Carbocyclization of Alkene-/Alkyne-Tethered Carbonyl Compounds Through *In Situ* Acetal Formation

A Thesis

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DOCTOR OF PHILOSOPHY

In

CHEMISTRY

By

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(Regd. No. 15CHPH27)

Under the Supervision of

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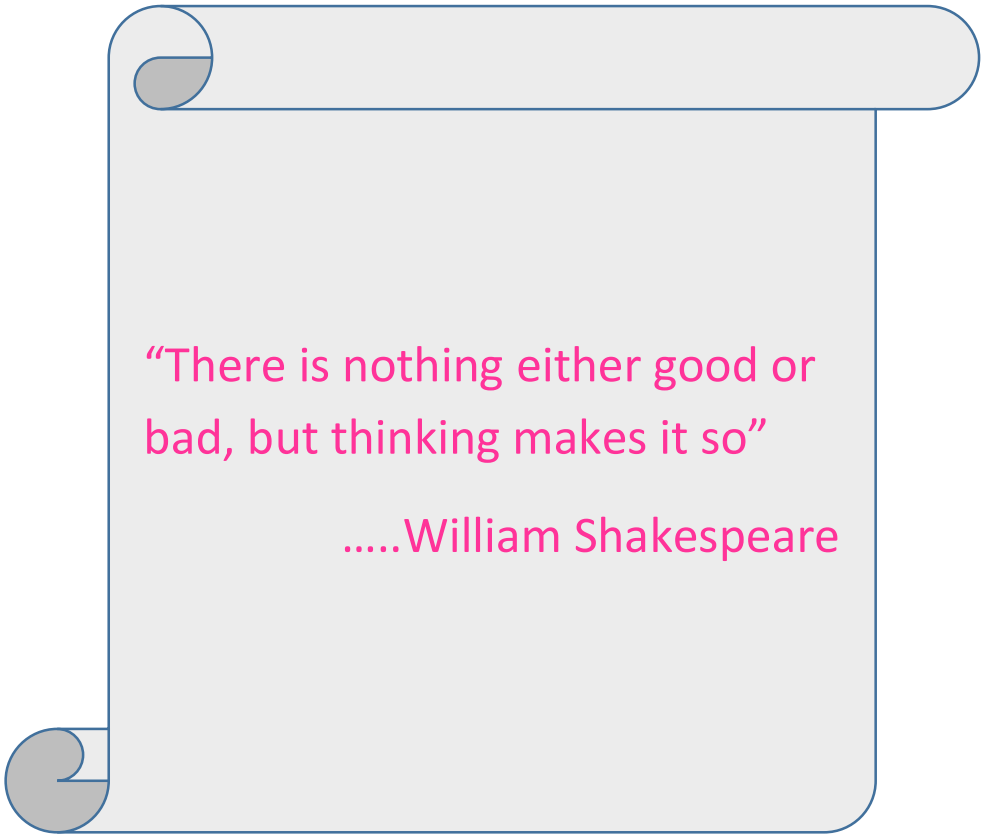
“There is nothing either good or bad, but thinking makes it so”
…..William Shakespeare

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Declaration

I, Golla Ramesh hereby declare that this thesis entitled ***"Carbocyclization of Alkene-/Alkyne-Tethered Carbonyl Compounds Through In Situ Acetal Formation"*** submitted by me under the supervision of **Prof. R. Balamurugan** is a bonafide research work carried out by me in the School of Chemistry, University of Hyderabad, India. I also declare that it has not been submitted previously in part or in full to this University or Institution for the award of any degree or diploma.

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This is to certify that the thesis entitled "**Carbocyclization of Alkene-/Alkyne-Tethered Carbonyl Compounds Through *In Situ* Acetal Formation**" submitted by **Golla Ramesh** bearing Registration Number 15CHPH27 in partial fulfilment of the requirements for award of Doctor of Philosophy in the School of Chemistry is a bonfide work carried out by him under my supervision and guidance.

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2. **Ramesh, G.**; Ramulu, B. V.; Balamurugan, R. *J. Org. Chem.* **2022**, *87*, 8633-8647.
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4. Naveen, N.; **Ramesh. G.**; Balamurugan, R. *ChemistrySelect* **2019**, *4*, 13610-13614

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1. XIII J-NOST Conference-2017; 2. ChemFest-2019; 3. ChemFest-2020.

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Course Code	Name	Credits	Pass/Fail
CY801	Research Proposal	3	Pass
CY805	Instrumental Methods-A	3	Pass
CY501	Spectroscopic Methods for Structure Elucidation	3	Pass
CY402	Physical Organic Chemistry	3	Pass

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Ramesh

Table of Contents

List of Acronyms

2D	**Two dimensional**
Å	Angstrom
ACS	American Chemical Society
AIDS	Acquired immunodeficiency syndrome
Ar	Aryl
BA	Brønsted acid
Bn	Benzyl
bs	Broad singlet (spectral)
***n*-Bu**	*n*-Butyl
***t*-Bu**	*tert*-Butyl
BIM	Bis-indolylmethanes
°C	Degree celsius
calcd	Calculated
cat.	Catalytic
cm^{-1}	wavenumber
CADA	Catalytic asymmetric dearomatization
CCDC	Cambridge Crystallographic Data Centre
***m*-CPBA**	meta-Chloroperoxybenzoic acid
COSY	Correlated spectroscopy
δ	Chemical shift in parts per million
d	Doublet (spectral)
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DCM	Dichloromethane
dd	Doublet of doublet (spectral)
dddd	Doublet of doublet of doublet of doublet (spectral)
DIPA	Diisopropylamine
DMEDA	1,2-Dimethylethylenediamine
DMF	Dimethylformamide
DMOP	2,2-Dimethoxypropane
DOI	Digital object identifier
dq	Doublet of quartet (spectral)
dr	Diastereomeric ratio
dt	Doublet of triplet (spectral)
equiv	Equivalent
ESI	Electrospray ionization
Et	Ethyl

EtOAc	Ethyl acetate
g	Gram(s)
h	Hour(s)
HDAC	Histone deacetylases
HFIP	Hexafluoroisopropanol
HIV	Human immunodeficiency
HMBC	Heteronuclear Multiple Bond Correlation
HRMS	High-resolution mass spectrometry
HSQC	Heteronuclear Single Quantum Coherence
Hz	Hertz
***i*-Pr**	Isopropyl
IR	Infrared
J	Coupling constant (in NMR spectroscopy)
LA	Lewis acid
LR	Laboratory reagent
m	Multiplet (spectral)
MAP	Mitogen-activated protein
Me	Methyl
mg	Milligram(s)
MHz	Megahertz
min	Minute(s)
mL	Millilitre(s)
mmol	Millimole(s)
mp	Melting point
µL	Micrilitre(s)
N_2	Nitrogen
NAD	Nicotinamide adenine dinucleotide
NBS	N-Bromosuccinimide
NHC	N-Heterocyclic carbene
NMR	Nuclear magnetic resonance
NNRTI	Non-Nucleoside Reverse Transcriptase
NOESY	Nuclear Overhauser Effect Spectroscopy
NR	No reaction
ORTEP	Oak Ridge Thermal-Ellipsoid Plot
OTf	Trifluoromethyl
PCC	Pyridinium chlorochromate
Ph	Phenyl
PIFA	Phenyliodine bis(trifluoroacetate)
PTSA	p-Toluenesulfonic acid
PVP	Polyvinylpyrrolidon

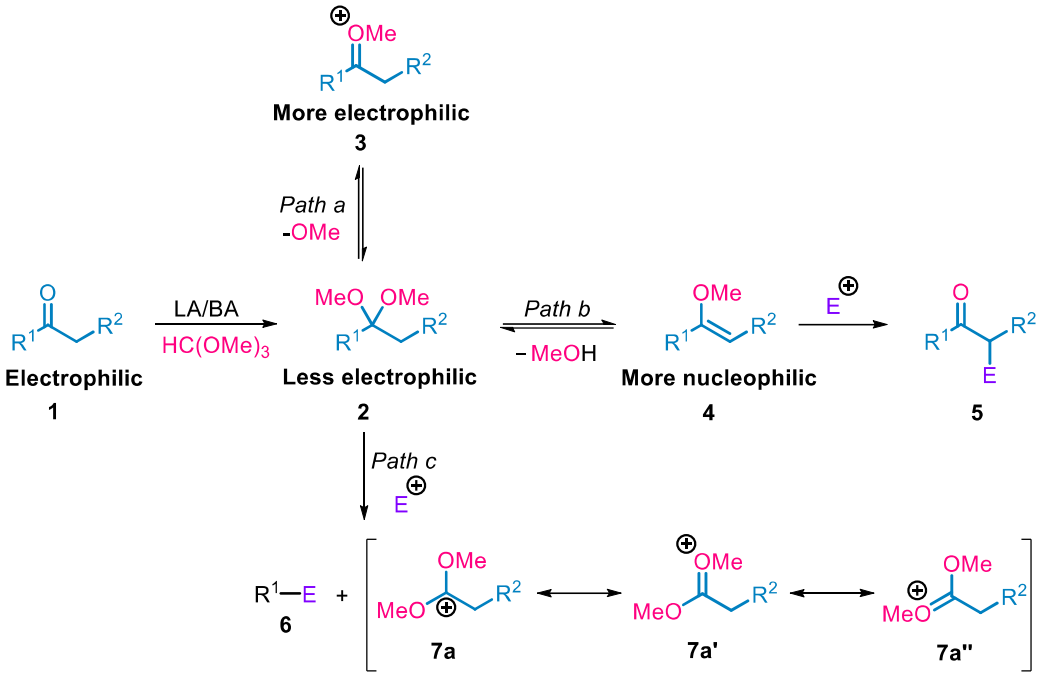
PWA	Phosphotungstic acid
q	Quartet (spectral)
QM	quinone methide
R_f	Retardation factor
rt	Room temperature
s	Singlet (spectral)
t	Triplet (spectral)
td	Triplet of doublet (spectral)
tdd	Triplet of doublet of doublet (spectral)
TEOF	Triethyl orthoformate
TfOH	Triflic acid
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIM	Trisindolylmethanes
TLC	Thin-layer chromatography
TMOF	Trimethyl orthoformate
TMS	Tetramethylsilane
TOF	Time of flight
tt	Triplet of triplet (spectral)
TTBP	2,4,6-Tri-tert-butylpyridine
UV	Ultraviolet
VCH	Verlag Chemie
ZSM-5	Zeolite Socony Mobil–5

Synopsis

This thesis contains four chapters.

Chapter 1: ***In Situ* Formed Acetals in Organic Synthesis**: **A Concise Literature Survey**

Chapter 1 presents the different reaction modes of *in situ* formed acetals and selected important literature. Acetals formed *in situ* by the reaction of carbonyl compounds **1** with alcohols or trialkyl orthoformates (eg. trimethyl orthoformate (TMOF)) in the presence of Lewis/Brønsted acid (LA/BA) catalysts react in three routes. Generally, reactions occurring through more reactive oxocarbenium ion **3** (Scheme 1, *path a*) are more studied. The more nucleophilic enol ether **4** formed from the acetal has also been utilized in several reactions (Scheme 1, *path b*). The applications of the third possibility *i.e.*, the migration/transfer of R^1 group (Scheme 1, *path c*) are limited. In this chapter, reactions developed based on the above pathways are discussed in detail with mechanisms.

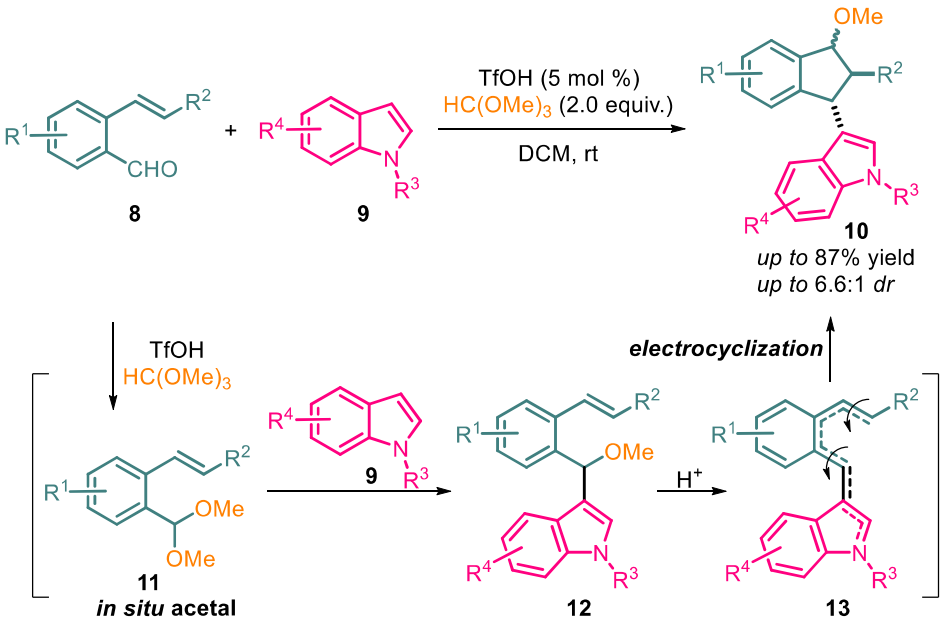


Scheme 1: Different modes of reactions of *in situ* formed acetal

Chapter 2: **Triflic Acid-Catalyzed Synthesis of Indole-Substituted Indane Derivatives *via In Situ* Formed Acetals**

Chapter 2 describes the diastereoselective synthesis of indole-substituted indane derivatives **10** from *o*-alkenylbenzaldehydes **8** and *N*-protected indoles **9** *via in situ* formed acetals under triflic acid catalysis (Scheme 2). In striking contrast to indole's usual reactivity towards

aldehydes of forming bis-indolylmethanes, this transformation involves intramolecular trapping of the carbocation formed after the reaction of one indole molecule. Owing to the importance and ubiquitous nature of the indane core, the construction of indane ring having a biologically active indole ring is always a useful method. The substrate scope has been evaluated with different substrates. Further, from a set of control experiments, the mechanism of the reaction was proposed. This reaction proceeds *via* the formation of oxocarbenium ion generated from acetal **11** derived *in situ* from *o*-alkenylbenzaldehydes **8** and TMOF in the presence of triflic acid. The oxocarbenium ion is then trapped by indole **9** to give bisarylmethyl methyl ether **12**. Finally, intermediate **13** undergoes a conrotatory 4π-electron-5-carbon electrocyclization to afford indole-substituted indane derivative **10**. The *cis* and *trans* isomers of *o*-alkenylbenzaldehydes show different reactivity in this transformation due to their steric environments.

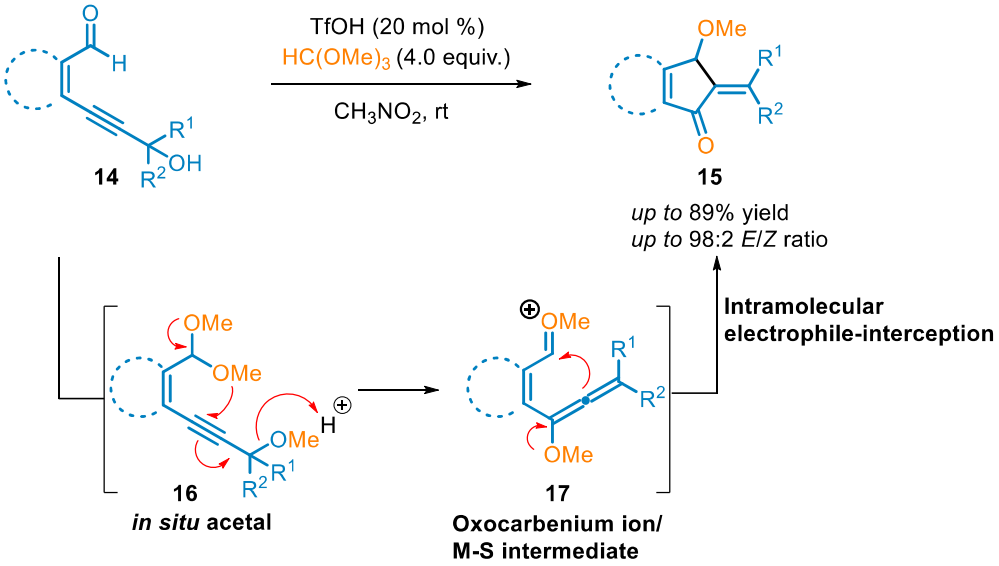


Scheme 2: Synthesis of indole-substituted indanes *via in situ* formed acetals

Chapter 3: **Intramolecular Electrophile Intercepted Meyer-Schuster Rearrangement under Acetalization Conditions**

Chapter 3 demonstrates the synthesis of indanone derivatives **15** *via* intramolecular electrophile intercepted Meyer-Schuster (M-S) rearrangement of *o*-propargyl alcohol benzaldehydes **14** (Scheme 3). Control experiments and NMR studies have been carried out to get more insight into the mechanism of this transformation. This reaction proceeds *via* the formation of acetal **16** *in situ* from *o*-propargyl alcohol benzaldehydes **14** and TMOF in the presence of triflic acid followed by the formation of M-S intermediate **17** which would attack oxocarbenium ion in an intramolecular fashion to afford indanone derivatives **15**. The acetalization conditions allowed even less reactive substrates to undergo the reaction smoothly to provide the desired products.

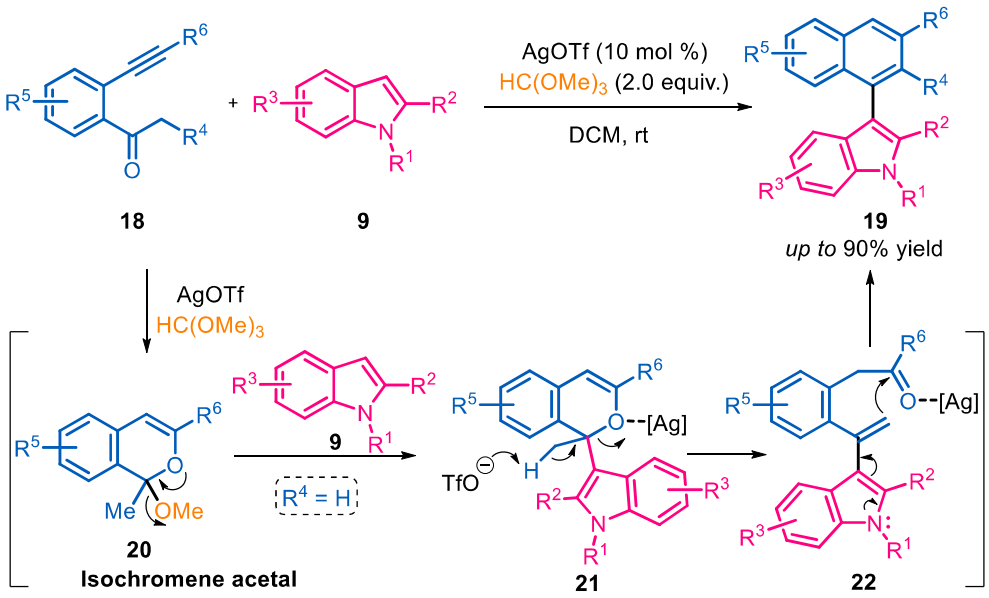
Furthermore, an alkene-aryl atropisomerism was observed in the corresponding products of *o*-propargyl alcohol benzaldehydes having *ortho*-substituents on the aryl ring at the carbinol center. Formation of a polycyclic compound having cyclic acetal, keto, and conjugated carbonyl functions was observed *via* dimerization of the corresponding M-S intermediate with one of the substrates. The product indanone having different functionalities was further functionalized by performing epoxidation, Grignard reaction, Luche's reduction, and allylation.



Scheme 3: Acetal-assisted intramolecular electrophile-intercepted M-S rearrangement

Chapter 4: **Ag(I)-Catalyzed Cyclization of *o*-Alkynylacetophenones for the Synthesis of C3-Naphthyl Indole Derivatives**

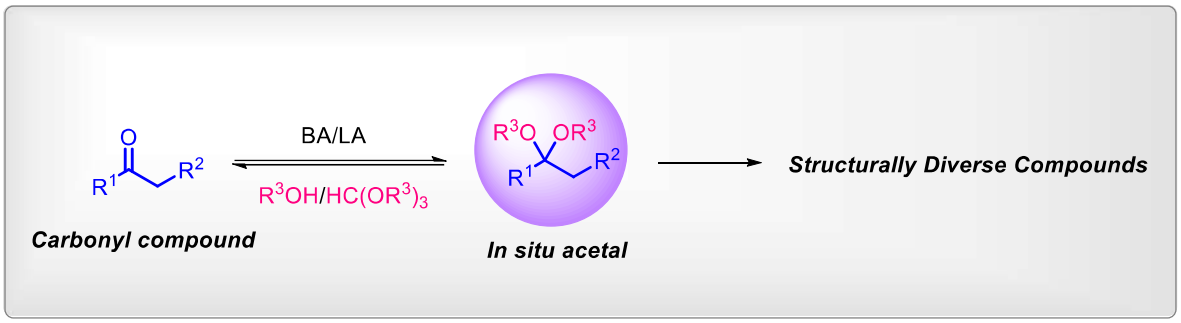
Chapter 4 deals with the synthesis of C3-naphthyl indole derivatives **19** from *o*-alkynylacetophenones **18** and indoles **9** under acetalization conditions using TMOF in the presence of Ag(I) catalyst (Scheme 4). The possible reaction intermediates have been evaluated by conducting control experiments. It involves the *in situ* formation of isochromene acetal **20** from *o*-alkynylacetophenones **18** and TMOF in the presence of AgOTf. The formed acetal reacts with indole **9** to afford isochromen-1-yl-substituted indole derivative **21** followed by skeletal rearrangements to give extended enamine **22** which would cyclize to furnish the product **19**. An alternative mechanism involving acyclic acetal was also proposed for this transformation.



Scheme 4: Ag(I)-Catalyzed synthesis of C3-naphthyl indole derivatives *via in situ* formed acetal

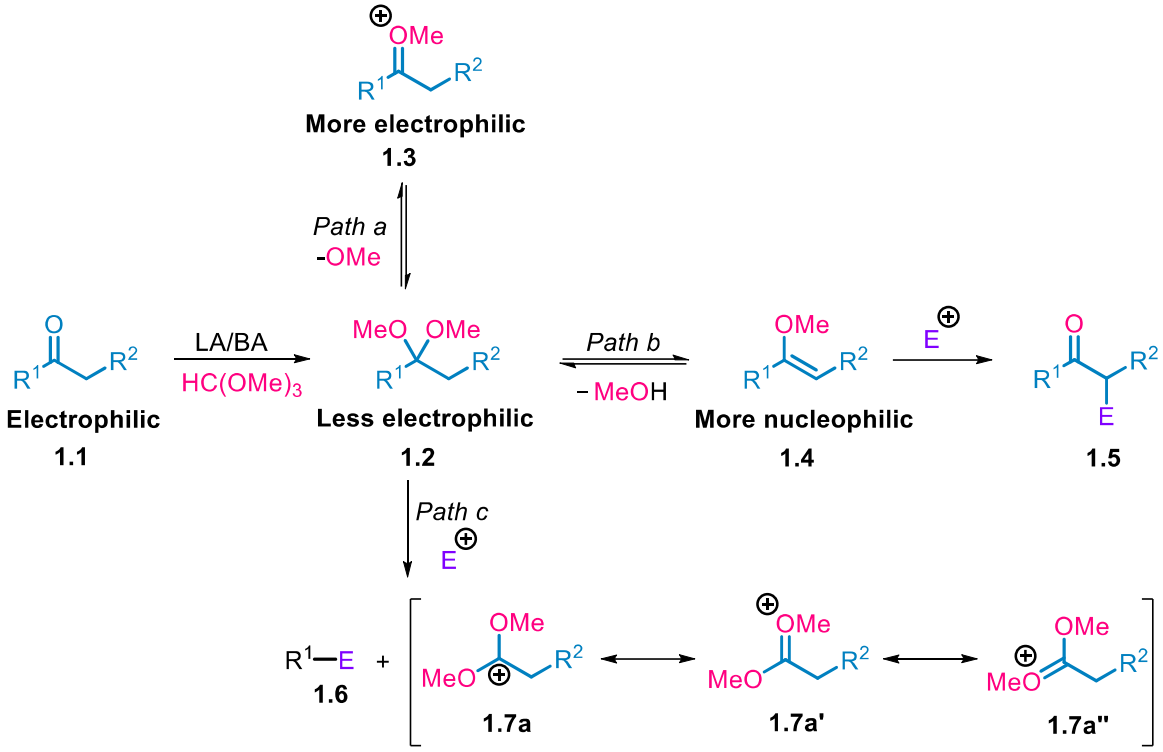
Chapter 1

In Situ Formed Acetals in Organic Synthesis: A Concise Literature Survey



1.1 Introduction

Acetals are a class of protecting groups in synthetic organic chemistry. Being inert to many reaction conditions, they are used as protecting groups for carbonyl compounds in multi-step syntheses.[1] Apart from being used as protecting groups, acetals could be employed in various interesting transformations. These transformations are generally conducted under non-acidic conditions as they undergo facile deprotection under acidic conditions. More electrophilic oxocarbenium ions formed under acidic conditions have extensively been used in nucleophilic addition reactions.[2] The potential drawback associated with the reactions of acetals under acidic conditions is their conversion back to the parent carbonyl compound. However, when acetals are made under the conditions, such drawback could be countered as the concentration of acetal is maintained by regeneration. This chapter briefly reviews the developments that have been made by exploiting *in situ* formed acetals to construct interesting molecular scaffolds.



Scheme 1.1: Different modes of reactions of *in situ* formed acetal

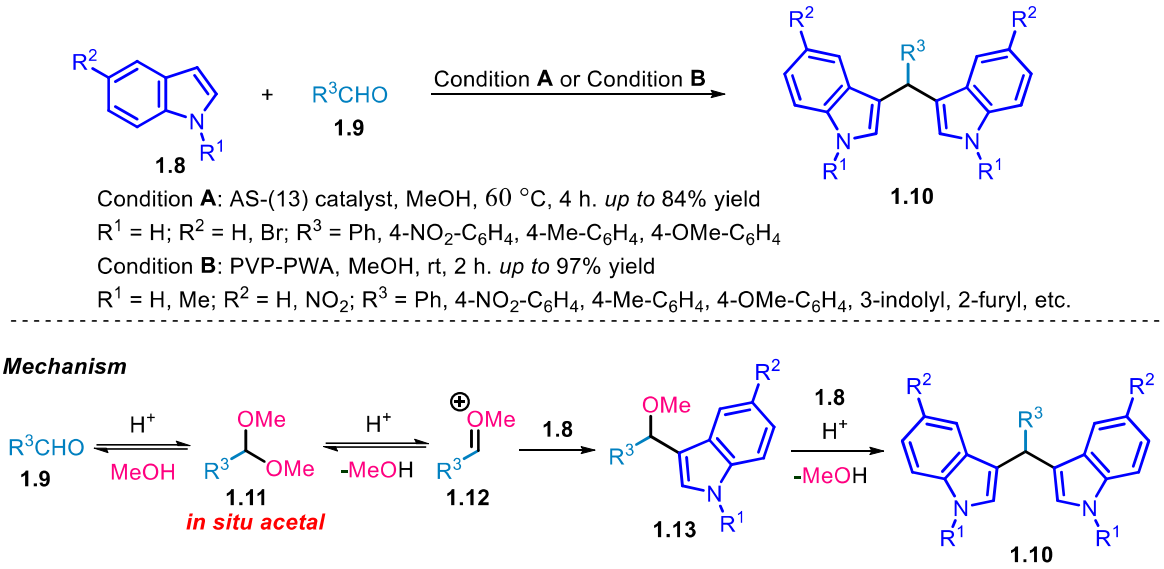
An Acetal **1.2** can easily be generated *in situ* by treating the carbonyl compound **1.1** with MeOH or trialkyl orthoformates (e.g., trimethyl orthoformate (TMOF)) under Lewis/Brønsted acid (LA/BA) catalysis.[3] (Scheme 1.1). A base-promoted acetal formation has also been reported.[4] Typical modes of reactions of this acetal formed *in situ* are mainly of threefold: (1) a more electrophilic and reactive oxocarbenium ion **1.3** could be formed by the removal of one of the methoxy groups of the acetal **1.2** in the presence of LA/BA (Scheme 1.1, *path a*); This

oxocarbenium ion **1.3** will undergo further transformations with various nucleophiles either in intermolecular or intramolecular fashion to afford acyclic or cyclic products respectively, (2) a more nucleophilic enol ether **1.4** could be formed by the elimination of an alcohol (here MeOH), which would react with different electrophiles in either intermolecular fashion to produce α-functionalized compounds or intramolecular fashion to give cyclic products (Scheme 1.1, *path b*) and (3) migration of R^1 group from acetal **1.2** to an electrophilic center would make a new bond and generate a carbocation intermediate which will be stabilized by the two methoxy groups of acetal (Scheme 1.1, path c). The following sections will describe the reactions developed using *in situ* formed acetals.

1.2 Synthetic strategies employing *in situ* formed acetals

1.2.1 Friedel-Crafts-type reactions

Synthesis of bis(indolyl)methanes (BIMs) from aldehydes and indoles is a conventional method. Generally, these reactions proceed slowly and give lower yields.[5] This limitation could be overcome by replacing the aldehydes with corresponding acetals by generating them *in situ* during the reaction. Aldehyde **1.9** generates acetal **1.11** *in situ* upon treatment with methanol in the presence of nanoporous aluminosilicate AS-(13)/polyvinylpyrrolidone (PVP)-phosphotungstic acid (PWA) (Scheme 1.2).[6] The oxocarbenium ion **1.12**, which is formed from acetal **1.11** undergoes Friedel-Crafts reaction with indole **1.8** to give BIM product **1.10**.

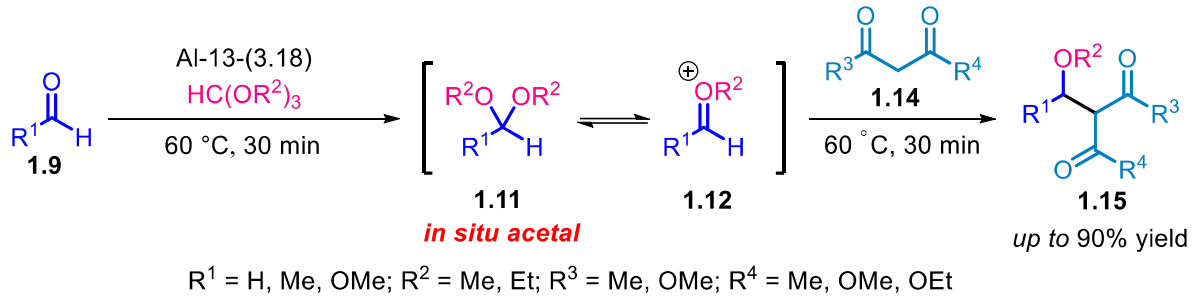


Scheme 1.2: Synthesis of bisindolylmethanes from indoles and aldehydes

1.2.2 Aldol-type reactions

Graham and co-workers reported a direct aldol addition on aldehyde **1.9** for the synthesis of aldol adduct **1.15** catalyzed by nanoporous aluminosilicate catalyst (Scheme 1.3).[7] Aldehyde

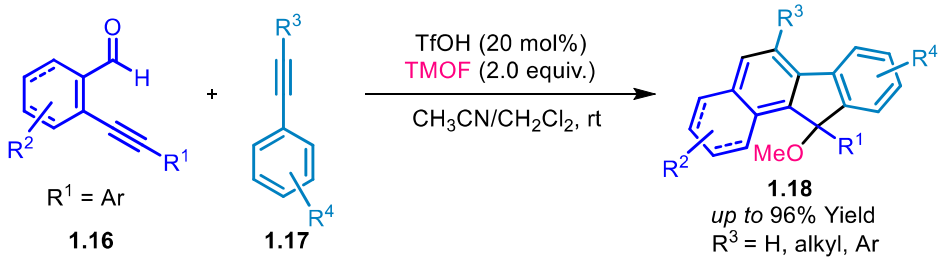
1.9 was reacted with 1,3-dicarbonyl compound **1.14** in the presence of acetalizing agents trialkyl orthoformates, and an aluminosilicate catalyst. By doing so, aldehyde **1.9** will be converted into its acetal **1.11** which will be in equilibrium with the oxocarbenium ion **1.12**. Subsequent aldol addition of 1,3-dicarbonyl compound **1.14** to **1.12** resulted the aldol addition product **1.15**.



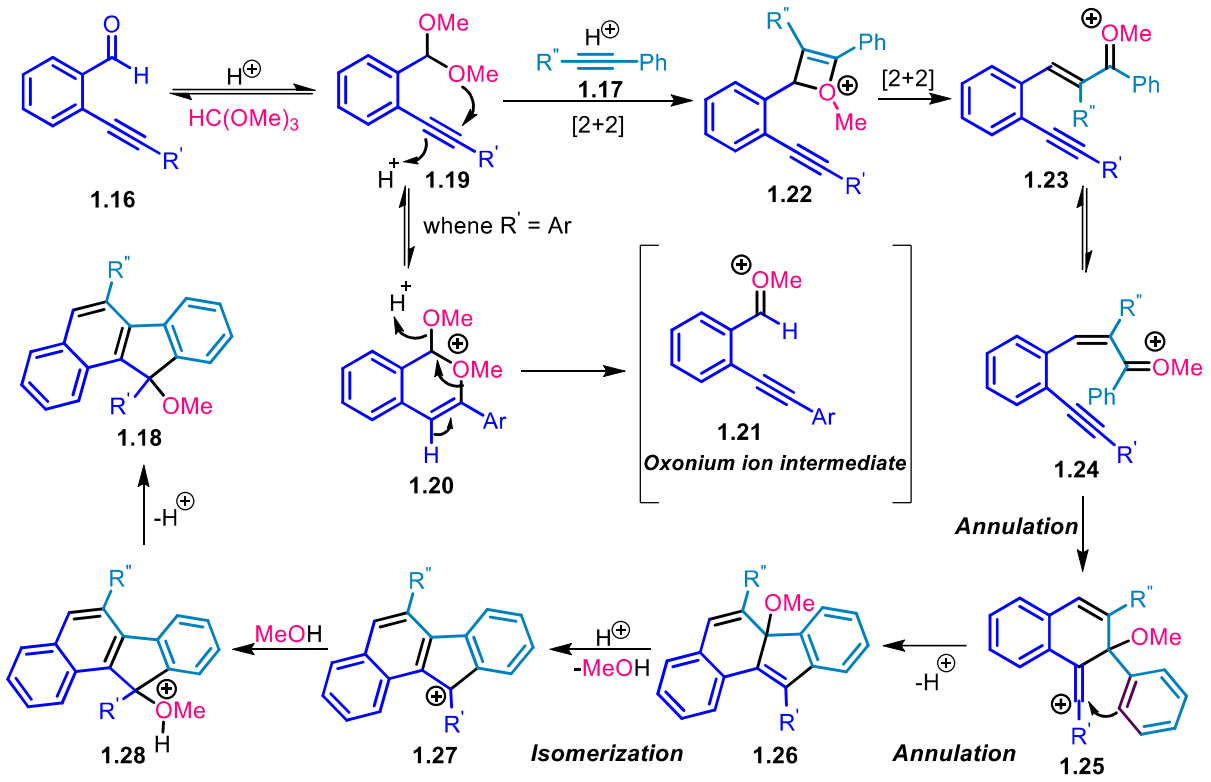
Scheme 1.3: Direct aldol addition of 1,3-dicarbonyl compounds with aldehyde through acetal formation

1.2.3 Acetal-assisted cycloisomerizations

In 2014, our group reported the synthesis of benzo[*a*]fluorene derivatives **1.18** from *o*-alkynylbenzaldehydes **1.16** and arylalkynes **1.17** in the presence of TMOF under TfOH catalysis (Scheme 1.4).[8] This transformation proceeds *via* the formation acetal **1.19** *in situ* followed by heteroalkyne metathesis between the oxocarbenium ion **1.21** and the arylalkyne **1.17** to form oxetene intermediate **1.22**. Ring-opening of **1.22** would afford the enone intermediate **1.23** which will be in equilibrium with its *cis* stereo isomer **1.24**. Intramolecular nucleophilic attack of the alkyne moiety on the enone in intermediate **1.24** gives the vinyl carbocation intermediate **1.25**. Subsequent intramolecular attack of aryl group and isomerization would afford the benzo[*a*]fluorene derivative **1.18**.

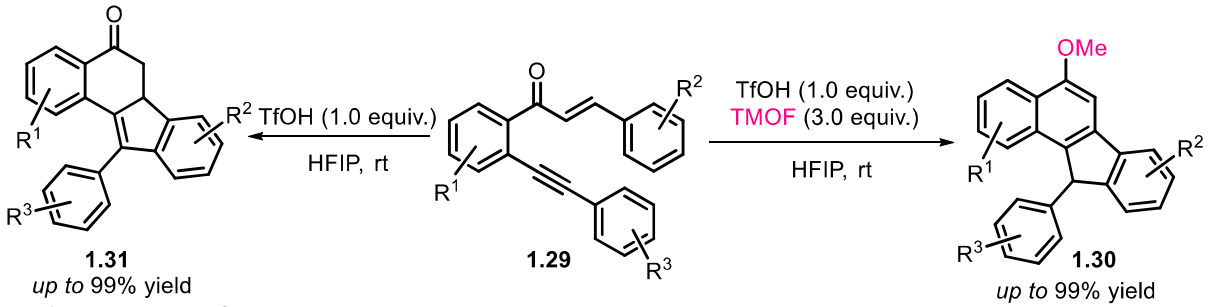


Scheme 1.4: Synthesis of benzo[*a*]fluorene derivatives from *o*-alkynylbenzaldehydes and arylalkynes



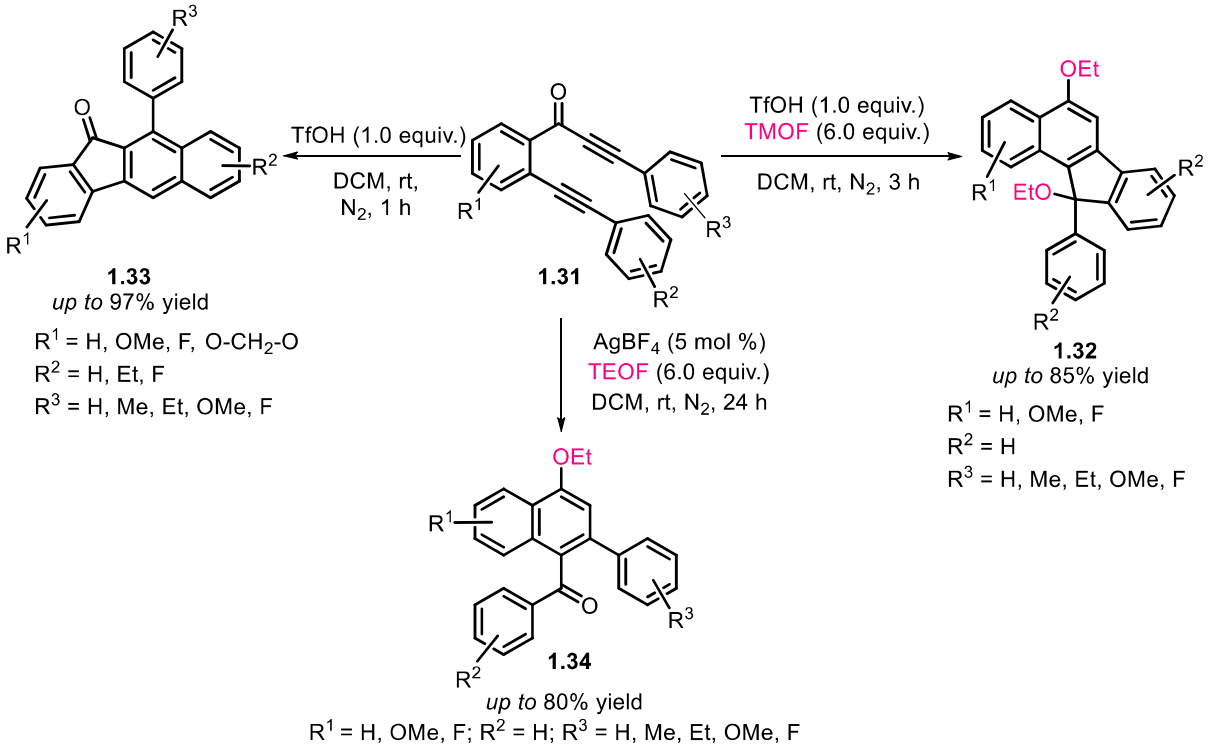
Scheme 1.4: Mechanism for the formation of benzo[*a*]fluorene derivatives from *o*-alkynylbenzaldehydes and arylalkynes

Later, in 2018, our group developed a simple and straightforward method for the synthesis of benzo[*a*]fluorenes **1.30** and benzo[*a*]fluorenones **1.31** from enynones **1.29** in the presence or absence of TMOF respectively using TfOH as the promotor (Scheme 1.5).[9] The reaction involving TMOF proceeds through the formation of oxocarbenium ion *via in situ* generated acetal, 1,4-addition, annulation, and subsequent isomerisation to form benzo[*a*]fluorenes **1.30**. Whereas, the formation of benzo[*a*]fluorenones **1.31** involves the activation of enynone **1.29** by an acid, 1,4-addition, annulation, and keto-enol tautomerism.



Scheme 1.5: Synthesis of benzo[*a*]fluorenes and benzo[*a*]fluorenones

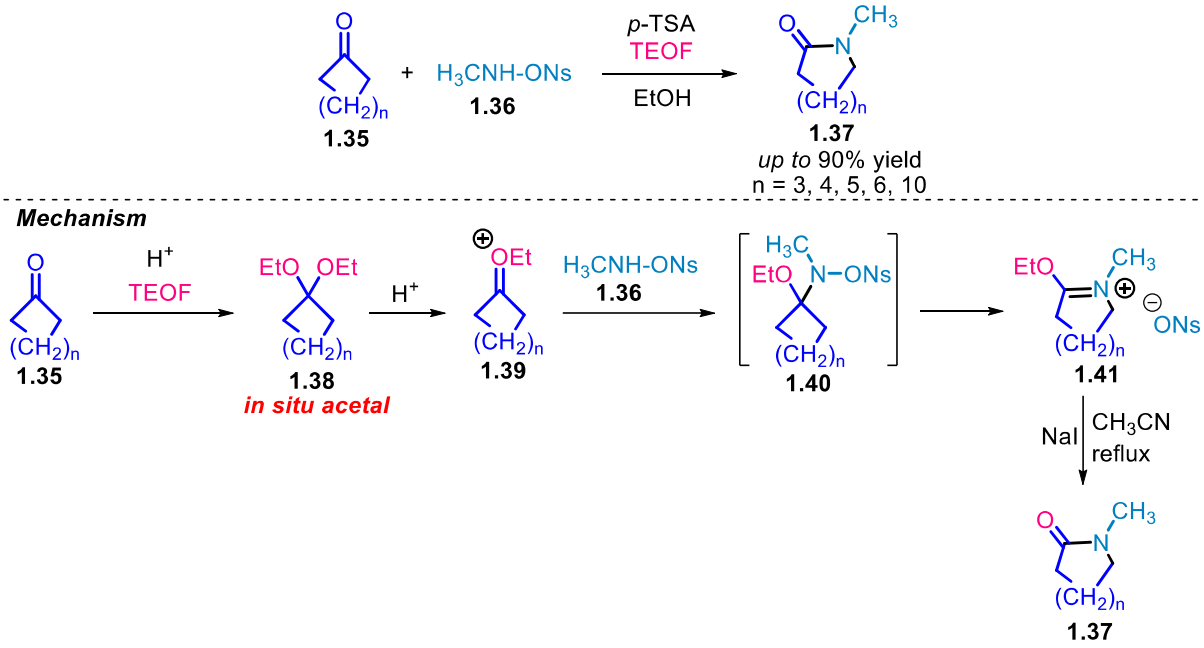
A divergent synthesis of benzo[*a*]fluorenes **1.32**, benzo[*b*]fluorenones **1.33**, and naphthyl ketones **1.34** from aryl-fused 1,6-diyn-3-ones **1.31** was reported by Mou *et al*. (Scheme 1.6).[10] The synthesis of benzo[*a*]fluorenes **1.32**, has been achieved in the presence of stoichiometric TfOH and excess of TMOF. On the other hand, TfOH alone was sufficient to promote the formation of benzo[*b*]fluorenones **1.33**. In addition, synthesis of naphthyl ketones **1.34** was achieved in the presence of TMOF under $AgBF_4$ catalysis. This protocol involves the formation of an oxocarbenium ion *via* an *in situ* generated acetal, annulation, and subsequent cycloisomerization to afford benzo[*a*]fluorenes **1.32** and naphthyl ketones **1.34**. Whereas, the formation of benzo[*b*]fluorenones **1.33** proceeds *via* a radical mechanism.



Scheme 1.6: Synthesis of benzo-fused fluorenes and fluorenones and naphthyl ketones

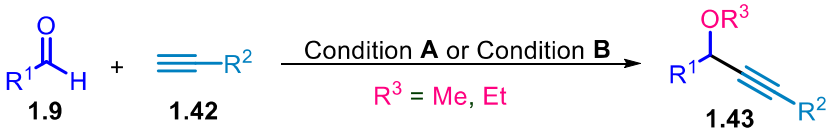
1.2.4 Nucleophilic additions to acetals

Hoffman and Salvador developed a one-pot conversion of ketones **1.35** into *N*-methyl lactams **1.37** in the presence of TEOF under *p*-TSA catalysis (Scheme 1.7).[11] The reaction of ketones **1.35** with TEOF in the presence of *p*-TSA would generate acetal **1.38** *in situ*, which would lose one ethoxy group as ethanol to give oxocarbenium ion **1.39**. Nucleophilic attack of *N*-(((*p*-nitrobenzene)sulfonyl)oxy)methylamine **1.36** furnishes imidate salt **1.41** and subsequent dealkylation of *O*-ethyl imidate salt **1.41** in the presence of sodium iodide in refluxing acetonitrile would lead to *N*-methyl lactam **1.37**.



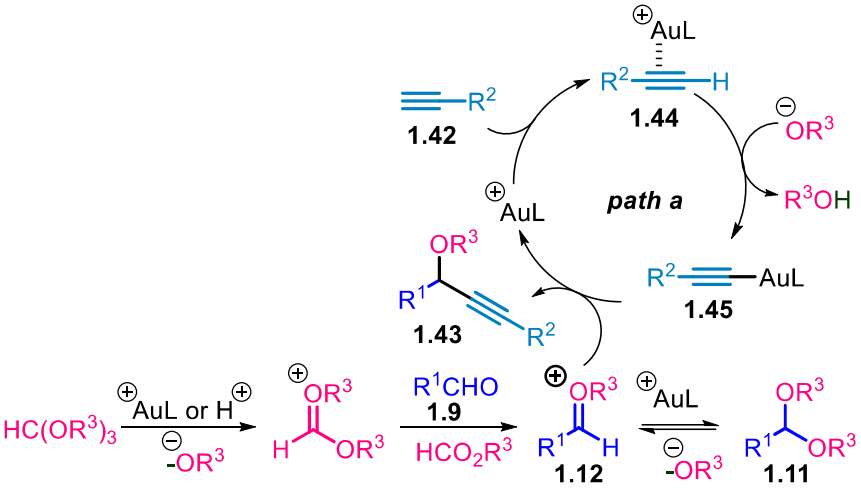
Scheme 1.7: Synthesis of *N*-methyl lactams from ketones

Wang and Cai independently reported the synthesis of propargyl ethers **1.43** from aldehydes **1.9**, terminal alkynes **1.42**, and trialkyl orthoformate under gold catalysis (Scheme 1.8).[12] This reaction would proceed through the formation of gold alkynilide **1.45** which would attack on oxocarbenium ion **1.12** generated from aldehyde **1.9** and trialkyl orthoformate in the presence of gold or acid catalyst to afford propargyl ethers **1.43**.



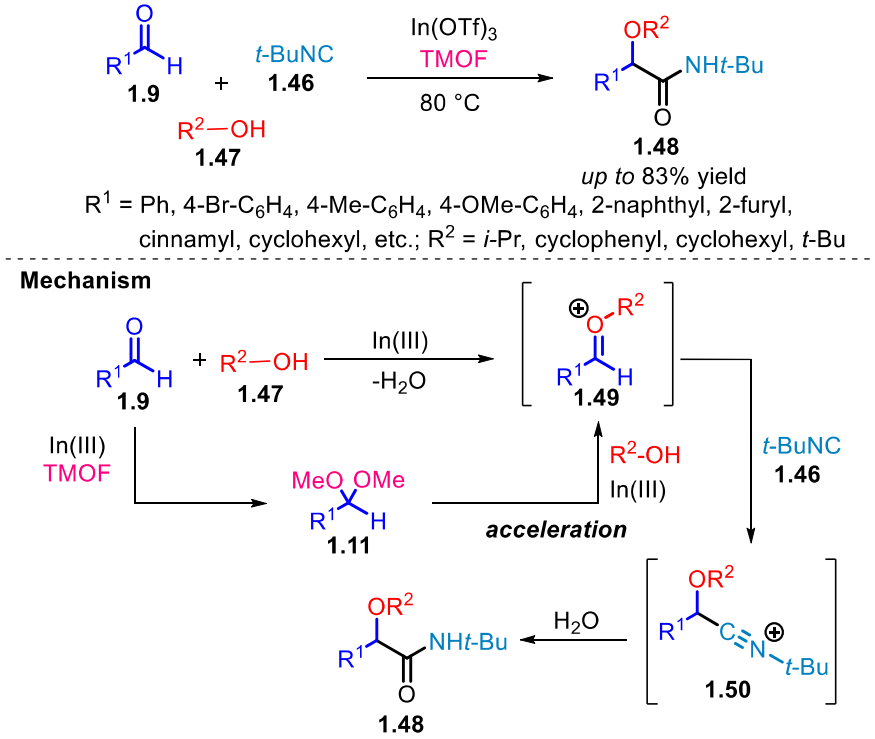
Condition **A**: $AuPPh_3Cl$ (5 mol %), AgOTf (5 mol %), $HC(OR^3)_3$ (1.2 equiv.)
DCE, reflux. *up to* 87% yield
R^1 = Ph, *o*-Me-C_6H_4, *m*-Br-C_6H_4, *m*-OMe-C_6H_4, *p*-Cl-C_6H_4, 1-naphthyl, etc.
R^2 = Ph, *p*-Br-C_6H_4, *p*-Ph-C_6H_4, *p*-NO_2-C_6H_4, 2-naphthyl
Condition **B**: Fe_3O_4@SiO_2–P–AuOTf (5 mol %)
$HC(OR^3)_3$ (1.2 equiv.), DCE, reflux. *up to* 87% yield
R^1 = Ph, *2*-Me-C_6H_4, 4-Br-C_6H_4, 3-OMe-C_6H_4, *4*-Cl-C_6H_4, 1-naphthyl, etc.
R^2 = Ph, 4-Cl-C_6H_4,*4*-OMe-C_6H_4

Scheme 1.8: Nucleophilic addition of gold alkylidines to activated C=O bond



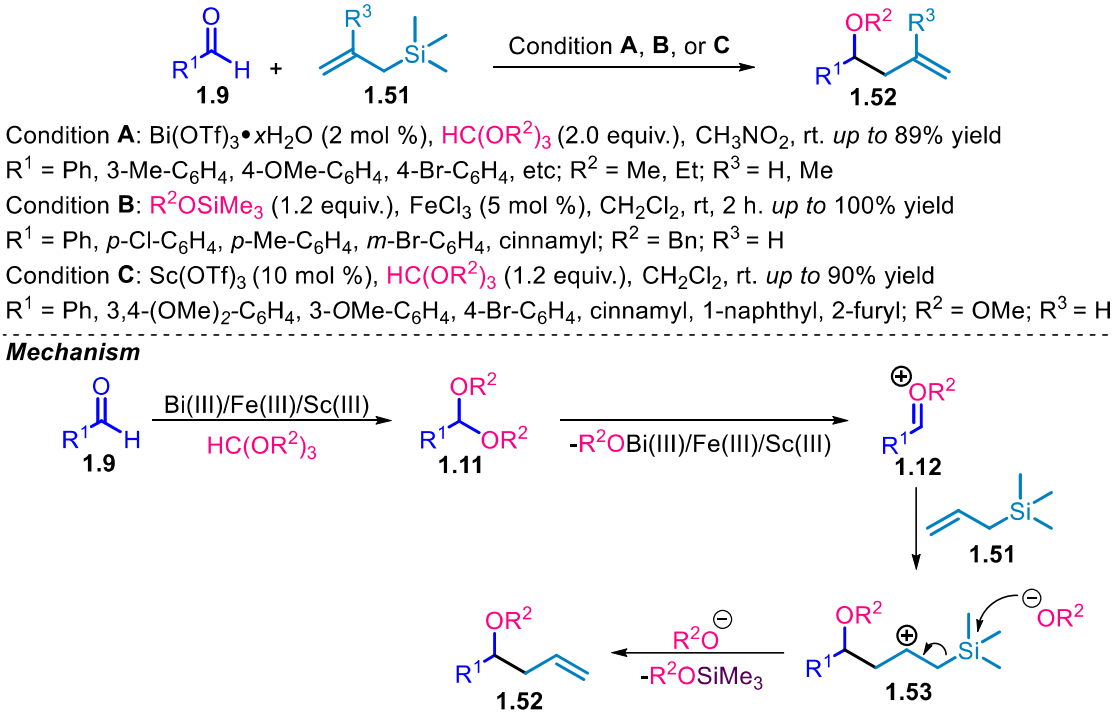
Scheme 1.8: Mechanism of nucleophilic addition of gold alkylidines on activated C=O bond

Taguchi and co-workers reported acceleration of the In-catalyzed alkylative Passerini reaction of aldehydes **1.9** and isocyanides **1.46** with free aliphatic alcohols **1.47** in the presence of TMOF for the synthesis of α-alkoxy amide derivatives **1.48** (Scheme 1.9).[13] This reaction proceeds *via* the formation of an oxocarbenium ion **1.49** from aldehydes **1.9** and alcohols **1.47**. The rate of the reaction is accelerated by the addition of TMOF through the formation of acetal **1.11** *in situ*. Nucleophilic attack of *tert*-butyl isocyanide **1.46** on oxocarbenium ion **1.49** followed by the hydrolysis of nitrilium intermediate **1.50** by water would give α-alkoxy amide derivative **1.48**.



Scheme 1.9: Alkylative Passerini reaction *via in situ* formed acetals

Homoallylation of aldehydes **1.9** with allylsilanes **1.51** in the presence of trialkyl orthoformate or alkyloxytrimethylsilane under Bi(III)/Fe(III)/Sc(III) catalysis was independently achieved by Mohan, Oriyama, and Yadav groups (Scheme 1.10).[14] These reactions proceed through an oxocarbenium ion **1.12** derived from the acetal **1.11** generated *in situ* from aldehydes **1.9** and trialkyl orthoformate or alkyloxytrimethylsilane in the presence of a Lewis acid catalyst. Facile nucleophilic attack of allylsilane **1.51** on oxocarbenium ion **1.12** followed by desilylation would lead to the formation of homoallyl ether **1.52**.

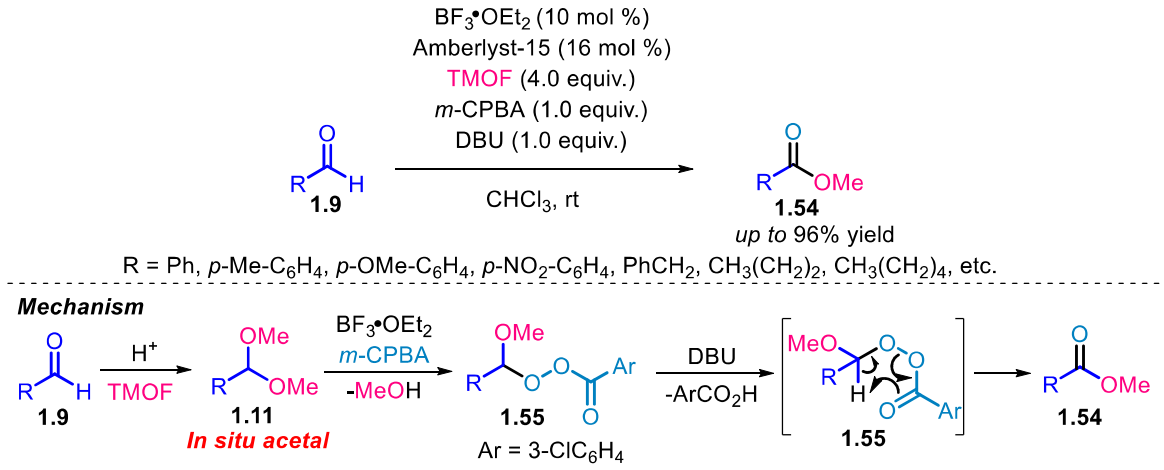


Scheme 1.10: Synthesis of homoallyl ethers from aldehydes

1.2.5 Acetal-assisted oxidation of aldehydes

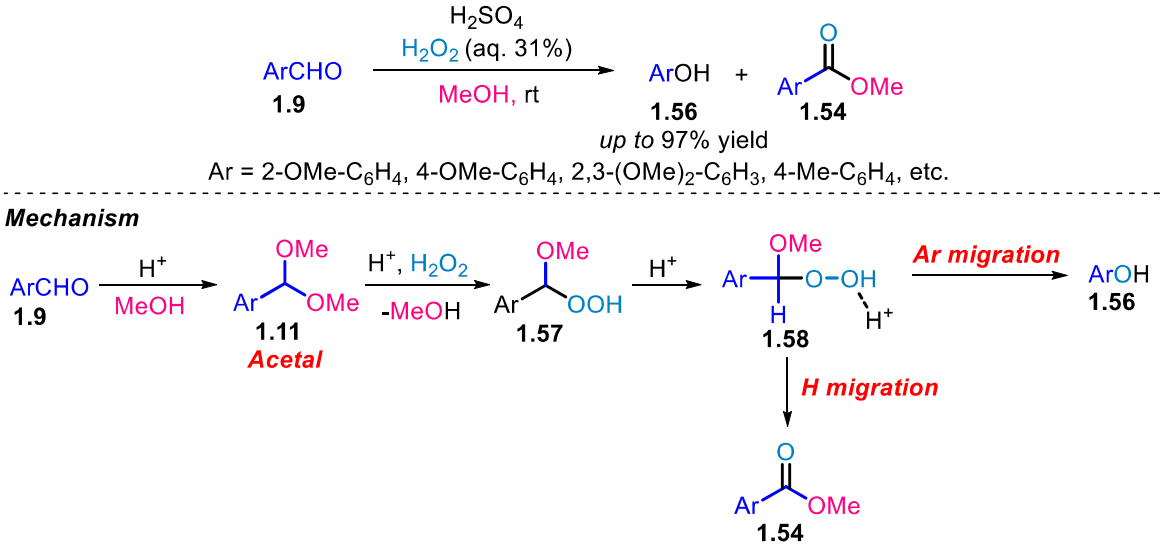
Esters are useful class of organic compounds present in materials, natural products and pharmaceuticals.[15] Synthesis of esters mainly utilizes carboxylic acids or their derivatives such as acyl chlorides, anhydrides and carbodiimides etc.[16] Esterification of aldehydes by converting them into acetals followed by oxidation of acetals is rather a straightforward approach.[17] Rhee *et al.* have demonstrated this strategy for the direct synthesis of esters from aldehydes **1.9** utilizing their *in situ* formed acetals (Scheme 1.11).[18] Formation of acetal **1.11** from aldehyde **1.9** in the presence of TMOF and amberlyst-15 initiates the reaction. Nucleophilic attack of *m*-CPBA on the oxocarbenium ion formed from the acetal **1.11** in the presence of $BF_3{\cdot}OEt_2$ would lead to the

formation of peroxy intermediate **1.55**. Treatment of the peroxy intermediate **1.55** with DBU would eliminate 3-chlorobenzoic acid to afford the ester derivative **1.54**.



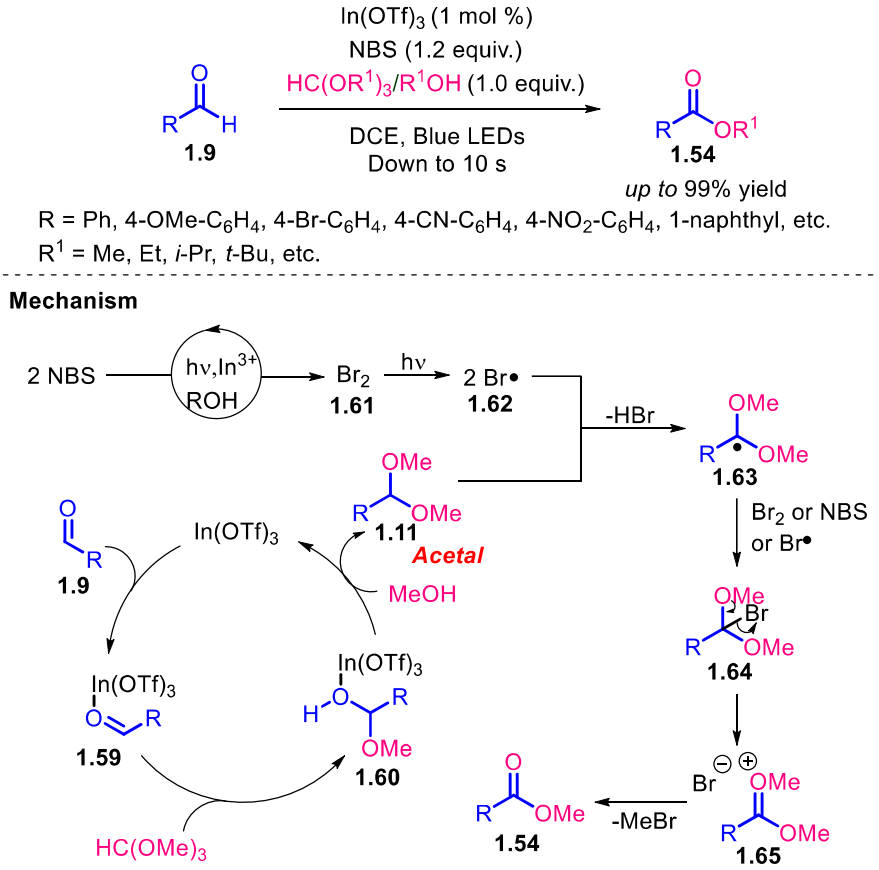
Scheme 1.11: Acetal-assisted oxidative esterification of aldehydes

Mastumoto *et al.* developed oxidation of aryl aldehydes **1.9** to phenols **1.56** in the presence of MeOH, hydrogen peroxide, and sulphuric acid (Scheme 1.12).[19] The acetal intermediate **1.11** is generated *in situ* from aldehyde **1.9** and MeOH under acidic conditions. Nucleophilic addition of hydrogen peroxide to the acetal **1.11** would lead to the formation of peroxy intermediate **1.58**, which on subsequent methoxy group-assisted aryl migration afforded the desired phenol derivative **1.56** as the major product. Product of H-migration, the ester derivative **1.54** was formed as a minor product.



Scheme 1.12: Synthesis of phenols *via* acetal-assisted oxidation of aldehydes

Wallentin and co-workers reported a one-pot oxidation of aldehydes **1.9** in the presence of trialkyl orthoformates or alcohols, *N*-bromosuccinimide, and the catalyst $In(OTf)_3$ mediated by visible-light (Scheme 1.13).[20] Formation of acetal intermediate **1.11** from aldehyde **1.9** in the presence of $In(OTf)_3$ initiates the reaction. Next, generation of bromine radical **1.62** occurs *via* visible-light induced cleavage of molecular bromine **1.61** formed from NBS. Thus, formed bromine radical **1.62** would abstract the activated proton from the acetal intermediate **1.11** to afford acetal radical **1.63** that abstracts bromine from NBS or molecular bromine **1.61** to give brominated intermediate **1.64**. This would lose bromine as bromide to give oxocarbenium ion **1.65** which finally affords the ester derivative **1.54**.

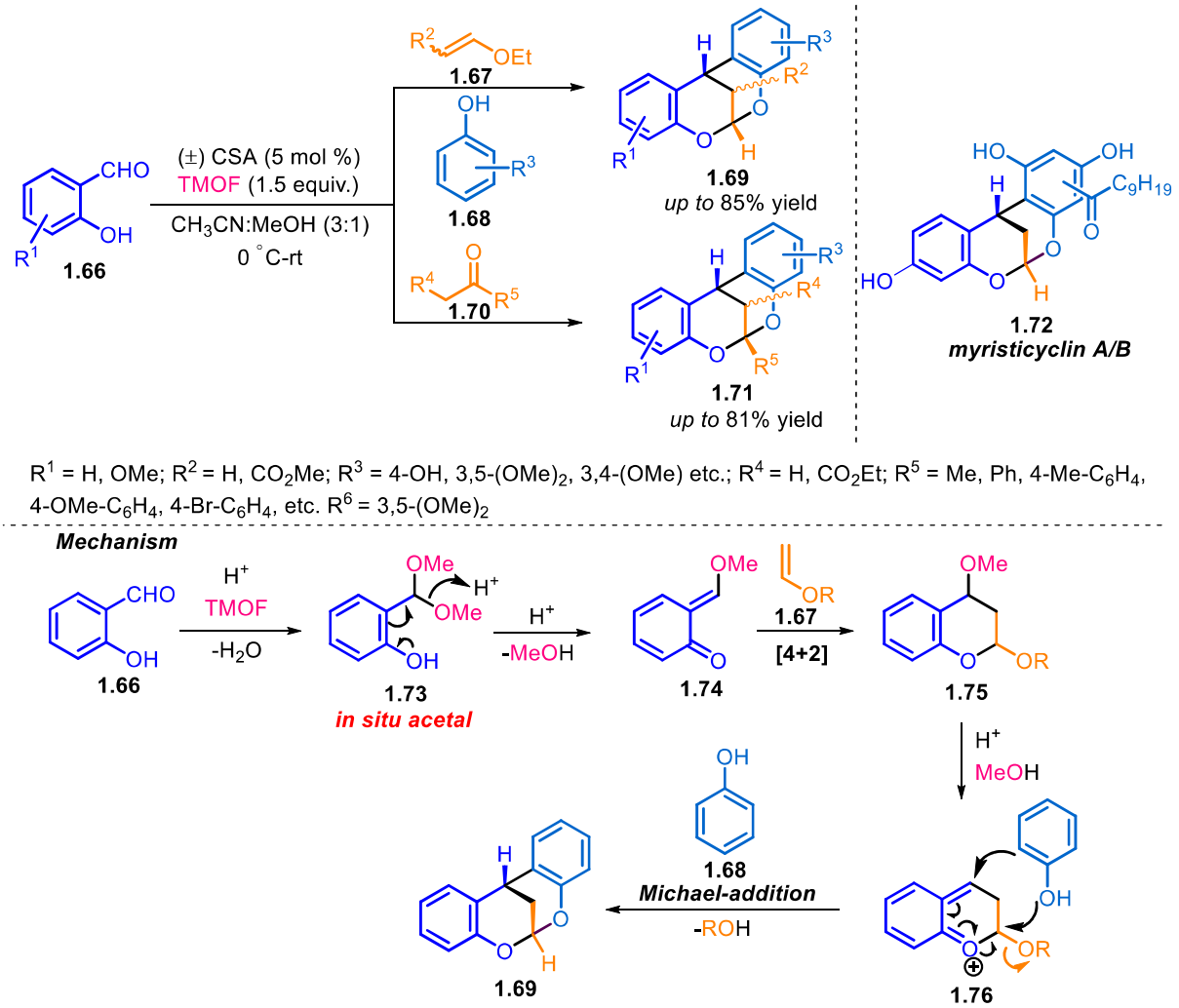


Scheme 1.13: Oxidative esterification of aldehydes

1.2.6 [4+2] Cycloadditions of *o*-quinone methides

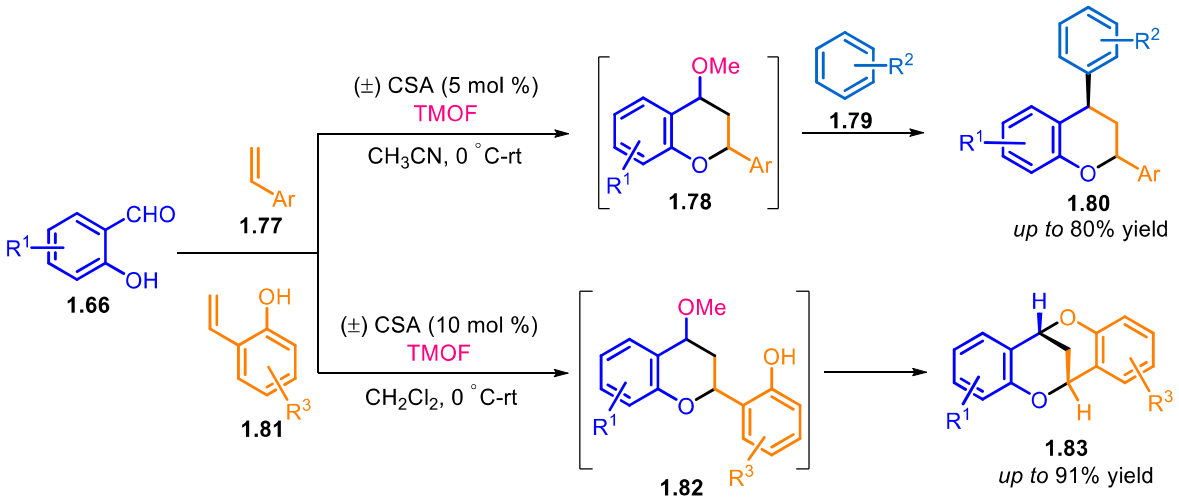
Gharpure and co-workers reported the synthesis of flavonoids **1.69**/**1.71** from *o*-hydroxy benzaldehydes **1.66** by reacting them with an ethyl vinyl ether **1.67** or ketones **1.70** and a phenol derivative **1.68** in the presence of TMOF under camphor sulphonic acid catalysis (Scheme 1.14).[21a] This reaction proceeds through generation of *o*-quinone methide (*o*-QM) **1.74** *via in situ* generated acetal **1.73** from *o*-hydroxy benzaldehydes **1.66** in the presence of TMOF and an acid catalyst

followed by [4+2] cycloaddition of *o*-QM **1.74** with ethyl vinyl ether **1.67** or ketones **1.70** to give Diels-Alder adduct **1.75**. This Diels-Alder adduct **1.75** would generate another *o*-QM **1.76** which will undergo intermolecular Michael addition with phenol derivatives **1.68** to furnish flavonoid derivatives **1.69**/**1.71**. This strategy was successfully utilized for the synthesis of myristicyclin A/B **1.72**.



Scheme 1.14: [4+2] Cycloadditions of *o*-quinone methides

Later, the same group demonstrated the synthesis of cassiaflavan (2,4-diarylbenzopyran) derivatives **1.80** and cycloflavan (dioxabicyclo[3.3.1]nonane) derivatives **1.83** from *o*-hydroxy benzaldehydes **1.66** and styrenes **1.77**/**1.81** in the presence of TMOF under camphor sulphonic acid catalysis (Scheme 1.15).[22] This strategy was successfully utilized for the synthesis of myristinins A-F.

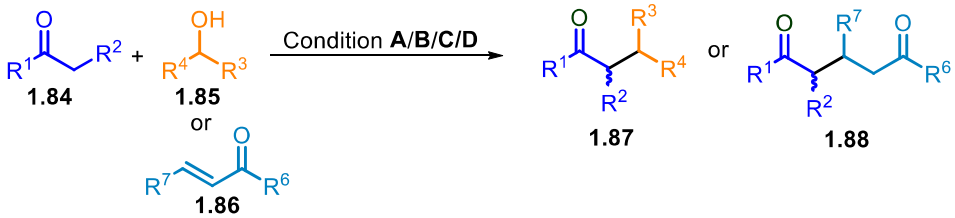


R^1 = H, OMe; Ar = Ph, 4-OMe-C_6H_4, etc.; R^2 = 1,3,5-$(OMe)_3$, 2,4-$(OH)_2$, etc.; R^3 = H, OMe

Scheme 1.15: [4+2] Cycloadditions of *o*-quinone methides

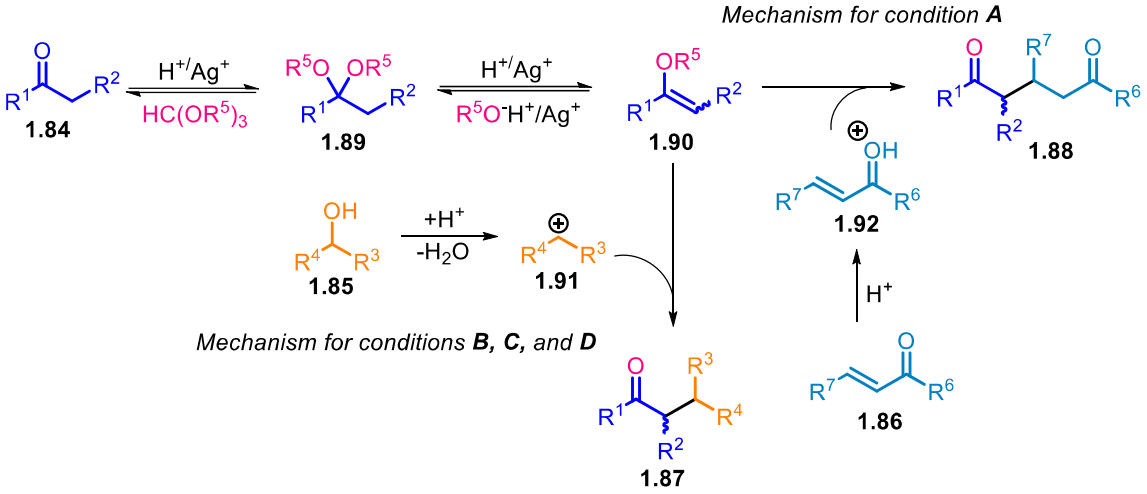
1.2.7 Direct α-alkylation of ketones

α-Alkylation is an important organic transformation to generate a C-C bond at α-carbon of carbonyl compounds.[23] Generally, a strong base is required to get the reactive enolate from the ketone. In this context, direct α-alkylation of ketones with alcohols is a very challenging task. However, the nucleophilicity of the α-carbon of the alkyl ketones can be increased by converting them into enol ethers through acetals. On the basis of this concept, α-alkylation of ketones have been achieved on unactivated ketones **1.84** with alcohols **1.85** in the presence of trialkyl orthoformates and stoichiometric triflic acid or amberlyst-15 or catalytic $AgSbF_6$ (Scheme 1.16).[24] Ketone **1.84** generates acetal **1.89** upon treatment with a trialkyl orthoester in the presence of H^+/Ag^+ followed by the formation of enol ether **1.90**. This enol ether **1.90** reacts with the carbocation **1.91** generated from alcohol **1.85** in the presence of H^+/Ag^+ to give the α-alkylated ketone **1.87**. In addition, the enol ether **1.90** generated *in situ* was reacted with activated chalcones **1.92** to form the Michael adducts **1.88**.



Condition **A**: TfOH (1.0 equiv.), TMOF (1.0 equiv.), CCl_4, rt. *up to* 97% yield
Condition **B**: Amberlyst-15 (4.0 equiv.), [Bmim] [PF_6], TEOF (1.0 equiv.). *up to* 75% yield
Condition **C**: $AgSbF_6$ (10 mol %), TMOF (2.0 equiv.), CH_2Cl_2, rt/heat. *up to* 88% yield
Condition **D**: TfOH (1.0 equiv.), TMOF (1.0 equiv.), CCl_4, rt. *up to* 97% yield
R^1 = Aryl/alkyl; R^2 = H/alkyl; R^3 = Aryl/cinnamyl/phenyl/alkynyl/alkyl; R^4 = Phenyl

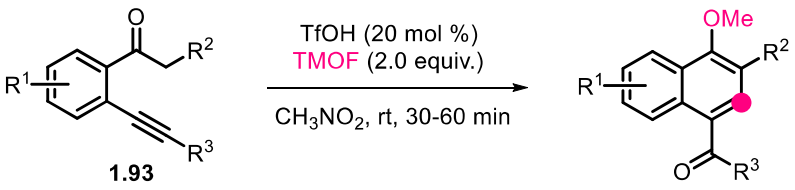
Scheme 1.16: Direct α-alkylation of ketones with alcohols and Michael addition on chalcones



Scheme 1.16: Mechanism for direct α-alkylation of ketones with alcohols and Michael addition on chalcones

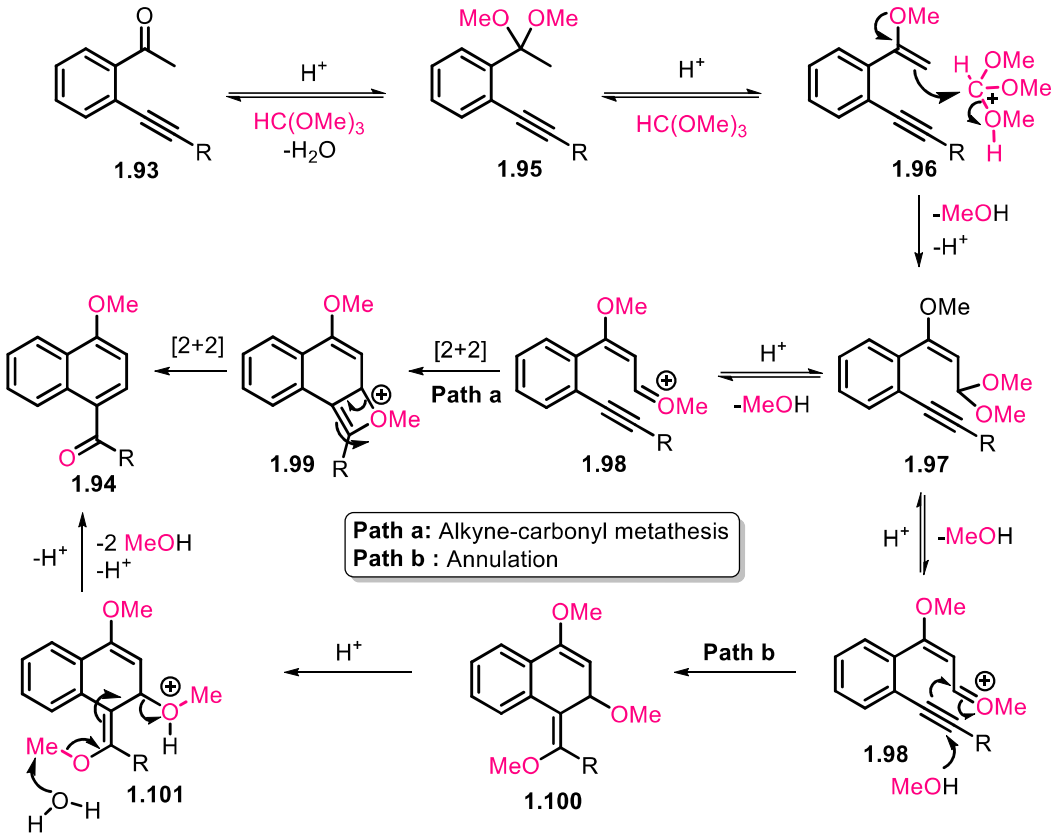
1.2.8 Incorporation of acetal and cyclization

Incorporation of an acetal moiety at the α-position of ketones is a useful strategy to achieve α-formylated ketones, which, in turn, can be utilized in subsequent transformations for the synthesis of interesting and biologically important compounds.[25] In 2014, our group reported the synthesis of naphthalene derivatives **1.94** from *o*-alkynylacetophenones **1.93** in the presence of TMOF under triflic acid catalysis (Scheme 1.17).[26] This strategy involves the incorporation of acetal to give intermediate **1.97** *via in situ* formed acetal **1.95** and the corresponding enol ether **1.96**. Thus, formed intermediate **1.97** will give enone intermediate **1.98** after exclusion of MeOH in the presence of acid. In *path a*, intermediate **1.98** will undergo [2+2]-cycloaddition to afford the desired naphthyl ketone derivatives **1.94** *via* an oxetane intermediate **1.99**. On the other hand, in *path b*, nucleophilic addition of MeOH on alkyne moiety of intermediate **1.98** and intramolecular cyclization would afford intermediate **1.100**. Further, protonation and elimination of MeOH will give the final product **1.94**.



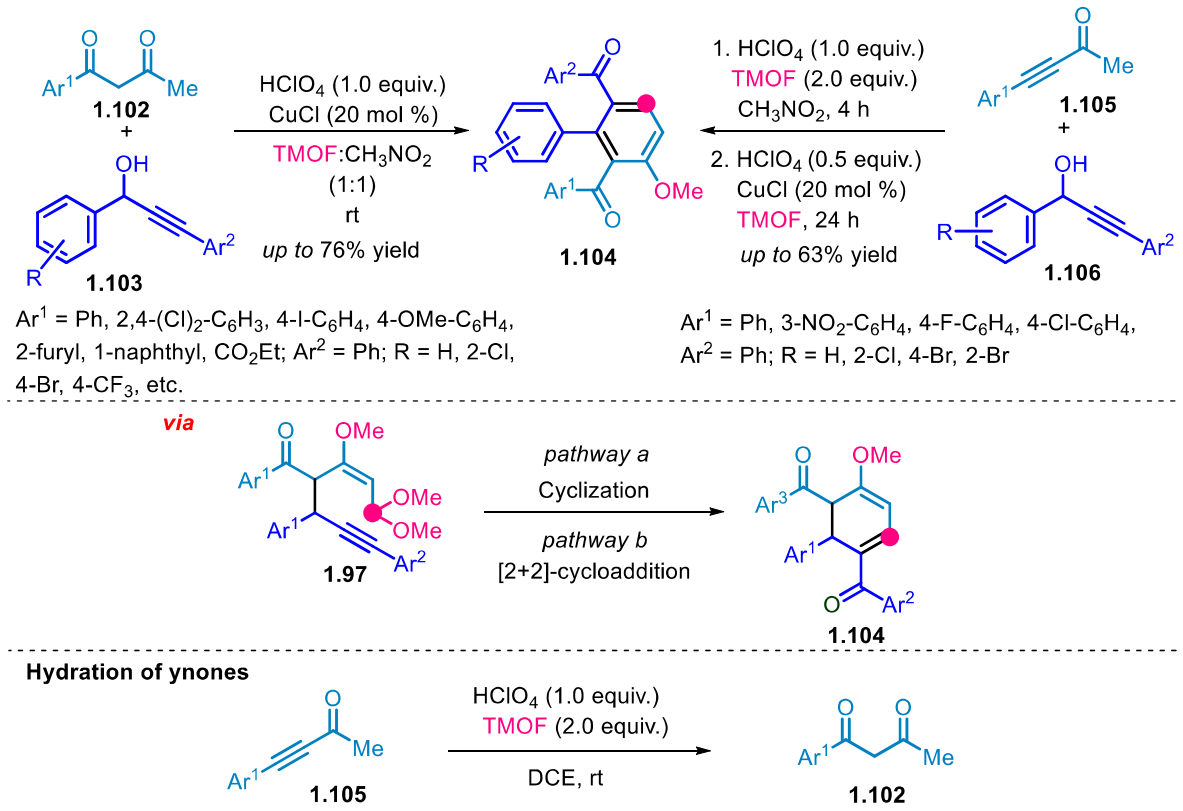
R^1 = H, OMe, -O-CH_2-O-; R^2 = H, *n*-Pr; R^3 = Ph, 4-Me-C_6H_4, 2-OMe-C_6H_4, 2-OMe-C_6H_4, 2-furyl, *n*-butyl, *n*-hexyl

Scheme 1.17: Synthesis of naphthalene derivatives *via* incorporation of acetal



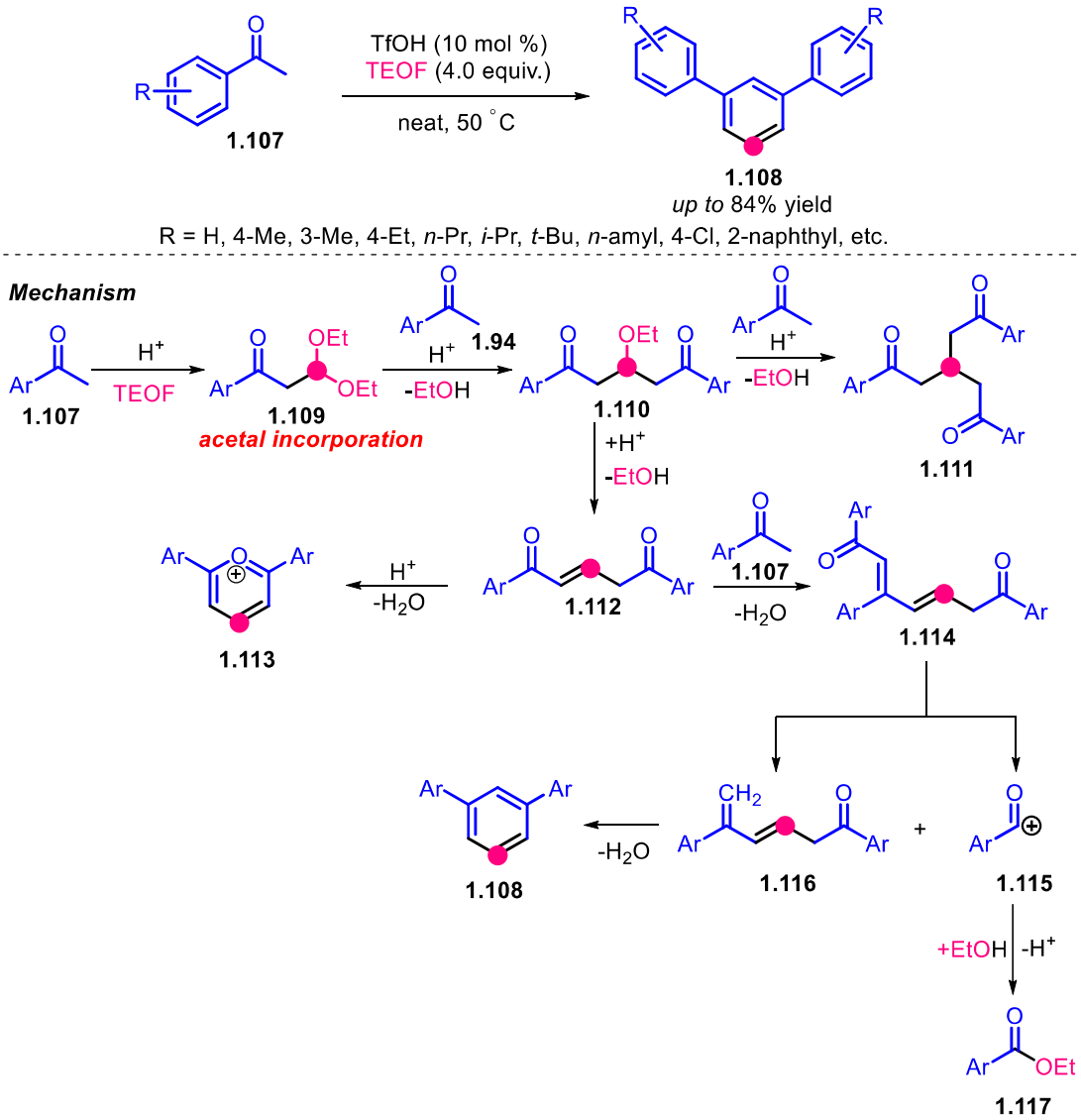
Scheme 1.17: Plausible mechanism for the synthesis of naphthyl ketone derivatives

In 2021, our group reported the synthesis of biaryls **1.104** from 1,3-dicarbonyls **1.102** and propargyl alcohols **1.103** by treating them with TMOF in the presence of $HClO_4$ and a Cu(I) catalyst (Scheme 1.18).[27] This reaction proceeds *via* an α-formylated intermediate followed by intramolecular annulation (*pathway a*) or [2+2]-cycloaddition (*pathway b*) to afford biaryl derivatives **1.104**. It is interesting to mention that ynones **1.105** could be employed in the place of 1,3-carbonyl compounds **1.102** as the former will be converted to the later by hydration under the reaction conditions.



Scheme 1.18: Synthesis of biaryls *via* incorporation of acetal

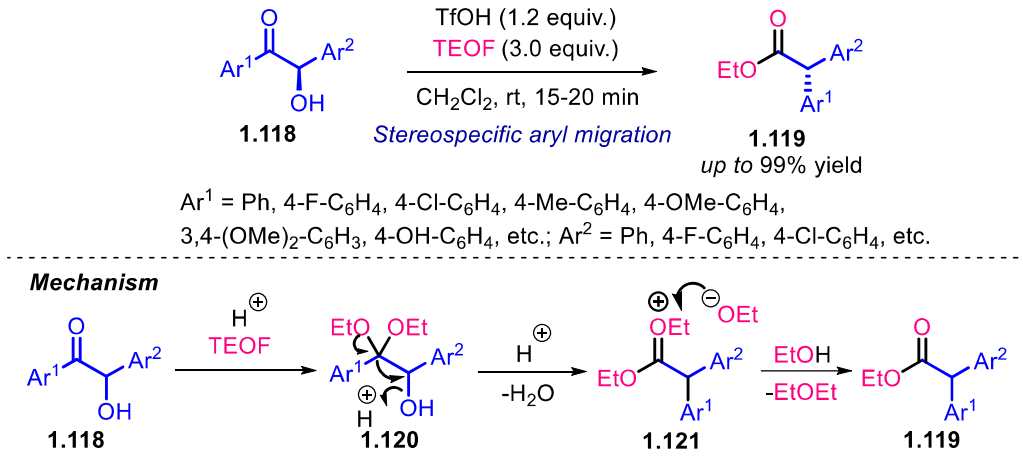
Recently, Tang *et al.* reported the synthesis of *m*-terphenyls **1.108** from aryl methyl ketones **1.107** in the presence of TEOF under TfOH catalysis (Scheme 1.19).[28] This reaction proceeds through the initial incorporation of acetal at the α-position of ketone **1.107** to give acetal **1.109**. Nucleophilic attack of another molecule of ketone **1.107** on acetal **1.109** would afford compound **1.110**. Compound **1.110** would either react with another molecule of ketone **1.107** to produce compound **1.111** or give intermediate **1.112** by the elimination of ethanol. Later, intermediate **1.112** will either undergo self-condensation to afford ion **1.113**[29] or produce another intermediate **1.114** by reacting with ketone **1.107**. The intermediate **1.114** eliminates a benzoyl cation **1.115** and form the intermediate **1.116**. The benzoyl cation **1.115** would react with ethanol to give the ester **1.117**. Finally, intermediate **1.116** will undergo self-condensation to afford *m*-terphenyl derivative **1.108**.



Scheme 1.19: Synthesis of *m*-terphenyls from aryl methyl ketones *via* incorporation of acetal

1.2.9 1,2-Aryl migration

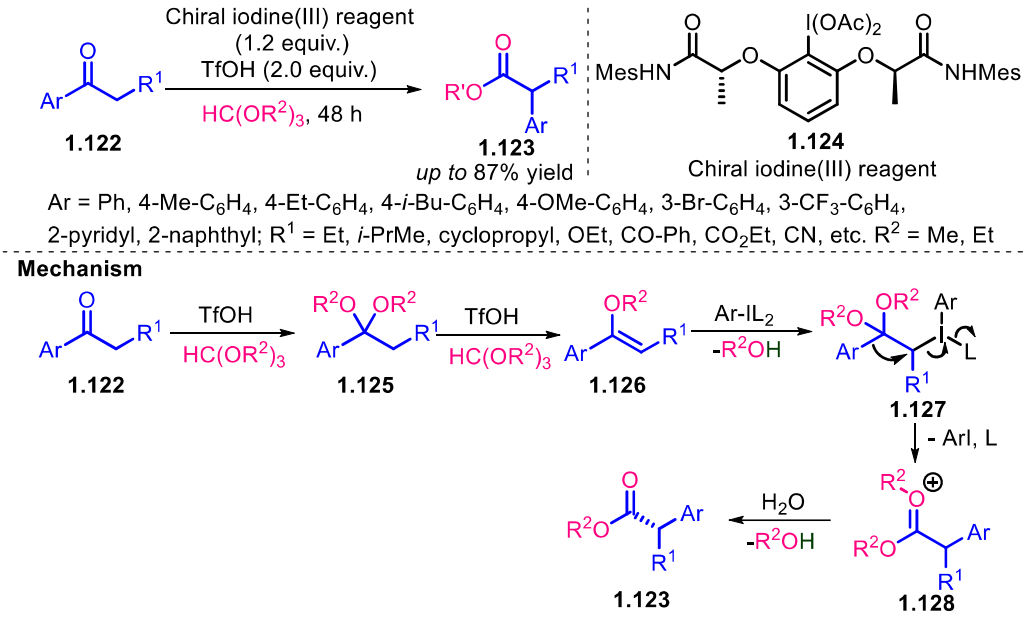
In 2014, our group developed a simple protocol for the synthesis of α-diarylacetates **1.119** from benzoins **1.118** in the presence of TEOF and TfOH in short reaction times (Scheme 1.20).[30] This reaction involves the generation of acetal **1.120** *in situ* from benzoins **1.118**. In the presence of an acid, the hydroxy group gets protonated and a dehydrative aryl migration, assisted by an ethoxy group, will give an oxocarbenium intermediate **1.121**. Ethanol formed during the reaction captures the ethyl group from oxocarbenium ion **1.121** to afford α-diarylacetate derivative **1.119**. Furthermore, this method could also be applied to make various enantioenriched α-diarylacetate derivatives.



Scheme 1.20: Synthesis of α-diarylacetates *via in situ* generated acetal assisted 1,2-aryl migration

1.2.10 Oxidative rearrangements

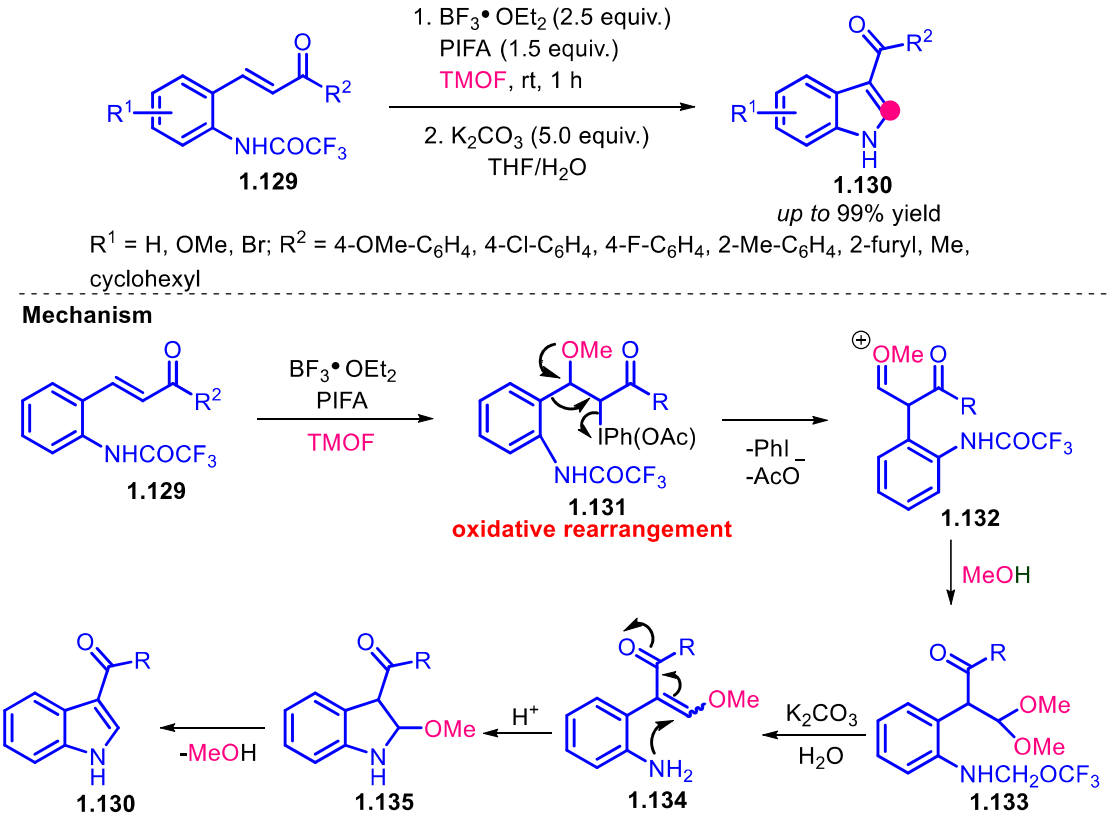
In 2016, Wirth *et al.* disclosed the synthesis of 2-arylpropionate derivatives **1.123** *via* a chiral hypervalent iodine(III) **1.124** mediated stereoselective rearrangement of aryl alkyl ketones **1.122** in the presence of TfOH and trialkyl orthoformates (Scheme 1.21).[31] The enol ether **1.126** is formed from the acetal **1.125** generated *in situ* from aryl alkyl ketone **1.122**. Electrophilic addition of iodine(III) reagent assisted by nucleophilic attack of MeOH on enol ether **1.126** afforded intermediate **1.127**. Migration of the aryl group assisted by the methoxy groups will lead to the formation of an oxocarbenium ion **1.128**, which upon quenching with water would afford the 2-arylpropionate derivatives **1.123**.



Scheme 1.21: Iodine(III)-mediated oxidative rearrangement of aryl ketones

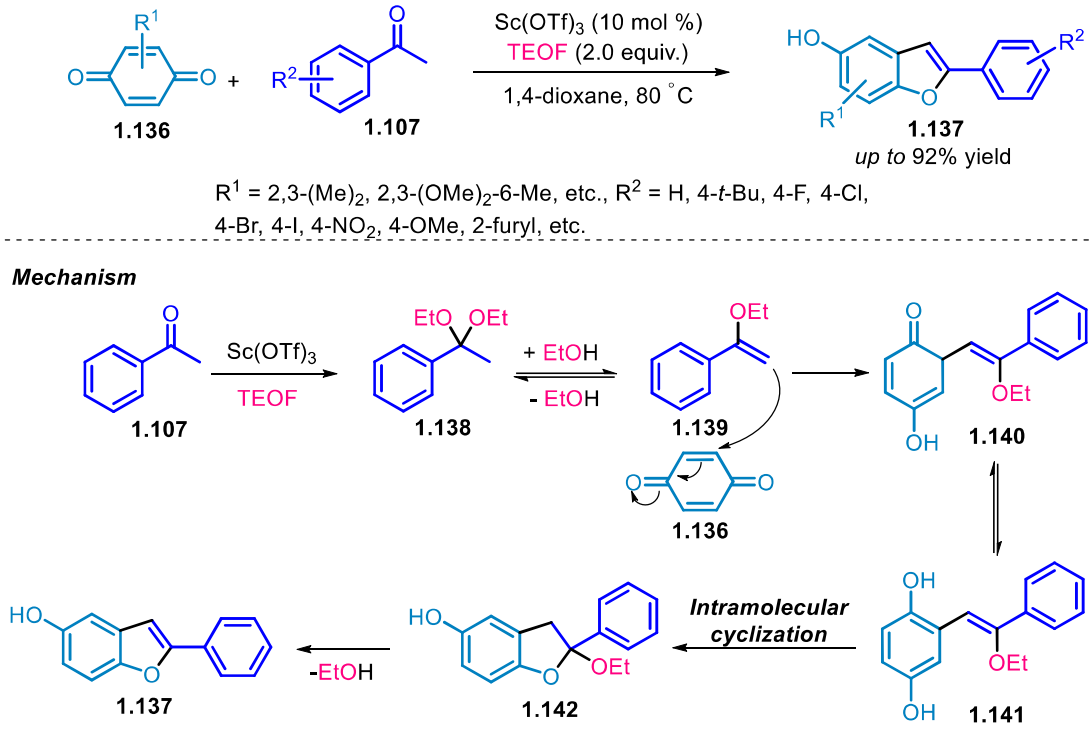
1.2.11 Miscellaneous

Miki and co-workers reported a phenyliodine(III)bis(trifluoroacetate) (PIFA)-mediated oxidative rearrangement of 2-aminochalcones **1.129** in the presence of $BF_3{\cdot}Et_2O$ and trimethyl orthoformate (TMOF) followed by intramolecular cyclization under basic conditions for the synthesis of 3-acylindoles **1.130** (Scheme 1.22).[32] This reaction proceeds through an initial formation of intermediate **1.131** by the electrophilic addition of $PhI(OAc)_2$ to the double bond of chalcone **1.129** in the presence of MeOH and $BF_3{\cdot}Et_2O$. An oxidative rearrangement assisted by the methoxy group followed by the migration of aryl moiety forms the oxocarbenium ion **1.132**. Nucleophilic addition of MeOH to the oxocarbenium ion **1.132** would generate the acetal **1.133**. Deprotection of N-$COCF_3$ group followed by elimination of methoxy group in **1.133** affords intermediate **1.134** which subsequently undergoes intermolecular cyclization and aromatization to afford 3-acylindoles **1.130**.



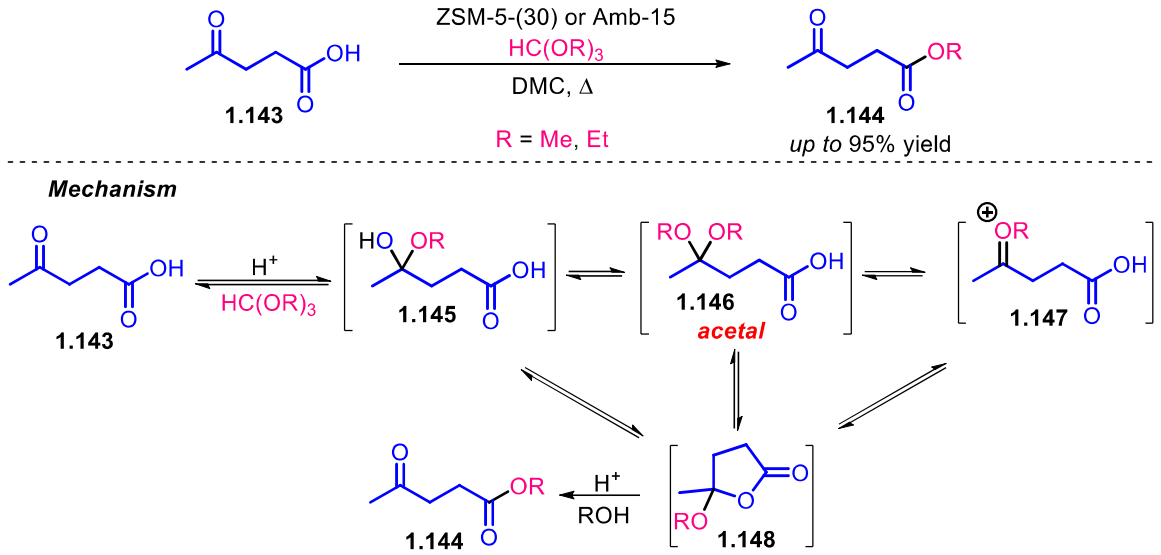
Scheme 1.22: PIFA-mediated oxidative rearrangement of 2-aminochalcones

Gu *et al.* reported a simple and efficient method for the synthesis of benzofuran derivatives **1.137** from enolizable ketones **1.107** and benzoquinones **1.136** in the presence of TEOF *via* a sequential Michael addition and cyclization under Sc(III) catalysis (Scheme 1.23).[33] This reaction proceeds through the formation of enol ether **1.139** derived from an acetal **1.138** generated *in situ* from the ketone **1.107** in the presence of TEOF and Sc(III) catalyst. This enol ether **1.139** attacks benzoquinone **1.136** in Michael addition fashion and the cyclization of the intermediate **1.141** would afford benzofuran derivatives **1.137**. A variety of 5-hydroxy benzofurans were synthesized by this methodology.



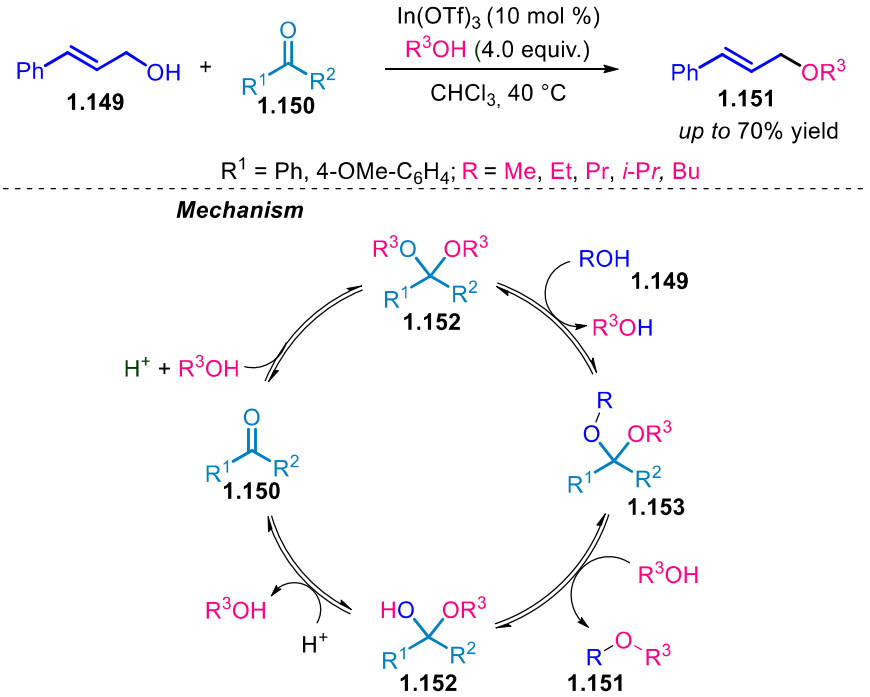
Scheme 1.23: Synthesis of benzofuran derivatives

Graham *et al.* reported the esterification of levulinic acid **1.143** in the presence of trialkyl orthoformates catalyzed by ZSM-5-(30) and amberlyst-15 under mild reaction conditions in short reaction times (Scheme 1.24).[34] Acetalization of carbonyl function of levulinic acid **1.143** in the presence of trialkyl orthoformates and an acid catalyst would initiate the reaction. Intramolecular cyclization of the hemiacetal **1.145** or the oxocarbenium ion **1.147** afford pseudo lactone intermediate **1.148** which undergoes subsequent ring-opening with alcohol to lead to the formation of levulinate ester **1.144**.



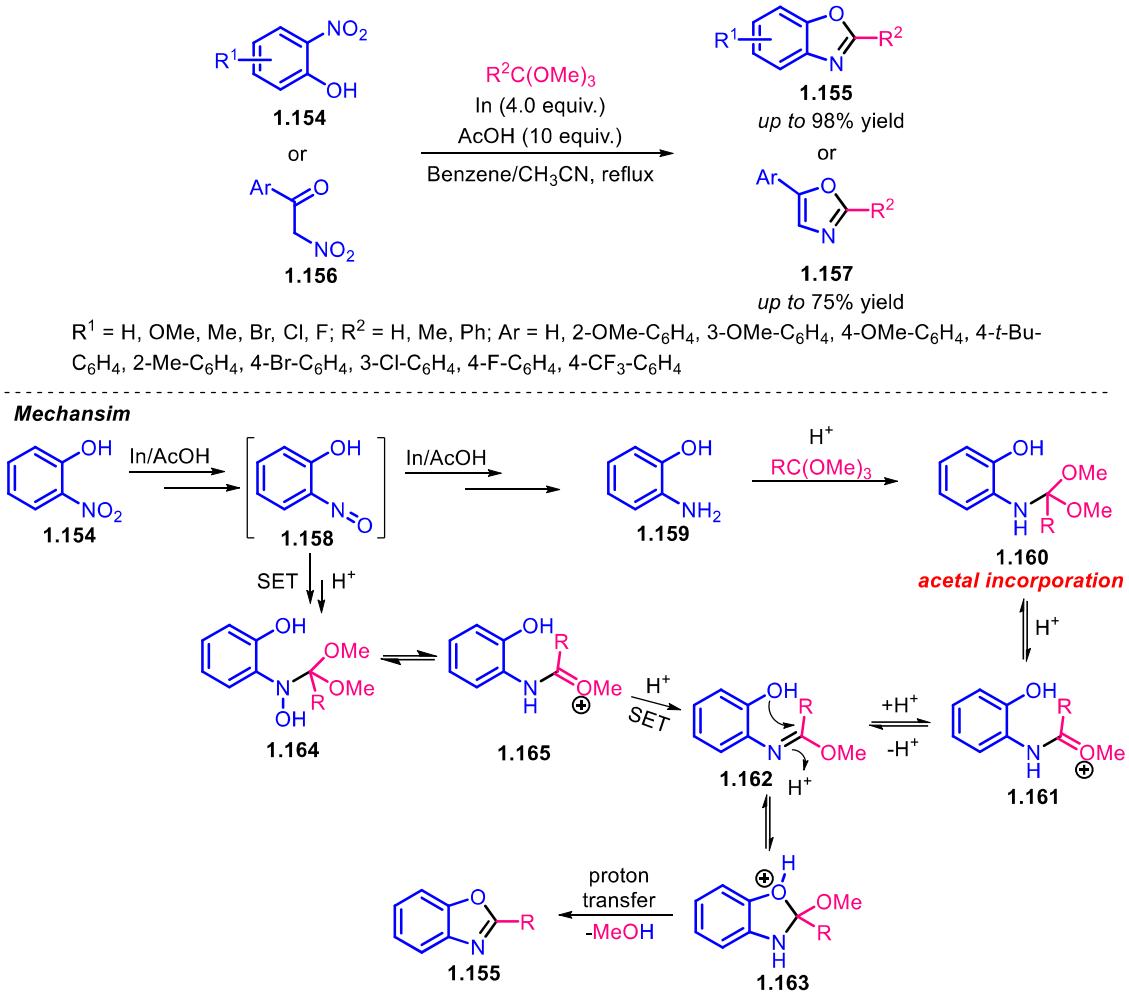
Scheme 1.24: Conversion of levulinic acid into levulinate ester

Later, the same group achieved etherification of cinnamyl alcohol **1.149** promoted by acetal in the presence of $In(OTf)_3$ catalyst (Scheme 1.25).[35] Nucleophilic attack of alcohol **1.149** on acetal **1.152** would afford a mixed acetal derivative **1.153**, which reacts with alcohol to lead to the formation of the desired ether product **1.151**. The acetal intermediate **1.152** which promotes the reaction will be regenerated from the resulting starting carbonyl compound **1.150** in the presence of a small excess of alcohol under acidic conditions.



Scheme 1.25: Acetal-promoted etherification of alcohols

Synthesis of benzoxazoles **1.155** from 2-nitrophenols **1.154** and oxazoles **1.157** from α-nitro ketones **1.156** has been achieved by employing trimethyl orthoesters, indium powder, and AcOH *via* reductive heterocyclization (Scheme 1.26).[36] This reaction proceeds through the initial reduction of the nitro group of 2-nitrophenols **1.154** to form the aniline derivative **1.159** *via* the nitroso intermediate **1.158** by electron and proton transfer processes. Incorporation of acetal to the amine group would take place to give intermediate **1.160** and subsequently the oxocarbenium ion **1.161** intermediate. This would undergo heterocyclization through oxygen to give benzoxazoles **1.155**/oxazoles **1.157**. An alternate mechanism involving the imidate intermediate **1.162** has also been proposed by the authors.



Scheme 1.26: Synthesis of benzoxazoles/oxazoles *via* incorporation of acetal

1.3 Conclusions

Apart from being used as protecting groups to perform chemoselective reactions, acetals in their pre-formed state have been used in various organic transformations which are otherwise difficult to achieve or not possible in the absence of them. However, these reactions will end up with lower yields as acetals will form the parent carbonyl compounds under acidic conditions. This drawback could be overcome by generating acetals *in situ* under the reaction conditions as the concentration of acetal is maintained by regeneration.

Since the pioneering work of Mukaiyama *et al.*,[37] acetals as electrophiles have seen spectacular growth in C-C bond forming reactions with different nucleophiles in the past decades. These reactions such as Friedel-Crafts-type reactions, Aldol-type reactions, cycloisomerizations, nucleophilic additions, oxidation of aldehydes, [4+2] cycloadditions of *o*-quinone methides, etc. proceed through oxocarbenium ion which is more reactive than the corresponding parent carbonyl compounds. Moreover, carbonyl compounds having an α-hydrogen could generate more nucleophilic and more reactive enol ether from their corresponding acetals. This enol ether involves in interesting transformations such as direct α-alkylation of ketones, incorporation of acetal and cyclization, etc. for new C-C bond formation at the α-position of the ketones. Furthermore, valuable molecular scaffolds could easily be achieved by 1,2-aryl migrations, and oxidative rearrangements *via in situ* generated acetals.

The next chapters will describe the exploitation of *in situ* formed acetals in interesting transformations developed in our laboratory.

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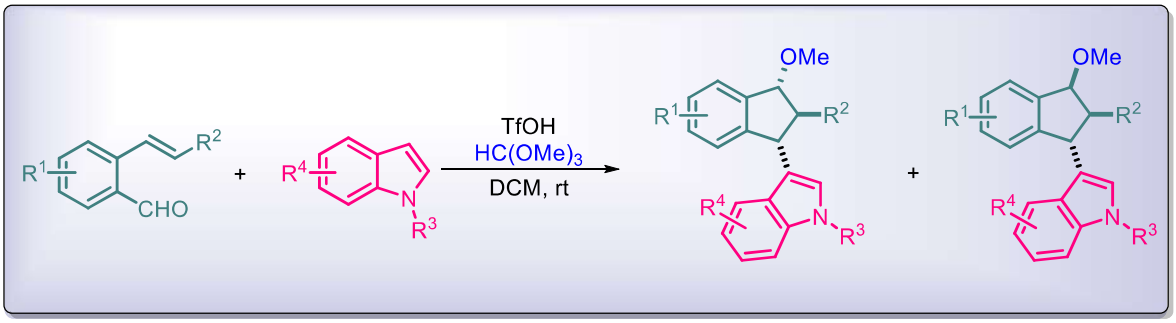
Chapter 2

Triflic Acid-Catalyzed Synthesis of Indole Substituted Indane Derivatives *via In Situ* Formed Acetals



This work was published. Ref: *J. Org. Chem.* **2021**, *86*, 16278-16292.

2.1 Introduction

Indane scaffold exists in numerous natural products and pharmaceuticals having diverse biological activities.[1] Notably, Crixivan®, an HIV protease inhibitor used as an important drug developed by Merck for the treatment of AIDS, resveratrol derived natural products such as caraphenols, α-diisoeugenol and endothelin receptor antagonist SB 209670 are a few other biologically important compounds to mention (Figure 2.1).[2] Owing to their widespread natural and biological relevance, the indane scaffold attracted researchers to pursue its chemical synthesis, and eventually, different protocols have been reported in the literature for the synthesis of indane derivatives in both racemic and asymmetric manner (Figure 2.2).[3-11] These reactions include Friedel-Crafts cyclization,[3] Michael-type addition,[4] Heck-type cyclizations,[5] radical-type,[6] NHC-catalysis,[7] ring-expansion,[8] ring-contraction,[9] miscellaneous,[10] and asymmetric catalysis (Figure 2.2).[11]

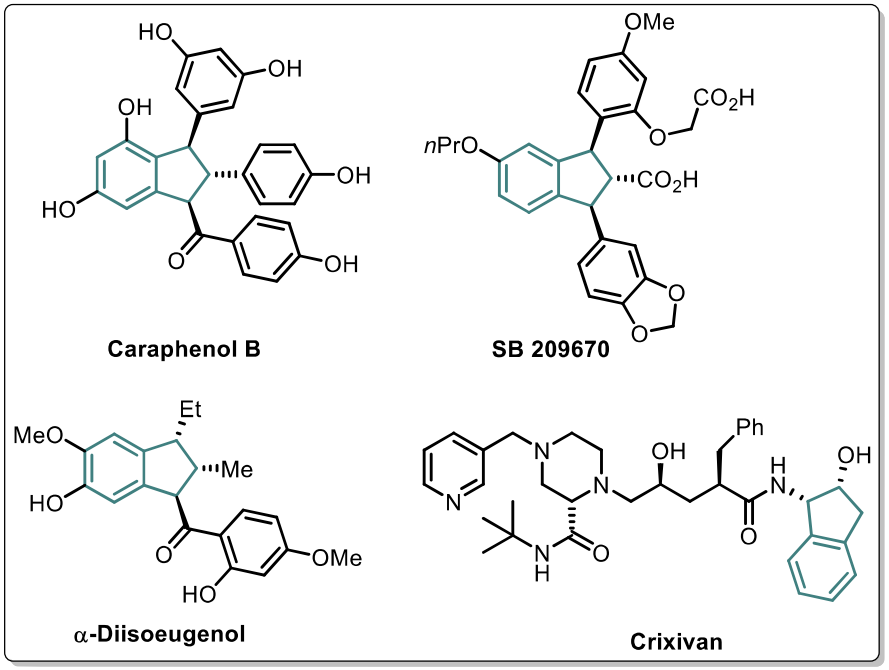


Figure 2.1: Representative natural products and pharmaceutically important compounds containing indane core

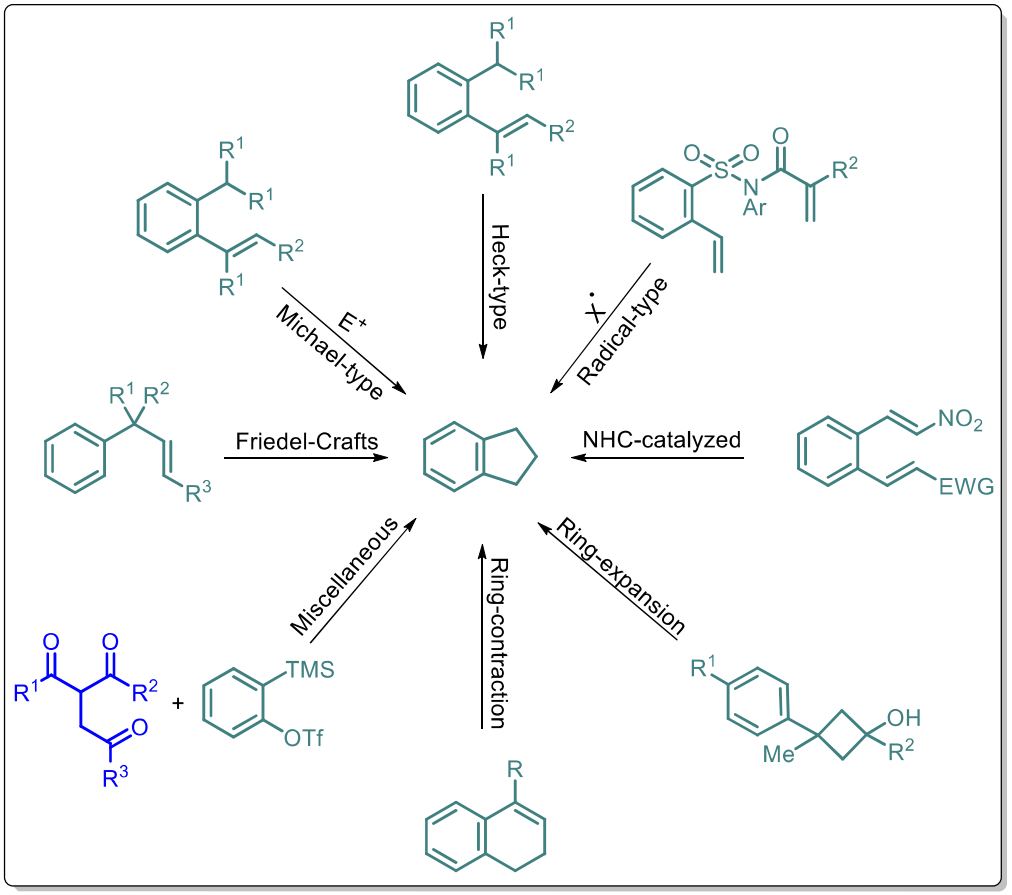
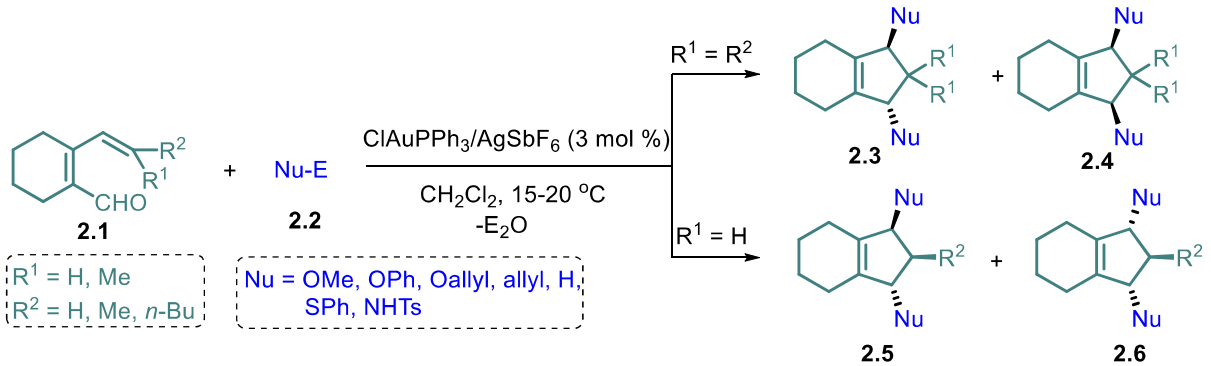


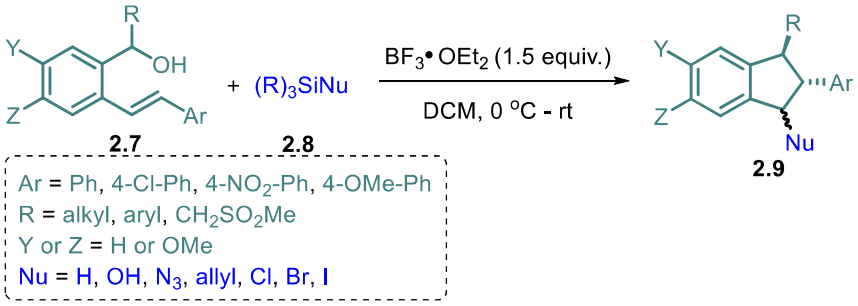
Figure 2.2: Selected strategies for the construction of indane core

However, the synthesis of indanes involving the addition of an external nucleophile is a more useful method to access highly functionalized indanes. In 2007, Liu and co-workers reported a cyclization/1,4-double addition of two nucleophiles **2.2** for the synthesis of cyclopentene derivatives **2.3-2.6** from 2,4-dien-1-als **2.1** under gold catalysis (Scheme 2.1).[12]



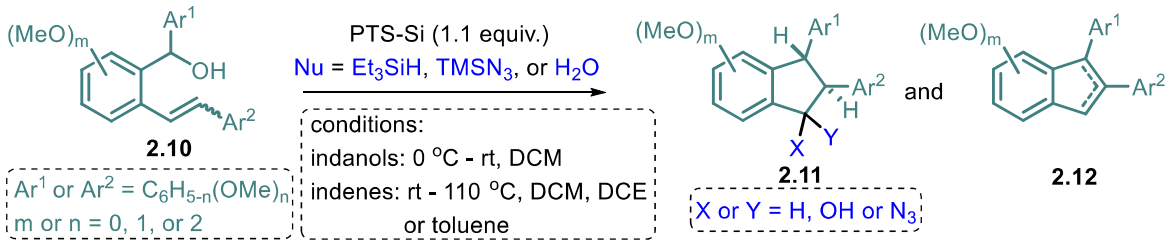
Scheme 2.1: Au-catalyzed cyclization of cis-2,4-dien-1-als with regioselective addition of two nucleophiles

In 2013, Ploypradith and co-workers reported a $BF_3{\cdot}Et_2O$-mediated synthesis of substituted 2-arylindanes **2.9** from *E*-(2-stilbenyl)methanols **2.7** and trialkylsilyl reagents **2.8** (Scheme 2.2).[13a] This protocol involves the generation of a carbocation at the carbinol carbon followed by cyclization and nucleophilic transfer from trialkylsilyl reagent to afford **2.9**.



