TRANSITION METAL CATALYZED C-C AND C-N BOND FORMATION VIA C-H ACTIVATION/ FUNCTIONALIZATION OF INDOLE AND CHROMENE BASED SYSTEMS

A THESIS

SUBMITTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN CHEMISTRY

By

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HYDERABAD - 500 046

INDIA

SEPTEMBER 2016

Dedicated to
My parents

Late Sri. T. S.Ramayyar
(Bappa)

T. S. Susheela
(Amma)

CONTENTS

TRANSITION METAL CATALYZED C-C AND C-N BOND FORMATION VIA C-H ACTIVATION/ FUNCTIONALIZATION OF INDOLE AND CHROMENE BASED SYSTEMS

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
September 2016

R. N. Prasad Tulichala

DECLARATION

I, **R. N. PRASAD TULICHALA** hereby declare that this thesis entitled "***Transition Metal Catalyzed C-C and C-N Bond Formation via C-H Activation/ Functionalization of Indole and Chromene Based Systems***" 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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Name: R. N. Prasad Tulichala

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Regd. No.: 10CHPH28

Signature of the Supervisor:

CERTIFICATE

This is to certify that the work described in this thesis entitled "***Transition Metal Catalyzed C-C and C-N Bond Formation via C-H Activation/ Functionalization of Indole and Chromene Based Systems***" has been carried out by **Mr. R. N. Prasad Tulichala** bearing Regd. No. **10CHPH28** in partial fulfilment of the requirements for the award of Doctor of Philosophy in Chemistry under my supervision and the same has not been submitted elsewhere for any degree.

Hyderabad

September 2016

Prof. K. C. Kumara Swamy

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Dean
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R. N. Prasad Tulichala

LIST OF PUBLICATIONS

1 $P(n\text{-}Bu)_3$ Catalyzed reactions of salicyl *N*-thiophosphinyl imines with allenylphosphonates: synthesis of phosphono-chromans

R. Rama Suresh, **R. N. Prasad Tulichala**, Ramesh Kotikalapudi and K. C. Kumara Swamy*

J. Heterocycl. Chem. **2014**, *51*, 760.

2 Spontaneous resolution upon crystallization of allenyl-bis-phosphine oxides

G. Gangadhararao, **R. N. Prasad Tulichala** and K. C. Kumara Swamy*

Chem. Commun. **2015**, *51*, 7168.

3 Palladium-catalyzed decarboxylative nitrile insertion via C-H activation or self-coupling of indole-2-carboxylic acids: A new route to indolocarbolines and triindoles

R. N. Prasad Tulichala and K. C. Kumara Swamy*

Chem. Commun. **2015**, *51*, 12008.

4 Reactivity of alkynylindole-2-carboxamides in [Pd]-catalysed C–H activation and phase transfer catalysis: formation of pyrrolo-diindolones vs. β-carbolinones

R. N. Prasad Tulichala and K. C. Kumara Swamy*

Org. Biomol. Chem. **2016**, *14*, 4519.

5. Palladium-catalyzed decarboxylative amidation of indole-3-carboxylic acids with isothiocyanates using carboxyl group as a traceless directing group: Formation of indole-2-carboxamides and their utility in synthesizing diindole fused pyridones

R. N. Prasad Tulichala, Mallepalli Shankar and K. C. Kumara Swamy* (*to be communicated*)

6 Ruthenium-catalyzed oxidative annulation and/or hydroarylation of chromene-3-carboxamides with alkynes via C-H functionalization

R. N. Prasad Tulichala and K. C. Kumara Swamy* (*to be communicated*)

Additional Publications

7. Oxy-Wittig reactions of 1-naphthyl(aryl)methylphosphonates: a new approach to naphthylarylketones

M. B. Zubair Khalid, Gangaram Pallikonda, **R. N. Prasad Tulichala**, Manab Chakravarty*

Tetrahedron **2016**, *72*, 2094.

8. Metal-free arylation to access distinct anthracenylphosphonates and anticancer activities for these and allied phosphonates

M. Zubair K. Baig, Gangaram Pallikonda, Prakruti Trivedi, **R. N. Prasad Tulichala**, Balaram Ghosh and Manab Chakravarty*

ChemistrySelect **2016**, 1, 4332.

9. A single fluorescent probe in selective and systematic sensing of multiple metal ions: focus on detection and bio-imaging of Pd^{2+}

M. Zubair Khalid Baig, **R. N. Prasad Tulichala**, Shweta Pawar, Amit Nag* and Manab Chakravarty* (*communicated*)

10. Easy access to 9-or10-arylated anthracenyl π-conjugates in search of distinct AIE active luminogens

Zubair Khalid Baig, Debashish Majhi, **R. N. Prasad Tulichala**, Moloy Sarkar and Manab Chakravarty* (*communicated*)

Posters presented in symposia

1. Decarboxylative nitrile insertion via C-H activation or self-coupling of indole-2-carboxylic acids through Pd-Catalysis: A novel route to indolocarbolines and triindoles
   R. N. Prasad Tulichala and K. C. Kumara Swamy*
   Chemfest-2015 (Annual in-house symposium), School of Chemistry, University of Hyderabad, Feb-**2015**.
   (**Poster & Oral Presentation**)

2 Decarboxylative nitrile insertion via C-H activation or self-coupling of indole-2-carboxylic acids through Pd-Catalysis: A novel route to indolocarbolines and triindoles
   R. N. Prasad Tulichala and K. C. Kumara Swamy*
   CATALYST 2015, Dr. Reddy's Laboratories, Hyderabad, INDIA, July-**2015**
   (**Poster Presentation**)

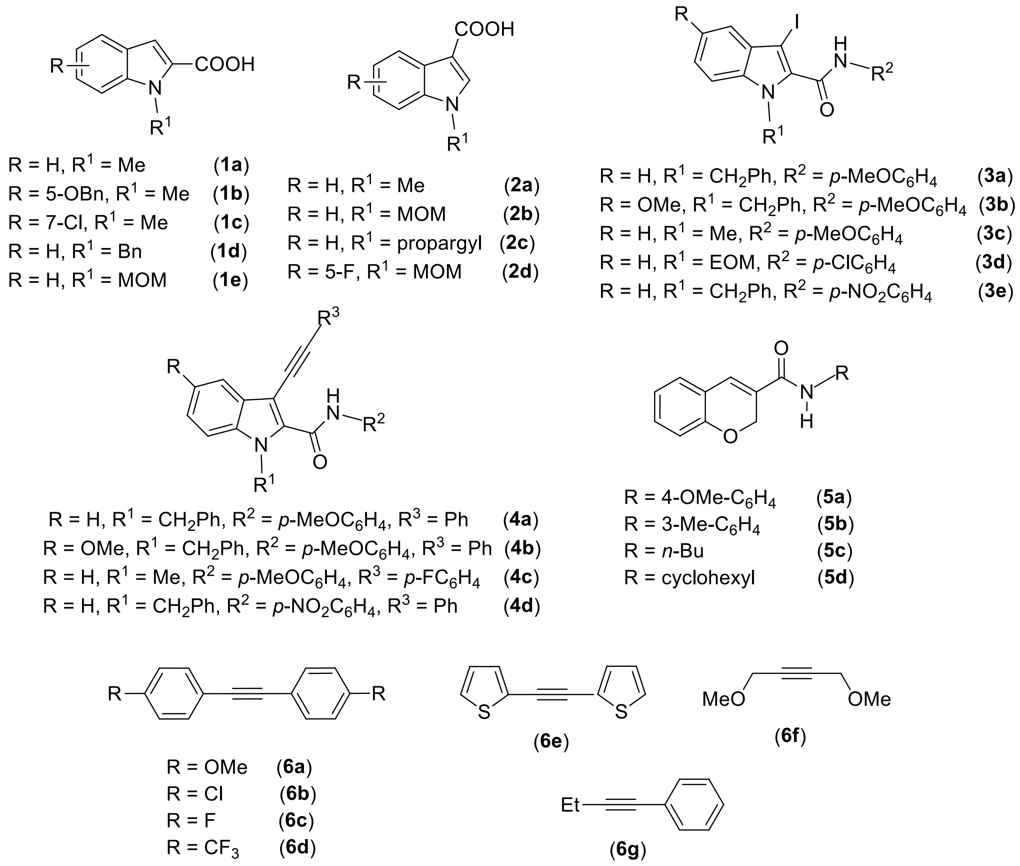
Synopsis

This thesis is divided into three chapters: **Chapter 1** (Introduction), **Chapter 2** (Results and Discussion) and **Chapter 3** (Experimental Section). Chapter 1 deals with a review of literature on aspects relevant to this work. In Chapter 2, the results obtained in the present work are discussed. The topics include (i) synthesis of indole fused α-carbolines from indole-2-carboxylic acids by decarboxylative nitrile insertion in [Pd]-catalyzed reaction *via* dual C-H activation and synthesis of triindoles by trimerization of the same precursor in the absence of nitrile, (ii) synthesis of pentacyclic pyrrolodiindolones *via* [Pd]-catalyzed C-H activation and tricyclic β-carbolinones *via* phase-transfer catalysis by using the same 3-alkynylindole-2-carboxamides, (iii) [Pd]-catalyzed *ortho*-amidation of indole-3-carboxylic acids with isothiocyanates using carboxyl group as a traceless directing group and utility of the indole-2-carboxamides for the formation of diindole fused 2-pyridones by [Pd]-catalysis, and (iv) [Ru]-catalyzed oxidative annulation of 2*H*-chromene-3-carboxamides with alkynes *via* C-H activation for the synthesis of benzopyran fused 2-pyridones and double C-H activation products through annulation along with hydroarylation. In Chapter 3, the experimental details are presented.

The compounds synthesized in the present study are, in general, characterized by mp (for solids), IR and NMR (^{1}H & ^{13}C as applicable) techniques followed by HRMS or elemental analyses in conjunction with LC-MS. X-ray structure determination is undertaken wherever required. Summary is presented at the end of Chapter 2 while references are given at the end of Chapter 3.

Coming to the specifics, the precursors used in the present study are shown in Chart 1 [*Note*: The numbering of compounds given here is different from that in the main part of the thesis]. Many more analogous precursors which are not listed here are discussed in the thesis in detail. They are prepared by methodologies available (with modifications where necessary) in the literature.

Chart 1. Precursors used in the present work



R = H, R^1 = Me (**1a**)
R = 5-OBn, R^1 = Me (**1b**)
R = 7-Cl, R^1 = Me (**1c**)
R = H, R^1 = Bn (**1d**)
R = H, R^1 = MOM (**1e**)

R = H, R^1 = Me (**2a**)
R = H, R^1 = MOM (**2b**)
R = H, R^1 = propargyl (**2c**)
R = 5-F, R^1 = MOM (**2d**)

R = H, R^1 = CH_2Ph, R^2 = *p*-$MeOC_6H_4$ (**3a**)
R = OMe, R^1 = CH_2Ph, R^2 = *p*-$MeOC_6H_4$ (**3b**)
R = H, R^1 = Me, R^2 = *p*-$MeOC_6H_4$ (**3c**)
R = H, R^1 = EOM, R^2 = *p*-ClC_6H_4 (**3d**)
R = H, R^1 = CH_2Ph, R^2 = *p*-$NO_2C_6H_4$ (**3e**)

R = H, R^1 = CH_2Ph, R^2 = *p*-$MeOC_6H_4$, R^3 = Ph (**4a**)
R = OMe, R^1 = CH_2Ph, R^2 = *p*-$MeOC_6H_4$, R^3 = Ph (**4b**)
R = H, R^1 = Me, R^2 = *p*-$MeOC_6H_4$, R^3 = *p*-FC_6H_4 (**4c**)
R = H, R^1 = CH_2Ph, R^2 = *p*-$NO_2C_6H_4$, R^3 = Ph (**4d**)

R = 4-OMe-C_6H_4 (**5a**)
R = 3-Me-C_6H_4 (**5b**)
R = *n*-Bu (**5c**)
R = cyclohexyl (**5d**)

R = OMe (**6a**)
R = Cl (**6b**)
R = F (**6c**)
R = CF_3 (**6d**)

(**6e**)

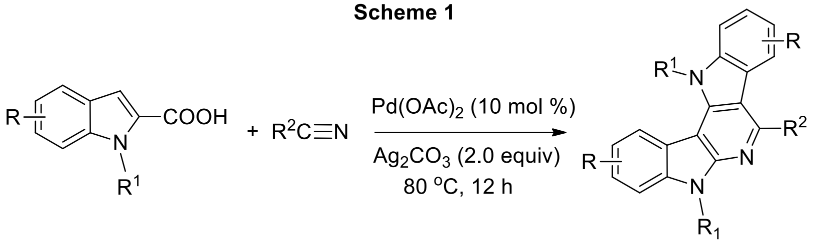
(**6f**)

(**6g**)

(i) (a) Palladium-catalyzed decarboxylative nitrile insertion *via* dual C-H activation: Synthesis of indole fused α-carbolines from indole-2-carboxylic acids and nitriles

In general, the nitrile group is considered to be inert in most of the palladium-catalyzed reactions and thus acetonitrile is one of the frequently used solvents. To our knowledge, there is hardly any report on the incorporation of the nitrile group directly into a cyclic structure. Such reactions utilizing the indole system could lead to carbolines that are another important class of medicinally useful products. Thus, the reaction of *N*-substituted-indole-2-carboxylic acids with nitriles in the presence of $Pd(OAc)_2$ (10 mol %) and Ag_2CO_3 (2.0 equiv) as an oxidant under solvent-free condition (neat) afforded indolocarbolines in moderate to good yields (Scheme 1). High functional group tolerance was achieved with respect to both indole-2-carboxylic acids and nitriles.

Scheme 1



R = H, R^1 = Me, R^2 = Me (**7a**) (38%, X-ray)
R = H, R^1 = Me, R^2 = Ph (**7b**) (65%)
R = H, R^1 = Me, R^2 = 3-Me-C_6H_4 (**7c**) (61%, X-ray)
R = H, R^1 = Me, R^2 = Pr (**7d**) (56%)
R = H, R^1 = Me, R^2 = thiophene (**7e**) (59%)
R = 5-OBn, R^1 = Me, R^2 = Ph (**7f**) (64%)
R = 7-Cl, R^1 = Me, R^2 = Ph (**7g**) (56%)
R = H, R^1 = EOM, R^2 = Ph (**7c**) (50%)
(more examples)

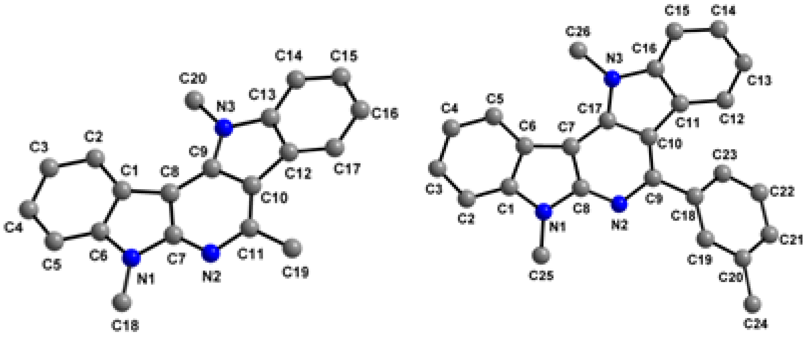
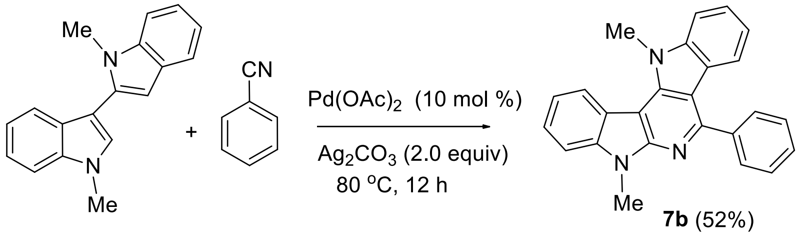


Figure 1. Ball-and-stick models of compounds **7a** (left) and **7c** (right)

Formation of indole fused α-carboline as shown above is assumed to take place *via* biindolyl intermediate by dual C-H activation. To examine this, we performed a reaction between biindolyl and benzonitrile. Satisfyingly, this reaction afforded α-carboline **7b** *via* double C-H activation in 52% yield (Scheme 2) vindicating our proposal.

Scheme 2



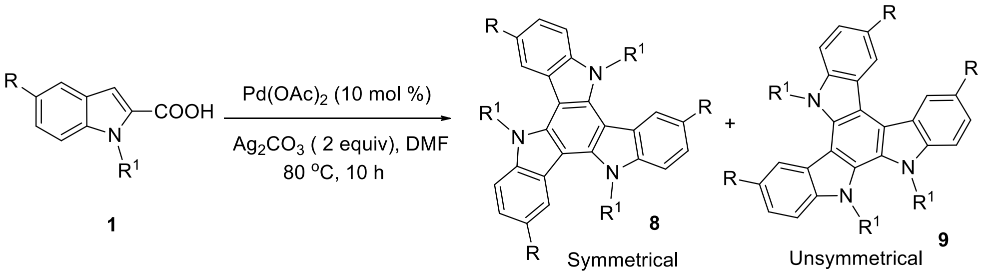
7b (52%)

The above indolocarbolines are fluorescence active in solution, and hence a preliminary study of the absorption and emission spectra for all the synthesized indolocarbolines is also performed in this work.

(b) Synthesis of triindoles via [Pd]-catalyzed decarboxylative trimerization of 1-alkyl-indole-2-carboxylic acids

In one of the above reactions, formation of a triindoles, that does not involve the nitrile component, was noticed. Since triindoles are of interest in organic electronics, we have explored this aspect also. Thus we found that by using the same indole-2-carboxylic acid precursors in the *absence of nitrile*, trimerization occurred *via* palladium-catalyzed decarboxylative reaction using $Pd(OAc)_2$ (10 mol %) and Ag_2CO_3 (2.0 equiv) in DMF solvent. These reactions afforded a mixture of symmetrical and unsymmetrical triindoles in moderate yields (Scheme 3). As expected, R_f values of the two isomeric triindoles were very close. Hence we were able to separate both the isomers only in selected cases. The unsymmetrical triindoles were obtained in a pure state in all the cases except when R = OMe and R^1 = Bn. Overall, four symmetrical triindoles (**8a, 8d, 8e,** and **8f**) and five unsymmetrical triindoles (**9a**, **9b**, **9c**, **9d**, and **9f**) have been obtained in a pure state. The triindoles upon passing dry HCl gas produce green coloured solids that exhibit clean EPR spectra in the solid state. We believe that these green solids may contain radical cations. Attempts to obtain single crystals of this species are yet to meet with success though.

