ANNULATION/CYCLOADDITION REACTIONS OF INDOLE/CHROMENE/COUMARIN CARBOXYLIC ACIDS OR TETRAZINE WITH C-C II-COMPONENTS

A THESIS
SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

By

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MAY 2022

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CONTENTS

STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad, Hyderabad, under the supervision of Prof. K. C. Kumara Swamy.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

Hyderabad
May 2022

31/05/22
Mallepalli Shankar

DECLARATION

I, **Mallepalli Shankar** hereby declare that this thesis entitled ***"Annulation/Cycloaddition Reactions of Indole/Chromene/Coumarin Carboxylic Acids or Tetrazine with C-C π-Components"*** submitted by me under the guidance and supervision of **Professor K. C. Kumara Swamy** is a bonafide research work which is also free from plagiarism. I also declare that it has not been submitted previously in part or in full to this University or any other University or Institution for the award of any degree or diploma. I hereby agree that my thesis can deposited in Shodganga/INFLIBNET.

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CERTIFICATE

This is to certify that the thesis entitled ***"Annulation/Cycloaddition Reactions of Indole/Chromene/Coumarin Carboxylic Acids or Tetrazine with C-C π-Components"*** submitted by **Mr. MALLEPALLI SHANKAR** bearing registration number **15CHPH13** in partial fulfillment of the requirements for award of Doctor of Philosophy in the School of Chemistry is a bonafide work carried out by him under my supervision and guidance.

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

Part of this thesis has been published in the following publication:

1. Shankar, M.; Anasuyamma, U.; Kumara Swamy, K. C. *Adv. Synth. Catal*. **2022**, *364*, 643.

The following papers are to be communicated.

2. Shankar, M.; Kalyani, A.; Anitha, M.; Siva Reddy, A.; Kumara Swamy, K. C. (*to be communicated*)
3. Shankar, M.; Kumara Swamy, K. C. (*to be communicated*).
4. Shankar, M.; Kumara Swamy, K. C. (*to be communicated*).

He has also made presentations in the following conferences:

1. Poster presentation in the *Chemfest-2017* (annual in-house symposium), School of Chemistry, University of Hyderabad, INDIA, Feb-**2017**.
2. Poster presentation in the *XIVth J-NOST Conference for Research Scholars*, IICT, Hyderabad, INDIA, Nov-Dec, **2018**.
3. Oral and Poster presentation in the *Chemfest-2020* (annual in-house symposium), School of Chemistry, University of Hyderabad, INDIA, Feb-**2020**.

Further the student has passed the following courses towards fulfillment of coursework requirement for Ph. D.:

Sl. No.	Course	Title	Credits	Pass/Fail
1.	CY452	Organic Reactions and Mechanisms	3	Pass
2.	CY573	Stereoselective Organic Synthesis	2	Pass
3.	CY580	Natural Products and Medicinal Chemistry	2	Pass
4.	CY801	Research Proposal	3	Pass
5.	CY805	Instrumental Methods A	3	Pass

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Mallepalli Shankar.....

LIST OF PUBLICATIONS

(A) Published papers:

1. Reaction of Indole-2-Carboxylates/Carboxylic Acids with Propargylic Alcohols: Dearomative Ring Expansion/Spirocyclization vs Fused Pentacyclics.
Mallepalli Shankar, Uruvakili Anasuyamma, K. C. Kumara Swamy*
Adv. Synth. Catal. **2022**, *364*, 643.

2. Reactivity of Epoxy-Ynamides with Metal Halides: Nucleophile (Br/Cl/OH)-Assisted Tandem Intramolecular 5-*exo-dig* or 6-*endo-dig* Cyclization and AgF_2-Promoted Oxidation.
Mandala Anitha, **Mallepalli Shankar**, K. C. Kumara Swamy*
Org. Chem. Front. **2019**, *6*, 1133.

3. Reactivity of Allenylphosphonates/Allenylphosphine Oxides Some New Addition/Cycloaddition and Cyclization Pathways.
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Pure Appl. Chem. **2019**, *91*, 773.

4. Ruthenium-Catalyzed Oxidative Annulation and Hydroarylation of Chromene-3-carboxamides with Alkynes *via* Double C-H Functionalization.
R. N. Prasad Tulichala, **Mallepalli Shankar**, K. C. Kumara Swamy
J. Org. Chem. **2017**, *82*, 5068.

(B) The following papers are to be communicated.

5. Reactions of Phosphorus/Sulfur Based Allenes: Pd(II)-Catalyzed Cyclization/Cycloadditions and Thermally Induced Cycloadditions with 3,6-Diphenyl 1,2,4,5-Tetrazine.
Mallepalli Shankar,[a] Adula Kalyani,[a] Mandala Anitha, K. C. Kumara Swamy (*to be communicated*)

6. Decarboxylative Annulations of Coumarin-3-carboxylic Acids with *tert*-Propargylic Alcohols Under Cu (II)-Catalysis: Formation of Naphthochromenones
Mallepalli Shankar and K C Kumara Swamy* (*to be communicated*).

7. Ruthenium(II)-Catalyzed Oxidative [4+2] Annulations of Chromene and Coumarin-3-carboxylic Acids with Alkynes *via* sp^2 C-H bond activation.
Mallepalli Shankar and K C Kumara Swamy* (*to be communicated*).

Participation in Conferences/ Symposia

1. Catalytic Transformations Involving Allenes/Alkynes and Ynamides- Identification of Some Intermediates.
K. C. Kumara Swamy,* K. Sandeep, **Mallepalli Shankar**, Adula Kalyani and Mandala Anitha
(*OMCOS-2019*) *20th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis, Heidelberg, Germany, July-2019.*

2. Reactivity of Phosphonate and Sulfonate Based Systems: Some New Findings.
K. C. Kumara Swamy,* A. Kalyani, Suraj, **Mallepalli Shankar** and A. Srinivasarao
International Conference on Main-group Molecules to Materials-II, NISER-Bhubaneswar, Dec-2021.

3. New Aspects of Iodination/DeIodination and Related Reactions Involving Allenylphosphonates/Allenylphosphine oxides.
K. C. Kumara Swamy,* A. Kalyani, M. Anitha and **Mallepalli Shankar**
(ICPC-22) 22nd International Conference on Phosphorus Chemistry, Budapest, Hungary, July-2018.

4. Ruthenium(II)-Catalyzed Oxidative [4+2] Annulations of Chromene-/Coumarin-3-carboxylic Acids with Alkynes *via* sp2 C-H Bond Activation.
Mallepalli Shankar and K. C. Kumara Swamy*
XIV J-NOST Conference for Research Scholars, CSIR-Indian Institute of Chemical Technology, Hyderabad (28th November-1st December, 2018) (**Poster presentation**).

5. Ruthenium-Catalyzed Oxidative Annulation of Coumarin-3-Carboxylic Acid and 2*H*-Chromene-3-Carboxylic Acids with Alkynes and Catalytic Transformations of 2-Substituted Indoles (Acids/Esters) with Propargylic Alcohols.

Mallepalli Shankar and K. C. Kumara Swamy*

ChemFest-2020 (annual in-house symposium) School of Chemistry, University of Hyderabad, INDIA, Feb-2020 (**Oral** and **Poster Presentation**).

6. Synthesis and Structural Aspects of Novel Acyclic Nucleoside Phosphonates

Srinivasarao Allu, **Mallepalli Shankar** and K. C. Kumara Swamy*

ChemFest-2017 (annual in-house symposium), School of Chemistry, University of Hyderabad, INDIA, Feb-2017 (**Poster Presentation**).

Synopsis

This thesis deals with the following topics: (i) Reaction of indole-2-carboxylates/carboxylic acids with propargylic alcohols that involves dearomative ring expansion/spirocyclization and formation of fused pentacyclics, (ii) Decarboxylative annulation of coumarin-3-carboxylic acids with *tert*-propargylic alcohols under Cu(II)-catalysis leading to naphthochromenones, (iii) Ruthenium(II)-catalyzed oxidative [4+2] annulation of chromene and coumarin-3-carboxylic acids with alkynes *via* C(sp^2)-H bond activation, and (iv) Thermally induced regioselective [4+2] cycloaddition reactions of phosphorus/sulfur based allenes and allenoates with 3,6-diphenyl-1,2,4,5-tetrazine.

This thesis is subdivided into three chapters: (a) Introduction (literature survey), (b) Results and Discussion, and (c) Experimental Section. In Chapter 1, a review of literature on aspects relevant to the present work is presented. In Chapter 2, the results obtained on these aspects are discussed while in Chapter 3, the experimental details are described. The compounds prepared in the present study are characterized by MP (as applicable), IR and NMR (^{1}H, ^{13}C, ^{19}F and ^{31}P as appropriate) techniques followed by HRMS. X-ray structure determination has been performed wherever appropriate. Summary as well as references are given at the end of Chapter 3.

Precursors used in the present study are shown in Chart 1. Among these, **2a-b**, **6a**, **6e-j** and **7** are commercially available, and others are prepared by methodologies available in the literature. Compound numbers given here are different from that in the main part of the thesis.

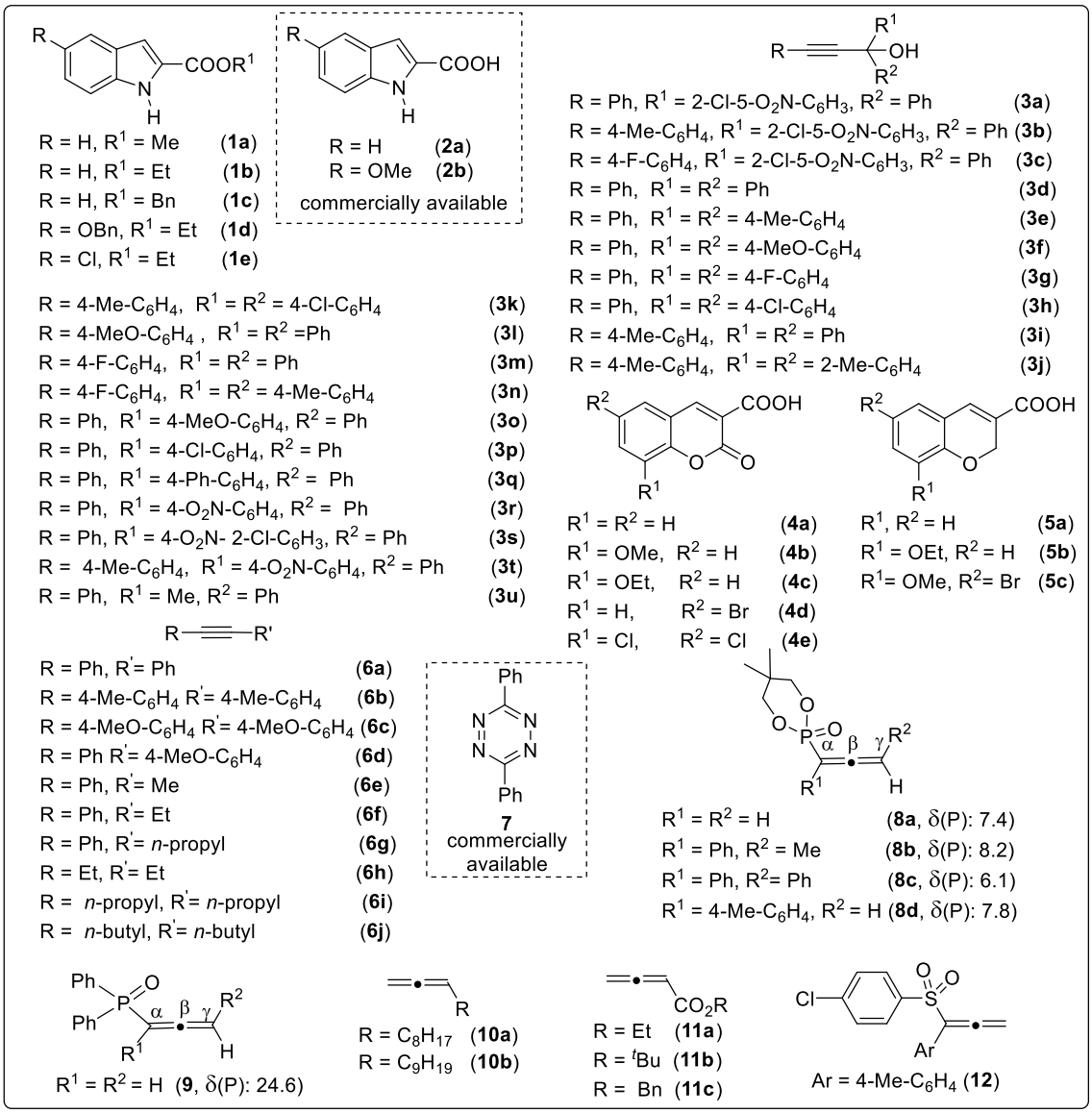
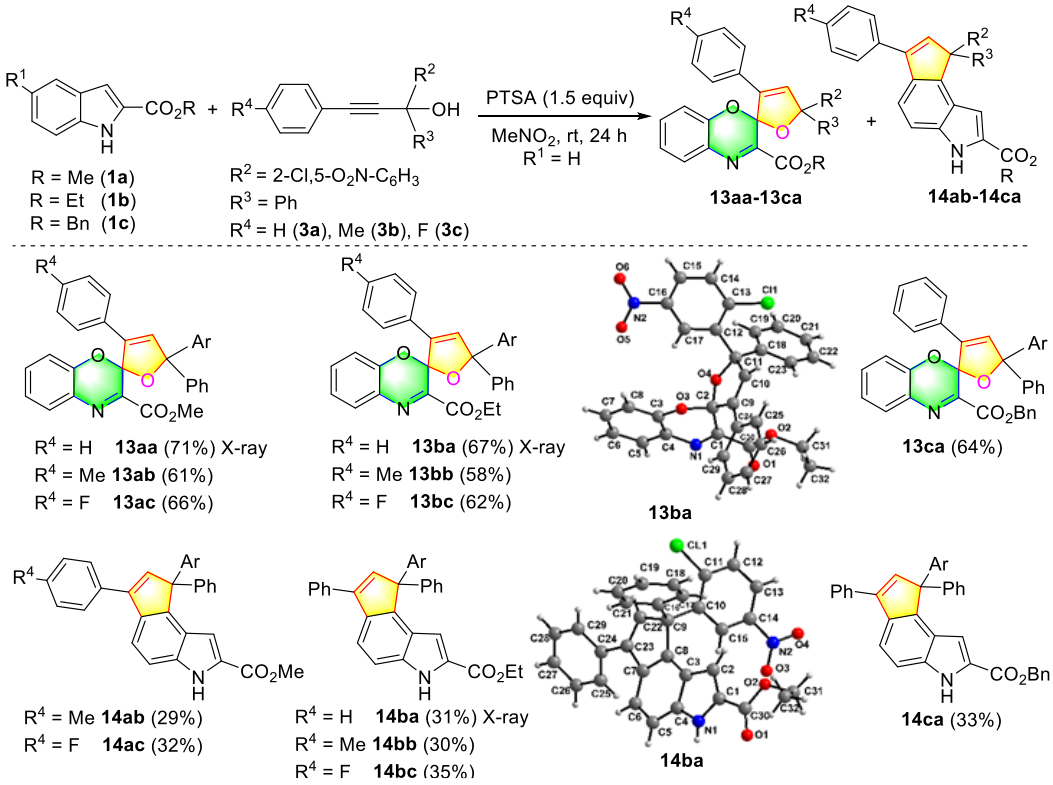


Chart 1: Precursors used in the present study.

(i)(a) PTSA mediated dearomative ring expansion followed by spirocyclization of indole-2-carboxylates with propargylic alcohols leading to spiro or fused heterocyclics

Spirocyclics and fused N/O-containing heterocyclics have always been important structural motifs in pharmaceutical chemistry. In the present study, we have demonstrated a viable synthetic route for spiro[benzo-oxazinefurans] **13** and cyclopenta[*e*]indole-2-carboxylates **14** by the reaction of indole-2-carboxylates (**1a-c**) with *tert*-propargylic alcohols (**3a-c**) in the presence of PTSA (*p*-TsOH) in $MeNO_2$ and open air at room temperature (25 ^oC) for 24 h (Scheme 1). Here, formation of spirocyclic compounds of type **13** involves

dearomative ring expansion through oxygen insertion followed by spirocyclization under aerobic conditions. The structures of products **13aa**, **13ba** and **14ba** were confirmed by X-ray crystallographic analysis.

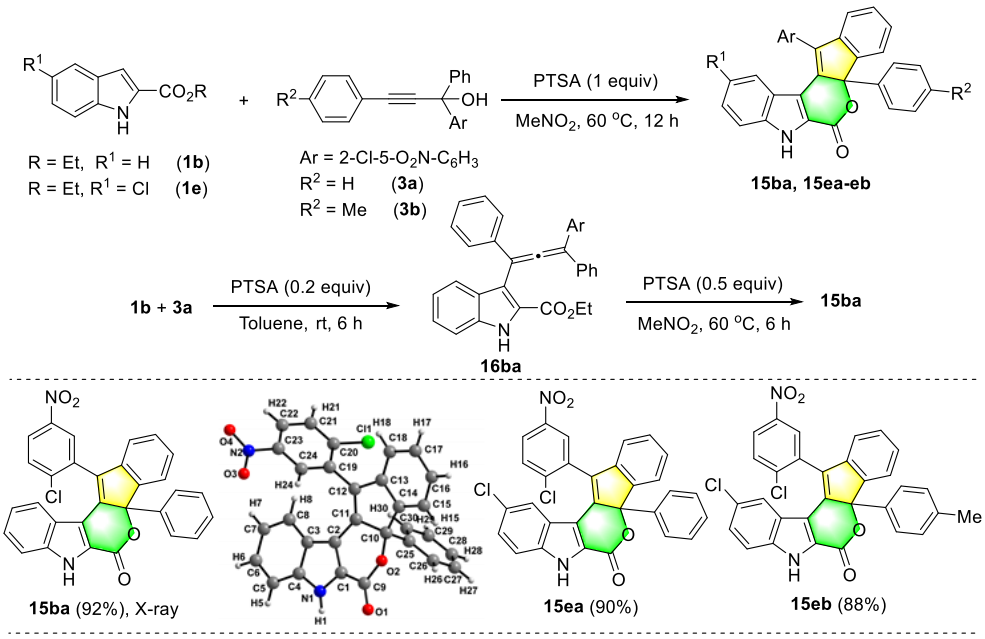


Scheme 1. Synthesis of spiro[benzo-oxazinefurans] **13** and cyclopenta-indole-2-carboxylates **14**

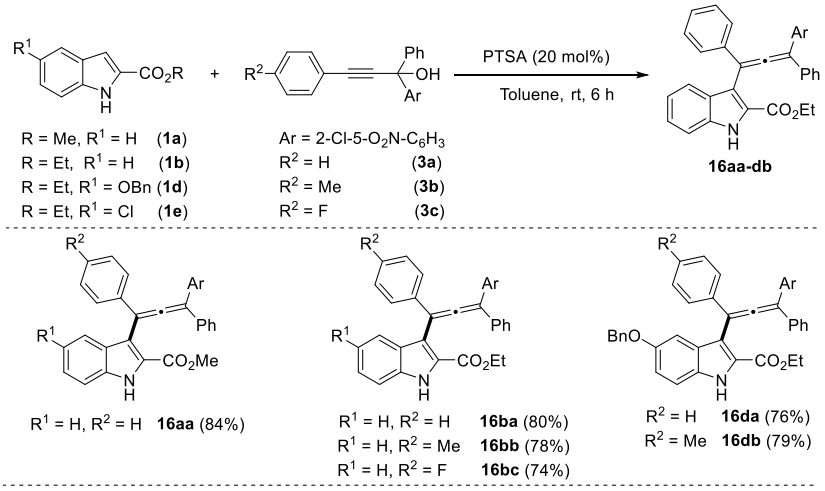
(i)(b) PTSA Mediated synthesis of indene fused pyrano-indolones from indole-2-carboxylates and propargylic alcohols

In an attempt to enhance the yield of products **13** or **14** (cf. Scheme 1), we treated indole-2-carboxylate **1b** with propargylic alcohol **2a** in the presence of PTSA in $MeNO_2$ for 12 h by increasing the temperature to 60 ^oC. To our surprise, we obtained the double cyclized indene fused pyrano-indolone (a fused pentacyclic) **15ba** (X-ray) in 92% yield probably by cyclization of the *in-situ* generated carboxylic acid. It is noteworthy to mention that compound **15ba** can be synthesized from the isolatable allene intermediate **16ba** in the presence of PTSA in $MeNO_2$ at 60 ^oC/ 6 h (Scheme 2), which in turn proves that the reaction takes place *via* allene

intermediate under the conditions employed herein. Formation of allene intermediate is exemplified by the isolation of **16aa** as well as **16ba-bc** and **16da-db** (Scheme 3).



Scheme 2. Synthesis of substituted indene fused pyrano-indolones

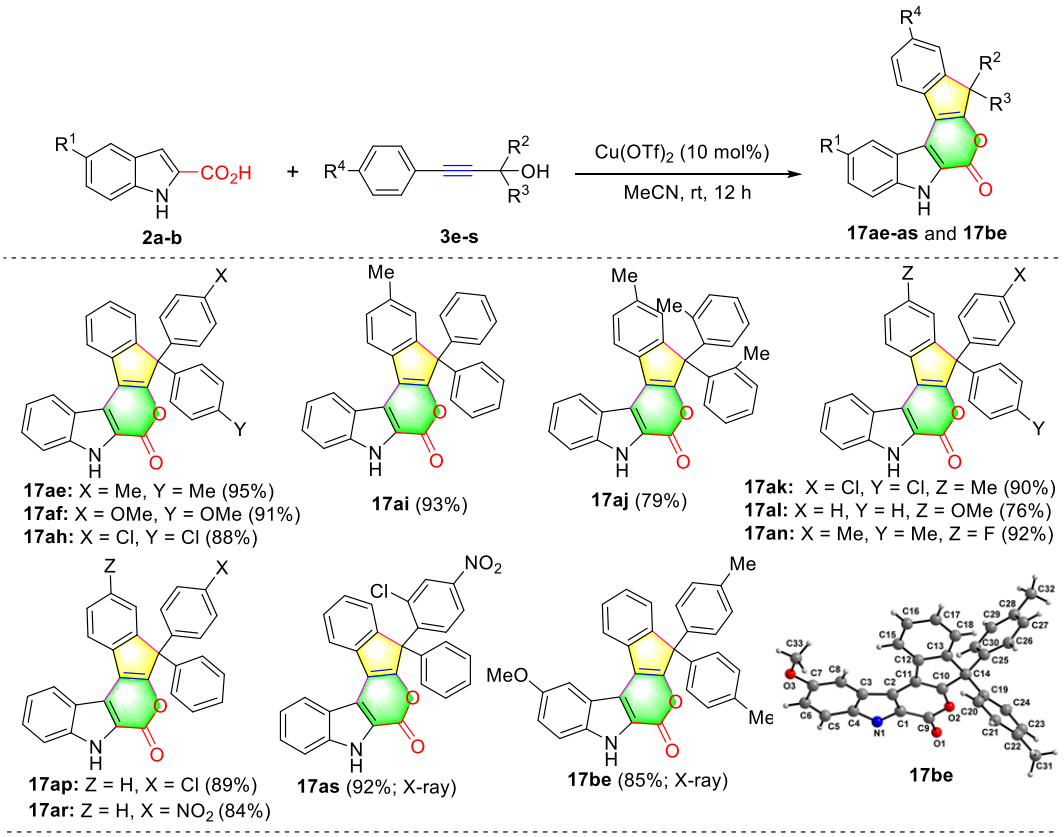


Scheme 3. Formation of substituted 3-allenyl indole intermediates **16aa**, **16ba-bc** and **16da-db**

(i)(c) Cu(II)-Catalyzed annulation of indole-2-carboxylic acids with propargylic alcohols leading to pentacyclic indene fused pyrano-indolones

In the above reactions, we have utilized indole-2-carboxylates. However, we surmised that the course of the reaction could be altered if the carboxylic acid itself is used because of the

availability of the acidic –OH group. Thus, by treating equimolar amounts of the readily available indole-2-carboxylic acid **2a** and propargylic alcohol **3e** with $Cu(OTf)_2$ in MeCN at 25 ^oC for 12 h, we obtained the indene fused pentacyclic product **17ae** in 95% yield. A wide variety of other examples **17af-as** and **17be** could also be readily prepared by this methodology (Scheme 4). Structures of compounds **17as** and **17be** were confirmed by the X-ray crystallographic analysis. Possible mechanistic pathways have been discussed in the thesis.

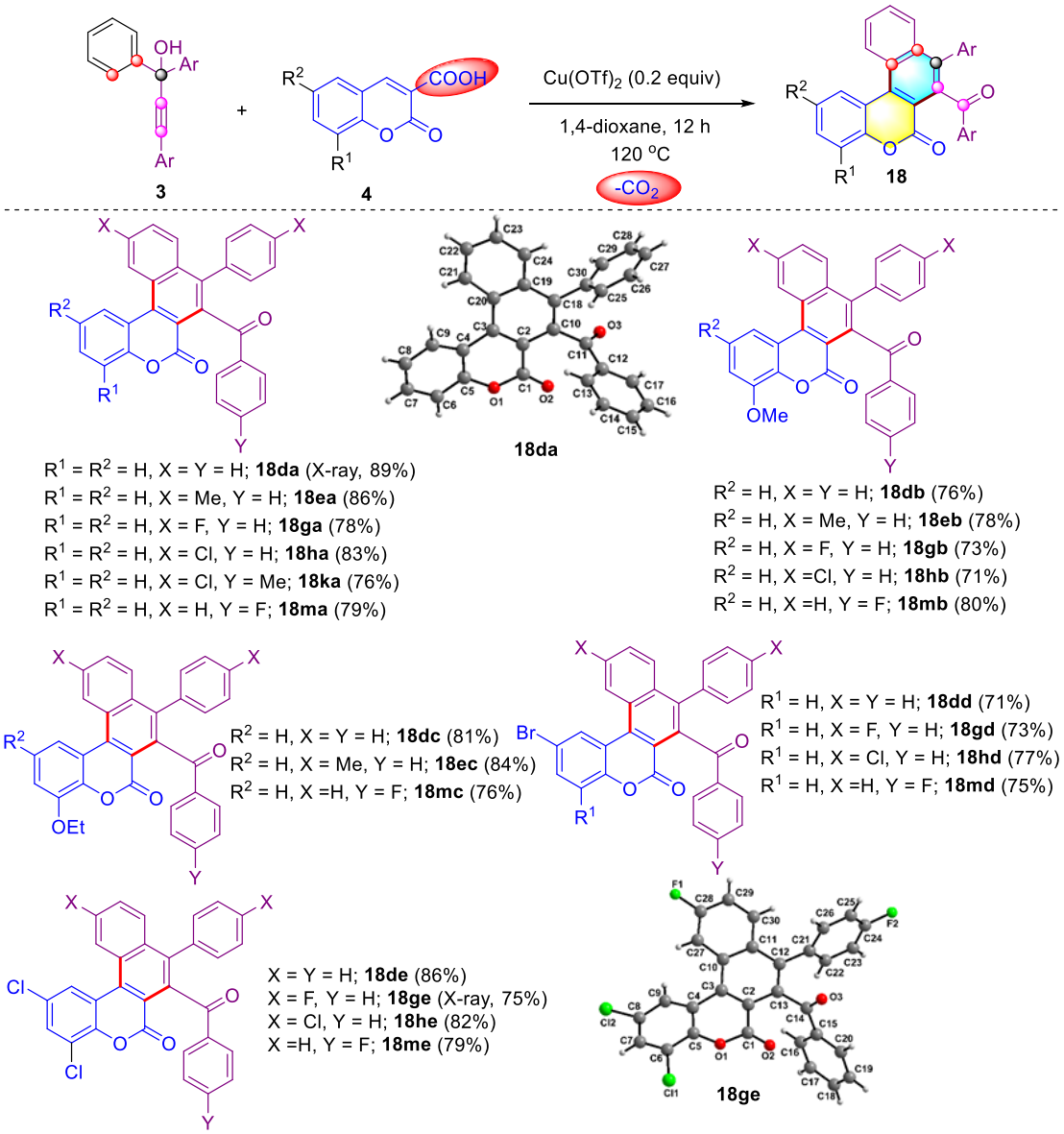


Scheme 4. Synthesis of substituted indene fused pyrano-indolones

(ii) Decarboxylative annulation of coumarin-3-carboxylic acids with *tert*-propargylic alcohols under Cu (II)-catalysis: Formation of naphthochromenones

In continuation of the previous section, we envisioned that instead of indole carboxylic acids, use of other carboxylic acids may lead to a different line of reactivity. For this purpose, we chose chromene carboxylic acid and coumarin carboxylic acid both of which have a double bond in conjugation with the phenyl ring. Thus, we treated propargylic alcohol **3d** with coumarin-3-carboxylic acid **4a** in the presence of $Cu(OTf)_2$ (20 mol%) in 1,4-dioxane at 120 ^oC (oil bath) for 12 h. Pleasingly, this reaction afforded the naphthochromenone **18da** in 89%

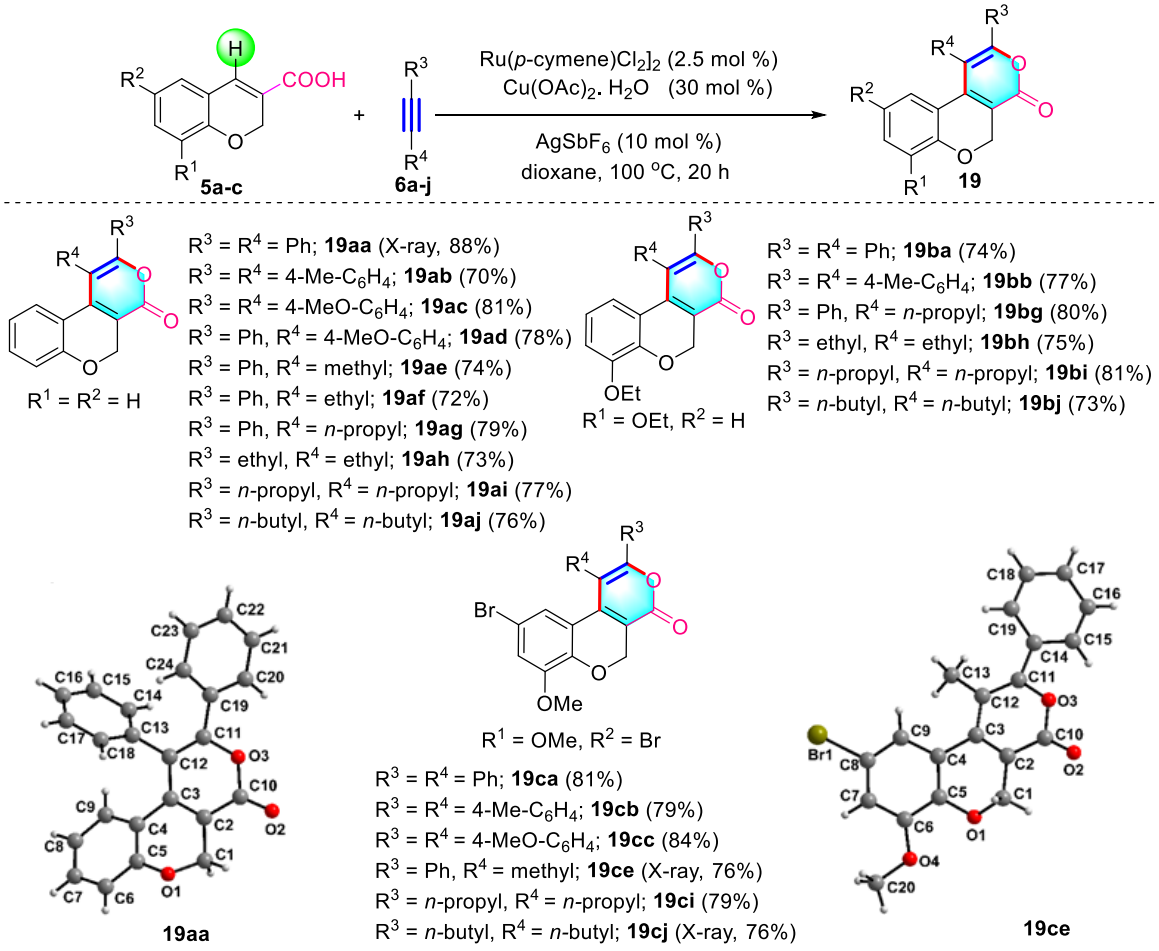
yield. The optimized conditions were employed to obtain other naphthochromenones (Scheme 5). Structures of compounds **18da** and **18ge** were confirmed by X-ray crystallographic analysis. The reaction involves decarboxylation of coumarin-3-carboxylic acid in the presence of $Cu(OTf)_2$; this decarboxylated intermediate with -Cu(OTf) moiety undergoes *anti*-Michael addition with α,β-unsaturated carbonyl compound (generated through Meyer-Schuster rearrangement of propargylic alcohol) followed by intramolecular electro-cyclization and oxidation/aromatization process delivering the annulated product.



Scheme 5. Synthesis of naphtha-chromen-6-ones from coumarin-3-carboxylic acids and propargylic alcohols under Cu(II)-catalysis

(iii)(a) Ruthenium(II)-catalyzed oxidative [4+2] annulation of chromene-3-carboxylic acids with alkynes *via* C(sp^2)-H bond activation

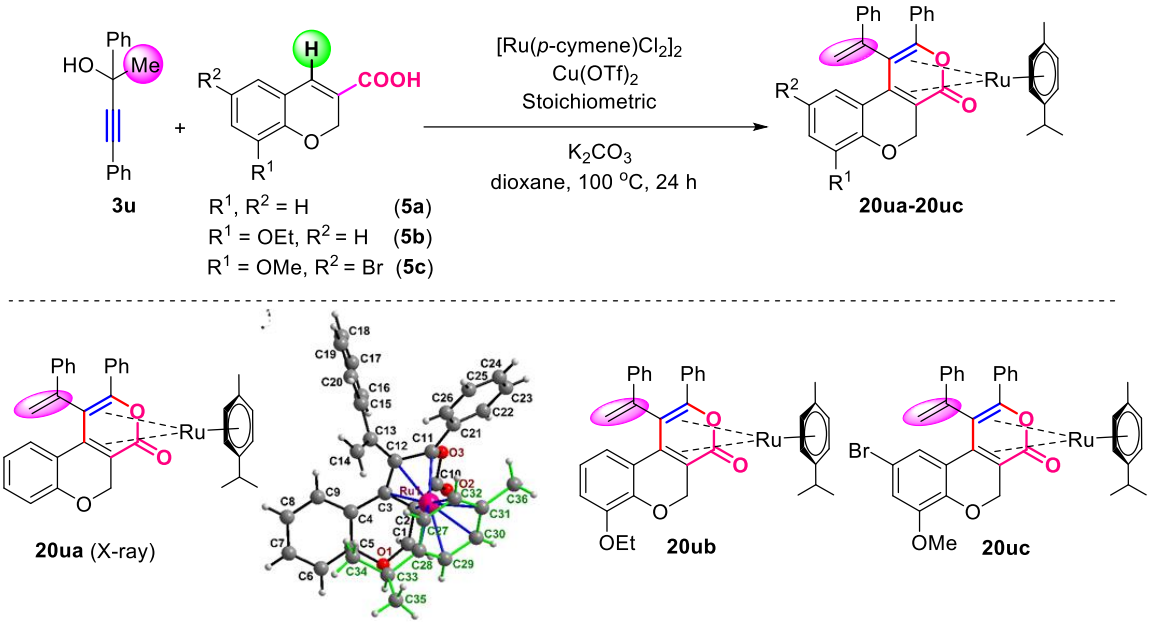
In continuation of the above studies, we wanted to check the reactivity of alkynes instead of propargylic alcohols with chromene/coumarin-3-carboxylic acids. Hence, we treated chromene-3-carboxylic acid **5a** with diphenylacetylene **6a** in the presence of $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%) as catalyst, $Cu(OAc)_2{\cdot}H_2O$ (30 mol%) as the oxidant and $AgSbF_6$ (10 mol%) as the additive in 1,4-dioxane solvent at 100 °C for 20 h. Satisfyingly, we obtained the desired annulated product **19aa** in 88% yield; under the same conditions similar reactions delivered the other pyrano chromenes (Scheme 6). This reaction proceeds through cascade cyclo-metalation with Ru(II)/C-H activation, alkyne coordination/insertion followed by the elimination affording the annulated products. The structures of compounds **19aa**, **19ce** and **19cj** were confirmed by X-ray crystallographic analysis.



Scheme 6. Synthesis of substituted pyrano-chromen-4-ones under Ru(II)-catalysis

(iii)(b) Formation of Ruthenium(0)-metal complexes from chromene-3-carboxylic acids and propargylic alcohols

As an extension of the above reaction, we wanted to check the reactivity of propargylic alcohols **3** with chromene-3-carboxylic acid **5**, since a reaction similar to that discussed above can also take place. Thus, we employed equimolar ratio of propargylic alcohol **3u** and chromene-3-carboxylic acid **5a** using stoichiometric [Ru(*p*-cymene)Cl_2]$_2$, Cu(OTf)$_2$ and K_2CO_3 in 1,4-dioxane at 100 ^oC for 24 h we obtained the [Ru]-complex **20ua** [*Note*: Initially, we had used only 5 mol% of [Ru(*p*-cymene)Cl_2]$_2$]. Two more complexes were also synthesized under the same reaction conditions (Scheme 7). The structure of **20ua** was confirmed by the X-ray crystallographic analysis. Removal of ruthenium to get the [Ru]-free annulated product have not been successful so far.

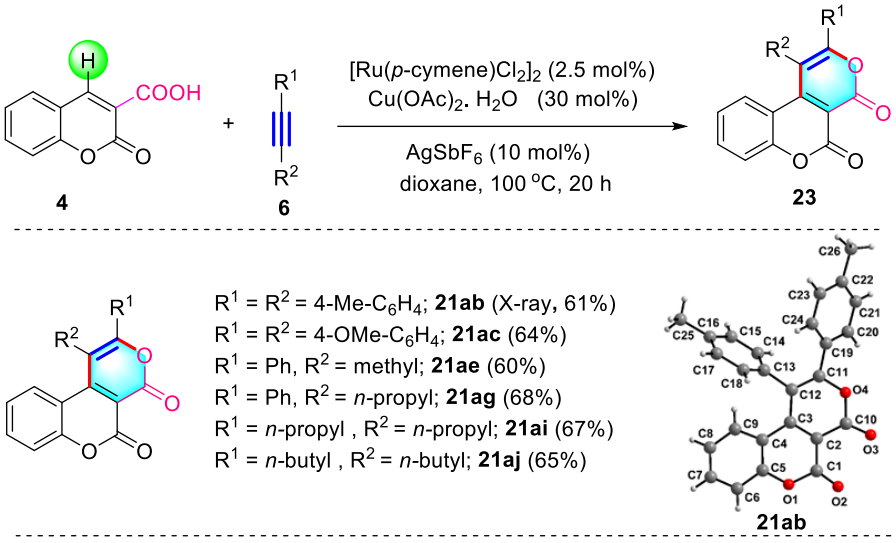


Scheme 7. Synthesis of Ru(0)-metal complexes

(iii)(c) Ruthenium(II)-catalyzed oxidative [4+2] annulation of coumarin-3-carboxylic acids with alkynes *via* C(sp^2)-H bond activation

In an effort to extend the above [Ru]-catalyzed cyclization, we wanted to check the reactivity of coumarin-3-carboxylic acid under the same reaction conditions in order to know the effect of the additional carbonyl group on product formation. Hence we employed

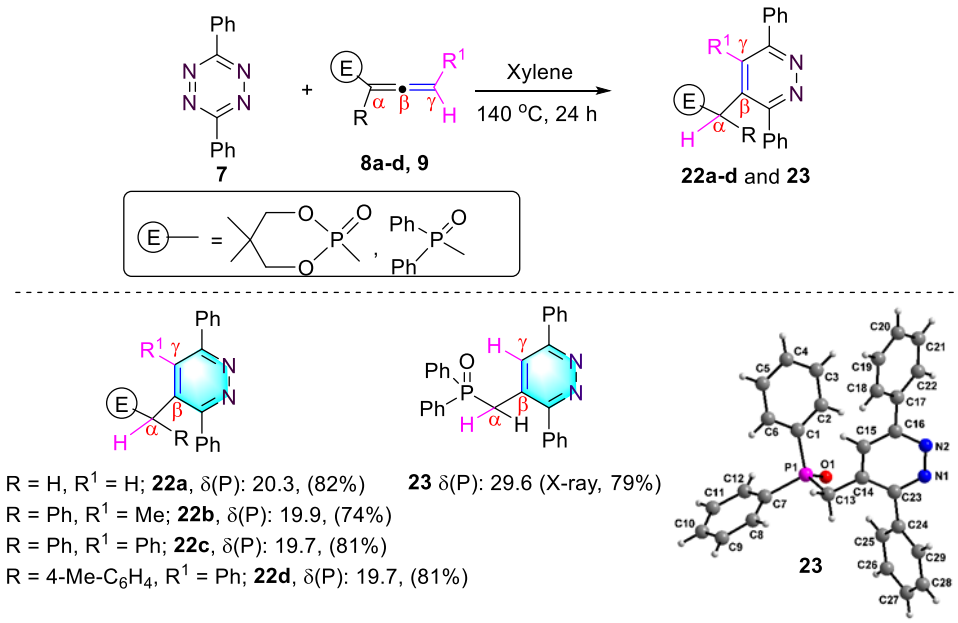
coumarin-3-carboxylic acid **4a** with alkyne **6b** and as expected, [4+2] annulation occurred to give the annulated product **21ab** in 61% yield; similarly other internal alkynes were employed along with **4a** to afford the annulated products as shown in Scheme 8. The structure of compound **21ab** was confirmed by single crystal X-ray crystallography.



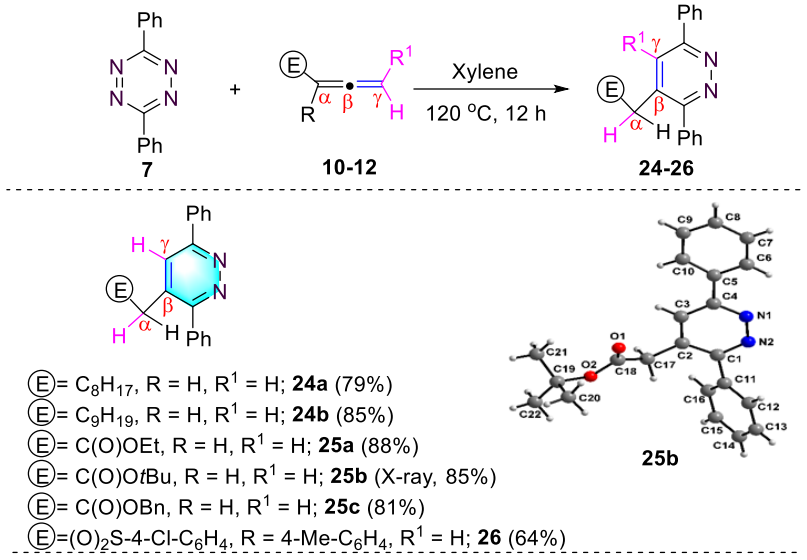
Scheme 8. Synthesis of substituted pyrano[3,4-*c*]chromene-4,5-diones from coumarin-3-carboxylic acid and alkynes

(iv) Thermally induced [4+2] cycloaddition of phosphorus/sulfur based allenes and allenoates with 3,6-diphenyl-1,2,4,5-tetrazine

Tetrazine can act as a diene in Inverse Electron Demand Diels-Alder (IED D-A) reaction with dienophiles. Tetrazines have been utilized for the cycloaddition reactions, but so far, the reacting partners have been limited mainly to alkynes and to our knowledge, cycloaddition reactions of tetrazines with allenes is rather known scantily. The resulting compounds, pyridazines, show very interesting biological activities. In our study, the reaction of 3,6-diphenyl-1,2,4,5-tetrazine **7** with allenyl phosphonate **8a** in xylene at 140 for 24 h afforded the cycloaddition adduct **22a** in 82% yield. The same reaction conditions were employed with other allenes also to afford a variety of pyridazines (Scheme 9). This reaction proceeds through the IED D-A reaction followed by [1,3]-H shift to deliver the substituted pyridazines. Allenes **10-12** underwent the reaction at a comparatively lower temperature of 120 °C within 12 h to deliver the cycloadducts **24a-b**, **25a-d** and **26** (Scheme 10). Structures of compounds **23** and **25b** have been established by X-ray crystallographic analysis.



Scheme 9. Synthesis of phosphorus based substituted pyridazines



Scheme 10. Synthesis of substituted pyridazines via allenes

Chapter 1

INTRODUCTION

This chapter deals with the literature relevant to the topics that will be discussed in Chapter 2. General introduction for the annulation reactions of indole carboxylates/carboxylic acids and chromene/coumarin carboxylic acids with C-C π components is presented in section 1.1; the importance and the reactivity pattern in cycloadditions involving tetrazine and alkynes/allenes is also briefly alluded to. Recent literature on intra- and inter-molecular annulation reactions of indoles with C≡C/C=C bonded systems are discussed in sections 1.2-1.3. In section 1.4, decarboxylative annulation reactions of aromatic/heteroaromatic carboxylic acids with unsaturated compounds under transition metal catalysis are presented. Section 1.5 delves on annulation reactions of aromatic/hetero-aromatic carboxylic acids with C≡C/C=C scaffolds under transition metal catalysis. The available literature on Inverse Electron Demand Diels-Alder (IED-D-A) reactions of tetrazines with dienophiles is presented in the section 1.6.

1.1 General Introduction

Transition metal catalyzed annulation involving the carboxylic acids for the synthesis of poly/heterocyclic architectures is one of the broadly studied fields in organic chemistry.[1] The carboxylate moiety of aromatic carboxylic acids can act as a traceless directing group for the metal assisted C-H functionalization to afford the diverse functionalized motifs.[1k] It can also be involved in [4+2],[1a-b, 1f-n] [4+1][2] and [3+2][3] annulations with C-C π components under transition metal catalysis *via* carboxylate directed *ortho*-C-H/O-H functionalization. In addition, it can also undergo decarboxylative annulation reactions with C=C or C≡C systems.[4] Because of the versatility and synthetic utility, the annulation reactions involving indole carboxylic acid and chromene/coumarin carboxylic acids with unsaturated compounds is an emerging field in organic chemistry. Indole is more reactive towards the electrophilic substitution reactions and undergoes a variety of annulation reactions.[5,6] Indole containing drugs have been approved as anti-cancer,[7] anti-hypertension,[8] antimicrobial,[9] anti-depressant[10] and erectile-dysfunction[11] agents. Molecules possessing chromene/coumarin scaffolds also

show significant anti-HIV RT,[12a-b] antimicrobial, anti-tuberculosis,[12c] diuretic, analgesic,[12d] and anti-cancer[12e-g] properties. Selected indole and coumarin containing drug molecules are shown in Figure 1.

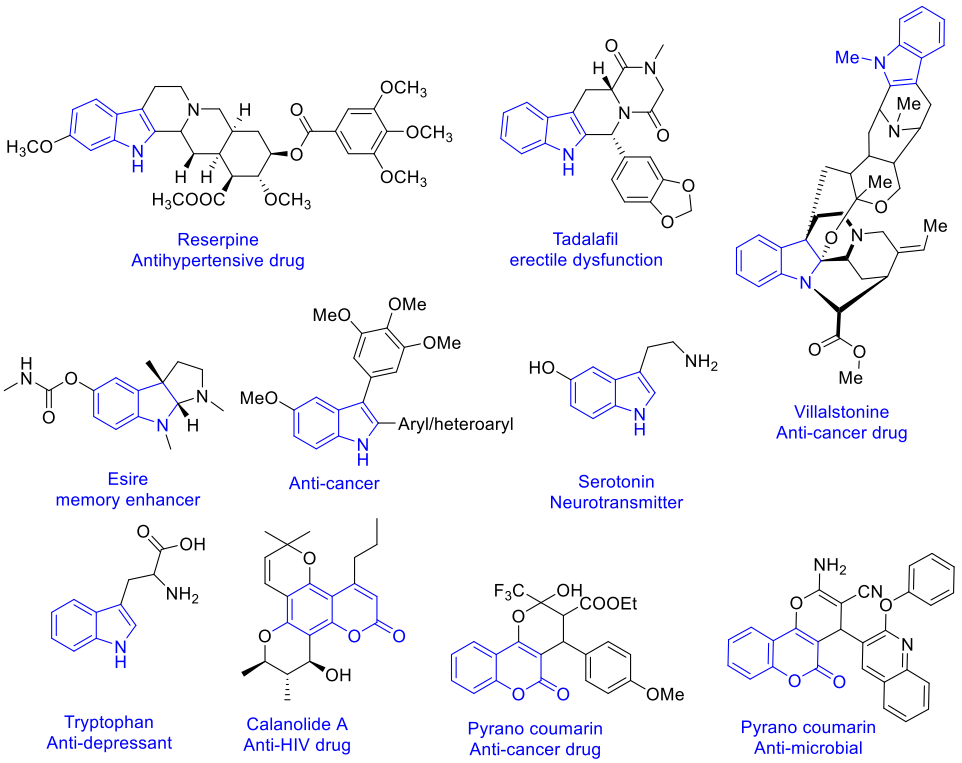


Figure 1. Selected indole and coumarin containing drug molecules

The past six decades have seen an incredible growth in the applications of Inverse Electron Demand Diels-Alder (IED-D-A) or bioorthogonal reactions of electron poor dienes with electron rich counterparts (dienophiles) for the development of novel heterocyclic architectures.[13] The basic difference between the general Diels-Alder and IED-D-A reactions is the addition process of diene and dienophile. In Diel-Alder reaction, HOMO of the electron rich diene and LUMO of the electron poor dienophile will participate in the cycloaddition. In contrast to this, in the IED-D-A reactions, LUMO of the electron poor diene and HOMO of the electron rich dienophile will take part in the reaction.[13b-c,14] IED-D-A reactions are well-utilized in the fields of peptide research, total synthesis and medicinal/ biological chemistry for the detection of the living cells or for imaging the small molecules in the living organisms.[13a-l,13s] There are

several electron deficient dienes such as tetrazines, triazines, diazines and oxadiazoles.[15] Among these, cycloadditions involving tetrazine are more versatile compared to other conventional biorthogonal cycloaddition reactions. The main advantages of the tetrazine cycloaddition reactions are: (i) they do not require a metal catalyst, (ii) reaction rates are high compared to other cycloadditions and (iii) reactions can be performed with micromolar quantities. The fluorogenic properties of the formed pyridazines/1,2-diazine and 'turn on' fluorescence nature upon cycloaddition is also important in connection with the labeling of the live cells in microorganisms and intracellular bioimaging of the small molecules.[13] In most cases, active fluorophore pyridazines/1,2-diazines as the final products are generated. The resulting compounds, pyridazines, are popular pharmacophores and present in herbicides[16] such as credazine,[16c] pyridafol[16d] and pyridate.[16e] Alongside, pyridazines are structurally important motifs with high potential anti-cancer,[17] anti-depressant,[18] anti-hypertension,[19] anti-inflammatory[20] and anti-alzheimers[21] activity. However, the natural abundance of the pyridazines is limited. Representative pyridazine based drug molecules are depicted in Figure 2.

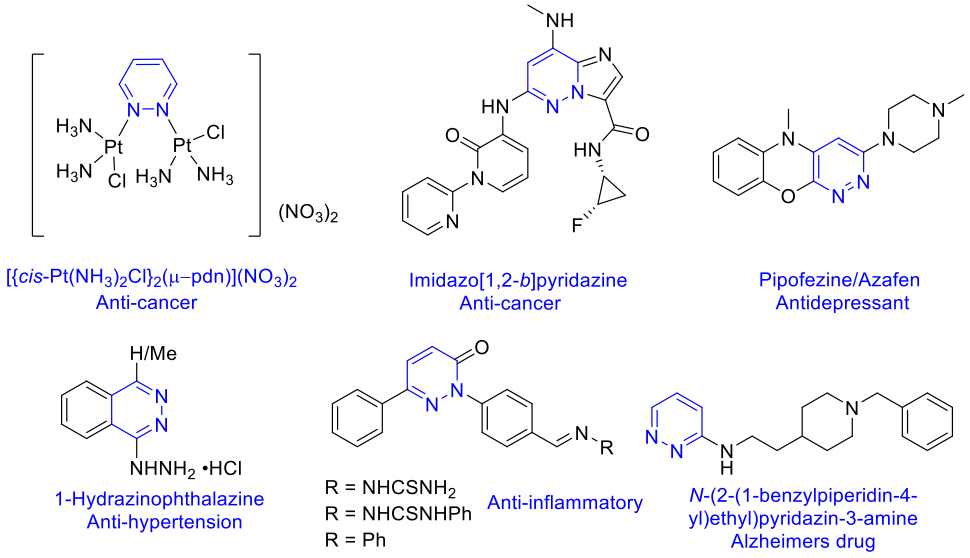
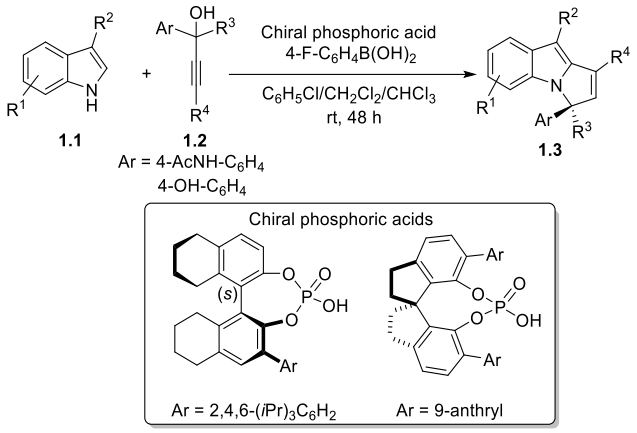


Figure 2. Representative pyridazine based drug molecules

In the current work, we plan to utilize indole and chromene/coumarin carboxylic acids for annulations with C-C π components (alkynes and propargylic alcohols) under transition metal catalysis and 3,6-diphenyl-1,2,4,5-tetrazine for the thermally induced cycloaddition reaction with allenes. The relevant literature is outlined in the following sections.

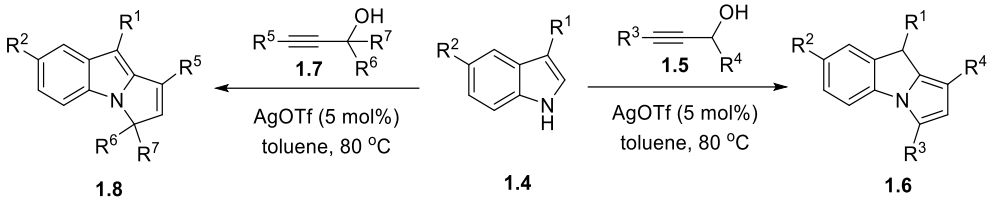
1.2 Intermolecular annulation reactions of indole substrates with propargylic alcohols

Very recently, Li's group developed a regio- and enantio-selective phosphoric acid catalyzed asymmetric [3+2] cycloaddition of 3-substituted indoles **1.1** with directing group (*p*-NHAc or *p*-OH) tethered *tert*-propargylic alcohols **1.2** for the synthesis of chiral pyrroloindoles **1.3** using mild reaction conditions (Scheme 1.1).[22] Here, *p*-NHAc acts as activating as well as directing group and is crucial for the cycloaddition. It participates in hydrogen bonding to chiral phosphoric acid catalyst facilitating chiral induction.



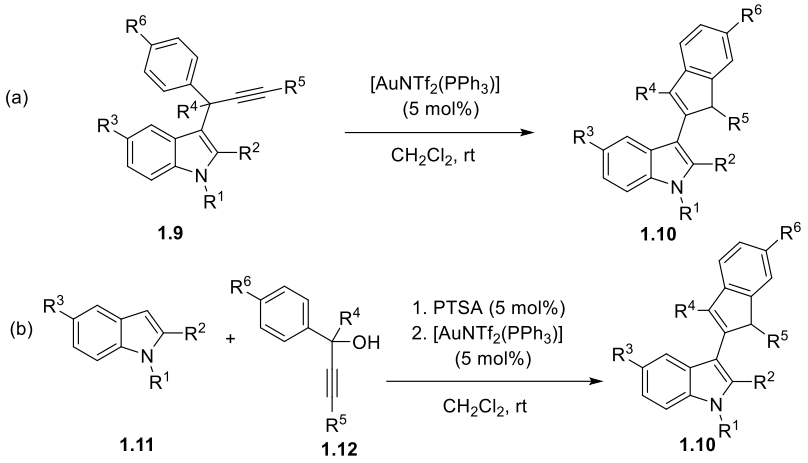
Scheme 1.1. Chiral phosphoric acid catalyzed [3+2] cycloaddition reactions of indoles with propargylic alcohols

Zhan *et al.* developed an effective protocol for the chemoselective synthesis of two different types of pyrroloindoles (**1.6** and **1.8**) from the readily available indoles **1.4** and *sec*-/*tert*-propargylic alcohols **1.5/1.7** under the same conditions using AgOTf as the catalyst without using any base or ligand (Scheme 1.2).[23]



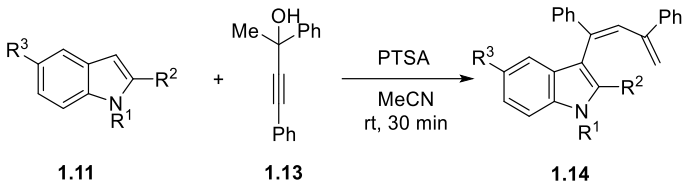
Scheme 1.2. Ag(I)-catalyzed chemoselective cascade synthesis of pyrroloindoles

Sanz *et al*. discovered a method for the synthesis of 3-indenyl indoles **1.10** through 1,2-indole migration of the C3-propargylated indoles **1.9** under gold-catalysis. This process involves 1,2-indole migration followed by C-H insertion or Nazarov cyclization of C3 propargylated indoles. When indole **1.9** was treated with gold(I)-catalyst in dichloromethane solvent at room temperature, 3-indenyl indole **1.10** is obtained (Scheme 1.3a).[24] On the other hand, **1.10** can also be synthesized directly from indole **1.11** and propargylic alcohols **1.12** in a sequential one pot manner by using PTSA and gold(I)-catalyst (Scheme 1.3b).



Scheme 1.3. Gold(I)-catalyzed annulations of the indoles with propargylic alcohols

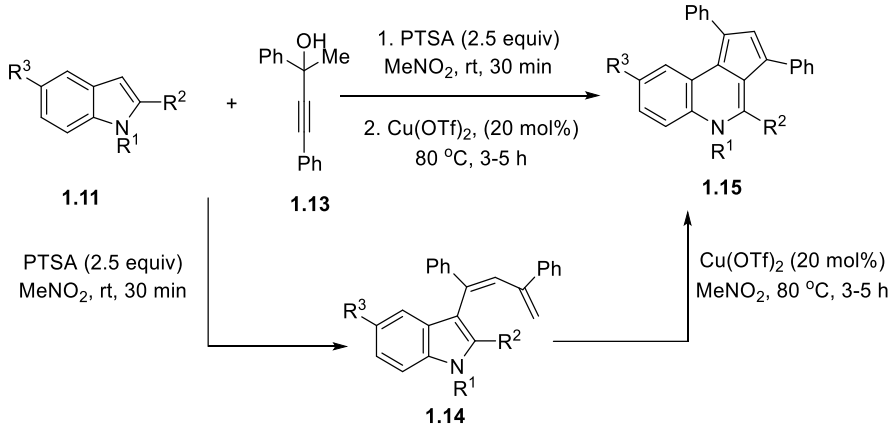
Later, the same Sanz's group reported a methodology for the synthesis of 3-(1,3-butadienyl)indoles **1.14** by the reaction of **1.11** with propargylic alcohols **1.13** under PTSA catalysis at room temperature as shown in Scheme 1.4.[25] But they did not utilize the formed active indole-substituted butadienes **1.14** for post-functionalization/annulation to generate new heterocyclic motifs, although several possibilities exist.



1.11 1.13 1.14

Scheme 1.4. PTSA-catalyzed butadienylation of indoles with propargylic alcohols

Later, our group successfully demonstrated a novel sequential one-pot methodology for the construction of highly conjugated cyclopenta[*c*]quinolines **1.15** *via* 3-allenylindoles/3-(1,3-butadienyl indoles) **1.14** using $Cu(OTf)_2$ and PTSA through the dearomatized oxidative ring expansion of the formed intermediate **1.14** with air as the sole oxidant (Scheme 1.5). The reaction proceeds through Brønsted acid mediated allenylation and isomerization to afford intermediate **1.14**, which upon copper-catalyzed dearomatization/oxidative ring expansion gives the final product **1.15**.[26]

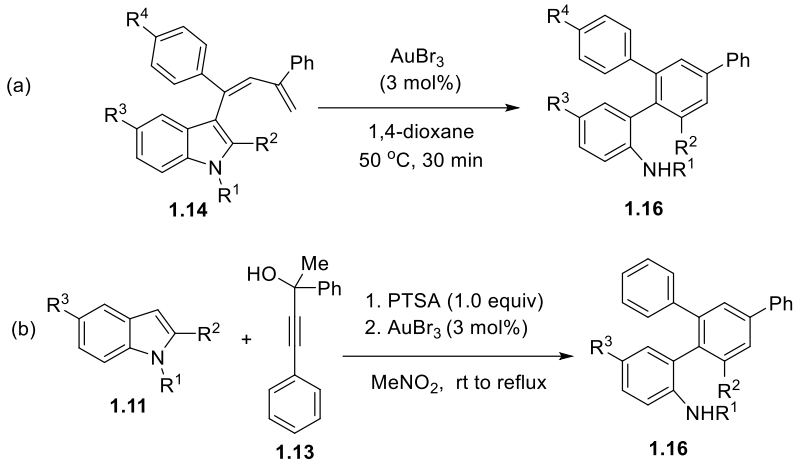


1.11 1.13 1.15 1.14

Scheme 1.5. Sequential or one pot synthesis of fused cyclopenta[*c*]quinolines using PTSA and $Cu(OTf)_2$

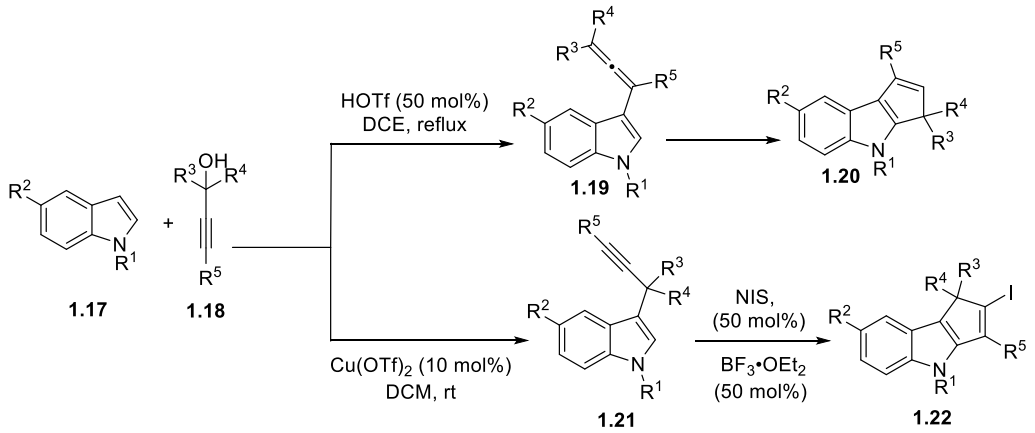
Recently, our group reported a pathway for the generation of the terphenylamines **1.16** from indoles **1.11** and propargylic alcohols **1.13** by the intramolecular cyclization of 3-butadienyl indoles **1.14** under gold(III)-catalysis.[27] This reaction can also be achieved by starting with the indole and propargylic alcohol. In the case of sequential reaction, first the indole partner **1.11** reacts with the propargylic alcohol **1.13** in the presence of PTSA to give

butadienyl intermediate **1.14** which upon reaction with 3 mol% of the gold(III)bromide gives functionalized terphenylamines **1.16** as the final products (Scheme 1.6).



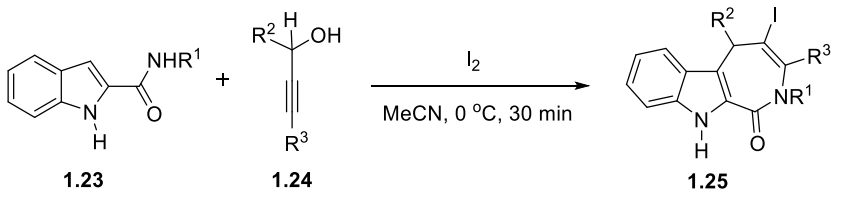
Scheme 1.6. Gold(III)-catalyzed sequential/one pot synthesis of terphenylamines

Wang and Lu described the distinction in the reactivity of indoles **1.17** with propargylic alcohols **1.18** under Lewis and Brønsted acid catalysis for the selective synthesis of dihydrocyclopentaindoles **1.20** and dihydrocyclopentaindoles **1.22** (Scheme 1.7).[28] In the presence of TfOH, 3-alkenylation/allenylation followed by intramolecular cyclization of indole with propargylic alcohols **1.18** was observed to give product **1.20**. In contrast, in the presence of Lewis acid $Cu(OTf)_2$, 3-alkylation/propargylation of indole **1.17** followed by cyclization in the presence of the NIS and $BF_3{\cdot}OEt_2$ afforded **1.22**.



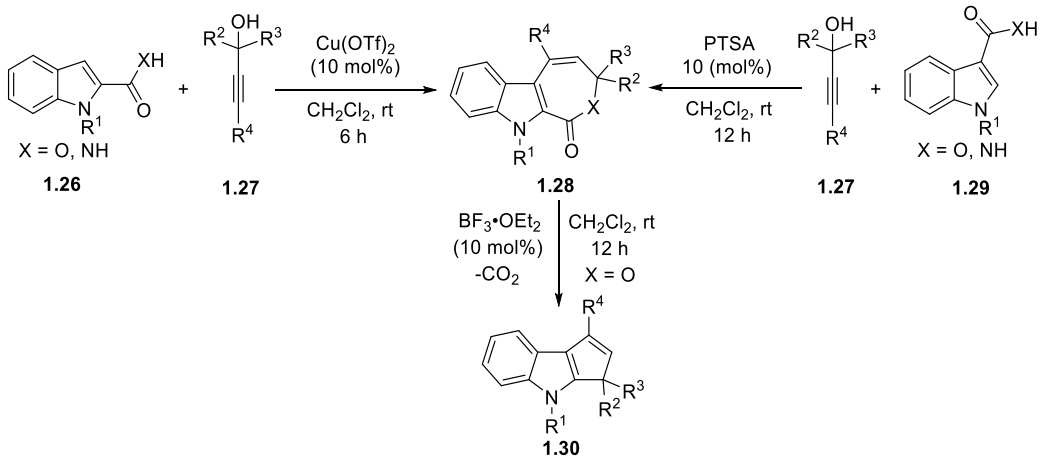
Scheme 1.7. Catalyst driven divergent annulations of indoles and propargylic alcohols

Kundu and coworkers developed an effective and simple methodology for the synthesis of the iodo-indoloazepinone **1.25** framework from the reaction of indole-2-carboxamides **1.23** and *sec*-propargyl alcohols **1.24** (Scheme 1.8).[29] The synthesis involves iodine-mediated C-H functionalization, alkyne activation and intramolecular cyclization utilizing the amide functionality followed by deprotonation to afford 4-iodoindoloazepinones **1.25**.



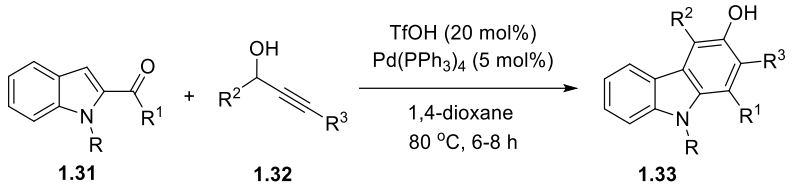
Scheme 1.8. Iodo-cyclization of indole-2-carboxamides and propargylic alcohols

Recently, our group discovered [4+3]-annulation reactions of the indole-2-carboxylic acids/amides **1.26** with propargyl alcohols **1.27** under Cu(II)-catalysis for the synthesis of ε-lactones/ε-lactams **1.28**. Surprisingly, similar [4+3] annulated product **1.28** was observed when indole-3-carboxylic acid/amide **1.29** along with propargylic alcohol **1.27** was used under PTSA-catalysis *via* migration of the acid/amide functionality from the indole-C3 position to indole-C2 position (Scheme 1.9).[1a] The important advantage of the reaction is that the ε-lactones obtained from the annulation undergo decarboxylative cyclization to afford 3,4-dihydrocyclopenta[*b*]indoles **1.30**.



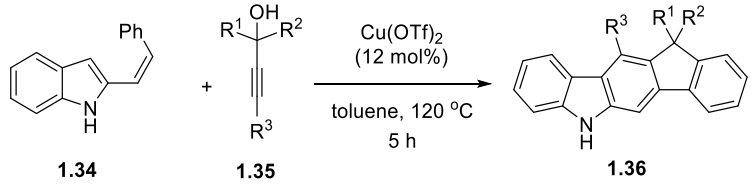
Scheme 1.9. Annulation reactions of the indole-carboxylates/carboxamides with propargylic alcohols under Lewis or Brønsted acid catalysis

Recently, Raji Reddy *et al.* developed a methodology for the construction of fully substituted 3-hydroxycarbazoles **1.33** from 2-acyl indoles **1.31** and propargylic alcohols **1.32** in a sequential one-pot method using TfOH /Pd(0)-catalytic system (Scheme 1.10).[30] This methodology involves the reaction of 2-acyl indole with propargylic alcohol in the presence of TfOH to give the 3-propargylated indole, which, in the presence of Pd(0)-catalyst leads to the formation of the fully substituted 3-hydroxy carbazoles.



Scheme 1.10. Synthesis of 3-hydroxy carbazoles from indoles and propargylic alcohols

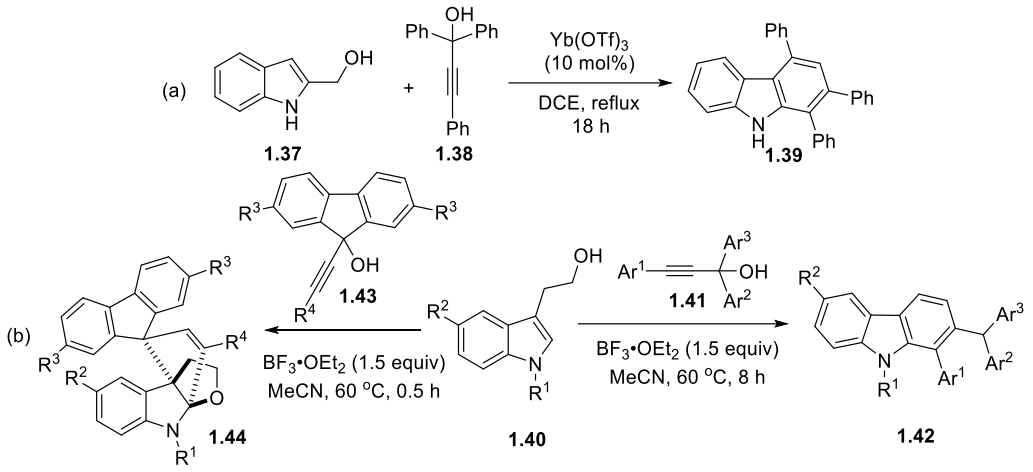
Liang's group reported a Cu(II)-catalyzed intermolecular annulation leading to fused pentacyclics **1.36** containing carbazole motifs from the reaction of (*Z*)-2-styryl-1*H*-indoles **1.34** with propargylic alcohols **1.35** (Scheme 1.11).[31] Here, the product formation involves sequential Meyer-Schuster rearrangement/isomerization followed by cyclization.



Scheme 1.11. Cu(II)-catalyzed annulations of propargylic alcohols with (*Z*)-2-styryl-1*H*-indoles

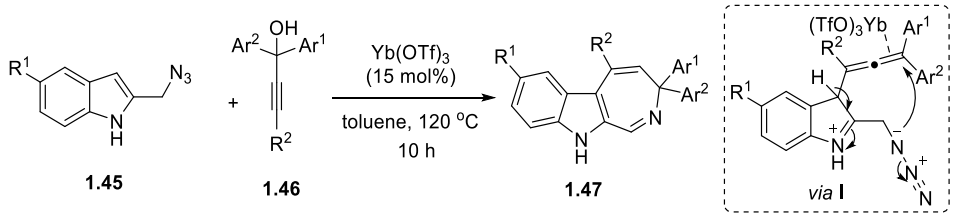
Wang *et al*. demonstrated an atom and step-economy Yb(III)-catalyzed dehydrative [3+3]-annulation of indole alcohols **1.37** with propargylic alcohols **1.38** for the construction of substituted carbazoles **1.39** with water as the only byproduct. This reaction proceeds through Friedel−Crafts-type of alkenyl/allenylation followed by 1,5-[H] shift and intramolecular cyclization involving the indole alcohol to get the carbazole motif (Scheme 1.12a).[32] Wang and Lu demonstrated the divergent reactivity of *tert*-propargylic alcohols **1.41** and tryptophols

1.43 with substituted indolyl alcohol **1.40** in the presence of $BF_3 \cdot OEt_2$. They were successful in generating substituted carbazoles **1.42** and cyclopenta[*b*]furo[2,3-*b*]indoles **1.44** with excellent selectivity (Scheme 1.12b).[33]



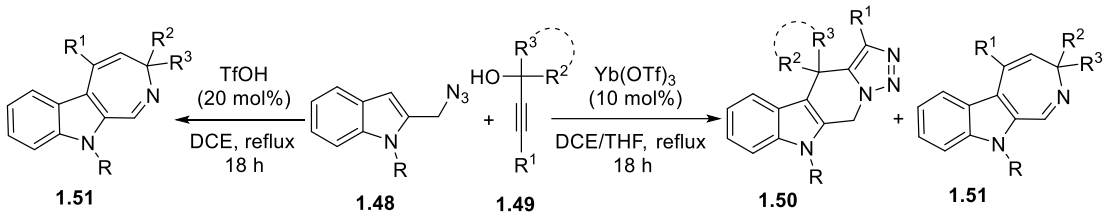
Scheme 1.12. Yb(III)-catalyzed dehydrative [3+3] cycloaddition reactions of indole alcohols with propargylic alcohols

Liang's group reported a methodology for the construction of fused seven-membered indoloazepine motifs **1.47** by using indolyl methyl azides **1.45** and propargylic alcohols **1.46** under Lewis acid catalysis *via* formal [4+3] cycloaddition of propargylic alcohols with azides (Scheme 1.13).[34] This reaction proceeds through alkenylation/allenylation of indole azide with propargylic alcohol in the presence of $Yb(OTf)_3$ (*via* intermediate **I**) followed by intramolecular cyclization with azide and subsequent elimination of N_2 delivering the indolo-azepines **1.47**.



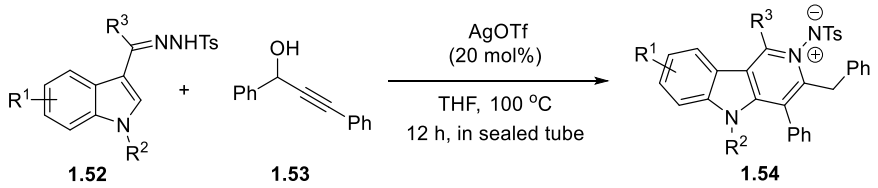
Scheme 1.13. Yb(III)-catalyzed [4+3] cycloaddition of indole azides with propargylic alcohols

More recently, Wang's group described catalyst driven divergent reactivity of 2-indolylmethyl azides **1.48** with propargylic alcohols **1.49** for the formation of fused tetrahydro-*β*-carbolines **1.50** and indole azepines **1.51** under Lewis or Brønsted acid catalysis. When **1.48** was treated with the propargylic alcohol **1.49** in the presence of $Yb(OTf)_3$, it delivered tetrahydro-*β*-carboline **1.50** along with substituted indole azepine **1.51**. By contrast, the same two starting materials when treated with the Brønsted acidic catalyst TfOH delivered substituted indole azepine **1.51** as the sole product (Scheme 1.14).[35]



Scheme 1.14. Divergent annulations of the 2-indolylmethyl azides with propargylic alcohols

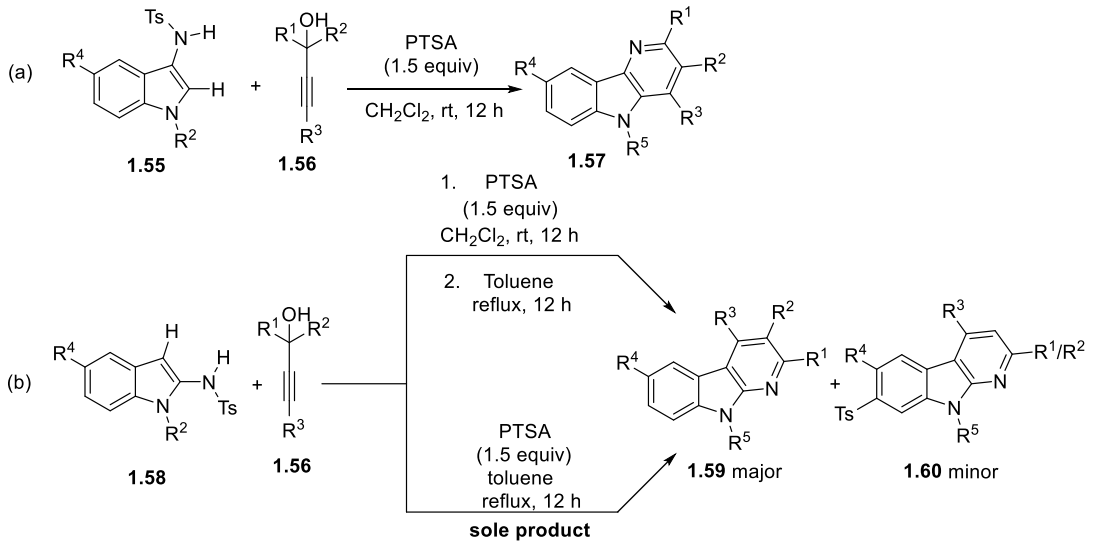
A regioselective approach for the effective synthesis of *N*-imino-*γ*-carbolinium ylides **1.54** from the readily available indole-3-hydrazones **1.52** on reaction with the propargylic alcohol **1.53** in the presence of AgOTf-catalyst has been developed by Zhan's group (Scheme 1.15).[36] In this reaction, sequential Friedel–Crafts alkylation followed by intramolecular N–C bond formation in the presence of silver(I) triflate takes place.



Scheme 1.15. Ag(I)-catalyzed annulation of indole-3-hydrazones with propargylic alcohols

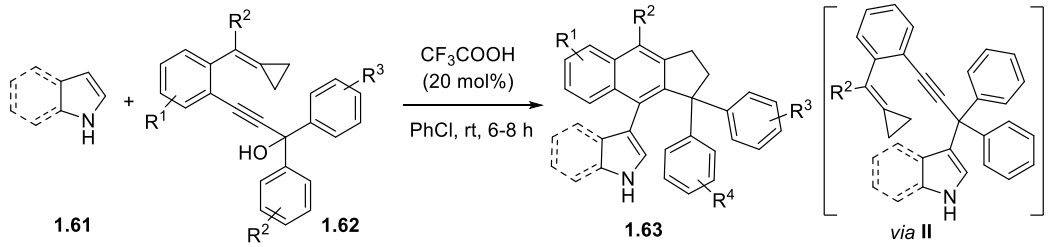
Recently, our group developed a protocol for the construction of fully-substituted *δ*- and *α*-carbolines **1.57** and **1.59** under transition metal-free conditions by reacting 2- or 3-substituted sulfonamido-indoles/indolines **1.55** and **1.58** with *tert*-propargylic alcohols **1.56** in the presence of PTSA at room temperature. When **1.58** was treated with the propargylic alcohol **1.56**, along with the major *α*-carbolines **1.59**, unexpected tosyl migrated *α*-carbolines **1.60** were

also observed as minor products (Scheme 1.16).[37] In contrast, the single product **1.59** was observed when the same reaction was performed using PTSA in toluene at reflux conditions. The reaction proceeded through sequential Friedel-Crafts alkylation, [1,5]-H shift, 6π-electrocyclization, elimination/[1,2]-aryl migration and aromatization to give carbolines.



