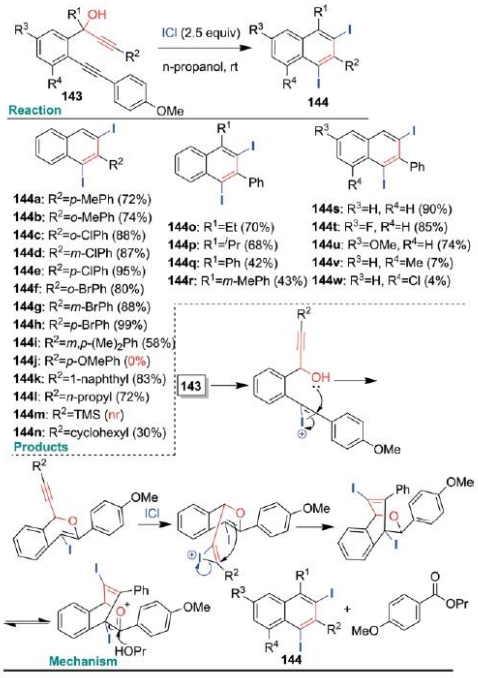
5.3. Iodonaphthylenes

Naphthalenes[87] are bicyclic aromatic hydrocarbons which are mainly used as precursors to other chemicals. Naphthyl derivatives are widely used in various commercial and industrial applications including mothballs, lavatory scent disks and soil fumigants. Yamamoto[88] and Liang[40] separately reported the synthesis of diiodinated dihydro naphthalenes (**141**) using I_2 in nitromethane at r.t. Yamamoto group reported higher yields of the product by using an excess amount of iodine (Scheme 57). In the case of alkyl/phenyl substitution at benzylic position of **140**, the reaction yielded exclusively dihydro-diiodinated naphthalene derivatives **141**. However, when there is an alkoxy

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Scheme 57.



Scheme 58.

substitution at benzylic position (**140**), it was observed that a mixture of diiodo naphthalene (**141**) and diiodo furans (**142**) were formed. By increasing the steric bulk at ether, more of the iodofuran was formed (**142c**). Synthesis of highly substituted 1,3-diiodinated naphthalene(**144**) derivatives is also reported with electrophilic iodocyclization under mild conditions using 2.5 equiv. of ICl in *n*-propanol at r.t.[89] Structure of 1,3-diiodonaphthalene was also confirmed by single-crystal X-ray analysis. Methoxy phenyl was optimized to be a better leaving group as methoxyphenyl containing substrate show increase in reactivity. *p*-methoxy phenyl (**144j**) and trimethylsilyl (**144m**) as R^2 substituent did not give iodonaphthalene derivative, whereas the cyclohexyl group is showing less reactivity, and gave slightly lower yield (Scheme 58).

Acknowledgments

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Keywords: Iodocyclization · Propargyl alcohols · Iodoheterocycles · Carbocyclic iodides · Regioselective cyclization

[1] For reviews on reactions of propargyl alcohols see: a) Y. Zhu, L. Sun, P. Lu, Y. Wang, *ACS Catal.* **2014**, *4*, 1911–1925; b) C. R. Reddy, R. Ranjan, P. Kumaraswamy, M. D. Reddy, R. Gree, *Curr. Org. Chem.* **2014**, *18*, 2603–2645; c) L. Zhang, G. Fanga, R. K. Kumar, X. Bi, *Synthesis* **2015**, *47*, 2317–2346; d) B. J. Ayers, P. W. H. Chan, *Synlett* **2015**, *26*, 1305–1339; e) D. Roy, P. Tharra, B. Baire, *Asian J. Org. Chem.* **2018**, *7*, 1015–1032; f) H. Qiana, D. Huang, Y. Bib, G. Yana, https://doi.org/10.1002/adsc.201801719.

[2] For reviews on iodocyclization see: a) A. K. Banerjee, W. Vera, H. Mora, M. S. Laya, L. Bedoya, E. V. Cabrera, *J. Sci. Ind. Res.* **2006**, *65*, 299–308; b) M. J. Mphahlele, *Molecules* **2009**, *14*, 4814–4837; c) A. K. Banerjee, M. S. Laya, E. V. Cabrera, *Curr. Org. Chem.* **2011**, *15*, 1058–1080; d) A. V. Dubrovskiy, N. A. Markina, R. C. Larock, *Comb. Chem. High Throughput Screening* **2012**, *15*, 451–472; e) Yi.-M. Ren, C. Cai, R.-C. Yanga, *RSC Adv.* **2013**, *3*, 7182–7204; f) B. Gabriele, R. Mancuso, R. C. Larock, *Curr. Org. Chem.* **2014**, *18*, 341–358; g) T. Aggarwal, S. Kumar, A. K. Verma, *Org. Biomol. Chem.* **2016**, *14*, 7639–7653.

[3] a) J. E. Baldwin, *J. Chem. Soc., Chem. Commun.* **1976**, 734–736; b) K. Gilmore, I. V. Alabugin, *Chem. Rev.* **2011**, *111*, 6513–6556; c) I. V. Alabugin, K. Gilmore, *Chem. Commun.* **2013**, *49*, 11246–11250; d) K. Gilmore, R. K. Mohamed, I. V. Alabugin, *WIREs Comput. Mol. Sci.* **2016**, *6*, 487–514.

[4] a) C. Chen, C.-G. Wang, L. Xiao, A. Goto, *Chem. Commun.* **2018**, *54*, 13738–13741; b) P.-L. T. Boudreault, S. Beaupré, M. Leclerc, *Polym. Chem.* **2010**, *1*, 127–136; c) J.-F. Morin, M. Leclerc, D. Adès, A. Siove, *Macromol. Rapid Commun.* **2005**, *26*, 761–778.

[5] a) L. Zhang, X.-M. Peng, G. L. V. Damu, R.-X. Geng, C.-H. Zhou, *Med. Res. Rev.* **2014**, *34*, 340–437; b) D. Krishnaiah, R. Sarbatly, R. Nithyanandam, *Food Bioprod. Process.* **2011**, *89*, 217–233; c) V. Bhalla, V. Vij, M. Kumar, P. R. Sharma, T. Kaur, *Org. Lett.* **2012**, *14*, 1012–1015.

[6] a) K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467–4470; b) N. Miyaura, *Chem. Rev.* **1995**, *95*, 2457; c) S. Brase, A. D. Meijer in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**, p. 99; d) A. Suzuki in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weinheim, **1998**, p. 49; e) A. Suzuki, *J. Organomet. Chem.* **1999**, *576*, 147–168; f) K. Semba, Y. Nakao, *Tetrahedron* **2019**, *75*, 709–719; g) L.-C. Campeau, N. Hazari, *Organometallics* **2019**, *38*, 3–35; h) Y.-F. Zhang, Z.-J. Shi, *Acc. Chem. Res.* **2019**, *52*, 161–169.

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[7] a) R. J. Cross, R. L. Wolfgang, *Radiochim. Acta* **1964**, *2*, 112–116; b) N. S. Zefirov, V. V. Zhdankin, G. V. Makhon'kova, Y. V. Dan'kov, A. S. Koz'min, *J. Org. Chem.* **1985**, *50*, 1872–1876.
[8] a) G. W. Gribble, *Acc. Chem. Res.* **1998**, *31*, 141–152; b) L. Wang, X. Zhou, M. Fredimoses, S. Liaoa, Y. Liu, *RSC Adv.* **2014**, *4*, 57350–57376.
[9] a) C. Semeyn, R. H. Blaauw, H. Hiemstra, W. N. Speckamp, *J. Org. Chem.* **1997**, *62*, 3426–3427; b) Pigman, Horton, *The Carbohydrates: Chemistry and Biochemistry Vol 1A* (2nd ed.), San Diego, Academic Press. 1–67.
[10] a) L. J, *Machlin, Handbook of vitamins* **1991**; b) R. Dua, S. Shrivastava, S. K. Sonwane, S. K. Srivastava, *Adv. Biol. Res.* **2011**, *5*, 120–144; c) G. W. Burton, K. U. Ingold, *Acc. Chem. Res.* **1986**, *19*, 194–201.
[11] a) R. E. Ziegert, J. Torang, K. Knepper, S. Brase, *J. Comb. Chem.* **2005**, *7*, 147–169; b) J. E. Halver, *Fish Nutrition* (Third Edition) **2003**, p. 61–141.
[12] a) K. Rajeev, K. Rupinder, S. A. Kumar, *Eur. J. Biomed. Pharm. Sci.* **2014**, *1*, 401–420; b) E. Milkyas, E. Mate, *Targets Heterocycl. Syst.* **2012**, *16*, 184–220.
[13] H. K. Jitka, A. Zdenek, S. Frantisek, C. Czechoslovak, *J. Chem. Soc., Chem. Commun.* **1973**, *38*, 1165–1167.
[14] a) X. L. Hou, H. Y. Cheung, T. Y. Hon, P. L. Kwan, T. H. Lo, S. Y. Tong, H. N. C. Wong, *Tetrahedron* **1998**, *54*, 1955–2020; b) Chemical innovation, **2001**, *31*, 17–21; D. L. Wright, *Chemical innovation*, **2001**, 906 *31*, 17–21; c) R. Banerjee, H. K. S. Kumar, M. Banerjee, *Int. J. Rev. Life Sci.* **2012**, *2*, 7–16; d) J. Rieb, A. Raba, S. Haslinger, M. Kaspar, A. Pöthig, M. Cokoja, J.-M. Basset, F. E. Kühn, *Inorg. Chem.* **2014**, *53*, 9598–9606.
[15] S. P. Bew, D. W. Knight, *Chem. Commun.* **1996**, 1007–1008.
[16] G. M. M. E. Taeb, A. B. Evans, S. Jones, D. W. Knigh, *Tetrahedron Lett.* **2001**, *42*, 5945–5948.
[17] R. Spina, E. Colacino, B. Gabriele, G. Salerno, J. Martinez, F. Lamaty, *Synlett* **2012**, *23*, 1481–1484.
[18] B. Crone, S. F. Kirsch, *J. Org. Chem.* **2007**, *72*, 5435–5438.
[19] S. Arimitsu, J. M. Jacobsen, G. B. Hammond, *J. Org. Chem.* **2008**, *73*, 2886–2889.
[20] L. Su, C.-Y. Lei, W.-Y. Fan, L.-X. Liu, *Synth. Commun.* **2011**, *41*, 1200–1207.
[21] a) K.-G. Ji, H.-T. Zhu, F. Yang, X.-Z. Shu, S.-C. Zhao, X.-Y. Liu, A. Shaukat, Y.-M. Liang, *Chem. Eur. J.* **2010**, *16*, 6151–6154; b) K.-G. Ji, H.-T. Zhu, F. Yang, A. Shaukat, X.-F. Xia, Y.-F. Yang, X.-Y. Liu, Y.-M. Liang, *J. Org. Chem.* **2010**, *75*, 5670–5678; c) F. Yang, T. Jin, M. Bao, Y. Yamamoto, *Tetrahedron* **2011**, *67*, 10147–10155.
[22] A. A. Kruglov, *Zh. Obshch. Khim.* **1937**, *7*, 2605.
[23] F. Yang, T. Jin, M. Baoc, Y. Yamamoto, *Chem. Commun.* **2011**, *47*, 4541–4543.
[24] Y.-X. Xie, X.-Y. Liu, L.-Y. Wu, Y. Han, L.-B. Zhao, M.-J. Fan, Y.-M. Liang, *Eur. J. Org. Chem.* **2008**, 1013–1018.
[25] T. Okitsu, D. Nakazawa, A. Kobayashi, M. Mizohata, Y. In, T. Ishida, A. Wada, *Synlett* **2010**, *2*, 203–206.
[26] a) D. Kumar, P. Sharma, H. Singh, K. Nepali, G. K. Gupta, S. K. Jain, F. Ntie-Kang, *RSC Adv.* **2017**, *7*, 36977–36999; b) S. R. Parker, H. G. Cutler, J. M. Jacyno, R. A. Hill, *J. Agric. Food Chem.* **1997**, *45*, 2774–2776; c) J. Kuthan, P. Sebek, S. Bohim, *Adv. Heterocycl. Chem.* **1995**, *62*, 1–418.
[27] Y.-X. Xie, Z.-Y. Yan, D.-Z. Wang, L.-Y. Wu, B. Qian, X.-Y. Liu, Y.-M. Liang, *Eur. J. Org. Chem.* **2009**, *2009*, 2283–2288.
[28] a) J. D. Hepworth, B. MarkHeron, *Prog. Heterocycl. Chem.* **2009**, *20*, 365–398; b) K. Piyush, S. Kuldeep, R. M. Azizur, H. S. Misbahul, W. Pranay, *Asian J. Pharm. Clin. Res.* **2018**, *11*, 43–46; c) A. N. Panche, A. D. Diwan, S. R. Chandra, *J. Nutr. Sci.* **2016**, *5*, 1–15; d) M. M. Biddle, M. Lin, K. A. Scheidt, *J. Am. Chem. Soc.* **2007**, *129*, 3830–3831.
[29] Y.-F. Qiu, Y.-Y. Ye, X.-R. Song, X.-Y. Zhu, F. Yang, B. Song, J. Wang, H.-L. Hua, Y.-T. He, Y.-P. Han, X.-Y. Liu, Y.-M. Liang, *Chem. Eur. J.* **2015**, *21*, 3480–3487.
[30] S. Yaragorla, A. Pareek, R. Dada, *Tetrahedron Lett.* **2017**, *58*, 4642–4647.
[31] S. Yaragorla, P. Rajesh, A. Pareek, A. Kumar, *Adv. Synth. Catal.* **2018**, *360*, 4422–4428.
[32] J. Wang, H.-T. Zhu, Y.-X. Li, L.-J. Wang, Y.-F. Qiu, Z.-H. Qiu, M.-J. Zhong, X.-Y. Liu, Y.-M. Liang, *Org. Lett.* **2014**, *16*, 2236–2239.
[33] a) S. A. Worlikar, T. Kesharwani, T. Yao, R. C. Larock, *J. Org. Chem.* **2007**, *72*, 1347–1353; b) J. Barluenga, M. Trincado, M. Marco-Arias, A. Ballesteros, E. Rubio, J. M. Gonza'lez, *Chem. Commun.* **2005**, 2008–2010; c) T. Sasaki, K. Miyagi, K. Moriyama, H. Togo, *Org. Lett.* **2016**, *18*, 944–947.
[34] B. Godoi, A. Speranc, D. F. Back, R. Brandao, C. W. Nogueira, G. Zeni, *J. Org. Chem.* **2009**, *74*, 3469–3477.
[35] K. C. Majumdar, I. Ansary, B. Sinha, B. Roy, B. Sridhar, *Synthesis* **2011**, *20*, 3287–3296.
[36] K. C. Talluri, R. Nagarajan, *J. Chem. Sci.* **2012**, *124*, 487–494.
[37] J. Mo, W. Choi, J. Min, C.-E. Kim, D. Eom, S. H. Kim, P. H. Lee, *J. Org. Chem.* **2013**, *78*, 11382–11388.
[38] S.-G. Wen, W.-M. Liu, Y.-M. Liang, *J. Org. Chem.* **2008**, *73*, 4342–4344.
[39] a) D. Faulkner, *J. Nat. Prod. Rep.* **1984**, *1*, 251–280; b) E. Tojo, D. Dominguez, L. Castedo, *Phytochemistry* **1991**, *30*, 1005–1010; c) M. Stefinovic, V. Snieckus, *J. Org. Chem.* **1998**, *63*, 2808–2809; d) M. Yoshida, K. Nakatani, K. Shishido, *Tetrahedron* **2009**, *65*, 5702–5708; e) H. Furuta, Y. Hasegawa, Y. Mori, *Org. Lett.* **2009**, *11*, 4382–438; f) M. Bruder, P. L. Haseler, M. Muscarella, W. Lewis, C. J. Moody, *J. Org. Chem.* **2010**, *75*, 353–358.
[40] H.-T. Zhu, K.-G. Ji, F. Yang, L.-J. Wang, S.-C. Zhao, S. Ali, X.-Y. Liu, Y.-M. Liang, *Org. Lett.* **2011**, *13*, 684–687.
[41] K. C. Majumdar, B. Sinha, I. Ansary, S. Chakravorty, *Synlett* **2010**, *9*, 1407–1411.
[42] a) C. W. Wilson III, P. E. Shaw, R. J. Knight, *J. Agric. Food Chem.* **1990**, *38*, 1556–1559; b) L. Dufossé, A. Latrasse, H.-E. Spinnler, *Sci. Aliments* **1994**, *14*, 17–50.
[43] O. Kitagawa, T. Inoue, K. Hirano, T. Taguchi, *J. Org. Chem.* **1993**, *58*, 3106–3112.
[44] H.-T. Zhu, X. Dong, L.-J. Wang, M.-J. Zhong, X.-Y. Liu, Y.-M. Liang, *Chem. Commun.* **2012**, *48*, 10748–10750.
[45] M. S. Reddy, N. Thirupathi, M. H. Babu, S. Puri, *J. Org. Chem.* **2013**, *78*, 5878–5888.
[46] a) V. Yeh, R. Iyengar, *Comprehensive Heterocyclic Chemistry III* **2008**, *4*, p. 487–543; b) D. A. Evans, P. Nagorny, R. Xu, *Org. Lett.* **2006**, *8*, 5669–5671.
[47] a) T. Okitsu, K. Sato, T. M. Potewar, A. Wada, *J. Org. Chem.* **2011**, *76*, 3438–3449.
[48] O. F. Foot, D. W. Knight, A. C. L. Low, Y. Li, *Tetrahedron Lett.* **2007**, *48*, 647–650.
[49] Y. Zhu, G. Yin, L. Sun, P. Lu, Y. Wang, *Tetrahedron* **2012**, *68*, 10194–10200.
[50] a) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257–10274; b) A. P. Taylor, R. P. Robinson, Y. M. Fobian, D. C. Blakemore, L. H. Jones, O. Fadeyi, *Org. Biomol. Chem.* **2016**, *14*, 6611–6637.
[51] a) G. K. Sims, *Soil Biol. Biochem.* **2006**, *38*, 2478–2480; b) C. L. Barth, L. F. Elliott, S. W. Melvin, *Trans. ASAE* **2013**, *27*, 0859–0864.
[52] a) A. R. Katritzky, C. A. Ramsden, J. A. Joule, V. V. Zhdankin, *Handbook of Heterocyclic Chemistry (Third Edition)* **2010**, p. 383–472.
[53] a) A. R. Katritzky, C. A. Ramsden, J. A. Joule, V. V. Zhdankin, *Handbook of Heterocyclic Chemistry (Third Edition)* **2010**, p. 383–472; b) R. Kaur, V. Rani, V. Abbot, Y. Kapoor, D. Konar, K. Kumar, *J. Pharm. Chem. Chem. Sci.* **2017**, *1*, 17–32; D. W. Knight, H. C. Rost, C. M. Sharland, J. Singkhonrat, *Tetrahedron Lett.* **2007**, *48*, 7906–7910.
[54] K.-G. Ji, H.-T. Zhu, F. Yang, X.-Z. Shu, S.-C. Zhao, X.-Y. Liu, A. Shaukat, Y.-M. Liang, *Chem. Eur. J.* **2010**, *16*, 6151–6154.
[55] a) M. Benaglia, T. Danelli, F. Fabris, D. Sperandio, G. Pozzi, *Org. Lett.* **2002**, *4*, 4229–4232; b) S. Chandrasekhar, C. Narsihmulu, S. S. Sultana, N. R. Reddy, *Org. Lett.* **2002**, *4*, 4399–4401; c) S. Chandrasekhar, S. S. Sultana, S. Yaragorla, N. R. Reddy, *Synthesis* **2006**, 0839–0842; d) P. C. Nalam, J. N. Clasohm, A. Mashaghi, N. D. Spencer, *Tribol. Lett.* **2010**, *37*, 541–552.
[56] a) N. K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. H. Kim, A. K. Verma, E. H. Choi, *Molecules* **2013**, *18*, 6620–6662; b) T. V. Sravanthi, S. L. Manju, *Eur. J. Pharm. Sci.* **2016**, *91*, 1–10.
[57] a) K. O. Hessian, B. L. Flynn, *Org. Lett.* **2006**, *8*, 243–246; b) P. Kothandaraman, S. J. L. Lauw, P. W. H. Chan, *Tetrahedron* **2013**, *69*, 7471–7480.
[58] R. Halim, P. J. Scammells, B. L. Flynn, *Org. Lett.* **2008**, *10*, 1967–1970.
[59] J. Wang, H. T. Zhu, S. Chen, Y. Xia, D. P. Jin, Y. F. Qiu, Y. X. Li, Y.-M. Liang, *J. Org. Chem.* **2016**, *81*, 10975–10986.
[60] a) D. A. James, K. Koya, H. Li, G. Liang, Z. Xia, W. Ying, Y. Wu, L. Sun, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1784–1789; b) T. Weide, L. Arve, H. Prinz, H. Waldmann, H. Kessler, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 59–63; c) S. Teklu, L.-L. Gunderson, T. Larson, K. E. Malterud, F. Rise, *Bioorg. Med. Chem.* **2005**, *13*, 3127–3139.
[61] I. Kim, J. Choi, H. K. Won, G. H. Lee, *Tetrahedron Lett.* **2007**, *48*, 6863–6867.
[62] J. Choi, G. H. Lee, I. Kim, *Synlett* **2008**, *8*, 1243–1249.
[63] a) C. Portela, C. M. M. Afonso, M. M. Pinta, M. J. Ramos, *Bioorg. Med. Chem.* **2004**, *12*, 3313–3321; b) A. A. Joshi, C. L. Vishwanathan, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2613–2617.

 © 2019 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[64] a) S. Ali, H.-T. Zhu, X.-F. Xia, K.-G. Ji, Y.-F. Yang, X.-R. Song, Y.-M. Liang, *Org. Lett.* **2011**, *13*, 2598–2601; b) M. S. Reddy, N. Thirupathi, Y. K. Kumar, *RSC Adv.* **2012**, *2*, 3986–3992; c) S. Yaragorla, A. Pareek, R. Dada, P. L. Saini, *Eur. J. Org. Chem.* **2017**, 4600–4608.
[65] S. Yaragorla, A. Pareek, *Eur. J. Org. Chem.* **2018**, 1863–1871.
[66] a) E. J. Hennessy, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 12084–12085; b) J. Bergman, *Adv. Heterocycl. Chem.* **2015**, *117*, 1–81; c) E. V. Zaryanova, A. A. Ignatov, N. A. Lozynskaya, *Tetrahedron* **2017**, *73*, 6887–6893.
[67] P. Kothandaraman, B. Q. Koh, T. Limpanuparb, H. Hirao, P. W. H. Chan, *Chem. Eur. J.* **2013**, *19*, 1978–1985.
[68] a) K. Hiratani, M. Albrecht, *Chem. Soc. Rev.* **2008**, *37*, 2413–14231; b) R. M. Adhikari, D. C. Neckers, B. K. Shah, *J. Org. Chem.* **2009**, *74*, 3341–3349; c) J. Barluenga, E. Tudela, R. Vicente, A. Ballesteros, M. Tomas, *Angew. Chem. Int. Ed.* **2011**, *50*, 2107–2110; *Angew. Chem.* **2011**, *123*, 2155; d) C. Wang, X. Xie, J. Liu, Y. Liu, Y. Li, *Chem. Eur. J.* **2015**, *21*, 559–564.
[69] J. Wang, H.-T. Zhu, Y.-F. Qiu, Y. Niu, S. Chen, Y.-X. Li, X.-Y. Liu, Y.-M. Liang, *Org. Lett.* **2015**, *17*, 3186–3189.
[70] S. Yaragorla, D. Bag, R. Dada, K. V. J. Jose, *ACS Omega* **2018**, *3*, 15024–15034.
[71] a) A. E. A. Harb, F. H. Mostafa, S. A. Metwally, *Arch. Pharmacal Res.* **1990**, *13*, 187–191; b) I. Islam, E. B. Skibo, R. T. Dorr, D. S. Alberts, *J. Med. Chem.* **1991**, *34*, 2954–2961; c) G. Domany, T. Gizur, A. Gera, *Eur. J. Med. Chem.* **1998**, *33*, 181–187.
[72] X. Zhang, Y. Zhou, H. Wang, D. Guo, D. Ye, Y. Xu, H. Jiang, H. Liu, *Adv. Synth. Catal.* **2011**, *353*, 1429–1437.
[73] a) M. E. Kuruvilla, D. A. Khan, Mandell, *Douglas, and Bennet's Principles and Practice of Infectious Diseases (Eight Edition)* **2015**, vol. 1, p. 298–303; b) R. R. Watkins, R. A. Bonomo, *Infectious Diseases (Fourth Edition)* **2017**, *2*, p. 1203–1216.
[74] S. K. Sharma, A. K. Mandadapu, B. Kumar, B. Kundu, *J. Org. Chem.* **2011**, *76*, 6798–6805.
[75] a) P. J. De Clercq, *Chem. Rev.* **1997**, *97*, 1755–1792; b) T. Y. Zhang, J. O'Toole, C. S. Proctor, *Sulfur Rep.* **1999**, *22*, 1–47; c) S. Brandau, E. Maerten, K. Jorgensen, *J. Am. Chem. Soc.* **2006**, *128*, 14986–14991; d) C. Viglianisi, L. Becucci, C. Faggi, S. Piantini, P. Procacci, S. Menichetti, *J. Org. Chem.* **2013**, *78*, 3496–3502.
[76] F. Yang, T. Jin, M. Bao, Y. Yamamoto, *Tetrahedron Lett.* **2011**, *52*, 936–938.
[77] B. Gabriele, R. Mancuso, G. Salerno, R. C. Larock, *J. Org. Chem.* **2012**, *77*, 7640–7645.
[78] K. O. Hessian, B. L. Flynn, *Org. Lett.* **2003**, *5*, 4377–4380.
[79] T. Kesharwani, J. Craig, C. D. Rosario, R. Shavnore, C. Kornman, *Tetrahedron Lett.* **2014**, *55*, 6812–6816.
[80] a) M. P. Rayman, *Lancet* **2000**, *356*, 233–241; b) S. Shabaan, L. A. Ba, M. Abbas, T. Burkholz, A. Denkert, A. Gohr, L. A. Wessjohann, F. Sasse, W. Weber, C. Jacob, *Chem. Commun.* **2009**, 4702–4704; c) C. Santi, S. Santoro, B. Battistelli, *Curr. Org. Chem.* **2010**, *14*, 2442–2462; d) V. Jamier, L. A. Ba, C. Jacob, *Chem. Eur. J.* **2010**, *16*, 10920–10928.
[81] K. K. Casola, M. R. Gomes, D. F. Back, G. Zeni, *J. Org. Chem.* **2018**, *83*, 6706–6718.
[82] a) I. Yavari, A. Khajeh-Khezri, *Synthesis* **2018**, *50*, 3947–3973; b) T. F. Jenny, N. Previsani, S. A. Benner, *Tetrahedron Lett.* **1991**, *32*, 7029–7032.
[83] F. Yang, K.-G. Ji, H.-T. Zhu, A. Shaukat, X.-Y. Liu, Y.-M. Liang, *Chem. Eur. J.* **2011**, *17*, 4986–4990.
[84] a) L. Yang, L. Guo, A. Pasternak, R. Mosley, S. Rohrer, E. Birzin, F. Foor, K. Cheng, J. Schaeffer, A. A. Patchett, *J. Med. Chem.* **1998**, *41*, 2176–2179; b) J. A. Cabeza, I. del Ri'o, J. M. Ferna'ndez-Colinas, P. G. Lvarez, D. Miguel, *Organometallics* **2007**, *26*, 1414–1423; c) M. Miyamoto, Y. Harada, M. Tobisu, N. Chatani, *Org. Lett.* **2008**, *10*, 2975–2978; d) C.-R. Liu, F.-L. Yang, Y.-Z. Jin, X.-T. Ma, D.-J. Cheng, N. Li, S.-K. Tian, *Org. Lett.* **2010**, *12*, 3832–3835; e) B. Gabriele, R. Mancuso, L. Veltri, *Chem. Eur. J.* **2016**, *22*, 5056–5094.
[85] Y. Zhu, G. Yin, D. Hong, P. Lu, Y. Wang, *Org. Lett.* **2011**, *13*, 1024–1027.
[86] C. Zhou, X. Chen, P. Lu, Y. Wang, *Tetrahedron* **2012**, *68*, 2844–2850.
[87] a) J. Barluenga, H. Vazquez-Villa, A. Ballesteros, J. M. Gonzalez, *Org. Lett.* **2003**, *5*, 4121–4123; b) J.-J. Lian, R.-S. Liu, *Chem. Commun.* **2007**, 1337–1339; c) Y. Dawei, N.-C. Della, R.-C. Larock, *J. Org. Chem.* **2006**, *71*, 3381–3388.
[88] F. Yang, T. Jin, M. Baoc, Y. Yamamoto, *Chem. Commun.* **2011**, *47*, 4013–4015.
[89] L.-J. Wang, H. T. Zhu, L. Lu, F. Yang, X.-Y. Liu, Y.-M. Liang, *Org. Lett.* **2012**, *14*, 1990–1993.

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Cyclocarbonylation-Iodination of terminal alkynes with ketones and ICl via 1,2-migration

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ABSTRACT

A simple, three-component, one-pot, room-temperature reaction of cyclocarbonylation-iodination is developed from terminal alkynes, ketones, and ICl. The reaction proceeds through the formation of 3°-propargyl alcohols and a subsequent 1,2-shift lead to the formation of β-iodo-α,β-unsaturated cyclic and acyclic ketones in good yields. In the case of cyclic ketones, the products are obtained with ring expansion.

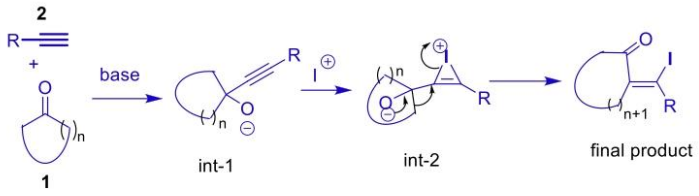
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Alkynes are one of the key feed-stock compounds in organic synthesis. The alkenylation reaction of alkynes by a partial reduction by means of halogenation [1a], hydrohalogenation [1b], hydrogenation [1c,1d] and hydroboration [1e,1f] reactions are a few to list. On the other hand, α-iodounsaturated ketones [2] and β-iodounsaturated ketones [3] are used as the versatile intermediates for the synthesis of many biologically active molecules, and also served extensively in cross-coupling reactions. A typical preparation of α-iodo iodounsaturated ketones involves a 1,4-conjugate addition of enones with a nucleophile followed by quenching with electrophilic iodine [4,5]. In recent years, an alternative rearrangement method from propargyl alcohols is also well explored for the synthesis of α- iodounsaturated ketones [6], and the synthesis of β-iodounsaturated carbonyl compounds from *tert*-propargyl alcohols using various iodine reagents were developed [7]. However the synthesis of β-iodo-α,β-unsaturated carbonyl compounds is still a challenging task since they usually more reactive with organometallic reagents via an addition/elimination pathway [8]. Recently, we have successfully demonstrated the *in situ* synthesis of *tert*-propargyl alcohols from terminal alkynes and ketones, followed by their iodocyclizations to obtain the heterocyclic compounds [9]. With this experience, herein we report a cyclocarbonylation-iodination of terminal alkynes with ketones and ICl *via* the *tert*-ynols as the *in situ* intermediates.

As depicted in Scheme 1, appropriate alkyne and ketone will produce the alkoxy anion in the presence of a base. Electrophilic activation of the triple bond by the appropriate source of I^+ and a subsequent rearrangement should lead to the formation of the final product. Accordingly, we commenced testing this hypothesis by selecting cyclohexanone (**1a**) and phenylacetylene (**2a**) as the model substrates and stirred with potassium tertiarybutoxide [10] under nitrogen atmosphere for 2 h (Table 1). After observing the formation of ynol (on TLC), iodine (2 equiv.) was added to the reaction vessel along with 2 mL of nitromethane solvent and continued to stir for 24 h. After the addition of iodine ynol **3aa** was present for some time (1 h) and started decomposing or producing a complex TLC (entry 1, Table 1). Indeed, the same observation was made, when *N*-iodosuccinimide (NIS) was used as the iodine source (entry 2). Then we utilized ICl as the alternative electrophilic iodine source, and delightfully observed the formation of the desired product (*Z*)-2-(iodo(phenyl)methylene)cycloheptan-1-one (**3a**) [7] in 78% yield after 1 h (entry 3). Further continuing the reaction leads to a decrease in the yield of the product **3a** (entry 4). To increase the reaction yield, we have screened other solvents such as dichloromethane (entry 5), 1,2-dichloroethane (entry 6), acetonitrile (entry 7), toluene (entry 8), ethyl acetate (entry 9), tetrahydrofuran (entry 10), and aqueous-nitromethane (entry 11), however, none of these solvents proved to be better than

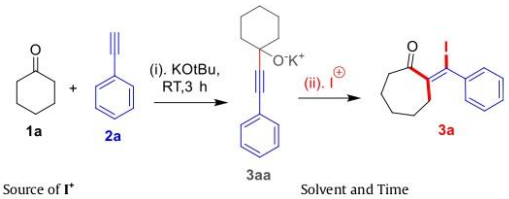
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Scheme 1. Synthetic plan.