Scheme 3



R = H, R^1 = Me **8a** (20%) + **9a** (28%); overall yield: 48%
R = OMe, R^1 = Me **8b** (not isolated) + **9b** (30%, X-ray); overall yield: 45%
R = H, R^1 = Bn **8c** (not isolated) + **9c** (32%); overall yield: 43%
R = H, R^1 = EOM **8d** (21%) + **9d** (31%); overall yield: 52%
R = OMe, R^1 = Bn **8e** (35%, X-ray) + **9e** (not isolated); overall yield: 44%
R = H, R^1 = *n*-Bu **8f** (20%) + **9f** (30%); overall yield: 50%

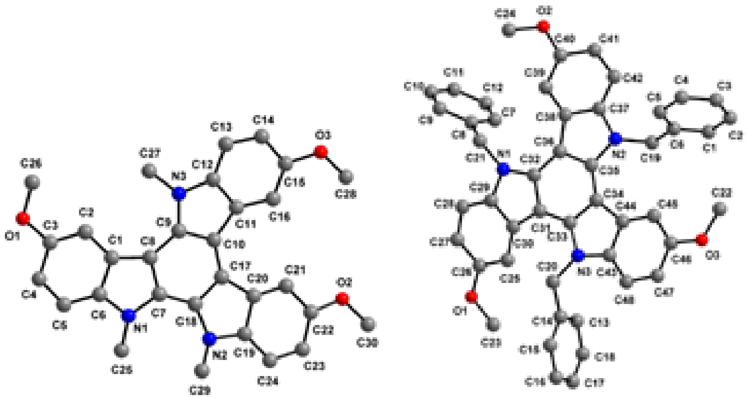
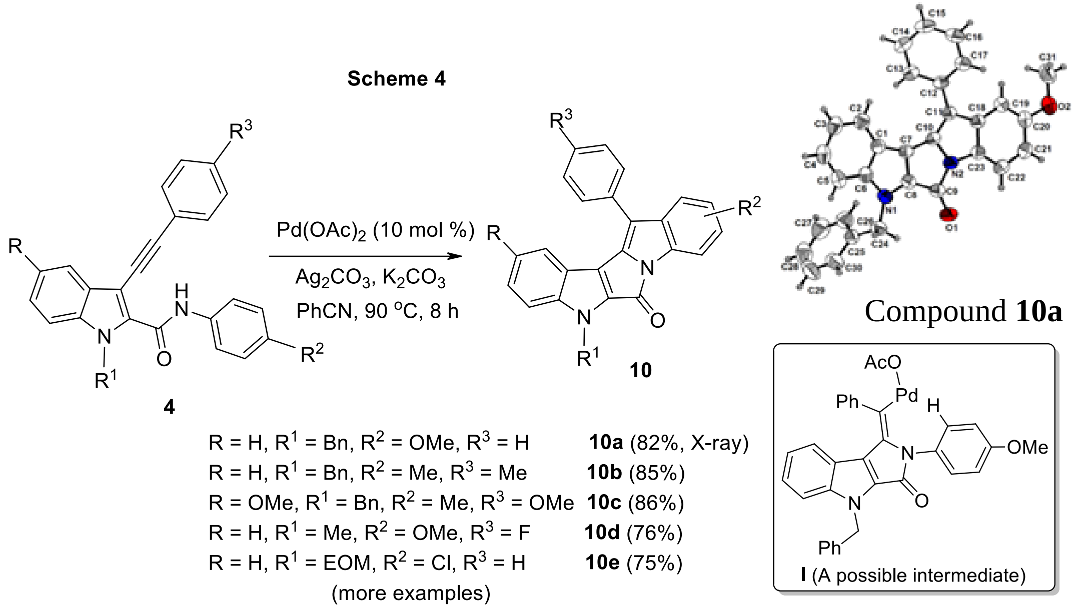


Figure 2. Ball-and-stick models of compounds **9b** (left) and **8e** (right)

(ii) (a) Palladium catalyzed synthesis of pyrrolodiindolones via oxidative double cyclization of 3-alkynylindole-2-carboxamides involving C-H activation

For the above purpose, we first converted indole-2-carboxylic acids to substituted 3-alkynylindole-2-carboxamides. Reaction of these carboxamides in the presence of $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2.0 equiv) and K_2CO_3 (1.0 equiv) in PhCN afforded the pentacyclic pyrrolodiindolones **10** in good to excellent yields (Scheme 4). The structure of the compound **10a** was confirmed by X-ray crystallography. The reaction worked well with a wide variety of substituents that included 4-Me, 4-OMe, 3-Me, 4-Cl, and 4-F, affording the pyrrolodiindolones in 75-86% yield. A possible pathway involves the formation of vinylpalladium species **I** from the activated alkynic π-bond by the attack of amidic anion *via* 5-*endo-dig* mode of cyclization. This species may undergo intramolecular C-H activation followed by reductive elimination producing the pyrrolodiindolone.

Scheme 4

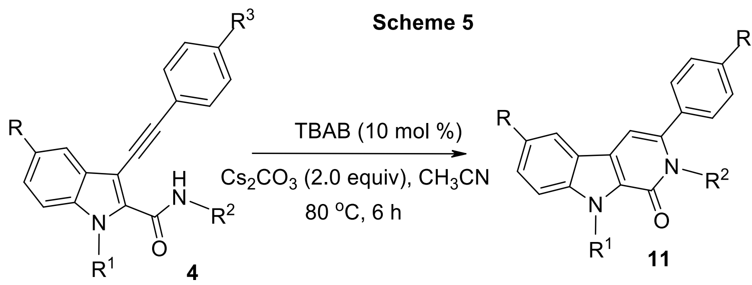


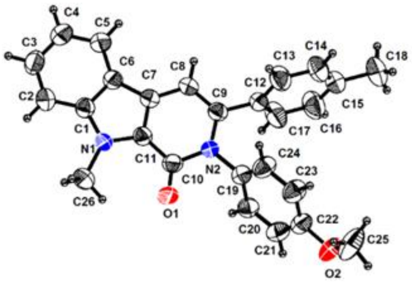
R = H, R^1 = Bn, R^2 = OMe, R^3 = H **10a** (82%, X-ray)
R = H, R^1 = Bn, R^2 = Me, R^3 = Me **10b** (85%)
R = OMe, R^1 = Bn, R^2 = Me, R^3 = OMe **10c** (86%)
R = H, R^1 = Me, R^2 = OMe, R^3 = F **10d** (76%)
R = H, R^1 = EOM, R^2 = Cl, R^3 = H **10e** (75%)
(more examples)

(b) Phase transfer (solid-liquid) catalyzed intramolecular cyclization of 3-alkynylindole-2-carboxamides towards the synthesis of β-carbolinones

In contrast to the above reaction, when we used tetra-*n*-butyl ammonium bromide (TBAB) as the catalyst, the 3-alkynylindole-2-carboxamides underwent intramolecular cyclization to produce β-carbolinones with remarkable regio- and chemo-selectivity. Thus treatment of 3-alkynylindole-2-carboxamides **4** in the presence of TBAB (10 mol %) and Cs_2CO_3 (2.0 equiv) in CH_3CN led to the formation of β-carbolinones **11** in excellent yields (Scheme 5). The reaction features high regio- and chemo-selectivity, good substrate scope, is atom economical and provides a new strategy for the synthesis of synthetically and medicinally useful β-carbolinones. Formation of β-carbolinones may be rationalized by solid-liquid phase transfer catalytic (SL-PTC) mechanism. Notably, depending on the catalyst, a switch to trigger different reaction pathways affording two types of products from the same starting material, is demonstrated. These β-carbolinones may be formed by the attack of amidic anion on the β-carbon of the alkyne in the intermediate **II** *via* 6-*endo-dig* mode cyclization followed by protonation.

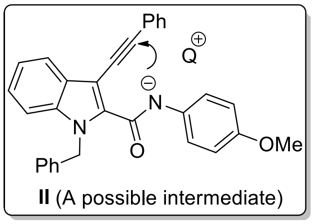
Scheme 5





Compound **11d**

R = H, R^1 = Bn, R^2 = 4-MeO-C$_6$H$_4$, R^3 = H **11a** (94%)
R = H, R^1 = Bn, R^2 = 4-Me-C$_6$H$_4$, R^3 = Me **11b** (76%)
R = OMe, R^1 = Bn, R^2 = 3-Me-C$_6$H$_4$, R^3 = OMe **11c** (85%)
R = H, R^1 = Me, R^2 = 4-MeO-C$_6$H$_4$, R^3 = Me **11d** (83%, X-ray)
R = H, R^1 = EOM, R^2 = 4-Cl-C$_6$H$_4$, R^3 = H **11e** (78%)
R = H, R^1 = Bn, R^2 = Me, R^3 = H **11f** (93%)
(more examples)

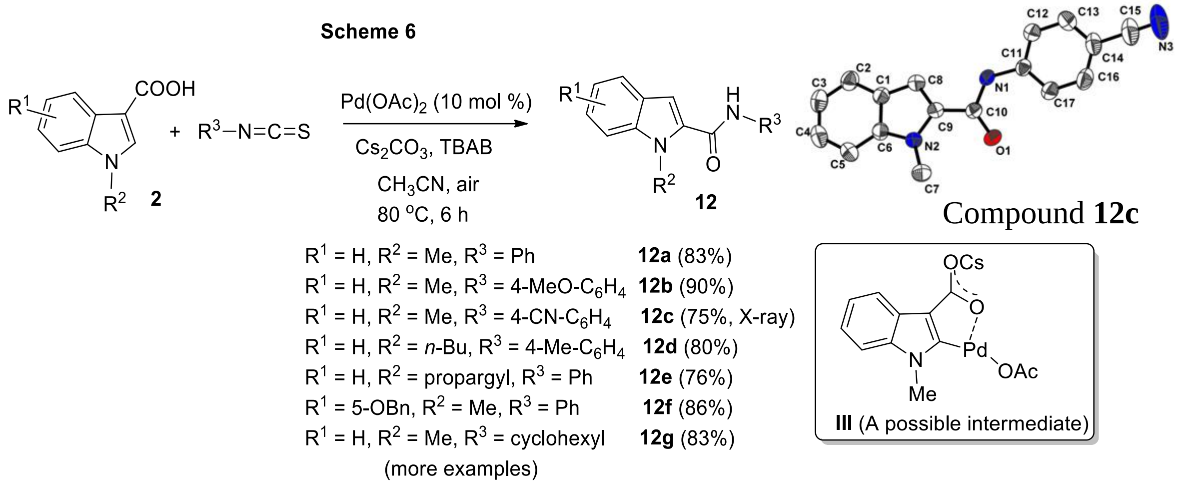


II (A possible intermediate)

(iii) (a) [Pd]-Catalyzed *ortho*-amidation of indole-3-carboxylic acid derivatives by using the carboxyl group as a traceless directing group

In the reactions discussed under section (i) above, decarboxylative nitrile insertion of indole-2-carboxylic acids had taken place and hence we surmised that this decarboxylative coupling is an equally interesting approach for *ortho* C-H functionalization. Notably, this carboxyl group can direct the regioselectivity and the only waste product from the reaction is CO$_2$. This feature indicates that the carboxyl group may act as a unique, traceless directing group (or removable directing group). With this in mind, we have chosen indole-3-carboxylic acid as the precursor for C-H functionalization, especially for C-H amidation, where carboxyl group can act as traceless directing group. Thus, the reaction of indole-3-carboxylic acids **2** with isothiocyanates in the presence of Pd(OAc)$_2$ (10 mol %), Cs$_2$CO$_3$ (1.0 equiv) and TBAB (0.5 equiv) in CH$_3$CN solvent in open air afforded indole-2-carboxamides in excellent yields (Scheme 6). This protocol has high functional group tolerance in terms of isothiocyanate substrates. The structure of the compound **12c** was further confirmed by single crystal X-ray analysis. The reaction may involve formation of a five-membered palladacycle intermediate **III**, derived from the coordination of Pd(OAc)$_2$ to the carboxyl oxygen, followed by subsequent *ortho*-C-H bond activation, insertion of isothiocyanate and protonation resulting in the formation of desired products.

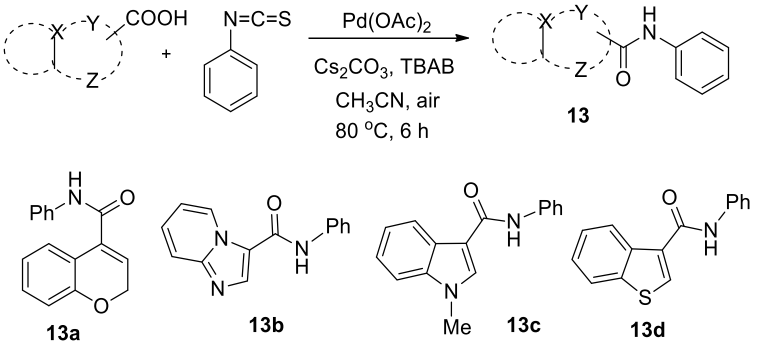
Scheme 6



R^1 = H, R^2 = Me, R^3 = Ph **12a** (83%)
R^1 = H, R^2 = Me, R^3 = 4-MeO-C_6H_4 **12b** (90%)
R^1 = H, R^2 = Me, R^3 = 4-CN-C_6H_4 **12c** (75%, X-ray)
R^1 = H, R^2 = *n*-Bu, R^3 = 4-Me-C_6H_4 **12d** (80%)
R^1 = H, R^2 = propargyl, R^3 = Ph **12e** (76%)
R^1 = 5-OBn, R^2 = Me, R^3 = Ph **12f** (86%)
R^1 = H, R^2 = Me, R^3 = cyclohexyl **12g** (83%)
(more examples)

To extend the scope of above amidation reaction, we investigated the decarboxylative amidation of heteroaromatic carboxylic acids also with phenylisothiocyanate. Thus, under the above catalytic conditions, heteroaromatic carboxylic acids were also successfully converted to *ortho*-amidation products as shown in Scheme 7.

Scheme 7



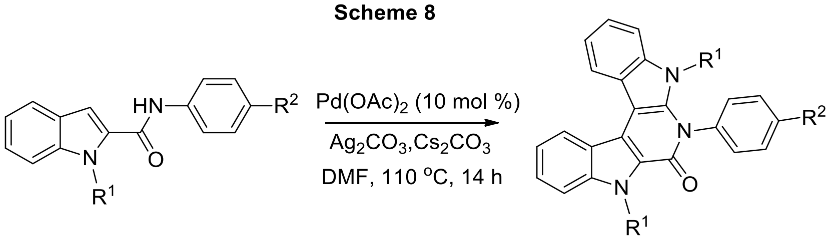
(a few more examples)

(iii) (b) Utility of indole-2-carboxamides: Synthesis of diindole-fused pyridones via palladium-catalyzed C-H bond activation

Surmising that the above indole-2-carboxamides can be used as an excellent precursors for the [Pd]-catalyzed nitrile insertion reaction *via* C-H and N-H bond cleavage, we conducted nitrile insertion reaction by palladium catalysis. Surprisingly, we did not observe nitrile inserted product but instead obtained the diindole fused 2-

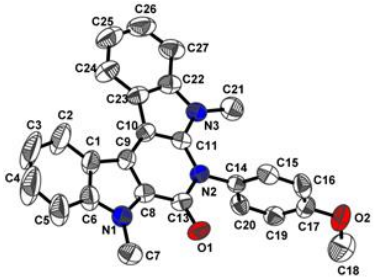
pyridone **14** by C-C and C-N bond formation in moderate yields. After screening of several conditions, good yields of diindole fused 2-pyridones (**14a** and **14b**) could be obtained in the presence of $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2.0 equiv) and Cs_2CO_3 (1.0 equiv) in DMF solvent (Scheme 8). The structure of the compound **14a** was confirmed by single crystal X-ray analysis. We are still working on this system to improve the yield of diindole fused 2-pyridones and also to examine the substrate scope by using diverse indole-2-carboxamides.

Scheme 8



R^1 = Me, R^2 = OMe; **12b**
R^1 = *n*-Bu, R^2 = Me; **12d**

R^1 = Me, R^2 = OMe; **14a** (78%, X-ray)
R^1 = *n*-Bu, R^2 = Me; **14b** (70%)



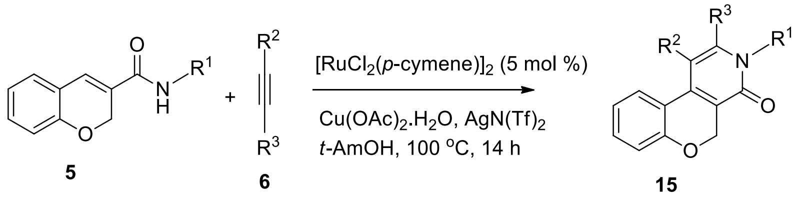
Compound **14a**

(iv) Ruthenium-catalyzed synthesis of benzopyran-fused 2-pyridones via C-H/N-H bond functionalization

Ruthenium-catalyzed oxidative annulations with alkynes by C-H functionalizations have attracted the attention of a large number of synthetic chemists as they avoid the multistep synthesis of pre-activated starting materials. Thus, in an effort to further explore C-H/N-H bond functionalization, we have chosen a benzopyran with amide functionality at the 3rd position as the precursor. C-H Functionalization on this benzopyran ring system with amide directing group has not reported so far. In this part, we report the synthesis of benzopyran-fused 2-pyridones *via* ruthenium catalyzed oxidative annulation of chromene-3-carboxamides with alkynes through C-H and N-H bond cleavage. Thus, the reaction of chromene-3-carboxamides **5** with alkynes **6** in the presence of $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), with $Cu(OAc)_2{\cdot}H_2O$ as an oxidant and $AgNTf_2$ as an additive in *t*-AmOH solvent afforded benzopyran-fused 2-pyridones **15** in excellent yields (Scheme 9). The annulation reaction with unsymmetrical alkynes proceeded in a highly regioselective manner and only one regioisomer was formed. The regioselectivity in the product was further confirmed by using X-ray crystallography.