Scheme 1.16. PTSA-mediated annulation reactions of the sulfonamido-indoles/indolines with propargylic alcohols leading to fully-substituted carbolines

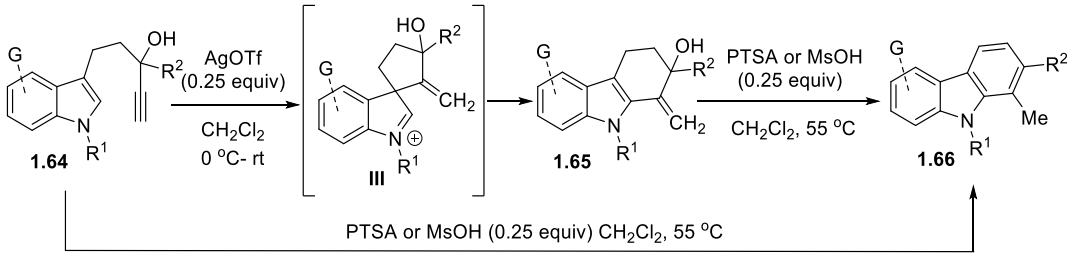
Recently, Min Shi's group developed a novel transition metal-free methodology for the construction of indole or pyrrole containing tetrahydro-cyclopenta[*b*]naphthalenes **1.63** (*via* intermediate **II**) from the reaction of indole/pyrrole **1.61** and propargylic alcohol-tethered alkylidene-cyclopropanes **1.62** under Brønsted acid-catalysis (Scheme 1.17).[38] This reaction proceeds through cascade nucleophilic addition of propargylic carbocation with pyrrole or indole/intramolecular electrocyclization followed by ring opening and rearrangement to give the final product. However, indole or pyrrole does not take part in the cyclization process.



Scheme 1.17. Brønsted acid-catalyzed reaction of propargylic alcohol-*tethered* alkylidenecyclopropanes with indoles/ pyrroles

1.3 Intramolecular annulations of indole tethered-propargylic alcohols

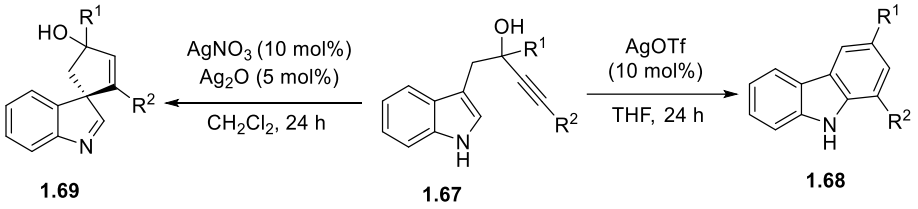
Baire and Tharra reported regioselective cyclization of (indol-3-yl)pentyn-3-ols **1.64** under Lewis as well as Brønsted acid catalysis for the selective synthesis of tetrahydro-carbazoles **1.65** and carbazoles **1.66**. The divergence in the reactivity of **1.64** was explained in detail with respect to both Lewis and Brønsted acid catalysis. Thus **1.64** upon treatment with AgOTf gives tetrahydro-carbazoles **1.65** *via* intermediate **III**; this can be converted into the corresponding carbazoles **1.66** in the presence of PTSA or MsOH (Scheme 1.18).[39a] In the presence of protic acids at elevated temperatures, **1.64** was directly converted into carbazoles **1.66**. There are some other reports from the same group where they studied extensively about the reactivity/annulations of *tert*-propargylic alcohols.[39b-d]



Scheme 1.18. Regioselective cyclization of (indol-3-yl)pentyn-3-ols for the synthesis of (tetrahydro)carbazoles

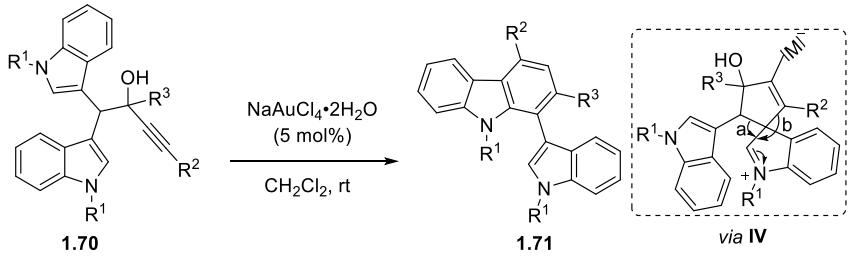
The research group of Taylor and Unsworth described a divergent intramolecular cyclization of the indole tethered propargylic alcohol **1.67** under silver(I)-catalysis at room temperature to get diverse carbazoles **1.68** and spirocyclic indolenines **1.69** from the single starting material **1.67**. In the presence of $AgNO_3$+Ag_2O, dearomatized spirocyclic viny silver

intermediate was generated to give the indolenines **1.69** whereas in the presence of AgOTf, six membered vinyl silver intermediate was invoked for the formation of carbazole motifs **1.68** (Scheme 1.19).[40] The products in these reactions were mutually exclusive.



Scheme 1.19. Silver(I)-catalyzed divergent reactivity of the alkyne tethered indoles for the synthesis of spirocyclic indolines and carbazoles

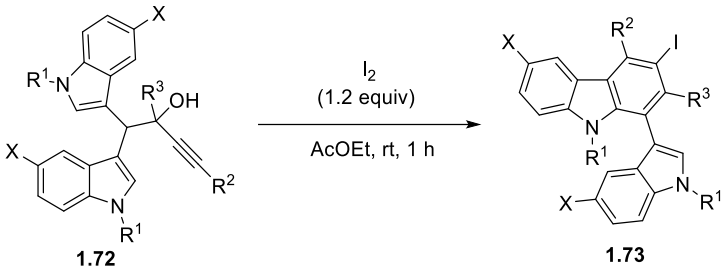
Sanz *et al*. reported a simple gold(III)-catalyzed synthesis of substituted 1-(indol-3-yl)carbazoles **1.71** exclusively from bis(indolyl)methyl alkynols **1.70** by intramolecular cyclization. The key step in the formation of carbazoles consists of selective 1,2-rearrangement involving the migration of an indolylmethyl (intermediate **IV**; path a) group over the alkenyl group after the early spirocyclization reaction that is initiated by the attack of the indole on the activated alkyne (Scheme 1.20).[41] Bisindolyl moiety plays a crucial role in the formation of carbazole motifs as revealed by DFT studies.



Scheme 1.20. Synthesis of 1-(indol-3-yl)carbazoles under gold(III)-catalysis

Yaragorla *et al*. described an operationally simple methodology for the construction of densely substituted 3-iodocarbazoles **1.73** from aryl(indol-3yl)methane-tethered propargyl alcohols **1.72** *via* intramolecular iodocyclization at room temperature through cycloisomerization/1,2-alkyl migration (Scheme 1.21).[42]. This methodology allows access to

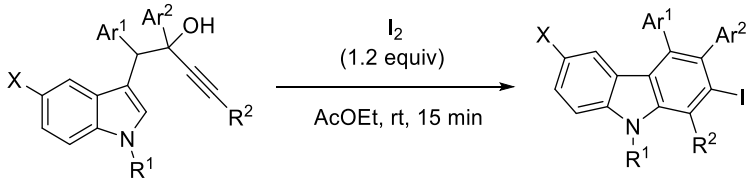
a wide variety of iodo-carbazoles which can be utilized further for post-functionalization to get diverse carbazoles.



1.72 1.73

Scheme 1.21. Intramolecular iodo-cyclization of the aryl(indol-3yl)methane tethered propargylic alcohols to access 3-iodo-carbazoles

Later, the same Yaragorla's group presented a rapid intramolecular cycloisomerization of (indole-arylyl)methane tethered propargyl alcohols **1.74** to access substituted 2-iodocarbazoles **1.75** by using molecular iodine (Scheme 1.22).[43] This reaction proceeds through a sequential regioselective 5-*endo*-spirocyclization followed by selective 1,2-vinyl migration over the 1,2-alkyl migration controlled by the substituent Ar^1 and finally with aromatization allows access to 2-iodocarbazoles.

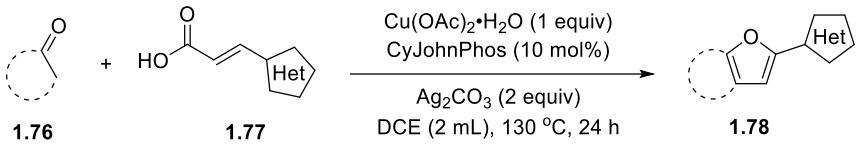


1.74 1.75

Scheme 1.22. Intramolecular iodo-cyclization of (indole-arylyl)methane tethered propargylic alcohols to access 2-iodo-carbazoles

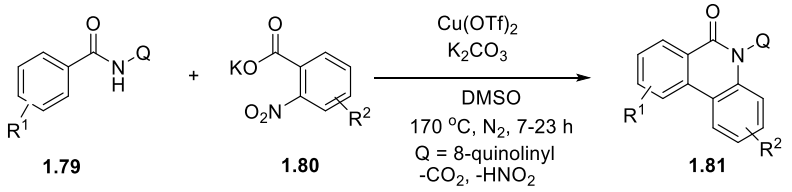
1.4 Decarboxylative annulations of the aromatic carboxylic acids

Maiti's group developed a methodology for decarboxylative annulation of *α,β*-unsaturated aromatic heterocyclic carboxylic acids **1.77** with aliphatic cyclic ketones **1.76** leading to the regioselective synthesis of fused furan architectures **1.78** under Cu(II)-catalysis (Scheme 1.23).[4a]. This methodology is versatile in terms of both the starting materials involved, and allows access to large ring fused di-heterocyclic motifs. The reaction proceeds through tautomerization of the aliphatic ketone in the presence of Cu(II)-catalyst, then addition of the unsaturated carboxylic acid and intramolecular cyclization followed by decarboxylation.



Scheme 1.23. Cu(II)-catalyzed decarboxylative annulation of *α,β*-unsaturated carboxylic acids with aliphatic ketones

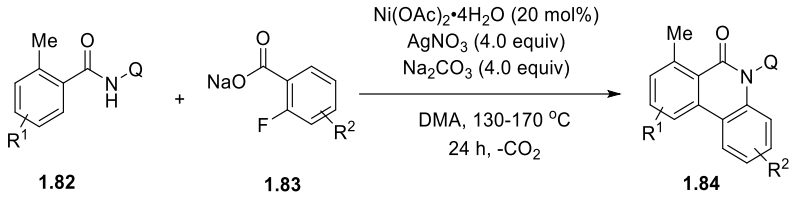
Miura and Hirano developed a protocol for the quinoline-directed decarboxylative coupling of benzamides **1.79** with *ortho*-nitrobenzoic acids **1.80** under Cu(II)-catalysis. The cross-coupled products were successfully converted into *N*-aryl phenanthridinones **1.81** using $Cu(OTf)_2/K_2CO_3$ couple (Scheme 1.24).[4b]



Scheme 1.24. Decarboxylative cross-coupling followed by annulation using *ortho*-nitro benzoates and benzamides

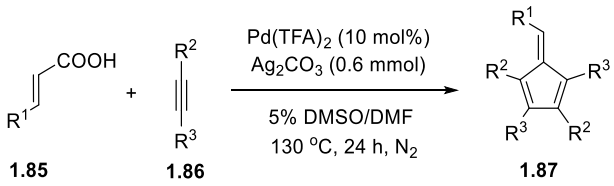
A reaction similar to the one shown above was recently reported by Honeycutt and Hoover using Ni(II)-catalyzed oxidative decarboxylative annulation of *ortho*-fluorobenzoates **1.83** with benzamides **1.82** for the synthesis of substituted *N*-heterocyclic phenanthridinones **1.84**.[4c] This decarboxylative methodology worked well for aromatic and *hetero*-aromatic benzoates

with a variety of substituted benzamides and allowed access to diverse phenanthridinones (Scheme 1.25). However, a large quantity of the silver salt is utilized for the reaction.



Scheme 1.25. Decarboxylative cross-coupling followed by annulations of the *ortho*-nitro benzoates with benzamides under Cu(II)-catalysis

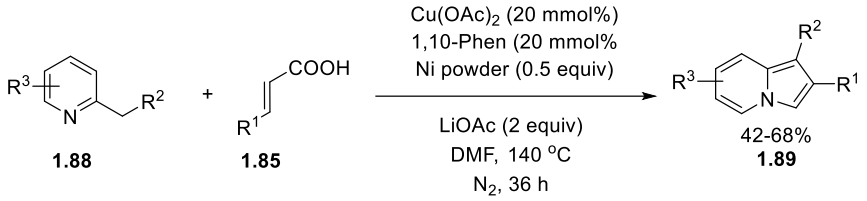
The research group of Peng and Wang has developed a novel oxidative/decarboxylative [2+2+1] cyclization of *α,β*-unsaturated carboxylic acids **1.85** with internal alkynes **1.86** under palladium(II)-catalysis for the synthesis of functionalized pentafulvenes **1.87** (Scheme 1.26).[4d]. This methodology involves decarboxylative annulation; the fulvene products were further utilized for the post-functionalization under oxidation/reduction or for Scholl reaction.



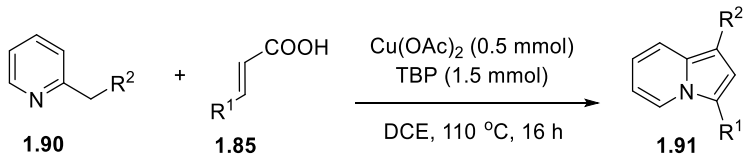
Scheme 1.26. Pd(II)-catalyzed intermolecular decarboxylative annulations of *α,β*-unsaturated carboxylic acids with internal alkynes

Zhang's group reported a Cu(II)-catalyzed decarboxylative annulation methodology for the synthesis of indolizines **1.89** from the readily available 2-alkylazaarenes **1.88** and *α,β*-unsaturated carboxylic acids **1.85**. This reaction proceeds through decarboxylative amination and C-H olefination to afford C2-substituted *N*-fused heterocyclics in moderate yields (42-68%) as shown in Scheme 1.27.[4e] Later, Gu and Cai reported a similar copper mediated radical decarboxylative methodology for the annulation reaction of *α,β*-unsaturated carboxylic acids **1.85** with 2-(pyridin-2-yl)acetate **1.90** for the synthesis of indolizines **1.91** (Scheme 1.28).[44]

For the mechanistic investigations, a radical-trapping experiment was conducted which revealed that the reaction proceeded through a free-radical pathway.

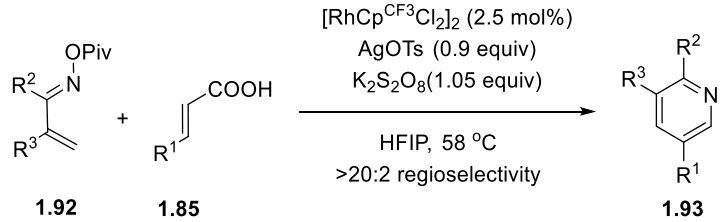


Scheme 1.27. Cu(II)-catalyzed intermolecular decarboxylative annulation of acrylic acids with 2-alkylazaarines



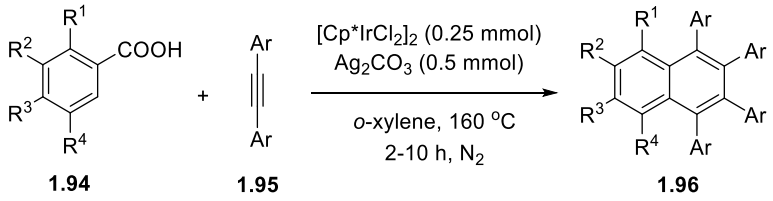
Scheme 1.28. Cu(II)-catalyzed decarboxylative annulation of *α,β*-unsaturated carboxylic acids with 2-(pyridin-2-yl)acetate

Rovis and Neely developed Rh(III)-catalyzed decarboxylative annulation of acrylic acid **1.85** with *α,β*-unsaturated oximes **1.92** for the regioselective synthesis of substituted pyridines **1.93**. This methodology utilizes the advantage of a carboxylic acid as a traceless directing/leaving group to generate substituted pyridines (Scheme 1.29).[45] Mechanistic investigations suggested that decarboxylation was not going through general picolinic acid intermediate, but rather unexpectedly, going *via* 5-membered cyclic rhodium intermediate.



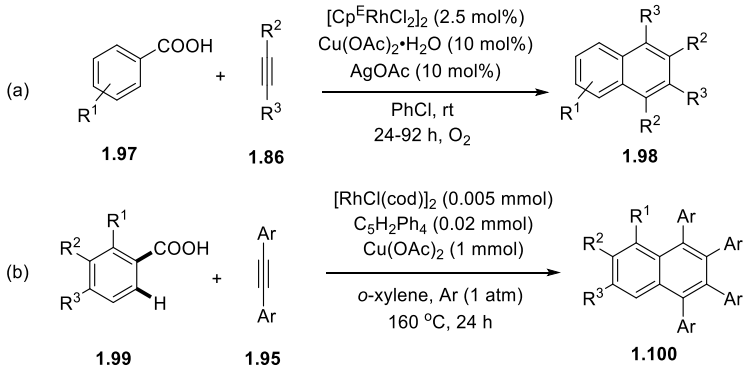
Scheme 1.29. Rh(III)-catalyzed decarboxylative annulation of acrylic acids with unsaturated oxime esters

Satoh and Miura have developed Ir(III)-catalyzed decarboxylative double annulation of substituted benzoic acids **1.94** with internal alkynes **1.95** for the synthesis of fully-substituted naphthalenes **1.96** by using 1:2 ratio of the acid and alkyne (Scheme 1.30).[1g] This double annulation reaction proceeds through acid directed alkenylation and C-H activation followed by decarboxylation and annulation with alkyne partner delivering the naphthalene scaffolds.



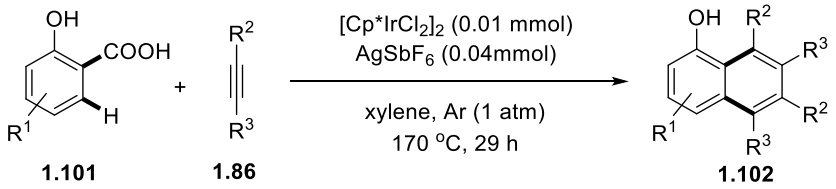
Scheme 1.30. Ir(III)-catalyzed decarboxylative double annulation of benzoic acids with internal alkynes

Shibata and Tanaka's group described Rh(III)-catalyzed decarboxylative oxidative [2+2+2] annulation of the aromatic carboxylic acids **1.97** with internal alkynes **1.86** for the synthesis of fully substituted naphthalene scaffolds **1.98** at room temperature using molecular oxygen as the co-oxidant. Here the choice of solvent and the catalyst played the key role for the decarboxylative annulation. This methodology worked well for a broad range of aromatic as well as aliphatic carboxylic acids (Scheme 1.31a).[46] More recently, Satoh's group reported a similar decarboxylative [2+2+2] annulation of aromatic carboxylic acids **1.99** with internal alkynes **1.95** in the presence of the Rh(III)/$C_5H_2Ph_4$-catalyst combination using $Cu(OAc)_2$ as the oxidant for the synthesis of fully-substituted naphthalenes **1.100** (Scheme 1.31b) and benzothiophene scaffolds.[47]



Scheme 1.31. Rh(III)-catalyzed intermolecular decarboxylative annulation of benzoic acids with internal alkynes

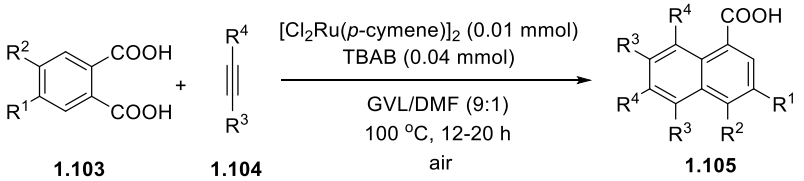
Recently, the same Satoh's group demonstrated a chemoselective/oxidative decarboxylative [2+2+2] annulation of the salicylic acids **1.101** with internal alkynes **1.86** for the synthesis of *α*-naphthols **1.102** under Ir(III)-catalysis without any external oxidant.[48] This reaction was selective towards the carboxylic acid and *ortho* C-H functionalization rather than alcohol annulations. This methodology tolerated essentially all the functional groups and delivered multisubstituted *α*-naphthol motifs (Scheme 1.32).



1.101 **1.86** **1.102**

Scheme 1.32. Ir(III)-catalyzed decarboxylative annulation of salicylic acids with internal alkynes

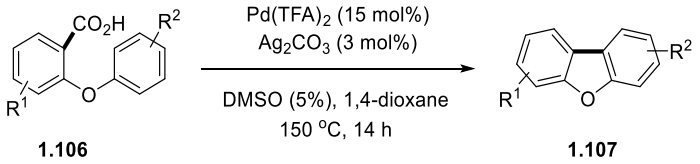
Zheng's group reported an efficient methodology for the selective decarboxylative [2+2+2] annulations of phthalic acids/anhydrides **1.103** with internal alkynes **1.104** for the synthesis of fully substituted 1-naphthoic acids **1.105** under Ru(II)-catalysis *via* carboxylate assisted *ortho*-C–H activation followed by annulation (Scheme 1.33).[49] This reaction proceeds by utilizing the aerobic oxygen and allows access to polysubstituted *α*-naphthoic acid scaffolds.



1.103 **1.104** **1.105**

Scheme 1.33. Ru(II)-catalyzed decarboxylative annulation of phthalic acids with internal alkynes

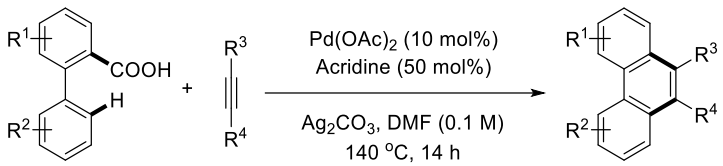
Glorius's group reported intramolecular decarboxylative annulation of 2-phenoxy benzoic acids **1.106** in the presence of Pd(II)-catalyst that led to substituted dibenzofurans **1.107**. The reaction proceeds through decarboxylation in the presence of Ag_2CO_3 followed by *trans*-metalation with Pd(II)-catalyst, C-H functionalization and subsequent intramolecular cyclization/reductive elimination (Scheme 1.34).[50]



1.106 **1.107**

Scheme 1.34. Pd(II)-catalyzed decarboxylative annulation of 2-phenoxy benzoic acids

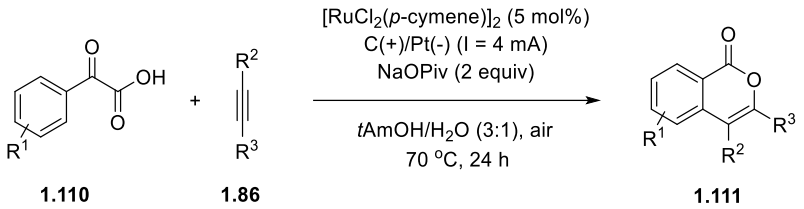
Later, the same Glorius's group reported intermolecular decarboxylative [4+2] annulation protocol involving 2-phenylbenzoic acids **1.108** and internal alkynes **1.104** for the synthesis of substituted phenanthrenes **1.109** under palladium-catalysis *via* C-H and C-C bond activation. Acridine played a key role and was essential for the conversion (Scheme 1.35).[51] This protocol involves the cascade decarboxylation/*trans*-metalation/alkyne insertion followed by reductive elimination delivering phenanthrene scaffolds without any side reaction.



1.108 **1.104** **1.109**

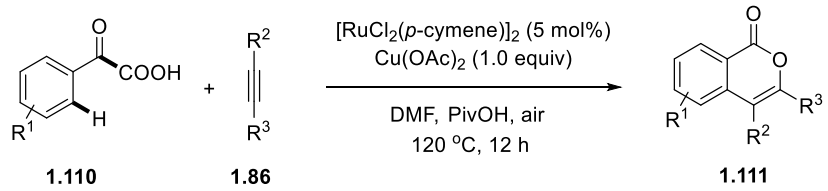
Scheme 1.35. Pd(II)-catalyzed intermolecular decarboxylative annulation of 2-phenyl benzoic acids with alkynes

A decarboxylative regioselective [4+2] annulation route by C–H functionalization under electrochemical anodic ruthenium catalysis involving α-keto carboxylic acids **1.110** and internal alkynes **1.86** was reported by Li's group. This protocol allows access to 1*H*-isochromen-1-ones **1.111** *via* sequential decarboxylation, oxygen-insertion (from water), followed by C–H functionalization and annulation (Scheme 1.36).[52]



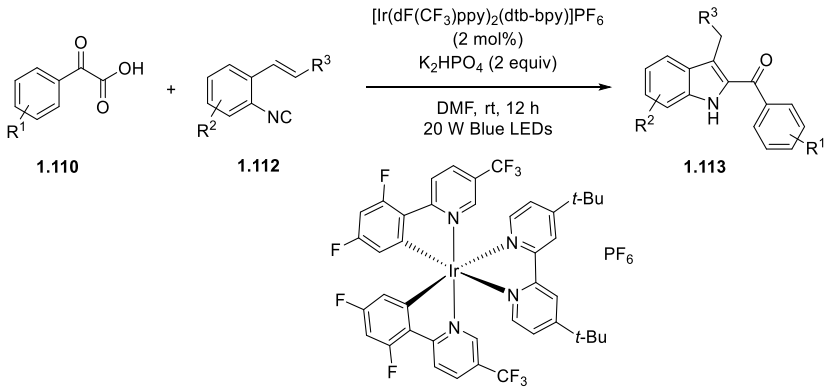
Scheme 1.36. Decarboxylative annulation of the arylglyoxylic acids with internal alkynes under electrochemical ruthenium-catalysis

Later, Li and Wang's group established a [Ru]-catalyzed decarboxylative annulation of *α*-keto acids **1.110** with internal alkynes **1.86** for the synthesis of substituted isocoumarins **1.111** (Scheme 1.37).[53] This protocol proceeds through cascade oxidative addition, C-H-functionalization, alkyne insertion and decarboxylation followed by reductive elimination to afford the isocoumarins.



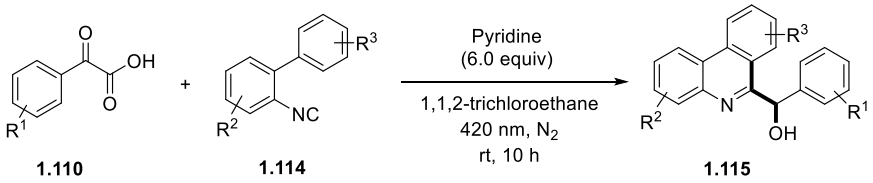
Scheme 1.37. [Ru]-catalyzed decarboxylative annulation of α-keto acids with internal alkynes

Very recently, Zhang and coworkers reported an operationally simple photo-catalytic methodology by using visible light source for the decarboxylative annulation of 2-alkenylarylisocyanides **1.112** with arylglyoxylic acids **1.110** to synthesize substituted 2-acylindoles **1.113** under iridium-catalysis without any external oxidant. This reaction involves cascade photolytic acyl radical addition/annulation with an Ir(III) catalyst (Scheme 1.38).[54]



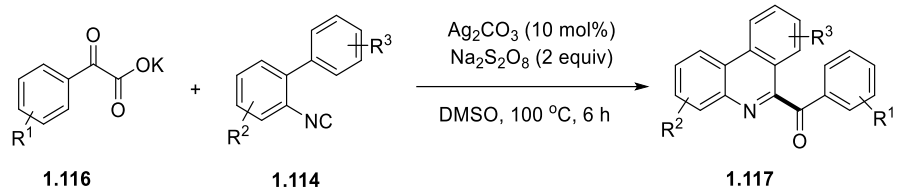
Scheme 1.38. Decarboxylative annulation of the α-oxo carboxylic acids with 2-alkenyl aryl isocyanides under iridium photo-catalysis

Wang and coworkers reported visible-light-induced decarboxylative annulation/hydrogenation of α-oxocarboxylic acids **1.110** with 2-isocyanobiaryls **1.114** for the synthesis of phenanthridin-6-yl(aryl)methanols **1.115** in the absence of external photosensitizer or oxidant/reductant(Scheme 1.39).[55] Mechanistic investigations revealed cascade decarboxylation and radical addition/cyclization of the two reaction partners.



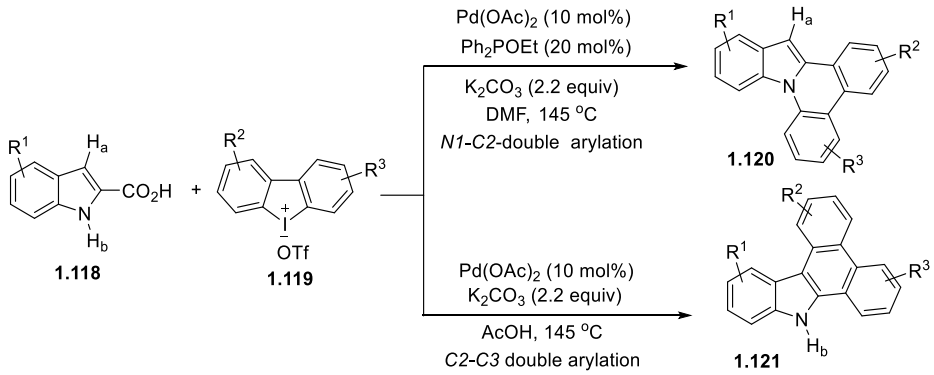
Scheme 1.39. Decarboxylative annulation of the α-oxo-carboxylic acids with 2-cyanobiaryls under base and visible light mediation

Lei's group developed a methodology for the construction of substituted 6-acyl phenanthridines **1.117** from 2-oxocarboxylates **1.116** and 2-isocyanobiaryls **1.114** under Ag(I)-catalysis at elevated temperatures by radical decarboxylative annulation.[56] This reaction proceeds through the addition of benzoyl radical (generated by the [Ag]/sodium peroxydisulfate couple) to the *isocyano* moiety of biaryls followed by intramolecular electrocyclization and subsequent aromatization affording phenanthridines **1.117** (Scheme 1.40).



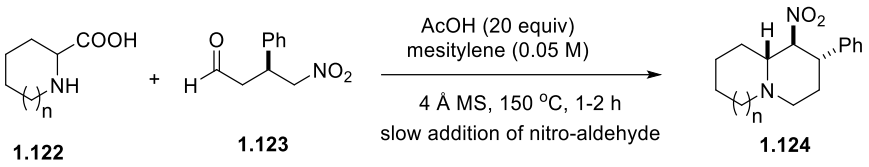
Scheme 1.40. Oxidative radical decarboxylative annulations of α-oxo carboxylates with 2-cyanobiaryls under Ag(I)-catalysis

Recently, Zhang's group reported a methodology for the cascade decarboxylative annulation of the readily available indole-2-carboxylic acids **1.118** with diaryliodonium salts **1.119** for the divergent synthesis of phenanthridine (**1.120**) and carbazole (**1.121**) scaffolds under Pd(II)-catalysis. This protocol may occur *via* two different pathways depending upon the conditions employed.[57] Thus indole-2-carboxylic acid **1.118** reacted with **1.119** in the presence of Pd(II)/P(III) catalyst couple affording phenanthridines by *N1-C2* arylation. By contrast, the same two starting materials under Pd(II)/K_2CO_3 couple afforded carbazoles **1.121** *via C2-C3* arylation. Here, carboxylic acid acts as directing as well as leaving group (Scheme 1.41).



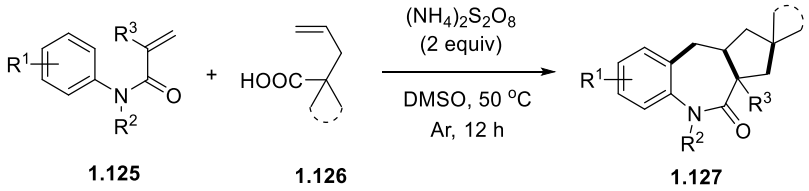
Scheme 1.41. Pd(II)-catalyzed decarboxylative annulation of indole-2-carboxylic acids with diaryliodonium salts

Kang and Seidel developed a novel methodology for the construction of indolizidine and quinolizidine scaffolds of type **1.124** from α-amino acids **1.122** and γ-nitroaldehydes **1.123** under AcOH mediation (Scheme 1.42).[58] This reaction proceeds through an active azomethine ylide and decarboxylative annulation.



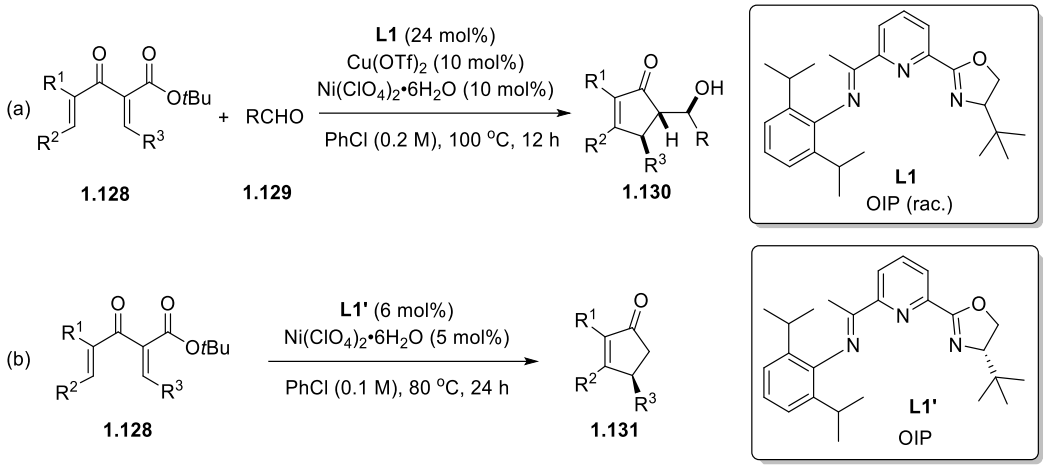
Scheme 1.42. Decarboxylative annulation of α-amino acids with γ-nitroaldehydes

Li's group reported a novel transition metal-free oxidative decarboxylative [3+2]/[5+2] annulation of *N*-arylacrylamide **1.125** with vinyl acids **1.126** to synthesize fused seven-membered *N*-heterocyclics **1.127** by using $(NH_4)_2S_2O_8$ as the oxidant (Scheme 1.43).[59] Three new C-C bonds are formed in the reaction which allows access to functionalized benzo[*b*]azepin-2-ones in a single step under mild reaction conditions.



Scheme 1.43. Metal-free decarboxylative annulation of *N*-arylacrylamides with vinyl acids

Zhang and Lu established a protocol for the nickel/copper couple catalyzed sequential Nazarov cyclization/decarboxylative aldol reaction of substituted α-*tert*-butyl ester of divinyl ketones (**1.128**) with aldehydes (**1.129**) in the presence of ligand **L1** for the stereoselective synthesis of highly substituted β-hydroxycyclopentenones **1.130** having three consecutive chiral centers. This reaction proceeds through nucleophilic addition of the aldehyde to the divinyl ketone which initiates the Nazarov-cyclization. This is followed by decarboxylative aldol reaction to afford substituted cyclopentenones (Scheme 1.44a).[60] Later, the same group described intramolecular Ni(II)-catalyzed enantioselective cascade for the Nazarov cyclization/decarboxylation of divinyl ketone α-esters **1.128** for the enantioselective synthesis of cyclopentenones **1.131** by using the chiral oxazoline iminopyridine (OIP) ligand **L1'**. This methodology involves **L1'** directed sequential intramolecular Nazarov cyclization followed by decarboxylation to access cyclopentenones enantioselectively (Scheme 1.44b).[61]

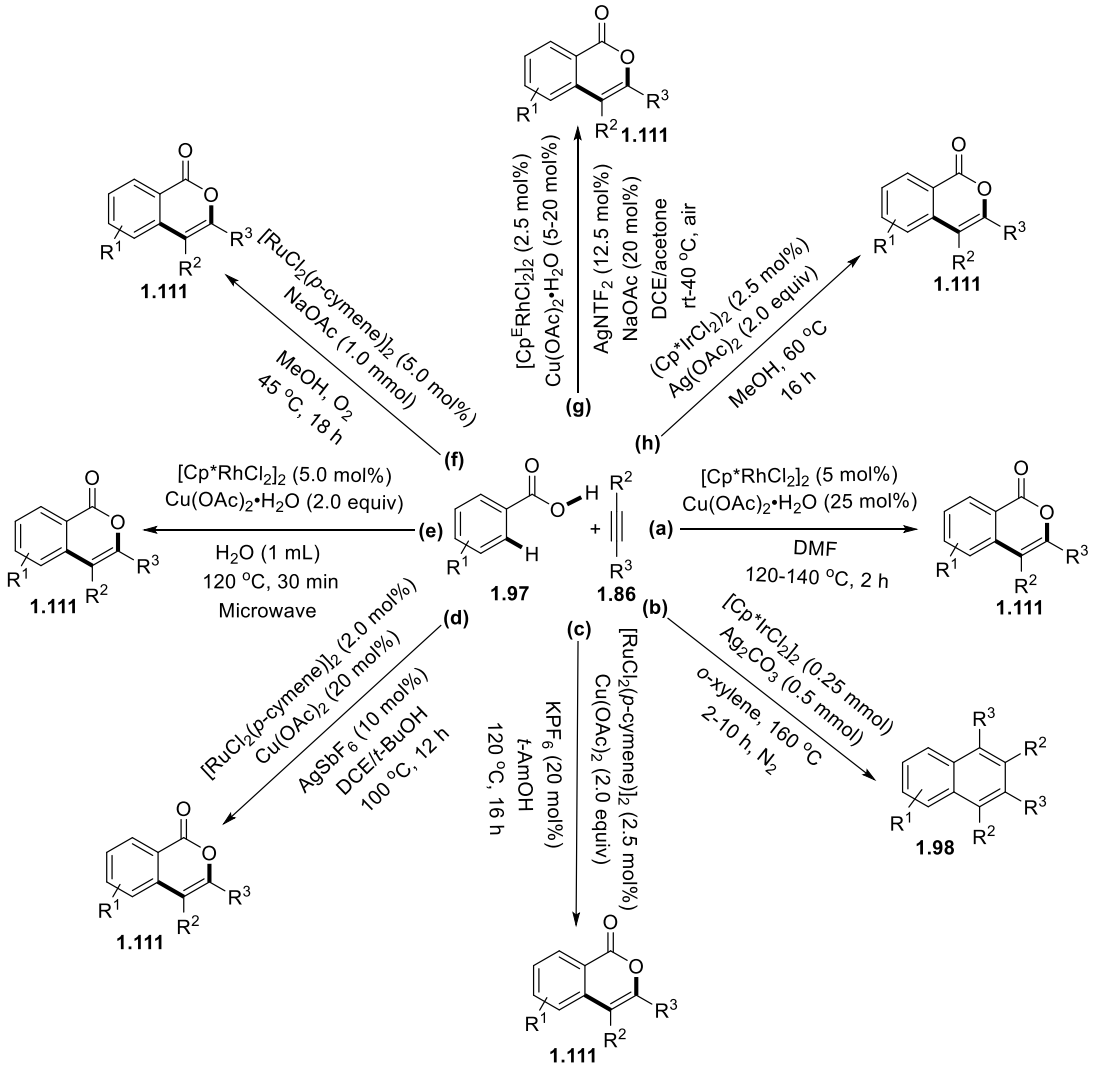


Scheme 1.44. Cu/Ni-couple and Ni(II)-catalyzed intramolecular decarboxylative annulation/Nazarov cyclization involving *α-tert*-butyl ester of divinyl ketones

1.5 Transition metal catalyzed annulations of carboxylic acids with C-C π-components

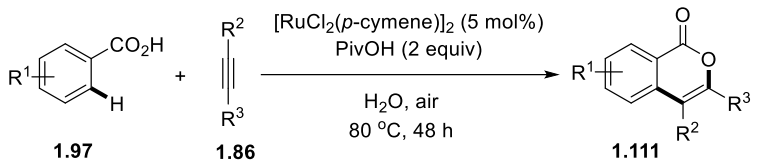
In the year 2007, Satoh and Miura discovered an efficient methodology for the annulation of aromatic carboxylic acids with alkynes *via ortho*-C-H/O-H bond activation/functionalization under Rh/Cu-catalysis. In this reaction, when benzoic acids **1.97** were treated with internal alkynes **1.86** in the presence of the Rh/Cu-catalysts in open air, a regioselective [4+2] annulation took place and afforded the substituted isocoumarins **1.111** (Scheme 1.45a).[1f] Later, when they employed the same two starting materials with the Ir-catalyst in the presence of Ag_2CO_3, instead of carboxy-annulation, a decarboxylative double annulation took place to give the fully substituted naphthalenes **1.98** *via* regioselective C-H bond cleavage followed by decarboxylative annulation (Scheme 1.45b).[1g] When the reaction was conducted under Ru/Cu-catalysis using KPF_6 in *t*-AmOH at 120 °C for 16 h, isocoumarins were obtained *via* addition/insertion and elimination as demonstrated by Ackermann's group (Scheme 1.45c).[1h] In the same year, Jeganmohan and Chinnagolla reported analogous annulation of benzoic acids with alkynes under Ru/Cu-catalysis by using lower loadings of catalyst (2 mol%), oxidant (20 mol%) and additive $AgSbF_6$ (10 mol%) to get the isocoumarins with excellent regioselectivity (Scheme 1.45d).[1i] Later, Xu and Yi's group demonstrated a green, rapid and efficient methodology for the synthesis of isocoumarins with Rh/Cu-catalyst *via* microwave-assisted C–H/O–H bond functionalization by using water as the only solvent.

In addition to benzoic acids, they have also utilized heterocyclic and acyclic carboxylic acids (Scheme 1.45e).[1j] Annulation of the benzoic acid with alkynes under Ru-catalysis for the efficient synthesis of isocoumarins with excellent *regio*- and *chemo*-selectivity with water as the only byproduct and O_2/air as the sole oxidant was also developed by Ackermann's group (Scheme 1.45f).[1k] They also isolated the annulated Ru(0)-metal complexes for the first time. Another protocol for the synthesis of isocoumarins was established by Tanaka's group under Rh(III)-catalysis *via* the oxidative annulation of arene carboxylic acids with alkynes in air; mechanistic investigations revealed the formation of Rh(0)-metal complex (Scheme 1.45g).[1l] Ison's group has demonstrated the annulation of benzoic acids **1.97** with alkynes **1.86** for the synthesis of the isocoumarins **1.111** under Ir(III)-catalysis. They have also performed computational studies for the confirmation of the mechanism involved and concluded that the acetate group plays a crucial role in the annulation process (Scheme 1.45h).[1m]



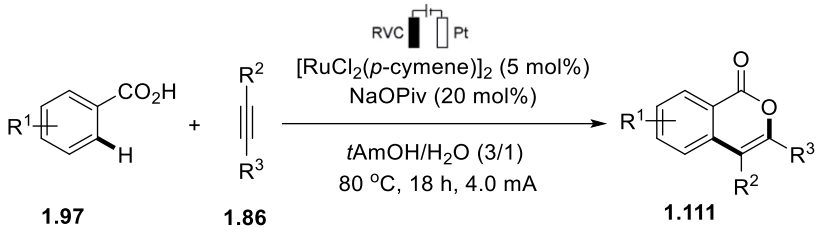
Scheme 1.45. Transition metal-catalyzed annulation of benzoic acids with alkynes *via ortho*-C-H bond activation

Recently, Wu and Shang's group reported a green protocol for the synthesis of isocoumarins/ α-pyrones **1.111** from oxidative annulation of benzoic acids **1.97** with alkynes **1.86** or alkenes under Ru(II)-catalysis using aerobic oxidation (open air; Scheme 1.46).[62] This reaction was performed in the presence of green solvent water; this methodology also allowed access to isobenzo-furan-1-one scaffolds on reaction with activated alkenes.



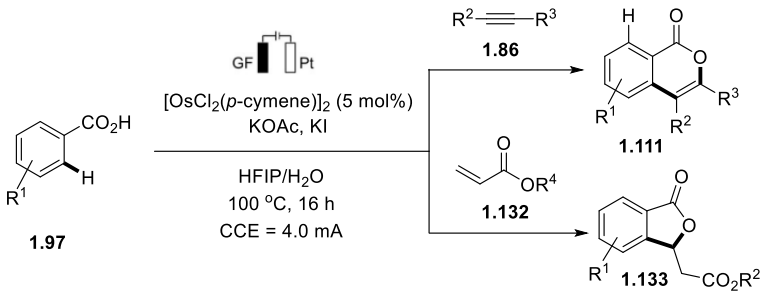
Scheme 1.46. Ru(II)-catalyzed oxidative annulation of the benzoic acids with alkynes in air

Ackermann's group developed a novel electro-oxidative annulation strategy for the first time to prepare substituted isocoumarins **1.111** with excellent regioselectivity from weakly coordinating aromatic carboxylic acids **1.97** (rather than using strong *N*-coordination) and alkynes **1.86** under Ru(II)-catalysis in the absence of the external metal oxidant. Here, they were successful in utilizing electricity as sole oxidant for the reoxidation of Ru(0)-metal complex to get active Ru(II)-metal catalyst which is actually catalyzing the annulation reaction *via ortho*-C-H/O-H functionalization to afford annulated product (Scheme 1.47).[63]



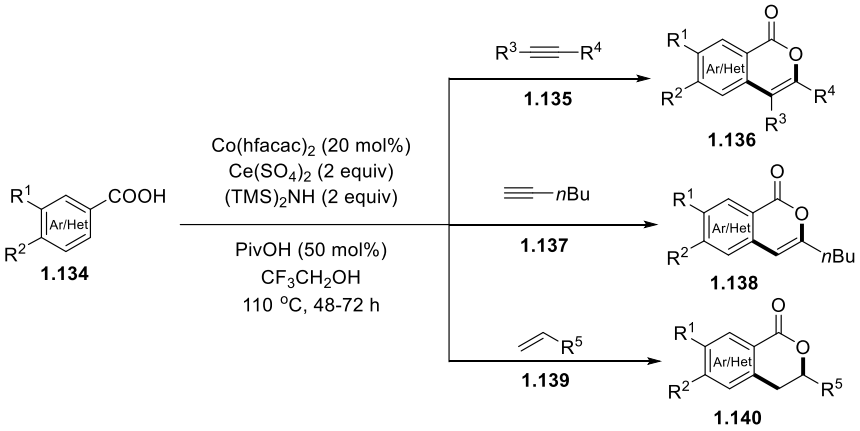
Scheme 1.47. Ru(II)-catalyzed electro-oxidative annulation of the benzoic acids with alkynes

More recently, the same Ackermann's group disclosed electro-catalytic oxidative [4+2] and [4+1] annulation of aromatic carboxylic acids **1.97** with alkynes **1.86** or activated alkenes **1.132** *via ortho* C-H/O-H functionalization under Os(II)-catalysis in the absence of external oxidant for the synthesis of isocoumarins **1.111** and isobenzo-furan-1-ones **1.133** in excellent *regio*- and *chemo*-selectivities (Scheme 1.48).[64] Mechanistic investigations were also conducted; they have also isolated and characterized the unprecedented key Os(0) and Os(II) intermediates involved in the product formation. This methodology has clearly opened the gate for the annulation of carboxylic acids with unsaturated compounds under transition metal catalysts using electro-oxidative processes.



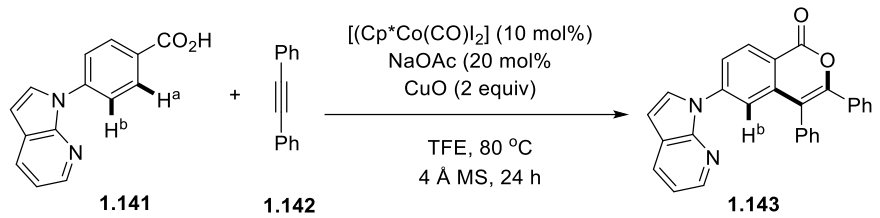
Scheme 1.48. Os(II)-catalyzed electro-oxidative annulation of benzoic acids with alkynes/ alkenes

Daugulis's group reported oxidative annulation of aromatic/hetero-aromatic carboxylic acids **1.134** with a variety of C-C π components (internal alkynes **1.135**, terminal alkynes **1.137** and styrenes **1.139**) for the synthesis of isocoumarins **1.136**, **1.138** and **1.140** under Co(II)/Ce(IV)-catalysis by using an external oxidant and base (Scheme 1.49).[65] This reaction also proceeded through the *ortho* C-H/O-H functionalization and worked well for internal as well as terminal alkynes/alkenes with excellent regioselectivity.



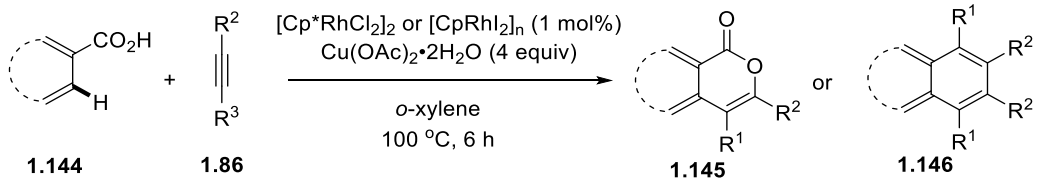
Scheme 1.49. Co(II)-catalyzed annulation of carboxylic acids with the C-C π components

Co(III)-catalysis has been utilized by Mandal and Sundararaju for the oxidative [4+2] annulation of benzoic acids **1.141** with alkynes **1.142** to synthesize substituted isocoumarins **1.143** with excellent regioselectivity by overcoming the strong chelation of 7-aza-indole directing group over the weak chelating/traceless directing carboxylic acid (Scheme 1.50).[66]



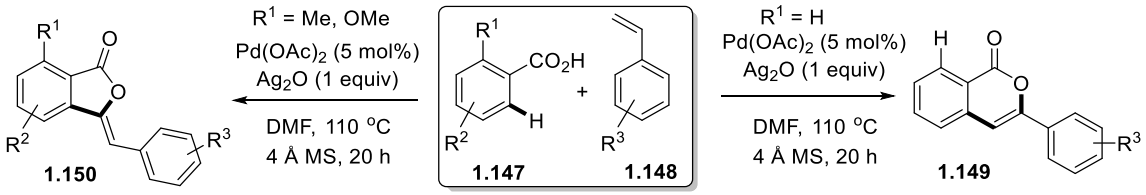
Scheme 1.50. Co(III)-catalyzed annulation of the substituted benzoic acids with alkynes

As reported by Loginov's group, depending upon the Rh(III)/Cu(II)-catalyst combination, isocoumarins **1.145** or polycyclic aromatic hydrocarbons **1.146** are formed from aromatic carboxylic acids **1.144** and alkynes **1.86** *via* oxidative annulations. The reactivity of carboxylic acids was driven by the methylation on ligand(Scheme 1.51).[67] When $[Cp^*RhCl_2]_2$ was used, reaction proceeded through carboxyl assisted oxidative annulation *via ortho*-C-H/O-H functionalization to give isocoumarins **1.145**. On the other hand, when $[CpRhI_2]_n$ was used as the catalyst, naphthalene scaffolds **1.146** are predominantly formed by decarboxylative double annulation. Thus, the chemo-selectivity was driven by the ligand present on [Rh]-catalyst.



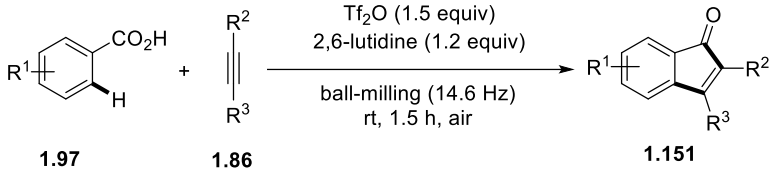
Scheme 1.51. Rh(III)-catalyzed oxidative annulation of the benzoic acids with alkynes

Lee's group utilized Pd(II)/Ag(I) catalysis to synthesize substituted isocoumarins **1.149** and 3-benzylidenephthalides **1.150** from benzoic acids and vinyl arenes through oxidative [4+2] annulation (Scheme 1.52).[68] Here, the substitution at *ortho*-position of benzoic acid played a key role in the formation of distinct products from the same starting materials.



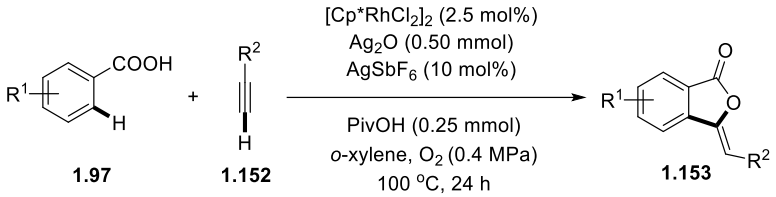
Scheme 1.52. Pd(II)-catalyzed annulation of the substituted benzoic acids with vinyl arenes

Very recently, Li and Wang reported the synthesis of substituted indenones **1.151** from aromatic carboxylic acids **1.97** and alkynes **1.86** using Tf_2O/base mediated annulation in air under solvent-free and transition metal-free conditions without any external metal oxidant. Unlike the general transition metal catalyzed [4+2] annulation, this reaction took place by unprecedented [3+2] annulation *via ortho* C-H/C-C functionalization (Scheme 1.53).[3a] This protocol allowed access to diverse indenones including the biologically active PPARγ kind of agonists.



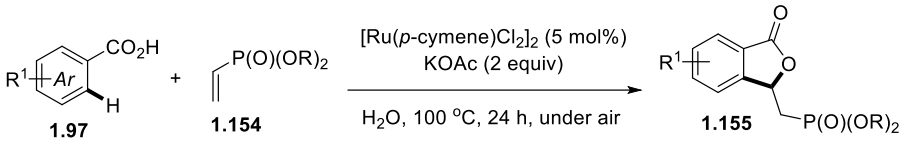
Scheme 1.53. Tf_2O-mediated annulation of the benzoic acids with alkynes

Yang and You's group have disclosed a novel oxidative [4+1] annulation of benzoic acids **1.97** with terminal alkynes **1.152** for the first time under Rh(III)/Ag(I)-catalysis to obtain 3-ylidenephthalides **1.153** in a *Z*-selective fashion (Scheme 1.54).[2a] When internal alkynes were used for the annulation with carboxylic acids, the reaction proceeds through metal catalyzed *ortho*-C-H alkenylation followed by annulation to afford substituted isocoumarin scaffolds, whereas in the case of terminal alkynes, first acid directed *ortho*-C-H alkynylation in the presence of Rh(III)/Ag(I)-catalysis took place to give the *ortho*-alkynylated carboxylic acids which undergoes metal catalyzed annulation reaction to afford unusual 3-ylidenephthalides **1.153** *via* [4+1] annulation.



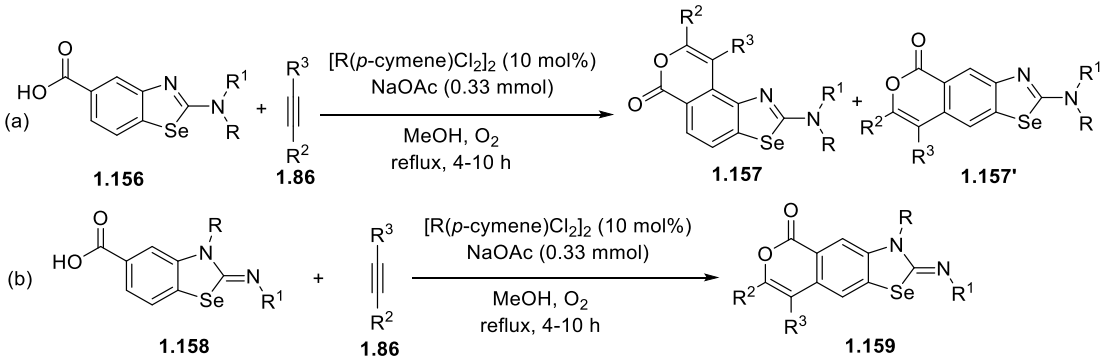
Scheme 1.54. Rh(III)-catalyzed [4+1] annulations of the benzoic acids with terminal alkynes

Substituted phthalides **1.155** can be obtained *via* [4+1] annulation under green conditions by dehydrogenative/oxidative coupling of aromatic carboxylic acids **1.97** with alkenes **1.154** using Ru(II)-catalysis and air as the sole oxidant as shown by Baidya's group (Scheme 1.55).[2b] This protocol allowed access to substituted phthalides along with Heck-type of products.



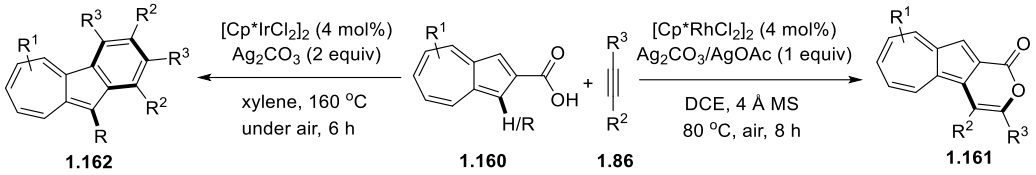
Scheme 1.55. Ru(II)-catalyzed oxidative annulation of the benzoic acids with activated alkenes

Regioselective synthesis of novel isocoumarin selenazoles **1.157** and **1.159** could be achieved from oxidative annulation of benzoselenazoles **1.156** and **1.158** with alkynes **1.86** under Ru(II)-catalysis using molecular oxygen as shown by Sun and coworkers.[69] When simple benzoselenazole **1.156** was used, a mixture of annulated products (**1.157** + **1.157'**) was obtained (Scheme 1.56a). On the other hand, only the annulated product **1.159** was observed when *N*-substituted dihydro-benzoselenazole was used (Scheme 1.56b). This may be due to the substitution on azole nitrogen which controls the regioselectivity for the annulation.



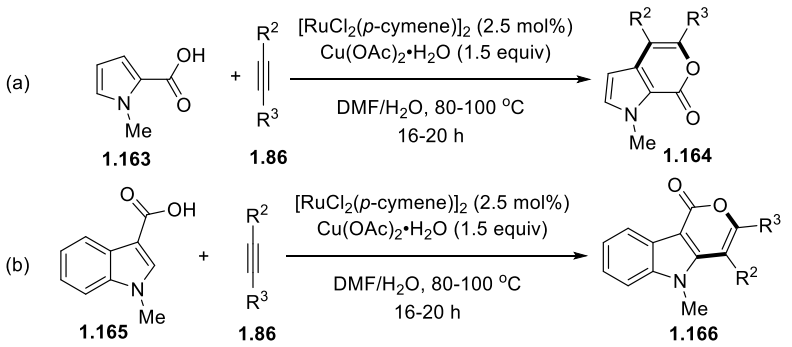
Scheme 1.56. Ru(II)-catalyzed oxidative annulation of benzoselenazole carboxylic acids with alkynes

Recently, Lee's group demonstrated the divergent reactivity of azulene carboxylic acids with internal alkynes under Rh(III)/Ir(III)-catalysis under aerobic conditions. Thus, azulene carboxylic acids **1.160** in the presence of Rh(III)/Ag(I)-catalytic system underwent oxidative [4+2] annulation *via* C-H/O-H functionalization with alkynes **1.86** to afford the azulenolactone scaffolds **1.**161.[70] In contrast to this, the same azulene carboxylic acids in the presence of Ir(III)/Ag(I)-catalytic system underwent sequential [2+2+2] annulation *via* oxidative decarboxylation and afforded the polysubstituted benzoazulene motifs **1.162** (Scheme 1.57).



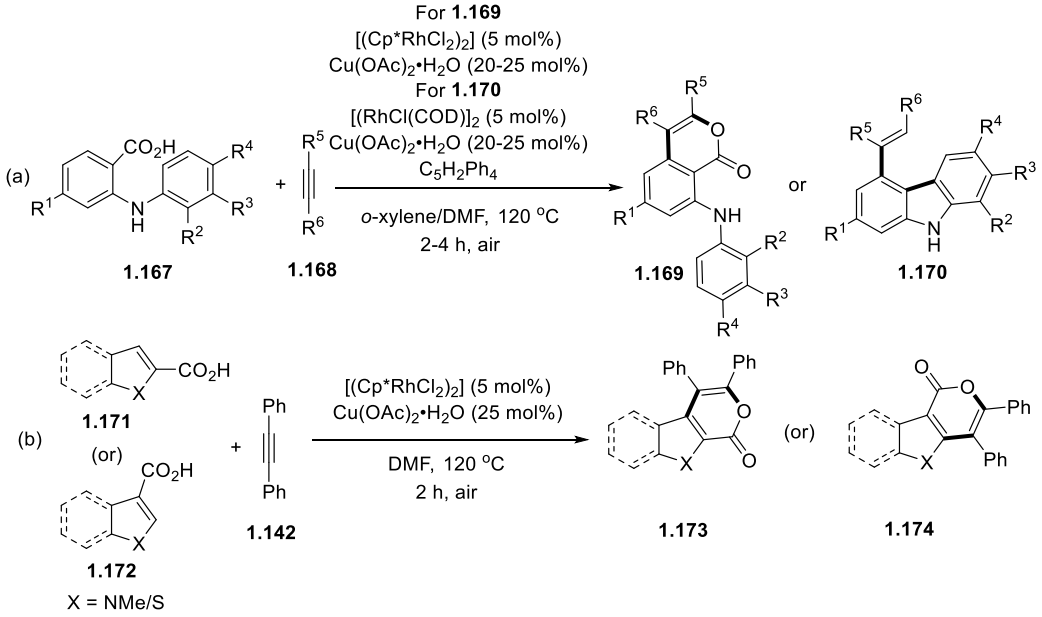
Scheme 1.57. Rh(III)/Ir(III)-catalyzed annulation of azulene carboxylic acids with alkynes

Direct and selective bifunctionalization of pyrrole and indole is still a challenge. Dixneuf's group developed a protocol for the regioselective construction of active pyrrole or indole fused isocoumarins **1.164** and **1.166** under Ru(II)/Cu(II)-catalysis by the reaction of the hetero-aromatic carboxylic acids 1-methylpyrrole-2-carboxylic acid **1.163** and 1-methylindole-3-carboxylic acid **1.165** with alkynes **1.86** in DMF or water solvent *via* sequential *ortho* C-H bond activation and [4+2] annulation (Scheme 1.58).[71]



Scheme 1.58. [Ru]-catalyzed annulation of *N*-methylindole-3-carboxylic acids with alkynes

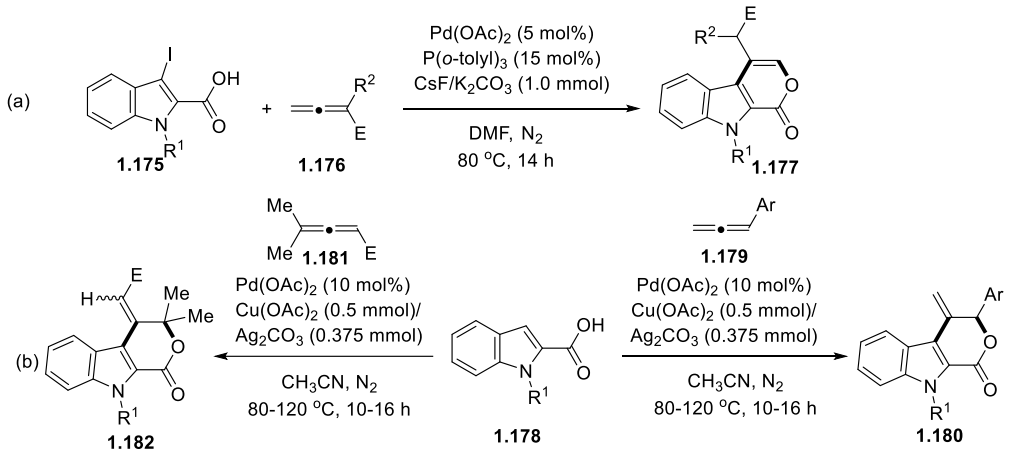
Miura's group demonstrated an oxidative annulation methodology for the reaction of 2-amino- and 2-hydroxybenzoic acids **1.167** with alkynes **1.168** under [Rh]/[Cu]-catalysis in air to obtain substituted coumarins **1.169** *via* [4+2] annulation. In contrast to this, the same starting materials, using $[RhCl(cod)_2]/C_5H_2Ph_4/Cu(OAc)_2$, underwent carboxylate directed *ortho*-alkenylation followed by decarboxylative annulation to give substituted carbazoles **1.170** (Scheme 1.59a). This methodology can also be applied in reactions of indole/benzothiophene 2-/3-carboxylic acids **1.171**/**1.172** with diphenylacetylenes **1.142** to get fused heterocyclic isocoumarins **1.173**/**1.174** (Scheme 1.59b).[72] Photophysical studies of some of the products revealed that they exhibit solid-state fluorescence.



Scheme 1.59. [Rh]-catalyzed annulation of the heterocyclic carboxylic acids with alkynes

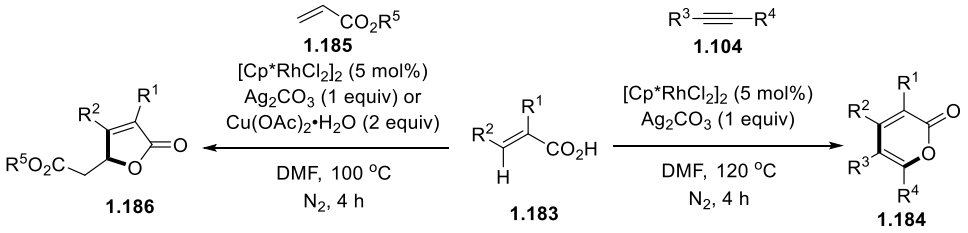
Unlike simple alkenes and alkynes, where there is no selectivity with respect to alkene/alkyne, annulation reaction of allenes with carboxylic acids can show regioselectivity. Our research group presented a novel oxidative [4+2] annulation strategy using substituted/indole-2-carboxylic acids and allenes for the regioselective synthesis of pyrano-indolones having active stereocenters under Pd(II)/Cu(II) or Ag(I)-catalysis *via* C-H/O-H functionalization. Here, 3-iodo-indole-2-carboxylic acids **1.175** on reaction with allenes **1.176** in the presence of the Pd(II)-catalyst underwent regioselective [4+2] annulation involving the *β,γ*-double bond to afford the indolo[2,3-*c*]pyrane-1-ones (pyrano-indoles) **1.177** (Scheme

1.60a). In contrast to this, the reaction of simple indole-2-carboxylic acids **1.178** with aromatic allenes **1.179** in the presence of Pd(II)-catalyst afforded 3,4-disubstituted indolo[2,3-*c*]pyrane-1-ones **1.180** by selective oxidative annulation of the *α,β*-double bond *via* C3-H functionalization. The *γ*-disubstituted allenes also gave the pyrano-indolones **1.182** by selective addition at the *β,γ*-double bond under the same reaction conditions (Scheme 1.60b).[1n]

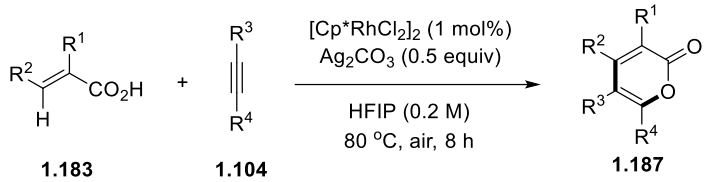


Scheme 1.60. Pd(II)-catalyzed annulation of substituted/indole-2-carboxylic acids with allenes

Substituted pyrones **1.184** and butenolides **1.186** can be synthesized from acrylic acids **1.183** and alkynes **1.104** or activated olefins **1.185** under Rh(III)-catalysis *via* vinylic C-H activation/functionalization as shown by Miura's group (Scheme 1.61).[73] Here, while the reaction of acrylic acids with alkynes by [4+2] oxidative annulation gave fully substituted pyrones **1.184**, analogous reaction with alkyl acrylates proceeded through [3+2] annulation to give substituted butenolides **1.186**. Zhang and Zhao's group also reported a similar methodology for the construction of *α*-pyrones **1.187** from acrylic acids **1.183** and alkynes **1.104** under Rh(III)/Ag(I)-catalysis. This methodology worked well for a variety of alkynes as well as substituted acrylic acids and delivered *α*-pyrone scaffolds **1.187** (Scheme 1.62).[74]

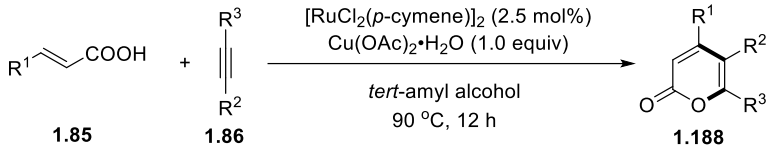


Scheme 1.61. Rh(III)-catalyzed annulation of the vinyl carboxylic acids with alkynes and activated alkenes



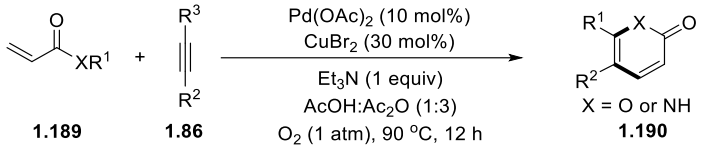
Scheme 1.62. Rh(III)-catalyzed oxidative annulation of acrylic acids with alkynes to afford pyrones

Gogoi's group also reported a regioselective [4+2] oxidative annulation of substituted cinnamic acids **1.85** with internal alkynes **1.86** under Ru(II)/Cu(II)-catalysis for the synthesis of substituted α-pyrones **1.188** (Scheme 1.63).[75] This reaction also proceeded through cascade oxidative addition and alkyne coordination followed by insertion and finally, reductive elimination.



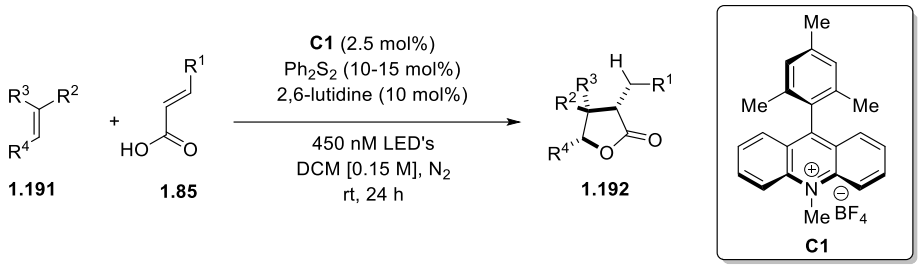
Scheme 1.63. Ru(II)-catalyzed oxidative annulation of the cinnamic acids with alkynes

α-Pyrones/ pyridones **1.190** can be synthesized in excellent regioselectivity by oxidative [4+2] annulations of acrylic acids/ acrylamides **1.189** with internal alkynes **1.86** under Pd(II)/Cu-catalysis by using O_2.as the oxidant in basic medium as reported by Jiang's group (Scheme 1.64).[76]



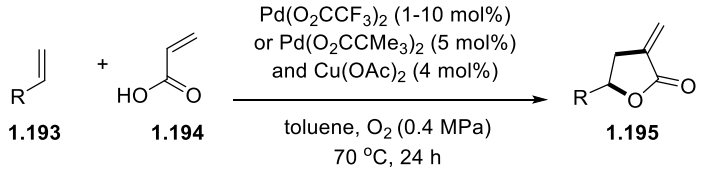
Scheme 1.64. Pd(II)-catalyzed oxidative annulations of the acrylic derivatives with alkynes

Nicewicz's group developed a polar radical cross-over cycloaddition (PRCC) methodology for the stereoselective synthesis of *γ*-butyrolactones **1.192** from substituted alkenes **1.191** and unsaturated carboxylic acids **1.85** by using Fukuzumi's acridinium photo-oxidant catalyst **C1** along with the redox active co-catalyst (Scheme 1.65).[3b] This methodology proceeded through stereo-controlled oxidative [3+2] annulation by *ortho*-C-H/O-H functionalization.



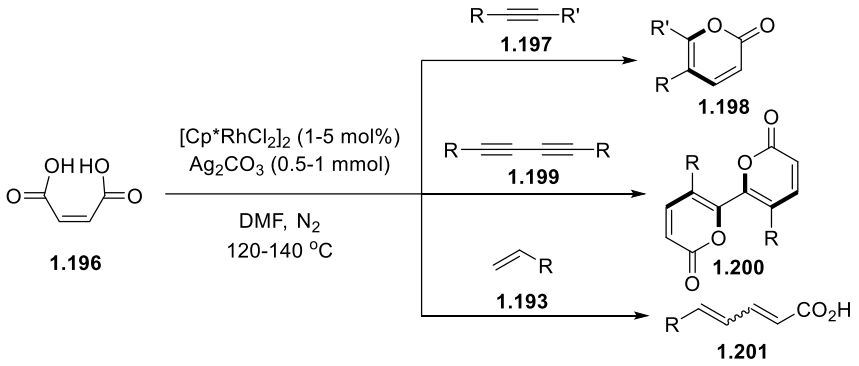
Scheme 1.65. Photo-catalyzed annulation of *α,β*-unsaturated carboxylic acids with alkenes

Yonehara's group developed a methodology for the construction of *α*-methylene-*γ*-butyrolactones **1.195** from intermolecular aerobic [3+2] annulation of acrylic acids **1.194** with alkenes **1.193** by *ortho* C-H functionalization under P(II)/Cu(II) or under simple Pd(II)-catalysis (Scheme 1.66).[3c] In this reaction, carboxylate ligand plays a key role and allows greater reactivity for the annulations/couplings.



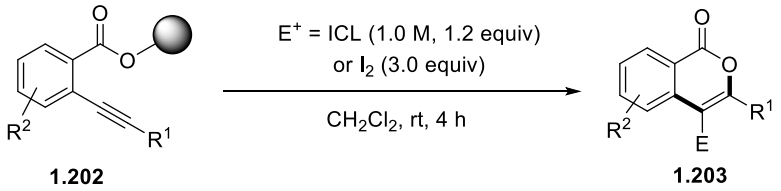
Scheme 1.66. Pd(II)-catalyzed [3+2] annulation of acrylic acids with alkenes

Miura's group revealed the coupling/annulation methodology for the divergent reactivity of maleic acids **1.196** with unsaturated compounds *via* decarboxylative and dehydrogenation process under the Rh(III)/Ag(I)-catalysis. In this reaction, when maleic acid was treated with the internal alkyne **1.197**, decarboxylative oxidative [4+2] annulation took place to afford α-pyrones **1.198**. When maleic acid was treated with 1,3-dialkynes **1.199**, double decarboxylative annulation took place using both the triple bonds to give dienoic acids **1.200**. In contrast to this, when maleic acid was treated with substituted alkene **1.193**, instead of annulation, decarboxylative and dehydrogenative coupling took place to give 1,3-butadienes **1.201** (Scheme 1.67).[77]



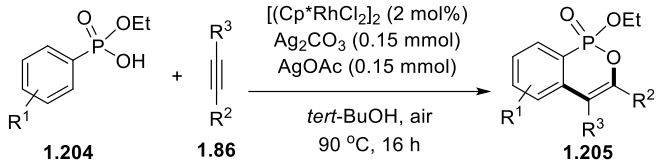
Scheme 1.67. Rh(III)-catalyzed annulation of maleic acids with the alkynes/alkenes

Lisowski's group developed an alternative simple transition metal-free protocol for the construction of 4-halo-isocoumarin scaffolds **1.203** using electrophilic reagents and solid-phase polymer bound benzoates **1.202** *via* intramolecular halo cyclization process (Scheme 1.68).[78] In this reaction, first *ortho*-halo benzoates undergo Sonogashira cross-coupling reaction to give *ortho*-alkynylated benzoates which upon intramolecular cyclization in the presence of electrophilic reagents, afford 4-halo-isocoumarins.



Scheme 1.68. Solid-phase synthesis of isocoumarins *via* halocyclization

In contrast to simple benzoic acid annulations with unsaturated components for the generation of isocoumarins, Lees's group utilized arylphosphonic acid monoesters **1.204** for the oxidative annulation with alkynes **1.86** to synthesize phospho-isocoumarins **1.205** regioselectively under Rh(III)/Ag(I) catalysis (Scheme 1.69).[79] This reaction also proceeded through cascade oxidative annulation/alkyne insertion and reductive elimination.

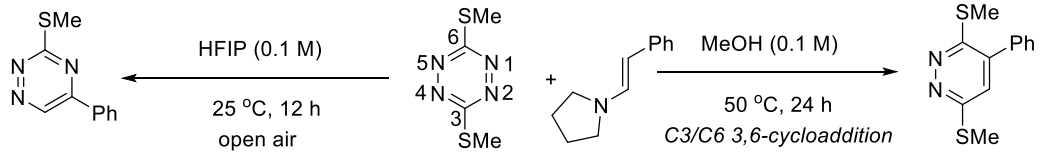


1.204 **1.86** **1.205**

Scheme 1.69. Rh(III)-catalyzed annulations of arylphosphonic acid monoesters with alkynes

1.6 Cycloaddition reactions of tetrazines with alkynes and related substrates

Very recently, Boger's group reported a solvent driven selective cycloaddition reaction of 3,6-disubstituted-1,2,4,5-tetrazine **1.206** with cyclic enamine **1.207** under mild reaction conditions with excellent selectivity (Scheme 1.70).[80] Interesting part of the reaction is that a switch in the solvent altered the reactivity pattern to give two different kinds of cycloaddition adducts involving N1-N4. In the presence of HFIP (hexafluoroisopropanol) solvent, due to hydrogen bonding involving one of the tetrazine nitrogen atoms, 1,2,4-triazines **1.208** are formed. By contrast, in the presence of MeOH solvent at elevated temperatures, a general [4+2] cycloaddition involving C3-C4 was observed to afford substituted pyridazines **1.209** as the final products. Hydrogen bonding again played a key role in the addition process.

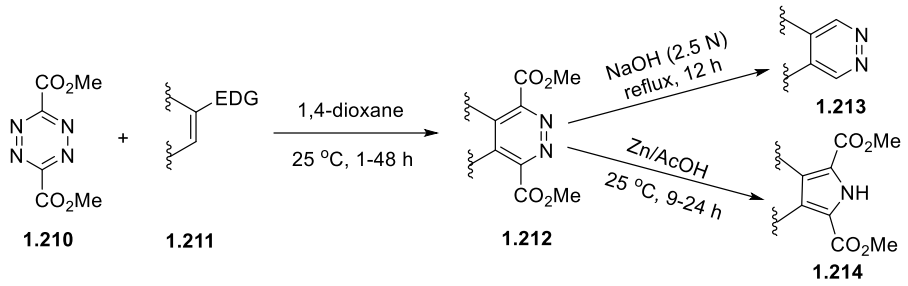


1.208 **1.206** **1.207** **1.209**

Scheme 1.70. HFIP driven selective N1-N4 cycloaddition of 1,2,4,5-tetrazine with enamines

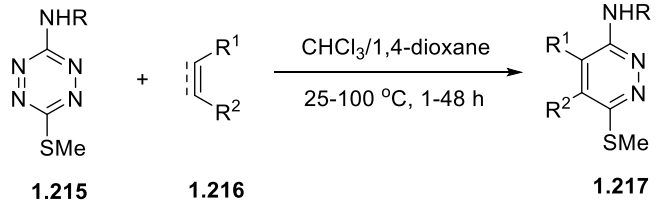
The same Boger's group also reported a route for the synthesis of 1,2-diazines **1.213** and pyrroles **1.214** by the inverse electron demand Diels-Alder reaction (IED-D-A) of dimethyl l,2,4,5-tetrazine-3,6-di-carboxylates **1.210** with electron-donating group containing olefins

1.211 (Scheme 1.71).[81] The importance of the reaction lies in post-functionalization of the formed cycloadduct **1.212**. When products **1.212** were subjected to reduction in the presence of the Zn/AcOH, highly substituted pyrroles **1.213** are formed, but under simple basic-hydrolysis gave 1,2-diazines **1.214** as the final products.



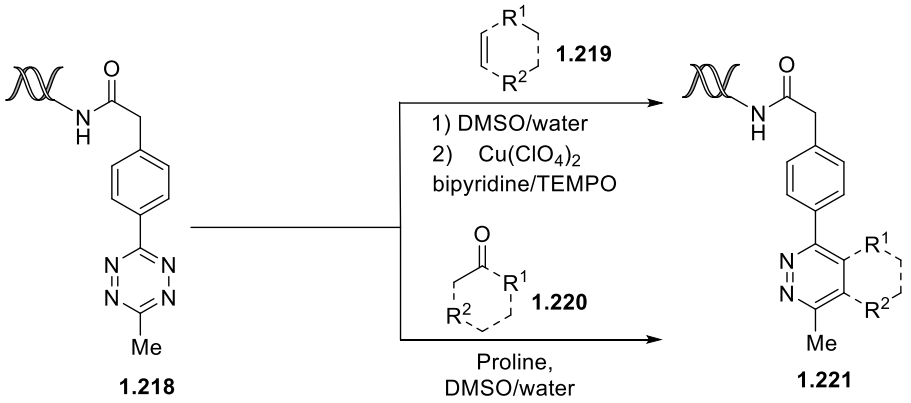
Scheme 1.71. Thermal [4+2] cycloaddition of dimethyl tetrazine-3,6-dicarboxylate with electron-rich olefins

Later, the same Boger's group disclosed regioselective inverse electron demand Diels-Alder reactions of 6-[(alkyl/aryl/-oxycarbonyl)-amino]-3-(methylthio)-1,2,4,5-tetrazine **1.215** with electron-rich dienophiles **1.216** for the construction of functionalized 1,2-diazines **1.217** in excellent yields.[82] They also studied the reactivity order of the electron-rich dienophiles with respect to the diene **1.215** (Scheme 1.72). The regioselectivity is consistent with respect to the diene in which the partial negative charge at C-3 position was stabilized by the methylthio group, whereas the partial positive charge at C-6 position was stabilized by the *N*-acylamino group. There are several other reports from the same group on tetrazine cycloaddition reactions.[13k,13m,13o,83,84]



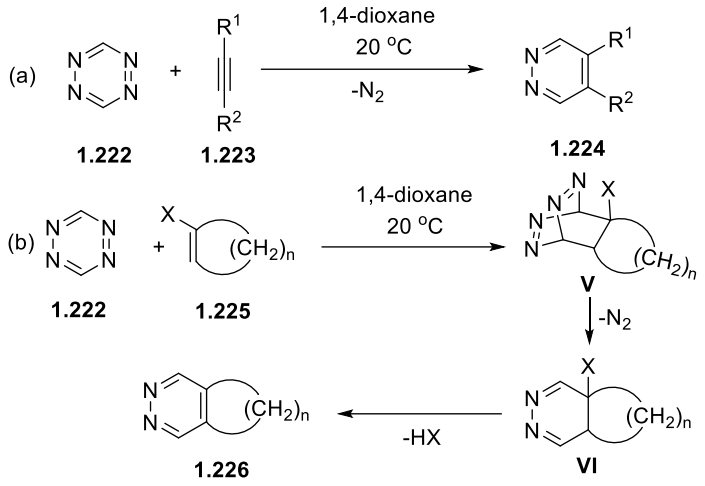
Scheme 1.72. Regioselective IED-D-A reaction of *N*-acyl-6-amino-3-(methylthio)tetrazines

Dai's group successfully demonstrated a methodology for the synthesis of substituted pyridazines on DNA **1.221** (effectively) in aqueous medium using IED-D-A reactions of 1,2,4,5- tetrazines **1.218** with alkenes **1.219** and carbonyl compounds **1.220** (Scheme 1.73).[85] The formed DNA cycloadducts were utilized further for Suzuki−Miyaura coupling, acylation, and S_NAr substitution reactions.