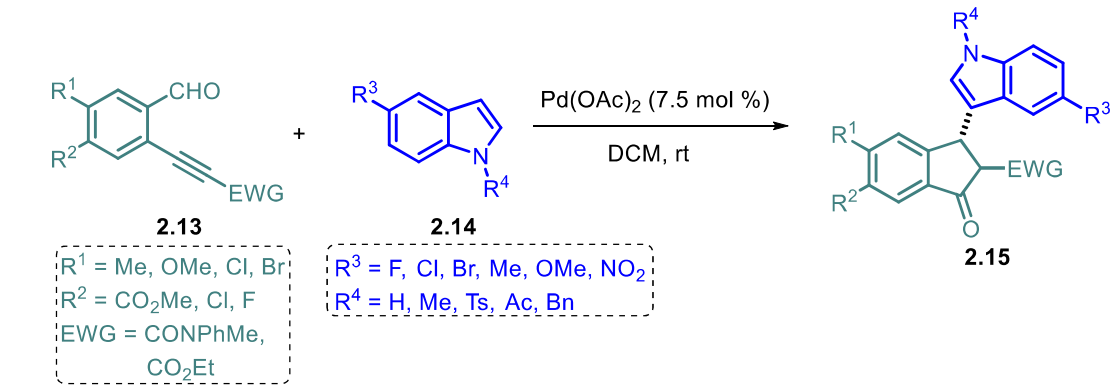
Scheme 2.2: Lewis acid-mediated cyclization of stilbenyl methanols and nucleophilic transfer from trialkylsilyl reagents

Later, the same group, in 2018, extended the cyclizations of (*Z*)- and (*E*)-(2-stilbenyl)methanols **2.10** for the divergent synthesis of indanols **2.11** and indenes **2.12** using PTSA immobilized on silica (Scheme 2.3).[13b] Indanones, which are structurally related to the natural product paucifloral F could be synthesized simply by the oxidation of obtained indanols **2.11**.



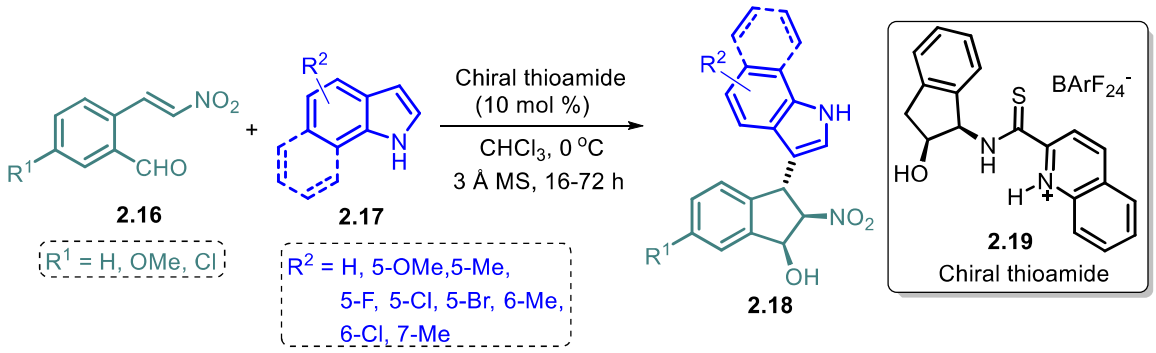
Scheme 2.3: Brønsted acid-mediated cyclization of (*Z*)- and (*E*)-(2-stilbenyl)methanols

Indoles are ubiquitous in nature and several natural and bioactive compounds contain substituted indole rings in their structural frameworks.[14] In this regard, developing strategies addressing the synthesis of indole substituted indanes or their analogues such as indanones have actively been pursued in the recent past. In 2016, Lu and co-workers have shown a palladium-catalyzed synthesis of indole-substituted indanones **2.15** from *o*-alkynylbenzaldehydes **2.13** involving the nucleophilic attack of indoles **2.14** followed by intramolecular cyclization (Scheme 2.4).[15] The formation of indanone ring depends on the electron-withdrawing group attached to the alkyne and the nucleophilicity of indole.



Scheme 2.4: Pd(II)-catalyzed tandem reaction of *o*-alkynyl aryl aldehydes with indoles

In 2013, Ender's group has developed a Michael/Henry domino reaction for the synthesis of chiral indole-substituted indanols **2.18** from *o*-nitrovinylbenzaldehydes **2.16** and indoles **2.17** in the presence of Seidel's thioamide organocatalyst **2.19** (Scheme 2.5).[16]



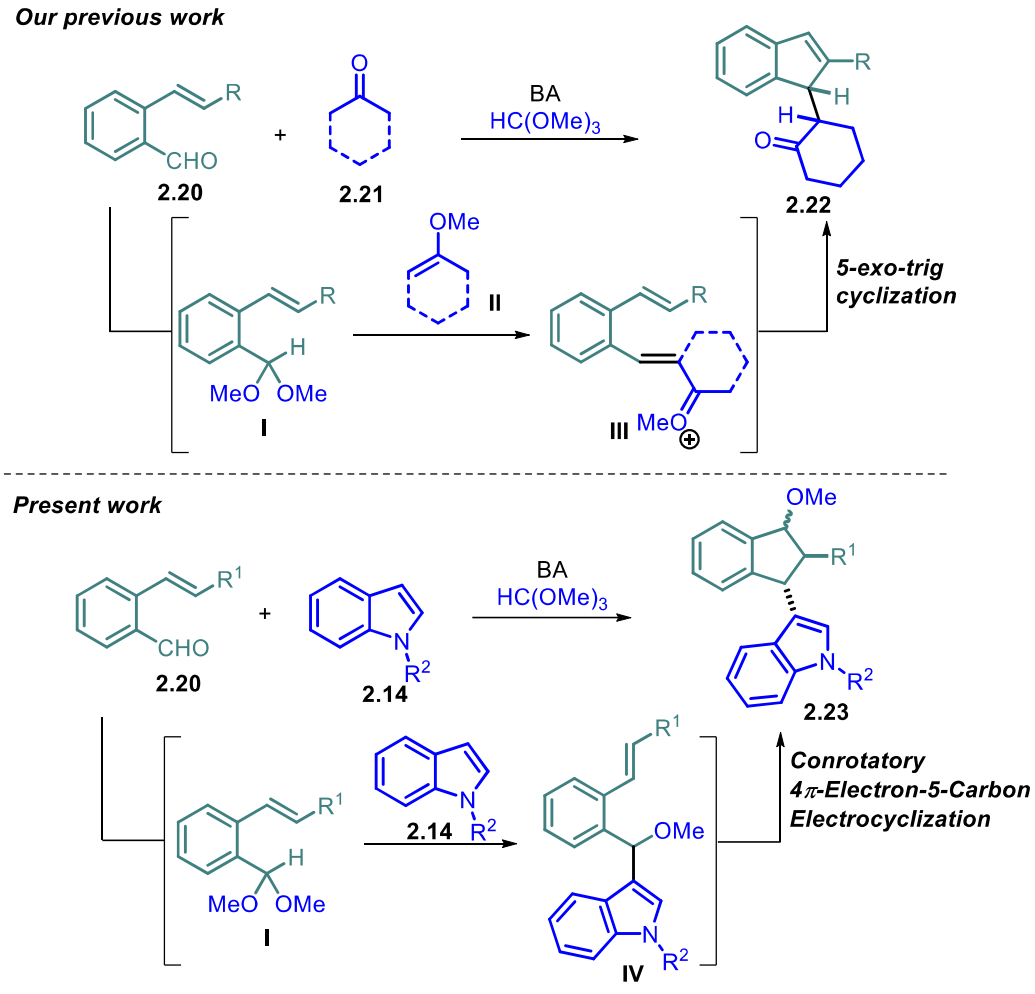
Scheme 2.5: Organocatalytic Michael/Henry domino reaction of *o*-nitrovinylbenzaldehydes with indoles

Yet, there is a necessity for developing a simple strategy to make indole-substituted indanes that does not use expensive transition metal catalysts.

2.2 Background

During our investigations on studying the reactions of *in situ* formed acetals,[17] we found out the formation of indene derivatives **2.22** from *o*-alkenylbenzaldehydes **2.20** and an enolizable ketone **2.21** in the presence of trimethyl orthoformate and catalytic TfOH (Scheme 2.6, our previous work).[17e] This reaction takes place *via* a Claisen-Schmidt condensation between the oxocarbenium ion generated from *in situ* formed acetal **I** of *o*-alkenylbenzaldehyde **2.20** and the enol ether **II** derived from the enolizable ketone **2.21** followed by cyclization of the double bond on the enone **III**. Inspired by this work, we were curious to know the reactivity of indole **2.14** with *o*-alkenylbenzaldehyde **2.20** under similar conditions. Gratifyingly, indole **2.14** reacted with *o*-

alkenylbenzaldehyde **2.20** in the presence of trimethyl orthoformate (TMOF) under triflic acid (TfOH) catalysis to afford indole-substituted indane derivatives **2.23** in a diastereoselective manner (Scheme 2.6, present work). This reactivity is significantly different from the usual reactivity of indoles of giving bisindolylmethanes upon reaction with activated carbonyls.[18] This reaction would proceed *via* a nucleophilic attack of indole **2.14** on oxocarbenium ion derived from the acetal **I** of *o*-alkenylbenzaldehyde **2.20** to form biarylmethyl methyl ether intermediate **IV** followed by a conrotatory 4π-electron-5-carbon electrocyclization of intermediate **IV** to furnish the product **2.23**. With this preliminary result, we turned our attention to optimize the reaction conditions of this reaction.



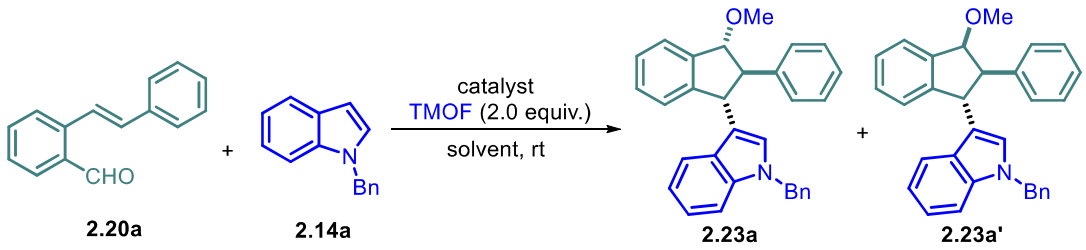
Scheme 2.6: Synthesis of indene derivatives (our previous work) and indole substituted indane derivatives (present work)

2.3 Results and discussion

2.3.1 Reaction optimization study

o-Alkenylbenzaldehyde **2.20a** and *N*-benzylindole **2.14a** were chosen as model substrates to optimize the reaction condition. Initially, we examined the reaction with different catalysts and solvents to find out the most appropriate Brønsted acid and solvent for this transformation.

Table 2.1 Optimization of the reaction conditions[a]



Entry	Amount of **2.14a** (equiv.)	Catalyst (mol %)	Solvent	Yield[b] (%)	**2.23a**:**2.23a'**[c]
1	1.2	TfOH (5)	DCM	85	1.3:1
2	1.2	TFA (5)	DCM	NR	-
3	1.2	$(Tf)_2NH$ (5)	DCM	65	1.3:1
4	1.2	*P*-TSA (5)	DCM	NR	-
5	1.2	$Cu(OTf)_2$ (5)	DCM	NR	-
6	1.2	$AuBr_3$ (5)	DCM	NR	-
7	1.2	$Sc(OTf)_3$ (5)	DCM	NR	-
8	1.2	TfOH (5)	DCE	86	1.3:1
9	1.2	TfOH (5)	$CHCl_3$	79	1.3:1
10	1.2	TfOH (5)	CH_3NO_2	60	1.2:1
11	1.2	TfOH (5)	CH_3CN	48	1.3:1
12	1.2	TfOH (10)	DCM	78	1.5:1
13[d]	1.2	TfOH (5)	DCM	70	1.3:1
14[e]	1.2	TfOH (5)	DCM	76	1.4:1
15[f]	**1**	**TfOH (5)**	**DCM**	**87**	**1.4:1**
16[g]	1.2	TfOH (5)	DCM	-	-
17[h]	1	TfOH (5)	DCM	62	2:1

[a]Reaction conditions: 1.0 equiv. of **2.20a** and 1.2 equiv. of **2.14a**, solvent (2 mL/100 mg of **2.20a**). [b]isolated yield after column chromatography. [c]diastereomeric ratio was discerned from ^1H NMR. [d]1.0 equiv of TMOF was used. [e]3.0 equiv of TMOF was used. [f]1.0 equiv. of **2.14a** and 1.2 equiv. of **2.20a** were taken. [g]Reaction was carried out in the absence of TMOF. [h]MeOH was used instead of TMOF.

Reaction of 1.0 equiv. of *o*-alkenylbenzaldehyde **2.20a** with 1.2 equiv. of *N*-benzylindole **2.14a** in the presence of 2.0 equiv. of TMOF and 5 mol% of triflic acid in dichloromethane at room temperature resulted in indole-substituted indanes **2.23a** and **2.23a'** in 85% yield as an inseparable mixture with a diastereoselectivity of 1.3:1 (Table 2.1, entry 1). It is interesting to note that only two diastereomers were obtained despite the presence of three stereocenters in the indane ring. Milder Brønsted acids like TFA and *p*-TSA were not suitable for this reaction (Table 2.1, entries 2 and 4). The yield of the product decreased considerably when bistriflimide was used (Table 2.1, entry 3). Lewis acids, such as copper triflate, gold(III) bromide, and scandium triflate were found to be ineffective to furnish the desired product (Table 2.1. entries 5-7). Triflic acid was found to be the optimal catalyst for this transformation. The TfOH-catalyzed reaction was screened in other solvents as well. Other chlorinated solvents such as DCE and $CHCl_3$ were also effective in promoting the reaction (Table 2.1, entries 8 and 9). Comparatively lower yields were noticed when the reaction was carried out in nitromethane and acetonitrile (Table 2.1, entries 10 and 11) respectively. Using 1.0 equiv. of indole **2.14a** was equally good as it resulted in 87% yield of the product with a *dr* of 1.4:1 (Table 2.1, entry 15). This condition was used for the evaluation of substrate scope. Presence of TMOF is crucial for the formation of the indane product **2.23a**/**2.23a'** as the starting *o*-alkenylbenzaldehyde **2.20a** was isolated back when a reaction was carried out in the absence of TMOF (Table 1, entry 16). In this reaction, the indole **2.14a** got decomposed in the presence of TfOH. Interestingly, this reaction underwent smoothly to afford the desired product **2.23a**/**2.23a'** with a considerable decreased yield when methanol was used as an acetalysing agent instead of TMOF (Table 2.1, entry 17).

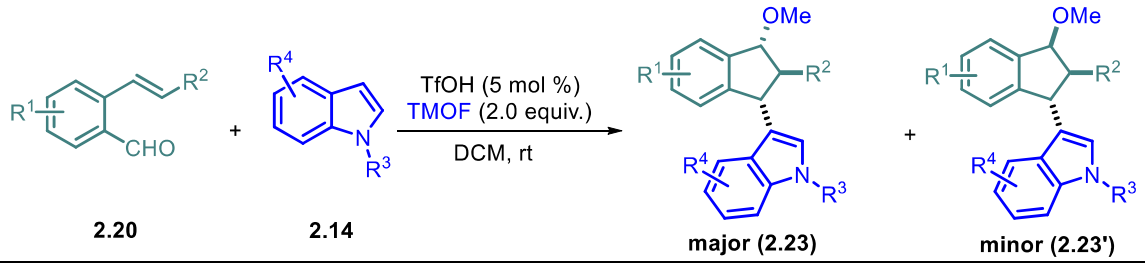
2.3.2 Substrate scope

The outcome of evaluation of the substrate scope for this transformation is depicted in the Table 2.2. The products were obtained as an inseparable mixture of diastereomers in most of the cases except **2.23g**, **2.23n**, **2.23o**, and **2.23v** where the diastereomers could be separated by column chromatography. The relative stereochemistry of the substituents in the five-membered ring of the indane products was assigned based on NOESY spectra of major and minor diastereomers of **2.23o** and diastereomeric mixture of **2.23w**. Interestingly, in both the diastereomers, the indole and the aryl ring on the adjacent carbon are in *trans* stereo relationship. In the major and the minor isomers, the OMe and the aryl groups are in *trans* and *cis* configuration respectively. These assignments were further supported by the single crystal X-ray structures of the minor isomer of **2.23g** and the major isomer of **2.23l** (Figure 2.3).

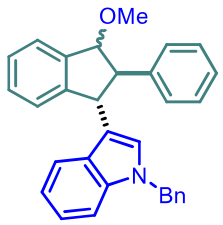
Various substituted *N*-benzylindoles (such as 5-F, 5-Br, 5-Cl, 5-CN, and 5-OMe) were subjected to react with **2.20a** under the optimized reaction conditions and the corresponding products **2.23b**, **2.23c**, **2.23d**, **2.23e**, and **2.23f** were obtained in moderate to good yields. The diastereoselectivities were generally just above 1.5:1. Indoles bearing different protecting groups such as methyl, tosyl, and allyl groups were also employed to get their respective products **2.23g**, **2.23h** and **2.23i** with yields comparatively lower than that of **2.23a**. Yield decreased considerably when *N*-tosylindole **2.14h** was used as a substrate. 2-Phenylindole gave the desired product in a

comparatively lower yield (**2.23j**, 66%). Unfortunately, the formation of indole-substituted indane derivative was not observed when indole with free N-H was employed as it was completely decomposed under reaction conditions. Although the phenyl substituent on the C2-position of indole had an effect on the yield, it did not have a notable effect on the diastereoselectivity. This is understandable as the indole and the aryl rings are in *trans* orientation in both the diastereomers. Then the effect of substituents present on the phenyl ring of *o*-alkenylbenzaldehyde **2.20** was evaluated. *o*-Alkenylbenzaldehyde **2.20** having methoxy, methyl, Cl, and F on the phenyl ring were explored. While the substrates having methoxy and methyl groups resulted in good yield of the products (**2.23k**-**2.23m**), halogen substituted substrates offered comparatively a lower yield of the products (**2.23n** and **2.23o**). It is remarkable to note that the diastereoselectivity is high (**2.23l**, 6.6:1) in the reaction of the substrate having *o*-methyl substituent on phenyl against the no diastereoselection when the methyl is at the *para* position of the phenyl (**2.23m**, 1:1). Substrate having a naphthyl ring also showed good diastereoselection {**2.23p** (3.9:1), **2.23u** (6.4:1)}. These results suggest that the steric interactions between the phenyl's *ortho*-substituent and the -OMe during quenching of the carbocation formed after the cyclization impact the diastereoselectivity (*vide supra*). *o*-Alkenylbenzaldehyde having an alkyl substituent such as **2.20q** also underwent the reaction to result in the corresponding product **2.23q** in moderate yield (56%). Substrates having substituents such as Me and F on the aryl ring were also examined and found smooth conversion to their respective products **2.23r** and **2.23s** in good yields. The reaction occurred through the C-2 carbon of the indole when the C-3 position of the indole was blocked. For example, product **2.23w** was isolated in 62% yield with 1.6:1 diastereomeric ratio when 3-methyl-*N*-benzylindole was reacted with **2.20a**. It has to be noted that the methyl substituent on the indole did not have any influence on the diastereoselectivity.

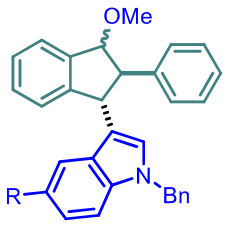
Table 2.2 Scope of indole-substituted indane synthesis[a]



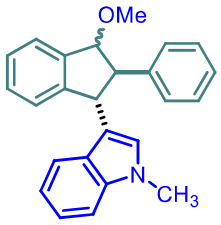
2.20 **2.14** **major (2.23)** **minor (2.23')**



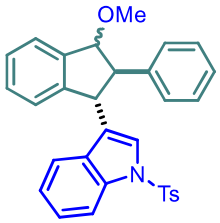
87%
2.23a/2.23a' = 1.5:1[b]



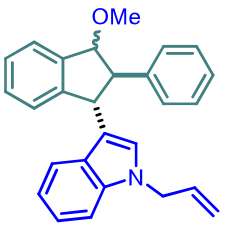
R = 5-F; 75%, **2.23b/2.23b'** = 2.3:1[b]
R = 5-Br; 58%, **2.23c/2.23c'** = 1.8:1[b]
R = 5-Cl; 62%, **2.23d/2.23d'** =1.6:1[b]
R = 5-CN; 66%, **2.23e/2.23e'** = 1.5:1[b]
R = 5-OMe; 75%, **2.23f/2.23f'** = 1.6:1[b]



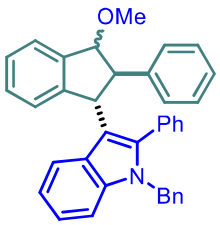
73%
2.23g/2.23g' = 1.8:1[c]



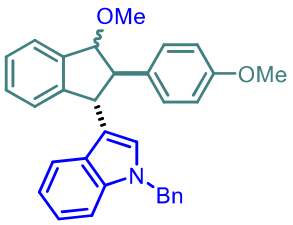
45%
2.23h/2.23h' = 1.8:1[b]



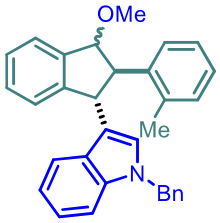
71%
2.23i/2.23i' = 1:1[b]



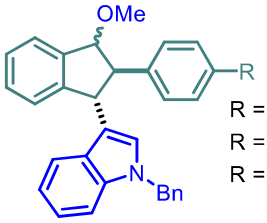
66%
2.23j/2.23j' = 1.1:1[b]



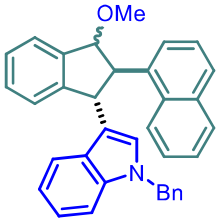
74%
2.23k/2.23k' = 1.8:1[b]



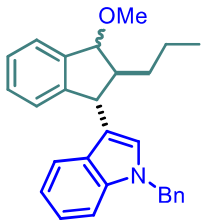
83%, **2.23l/2.23l'** = 6.6:1[b]



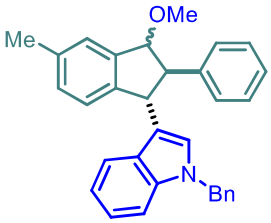
R = 4-Me; 78%, **2.23m/2.23m'** = 1:1[b]
R = 4-Cl; 63%, **2.23n/2.23n'** = 1.1:1[c]
R = 4-F; 51%, **2.23o/2.23o'** = 1.1:1[c]



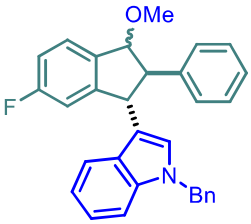
78%, **2.23p/2.23p'** = 3.9:1[b]



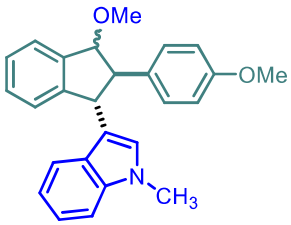
56%, **2.23q/2.23q'** = 2.1:1[b]



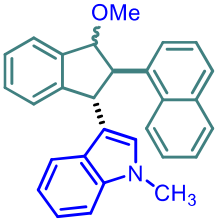
84%, **2.23r/2.23r'** = 2.4:1[b]



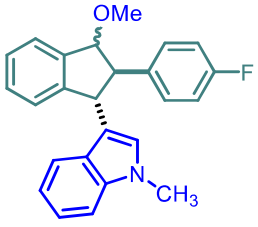
76%, **2.23s/2.23s'** = 3.6:1[b]



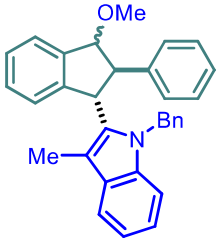
65%, **2.23t/2.23t'** = 2:1[b]



70%, **2.23u/2.23u'** = 6.4:1[b]



46%, **2.23v/2.23v'** = 1.3:1[c]

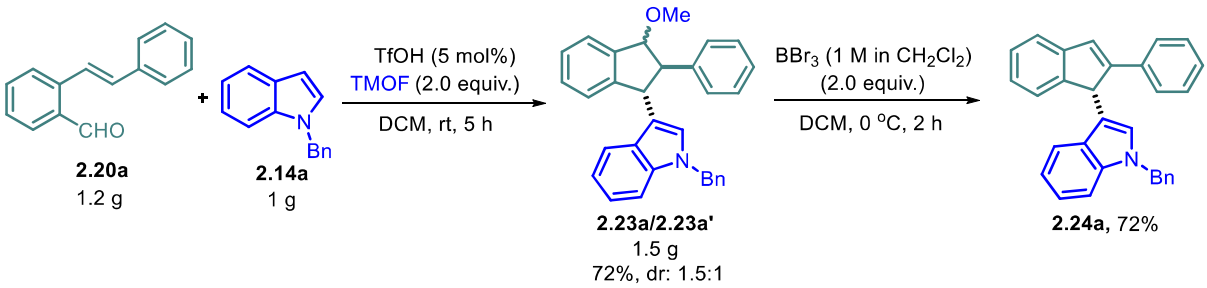


62%, **2.23w/2.23w'** = 1.6:1[b]

[a]Reaction conditions: 2.20 (1.2 equiv.), 2.14 (1.0 equiv., 100 mg), TfOH (5 mol %), TMOF (2.0 equiv.), solvent (2 mL/100 mg of 2.14). [b]d.r. was determined by ^{1}H NMR. [c]d.r. was calculated from the isolated yields.

2.3.3 Scale-up and subsequent synthetic transformation

To check the robustness of this protocol, a gram scale reaction of **2.14a** with **2.20a** under the optimized reaction condition was carried out to afford **2.23a**/**2.23a'** in 72% yield with 1.5:1 diastereoselectivity (Scheme 2.7). Treatment of **2.23a**/**2.23a'** with 2.0 equiv. of BBr_3 in DCM at 0 °C for 2 h resulted in indole-substituted indene derivative **2.24a** in 72% yield.[19]

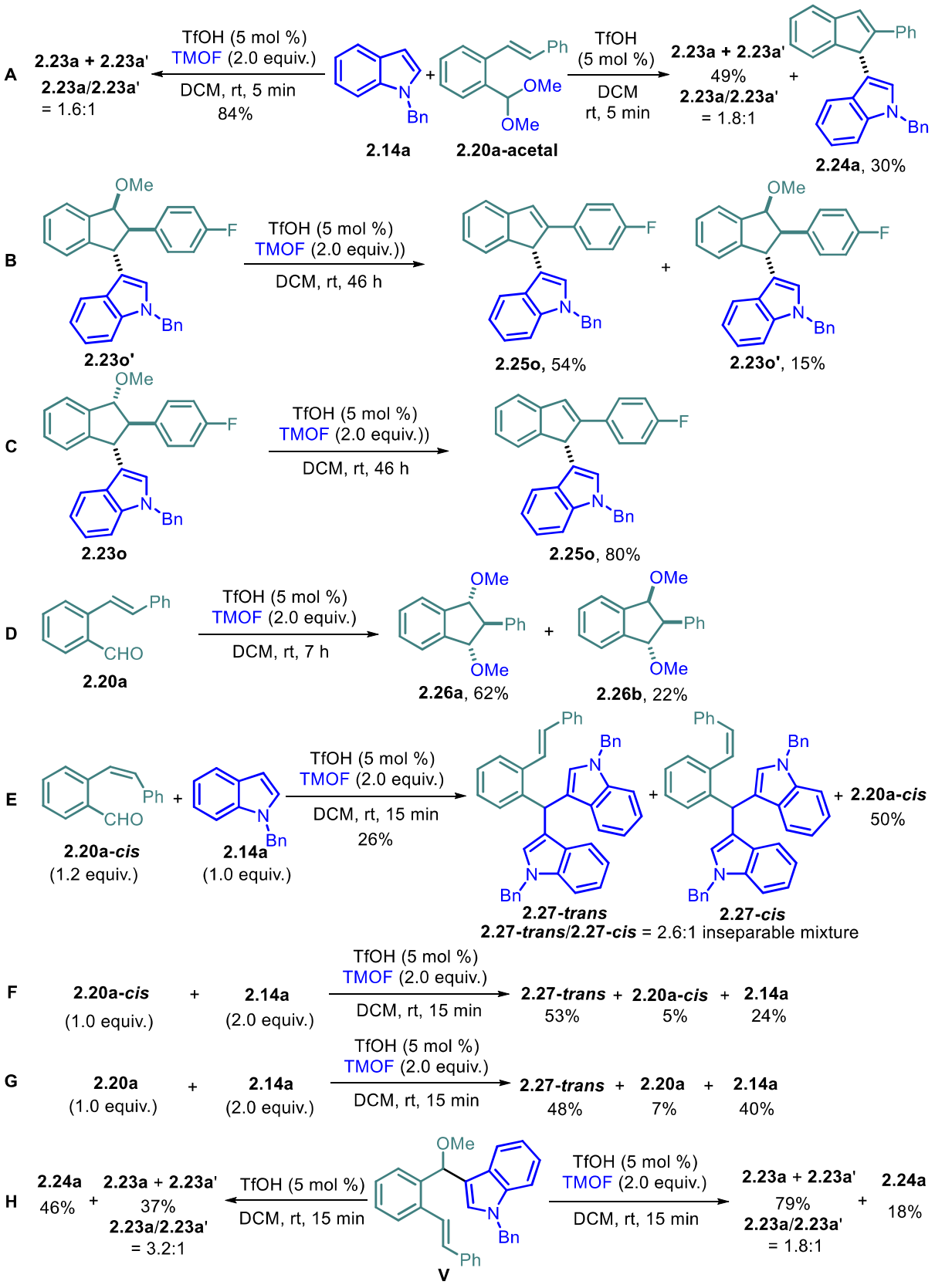


Scheme 2.7: Scale-up reaction

2.3.4 Control Experiments

In order to gain more insights into the mechanism, a series of control reactions were performed. To deduce the involvement of acetal, substrate **2.20a**-acetal[23] was synthesized from the corresponding aldehyde **2.20a**, and treated with **2.14a** in the presence of 5 mol% of triflic acid in dichloromethane at room temperature. The indole-substituted indane derivative **2.23a** was obtained in 49% yield with 1.8:1 diastereomeric ratio in addition to 30% of the corresponding indene derivative **2.24a** (Scheme 2.8A). On the other hand, the same reaction, in the presence of 2 equivalents of TMOF, yielded **2.23a** exclusively in 84% yield with 1.6:1 diastereoselectivity in 5 minutes (Scheme 2.8A). These experiments clearly demonstrate that the reaction occurs *via* the formation of acetal and the presence of TMOF in the reaction prevents the formation of eliminated product indene from the actual product indane. In addition, to check whether the diastereoselectivity is due to kinetic or thermodynamic outcome, the major and minor isomers of **2.23o** were subjected to the reaction conditions separately. From the TLC analysis, it was noted that there was no interconversion between the diastereomers. Moreover, the minor isomer of **2.23o** resulted in the formation of indene derivative **2.25o** in 54% yield after 46 h along with the unreacted **2.23o** (minor isomer), as confirmed by ^{1}H NMR (Scheme 2.8B). The major isomer of **2.23o** completely converted to **2.25o** in 46 h under the reaction conditions (Scheme 2.8C). Substrate **2.20a** was subjected to the reaction condition in the absence of indole for 7 h (Scheme 2.8D). This reaction resulted in the formation of **2.26a** and **2.26b** in a 2.5:1 diastereomeric ratio, and methanol generated from TMOF has acted as a nucleophile. In this reaction, there is a

possibility of formation of two *meso* compounds in addition to the *dl* isomer. However, only two diastereomers were obtained and, from the ^{1}H and ^{13}C NMR spectra, it was found that the major product is *meso* and the minor product is *dl* forms. NOESY spectra of the *meso* isomer **2.26a** revealed a *trans* stereorelationship between the -OMe and phenyl groups. Other possible *meso* isomer having all *cis* orientation of indane substituents was not isolated at all. However, the results are not sufficient to establish whether the reaction proceeds *via* an *iso*-Nazarov cyclization of the initially formed indole added product followed by trapping of the carbocation or concerted addition of methoxy on the double bond followed by cyclization on the oxocarbenium ion. In two separate reactions, compounds **2.26a** and **2.26b** were treated with indole **2.14a** in the presence of TfOH catalyst to check whether the compounds **2.26a** and **2.26b** are intermediates during the formation of **2.23a**. However, in both reactions, **2.23a** was not formed even after 24 h, and more than 75% of the starting materials were recovered back. Some complex product mixtures were obtained in very less amounts. Therefore, the involvement of bismethoxy compounds as intermediates in this transformation can be omitted conveniently.


A
2.23a + 2.23a'
2.23a/2.23a'
= 1.6:1
TfOH (5 mol %)
TMOF (2.0 equiv.)
DCM, rt, 5 min
84%
2.14a
2.20a-acetal
TfOH
(5 mol %)
DCM
rt, 5 min
2.23a + 2.23a'
49%
2.23a/2.23a'
= 1.8:1
2.24a, 30%
B
2.23o'
TfOH (5 mol %)
TMOF (2.0 equiv.))
DCM, rt, 46 h
2.25o, 54%
2.23o', 15%
C
2.23o
TfOH (5 mol %)
TMOF (2.0 equiv.))
DCM, rt, 46 h
2.25o, 80%
D
2.20a
TfOH (5 mol %)
TMOF (2.0 equiv.)
DCM, rt, 7 h
2.26a, 62%
2.26b, 22%
E
2.20a-cis
(1.2 equiv.)
2.14a
(1.0 equiv.)
TfOH (5 mol %)
TMOF (2.0 equiv.)
DCM, rt, 15 min
26%
2.20a-cis
50%
2.27-trans
2.27-cis
2.27-trans/2.27-cis = 2.6:1 inseparable mixture
F
2.20a-cis
(1.0 equiv.)
2.14a
(2.0 equiv.)
TfOH (5 mol %)
TMOF (2.0 equiv.)
DCM, rt, 15 min
2.27-trans 53%
2.20a-cis 5%
2.14a 24%
G
2.20a
(1.0 equiv.)
2.14a
(2.0 equiv.)
TfOH (5 mol %)
TMOF (2.0 equiv.)
DCM, rt, 15 min
2.27-trans 48%
2.20a 7%
2.14a 40%
H
2.24a
46%
2.23a + 2.23a'
37%
2.23a/2.23a'
= 3.2:1
TfOH (5 mol %)
DCM, rt, 15 min
V
TfOH (5 mol %)
TMOF (2.0 equiv.)
DCM, rt, 15 min
2.23a + 2.23a'
79%
2.23a/2.23a'
= 1.8:1
2.24a
18%

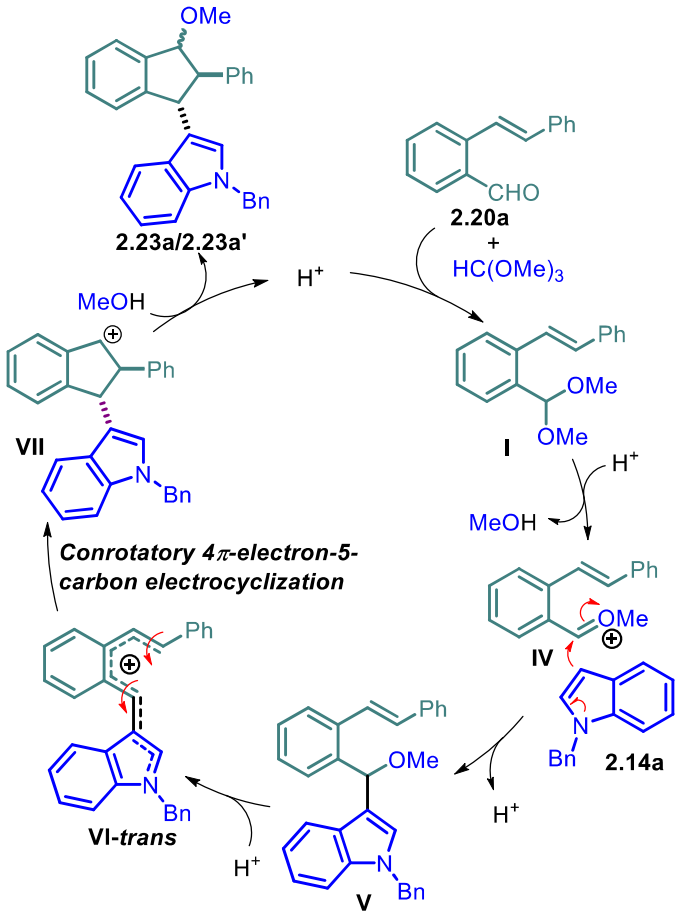
Scheme 2.8: Control Experiments

As the reactivity of a methoxy group and indole are different, there is a chance that both might have reacted differently. To get more insight, the *cis*-isomer **2.20a-*cis*** was synthesized by a slightly modified literature procedure[13b] and subjected to reaction under the optimized reaction condition (Scheme 2.8E). Interestingly, the reaction resulted in an inseparable mixture of two products along with 50% of the unreacted **2.20a-*cis***. None of the products in the mixture had an -OMe in it. From the NMR analysis of the mixture, the major and minor products were identified as bis-indolylmethane derivative **2.27-*trans*** and bis-indolylmethane derivative **2.27-*cis*** respectively in a ratio of 2.6:1. This suggested that the initial attack of indole might have happened at the carbonyl carbon activated by the formation of oxocarbenium ion. Thus, the formed diaryl methyl ether ionizes under the acidic condition to form a carbocation which might have isomerized the double bond partially before getting quenched by a molecule of indole. Certainly, the steric constraint posed by the *cis* olefin had prevented the cyclization to happen at this stage and promoted the addition of another molecule of indole on the resonance-stabilized carbocation leading to bis-indolylmethane derivative with partial isomerization of the double bond. In the presence of 2 equiv. of indole **2.14a**, the substrate **2.20a-*cis*** resulted in 53% yield of **2.27-*trans*** in 15 minutes (Scheme 2.8F). The structure of **2.27-*trans*** was further confirmed by single crystal X-ray analysis. This prompted us to react **2.20a** with 2 equiv. of **2.14a** as well. This reaction also resulted in **2.27-*trans*** in 48% yield after 15 min. It has to be noted that, in either of the cases, the formation of 1,3-bisindole substituted indane derivative *via* indole addition on oxocarbenium ion, 4π-electrocyclization, and trapping of carbocation by indole sequence was not noted. The high reactivity of indole towards aldehydes followed its usual pathway to result in bis-indolylmethane derivative. To substantiate the involvement of the addition of indole to oxocarbenium ion during the reaction, compound **V** was synthesized and subjected to two different reaction conditions separately. In the first reaction, it was treated with 5 mol% triflic acid and the product **2.23** was obtained in 37% yield with a diastereoselectivity of 3.2:1 (**2.23a/2.23a'**) along with indene derivative **2.24a** in 46% yield (Scheme 2.8H). On the other hand, compound **V**, when treated with 5 mol% of TfOH in the presence of 2 equivalents of TMOF, resulted in 79% of **2.23** (**2.23a/2.23a'** = 1.8:1) along with the indene derivative **2.24a** in 18% yield (Scheme 2.8H). These two reactions strongly support the involvement of **V** as an intermediate during the formation of the product.

2.3.5 Mechanism

Based on the control experiments, the structure of compound **2.23s** in corroboration with NOESY, and other 2D-NMR experiments, a pathway, as shown in the Scheme 2.9, can be proposed to explain the mechanism and the stereochemical outcome of the reaction. The cyclization step may be termed as 4π-electron-5-carbon electrocyclization.[20] As the reaction does not occur in the absence of TMOF, the formation of acetal **I** in the presence of catalytic TfOH is expected to initiate the reaction. This can, in turn, generate a more reactive oxocarbenium ion **IV**. At this stage, indole attacks the oxocarbenium ion to form biarylmethyl methyl ether **V**. This will undergo a facile ionization in the presence of strong TfOH to generate a resonance stabilized

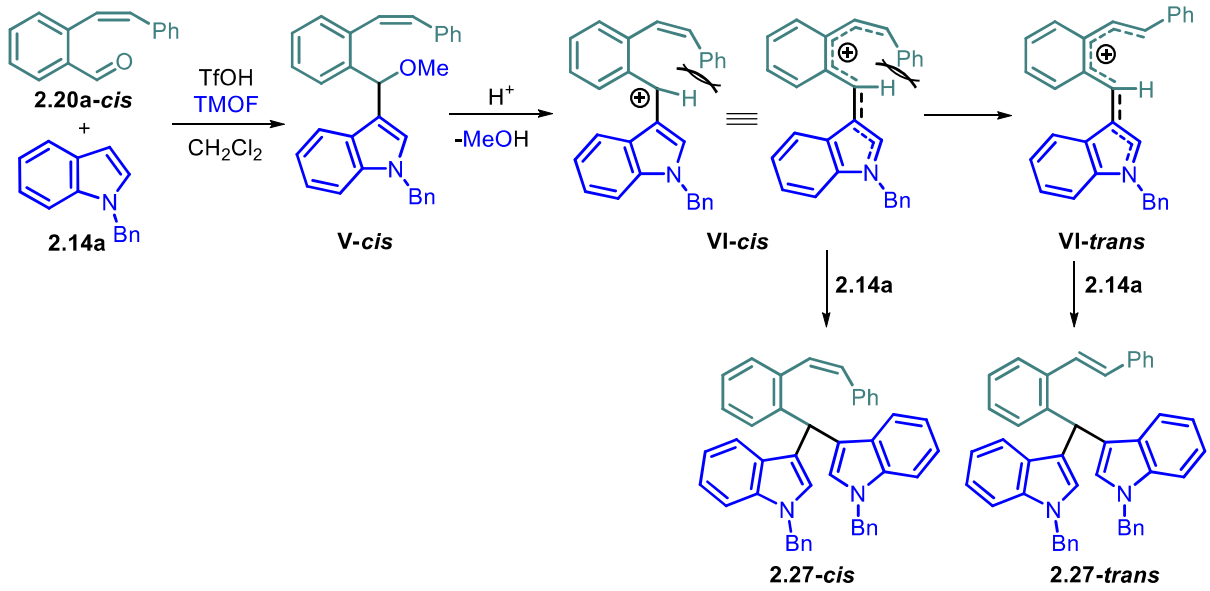
carbocation **VI**. Now a conrotatory 4π-electron-5-carbon electrocyclization[20c] can occur to form a carbocationic intermediate **VII** which will be quenched by MeOH to furnish the final product **2.23**. The exclusive *trans* stereorelationship of indole and C-2 substituent (aryl/alkyl) is due to the conrotatory electrocyclic ring-closing process. Moreover, the observed high diasteroselectivity in products **2.23l**, **2.23p**, and **2.23u** may be explained by the steric crowding at the *ortho* position of the Ar substituent, which made the MeOH to approach from the opposite side more.



Scheme 2.9: Plausible mechanism for the synthesis of **2.23**

The formation of bis-indolylmethane derivatives **2.27-*cis*** and **2.27-*trans*** may be explained based on the mechanism shown in Scheme 2.10. The intermediate **V-*cis*** which is formed after the initial addition of indole on the oxocarbenium ion of **2.20a-*cis***, would ionize in the presence of acid to form the intermediate **VI-*cis***. This will have a strong destabilizing steric interaction due to the *cis* geometry of the olefin and thus might not allow it to undergo a 4π-electrocyclization reaction. Quenching this intermediate **VI-*cis*** with another molecule of indole **2.14a** will lead to the formation of **2.27-*cis***. The presence of conjugation in **VI-*cis*** will facilitate the isomerization of the *cis* olefin to *trans* olefin to form intermediate **VI-*trans*** which on reaction with another

molecule of indole will result in **2.27-*trans***. It has to be remembered that **2.20a** (*trans* isomer), under the standard optimized condition (Table 2.1), furnished 87% of indane derivative **2.23a**. This suggests that the first indole addition to the oxocarbenium ion of **2.20a** is very fast, that all the indole (1.0 equiv.) instantly reacted with the oxocarbenium ion of **2.20a** (1.2 equiv.) to form intermediate **V** exclusively to result **2.23a** in high yield *via* 4π-electrocyclization reaction as there is no steric constraint (Scheme 2.9).



Scheme 2.10: Plausible mechanism for the formation of **2.27-*trans*** and **2.27-*cis***

2.3.6 ORTEP diagrams of 2.23g', 2.23l and 2.27-*trans*

Single crystal X-ray data for the compounds **2.23g'**, **2.23l** and **2.27-*trans*** were collected using a Bruker D8 Quest CMOS detector system [λ(Mo-Kα) = 0.71073 Å] at 298K, graphite monochromator with a ω scan width of 0.3o, crystal-detector distance 60 mm, collimator 0.5 mm. The SMART software was used for the intensity data acquisition and the SAINTPLUS software was used for the data extraction. In each case, absorption correction was performed with the help of SADABS program, an empirical absorption correction using equivalent reflections was performed with the program. The structure was solved using SHELXS-97, and full-matrix least-squares refinement against F2 was carried out using SHELXL-97.

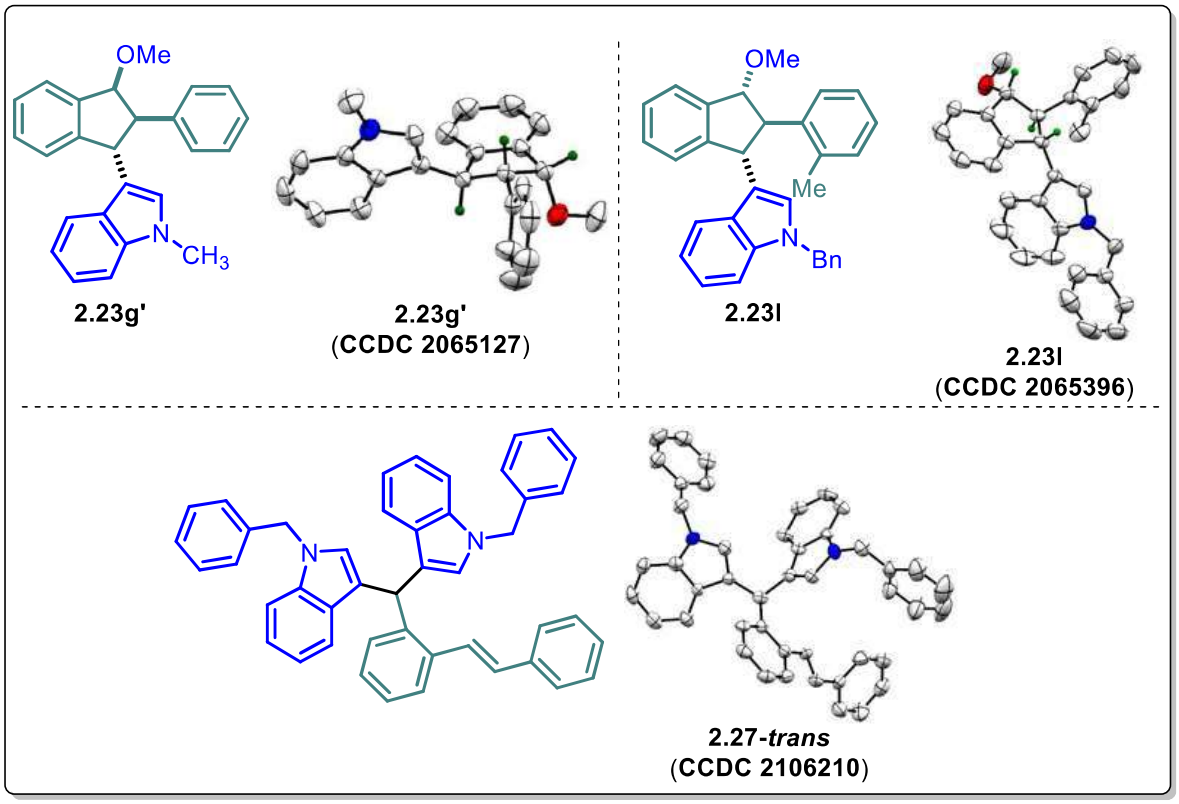


Figure 2.3: ORTEP diagrams of **2.23g'**, **2.23l** and **2.27-*trans***

2.4 Conclusions

In summary, a catalytic protocol for the synthesis of indole-substituted indane derivatives from *o*-alkenylbenzaldehydes and *N*-protected indoles has been achieved exploiting the reactivity of acetal formed *in situ*. The *cis* and *trans* isomers of *o*-alkenylbenzaldehyde show different reactivity due to their different steric environments. The success of the cyclization reaction with the *trans* isomer of *o*-alkenylbenzaldehydes is due to the high reactivity of indole on the oxocarbenium ion generated under the reaction condition and thermodynamically favourable 4π-electrocyclization with the *trans* geometry of the olefin. The 4π-conrotatory electrocyclic ring-closing process takes care of the exclusive *trans* geometry of indole and C-2 substituents in the products.

2.5 Experimental section

2.5.1 General information

Unless otherwise mentioned, all chemicals obtained from commercial suppliers were used without further purification. TfOH and TMOF were obtained from Sigma-Aldrich and Avra synthesis respectively, and were used without further purification. All reactions were performed under nitrogen atmosphere and in an oven-dried glassware with magnetic stirring. Dichloromethane (DCM) was dried in the presence of calcium hydride and distilled before use.

Reactions were monitored using silicagel plates 60 F_{254} and were visualized with UV light (254 nm), with Seebach stain followed by heating. Column chromatography was carried out using silica gel (100-200 mesh) packed in glass columns. NMR spectra were recorded at 400, 500 MHz (^{1}H) and at 100, 125 MHz (^{13}C), respectively. Chemical shifts (δ) are reported in ppm, using the residual solvent peak in $CDCl_3$ (H: δ = 7.26 and C: δ = 77.0 ppm) as internal standard, and coupling constants (J) are indicated in Hz. HRMS were recorded using ESI-TOF techniques.

2.5.2 Experimental procedures, analytical and spectral data

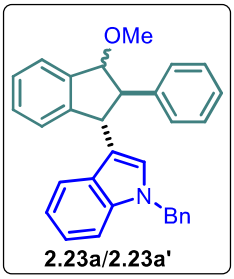
Synthesis of *o*-alkenylbenzaldehydes (2.20) and *N*-protected indoles (2.14):

o-Alkenylbenzaldehydes were prepared according to the previously reported literature.[21] *N*-protected indoles were synthesized according to the literature procedure.[22]

General procedure for the synthesis of indole substituted indane derivatives 2.23

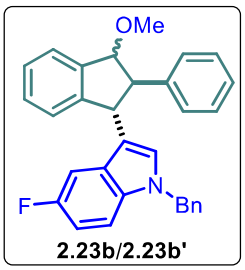
To a stirred solution of aldehyde **2.20** (1.2 equiv.), *N*-protected indole **2.14** (100 mg, 1.0 equiv.) and TMOF (2.0 equiv.) in dichloromethane (2 mL) was added triflic acid (0.05 equiv.) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at the same temperature. After completion of the reaction, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted with ethyl acetate (3x 20 mL). The combined organic layers were washed with saturated brine solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc mixture as eluent) to afford the pure product **2.23**.

2.23a/2.23a'. This compound was synthesized according to the general procedure as described above as a brown solid in 87% yield (180 mg from 100 mg of **2.14a**), mp 141-142 °C, R_f = 0.5 (10% EtOAc/hexanes). A mixture of inseparable two diastereomers (1.5:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (d, J = 7.5 Hz, 1H, major), 7.50 (d, J = 7.0 Hz, 1H, minor), 7.39-7.26 (m, 8H), 7.25-7.16 (m, 12H), 7.13-7.08 (m, 5H), 7.08-7.6.91 (m, 6H), 6.84 (s, 1H, minor), 6.83 (s, 1H, major), 5.23 (d, J = 7.0 Hz, 1H, major, one of the peak of the doublet of the major isomer is merged with N-CH peak, and the coupling constant of doublet of major isomer was calculated by using chemical shifts of N-CH peak and one of the doublet peak), 5.23 (s, 2H, N-CH, major), 5.19 (s, 2H, N-CH, minor), 5.12 (d, J = 9.0 Hz, 1H, minor), 4.85 (d, J = 5.5 Hz, 1H, minor), 4.53 (d, J = 9.0 Hz, 1H, major), 3.92 (dd, J = 9.0, 5.5 Hz, 1H, minor), 3.72 (dd, J = 9.0, 7.5 Hz, 1H, major), 3.40 (s, 3H, major), 3.21 (s, 3H, minor). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 147.0, 144.1, 143.2, 142.0, 141.5, 139.2, 137.8, 137.7, 137.1, 129.5, 128.8, 128.6, 128.5, 128.4, 127.9, 127.8, 127.6, 127.5, 127.4, 127.3, 127.2, 126.8, 126.7, 126.6, 126.5, 126.4, 125.4, 125.3, 124.9, 124.3, 121.7, 121.6, 120.1, 119.9, 119.0, 118.9, 116.2, 115.9, 109.8, 109.7, 89.5, 85.4, 62.2, 58.8, 57.6, 57.1, 49.8, 49.7, 46.5. IR (neat, cm^{-1}): 3059, 3028, 2926, 2823, 1726, 1605, 1552, 1494, 1466, 1334, 1300, 1206, 1172, 1112, 1088, 1016, 966, 739, 700. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{31}H_{28}NO$ 430.2165; found 430.2161.



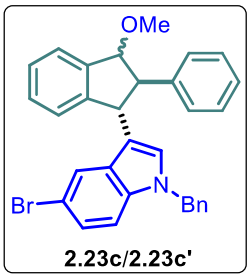
2.23a/2.23a'

2.23b/2.23b'. This compound was synthesized according to the general procedure as described above as a light brown solid in 75% yield (148 mg from 100 mg of **2.14b**), mp 157-159 °C, R_f = 0.4 (in 10% EtOAc/hexanes). A mixture of inseparable two diastereomers (2.3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 7.6 Hz, 1H, major), 7.52 (d, J = 6.8 Hz, 1H, minor), 7.43-7.24 (m, 19H), 7.17-7.08 (m, 4H), 7.01 (dd, J = 8.0, 2.0 Hz, 2H), 6.94 (dd, J = 7.2, 3.2 Hz, 1H), 6.92 (s, 1H, minor), 6.90 (s, 1H, major), 6.88-6.82 (m, 2H), 6.74 (dd, J = 9.6, 2.4 Hz, 1H), 5.24 (d, J = 7.1 Hz, 1H, major), 5.23 (s, 2H, N-CH, major), 5.20 (s, 2H, N-CH, minor), 5.07 (d, J = 9.6 Hz, 1H, minor), 4.85 (d, J = 5.6 Hz, 1H, minor), 4.49 (d, J = 9.2 Hz, 1H, major), 3.87 (dd, J = 9.2, 5.2 Hz, 1H, minor), 3.66 (dd, J = 9.2, 7.6 Hz, 1H, major), 3.42 (s, 3H, major), 3.23 (s, 3H, minor). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 158.5, 156.2, 146.2, 143.6, 143.0, 142.0, 141.5, 138.9, 137.4, 137.3, 133.7, 133.6, 129.5, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 127.9, 127.7, 127.6, 127.5, 127.4, 126.8, 126.7, 126.6, 126.5, 126.4, 125.4, 125.2, 124.7, 124.4, 116.2, 116.1, 115.7, 115.6, 110.5, 110.4, 110.3, 110.2, 110.1, 109.9, 109.8, 105.0, 104.9, 104.8, 104.7, 89.4, 85.3, 62.4, 58.9, 57.7, 57.1, 50.2, 50.1, 49.6, 46.5. IR (KBr, cm^{-1}): 3028, 2910, 2822, 1629, 1577, 1484, 1448, 1391, 1319, 1247, 1221, 1164, 1081, 1030, 978, 916, 854, 797, 704, 642, 606, 565. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{31}H_{26}FNO$ 448.2071; found 448.2073.



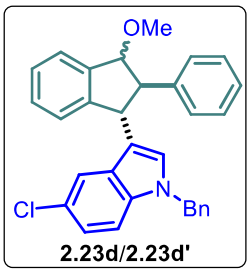
2.23b/2.23b'

2.23c/2.23c'. This compound was synthesized according to the general procedure as described above as a light brown solid in 58% yield (104 mg from 100 mg of **2.14c**), mp 166-170 °C, R_f = 0.5 (in 10% EtOAc/hexanes). A mixture of inseparable two diastereomers (1.8:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 7.6 Hz, 1H, major), 7.56 (d, J = 6.8 Hz, 1H, minor), 7.53-7.27 (m, 23H), 7.23-6.93 (m, 10H), 6.90 (s, 1H, minor), 6.89 (s, 1H, major), 5.27 (d, J = 7.6 Hz, 1H, major), 5.19 (s, 2H, N-CH, major), 5.15 (s, 2H, N-CH, minor), 4.88 (d, J = 3.2 Hz, 1H, minor), 4.87 (d, J = 4.0 Hz, 1H, minor) 4.55 (d, J = 9.2 Hz, 1H, major), 3.91 (dd, J = 9.6, 5.6 Hz, 1H, minor), 3.69 (dd, J = 8.8, 7.2 Hz, 1H, major), 3.46 (s, 3H), 3.26 (s, 3H, minor). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 146.6, 143.5, 142.9, 142.1, 141.5, 141.4, 138.9, 137.2, 135.8, 135.7, 129.6, 129.2, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 126.9, 126.8, 126.7, 126.5, 126.4, 125.6, 125.2, 124.9, 124.8, 124.7, 124.6, 124.5, 122.5, 122.4, 115.9, 115.4, 112.5, 112.4, 111.4, 111.3, 89.4, 88.8, 85.2, 62.7, 59.9, 59.0, 57.9, 57.3, 57.1, 50.1, 50.0, 49.5, 46.3. IR (KBr, cm^{-1}): 3023, 2915, 1598, 1546, 1489, 1463, 1391, 1350, 1303, 1200, 1164, 1081, 1030, 962, 864, 787, 756, 694, 642, 570, 529. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{31}H_{27}BrNO$ 508.1271; found 508.1278.



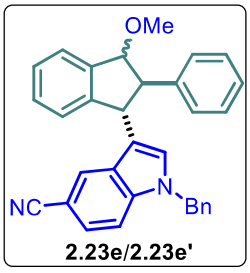
2.23c/2.23c'

2.23d/2.23d'. This compound was synthesized according to the general procedure as described above as a brown solid in 62% yield (116 mg from 100 mg of **2.14d**), mp 161-163 °C, R_f = 0.3 (in 10% EtOAc/hexanes). A mixture of inseparable two diastereomers (1.6:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, J = 7.5 Hz, 1H, major), 7.48 (d, J = 7.0 Hz, 1H, minor), 7.40-7.26 (m, 13H), 7.24 -7.21 (m, 7H), 7.13 -7.02 (m, 8H), 6.96 (dd, J = 8.0, 2.0 Hz, 2H), 6.90 (dd, J = 7.0, 3.5 Hz, 1H), 6.87 (s, 1H, minor), 6.85 (s, 1H, major), 5.20 (d, J = 5.1 Hz, 1H, major), 5.19 (s, 2H, N-CH, major), 5.17 (s, 1H, N-CH, minor), 5.05 (d, J = 9.5 Hz, 1H, minor), 4.81 (d, J = 5.5 Hz, 1H, minor), 4.47 (d, J = 9.0 Hz, 1H, major), 3.83 (dd, J = 9.5, 5.5 Hz, 1H, minor), 3.61 (dd, J = 9.0, 7.5 Hz, 1H, major), 3.39 (s, 3H), 3.19 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 146.6, 143.5, 142.9, 142.0, 141.4, 138.8, 137.3, 137.2, 135.5, 135.4, 129.5, 129.2, 129.1, 129.0, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.9, 127.8, 127.7, 127.6, 127.5, 126.8, 126.6, 126.5, 126.4, 126.3, 125.5, 125.2, 125.0, 124.9, 124.8, 124.7, 124.4, 122.0, 121.9, 119.4, 119.3, 115.9, 115.4, 110.8, 89.4, 88.7, 85.2, 62.5, 59.8, 58.9, 57.8, 57.2, 57.0, 50.1, 50.0, 49.4, 46.4. IR (KBr, cm^{-1}): 3065, 3023, 2977, 2915, 2822, 1603, 1541, 1469, 1386, 1303, 1360, 1303, 1200, 1196, 1086, 1024, 968, 792. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{31}H_{26}ClNO$ 464.1776; found 464.1784.



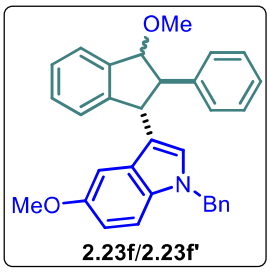
2.23d/2.23d'

2.23e/2.23e'. This compound was synthesized according to the general procedure as described above as a light brown solid in 66% yield (135 mg from 100 mg of **2.14e**), mp 152-155 °C, R_f = 0.4 (20% EtOAc/hexanes). A mixture of inseparable two diastereomers (1.5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.21 (m, 28H), 7.09-6.90 (m, 7H), 5.27 (s, 2H), 5.25-5.20 (m, 5H, one doublet corresponding to the proton bound to the carbon attached to 'OMe' group was merged with the peak corresponding to benzylic 'CH_2' group of minor isomer), 5.09 (d, J = 9.6 Hz, 1H, minor), 4.81 (d, J = 5.2 Hz, 1H, minor), 4.52 (d, J = 8.8 Hz, 1H, major), 3.79 (dd, J = 9.6, 5.2 Hz, 1H, minor), 3.56 (dd, J = 9.2, 7.6 Hz, 1H, major), 3.40 (s, 3H, major), 3.21 (s, 3H, minor). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 146.0, 142.9, 142.6, 142.1, 141.5, 138.6, 138.5, 138.4, 136.5, 129.5, 129.1, 129.0, 128.9, 128.8, 128.7, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 127.1, 127.0, 126.9, 126.7, 126.6, 126.5, 126.4, 125.8, 125.7, 125.6, 125.0, 124.8, 124.7, 124.6, 124.5, 120.8, 120.6, 117.7, 116.9, 110.7, 110.6, 102.1, 102.0, 89.3, 85.1, 63.1, 59.5, 57.9, 57.1, 50.2, 50.1, 49.4, 46.5. IR (KBr, cm^{-1}): 3023, 2920, 2218, 1608, 1474, 1458, 1360, 1174, 1081, 1030, 797, 746, 699. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{32}H_{27}N_2O$ 455.2118; found 455.2114.



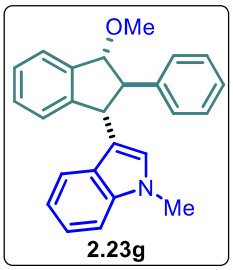
2.23e/2.23e'

2.23f/2.23f'. This compound was synthesized according to the general procedure as described above as a white solid in 75% yield (145 mg from 100 mg of **2.14f**), mp 145-147 °C, R_f = 0.5 (in 10% EtOAc/hexanes). A mixture of inseparable two diastereomers (1.6:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, J = 7.6 Hz, 1H), 7.48-7.46 (m, 1H), 7.39 (dt, J = 8.4, 1.2 Hz, 1H), 7.33 (tt, J = 8.4, 1.2 Hz, 1H), 7.29-7.19 (m, 17H), 7.13 (d, J = 7.6 Hz, 1H), 7.05 (m, 2H), 6.98 (dd, J = 8.0, 1.6 Hz, 2H), 6.92 (dd, J = 8.0, 2.8 Hz, 1H), 6.80 (s, 1H, major), 6.79 (s, 1H, minor), 6.76-6.72 (m, 2H), 6.67 (d, J = 2.4 Hz, 1H), 6.46 (d, J = 2.4 Hz, 1H), 5.20 (d, J = 7.2 Hz, 1H, major), 5.17 (s, 2H, N-CH, major), 5.13 (s, 2H, minor, N-CH, minor), 5.08 (d, J = 9.2 Hz, 1H, minor), 4.82 (d, J = 5.2 Hz, 1H, minor), 4.52 (d, J = 9.2 Hz, 1H, major), 3.84 (dd, J = 9.2, 5.6 Hz, 1H, minor), 3.66 (s, 3H, minor), 3.62 (dd, J = 8.8, 7.6 Hz, 1H, major), 3.55 (s, 3H, major), 3.37 (s, 3H, major), 3.19 (s, 3H, minor). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 153.6, 153.5, 146.9, 143.9, 143.6, 142.1, 141.6, 139.3, 137.9, 137.8, 132.3, 133.2, 129.5, 128.9, 128.8, 128.7, 128.6, 128.5, 128.2, 128.0, 127.9, 127.7, 127.5, 127.4, 127.3, 127.1, 127.0, 126.7, 126.5, 126.4, 125.5, 125.4, 125.0, 124.4, 116.1, 115.6, 111.9, 111.7, 110.6, 110.5, 101.8, 101.5, 89.8, 85.4, 62.5, 58.9, 57.6, 57.1, 55.7, 55.5, 50.1, 50.0, 49.8, 46.5. IR (neat, cm^{-1}): 3029, 2910, 1485, 1449, 1313, 1230, 1043, 791, 706, 691. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{32}H_{30}NO_2$ 460.2271; found 460.2272.



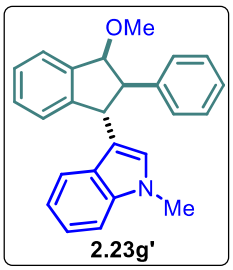
2.23f/2.23f'

2.23g (major isomer). This compound was synthesized according to the general procedure as described above as a brown solid in 47% yield (126 mg from 100 mf of **2.14g**), mp 135-137 °C, R_f = 0.4 (in 10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 7.6 Hz, 1H), 7.38 (t, J = 7.2 Hz, 1H), 7.33-7.31 (m, 2H), 7.28-7.19 (m, 5H), 7.15 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 6.96 (t, J = 6.8 Hz, 1H), 6.79 (s, 1H), 5.21 (d, J = 6.8, Hz, 1H), 4.59 (d, J = 8.8 Hz, 1H), 3.76-3.69 (m, 4H/peaks of -OMe group and H at second carbon of indane ring have merged), 3.44 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 144.4, 143.5, 141.8, 137.4, 128.6, 128.5, 127.8, 127.3, 127.0, 126.4, 125.0, 124.3, 121.4, 119.9, 118.6, 115.9, 109.1, 90.1, 62.1, 57.7, 49.4, 32.6. IR (neat, cm^{-1}): 3027, 2926, 2825, 1611, 1472, 1330, 1235, 1112, 1090, 957, 743, 702. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{25}H_{24}NO$ 354.1852; found 354.1840.



2.23g

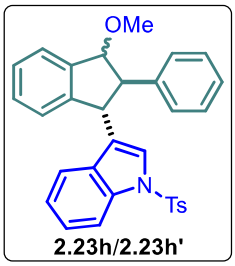
2.23g' (minor isomer). This compound was synthesized according to the general procedure as described above as a brown solid in 26% yield (70 mg from 100 mg of **2.14g**), mp 148-150 °C, R_f = 0.43 (in 10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, J = 7.0 Hz, 1H), 7.39-7.37 (m, 2H), 7.32-7.28 (m, 2H), 7.27-7.26 (m, 2H), 7.25-7.24 (m, 2H), 7.21-7.16 (m, 2H), 7.12 (d, J = 7.5 Hz, 1H), 7.00-6.97 (m, 1H), 6.74 (s, 1H), 5.10 (d, J = 8.5 Hz, 1H), 4.85 (d, J = 5.5 Hz, 1H), 3.93 (dd, J = 8.5, 5.5 Hz, 1H), 3.66 (s, 3H), 3.17 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 147.1, 141.5, 139.3, 137.4, 129.4, 128.7, 127.9, 127.3, 126.8, 126.6, 126.4, 125.4, 125.2, 121.4, 119.7, 118.6, 115.4, 109.2, 85.5, 58.6, 57.1, 46.1,



2.23g'

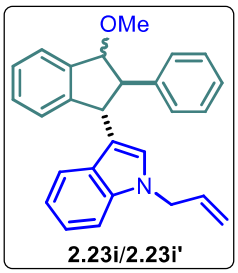
32.6. IR (neat, cm^{-1}): 2921, 1611, 1470, 1330, 1258, 1081, 921, 791, 696. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{25}H_{24}NO$ 354.1852; found 354.1848.

2.23h/2.23h'. This compound was synthesized according to the general procedure as described above as a light yellow solid in 45% yield (83 mg from 100 mg of **2.14h**), mp 228-230 °C, R_f = 0.5 (in 10% EtOAc/hexanes). A mixture of inseparable two diastereomers (1.8:1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.94-7.90 (m, 2H), 7.60 (d, J = 8.0 Hz, 2.4H), 7.52-7.20 (m, 23H), 7.17-6.98 (m, 12H), 6.93 (d, J = 8.0 Hz, 3H), 5.18 (d, J = 7.2 Hz, 1H, major), 5.02 (d, J = 9.2 Hz, 1H, minor), 4.78 (d, J = 5.6 Hz, 1H, minor), 4.42 (d, J = 8.8 Hz, 1H, major), 3.79 (dd, J = 9.2, 5.2, Hz, 1H, minor), 3.57 (dd, J = 8.8, 7.2, Hz, 1H, major), 3.36 (s, 3H, major), 3.18 (s, 3H, minor), 2.34 (s, 3H, major), 2.29 (s, 3H, minor). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 145.2, 144.7, 144.5, 142.4, 142.2, 142.0, 141.5, 138.2, 135.8, 135.0, 134.8, 130.2, 129.8, 129.7, 129.4, 129.0, 128.8, 128.6, 128.0, 127.8, 127.6, 127.1, 126.8, 126.7, 126.5, 125.6, 125.0, 124.6, 124.5, 124.4, 124.3, 123.5, 123.4, 123.0, 122.9, 120.6, 120.3, 113.9, 113.8, 89.6, 85.1, 61.5, 58.3, 57.1, 49.5, 46.2, 21.6, 21.5. IR (KBr, cm^{-1}): 3202, 2925, 2282, 1598, 1448, 1365, 1257, 1123, 1092, 1019, 973, 756, 704. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{31}H_{28}NO_3S$ 494.1784; found 494.1781.



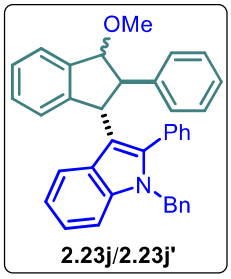
2.23h/2.23h'

2.23i/2.23i'. This compound was synthesized according to the general procedure described above as a light yellow solid in 71% yield (171 mg from 100 mg of **2.14i**), mp 128-130 °C, R_f = 0.4 (in 10% EtOAc/hexanes). A mixture of inseparable two diastereomers (1:1). ^1H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, J = 7.2 Hz, 1H, major), 7.49 (d, J = 6.8 Hz, 3.5H), 7.39-7.06 (m, 24H), 7.01-6.90 (m, 2H), 6.79 (s, 1H, major), 6.78 (s, 1H, minor), 5.98-5.86 (m, 2H), 5.20 (d, J = 7.2 Hz, 1H), 5.16-5.09 (m, 3H, one doublet corresponding to the proton bound to the carbon which is attached to the methoxy group was merged in the multiplet), 5.01-4.93 (m, 2H), 4.86 (d, J = 5.6 Hz, 1H), 4.64-4.62 (m, 2H), 4.61-4.59 (m, 2H), 4.54 (d, J = 8.8, Hz, 1H), 3.93 (dd, J = 8.8, 5.6 Hz, 1H), 3.70 (dd, J = 8.8, 7.6 Hz, 1H), 3.40 (s, 3H), 3.19 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 147.1, 144.3, 143.4, 141.9, 141.5, 139.2, 136.9, 133.5, 129.4, 128.8, 128.5, 128.4, 128.2, 127.9, 127.8, 127.5, 127.3, 127.2, 126.6, 126.5, 126.4, 126.1, 126.0, 125.4, 125.2, 124.9, 124.3, 121.4, 120.0, 119.8, 118.8, 117.0, 116.9, 116.2, 115.8, 109.6, 109.5, 89.8, 85.4, 62.1, 58.6, 57.6, 57.1, 49.6, 48.6, 48.5, 46.3. IR (neat, cm^{-1}): 2998, 1641, 1347, 1230, 1076, 965, 833, 790, 652. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{27}H_{25}NNaO$ 402.1828; found 402.1833.



2.23i/2.23i'

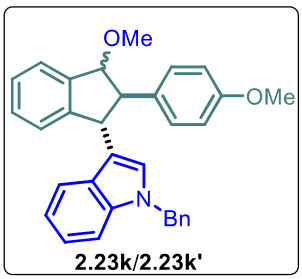
2.23j/2.23j'. This compound was synthesized according to the general procedure described above as a light yellow solid in 66% yield (135 mg from 100 mg of **2.14j**), mp 123-125 °C, R_f = 0.4 (in



2.23j/2.23j'

10% EtOAc/hexanes). A mixture of inseparable two diastereomers (1.1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, J = 6.8 Hz 1H, major), 7.49 (d, J = 7.0 Hz, 1H), 7.34-7.27 (m, 6H), 7.22-7.15 (m, 19H), 7.14-7.04 (m, 15H), 6.95-6.76 (m, 11H), 5.26 (d, J = 8.0 Hz, 1H, major), 5.11 (s, 2H, N-CH, major), 5.10 (s, 2H, N-CH, minor), 4.91 (d, J = 10.0 Hz, 1H, minor), 4.77 (d, J = 5.5 Hz, 1H, minor), 4.23 (d, J = 10.0 Hz, 1H, major), 4.03 (dd, J = 10.5, 5.5 Hz, 1H, minor), 3.96 (t, J = 8.5 HZ, 1H, major), 3.40 (s, 3H, minor), 3.14 (s, 3H, major). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 147.6, 143.8, 142.6, 141.8, 141.3, 140.7, 140.4, 138.6, 138.3, 137.2, 137.1, 131.3, 130.9, 130.1, 129.0, 128.9, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.5, 127.2, 127.0, 126.9, 126.5, 126.4, 126.3, 126.2, 126.0, 125.9, 125.5, 125.4, 124.6, 124.1, 121.7, 121.5, 120.7, 120.3, 119.3, 119.0, 112.5, 112.4, 110.4, 88.6, 85.5, 61.9, 58.3, 57.8, 57.0, 49.8, 47.3, 46.8. IR (KBr, cm^{-1}): 3029, 2824, 1492, 1365, 1140, 1027, 926, 762, 694. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{37}H_{32}NO$ 506.2478; found 506.2486.

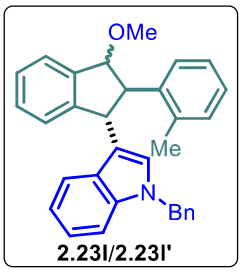
2.23k/2.23k'. This compound was synthesized according to the general procedure described above



2.23k/2.23k'

as a light yellow solid in 74% yield (163 mg from 100 mg of **2.14a**), mp 176-178 °C, R_f = 0.4 (in 10% EtOAc/hexanes). A mixture of inseparable two diastereomers (1.8:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, J = 7.6 Hz, 1H, major), 7.50 (d, J = 7.2 Hz, 1H, minor), 7.37-7.22 (m, 16H), 7.20-6.92 (m, 13H), 6.85-6.81 (m, 5H), 5.24 (s, 2H, N-CH, major), 5.21 (s, 2H, minor, N-CH, minor), 5.19 (d, J = 7.6 Hz, 1H, major), 5.06 (d, J = 9.2 Hz, 1H, minor), 4.81 (d, J = 5.6 Hz, 1H, minor), 4.48 (d, J = 9.2 Hz, 1H, major), 3.87 (dd, J = 9.2, 5.6 Hz, 1H, minor), 3.79 (s, 3H, major), 3.78 (s, 3H, minor), 3.68 (t, J = 8.4 Hz, 1H, major), 3.42 (s, 3H, major), 3.23 (s, 3H, minor). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 158.2, 147.1, 144.1, 142.0, 141.5, 137.8, 137.7, 137.1, 135.2, 131.2, 130.4, 128.8, 128.7, 128.6, 128.5, 127.6, 127.5, 127.4, 127.2, 126.8, 126.7, 126.6, 126.5, 126.3, 125.4, 125.3, 124.9, 124.2, 121.6, 120.1, 119.9, 118.9, 116.2, 115.9, 113.8, 113.3, 109.8, 109.7, 89.5, 85.3, 61.4, 58.0, 57.7, 57.1, 55.2, 55.1, 49.6, 46.8. IR (KBr, cm^{-1}): 3023, 2977, 1603, 1551, 1463, 1360, 1303, 1252, 1179, 1092, 1024, 962, 839, 740, 699. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{32}H_{30}NO_2$ 460.2271; found 460.2277.

2.23l/2.23l'. This compound was synthesized according to the general procedure described above

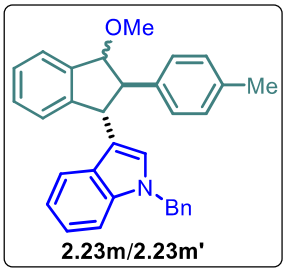


2.23l/2.23l'

as a white solid in 83% yield (177 mg from 100 mg of **2.14a**), mp 156-158 °C, R_f = 0.3 (5% EtOAc/hexanes). A mixture of inseparable two diastereomers (6.6:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 7.6 Hz, 1H, minor), 7.54 (d, J = 7.6 Hz, 1H, major), 7.50 (d, J = 7.2 Hz, 1H, minor), 7.46 (d, J = 7.6 Hz, 1H, major), 7.37 (t, J = 7.2 Hz, 1H), 7.32-7.08 (m, 12H), 7.05-6.87 (m, 6H), 6.83 (s, 1H), 5.25-5.20 (m, 4H, peaks of 'H' bound to the carbon which is attached to methoxy group and benzylic 'CH_2' group were merged), 4.85 (d, J = 5.2 Hz, 1H, minor), 4.52 (d, J = 9.2 Hz, 1H, major), 4.20 (dd, J = 10.0, 5.6 Hz, 1H, minor), 4.04 (t, J = 8.4 Hz, 1H, major), 3.35 (s, 3H, major), 3.17 (s, 3H, minor), 2.22 (s,

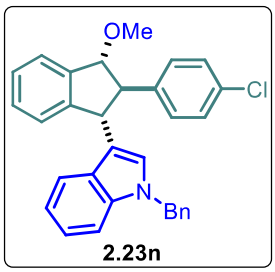
3H, minor), 1.85 (s, 3H, major). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 147.3, 144.1, 142.2, 142.0, 137.8, 137.7, 137.0, 136.7, 136.6, 130.2, 129.8, 129.2, 128.8, 128.6, 128.1, 127.7, 127.5, 127.4, 127.3, 127.2, 126.8, 126.6, 126.5, 126.2, 126.1, 126.0, 125.6, 125.5, 125.3, 124.8, 124.3, 121.6, 121.5, 120.0, 119.9, 118.9 (two peaks at same δ value), 116.4, 115.4, 109.7, 109.6, 90.4, 83.6, 58.1, 57.6, 57.2, 54.6, 50.6, 49.8, 46.0, 20.1, 19.9. IR (neat, cm^{-1}): 3027, 2926, 2824, 1605, 1553, 1493, 1464, 1354, 1334, 1300, 1203, 1171, 1110, 1088, 1015, 966, 739. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{32}H_{30}NO$ 444.2322; found 444.2325.

2.23m/2.23m'. This compound was synthesized according to the general procedure described above as a white solid in 78% yield (167 mg from 100 mg of **2.14a**), mp 149-151 °C, R_f = 0.4 (in 10% EtOAc/hexanes).A mixture of inseparable two diastereomers (1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, J = 7.5 Hz, 1H, major), 7.48 (d, J = 7.0 Hz, 1H, minor), 7.35-7.19 (m, 18H), 7.16-7.06 (m, 12H), 7.02-6.91 (m, 7H), 6.84 (s, 2H), 5.23 (s, 2H, N-CH, minor), 5.20-5.19 (m, 3H, peaks of 'H' bound to the carbon which is attached to methoxy group and benzylic 'CH_2' group were merged), 5.08 (d, J = 9.0 Hz, 1H, minor), 4.82 (d, J = 5.5 Hz, 1H, minor), 4.49 (d, J = 9.0 Hz, 1H, major) 3.89 (dd, J = 9.0, 5.5 Hz, 1H, minor), 3.68 (t, J = 7.5 Hz, 1H, major), 3.40 (s, 3H, minor), 3.21 (s, 3H, major), 2.32 (s, 3H, minor), 2.30 (s, 3H, major). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 147.2, 144.3, 142.0, 141.5, 140.2,137.8, 137.7, 137.1, 136.1, 136.0, 135.9, 129.3, 129.2, 128.8, 128.7, 128.6, 127.7, 127.6, 127.5, 127.4, 127.3 (two peaks at same δ value), 126.8, 126.7, 126.6, 126.5, 125.5, 125.4, 124.9, 124.3, 121.6, 120.2, 120.0, 118.9, 116.3, 116.0, 109.8, 109.7, 89.6, 85.4, 61.7, 58.4, 57.7, 57.1, 49.8, 46.5, 21.2, 21.1. IR (neat, cm^{-1}): 3028, 2925, 2817, 1613, 1469, 1350, 1329, 1112, 1205, 1086, 1014, 962, 802, 740. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{32}H_{30}NO$ 444.2322; found 444.2318.



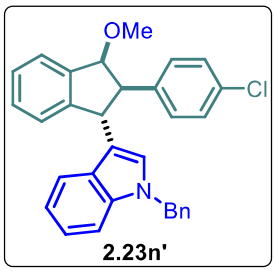
2.23m/2.23m'

2.23n (major isomer). This compound was synthesized according to the general procedure described above as a white solid in 34% yield (75 mg from 100 mg of **2.14a**), mp 148-150 °C, R_f = 0.4 (10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, J = 7.6 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.29-7.23 (m, 5H), 7.22-7.21 (m, 2H), 7.16-7.13 (m, 2H), 7.11-7.04 (m, 3H), 7.00-6.98 (m, 2H), 6.92 (t, J = 7.2 Hz, 1H), 6.80 (s, 1H), 5.21 (s, 2H), 5.17 (d, J = 7.6 Hz, 1H), 4.44 (d, J = 9.6 Hz, 1H), 3.67 (t, J = 8.8 Hz, 1H), 3.38 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 143.7, 141.7, 141.6, 137.6, 137.2, 132.2, 129.1, 128.8, 128.7, 128.6, 127.5, 127.4, 127.0, 126.8, 126.6, 124.9, 124.3, 121.7, 120.0, 119.0, 115.6, 109.8, 89.3, 61.6, 57.8, 49.8, 49.7. IR (KBr, cm^{-1}): 3028, 2930, 1494, 1458, 1396, 1355, 1205, 1174, 1123, 1092, 1009, 962, 828, 751. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{31}H_{27}ClNO$ 464.1776; found 464.1776.



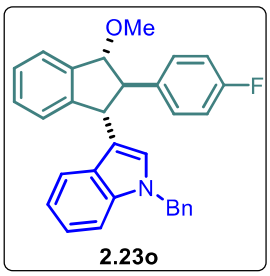
2.23n

2.23n' (minor isomer). This compound was synthesized according to the general procedure described above as a light brown solid in 29% yield (65 mg from 100 mg of **2.14a**), mp 160-162 °C, R_f = 0.5 (10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, J = 6.8 Hz, 1H), 7.31-7.25 (m, 5H), 7.22-7.21 (m, 3H), 7.19-7.08 (m, 5H), 6.98-6.91 (m, 3H), 6.80 (s, 1H), 5.17 (s, 2H), 5.02 (d, J = 9.2 Hz, 1H), 4.79 (d, J = 5.6 Hz, 1H), 3.85 (dd, J = 9.2, 5.6 Hz, 1H), 3.21 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 146.8, 141.2, 137.7, 137.6, 137.1, 132.2, 130.9, 129.0, 128.7, 128.0, 127.5, 127.3, 126.7, 126.5, 125.5, 125.4, 121.7, 119.9, 119.0, 115.4, 109.9, 85.1, 58.3, 57.0, 49.8, 46.9. IR (KBr, cm^{-1}): 3013, 2977, 2920, 2868, 2812, 1598, 1551, 1494, 1463, 1360, 1329, 1298, 1185, 1086, 1014, 962, 828, 746, 611, 503. HRMS (ESI-TOF) m/z: [M+H]$^+$ calcd for $C_{31}H_{27}ClNO$ 464.1776; found 464.1774.



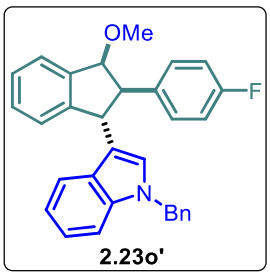
2.23n'

2.23o (major isomer). This compound was synthesized according to the general procedure described above as a white solid in 27% yield (57 mg from 100 mg of **2.14a**), mp 128-130 °C, R_f = 0.4 (10% EtOAc/hexanes). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.55 (d, J = 7.5 Hz, 1H), 7.32-7.27 (m, 5H), 7.24-7.21 (m, 2H), 7.15 (t, J = 7.5 Hz, 2H), 7.10 (d, J = 7.5 Hz, 1H), 7.04-7.03 (m, 2H), 7.00-6.94 (m, 4H), 6.85 (s, 1H), 5.25 (s, 2H), 5.21 (d, J = 8.0 Hz, 1H), 4.49 (d, J = 9.5 Hz, 1H), 3.73 (dd, J = 8.5, 7.5 Hz, 1H), 3.43 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 162.6, 160.7, 143.8, 141.8, 138.8, 138.7, 137.6, 137.2, 129.2, 129.1, 128.7, 128.6, 127.5, 127.4, 127.1, 126.7, 126.6, 124.9, 124.3, 121.7, 120.0, 119.0, 115.8, 115.3, 115.2, 109.8, 89.4, 61.5, 57.7, 49.8, 49.7. IR (neat, cm^{-1}): 2921, 2850, 1603, 1507, 1463, 1220, 1158, 1085, 740, 698. HRMS (ESI-TOF) m/z: [M+H]$^+$ calcd for $C_{31}H_{27}FNO$ 448.2071; found 448.2070.



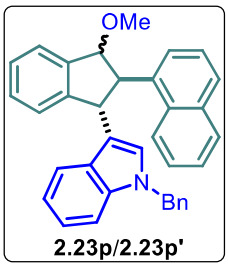
2.23o

2.23o' (minor isomer). This compound was synthesized according to the general procedure described above as a white solid in 24% yield (51 mg from 100 mg of **2.14a**), mp 134-136 °C, R_f = 0.4 (10% EtOAc/hexanes). ^{1}H NMR (500MHz, $CDCl_3$): δ 7.52 (d, J = 7.5 Hz, 1H), 7.37-7.35 (m, 3H), 7.33-7.29 (m, 2H), 7.28-7.26 (m, 2H), 7.25-7.23 (m, 2H), 7.19 (d, J = 7.5 Hz, 1H), 7.15 (t, J = 7.5 Hz, 1H), 7.02-6.95 (m, 5H), 6.85 (s, 1H), 5.23 (s, 2H), 5.07 (d, J = 9.5 Hz, 1H), 4.83 (d, J = 5.5 Hz, 1H), 3.91 (dd, J = 9.5, 5.5 Hz, 1H), 3.26 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 162.6, 160.7, 146.8, 141.3, 137.6, 137.1, 134.9, 134.8, 131.0, 130.9, 128.9, 128.7, 127.5, 127.4, 126.8, 126.7, 126.5, 125.5, 125.4, 121.7, 119.9, 119.0, 115.5, 114.7, 114.6, 109.9, 85.1, 58.1, 57.0, 49.8, 47.0. IR (neat, cm^{-1}): 3059, 3023, 2925, 2817, 1598, 1505, 1458, 1355, 1329, 1298, 1226, 1154, 1092, 1019, 962, 828, 735. HRMS (ESI-TOF) m/z: [M+H]$^+$ calcd for $C_{31}H_{27}FNO$ 448.2071; found 448.2070.



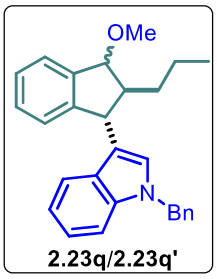
2.23o'

2.23p/2.23p'. This compound was synthesized according to the general procedure described above as a red solid in 78% yield (180 mg from 100 mg of **2.14a**), mp 173-175 °C, R_f = 0.4 (10% EtOAc/hexanes). A mixture of inseparable two diastereomers (3.9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88-7.58 (m, 7H), 7.50-7.15 (m, 15H), 7.06-6.90 (m, 4H), 6.86 (s, 1H), 5.41 (d, J = 7.2 Hz, 1H, major), 5.31 (d, J = 9.2 Hz, 1H, minor), 5.21 (s, 2H, N-CH, major), 5.17 (s, 2H, N-CH, minor), 4.99 (d, J = 4.8 Hz, 1H, minor), 4.69 (d, J = 9.2 Hz, 1H, major), 4.15 (dd, J = 9.2, 5.6 Hz, 1H, minor), 3.98 (t, J = 8.8 Hz, 1H, major), 3.46 (s, 3H, major), 3.26 (s, 1H, minor). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 147.1, 144.1, 142.0, 140.8, 137.7, 137.2, 133.6, 132.5, 129.0, 128.7, 128.6, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.4, 127.3, 127.1, 127.0, 126.9, 126.7, 126.6, 126.5, 126.0, 125.9, 125.6, 125.5, 125.4, 125.3, 124.4, 121.7, 120.3, 120.0, 119.0, 115.9, 109.8, 89.6, 85.6, 62.4, 59.0, 57.9, 57.2, 50.0, 49.8, 46.7. IR (neat, cm^{-1}): 3044, 3023, 2925, 1608, 1556, 1469, 1350, 1303, 1200, 1086, 1019, 859, 818, 740. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{35}H_{29}NNaO$ 502.2141; found 502.2141.



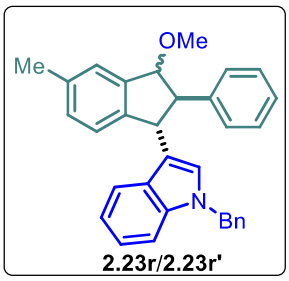
2.23p/2.23p'

2.23q/2.23q'. This compound was synthesized according to the general procedure as described above as a light brown solid in 56% yield (107 mg from 100 mg of **2.14a**), mp 142-144 °C, R_f = 0.4 (5% EtOAc/hexanes). A mixture of inseparable two diastereomers (2.1:1). ^{1}H NMR (500 MHz, $CDCl_3$): 7.48 (d, J = 7.5 Hz, 2H), 7.40 (d, J = 8.0 Hz, 1H), 7.32-7.24 (m, 12H), 7.20-7.01 (m, 12H), 6.98 (s, 1H, major), 6.86 (s, 1H, minor), 5.30 (s, 4H, N-CH, major and minor resonated at same δ value), 5.13 (d, J = 7.5 Hz, 1H, minor), 4.74 (d, J = 6.5 Hz, 1H, major), 4.69 (d, J = 2.5 Hz, 1H, minor), 4.14 (d, J = 7.5 Hz, 1H, major), 3.57 (s, 3H, major), 3.51 (s, 3H, minor), 2.76-2.66 (m, 2H), 1.78-1.66 (m, 2H), 1.53-1.42 (m, 2H), 1.35-1.25 (m, 3H), 1.08-0.95 (m, 2H), 0.90 (q, J = 7.5 Hz, 6H), 0.73 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 146.3, 145.7, 142.2, 142.0, 137.8, 137.7, 137.0, 136.7, 128.7, 128.6, 128.2, 127.5, 127.2, 126.8, 126.7, 126.6, 126.5, 126.4, 125.6, 125.0, 124.2, 121.7, 121.6, 119.8, 119.6, 119.0, 118.9, 118.1, 114.6, 109.7, 109.6, 88.9, 88.5, 56.4, 56.3, 53.2, 49.9, 49.8, 49.7, 46.2, 43.5, 36.2, 34.1, 31.3, 22.3, 21.1, 20.8, 14.6, 14.2, 14.0. IR (neat, cm^{-1}): 3028, 2953, 1453, 1351, 1172, 1077, 730, 693, 615, 573. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{28}H_{30}NO$ 396.2322; found 396.2321.



2.23q/2.23q'

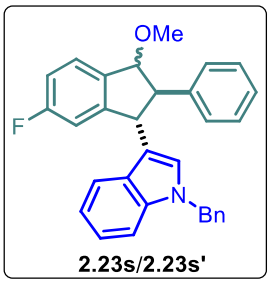
2.23r. This compound was synthesized according to the general procedure described above as a yellow solid in 84% yield (179 mg from 100 mg **2.14a**), mp 83-85 °C, R_f = 0.4 (10% EtOAc/hexanes). A mixture of inseparable two diastereomers (2.4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.20 (m, 21H), 7.16-7.06 (m, 6H), 7.03-6.91 (m, 7H), 6.84 (s, 1H), 5.23 (s, 2H, N-CH, major), 5.21 (d, J = 4.5 Hz, 1H, major), 5.20 (s, 2H, N-CH, major), 5.07 (d, J = 8.8 Hz, 1H, minor), 4.84 (d, J = 5.6 Hz, 1H, minor), 4.49 (d, J = 9.2 Hz, 1H, major), 3.92 (dd, J = 8.8, 5.6 Hz, 1H, minor), 3.70 (dd, J = 8.4, 7.2 Hz, 1H, major), 3.40 (s, 3H, major), 3.21 (s, 3H, minor), 2.4 (s, 3H, major), 1.56 (s, 3H, minor).



2.23r/2.23r'

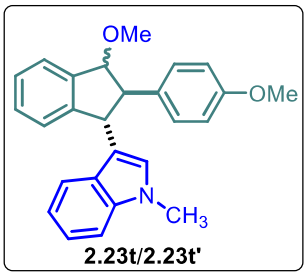
$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 143.9, 143.5, 142.0, 141.7, 141.2, 139.4, 137.8, 137.7, 137.2, 137.1 (two peaks at same δ value), 136.3, 129.7, 129.6, 129.5, 128.6, 128.4, 127.9, 127.8, 127.6, 127.5, 127.4, 127.2, 126.8, 126.7, 126.6, 126.5, 126.4, 125.9, 125.1, 124.8, 124.7, 121.6, 120.2, 120.0, 118.9, 116.5, 116.3, 109.8, 109.7, 89.6, 85.5, 62.4, 58.9, 57.7, 57.2, 49.8, 49.6, 46.3, 21.4. IR (neat, cm^{-1}): 3027, 2922, 2823, 1552, 1465, 1300, 1261, 1030, 965, 740. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{32}H_{30}NO$ 444.2322; found 444.2324.

2.23s/2.23s'. This compound was synthesized according to the general procedure described above as a yellow solid in 76% yield (163 mg from 100 mg of **2.14a**), mp 114-116 °C, R_f = 0.4 (10% EtOAc/hexanes). A mixture of inseparable two diastereomers (3.6:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (dd, J = 8.4, 5.2 Hz, 1H), 7.45 (dd, J = 9.0, 5.2 Hz, 1H, minor), 7.39-7.37 (m, 1H, minor), 7.31-7.21 (m, 13H), 7.15-6.93 (m, 9H), 6.86 (s, 1H, minor), 6.84 (s, 1H, major), 6.76 (dd, J = 8.8, 1.6 Hz, 1H), 5.24 (s, 2H, N-CH, major), 5.21 (s, 2H, N-CH, minor), 5.17 (d, J = 7.2 Hz, 1H, major), 5.10 (d, J = 9.6 Hz, 1H, minor), 4.81 (d, J = 5.6 Hz, 1H, minor), 4.49 (d, J = 9.2 Hz, 1H, major), 3.95 (dd, J = 9.6, 5.6 Hz, 1H, minor), 3.74 (dd, J = 8.8, 7.2 Hz, 1H, major), 3.38 (s, 3H, major), 3.18 (s, 1H, minor). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 163.5 (d, J = 244.0 Hz), 146.6 (d, J = 8.0 Hz), 138.7, 137.6, 137.5, 137.1, 129.4, 128.7, 128.5, 127.9, 127.7, 127.5, 127.4, 126.9, 126.8, 126.7, 126.6, 126.5, 125.7 (d, J = 9.0 Hz), 121.7, 119.9, 119.7, 119.1, 115.4, 115.0, 114.6 (d, J = 23.0 Hz), 113.8, 112.5, 112.3, 111.7 (d, J = 22.0 Hz), 109.9, 109.8, 88.8, 84.6, 62.5, 59.1, 57.7, 57.0, 49.8, 49.7. IR (neat, cm^{-1}): 3023, 2921, 1605, 1486, 1356, 1350, 1262, 1211, 1200, 1174, 1100, 948, 863, 817, 745. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{31}H_{26}FNNaO$ 470.1891; found 470.1892.



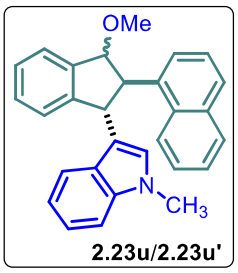
2.23s/2.23s'

2.23t/2.23t'. This compound was synthesized according to the general procedure as described above as a red solid in 65% yield (191 mg from 100 mg of **2.14g**), mp 155-157 °C, R_f = 0.4 (10% EtOAc/hexanes). A mixture of inseparable two diastereomers (2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, J = 7.5 Hz, 1H, major), 7.48 (d, J = 7.0, Hz, 1H, minor), 7.35-7.23 (m, 8H), 7.20-7.11 (m, 6H), 7.05 (d, J = 7.5 Hz, 1H),7.01-6.92 (m, 2H), 6.84-6.80 (m, 3H), 6.76 (s, 1H, major), 6.74 (s, 1H, minor), 5.12 (d, J = 7.5 Hz, 1H, major), 5.05 (d, J = 8.5 Hz, 1H, minor), 4.80 (d, J = 5.5 Hz, 1H, minor), 4.51 (d, J = 8.5 Hz, 1H, major), 3.87 (dd, J = 9.0, 5.5 Hz, 1H, minor), 3.79 (s, 3H, major), 3.77 (s, 3H, minor), 3.70 (s, 3H, major), 3.68-3.64 (m, 4H, 'dd' of major isomer and 's' of minor isomer were merged), 3.42 (s, 3H, major), 3.20 (s, 3H, minor). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 158.3, 147.3, 144.5, 142.0, 141.6, 137.5, 135.5, 131.3, 130.4, 128.8, 128.5, 127.4, 127.3, 127.1, 127.0, 126.6, 125.5, 125.4, 125.0, 124.3, 121.4, 120.0, 119.8, 118.7, 115.9, 115.4, 113.9, 113.4, 109.3, 109.2, 90.1, 85.5, 61.4, 58.0, 57.7, 57.1, 55.2, 55.1, 49.3, 46.4, 32.6. IR (neat, cm^{-1}): 2932, 2828, 1610, 1510, 1462, 1244, 1177, 1108, 1085, 1032, 826, 738. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{26}H_{25}NNaO_2$ 406.1778; found 406.1781.



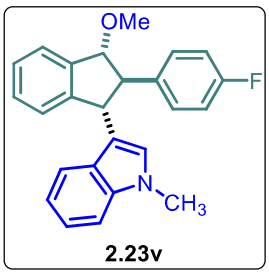
2.23t/2.23t'

2.23u/2.23u'. This compound was synthesized according to the general procedure described above as a red solid in 70% yield (215 mg from 100 mg of **2.14g**), mp 154-156 °C, R_f = 0.4 (10% EtOAc/hexanes). A mixture of inseparable two diastereomers (6.4:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81-7.28 (m, 5H), 7.60 (dd, J = 8.5, 2.0 Hz, 1H), 7.56 (d, J = 7.5 Hz, 1H, minor), 7.53 (d, J = 7.0 Hz, 1H, major), 7.47-7.40 (m, 3H), 7.38(tt, J = 8.5,1.0 Hz, 1H, minor), 7.34 (tt, J = 7.5, 1.0 Hz, 1H, major), 7.30-7.24 (m, 4H), 7.20-7.08 (m, 3H), 7.01-6.98 (m, 1H, major), 6.93-6.90 (m, 1H, minor), 6.76 (s, 1H, major), 6.74 (s, 1H, minor), 5.28 (d, J = 7.5 Hz, 1H, minor), 5.24 (d, J = 9.0 Hz, 1H, major), 4.93 (d, J = 6.0 Hz, 1H, major), 4.67 (d, J = 8.5 Hz, 1H, minor), 4.10 (dd, J = 9.0, 5.5 Hz, 1H, major), 3.90 (dd, J = 8.5, 7.0 Hz, 1H, minor), 3.67 (s, 3H, minor), 3.63 (s, 3H, major), 3.41 (s, 3H, minor), 3.18 (s, 3H, major). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 147.2, 144.4, 141.9, 141.4, 141.0, 137.5, 137.0, 133.6, 133.4, 132.5, 132.4, 128.9, 128.7, 128.2, 128.1, 127.9, 127.8, 127.7, 127.5, 127.4, 127.3, 127.2, 127.1, 126.9, 126.7, 126.0, 125.6, 125.5, 125.4, 125.3, 125.1, 124.4, 121.4, 121.0, 119.8, 118.6, 115.7, 115.2, 109.3, 109.2, 90.2, 85.7, 62.4, 59.0, 57.9, 57.2, 49.7, 46.3, 32.6. IR (neat, cm^{-1}): 2846, 1508, 1272, 1182, 1142, 948, 855, 764. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{29}H_{26}NO$ 404.2009; found 404.2016.



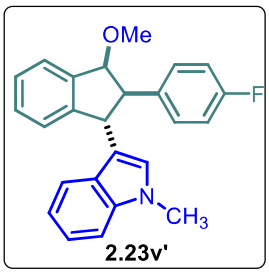
2.23u/2.23u'

2.23v (major isomer). This compound was synthesized according to the general procedure as described above as a white solid in 26% yield (72 mg from 100 mg of **2.14g**), mp 125-127 °C, R_f = 0.3 (10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (d, J = 7.5 Hz, 1H), 7.36 (tt, J = 7.5, 1.0 Hz, 1H), 7.31-7.27 (m, 2H), 7.25-7.22 (m, 2H), 7.22-7.18 (m, 1H), 7.12 (dt, J = 8.0, 1.0 Hz, 1H), 7.08 (d, J = 7.5 Hz, 1H), 6.99 (dt, J = 9.0, 3.0 Hz, 1H), 6.97-6.94 (m, 2H), 6.77 (s, 1H), 5.15 (d, J = 7.0 Hz, 1H), 4.52 (d, J = 9.0 Hz, 1H), 3.72-3.71 (m, 4H, dd and s appearing together), 3.43 (s, 3H) ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 162.6, 160.7, 144.2, 141.7, 139.06, 139.04, 137.4, 129.2, 129.1, 128.6, 127.3, 127.0, 126.9, 125.0, 124.3, 121.5, 119.8, 118.7, 115.6, 115.4, 115.2, 109.2, 90.0, 61.4, 57.7, 49.4, 32.6. IR (neat, cm^{-1}): 2932, 2825, 1507, 1472, 1222, 1155, 1092, 836, 739. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{25}H_{23}FNO$ 372.1758; found 372.1761.



2.23v

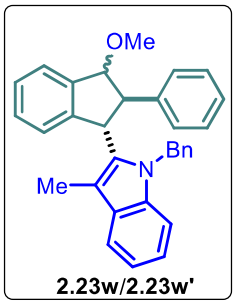
2.23v' (minor isomer). This compound was synthesized according to the general procedure as described above as a light brown solid in 20% yield (55 mg from 100 mg of **2.14g**), mp 158-160 °C, R_f = 0.4 (10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 (d, J = 7.0 Hz, 1H), 7.37-7.33 (m, 3H), 7.32-7.30 (m, 1H), 7.92-7.27 (m, 2H), 7.24-7.22 (m, 1H), 7.20-7.18 (m, 1H), 7.13 (d, J = 7.0 Hz, 1H), 7.02-6.98 (m, 1H), 6.96 (tt, J = 9.0, 3.0 Hz, 2H), 6.74 (s, 1H), 5.04 (d, J = 9.0 Hz, 1H), 4.82 (d, J = 5.5 Hz, 1H), 3.90 (dd, J = 9.0 Hz, 5.5 Hz, 1H), 3.68 (s, 3H), 3.21 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 162.6, 160.7, 146.9, 141.3, 137.5, 134.9, 134.9, 130.9, 130.8, 128.8, 127.2, 126.9, 126.7, 125.4, 125.3, 121.5, 119.7, 118.6, 115.2, 114.7, 114.6, 109.3, 85.3, 58.1, 57.0, 46.7, 32.6. IR (neat,



2.23v'

cm^{-1}): 2932, 2890, 1506, 1471, 1218, 1154, 1068, 991, 738. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{25}H_{23}FNO$ 372.1758; found 372.1758.

2.23w/2.23w'. This compound was synthesized according to the general procedure as described above as a brown solid in 62% yield (120 mg from 100 mg of **2.14k**), mp 90-92 °C, R_f = 0.4 (10% EtOAc/hexanes). A mixture of inseparable two diastereomers (1.6:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (d, J = 7.0 Hz, 1H), 7.52-7.49 (m, 4H), 7.35-7.27 (m, 7H), 7.23-7.21 (m, 12H), 7.18-7.15 (m, 4H), 7.13-7.11 (m, 5H), 7.08-7.05 (m, 4H), 6.87 (d, J = 7.5 Hz, 1H), 6.84 (d, J = 7.5 Hz, 1H), 6.79 (d, J = 7.0 Hz, 2H, major), 6.75 (d, J = 6.0 Hz, 2H, minor), 5.20 (d, J = 7.5 Hz, 1H, major), 5.15 (d, J = 7.0 Hz, 1H, minor), 5.11 (d, J = 18.0 Hz, 1H, N-CH, minor), 5.01 (d, J = 17.0 Hz, 1H, N-CH, major), 4.95 (d, J = 17.5 Hz, 1H, N-CH, minor), 4.88 (d, J = 10.0 Hz, 1H, minor), 4.42 (d, J = 9.5 Hz, 1H, major), 4.29 (d, J = 17.5 Hz, 1H, N-CH, major), 3.74 (t, J = 8.5 Hz, 1H, major), 3.52 (t, J = 8.5 Hz, 1H, minor), 3.39 (s, 3H, major), 3.09 (s, 3H, minor), 1.99 (s, 3H, minor), 1.91 (s, 3H, major). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 142.7, 142.6, 142.0, 141.9, 141.6, 141.5, 138.3, 138.2, 138.1, 137.6, 136.5, 136.3, 133.9, 129.8, 128.9, 128.8, 128.6, 128.5, 128.4, 128.1, 127.8, 127.6, 127.4, 127.11, 127.09, 127.0, 126.8, 126.6, 126.0, 125.8, 125.6, 124.8, 124.5, 124.4, 124.1, 121.6, 121.3, 118.9, 118.5, 118.2, 110.9, 109.7, 109.3, 109.1, 108.5, 89.8, 89.2, 62.5, 58.9, 57.8, 57.3, 56.8, 49.6, 49.3, 47.5, 45.8, 9.5, 9.3. IR (neat, cm^{-1}): 3059, 3023, 2920, 2822, 1603, 1469, 1350, 1262, 1179, 1092, 1030, 746, 694. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{32}H_{30}NO$ 444.2322; found 444.2317.

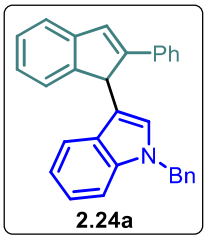


2.23w/2.23w'

Reaction of 2.20a-acetal with 2.14a:

To a stirred solution of **2.14a** (83 mg, 0.4 mmol, 1.0 equiv.) and **2.20a-acetal**[23] (122 mg, 0.48 mmol, 1.2 equiv.) in CH_2Cl_2 (4 mL) was added triflic acid (1.8 µL, 0.02 mmol, 0.05 equiv.) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 5 min. Then, the reaction mixture was quenched with saturated aqueous sodium bicarbonate solution, and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with saturated aqueous brine solution, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/hexanes mixture as eluent) to afford pure **2.23a** in 49% (84 mg) and **2.24a** in 30% yield respectively.

2.24a. white solid, mp 163-165 °C, R_f = 0.5 (5% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 7.6 Hz, 2H), 7.38 (s, 1H), 7.35 (d, J = 7.2 Hz, 1H), 7.27-7.22 (m, 3H), 7.20-7.18 (m, 3H), 7.17-7.15 (m, 2H), 7.08 (t, J = 6.8 Hz, 2H), 6.99 (t, J = 7.6 Hz, 1H), 6.92 (s, 1H), 6.89-6.88 (m, 2H), 5.31 (s, 1H), 5.22, 5.17 (ABq, 2H, J_{AB} = 16.4 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 149.8, 148.9, 143.1, 137.6, 136.8, 135.4, 128.6, 128.2, 127.6, 127.4, 127.3, 127.1, 126.9, 126.8, 126.4, 125.3, 123.7, 121.7, 121.0, 119.5, 119.2, 112.9,

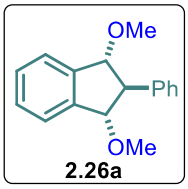


2.24a

109.7, 49.7, 47.7. IR (neat, cm^{-1}): 3023, 2920, 1460, 1332, 1172, 1023, 867, 750, 731. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{30}H_{24}N$ 398.1903; found 398.1907.

Synthesis of 2.26a and 2.26b: To a stirred solution of **2.20a** (50 mg, 0.24 mmol, 1.0 equiv.) in CH_2Cl_2 (1 mL) was added TMOF (51 µL, 0.48 mmol, 2.0 equiv.), and TfOH (1.0 µL, 0.012 mmol, 0.05 equiv.) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 7 h. After complete conversion of the starting material as shown by TLC, the reaction mixture was quenched with saturated aqueous sodium bicarbonate solution, and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with saturated aqueous brine solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/hexanes mixture as eluent) to afford the pure **2.26a** and **2.26b**.

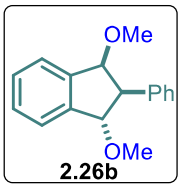
2.26a (major isomer): This compound was obtained as a yellow liquid in 62% yield (38 mg from



2.26a

50 mg of **2.20a**), R_f = 0.5 (5% EtOAc/hexanes). ^1H NMR (500 MHz, $CDCl_3$): δ 7.46-7.43 (m, 2H), 7.41-7.37 (m, 2H), 7.35-7.32 (m, 2H), 7.30-7.28 (m, 2H), 7.26 (tt, J = 9.0, 1.5 Hz, 1H), 4.80 (d, J = 6.0 Hz, 2H), 3.49 (t, J = 6.0 Hz, 1H), 3.38 (s, 6H (2×OMe)). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 143.3, 141.5 (2×C), 129 (2×C), 128.9 (2×C), 127.6 (2×C), 126.7, 124.8 (2×C), 88.7 (2×C), 59.9, 57.2 (2×C (OMe)). IR (neat, cm^{-1}): HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{17}H_{18}NaO_2$ 277.1199; found 277.1200.

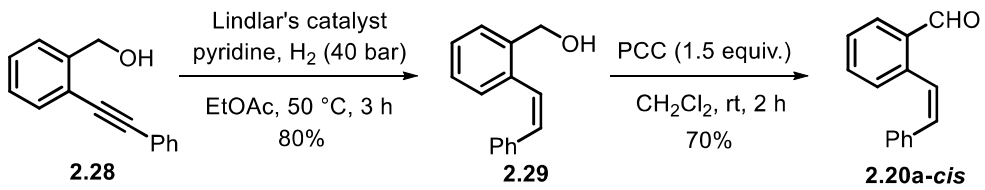
2.26b (minor isomer): This compound was obtained as a yellow liquid in 22% yield (13.2 mg from



2.26b

50 mg of **2.20a**), R_f = 0.6 (5% EtOAc/hexanes). ^1H NMR (500 MHz, $CDCl_3$): δ 7.47-7.45 (m, 1H), 7.43-7.41 (m, 1H), 7.38-7.35 (m, 2H), 7.30-7.29 (m, 4H), 7.26-7.7.22 (m, 1H), 5.15 (d, J = 5.5 Hz, 1H), 4.88 (d, J = 6.0 Hz, 1H), 3.65 (t, J = 6.0 Hz, 1H), 3.37 (s, 3H), 3.14 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 142.9, 142.0, 138.7, 129.3 (2×C), 128.8, 128.5, 128.1 (2×C), 126.7, 125.4, 125.1, 88.0, 84.5, 57.8, 57.7, 57.3. IR (neat, cm^{-1}): HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{17}H_{18}NaO_2$ 277.1199; found 277.1199.

Synthesis of 2.20a-*cis*:



2.28 **2.29** **2.20a-*cis***

Scheme 2.11: Synthesis of **2.20a-*cis***

Step 1:

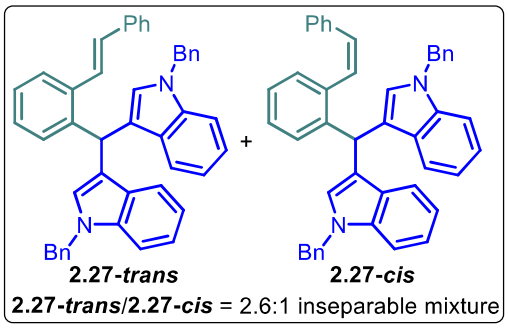
Pyridine (348 µL, 4.32 mmol, 3.0 equiv.) was added to a solution of the compound **2.28**[13b] (300 mg, 1.44 mmol, 1.0 equiv.) in ethyl acetate and the resulting solution was allowed to pass through H-cube instrument. Catcart was filled with Lindlar's catalyst (300 mg) and silica gel. After 3 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/hexanes mixture as eluent) to get the pure compound **2.29** in 80% (240 mg) yield as a yellow sticky gum.[13b]

Step 2:

To a stirred solution of **2.29** (200 mg, 0.94 mmol, 1.0 equiv.) in CH_2Cl_2 (8 mL) was added pyridinium chlorochromate (PCC) (304 mg, 1.41 mmol, 1.5 equiv.) at room temperature for 2 h. The resulting mixture was filtered over celite and concentrated. The residue was purified by column chromatography (silica gel, EtOAc/hexanes mixture as eluent) to get pure compound **2.20a-*cis*** (138 mg) as a yellow sticky gum.[13b] ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.25 (s, 1H), 7.89 (dd, J = 7.5, 1.0 Hz, 1H), 7.47 (td, J = 7.5, 1.0 Hz, 1H), 7.42-7.38 (m, 1H), 7.28 (d, J = 7.5 Hz, 1H), 7.16-7.13 (m, 3H), 7.05-7.02 (m, 2H), 6.98 (d, J = 12.5 Hz, 1H), 6.38 (d, J = 12.0 Hz, 1H).

Reaction of 2.20a-*cis* with indole 2.14:

To a stirred solution of **2.14a** (20 mg, 0.096 mmol, 1.0 equiv.), **2.20a-*cis*** (24 mg, 0.1152 mmol, 1.2 equiv.), and TMOF (21 µL, 0.192 mmol, 2.0 equiv.) in CH_2Cl_2 (1.0 mL) was added TfOH (0.42 µL, 0.0048 mmol, 0.05 equiv.) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 15 min and found complete consumption of **2.14a**. Then the reaction mixture was quenched with saturated aqueous sodium bicarbonate solution, and extracted with ethyl acetate (3 x 3 mL). The combined organic layers were washed with saturated brine solution, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/hexanes mixture as eluent) to afford **2.27-*trans*** and **2.27-*cis*** as an inseparable mixture in 26% yield (15 mg). In addition, 50% of unreacted **2.20a-*cis*** was also recovered.