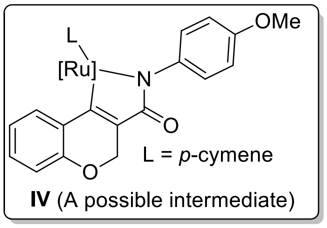
The reaction features high regioselectivity, good substrate scope, and large functional group tolerance. The reaction is assumed to proceed *via* the formation of active cationic ruthenium complex [RuOAc(*p*-cymene)]$^+$ which undergoes coordination from the amide nitrogen followed by subsequent N-H bond cleavage and *ortho*-metallation. A five-membered ruthenacycle intermediate **IV** is also likely to be involved at a later stage.

Scheme 9



5 **6** **15**

R^1 = 4-MeO-C_6H_4, R^2 = R^3 = Ph **15a** (88%)
R^1 = 4-MeO-C_6H_4, R^2 = R^3 = 4-MeO-C_6H_4 **15b** (92%)
R^1 = 4-MeO-C_6H_4, R^2 = R^3 = 4-CF_3-C_6H_4 **15c** (78%)
R^1 = 4-Me-C_6H_4, R^2 = R^3 = Ph **15d** (86%, X-ray)
R^1 = 4-MeO-C_6H_4, R^2 = Et, R^3 = Ph **15e** (75%, X-ray)
R^1 = *i*-Pr, R^2 = R^3 = Ph **15f** (90%)
(more examples)



IV (A possible intermediate)

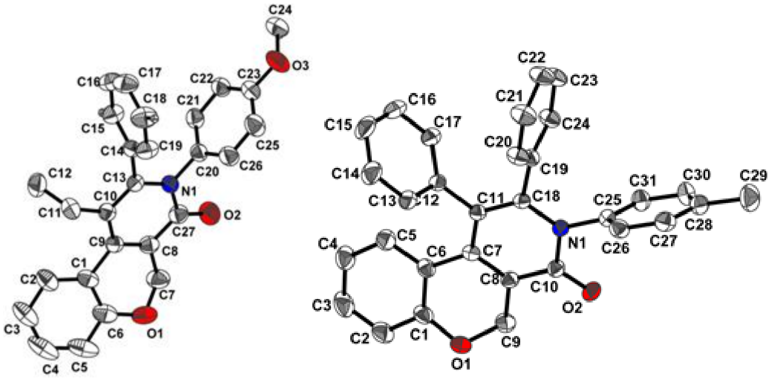
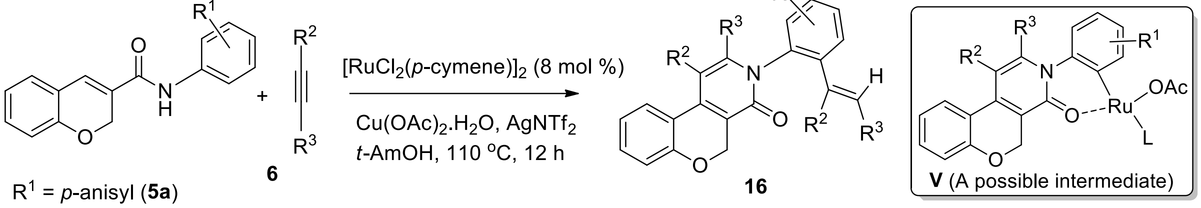


Figure 3. ORTEPs of compounds **15d** (left) and **15e** (right)

In addition to the above, we were pleased to note that when an excess of alkyne was used, the *double C-H activation* products were obtained in excellent yields. Thus, the reaction of *N*-(4-methoxyphenyl)-2*H*-chromene-3-carboxamide **5a** with 2.5 equiv of alkyne **6a** in the presence of [RuCl$_2$(*p*-cymene)]$_2$ (8 mol %), Cu(OAc)$_2$.H$_2$O and AgNTf$_2$ in *t*-AmOH afforded compound **16a** in 88% yield (Scheme 10). Compounds

16b-16g were prepared similarly. In these reactions, one alkyne moiety undergoes annulation with chromene-3-carboxamides and the other alkyne moiety is used up for hydroarylation. The structures of **16b** and **16g** were confirmed by single crystal X-ray diffraction technique. Formation of these double C-H activation products may take place *via* the active cationic ruthenium complex $[RuOAc(p\text{-cymene})]^+$ which is coordinated to the carbonyl oxygen atom of annulated products formed in the first catalytic cycle. This is followed by *ortho* metalation at the phenyl ring of amide moiety resulting in intermediate **V**. Migratory insertion of alkyne into the Ru-C bond followed by protonation in the presence of AcOH furnishes the products.

Scheme 10



V (A possible intermediate)

R^1 = *p*-anisyl (**5a**)
R^1 = *m*-tolyl (**5b**)

R^1 = 4-OMe, $R^2 = R^3$ = 4-MeO-C_6H_4	**16a** (88%)
R^1 = 4-OMe, $R^2 = R^3$ = 3,5-di Me-C_6H_3	**16b** (86%, X-ray)
R^1 = 4-OMe, $R^2 = R^3$ = 4-CF_3-C_6H_4	**16c** (76%)
R^1 = 4-OMe, $R^2 = R^3$ = 4-F-C_6H_4	**16d** (75%)
R^1 = 4-OMe, $R^2 = R^3$ = 4-Cl-C_6H_4	**16e** (82%)
R^1 = 4-OMe, $R^2 = R^3$ = Et	**16f** (78%)
R^1 = 3-Me-C_6H_4, $R^2 = R^3$ = Ph	**16g** (80%, X-ray)

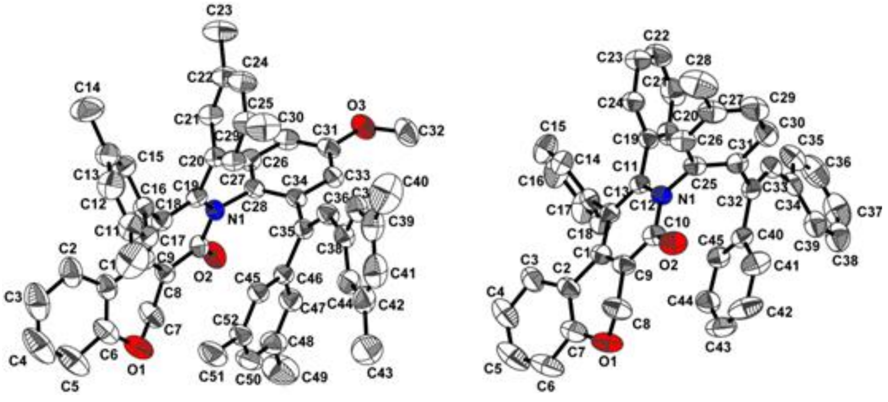
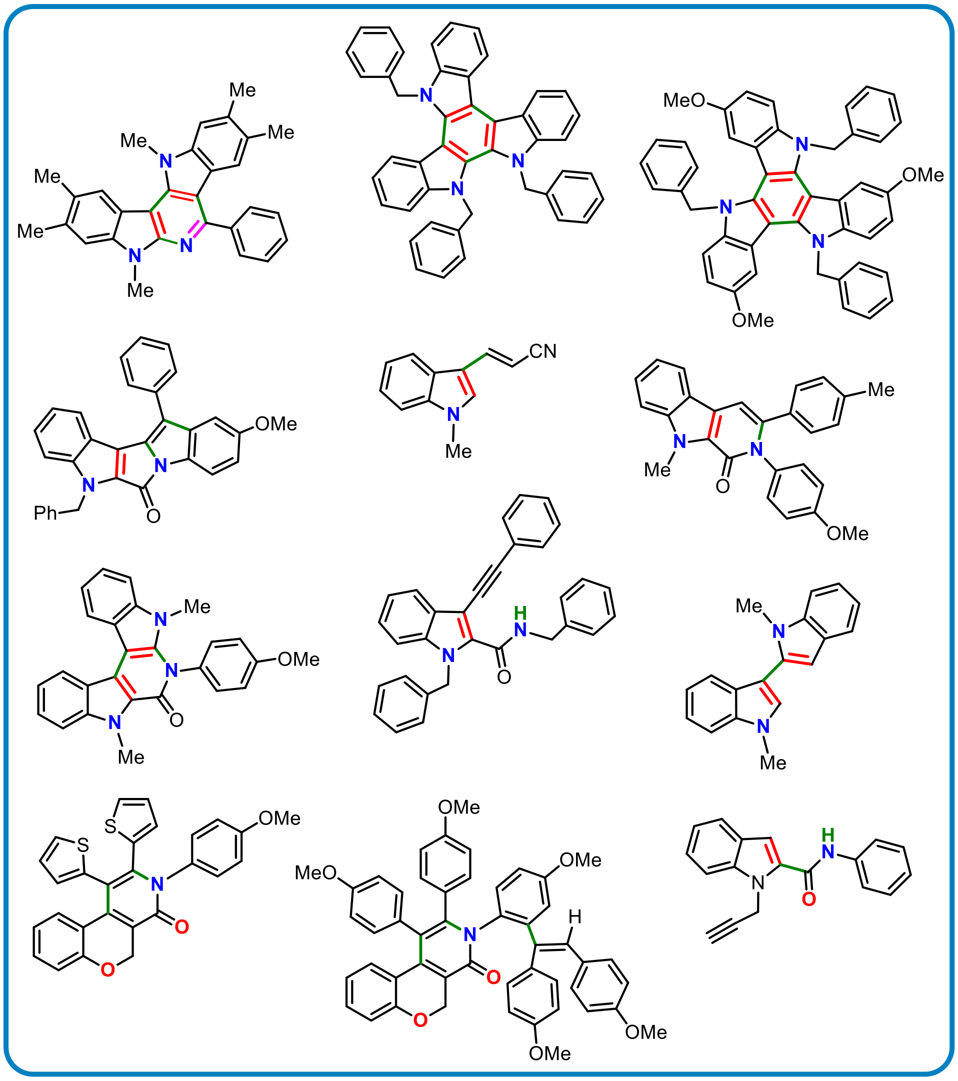


Figure 4. ORTEPs of compounds **16b** (left) and **16g** (right)

TRANSITION METAL CATALYZED C-C AND C-N BOND FORMATION VIA C-H ACTIVATION/ C-H FUNCTIONALIZATION OF INDOLE AND CHROMENE BASED SYSTEMS



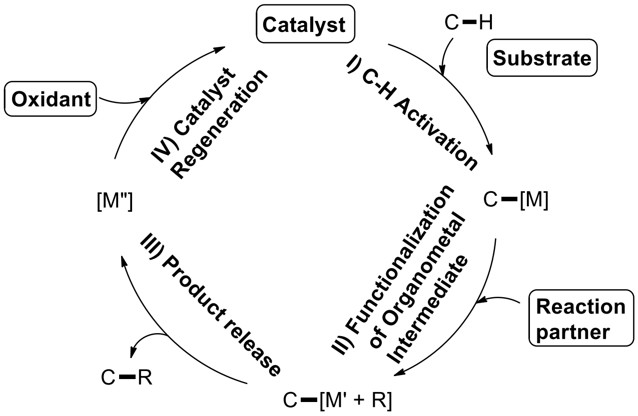
Chapter 1

INTRODUCTION

1.1 General Introduction: C-H Activation/Functionalization

Coupling reactions which use the non-activated C-H bonds as reaction sites appeared to be an unrealistic dream at the beginning of this century, because the C-H bond is traditionally not reactive. The activation of C-H bond is a challenge due to the large C-H bond dissociation energy [~473 kJmol^{-1} for C(aryl)–H bond]. To cleave the high energy C-H bond, harsh reaction conditions are typically required, giving limited substrate scope and low functional group tolerance. Direct activation/functionalization of C-H bonds, if and when attained, may lead to a streamlined and efficient synthesis of desired compounds compared to classical free radical, carbocation, or carbanion mediated reactions. The development of practical C-H activation/functionalization strategies involves two basic challenges: activity and selectivity. Transition metals can overcome the first challenge by converting C-H bonds into C-M bonds. Traditionally, this step is termed as “C-H activation”.[1] Thus formed C-M species shows more activity than the corresponding C-H counterparts. This activated C-M species is converted to new functional groups under mild conditions. The latter step is referred to as C-H functionalization. Compounds of the transition metals palladium, rhodium, iridium and ruthenium are widely used as catalysts to promote C–H bond activation[2] and functionalization.[3] The generalized mechanistic pathway for the C-H activation and C-H functionalization is shown in Scheme 1.1.[4] The transformation between the substrate with C-H bonds and an appropriate reactant involves four general mechanistic steps: (i) C-H activation, (ii) functionalization, (iii) release of product, and (iv) regeneration of the catalyst.

Scheme 1.1



The substrates which contain suitable coordinating ligands, commonly referred to as directing groups (DG), can conquer the second challenge of functionalization in a highly site-selective manner. The DGs can bind to the metal center by cyclometalation and direct the catalyst to an adjacent C-H bond in a selective manner.

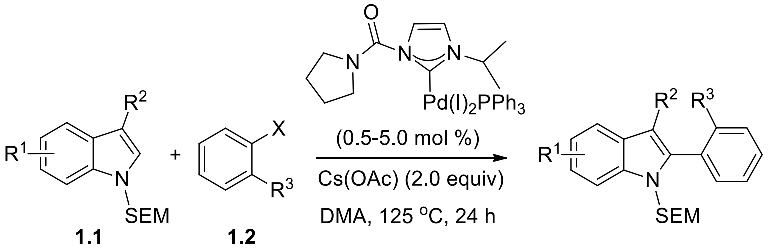
1.2 Palladium-catalyzed C-H activation/C-H functionalization of indoles

Indole is considered to be a “privileged” structural unit in organic chemistry. The recurrence of indole moiety in a large number of natural products[5] and pharmaceuticals[6] has attracted the attention of synthetic and biological chemists alike. The selective and controllable C-H functionalization of indoles has been extensively carried out by using transition metal catalysts in recent years. In particular, palladium catalytic systems are widely used for such transformations and are important tools to construct and convert the indole core motif into more complex structures. Great attention has been given to the use of palladium catalysis in the synthesis and functionalization of heterocyclic compounds, including indoles. For this reason, the synthesis as well as functionalization of indoles is currently an important area of research. Our study mainly deals with C-H activation/functionalization of this versatile indole ring system as the substrate. In the following subsection, selected reactions of C-H activation/functionalization of indole moiety from the literature are discussed. An important feature of this indole system is that the C-H bonds at C-2 and C-3 can be readily functionalized.

1.2.1 Arylation of indoles at C2 or C3-position

Sames and co-workers revealed an early example of arylation of indoles by using a Pd-NHC complex (Scheme 1.2).[7a] They were successful in coupling the bromo and iodo-arenes **1.2** with 2-(trimethylsilyl)ethoxymethyl (SEM) protected indole **1.1**. C2-Arylated products **1.3a-c** were obtained in moderate to excellent yields depending on the substituents present on the arene partner. Compared to bromoarenes, iodoarenes reacted well with low catalyst loading and afforded the arylated products in excellent yields.

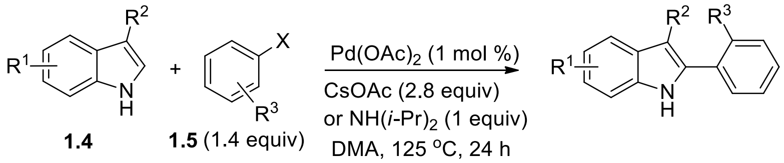
Scheme 1.2



X = I, $R^1 = R^2 = R^3 = H$ **1.3a** (91%)
X = Br, $R^1 = R^2 = R^3 = H$ **1.3a** (58%)
X = I, R^1 = 5-CN, R^2 = H, R^3 = H **1.3b** (82%)
X = I, R^1 = H, R^2 = Me, R^3 = H **1.3c** (67%)
X = I, R^1 = H, R^2 = CO_2Me, R^3 = H **1.3d** (22%)

Later, the same group established the palladium catalyzed phosphine-free C2-arylation of unprotected indoles with iodo- and bromo-arenes (Scheme 1.3).[7b] In the absence of ligand, only $Pd(OAc)_2$ (1 mol %) along with CsOAc (for iodo-arenes) or CsOAc/NH(*i*-Pr)$_2$ (for bromoarenes). could catalyze this reaction The scope of this protocol was thoroughly investigated with various substituted indoles **1.4** using bromo-/ iodo-arenes **1.5** for the synthesis of 2-aryl substituted indoles **1.6a-d**.

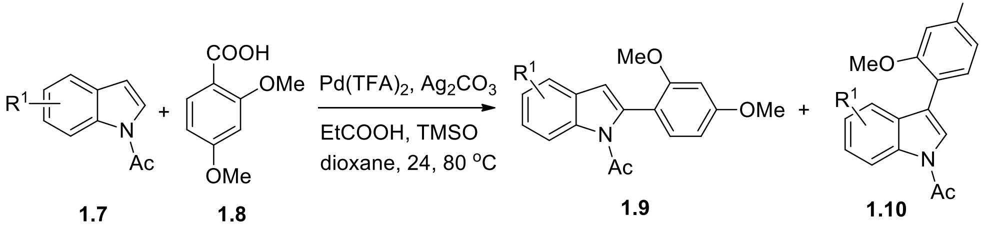
Scheme 1.3



X= I, R^1 = 5-OMe, $R^2 = R^3$ = H **1.6a** (64%)
X= I, R^1 = NHCO^{t}Bu, $R^2 = R^3$ = H **1.6b** (62%)
X= Br, R^1 = H, R^2 = Me, R^3 = H **1.6c** (62%)
X= I, R^1 = NHCO^{t}Bu, $R^2 = R^3$ = H **1.6d** (62%)

Recently, Su *et al* reported a combination of palladium catalyst, silver salt and propionic acid as an effective catalytic system for the regioselective arylation of *N*-acetyl indoles with 2,4-dimethoxy benzoic acid **1.8** as the coupling partner (arylating agent). This protocol proved to be the most efficient and attractive method than the existing methods for arylation of indoles. There was a possibility for the formation of C3-arylated indoles **1.10** also (Scheme 1.4).[8] The catalytic system [$Pd(TFA)_2$, Ag_2CO_3, EtCOOH and TMSO] they used for this arylation could overcome this selectivity issue. The reaction was compatible with both electron-rich and electron-withdrawing substituents on the indole **1.7** with good selectivity for C2 arylation.