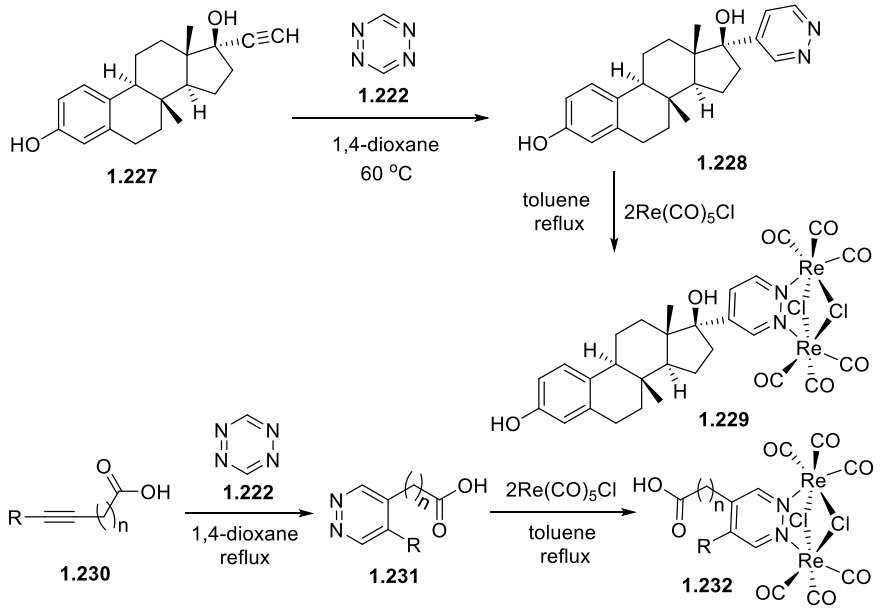
Scheme 1.73. Synthesis of pyridazines on DNA from the IED-D-A reaction of tetrazine

Sauer's group described IED-D-A reactions of the electron deficient tetrazine **1.222** with a wide variety of substituted terminal or internal alkynes **1.223** for the synthesis of substituted pyridazines **1.224** (Scheme 1.74a).[86] Not only alkynes, but also substituted acyclic alkenes or cyclic alkenes **1.225** could be utilized for the reaction with tetrazine **1.222** to successfully obtain fused pyridazines **1.226** (Scheme 1.74b) *via* intermediates **V** and **VI**. They have also conducted kinetic studies and determined the rate constants for each reaction. The results could be useful in the future for studies related to tetrazine and its IED-D-A reaction with a variety of dienophiles.



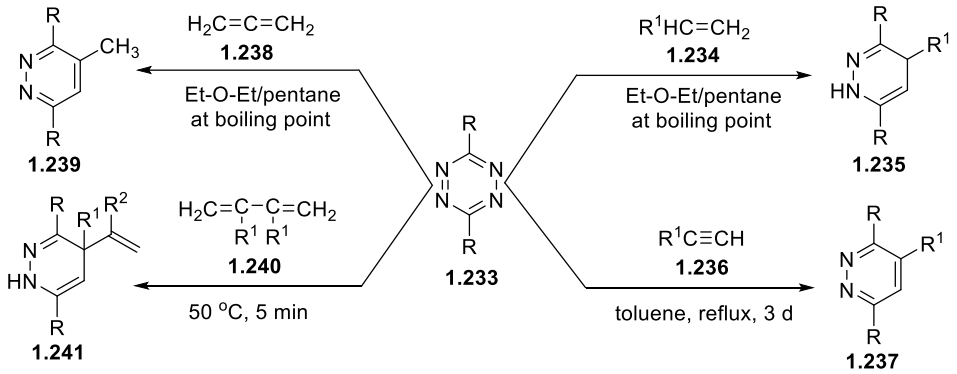
Scheme 1.74. [4+2] cycloaddition reactions of 1,2,4,5-tetrazine with alkynes and alkenes

Sugni and coworkers reported synthesis of luminescent dinuclear rhenium metal complexes **1.229** and **1.232** by IED-D-A reaction of the electron deficient tetrazine **1.222** with estradiol **1.227** or alkynic carboxylic acids **1.230** (Scheme 1.75).[87] Here, estradiol possessing terminal alkyne and alkynic carboxylic acids first undergo [4+2] cycloaddition with tetrazine to give the intermediate IED-D-A cycloadducts **1.228** or **1.231**; these intermediates react with $Re(CO)_5Cl$ to give the final rhenium complexes **1.229** or **1.232**. They have successfully utilized the photoluminescence turn on property of these complexes for photoimaging of living cells



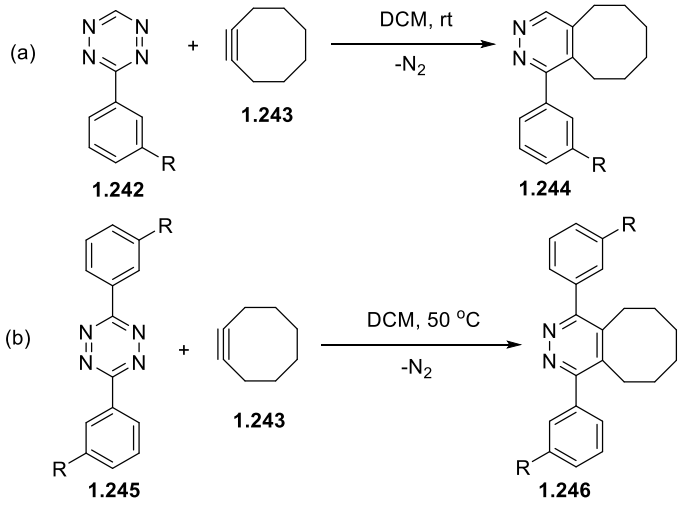
Scheme 1.75. Luminescent dinuclear rhenium metal complexes from the IED-D-A reaction

Carboni and Lindsey reported [4+2] cycloaddition reactions of symmetrical 1,2,4,5-tetrazines with a wide variety of alkenes (**1.234**), alkynes (**1.236**), allene (**1.238**) and 1,3-butadienes (**1.240**) for the synthesis of the substituted pyridazines. Alkene **1.234** and butadiene **1.240** underwent reaction with tetrazine **1.233** to give substituted dihydropyridazines **1.235** and **1.241** as the final products, respectively. The reaction with alkyne **1.236** and allene **1.238** afforded fully aromatized pyridazines **1.237** and **1.239**, respectively, as the final products *via* IED-D-A reaction (Scheme 1.76).[88]



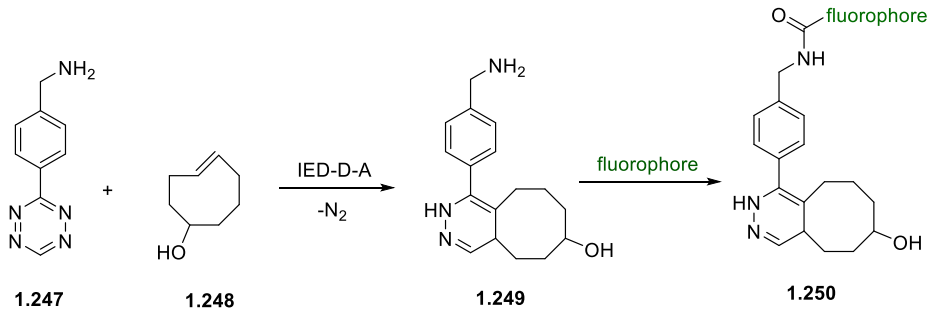
Scheme 1.76. [4+2] Cycloaddition of substituted 1,2,4,5-tetrazines with unsaturated compounds

Pierre's group described IED-D-A reactions of mono- and di-substituted 1,2,4,5-tetrazines with cyclooctyne in dichloromethane at two different temperatures (Scheme 1.77).[89] When monosubstituted tetrazine **1.242** was treated with cyclooctyne **1.243** at room temperature, the reaction progressed smoothly *via* IED-D-A pathway and delivered the cyclooctyne fused pyridazines **1.244** (Scheme 1.77a). But for the reaction of disubstituted tetrazine **1.245** with **1.243**, a slightly higher temperature of 50 °C was needed to get product **1.246** (Scheme 1.77b). The cycloaddition products **1.244** and **1.246** were found to be good photoluminescent materials.



Scheme 1.77. [4+2] IED-D-A cycloaddition of *mono*/*di*-substituted 1,2,4,5-tetrazines with cyclooctyne

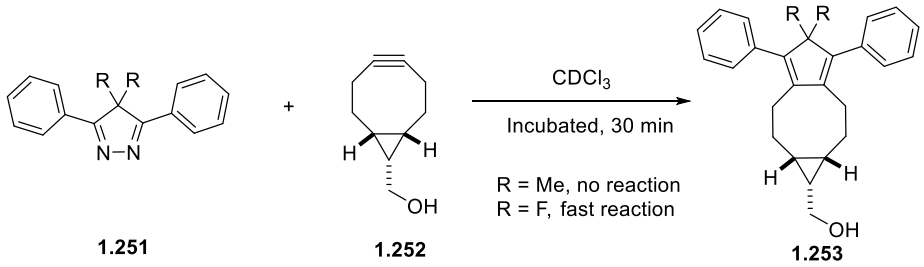
Recently, Weissleder's group successfully reported a method for the covalent labeling of live cancer cells by the IED-D-A reaction of substituted tetrazines **1.247** with strained *trans*-cyclooctenol **1.248** to get the amine containing cycloadduct **1.249** (Scheme 1.78),[90] which is actually the key intermediate in the pre-targeting method of detecting live cancer cells. They treated the amine adduct **1.249** with amino acid fluorophore, a cell-permeable labeling mediator, and obtained product **1.250**. This was used to detect live cancer cells in *in vivo* process for the detection of cells by utilizing its turn on fluorescence properties.



Scheme 1.78. IED-D-A reactions of substituted 1,2,4,5-tetrazine with *trans*-cyclooctenol

Recently, Raines and Houk proved that not only tetrazine and its derivatives can act as electron deficient dienes in the IED-D-A reactions, but also 4,4-difluoro-3,5-diphenyl-4*H*-pyrazole **1.251** can act as electron deficient diene in IED-D-A reaction with bicyclo[6.1.0]non-

4-yn-9-ylmethanol (BCN) **1.252** to give fused cycloadducts **1.253** (Scheme 1.79)[91] with greater reaction rates compared to tetrazine. The reactivity of **1.251** with BCN was examined experimentally as well as computationally. These studies revealed that the rate of the reaction for **1.251** was higher compared to that for tetrazine, and that the reaction can proceed with mM quantities also. The enhancement in the rate of the reaction was because of the hyperconjugative antiaromaticity developed by difluorination at 4-position, which was not observed in the case of demethylated pyrazole and hence the reaction failed in the latter case.



1.251 1.252 1.253

Scheme 1.79. IED-D-A Reaction of electron deficient 4,4-difluoro-3,5-diphenylpyrazole with BCN

Along with the above-mentioned reports for the cycloaddition reactions of electron deficient tetrazines with electron rich unsaturated dienophiles, there are a few reports involving the tetrazines with other electron rich dienophiles in the IED-D-A reactions, but are not elaborated here.[92] However, reaction of tetrazines with allenes has been very rarely explored till now.

OBJECTIVES OF THE PRESENT WORK

The objective of the present work was to study the reactivity/annulation reactions of aromatic heterocyclic carboxylic acids, 2-sustituted indoles (indole-2-carboxylates/carboxylic acids) and chromene/coumarin-3-carboxylic acids with C-C π components (*tert*-propargylic alcohols or alkynes) under Brønsted acid or transition metal catalysis. In addition, it was also intended to study cycloaddition reactions of 3,6-diphenyl 1,2,4,5-tetrazine with allenes. Specifically, the aim was

(i) To explore the reactivity of indole-2-carboxylates/carboxylic acids with multi-substituted propargylic alcohols in an effort to develop new synthetic methodologies to indole fused polycyclic heterocycles under Brønsted or Lewis acid catalysis,

(ii) To investigate transition metal catalyzed decarboxylative annulation reactions of coumarin-3-carboxylic acids with propargylic alcohols to obtain coumarin containing fused naphthalene heterocyclics,

(iii) To study oxidative [4+2] annulation reactions of chromene/coumarin-3-carboxylic acids with alkynes or propargylic alcohols that may lead to pyrano-chromene/coumarins under [Ru]-catalysis, and

(iv) To probe thermally induced regioselective [4+2] cycloaddition reactions of 3,6-diphenyl-1,2,4,5-tetrazine with allenes in an effort to synthesize novel pyridazines.

RESULTS AND DISCUSSION

This chapter deals with the results on annulation reactions of aromatic heterocyclic carboxylic acids and related substrates leading to extended heterocyclic architectures. The regioselective [4+2] cycloaddition reaction of 3,6-diphenyl-1,2,4,5-tetrazine with allenes to afford substituted pyridazine motifs is also covered briefly. Details on the precursors utilized for the present study are presented in section 2.1. After this, in section 2.2, annulation reactions of 2-substituted indoles with propargylic alcohols under PTSA mediation or Cu(II)-catalysis are discussed. In section 2.3, Cu(II)-catalyzed decarboxylative annulation reaction of coumarin-3-carboxylic acids with propargylic alcohols is presented. Section 2.4 deals with Ru(II)-catalyzed oxidative annulation reaction of chromene/coumarin-3-carboxylic acids with alkynes/propargylic alcohols. The last section 2.5 corresponds to the cycloaddition reactions of 3,6-diphenyl-1,2,4,5-tetrazine with allenes. The products obtained in this work are characterized by using IR, NMR, LCMS/CHN or HRMS and mp (for solids); the assigned regio- or stereo-chemistry of the products is generally based on X-ray crystallographic studies on representative compounds.

2.1 Precursors used in the present study

2.1.1 1*H*-Indole-2-carboxylates 1a-e and propargylic alcohols 3a-c and 4a-r

The 1*H*-indole-2-carboxylates **1a-e** were synthesized by esterification of indole-2-carboxylic acids using catalytic H_2SO_4,[93] while the indole-2-carboxylic acids **2a-b** are commercially available (Chart 1). Propargylic alcohols **3a-c** and **4a-r** were prepared from the corresponding carbonyl compounds and terminal alkynes following literature procedures (Scheme 1).[94]

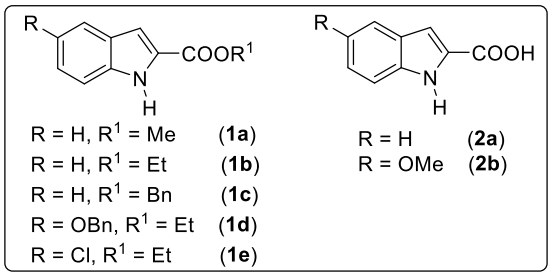
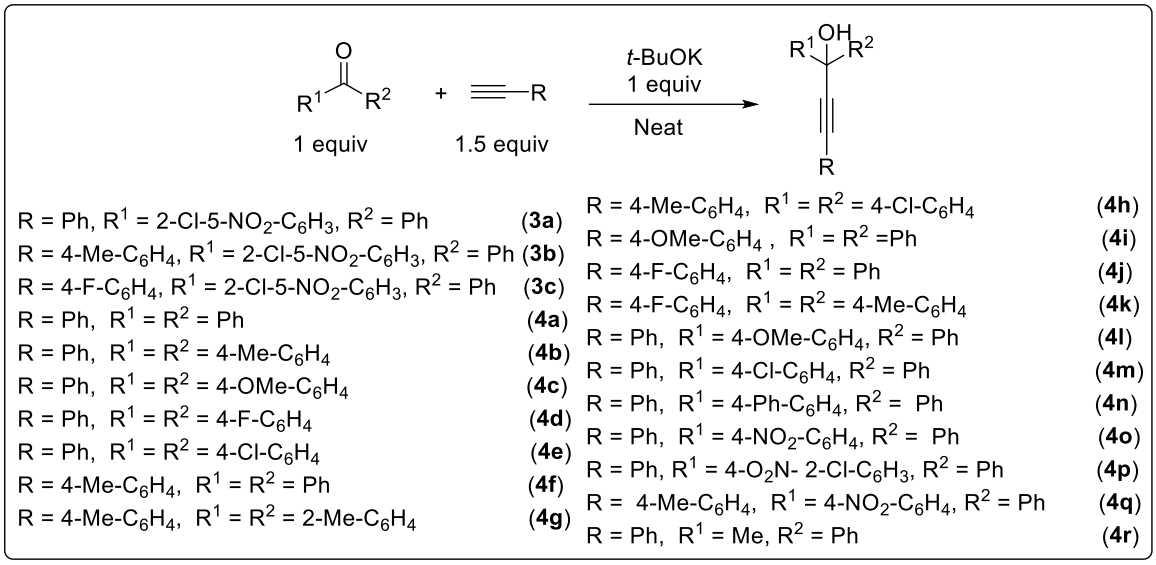


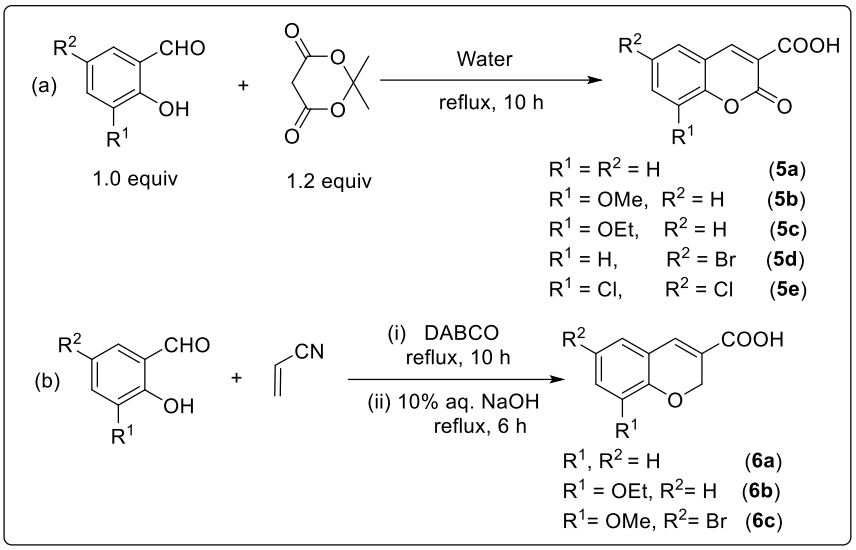
Chart 1. Indole-2-carboxylates and indole-2-carboxylic acids used in the present study



Scheme 1. Synthesis of propargylic alcohols **3a-c** and **4a-r**

2.1.2 Coumarin-3-carboxylic acids 5a-e and chromene-3-carboxylic acids 6a-c

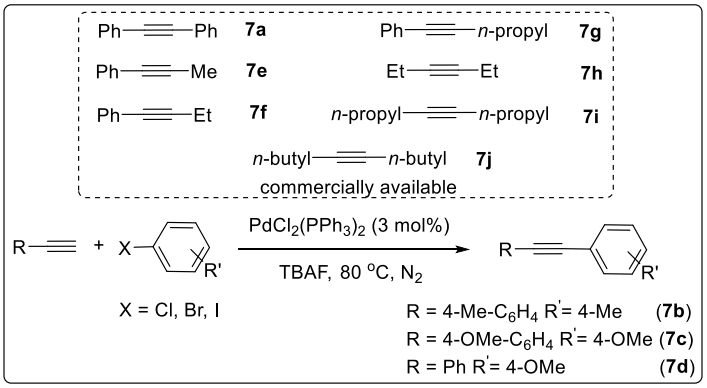
The coumarin-3-carboxylic acids **5a-e** were synthesized by using salicylaldehyde and Meldrum's acid in water at reflux conditions for 10 h as shown in Scheme 2a.[95] The 2*H*-chromene-3-carboxylic acids **6a-c** were synthesized by treating salicylaldehyde with acrylonitrile in the presence of DABCO under reflux for 10 h followed by basic hydrolysis of the obtained chromene-3-nitrile using 10% aqueous NaOH at reflux conditions for 6 h (Scheme 2b).[96]



Scheme 2. Synthesis of coumarin-3-carboxylic acids **5a-e** and chromene carboxylic acids **6a-c**

2.1.3 Disubstituted alkynes 7a-j

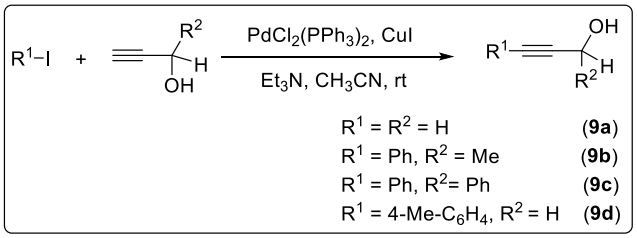
The alkyne precursors **7a** and **7e-j** are commercially available. Other alkynes **7b-d** were prepared by using aryl halides and terminal alkynes under Sonogashira cross-coupling conditions (Scheme 3).[97]



Scheme 3. Availability/ synthesis of disubstituted alkynes **7a-j**

2.1.4 3,6-Diphenyl-1,2,4,5-tetrazine 8 and arylated *sec*-propargylic alcohols 9a-d

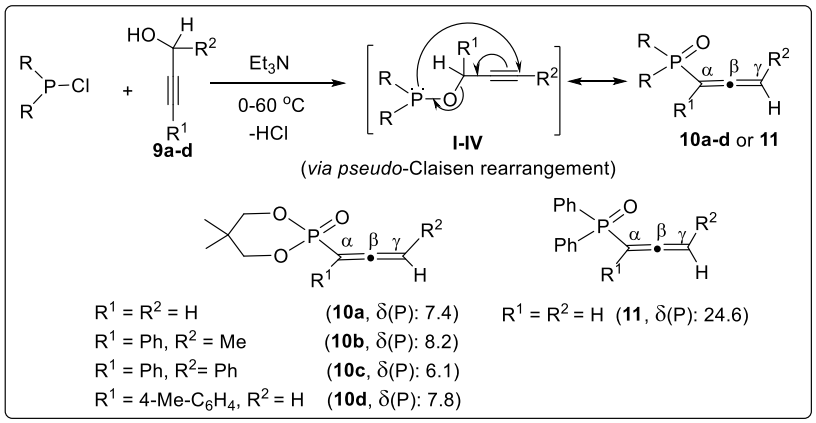
3,6-diphenyl-1,2,4,5-tetrazine **8** is commercially available. Substituted *sec*-propargylic alcohols **9a-d**, required for the synthesis of allenes, were synthesized by using standard Sonogashira-cross coupling reaction conditions using a Pd(II)-catalyst (Scheme 4).[98]



Scheme 4. Synthesis of substituted propargylic alcohols **9a-d**

2.1.5 Allenylphosphonates 10a-d and allenylphosphine oxide 11

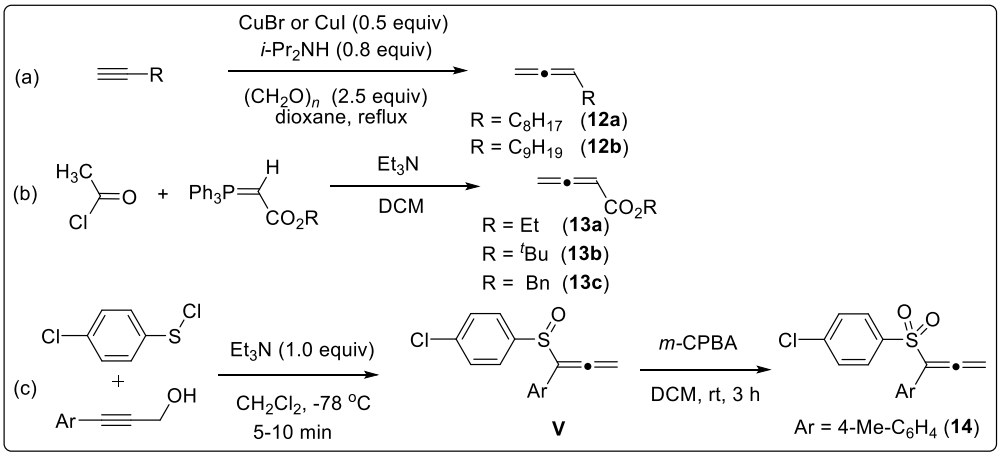
Allenylphosphonates **10a-d** and allenylphosphine oxide **11** were prepared by using a methodology developed from our group.[99] This involves the reaction of R_2PCl [R_2 = Ph_2 or ($OCH_2CMe_2CH_2O$)] with propargylic alcohols **9a-d** in the presence of triethylamine. The intermediates **I-IV** upon *pseudo*-Claisen rearrangement give the phosphorus based allene (Scheme 5). The ^{31}P NMR spectra of allenylphosphonates **10a-d** and allenylphosphine oxide **11** show peaks in the δ range 6-8 and 27-30 ppm, respectively.



Scheme 5. Synthesis of allenylphosphonates **10a-d** and allenylphosphine oxide **11**

2.1.6 Synthesis of alkyl allenes 12a-b, ester allenes 13a-c and allenylsulfone 14

Synthesis of terminal alkylated allenes was achieved by the reaction of terminal alkynes with paraformaldehyde in the presence of the Cu-salts and amines as depicted in the Scheme 6a.[100] In another case, synthesis of ester allenes involves the reaction of the phosphorus ylide with acetyl chloride in the presence of triethylamine in dichloromethane solvent as shown in Scheme 6b.[101] Allenyl sulfone synthesis involves two steps: first step comprises the reaction of propargylic alcohol with 4-chlorophenyl hypochlorothioite and gives the intermediate **V** which upon oxidation with *m*CPBA gives the final allenyl sulfone **14** as shown in Scheme 6c.[102]



Scheme 6. Synthesis of allenes **12a-b**, ester allenes **13a-c** and allenylsulfone **14**

2.2 Annulation reactions of indole-2-carboxylates/carboxylic acids with propargylic alcohols

As described in Chapter 1,[5,6] indole is one of the broadly studied molecules of heterocyclic family because of its high reactivity towards annulation/cyclization for the generation of a plethora of heterocyclic architectures, many of which are pharmaceutically important. In the present work, we wanted to explore the reactivity of 2-substituted indoles with propargylic alcohols under Brønsted or Lewis acid catalysis. For this purpose, we have selected indole-2-carboxylates along with *tert*-propargylic alcohols as our model substrates. The products include spirocyclic indoles from dearomative ring expansion and fused indole pentacyclics by annulation. To the best of our knowledge, there had been no precedence for these types of reactions.

2.2.1 PTSA mediated dearomative ring expansion followed by spirocyclization (*via* oxygen insertion) of indole-2-carboxylates with propargylic alcohols

Our initial investigation began by performing the reaction of ethyl 1*H*-indole-2-carboxylate **1b** with propargylic alcohol **3a** in the presence of *p*-toluene sulfonic acid (PTSA) in acetonitrile at rt (25 ^{o}C) for 12 h (Table 1, entry 1). Rather unexpectedly, we isolated the spirocyclic compound **15ba** in 40% yield along with 10% of dihydrocyclopenta[*e*]indole-2-carboxylate **16ba**. Among the solvents MeCN, toluene, DCM, DMSO, THF, dioxane, PEG-400, EtOH, and $MeNO_2$ (entries 1-9), $MeNO_2$ offered the best yield of **15ba** (50%) along with **16ba** (20%) (entry 9). Increasing the reaction time to 24 h increased the yield of **15ba** to 60% and of **16ba** to 30% (entry 10). Use of 1.5 equiv of PTSA after 24 h of reaction time at room temperature afforded the final products **15ba** and **16ba** in the ratio 67:31 (entry 11). Use of the Brønsted acid TfOH gave < 20% of **15ba** along with other unidentified products. Acetic acid did not work for our reaction but trifluoroacetic acid (TFA) gave a trace amount of **15ba** along with allene intermediate **18ba** as the major product (entries 12-14). Although starting materials were consumed when H_2O_2 or TBHP was added, the reaction mixture showed many products with the exclusion of **15ba** (entries 15-16). By increasing the quantity of PTSA to 2 equiv, only marginal increase in the yield of **15ba** (69%) and decrease in the yield of **16ba** (28%) were observed (entry 17). No desired product formation was observed at 100 ^{o}C in toluene or $MeNO_2$ (entries 18-19). We have performed the reaction using oxygen balloon and isolated **15ba** in 78% yield along with **16ba** (14%). In contrast to this, use of nitrogen balloon delivered **15ba** in <10% yield and **16ba** in 30% yield (entries 20-21). Hence these experiments suggest that the presence of molecular oxygen is essential for the formation of spirocyclic compound. When we performed the reaction by adding 2 equiv of water, we obtained 80% of the spirocyclic product **15ba** along with <10% of **16ba** (entry 22). None of the Lewis acid catalysts $Cu(OTf)_2$, $Zn(OTf)_2$, $Yb(OTf)_3$ or AgOTf afforded the final products. Thus, the conditions used in entry 11 were chosen for the conversion because both the products were novel and we wanted to utilize the conditions which gave good yields of both the products. We have also utilized the conditions mentioned in entries 20 and 22 to get the spirocyclic products **15aa** and **15ab** in better yields compared to conditions utilized in entry 11.

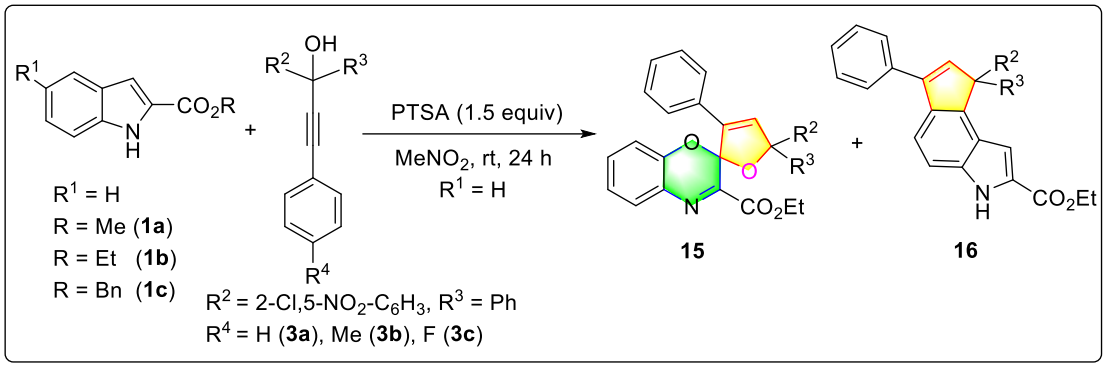
Table 1. Optimization study of PTSA mediated annulation reaction between **1b** and **3a** for the formation of spiro[benzo-oxazinefuran] **15ba** and cyclopenta[*e*]indole-2-carboxylate **16ba** [a]

Entry	Acid	Solvent	Time (h)	Yield[b] (**15ba**:**16ba**, %)
1	PTSA	MeCN	12	40:10
2	PTSA	Toluene	12	<10:0
3	PTSA	DCM	12	20:30
4	PTSA	DMSO	12	n.d.
5	PTSA	THF	12	n.d.
6	PTSA	Dioxane	12	20:0
7	PTSA	PEG-400	12	n.d.
8	PTSA	EtOH	12	n.d.
9	PTSA	$MeNO_2$	12	50:20
10	PTSA	$MeNO_2$	24	60:30
11	**PTSA**	**$MeNO_2$**	**24**	**67:31**
12	TfOH	$MeNO_2$	24	<20:0
13	AcOH	$MeNO_2$	24	n. r
14	TFA	$MeNO_2$	24	trace:0
15	H_2O_2	$MeNO_2$	24	n.d.
16	TBHP	$MeNO_2$	24	n.d.
17	PTSA	$MeNO_2$	24	69:28
18	PTSA	$MeNO_2$	24	n.d.

19	PTSA	Toluene	24	n.d.
20[c]	PTSA	$MeNO_2$	24	78:14
21[d]	PTSA	$MeNO_2$	24	<10:30
22[e]	**PTSA**	**$MeNO_2$**	**24**	**80:<10**

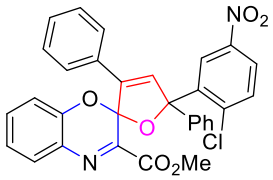
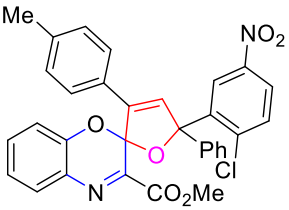
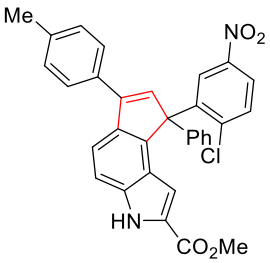
[a)] Reaction conditions: **1b** (100 mg, 0.57 mmol), **3a** (0.57 mmol), and acid (1.0 equiv for entries 1-10; 1.5 equiv for entries 11-16 and 18-22; 2.0 equiv for entry 17) in solvent (2.0 mL); temperature (25 °C for entries 1-17 and 20-22; 100 °C for entries 18 and 19). [b)] Isolated yield. [c)] under O_2 balloon. [d)] under N_2 balloon. [e)] with 2.0 equiv of H_2O.

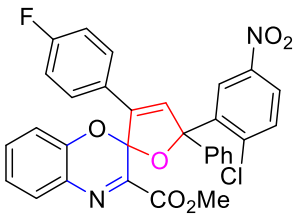
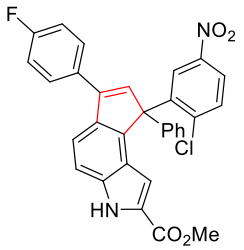
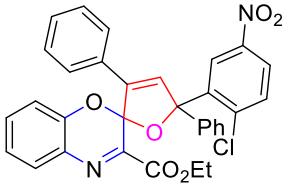
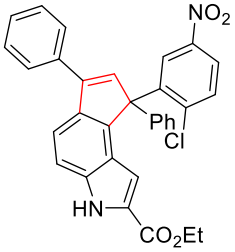
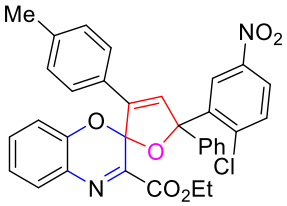
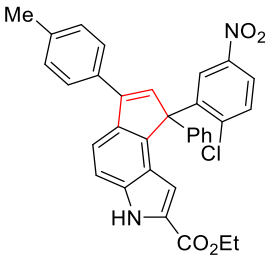
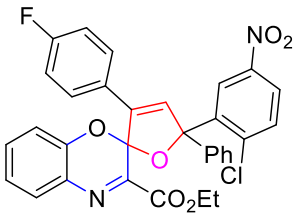
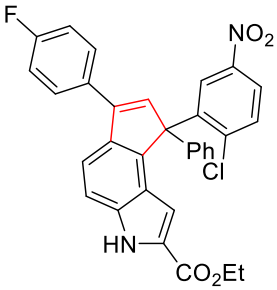
After having the optimized reaction conditions in hand, we examine the substrate scope. Although initially we could not get these spirocyclic products exclusively, the reaction of methyl indole-2-carboxylate **1a** (1 equiv) with **3a** (1 equiv) in the presence of PTSA (1.5 equiv) in $MeNO_2$ at room temperature (25 °C) in open air for 24 h afforded only the spirocyclic product **15aa** in 71% yield. We have also utilized methyl, ethyl and benzyl indole-2-carboxylates **1a-c** and obtained good yields of the spirocycles **15aa-15bc** and **15ca** along with substituted dihydrocyclopenta[*e*]indole-2-carboxylates **16ab-16bc** and **16ca** in moderate yields. As far as propargylic alcohols are concerned, we have utilized **3a-c** that have aryl groups at the alkynic end to obtain the desired products (Table 2). We have also attempted the reaction with electron donating group containing propargylic alcohols such as PhC≡CC(Me)Ph(OH) and PhC≡CCH_2OH but did not observe the desired product formation (see later for mechanism).[103] The *N*-methylated precursor, methyl 1-methyl-1*H*-indole-2-carboxylate,[103] as expected, did not afford the ring expanded spirocyclic product. This is because of the absence of free N-H which is required for the ring enlargement (see later for the mechanistic pathway). The structures of the products **15aa**, **15ba** and **16ba** were further confirmed by X-ray crystallographic analysis (Figure 1).

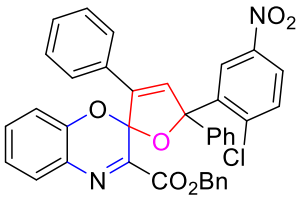
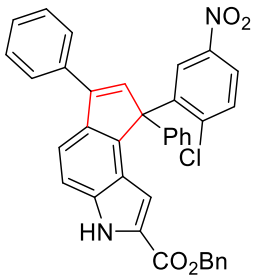


Scheme 7. Synthesis of spiro[benzo-oxazinefurans]**15** or cyclopenta[*e*]indole-2-carboxylates **16**

Table 2. Substrate scope for the spiro[benzo-oxazinefurans] and cyclopenta[*e*]indole-2-carboxylates[a]

Entry	Indole-2-carboxylate	Propargylic alcohol	Spiro[benzo-oxazinefuran]	Cyclopenta[*e*]indole-2-carboxylate	Overall yield[b]
1	**1a**	**3a**	 **15aa** (71%) **X-ray**	Not isolated	71%
2	**1a**	**3b**	 **15ab** (61%)	 **16ab** (29%)	90

3	**1a**	**3c**	 **15ac** (66%)	 **16ac** (32%)	98
4	**1b**	**3a**	 **15ba** (67%) **X-ray**	 **16ba** (31%) **X-ray**	98
5	**1b**	**3b**	 **15bb** (58%)	 **16bb** (30%)	88
6	**1b**	**3c**	 **15bc** (62%)	 **16bc** (35%)	97

7	**1c**	**3a**	 **15ca** (64%)	 **16ca** (33%)	97

[a]Indole-2-carboxylate (**1a-c**, 0.57 mmol), propargylic alcohol (one of **3a-c**, 0.57 mmol), and PTSA (0.85 mmol) in $MeNO_2$ (2 mL) in open air at rt for 24 h. [b]Isolated yields.

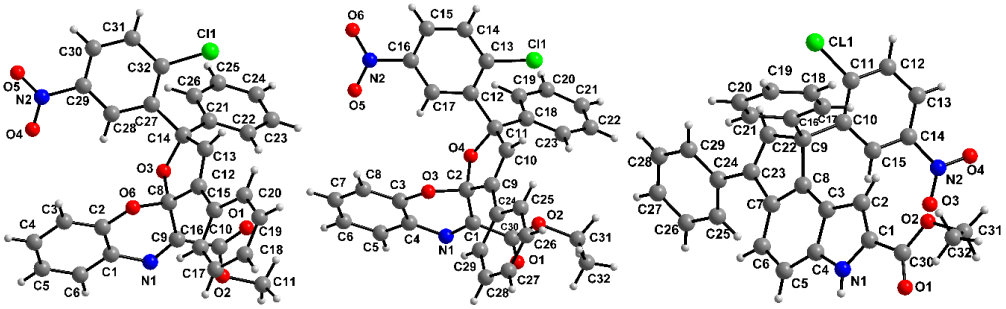
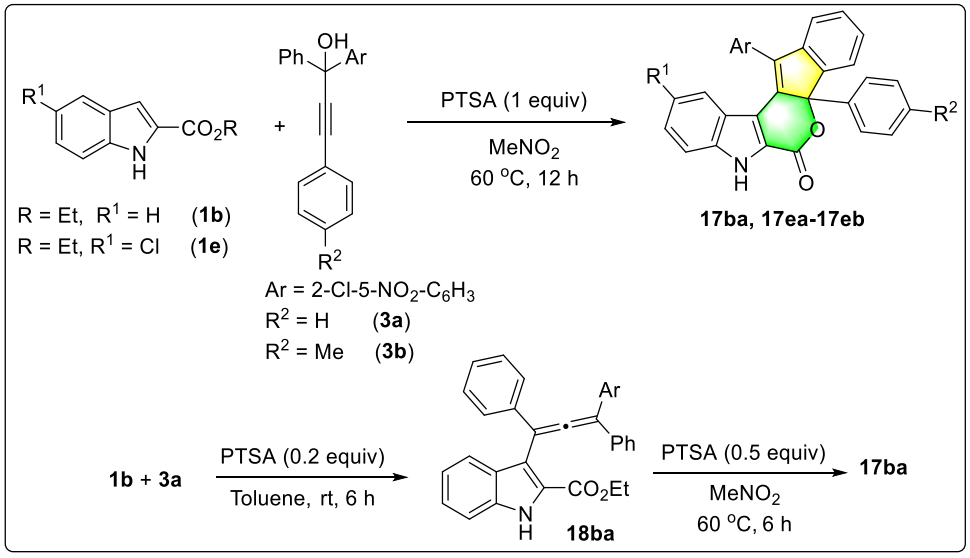


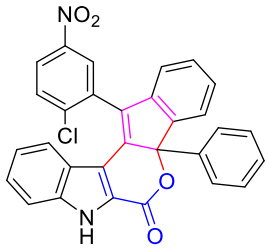
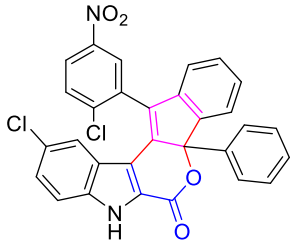
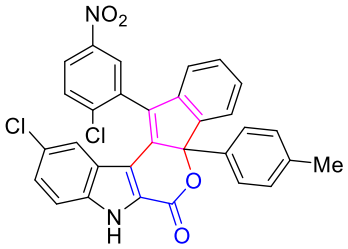
Figure 1: Molecular structures of compounds **15aa** (left), **15ba** (center) and **16ba** (right). Selected bond lengths in [Å] with esds in parenthesis: Compound **15aa**: C(1)-C(2) 1.387(5), C(2)-O(6) 1.379(4), O(6)-C(8) 1.442(4), C(8)-C(9) 1.528(5), C(9)-N(1) 1.270(5), N(1)-C(1) 1.397(4), C(8)-O(3)- 1.418(5), O(3)-C(14) 1.454(4), C(14)-C(13) 1.495(6), C(13)-C(12) 1.323(5), C(12)-C(8) 1.512(5), C(1)-C(6) 1.388(5), C(2)-C(3) 1.376(5), C(14)-C(21) 1.522(5), C(14)-C(27) 1.538(5), C(12)-C(15) 1.472(6), C(9)-C(10) 1.496(5). Compound **15ba**: C(1)-C(2) 1.532(6), C(2)-O(3) 1.438(5), O(3)-C(3) 1.380(6), C(3)-C(4) 1.395(6), C(4)-N(1), 1.385(5), N(1)-C(1) 1.278(6), C(2)-O(4) 1.416(5), O(4)-C(11) 1.470(5), C(11)-C(10) 1.500(6), C(10)-C(9) 1.325(6), C(9)-C(2) 1.493(7), C(4)-C(5) 1.378(8), C(3)-C(8) 1.369(6), C(11)-C(12) 1.526(7), C(11)-C(18) 1.512(6), C(9)-C(24) 1.471(6), C(1)-C(30) 1.491(7). Compound **16ba**: C(7)-C(8) 1.391, C(8)-C(9) 1.528(8), C(9)-C(22) 1.526(8), C(22)-C(23) 1.342(8), C(23)-C(7) 1.473(8), C(7)-C(6) 1.402(8), C(8)-C(3) 1.396(8), C(9)-C(10) 1.533(8), C(9)-C(16) 1.539(8), C(21)-H(21) 0.9300.

In an attempt to enhance the yield of products **15ba** and **16ba**, we treated indole-2-carboxylate **1b** with propargylic alcohol **3a** in the presence of PTSA in $MeNO_2$ by increasing the temperature to 60 ^oC for 12 h. To our surprise, we obtained the double cyclized indene fused pyrano-indolone (a fused pentacyclic) **17ba** (X-ray; Figure 2) in 92% yield probably by cyclization *via in-situ* generated carboxylic acid. Similarly, **17ea** (90%) and **17eb** (88%) were obtained from the reaction of **1e** with **3a** or **3b**. It is noteworthy to mention that compound **17ba** can be synthesized from the isolatable allene intermediate **18ba** (see Table 4 for data on allenes **18aa-18db**) in the presence of 50 mol% of the PTSA in $MeNO_2$ at 60 ^oC/ 6 h (*cf.* Scheme 8), which in turn proves that the reaction takes place *via* allene intermediate. Under the conditions employed herein, formation of indene fused pyrano-indolone is limited to propargylic alcohols **3a-c**.



Scheme 8. Synthesis of substituted indene fused pyrano-indolones

Table 3. Substrate scope for the indene fused pyrano-indolones[a]

Entry	Indole-2-carboxylate	Propargylic alcohol	Indene fused pyrano-indolone	Yield[b] (%)
1	**1b**	**3a**	 **17ba (X-ray)**	92
2	**1e**	**3a**	 **17ea**	90
3	**1e**	**3b**	 **17eb**	88

[a]Indole 2-carboxylate (**1b** or **1e**, 0.53 mmol), propargylic alcohol (one of **3a-b**, 0.53 mmol), and PTSA (0.53 mmol) $MeNO_2$ (2 mL) at 60 °C (oil bath temperature) for 12 h. [b]Isolated yields.

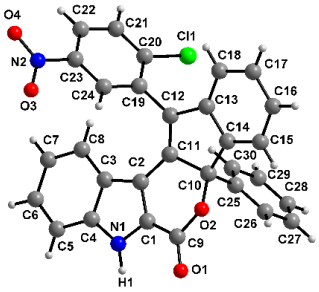
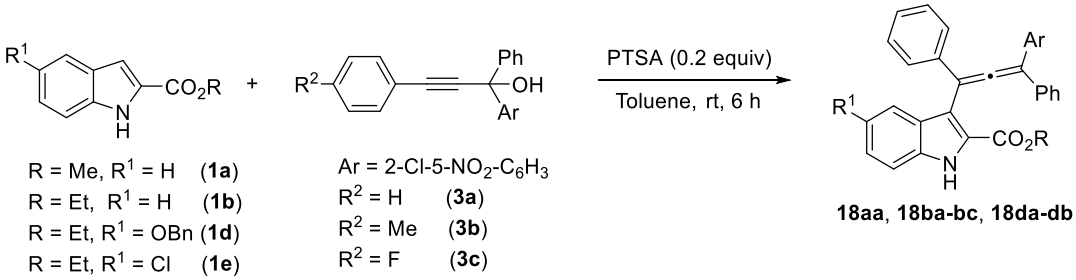


Figure 2: Molecular structure of the compound **17ba**. Selected bond lengths in [Å] with esds in parenthesis: C(1)-C(2) 1.392(6), C(2)-C(11) 1.449(6), C(11)-C(10) 1.513(4), C(10)-O(2) 1.466(5), O(2)-C(9) 1.358(5), C(9)-C(1) 1.448(5), C(9)-O(1) 1.211(6), C(11)-C(12) 1.344(5), C(12)-C(13) 1.476(6), C(13)-C(14) 1.391(6), C(14)-C(10) 1.512(5), C(1)-N(1) 1.355(6), C(2)-C(3) 1.422(6), C(12)-C(19) 1.480(5), C(13)-C(18) 1.395(5), C(14)-C(15) 1.374(6), C(10)-C(25)1.530(8),

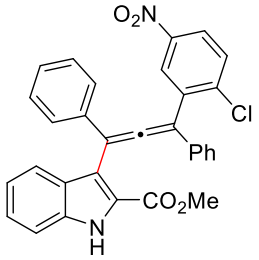
Table 4. 3-Allenyl indole-2-carboxylates isolated in the present study[a]

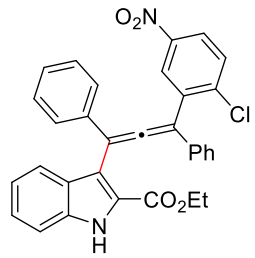
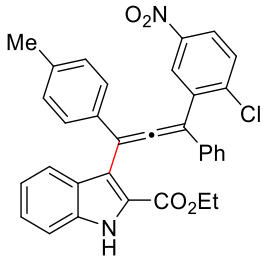
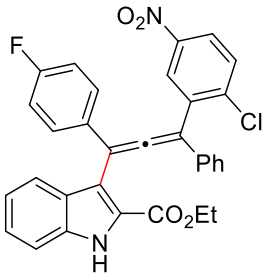
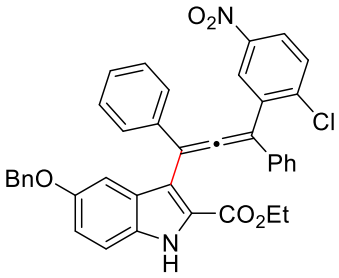


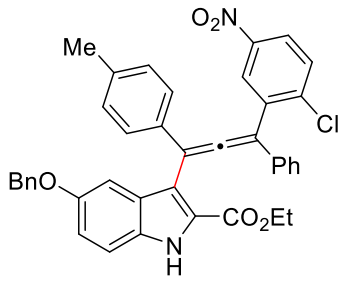
R = Me, R^1 = H (**1a**)
R = Et, R^1 = H (**1b**)
R = Et, R^1 = OBn (**1d**)
R = Et, R^1 = Cl (**1e**)

Ar = 2-Cl-5-NO_2-C_6H_3
R^2 = H (**3a**)
R^2 = Me (**3b**)
R^2 = F (**3c**)

18aa, **18ba-bc**, **18da-db**

Entry	Indole-2-carboxylate	Propargylic alcohol	3-allenyl-indole-2-carboxylates	Yield[b] (%)
1	**1a**	**3a**	 **18aa**	84

2	**1b**	**3a**	 **18ba**	80
3	**1b**	**3b**	 **18bb**	78
4	**1b**	**3c**	 **18bc**	74
5	**1d**	**3a**	 **18da**	76

6	**1d**	**3b**	 **18db**	79

[a]Indole-2-carboxylate (**1a-b**, **1d**; 0.53 mmol), propargylic alcohol (one of **3a-c**, 0.26 mmol), and PTSA (20 mol%), toluene (2 mL), at rt for 6 h. [b]Isolated yields.

2.2.2 Cu(II)-catalyzed annulations of indole-2-carboxylic acids and propargylic alcohols leading to indene fused pyrano-indolones (pentacyclics)

In the above reactions, we have utilized indole-2-carboxylates. However, we surmised that the course of the reaction could be altered if the carboxylic acid itself is used because of the availability of the acidic –OH group. Indeed, this assumption proved to be valid since by treating equimolar amounts of the readily available indole-2-carboxylic acid **2a** with propargylic alcohol **4b** in the presence of PTSA in toluene at rt (25 ^{o}C), we obtained the indene fused pentacyclic product **19ab** in 31% yield (Table 5, entry 1). Encouraged by the outcome, we went further for the optimization of the reaction conditions. For that we have used solvents like DCM, $MeNO_2$, dioxane, THF, DMSO and DMF but none of them worked for the reaction; use of either DCM or $MeNO_2$ afforded the product in yields of 14% or 35% respectively (Table 5, entries 2-7). Better solvents were MeOH and MeCN (entries 8-9); however, increasing the temperature to 80 ^{o}C lowered the yield to 39% (entry 10). Higher loading of PTSA (2 equiv) did not improve the yield (entry 11). To our delight, 84% yield of **19ab** was obtained by using catalytic $Cu(OTf)_2$ (0.1 equiv; entry 12); increase in the reaction time to 12 h increased the yield to 95% (entry 13). A higher catalyst loading 0.2 equiv only marginally increased the yield (96%, entry 14), but decreasing catalyst loading to 0.05 equiv decreased the yield drastically 64% (entry 15). Other Lewis acids like $Zn(OTf)_2$, $Yb(OTf)_3$, $BF_3{\cdot}OEt_2$, $Bi(OTf)_3$, $FeCl_3$, and $AlCl_3$ were ineffective or gave very poor yields (entries 16-21). Although use of triflic acid itself does give the product, the yield is only moderate (entry 22). There was no reaction in the absence of the catalyst (entry 23). Thus, conditions used in entry 13 were the best for the reaction.

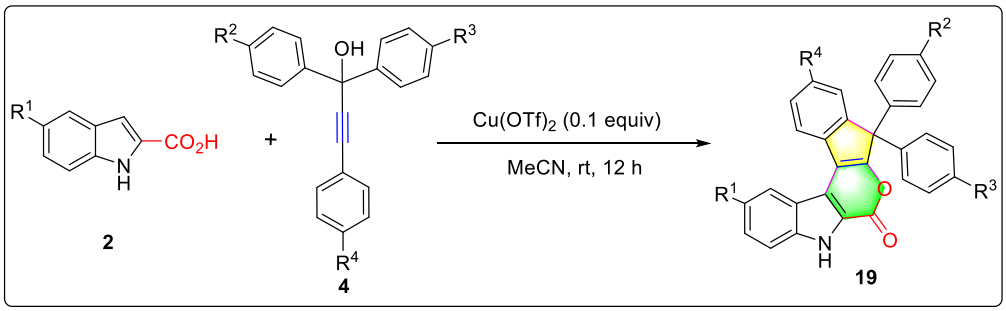
Table 5. Optimization study of Cu(II)-catalyzed annulation reaction between **2a** and **4b** for the formation of fused pentacyclic **19ab** [a]

Entry	Acid	Solvent	Time (h)	Yield[b] (%)
1	PTSA	Toluene	8	31
2	PTSA	DCM	8	14
3	PTSA	$MeNO_2$	8	35
4	PTSA	Dioxane	8	n.d.
5	PTSA	THF	8	n.d.
6	PTSA	DMSO	8	n.d.
7	PTSA	DMF	8	n.d.
8	PTSA	MeOH	8	49
9	PTSA	MeCN	8	65
10	PTSA	MeCN	8	39
11	PTSA	MeCN	8	53
12	$Cu(OTf)_2$	MeCN	8	84
13	**$Cu(OTf)_2$**	**MeCN**	**12**	**95**
14	$Cu(OTf)_2$	MeCN	12	96
15	$Cu(OTf)_2$	MeCN	12	64
16	$Zn(OTf)_2$	MeCN	12	n.d.
17	$BF_3{\cdot}OEt_2$	MeCN	12	10
18	$Yb(OTf)_3$	MeCN	12	n.d.
19	$Bi(OTf)_3$	MeCN	12	28

20	$FeCl_3$	MeCN	12	traces
21	$AlCl_3$	MeCN	12	n.d.
22	TfOH	MeCN	12	42
23	-	MeCN	12	n.d.

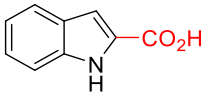
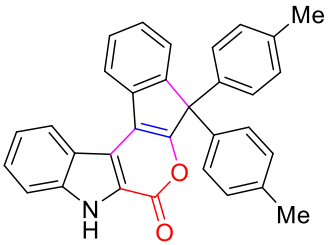
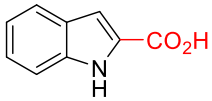
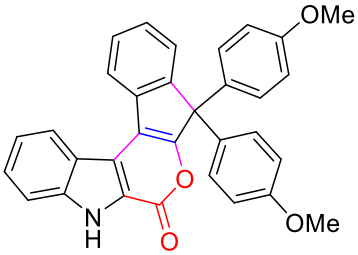
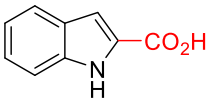
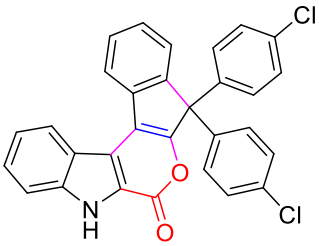
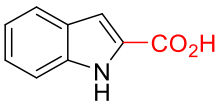
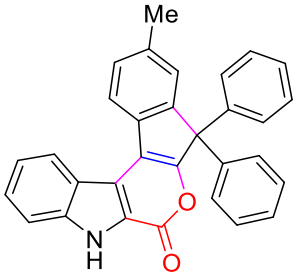
[a)] Reaction conditions: **2a** (0.62 mmol), **4b** (0.62 mmol), and acid (1.0 equiv for entries 1-10, 17 and 20-22; 2.0 equiv for entry 11; 10 mol% for entries 12, 13, 16, 18 and 19; 20 mol% for entry 14; 5 mol% for entry 15 in solvent (2.0 mL) at temperature (25 °C for entries 1-9 and 11-23; 80 °C for entry 10). [b)] Isolated yield.

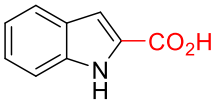
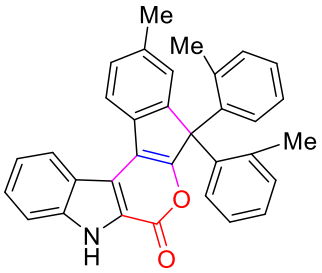
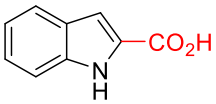
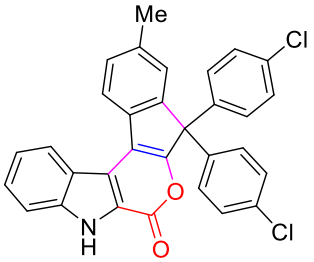
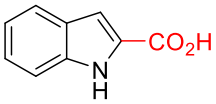
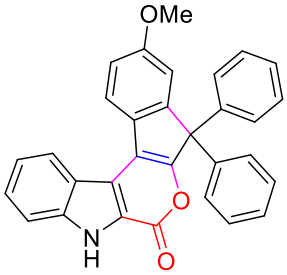
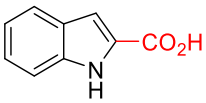
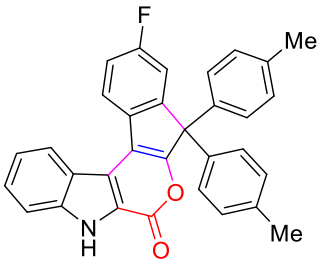
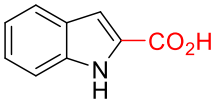
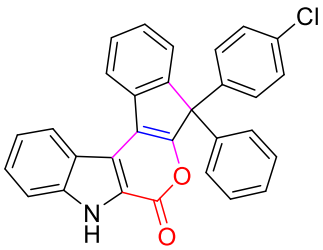
Using the established optimized reaction conditions, we checked the generality of the developed methodology by using indole-2-carboxylic acids **2a-b** and various substituted propargylic alcohols. In almost all the cases, the reaction progressed well and afforded the final fused pentacyclic products **19ab-19bb** in good to excellent yields (Table 6). It is noteworthy to mention that the *ortho*-di-substituted propargylic alcohol **4g** also reacted nicely without any steric problem and afforded the final product **19ag** in 79% yield. Other symmetrical propargylic alcohols like **4h**, **4i** and **4k** also worked well to give the final products **19ah-19ak** in excellent yields (76-92%). Use of unsymmetrical or electron withdrawing group containing propargylic alcohols **4m** and **4o-q** also gave very good yields 84-92% of the fused pentacyclics **19am** and **19ao-19aq**. 5-Methoxy-indole-2-carboxylic acid **2b** upon reaction with propargylic alcohol **4b** afforded the product **19bb** in 85% yield. The structures of **19ap** and **19bb** were further confirmed by the X-ray crystallography (Figure 3).

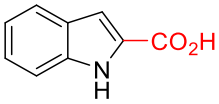
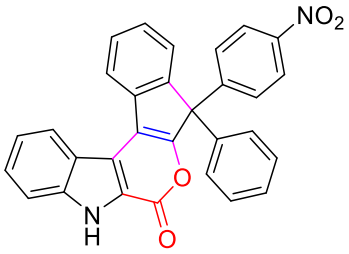
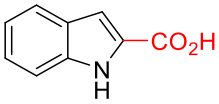
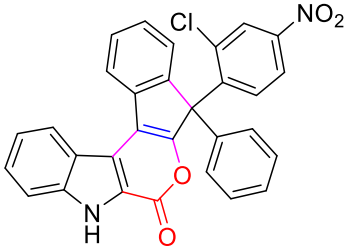
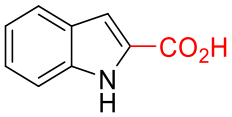
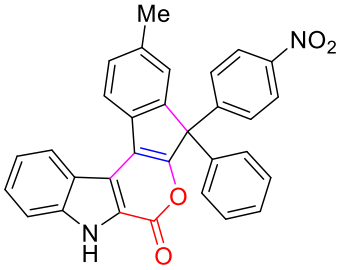
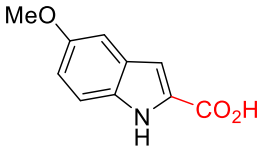
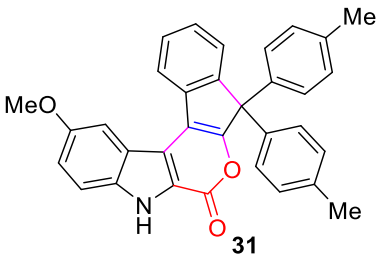


Scheme 9. Synthesis of indene fused pyrano-indolones (fused pentacyclics)

Table 6. Substrate scope for the fused pentacyclics **19**[a]

Entry	Indole-2-carboxylic acid	Propargylic alcohol	Fused pentacyclic	Yield[b] (%)
1	 **2a**	**4b**	 **19ab**	95
2	 **2a**	**4c**	 **19ac**	91
3	 **2a**	**4e**	 **19ae**	88
4	 **2a**	**4f**	 **19af**	93

5	 **2a**	**4g**	 **19ag**	79
6	 **2a**	**4h**	 **19ah**	90
8	 **2a**	**4i**	 **19ai**	76
7	 **2a**	**4k**	 **19ak**	92
9	 **2a**	**4m**	 **19am**	89

10	 **2a**	**4o**	 **19ao**	84
12	 **2a**	**4p**	 **19ap (X-ray)**	92
11	 **2a**	**4q**	 **19aq**	86
13	 **2b**	**4b**	 **19bb (X-ray)**	85

[a]Indole-2-carboxylic acid (**2a-b**, 0.62 mmol), propargylic alcohol (**4**, 0.62 mmol) and $Cu(OTf)_2$ (10 mol%) in MeCN (2 mL) at room temperature (25 °C) for 12 h. [b]Isolated yields.

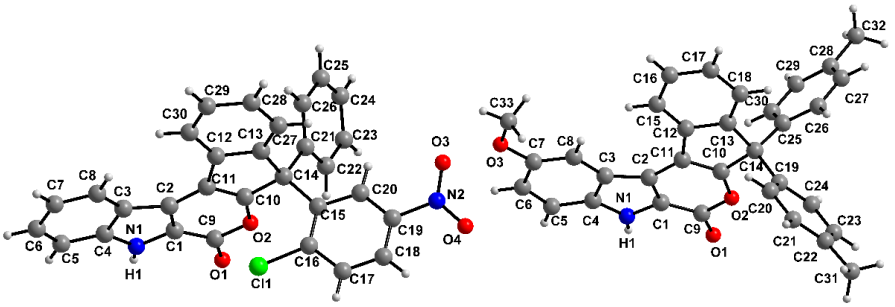
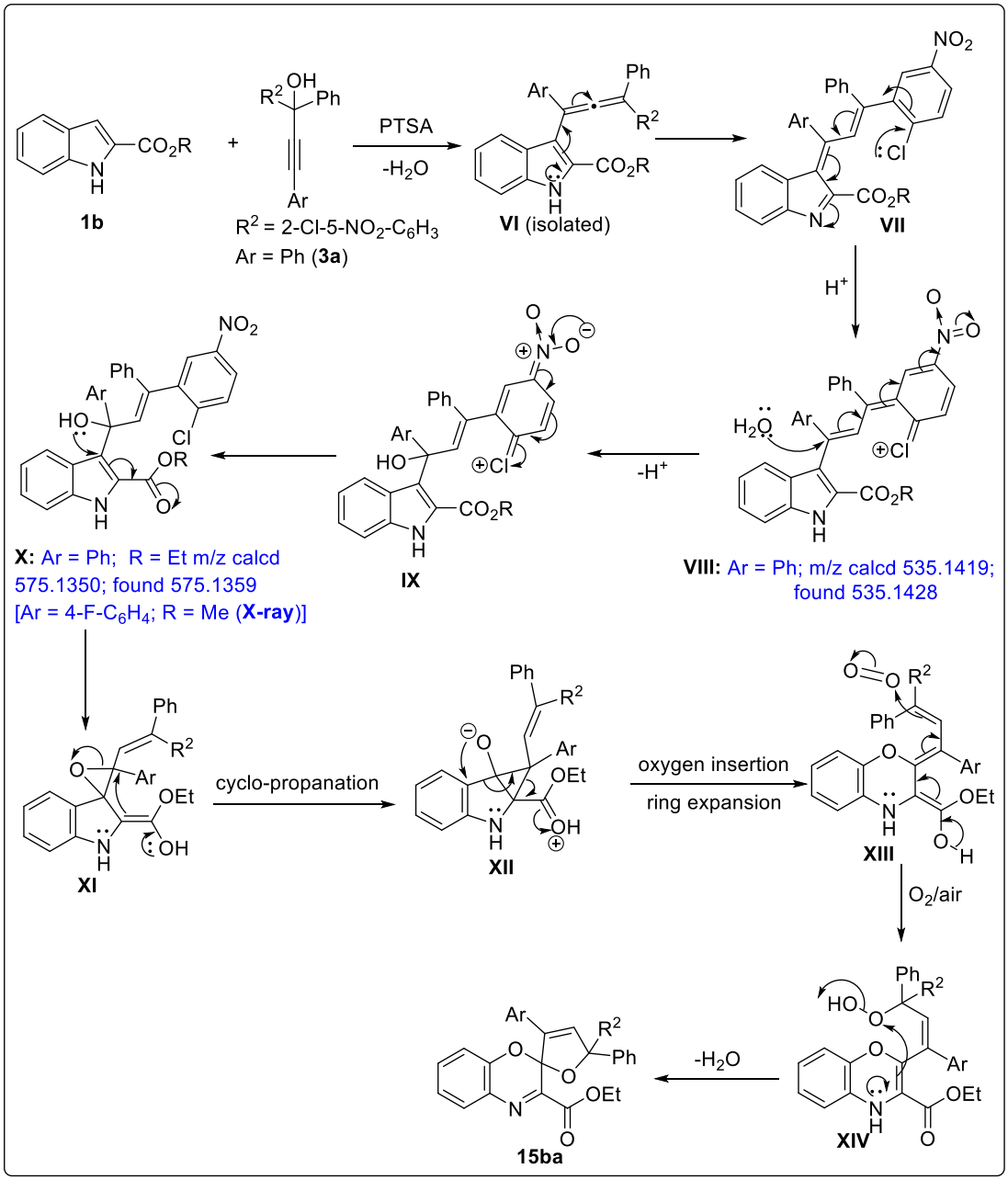


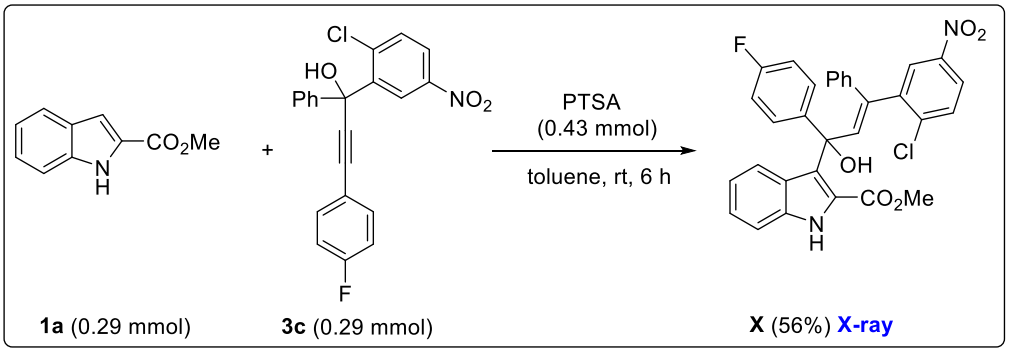
Figure 3: Molecular structures of compounds **19ap** (left) and **19bb** (right). Selected bond lengths in [Å] with esds in parenthesis: Compound **19ap**: C(1)-C(2) 1.397(5), C(2)-C(11) 1.412(5), C(11)-C(10) 1.342(5), C(10)-O(2) 1.366(5), O(2)-C(9) 1.379(6), C(9)-C(1) 1.418(6), C(9)-O(1) 1.225(5), C(11)-C(12) 1.484(7), C(12)-C(13) 1.409(8), C(13)-C(14) 1.529(6), C(14)-C(10) 1.503(6), C(10)-C(11) 1.342(5), C(1)-N(1) 1.356(5), C(2)-C(3) 1.460(6), C(12)-C(30) 1.369(6), C(13)-C(27) 1.353(8), C(14)-C(21) 1.560(7), C(14)-C(15) 1.552(7). Compound **19bb**: C(1)-C(2) 1.394(4), C(2)-C(11) 1.437(4), C(11)-C(10) 1.358(5), C(10)-(O2) 1.368(3), O(2)-C(9) 1.374(4), C(9)-C(1) 1.412(5), C(9)-O(1) 1.220(4), C(11)-C(12) 1.472(4), C(12)-C(13) 1.411(4), C(13)-C(14)-1.528(4), C(14)-C(10)-1.509(4), C(1)-N(1) 1.372(4), C(2)-C(3) 1.440(4), C(12)-C(15) 1.381(4), C(13)-C(18) 1.378(4), C(14)-C(19) 1.548(4), C(14)-C(25) 1.531(4),

Based on literature reports[104,105] and our own observations, we propose a plausible pathway for the formation of spirocyclic compounds **15ba** in Scheme 10. Initially, the indole ester undergoes allenation to give 3-allenyl indole ester **VI** [isolated (cf. compounds **18aa-18db**) and identified in the reaction mixture]; this intermediate upon isomerization followed by oxa-Michael addition (adventitious water addition) delivers **IX** (*via* **VII-VIII**), which rearranges to give the intermediate **X** [cf. Scheme 11; HRMS and X-ray evidence (Figure 4)]. It is noteworthy to mention that the intermediates **III-IV** are not possible in the case of electron donating as well as unsubstituted propargylic alcohols. Hence, we observed dearomative ring expanded spirocyclization only with chloro- and nitro- substituted precursors. Another possibility to get the intermediate **X** is the reaction of indole ester with Meyer-Schuster rearranged unsaturated ketone but this did not work. Intermediate **X** {$[M+Na]^+$ 575.1359} upon intramolecular cyclization gives epoxy-intermediate **XI** that undergoes epoxide ring opening followed by cyclopropanation giving the intermediate **XII**. Ring expansion with oxygen insertion *via* cyclopropane ring opening gives intermediate **XIII**.[104] Species **XIII** reacts

with adventitious molecular oxygen (aerobic) to give peroxide intermediate **XIV** that undergoes water elimination *via* peroxide bond (known to be weak) breakage and gives the final product **15ba**.[105]



Scheme 10. Plausible pathway for the formation of spirocyclic compounds of type **15ba**



Scheme 11. Synthesis of intermediate **X**

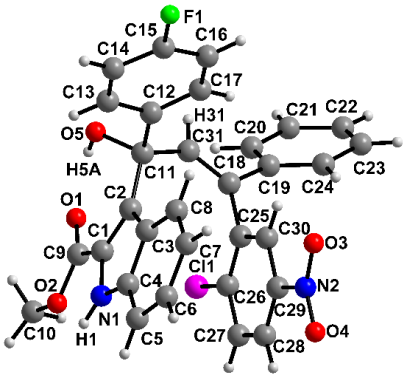
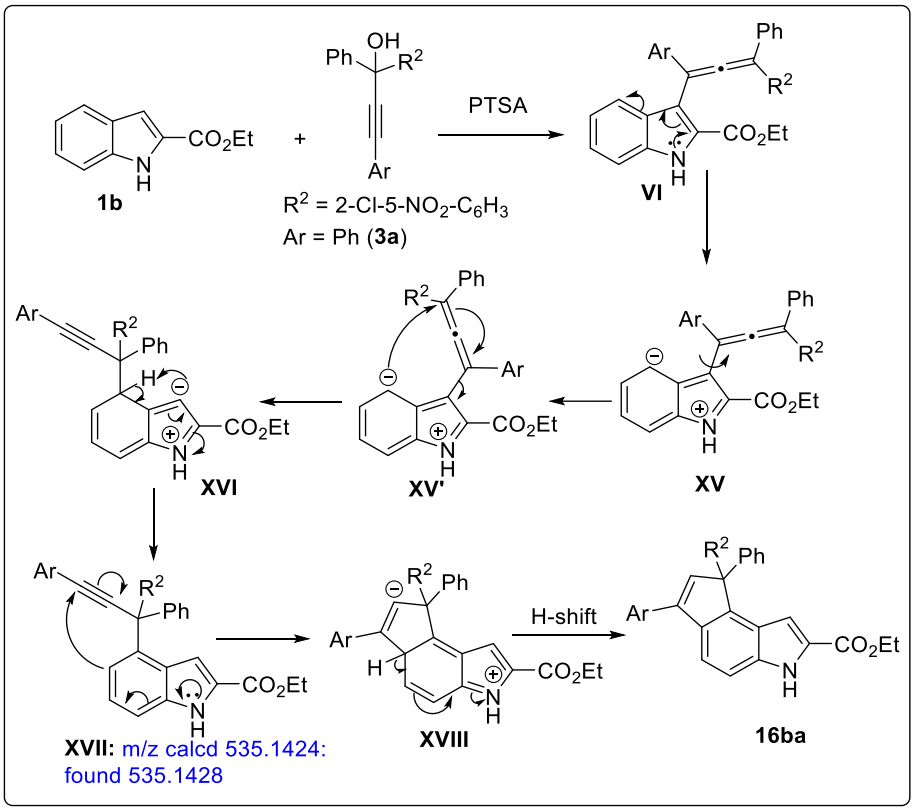


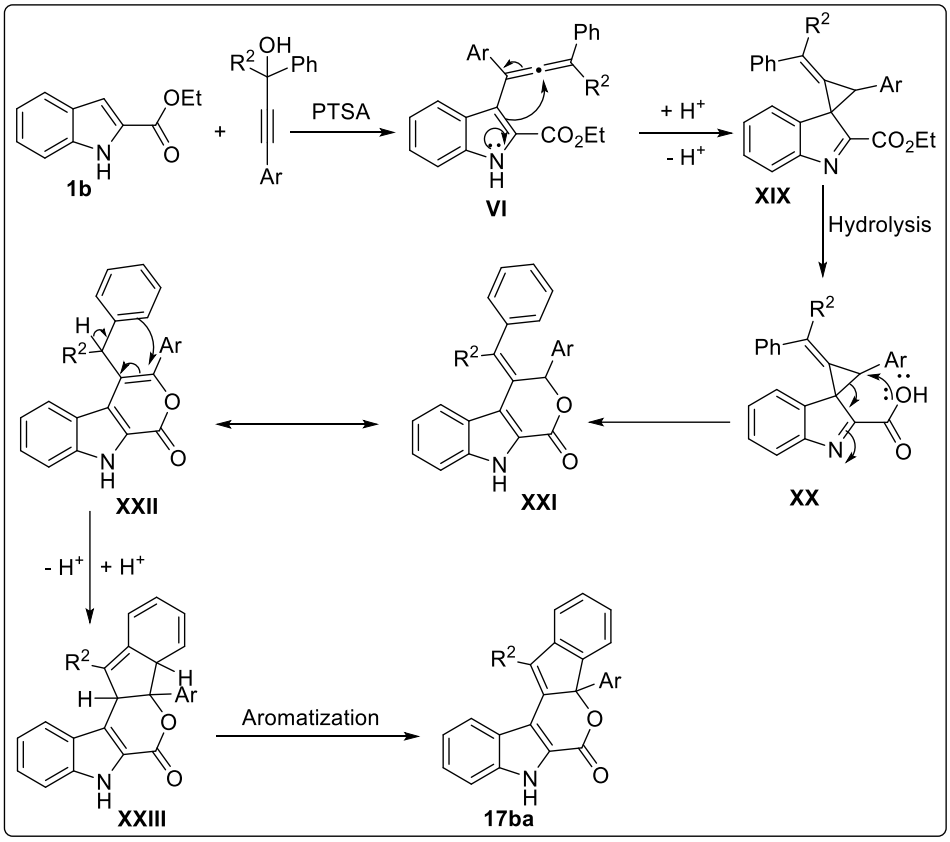
Figure 4: Molecular structure of intermediate **X**. Selected bond lengths in [Å] with esds in parenthesis: C(2)-C(11) 1.525(6), C(11)-O(5) 1.455(5), O(5)-H(5A) 0.821(3), C(11)-C(31) 1.497(7), C(31)-C(18) 1.319(6), C(31)-H(31) 0.929(4), C(1)-C(2) 1.389(6), C(11)-C(12) 1.532(6), C(18)-C(19) 1.507(7), C(18)-C(25) 1.497(6).

A plausible pathway for the formation of dihydrocyclopenta[*e*]indole-2-carboxylate **16ba** is shown in Scheme 12. As we already discussed, initially, indole ester undergoes allenation to give 3-allenyl indole ester V**I**. This intermediate undergoes sequential intramolecular rearrangement to give **XVI** (*via* **XV'**). Intermediate **XVI** rearranges to give **XVII** (HRMS evidence) which upon intramolecular cyclization gives the final product **16ba** *via* **XVIII**.



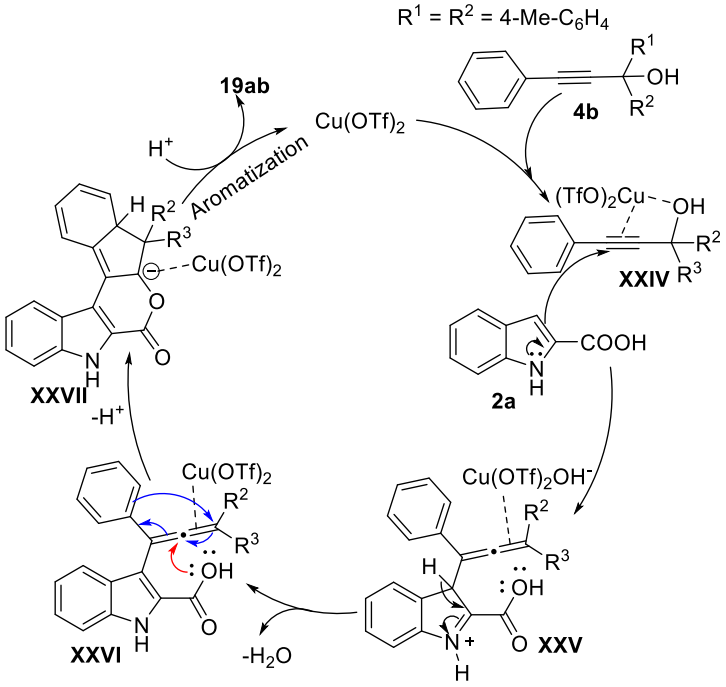
Scheme 12. Plausible pathway for the formation of **16ba**

Formation of compounds of type **17ba (**Scheme 13) involves allenation to give 3-allenyl indole ester **VI**. This intermediate undergoes cyclopropanation to afford **XIX** which upon ester hydrolysis gives **XX**. This intermediate undergoes intramolecular cyclization involving carboxylic acid *via* cyclopropane ring opening to furnish **XXI** which rearranges to give intermediate **XXII**. Species **XXII** upon intramolecular cyclization followed by aromatization affords the final product **17ba**.



Scheme 13. A plausible pathway for the formation of compounds of type **17**

In the formation of compound **19ab** (Scheme 14),[106] propargylic alcohol co-ordinates to $Cu(OTf)_2$ to give **XXIV** and makes the carbon center more electrophilic, which facilitates the indole carboxylic acid addition to propargylic alcohol. Thus, intermediate **XXIV** undergoes addition with indole carboxylic acid to give **XXV**, which upon dehydration gives intermediate **XXVI**. Intermediate **XXVI** undergoes intramolecular cyclization to give **XXVII**, which upon protonation followed by aromatization gives the cyclized product **19ab** and regenerates $Cu(OTf)_2$ for the next catalytic cycle.