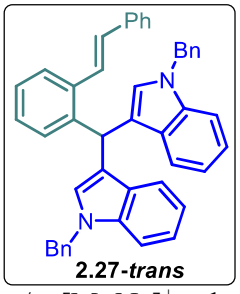
2.27-*trans* and **2.27-*cis***: mp 148-150 °C, R_f = 0.25 (in 5% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69-7.67 (m, 0.68H), 7.57 (d, J = 16.0 Hz, 0.72H), 7.42 (d, J = 8.0 Hz, 1.4H), 7.35 (d, J = 8.0 Hz, 0.62H), 7.28-7.12 (m, 18H), 7.08 (ddd, J = 13.0, 5.5, 1.0 Hz, 0.62H), 7.03-6.98 (m, 6H), 6.97-6.94 (m, 0.63H), 6.75 (d, J = 12.0 Hz, 0.28H), 6.68 (s, 1H), 6.64 (s, 0.51H), 6.56 (d, J = 12.0 Hz, 0.26H), 6.29 (s, 0.66H), 6.17 (s, 0.24H), 5.24, 5.20 (ABq, 2.6H, J_{AB} = 16.4 Hz), 5.21 (s, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 141.9, 141.5, 137.9, 137.8, 137.6, 137.1, 136.9, 136.8, 136.2, 130.7, 130.2, 129.5, 129.0, 128.7, 128.65, 128.62, 128.60, 128.5, 128.3, 128.2, 128.0, 127.9, 127.8, 127.5, 127.4, 127.35, 127.33, 126.9, 126.5, 126.48, 126.41, 126.3, 126.1, 125.9, 121.7, 121.6, 120.2, 120.1, 119.0, 118.9,

118.2, 118.1, 109.7, 49.9, 36.9, 36.7. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{45}H_{36}N_2Na$ 627.2771; found 627.2764. $[M+H]^+$ calcd for $C_{45}H_{37}N_2$ 605.2951; found 605.2936.

Reaction of 2.20a-*cis* with 2 equivalents of indole 2.14a:

To a stirred solution of **2.20a-*cis*** (10 mg, 0.05 mmol, 1.0 equiv.), **2.14a** (21 mg, 0.1 mmol, 2.0 equiv.) and TMOF (11 µL, 0.1 mmol, 2.0 equiv.) in CH_2Cl_2 (0.5 mL) was added TfOH (0.22 µL, 0.0025 mmol, 0.05 equiv.) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 15 min. The reaction mixture was then quenched with saturated aqueous sodium bicarbonate solution, and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were washed with saturated aqueous brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/hexanes mixture as eluent) to afford the pure **2.27-*trans*** as a white solid in 53% yield (16 mg) In addition, 5% of **2.20a-*cis*** and 16% of **2.14a** were recovered.

2.27-*trans*: mp 148-150 °C, R_f = 0.25 (in 5% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.71 (d, J = 7.5 Hz, 1H), 7.59 (d, J = 16.0 Hz, 1H), 7.45 (d, J = 7.5 Hz, 2H), 7.30-7.28 (m, 3H), 7.27-7.23 (m, 6H), 7.22-7.20 (m, 6H), 7.19-7.15 (m, 3H), 7.05-7.01 (m, 7H), 6.70 (s, 2H), 6.32 (s, 1H), 5.27, 5.23 (ABq, 2H, J_{AB} = 17.0 Hz). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 141.5, 137.8, 137.6, 137.1, 136.2, 130.2, 129.0, 128.7, 128.6, 128.5, 127.8, 127.5, 127.4, 127.3, 126.7, 126.6, 126.5, 126.3, 125.9, 121.7, 120.1, 119.0, 118.1, 109.7, 49.9, 36.7. IR (neat, cm^{-1}): 2960, 1445, 1327, 1257, 1011, 867, 790, 743, 631. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{45}H_{36}N_2Na$ 627.2771; found 627.2772.

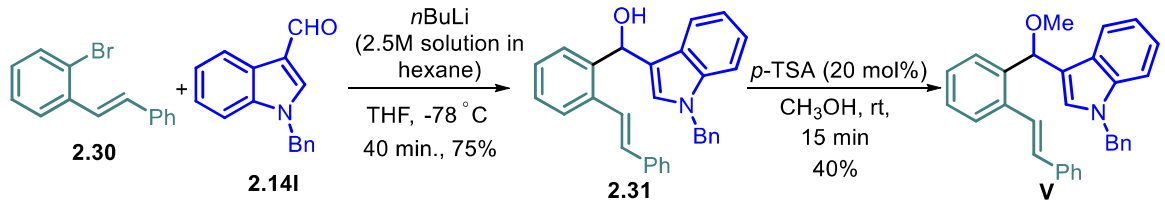


2.27-*trans*

Reaction of 2.20a with 2 equivalents of indole 2.14a:

To a stirred solution of **2.20a** (15 mg, 0.072 mmol, 1.0 equiv.), **2.14a** (30 mg, 0.144 mmol, 2.0 equiv.) and TMOF (16 µL, 0.144 mmol, 2.0 equiv.) in CH_2Cl_2 (1 mL) was added TfOH (0.32 µL, 0.0036 mmol, 0.05 equiv.) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 15 min. Then it was quenched with saturated aqueous sodium bicarbonate solution, and extracted with ethyl acetate (3 x 3 mL). The combined organic layers were washed with saturated aqueous brine solution, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/hexane mixture as eluent) to afford pure **2.27-*trans*** as a white solid in 48% yield (21 mg). In addition, 7% of **2.20a** and 27% of **2.20a** were recovered.

Synthesis of compound V:



Scheme 2.12: Synthesis of compound **V**

Step 1: To a stirred solution of **2.30**[24] (658 mg, 2.54 mmol, 2.0 equiv.) in THF (20 mL) was added *n*-BuLi (2.5 M solution in hexane, 1 mL, 2.54 mmol, 2.0 equiv.) at -78 ˚C under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 30 minutes. After 30 minutes, compound **2.14l**[25] (300 mg, 1.27 mmol, 1.0 equiv.) in 5 mL of THF was added dropwise to the above mixture and the contents were stirred for 10 minutes at the same temperature. Upon consumption of **2.14l** as indicated by TLC, the reaction mixture was quenched with a saturated aqueous ammonium chloride solution, and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/hexanes mixture as eluent (+ 1% Et_3N) to afford pure **2.31** as a white solid in (400 mg, 75%). This material was stored at -18 ˚C after isolation as it decomposed at room temperature. mp 90-92 ˚C, R_f = 0.5 (in 40% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75-7.71 (m, 2H), 7.64-7.62 (m, 1H), 7.42 (d, J = 16.0 Hz, 1H), 7.37-7.33 (m, 3H), 7.31-7.29 (m, 2H), 7.28-7.27 (m, 1H), 7.24-7.23 (m, 1H), 7.23-7.22 (m, 1H), 7.21-7.18 (m, 2H), 7.17-7.15 (m, 1H), 7.14-7.11 (m, 2H), 6.99- 6.97 (m, 2H), 6.92 (d, J = 16.5 Hz, 1H), 6.83 (s, 1H), 6.53 (d, J = 4.0 Hz, 1H), 5.21 (s, 2H), 2.26 (d, J = 4.5 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 140.7, 137.5, 137.4, 137.2, 137.0, 135.5, 130.6, 128.7, 128.68, 128.64, 128.5, 127.7, 127.6, 127.5, 126.6, 126.5, 126.4, 126.09, 126.04, 122.2, 119.8, 118.2, 110.0, 67.6, 50.1. IR (neat, cm^{-1}): 3340, 1546, 1493, 1465, 1451, 1353, 1332, 1214, 1169, 1027, 960, 736, 690. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{30}H_{25}NNaO$ 438.1828; found 438.1828.

Step 2: Compound **V** was prepared by a slightly modified reported procedure.[26] To a stirred solution of **2.31** (130 mg, 0.31 mmol, 1.0 equiv.) in methanol (2 mL) was added *p*-TSA (10.6 mg, 0.062 mmol, 0.2 equiv.) at room temperature. The reaction mixture was stirred for 15 minutes. After 15 minutes, upon consumption of **2.31** as indicated by TLC, the reaction mixture was quenched with saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/hexanes mixture as eluent) to afford pure **V** as a white solid (54 mg, 40%), mp 120-122 ˚C, R_f = 0.4 (in 10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75-7.73 (m, 1H), 7.68-7.63 (m, 2H), 7.47 (d, J = 16.0 Hz, 1H), 7.35-7.33 (m, 4H), 7.29-7.26 (m, 3H), 7.23-7.20 (m, 2H), 7.19-7.17 (m, 1H), 7.16-7.14 (m, 2H), 7.13-7.12 (m, 1H), 6.98 (dd, J = 1.0, 7.5 Hz, 2H), 6.93 (d, J = 16.0 Hz, 1H), 6.78 (s, 1H), 5.94 (s, 1H), 5.21, 5.18 (ABq, 2H, J_{AB} = 16.0 Hz), 3.48 (s, 3H).

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 138.7, 137.5, 137.4, 137.0, 136.4, 130.4, 128.7, 127.9, 127.7, 127.6, 127.5, 127.3, 126.6, 126.5, 126.2, 126.1, 122.1, 119.9, 119.8, 116.3, 110.0, 56.9, 50.0. IR (neat, cm^{-1}): 1548, 1493, 1464, 1451, 1353, 1333, 1170, 1074, 960, 970, 731, 691. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{31}H_{27}NNaO$ 452.1985; found 452.1983.

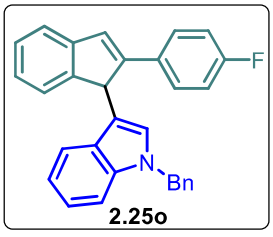
Gram scale synthesis of 2.23a:

To a stirred solution of **2.14a** (1.0 g, 4.82 mmol, 1.0 equiv.), **2.20a** (1.2 g, 5.84 mmol, 1.2 equiv.) and TMOF (1.0 mL, 9.64 mmol, 2.0 equiv.) in CH_2Cl_2 (10 mL) was added TfOH (21 µL, 0.24 mmol, 0.05 equiv.) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at the same temperature. After 5 h, the reaction mixture was quenched with a saturated aqueous sodium bicarbonate solution, and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with saturated aqueous brine solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/hexanes mixture as eluent) to afford the pure **2.23a** in 72% (1.5 g) yield with 1.5:1 diastereoselectivity.

Treatment of 2.23a with BBr_3: To a stirred solution of indane derivative **2.23a** (40 mg, 0.093 mmol, 1.0 equiv.) in CH_2Cl_2 (1 mL) was added boron tribromide {(1 M in CH_2Cl_2), (160 µL, 0.186 mmol, 2.0 equiv.)} at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at the same temperature for 2 h. Then, the reaction mixture was quenched with H_2O, and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with saturated aqueous brine solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/hexanes mixture as eluent) to afford the pure **2.24a** in 72% yield (27 mg).

2.25o: To a stirred solution of indane derivative **2.23o** (major) (40 mg, 0.09 mmol, 1.0 equiv.) in CH_2Cl_2 (1 mL) was added TMOF (20 µL, 0.18 mmol, 2.0 equiv.), and TfOH (0.4 µL, 0.0044 mmol, 0.05 equiv.) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at same temperature for 46 h. The reaction mixture was quenched with saturated sodium bicarbonate solution, and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with saturated brine solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/hexanes mixture as eluent) to afford the pure **2.25o** as a white solid in 80% yield (30 mg).

2.25o. mp 148-150 °C, R_f = 0.54 (10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53-7.50 (m, 2H), 7.46-7.42 (m, 2H), 7.3 (d, J = 7.5 Hz, 1H), 7.32 (s, 1H), 7.28 (d, J = 7.5 Hz, 1H), 7.23-7.22 (m, 3H), 7.19 (d, J = 8.0 Hz, 1H), 7.10 (q, J = 7.5 Hz, 2H), 7.01 (t, J = 7.5 Hz, 1H), 6.931-6.89 (m, 5H), 5.27 (s, 1H), 5.23, 5.19 (ABq, 2H, J_{AB} = 16.2 Hz). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 163.0, 161.0, 148.7, 148.6, 137.6, 136.8, 131.7, 131.6, 128.6, 128.4, 128.3, 127.4, 127.0, 126.98, 126.92, 126.7, 126.4, 125.3, 123.6, 121.8,



2.25o

121.0, 119.5, 119.2, 115.2, 115.1, 112.7, 109.7, 49.7, 47.9. IR (neat, cm^{-1}): 1501, 1463, 1222, 1156, 827, 746, 733, 702. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{30}H_{23}FN$ 416.1809; found 416.1812.

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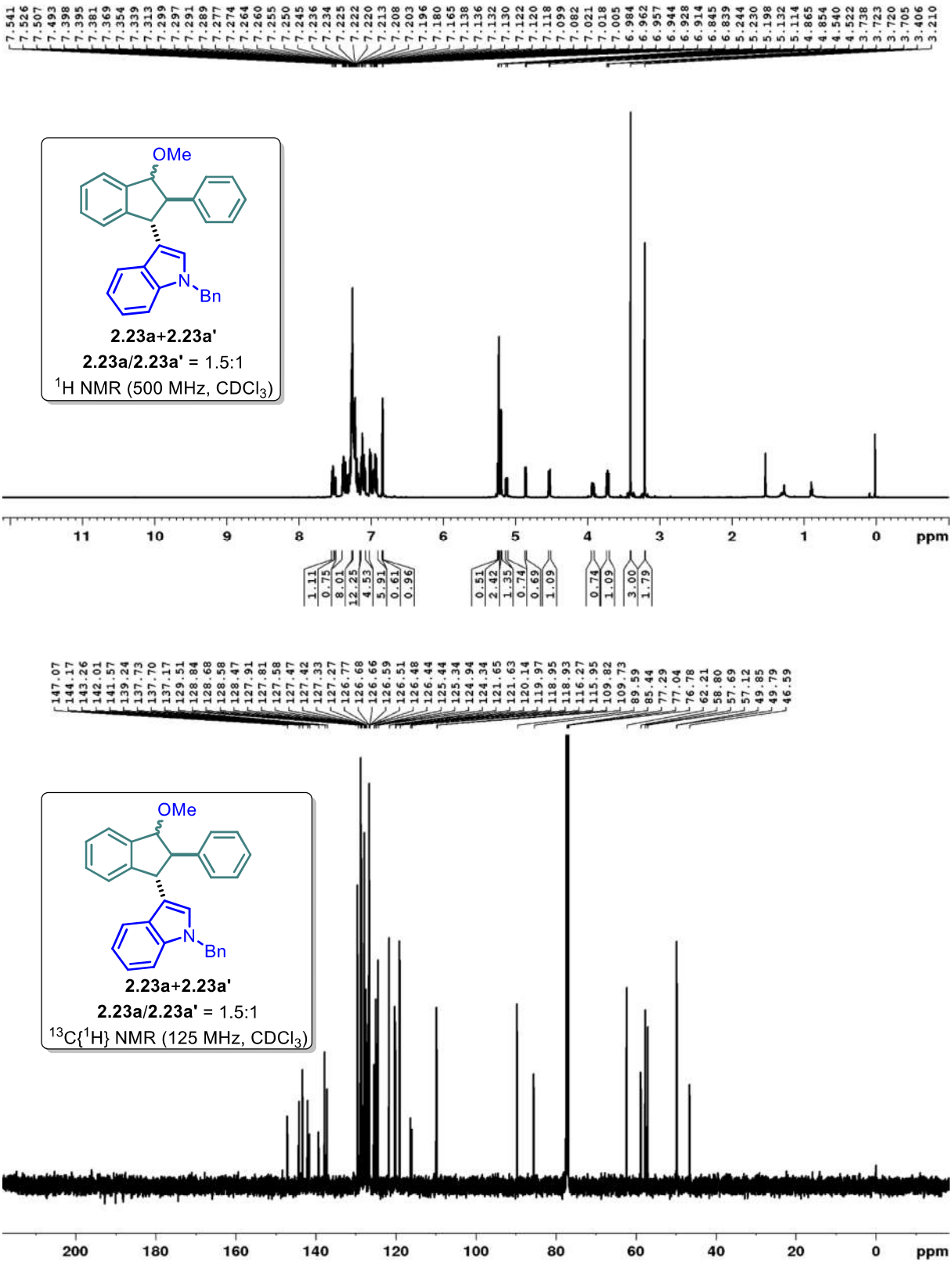
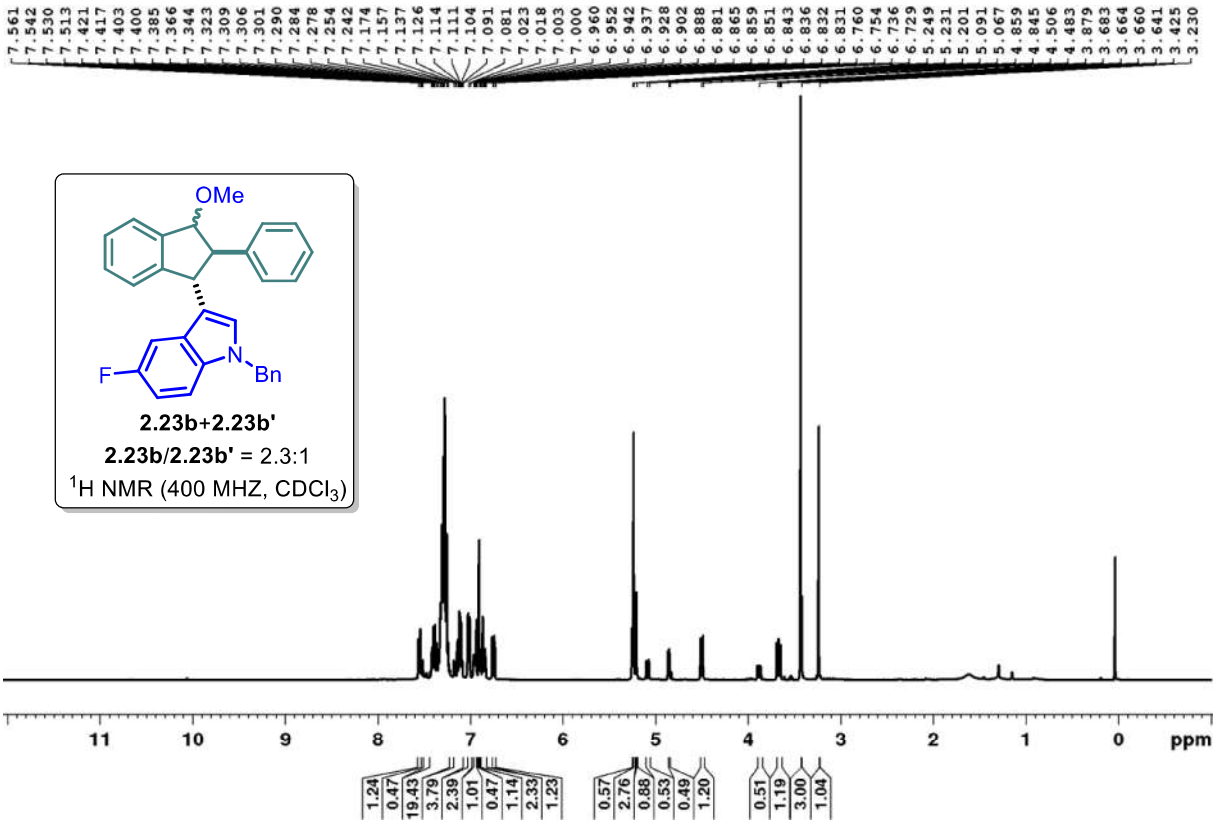
2.7 Representative spectra




OMe
F
N
Bn
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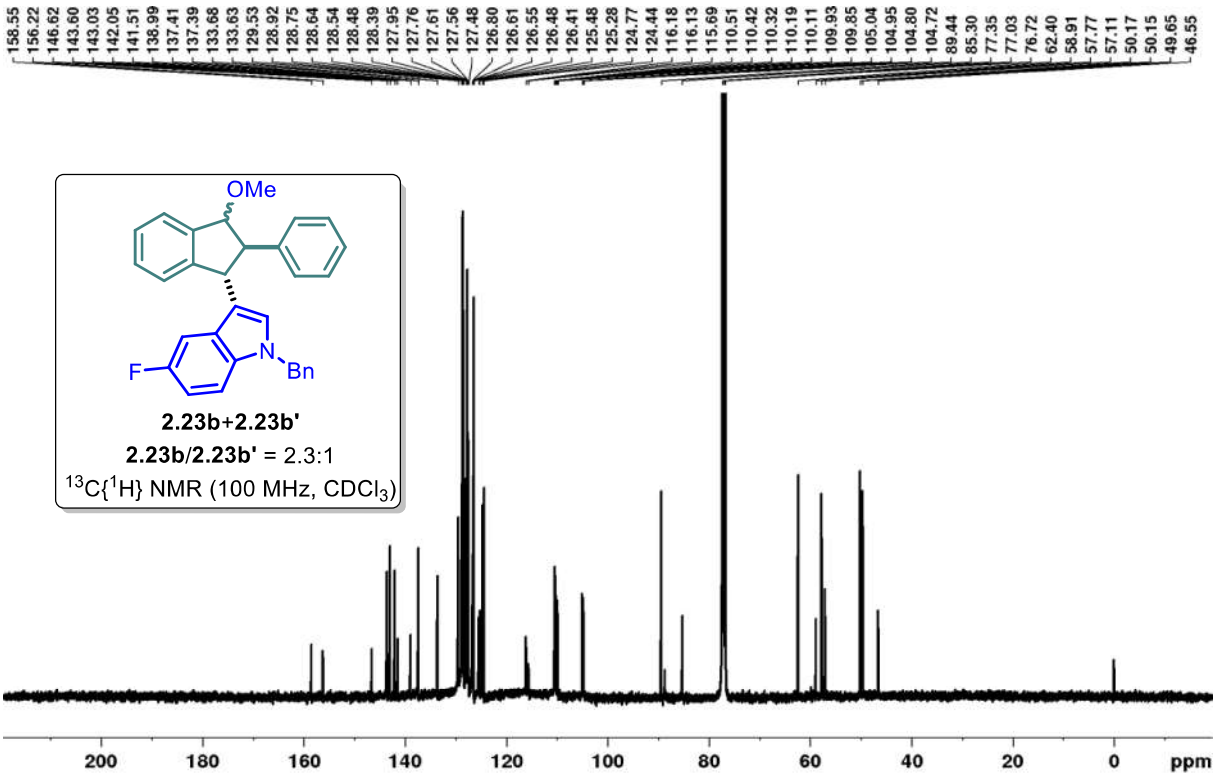
2.23b/2.23b' = 2.3:1
^{1}H NMR (400 MHZ, $CDCl_3$)
ppm


OMe
F
N
Bn
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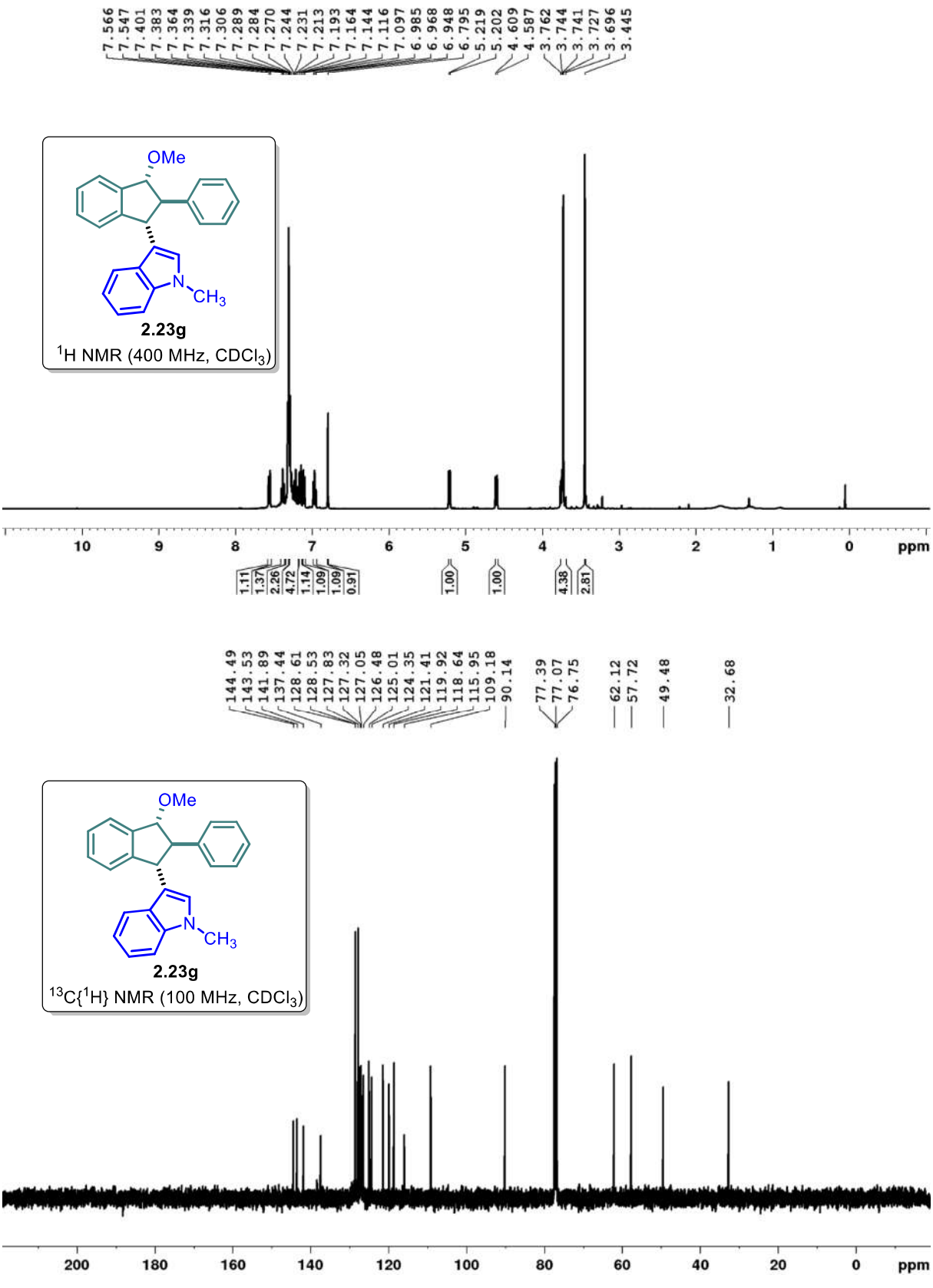
2.23b/2.23b' = 2.3:1
$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$)
ppm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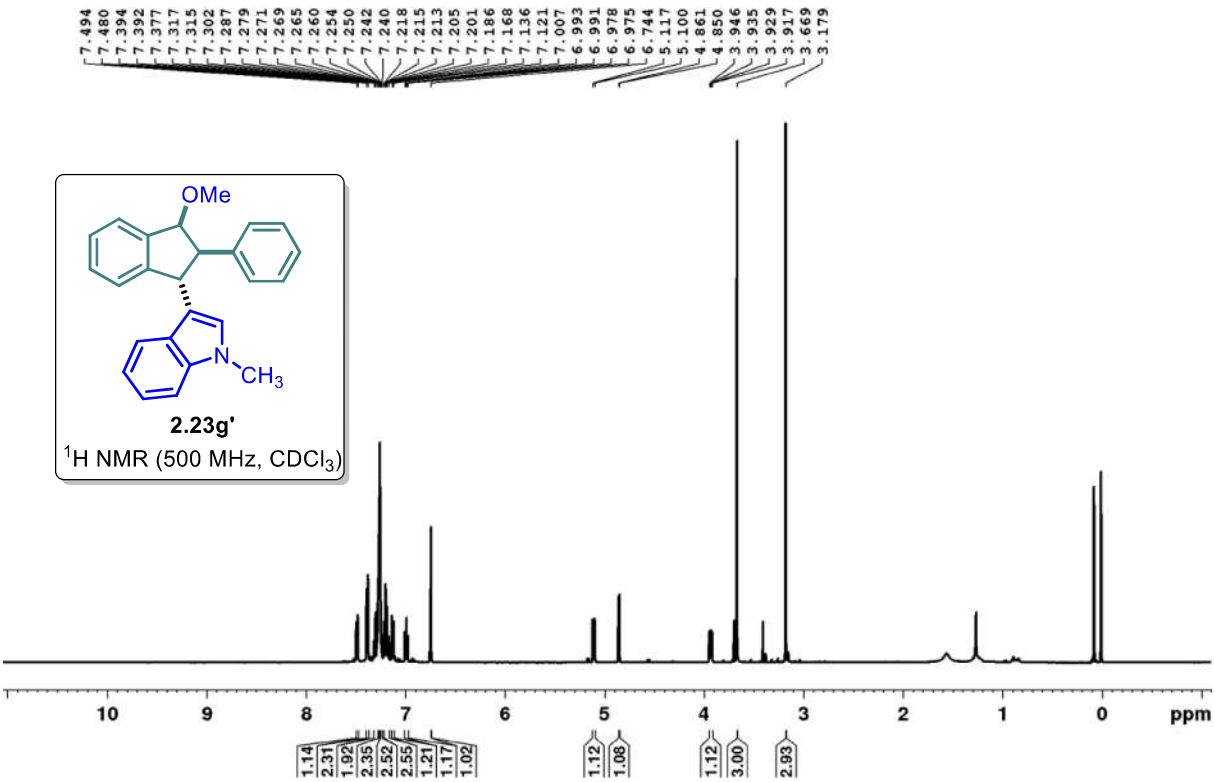
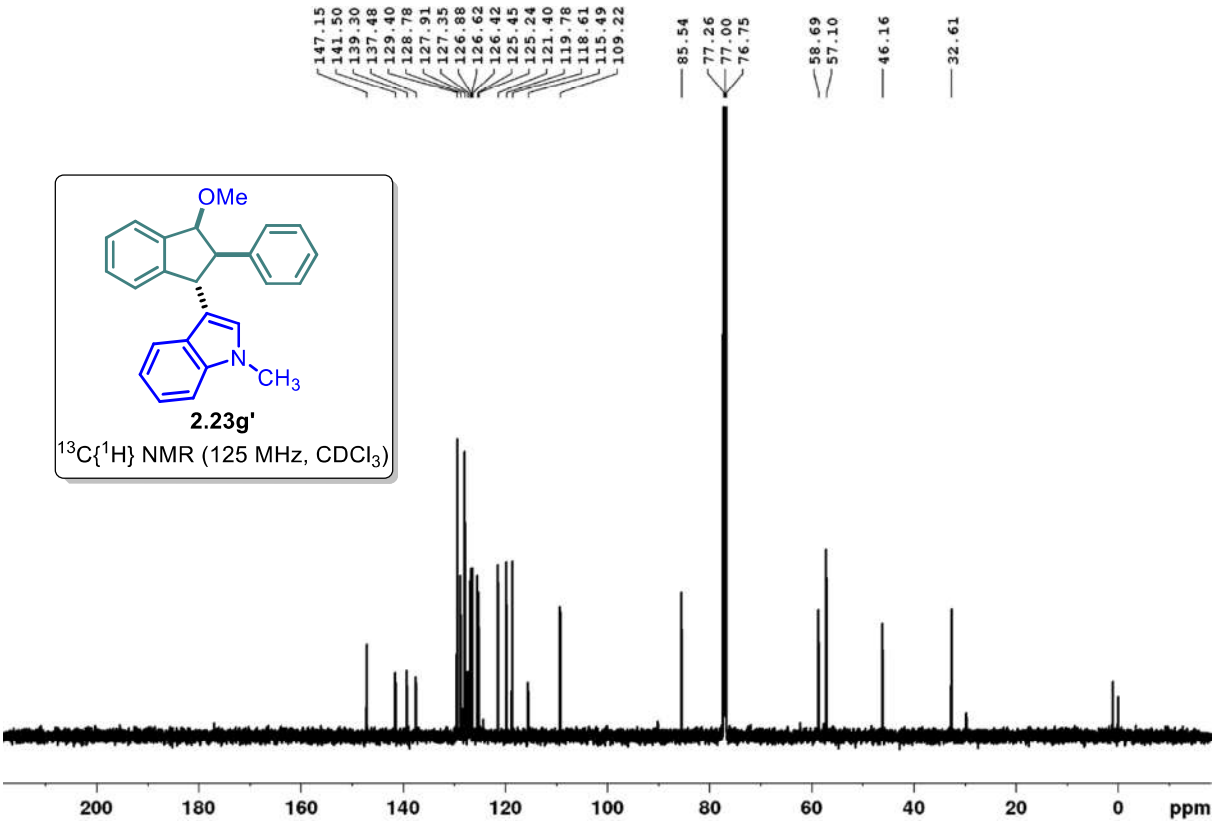
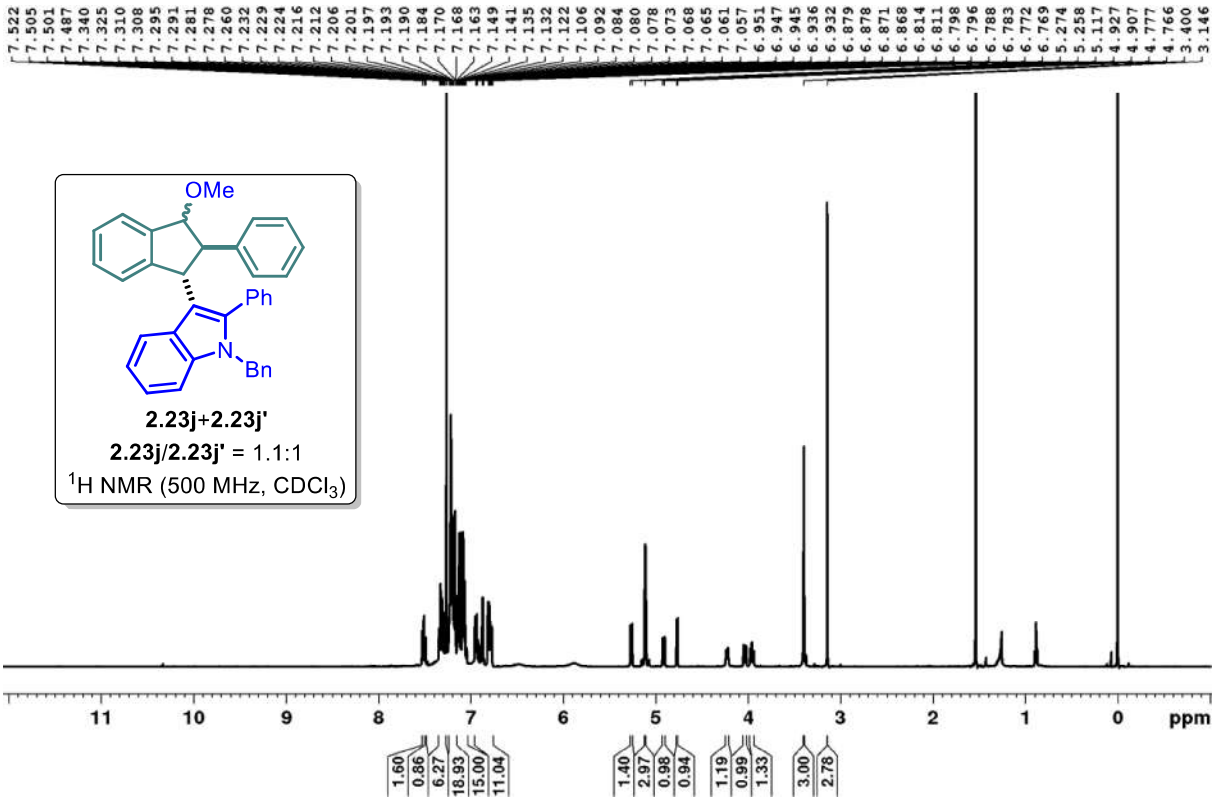
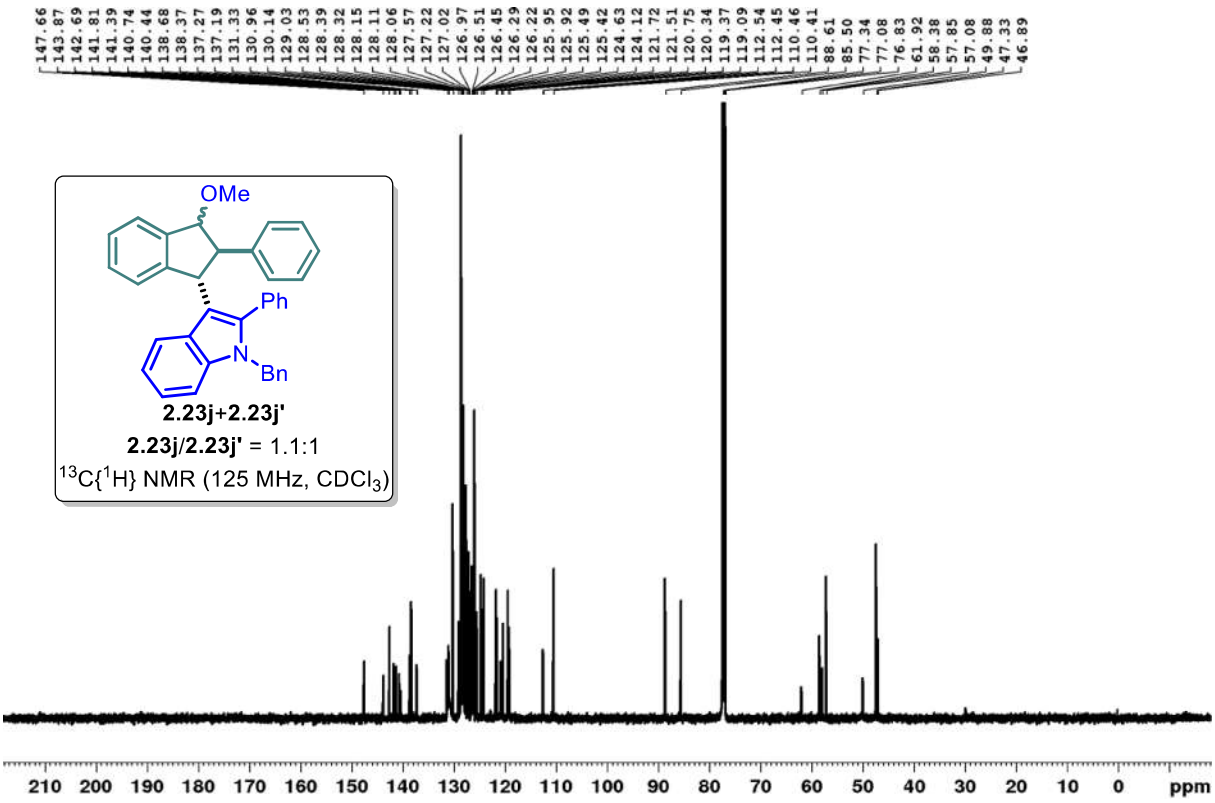
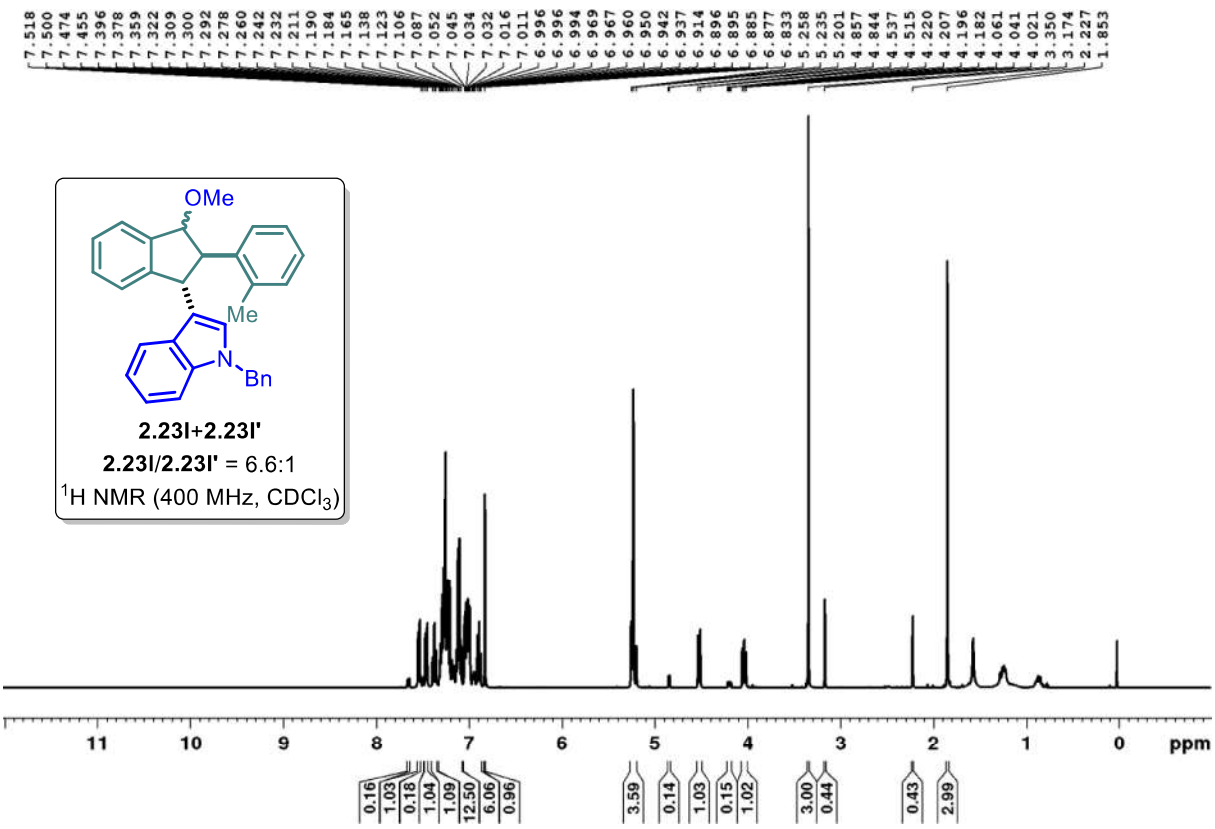
7.547
7.401
7.383
7.364
7.339
7.316
7.306
7.289
7.284
7.270
7.244
7.231
7.213
7.193
7.164
7.144
7.116
7.097
6.985
6.968
6.948
6.795
5.219
5.202
4.609
4.587
3.762
3.744
3.741
3.727
3.696
3.445
OMe
N
CH3
2.23g
1H NMR (400 MHz, CDCl3)
10
9
8
7
6
5
4
3
2
1
0
ppm
1.11
1.37
2.26
4.72
1.14
1.09
1.09
0.91
1.00
1.00
4.38
2.81
144.49
143.53
141.89
137.44
128.61
128.53
127.83
127.32
127.05
126.48
125.01
124.35
121.41
119.92
118.64
115.95
109.18
90.14
77.39
77.07
76.75
62.12
57.72
49.48
32.68
OMe
N
CH3
2.23g
13C{1H} NMR (100 MHz, CDCl3)
200
180
160
140
120
100
80
60
40
20
0
ppm

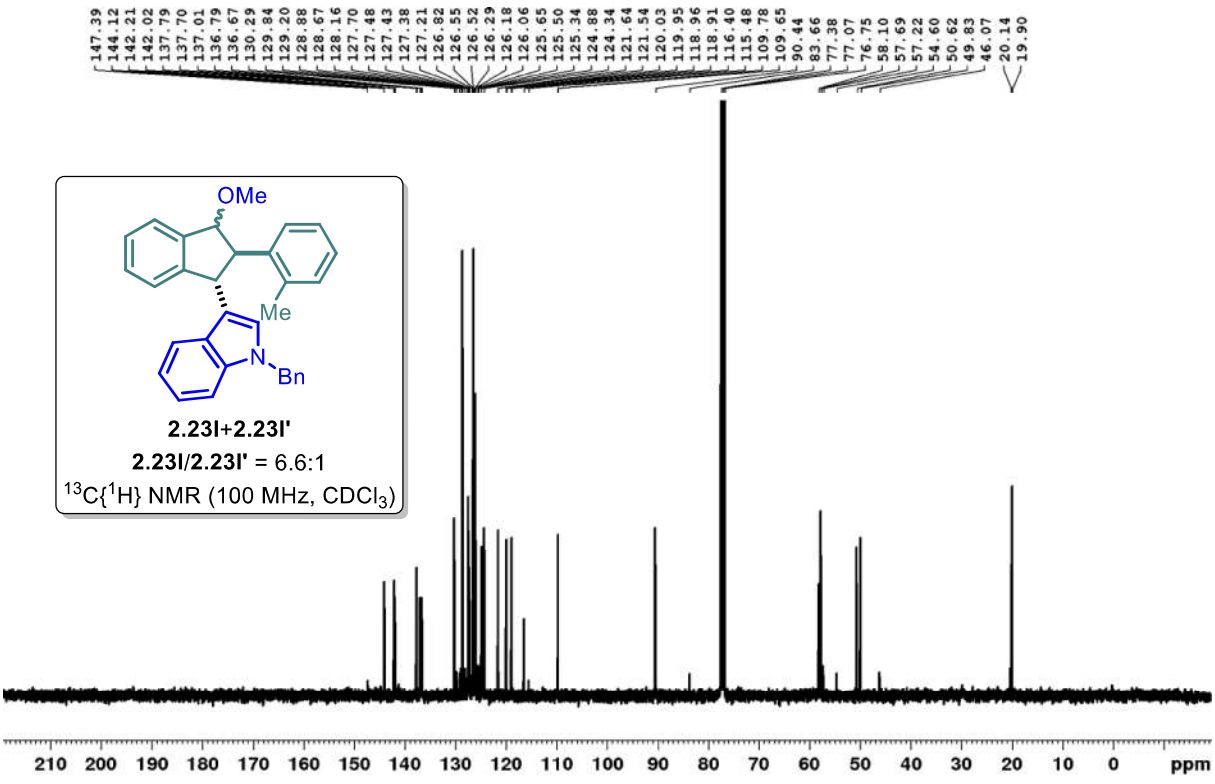

OMe
N
CH3
2.23g'
1H NMR (500 MHz, CDCl3)
ppm

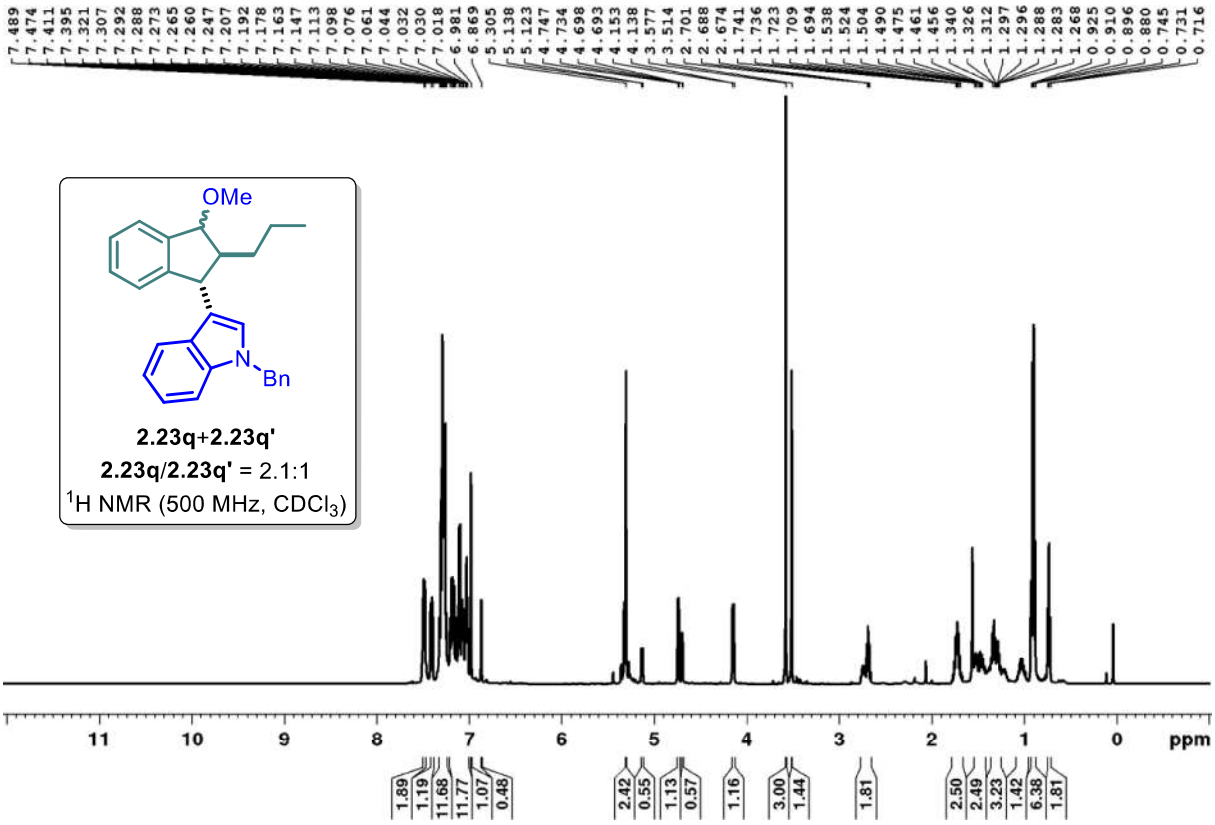

OMe
N
CH3
2.23g'
13C{1H} NMR (125 MHz, CDCl3)
ppm

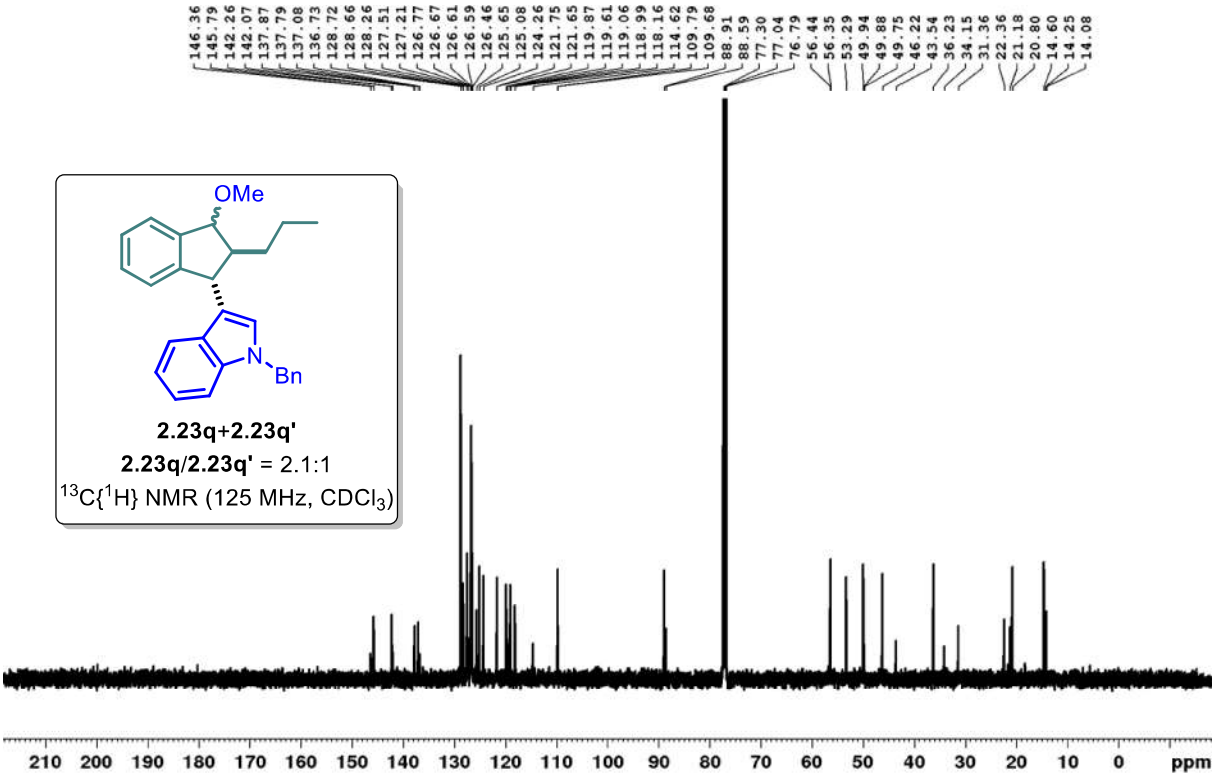

OMe
Ph
N
Bn
2.23j+2.23j'
2.23j/2.23j' = 1.1:1
1H NMR (500 MHz, CDCl3)
ppm

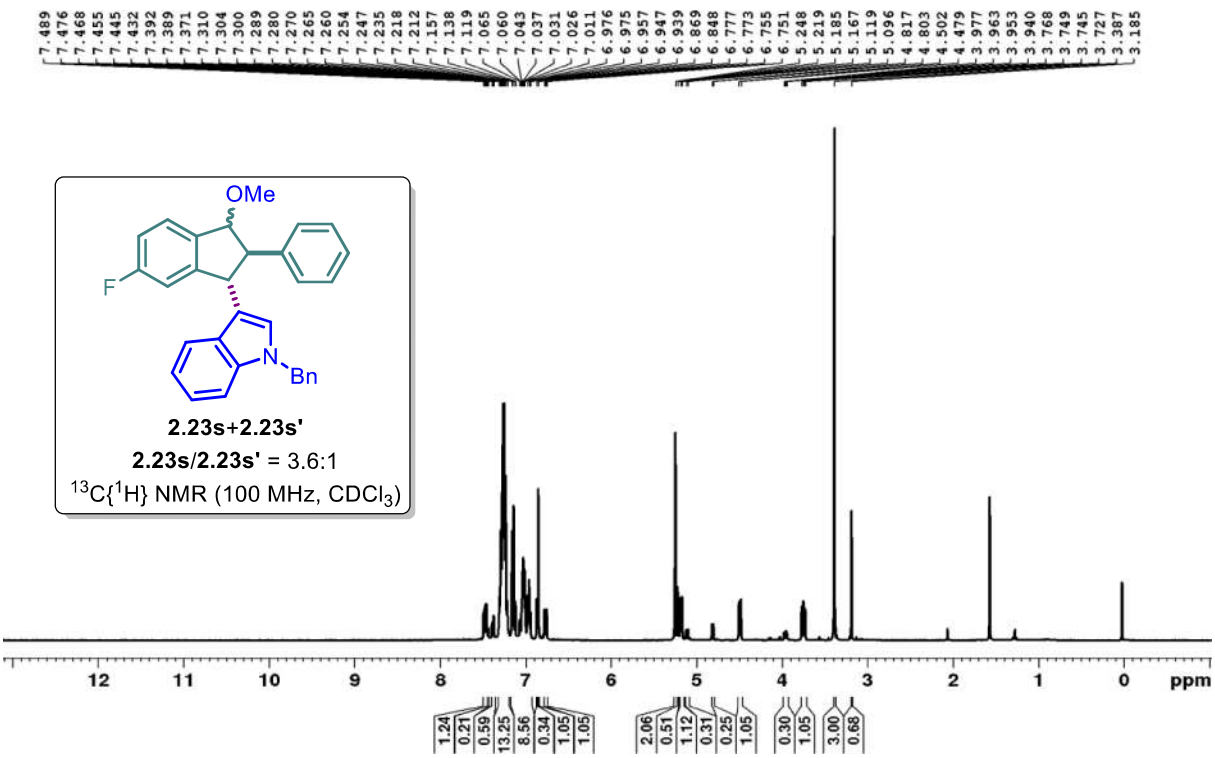

OMe
Ph
N
Bn
2.23j+2.23j'
2.23j/2.23j' = 1.1:1
13C{1H} NMR (125 MHz, CDCl3)
ppm

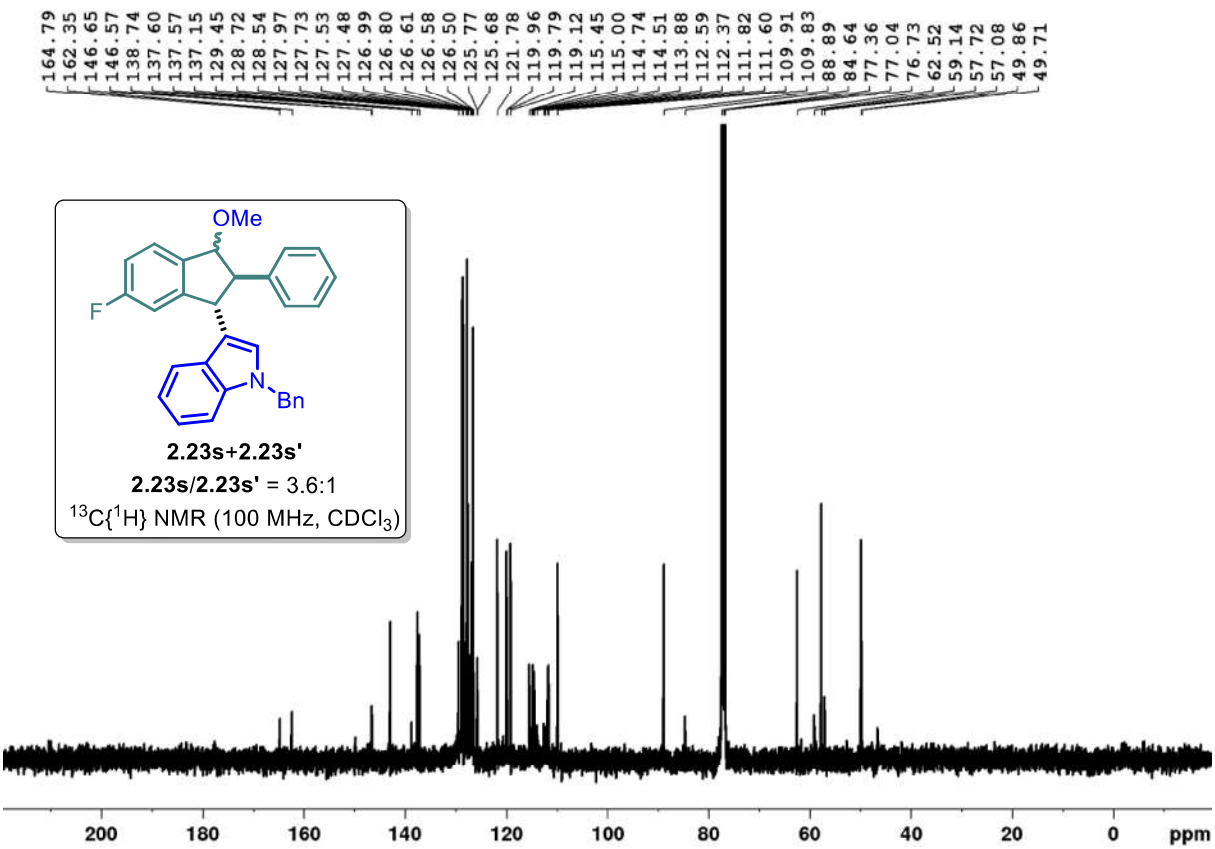

OMe
Me
N
Bn
2.23l+2.23l'
2.23l/2.23l' = 6.6:1
^{1}H NMR (400 MHz, CDCl$_3$)
ppm

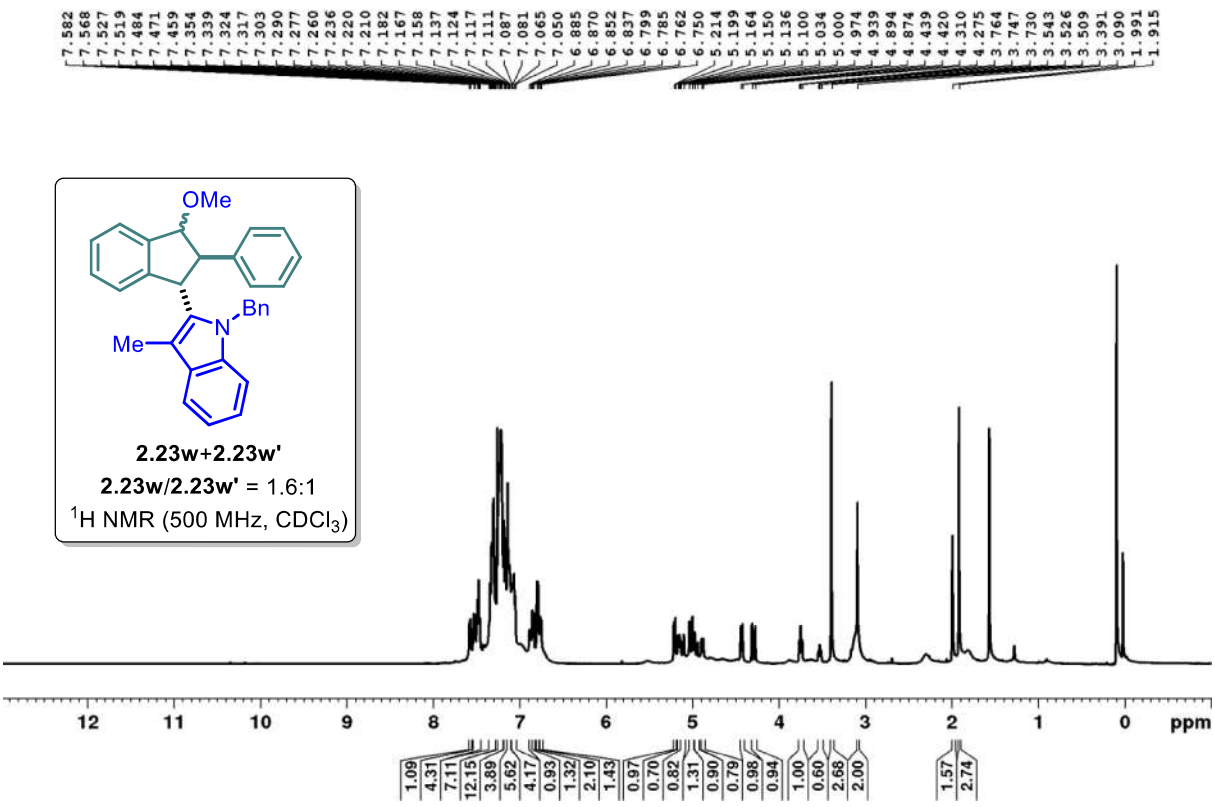

OMe
Me
N
Bn
2.23l+2.23l'
2.23l/2.23l' = 6.6:1
^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)
ppm


OMe
N
Bn
2.23q+2.23q'
2.23q/2.23q' = 2.1:1
1H NMR (500 MHz, CDCl3)
ppm


OMe
N
Bn
2.23q+2.23q'
2.23q/2.23q' = 2.1:1
13C{1H} NMR (125 MHz, CDCl3)
ppm


OMe
F
N
Bn
2.23s+2.23s'
2.23s/2.23s' = 3.6:1
13C{1H} NMR (100 MHz, CDCl3)
ppm


OMe
F
N
Bn
2.23s+2.23s'
2.23s/2.23s' = 3.6:1
13C{1H} NMR (100 MHz, CDCl3)
ppm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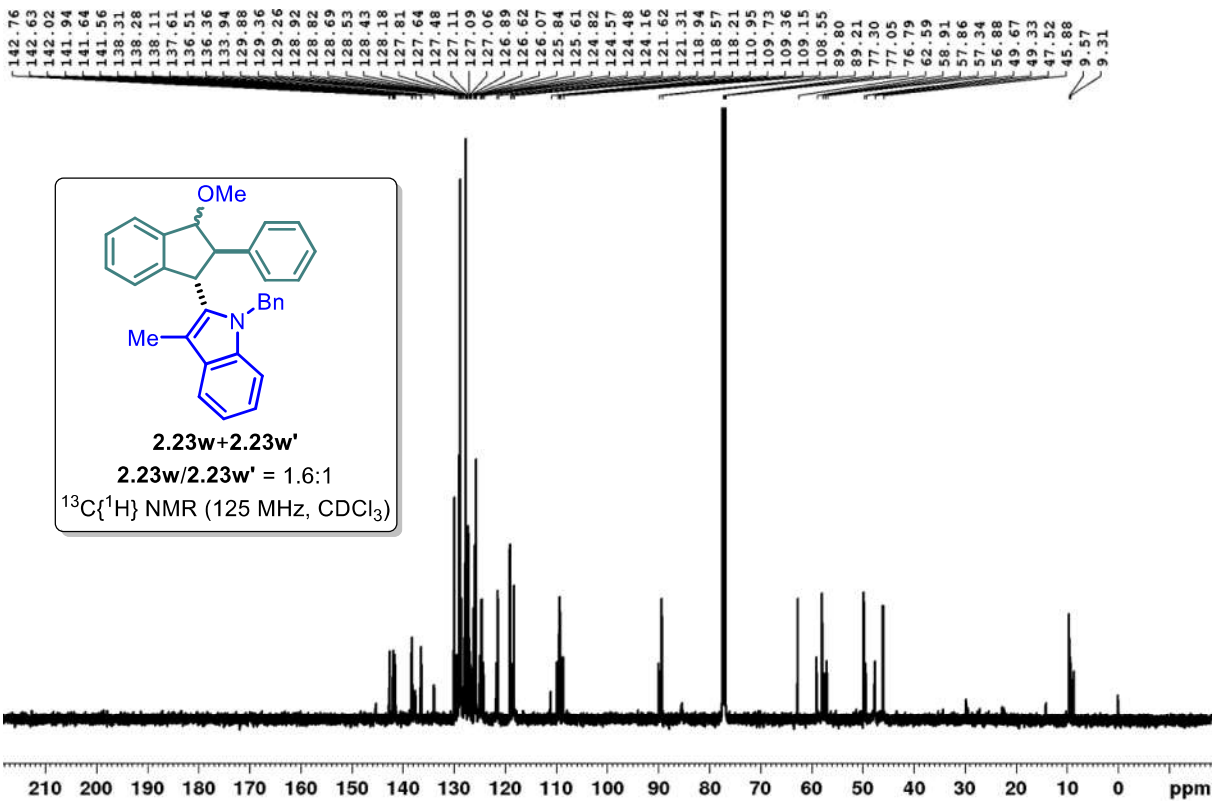
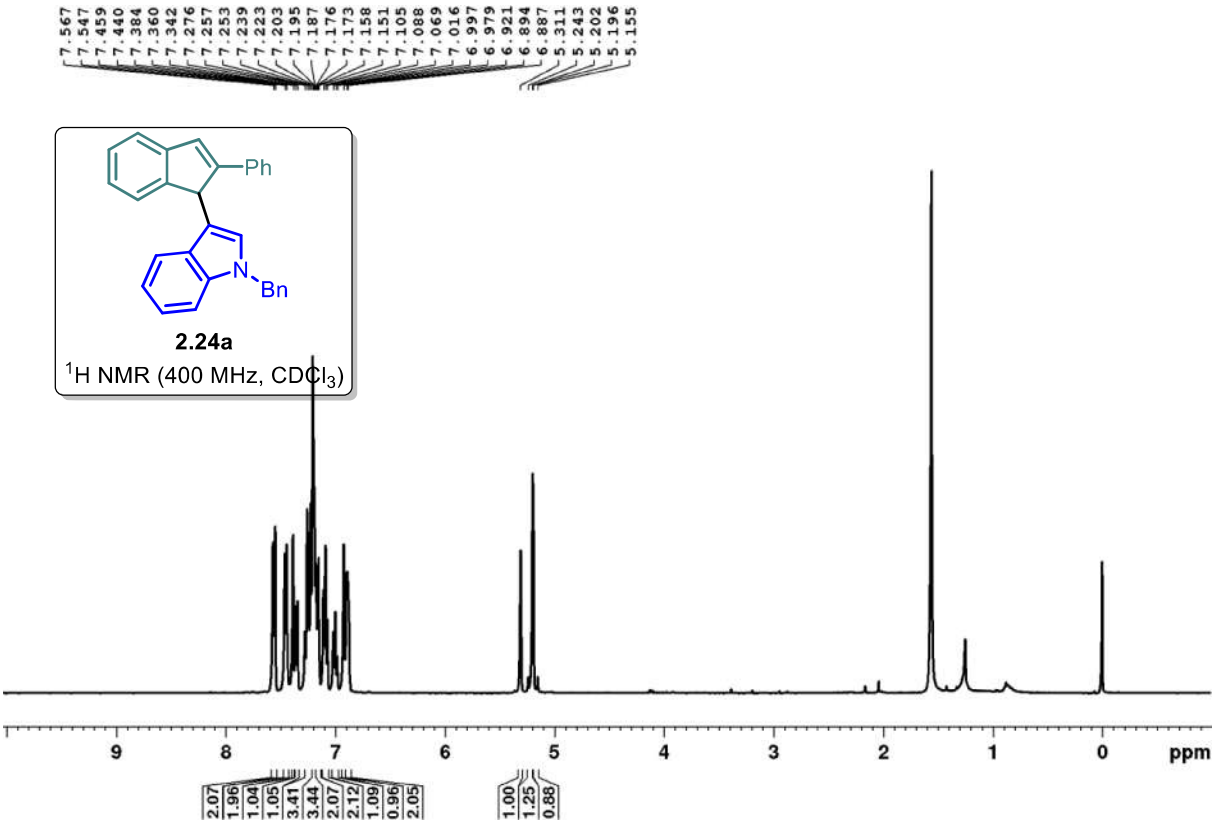
Bn
N
Me
2.23w+2.23w'
2.23w/2.23w' = 1.6:1
1H NMR (500 MHz, CDCl3)
ppm


OMe
Bn
N
Me
2.23w+2.23w'
2.23w/2.23w' = 1.6:1
13C{1H} NMR (125 MHz, CDCl3)
ppm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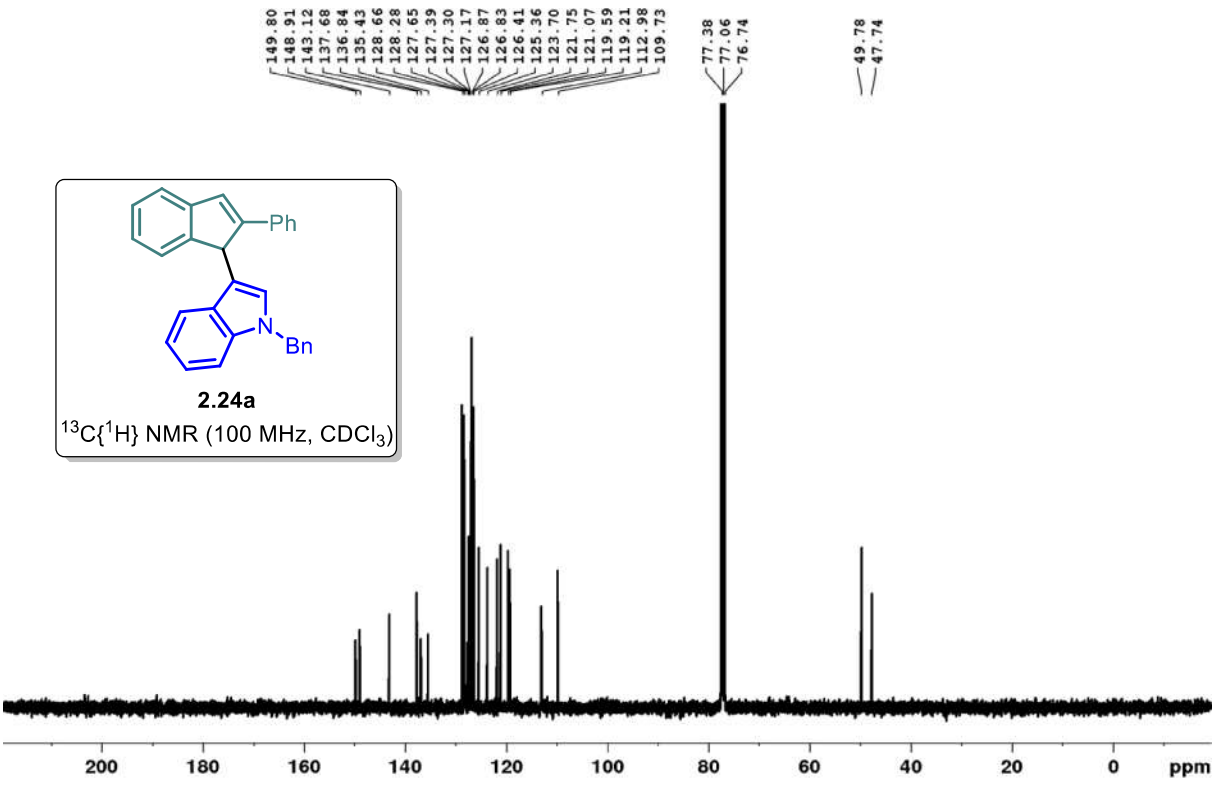
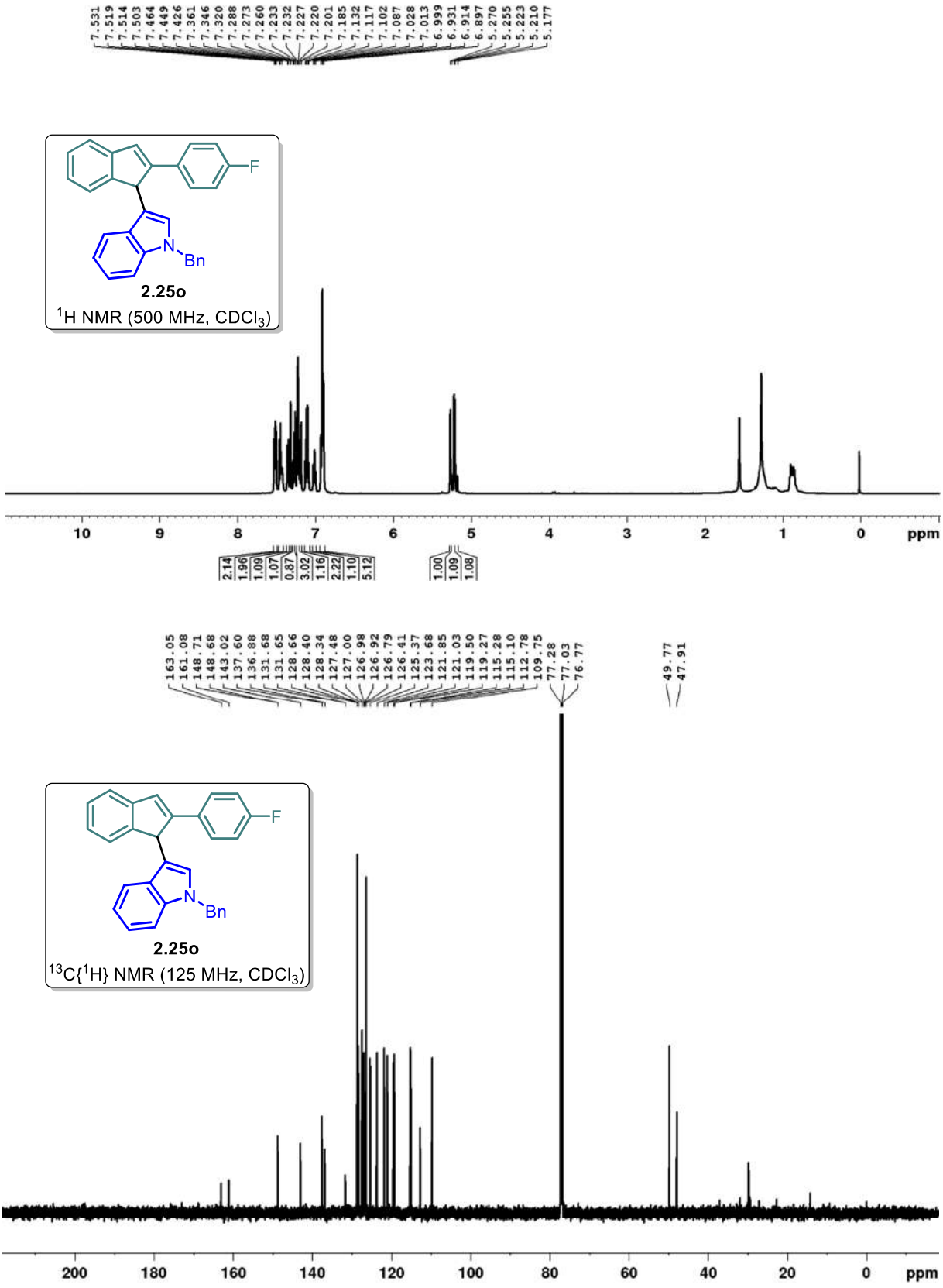
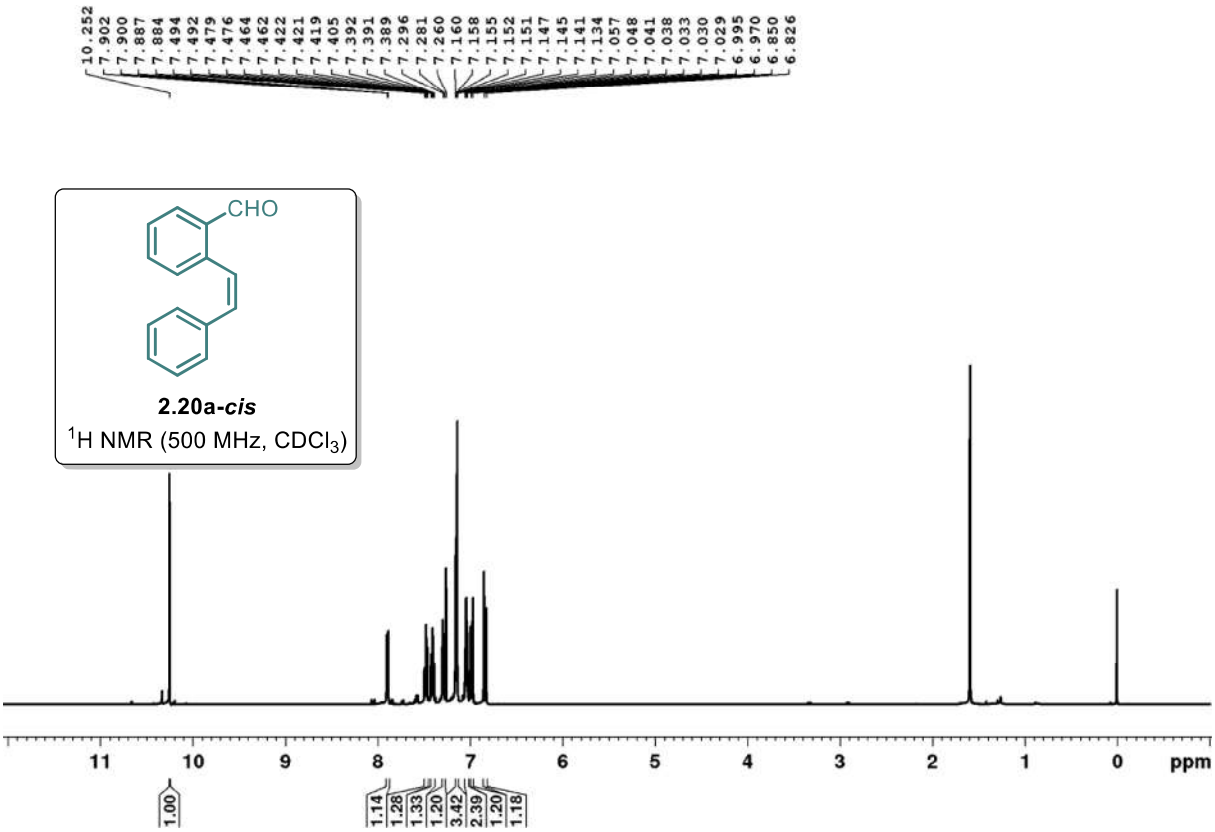
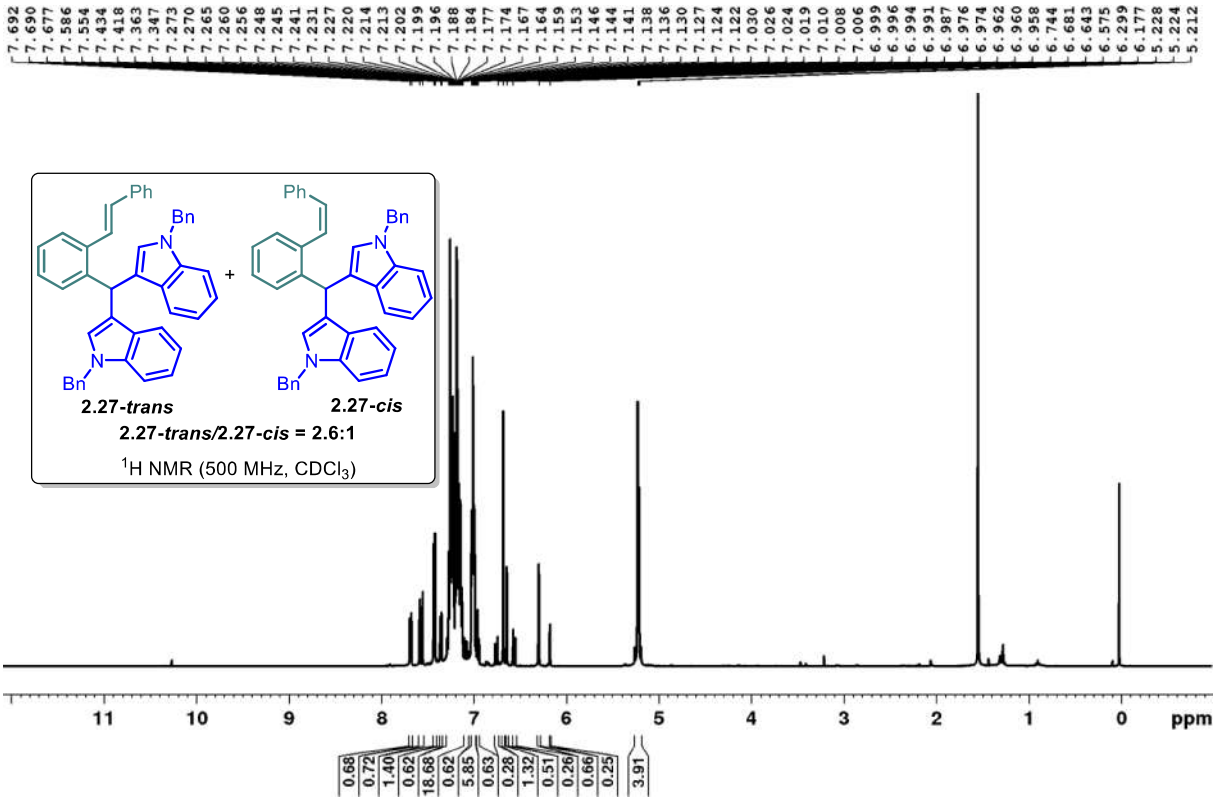
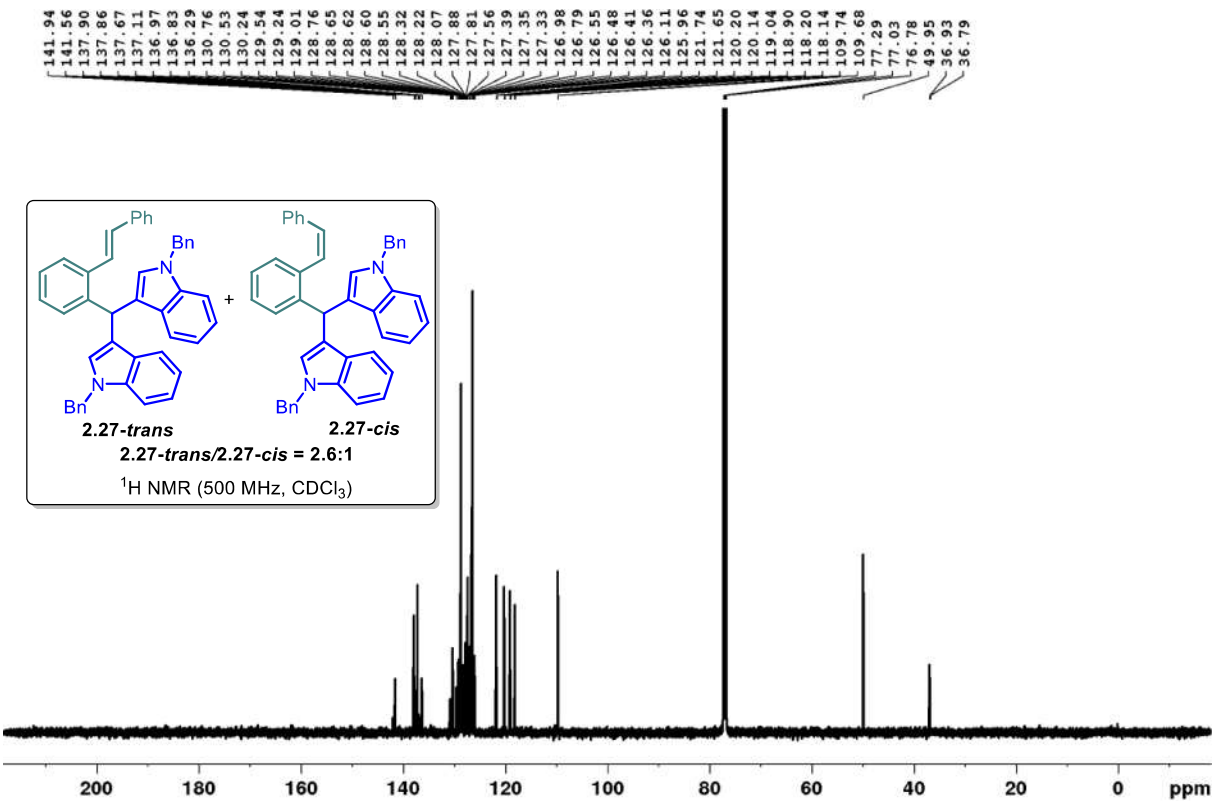
7.547
7.459
7.440
7.384
7.360
7.342
7.276
7.257
7.253
7.239
7.223
7.203
7.195
7.187
7.176
7.173
7.158
7.151
7.105
7.088
7.069
7.016
6.997
6.979
6.921
6.894
6.887
5.311
5.243
5.202
5.196
5.155
Ph
N
Bn
2.24a
^{1}H NMR (400 MHz, $CDCl_3$)
9
8
7
6
5
4
3
2
1
0
ppm
2.07
1.96
1.04
1.05
3.41
3.44
2.07
2.12
1.09
0.96
2.05
1.00
1.25
0.88

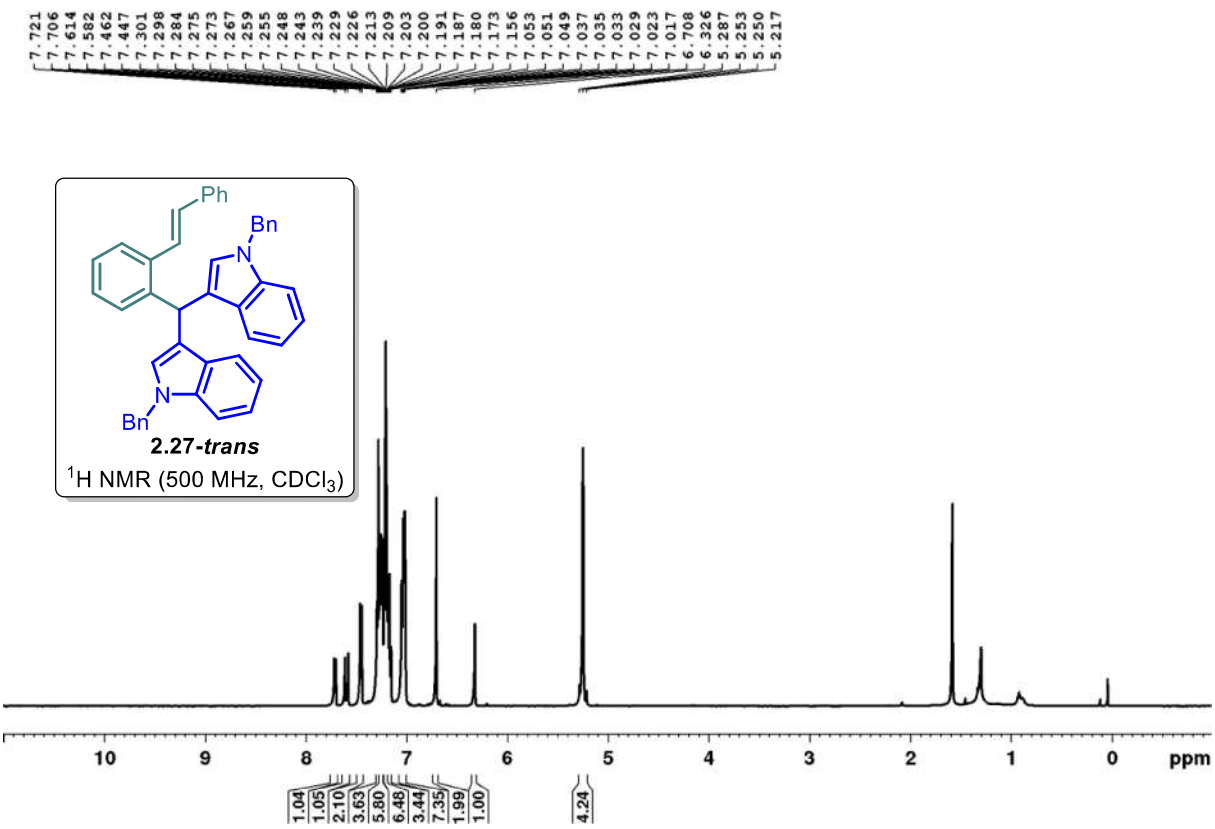

149.80
148.91
143.12
137.68
136.84
135.43
128.66
128.28
127.65
127.39
127.30
127.17
126.87
126.83
126.41
125.36
123.70
121.75
121.07
119.59
119.21
112.98
109.73
77.38
77.06
76.74
49.78
47.74
Ph
N
Bn
2.24a
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$)
200
180
160
140
120
100
80
60
40
20
0
ppm


7.531
7.519
7.514
7.503
7.464
7.449
7.426
7.361
7.346
7.320
7.288
7.273
7.260
7.233
7.232
7.227
7.220
7.201
7.185
7.132
7.117
7.102
7.087
7.028
7.013
6.999
6.931
6.914
6.897
5.270
5.255
5.223
5.210
5.177
F
N
Bn
2.25o
1H NMR (500 MHz, CDCl3)
10
9
8
7
6
5
4
3
2
1
0
ppm
2.14
1.96
1.09
1.07
0.87
3.02
1.16
2.22
1.10
5.12
1.00
1.09
1.08
163.05
161.08
148.71
148.68
143.02
137.60
136.88
131.68
131.65
128.66
128.40
128.34
127.48
127.00
126.98
126.92
126.79
126.41
125.37
123.68
121.85
121.03
119.50
119.27
115.28
115.10
112.78
109.75
77.28
77.03
76.77
49.77
47.91
F
N
Bn
2.25o
13C{1H} NMR (125 MHz, CDCl3)
200
180
160
140
120
100
80
60
40
20
0
ppm


10.252
7.902
7.900
7.887
7.884
7.494
7.492
7.479
7.476
7.464
7.462
7.422
7.421
7.419
7.405
7.392
7.391
7.389
7.296
7.281
7.260
7.160
7.158
7.155
7.152
7.151
7.147
7.145
7.141
7.134
7.057
7.048
7.041
7.038
7.033
7.030
7.029
6.995
6.970
6.850
6.826
CHO
2.20a-*cis*
^{1}H NMR (500 MHz, $CDCl_3$)
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.14
1.28
1.33
1.20
3.42
2.39
1.20
1.18


Ph
Bn
N
Bn
+
2.27-trans
2.27-cis
2.27-trans/2.27-cis = 2.6:1
1H NMR (500 MHz, CDCl3)
ppm


Ph
Bn
N
Bn
+
2.27-trans
2.27-cis
2.27-trans/2.27-cis = 2.6:1
1H NMR (500 MHz, CDCl3)
ppm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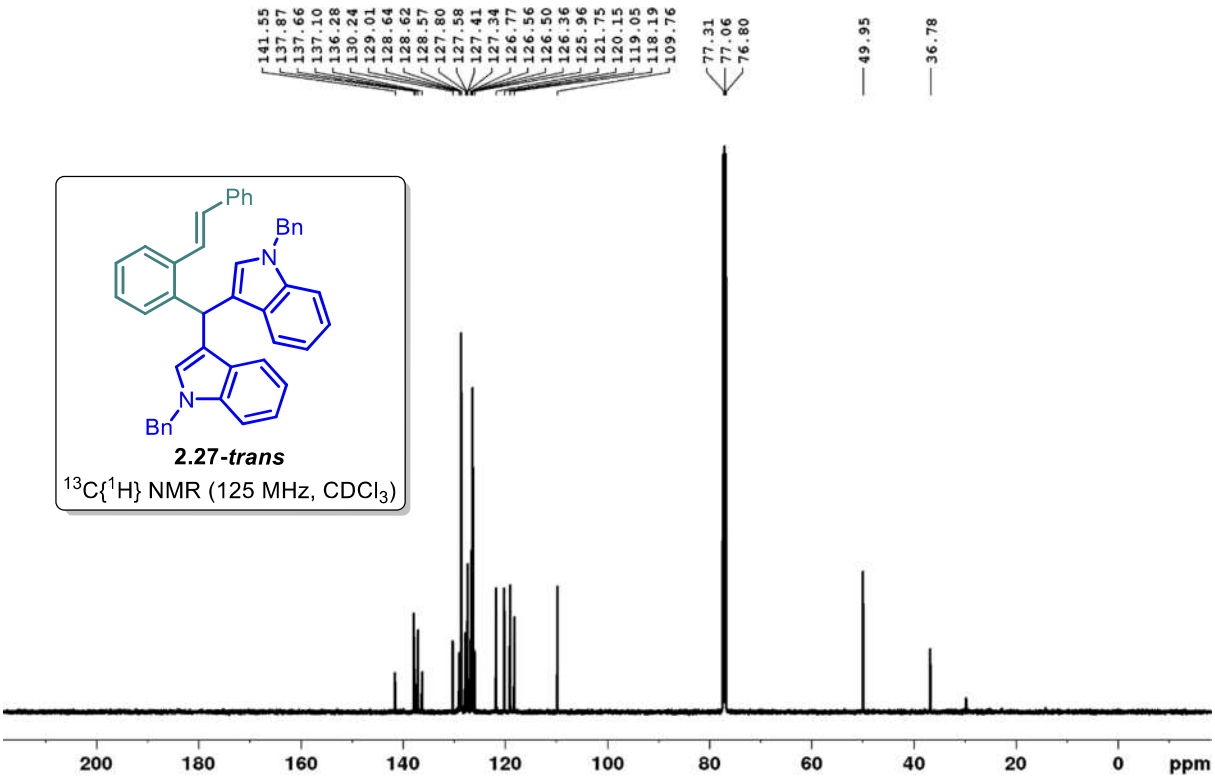
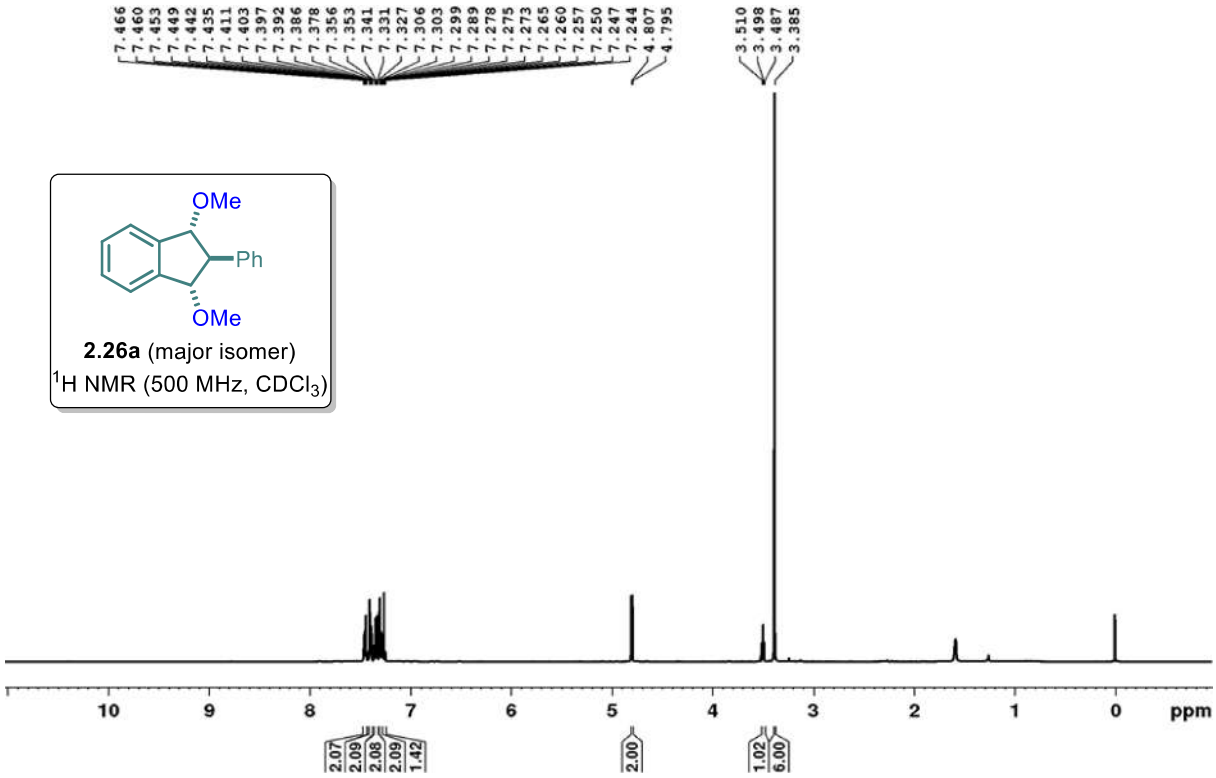
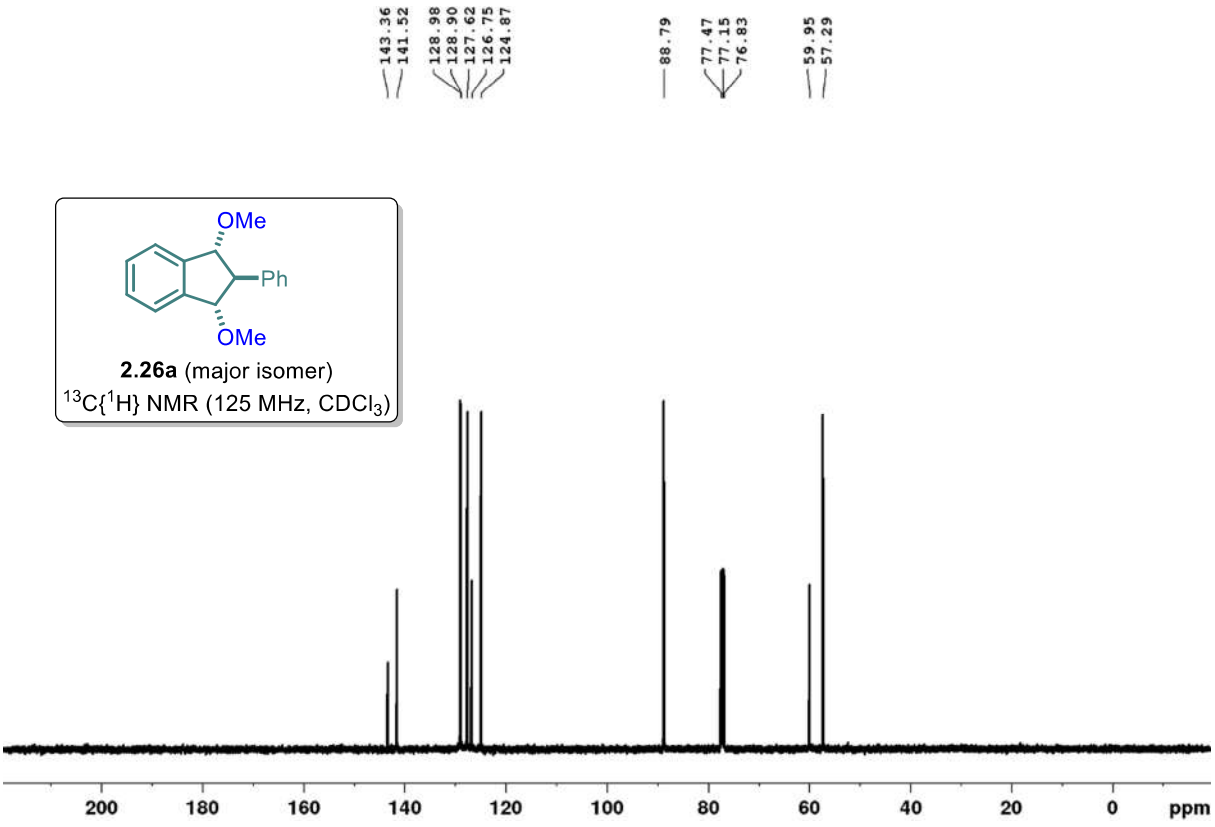
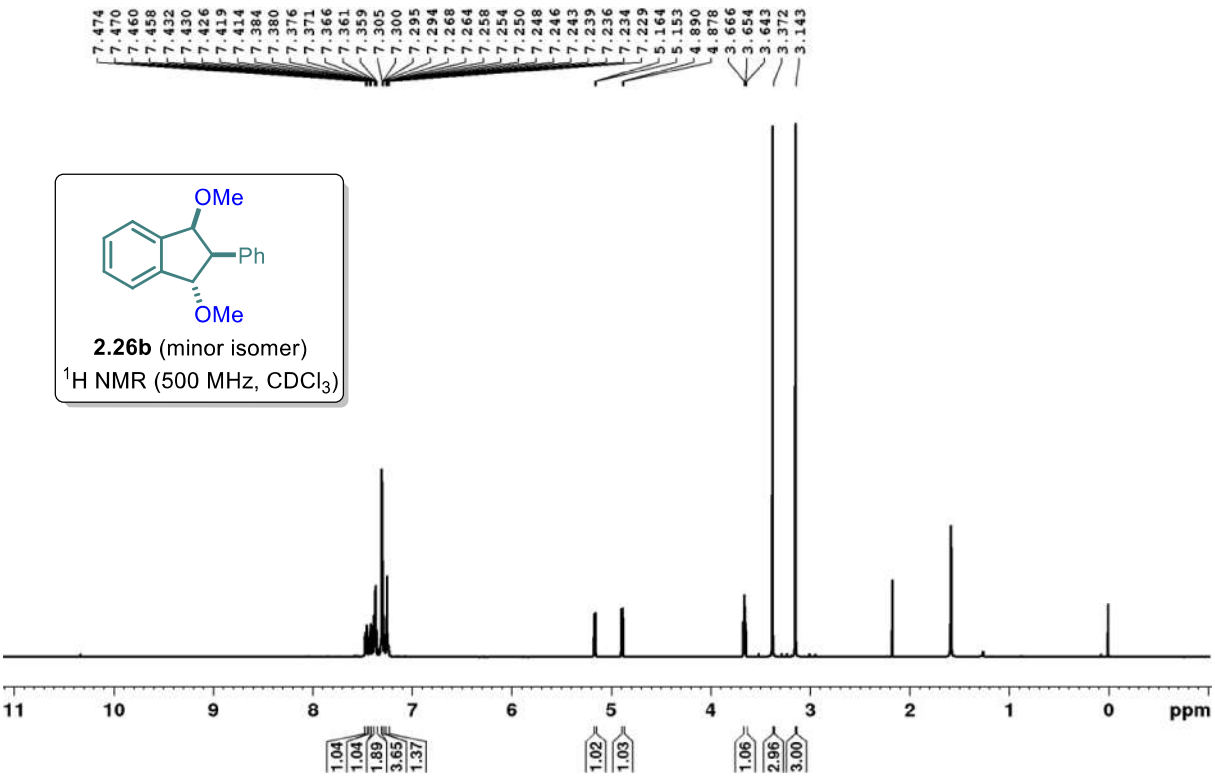
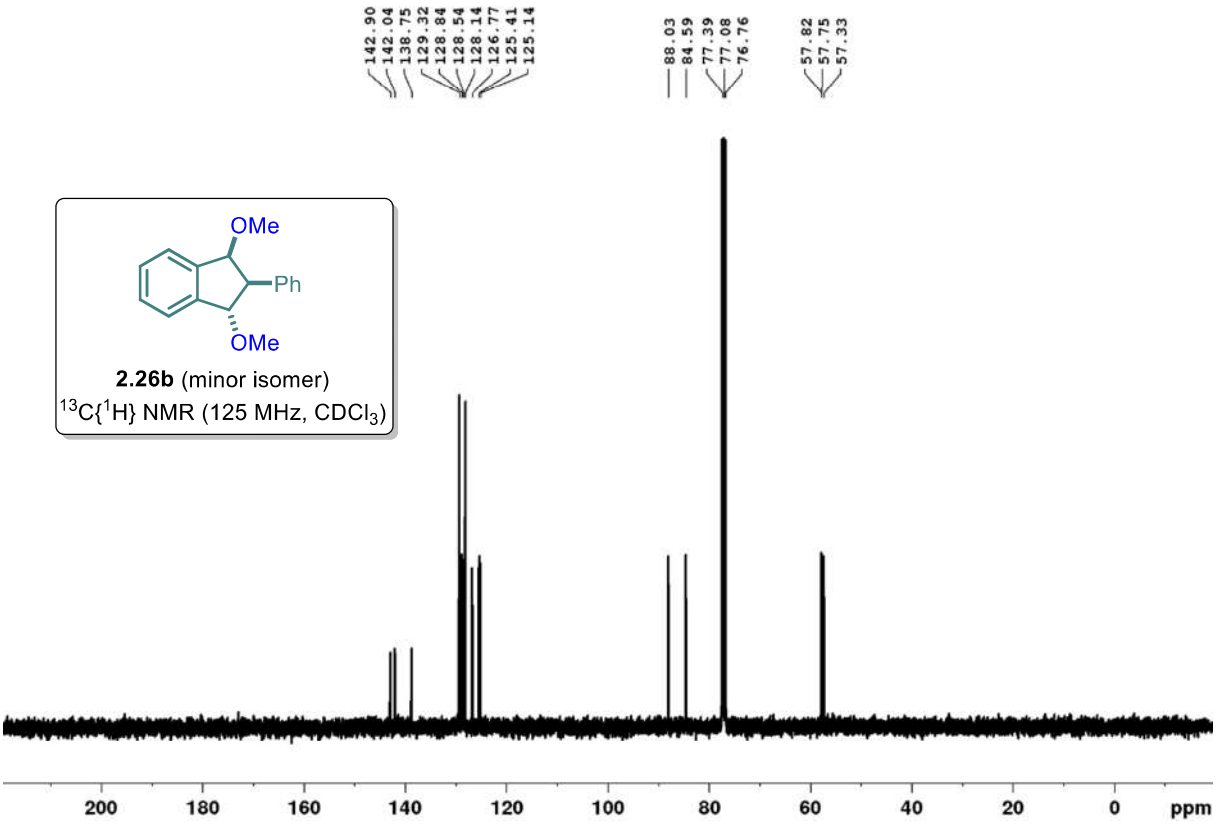
7.614
7.582
7.462
7.447
7.301
7.298
7.284
7.275
7.273
7.267
7.259
7.255
7.248
7.243
7.239
7.229
7.226
7.213
7.209
7.203
7.200
7.191
7.187
7.180
7.173
7.156
7.053
7.051
7.049
7.037
7.035
7.033
7.029
7.023
7.017
6.708
6.326
5.287
5.253
5.250
5.217
Ph
Bn
N
Bn
N
2.27-*trans*
^{1}H NMR (500 MHz, $CDCl_3$)
10
9
8
7
6
5
4
3
2
1
0
ppm
1.04
1.05
2.10
3.63
5.80
6.48
3.44
7.35
1.99
1.00
4.24

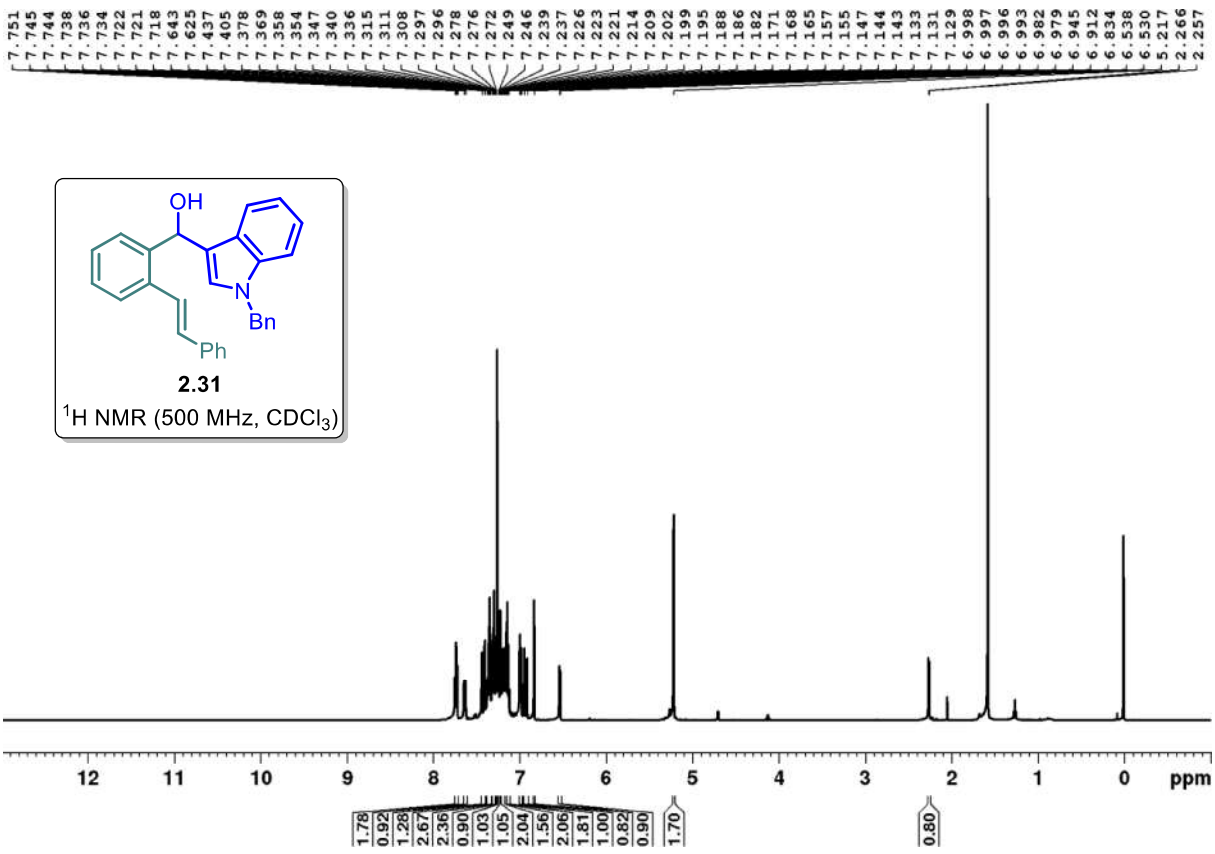

141.55
137.87
137.66
137.10
136.28
130.24
129.01
128.64
128.62
128.57
127.80
127.58
127.41
127.34
126.77
126.56
126.50
126.36
125.96
121.75
120.15
119.05
118.19
109.76
77.31
77.06
76.80
49.95
36.78
Ph
Bn
N
Bn
N
2.27-*trans*
^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$)
200
180
160
140
120
100
80
60
40
20
0
ppm

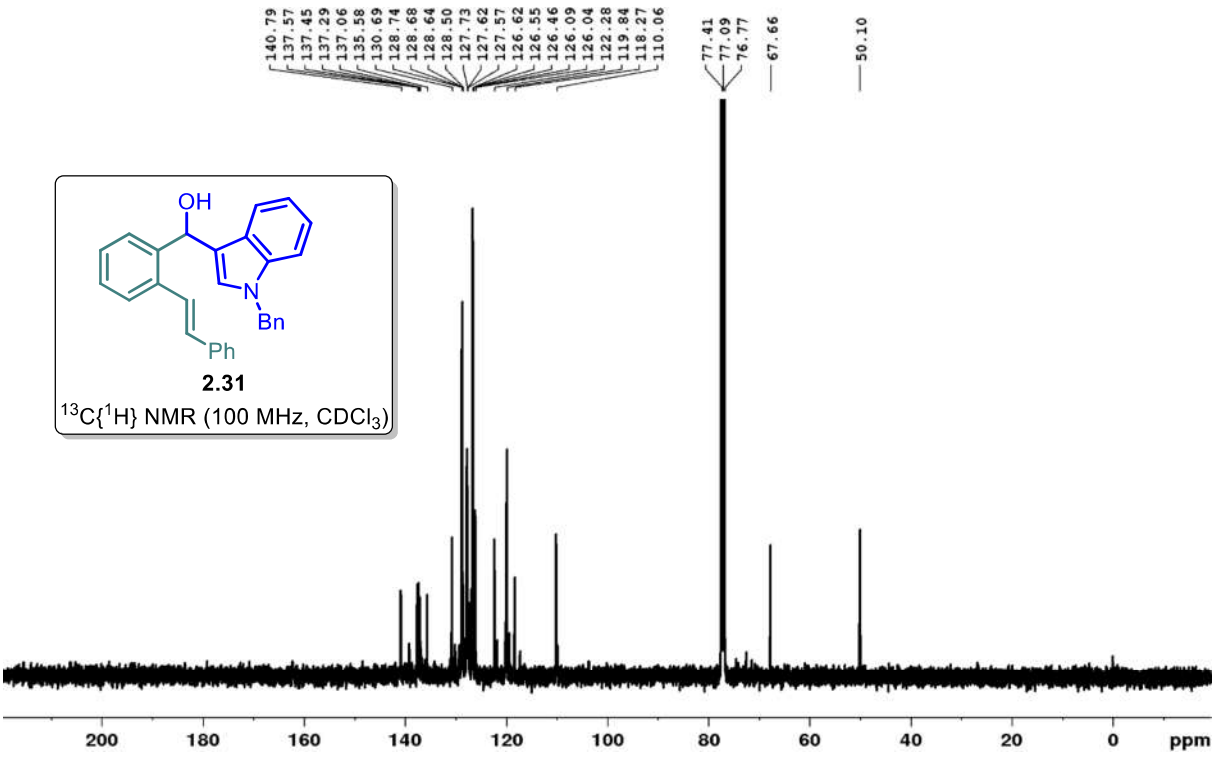

7.466
7.460
7.453
7.449
7.442
7.435
7.411
7.403
7.397
7.392
7.386
7.378
7.356
7.353
7.341
7.331
7.327
7.306
7.303
7.299
7.289
7.278
7.275
7.273
7.265
7.260
7.257
7.250
7.247
7.244
4.807
4.795
3.510
3.498
3.487
3.385
OMe
Ph
OMe
2.26a (major isomer)
1H NMR (500 MHz, CDCl3)
10
9
8
7
6
5
4
3
2
1
0
ppm
2.07
2.09
2.08
2.09
1.42
2.00
1.02
6.00

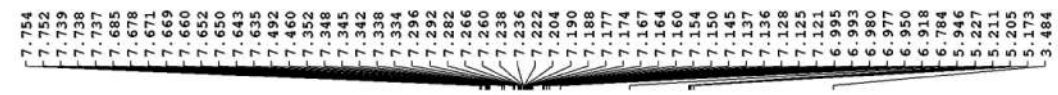

143.36
141.52
128.98
128.90
127.62
126.75
124.87
88.79
77.47
77.15
76.83
59.95
57.29
OMe
Ph
OMe
2.26a (major isomer)
13C{1H} NMR (125 MHz, CDCl3)
200
180
160
140
120
100
80
60
40
20
0
ppm

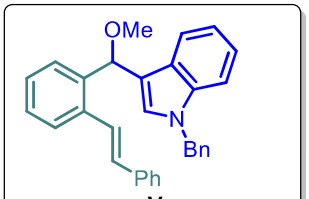

7.474
7.470
7.460
7.458
7.432
7.430
7.426
7.419
7.414
7.384
7.380
7.376
7.371
7.366
7.361
7.359
7.305
7.300
7.295
7.294
7.268
7.264
7.258
7.254
7.250
7.248
7.246
7.243
7.239
7.236
7.234
7.229
5.164
5.153
4.890
4.878
3.666
3.654
3.643
3.372
3.143
OMe
Ph
OMe
2.26b (minor isomer)
^{1}H NMR (500 MHz, CDCl$_3$)
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.04
1.04
1.89
3.65
1.37
1.02
1.03
1.06
2.96
3.00


142.90
142.04
138.75
129.32
128.84
128.54
128.14
126.77
125.41
125.14
88.03
84.59
77.39
77.08
76.76
57.82
57.75
57.33
OMe
Ph
OMe
2.26b (minor isomer)
^{13}C{^{1}H} NMR (125 MHz, CDCl$_3$)
200
180
160
140
120
100
80
60
40
20
0
ppm


OH
N
Bn
Ph
2.31
^{1}H NMR (500 MHz, CDCl$_3$)
ppm

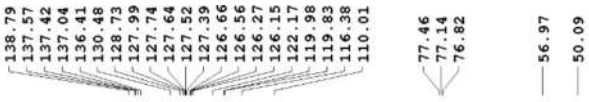

OH
N
Bn
Ph
2.31
^{13}C{^{1}H} NMR (100 MHz, CDCl$_3$)
ppm

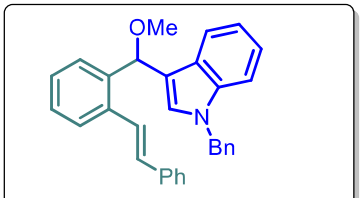




V

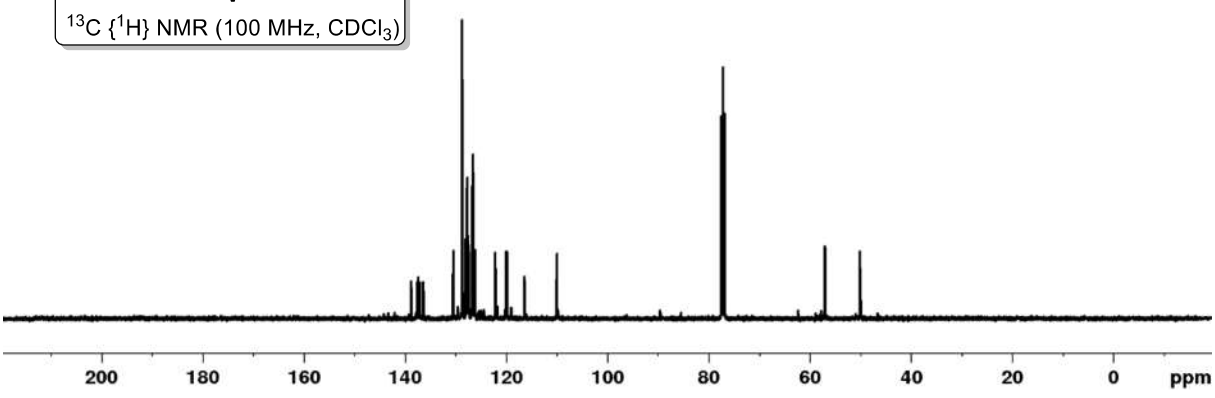
^{1}H NMR (500 MHz, $CDCl_3$)