Scheme 1.4



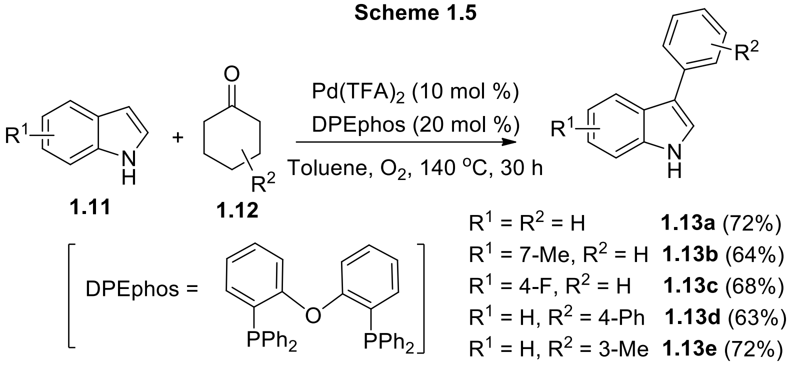
R^1 = H, 78%; **1.9a/1.10**a = 16.5:1
R^1 = 4-OMe, 65%; **1.9b/1.10b** = 7.1:1
R^1 = 5-F, 69%; **1.9c/1.10c** >99:1
R^1 = 5-NO_2, 45%; **1.9d/1.10d** >99:1
R^1 = CO_2Me, 45%; **1.9e/1.10e** >99:1

Various groups[9] have investigated the C2-arylation of indoles with different coupling partners. Fagnou *et al* used *N*-pivolyl protected indoles with simple benzene as arene partner.[9a] Lavilla *et al* reported the C2-arylation of tryptophan derivatives with iodoarenes.[9b] Sanford and co-workers have used alternative coupling partners like diaryliodonium salts.[9c] Shi *et al* reported the [Pd]-catalyzed C2-arylation of indole by using phenylboronic acids,[9d] while Cheng *et al* utilized aryl trifluoroborate salts as coupling partners.[9e] Zhang et *al* reported [Pd]-catalyzed C2-arylation of indoles with arylsiloxanes as coupling partners.[9f] Since these are not directly related to our present work, they are not elaborated further.

The oxidative arylation at the C3-position of indoles has been achieved with a variety of coupling partners compared to that at C2-position. Most of these methods involve coupling with aryl halides.[10] He *et al* developed arylation of indoles[10a] with bromoarenes as coupling partners in the presence of palladium complex having phosphinous acid ligands along with the base. Later, Rossi and co-workers reported arylation with bromoarenes in the presence of $Pd(OAc)_2$ and a phase transfer catalyst.[10b] Djakovitch *et al* utilized $[Pd(NH_3)_4]_2^+$ on NaY zeolite in the presence of K_2CO_3 in dioxane that afforded the 3-arylated indoles in good yields.[10c] Larrosa *et al* employed substituted benzoic acids instead of aryl halides as coupling partners for the C3-arylation,[10d] but this method failed completely when there is no electron-withdrawing group present at *ortho* position of the benzoic acid. Later, Chen *et al* investigated aryl hydrazines as coupling partners for the C3-arylation.[10e] The yields were moderate to good in most cases, but the reaction was sluggish when extremely electron deficient indoles (CN or NO_2 groups at C-5 position) were used.

Recently, Deng *et al* reported a novel approach for the C3-arylation of indoles with cyclohexanones under palladium catalysis (Scheme 1.5).[11] This is a good approach for the synthesis of biaryls by using readily available cyclohexanones and showed good selectivity. A variety of 3-arylated indoles **1.13a-e** were synthesized in moderate to good yields by starting with diversely substituted indoles **1.11** with various cyclohexanones **1.12**.

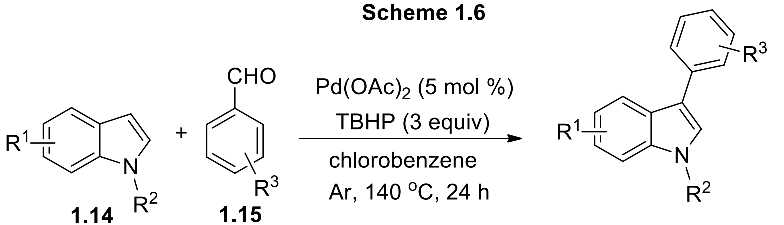
Scheme 1.5



1.2.2 Acylation of indoles at C2 or C3-position

Traditionally, Friedel−Crafts acylation, Vilsmeier−Haack acylation, and the reactions of indole salts with acyl chlorides are used for the synthesis of 3-acylindoles. These methods suffer from the requirement of stoichiometric metal Lewis acids, harsh reaction conditions (moisture sensitive), selectivity issues, and unwanted waste. Thus, the development of new, catalytic routes for selective synthesis of 3-acylindoles using readily available precursors is highly desirable. Palladium-catalyzed acylation of indoles is one of the most efficient methods for the selective synthesis acylated indoles with good yields. Li *et al* reported the palladium-catalyzed 3-acylation of indoles by using α-amino carbonyl compounds as the acylating source.[12a] Sarkar *et al* utilized the nitriles for acylation of indoles (aryl ketones are formed) by using palladium catalyzed reaction.[12b] Recently, Foroumadi *et al* reported acylation of indoles by using simple benzaldehydes *via* palladium catalyzed oxidative coupling (Scheme 1.6).[12c] Thus reaction of *N*-alkyl or aryl indoles **1.14** with substituted benzaldehydes **1.15** in the presence of $Pd(OAc)_2$ and TBHP afforded the corresponding 3-acyl indoles **1.16a-d** in good yields. This protocol led to the formation of 3-acylation products in good yields and high regioselectivity.

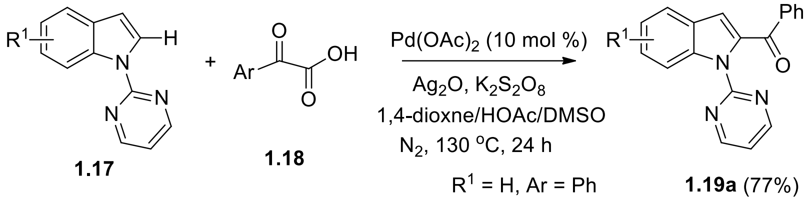
Scheme 1.6



R^1 = H, R^2 = Me, R^3 = 4-Me **1.16a** (71%)
R^1 = H, R^2 = *p*-tolyl, R^3 = 4-Me **1.16b** (64%)
R^1 = H, R^2 = Et, R^3 = 4-CO_2Me **1.16c** (86%)
R^1 = 7-Et, R^2 = Et, R^3 = 4-OMe **1.16d** (76%)

When compared to C3-functionalization of indoles, only a few reports are available for C2-functionalization of indoles except for the well-explored C2-arylation (*vide supra*, section 1.2.1). The challenging task for an organic chemist is the regioselective C–H functionalization at the C2 position of indole. The introduction of a suitable directing group at N1 could promote the regioselectivity at C2 position. C2-Acylation and C2-alkenylations of indoles were carried by this directing group strategy. A wide range of nitrogen-containing directing groups like pyrimidine, pyridyl, 2-pyridylsulfonyl, 2-pyridylmethyl group, *N*,*N*-dimethylcarbonyl and *O*-aminophenyl have been utilized in the literature for this purpose.[13] Zhu *et al* reported palladium-catalyzed decarboxylative C2-acylation of indoles with α-oxocarboxylic acids as the acylating source (Scheme 1.7).[14] In this report, they utilized pyrimidyl directing group that alters the selectivity from C3 to C2. The scope of substrates was checked for both indoles and α-oxocarboxylic acids, and 2-acyl indoles **1.19a-e** were obtained in good yields. Both indoles and α-oxocarboxylic acids possessing electron-withdrawing groups gave lower yields than those with electron donating groups.

Scheme 1.7

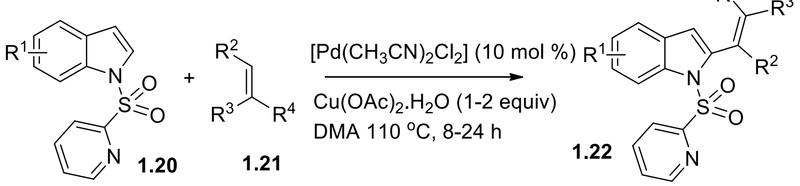


R^1 = H, Ar = Ph **1.19a** (77%)
R^1 = H, Ar = 4-Me-C_6H_4 **1.19b** (80%)
R^1 = H, Ar = 4-CF_3-C_6H_4 **1.19c** (70%)
R^1 = H, Ar = thiophenyl **1.19d** (61%)
R^1 = 7-Me, Ar = Ph **1.19e** (84%)

1.2.3 Alkenylation of indoles C2 or C3-position

As discussed above, the introduction of a suitable directing group at N1 position could promote the regioselectivity at C2 position. Carretero and co-workers reported palladium-catalyzed direct C2-alkenylation of indoles by using 2-pyridylsulfonyl directing group (Scheme 1.8).[15a] Reaction of *N*-(2-pyridyl)sulfonyl indoles **1.20** with alkenes **1.21** in the presence of $[Pd(CH_3CN)_2Cl_2]$ and $Cu(OAc)_2.H_2O$ led to the C2-alkenylated indoles **1.22a-d** in moderate to good yields with high functional group tolerance. The reductive removal of the directing group could be achieved using either Zn or Mg, thus demonstrating the synthetic versatility of this process. The same research group also developed a protocol for C2-alkenylation and dehydrogenative homocoupling of indoles assisted by the removable *N*-(2-pyridyl)sulfonyl group.[15b]

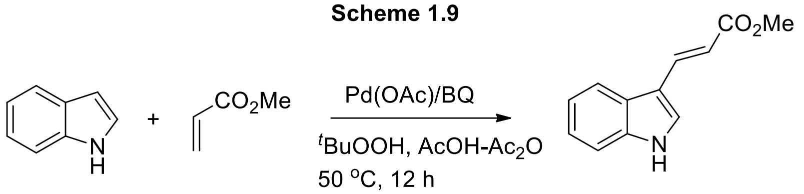
Scheme 1.8



R^1= R^2 = H, R^3 = $CO_2{}^tBu$, R^4 = H **1.22a** (78%)
R^1= R^2 = H, R^3 = Ph, R^4 = H, **1.22b** (85%)
R^1= H, R^2 = Me, R^3 = CO_2Me, R^4 = H **1.22c** (60%)
R^1= 6-CO_2Me, R^2 = H, R^3 = CO_2Me, R^4 = H **1.22d** (76%)

Introduction of alkenyl groups at C3-position has not received the same attention as similar transformations at C2 position. Fujiwara *et al* described a highly efficient palladium-catalyzed coupling of indole with an olefin like methyl acrylate in the presence of $Pd(OAc)_2$ as the catalyst and ${}^tBuOOH$ as the oxidant (Scheme 1.9),[16] that gave 3-alkenylated indole **1.23** in 52% yield.

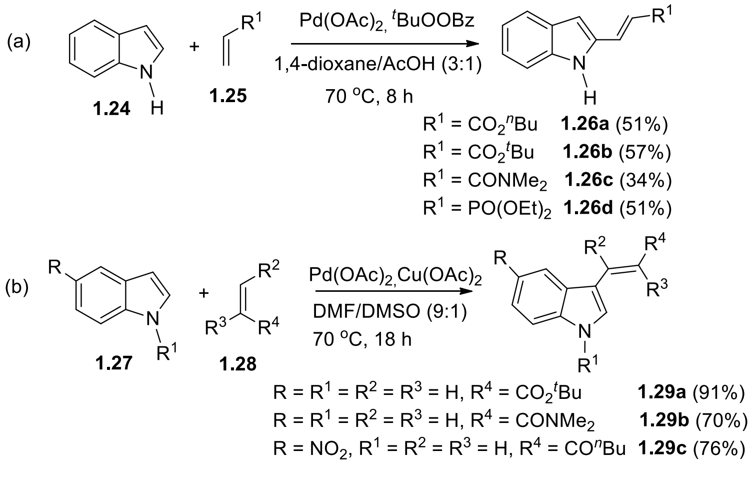
Scheme 1.9



1.23 (52%)

Gaunt and co-workers reported solvent controlled alkenylations by C-H functionalization of indoles by the palladium-catalysis.[17] In this protocol, they altered C-H alkenylation of indoles at C2 or C3 positions by changing the solvent and oxidant. To achieve the C2-alkenylation (Scheme 1.10a) they employed $Pd(OAc)_2$ and *tert*-butyl benzoyl peroxide (${}^tBuOOBz$) in 1,4-dioxane/AcOH (3:1) solvent mixture and for C3-alkenyaltion (Scheme 1.10b) they used $Pd(OAc)_2$ and $Cu(OAc)_2$ in DMF/DMSO (9:1) solvent mixture.

Scheme 1.10

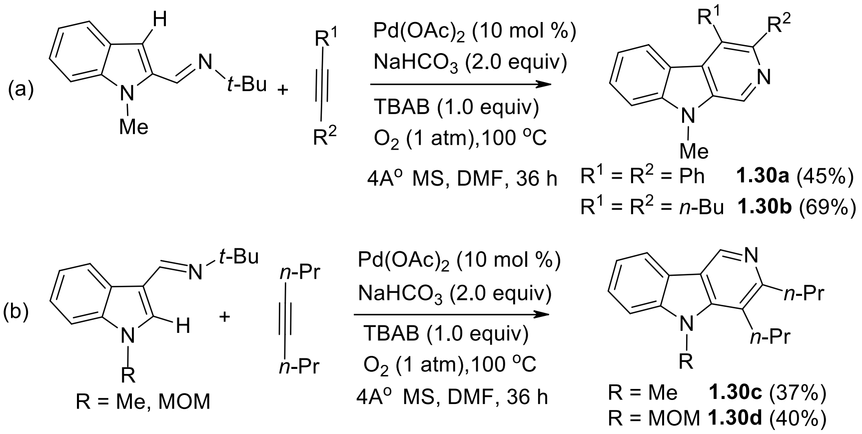


1.2.4 Annulation reactions of indoles

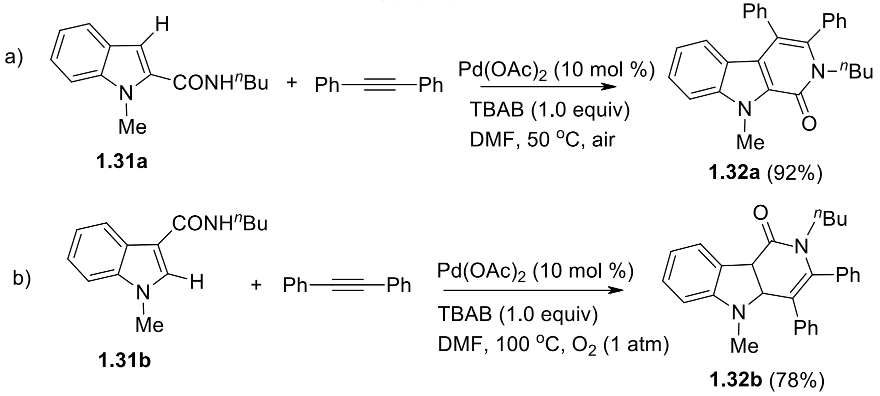
[Pd]-catalyzed oxidative annulation of indoles to form polycyclic indoles is an active area in indole chemistry. Jiao and co-workers synthesized carbolines **1.30a-d** by

Pd(II)-catalyzed direct-dehydrogenative annulation (DDA) of internal alkynes and *tert*-butylimines derived from *N*-substituted indole carboxaldehydes *via* C-H bond activation (Scheme 1.11a-b).[18a] This cyclization protocol is achieved using oxygen as oxidant in the absence of any ligand or metal based oxidant. As a continuation of this work, the same group disclosed a novel Pd-catalyzed direct dehydrogenative annulation (DDA) of indole carboxamides **(1.31a-b)** with internal alkynes using air or oxygen as the oxidant (Scheme 12a-b).[18b] This reaction provides a new synthetic strategy for synthetically and medicinally important β- and γ-carbolinones **1.32a-b** *via* C-H and N-H bond cleavage.