Scheme 14. Plausible catalytic pathway for the formation of compound **19ab**

2.3 Decarboxylative annulations of coumarin-3-carboxylic acids with *tert*-propargylic alcohols under Cu (II)-catalysis: Formation of naphthochromenones

In continuation of the previous section, we envisioned that instead of indole carboxylic acids, use of other carboxylic acids may lead to a different line of reactivity. For this purpose, we chose chromene/coumarin carboxylic acids both of which have a double bond in conjugation with the phenyl ring. Coumarin and its derivatives are naturally abundant and pharmaceutically important;[12] they can be synthesized readily by using simple starting materials. To our knowledge, there is no significant report on the annulation reactions of chromene/coumarin-3-carboxylic acids with propargylic alcohols. Keeping this in mind, we treated propargylic alcohol **4a** (1 equiv) with coumarin-3-carboxylic acid **5a** (1 equiv) in the presence of $Cu(OAc)_2 \cdot H_2O$ (1 equiv) and $AgSbF_6$ (additive; 0.3 equiv, 30 mol%) in 1,4-dioxane at 100 ^oC for 24 h (Table 7, entry 1). To our delight, we isolated the decarboxylative annulation product **20aa** in 41% yield. Encouraged by this positive outcome, we extended our investigations to enhance the yield of **20aa**. When we increased the temperature to 120 ^oC, there was an increase in the yield (55%; entry 2); a slightly better yield of 58% was obtained when the reaction time was reduced to 12 h (entry 3). When the $Cu(OAc)_2$ loading was reduced

to 0.3 equiv, we observed 60% yield of **20aa** (entry 4). Additives/catalysts like AgOAc and $AgNO_3$ were ineffective (entries 5-6). The additive/catalyst $Ag(O_2CCF_3)$ gave 56% yield (entry 7); $AgBF_4$ (0.3 equiv) also worked well and afforded the final product in 61% yield (entry 8). In place of 1,4-dioxane, use of other solvents like toluene, xylene, $MeNO_2$ and DMF did not improve the yield (entries 9-12). Better results were observed when the catalyst was changed to $Cu(OTf)_2$ along with $AgBF_4$ affording **20aa** (75%; entry 13). Use of 20 mol% of the $AgBF_4$ along with $Cu(OTf)_2$ also gave 79% of the product (entry 14). $AgSbF_6$ and $Ag(O_2CCF_3)$ along with $Cu(OTf)_2$ afforded **20aa** in 82% and 77% of yields respectively (entries 15-16). To our surprise, use of 20 mol% of the $Cu(OTf)_2$ alone in 1,4-dioxane solvent at 120 ^oC for 12 h worked very well and gave an excellent yield of the annulated product **20aa** (89%; entry 17). A marginally lower yield of 83% was observed using $Cu(OTf)_2$ when the reaction time was reduced to 8 h (entry 18). $AgBF_4$ also proved to be viable for the conversion but comparatively lower yield 72% of **20aa** was observed (entry 19). When we employed other Lewis acid catalysts like $Zn(OTf)_2$, $Yb(OTf)_3$, $In(OTf)_3$, NaOTf and AgOTf, the yield was much lower or the product was not formed (entries 20-24). Thus, the conditions used in entry 17 were the best for the formation of the decarboxylative annulated product **20aa**.

Table 7. Optimization study of Cu(II)-catalyzed decarboxylative annulation reaction between **4a** and **5a** for the formation of naphthochromenone **20aa**[a]

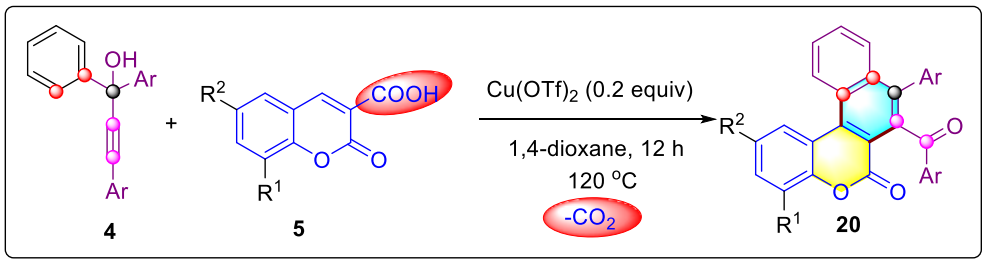
Entry	Catalyst (equiv)	Additive (equiv)	Solvent	Temp (^oC)	Time (h)	Yield[b] (%)
1	$Cu(OAc)_2 \cdot H_2O$ (1.0)	$AgSbF_6$ (0.3)	1,4-dioxane	100	24	41
2	$Cu(OAc)_2 \cdot H_2O$ (1.0)	$AgSbF_6$ (0.3)	1,4-dioxane	120	24	55
3	$Cu(OAc)_2 \cdot H_2O$ (1.0)	$AgSbF_6$ (0.3)	1,4-dioxane	120	12	58
4	$Cu(OAc)_2 \cdot H_2O$ (0.3)	$AgSbF_6$ (0.3)	1,4-dioxane	120	12	60
5	$Cu(OAc)_2 \cdot H_2O$ (0.3)	AgOAc (0.3)	1,4-dioxane	120	12	n.r.
6	$Cu(OAc)_2 \cdot H_2O$ (0.3)	$AgNO_3$ (0.3)	1,4-dioxane	120	12	n.r.
7	$Cu(OAc)_2 \cdot H_2O$ (0.3)	CF_3COOAg (0.3)	1,4-dioxane	120	12	56

8	$Cu(OAc)_2 \cdot H_2O$ (0.3)	$AgBF_4$ (0.3)	1,4-dioxane	120	12	61
9	$Cu(OAc)_2 \cdot H_2O$ (0.3)	$AgSbF_6$ (0.3)	toluene	120	12	31
10	$Cu(OAc)_2 \cdot H_2O$ (0.3)	$AgSbF_6$ (0.3)	xylene	120	12	47
11	$Cu(OAc)_2 \cdot H_2O$ (0.3)	$AgSbF_6$ (0.3)	$MeNO_2$	120	12	n.d.
12	$Cu(OAc)_2 \cdot H_2O$ (0.3)	$AgSbF_6$ (0.3)	DMF	120	12	n.d.
13	$Cu(OTf)_2$ (0.3)	$AgBF_4$ (0.3)	1,4-dioxane	120	12	75
14	$Cu(OTf)_2$ (0.3)	$AgBF_4$ (0.2)	1,4-dioxane	120	12	79
15	$Cu(OTf)_2$ (0.2)	$AgSbF_6$ (0.2)	1,4-dioxane	120	12	82
16	$Cu(OTf)_2$ (0.2)	CF_3COOAg (0.2)	1,4-dioxane	120	12	77
17	**$Cu(OTf)_2$ (0.2)**	**-**	**1,4-dioxane**	**120**	**12**	**89**
18	$Cu(OTf)_2$ (0.2)	-	1,4-dioxane	120	8	83
19	-	$AgBF_4$ (0.3)	1,4-dioxane	120	12	72
20	$Zn(OTf)_2$ (0.2)	-	1,4-dioxane	120	12	n.d.
21	$Yb(OTf)_3$ (0.2)	-	1,4-dioxane	120	12	n.d.
22	$In(OTf)_3$ (0.2)	-	1,4-dioxane	120	12	trace
23	NaOTf (0.2)	-	1,4-dioxane	120	12	20
24	AgOTf	-	1,4-dioxane	120	12	48

[a)] Coumarin-3-carboxylic acid **5a** (0.53 mmol), propargylic alcohol **4a** (0.53 mmol), solvent (2 mL), temp (^oC), time (h), [b)] Isolated yield.

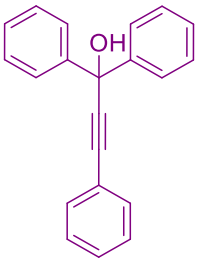
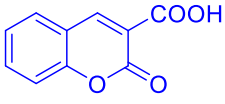
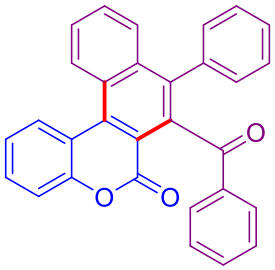
For the substrate scope, we have utilized a variety of acids and alcohols under the optimized conditions. In all the cases we obtained good to excellent yields of the annulated products **20aa-20le/20le'**. Symmetrical propargylic alcohols having substitution on phenyl rings (with -Me, -OMe, -F and -Cl) both at propargylic as well as alkynic ends of the propargylic alcohols

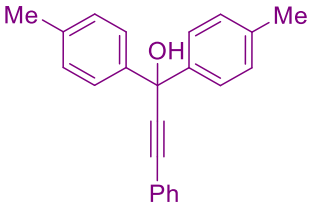
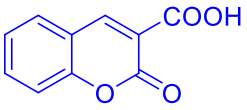
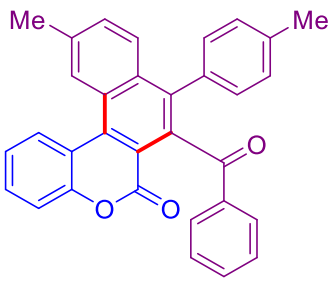
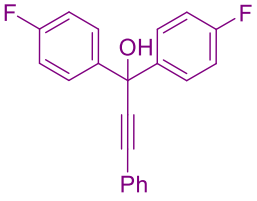
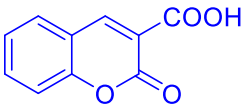
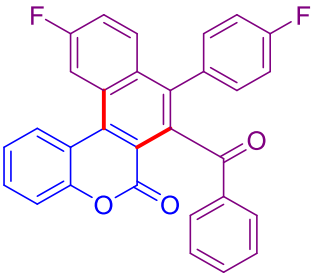
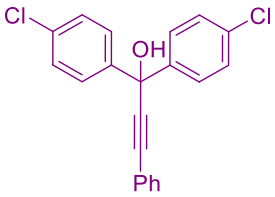
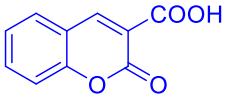
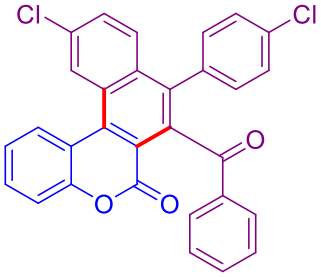
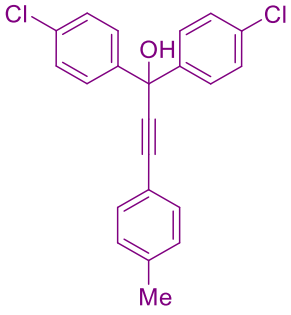
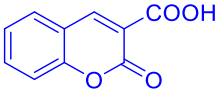
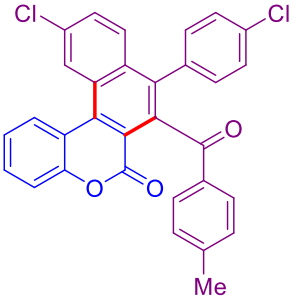
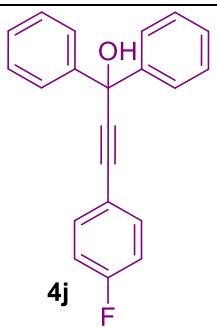
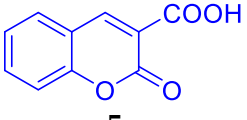
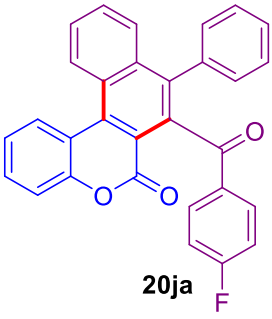
worked well and delivered the annulated products in good to excellent yields. The unsymmetrical propargylic alcohols like **4l**, **4m** and **4n** afforded isomeric products (cf. **20ld/20ld'**, **20ma/ 20ma'**, **20na/20na'**) as expected with no specific preference to either of the isomers. We then checked the substituted (-OMe, -OEt) coumarin-3-carboxylic acids **5b** and **5c**; in these cases also, we obtained the final products in excellent yields. It is noteworthy to mention that the *bromo* (or) *dichloro* substituted coumarin-3-carboxylic acids **5d** and **5e** also worked very well with symmetrical as well as unsymmetrical propargylic alcohols and afforded the products **20ad**-**20le'** in excellent yields. The structures of **20aa** and **20de** were confirmed by the X-ray crystallography (Figure 5).

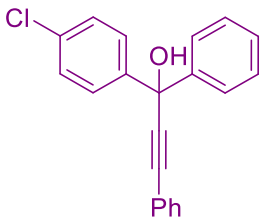
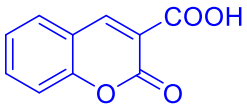
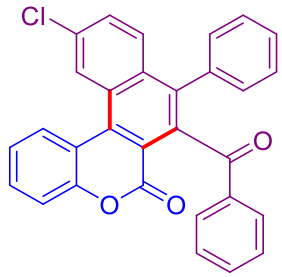
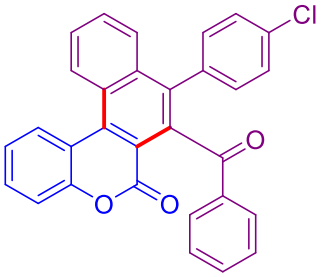
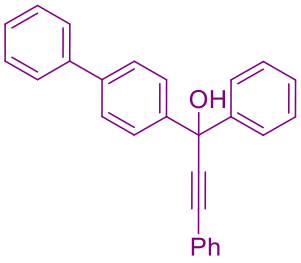
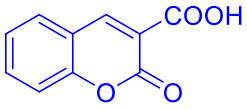
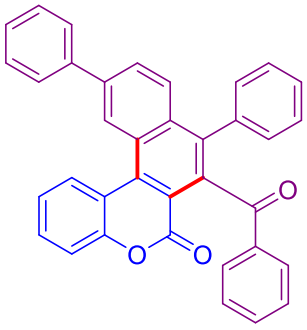
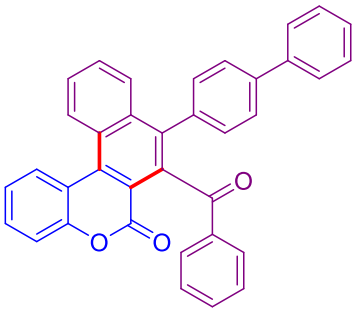
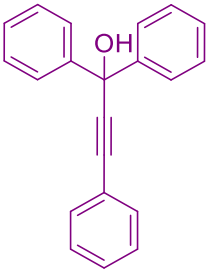
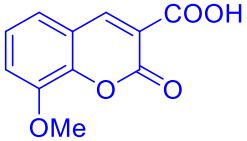
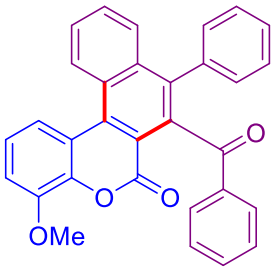


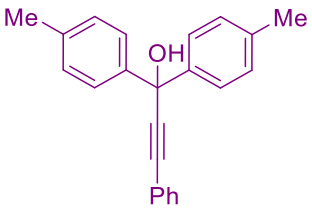
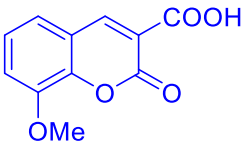
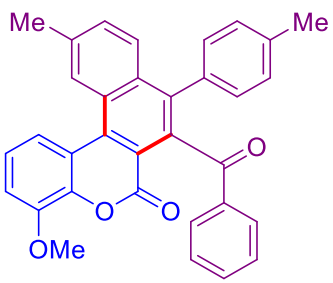
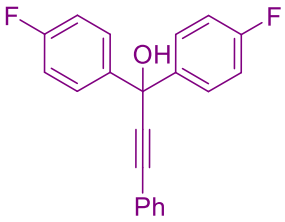
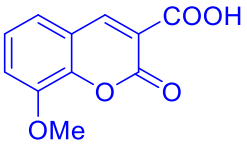
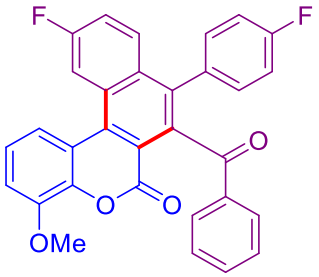
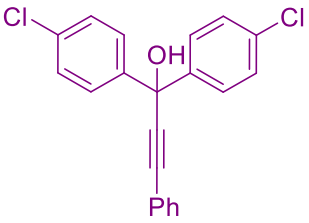
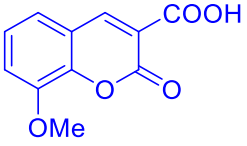
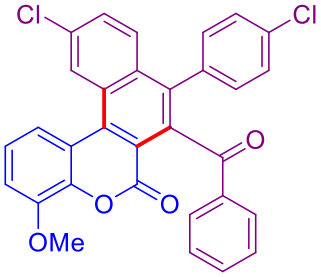
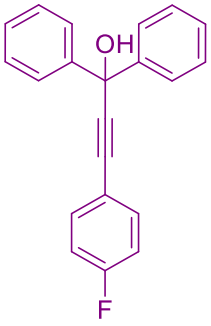
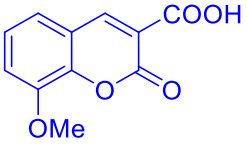
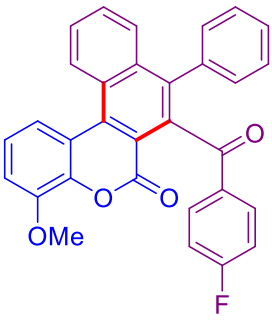
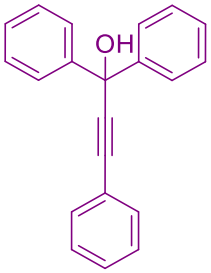
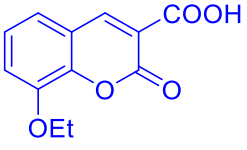
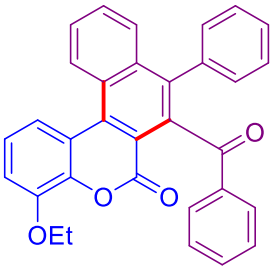
Scheme 15. Synthesis of 6*H*-naphtho[2,1-*c*]chromen-6-ones from coumarin-3-carboxylic acids and propargylic alcohols under Cu(II)-catalysis

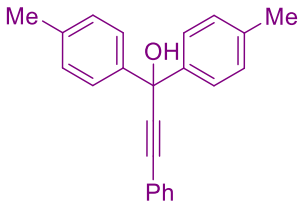
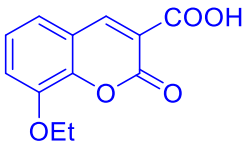
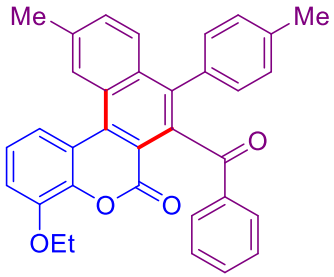
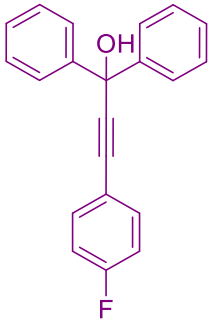
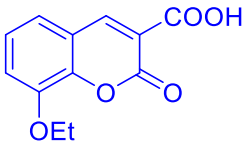
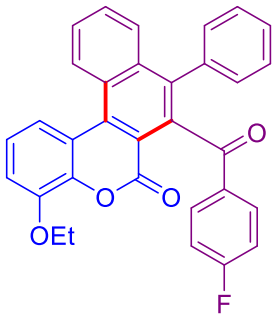
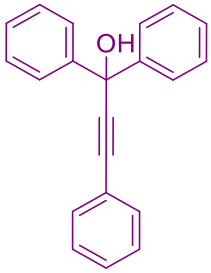
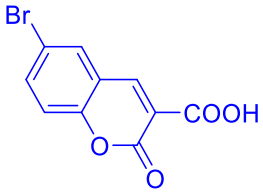
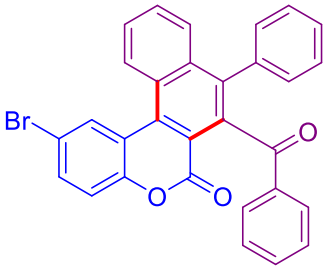
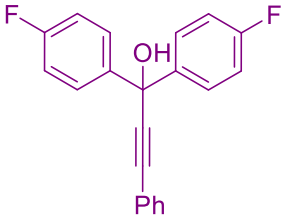
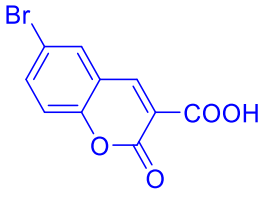
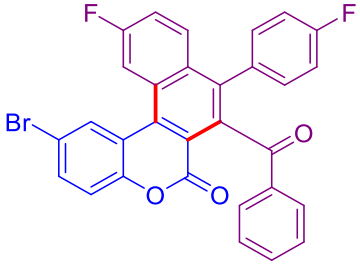
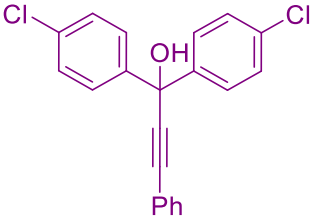
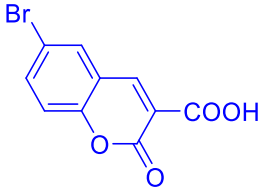
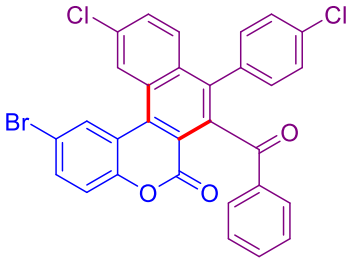
Table 8. Substrate scope for the 6*H*-naphtho[2,1-*c*]chromen-6-ones[a]

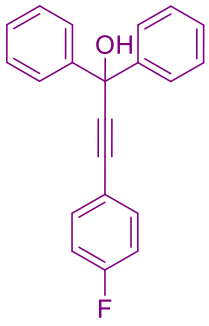
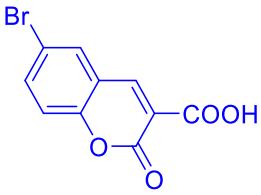
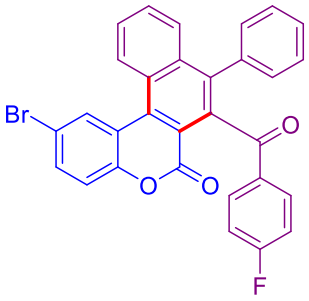
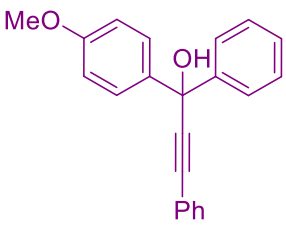
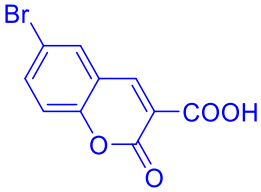
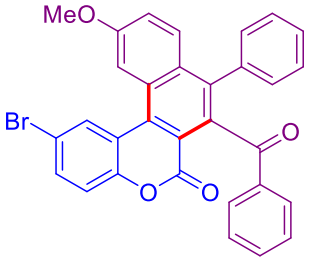
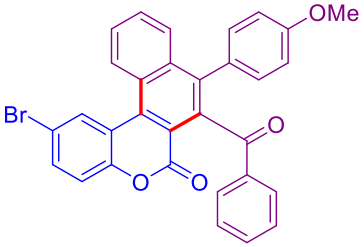
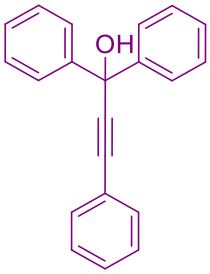
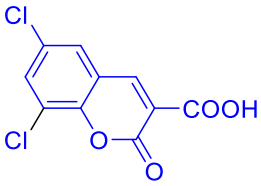
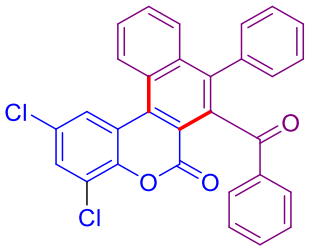
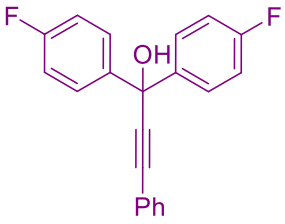
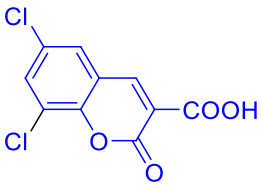
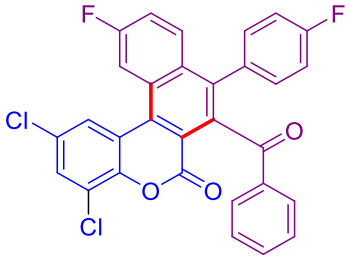
Entry	Propargylic alcohol	Carboxylic acid	6*H*-naphtho[2,1-*c*]chromen-6-one	Overall yield[b] (%)
1	 **4a**	 **5a**	 **20aa (X-ray)**	89

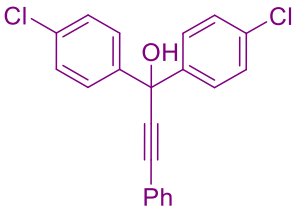
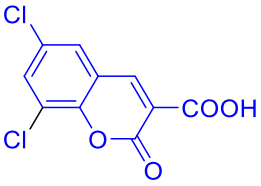
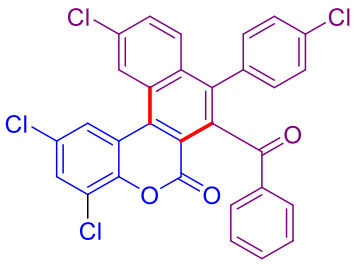
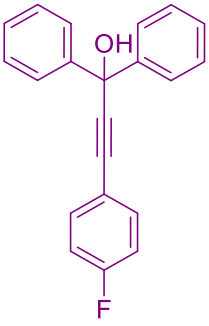
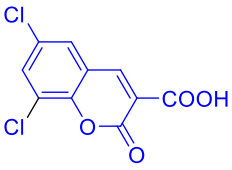
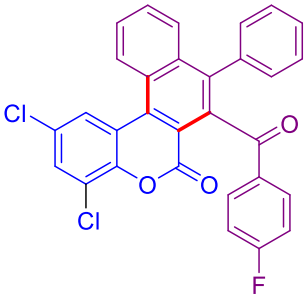
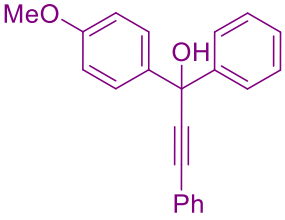
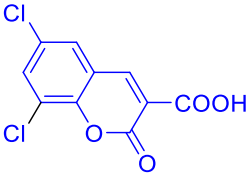
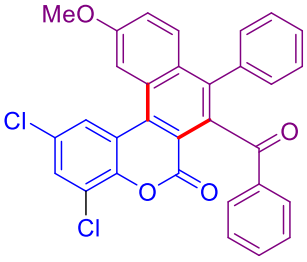
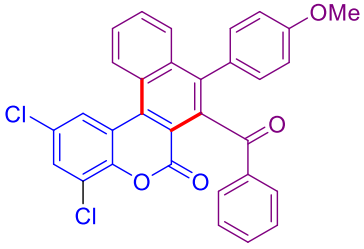
2	 **4b**	 **5a**	 **20ba**	86
3	 **4d**	 **5a**	 **20da**	78
4	 **4e**	 **5a**	 **20ea**	83
7	 **4h**	 **5a**	 **20ha**	76
8	 **4j**	 **5a**	 **20ja**	79

5	 **4m**	 **5a**	 **20ma**  **20ma'**	85
6	 **4n**	 **5a**	 **20na**  **20na'**	87
9	 **4a**	 **5b**	 **20ab**	76

10	 **4b**	 **5b**	 **20bb**	78
11	 **4d**	 **5b**	 **20db**	73
12	 **4e**	 **5b**	 **20eb**	71
13	 **4j**	 **5b**	 **20jb**	80
14	 **4a**	 **5c**	 **20ac**	81

15	 **4b**	 **5c**	 **20bc**	84
16	 **4j**	 **5c**	 **20jc**	76
17	 **4a**	 **5d**	 **20ad**	71
18	 **4d**	 **5d**	 **20dd**	73
19	 **4e**	 **5d**	 **20ed**	77

20	 **4j**	 **5d**	 **20jd**	75
21	 **4l**	 **5d**	 **20ld**  **20ld'**	87
22	 **4a**	 **5e**	 **20ae**	86
23	 **4d**	 **5e**	 **20de (X-ray)**	75

24	 **4e**	 **5e**	 **20ee**	82
25	 **4j**	 **5e**	 **20je**	79
26	 **4l**	 **5e**	 **20le**  **20le'**	86

[a)] Coumarin-3-carboxylic acid **5** (1.0 equiv), propargylic alcohol **4a** (1.0 equiv), $Cu(OTf)_2$ (20 mol%) 1,4-dioxane (2 ml), 120 ^oC (oil bath temperature), 12 h, [b)] Isolated yield.

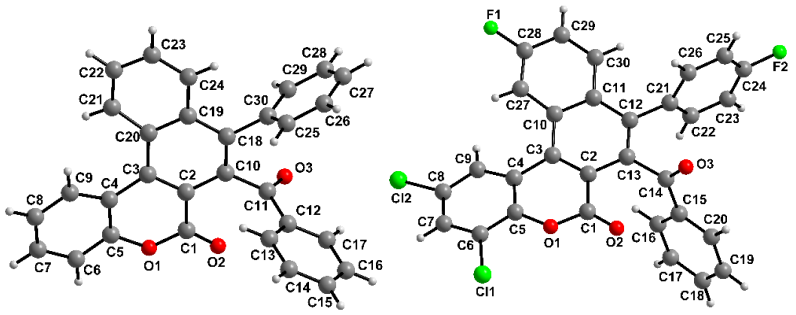
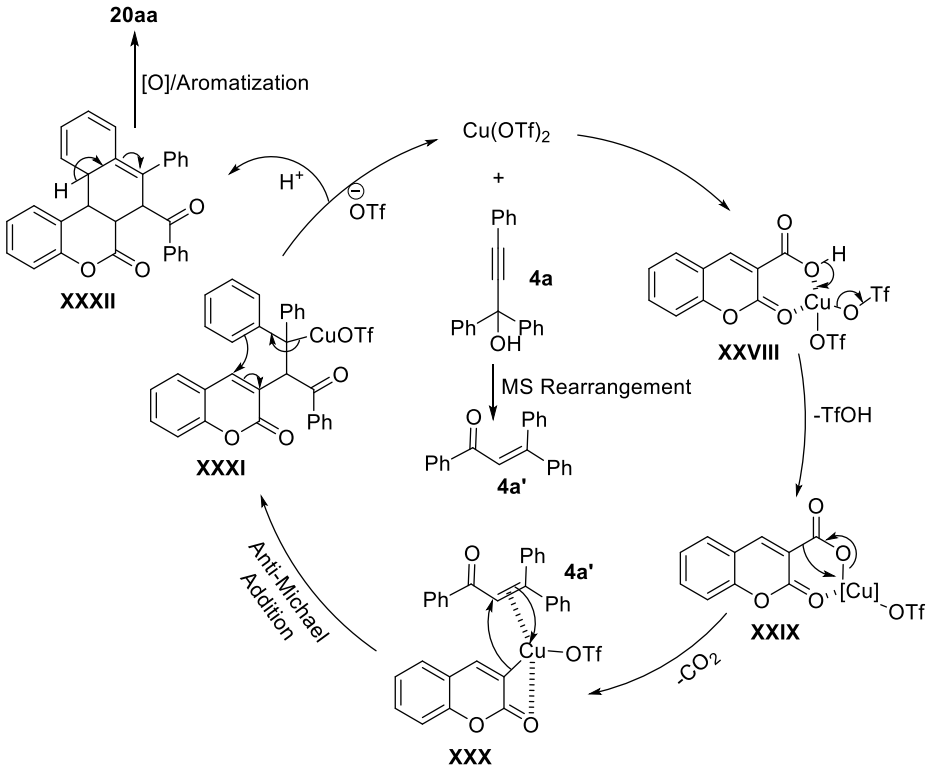


Figure 5: Molecular structures of compounds **20aa** (left) and **20de** (right). Selected bond lengths in [Å] with esds are given in parentheses. Compound **20aa**: C(2)-C(3) 1.392(2), C(3)-C(20) 1.440(3), C(20)-C(19) 1.412(3), C(19)-C(18) 1.435(3), C(18)-C(10) 1.363(3), C(2)-C(10) 1.421(3), C(2)-C(1) 1.468(3), C(1)-O(2) 1.198(2), C(3)-C(4) 1.464(3), C(20)-C(21) 1.419(2), C(19)-C(24) 1.411(3), C(10)-C(11) 1.511(3), C(11)-O(3) 1.213(2), C(12)-C(11) 1.476(3): Compound **20de**: C(2)-C(3) 1.379(7), C(3)-C(10) 1.456(6), C(10)-C(11) 1.433(7), C(11)-C(12) 1.428(7), C(12)-C(13) 1.370(6), C(13)-C(2) 1.433(7), C(2)-C(1).481(6), C(1)-O(2) 1.194(6), C(3)-C(4) 1.485(6), C(10)-C(27) 1.400(7), C(11)-C(30) 1.438(6), C(12)-C(21) 1.486(7), C(13)-C(14) 1.524(7), C(14)-O(3) 1.218(5), C(14)-C(15) 1.483(7).

A plausible catalytic pathway based on literature reports and our own experimental studies for the formation of product **20aa** is depicted in Scheme 16.[107] Initially, the coumarin-3-carboxylic acid co-ordinates to $Cu(OTf)_2$ and gives the intermediate **XXVIII**, which upon triflic acid elimination gives species **XXIX**; this species **XXIX** undergoes decarboxylation to give intermediate **XXX**. Species **XXX** undergoes *anti*-Michael addition with *α,β* unsaturated carbonyl compound **4a'** (which is formed by the Meyer-Shuster rearrangement of the propargylic alcohol **4a**) gives intermediate **XXXI**. Intermediate **XXXI** upon intramolecular cyclization followed by aromatization gives the final product **20aa** (*via* **XXXII**).



Scheme 16. Plausible catalytic pathway for the formation of compound **20aa**

2.4.1 Ruthenium(II)-catalyzed oxidative [4+2] annulation of chromene and coumarin-3-carboxylic acids with alkynes *via* C(sp^2)-H bond activation

In continuation of the above studies, we wanted to check the reactivity of chromene/coumarin-3-carboxylic acids with alkynes instead of propargylic alcohols. To begin with, we treated 2*H*-chromene-3-carboxylic acid **6a** (0.57 mmol) with diphenylacetylene **7a** (0.57 mmol) in the presence of $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol%) as catalyst, $Cu(OAc)_2 \cdot H_2O$ (30 mol%) as the oxidant and $AgSbF_6$ (10 mol%) as the additive in DCE solvent at 80 ^oC for 14 h. As expected, we obtained the desired annulated product **21aa** in moderate yield of 48% (Table 9 entry 1). Increasing the temperature to 100 ^oC increased the yield of **21aa** to 56% (entry 2); use of anhydrous $Cu(OAc)_2$ decreased the yield to 35% (entry 3). We have also used other solvents like MeOH, *t*-AmOH, CH_3CN, THF, xylene, PEG-400 and 1,4-dioxane (entries 4-10 at mentioned temperatures) for the reaction. A better yield of 76% was obtained when the solvent was 1,4-dioxane (entry 10); decreasing the temperature to 80 ^oC decreased the yield to 65% (entry 11). Increasing the reaction time to 20 h led to a very good yield of the final product **21aa** (88%; entry 12). There was a marginal increase in the yield (92%) by increasing the

catalyst loading to 5 mol% (entry 13). We have tested the additives AgOAc, KPF_6, AgOTf, $AgNTf_2$ and Ag_2CO_3; out of which $AgNTf_2$ and Ag_2CO_3 gave good yields of 74% and 53% of the final product respectively (entries 14-18). In the absence of the catalyst or oxidant, reaction failed to give the product, but without the additive reaction occurred and gave the final product in 43% yield (entries 19-21). Finally, we concluded that the conditions used in entry 12 were the best for the reaction, since we wanted to keep the catalyst loading lower than that in entry 13.

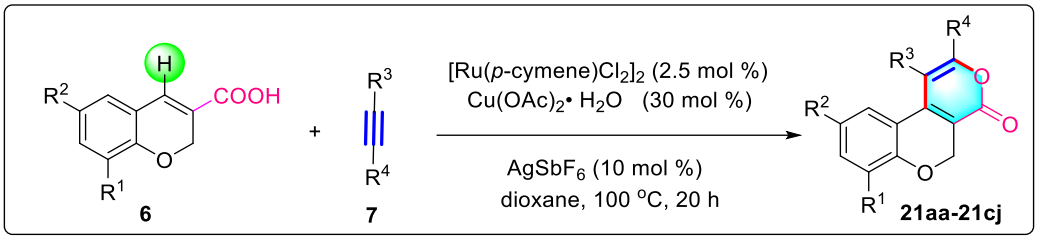
Table 9. Optimization study of Ru(II)-catalyzed annulation reaction between **6a** and **7a** for the formation of pryano chromenes **21aa**[a]

Entry	Catalyst	Oxidant	Additive	Solvent	Temp (^oC)	Yield[b] (%)
1	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	$AgSbF_6$	DCE	80	48
2	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	$AgSbF_6$	DCE	100	56
3	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2$	$AgSbF_6$	DCE	100	35
4	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	$AgSbF_6$	MeOH	80	trace
5	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	$AgSbF_6$	*t*-AmOH	100	25
6	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	$AgSbF_6$	CH_3CN	80	51
7	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	$AgSbF_6$	THF	80	trace
8	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	$AgSbF_6$	xylene	100	12
9	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	$AgSbF_6$	PEG-400	100	n.r.
10	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	$AgSbF_6$	dioxane	100	76
11	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	$AgSbF_6$	dioxane	80	65
12	**$[RuCl_2(p\text{-cymene})]_2$**	**$Cu(OAc)_2 \cdot H_2O$**	**$AgSbF_6$**	**dioxane**	**100**	**88**
13	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	$AgSbF_6$	dioxane	100	92[c]
14	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	AgOAc	dioxane	100	21

15	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	KPF_6	dioxane	100	31
16	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	AgOTf	dioxane	100	26
17	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	$AgNTf_2$	dioxane	100	74
18	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	Ag_2CO_3	dioxane	100	53
19	-	$Cu(OAc)_2 \cdot H_2O$	$AgSbF_6$	dioxane	100	n.d.
20	$[RuCl_2(p\text{-cymene})]_2$	-	$AgSbF_6$	dioxane	100	n.d.
21	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2 \cdot H_2O$	-	dioxane	100	43

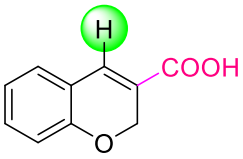
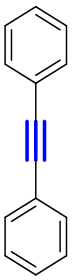
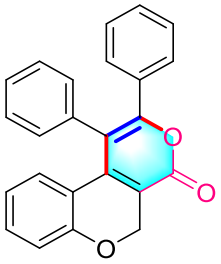
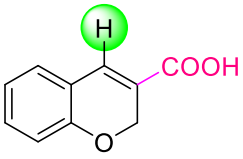
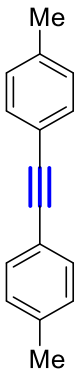
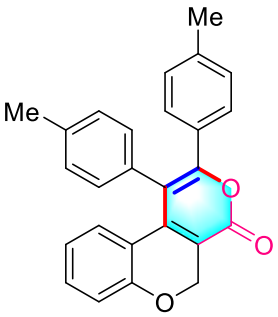
[a)] Chromene-3-carboxylic acid **6a** (0.57 mmol), diphenylacetylene **7a** (0.57 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), oxidant (30 mol %), additive (10 mol %), solvent (2 mL), temp ^oC (oil bath temperature). Reaction time: 14 h for entries 1-11 and 20 h for entries 12-21. [b)] Isolated yield, [c)] 5 mol% of the catalyst was used.

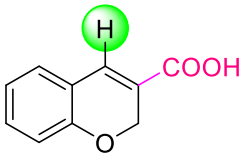
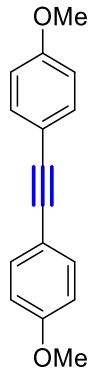
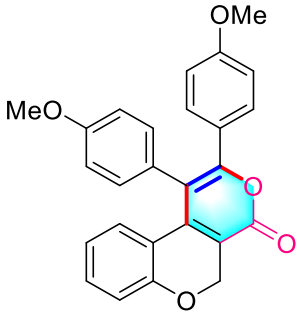
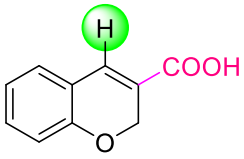
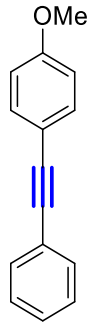
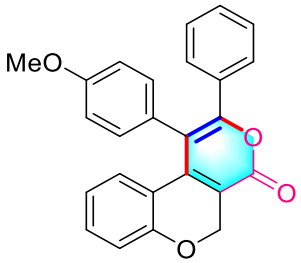
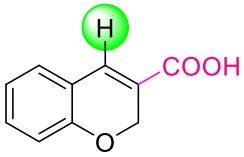
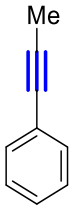
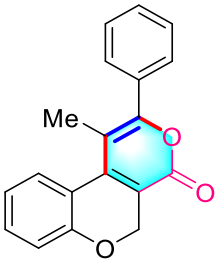
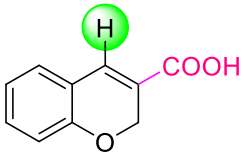
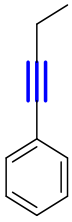
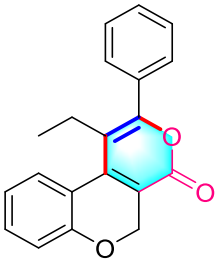
As shown in the Scheme 17 and Table 10, reaction of **6a** with **7a** under optimized conditions gave **21aa** in 88% yield. The structure of **21aa** was confirmed by X-ray crystallography (Figure 6). Various internal symmetrical (alkyl/alkyl or aryl/aryl; **7a-c**, **7h-7j**) and unsymmetrical alkynes (alkyl/aryl or aryl/aryl; **7d-7g**) worked very well and delivered the final products **21aa-21cj** in good to excellent yields. It is noteworthy that in the case of unsymmetrical alkyne **7d**, we observed excellent regioselectivity (cf. compound **21ad**); the other isomer was present (<10%) but could not be isolated. Reaction of **6a** with electron rich aryl alkynes **7a-c** worked nicely under the optimized conditions and afforded the products **21aa-21ac** in 70-88% yields. Unsymmetrical (alkyl/aryl) alkynes **7d-g** also reacted well with excellent regioselectivity and delivered the final products **21ad-21ag** in good yields. Dialkyl alkynes **7h-j** were also amenable for this reaction and reacted with **6a-b** delivering the products in good yields. The scope of this oxidative annulation reaction was extended to substituted chromene-3-carboxylic acids also. Thus 8-ethoxy-2*H*-chromene-3-carboxylic acid (**6b**) and 6-bromo-8-methoxy-2*H*-chromene-3-carboxylic acid (**6c**) upon treatment with alkyne partners afforded the final products **21ba-21cj** in good yields.

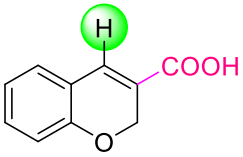
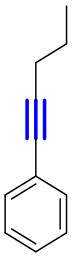
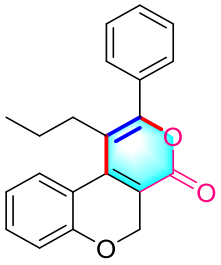
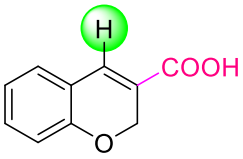
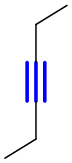
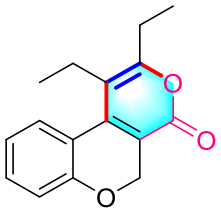
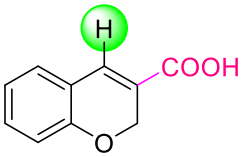
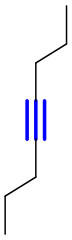
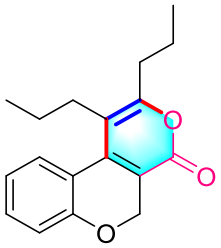
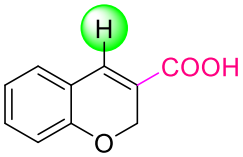
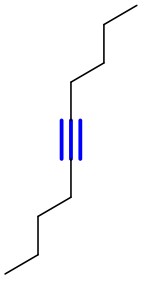
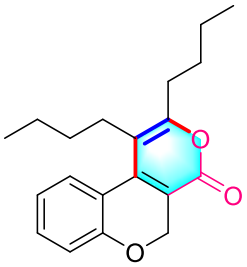


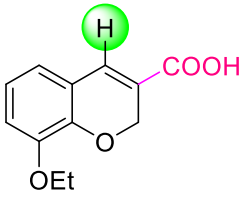
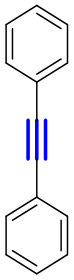
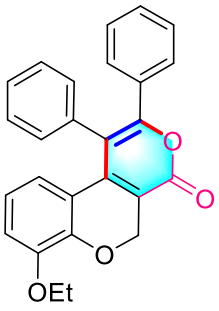
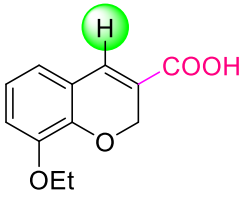
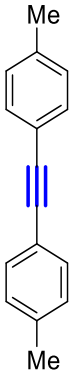
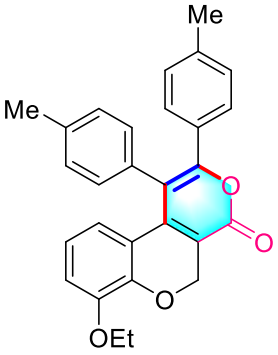
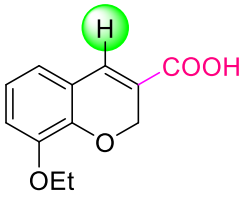
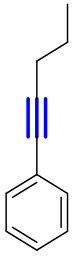
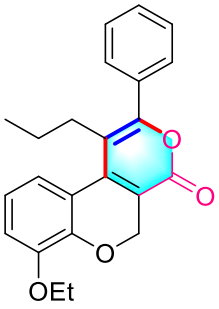
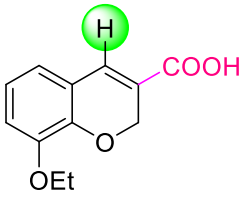
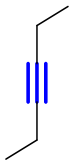
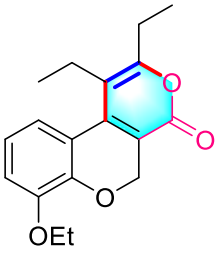
Scheme 17. Synthesis of substituted 4*H*,5*H*-pyrano[3,4-*c*]chromen-4-ones under Ru(II)-catalysis

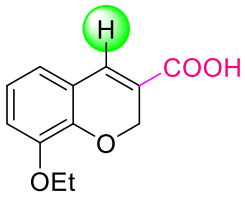
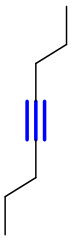
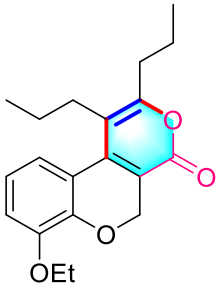
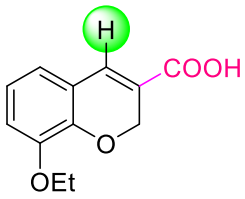
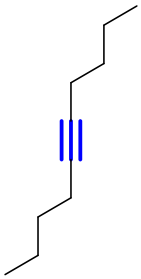
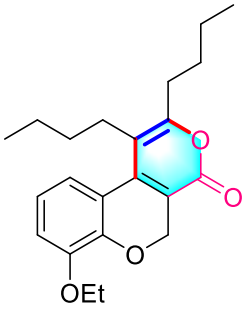
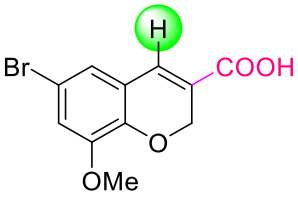
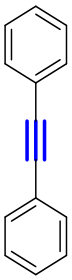
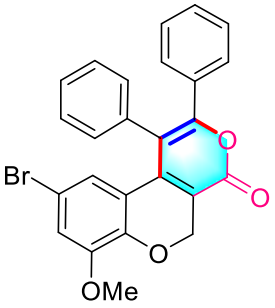
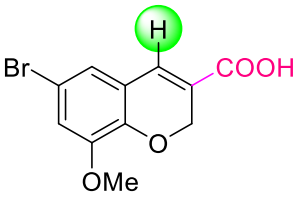
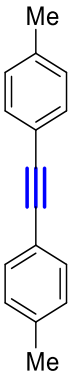
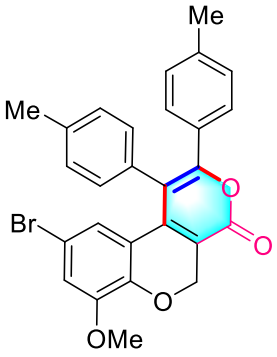
Table 10. Substrate scope for the oxidative annulation of chromene-3-carboxylic acids **6** with alkynes **7**[a]

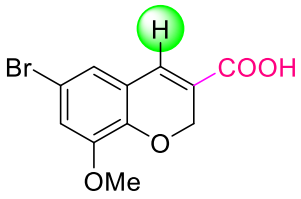
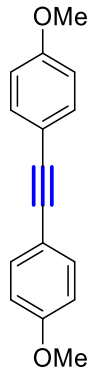
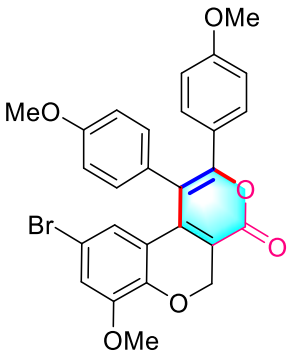
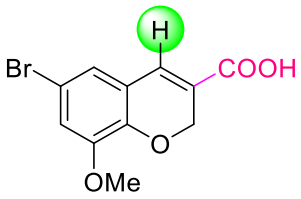
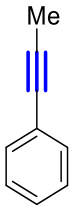
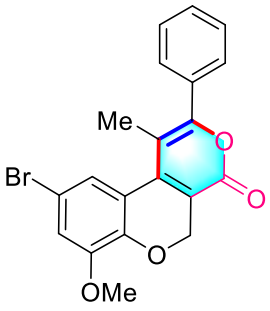
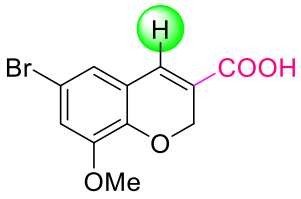
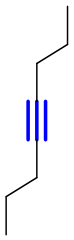
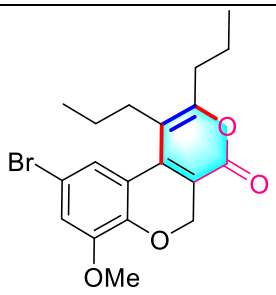
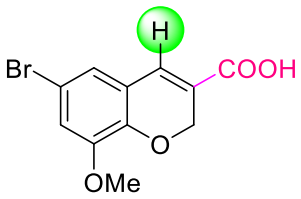
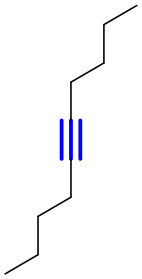
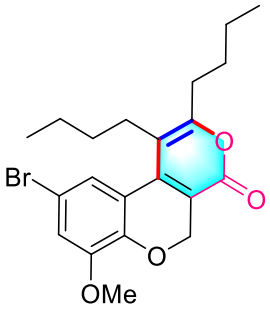
Entry	Chromene-3-carboxylic acid	Alkyne	4*H*,5*H*-pyrano[3,4-*c*]chromen-4-one	Yield (%)
1	 **6a**	 **7a**	 **21aa (X-ray)**	88
2	 **6a**	 **7b**	 **21ab**	70

3	 **6a**	 **7c**	 **21ac**	81
4	 **6a**	 **7d**	 **21ad**	78
5	 **6a**	 **7e**	 **21ae**	74
6	 **6a**	 **7f**	 **21af**	72

7	 **6a**	 **7g**	 **21ag**	79
8	 **6a**	 **7h**	 **21ah**	73
9	 **6a**	 **7i**	 **21ai**	77
10	 **6a**	 **7j**	 **21aj**	76

11	 **6b**	 **7a**	 **21ba**	74
12	 **6b**	 **7b**	 **21bb**	77
13	 **6b**	 **7g**	 **21bg**	80
14	 **6b**	 **7h**	 **21bh**	75

15	 **6b**	 **7i**	 **21bi**	81
16	 **6b**	 **7j**	 **21bj**	73
17	 **6c**	 **7a**	 **21ca**	81
18	 **6c**	 **7b**	 **21cb**	79

19	 **6c**	 **7c**	 **21cc**	84
20	 **6c**	 **7e**	 **21ce (X-ray)**	76
21	 **6c**	 **7i**	 **21ci**	79
22	 **6c**	 **7j**	 **21cj (X-ray)**	76

[a] Chromene-3-carboxylic acid **6** (0.57 mmol), alkyne **7** (0.57 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol%), Cu(OAc)$_2$·H_2O (30 mol%), $AgSbF_6$ (10 mol%), 1,4-dioxane (2 ml), 100 °C (oil bath temperature), for 20 h, [b] Isolated yield.

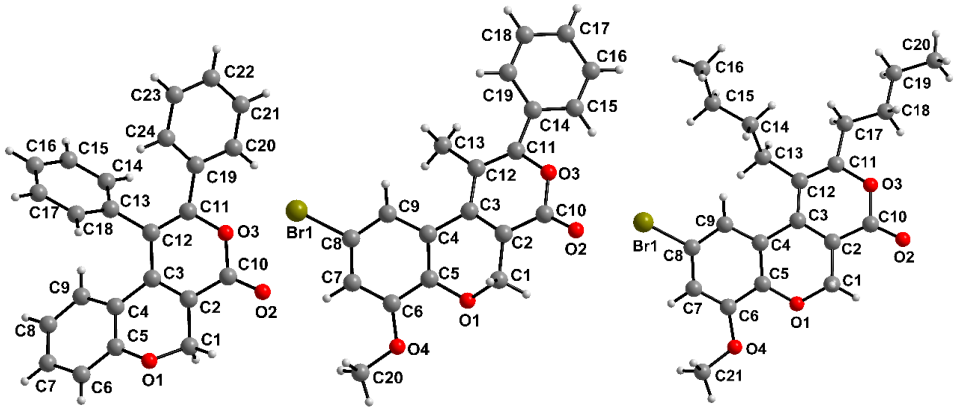


Figure 6: Molecular structures of compounds **21aa** (left), **21ce** (center) and **21cj** (right). Selected bond lengths in [Å] with esds in parenthesis. Compound **21aa**: C(2)-C(3) 1.363(3), C(3)-C(12) 1.453(3), C(12)-C(11) 1.364(3), C(11)-O(3) 1.380(2), O(3)-C(10) 1.379(3), C(10)-C(2) 1.435(3), C(10)-O(2) 1.208(3), C(2)-C(1) 1.497(4), C(3)-C(4) 1.481(3), C(12)-C(13) 1.494(3), C(11)-C(19) 1.484(3); Compound **21ce**: C(2)-C(3) 1.363(4), C(3)-C(12) 1.455(5), C(12)-C(11) 1.355(4), C(11)-O(3) 1.381(4), O(3)-C(10) 1.367(4), C(10)-C(2) 1.428(5), C(10)-O(2) 1.211(4), C(2)-C(1) 1.493(5), C(3)-C(4) 1.473(4), C(12)-C(13) 1.508(4), C(11)-C(14) 1.469(5); Compound **21cj**: C(2)-C(3) 1.367(8), C(3)-C(12) 1.438(8), C(12)-C(11) 1.345(9), C(11)-O(3) 1.372(7), O(3)-C(10) 1.379(8), C(10)-C(2) 1.425(9), C(10)-O(2) 1.207(9), C(2)-C(1) 1.495(9), C(3)-C(4) 1.500(8), C(12)-C(13) 1.529(8), C(11)-C(17) 1.509(11).

2.4.2 Synthesis of Ruthenium(0)-metal complexes from chromene-3-carboxylic acids, propargylic alcohols and [$RuCl_2$(*p*-cymene)]$_2$

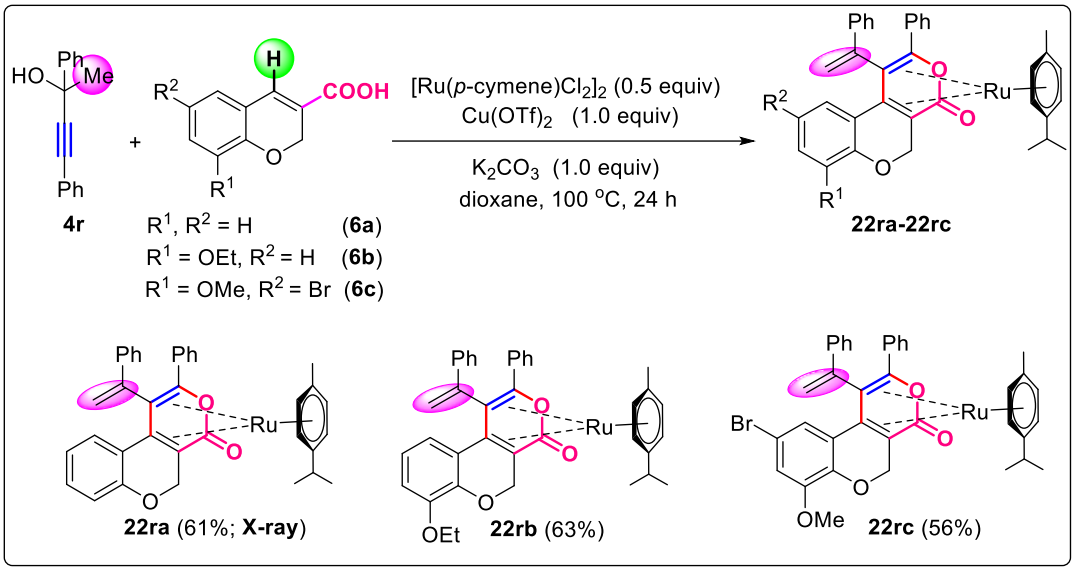
As an extension of the above reaction, we wanted to check the reactivity of propargylic alcohols **4** with chromene-3-carboxylic acid **6** in the presence of [$RuCl_2$(*p*-cymene)]$_2$, since a reaction similar to that discussed above can also take place. Thus, we employed equimolar ratio of propargylic alcohol **4r** with chromene-3-carboxylic acid **6a** under the above optimized reaction conditions but did not observe any product formation (Table 11, entry 1). Based on our earlier observations on the reactivity of the propargylic alcohols, we thought that change

of the oxidant to $Cu(OTf)_2$ (0.5 equiv) would help, but no reaction was observed (entry 2). Unexpectedly, by using $Cu(OTf)_2$ (0.5 equiv) along with K_2CO_3 (1.0 equiv) in dioxane at 100 ^oC for 24 h, the reaction afforded the Ru(*p*-cymene) containing [4+2] annulated metal complex **22ra** in moderate yield (41% *based on* [Ru] *precursor*; entry 3). In the absence of $AgSbF_6$ also, the complex was obtained in 49% yield (entry 4). When 0.3 equiv of $Cu(OTf)_2$ was used, we obtained 67% yield of the ruthenium complex (entry 5). Better yield of 72% was observed when 0.5 equiv of the K_2CO_3 was used (entry 6); decrease in reaction time to14 h decreased the yield to 58% (entry 7). However, as can be noticed from the formula, stoichiometrically, 0.5 mole of $[RuCl_2(p\text{-cymene})]_2$ is required per each mole of **4r** and **6a**. Under this stoichiometry, we obtained an yield of 61% of **22ra**. Similarly, by using propargylic alcohol **4r**, chromene-3-carboxylic acids **6b-c** and $[RuCl_2(p\text{-cymene})]_2$ we obtained the ruthenium metal complexes **22ra-22rc** in decent yields (cf. Scheme 18). One of the metal complexes **22ra** was further confirmed by the single crystal X-ray analysis (Figure 7). Although a complex similar to **22ra** has been reported by Ackermann,[108c] the fact that it may be general reaction has not been explored. Although we tried to remove Ru(*p*-cymene) component from **22ra** by treating it with $SOCl_2$, we did not succeed. Still, we are working to get the [4+2] annulated product by the removal of the metal.

Table 11. Conditions utilized to check the formation of Ru(0)-complex **22ra** using **4r**, **6a** and $[RuCl_2(p\text{-cymene})]_2$[a]

Entry	Catalyst	Oxidant	Additive	Base	Solvent	Yield[b] (%)
1	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2{\cdot}H_2O$	$AgSbF_6$	-	dioxane	n.d.
2	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OTf)_2$	$AgSbF_6$	-	dioxane	n.d.
3	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OTf)_2$	$AgSbF_6$	K_2CO_3	dioxane	41
4	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OTf)_2$	-	K_2CO_3	dioxane	49
5	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OTf)_2$	-	K_2CO_3	dioxane	67
6	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OTf)_2$	-	K_2CO_3	dioxane	72
7	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OTf)_2$	-	K_2CO_3	dioxane	58
8	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OTf)_2$	-	K_2CO_3	dioxane	61

[a] Chromene-3-carboxylic acid **6a** (0.57 mmol), propargylic alcohol **4r** (0.57 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), oxidant (0.30 equiv for entries 1 and 5-7 and 0.5 equiv for entries 2-4), additive (10 mol %), base (1.0 equiv for entries 3-5, 0.5 equiv for entries 6-7), solvent (2 mL), 100 °C (oil bath temperature), reaction time: 24 h for entries 1-6 and 14 h for entry 7. [b] Isolated yield.



Scheme 18. Synthesis of Ru(0)-metal complexes **22ra**-**22rc**

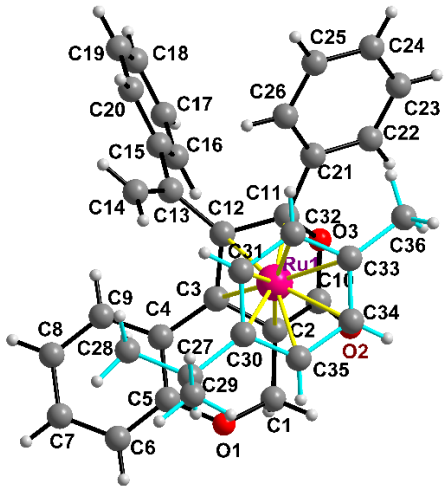
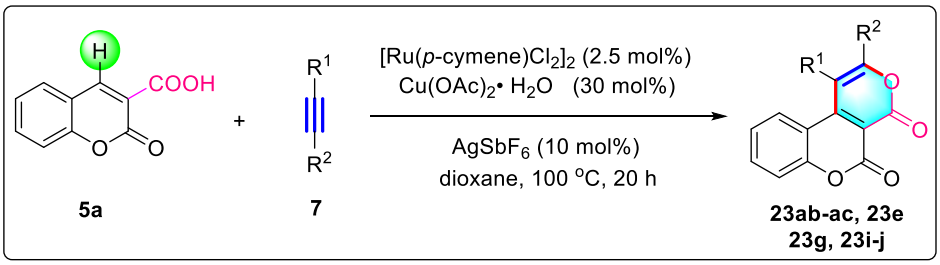


Figure 7: Molecular structure of compound **22ra**. Selected bond lengths in [Å] with esds in parenthesis. C(2)-C(3) 1.462(2), C(3)-C(12) 1.438(2), C(12)-C(11) 1.454(2), C(11)-O(3) 1.459(2), O(3)-C(10) 1.343(2), C(10)-C(2) 1.464(3), C(10)-O(2) 1.211(2), Ru(1)-C(2)

2.123(17), Ru(1)-C(3) 2.141(17), Ru(1)-C(12) 2.143(16), Ru(1)-C(11) 2.130(18), Ru(1)-C(30) 2.297(18), Ru(1)-C(31) 2.251(18), Ru(1)-C(32) 2.224(19), Ru(1)-C(33) 2.251(19), Ru(1)-C(34) 2.210(19), Ru(1)-C(35) 2.213(19.

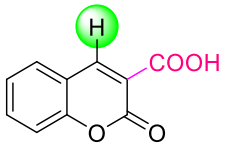
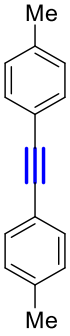
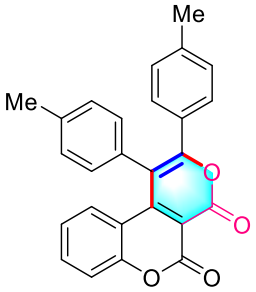
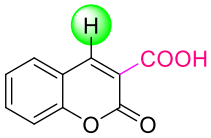
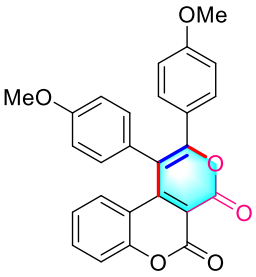
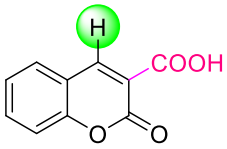
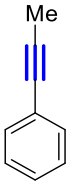
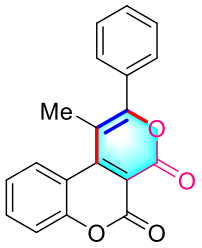
2.4.3 Ruthenium(II)-catalyzed oxidative [4+2] annulations of coumarin-3-carboxylic acids with alkynes *via* C(sp^2)-H bond activation

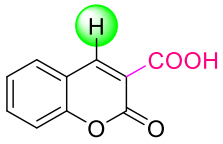
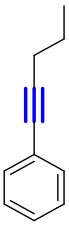
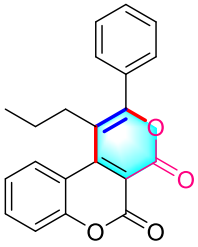
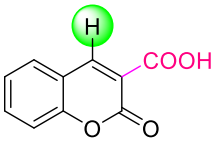
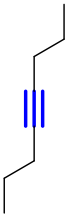
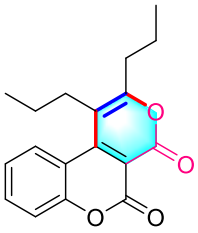
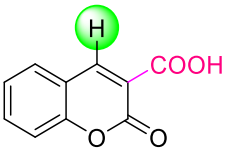
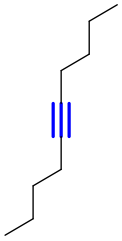
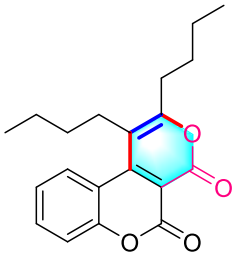
In an effort to extend the above [Ru]-catalyzed cyclization, we wanted to check the reactivity of coumarin-3-carboxylic acid under the same reaction conditions in order to know the effect of the additional carbonyl group on product formation. Hence we employed coumarin-3-carboxylic acid **5a** along with alkyne **7b** and as expected, [4+2] annulation occurred to give the annulated product **23ab** in 61% of the yield. Similarly, **7c** gave the pyrano[3,4-*c*]chromene-4,5-dione **23ac** in 64% yield. Unsymmetrical alkynes **7e** (methyl, phenyl) and **7g** (*n*-propyl, phenyl) also reacted well and afforded products **23ae** and **23ag** in 60% and 68% yields, respectively, with excellent regioselectivity. The dialkyl substituted alkynes **7i** and **7j** also provided the annulation products **23ai** and **23aj** in good yields. These results are shown in Table 12. The yields are a bit lower as compared to the reaction using chromene-3-carboxylic acid. This may be because of the co-ordination of the metal catalyst with the carbonyl functionality making it less accessible for the annulation process *via* C-H activation. The structure of the annulated product **23ab** was confirmed by single crystal X-ray diffraction studies (Figure 8).



Scheme 19. Synthesis of substituted 4*H*,5*H*-pyrano[3,4-*c*]chromene-4,5-diones from coumarin-3-carboxylic acid and alkynes

Table 12. Substrate scope for the formation of pyrano[3,4-*c*]chromene-4,5-diones **23** [a]

Entry	Coumarin-3-carboxylic acid	Alkyne	Pyrano[3,4-*c*]chromene-4,5-dione	Yield[b] (%)
1	 **5a**	 **7b**	 **23ab (X-ray)**	61
2	 **5a**	 **7c**	 **23ac**	64
3	 **5a**	 **7e**	 **23ae**	60

4	 **5a**	 **7g**	 **23ag**	68
5	 **5a**	 **7i**	 **23ai**	67
6	 **5a**	 **7j**	 **23aj**	65

[a] Coumarin-3-carboxylic acid **5a** (0.53 mmol), alkyne **7** (0.53 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (2.5 mol%), Cu(OAc)$_2$·H_2O (30 mol%), $AgSbF_6$ (10 mol%), 1,4-dioxane (2 mL), 100 °C (oil bath temperature), for 20 h. [b] Isolated yield.

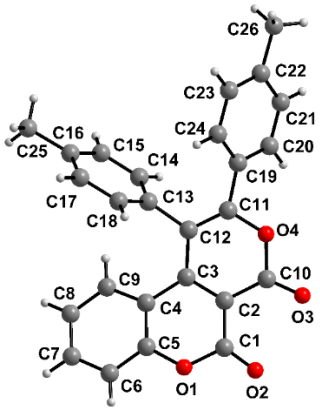
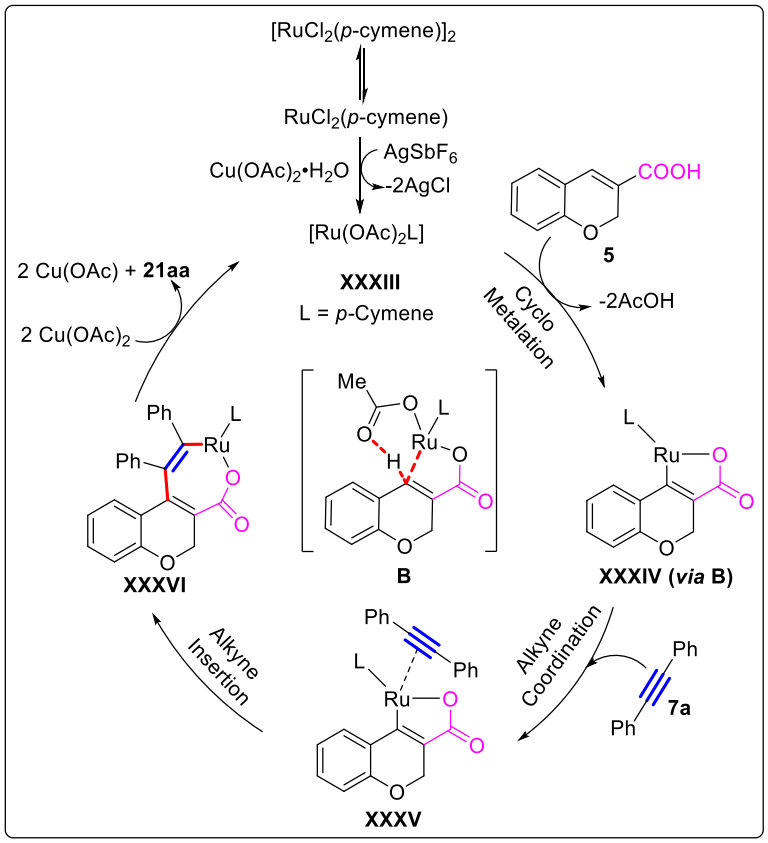


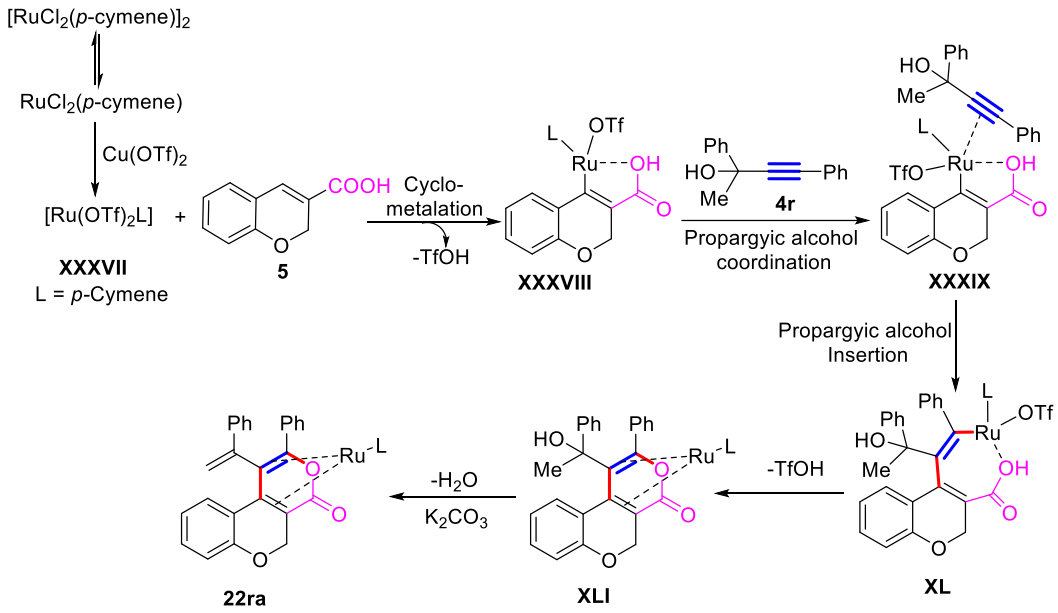
Figure 8: Molecular structure of compound **23ab**. Selected bond lengths in [Å] with esds in parenthesis: C(2)-C(3) 1.389(3), C(3)-C(12) 1.448(3), C(12)-C(11) 1.347(3), C(11)-O(4) 1.367(3), O(4)-C(10) 1.384(3), C(10)-C(2) 1.446(3), C(10)-O(3) 1.203(3), C(2)-C(1) 1.467(3), C(1)-O(2) 1.199(3), C(3)-C(4) 1.465(3), C(12)-C(13) 1.502(3), C(19)-C(11) 1.483(3).

Based on our experimental studies and previous literature reports for the annulation of carboxylic acids with alkynes,[108] we suggest the catalytic cycle shown in Scheme 20 for the annulation of the chromene/ coumarin carboxylic acids (**5** or **6**) with alkynes **7**. Here, ruthenium complex first undergoes ligand exchange with $Cu(OAc)_2 \cdot H_2O$ and $AgSbF_6$ and generates the active intermediate **XXXIII**. Then the acid partner **5** undergoes cyclometalation with intermediate **XXXIII** to give the five membered cyclic ruthenium intermediate **XXXIV** (*via* **B**). Then alkyne coordinates with intermediate **XXXIV** to produce species **XXXV**. This species undergoes alkyne insertion to give seven membered cyclic intermediate **XXXVI**, which upon reductive elimination gives the annulated product **21aa**. The catalyst may be regenerated by oxidation with $Cu(OAc)_2 \cdot H_2O$ for the next cycle.



Scheme 20. Plausible catalytic pathway for the formation of the pyrano-chromones

Based on our experimental studies and previous literature reports for the annulations of carboxylic acids with alkynes and Ru(0)-metal complex formation,[108] we suggest the possible pathway shown in Scheme 21 for the Ru(0)-metal complex formation from the chromene-3-carboxylic acid **5** and propargylic alcohols **4r**. Here, ruthenium complex first undergoes ligand exchange with $Cu(OTf)_2$ to generates the active intermediate **XXXVII**. Then the acid partner **5** undergoes cyclometalation with intermediate **XXXVII** to give the ruthenium intermediate **XXXVIII**. Then propargylic alcohol **4r** coordinates with intermediate **XXXVIII** to produce species **XXXIX**. This species undergoes propargylic alcohol insertion to give intermediate **XL**, which subsequently converts to intermediate **XLI** by elimination of TfOH. This species upon dehydration in the presence of K_2CO_3 delivers the Ru(0)-metal complex. At the moment, we are not sure about the reduction of Ru from **XL** to **XLI**.



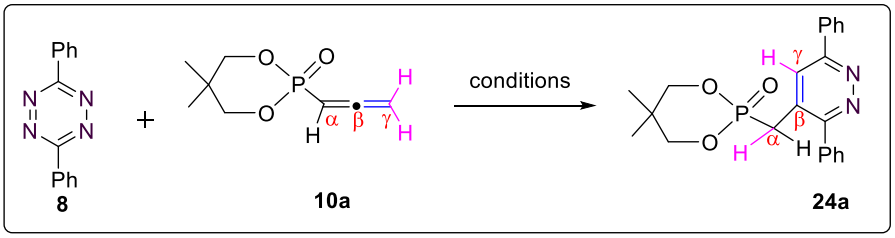
Scheme 21. Plausible pathway for the formation of Ru(0)-metal complexes

2.5.1 Thermally induced [4+2] cycloaddition reaction of phosphorus/sulfur based allenes or allenoates with 3,6-diphenyl-1,2,4,5-tetrazine

Allenes, like alkynes, possess an *sp*-hybridized carbon, but because of the two cumulative double bonds they may offer more variety as cycloaddition partners. Our interest in this context was to use them as dienophiles with tetrazines. Tetrazine can act as a diene undergoing Inverse Electron Demand Diels-Alder (IED D-A) reaction with dienophiles. Tetrazines have been utilized for cycloaddition reactions, but so far the reacting partners have been essentially alkenes/alkynes[80-91] and to our knowledge, cycloaddition reactions of tetrazines with allenes have not been investigated in detail. The resulting compounds, pyridazines, are popular pharmacophores and present in herbicides such as credazine, pyridafol and pyridate.[16] In the reaction of symmetrical tetrazines with alkynes there is no question of selectivity whereas in the case of substituted allenes, we may encounter selectivity issues because of the presence of two cumulative [(α,β) and (β,γ)] double bonds. In the current work, we planned to utilize a substituted symmetrical tetrazine for cycloaddition reactions with allenes.

Our initial investigation started with the reaction of 3,6-diphenyl-1,2,4,5-tetrazine **8** with allenyl phosphonate **10a** in toluene at 100 ^{o}C (oil bath temperature) for 12 h (Scheme 22). To our delight, the cycloaddition adduct **24a** could be isolated in 45% yield. We then went for

optimization of the reaction conditions. Among the solvents xylene, MeCN, DMSO, DMF, THF, dioxane, PEG-400 and EtOH tested, xylene offered the better yield 52% of **24a**. Increasing the reaction time to 24 h increased the yield of **24a** to 63%. When the reaction was conducted at 140 ^{o}C for 24 h, we obtained a very good yield of 82% after isolation. These were taken as the best (optimized) conditions for our reaction. Notably, completion of the reaction can be recognized by the color change during the reaction. The initial violet-red color of the tetrazine disappears upon completion of the reaction. When we applied the optimized conditions to the reaction of allenes **12-14** with tetrazine **8**, the yields of final the product was lower perhaps due to the instability of the allene. Hence in these cases, we used 2 equiv of allenes **12-14** for 1 equiv of 3,6-diphenyl-1,2,4,5-tetrazine **8** in addition decreasing the temperature (to 120 ^{o}C) and time (12 h).