Table 1
Optimization of reaction conditions.[a]



Entry	Source of I^+	Solvent and Time	Yield of **3a** (%)[b]
1	I_2 (2 equiv)	Nitromethane, 24 h	–[d]
2	NIS (2 equiv)	Nitromethane, 24 h	–[d]
3[c]	**ICl (2 equiv)**	Nitromethane, **1 h**	**78%**
4	ICl (2 equiv)	Nitromethane, 3 h	55%
5	ICl (2 equiv)	Dichloromethane, 1 h	50%
6	ICl (2 equiv)	1,2-Dichloro ethane, 1 h	43%
7	ICl (2 equiv)	Acetonitrile, 1 h	70%
8	ICl (2 equiv)	Toluene, 1 h	–[d]
9	ICl (2 equiv)	Ethyl acetate, 1 h	20%
10	ICl (2 equiv)	Tetrahydrofuran, 1 h	10%
11	ICl (2 equiv),	Aqueous-nitromethane, 2 h	46%
12	ICl (1 equiv)	Nitromethane, 1 h	35%
13	ICl (1.5 equiv)	Nitromethane, 2 h	50%
14	ICl (3 equiv)	Nitromethane, 1 h	45%

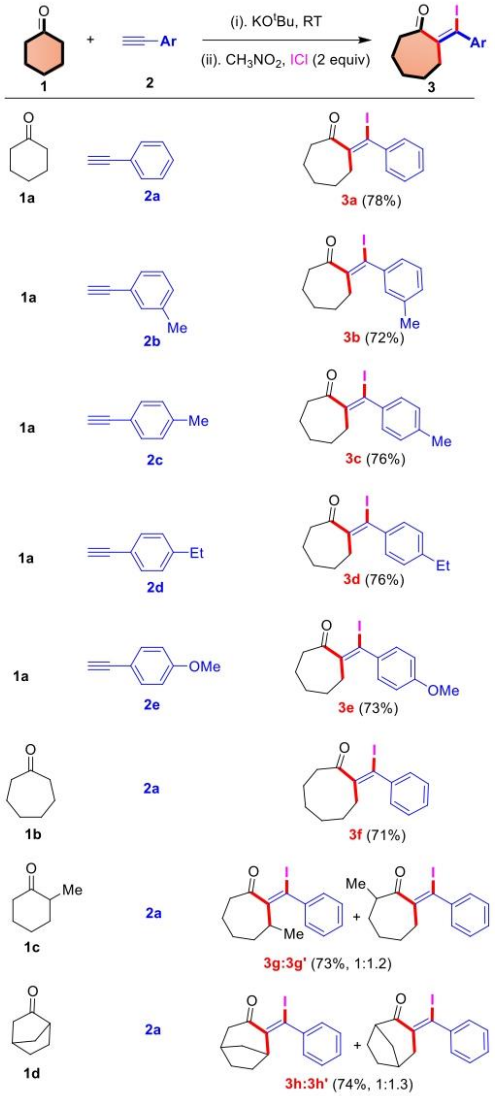
[a] 1 equiv of **1a**, 1.2 equiv. of **2a**, and 1.5 equiv. of KO^{t}Bu were used, all reactions were performed at room temperature (30 °C).
[b] Isolated yields.
[c] Optimum conditions.
[d] Compound **3aa** was recovered or decomposed after a long time.

nitromethane. In the next stage, we investigated the amount of ICl that required to produce the best yield of **3a** and found that neither the increase nor the decrease could be the better option (entries 12–14, Table 1). Finally, we realized that this three-component reaction offers the best reaction yield by stirring **1a** (1 equiv.), **2a** (1.2 equiv.), and ICl (2 equiv.) in nitromethane at room temperature (entry 3, Table 1).

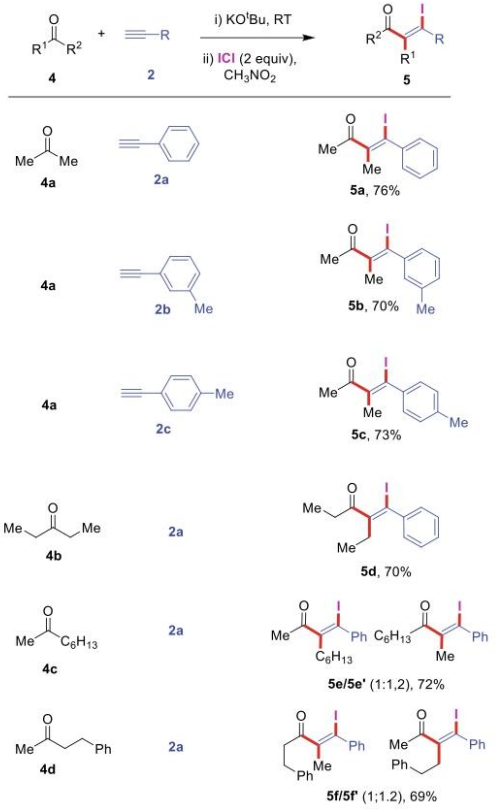
Having the optimum condition in hand, we plan to check the generality of this protocol with respect to alkynes and cyclic ketones (Scheme 2). Therefore, we treated ketone **1a** with 3-methylphenylacetylene (**2b**) under standard reaction conditions and obtained the desired compound **3b** in 72% yield. Similarly, 4-methylphenylacetylene (**2c**), 4-ethylphenylacetylene (**2d**), and 4-methoxyphenylacetylene (**2e**) reacted with ketone **1a**, to produce the corresponding β-iodo-α, β-unsaturated systems **3c**, **3d** and **3e** in good yields. Latter, cycloheptanone (**1b**) was treated with alkyne **2a** to obtain corresponding cyclooctanone derivative, **3f** with ring expansion in 71% yield. Next, we took an unsymmetrical ketone, 2-methylcyclohexanone and treated with **2a** under standard reaction conditions, as expected the reaction produced a mixture of products **3 g**/**3g'** in 1:1.2 ration with a total yield of 73% [11].

Another unsymmetrical ketone **1d** has also furnished the mixture of products **3 h**/**3h'** with a 74% yield in a 1:1.3 ratio (Scheme 2). It is worth noting that, though aliphatic alkynes furnished the propargyl alcohols as the key intermediates, in the next step the reaction profile (on TLC) was complex and we could not isolate any product under these conditions.

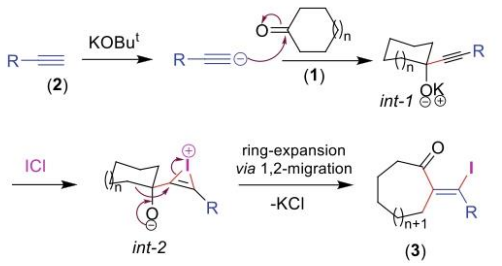
Next, we planned to check the scope of acyclic ketones (**4**) in this carbonylation-iodination reaction of alkynes (Scheme 3). Initially, acetone (**4a**) was treated with alkyne **2a** under standard reaction condition and obtained 4-iodo-3-methyl-4-phenylbut-3-en-2-one (**5a**) in 76% yield with a methyl migration. This followed by the other alkynes **2b**, **2c** to afford the corresponding products **5b** and **5c** in good yields (Scheme 3). Next, diethyl ketone also showed a similar reactivity with **2a** to furnish **5d** in 66% yield with ethyl migration. Later, an unsymmetrical ketone, 2-octanone (**4c**) was subjected to standard reaction condition with **2a**, surprisingly the reaction did not show any selectivity during the 1,2-migration step (that is methyl verses hexyl) and furnished the mixture of isomers **5e**/**5e'** in 1:1.18 ratio with a total yield of 72% [10]. Another unsymmetrical ketone 4-phenylbutan-2-one (**4d**) also reacted with **2a** and furnished mixture of products **5f**/**5f'** in 69% yield with no selectivity (1:1.13 ratio) [12]. Probably, the reaction conditions may need to be further optimized to achieve a reasonable selectivity during the 1,2-migration step, and it is worth mentioning that aryl ketones/biaryl ketones and tetralones did not furnish the



Scheme 2. Substrate scope with cyclic ketones.



Scheme 3. Substrate scope with acyclic ketones:

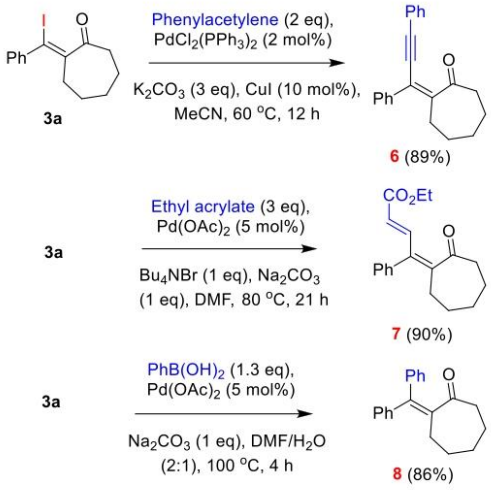


Scheme 4. Plausible reaction mechanism.

desired compounds under the standard reaction conditions, these ketones resulted the formation of an inseparable complex mixture.

The possible reaction mechanism for the three-component synthesis of β-iodo-α,β-unsaturated compounds is described in Scheme 4. The acetylenic anion generated from alkyne (**2**) by the base will add to the electrophilic carbonyl carbon of **1** to provide propargylic oxide intermediate-1. To prove the presence of intermediate, we have isolated propargyl alcohol **3aa** and treated with ICl to get the respective product **3a** from **1a** and **2a**. Electrophilic activation of ynol intermediate-1 with ICl gives the cyclic iodonium intermediate-2, and a subsequent 1,2- migration takes place to furnish the desired compounds **3** and **5** (Scheme 4).

Since the products having reactive iodide functionality, we designed a few cross-coupling reactions to show the synthetic ability to demonstrate the usefulness as key intermediates in organic synthesis (Scheme 5). Initially, iodide **3a** was subjected to Sonogashira cross-coupling [13] with phenylacetylene to obtain compound **6** in an 89% yield. Next, Heck coupling [14] was



Scheme 5. Cross-coupling reactions of **3a** (Sonogashira, Heck, and Suzuki).

performed with **3a** and ethyl acrylate to get a highly conjugated system **7** in 90% yield. Finally, Suzuki cross-coupling [15] between **3a** and phenylboronic acid gave 2-(diphenylmethylene)cycloheptan-1-one, **8** in 86% yield (Scheme 5).

In summary, we have developed an efficient, one-pot, three-component synthesis of β-iodo-α,β-unsaturated cyclic, and acyclic ketones from terminal alkynes, ketones, and ICl. The reaction was performed at room temperature in a sequential manner. With cyclic ketones, we observed the ring expansion, and in the case of unsymmetrical ketones (cyclic and acyclic), the reaction did not show any remarkable selectivity during the 1,2-migration stage and hence furnished the mixture of products. Further investigations with aryl-ketones are currently ongoing in our laboratory.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152374.

References

[1] (a) R.C. Larock, L. Zhang, Halogenation of alkynes in Comprehensive Organic Transformations: A Guide to Functional Group Preparations, John Wiley & Sons Inc, 2018;
(b) M.R. Uehling, R.P. Rucker, G. Lalic, J. Am. Chem. Soc. 136 (2014) 8799–8803, and references cited therein;
(c) H. Lindlar, R. Dubuis, Org. Synth. 46 (1966) 89;
(d) K. Murugesan, C.B. Bheeter, P.R. Linnebank, A. Spannenberg, J.N.H. Reek, R. V. Jagadeesh, M. Beller, ChemSusChem 12 (2019) 3363–3369, and references cited therein;
(e) H.C. Brown, M. Zaidlewicz, Organic Syntheses via Boranes, Aldrich Chemical, Milwaukee, WI 2 (2001);
(f) T. Ohmura, Y. Yamamoto, N. Miyaura, J. Am. Chem. Soc 122 (2000) 4990.
[2] (a) M. Gartner, J. Qu, G. Helmchen, J. Org. Chem. 77 (2012) 1186–1190;
(b) V. Rauniyar, Z.J. Wang, H.E. Burks, F.D. Toste, J. Am. Chem. Soc. 133 (2011) 8486–8489;
(c) T.J. Greshock, R.L. Funk, J. Am. Chem. Soc. 128 (2006) 4946–4947;
(d) T. Yao, X. Zhang, R.C. Larock, J. Am. Chem. Soc. 126 (2004) 11164–11165;
(e) M.G. Banwell, B.D. Kelly, O.J. Kokas, D.W. Lupton, Org. Lett. 5 (2003) 2497–2500;
(f) K.C. Nicolaou, D.L.F. Gray, T. Montagnon, S.T. Harrison, Angew. Chem. Int. Ed. 41 (2002) 996–1000;
(g) A.D. William, Y. Kobayashi, J. Org. Chem. 67 (2002) 8771–8782;
(h) N.G. Ramesh, E.H. Heijne, A.J.H. Klunder, B. Zwanenburg, Tetrahedron 58 (2002) 1361–1368;
(i) C.-K. Sha, K.C. Santhosh, C.-T. Tseng, C.-T. Lin, Chem. Commun. (1998) 397–398.
[3] A.E. Pohland, W.R. Benson, Chem. Rev. 66 (1966) 161–197.
[4] (a) D. Elsa, P. Bovonsombat, E.M. Nelis, Synth. Commun. 27 (1997) 2497–2503;
(b) C.R. Johnson, J.P. Adams, M.P. Braun, C.B.W. Senanayake, P.M. Wovkulich, M.R. Uskokovic, Tetrahedron Lett. 33 (1992) 917–918.
[5] (a) G. Liu, P.D. Wilkerson, C.A. Toth, H. Xu, Org. Lett. 14 (2012) 858–861;
(b) A.S.K. Hashmi, T. Haffner, M. Rudolph, F. Rominger, Eur. J. Org. Chem. (2011) 667–671;
(c) P. Bovonsombat, R. Rujiwarangkul, T. Bowornkiengkai, J. Leykajarakul, Tetrahedron Lett. 48 (2007) 8607–8610;
(d) M.E. Krafft, J.W. Cran, Synlett (2005) 1263–1266;
(e) A. Alimardanov, E. Negishi, Tetrahedron Lett. 40 (1999) 3839–3842.
[6] (a) D. Roy, P. Tharra, B. Baire, Asian J. Org. Chem. (2018) 1015–1032;
(b) H.-T. Zhu, M.-J. Fan, D.-S. Yang, X.-L. Wang, S. Ke, C.-Y. Zhang, Z.-H. Guan, Org. Chem. Front. 2 (2015) 506–509;
(c) S. Puri, N. Thirupathi, M.S. Reddy, Org. Lett. 16 (2014) 5246–5249;
(d) L. Ye, L. Zhang, Org. Lett. 11 (2009) 3646–3649;
(e) D.A. Engel, G.B. Dudley, Org. Biomol. Chem. 7 (2009) 4149–4158;
(f) S. Chen, J. Wang, J. Org. Chem. 72 (2007) 4993–4996;
(g) S. Swaminathan, K.V. Narayanan, Chem. Rev. 71 (1971) 429–438.
[7] (a) J.J. Janas, E.T. Asirvatham, E. McNelis, Tetrahedron Lett 26 (1985) 1967–1968;
(b) P. Bovonsombat, E. McNelii, Tetrahedron Lett 34 (1993) 4277–4280;
(c) J.-M. Chen, X. Huang, Synthesis (2004) 2459–2462.
[8] (a) N. Krause (Ed.), Modern Organocopper Chemistry, Wiley-VCH, Weinheim, Germany, 2002;
(b) R.J.K. Taylor (Ed.), Organocopper Reagents, IRL Press, Oxford, 1994.
[9] (a) S. Yaragorla, T. Khan, Eur. J. Org. Chem. (2019), 3989–3401;
(b) S. Yaragorla, A. Pareek, Eur. J. Org. Chem. (2018) 1863–1871;
(c) S. Yaragorla, A. Pareek, R. Dada, P.L. Saini, Eur. J. Org. Chem. (2017) 4600–4608.
[10] (a) S. Chen, F. Yuan, H. Zhao, B. Li, Res. Chem. Intermed. 39 (2013) 2391–2399;
(b) S. Yaragorla, R. Dada, G. Singh, A. Pareek, M. Rana, A.K. Sharma, ChemistrySelect 1 (2016) 6902–6906.
[11] The ratio of the mixture was based on the 1H NMR spectra
[12] (a) X.-M. Zhang, Y.-Q. Tu, F.-M. Zhang, Z.-H. Chen, S.-H. Wang, Chem. Soc. Rev 46 (2017) 2272–2305;
(b) R.J. Mawby, F. Basolo, R.G. Pearson, J. Am. Chem. Soc. 86 (1964) 5043–5044;
(c) W.H. Saunders, R.H. Paine, J. Am. Chem. Soc. 83 (1961) 882–885;
(d) S. Yaragorla, R. Dada, D. Bag, Eur. J. Org. Chem (2019) 6983–6988;
(e) S. Yaragorla, D. Bag, R. Dada, K.V.J. Jose, ACS Omega 3 (2018) 15024–15034.
[13] (a) J.H. Li, Y. Liang, Y.X. Xie, J. Org. Chem. 70 (2005) 4393–4396;
(b) K. Sonogashira, Y. Tohda, N. Hagihara, Tetrahedron Lett. 16 (1975) 4467–4470.
[14] (a) R. F. Heck, Palladium Reagents in Organic Synthesis; Academic Press: San Diego, CA, 1985; 276-287.
[15] (a) A. Suzuki, J. Organomet. Chem. 576 (1999) 147-168; b) A. Suzuki, Metal Catalyzed Cross-Coupling Reactions; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, (1998), 49.

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Thermal Ring Rearrangement

Brønsted Acid Promoted Thermal-Ring-Rearrangement of Fluorenopyrans to 2-(1*H*-Inden-3-yl)-9*H*-fluoren-3-ols Bearing Two All-Carbon-Quaternary Centres

Tabassum Khan,[a] P. Rajesh,[a] Dudam Praveen,[a] K. V. Jovan Jose,*[a] and Srinivasarao Yaragorla*[a]

Abstract: 4-Aryl-fluorenopyrans bearing quaternary centre at C2 and C6 positions underwent a thermal-ring-rearrangement with a catalytic amount of *p*TsOH to furnish 2-(1*H*-inden-3-yl)-9*H*-fluoren-3-ols with two all carbon-quaternary centres, in which one is retained and the other is created. Interestingly, these compounds exhibit atropisomerism, when they have at least one unsymmetrical quaternary centre. DFT studies of structure and energetics of these atropisomers were offered, and the calculated ^{1}H-NMR chemical shifts of the hydroxyl (–OH) functional group in the atropisomers corroborate well with the experiment.

Introduction

Ring-rearrangement reactions are the ring-opening-cyclization of a single substrate by means of an acid/base or a metal catalyst under thermal conditions.[1–4] These ring-rearrangements involve a cascade of reactions that take place in a single-pot with maximum atom economy (≈ 100 %) and hence fall under green chemical synthesis.[5] Particularly, the ring rearrangement reactions of benzochromene derivatives bearing a C2-quaternary centre is depicted in Figure 1. For example, when naphthopyran [**IA**] was heated with a catalytic amount of *p*TsOH in toluene, it underwent an irreversible ring-rearrangement to give highly coloured benzopentaleno-naphthalenones [**IB**], however, there are only two examples described using this method.[2] Later, 3-(2-ethoxyethyl)-2,2-diphenyl-2*H*-chromene [**IC**] was also underwent ring-rearrangement with scandium triflate at 60 °C to furnish 2-(3-phenyl-1*H*-inden-1-yl)phenol [**ID**], but a single example was demonstrated using this method.[3] Then a general method was reported by us that a naphthopyran [**IE**] can be effectively rearranged to (inden-3-yl)naphthalenol [**IF**].[4] On the other hand, while we are working on annulation reactions to construct the fluorenopyran **1a**,[6] we observed that the addition of trifluoroacetic acid, lead to the formation of an intense brick red colour solution, and this becomes colourless when triethylamine was added (Figure 2). This colour changes can be understood based on the ring-opening of **1a** with protonation and ring closure with base (NEt_3) as depicted in Figure 2. Further investigations on the acidochromic behaviour[7,8] of this substrate with a series of Bronsted acids,[9] lead to the formation of a new chemical entity (1*H*-inden-3-yl)-9*H*-fluoren-3-ol through a ring-rearrangement reaction (Figure 1, Equ. iv). Intrigued by this observation, we decided to explore the generality, scope, limitations and mechanistic insights of this ring-rearrangement reaction.

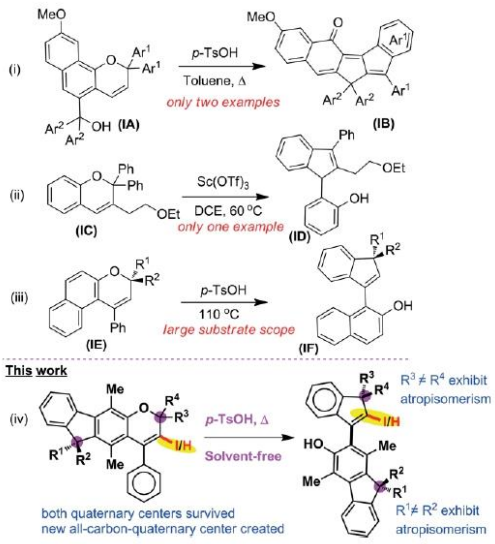


Figure 1. Ring-rearrangement reactions of chromenes.

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Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.202000251.

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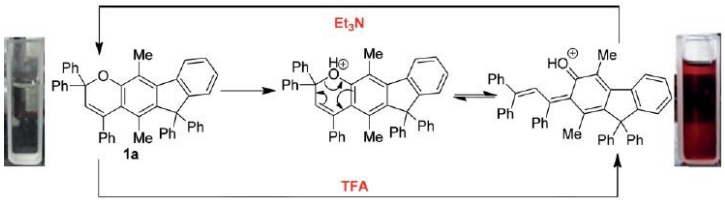
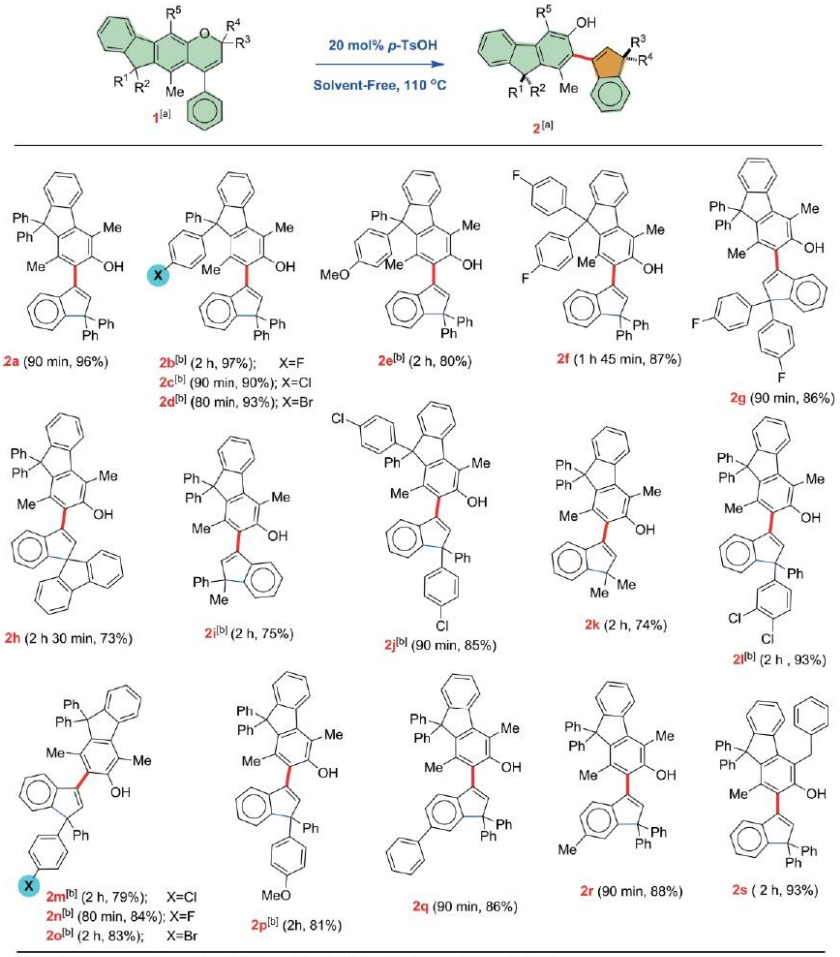


Figure 2. Acidochrmoic nature of **1a**.

Results and Discussion

To find out the suitable reaction conditions of the ring-rearrangement reaction, we have selected 5,11-dimethyl-2,2,4,6,6-pentaphenyl-2,6-dihydroindeno[2,1-*g*] chromene **1a** as the model substrate, which was synthesized using a reported method.[6] Among the various reaction conditions studied,[9] we

Table 1. Substrate scope of fluorenopyrans in TRR.



[a] Conditions: All reactions were performed in a 0.15 mmol scale; [b] isolated as a mixture of diastereomers.

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found that when **1a** was heated at 110 °C with 20 mol-% of *p*TsOH the reaction gave the best yield, Under these conditions, compound **1a** underwent an irreversible ring-rearrangement via ring-opening-cyclization to furnish 2-(1,1-diphenyl-1*H*-inden-3-yl)-1,4-dimethyl-9,9-diphenyl-9*H*-fluoren-3-ol **2a** in nearly quantitative yield after 90 minutes. Encouraged by this outcome, we planned to check the generality of this protocol with differently substituted fluorenopyrans as depicted in Table 1.

Interestingly, this method showed excellent substrate scope in delivering the desired products **2a**–**2s** in high yields. The halo-substitutions such as F, Cl, Br, on the phenyl rings of both the quaternary centres (**2b**–**2d**, **2f**, **2g**, **2j**, **2l**–**2o**) and the methoxy-substitution on one of the phenyl rings of quaternary centre (**2e, 2p**) were well tolerated under these conditions. Further at the quaternary centres, not only aryl-aryl, groups but also aryl-methyl (**2i**) and methyl-methyl (**2k**) groups were also synthesized with this protocol. Compound **2h** indicates that this rearrangement reaction can facilitate to have a spirocyclic moiety without much loss of the yield. Unlike other compounds, the synthesis of **2s** indicates the compatibility of benzyl substitution on fluorenol. Further, we confirmed the adaptability of this method to have phenyl, methyl substitutions on the indene's benzene (**2q**, **2r**). A single-crystal X-ray structure of compound **2c** was obtained to conform its structure without any ambiguity (Figure 4). More interestingly, the ^{1}H NMR spectra of the products bearing unsymmetrical substitutions on at least one of the quaternary centres indicated that the products are formed as mixture of diastereomers. This could be due to the hindered rotation of the C–C bond between fluorenol and Indene, which is generally known as axial chirality or atropisomerism.[10] For example, compounds **2b**, **2c**, **2d** and **2e** (bearing unsymmetrical substitutions at fluorenol quaternary centre) and **2i**, **2j**, **2l**–**2p** were isolated as an inseparable diastereomeric mixture. A similar trend was noticed with compound **2j**, bearing two unsymmetrical quaternary centres. Notably, the hydroxyl-proton of these compounds in ^{1}H NMR spectrum showed two clear signals around five ppm, and in case of compounds having a stereogenic centre on indene the difference of hydroxyl signals is 0.005–0.007 ppm and that for a stereogenic centre on fluorenol is in the range of 0.02–0.03 ppm. In addition to this, we also observed that the compounds bearing a stereogenic centre on indene part, showed the presence of two compounds on TLC ($R_f \approx 0.48$ and 0.49, mobile phase: 3 % EtOAc in hexane), whereas the diastereomers with chiral centre at 9-fluorenyl moiety appeared as a single spot on the TLC. Visibility of the two spots on TLC excited us to separate the diastereomeric mixture (**2o**), however our attempts by column chromatography (100–200 and 230–400 silica mesh, using pure hexane as the mobile phase), preparative TLC method was unsuccessful. We also recorded the High-temperature ^{1}H NMR[11] of compound **2o** in $CDCl_3$ (at 50 °C) and [D_6]DMSO (at 50 and 80 °C) but it did not give any conclusion although in [D_6]DMSO the signals for hydroxyl were merged and shifted slightly upfield. However, LCMS separation using a C8 HPLC column resulted in two peaks in nearly 1:1 ratio on the chromatogram (Figure 3-top), which gave the required mass for each peak.[12]

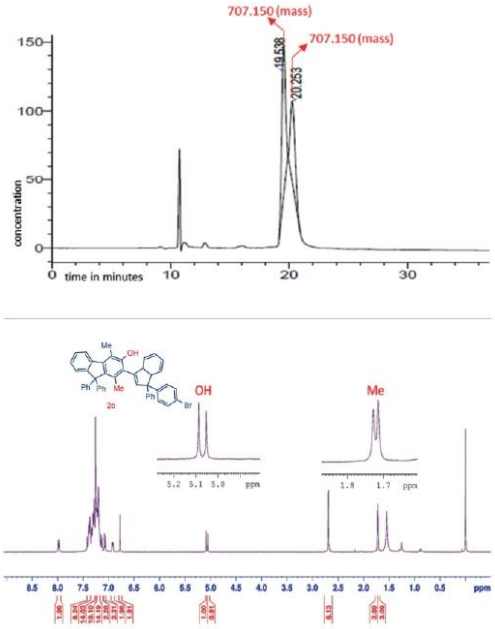


Figure 3. Diastereomers (atropisomers) in compound 2o (LCMS chromatogram-top; ^{1}H NMR showing two compounds-bottom).

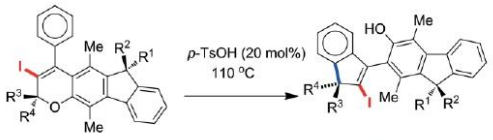
With this success in hand, we further interested to see the TRR of **3a**, because to the best of our knowledge, so far no reports are available on the ring-rearrangement of fully substituted pyran (of benzo/naphthopyran) systems. Therefore, we selected compound **3a** bearing an iodide substitution at C3-position to test the TRR under standard reaction conditions. Delightfully, the product **4a** was obtained in 62 % yield after 2 h (Table 2), in which the iodide functionality was intact with the final molecule but on a newly constructed ring. Encouraged by this unprecedented observation, we sought the generality of this reaction, and hence a number of 3-iodo-fluorenopyrans **3b**–**3f** were subjected to ring-rearrangement reaction and obtained the respective products **4b**–**4f** in good yields. The structure of these products was unambiguously determined by a single-crystal X-ray structure of **4e** (CCDC No. 1951991) (Figure 4). The ^{1}H NMR spectra of compounds **4b**–**4d** and **4f** indicated that these compounds exhibit atropisomerism.

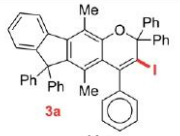
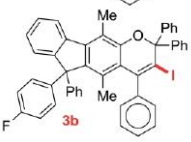
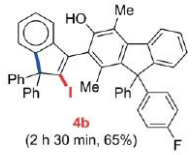
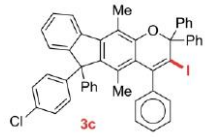
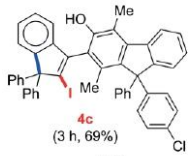
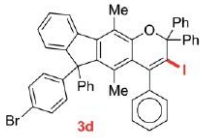
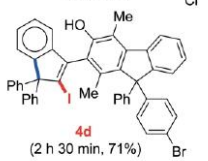
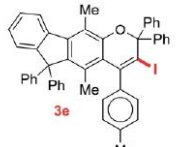
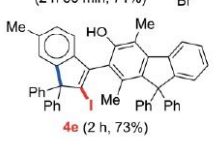
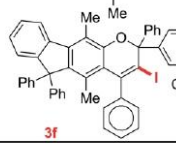
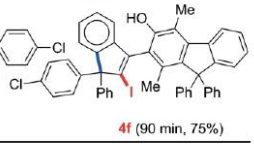
After the establishment of a general protocol for the TRR of fluorenopyrans (Table 1) and iodo-fluorenopyrans (Table 2), we further supplemented the efficacy of this method by demonstrating the gram scale reaction of **1a** and **3a** to obtain the corresponding products **2a** (0.824 g) and **4a** (0.607 g) in 82 % and 60 % respective yields (Scheme 1).

To show the synthetic potential of these products, indene iodide **4f** was subjected to dehydrohalogenation by heating in DMSO at 170 °C with copper(I)oxide and quinoline for 16 h.[13] This reaction furnished a linearly fused hexacyclic system **5** in

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Table 2. TRR of 3-iodo-fluorenopyrans.



Entry	Substrate	Product
1	 3a	 4a (2 h, 62%)
2	 3b	 4b (2 h 30 min, 65%)
3	 3c	 4c (3 h, 69%)
4	 3d	 4d (2 h 30 min, 71%)
5	 3e	 4e (2 h, 73%)
6	 3f	 4f (90 min, 75%)

86 % yield (Scheme 2). It is worth highlighting that the ^{1}H NMR of **4f** indicated the presence of diastereomers (atropisomers) but after the cyclization, it gave a single isomer **5**. This indicates us that the C–C bond rotation was locked to a cyclic system, and hence the product cannot exhibit axial chirality. Further compound **4a** was converted as methyl ether **6** by refluxing in acetone with potassium carbonate and dimethyl sulfate[14] (Scheme 3). Next, we planned an iodocyclization reaction[15] through the formation of propargyl ether of **2a**. Accordingly, 2a was refluxed in acetone with propargyl bromide and potassium

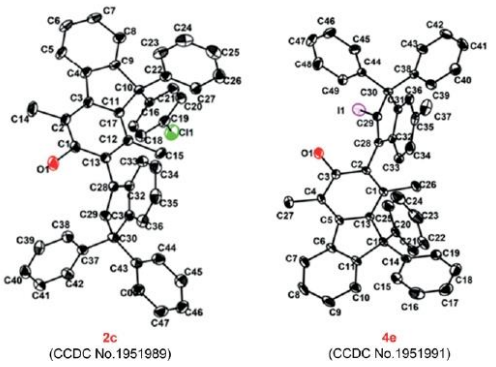
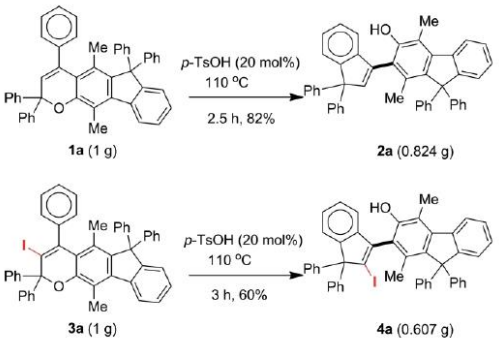
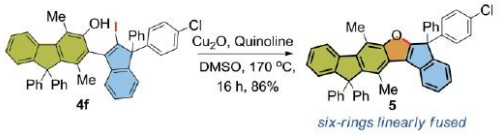


Figure 4. Single-crystal XRD of **2c** and **4e**.