Scheme 1.11

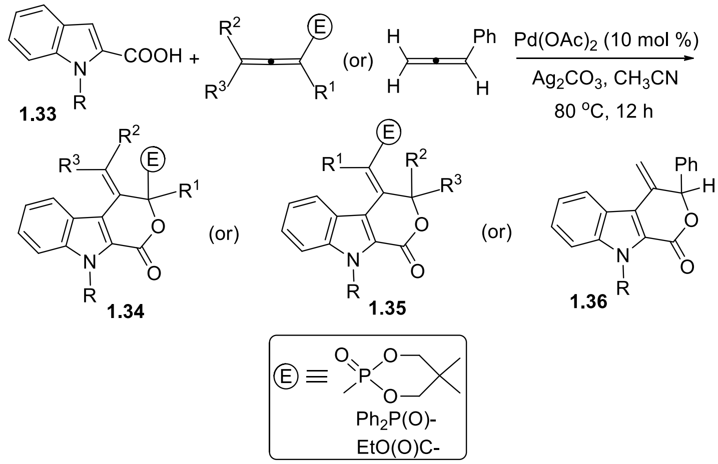


Scheme 1.12



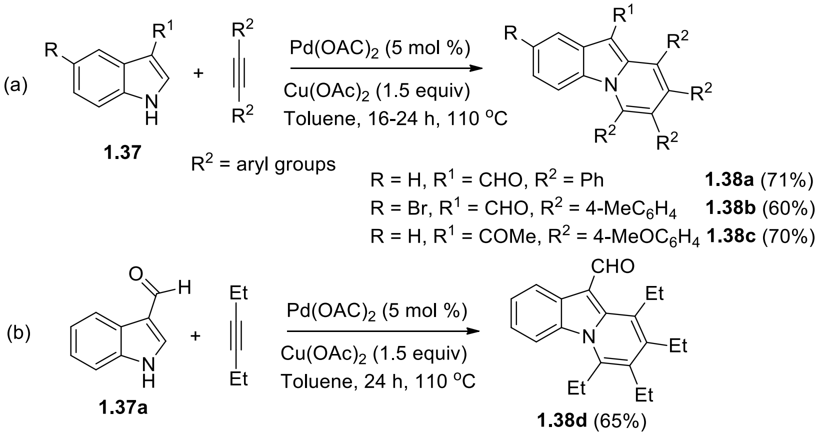
A highly efficient approach to indolo[2,3-*c*]pyrane-1-ones through the Pd-catalyzed regioselective annulation of allenes with indole-2-carboxylic acids *via* C-H functionalization was reported from our laboratory (Scheme 1.13).[19] This reaction involves the palladium catalyzed oxidative annulation of allenes *via* direct C-H functionalization of indole-2-carboxylic acids **1.33** at the C-3 position affording the desired indolo pyranones **1.34-1.36** in moderate to good yields.

Scheme 1.13



Recently, Kundu and co-workers synthesized highly fluorescent pyrido[1,2-a]indoles through the palladium-catalyzed annulation of 3-acyl indoles with alkynes *via* C-H/N-H activation (Scheme 1.14).[20] This method was established for the annulation of C-3 functionalized indoles with aliphatic as well as aromatic internal alkynes. Thus treatment of 3-acyl indoles **1.37** with dialkyl or diaryl acetylenes in the presence of Pd(OAc)$_2$/ Cu(OAc)$_2$ afforded fluorescent pyrido[1,2-a]indoles **1.38a-d**. Photophysical properties and cell imaging for the synthesized compounds were also investigated.

Scheme 1.14

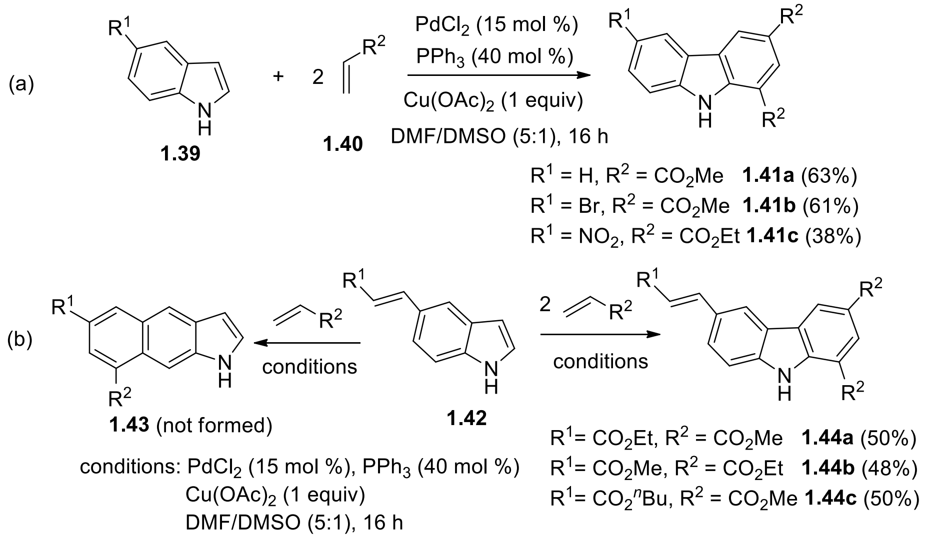


R = H, R^1 = CHO, R^2 = Ph **1.38a** (71%)
R = Br, R^1 = CHO, R^2 = 4-MeC$_6$H$_4$ **1.38b** (60%)
R = H, R^1 = COMe, R^2 = 4-MeOC$_6$H$_4$ **1.38c** (70%)

1.38d (65%)

Very recently, Choudhary *et al* reported palladium-catalyzed synthesis of functionalized carbazoles from indoles by successive triple C-H functionalization with alkenes (oxidative Heck reaction).[21] A variety of free (NH) indoles **1.39** bearing electron-rich, electron-neutral, and electron-deficient substituents reacted with alkene **1.40** to provide functionalized carbazoles **1.41a-c** in moderate to good yields with excellent functional group tolerance (Scheme 1.15a). The regioselectivity of the reaction was also investigated by using vinyl indoles **1.42** with acrylates, resulting in carbazoles **1.44a-c** with excellent regioselectivity. This implied that the reaction takes place *via* C-H functionalization and not through Diels-Alder reaction. There are several other reports on the annulation reactions of indoles,[22] but since these are not directly relevant to the present work, they are not discussed here.

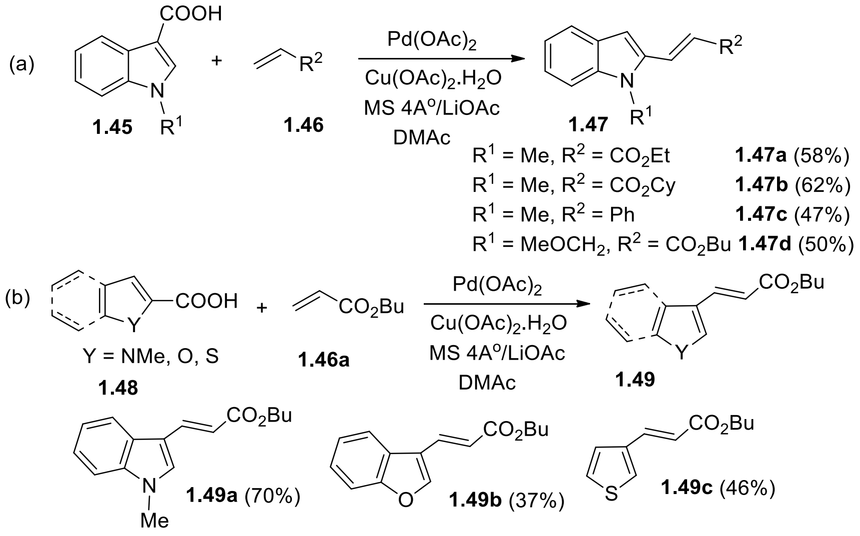
Scheme 1.15



1.2.5 Palladium-catalyzed decarboxylative C-H functionalization of indole carboxylic acids

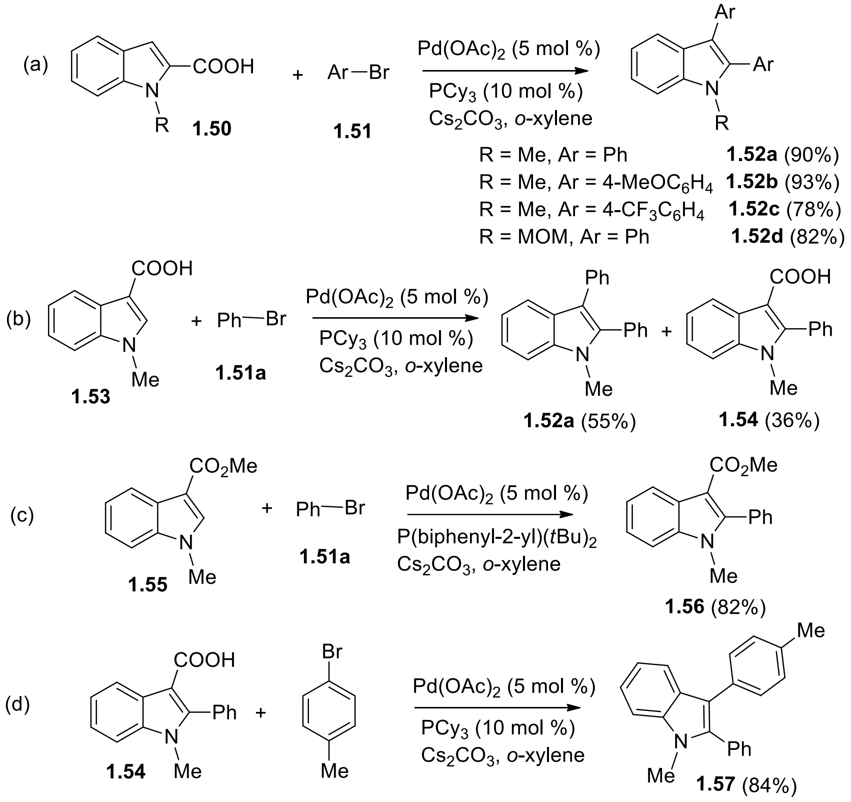
Carboxylic acid group is a very common functionality in organic chemistry. Palladium-catalyzed decarboxylative direct C-H activated coupling has received great attention in recent years. As a weekly coordinating group, carboxylic acid coordinates to the metal to induce selective C-H bond cleavage followed by decarboxylation with the exclusion of CO_2. Miura *et al* reported an unusual oxidative coupling of indole-2 or indole-3-carboxylic acids with acrylates *via* palladium-catalyzed C-H functionalization.[23] Thus reaction of indole-3-carboxylic acids **1.45** with acrylates or styrene **1.46** in the presence of $Pd(OAc)_2$ and $Cu(OAc)_2.H_2O$ afforded the corresponding 3-vinyl indoles **1.47a-d** in moderate yields (Scheme 1.16a). Except for 1-unprotected indole-3-carboxylic acids, the vinylation reaction was well tolerated for various hetero-aromatic carboxylic acids containing pyrrole, furan, thiophene, benzofuarn and benzothiophene moieties (Scheme 1.16b).

Scheme 1.16



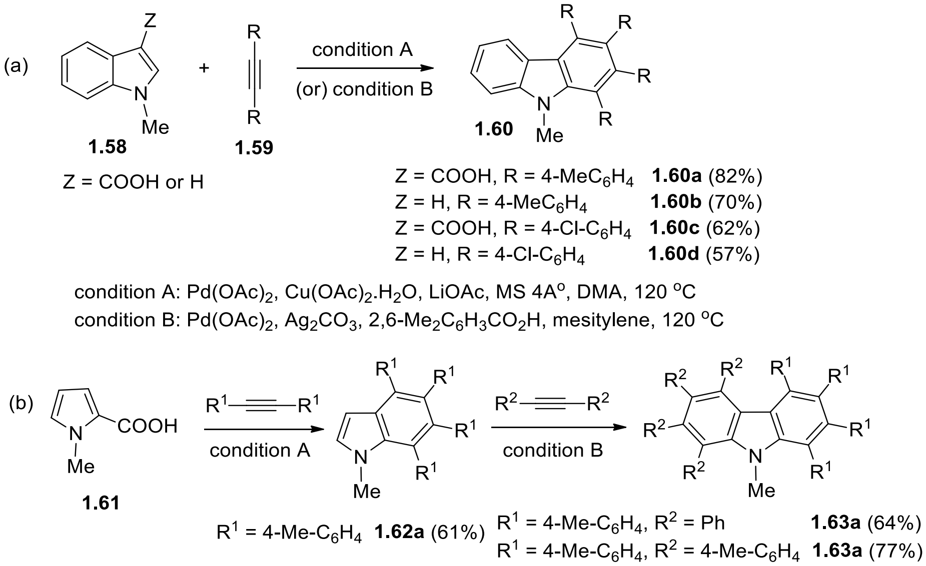
Later, the same group has demonstrated palladium-catalyzed direct decarboxylative arylation of indole-2- or indole-3-carboxylic acids with aryl bromides. Thus treatment of *N*-protected indole-2-carboxylic acids **1.50** with aryl bromides **1.51** in the presence of $Pd(OAc)_2$ (5 mol %), PCy_3 (Cy = cyclohexyl, 10 mol %), and Cs_2CO_3 in *o*-xylene afforded diarylated indoles **1.52a-d** in excellent yields (Scheme 1.17a).[24] In the reaction of 1-methyl-indole-3carboxylic acid **1.53** with bromobenzene **1.51a** under the same conditions, a mixture of diarylated [**1.52a** (55%)] and monoarylated [**1.54** (36%)] indoles were obtained (Scheme 1.17b). The second arylation at the *ipso* position appears to be a relatively slower process. They also examined step-wise diarylation for the selective synthesis of indoles with different aryl groups at 2- and 3-positions. Thus as shown in Schemes 1.17c-d, the diarylated compound **1.57** was prepared in a step wise manner.

Scheme 1.17



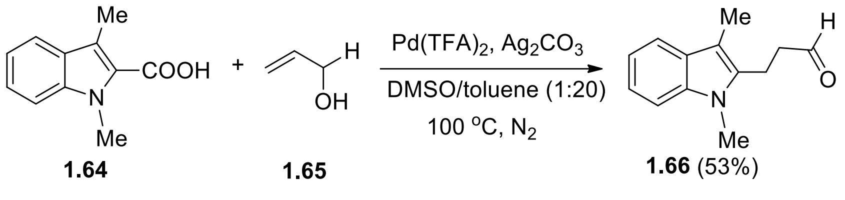
One more report from the same research group has revealed the palladium-catalyzed decarboxylative oxidative coupling of indoles or indole-3-carboxylic acids with alkynes to furnish 1,2,3,4-tetrasubstituted carbazoles.[25] Thus treatment of 1-methyl-indole-3-carboxylic acid or indole **1.58** with disubstituted alkynes **1.59** under condition A or condition B afforded the tetrasubstituted carbazoles **1.60a-d** in good yields (Scheme 1.18a). For step-wise synthesis of unsymmetrically substituted carbazoles, they treated 1-methyl-pyrrole-2-carboxylic acid **1.61** with 1,2-di-*p*-tolylethyne under condition A to furnish compound **1.62a**; compound **1.62a** was treated with diphenyl acetylene under condition B to afford the corresponding unsymmetrical tetrasubstituted carbazole **1.63a** in 64% yield (Scheme 1.18b).

Scheme 1.18



Jiang *et al* reported a simple and efficient method for the synthesis of *β*-aryl ketones and aldehydes through *β*-hydride elimination in palladium-catalyzed decarboxylative Heck-type reaction of benzoic acids with allylic alcohols.[26] They also successfully coupled indole-2-carboxylic acid **1.64** with allylic alcohol **1.65** in the presence of $Pd(TFA)_2$ and Ag_2CO_3 in DMSO/toluene (1:20) solvent mixture to obtain the corresponding indole aldehyde **1.66** in 53% yield (Scheme 1.19).

Scheme 1.19

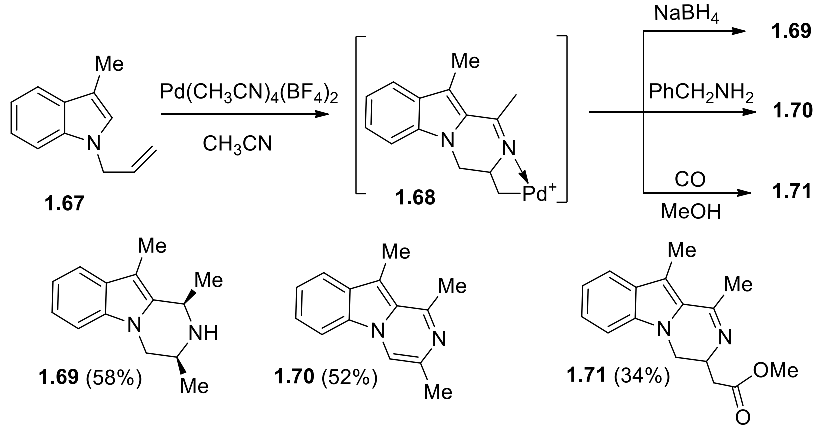


1.3 Palladium-catalyzed nitrile insertion reactions

Nitriles are broadly available, inexpensive and could serve as valuable precursors in insertion reactions. The nitrile group has been considered as inert to organopalladium reagents for a long time. Acetonitrile is one of the most common solvents in palladium catalyzed reactions.[27] To the best of our knowledge, there is hardly any report on nitrile insertion directly into the cyclic structure, however there are reports of nitrile group insertion or involvement in metal catalyzed reactions leading to other functional groups. Some of these are described below.

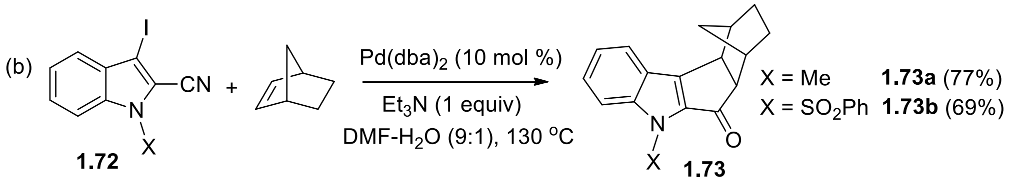
In the year 1986, Asada *et al* reported the attack of nitriles on olefins by palladium catalyzed reaction.[28] To our knowledge, it is the first report on palladium catalyzed nitrile insertion reaction. Here, reaction of *N*-allylskatole **1.67** with stoichiometric amount of [Pd(CH_3CN)$_4$(BF_4)$_2$] in acetonitrile led to the formation of the relatively stable palladium complex **1.68** (Scheme 1.20).[28] This complex on reduction with $NaBH_4$ gave 1,2,3,4-tetrahydropyrazino[1,2-a]indole **1.69** in 58% yield. Treatment of complex **1.68** with an excess of benzylamine resulted in *β*-hydride elimination and rearrangement to give pyrazinoindole **1.70** in 52% yield. Carbon monoxide (CO) also reacted with the complex **1.68** in methanol and furnished the ester **1.71**, albeit in low yield.