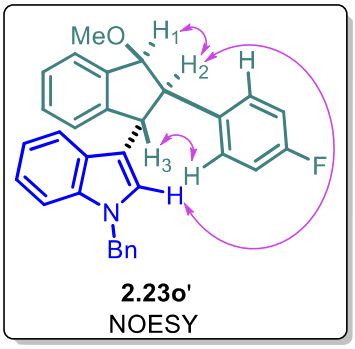




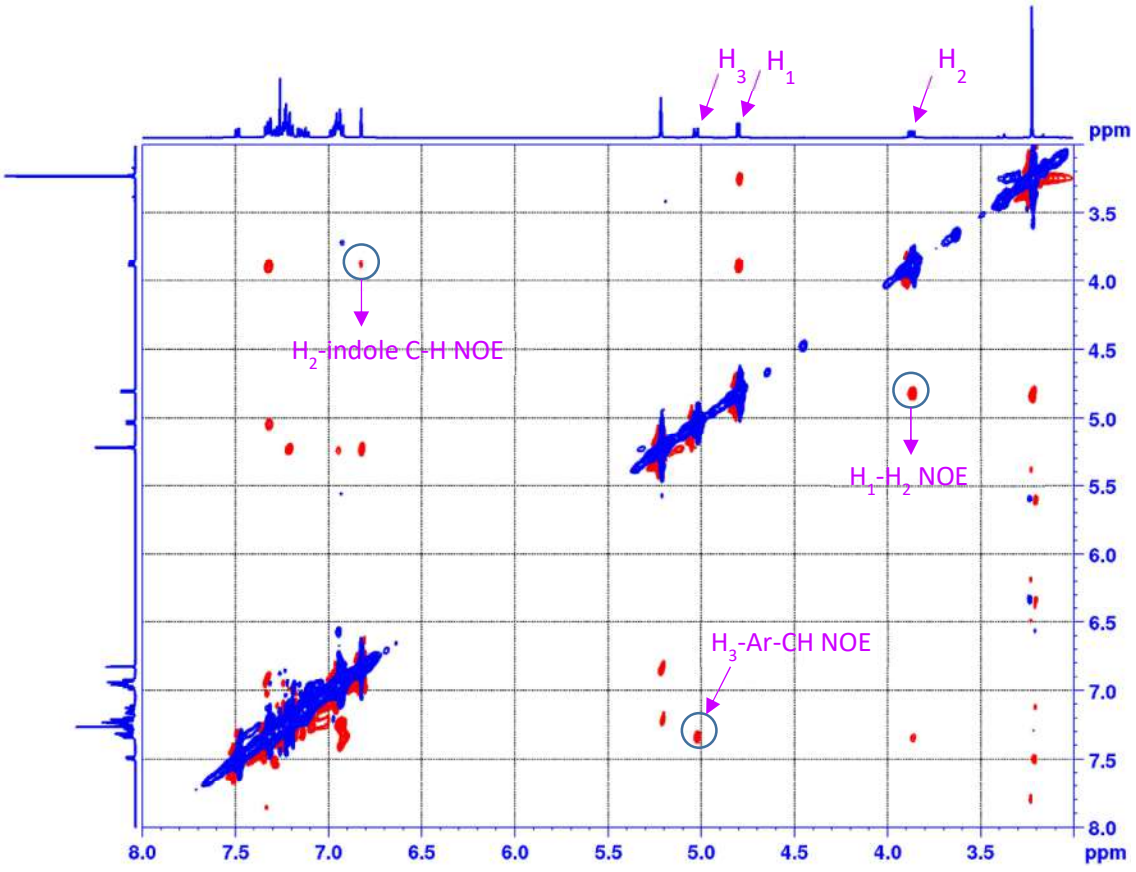
V

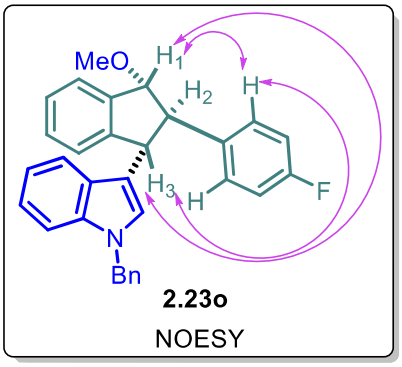
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$)

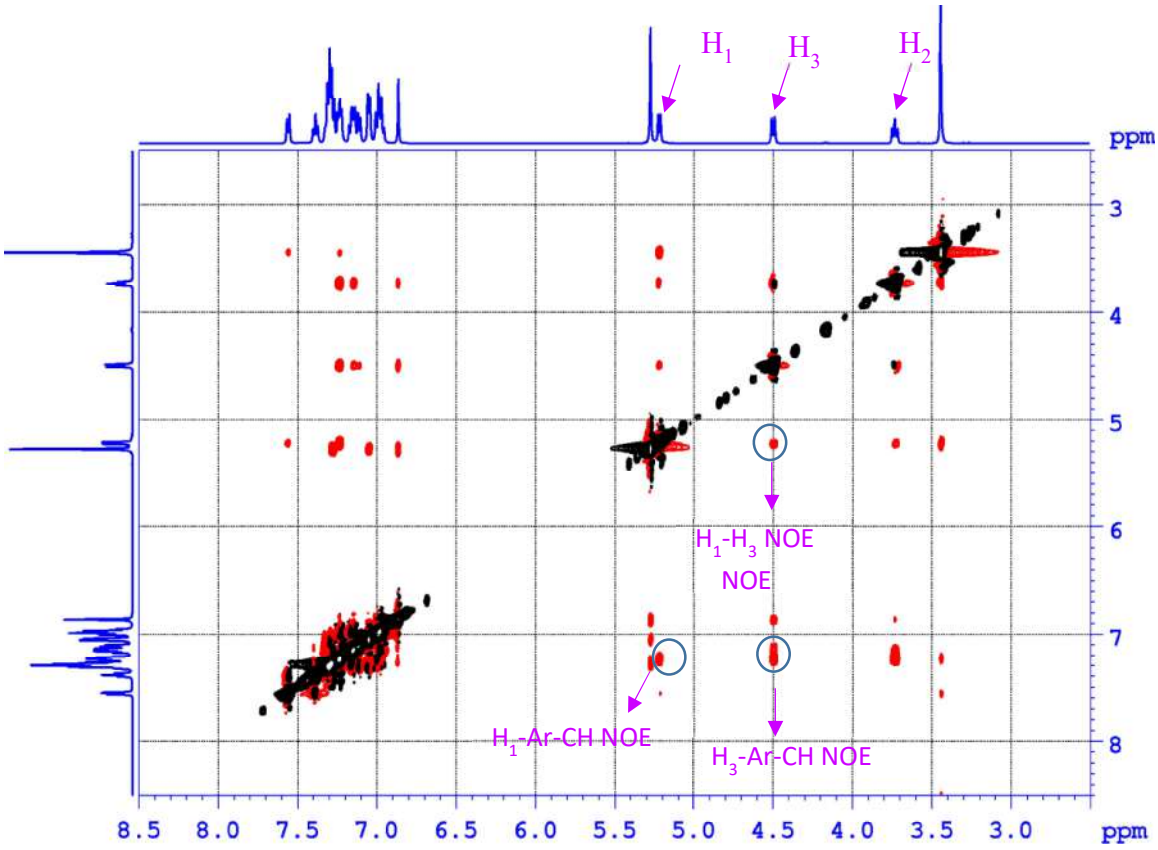


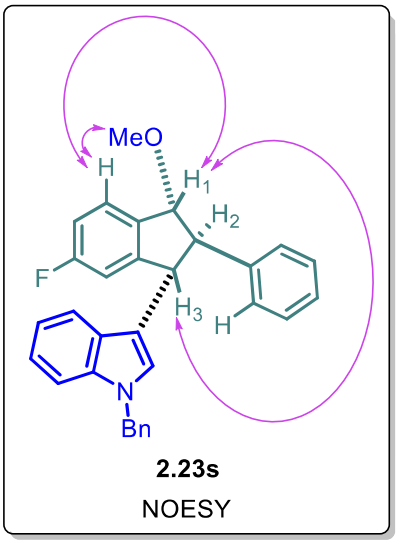

MeO
H1
H2
H
H3
H
F
H
N
Bn

2.23o'
NOESY


H3
H1
H2
ppm
H2-indole C-H NOE
H1-H2 NOE
H3-Ar-CH NOE
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm

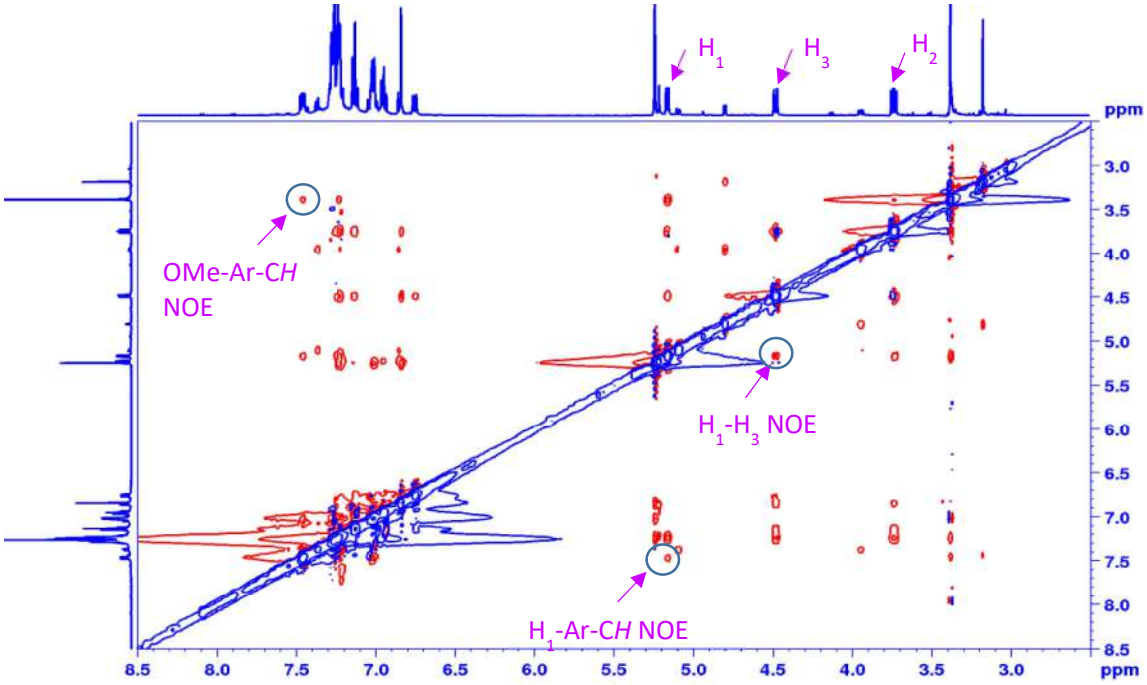

MeO
H1
H2
H
H3
H
F
N
Bn
2.23o
NOESY

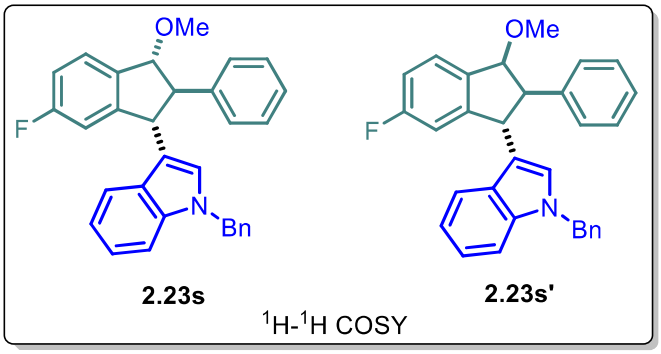

H1
H3
H2
ppm
H1-H3 NOE
NOE
H1-Ar-CH NOE
H3-Ar-CH NOE
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm

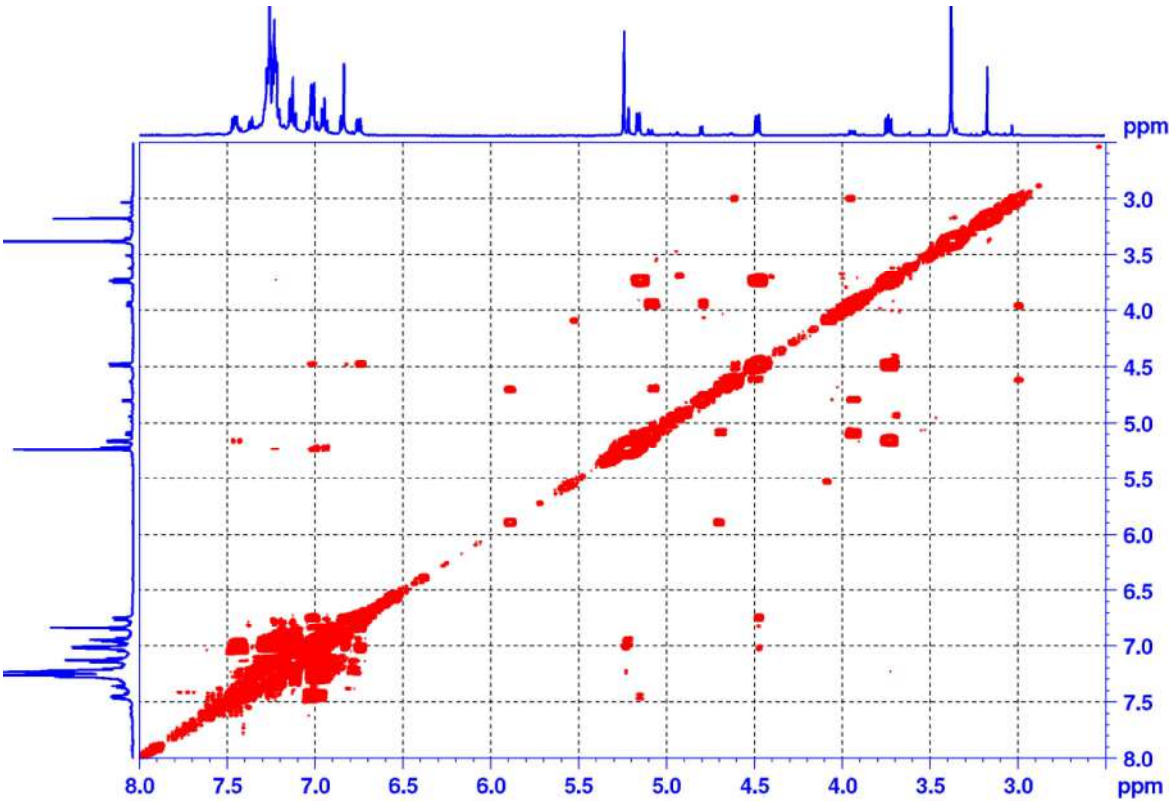

MeO
H
H1
H2
F
H3
H
N
Bn

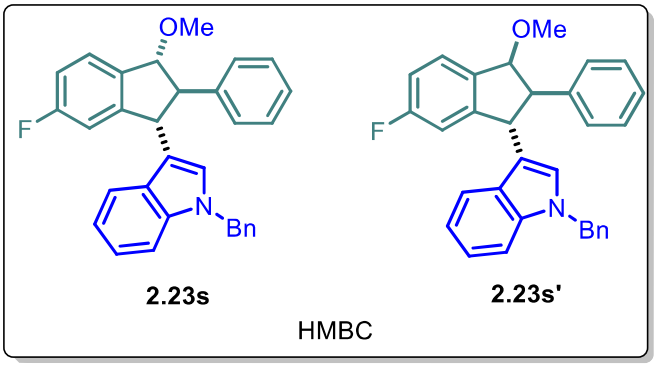
2.23s

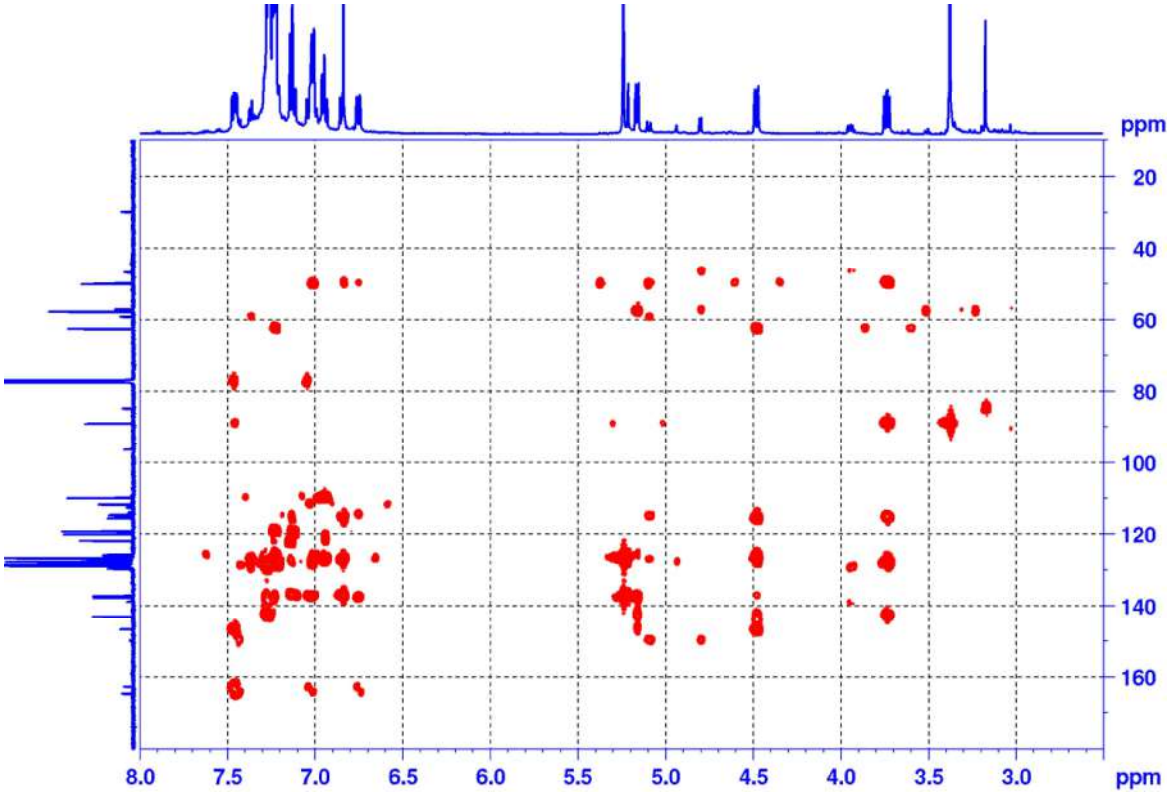
NOESY

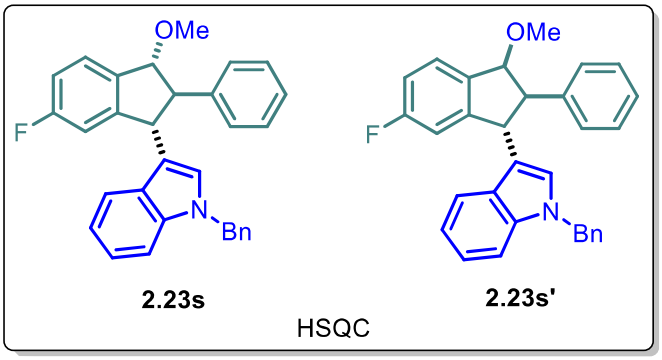

H1
H3
H2
ppm
OMe-Ar-CH
NOE
H1-H3 NOE
H1-Ar-CH NOE
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm

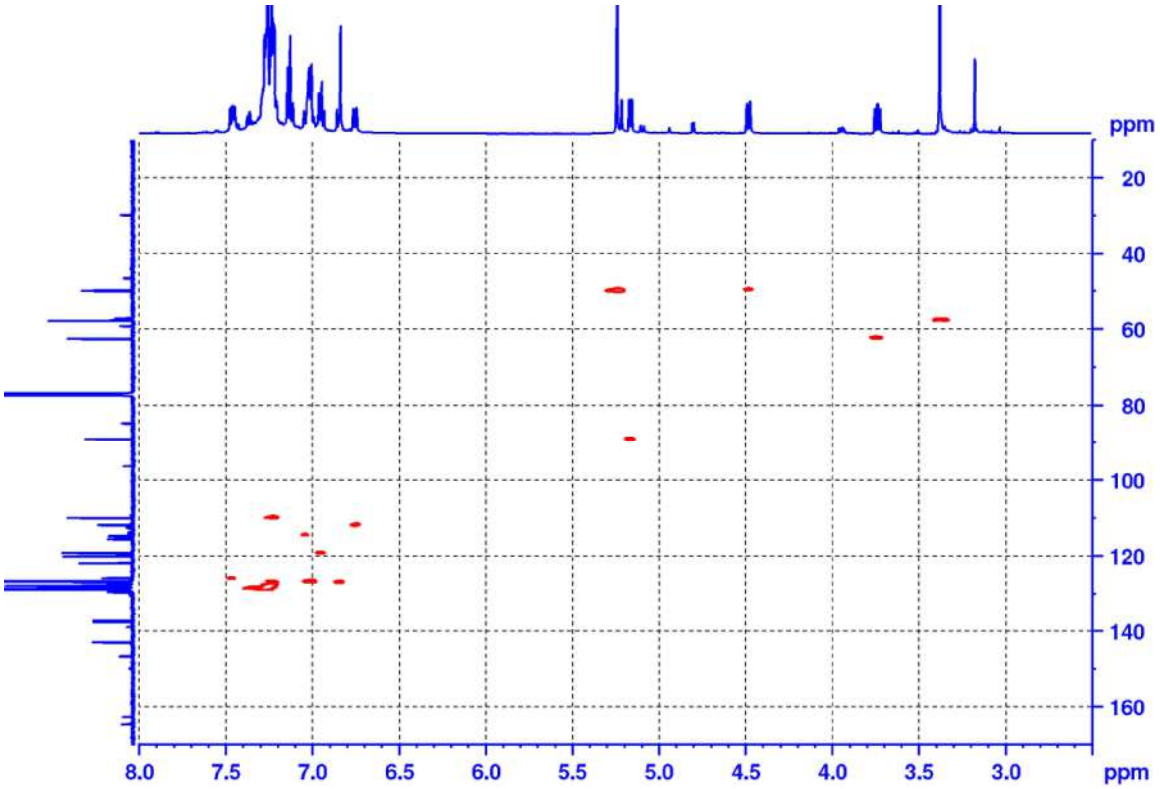

OMe
F
N
Bn
2.23s
OMe
F
N
Bn
2.23s'
^{1}H-^{1}H COSY

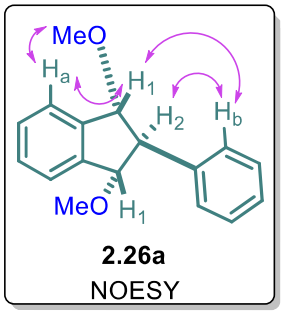

ppm
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm


OMe
F
N
Bn
2.23s
OMe
F
N
Bn
2.23s'
HMBC

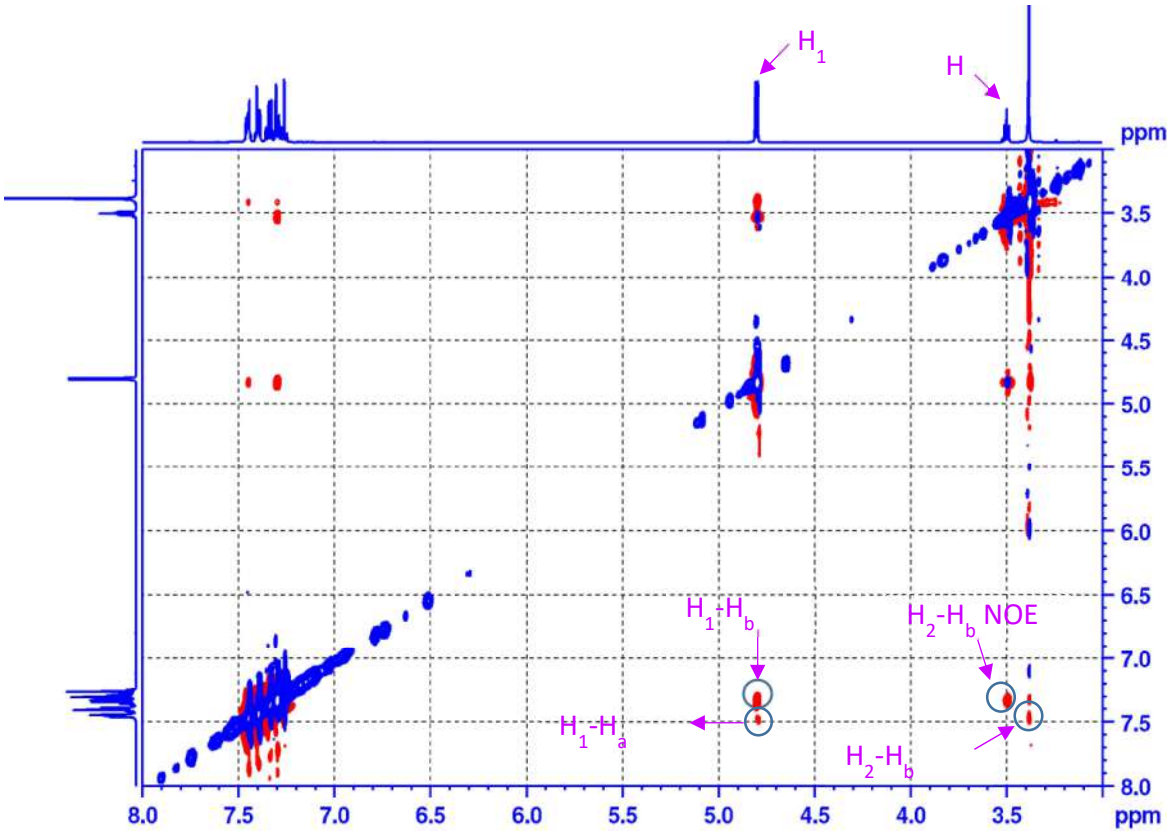

ppm
20
40
60
80
100
120
140
160
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm

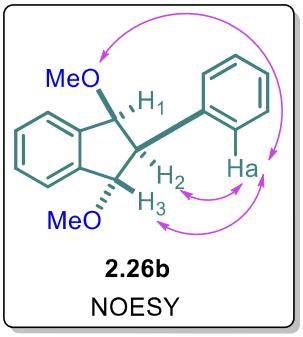

OMe
F
N
Bn
2.23s
OMe
F
N
Bn
2.23s'
HSQC


ppm
20
40
60
80
100
120
140
160
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm


MeO
Ha
H1
H2
Hb
MeO H1

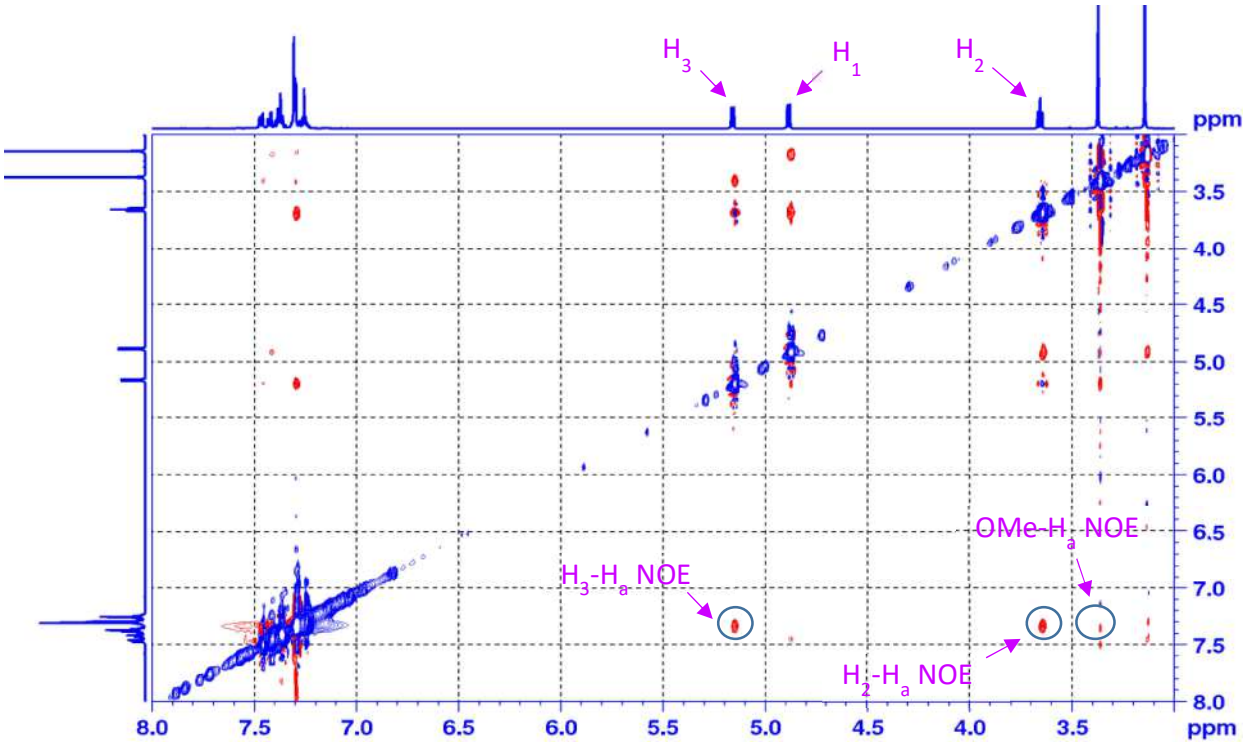
2.26a
NOESY


H1
H
ppm
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
H1-Hb
H2-Hb NOE
H1-Ha
H2-Hb
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm


MeO
H1
H2
Ha
H3
MeO

2.26b

NOESY


H3
H1
H2
ppm
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
OMe-Ha NOE
H3-Ha NOE
H2-Ha NOE
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
ppm

2.8 Crystallographic data

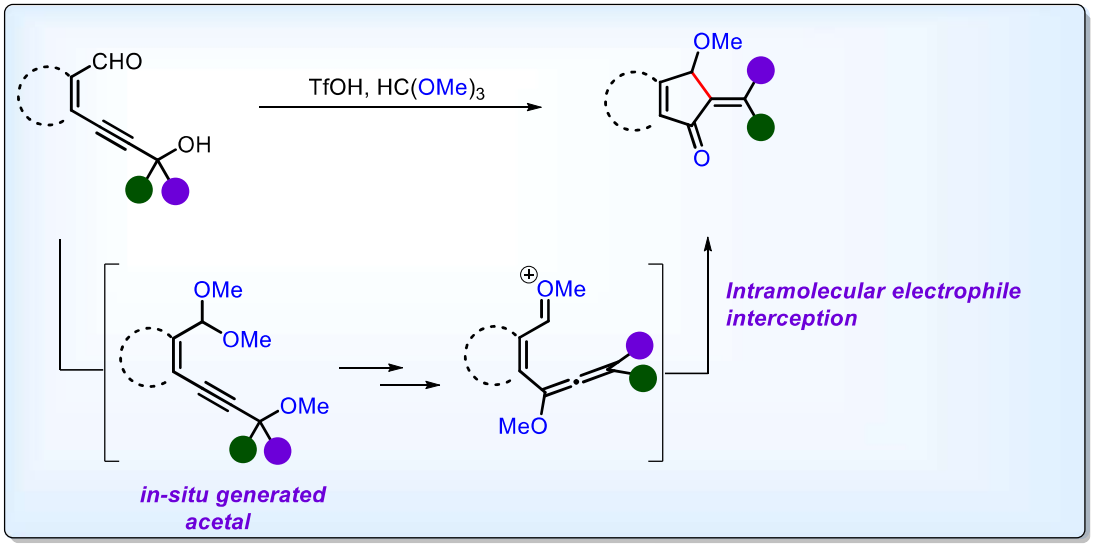
Table 2.3: **Crystallographic data for 2.23g', 2.23l and 2.27-*trans***

Compound	**2.23g'**	**2.23l**	**2.27-*trans***
Identification code	RB 44	RB 24	RB 26a
CCDC	**2065127**	**2065396**	**2106210**
Empirical formula	$C_{25}H_{23}NO$	$C_{32}H_{30}NO$	$C_{45}H_{36}N_2$
Formula weight	353.44	444.57	605.93
Temperature/K	296	273	119
Crystal system	Monoclinic	Triclinic	Monoclinic
Space group	P 21/C	P-1	P 1 21/n 1
a/Å	14.865(2)	10.7604(8)	16.8700 (9)
b/ Å	8.3723(13)	11.0540(8)	9.7170 (4)
c/ Å	15.690(2)	11.8385(8)	20.3903 (9)
$\alpha/^0$	90	99.344(3)	90
$\beta/^0$	101.970(6)	114.034(3)	98.286 (4)
$\gamma/^0$	90	100.665(3)	90
Volume/$Å^3$	1910.2(5)	1218.70(16)	3307.6 (3)
Z	4	2	4
Density(ρ)calc g/cm^3	1.229	1.209	1.217
Absorption Coefficient(μ) (mm^{-1})	0.074	0.072	0.070
F(000)	752.0	472.2	1282.0
Crystal size/mm^3	0.02 x 0.02 x 0.01	0.02 x 0.02 x 0.01	0.02 x 0.02 x 0.01
Reflections collected	3906	5079	5819
Independent reflections	2143	3552	2788

Completeness to theta = 26.379	99.5%	99.3%	99.9%
R (reflections)	0.0731 (2143)	0.0489 (3552)	0.0977 (2788)
wR2 (reflections)	0.1753 (3906)	0.1253 (5079)	0.2811 (5819)

Chapter 3

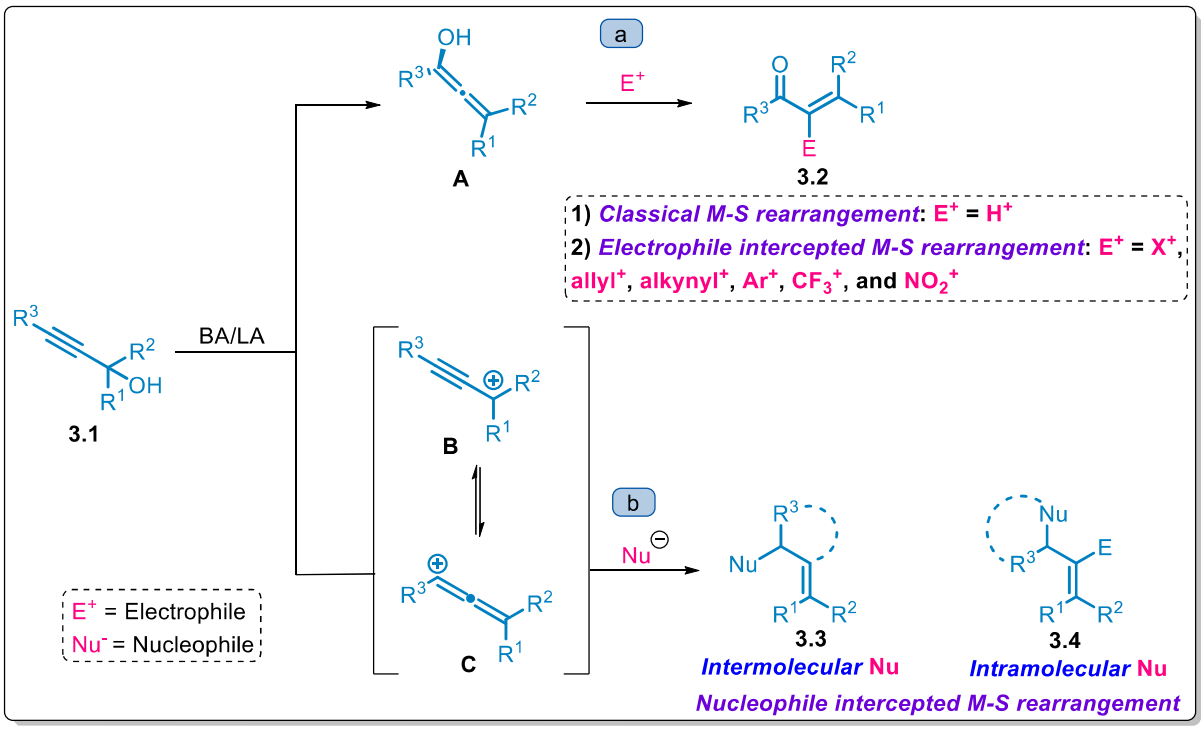
Intramolecular Electrophile Intercepted Meyer-Schuster Rearrangement under Acetalization Conditions



This work was published. Ref: *J. Org. Chem.* **2022**, *86*, 8633-8647.

3.1 Introduction

Synthesis of α, β-unsaturated carbonyl compounds **3.2** by treating propargyl alcohols **3.1** with an acid promoter is known as Meyer-Schuster (M-S) rearrangement (Scheme 3.1).[1a] This transformation involves a 1,3-hydroxyl shift to generate an allenol intermediate **A** or Meyer-Schuster (M-S) intermediate in the presence of a Brønsted or Lewis acid (BA or LA). This allenol intermediate **A** could be trapped in two different ways: a) by a proton (Classical M-S rearrangement) in an intermolecular fashion {Scheme 3.1a(1)},[1b-h] or by an electrophile other than a proton {Scheme 3.1a(2)}, or b) a nucleophile (Scheme 3.1b) in either inter- or intramolecular fashion leading to a new C-C or C-X (heteroatom) bond formation (intercepted M-S rearrangement). The intercepted M-S rearrangement offers a wide scope for its products as they are highly functionalized. Over the past decade, intercepted M-S rearrangement, in particular, electrophile intercepted M-S rearrangement has extensively been studied.[2] Groups such as halogen,[2a-c] allyl,[2d] alkynyl,[2e] aryl,[2f-g] trifluoromethyl,[2h] and nitro[2i] have been employed as electrophiles in such intercepted M-S rearrangements.

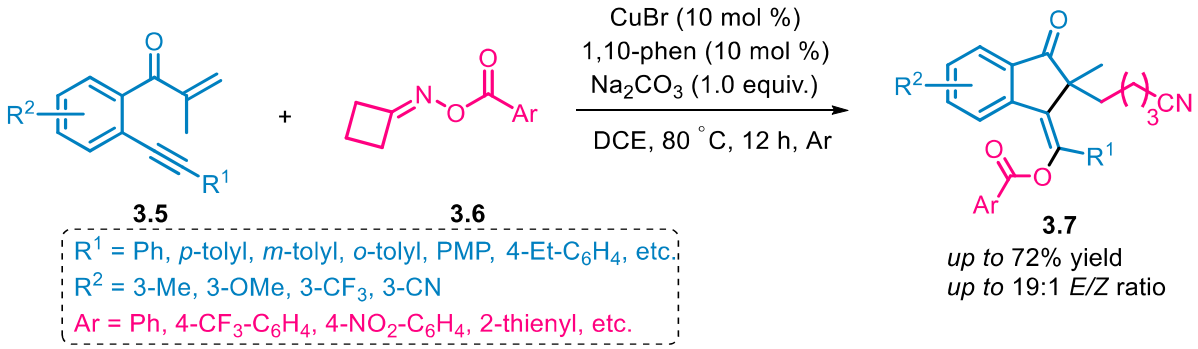


Scheme 3.1: Classical and intercepted (electrophile and nucleophile) M-S rearrangements

3.1.1 Selected previous approaches for the synthesis of indanones

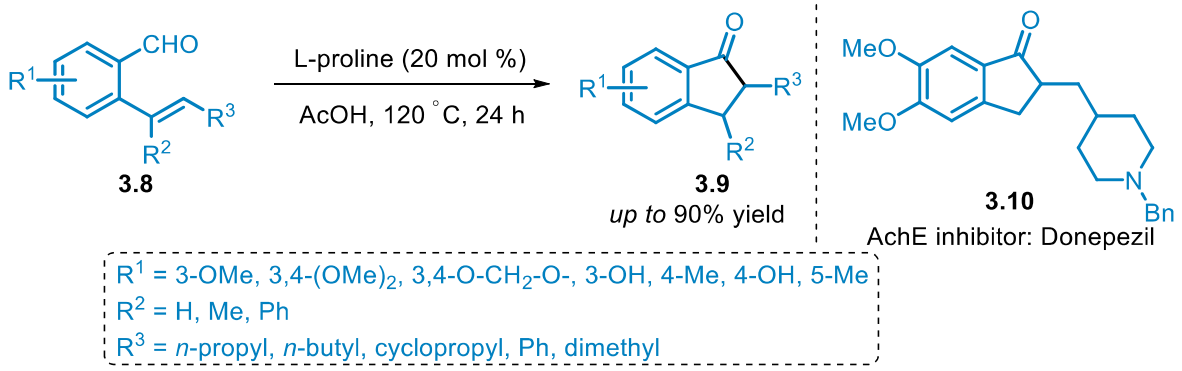
In 2021, Jiang *et al.* reported a stereoselective synthesis of 1-indanones **3.7** bearing cyano and ester groups from 1,6-enynes **3.5** and cyclobutanone oxime esters **3.6** under Cu(I)-catalysis (Scheme 3.2).[3] This reaction allows cyclobutanone oxime esters **3.6** to undergo direct

deconstructive functionalization to form multiple chemical bonds in a one-pot operation *via* a sequential cyanopropyl radical-induced 1,6-addition followed by 5-*exo-dig* cyclization, oxidative addition, and reductive elimination.



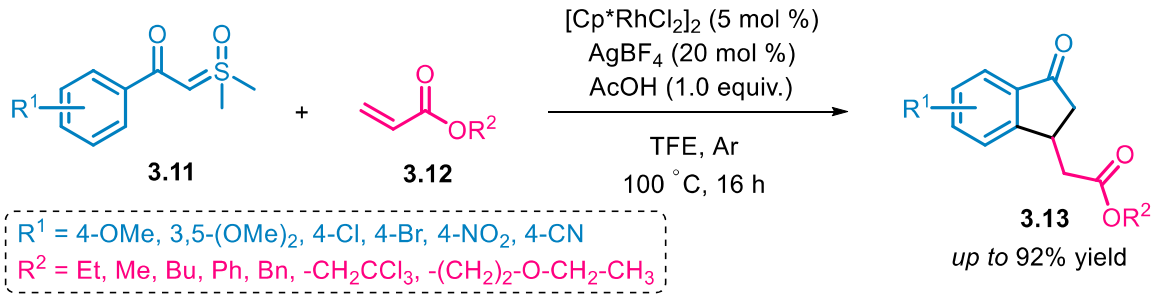
Scheme 3.2: Cu(I)-catalyzed cyanoalkyl esterification of 1,6-enynes by cyclic oxime esters

Zhou and co-workers developed a facile protocol for the synthesis of indanones **3.9** through an intramolecular hydroacylation of 2-vinylbenzaldehydes **3.8** under L-proline catalysis (Scheme 3.3).[4] Furthermore, this method was utilized for the synthesis of AchE inhibitor, donepezil **3.10**.



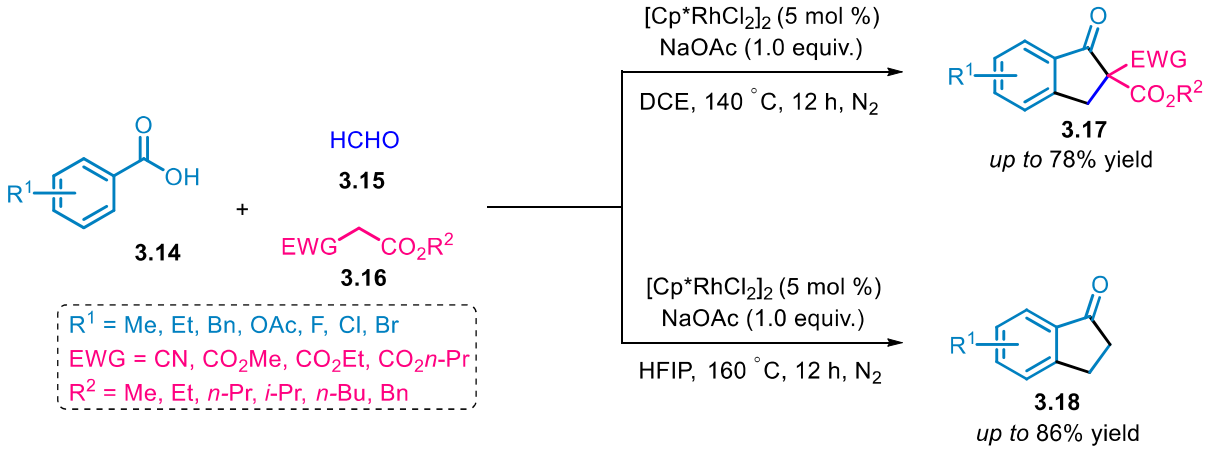
Scheme 3.3: L-proline-catalyzed intramolecular hydroacylation of 2-vinylbenzaldehydes

Rh(III)-catalyzed C-H activation and tandem (4+1) annulation of sulfoxonium ylide **3.11** with acrylates **3.12** for the synthesis of indanone derivatives **3.13** was demonstrated by Prabhu and co-workers (Scheme 3.4).[5] In this protocol, sulfoxonium ylides **3.11** acted as a traceless directing group as well as an internal oxidant.



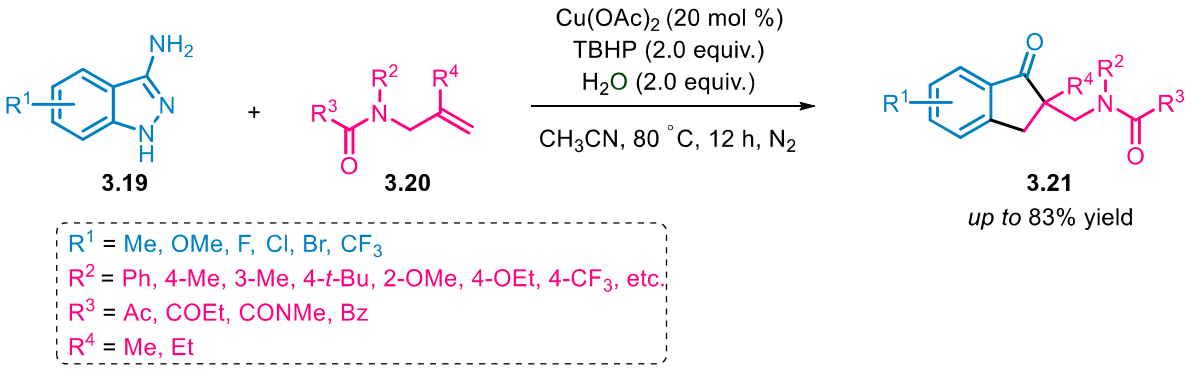
Scheme 3.4: Rh(III)-catalyzed C-H activation and tandem (4+1) annulation

Zhang *et al.* described a Rh-catalyzed C-H activation of benzoic acids **3.14** and reacted them with formaldehyde **3.15** and malonates **3.16** for the synthesis of indanone derivatives **3.17** and **3.18** (Scheme 3.5).[6] The solvent plays a vital role in this transformation, and 2-substituted indanones **3.17** were obtained when DCE is used as a solvent. Whereas, nonsubstituted indanones **3.18** were obtained when the reactions were conducted in HFIP solvent.



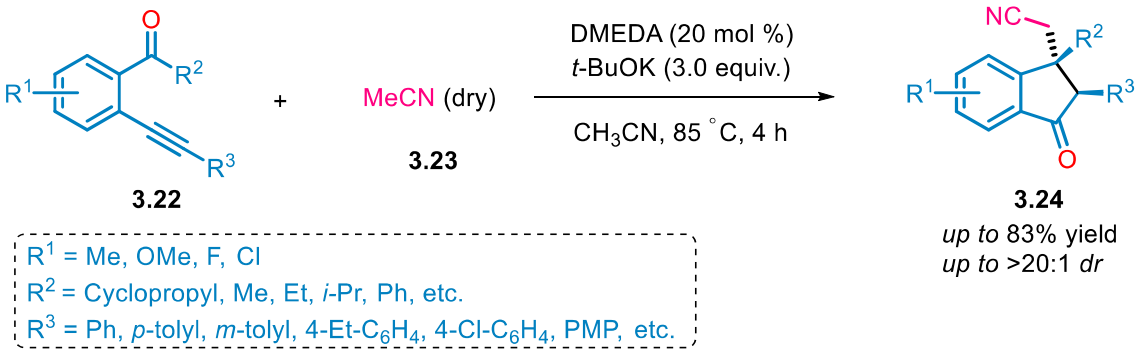
Scheme 3.5: Rh-catalyzed C-H activation of benzoic acids

Copper-catalyzed denitrogenative transannulation/hydrolyzation of 3-aminoindazoles **3.19** with *N*-(2-methylallyl)anilines **3.20** for the synthesis of 2-(aminomethyl)-2-methyl-indanones **3.21** was developed by Cheng *et al*. (Scheme 3.6).[7]



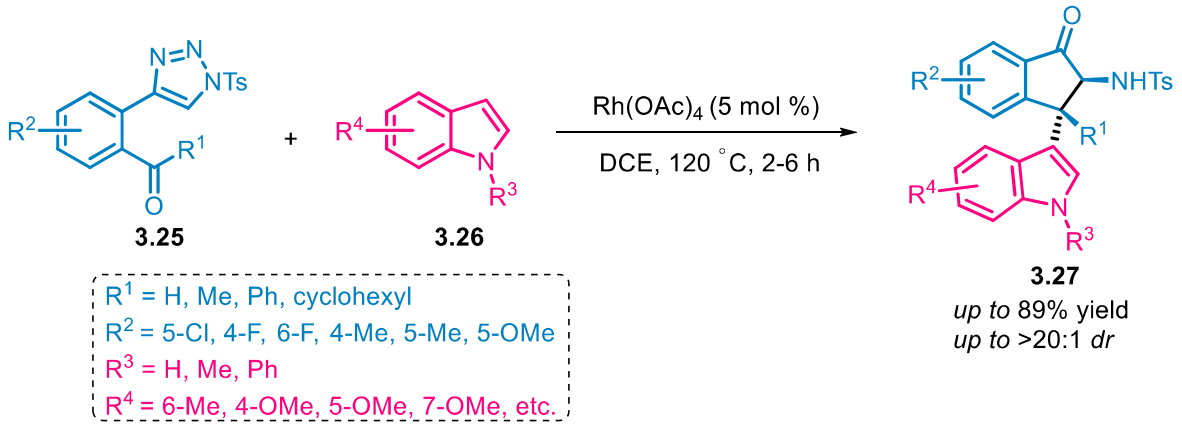
Scheme 3.6: Synthesis of 2,2-disubstituted indanones from 3-aminoindazoles under Cu(II)-catalysis

Jiang and co-workers reported the diastereoselective synthesis of 1-indanones **3.24** from *β*-alkynyl ketones **3.22** and acetonitrile **3.23** *via* 1,4-*oxo*-migration/cyclization strategy co-promoted by *t*-BuOK and DMEDA (Scheme 3.7).[8]



Scheme 3.7: 1,4-*Oxo*-Migration/cyclization of *o*-alkynylphenyl alkyl ketones promoted by two bases

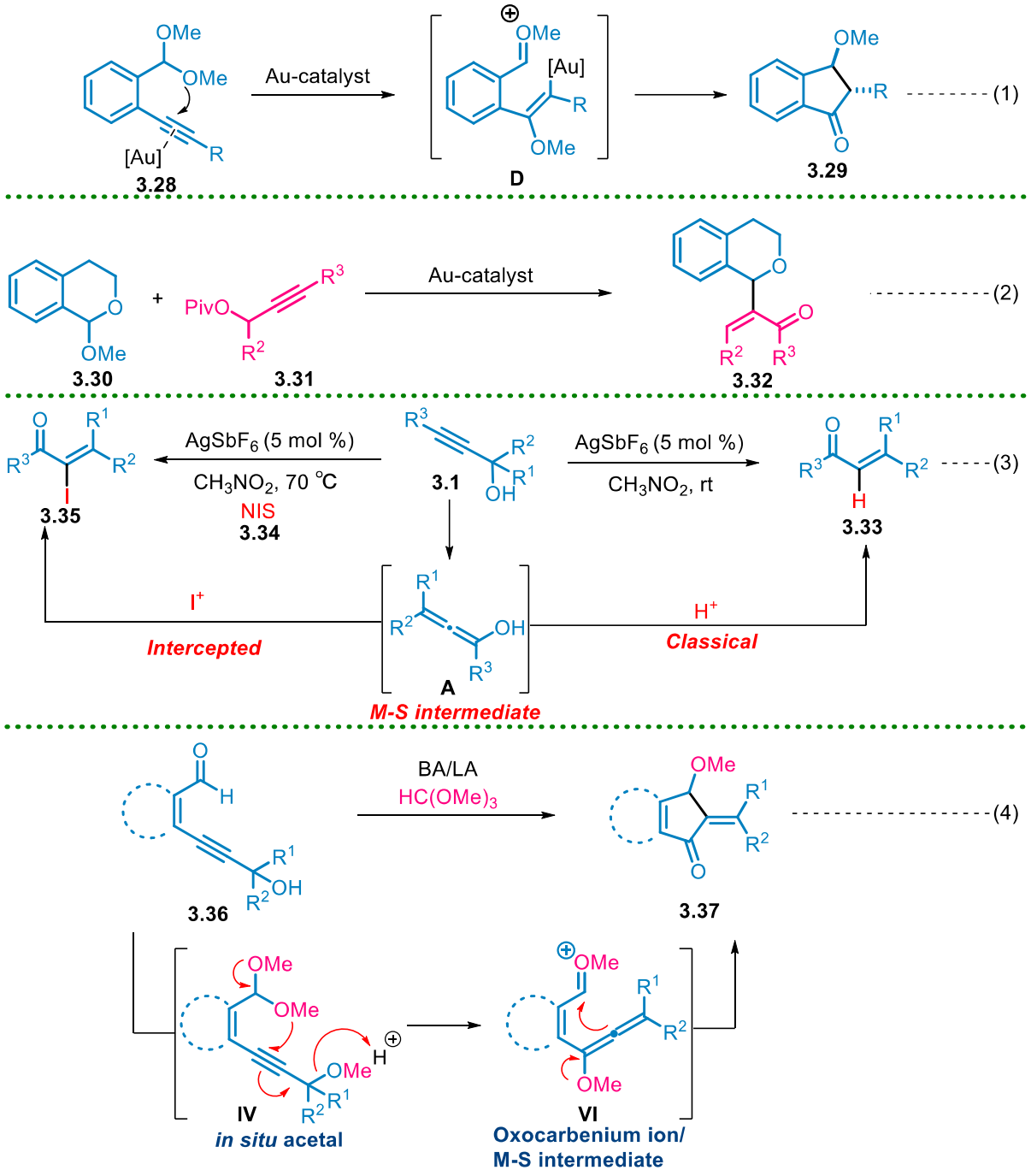
Yang *et al*. developed an efficient method for the synthesis of indole-substituted indanones **3.27** from *N*-sulfonyltriazoles **3.25** and indoles **3.26** under rhodium catalysis (Scheme 3.8).[9] *N*-sulfonyltriazoles **3.25** undergo denitrogenation in the presence of rhodium(II)-catalyst to generate an oxonium ylide, which would be attacked by indole **3.26** followed by subsequent skeletal rearrangement to furnish corresponding indole-substituted indanones **3.27** bearing an all-carbon quaternary stereocenter.



Scheme 3.8: Rh(II)-catalyzed tandem reaction of *N*-sulfonyl triazoles with indoles

3.2 Background

Transfer of an -OMe to an alkyne moiety in *o*-alkynylbenzaldehyde acetal **3.28** upon activation using a gold catalyst is a useful method for the synthesis of indanone derivatives **3.29** (Scheme 3.9, eq. 1).[10] This is followed by electrophilic trapping of vinylgold species with oxocarbenium ion **D** to afford indanones **3.29**. In a related approach, Hashmi's group has reported a gold-catalyzed intermolecular electrophilic trapping of the M-S type intermediate generated from pivaloyl ester **3.31** of propargyl alcohol with an oxocarbenium ion generated from isochromane acetals **3.30** for the synthesis of isochromane derivatives **3.32** (Scheme 3.9, eq. 2).[11]

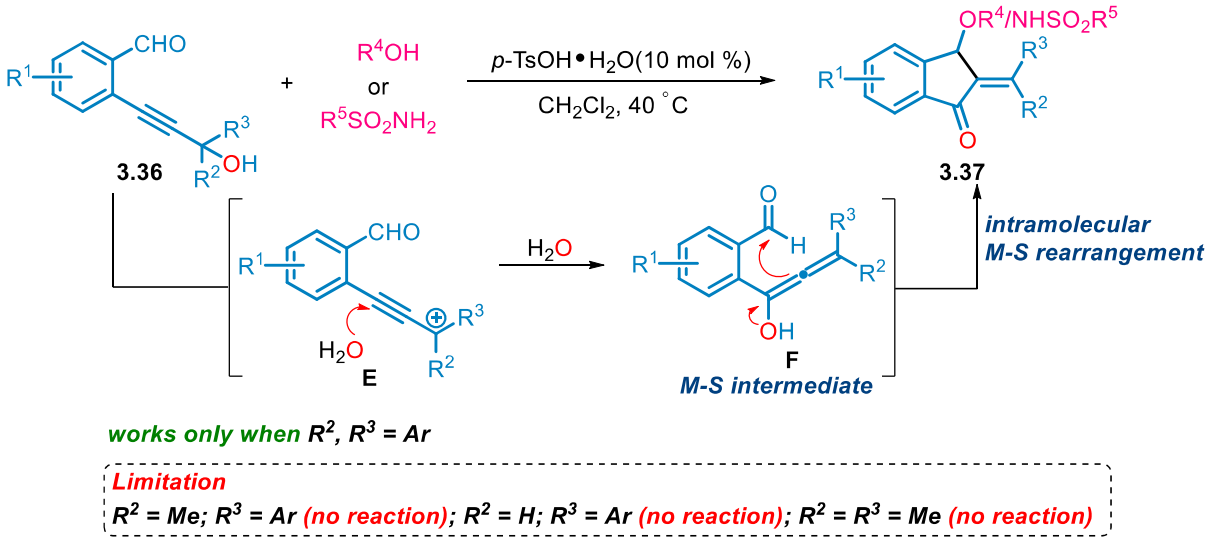


Scheme 3.9: Literature background and design of our work

In 2019, we reported an M-S rearrangement protocol for the synthesis of enones **3.33**/α-iodoenones **3.35** employing a silver catalyst (Scheme 3.9. eq. 3).[2b] In this method, iodonium ion generated from *N*-iodosuccinimide **3.34** was successfully trapped by allenol intermediate **A** through an intermolecular M-S rearrangement of tertiary propargyl alcohol **3.1**. Inspired by the

above works and in continuation of our efforts towards the development of methodologies using *in situ* generated acetals,[12] we wished to introduce an electrophilic group such as formyl within the same propargyl alcohol **3.1** to explore the electrophilic trapping of the M-S intermediate. The more reactive oxonium ion that will be generated in the presence of TMOF is expected to be handy for the electrophilic trapping. We envisaged that the reaction of *o*-propargyl alcohol benzaldehydes **3.36** with trimethyl orthoformate (TMOF) would lead to the formation of indanone derivative **3.37** under acid catalysis (Scheme 3.9, eq. 4). The acetal **IV** generated under the reaction condition might transfer an -OMe group to the *ortho*-alkyne moiety to form the M-S type intermediate, allenyl methyl ether **VI**. This intermediate **VI** is expected to cyclize on the electrophilic oxocarbenium ion to form the indanone derivative **3.37**.

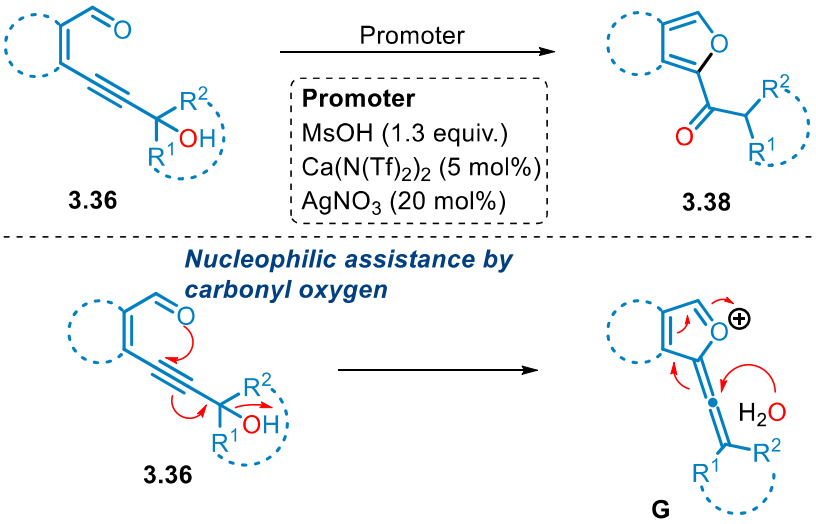
While successfully exploring this hypothesis, a report by Zhu's group appeared in the literature in which an electrophile intercepted M-S rearrangement using the same system *i.e., o*-propargyl alcohol benzaldehydes **3.36** in the presence of *p*-TSA·H_2O and alcohol or sulphonamide at 40 ˚C for the synthesis of 3-alkoxy and 3-sulfamido indanones **3.37** was achieved (Scheme 3.10).[13] Not surprisingly, the reaction worked only when the substrate contained two aryl rings attached to the propargyl alcohol carbon, as they readily generate the propargyl cation to form the required allenol intermediate for the intramolecular intercepted M-S rearrangement. Other substrates having one aryl/two alkyls/one aryl and one alkyl group on the carbinol carbon of the substrate failed to undergo the reaction. On this basis, it was proposed that an allenol M-S intermediate **F** is formed by the attack of water at the triple bond of the propargyl cation **E** formed from the starting material.



Scheme 3.10: Brønsted acid-catalyzed intramolecular electrophile-intercepted M-S rearrangement

Gratifyingly, under the acetalization condition, *i.e.,* in the presence of TMOF and catalytic TfOH, such less reactive substrates also underwent smooth intercepted M-S rearrangement (*vide infra*). It is believed that the acetal formed under the reaction conditions, through nucleophilic participation, might assist the reaction.

In a sharp contrast, nucleophilic participation of the carbonyl function in similar substrates **3.36** having two alkyl groups on the carbinol carbon to form allenyl ethers **G** in the presence of stoichiometric MsOH has been proposed by Beeraiah and co-workers (Scheme 3.11). Thus formed allenyl ether **G** subsequently transformed into 2-acylfurans **3.38** *via* an intermolecular attack of water.[14] Therefore, the nucleophilic participation of acetal formed under the reaction conditions offers a unique advantage to intercepted M-S rearrangement. The details of this study are presented below.



Scheme 3.11: Intramolecular nucleophile intercepted M-S rearrangement for the synthesis of 2-acylfurans

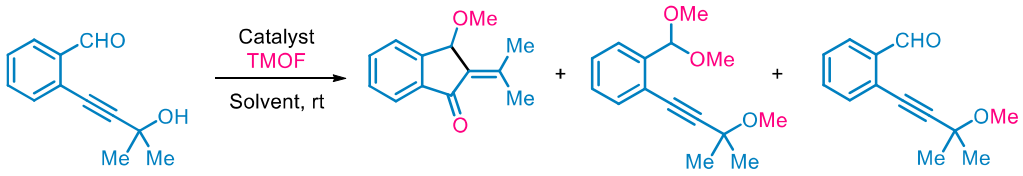
3.3 Results and discussion

3.3.1 Reaction optimization study

The substrate **3.36** having a less labile propargyl alcohol was chosen as a model substrate to optimize the reaction conditions of this intercepted M-S rearrangement taking the advantage of *in situ* formed acetal. Formation of the intercepted M-S product, indanone **3.37a** in 45% yield upon treatment of **3.36** with 20 mol% of TfOH and 2.0 equiv. of TMOF (Table 3.1, entry 1) in nitromethane at room temperature, prompted us to evaluate the optimal conditions to get a better yield of **3.37a**. In this regard, different Brønsted and Lewis acids were screened in the presence of 2.0 equiv. of TMOF in CH_3NO_2. However, in the reactions involving catalytic CH_3SO_3H, *p*-TsOH·H_2O, and $HClO_4$, other products **3.38a** and/or **3.39a** were also obtained along with the

desired product **3.37a** (Table 3.1, entries 2-4). These products **3.38a** and **3.39a** are, perhaps, the intermediates formed prior to the cyclization step as both of them were convertible into **3.37a** upon treatment with TMOF and cat. TfOH (*vide infra*). The desired product **3.37a** was obtained in 12% yield along with 15% of **3.39a** when Lewis acid such as $AgSbF_6$ was used (Table 3.1, entry 5). On the other hand, other Lewis acids, such as $Cu(OTf)_2$ and $Sc(OTf)_3$ did not give the cyclized product **3.37a** (Table 3.1, entries 6 and 7). Therefore, further optimization studies were carried out to find out the appropriate amounts of TfOH, TMOF, and the suitable solvent.

Table 3.1 Optimization of the reaction conditions[a]



3.36 **3.37a** **3.38a** **3.39a**

Entry	Catalyst (mol %)	TMOF (equiv.)	Solvent	Time (h)	Yield (%)[b]		
					3.37a	**3.38a**	**3.39a**
1	TfOH (20)	2	CH_3NO_2	7	45	-	-
2	CH_3SO_3H (20)	2	CH_3NO_2	24	15	10	12
3	*p*-TsOH·H_2O (20)	2	CH_3NO_2	24	10	12	20
4	$HClO_4$ (20)	2	CH_3NO_2	24	15	-	10
5	$AgSbF_6$ (20)	2	CH_3NO_2	24	12	-	15
6	$Cu(OTf)_2$ (20)	2	CH_3NO_2	24	-	15	25
7	$Sc(OTf)_3$ (20)	2	CH_3NO_2	24	-	20	30
8	TfOH (5)	2	CH_3NO_2	48	37	-	11
9	TfOH (10)	2	CH_3NO_2	24	39	-	9
10	TfOH (20)	2	Toluene	24	10		37
11	TfOH (20)	2	CH_3CN	24	19	-	37
12	TfOH (20)	2	CCl_4	12	-	50	15
13	TfOH (20)	2	CH_2Cl_2	24	29	-	22
14	TfOH (20)	1	CH_3NO_2	24	18	-	22
15	TfOH (20)	3	CH_3NO_2	24	48	-	-

16	**TfOH (20)**	**4**	**CH_3NO_2**	**7**	**52**	**-**	**-**
17	TfOH (20)	nil	CH_3NO_2	24	-	-	-

[a]Reaction conditions: **3.36** (100 mg), solvent (3 mL/0.2 mmol). [b]Isolated yield after column chromatography.

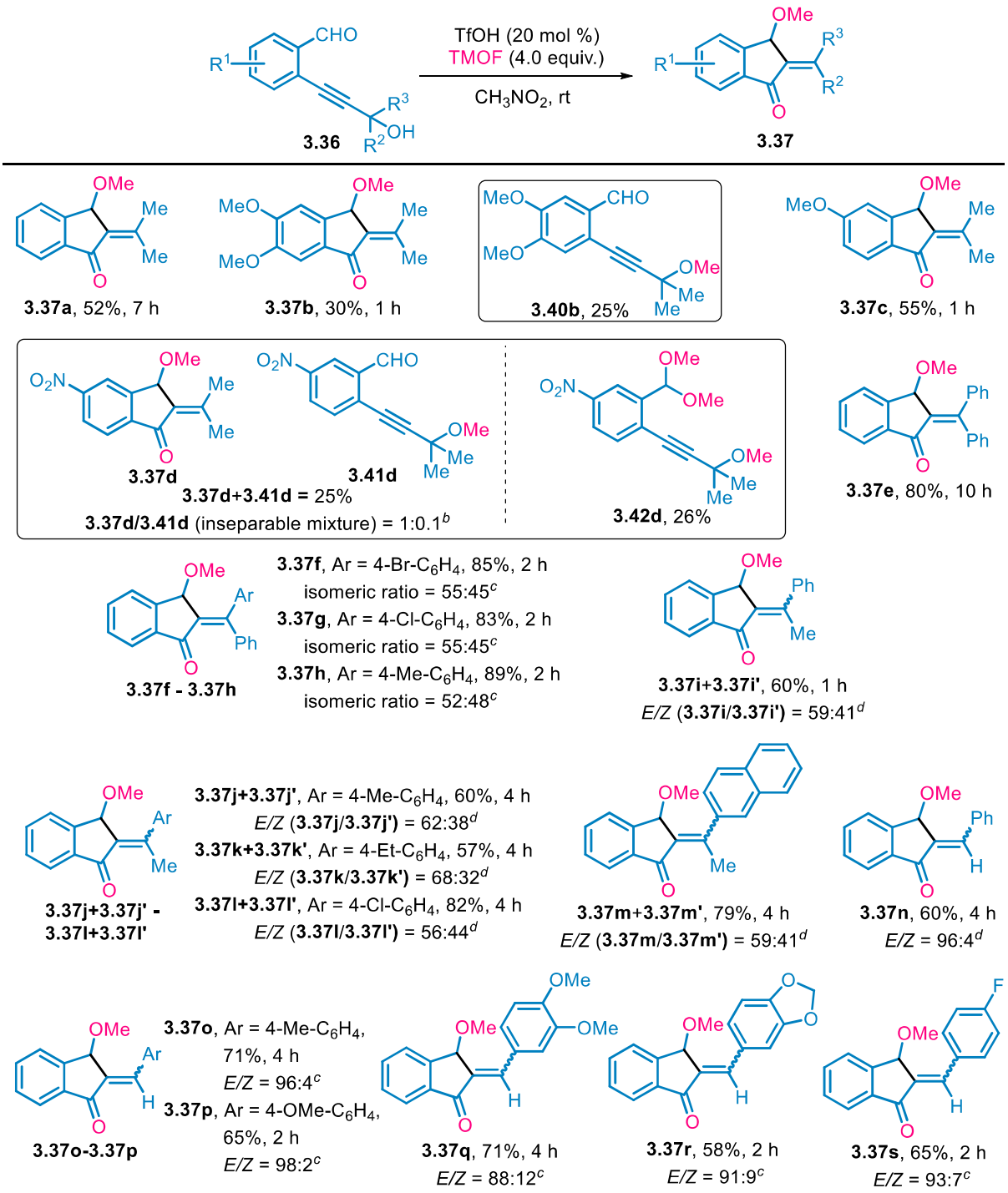
The yield of **3.37a** decreased When 5 or 10 mol % of triflic acid was used (Table 3.1, entries 8 and 9). Solvents such as toluene, CH_3CN, CCl_4, and CH_2Cl_2 were found to be less appropriate (Table 3.1, entries 10-13). Decreasing the amount of TMOF to 1.0 equiv. had a drastic effect and only 18% of the product **3.37a** was obtained (Table 3.1, entry 14). As the reaction involving 4.0 equiv. of TMOF resulted in 52% of **3.37a**, the condition mentioned in entry 16 of Table 3.1 was found to be the optimal condition to evaluate the substrate scope of this transformation. Although this yield is not very attractive, it is yet significant considering the less reactivity of this dialkyl substrate. The low yields obtained in the case of substrates having alkyl substituents at the carbinol carbon might be attributed to the decomposition triggered by the elimination in the presence of strong Brønsted acid (TfOH). It should be mentioned that substrate **3.36** got decomposed when the reaction was conducted in the absence of TMOF (Table 3.1, entry 17). This result hints at the importance of acetal formed under the reaction conditions for the success of the reaction.

3.3.2 Substrate scope

We have next turned our attention to check the electronic and steric effects of differently substituted *o*-propargyl alcohol benzaldehydes **3.36** in this *in situ* formed acetal-assisted intramolecular electrophile intercepted M-S rearrangement, and the results are summarized in Table 3.2. More attention was given to substrates having less reactive propargyl alcohols. At the outset, substrates having symmetrical substituents on the carbinol carbon such as dimethyl, and diphenyl were studied. When the internal aryl group of the benzaldehyde contained electron-donating groups such as -OMe, the reactions were sluggish. For example, product **3.37b** was obtained in 30% only along with the methoxy ether derivative of the starting material **3.40b** (25%). In the case of a similar dioxolane derivative, only the methyl ether **3.44ac** was obtained in 45% yield in 15 minutes (Figure 3.2). Prolonging the reaction time resulted in decomposition of **3.44ac**. Electron-donating alkoxy groups are expected to reduce the electrophilic nature of aldehyde. It is interesting to note that the normal M-S rearrangement of the propargyl alcohol was also not observed in these cases, hinting at a certain role of acetal in the formation of intercepted M-S products in the successful cases. However, a yield of 55% (product **3.37c)** was noticed when the substrate with the 5-OMe group was subjected to the reaction conditions. Perhaps, in the substrate **3.36b**, the -OMe group *para* to aldehyde might reduce the electrophilicity of the aldehyde carbon to reduce its propensity to undergo cyclization. An electron-withdrawing group such as NO_2 in the arene ring did not facilitate the cyclization, as it resulted in a poor yield of the desired product **3.37d** together with corresponding methylated product **3.41d** as an inseparable mixture with a 1:0.1 ratio besides the corresponding acetal **3.42d** in 26% yield. This shows that the -NO_2 group

might make the formation of oxocarbenium ion less favourable. More reactive propargyl alcohol derivatives having two aryl groups on the carbinol carbon underwent smooth reactions to yield

Table 3.2 Substrate scope[a]



[a]Reaction conditions: **3.36** (100 mg, 1.0 equiv.), CH_3NO_2 (3 mL/0.2 mmol), TfOH (20 mol %), TMOF (4.0 equiv.). [b]Ratio was based on ^{1}H NMR. [c]*E*/*Z* ratio was determined by ^{1}H NMR. [d]*E*/*Z* ratio was based on isolated yield.

their respective indanone products in very good yields (Table 3.2, products **3.37e** – **3.37h**). Substrates having alkyl and aryl groups at the propargylic alcohol carbon were also tested. It has to be mentioned that these substrates were unreactive in the electrophile intercepted M-S rearrangement catalyzed by *p*-TsOH·H_2O.[13] Products **3.37i** – **3.37m** were obtained in good yields from their respective propargylic alcohol derivatives. The *E* isomers were formed in more amounts than their corresponding *Z* isomers in these reactions. Importantly, they could be separated by column chromatography. The reactions of aryl propargyl alcohol substrates, which were also unreactive under *p*-TsOH·H_2O-promoted intercepted M-S rearrangement[13] were then evaluated under the present reaction conditions. Interestingly, these substrates also underwent facile intramolecular electrophile intercepted M-S rearrangement to form products **3.37n** – **3.37s** as inseparable mixtures of *E* and *Z* isomers. *E*/*Z* selectivity was generally excellent (> 15:1) in these products except in a couple of cases where a meta substituent was present {**3.37q** (*E*/*Z* = 7.3:1) and **3.37r** (*E*/*Z* = 10.1:1)}. The steric interaction between meta substituent of the aryl and -OMe substituent during cyclization to form *E*-isomer could be the reason for the slight reduction in selectivity.

There has been a quite interest in atropisomerism both in terms of finding new types of atropisomers in addition to the classical biaryl systems, and finding applications in catalysis and biology.[15] In this regard, alkene-aryl atropisomerism has drawn certain attention.[16] We explored such atropisomerism in the products of intercepted M-S rearrangement using substrates having *ortho*-substituted aryl ring and a methyl group at the propargyl alcohol carbon. The main reason for the selection of such substrates is the separation of *E* and *Z* isomers in the methyl containing substrates **3.37i** – **3.37m**. The *E* and *Z* isomers were separated in these cases as well. Interestingly, as expected, atropo-diastereomerism was noted in the products **3.37t**/**3.37t'** – **3.37w**/**3.37w'** (Figure 3.1). The diastereomeric ratios were discerned from the ^{1}H NMR. While the *Z*-isomer contained an almost 1:1 mixture of atropo-diastereomers, the *E*-isomer showed a slight atropodiastereoselectivity which might be due to the interaction of indane ring -OMe with the aryl ring. ^{1}H NMR of atropo-diastereomers of **3.37w** and **3.37w'** are displayed in Figure 3.1.

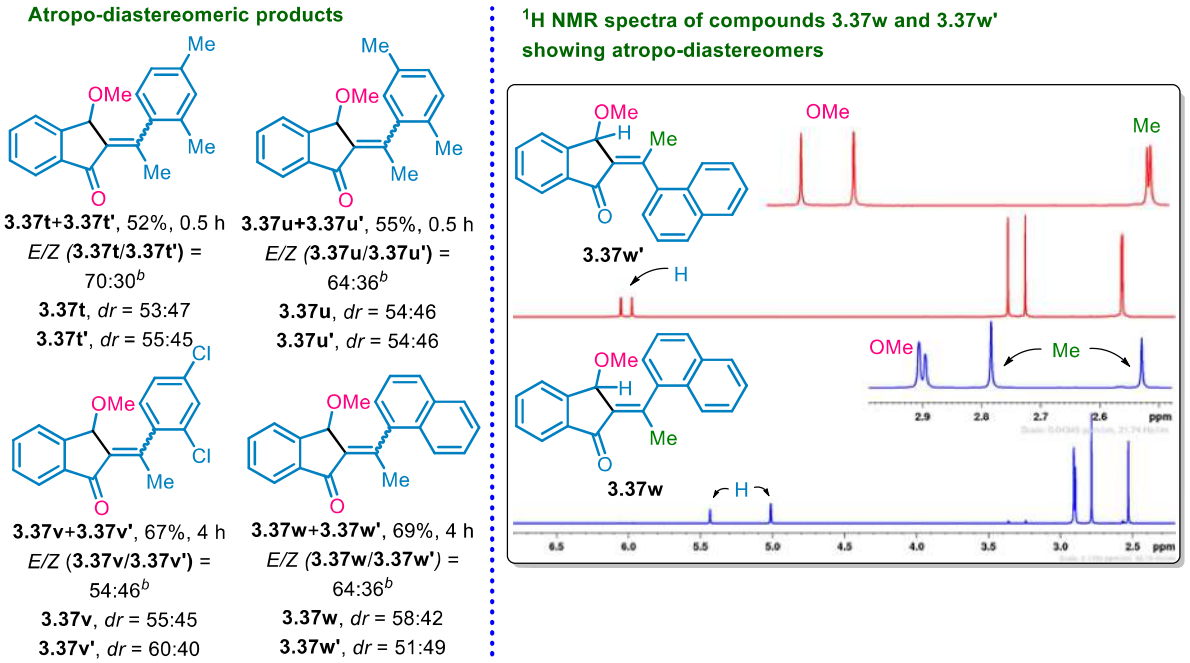
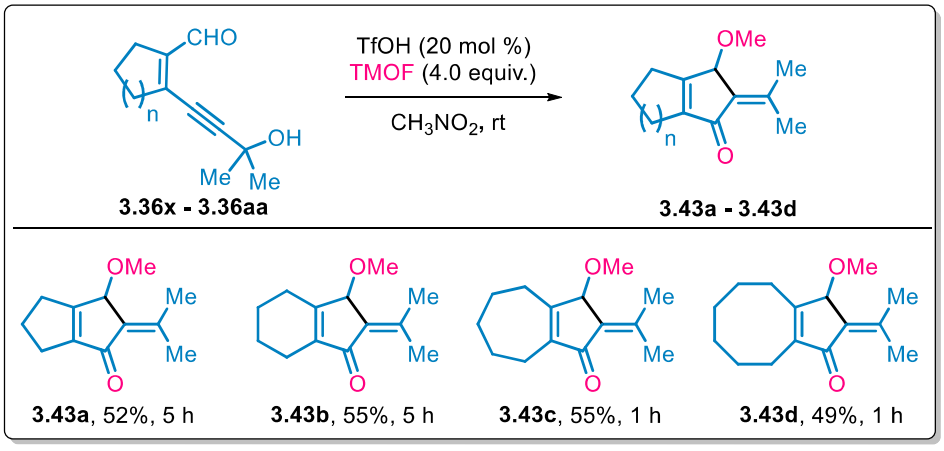


Figure 3.1 Atropo-diastereomeric products (**3.37t**/**3.37t'** – **3.3wt**/**3.37w'**) and representative ^{1}H NMR spectra of compounds **3.37w** and **3.37w'** showing atropo-diastereomers

The scope of this reaction has also been extended to the substrates bearing different cyclic tethers **3.36x** – **3.36aa**, and the corresponding products **3.43a** – **3.43d** were obtained in moderate yields (Table 3.3). It should be mentioned that the same substrates, in the absence of TMOF lead to the formation of 2-acylfuran, as reported by Baire's group.[14]

Table 3.3 Substrate scope of *o*-propargyl alcohol aldehydes bearing various tethers



[a]Reaction conditions: **3.36** (100 mg, 1.0 equiv.), CH_3NO_2 (3 mL/0.2 mmol), TfOH (20 mol %), TMOF (4.0 equiv.).

Unfortunately, substrates **3.36ab** – **3.36ae** failed to give the desired indanone product but gave the corresponding methylated products **3.44ab** – **3.44ae** respectively instead (Figure 3.2).

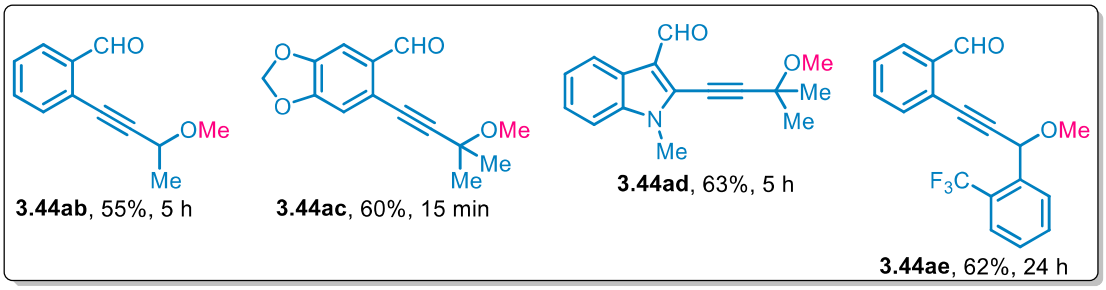
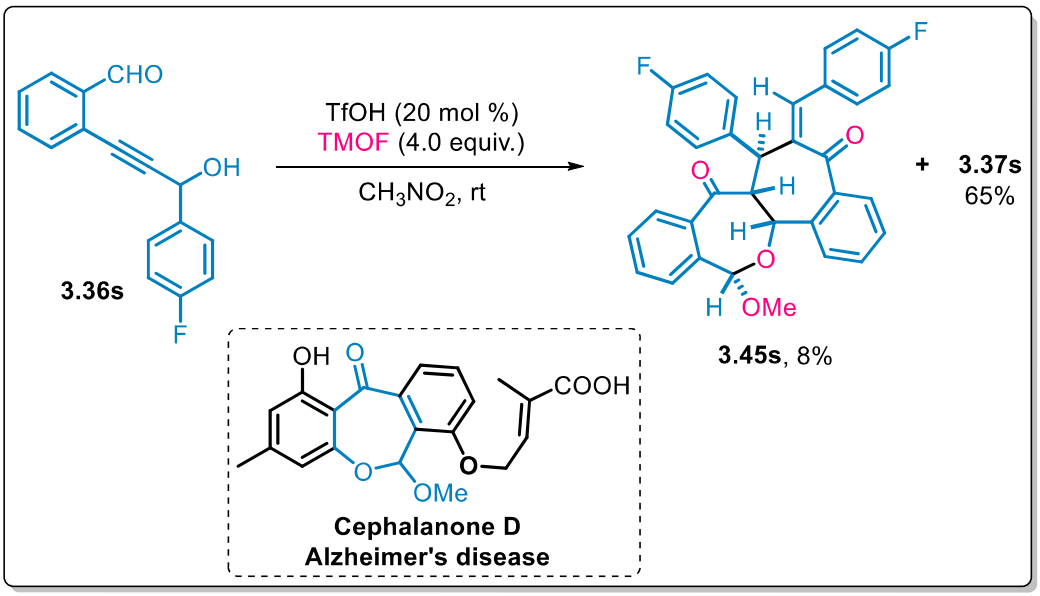


Figure 3.2: Products of unsuccessful cases

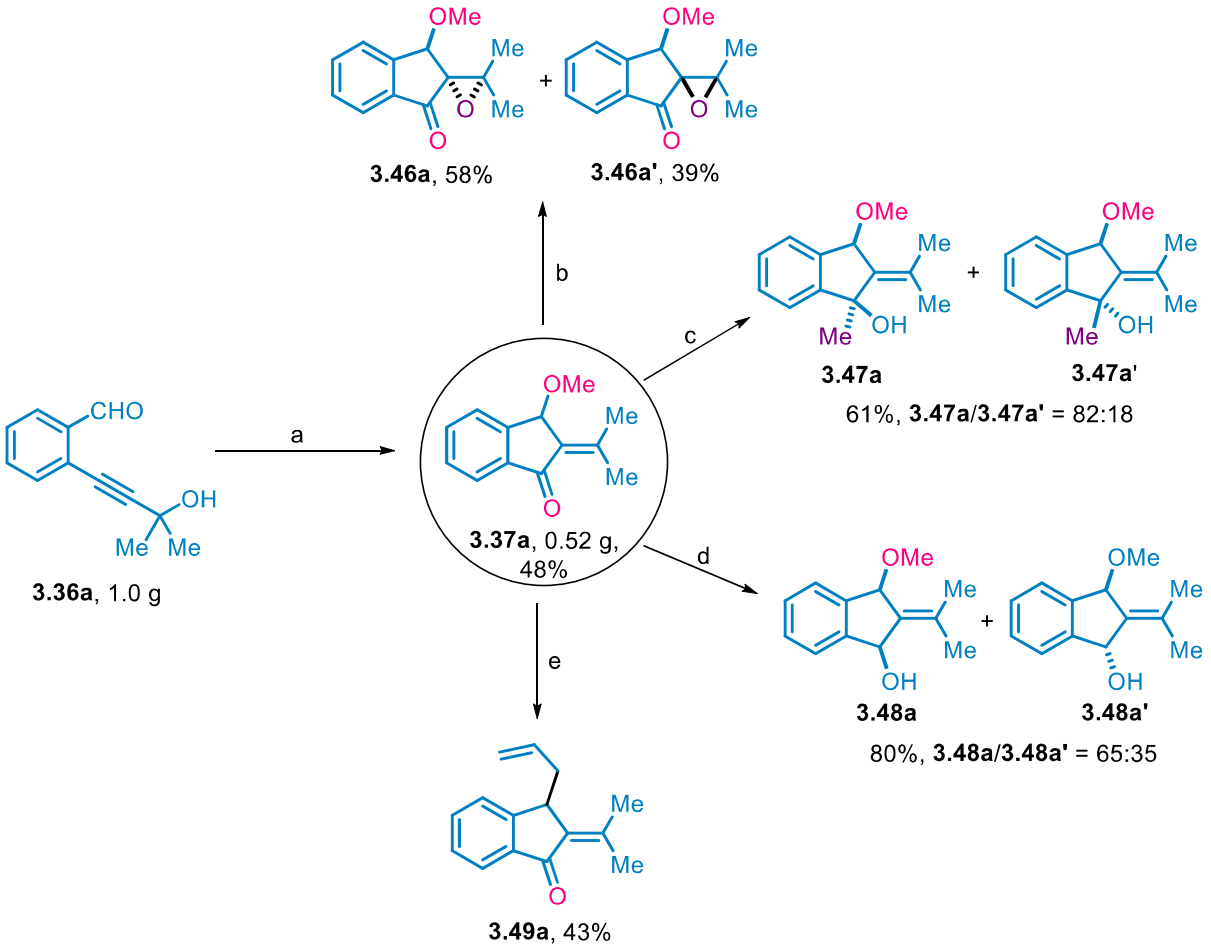
Interestingly, a polycyclic by-product **3.45s** along with the desired product **3.37s** was obtained in 8% and 65% yield respectively. The structure of **3.45s** was identified by X-ray single crystal analysis. This kind of oxepinone core is ubiquitous in natural products and biologically active molecules (Scheme 3.12).[17] Formation of this product is specific to 4-F-Ph containing substrate. To check whether an electron-withdrawing substituent on the aryl ring of the aryl propargyl alcohol moiety would facilitate the formation of such a product, *o*-propargyl alcohol benzaldehyde derivative with a CF_3 group in the aryl ring **3.36ae** was treated under the standard reaction conditions. However, it resulted in neither the indane product nor the polycyclic compound. Corresponding methyl propargyl ether **3.44ae** was isolated in 62% yield. A mechanism as shown in Scheme 3.16 could be proposed for the formation of **3.45s**. However, the exact reason for its formation in this particular example is not clear.



Scheme 3.12: Dimerization of M-S intermediate

3.3.3 Scale-up reaction and subsequent synthetic transformations

The scalability of this methodology was evaluated by subjecting 1.0 g of **3.36a** to the standard reaction conditions. In this case, the indanone **3.37a** was obtained in 48% yield after 10 h (Scheme 3.13a). Late-stage functionalizations of indanone **3.37a** were explored as it possesses a carbonyl group and an unsaturation at the α,β-position. Indanone **3.37a** was treated with *m*-CPBA in CH_2Cl_2 for 12 h and two diastereomeric epoxides **3.46a** and **3.46a'** were obtained in 97% yield with a *dr* of 60:40 (Scheme 3.13b). The structure and stereochemistry of the major diastereomer **3.46a** were further confirmed by single crystal X-ray analysis. The addition of methyl magnesium bromide to **3.37a** in THF at 0 °C exhibited 1,2-addition of methyl group exclusively to yield the indanol derivative as a mixture of diastereomers **3.47a**/**3.47a'** in 61% yield with a *dr* of 82:18 (Scheme 3.13c). Not surprisingly, the methyl group was preferably delivered to the carbonyl from the face opposite to the -OMe group. Indanol **3.48** was obtained in 80% yield with moderate diastereoselectivity under Luche's reduction conditions (Scheme 3.13d). Finally, allylation of **3.37a** was demonstrated by treating it with allyltrimethylsilane in the presence of catalytic $FeCl_3$ in CH_3NO_2 at room temperature for 24 h (Scheme 3.13e). Though there is an enone, allylation occurred preferentially at the benzylic position and no 1,2- or 1,4-allylation was noted.

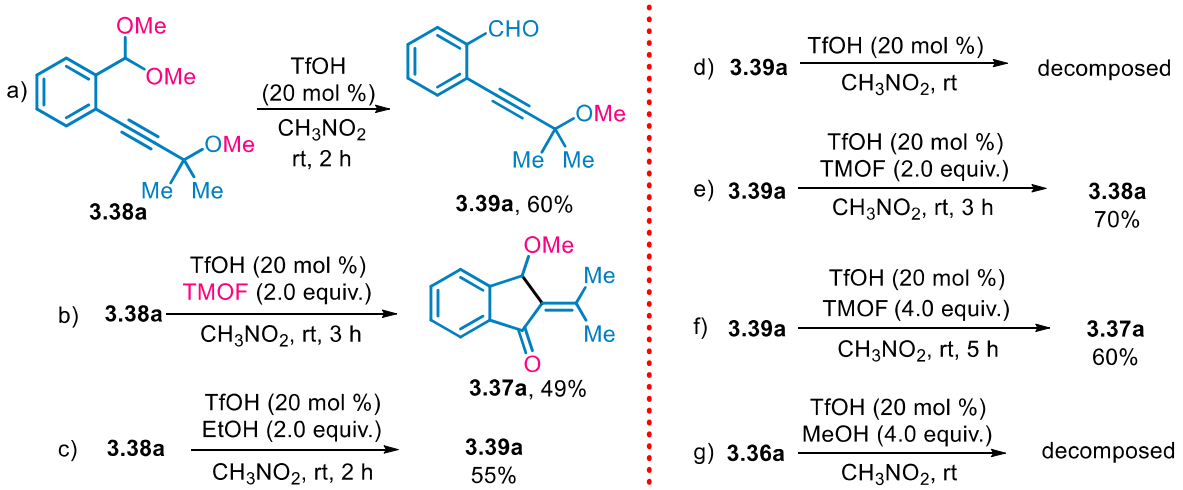


Scheme 3.13: Scale-up reaction and synthetic applications of indanones[a]

[a]Reaction conditions: (a) TfOH (20 mol %), TMOF (4.0 equiv.), CH_3NO_2, rt, 10 h; (b) *m*-CPBA (≥ 77%) (1.5 equiv.), CH_2Cl_2, 0-25 °C, 12 h; (c) MeMgBr (2.0 M in THF) (2.0 equiv.), THF, 0 °C, 2 h; (d) $NaBH_4$ (3.0 equiv.), $CeCl_3 \cdot 7H_2O$ (1.1 equiv.), MeOH, 0 °C, 1 h; (e) Allyltrimethylsilane (1.2 equiv.), $FeCl_3$ (5 mol %), CH_3NO_2, rt, 24 h.

3.3.4 Control Experiments

A series of control experiments were performed in order to ascertain the role of acetal that could form under the reaction condition (Scheme 3.14). The formation of side products **3.38a** and **3.39a** in some of the optimization experiments (Table 3.1) prompted us to check whether they were involved as intermediates during the formation of indanone products. Compound **3.38a**, when treated with 20 mol % of TfOH, did not cyclize to give **3.37a**, and instead resulted in 60% of **3.39a** by deprotection of acetal (Scheme 3.14a). However, in the presence of 2.0 equiv. of TMOF, **3.38a** resulted in the expected product *i.e.*, indanone **3.37a** in 49% isolated yield (Scheme 3.14b). An experiment using ethanol in the place of TMOF to check whether it gets incorporated in the product indanone was not successful as deprotection of acetal was only noted (Scheme 3.14c). Even the methoxy at the propargylic position was intact and no exchange with ethoxy was noted. Then a similar set of reactions were attempted on **3.39a**. While **3.39a**, when treated with TfOH (20 mol %), got decomposed, it gave 70% of **3.38a** when the same reaction was carried along with 2.0 equiv. of TMOF (Schemes 3.14d and 3.14e). The actual product **3.37a** was obtained from **3.39a** when it was reacted with 4.0 equiv. of TMOF and catalytic TfOH (Scheme 3.14f). These experiments suggest that acetal derivative **3.38a** has a strong tendency to undergo deprotection in the presence of strong Brønsted acid like TfOH, and a good amount of TMOF is required to keep its concentration sufficient enough to form the intercepted M-S reaction product. Isolation of considerable amounts **3.38a** in the reaction involving comparatively weaker Brønsted acids such as MsOH and *p*-TSA (Table 3.1, entries 2 and 3, *vide infra*) reveals that it could be one of the intermediates. Methanol, though less effective than TMOF, is also known for its ability to form acetals of aldehydes in the presence of an acid catalyst. A reaction of **3.36a** in the presence of MeOH and catalytic TfOH ended up in the decomposition of the starting material (Scheme 3.14g). This highlights the unique advantage of TMOF for the success of this transformation through *in situ* formed acetal.



Scheme 3.14: Control Experiments

The formation of methyl ether **3.39a** from more labile propargyl alcohol such as diaryl propargyl alcohol under acidic conditions is understandable as the propargyl alcohol is prone to ionization. However, the formation of methyl ether **3.39a** and **3.44ab** from less reactive propargyl alcohols in this study is a distinctive observation. A possible reason for this is discussed in the proposed mechanism.

3.3.5 ^{1}H NMR monitoring of interrupted M-S rearrangement of 3.36a

In addition to the above-mentioned control experiments, the reaction was followed by ^{1}H NMR as well in order to get furthermore insight into the intermediates involved and the mechanism (Figure 3.3). Although, the chlorinated solvents such as CH_2Cl_2 and CCl_4, as realized during the optimization studies, were found to be less effective for this transformation (Table 3.1), a reaction in $CDCl_3$ was followed by NMR just to know the intermediates involved. In this regard, **3.36a** was treated with 1.0 equiv. of TMOF in the presence of 20 mol % of triflic acid in 2.0 mL of $CDCl_3$ at room temperature (Figure 3.3A). 1,2-Dibromoethane (1.0 equiv.) was added to the reaction mixture as an internal standard. ^{1}H NMR spectra of aliquots of the reaction mixture (0.2 mL) withdrawn at regular intervals mixed with 0.2 mL of $CDCl_3$ were recorded. As seen from the spectra, 90% of the starting material **3.36a** whose methyl and aldehyde protons appeared at 1.65 ppm and 10.49 ppm respectively got consumed and the methyl ether derivative **3.39a** (δCH_3 = 1.57 ppm; δOCH_3 = 3.43 ppm; δCHO = 10.51 ppm) and the indanone product **3.37a** (δCH_3 = 2.48 ppm and 2.14 ppm; $\delta CHOCH_3$ = 5.62 ppm; δOCH_3 = 2.98 ppm) were formed in 3:1 ratio in 5 minutes. In addition, the signals corresponding to methanol and methyl formate were also observed ($\delta MeOH$ = 3.49 ppm; δHCO_2Me = 3.75 ppm; δHCO_2Me = 8.06 ppm). Further, the conversion of **3.39a** into **3.37a** in $CDCl_3$ was found to be very slow and the ratio of **3.39a**:**3.37a** became 0.7:1 after 22 h. Another reaction using 2.0 equiv. of TMOF was carried out and followed by ^{1}H NMR (Figure 3.3B). In this case, the product **3.37a**, acetal derivative **3.38a** and methyl ether derivative

3.39a were all observed in ^{1}H NMR after 5 min of the start of the reaction. However, a similar result was observed in this case also *i.e.*, the formation of the product was slow.

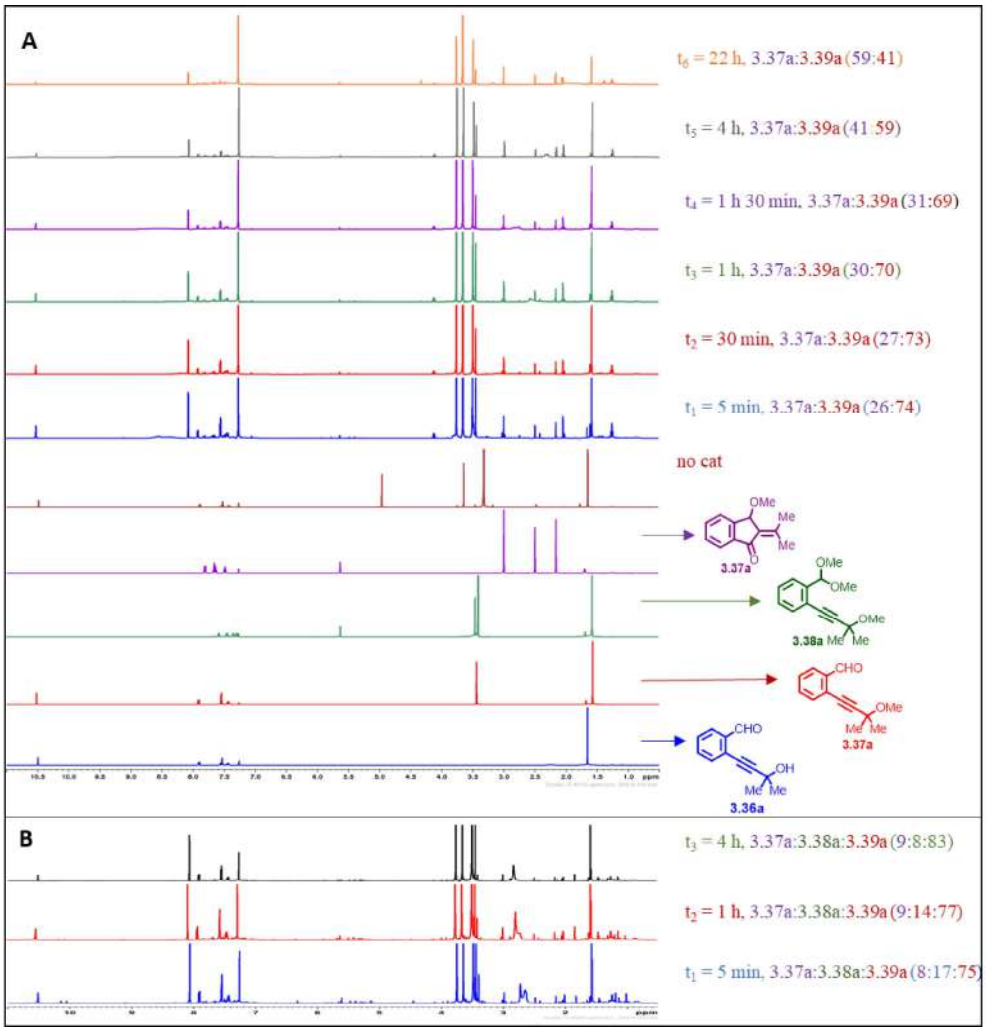
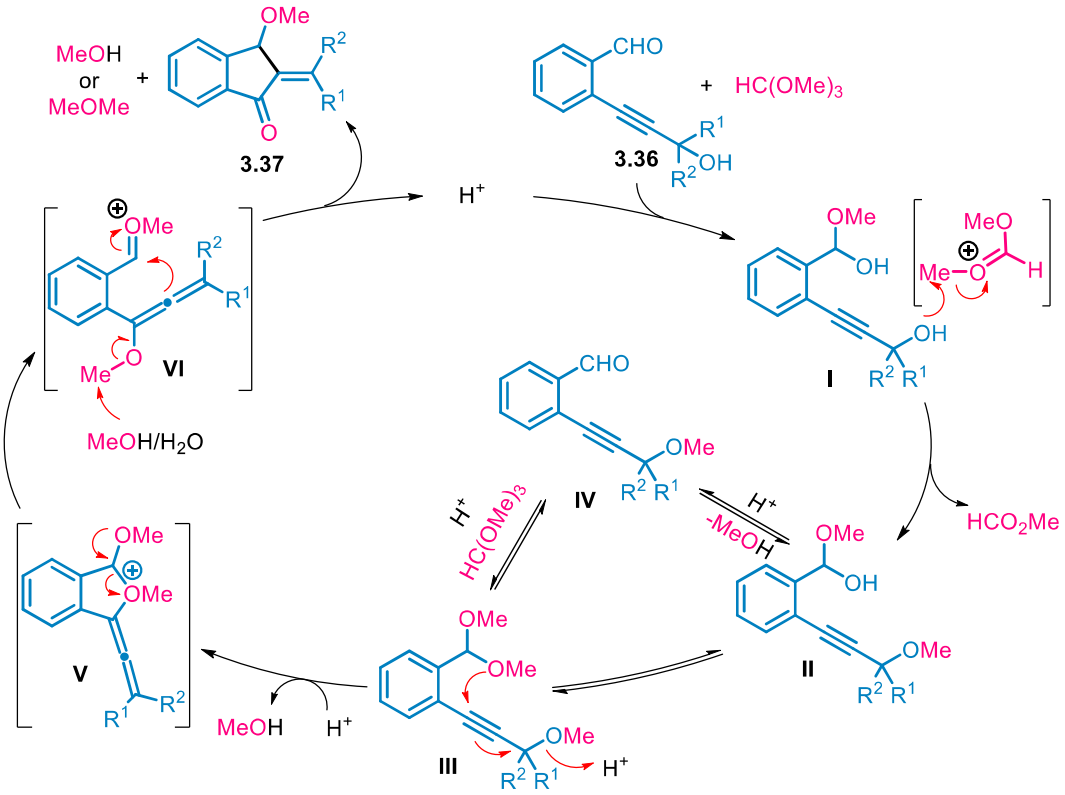


Figure 3.3: ^{1}H NMR monitoring of interrupted M-S rearrangement of **1a** in $CDCl_3$. **A**. Reaction was carried out using 1.0 equiv. of TMOF. **B**. Reaction was carried out using 2.0 equiv. of TMOF

3.3.6 Plausible mechanism

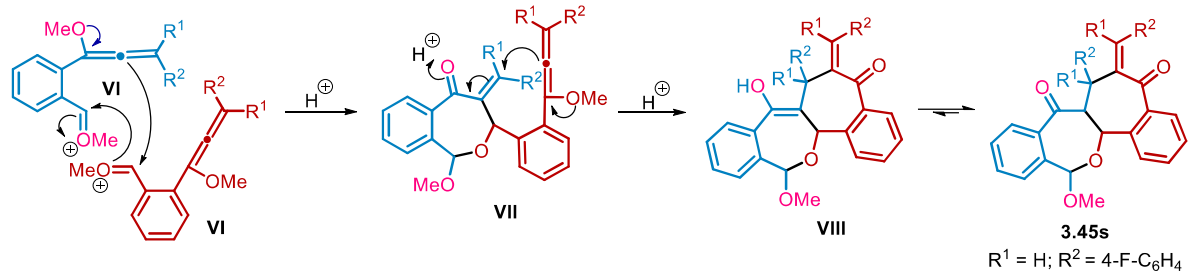
Based on the control experiments, ^{1}H NMR studies of the reaction, and our previous reports,[12] a plausible mechanism, as depicted in Scheme 3.15, could be proposed for the formation of indanone derivatives **3.37** *via* intramolecular electrophile intercepted M-S rearrangement of *o*-propargyl alcohol benzaldehydes **3.36**. *o*-Propargyl alcohol benzaldehyde **3.36a** reacts with TMOF in the presence of TfOH catalyst to generate hemiacetal **I** *in situ*. In the presence of TMOF, the acetalization of aldehyde might block the pathway leading to benzofuran, as reported by the Baire's group.[14] At this point, the propargyl alcohol may get methylated under the reaction

condition to form **II**.[18] With more amounts of TMOF, as seen in the NMR experiments using 2.0 equiv. of TMOF and the control experiment (Scheme 3.14e), the equilibrium may shift to form acetal intermediate **III**. As noted from the control experiment (Scheme 3.14a), the intermediate **II** might undergo fast deacetalization in the presence of an acid catalyst to form the intermediate **IV** which was observed in good amounts in the ^{1}H NMR experiments (Figure 3.3). When there is a sufficient concentration of acetal **III**, it will undergo an intramolecular attack of acetal -OMe on the alkyne with concurrent elimination of -OMe as MeOH to form intermediate **V**. Ring-opening followed by intramolecular trapping of the oxocarbenium ion, as indicated in intermediates **V** and **VI** would lead to the final product **3.37**. Control experiments (Schemes 3.14b and 3.14f) substantiate the necessity of acetal for a favorable cyclization step.



Scheme 3.15: Plausible mechanism for the intercepted M-S rearrangement

In a similar way, a plausible mechanism for the formation of the side product **3.45s** involving dimerization of the corresponding M-S intermediate **VI** of **3.36s** could be proposed as shown in Scheme 3.16. Nucleophilic attack of allenol ether of the first M-S intermediate **VI** on the oxocarbenium ion of the second M-S intermediate could deliver intermediate **VII**. Then, an intramolecular Michael addition on the protonated enone would afford the dimerized product **3.45s**.



Scheme 3.16: Plausible mechanism for the formation of **3.45s**

3.3.7 ORTEP diagrams of 3.37m', 3.37r, 3.37s, 3.45s, and 3.46a

Single crystal X-ray data for the compounds **3.37m'**, **3.37r, 3.37s, 3.45s and 3.46a** were collected using the Bruker D8 Quest CMOS detector system [λ(Mo-Kα) = 0.71073 Å] at 298K, graphite monochromator with a ω scan width of 0.3o, crystal-detector distance 60 mm, collimator 0.5 mm. The SMART software was used for the intensity data acquisition and the SAINTPLUS software was used for the data extraction. In each case, absorption correction was performed with the help of SADABS program. An empirical absorption correction using equivalent reflections was performed with the same program. The structure was solved using SHELXS-97, and full-matrix least-squares refinement against F2 was carried out using SHELXL-97.

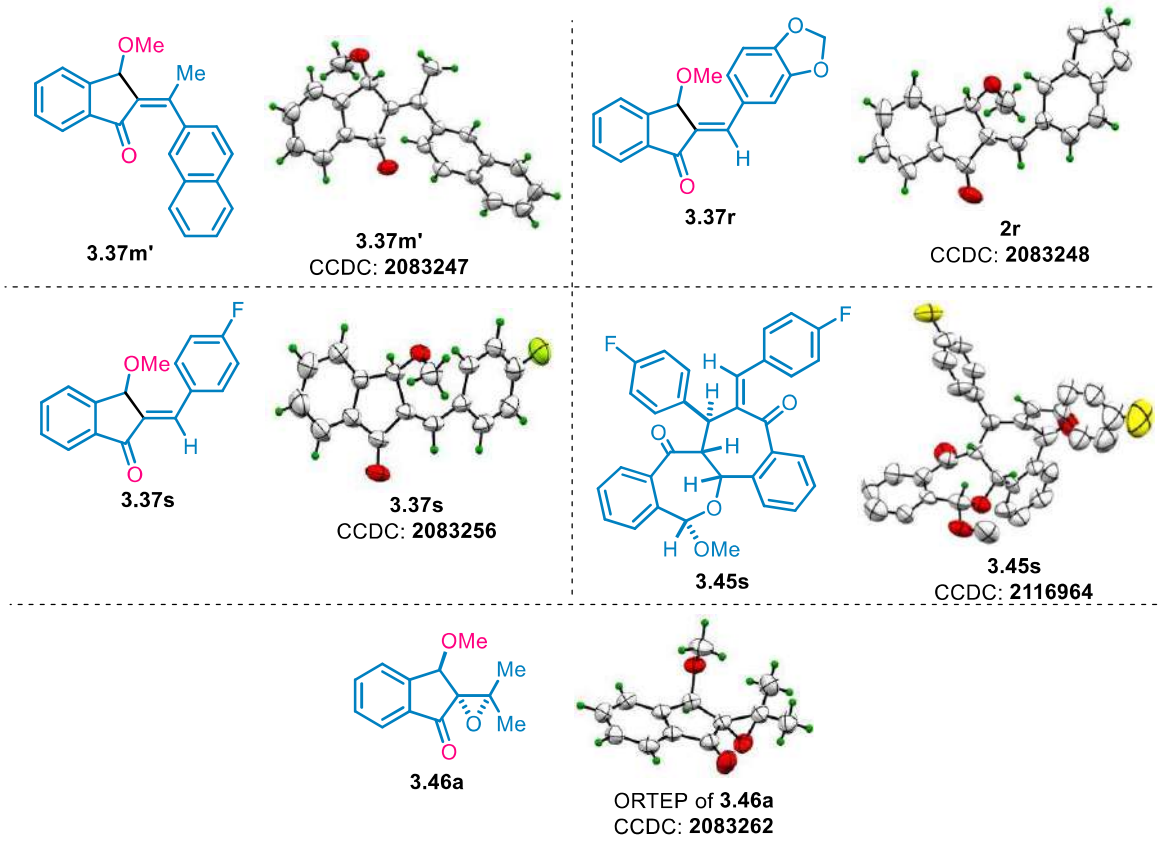


Figure 3.4: ORTEP diagrams of **3.37m'**, **3.37r**, **3.37s**, **3.45s**, and **3.46a**

3.4 Conclusion

We have successfully demonstrated the synthesis of indanone derivatives *via* intramolecular electrophile intercepted M-S rearrangement of *o*-propargyl alcohol benzaldehydes. Actealization conditions make even the less reactive members of title substrates to take part in the reaction. This may be attributed to the better leaving ability of -OMe of the propargyl methyl ether formed under the reaction condition combined with the intramolecular transfer of -OMe of acetal to form the allenoate M-S intermediate along with more electrophilic oxocarbenium ion. The dimerization of the M-S intermediate to form a polycyclic compound as observed in one example. The functionalities in the indanones offer ample opportunities for further functionalization.

3.5 Experimental section

3.5.1 General information

All chemicals obtained from commercial suppliers were used without further purification. Triflic acid and TMOF were obtained from Sigma-Aldrich, and Avra synthesis respectively, and used without further purification. All reactions were performed in closed and oven-dried glasswares under stirring. LR grade CH_3NO_2 was purchased from Finar Company, and used without further purification. Reactions were monitored using silica gel plates 60 F_{254} and the spots were visualized with UV light (254 nm), with Seebach stain followed by heating. Column chromatography was carried out using silica gel (100-200 mesh) packed in glass columns. NMR spectra were recorded at 400 and 500 MHz spectrometers. Chemical shifts (δ) are reported in ppm, calibrated to the residual solvent peak in $CDCl_3$ (H: δ = 7.26 and C: δ = 77.0 ppm) as internal standard, and coupling constants (J) are indicated in Hz. HRMS were recorded using ESI-TOF technique.

3.5.2 Experimental procedures, analytical, and spectral data

Synthesis of *o*-propargyl alcohol benzaldehydes:

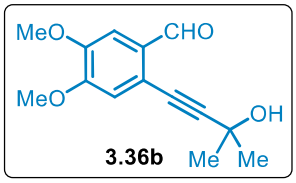
o-Propargyl alcohol benzaldehydes **3.36a**, **3.36i, 3.36c**, **3.36e-3.36h**, **3.36n**, **3.36p, 3.36ab-3.36ac**, **and 3.36x-3.36aa** were synthesized according to the previous reports.[19a-f] The other derivatives were synthesized by following the general procedure A or B.

General Procedure A: An example is given for the synthesis of **2-(3-hydroxy-3-methylbut-1yn-1-yl)-4,5-dimethoxybenzaldehyde 3.36b**:

To a stirred solution of 2-bromo-4,5-dimethoxybenzaldehyde (500 mg, 2.04 mmol, 1.0 equiv.), $PdCl_2(PPh_3)_2$ (36 mg, 0.051 mmol, 2.5 mol %), CuI (19 mg, 0.102 mmol, 5 mol %) in freshly degassed Et_3N (16 mL) was added 2-methylbut-3-yn-2-ol (342 µL, 2.65 mmol, 1.3 equiv.) under N_2 atmosphere. The resulting reaction mixture was stirred in an oil bath at 50 °C until the reaction was completed. Then the reaction mixture was filtered through a celite pad and evaporated

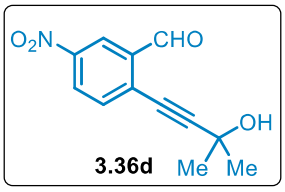
under reduced pressure. The crude product was purified by column chromatography (silica gel, hexane/ethyl acetate mixture as eluent) to obtain the pure product **3.36b** as a yellow solid in 75% (380 mg) yield.

2-(3-hydroxy-3-methylbut-1yn-1-yl)-4,5-dimethoxybenzaldehyde 3.36b:



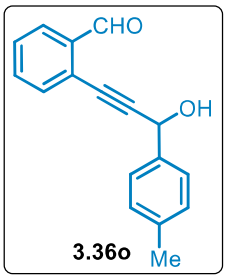
mp 151-153 °C, R_f = 0.4 (in 40% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.34 (s, 1H), 7.37 (s, 1H), 6.93 (s, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 2.27 (s, 1H), 1.65 (s, 6H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 190.4, 153.5, 149.5, 130.0, 121.0, 114.3, 108.0, 96.6, 77.4, 65.5, 56.1, 56.0, 31.2. IR (neat, cm^{-1}): 3364, 1679, 1654, 1586, 1504, 1437, 1352, 1281, 1104, 998, 759. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{14}H_{17}O_4$ 249.1121; found 249.1125.

2-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-nitrobenzaldehyde 3.36d:



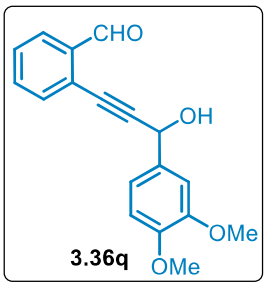
Synthesized according to the general procedure **A** using 2-bromo-5-nitrobenzaldehyde (300 mg, 1.3 mmol, 1.0 equiv.) and 2-methylbut-3-yn-2-ol (164 µL, 1.69 mmol, 1.3 equiv.) as a brown liquid in 75% yield (230 mg), R_f = 0.2 (in 30% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.49 (s, 1H), 8.71 (d, J = 2.5 Hz, 1H), 8.37 (dd, J = 8.5, 2.5 Hz, 1H), 7.71 (d, J = 8.5 Hz, 1H), 2.27 (bs, 1H), 1.67 (s, 6H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 189.2, 147.3, 136.6, 134.4, 131.7, 127.6, 122.5, 106.1, 83.9, 65.7, 31.0. IR (neat, cm^{-1}): 3378, 2981, 1694, 1600, 1581, 1523, 1471, 1340, 1269, 1241, 1163, 1071, 962, 940, 913, 846, 807, 744, 694. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{12}H_{12}NO_4$ 234.0761; found 234.0760.

2-(3-Hydroxy-3-(p-tolyl)prop-1-yn-1-yl)benzaldehyde 3.36o:



Synthesized according to the general procedure **A** using 2-bromobenzaldehyde (500 mg, 2.7 mmol, 1.0 equiv.) and 1-(p-tolyl)prop-2-yn-1-ol[20] (513 mg, 3.51 mmol, 1.3 equiv.) as a brown liquid in 40% (270 mg) yield, R_f = 0.4 (in 40% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.49 (s, 1H), 7.91 (d, J = 7.7 Hz, 1H), 7.54-7.59 (m, 2H), 7.50 (d, J = 7.9 Hz, 2H), 7.45 (t, J = 7.4 Hz, 1H), 7.23 (d, J = 7.6 Hz, 2H), 5.72 (s, 1H), 2.92 (s, 1H), 2.38 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 191.5, 138.4, 137.5, 136.0, 133.6, 133.43, 133.41, 128.8, 127.3, 126.5, 125.9, 96.2, 81.8, 64.8, 21.1. IR (neat, cm^{-1}): 3412, 1693, 1601, 1575, 1511, 1451, 1406, 1267, 1194, 1030, 972, 818, 755. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{17}H_{15}O_2$ 251.1067; found 251.1067.

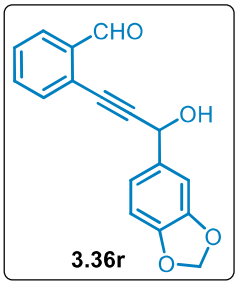
2-(3-(3,4-Dimethoxyphenyl)-3-hydroxyprop-1-yn-1-yl)benzaldehyde 3.36q:



3.36q

Synthesized according to the general procedure **A** using 2-bromobenzaldehyde (500 mg, 2.7 mmol, 1.0 equiv.) and 1-(3,4-dimethoxyphenyl)prop-2-yn-1-ol[21] (674 mg, 3.51 mmol, 1.3 equiv.) as a brown liquid in 46% (240 mg) yield, R_f = 0.4 (in 40% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.48 (s, 1H), 7.89 (d, J = 7.5 Hz, 1H), 7.55 (qd, J = 7.5, 1.0 Hz, 3H), 7.46-7.43 (m, 1H), 7.14 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.0 Hz, 1H), 5.69 (s, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.02 (bs, 1H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 191.3, 149.3, 149.2, 136.1, 133.6, 133.4, 132.9, 128.8, 127.6, 125.7, 119.0, 111.1, 109.9, 96.0, 81.9, 64.8, 55.93, 55.90. IR (neat, cm^{-1}): 3455, 1693, 1592, 1511, 1461, 1418, 1260, 1137, 1077, 1022, 861, 810, 760. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{18}H_{17}O_4$ 297.1121; found 297.1126.

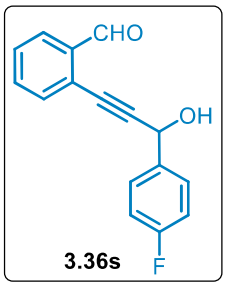
2-(3-(Benzo[d][1,3]dioxol-5-yl-)-3-hydroxyprop-1-yn-1-yl)benzaldehyde 3.36r:



3.36r

Synthesized according to the general procedure **A** using 2-bromobenzaldehyde (600 mg, 3.24 mmol, 1.0 equiv.) and 1-(benzo[d][1,3]dioxol-5-yl)prop-2-yn-1-ol[22] (741 mg, 4.2 mmol, 1.3 equiv.) as a brown liquid in 40% (302 mg) yield, R_f = 0.3 (in 40% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.50 (d, J = 0.5 Hz, 1H), 7.94 (dd, J = 8.0, 1.0 Hz, 1H), 7.62-7.57 (m, 2H), 7.50-7.47 (m, 1H), 7.13 (d, J = 2.0 Hz, 1H), 7.09-7.07 (m, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.01 (s, 2H), 5.68 (s, 1H), 2.48 (bs, 1H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 191.5, 147.9, 147.8, 136.0, 134.1, 133.7, 133.4, 128.9, 127.5, 125.6, 120.3, 108.2, 107.2, 101.2, 95.8, 82.0, 64.8. IR (neat, cm^{-1}): 3377, 1691, 1592, 1484, 1440, 1237, 1094, 1033, 931, 758. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{17}H_{13}O_4$ 281.0808; found 281.0808.