Scheme 1. Gram scale synthesis of **2a** and **4a**.

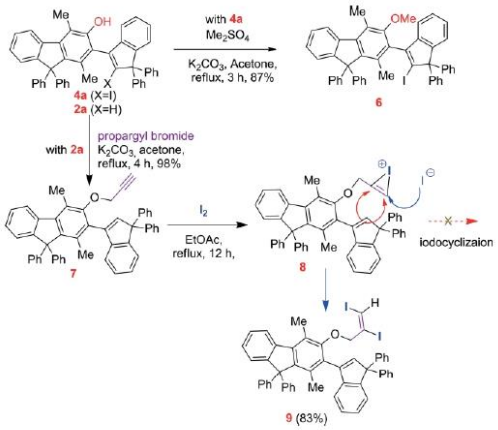
carbonate to obtain the propargyl ether **7** in quantitative yield.[16] Later it was subjected to iodination followed by cyclization as proposed in the structure **8**. However, it was observed that indene was not nucleophilic enough to react with cyclic iodonium intermediate, instead it gave diiodide **9** in 83 % yield (Scheme 3).



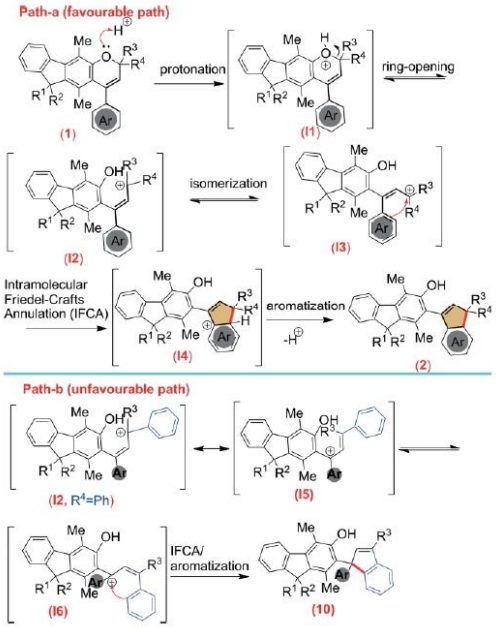
Scheme 2. Synthetic transformation of indene 4f.

The plausible reaction mechanism of TRR is described in Scheme 4, initially protonation of **1** with the Bronsted acid gives oxonium TS (**I1**), which undergoes ring opening to form cationic TS (**I2**). Isomerization of **I2** followed by intramolecular Friedel-Crafts annulation gives product **2** via **I4** (path-a). Alternatively, the cationic TS **I2** can resonate to give **I5**, which on isomerization may give **I6**. Intramolecular Friedel-Crafts annulation of **I6** can result in indenyl-fluorenol **10** (path-b). We also per-

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Scheme 3. Synthetic transformations of **2a** and **4a**.



Scheme 4. The reaction mechanism.

formed a control experiment to see the possibility of path-b, by performing the TRR of **1** bearing a C4-cyclopropyl group (instead of aryl group) and found that it could not give the rearranged product under these conditions. To understand more about the atropisomerism of these compounds we have performed DFT calculations, because so far there is no report on the computational study of the TRR, though some reports devoted to study the atropisomersim.[17–20] Single point energies and geometry optimizations were performed at the DFT level using the M062X functional and 6-31G(d,p) basis functions. Optimized geometries were employed to calculate the ^{1}H-NMR chemical shift at the same level of theory in the presence of a solvent. Here, calculations were performed on selected molecules. From the results, it was observed that conformers of compounds with achiral indene and fluorenyl centre exhibit no energy difference and no difference in ^{1}H-NMR chemical shift values (ppm). Thus, we observe only one peak in **2a**. Though **2c**, **2e** conformers did not show energy difference in the DFT calculation, experimental data of these conformers show a small difference (0.005–0.007 ppm) in the ^{1}H-NMR chemical shift values of the hydroxy proton. However, two of the molecules (**2j**, **2m**) exhibit energy difference (ΔE) of –1.34 and –1.38 in kcal/mol, as mentioned in Table 3.

Because of the different chemical environment around the hydroxy group due to a quaternary center of indene, it is expected that the molecular conformers exhibit variations in the energy and the ^{1}H-NMR values (0.02–0.003 ppm). The energy profile of the reaction mechanism (Scheme 4) is depicted in Figure 5, Path-a (in green) represents favourable reaction and Path-b (in red) represents unfavourable reaction.

The relative energies of the transition states **I3** and **I4** are –2.6 and 18.8 kcal/mol, respectively concerning the common TS (**I2**). The final product (**2**) is stable relative to **1** with an interaction energy –7.7 kcal/mol. The less favoured reaction mechanism depicted in red (Path-b), with transition states (**I5**, **I6**) and product (**10**) with relative energies 0.3, 26.8, and 3.0 kcal/mol, respectively. The relative energies of products (**2** and **10**) are calculated relative to the initial reactant molecule (**1**) depicted in Scheme 4. The final products depicted in Figure 5 differ in energy by 10.3 kcal/mol. The energy profile evaluated at M062X/6-31+G(d,p) shows that the mechanism path is shown in green, i.e. Path-a is more preferred over the Path-b. The transition states were also characterized by calculating the imagi-

Table 3. Single point energies of conformers are designated as E_1 and E_2, respectively at M062X/6-31+G(d,p). ΔE represents the energy differences (in kcal/mol) between the two conformers; NMR-1 & NMR-2 are the ^{1}H NMR chemical shift of the –OH functional groups (in ppm) of the conformers, respectively. ΔNMR is the difference in the NMR values (in ppm).

Molecules	E_1 [Hartree]	E_2 [Hartree]	ΔE [kcal/mol]	NMR-1 [ppm]	NMR-2 [ppm]	ΔNMR [ppm]
2a	–1925.29508	–1925.29508	0.00	5.369	5.369	0.00
2c	–2384.86128	–2384.86128	0.00	5.489	5.489	0.00
2e	–2039.77480	–2039.77480	0.00	5.336	5.336	0.00
2j	–2844.43405	–2844.43191	–1.34	5.309	5.075	0.234
2m	–2384.86444	–2384.86224	–1.38	5.434	5.173	0.262

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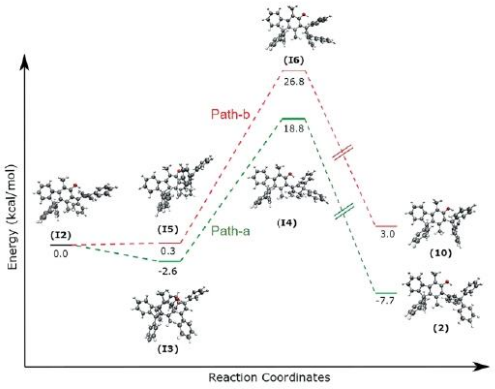


Figure 5. Energy profile of two-possible transition states, based on mechanism depicted in Scheme 4.The reaction energies are reported in kcal/mol.

nary frequencies of I4 (–668.4 cm^{-1}) and I6 (–885.5 cm^{-1}). The additional information is available in supporting information. Figure 6 depicts the energy difference (kcal/mol) of two conformers of molecules **2a**, **2c**, **2e**, **2j**, and **2m**. The conformers of molecules (**2a**, **2c**, **2e**) show ΔE = 0, due to which the compound **2a** was observed as a single compound and **2c** and **2e** were present as diastereomers with a very minute difference in the chemical shift values of the hydroxy peak. The conformers of molecule **2j** and **2m** show energy differences of –1.34 and –1.38 respectively (Figure 6).

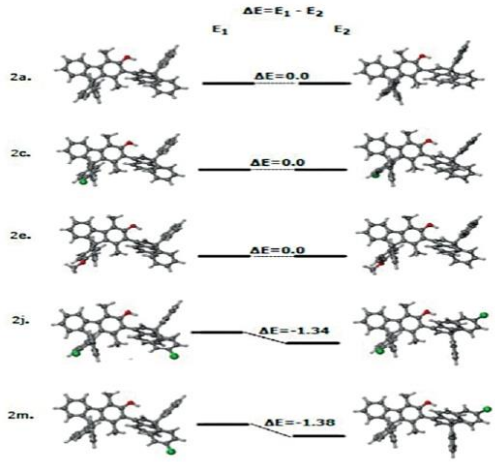


Figure 6. The energies (E_1 and E_2) and the relative energy differences (ΔE) in kcal/mol of **2a**, **2c**, **2e**, **2j** and **2m**. The atom oxygen is depicted in red, the carbon in grey, hydrogen in white and chlorine in green color, respectively.

Table 3 represents the M062X/6-31+G(d,p) calculated energies (E_1 and E_2 in Hartree) of conformers and the difference in energies in kcal/mol. The NMR chemical shift of –OH functional group and differences (in ppm) of the selected molecules depicted in Figure 6. The computational results of the molecules (**2a**, **2c**, **2e**, **2j** and **2m**) shows that the conformers having a stereogenic centre on indene, show a difference in energies and ^{1}H-NMR chemical shifts. The theoretical ^{1}H-NMR chemical shifts corroborate well with the experimental, thus attributing the difference in NMR chemical shifts as the feature of the atropisomerism.

Conclusion

In conclusion, we have developed a thermal ring rearrangement reaction of fluorenopyrans to 2-(1*H*-inden-3-yl)-9*H*-fluoren-3-ols using *p*TsOH under solvent-free conditions for the first time. Besides, we have also extended this TRR to 3-iodofluorenopyrans (**3**) and obtained the corresponding 2-(2-iodo-1*H*-inden-3-yl)-1,4-dimethyl-9*H*-fluoren-3-ols (**4**) bearing all carbon-quaternary centres at C1 and C9 positions. The presence of asymmetric centre either on indene or fluorine or on both resulted in the formation of diastereomeric atropisomers, which were clearly seen in their NMR spectra, also the two chromatograms in LCMS. DFT calculations were in agreement with the experimental observations.

Experimental Section

General Information: Unless otherwise noted, all reagents were used as received from commercial suppliers. *p*TsOH, $Ca(OTf)_2$ and Bu_4NPF_6, KO*t*Bu, 2,4-diones, alkyne, and ketones were purchased from commercial suppliers such as Sigma-Aldrich, Alfa Aesar, TCI chemicals, and Spectrochem which were used without further purification. Reactions were performed in flame-dried or oven-dried glassware with magnetic stirring. Reactions were monitored by thin-layer chromatography (TLC) using aluminium sheets silica gel 60 F_{254} from Merck. TLC plates were visualized with UV light (254 nm), iodine treatment or using *p*-anisaldehyde or $KMnO_4$ stain. Column chromatography was carried out using silica gel 60–120 mesh as the stationary phase. NMR spectra were recorded at 500 MHz and 400 MHz (^{1}H) and at 125 MHz and 100 MHz (^{13}C), respectively on Avance Bruker spectrometer. Chemical shifts (δ) are reported in ppm, using the residual solvent peak in $CDCl_3$ (^{1}H: δ = 7.26 and ^{13}C: δ = 77.16 ppm) as internal standard, and coupling constants (J) are given in Hz. HRMS were recorded using ESI-TOF techniques. Melting points were measured with the Labindia MEPA melting point apparatus.

Computational Methods: The geometry optimization of the structures depicted in Figure 6 is performed at M06X/6-31G(d) using the Gaussian 09 suite of packages.[21] A single point energy calculations were carried out on the optimized structures at M062X[22] density functional, with 6-31+G(d,p)[23] basis set for the main group atoms, and the LANL2DZ[24] electron core potential and its associated basis set for the chlorine atom. The ^{1}H-NMR chemical shifts of atropisomer are calculated at the same level of theory with chloroform as the solvent. The NMR chemical shifts reported in Table 3 are calculated relative to the tetramethylsilane (TMS) molecule. The TMS molecule is optimized and ^{1}H-NMR chemical shift values evaluated at the same level of theory and basis, the same as that for atropisomers. The solvation effect is incorporated using the solvation model based on the density (SMD) implicit solvation model[25] with chloroform as the solvent, as implemented in the Gaussian 09 package.

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General Experimental Procedure for the Synthesis of Compounds 2a–s): 5,11-Dimethyl-2,2,4,6,6-pentaphenyl-2,6-dihydroindeno[2,1-*g*] chromene **1**a (100 mg, 0.15 mmol) was treated with *p*TsOH (20 mol-%) at 110 °C in solvent free condition for 90 min. After completion of the reaction (monitor by TLC) the crude product was purified by silica gel column chromatography (0–5 % EtOAc in pet-ether) to obtain the desired product **2**a in 96 % yield.

2-(1,1-Diphenyl-1*H*-inden-3-yl)-1,4-dimethyl-9,9-diphenyl-9*H*-fluoren-3-ol (2a): Following general experimental procedure; white solid, mp: 246–248 °C; yield: 96 % (0.096 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8 Hz, 1H), 7.42–7.40 (m, 1H), 7.39–7.37 (m, 2H), 7.35–7.32 (m, 2H), 7.30–7.28 (m, 4H), 7.27–7.24 (m, 7H), 7.23–7.19 (m, 10H), 6.90 (dd, J_1 = 2 Hz, J_2 = 6.5 Hz, 1H), 6.83 (s, 1H), 5.13 (s, 1H), 2.68 (s, 3H), 1.74 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9, 151.2, 150.7, 146.0, 143.5, 142.9, 142.8, 142.7, 142.1, 140.9, 137.9, 132.3, 129.3, 129.0, 128.8, 128.6, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.3, 127.2, 127.0, 126.8, 126.8, 126.5, 126.4, 125.5 (2), 123.4, 121.6, 120.0, 117.2, 66.9, 64.9, 18.0, 12.8 ppm; HRMS (ESI-TOF): *m/z* calculated for $C_{48}H_{36}O$ $[M + H]^+$ 629.2844, found 629.2845.

2-(1,1-Diphenyl-1*H*-inden-3-yl)-9-(4-fluorophenyl)-1,4-dimethyl-9-phenyl-9*H*-fluoren-3-ol (2b): Following general experimental procedure; white solid, mp: 256–258 °C; yield: 97 % (0.097 g); isolated as 1:1.02 of diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 9.5 Hz, 2H), 7.42–7.40 (m, 2H), 7.36–7.33 (m, 4H), 7.32–7.28 (m, 8 H), 7.27–7.24 (m, 15H), 7.23–7.20 (m, 17H), 6.95–6.86 (m, 6H), 6.835 (s, 1H), 6.833 (s, 1H), 5.14 (s, 1H), 5.13 (s, 1H), 2.68 (s, 6H), 1.73 (s, 3H), 1.72 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7, 151.3, 150.7, 146.1, 146.0, 143.4, 143.2, 142.7, 142.5, 142.0, 140.8, 140.0, 137.8 (2), 132.2 (2), 130.9 (2), 130.7, 130.6, 129.1, 128.8, 128.6, 128.1, 128.0, 127.7 (2), 127.6, 127.5, 127.3 (2), 127.1, 126.8, 126.7, 126.5, 125.5, 125.3, 123.4, 121.5 (2), 120.1, 117.4, 114.8 (2), 114.6 (2), 66.9, 64.4, 18.0, 12.8 ppm; HRMS (ESI-TOF): *m/z* calculated for $C_{48}H_{35}FO$ $[M + K]^+$ 685.2309, found 685.2301.

9-(4-Chlorophenyl)-2-(1,1-diphenyl-1*H*-inden-3-yl)-1,4-dimethyl-9-phenyl-9*H*-fluoren-3-ol (2c): Following general experimental procedure; yellow viscous liquid; yield: 90 % (0.090 g); isolated as 1:1.04 of diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 7.5 Hz, 2H), 7.41 (d, *J* = 7 Hz, 2H), 7.36–7.29 (m, 11H), 7.26–7.24 (m, 12H), 7.23–7.22 (m, 6H), 7.21–7.19 (m, 13H), 7.18–7.15 (m, 6H), 6.92–6.89 (m, 2H), 6.83 (s, 2H), 5.16 (s, 1H), 5.15 (s, 1H), 2.68 (s, 6H), 1.73 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.4, 151.4, 150.7, 146.2, 146.1, 143.4, 143.3, 142.7, 142.4, 142.2, 141.7(2), 141.5, 140.9, 140.0, 137.8, 137.7, 132.4, 132.2, 130.8, 130.4, 129.1, 128.9, 128.8, 128.6 (2), 128.2, 128.1, 127.7 (2), 127.6, 127.4, 127.3, 127.1, 127.0, 126.9, 126.8, 126.7, 126.6, 125.6, 125.3, 123.5, 121.5, 121.4, 120.2, 117.4, 66.9, 64.5, 18.0, 12.8 ppm; HRMS (ESI-TOF): *m/z* calculated for $C_{48}H_{35}ClO$ $[M + H]^+$ 663.2455, found 663.2454.

9-(4-Bromophenyl)-2-(1,1-diphenyl-1*H*-inden-3-yl)-1,4-dimethyl-9-phenyl-9*H*-fluoren-3-ol (2d): Following general experimental procedure; white solid, mp: 269–271 °C yield: 93 % (0.093 g); isolated as 1:1.02 of diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 7.5 Hz, 2H), 7.42 (d, *J* = 7 Hz, 2 H), 7.37–7.33 (m, 7H), 7.32–7.28 (m, 8H), 7.27–7.25 (m, 15H), 7.24–7.23 (m, 4H), 7.21–7.20 (m, 10H), 7.18–7.15 (m, 4H), 6.91–6.87 (m, 2H), 6.836 (s, 1H), 6.832 (s, 1H), 5.15 (s, 1H), 5.14 (s, 1H), 2.68 (s, 6H), 1.72 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.3, 151.4, 150.8, 146.2, 146.1, 146.0, 143.4, 142.7, 142.4, 142.3, 142.2, 141.7, 140.9, 140.0, 137.7, 132.2, 131.2, 131.1, 131.0, 130.8, 129.4, 129.2, 129.0, 128.9, 128.6 (2), 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 127.3, 127.1, 126.9, 126.9, 126.8, 126.6, 125.6, 125.3, 123.5, 121.5 (2), 120.5, 120.4, 120.2, 117.5, 67.0, 64.6, 18.0(2), 12.8 ppm; IR: $\tilde{\nu}_{max}$ = 3505, 3057, 2921, 1445, 748, 697 cm^{-1}; HRMS (ESI-TOF): *m/z* calculated for $C_{48}H_{35}BrO$ $[M + H]^+$ 707.1950, found 707.1945.

2-(1,1-Diphenyl-1*H*-inden-3-yl)-9-(4-methoxyphenyl)-1,4-dimethyl-9-phenyl-9*H*-fluoren-3-ol (2e): Following general experimental procedure; white solid, mp: 268–269 °C; yield: 80 % (0.080 g); isolated as 1:0.99 of diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 7.5 Hz, 2H), 7.42–7.41 (m, 2 H), 7.37 (d, *J* = 7 Hz, 2H), 7.34–7.31 (m, 3H), 7.30–7.29 (m, 4H), 7.28–7.27 (m, 9H), 7.26–7.22 (m, 8H), 7.21–7.19 (m, 15H), 7.18–7.15 (m, 3H), 6.93–6.90 (m, 2H), 6.83 (d, *J* = 1 Hz, 2H), 6.79–6.74 (m, 4H), 5.14 (s, 1H), 5.13 (s, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 2.68 (s, 6H), 1.74 (s, 3H), 1.74 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.2, 158.0, 156.2, 156.1, 151.1, 150.7, 146.0 (2), 143.5, 143.3, 143.2, 143.0, 142.8, 142.3, 140.8, 140.0, 137.9 (2), 134.7, 134.5, 132.3, 130.4, 130.1, 129.3, 128.9, 128.8, 128.6, 128.0, 127.9, 127.7 (2), 127.6, 127.5, 127.2, 127.1, 127.0, 126.8, 126.5, 126.3, 125.5, 125.3, 123.3, 121.6, 120.0, 117.2, 113.3, 113.2, 66.9, 64.3, 18.0, 17.9, 12.8 ppm; HRMS (ESI-TOF): *m/z* calculated for $C_{49}H_{38}O_2$ $[M - H]^+$ 657.2794, found 657.2822.

2-(1,1-Diphenyl-1*H*-inden-3-yl)-9,9-bis(4-fluorophenyl)-1,4-dimethyl-9*H*-fluoren-3-ol (2f): Following general experimental procedure; white solid; mp: 186–188 °C yield: 87 % (0.087 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8 Hz, 1H), 7.38–7.37 (m, 2H), 7.36–7.34 (m, 2H), 7.32–7.31 (m, 1H), 7.30–7.28 (m, 2H), 7.26–7.23 (m, 5H), 7.21–7.18 (m, 6H), 7.15–7.13 (m, 2H), 6.98 (t, *J* = 8.5 Hz, 2H), 6.93–6.91 (m, 1H), 6.88 (t, *J* = 8.5 Hz, 2H), 6.75 (s, 1H), 5.04 (s, 1H), 2.68 (s, 3H), 1.72 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.1, 163.0, 161.1, 161.0, 155.9, 151.1, 150.5, 145.6, 142.9, 142.6, 142.6, 142.3, 140.9, 140.3, 139.0 (2), 138.9, 138.8, 138.2, 132.3, 129.4, 129.3, 129.2, 129.1 (2), 129.0, 128.0, 127.9, 127.8, 127.6, 127.2, 127.0, 126.6, 126.4, 125.5, 125.3, 123.4, 121.8, 119.8. 117.4, 115.8, 115.7, 115.6, 115.4, 65.6, 65.0, 18.0, 12.8 ppm; HRMS (ESI-TOF): *m/z* calculated for $C_{48}H_{34}F_2O$ $[M + Na]^+$ 687.9898, found 687.9812.

2-[1,1-Bis(4-fluorophenyl)-1*H*-inden-3-yl]-1,4-dimethyl-9,9-diphenyl-9*H*-fluoren-3-ol (2g): Following general experimental procedure; white solid, mp: 281–283 °C; yield: 86 % (0.086 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 7.5 Hz, 1H), 7.38–7.33 (m, 4H), 7.30–7.28 (m, 3H), 7.25–7.17 (m, 11H), 7.15–7.13 (m, 2H), 7.00–6.95 (m, 2H), 6.93–6.86 (m, 3H), 6.75 (s, 1H), 5.04 (s, 1H), 2.68 (s, 3H), 1.72 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.1, 163.0, 161.1, 161.0, 155.9, 151.2, 150.6, 145.6, 142.9, 142.7, 142.6, 142.3, 140.9, 140.3, 139.0 (2), 138.9, 138.8, 138.2, 132.3, 129.4, 129.3, 129.2, 129.1 (2), 129.0, 128.0, 127.9, 127.8, 127.6, 127.2, 127.0, 126.6, 126.4, 125.5, 125.3, 123.4, 121.8, 119.8. 117.4, 115.8, 115.7, 115.6, 115.4, 65.6, 65.0, 18.0, 12.8 ppm; IR: $\tilde{\nu}$max = 3512, 3061, 1501, 1226, 828, 773, 572 cm^{-1}; HRMS (ESI-TOF): *m/z* calculated for $C_{48}H_{34}F_2O$ $[M + Na]^+$ 665.2656, found 665.2653.

1,4-Dimethyl-9,9-diphenyl-2-(spiro[fluorene-9,1′-inden]-3′-yl)-9*H*-fluoren-3-ol (2h): Following general experimental procedure; white solid, mp: 253–254 °C; yield: 73 % (0.073 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 7.5 Hz, 1H), 7.83–7.79 (m, 2H), 7.43–7.39 (m, 2H), 7.38–7.36 (m, 2H),7.34–7.27 (m, 6H), 7.24–7.15 (m, 7H), 7.10 (t, *J* = 7.5 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 7.5 Hz, 2H), 6.85 (d, *J* = 7.5 Hz, 1H), 6.73–6.71 (m, 1H), 6.28 (s, 1H), 5.51 (s, 1H), 2.75 (s, 3H), 1.90 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.9, 151.0, 148.7, 144.5, 144.2, 142.8, 142.4, 142.3, 142.2, 141.4, 141.2, 141.0, 132.1, 129.3, 129.1, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 127.2, 127.1, 126.6, 126.4, 125.5, 123.7, 123.4, 123.2, 123.1, 121.0, 120.6, 120.4, 120.3, 117.4, 68.1, 65.0, 18.2, 12.9 ppm; HRMS (ESI-TOF): *m/z* calculated for $C_{48}H_{34}O$ $[M - H]^+$ 625.2532, found 625.2525.

1,4-Dimethyl-2-(1-methyl-1-phenyl-1*H*-inden-3-yl)-9,9-diphenyl-9*H*-fluoren-3-ol (2i): Following general experimental pro-

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cedure; yellow solid; mp: 206–208 °C; yield: 75 % (0.075 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.97 (d, J = 7.5 Hz, 1H), 7.39–7.34 (m, 4H), 7.32–7.26 (m, 6H), 7.25–7.23 (m, 3H),7.22–7.17 (m, 8H), 6.90 –6.89 (m, 1H), 6.59 (s, 1H), 5.32 (s, 1H), 2.70 (s, 3H), 1.76 (s, 3H), 1.71 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8, 153.8, 153.5, 151.2, 151.0, 147.8, 147.7, 142.9, 142.8, 142.7 (2), 142.5, 142.4, 142.3, 142.1 (2), 142.0, 141.0, 139.9 (2), 137.0,132.4, 132.2, 129.3 (2), 129.0, 128.9, 128.6, 128.0, 127.9, 127.8, 127.4, 127.2, 127.1, 126.9, 126.8, 126.7, 126.6, 126.5, 126.3, 126.2, 126.0, 125.4, 123.3, 123.2, 121.2 (2), 120.2 (2), 117.1, 64.9, 57.0, 56.9, 23.5, 23.2, 18.1, 17.8, 12.8(2) ppm; HRMS (ESI-TOF): m/z calculated for $C_{43}H_{34}O$ $[M + H]^+$ 567.2688, found 567.2689.

9-(4-Chlorophenyl)-2-[1-(4-chlorophenyl)-1-phenyl-1*H*-inden-3-yl]-1,4-dimethyl-9-phenyl-9*H*-fluoren-3-ol (2j): Following general experimental procedure; white solid; mp: 220–222 °C yield: 85 % (0.085 g); isolated as 1:1.01 and 1:0.94 of diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, J = 8 Hz, 4H), 7.39–7.37 (m, 4H), 7.36–7.35 (m, 2H), 7.34–7.33 (m, 4H), 7.32–7.30 (m, 11H), 7.29–7.28 (m, 10H), 7.27–7.25 (m, 18H), 7.24–7.23 (m, 12H), 7.22–7.20 (m, 18H), 7.18–7.15 (m, 12H), 7.14–7.11 (m, 5H), 6.93–6.88 (m, 4H), 6.78 (s, 4H), 5.10 (s, 1H), 5.09 (s, 1H), 5.07, (s, 1H), 5.06 (s, 1H), 2.68 (s, 12H), 1.71 (s, 6H), 1.70 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.4, 151.3, 150.3, 145.6, 142.9, 142.8, 142.6, 142.4, 142.1, 142.0, 141.7, 141.6, 141.4, 140.8, 140.1, 138.1, 133.1, 132.9, 132.4, 132.2, 130.8, 130.4, 129.1 (2), 129.0 (2), 128.8, 128.7, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5 (2), 127.4, 127.3, 127.0, 126.8, 126.6, 125.4, 125.3, 123.5, 121.7, 121.6, 119.9, 117.5, 66.4, 64.5, 18.0 (2), 12.8 ppm; HRMS (ESI-TOF): m/z calculated for $C_{48}H_{34}Cl_2O$ $[M + H]^+$ 697.2065, found 697.2021.

2-(1,1-Dimethyl-1*H*-inden-3-yl)-1,4-dimethyl-9,9-diphenyl-9*H*-fluoren-3-ol (2k): Following general experimental procedure; yellowish solid; mp: 217–219 °C yield: 74 % (0.074 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.00 (d, J = 8.0 Hz, 1H), 7.40–7.39 (m, 3H), 7.37–7.35 (m, 1H), 7.34–7.31 (m, 3H), 7.27–7.24 (m, 3H), 7.23–7.17 (m, 6H), 6.87 (d, J = 7.5 Hz, 1H), 6.44 (s, 1H), 5.36 (s, 1H), 2.74 (s, 3H), 1.69 (s, 3H), 1.48 (s, 3H), 1.38 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9, 153.8, 151.1, 148.2, 143.0, 142.7, 142.0, 141.9, 141.1, 139.8, 136.4, 132.0, 129.4, 129.2, 129.0, 128.0, 127.8, 127.4, 127.1, 126.9, 126.5, 126.3, 126.2, 125.4, 123.3, 121.5, 121.0, 120.5, 117.0, 65.0, 49.6, 24.9, 24.8, 17.8, 12.9 ppm; HRMS (ESI-TOF): m/z calculated for $C_{38}H_{32}O$ $[M + Na]^+$ 433.1568, found 433.1563.

2-[1-(3,4-Dichlorophenyl)-1-phenyl-1*H*-inden-3-yl]-1,4-dimethyl-9,9-diphenyl-9*H*-fluoren-3-ol (2l): Following general experimental procedure; white solid, mp: 256–258 °C; yield: 93 % (0.093 g); isolated as 1:0.90 of diastereomer. ^{1}H NMR (400 MHz,$CDCl_3$): δ = 7.97 (d, J = 7.6 Hz, 2H), 7.39–7.36 (m, 9H), 7.34–7.33 (m, 2 H), 7.31–7.28 (m, 10H), 7.27–7.24 (m, 11H), 7.22–7.20 (m, 8H), 7.197–7.190 (m, 3H), 7.17–7.15 (m, 3H), 7.10–7.08 (m, 1H), 7.03–7.00 (m, 1H), 6.94–6.92 (m, 2H), 6.756 (s, 1H), 6.751 (s, 1H), 5.04 (s, 1H), 5.01 (s, 1H), 2.69 (s, 3H), 2.68 (s, 3H), 1.73 (s, 3H), 1.72 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9, 151.1 (2), 149.8, 149.7, 144.8, 144.7, 144.0, 143.8, 142.8 (2), 142.7, 142.6, 142.4, 142.3, 142.1, 140.8, 138.9 (2), 132.6, 132.3, 132.2, 130.7, 130.5, 129.7, 129.5, 129.3, 129.1, 129.0, 128.8, 128.0, 127.9, 127.7, 127.6, 127.5, 127.2, 127.1, 126.6, 126.4 (2), 125.5, 125.3, 123.4, 121.9, 119.7 (2), 117.4, 66.1, 65.0, 18.0, 12.8 ppm; IR (KBr): $\tilde{\nu}$ 3528, 2958, 1585, 1157, 761cm^{-1}; HRMS (ESI-TOF): m/z calculated for $C_{48}H_{34}Cl_2O$ $[M + Na]^+$ 697.2065, found 697.2014.

2-[1-(4-Chlorophenyl)-1-phenyl-1*H*-inden-3-yl]-1,4-dimethyl-9,9-diphenyl-9*H*-fluoren-3-ol (2m): Following general experimental procedure; yellow solid, mp: 246–248 °C; yield: 79 % (0.079 g); isolated as 1:0.92 of diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, J = 7.6 Hz, 2H), 7.38–7.35 (m, 7H), 7.33–7.26 (m,12H), 7.24–7.23 (m, 12H), 7.21–7.17 (m, 15H), 7.15–7.11 (m, 4H), 6.90–6.91 (m, 2H), 6.78 (s, 2H), 5.09 (s, 1H), 5.06 (s, 1H), 2.68 (s, 6H), 1.73 (s, 3H), 1.70 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9, 151.2, 150.4, 145.5, 143.0, 142.9, 142.7, 142.6, 142.2, 142.1, 141.9, 140.9, 140.2, 138.4, 138.3, 133.1, 132.9, 132.3, 132.2, 129.3, 129.1, 129.0, 128.7, 128.0, 127.9, 127.8, 127.6, 127.5 (2), 127.3, 127.2, 126.9, 126.6, 126.4, 125.5, 125.4, 123.4, 121.7, 119.8, 117.3, 66.4, 65.0, 18.0, 12.8 ppm; IR: $\tilde{\nu}$max = 3503, 3056, 1445, 748, 696 cm^{-1}; HRMS (ESI-TOF): m/z calculated for $C_{48}H_{35}ClO$ $[M + Na]^+$ 663.2454, found 663.2411.