Scheme 1.20



Larock *et al* reported an efficient method for the synthesis of 2,3-diarylindenones and polycyclic aromatic ketones by the palladium-catalyzed annulation of alkynes and bicyclic alkenes with 2-iodoarenenitriles.[29] This protocol is compatible with various functional groups and produces the ketones in good to excellent yields. Annulation of *N*-protected-3-iodo-indole-2-carbonitrile **1.72** with norbornene in the presence of palladium bis(dibenzylideneacetone) and Et_3N in DMF-H_2O (9:1) solvent mixture to afford the corresponding ketones **1.73a-b** in good yields was also successfully carried out (Scheme 1.21). Unprotected 3-iodo-indole-2-carbonitrile failed to produce the annulated product; instead, 2-cyanoindole was obtained as the major product.

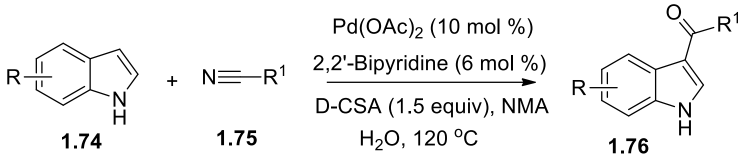
Scheme 1.21



X = Me **1.73a** (77%)
X = SO$_2$Ph **1.73b** (69%)

Wang *et al* demonstrated the palladium-catalyzed 3-acylation of N-H-free indoles with nitriles as the acylating source.[30a] Thus free (NH) indoles **1.74** reacted with aryl or alkyl nitriles **1.75** in the presence of Pd(OAc)$_2$, 2,2'-bipyridine and D-(+)-camphorsulfonic acid (D-CSA) in NMA affording the corresponding 3-acylated indoles **1.76a-f** in good to excellent yields (Scheme 1.22).

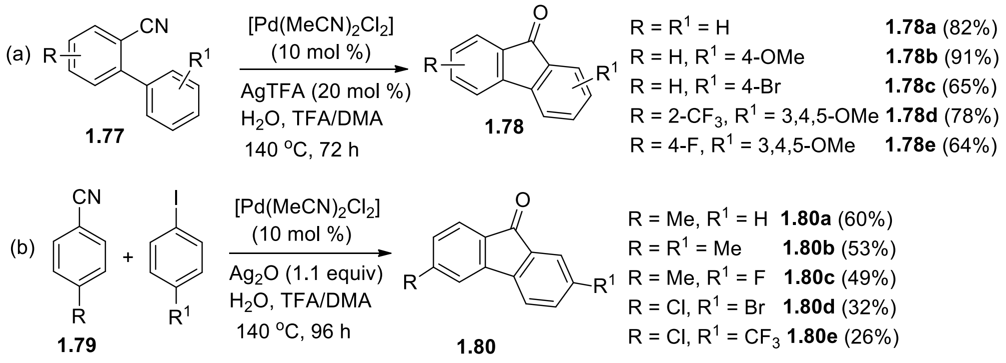
Scheme 1.22



R = H, R^1 = Ph	**1.76a** (74%)
R = H, R^1 = 4-Me-C$_6$H$_4$	**1.76b** (75%)
R = H, R^1 = 4-Cl-C$_6$H$_4$	**1.76c** (90%)
R = H, R^1 = 4-NO$_2$-C$_6$H$_4$	**1.76d** (80%)
R = 5-OMe, R^1 = 4-Cl-C$_6$H$_4$	**1.76e** (77%)
R = H, R^1 = Me	**1.76f** (95%)

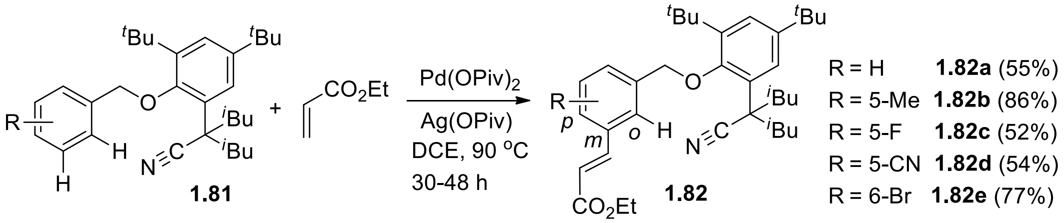
Hsieh and his co-workers reported a palladium-catalyzed nitrile insertion reaction *via* C-H and dual C-H bond activation for the synthesis of fluorenones.[31] This palladium-catalyzed nitrile insertion was successfully applied to various substituted 2-phenyl benzonitriles **1.77** affording the corresponding fluorenones **1.78a-e** in good yields as shown in Scheme 1.23a. The same protocol (with slight modification of silver source and ratio of reagents) was applied to obtain fluorenones *via* dual C-H activation by intermolecular reaction of nitriles with iodobenzenes. Thus, reactions of *para*-substituted benzonitriles **1.79** with *para*-substituted iodobenzenes under the same conditions, but excluding AgTFA, furnished the fluorenones **1.80** in moderate yields (Scheme 1.23b).

Scheme 1.23



Nitriles are also used as end-on templates in metal catalyzed selective C-H functionalization reactions. An important report by Yu *et al* is shown in the Scheme 1.24.[32] Here, the activation of remote *meta*-C-H bonds of arene substrates is accomplished with excellent selectivity by using olefins and directed by nitrile as end-on template. They successfully applied the *meta* selective olefination on a variety of substituted arenes **1.81** by taking ethyl acrylate as the olefin substrate in the presence of Pd(OPiv)$_2$ and Ag(OPiv) in DCE to obtain the meta olefinated products **1.82a-e** in good yields and excellent selectivity regardless of the electronic properties of the substituents (Scheme 1.24).

Scheme 1.24



1.4 Palladium-catalyzed synthesis of pyrroloindolones

Efforts towards the application of the indole C–H functionalization providing multifunctionalized *N*-fused indole cores have been rare. Among various indole fused heterocycles, pyrroloindolone **1.83** (a tricyclic skeleton, Fig. 1) is an important structural motif that is still widely studied because of its promising biological role including anticancer, antitumor, antifungal and antibacterial activities.[33] These compounds have been established as high affinity ligands for the melatonin MT3 binding sites (e.g. **1.84**, Fig. 1),[33a,b] as anti-tumor agents (compound **1.85**),[33c,d] as agents having serotonin receptor affinity (compound **1.86**),[34] as synthetic intermediates *en route* to bacterial NorA pump inhibitors,[35] or as conformationally-restricted model compounds for structure activity exploration.[36] Compounds **1.84-1.86** show DNA binding abilities and more importantly, antiproliferative effects against HT29 and L1210 leukemia cells.[33c,d] Selected recent routes to the pyrroloindolone skeleton **1.83** are discussed below.

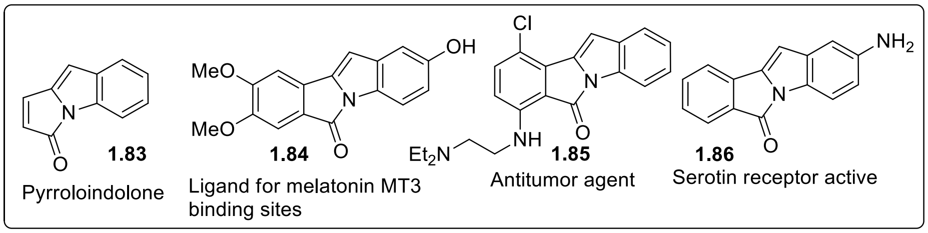
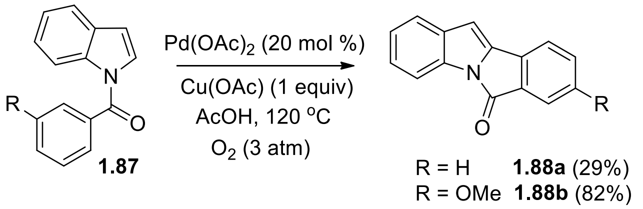


Fig. 1. Examples of pharmaceutically important pyrroloindolone motifs (**1.83-1.86**)

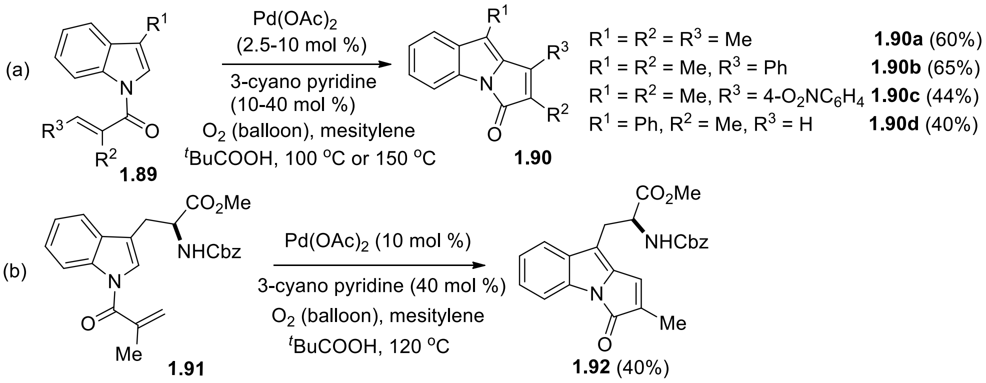
DeBoef *et al* reported a C-C bond formation reaction *via* double C-H functionalization by palladium-catalyzed oxidative coupling reaction for the synthesis of pyrroloindolones.[37] Thus the intramolecular oxidative coupling reaction of *N*-benzoyl indole **1.87** in the presence of $Pd(OAc)_2$, CuOAc and AcOH afforded the pyrroloindolones **1.88a-b** (Scheme 1.25). In this report, they focused mainly on aerobic oxidative coupling of benzofurans with benzene derivatives. They synthesized only two pyrroloindolone compounds; compound **1.88a** was obtained in very low yield (29%) but an electron-donating group present on tethered arene increased the yield of pyrroloindolone (**1.88b**) to 82%.

Scheme 1.25



A series of indole precursors **1.89** were cyclized in presence catalytic Pd(OAc)$_2$ with 3-cyanopyridine as the ligand and ^{t}BuCOOH in mesitylene solvent to obtain the corresponding 1,2,9-trisubstituted 3*H*-pyrrolo[1,2-a]indole-3-ones **1.90a-d** *via* 5-*endo-trig* cyclization as reported by Oestreich *et al* (Scheme 1.26a).[38] They also examined the standard protocol to aerobic *endo* cyclization for the tryptophan derived precursor **1.91** to obtain the pyrroloindolone **1.92** (Scheme 1.26b). This method allows the C-H bond alkenylation of indoles with complete diastereo-control of the substituted double bonds when compared to the [Pd]-catalyzed C2-alkenylation of indoles with disubstituted alkenes (*vide supra*, Scheme 1.8), as they are often not completely diastereoselcetive.[15]

Scheme 1.26

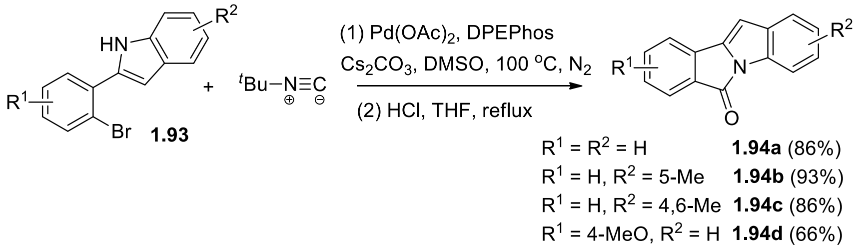


1.89 **1.90** **1.91** **1.92** (40%)

R^1 = R^2 = R^3 = Me **1.90a** (60%)
R^1 = R^2 = Me, R^3 = Ph **1.90b** (65%)
R^1 = R^2 = Me, R^3 = 4-O$_2$NC$_6$H$_4$ **1.90c** (44%)
R^1 = Ph, R^2 = Me, R^3 = H **1.90d** (40%)

Recently, Zhu *et al* reported the synthesis of 6H-isoindolo[2,1-a]indol-6-ones by palladium-catalyzed isocyanide insertion.[39] Thus treatment of 2-(2-bromophenyl)-1*H*-indole precursors **1.93** with *tert*-butyl isocyanide in the presence of Pd(OAc)$_2$, DPEPhos and Cs$_2$CO$_3$ in DMSO resulted in the *N*-(6*H*-isoindolo[2,1-a]indol-6-ylidene)-2-methylpropan-2-amine which upon acid hydrolysis afforded the corresponding 6H-isoindolo[2,1-a]indol-6-ones **1.94a-d** in good to excellent yields (Scheme 1.27).

Scheme 1.27

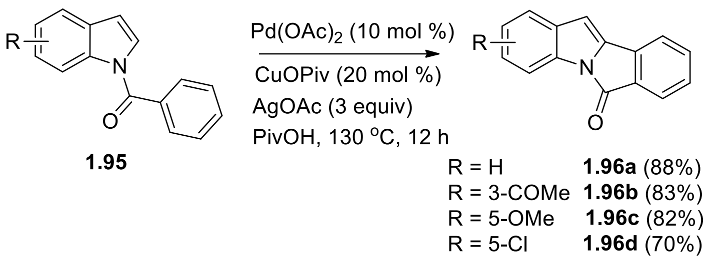


1.93

R^1 = R^2 = H **1.94a** (86%)
R^1 = H, R^2 = 5-Me **1.94b** (93%)
R^1 = H, R^2 = 4,6-Me **1.94c** (86%)
R^1 = 4-MeO, R^2 = H **1.94d** (66%)

In a more recent report, Laha *et al* described the synthesis of 6-oxo-isoindolo[2,1-*a*]indoles **1.96a-d** by palladium-catalyzed intramolecular oxidative coupling of *N*-benzoyl indoles **1.95** (Scheme 1.28).[40] This method could overcome some disadvantages of DeBoef's protocol (depicted in Scheme 1.25) which include high catalyst loading, poor substrate scope and lower yields.

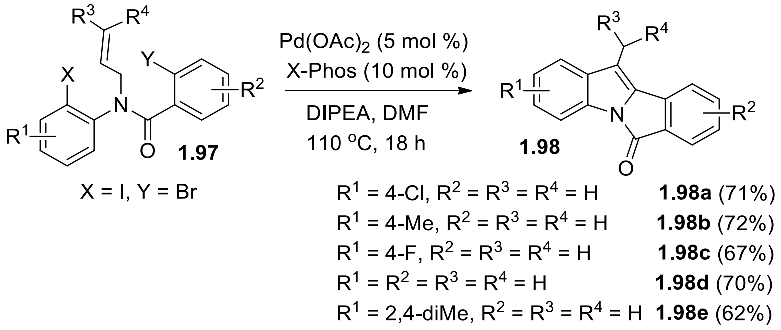
Scheme 1.28



R = H **1.96a** (88%)
R = 3-COMe **1.96b** (83%)
R = 5-OMe **1.96c** (82%)
R = 5-Cl **1.96d** (70%)

Another protocol for the synthesis of pyrroloindolones was recently achieved by Manojit Pal and co-workers.[41] This method involves palladium-mediated single-step synthesis of 11-substituted 6*H*-isoindolo[2,1-*a*]indol-6-ones **1.98a-e** *via* a sequential Heck reaction of the corresponding dihalo-*N*-allyl substituted *N*-arylbenzamides **1.97** (Scheme 1.29). Some of these compounds showed promising antiproliferative properties when tested against a number of cancer cell lines *in vitro* showing usefulness of this class of compounds for potential medicinal applications.

Scheme 1.29



R^1 = 4-Cl, $R^2 = R^3 = R^4$ = H **1.98a** (71%)
R^1 = 4-Me, $R^2 = R^3 = R^4$ = H **1.98b** (72%)
R^1 = 4-F, $R^2 = R^3 = R^4$ = H **1.98c** (67%)
$R^1 = R^2 = R^3 = R^4$ = H **1.98d** (70%)
R^1 = 2,4-diMe, $R^2 = R^3 = R^4$ = H **1.98e** (62%)

1.5 Synthetic routes to β-carbolinones

β-Carbolinone (9*H*-pyrido[3,4-*b*]indol-1(2*H*)-one) moiety is found in several natural products and many of these were reported to exhibit significant pharmacological activities.[42] β-Carbolinone is also an important intermediate for the synthesis of alkaloids such as shishijimicin A, manzamine A, pauridianthine, pauridianthinine and nitramarine.[43] Selected examples of pharmaceutically important β-carbolinone motifs (**1.99-1.102**) are shown in Figure 2.

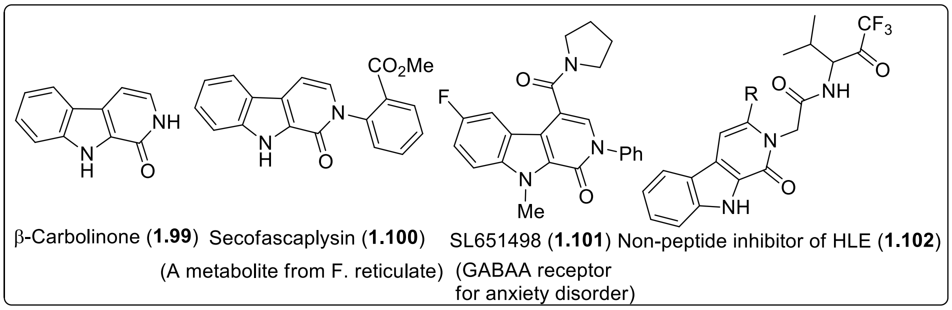
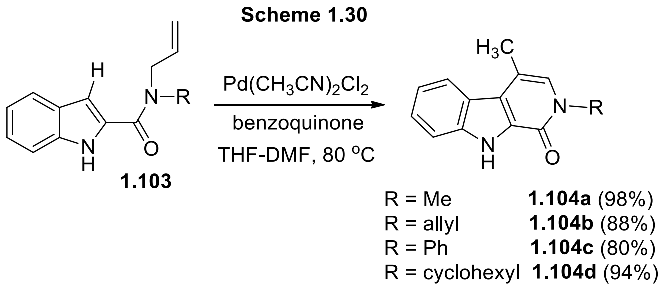


Fig. 2. Examples of pharmaceutically important β-carbolinone motifs (**1.99-1.102**).