2-(3-(4-Fluorophenyl)-3-hydroxyprop-1-yn-1-yl)benzaldehyde 3.36s:

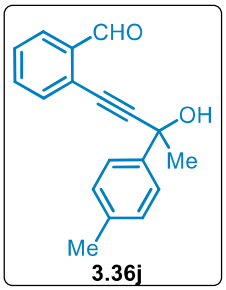


3.36s

Synthesized according to the general procedure **A** using 2-bromobenzaldehyde (500 mg, 2.7 mmol, 1.0 equiv.) and 1-(4-fluorophenyl)prop-2-yn-1-ol[23] (500 mg, 3.51 mmol, 1.3 equiv.) as a brown liquid in 35% (245 mg) yield, R_f = 0.4 (in 40% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.45 (d, J = 0.5 Hz, 1H), 7.91-7.89 (m, 1H), 7.59-7.54 (m, 4H), 7.48-7.44 (m, 1H), 7.11-7.06 (m, 2H), 5.73 (s, 1H), 2.82 (bs, 1H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 191.3, 163.8, 161.8, 136.1, 136.06, 136.04, 133.7, 133.5, 129.0, 128.5, 128.4, 127.7, 125.4, 115.7, 115.6, 95.5, 82.4, 64.4. IR (neat, cm^{-1}): 3379, 1691, 1592, 1505, 1476, 1220, 1156, 1012, 963, 836, 758. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{16}H_{12}FO_2$ 255.0816; found 255.0818.

General Procedure B: An example is given for the synthesis of **2-(3-hydroxy-(p-tolyl)-but-1-yn-1-yl)benzaldehyde 3.36j**:

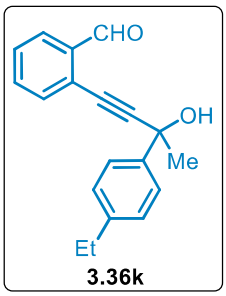
To a stirred solution of 2-bromobenzaldehyde (500 mg, 2.7 mmol, 1.0 equiv.), $PdCl_2(PPh_3)_2$ (25 mg, 0.135 mmol, 2.5 mol %), CuI (37 mg, 0.054 mmol, 5 mol %) in freshly degassed Et_3N (8 mL) was added 2-(p-tolyl)but-3-yn-2-ol (562 mg, 3.51 mmol, 1.3 equiv.) in THF (8 mL) under N_2 atmosphere. The resulting reaction mixture was stirred in an oil bath at 50 °C until the reaction was completed. After completion of the reaction, the reaction mixture was filtered through a pad of celite and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, hexane/ethyl acetate mixture as eluent) to obtain the pure product **3.36j** as a brown liquid in 75% (540 mg) yield, $R_f = 0.3$ (in 30% EtOAc/hexanes).



3.36j

^{1}H NMR (500 MHz, $CDCl_3$): δ 10.51 (s, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.59-7.57 (m, 3H), 7.55 (d, J = 8.0 Hz, 1H), 7.47-7.44 (m, 1H), 7.20 (d, J = 8.0 Hz, 2H), 2.67 (bs, 1H), 2.36 (s, 3H), 1.90 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 191.4, 142.1, 137.6, 136.1, 133.7, 133.4, 129.1, 128.7, 127.4, 126.0, 124.7, 99.8, 80.3, 70.2, 32.9, 21.0. IR (neat, cm^{-1}): 3427, 1694, 1599, 1482, 1284, 1072, 1019, 936, 817. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{18}H_{16}NaO_2$ 287.1043; found 287.1036.

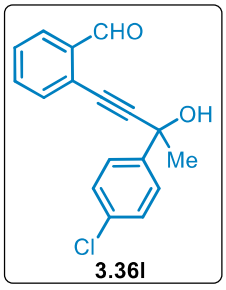
2-(3-(4-Ethylphenyl)-3-hydroxy-but-1-yn-1-yl)benzaldehyde 3.36k:



3.36k

Synthesized according to the general procedure **B** using 2-bromobenzaldehyde (500 mg, 2.7 mmol, 1.0 equiv.) and 2-(4-ethylphenyl)but-3-yn-2-ol (611 mg, 3.51 mmol, 1.3 equiv.) as a brown liquid in 72% (545 mg) yield, $R_f = 0.4$ (in 30% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.51 (d, J = 0.5 Hz, 1H), 7.91-7.89 (m, 1H), 7.62-7.60 (m, 2H), 7.58-7.51 (m, 2H), 7.45-7.42 (m, 1H), 7.22 (d, J = 8.5 Hz, 2H), 2.91 (bs, 1H), 2.65 (q, J = 7.5 Hz, 2H), 1.89 (s, 3H), 1.24 (t, J = 8.0 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 191.5, 144.0, 142.3, 136.0, 133.7, 133.4, 128.7, 127.9, 127.4, 126.0, 124.8, 99.8, 80.2, 70.3, 32.9, 28.4, 15.4. IR (neat, cm^{-1}): 3437, 1694, 1600, 1576, 1453, 1411, 1367, 1322, 1204, 1072, 1030, 956, 834, 755. HRMS (ESI-TOF) m/z: $[M+H]^+$calcd. for $C_{19}H_{19}O_2$ 279.1380; found 279.1386.

2-(3-(4-Chlorophenyl)-3-hydroxy-but-1-yn-1-yl)benzaldehyde 3.36l:

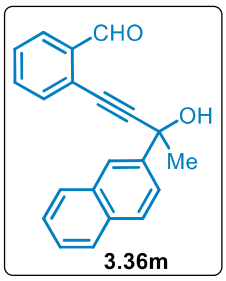


3.36l

Synthesized according to the general procedure **B** using 2-bromobenzaldehyde (500 mg, 2.7 mmol, 1.0 equiv.) and 2-(4-chlorophenyl)but-3-yn-2-ol[24] (634 mg, 3.51 mmol, 1.3 equiv.) as a brown liquid in 66% (520 mg) yield, $R_f = 0.4$ (in 30% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.46 (s, 1H), 7.90 (d, J = 7.6 Hz, 1H), 7.63 (dt, J = 8.8, 2.4 Hz, 2H), 7.57-7.55 (m, 2H), 7.48-7.44 (m, 1H), 7.34 (dt, J = 8.4, 2.4 Hz, 2H), 3.06 (bs, 1H), 1.88 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 191.3, 143.6, 136.0, 133.78, 133.73, 133.4, 129.0, 128.5, 127.8, 126.3, 125.5, 99.0, 80.7, 69.9, 33.1. IR (neat, cm^{-1}): 3447, 1694, 1594, 1487,

1398, 1362, 1264, 1196, 1092, 1029, 1012, 937, 896, 830, 731, 702. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{17}H_{14}ClO_2$ 285.0677; found 285.0682.

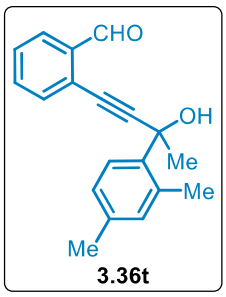
2-(3-Hydroxy-3-(naphthalene-2-yl)-but-1-yn-1-yl)benzaldehyde 3.36m:



3.36m

Synthesized according to the general procedure **B** using 2-bromobenzaldehyde (500 mg, 2.7 mmol, 1.0 equiv.) and 2-(naphthalen-2-yl)but-3-yn-2-ol[20] (688 mg, 3.51 mmol, 1.3 equiv.) as a brown liquid in 76% (620 mg) yield, R_f = 0.4 (in 40% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.55 (d, J = 0.4 Hz, 1H), 8.18-8.17 (m, 1H), 7.94-7.92 (m, 1H), 7.89-7.80 (m, 2H), 7.87-7.84 (m, 1H), 7.79 (dd, J = 8.8, 2.0 Hz, 1H), 7.63-7.60 (m, 1H), 7.57 (td, J = 7.2, 1.6 Hz, 1H), 7.53-7.51 (m, 1H), 7.50-7.48 (m, 2H), 7.47-7.44 (m, 1H), 2.88 (bs, 1H), 1.99 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 191.4, 142.2, 136.0, 133.7, 133.4, 132.9, 132.8, 128.8, 128.4, 128.2, 127.5, 126.3, 126.2, 123.28, 123.25, 99.5, 80.6, 70.5, 32.8. IR (neat, cm^{-1}): 3397, 1692, 1592, 1505, 1475, 1359, 1272, 1244, 1192, 1076, 1047, 940, 897, 748, 701. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{21}H_{17}O_2$ 301.1223; found 301.1226.

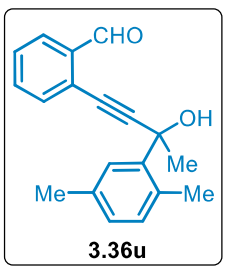
2-(3-(2,4-Dimethylphenyl)-3-hydroxybut-1-yn-1-yl)benzaldehyde 3.36t:



3.36t

Synthesized according to the general procedure **B** using 2-bromobenzaldehyde (555 mg, 3.0 mmol, 1.0 equiv.) and 2-(2,4-dimethylphenyl)but-3-yn-2-ol (624 mg, 3.9 mmol, 1.3 equiv.) as a brown liquid in 63% yield (530 mg), R_f = 0.4 (in 30% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.46 (d, J = 1.0 Hz, 1H), 7.89 (dt, J = 8.5, 7.5 Hz, 1H), 7.59 (d, J = 7.5 Hz, 1H), 7.53-7.52 (m, 2H), 7.45-7.40 (m, 1H), 7.02-7.01 (m, 2H), 2.72 (s, 1H), 2.64 (s, 3H), 2.31 (s, 3H), 1.97 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 191.5, 138.7, 137.6, 136.0, 135.4, 133.7, 133.28, 133.24, 128.7, 127.3, 126.4, 126.1, 124.9, 100.1, 80.9, 69.9, 30.8, 21.0, 20.7. IR (KBr, cm^{-1}): 3423, 1691, 1592, 1475, 1448, 1271, 1192, 1071, 930, 821, 760. HRMS (ESI): $[M+Na]^+$ calcd. for $C_{19}H_{18}NaO_2$ 301.1204; found 301.1196.

2-(3-(2,5-Dimethylphenyl)-3-hydroxybut-1-yn-1-yl)benzaldehyde 3.36u:

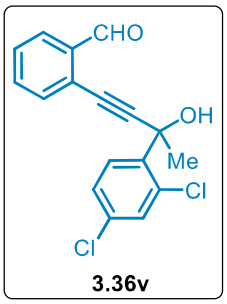


3.36u

Synthesized according to the general procedure **B** using 2-bromobenzaldehyde (555 mg, 3.0 mmol, 1.0 equiv.) and 2-(2,5-dimethylphenyl)but-3-yn-2-ol (624 mg, 3.9 mmol, 1.3 equiv.) as a brown liquid in 61% yield (510 mg), R_f = 0.4 (in 30% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.48 (d, J = 0.5 Hz, 1H), 7.91 (dt, J = 8.0, 1.0 Hz, 1H), 7.56-7.54 (m, 3H), 7.47-7.42 (m, 1H), 7.10 (d, J = 7.5 Hz, 1H), 7.05 (dd, J = 7.5, 1.0 Hz, 1H), 2.63 (s, 3H), 2.35 (s, 3H), 2.34 (s, 3H), 1.97 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 191.5, 141.3, 136.0, 135.3, 133.7, 133.2, 132.3, 132.2, 128.7, 128.5, 127.4, 126.1, 125.5, 99.9, 80.1, 70.0, 30.7, 21.1, 20.7. IR (KBr) (neat, cm^{-1}): 3462, 1693, 1598,

1575, 1452, 1321, 1200, 1101, 1024, 813, 752. HRMS (ESI): $[M+Na]^+$ calcd. for $C_{19}H_{18}NaO_2$ 301.1199; found 301.1198.

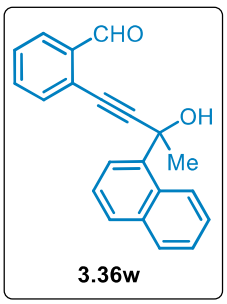
2-(3-(2,4-Dichlorophenyl)-3-hydroxybut-1-yn-1-yl)benzaldehyde 3.36v:



3.36v

Synthesized according to the general procedure **B** using 2-bromobenzaldehyde (555 mg, 3.0 mmol, 1.0 equiv.) and 2-(2,4-dichlorophenyl)but-3-yn-2-ol (624 mg, 3.9 mmol, 1.3 equiv.) as a yellow solid in 54% yield (520 mg), mp 160-162 °C, R_f = 0.4 (in 30% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.44 (d, J = 0.5 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.55-7.53 (m, 2H), 7.45-7.42 (m, 2H), 7.29 (dd, J = 2.0, 8.5 Hz, 1H), 3.44 (s, 1H), 2.02 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 191.6, 139.6, 136.0, 134.2, 133.7, 133.3, 133.2, 130.9, 128.9, 127.5, 127.2, 125.7, 97.9, 80.3, 68.6, 29.5. IR (neat, cm^{-1}): 3348, 1678, 1586, 1464, 1447, 1387, 1365, 1295, 1269, 1242, 1193, 1162, 1132, 1085, 1067, 1033, 954, 934, 895, 752, 720. HRMS (ESI): $[M+Na]^+$ calcd. for $C_{17}H_{12}Cl_2NaO_2$ 341.0107; found 341.0102.

2-(3-Hydroxy-3-(naphthalen-1-yl)but-1-yn-1-yl)benzaldehyde 3.36w:



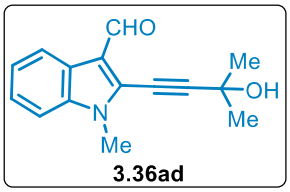
3.36w

Synthesized according to the general procedure **B** using 2-bromobenzaldehyde (555 mg, 3.0 mmol, 1.0 equiv.) and 2-(naphthalen-1-yl)but-3-yn-2-ol (624 mg, 3.9 mmol, 1.3 equiv.) as a brown liquid in 56% yield (505 mg), R_f = 0.4 (in 40% EtOAc/Hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.41 (d, J = 0.8 Hz, 1H), 8.82 (d, J = 8.4 Hz, 1H), 7.93 (dd, J = 7.6, 1.2 Hz, 1H), 7.90-7.87 (m, 2H), 7.83 (d, J = 8.4 Hz, 1H), 7.57-7.55 (m, 1H), 7.53-7.51 (m, 3H), 7.50-7.46 (m, 1H), 7.44-7.39 (m, 1H), 2.99 (s, 1H), 2.19 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 191.4, 139.2, 136.1, 134.6, 133.6, 133.4, 129.9, 129.4, 129.0, 128.8, 127.4, 125.94, 125.91, 125.7, 125.5, 124.9, 122.8, 100.2, 81.1, 70.3, 31.5. IR (neat, cm^{-1}): 3416, 1693, 1593, 1508, 1475, 1449, 1390, 1364, 1272, 1248, 1193, 1116, 1076, 1056, 1025, 994, 962, 935, 896, 777. HRMS (ESI): $[M+Na]^+$ calcd. for $C_{21}H_{16}NaO_2$ 323.1043; found 323.1045.

2-(3-Hydroxy-3-methylbut-1-yn-1-yl)-1-methyl-1H-indole-3-carbaldehyde 3.36ad:[25b]

o-Propargyl alcohol aldehyde **3.36ad** was synthesized by a slightly modified procedure of the reported procedure. To a stirred solution of 2-bromo-1-methyl-1*H*-indole-3-carbaldehyde[25a] (300 mg, 1.26 mmol, 1.0 equiv.), $PdCl_2(PPh_3)_2$ (17 mg, 0.0252, 2.0 mol %), and CuI (2.5 mg, 0.0126, 1.0 mol %) in CH_3CN (10 mL) were added Et_3N (0.2 mL, 1.52 mmol, 1.2 equiv.) and 2-methylbut-3-yn-2-ol (150 µL, 1.52 mmol, 1.2 equiv.) under N_2 atmosphere. The resulting reaction mixture was stirred in an oil bath at 70 °C for 2 h. After completion of the reaction, the mixture was filtered through a celite pad and evaporated under reduced pressure. The crude product was purified by column chromatography (silica gel, hexane/ethyl acetate mixture as eluent) to obtain

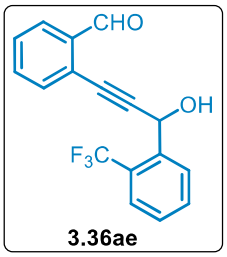
the pure product **3.36ad** as a yellow solid in 89% (270 mg) yield. mp 152-154 °C, R_f = 0.28 (in 40% EtOAc/hexanes).



3.36ad

^{1}H NMR (500 MHz, $CDCl_3$): δ 10.03 (s, 1H), 8.24 (dd, J = 6.5, 1.5 Hz, 1H), 7.31-7.27 (m, 2H), 3.74 (s, 1H), 3.46 (s, 3H), 1.70 (s, 6H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 185.5, 137.0, 132.0, 124.8, 124.0, 123.4, 121.9, 119.3, 109.6, 106.9, 65.4, 31.0, 30.6. IR (neat, cm^{-1}): 3301, 2976, 1623, 1465, 1370, 1169, 1047, 947, 738. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{15}H_{16}NO_2$ 242.1176; found 242.1177.

2-(3-hydroxy-3-(2-(trifluoromethyl)phenyl)prop-1-yn-1-yl)benzaldehyde 3.36ae:



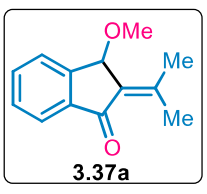
3.36ae

Synthesized according to the general procedure **B** using 2-bromobenzaldehyde (500 mg, 2.7 mmol, 1.0 equiv.) and 1-(2-(trifluoromethyl)phenyl)prop-2-yn-1-ol[26] (702 mg, 3.51 mmol, 1.3 equiv.) as a brown liquid in 55% yield (450 mg), R_f = 0.32 (in 40% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.41 (d, J = 0.5 Hz, 1H), 8.07 (d, J = 7.5 Hz, 1H), 7.90 (dt, J = 7.5, 1.0 Hz, 1H), 7.69 (d, J = 8.5 Hz, 1H), 7.66 (d, J = 7.5 Hz, 1H), 7.58-7.53 (m, 2H), 7.49-7.44 (m, 2H), 6.14 (d, J = 4.5 Hz, 1H), 2.71 (d, J = 4.5 Hz, 1H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 191.5, 138.8, 136.0, 133.7, 133.4, 132.6, 129.0, 128.8, 128.6, 127.5, 127.1, 126.8, 125.8 (q, J = 28.2 Hz), 125.4, 95.2, 82.1, 60.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ -58.1. IR (KBr, cm^{-1}): 3387, 1691, 1592, 1452, 1309, 1157, 1109, 1059, 1031, 962, 819, 760. HRMS (ESI): $[M+Na]^+$ calcd. for $C_{17}H_{11}F_3NaO_2$ 327.0603; found 327.0605.

General Procedure for the Synthesis of Indanones:

An example is given for the synthesis of **3-Methoxy-2-(propan-2-ylidene)-2,3-dihydro-1H-inden-1-one 3.37a**:

To a stirred solution of 2-(3-hydroxy-3-methylbut-1-yn-1-yl)benzaldehyde **3.36a** (100 mg, 0.49 mmol, 1.0 equiv.) and TMOF (215 µL, 1.96 mmol, 4.0 equiv.) in CH_3NO_2 (6 mL) was added triflic acid (8.6 µL, 0.098 mmol, 20 mol %) at room temperature and stirred for 7 h at the same temperature. Then, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (10 mL) and extracted with ethyl acetate (3 × 20 mL). Combined organic layers were washed with saturated aqueous brine solution, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate mixture as eluent) to afford the indanones **3.37a** as a yellow solid in 52% (56 mg) yield.

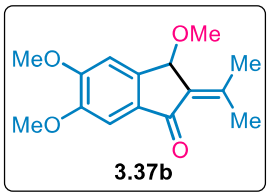


3.37a

mp 95-97 °C, R_f = 0.4 (in 10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 7.6 Hz, 1H), 7.67-7.61 (m, 2H), 7.50-7.46 (m, 1H), 5.63 (s, 1H), 2.99 (s, 3H), 2.49 (s, 3H), 2.15 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 192.4, 156.0, 146.9, 140.2, 134.2, 130.1, 129.4, 125.9, 123.3, 76.1, 50.8, 23.8,

21.0. IR (neat, cm^{-1}): 1692, 1634, 1273, 1116, 1070, 975, 783, 682. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{13}H_{14}NaO_2$ 225.0886; found 225.0888.

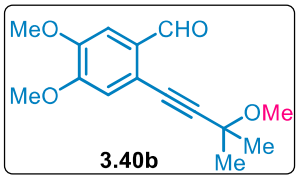
3,5,6-Trimethoxy-2-(propan-2-ylidene)-2,3-dihydro-1*H*-inden-1-one 3.37b:



3.37b

Synthesized according to the general procedure described above as a yellow solid in 30% (32 mg) yield, mp 145-147 °C, R_f = 0.3 (in 40% EtOAc/hexanes). ^1H NMR (500 MHz, $CDCl_3$): δ 7.24 (s, 1H), 7.06 (s, 1H), 5.59 (s, 1H), 4.00 (s, 3H), 3.95 (s, 3H), 2.92 (s, 3H), 2.47 (s, 3H), 2.12 (s, 3H). ^{13}C $\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 191.5, 155.1, 153.3, 150.9, 141.6, 133.9, 130.1, 106.6, 104.6, 75.8, 56.3, 56.1, 49.9, 23.5, 20.7. IR (neat, cm^{-1}): 1678, 1632, 1589, 1498, 1276, 1061, 873, 751. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{15}H_{18}NaO_4$ 285.1097; found 285.1090.

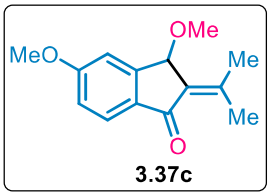
4,5-Dimethoxy-2-(3-methoxy-3-methylbut-1-yn-1-yl)benzaldehyde 3.40b:



3.40b

Obtained as a yellow solid in 25% (27 mg) yield during the synthesis of **3.37b**. mp 96-98 °C, R_f = 0.5 (in 40% EtOAc/hexanes). ^1H NMR (500 MHz, $CDCl_3$): δ 10.37 (s, 1H), 7.39 (s, 1H), 6.95 (s, 1H), 3.97 (s, 3H), 3.94 (s, 3H), 3.44 (s, 3H), 1.58 (s, 6H). ^{13}C $\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 190.3, 153.8, 149.6, 130.2, 121.0, 114.4, 108.0, 96.9, 79.6, 71.0, 56.2, 56.0, 51.9, 28.2. IR (neat, cm^{-1}): 2982, 1680, 1587, 1503, 1350, 1219, 1103, 1072, 1004, 868, 752. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{15}H_{18}NaO_4$ 285.1097; found 285.1095.

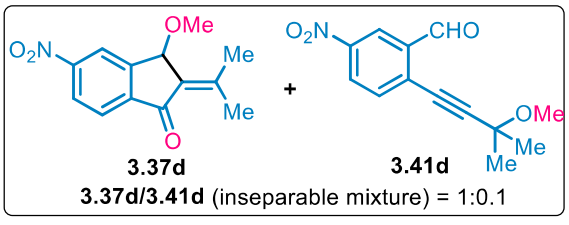
3,5-Dimethoxy-2-(propan-2-ylidene)-2,3-dihydro-1H-inden-1-one 3.37c:



3.37c

Synthesized according to the general procedure described above as a yellow liquid in 55% (59 mg) yield, R_f = 0.45 (in 30% EtOAc/hexanes). ^1H NMR (500 MHz, $CDCl_3$): δ 7.24 (s, 1H), 7.06 (s, 1H), 5.59 (s, 1H), 4.00 (s, 3H), 3.95 (s, 3H), 2.92 (s, 3H), 2.47 (s, 3H), 2.12 (s, 3H). ^{13}C $\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 191.2, 164.9, 125.3, 149.7, 133.8, 130.1, 125.1, 117.1, 108.8, 75.9, 55.6, 50.4, 23.6, 20.7. IR (neat, cm^{-1}): 1687, 1633, 1595, 1487, 1337, 1246, 1089, 1066, 1024, 836, 792. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{14}H_{17}O_3$ 233.1172; found 233.1172.

3-Methoxy-5-nitro-2-(propan-2-ylidene)-2,3-dihydro-1H-inden-1-one 3.37d & 2-(3-hydroxy-3-methylbut-1-yn-1-yl)-5-nitrobenzaldehyde 3.41d:



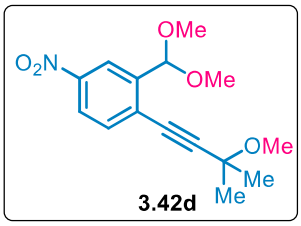
3.37d **3.41d**

3.37d/3.41d (inseparable mixture) = 1:0.1

Synthesized according to the general procedure described above as a yellow solid in 25% (27 mg), an inseparable mixture (1:0.1), R_f = 0.42 (in 5% EtOAc/$CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 10.51 (s, 1H, **3.41d**), 8.72 (d, J = 2.0 Hz, 1H, **3.41d**), 8.51 (d, J = 1.5 Hz, 1H, **3.37d**), 8.38 (dd,

J = 8.5, 2.0 Hz, 1H, **3.41d**), 8.33 (dd, J = 8.0, 1.5 Hz, 1H, **3.37d**), 7.94 (d, J = 8.5 Hz, 1H, **3.37d**), 7.72 (d, J = 8.5 Hz, 1H, **3.41d**), 5.67 (s, 1H, **3.37d**), 3.44 (s, 3H, **3.41d**), 3.05 (s, 3H, **3.37d**), 2.50 (s, 3H, **3.37d**), 2.19 (s, 3H, **3.37d**), 1.59 (s, 6H, **3.41d**). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 190.0, 189.0, 159.6, 151.5, 148.0, 147.4, 144.2, 136.7, 134.6, 131.7, 129.9, 127.5, 124.9, 124.5, 122.5, 121.5, 104.0, 78.5, 75.8, 71.1, 52.1, 51.6, 27.9, 24.1, 21.4. IR (neat, cm^{-1}): 2927, 1695, 1601, 1522, 1459, 1342, 1272, 1244, 1172, 1148, 1104, 1071, 974, 935, 892, 863, 838, 792, 736, 681, 641. HRMS (ESI-TOF) m/z: [M+Na]$^+$ calcd. for $C_{13}H_{13}NNaO_4$ 270.0737; found 270.0739.

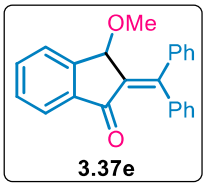
2-(Dimethoxymethyl)-1-(3-methoxy-3-methylbut-1-yn-1-yl)-4-nitrobenzene 3.42d:



3.42d

Obtained as a yellow liquid in 26% (33 mg) yield during the synthesis of **3.37d**. R_f = 0.5 (in 5% EtOAc/$CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.45 (d, J = 2.5 Hz, 1H), 8.13 (dd, J = 8.5, 2.5 Hz, 1H), 7.58 (d, J = 8.5 Hz, 1H), 5.62 (s, 1H), 3.44 (s, 3H), 3.39 (s, 6H), 1.58 (s, 6H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 147.0, 141.5, 133.3, 128.2, 123.1, 121.8, 101.2, 101.1, 80.2, 71.0, 54.0, 51.9, 28.0. IR (neat, cm^{-1}): 1521, 1464, 1342, 1274, 1171, 1067, 982, 867, 835, 792, 735. HRMS (ESI-TOF) m/z: [M+Na]$^+$ calcd. for $C_{15}H_{19}NNaO_5$ 316.1155; found 316.1151.

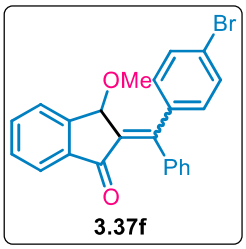
2-(Diphenylmethylene)-3-methoxy-2,3-dihydro-1H-inden-1-one 3.37e:



3.37e

Synthesized according to the general procedure described above as a yellow solid in 80% (84 mg) yield, mp 210-212 °C, R_f = 0.6 (in 20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 7.6 Hz, 1H), 7.70-7.64 (m, 2H), 7.54-7.50 (m, 1H), 7.43-7.38 (m, 8H), 7.32-7.29 (m, 2H), 5.82 (s, 1H), 3.01 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 191.0, 155.2, 147.9, 141.3, 139.7, 139.6, 134.5, 129.5, 129.4, 128.9, 128.7, 128.6, 128.1, 127.8, 125.7, 123.7, 76.7, 52.4. IR (neat, cm^{-1}): 1687, 1602, 1255, 1130, 1075, 987, 769, 696. HRMS (ESI-TOF) m/z: [M+Na]$^+$ calcd. for $C_{23}H_{18}NaO_2$ 349.1199; found 349.1198.

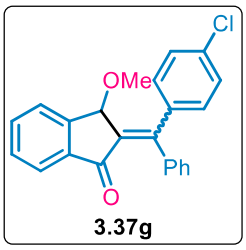
2-((4-Bromophenyl)(phenyl)methylene)-3-methoxy-2,3-dihydro-1*H*-inden-1-one 3.37f:



3.37f

Synthesized according to the general procedure described above as a yellow solid in 85% (90 mg) yield, *E*:*Z* ratio: 55:45, mp 183-185 °C, R_f = 0.4 (in 10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 7.4 Hz, 2H), 7.71-7.63 (m, 4H), 7.57-7.50 (m, 6H), 7.45-7.36 (m, 9H), 7.30-7.29 (m, 1H), 7.27-7.24 (m, 3H), 7.18-7.15 (m, 2H), 5.78 (s, 1H, major), 5.77 (s, 1 H, minor), 3.02 (s, 3H, major), 2.99 (s, 3H, minor). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 191.0, 190.9, 153.7, 147.9, 147.6, 140.8, 140.1, 139.7, 139.5, 139.1, 138.4, 134.8, 134.7, 133.9, 133.8, 131.4, 131.2, 131.0, 130.7, 129.7, 129.4, 129.0, 128.9, 128.8, 128.3, 127.9, 125.8, 123.83, 123.82, 123.80, 123.2, 123.0, 76.5, 52.7, 52.2. IR (neat, cm^{-1}): 1683, 1578, 1483, 1276, 1129, 1070, 1009, 986, 831, 747. HRMS (ESI-TOF) m/z: [M+H]$^+$ calcd for $C_{23}H_{18}BrO_2$ 405.0485; found 405.0484.

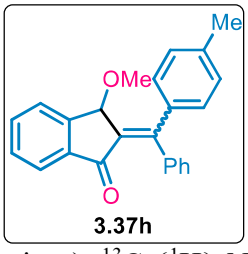
2-((4-Chlorophenyl)(phenyl)methylene)-3-methoxy-2,3-dihydro-1*H*-inden-1-one 3.37g:



3.37g

Synthesized according to the general procedure described above as a yellow solid in 83% (87 mg) yield, *E*:*Z* ratio: 55:45, mp 182-184 °C, R_f = 0.43 (in 10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (d, J = 7.6 Hz, 2H), 7.68-7.61 (m, 4H), 7.50 (t, J = 7.4 Hz, 2H), 7.41-7.31 (m, 15H), 7.25-7.20 (m, 4H), 5.77 (s, 1H, major), 5.76 (s, 1H, minor), 2.99 (s, 3H, minor), 2.97 (s, 3H, major). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 190.9, 190.8, 153.6, 147.96, 147.64, 140.9, 139.6, 139.5, 139.2, 137.9, 134.8, 134.75, 134.71, 133.9, 133.8, 130.9, 130.4, 129.7, 129.4, 128.99, 128.94, 128.7, 128.4, 128.2, 128.1, 127.9, 125.8, 123.7, 76.7, 76.5, 52.7, 52.2. IR (neat, cm^{-1}): 1682, 1599, 1463, 1442, 1397, 1285, 1255, 1195, 1153, 1074, 986, 928, 858, 834, 747. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{23}H_{18}ClO_2$ 361.0990; found 361.0995.

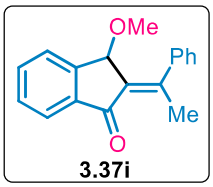
3-Methoxy-2-(phenyl(p-tolyl)methylene)-2,3-dihydro-1*H*-inden-1-one 3.37h:



3.37h

Synthesized according to the general procedure described above as a yellow solid in 89% (91 mg) yield, *E*:*Z* ratio: 52:48, mp 162-164 °C, R_f = 0.5 (in 10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (dd, J = 7.2, 5.1 Hz, 2H), 7.63-7.69 (m, 5H), 7.51 (t, J = 7.4 Hz, 2H), 7.37-7.43 (m, 9H), 7.27-7.31 (m, 5H), 7.23 (d, J = 8.1 Hz, 2H), 5.88 (s, 1H, major), 5.80 (s, 1H, minor), 3.00 (s, 3H, major), 2.98 (s, 3H, minor), 2.41 (s, 6H, major and minor). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 191.0, 190.9, 155.5, 155.3, 147.9, 147.8, 141.6, 139.9, 139.8, 138.9, 138.7, 138.4, 136.6, 134.4, 133.2, 133.0, 129.6, 129.5, 129.4, 129.1, 129.0, 128.8, 128.6, 128.5, 128.1, 127.7, 125.76, 125.73, 123.67, 123.63, 76.8, 76.6, 52.5, 52.0. IR (neat, cm^{-1}): 1679, 1598, 1488, 1335, 1285, 1256, 1196, 1075, 1021, 985, 929, 819, 750. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{24}H_{21}O_2$ 341.1536; found 341.1536.

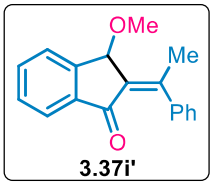
(*E*)-3-Methoxy-2-(1-phenylethylidene)-2,3-dihydro-1*H*-inden-1-one 3.37i:



3.37i

Synthesized according to the general procedure described above as a yellow solid in 35% (36 mg) yield, mp 94-96 °C, R_f = 0.4 (in 10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (d, J = 7.6 Hz, 1H), 7.63 (td, J = 7.4, 1.0 Hz, 1H), 7.57 (d, J = 7.4 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.44-7.47 (m, 2H), 7.42-7.38 (m, 3H), 5.48 (s, 1H), 2.88 (s, 3H), 2.79 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 193.4, 155.3, 147.7, 142.8, 139.7, 134.4, 132.2, 129.4, 128.5, 128.0, 126.5, 125.8, 123.4, 76.2, 52.1, 21.2. IR (neat, cm^{-1}): 1680, 1603, 1488, 1367, 1258, 1083, 938, 749. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{18}H_{17}O_2$ 265.1223; found 265.1230.

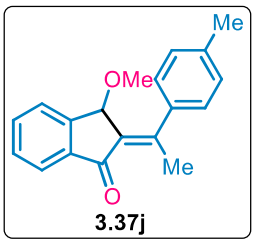
(*Z*)-3-Methoxy-2-(1-phenylethylidene)-2,3-dihydro-1*H*-inden-1-one 3.37i':



3.37i'

Synthesized according to the general procedure described above as a yellow liquid in 25% (25.5 mg) yield, R_f = 0.3 (in 10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, J = 8.2 Hz, 2H), 7.63 (td, J = 7.3, 1.1 Hz, 1H), 7.57 (t, J = 7.9 Hz, 1H), 7.45-7.38 (m, 3H), 7.33-7.31 (m, 2H), 5.82 (s, 1H), 3.16 (s, 3H), 2.46 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 189.9, 154.9, 146.9, 141.0, 140.0, 134.5, 131.1, 129.6, 128.0, 127.9, 127.1, 125.9, 123.6, 76.2, 51.1, 24.1. IR (neat, cm^{-1}): 1695, 1601, 1489, 1369, 1242, 1152, 1074, 927, 748. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{18}H_{16}NaO_2$ 287.1043; found 287.1037.

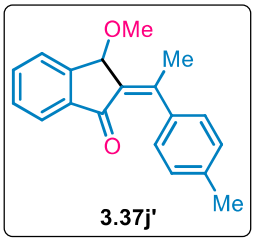
(*E*)-3-Methoxy-2-(1-(p-tolyl)ethylidene)-2,3-dihydro-1*H*-inden-1-one 3.37j:



3.37j

Synthesized according to the general procedure described above as a yellow liquid in 37% (39.2 mg) yield, R_f = 0.6 (in 20% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, J = 7.6 Hz, 1H), 7.61 (td, J = 7.4, 1.1 Hz, 1H), 7.54 (d, J = 7.4 Hz, 1H), 7.48 (t, J = 7.5 Hz, 1H), 7.32-7.30 (m, 2H), 7.24 (d, J = 7.9 Hz, 2H), 5.51 (s, 1H), 2.85 (s, 3H), 2.75 (d, J = 0.85 Hz, 3H), 2.39 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 193.4, 155.5, 147.6, 139.9, 139.8, 138.0, 134.3, 131.9, 129.4, 128.9, 126.5, 125.8, 123.4, 76.2, 51.7, 21.3, 21.2. IR (neat, cm^{-1}): 1688, 1603, 1509, 1322, 1257, 1075, 938, 816, 749. HRMS (ESI-TOF) m/z: calcd for $[M+Na]^+$ $C_{19}H_{18}NaO_2$ 301.1199; found 301.1194.

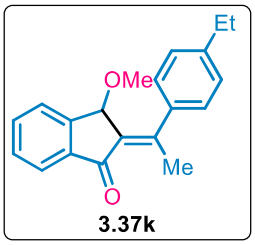
(*Z*)-3-Methoxy-2-(1-(p-tolyl)ethylidene)-2,3-dihydro-1*H*-inden-1-one 3.37j':



3.37j'

Synthesized according to the general procedure described above as a yellow liquid in 23% (24.5 mg) yield, R_f = 0.5 (in 20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73-7.70 (m, 2H), 7.67-7.63 (m, 1H), 7.48-7.45 (m, 1H), 7.21 (s, 4H), 5.79 (s, 1H), 3.12 (s, 3H), 2.42 (s, 3H), 2.39 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 189.8, 155.1, 146.9, 140.1, 138.0, 137.9, 134.4, 130.9, 129.5, 128.6, 127.2, 125.9, 123.5, 76.4, 51.1, 24.0, 21.3. IR (neat, cm^{-1}): 1695, 1604, 1509, 1462, 1241, 1185, 1073, 927, 814, 749. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{19}H_{18}NaO_2$ 301.1199; found 301.1197.

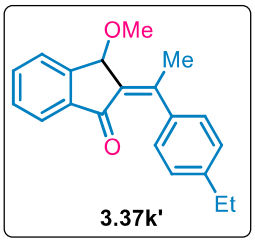
(*E*)-2-(1-(4-Ethylphenyl)ethylidene)-3-methoxy-2,3-dihydro-1*H*-inden-1-one 3.37k:



3.37k

Synthesized according to the general procedure described above as a yellow liquid in 39% (40.9 mg) yield, R_f = 0.43 (in 10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (d, J = 7.6 Hz, 1H), 7.63 (td, J = 7.5, 1.1 Hz, 1H), 7.57 (d, J = 7.2 Hz, 1H), 7.49-7.52 (m, 1H), 7.37-7.35 (m, 2H), 7.28 (d, J = 8.1 Hz, 2H), 5.51 (s, 1H), 2.88 (s, 3H), 2.78 (s, 3H), 2.72 (q, J = 7.6 Hz, 2H), 1.30 (t, J = 7.6 Hz, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 189.9, 155.2, 146.9, 144.3, 140.1, 138.1, 134.4, 130.9, 129.6, 127.3, 125.9, 123.6, 76.4, 51.1, 28.6, 24.0, 15.2. IR (neat, cm^{-1}): 1695, 1604, 1508, 1461, 1291, 1242, 1187, 1151, 1074, 928, 906, 830, 749. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{20}H_{21}O_2$ 293.1536; found 293.1540.

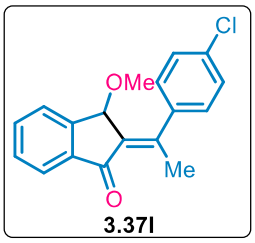
(*Z*)-2-(1-(4-Ethylphenyl)ethylidene)-3-methoxy-2,3-dihydro-1*H*-inden-1-one 3.37k':



3.37k'

Synthesized according to the general procedure described above as a yellow liquid in 18% (19.5 mg) yield, R_f = 0.43 (in 10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (t, J = 7.4 Hz, 2H), 7.66 (td, J = 7.2, 1.0 Hz, 1H), 7.49-7.46 (m, 1H), 7.24 (s, 4H), 5.80 (s, 1H), 3.12 (s, 3H), 2.70 (q, J = 7.6 Hz, 2H), 2.43 (d, J = 0.3 Hz, 3H), 1.28 (t, J = 7.6 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 189.9, 155.2, 146.9, 144.3, 140.1, 138.1, 134.4, 130.9, 129.6, 127.37, 127.36, 125.9, 123.6, 76.4, 51.1, 28.6, 24.0, 15.2 . IR (neat, cm^{-1}): 1695, 1604, 1508, 1461, 1291, 1242, 1187, 1074, 928, 830, 749. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{20}H_{21}O_2$ 293.1536; found 293.1540.

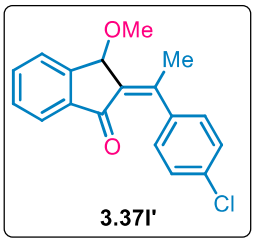
(*E*)-2-(1-(4-Chlorophenyl)ethylidene)-3-methoxy-2,3-dihydro-1*H*-inden-1-one 3.37l:



3.37l

Synthesized according to the general procedure described above as a yellow liquid in 46% (48.2 mg) yield, R_f = 0.5 (in 10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86 (d, J = 7.7 Hz, 1H), 7.60 (td, J = 7.6, 0.7 Hz, 1H), 7.57 (d, J = 7.5 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.43-7.31 (m, 2H), 7.37-7.34 (m, 2H), 5.43 (s, 1H), 2.89 (s, 3H), 2.75 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 193.1, 153.6, 147.4, 141.1, 139.7, 134.5, 134.0, 132.7, 129.5, 128.5, 128.0, 125.9, 123.5, 76.2, 52.1, 21.0. IR (neat, cm^{-1}): 1685, 1586, 1484, 1326, 1259, 1153, 1070, 1010, 936, 825, 700, 616. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{18}H_{16}ClO_2$ 299.0833; found 299.0830.

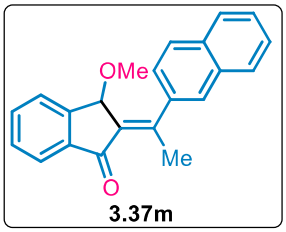
(*Z*)-2-(1-(4-Chlorophenyl)ethylidene)-3-methoxy-2,3-dihydro-1*H*-inden-1-one 3.37l':



3.37l'

Synthesized according to the general procedure described above as a yellow solid in 36% (38 mg) yield, mp 113-115 °C, R_f = 0.4 (in 10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75-7.73 (m, 2H), 7.69 (td, J = 7.2, 1.0 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.39 (dt, J = 8.4, 2.4 Hz, 2H), 7.26 (dt, J = 8.5, 2.3 Hz, 2H), 5.81 (s, 1H), 3.15 (s, 3H), 2.42 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 189.8, 153.2, 147.0, 139.8, 139.3, 134.6, 133.9, 131.7, 129.7, 128.7, 128.1, 125.9, 123.6, 76.2, 51.3, 23.8. IR (neat, cm^{-1}): 1696, 1618, 1525, 1460, 1377, 1337, 1320, 1293, 1240, 1208, 1183, 1149, 1075, 1004, 924, 837, 820, 796, 752, 718, 702, 679. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{18}H_{16}ClO_2$ 299.0833; found 299.0832.

(*E*)-3-Methoxy-2-(1-(naphthalene-2-yl)ethylidene)-2,3-dihydro-1*H*-inden-1-one 3.37m:

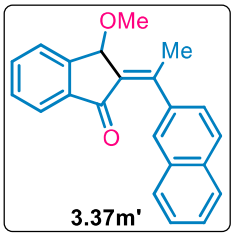


3.37m

Synthesized according to the general procedure described above as a yellow liquid in 46% (48.3 mg) yield, R_f = 0.5 (in 10% EtOAc/Hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94-7.88 (m, 5H), 7.63 (td, J = 7.4, 1.2 Hz, 1H), 7.56-7.50 (m, 5H), 5.51 (s, 1H), 2.90 (s, 3H), 2.88 (d, J = 0.4 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 193.4, 155.1, 147.8, 140.2, 139.8, 134.4, 133.0, 132.9, 132.8, 129.5, 128.2, 127.9, 127.7, 126.42, 126.40, 125.8, 125.7, 123.5, 76.5, 52.5, 21.2. IR (neat, cm^{-1}): 1688, 1603, 1502, 1463,

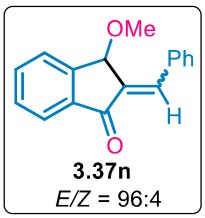
1432, 1367, 1332, 1260, 1198, 1152, 1124, 1075, 1017, 956, 936, 859, 819, 747, 702, 671, 656. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{22}H_{18}NaO_2$ 337.1199; found 337.1202.

(*Z*)-3-Methoxy-2-(1-(naphthalene-1-yl)ethylidene)-2,3-dihydro-1*H*-inden-1-one 3.37m':



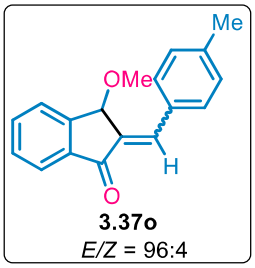
Synthesized according to the general procedure described above as a yellow solid in 33% (33.8 mg) yield, mp 152-154 °C, R_f = 0.4 (in 10% EtOAc/Hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89-7.85 (m, 3H), 7.80-7.75 (m, 3H), 7.70 (td, J = 7.3, 1.3 Hz, 1H), 7.53-7.48 (m, 3H), 7.44 (dd, J = 8.4, 1.7 Hz, 1H), 5.89 (s, 1H), 3.21 (s, 3H), 2.55 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 189.8, 154.7, 147.0, 140.0, 138.6, 134.5, 133.1, 133.0, 131.4, 129.6, 128.2, 127.7, 127.2, 126.1, 126.03, 126.02, 125.98, 125.93, 123.6, 76.4, 51.2, 24.2. IR (neat, cm^{-1}): 1694, 1620, 1599, 1500, 1462, 1431, 1365, 1341, 1291, 1248, 1231, 1198, 1153, 1123, 1080, 1055, 953, 930, 910, 891, 864, 821, 745, 684. HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{22}H_{18}NaO_2$ 337.1199; found 337.1182.

2-Benzylidene-3-methoxy-2,3-dihydro-1*H*-inden-1-one 3.37n:



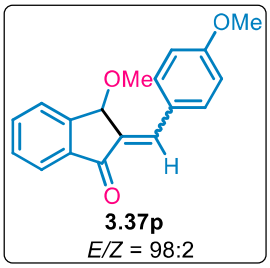
Synthesized according to the general procedure described above as a yellow oil in 60% (68 mg) yield, *E*:*Z* ratio: 96:4, R_f = 0.4 (in 10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, J = 7.2 Hz, 2H), 7.93 (d, J = 7.6 Hz, 1H), 7.86 (s, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.73 (t, J = 7.2 Hz, 1H), 7.56 (t, J = 7.2 Hz, 1H), 7.50-7.43 (m, 3H), 6.00 (s, 1H, major), 5.29 (s, 1H, minor), 3.19 (s, 1H, minor), 2.94 (s, 3H, major). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 192.3, 148.5, 138.7, 138.6, 135.0, 134.0, 133.4, 131.9, 130.4, 129.7, 128.8, 126.1, 123.6, 74.7, 50.4. IR (neat, cm^{-1}): 1698, 1625, 1464, 1332, 1261, 1064, 967, 748, 688. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{15}O_2$ 251.1067; found 251.1069.

3-Methoxy-2-(4-methylbenzylidene)-2,3-dihydro-1*H*-inden-1-one 3.37o:



Synthesized according to the general procedure described above as a yellow liquid in 71% (79 mg) yield, *E*:*Z* ratio: 96:4, R_f = 0.43 (in 10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, J = 8.0 Hz, 1H, minor), 7.93 (d, J = 7.6 Hz, 1H), 7.88 (d, J = 8.1 Hz, 2H), 7.85 (d, J = 1.3 Hz, 1H), 7.77 (d, J = 7.4 Hz, 1H), 7.73 (td, J = 7.2, 1.0 Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 5.99 (s, 1H, major), 5.61 (s, 1H, minor), 3.16 (s, 3H, minor), 2.92 (s, 3H, major), 2.41 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 192.5, 148.5, 141.1, 138.8, 138.7, 134.9, 132.3, 132.0, 131.3, 129.7, 129.6, 126.1, 123.6, 74.8, 50.3, 21.5. IR (neat, cm^{-1}): 1685, 1600, 1510, 1332, 1261, 1184, 1067, 968, 744. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{18}H_{17}O_2$ 265.1223; found 265.1227.

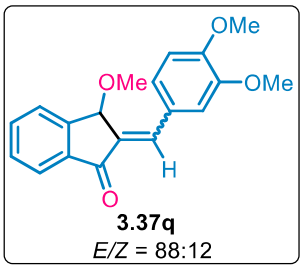
3-Methoxy-2-(4-methoxybenzylidene)-2,3-dihydro-1*H*-inden-1-one 3.37p:



3.37p
E/*Z* = 98:2

Synthesized according to the general procedure described above as a yellow liquid in 65% (68 mg) yield, *E*:*Z* ratio: 98:2, R_f = 0.4 (in 30% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.32 (d, *J* = 9.0 Hz, 1H, minor), 7.95 (d, *J* = 8.8 Hz, 2H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.83 (s, 1H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.72 (t, *J* = 7.1 Hz, 1H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.01 (d, *J* = 8.7 Hz, 2H), 5.99 (s, 1H, major), 5.61 (s, 1H, minor), 3.89 (s, 3H, major), 3.84 (s, 3H, minor), 3.21 (s, 3H, minor), 2.93 (s, 3H, major). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 192.4, 161.5, 148.3, 138.8, 138.6, 134.8, 134.0, 130.7, 129.6, 126.8, 126.0, 123.5, 114.4, 74.8, 55.3, 50.2. IR (neat, cm^{-1}): 1694, 1594, 1509, 1173, 1127, 1065, 968, 829, 744. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{18}H_{16}NaO_3$ 303.0992; found 303.1002.

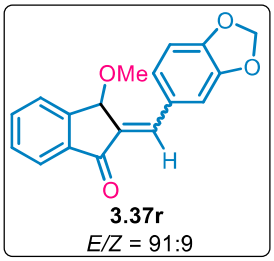
3-Methoxy-2-(3,4-dimethoxybenzylidene)-2,3-dihydro-1*H*-inden-1-one 3.37q:



3.37q
E/*Z* = 88:12

Synthesized according to the general procedure described above as a yellow solid in 71% (77 mg) yield, *E*:*Z* ratio: 88:12, mp 156-158 °C, R_f = 0.35 (in 15% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 7.6 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H, minor), 7.78 (dd, *J* = 14.8, 1.6 Hz, 2H), 7.47 (d, *J* = 7.2 Hz, 1H), 7.70 (td, *J* = 6.8, 0.8 Hz, 1H), 7.55-7.53 (m, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.49 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.95 (d, *J* = 8.4 Hz, 1H, major), 6.90 (d, *J* = 8.4 Hz, 1H, minor), 5.96 (s, 1H, major), 5.60 (s, 1H, minor), 4.05 (s, 3H, minor), 3.97 (s, 3H, major), 3.94 (s, 3H, major), 3.13 (s, 3H, minor), 2.92 (s, 3H, major). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 192.4, 190.5, 151.5, 151.4, 149.2, 148.5, 148.3, 147.1, 142.5, 140.7, 139.2, 138.9, 134.8, 134.4, 132.3, 131.0, 129.7, 129.6, 128.0, 127.3, 127.1, 127.0, 126.1, 125.9, 123.7, 123.6, 114.2, 114.0, 111.1, 110.3, 75.1, 56.09, 56.00, 55.97, 55.92, 51.5, 50.2. IR (neat, cm^{-1}): 1693, 1619, 1593, 1509, 1462, 1419, 1293, 1376, 1293, 1276, 1186, 1162, 1144, 1090, 1070, 1014, 986, 948, 935, 890, 856, 806, 790, 758, 702. HRMS (ESI-TOF) m/z: [M+H] calcd for $C_{19}H_{19}O_4$ 311.1278; found 311.1271.

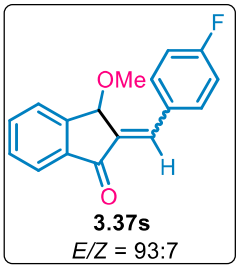
2-(Benzo[d][1,3]dioxol-5-ylmethylene)-3-methoxy-2,3-dihydro-1*H*-inden-1-one 3.37r:



3.37r
E/*Z* = 91:9

Synthesized according to the general procedure described above as a yellow solid in 58% (62 mg) yield, *E*:*Z* ratio: 91:9, mp 177-179 °C, R_f = 0.3 (in 20% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, *J* = 7.6 Hz, 1H), 7.86 (d, *J* = 7.7 Hz, 1H, minor), 7.77-7.66 (m, 5H), 7.54 (t, *J* = 7.0 Hz, 1H), 7.41 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.91 (d, *J* = 8.1 Hz, 1H, major), 6.86 (d, *J* = 8.1 Hz, 1H, minor), 6.05 (q, *J* = 3.2 Hz, 2H), 5.95 (s, 1H, major), 5.59 (s, 1H, minor), 3.14 (s, 3H, minor), 2.93 (s, 3H, major). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 192.4, 149.8, 148.4, 148.3, 138.87, 138.81, 134.9, 131.2, 129.7, 128.8, 128.5, 126.1, 123.6, 110.7, 108.6, 101.6, 74.7, 50.2. IR (neat, cm^{-1}): 1693, 1582, 1496, 1442, 1241, 1030, 922, 791, 608. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{18}H_{15}O_4$ 295.0965; found 295.0959.

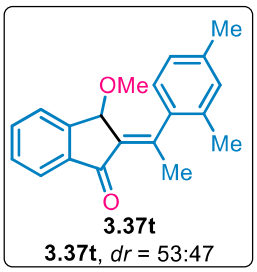
2-(4-Fluorobenzylidene)-3-methoxy-2,3-dihydro-1*H*-inden-1-one 3.37s:



3.37s
E/*Z* = 93:7

Synthesized according to the general procedure described above as a yellow solid in 65% (58 mg) yield, *E*:*Z* ratio: 93:7, mp 132-136 °C, R_f = 0.5 (in 20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (dd, *J* = 8.7, 5.6 Hz, 2H, minor), 7.97 (dd, *J* = 8.7, 5.5 Hz, 2H, major), 7.92 (d, *J* = 7.6 Hz, 1H), 7.86 (d, *J* = 7.5 Hz, 1H, minor), 7.80 (s, 1H), 7.76-7.70 (m, 2H), 7.57-7.53 (m, 1.1H), 7.18-7.09 (m, 2H), 5.96 (s, 1H, major), 5.60 (s, 1H, minor), 3.17 (s, 3H, minor); 2.92 (s, 3H, major). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 192.2, 163.9 (d, *J* = 251.5 Hz), 148.3, 147.2, 140.5, 138.6, 137.4, 135.1, 134.7, 134.1 (d, *J* = 8.6 Hz), 134.0 (d, *J* = 8.6 Hz), 133.9, 132.95, 132.93, 130.39, 130.35, 129.8, 129.7, 126.1, 125.9, 123.9, 123.8, 116.1 (d, *J* = 21.4 Hz), 115.2 (d, *J* = 21.3 Hz), 78.4, 74.6, 51.9, 50.3. ^{19}F NMR (470 MHz, $CDCl_3$): δ −108.3. IR (neat, cm^{-1}): 1685, 1593, 1506, 1222, 1058, 932, 819, 740. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{17}H_{13}FNaO_2$ 291.0792; found 291.0794.

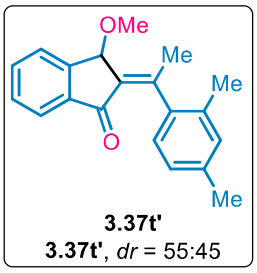
(*E*)-2-(1-(2,4-Dimethylphenyl)ethylidene)-3-methoxy-2,3-dihydro-1*H*-inden-1-one 3.37t:



3.37t
3.37t, *dr* = 53:47

Synthesized according to the general procedure described above as a yellow liquid in 36% (37.9 mg) yield, R_f = 0.6 (in 20% EtOAc/hexanes). A Mixture of atropo-diastereomers (*dr* = 53:47). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, *J* = 7.6 Hz, 1H), 7.61 (t, *J* = 7.4 Hz, 2H), 7.53-7.47 (m, 4H), 7.09-7.02 (m, 5H), 6.92 (d, *J* = 7.6 Hz, 1H), 5.27 (s, 1H, major), 5.04 (s, 1H, minor), 2.84 (s, 3H, minor), 2.83 (s, 3H, major), 2.66 (s, 6H), 2.35 (s, 6H), 2.25 (s, 3H, major), 2.17 (s, 3H, minor). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 193.3, 193.2, 157.2, 156.5, 148.1, 147.6, 139.88, 139.80, 139.0, 137.2, 134.58, 134.52, 134.4, 133.3, 132.5, 131.7, 131.0, 130.9, 129.4, 126.46, 126.42, 126.1, 125.9, 125.8, 125.2, 123.5, 123.4, 76.5, 76.58, 76.51, 54.3, 52.4, 21.5, 21.3, 21.1, 19.3, 19.0. IR (neat, cm^{-1}): 1692, 1629, 1497, 1332, 1258, 1151, 1080, 941, 819, 751. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{20}H_{20}NaO_2$ 315.1356; found 315.1355.

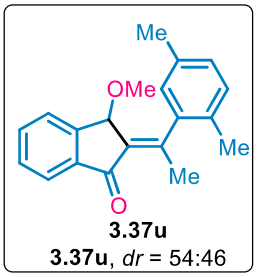
(*Z*)-2-(1-(2,4-Dimethylphenyl)ethylidene)-3-methoxy-2,3-dihydro-1*H*-inden-1-one 3.37t':



3.37t'
3.37t', *dr* = 55:45

Synthesized according to the general procedure described above as a yellow liquid in 16% (16.5 mg) yield, R_f = 0.54 (in 20% EtOAc/hexanes). Mixture of atropo-diastereomers (*dr* = 55:45). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73-7.64 (m, 6.4H), 7.46 (t, *J* = 7.4 Hz, 2H), 7.07 (s, 2H), 7.04 (d, *J* = 7.6 Hz, 2H), 6.93 (d, *J* = 7.6 Hz, 0.9H), 6.87 (d, *J* = 7.6 Hz, 1H), 5.86 (s, 1H, minor), 5.84 (s, 1H, major), 3.13 (s, 3H, minor), 3.12 (s, 3H, major), 2.36 (s, 2.9H), 2.36 (s, 5.6H), 2.35 (s, 3H, major), 2.21 (s, 3H, major), 2.13 (s, 3H, minor). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 190.0, 189.9, 154.9, 154.5, 147.3, 147.2, 140.0, 139.9, 138.8, 138.7, 136.9, 136.8, 134.4, 133.5, 133.1, 132.0, 131.8, 130.8, 130.6, 129.5, 126.5, 126.4, 126.0, 125.5, 123.5, 76.1, 75.8, 51.2, 50.8, 23.7, 23.5, 21.1, 19.4, 19.0. IR (neat, cm^{-1}): 1699, 1633, 1497, 1243, 1191, 1073, 900, 813, 749. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{20}H_{20}NaO_2$ 315.1356; found 315.1351.

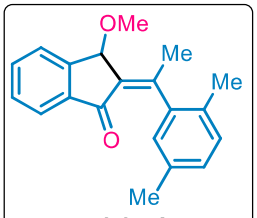
(*E*)-2-(1-(2,5-Dimethylphenyl)ethylidene)-3-methoxy-2,3-dihydro-1*H*-inden-1-one 3.37u:



3.37u
3.37u, *dr* = 54:46

Synthesized according to the general procedure described above as a yellow liquid in 35% (37.8 mg) yield, R_f = 0.35 (in 10% EtOAc/hexanes). A Mixture of atropo diastereomers (*dr* = 54:46). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, *J* = 7.5 Hz, 2H), 7.61 (t, *J* = 7.5 Hz, 2H), 7.53 (t, *J* = 7.0 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.14 (t, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.96 (s, 1H, minor), 6.84 (s, 1H, major), 5.25 (s, 1H, major), 4.99 (s, 1H, minor), 2.85 (s, 3H, minor), 2.83 (s, 3H, major), 2.67 (s, 3H, minor), 2.66 (s, 3H, major), 2.35 (s, 3H, minor), 2.33 (s, 3H, major), 2.24 (s, 3H, major), 2.16 (s, 3H, minor). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 193.3, 193.2, 157.1, 156.3, 148.2, 147.8, 142.6, 141.7, 139.83, 139.80, 135.1, 134.8, 134.56, 134.50, 133.2, 132.6, 131.4, 130.19, 130.11, 129.47, 129.45, 128.7, 128.36, 128.30, 127.2, 125.9, 125.88, 125.83, 123.55, 123.51, 54.6, 53.1, 21.3, 21.1, 20.98, 20.93, 18.8, 18.6. IR (neat, cm^{-1}): 1692, 1631, 1462, 1259, 1199, 1079, 944, 809, 750. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{20}H_{21}O_2$ 293.1536; found 293.1538.

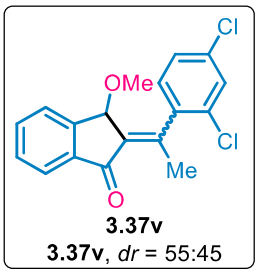
(*Z*)-2-(1-(2,5-Dimethylphenyl)ethylidene)-3-methoxy-2,3-dihydro-1*H*-inden-1-one 3.37u':



3.37u'
3.37u, *dr* = 54:46

Synthesized according to the general procedure described above as a yellow liquid in 20% (20.8 mg) yield, R_f = 0.27 (in 10% EtOAc/hexanes). Mixture of atropo diastereomers (*dr* = 54:46). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74-7.65 (m, 6H), 7.46 (t, *J* = 7.0 Hz, 2H), 7.13 (dd, *J* = 8.0, 3.0 Hz, 2H), 7.06 (dt, *J* = 7.5, 2.5 Hz, 2H), 6.84 (s, 1H, minor), 6.79 (s, 1H, major), 5.86 (s, 1H, minor), 5.85 (s, 1H, major), 3.13 (s, 3H, minor), 3.12 (s, 3H, major), 2.36 (s, 3H, major), 2.35 (s, 3H, minor), 2.33 (s, 3H, minor), 2.32 (s, 3H, major), 2.20 (s, 3H, major), 2.11 (s, 3H, minor). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 190.06, 190.00, 154.8, 154.5, 147.3, 147.2, 141.6, 141.5, 139.94, 139.91, 135.1, 135.0, 134.5, 131.8, 131.5, 130.4, 130.0, 129.8, 129.68, 129.61, 128.1, 126.4, 126.0, 123.5, 76.0, 75.8, 51.1, 50.8, 23.7, 23.5, 21.06, 21.04, 19.0, 18.6. IR (neat, cm^{-1}): 1700, 1634, 1603, 1462, 1247, 1202, 1075, 940, 875, 807, 750. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd for $C_{20}H_{20}NaO_2$ 315.1356; found 315.1359.

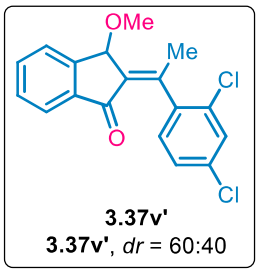
(*E*)-2-(1-(2,4-Dichlorophenyl)ethylidene)-3-methoxy-2,3-dihydro-1*H*-inden-1-one 3.37v:



3.37v
3.37v, *dr* = 55:45

Synthesized according to the general procedure described above as a yellow solid in 36% (37.4 mg) yield, mp 126-128 °C, R_f = 0.51 (in 10% EtOAc/hexanes). Mixture of atropo-diastereomers (*dr* = 55:45). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (d, *J* = 7.5 Hz, 2H), 7.66 (t, *J* = 7.5 Hz, 2H), 7.57 (d, *J* = 7.5 Hz, 2H), 7.52 (q, *J* = 7.5 Hz, 4H), 7.33 (t, *J* = 7.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 0.8H), 5.44 (s, 1H, minor), 5.20 (s, 1H, major), 2.89 (s, 3H, major), 2.87 (s, 3H, minor), 2.73 (s, 3H, minor), 2.68 (s, 3H, major). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 192.7, 152.5, 151.0, 147.5, 140.0, 139.9, 139.8, 139.3, 134.8, 134.17, 134.11, 133.9, 132.9, 130.7, 129.8, 129.6, 129.4, 128.1, 127.3, 126.9, 126.0, 123.6, 76.6, 75.6, 52.8, 52.5, 20.4, 20.1. IR (neat, cm^{-1}): 1687, 1626, 1601, 1466, 1373, 1334, 1290, 1266, 1209, 1196, 1145, 1101, 1079, 1031, 944, 916, 861, 814, 789, 749, 725. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{18}H_{15}Cl_2O_2$ 333.0444; found 333.0440.

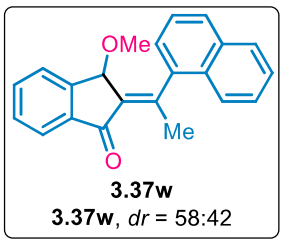
(*Z*)-2-(1-(2,4-Dichlorophenyl)ethylidene)-3-methoxy-2,3-dihydro-*1H*-inden-1-one 3.37v':



3.37v'
3.37v', *dr* = 60:40

Synthesized according to the general procedure described above as a yellow liquid in 31% (32 mg) yield, R_f = 0.38 (in 10% EtOAc/hexanes). Mixture of atropo-diastereomers (*dr* = 60:40). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74-7.66 (m, 5.6H), 7.49 (d, *J* = 7.3 Hz, 1.5H), 7.46 (d, *J* = 1.9 Hz, 1H), 7.45 (d, *J* = 2.0 Hz, 0.4H), 7.30 (t, *J* =1.9 Hz, 0.8H), 7.28 (t, *J* = 1.9 Hz, 2H), 7.09 (d, *J* = 8.2 Hz, 0.7H), 7.04 (d, *J* = 8.2 Hz, 1H), 5.88 (s, 1H, major), 5.84 (s, 1H, minor), 3.16 (s, 3H, minor), 3.09 (s, 3H, major), 2.37 (d, *J* = 0.4 Hz, 3H, major), 2.36 (d, *J* = 0.5 Hz, 3H, minor). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 189.8, 189.7, 149.7, 149.3, 147.4, 139.5, 139.4, 139.3, 139.0, 134.9, 134.8, 133.7, 133.4, 133.3, 131.6, 131.4, 129.8, 129.7, 129.3, 129.2, 129.1, 128.6, 127.2, 127.0, 126.1, 123.7, 123.6, 75.8, 75.5, 51.6, 50.7, 22.4, 22.3. IR (neat, cm^{-1}): 1692, 1632, 1584, 1468, 1372, 1239, 1034, 930, 814, 746. HRMS (ESI): $[M+H]^+$ calcd for $C_{18}H_{16}Cl_2O_2$ 333.0444; found 333.0442.

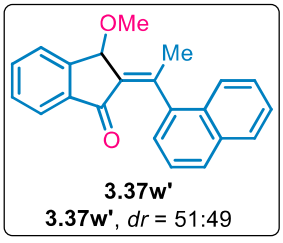
(*E*)-3-Methoxy-2-(1-(naphthalene-1-yl)ethylidene)-2,3-dihydro-1*H*-inden-1-one 3.37w:



3.37w
3.37w, *dr* = 58:42

Synthesized according to the general procedure described above as a yellow liquid in 44% yield (45.6 mg), R_f = 0.45 (in 10% EtOAc/hexanes). Mixture of atropo-diastereomers (*dr* = 58:42). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95-7.87 (m, 5.6H), 7.81-7.76 (m, 2H), 7.64-7.56 (m, 3H), 7.55-7.49 (m, 6H), 7.48-7.42 (m, 3.6H), 5.43 (s, 1H, minor), 5.01 (s, 1H, major), 2.90 (d, *J* = 0.9 Hz, 3H, major), 2.89 (d, *J* = 0.9 Hz, 3H, minor), 2.78 (s, 3H, major), 2.52 (s, 3H, minor). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 193.1, 193.0, 155.7, 154.4, 148.1, 147.7, 141.1, 139.83, 139.82, 139.7, 134.6, 134.4, 133.8, 133.58, 133.53, 130.2, 129.4, 128.7, 128.6, 128.2, 127.95, 127.91, 126.5, 125.97, 125.90, 125.8, 125.3, 125.1, 124.4, 124.0, 123.54, 123.50, 122.2, 76.53, 76.50, 53.5, 52.4, 22.0, 21.9. IR (neat, cm^{-1}): 1691, 1630, 1603, 1505, 1463, 1431, 1393, 1365, 1334, 1289, 1261, 1200, 1153, 1106, 1072, 1019, 997, 935, 862, 838, 801, 777, 751. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{22}H_{19}O_2$ 315.1380; found 315.1385.

(*Z*)-3-Methoxy-2-(1-(naphthalene-1-yl)ethylidene)-2,3-dihydro-1*H*-inden-1-one 3.37w':

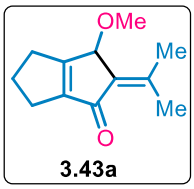


3.37w'
3.37w', *dr* = 51:49

Synthesized according to the general procedure described above as a yellow liquid in 25% yield (25.8 mg), R_f = 0.32 (in 10% EtOAc/hexanes). Mixture of atropo diastereomers (*dr* = 51:49). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.2 Hz, 2H), 7.89 (d, *J* = 8.2 Hz, 2H), 7.81-7.78 (m, 3.3H), 7.72-7.69 (m, 3.3H), 7.66 (d, *J* = 7.6 Hz, 2H), 7.56-7.52 (m, 2.7H), 7.51-7.41 (m, 6.7H), 7.31 (dd, *J* = 6.9, 0.8 Hz, 1H), 7.24 (dd, *J* = 6.9, 0.8 Hz, 0.9H), 6.05 (s, 1H, major), 5.97 (s, 1H, minor), 3.36 (s, 3H, minor), 3.24 (s, 3H, major), 2.57 (s, 3H, minor), 2.56 (s, 3H, major). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 189.6, 153.3, 153.0, 147.2, 140.3, 140.0, 139.9, 134.5, 134.4, 133.1, 130.3, 129.8, 129.6, 128.6, 127.6, 127.5, 126.1, 126.0, 125.7, 125.4, 125.3, 124.45, 124.40, 123.69, 123.65, 123.6, 123.4, 122.9, 76.4, 75.9, 52.0, 51.1, 24.3, 24.1. IR (neat, cm^{-1}): 1699, 1635, 1602, 1506, 1463, 1433, 1393, 1367, 1334, 1292,

1257, 1241, 1201, 1152, 1107, 1071, 1019, 998, 925, 906, 867, 837, 799, 776, 751, 684, 647. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{22}H_{19}O_2$ 315.1380; found 315.1380.

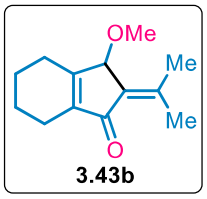
3-Methoxy-2-(propan-2-ylidene)-3,4,5,6-tetrahydropentalen-1(2*H*)-one 3.43a:



3.43a

Synthesized according to the general procedure described above as a yellow liquid in 52% (56 mg) yield, R_f = 0.41 (in 10% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.93 (s, 1H), 3.15 (s, 3H), 2.72-2.65 (m, 1H), 2.59-2.40 (m, 3H), 2.34-2.27 (m, 5H, one of the methyl groups was merged in the multiplet at 2.30 ppm), 1.95 (s, 3H), 1.79-1.68 (m, 4H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 190.8, 173.5, 155.2, 149.1, 133.7, 75.1, 52.5, 30.1, 26.8, 25.2, 23.0, 19.9. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{12}H_{16}NaO_2$ 215.1043; found 215.1047.

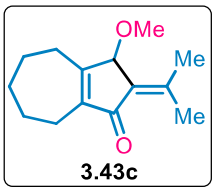
3-Methoxy-2-(propan-2-ylidene)-2,3,4,5,6,7-hexahydro-1*H*-inden-1-one 3.43b:



3.43b

Synthesized according to the general procedure described above as a yellow solid in 55% (59 mg) yield, mp 88-90 °C, R_f = 0.4 (in 15% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.94 (s, 1H), 2.98 (s, 3H), 2.45-2.40 (m, 1H), 2.34 (s, 3H), 2.26-2.20 (m, 3H), 1.99 (s, 3H), 1.79-1.68 (m, 4H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 194.6, 161.5, 149.1, 145.0, 128.2, 78.2, 50.2, 24.5, 23.0, 22.0, 21.6, 20.0, 19.9. IR (neat, cm^{-1}): 1679, 1633, 1432, 1276, 1190, 1054, 967, 876, 785. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{13}H_{18}NaO_2$ 229.1199; found 229.1189.

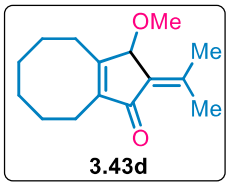
3-Methoxy-2-(propan-2-ylidene)-3,4,5,6,7,8-hexahydroazulen-1(2*H*)-one 3.43c:



3.43c

Synthesized according to the general procedure described above as a yellow liquid in 55% (56 mg) yield, R_f = 0.52 (in 20% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.93 (s, 1H), 2.91 (s, 3H), 2.57-2.40 (m, 3H), 2.34 (s, 3H), 1.99 (s, 3H), 1.87-1.67 (m, 3H), 1.66-1.49 (m, 4H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 194.5, 164.3, 149.5, 148.5, 127.5, 78.5, 49.5, 31.1, 28.9, 26.6, 26.4, 23.5, 23.0, 20.1. IR (neat, cm^{-1}): 1683, 1661, 1638, 1439, 1366, 1279, 1138, 1074, 972, 827, 750. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{14}H_{20}NaO_2$ 243.1356; found 243.1359.

3-Methoxy-2-(propan-2-ylidene)-2,3,4,5,6,7,8,9-octahydro-1*H*-cyclopenta[8]annulen-1-one 3.43d:

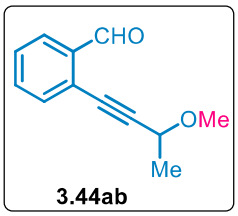


3.43d

Synthesized according to the general procedure described above as a yellow liquid in 49% (56 mg) yield, R_f = 0.40 (in 20% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.98 (s, 1H), 2.93 (s, 3H), 2.57-2.51 (m, 3H), 2.39-2.29 (m, 4H, methyl peak was merged in the multiplet), 2.00 (s, 3H), 1.87-1.80 (m, 1H), 1.76-1.66 (m, 2H), 1.58-1.49 (m, 2H), 1.47-1.42 (m, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 194.6, 163.0, 149.3, 146.4, 127.4, 77.7, 49.9, 27.7, 27.1, 26.3, 26.1, 25.6,

23.0, 21.0, 20.1. IR (neat, cm^{-1}): 1684, 1658, 1637, 1443, 1367, 1276, 1133, 1072, 991, 794. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{15}H_{23}O_2$ 235.1693; found 235.1692.

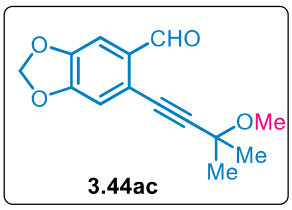
2-(3-Methoxybut-1-yn-1-yl)benzaldehyde 3.44ab:



3.44ab

Synthesized according to the general procedure described above as a yellow oil in 55% (59 mg) yield, R_f = 0.4 (in 20% EtOAc/hexanes). ^1H NMR (500 MHz, $CDCl_3$): δ 10.52 (d, J = 1.0 Hz, 1H), 7.91 (tt, J = 8.0, 1.0 Hz, 1H), 7.56-7.53 (m, 2H), 7.45-7.42 (m, 1H), 4.35 (q, J = 6.5 Hz, 1H), 3.48 (s, 3H), 1.55 (d, J = 6.5 Hz, 3H). ^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 191.5, 135.9, 133.7, 133.4, 128.7, 127.1, 126.2, 96.1, 80.6, 67.3, 56.5, 21.8. IR (neat, cm^{-1}): 2932, 1695, 1590, 1448, 1238, 1190, 1064, 909, 818, 762. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{12}H_{12}NaO_2$ 211.0730; found 211.0736.

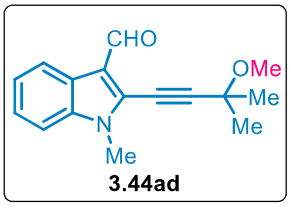
6-(3-Methoxy-3-methylbut-1-yn-1-yl)benzo[d][1,3]dioxole-5-carbaldehyde 3.44ac:



3.44ac

Synthesized according to the general procedure described above as a yellow solid in 60% (64 mg) yield, mp 96-98 °C, R_f = 0.5 (in 20% EtOAc/hexanes). ^1H NMR (500 MHz, $CDCl_3$): δ 10.34 (s, 1H), 7.32 (s, 1H), 6.92 (s, 1H), 3.41 (s, 3H), 1.55 (s, 6H). ^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 189.8, 152.3, 148.6, 132.2, 123.1, 112.2, 106.0, 102.3, 97.1, 79.6, 71.0, 51.9, 28.1. IR (neat, cm^{-1}): 2919, 2851, 1672, 1604, 1498, 1476, 1361, 1238, 1066, 1028, 929, 846. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{14}H_{14}NaO_4$ 269.0784; found 269.0785.

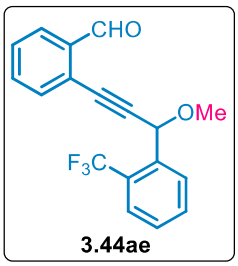
2-(3-Methoxy-3-methylbut-1-yn-1-yl)-1-methyl-1*H*-indole-3-carbaldehyde 3.44ad:



3.44ad

Synthesized according to the general procedure described above as a white solid in 63% (68 mg) yield, mp 130-132 °C, R_f = 0.5 (in 20% EtOAc/hexanes). ^1H NMR (500 MHz, $CDCl_3$): δ 10.16 (s, 1H), 8.31 (m, 1H), 7.39-7.36 (m, 1H), 7.33-7.30 (m, 2H), 3.84 (s, 3H), 3.47 (s, 3H), 1.63 (s, 6H). ^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 184.9, 137.3, 131.5, 125.0, 124.3, 123.5, 122.2, 120.0, 109.6, 103.7, 72.6, 71.2, 52.1, 31.0, 28.1. IR (neat, cm^{-1}): 2921,645, 1463, 1382, 1243, 1174, 1067, 833, 741. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{16}H_{17}NNaO_2$ 278.1151; found 278.1150.

2-(3-Methoxy-3-(2-(trifluoromethyl)phenyl)prop-1-yn-1-yl)benzaldehyde 3.44ae:

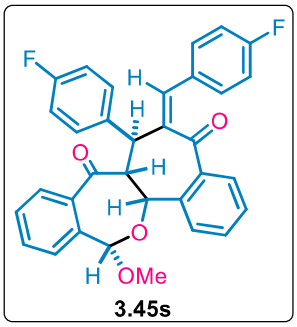


3.44ae

Synthesized according to the general procedure described above as a yellow liquid in 62% (65 mg) yield, R_f = 0.40 (in 10% EtOAc/hexanes). ^1H NMR (500 MHz, $CDCl_3$): δ 10.43 (s, 1H), 7.97 (d, J = 7.5 Hz, 1H), 7.91 (d, J = 7.5 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.65 (t, J = 7.5 Hz, 1H), 7.58-7.53 (m, 2H), 7.49-7.44 (m, 2H), 5.61 (s, 1H), 3.53 (s, 3H).97 (s, 3H), 3.94 (s, 3H), 3.44 (s, 3H), 1.58 (s, 6H). ^{13}C {^1H} NMR (100 MHz, $CDCl_3$): δ 191.2, 137.1, 136.1, 133.7, 133.5, 132.5, 129.1, 129.0, 128.7, 127.2, 125.8 (q, J = 18.5 Hz), 125.6,

93.6, 83.0, 69.4, 57.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ -58.3. IR (neat, cm^{-1}): 1697, 1593, 1452, 1310, 1272, 1158, 1115, 1079, 1034, 994, 823, 761. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{18}H_{13}F_3NaO_2$ 341.0760; found 341.0760.

(*Z*)-6-(4-Fluorobenzylidene-7-(4-fluorophenyl)-13-methoxy-6,7,7a,14a-tetrahydro-5*H*-benzo[e]benzo[6,7]cyclohepta[1,2-b]oxepine-5,8(13*H*)-dione 3.45s:



3.45s

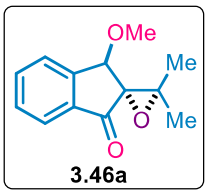
Yellow solid. 8% (17 mg) yield, mp 180-182 °C, R_f = 0.4 (in 20% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (dd, J = 8.0, 1.5 Hz, 1H), 7.84 (d, J = 7.5 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.59 (tdd, J = 15, 3.5,1.5 Hz, 2H), 7.55 (dd, J = 7.5, 1.0 Hz, 1H), 7.52 (td, J = 7.5, 1.0 Hz, 1H), 7.45 (td, J = 7.5, 0.5 Hz, 1H), 7.37-7.34 (m, 2H), 7.06-7.02 (m, 2H), 6.99-6.92 (m, 4H), 6.26 (s, 1H), 6.16 (s, 1H), 5.72 (d, J = 8.0 Hz, 1H), 4.46 (d, J = 11.0 Hz, 1H), 4.27 (dd, J = 11.0, 8.5 Hz, 1H), 3.67 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 197.5, 194.2, 163.3 (d, J = 135 Hz), 161.3 (d, J = 132.5 Hz), 141.9, 141.8, 139.5, 138.4, 136.7, 134.6 (d, J = 2.5 Hz), 134.5, 133.6, 131.7, 131.5, 131.4, 131.1 (d, J = 2.5 Hz), 129.8, 129.7, 129.5, 129.0, 128.7, 127.9, 126.7, 125.7, 115.6 (d, J = 21.2 Hz), 115.2 (d, J = 21.2 Hz), 101.4, 74.9, 60.8, 55.5, 45.1. ^{19}F NMR (470 MHz, $CDCl_3$): δ −111.3, −115.1. IR (neat, cm^{-1}):1724, 1682, 1665, 1597, 1506, 1448, 1373, 1325, 1223, 1202, 1125, 1093, 991, 905, 826, 765, 744, 693. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{33}H_{24}F_2NaO_4$ 545.1535; found 545.1545.

Scale-up Reaction and Synthetic Applications of Indanones:

Typical Procedure for a Gram Scale Synthesis of 3.37a. A solution of TfOH (94 µL, 1.06 mmol, 20 mol %) was added to a stirred solution of 2-(3-hydroxy-3-methylbut-1-yn-1-yl)benzaldehyde **3.36a** (1.0 g, 5.3 mmol, 1.0 equiv.) and TMOF (2.32 mL, 21.2 mmol, 4.0 equiv.) in CH_3NO_2 (75 mL) at room temperature and allowed to stir at the same temperature. After completion of the reaction (10 h), the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (60 mL) and extracted with ethyl acetate (3 × 60 mL). Combined organic layers were washed with saturated aqueous brine solution, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/ethyl acetate mixture as eluent) to afford the indanone **3.37a** in 48% (0.52 g) isolated yield.

Synthesis of 3.46a and 3.46': A sample of *m*-CPBA (0.22 mmol, 39 mg, 1.5 equiv.) was added in one portion to a stirred solution of indanone **3.37a** (0.15 mmol, 30 mg, 1.0 equiv.) in dry CH_2Cl_2 (1 mL), at 0 °C. The reaction was brought to room temperature and stirred for 12 h at the same temperature. The solvent was removed and the crude was subjected to silica gel column chromatography (10% hexanes/ethyl acetate) to separate **3.46a** and **3.46'**.[27]

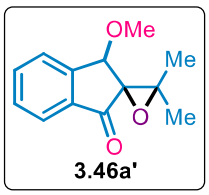
1-Methoxy-3,3'-dimethylspiro[indene-2,2'-oxiran]-3(1*H*)-one 3.46a:



3.46a

Yellow solid, 58% (19 mg) yield, mp 90-92 °C, R_f = 0.6 (in 20% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (d, J = 7.7 Hz, 1H), 7.74 (t, J = 7.5 Hz, 1H), 7.70 (d, J = 7.7 Hz, 1H), 7.54 (d, J = 7.5 Hz, 1H), 5.09 (s, 1H), 3.26 (s, 3H), 1.74 (s, 3H), 1.66 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 198.6, 149.4, 137.6, 135.5, 129.8, 126.0, 123.4, 79.7, 68.1, 54.7, 23.1, 19.0. IR (neat, cm^{-1}): 1717, 1462, 1372, 1191, 1122, 1073, 970, 908, 742, 672. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{13}H_{14}NaO_3$ 241.0835; found 241.0831.

1-Methoxy-3,3'-dimethylspiro[indene-2,2'-oxiran]-3(1*H*)-one 3.46':



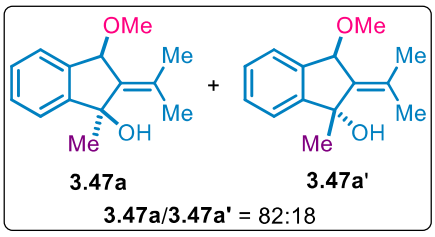
3.46a'

Yellow solid, 39% (13 mg) yield, mp 97-99 °C, R_f = 0.4 (in 20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 7.6 Hz, 1H), 7.75 (td, J = 7.6, 1.2 Hz, 1H), 7.71-7.69 (m, 1H), 7.59-7.55 (m, 1H), 5.04 (s, 1H), 3.24 (s, 3H), 1.58 (s, 3H), 1.57 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 199.0, 148.7, 137.2, 135.5, 130.2, 127.0, 123.3, 68.7, 66.1, 22.7, 18.1. IR (neat, cm^{-1}): 1717, 1395, 1259, 1152, 1080, 1017, 906, 845, 755. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{13}H_{14}NaO_3$ 241.0835; found 241.0832.

Synthesis of 3-methoxy-1-methyl-2-(propan-2-ylidene)-2,3-dihydro-1*H*-inden-1-ol (3.47a/3.47a'):

A solution of MeMgBr (2.0M in THF, 0.3 mmol, 150 µL, 2.0 equiv.) was added slowly to a stirred solution of indanone **3.37a** (0.15 mmol, 30 mg, 1.0 equiv.) in dry THF (1 mL), at 0 °C under N_2 atmosphere. The resulting solution was stirred for 2 h at the same temperature. Then, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (5 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with saturated aqueous brine solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/hexane mixture as eluent) to afford the pure product **3.47a**/**3.47a'** as an inseparable diastereomeric mixture.

3-methoxy-1-methyl-2-(propan-2-ylidene)-2,3-dihydro-1*H*-inden-1-ol 3.47a/3.47a':



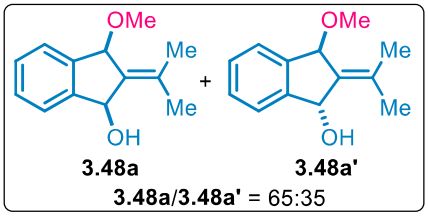
3.47a 3.47a'
3.47a/3.47a' = 82:18

Colourless liquid in 61% (20 mg) yield. *dr* = 82:18, R_f = 0.4 (in 20% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45-7.29 (m, 5.2H), 5.46 (s, 1H, major), 5.39 (s, 1H, minor), 3.21 (s, 3H, minor), 2.99 (s, 3H, major), 2.15 (d, J = 2 Hz, 1H), 2.11 (d, J = 1.5 Hz, 3H, major), 2.09 (s, 3H, minor), 1.93 (s, 3H, major), 1.92 (s, 3H, minor), 1.72 (s, 3H, minor), 1.64 (s, 3H, major). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 150.7, 150.0, 139.0, 138.4, 137.9, 137.7, 137.0, 129.5, 129.4, 128.6, 128.3, 125.3, 125.1, 123.2, 123.0, 81.1, 79.9, 79.6, 78.3, 53.5, 50.8, 28.4, 28.1, 22.5, 22.0, 20.8, 20.4. IR (neat, cm^{-1}): 3409, 1670, 1440, 1366, 1260, 1102, 1032, 930, 895, 764, 659. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{14}H_{18}NaO_2$ 241.1199; found 241.1200.

Synthesis of 3-methoxy-2-(propan-2-ylidene)-2,3-dihydro-1*H*-inden-1-ol 3.48a/3.48a':

A pure sample of $NaBH_4$ (0.3 mmol, 11 mg, 3.0 equiv.) was added in portion wise over 5 minutes to a stirred solution of indanone **3.37a** (0.15 mmol, 30 mg, 1.0 equiv.), $CeCl_3 \cdot 7H_2O$ (0.16 mmol, 61 mg, 1.1 equiv.) in MeOH (1 mL), at 0 °C. The resulting solution was stirred for 2 h at the same temperature. Water (3 mL) was added to the reaction mixture and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated and purified by column chromatography (silica gel, EtOAc/hexanes mixture as eluent) to afford **3.48a/3.48a'**.

3-methoxy-2-(propan-2-ylidene)-2,3-dihydro-1*H*-inden-1-ol 3.48a/3.48a':

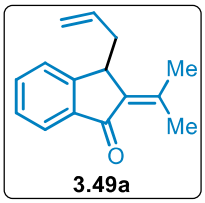


Colourless liquid, 80% (24 mg) yield, *dr* = 65:35. R_f = 0.4 (in 20% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50 (d, J = 7.0 Hz, 1H), 7.47-7.44 (m, 1.6H), 7.41-7.35 (m, 2.1H), 7.28-7.25 (m, 0.6H), 7.22-7.16 (m, 1.2H), 6.60 (s, 0.5H), 5.69 (s, 1H), 5.66 (s, 0.9H), 5.25 (s, 0.5H), 3.25 (s, 1.9H), 2.96 (s, 3H), 2.05 (s, 3H), 1.95 (s, 3H), 1.56 (s, 1.7H), 1.54 (s, 1.8H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 153.4, 145.2, 142.5, 141.5, 140.6, 139.6, 135.0, 129.4, 128.7, 127.0, 125.5(7), 125.5(3), 125.1, 123.9, 121.4, 83.4, 80.5, 74.1, 71.0, 53.6, 51.0, 31.1, 29.2, 21.5, 21.2. IR (neat, cm-1): 3384, 1678, 1458, 1371, 1200, 1074, 935, 864, 750, 632. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{13}H_{16}NaO_2$ 227.1043; found 227.1044.

Synthesis of 3-allyl-2-(propan-2-ylidene)-2,3-dihydro-1*H*-inden-1-one 3.49a:

It was synthesized using a slightly modified procedure of the reported allylation protocol.[28] To a stirred solution of $FeCl_3$ (0.0055 mmol, 0.9 mg, 5 mol %) in CH_3NO_2 (0.5 mL), allyltrimethylsilane (0.132 mmol, 21 µL, 2.0 equiv.) and a solution of indanone **3.37a** (0.11 mmol, 20 mg, 1.0 equiv.) in CH_3NO_2 (0.5 mL) were added at room temperature under N_2 atmosphere. The resulting solution was stirred for 24 h at the same temperature. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (5 mL), and extracted with Et_2O (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, EtOAc/hexane mixture as eluent) to get the pure product **3.49a**.

3-allyl-2-(propan-2-ylidene)-2,3-dihydro-1*H*-inden-1-one3.49a:



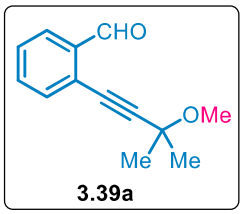
White solid. 43% yield (10 mg), mp 96-98 °C, R_f = 0.56 (in 5% EtOAc/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, J = 7.5 Hz, 1H), 7.53 (td, J = 7.5, 1.0 Hz, 1H), 7.47 (dq, J = 7.5, 1.0 Hz, 1H), 7.37-7.34 (m, 1H), 5.54 (dddd, J = 14.5, 10.0, 8.0, 6.5 Hz, 1H), 4.92-4.86 (m, 2H), 3.98 (dd, J = 7.0, 3.5 Hz, 1H), 2.71-2.65 (m, 1H), 2.50-2.43 (m, 1H), 2.41 (s, 3H), 2.05 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 194.0, 151.8, 148.9, 139.4, 134.5, 134.2, 133.6, 127.4, 125.3, 123.6, 117.5, 42.3, 38.9, 24.3, 20.7. IR (neat, cm^{-1}): 2919, 1684, 1622, 1602, 1464, 1285, 1087, 914, 847, 744. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{15}H_{17}O$ 213.1274; found 213.1275.

Control Experiments and Characterization:

(a) **Conversion of 3.38a into 3.39a** (Scheme 3.14a): TfOH (0.04 mmol, 3.5 µL, 20 mol %) was added to a stirred solution of **3.38a** (0.2 mmol, 50 mg, 1.0 equiv.) in CH_3NO_2 (2 mL), at room

temperature. The resulting solution was stirred for 2 h at the same temperature. Then the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (5 mL), extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated and purified by column chromatography (silica gel, EtOAc/hexanes mixture as eluent) to get **3.39a** as a yellow liquid in 60% isolated yield (24 mg).

2-(3-Methoxy-3-methylbut-1-yn-1-yl)benzaldehyde 3.39a:



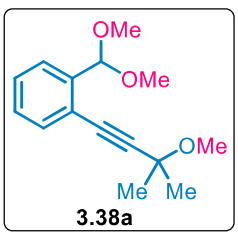
3.39a

^{1}H NMR (500 MHz, $CDCl_3$): δ 10.51 (s, 1H), 7.90 (d, J = 7.5 Hz, 1H), 7.54 (d, J = 4.0 Hz, 2H), 7.43 (hept, J = 4.0 Hz, 1H), 3.43 (s, 3H), 1.57 (s, 6H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 191.4, 135.9, 133.7, 133.3, 128.6, 127.1, 126.3, 98.4, 79.8, 71.0, 51.9, 28.1. IR (neat, cm^{-1}): 1696, 1594, 1276, 1170, 1070, 824, 757. HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{13}H_{14}NaO_2$ 225.0886; found 225.0886.

(b) **Conversion of 3.38a into 3.37a** (Scheme 3.14b): TfOH (0.04 mmol, 3.5 µL, 20 mol %) was added to a stirred solution of **3.38a** (0.2 mmol, 50 mg, 1.0 equiv.) and TMOF (0.4 mmol, 44 µL, 2.0 equiv.) in CH_3NO_2 (2 mL) at room temperature. The resulting solution was stirred for 3 h at the same temperature. Then the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated and purified by column chromatography (silica gel, EtOAc/hexane mixture as eluent) to afford **3.37a** as a yellow solid in 49% (36 mg) yield.

(c) **Conversion of 3.39a into 3.38a** (Scheme 3.14e): TfOH (0.04 mmol, 3.5 µL, 20 mol %) was added to a stirred solution of **3.39a** (0.2 mmol, 40 mg, 1.0 equiv.), TMOF (0.4 mmol, 44 µL, 2.0 equiv.) in CH_3NO_2 (2 mL), at room temperature. The resulting solution was stirred for 3 h at the same temperature. The reaction mixture was then quenched with saturated $NaHCO_3$ solution (5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by column chromatography (silica gel, EtOAc/hexane mixture as eluent) to afford **3.38a**.

1-(Dimethoxymethyl)-2-(3-methoxy-3-methylbut-1-yn-1-yl)benzene 3.38a:



3.38a

Yellow liquid in 70% (35 mg) yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 (d, J = 7.5 Hz, 1H), 7.44 (dd, J = 8.0, 1.5 Hz, 1H), 7.34 (td, J = 7.5, 1.0 Hz, 1H), 7.28 (dd, J = 7.5, 1.5 Hz, 1H), 5.61 (s, 1H), 3.45 (s, 3H), 3.40 (s, 6H), 1.57 (s, 6H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 139.6, 132.4, 128.2, 126.0, 121.7, 102.8, 95.7, 81.7, 71.0, 54.3, 51.7, 28.3. IR (neat, cm^{-1}) 1360, 1272, 1171, 1146, 1071, 1052, 978, 759: HRMS (ESI-TOF) m/z: $[M+Na]^+$ calcd. for $C_{15}H_{20}NaO_3$ 271.1305; found 271.1306.

(d) **Conversion of 3.39a to 3.37a** (Scheme 3.14f): TfOH (0.04 mmol, 3.5 µL, 20 mol %) was added to a stirred solution of **3.39a** (0.2 mmol, 40 mg, 1.0 equiv.), TMOF (0.8 mmol, 88 µL, 4.0 equiv.) in CH_3NO_2 (2 mL), at room temperature. The resulting solution was stirred for 5 h at the same temperature. Then, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, concentrated, and purified by column chromatography (silica gel, EtOAc/hexane mixture as eluent) to afford **3.37a** as a yellow solid in 60% (24 mg) yield.

3.6 References

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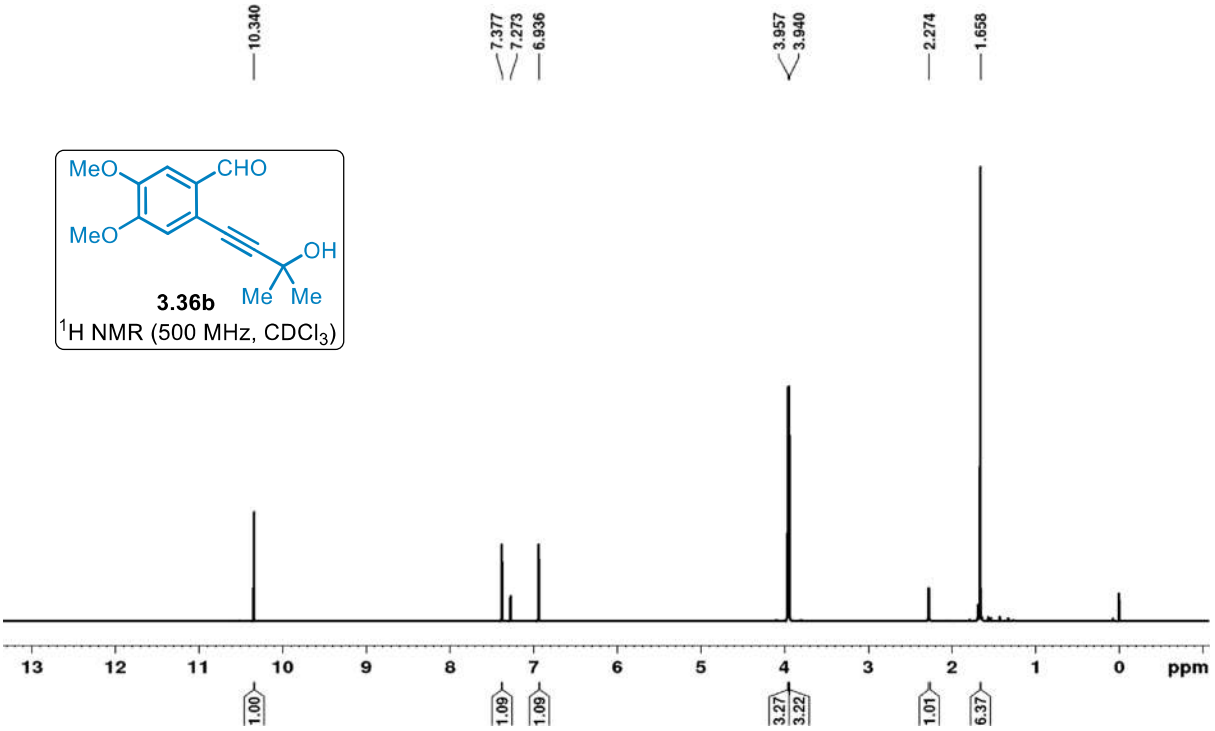
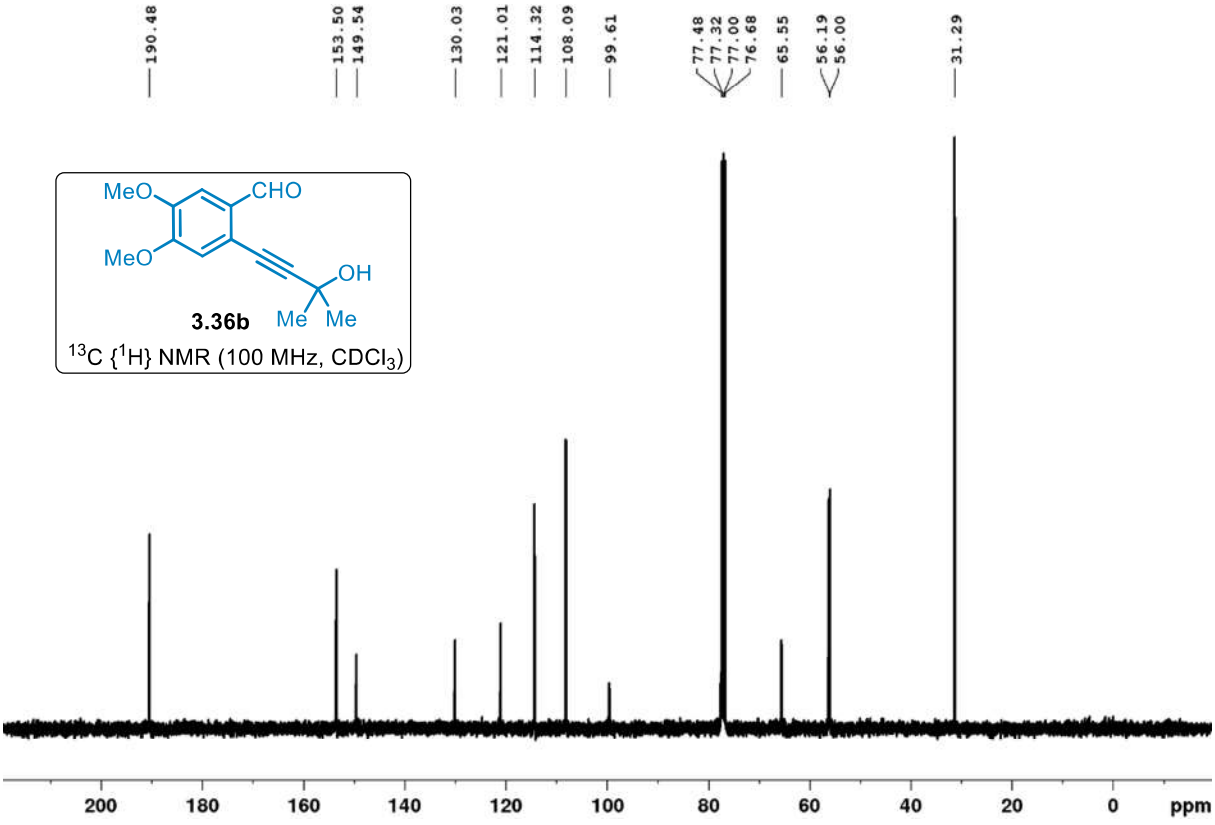
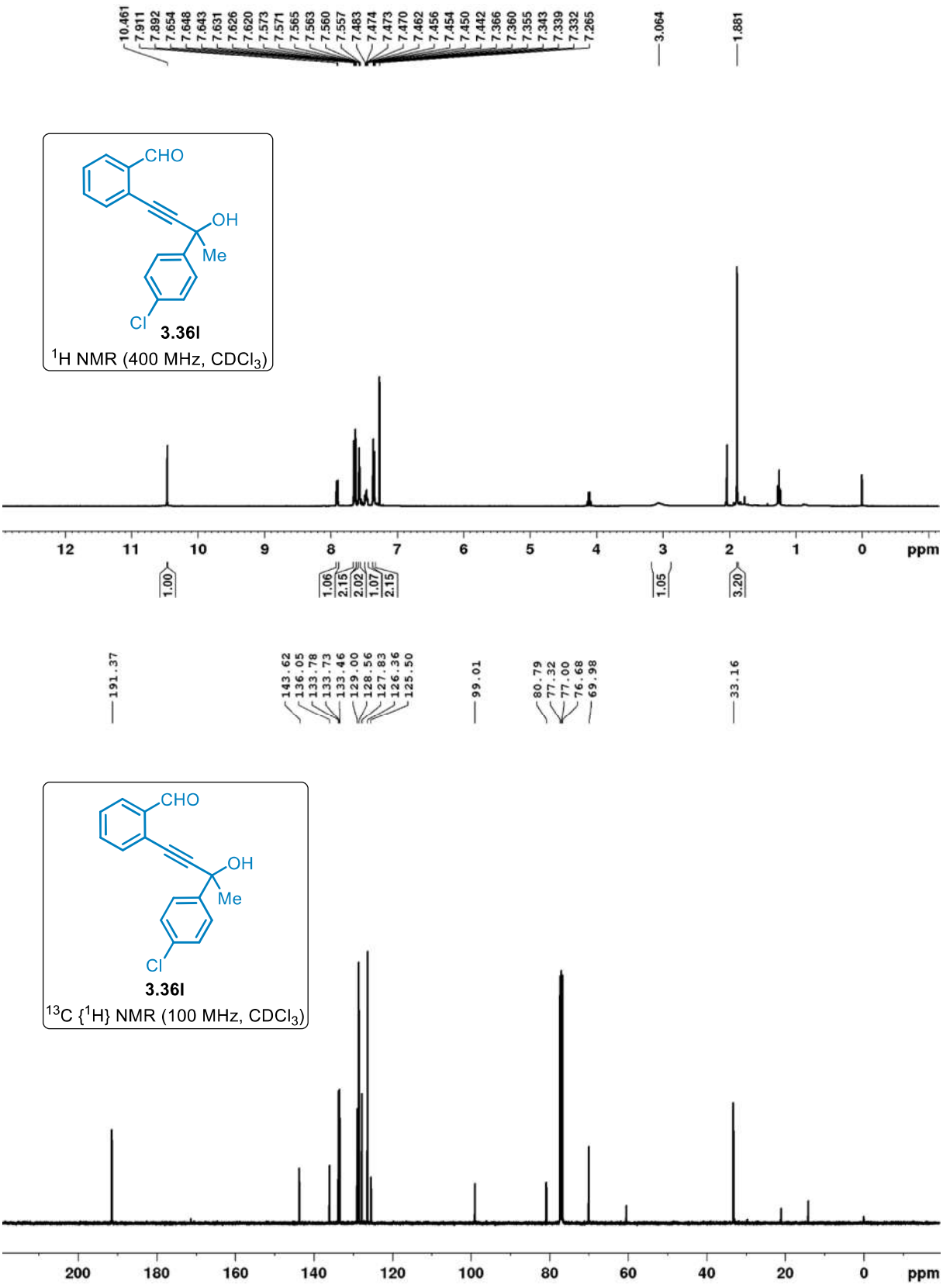
3.7 Representative spectra