2-[1-(4-Fluorophenyl)-1-phenyl-1*H*-inden-3-yl]-1,4-dimethyl-9,9-diphenyl-9*H*-fluoren-3-ol (2n): Following general experimental procedure; white solid, mp: 238–240 °C; yield: 84 % (0.084 g); isolated as 1:0.91 of diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.97 (d, J = 8 Hz, 2H), 7.38–7.32 (m, 10H), 7.31–7.27 (m, 10H), 7.25–7.21 (m, 14H), 7.20–7.19 (m, 8H), 7.17–7.14 (m, 4H), 6.97 (t, J = 8.5 Hz, 2H), 6.92–6.88 (m, 4H), 6.79 (s, 2H), 5.10 (s, 1H), 5.08 (s, 1H), 2.68 (s, 6H), 1.73 (s, 3H), 1.72 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.9, 151.2, 151.1, 150.6, 145.8, 143.3, 143.1, 142.9, 142.7, 142.6, 142.3, 142.2, 140.9, 140.2, 139.2, 139.0, 138.1, 138.0, 132.3, 132.2, 129.4, 129.3, 129.2 (2), 129.0, 128.9, 128.7, 128.0, 127.9, 127.7, 127.6, 127.5, 127.4, 127.2, 126.9, 126.5, 126.4, 125.5, 125.4, 123.4, 121.7, 119.9, 117.3, 115.7, 115.5 (2), 115.3, 66.3, 65.0, 18.0, 12.8 ppm; HRMS (ESI-TOF): m/z calculated for $C_{48}H_{35}FO$ $[M - H]^+$ 645.2594, found 645.2592.

2-[1-(4-Bromophenyl)-1-phenyl-1*H*-inden-3-yl]-1,4-dimethyl-9,9-diphenyl-9*H*-fluoren-3-ol (2o): Following general experimental procedure; white solid, mp: 274–276 °C; yield: 83 % (0.083 g); isolated as 1:0.94 of diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.97 (d, J = 7 Hz, 2H), 7.41–7.35 (m, 8H), 7.36–7.28 (m, 14H), 7.25–7.23 (m, 10H), 7.21–7.16 (m, 14H), 7.14–7.13 (m, 2H), 7.07–7.06 (m, 2H), 6.93–6.91 (m, 2H), 6.77 (s, 2H), 5.09 (s, 1H), 5.05 (s, 1H), 2.68 (d, J = 1.5, 6H), 1.73 (s, 3H), 1.71 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.9, 151.1, 150.2, 145.4, 142.9, 142.7, 142.6, 142.5, 140.9, 140.2, 138.3, 131.9, 131.7, 129.5, 129.4, 129.3, 129.0, 128.7, 128.0, 127.9, 127.8, 127.6, 127.5 (2), 127.3, 127.2, 127.0, 126.6, 126.4, 125.5, 125.4, 123.4, 121.7, 121.0, 119.8, 117.3, 66.4, 64.9, 18.0, 12.8 ppm; IR: $\tilde{\nu}$max = 3514, 2919, 2360, 1487, 748, 699, 577 cm^{-1}; HRMS (ESI-TOF): m/z calculated for $C_{48}H_{35}BrO$ $[M + Na]^+$ 707.1949, found 707.1917.

2-[1-(4-Methoxyphenyl)-1-phenyl-1*H*-inden-3-yl]-1,4-dimethyl-9,9-diphenyl-9*H*-fluoren-3-ol (2p): Following general experimental procedure; white solid; mp: 254–256 °C yield: 81 % (0.081 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.90 (d, J = 8 Hz, 2H), 7.33–7.28 (m, 8H), 7.24–7.19 (m, 12H), 7.17–7.13 (m, 12H), 7.12–7.09 (m, 13H),7.03 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 6.5 Hz, 2H), 6.75–6.73 (m, 3H), 6.66 (s, 1H), 6.65 (s, 1H), 5.08 (s, 2H), 3.70 (s, 3H), 3.65 (s, 3H), 2.61 (s, 6H), 1.67 (s, 3H), 1.65 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8, 158.6, 155.9, 151.2, 1561.1, 146.2, 143.7, 143.5, 142.9, 142.7, 142.1, 141.0, 140.1, 137.5, 135.3, 135.0, 132.3, 129.3, 129.0, 128.8, 128.7, 123.3, 121.5, 120.1, 117.2, 114.2, 113.9, 66.2, 65.0, 55.4, 55.3, 29.8, 18.0, 12.8 ppm; IR: $\tilde{\nu}$max = 3501, 2953, 1597, 1446, 1294, 775, 699 cm^{-1}; HRMS (ESI-TOF): m/z calculated for $C_{49}H_{38}O_2$ $[M + H]^+$ 659.2950, found 659.2864.

1,4-Dimethyl-9,9-diphenyl-2-(1,1,6-triphenyl-1*H*-inden-3-yl)-9*H*-fluoren-3-ol (2q): Following general experimental procedure; yellow solid, mp: 284–286 °C; yield: 88 % (0.088 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, J = 8 Hz, 1H), 7.62 (d, J = 0.8 Hz, 1H), 7.52 (d, J = 7.2 Hz, 2H), 7.45 (dd, J_1 = 1.2 Hz, J_2 = 6.4 Hz, 1H), 7.40–7.36 (m, 5H), 7.34–7.29 (m, 8H), 7.28–7.22 (m, 7H), 7.22–7.17 (m, 6H), 6.97 (d, J = 7.6 Hz, 1H), 6.85 (s, 1H), 5.16 (s, 1H), 2.70 (s, 3H), 1.77 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9, 151.4, 151.2, 146.2, 143.4, 143.3, 142.9, 142.7, 142.3, 142.1, 140.2, 140.0, 137.7, 132.4,

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129.3, 129.0, 128.9, 128.8, 128.6, 128.0, 127.9, 127.8, 127.7, 127.5, 127.4, 127.3, 127.2, 127.1, 126.8, 126.6, 126.4, 125.5, 124.4, 123.4, 121.8, 120.1, 117.3, 67.1, 65.0, 18.1, 12.8 ppm; HRMS (ESI-TOF): *m/z* calculated for $C_{54}H_{40}O$ [M + K]$^+$ 743.2716, found 743.2712.

1,4-Dimethyl-2-(6-methyl-1,1-diphenyl-1*H*-inden-3-yl)-9,9-diphenyl-9*H*-fluoren-3-ol (2r): Following general experimental procedure; yellow solid; mp: 280–281 °C; yield: 86 % (0.086 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.96 (d, *J* = 8 Hz, 1H), 7.38–7.33 (m, 3H), 7.31–7.28 (m, 4H), 7.27–7.24 (m, 6H), 7.22–7.16 (m, 11H), 7.02 (d, *J* = 7 Hz, 1H), 6.78 (d, *J* = 7.5 Hz, 1H), 6.74 (s, 1H), 5.17 (s, 1H), 2.68 (s, 3H), 2.33 (s, 3H), 1.73 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.9, 151.23, 151.0, 145.0, 143.7, 143.5, 142.9, 142.7, 142.1, 141.0, 140.1, 140.0, 137.7, 136.7, 132.3, 129.3, 129.0, 128.8, 128.5, 128.3, 128.0, 127.9, 127.8, 127.7, 127.4, 127.1, 126.9, 126.5, 126.3, 125.4, 123.3, 121.3, 120.2, 117.2, 66.7, 64.9, 21.8, 18.0, 12.8 ppm; IR: $\tilde{\nu}$max = 3497, 3052, 1489, 759, 744, 694, 479 cm^{-1}; HRMS (ESI-TOF): *m/z* calculated for $C_{49}H_{38}O$ [M + H]$^+$ 643.3001, found 643.001.

4-Benzyl-2-(1,1-diphenyl-3a,7a-dihydro-1*H*-inden-3-yl)-1-methyl-9,9-diphenyl-9*H*-fluoren-3-ol (2s): Following general experimental procedure; yellow viscous liquid; yield: 93 % (0.093 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 5.6, 1H), 7.42–7.36 (m, 4H), 7.34–7.32 (m, 4H), 7.27–7.26 (m, 8H), 7.24–7.15 (m, 12H), 7.13–7.11 (m, 3H), 6.90–6.88 (m, 1H), 6.86 (s, 1H), 5.16 (s, 1H), 4.60 (s, 2H), 1.79 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.0, 151.9, 150.7, 146.0, 143.5, 143.1, 142.9, 142.8, 142.6, 142.5, 140.7, 140.0, 139.7, 137.7, 133.6, 129.9, 129.4, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 127.3, 127.2, 127.0, 126.8, 126.6, 126.4, 126.1, 125.6, 125.4, 123.3, 121.5, 120.3, 119.0, 67.0, 65.0, 32.1, 18.3 ppm; HRMS (ESI-TOF): *m/z* calculated for $C_{54}H_{40}O$ [M + H]$^+$ 705.3157, found 705.3122.

General Experimental Procedure for the Synthesis of Compounds 4a–f: 3-Iodo-5,11-dimethyl-2,2,4,6,6-pentaphenyl-2,6-dihydroindeno[2,1-*g*]chromene **3a** (100 mg, 0.13 mmol) was treated with *p*TsOH (20 mol-%) at 110 °C in solvent free condition for 2 h. After completion of the reaction (monitor by TLC) the crude product was purified by silica gel column chromatography (0–5 % EtOAc in pet-ether) to obtain the desired product **4**a in 62 % yield.

2-(2-Iodo-1,1-diphenyl-1*H*-inden-3-yl)-1,4-dimethyl-9,9-diphenyl-9*H*-fluoren-3-ol (4a): Following general experimental procedure; white solid, mp: 130–131 °C; yield: 62 % (0.062 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8 Hz, 1H), 7.42–7.40 (m, 2H), 7.37 (d, *J* = 7.0 1H), 7.33–7.29 (m, 8H), 7.26–7.25 (m, 4H), 7.23–7.19 (m, 9H), 7.16–7.13 (m, 2H), 6.88–6.87 (m, 1H), 4.76 (s, 1H), 2.72 (s, 3H), 1.68 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.0, 152.4, 150.7, 146.4, 143.2, 142.6, 142.3, 142.2, 142.1, 141.7, 140.9, 132.4, 130.7, 129.4, 129.1, 128.8, 128.7, 128.5, 128.4, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.2, 126.9, 126.5, 126.4, 125.5, 125.4, 123.4, 122.0, 121.4, 120.8, 117.7, 80.1, 71.0, 64.9, 17.4, 12.8 ppm; IR: $\tilde{\nu}$max = 3534, 3058, 2959, 1597, 1446, 744, 698, 579 cm^{-1}; HRMS (ESI-TOF): *m/z* calculated for $C_{48}H_{35}IO$ [M + H]$^+$ 755.1811, found 755.1807.

9-(4-Fluorophenyl)-2-(2-iodo-1,1-diphenyl-1*H*-inden-3-yl)-1,4-dimethyl-9-phenyl-9*H*-fluoren-3-ol (4b): Following general experimental procedure; white solid, mp: 141–142 °C; yield: 65 % (0.065 g); isolated as 1:0.93 of diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.4 Hz, 2H), 7.41–7.37 (m, 3H), 7.36–7.34 (m, 5H), 7.33–7.29 (m, 14H), 7.28–7.27 (m, 5H), 7.247–7.241 (m, 4H), 7.23–7.22 (m, 3H), 7.20–7.18 (m, 8H), 7.12–7.13 (m, 4H), 6.92–6.87 (m, 6H), 4.77 (s, 1H), 4.76 (s, 1H), 2.72 (s, 6H), 1.67 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7, 151.3, 150.7, 146.1, 143.4, 143.3, 142.7, 142.1, 140.8, 140.0, 137.8, 132.2, 131.7, 130.9 (2), 130.7, 130.6, 129.1, 128.8, 128.6, 128.4, 128.2, 128.1, 128.0, 127.7 (2), 127.6, 127.3, 127.1, 127.0, 126.8, 126.7, 126.5, 125.5, 125.3, 123.4, 123.3, 122.0, 121.5, 120.2, 117.4, 114.8 (2), 114.6 (2), 90.7, 88.5, 66.9, 64.4, 23.6, 18.0, 12.8 ppm; HRMS (ESI-TOF): *m/z* calculated for $C_{48}H_{34}FIO$ [M + H]$^+$ 755.1811, found 755.1806.

9-(4-Bromophenyl)-2-(2-iodo-1,1-diphenyl-1*H*-inden-3-yl)-1,4-dimethyl-9-phenyl-9*H*-fluoren-3-ol (4c): Following general experimental procedure; yellow viscous liquid; yield: 90 % (0.090 g); isolated as 1:1.08 of diastereomer. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.4 Hz, 2H), 7.40–7.37 (m, 2H), 7.35–7.31 (m, 14H), 7.27–7.25 (m, 4H), 7.24–7.22 (m, 12H), 7.21–7.19 (m, 8H), 7.18–7.16 (m, 6H), 7.15–7.13 (m, 4H), 6.89–6.86 (m, 2H), 4.78 (s, 1H), 4.77 (s, 1H), 2.72 (s, 6H), 1.68 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.5, 152.4 (2), 150.9, 146.2, 142.7, 142.1 (2),142.0 (3), 141.7 (2), 141.6, 141.0, 140.8, 140.6, 132.4, 132.3, 132.2, 130.8, 130.5, 129.2, 128.9, 128.7 (2), 128.5, 128.4 (2), 128.2 (2), 128.1, 127.7 (2), 127.5 (2), 127.4, 127.1, 127.0, 126.8, 126.6, 125.4, 125.3, 123.5, 122.2, 122.1, 121.5, 120.7 (2), 117.8, 71.0, 64.4, 17.4, 12.8 ppm; HRMS (ESI-TOF): *m/z* calculated for $C_{48}H_{34}ClIO$ [M + H]$^+$ 343.2061, found 343.2061.

9-(4-Chlorophenyl)-2-(2-iodo-1,1-diphenyl-1*H*-inden-3-yl)-1,4-dimethyl-9-phenyl-9*H*-fluoren-3-ol (4d): Following general experimental procedure; yellow viscous liquid; yield: 89 % (0.089 g); isolated as 1:0.7 of diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.5 Hz, 2H), 7.39–7.37 (m, 2H), 7.34–7.30 (m, 19H), 7.29–7.27 (m, 3H), 7.26–7.25 (m, 2H), 7.25–7.23 (m, 6H), 7.22–7.21 (m, 3H), 7.21–7.20 (m, 6H), 7.19–7.17 (m, 4H), 7.16–7.13 (m, 5H), 6.89–6.86 (m, 2H), 4.78 (s, 1H), 4.77 (s, 1H), 2.72 (s, 6H), 1.67 (s, 6H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.4, 152.4, 150.9, 146.2, 142.6 (2), 142.1, 142.0 (2), 141.7, 141.6, 140.8, 140.6, 132.3, 131.2, 131.1, 130.9 (2), 129.2, 128.9, 128.8, 128.7, 128.5, 128.4 (2), 128.2, 128.0, 127.8, 127.7, 127.5, 127.4, 127.1, 127.0, 126.8, 126.6, 125.5, 125.3, 123.5, 122.2, 122.1, 121.5, 120.7, 120.3, 117.8, 71.0, 64.5, 17.4, 12.8 ppm; HRMS (ESI-TOF): *m/z* calculated for $C_{48}H_{34}BrIO$ [M + H]$^+$ 363.1748, found 363.1748.

2-(2-Iodo-6-methyl-1,1-diphenyl-1*H*-inden-3-yl)-1,4-dimethyl-9,9-diphenyl-9*H*-fluoren-3-ol (4e): Following general experimental procedure; colorless viscous liquid; mp: 284–285 °C; yield: 79 % (0.079 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 6.6 Hz, 1H), 7.42–7.36 (m, 5H), 7.32–7.29 (m, 7H), 7.26–7.23 (m, 5H), 7.22–7.17 (m, 6H), 7.10 (s, 1H), 6.95 (d, *J* = 6.6 Hz, 1H), 6.79–6.76 (m, 1H), 4.77 (s, 1H), 2.72 (s, 3H), 2.25 (s, 3H), 1.68 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.0, 152.6, 150.7, 146.2, 143.2, 142.5, 142.4, 142.3, 141.9, 140.9, 140.6, 139.6, 137.1, 132.4, 129.4, 129.1, 128.8, 128.7, 128.6, 128.4, 128.0, 127.8, 127.6, 127.5, 127.4, 127.2, 126.5, 126.4, 126.2, 125.5, 123.4, 121.5, 120.5, 117.6, 76.8, 70.8, 64.9, 21.7, 17.4, 12.8 ppm; IR: $\tilde{\nu}$max = 3534, 3056, 2922, 1595, 1445, 741, 696, 642, cm^{-1}; HRMS (ESI-TOF): *m/z* calculated for $C_{49}H_{37}IO$ [M + H]$^+$ 331.1697, found 331.1697.

2-[1-(4-Chlorophenyl)-2-iodo-1-phenyl-1*H*-inden-3-yl]-1,4-dimethyl-9,9-diphenyl-9*H*-fluoren-3-ol (4f): Following general experimental procedure; yellow viscous liquid; yield: 53 % (0.053 g); isolated as 1:1.06 of diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8 Hz, 2H), 7.42–7.37 (m, 6H), 7.33–7.31 (m, 5H), 7.30–7.28 (m, 8H), 7.25–7.24 (m, 11H), 7.23–7.20 (m, 10H), 7.19–7.18 (m, 4H), 7.16–7.14 (m, 4H), 7.11 (d, *J* = 8.5 Hz, 2H), 6.90–6.88 (m, 2H), 4.74 (s, 1H), 4.69 (s, 1H), 2.72 (s, 6H), 1.68 (s, 3H), 1.65 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.0, 151.9, 150.6, 143.1, 142.6, 140.8, 130.1, 130.0, 129.4, 129.0, 128.9, 128.6, 128.4, 128.1, 127.8, 127.6, 127.2, 127.1, 126.6, 126.4, 125.4, 125.3, 123.4, 121.2, 120.9, 117.6, 70.4, 64.9, 17.4, 12.8 ppm; HRMS (ESI-TOF): *m/z* calculated for $C_{48}H_{34}ClIO$ [M + Na]$^+$ 433.1568, found 433.1563.

Experimental Procedure for the Synthesis of 7-(4-Chlorophenyl)-5,12-dimethyl-7,13,13-triphenyl-7,13-dihydrofluo-

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reno[3,2-*b*]indeno[1,2-*d*]furan (5): To a stirring solution of 2-[1-(4-chlorophenyl)-2-iodo-1-phenyl-1*H*-inden-3-yl]-1,4-dimethyl-9,9-diphenyl-9*H*-fluoren-3-ol **4f** (100 mg, 0.12 mmol) in DMSO (3.0 mL), Cu_2O (18.0 mg, 0.12 mmol) and quinoline (1 mL) were added. The resulting reaction mixture was heated at 170 °C for 16 h. After completion purified by silica gel column chromatography to afford the polycyclic compound **5** as white solid in 86 % yield.

7-(4-Chlorophenyl)-5,12-dimethyl-7,13,13-triphenyl-7,13-dihydrofluoreno[3,2-*b*]indeno[1,2-*d*]furan (5): White solid, mp: > 300 °C; yield: 86 % (0.085 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, J = 8 Hz, 1H), 7.68 (d, J = 7.2 Hz, 1H), 7.37–7.36 (m, 2H), 7.35–7.34 (m, 3 H), 7.30–7.24 (m, 7H), 7.23 (d, J = 1.2 Hz, 5H), 7.21 (s, 2H), 7.21–7.18 (m, 4H), 7.16–7.12 (m, 2H), 2.88 (s, 3H), 2.49 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 159.9, 155.3, 149.9, 145.6, 142.9 (2), 141.8, 141.0, 140.9, 135.9 (2), 133.2, 129.7, 129.1, 128.7 (2), 128.2, 128.0, 127.8, 127.5, 127.3, 127.2, 126.5 (2), 125.5, 125.4, 124.9, 124.3, 122.7, 121.5, 115.8, 64.8, 59.9, 19.6, 13.1 ppm; HRMS (ESI-TOF): *m/z* calculated for $C_{48}H_{33}ClO$ $[M + H]^+$ 661.2298, found 661.2323.

Experimental Procedure for the Synthesis of 2-(2-Iodo-1,1-diphenyl-1*H*-inden-3-yl)-3-methoxy-1,4-dimethyl-9,9-diphenyl-9*H*-fluorene (6): To a stirring solution of 2-(2-iodo-1,1-diphenyl-1*H*-inden-3-yl)-1,4-dimethyl-9,9-diphenyl-9*H*-fluoren-3-ol **4a** (100 mg, 0.13 mmol) in anhydrous acetone (5.0 mL), K_2CO_3 (45.75 mg, 0.33 mmol) and Me_2SO_4 (0.26 mmol) were added. The resulting reaction mixture was heated at 80 °C for 3 h. After completion of the reaction, it was filtered through a short plug of celite, and the filtrate was concentrated in a rotary evaporator and purified by silica gel column chromatography to afford the methyl protected compound **6** as a white solid in 87 % yield.

2-(2-Iodo-1,1-diphenyl-1*H*-inden-3-yl)-3-methoxy-1,4-dimethyl-9,9-diphenyl-9*H*-fluorene (6): White solid, mp: 268–270 °C; yield: 96 % (0.088 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.95 (d, J = 7.5 Hz, 1H), 7.42–7.40 (m, 2H), 7.39–7.37 (m, 3H), 7.33–7.29 (m, 6H), 7.27–7.24 (m, 2H), 7.22–7.21 (m, 6H), 7.21–7.16 (m, 5H), 7.12–7.08 (m, 2H), 6.87–6.85 (m, 1H), 2.89 (s, 3H), 2.75 (s, 3H), 1.72 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.6, 155.9, 152.0, 148.1, 146.2, 143.7, 142.9, 142.5, 142.3, 141.9, 140.9, 140.8, 133.4, 129.5, 129.4, 129.1, 129.0 (2), 128.5, 128.4, 128.3, 128.2, 128.1, 127.9 (2), 127.6, 127.4, 127.3, 127.2 (2), 126.6, 126.5, 126.2, 125.5, 125.1, 124.5, 123.3, 120.5, 118.8, 70.7, 65.2, 61.7, 17.2, 13.5 ppm; IR: $\tilde{\nu}$max = 3396, 3056, 2923, 1594, 1443, 1029, 743, 724, 646 cm^{-1}; HRMS (ESI-TOF): *m/z* calculated for $C_{49}H_{37}IO$ $[M + H]^+$ 769.1967, found 769.1927.

Experimental Procedure for the Synthesis of 2-(1,1-Diphenyl-1*H*-inden-3-yl)-1,4-dimethyl-9,9-diphenyl-3-(prop-2-yn-1-yloxy)-9*H*-fluorene (7): To a stirring solution of 2-(1,1-diphenyl-1*H*-inden-3-yl)-1,4-dimethyl-9,9-diphenyl-9*H*-fluoren-3-ol **2a** (100 mg, 0.16 mmol) in anhydrous acetone (5.0 mL), K_2CO_3 (54.9 mg, 0.39 mmol) and propargyl bromide (0.23 mmol) were added. The resulting reaction mixture was heated at 80 °C for 4 h. After completion of the reaction, it was filtered through a short plug of celite, and the filtrate was concentrated in a rotary evaporator and purified by silica gel column chromatography to afford the propargyl protected compound **7** as a white solid in 98 % yield.

2-(1,1-Diphenyl-1*H*-inden-3-yl)-1,4-dimethyl-9,9-diphenyl-3-(prop-2-*yn*-1-yloxy)-9*H*-fluorene (7): White solid, mp: 273–275 °C; yield: 98 % (0.110 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.96 (d, J = 7.5 Hz, 1H), 7.38–7.34 (m, 6H), 7.31 (d, J = 8 Hz, 1H), 7.29–7.25 (m, 6H), 7.24–7.21 (m, 3H), 7.20–7.17 (m, 10H), 6.85–6.84 (m, 1H), 6.67 (s, 1H), 4.11–4.10 (m, 2H), 2.79, (s, 3H), 2.35–2.34 (m, 1H), 1.72 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.7, 154.8, 150.2, 146.4, 144.4, 144.0, 143.8, 142.4, 142.2, 140.7, 140.1, 138.3, 133.5, 129.3, 129.0, 128.5, 128.4 (2), 128.0, 127.9 (2), 127.6, 127.3, 127.2, 126.8, 126.7, 126.6, 126.5, 125.9, 125.5, 125.3, 125.0, 123.3, 121.2, 79.3, 74.9, 66.8, 65.2, 61.1, 17.8, 14.2 ppm; IR: $\tilde{\nu}$max = 3276, 1489, 1445, 1078, 756, 747, 699, 652 cm^{-1}; HRMS (ESI-TOF): *m/z* calculated for $C_{51}H_{38}O$ $[M + K]^+$ 705.2560, found 705.2586.

Experimental Procedure for the Synthesis of (E)-3-[(2,3-Diiodoallyl)oxy]-2-(1,1-diphenyl-1*H*-inden-3-yl)-1,4-dimethyl-9,9-diphenyl-9*H*-fluorene (9): To the solution of 2-(1,1-diphenyl-1*H*-inden-3-yl)-1,4-dimethyl-9,9-diphenyl-3-(prop-2-yn-1-yloxy)-9*H*-fluorene **7** (100 mg, 0.15 mmol) in ethyl acetate (5.0 mL), I_2 (76.0 mg, 0.30 mmol) was added and refluxed for 12 h. After completion of the reaction, it was quenched with hypo and extracted with ethyl acetate thrice, the organic layer was concentrated in rotary evaporator and purified by silica gel column chromatography to afford the 3-[(2,3-diiodoallyl)oxy]-2-(1,1-diphenyl-1*H*-inden-3-yl)-1,4-dimethyl-9,9-diphenyl-9*H*-fluorene **9** as white solid in 83 % yield.

(*E*)-3-[(2,3-Diiodoallyl)oxy]-2-(1,1-diphenyl-1*H*-inden-3-yl)-1,4-dimethyl-9,9-diphenyl-9*H*-fluorene (9): White solid, mp: 295–296 °C; yield: 83 % (0.114 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.95 (d, J = 7.8 Hz, 1H), 7.39–7.34 (m, 6H), 7.31 (d, J = 7.5 Hz, 1H), 7.28–7.23 (m, 6H), 7.22–7.19 (m, 5H), 7.18–7.15 (m, 8H), 6.93 (d, J = 7 Hz, 1H), 6.86 (s, 1H), 6.70 (s, 1H), 4.19 (d, J = 12.5 Hz, 1H), 4.06 (dd, J_1 = 1 Hz, J_2 = 11 Hz, 1H), 2.80 (s, 3H), 1.72 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.8, 154.8, 150.3, 146.6, 144.6, 144.2, 143.9, 143.8, 142.4, 142.2, 140.7, 140.1, 138.4, 133.8, 129.3, 129.0, 128.7, 128.3, 128.0 (2), 127.9, 127.6, 127.4, 127.2, 126.9, 126.7, 126.5, 125.8, 125.5 (2), 124.5, 123.3, 121.5, 98.0, 81.0, 79.1, 66.7, 65.2, 17.8, 14.5 ppm; HRMS (ESI-TOF): *m/z* calculated for $C_{51}H_{38}I_2O$ $[M + K]^+$ 959.0649, found 959.0690.

CCDC 1951989 (for **2c**), and 1951991 (for **4e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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Keywords: All-carbon-quaternary centre · Bronsted acid · Fluorenol · Indene · Friedel-Crafts annulation

[1] a) S. Yaragorla, R. Dada, D. Bag, *Eur. J. Org. Chem.* **2019**, 6983–6988; b) S. Yaragorla, A. Pareek, R. Dada, *Adv. Synth. Catal.* **2017**, *359*, 3068–3075; c) A. Suarez, S. Suarez-Pantiga, O. Nieto-Faza, R. Sanz, *Org. Lett.* **2017**, *19*, 5074–5077; d) M. Hronec, K. Fulajtarová, T. Liptaj, *Appl. Catal. A* **2012**, *437–438*, 104–111; e) M. Donnard, T. Tschamber, S. Desrat, K. Hinsinger, J. Eustache, *Tetrahedron Lett.* **2008**, *49*, 1192–1195; f) A. R. Hergueta, H. W. Moore, *J. Org. Chem.* **2002**, *67*, 1388–1391; g) L. T. Scott, N. H. Roelofs, *J. Am. Chem. Soc.* **1987**, *109*, 5461–5465.
[2] C. D. Gabbutt, B. M. Heron, C. Kilner, S. B. Kolla, *Chem. Commun.* **2010**, *46*, 8481–8483.
[3] M. Jiang, M. Shi, *Org. Lett.* **2010**, *12*, 2606–2609.
[4] S. Yaragorla, T. Khan, *Org. Biomol. Chem.* **2018**, *16*, 7920–7925.
[5] a) B. M. Trost, Y. Shi, *J. Am. Chem. Soc.* **1992**, *114*, 791–792; b) C.-J. Li, B. M. Trost, *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 13197–13202; c) A. Moores, *Atom Economy – Principles and Some Examples in Homogeneous Catalysis* (Ed.: Robert H. Crabtree, P. Anastas), Pub. Wiley & Sons, **2009**, p. 1–15; d) C. M. Marson, *Chem. Soc. Rev.* **2012**, *41*, 7712–7722.
[6] S. Yaragorla, P. Rajesh, A. Pareek, A. Kumar, *Adv. Synth. Catal.* **2018**, *360*, 4422–4428.

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[7] a) S. Kumar, D. Hernandez, B. Hoa, Y. Lee, J. S. Yang, A. McCurdy, *Org. Lett.* **2008**, *10*, 3761–3764; b) J. N. Moorthy, P. Venkatakrishnan, S. Samanta, D. K. Kumar, *Org. Lett.* **2007**, *9*, 919–922; c) H. Bouas-Laurent, H. Durr, *Pure Appl. Chem.* **2001**, *73*, 639–665; d) R. S. Becker, J. Michl, *J. Am. Chem. Soc.* **1966**, *88*, 5931–5933.
[8] a) G. Kunpeng, C. Yi, *J. Mater. Chem.* **2010**, *20*, 4193–4197; b) W. Sriprom, M. Neel, C. D. Gabbutt, B. M. Heron, S. Perrier, *J. Mater. Chem.* **2007**, *17*, 1885–1893.
[9] See SI for the optimization table.
[10] a) L. Wang, J. Zhong, X. Lin, *Angew. Chem. Int. Ed.* **2019**, *58*, 15824–15828; *Angew. Chem.* **2019**, *131*, 15971–15975; b) G. H. Christie, J. Kenner, *J. Chem. Soc. Trans.* **1922**, *121*, 614–620.
[11] a) D. X. Hu, P. Grice, S. V. Ley, *J. Org. Chem.* **2012**, *77*, 5198–5202; b) J. H. Frank, Y. L. Powder-George, R. S. Ramsewak, W. F. Reynolds, *Molecules* **2012**, *17*, 7914–7926.
[12] See SI for LCMS chromatogram and variable temperature ^{1}H NMR.
[13] K. E. Litians, D. N. Nicolaides, *J. Chem. Soc. Trans.* **1985**, 429–435.
[14] a) S. Singh, R. Samineni, S. Pabbaraja, G. Mehta, *Angew. Chem. Int. Ed.* **2018**, *57*, 16847–16851; *Angew. Chem.* **2018**, *130*, 17089; b) K. Tanaka, H. Aoki, H. Hosomi, S. Ohba, *Org. Lett.* **2000**, *2*, 2133–2134.
[15] a) S. Yaragorla, T. Khan, *Eur. J. Org. Chem.* **2019**, 3989–4012; b) J. M. Timonen, P. A. Turhanen, *ACS Omega* **2019**, *4*, 14663–14668; c) D. S. Rao, T. R. Reddy, S. Kashyap, *Org. Biomol. Chem.* **2018**, *16*, 1508–1518; d) S. Yaragorla, D. Bag, R. Dada, K. V. J. Jose, *ACS Omega* **2018**, *3*, 15024–15034.
[16] a) S. Keskin, M. Balci, *Org. Lett.* **2015**, *17*, 964–967; b) S. Yaragorla, P. Rajesh, *Eur. J. Org. Chem.* **2019**, 5740–5748.
[17] G. Bringmann, T. Gulder, T. A. M. Gulder, M. Breuning, *Chem. Rev.* **2011**, *111*, 563–639.
[18] K. Zhang, Y. Liu, Z. Shang, C. J. Evans, S. Yang, *J. Phys. Org. Chem.* **2019**, *32*, e3926.
[19] M. Ambrogi, A. Ciogli, M. Mancinelli, S. Ranieri, A. Mazzanti, *J. Org. Chem.* **2013**, *78*, 3709–3719.
[20] J. E. Smyth, N. M. Butler, P. A. Keller, *Nat. Prod. Rep.* **2015**, *32*, 1562–1583.
[21] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian 09, Revision E.01*, Gaussian, Inc., Wallingford CT, **2009**.
[22] Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215–241.
[23] R. Ditchfield, W. J. Hehre, J. A. Pople, *J. Chem. Phys.* **1971**, *54*, 724–728.
[24] P. J. Hay, W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 299–310.
[25] A. V. Marenich, C. J. Cramer, D. G. Truhlar, *J. Phys. Chem. B* **2009**, *113*, 6378–6396.

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Stereoselective sulfenylation of oxindole-derived propargyl alcohols to access sulfenylated-3-alkenyloxindoles†

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A Ca-catalyzed, tetrasubstituted alkenyl-sulfenylation was achieved using readily available aryl/alkyl thiols and easily prepared oxindole-derived propargyl alcohols under solvent-free conditions. The reaction proceeded with hydrogen bonding assisted regioselective α-thiolation and subsequent calcium catalyzed stereoselective alkenylation to yield *E*-alkenyl thioethers with high diastereoselectivity.