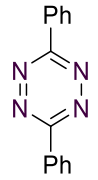
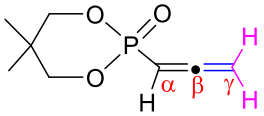
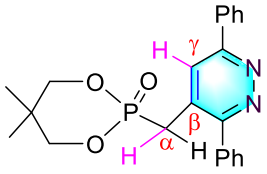
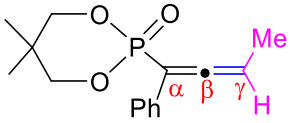
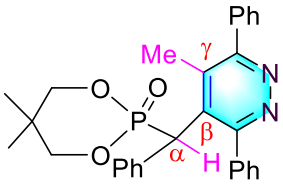
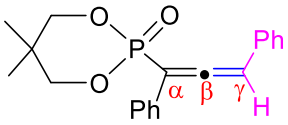
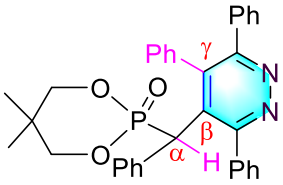


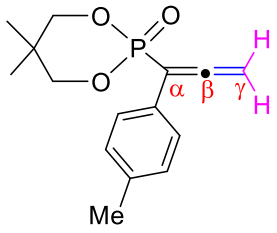
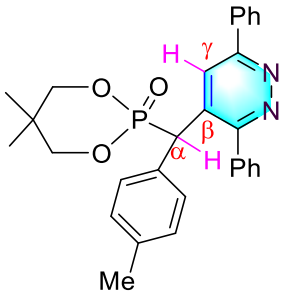
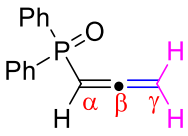
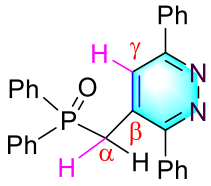
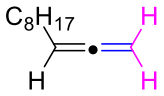
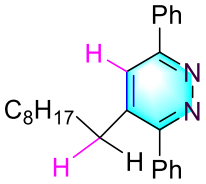
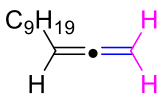
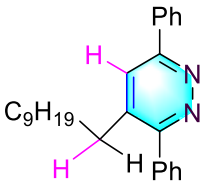
Scheme 22. Reaction of 3,6-diphenyl-1,2,4,5-tetrazine **8** with allenylphosphonate **10a**

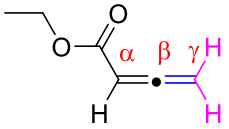
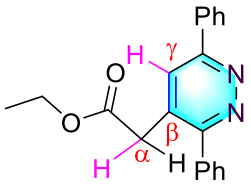
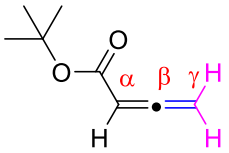
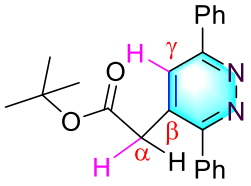
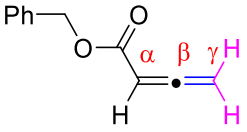
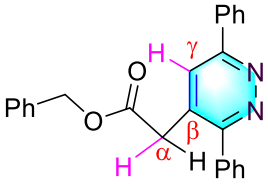
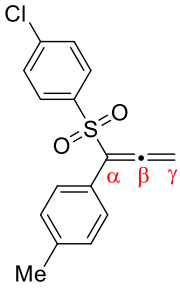
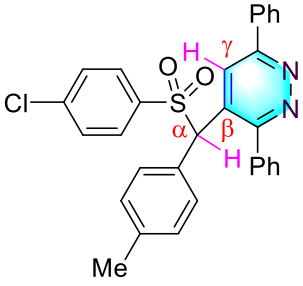
As far as allene part is concerned, we have utilized the precursors **10a-d**, **11**, **12a-b**, **13a-c** and **14**. The cycloaddition products **24a-24d**, **25**, **26a-b**, **27a-c** and **28** (Table 13) were obtained in very good yields (69-88%) with excellent regioselectivity by the selective addition at terminal (*β,γ*) double bond of the allene followed by [1,3]-H shift. This may be because of the direct conjugation of the (*α,β)* double bond with phosphorus (P=O) double bond making it unavailable for the cycloaddition. We have also checked the reaction using *γ*-disubstituted allene ($OCH_2CMe_2CH_2O$)P(O)CH=C=CMe_2 but did not observe the product formation. This may be because of the steric effect at *γ*-position for the formation of pyridazines (*cf*. Scheme 23). The solid-state structure of pyridazine **25** was confirmed by single crystal X-ray diffraction (Figure 9). The alkylated allenes **12a** and **12b** reacted with tetrazine **8** to afford the pyridazines **26a** and **26b** in 79-85% yield. Ethyl, *tert*-butyl or benzyl substituted ester allenes **13a-c** also worked well and delivered the final products **27a-c** in good to excellent yields. Even

allenyl sulfone underwent the reaction with tetrazine and gave the product **28** in a moderate yield of 64%. Pyridazine **27b** (Figure 9) has been characterized by single crystal X-ray crystallography.

Table 13. Substrate scope for the substituted 3,6-diphenylpyridazine **24-28**[a]

Entry	Tetrazine	Allene	3, 6-diphenylpyridazine	Yield[b] (%)
1	 **8**	 **10a**	 **24a**, δ(P): 20.3	82
2	**8**	 **10b**	 **24b**, δ(P): 19.9	74
3	**8**	 **10c**	 **24c**, δ(P): 19.7	81

4	**8**	 **10d**	 **24d**, δ(P): 18.6	69
5	**8**	 **11**	 **25**, δ(P): 29.6 (**X-ray**)	79
6	**8**	 **12a**	 **26a**	79
7	**8**	 **12b**	 **26b**	85

8	**8**	 **13a**	 **27a**	88
9	**8**	 **13b**	 **27b (X-ray)**	85
10	**8**	 **13c**	 **27c**	81
11	**8**	 **14**	 **28**	64

[a]Reaction conditions: **8** (50.0 mg, 0.21 mmol) with one of **10a-d**, **11**, (0.32 mmol) and **12a-b**, **13a-c**, **14** (0.42 mmol) in xylene (2 mL) at 140 °C (oil bath temperature) for 24 h for entries 1-5; at 120 °C (oil bath temperature) for 12 h for entries 6-11. [b]Isolated yields.

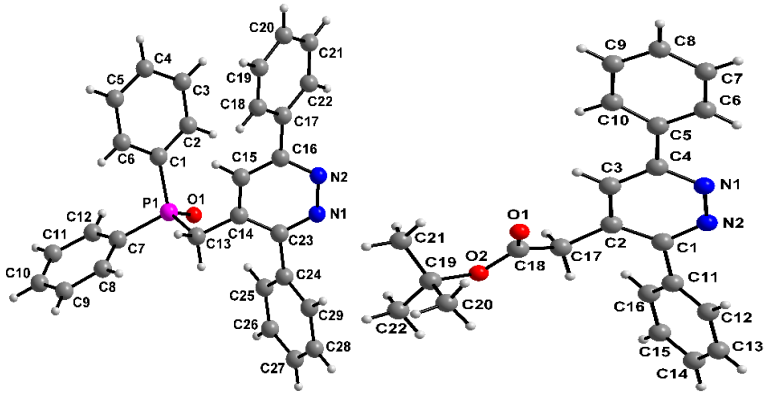
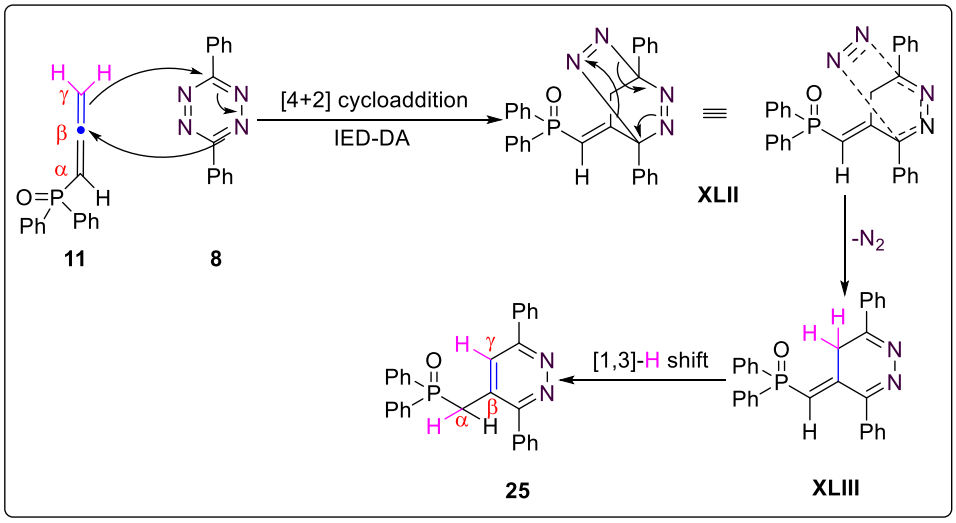


Figure 9: Molecular structures of compounds **25**.and **27b** selected bond lengths in [Å] with esds in parenthesis: Compound **25**: N(1)-N(2) 1.344(6), N(2)-C(16) 1.354(8), C(16)-C(15) 1.385(8), C(15)-C(14) 1.380(9), C(14)-C(23) 1.413(8), C(23)-N(1) 1.339(6), C(14)-C(13) 1.497(7), C(13)-P(1) 1.808(13), P(1)-O(1) 1.493(6), P(1)-C(1) 1.789(5), P(1)-C(1) 1.789(5), C(23)-C(24) 1.484(7), C(16)-C(17) 1.479(9). Compound **27b**: N(1)-N(2) 1.333(3), N(2)-C(1) 1.337(3), C(1)-C(2) 1.405(3), C(2)-C(3) 1.368(3), C(3)-C(4) 1.392(3), C(4)-N(1) 1.332(3), C(2)-C(17) 1.507(3), C(17)-C(18) 1.501(4), C(18)-O(1) 1.179(4), C(18)-O(2) 1.304(3), C(1)-C(11) 1.486(3), C(4)-C(5) 1.484(3)

A plausible pathway for the formation of substituted 3, 6-diphenylpyridazines **25** is shown in Scheme 23.[109] Initially, 3,6-diphenyl-1,2,4,5-tetrazine **8** undergoes regioselective [4+2] cycloaddition with allene **11** involving *β,γ*-(terminal) double bond *via* Inverse Electron Demand Diels-Alder (IED-DA) reaction to give intermediate **XLII**. This upon N_2 elimination *via* retro-DA reaction gives intermediate **XLIII**. This intermediate undergoes [1,3]-H shift to give the final product **25**. Similarly, other pyridazines are formed. As can be seen readily, substitution at the *γ*-carbon [e.g., $(OCH_2CMe_2CH_2O)P(O)CH=C=CMe_2$] of the allene has deleterious effect on the formation of intermediate **XLII** and hence in these cases we were not able to obtain the cycloaddition products. However, this allene route offers a simple route to a new class of pyridazines that may be explored further.



Scheme 23. Plausible pathway for the formation of substituted 3,6-diphenylpyridazine **25**

(v) We have developed a simple and viable synthetic route to benzo-oxazine based spirocycles (*via* dearomative ring expansion/ aerobic oxidation) and dihydrocyclopenta[*e*]indole-2-carboxylates by using indole-2-carboxylates and propargylic alcohols under PTSA mediation. Novel indene fused pyrano-indolones (fused pentacyclics) are also obtained using indole-2-carboxylic acids and propargylic alcohols under Cu(II)-catalysis.

(vi) A novel decarboxylative [4+2] annulation methodology has been developed by using coumarin-3-carboxylic acids and propargylic alcohols under Cu(II)-catalysis for the synthesis of coumarin fused naphthalene scaffolds.

(vii) Ruthenium catalyzed regioselective oxidative [4+2] annulation of chromene/coumarin-3-carboxylic acids with alkynes/ propargylic alcohols for the construction of pyrano chromenes has been developed. Novel Ru(0) complexes have been isolated from the reaction of chromene carboxylic acids with propargylic alcohols in the presence of [Ru(*p*-cymene)Cl_2]$_2$.

(viii) Thermally induced regioselective [4+2] cycloaddition reactions of 3,6-diphenyl-1,2,4,5-tetrazine with allenes leads to disubstituted pyridazines. In these reactions, cycloaddition is accompanied by 1,3-H shift.

EXPERIMENTAL SECTION

General information: Chemicals and solvents were purchased from Aldrich or other local manufacturing agencies and used without any further purification. Purification of solvents was done using standard literature procedures wherever required.[110] All operations, unless otherwise specified, were carried out under dry nitrogen atmosphere using standard vacuum line techniques.[111]

Melting point: Melting points were determined using a SUPERFIT hot stage apparatus and are uncorrected.

Elemental analyses: Elemental analyses were carried out on a Perkin-Elmer 240C CHN or Thermo Finnigan EA1112 CHNS analyzer.

Infrared spectroscopy: IR spectra were recorded on a JASCO FT/IR 5300 spectrophotometer.

NMR spectroscopy: For sections 3.1-3.9, ^{1}H, $^{13}C\{^{1}H\}$ and ^{19}F NMR spectra were recorded using 5 mm tubes on a Bruker 400 MHz NMR spectrometer (unless specified otherwise) [field strengths: 400 and 100 MHz respectively] in $CDCl_3$ solution (unless specified otherwise) with shifts referenced to $SiMe_4$ (^{1}H, ^{13}C: $\delta = 0$) or $CFCl_3$ [^{19}F: $\delta = 0$]. For sections 3.10-3.11, ^{1}H, $^{13}C\{^{1}H\}$ and ^{31}P NMR spectra were recorded using 5 mm tubes on a Bruker 500 MHz NMR spectrometer (unless specified otherwise) [field strengths: 500, 125 and 202 MHz respectively] in $CDCl_3$ solution (unless specified otherwise) with shifts referenced to $SiMe_4$ (^{1}H, ^{13}C: $\delta = 0$). All *J* values are in Hz.

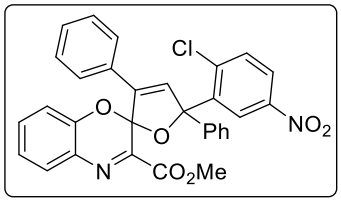
LC-MS and HRMS: LC-MS equipment was used to record mass spectra for isolated compounds where appropriate. LC-MS data were obtained using electrospray ionization (positive mode) on a C-18 column. Mass spectra were recorded using HRMS (ESI-TOF analyzer) equipment.

The precursors 1*H*-indole-2-carboxylates **1a-e**[93] and 1-*H* indole-2-carboxylic acids **2a-b** are commercially available. Substituted *tert*-propargylic alcohols **3a-c** and **4a-r**,[94] coumarin-3-carboxylic acids **5a-e**,[95] 2*H*-chromene-3-carboxylic acids **6a-c**,[96] and alkynes **7b-d**[97] were prepared by following the standard literature procedures. 3,6-Diphenyl 1,2,4,5-tetrazine (**8**) is

commercially available. *sec*-Propargylic alcohols **9a-d,**[98] allenylphosphonates **10a-d,**[99] allenylphoshine oxide **11**,[99] terminal alkyl allenes **12a-b**,[100] ester allenes **13a-c**[101] and allenylsulfone **14**[102] were prepared by using standard literature reports.

3.1 Synthesis of spiro[benzo-oxazinefurans] or cyclopenta[*e*]indole-2-carboxylates: General procedure for the synthesis of compounds 15-16: In an oven dried 10 mL round-bottomed flask, indole 2-carboxylate (**1a**, 0.57 mmol), propargylic alcohol (**3b**, 0.57 mmol) and PTSA (0.85 mmol) were taken. To this mixture, $MeNO_2$ (2 mL) was added and the contents were stirred in open air at rt for 24 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was quenched by adding water (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL). Then the combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and the crude product purified by silica gel column chromatography by using hexane/ethyl acetate (9:1) mixture as the eluent to afford the corresponding final products **15** and **16**.

Compound 15aa



Yield: 224.1 mg (71%, white solid, R_f = 0.45 (9:1 hexane/ethyl acetate)).

Mp: 234-236 ^oC.

IR (neat): ν_{max} 2924, 2856, 2193, 1733, 1673, 1525, 1464, 1347, 1251, 1055, 911, 759, 743, 698 cm^{-1}.

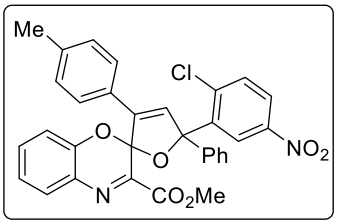
^1H NMR (500 MHz, $CDCl_3$): δ 8.62 (d, *J* = 2.5 Hz, 1H), 8.09 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.70 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.53 (s, 1H), 7.48-7.43 (m, 4H), 7.27-7.23 (m, 5H), 7.22-7.18 (m, 4H), 6.96 (dd, *J* = 8.5, 1.5 Hz, 1H), 3.59 (s, 3H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 161.9, 146.9, 146.7, 144.4, 143.5, 140.9, 140.0, 138.3, 132.6, 131.8, 131.0, 130.9, 129.8, 129.0, 128.8, 128.7, 128.4, 128.0, 127.4, 126.8, 123.9, 123.6, 123.4, 117.7, 103.8, 95.0, 52.8 ppm.

HRMS (ESI-TOF): Calcd. for $C_{31}H_{22}ClN_2O_6$ [M^+ + H] and [M^+ + H + 2]: *m/z* 553.1166, 555.1136. Found: 553.1169, 555.1158.

This compound was crystallized from ethyl acetate–hexane (2:1) mixture at room temperature. X-ray structure has been determined for this compound.

Compound 15ab



Yield: 197.4 mg (61%, white solid, R_f = 0.49 (9:1 hexane/ethyl acetate)).

Mp: 198-200 °C.

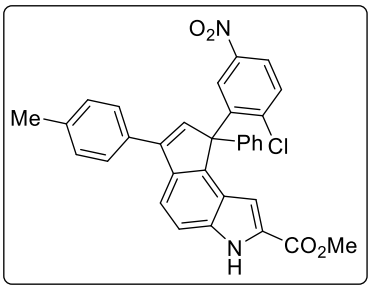
IR (neat): ν_{max} 2921, 2852, 1727, 1572, 1522, 1450, 1342, 1302,1251, 1134, 1028, 906, 811, 760, 741, 697 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.39 (d, *J* = 2.5 Hz, 1H), 8.07 (dd, *J* = 8.5, 3.0 Hz, 1H), 7.69 (d, *J* = 7.0, 1H), 7.46 (s, 1H), 7.44-7.41 (m, 2H), 7.32 (d, *J* = 8.0, 2H), 7.24-7.22 (m, 3H), 7.20-7.17 (m, 3H), 7.04 (d, *J* = 8.0, 2H), 6.95 (d, *J* = 8.0, 1H), 3.58 (s, 3H), 2.25 (s, 3H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 161.9, 147.2, 146.7, 144.5, 143.7, 140.9, 140.1, 139.1, 138.3, 132.5, 131.8, 131.0, 129.8, 129.5, 128.7, 128.3, 128.1, 127.4, 127.0, 126.8, 123.8, 123.5, 123.3, 117.7, 103.9, 95.0, 52.7, 21.3 ppm.

HRMS (ESI-TOF): Calcd. for $C_{32}H_{24}ClN_2O_6$ [M^+ + H]: *m/z* 567.1323 Found: 567.1322.

Compound 16ab



Yield: 88.6 mg (29%, yellow solid, R_f = 0.43 (9:1 hexane/ethyl acetate)).

Mp: >300 °C.

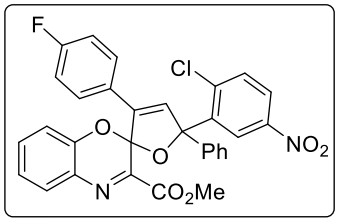
IR (neat): ν_{max} 3320, 2922, 2853, 1713, 1605, 1526, 1460, 1345, 1264, 1121, 1050, 739, 702 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 9.06 (s, 1H), 8.13 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.98 (d, *J* = 3.0 Hz, 1H), 7.66-7.61 (m, 4H), 7.50-7.48 (m, 1H), 7.32 (d, *J* = 7.5 Hz, 2H), 7.29-7.28 (br, 2H), 7.25-7.24 (m, 3H), 7.22-7.18 (m, 1H), 6.92 (s, 1H), 3.90 (s, 3H), 2.45 (s, 3H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 162.0, 146.7, 146.1, 143.5, 143.3, 140.4, 140.2, 138.1, 136.5, 134.8, 134.6, 132.3, 132.2, 129.4, 128.8, 128.6, 127.8, 126.9, 125.0, 124.5, 123.2, 119.8, 112.0, 106.0, 66.0, 52.1, 31.0, 21.4 ppm.

HRMS (ESI-TOF): Calcd. for $C_{32}H_{24}ClN_2O_4$ $[M^+ + H]$: *m/z* 535.1424 Found: 535.1426.

Compound 15ac



Yield: 215.1 mg (66%, white solid, R_f = 0.47 (9:1 hexane/ethyl acetate)).

Mp: 222-224 °C.

IR (neat): ν_{max} 3054, 2985, 1731, 1605, 1527, 1511, 1347, 1265, 1162, 1033, 896, 830, 739, 704 cm^{-1}.

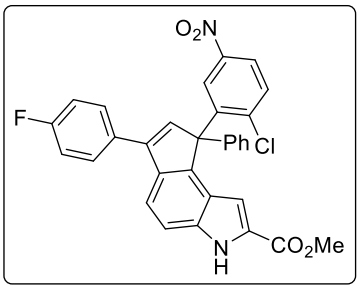
^1H NMR (500 MHz, $CDCl_3$): δ 8.69 (d, *J* = 2.5 Hz, 1H), 8.18 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.57-7.52 (m, 5H), 7.33-7.32 (m, 3H), 7.29-7.28 (m, 3H), 7.07-7.02 (m, 3H), 3.70 (s, 3H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.0 (d, *J* = 249.0 Hz), 161.9, 146.7, 144.3, 143.4, 140.0, 139.9, 138.3, 132.7, 131.9, 131.0, 130.1, 129.9, 129.0, 128.8, 128.6 (d, *J* = 41.0 Hz), 127.9, 127.4, 127.3, 124.0, 123.8, 123.3, 117.8, 116.0 (d, *J* = 21.0 Hz), 103.8, 95.1, 53.0 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ -111.4 ppm.

HRMS (ESI-TOF): Calcd. for $C_{31}H_{21}ClFN_2O_6$ $[M^+ + H]$ and $[M^+ + H + 2]$: *m/z* 571.1072, 573.1041 Found: 571.1074, 573.1041.

Compound 16ac



Yield: 98.4 mg (32%, yellow solid, R_f = 0.41 (9:1 hexane/ethyl acetate)).

Mp: >300 ºC.

IR (neat): ν_{max} 3329, 2923, 2853, 1716, 1600, 1526, 1507, 1460, 1345, 1232, 1049, 806, 742, 699 cm^{-1}.

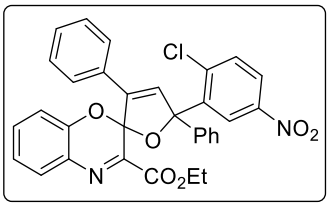
^1H NMR (400 MHz, $CDCl_3$): δ 9.05 (s, 1H), 8.14 (dd, *J* = 8.6 Hz, 3.0 Hz, 1H), 7.98 (d, *J* = 2.4 Hz, 1H), 7.71-7.68 (m, 2H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.50 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.29 (s, 1H), 7.26-7.18 (m, 7H), 6.92 (s, 1H), 3.91 (s, 3H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.7 (d, *J* = 246.0 Hz), 161.9, 146.7, 145.3, 143.5, 143.2, 140.2, 139.9, 136.6, 135.0, 134.5, 132.2, 129.6 (d, *J* = 8.0 Hz), 128.8$_3$, 128.7$_6$, 127.0, 126.1, 125.0, 124.5, 123.3, 119.4, 115.7 (d, *J* = 21.1 Hz), 112.1, 106.0, 66.0, 52.1 ppm.

^{19}F NMR (470 MHz, $CDCl_3$): -116.7 ppm.

HRMS (ESI-TOF): Calcd. for $C_{31}H_{21}ClFN_2O_4$ $[M^+ + H]$: *m/z* 539.1174 found 539.1178.

Compound 15ba



Yield: 200.8 mg (67%, white solid, R_f = 0.50 (9:1 hexane/ethyl acetate)).

Mp: 240-242 ºC.

IR (neat): ν_{max} 3054, 2986, 1731, 1526, 1422, 1348, 1265, 1044, 896, 739, 705 cm^{-1}.

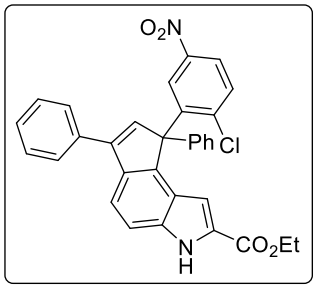
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.69 (d, *J* = 3.0 Hz, 1H), 8.18 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.79 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.63 (s, 1H), 7.56-7.51 (m, 4H), 7.36-7.28 (m, 9H), 7.02 (dd, *J* = 8.5, 1.0 Hz, 1H), 4.16 (q, *J* = 7.0, 2H), 1.06 (t, *J* = 7.0, 3H) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 161.5, 147.3, 146.7, 144.4, 143.6, 141.0, 140.0, 138.3, 132.4, 131.8, 131.1, 130.9, 129.8, 129.0, 128.8, 128.7, 128.3, 127.9, 127.4, 126.9, 123.9, 123.5, 123.4, 117.6, 103.8, 94.9, 62.0, 13.8 ppm.

HRMS (ESI-TOF): Calcd. for $C_{32}H_{24}ClN_2O_6$ [M^+ + H] and [M^+ + H + 2]: *m/z* 567.1323, 569.1293 Found: 567.1327, 569.1293.

This compound was crystallized from ethyl acetate–hexane (2:1) mixture at room temperature. X-ray structure has been determined for this compound.

Compound 16ba



Yield: 87.7 mg (31%, yellow solid, R_f = 0.46 (9:1 hexane/ethyl acetate)).

Mp: >300 °C.

IR (neat): ν_{max} 3324, 2923, 2853, 2360, 2340, 1706, 1603, 1571, 1524, 1491, 1445, 1379, 1275, 1244, 1199, 1116, 1050, 1021, 810, 758, 700 cm^{-1}.

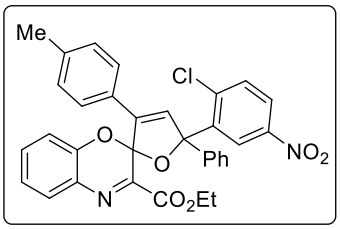
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.05 (s, 1H), 8.14 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.99 (d, *J* = 2.4 Hz, 1H), 7.74-7.72 (m, 2H), 7.64 (d, *J* = 8.8 Hz, 2H), 7.53-7.48 (m, 3H), 7.47-7.42 (m, 1H), 7.32 (s, 1H), 7.26-7.25 (m, 4H), 7.23-7.18 (m, 1H), 6.92 (s, 1H), 4.38 (q, *J* = 7.2 Hz, 2H), 1.39 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 161.4, 146.8, 146.2, 143.5, 143.2, 140.4, 140.1, 136.5, 135.3, 135.1, 134.6, 132.2, 129.0, 128.8, 128.7, 128.2, 127.9, 126.9, 126.2, 125.0, 124.5, 123.2, 119.6, 112.0, 105.8, 66.1, 61.2, 14.4 ppm.

HRMS (ESI-TOF): Calcd. for $C_{32}H_{24}ClN_2O_4$ [M^+ + H] and [M^+ + H + 2]: *m/z* 535.1424, 537.1394 Found: 535.1426, 537.1398.

This compound was crystallized from ethyl acetate–hexane (2:1) mixture at room temperature. X-ray structure has been determined for this compound.

Compound 15bb



Yield: 178.1 mg (58%, white solid, R_f = 0.54 (9:1 hexane/ethyl acetate)).

Mp: 205-207 ^oC.

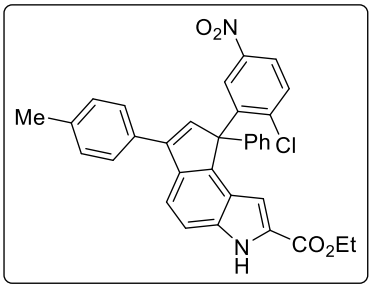
IR (neat): ν_{max} 2923, 2853, 1725, 1607, 1572, 1524, 1450, 1345, 1298, 1265, 1179, 1137, 1033, 1007, 955, 920, 814, 762, 740, 698 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.59 (d, *J* = 2.5 Hz, 1H), 8.07 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.69 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.47 (s, 1H), 7.44-7.40 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.23-7.20 (m, 3H), 7.19-7.16 (m, 3H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.92 (dd, *J* = 8.0, 1.0 Hz, 1H), 4.06 (q, *J* = 7.0, 2H), 0.98 (t, *J* = 7.0 Hz, 3H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 161.5, 147.5, 146.7, 144.5, 143.7, 140.9, 140.1, 139.1, 138.3, 132.3, 131.8, 131.1, 129.7, 129.5, 128.6, 128.3, 128.1, 127.4, 126.9, 126.8, 123.8, 123.5, 123.4, 117.6, 103.8, 94.9, 62.0, 21.3, 13.8 ppm.

HRMS (ESI-TOF): Calcd. for $C_{33}H_{26}ClN_2O_6$ $[M^+ + H]$: *m/z* 581.1479 Found: 581.1472.

Compound 16bb



Yield: 87.0 mg (30%, yellow solid, R_f = 0.49 (9:1 hexane/ethyl acetate)).

Mp: >300 ^oC.

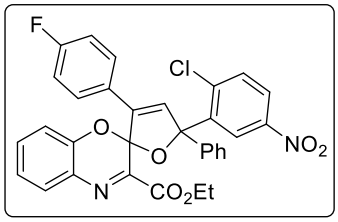
IR (neat): ν_{max} 3328, 2923, 2854, 1712, 1605, 1572, 1525, 1460, 1376, 1344, 1247, 1120, 1072, 1049, 1022, 804, 741, 699 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 9.04 (s, 1H), 8.13 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.98 (d, *J* = 2.5 Hz, 1H), 7.65-7.61 (m, 4H), 7.49 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.28_2-7.28_0 (br, 2H), 7.25-7.24 (m, 3H), 7.22-7.18 (m, 1H), 6.91 (s, 1H), 4.37 (q, *J* = 7.0 Hz, 2H), 2.45 (s, 3H), 1.39 (t, *J* = 7.0 Hz, 3H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 161.5, 146.7, 146.1, 143.5, 143.2, 140.4, 140.2, 138.1, 136.5, 134.8, 134.6, 132.4, 132.2, 129.4, 129.0, 128.8, 127.8, 126.9, 126.2, 125.0, 124.5, 123.2, 119.7, 112.0, 105.9, 66.0, 61.2, 21.3, 14.4 ppm.

HRMS (ESI-TOF): Calcd. for $C_{33}H_{26}ClN_2O_4$ $[M^+ + H]$: *m/z* 549.1581 Found: 549.1586.

Compound 15bc



Yield: 200.1 mg (62%, white solid, R_f = 0.53 (9:1 hexane/ethyl acetate)).

Mp: 220-222 °C.

IR (neat): ν_{max} 3053, 2989, 1724, 1605, 1527, 1422, 1347, 1265, 1033, 896, 744, 705 cm^{-1}.

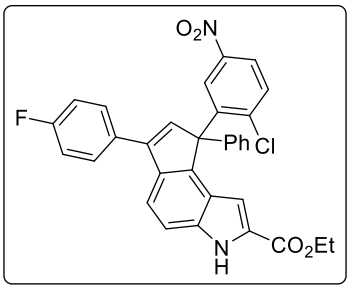
^1H NMR (500 MHz, $CDCl_3$): δ 8.68 (d, *J* = 2.5 Hz, 1H), 8.18 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.79 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.56-7.52 (m, 5H), 7.33-7.30 (m, 3H), 7.29-7.28 (m, 3H), 7.06-7.02 (m, 3H), 4.17 (q, *J* = 7.0 Hz, 2H), 1.10 (t, *J* = 7.0 Hz, 3H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.8 (d, *J* = 267.0 Hz), 161.7, 147.1, 146.7, 144.3, 143.4, 140.0, 139.9, 138.3, 132.5, 131.9, 131.1, 129.9, 128.9, 128.6 (d, *J* = 37.0 Hz), 127.8, 127.4, 127.2, 124.0, 123.7, 123.4, 117.7, 115.9 (d, *J* = 22 Hz), 103.8, 95.0, 62.2, 13.9 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ -111.5 ppm.

HRMS (ESI-TOF): Calcd. for $C_{32}H_{23}ClFN_2O_6$ $[M^+ + H]$ and $[M^+ + H + 2]$: *m/z* 585.1228, 587.1198 Found: 585.1228, 587.1197.

Compound 16bc



Yield: 102.3 mg (35%, yellow solid, R_f = 0.44 (9:1 hexane/ethyl acetate)).

Mp: >300 ºC.

IR (neat): ν_{max} 3318, 2922, 2851, 1707, 1597, 1505, 1444, 1344, 1229, 1202, 1157, 1050, 1020, 807, 742, 700 cm^{-1}.

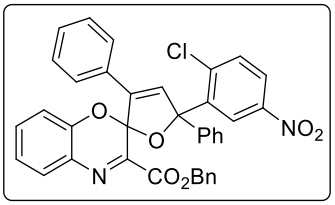
^1H NMR (500 MHz, $CDCl_3$): δ 9.05 (s, 1H), 8.14 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.98 (d, *J* = 2.5 Hz, 1H), 7.71-7.68 (m, 2H), 7.65 (d, *J* = 9.0 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.50 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.28 (s, 1H), 7.26-7.24 (m, 4H), 7.22-7.18 (m, 3H), 6.91 (s, 1H), 4.38 (q, *J* = 7.0 Hz, 2H), 1.39 (t, *J* = 7.0 Hz, 3H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 162.7 (d, *J* = 246.4 Hz), 161.4, 146.7, 145.2, 143.5, 143.2, 140.2, 139.9, 136.5, 135.0, 134.4, 132.2, 131.3, 129.6 (d, *J* = 7.7 Hz), 129.1, 128.8, 127.0, 126.1, 125.0, 124.5, 123.2, 119.3, 115.7 (d, *J* = 21.6 Hz), 112.1, 105.8, 66.0, 61.2, 14.4 ppm.

^{19}F NMR (470 MHz, $CDCl_3$): δ -113.5 ppm.

HRMS (ESI-TOF): Calcd. for $C_{32}H_{23}FClN_2O_4$ $[M^+ + H]$ and $[M^+ + H + 2]$: *m/z* 553.1330, 555.1300 Found: 553.1343, 555.1304.

Compound 15ca



Yield: 160.2 mg (64%, white solid, R_f = 0.52 (9:1 hexane/ethyl acetate)).

Mp: 218-220 ºC.

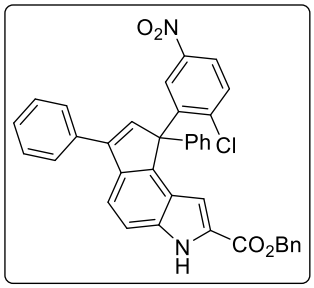
IR (neat): ν_{max} 3054, 2985, 1731, 1605, 1527, 1347, 1265, 1033, 982, 896, 830, 739, 704 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.68 (d, *J* = 2.5 Hz, 1H), 8.17 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.60 (s, 1H), 7.54-7.49 (m, 4H), 7.32-7.28 (m, 6H), 7.26-7.21 (m, 6H), 7.04-7.00 (m, 3H), 5.14 (q, *J* = 12.5 Hz, 2H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 161.4, 147.0, 146.7, 144.4, 143.6, 140.8, 139.9, 138.3, 135.0, 132.5, 131.8, 131.2, 130.8, 129.9, 129.0, 128.8, 128.7, 128.4_2, 128.4_0, 128.2, 128.0, 127.4, 126.9, 123.9, 123.6, 123.4, 117.6, 103.8, 94.9, 67.4 ppm.

HRMS (ESI-TOF): Calcd. for $C_{37}H_{25}ClN_2O_6Na$ [M^+ + Na] and [M^+ + Na + 2]: *m/z* 651.1299, 653.1269 Found: 651.1298, 653.1299.

Compound 16ca



Yield: 78.1 mg (33%, yellow solid, R_f = 0.44 (9:1 hexane/ethyl acetate)).

Mp: >300 °C.

IR (neat): ν_{max} 3323, 2924, 1707, 1570, 1523, 1493, 1447, 1344, 1226, 1186, 1130, 1077, 1048, 965, 907, 830, 735, 697 cm^{-1}.

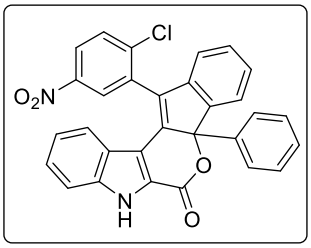
^1H NMR (500 MHz, $CDCl_3$): δ 9.02 (s, 1H), 8.33 (d, *J* = 2.5 Hz, 1H), 8.20 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.69 (d, *J* = 8.5 Hz, 1H), 7.50 (d, *J* = 9.0 Hz, 2H), 7.44-7.37 (m, 2H), 7.36-7.28 (m, 4H), $7.25\text{-}7.23_1$ (m, 3H), 7.23-7.20 (m, 2H), 7.18-7.17 (m, 2H), 7.09-7.07 (m, 2H), 6.83-6.80 (m, 1H), 6.36 (d, *J* = 8.5 Hz, 1H), 5.12 (d, *J* = 12.0 Hz, 1H), 4.68 (d, *J* = 12.0 Hz, 1H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 161.2, 150.7, 146.5, 145.2, 144.5, 141.7, 140.6, 138.4, 137.7, 136.2, 135.7, 135.4, 130.8, 128.7, 128.5, 128.4, 127.4, 126.8, 126.4, 126.1, 126.0, 125.9, 125.1, 123.7, 123.4, 121.7, 121.1, 120.2, 111.7, 66.7, 62.6 ppm.

HRMS (ESI-TOF): Calcd. for $C_{37}H_{26}ClN_2O_4$ [M^+ + H] and [M^+ + H +2]: *m/z* 597.1581, 599.1551 Found: 597.1581, 599.1570.

3.2 Synthesis of indene fused pyrano-indolones: General procedure for the synthesis of compounds 17ba and 17ea-eb: To an oven dried 10 mL round-bottomed flask indole 2-carboxylate (**1b** or **1e**, 0.53 mmol), propargylic alcohol (one of **3a-b**, 0.53 mmol) and PTSA (0.53 mmol) were added. To this mixture, $MeNO_2$ (2 mL) was added, and the contents were stirred at 60 ^oC (oil bath temperature) for 12 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was quenched by adding water (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL). Then the combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography by using hexane/ethyl acetate (9:1) mixture as the eluent to afford the corresponding annulated products **17ba** and **17ea-eb**.

Compound 17ba



Yield: 246.2 mg (92%, white solid, R_f = 0.48 (9:1 hexane/ethyl acetate)).

Mp: 242-244 ^oC.

IR (neat): ν_{max} 3282, 2924, 2853, 1700, 1570, 1526,1462, 1346, 1288, 1260, 1133, 1050, 1012, 799, 741, 697 cm^{-1}.

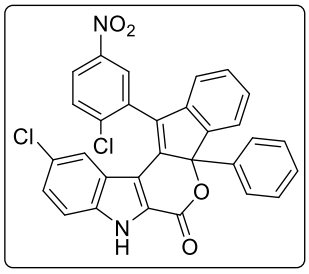
^1H NMR (400 MHz, $CDCl_3$): major isomer δ 9.33 (s, 1H), 8.40 (dd, *J* = 8.8, 2.8 Hz, 1H), 8.17 (d, *J* = 2.8 Hz, 1H), 7.98 (d, *J* = 8.8 Hz, 1H), 7.74-7.71 (m, 2H), 7.64-7.62 (m, 1H), 7.50-7.48 (m, 1H), 7.43-7.41 (m, 1H), 7.28-7.27 (m, 2H), 7.26-7.21 (m, 3H), 7.02-7.00 (m, 1H), 6.88-6.84 (m, 1H), 6.24 (d, *J* = 1.0 Hz, 1H) ppm; minor isomer δ 9.31 (s, 1H), 8.72 (d, *J* = 2.4 Hz, 1H), 7.69-7.62 (m, 1H), 7.34-7.31 (m, 1H), 7.21-7.20 (m, 1H), 6.92-6.89 (m, 1H), 6.36-6.33 (m, 1H) ppm.

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): major isomer δ 161.8, 146.8, 145.7, 142.0, 141.7, 141.5, 140.7, 139.0, 138.3, 135.9, 134.7, 131.0, 129.5, 129.1, 128.3, 127.5, 127.2, 126.8, 125.0, 124.5, 124.0, 123.1, 122.2, 121.7, 121.5, 117.0, 113.1, 94.5 ppm; minor isomer δ 161.9, 146.6, 145.5, 142.5, 141.9, 140.8, 139.2, 138.2, 135.1, 133.8, 131.5, 129.6, 129.1, 128.4, 127.7, 127.1, 126.3, 124.8, 124.3, 123.0, 122.7, 122.2, 121.6, 120.6, 118.4, 113.0 ppm.

HRMS (ESI-TOF): Calcd. for $C_{30}H_{17}ClN_2O_4Na$ $[M^+ + Na]$ and $[M^+ + Na + 2]$: *m/z* 527.0775, 529.0745 Found: 527.0778, 529.0747.

This compound was crystallized from dichloromethane–hexane (2:1) mixture at room temperature. X-ray structure has been determined for this compound.

Compound 17ea



Yield: 217.7 mg (90%, white solid, R_f = 0.49 (9:1 hexane/ethyl acetate)).

Mp: 241-243 ºC.

IR (neat): ν_{max} 2922, 2853, 1705, 1526, 1462, 1243, 1056, 855, 742, 698 cm^{-1}.

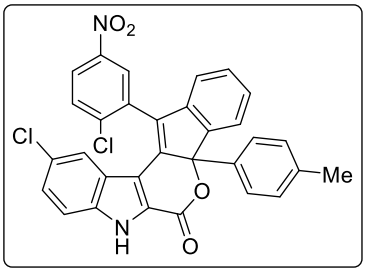
^{1}H NMR (400 MHz, $CDCl_3$): major isomer δ 9.51 (s, 1H), 8.45 (dd, *J* = 8.8, 2.8 Hz, 1H), 8.16 (d, *J* = 2.4 Hz, 1H), 8.01 (d, *J* = 8.8 Hz, 1H), 7.71 (d, *J* = 7.2 Hz, 2H), 7.49 (d, *J* = 6.8 Hz, 1H), 7.39-7.34 (m, 2H), 7.33-7.29 (m, 2H), 7.27_4-7.27_0 (m, 1H), 7.25-7.20 (m, 2H), 7.05 (d, *J* = 7.6 Hz, 1H), 6.07 (s, 1H) ppm; minor isomer δ 9.49 (s, 1H), 8.72 (d, *J* = 2.8 Hz, 1H), 7.62 (d, *J* = 1.6 Hz, 1H), 6.17 (s, 1H) ppm.

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): major isomer δ 161.5_5, 146.9, 145.6, 141.8, 140.6, 141.5, 140.5, 138.4, 136.6, 135.5, 135.3, 131.1, 129.6, 129.1, 128.4, 127.9, 127.7_4, 127.6, 126.8, 125.2, 124.4, 124.3, 124.1_3, 122.9, 121.7, 121.3, 116.5, 114.3, 94.4 ppm; minor isomer δ 161.6_4, 146.6, 145.4, 142.2, 141.6, 140.6, 138.6,

136.5, 134.8, 134.3, 130.5, 129.7, 129.2, 128.5, 127.6$_5$, 127.5, 126.2, 125.0, 124.3$_6$, 124.0$_9$, 123.7, 121.2, 120.8, 117.8, 114.2 ppm.

HRMS (ESI-TOF): Calcd. for $C_{30}H_{17}Cl_2N_2O_4$ [M^+ + H] and [M^+ + H +2]: *m/z* 539.0565, 541.0535 Found: 539.0565, 541.0544.

Compound 17eb



Yield: 217.5 mg (88%, white solid, R_f = 0.49 (9:1 hexane/ethyl acetate)).

Mp: 246-248 ^oC.

IR (neat): ν_{max} 3299, 2922, 2853, 1698, 1525, 1459, 1374, 1341, 1244, 1135, 1056, 996, 972, 862, 806, 767 cm^{-1}.

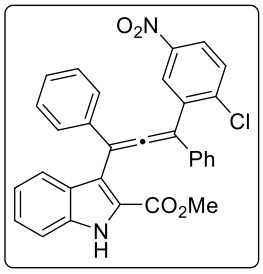
^1H NMR (500 MHz, $CDCl_3$): major isomer δ 9.38 (s, 1H), 8.44 (dd, *J* = 9.0, 2.5 Hz, 1H), 8.14 (d, *J* = 2.5 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.48 (d, *J* = 7.5 Hz, 2H), 7.34-7.33 (m, 1H), 7.31-7.29 (m, 1H), 7.24-7.23 (m, 1H), 7.09-7.08 (m, 2H), 7.04-7.02 (m, 1H), 6.06 (s, 1H), 2.25 (s, 3H) ppm; minor isomer δ 9.36 (s, 1H), 8.70 (d, *J* = 2.5 Hz, 1H), 7.71 (d, *J* = 9.0 Hz, 1H), 7.27-7.25 (m, 1H), 7.22-7.21 (m, 1H), 7.11 (br s, 1H), 6.15 (s, 1H), 2.26 (s, 1H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): major isomer δ 161.4, 146.9, 145.7, 141.7, 141.5, 138.4, 138.3, 137.7, 137.5, 136.5, 135.5, 135.1, 131.1, 129.8, 129.5, 127.7$_0$, 127.6$_5$, 127.5$_8$, 126.8, 125.1, 124.4, 124.0, 123.0, 121.6, 121.3, 116.4, 114.2, 94.4 ppm; minor isomer δ 161.5, 146.6, 145.6, 144.9, 142.2, 141.7, 138.6, 136.4, 134.8, 131.6, 129.9, 129.6, 127.9, 127.5, 126.2, 125.0, 124.2$_3$, 124.1$_8$, 123.8, 121.3, 120.8, 117.8, 114.1 ppm.

HRMS (ESI-TOF): Calcd. for $C_{31}H_{19}Cl_2N_2O_4$ [M^+ + H] and [M^+ + H +2]: *m/z* 553.0722, 555.0692 Found: 553.0725, 555.0702.

3.3 Synthesis of 3-allenyl-indole-2-carboxylates: General procedure for the synthesis of compounds 18aa-18db: To an oven dried 10 mL round-bottomed flask, indole 2-carboxylate (**1a-b**, **1d**; 0.53 mmol), propargylic alcohol (one of **3a-c**, 0.26 mmol) and PTSA (20 mol%) were added. To this mixture, toluene (2 mL) was added, and the contents were stirred at rt for 6 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was quenched by adding water (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL). Then the combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography by using hexane/ethyl acetate (9:1) mixture as the eluent to afford the corresponding product.

Compound 18aa



Yield: 249.8 mg (84%, yellow solid, R_f = 0.52 (9:1 hexane/ethyl acetate)).

Mp: 172-174 ºC.

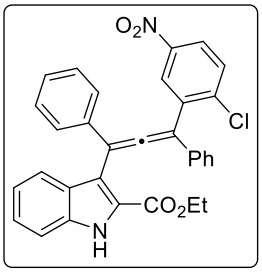
IR (neat): ν_{max} 3442, 3054, 2986, 1702, 1528, 1446, 1347, 1265, 1050, 896, 739, 705 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 9.07 (s, 1H), 8.14-8.10 (m, 2H), 7.56 (d, *J* = 8.5 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.32-7.28 (m, 3H), 7.26-7.22 (m, 4H), 7.20-7.15 (m, 5H), 7.01-6.98 (m, 1H), 3.47 (s, 3H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 207.2, 162.2, 146.6, 141.6, 136.9, 135.9, 135.5, 134.6, 130.8, 128.9, 128.6, 128.1, 127.9, 127.7, 127.0, 126.9, 126.8, 126.1, 124.3, 123.8, 121.6, 121.2, 115.9, 112.0, 108.1, 106.0, 51.8 ppm.

HRMS (ESI-TOF): Calcd. for $C_{31}H_{22}ClN_2O_4$ $[M^+ + H]$ and $[M^+ + H + 2]$: *m/z* 521.1268, 523.1238. Found: 521.1266, 523.1231.

Compound 18ba



Yield: 226.2 mg (80%, yellow solid, R_f = 0.54 (9:1 hexane/ethyl acetate)).

Mp: 242-244 °C.

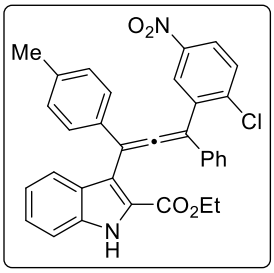
IR (neat): ν_{max} 3315, 2924, 1678, 1523, 1491, 1446, 1343, 1327, 1238, 1181, 1143, 1084, 1048, 1018, 853, 762, 741, 691 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 9.11 (s, 1H), 8.24-8.21 (m, 2H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.42-7.37 (m, 4H), 7.36-7.28 (m, 7H), 7.27-7.24 (m, 1H), 7.11-7.08 (m, 1H), 4.18-4.06 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 207.0, 161.6, 146.6, 141.6, 136.9, 135.8, 135.7, 134.5, 130.8, 128.8, 128.5, 128.3, 127.8, 127.6, 127.0, 126.8, 126.7, 126.0, 124.6, 123.8, 121.3, 121.2, 115.6, 111.9, 108.2, 106.3, 61.0, 13.8 ppm.

HRMS (ESI-TOF): Calcd. for $C_{32}H_{24}ClN_2O_4$ [M^+ + H] and [M^+ + H + 2]: *m/z* 535.1424, 537.1394. Found: 535.1426, 537.1395.

Compound 18bb



Yield: 226.3 mg (78%, yellow solid, R_f = 0.54 (9:1 hexane/ethyl acetate)).

Mp: 224-226 °C.

IR (neat): ν_{max} 3315, 2922, 1678, 1523, 1446, 1341, 1238, 1179, 1143, 1084, 1048, 1018, 853, 821, 764, 740, 692 cm^{-1}.

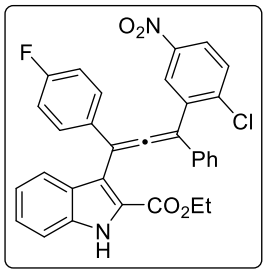
^1H NMR (500 MHz, $CDCl_3$): δ 9.19 (s, 1H), 8.23-8.20 (m, 2H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.41-7.37 (m, 2H), 7.36-7.35 (m, 1H), 7.33-7.26 (m, 6H),

7.12-7.07 (m, 3H), 4.21-4.03 (m, 2H), 2.35 (s, 3H), 0.99 (t, *J* = 7.3 Hz, 3H) ppm.

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 206.8, 161.7, 146.6, 141.6, 137.5, 137.0, 135.8, 134.6, 132.7, 130.8, 129.3, 128.8, 128.3, 127.7, 127.0, 126.6$_9$, 126.6$_7$, 126.0, 124.6, 123.7, 121.4, 121.2, 115.8, 111.9, 108.0, 106.2, 61.0, 21.2, 13.8 ppm.

HRMS (ESI-TOF): Calcd. for $C_{33}H_{25}ClN_2O_4Na$ [M^+ + Na] and [M^+ + Na + 2]: *m/z* 571.1401, 573.1371. Found: 571.1404, 573.1377.

Compound 18bc



Yield: 216.3 mg (74%, yellow solid, R_f = 0.57 (9:1 hexane/ethyl acetate)).

Mp: 230-232 ^{o}C.

IR (neat): ν_{max} 3324, 2923, 2853, 1702, 1600, 1527, 1505, 1450, 1343, 1233, 1184, 1155, 1049, 1018, 907, 837, 732, 693 cm^{-1}.

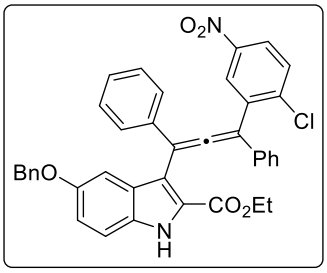
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.19 (s, 1H), 8.25-8.21 (m, 2H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.41-7.27 (m, 9H), 7.11-7.07 (m, 1H), 7.03-6.98 (m, 2H), 4.22-4.07 (m, 2H), 1.02 (t, *J* = 7.2 Hz, 3H) ppm.

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 206.7, 163.3 (d, *J* = 196.4 Hz), 161.5, 146.6, 141.5, 136.7, 135.8, 134.3, 131.7, 130.9, 128.9, 128.4 (d, *J* = 6.4 Hz), 128.1, 127.9, 127.0, 126.7, 126.1, 124.5, 123.9, 121.3 (d, *J* = 12.3 Hz), 115.5 (d, *J* = 17.3 Hz), 115.5, 112.0, 108.3, 105.4, 61.1, 13.9 ppm.

^{19}F NMR (375 MHz, $CDCl_3$): δ -114.5 ppm.

HRMS (ESI-TOF): Calcd. for $C_{32}H_{22}ClFN_2O_4Na$ [M^+ + Na] and [M^+ + Na + 2]: *m/z* 575.1150, 577.1120. Found: 575.1149, 577.1122.

Compound 18da



Yield: 165.3 mg (76%, yellow solid, R_f = 0.48 (9:1 hexane/ethyl acetate)).

Mp: 246-248 °C.

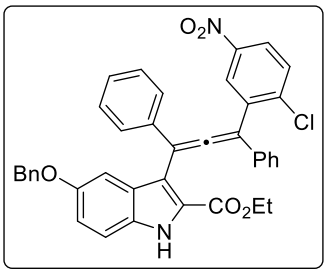
IR (neat): ν_{max} 3314, 2919, 1679, 1525, 1462, 1343, 1224, 1184, 1016, 799, 693 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 9.06 (s, 1H), 8.25 (d, *J* = 2.5 Hz, 1H), 8.16 (dd, *J* = 8.8 Hz, 3.0 Hz, 1H), 7.64 (d, *J* = 9.0 Hz, 1H), 7.43-7.40 (m, 2H), 7.39-7.36 (m, 3H), 7.35-7.31 (m, 9H), 7.28-7.24 (m, 2H), 7.09 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.84 (d, *J* = 2.5 Hz, 1H), 4.57 (d, *J* = 11.0 Hz,, 1H), 4.49 (d, *J* = 11.0 Hz,, 1H), 4.14-4.03 (m, 2H), 0.93 (t, *J* = 7.0 Hz, 3H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 207.5, 161.4, 154.3, 146.6, 141.6, 136.9, 135.9, 135.1, 131.2, 130.9, 128.9, 128.7, 128.5_1, 128.5_0, 127.9, 127.8, 127.6, 127.0, 126.9, 126.8, 125.1, 123.7, 118.3, 115.1, 112.9, 108.0, 106.5, 102.3, 70.2, 60.9, 13.7 ppm.

HRMS (ESI-TOF): Calcd. for $C_{39}H_{30}ClN_2O_5$ $[M^+ + H]$ and $[M^+ + H + 2]$: *m/z* 641.1843, 643.1813. Found: 641.1841, 643.1827.

Compound 18db



Yield: 175.2 mg (79%, yellow solid, R_f = 0.50 (9:1 hexane/ethyl acetate)).

Mp: 218-220 °C.

IR (neat): ν_{max} 3322, 2923, 2852, 1710, 1527, 1455, 1344, 1264, 1223, 1186, 1021, 898, 735, 702 cm^{-1}.

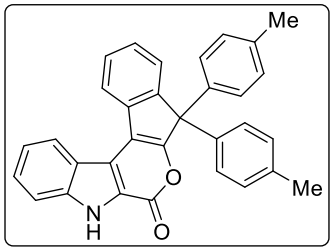
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.06 (s, 1H), 8.24 (d, *J* = 2.8 Hz, 1H), 8.15 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.39-7.34 (m, 4H), 7.33-7.24 (m, 9H), 7.14-7.07 (m, 3H), 6.84 (d, *J* = 2.4 Hz, 1H), 4.57 (d, *J* = 11.0 Hz, 1H), 4.49 (d, *J* = 11.0 Hz, 1H), 4.17-4.01 (m, 2H), 2.36 (s, 3H), 0.95 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 207.3, 161.5, 154.2, 146.6, 141.6, 137.5, 137.0, 136.9, 135.2, 132.8, 131.1, 130.9, 129.3, 128.8, 128.7, 128.5,127.9, 127.8_3, 127.8_0, 126.9_9, 126.9_5, 126.7, 125.0, 123.6, 118.3, 115.3, 112.8, 107.9, 106.4, 102.2, 70.1, 60.9, 21.2, 13.8 ppm.

HRMS (ESI-TOF): Calcd. for $C_{40}H_{31}ClN_2O_5Na$ [M^+ + Na] and [M^+ + Na + 2]: *m/z* 677.1819, 679.1789. Found: 677.1819, 679.1804.

3.4 Synthesis of indene fused pyrano-indolones (fused pentacyclics): General procedure for the synthesis of compounds 19aa-19bb: To an oven dried 10 mL round-bottomed flask, indole-2-carboxylic acid (**2a-b**, 0.62 mmol), propargylic alcohol (one of **4b-c**, **4e-i**, **4k**, **4m**, **4o** and **4p-q** 0.62 mmol), and $Cu(OTf)_2$ (10 mol%) were added. To this mixture, MeCN (2 mL) was added and the contents were stirred at room temperature (25 °C) for 12 h. Progress of the reaction was monitored by TLC. After the completion of the reaction, solvent was removed under the vacuum, and the crude product was purified by silica gel column chromatography by using hexane/ethyl acetate (9:1) mixture as the eluent to afford the corresponding product.

Compound 19ab



Yield: 267.4 mg (95%, white solid, R_f = 0.47 (9:1 hexane/ethyl acetate)).

Mp: >300 °C.

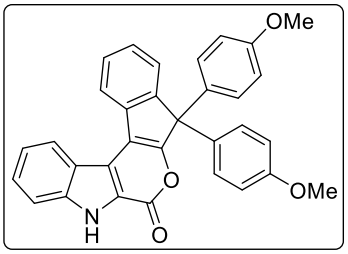
IR (neat): ν_{max} 3254, 2920, 2851, 1693, 1508, 1451, 1334, 1185, 1118, 1082, 1018, 810, 741, 697 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.34 (s, 1H), 8.50 (d, *J* = 8.4 Hz, 1H), 8.26 (d, *J* = 7.6 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.57-7.49 (m, 2H), 7.44-7.37 (m, 2H), 7.35-7.32 (m, 1H), 7.23-7.21 (m, 4H), 7.13-7.11 (m, 4H), 2.34 (s, 6H) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 161.2, 160.0, 146.7, 140.4, 139.0, 137.3, 137.1, 129.2, 128.3, 128.0, 127.7, 126.2, 126.0, 124.2, 122.4, 121.5, 121.5, 121.4, 115.8, 113.6, 63.4, 21.1 ppm.

HRMS (ESI-TOF): Calcd. for $C_{32}H_{24}NO_2$ [M^+ + H]: *m/z* 454.1807. Found: 454.1801.

Compound 19ac



Yield: 273.0 mg (91%, white solid, R_f = 0.44 (9:1 hexane/ethyl acetate)).

Mp: >300 ºC.

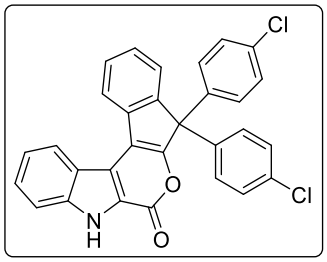
IR (neat): ν_{max} 3248, 2922, 2852, 1690, 1604, 1506, 1460, 1375, 1335, 1296, 1247, 1177, 1118, 1082, 1030, 910, 826, 741 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.93 (s, 1H), 8.50 (d, *J* = 8.5 Hz, 1H), 8.26 (d, *J* = 7.5 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.60-7.55 (m, 1H), 7.52-7.49 (m, 1H), 7.42-7.39 (m, 2H), 7.35-7.32 (m, 1H), 7.24-7.22 (m, 4H), 6.84-6.82 (m, 4H), 3.79 (s, 6H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 161.7, 158.8, 157.5, 146.9, 139.9, 137.1, 133.9, 129.4, 128.1, 127.7, 126.2, 125.9, 124.4, 122.3_3, 122.3_0, 121.7, 121.3, 115.2, 113.9, 113.2, 62.7, 55.3 (s, 2C) ppm.

HRMS (ESI-TOF): Calcd. for $C_{32}H_{24}NO_4$ [M^+ + H]: *m/z* 486.1705. Found: 486.1707.

Compound 19ae



Yield: 269.2 mg (88%, white solid, R_f = 0.49 (9:1 hexane/ethyl acetate)).

Mp: >300 ºC.

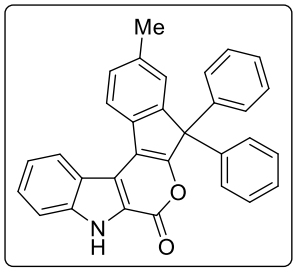
IR (neat): ν_{max} 3277, 2922, 2850, 1691, 1622, 1590, 1558, 1521, 1488, 1461, 1398, 1339, 1221, 1121, 1083, 1013, 911, 815, 773, 733, 606 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 9.86 (s, 1H), 8.50 (d, *J* = 8.5 Hz, 1H), 8.28 (d, *J* = 7.5 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.61-7.58 (m, 1H), 7.57-7.53 (m, 1H), 7.45-7.42 (m, 1H), 7.38-7.35 (m, 2H), 7.29-7.27 (m, 4H), 7.23-7.21 (m, 4H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 160.3, 157.2, 145.7, 140.2, 140.1, 137.4, 133.9, 129.9, 129.1, 128.5_3, 128.5_2, 126.7, 126.1, 124.6, 122.8, 122.2_1, 122.2_0, 121.9, 121.7, 116.1, 113.4, 63.2 ppm.

HRMS (ESI-TOF): Calcd. for $C_{30}H_{17}Cl_2NO_2Na$ [M^+ + Na] and [M^+ + Na +2]: *m/z* 516.0534, 518.0504. Found: 516.0531, 518.0501.

Compound 19af



Yield: 253.6 mg (93%, white solid, R_f = 0.48 (9:1 hexane/ethyl acetate)).

Mp: >300 ºC.

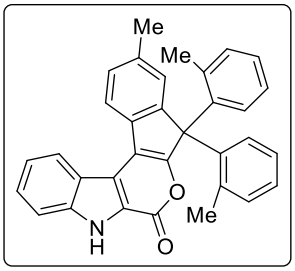
IR (neat): ν_{max} 3302, 2920, 2852, 1694, 1621, 1559, 1526, 1492, 1467, 1337, 1204, 1086, 1021, 912, 804, 732, 698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.92 (s, 1H), 8.49 (d, *J* = 8.0 Hz, 1H), 8.14 (d, *J* = 7.5 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.57-7.54 (m, 1H), 7.42-7.39 (m, 1H), 7.32-7.28 (m, 11H), 7.23 (s, 1H), 2.40 (s, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 160.5, 157.4, 146.4, 142.0, 139.9, 136.1, 134.4, 128.5, 128.4_4, 128.4_1, 128.0, 127.3, 126.8, 124.4, 122.3, 122.1, 121.7, 121.6, 121.4, 115.7, 113.1, 63.9, 21.7 ppm.

HRMS (ESI-TOF): Calcd. for $C_{31}H_{21}NO_2Na$ [M^+ + Na]: *m/z* 462.1470. Found: 462.1471.

Compound 19ag



Yield: 229.0 mg (79%, white solid, R_f = 0.53 (9:1 hexane/ethyl acetate)).

Mp: >300 ^{o}C.

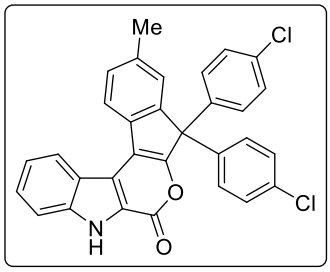
IR (neat): ν_{max} 3265, 2915, 2848, 1691, 1619, 1508, 1466, 1334, 1237, 1162, 1082, 1027, 912, 803, 758, 736, 622 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.57 (s, 1H), 8.47 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.54-7.50 (m, 1H), 7.38-7.35 (m, 1H), 7.32-7.29 (m, 1H), 7.26-7.24 (m, 4H), 7.16-7.14 (m, 5H), 2.44 (s, 3H), 2.37 (s, 6H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 160.8, 157.7, 146.9, 140.1, 139.1, 136.9, 136.0, 134.4, 129.2, 128.3, 127.9, 126.7, 124.3, 122.4, 122.0, 121.7, 121.5, 121.4, 115.5, 113.3, 63.3, 21.7, 21.0 ppm.

HRMS (ESI-TOF): Calcd. for $C_{33}H_{25}NO_2Na$ [M^+ + Na]: *m/z* 490.1783. Found: 490.1785.

Compound 19ah



Yield: 283.2 mg (90%, white solid, R_f = 0.46 (9:1 hexane/ethyl acetate)).

Mp: >300 ^oC.

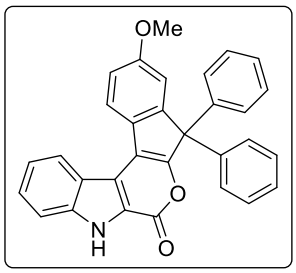
IR (neat): ν_{max} 3286, 1693, 1620, 1557, 1524, 1487, 1399, 1337, 1166, 1092, 1079, 1013, 913, 874, 826, 801, 773, 735, 657 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 10.01 (s, 1H), 8.48 (d, *J* = 8.5 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.60-7.56 (m, 1H), 7.44-7.41 (m, 1H), 7.34 (d, *J* = 7.5 Hz, 1H), 7.29-7.27 (m, 4H), 7.23-7.21 (m, 4H), 7.15 (s, 1H), 2.43 (s, 3H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 159.4, 157.2, 145.7, 140.1, 140.0, 136.5, 134.3, 133.6, 129.7, 128.9, 128.8, 128.2, 126.5, 124.3, 122.4, 122.1, 121.8, 121.7, 121.4, 115.9, 113.2, 62.8, 21.6 ppm.

HRMS (ESI-TOF): Calcd. for $C_{31}H_{20}Cl_2NO_2$ $[M^+ + H]$, $[M^+ + H + 2]$ and $[M^+ + H + 4]$: *m/z* 508.0871, 510.0841 and 512.0811. Found: 508.0860, 510.0835 and 512.0820.

Compound 19ai



Yield: 214.8 mg (76%, white solid, R_f = 0.48 (9:1 hexane/ethyl acetate)).

Mp: >300 ^oC.

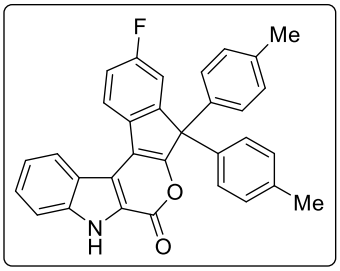
IR (neat): ν_{max} 3294, 3057, 2929, 2834, 1695, 1621, 1581, 1560, 1528, 1469, 1425, 1345, 1279, 1236, 1104, 1087, 1017, 912, 863, 796, 729, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.67 (s, 1H), 8.47 (d, *J* = 8.0 Hz, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.59-7.56 (m, 1H), 7.43-7.39 (m, 1H), 7.31-7.28 (m, 10H),7.04 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.99 (d, *J* = 2.5 Hz, 1H), 3.85 (s, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 159.7, 158.4, 157.2, 148.2, 141.9, 139.8, 129.8, 128.5, 128.4, 128.0, 127.4, 124.3, 123.0, 122.2, 121.8, 121.6, 121.4, 115.4, 113.2, 113.1, 112.4, 64.1, 55.5 ppm.

HRMS (ESI-TOF): Calcd. for $C_{31}H_{22}NO_3$ [M^+ + H]: *m/z* 456.1599. Found: 456.1592.

Compound 19ak



Yield: 269.2 mg (92%, white solid, R_f = 0.49 (9:1 hexane/ethyl acetate)).

Mp: >300 ^{o}C.

IR (neat): ν_{max} 3251, 3026, 2961, 2913, 1694, 1620, 1586, 1560, 1508, 1472, 1338, 1263, 1118, 1082, 1022, 913, 859, 803, 767, 733, 679 cm^{-1}.

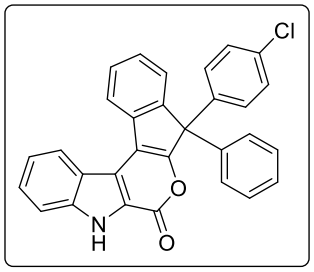
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H), 8.43 (d, *J* = 8.4 Hz, 1H), 8.18 (dd, *J* = 8.4, 4.8 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.59-7.55 (m, 1H), 7.43-7.39 (m, 1H), 7.22-7.20 (m, 1H), 7.19-7.17 (m, 4H), 7.17-7.13 (m, 5H), 2.34 (s, 6H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 161.5 (d, *J* = 243.8 Hz), 160.9, 157.2, 149.1 (d, *J* = 7.6 Hz), 139.9, 138.4, 137.3, 133.1, 129.3, 128.1$_3$, 128.0$_9$, 124.1, 123.2, 123.1, 121.9, 121.7, 121.6, 121.4, 114.7, 114.4 (d, *J* = 22.5 Hz), 113.9, 113.8, 113.3, 63.6, 21.0 ppm.

^{19}F NMR (376 MHz, $CDCl_3$): δ -114.7 ppm

HRMS (ESI-TOF): Calcd. for $C_{32}H_{23}FNO_2$ [M^+ + H]: *m/z* 472.1713. Found: 472.1693.

Compound 19am



Yield: 254.0 mg (89%, white solid, R_f = 0.47 (9:1 hexane/ethyl acetate)).

Mp: >300 °C.

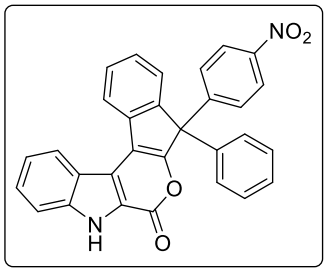
IR (neat): ν_{max} 3277, 3059, 1680, 1620, 1589, 1558, 1523, 1488, 1460, 1340, 1255, 1221, 1122, 1087, 1014, 915, 841, 826, 780, 739, 702, 681 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 8.51 (d, *J* = 8.0 Hz, 1H), 8.28 (d, *J* = 7.6 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.60-7.56 (m, 1H), 7.56- 7.52 (m, 1H), 7.45-7.40 (m, 1H), 7.39-7.33 (m, 2H), 7.31-7.28 (m, 5H), 7.27-7.24 (m, 4H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.5, 157.1, 145.8, 141.4, 140.3, 139.8, 137.2, 133.4, 129.8, 128.7, 128.2, 128.1, 127.6, 126.4, 126.0, 124.4, 122.5, 122.1, 121.9, 121.7, 121.4, 115.8, 113.1, 63.4 ppm.

HRMS (ESI-TOF): Calcd. for $C_{30}H_{19}ClNO_2$ $[M^+ + H]$, $[M^+ + H + 2]$: *m/z* 460.1104, 462.1074. Found: 460.1100, 462.1084.

Compound 19ao



Yield: 245.0 mg (84%, white solid, R_f = 0.46 (9:1 hexane/ethyl acetate)).

Mp: >300 °C.

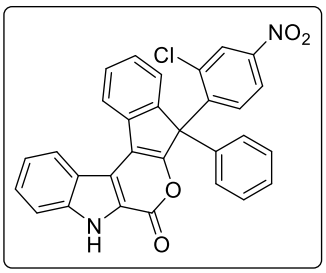
IR (neat): ν_{max} 3271, 2930, 1693, 1590, 1559, 1516, 1343, 1222, 1085, 1014, 911, 851, 736, 693, 605 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.51 (s, 1H), 8.51 (d, *J* = 7.5 Hz, 1H), 8.30 (d, *J* = 7.5 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, 2H), 7.67-7.57 (m, 3H), 7.47 (d, *J* = 8.0 Hz, 3H), 7.38-7.28 (m, 7H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 156.9, 149.6, 147.3, 145.0, 140.5, 139.8, 137.3, 129.3, 128.9, 128.5, 128.4, 128.2, 128.0, 126.6, 126.0, 124.3, 123.8, 122.7, 122.0, 121.8, 121.7, 121.4, 116.3, 113.2, 63.8 ppm.

HRMS (ESI-TOF): Calcd. for $C_{30}H_{19}N_2O_4$ [M^+ + H]: *m/z* 471.1345. Found: 471.1344.

Compound 19ap



Yield: 287.8 mg (92%, white solid, R_f = 0.46 (9:1 hexane/ethyl acetate)).

Mp: >300 ^{o}C.

IR (neat): ν_{max} 3256, 1683, 1590, 1560, 1520, 1461, 1341, 1224, 1122, 1086, 1051, 1020, 916, 737, 695 cm^{-1}.

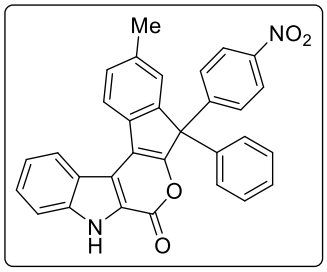
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.93 (s, 1H), 8.48 (d, *J* = 8.0 Hz, 1H), 8.31 (d, *J* = 7.6 Hz, 1H), 8.12-8.10 (m, 2H), 7.68-7.56 (m, 4H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.44-7.35 (m, 6H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 160.0, 156.9, 146.5, 142.7, 141.5, 140.9, 139.9, 139.1, 138.3, 132.7, 129.0, 128.8, 128.3_2, 128.3_0, 127.0, 126.4, 125.8, 124.3, 123.5, 122.6, 122.4, 121.8, 121.6, 121.3, 116.2, 113.2, 63.3 ppm.

HRMS (ESI-TOF): Calcd. for $C_{30}H_{18}ClN_2O_4$ [M^+ + H], [M^+ + H +2]: *m/z* 505.0955, 507.0925. Found: 505.0957, 507.0936.

This compound was crystallized from ethyl acetate–hexane (2:1) mixture at room temperature. X-ray structure has been determined for this compound.

Compound 19aq



Yield: 258.4 mg (86%, white solid, R_f = 0.46 (9:1 hexane/ethyl acetate)).

Mp: >300 °C.

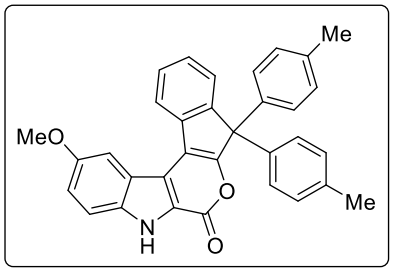
IR (neat): ν_{max} 3263, 2932, 1695, 1592, 1558, 1519, 1345, 1104, 1083, 1020, 912, 852, 802, 737, 706 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 9.66 (s, 1H), 8.49 (d, *J* = 8.0 Hz, 1H), 8.18-8.14 (m, 3H), 7.67-7.58 (m, 2H), 7.47-7.43 (m, 3H), 7.37-7.23 (m, 6H), 7.18 (s, 1H), 2.43 (s, 3H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 158.9, 157.1, 149.8, 147.2, 145.2, 140.7, 139.8, 136.6, 134.4, 129.3, 129.1, 128.9, 128.3, 128.2, 127.9, 126.7, 124.3, 123.8, 122.5, 122.0, 121.7, 121.4, 116.3, 113.2, 63.7, 21.7 ppm.

HRMS (ESI-TOF): Calcd. for $C_{31}H_{21}N_2O_4$ $[M^+ + H]$: *m/z* 485.1501. Found: 485.1502.

Compound 19bb



Yield: 214.8 mg (85%, white solid, R_f = 0.51 (9:1 hexane/ethyl acetate)).

Mp: >300 °C.

IR (neat): ν_{max} 3259, 2922, 2852, 1697, 1509, 1485, 1461, 1259, 1212, 1080, 1017, 799, 739, 700 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ 9.70 (s, 1H), 8.20 (d, *J* = 7.6 Hz, 1H), 7.88 (d, *J* = 2.0 Hz, 1H), 7.56 (d, *J* = 9.2 Hz, 1H), 7.49 (td, *J* = 7.6, 1.2 Hz 1H), 7.41 (d, *J* = 7.2 Hz, 1H),

7.34-7.30 (m, 1H), 7.28-7.25 (m, 1H), 7.19-7.18 (m, 4H), 7.11-7.09 (m, 4H), 4.03 (s, 3H), 2.33 (s, 6H) ppm.

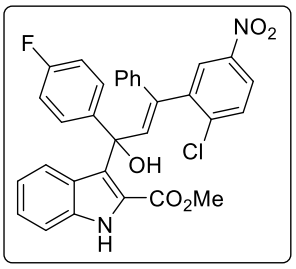
$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 161.0, 157.2, 155.1, 146.8, 138.9, 137.4, 137.0, 135.2, 129.1, 128.2, 127.6, 126.1, 126.0, 122.1, 121.9$_3$, 121.9$_0$, 121.7, 118.9, 115.2, 113.8, 105.6, 63.4, 56.1, 21.0 ppm.

HRMS (ESI-TOF): Calcd. for $C_{33}H_{26}NO_3$ $[M^+ + H]$: *m/z* 484.1912. Found: 484.1916.

This compound was crystallized from chloroform–hexane (2:1) mixture at room temperature. X-ray structure has been determined for this compound.

3.5 Synthesis of methyl (*E*)-3-(3-(2-chloro-5-nitrophenyl)-1-(4-fluorophenyl)-1-hydroxy-3-phenylallyl)-1*H*-indole-2-carboxylate intermediate X: To an oven dried 10 mL round-bottomed flask indole 2-carboxylate (**1a**, 0.53 mmol), propargylic alcohol (one of **3c**, 0.26 mmol) and PTSA (0.43 mmol) were added. To this mixture, toluene (2 mL) was added, and the contents were stirred at rt for 6 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was quenched by adding water (20 mL). The aqueous layer was extracted with ethyl acetate (3 × 10 mL). Then the combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography by using hexane/ethyl acetate (9:1) mixture as the eluent to afford **X**.

Intermediate X



Yield: 89.0 mg (56%, yellow solid, R_f = 0.35 (4:1 hexane/ethyl acetate))).

Mp: >250 °C.

IR (neat): ν_{max} 3336, 2923, 2853, 1715, 1602, 1523, 1506, 1444, 1344, 1252, 1157, 1048, 911, 837, 765, 743, 697 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (s, 1H), 7.82 (d, *J* = 2.4 Hz, 1H), 7.66-7.59 (m, 2H), 7.42 (s, 1H), 7.33-7.28 (m, 3H), 7.25-7.21 (m, 2H), 7.16 (d, *J* = 5.5 Hz, 3H), 7.11-7.06 (m, 3H), 7.028 (br, 1H), 6.76-6.73 (m, 1H), 6.29 (d, *J* = 8.4 Hz, 1H), 3.98 (s, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 163.3, 162.4 (d, *J* = 246.6 Hz), 145.0, 140.2, 139.9, 139.1, 138.4, 137.4, 135.1, 131.3, 130.5, 130.1, 129.4, 129.2, 128.3 (d, *J* = 63.6 Hz), 127.5, 126.8, 126.1, 124.3, 123.8, 123.3, 122.4, 122.2, 121.9, 120.9, 115.2 (d, *J* = 21.4 Hz), 111.4, 76.2, 52.9 ppm.

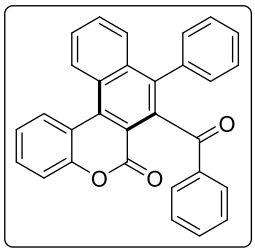
^{19}F NMR (376 MHz, $CDCl_3$): -114.2 ppm.

HRMS (ESI-TOF): Calcd. for $C_{31}H_{22}ClFN_2O_5Na$ [M^+ + Na], [M^+ + Na + 2]: *m/z* 579.1099, 581.1069. Found: 579.1099, 581.1095.

This compound was crystallized from ethyl acetate–hexane (2:1) mixture at room temperature. X-ray structure has been determined for this compound.

3.6 Synthesis of 6*H*-naphtho[2,1-*c*]chromen-6-ones: General procedure for the synthesis of compounds 20aa-20le: To an oven dried Schlenk tube, coumarin-3-carboxylic acid (**5a**, 0.53 mmol), propargylic alcohol (one of **4**, 0.53 mmol) and $Cu(OTf)_2$ (20 mol%) were added. To this mixture, 1,4-dioxane (2 mL) was added and the contents were stirred at 120 ^{o}C for 12 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and ethyl acetate (20 mL) was added. The solution was concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography by using hexane/ethyl acetate (9:1) mixture as the eluent to afford the corresponding annulated products **20**.

Compound 20aa



Yield: 199.6 mg (89%, white solid, R_f = 0.43 (9:1 hexane/ethyl acetate)).

Mp: 222-224 ºC.

IR (neat): ν_{max} 3059, 2821, 1714, 1673, 1452, 1376, 1232, 760, 738, 601 cm^{-1}.

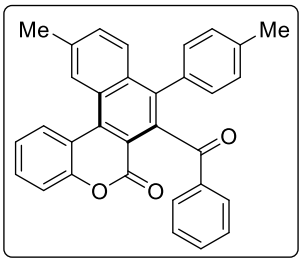
^1H NMR (500 MHz, $CDCl_3$): δ 8.88 (d, *J* = 8.5 Hz, 1H), 8.47 (d, *J* = 8.0 Hz, 1H), 7.70-7.67 (m, 1H), 7.61-7.57 (m, 2H), 7.55-7.49 (m, 3H), 7.43-7.37 (m, 2H), 7.35-7.29 (m, 3H), 7.21-7.17 (m, 3H), 7.03-7.00 (m, 1H), 6.86 (d, *J* = 8.0 Hz, 1H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 196.2, 160.1, 151.7, 139.2, 138.2, 136.6, 136.3, 135.5_1, 135.4_6, 132.5, 131.8, 130.6, 130.1, 129.6, 128.8, 128.5, 128.3, 128.1, 127.9_2, 127.8_6, 127.8, 127.4_4, 127.3_9, 124.3, 118.4, 117.9 ppm.