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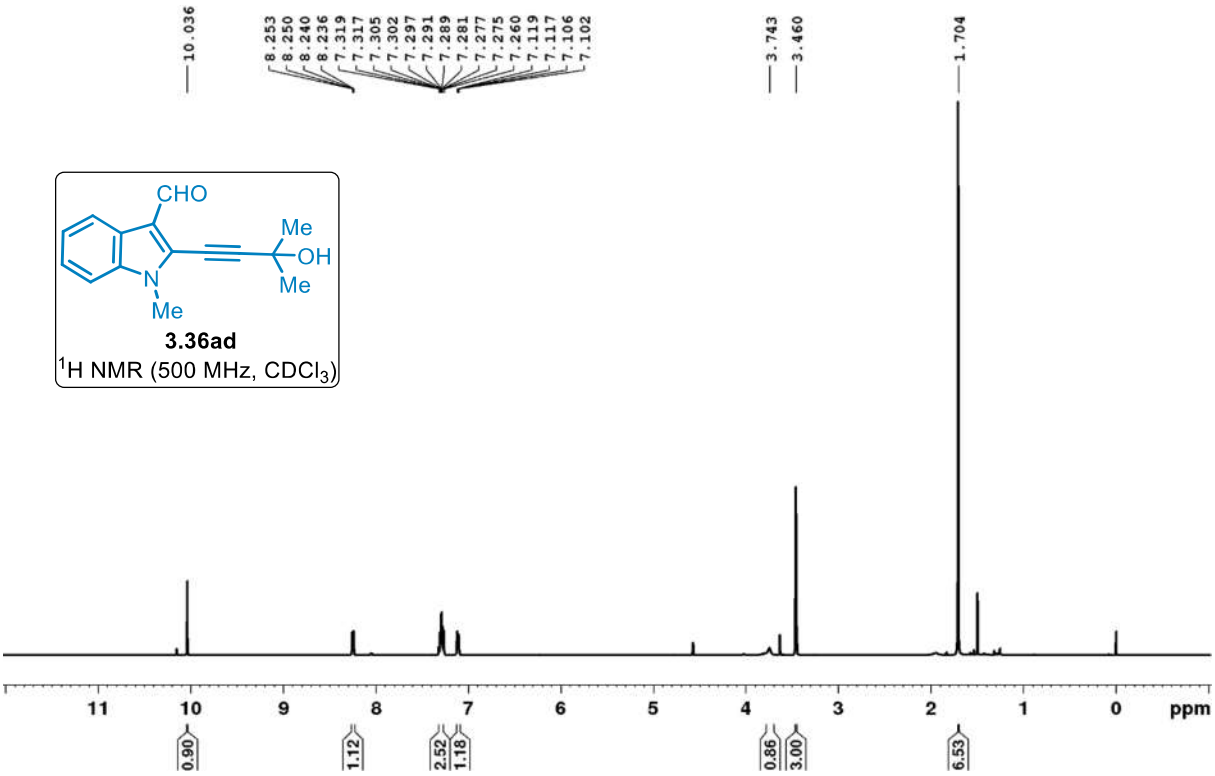
7.911
7.892
7.654
7.648
7.643
7.631
7.626
7.620
7.573
7.571
7.565
7.563
7.560
7.557
7.483
7.474
7.473
7.470
7.462
7.456
7.454
7.450
7.442
7.366
7.360
7.355
7.343
7.339
7.332
7.265
3.064
1.881
CHO
OH
Me
Cl
3.36l
^{1}H NMR (400 MHz, $CDCl_3$)
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.06
2.15
2.02
1.07
2.15
1.05
3.20
191.37
143.62
136.05
133.78
133.73
133.46
129.00
128.56
127.83
126.36
125.50
99.01
80.79
77.32
77.00
76.68
69.98
33.16
CHO
OH
Me
Cl
3.36l
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$)
200
180
160
140
120
100
80
60
40
20
0
ppm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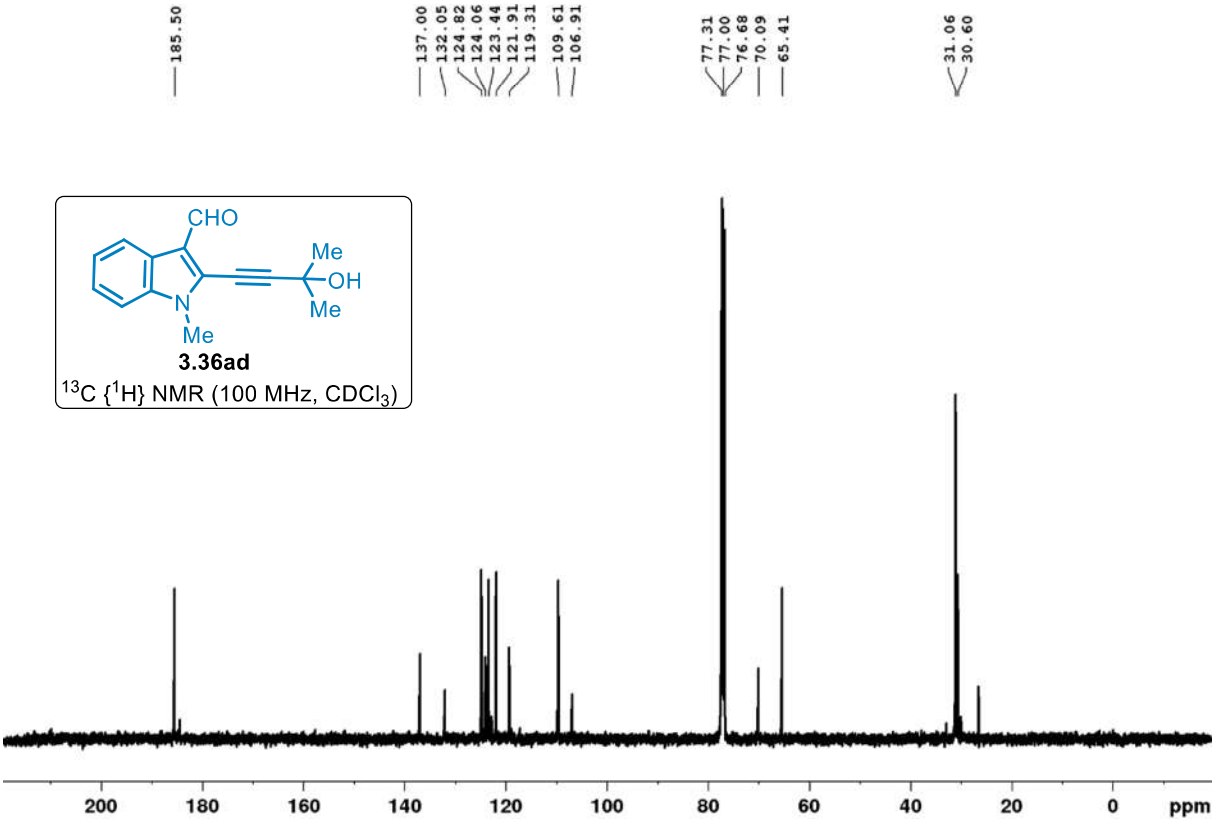
8.253
8.250
8.240
8.236
7.319
7.317
7.305
7.302
7.297
7.291
7.289
7.281
7.277
7.275
7.260
7.119
7.117
7.106
7.102
3.743
3.460
1.704
CHO
Me
OH
Me
N
Me
3.36ad
1H NMR (500 MHz, CDCl3)
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.90
1.12
2.52
1.18
0.86
3.00
6.53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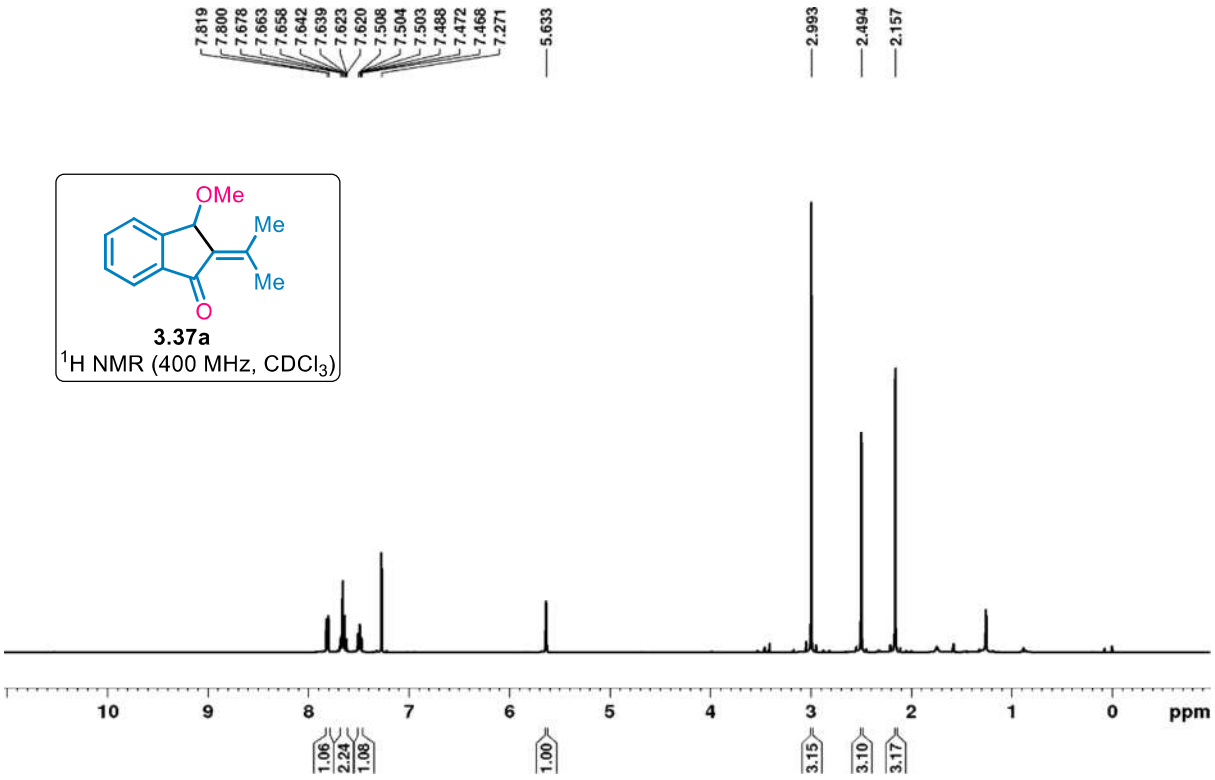
137.00
132.05
124.82
124.06
123.44
121.91
119.31
109.61
106.91
77.31
77.00
76.68
70.09
65.41
31.06
30.60
CHO
Me
OH
Me
N
Me
3.36ad
13C {1H} NMR (100 MHz, CDCl3)
200
180
160
140
120
100
80
60
40
20
0
ppm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7.800
7.678
7.663
7.658
7.642
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7.623
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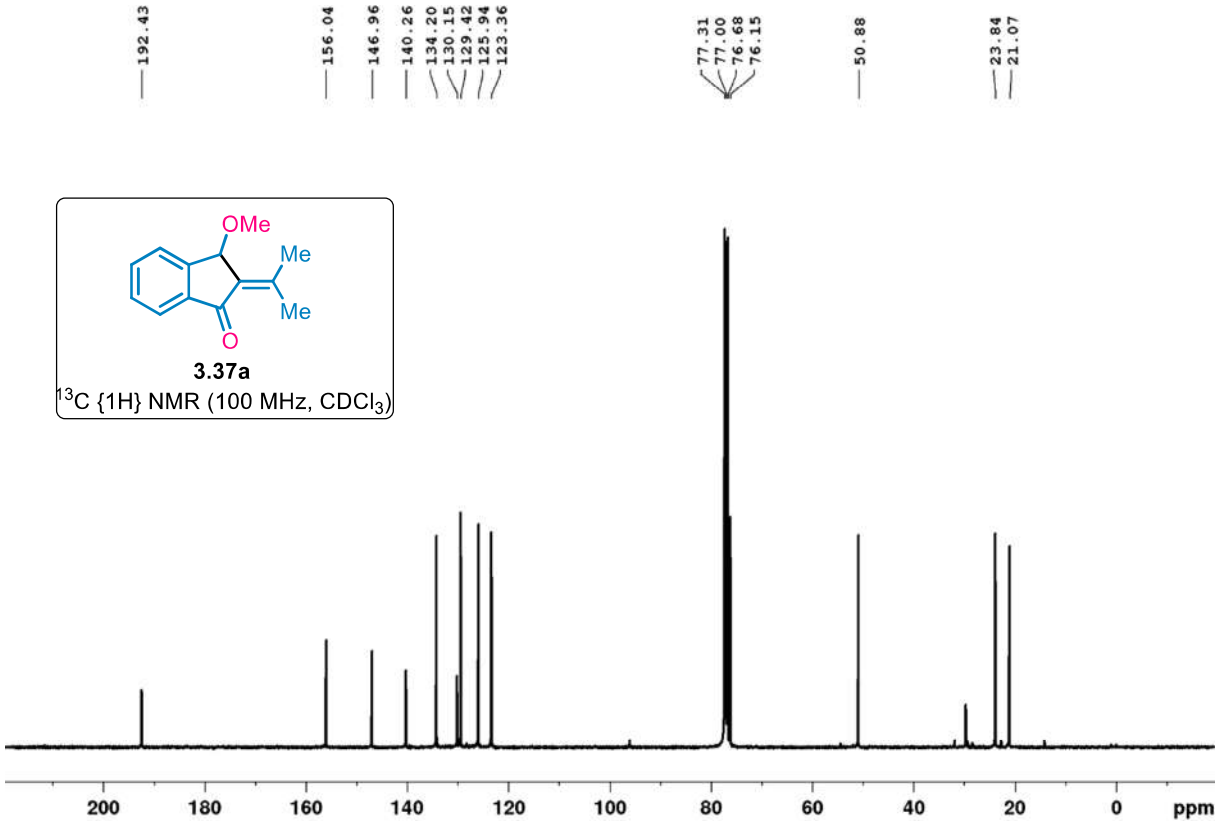
7.504
7.503
7.488
7.472
7.468
7.271
5.633
2.993
2.494
2.157
OMe
Me
Me
O
3.37a
^{1}H NMR (400 MHz, CDCl$_3$)
10
9
8
7
6
5
4
3
2
1
0
ppm
1.06
2.24
1.08
1.00
3.15
3.10
3.17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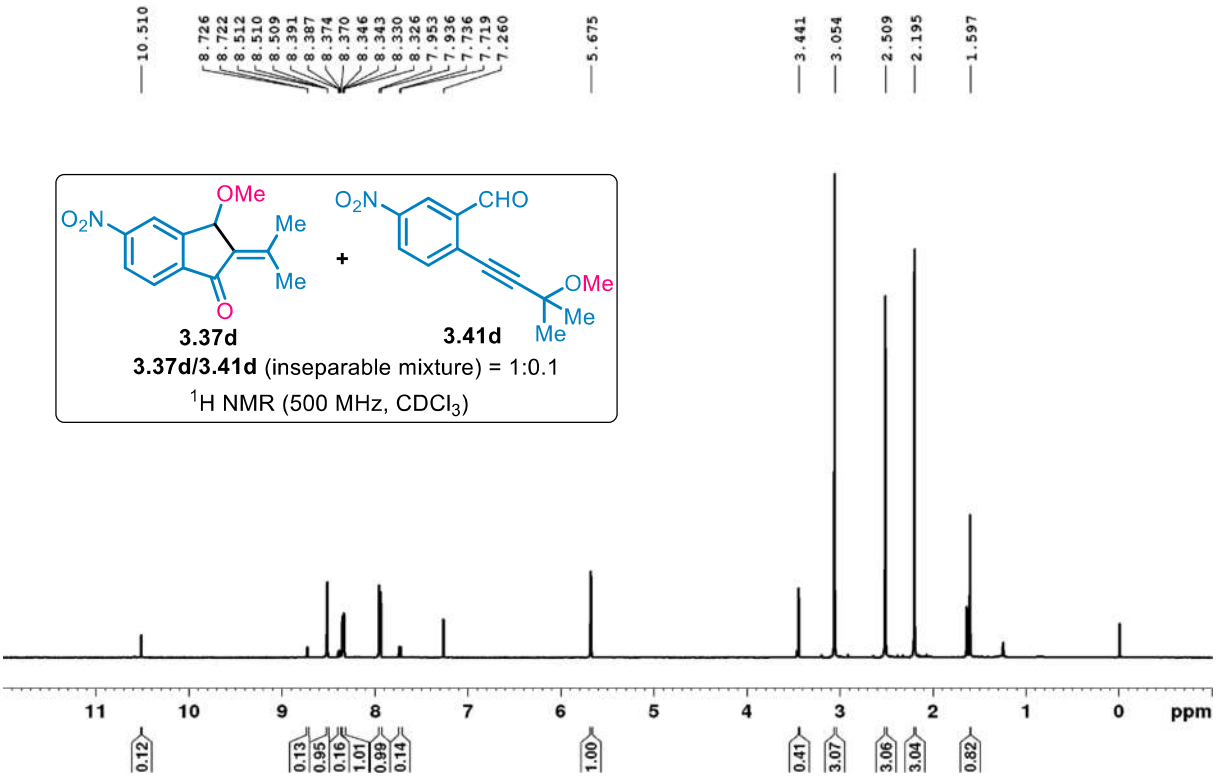
156.04
146.96
140.26
134.20
130.15
129.42
125.94
123.36
77.31
77.00
76.68
76.15
50.88
23.84
21.07
OMe
Me
Me
O
3.37a
^{13}C {1H} NMR (100 MHz, CDCl$_3$)
200
180
160
140
120
100
80
60
40
20
0
ppm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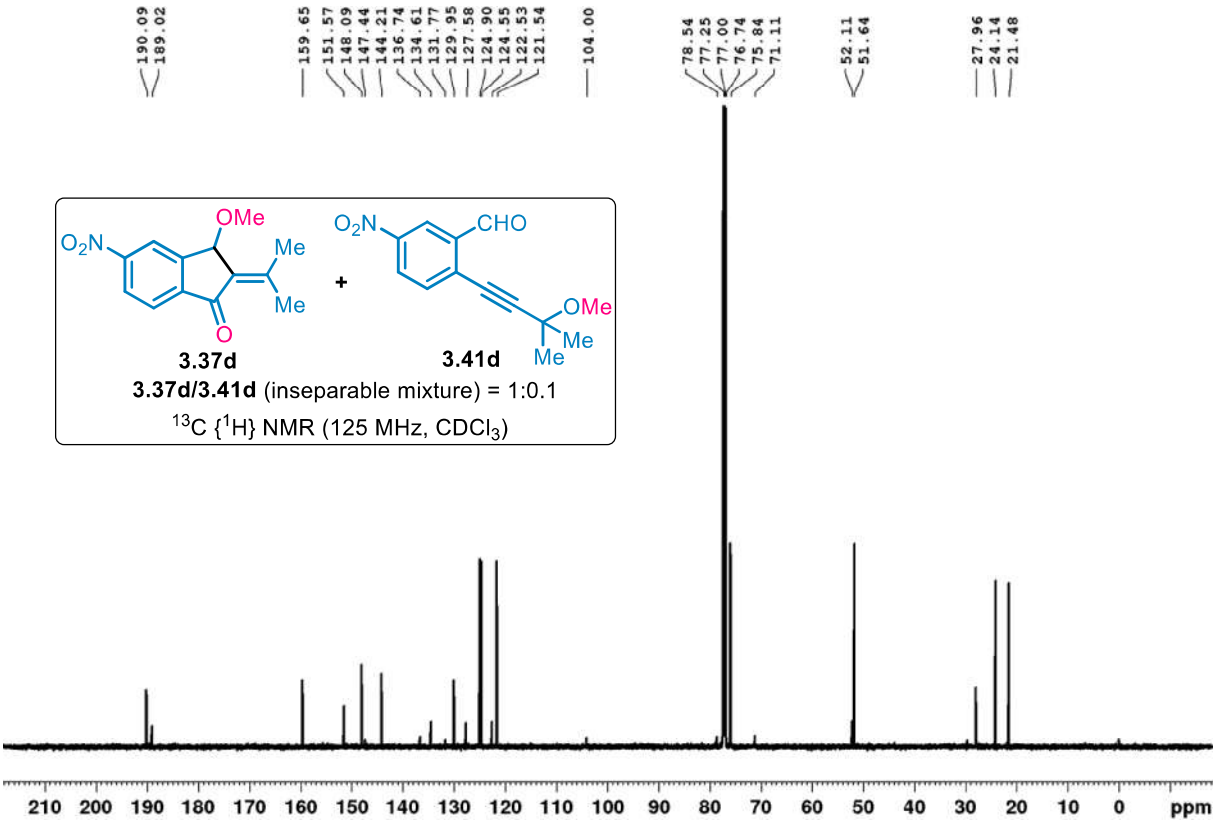
8.726
8.722
8.512
8.510
8.509
8.391
8.387
8.374
8.370
8.346
8.343
8.330
8.326
7.953
7.936
7.736
7.719
7.260
5.675
3.441
3.054
2.509
2.195
1.597
O2N
OMe
Me
Me
O
3.37d
+
O2N
CHO
OMe
Me
Me
3.41d
3.37d/3.41d (inseparable mixture) = 1:0.1
1H NMR (500 MHz, CDCl3)
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.12
0.13
0.95
0.16
1.01
0.99
0.14
1.00
0.41
3.07
3.06
3.04
0.82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189.02
159.65
151.57
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147.44
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136.74
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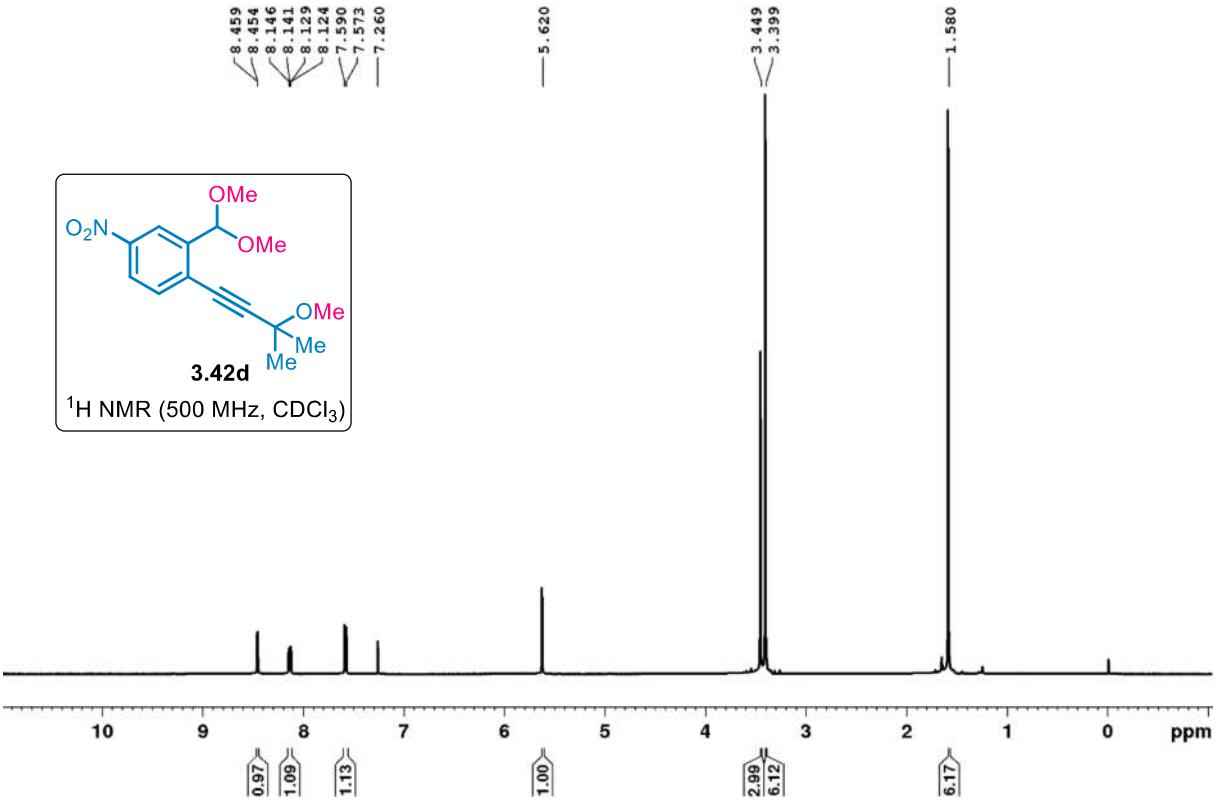
124.90
124.55
122.53
121.54
104.00
78.54
77.25
77.00
76.74
75.84
71.11
52.11
51.64
27.96
24.14
21.48
O2N
OMe
Me
Me
O
3.37d
+
O2N
CHO
OMe
Me
Me
3.41d
3.37d/3.41d (inseparable mixture) = 1:0.1
13C {1H} NMR (125 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm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7.260
5.620
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3.399
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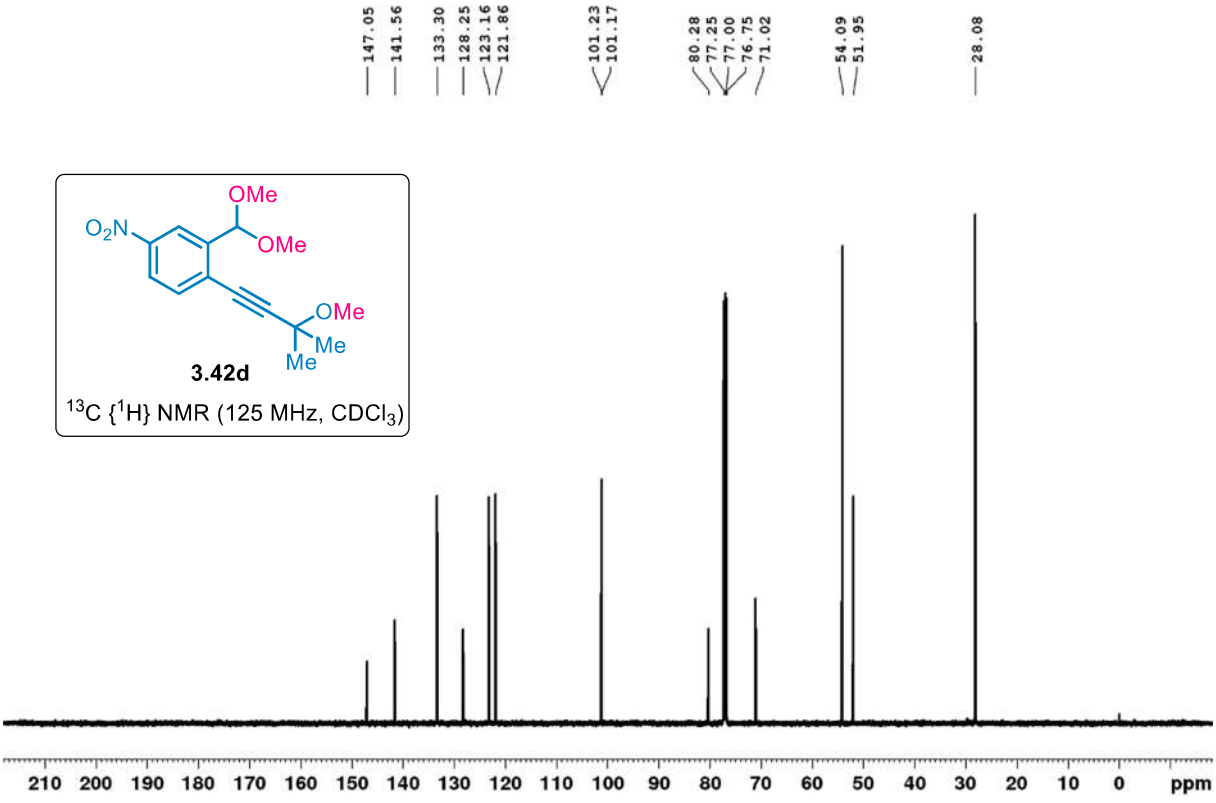
OMe
O2N
OMe
OMe
Me
Me
3.42d
1H NMR (500 MHz, CDCl3)
10
9
8
7
6
5
4
3
2
1
0
ppm
0.97
1.09
1.13
1.00
2.99
6.12
6.17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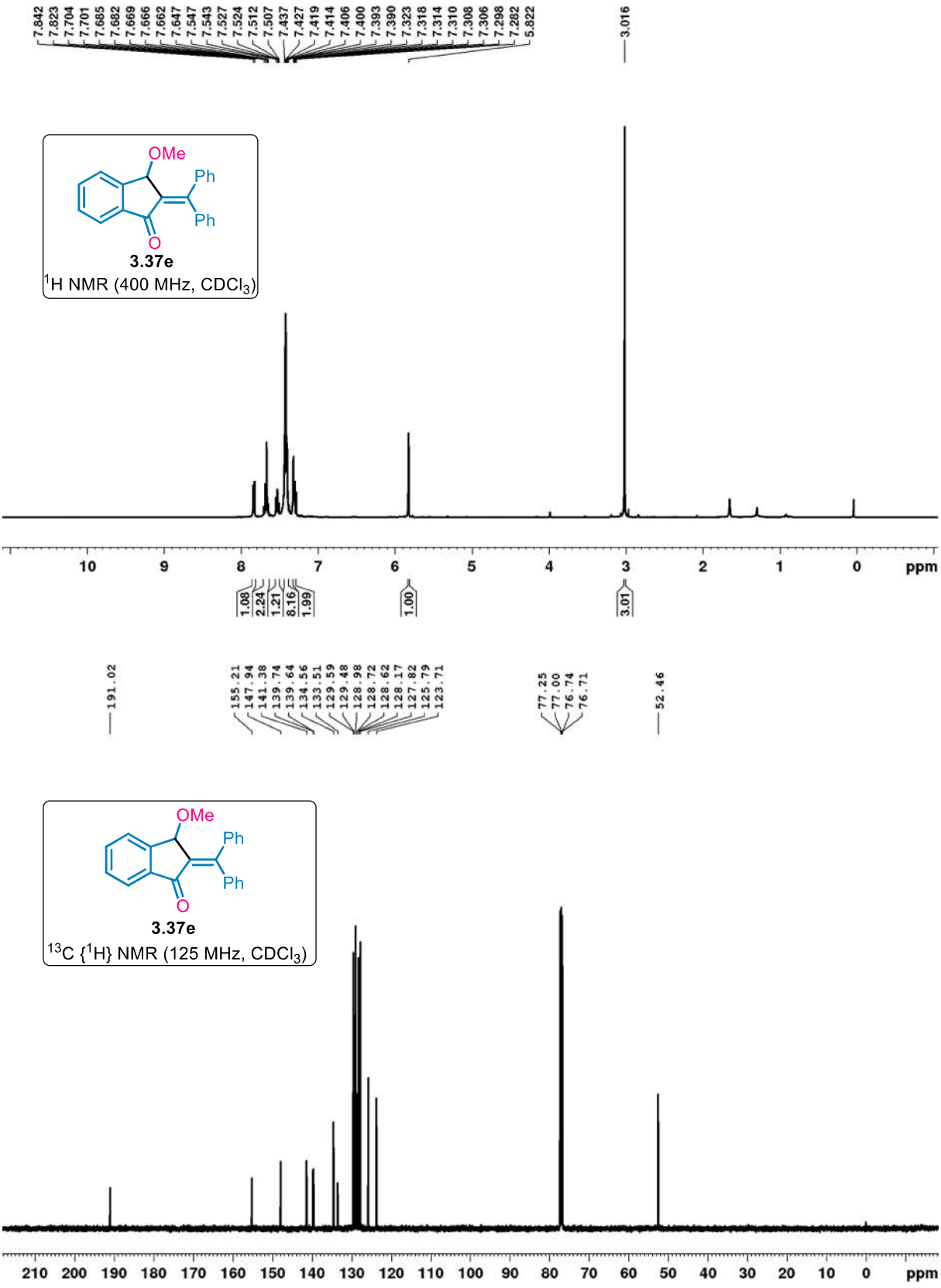
141.56
133.30
128.25
123.16
121.86
101.23
101.17
80.28
77.25
77.00
76.75
71.02
54.09
51.95
28.08
OMe
O2N
OMe
OMe
Me
Me
3.42d
13C {1H} NMR (125 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm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7.512
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7.437
7.427
7.419
7.414
7.406
7.400
7.393
7.390
7.323
7.318
7.314
7.310
7.308
7.306
7.298
7.282
5.822
3.016
OMe
Ph
Ph
O
3.37e
1H NMR (400 MHz, CDCl3)
10
9
8
7
6
5
4
3
2
1
0
ppm
1.08
2.24
1.21
8.16
1.99
1.00
3.01
191.02
155.21
147.94
141.38
139.74
139.64
134.56
133.51
129.59
129.48
128.98
128.72
128.62
128.17
127.82
125.79
123.71
77.25
77.00
76.74
76.71
52.46
OMe
Ph
Ph
O
3.37e
13C {1H} NMR (125 MHz, CDCl3)
210
200
190
180
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150
140
130
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110
100
90
80
70
60
50
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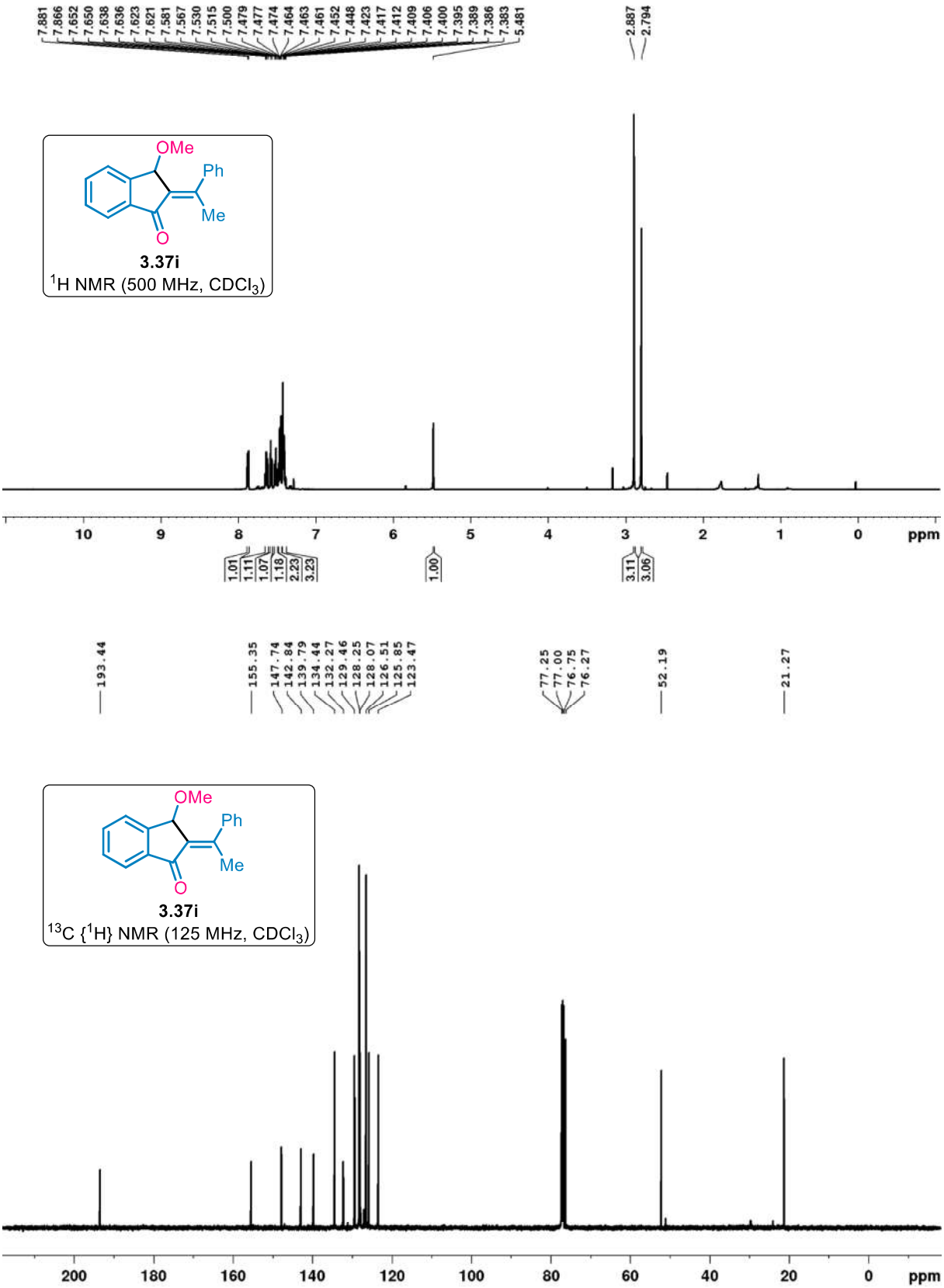
20
10
0
ppm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7.636
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7.567
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7.515
7.500
7.479
7.477
7.474
7.464
7.463
7.461
7.452
7.448
7.423
7.417
7.412
7.409
7.406
7.400
7.395
7.389
7.386
7.383
5.481
2.887
2.794
OMe
Ph
Me
O
3.37i
^{1}H NMR (500 MHz, CDCl$_3$)
10
9
8
7
6
5
4
3
2
1
0
ppm
1.01
1.11
1.07
1.18
2.23
3.23
1.00
3.11
3.06
193.44
155.35
147.74
142.84
139.79
134.44
132.27
129.46
128.25
128.07
126.51
125.85
123.47
77.25
77.00
76.75
76.27
52.19
21.27
OMe
Ph
Me
O
3.37i
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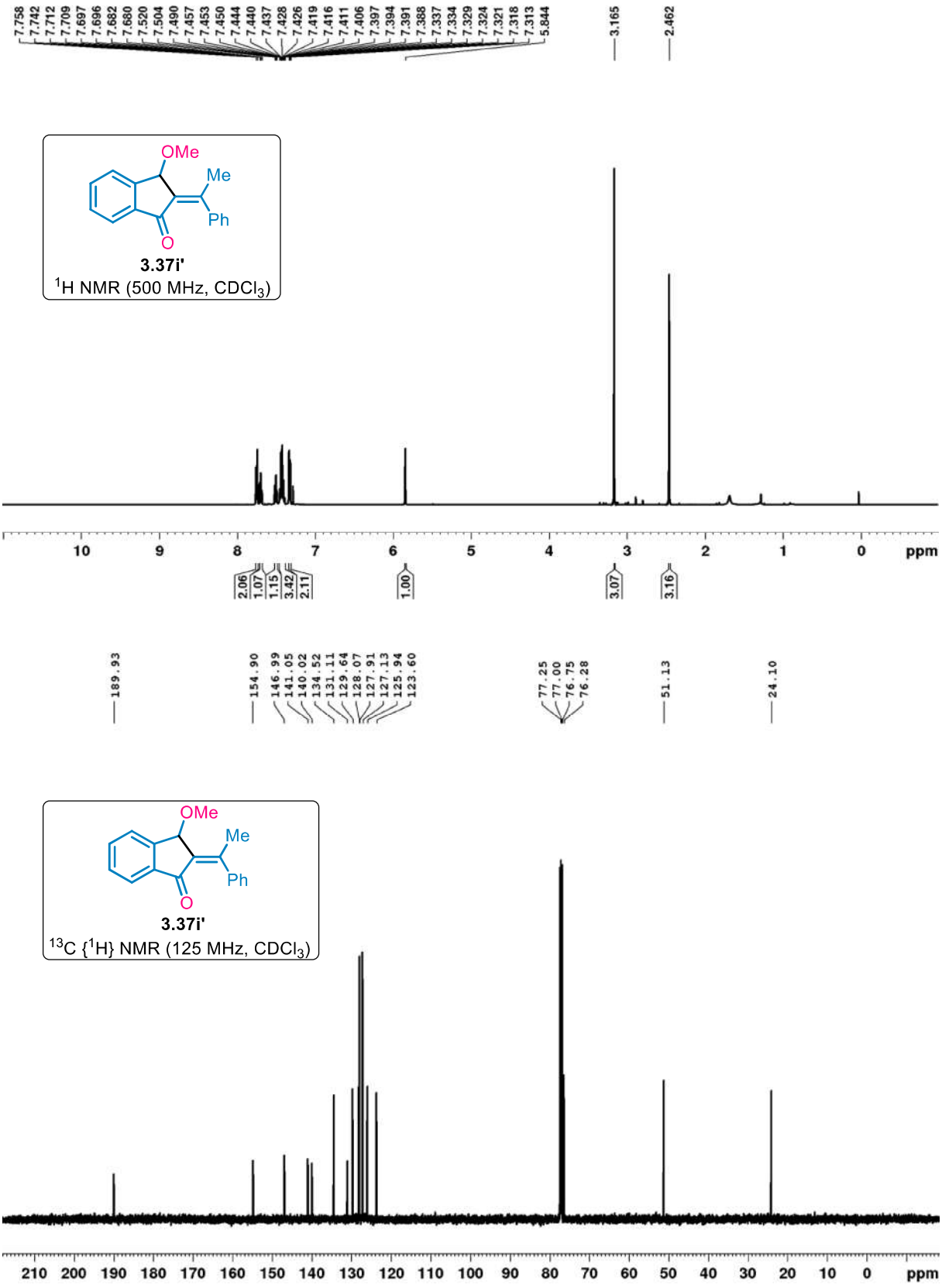
200
180
160
140
120
100
80
60
40
20
0
ppm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7.490
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7.450
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7.428
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7.318
7.313
5.844
3.165
2.462
OMe
Me
Ph
O
3.37i'
1H NMR (500 MHz, CDCl3)
10 9 8 7 6 5 4 3 2 1 0 ppm
2.06
1.07
1.15
3.42
2.11
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128.07
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125.94
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77.25
77.00
76.75
76.28
51.13
24.10
OMe
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Ph
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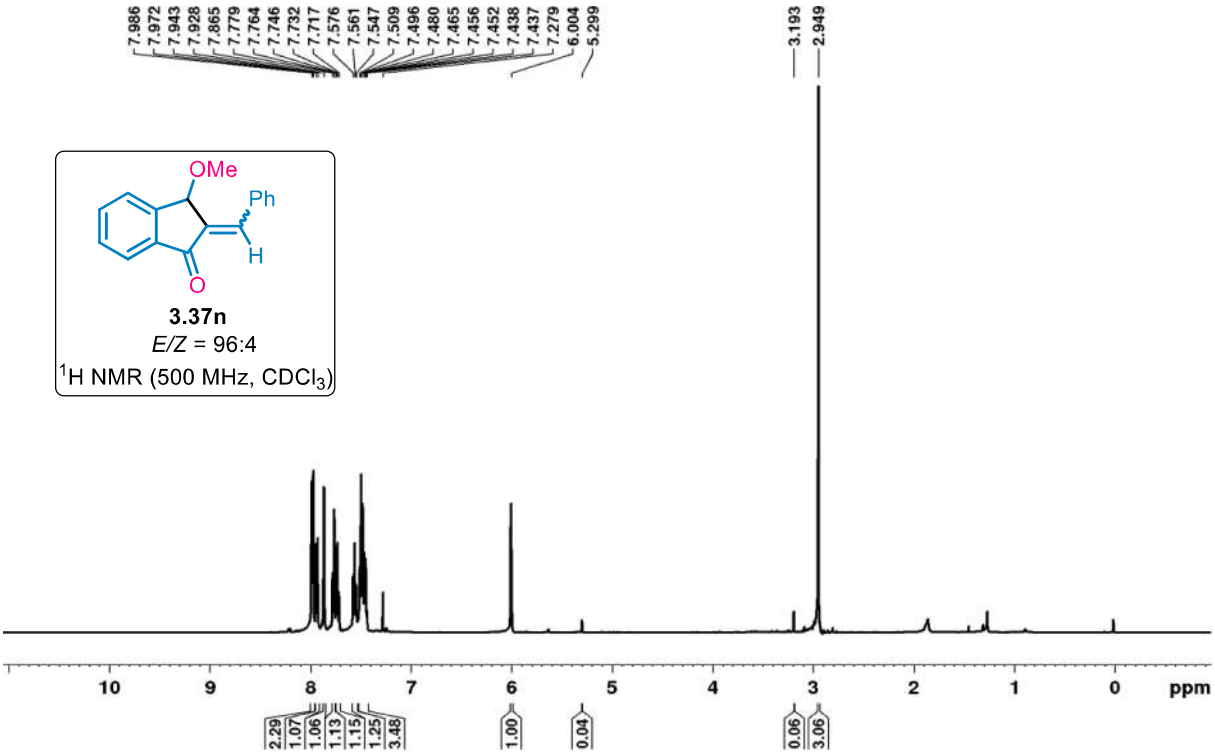
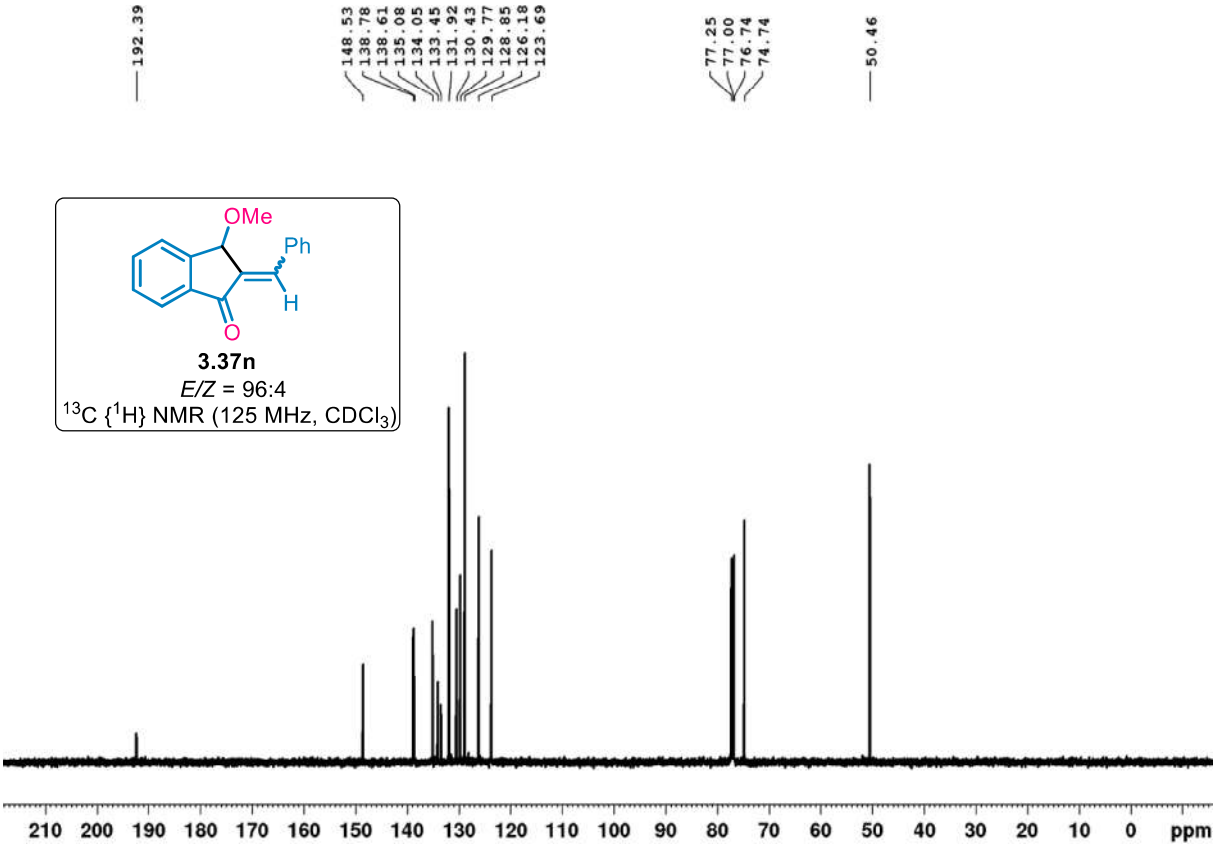
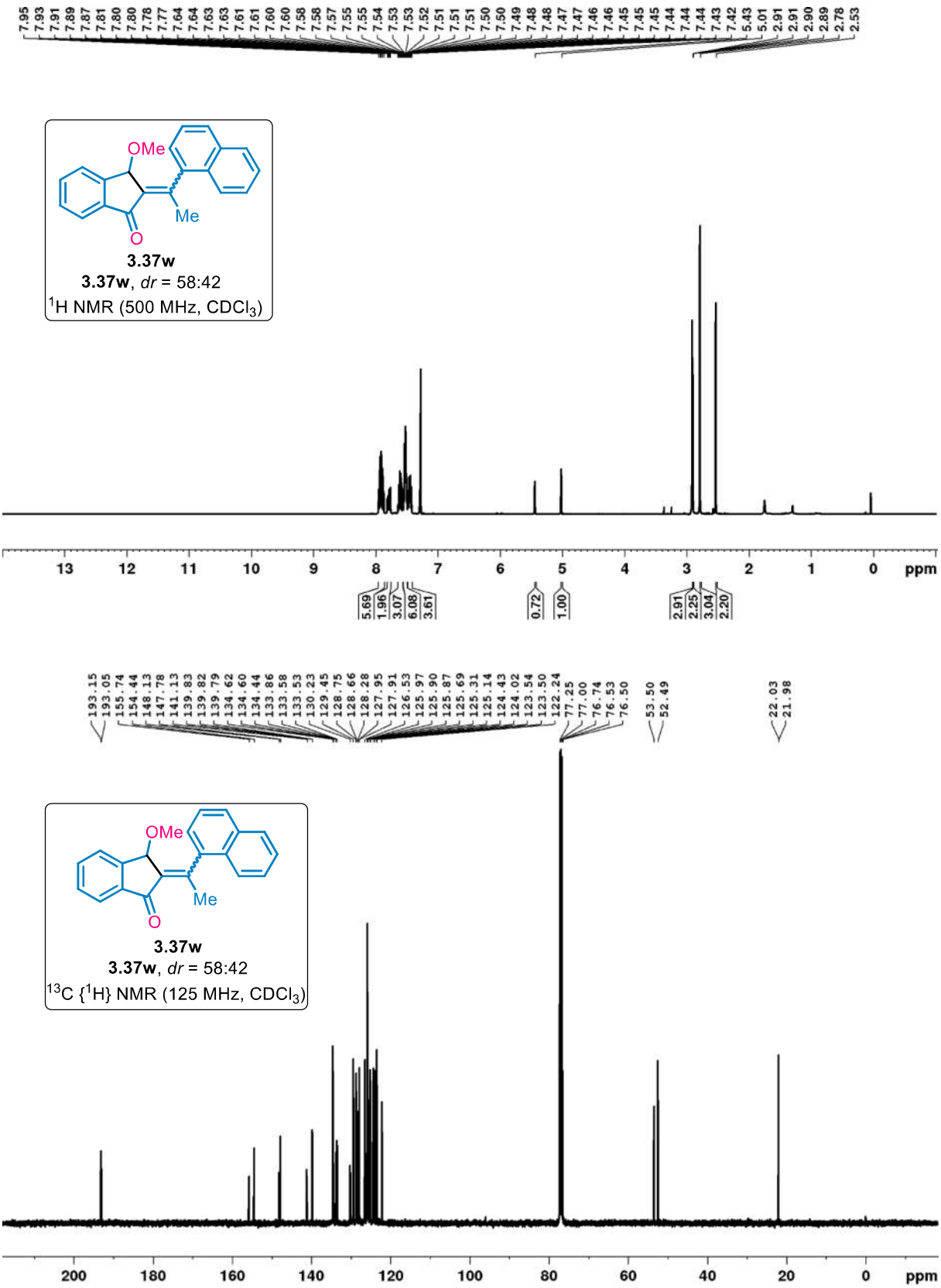
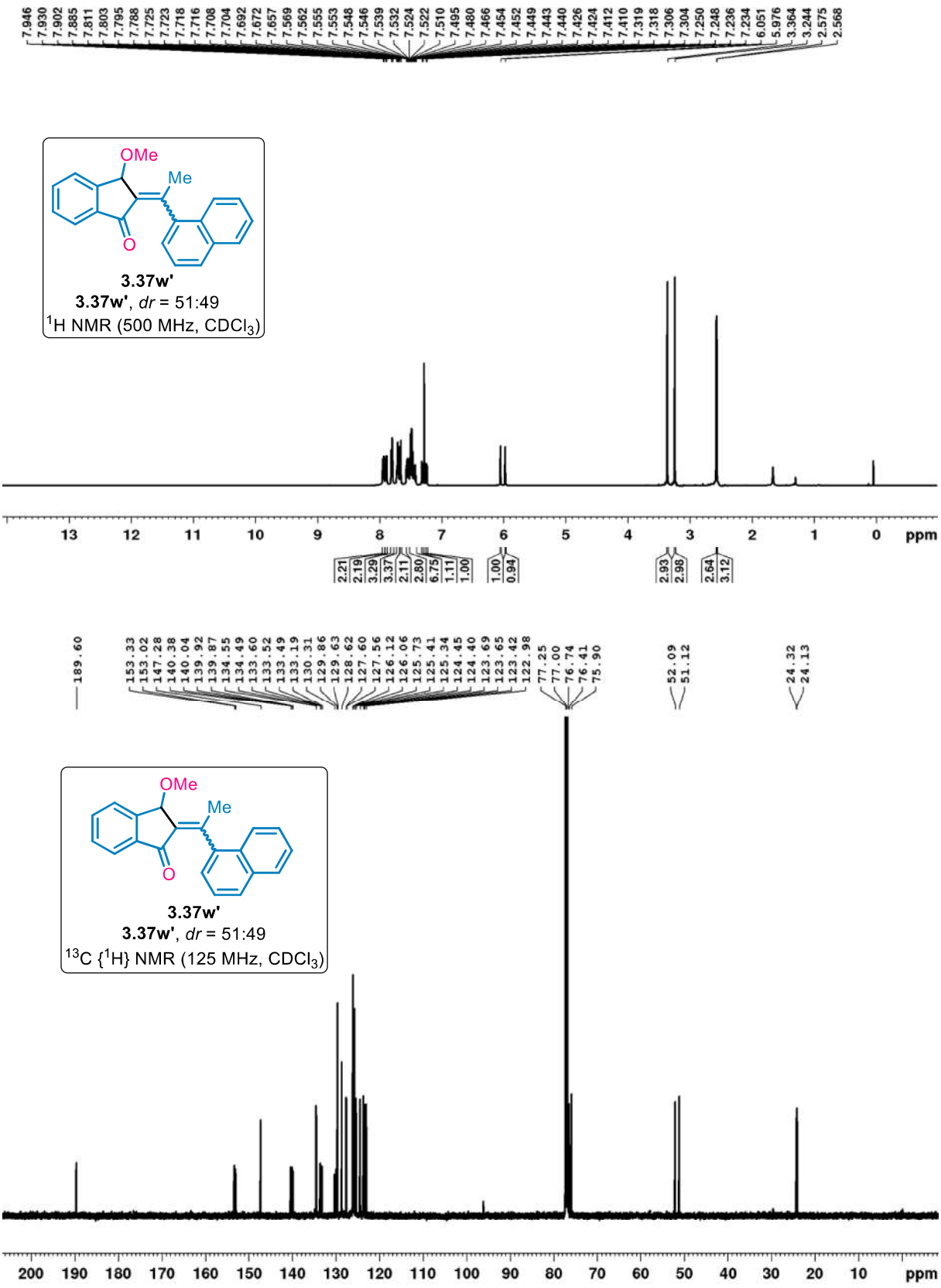
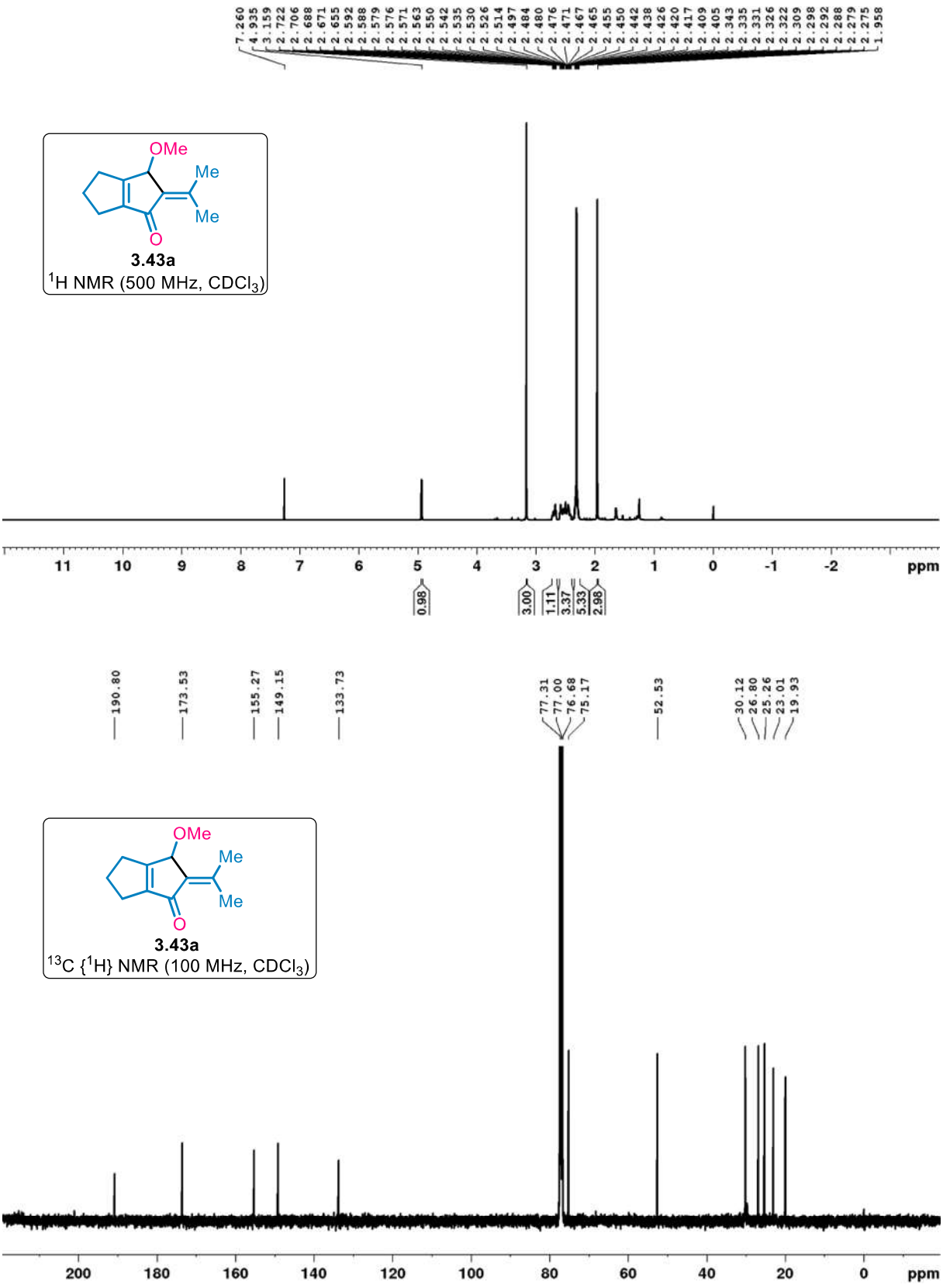
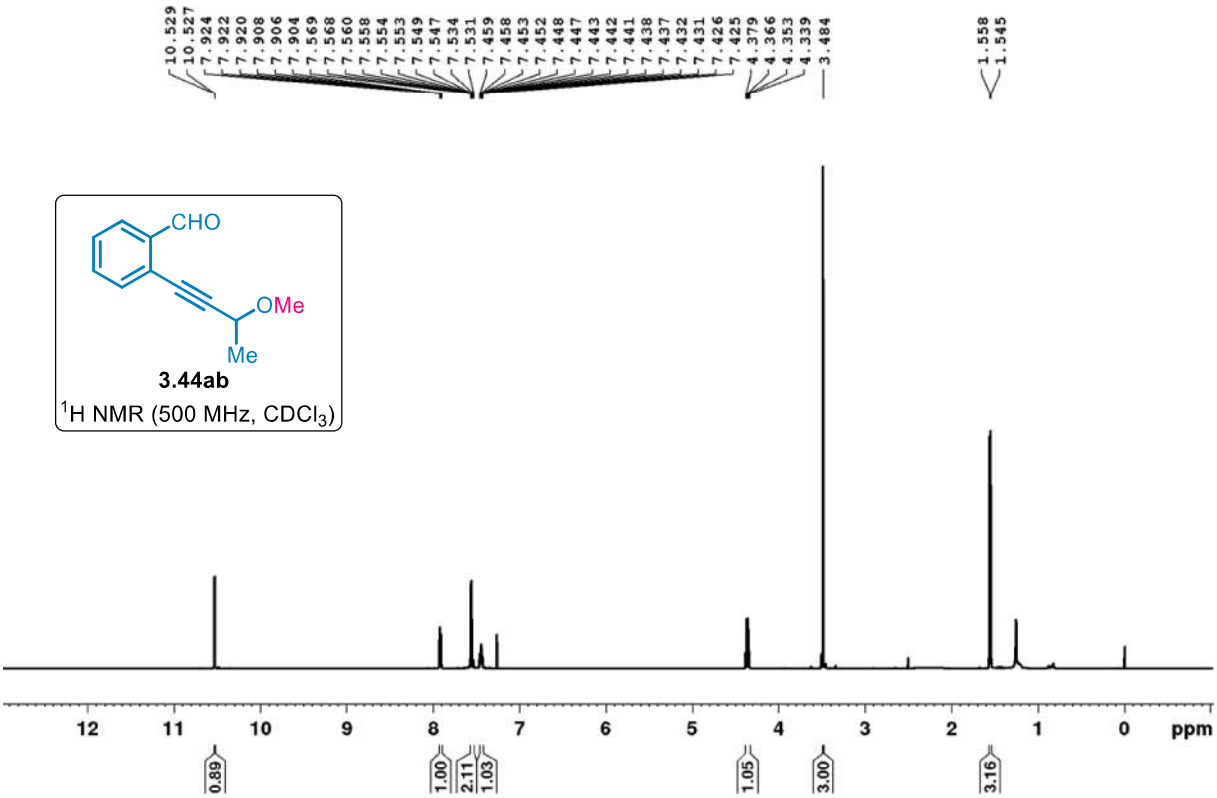

7.986
7.972
7.943
7.928
7.865
7.779
7.764
7.746
7.732
7.717
7.576
7.561
7.547
7.509
7.496
7.480
7.465
7.456
7.452
7.438
7.437
7.279
6.004
5.299
3.193
2.949
OMe
Ph
H
O
3.37n
E/Z = 96:4
1H NMR (500 MHz, CDCl3)
10
9
8
7
6
5
4
3
2
1
0
ppm
2.29
1.07
1.06
1.13
1.15
1.25
3.48
1.00
0.04
0.06
3.06

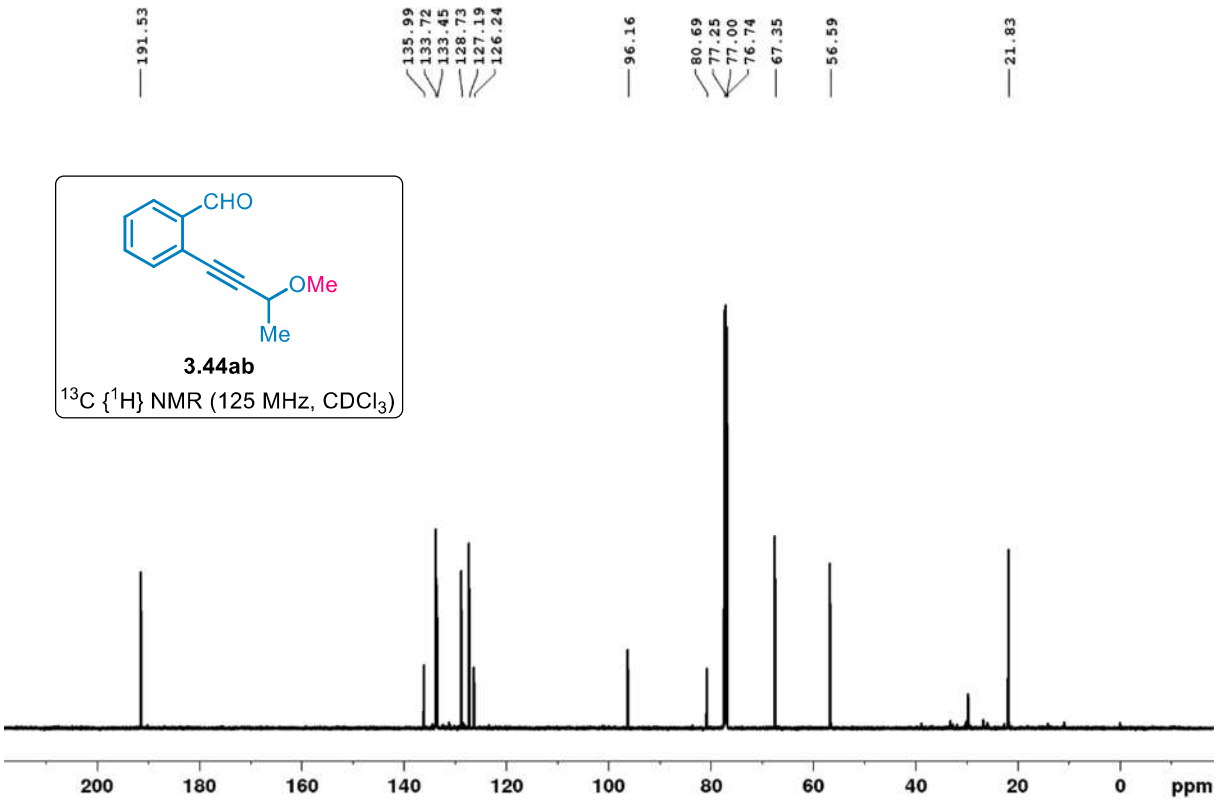

192.39
148.53
138.78
138.61
135.08
134.05
133.45
131.92
130.43
129.77
128.85
126.18
123.69
77.25
77.00
76.74
74.74
50.46
OMe
Ph
H
O
3.37n
E/Z = 96:4
13C {1H} NMR (125 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

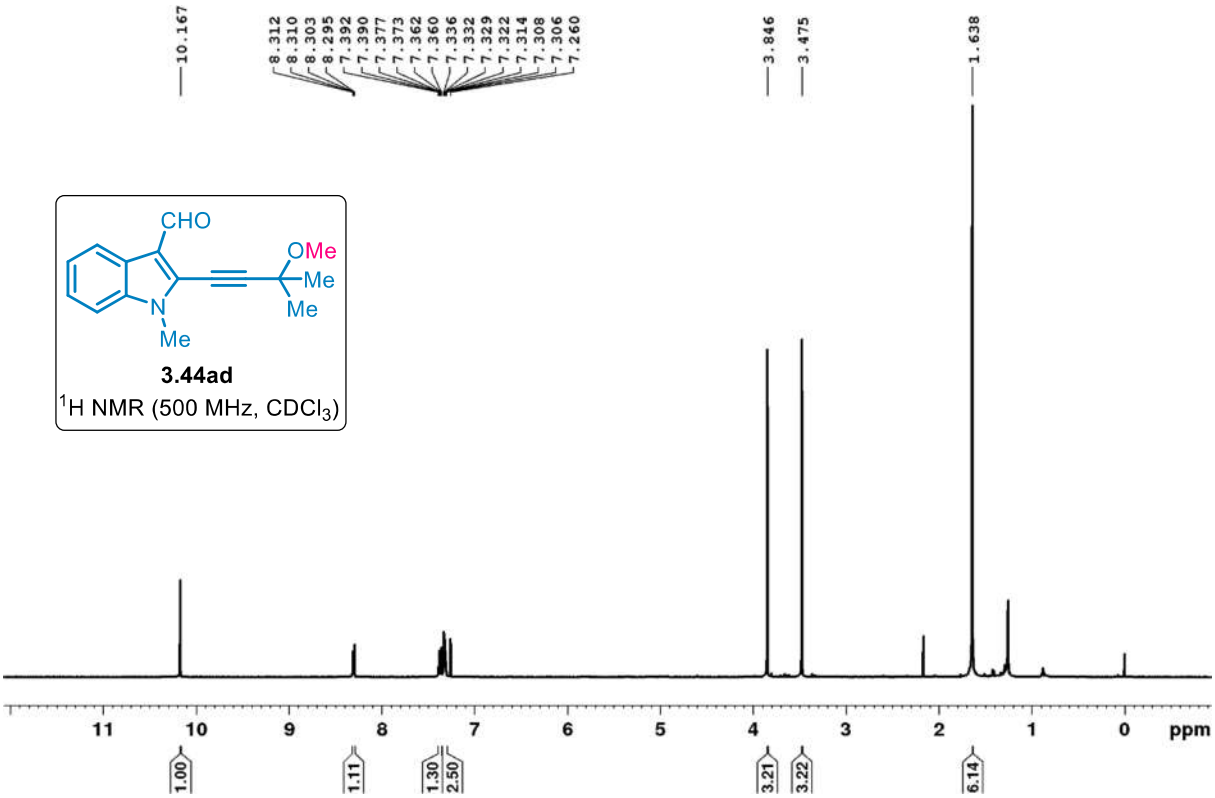

7.95 7.93 7.91 7.89 7.87 7.81 7.80 7.80 7.78 7.77 7.64 7.64 7.63 7.63 7.61 7.61 7.60 7.60 7.58 7.58 7.57 7.55 7.55 7.54 7.53 7.53 7.52 7.51 7.51 7.51 7.50 7.50 7.49 7.48 7.48 7.47 7.47 7.46 7.46 7.45 7.45 7.44 7.44 7.44 7.43 7.42 5.43 5.01 2.91 2.91 2.90 2.89 2.78 2.53
OMe
Me
O
3.37w
3.37w, dr = 58:42
1H NMR (500 MHz, CDCl3)
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
5.69 1.96 3.07 6.08 3.61 0.72 1.00 2.91 2.25 3.04 2.20
193.15 193.05 155.74 154.44 148.13 147.78 141.13 139.83 139.82 139.79 134.62 134.60 134.44 133.86 133.58 133.53 130.23 129.45 128.75 128.66 128.28 127.95 127.91 126.53 125.97 125.90 125.87 125.69 125.31 125.14 124.43 124.02 123.54 123.50 122.24 77.25 77.00 76.74 76.53 76.50 53.50 52.49 22.03 21.98
OMe
Me
O
3.37w
3.37w, dr = 58:42
13C {1H} NMR (125 MHz, CDCl3)
200 180 160 140 120 100 80 60 40 20 0 ppm

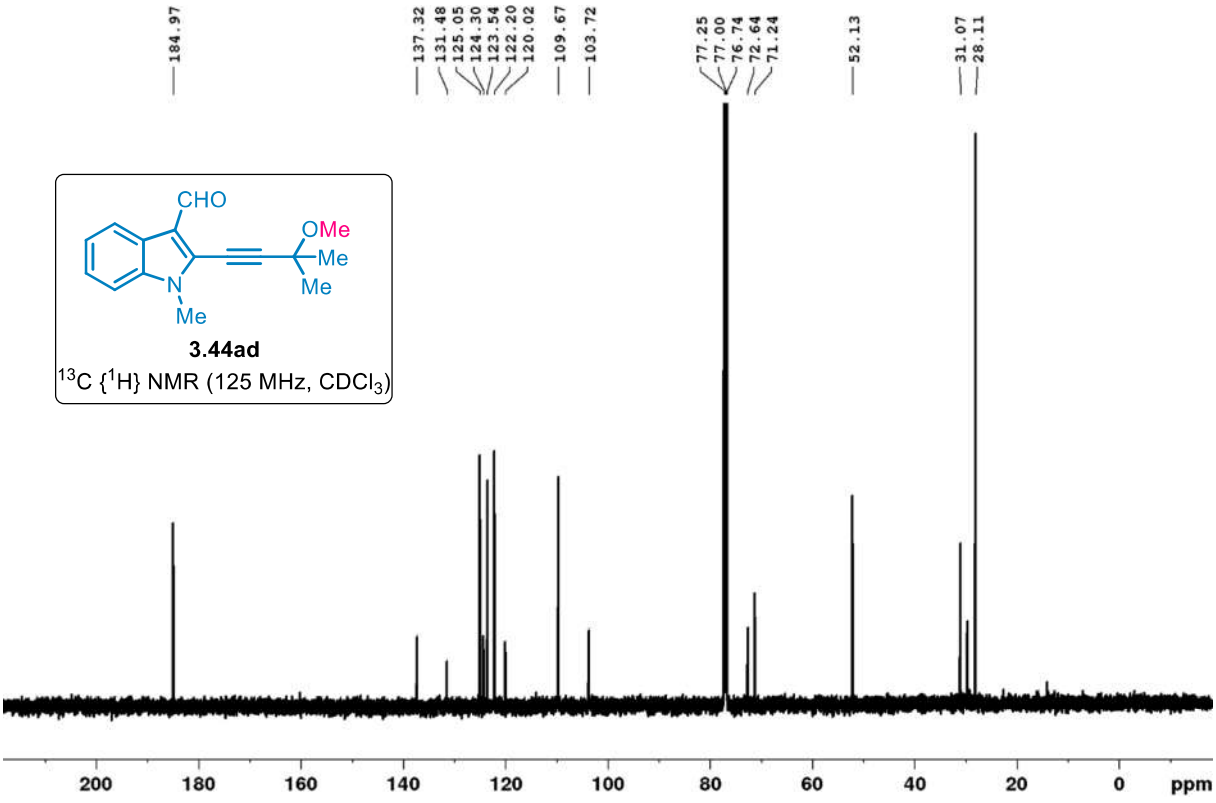

7.946 7.930 7.902 7.885 7.811 7.803 7.795 7.788 7.725 7.723 7.718 7.716 7.708 7.704 7.692 7.672 7.657 7.569 7.562 7.555 7.553 7.548 7.546 7.539 7.532 7.524 7.522 7.510 7.495 7.480 7.466 7.454 7.452 7.449 7.443 7.440 7.426 7.424 7.412 7.410 7.319 7.318 7.306 7.304 7.250 7.248 7.236 7.234 6.051 5.976 3.364 3.244 2.575 2.568
OMe
Me
O
3.37w'
3.37w', dr = 51:49
1H NMR (500 MHz, CDCl3)
13 12 11 10 9 8 7 6 5 4 3 2 1 0 ppm
2.21 2.19 3.29 3.37 2.11 2.80 6.75 1.11 1.00 1.00 0.94 2.93 2.98 2.64 3.12
189.60 153.33 153.02 147.28 140.38 140.04 139.92 139.87 134.55 134.49 133.60 133.52 133.49 133.19 130.31 129.86 129.63 128.62 127.60 127.56 126.12 126.06 125.73 125.41 125.34 124.45 124.40 123.69 123.65 123.42 122.98 77.25 77.00 76.74 76.41 75.90 52.09 51.12 24.32 24.13
OMe
Me
O
3.37w'
3.37w', dr = 51:49
13C {1H} NMR (125 MHz, CDCl3)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

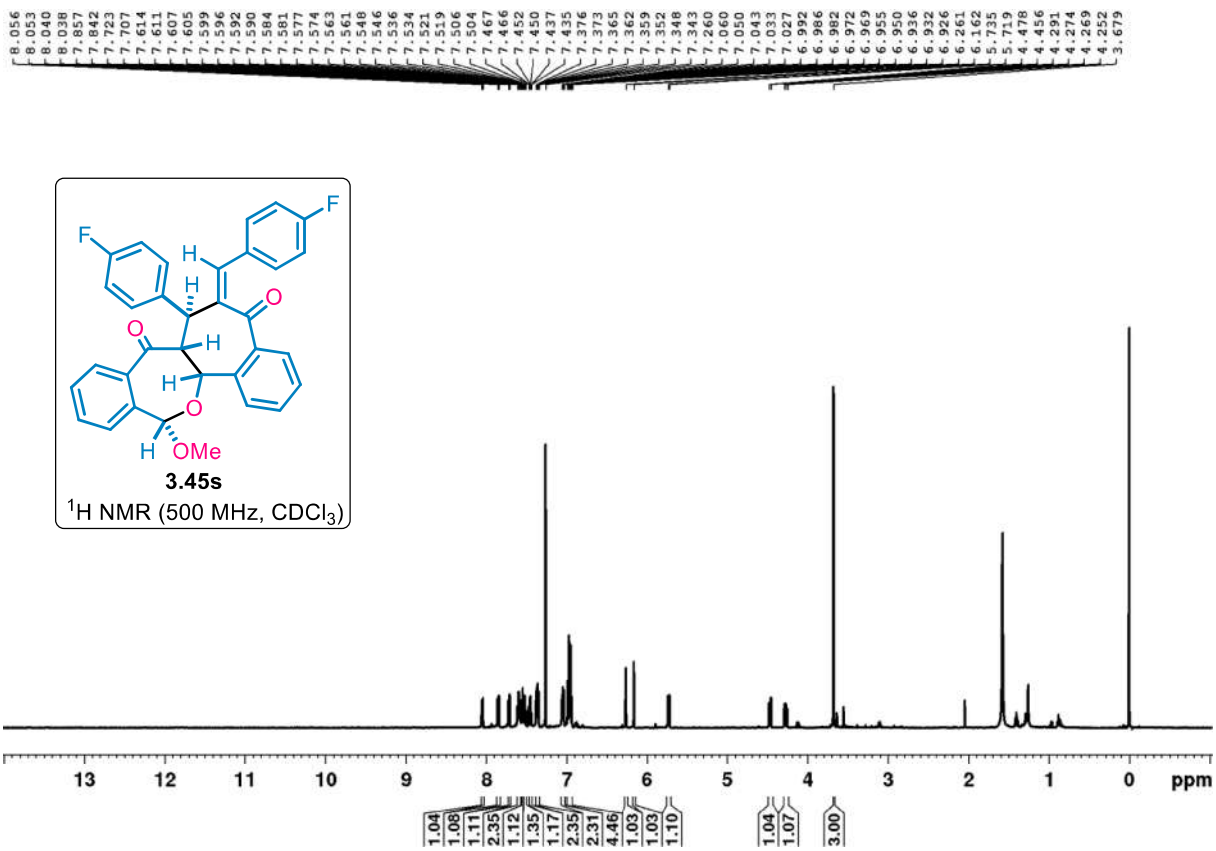

7.260
4.935
3.159
2.722
2.706
2.688
2.671
2.655
2.592
2.588
2.579
2.576
2.571
2.563
2.550
2.542
2.535
2.530
2.526
2.514
2.497
2.484
2.480
2.476
2.471
2.467
2.465
2.455
2.450
2.442
2.438
2.426
2.420
2.417
2.409
2.405
2.343
2.335
2.331
2.326
2.322
2.309
2.298
2.292
2.288
2.279
2.275
1.958
OMe
Me
Me
O
3.43a
1H NMR (500 MHz, CDCl3)
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
ppm
0.98
3.00
1.11
3.37
5.33
2.98
190.80
173.53
155.27
149.15
133.73
77.31
77.00
76.68
75.17
52.53
30.12
26.80
25.26
23.01
19.93
OMe
Me
Me
O
3.43a
13C {1H} NMR (100 MHz, CDCl3)
200
180
160
140
120
100
80
60
40
20
0
ppm

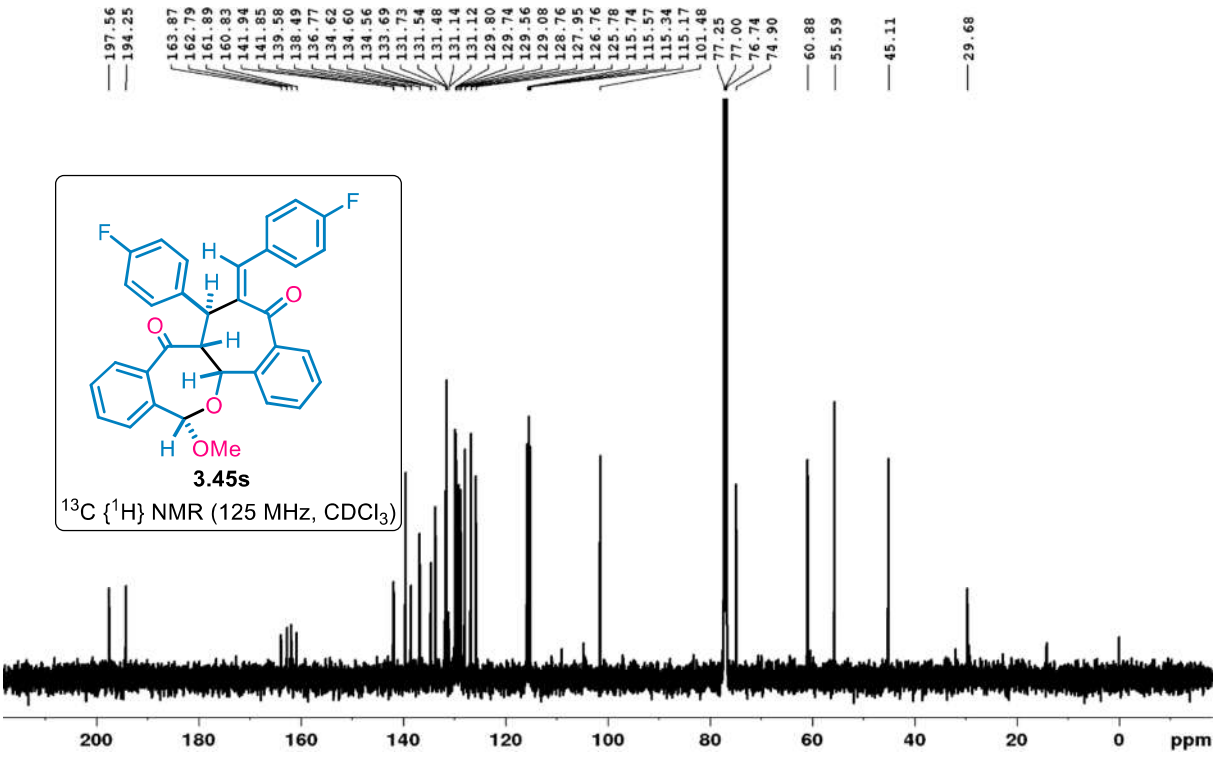

10.529
10.527
7.924
7.922
7.920
7.908
7.906
7.904
7.569
7.568
7.560
7.558
7.554
7.553
7.549
7.547
7.534
7.531
7.459
7.458
7.453
7.452
7.448
7.447
7.443
7.442
7.441
7.438
7.437
7.432
7.431
7.426
7.425
4.379
4.366
4.353
4.339
3.484
1.558
1.545
CHO
OMe
Me
3.44ab
^{1}H NMR (500 MHz, CDCl$_3$)
12
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.89
1.00
2.11
1.03
1.05
3.00
3.16

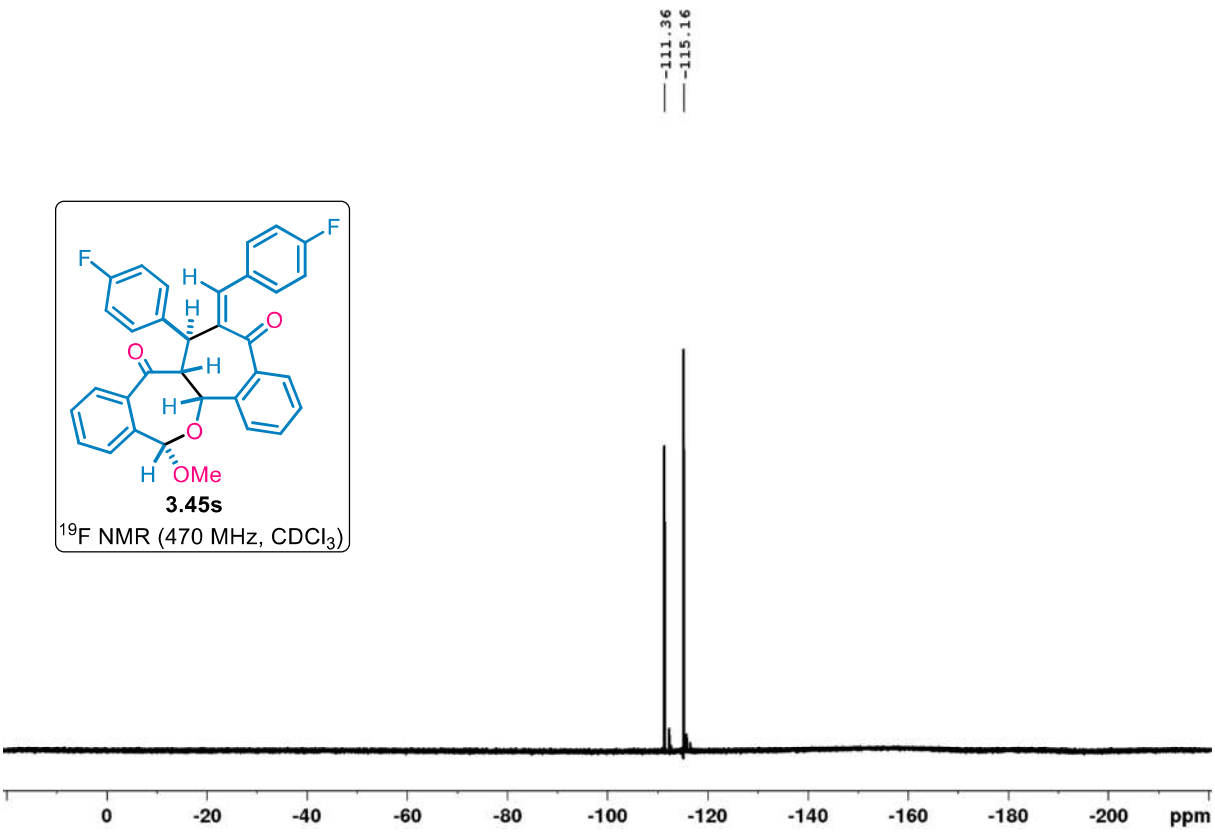

191.53
135.99
133.72
133.45
128.73
127.19
126.24
96.16
80.69
77.25
77.00
76.74
67.35
56.59
21.83
CHO
OMe
Me
3.44ab
^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$)
200
180
160
140
120
100
80
60
40
20
0
ppm

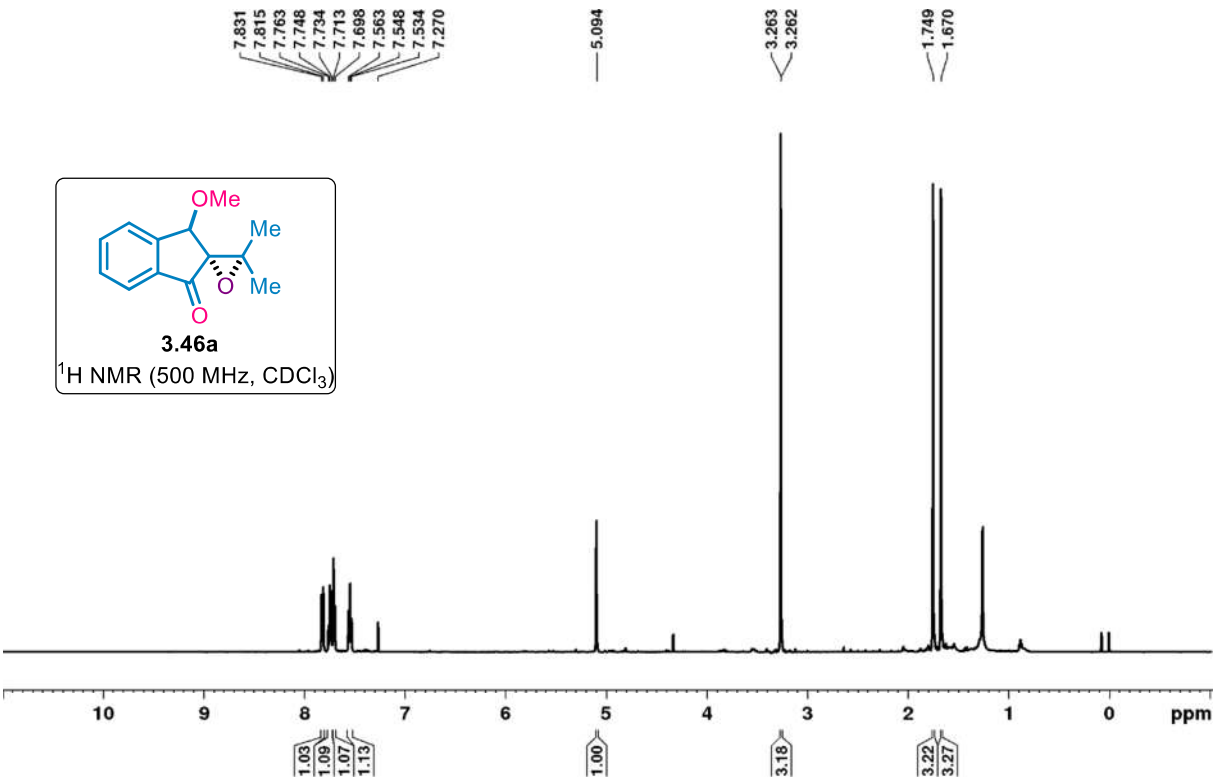

10.167
8.312
8.310
8.303
8.295
7.392
7.390
7.377
7.373
7.362
7.360
7.336
7.332
7.329
7.322
7.314
7.308
7.306
7.260
3.846
3.475
1.638
CHO
OMe
Me
Me
N
Me
3.44ad
1H NMR (500 MHz, CDCl3)
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.11
1.30
2.50
3.21
3.22
6.14

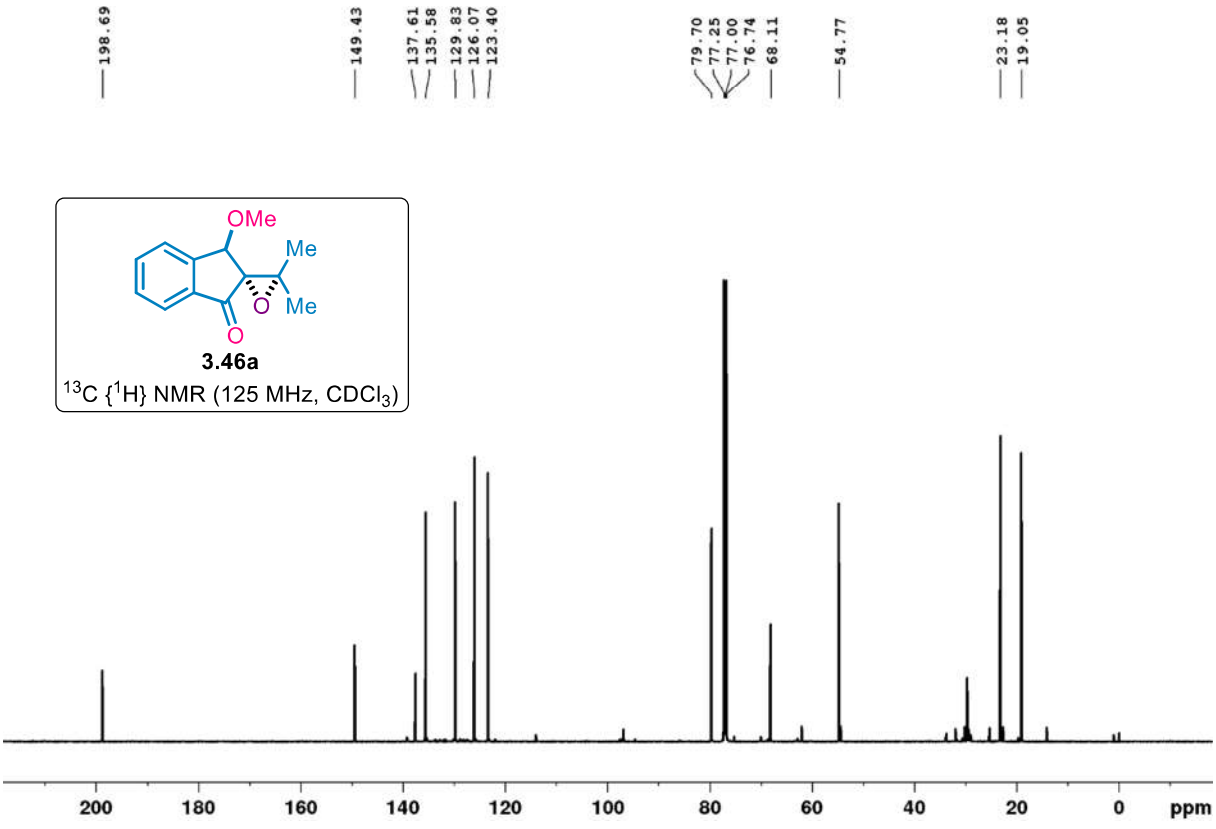

184.97
137.32
131.48
125.05
124.30
123.54
122.20
120.02
109.67
103.72
77.25
77.00
76.74
72.64
71.24
52.13
31.07
28.11
CHO
OMe
Me
Me
N
Me
3.44ad
13C {1H} NMR (125 MHz, CDCl3)
200
180
160
140
120
100
80
60
40
20
0
ppm

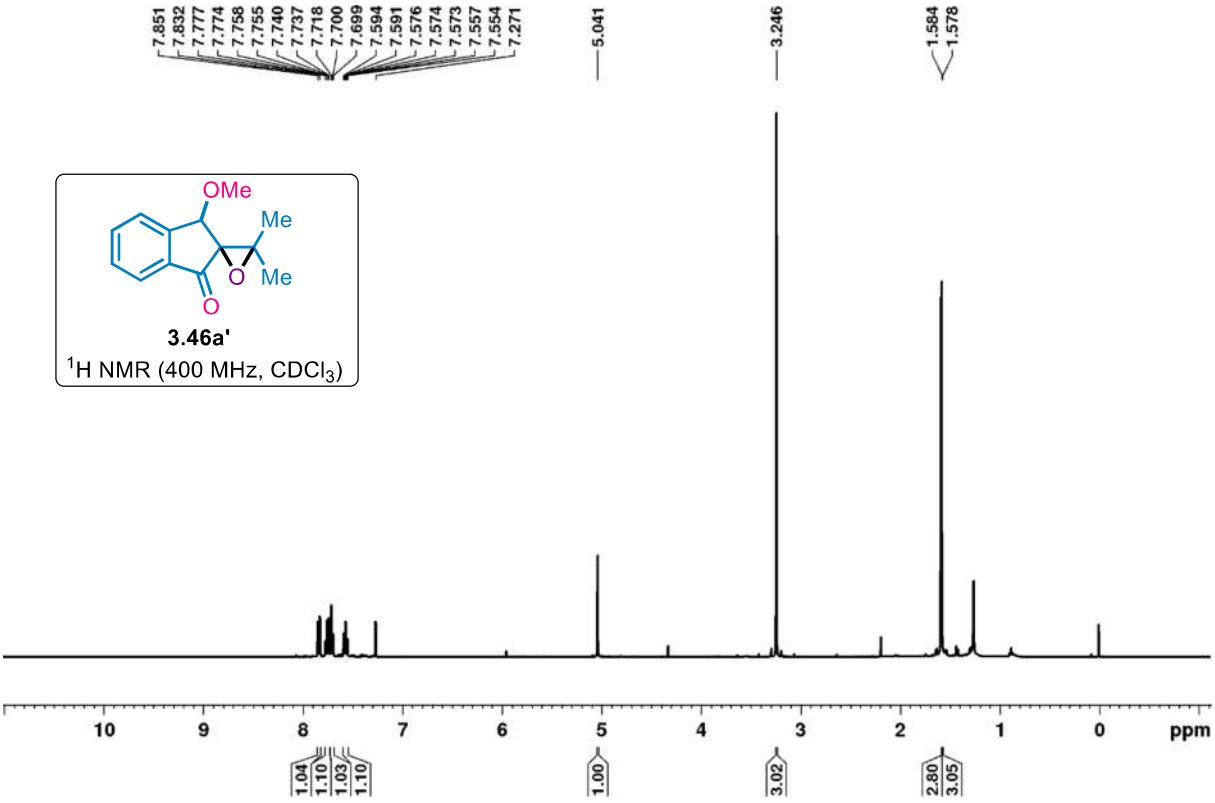

3.45s
^{1}H NMR (500 MHz, CDCl$_3$)
ppm

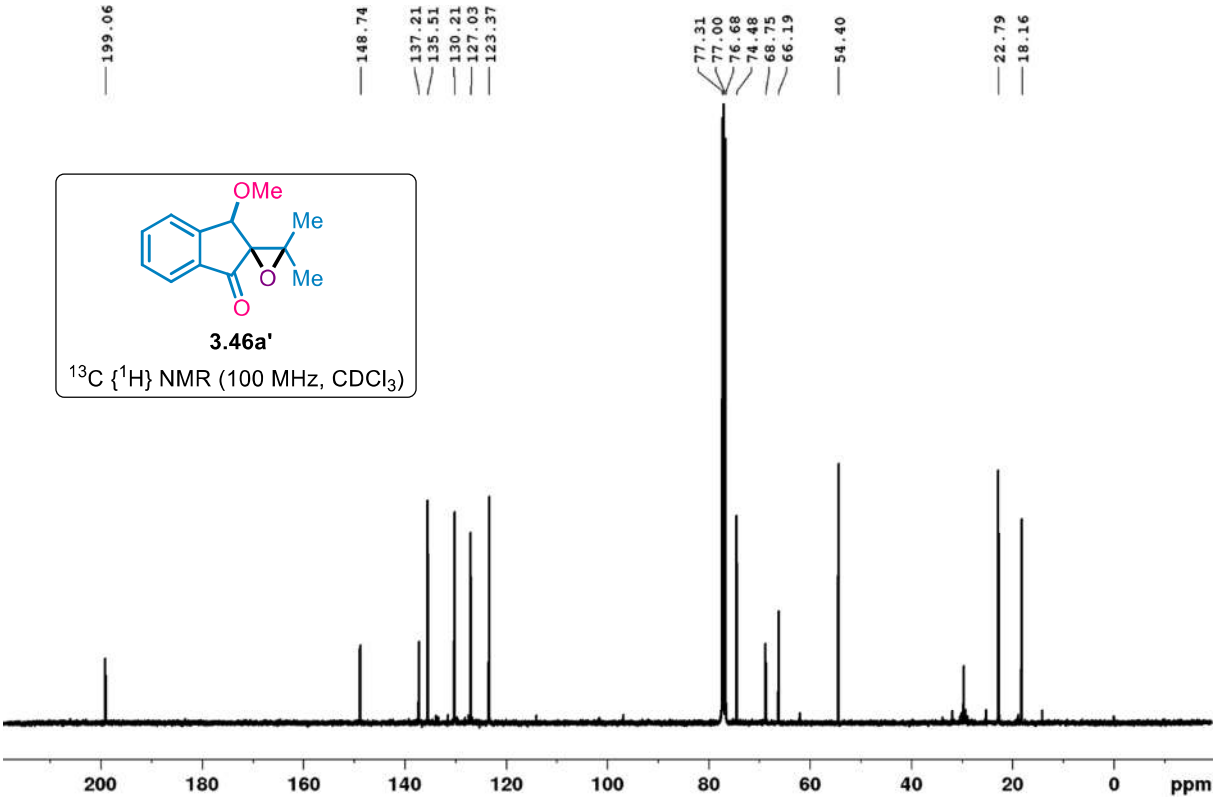

3.45s
^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$)
ppm

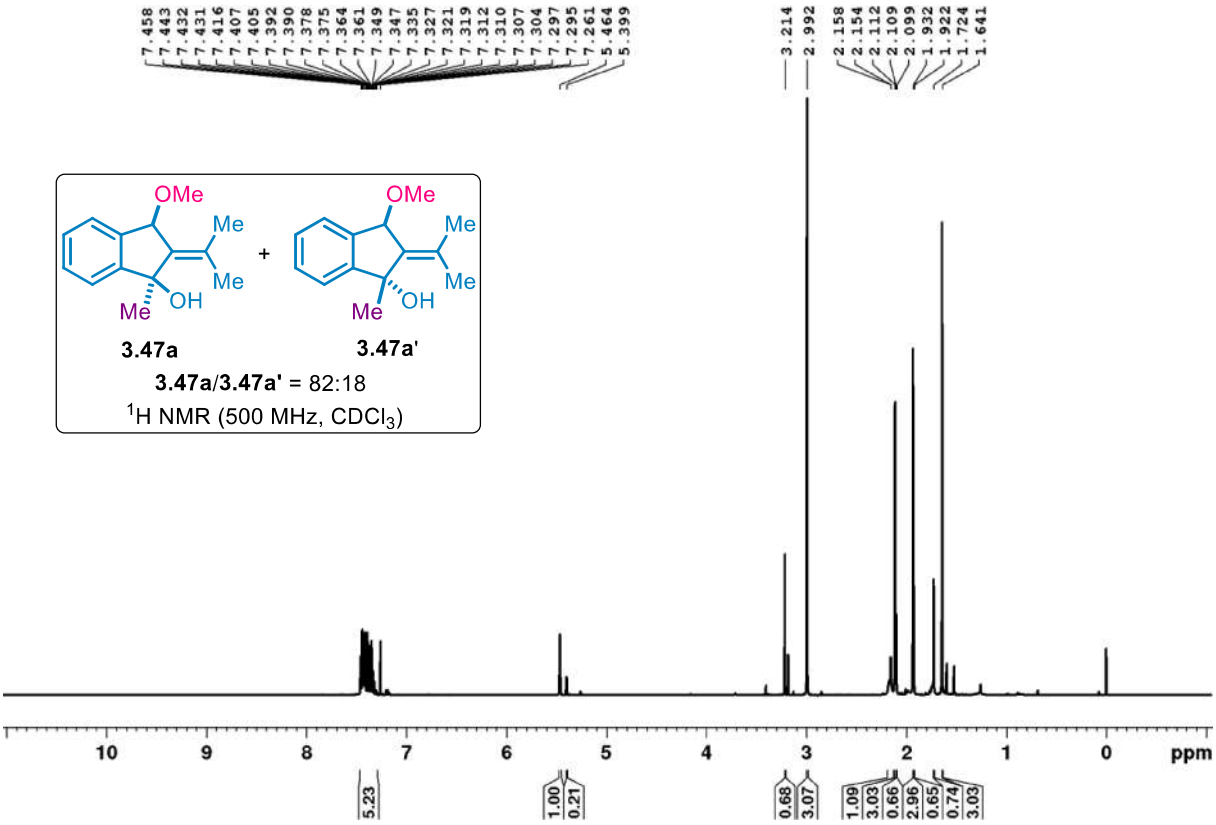

-111.36
-115.16
F
F
H
H
O
O
H
H
O
H
OMe
3.45s
19F NMR (470 MHz, CDCl3)
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
ppm

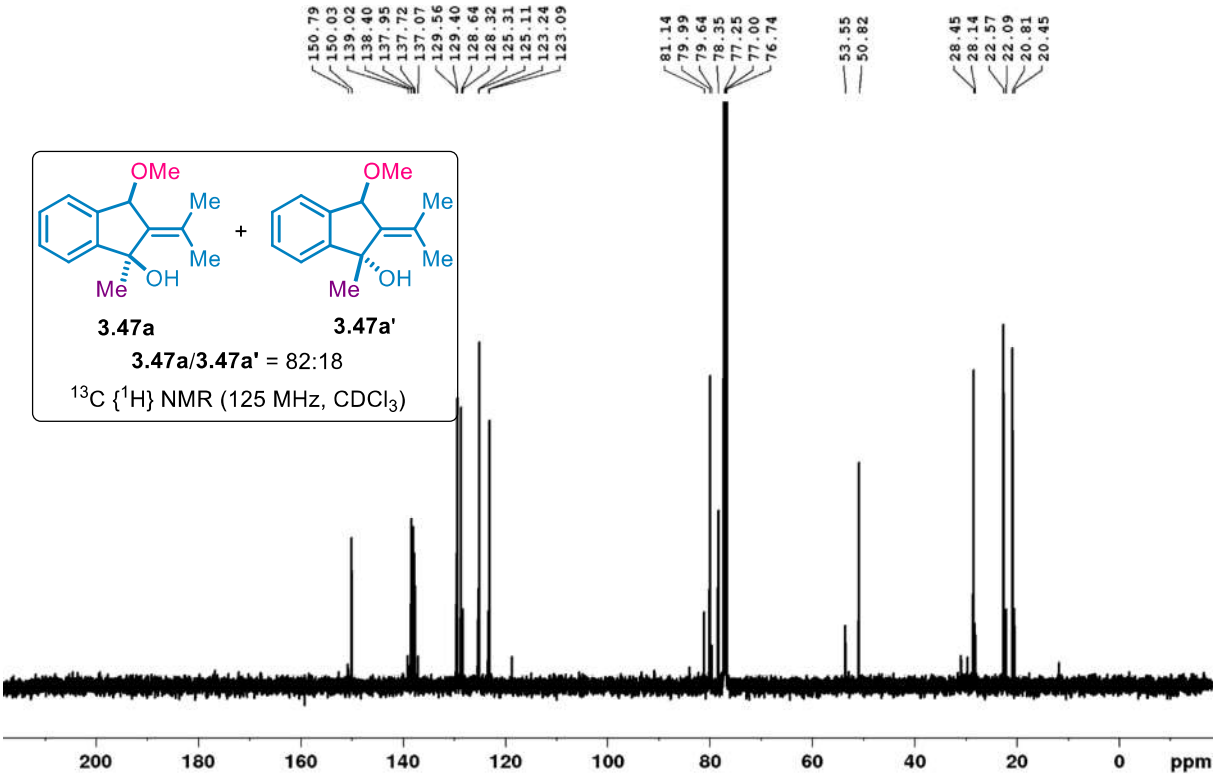

7.831
7.815
7.763
7.748
7.734
7.713
7.698
7.563
7.548
7.534
7.270
5.094
3.263
3.262
1.749
1.670
OMe
Me
O
Me
O
3.46a
^{1}H NMR (500 MHz, CDCl$_3$)
10
9
8
7
6
5
4
3
2
1
0
ppm
1.03
1.09
1.07
1.13
1.00
3.18
3.22
3.27

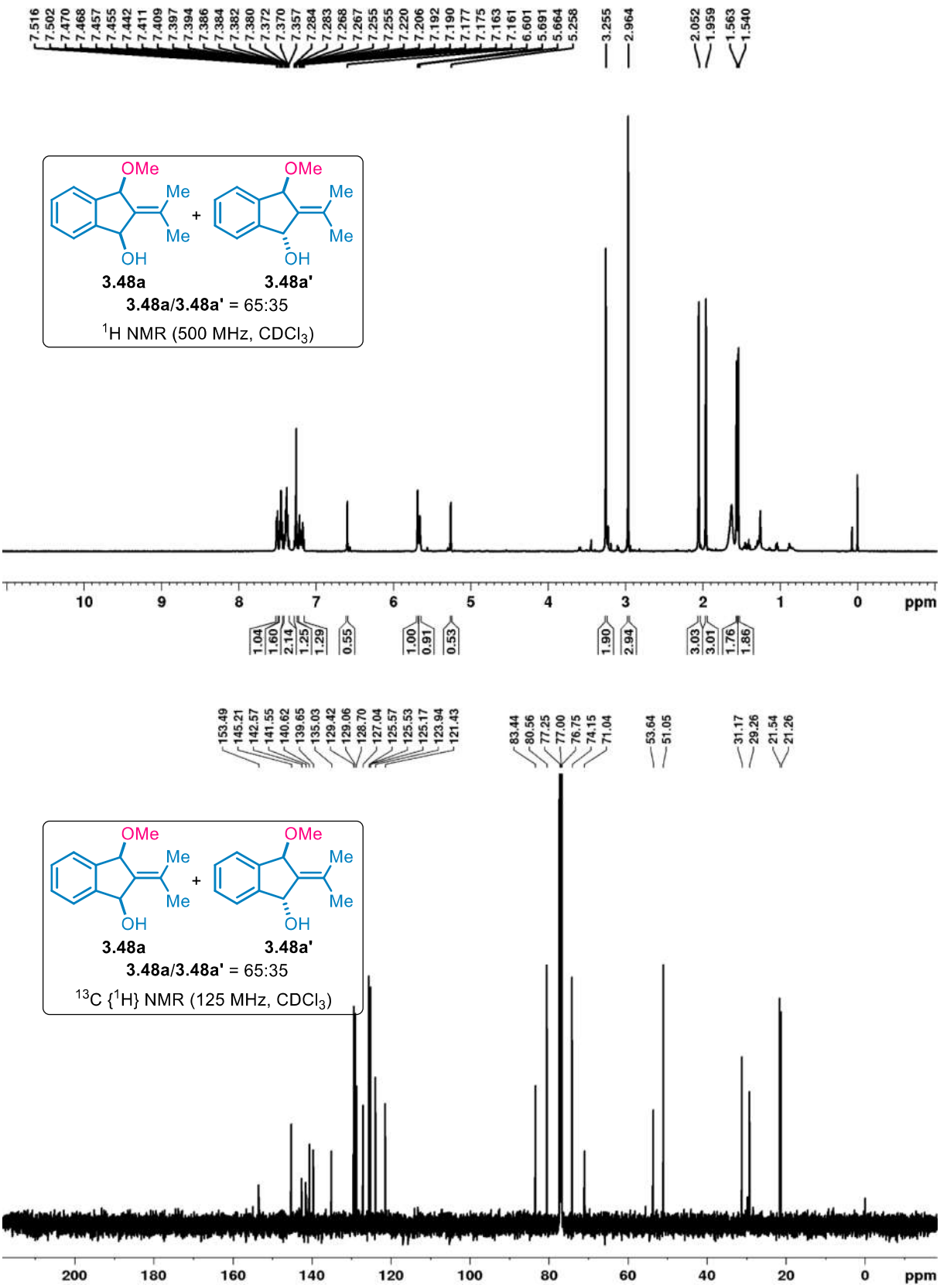

198.69
149.43
137.61
135.58
129.83
126.07
123.40
79.70
77.25
77.00
76.74
68.11
54.77
23.18
19.05
OMe
Me
O
Me
O
3.46a
^{13}C {^{1}H} NMR (125 MHz, CDCl$_3$)
200
180
160
140
120
100
80
60
40
20
0
ppm

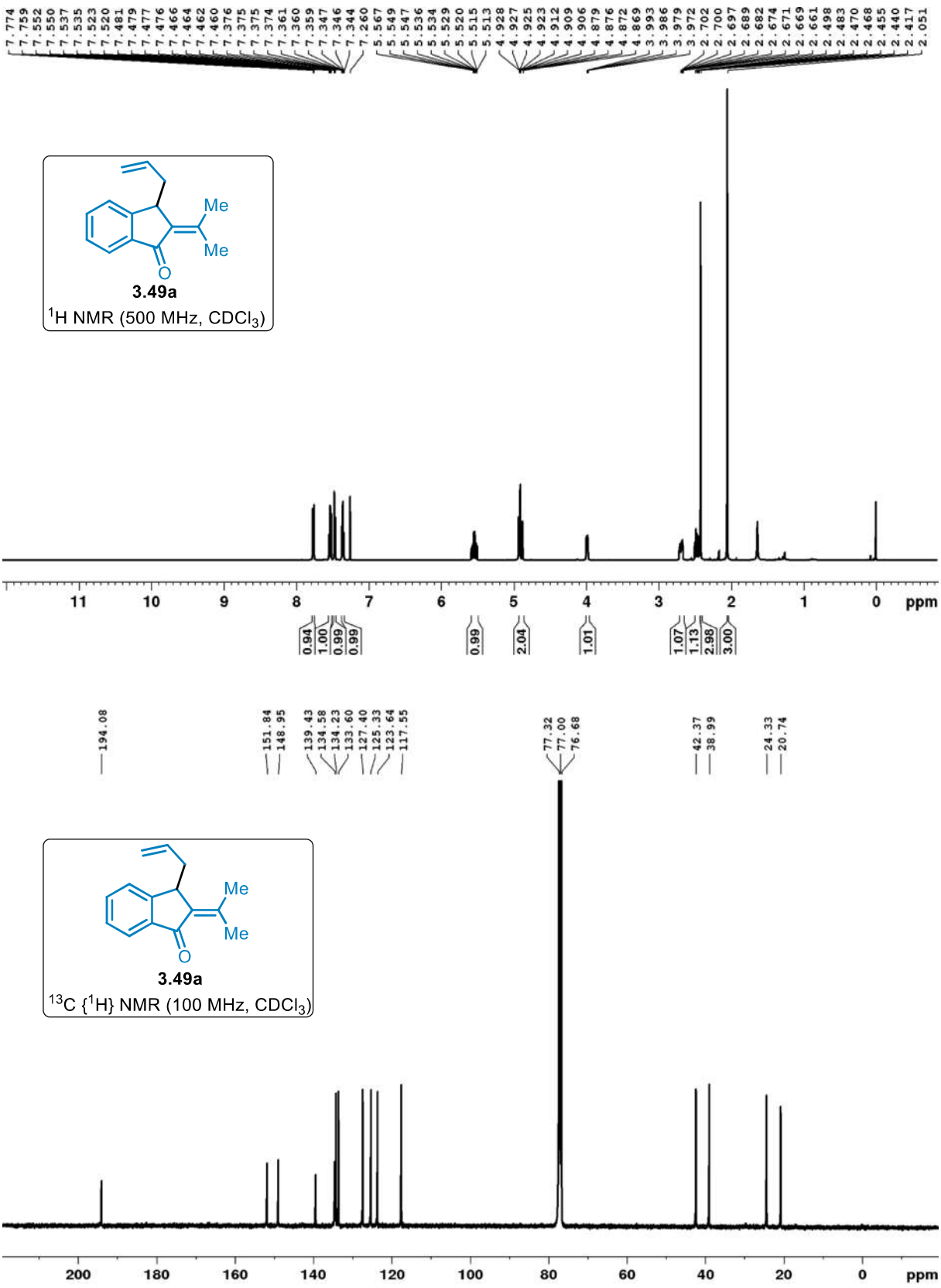

7.851
7.832
7.777
7.774
7.758
7.755
7.740
7.737
7.718
7.700
7.699
7.594
7.591
7.576
7.574
7.573
7.557
7.554
7.271
5.041
3.246
1.584
1.578
OMe
Me
Me
O
O
3.46a'
1H NMR (400 MHz, CDCl3)
10
9
8
7
6
5
4
3
2
1
0
ppm
1.04
1.10
1.03
1.10
1.00
3.02
2.80
3.05

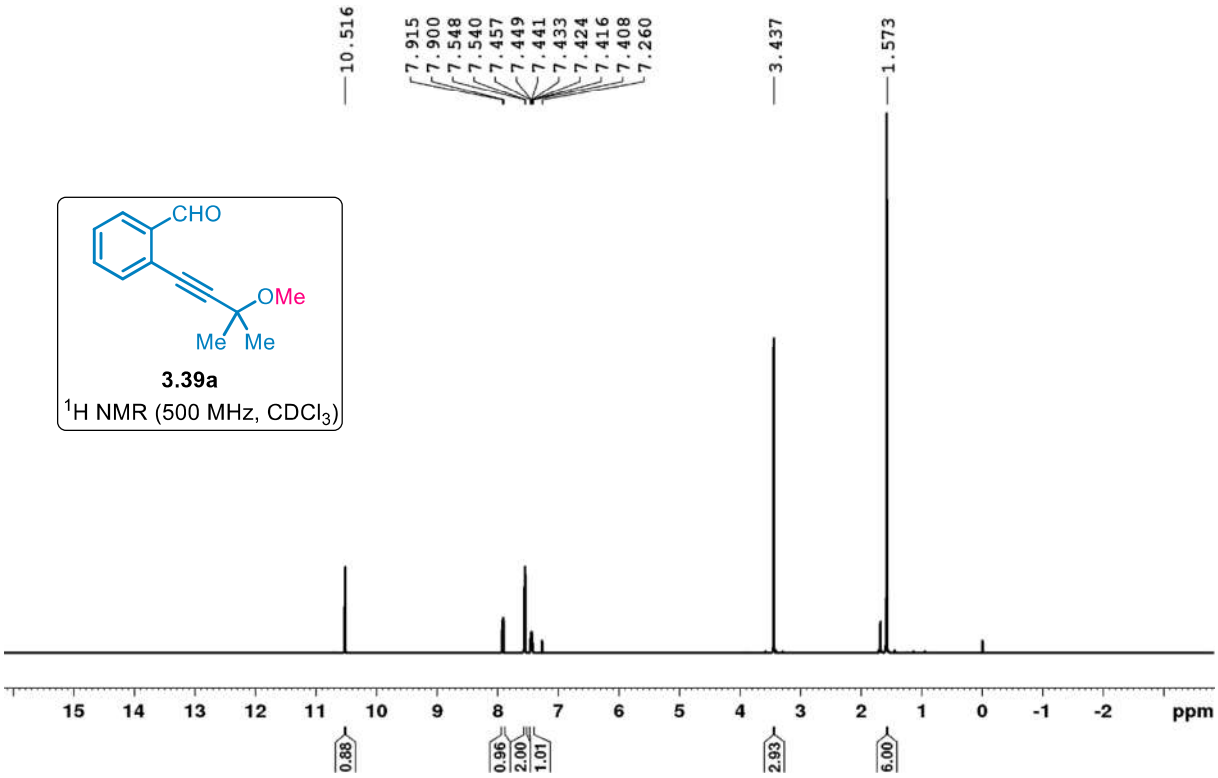

199.06
148.74
137.21
135.51
130.21
127.03
123.37
77.31
77.00
76.68
74.48
68.75
66.19
54.40
22.79
18.16
OMe
Me
Me
O
O
3.46a'
13C {1H} NMR (100 MHz, CDCl3)
200
180
160
140
120
100
80
60
40
20
0
ppm


7.458
7.443
7.432
7.431
7.416
7.407
7.405
7.392
7.390
7.378
7.375
7.364
7.361
7.349
7.347
7.335
7.327
7.321
7.319
7.312
7.310
7.307
7.304
7.297
7.295
7.261
5.464
5.399
3.214
2.992
2.158
2.154
2.112
2.109
2.099
1.932
1.922
1.724
1.641
OMe
Me
Me
Me
OH
OMe
Me
Me
Me
OH
3.47a
3.47a'
3.47a/3.47a' = 82:18
1H NMR (500 MHz, CDCl3)
10
9
8
7
6
5
4
3
2
1
0
ppm
5.23
1.00
0.21
0.68
3.07
1.09
3.03
0.66
2.96
0.65
0.74
3.03


150.79
150.03
139.02
138.40
137.95
137.72
137.07
129.56
129.40
128.64
128.32
125.31
125.11
123.24
123.09
81.14
79.99
79.64
78.35
77.25
77.00
76.74
53.55
50.82
28.45
28.14
22.57
22.09
20.81
20.45
OMe
Me
Me
Me
OH
OMe
Me
Me
Me
OH
3.47a
3.47a'
3.47a/3.47a' = 82:18
13C {1H} NMR (125 MHz, CDCl3)
200
180
160
140
120
100
80
60
40
20
0
ppm


7.516
7.502
7.470
7.468
7.457
7.455
7.442
7.411
7.409
7.397
7.394
7.386
7.384
7.382
7.380
7.372
7.370
7.357
7.284
7.283
7.268
7.267
7.255
7.255
7.220
7.206
7.192
7.190
7.177
7.175
7.163
7.161
6.601
5.691
5.664
5.258
3.255
2.964
2.052
1.959
1.563
1.540
OMe
Me
Me
OH
+
OMe
Me
Me
OH
3.48a
3.48a'
3.48a/3.48a' = 65:35
1H NMR (500 MHz, CDCl3)
10
9
8
7
6
5
4
3
2
1
0
ppm
1.04
1.60
2.14
1.25
1.29
0.55
1.00
0.91
0.53
1.90
2.94
3.03
3.01
1.76
1.86
153.49
145.21
142.57
141.55
140.62
139.65
135.03
129.42
129.06
128.70
127.04
125.57
125.53
125.17
123.94
121.43
83.44
80.56
77.25
77.00
76.75
74.15
71.04
53.64
51.05
31.17
29.26
21.54
21.26
OMe
Me
Me
OH
+
OMe
Me
Me
OH
3.48a
3.48a'
3.48a/3.48a' = 65:35
13C {1H} NMR (125 MHz, CDCl3)
200
180
160
140
120
100
80
60
40
20
0
ppm


7.774
7.759
7.552
7.550
7.537
7.535
7.523
7.520
7.481
7.479
7.477
7.476
7.466
7.464
7.462
7.460
7.376
7.375
7.375
7.374
7.361
7.360
7.359
7.347
7.346
7.344
7.260
5.567
5.549
5.547
5.536
5.534
5.529
5.520
5.515
5.513
4.928
4.927
4.925
4.923
4.912
4.909
4.906
4.879
4.876
4.872
4.869
3.993
3.986
3.979
3.972
2.702
2.700
2.697
2.689
2.682
2.674
2.671
2.669
2.661
2.498
2.483
2.470
2.468
2.455
2.440
2.417
2.051
Me
Me
O
3.49a
^{1}H NMR (500 MHz, $CDCl_3$)
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.94
1.00
0.99
0.99
0.99
2.04
1.01
1.07
1.13
2.98
3.00
194.08
151.84
148.95
139.43
134.58
134.23
133.60
127.40
125.33
123.64
117.55
77.32
77.00
76.68
42.37
38.99
24.33
20.74
Me
Me
O
3.49a
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$)
200
180
160
140
120
100
80
60
40
20
0
ppm


10.516
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7.540
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7.441
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7.260
3.437
1.573
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Me Me
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0.96
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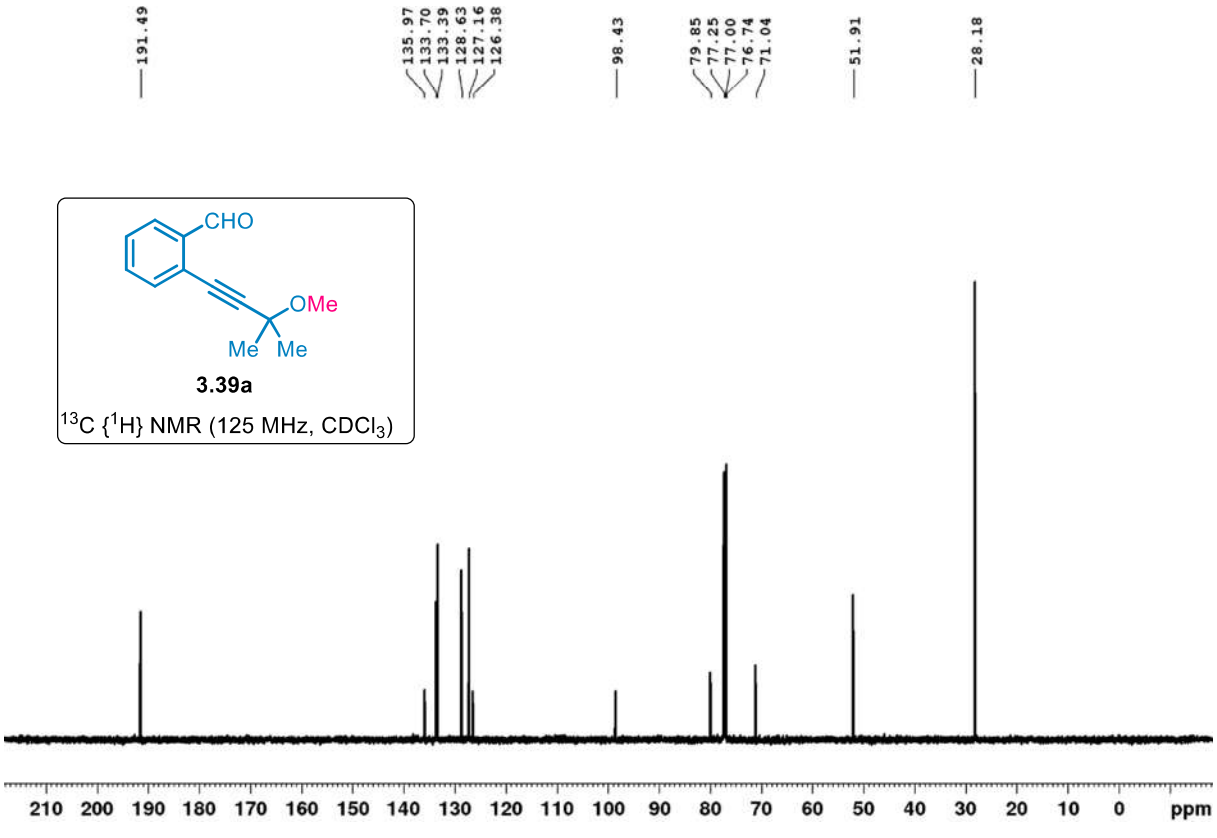
6.00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133.39
128.63
127.16
126.38
98.43
79.85
77.25
77.00
76.74
71.04
51.91
28.18
CHO
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Me Me
3.39a
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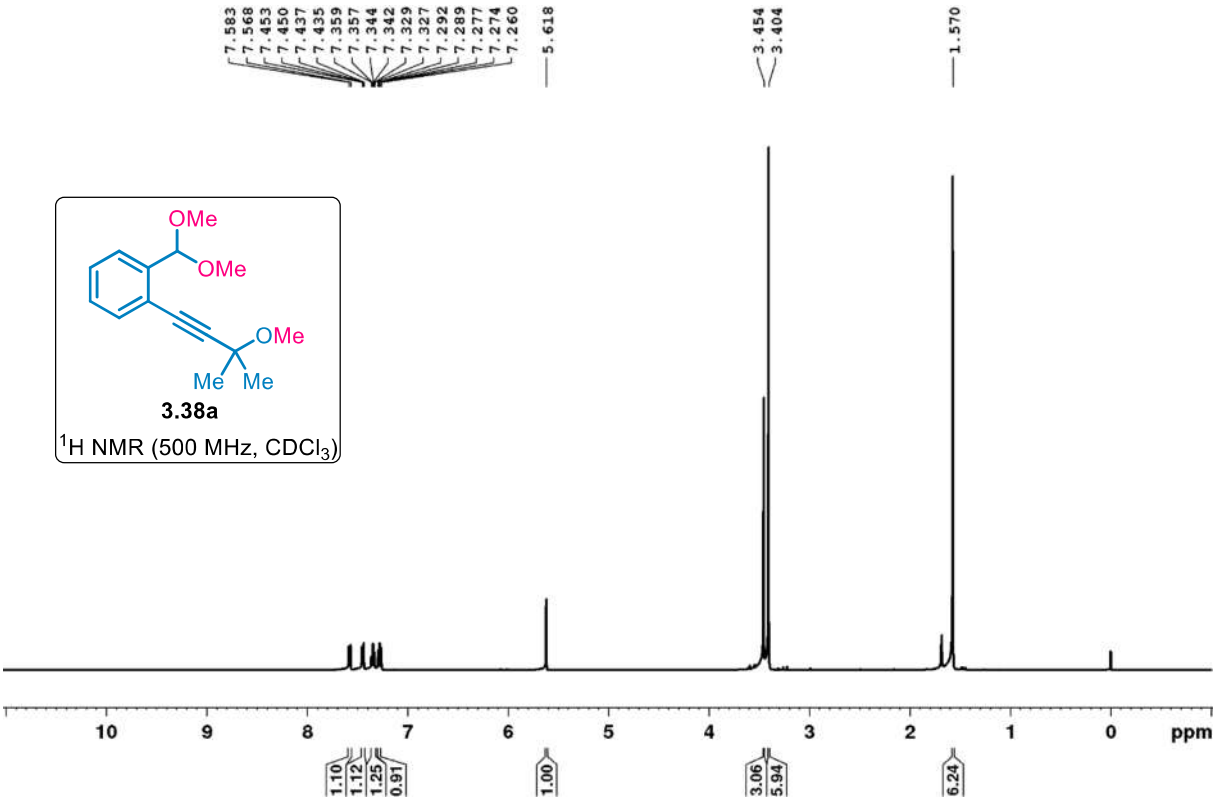
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7.292
7.289
7.277
7.274
7.260
5.618
3.454
3.404
1.570
OMe
OMe
OMe
Me
Me
3.38a
^{1}H NMR (500 MHz, CDCl$_3$)
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9
8
7
6
5
4
3
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1
0
ppm
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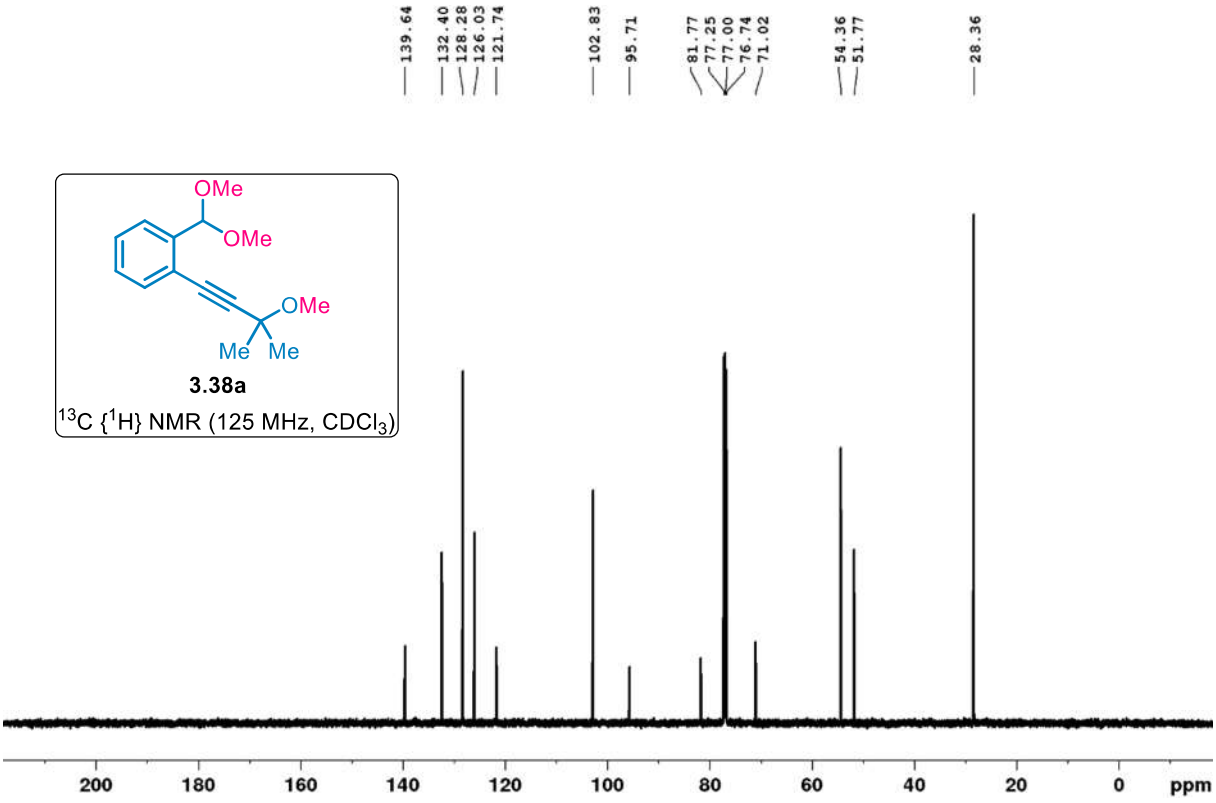
6.24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95.71
81.77
77.25
77.00
76.74
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54.36
51.77
28.36
OMe
OMe
OMe
Me
Me
3.38a
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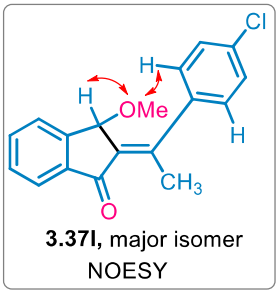
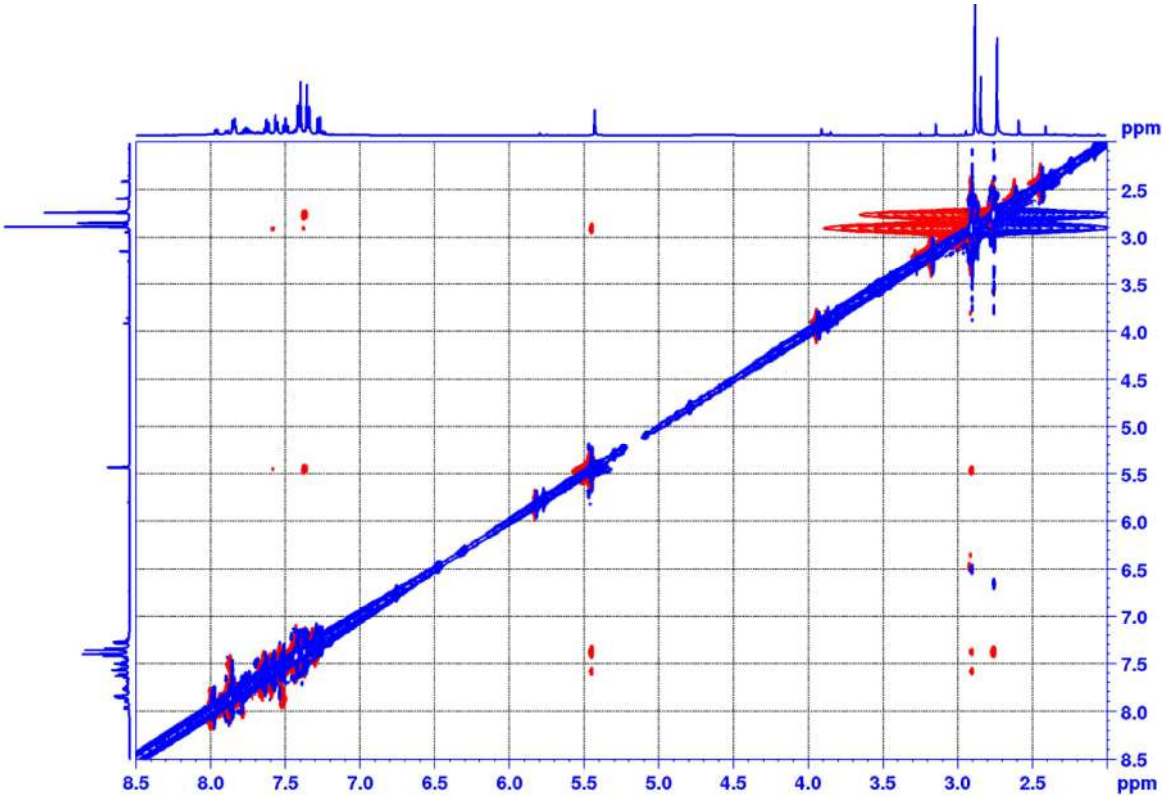
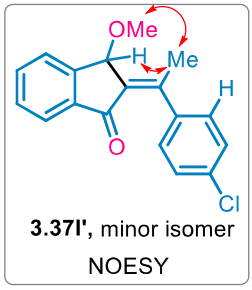
60
40
20
0
ppm



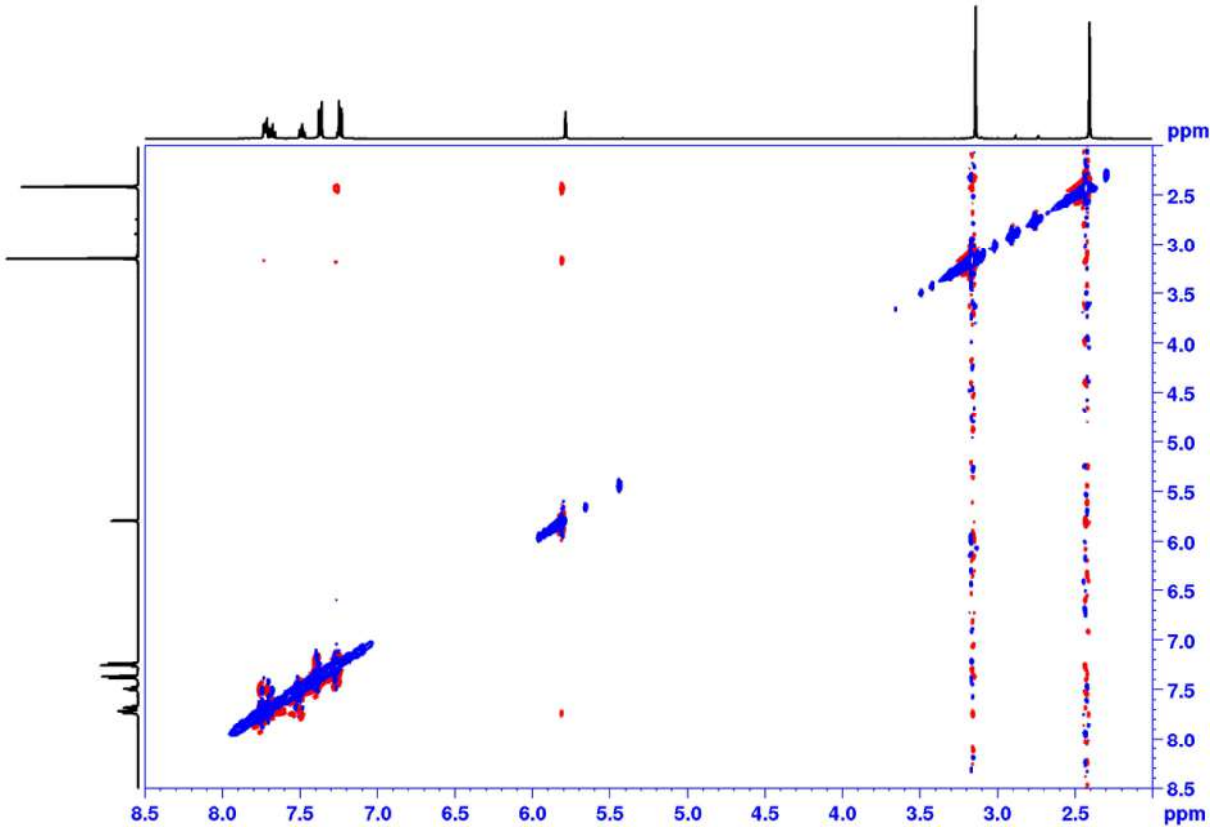
3.37l, major isomer
NOESY

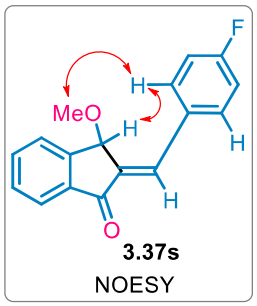


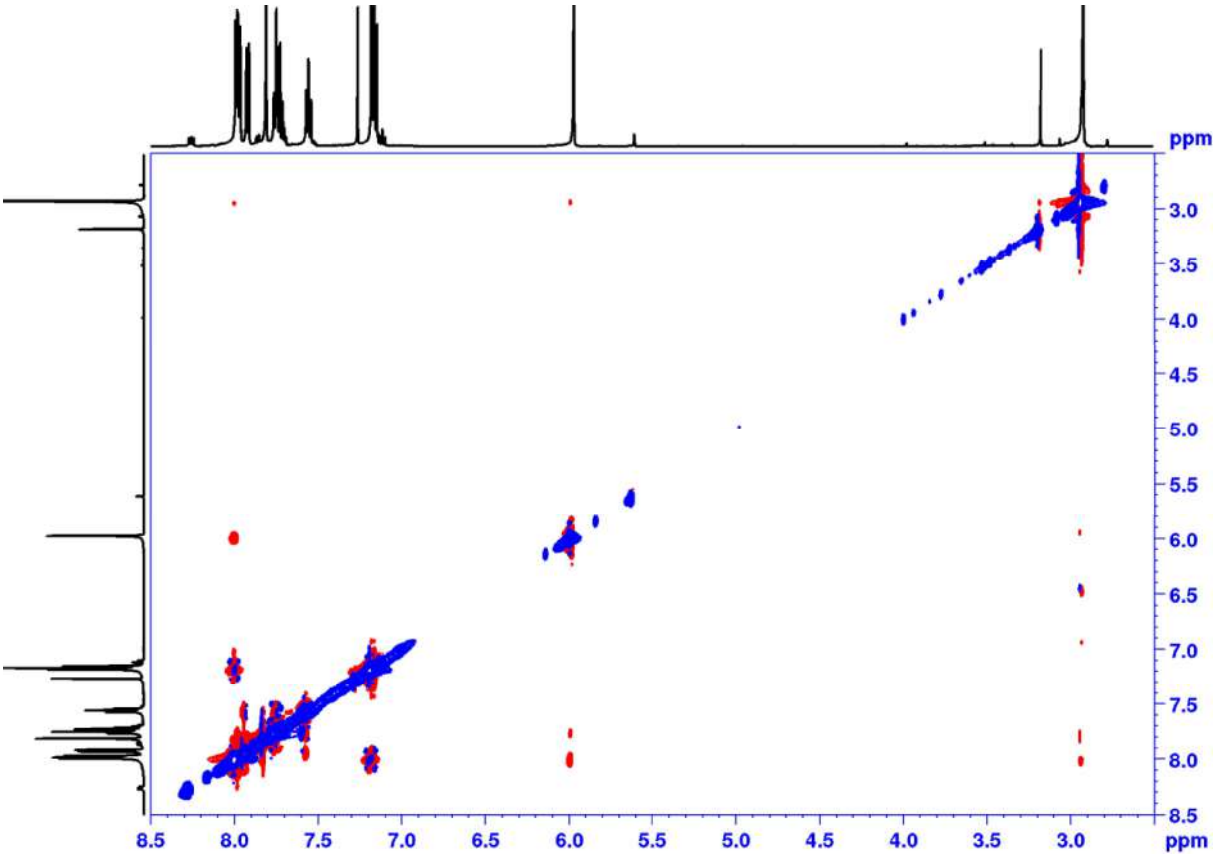


3.37l', minor isomer

NOESY




F
H
MeO
H
H
H
O
3.37s
NOESY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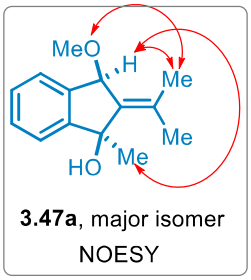
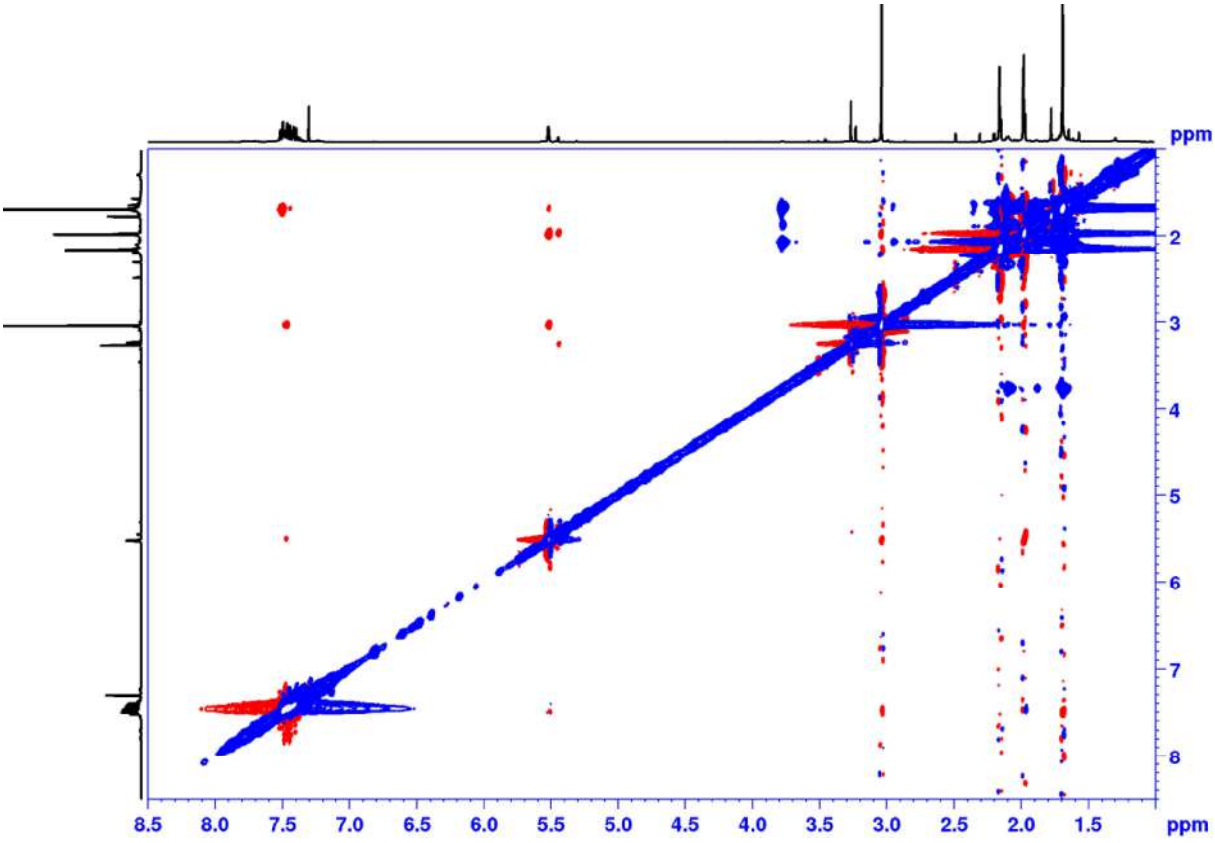
6.0
5.5
5.0
4.5
4.0
3.5
3.0
ppm



3.47a, major isomer
NOESY



3.8 Crystallographic data

Table 3.4 Crystal and Structure refinement for **3.37m'**

Identification code	rb114_0m_a
CCDC	**2083247**
Empirical formula	$C_{12}H_{18}O_2$
Formula weight	314.36
Temperature/K	299K
Crystal system	Monoclinic
Space group	P 1 21/ C 1
a/Å	5.9683(6)
b/ Å	25.166(3)
c/ Å	11.2165(12)
$\alpha/^0$	90
$\beta/^0$	94.676 (6)
$\gamma/^0$	90
Volume/$Å^3$	1679.1(3)
Z	49
Density(ρ)calc g/cm^3	1.244
Absorption Coefficient(μ) (mm^{-1})	0.078
F(000)	664.0
Crystal size/mm^3	0.02 x 0.02 x 0.01
Reflections collected	3860
Independent reflections	1675
Completeness to theta = 27.538	99.6%
R (reflections)	0.0638 (1675)
wR2 (reflections)	0.1542 (3860)

Table 3.5 Crystal and Structure refinement for **3.37r**

Identification code	rb_a
CCDC	**2083248**
Empirical formula	$C_{18}H_{14}O_4$
Formula weight	294.29
Temperature/K	299K
Crystal system	Orthorhombic
Space group	P n a 21
a/Å	17.294(2)
b/ Å	5.7918(7)
c/ Å	14.7449(16)
$\alpha/^0$	90
$\beta/^0$	90
$\gamma/^0$	90
Volume/$Å^3$	1476.9(3)
Z	43
Density(ρ)calc g/cm^3	1.324
Absorption Coefficient(μ) (mm^{-1})	0.094
F(000)	616.0
Crystal size/mm^3	0.02 x 0.02 x 0.01
Reflections collected	2862
Independent reflections	2706
Completeness to theta = 26.390	95%
R (reflections)	0.0352 (2706)
wR2 (reflections)	0.0931 (2862)

Table 3.6 Crystal and Structure refinement for **3.37s**

Identification code	rb_a
CCDC	**2083256**
Empirical formula	$C_{17}H_{13}FO_2$
Formula weight	268.27
Temperature/K	299K
Crystal system	Monoclinic
Space group	P 1 21/ C 1
a/Å	12.184(3)
b/ Å	13.177(3)
c/ Å	8.3915(16)
$\alpha/^0$	90
$\beta/^0$	95.349 (7)
$\gamma/^0$	90
Volume/$Å^3$	1341.4(5)
Z	30
Density(ρ)calc g/cm^3	1.328
Absorption Coefficient(μ) (mm^{-1})	0.095
F(000)	560.0
Crystal size/mm^3	0.02 x 0.02 x 0.01
Reflections collected	3083
Independent reflections	2122
Completeness to theta = 27.561	99.6%
R (reflections)	0.0512 (2122)
wR2 (reflections)	0.1283 (3083)

Table 3.7 Crystal and Structure refinement for **3.45s**

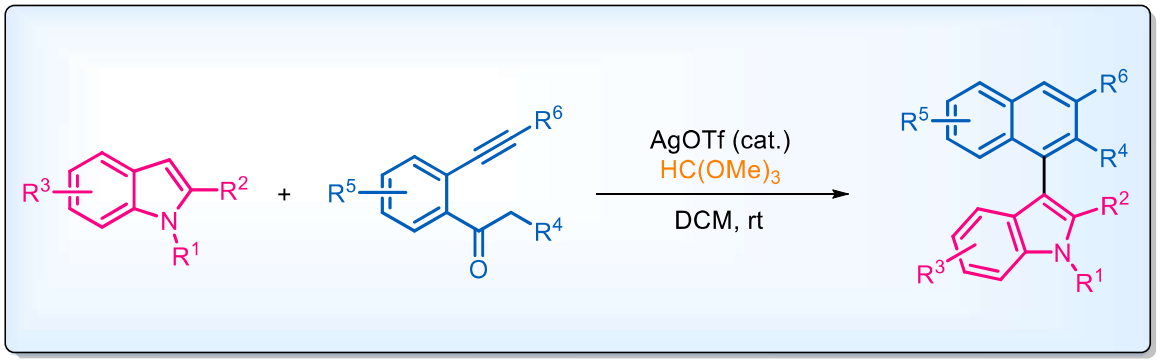
Identification code	rb02
CCDC	**2083262**
Empirical formula	$C_{13}H_{14}O_3$
Formula weight	218.24
Temperature/K	293K
Crystal system	Monoclinic
Space group	P 1 21/C 1
a/Å	9.8985(3)
b/ Å	14.4405(4)
c/Å	8.3941(3)
α/^{0}	90
β/^{0}	108.731(6)
γ/^{0}	90
Volume/Å^3	1136.30(6)
Z	12
Density(ρ)calc g/cm^3	1.276
Absorption Coefficient(μ) (mm^{-1})	0.090
F(000)	464.0
Crystal size/mm^3	0.02 x 0.02 x 0.01
Reflections collected	1997
Independent reflections	1752
Completeness to theta = 25.000	99.8%
R (reflections)	0.0341 (1752)
wR2 (reflections)	0.1062 (1997)

Table 3.8 Crystal and Structure refinement for **3.46a**

Identification code	rb01
CCDC	**2116964**
Empirical formula	$C_{33}H_{24}F_2O_4$
Formula weight	522.52
Temperature/K	296 K
Crystal system	Orthorhombic
Space group	P b c n
a/Å	22.203 (3)
b/ Å	11.9393 (12)
c/Å	20.097 (2)
$\alpha/^0$	90
$\beta/^0$	90
$\gamma/^0$	90
Volume/$Å^3$	5327.4 (10)
Z	8
Density(ρ)calc g/cm^3	1.303
Absorption Coefficient(μ) (mm^{-1})	0.094
F(000)	2176.0
Crystal size/mm^3	0.02 x 0.02 x 0.01
Reflections collected	5607
Independent reflections	1013
Completeness to theta = 27.033	96.1
R (reflections)	0.1221 (1013)
wR2 (reflections)	0.3700 (5607)

Chapter 4

Ag(I)-Catalyzed Cyclization of *o*-Alkynylacetophenones for the Synthesis of C3-Naphthyl Indole Derivatives



This work has been published. Ref: *Org. Biomol. Chem.* **2022**, *20*, 9698-9702.