Introduction

Sulfur-containing molecules, particularly thioethers, are privileged scaffolds often found in organic materials, agrochemicals and pharmaceutically important molecules.[1] Although several synthetic methods have been developed for the thioetherification reaction, alkenyl-sulfenylation is not fully explored;[2] even then, the available methods focussed upon the hydrothiolation of alkynes with various transition metal catalysts,[3] which often suffered from low regioselectivity with unsymmetrical alkynes. On the other hand, oxindole derivatives,[4] particularly methylene oxindole moieties, are an integral part of many natural products and display a broad range of biological activities and have thus become challenging targets in medicinal and synthetic chemistry.[5] For example, sunitinib (SU11248) is an orally active receptor tyrosine kinase (RTK) inhibitor marketed by Pfizer as Sutent® (Fig. 1) which was approved for the treatment of advanced renal cell carcinoma and gastrointestinal stromal tumours by the FDA in 2006.[6] Consequently, the development of new synthetic methodologies to access oxindole derivatives from various starting materials has become an interesting research topic.[7,8]

In recent years, oxindole derived propargyl alcohols have been identified as potential substrates for synthesizing oxindole derivatives due to their easy availability/preparation and their ambiphilic nature.[8] Although a few groups have integrated thiolation with propargyl alcohols, most of the time, the products were obtained from a direct substitution reaction with transition metal catalysts (Scheme 1, eqn (a)).[9–15] In another method, secondary and primary propargyl alcohols reacted with thiophenols and furnished the corresponding α-sulfenyl carbonyl products *via* a 1,2-hydride shift in the presence of AuCl (Scheme 1, eqn (b)).[16] In this connection, we envisaged that if we can have a rigid system at the propargylic carbon without having any hydrogen attached to it, then the 1,2-hydride shift is arrested for forming the carbonyl group. As

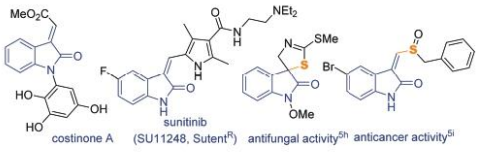
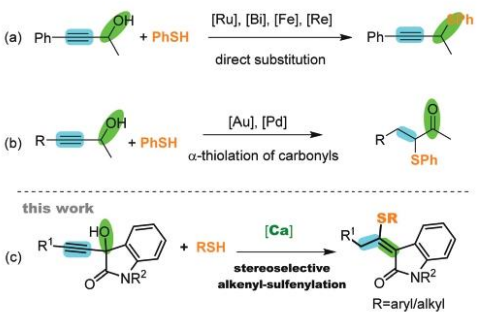


Fig. 1 Representative examples of natural and biologically potent oxindole derivatives.



Scheme 1 Previous (a, b) and current (c) approaches for the thiolation of propargyl alcohols.

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a continuation of our research to develop new reactions from propargylic alcohols using non-toxic, biodegradable, and highly abundant alkaline earth catalysts, we report the sulfenylation of oxindole-derived propargyl alcohols with Ca(II) under solvent-free conditions to construct 3-alkenyl thioethers (Scheme 1, eqn (c)).

Results and discussion

We commenced our study with the reaction of 3-hydroxy-3-(phenylethynyl)indolin-2-one, **1a** (synthesized from isatin and phenylacetylene using a reported method)[17,8b] and thiophenol (**2a**) by refluxing them in 1,2-dichloroethane with 5/10 mol% $Ca(OTf)_2/Bu_4NPF_6$ (entry 1, Table 1). The TLC profile of the reaction looked complex and did not change from 3 h to 12 h. However, we could isolate one of the compounds in a 20% yield; gratifyingly, the spectral data of the isolated compound indicated that it is the 3-alkenyl oxindole derivative **3a**. Furthermore, the structure of **3a** was confirmed using single crystal X-ray diffraction (XRD) analysis (CCDC 2109891†),[18] which also indicated that the addition of thiophenol is *E*-stereoselective. Encouraged by this unprecedented observation, we continued to explore the suitable reaction conditions for this transformation and noticed that the reaction did not proceed when we switched the solvent to DCM; however, to our delight, toluene gave **3a** in a yield of 70% (entry 3), and a moderate yield was observed in acetonitrile and THF (entries 4 and 5). The best yield of **3a** was obtained under solvent-free conditions at 80 °C as a complement. Higher temperatures were found to be unsuitable (entries 7 and 8), and there was no reaction without a catalyst even after heating for 24 h at 80 °C (entry 9). Using other catalysts like *p*-TSA, $FeCl_3$, and $Cu(OTf)_2$ resulted in moderate yields (entries 10–13). To check the diastereoselectivity (ratio of *E*/*Z* isomers) of the reaction, we performed the reaction of **1a** and **2a** under the conditions shown in entry 6, and recorded the ^{1}H NMR spectrum of the crude reaction mass. Surprisingly, the reaction yielded a single diastereomer (**3a**). Note that sulfenylated oxindoles have been previously reported by treating thiols with 2-(alkynyl)aryl isocyanates[19] and 3-(*N*,*N*-dimethylaminomethylene)indolin-2-ones[20] and obtained as a mixture of *E*/*Z* isomers.

Table 1 Optimization of reaction conditions[a]



Entry	Reaction conditions[b]	Yield[c] (%)
1	$Ca(OTf)_2/Bu_4NPF_6$ (5/10), DCE, 90 °C, 12 h	20
2	$Ca(OTf)_2/Bu_4NPF_6$ (5/10), DCM, 60 °C, 12 h	nr
3	$Ca(OTf)_2/Bu_4NPF_6$ (5/10), toluene, 120 °C, 20 h	70
4	$Ca(OTf)_2/Bu_4NPF_6$ (5/10), CH_3CN, 90 °C, 12 h	40
5	$Ca(OTf)_2/Bu_4NPF_6$ (5/10), THF, 70 °C, 12 h	40
6[d]	**$Ca(OTf)_2/Bu_4NPF_6$ (5/10), neat, 80 °C, 30 min**	**84**
7	$Ca(OTf)_2/Bu_4NPF_6$ (5/10), neat, 120 °C, 2 h	35[e]
8	$Ca(OTf)_2/Bu_4NPF_6$ (5/10), neat, 150 °C, 2 h	35[e]
9	Neat, 80 °C, 24 h	nr
10	pTSA (10), neat, 80 °C, 3 h	53[e]
11	pTSA (10), DCE, 90 °C, 12 h	60[e]
12	$FeCl_3$ (10), DCE, 90 °C, 2 h	67
13	$Cu(OTf)_2$ (10), DCE, 90 °C, 2 h	45[e]

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (1.4 mmol), all reactions were monitored up to 24 h. [b] Oil bath temperature mentioned, diphenyl disulfide is the byproduct in all the reactions. [c] Isolated yields. [d] Optimum conditions. [e] Most of these reactions resulted in a complex TLC. nr = no reaction.

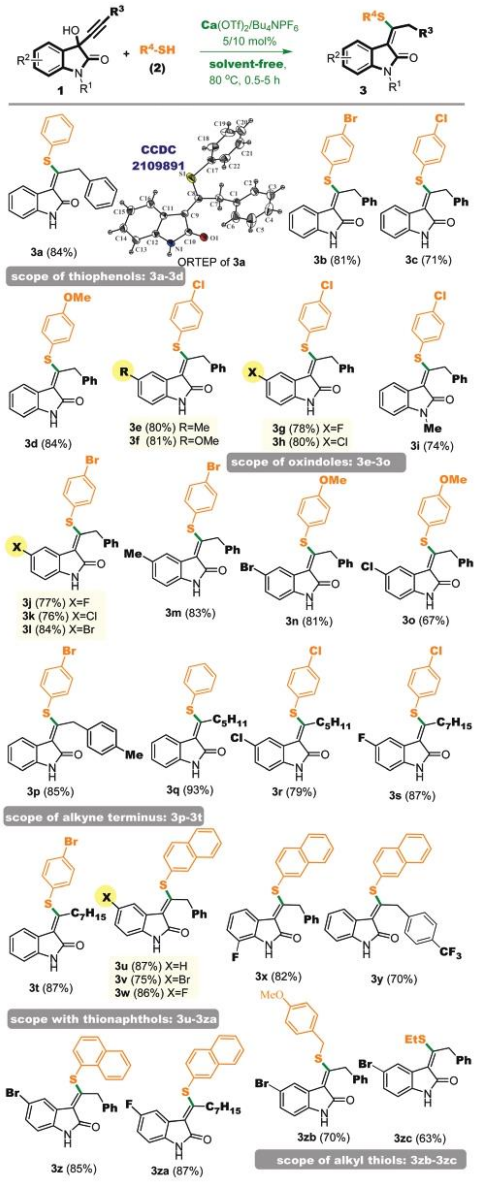
With the best conditions in hand, we explored the substrate scope of this synthetic transformation (Scheme 2). Halo-substituted thiophenols **2b** and **2c** and 4-methoxy thiophenol **2d** were reacted with **1a** under the standard conditions to produce the corresponding vinyl-thioethers **3b–3d** in good yields. Next, we took various substituted oxindoles bearing halide, alkyl and alkoxy groups and subjected them to the reaction conditions with *p*-halo thiophenols to furnish the corresponding thioethers **3e–3o** in excellent yields. It is of note that these substitutions did not show any considerable change in the reaction yield. Next, the substitution on the alkyne terminus of **1** was also studied under the reaction conditions, and it seemed that the reaction yield was not compromised when we switched from aryl to alkyl substitutions (**3p–3t**). Furthermore, we observed that thionaphthols reacted under the conditions with substituted oxindoles having aryl and alkyl groups on the alkyne terminus, which yielded the desired vinyl-thioethers in similar yields (**3u–3za**). Notably, when we tried a hetero arylthiol (benzo[*d*]thiazole-2-thiol), the reaction showed a complex TLC; probably, the hetero atom interaction might be playing a role. After verifying the participation of aryl thiols in this reaction, we next tested with *p*-methoxy benzylthiol; gratifyingly, it gave the corresponding alkenyl thioether (**3zb**) in 70% yield. Similarly, ethane thiol also furnished **3zc** in 63% yield.

We then shifted our focus to gram scale synthesis and synthetic applications (Scheme 3). First, we applied our reaction conditions to show the gram-scale synthesis of **3b** (1.12 g). Then, **3b** was subjected to oxidation using hydrogen peroxide[21] and triflic anhydride and the corresponding sulfinyl compound **4** was obtained in 70% yield. As expected, benzylic hydrogens showed excellent diastereotopicity, as shown in Scheme 3. Next, the copper-catalyzed benzylic oxidation of **3b** furnished the α-sulfenyl-enone **5** in 85% yield.

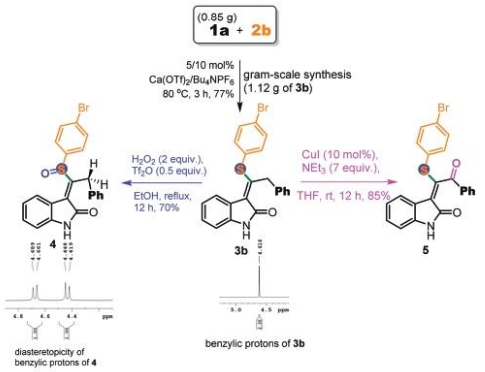
To shed light on the reaction mechanism, we performed a few experiments as mentioned; firstly, the reaction of **1a** with one equivalent of **2a** under the standard conditions resulted in poor conversion; doubling the stoichiometry of **2a** also showed a poor conversion. However, three equivalents of **2a** furnished the best yield of **3a**, and without the catalyst, there was no reaction. Another critical point to note is that in all the cases, diphenyl disulfide was formed as the byproduct. However, there is also a chance that diphenyl disulfide can be formed under aerial oxidation. To check this, we performed the reaction of **1a** (1 equiv.) with **2b** (3 equiv.) under a nitrogen atmo-

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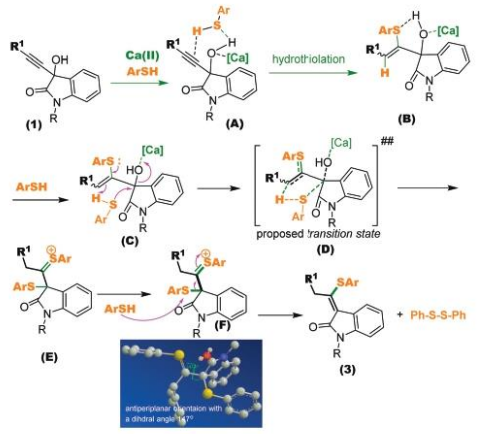


Scheme 2 Substrate scope.



Scheme 3 Gram scale synthesis and functional group transformations.

sphere; surprisingly, product **3b** was obtained in 73% yield. Although the yield is slightly less than that of the non-inert (aerial) reaction, this may be an indirect evidence that the formation of diphenyl disulfide is part of the reaction mechanism. Next, the ^{1}H NMR spectrum of the crude compound **3a** indicated the formation of a single diastereomer. Based on these observations, we described the possible reaction mechanism, as shown in Scheme 4. The reaction initiated by calcium promoted the hydrogen bonding assisted hydrothiolation of alkynol (**1**) with arene thiol (**2**) to furnish alkene thiol **B**. In the next step, the protonation of alkene **B** with a second mole of arene thiol and a subsequent displacement of the 3°-hydroxyl group by the sulfide ion in the presence of an oxophilic calcium catalyst to form intermediate **E** may take place from **C** through the proposed transition state **D**. The third mole of arene thiol will take out the 3°-sulfide, which is antiperiplanar to the other thioether (see intermediate **F**), to yield *E*-alkene exclusively. An approximate dihedral angle of S–C–C–S for the



Scheme 4 Proposed reaction mechanism.

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energy minimized structure of intermediate **F** was noted close to 150° with the help of Chem3D Pro14.0 (Scheme 4). Probably this antiperiplanar elimination could be responsible for the high diastereoselectivity of this protocol; further studies are required to authenticate/verify the proposed mechanism.

Conclusions

In summary, we have described a non-transition metal-mediated, stereoselective alkenyl-thioetherification of oxindole derived propargyl alcohols and arene thiols. The products were obtained with high diastereoselectivity due to the antiperiplanar elimination. Single-crystal X-ray diffraction analysis of **3a** was performed to confirm the stereochemistry of the double bond. Furthermore, we demonstrated the use of alkaline earth catalysts and solvent-free conditions, good substrate scope with high yields, gram scale synthesis and functional group transformations for this protocol.

Experimental section

General remarks

All solvents used were of analytical grade and used as purchased without further purification. Reactions were monitored by thin-layer chromatography (TLC). Visualization of the spots on TLC plates was done under UV light. Commercial silica gel (60–120 and 100–200 mesh size) was used for column chromatography. ^{1}H NMR spectra were recorded in $CDCl_3$, and ^{13}C NMR spectra were recorded in $CDCl_3$ and 1–2 drops of DMSO-d_6; chemical shifts are expressed in parts per million (δ) using tetramethylsilane as an internal standard. The standard abbreviations s, d, dd, t, and m refer to the singlet, doublet, doublet of a doublet, triplet, and multiplet, respectively. Coupling constants (J) have been reported in Hz. Oxindole derived propargyl alcohols were synthesized using a reported procedure. Isatins, alkynes, KO^{t}Bu, thiophenols, 2-naphthalenethiol, 1-naphthalenethiol, $Ca(OTf)_2$, Bu_4NPF_6 and other reagents required were purchased from Sigma-Aldrich, Alfa Aesar, Spectrochem, TCI Chemicals and Avra Synthesis. Solvents and silica gel (60–120, 100–200 mesh) and other common reagents were procured from local suppliers. Thin-layer chromatography (TLC) was carried out on Merck silica gel plates (60 F254). ^{1}H and ^{13}C{1H} NMR spectra were recorded on Bruker Ultrashield 500 and 400 MHz instruments. Melting points were measured with a MEPA LABINDIA melting point apparatus. Single-crystal X-ray diffraction data were collected using Bruker D8-Quest diffractometers.

A. Experimental procedure for the synthesis of 3a. An oven-dried RB was charged with a magnetic stirrer, and oxindole derived propargylic alcohol **1a** (100 mg, 0.4016 mmol), thiophenol **2a** (154.6 mg, 1.4056 mmol), 5 mol% $Ca(OTf)_2$, and 10 mol% Bu_4NPF_6 were added, and the reaction mixture was stirred at 80 °C under solvent-free conditions. The reaction was monitored by TLC (2 : 8 EtOAc/hexanes), and after completion of the reaction, the desired product **3a** was isolated by column chromatography.

B. Experimental procedure for the synthesis of 4. To a solution of Tf_2O (0.1184 mmol) and H_2O_2 (0.5211 mmol) in ethanol, 0.2369 mmol of compound **3b** was added, and the reaction was refluxed for 12 h. The reaction was quenched with water, and the aqueous layer was separated and extracted with ethyl acetate (2 × 30 ml); the combined organic layer was washed (brine) and dried (Na_2SO_4), and the solvent was removed *in vacuo*. The crude residue was purified by column chromatography to obtain compound **4** in 70% yield.

C. Experimental procedure for the synthesis of 5. 0.2369 mmol of compound **3b** was treated with 0.0118 mmol of CuI in THF; then triethylamine (1.6587 mmol) was introduced to the reaction mixture slowly and allowed to stir at room temperature until completion of the reaction, which was monitored by TLC. After completion, the reaction was quenched with water, and the aqueous layer was separated and extracted with ethyl acetate (2 × 25 ml); the combined organic layer was washed (brine) and dried (Na_2SO_4), and the solvent was removed *in vacuo*. The crude residue was purified by column chromatography to isolate compound **5** in 85% yield.

Spectral data

(*E*)-3-(2-Phenyl-1-(phenylthio)ethylidene)indolin-2-one (3a). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 5–10% EtOAc in petroleum ether) and the product was obtained as a yellow solid (115 mg, 84%); mp: 212–213 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.59 (s, 1H), 8.14 (d, J = 7.5 Hz, 1H), 7.41–7.37 (m, 1H), 7.31–7.28 (m, 3H), 7.27–7.24 (m, 1H), 7.21–7.18 (m, 1H), 7.13–7.10 (m, 3H), 7.08–7.05 (m, 1H), 6.88–6.86 (m, 2H), 6.83–6.81 (m, 1H), 4.62 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$ and one drop of DMSO-d_6): δ 167.9, 158.1, 139.8, 138.0, 135.9, 129.6, 129.0, 128.2, 128.1, 128.0, 125.9, 125.5, 123.6, 121.9, 121.4, 109.3, 35.5 ppm; HRMS (ESI-TOF): calcd for $C_{22}H_{18}NOS$ $[M + H]^+$ 344.1109, found 344.1110; IR (film): ν_{max} 3157, 3056, 1670, 1555, 1212, 1100, 686 cm^{-1}.

(*E*)-3-(1-((4-Bromophenyl)thio)-2-phenylethylidene)indolin-2-one (3b). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 5–10% EtOAc in petroleum ether) and the product was obtained as a yellow solid (137 mg, 81%); mp: 195–196 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 8 Hz, 2H), 7.40–7.38 (m, 2H), 7.25–7.21 (m, 1H), 7.15–7.13 (m, 5H), 7.10–7.06 (m, 1H), 6.88–6.85 (m, 3H), 4.61 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$ and one drop of DMSO-d_6): δ 167.5, 155.8, 140.1, 137.7, 137.0, 132.3, 132.0, 128.2, 128.0, 127.9, 127.5, 125.9, 125.3, 124.1, 123.3, 122.8, 121.2, 109.2, 35.4 ppm; HRMS (ESI-TOF): calcd for $C_{22}H_{17}BrNOS$, $[M + H]^+$ 422.0124, found 422.0124; IR (film): ν_{max} 3169, 3053, 1680, 1570, 1465, 1211, 1007, 729, 696 cm^{-1}.

(*E*)-3-(1-((4-Chlorophenyl)thio)-2-phenylethylidene)indolin-2-one (3c). Following general experimental procedure A, the

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crude reaction mixture was purified by column chromatography (100–200 silica gel, 6–8% EtOAc in petroleum ether) and the product was obtained as a yellow solid (107 mg, 71%); mp: 188–189 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, J = 7.5 Hz, 1H), 8.04 (s, 1H), 7.25–7.19 (m, 5H), 7.16–7.13 (m, 3H), 7.08 (t, J = 7.5 Hz, 1H), 6.88–6.84 (m, 3H), 4.61 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ and one drop of DMSO-d_6): δ 167.5, 155.9, 140.0, 137.6, 136.8, 135.8, 128.9, 128.1, 127.9, 127.8, 126.6, 125.8, 125.2, 123.1, 122.6, 121.0, 109.2, 35.2 ppm; HRMS (ESI-TOF): calcd for $C_{22}H_{17}ClNOS$ $[M + H]^+$ 378.0719, found 378.0719.

(*E*)-3-(1-((4-Methoxyphenyl)thio)-2-phenylethylidene)indolin-2-one (3d). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 5–10% EtOAc in petroleum ether) and the product was obtained as a yellow solid (125 mg, 84%); mp: 212–213 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.15 (s, 1H), 7.24–7.18 (m, 3H), 7.15–7.08 (m, 4H), 6.88–6.85 (m, 3H), 6.78 (d, J = 9 Hz, 2H), 4.58 (s, 2H), 3.82 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.6, 161.3, 160.7, 139.0, 138.2, 138.0, 128.3, 128.2, 128.0, 126.1, 120.6, 118.5, 114.8, 109.1, 55.6, 35.7 ppm; HRMS (ESI-TOF): calcd for $C_{23}H_{20}NO_2S$, $[M + H]^+$ 374.1215, found 374.1213; IR (film): ν_{max} 3198, 1680, 1492, 1249 cm^{-1}.

(*E*)-3-(1-((4-Chlorophenyl)thio)-2-phenylethylidene)-5-methylindolin-2-one (3e). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 6–8% EtOAc in petroleum ether) and the product was obtained as a yellow solid (118 mg, 80%); mp: 236–237 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.83 (s, 1H), 7.26–7.19 (m, 4H), 7.15–7.13 (m, 3H), 7.03 (d, J = 7.5 Hz, 1H), 6.87–6.86 (m, 2H), 6.73 (d, J = 8 Hz, 1H), 4.60 (s, 2H), 2.38 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ and one drop of DMSO-d_6): δ 167.8, 156.5, 137.9, 137.5, 137.1, 136.1, 130.9, 129.2, 128.7, 128.2, 128.1, 126.9, 126.3, 126.1, 123.6, 122.7, 109.0, 35.6, 21.5 ppm; HRMS (ESI-TOF): calcd for $C_{23}H_{19}ClNOS$, $[M + H]^+$ 392.0876, found 392.0878.

3-(1-((4-Chlorophenyl)thio)-2-phenylethylidene)-5-methoxyindolin-2-one (3f). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 10–15% EtOAc in petroleum ether) and the product was obtained as a yellow solid (124 mg, 85%); mp: 219–220 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.77 (d, J = 2 Hz, 1H), 7.25–7.19 (m, 4H), 7.15–7.13 (m, 3H), 6.88–6.86 (m, 2H), 6.80–6.74 (m, 2H), 4.62 (s, 2H), 3.82 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 158.1, 155.3, 137.9, 137.2, 136.5, 133.2, 129.4, 124.3, 126.8, 126.3, 124.5, 122.7, 113.6, 112.8, 109.4, 56.1, 35.9 ppm; HRMS (ESI-TOF): calcd for $C_{23}H_{19}ClNO_2S$, $[M + H]^+$ 408.0825, found 408.0825.

(*E*)-3-(1-((4-Chlorophenyl)thio)-2-phenylethylidene)-5-fluoroindolin-2-one (3g). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 6–8% EtOAc in petroleum ether) and the product was obtained as a yellow solid (114 mg, 78%); mp: 191–192 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.47 (s, 1H), 7.89–7.87 (m, 1H), 7.29–7.23 (m, 2H), 7.21–7.18 (m, 2H), 7.16–7.13 (m, 3H), 6.94–6.90 (m, 1H), 6.87–6.85 (m, 2H), 6.75–6.73 (m, 1H), 4.61 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 160.0, 159.7, 157.3, 137.6, 137.3, 136.7, 135.5, 129.4, 128.4, 128.2, 126.4, 126.1, 124.4, 124.3, 121.9, 114.6, 114.4, 113.3, 113.0, 109.8, 109.7, 36.0 ppm; HRMS (ESI-TOF): calcd for $C_{22}H_{16}ClFNOS$, $[M + H]^+$ 396.0625, found 396.0625.

(*E*)-5-Chloro-3-(1-((4-chlorophenyl)thio)-2-phenylethylidene) indolin-2-one (3h). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 6–8% EtOAc in petroleum ether) and the product was obtained as a yellow solid (116 mg, 80%); mp: 179–180 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.88 (s, 1H), 7.26–7.24 (m, 2H), 7.22–7.19 (m, 3H), 7.15–7.14 (m, 3H), 6.85–6.83 (m, 2H), 6.77 (d, J = 8.5 Hz, 1H), 4.59 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 160.5, 137.5, 136.8, 129.5, 128.4, 128.2, 128.0, 127.2, 126.4, 126.1, 125.7, 125.0, 121.0, 110.0, 36.0 ppm; HRMS (ESI-TOF): calcd for $C_{22}H_{16}Cl_2NOS$ $[M + H]^+$ 412.0330, found 412.0333.

(*E*)-3-(1-((4-Chlorophenyl)thio)-2-phenylethylidene)-1-methylindolin-2-one (3i). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 5–10% EtOAc in petroleum ether) and the product was obtained as a yellow solid (110 mg, 74%); mp: 144–146 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, J = 7.5 Hz, 1H), 7.32–7.29 (m, 1H), 7.24–7.19 (m, 4H), 7.16–7.08 (m, 4H), 6.89–6.85 (m, 3H), 4.63 (s, 2H), 3.27 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$: δ 166.2, 156.8, 142.3, 138.0, 137.1, 136.3, 129.4, 128.5, 128.3 (2), 127.1, 126.2, 125.4, 122.9, 122.3, 121.9, 107.6, 35.9, 26.1 ppm; HRMS (ESI-TOF): calcd for $C_{23}H_{19}ClNOS$, $[M + H]^+$ 392.0876, found 392.0876; IR (film): ν_{max} 1663, 1253, 811, 772, 723 cm^{-1}.

(*E*)-3-(1-((4-Bromophenyl)thio)-2-phenylethylidene)-5-fluoroindolin-2-one (3j). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 25–30% EtOAc in petroleum ether) and the product was obtained as a yellow solid (127 mg, 77%); mp: 204–206 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.90–7.88 (m, 1H), 7.42–7.39 (m, 2H), 7.17–7.12 (m, 5H), 6.96–6.92 (m, 1H), 6.87–6.85 (m, 2H), 6.77–6.75 (m, 1H), 4.61 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$ and one drop of DMSO-d_6): δ 167.4, 158.7, 157.6, 156.8, 137.4, 137.2, 136.9, 136.2, 132.9, 131.9, 128.1, 128.0, 127.9, 126.8, 126.1, 125.9, 124.2, 124.0, 123.9, 122.5, 114.2, 114.0, 112.7, 112.4, 109.4, 109.3, 35.3 ppm; HRMS (ESI-TOF): calcd for $C_{22}H_{16}BrFNOS$ $[M + H]^+$ 440.0120, found 440.0120; IR (film): ν_{max} 1663, 1253, 811, 772, 723 cm^{-1}.

(*E*)-3-(1-((4-Bromophenyl)thio)-2-phenylethylidene)-5-chloroindolin-2-one (3k). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 5–10% EtOAc in petroleum ether) and the product was obtained as a yellow solid (121 mg, 76%); mp: 204–206 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 2 Hz, 1H), 7.93 (s, 1H), 7.42–7.39 (m, 2H), 7.22–7.20 (m, 1H), 7.15–7.12 (m, 5H), 6.86–6.84 (m, 2H), 6.78 (d, J = 8 Hz, 1H), 4.60 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ and a drop of DMSO-$d6$): δ 167.4, 158.8, 138.5, 137.6, 137.4, 132.3, 128.2(2),

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127.9, 126. + 9, 126.6, 126.2, 125.4, 124.6, 124.8, 124.7, 121.8, 110.2, 35.7 ppm; HRMS (ESI-TOF): calcd for $C_{22}H_{15}BrClNOSK$, $[M + K]^+$ 493.9383, found 493.9384.

(*E*)-5-Bromo-3-(1-((4-bromophenyl)thio)-2-phenylethylidene) indolin-2-one (3l). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 6–8% EtOAc in petroleum ether) and the product was obtained as a yellow solid (127 mg, 84%); mp: 164–165 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (s, 1H), 7.81 (s, 1H), 7.41–7.35 (m, 3H), 7.15–7.12 (m, 4H), 6.85–6.84 (m, 3H), 6.75 (d, J = 8.5 Hz, 1H), 4.59 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ and one drop of DMSO-d_6): δ 167.0, 158.1, 139.1, 134.4, 137.1, 132.0, 130.5, 127.9 (2), 127.7, 126.7, 126.0, 124.9, 124.4, 121.7, 113.4, 110.5, 35.4 ppm; HRMS (ESI-TOF): calcd for $C_{22}H_{16}Br_2NOS$ $[M + H]^+$ 499.9319, found 499.9319.

(*E*)-3-(1-((4-Bromophenyl)thio)-2-phenylethylidene)-5-methyl-indolin-2-one (3m). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 6–8% EtOAc in petroleum ether) and the product was obtained as a yellow solid (136 mg, 83%); mp: 219–220 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (s, 1H), 7.90 (s, 1H), 7.40–7.38 (m, 2H), 7.15–7.12 (m, 5H), 7.05–7.03 (m, 1H), 6.88–6.86 (m, 2H), 6.73 (d, J = 7.5 Hz, 1H), 4.61 (s, 2H), 2.38 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$ and one drop of DMSO-d_6): δ 167.7, 156.0, 137.9, 137.5, 137.2, 132.1, 130.8, 128.8, 128.2, 128.1, 128.1, 127.6, 126.2, 126.1, 124.3, 123.6, 122.9, 109.0, 35.6, 21.5 ppm; HRMS (ESI-TOF): calcd for $C_{23}H_{19}BrNOS$, $[M + H]^+$: calculated 436.0371, found 436.0369.

(*E*)-5-Bromo-3-(1-((4-methoxyphenyl)thio)-2-phenylethylidene) indolin-2-one (3n). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 5–10% EtOAc in petroleum ether) and the product was obtained as a yellow solid (122 mg, 81%); mp: 234–235 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 8.27 (d, J = 1.5 Hz, 1H), 7.72 (s, 1H), 7.35–7.33 (m, 1H), 7.26 (s, 3H), 7.20–7.17 (m, 1H), 7.14–7.11 (m, 2H), 6.86–6.84 (m, 2H), 6.80–6.77 (m, 2H), 6.73 (d, J = 8 Hz, 1H), 4.56 (s, 2H), 3.06 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 162.1, 161.2, 138.6, 137.9, 137.8, 130.3, 128.1(2), 126.0, 125.5, 120.0, 117.8, 114.7, 113.8, 110.5, 55.5, 35.5 ppm; HRMS (ESI-TOF): calcd for $C_{23}H_{18}BrNO_2SNa$ $[M + Na]^+$ 474.0139, found 474.0137 IR (film): ν_{max} 3198, 1680, 1492, 1249 cm^{-1}.

(*E*)-5-Chloro-3-(1-((4-methoxyphenyl)thio)-2-phenylethylidene) indolin-2-one (3o). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 6–8% EtOAc in petroleum ether) and the product was obtained as a yellow solid (136 mg, 83%); mp: 138–140 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, J = 1.5 Hz, 1H), 7.94 (s, 1H), 7.20–7.17 (m, 3H), 7.14–7.13 (m, 3H), 6.86–6.85 (m, 2H), 6.80–6.76 (m, 3H), 4.17 (s, 2H), 3.83 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$ and one drop of DMSO-d_6): δ 167.5, 161.7, 161.1, 138.2, 137.8, 137.7, 128.1, 128.0, 127.3, 126.3, 125.9, 125.2, 124.9, 120.2, 117.7, 114.6, 109.9, 55.4, 35.3 ppm; HRMS (ESI-TOF): calcd for $C_{23}H_{19}ClNO_2S$ $[M + H]^+$ 408.0825, found 408.0829.

(*E*)-3-(1-((4-Bromophenyl)thio)-2-(*p*-tolyl)ethylidene)indolin-2-one (3p). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 6–8% EtOAc in petroleum ether) and the product was obtained as a yellow solid (140 mg, 85%); mp: 217–218 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, J = 8 Hz, 1H), 7.91 (s, 1H), 7.41 (d, J = 8 Hz, 2H), 7.26–7.21 (m, 2H), 7.17–7.16 (m, 2H), 7.07 (t, J = 7.8 Hz, 1H), 6.96 (d, J = 7.5 Hz, 1H), 6.85 (d, J = 7.5 Hz, 1H), 6.78 (d, J = 8 Hz, 2H), 4.54 (s, 2H), 2.28 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.7, 158.0, 139.3, 138.1, 137.3, 135.8, 134.8, 132.3, 129.5, 129.0, 128.4, 128.2, 127.7(2), 125.7, 124.6, 123.7, 121.9, 109.2, 35.2, 21.2 ppm; HRMS (ESI-TOF): calcd for $C_{23}H_{19}BrNOS$ $[M + H]^+$ 436.0371, found 436.0372.

(*E*)-3-(1-(Phenylthio)hexylidene)indolin-2-one (3q). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 5–10% EtOAc in petroleum ether) and the product was obtained as a yellow solid (129 mg, 74%); mp: 110–112 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, J = 7.5 Hz, 1H), 7.82 (s, 1H), 7.61–7.59 (m, 2H), 7.49–7.42 (m, 3H), 7.21–7.18 (m, 2H), 6.85–6.83 (m, 1H), 3.03–2.99 (m, 2H), 1.47–1.44 (m, 2H), 1.13–1.09 (m, 4H), 0.77 (t, J = 7 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.8, 167.7, 163.1, 139.3, 139.2, 136.0, 129.9, 129.5, 129.3, 129.0, 127.7, 125.3, 124.1, 121.6, 119.8, 109.1, 109.0, 31.7, 31.1, 29.8, 22.2, 14.0 ppm; HRMS (ESI-TOF): calcd for $C_{20}H_{22}NOS$ $[M + H]^+$ 324.1422, found 324.1422.