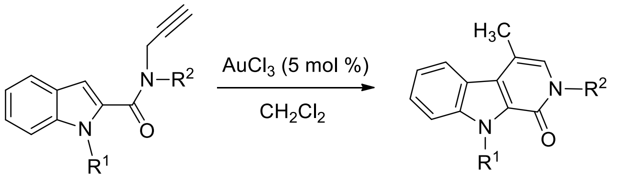
Zoni *et al* reported the synthesis of β-carbolinones by palladium-catalyzed intramolecular Heck reaction using *N*-Allyl-*N*-alkyl-1*H*-indole-2-carboxamides as precursors.[44] Thus treatment of indole-2-carboxamides **1.103** in the presence of $Pd(CH_3CN)_2Cl_2$ as the catalyst and benzoquinone as oxidant in THF-DMF solvent mixture afforded the corresponding β-carbolinones **1.104a-d** in excellent yields (Scheme 1.30). However, the method was limited to only four β-carbolinone derivatives with *N*-Me, *N*-allyl, *N*-phenyl and *N*-cyclohexyl substituents.



Padwa and England reported gold catalyzed cycloisomerization of *N*-propargyl-indole-2-carboxamides **1.105** for the synthesis of β-carbolinones **1.106a-d** (Scheme

1.31).[45] Later, they investigated the application of this gold catalyzed cycloisomerization for the synthesis of Lavendamycin analogue, a potent antitumor antibiotic. Jio and co-workers have synthesized β-carbolinones by palladium-catalyzed annulation of indolecarboxamides (cf. section 1.2.4 and Scheme 1.12).[18b]

Scheme 1.31

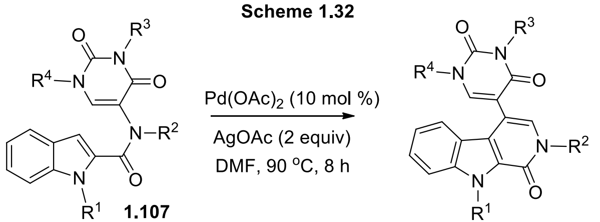


1.105

R^1 = Me, R^2 = Ts **1.106a** (85%)
R^1 = Bn, R^2 = Me **1.106b** (87%)
R^1 = Bn, R^2 = Ac **1.106c** (78%)
R^1 = Me, R^2 = BOC **1.106d** (60%)

Very recently, Brindaban Roy *et al* reported an expedient synthesis of uracil-annulated β-carbolinones by the palladium-catalyzed dehydrogenative C-H activation.[46] The *N*-uracil-indole-2-carboxamides **1.107** were heated in the presence of Pd(OAc)$_2$ and AgOAc in DMF to afford the corresponding uracil annulated β-carbolinones **1.108a-d** in excellent yields of 85–92% (Scheme 1.32). No steric influence was observed when the indole-*N*-methyl group was replaced by ethyl, butyl or benzyl group. However, the reaction was not successful with the unsubstituted indole precursor.

Scheme 1.32



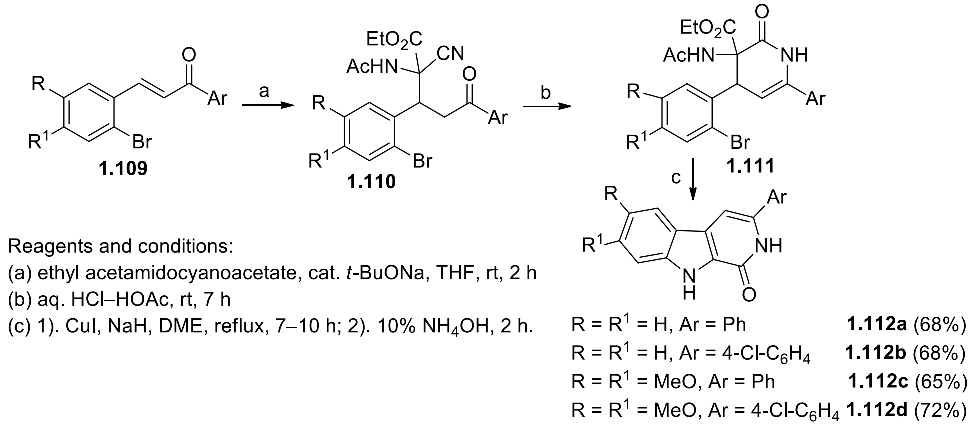
1.107

R^1 = R^2 = R^3 = R^4 = Me **1.108a** (91%)
R^1 = R^2 = Me, R^3 = R^4 = Et **1.108b** (90%)
R^1 = *n*-Bu, R^2 = Me, R^3 = R^4 = Et **1.108c** (90%)
R^1 = Bn, R^2 = R^3 = R^4 = Et **1.108d** (85%)

Hu *et al* reported a three step synthetic route for 3-aryl-β-carbolinones by copper-catalyzed *N*-arylation.[47] This expedient route starts with Michael addition of ethyl acetamidocyanoacetate to chalcone **1.109** in the presence of catalytic amount of ^{t}BuONa in THF to afford compound **1.110** with introduction of two nitrogen atoms.

Then compound **1.110** undergoes intramolecular ketone-nitrile annulation in the presence of aq. HCl-AcOH at room temperature to give dihydropyridone **1.111**. Finally, Cu(I) catalyzed intramolecular *N*-arylation of amide **1.111** in the presence NaH in DME followed by hydrolysis leads to the formation of 3-aryl-β-carbolinones **1.112a-d** in good yields (Scheme 1.33).

Scheme 1.33

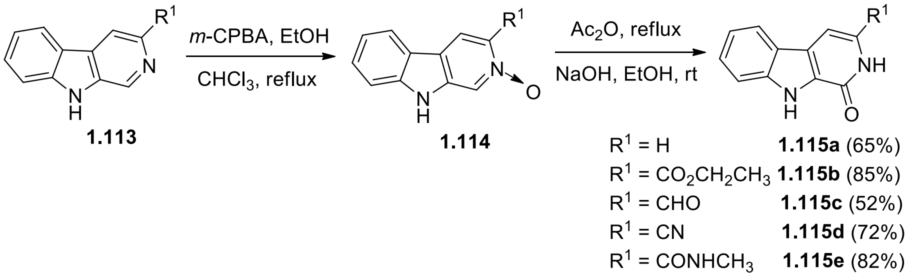


Reagents and conditions:
(a) ethyl acetamidocyanoacetate, cat. *t*-BuONa, THF, rt, 2 h
(b) aq. HCl–HOAc, rt, 7 h
(c) 1). CuI, NaH, DME, reflux, 7–10 h; 2). 10% NH_4OH, 2 h.

R = R^1 = H, Ar = Ph **1.112a** (68%)
R = R^1 = H, Ar = 4-Cl-C_6H_4 **1.112b** (68%)
R = R^1 = MeO, Ar = Ph **1.112c** (65%)
R = R^1 = MeO, Ar = 4-Cl-C_6H_4 **1.112d** (72%)

Lu *et al* reported a two-step synthesis of 3-substituted β-carbolinones from 3-substituted β-carbolines (Scheme 1.34).[48] Initially, β-carbolines **1.113** were treated 3-chloro-peroxybenzoic acid (*m*-CPBA) giving the corresponding *N*-oxides **1.114**. The second step involved formation of β-carbolinones **1.115a-e** by regioselective rearrangement of β-carboline-*N*-oxides **1.113** in refluxing acetic anhydride and subsequent hydrolysis. This protocol provided a facile way to introduce various electron-withdrawing or electron-rich substituents into β-carbolinones at the 3-position.

Scheme 1.34

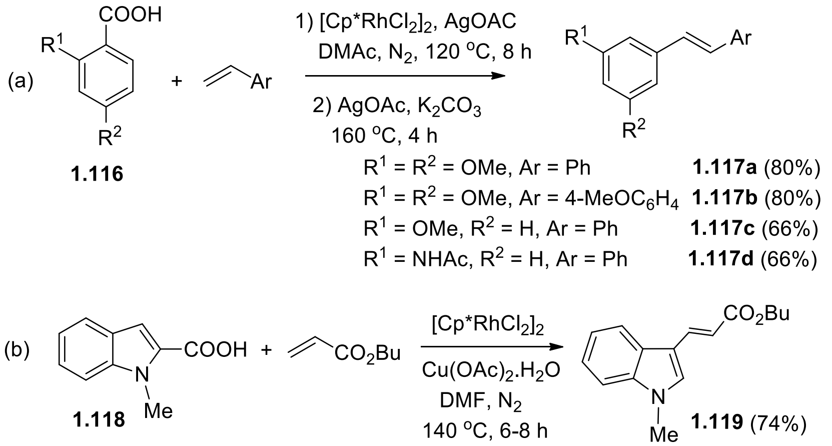


R^1 = H **1.115a** (65%)
R^1 = $CO_2CH_2CH_3$ **1.115b** (85%)
R^1 = CHO **1.115c** (52%)
R^1 = CN **1.115d** (72%)
R^1 = $CONHCH_3$ **1.115e** (82%)

1.6 Carboxyl moiety as a traceless directing group in transition-metal-catalyzed C-H functionalization

The concept of removable directing groups (also named traceless directing groups) has been developed recently for direct C-H functionalization.[49] By using Ru, Pd, Rh and Ir catalysts, the traceless directing group strategy has been implemented for the C-H arylation, acyloxylation, borylation, silylation, and halogenation of arenes. It is important to exploit traceless directing group strategy for C-H functionalization as well as removal of the directing group in a one-pot fashion. An earlier work on this removable directing group strategy was demonstrated by Miura *et al* in palladium-catalyzed regioselective vinylation of indoles by a removable carboxyl group (cf. section 1.3.1 and Scheme 1.16).[23] They also reported rhodium-catalyzed decarboxylative olefination of benzoic acids and heteroaromatic carboxylic acids with styrenes, directed by removable carboxyl group. They observed that initial treatment of benzoic acids **1.116** with styrenes in the presence of $[Cp^*RhCl_2]_2$ and AgOAc in DMA solvent led to the formation of olefinated product without the loss of COOH group. The acid group was removed by adding AgOAc and K_2CO_3 in the same pot resulting in the decarboxylated olefination products **1.117a-d** in moderate to good yields (Scheme 1.35a).[50] Hetero-arene carboxylic acids tend to undergo decarboxylation more readily than benzoic acids. With this in mind, hetero arene-2-carboxylic acids of pyrrole, furan, thiophene, benzofuran, benzothiophene were decarboxylated successfully affording 3-olefinated products. Thus indole-2-carboxylic acid **1.118** on reaction with butyl acrylate in the presence of $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2$ in DMF provided 3-alkenylated indole **1.119** in 74% yield (Scheme 1.35b).[50]

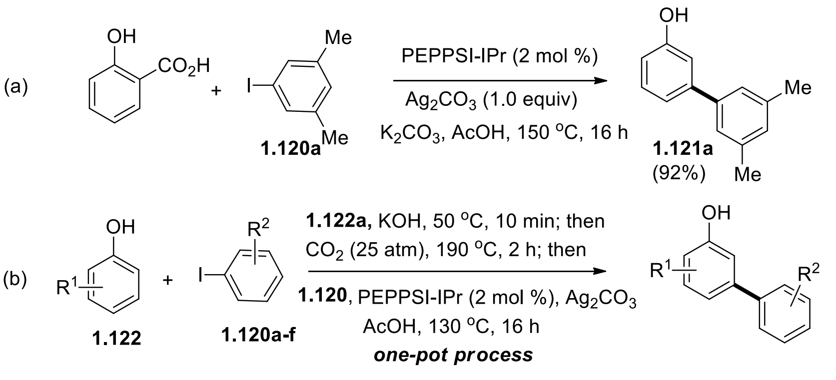
Scheme 1.35



$R^1 = R^2 =$ OMe, Ar = Ph **1.117a** (80%)
$R^1 = R^2 =$ OMe, Ar = 4-MeOC_6H_4 **1.117b** (80%)
$R^1 =$ OMe, $R^2 =$ H, Ar = Ph **1.117c** (66%)
$R^1 =$ NHAc, $R^2 =$ H, Ar = Ph **1.117d** (66%)

Recently, Larrosa *et al* reported palladium-catalyzed *meta*-selective arylation of phenols *via* a traceless directing group relay strategy. Initially, they demonstrated tandem arylation/decarboxylation process by treating salicylic acid with 3,5-dimethyl iodobenzene **1.120a** in the presence of PEPPSI-IPr ([1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride) as the catalyst and Ag_2CO_3 as the oxidant with K_2CO_3 as an additive in AcOH affording the meta-arylated phenol **1.121a** in 92% yield (Scheme 1.36a).[51] In order to develop a truly simple process, phenols were converted *in situ* to salicylic acids with KOH/ CO_2. Then arylation with Pd-catalyst/ Ag_2CO_3 / AcOH allowed the direct formation of meta-arylated phenols **1.121a-f** in moderate to good yields (Scheme 1.36b).[51]

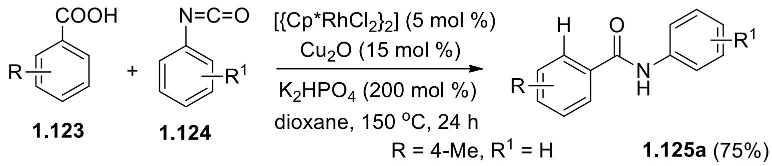
Scheme 1.36



$R^1 =$ H, $R^2 =$ 3,5-diMe **1.121a** (65%)
$R^1 =$ H, $R^2 =$ 4-Ph **1.121b** (56%)
$R^1 =$ H, $R^2 =$ 4-NO_2 **1.121c** (54%)
$R^1 =$ H, $R^2 =$ 4-CH_2OAc **1.121d** (59%)
$R^1 =$ 3-OCF_3, $R^2 =$ 3,5-diMe **1.121e** (69%)
$R^1 =$ 3-Me, $R^2 =$ 3,5-diMe **1.121f** (75%)

Recently, Li and co-workers reported rhodium-catalyzed synthesis of *N*-aryl benzamides from benzoic acids by *o*-amidation and decarboxylation *via* traceless directing group approach.[52] Treatment of substituted benzoic acids **1.123** with substituted isocyanates **1.124** in the presence of [Cp*RhCl$_2$]$_2$, Cu$_2$O and K$_2$HPO$_4$ in dioxane afforded *N*-aryl benzamides **1.125a-e** in good yields (Scheme 1.37). Compared to the *ortho*-substituted benzoic acids, *para*-substituted benzoic acids were more readily converted to the corresponding amides in high yields. Thus *meta*-substituted *N*-aryl benzamides were readily obtained from *para*- or *ortho*-substituted benzoic acids by this protocol.

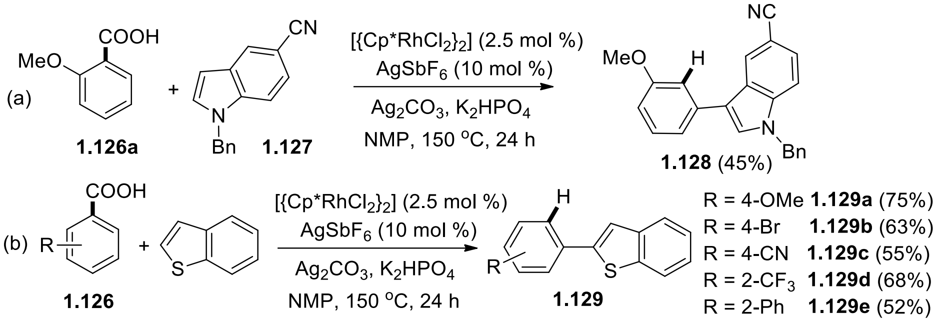
Scheme 1.37



R = 4-Me, R^1 = H **1.125a** (75%)
R = 4-Cl, R^1 = H **1.125b** (57%)
R = 3,4,5-tri OMe, R^1 = H **1.125c** (67%)
R = 2,4-di Me, R^1 = 3-Me **1.125d** (74%)
R = 2,4-di Me, R^1 = 4-Cl **1.125e** (63%)

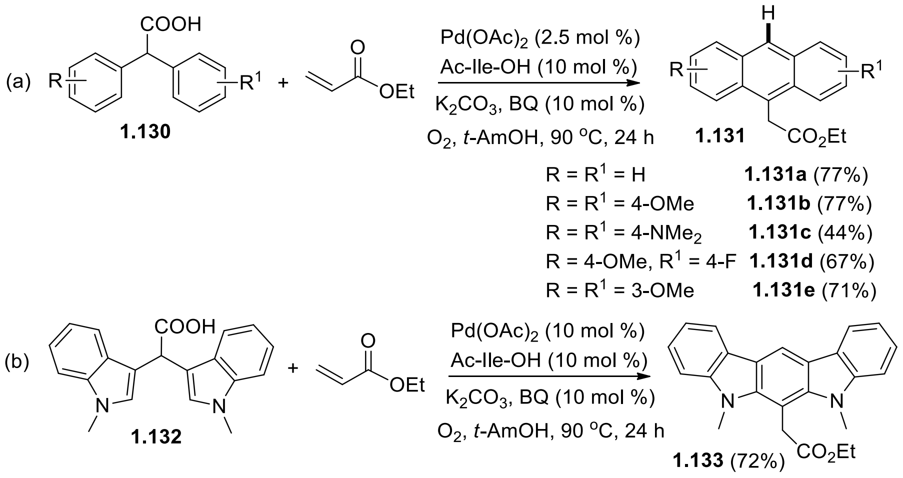
You *et al* developed a rhodium-catalyzed *ortho*-heteroarylation of aromatic carboxylic acids with various hetero-arenes by using carboxylic acid as a traceless directing group. Reaction of 2-methoxy benzoic acid **1.126a** with the indole **1.127** in the presence of [Cp*RhCl$_2$]$_2$, AgSbF$_6$, Ag$_2$CO$_3$ and K$_2$HPO$_4$ in NMP led to the formation of *ortho*-heteroarylated product **1.128** in 45% yield (Scheme 1.38a).[53] Other electron-rich heteroarenes such as furans, thiophenes, azoles, xanthines, and indolizines also reacted with 2-methoxybenzoic acid to produce the *meta*-heteroarylated products in moderate to good yields. The authors also examined the scope of aromatic carboxylic acids. The *ortho*- or *para*-substituted benzoic acids **1.126** were successfully coupled with benzothiophene under the optimized conditions affording the *meta*-hetero arylated products **1.129a-e** in good yields (Scheme 1.38b).