4.1 Introduction

Indole-linked carbo and heterocycles show plenty of applications in developing biologically active molecules.[1] Having bioactive indole core attached to the ring systems adds more value to these systems. In this context, there has been interest to device efficient strategy to make C3-arylated indoles as they show diverse bioactivities.[2] In particular, C3-naphthyl indoles show their usefulness as chiral catalysts and antibacterial, antioxidant, and cytotoxic agents. Representative C3-naphthyl indoles have been presented in Figure 4.1.[3] With regard to their synthesis, cyclization accompanied by indole incorporation is an attractive and preferred strategy as both complexity and regioselectivity are achieved in a single operation.

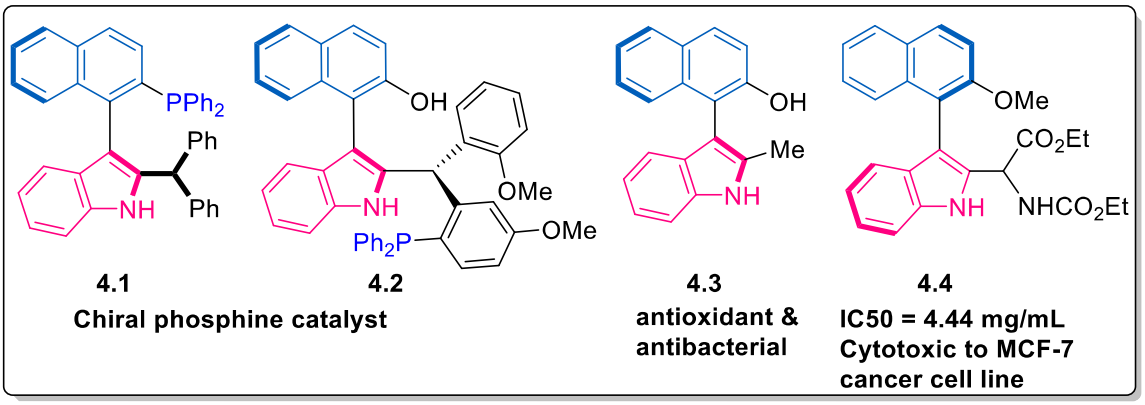
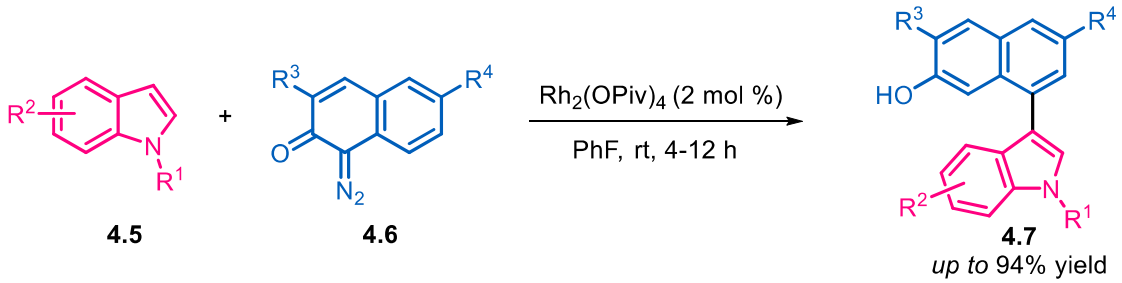


Figure 4.1: C3-Napthyl indole core containing chiral catalysts and bioactive molecules

4.1.1 Selected approaches for the synthesis of C3-naphthyl indoles

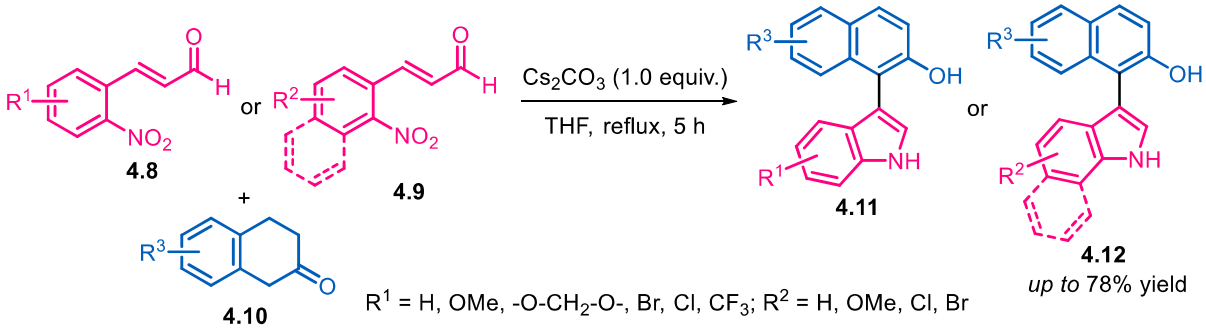
In 2015, Lee and co-workers reported a Rh(II)-catalyzed direct 3-arylation of indoles **4.5** with 1-diazonaphthalen-2(*1H*)-ones **4.6** for the synthesis of C3-naphthyl indoles **4.7** (Scheme 4.1).[4] This reaction takes place *via* the formation of rhodium carbenoid from diazo compound **4.6** followed by nucleophilic addition of indole **4.5** on rhodium carbenoid, subsequent deprotonation, and removal of rhodium catalyst afforded the C3-naphthyl indoles **4.7**.



R^1 = H, Me; R^2 = 5-OMe, 5-Me, 5-F, 5-Br, 5-CF_3, 6-CF_3, 7-Me, 7-NO_2
R^3 = H, OMe; R^4 = H, OMe, Br

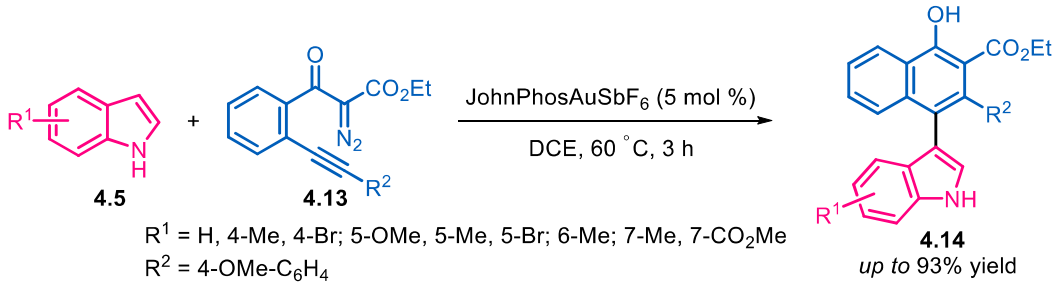
Scheme 4.1: A Rh(II)-catalyzed synthesis of C3-naphthyl-indoles

Later, the same group, in 2017, reported the synthesis of C3-naphthyl indole **4.11** and 3-naphthylbenzo[*g*]indole fluorophores **4.12** *via* a base-promoted indole annulation-oxidative cross-coupling of 2-nitrocinnamaldehydes **4.8** or **4.9** with β-tetralones **4.10** (Scheme 4.2).[5] This reaction proceeds *via* a sequence of transformations *viz* domino Michael addition, hemiacetalization, intramolecular attack of an enolate on the nitro group, decarbonylation, and oxidative aromatization. Moreover, the products C3-naphthyl indole **4.11** and 3-naphthylbenzo[*g*]indoles **4.12** have been reported to show excellent photophysical properties.



Scheme 4.2: Synthesis of C3-naphthyl indoles and 3-naphthylbenzo[*g*]indoles promoted by a base

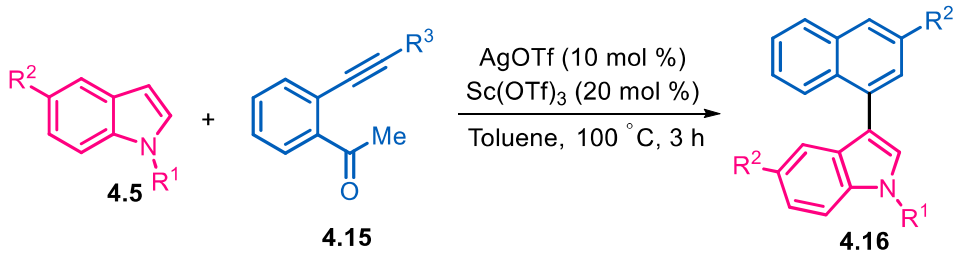
Synthesis of C3-naphthyl indole derivatives **4.14** from 1,3-dicarbonyl diazo compounds **4.13** and indoles **4.5** *via* intermolecular aromatic substitution under gold(I)-catalysis was demonstrated by Hu and co-workers (Scheme 4.3).[6] A vinyl gold carbene was proposed as the key intermediate from the diazo compound, which by an intermolecular electrophilic aromatic substitution reaction with indole **4.5** would lead to the formation of C3-naphthyl indole derivatives **4.14**.



Scheme 4.3: Au(I)-catalyzed synthesis of polyfunctionalized C3-naphthyl-indole derivatives

Recently, when we were developing the present reaction in an extension of our ongoing research on using *in situ* acetals, a synthesis of C3-naphthyl indole derivatives **4.16** from *o*-alkynylacetophenones **4.15** with indoles **4.5** in the presence of 10 mol % of AgOTf along with 20

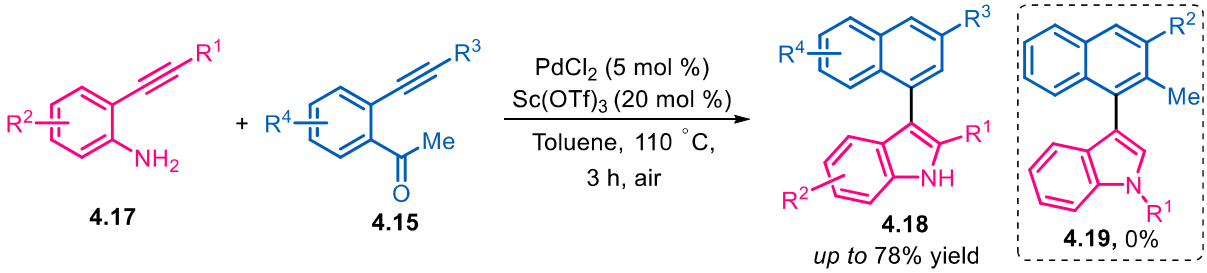
mol % of $Sc(OTf)_3$ at 100 °C was reported by Hao and co-workers (Scheme 4.4).[7] However, their reaction required 20 mol% of $Sc(OTf)_3$ in addition to AgOTf (10 mol%) and heating at 100 °C. The catalyst $Sc(OTf)_3$ was required to activate the methyl ketone for the attack of indole to form the extended enamine which attacks the [Ag]-activated alkyne to form C3-naphthyl indoles.[10] Further, this method is limited to acetophenone derivatives only and, that to, having aryl group as R^2.



R^1 = H, Me; R^2 = H, Me, OMe, Cl; R^3 = Ph, 4-Cl-C_6H_4, *p*-tolyl, 4-Et-C_6H_4, 4-OMe-C_6H_4, 4-F-C_6H_4

Scheme 4.4: Synthesis of C3-naphthyl indole derivatives from *o*-alkynylacetophenones with indoles

Later, the same group demonstrated the synthesis of C3-naphthyl indole derivatives **4.18** from *o*-alkynylacetophenones **4.15** with *o*-alkynyl anilines **4.17** *via* facile double annulation under dual palladium/scandium catalysis at 110 °C (Scheme 4.5).[8] However, this reaction was completely shut down when the acetyl group on the *o*-alkynylacetophenone was replaced by a propionyl group to give the corresponding product **4.19**. This reaction proceeds *via* a double annulation sequence under $PdCl_2$\$Sc(OTf)_3$ cooperative catalysis.

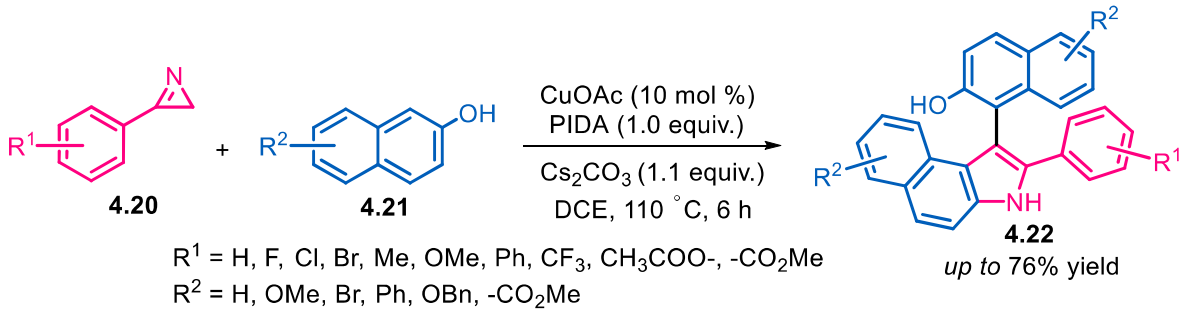


R^1 = H, Me, Cl; R^2 = Ph, *p*-tolyl, PMP, 4-Cl-C_6H_4, cyclopropyl, 4-Et-C_6H_4
R^3 = H, *p*-tolyl, *m*-tolyl, *o*-tolyl, PMP, 4-Cl-C_6H_4, 4-F-C_6H_4

Scheme 4.5: Synthesis of C3-naphthyl indoles from *o*-alkynylacetophenones and *o*-alkynyl anilines

Very recently, in 2021, Xie and co-workers reported a copper-catalyzed synthesis of C3-naphthol-benzo[*e*]indoles **4.22** from 3-aryl-2*H*-azirines **4.20** and 2-naphthols **4.21** for the first time

(Scheme 4.6).[9] This reaction is believed to proceed through azirine ring-opening followed by intramolecular cyclization and subsequent cross-dehydrogenative coupling to afford the desired product.

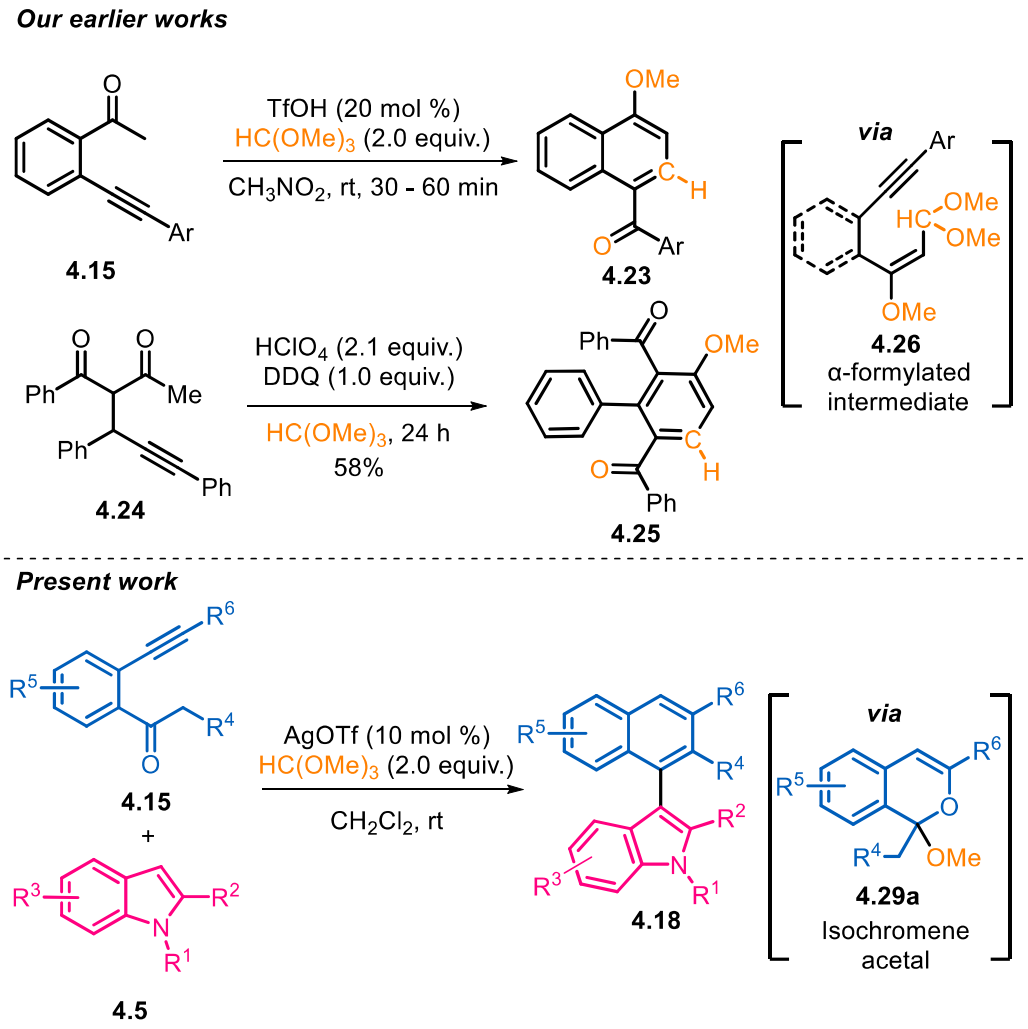


Scheme 4.6: A copper-catalyzed synthesis of C3-naphthol-benzo[*e*]indoles

In addition to these racemic protocols, elegant methods for the atropselective synthesis of axially chiral C3-naphthyl indoles have been reported in the literature.[10]

4.2 Background

Over the years we have realized that carrying out reactions of carbonyl compounds in the presence of TMOF and a Brønsted/Lewis acid provides a unique opportunity to find new reaction pathways through the formation of acetals under the reaction conditions.[11] In this context, we disclosed the construction of naphthyl ketones **4.23** and benzene rings **4.25** from *o*-alkynylacetophenones **4.15** and propargylated benzoylacetones **4.24** respectively (Scheme 4.7, our earlier works).[12] These reactions proceeded through the formation of an α-formylated intermediate **4.26** which cyclized on the alkyne. Another reason for us to undertake this study was the contrast reactivity shown by *o*-alkenylbenzaldehydes towards enolizable ketones and indoles under the acetalization conditions.[13] We were curious to study the reaction of *o*-alkynylacetophenones with indoles under acetalization conditions. As anticipated, the reaction of *o*-alkynylacetophenones **4.15** with indole **4.5** in the presence of TMOF and AgOTf resulted in C3-naphthyl indoles **4.18** through a different reaction pathway (Scheme 4.7, present work). In contrast to the work of Jiang, where the reaction required 20 mol% of $Sc(OTf)_3$ in addition to AgOTf (10 mol%) and heating at 100 °C,[7] our reaction occurred at room temperature itself in the presence of TMOF and AgOTf (10 mol%) alone as the sole catalyst. Certainly, assistance through the formation of acetal of the ketone might have helped the reaction to occur under mild conditions. Importantly, this protocol is applicable to substrates having alkyl and heteroaryl groups at R^6 and ethyl ketone.



Scheme 4.7: Reactions of alkyne-tethered methyl ketones under acetalization conditions

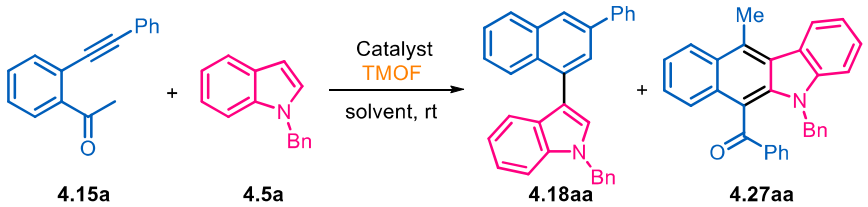
4.3 Results and Discussion

4.3.1 Reaction optimization study

The reaction optimization was carried out on the unsubstituted *o*-alkynylacetophenone derivative **4.15a** and *N*-benzylindole **4.5a** using different acid catalysts. Based on our earlier experiences,[12] the reaction was examined in the presence of Brønsted acids and 2 equivalents of TMOF. In the case of reactions involving TfOH and $HClO_4$, decomposition of indole was noted (Table 4.1, entries 1 and 2). Whereas, no reaction was observed in the presence of TFA and *p*-TSA as catalysts (Table 4.1, entries 3 and 4). Gratifyingly, in the presence of 2 equivalents of TMOF, silver catalysts effected the reaction at room temperature to afford the product **4.18aa** (Table 4.1, entries 5-8). Among them, AgOTf was found to be superior as it resulted in 84% yield of the product. In these reactions, compound **4.27aa** was also isolated in low amounts along with the

actual product. While the catalyst $Sc(OTf)_3$ did not promote the reaction, $Cu(OTf)_2$ catalyzed the reaction to give **4.18aa** in moderate yield suggesting the need for the activation of the alkyne (Table 4.1, entries 9-10). From a set of experiments (Table 4.1, entries 11-17) it is learnt that the condition involving 10 mol% of AgOTf and 2 equivalents of TMOF in dichloromethane gave a better yield. To our favor, formation of the side product **4.27aa** was almost suppressed when the stoichiometry of the reacting partners **4.15a** and **4.5a** was changed (Table 4.1, entry 18). The product yield considerably decreased with 1.0 equiv. of TMOF (Table 4.1, entry 19). A reaction using MeOH in the place of TMOF was also performed and a considerable reduction in the yield of the product was observed (Table 4.1, entry 20).

Table 4.1 Optimization of the reaction conditions[a]



Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)	
				4.18aa	**4.27aa**
1	TfOH	DCE	24	-[c]	-[c]
2	$HClO_4$	DCE	24	-[c]	-[c]
3	TFA	DCE	24	N.R.	N.R.
4	*p*-TSA	DCE	24	N.R.	N.R.
5	$AgSbF_6$	DCE	1.5	64	21
6	$AgBF_4$	DCE	2.5	42	10
7	AgOTf	DCE	2.5	84	13
8	$AgNTf_2$	DCE	2.5	54	11
9	$Sc(OTf)_3$	DCE	24	N.R.	N.R.
10	$Cu(OTf)_2$	DCE	4	48	13
11	AgOTf	DCM	2.5	86	9
12	AgOTf	CH_3CN	24	N.R.	N.R.
13	AgOTf	CH_3NO_2	2.5	40	8

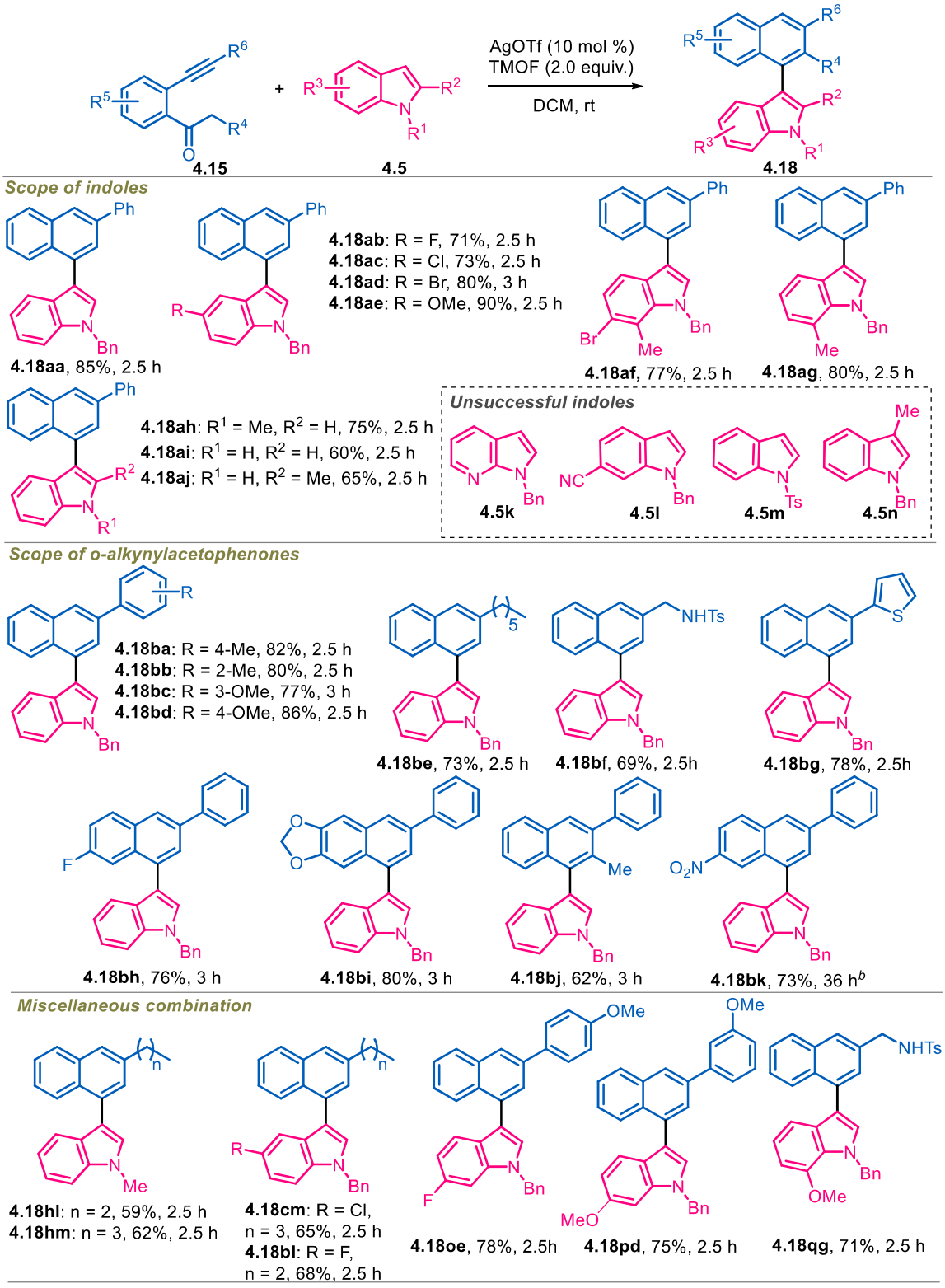
14[d]	AgOTf	Toluene	24	-	-
15[e]	AgOTf	DCM	6	79	14
16[f]	AgOTf	DCM	2.5	60	15
17[g]	AgOTf	DCM	2.5	73	12
18[h]	**AgOTf**	**DCM**	**2.5**	**85**	**trace**
19[i]	AgOTf	DCM	2.5	64	7
20[j]	AgOTf	DCM	2.5	52	12
21[k]	AgOTf	DCM	2.5	53	26

[a]Reaction conditions: **4.15a** (0.4 mmol), **4.5a** (0.48 mmol), TMOF (0.8 mmol), catalyst, and solvent (4 mL) at rt. [b]isolated yields. [c]Indole got decomposed. N.R. = No reaction. [d]isochromen-1-yl-substituted indole derivative **4.28aa** was obtained in 67% yield. [e]5 mol % of AgOTf was used. [f]20 mol % of AgOTf was used. [g]5.0 equiv. of TMOF was used. [h]1.0 equiv. of **4.5a** and 1.2 equiv. of **4.15a** were used. [i]1.0 equiv. of TMOF was used. [j]2.0 equiv. of MeOH was used. [k]Reaction was carried out in the absence of TMOF.

4.3.2 Substrate scope

The substrate scope of this transformation was explored using the condition presented in entry 18 of Table 4.1 and the results are summarized in Table 4.2. Firstly, the scope of indoles was evaluated using different substituted indoles **4.5** by reacting them individually with **4.15a**. Indoles containing halogen substituents such as 5-F-, 5-Cl-, and 5-Br- underwent the smooth reaction to afford their corresponding C3-naphthyl indoles **4.18ab**, **4.18ac**, and **4.18ad** respectively in good yields. Indole bearing an electron-donating OMe at the C-5 position gave the corresponding product **4.18ae** in a slightly better yield. 1-Benzyl indoles bearing 6-Br-7-Me and 7-Me groups reacted smoothly to give products **4.18af** and **4.18ag** in 77% and 80% yield respectively. The structure of compound **4.18af** was further confirmed by a single crystal X-ray diffraction analysis. Both *N*-methyl and *N*-unprotected indoles gave their respective C3-naphthyl indoles **4.18ah**, **4.18ai** and **4.18aj**. The yields of the products obtained from *N*-unprotected indoles were slightly less. Next, the scope of *o*-alkynylacetophenones was examined using substrates having different R^4, R^5 and R^6 groups. *o*-Alkynylacetophenones having electron-donating methyl and methoxy groups in the phenyl ring attached to the alkyne resulted in the products **4.18ba**-**4.18bd** in promising yields. Interestingly, substrates having an alkyl group at the alkyne also reacted smoothly to furnish the corresponding C3-naphthyl indoles (**4.18be** and **4.18bf**). Heterocycle, thiophene attached *o*-alkynylacetophenone tolerated the reaction condition to furnish the product **4.18bg** in 78% yield. *o*-Alkynylacetophenones having fluoro and -OCH_2O- groups in the core aryl ring reacted well in giving their respective products **4.18bh** and **4.18bi**. More importantly, a substrate having an ethyl ketone also reacted and resulted in a moderate yield of the product (**4.18bj**).

Table 4.2 Substrate scope[a]



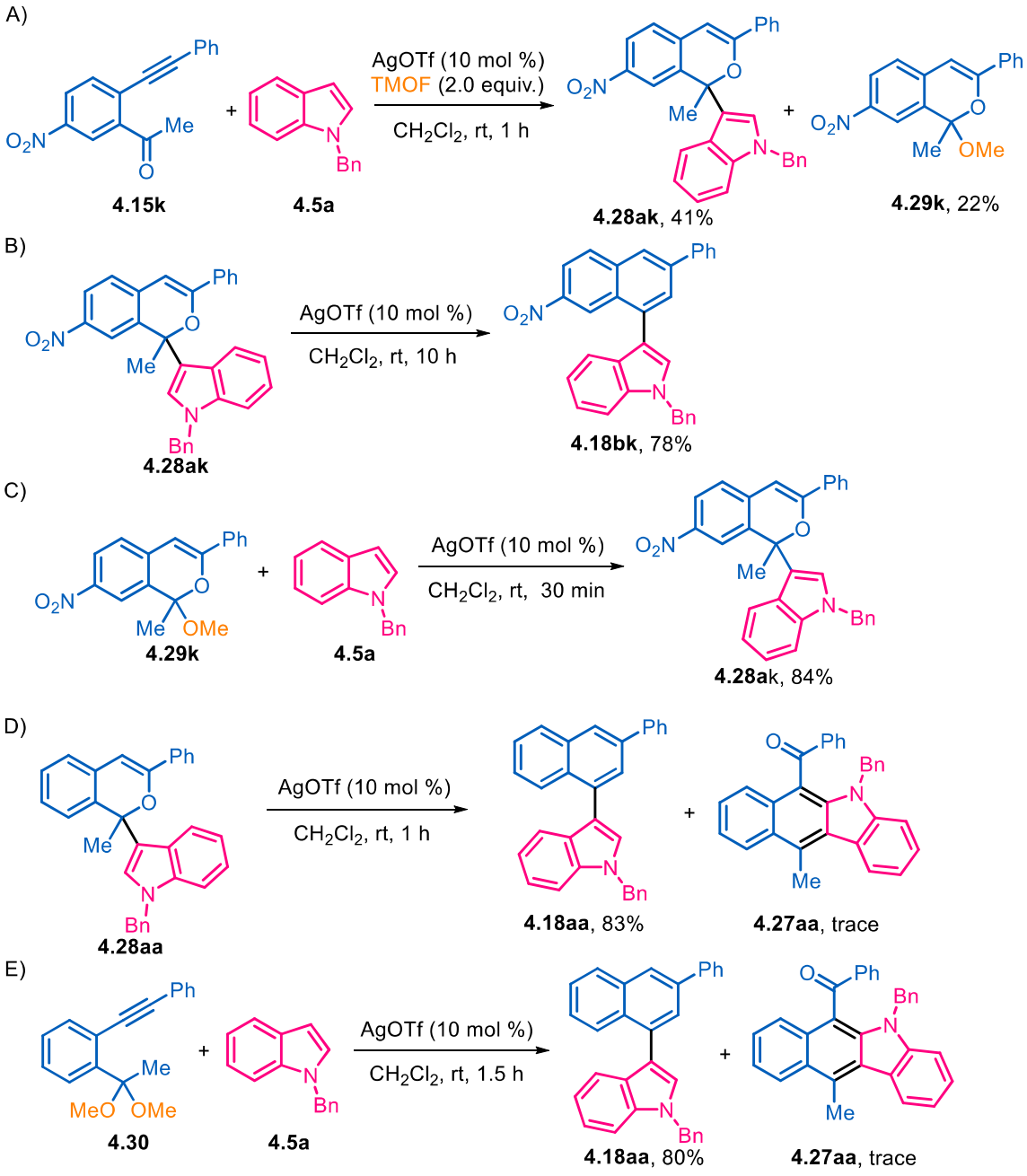
[a]Reaction conditions: **4.15** (1.2 equiv.), **4.5** (1 equiv., 0.4 mmol), AgOTf (10 mol %), TMOF (2 equiv.), DCM (4 mL/0.4 mmol of 2). [b]An additional 10 mol % of AgOTf was added after 20 h.

It has to be mentioned that substrates having alkyl and heterocycle on the alkyne and ethyl ketone were not reported in the published work utilizing AgOTf/$Sc(OTf)_3$ catalytic system.[7] Further, the same group, in the extension of their initial work,[7] was not successful in obtaining **4.18bj**.[8] However, a reaction of the substrate having a propyl ketone resulted in a complex mixture of products. When R^5 is a strong electron-withdrawing NO_2 group, an additional amount of AgOTf (10 mol %) had to be added after 20 h of the reaction to form the corresponding naphthyl indole derivative **4.18bk**.

Then a few more reactions were carried out using random choice of *o*-alkynylacetophenones and indoles. Moderate to good yields of the products were obtained in these cases (products **4.18hl**, **4.18hm**, **4.18cm**, **4.18bl**, **4.18oe**, **4.18pd,** and **4.18qg**).

4.3.3 Control experiments

A series of control experiments were performed to understand the importance of expected acetal formation under the reaction conditions (Scheme 4.8). To our favor, the less reactive *o*-alkynylacetophenone derivative **4.15k** afforded a separable mixture of isochromen-1-yl-substituted indole derivative **4.28ak** and isochromene acetal derivative **4.29k** after 1 h (Scheme 4.8A). The structure of compound **4.28ak** was unambiguously determined by single crystal X-ray diffraction analysis. Assuming these compounds as the likely intermediates, isochromen-1-yl-substituted indole derivative **4.28ak** was treated with 10 mol% of AgOTf. The product C3-naphthylindole **4.18bk** was obtained in 78% after 10 h (Scheme 4.8B). However, the isochromene acetal derivative **4.29k** resulted in **4.28ak** only upon treatment with 10 mol% of AgOTf and did not react further to afford **4.18bk** (Scheme 4.8C).[14] The same observation was noted during the evaluation of substrate scope to synthesize **4.18bk** from **4.15k**. A probable reason for this could be the electron-withdrawing $–NO_2$ group could reduce the reactivity of the vinyl moiety for its attack on the carbonyl function in intermediate **IV** (Scheme 4.9). These experiments suggest that the reaction proceeds *via* the initial formation of acetal which subsequently transforms into 1-methoxy-isochrome followed by isochromen-1-yl-substituted indole derivative before resulting the product in contrast to the extended enamine intermediate proposed in the reaction involving AgOTf/$Sc(OTf)_3$.[8] In a different experiment, the isochromen-1-yl-substituted indole derivative **4.28aa**, obtained during the optimization experiment in toluene, was treated with AgOTf catalyst and the product **4.18aa** was obtained in 83% yield in 1h (Scheme 4.8D). Finally, an AgOTf-catalyzed reaction of the preformed acetal **4.30** with indole **4.5a** was carried out. Formation of the desired product **4.18aa** in 1.5 h (Scheme 4.8E) suggests that acetal generated under the reaction condition facilitates the reaction to occur at room temperature.



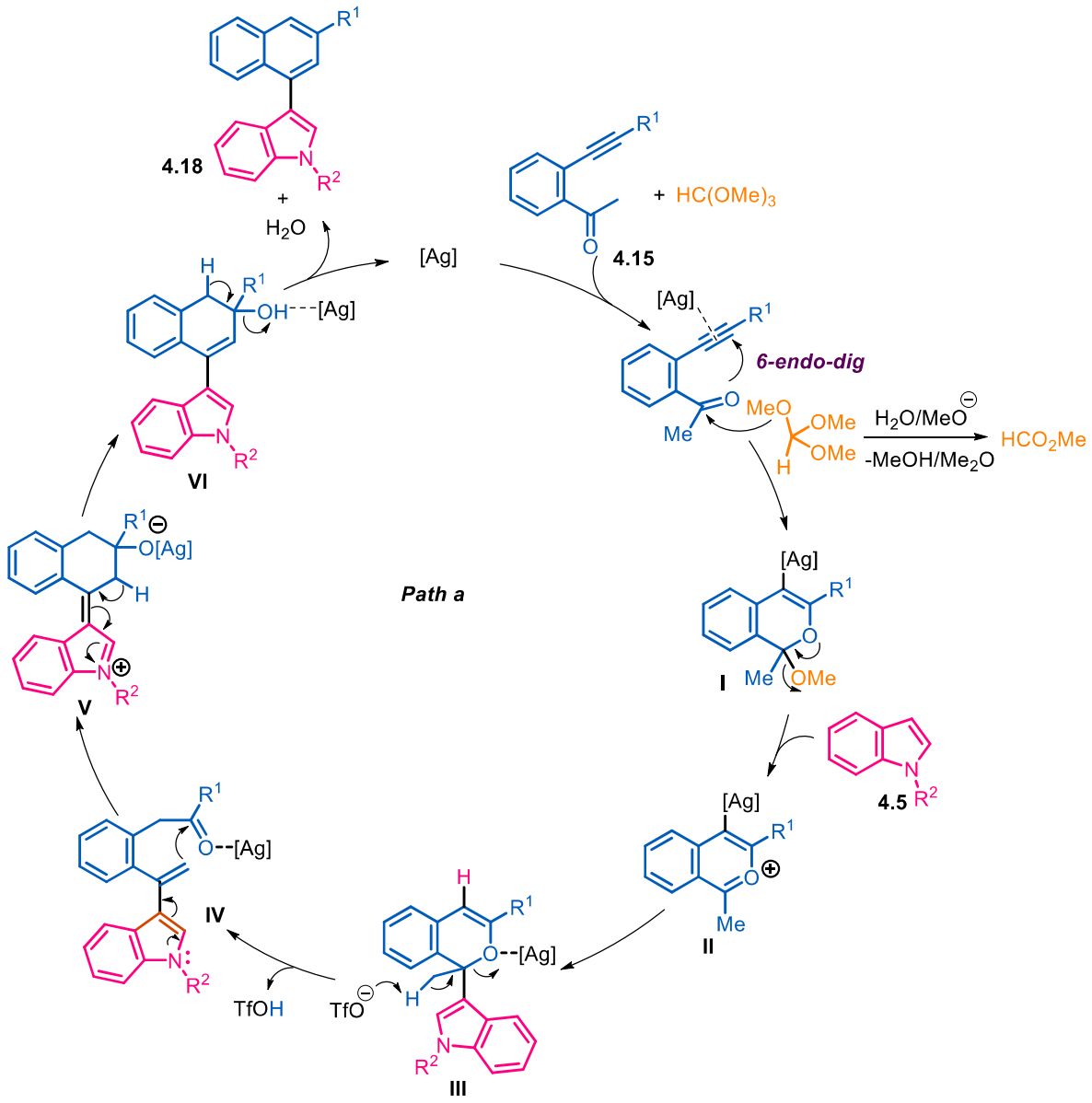
Scheme 4.8: Control experiments

4.3.4 Plausible mechanism

In the mechanistic proposal by Jiang and co-workers, for the formation C3-naphthyl indoles from *o*-alkynyl acetophenones and indoles, activation of the carbonyl of the acetophenone derivative by $Sc(OTf)_3$ for the attack of indole was considered as the key.[8] In the present reaction, on the basis of the control experiments and our previous reports,[12] two plausible pathways are

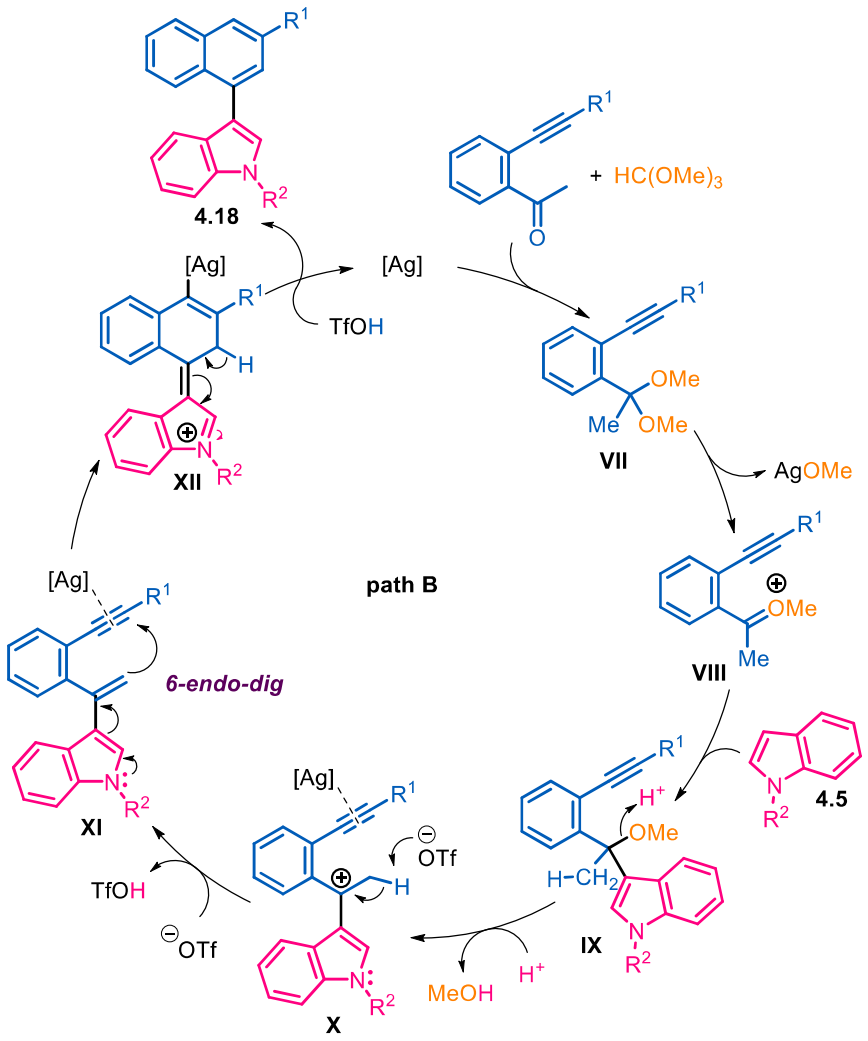
proposed involving the participation of TMOF for the formation of C3-naphthyl indole **3** (Scheme 4.9, *paths a* and *b*).

It is well-known that *o*-alkynyl benzaldehydes/acetophenones form an isobenzopyrylium intermediate upon activation using a silver catalyst.[15] In the present reaction, TMOF can promote the formation of such an intermediate **II** by attacking the carbonyl carbon *via* intermediate **I**. Formation of the product **4.29k** in the control reaction (Scheme 4.8A) supports the involvement of intermediate **I** as a simple protodemetalation of **I** would result in it. Besides, dimethoxymethylium ion will be formed from TMOF after it attacks *o*-alkynylacetophenone. Eventually, H_2O/OMe- would attack the dimethoxymethylium ion to give methyl formate. Indole will readily attack intermediate **II** to form the intermediate **III**. Isolation of the product **4.28ak** in the control experiment supports the formation of **III**. Abstraction of a proton from methyl and ring-opening would result in intermediate **IV** having a carbonyl[16] and extended enamine moieties. This will undergo a facile cyclization followed by aromatization with the loss of water to form the product **4.18**.



Scheme 4.9: Plausible mechanism (*path a*)

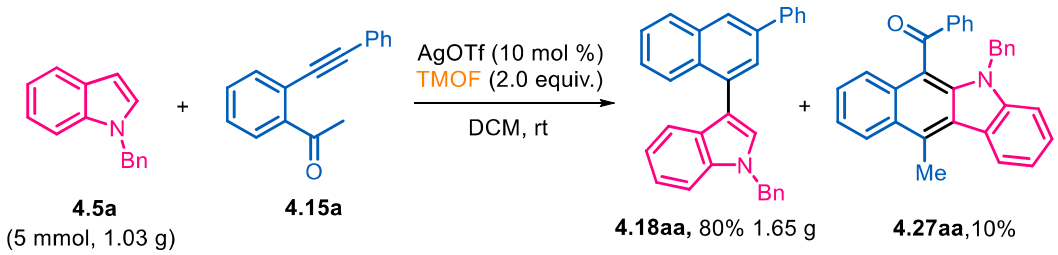
Since the reaction is facilitated by the presence of TMOF, a mechanism involving the formation of acetal **VII** of *o*-alkynyl acetophenones under the reaction condition cannot be ruled out. This possibility is shown in scheme 4.10. The intermediate **VII** will readily form the oxocarbenium ion **VIII** under the Lewis acidic condition. Addition of indole followed by MeOH elimination would result in the extended enamine **XI**, which will cyclize on the Ag-activated alkyne to form the intermediate **XII**. Finally, protodemetallation would result the product **4.18**.



Scheme 4.10: Plausible mechanism (*path b*)

4.3.5 Scale-up reaction

The robustness and scalability of the strategy were demonstrated by performing a gram scale reaction using **4.5a** (1.03 g, 5 mmol) and **4.15a**. The desired product **4.18aa** was obtained in 80% (1.65 g) yield along with 10% of product **4.27aa** (Scheme 4.11).



Scheme 4.11: Scale-up reaction

4.3.6 ORTEP diagrams of **4.18af** and **4.28ak**

Single crystal X-ray data for the compounds **4.18af** and **4.28ak** was collected using the Bruker D8 Quest CMOS detector system [λ(Mo-Kα) = 0.71073 Å] at 298K, graphite monochromator with a ω scan width of 0.3o, crystal-detector distance 60 mm, collimator 0.5 mm. The SMART software was used for the intensity data acquisition and the SAINTPLUS software was used for the data extraction. In each case, absorption correction was performed with the help of SADABS program, an empirical absorption correction using equivalent reflections was performed with the program. The structure was solved using SHELXS-97, and full-matrix least-squares refinement against F2 was carried out using SHELXL-97.

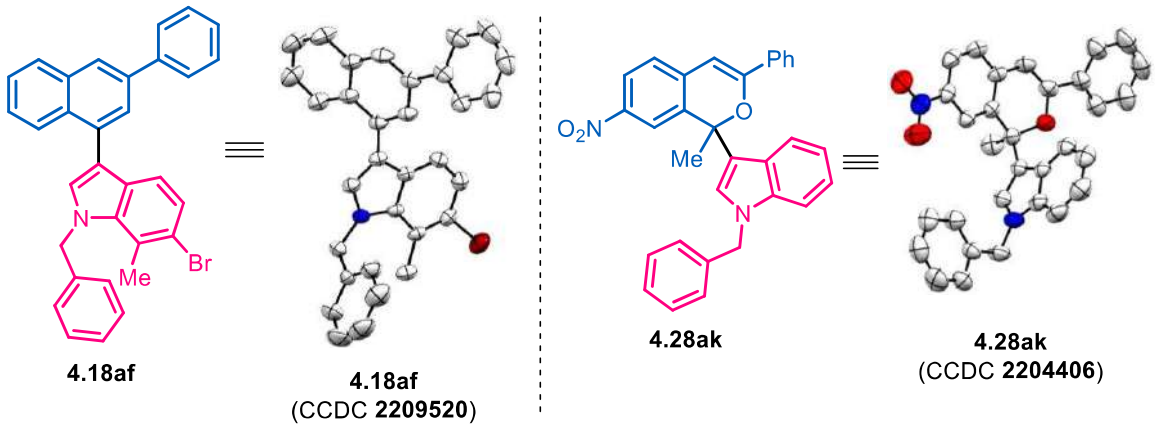


Figure 4.2: ORTEP diagrams of **4.18af** and **4.28ak**

4.4 Conclusions

In conclusion, we have developed a facile protocol for the synthesis of C3-naphthyl indole derivatives from *o*-alkynylacetophenones and indoles under acetalization conditions using TMOF in the presence of AgOTf catalyst. Presence of TMOF makes the reaction to occur at the room temperature itself by forming acetal. A range of C3-naphthyl indole derivatives have been synthesized in moderate to good yields. Reactions of carbonyl compounds in the presence of TMOF offer beneficial effects in terms of enhancing reactivity or forcing to take new reaction pathways.

4.5 Experimental section

4.5.1 General information

Unless otherwise mentioned, all chemicals obtained from commercial suppliers were used without further purification. AgOTf and TMOF were purchased from Sigma-Aldrich, Avra synthesis respectively, and were used without further purification. All reactions were performed under nitrogen atmosphere and in oven-dried glassware with magnetic stirring. Dichloromethane (DCM) was dried in the presence of calcium hydride and distilled before use. Reactions were

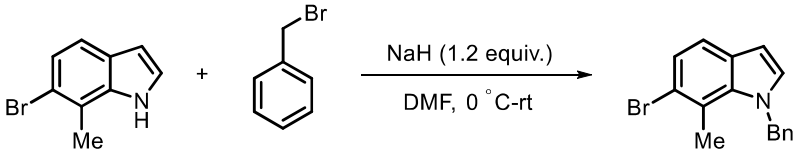
monitored using silica gel plates 60 F_{254} and were visualized with UV light (254 nm), with Seebach stain followed by heating. Column chromatography was carried out using silica gel (100-200 mesh) packed in glass columns. NMR spectra were recorded at 400, 500 MHz (^{1}H) and at 100, 125 MHz (^{13}C), respectively. Chemical shifts (δ) are reported in ppm, using the residual solvent peak in $CDCl_3$ (H: δ = 7.26 and C: δ = 77.0 ppm) as internal standard, and coupling constants (J) are indicated in Hz. HRMS were recorded using ESI-TOF techniques.

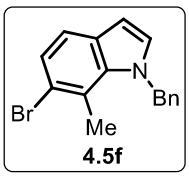
4.5.2 Experimental procedures, analytical, and spectral data

Synthesis of *N*-protected indoles:

N-protected indoles **4.5a-4.5e**, **4.5g**, **4.5h**, and **4.5o-4.5q** were synthesized according to the previous reports.[17] The other indole derivative **4.5f** was synthesized by the following procedure.

Procedure for the synthesis of 1-benzyl-6-bromo-7-methyl-1H-indole 4.5f:



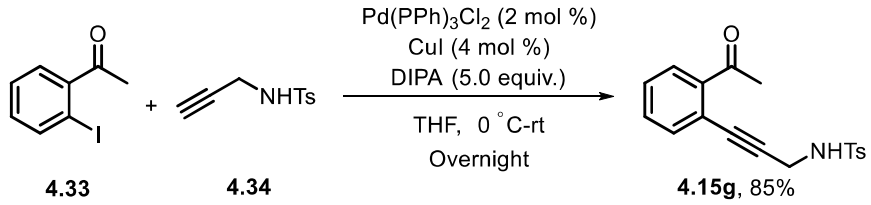


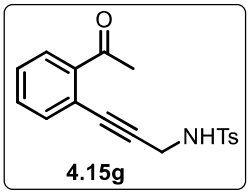
To a stirred solution of 6-bromo-7-methyl-1*H*-indole **4.31** (120 mg, 0.4 mmol) in DMF (3 mL) was added NaH (22 mg, 0.48 mmol) at 0 ˚C under nitrogen atmosphere. The reaction mixture was brought up to room temperature and stirred for 30 minutes before adding benzyl bromide **4.32** (53 µL, 0.44 mmol) at 0 ˚C. Then, the reaction mixture was allowed to stir overnight at room temperature. After completion of the reaction, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with saturated brine solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc mixture as eluent) to afford the pure product **4.5f** as a white solid in 91% (137 mg) yield. mp 98-100 ˚C, R_f = 0.51 (in 5% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.25 (m, 5H), 7.06 (d, J = 3.2 HZ, 1H), 6.91-6.89 (m, 2H), 6.53 (d, J = 3.2 Hz, 1H), 5.57 (s, 2H), 2.60 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.1, 135.5, 131.3, 129.1, 128.9, 127.4, 125.3, 124.7, 120.7, 119.9, 119.8, 102.1, 52.8, 18.4. IR (neat, cm^{-1}): 1514, 1492, 1447, 1371, 1384, 1353, 1315, 1177, 1101, 1027, 972, 798, 721, 693. HRMS (ESI): calcd. for $[C_{16}H_{15}BrN]$ $[M+H]^+$: 300.0382; found: 300.0381.

Synthesis of *o*-alkynylacetophenones 4.16:

o-Alkynylacetophenones **4.15a-4.15e**, **4.15g**, **4.15h-4.15j**, and **4.15l-4.15m** were synthesized according to the previous reports.[18] Oher *o*-alkynylacetophenone derivatives **4.15f** and **4.15k** were synthesized by the following procedures.

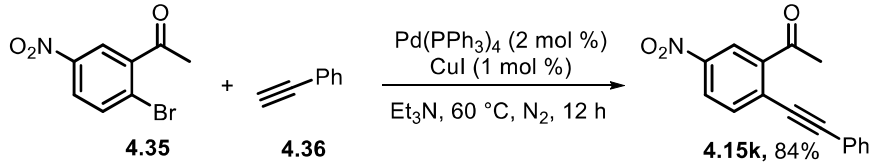
Procedure for the synthesis of *N*-(3-(2-Acetylphenyl)prop-2-yn-1-yl)-4-methylbenzenesulfonamide 4.15g:[19]

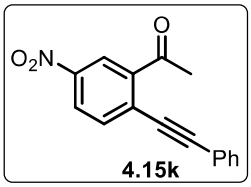




2-Iodoacetophenone **4.33** (400 mg, 1.62 mmol), and 4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide **4.34** (405 mg, 1.94 mmol), were dissolved in dry THF (17 mL) and then diisopropylamine (DIPA) (1.2 mL, 8.1 mmol) was added to the above stirred solution before cooling down to the 0 ˚C. Later, $Pd(PPh_3)_3Cl_2$ (12 mg, 0.064 mmol), and CuI (22 mg, 0.03 mmol) were added and the reaction mixture was allowed to warm to room temperature and stirred for overnight. After completion of the reaction, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with saturated brine solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc mixture as eluent) to afford the pure product **4.15g** as a yellow solid in 85% (461 mg) yield, mp 103–105 ˚C, R_f = 0.33 (in 40% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (dt, J = 8.5, 2.0 Hz, 2H), 7.67-7.65 (m, 1H), 7.40-7.34 (m, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.22-7.20 (m, 1H), 4.90 (t, J = 5.5 Hz, 1H), 4.10 (d, J = 6.0 Hz, 2H), 2.55 (s, 3H), 2.33 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 199.7, 143.6, 140.3, 136.7, 134.1, 131.1, 129.6, 128.5, 128.4, 127.3, 126.3, 120.5, 88.8, 83.6, 33.8, 29.4, 21.3. IR (neat, cm^{-1}): 3282, 1682, 1594, 1478, 1426, 1322, 1246, 1157, 1067, 964, 812, 767, 662, 608. HRMS (ESI): calcd. for [$C_{18}H_{17}NNaO_3S$] [M+Na]$^+$: 350.0821; found: 350.0827.

Procedure for the synthesis of 1-(5-nitro-2-(phenylethynyl)phenyl)ethan-1-one 4.15k:

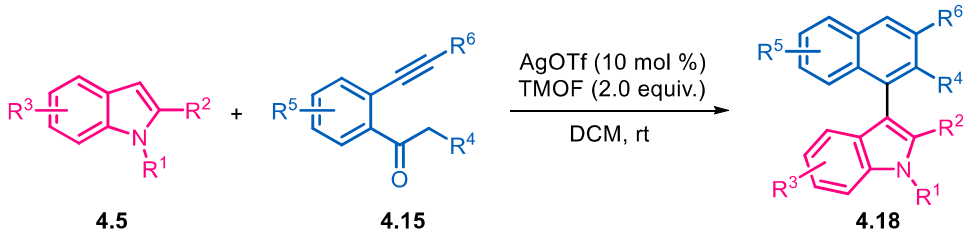




To a stirred solution of 1-(2-bromo-5-nitrophenyl)ethan-1-one[20] **4.35** (500 mg, 2.05 mmol) in triethylamine, $Pd(PPh_3)_4$ (47 mg, 0.041 mmol) was added under nitrogen atmosphere, and the resulting solution was stirred for 5 min before adding CuI (4 mg, 0.021 mmol). The resulting solution was stirred for another 5 min. After 5 min, phenylacetylene **4.36** (0.27 mL, 2.46 mmol) was added, and the resulting solution was stirred at 60 ℃ for 12 h. The reaction mixture was then diluted with EtOAc, filtered through a celite pad, and evaporated under reduced pressure. The crude reaction mixture was purified by column chromatography to obtain pure 1-(5-nitro-2-

(phenylethynyl)phenyl)ethan-1-one **4.15k** as a yellow solid (461 mg, 84%). mp = 111-113˚C, R_f = 0.46 (in 10% EtOAc/Hex). IR (neat, cm^{-1}): 3103, 2214, 1686, 1599, 1574, 1509, 1490, 1340, 1294, 1259, 1109, 1061, 910, 890, 845, 743, 685. ^1H NMR (500 MHz, $CDCl_3$): δ 8.61 (d, J = 2.0 Hz, 1H), 8.31 (dd, J = 8.5, 2.5 Hz, 1H), 7.79 (d, J = 8.5 Hz, 1H), 7.59-7.57 (m, 2H), 7.45-7.39 (m, 3H), 2.83 (s, 3H). ^{13}C {^1H} NMR (100 MHz, $CDCl_3$): δ 197.6, 146.7, 141.3, 134.9, 131.8, 129.8, 128.6, 128.0, 125.5, 123.9, 121.8, 100.5, 87.1, 29.7. HRMS (ESI): calcd. for [$C_{16}H_{12}NO_3$] [M+H]$^+$: 266.0812; found: 266.0813.

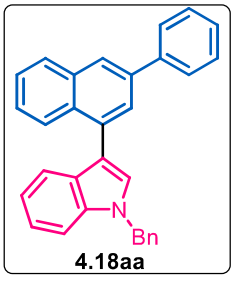
General procedure for the synthesis of C3-naphthyl indole derivatives 4.18:



4.5 **4.15** **4.18**

To a stirred solution of *o*-alkynylacetophenone **4.15** (1.2 equiv.), *N*-protected indole **4.5** (0.4 mmol, 1.0 equiv.) and TMOF (2.0 equiv.) in DCM (4 mL) was added AgOTf (10 mol %) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at the same temperature. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc mixture as eluent) to afford the pure product **4.18**.

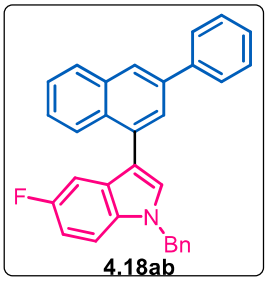
1-Benzyl-3-(3-phenylnaphthalene-1-yl)-1*H*-indole 4.18aa:



4.18aa

White solid, 85% (140 mg) yield, mp 88-90 ˚C, R_f = 0.5 (in 5% EtOAc/Hex). ^1H NMR (500 MHz, $CDCl_3$): δ 8.15 (d, J = 8.5 Hz, 1H), 8.08 (s, 1H), 8.49 (d, J = 8.0 Hz, 1H), 7.94-7.93 (m, 1H), 7.81-7.79 (m, 2H), 7.61 (dd, J = 8.0, 0.5 Hz, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.52-7.49 (m, 2H), 7.45-7.40 (m, 3H), 7.38-7.35 (m, 3H), 7.33-7.28 (m, 2H), 7.26 (d, J = 7.0 Hz, 2H), 7.18-7.15 (m, 1H), 5.46 (s, 2H). ^{13}C {^1H} NMR (125 MHz, $CDCl_3$): δ 141.1, 138.2, 137.3, 136.6, 134.4, 133.5, 131.7, 128.9, 128.8, 128.6, 128.4, 127.7, 127.5, 127.4, 127.3, 127.0, 126.4, 126.1, 125.8, 124.9, 122.2, 120.6, 119.9, 115.6, 110.0, 50.3. IR (neat, cm^{-1}): 1549, 1493, 1451, 1383, 1337, 1257, 1167, 1074, 1014, 883, 763, 736, 693. HRMS (ESI): calcd. for [$C_{31}H_{24}N$] [M+H]$^+$: 410.1903; found: 410.1905.

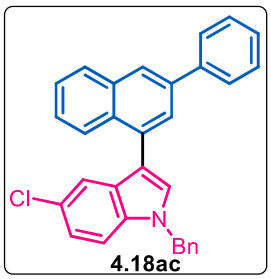
1-Benzyl-5-fluoro-3-(3-phenylnaphthalene-1-yl)-1*H*-indole 4.18ab:



4.18ab

White solid, 71% (121 mg) yield, mp 140-142 ˚C, R_f = 0.38 (in 5% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08 (d, J = 8.5 Hz, 2H), 7.98 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 2.0 Hz, 1H), 7.78 (dd, J = 8.5, 1.0 Hz, 2H), 7.55-7.52 (m, 1H), 7.51-7.48 (m, 2H), 7.45-7.42 (m, 1H), 7.42 (s, 1H), 7.39-7.38 (m, 1H), 7.37-7.35 (m, 2H), 7.33-7.28 (m, 2H), 7.26-7.20 (m, 3H), 7.00 (td, J = 9.5, 2.5 Hz, 1H), 5.43 (s, 2H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 159.1, 157.2, 141.0, 138.2, 136.9, 134.3, 133.1, 132.9, 131.5, 129.2, 128.9, 128.8, 128.6, 127.8, 127.4, 127.3, 127.2, 126.8, 126.1 (d, J_{CF} = 30 Hz), 125.9, 125.0, 115.5 (d, J_{CF} = 20 Hz), 110.7 (d, J_{CF} = 15 Hz), 110.6, 110.5, 105.4, 105.2, 50.5. ^{19}F NMR (470 MHz, $CDCl_3$), -124.0. IR (neat, cm^{-1}): 1542, 1480, 1447, 1246, 1181, 955, 895, 853, 790, 761, 693, 651. HRMS (ESI): calcd. for $[C_{31}H_{23}FN]$ $[M+H]^+$: 428.1809; found: 428.1809.

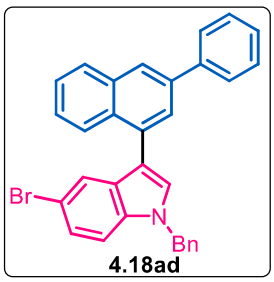
1-Benzyl-5-chloro-3-(3-phenylnaphthalene-1-yl)-1*H*-indole 4.18ac:



4.18ac

White solid, 73% (130 mg) yield, mp 158-160 ˚C, R_f = 0.41 (in 5% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (s, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 1.5 Hz, 1H), 7.77 (d, J = 7.5 Hz, 2H), 7.54 (d, J = 7.0 Hz, 1H), 7.51-7.48 (m, 3H), 7.45-7.42 (m, 1H), 7.41-7.39 (m, 1H), 7.37 (s, 1H), 7.35 (d, J = 7.5 Hz, 2H), 7.30-7.29 (m, 2H), 7.23-7.19 (m, 3H), 5.42 (s, 2H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 140.9, 138.2, 136.8, 134.9, 134.3, 132.7, 131.6, 129.3, 128.9, 128.8, 128.6, 127.9, 127.44, 127.40, 127.3, 126.8, 126.2, 126.0, 125.9, 125.8, 125.2, 122.5, 119.8, 115.2, 111.0, 50.4. IR (neat, cm^{-1}): 1595, 1494, 1467, 1349, 1267, 1169, 1065, 1028, 884, 851, 747, 693, 642. HRMS (ESI): calcd. for $[C_{31}H_{23}ClN]$ $[M+H]^+$: 444.1514; found: 444.1514.

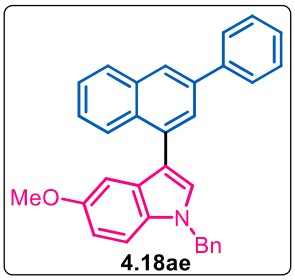
1-Benzyl-5-bromo-3-(3-phenylnaphthalene-1-yl)-1*H*-indole 4.18ad:



4.18ad

White solid, 80% (156 mg) yield, mp 64-66 ˚C, R_f = 0.48 (in 5% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 1.6 Hz, 1H), 7.99 (dd, J = 13.6, 8.4 Hz, 2H), 7.83 (d, J = 2.0 Hz, 1H), 7.78-7.75 (m, 2H), 7.65 (d, J = 2.0 Hz, 1H), 7.55-7.47 (m, 3H), 7.45-7.40 (m, 1H), 7.39-7.35 (m, 3H), 7.34-7.30 (m, 3H), 7.25 (d, J = 8.4 Hz, 1H), 7.21 (d, J = 6.8 Hz, 2H), 5.42 (s, 2H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 140.9, 138.2, 136.8, 135.1, 134.3, 132.6, 131.6, 130.0, 128.9, 128.8, 128.7, 128.6, 127.9, 127.4, 127.3, 126.8, 126.2, 126.09, 126.00, 125.2, 125.1, 122.9, 115.1, 113.4, 111.4, 50.4. IR (neat, cm^{-1}): 1595, 1493, 1466, 1349, 1266, 1168, 1027, 884, 789, 749, 693. HRMS (ESI): calcd. for $[C_{31}H_{23}BrN]$ $[M+H]^+$: 488.1008; found: 488.1008.

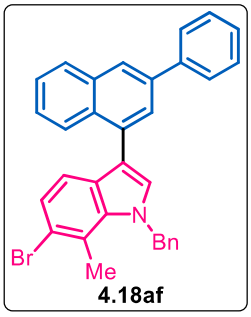
1-Benzyl-5-methoxy-3-(3-phenylnaphthalene-1-yl)-1*H*-indole 4.18ae:



4.18ae

White solid, 90% (159 mg) yield, mp 62-64 ˚C, R_f = 0.4 (in 5% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (d, J = 8.5 Hz, 1H), 8.06 (d, J = 1.5 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 2.0 Hz, 1H), 7.79-7.77 (m, 2H), 7.54-7.51 (m, 1H), 7.50-7.47 (m, 2H), 7.44-7.40 (m, 1H), 7.39 (dt, J = 7.5, 1.0 Hz, 1H), 7.36 (dt, J = 3.5, 1.0 Hz, 1H), 7.35-7.33 (m, 2H), 7.30-7.27 (m, 2H), 7.24-7.22 (m, 2H), 6.98 (d, J = 2.0 Hz, 1H), 6.91 (dd, J = 9.0, 2.5 Hz, 1H), 5.41 (s, 2H), 3.71 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 154.4, 141.0, 138.2, 137.3, 134.3, 133.6, 131.7, 131.6, 128.8, 128.6, 128.5, 128.3, 127.7, 127.4, 127.3, 127.2, 126.8, 126.5, 126.1, 125.7, 124.8, 115.1, 112.6, 110.8, 101.9, 55.8, 50.4. IR (neat, cm^{-1}): 1482, 1448, 1338, 1282, 1213, 1175, 1040, 886, 790, 748, 694. HRMS (ESI): calcd. for $[C_{32}H_{26}NO]$ $[M+H]^+$: 440.2009; found: 440.2009.

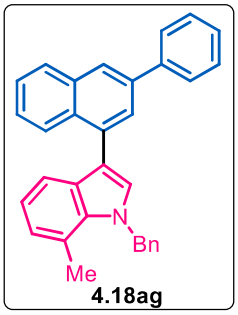
1-Benzyl-6-bromo-7-methyl-3-(3-phenylnaphthalen-1-yl)-1*H*-indole 4.18af:



4.18af

White solid, 77% (156 mg) yield, mp 164-166 ˚C, R_f = 0.58 (in 10% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, J = 1.5 Hz, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 2.0 Hz, 1H), 7.76 (dt, J = 8.0, 1.5 Hz, 2H), 7.53-7.47 (m, 3H), 7.42-7.41 (m, 1H), 7.39 (dt, J = 7.5, 1.0 Hz, 1H), 7.36-7.33 (m, 2H), 7.31-7.28 (m, 3H), 7.21 (dd, J = 8.5, 0.5 Hz, 1H), 7.05 (d, J = 7.0 Hz, 2H), 5.70 (s, 2H), 2.69 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 140.9, 138.9, 138.1, 135.7, 134.3, 132.7, 131.6, 130.6, 129.0, 128.8, 128.7, 128.6, 127.5, 127.49, 127.43, 127.3, 126.2, 126.1, 125.8, 125.4, 125.1, 124.9, 121.0, 120.3, 119.3, 115.6, 52.9, 18.4. IR (neat, cm^{-1}): 1599, 1493, 1448, 1410, 1351, 1171, 1014, 963, 877, 820, 790, 757, 689. HRMS (ESI): calcd. for $[C_{32}H_{25}BrN]$ $[M+H]^+$: 502.1165; found: 502.1164.

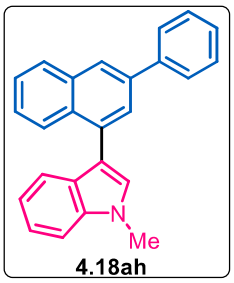
1-Benzyl-7-methyl-3-(3-phenylnaphthalen-1-yl)-1*H*-indole 4.18ag:



4.18ag

White solid, 80% (136 mg) yield, mp 102-104 ˚C, R_f = 0.57 (in 10% EtOAc/Hex). ^{1}H NMR (MHz, $CDCl_3$): 8.12 (d, J = 8.5 Hz, 1H), 8.08 (s, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 2.0 Hz, 1H), 7.79 (dt, J = 8.0, 1.0 Hz, 2H), 7.55-7.49 (m, 3H), 7.45-7.43 (m, 1H), 7.42 (dt, J = 7.0, 1.5 Hz, 1H), 7.39 (dt, J = 7.5, 1.5 Hz, 1H), 7.35 (tt, J = 7.0, 1.0 Hz, 2H), 7.31 (s, 1H), 7.30-7.27 (s, 1H), 7.08 (d, J = 7.5 Hz, 2H), 7.04 (t, J = 7.0 Hz, 1H), 6.99 (d, J = 7.0 Hz, 1H), 5.71 (s, 2H), 2.64 (s, 3H). δ ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 141.0, 139.4, 138.1, 135.2, 134.3, 133.4, 131.7, 129.6, 129.3, 128.9, 128.8, 128.5, 127.4, 127.3, 126.4, 126.1, 125.7, 125.5, 125.0, 124.8, 121.3, 120.1, 118.6, 115.5, 52.3, 19.6. IR (neat, cm^{-1}): 1597, 1493, 1448, 1414, 1375, 1169, 1074, 1028, 883, 812, 745, 693. HRMS (ESI): calcd. for $[C_{32}H_{26}N]$ $[M+H]^+$: 424.2060; found: 424.2060.

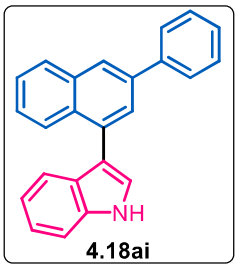
1-Methyl-3-(3-phenylnaphthalen-1-yl)-1*H*-indole 4.18ah:



4.18ah

White solid, 75% (100 mg) yield, mp 92-94 ˚C, R_f = 0.58 (in 5% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, J = 8.4 Hz, 1H), 8.06 (s, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 1.6 Hz, 1H), 7.80-7.78 (m, 2H), 7.58 (d, J = 8.0 Hz, 1H), 7.55-7.49 (m, 3H), 7.48-7.43 (m, 2H), 7.42-7.39 (m, 1H), 7.37-7.33 (m, 1H), 7.31 (s, 1H), 7.17-7.13 (m, 1H), 3.93 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 141.1, 138.1, 136.9, 134.3, 133.6, 131.7, 128.8, 128.5, 128.3, 128.0, 127.4, 127.28, 127.24, 126.4, 126.1, 125.6, 124.7, 121.9, 120.4, 119.6, 114.9, 109.4, 32.8. IR (neat, cm^{-1}): 1594, 1472, 1355, 1227, 1154, 1114, 1064, 1012, 883, 735, 694. HRMS (ESI): calcd. for $[C_{25}H_{20}N]$ $[M+H]^+$: 334.1590; found: 334.1593.

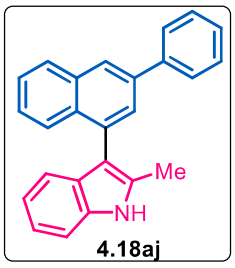
3-(3-Phenylnaphthalen-1-yl)-1*H*-indole 4.18ai:



4.18ai

White solid, 60% (80 mg) yield, mp 95-97 ˚C, R_f = 0.30 (in 10% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (bs, 1H), 8.11-8.08 (m, 2H), 7.99 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 2.0 Hz, 1H), 7.80-7.78 (m, 2H), 7.57 (d, J = 8.0 Hz, 1H), 7.56-7.53 (m, 1H), 7.52-7.48 (m, 3H), 7.44-7.41 (m, 2H), 7.38 (dt, J = 7.2, 2.0 Hz, 1H), 7.32-7.28 (m, 1H), 7.18-7.14 (m, 1H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 141.0, 138.1, 136.0, 134.3, 133.5, 131.7, 128.8, 128.5, 127.6, 127.4, 127.34, 127.33, 126.3, 126.1, 125.7, 124.9, 123.6, 122.4, 120.3, 120.1, 116.4, 111.2. IR (neat, cm^{-1}): 3412, 1594, 1492, 1452, 1418, 1243, 1092, 884, 739, 694. HRMS (ESI): calcd. for $[C_{24}H_{18}N]$ $[M+H]^+$: 320.1434; found: 320.1436.

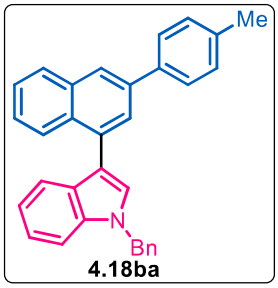
2-Methyl-3-(3-phenylnaphthalen-1-yl)-1*H*-indole 4.18aj:



4.18aj

Yellow liquid, 65% (87 mg) yield, R_f = 0.33 (in 20% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (bs, 1H), 8.09 (s, 1H), 7.99 (d, J = 8.0 Hz, 1H), 7.81-7.77 (m, 4H), 7.53-7.46 (m, 3H), 7.42-7.36 (m, 3H), 7.30 (d, J = 8.0 Hz, 1H), 7.20 (dt, J = 7.5, 1.5 Hz, 1H), 7.08-7.04 (m, 1H), 2.37 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 141.1, 138.1, 135.2, 134.2, 133.5, 132.7, 132.1, 129.3, 128.8, 128.5, 128.1, 127.4, 127.3, 126.6, 126.0, 125.6, 124.9, 121.4, 119.8, 119.3, 112.8, 110.2, 12.5. IR (neat, cm^{-1}): 3399, 1595, 1494, 1457, 1324, 1303, 1244, 1212, 1011, 883, 741, 694. HRMS (ESI): calcd. for $[C_{25}H_{20}N]$ $[M+H]^+$: 334.1590; found: 334.1603.

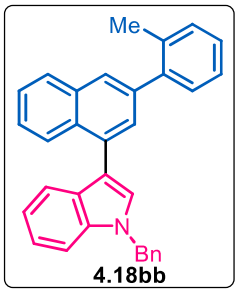
1-Benzyl-3-(3-(p-tolyl)naphthalen-1-yl)-1*H*-indole 4.18ba:



4.18ba

White solid, 82% (140 mg) yield, mp 66–68 °C, R_f = 0.59 (in 10% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 1.6 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 2.0 Hz, 1H), 7.68 (dt, J = 8.0, 2.4 Hz, 2H), 7.59 (dt, J = 8.0, 1.2 Hz, 1H), 7.53-7.49 (m, 1H), 7.42-7.40 (m, 2H), 7.38-7.33 (m, 3H), 7.31-7.28 (m, 3H), 7.26-7.24 (m, 3H), 7.16-7.12 (m, 1H), 5.45 (s, 2H), 2.42 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 138.1, 138.0, 137.2, 137.0, 136.5, 134.3, 133.3, 131.5, 129.5, 128.8, 128.5, 128.3, 127.7, 127.6, 127.2, 126.8, 126.3, 126.0, 125.5, 124.4, 122.1, 120.5, 119.8, 115.5, 109.9, 50.1, 21.1. IR (neat, cm^{-1}): 1597, 1495, 1464, 1336, 1255, 1168, 1016, 887, 813, 731, 698. HRMS (ESI): calcd. for $[C_{32}H_{26}N]$ $[M+H]^+$: 424.2060; found: 424.2061.

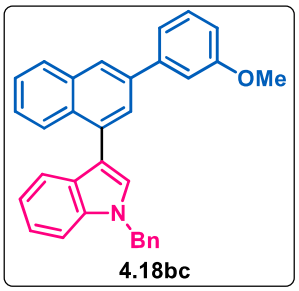
1-benzyl-3-(3-(*o*-tolyl)naphthalen-1-yl)-1*H*-indole 4.18bb:



4.18bb

Yellow liquid, 80% (136 mg) yield, R_f = 0.41 (in 5% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (d, J = 8.5 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 1.5 Hz, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.54-7.51 (m, 1H), 7.45-7.41 (m, 1H), 7.40-7.39 (m, 2H), 7.36-7.30 (m, 6H), 7.29-7.27 (m, 2H), 7.24-7.23 (m, 2H), 7.15-7.12 (m, 1H), 5.44 (s, 2H), 2.39 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 141.8, 139.2, 137.2, 136.6, 135.5, 133.9, 132.6, 131.3, 130.3, 130.0, 129.4, 128.8, 128.37, 128.33, 127.75, 127.72, 127.3, 126.9, 126.8, 126.4, 125.9, 125.7, 125.6, 122.1, 120.5, 119.8, 115.5, 109.9, 50.2, 20.6. IR (neat, cm^{-1}): 1595, 1492, 1463, 1336, 1168, 1015, 905, 889, 725, 647. HRMS (ESI): calcd. for $[C_{32}H_{26}N]$ $[M+H]^+$: 424.2060; found: 424.2060.

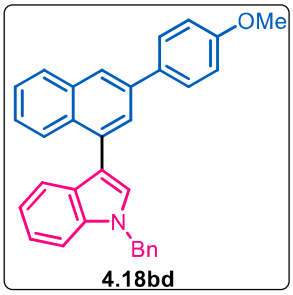
1-benzyl-3-(3-(3-methoxyphenyl)naphthalen-1-yl)-1*H*-indole 4.18bc:



4.18bc

Yellow liquid, 77% (136 mg) yield, R_f = 0.39 (in 5% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (d, J = 8.0 Hz, 1H), 8.04 (s, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 2.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.52-7.49 (m, 1H), 7.41-7.38 (m, 3H), 7.37-7.36 (m, 2H), 7.34-7.32 (m, 2H), 7.29-7.28 (m, 2H), 7.25-7.23 (m, 3H), 7.12 (t, J = 7.0 Hz, 1H), 6.93-6.91 (m, 1H), 5.44 (s, 2H), 3.88 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.9, 142.6, 138.0, 137.2, 136.5, 134.3, 133.4, 131.7, 129.7, 128.8, 128.5, 128.3, 127.7, 127.3, 126.9, 126.4, 126.1, 125.7, 124.9, 122.1, 120.5, 119.9(8), 119.9(2), 115.5, 113.1, 112.8, 109.9, 55.3, 50.2. IR (neat, cm^{-1}): 1595, 1490, 1383, 1247, 1169, 1041, 780, 730, 693, 618. HRMS (ESI): calcd. for $[C_{32}H_{26}NO]$ $[M+H]^+$: 440.2009; found: 440.2010.

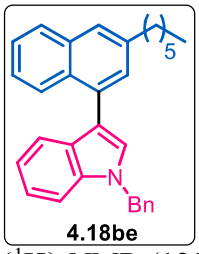
1-Benzyl-3-(3-(4-methoxyphenyl)naphthalen-1-yl)-1*H*-indole 4.18bd:



4.18bd

Yellow liquid, 86% (152 mg) yield, R_f = 0.31 (in 5% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, J = 8.0 Hz, 1H), 8.00 (s, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.86 (s, 1H), 7.71 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 7.5 Hz, 1H), 7.50 (t, J = 7.0 Hz, 1H), 7.40 (t, J = 8.0 Hz, 1H), 7.36 (s, 1H), 7.34 (d, J = 7.0 Hz, 1H), 7.29 (t, J = 7.0 Hz, 1H), 7.26-7.24 (m, 3H), 7.13 (t, J = 7.5 Hz, 1H), 7.02 (d, J = 8.5 Hz, 2H), 5.45 (s, 2H), 3.87 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.1, 137.7, 137.2, 136.5, 134.4, 133.5, 133.3, 131.3, 128.7, 128.4, 128.3, 127.7, 127.1, 126.8, 126.3, 126.0, 125.4, 124.0, 122.1, 120.5, 119.8, 115.5, 114.2, 109.9, 55.2, 50.1. IR (neat, cm^{-1}): 1606, 1512, 1462, 1244, 1029, 827, 730, 698. HRMS (ESI): calcd. for [$C_{32}H_{26}NO$] [M+H]$^+$: 440.2009; found: 440.2009.

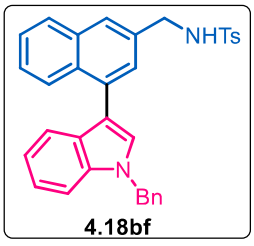
1-Benzyl-3-(3-hexylnaphthalen-1-yl)-1*H*-indole 4.18be:



4.18be

Yellow liquid, 73% (122 mg) yield, R_f = 0.7 (in 10% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$): δ. 8.06 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.63 (s, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 1.5 Hz, 1H), 7.47-7.44 (m, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.35 (tt, J = 7.0, 1.5 Hz, 3H), 7.33-7.26 (m, 3H), 7.25-7.23 (m, 3H), 7.14-7.11 (m, 1H), 5.44 (s, 2H), 2.81 (t, J = 7.5 Hz, 2H), 1.78-1.72 (m, 2H), 1.45-1.39 (m, 2H), 1.37-1.31 (m, 4H), 0.90 (t, J = 7.0 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ. 140.1, 137.4, 136.5, 134.3, 132.6, 130.9, 129.3, 128.8, 127.7, 127.6(9), 127.6(0), 126.9, 126.3, 125.6, 125.4, 124.8, 122.0, 120.5, 119.7, 115.7, 109.8, 50.2, 36.1, 31.7, 31.3, 29.1, 22.6. 14.0. IR (neat, cm^{-1}): 1599, 1543, 1495, 1463, 1386, 1352, 1252, 1168, 1075, 1014, 955, 877, 783, 737, 694, 616. HRMS (ESI): calcd. for [$C_{31}H_{32}N$] [M+H]$^+$: 418.2529; found: 418.2529.

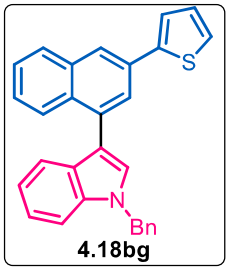
N-((4-(1-benzyl-1*H*-indol-3-yl)naphthalen-2-yl)methyl)-4-methylbenzenesulfonamide 4.18bf:



4.18bf

Yellow liquid, 69% (143 mg) yield, R_f = 0.28 (in 20% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (d, J = 8.5 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.61 (s, 1H), 7.47 (t, J = 7.0 Hz, 1H), 7.41-7.36 (m, 5H), 7.34 (d, J = 7.5 Hz, 2H), 7.31-7.28 (m, 2H), 7.22 (t, J = 7.5 Hz, 5H), 7.10 (t, J = 7.5 Hz, 1H), 5.42 (s, 2H), 4.73 (t, J = 6.0 Hz, 1H), 4.33 (d, J = 6.5 Hz, 2H), 2.32 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ.143.4, 137.2, 136.9, 136.5, 133.8, 133.7, 133.2, 131.9, 129.6, 128.8, 128.1, 127.7, 127.6, 127.2, 127.1, 126.9, 126.5, 126.1, 125.9, 125.7, 122.2, 120.4, 119.9, 115.1, 109.9, 50.2, 47.4, 21.3. IR (neat, cm^{-1}): 3276, 3029, 2923, 1598, 1494, 1464, 1452, 1323, 1153, 1091, 880, 812, 739, 663, 547. HRMS (ESI): calcd. for [$C_{33}H_{29}N_2O_2S$] [M+H]$^+$: 517.1944; found: 517.1945.

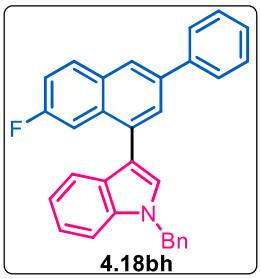
1-Benzyl-3-(3-(thiophen-2-yl)naphthalen-1-yl)-1*H*-indole 4.18bg:



4.18bg

Yellow liquid, 78% (130 mg) yield, R_f = 0.4 (in 5% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07-8.06 (m, 2H), 7.92 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 1.5 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.52-7.48 (m, 1H), 7.46 (dd, J = 3.5 1.0 Hz, 1H), 7.42-7.38 (m, 2H), 7.37 (s, 1H), 7.37-7.36 (m, 2H), 7.33-7.32 (m, 1H), 7.30-7.28 (m, 1H), 7.26-7.25 (m, 3H), 7.16-7.12 (m, 2H), 5.45 (s, 2H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 144.5, 137.2, 136.5, 134.3, 133.6, 131.8, 131.4, 128.8, 128.3, 128.2, 128.0, 127.7, 126.9, 126.4, 126.3, 126.0, 125.7, 124.9, 123.4, 123.3, 122.2, 120.4, 119.9, 115.2, 109.9, 50.2. IR (neat, cm^{-1}): 1596, 1542, 1494, 1463, 1385, 1352, 1234, 1167, 1028, 1012, 880, 853, 821, 729, 693. HRMS (ESI): calcd. for [$C_{29}H_{22}NS$] [M+H]$^+$: 416.1467; found: 416.1472.

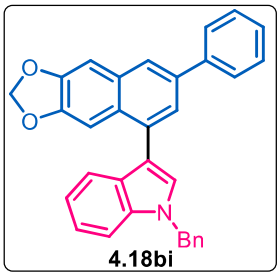
1-Benzyl-3-(7-fluoro-3-phenylnaphthalen-1-yl)-1*H*-indole 4.18bh:



4.18bh

White solid, 76% (130 mg) yield, mp 60–62 ˚C, R_f = 0.5 (in 10% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$): δ. 8.04 (s, 1H), 7.98-7.93 (m, 2H), 7.77-7.74 (m, 3H), 7.58 (dt, J = 7.6, 1.2 Hz, 1H), 7.51-7.47 (m, 2H), 7.43-7.38 (m, 2H), 7.37-7.34 (m, 3H), 7.33-7.25 (m, 6H), 7.18-7.14 (m, 1H), 5.46 (s, 2H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 160.8 (d, J = 244.0 Hz), 140.8, 137.5 (d, J = 2.5 Hz), 137.1, 136.6, 132.8 (dd, J = 50, 5 Hz), 131.3, 130.9, 130.8, 128.8(7), 128.8(5), 128.1(9), 128.1(0), 127.7, 127.6, 127.3, 126.9, 124.6, 122.3, 120.2 (d, J = 21.2 Hz), 116.4 (d, J = 26.2 Hz), 115.0, 110.0, 109.8 (d, J = 21.2 Hz), 50.2. ^{19}F NMR (470 MHz, $CDCl_3$): δ -114.0. IR (neat, cm^{-1}): 1598, 1543, 1497, 1451, 1386, 1328, 1241, 1173, 1075, 958, 915, 881, 805, 760, 725, 693. HRMS (ESI): calcd. for [$C_{31}H_{23}FN$] [M+H]$^+$: 428.1809; found: 428.1809.

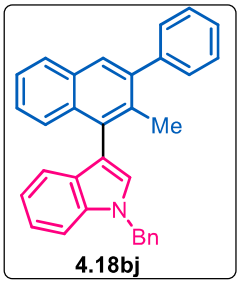
1-Benzyl-3-(7-phenylnaphtho[2,3-d][1,3]dioxol-5-yl)-1*H*-indole 4.18bi:



4.18bi

Yellow liquid, 80% (146 mg) yield, R_f = 0.27 (in 5% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J = 2.0 Hz, 1H), 7.74-7.72 (m, 3H), 7.56 (dt, J = 8.0, 1.0 Hz, 1H), 7.48-7.44 (m, 2H), 7.40 (d, J = 9.0 Hz, 2H), 7.37-7.33(7) (m, 3H), 7.33 (s, 1H), 7.31-7.27 (m, 1H), 7.25-7.23 (m, 3H), 7.15-7.12 (m, 1H), 6.02 (s, 2H), 5.44 (s, 2H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 147.7, 147.6, 141.1, 137.3, 136.8, 136.5, 132.6, 131.5, 128.9, 128.8, 128.7, 128.2, 127.7, 127.4, 127.2, 127.0, 126.9, 126.0, 124.1, 122.1, 120.5, 119.9, 115.9, 109.9, 104.3, 102.9, 101.0, 50.2. IR (neat, cm^{-1}): 2922, 1603, 1494, 1455, 1278, 1231, 1173, 1035, 951, 882, 737, 693. HRMS (ESI): calcd. for [$C_{32}H_{24}NO_2$] [M+H]$^+$: 454.1802; found: 458.1802.

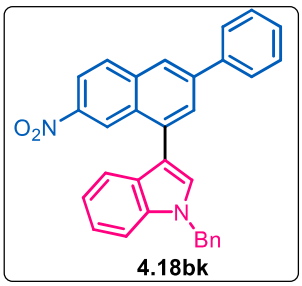
1-Benzyl-3-(2-methyl-3-phenylnaphthalen-1-yl)-1*H*-indole 4.18bj:



4.18bj

White solid, 62% (105 mg) yield, mp 62–64 ˚C, R_f = 0.35 (in 5% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 8.0 Hz, 1H), 7.78 (s, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.49-7.46 (m, 4H), 7.44-7.36 (m, 4H), 7.35-7.30 (m, 3H), 7.29-7.26 (m, 1H), 7.25-7.22 (m, 3H), 7.18 (s, 1H), 7.10-7.06 (m, 1H), 5.47 (s, 2H), 2.18 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 142.7, 141.2, 137.6, 136.5, 133.9, 133.5, 131.8, 131.4, 129.4, 128.9, 128.8, 128.0(9), 128.0(4), 127.9, 127.7, 127.6, 126.8, 126.7, 126.6, 125.6, 125.1, 121.9, 120.5, 119.6, 114.2, 109.8, 50.1, 19.4. IR (neat, cm^{-1}): 1595, 1493, 1464, 1451, 1422, 1385, 1349, 1259, 1212, 1171, 1149, 908, 886, 734, 693. HRMS (ESI): calcd. for [$C_{32}H_{26}N$] [M+H]$^+$: 424.2060; found: 424.2061.

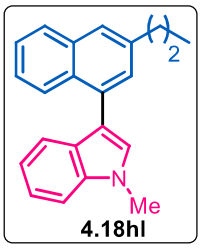
1-Benzyl-3-(7-nitro-3-phenylnaphthalen-1-yl)-1*H*-indole derivative 4.18bk:



4.18bk

Yellow solid, (132 mg, 73%), mp 160-162 ˚C, R_f = 0.40 (in 10% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.15 (d, J = 2.5 Hz, 1H), 8.26 (dd, J = 9.0, 2.5 Hz, 1H), 8.09-8.08 (m, 2H), 8.05 (d, J = 9.0 Hz, 1H), 7.94-7.77 (m, 2H), 7.62 (dt, J = 5.0, 1.0 Hz, 1H), 7.53-7.50 (m, 2H), 7.47-7.45 (m, 1H), 7.44 (tt, J = 7.5, 1.0 Hz, 1H), 7.40 (s, 1H), 7.39-7.37 (m, 1H), 7.33-7.29 (m, 4H), 7.20-7.16 (m, 1H), 5.49 (s, 2H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 145.4, 142.1, 140.0, 137.1, 136.8, 123.2, 130.3, 129.0(6), 129.0(0), 128.8, 128.2, 128.1, 127.9, 127.5, 127.1, 124.2, 123.5, 122.7, 120.6, 119.6, 113.8, 110.2, 50.3. IR (neat, cm^{-1}): 2919, 2850, 1615, 1520, 1487, 1461, 1334, 1157, 1078, 886, 828, 735, 628. HRMS (ESI): calcd. for [$C_{31}H_{23}N_2O_2$] [M+H]$^+$: 455.1754; found: 455.1754

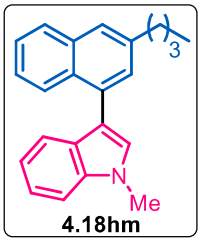
1-Methyl-3-(3-propylnaphthalen-1-yl)-1*H*-indole 4.18hl:



4.18hl

Yellow liquid, 59% (70 mg) yield, R_f = 0.4 (in 10% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.67 (s, 1H), 7.58-7.57 (m, 1H), 7.51-7.48 (m, 2H), 7.46 (d, J = 8.5 Hz, 1H), 7.40-7.33 (m, 2H), 7.28 (s, 1H), 7.19-7.16 (m, 1H), 3.92 (s, 3H), 2.84 (t, J = 7.0 Hz, 2H), 1.83 (sext, J = 7.5 Hz, 2H), 1.06 (t, J = 7.0 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 139.8, 136.9, 134.2, 132.7, 130.9, 129.2, 128.1, 128.0, 127.7, 126.3, 125.6, 125.4, 124.7, 121.8, 120.4, 119.5, 115.0, 109.3, 38.1, 32.8, 24.4, 13.9. IR (neat, cm^{-1}): 1613, 1597, 1574, 1540, 1498, 1476, 1372, 1333, 1244, 1225, 1149, 1130, 1113, 1056, 1011, 920, 850, 823, 807, 734, 647. HRMS (ESI): calcd. for [$C_{22}H_{22}N$] [M+H]$^+$: 300.1747; found: 300.1747.

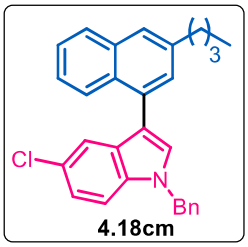
3-(3-Butylnaphthalen-1-yl)-1-methyl-1*H*-indole 4.18hm:



4.18hm

Yellow liquid, 62% (78 mg) yield, R_f = 0.5 (in 5% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, J = 8.5 Hz, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.62 (s, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.47-7.45 (m, 2H), 7.43 (d, J = 8.5 Hz, 1H), 7.35-7.29 (m, 2H), 7.25(5)-7.25(2) (m, 1H), 7.14-7.11 (m, 1H), 3.92 (s, 3H), 2.81 (t, J = 8.0 Hz, 2H), 1.77-1.70 (m, 2H), 1.47-1.39 (m, 2H), 0.96 (t, J = 7.5 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 140.0, 136.9, 134.2, 132.7, 130.9, 129.2, 128.1, 128.0, 127.7, 126.3, 125.6, 125.3, 124.7, 121.8, 120.4, 119.5, 115.0, 109.3, 35.8, 33.5, 32.8, 22.4, 14.0. IR (neat, cm^{-1}): 1598, 1542, 1463, 1422, 1358, 1332, 1245, 1227, 1152, 1130, 1115, 1059, 1011, 875, 810, 735, 646. HRMS (ESI): calcd. for [$C_{23}H_{24}N$] [M+H]$^+$: 314.1903; found: 314.1904.

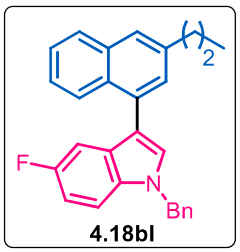
1-Benzyl-3-(3-butylnaphthalen-1-yl)-5-chloro-1*H*-indole 4.18cm:



4.18cm

Yellow liquid, 65% (110 mg) yield, R_f = 0.6 (in 10% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 8.5 Hz, 1H), 7.64 (s, 1H), 7.48-7.43 (m, 3H), 7.38-7.36 (m, 2H), 7.34-7.33 (m, 2H), 7.32 (d, J = 7.0 Hz, 1H), 7.28 (d, J = 9.0 Hz, 1H), 7.21 (d, J = 7.5 Hz, 2H), 7.19-7.17 (m, 1H), 5.41 (s, 2H), 2.82 (t, J = 8.0 Hz, 2H), 1.74 (quint, J = 7.5 Hz, 2H), 1.44 (sext, J = 7.5 Hz, 2H), 0.98 (t, J = 7.5 Hz, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 140.0, 136.9, 134.8, 134.2, 131.8, 130.8, 129.4, 129.3, 128.9, 128.8, 127.8(5), 127.8(3), 126.7, 125.9, 125.8, 125.7(7), 125.7(1), 125.0, 122.4, 119.9, 115.3, 110.9, 50.3, 35.7, 33.5, 22.4, 14.0. IR (neat, cm^{-1}): 1600, 1495, 1468, 1386, 1352, 1261, 1169, 1065, 1025, 956, 872, 849, 789, 747, 729, 696. HRMS (ESI): calcd. for [$C_{29}H_{27}ClN$] [M+H]$^+$: 424.1827; found: 424.1827.

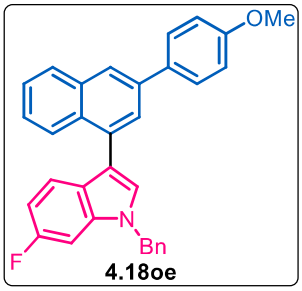
1-Benzyl-5-fluoro-3-(3-propylnaphthalen-1-yl)-1*H*-indole 4.18bl:



4.18bl

Yellow liquid, 68% (108 mg) yield, R_f = 0.51 (in 5% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.65 (s, 1H), 7.50-7.45 (m, 2H), 7.39-7.36 (m, 3H), 7.35-7.30 (m, 2H), 7.29-7.26 (m, 1H), 7.24-7.22 (m, 2H), 7.18 (dd, J = 9.6, 2.4 Hz, 1H), 6.99 (td, J = 8.8, 2.4 Hz, 1H), 5.41 (s, 2H), 2.80 (t, J = 7.6 Hz, 2H), 1.8 (sext, J = 7.6 Hz, 2H), 1.03 (t, J = 7.2 Hz, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 158.1 (d, J = 233 Hz), 139.8, 137.0, 134.2, 133.1, 132.0, 130.8, 129.2 (d, J = 4.0 Hz), 128.9, 128.7 (d, J = 10 Hz), 127.8 (d, J = 2.0 Hz), 126.8, 126.0, 125.7 (d, J = 7.0 Hz), 125.0, 115.6 (d, J = 5.0 Hz), 110.6 (d, J = 3.0 Hz), 110.5, 110.4, 105.3 (d, J = 24 Hz), 50.5, 38.1, 24.4, 13.9. ^{19}F NMR (470 MHz, $CDCl_3$): δ -124.3. IR (neat, cm^{-1}): 1599, 1576, 1481, 1451, 1353, 1245, 1181, 1092, 1024, 928, 889, 850, 789, 748, 702, 651. HRMS (ESI): calcd. for [$C_{28}H_{25}FN$] [M+H]$^+$: 394.1966; found: 394.1966.

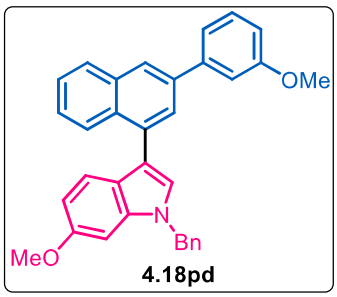
1-Benzyl-6-fluoro-3-(3-(4-methoxyphenyl)naphthalen-1-yl)-1H-indole 4.18oe:



4.18oe

White solid, 78% (143 mg) yield, mp 78-80 ˚C, R_f = 0.48 (in 5% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (d, J = 8.5 Hz, 1H), 8.00 (s, 1H), 7.95 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 1.5 Hz, 1H), 7.70 (dt, J = 9.0, 3.0 Hz, 2H), 7.52-7.49 (m, 1H), 7.45 (dd, J = 8.5, 5.5 Hz, 1H), 7.41-7.39 (m, 1H), 7.38-7.35 (m, 2H), 7.34 (s, 1H), 7.32 (m, 1H), 7.24-7.23 (m, 2H), 7.05 (dd, J = 10, 5.0 Hz, 1H), 7.02 (dt, J = 9.0, 3.0 Hz, 2H), 6.88 (td, J = 9.0, 2.0 Hz, 1H), 5.38 (s, 2H), 3.87 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 160.0 (d, J = 236 Hz), 159.2, 137.7, 136.8, 136.5 (d, J = 11.2 Hz), 134.4, 133.4, 132.9, 131.2, 128.9, 128.4(8), 128.4(2), 127.9(3), 127.9(1), 127.8, 127.1, 126.9, 126.1 (d, J = 20 Hz), 125.5, 124.9, 124.3, 121.4 (d, J = 40 Hz), 115.8, 114.2, 108.6 (d, J = 25 Hz), 96.3 (d, J = 25 Hz), 55.3, 50.4. ^{19}F NMR (470 MHz, $CDCl_3$): δ -120.1. IR (neat, cm^{-1}): 1606, 1579, 1545, 1512, 1466, 1452, 1332, 1281, 1244, 1170, 1112, 1089, 1029, 951, 907, 859, 826, 749, 701, 615. HRMS (ESI): calcd. for [$C_{32}H_{25}FNO$] [M+H]$^+$: 458.1915; found: 458.1922.