(*E*)-5-Chloro-3-(1-((4-chlorophenyl)thio)hexylidene)indolin-2-one (3r). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 5–10% EtOAc in petroleum ether) and the product was obtained as a yellow solid (129 mg, 74%); mp: 179–180 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (s, 1H), 8.08 (d, J = 1.5 Hz, 2H), 7.53 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.5 Hz, 1H), 7.18–7.16 (m, 1H), 6.77 (d, J = 8 Hz, 1H), 3.01–2.98 (m, 2H), 1.46–1.42 (m, 2H), 1.15–1.13 (m, 4H), 0.80 (t, J = 6.5 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.2, 164.4, 137.5, 137.2, 136.9, 129.9, 127.5, 126.9, 125.3, 125.2, 119.3, 109.9, 31.7, 31.2, 29.8, 22.2, 14.0 ppm; HRMS (ESI-TOF): calcd for $C_{20}H_{20}Cl_2NOS$ $[M + H]^+$ 392.0643, found 392.0642.

(*E*)-3-(1-((4-Chlorophenyl)thio)octylidene)-5-fluoroindolin-2-one (3s). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 5–10% EtOAc in petroleum ether) and the product was obtained as a yellow solid (156 mg, 87%); mp: 207–208 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.56 (s, 1H), 7.85–7.83 (m, 1H), 7.54–7.51 (m, 2H), 7.44–7.42 (m, 2H), 6.92–6.88 (m, 1H), 6.77–6.75 (m, 1H), 3.01 (t, J = 7.5 Hz, 2H), 1.76 (s, 1H), 1.46–1.42 (m, 2H), 1.26–1.19 (m, 2H), 1.16–1.082 (m, 5H), 0.88–0.83 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.9, 159.6, 157.3, 137.2, 136.8, 129.9, 127.0, 124.7, 114.1, 113.9, 112.9, 112.7, 109.3, 31.8, 31.2, 30.2, 29.5, 28.8, 22.7, 14.2 ppm; HRMS (ESI-TOF): calcd for $C_{22}H_{24}ClFNOS$ $[M + H]^+$ 404.1251, found 404.1251; IR (film): ν_{max} 2924, 1679, 1551, 1193, 797 cm^{-1}.

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(*E*)-3-(1-((4-Bromophenyl)thio)octylidene)indolin-2-one (3t). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 6–8% EtOAc in petroleum ether) and the product was obtained as a white solid (144 mg, 87%); mp: 137–138 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, J = 8 Hz, 1H), 7.92 (s, 1H), 7.58–7.55 (m, 2H), 7.46–7.43 (m, 2H), 7.21–7.18 (m, 1H), 7.07–7.03 (m, 1H), 6.84 (d, J = 7.5 Hz, 1H), 3.03–3.00 (m, 2H), 1.47–1.42 (m, 2H), 1.25–1.19 (m, 2H), 1.18–1.08 (m, 6H), 0.85 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 161.5, 139.3, 137.2, 132.7, 128.2, 127.9, 125.2, 124.7, 123.8, 121.6, 120.5, 109.2, 31.8, 31.1, 30.1, 29.4, 28.8, 22.7, 14.2 ppm; HRMS (ESI-TOF): calcd for $C_{22}H_{25}BrNOS$ $[M + H]^+$: calculated 430.0840, found 430.0841.

(*E*)-3-(1-(Naphthalen-2-ylthio)-2-phenylethylidene)indolin-2-one (3u). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 5–10% EtOAc in petroleum ether) and the product was obtained as a yellow solid (137 mg, 87%); mp: 152–153 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (d, J = 7.5, 1H), 7.90 (s, 1H), 7.85 (d, J = 8 Hz, 1H), 7.76 (d, J = 9 Hz, 2H), 7.66 (d, J = 7.5 Hz, 1H), 7.56–7.52 (m, 2H), 7.37–7.35 (m, 1H), 7.24 (d, J = 4.5 Hz, 1H), 7.12–7.04 (m, 4H), 6.87 (d, J = 8 Hz, 1H), 6.79 (d, J = 7 Hz, 2H), 4.60 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 159.2, 139.4, 138.2, 136.5, 133.4(2), 131.9, 129.4, 128.8, 128.4, 128.3, 128.2, 127.9, 127.6, 126.9, 126.2, 125.7, 125.5, 124.9, 123.9, 121.9, 109.4, 36.1 ppm; HRMS (ESI-TOF): calcd for $C_{26}H_{20}NOS$ $[M + H]^+$ 394.1266, found 394.1266; IR (film): ν_{max} 3189, 1700, 1466, 1261, 732 cm^{-1}.

(*E*)-5-Bromo-3-(1-(naphthalen-2-ylthio)-2-phenylethylidene) indolin-2-one (3v). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 5–10% EtOAc in petroleum ether) and the product was obtained as a yellow solid (118 mg, 75%); mp: 203–204 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (s, 1H), 7.86 (d, J = 7.5 Hz, 2H), 7.77 (d, J = 7.5 Hz, 1H), 7.72 (s, 1H), 7.63–7.53 (m, 3H), 7.35–7.33 (m, 1H), 7.28–7.23 (m, 4H), 6.85 (d, J = 8 Hz, 2H), 6.81 (d, J = 8 Hz, 1H), 4.64 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 142.1, 136.9, 133.6, 133.4 131.7, 129.2, 128.5, 128.1 (2), 127.9, 127.4, 127.3, 125.9, 125.1 (2), 125.0, 124.3, 110.1, 36.1 ppm; HRMS (ESI-TOF): calcd for $C_{26}H_{19}BrNOS$ $[M + H]^+$ 472.0371, found 472.0371; IR (film): ν_{max} 3031, 1674, 1325, 1109, 807 cm^{-1}.

(*E*)-5-Fluoro-3-(1-(naphthalen-2-ylthio)-2-phenylethylidene) indolin-2-one (3w). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 5–10% EtOAc in petroleum ether) and the product was obtained as a yellow solid (132 mg, 86%); mp: 232–233 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99–7.97 (m, 1H), 7.94 (s, 1H), 7.86 (d, J = 8 Hz, 1H), 7.78–7.77 (m, 2H), 7.68–7.66 (m, 1H), 7.59–7.56 (m, 2H), 7.54–7.51 (m, 1H), 7.36–7.34 (m, 1H), 7.10–7.04 (m, 3H), 6.97–6.93 (m, 1H), 6.80–6.77 (m, 3H), 4.60 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 161.6, 137.9, 136.8, 133.6, 133.4, 131.8, 128.9, 128.4, 128.2, 127.9, 127.8, 127.0, 126.5, 126.3, 124.9, 122.3, 121.5, 115.1, 114.9, 36.1 ppm; HRMS (ESI-TOF): calcd for $C_{26}H_{19}FNOS$ $[M + H]^+$: calculated 412.1171, found 412.1174.

(*E*)-7-Fluoro-3-(1-(naphthalen-2-ylthio)-2-phenylethylidene) indolin-2-one (3x). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 5–10% EtOAc in petroleum ether) and the product was obtained as a yellow solid (126 mg, 82%); mp: 232–233 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (d, J = 8 Hz, 1H), 7.86 (d, J = 8 Hz, 1H), 7.77–7.74 (m, 3H), 7.66 (d, J = 8 Hz, 1H), 7.57–7.52 (m, 2H), 7.35 (d, J = 8.5 Hz, 1H), 7.10–7.04 (m, 5H), 6.77 (d, J = 7.5 Hz, 2H), 4.6 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 161.6, 137.9, 136.8, 133.6, 133.4, 131.8, 128.9, 128.4, 128.2, 127.9, 127.8, 127.0, 126.5, 126.3, 124.9, 122.3, 121.5, 115.1, 114.9, 36.1 ppm; HRMS (ESI-TOF): calcd for $C_{26}H_{19}FNOS$ $[M + H]^+$ 412.1171, found 412.1174; IR (film): ν_{max} 3024, 2825, 1684, 1203, 717 cm^{-1}.

(*E*)-3-(1-(Naphthalen-2-ylthio)-2-(4-(trifluoromethyl)phenyl) ethylidene)indolin-2-one (3y). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 5–10% EtOAc in petroleum ether) and the product was obtained as a yellow solid (101 mg, 70%); mp: 176–177 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20 (d, J = 8 Hz, 1H), 7.85 (d, J = 8 Hz, 2H), 7.77–7.73 (m, 2H), 7.63–7.52 (m, 3H), 7.36–7.34 (m, 1H), 7.28–7.25 (m, 3H), 7.13 (t, J = 8 Hz, 1H), 6.88 (d, J = 8 Hz, 3H), 4.66 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 157.6, 142.4, 139.5, 136.8, 133.5, 133.3, 131.8, 129.0, 128.5, 128.0, 127.9, 127.2, 125.8, 125.0, 123.6, 122.1, 110.2, 109.6, 36.1 ppm; HRMS (ESI-TOF): calcd for $C_{27}H_{19}F_3NOS$ $[M + H]^+$ 461.1139, found 461.1192; IR (film): ν_{max} 3023, 1686, 1565, 1320, 1108, 738 cm^{-1}.

(*E*)-5-Bromo-3-(1-(naphthalen-1-ylthio)-2-phenylethylidene) indolin-2-one (3z). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 5–10% EtOAc in petroleum ether) and the product was obtained as a yellow solid (133 mg, 85%); mp: 203–204 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.60 (s, 1H), 8.41 (s, 1H), 8.12 (d, J = 8 Hz, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.89 (d, J = 8 Hz, 1H), 7.54–7.45 (m, 3H), 7.37–7.31 (m, 3H), 7.01–6.96 (m, 2H), 6.83 (d, J = 8 Hz, 1H), 6.60 (d, J = 8 Hz, 2H), 4.37 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$ and one drop of DMSO-d_6): 166.1, 158.9, 138.6, 136.5, 135.6, 133.8, 132.8, 130.4, 129.5, 127.6, 126.9, 126.7, 126.8, 126.7, 125.6, 124.9, 124.3, 123.9, 123.5, 120.4, 112.2, 109.8, 34.5 ppm; HRMS (ESI-TOF): calcd for $C_{26}H_{19}BrNOS$ $[M + H]^+$ 472.0371, found 472.0371; IR (film): ν_{max} 3031, 1674, 1325, 1109, 807 cm^{-1}.

(*E*)-5-Fluoro-3-(1-(naphthalen-2-ylthio)octylidene)indolin-2-one (3za). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 5–10% EtOAc in petroleum ether) and the product was obtained as a yellow solid (137 mg, 74%); mp: 115–116 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (s, 1H), 8.10 (s, 1H), 7.95–7.86 (m, 4H), 7.61–7.56 (m, 3H), 6.93–6.89 (m, 1H), 6.78–6.75 (m, 1H), 3.03 (t, J = 8 Hz, 2H), 1.52–1.46 (m, 2H), 1.07–1.02 (m, 4H), 1.01–0.95 (m, 4H), 0.73 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 165.4, 159.7,

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(*E*)-3-(1-((4-Bromophenyl)thio)octylidene)indolin-2-one (3t). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 6–8% EtOAc in petroleum ether) and the product was obtained as a white solid (144 mg, 87%); mp: 137–138 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, J = 8 Hz, 1H), 7.92 (s, 1H), 7.58–7.55 (m, 2H), 7.46–7.43 (m, 2H), 7.21–7.18 (m, 1H), 7.07–7.03 (m, 1H), 6.84 (d, J = 7.5 Hz, 1H), 3.03–3.00 (m, 2H), 1.47–1.42 (m, 2H), 1.25–1.19 (m, 2H), 1.18–1.08 (m, 6H), 0.85 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 161.5, 139.3, 137.2, 132.7, 128.2, 127.9, 125.2, 124.7, 123.8, 121.6, 120.5, 109.2, 31.8, 31.1, 30.1, 29.4, 28.8, 22.7, 14.2 ppm; HRMS (ESI-TOF): calcd for $C_{22}H_{25}BrNOS$ $[M + H]^+$: calculated 430.0840, found 430.0841.

(*E*)-3-(1-(Naphthalen-2-ylthio)-2-phenylethylidene)indolin-2-one (3u). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 5–10% EtOAc in petroleum ether) and the product was obtained as a yellow solid (137 mg, 87%); mp: 152–153 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (d, J = 7.5, 1H), 7.90 (s, 1H), 7.85 (d, J = 8 Hz, 1H), 7.76 (d, J = 9 Hz, 2H), 7.66 (d, J = 7.5 Hz, 1H), 7.56–7.52 (m, 2H), 7.37–7.35 (m, 1H), 7.24 (d, J = 4.5 Hz, 1H), 7.12–7.04 (m, 4H), 6.87 (d, J = 8 Hz, 1H), 6.79 (d, J = 7 Hz, 2H), 4.60 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 159.2, 139.4, 138.2, 136.5, 133.4(2), 131.9, 129.4, 128.8, 128.4, 128.3, 128.2, 127.9, 127.6, 126.9, 126.2, 125.7, 125.5, 124.9, 123.9, 121.9, 109.4, 36.1 ppm; HRMS (ESI-TOF): calcd for $C_{26}H_{20}NOS$ $[M + H]^+$ 394.1266, found 394.1266; IR (film): ν_{max} 3189, 1700, 1466, 1261, 732 cm^{-1}.

(*E*)-5-Bromo-3-(1-(naphthalen-2-ylthio)-2-phenylethylidene) indolin-2-one (3v). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 5–10% EtOAc in petroleum ether) and the product was obtained as a yellow solid (118 mg, 75%); mp: 203–204 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (s, 1H), 7.86 (d, J = 7.5 Hz, 2H), 7.77 (d, J = 7.5 Hz, 1H), 7.72 (s, 1H), 7.63–7.53 (m, 3H), 7.35–7.33 (m, 1H), 7.28–7.23 (m, 4H), 6.85 (d, J = 8 Hz, 2H), 6.81 (d, J = 8 Hz, 1H), 4.64 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 142.1, 136.9, 133.6, 133.4 131.7, 129.2, 128.5, 128.1 (2), 127.9, 127.4, 127.3, 125.9, 125.1 (2), 125.0, 124.3, 110.1, 36.1 ppm; HRMS (ESI-TOF): calcd for $C_{26}H_{19}BrNOS$ $[M + H]^+$ 472.0371, found 472.0371; IR (film): ν_{max} 3031, 1674, 1325, 1109, 807 cm^{-1}.

(*E*)-5-Fluoro-3-(1-(naphthalen-2-ylthio)-2-phenylethylidene) indolin-2-one (3w). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 5–10% EtOAc in petroleum ether) and the product was obtained as a yellow solid (132 mg, 86%); mp: 232–233 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99–7.97 (m, 1H), 7.94 (s, 1H), 7.86 (d, J = 8 Hz, 1H), 7.78–7.77 (m, 2H), 7.68–7.66 (m, 1H), 7.59–7.56 (m, 2H), 7.54–7.51 (m, 1H), 7.36–7.34 (m, 1H), 7.10–7.04 (m, 3H), 6.97–6.93 (m, 1H), 6.80–6.77 (m, 3H), 4.60 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 161.6, 137.9, 136.8, 133.6, 133.4, 131.8, 128.9, 128.4, 128.2, 127.9, 127.8, 127.0, 126.5, 126.3, 124.9, 122.3, 121.5, 115.1, 114.9, 36.1 ppm; HRMS (ESI-TOF): calcd for $C_{26}H_{19}FNOS$ $[M + H]^+$: calculated 412.1171, found 412.1174.

(*E*)-7-Fluoro-3-(1-(naphthalen-2-ylthio)-2-phenylethylidene) indolin-2-one (3x). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 5–10% EtOAc in petroleum ether) and the product was obtained as a yellow solid (126 mg, 82%); mp: 232–233 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (d, J = 8 Hz, 1H), 7.86 (d, J = 8 Hz, 1H), 7.77–7.74 (m, 3H), 7.66 (d, J = 8 Hz, 1H), 7.57–7.52 (m, 2H), 7.35 (d, J = 8.5 Hz, 1H), 7.10–7.04 (m, 5H), 6.77 (d, J = 7.5 Hz, 2H), 4.6 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 161.6, 137.9, 136.8, 133.6, 133.4, 131.8, 128.9, 128.4, 128.2, 127.9, 127.8, 127.0, 126.5, 126.3, 124.9, 122.3, 121.5, 115.1, 114.9, 36.1 ppm; HRMS (ESI-TOF): calcd for $C_{26}H_{19}FNOS$ $[M + H]^+$ 412.1171, found 412.1174; IR (film): ν_{max} 3024, 2825, 1684, 1203, 717 cm^{-1}.

(*E*)-3-(1-(Naphthalen-2-ylthio)-2-(4-(trifluoromethyl)phenyl) ethylidene)indolin-2-one (3y). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 5–10% EtOAc in petroleum ether) and the product was obtained as a yellow solid (101 mg, 70%); mp: 176–177 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20 (d, J = 8 Hz, 1H), 7.85 (d, J = 8 Hz, 2H), 7.77–7.73 (m, 2H), 7.63–7.52 (m, 3H), 7.36–7.34 (m, 1H), 7.28–7.25 (m, 3H), 7.13 (t, J = 8 Hz, 1H), 6.88 (d, J = 8 Hz, 3H), 4.66 (s, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 157.6, 142.4, 139.5, 136.8, 133.5, 133.3, 131.8, 129.0, 128.5, 128.0, 127.9, 127.2, 125.8, 125.0, 123.6, 122.1, 110.2, 109.6, 36.1 ppm; HRMS (ESI-TOF): calcd for $C_{27}H_{19}F_3NOS$ $[M + H]^+$ 461.1139, found 461.1192; IR (film): ν_{max} 3023, 1686, 1565, 1320, 1108, 738 cm^{-1}.

(*E*)-5-Bromo-3-(1-(naphthalen-1-ylthio)-2-phenylethylidene) indolin-2-one (3z). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 5–10% EtOAc in petroleum ether) and the product was obtained as a yellow solid (133 mg, 85%); mp: 203–204 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.60 (s, 1H), 8.41 (s, 1H), 8.12 (d, J = 8 Hz, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.89 (d, J = 8 Hz, 1H), 7.54–7.45 (m, 3H), 7.37–7.31 (m, 3H), 7.01–6.96 (m, 2H), 6.83 (d, J = 8 Hz, 1H), 6.60 (d, J = 8 Hz, 2H), 4.37 (s, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$ and one drop of DMSO-d_6): 166.1, 158.9, 138.6, 136.5, 135.6, 133.8, 132.8, 130.4, 129.5, 127.6, 126.9, 126.7, 126.8, 126.7, 125.6, 124.9, 124.3, 123.9, 123.5, 120.4, 112.2, 109.8, 34.5 ppm; HRMS (ESI-TOF): calcd for $C_{26}H_{19}BrNOS$ $[M + H]^+$ 472.0371, found 472.0371; IR (film): ν_{max} 3031, 1674, 1325, 1109, 807 cm^{-1}.

(*E*)-5-Fluoro-3-(1-(naphthalen-2-ylthio)octylidene)indolin-2-one (3za). Following general experimental procedure A, the crude reaction mixture was purified by column chromatography (100–200 silica gel, 5–10% EtOAc in petroleum ether) and the product was obtained as a yellow solid (137 mg, 74%); mp: 115–116 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (s, 1H), 8.10 (s, 1H), 7.95–7.86 (m, 4H), 7.61–7.56 (m, 3H), 6.93–6.89 (m, 1H), 6.78–6.75 (m, 1H), 3.03 (t, J = 8 Hz, 2H), 1.52–1.46 (m, 2H), 1.07–1.02 (m, 4H), 1.01–0.95 (m, 4H), 0.73 (t, J = 7.5 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 165.4, 159.7,

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2181; (*l*) P. Pali, G. Shukla, P. Saha and M. S. Singh, *Org. Lett.*, 2021, **23**, 3809–3813.

4 (*a*) Y. M. Khetmalis, M. Shivani, S. Murugesan and K. V. G. Chandrasekhar, *Biomed. Pharmacother.*, 2021, **141**, 111842; (*b*) W. C. Sumpter, *Chem. Rev.*, 1945, **37**, 443–479; (*c*) M. Kaur, M. Singh, N. Chandra and O. Silakari, *Eur. J. Med. Chem.*, 2016, **123**, 858–894; (*d*) G. M. Ziarani, F. Javadi and F. Mohajer, *Curr. Org. Chem.*, 2021, **25**, 779–818; (*e*) S. Yaragorla, G. Singh and R. Dada, *Tetrahedron Lett.*, 2016, **57**, 591–594.

5 (*a*) L. Sun, N. Tran, F. Tang, H. App, P. Hirth, G. McMahon and C. Tang, *J. Med. Chem.*, 1998, **41**, 2588–2603; (*b*) S. Hauf, R. W. Cole, S. LaTerra, C. Zimmer, G. Schnapp, R. Walter, A. Heckel, J. van Meel, C. L. Rieder and J.-M. Peters, *J. Cell Biol.*, 2003, **161**, 281–294; (*c*) F. Hilberg, G. J. Roth, M. Krssak, S. Kautschitsch, W. Sommergruber, U. Tontsch-Grunt, P. Garin-Chesa, G. Bader, A. Zoephel, J. Quant, A. Heckel and W. J. Rettig, *Cancer Res.*, 2008, **68**, 4774–4782; (*d*) A. Millemaggi and R. J. K. Taylor, *Eur. J. Org. Chem.*, 2010, 4527–4547; (*e*) G. M. Ziarani, P. Gholamzadeh, N. Lashgari and P. Hajiabbasi, *ARKIVOC*, 2013, 470–535; (*f*) B. M. Trost and M. K. Brennan, *Synthesis*, 2009, 3003–3025; (*g*) R. M. Williams and R. J. Cox, *Acc. Chem. Res.*, 2003, **36**, 127–139; (*h*) M. S. C. Pedras and M. Hossain, *Org. Biomol. Chem.*, 2006, **4**, 2581–2590; (*i*) L. Tang, T. Peng, G. Wang, X. Wen, Y. Sun, S. Zhang, S. Liu and L. Wang, *Molecules*, 2017, **22**, 1979.

6 (*a*) C. Le Tourneau, E. Raymond and S. Faivre, *Ther. Clin. Risk Manage.*, 2007, **3**, 341–348; (*b*) H. Huyhn, V. C. Ngo, S. P. Choo, D. Poon, H. N. Koong, C. H. Thng, H. C. Toh, L. Zheng, L. C. Ong, Y. Jin, I. C. Song, A. P. C. Chang, H. S. Ong, A. Y. F. Chung, P. K. H. Chow and K. C. Soo, *Curr. Cancer Drug Targets*, 2009, **9**, 738–747; (*c*) S. Shukla, R. W. Robey, S. E. Bates and S. V. Ambudkar, *Drug Met. Depos.*, 2009, **37**, 359–365.

7 Selected examples: (*a*) S. Lin and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, 2001, **40**, 1967–1970, (*Angew. Chem.*, 2001, **113**, 2021–2024); (*b*) R. Yanada, S. Obika, T. Inokuma, K. Yanada, M. Yamashita, S. Ohta and Y. Takemoto, *J. Org. Chem.*, 2005, **70**, 6972–6975; (*c*) R. Shintani, T. Yamagami and T. Hayashi, *Org. Lett.*, 2006, **8**, 4799–4801.

8 (*a*) H. J. Roh, J. W. Lim, Y. J. Yeon, J. Lee and J. N. Kim, *Tetrahedron Lett.*, 2016, **57**, 4280–4283; (*b*) N. Kumaraswamyreaddy and V. Kesavan, *Eur. J. Org. Chem.*, 2016, 5301–5308; (*c*) S. Yaragorla, R. Dada, G. Singh, A. Pareek, M. Rana and A. K. Sharma, *ChemistrySelect*, 2016, **1**, 6902–6906; (*d*) H. J. Roh, S. Y. Kim, B. K. Min and J. N. Kim, *Tetrahedron Lett.*, 2017, **58**, 21–24; (*e*) S. Yaragorla, A. Pareek and R. Dada, *Adv. Synth. Catal.*, 2017, **359**, 3068–3075; (*f*) B. Kalavacharla, S. Batthula, S. Balasubramanian and R. K. Palakodety, *Org. Lett.*, 2018, **20**, 3824–3828; (*g*) S. Yaragorla, R. Dada and A. Pareek, *ChemistrySelect*, 2018, **3**, 495–499; (*h*) S. Yaragorla, R. Dada, P. Rajesh and M. Sharma, *ACS Omega*, 2018, **3**, 2934–2946; (*i*) Y.-W. Xu, L. Li and X.-P. Hu, *Org. Lett.*, 2020, **22**, 9534–9538.

9 S. Biswas and J. S. M. Samec, *Chem. – Asian J.*, 2013, **8**, 974–981.

10 Z.-P. Zhan, W.-Z. Yang, R.-F. Yang, J.-L. Yu, J.-P. Li and H.-J. Liu, *Chem. Commun.*, 2006, 3352–3354.

11 Z.-P. Zhan, J.-L. Yu, H.-J. Liu, Y.-Y. Cui, R.-F. Yang, W.-Z. Yang and J.-P. Li, *J. Org. Chem.*, 2006, **71**, 8298–8301.

12 Y. Inada, Y. Nishibayashi, M. Hidai and S. Uemura, *J. Am. Chem. Soc.*, 2002, **124**, 15172–15173.

13 M. Yoshimatsu, T. Otani, S. Matsuda, T. Yamamoto and A. Sawa, *Org. Lett.*, 2008, **10**, 4251–4254.

14 R. Sanz, A. Martínez, J. M. Álvarez-Gutiérrez and F. Rodríguez, *Eur. J. Org. Chem.*, 2006, 1383–1386.

15 N. Velasco, A. Suárez, F. Martínez-Lara, M. Á. Fernández-Rodríguez, R. Sanz and S. Suárez-Pantiga, *J. Org. Chem.*, 2021, **86**, 7078–7091.

16 (*a*) S. Biswas and J. S. M. Samec, *Chem. Commun.*, 2012, **48**, 6586–6588; (*b*) S. Biswas, R. A. Watile and J. S. M. Samec, *Chem. – Eur. J.*, 2014, **20**, 2159–2163.

17 S. Chen, F. Yuan, H. Zhao and B. Li, *Res. Chem. Intermed.*, 2013, **39**, 2391–2399.

18 Refer to the ESI† for the X-ray and other spectral data.

19 T. Miura, T. Toyoshima, Y. Ito and M. Murakami, *Chem. Lett.*, 2009, **38**, 1174–1175.

20 S. P. Kumar, J. Gut, R. C. Guedes, P. J. Rosenthal, M. M. M. Santos and R. Moreira, *Eur. J. Med. Chem.*, 2011, **46**, 927–933.

21 M. M. Khodaei, K. Bahrami and A. Karimi, *Synthesis*, 2008, 1682–1684.

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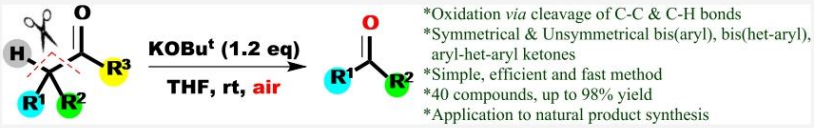
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Oxidative Cleavage of C_{sp^3}–C_{sp^2} and C_{sp^3}–H Bonds with KO^{t}Bu: Highly Robust and Practical Synthesis of Diaryl/(het-Ar) Ketones

Srinivasarao Yaragorla,* Tabassum Khan, and Ahalya Behera

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ABSTRACT: Herein, we report an efficient and practical approach for synthesizing diaryl(het) ketones from R–CO–CHR–Ar through a simultaneous oxidative cleavage of C–C and C–H bonds using KO^{t}Bu. This method enables synthesizing a variety of unsymmetrical and symmetrical (hetero)aryl ketones in excellent yields, which are otherwise difficult to make. Besides, we synthesized natural products using this method.

INTRODUCTION

Functional group transformations are essential reactions in synthetic and industrial organic chemistry. In recent years, the pharmaceutical industry has grown interest in developing cost-effective and environmentally benign oxidation methods,[1] as ketones and their derivatives are well-known precursors for synthesizing drugs, biologically active molecules, natural products, and polymers (Figure 1).[2] Among several oxidation

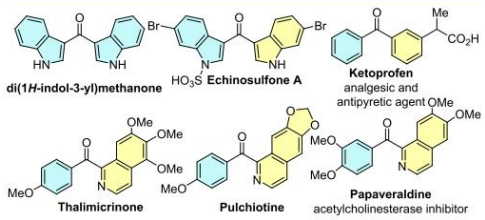


Figure 1. Representative examples of natural and pharmaceutical diaryl ketones.

methods available for diaryl ketones,[1,3] sp^3 C–H oxidation has become one of the attractive methods due to its atom economy.[4] Nevertheless, most of them require either transition-metal catalysts[5] or excessive use of chemical oxidants such as oxone,[6] peroxides,[7] and PhIO,[8] which needs to be addressed.

On the other hand, due to the inert nature of the carbon–carbon single bonds, their oxidative cleavage is challenging, and controlled oxidation is further problematic. The cleavage of C_{sp^3}–C_{sp^2} bonds [such as C(CO)–C] has been performed to produce corresponding acids,[9] esters,[10] amides,[11] and other derivatives.[12] However, the synthesis of diaryl ketones from these substrates via cleavage of C–C bond/oxidation of C–H bond is limited. Maji et al. reported the synthesis of diaryl ketones using copper-catalyzed removal of benzylic CH_2 and CO groups (Scheme 1, eq-i).[13] Later, Chaudhari et al. reported an α-C(sp^3)–H hydroxylation of a carbonyl compound with KO^{t}Bu/DMSO (Scheme 1, eq-ii);[14] however, this method works mainly with cyclic carbonyls bearing α-benzyl substitutions but not alkyl substitutions. In this connection, we report a simple and practical synthesis of diaryl(het-aryl)ketones via simultaneous C–C bond cleavage and C–H bond oxidation using potassium *tert*-butoxide in the presence of aerial oxygen. In recent years, KO^{t}Bu has become a privileged reagent for oxidation and electron transfer reactions,[15] besides acting as a non-nucleophilic base. Due to its low cost, simple availability, and easy handling, it has been explored as an environmentally benign and transition-metal-free oxidating reagent in a few cases.[15,16] For a recent example, Wang et al. reported direct benzylic oxidation to generate di(hetero)aryl ketones using KO^{t}Bu/18-crown-6, O_2 in DMF.[16]

RESULTS AND DISCUSSION

Motivated by these facts, we started our investigation with the oxidation of 2,2-bis(1-benzyl-1*H*-indol-3-yl)-1-phenylethan-1-one (**1a**) using KO^{t}Bu (Table 1). Initially, we treated

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Scheme 1. Diaryl Ketone Synthesis via Sp^3 C−H Oxidation

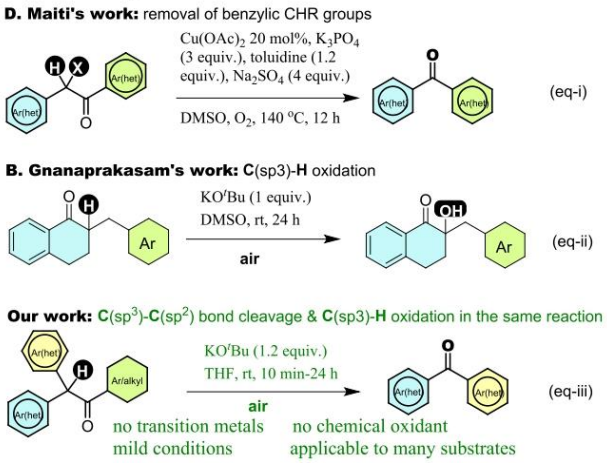
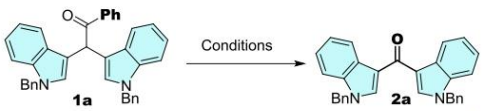


Table 1. Optimization of Reaction Conditions[a]



entry	reaction conditions	yield(%)[b]
1	KO^{t}Bu (1 equiv), THF, rt, 2 h	76
2	KO^{t}Bu (1.2 equiv), THF, rt, 20 min	81
3	KO^{t}Bu (1.5 equiv), THF, rt, 20 min	79
4	KO^{t}Bu (2 equiv), THF, rt, 20 min	70
5	KO^{t}Bu (1.2 equiv), THF, 0 °C, 5 h	72
6	KO^{t}Bu (1.2 equiv), THF, 60 °C, 20 min	62
7	KO^{t}Bu (1.2 equiv), 18C6, THF, rt, 1 h	60
8	KO^{t}Bu (1.2 equiv), DMF, rt, 20 min	60
9	KO^{t}Bu (1.2 equiv), DMSO, rt, 2 h	40
10	KO^{t}Bu (1.2 equiv), MeCN, rt, 2 h	35
11	KO^{t}Bu (1.2 equiv), toluene, rt, 2 h	95
12[c]	KO^{t}Bu (1.2 equiv), THF, rt, closed vessel, 20 min	98
13	KO^{t}Bu (1.2 equiv), THF, rt, degas, 24 h	trace
14	KO^{t}Bu (1.2 equiv), THF, rt, O_2, 20 min	98
15	KO^{t}Bu (1.2 equiv), THF, rt, O_2, 2 h	90
16	K_2CO_3 (1.2 equiv), THF, rt, 24 h	nr
17	DBU (1.2 equiv), THF, rt, 24 h	05
18	DABCO (1.2 equiv), THF, rt, 24 h	05
19	NaH (1.2 equiv), THF, rt, 1 h	40
20	H_2O_2 (1.2 equiv), THF, rt, 24 h	nr
21	TBHP (1.2 equiv), THF, rt, 24 h	nr
22	DTBP (1.2 equiv), THF, rt, 24 h	nr

[a]Unless mentioned, all of the reactions were carried out with **1a** (100 mg, 0.1884 mmol) at rt (25−30 °C) under specified conditions. [b]Isolated yields. [c]Optimum condition.