HRMS (ESI-TOF): Calcd. for $C_{30}H_{19}O_3$ $[M^+ + H]$: *m/z* 427.1334. Found: 427.1339.

This compound was crystallized from ethyl acetate–hexane (2:1) mixture at room temperature. X-ray structure has been determined for this compound.

Compound 20ba



Yield: 205.6 mg (86%, white solid, R_f = 0.50 (9:1 hexane/ethyl acetate)).

Mp: 218-220 ºC.

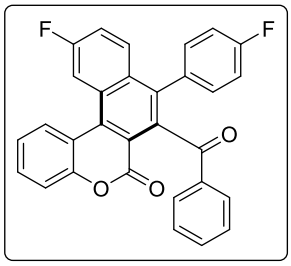
IR (neat): ν_{max} 2920, 2851, 1720, 1683, 1599, 1450, 1366, 1257, 1230, 1171, 1132, 1110, 1022, 958, 904, 832, 805, 769, 720 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.65 (s, 1H), 8.47 (d, *J* = 7.5 Hz, 1H), 7.56-7.47 (m, 4H), 7.41-7.36 (m, 3H), 7.34-7.31 (m, 1H), 7.20-7.16 (m, 3H), 7.14-7.12 (m, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.74 (dd, *J* = 8.0, 1.5 Hz, 1H), 2.57 (s, 3H), 2.24 (s, 3H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 196.4, 160.2, 151.7, 139.3, 138.4, 138.0, 137.6, 135.7, 134.7, 132.6, 132.4, 131.6, 130.3, 129.8, 129.0, 128.8, 128.5, 128.4, 128.1, 128.0, 127.8, 126.6, 124.2, 118.6, 118.0, 117.9, 22.1, 21.3 ppm.

HRMS (ESI-TOF): Calcd. for $C_{32}H_{23}O_3$ $[M^+ + H]$: *m/z* 455.1647. Found: 455.1642.

Compound 20da



Yield: 189.7 mg (78%, white solid, R_f = 0.53 (9:1 hexane/ethyl acetate)).

Mp: 210-212 °C.

IR (neat): ν_{max} 2959, 2922, 2852, 1722, 1677, 1601, 1512, 1487, 1453, 1431, 1369, 1292, 1259, 1207, 1174, 1155, 1127, 1092, 957, 938, 801, 773, 761 cm^{-1}.

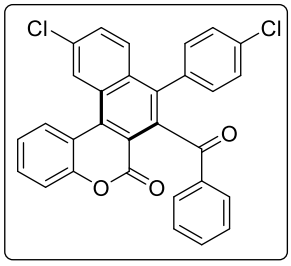
^1H NMR (500 MHz, $CDCl_3$): δ 8.54 (dd, *J* = 11.0, 2.5 Hz, 1H), 8.42 (d, *J* = 8.0 Hz, 1H), 7.60-7.57 (m, 1H), 7.55-7.51 (m, 3H), 7.43-7.33 (m, 4H), 7.28-7.25 (m, 1H), 7.22-7.18 (m, 2H), 7.05-7.01 (m, 1H), 6.83-6.80 (m, 1H), 6.74-6.70 (m, 1H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 195.9, 162.4 (d, *J* = 247.2 Hz), 162.1 (d, *J* = 247.9 Hz), 159.8, 151.6, 138.0 (d, *J* = 21.3 Hz), 136.6, 134.9, 133.6, (d, *J* = 7.7 Hz), 133.3, 132.8, 131.7 (d, *J* = 8.1 Hz), 130.9, 130.4 (d, *J* = 8.8 Hz), 129.4 (d, *J* = 9.0 Hz), 128.8, 128.3, 127.7, 124.7, 119.8, 119.5, 118.9, 118.1, 115.6 (d, *J* = 21.6 Hz), 114.7 (d, *J* = 21.6 Hz), 111.9 (d, *J* = 21.0 Hz) ppm.

^{19}F NMR (471 MHz, $CDCl_3$): δ -110.7, -113.1 ppm.

HRMS (ESI-TOF): Calcd. for $C_{30}H_{17}F_2O_3$ $[M^+ + H]$: *m/z* 463.1146. Found: 463.1148.

Compound 20ea



Yield: 216.2 mg (83%, white solid, R_f = 0.51 (9:1 hexane/ethyl acetate)).

Mp: 168-170 °C.

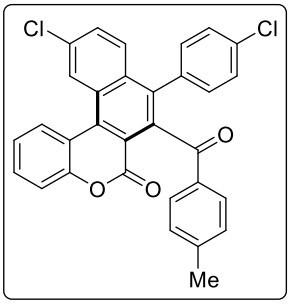
IR (neat): ν_{max} 2969, 2929, 1737, 1674, 1597, 1453, 1366, 1264, 1229, 1090, 1016, 955, 899, 732, 703 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.0 (s, 1H), 8.48 (d, *J* = 7.5 Hz, 1H), 7.66-7.59 (m, 5H), 7.55-7.51 (m, 2H), 7.47-7.44 (m, 1H), 7.42 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.33-7.30 (m, 3H), 7.11 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.87 (dd, *J* = 8.0, 2.5 Hz, 1H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 195.6, 159.6, 151.7, 137.8$_4$, 137.7$_6$, 137.2, 134.8, 134.7, 134.5, 134.4, 133.4, 133.1, 132.8, 131.2, 131.0, 130.5, 129.0, 128.7, 128.3, 128.0, 127.9, 126.6, 124.7, 118.8, 118.1, 117.8 ppm.

HRMS (ESI-TOF): Calcd. for $C_{30}H_{17}Cl_2O_3$ [M^+ + H]: *m/z* 495.0554. Found: 495.0558.

Compound 20ha



Yield: 203.6 mg (76%, white solid, R_f = 0.55 (9:1 hexane/ethyl acetate)).

Mp: 152-154 ^{o}C.

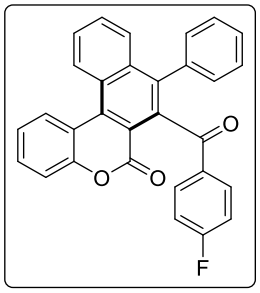
IR (neat): ν_{max} 2960, 2922, 2856, 1722, 1660, 1604, 1489, 1453, 1418, 1369, 1258, 1235, 1174, 1086, 1015, 953, 897, 798, 758 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.85 (s, 1H), 8.38 (d, *J* = 8.0 Hz, 1H), 7.55-7.48 (m, 3H), 7.44-7.41 (m, 4H), 7.32 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.23 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.05-7.00 (m, 3H), 6.80 (dd, *J* = 8.0, 2.0 Hz, 1H), 2.26 (s, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 195.2, 159.5, 151.7, 143.7, 137.7, 137.3, 135.5, 134.8, 134.6, 134.4, 133.5, 133.1, 131.2, 131.0, 130.5, 129.1, 129.0, 128.8, 128.7, 128.0, 127.9, 126.5, 124.7, 118.8, 118.1, 117.9, 21.7 ppm.

HRMS (ESI-TOF): Calcd. for $C_{31}H_{19}Cl_2O_3$ [M^+ + H]: *m/z* 509.0711. Found: 509.0710.

Compound 20ja



Yield: 184.6 mg (79%, white solid, R_f = 0.50 (9:1 hexane/ethyl acetate)).

Mp: 174-176 ºC.

IR (neat): ν_{max} 2923, 2852, 1720, 1676, 1596, 1545, 1505, 1454, 1377, 1263, 1232, 1152, 1048, 961, 849, 806, 752, 702 cm^{-1}.

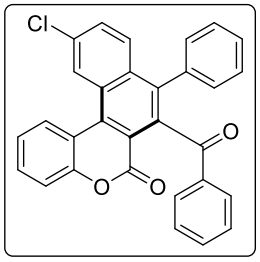
^1H NMR (500 MHz, $CDCl_3$): δ 8.96 (d, *J* = 8.5 Hz, 1H), 8.54 (d, *J* = 8.0 Hz, 1H), 7.78-7.75 (m, 1H), 7.68-7.66 (m, 2H), 7.64-7.57 (m, 3H), 7.51-7.44 (m, 2H), 7.41-7.39 (m, 1H), 7.36-7.34 (m, 1H), 7.23-7.26 (m, 1H), 7.14-7.11 (m, 1H), 6.94-6.91 (m, 3H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 194.8, 165.3 (d, *J* = 252.8 Hz), 160.1, 151.7, 139.2, 136.2, 135.7, 135.4, 134.7, 131.8, 131.3 (d, *J* = 9.1 Hz), 130.7, 130.0, 129.8, 129.0, 128.5, 128.4, 128.2, 128.1, 127.9 (d, *J* = 6.6 Hz), 127.5, 124.4, 118.3, 118.0, 117.8, 115.3 (d, *J* = 21.8 Hz) ppm.

^{19}F NMR (471 MHz, $CDCl_3$): δ -106.1 ppm.

HRMS (ESI-TOF): Calcd. for $C_{30}H_{18}FO_3$ $[M^+ + H]$: *m/z* 445.1240. Found: 445.1242.

Compound 20ma



Yield: 140.6 mg (58%, white solid, R_f = 0.50 (9:1 hexane/ethyl acetate)).

Mp: 164-166 ºC.

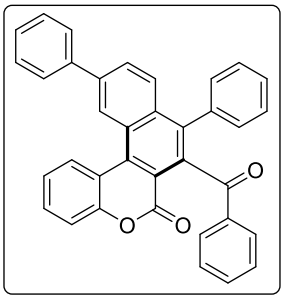
IR (neat): ν_{max} 3051, 2960, 2922, 2852, 1729, 1667, 1601, 1583, 1486, 1454, 1367, 1257, 1233, 1184, 1091, 1016, 951, 799, 752, 728, 701 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.86 (s, 1H), 8.40 (d, *J* = 8.0 Hz, 1H), 7.56-7.51 (m, 4H), 7.45-7.42 (m, 2H), 7.35-7.32 (m, 2H), 7.28-7.27 (m, 1H), 7.22-7.18 (m, 4H), 7.04-7.01 (m, 1H), 6.84 (d, *J* = 8.0 Hz, 1H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 195.8, 159.7, 151.7, 139.1, 138.0, 137.0, 135.0, 134.6, 134.5, 132.6, 131.7, 130.9, 130.3, 130.0, 129.5, 129.0, 128.8, 128.4, 128.1, 128.0, 127.5, 126.4, 124.6, 118.9, 118.1, 118.0 ppm.

HRMS (ESI-TOF): Calcd. for $C_{30}H_{18}ClO_3$ $[M^+ + H]$: *m/z* 461.0944. Found: 461.0944.

Compound 20na



Yield: 148.0 mg (56%, white solid, R_f = 0.46 (9:1 hexane/ethyl acetate)).

Mp: 192-194 ºC.

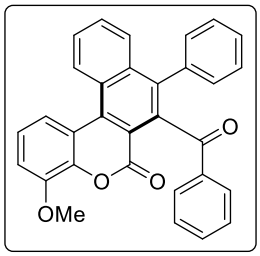
IR (neat): ν_{max} 3059, 2921, 2851, 1712, 1671, 1600, 1484, 1450, 1368, 1310, 1254, 1231, 1175, 1135, 949, 802, 758, 733, 699 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 9.06 (s, 1H), 8.51 (d, *J* = 8.0 Hz, 1H), 7.83 (dd, *J* = 9.0, 1.5 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 3H), 7.56 (d, *J* = 7.5 Hz, 2H), 7.53-7.43 (m, 4H), 7.41-7.37 (m, 2H), 7.35-7.32 (m, 3H), 7.22-7.18 (m, 3H), 7.05-7.02 (m, 1H), 6.89 (d, *J* = 8.0 Hz, 1H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 196.2, 160.0, 151.8, 140.6, 140.0, 139.1, 138.2, 136.6, 135.6, 135.4, 135.3, 132.5, 131.8, 130.6, 130.1, 129.3, 129.2, 128.8, 128.4_0, 128.3_6, 128.3, 128.2, 128.1, 128.0, 127.5, 125.4, 124.4, 118.5, 118.3, 118.0 ppm.

HRMS (ESI-TOF): Calcd. for $C_{36}H_{23}O_3$ $[M^+ + H]$: *m/z* 503.1647. Found: 503.1648.

Compound 20ab



Yield: 157.6 mg (76%, red solid, R_f = 0.44 (9:1 hexane/ethyl acetate)).

Mp: 204-206 °C.

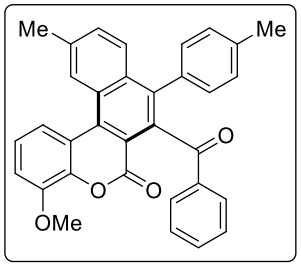
IR (neat): ν_{max} 3056, 2922, 2849, 1715, 1671, 1588, 1554, 1470, 1441, 1377, 1299, 1274, 1242, 1211, 1173, 1123, 1082, 947, 812, 768, 728, 692 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.98 (d, *J* = 8.5 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.78-7.75 (m, 1H), 7.69-7.62 (m, 4H), 7.45-7.38 (m, 4H), 7.31-7.25 (m, 3H), 7.18-7.16 (m, 1H), 7.13-7.10 (m, 1H), 6.95 (d, *J* = 7.5 Hz, 1H), 4.02 (s, 3H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 196.1, 159.6, 148.3, 141.7, 139.4, 138.2, 136.5, 136.3, 135.7, 135.5, 132.5, 131.8, 130.0, 129.6, 128.8, 128.3, 128.1, 127.9, 127.8, 127.7, 127.5, 123.9, 120.1, 119.2, 118.0, 112.7, 56.5 ppm.

HRMS (ESI-TOF): Calcd. for $C_{31}H_{21}O_4$ $[M^+ + H]$: *m/z* 457.1440. Found: 457.1439.

Compound 20bb



Yield: 171.7 mg (78%, white solid, R_f = 0.48 (9:1 hexane/ethyl acetate)).

Mp: 178-180 °C.

IR (neat): ν_{max} 2920, 2851, 1719, 1670, 1599, 1462, 1392, 1370, 1302, 1259, 1178, 1079, 1022, 955, 803, 760, 732, 691 cm^{-1}.

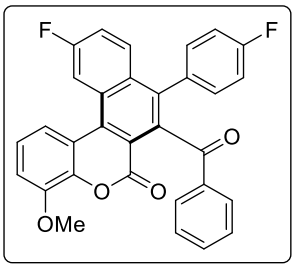
^1H NMR (500 MHz, $CDCl_3$): δ 8.72 (s, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.62-7.57 (m, 3H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.40-7.35 (m, 2H), 7.26-7.20 (m, 4H), 7.13 (d, *J* = 8.0 Hz,

1H), 6.89 (d, *J* = 7.5 Hz 1H), 6.80 (d, *J* = 7.5 Hz, 1H), 3.99 (s, 3H), 2.63 (s, 3H), 2.31 (s, 3H) ppm.

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 196.3, 159.6, 148.3, 141.6, 139.5, 138.4, 137.8, 137.5, 135.6, 134.8, 134.7, 132.7, 132.3, 131.6, 129.7, 128.9, 128.8, 128.2, 128.0, 127.8, 126.8, 123.8, 120.0, 119.3, 118.0, 112.5, 56.5, 22.1, 21.3 ppm.

HRMS (ESI-TOF): Calcd. for $C_{33}H_{24}O_4Na$ [M^+ + Na]: *m/z* 507.1573. Found: 507.1584.

Compound 20db



Yield: 163.3 mg (73%, white solid, R_f = 0.51 (9:1 hexane/ethyl acetate)).

Mp: 238-240 °C.

IR (neat): ν_{max} 2925, 2852, 1724, 1676, 1602, 1513, 1469, 1369, 1275, 1207, 1158, 1120, 1077, 1000, 962, 769, 734 cm^{-1}.

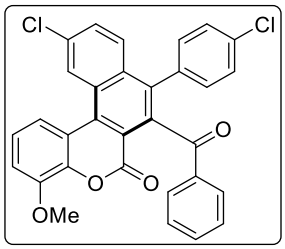
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.64 (d, *J* = 10.5 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.68-7.65 (m, 1H), 7.60 (d, *J* = 7.5, Hz, 2H), 7.47-7.41 (m, 3H), 7.38-7.36 (m, 1H), 7.30-7.28 (m, 2H), 7.18 (d, *J* = 8.5, Hz, 1H), 7.15-7.12 (m, 1H), 6.91-6.89 (m, 1H), 6.83-6.80 (m, 1H), 4.02 (s, 3H) ppm.

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 195.8, 162.5 (d, *J* = 246.0 Hz), 162.0 (d, *J* = 249.2 Hz), 159.3, 148.4, 141.6, 138.3, 138.0, 133.6 (d, *J* = 8.3 Hz), 133.3, 132.7, 131.6 (d, *J* = 8.1 Hz), 131.1, 130.3 (d, *J* = 8.9 Hz), 129.6 (d, *J* = 9.4 Hz), 128.8, 128.2, 124.3, 119.5 (d, *J* = 24.0 Hz), 119.2, 119.0, 118.8, 115.5 (d, *J* = 21.4 Hz), 114.8 (d, *J* = 21.6 Hz), 112.9, 112.2 (d, *J* = 23.7 Hz), 56.5 ppm.

^{19}F NMR (471 MHz, $CDCl_3$): δ -110.8, -113.2 ppm

HRMS (ESI-TOF): Calcd. for $C_{31}H_{19}F_2O_4$ [M^+ + H]: *m/z* 493.1251. Found: 493.1251.

Compound 20eb



Yield: 169.4 mg (71%, white solid, R_f = 0.47 (9:1 hexane/ethyl acetate)).

Mp: >300 ºC.

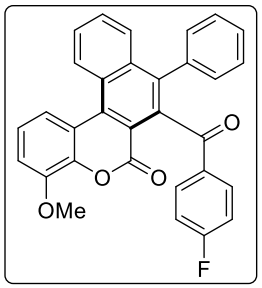
IR (neat): ν_{max} 2925, 2853, 1713, 1675, 1592, 1553, 1484, 1467, 1365, 1264, 1172, 1127, 1090, 1015, 955, 830, 732, 700 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 9.0 (s, 1H), 8.48 (d, *J* = 7.5 Hz, 1H), 7.66-7.59 (m, 5H), 7.55-7.51 (m, 2H), 7.47-7.44 (m, 1H), 7.42 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.33-7.30 (m, 3H), 7.11 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.87 (dd, *J* = 8.0, 2.5 Hz, 1H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 195.6, 159.6, 151.7, 137.8$_4$, 137.7$_6$, 137.2, 134.8, 134.7, 134.5, 134.4, 133.4, 133.1, 132.8, 131.2, 131.0, 130.5, 129.1, 129.0, 128.7, 128.3, 128.0, 127.9, 126.6, 124.9, 124.7, 118.8, 118.1, 117.8 ppm.

HRMS (ESI-TOF): Calcd. for $C_{31}H_{19}Cl_2O_4$ $[M^+ + H]$: *m/z* 525.0660. Found: 525.0663.

Compound 20jb



Yield: 172.4 mg (80%, white solid, R_f = 0.46 (9:1 hexane/ethyl acetate)).

Mp: 204-206 ºC.

IR (neat): ν_{max} 2923, 2852, 1719, 1676, 1596, 1554, 1504, 1471, 1440, 1377, 1264, 1232, 1151, 1123, 1083, 949, 849, 785, 733, 701 cm^{-1}.

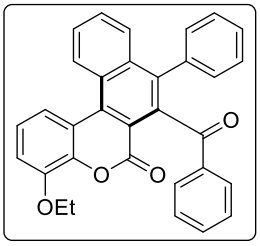
^1H NMR (500 MHz, $CDCl_3$): δ 8.97 (d, *J* = 8.5 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.77-7.76 (m, 1H), 7.68-7.63 (m, 2H), 7.44-7.41 (m, 2H), 7.39-7.38 (m, 3H), 7.33-7.28 (m, 1H), 7.18-7.13 (m, 2H), 6.95-6.92 (m, 3H), 4.02 (s, 3H) ppm.

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 194.6, 165.2 (d, *J* = 252.4 Hz), 159.6, 148.3, 141.7, 139.3, 136.2, 135.8, 135.4, 134.8, 131.8, 131.3 (d, *J* = 9.5 Hz), 129.9, 129.7, 128.4, 128.3, 128.0, 127.8, 127.7 (d, *J* = 6.4 Hz), 127.5, 123.9, 120.0, 119.1, 117.8, 115.2, (d, *J* = 21.9 Hz), 112.8, 56.5 ppm.

^{19}F NMR (471 MHz, $CDCl_3$): δ -106.3 ppm

HRMS (ESI-TOF): Calcd. for $C_{31}H_{20}FO_4$ $[M^+ + H]$: *m/z* 475.1345. Found: 475.1350.

Compound 20ac



Yield: 162.7 mg (81%, white solid, R_f = 0.45 (9:1 hexane/ethyl acetate)).

Mp: 228-230 °C.

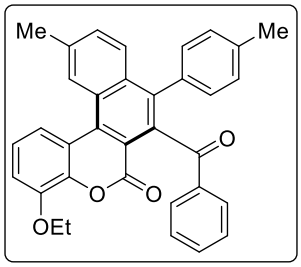
IR (neat): ν_{max} 3059, 2918, 2849, 1720, 1658, 1598, 1583, 1462, 1377, 1312, 1274, 1238, 1078, 951, 857, 767, 728, 694 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.98 (d, *J* = 8.5 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.77-7.74 (m, 1H), 7.69-7.66 (m, 2H), 7.64-7.62 (m, 2H), 7.45-7.41 (m, 3H), 7.40-7.36 (m, 1H), 7.31-7.26 (m, 3H), 7.17-7.15 (m, 1H), 7.13-7.10 (m, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 4.25-4.21 (m, 2H), 1.52 (t, *J* = 7.0 Hz, 3H) ppm.

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 196.0, 159.7, 147.6, 142.0, 139.3, 138.3, 136.5, 136.3, 135.8, 135.6, 132.4, 131.8, 130.0, 129.5, 128.8, 128.2, 128.0, 127.8, 127.7, 127.6, 127.4, 123.9, 120.1, 119.2, 118.0, 114.2, 65.3, 14.8 ppm.

HRMS (ESI-TOF): Calcd. for $C_{32}H_{23}O_4$ $[M^+ + H]$: *m/z* 471.1596 Found: 471.1599.

Compound 20bc



Yield: 178.8 mg (84%, white solid, R_f = 0.49 (9:1 hexane/ethyl acetate)).

Mp: 196-198 ºC.

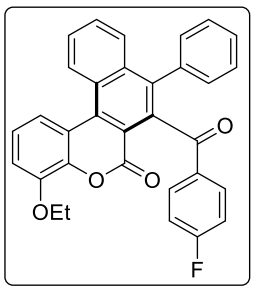
IR (neat): ν_{max} 2922, 2852, 1719, 1675, 1597, 1554, 1469, 1368, 1273, 1247, 1204, 1169, 1129, 1083, 1021, 956, 807, 761, 733 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.72 (s, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.62-7.57 (m, 3H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.40-7.33 (m, 2H), 7.27-7.25 (m, 2H), 7.23-7.20 (m, 2H), 7.12 (d, *J* = 8.0 Hz, 1H), 6.90 (d, *J* = 7.5 Hz 1H), 6.82 (d, *J* = 7.5 Hz, 1H), 4.23-4.19 (m, 2H), 2.63 (s, 3H), 2.31 (s, 3H), 1.50 (t, *J* = 7.0 Hz, 3H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 196.3, 159.8, 147.6, 141.8, 139.4, 138.4, 137.8, 137.5, 135.6, 134.9, 134.7, 132.7, 132.3, 131.6, 129.7, 128.9, 128.8, 128.2, 128.0, 127.8, 126.9, 123.8, 120.0, 119.4, 118.0, 113.9, 65.3, 22.1, 21.3, 14.8 ppm.

HRMS (ESI-TOF): Calcd. for $C_{34}H_{26}O_4Na$ $[M^+ + Na]$: *m/z* 521.1729 Found: 521.1721.

Compound 20jc



Yield: 158.5 mg (76%, white solid, R_f = 0.47 (9:1 hexane/ethyl acetate)).

Mp: 184-186 ºC.

IR (neat): ν_{max} 2921, 2850, 1738, 1680, 1596, 1466, 1368, 1263, 1229, 1080, 896, 732, 702 cm^{-1}.

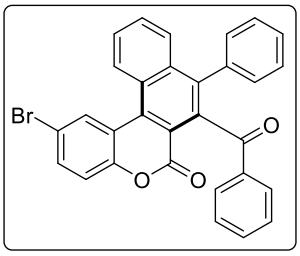
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.97 (d, *J* = 8.0 Hz, 1H), 8.09 (d, *J* = 7.0 Hz, 1H), 7.76 (br s, 1H), 7.67-7.64 (m, 3H), 7.42-7.37 (m, 3H), 7.35-7.27 (m, 2H), 7.16-7.13 (m, 2H), 6.95-6.91 (m, 3H), 4.23 (q, *J* = 13.0, 7.5 Hz, 2H), 1.52 (t, *J* = 7.0 Hz, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 194.6, 165.2 (d, *J* = 252.0 Hz), 159.8, 147.7, 141.9, 139.2, 136.2 (d, *J* = 9.8 Hz), 135.9, 135.4, 134.8, 131.8, 131.3 (d, *J* = 9.1 Hz), 129.9, 129.6, 128.4, 128.3, 128.0, 127.8, 127.7, 127.5, 123.9, 120.1, 119.1, 117.8, 115.2, (d, *J* = 22.0 Hz), 114.2, 65.3, 14.8 ppm.

^{19}F NMR (471 MHz, $CDCl_3$): δ -106.3 ppm

HRMS (ESI-TOF): Calcd. for $C_{32}H_{22}FO_4$ [M^+ + H]: *m/z* 489.1502 Found: 489.1503.

Compound 20ad



Yield: 133.4 mg (71%, white solid, R_f = 0.49 (9:1 hexane/ethyl acetate)).

Mp: 208-210 ºC.

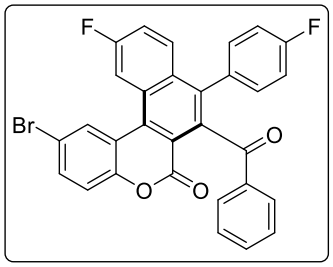
IR (neat): ν_{max} 3056, 2923, 2852, 1729, 1676, 1597, 1476, 1448, 1415, 1377, 1262, 1233, 1115, 1037, 962, 908, 821, 733, 700 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.90 (d, *J* = 8.5 Hz, 1H), 8.68 (s, 1H), 7.85-7.83 (m, 1H), 7.71-7.61 (m, 5H), 7.44-7.37 (m, 4H), 7.30-7.27 (m, 3H), 7.13-7.10 (m, 1H), 6.94 (d, *J* = 7.0 Hz, 1H) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 196.0, 159.6, 150.6, 140.0, 138.0, 136.6, 136.3, 135.2, 134.1, 133.3, 132.6, 131.7, 130.9, 130.0, 129.9, 128.8, 128.4, 128.3, 128.1_4, 128.0_8, 127.5, 126.9, 120.1, 119.6, 118.1, 117.2 ppm.

HRMS (ESI-TOF): Calcd. for $C_{30}H_{18}{}^{79}BrO_3$ [M^+ + H]: *m/z* 505.0439 Found: 505.0453.

Compound 20dd



Yield: 146.9 mg (73%, white solid, R_f = 0.51 (9:1 hexane/ethyl acetate)).

Mp: 228-230 ºC.

IR (neat): ν_{max} 3061, 2923, 1725, 1675, 1598, 1512, 1475, 1448, 1416, 1371, 1287, 1230, 1204, 1173, 1158, 1126, 1041, 992, 958, 921, 867, 818, 735 cm^{-1}.

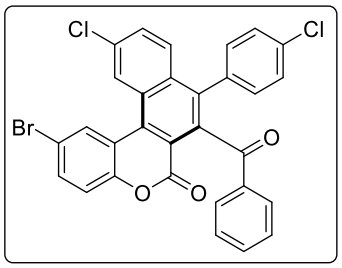
^1H NMR (500 MHz, $CDCl_3$): δ 8.62 (d, *J* = 2.0 Hz, 1H), 8.55 (dd, *J* = 10.5, 2.0 Hz, 1H), 7.72-7.69 (m, 2H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.52-7.48 (m, 1H), 7.47-7.44 (m, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.36-7.33 (m, 1H), 7.32-7.28 (m, 2H), 7.15-7.11 (m, 1H), 6.92-6.89 (m, 1H), 6.84-6.80 (m, 1H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 195.5, 162.5 (d, *J* = 247.1 Hz), 162.3 (d, *J* = 249.5 Hz), 159.2, 150.4, 138.9, 137.8, 136.6, 133.6, 133.5 (d, *J* = 8.1 Hz), 133.4 (d, *J* = 5.1 Hz), 132.8, 131.7 (d, *J* = 8.3 Hz), 130.6 (d, *J* = 9.0 Hz), 130.1, 129.2 (d, *J* = 9.1 Hz), 128.7, 128.3, 120.0, 119.8_1, 119.7_6, 119.7_2, 119.2, 117.4, 115.6 (d, *J* = 21.5 Hz), 114.8 (d, *J* = 21.6 Hz), 111.4 (d, *J* = 23.4 Hz) ppm.

^{19}F NMR (471 MHz, $CDCl_3$): δ -109.4, -112.8 ppm

HRMS (ESI-TOF): Calcd. for $C_{30}H_{16}BrF_2O_3$ $[M^+ + H]$: *m/z* 541.0251 Found: 541.0250.

Compound 20ed



Yield: 164.3 mg (77%, white solid, R_f = 0.48 (9:1 hexane/ethyl acetate)).

Mp: 210-212 ºC.

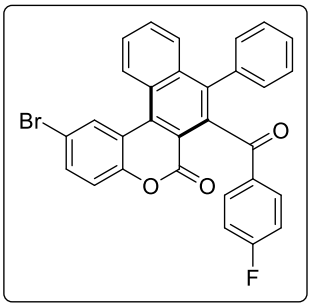
IR (neat): ν_{max} 3056, 2923, 2853, 1737, 1676, 1596, 1473, 1416, 1368, 1264, 1231, 1090, 954, 822, 732, 702 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.86 (s, 1H), 8.59 (s, 1H), 7.72-7.65 (m, 2H), 7.62-7.59 (m, 3H), 7.48-7.45 (m, 1H), 7.42-7.39 (m, 2H), 7.33-7.28 (m, 2H), 7.12-7.09 (m, 2H), 6.87 (d, *J* = 7.0 Hz, 1H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 195.4, 159.1, 150.5, 138.6, 137.7, 137.2, 135.3, 134.6, 134.4, 133.8, 133.4, 133.2, 133.0, 131.2, 130.8, 130.4, 129.3, 129.0, 128.8, 128.4, 128.0, 126.0, 119.8, 119.6, 119.0, 117.5 ppm.

HRMS (ESI-TOF): Calcd. for $C_{30}H_{16}BrCl_2O_3$ $[M^+ + H]$: *m/z* 572.9660 Found: 572.9664.

Compound 20jd



Yield: 145.9 mg (75%, white solid, R_f = 0.47 (9:1 hexane/ethyl acetate)).

Mp: 134-136 °C.

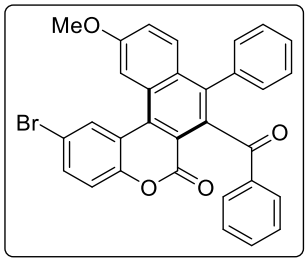
IR (neat): ν_{max} 3056, 2923, 2852, 1724, 1677, 1596, 1504, 1476, 1415, 1378, 1261, 1232, 1151, 1037, 963, 848, 814, 732, 700 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.89 (d, *J* = 8.5 Hz, 1H), 8.66 (s, 1H), 7.84-7.82 (m, 1H), 7.69-7.68 (m, 3H), 7.63-7.60 (m, 2H), 7.43-7.38 (m, 2H), 7.34-7.26 (m, 2H), 7.15-7.12 (m, 1H), 6.95-6.92 (m, 3H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 194.5, 165.3 (d, *J* = 252.6 Hz), 159.6, 150.6, 140.0, 136.2, 135.1, 134.6, 134.2, 133.4, 131.7, 131.3 (d, *J* = 9.2 Hz), 130.9, 130.0 (d, *J* = 6.5 Hz), 128.5, 128.4, 128.2, 128.1, 127.5, 126.9, 120.0, 119.6, 118.0, 117.2, 115.3 (d, *J* = 21.8 Hz) ppm.

HRMS (ESI-TOF): Calcd. for $C_{30}H_{17}{}^{79}BrFO_3$ $[M^+ + H]$: *m/z* 523.0345 Found: 523.0345.

Compound 20ld



Yield: 117.4 mg (59%, white solid, R_f = 0.46 (9:1 hexane/ethyl acetate)).

Mp: 210-212 ºC.

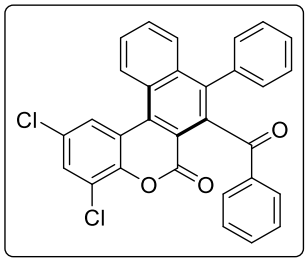
IR (neat): ν_{max} 3058, 2927, 1726, 1675, 1618, 1598, 1478, 1448, 1415, 1368, 1298, 1222, 1031, 957, 926, 835, 815, 789, 701 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.82 (s, 1H), 8.25 (s, 1H), 7.67 (d, *J* = 9.0 Hz, 1H), 7.62-7.60 (m, 3H), 7.43-7.34 (m, 5H), 7.29-7.26 (m, 3H), 7.12-7.09 (m, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 4.08 (s, 3H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 196.2, 159.7, 150.4, 140.0, 138.2, 135.4, 134.7, 132.9, 132.6, 132.3, 131.6, 131.4, 130.1, 129.9, 129.7, 128.8, 128.3, 128.1, 128.0, 127.4, 121.7, 120.4, 119.7, 118.7, 117.0, 106.3, 55.7 ppm.

HRMS (ESI-TOF): Calcd. for $C_{31}H_{20}BrO_4$ $[M^+ + H]$: *m/z* 535.0545 Found: 535.0548.

Compound 20ae



Yield: 164.5 mg (86%, white solid, R_f = 0.51 (9:1 hexane/ethyl acetate)).

Mp: 124-126 ºC.

IR (neat): ν_{max} 3059, 2923, 2851, 1734, 1677, 1596, 1546, 1454, 1419, 1371, 1259, 1177, 1116, 1035, 984, 946, 874, 803, 735, 697 cm^{-1}.

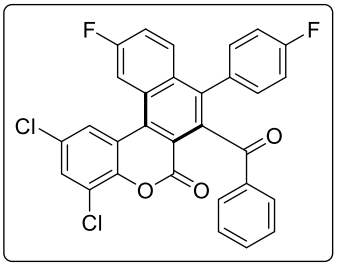
^1H NMR (500 MHz, $CDCl_3$): δ 8.83 (d, *J* = 8.5 Hz, 1H), 8.41 (s, 1H), 7.84-7.81 (m, 1H), 7.70_4-7.69_6 (m, 2H), 7.64_2-7.64_0 (m, 1H), 7.59 (d, *J* = 7.5 Hz, 2H), 7.43-7.40 (m, 2H),

7.36-7.35 (m, 1H), 7.29-7.24 (m, 3H), 7.12-7.09 (m, 1H), 6.94 (d, *J* = 7.5 Hz, 1H) ppm.

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 195.7, 158.6, 146.2, 140.7, 137.9, 136.5, 136.4, 135.1, 133.7, 132.7, 131.6, 130.6, 130.1, 129.9, 129.4, 128.8, 128.6, 128.4, 128.2, 128.0, 127.5, 126.8, 126.5, 123.9, 120.7, 118.2 ppm.

HRMS (ESI-TOF): Calcd. for $C_{30}H_{17}Cl_2O_3$ $[M^+ + H]$: *m/z* 495.0554 Found: 495.0559.

Compound 20de



Yield: 153.8 mg (75%, white solid, R_f = 0.55 (9:1 hexane/ethyl acetate)).

Mp: >250 °C.

IR (neat): ν_{max} 2961, 2920, 2856, 1734, 1671, 1598, 1506, 1456, 1365, 1258, 1157, 1090, 1015, 966, 793, 750 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.50 (dd, *J* = 10.5, 2.0 Hz, 1H), 8.37 (d, *J* = 2.0 Hz, 1H), 7.74-7.71 (m, 1H), 7.68 (d, *J* = 2.0, Hz, 1H), 7.60-7.59 (m, 2H), 7.54-7.50 (m, 1H), 7.47-7.44 (m, 1H), 7.37-7.33 (m, 1H), 7.32-7.28 (m, 2H), 7.16-7.12 (m, 1H), 6.94-6.91 (m, 1H), 6.86-6.82 (m, 1H) ppm.

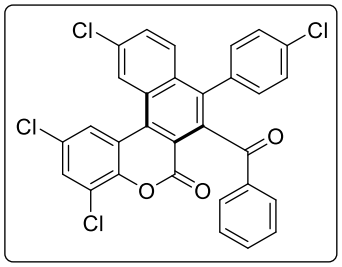
$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 195.3, 162.5 (d, *J* = 247.4 Hz), 162.4 (d, *J* = 250.5 Hz), 158.3, 146.1, 139.6, 137.7, 136.5, 133.5 (d, *J* = 8.3 Hz), 133.4, 132.9, 131.6 (d, *J* = 8.3 Hz), 130.9, 130.8 (d, *J* = 9.0 Hz), 129.8, 129.2 (d, *J* = 9.0 Hz), 128.7, 128.3, 125.7, 124.1, 120.3 (d, *J* = 16.5 Hz), 120.0, 119.3, 115.6 (d, *J* = 21.3 Hz), 114.8 (d, *J* = 21.6 Hz), 111.3 (d, *J* = 23.5 Hz) ppm.

^{19}F NMR (471 MHz, $CDCl_3$): δ -108.9, -112.6 ppm

HRMS (ESI-TOF): Calcd. for $C_{30}H_{15}Cl_2F_2O_3$ $[M^+ + H]$: *m/z* 531.0366 Found: 531.0362.

This compound was crystallized from ethyl acetate–hexane (2:1) mixture at room temperature. X-ray structure has been determined for this compound.

Compound 20ee



Yield: 178.6 mg (82%, white solid, R_f = 0.56 (9:1 hexane/ethyl acetate)).

Mp: >250 °C.

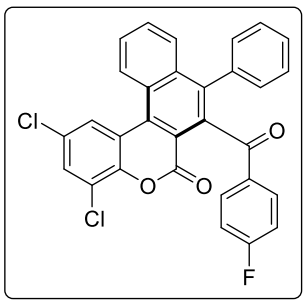
IR (neat): ν_{max} 3066, 2922, 2852, 1736, 1671, 1597, 1546, 1491, 1453, 1391, 1314, 1254, 1169, 1127, 1089, 1044, 954, 867, 835, 732, 714 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.82 (d, *J* = 2.0 Hz, 1H), 8.34 (dd, *J* = 2.0, 0.5 Hz, 1H), 7.70-7.67 (m, 2H), 7.64-7.59 (m, 3H), 7.49-7.45 (m, 1H), 7.43 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.33-7.28 (m, 3H), 7.13 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.88 (dd, *J* = 8.5, 2.5 Hz, 1H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 195.1, 158.2, 146.1, 139.2, 137.6, 137.1, 135.5, 134.7, 134.5, 133.1, 133.0_3, 132.9_8, 131.1, 129.9, 129.7, 129.4, 128.9, 128.8, 128.7, 128.4, 128.0, 126.0, 125.9, 124.2, 120.1, 119.1 ppm.

HRMS (ESI-TOF): Calcd. for $C_{30}H_{15}Cl_4O_3$ $[M^+ + H]$: *m/z* 562.9775 Found: 562.9775.

Compound 20je



Yield: 156.6 mg (79%, white solid, R_f = 0.49 (9:1 hexane/ethyl acetate)).

Mp: 208-210 °C.

IR (neat): ν_{max} 2923, 2852, 1735, 1674, 1596, 1505, 1420, 1372, 1261, 1233, 1153, 1096, 1036, 811, 735, 701 cm^{-1}.

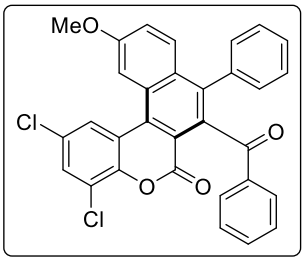
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.83 (d, *J* = 8.5 Hz, 1H), 8.41 (s, 1H), 7.85-7.82 (m, 1H), 7.71 (d, *J* = 3.5 Hz 2H), 7.66-7.60 (m, 3H), 7.43-7.40 (m, 1H), 7.35-7.33 (m, 1H), 7.31-7.28 (m, 1H), 7.16-7.13 (m, 1H), 6.95-6.92 (m, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 194.2, 165.4 (d, *J* = 252.8 Hz), 158.7, 146.1, 140.6, 136.3, 136.1, 135.0, 134.4, 133.9, 131.6, 131.3 (d, *J* = 9.1 Hz), 130.6, 130.2, 129.9, 129.5, 128.7, 128.4, 128.2, (d, *J* = 13.8 Hz), 127.6, 126.8, 126.5, 123.9, 120.6, 118.0, 115.3 (d, *J* = 21.9 Hz) ppm.

^{19}F NMR (370 MHz, $CDCl_3$): δ -105.6 ppm

HRMS (ESI-TOF): Calcd. for $C_{30}H_{16}Cl_2FO_3$ [M^+ + H]: *m/z* 513.0460 Found: 513.0464.

Compound 20le



Yield: 125.7 mg (62%, white solid, R_f = 0.48 (9:1 hexane/ethyl acetate)).

Mp: 238-240 ºC.

IR (neat): ν_{max} 3058, 2924, 2852, 1739, 1674, 1601, 1508, 1461, 1365, 1249, 1224, 1176, 1116, 1031, 963, 828. 736, 701 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.55 (s, 1H), 8.18 (s, 1H), 7.64-7.60 (m, 4H), 7.42-7.40 (m, 2H), 7.36-7.34 (m, 2H), 7.28-7.27 (m, 3H), 7.13-7.10 (m, 1H), 6.95-6.94 (m, 1H), 4.06 (s, 3H) ppm.

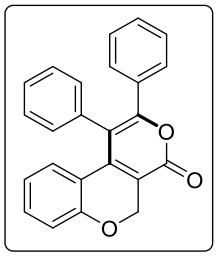
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 195.9, 159.8, 158.7, 146.0, 140.7, 138.1, 135.3, 134.6, 132.6, 132.0, 131.6, 130.2, 129.8, 129.7, 129.3, 128.8, 128.3, 128.1, 127.5, 125.6, 124.0, 121.7, 121.0, 118.8, 106.4, 55.7 ppm.

HRMS (ESI-TOF): Calcd. for $C_{31}H_{19}Cl_2O_4$ [M^+ + H]: *m/z* 525.0660 Found: 525.0655.

3.7 Synthesis of 4*H*,5*H*-pyrano[3,4-*c*]chromen-4-ones: General procedure for the synthesis of compounds 21

To an oven dried Schlenk tube, 2*H*-chromene-3-carboxylic acid (**6a-c**, 0.57 mmol), alkyne (one of **7a-j**, 0.57 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $Cu(OAc)_2{\cdot}H_2O$ (30 mol %) and $AgSbF_6$ (10 mol %) were added. To this mixture, 1,4-dioxane (2 mL) was added and the contents were stirred at 100 °C (oil bath temperature) for 20 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature, solvent was removed under the vacuum, and the crude product was purified by column chromatography by using silica gel with hexane/ethyl acetate (9:1) mixture as the eluent to afford the corresponding annulated products **21aa-cj**.

Compound 21aa



Yield: 176.0 mg (88%, white solid, R_f = 0.52 (9:1 hexane/ethyl acetate)).

Mp: 138-140 °C.

IR (neat): ν_{max} 2848, 2648, 1702, 1567, 1527, 1485, 1393, 1109, 998, 758, 696 cm^{-1}.

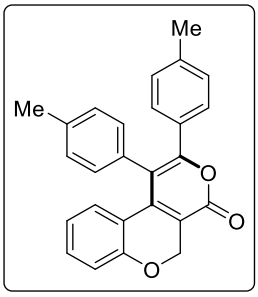
^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.34 (m, 2H), 7.32-7.30 (m, 2H), 7.29-7.26 (m, 3H), 7.21-7.20 (m, 2H), 7.12-7.10 (m, 2H), 7.04 (dd, J_1 = 8.3 Hz, J_2 = 1.5 Hz, 1H), 6.58-6.54 (m, 1H), 6.37 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 5.07 (s, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 158.0, 157.7, 143.9, 135.0, 132.8, 132.0, 131.3, 129.4, 129.3, 129.0, 128.8, 128.3, 127.8, 121.1, 120.1, 117.8, 116.3, 63.4 ppm.

HRMS (ESI-TOF): Calcd. for $C_{24}H_{17}O_3$ $[M^+ + H]$: *m/z* 353.1177. Found: 353.1177.

This compound was crystallized from ethyl acetate–hexane (2:1) mixture at room temperature. X-ray structure has been determined for this compound.

Compound 21ab



Yield: 151.2 mg (70%, pale yellow solid, R_f = 0.54 (9:1 hexane/ethyl acetate)).

Mp: 218-220 ºC.

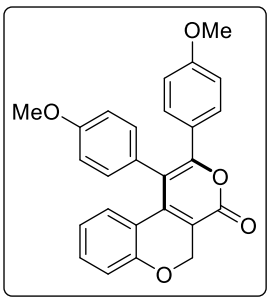
IR (neat): ν_{max} 2920, 2851, 1717, 1603, 1569, 1500, 1455, 1391, 1353, 1014, 820, 761 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.24-7.19 (m, 1H), 7.13-7.11 (m, 4H), 7.04-6.98 (m, 5H), 6.60-6.56 (m, 1H), 6.42 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 5.06 (s, 2H), 2.40 (s, 3H), 2.31 (s, 3H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 160.1, 158.1, 157.7, 144.1, 139.4, 138.0, 132.0, 131.9, 131.1, 130.0, 129.7, 129.2, 128.9, 128.5, 121.0, 120.3, 117.7, 115.8_8, 115.8_5, 63.4, 21.4, 21.3 ppm.

HRMS (ESI-TOF): Calcd. for $C_{26}H_{21}O_3$ $[M^+ + H]$: *m/z* 381.1490. Found: 381.1492.

Compound 21ac



Yield: 189.6 mg (81%, white solid, R_f = 0.46 (9:1 hexane/ethyl acetate)).

Mp: 199-201 ºC.

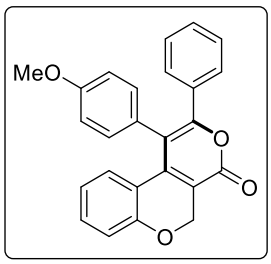
IR (neat): ν_{max} 2922, 2852, 1734, 1604, 1512, 1463, 1262, 1177, 1080, 1031, 970, 749 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.20 (m, 1H), 7.19-7.16 (m, 2H), 7.04-7.0 (m, 3H), 6.88-6.85 (m, 2H), 6.74-6.71 (m, 2H), 6.62-6.59 (m, 1H), 6.46 (dd, J_1 = 8.2 Hz, J_2 = 1.0 Hz, 1H), 5.05 (s, 2H), 3.86 (s, 3H), 3.79 (s, 3H) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.1$_8$, 160.1$_5$, 159.4, 158.0, 157.7, 144.3, 132.4, 131.9, 130.9, 128.9, 127.3, 125.3, 121.1, 120.4, 117.7, 115.5, 115.1, 114.6, 113.3, 63.4, 55.3, 55.2 ppm.

HRMS (ESI-TOF): Calcd. for $C_{26}H_{20}O_5$ [M^+ + Na]: *m/z* 435.1209. Found: 435.1209.

Compound 21ad



Yield: 169.3 mg (78%, pale yellow solid, R_f = 0.48 (9:1 hexane/ethyl acetate)).

Mp: 221-223 ^{o}C.

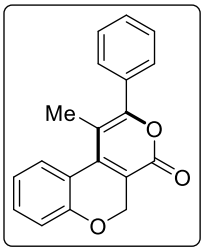
IR (neat): ν_{max} 3058, 2926, 2839, 1708, 1678, 1506, 1489, 1295, 1255, 1179, 1029, 836, 760, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.21 (m, 6H), 7.03 (dd, J_1 = 8.3 Hz, J_2 = 1.0 Hz, 1H), 7.01-6.98 (m, 2H), 6.85-6.82 (m, 2H), 6.63-6.60 (m, 1H), 6.47 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 5.06 (s, 2H), 3.84 (s, 3H) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.1, 159.5, 158.0, 157.7, 144.2, 132.9, 132.4, 132.0, 129.3, 129.2, 128.8, 127.9, 126.9, 121.2, 120.3, 117.8, 116.2, 115.9, 114.5, 63.4, 55.3 ppm.

HRMS (ESI-TOF): Calcd. for $C_{25}H_{19}O_4$ [M^+ + H]: *m/z* 383.1283. Found: 383.1283.

Compound 21ae



Yield: 121.9 mg (74%, pale yellow solid, R_f = 0.60 (9:1 hexane/ethyl acetate)).

Mp: 160-162 ºC.

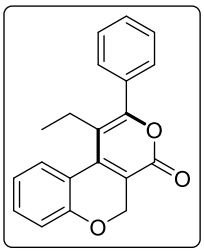
IR (neat): ν_{max} 2922, 2852, 1762, 1702, 1604, 1571, 1534, 1492, 1450, 751, 699 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (dd, J_1 = 8.3 Hz, J_2 = 1.5 Hz, 1H), 7.66-7.64 (m, 2H), 7.51-7.49 (m, 3H), 7.43-7.38 (m, 1H), 7.14-7.10 (m, 2H), 5.02 (s, 2H), 2.38 (s, 3H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.3, 158.3, 157.9, 145.7, 132.9, 132.3, 130.0, 129.4, 128.4, 121.7, 121.1, 118.1, 116.1, 109.2, 63.2, 18.2 ppm.

HRMS (ESI-TOF): Calcd. for $C_{19}H_{15}O_3Na$ [M^+ + Na]: *m/z* 313.0841. Found: 313.0842.

Compound 21af



Yield: 124.4 mg (72%, white solid, R_f = 0.62 (9:1 hexane/ethyl acetate)).

Mp: 122-124 ºC.

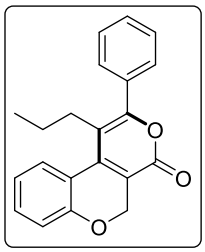
IR (neat): ν_{max} 2924, 2852, 1705, 1604, 1571, 1533, 1491, 751, 701 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.83 (dd, J_1 = 8.0 Hz, J_2 = 1.5 Hz, 1H), 7.56-7.54 (m, 2H), 7.50-7.49 (m, 3H), 7.41-7.39 (m, 1H), 7.14-7.09 (m, 2H), 5.00 (s, 2H), 2.85 (q, J = 9.0 Hz, 2H), 0.94 (t, J = 9.0 Hz, 3H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.1, 158.6, 157.7, 144.4, 133.3, 132.2, 129.8, 129.2, 128.5, 127.1, 122.1, 121.2, 118.2, 117.6, 115.7, 63.2, 21.6, 14.5 ppm.

HRMS (ESI-TOF): Calcd. for $C_{20}H_{17}O_3$ [M^+ + H]: *m/z* 305.1177. Found: 305.1117.

Compound 21ag



Yield: 142.8 mg (79%, yellow solid, R_f = 0.63 (9:1 hexane/ethyl acetate)).

Mp: 118-120 ^oC.

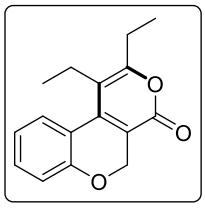
IR (neat): ν_{max} 2961, 2927, 2877, 1706, 1534, 1491, 1448, 1090, 750, 701 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 7.56-7.54 (m, 2H), 7.50-4.49 (m, 3H), 7.41-7.38 (m, 1H), 7.14-7.09 (m, 2H), 4.99 (s, 2H), 2.81-2.77 (m, 2H), 1.32-1.23 (m, 2H), 0.71 (t, J = 7.2 Hz, 3H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 160.2, 158.8, 157.6, 144.6, 133.4, 132.3, 129.8, 129.4, 128.5, 126.9, 122.0, 121.4, 118.3, 117.6, 114.2, 63.2, 30.4, 22.8, 13.5 ppm.

HRMS (ESI-TOF): Calcd. for $C_{21}H_{19}O_3$ $[M^+ + H]$: *m/z* 319.1334. Found: 319.1335.

Compound 21ah



Yield: 106.2 mg (73%, pale yellow solid, R_f = 0.64 (9:1 hexane/ethyl acetate)).

Mp: 221-223 ^oC.

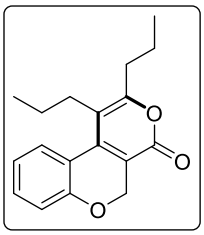
IR (neat): ν_{max} 2972, 2936, 1719, 1684, 1605, 1571, 1532, 1454, 1202, 1038, 981, 759, 736 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, J_1 = 8.2 Hz, J_2 = 1.6 Hz, 1H), 7.38-7.34 (m, 1H), 7.10-7.06 (m, 2H), 4.90 (s, 2H), 2.69-2.62 (m, 4H), 1.31-1.26 (m, 6H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.1, 160.7, 157.8, 144.9, 132.1, 127.3, 121.9, 120.9, 118.2, 115.5, 113.8, 63.2, 24.5, 20.4, 15.2, 12.3 ppm.

HRMS (ESI-TOF): Calcd. for $C_{16}H_{16}O_3Na$ $[M^+ + Na]$: *m/z* 279.0997. Found: 279.0995.

Compound 21ai



Yield: 124.3 mg (77%, pale yellow solid, R_f = 0.65 (9:1 hexane/ethyl acetate)).

Mp: 102-104 ºC.

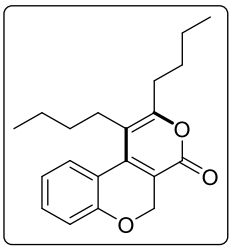
IR (neat): ν_{max} 2961, 2931, 2872, 1704, 1605, 1572, 1532, 1457, 1397, 1233, 758 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.40-7.35 (m, 1H), 7.11-7.07 (m, 2H), 4.90 (s, 2H), 2.62-2.56 (m, 4H), 1.82-1.72 (m, 2H), 1.65-1.56 (m, 2H), 1.03 (t, J = 7.4 Hz, 6H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 162.0, 160.6, 157.9, 144.7, 132.1, 127.1, 121.8, 121.1, 118.2, 115.7, 113.1, 63.2, 33.2, 29.4, 23.8, 21.3, 13.9_0, 13.8_6 ppm.

HRMS (ESI-TOF): Calcd. for $C_{18}H_{21}O_3$ $[M^+ + H]$: *m/z* 285.1490. Found: 285.1490.

Compound 21aj



Yield: 134.8 mg (76%, gummy liquid, R_f = 0.67 (9:1 hexane/ethyl acetate)).

Mp: Gummy liquid

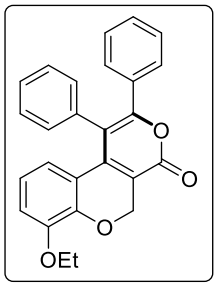
IR (neat): ν_{max} 2958, 2930, 2871, 1723, 1606, 1456, 1207, 1108, 1042, 979, 756 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.63-7.61 (m, 1H), 7.39-7.35 (m, 1H), 7.10-7.06 (m, 2H), 4.89 (s, 2H), 2.63-2.58 (m, 4H), 1.75-1.67 (m, 2H), 1.59-1.53 (m, 2H), 1.48-1.40 (m, 4H), 1.00-0.95 (m, 6H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 162.2, 160.6, 157.9, 144.7, 132.1, 127.2, 121.8, 121.1, 118.2, 115.6, 113.0, 63.2, 32.6, 31.1, 30.0, 27.1, 22.6, 22.5, 13.8, 13.7 ppm.

HRMS (ESI-TOF): Calcd. for $C_{20}H_{24}O_3Na$ $[M^+ + Na]$: *m/z* 335.1623. Found: 335.1623.

Compound 21ba



Yield: 133.2 mg (74%, pale yellow solid, R_f = 0.48 (9:1 hexane/ethyl acetate)).

Mp: 202-204 ^oC

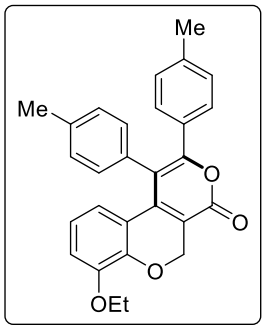
IR (neat): ν_{max} 3057, 2928, 2850, 1696, 1533, 1489, 1463, 1443, 1388, 1284, 1204, 1085, 779, 740, 696 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.32 (m, 1H), 7.30 (br, 1H), 7.29-7.25 (m, 2H), 7.22-7.19 (m, 4H), 7.10-7.08 (m, 2H), 6.86-6.84 (m, 1H), 6.48 (t, *J* = 8.3 Hz, 1H), 6.01-5.99 (m, 1H), 5.12 (s, 2H), 4.13 (q, *J* = 7.0 Hz, 2H), 1.49 (t, *J* = 7.0 Hz, 3H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 159.9, 158.0, 148.3, 147.3, 144.1, 135.0, 132.8, 131.3, 129.4, 129.3, 128.9, 128.2, 127.8, 121.1, 120.7, 120.4, 116.4, 155.7, 64.8, 63.6, 14.8 ppm.

HRMS (ESI-TOF): Calcd. for $C_{26}H_{21}O_4$ $[M^+ + H]$: *m/z* 397.1440. Found: 397.1442.

Compound 21bb



Yield: 148.4 mg (77%, pale yellow solid, R_f = 0.50 (9:1 hexane/ethyl acetate)).

Mp: 220-222 ^oC

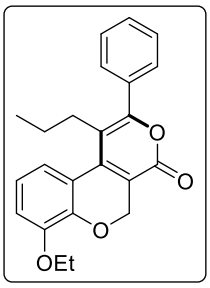
IR (neat): ν_{max} 2980, 2923, 2858, 1696, 1615, 1535, 1502, 1461, 1387, 1355, 1278, 1200, 1085, 1048, 1017, 823, 762, 741 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12-7.09 (m, 4H), 7.01-6.99 (m, 2H), 6.97-6.95 (m, 2H), 6.84 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 6.50 (t, J = 8.2 Hz, 1H), 6.04 (dd, J_1 = 8.2 Hz, J_2 = 1.6 Hz, 1H), 5.10 (s, 2H), 4.12 (q, J = 7.2 Hz, 2H), 2.39 (s, 3H), 2.30 (s, 3H), 1.49 (t, J = 7.2 Hz, 3H) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.1, 158.0, 148.2, 147.3, 144.3, 139.4, 137.9, 132.0, 131.1, 130.0, 129.6, 129.3, 128.5, 121.3, 120.8, 120.3, 116.0$_3$, 115.9$_9$, 115.5, 64.8, 63.7, 21.4, 21.3, 14.8 ppm.

HRMS (ESI-TOF): Calcd. for $C_{28}H_{25}O_4$ [M^+ + H]: *m/z* 425.1753. Found: 425.1753.

Compound 21bg



Yield: 131.7 mg (80%, pale yellow solid, R_f = 0.60 (9:1 hexane/ethyl acetate)).

Mp: 128-130 ºC

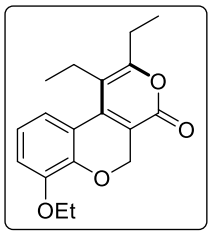
IR (neat): ν_{max} 3059, 2973, 2927, 1708, 1538, 1465, 1360, 1266, 1221, 1088, 1021, 732, 701 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56-7.53 (m, 2H), 7.50-7.48 (m, 3H), 7.41-7.38 (m, 1H), 7.03-7.02 (m, 2H), 5.03 (s, 2H), 4.18 (q, J = 9.5 Hz, 2H), 2.78 (t, J = 9.5 Hz, 2H), 1.52 (t, J = 9.0 Hz, 3H), 1.27-1.19 (m, 2H), 0.68 (t, J = 9.5 Hz, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 160.1, 158.7, 148.8, 147.3, 144.9, 133.4, 129.8, 129.4, 128.4, 122.4, 121.4, 118.6, 117.8, 115.8, 114.3, 64.8, 63.5, 30.4, 22.7, 14.8, 13.5 ppm.

HRMS (ESI-TOF): Calcd. for $C_{23}H_{23}O_4$ [M^+ + H]: *m/z* 363.1596. Found: 363.1597.

Compound 21bh



Yield: 102.3 mg (75%, yellow solid, R_f = 0.62 (9:1 hexane/ethyl acetate)).

Mp: 104-106 °C

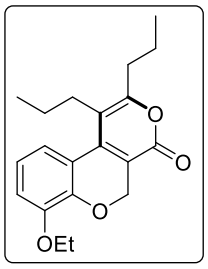
IR (neat): ν_{max} 2976, 2930, 2877, 1702, 1577, 1534, 1464, 1391, 1270, 1092, 1045, 874, 787, 738 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 (m, 1H), 7.02-7.00 (m, 2H), 4.95 (s, 2H), 4.15 (q, *J* = 7.0 Hz, 2H), 2.69-2.63 (m, 4H), 1.49 (t, *J* = 7.0 Hz, 3H), 1.30 (t, *J* = 7.5 Hz, 3H), 1.26 (t, *J* = 7.5 Hz, 3H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.0, 160.7, 148.8, 147.6, 145.1, 122.0, 121.3, 119.0, 115.8, 115.7, 113.9, 64.8, 63.6, 24.6, 20.4, 15.2, 14.8, 12.3 ppm.

HRMS (ESI-TOF): Calcd. for $C_{18}H_{21}O_4$ $[M^+ + H]$: *m/z* 301.1440. Found: 301.1441.

Compound 21bi



Yield: 120.8 mg (81%, pale yellow solid, R_f = 0.63 (9:1 hexane/ethyl acetate)).

Mp: 116-118 °C

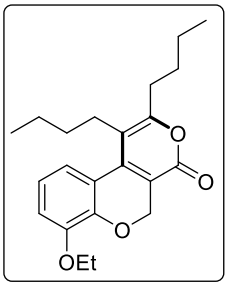
IR (neat): ν_{max} 2959, 2871, 1697, 1538, 1466, 1388, 1269, 1146, 1050, 1020, 759 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 7.21-7.18 (m, 1H), 7.02-6.98 (m, 2H), 4.93 (s, 2H), 4.14 (q, *J* = 7.0 Hz, 2H), 2.60-2.55 (m, 4H), 1.79-1.72 (m, 2H), 1.60-1.53 (m, 2H), 1.48 (t, *J* = 7.0 Hz, 3H), 1.01 (t, *J* = 7.5 Hz, 3H), 0.99 (t, *J* = 7.0 Hz, 3H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 162.0, 160.6, 148.8, 147.7, 145.0, 122.1, 121.2, 118.9, 115.8, 113.2, 64.8, 63.5, 33.2, 29.4, 23.8, 21.3, 14.8, 13.8_8, 13.8_5 ppm.

HRMS (ESI-TOF): Calcd. for $C_{20}H_{25}O_4$ [M^+ + H]: *m/z* 329.1753. Found: 329.1753.

Compound 21bj



Yield: 118.2 mg (73%, white solid, R_f = 0.65 (9:1 hexane/ethyl acetate)).

Mp: 102-104 °C

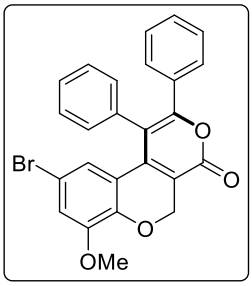
IR (neat): ν_{max} 2957, 2927, 2870, 1706, 1616, 1535, 1465, 1392, 1271, 1182, 1145, 1114, 789, 740 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.20 (m, 1H), 7.03-6.98 (m, 2H), 4.95 (s, 2H), 4.15 (q, *J* = 7.2 Hz, 2H), 2.63-2.58 (m, 4H), 1.75-1.67 (m, 4H), 1.58-1.47 (m, 3H), 1.46-1.37 (m, 4H), 0.99-0.95 (m, 6H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.2, 160.6, 148.8, 147.6, 145.1, 122.1, 121.1, 119.0, 115.7$_4$, 115.7$_0$, 113.1, 64.8, 63.6, 32.6, 31.1, 30.0, 27.1, 22.6, 14.8, 13.8, 13.7 ppm.

HRMS (ESI-TOF): Calcd. for $C_{22}H_{29}O_4$ [M^+ + H]: *m/z* 357.2066. Found: 357.2065.

Compound 21ca



Yield: 131.0 mg (81%, pale yellow solid, R_f = 0.44 (9:1 hexane/ethyl acetate)).

Mp: 246-248 °C

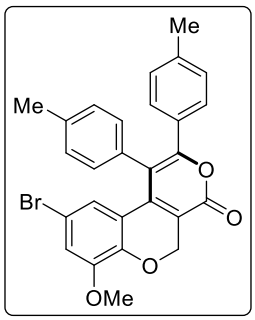
IR (neat): ν_{max} 3017, 2934, 2840, 2360, 1980, 1709, 1614, 1525, 1385, 1355, 1278, 1202, 1105, 875, 843, 712, 583 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.33 (m, 3H), 7.30-7.18 (m, 5H), 7.10-7.08 (m, 2H), 6.95 (d, *J* = 2.0 Hz, 1H), 6.02 (d, *J* = 2.4 Hz, 1H), 5.12 (s, 2H), 3.90 (s, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 159.7, 158.1, 149.6, 146.1, 142.9, 134.3, 132.5, 131.2, 129.5, 129.4, 129.1, 128.6, 127.9, 123.4, 122.0, 117.2, 116.5, 116.0, 112.8, 63.8, 56.4 ppm.

HRMS (ESI-TOF): Calcd. for $C_{21}H_{18}BrO_4$ [M^+ + H], [M^+ + H + 2]: *m/z* 461.0388, 463.0368. Found: 461.0386, 463.0369.

Compound 21cb



Yield: 135.6 mg (79%, yellow solid, R_f = 0.48 (9:1 hexane/ethyl acetate)).

Mp: 226-228 °C

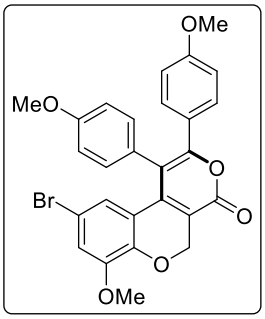
IR (neat): ν_{max} 3108, 2921, 1712, 1616, 1562, 1531, 1500, 1277, 1100, 1012, 973, 904, 819, 771, 731 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18-7.16 (m, 4H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.97-6.93 (m, 3H), 5.98 (d, *J* = 2.0 Hz, 1H), 5.09 (s, 2H), 3.88 (s, 3H), 2.41 (s, 3H), 2.30 (s, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 159.8, 158.1, 149.6, 146.2, 143.2, 139.7, 138.5, 131.5, 131.0, 129.8$_2$, 129.7$_8$, 129.3, 128.6, 123.6, 122.2, 117.1, 116.0, 115.6, 112.8, 63.8, 56.4, 21.3$_0$, 21.2$_5$ ppm.

HRMS (ESI-TOF): Calcd. for $C_{21}H_{22}BrO_4$ [M^+ + H], [M^+ + H + 2]: *m/z* 489.0701, 491.0681. Found: 489.0703, 491.0690.

Compound 21cc



Yield: 153.6 mg (84%, yellow solid, R_f = 0.40 (9:1 hexane/ethyl acetate)).

Mp: 228-230 ^oC

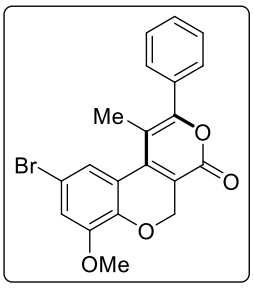
IR (neat): ν_{max} 2935, 2836, 1711, 1601, 1499, 1459, 1414, 1246, 1174, 1101, 1024, 973, 832, 771, 732 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.8 Hz, 2H), 7.01-6.98 (m, 2H), 6.95-6.91 (m, 3H), 6.74 (d, *J* = 8.8 Hz, 2H), 6.06 (d, *J* = 2.0 Hz, 1H), 5.09 (s, 2H), 3.89 (s, 3H), 3.88 (s, 3H), 3.80 (s, 3H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.3, 159.9, 158.0, 149.6, 146.2, 143.4, 132.3, 131.0, 126.7, 125.0, 123.6, 122.3, 116.9, 115.6, 114.8_4, 114.8_0, 113.4, 112.8, 63.8, 56.4, 55.5, 55.3 ppm.

HRMS (ESI-TOF): Calcd. for $C_{27}H_{22}BrO_6$ $[M^+ + H]$, $[M^+ + H + 2]$: *m/z* 521.0600, 523.058. Found: 521.0600, 523.0615.

Compound 21ce



Yield: 106.4 mg (76%, pale yellow solid, R_f = 0.46 (9:1 hexane/ethyl acetate)).

Mp: 182-184 ^oC

IR (neat): ν_{max} 2923, 2850, 2359, 2117, 1707, 1621, 1537, 1386, 1277, 1227, 1153, 1106, 1010, 883, 764, 700 cm^{-1}.

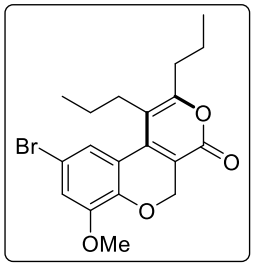
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.62 (m, 2H), 7.51-7.48 (m, 4H), 7.13 (d, *J* = 2.0 Hz, 1H), 5.06 (s, 2H), 3.94 (s, 3H), 2.35 (s, 3H) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.9, 158.6, 150.1, 146.3, 144.7, 132.7, 130.2, 129.4, 128.4, 123.1, 122.5, 117.5, 116.6, 113.5, 108.8, 63.6, 56.5, 18.1 ppm.

HRMS (ESI-TOF): Calcd. For $C_{20}H_{16}BrO_4$ [M^+ + H], [M^+ + H + 2]: *m/z* 399.0232, 401.0212. Found: 399.0231, 401.0217.

This compound was crystallized from dichloromethane–hexane (2:1) mixture at room temperature. X-ray structure has been determined for this compound.

Compound 21ci



Yield: 109.0 mg (79%, pale yellow solid, R_f = 0.48 (9:1 hexane/ethyl acetate)).

Mp: 150-152 ^{o}C

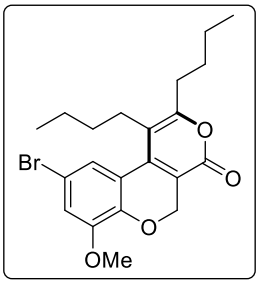
IR (neat): ν_{max} 2953, 2867, 1709, 1622, 1537, 1467, 1385, 1268, 1154, 1071, 933, 855, 831, 767 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 2.0 Hz, 1H), 7.10 (d, *J* = 2.0 Hz, 1H), 4.95 (s, 2H), 3.92 (s, 3H), 2.59 (t, *J* = 7.8 Hz, 2H), 2.55-2.52 (m, 2H), 1.80-1.73 (m, 2H), 1.64-1.56 (m, 2H), 1.04 (t, *J* = 7.3 Hz, 3H), 1.02 (t, *J* = 7.3 Hz, 3H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 162.4, 160.2, 150.2, 146.5, 143.7, 123.1, 121.6, 117.3, 116.0, 113.6, 112.8, 63.7, 56.5, 33.2, 29.3, 23.8, 21.2, 13.8, 13.7 ppm.

HRMS (ESI-TOF): Calcd. for $C_{19}H_{22}BrO_4$ [M^+ + H], [M^+ + H + 2]: *m/z* 393.0701, 395.0681. Found: 393.0702, 395.0686.

Compound 21cj



Yield: 112.3 mg (76%, yellow solid, R_f = 0.50 (9:1 hexane/ethyl acetate)).

Mp: 100-102 ^oC

IR (neat): ν_{max} 2957, 2931, 2869, 1699, 1614, 1529, 1459, 1414, 1383, 1267, 1212, 1154, 1011, 853, 838, 768, 686, 578 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 2.0 Hz, 1H), 7.09 (d, *J* = 2.0 Hz, 1H), 4.93 (s, 2H), 3.90 (s, 3H), 2.61-2.53 (m, 4H), 1.73-1.65 (m, 2H), 1.58-1.37 (m, 6H), 0.99 (t, *J* = 7.2 Hz, 3H), 0.96 (t, *J* = 7.2 Hz, 3H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.6, 160.3, 150.1, 146.4, 143.8, 123.0, 121.5, 117.2, 115.9, 113.6, 112.7, 63.7, 56.4, 32.6, 31.1, 30.0, 27.1, 22.5_4, 22.5_1, 13.8, 13.7 ppm.

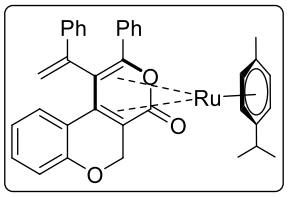
HRMS (ESI-TOF): Calcd. for $C_{21}H_{26}BrO_4$ $[M^+ + H]$, $[M^+ + H + 2]$: *m/z* 421.1014, 423.0994. Found: 421.1014, 423.0996.

This compound was crystallized from ethyl acetate–hexane (2:1) mixture at room temperature. X-ray structure has been determined for this compound.

3.8 Synthesis of Ru(0)-metal complexes: General procedure for the synthesis of compounds 22ra-rc. To an oven dried Schlenk tube, 2*H*-chromene-3-carboxylic acid (**6a**, 0.57 mmol), propargylic alcohol (**4r**, 0.57 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.173 g, 0.28 mmol, 50 mol%), $Cu(OTf)_2$ (0.57 mmol) and K_2CO_3 (0.57 mmol) were added. To this mixture, 1,4-dioxane (2 mL) was added, and the contents were stirred at 100 ^oC (oil bath temperature) for 24 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature, solvent removed under vacuum, and the crude product was purified by column chromatography by using silica gel with hexane/ethyl acetate

(4:1) mixture as the eluent to afford the corresponding final product **22ra**, same experimental procedure was followed to synthesize the compounds **2rb-2rc**.

Compound 22ra



Yield: 106.5 mg (61%, yellow solid, R_f = 0.40 (4:1 hexane/ethyl acetate)).

Mp: 142-144 ^oC

IR (neat): ν_{max} 3057, 2959, 2924, 2852, 1706, 1600, 1492, 1462, 1380, 1256, 1217, 1126, 1096, 1034, 1006, 978, 907, 757, 699 cm^{-1}.

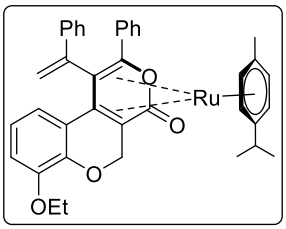
^1H NMR (500 MHz, $CDCl_3$): δ 7.71 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.52-7.47 (m, 4H), 7.23-7.20 (m, 2H), 7.17-7.13 (m, 2H), 7.08-7.05 (m, 2H), 6.97-6.95 (m, 1H), 6.91-6.89 (m, 1H), 6.81-6.78 (m, 1H), 6.20 (d, *J* = 1.5 Hz 1H), 5.85 (d, *J* = 1.0 Hz, 1H), 5.81 (d, *J* = 6.0 Hz, 1H), 5.65 (d, *J* = 5.5 Hz, 1H), 4.90 (d, *J* = 6.0 Hz, 1H), 4.79 (d, *J* = 6.0 Hz, 1H), 4.59 (d, *J* = 12.5 Hz, 1H), 4.49 (d, *J* = 13.0 Hz, 1H), 2.08-2.00 (m, 1H), 1.63 (s, 3H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 3H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 174.9, 155.8, 143.4, 142.5, 138.8, 128.7, 128.4, 128.0, 127.1, 126.9, 126.6, 125.0, 124.8, 124.1, 121.6, 121.1, 117.5, 112.0, 101.9, 89.6, 89.1, 88.4, 87.9, 87.6, 84.3, 84.1, 69.9, 58.0, 30.7, 25.1, 21.0, 17.6 ppm. All the *p*-cymene carbons are distinctly shown.

HRMS (ESI-TOF): Calcd. for $C_{36}H_{33}O_3Ru$ $[M^+ + H]$: *m/z* 615.1473. Found: 615.1477.

This compound was crystallized from ethyl acetate–hexane (2:1) mixture at room temperature. X-ray structure has been determined for this compound.

Compound 22rb



Yield: 94.3 mg (63%, yellow solid, R_f = 0.39 (4:1 hexane/ethyl acetate)).

Mp: 128-130 °C

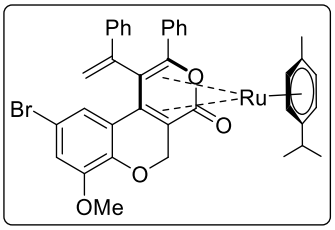
IR (neat): ν_{max} 2961, 2923, 2852, 1710, 1597, 1446, 1395, 1258, 1095, 1014, 863, 793, 695 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$): δ 7.50-7.46 (m, 3H), 7.31 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.23-7.20 (m, 2H), 7.17-7.14 (m, 1H), 7.07-7.04 (m, 2H), 6.97-6.94 (m, 1H), 6.81 (dd, *J* = 8.5, 1.5 Hz, 1H), 6.74-6.71 (m, 1H), 6.19 (d, *J* = 1.5 Hz, 1H), 5.84 (d, *J* = 1.5 Hz, 1H), 5.80 (d, *J* = 6.0 Hz, 1H), 5.64 (d, *J* = 5.5 Hz, 1H), 4.95 (d, *J* = 5.5 Hz, 1H), 4.83 (d, *J* = 6.0 Hz, 1H), 4.71 (d, *J* = 12.5 Hz, 1H), 4.46 (d, *J* = 12.5 Hz, 1H), 4.16 (q, *J* = 14.0, 7.0 Hz, 2H), 2.07-2.02 (m, 1H), 1.65 (s, 3H), 1.44 (t, *J* = 7.0 Hz, 3H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 177.1, 148.3, 145.6, 143.5, 142.5, 138.9, 128.4, 127.9, 126.9, 126.6, 125.3, 125.0, 124.8, 121.1, 121.0, 119.4, 113.2, 112.1, 101.8, 89.6, 89.0, 88.4, 88.0, 87.7, 84.3, 84.2, 70.3, 64.7, 58.2, 30.6, 25.0, 21.1, 17.5, 14.8 ppm.

HRMS (ESI-TOF): Calcd. for $C_{38}H_{37}O_4Ru$ [M^+ + H]: *m/z* 659.1735. Found: 659.1732.

Compound 22rc



Yield: 71.0 mg (56%, yellow solid, R_f = 0.38 (4:1 hexane/ethyl acetate)).

Mp: 204-206 °C

IR (neat): ν_{max} 3075, 2961, 2853, 1692, 1594, 1570, 1481, 1445, 1380, 1239, 1210, 1176, 1132, 1064, 989, 968, 893, 779, 762, 694 cm^{-1}.

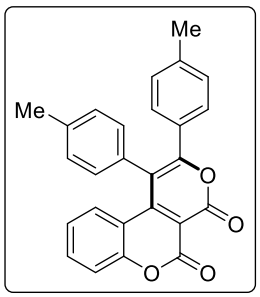
^1H NMR (400 MHz, $CDCl_3$): δ 7.50-7.46 (m, 5H), 7.25-7.22 (m, 2H), 7.21-7.15 (m, 1H), 7.10-7.06 (m, 2H), 7.00-6.96 (m, 1H), 6.91 (d, *J* = 2.4 Hz, 1H), 6.24 (d, *J* = 1.6 Hz, 1H), 5.82 (d, *J* = 1.2 Hz, 2H), 5.65 (d, *J* = 5.2 Hz, 1H), 4.96 (d, *J* = 5.6 Hz, 1H), 4.82-4.80 (m, 1H), 4.69 (d, *J* = 12.8 Hz, 1H), 4.46 (d, *J* = 12.8 Hz, 1H), 3.88 (s, 3H), 2.04-1.94 (m, 1H), 1.66 (s, 3H), 1.03 (d, *J* = 7.2 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H) ppm.

$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 174.4, 149.5, 144.0, 143.2, 142.3, 138.6, 128.5, 128.1, 127.0, 126.9, 126.6, 125.0, 121.8, 121.5, 114.5, 113.3, 112.6, 102.0, 89.8, 89.3, 88.7, 88.3, 85.6, 84.5, 84.4, 70.6, 57.5, 56.4, 30.6, 24.9, 21.2, 17.6 ppm.

HRMS (ESI-TOF): Calcd. for $C_{37}H_{34}BrO_4Ru$ $[M^+ + H]$: *m/z* 723.0684. Found: 723.0661.

3.9 Synthesis of substituted 4*H*,5*H*-pyrano[3,4-*c*]chromene-4,5-diones: General procedure for the synthesis of the compounds 23ab-aj. To an oven dried Schlenk tube coumarin-3-carboxylic acid (**5a**, 0.53 mmol), alkyne (**7**, 0.53 mmol), $[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %), $Cu(OAc)_2 \cdot H_2O$ (30 mol %) and $AgSbF_6$ (10 mol%) were added. To this mixture, 1,4-dioxane (2 mL) was added and the contents were stirred at 100 °C (oil bath temperature) for 20 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, mixture was cooled to room temperature, and solvent was removed under the vacuum, and the crude product was purified by column chromatography by using silica gel with hexane/ethyl acetate (9:1) mixture as the eluent to afford the corresponding annulated product.