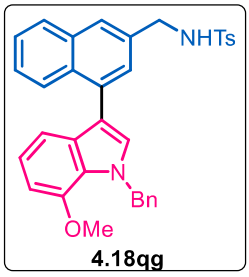
1-Benzyl-6-methoxy-3-(3-(3-methoxyphenyl)naphthalen-1-yl)-1*H*-indole 4.18pd:



4.18pd

White solid, 75% (141 mg) yield, mp 143–145 ˚C, R_f = 0.48 (in 5% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (d, J = 8.5 Hz, 1H), 8.03 (s, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 2.0 Hz, 1H), 7.53-7.49 (m, 1H), 7.44-7.38 (m, 3H), 7.37-7.34 (m, 3H), 7.31-7.28 (m, 2H), 7.26-7.24 (m, 4H), 6.93 (ddd, J = 8.0, 2.5, 1.0 Hz, 1H), 6.84 (d, J = 2.0 Hz, 1H), 6.80 (dd, J = 9.0, 2.5 Hz, 1H), 5.39, (s, 2H), 3.89 (s, 3H), 3.84 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 159.9, 156.6, 142.6, 138.0, 137.3, 137.2, 134.2, 133.5, 131.7, 129.7, 128.8, 128.5, 127.7, 127.1, 126.9, 126.6, 126.4, 126.1, 125.7, 124.8, 122.7, 121.2, 119.9, 115.5, 113.0, 112.7, 93.5, 55.7, 55.3, 50.1. IR (neat, cm^{-1}): 1595, 1571, 1488, 1453, 1331, 1257, 1212, 1168, 1094, 1040, 955, 879, 780, 748, 694. HRMS (ESI): calcd. for [$C_{33}H_{27}NNaO_2$] [M+Na]$^+$: 492.1934; found: 492.1932.

N-((4-(1-Benzyl-7-methoxy-1*H*-indol-3-yl)naphthalen-2-yl)methyl)-4-methylbenzenesulfonamide 4.18qg:

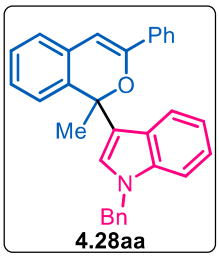


4.18qg

White solid, 71% (156 mg) yield, mp 90–92 ˚C, R_f = 0.41 (in 20% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.98 (d, J = 8.5 Hz, 1H), 7.76 (d, J = 8.5 Hz, 1H), 7.74 (dt, J = 8.0, 2.0 Hz, 2H), 7.58 (s, 1H), 7.47-7.44 (m, 1H), 7.37-7.34 (m, 1H), 7.33-7.29 (m, 3H), 7.26-7.23 (m, 1H), 7.21-7.19 (dd, J = 4H), 7.13 (s, 1H), 7.00-6.97 (m, 1H), 6.96-6.94 (m, 1H), 6.68 (dd, J = 7.0, 1.0 Hz, 1H), 5.72 (s, 2H), 4.75 (t, J = 6.0 Hz, 1H), 4.31 (d, J = 6.0 Hz, 2H), 3.88 (s, 3H), 2.31 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 147.6, 143.4, 139.3, 136.7, 133.8, 133.7, 133.1, 131.8, 130.1, 129.6, 128.5, 128.0, 127.2, 127.1, 126.8, 126.5, 126.1, 125.8, 125.7, 120.2, 115.3, 113.0, 103.0, 55.4, 52.5, 47.4, 21.3. IR (neat, cm^{-}

[1]): 1573, 1494, 1452, 1426, 1324, 1257, 1213, 1155, 1089, 1060, 811, 748, 695, 660. HRMS (ESI): calcd. for $[C_{34}H_{31}N_2O_3S]$ $[M+H]^+$: 547.2050; found: 547.2049.

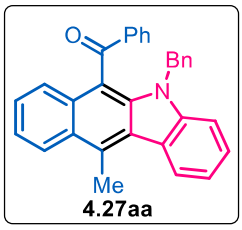
1-Benzyl-3-(1-methyl-3-phenyl-1H-isochromen-1-yl)-1*H*-indole 4.28aa:



4.28aa

Yellow solid, mp 150-152 °C, R_f = 0.46 (in 10% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74-7.72 (m, 2H), 7.67 (dt, J = 8.0, 1.0 Hz, 1H), 7.33-7.29 (m, 4H), 7.28-7.27 (m, 2H), 7.23 (dd, J = 7.5, 1.5 Hz, 1H), 7.21 (dt, J = 8.0, 1.0 Hz, 1H), 7.14 (dd, J = 7.5, 1.0 Hz, 1H), 7.12-7.07 (m, 4H), 7.02-6.98 (m, 1H), 6.97 (dt, J = 7.5, 1.0 Hz, 1H), 6.89 (s, 1H), 6.44 (s, 1H), 5.26 (s, 2H), 2.17 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 151.4, 137.5, 137.4, 135.2, 135.0, 131.2, 128.8, 128.5, 128.2, 127.8, 127.6, 126.7, 126.6, 126.5, 125.3, 124.5, 123.9, 122.0, 121.8, 119.6, 119.4, 109.9, 100.2, 79.6, 50.1, 26.0. IR (neat, cm^{-1}): 1594, 1494, 1450, 1384, 1167, 1027, 905, 733. HRMS (ESI): calcd. for $[C_{31}H_{26}NO]$ $[M+H]^+$: 428.2009; found: 428.2009.

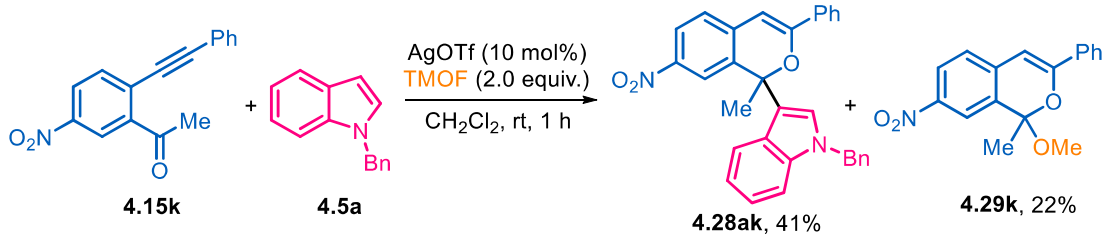
(5-Benzyl-11-methyl-5*H*-benzo[*b*]carbazol-6-yl)(phenyl)methanone 4.27aa:



4.27aa

Yellow solid, mp 185-187 °C, R_f = 0.36 (in 5% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.49 (d, J = 7.5 Hz, 1H), 8.38 (dq, J = 1.0, 0.5 Hz, 1H), 7.57 (dq, J = 1.5, 1.0 Hz, 3H), 7.49-7.42 (m, 2H), 7.37 (dt, 7.0, 1.5 Hz, 1H), 7.35-7.31 (m, 2H), 7.24 (d, J = 8.5 Hz, 1H), 7.15 (t, J = 8.0 Hz, 2H), 6.98-6.92 (m, 3H), 6.73-6.71 (m, 2H), 5.39 (s, 2H), 3.36 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 199.3, 138.3, 136.6, 133.3, 131.1, 130.2, 129.9, 128.4, 128.2, 127.1, 126.8, 126.7, 125.8, 125.5, 124.9, 124.2, 124.0, 123.8, 123.4, 122.8, 119.8, 114.3, 108.9, 48.1, 15.9. IR (neat, cm^{-1}): 1663, 1594, 1470, 1398, 1316, 1228, 1157, 1026, 929, 731. HRMS (ESI): calcd. for $[C_{31}H_{24}NO]$ $[M+H]^+$: 426.1852; found: 426.1857.

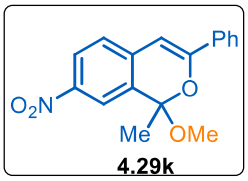
Procedure for the synthesis of 1-Methoxy-1-methyl-7-nitro-3-phenyl-1*H*-isochromene 4.29k and 1-Benzyl-3-(1-methyl-7-nitro-3-phenyl-*1H*-isochromen-1-yl)-1*H*-indole 4.28ak:



To a stirred solution of 1-(5-nitro-2-(phenylethynyl)phenyl)ethan-1-one **4.15k** (127 mg, 0.48 mmol), 1-benzyl-1*H*-indole **4.5a** (83 mg, 0.48 mmol) and TMOF (88 µL, 0.8 mmol) in DCM (4 mL) was added AgOTf (10 mg, 0.04 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at the same temperature. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was purified by column

chromatography (silica gel, hexane/EtOAc mixture as eluent) to afford the pure products 1-methoxy-1-methyl-7-nitro-3-phenyl-1*H*-isochromene **4.29k** and 1-benzyl-3-(1-methyl-7-nitro-3-phenyl-*1H*-isochromen-1-yl)-1*H*-indole **4.28ak** in 22% and 41% respectively.

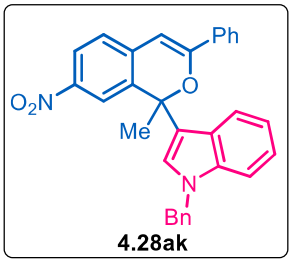
1-Methoxy-1-methyl-7-nitro-3-phenyl-1*H*-isochromene 4.29k:



4.29k

Yellow solid, 22% (30 mg) yield, mp 86-88 ˚C, R_f = 0.35 (in 10% EtOAc/Hex). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, J = 2.4 Hz, 1H), 8.18 (dd, J = 8.4, 2.4 Hz, 1H), 7.85-7.81 (m, 2H), 7.47-7.42 (m, 3H), 7.25 (d, J = 8.4 Hz, 1H), 6.51 (s, 1H), 3.32 (s, 3H), 1.97 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 154.4, 146.1, 137.8, 133.1, 130.5, 130.0, 128.6, 125.3, 124.6, 124.4, 120.6, 102.8, 97.9, 50.6, 25.7. IR (neat, cm^{-1}): 1670, 1579, 1526, 1349, 1196, 911, 836, 735, 666. HRMS (ESI): calcd. for $[C_{16}H_{12}NO_3]$ $[M\text{-}OMe]^+$: 266.0812; found: 266.0817.

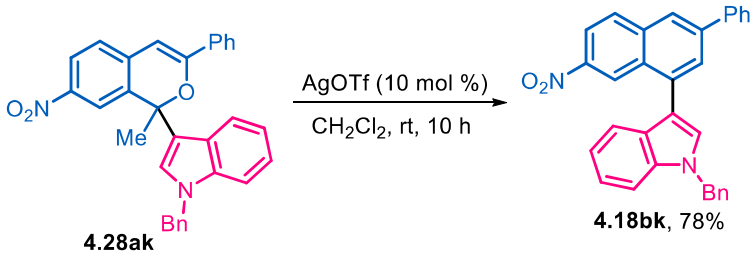
1-Benzyl-3-(1-methyl-7-nitro-3-phenyl-*1H*-isochromen-1-yl)-1*H*-indole 4.28ak:



4.28ak

Yellow solid, 41% (78 mg) yield, mp 142-144 ˚C, R_f = 0.15 (in 10% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (dd, J = 8.0, 2.0 Hz, 1H), 7.79-7.77 (m, 3H), 7.59 (d, J = 8.0 Hz, 1H), 7.37-7.36 (m, 3H), 7.34 (d, J = 7.5 Hz, 2H), 7.30-7.27 (m, 2H), 7.23 (d, J = 8.5 Hz, 1H), 7.15 (d, J = 7.5 Hz, 1H), 7.12 (d, J = 8.5 Hz, 2H), 7.01 (t, J = 7.0 Hz, 2H), 6.53 (s, 1H), 5.33 (s, 2H), 2.19 (s, 3H). ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$): δ 155.5, 145.9, 137.9, 137.6, 137.1, 135.3, 134.0, 129.8, 128.9, 128.4, 127.7, 127.4, 126.7, 126.2, 125.8, 124.0, 123.7, 122.3, 121.5, 120.4, 119.8, 118.3, 110.1, 98.6, 80.3, 50.1, 26.0. IR (neat, cm^{-1}): 1568, 1493, 1450, 1325, 1246, 1102, 1056, 899, 763, 718, 690. HRMS (ESI): calcd. for $[C_{31}H_{25}N_2O_3]$ $[M+H]^+$: 473.1860; found: 473.1864.

Synthesis of 1-benzyl-3-(7-nitro-3-phenylnaphthalen-1-yl)-1*H*-indole 4.18bk:

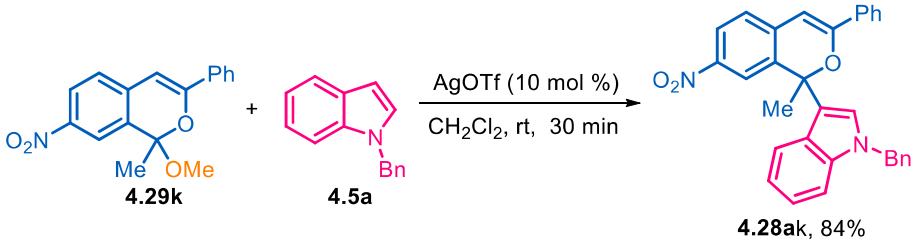


4.28ak **4.18bk**, 78%

To a stirred solution of 1-benzyl-3-(1-methyl-3-phenyl-1*H*-isochromen-1-yl)-1*H*-indole **4.28ak** (12 mg, 0.028 mmol) in DCM (1 mL) was added AgOTf (0.7 mg, 0.0028 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at the same temperature. After completion of the reaction, reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc mixture as eluent) to afford the pure 1-benzyl-3-(7-nitro-3-phenylnaphthalen-1-yl)-1*H*-indole derivative **4.18bk** as yellow solid in 78% (10 mg) yield, mp 160-162 ˚C, R_f = 0.40 (in 10% EtOAc/Hex). ^{1}H NMR (500

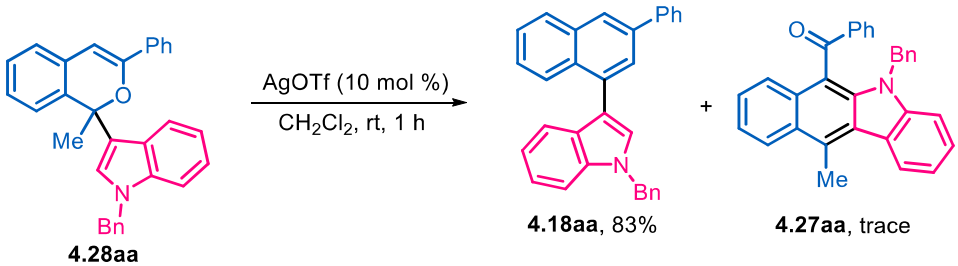
MHz, $CDCl_3$): δ 9.15 (d, J = 2.5 Hz, 1H), 8.26 (dd, J = 9.0, 2.5 Hz, 1H), 8.09-8.08 (m, 2H), 8.05 (d, J = 9.0 Hz, 1H), 7.94-7.77 (m, 2H), 7.62 (dt, J = 5.0, 1.0 Hz, 1H), 7.53-7.50 (m, 2H), 7.47-7.45 (m, 1H), 7.44 (tt, J = 7.5, 1.0 Hz, 1H), 7.40 (s, 1H), 7.39-7.37 (m, 1H), 7.33-7.29 (m, 4H), 7.20-7.16 (m, 1H), 5.49 (s, 2H). ^{13}C {^1H} NMR (100 MHz, $CDCl_3$): δ 145.4, 142.1, 140.0, 137.1, 136.8, 123.2, 130.3, 129.0(6), 129.0(0), 128.8, 128.2, 128.1, 127.9, 127.5, 127.1, 124.2, 123.5, 122.7, 120.6, 119.6, 113.8, 110.2, 50.3. IR (neat, cm^{-1}): 2919, 2850, 1615, 1520, 1487, 1461, 1334, 1157, 1078, 886, 828, 735, 628. HRMS (ESI): calcd. for $[C_{31}H_{23}N_2O_2]$ $[M+H]^+$: 455.1754; found: 455.1754.

Reaction of 1-methoxy-1-methyl-7-nitro-3-phenyl-1*H*-isochromene 4.29k with 1-benzyl-1*H*-indole 4.5a:



To a stirred solution of 1-methoxy-1-methyl-7-nitro-3-phenyl-1*H*-isochromene **4.29k** (15 mg, 0.06 mmol) and 1-benzyl-1*H*-indole **4.5a** (10 mg, 0.05 mmol) in DCM (1 mL) was added AgOTf (1.2 mg, 0.005 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at the same temperature. After completion of the reaction, reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc mixture as eluent) to afford the pure 1-benzyl-3-(1-methyl-7-nitro-3-phenyl-1*H*-isochromen-1-yl)-1*H*-indole **4.28ak** as a yellow solid in 84% (10 mg) yield.

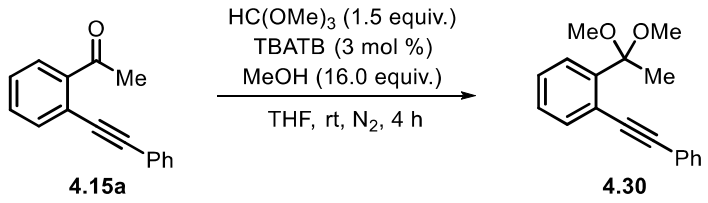
Synthesis of 1-benzyl-3-(3-phenylnaphthalen-1-yl)-1*H*-indole 4.18aa from 1-benzyl-3-(1-methyl-3-phenyl-1*H*-isochromen-1-yl)-1*H*-indole 4.28aa:



To a stirred solution of 1-benzyl-3-(1-methyl-3-phenyl-1*H*-isochromen-1-yl)-1*H*-indole **4.28aa** (23 mg, 0.05 mmol) in DCM (1 mL) was added AgOTf (1.4 mg, 0.005 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at the same temperature. After completion of the reaction, reaction mixture was concentrated under reduced pressure. The

residue was purified by column chromatography (silica gel, hexane/EtOAc mixture as eluent) to afford the pure 1-benzyl-3-(3-phenylnaphthalen-1-yl)-1*H*-indole **4.18aa** in 83% (17 mg) yield along with trace amount of (5-benzyl-11-methyl-5*H*-benzo[*b*]carbazol-6-yl)(phenyl)methanone **4.27aa**.

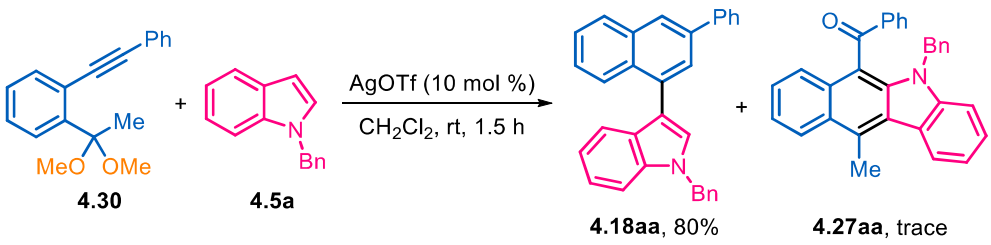
Procedure for the synthesis of 1-(1,1-dimethoxyethyl)-2-(phenylethynyl)benzene 4.30:[21]



4.15a **4.30**

A solution of 1-(2-(phenylethynyl)phenyl)ethan-1-one **4.15a** (250 mg, 1.1 mmol), MeOH (712 µL, 17.6 mmol), TMOF (182 µL, 1.65 mmol), tetrabutylammonium tribromide (TBATB) (16 mg, 0.03 mmol) and THF (2 mL) were stirred for 4 h at room temperature. After completion of the reaction, the reaction mixture was diluted with EtOAc (15 mL), and washed with saturated aqueous solution of $NaHCO_3$. The resulting organic layer was concentrated under reduced pressure and purified by column chromatography (silica gel, hexane/EtOAc mixture as eluent) to afford the pure product 1-(1,1-dimethoxyethyl)-2-(phenylethynyl)benzene **4.30** as a yellow liquid in 58% (170 mg) yield, R_f = 0.43 (in 5% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (dd, J = 8.0, 1.5 Hz, 1H), 7.57 (dd, J = 7.5, 1.5 Hz, 1H), 7.55-7.53 (m, 2H), 7.36-7.32 (m, 3H), 7.32-7.30 (m, 1H), 7.28 (dd, J = 7.5, 1.5 Hz, 1H), 3.25 (s, 6H), 1.75 (s, 3H). ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$): δ 144.0, 134.0, 131.4, 128.2, 128.04, 128.02, 127.5, 127.4, 123.9, 120.8, 101.5, 93.1, 89.1, 48.8, 23.7. IR (neat, cm^{-1}): 1678, 1592, 1491, 1440, 1355, 1275, 1244, 1068, 956, 753, 688, 595. HRMS (ESI): calcd. for $[C_{18}H_{18}NaO_2]$ $[M+Na]^+$: 289.1199; found: 289.1194.

Reaction of 1-(1,1-dimethoxyethyl)-2-(phenylethynyl)benzene 4.30 with 1-benzyl-1*H*-indole 4.5a:



4.30 **4.5a** **4.18aa**, 80% **4.27aa**, trace

To a stirred solution of 1-(1,1-dimethoxyethyl)-2-(phenylethynyl)benzene **4.30** (64 mg, 0.24 mmol) and 1-benzyl-1*H*-indole **4.5a** (41 mg, 0.2 mmol) in DCM (2 mL) was added AgOTf (5 mg, 0.02 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at the same temperature. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica

gel, hexane/EtOAc mixture as eluent) to afford the pure 1-benzyl-3-(3-phenylnaphthalen-1-yl)-1*H*-indole **4.18aa** in 80% (66 mg) yield along with trace amount of (5-benzyl-11-methyl-5*H*-benzo[*b*]carbazol-6-yl)(phenyl)methanone **4.27aa**.

Procedure of scale-up reaction for the synthesis of 4.18aa:

To a stirred solution of 1-(2-(phenylethynyl)phenyl)ethan-1-one **4.15a** (1.32 g, 6 mmol), 1-benzyl-1*H*-indole **4.5a** (1.03 g, 5 mmol) and TMOF (1.09 mL, 10 mmol) in DCM (40 mL) was added AgOTf (128 mg, 0.5 mmol) at room temperature under nitrogen atmosphere. The reaction mixture was stirred at the same temperature. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/EtOAc mixture as eluent) to afford the pure product **4.18aa** in 80% (1.65 g) yield along with 10% (212 mg) of the product **4.27aa**.

4.6 References

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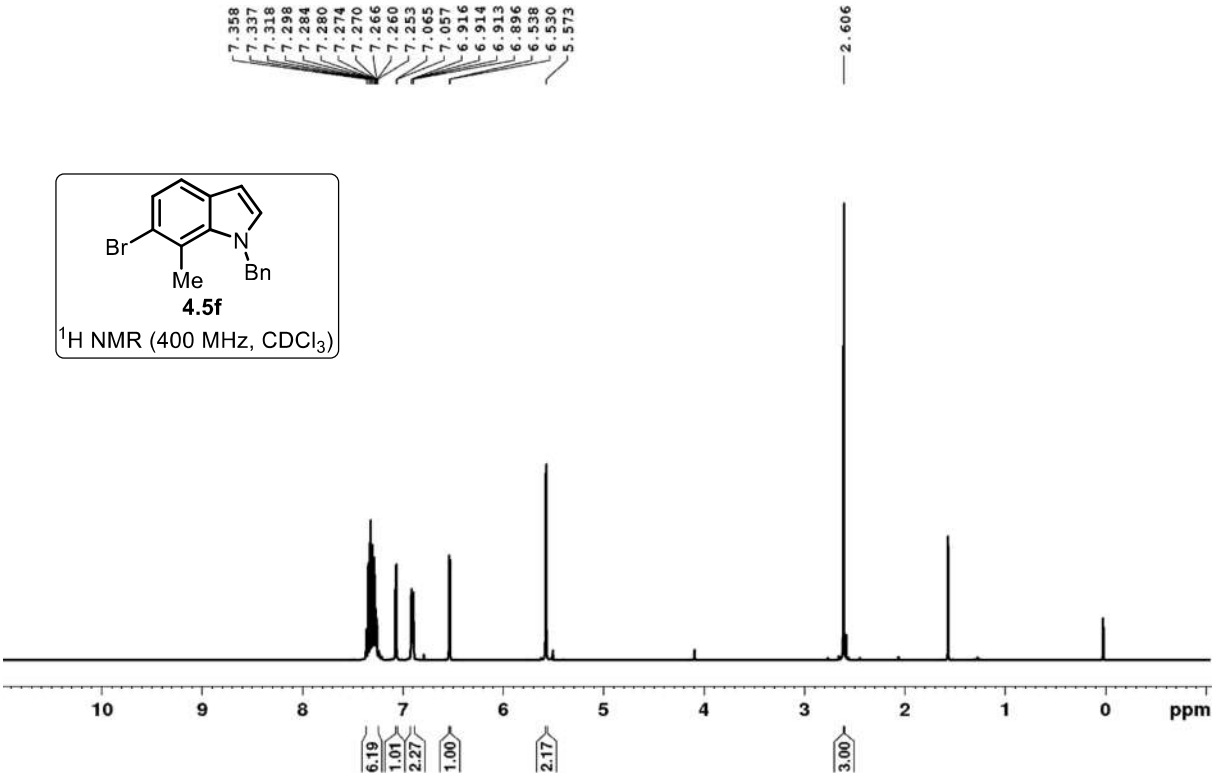
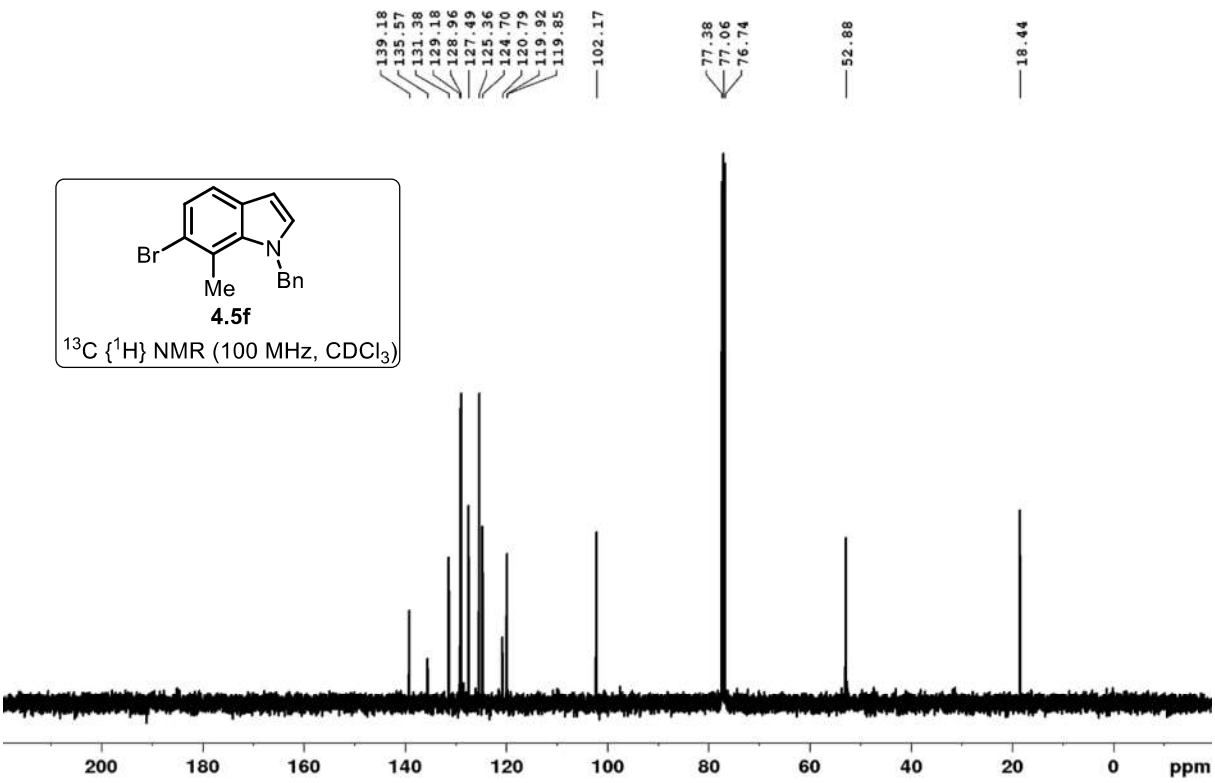
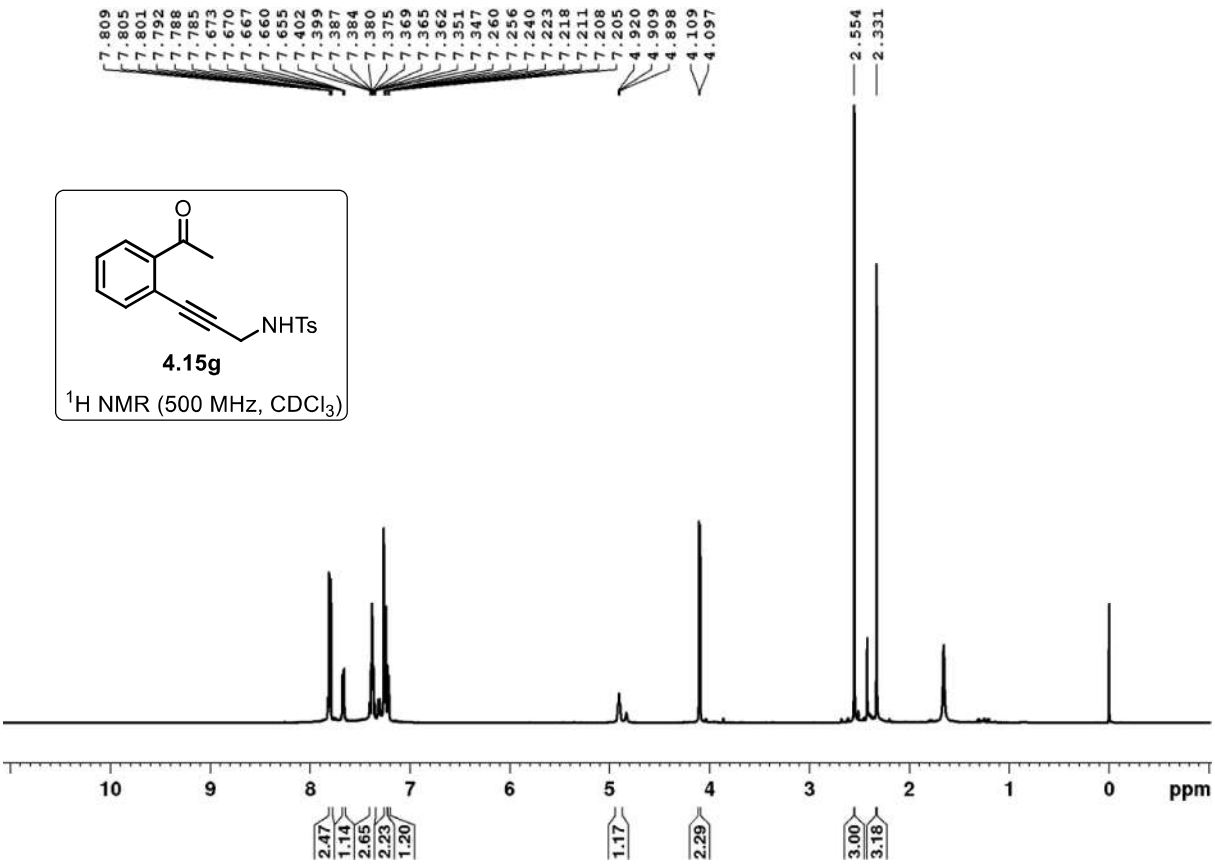
4.7 Representative spectra



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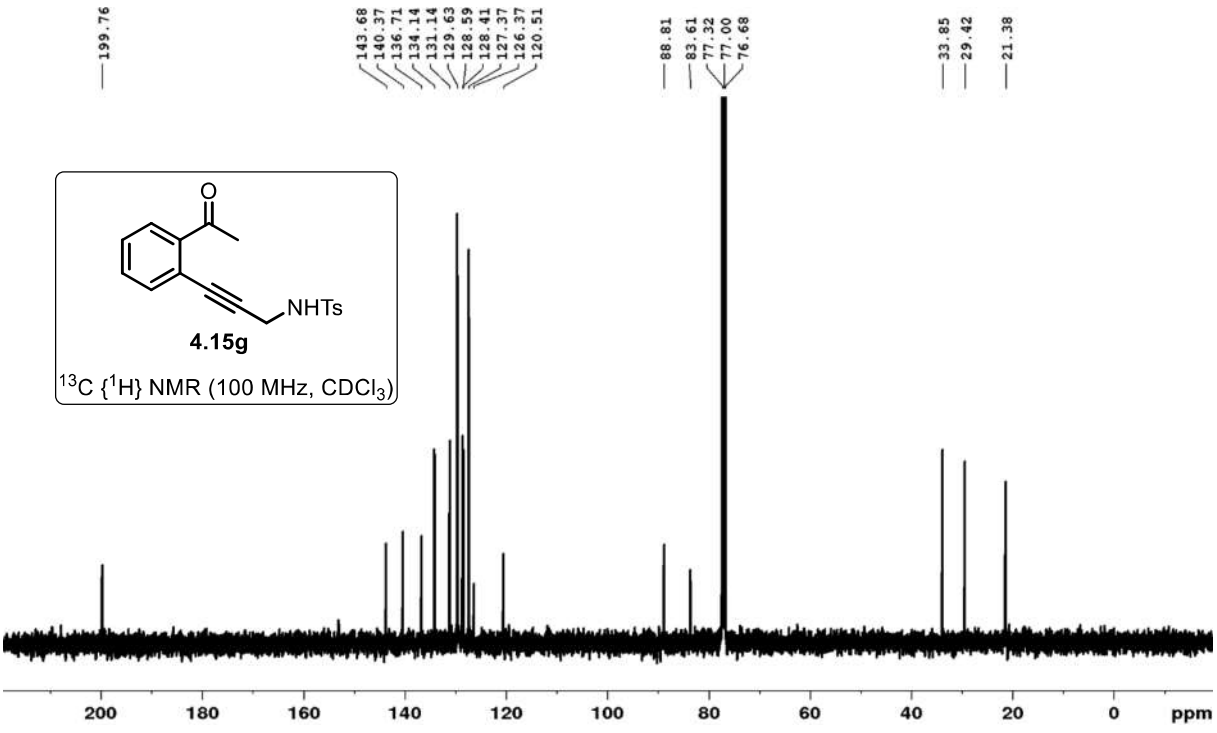
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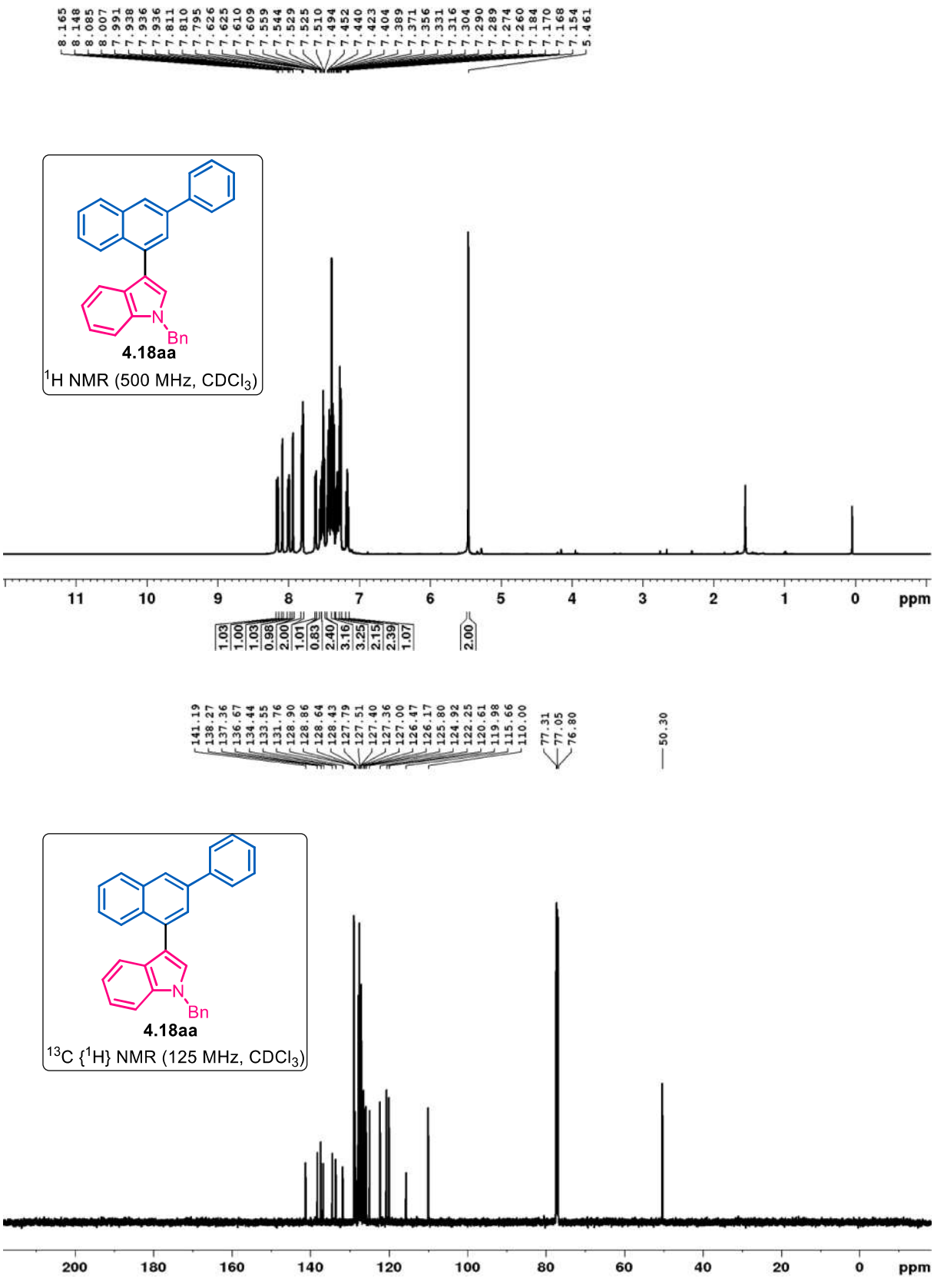
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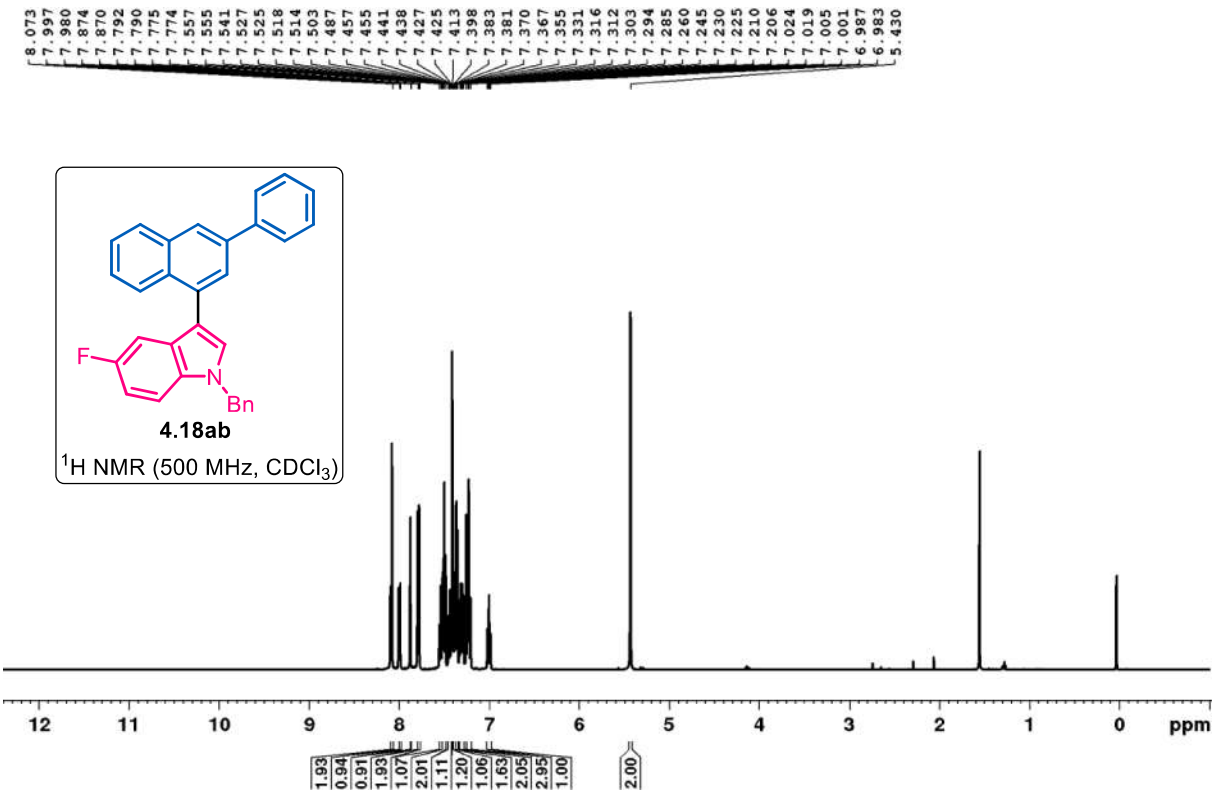
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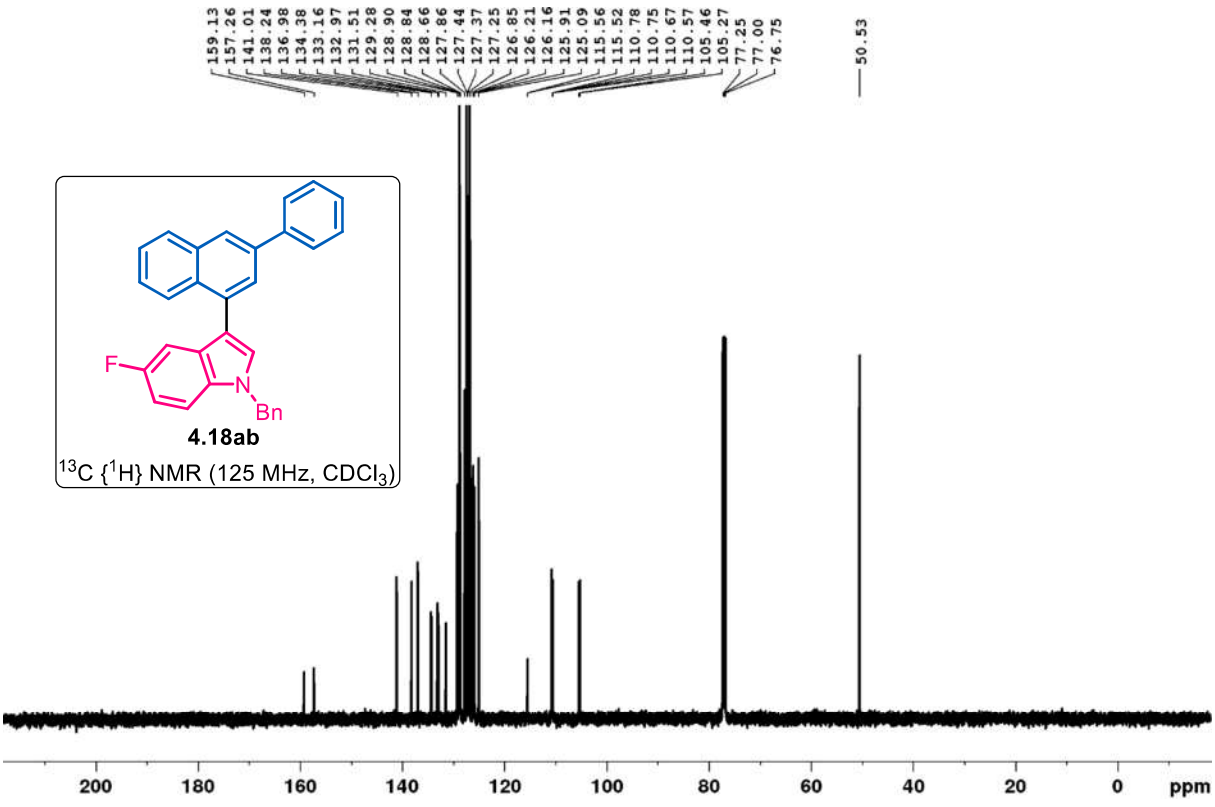
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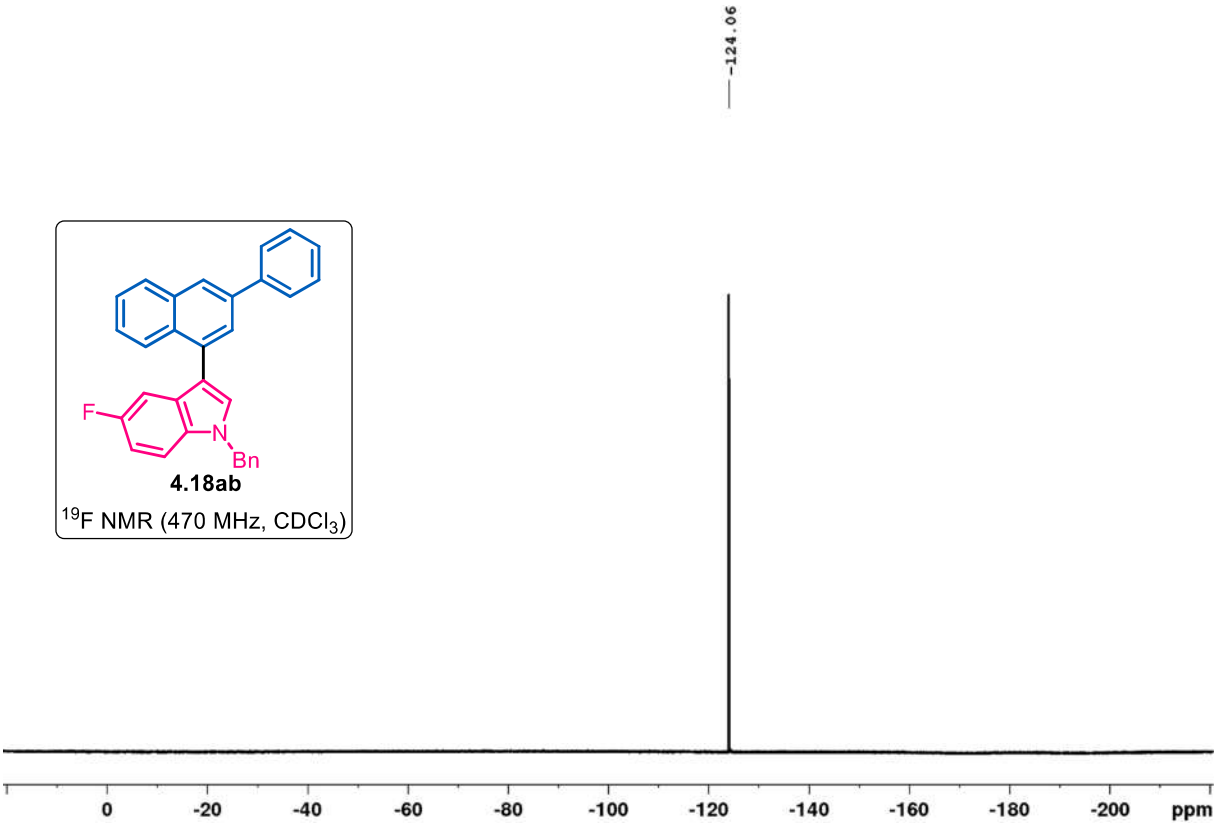
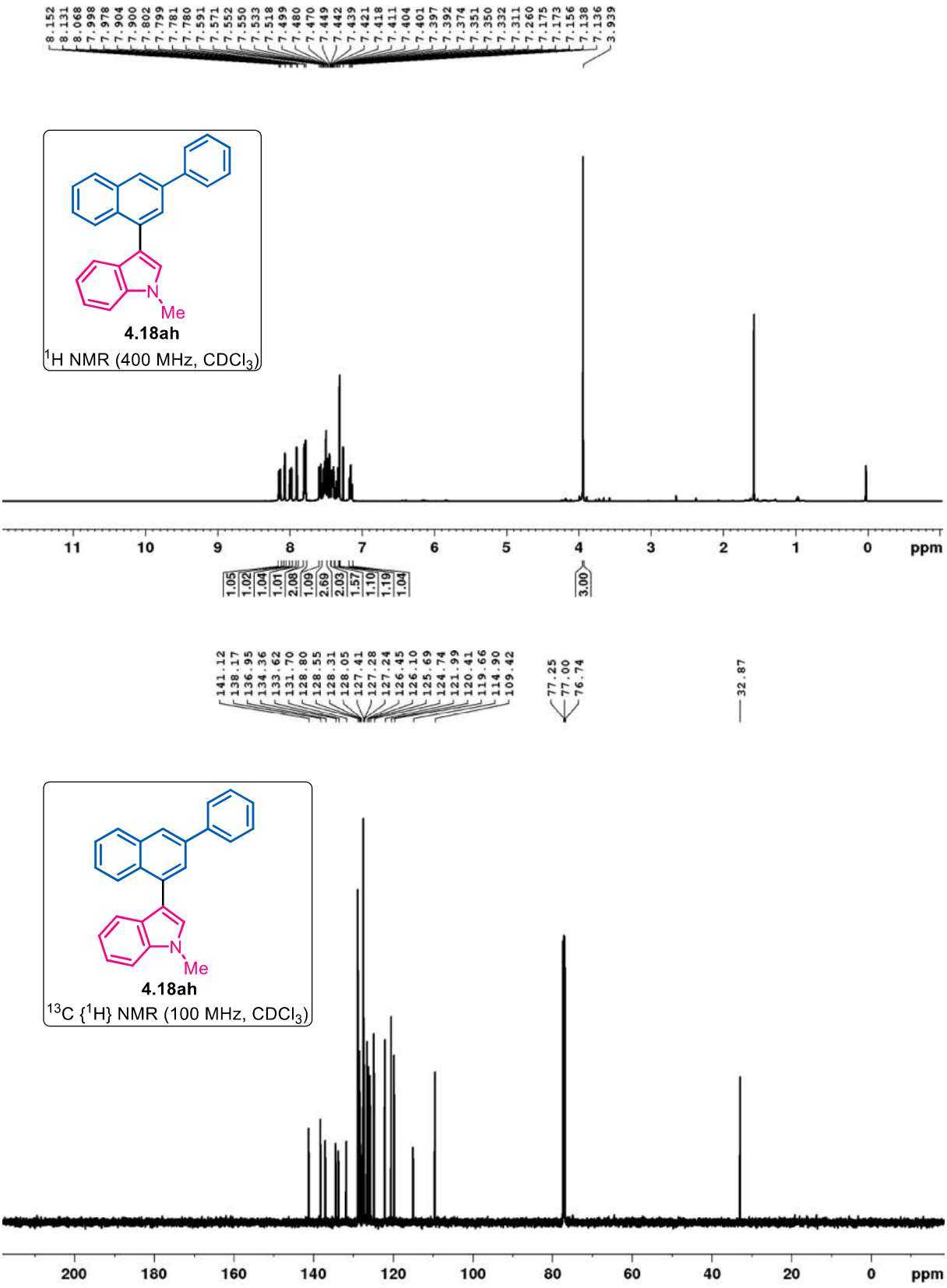
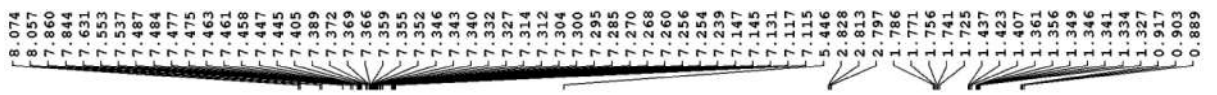
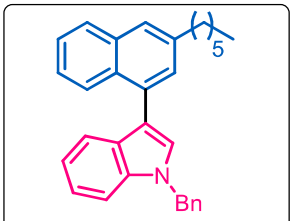
129.28
128.90
128.84
128.66
127.86
127.44
127.37
127.25
126.85
126.21
126.16
125.91
125.09
115.56
115.52
110.78
110.75
110.67
110.57
105.46
105.27
77.25
77.00
76.75
50.53
F
N
Bn
4.18ab
13C {1H} NMR (125 MHz, CDCl3)
200
180
160
140
120
100
80
60
40
20
0
ppm


-124.06
F
N
Bn
4.18ab
19F NMR (470 MHz, CDCl3)
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
ppm

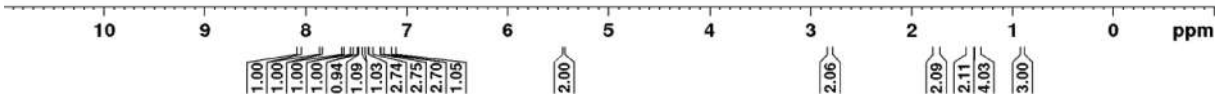

8.152
8.131
8.068
7.998
7.978
7.904
7.900
7.802
7.799
7.781
7.780
7.591
7.571
7.552
7.550
7.533
7.518
7.499
7.480
7.470
7.449
7.442
7.439
7.421
7.418
7.411
7.404
7.401
7.397
7.392
7.374
7.351
7.350
7.332
7.311
7.260
7.175
7.173
7.156
7.138
7.136
3.939
Me
4.18ah
1H NMR (400 MHz, CDCl3)
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.05
1.02
1.04
1.01
2.08
1.09
2.69
2.03
1.57
1.10
1.19
1.04
3.00
141.12
138.17
136.95
134.36
133.62
131.70
128.80
128.55
128.31
128.05
127.41
127.28
127.24
126.45
126.10
125.69
124.74
121.99
120.41
119.66
114.90
109.42
77.25
77.00
76.74
32.87
Me
4.18ah
13C {1H} NMR (100 MHz, CDCl3)
200
180
160
140
120
100
80
60
40
20
0
ppm

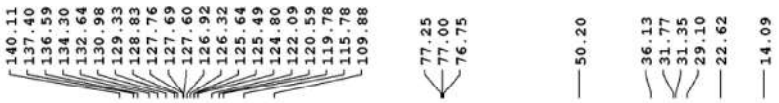


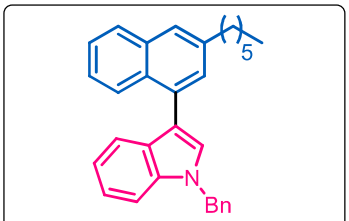


4.18be

^{1}H NMR (500 MHz, $CDCl_3$)

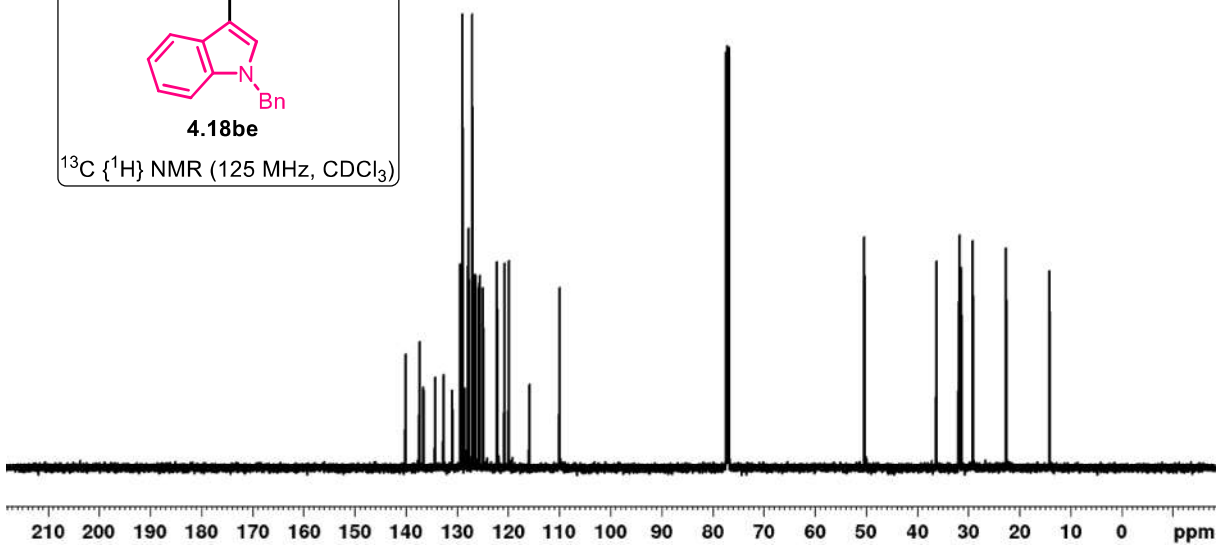


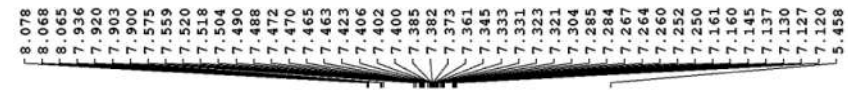


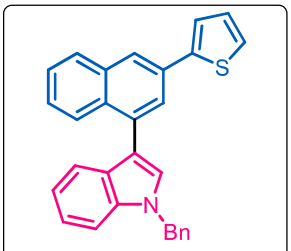


4.18be

^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)

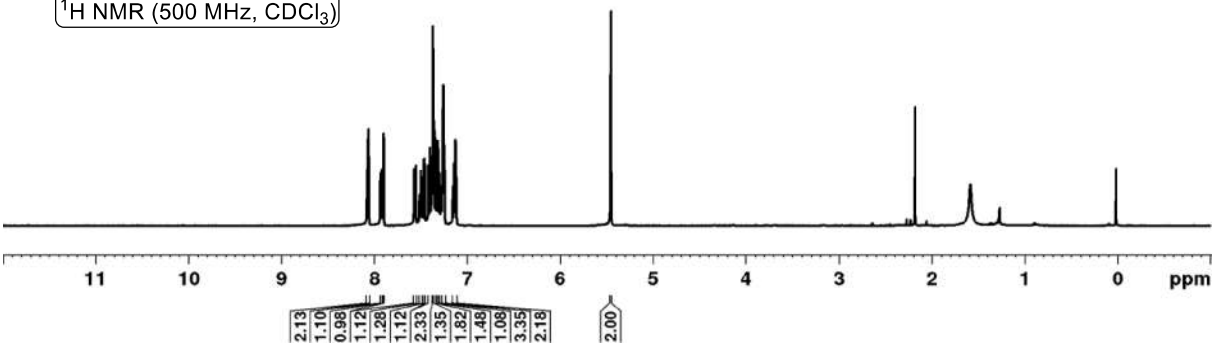


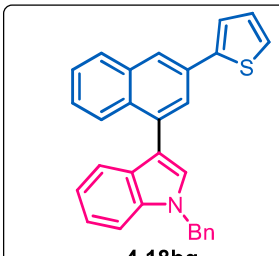




4.18bg

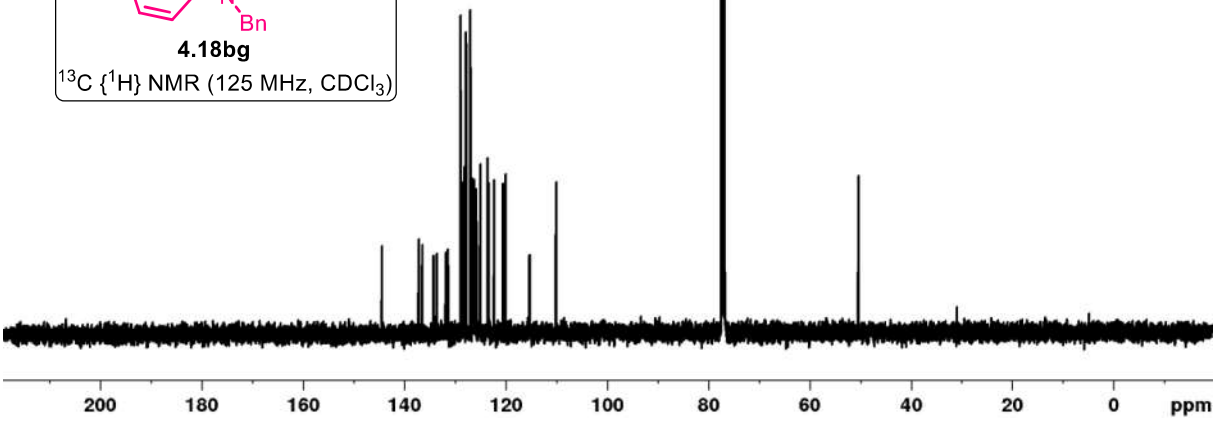
^{1}H NMR (500 MHz, $CDCl_3$)

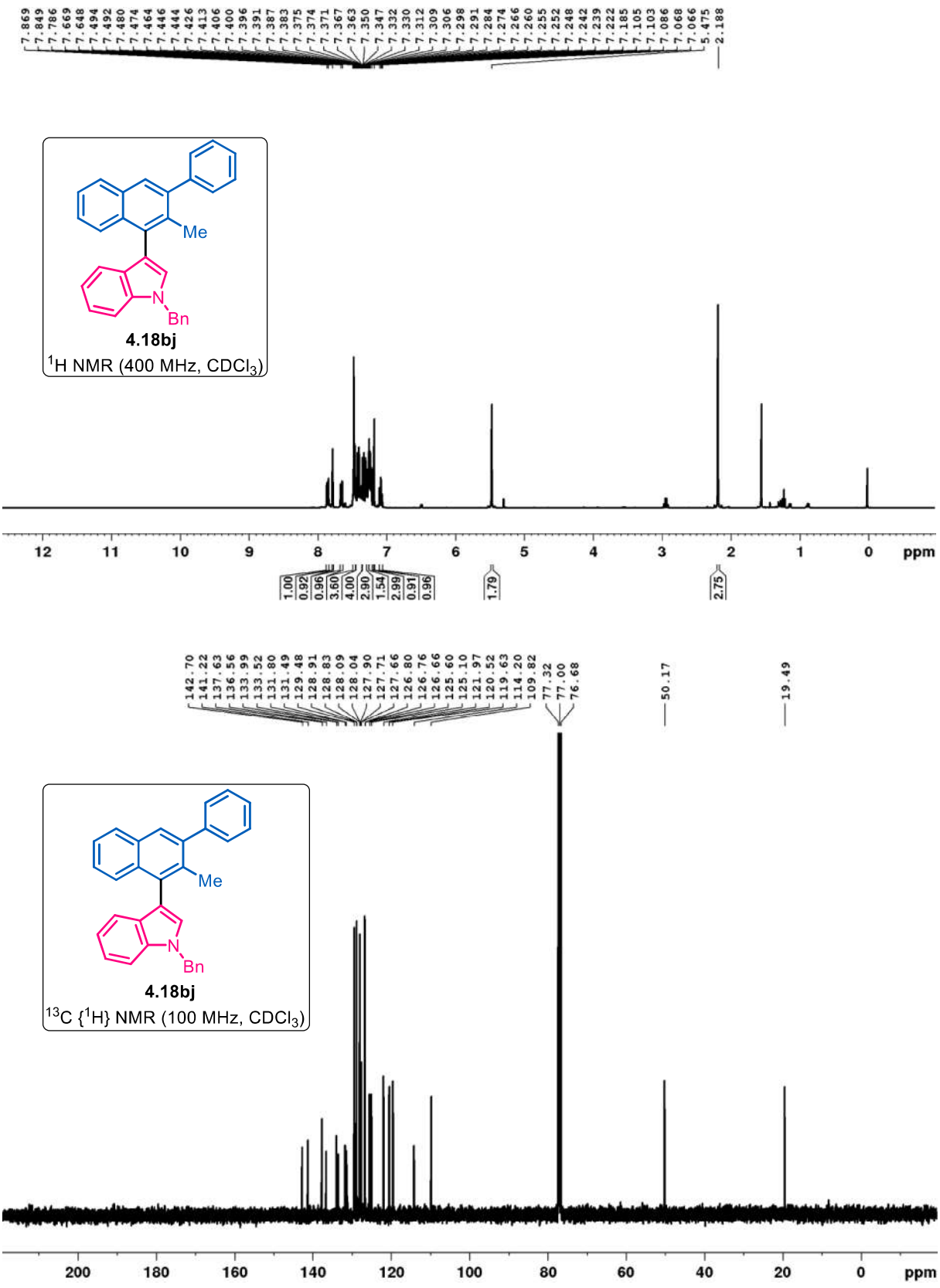


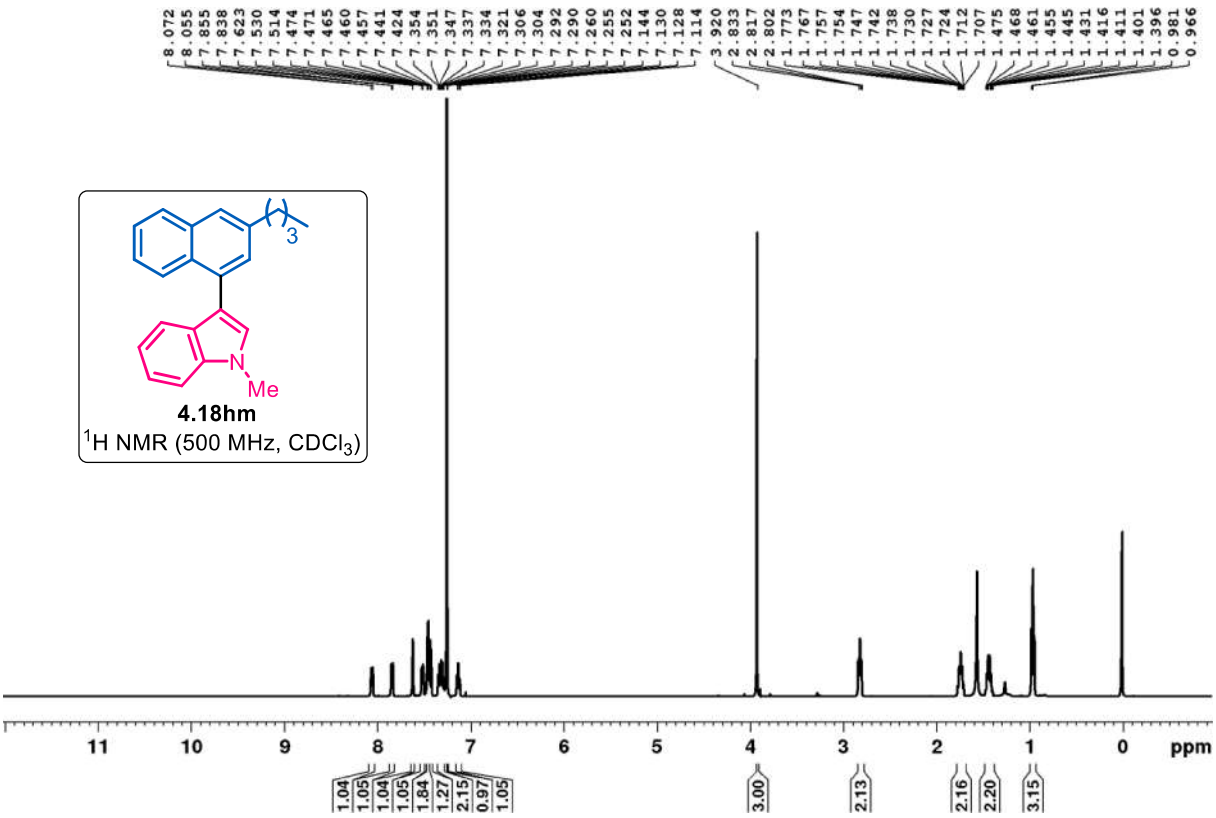


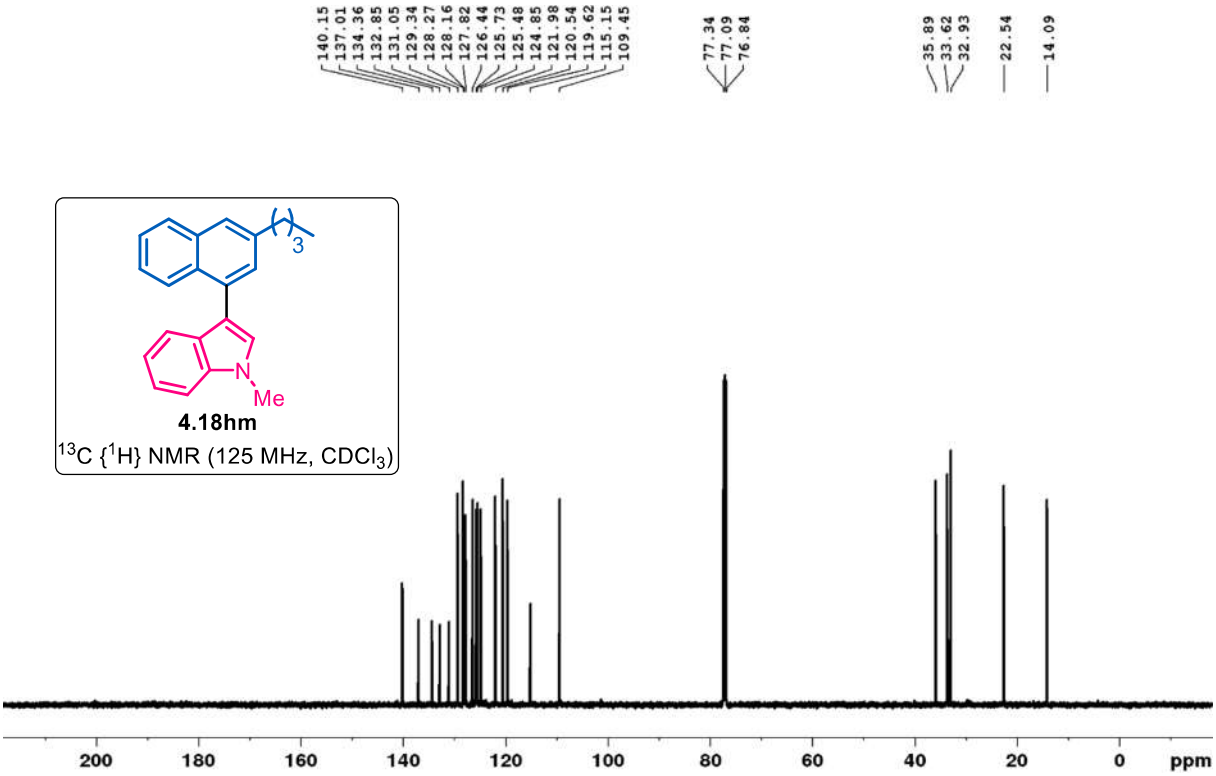
4.18bg

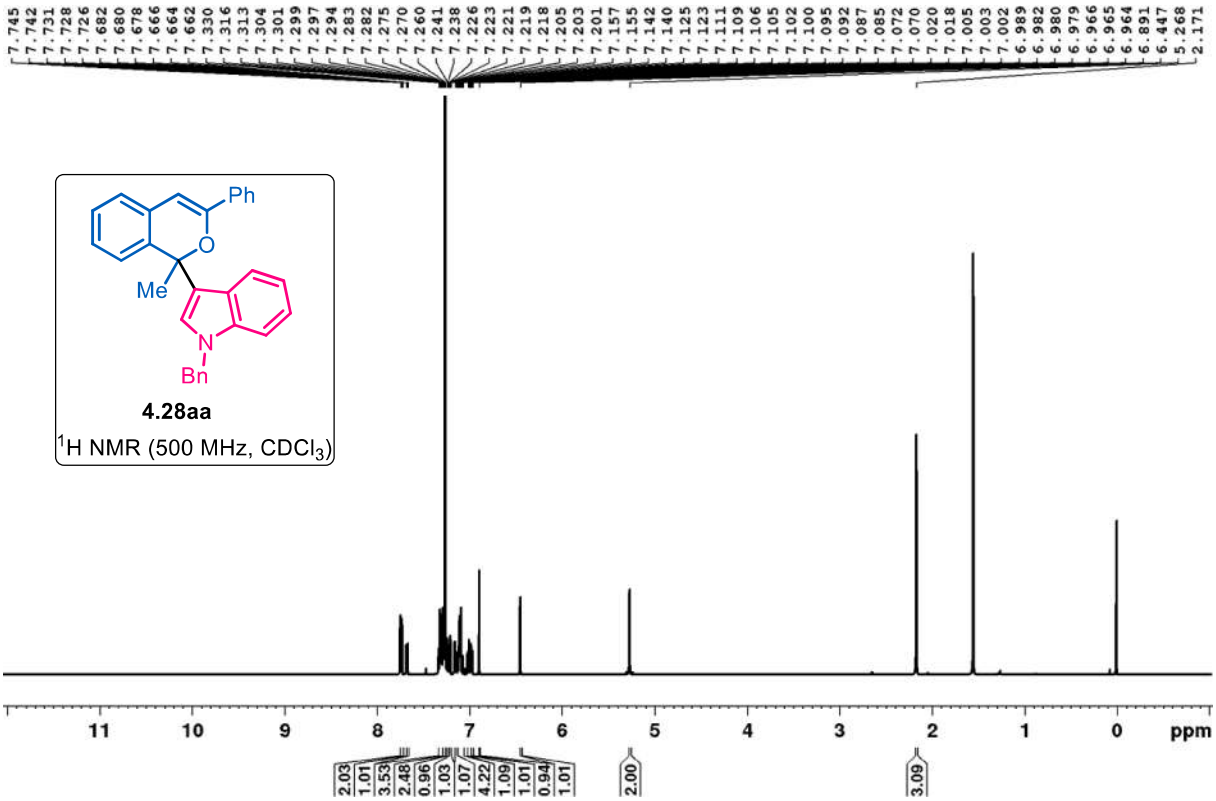
^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$)

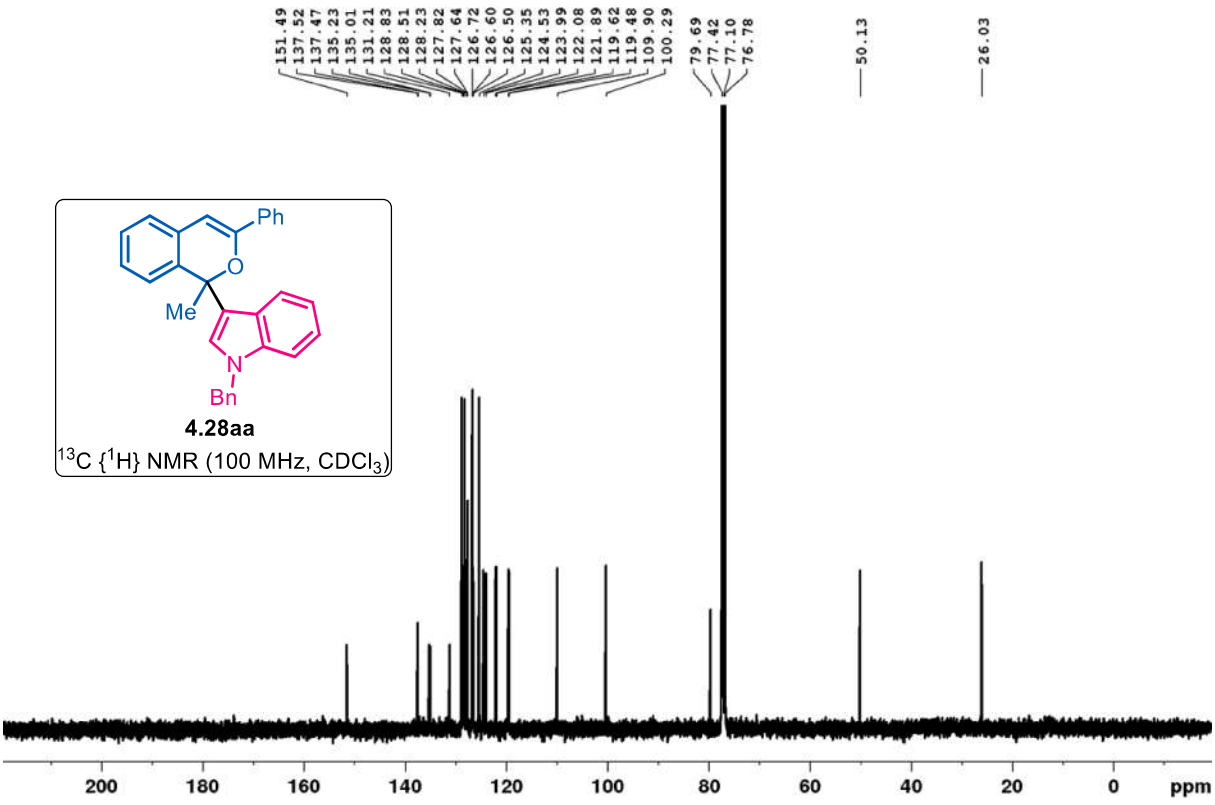


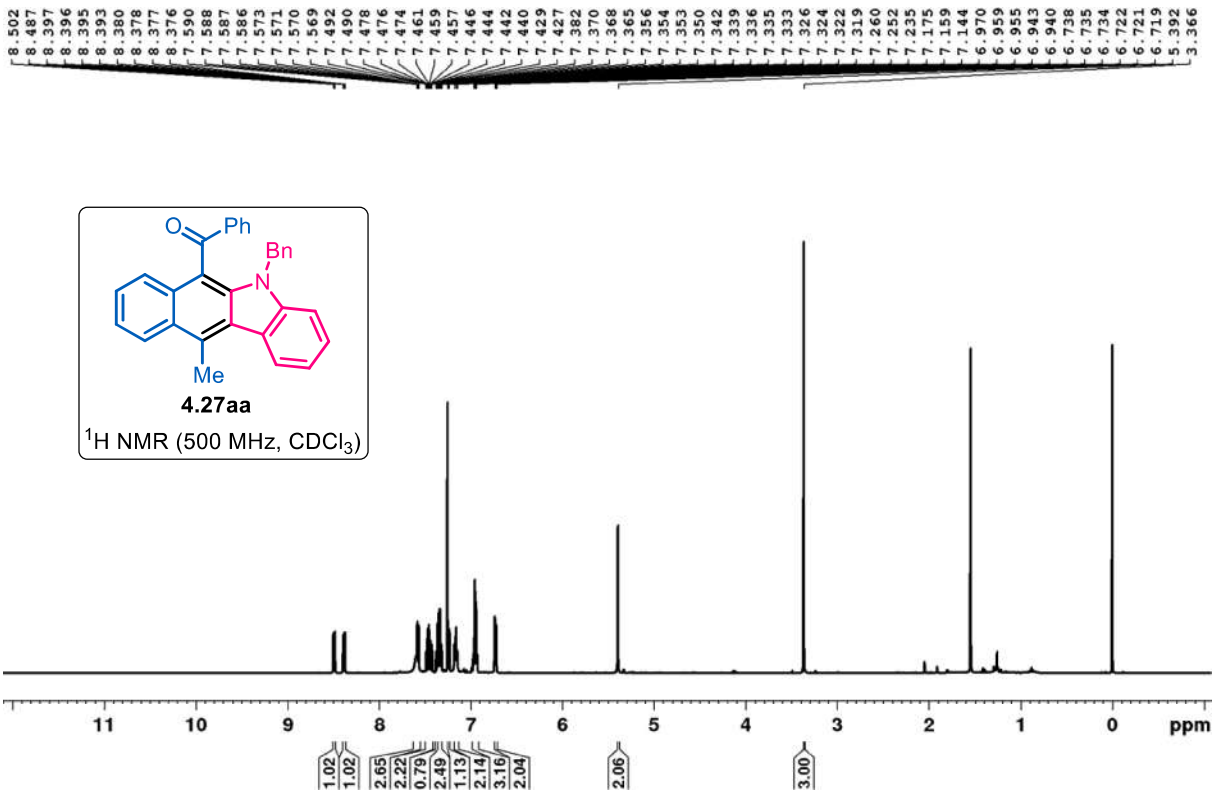

Me
N
Bn
4.18bj
1H NMR (400 MHz, CDCl3)
ppm
Me
N
Bn
4.18bj
13C {1H} NMR (100 MHz, CDCl3)
ppm

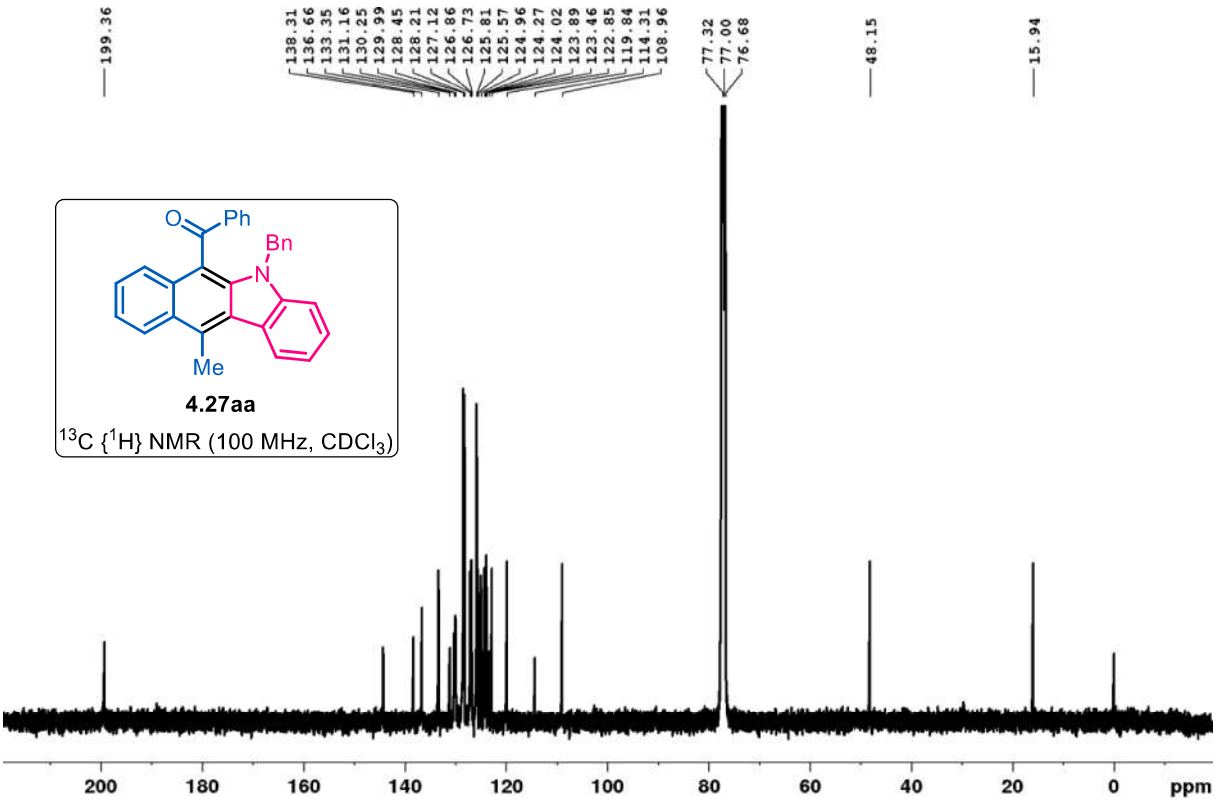

8.072
8.055
7.855
7.838
7.623
7.530
7.514
7.474
7.471
7.465
7.460
7.457
7.441
7.424
7.354
7.351
7.347
7.337
7.334
7.321
7.306
7.304
7.292
7.290
7.260
7.255
7.252
7.144
7.130
7.128
7.114
3.920
2.833
2.817
2.802
1.773
1.767
1.757
1.754
1.747
1.742
1.738
1.730
1.727
1.724
1.712
1.707
1.475
1.468
1.461
1.455
1.445
1.431
1.416
1.411
1.401
1.396
0.981
0.966
3
N
Me
4.18hm
1H NMR (500 MHz, CDCl3)
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.04
1.05
1.04
1.05
1.84
1.27
2.15
0.97
1.05
3.00
2.13
2.16
2.20
3.15

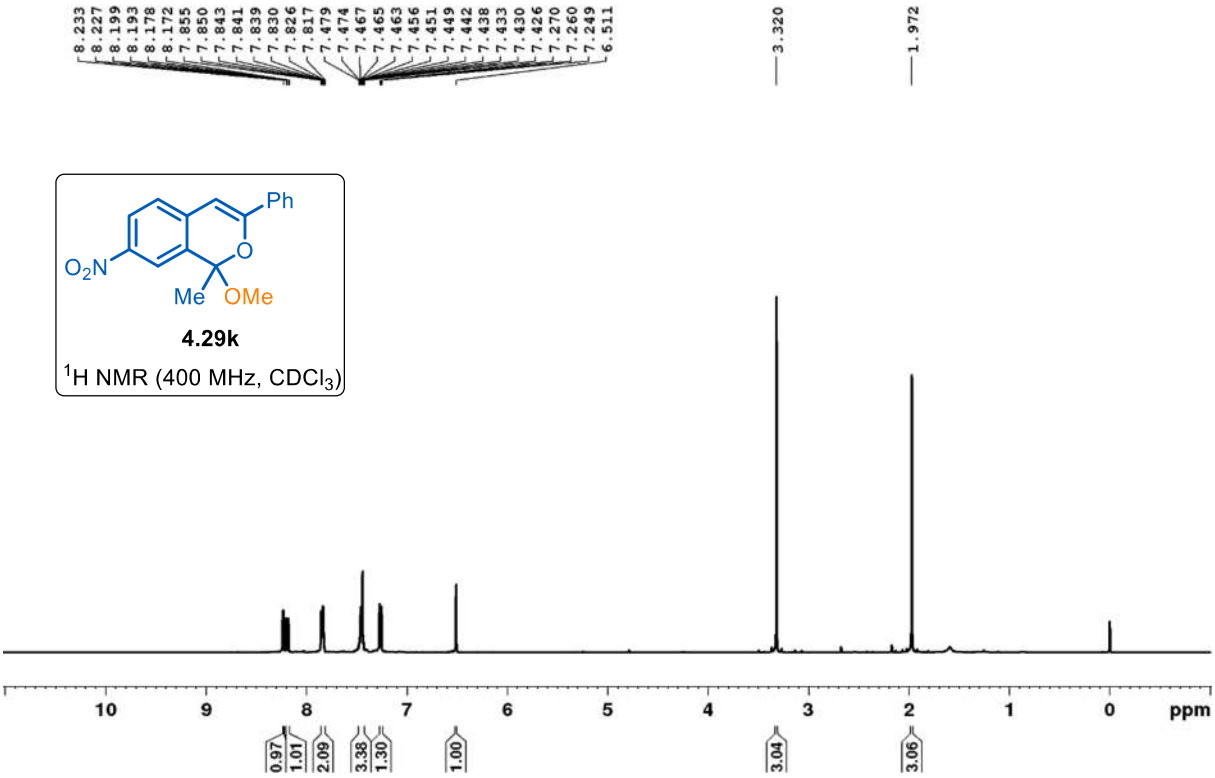

140.15
137.01
134.36
132.85
131.05
129.34
128.27
128.16
127.82
126.44
125.73
125.48
124.85
121.98
120.54
119.62
115.15
109.45
77.34
77.09
76.84
35.89
33.62
32.93
22.54
14.09
3
N
Me
4.18hm
13C {1H} NMR (125 MHz, CDCl3)
200
180
160
140
120
100
80
60
40
20
0
ppm

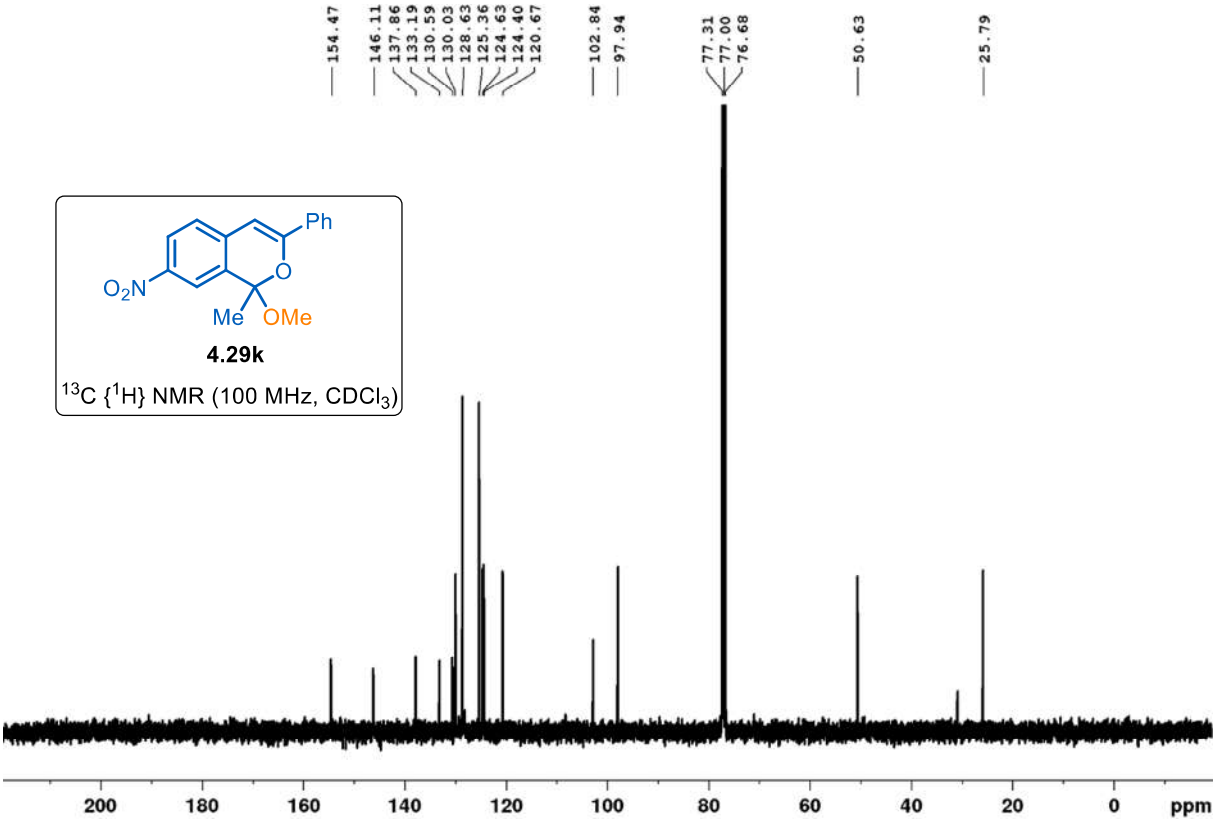

Ph
O
Me
N
Bn
4.28aa
^{1}H NMR (500 MHz, $CDCl_3$)
ppm

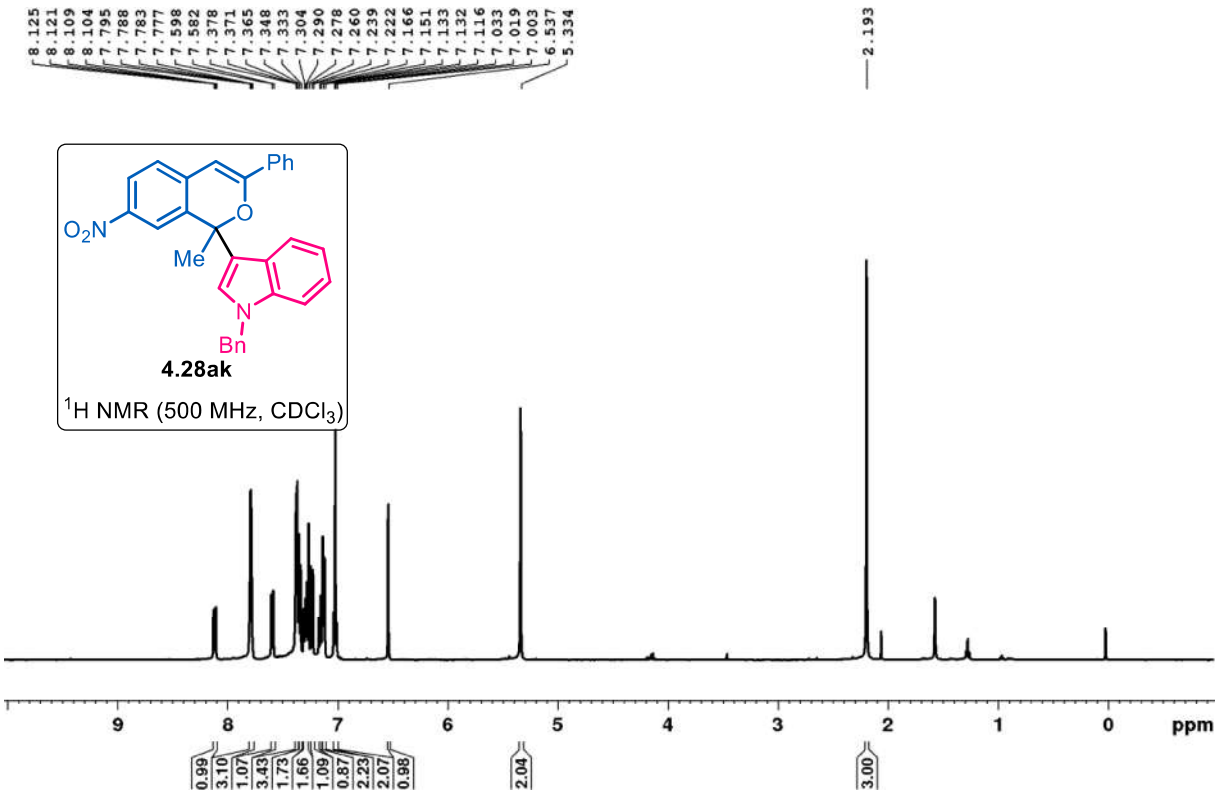

Ph
O
Me
N
Bn
4.28aa
^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$)
ppm

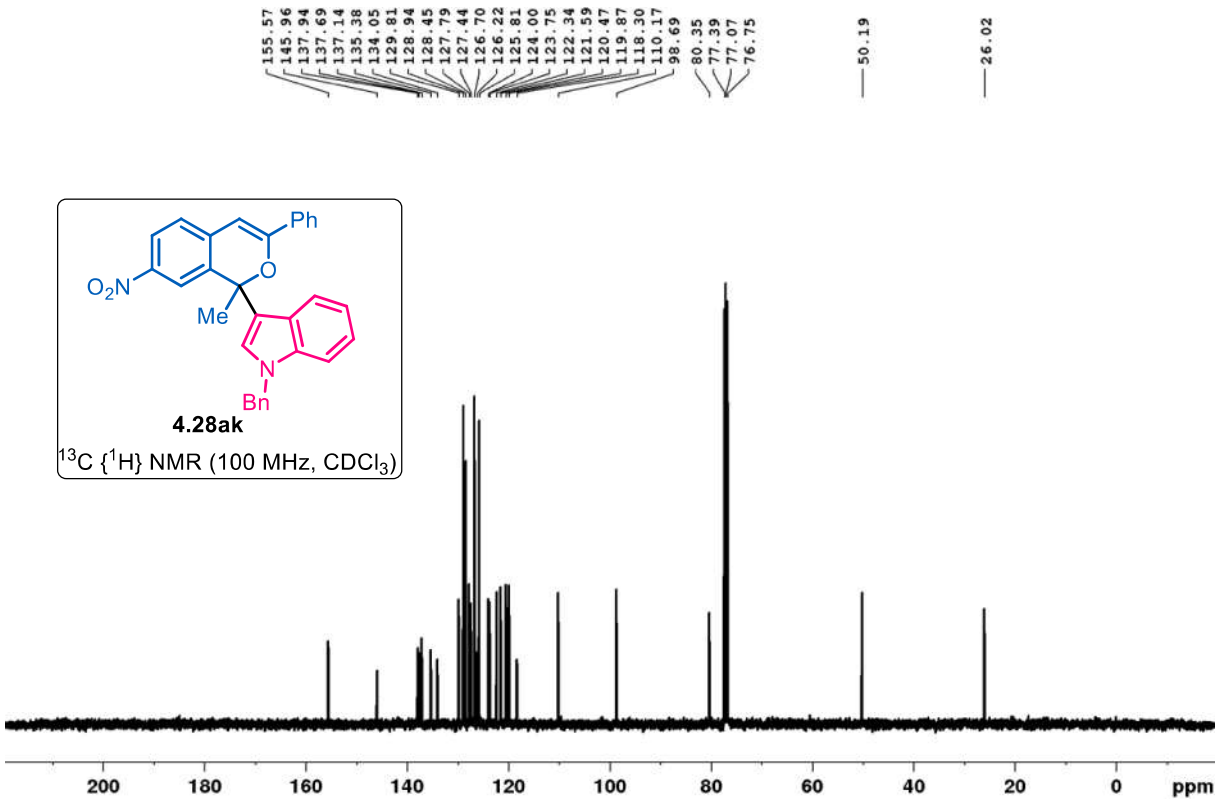

8.502
8.487
8.397
8.396
8.395
8.393
8.380
8.378
8.377
8.376
7.590
7.588
7.587
7.586
7.573
7.571
7.570
7.569
7.492
7.490
7.478
7.476
7.474
7.461
7.459
7.457
7.446
7.444
7.442
7.440
7.429
7.427
7.382
7.370
7.368
7.365
7.356
7.354
7.353
7.350
7.342
7.339
7.336
7.335
7.333
7.326
7.324
7.322
7.319
7.260
7.252
7.235
7.175
7.159
7.144
6.970
6.959
6.955
6.943
6.940
6.738
6.735
6.734
6.722
6.721
6.719
5.392
3.366
O
Ph
Bn
N
Me
4.27aa
1H NMR (500 MHz, CDCl3)
11
10
9
8
7
6
5
4
3
2
1
0
ppm
1.02
1.02
2.65
2.22
0.79
2.49
1.13
2.14
3.16
2.04
2.06
3.00

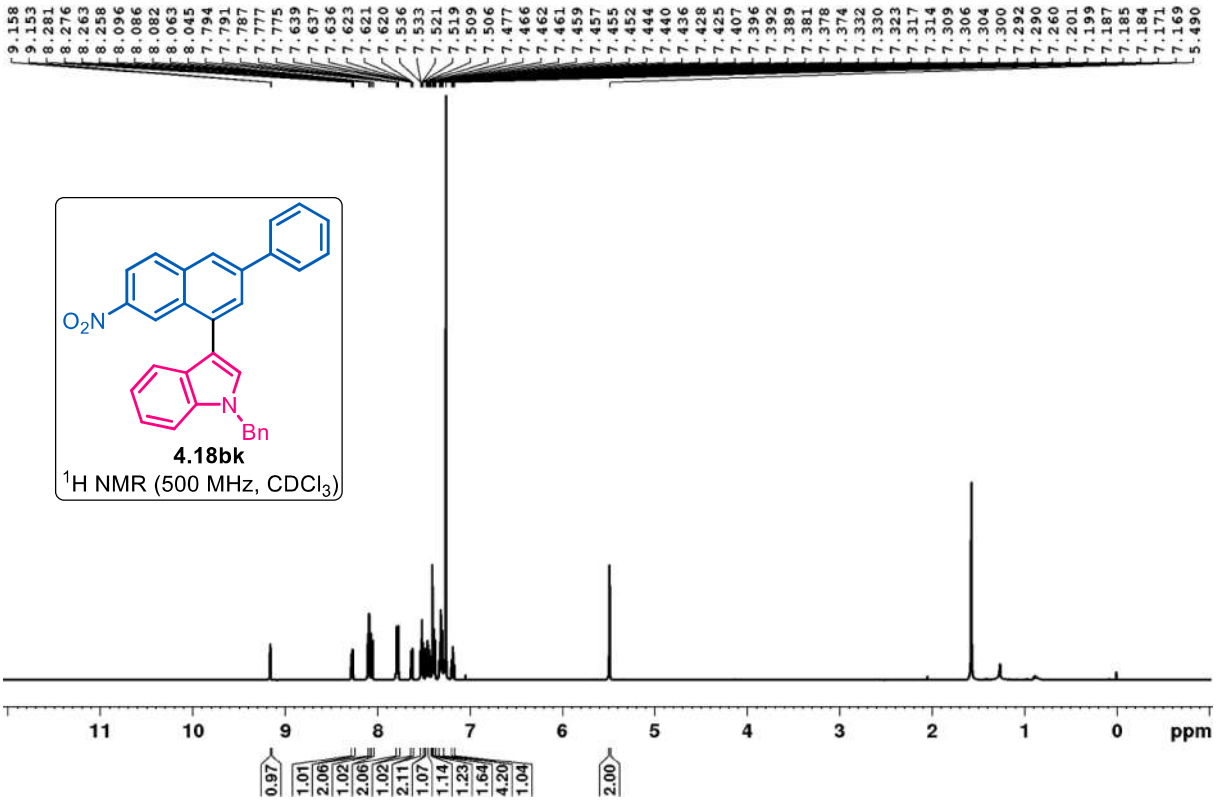

199.36
138.31
136.66
133.35
131.16
130.25
129.99
128.45
128.21
127.12
126.86
126.73
125.81
125.57
124.96
124.27
124.02
123.89
123.46
122.85
119.84
114.31
108.96
77.32
77.00
76.68
48.15
15.94
O
Ph
Bn
N
Me
4.27aa
13C {1H} NMR (100 MHz, CDCl3)
200
180
160
140
120
100
80
60
40
20
0
ppm

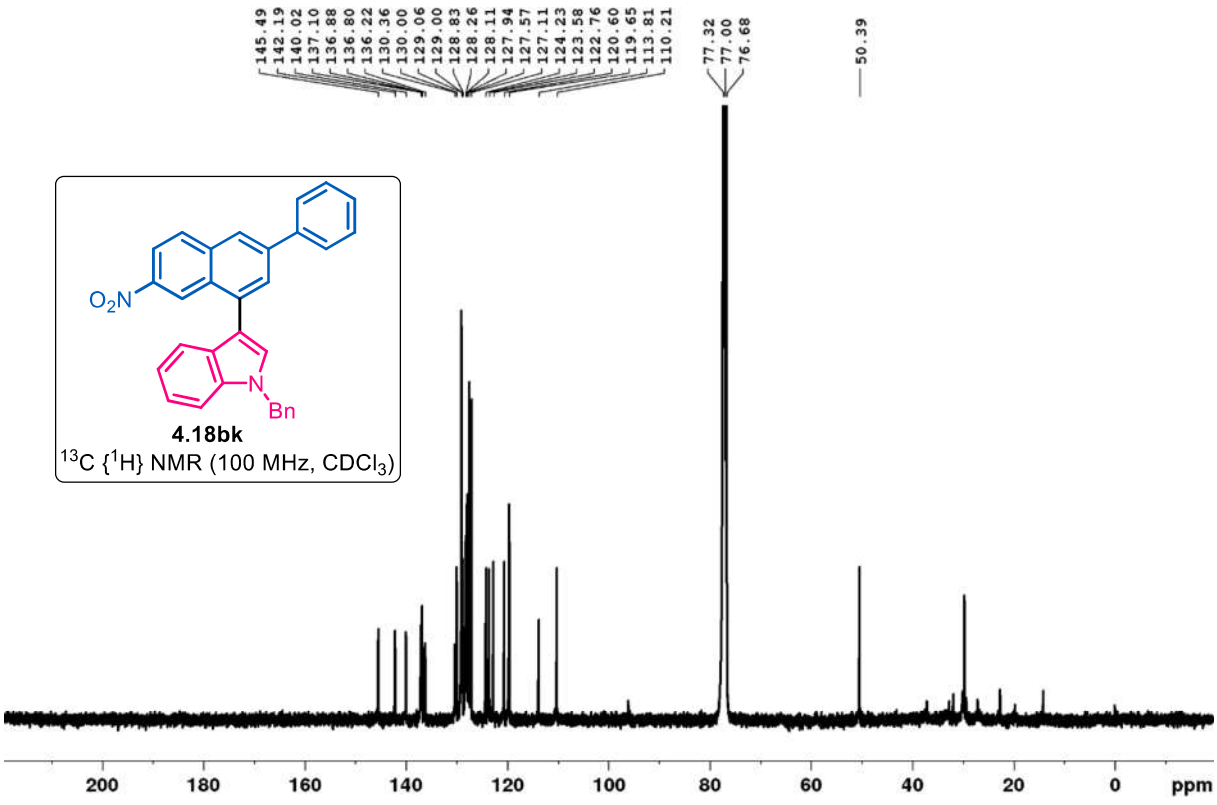

8.233
8.227
8.199
8.193
8.178
8.172
7.855
7.850
7.843
7.841
7.839
7.830
7.826
7.817
7.479
7.474
7.467
7.465
7.463
7.456
7.451
7.449
7.442
7.438
7.433
7.430
7.426
7.270
7.260
7.249
6.511
3.320
1.972
Ph
O
O2N
Me
OMe
4.29k
1H NMR (400 MHz, CDCl3)
10
9
8
7
6
5
4
3
2
1
0
ppm
0.97
1.01
2.09
3.38
1.30
1.00
3.04
3.06

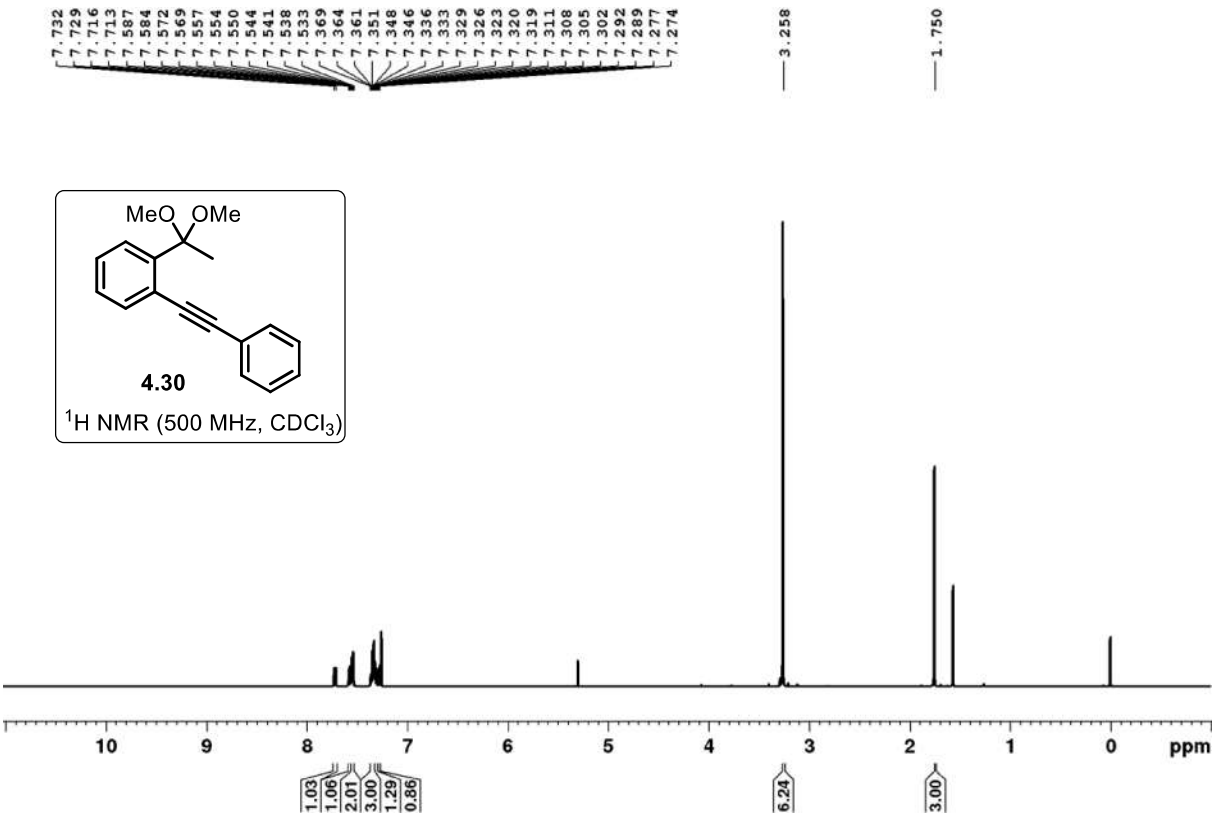

154.47
146.11
137.86
133.19
130.59
130.03
128.63
125.36
124.63
124.40
120.67
102.84
97.94
77.31
77.00
76.68
50.63
25.79
Ph
O
O2N
Me
OMe
4.29k
13C {1H} NMR (100 MHz, CDCl3)
200
180
160
140
120
100
80
60
40
20
0
ppm

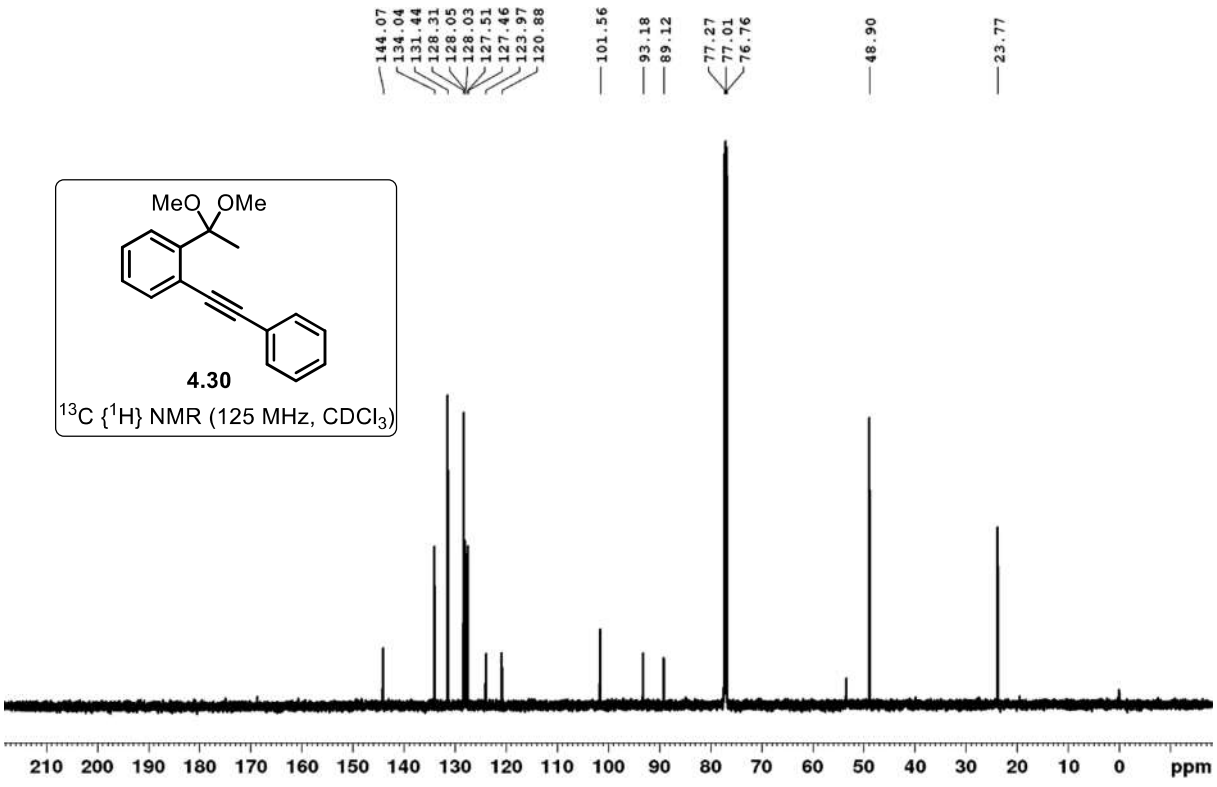

8.125
8.121
8.109
8.104
7.795
7.788
7.783
7.777
7.598
7.582
7.378
7.371
7.365
7.348
7.333
7.304
7.290
7.278
7.260
7.239
7.222
7.166
7.151
7.133
7.132
7.116
7.033
7.019
7.003
6.537
5.334
2.193
Ph
O
O2N
Me
N
Bn
4.28ak
1H NMR (500 MHz, CDCl3)
9
8
7
6
5
4
3
2
1
0
ppm
0.99
3.10
1.07
3.43
1.73
1.66
1.09
0.87
2.23
2.07
0.98
2.04
3.00


155.57
145.96
137.94
137.69
137.14
135.38
134.05
129.81
128.94
128.45
127.79
127.44
126.70
126.22
125.81
124.00
123.75
122.34
121.59
120.47
119.87
118.30
110.17
98.69
80.35
77.39
77.07
76.75
50.19
26.02
Ph
O
O2N
Me
N
Bn
4.28ak
13C {1H} NMR (100 MHz, CDCl3)
200
180
160
140
120
100
80
60
40
20
0
ppm


9.158
9.153
8.281
8.276
8.263
8.258
8.096
8.086
8.082
8.063
8.045
7.794
7.791
7.787
7.777
7.775
7.639
7.637
7.636
7.623
7.621
7.620
7.536
7.533
7.521
7.519
7.509
7.506
7.477
7.466
7.462
7.461
7.459
7.457
7.455
7.452
7.444
7.440
7.436
7.428
7.425
7.407
7.396
7.392
7.389
7.381
7.378
7.374
7.332
7.330
7.323
7.317
7.314
7.309
7.306
7.304
7.300
7.292
7.290
7.260
7.201
7.199
7.187
7.185
7.184
7.171
7.169
5.490
O2N
N
Bn
4.18bk
1H NMR (500 MHz, CDCl3)
11
10
9
8
7
6
5
4
3
2
1
0
ppm
0.97
1.01
2.06
1.02
2.06
1.02
2.11
1.07
1.14
1.23
1.64
4.20
1.04
2.00


145.49
142.19
140.02
137.10
136.88
136.80
136.22
130.36
130.00
129.06
129.00
128.83
128.26
128.11
127.94
127.57
127.11
124.23
123.58
122.76
120.60
119.65
113.81
110.21
77.32
77.00
76.68
50.39
O2N
N
Bn
4.18bk
13C {1H} NMR (100 MHz, CDCl3)
200
180
160
140
120
100
80
60
40
20
0
ppm


7.732
7.729
7.716
7.713
7.587
7.584
7.572
7.569
7.557
7.554
7.550
7.544
7.541
7.538
7.533
7.369
7.364
7.361
7.351
7.348
7.346
7.336
7.333
7.329
7.326
7.323
7.320
7.319
7.311
7.308
7.305
7.302
7.292
7.289
7.277
7.274
3.258
1.750
MeO OMe
4.30
1H NMR (500 MHz, CDCl3)
10
9
8
7
6
5
4
3
2
1
0
ppm
1.03
1.06
2.01
3.00
1.29
0.86
6.24
3.00


144.07
134.04
131.44
128.31
128.05
128.03
127.51
127.46
123.97
120.88
101.56
93.18
89.12
77.27
77.01
76.76
48.90
23.77
MeO OMe
4.30
13C {1H} NMR (125 MHz, CDCl3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

4.8 Crystallographic data

Table 4.3: Crystallographic data for 4.18af

Compound	**4.18af**
Identification code	RB61
CCDC	**2209520**
Empirical formula	$C_{32}H_{24}BrN$
Formula weight	502.46
Temperature/K	300
Crystal system	Triclinic
Space group	P -1
a/Å	9.1848 (2)
b/ Å	9.7094 (2)
c/ Å	14.2815 (2)
$\alpha/^0$	95.361 (2)
$\beta/^0$	92.618 (1)
$\gamma/^0$	109.065 (2)
Volume/$Å^3$	1194.55 (4)
Z	2
Density(ρ)calc g/cm^3	1.397
Absorption Coefficient(μ) (mm^{-1})	1.742
F(000)	515.6
Crystal size/mm^3	0.02 x 0.02 x 0.01
Reflections collected	4208
Independent reflections	3396

Completeness to theta = 24.995	99.9%
R (reflections)	0.0385 (3396)
wR2 (reflections)	0.0823 (4208)

Table 4.4: Crystallographic data for 4.28ak

Compound	**4.28ak**
Identification code	rb005a
CCDC	**2204406**
Empirical formula	$C_{31}H_{24}N_2O_3$
Formula weight	472.52
Temperature/K	300
Crystal system	Monoclinic
Space group	C12/C1
a/Å	27.630(4)
b/ Å	9.6103(12)
c/ Å	22.543(3)
$\alpha/^0$	90
$\beta/^0$	123.585(4)
$\gamma/^0$	90
Volume/$Å^3$	4986.5(11)
Z	8
Density(ρ)calc g/cm^3	1.259
Absorption Coefficient(μ) (mm^{-1})	0.082
F(000)	1984.0
Crystal size/mm^3	0.02 x 0.02 x 0.01

Reflections collected	3602
Independent reflections	4385
Completeness to theta = 24.995	99.9%
R (reflections)	0.0553 (3602)
wR2 (reflections)	0.1521 (4385)

List of publications

1. Triflic Acid-Catalyzed Synthesis of Indole-Substituted Indane Derivatives *via In Situ* Formed Acetal-Facilitated Nucleophilic Addition and 4π-Electron-5-Carbon Electrocyclization Sequence
   Ramesh, **G**.; Balamurugan, R.
   J. Org. Chem. **2021**, *86,* 16278-16292.

2. Activation of *o*-Propargyl Alcohol Benzaldehydes under Acetalization Conditions for Intramolecular Electrophile Intercepted Meyer-Schuster Rearrangement
   Ramesh, **G**.; Ramulu, B. V.; Balamurugan, R.
   J. Org. Chem. **2022**, *87*, 8633-8647.

3. Ag(I)-Catalyzed Cyclization of *o*-Alkynylacetophenones Facilitated Through Acetal Formation: Synthesis of C3-Naphthyl Indole Derivatives
   Ramesh, **G**.; Srivardhan, V.; Balamurugan, R.
   Org. Biomol. Chem. **2022**, *20*, 9698-9702.

4. Naveen, N.; **Ramesh**, **G**.; Balamurugan, R. Silver catalyzed Synthesis of Enones/α-Iodoenones from Tertiary Propargyl Alcohols. *ChemistrySelect* **2019**, *4*, 13610-13614.

Posters and oral presentations

1. Participated and delivered an oral presentation on "*In situ* Generated Acetal Assisted Synthesis of Indanones *via* an Intramolecular Meyer-Schuster Rearrangement" in **CHEM-FEST 2020**, 17th Annual In-House Symposium, held at School of Chemistry, University of Hyderabad, Hyderabad, February 2020.

2. Participated, organizing member, and presented a poster on "Diastereoselective Synthesis of Indole-Substituted Indane Derivatives *via in situ* Formed Acetals", in **CHEM-FEST 2019**, 16th Annual In-House Symposium, held at the School of Chemistry, University of Hyderabad, Hyderabad, February 2019.

3. Participated and delivered an oral presentation on "Diastereoselective Synthesis of Indole-Substituted Indane Derivatives *via in situ* Formed Acetals", in **XIIIth Junior-National Organic Symposium Trust** (**J-NOST**) Conference, held at Banaras Hindu University (BHU), Varanasi, November 2017.

Carbocyclization of Alkene-/Alkyne-Tethered Carbonyl Compounds Through In Situ Acetal Formation

by Golla Ramesh

Submission date: 22-Dec-2022 11:04AM (UTC+0530)
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Carbocyclization of Alkene-/Alkyne-Tethered Carbonyl Compounds Through In Situ Acetal Formation

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PRIMARY SOURCES

1	Golla Ramesh, Bokka Venkat Ramulu, Rengarajan Balamurugan. " Activation of -Propargyl Alcohol Benzaldehydes under Acetalization Conditions for Intramolecular Electrophile Intercepted Meyer–Schuster Rearrangement ", The Journal of Organic Chemistry, 2022 Publication	19%
2	Golla Ramesh, Rengarajan Balamurugan. " Triflic Acid-Catalyzed Synthesis of Indole-Substituted Indane Derivatives via Formed Acetal-Facilitated Nucleophilic Addition and 4π-Electron-5-Carbon Electrocyclization Sequence ", The Journal of Organic Chemistry, 2021 Publication	17%
3	Ramesh Golla, Srivardhan Valmuri, Rengarajan Balamurugan. "Ag(I)-Catalyzed Cyclization of o-Alkynylacetophenones Facilitated Through Acetal Formation:	8%

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Synthesis of C3-Naphthyl Indole Derivatives", Organic & Biomolecular Chemistry, 2022
Publication

4	Golla Ramesh, Valmuri Srivardhan, Rengarajan Balamurugan. " Ag( )-catalyzed cyclization of -alkynylacetophenones facilitated through acetal formation: synthesis of C3-naphthyl indole derivatives ", Organic & Biomolecular Chemistry, 2022 Publication	3%
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7	Seetharaman Manojveer, Rengarajan Balamurugan. " Synthesis of Naphthalene Derivatives from -Alkynylacetophenone Derivatives via Tandem Incorporation of Acetal and Intramolecular Heteroalkyne Metathesis/Annulation ", Organic Letters, 2014 Publication	<1%
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