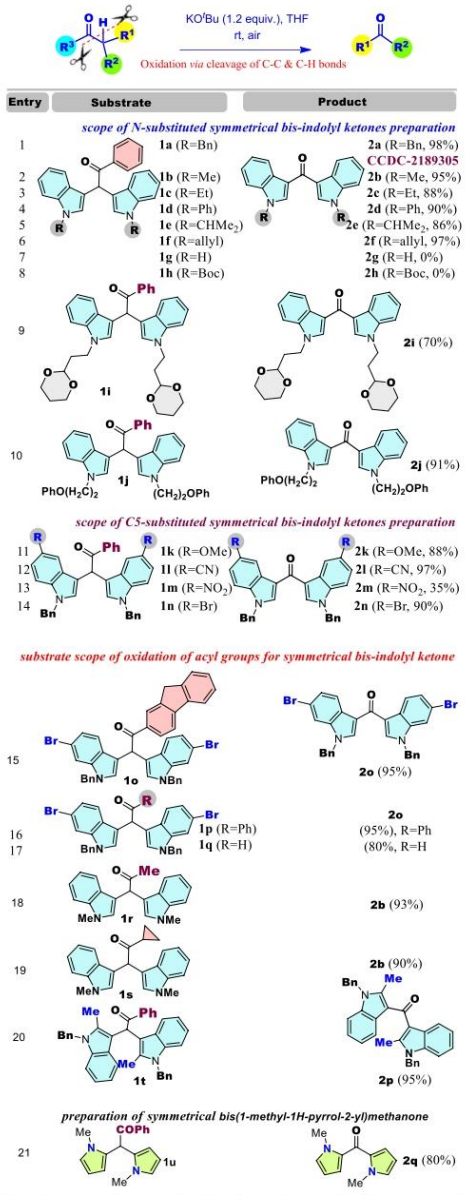
compound **1a** (100 mg) with 1 equiv of KO^{t}Bu in tetrahydrofuran (THF) at room temperature under a nitrogen atmosphere for 2 h and gratefully observed the formation of bis-indolyl ketone **2a** in 76% yield. Note that the reaction flask contains aerial oxygen inside, and a nitrogen balloon was used to stop the quenching of the base with external moisture; the same can also be achieved by closing the reaction flask with a stopper. The structure of **2a** was unambiguously confirmed by NMR, mass, IR, and single-crystal X-ray data (CCDC-2189305).[17] Encouraged by this result, we focused on increasing the reaction yield by increasing the amount of KO^{t}Bu and found that 1.2 equiv is best (entries 2−4). Neither decreasing nor increasing the reaction temperature was suitable (entries 5 and 6). The oxidation in 18C6 could not improve the yield (entry 7). Other solvents like DMF, DMSO, and MeCN were not found suitable (entries 8−10), whereas 95% of **2a** was observed in toluene. Surprisingly, when the reaction was performed in a closed flask (without nitrogen), it gave a nearly quantitative yield (entry 12) and only a trace of the product was observed in degassing conditions. These observations infer that the aerial oxygen present in the reaction flask was sufficient for this oxidation reaction.

It was observed that in the presence of O_2 balloon in THF, **2a** was obtained in 98% yield after 20 min (entry 14), but a further continuation of the reaction leads to the oxidation of *N*-benzylic protons of **2a**; thus, a slight decrease in the yield of **2a** was observed (entry 15). Neither the other bases (entries 16−19) nor the peroxide reagents (entries 20−22) were proved good for this oxidation.

Having established the optimized reaction conditions (entry 12, Table 1), we then started investigating the scope of this oxidative transformation. As depicted in Table 2, this reaction protocol smoothly converted bis-indolyl-benzoyl methanes to the desired di(3-indolyl)methanones in excellent yields. This protocol tolerated a variety of *N*-substituted indoles in delivering the corresponding diaryl ketones (**2a**−**2j**). However, NH and NBoc indoles did not furnish the desired products. Then, we also observed that substitutions on indole's benzene rings were also tolerated under these conditions and furnished the corresponding ketones in excellent yields (**2k**−**2n**). Further, we explored that not only phenyl ketones but also 2-fluorenyl, methyl, and cyclopropyl ketones (**1o**−**1s**) underwent oxidation to deliver the desired bis-indolyl ketones. Further, the reactivity of C2-substituted bis-indolyl phenylethan-1-one was tested, which resulted in product **2p**.

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Table 2. Substrate Scope of Symmetrical Bis-het-aryl Ketone Synthesis[a]



[a]Conditions: bisheteroaryl phenylethan-1-one 1 (100 mg, 0.188 mmol) and KO^{t}Bu (0.22 mmol) in 0.5 mL of THF was stirred at rt in the presence of aerial oxygen.

Similarly, symmetrical bispyrrolyl ketone **2q** was prepared from **1u**.

To expand the scope of this oxidative protocol, we then tested other typical compounds having benzylic sp^3 C−H bonds and synthesized unsymmetrical bisheteroaryl ketones **2r**−**2t**, aryl-heteroaryl ketones (**2u**−**2y**) in excellent yields (Table 3). With the success of symmetrical and unsymmetrical bisheteroaryl ketones and aryl-heteroaryl ketone synthesis, we then checked the scope of oxidation to get diaryl ketones. Under the standard conditions, benzophenone was made in 65% yield from 1,2,2-triphenylethan-1-one after 12 h. Further efforts to increase the yield of **2z** to 78% were successful by switching the solvent to toluene. Electron-rich symmetrical diaryl ketones **2aa**−**2ac** were made in excellent yields in THF in a short time. Accordingly, unsymmetrical diaryl ketones **2ad**−**2ag** were prepared in good yields in the presence of KO^{t}Bu (1.2 equiv) in toluene at rt. These observations inferred that toluene is a suitable solvent for less electron-rich systems than THF. It is worth noting that compound **2ab** is a key precursor for an organic dye crystal violet.[18]

To check the effect of R group on the rate of this oxidative cleavage reaction, we have performed 50 mg reactions of various substrates, and the reaction completion times are summarized in Figure 2. The results indicated that the reactions were relatively slow with alkyl groups compared to aryls. The electronic effects on the aryl ring are also consistent with the obtained results.

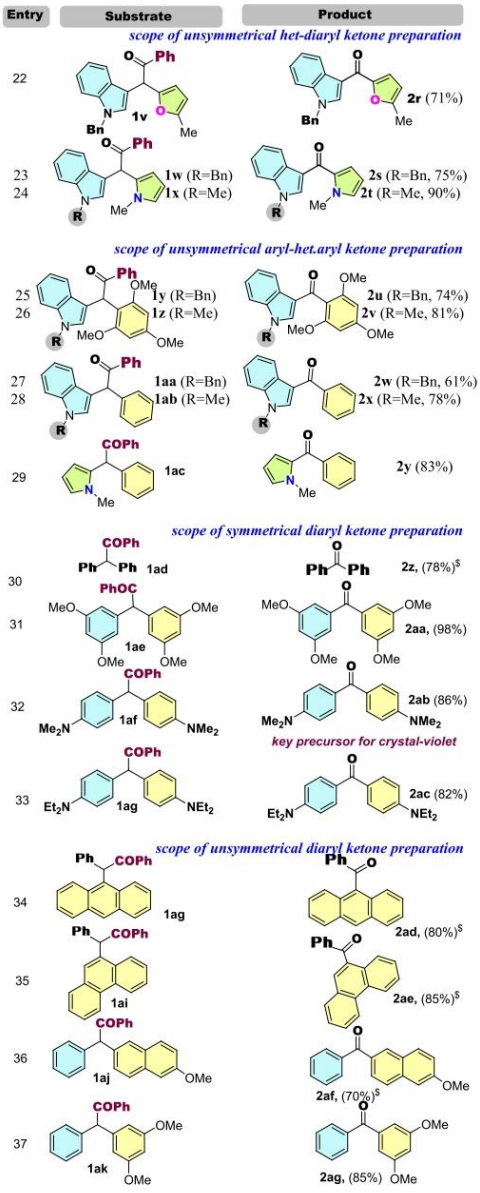
The synthetic potential of this protocol was demonstrated by synthesizing a Di(1*H*-indol-3-yl)methanone **2g**, a natural product,[19] which is also a precursor for other natural products, and an anti-breast-cancer drug Arudine.[20] The synthesis was commenced by preparing **1a** from *N*-benzyl indole and phenylglyoxal using a reported method[21] (Scheme 2). Next, treatment of **1a** with an excess of KO^{t}Bu in THF at rt yielded initially **2a**, further continuing the reaction in an oxygen atmosphere leads to the formation of desired natural ketone **2g** (37% from **1a**) along with its mono *N*-benzyl derivative **3** in 12 h (Scheme 2). However, treatment of **2a** with KO^{t}Bu/DMSO at rt in oxygen atmosphere gave 83% of **2g** in 5 h.[22] Next, we demonstrate a formal synthesis of another natural product, Echinosulfone A,[23] from **1p**, which was prepared using the known method and subjected to oxidation to get ketone **2o**. Oxidative debenzylation of **2o** gave **4** in 77% yield, which was previously converted to Echinosulphone A.[23]

Next, to demonstrate the scalability and operational simplicity of the protocol, we performed the gram scale synthesis of ketone **2a** (0.76 g, 92%). Then, **2a** was subjected to C1-Wittig olefination to get alkene **5** in 83% yield; also, **2a** was treated with Lawesson's reagent to obtain the corresponding thione **6** (Scheme 3).

To gain insight into this oxidative reaction, we employed TEMPO as a radical scavenger in the reaction but did not observe a significant change in the reaction yield of **2a**. Even the TEMPO adduct was not detected in HRMS of the crude mass. This indicated that the reaction may not proceed through the radical path. Based on these observations as well as previous reports,[14,21,24] we proposed a possible mechanism for this oxidation reaction (Scheme 4). The reaction is initiated by the abstraction of sp^3 C−H proton of compound **1** by the base, followed by the addition of oxygen to form peroxy ketone **1A**, which undergoes intramolecular addition of peroxy anion to carbonyl carbon forms a four-membered 1,2-dioxetan-3-olate

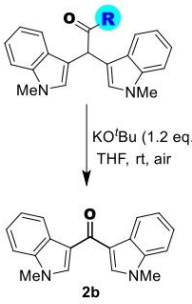
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J. Org. Chem. 2023, 88, 2103−2112

Table 3. Substrate Scope of Unsymmetrical Ketone Synthesis[a]



[a]Conditions: bis-aryl phenylethan-1-one **1** (100 mg, 0.188 mmol) and KO^{t}Bu (0.22 mmol) in 0.5 mL of THF was stirred at rt in the presence of aerial oxygen, $dry toluene (0.5 mL).

1B. Oxidative cleavage of this unstable ring furnishes the diaryl ketone (**2**).[24]



R	Time (minutes)
Me	80
cyclopropyl	30
Ph	20
Ph(4-Me)	07
Ph(4-Br)	12
Ph(4-Me)	40

Figure 2. Effect of R group on the rate of the reaction.

In summary, we have developed a simple protocol for synthesizing symmetrical and unsymmetrical diaryl, diheteroaryl ketones using readily available KO^{t}Bu. The reaction involved in transition-metal-free cleavage of carbon(sp^3)–carbon(sp^2) and carbon(sp^3)–hydrogen bonds simultaneously. This protocol tolerated a broad range of substrates and produced the ketones in excellent yields. TEMPO experiments suggested that the reaction does not proceed in a radical path, hence the proposed ionic route. A short synthesis of natural products **2g** and formal synthesis of echinosulfone A were achieved using this protocol. Further investigations to explore oxidations with KO^{t}Bu and mechanism are currently ongoing in our lab.

■ EXPERIMENTAL SECTION

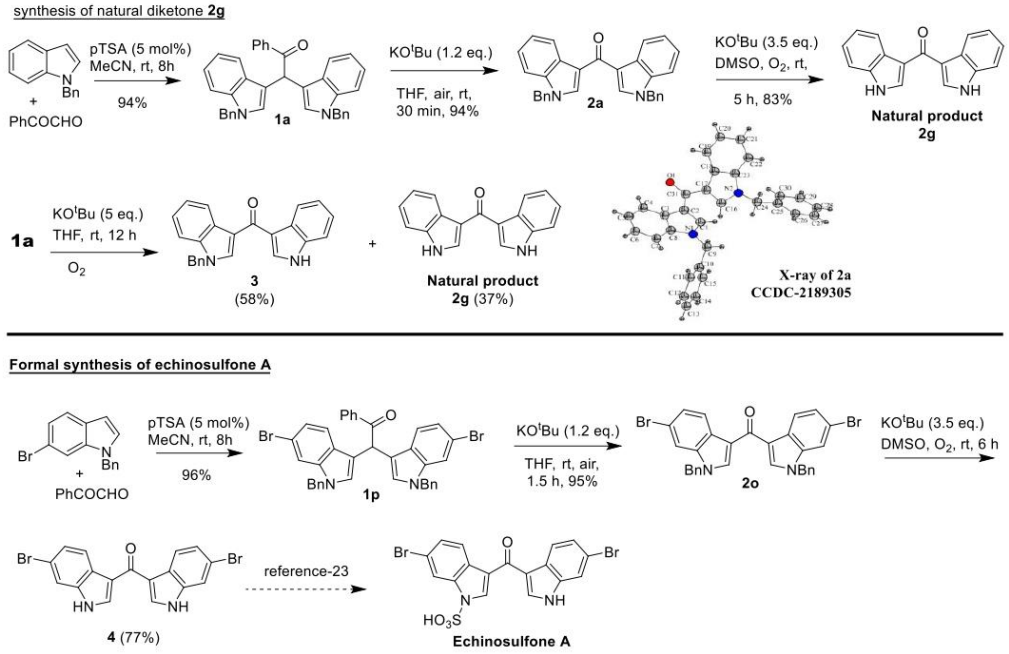
General Information. Unless otherwise noted, all reagents were used as received from commercial suppliers or were synthesized by following the reported procedures discussed below. Reactions were performed in flame-dried or oven-dried glassware with magnetic stirring. Reactions were monitored using thin-layer chromatography (TLC) with aluminum sheets of silica gel 60 F_{254} from Merck. TLC plates were visualized with ultraviolet (UV) light (254 nm), iodine treatment, or using *p*-anisaldehyde or $KMnO_4$ stain. Column chromatography was carried out using silica gel 60–120 and 100–200 mesh size as stationary phase. NMR spectra were recorded at 500 and 400 MHz (^{1}H) and 125 and 100 MHz (^{13}C{^{1}H}), respectively, on the Avance Bruker spectrometer. NMR spectra were solved using Bruker Topspin software. Chemical shifts (δ) are reported in ppm, using the residual solvent peak in $CDCl_3$ (^{1}H: δ = 7.26 and ^{13}C{^{1}H}: δ = 77.16 ppm) as internal standard, and coupling constants (J) are given in hertz. HRMS were recorded using ESI-TOF techniques. Melting points were measured with the LABINDIA mepa melting apparatus.

General Experimental Procedure for the Preparation of Ketones (2). A mixture of bis-aryl, arylethanone **1** (100 mg), and KO^{t}Bu (1.2 equiv) was weighed into a 10 mL RB flask, and dry THF or dry toluene (0.5 mL) was added to the reaction mixture and stirred at room temperature (RB flask was closed with a stopper, to avoid quenching of the base with atmospheric moisture). The progress of the reaction was monitored by TLC. After the complete consumption of starting materials, the base was quenched with water, and the product was extracted with EtOAc (thrice), the combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated to obtain the crude product The crude was purified by column chromatography using an eluent of ethyl acetate and pet ether (20–30% ethyl acetate in pet ether) to afford the desired ketone in good to excellent yield.

Experimental Procedure for the Synthesis of (1-Benzyl-1*H*-indol-3-yl)(1*H*-indol-3-yl)methanone (3) and Di(1*H*-indol-3-yl)methanone (2g). A round-bottom flask was charged with 2,2-

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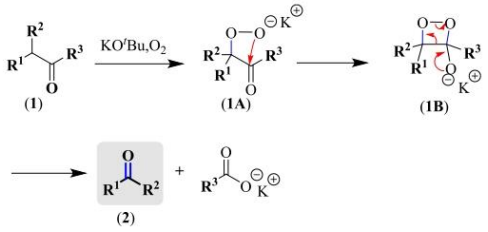
Scheme 2. One-Pot Synthesis of Di(1*H*-indol-3-yl)methanone 2g and Formal Synthesis of Echinosulfone A



Scheme 3. Synthetic Applications of 2a



Scheme 4. Proposed Reaction Mechanism



bis(1-benzyl-1*H*-indol-3-yl)-1-phenylethan-1-one **1a** (100 mg, 0.1886 mmol), KO^{t}Bu (216 mg, 0.9430 mmol), and 0.5 mL of dry THF, and the reaction mixture was stirred at room temperature, and the progress of the reaction was monitored by TLC. After the complete consumption of starting material, an oxygen balloon was introduced to the reaction mixture and stirred at room temperature for 12 h. The base was quenched with water, and the product was extracted with EtOAc (thrice), the combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated to obtain the crude product. The crude was purified by column chromatography to afford the desired product. Alternatively, compound **2a** (100 mg, 0.2272 mmol) was treated with KO^{t}Bu (151 mg, 0.7952 mmol) in DMSO under O_2 atmosphere, the reaction mixture was stirred at room temperature, and the progress of the reaction was monitored by TLC. After complete consumption of starting material, the base was quenched with water and the product was extracted with EtOAc (thrice), the combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was evaporated to obtain the crude product. The crude was purified by column chromatography to afford the desired product **2g** in 85% yield.

Spectral Data of Selected Compounds (Complete Details Are Provided in the SI). *Bis(1-benzyl-1H-indol-3-yl)methanone (**2a**).* Isolated (R_f = 0.25, EtOAc/petroleum ether, 1:3 v/v) as a yellow solid (mp. 123−125 °C), yield 98% (0.081 g); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.40−8.38 (m, 2H), 7.65 (s, 2H), 7.33−7.31 (m, 4H), 7.30−7.28 (m, 5H), 7.26−7.25 (m, 3H), 7.14 (d, 4H, J = 7 Hz), 5.35 (s, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 185.0, 137.1, 136.3, 134.0, 129.1, 128.2, 127.5, 127.1, 123.5, 122.6, 122.2, 118.2, 110.1, 50.7; IR (KBr): 3030, 2921, 1686, 1594, 1570, 1517, 1494, 1449, 1389, 1351, 1330, 1302, 1247, 1172, 1079, 1009, 829, 779, 736, 695, 624, 572 cm^{-1}; HRMS (ESI): calcd. for $C_{31}H_{25}N_2O$ $[M + H]^+$ 441.1967; found 441.1965.

*Bis(1-methyl-1H-indol-3-yl)methanone (**2b**).* Isolated (R_f = 0.25, EtOAc/petroleum ether, 1:3 v/v) as a yellow solid (mp. 111−113 °C), yield 95% (0.072 g); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.40−8.38 (m, 2H), 7.50 (s, 2H), 7.30−7.29 (m, 5H), 7.28−7.27 (m, 1H), 3.77 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 184.8, 137.4, 134.5, 127.3, 123.1, 122.4, 121.9, 117.3, 109.5, 33.3; IR (KBr): 3123, 2911, 1667, 1597, 1517, 1466, 1373, 1244, 1210, 1128,

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1002, 839, 775, 740, 645, 573 cm^{-1}; HRMS (ESI): calcd. for $C_{19}H_{17}N_2O$ $[M + H]^+$ 289.1341; found 289.1342.

*Bis(1-ethyl-1H-indol-3-yl)methanone (**2c**).* Isolated (R_f = 0.25, EtOAc/petroleum ether, 1:3 v/v) as a colorless solid (mp. 285−286 °C), yield 88% (0.068 g); ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.37 (d, 2H, J = 7.0 Hz), 7.69 (s, 2H), 7.39 (d, 2H, J = 8.0 Hz), 7.32−7.25 (m, 4H), 4.25−4.21 (m, 4H), 1.52 (t, 6H, J = 7 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 185.0, 136.5, 133.0, 127.4, 123.0, 122.5, 121.8, 117.6, 109.7, 41.6, 15.4; IR (KBr): 2982, 2886, 1666, 1592, 1514, 1484, 1451, 1391, 1351, 1310, 1233, 1192, 1131, 1081, 1007, 838, 822, 741, 715, 642, 560, 508 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{21}N_2O$ $[M + H]^+$ 317.1654; found 317.1655.

*Bis(1-phenyl-1H-indol-3-yl)methanone (**2d**).* Isolated (R_f = 0.25, EtOAc/petroleum ether, 1:3 v/v) as a colorless viscous compound, yield 90% (0.073 g); ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.51−8.49 (m, 2H), 7.93 (s, 2H), 7.57−7.52 (m, 10H), 7.45−7.42 (m, 2H), 7.38−7.35 (m, 2H), 7.34−7.31 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 185.1, 138.7, 137.0, 133.5, 129.9, 127.8, 127.7, 125.0, 124.0, 122.7, 119.4, 110.8.; IR (KBr): 3103, 3043, 1738, 1589, 1519, 1499, 1480, 1454, 1359, 1297, 1232, 1208, 1184, 1095, 1075, 1030, 947, 829, 777, 743, 717, 689, 661, 579, 533 cm^{-1}; HRMS (ESI): calcd. for $C_{29}H_{21}N_2O$ $[M + H]^+$ 413.1654; found 413.1656.

*Bis(1-isopropyl-1H-indol-3-yl)methanone (**2e**).* Isolated (R_f = 0.25, EtOAc/petroleum ether, 1:3 v/v) as a yellow solid (mp. 128−130 °C), yield 86% (0.068 g); ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.33−8.31 (m, 2H), 7.81 (s, 2H), 7.43 (d, 2H, J = 8 Hz), 7.32−7.29 (m, 2H), 7.28−7.25 (m, 2H), 4.76−4.71 (m, 2H), 1.58 (s, 6H), 1.57 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 185.2, 136.4, 130.1, 127.3, 122.9, 122.4, 121.8, 117.9, 109.9, 47.6, 22.7; IR (KBr): 3107, 2974, 2927, 1604, 1582, 1511, 1458, 1397, 1368, 1346, 1302, 1234, 1178, 1130, 1064, 1014, 851, 827, 781, 754, 702, 605, 554, 508 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{25}N_2O$ $[M + H]^+$ 345.1967; found 345.1966.

*Bis(1-allyl-1H-indol-3-yl)methanone (**2f**).* Isolated (R_f = 0.25, EtOAc/petroleum ether, 1:3 v/v) as a colorless solid (mp. 100−102 °C), yield 97% (0.076 g); ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.39−8.37 (m, 2H), 7.68 (s, 2H), 7.39−7.35 (m, 2H), 7.33−7.30 (m, 2H), 7.29−7.27(m, 2H), 6.07−6.03 (m, 1H), 6.02−5.99 (m, 1H), 5.28−5.26 (m, 2H), 5.19−5.15 (m, 2H), 4.82−4.81 (m, 2H), 4.80−4.79 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 185.0, 136.9, 133.7, 132.5, 127.4, 123.3, 122.6, 122.1, 118.3, 118.0, 110.0, 49.3; IR (KBr): 3049, 2919, 1665, 1602, 1573, 1516, 1482, 1459, 1363, 1312, 1226, 1192, 1047, 932, 833, 779, 743, 564, 530 cm^{-1}; HRMS (ESI): calcd. for $C_{23}H_{21}N_2O$ $[M + H]^+$ 341.1654; found 341.1654.

*Bis(1-(2-(1,3-dioxan-2-yl)ethyl)-1H-indol-3-yl) methanone (**2i**).* Isolated (R_f = 0.25, EtOAc/petroleum ether, 1:3 v/v) as a brown solid (mp 114−116 °C), yield 70% (0.055 g); ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.40 (d, 2H, J = 7.0 Hz), 7.67 (s, 2H), 7.42 (d, 2H, J = 7.5 Hz), 7.33−7.27 (m, 4H), 4.45−4.43 (m, 2H), 4.35−4.32 (m, 4H), 4.10−4.07 (m, 4H), 3.70−3.65 (m, 4H), 2.17−2.12 (m, 4H), 2.11−2.02 (m, 2H), 1.33 (d, 2H, J = 13.5 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 185.0, 136.8, 133.7, 127.4, 123.3, 122.6, 122.0, 117.8, 109.9, 99.2, 66.9, 41.9, 35.3, 25.7; HRMS (ESI): calcd. for $C_{29}H_{33}N_2O_5$ $[M + H]^+$ 489.2389; found 489.2389.

*Bis(1-(2-phenoxyethyl)-1H-indol-3-yl)methanone (**2j**).* Isolated (R_f = 0.25, EtOAc/petroleum ether, 1:3 v/v) as a yellow solid (mp. 128−130 °C), Yield 91% (0.072 g); ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.42 (d, 2H, J = 8 Hz), 7.73 (s, 2H), 7.42 (d, 2H, J = 8 Hz), 7.34−7.31 (m, 2H), 7.30−7.27 (m, 2H), 7.25−7.21 (m, 4H), 6.94−6.91 (m, 2H), 6.84−6.82 (m, 4H), 4.53−4.51 (m, 4H), 4.31−4.29 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 185.0, 158.1, 136.7, 134.6, 129.7, 127.4, 123.3, 122.7, 122.1, 121.5, 117.9, 114.5, 109.5, 66.3, 46.2; IR (KBr): 2970, 1597, 1517, 1494, 1438, 1382, 1363, 1300, 1235, 1187, 1080, 931, 882, 827, 792, 740, 687, 569, 509 cm^{-1}; HRMS (ESI): calcd. for $C_{33}H_{29}N_2O_3$ $[M + H]^+$ 501.2178; found 501.2180.

*Bis(1-benzyl-5-methoxy-1H-indol-3-yl)methanone (**2k**).* Isolated (R_f = 0.25, EtOAc/petroleum ether, 1:3 v/v) as a colorless solid (mp. 242−244 °C), yield 88% (0.069 g); ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.93 (d, 2H, J = 2.5 Hz), 7.59 (s, 2H), 7.32−7.25 (m, 6H), 7.18 (d, 2H, J = 9 Hz), 7.13−7.11 (m, 4H), 6.91−6.89 (m, 2H), 5.31 (s, 4H), 3.88 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 185.3, 156.2, 136.3, 134.1, 132.1, 129.0, 128.3, 128.2, 127.0, 117.6, 114.4, 111.0, 103.4, 55.9, 50.9; HRMS (ESI): calcd. for $C_{33}H_{29}N_2O_3$ $[M + H]^+$ 501.2178; found 501.2173.

*3,3′-Carbonylbis(1-benzyl-1H-indole-5-carbonitrile) (**2l**).* Isolated (R_f = 0.25, EtOAc/petroleum ether, 1:3 v/v) as a brown solid (mp. 208−210 °C), yield 97% (0.077 g); ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.71−8.70 (m, 2H), 7.72 (s, 2H), 7.52 (d, 1H, J = 2 Hz), 7.50 (d, 1H, J = 1.5 Hz), 7.41−7.39 (m, 2H), 7.38−7.37 (m, 1H), 7.36 (s, 1H), 7.35−7.34 (m, 2H), 7.33−7.32 (m, 2H), 7.15−7.13 (m, 4H), 5.38 (s, 4H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$ and 2- drops of DMSO-d_6): δ (ppm) 182.5, 137.6, 136.0, 135.9, 134.8, 128.2, 127.4, 126.9, 126.8, 126.4, 126.1, 125.3, 119.2, 116.2, 50.0; HRMS (ESI): calcd. For $C_{33}H_{23}N_4O$ $[M + H]^+$ 491.1872; found 491.1871.

*Bis(1-benzyl-5-nitro-1H-indol-3-yl)methanone (**2m**).* Isolated (R_f = 0.25, EtOAc/petroleum ether, 1:3 v/v) as a yellow solid (mp. 256−258 °C), yield 35% (0.028 g); ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 9.08 (d, 2H, J = 2 Hz), 8.07−8.05 (m, 2H), 7.75 (s, 2H), 7.39−7.36 (m, 1H), 7.35−7.33 (m, 4H), 7.30 (d, 3H, J = 9.5 Hz), 7.18−7.17 (m, 4H), 5.40 (s, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$ and a drop of DMSO-d_6): δ (ppm) 182.8, 143.7, 139.7, 136.3, 134.9, 129.4, 128.8, 127.2, 126.6, 119.3, 119.1, 110.4, 51.3; HRMS (ESI): calcd. For $C_{31}H_{23}N_4O_5$ $[M + H]^+$ 531.1668; found 531.1669.

*Bis(1-benzyl-5-bromo-1H-indol-3-yl)methanone (**2n**).* Isolated (R_f = 0.25, EtOAc/petroleum ether, 1:3 v/v) as a brown solid (mp. 208−210 °C), yield 90% (0.071 g); ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.54 (d, 2H, J = 1.5 Hz), 7.59 (s, 2H), 7.34−7.33 (m, 2H), 7.32 (d, 2H, J = 2.5 Hz), 7.31−7.29 (m, 4H), 7.14 (s, 1H), 7.13−7.12 (m, 4H), 7.11 (s, 1H), 5.31 (s, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 183.9, 135.7, 134.5, 129.2, 128.9, 128.4, 127.0, 126.5, 125.1, 117.1, 115.9, 111.6, 51.0; IR (KBr): 1590, 1518, 1458, 1388, 1167, 1054, 821, 789, 744, 728, 699, 638, 599, 562, 495 cm^{-1}; HRMS (ESI): calcd. for $C_{31}H_{23}Br_2N_2O$ $[M + H]^+$ 597.0177; found 597.0166.

*Bis(1-benzyl-6-bromo-1H-indol-3-yl)methanone (**2o**).* Isolated (R_f = 0.25, EtOAc/petroleum ether, 1:3 v/v) as a yellow solid (mp. 236−238 °C), yield 95% (0.073 g); ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.22 (d, 2H, J = 8.5 Hz), 7.55 (s, 2H), 7.46 (d, 2H, J = 1.5 Hz), 7.38 (d, 1H, J = 1 Hz), 7.36 (d, 1H, J = 2 Hz), 7.35−7.33 (m, 2H), 7.32−7.31 (m, 3H), 7.30−7.29 (m, 1H), 7.12−7.10 (m, 4H), 5.27 (s, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 184.2, 137.9, 135.6, 134.2, 129.2, 128.4, 127.0, 126.2, 125.6, 123.8, 117.8, 117.2, 113.1, 50.7; HRMS (ESI): calcd. for $C_{31}H_{23}Br_2N_2O$ $[M + H]^+$ 597.0177; found 597.0176.

*Bis(1-benzyl-2-methyl-1H-indol-3-yl)methanone (**2p**).* Isolated (R_f = 0.25, EtOAc/petroleum ether, 1:3 v/v) as a yellow viscous compound, yield 95% (0.076 g); ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.56 (d, 2H, J = 8 Hz), 7.48−7.45 (m, 1H), 7.31−7.30 (m, 3H), 7.28−7.27 (m, 3H), 7.15−7.12 (m, 3H), 7.04−7.02 (m, 6H), 5.39 (s, 4H), 2.47 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 188.2, 142.2, 136.7, 136.5, 133.7, 130.3, 129.0, 128.6, 127.7, 127.1, 126.1, 122.2, 121.5, 121.0, 117.5, 109.5, 46.7, 12.1; HRMS (ESI): calcd. for $C_{33}H_{29}N_2O$ $[M + H]^+$ 469.2280; found 469.2278.

*Bis(1-methyl-1H-pyrrol-2-yl)methanone (**2q**).* Isolated (R_f = 0.5, EtOAc/petroleum ether, 1:3 v/v) as a brown liquid, yield 80% (0.054 g); ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 6.84 (d, 4H, J = 2 Hz), 6.13−6.12 (m, 2H), 3.94 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 176.6, 131.6, 130.2, 120.3, 107.6, 36.8; HRMS (ESI): calcd. for $C_{11}H_{13}N_2O$ $[M + H]^+$ 189.1028; found 189.1028.

*(1-Benzyl-1H-indol-3-yl)(furan-2-yl)methanone (**2r**).* Isolated (R_f = 0.4, EtOAc/petroleum ether, 1:3 v/v) as a yellow viscous compound, yield 71% (0.055 g); ^1H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.54 (d, 1H, J = 8.5 Hz), 8.23 (d, 1H, J = 0.5 Hz), 7.36−7.34 (m, 1H), 7.33−7.31 (m, 3H), 7.30 (s, 1H), 7.28−7.27 (m, 1H), 7.20−7.17 (s, 3H), 6.17 (d, 1H, J = 3.5 Hz), 5.41 (s, 2H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 176.0, 155.7, 153.0, 136.6, 135.8, 129.0, 128.1, 127.8, 127.0, 123.5, 123.0, 122.6,

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118.0, 114.7, 110.0, 108.6, 50.8, 14.1; HRMS (ESI): calcd. for $C_{21}H_{18}NO_2$ $[M + H]^+$ 316.1338; found 316.1337.