Compound 23ab



Yield: 126.5 mg (61%, yellow solid, R_f = 0.50 (9:1 hexane/ethyl acetate)).

Mp: 238-240 ºC

IR (neat): ν_{max} 3059, 3031, 2920, 1754, 1701, 1598, 1488, 1437, 1248, 1184, 1130, 826, 768, 753 cm^{-1}.

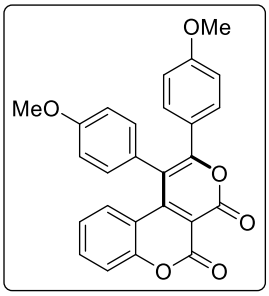
^1H NMR (400 MHz, $CDCl_3$) δ 7.53-7.48 (m, 1H), 7.34-7.32 (m, 1H), 7.23-7.21 (m, 2H), 7.15-7.09 (m, 4H), 7.04-7.02 (m, 2H), 6.83-6.82 (m, 2H), 2.45 (s, 3H), 2.32 (s, 3H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 164.2, 156.8, 156.5, 154.9, 154.5, 141.1, 139.2, 134.3, 131.9, 131.2, 130.5, 129.5, 129.2, 129.1, 128.7, 123.4, 117.9, 115.9, 115.4, 103.8, 21.5, 21.4 ppm.

HRMS (ESI-TOF): Calcd. for $C_{26}H_{18}O_4Na$ [M^+ + Na]: *m/z* 417.1103. Found: 417.1103.

This compound was crystallized from ethyl acetate–hexane (2:1) mixture at room temperature. X-ray structure has been determined for this compound.

Compound 23ac



Yield: 143.5 mg (64%, pale yellow solid, R_f = 0.46 (9:1 hexane/ethyl acetate)).

Mp: 148-150 ºC

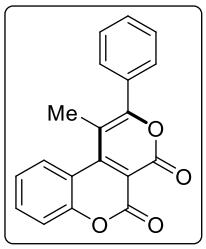
IR (neat): ν_{max} 2932, 2842, 2360, 1791, 1745, 1674, 1597, 1511, 1397, 1253, 1168, 1024, 983, 838, 733, 701, 614 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.5 Hz, 2H), 7.69-7.65 (m, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.30-7.25 (m, 3H), 6.93-6.90 (m, 4H), 3.88 (s, 3H), 3.81 (s, 3H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 170.6, 164.8, 164.6, 160.9, 156.5, 154.5, 135.3, 134.0, 129.4, 127.9, 126.6, 126.0, 124.7, 117.5, 115.5, 114.9, 113.9, 109.9, 92.6, 55.6, 55.4 ppm.

HRMS (ESI-TOF): Calcd. for $C_{26}H_{19}O_6$ [M^+ + H]: *m/z* 427.1181. Found: 427.1181.

Compound 23ae



Yield: 96.0 mg (60%, pale yellow solid, R_f = 0.48 (9:1 hexane/ethyl acetate)).

Mp: 137-139 ºC

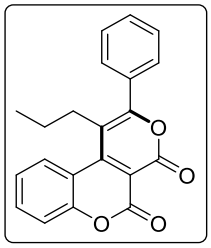
IR (neat): ν_{max} 3068, 2968, 1730, 1672, 1594, 1460, 1445, 1376, 1321, 1286, 1229, 1205, 1028, 976, 956, 928, 902, 791, 749, cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 8.41 (dd, J_1 = 7.5 Hz, J_2 = 1.0 Hz, 1H), 7.85-7.82 (m, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.63-7.61 (m, 2H), 7.60-7.56 (m, 1H), 7.51-7.49 (m, 1H), 7.48-7.44 (m, 2H), 2.35 (s, 3H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 162.6, 151.2, 138.8, 134.8, 133.3, 129.8, 129.5, 129.4, 128.5, 128.3, 128.0, 123.4, 120.8, 109.1, 100.0, 13.6 ppm.

HRMS (ESI-TOF): Calcd. for $C_{19}H_{13}O_4$ $[M^+ + H]$: *m/z* 305.0814. Found: 305.0814.

Compound 23ag



Yield: 118.9 mg (68%, pale yellow solid, R_f = 0.51 (9:1 hexane/ethyl acetate)).

Mp: 180-182 ºC

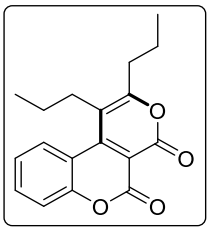
IR (neat): ν_{max} 2962, 1763, 1604, 1567, 1480, 1380, 1257, 1071, 998, 860, 764, 698 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 8.25 (dd, J_1 = 8.5 Hz, J_2 = 1.0 Hz, 1H), 7.73-7.69 (m, 1H), 7.64-7.63 (m, 2H), 7.59-7.52 (m, 3H), 7.45 (dd, J = 8.3 Hz, J_2 = 1.5 Hz, 1H), 7.41-7.38 (m, 1H), 3.04 (t, J = 7.8 Hz, 2H), 1.47-1.40 (m, 2H), 0.78 (t, J = 7.3 Hz, 3H) ppm.

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 164.7, 156.7, 156.2, 155.7, 154.6, 134.7, 132.5, 131.1, 129.5, 128.7, 127.7, 124.4, 118.5, 116.5, 113.5, 105.9, 32.4, 22.6, 13.6 ppm.

HRMS (ESI-TOF): Calcd. for $C_{21}H_{17}O_4$ $[M^+ + H]$: *m/z* 333.1127. Found: 333.1124.

Compound 23ai



Yield: 105.1 mg (67%, gummy liquid, R_f = 0.54 (9:1 hexane/ethyl acetate)).

Mp: -gummy liquid

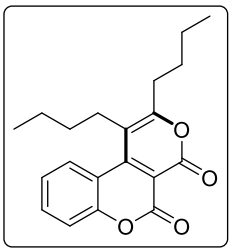
IR (neat): ν_{max} 2923, 2853, 1723, 1606, 1452, 1176, 1119, 998, 829,753 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 7.70-7.66 (m, 1H), 7.42-7.35 (m, 2H), 2.83-2.79 (m, 2H), 2.72-2.69 (m, 2H), 1.88-1.79 (m, 2H), 1.77-1.66 (m, 2H), 1.12 (t, J = 7.4 Hz, 3H), 1.07 (t, J = 7.4 Hz, 3H) ppm.

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 160.8, 154.1, 143.4, 131.9, 131.8, 130.0, 127.9, 126.2, 124.7, 124.4, 118.9, 116.9, 116.8, 116.6, 31.9, 29.7, 29.4, 22.7, 14.4, 14.1 ppm.

HRMS (ESI-TOF): Calcd. for $C_{18}H_{18}O_4Na$ $[M^+ + Na]$: *m/z* 321.1103. Found: 321.1103.

Compound 23aj



Yield: 111.6 mg (65%, gummy liquid, R_f = 0.58 (9:1 hexane/ethyl acetate)).

Mp: gummy liquid

IR (neat): ν_{max} 2924, 2853, 1729, 1606, 1563, 1453, 1178, 1102, 929, 828, 752 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H), 7.70-7.66 (m, 1H), 7.41 (dd, J = 8.4 Hz, J_2 = 1.2 Hz, 1H), 7.38-7.34 (m, 1H), 2.86-2.82 (m, 2H), 2.74-

2.70 (m, 2H), 1.81-1.75 (m, 2H), 1.73-1.68 (m, 2H), 1.58-1.51 (m, 2H), 1.50-1.43 (m, 2H), 1.05 (t, J = 7.4 Hz, 3H), 1.00 (t, J = 7.4 Hz, 3H) ppm.

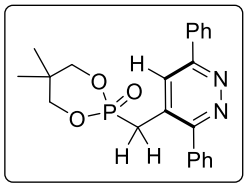
$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 169.5, 157.0, 156.3, 155.3, 154.6, 134.4, 127.7, 124.1, 118.5, 116.1, 112.7, 104.6, 32.2, 32.0, 29.7, 28.5, 22.6_3, 22.5_7, 13.7, 13.6 ppm.

HRMS (ESI-TOF): Calcd. for $C_{20}H_{22}O_4Na$ $[M^+ + Na]$: *m/z* 349.1416. Found: 349.1412.

3.10 Thermally induced [4+2] cycloaddition reactions of 3,6-diphenyl 1,2,4,5-tetrazine (8) with allenes: Representative procedure for the synthesis 3,6-diphenylpyridazines (24a-d and 25).

To an oven dried Schlenk tube, 3,6-diphenyl-1,2,4,5-tetrazine **8** (50 mg, 0.21 mmol) and allene (one of **10a-d** or **11**, 0.32 mmol) were added. To this mixture, xylene (2 mL) was added and the contents were stirred at 140 °C for 24 h. Progress of the reaction was monitored by TLC and can be identified by the disappearance of the violet-red color of the tetrazine in the reaction mixture. After completion of the reaction, the mixture was concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography by using hexane/ethyl acetate (3:2) mixture as the eluent to afford the products **24-25**.

Compound 24a



Yield: 69.0 mg (82%, white solid, R_f = 0.36 (3:2 hexane/ethyl acetate)).

Mp: 218-220 °C

IR (neat): ν_{max} 3056, 2961, 2901, 1585, 1477, 1445, 1401, 1369, 1262, 1241, 1056, 1006, 978, 916, 865, 813, 774, 756, 695, 645 cm^{-1}.

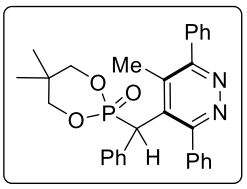
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, J = 6.8 Hz, 2H), 8.11 (d, J = 2.8 Hz, 1H), 7.69 (d, J = 6.4 Hz, 2H), 7.58-7.52 (m, 6H), 4.18 (dd, J = 10.8, 3.2 Hz, 2H), 3.63 (dd, J = 15.4, 4.0 Hz, 2H), 3.44 (d, J = 22.8 Hz, 2H), 0.95 and 0.85 (2s, 6H) ppm.

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 160.5 (d, *J* = 7.0 Hz), 157.7, 136.4, 135.9, 130.3 (d, *J* = 9.0 Hz), 130.1, 129.6, 129.2, 129.0, 128.7, 127.2, 125.8 (d, *J* = 6.0 Hz), 75.3 (d, *J* = 7.0 Hz), 32.5 (d, *J* = 6.0 Hz), 28.4 (d, *J* = 134.0 Hz), 21.4 and 21.2 ppm.

^{31}P NMR (162 MHz, $CDCl_3$): δ 20.3 ppm

HRMS (ESI-TOF): Calcd. for $C_{22}H_{24}N_2O_3P$ $[M^+ + H]$: *m/z* 395.1524. Found: 395.1524.

Compound 24b



Yield: 76.53 (74%, white solid, R_f = 0.38 (3:2 hexane/ethyl acetate)).

Mp: 204-206 ºC

IR (neat): ν_{max} 3053, 2966, 2926, 1598, 1497, 1468, 1446, 1376, 1255, 1178, 1053, 1004, 966, 917, 828, 777, 760, 648 cm^{-1}.

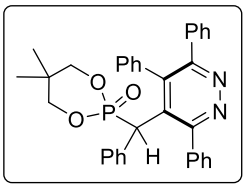
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64-7.62 (m, 2H), 7.57-7.54 (m, 2H), 7.50-7.44 (m, 8H), 7.41-7.37 (m, 2H), 7.34-7.30 (m, 1H), 5.41 (d, *J* = 30.4 Hz, 1H), 4.22-4.06 (m, 2H), 3.59-3.44 (m, 2H), 2.23 (s, 3H), 0.90 and 0.69 (2s, 6H) ppm.

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 163.0, 161.7 (d, *J* = 7.0 Hz), 137.9 (d, *J* = 5.0 Hz), 137.4, 137.2, 134.2 (d, *J* = 3.0 Hz), 133.4 (d, *J* = 6.0 Hz), 129.4, 129.3, 129.1, 129.0, 128.8, 128.5, 128.4, 128.3, 127.5, 75.3 (d, *J* = 7.0 Hz), 75.0 (d, *J* = 7.0 Hz), 44.8 (d, *J* = 135.0 Hz), 32.6 (d, *J* = 6.0 Hz), 21.5, 21.2 and 18.8 ppm.

^{31}P NMR (162 MHz, $CDCl_3$): δ 19.9 ppm

HRMS (ESI-TOF): Calcd. for $C_{29}H_{30}N_2O_3P$ $[M^+ + H]$: *m/z* 485.1994. Found: 485.1994.

Compound 24c



Yield: 94.50 (81%, white solid, R_f = 0.37 (3:2 hexane/ethyl acetate)).

Mp: 202-204 ºC

IR (neat): ν_{max} 2925, 2854, 1722, 1600, 1445, 1376, 1228, 1054, 1002, 910, 829, 762, 732, 699, 650, 631 cm^{-1}.

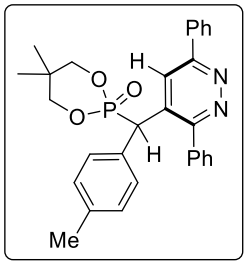
^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54-7.43 (m, 5H), 7.28-7.26 (m, 4H), 7.20-7.10 (m, 5H), 7.06-6.83 (m, 6H), 5.41 (d, *J* = 30.0 Hz, 1H), 4.13-4.08 (m, 2H), 3.48-3.35 (m, 2H), 0.84 and 0.62 (2s, 6H) ppm.

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 162.0 (d, *J* = 5.0 Hz), 160.8, 141.2, 138.1, 137.4, 134.5 (d, *J* = 2.8 Hz), 134.4, 132.9 (d, *J* = 5.4 Hz), 131.1, 130.5, 130.1, 129.9, 129.6 (d, *J* = 10.6 Hz), 128.5, 128.2, 128.0, 127.7, 127.5, 127.4, 126.9, 74.6 (d, *J* = 6.1 Hz), 44.9 (d, *J* = 137.5 Hz), 32.5 (d, *J* = 5.5 Hz), 21.7, 21.2 ppm.

^{31}P NMR (162 MHz, $CDCl_3$): δ 19.7 ppm

HRMS (ESI-TOF): Calcd. for $C_{34}H_{32}N_2O_3P$ $[M^+ + H]$: *m/z* 547.2150. Found: 547.2150.

Compound 24d



Yield: 71.35 (69%, white solid, R_f = 0.39 (3:2 hexane/ethyl acetate)).

Mp: 210-212 °C

IR (neat): ν_{max} 3050, 2970, 2923, 1585, 1512, 1448, 1398, 1372, 1270, 1055, 1004, 983, 944, 915, 869, 835, 800, 760, 701, 690 cm^{-1}.

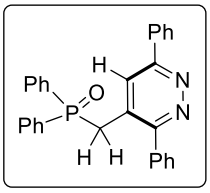
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, *J* = 2.0 Hz, 1H), 8.20-8.17 (m, 2H), 7.58-7.52 (m, 8H), 7.27-7.24 (m, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 4.82 (d, *J* = 23.6 Hz, 1H), 4.17-4.07 (m, 2H), 3.70-3.63 (m, 1H), 3.56-3.49 (m, 1H), 2.33 (s, 3H), 0.98 and 0.82 (2s, 6H) ppm.

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 160.5 (d, *J* = 10.0 Hz), 158.1, 138.1 (d, *J* = 2.0 Hz), 136.6, 136.1, 135.3 (d, *J* = 4.0 Hz), 130.9 (d, *J* = 7.0 Hz), 130.1, 129.9 (d, *J* = 2.0 Hz), 129.5, 129.2, 129.1, 129.0, 128.6, 127.4, 124.9 (d, *J* = 5.0 Hz), 75.9 (d, *J* = 7.0 Hz), 75.8 (d, *J* = 7.0 Hz), 43.9 (d, *J* = 134.0 Hz), 32.5 (d, *J* = 6.0 Hz), 21.3_4, 21.3_0, and 21.1 ppm.

^{31}P NMR (162 MHz, $CDCl_3$): δ 18.6 ppm

HRMS (ESI-TOF): Calcd. for $C_{29}H_{30}N_2O_3P$ [M^+ + H]: *m/z* 485.1994. Found: 485.1993.

Compound 25



Yield: 75.29 (79%, white solid, R_f = 0.41 (3:2 hexane/ethyl acetate)).

Mp: 208-210 °C

IR (neat): ν_{max} 3057, 2924, 2854, 1717, 1584, 1438, 1399, 1192, 1120, 1072, 1027, 909, 832, 730, 694, 645 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (d, *J* = 2.0 Hz, 1H), 8.10 (dd, *J* = 7.5, 1.5 Hz, 2H), 7.56-7.50 (m, 9H), 7.48-7.41 (m, 7H), 7.37-7.35 (m, 2H), 3.83 (d, *J* = 14.0 Hz, 2H) ppm.

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.5 (d, *J* = 4.0 Hz), 157.2, 136.1 (d, *J* = 39.3 Hz), 132.4 (d, *J* = 2.0 Hz), 131.6, 131.0, 130.9, 130.8, 130.7_1, 130.6_6, 130.0, 129.6, 128.9 (d, *J* -= 2.0 Hz), 128.8_3, 128.5, 127.3, 125.7 (d, *J* = 4.0 Hz), 33.2 (d, *J* = 50.0 Hz) ppm.

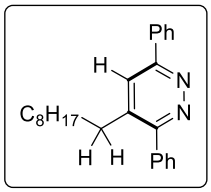
^{31}P NMR (202 MHz, $CDCl_3$): δ 29.6 ppm

HRMS (ESI-TOF): Calcd. for $C_{29}H_{24}N_2OP$ [M^+ + H]: *m/z* 447.1626. Found: 447.1626.

This compound was crystallized from ethyl acetate–hexane (2:1) mixture at room temperature. X-ray structure has been determined for this compound.

3.11 Synthesis of 3,6-diphenylpyridazines 26a-b, 27a-c and 28: To an oven dried Schlenk tube, 3,6-diphenyl-1,2,4,5-tetrazine **8** (50 mg, 0.21 mmol) and allene (one of **12a-b, 13a-c** or **14**, 0.42 mmol), were added. To this mixture, xylene (2 mL) was added and the contents were stirred at 120 °C for 12 h. After completion of the reaction, the mixture was concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography by using hexane/ethyl acetate (9:1) mixture as the eluent to afford the product.

Compound 26a



Yield: 60.45 (79%, gummy liquid, R_f = 0.52 (9:1 hexane/ethyl acetate)).

Mp: gummy liquid

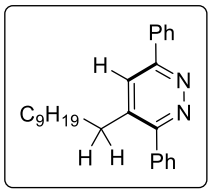
IR (neat): ν_{max} 2922, 2852, 1719, 1584, 1449, 1398, 1180, 1073, 1026, 908, 765, 695, 659 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 7.0 Hz, 2H), 7.75 (s, 1H), 7.60 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.55-7.48 (m, 6H), 2.72 (t, *J* = 7.5 Hz, 2H), 2.32 (t, *J* = 7.5 Hz, 1H), 1.65-1.55 (m, 3H), 1.21 (br, 8H), 0.90 (br, 2H), 0.89 (t, *J* = 5.8 Hz, 3H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 160.8, 157.8, 140.9, 137.1, 136.5, 129.9, 129.2, 129.0, 128.8, 128.4, 127.2, 124.3, 34.1, 32.1, 31.8, 29.7, 29.3, 29.2, 24.8, 22.7, 14.1 ppm.

HRMS (ESI-TOF): Calcd. for $C_{25}H_{31}N_2$ $[M^+ + H]$: *m/z* 359.2487. Found: 359.2488.

Compound 26b



Yield: 67.59 (85%, gummy liquid, R_f = 0.54 (9:1 hexane/ethyl acetate)).

Mp: gummy liquid

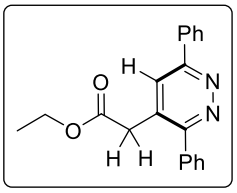
IR (neat): ν_{max} 3059, 2922, 2852, 1719, 1584, 1492, 1449, 1397, 1180, 1072, 1025, 913, 765, 694, 658 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ 8.16 (dd, *J* = 5.5 Hz, 2.0 Hz, 2H), 7.77 (s, 1H), 7.63-7.61 (m, 2H), 7.57-7.48 (m, 6H), 2.74 (t, *J* = 8.0 Hz, 2H), 1.63-1.55 (m, 2H), 1.31-1.22 (m, 14H), 0.90 (t, *J* = 7.0 Hz, 3H) ppm.

$^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$): δ 160.8, 157.7, 140.8, 137.2, 136.5, 129.8, 129.2, 129.0, 128.7, 128.4, 127.1, 124.2, 32.1, 31.9, 29.7, 29.5, 29.4, 29.3, 29.2_2, 29.1_5, 22.7, 14.1 ppm.

HRMS (ESI-TOF): Calcd. for $C_{26}H_{33}N_2$ $[M^+ + H]$: *m/z* 373.2643. Found: 373.2635.

Compound 27a



Yield: 59.80 (88%, white solid, R_f = 0.48 (9:1 hexane/ethyl acetate)).

Mp: 128-130 °C

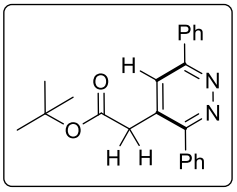
IR (neat): ν_{max} 2980, 2904, 1731, 1585, 1445, 1399, 1373, 1331, 1278, 1190, 1157, 1071, 1022, 935, 899, 866, 802,772, 751, 699 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.92 (s, 1H), 7.65-7.62 (m, 2H), 7.60-7.52 (m, 6H), 4.17 (q, *J* = 14.4, 7.2 Hz, 2H), 3.77 (s, 2H), 1.25 (t, *J* = 7.2 Hz, 3H) ppm.

$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 169.7, 160.5, 157.8, 136.5, 136.1, 132.6, 130.1, 129.3, 129.1, 129.0, 128.6, 127.2, 125.6, 61.6, 38.1, 14.1 ppm.

HRMS (ESI-TOF): Calcd. for $C_{20}H_{19}N_2O_2$ $[M^+ + H]$: *m/z* 319.1446. Found: 319.1449.

Compound 27b



Yield: 62.85 (85%, white solid, R_f = 0.51 (9:1 hexane/ethyl acetate)).

Mp: 124-126 °C

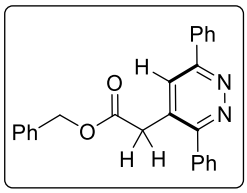
IR (neat): ν_{max} 2976, 2932, 1727, 1587, 1450, 1397, 1368, 1331, 1258, 1221, 1146, 1026, 847, 764, 696 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.90 (s, 1H), 7.66-7.64 (m, 2H), 7.59-7.51 (m, 6H), 3.69 (s, 2H), 1.42 (s, 9H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 168.9, 160.5, 157.7, 136.6, 136.1, 133.1, 130.0, 129.3, 129.1, 129.0, 128.5, 127.2, 125.7, 82.2, 39.5, 27.9 ppm.

HRMS (ESI-TOF): Calcd. for $C_{22}H_{23}N_2O_2$ [M^+ + H]: *m/z* 347.1759. Found: 347.1757.

Compound 27c



Yield: 65.77 (81%, white solid, R_f = 0.46 (9:1 hexane/ethyl acetate)).

Mp: 196-198 °C

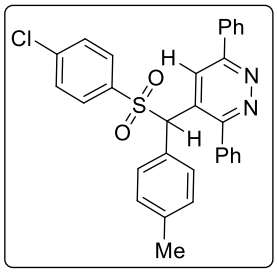
IR (neat): ν_{max} 3059, 3027, 2923, 2852, 1734, 1587, 1494, 1451, 1399, 1328, 1213, 1157, 1111, 1074, 1026, 974, 905, 764, 696 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 8.0, 1.5 Hz, 2H), 7.87 (s, 1H), 7.59-7.52 (m, 5H), 7.50-7.47 (m, 3H), 7.39-7.36 (m, 3H), 7.33-7.31 (m, 2H), 5.15 (s, 2H), 3.81 (s, 2H) ppm.

^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 169.5, 160.4, 157.8, 136.4, 136.0, 135.2, 132.3, 130.0, 129.3, 129.1, 129.0, 128.7, 128.6$_2$, 128.5$_6$, 128.5, 127.2, 125.5, 67.3, 38.0 ppm.

HRMS (ESI-TOF): Calcd. for $C_{25}H_{21}N_2O_2$ [M^+ + H]: *m/z* 381.1603. Found: 381.1605.

Compound 28



Yield: 69.80 (64%, red solid, R_f = 0.47 (9:1 hexane/ethyl acetate)).

Mp: 182-184 °C

IR (neat): ν_{max} 2921, 2851, 1736, 1460, 1376, 1087 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.47 (m, 4H), 7.39-7.36 (m, 2H), 7.30-7.24 (m, 8H), 7.16-7.12 (m, 3H), 7.06-7.04 (m, 2H), 4.85 (s, 1H), 2.39 (s, 3H) ppm.

$^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 160.6, 159.5, 141.7, 140.7, 138.6, 137.9, 136.8, 131.2, 129.9, 129.5, 129.4, 129.3, 129.2, 128.9, 128.7, 128.5, 127.9, 125.0, 124.6, 55.6, 21.3 ppm.

HRMS (ESI-TOF): Calcd. for $C_{30}H_{24}ClN_2O_2S$ $[M^+ + H]$: *m/z* 511.1247. Found: 511.1251.

This compound was crystallized from ethyl acetate–hexane (2:1) mixture at room temperature. X-ray structure has been determined for this compound.

3.12 X-ray crystallography:

A suitable crystal was mounted on a glass fiber (for **15aa**, **15ba**, **16ba**, **17ba**, **19ap**, **19bb**, **intermediate X**, **20aa**, **20de**, **21aa**, **21ce**, **21cj**, **22ra**, **23ab**, **25** and **27b**) and X-ray data were collected at 298 K on a Bruker AXS-SMART or on an OXFORD diffractometer using Mo-K_α radiation (λ = 0.71073 Å) or Cu- K_α (λ = 1.54184 Å). Structures were solved and refined using standard methods.[112] Absorption corrections were done using SADABS program, where applicable. All non-hydrogen atoms were refined anisotropically; hydrogen atoms were fixed by geometry or located by a Difference Fourier and refined isotropically. Crystal data are summarized in Tables 14-17.

Table 14: Crystal data for compounds **15aa**, **15ba**, **16ba,** and **17ba**[a]

Compound	**15aa**	**15ba**	**16ba**	**17ba**
Emp. formula	$C_{31}H_{21}ClN_2O_6$	$C_{32}H_{23}ClN_2O_6$	$C_{32}H_{23}ClN_2O_4$	$C_{30.25}H_{17.50}Cl_{1.50}N_2O_4$
Formula weight	552.95	566.97	534.97	526.14
Crystal system	Triclinic	Monoclinic	Triclinic	Triclinic
Space group	P-1	P2(1)/c	P-1	P-1
a /Å	9.8594(4)	13.8158(8)	8.7530(6)	9.7775(16)
b /Å	11.5298(5)	11.0100(6)	12.2409(12)	11.469(2)
c /Å	13.2242(6)	18.4437(10)	12.7350(9)	14.435(3)
α/deg	72.805(2)	90	104.721(7)	74.357(6)
β/deg	69.221(2)	103.283(5)	99.154(6)	80.618(6)

γ/deg	84.368(2)	90	101.014(7)	73.403(6)
V /Å^3	1342.65(10)	2730.5(3)	1264.03(18)	1487.2(5)
Z	2	4	2	2
Dcalc /g cm^{-3}]	1.368	1.379	1.406	1.182
μ /mm^{-1}	0.191	0.190	0.195	0.208
F(000)	572.0	1176.0	556.0	544.0
Data/ restraints/ parameters	4729/0/363	4781/0/372	4471/0/358	5231/2/350
S	1.018	0.938	1.048	1.207
R1 [I>2σ(I)]	0.0623	0.0700	0.0820	0.0842
wR2 [all data]	0.1444	0.2029	0.2348	0.3030
Max./min. residual electron dens. [eÅ^{-3}]	0.42/-0.43	0.34/-0.22	0.35/-0.36	0.71/-0.29

[a] $R1 = \Sigma||Fo| - |Fc||/\Sigma|Fo|$ and $wR2 = [\Sigma w(Fo^2-Fc^2)^2/\Sigma wFo^4]^{0.5}$

Table 15: Crystal data for compounds **19ap**, **19bb**, intermediate **X**, and **20aa**[a]

Compound	**19ap**	**19bb**	**X**	**20aa**
Emp. formula	$C_{30}H_{17}ClN_2O_4$	$C_{34}H_{26}Cl_3NO_3$	$C_{31}H_{22}ClFN_2O_5$	$C_{30}H_{18}O_3$
Formula weight	504.90	602.91	556.96	426.48
Crystal system	Monoclinic	Monoclinic	Orthorhombic	Monoclinic
Space group	P2(1)/c	P2(1)/c	Pca2(1)	P2(1)/c
a /Å	8.7144(2)	9.6019(3)	14.0858(11)	13.9566(5)
b /Å	16.0477(6)	14.9318(5)	12.2527(9)	12.3310(5)
c /Å	18.8759(7)	20.5601(7)	15.7897(10)	24.8503(9)
α/deg	90	90	90	90
β/deg	95.277(3)	95.004(3)	90	96.334(4)
γ/deg	90	90	90	90

V /Å^3	2628.53(15)	2936.54(17)	2725.1(3)	4250.6(3)
Z	4	4	4	8
Dcalc /g cm^{-3}]	1.276	1.364	1.358	1.333
μ /mm^{-1}	0.183	0.348	0.191	0.085
F(000)	1040.0	1248.0	1152.0	1776.9
Data/ restraints/ parameters	5492/0/334	5166/0/378	4505/1/367	8912/0/595
S	1.004	1.099	0.999	1.011
R1 [I>2σ(I)]	0.0893	0.0654	0.0575	0.0559
wR2 [all data]	0.3171	0.2010	0.1194	0.1716
Max./min. residual electron dens. [eÅ^{-3}]	1.23/-0.43	0.48/-0.36	0.29/-0.21	0.23/-0.30

[a]R1 = Σ||Fo| - |Fc||/Σ|Fo| and wR2 = [Σw(Fo^2-Fc^2)^2/ΣwFo^4]$^{0.5}$

Table 16: Crystal data for compounds **20de**, **21aa**, **21ce**, and **21cj**[a]

Compound	**20de**	**21aa**	**21ce**	**21cj**
Emp. formula	$C_{30}H_{14}Cl_2F_2O_3$	$C_{24}H_{16}O_3$	$C_{21}H_{15}BrClO_4$	$C_{21}H_{25}BrO_4$
Formula weight	531.31	352.37	446.69	421.32
Crystal system	Monoclinic	Orthorhombic	Monoclinic	Monoclinic
Space group	P2(1)/c	Pna2(1)	P2(1)/c	P2(1)
a /Å	11.552(4)	7.9771(3)	16.4674(10)	5.1663(2)
b /Å	19.301(6)	14.2651(6)	7.5481(5)	14.7442(5)
c /Å	11.711(3)	15.4453(7)	16.6864(10)	12.9318(5)
α/deg	90	90	90	90
β/deg	115.976(11)	90	117.646(2)	98.432(4)
γ/deg	90	90	90	90
V /Å^3	2347.4(13)	1757.58(13)	1837.3(2)	974.41(6)
Z	4	4	4	2
Dcalc /g cm^{-3}]	1.503	1.332	1.615	1.436
μ /mm^{-1}	0.326	0.087	2.408	2.132

F(000)	1080.0	736.0	900.0	436.0
Data/ restraints/ parameters	4107/0/334	2973/1/245	3187/0/246	2954/1/238
S	1.003	1.103	1.061	1.041
R1 [I>2σ(I)]	0.0945	0.0288	0.0462	0.0544
wR2 [all data]	0.2687	0.0747	0.1320	0.1402
Max./min. residual electron dens. [eÅ^{-3}]	0.76/-0.60	0.09/-0.08	0.53/-1.05	0.39/-0.36

[a] R1 = Σ||Fo| - |Fc||/Σ|Fo| and wR2 = [Σw(Fo^2-Fc^2)^2/ΣwFo^4]$^{0.5}$

Table 17: Crystal data for compounds **22ra**, **23ab**, **25** and **27b**[a]

Compound	**22ra**	**23ab**	**25**	**27b**
Emp. formula	$C_{36}H_{32}O_3Ru$	$C_{26}H_{18}O_4$	$C_{29}H_{23}N_2OP$	$C_{22}H_{22}N_2O_2$
Formula weight	613.72	394.40	446.46	346.42
Crystal system	Monoclinic	Orthorhombic	Monoclinic	Triclinic
Space group	P2(1)/c	Fdd2	P2(1)/c	P-1
a /Å	18.2137(11)	52.655(4)	10.5707(10)	6.6349(3)
b /Å	9.1058(6)	7.5681(4)	19.9949(16)	9.9311(5)
c /Å	17.3141(10)	19.8301(12)	11.3147(11)	15.1391(7)
α/deg	90	90	90	73.777(2)
β/deg	104.407(2)	90	108.576(10)	85.701(1)
γ/deg	90	90	90	84.283(1)
V /Å^3	2781.2(3)	7902.3(9)	2266.9(4)	951.90(8)
Z	4	16	4	2
*D*calc /g cm^{-3}]	1.466	1.326	1.308	1.209
μ /mm^{-1}	0.600	0.089	0.146	0.078
F(000)	1259.5	3296.0	936.0	368.0
Data/ restraints/ parameters	4886/0/364	3261/1/274	3994/0/298	3334/0/239

S	1.083	1.076	1.002	1.042
R1 [I>2σ(I)]	0.0201	0.0339	0.0802	0.0623
wR2 [all data]	0.0543	0.0873	0.1991	0.1819
Max./min. residual electron dens. [eÅ^{-3}]	0.33/-0.35	0.13/-0.14	0.32/-0.42	0.37/-0.28

^{a}R1 = Σ||Fo| - |Fc||/Σ|Fo| and wR2 = [Σw(Fo^2-Fc^2)^2/ΣwFo^4]$^{0.5}$

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Copies of $^{1}H/^{13}C$ NMR spectra for representative compounds

Compounds: 15aa, 16bb, 17ba, 18aa, 20ba, 21ac, 22ra, 23ac, 24d and 27b.