(1-Benzyl-1H-indol-3-yl)(1-methyl-1H-pyrrol-2-yl) methanone (**2s**). Isolated (R_f = 0.45, EtOAc/petroleum ether, 1:3 v/v) as a brown solid (mp. 107–109 °C), yield 75% (0.058 g); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.41–8.39 (m, 1H), 7.73 (s, 1H), 7.30–7.25 (m, 5H), 7.24–7.21 (m, 1H), 7.11 (d, 2H, J = 7 Hz), 6.82 (s, 1H), 6.77–6.76 (m, 1H), 6.12–6.11 (m, 1H), 5.30 (s, 2H), 3.97 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 180.8, 137.0, 136.1, 135.3, 132.2, 129.6, 129.0, 128.1, 127.6, 126.9, 123.5, 122.5, 122.3, 118.7, 117.2, 110.1, 107.6, 50.6, 36.7; IR (KBr): 3005, 1595, 1520, 1460, 1412, 1383, 1306, 1234, 1195, 1168, 1055, 1011, 892, 841, 729, 695, 667, 607, 578 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{19}N_2O$ $[M + H]^+$ 315.1497; found 315.1498.

(1-Methyl-1H-indol-3-yl)(1-methyl-1H-pyrrol-2-yl)methanone (**2t**). Isolated (R_f = 0.45, EtOAc/petroleum ether, 1:3 v/v) as a brown solid (mp. 129–131 °C) yield 90% (0.065 g); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.38–8.37 (m, 1H), 7.69 (s, 1H), 7.37–7.35 (m, 1H), 7.34–7.28 (m, 2H), 6.86–6.85 (m, 1H), 6.81–6.80 (m, 1H), 6.16–6.15 (m, 1H), 4.00 (s, 3H), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 180.8, 137.4, 136.0, 132.3, 129.5, 127.4, 123.3, 122.4, 122.1, 118.5, 116.7, 109.6, 107.5, 36.7, 33.4; HRMS (ESI): calcd. for $C_{15}H_{15}N_2O$ $[M + H]^+$ 239.1184; found 239.1185.

(1-Benzyl-1H-indol-3-yl)(2,4,6-trimethoxyphenyl)methanone (**2u**). Isolated (R_f = 0.45, EtOAc/petroleum ether, 1:3 v/v) as a brown solid (mp. 100–102 °C), yield 74% (0.060 g); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.28 (d, 1H, J = 6.5 Hz), 7.49 (s, 1H), 7.30–7.26 (m, 4H), 7.25–7.22 (m, 2H), 7.12–7.10 (m, 2H), 6.17 (s, 2H), 5.29 (s, 2H), 3.85 (s, 3H), 3.69 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 188.6, 161.9, 158.6, 137.7, 137.3, 136.1, 129.0, 128.1, 126.9, 126.7, 123.3, 122.7, 122.6, 119.0, 113.6, 110.2, 90.9, 55.9, 55.5, 50.7; HRMS (ESI): calcd. for $C_{25}H_{24}NO_4$ $[M + H]^+$ 402.1705; found 402.1704.

(1-Methyl-1H-indol-3-yl)(2,4,6-trimethoxyphenyl) methanone (**2v**). Isolated (R_f = 0.45, EtOAc/petroleum ether, 1:3 v/v) as a yellow solid (mp. 162–164 °C), yield 81% (0.060 g); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.29 (d, 1H, J = 4 Hz), 7.38 (s, 1H), 7.31–7.30 (m, 2H), 7.29–7.28 (m, 1H), 6.19 (s, 2H), 3.87 (s, 3H), 3.76 (s, 3H), 3.70 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 188.6, 161.8, 158.4, 138.2, 137.8, 126.4, 123.2, 122.6, 122.5, 118.5, 113.6, 109.6, 90.8, 56.0, 55.5, 33.5; HRMS (ESI): calcd. for $C_{19}H_{20}NO_4$ $[M + H]^+$ 326.1392; found 326.1392.

(1-Benzyl-1H-indol-3-yl)(phenyl)methanone (**2w**). Isolated (R_f = 0.45, EtOAc/petroleum ether, 1:3 v/v) as a yellow solid (mp. 140–142 °C), yield 61% (0.047 g); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.44–8.43 (m, 1H), 7.83–7.81 (m, 2H), 7.62 (s, 1H), 7.53–7.52 (m, 1H), 7.48–7.45 (m, 2H), 7.35–7.31 (m, 3H), 7.31–7.29 (m, 3H), 7.14–7.13 (m, 2H), 5.37 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 191.0, 140.9, 137.3, 137.2, 135.9, 131.3, 129.1, 128.8, 128.4, 128.2, 127.5, 126.9, 123.9, 122.9, 116.2, 110.3, 50.9; HRMS (ESI): calcd. for $C_{22}H_{18}NO$ $[M + H]^+$ 312.1388; found 312.1393.

(1-Methyl-1H-indol-3-yl)(phenyl)methanone (**2x**). Isolated (R_f = 0.45, EtOAc/petroleum ether, 1:3 v/v) as a brown solid (mp. 112–114 °C), yield 78% (0.056 g); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.43–8.41 (m, 1H), 7.80 (d, 2H, J = 7.5 Hz), 7.54–7.50 (m, 2H), 7.48–7.45 (m, 2H), 7.35–7.32 (m, 3H), 3.82 (m, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 190.7, 140.7, 137.9, 137.4, 130.9, 128.5, 128.2, 127.0, 123.4, 122.5, 122.4, 115.2, 109.6, 33.3; IR (KBr): 3046, 2933, 1611, 1572, 1521, 1467, 1391, 1367, 1265, 1230, 1124, 1073, 1007, 927, 872, 840, 790, 772, 715, 693, 666, 607, 572, 539 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{14}NO$ $[M + H]^+$ 236.1075; found 236.1075.

(1-Methyl-1H-pyrrol-2-yl)(phenyl)methanone (**2y**). Isolated (R_f = 0.5, EtOAc/petroleum ether, 1:3 v/v) as a yellow solid (mp. 261–263 °C), yield 83% (0.056 g); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.82–7.80 (m, 2H), 7.53–7.50 (m, 1H), 7.46–7.43 (m, 2H), 7.19–7.18 (m, 1H), 6.69–6.68 (m, 1H), 6.64–6.63 (m, 1H), 3.71 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 190.7, 140.2, 131.3, 129.0, 128.9, 128.2, 124.7, 123.4, 111.2, 36.7; HRMS (ESI): calcd. for $C_{12}H_{11}NO$ $[M + H]^+$ 186.0919; found 186.0918.

Benzophenone (**2z**). Isolated (R_f = 0.3), EtOAc/petroleum ether, 1:3 v/v as a colorless solid (mp. 50–52 °C), yield 78% (0.052 g); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.74–7.72 (m, 4H), 7.53–7.50 (m, 2H), 7.42–7.39 (m, 4H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ (ppm) 196.9, 137.7, 132.5, 130.2, 128.4; HRMS (ESI): calcd. for $C_{13}H_{11}O$ $[M + H]^+$ 183.0810; found 183.0815.

Bis(3,5-dimethoxyphenyl)methanone (**2aa**). Isolated (R_f = 0.3, EtOAc/petroleum ether, 1:3 v/v) as a colorless solid (mp. 146–148 °C), yield 98% (0.075g); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.50–7.48 (m, 2H), 6.50–6.48 (m, 2H), 6.42 (s, 2H), 3.84 (s, 6H), 3.66 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 193.0, 163.4, 160.1, 132.5, 123.8, 104.4, 98.4, 55.6, 55.4; HRMS (ESI): calcd. for $C_{17}H_{19}O_5$ $[M + H]^+$ 303.1323; found 303.1326.

Bis(4-(dimethylamino)phenyl)methanone (**2ab**). Isolated (R_f = 0.3, EtOAc/petroleum ether, 1:3 v/v) as a gray solid (mp. 164–166 °C), yield 86% (0.064 g); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.77–7.75 (m, 4H), 6.70–6.68 (m, 4H), 3.05 (s, 12H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 194.1, 152.8, 132.3, 126.4, 110.7, 40.2; HRMS (ESI): calcd. for $C_{17}H_{21}N_2O$ $[M + H]^+$ 269.1654; found 269.1655.

Bis(4-(diethylamino)phenyl)methanone (**2ac**). Isolated (R_f = 0.3, EtOAc/petroleum ether, 1:3 v/v) as a brown solid (mp. 177–178 °C), yield 82% (0.064 g); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.76–7.73 (m, 4H), 6.66–6.63 (m, 4H), 3.44–3.40 (m, 8H), 1.21 (t, 12H, J = 8.5 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 193.6, 150.4, 132.6, 125.7, 110.1, 44.5, 12.7; HRMS (ESI): calcd. for $C_{21}H_{29}N_2O$ $[M + H]^+$ 325.2280; found 325.2282.

Anthracen-9-yl(phenyl)methanone (**2ad**). Isolated (R_f = 0.3, EtOAc/petroleum ether, 1:3 v/v) as a yellow solid (mp. 101–103 °C), yeld 80% (0.061 g); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.49 (s, 1H), 7.99 (d, 2H, J = 8.5 Hz), 7.74 (d, 2H, J = 7.5 Hz), 7.65–7.63 (m, 2H), 7.52–7.48 (m, 1H), 7.41–7.38 (m, 2H), 7.34–7.30 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 200.3, 138.2, 134.1, 131.1, 130.2, 128.9, 128.7, 128.5, 126.6, 125.6, 125.4; IR (KBr): 3053, 2921, 2850, 1736, 1662, 1594, 1447, 1347, 1309, 1285, 1264, 1224, 1171, 1049, 1021, 898, 845, 812, 733, 703, 664, 621, 600, 557, 529 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{15}O$ $[M + H]^+$ 283.1123; found 283.1121.

Phenanthren-9-yl(phenyl)methanone (**2ae**). Isolated (R_f = 0.3, EtOAc/petroleum ether, 1:3 v/v) as a yellow solid (mp. 123–125 °C), yield 85% (0.064 g); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.65 (d, 1H, J = 8.5 Hz), 8.61 (d, 1H, J = 8 Hz), 8.01 (d, 1H, J = 8 Hz), 7.84 (d, 2H, J = 8.5 Hz), 7.77 (d, 1H, J = 7 Hz), 7.74 (s, 1H), 7.64–7.61 (m, 1H), 7.60–7.57 (m, 1H), 7.53–7.47 (m, 3H), 7.37–7.34 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 198.0, 138.3, 135.4, 133.4, 131.4, 130.7, 130.5, 130.1, 129.6, 126.4, 129.2, 128.6, 128.4, 127.3 (2), 126.7, 123.0, 122.8; IR (KBr): 3058, 1736, 1653, 1595, 1577, 1527, 1493, 1447, 1315, 1251, 1210, 1174, 1058, 1023, 881, 844, 745, 720, 700, 671, 615, 579, 506 cm^{-1}; HRMS (ESI): calcd. for $C_{21}H_{15}O$ $[M + H]^+$ 283.1123; found 283.1123.

(6-Methoxynaphthalen-2-yl)(phenyl)methanone (**2af**). Isolated (R_f = 0.3, EtOAc/petroleum ether, 1:3 v/v) as pink solid (mp. 121–123 °C), yield 70% (0.052 g); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.12 (d, 1H, J = 1.5 Hz), 7.86–7.84 (m, 1H), 7.76–7.46 (m, 2H), 7.73–7.74 (m, 2H), 7.53–7.50 (m, 1H), 7.44–7.40 (m, 2H), 7.12–7.09 (m, 2H), 3.87 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 196.7, 159.8, 138.3, 137.1, 132.7, 132.2, 132.1, 131.1, 130.0, 128.4, 127.7, 127.1, 126.6, 119.8, 105.8, 55.5; IR (KBr): 3004, 2844, 1646, 1617, 1594, 1476, 1436, 1385, 1304, 1211, 1167, 1078, 1028, 914, 863, 819, 715, 695, 633, 587, 528 cm^{-1}; HRMS (ESI): calcd. for $C_{18}H_{15}O_2$ $[M + H]^+$ 263.1072; found 263.1073.

(3,5-Dimethoxyphenyl)(phenyl)methanone (**2ag**). Isolated (R_f = 0.3, EtOAc/petroleum ether, 1:3 v/v) as a yellow solid (mp. 133–135 °C), yield 85% (0.062g); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.73–7.71 (m, 2H), 7.50–7.47 (m, 1H), 7.39–7.36 (m, 2H), 6.83 (d, 2H, J = 2 Hz), 6.59–6.58 (m, 1H), 3.73 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 196.4, 160.6, 139.5, 137.6, 132.5, 130.1, 128.3, 107.9, 104.8, 55.6; IR (KBr): 2937, 2837, 1657, 1589, 1451,

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1424, 1349, 1325, 1297, 1241, 1203, 1152, 1061, 986, 924, 845, 810, 721, 696, 662, 538 cm^{-1}; HRMS (ESI): calcd. for $C_{15}H_{15}O_3$ $[M + H]^+$ 243.1021; found 243.1021.

*Di(1H-indol-3-yl)methanone (**2g**).* Isolated (R_f = 0.2, EtOAc/petroleum ether, 1:1 v/v) as a colorless solid (mp. 305−307 °C), yield 37% (0.022 g) in case of one-pot reaction from **1a** and 85% (0.050 g) from **2a** with KO^{t}Bu/DMSO under O_2; ^{1}H NMR (500 MHz, $CDCl_3$ and a drop of DMSO-d_6): δ (ppm) 10.98 (s, 2H), 8.36−8.35 (m, 2H), 7.78−7.77 (m, 2H), 7.47−7.43 (m, 2H), 7.25−7.21 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$ and a drop of DMSO-d_6): δ (ppm) 185.6, 136.5, 131.0, 126.3, 122.5, 121.5, 121.1, 117.7, 111.4; HRMS (ESI): calcd. for $C_{17}H_{13}N_2O$ $[M + H]^+$ 261.1028; found 261.1028.

*(1-Benzyl-1H-indol-3-yl)(1H-indol-3-yl)methanone (**3**).* Isolated (R_f = 0.3, EtOAc/petroleum ether, 1:1 v/v) as pinkish solid (mp. 248−150 °C), yield 58% (0.046 g); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 10.91 (s, 1H), 8.41−8.38 (m, 1H), 8.35−8.33 (m, 1H), 7.80−7.78 (m, 2H), 7.47−7.45 (m, 1H), 7.41−7.40 (m, 1H), 7.35−7.29 (m, 3H), 7.28−7.23 (m, 4H), 7.18−7.16 (m, 2H), 5.40 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$ and a drop of DMSO-d_6): δ (ppm) 184.4, 136.1, 135.8, 133.6, 130.7, 128.1, 127.1, 126.7, 126.1, 125.8, 122.4, 122.1, 121.5, 121.0 (2), 120.6, 117.0, 116.8, 111.1, 109.5, 49.7; HRMS (ESI): calcd. for $C_{24}H_{19}N_2O$ $[M + H]^+$ 351.1497; found 351.1496.

*Bis(6-bromo-1H-indol-3-yl)methanone (**4**).* Isolated (R_f = 0.2, EtOAc/petroleum ether, 1:1 v/v) as a yellow solid (mp 330−332 °C), yield 77% (0.054 g); ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 11.90 (s, 2H), 8.14 (d, 2H, J = 2.5 Hz), 8.10 (d, 2H, J = 8.5 Hz), 7.60 (d, 2H, J = 1.5 Hz), 7.25−7.23 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6): δ (ppm) 184.0, 137.4, 132.9, 125.5, 124.0, 123.1, 116.5, 115.2, 114.6; HRMS (ESI): calcd. for $C_{17}H_{11}Br_2N_2O$ $[M + H]^+$ 416.9238; found 416.9235.

*3,3′-(Ethene-1,1-diyl)bis(1-benzyl-1H-indole) (**5**).* Isolated (R_f = 0.6, EtOAc/petroleum ether, 1:5 v/v) as a colorless solid (mp. 158−160 °C), yield 83% (0.083 g); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.77 (d, 2H, J = 8 Hz), 7.30−7.26 (m, 6H), 7.25−7.22 (m, 2H), 7.20−7.16 (m, 4H), 7.14−7.13 (m, 4H), 7.11−7.07 (m, 2H), 5.58 (s, 2H), 5.28 (s, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 137.4, 137.1, 135.7, 128.8, 128.7, 128.4, 127.7, 127.3, 126.9, 126.5, 122.0, 121.1, 119.8, 118.1, 110.0, 109.9, 50.1; HRMS (ESI): calcd. for $C_{32}H_{27}N_2$ $[M + H]^+$ 439.2174; found 439.2172.

*Bis(1-benzyl-1H-indol-3-yl)methanethione (**6**).* Isolated (R_f = 0.6, EtOAc/petroleum ether, 1:5 v/v) as a brown solid (mp. 213−215 °C), yield 77% (0.080 g); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.51−8.49 (m, 2H), 7.61 (s, 2H), 7.35−7.29 (m, 8H), 7.28−7.21 (m, 4H), 7.18−7.16 (m, 4H), 5.29 (s, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 212.0, 137.7, 135.9, 133.6, 129.1, 128.2, 127.9, 127.2, 123.8, 122.7, 122.6, 110.3, 50.7; HRMS (ESI): calcd. for $C_{31}H_{25}N_2S$ $[M + H]^+$ 457.1738; found 457.1735

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online supporting material.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c02519.

All experimental and characterization data; copies of spectra; and crystallographic data of **2a** have been deposited at the CCDC under 2189305 (PDF)

Accession Codes

CCDC 2189305 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Genovino, J.; Lütz, S.; Sames, D.; Toure, B. B. Complementation of Biotransformations with Chemical C−H Oxidation: Copper-Catalyzed Oxidation of Tertiary Amines in Complex Pharmaceuticals. *J. Am. Chem. Soc.* **2013**, *135*, 12346−12352. (b) Cavani, F.; Teles, J. H. Sustainability in Catalytic Oxidation: An Alternative Approach or a Structural Evolution? *ChemSusChem* **2009**, *2*, 508−534.

(2) (a) Hodkova, J.; Vesely, Z.; Koblicova, Z.; Holubek, J.; Trojanek, J. On alkaloids XXV minor alkaloids of poppy capsules. *Lloydia* **1972**, *35*, 61−68. (b) Kleemann, A.; Engel, J.; Kutscher, B.; Reichert, D. *Pharmaceutical Substances*, 4th ed.; Georg Thieme: Stuttgart, Germany, 2001. (c) Nachshon-Kedmi, M.; Yannai, S.; Fares, F. A. Induction of apoptosis in human prostate cancer cell line, PC3, by 3,3′-diindolylmethane through the mitochondrial pathway. *Br. J. Cancer* **2004**, *91*, 1358−1363.

(3) For selected recent reviews, see: (a) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. Recent Advances in Transition Metal Catalyzed Oxidation of Organic Substrates with Molecular Oxygen. *Chem. Rev.* **2005**, *105*, 2329−2364. (b) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. Recent advances in transition-metal catalyzed reactions using molecular oxygen as the oxidant. *Chem. Soc. Rev.* **2012**, *41*, 3381−3430. (c) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. Aerobic Copper-Catalyzed Organic Reactions. *Chem. Rev.* **2013**, *113*, 6234−6458. For selected recent reports, see: (d) Wakaki, T.; Togo, T.; Yoshidome, D.; Kuninobu, Y.; Kanai, M. Palladium-Catalyzed Synthesis of Diaryl Ketones from Aldehydes and (Hetero)-Aryl Halides via C−H Bond Activation. *ACS Catal.* **2018**, *8*, 3123−3128. (e) Dai, W.; Lv, Y.; Wang, L.; Shang, S.; Chen, B.; Li, G.; Gao, S. Highly efficient oxidation of alcohols catalyzed by a porphyrin-inspired manganese complex. *Chem. Commun.* **2015**, *51*, 11268−11271. (f) Kamijo, S.; Tao, K.; Takao, G.; Tonoda, H.; Murafuji, T. Photoinduced Oxidation of Secondary Alcohols Using 4-Benzoylpyridine as an Oxidant. *Org. Lett.* **2015**, *17*, 3326−3329. (g) Shen, D.; Miao, C.; Xu, D.; Xia, C.; Sun, W. Highly Efficient Oxidation of Secondary Alcohols to Ketones Catalyzed by Manganese Complexes of N4 Ligands with H_2O_2. *Org. Lett.* **2015**, *17*, 54−57. (h) Chebolu, R.; Bahuguna, A.; Sharma, R.; Mishra, V. K.; Ravikumar, P. C. An unusual chemoselective oxidation strategy by an unprecedented exploration of an electrophilic center of DMSO: a new facet to classical DMSO oxidation. *Chem. Commun.* **2015**, *51*, 15438−15441. (i) Song, H.; Kang, B.; Hong, S. H. Fe-Catalyzed Acceptorless

Dehydrogenation of Secondary Benzylic Alcohols. *ACS Catal.* **2014**, *4*, 2889−2895.
(4) For selected recent reviews, see: (a) Sun, C.-L.; Li, B.-J.; Shi, Z. J. Direct C−H Transformation via Iron Catalysis. *Chem. Rev.* **2011**, *111*, 1293−1314. (b) Liu, C.; Zhang, H.; Shi, W.; Lei, A. Bond Formations between Two Nucleophiles: Transition Metal Catalyzed Oxidative Cross-Coupling Reactions. *Chem. Rev.* **2011**, *111*, 1780−1824. (c) Campbell, A. N.; Stahl, S. S. Overcoming the "Oxidant Problem": Strategies to Use O2 as the Oxidant in Organometallic C−H Oxidation Reactions Catalyzed by Pd (and Cu). *Acc. Chem. Res.* **2012**, *45*, 851−863. (d) Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A. Oxidative Coupling between Two Hydrocarbons: An Update of Recent C−H Functionalizations. *Chem. Rev.* **2015**, *115*, 12138−12204.
(5) (a) Bonvin, Y.; Callens, E.; Larrosa, I.; Henderson, D. A.; Oldham, J.; Burton, A. J.; Barrett, A. G. M. Bismuth-Catalyzed Benzylic Oxidations with tert-Butyl Hydroperoxide. *Org. Lett.* **2005**, *7*, 4549−4552. (b) Nakanishi, M.; Bolm, C. Iron-Catalyzed Benzylic Oxidation with Aqueous tert-Butyl Hydroperoxide. *Adv. Synth. Catal.* **2007**, *349*, 861−864. (c) Kumar, R. A.; Maheswari, C. U.; Ghantasala, S.; Jyothi, C.; Reddy, K. R. Synthesis of 3H-Quinazolin-4-ones and 4H-3,1-Benzoxazin-4-ones via Benzylic Oxidation and Oxidative Dehydrogenation using Potassium Iodide-tert-Butyl Hydroperoxide. *Adv. Synth. Catal.* **2011**, *353*, 401−410. (d) Liu, P.; Liu, Y.; Wong, E. L.-M.; Xiang, S.; Che, C.-M. Iron oligopyridine complexes as efficient catalysts for practical oxidation of arenes, alkanes, tertiary amines and N-acyl cyclic amines with Oxone. *Chem. Sci.* **2011**, *2*, 2187−2195. (e) Hruszkewycz, D. P.; Miles, K. C.; Thiel, O. R.; Stahl, S. S. Co/NHPI-mediated aerobic oxygenation of benzylic C−H bonds in pharmaceutically relevant molecules. *Chem. Sci.* **2017**, *8*, 1282−1287.
(6) Moriyama, K.; Takemura, M.; Togo, H. Direct and Selective Benzylic Oxidation of Alkylarenes via C−H Abstraction Using Alkali Metal Bromides. *Org. Lett.* **2012**, *14*, 2414−2417.
(7) (a) Catino, A. J.; Nichols, J. M.; Choi, H.; Gottipamula, S.; Doyle, M. P. Benzylic Oxidation Catalyzed by Dirhodium(II,III) Caprolactamate. *Org. Lett.* **2005**, *7*, 5167−5170. (b) Zhang, J.; Wang, Z.; Wang, Y.; Wan, C.; Zheng, X.; Wang, Z. A metal-free catalytic system for the oxidation of benzylic methylenes and primary amines under solvent-free conditions. *Green Chem.* **2009**, *11*, 1973−1978. (c) Peng, H.; Lin, A.; Zhang, Y.; Jiang, H.; Zhou, J.; Cheng, Y.; Zhu, C.; Hu, H. Oxidation and Amination of Benzylic sp3 C−H Bond Catalyzed by Rhenium(V) Complexes. *ACS Catal.* **2012**, *2*, 163−167. (d) Shen, D.; Miao, C.; Wang, S.; Xia, C.; Sun, W. Efficient Benzylic and Aliphatic C−H Oxidation with Selectivity for Methylenic Sites Catalyzed by a Bioinspired Manganese Complex. *Org. Lett.* **2014**, *16*, 1108−1111. (e) Prakash, G. K. S.; Shakhmin, A.; Glinton, K. E.; Rao, S.; Mathew, T.; Olah, G. A. Poly(N-vinylpyrrolidone)−H_2O_2 and poly(4-vinylpyridine)−H_2O_2 complexes: solid H_2O_2 equivalents for selective oxidation of sulfides to sulfoxides and ketones to gem-dihydroperoxides. *Green Chem.* **2014**, *16*, 3616−3622. (f) Eliasen, A. M.; Thedford, R. P.; Claussen, K. R.; Yuan, C.; Siegel, D. A Protocol to Generate Phthaloyl Peroxide in Flow for the Hydroxylation of Arenes. *Org. Lett.* **2014**, *16*, 3628−3631.
(8) Dohi, T.; Takenaga, N.; Goto, A.; Fujioka, H.; Kita, Y. Clean and Efficient Benzylic C−H Oxidation in Water Using a Hypervalent Iodine Reagent: Activation of Polymeric Iodosobenzene with KBr in the Presence of Montmorillonite-K10. *J. Org. Chem.* **2008**, *73*, 7365−7368.
(9) (a) Doering, W. E.; Haines, R. M. Alkoxide-catalyzed Autoxidative Cleavage of Ketones and Esters. *J. Am. Chem. Soc.* **1954**, *76*, 482−486. (b) Boisselier, V.; Coin, C.; Postel, M.; Dunach, E. Molecular oxygen oxidative carbon-carbon bond cleavage of α-ketols catalysed by Bi(III) carboxylates. *Tetrahedron* **1995**, *51*, 4991−4996.
(10) (a) Zhang, N.; Vozzolo, J. Novel C−C Bond Cleavage under Mild, Neutral Conditions: Conversion of Electron-Deficient Aryl Alkyl Ketones to Aryl Carboxylic Esters. *J. Org. Chem.* **2002**, *67*, 1703−1704. (b) Paria, S.; Halder, P.; Paine, T. K. Oxidative Carbon-Carbon Bond Cleavage of a α-Hydroxy Ketone by a Functional Model of 2,4′-Dihydroxyacetophenone Dioxygenase. *Angew. Chem., Int. Ed.* **2012**, *51*, 6195−6199. (c) Zhang, C.; Feng, P.; Jiao, N. Cu-Catalyzed Esterification Reaction via Aerobic Oxygenation and C−C Bond Cleavage: An Approach to α-Ketoesters. *J. Am. Chem. Soc.* **2013**, *135*, 15257−15262.
(11) (a) Becker, J. Y.; Miller, L. L.; Siegel, T. M. Nitrogen-bound and carbon-bound xanthine complexes of ruthenium ammines. *J. Am. Chem. Soc.* **1975**, *97*, 849−853. (b) Ishihara, K.; Yano, T. Synthesis of Carboxamides by LDA-Catalyzed Haller−Bauer and Cannizzaro Reactions. *Org. Lett.* **2004**, *6*, 1983−1986. (c) Kuninobu, Y.; Uesugi, T.; Kawata, A.; Takai, K. Manganese-Catalyzed Cleavage of a Carbon-Carbon Single Bond between Carbonyl Carbon and α-Carbon Atoms of Ketones. *Angew. Chem., Int. Ed.* **2011**, *50*, 10406−10408.
(12) (a) Arisawa, M.; Kuwajima, M.; Toriyama, F.; Li, G. Z.; Yamaguchi, M. Rhodium-Catalyzed Acyl-Transfer Reaction between Benzyl Ketones and Thioesters: Synthesis of Unsymmetric Ketones by Ketone CO−C Bond Cleavage and Intermolecular Rearrangement. *Org. Lett.* **2012**, *14*, 3804−3807. (b) Yoshida, H.; Kishida, T.; Watanabe, M.; Ohshita, J. Fluorenes as new molecular scaffolds for carbon-carbon σ-bond cleavage reaction: acylfluorenylation of arynes. *Chem. Commun.* **2008**, 5963−5965. (c) Dreis, A. M.; Douglas, C. J. Catalytic Carbon−Carbon σ Bond Activation: An Intramolecular Carbo-Acylation Reaction with Acylquinolines. *J. Am. Chem. Soc.* **2009**, *131*, 412−413. (d) Sakurai, H.; Kamiya, I.; Kitahara, H.; Tsunoyama, H.; Tsukudad, T. Aerobic Oxygenation of Benzylic Ketones Promoted by a Gold Nanocluster Catalyst. *Synlett* **2009**, *2009*, 245−248.
(13) Maji, A.; Rana, S.; Akanksha; Maiti, D. Synthesis of Bis(heteroaryl) Ketones by Removal of Benzylic CHR and CO Groups. *Angew. Chem., Int. Ed.* **2014**, *53*, 2428−2432.
(14) Chaudhari, M. B.; Sutar, Y.; Malpathak, S.; Hazra, A.; Gnanaprakasham, B. Transition-Metal-Free C−H Hydroxylation of Carbonyl Compounds. *Org. Lett.* **2017**, *19*, 3628−3631.
(15) For selected examples of oxidations with KOtBu, see: (a) Bai, L.-G.; Zhou, Y.; Zhuang, X.; Zhang, L.; Xue, J.; Lin, X.-L.; Cai, T.; Luo, Q.-L. Base-promoted aerobic oxidation of N-alkyl iminium salts derived from isoquinolines and related heterocycles. *Green Chem.* **2020**, *22*, 197−203. (b) Tan, S.; Li, F.; Park, S.; Kim, S. Transition metal-free aerobic oxidative cleavage of the C−N bonds of α-amino esters. *Org. Chem. Front.* **2019**, *6*, 3854−3858. (c) Barham, J. P.; Coulthard, G.; Emery, K. J.; Doni, E.; Cumine, F.; Nocera, G.; John, M. P.; Berlouis, L. E. A.; McGuire, T.; Tuttle, T.; Murphy, J. A. KO^{t}Bu: A Privileged Reagent for Electron Transfer Reactions? *J. Am. Chem. Soc.* **2016**, *138*, 7402−7410. (d) Muhammad, I.; Balakrishnan, M. H.; Sasidharan, M.; Mannathan, S. Potassium tert-butoxide mediated aerobic hydroxylation of arylboronic acids: an application towards the synthesis of (E)-phenoxy acrylates. *New J. Chem.* **2019**, *43*, 11065−11068. (e) Wang, Z.; Zhang, J.; Shia, J.; Wang, H. KO^{t}Bu-promoted oxidative dimerizations of 2- methylquinolines to 2-alkenyl bisquinolines with molecular oxygen. *RSC Adv.* **2019**, *9*, 30139−30143.
(16) Wang, H.; Wang, Z.; Huang, H.; Tan, J.; Xu, K. KOtBu-Promoted Oxidation of (Hetero)benzylic Csp3−H to Ketones with Molecular Oxygen. *Org. Lett.* **2016**, *18*, 5680−5683.
(17) See supporting information for spectral and crystal data.
(18) Gessner, T.; Mayer, U. *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH: Weinheim, 2000.
(19) Nguyen, H.-H.; Do, T.-H.; Nguyen, T.-H.-T.; Duong, T.-H.; Vo, H.-C.; Do, V.-M.; Nguyen, T.-P.; Sichaem, J.; Nguyen, N.-H.; Nguyen, H. T. Two new phenolic compounds from *Boerhavia erecta* collected in Vietnam. *Nat. Prod. Res.* **2022**, 1−8.
(20) Praveen, P. J.; Parameswaran, P. S.; Majik, M. S. Bis(indolyl)-methane Alkaloids: Isolation, Bioactivity, and Syntheses. *Synthesis* **2015**, *47*, 1827−1837.
(21) Sua′rez, A.; Marti′nez, F.; Sua′rez-Pantiga, S.; Sanz, R. PTSA-Catalyzed Reaction of Indoles with 2-Oxoaldehydes: Synthesis of α, α-Bis(indol-3-yl) Ketones. *ChemistrySelect* **2017**, *2*, 787−790.

https://doi.org/10.1021/acs.joc.2c02519
J. Org. Chem. 2023, 88, 2103−2112

(22) Haddach, A. A.; Kelleman, A.; Deaton-Rewolinski, M. V. An efficient method for the N-debenzylation of aromatic heterocycles. *Tetrahedron Lett.* **2002**, *43*, 399−402.
(23) Holland, D. C.; Kiefel, M. J.; Carroll, A. R. Structure Revisions of the Sponge-Derived Dibrominated Bis-indole Alkaloids, Echinosulfone A and the Echinosulfonic Acids A to D. *J. Org. Chem.* **2020**, *85*, 3490−3496.
(24) By-product was confirmed by NMR and LCMS-ESI, negative mode.

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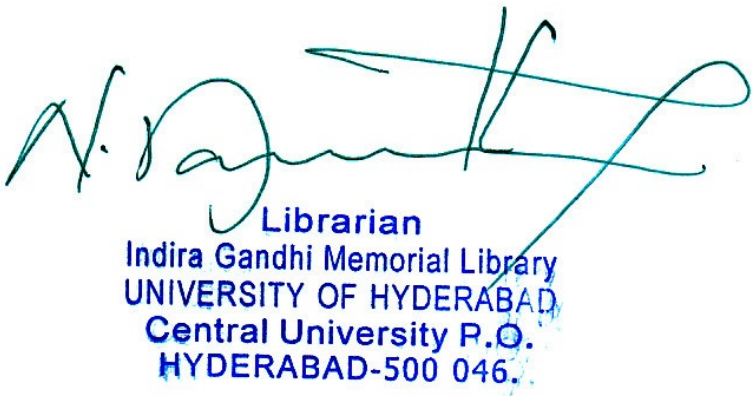
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