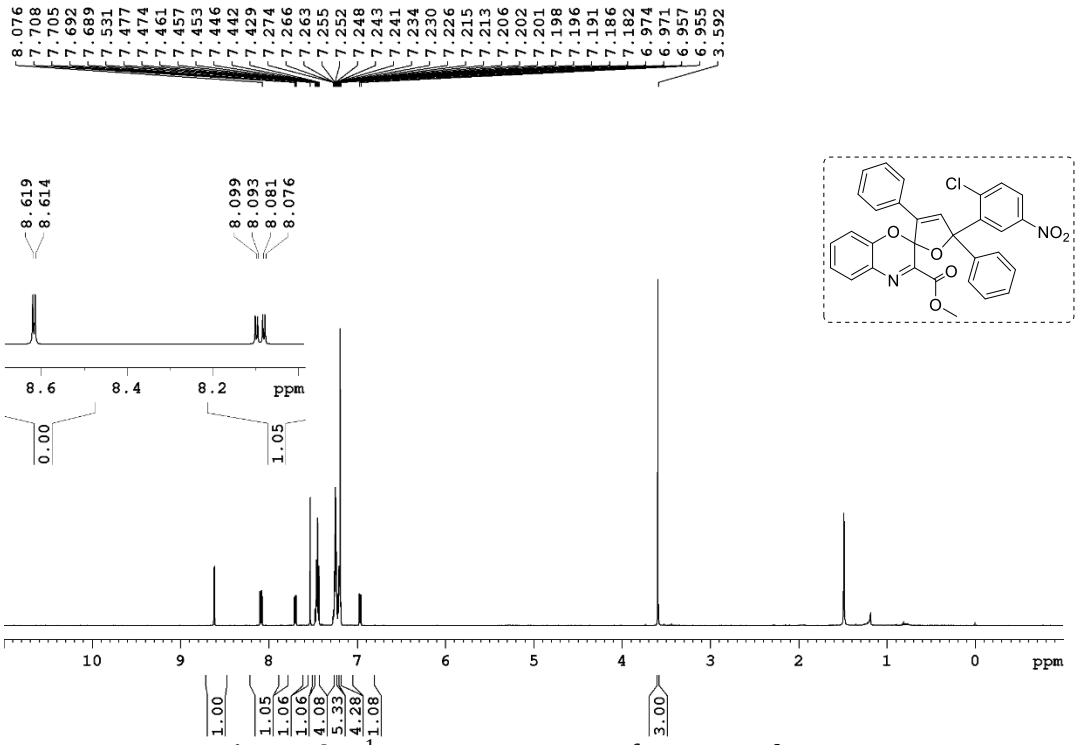

Figure A1. ^{1}H NMR spectrum of compound **15aa**

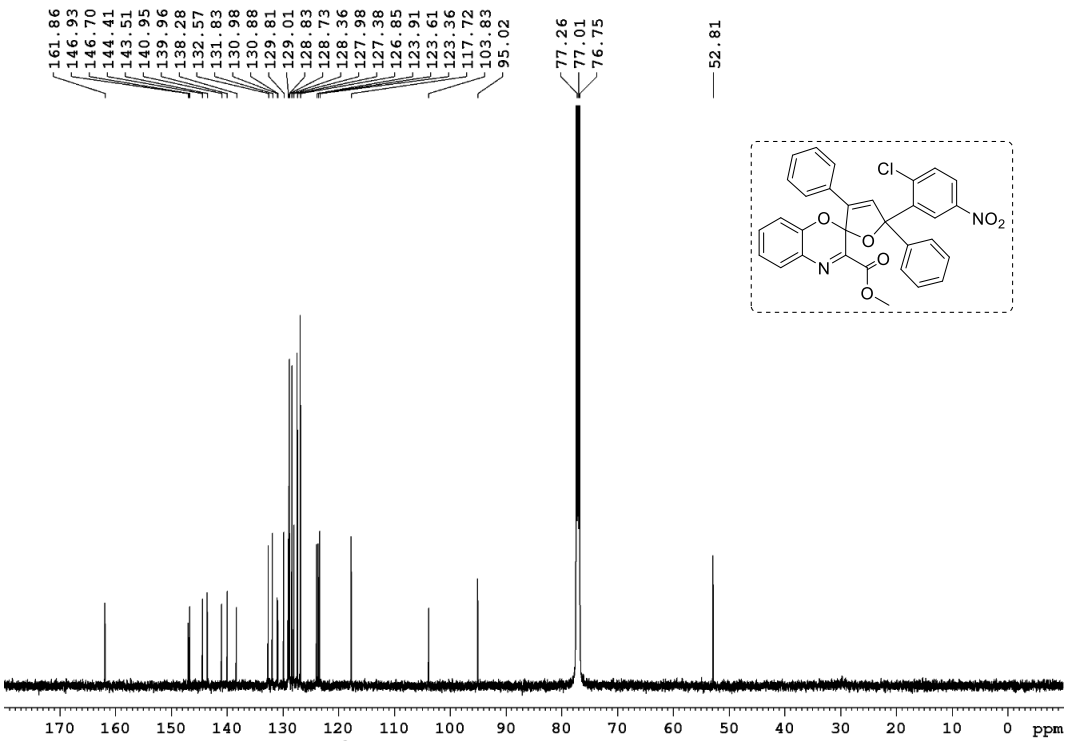

Figure A2. $^{13}C\{^{1}H\}$ NMR spectrum of compound **15aa**

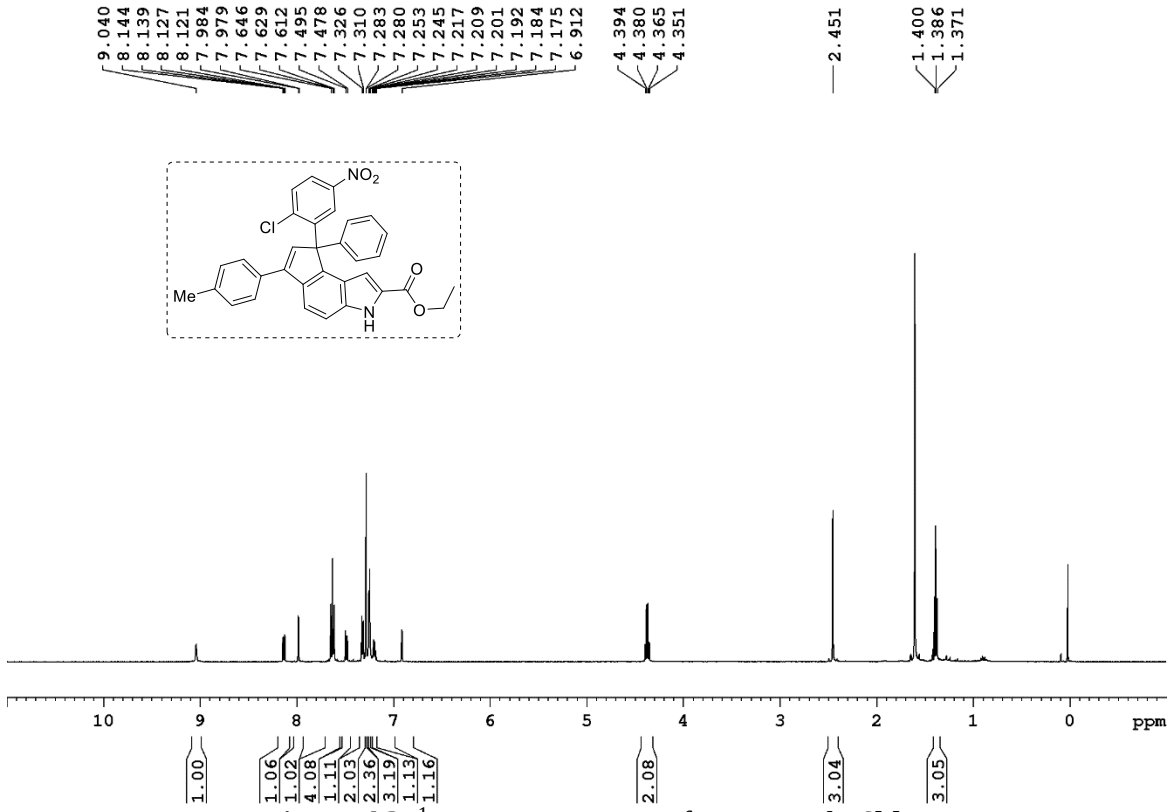

Figure A3. ^{1}H NMR spectrum of compound **16bb**

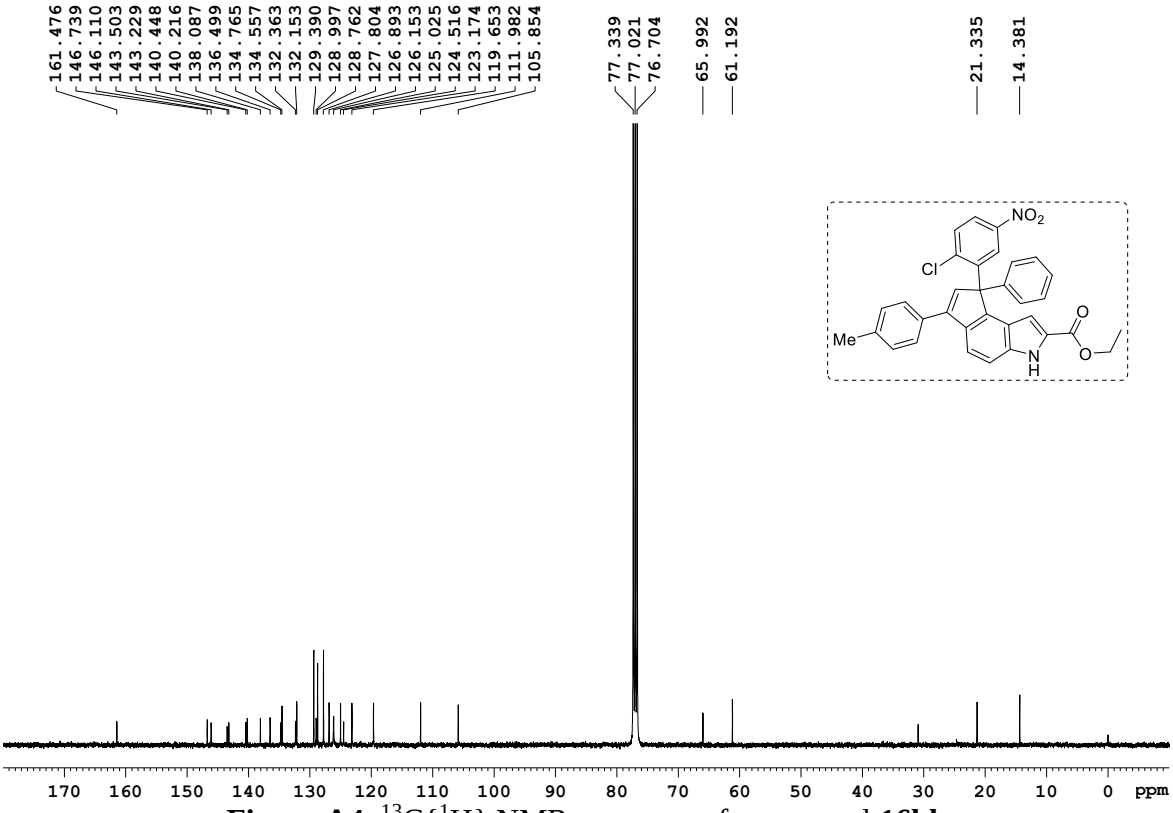

Figure A4. ^{13}C{^{1}H} NMR spectrum of compound **16bb**

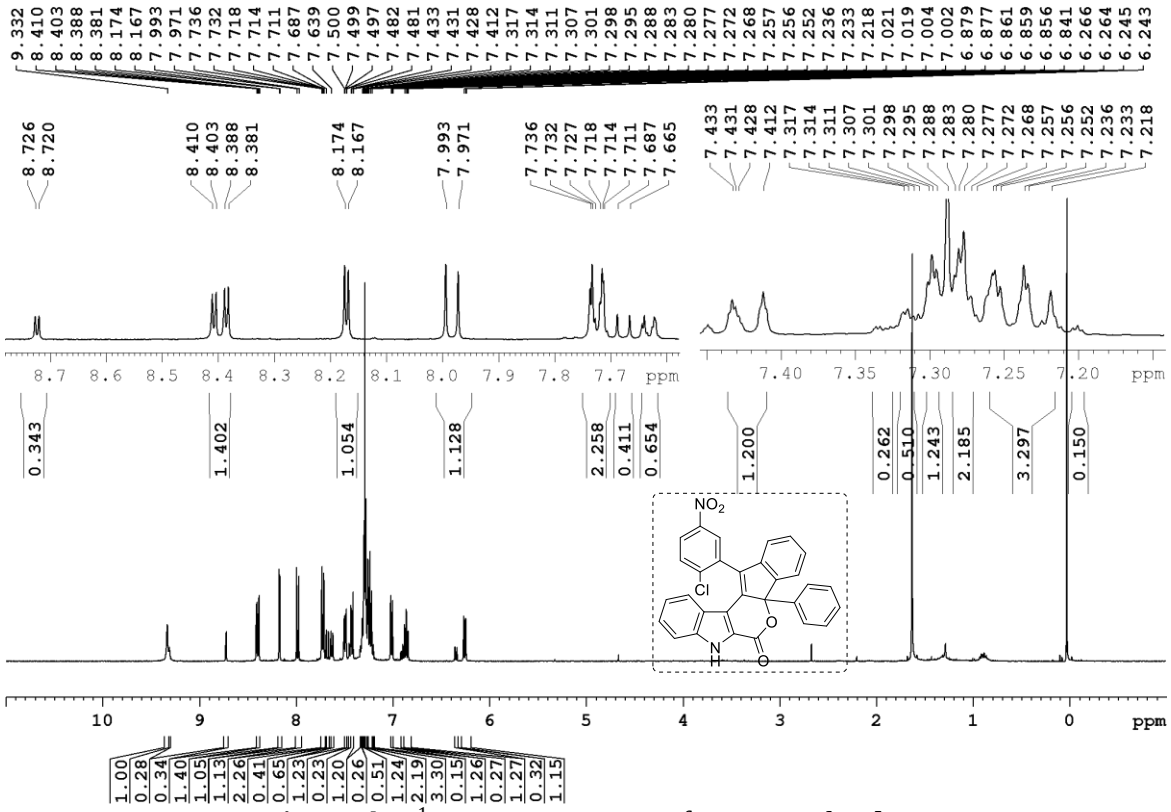

Figure A5. ^{1}H NMR spectrum of compound **17ba**

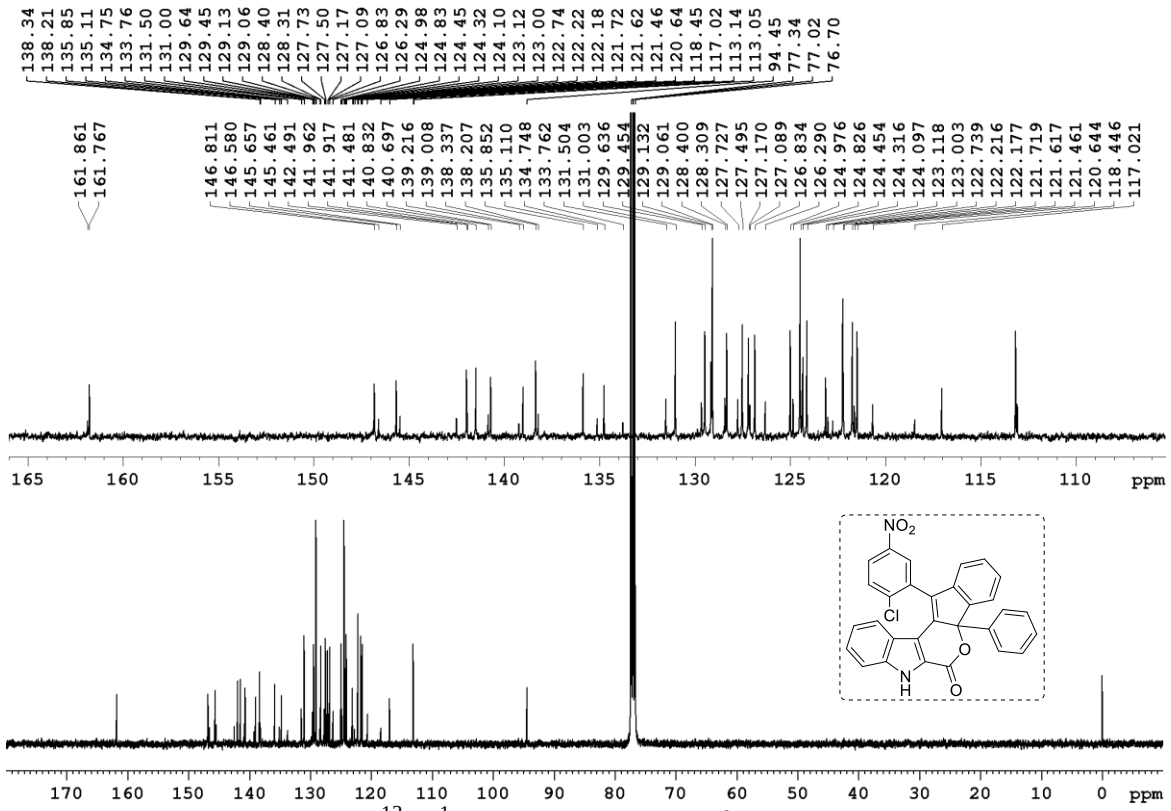

Figure A6. $^{13}C\{^{1}H\}$ NMR spectrum of compound **17ba**

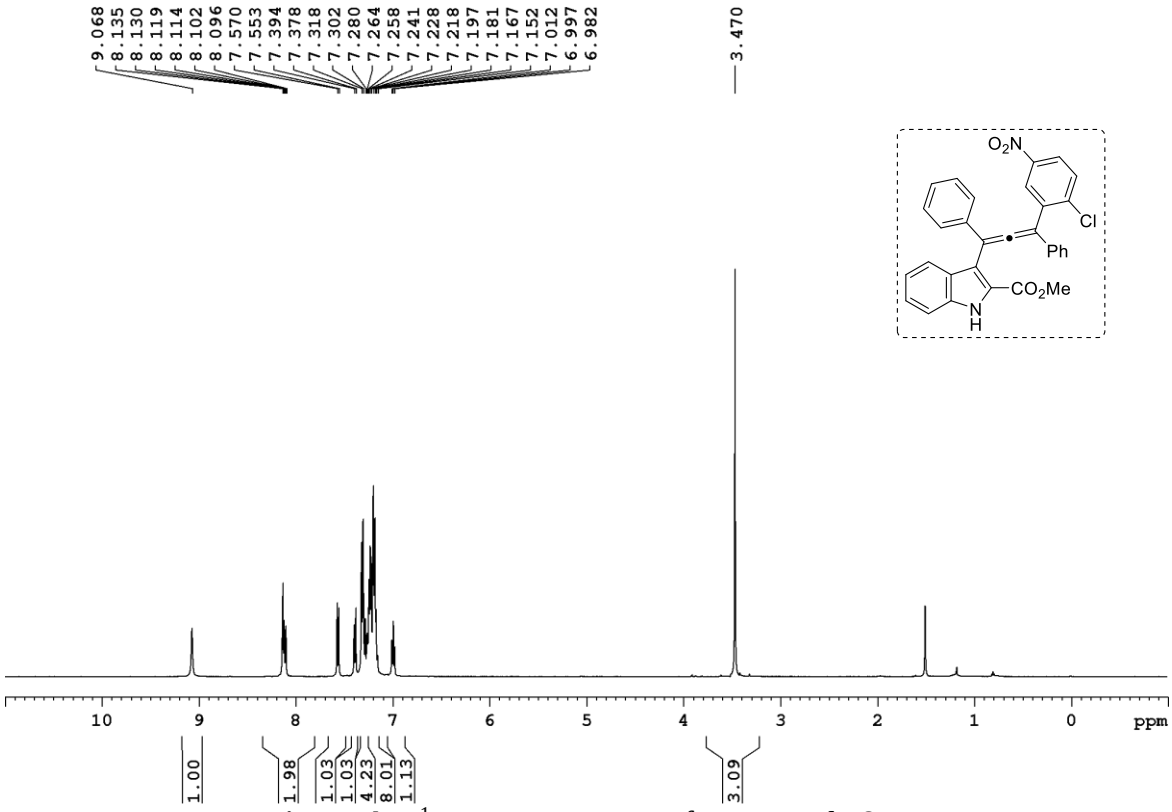

Figure A7. ^{1}H NMR spectrum of compound **18aa**

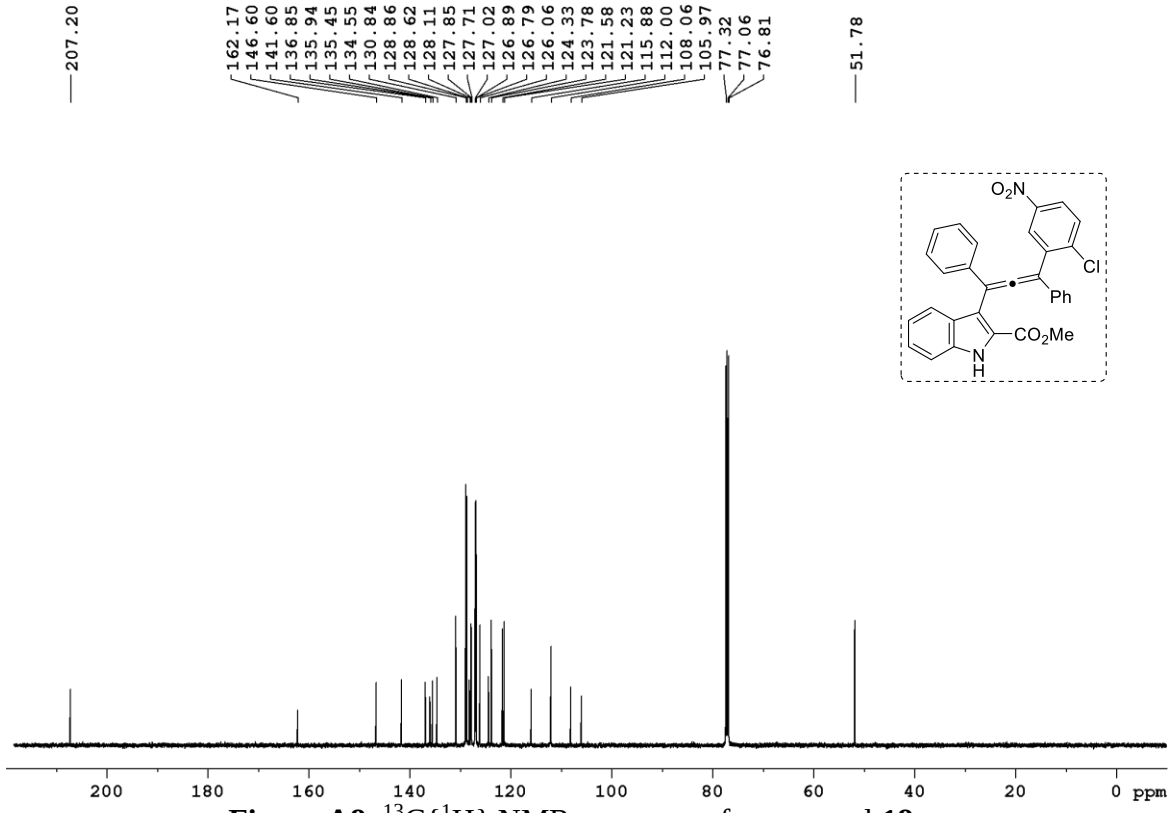

Figure A8. ^{13}C{^{1}H} NMR spectrum of compound **18aa**

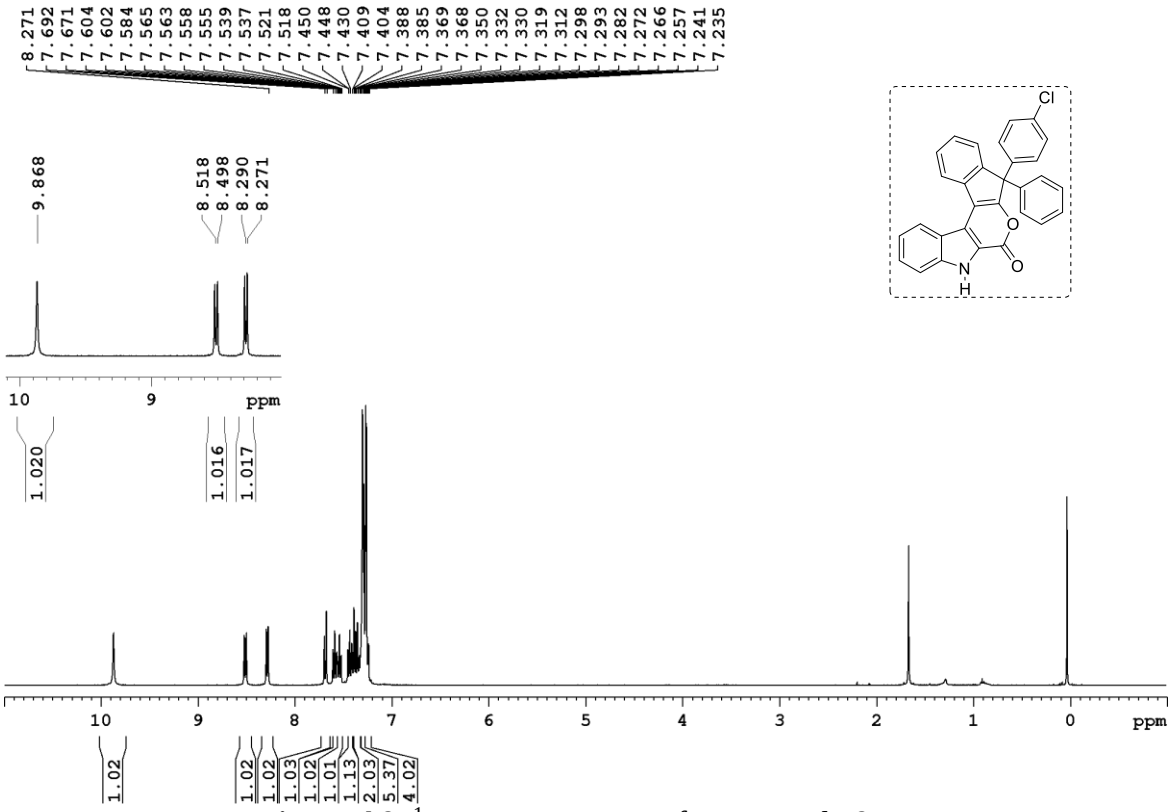

Figure A9. ^{1}H NMR spectrum of compound **19am**

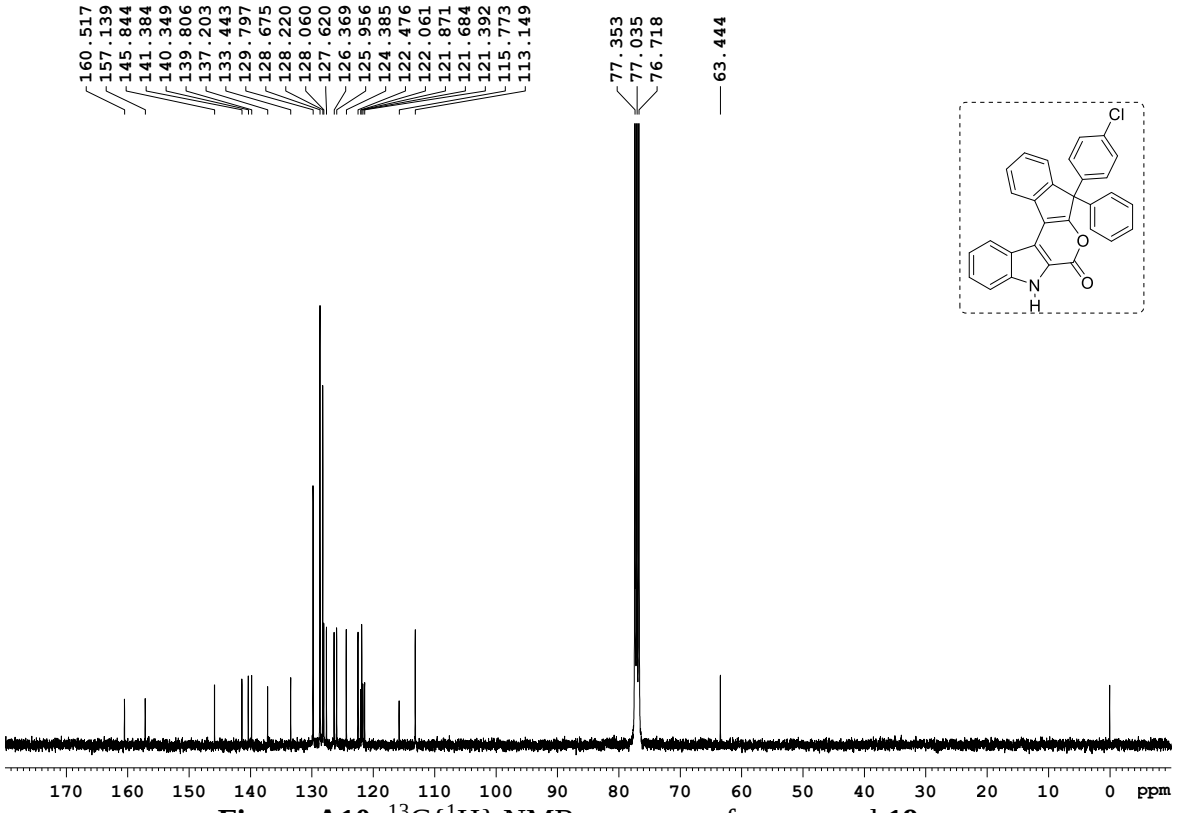

Figure A10. ^{13}C{^{1}H} NMR spectrum of compound **19am**

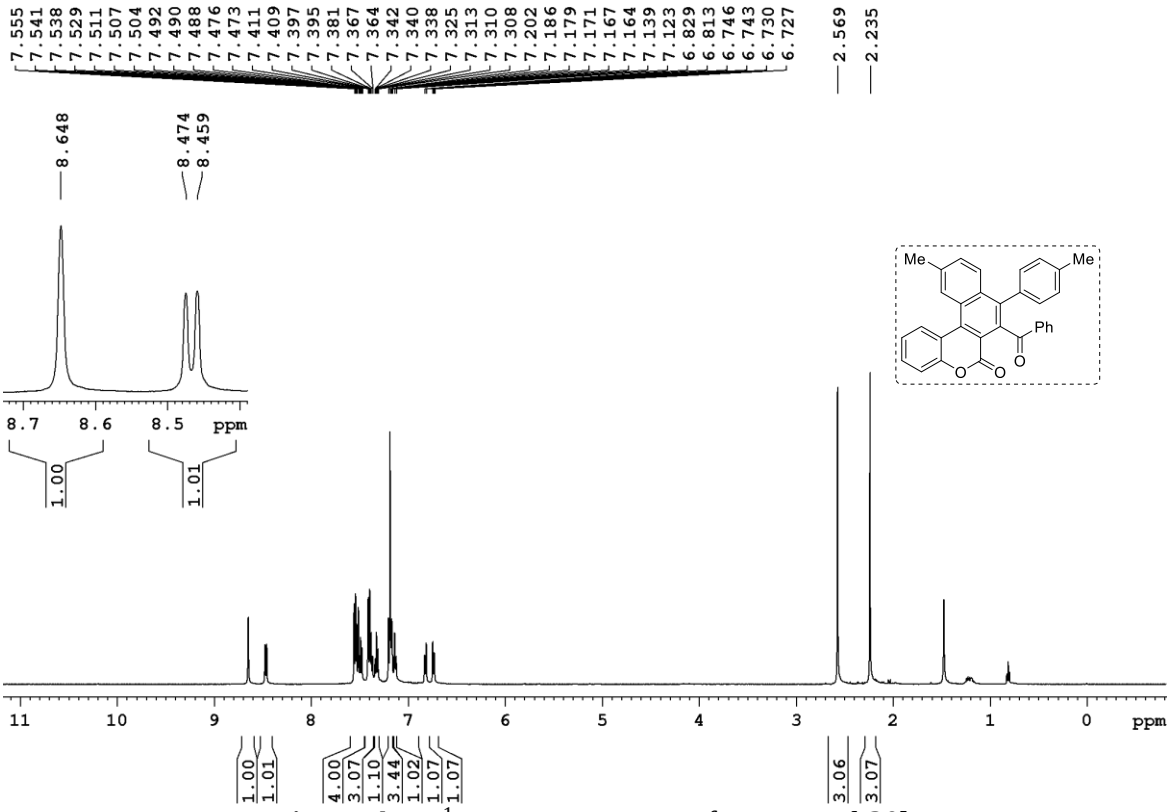

Figure A11. ^{1}H NMR spectrum of compound **20ba**

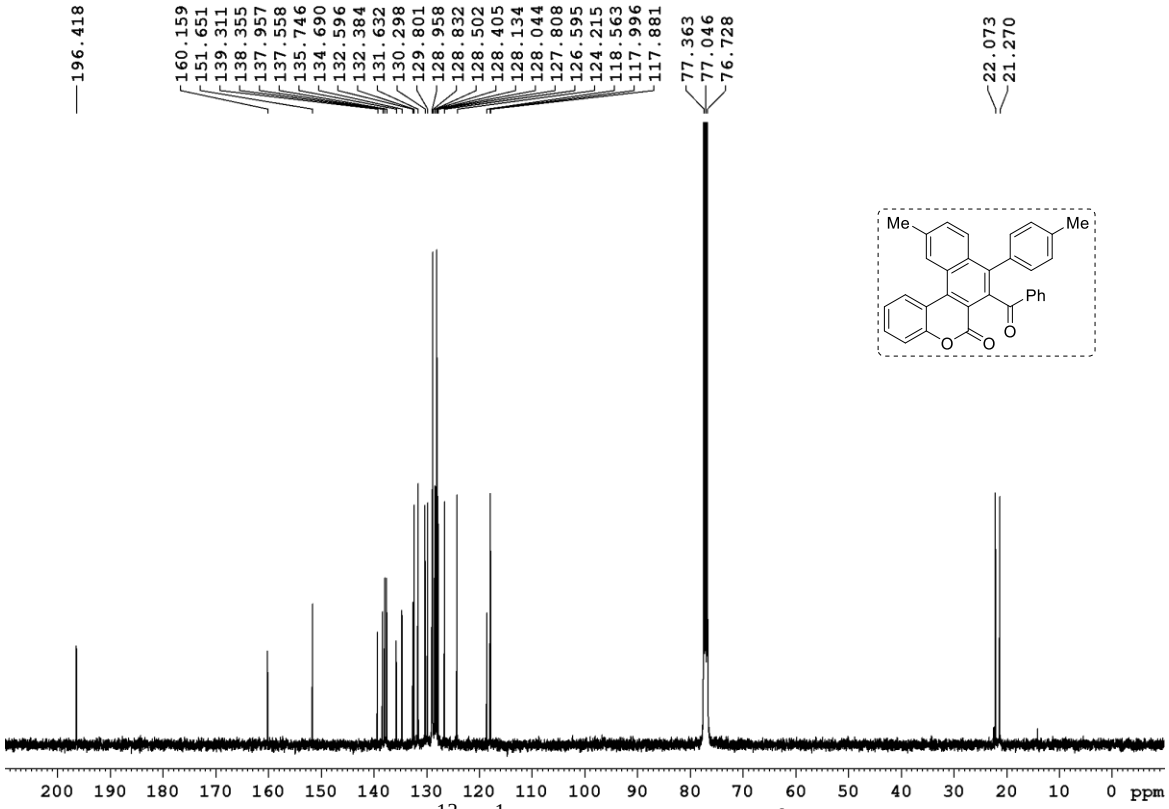

Figure A12. ^{13}C{^{1}H} NMR spectrum of compound **20ba**

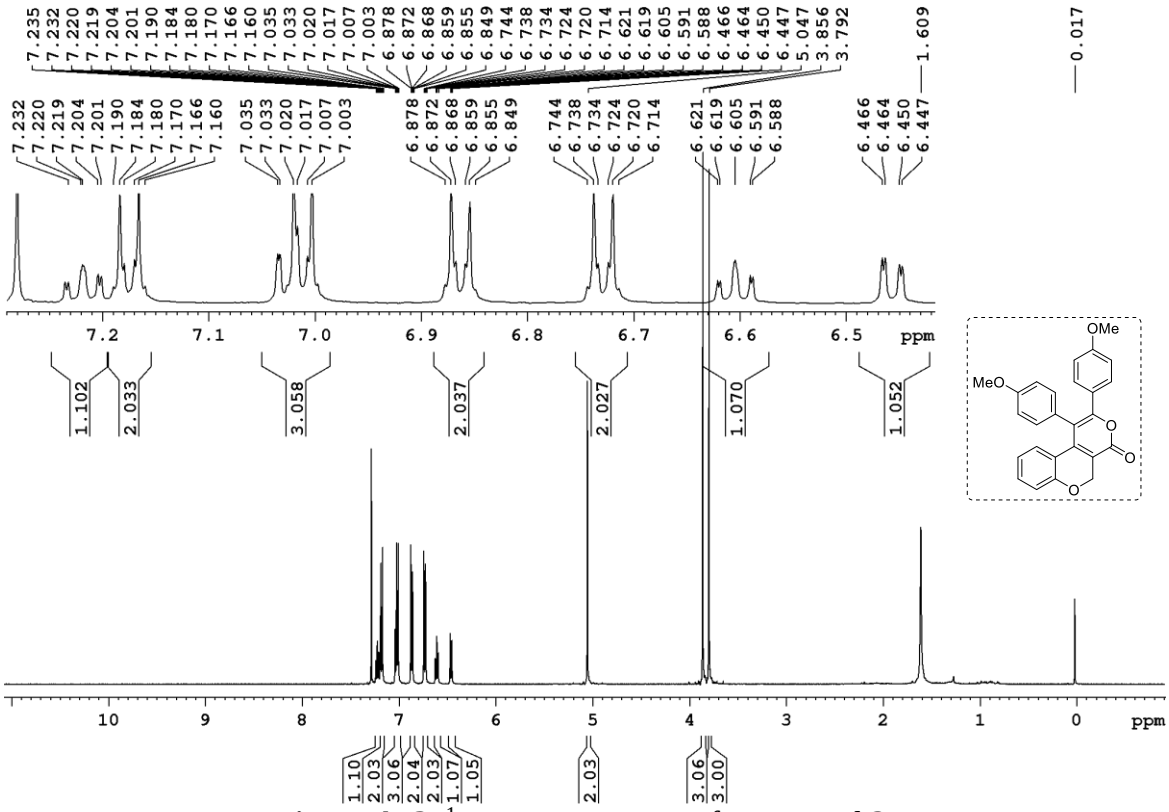

Figure A13. ^{1}H NMR spectrum of compound **21ac**

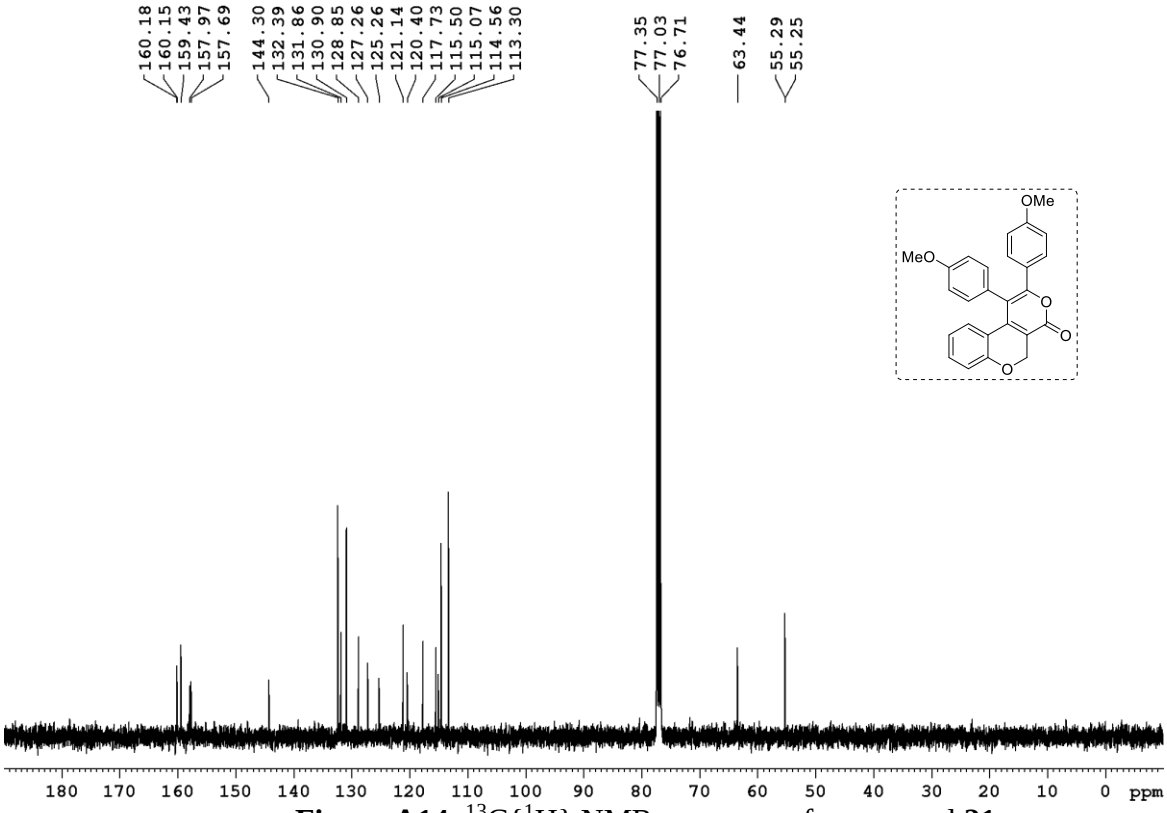

Figure A14. ^{13}C{^{1}H} NMR spectrum of compound **21ac**

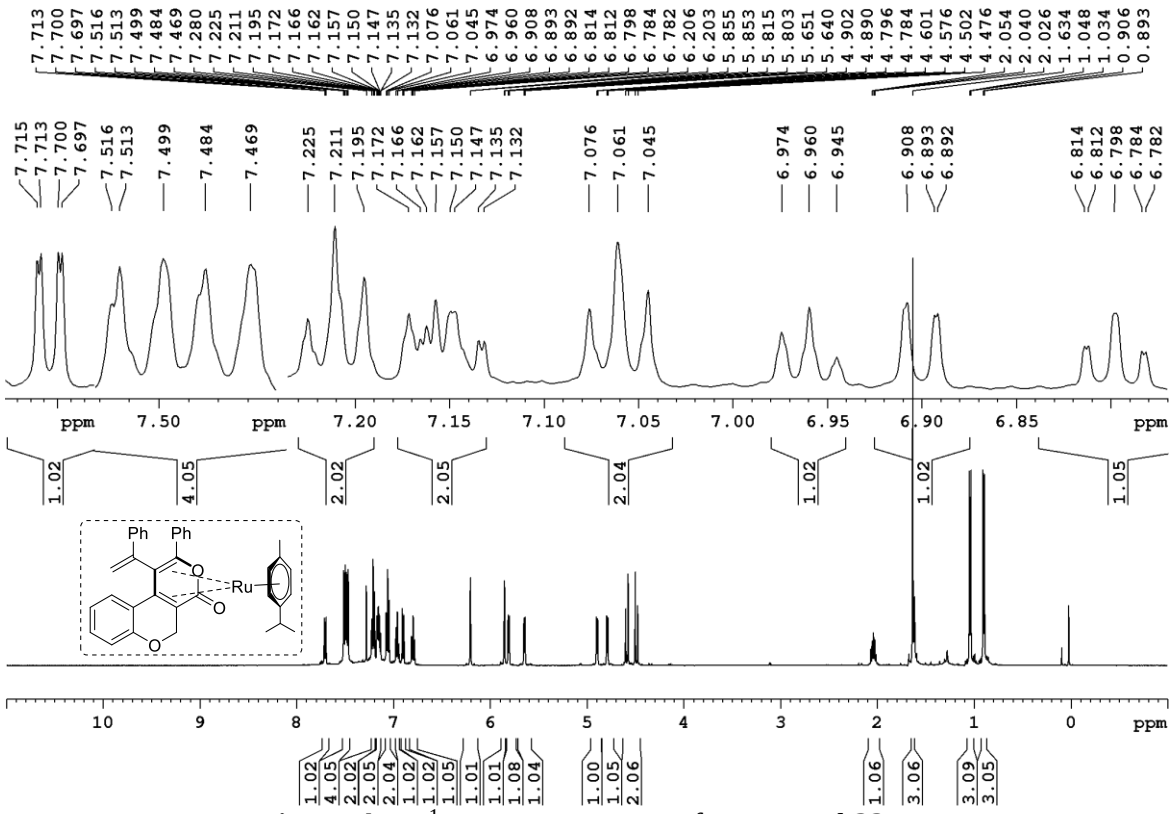

Figure A15. ^{1}H NMR spectrum of compound **22ra**

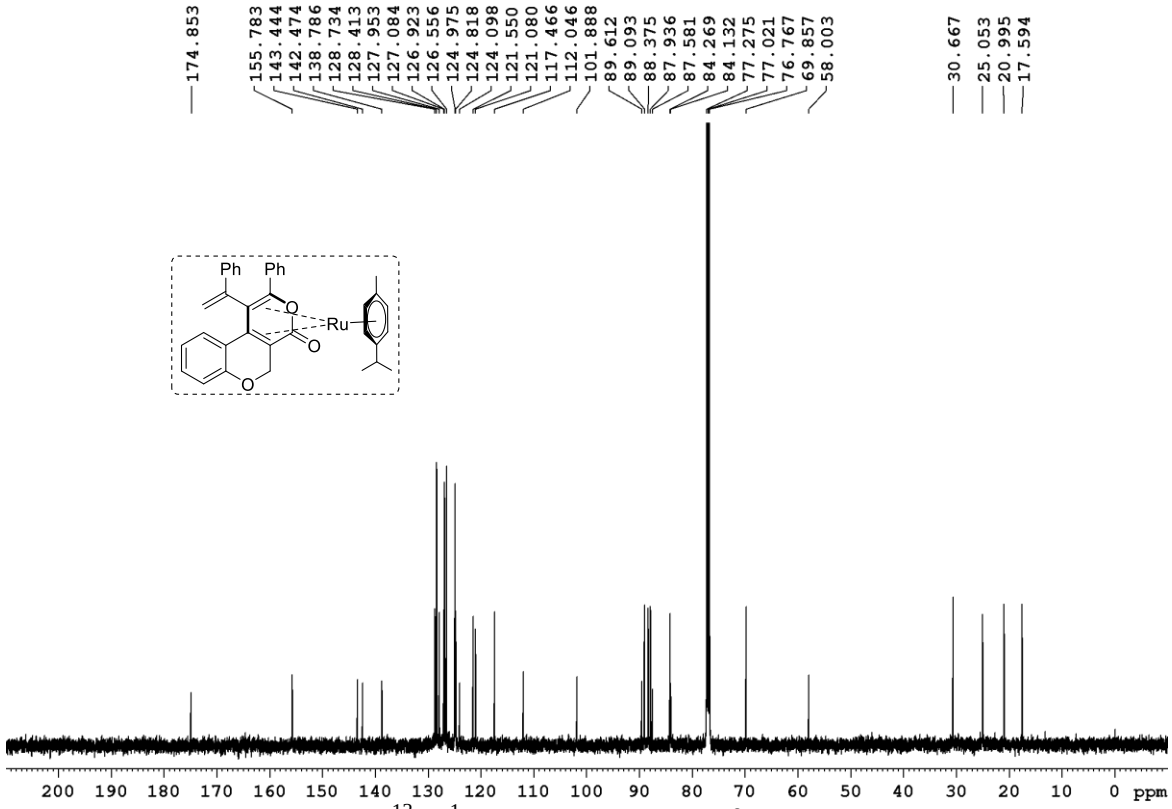

Figure A16. ^{13}C{^{1}H} NMR spectrum of compound **22ra**

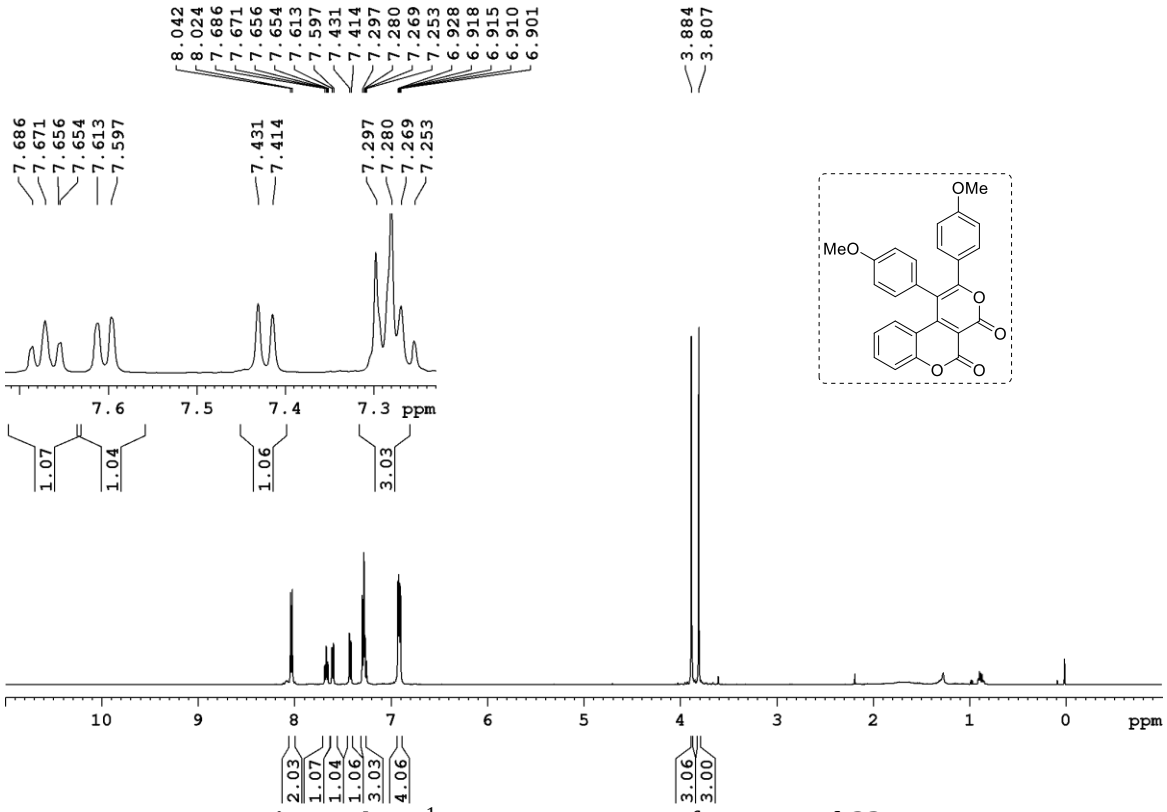

Figure A17. ^{1}H NMR spectrum of compound **23ac**

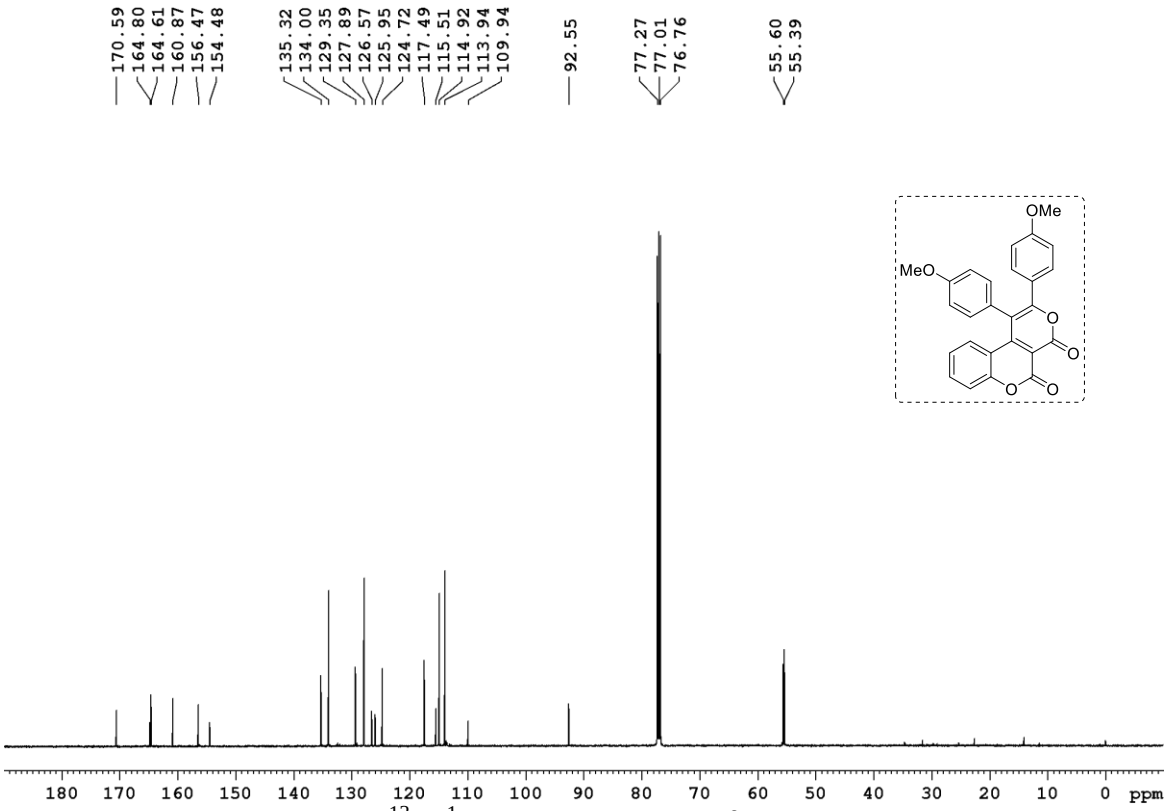

Figure A18. ^{13}C{^{1}H} NMR spectrum of compound **23ac**

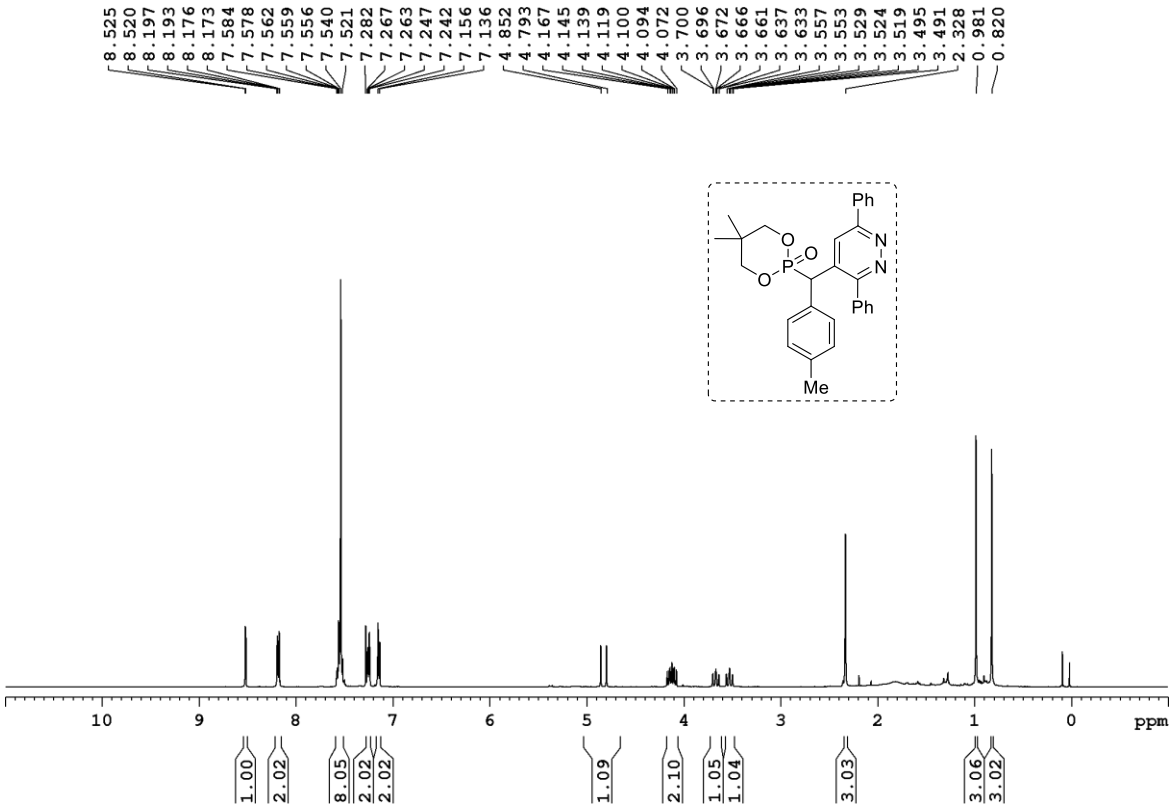

Figure A19. ^{1}H NMR spectrum of compound **24d**

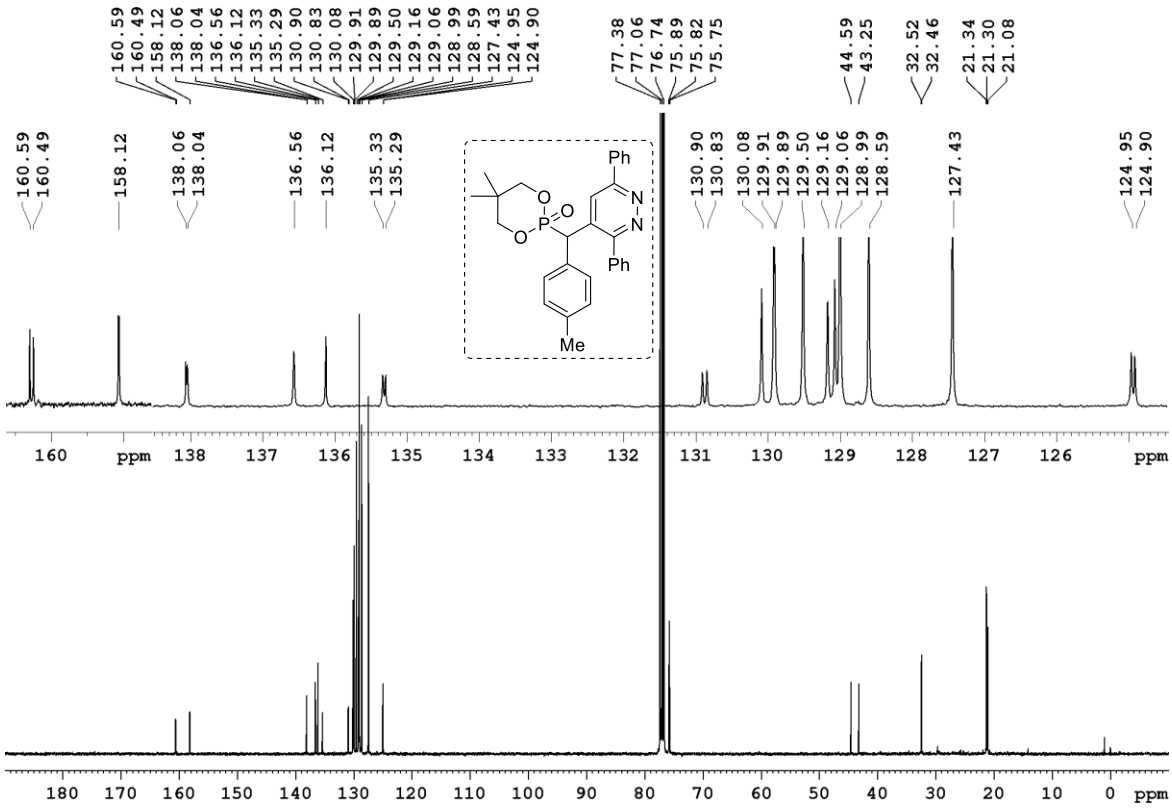

Figure A20. ^{13}C {^{1}H} NMR spectrum of compound **24d**

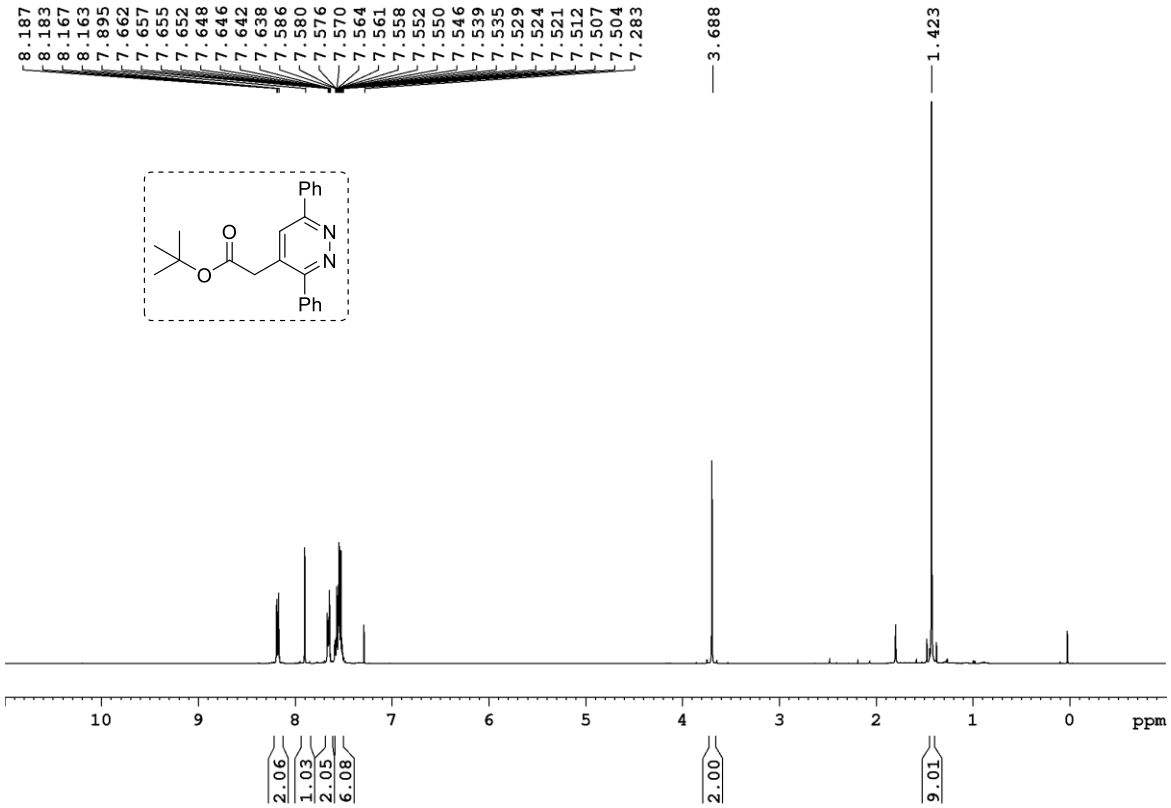

Figure A21. ^{1}H NMR spectrum of compound **27b**

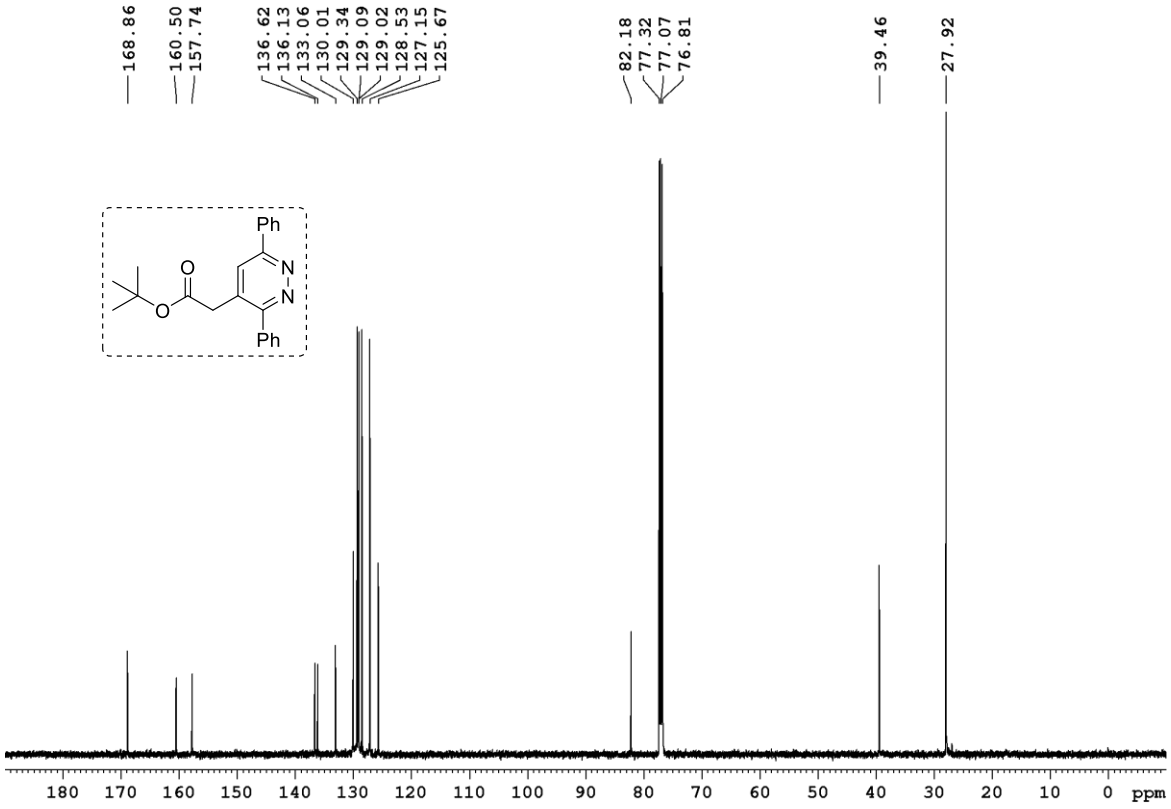

Figure A22. ^{13}C {^{1}H} NMR spectrum of compound **27b**

B) Publication numbers and atomic coordinates for X-ray structures reported in this thesis18

I. Publication numbers for the published compounds

Compounds: 15aa, 15ba, 16ba, 17ba, 19ap, 19bb and Intermediate X

(CCDC No.: 2100599, 2100600, 2100601, 2100602, 2100603, 2100604 and 2100605

Compounds: 20aa, 20de, 21aa, 21ce, 21cj, 22ra, 23ab, 25 and 27b (Unpublished)

<u>Compound: 20aa</u>

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) kck142cell

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No syntax errors found. CIF dictionary Interpreting this report

Datablock: kck142cell

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Bond precision:   C-C = 0.0035 A          Wavelength=0.71073

Cell:             a=13.9566(5)     b=12.3310(5)        c=24.8503(9)
                  alpha=90         beta=96.334(4)      gamma=90
Temperature:      299 K

                 Calculated                Reported
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Space group      P 21/c                    P 1 21/c 1
Hall group       -P 2ybc                   -P 2ybc
Moiety formula   C30 H18 O3                C30 H18 O3
Sum formula      C30 H18 O3                C30 H18 O3
Mr               426.44                    426.48
Dx,g cm-3        1.333                     1.333
Z                8                         8
Mu (mm-1)        0.085                     0.085
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F000'            1776.83
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Nref             9330                      8912
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Tmin'            0.998

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The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level B

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PLAT230_ALERT_2_B Hirshfeld Test Diff for    C50      --C51      .        7.5 s.u.
```

Alert level C

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PLAT241_ALERT_2_C High   'MainMol' Ueq as Compared to Neighbors of        C57 Check
PLAT242_ALERT_2_C Low    'MainMol' Ueq as Compared to Neighbors of        C12 Check
PLAT242_ALERT_2_C Low    'MainMol' Ueq as Compared to Neighbors of        C53 Check
PLAT331_ALERT_2_C Small Aver Phenyl C-C Dist C53      --C58      .       1.36 Ang.
PLAT410_ALERT_2_C Short Intra H...H Contact  H9       ..H21      .       1.94 Ang.
                                             x,y,z  =      1_555 Check
PLAT410_ALERT_2_C Short Intra H...H Contact  H38      ..H49      .       1.98 Ang.
                                             x,y,z  =      1_555 Check
PLAT790_ALERT_4_C Centre of Gravity not Within Unit Cell: Resd.  #          1 Note
            C30 H18 O3
PLAT905_ALERT_3_C Negative K value in the Analysis of Variance ...     -3.077 Report
```

Alert level G

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PLAT073_ALERT_1_G H-atoms ref, but _hydrogen_treatment Reported as     constr Check
PLAT720_ALERT_4_G Number of Unusual/Non-Standard Labels ..........          2 Note
PLAT910_ALERT_3_G Missing # of FCF Reflection(s) Below Theta(Min).          3 Note
PLAT912_ALERT_4_G Missing # of FCF Reflections Above STh/L=  0.600        420 Note
PLAT960_ALERT_3_G Number of Intensities with I  <   - 2*sig(I) ...          2 Check
PLAT978_ALERT_2_G Number C-C Bonds with Positive Residual Density.          0 Info
PLAT980_ALERT_1_G No Anomalous Scattering Factors Found in CIF ...     Please Check
```

```
   0 ALERT level A = Most likely a serious problem - resolve or explain
   2 ALERT level B = A potentially serious problem, consider carefully
   9 ALERT level C = Check. Ensure it is not caused by an omission or oversight
   7 ALERT level G = General information/check it is not something unexpected

   2 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
   9 ALERT type 2 Indicator that the structure model may be wrong or deficient
   4 ALERT type 3 Indicator that the structure quality may be low
   3 ALERT type 4 Improvement, methodology, query or suggestion
   0 ALERT type 5 Informative message, check
```

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

Publication of your CIF in IUCr journals

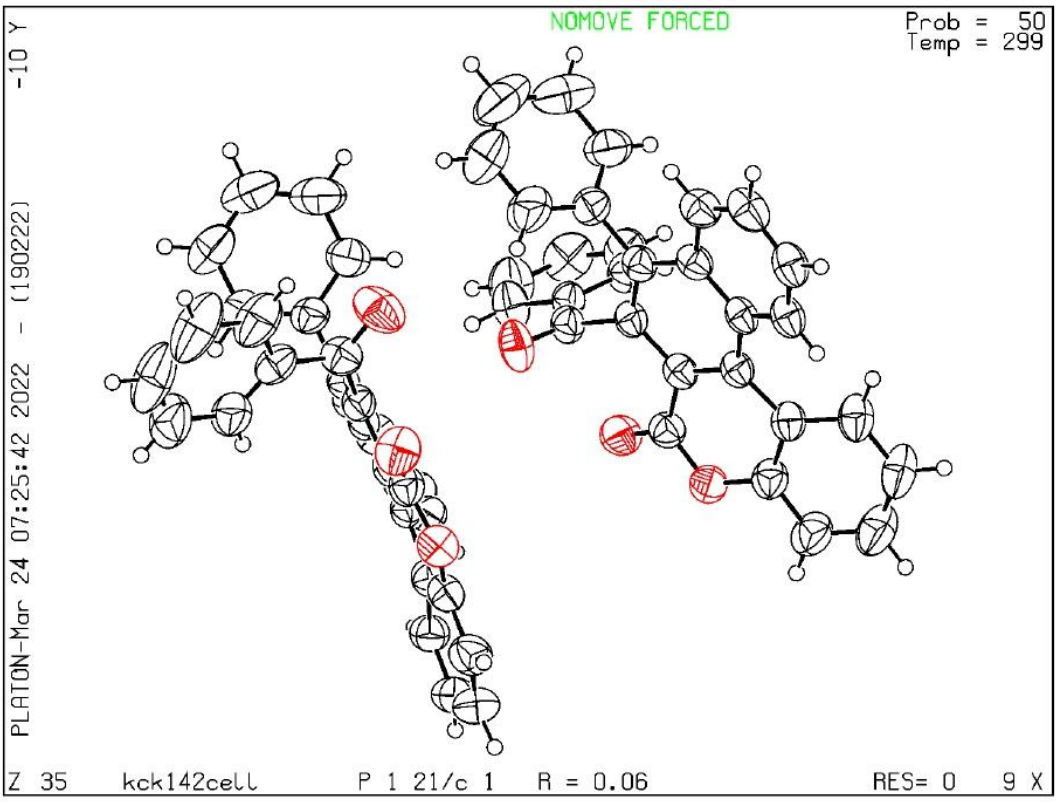
A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica*, *Journal of Applied Crystallography*, *Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E* or *IUCrData*, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

PLATON version of 19/02/2022; check.def file version of 19/02/2022

Datablock kck142cell - ellipsoid plot



Compound: 20de

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) kck033_0ma_a

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

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Temperature:      301 K

                 Calculated                Reported
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Hall group       -P 2ybc                   -P 2ybc
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Sum formula      C30 H14 Cl2 F2 O3         C30 H14 Cl2 F2 O3
Mr               531.31                    531.31
Dx,g cm-3        1.503                     1.503
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F000'            1081.74
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Tmin'            0.931

Correction method= Not given

Data completeness= 0.839           Theta(max)= 26.532

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                                                 0.2687( 4107)
S = 1.003                 Npar= 334
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Click on the hyperlinks for more details of the test.

Alert level B

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Alert level C

PLAT084_ALERT_3_C High wR2 Value (i.e. > 0.25) ..... 0.27 Report
PLAT334_ALERT_2_C Small Aver. Benzene C-C Dist C21 -C26 1.37 Ang.
PLAT340_ALERT_3_C Low Bond Precision on C-C Bonds ..... 0.00759 Ang.
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x,y,z = 1_555 Check
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Alert level G

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PLAT883_ALERT_1_G No Info/Value for _atom_sites_solution_primary . Please Do !
PLAT912_ALERT_4_G Missing # of FCF Reflections Above STh/L= 0.600 83 Note
PLAT978_ALERT_2_G Number C-C Bonds with Positive Residual Density. 0 Info

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4 ALERT type 3 Indicator that the structure quality may be low
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0 ALERT type 5 Informative message, check

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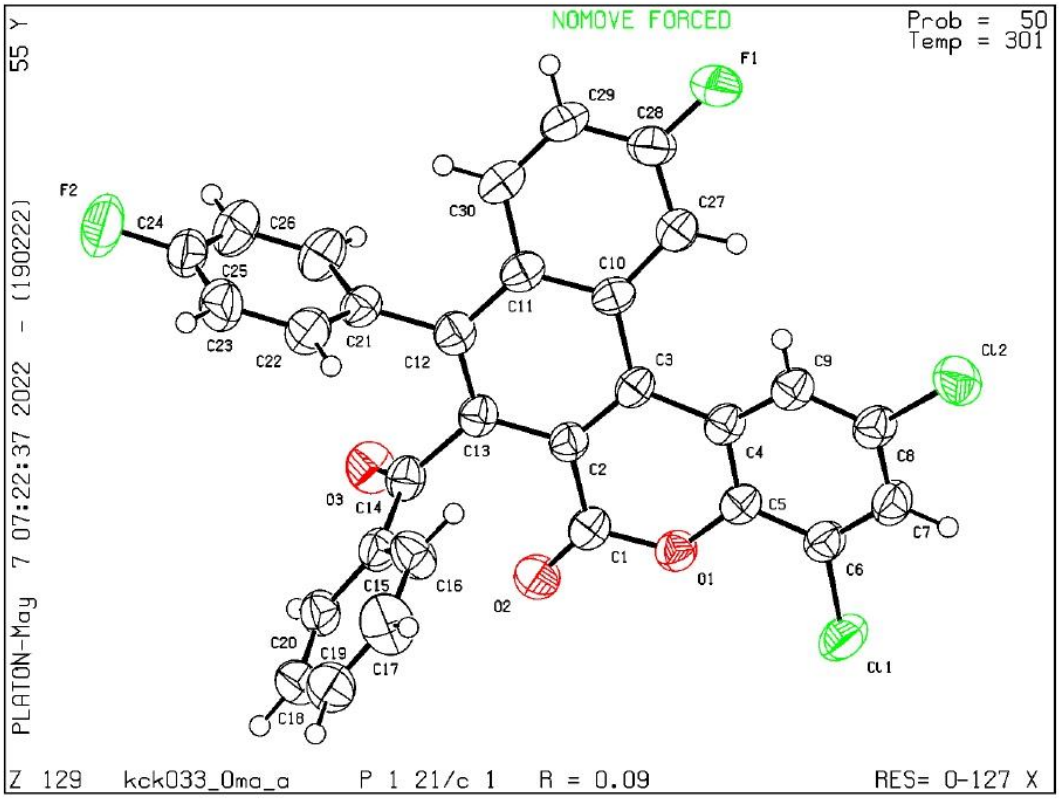
PLATON version of 19/02/2022; check.def file version of 19/02/2022

atablock kck033_0ma_a - ellipsoid plot



Compound: 21aa

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) kck75_0m_a_a

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: kck75_0m_a_a

```
Bond precision:   C-C = 0.0036 A          Wavelength=0.71073

Cell:              a=7.9771(3)      b=14.2651(6)      c=15.4453(7)
                   alpha=90         beta=90           gamma=90
Temperature:       293 K
```

	Calculated	Reported
Volume	1757.58(13)	1757.58(13)
Space group	P n a 21	P n a 21
Hall group	P 2c -2n	P 2c -2n
Moiety formula	C24 H16 O3	C24 H16 O3
Sum formula	C24 H16 O3	C24 H16 O3
Mr	352.37	352.37
Dx,g cm-3	1.332	1.332
Z	4	4
Mu (mm-1)	0.087	0.087
F000	736.0	736.0
F000'	736.36	
h,k,lmax	9,16,18	9,16,18
Nref	3099[1613]	2973
Tmin,Tmax	0.984,0.991	
Tmin'	0.983	

```
Correction method= Not given

Data completeness= 1.84/0.96        Theta(max)= 24.988

R(reflections)= 0.0288( 2815)                    wR2(reflections)=
                                                 0.0747( 2973)
S = 1.103                  Npar= 245
```

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level C

```
PLAT029_ALERT_3_C _diffrn_measured_fraction_theta_full value Low .      0.962 Why?
PLAT089_ALERT_3_C Poor Data / Parameter Ratio (Zmax < 18) ........       6.33 Note
PLAT911_ALERT_3_C Missing FCF Refl Between Thmin & STh/L=    0.594        61 Report
PLAT913_ALERT_3_C Missing # of Very Strong Reflections in FCF ....        20 Note
PLAT934_ALERT_3_C Number of (Iobs-Icalc)/Sigma(W) > 10 Outliers ..         1 Check
```

Alert level G

```
PLAT199_ALERT_1_G Reported _cell_measurement_temperature ..... (K)       293 Check
PLAT200_ALERT_1_G Reported   _diffrn_ambient_temperature ..... (K)       293 Check
PLAT883_ALERT_1_G No Info/Value for _atom_sites_solution_primary .    Please Do !
PLAT909_ALERT_3_G Percentage of I>2sig(I) Data at Theta(Max) Still        82% Note
PLAT910_ALERT_3_G Missing # of FCF Reflection(s) Below Theta(Min).         1 Note
PLAT933_ALERT_2_G Number of HKL-OMIT Records in Embedded .res File         1 Note
PLAT967_ALERT_5_G Note: Two-Theta Cutoff Value in Embedded .res ..      50.0 Degree
PLAT978_ALERT_2_G Number C-C Bonds with Positive Residual Density.         0 Info
PLAT992_ALERT_5_G Repd & Actual _reflns_number_gt Values Differ by         2 Check
```

```
   0 ALERT level A = Most likely a serious problem - resolve or explain
   0 ALERT level B = A potentially serious problem, consider carefully
   5 ALERT level C = Check. Ensure it is not caused by an omission or oversight
   9 ALERT level G = General information/check it is not something unexpected

   3 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
   2 ALERT type 2 Indicator that the structure model may be wrong or deficient
   7 ALERT type 3 Indicator that the structure quality may be low
   0 ALERT type 4 Improvement, methodology, query or suggestion
   2 ALERT type 5 Informative message, check
```

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Publication of your CIF in IUCr journals

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Publication of your CIF in other journals

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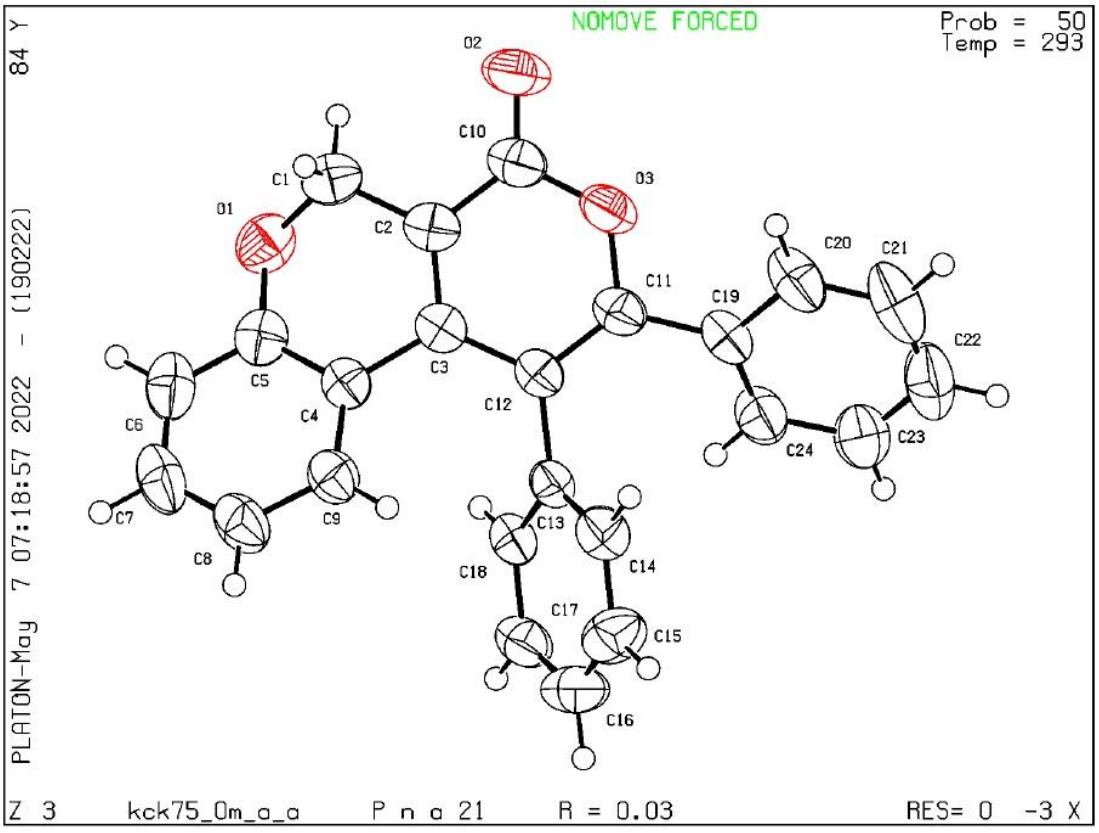
PLATON version of 19/02/2022; check.def file version of 19/02/2022

tablock kck75_0m_a_a - ellipsoid plot



Compound: 21ce

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) kck148_0m_a_a

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: kck148_0m_a_a

```
Bond precision:   C-C = 0.0063 A          Wavelength=0.71073

Cell:            a=16.4674(10)     b=7.5481(5)         c=16.6864(10)
                 alpha=90          beta=117.646(2)     gamma=90
Temperature:     297 K

                 Calculated                  Reported
Volume           1837.3(2)                   1837.3(2)
Space group      P 21/c                      P 1 21/c 1
Hall group       -P 2ybc                     -P 2ybc
Moiety formula   C20 H15 Br O4, 0.5(C2 Cl2)  C20 H15 Br O4, C Cl
Sum formula      C21 H15 Br Cl O4            C21 H15 Br Cl O4
Mr               446.68                      446.69
Dx,g cm-3        1.615                       1.615
Z                4                           4
Mu (mm-1)        2.408                       2.408
F000             900.0                       900.0
F000'            899.84
h,k,lmax         19,8,19                     19,8,19
Nref             3231                        3187
Tmin,Tmax        0.655,0.786
Tmin'            0.612

Correction method= Not given

Data completeness= 0.986           Theta(max)= 25.000

R(reflections)= 0.0462( 2695)                wR2(reflections)=
                                             0.1320( 3187)
S = 1.061                 Npar= 246
```

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level C

```
PLAT057_ALERT_3_C Correction for Absorption Required   RT(exp) ...       1.20 Do !
PLAT260_ALERT_2_C Large Average Ueq of Residue Including       Cl1      0.254 Check
PLAT341_ALERT_3_C Low Bond Precision on  C-C Bonds ...............    0.00629 Ang.
PLAT911_ALERT_3_C Missing FCF Refl Between Thmin & STh/L=    0.595        42 Report
PLAT913_ALERT_3_C Missing # of Very Strong Reflections in FCF ....        24 Note
```

Alert level G

```
PLAT042_ALERT_1_G Calc. and Reported Moiety Formula Strings Differ     Please Check
PLAT344_ALERT_2_G Unusual           Angle Range in Solvent/Ion for        C21 Check
PLAT367_ALERT_2_G Long?  C(sp?)-C(sp?) Bond  C21      - C21_a    .      1.64 Ang.
PLAT883_ALERT_1_G No Info/Value for _atom_sites_solution_primary .     Please Do !
PLAT909_ALERT_3_G Percentage of I>2sig(I) Data at Theta(Max) Still        63% Note
PLAT910_ALERT_3_G Missing # of FCF Reflection(s) Below Theta(Min).         2 Note
PLAT941_ALERT_3_G Average HKL Measurement Multiplicity ...........       4.7 Low
PLAT967_ALERT_5_G Note: Two-Theta Cutoff Value in Embedded .res ..      50.0 Degree
PLAT978_ALERT_2_G Number C-C Bonds with Positive Residual Density.         6 Info
```

0 **ALERT level A** = Most likely a serious problem - resolve or explain
0 **ALERT level B** = A potentially serious problem, consider carefully
5 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight
9 **ALERT level G** = General information/check it is not something unexpected

2 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
4 ALERT type 2 Indicator that the structure model may be wrong or deficient
7 ALERT type 3 Indicator that the structure quality may be low
0 ALERT type 4 Improvement, methodology, query or suggestion
1 ALERT type 5 Informative message, check

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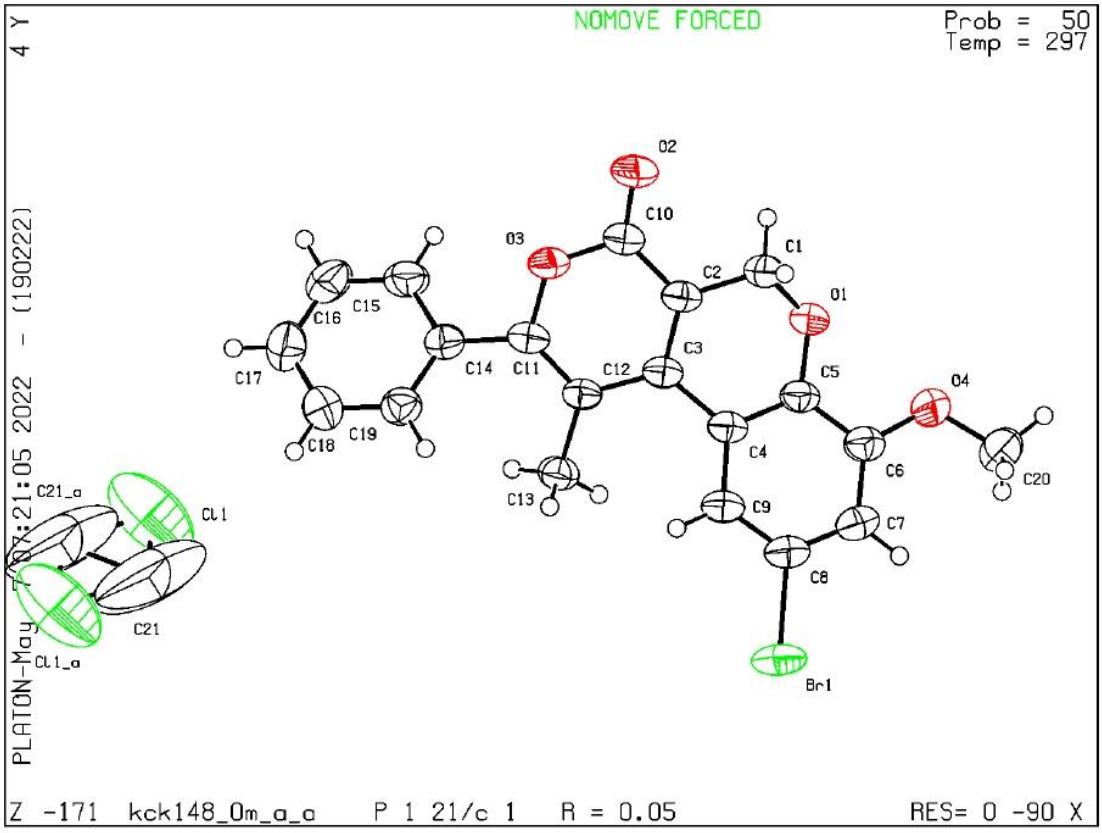
Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

PLATON version of 19/02/2022; check.def file version of 19/02/2022

Datablock kck148_0m_a_a - ellipsoid plot



Compound: 21cj

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) compd3cj

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: compd3cj

```
Bond precision:  C-C = 0.0094 A          Wavelength=0.71073

Cell:            a=5.1663(2)     b=14.7442(5)        c=12.9318(5)
                 alpha=90        beta=98.432(4)      gamma=90
Temperature:     293 K

                Calculated                Reported
Volume          974.41(6)                 974.41(6)
Space group     P 21                      P 1 21 1
Hall group      P 2yb                     ?
Moiety formula  C21 H25 Br O4             ?
Sum formula     C21 H25 Br O4             C21 H25 Br O4
Mr              421.31                    421.32
Dx,g cm-3       1.436                     1.436
Z               2                         2
Mu (mm-1)       2.132                     2.132
F000            436.0                     436.0
F000'           435.62
h,k,lmax        6,17,15                   6,17,15
Nref            3436[ 1793]               2954
Tmin,Tmax       0.605,0.681
Tmin'           0.594

Correction method= Not given

Data completeness= 1.65/0.86      Theta(max)= 25.000

R(reflections)= 0.0544( 2397)     wR2(reflections)= 0.1402( 2954)

S = 1.041                 Npar= 238
```

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level C

PLAT052_ALERT_1_C	Info on Absorption Correction Method Not Given	Please Do !
PLAT057_ALERT_3_C	Correction for Absorption Required RT(exp) ...	1.13 Do !
PLAT090_ALERT_3_C	Poor Data / Parameter Ratio (Zmax > 18)	7.53 Note
PLAT241_ALERT_2_C	High 'MainMol' Ueq as Compared to Neighbors of	C17 Check
PLAT242_ALERT_2_C	Low 'MainMol' Ueq as Compared to Neighbors of	C18 Check
PLAT341_ALERT_3_C	Low Bond Precision on C-C Bonds	0.0094 Ang.
PLAT360_ALERT_2_C	Short C(sp3)-C(sp3) Bond C17 - C18 .	1.43 Ang.
PLAT360_ALERT_2_C	Short C(sp3)-C(sp3) Bond C19 - C20 .	1.43 Ang.
PLAT915_ALERT_3_C	No Flack x Check Done: Low Friedel Pair Coverage	71 %
PLAT978_ALERT_2_C	Number C-C Bonds with Positive Residual Density.	0 Info

Alert level G

PLAT005_ALERT_5_G	No Embedded Refinement Details Found in the CIF	Please Do !
PLAT093_ALERT_1_G	No s.u.'s on H-positions, Refinement Reported as	mixed Check
PLAT199_ALERT_1_G	Reported _cell_measurement_temperature ..... (K)	293 Check
PLAT200_ALERT_1_G	Reported _diffrn_ambient_temperature ..... (K)	293 Check
PLAT899_ALERT_4_G	SHELXL97 is Deprecated and Succeeded by SHELXL	2018 Note
PLAT909_ALERT_3_G	Percentage of I>2sig(I) Data at Theta(Max) Still	44% Note
PLAT910_ALERT_3_G	Missing # of FCF Reflection(s) Below Theta(Min).	1 Note

0 **ALERT level A** = Most likely a serious problem - resolve or explain
0 **ALERT level B** = A potentially serious problem, consider carefully
10 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight
7 **ALERT level G** = General information/check it is not something unexpected

4 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
5 ALERT type 2 Indicator that the structure model may be wrong or deficient
6 ALERT type 3 Indicator that the structure quality may be low
1 ALERT type 4 Improvement, methodology, query or suggestion
1 ALERT type 5 Informative message, check

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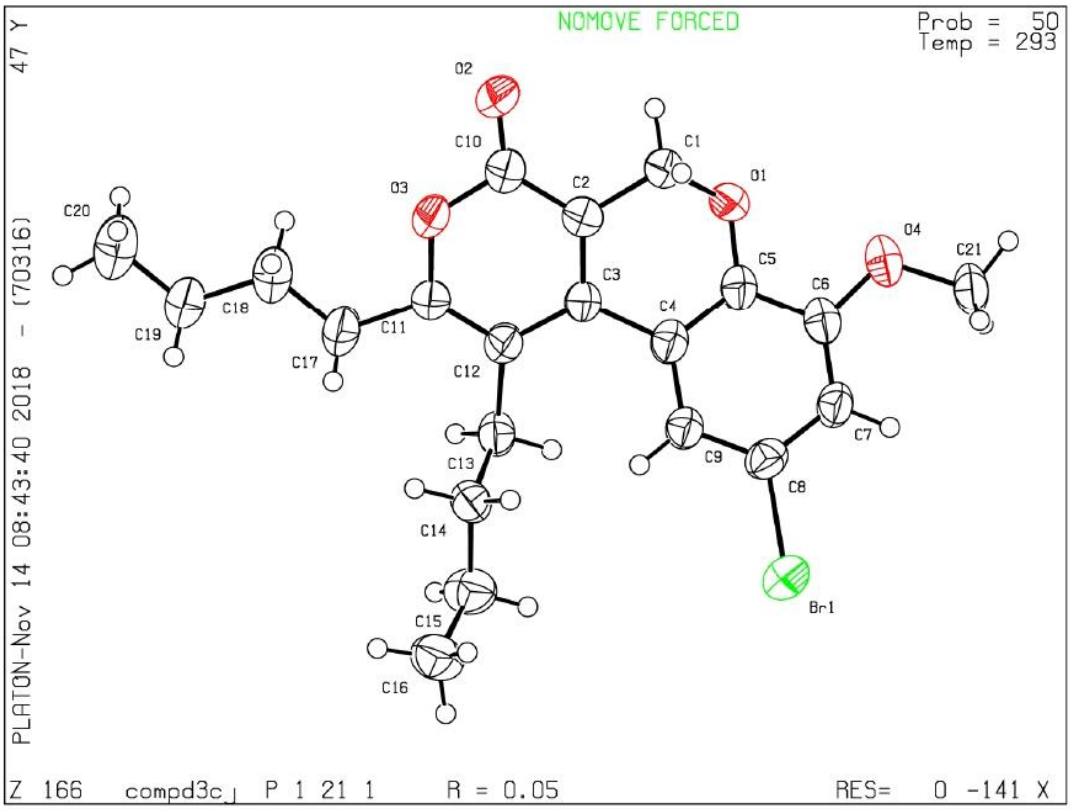
Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

PLATON version of 19/10/2018; check.def file version of 15/10/2018

Datablock compd3cj - ellipsoid plot



Compound: 22ra

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) KCK192_a

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: KCK192_a

```
Bond precision:   C-C = 0.0031 A          Wavelength=0.71073

Cell:            a=18.2137(11)    b=9.1058(6)         c=17.3141(10)
                 alpha=90         beta=104.407(2)     gamma=90
Temperature:     273 K

                 Calculated                Reported
Volume           2781.3(3)                 2781.2(3)
Space group      P 21/c                    P 1 21/c 1
Hall group       -P 2ybc                   -P 2ybc
Moiety formula   C36 H32 O3 Ru             C36 H32 O3 Ru
Sum formula      C36 H32 O3 Ru             C36 H32 O3 Ru
Mr               613.69                    613.72
Dx,g cm-3        1.466                     1.466
Z                4                         4
Mu (mm-1)        0.600                     0.600
F000             1264.0                    1259.5
F000'            1259.42
h,k,lmax         21,10,20                  21,10,20
Nref             4899                      4886
Tmin,Tmax        0.876,0.898
Tmin'            0.876

Correction method= Not given

Data completeness= 0.997           Theta(max)= 25.000

R(reflections)= 0.0201( 4499)                    wR2(reflections)=
                                                 0.0543( 4886)
S = 1.083                Npar= 364
```

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level C

```
PLAT220_ALERT_2_C NonSolvent   Resd 1  C   Ueq(max)/Ueq(min) Range        4.0 Ratio
PLAT242_ALERT_2_C Low    'MainMol' Ueq as Compared to Neighbors of        C27 Check
PLAT413_ALERT_2_C Short Inter XH3 .. XHn     H1B      ..H36A     .       2.14 Ang.
                                                  x,1+y,z  =      1_565 Check
PLAT910_ALERT_3_C Missing # of FCF Reflection(s) Below Theta(Min).          5 Note
PLAT911_ALERT_3_C Missing FCF Refl Between Thmin & STh/L=    0.595          8 Report
PLAT913_ALERT_3_C Missing # of Very Strong Reflections in FCF ....          7 Note
PLAT926_ALERT_1_C Reported and Calculated   R1 Differ by .........    -0.0018 Check
PLAT927_ALERT_1_C Reported and Calculated  wR2 Differ by .........    -0.0020 Check
```

Alert level G

```
PLAT068_ALERT_1_G Reported F000 Differs from Calcd (or Missing)...     Please Check
PLAT073_ALERT_1_G H-atoms ref, but _hydrogen_treatment Reported as     constr Check
PLAT199_ALERT_1_G Reported _cell_measurement_temperature ..... (K)        273 Check
PLAT200_ALERT_1_G Reported   _diffrn_ambient_temperature ..... (K)        273 Check
PLAT343_ALERT_2_G Unusual sp?      Angle Range in Main Residue for         C2 Check
PLAT367_ALERT_2_G Long?  C(sp?)-C(sp?) Bond  C1       - C2       .       1.51 Ang.
PLAT883_ALERT_1_G No Info/Value for _atom_sites_solution_primary .     Please Do !
PLAT909_ALERT_3_G Percentage of I>2sig(I) Data at Theta(Max) Still        86% Note
PLAT933_ALERT_2_G Number of HKL-OMIT Records in Embedded .res File        11 Note
PLAT960_ALERT_3_G Number of Intensities with I  <   - 2*sig(I) ...         6 Check
PLAT967_ALERT_5_G Note: Two-Theta Cutoff Value in Embedded .res ..       50.0 Degree
PLAT978_ALERT_2_G Number C-C Bonds with Positive Residual Density.        10 Info
PLAT980_ALERT_1_G No Anomalous Scattering Factors Found in CIF ...     Please Check
```

```
   0 ALERT level A = Most likely a serious problem - resolve or explain
   0 ALERT level B = A potentially serious problem, consider carefully
   8 ALERT level C = Check. Ensure it is not caused by an omission or oversight
  13 ALERT level G = General information/check it is not something unexpected

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   7 ALERT type 2 Indicator that the structure model may be wrong or deficient
   5 ALERT type 3 Indicator that the structure quality may be low
   0 ALERT type 4 Improvement, methodology, query or suggestion
   1 ALERT type 5 Informative message, check
```

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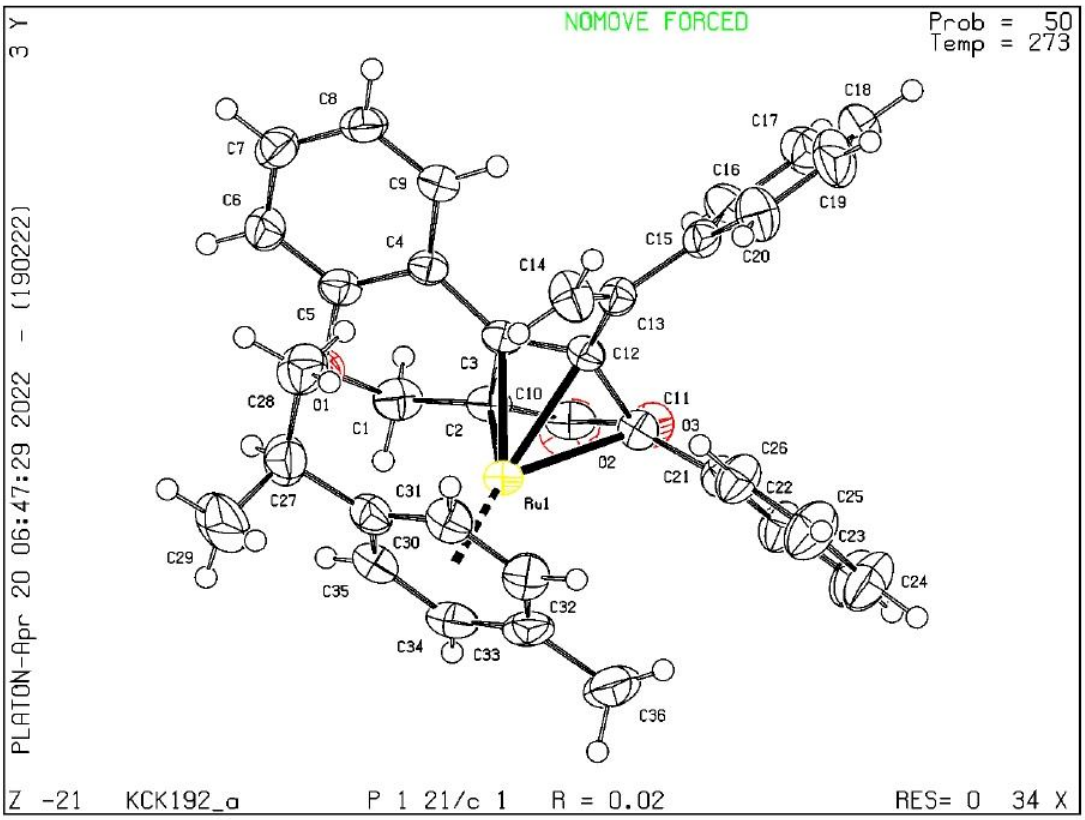
PLATON version of 19/02/2022; check.def file version of 19/02/2022

Datablock KCK192_a - ellipsoid plot



Compound: 23ab

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) compound5b

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: compound5b

```
Bond precision:  C-C = 0.0031 A          Wavelength=0.71073

Cell:             a=52.655(4)     b=7.5681(4)     c=19.8301(12)
                  alpha=90        beta=90         gamma=90
Temperature:      295 K
```

	Calculated	Reported
Volume	7902.3(9)	7902.3(9)
Space group	F d d 2	Fdd2
Hall group	F 2 -2d	?
Moiety formula	C26 H18 O4	?
Sum formula	C26 H18 O4	C26 H18 O4
Mr	394.40	394.40
Dx,g cm-3	1.326	1.326
Z	16	16
Mu (mm-1)	0.089	0.089
F000	3296.0	3296.0
F000'	3297.67	
h,k,lmax	62,8,23	61,8,23
Nref	3478[1795]	3261
Tmin,Tmax	0.979,0.984	
Tmin'	0.979	

```
Correction method= Not given

Data completeness= 1.82/0.94      Theta(max)= 25.000

R(reflections)= 0.0339( 3004)     wR2(reflections)= 0.0873( 3261)

S = 1.076                 Npar= 274
```

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level C

STRVA01_ALERT_4_C	Flack test results are meaningless.	
	From the CIF: _refine_ls_abs_structure_Flack 0.200	
	From the CIF: _refine_ls_abs_structure_Flack_su 1.000	
PLAT052_ALERT_1_C	Info on Absorption Correction Method Not Given	Please Do !
PLAT089_ALERT_3_C	Poor Data / Parameter Ratio (Zmax < 18)	6.49 Note
PLAT911_ALERT_3_C	Missing FCF Refl Between Thmin & STh/L= 0.595	13 Report
PLAT915_ALERT_3_C	No Flack x Check Done: Low Friedel Pair Coverage	88 %

Alert level G

PLAT005_ALERT_5_G	No Embedded Refinement Details Found in the CIF	Please Do !
PLAT032_ALERT_4_G	Std. Uncertainty on Flack Parameter Value High .	1.000 Report
PLAT093_ALERT_1_G	No s.u.'s on H-positions, Refinement Reported as	mixed Check
PLAT899_ALERT_4_G	SHELXL97 is Deprecated and Succeeded by SHELXL	2018 Note
PLAT909_ALERT_3_G	Percentage of I>2sig(I) Data at Theta(Max) Still	73% Note
PLAT910_ALERT_3_G	Missing # of FCF Reflection(s) Below Theta(Min).	2 Note
PLAT978_ALERT_2_G	Number C-C Bonds with Positive Residual Density.	7 Info

0 **ALERT level A** = Most likely a serious problem - resolve or explain
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2 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
1 ALERT type 2 Indicator that the structure model may be wrong or deficient
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Publication of your CIF in IUCr journals

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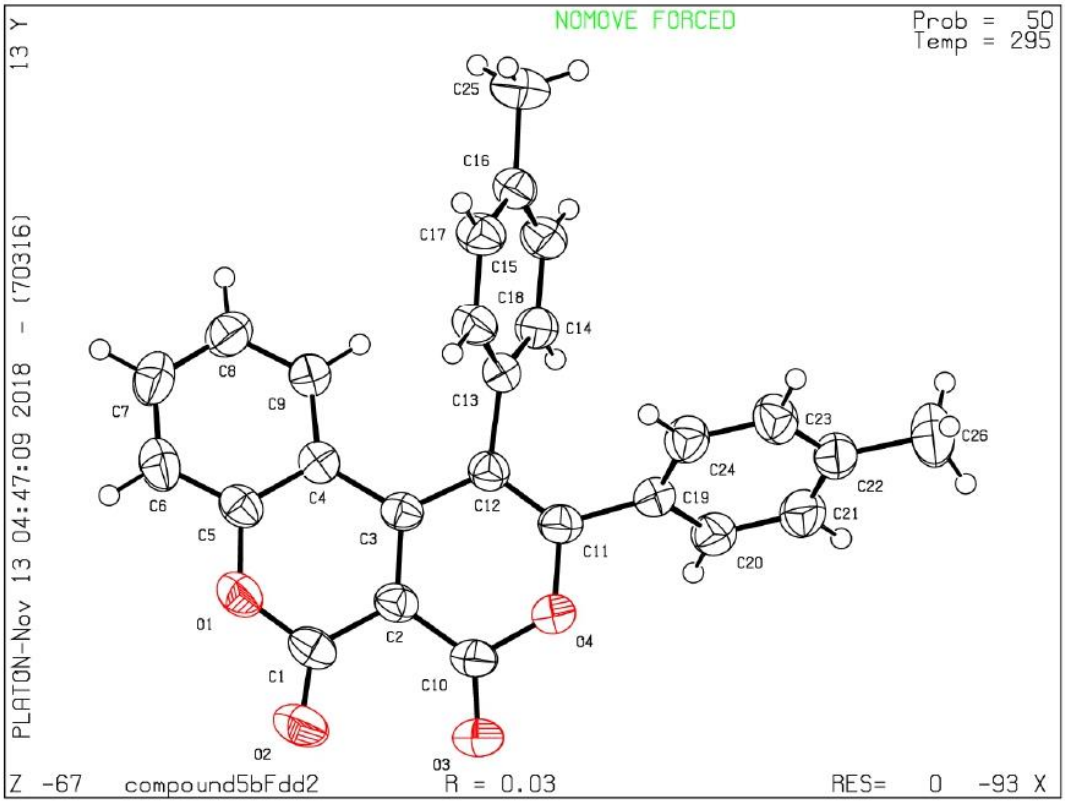
Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

PLATON version of 19/10/2018; check.def file version of 15/10/2018

Datablock compound5b - ellipsoid plot



Compound: 25

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) kck11

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: kck11

```
Bond precision:  C-C = 0.0082 A          Wavelength=0.71073

Cell:           a=10.5707(10)    b=19.9949(16)       c=11.3147(11)
                alpha=90         beta=108.576(10)    gamma=90
Temperature:    293 K

                 Calculated                Reported
Volume           2266.9(4)                 2266.9(4)
Space group      P 21/c                    P 21/c
Hall group       -P 2ybc                   ?
Moiety formula   C29 H23 N2 O P            ?
Sum formula      C29 H23 N2 O P            C29 H23 N2 O P
Mr               446.46                    446.46
Dx,g cm-3        1.308                     1.308
Z                4                         4
Mu (mm-1)        0.146                     0.146
F000             936.0                     936.0
F000'            936.74
h,k,lmax         12,23,13                  12,23,13
Nref             3994                      3994
Tmin,Tmax        0.966,0.974
Tmin'            0.966

Correction method= Not given

Data completeness= 1.000          Theta(max)= 25.000

R(reflections)= 0.0802( 1871)     wR2(reflections)= 0.1991( 3994)

S = 1.002                 Npar= 298
```

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level B

PLAT919_ALERT_3_B	Reflection # Likely Affected by the Beamstop ...	1 Check
PLAT934_ALERT_3_B	Number of (Iobs-Icalc)/SigmaW > 10 Outliers	3 Check

---

Alert level C

RINTA01_ALERT_3_C	The value of Rint is greater than 0.12 Rint given 0.130	
PLAT020_ALERT_3_C	The Value of Rint is Greater Than 0.12	0.130 Report
PLAT026_ALERT_3_C	Ratio Observed / Unique Reflections (too) Low ..	47% Check
PLAT052_ALERT_1_C	Info on Absorption Correction Method Not Given	Please Do !
PLAT220_ALERT_2_C	Non-Solvent Resd 1 C Ueq(max)/Ueq(min) Range	3.1 Ratio
PLAT241_ALERT_2_C	High 'MainMol' Ueq as Compared to Neighbors of	C19 Check
PLAT340_ALERT_3_C	Low Bond Precision on C-C Bonds	0.00817 Ang.
PLAT906_ALERT_3_C	Large K Value in the Analysis of Variance	12.823 Check
PLAT978_ALERT_2_C	Number C-C Bonds with Positive Residual Density.	0 Info

---

Alert level G

PLAT005_ALERT_5_G	No Embedded Refinement Details Found in the CIF	Please Do !
PLAT093_ALERT_1_G	No s.u.'s on H-positions, Refinement Reported as	mixed Check
PLAT199_ALERT_1_G	Reported _cell_measurement_temperature ..... (K)	293 Check
PLAT200_ALERT_1_G	Reported _diffrn_ambient_temperature ..... (K)	293 Check
PLAT899_ALERT_4_G	SHELXL97 is Deprecated and Succeeded by SHELXL	2018 Note

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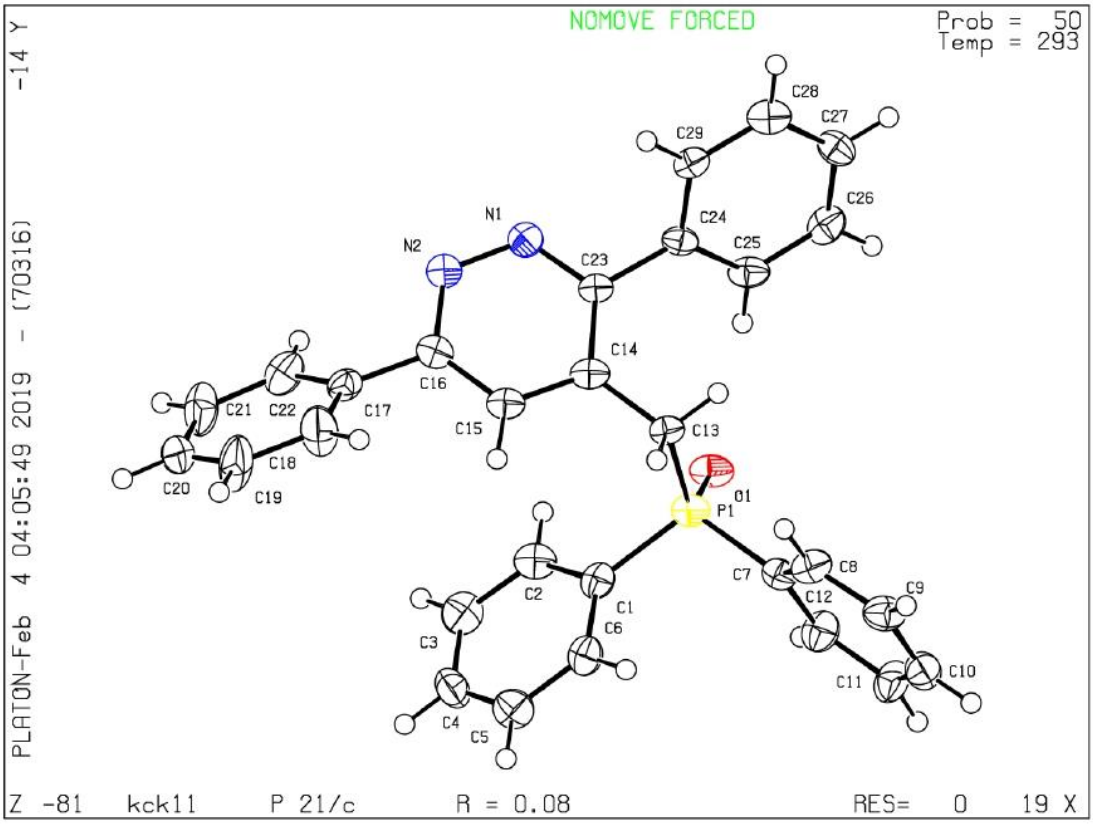
Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

PLATON version of 06/01/2019; check.def file version of 19/12/2018

Datablock kck11 - ellipsoid plot



Compound: 27b

checkCIF/PLATON report

Structure factors have been supplied for datablock(s) kck245_0m_a

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No syntax errors found. CIF dictionary Interpreting this report

Datablock: kck245_0m_a

```
Bond precision:   C-C = 0.0039 A          Wavelength=0.71073

Cell:           a=6.6349(3)       b=9.9311(5)       c=15.1391(7)
                alpha=73.777(2)   beta=85.701(1)    gamma=84.283(1)
Temperature:    301 K

                Calculated                Reported
Volume          951.90(8)                 951.90(8)
Space group     P -1                      P-1
Hall group      -P 1                      ?
Moiety formula  C22 H22 N2 O2             ?
Sum formula     C22 H22 N2 O2             C22 H22 N2 O2
Mr              346.42                    346.42
Dx,g cm-3       1.209                     1.209
Z               2                         2
Mu (mm-1)       0.078                     0.078
F000            368.0                     368.0
F000'           368.15
h,k,lmax        7,11,17                   7,11,17
Nref            3349                      3334
Tmin,Tmax       0.981,0.986
Tmin'           0.981

Correction method= Not given

Data completeness= 0.996          Theta(max)= 25.000

R(reflections)= 0.0623( 2604)                wR2(reflections)=
                                             0.1819( 3334)
S = 1.042                 Npar= 239
```

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level B

PLAT242_ALERT_2_B Low 'MainMol' Ueq as Compared to Neighbors of C19 Check

Alert level C

PLAT242_ALERT_2_C Low 'MainMol' Ueq as Compared to Neighbors of C5 Check
PLAT242_ALERT_2_C Low 'MainMol' Ueq as Compared to Neighbors of C18 Check
PLAT906_ALERT_3_C Large K Value in the Analysis of Variance ..... 4.711 Check
PLAT911_ALERT_3_C Missing FCF Refl Between Thmin & STh/L= 0.595 11 Report
PLAT913_ALERT_3_C Missing # of Very Strong Reflections in FCF .... 6 Note
PLAT918_ALERT_3_C Reflection(s) with I(obs) much Smaller I(calc) . 1 Check
PLAT934_ALERT_3_C Number of (Iobs-Icalc)/Sigma(W) > 10 Outliers .. 1 Check

Alert level G

PLAT005_ALERT_5_G No Embedded Refinement Details Found in the CIF Please Do !
PLAT093_ALERT_1_G No s.u.'s on H-positions, Refinement Reported as mixed Check
PLAT899_ALERT_4_G SHELXL97 is Deprecated and Succeeded by SHELXL/ 2018 Note
PLAT909_ALERT_3_G Percentage of I>2sig(I) Data at Theta(Max) Still 47% Note
PLAT910_ALERT_3_G Missing # of FCF Reflection(s) Below Theta(Min). 4 Note
PLAT978_ALERT_2_G Number C-C Bonds with Positive Residual Density. 0 Info

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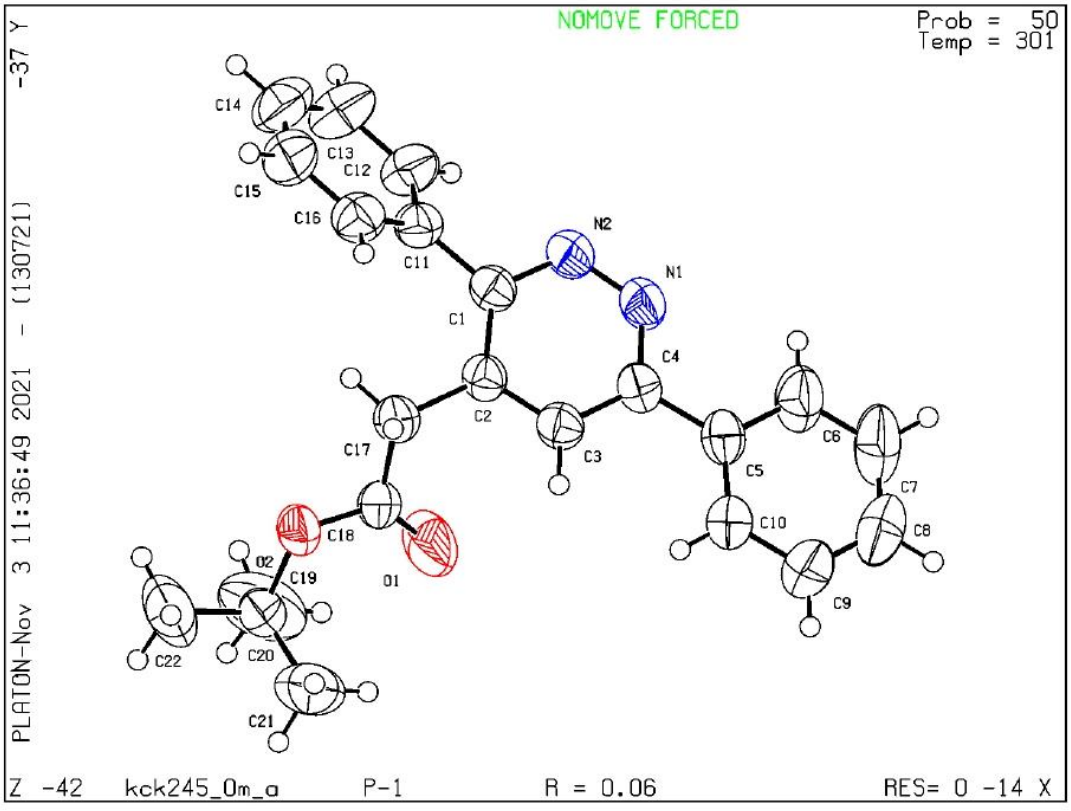
PLATON version of 13/07/2021; check.def file version of 13/07/2021

Datablock kck245_0m_a - ellipsoid plot



ANNULATION/CYCLOADDITION REACTIONS OF INDOLE/CHROMENE/COUMARIN CARBOXYLIC ACIDS OR TETRAZINE WITH C-C Π-COMPONENTS

by Mallepalli Shankar

Submission date: 26-May-2022 05:01PM (UTC+0530)
Submission ID: 1844560088
File name: Mallepalli_Shankar.pdf (6.19M)
Word count: 15386
Character count: 85149

ANNULATION/CYCLOADDITION REACTIONS OF INDOLE/CHROMENE/COUMARIN CARBOXYLIC ACIDS OR TETRAZINE WITH C-C Π-COMPONENTS

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SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

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2	Mallepalli Shankar, Uruvakili Anasuyamma, K. C. Kumara Swamy. "Reaction of Indole - 2 - Carboxylates/Carboxylic Acids with Propargylic Alcohols: Dearomative Ring Expansion/Spirocyclization vs Fused Pentacyclics", Advanced Synthesis & Catalysis, 2021 Publication	2%
3	Vadim P. Boyarskiy, Dmitry S. Ryabukhin, Nadezhda A. Bokach, Aleksander V. Vasilyev. "Alkenylation of Arenes and Heteroarenes with Alkynes", Chemical Reviews, 2016	1%

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Kumara Swamy

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University of Hyderabad
Hyderabad- 500 046, INDIA

	Publication	
4	Submitted to University of Hyderabad, Hyderabad Student Paper	<1 %
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8	Karuppu Selvaraj, Shubham Debnath, K. C. Kumara Swamy. "Reaction of Indole Carboxylic Acid/Amide with Propargyl Alcohols: [4 + 3]-Annulation, Unexpected 3- to 2- Carboxylate/Amide Migration, and Decarboxylative Cyclization", Organic Letters, 2019 Publication	<1 %

9	Ye Wei, Peng Hu, Min Zhang, Weiping Su. "Metal-Catalyzed Decarboxylative C–H Functionalization", Chemical Reviews, 2017 Publication	<1 %
10	Filipe Penteado, Eric F. Lopes, Diego Alves, Gelson Perin, Raquel G. Jacob, Eder J. Lenardão. "α-Keto Acids: Acylating Agents in Organic Synthesis", Chemical Reviews, 2019 Publication	<1 %
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13	Jian-Fei Bai, Lulu Zhao, Fang Wang, Fachao Yan, Taichi Kano, Keiji Maruoka, Yuehui Li. " Organocatalytic Formal (3 + 2) Cycloaddition toward Chiral Pyrrolo[1,2-]indoles via Dynamic Kinetic Resolution of Allene Intermediates ", Organic Letters, 2020 Publication	<1 %

14	Rajnikanth Sunke, Adula Kalyani, K. C. Kumara Swamy. " Cu(I)-Catalyzed Ligand-Free Tandem One-Pot or Sequential Annulation via Knoevenagel Intermediates: An Entry into Multifunctional Naphthalenes, Phenanthrenes, Quinolines, and Benzo[ ]carbazoles ", The Journal of Organic Chemistry, 2019 Publication	<1 %
15	Boger, Dale L., Robert P. Schaum, and Robert M. Garbaccio. "Regioselective Inverse Electron Demand Diels–Alder Reactions of *N*-Acyl 6-Amino-3-(methylthio)-1,2,4,5-tetrazines", The Journal of Organic Chemistry, 1998. Publication	<1 %
16	Prabhakararao Tharra, Beeraiah Baire. "Regioselective Cyclization of (Indol-3-yl)pentyn-3-ols as an Approach to (Tetrahydro)carbazoles", Organic Letters, 2018 Publication	<1 %
17	Anisley Suárez, Samuel Suárez-Pantiga, Olalla Nieto-Faza, Roberto Sanz. "Gold-Catalyzed Synthesis of 1-(Indol-3-yl)carbazoles: Selective 1,2-Alkyl vs 1,2-Vinyl Migration", Organic Letters, 2017 Publication	<1 %
18	Karuppu Selvaraj, K. C. Kumara Swamy. "Transition-Metal-Free, Brønsted Acid-	<1 %

Mediated Cascade Sequence in the Reaction of Propargyl Alcohols with Sulfonamido-indoles/-indolines: Highly Substituted δ- and α-Carbolines", The Journal of Organic Chemistry, 2018
Publication

19	"Organic Reaction Mechanisms · 2016", Wiley, 2020 Publication	<1 %
20	Gao-Ang Pan, Yang Li, Jin-Heng Li. " Metal-free decarboxylative annulation of -arylacrylamides with vinyl acids to synthesize benzo[ ]azepin-2-ones ", Organic Chemistry Frontiers, 2020 Publication	<1 %
21	Siva Kumari, A. Leela, and K. C. Kumara Swamy. "Divergence in the Reactivity Between Amine and Phosphine Catalyzed Cycloaddition Reactions of Allenoates with Enynals: One-pot Gold Catalyzed Synthesis of Trisubstituted Benzofurans from the [3+2] Cycloadduct via 1,2-Alkyl Migration and Dehydrogenation", The Journal of Organic Chemistry Publication	<1 %
22	archive.org Internet Source	<1 %

23	Submitted to Higher Education Commission Pakistan Student Paper	<1 %
24	Heyi Zhang, Zhan Lu. "Nickel/Copper Dual Catalysis for Sequential Nazarov Cyclization/Decarboxylative Aldol Reaction", Organic Letters, 2018 Publication	<1 %
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27	Gallego, Mar Gómez, and Miguel A. Sierra. "Level 2 — Case 30 Diels-Alder Reactions of N-Acyl-1,2,4,5-tetrazines", Organic Reaction Mechanisms, 2004. Publication	<1 %
28	Hummel, Joshua R, and Jonathan A. Ellman. "Cobalt(III)-Catalyzed Synthesis of Indazoles and Furans by C–H Bond Functionalization/Addition/Cyclization Cascades", Journal of the American Chemical Society Publication	<1 %
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Acids with Unsaturated Oxime Esters: Carboxylic Acids Serve as Traceless Activators", Journal of the American Chemical Society, 2014
Publication

30	Wei Shi, Fang Ma, Pinhua Li, Lei Wang, Tao Miao. "Visible-Light-Induced Decarboxylative Cyclization/Hydrogenation Cascade Reaction to Access Phenanthridin-6-yl(aryl)methanol by an Electron Donor–Acceptor Complex", The Journal of Organic Chemistry, 2020 Publication	<1 %
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Publication

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36	hdl.handle.net Internet Source	<1 %
37	scholars.unh.edu Internet Source	<1 %
38	Jürgen Sauer. "1,2,4,5-Tetrazines", Elsevier BV, 1996 Publication	<1 %
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40	Jun-Long Li, Qian Zhao, Chuan Gou, Qing-Zhu Li, Hai-Jun Leng, Qian-Wei Huang, Yue Liu. "Construction of Indole - fused Heterocycles Starting from 2 - Thioxoindolines, Iminoindolines, and their Derivatives", Advanced Synthesis & Catalysis, 2021 Publication	<1 %

41	Sharma, Sudhir K., Anil K. Mandadapu, Brijesh Kumar, and Bijoy Kundu. "Synthesis of Iodo-Indoloazepinones in an Iodine-Mediated Three-Component Domino Reaction via a Regioselective 7-*endo-dig* Iodo-Cyclization Pathway±CDRI Communication No. 8094", The Journal of Organic Chemistry, 2011. Publication	<1 %
42	Charles S. Yeung, Vy M. Dong. "Catalytic Dehydrogenative Cross-Coupling: Forming Carbon−Carbon Bonds by Oxidizing Two Carbon−Hydrogen Bonds", Chemical Reviews, 2011 Publication	<1 %
43	Popat M. Jadhav, Ambadas B. Rode, László Kótai, Rajendra P. Pawar, Sunil U. Tekale. "Revisiting applications of molecular iodine in organic synthesis", New Journal of Chemistry, 2021 Publication	<1 %
44	Rajaka Lingayya, Mari Vellakkaran, Kommu Nagaiah, Jagadeesh Babu Nanubolu. "Ruthenium as a Single Catalyst for Two Steps: One-Pot Ruthenium(II)-Catalyzed Aerobic Oxidative Dehydrogenation of Dihydroquinazolinones and Cross-Coupling/Annulation to give N-Fused	<1 %

Polycyclic Heteroarenes", Asian Journal of Organic Chemistry, 2015
Publication

45	Sarthak Jain, Kevin Neumann, Yichuan Zhang, Jin Geng, Mark Bradley. "Tetrazine-Mediated Postpolymerization Modification", Macromolecules, 2016 Publication	<1 %
46	Slawomir Berski, Juan Andrés, Bernard Silvi, Luis R. Domingo. "New Findings on the Diels–Alder Reactions. An Analysis Based on the Bonding Evolution Theory", The Journal of Physical Chemistry A, 2006 Publication	<1 %
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