Scheme 1.38



Very recently, Hong *et al* reported the tandem synthesis of acenes *via* palladium-catalyzed traceless directing group approach.[54] Various anthracene derivatives **1.131a-e** were synthesized in good yields by the treatment of diphenyl carboxylic acids **1.130** with ethyl acrylate in the presence of Pd(OAc)$_2$, (2S,3S)-2-acetamido-3-methylpentanoic acid (Ac-Ile-OH), K$_2$CO$_3$, and benzoquinone at 1 atm of O$_2$ as the oxidant in *t*-AmOH (Scheme 1.39a). A range of electron-donating and electron-withdrawing groups were tolerated under this protocol. This strategy was also expanded to polycenes (tetracene, pentacene etc) and hetero arenes fused to the benzenoid ring. Thus diindole carboxylic acid **1.132** was successfully converted to the corresponding diindole fused benzenoid ring derivative **1.133** in 72% yield (Scheme 1.39b) *via* decarboxylative coupling with ethyl acrylate under the optimized conditions.

Scheme 1.39

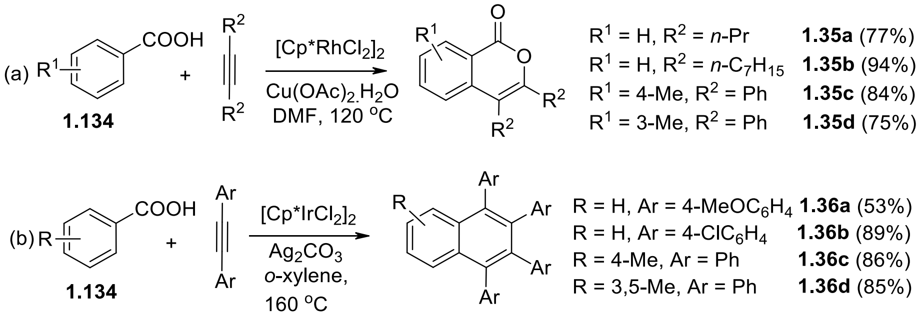


1.7 Transition metal catalyzed annulation reactions with alkynes *via* C-H bond functionalization

Transition metal catalyzed annulation reactions with alkynes that lead to the formation of heterocycles such as indoles, quinolones, isoquinolones etc. discovered by various groups *via* directing group assisted approach will be discussed in this section. Functional groups that include imine, anilide, amide, ester, heterocyclic, amine, carboxylic acid, ketone, and hydroxyl have been employed as directing groups for catalytic C–H bond functionalization.[55] The fundamental step involved in this C-H bond process is assumed to be the coordination of directing groups with transition metals.

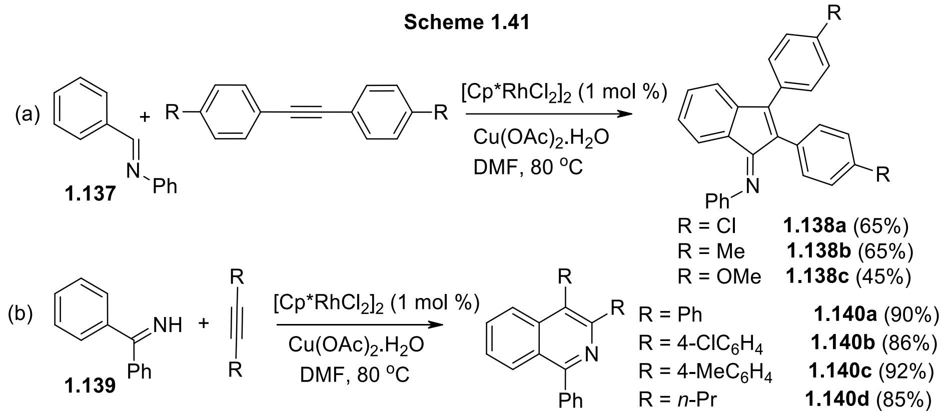
Miura *et al* reported the oxidative annulation of benzoic acids with alkynes in the presence of $[Cp^*RhCl_2]_2$ as a catalyst and $Cu(OAc)_2{\cdot}H_2O$ as an oxidant in DMF that led to the formation of isocoumarins **1.135a-d** in excellent yields (Scheme 1.40a).[56] The reaction protocol is compatible with both aliphatic and aromatic alkynes. Notably, $[Cp^*IrCl_2]_2$ as the catalyst and Ag_2CO_3 as the oxidant led to the formation of 1:2 coupled naphthalenes **1.136a-d** by dehydrogenation and decarboxylation (Scheme 1.40b).

Scheme 1.40



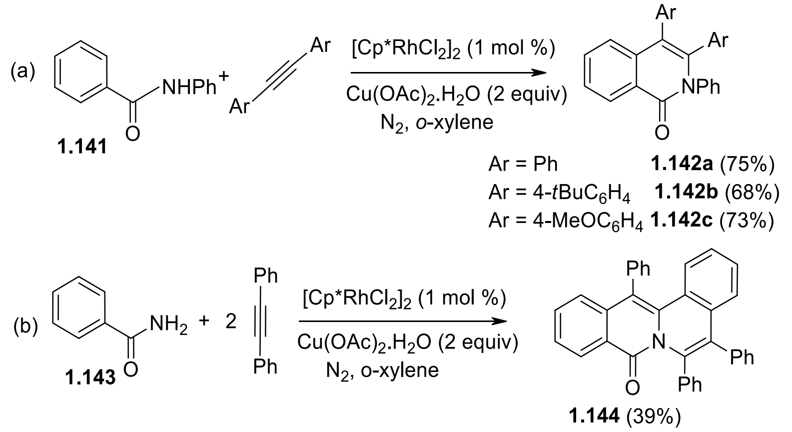
Later, the same group of Miura reported rhodium-catalyzed oxidative coupling of aromatic imines with alkynes *via* regio-selective C-H bond cleavage. Thus the reaction of benzylideneaniline **1.137** or benzophenone imine **1.139** with internal alkynes in the presence of $[Cp^*RhCl_2]_2$ as the catalyst and $Cu(OAc)_2{\cdot}H_2O$ as an oxidant led to the formation of indenone imine (**1.138**) and isoquinoline (**1.140**) derivatives, respectively (Scheme 1.41).[57] But the reaction using terminal alkyne (1-phenyl acetylene) led to the formation of only the alkyne dimer, diphenylbutadiyne.

Scheme 1.41



Benzamides also undergo oxidative coupling with alkynes and form isoquinolone derivatives.[58] Thus, the rhodium catalyzed reaction of *N*-monosubstituted benzamide **1.141`** with diarylacetylenes resulted in the formation of isoquinolones **1.142a-c** in good yields (Scheme 1.42a). Under similar optimized conditions, benzamide **1.143** underwent 1:2 coupling with alkynes to afford tetracyclic dibenzoquinolizinone **1.144** (Scheme 1.42b).

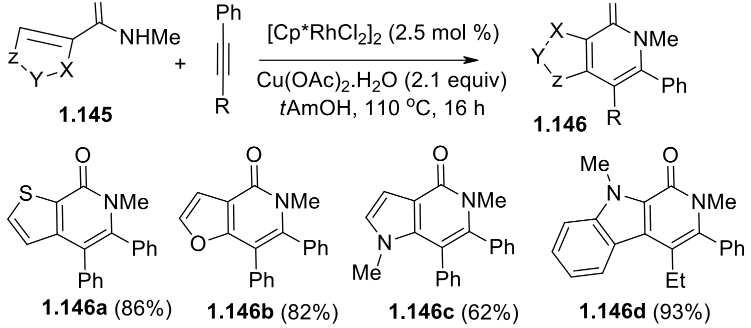
Scheme 1.42



Rovis *et al* reported rhodium-catalyzed synthesis of isoquinolones by oxidative annulation of benzamides with alkynes *via* C-H/N-H bond activation.[59] Various benzamides and alkynes were utilized for the synthesis of isoquinolones in the presence of rhodium complex $[Cp^*RhCl_2]_2$, $Cu(OAc)_2.H_2O$ in *t*-AmOH solvent (Scheme 1.43).

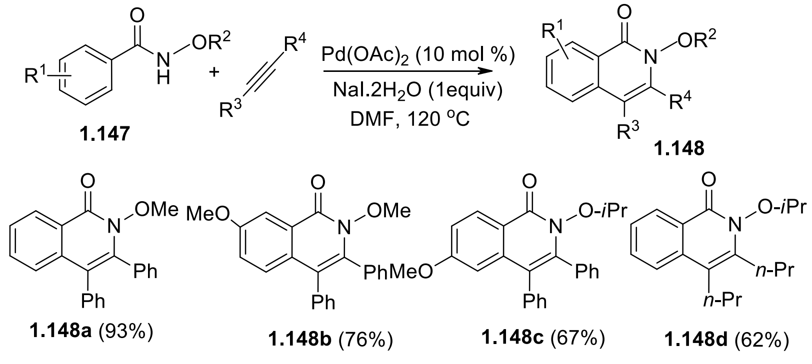
The reaction has good functional group compatibility. Heteroaryl substituted carboxamides **1.145** also successfully coupled with alkynes furnishing the corresponding products **1.146a-d** in excellent yields.

Scheme 1.43



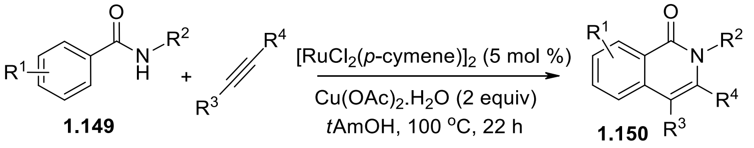
Huang *et al* developed the first palladium-catalyzed process for isoquinolones **1.148a-d** from *N*-alkoxybenzamides **1.147** and alkynes *via* C-H bond and N-H bond double activation in the presence of Pd(OAc)$_2$ and NaI.2H$_2$O in DMF (Scheme 1.44).[60] High regio-selectivity was achieved in the case of unsymmetrical alkynes. An one-pot synthesis of *N*-H isoquinolones was also achieved by using NaH through dealkoxylation. Very recently, Li and Wang developed a protocol for the synthesis of isoquinolones from benzamides and alkynes under ligand-free conditions using Pd/C as a heterogeneous catalytic system.[61]

Scheme 1.44



Pioneering work by Ackermann *et al* disclosed that less expensive ruthenium complex can also catalyze the annulation reactions of benzamides with alkynes.[62] Thus the reaction of *N*-substituted benzamides **1.149** with internal alkynes in the presence of $[RuCl_2(p\text{-cymene})]_2$ with $Cu(OAc)_2{\cdot}H_2O$ as an oxidant afforded isoquinolones **1.150a-c** with good substrate scope (Scheme 1.45). The reaction worked well with both symmetrical and unsymmetrical alkynes, and in the case of unsymmetrical alkynes, high regioselectivity was achieved. The same group discovered a green protocol for the synthesis of isoquinolones from *N*-methoxybenzamides in water.[63a] In this protocol, carboxylate salts were used as additives along with the ruthenium complex. The green protocol was viable with free hydroxamic acids also. Li *et al* also reported the synthesis of isoquinolones using *N*-methoxybenzamides under mild reaction conditions in the presence of ruthenium catalyst without any external oxidant.[63b]

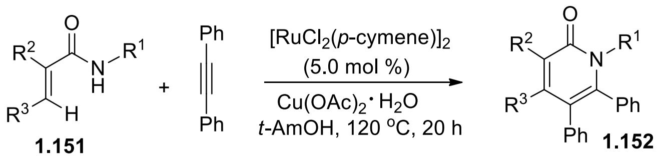
Scheme 1.45



R^1 = 4-Cl, R^2 = Me, R^3 = R^4 = Ph **1.150a** (78%)
R^1 = H, R^2 = Me, R^3 = R^4 = cyclopropyl **1.150b** (83%)
R^1 = H, R^2 = Me, R^3 = cyclopropyl, R^4 = Ph **1.150c** (71%)

Ackermann *et al* demonstrated that the reaction of acrylamides **1.151** with alkynes in the presence of $[RuCl_2(p\text{-cymene})]_2$ with $Cu(OAc)_2{\cdot}H_2O$ as an oxidant afforded the corresponding 2-pyridones **1.152a-d** (Scheme 1.46).[64] This inexpensive ruthenium catalyst has shown good chemo- and regio-selectivity with good substrate scope when compared to the rhodium catalyst.

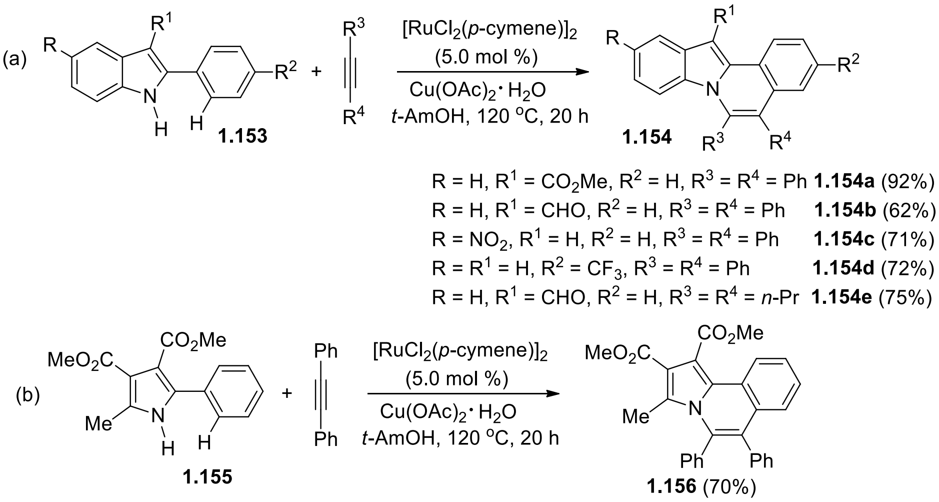
Scheme 1.46



R^1 = R^2 = Me, R^3 = H **1.152a** (92%)
R^1 = *n*-Bu, R^2 = Me, R^3 = H **1.152b** (81%)
R^1 = Ph, R^2 = Me, R^3 = H **1.152c** (82%)
R^1 = 4-$O_2NC_6H_4$, R^2 = R^3 = H **1.152d** (76%)

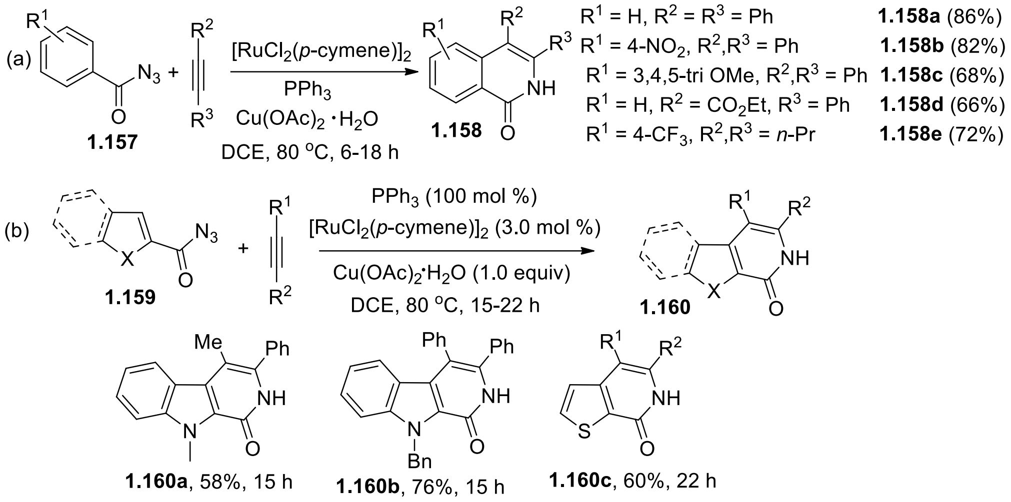
Later, the same group of Ackermann *et al* found that diversely substituted 2-aryl indoles **1.153** can be coupled with diaryl or dialkyl alkynes to obtain indolo[2,1-*a*]isoquinoline **1.154a-e** in good yields (Scheme 1.47a).[65] They also reported that 2-aryl pyrroles **1.155** can be successfully annulated with alkynes under the same optimized conditions to afford pyrrolo[2,1-*a*]isoquinolines **1.156** (Scheme 1.47b) which are indispensable structural units of *inter alia* bioactive lamellarine alkaloids.

Scheme 1.47



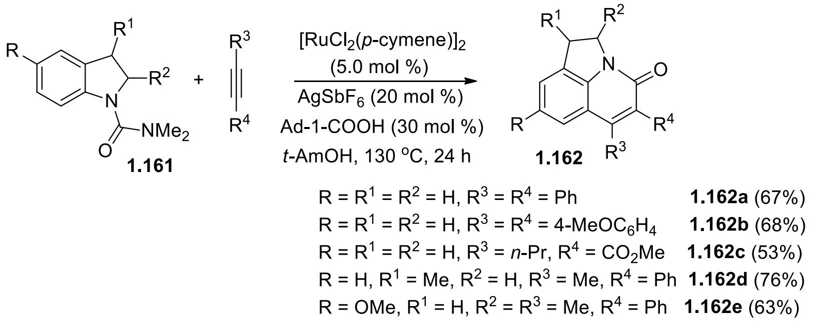
Kundu and co-workers developed a one-pot synthesis of 1-(2H)-isoquinolones by **1.158a-e** ruthenium-catalyzed C-H activation/C-N bond formation involving aryl acyl azides **1.157** and alkynes *via in situ* generated iminophosphoranes as the directing group (Scheme 1.48a).[66] The versatility of this strategy was demonstrated by replacing benzoyl azides with thiophene and indole-based acyl azides **1.159** that furnished the corresponding annulated products **1.160a-c** in moderate to good yields (Scheme 1.48b). The important feature of this protocol is the *in situ* generation of iminophosphorane, which can coordinate to the Ru metal resulting in the *ortho*-cyclometallation, alkyne insertion, protonation and reductive elimination in a domino sequence.

Scheme 1.48



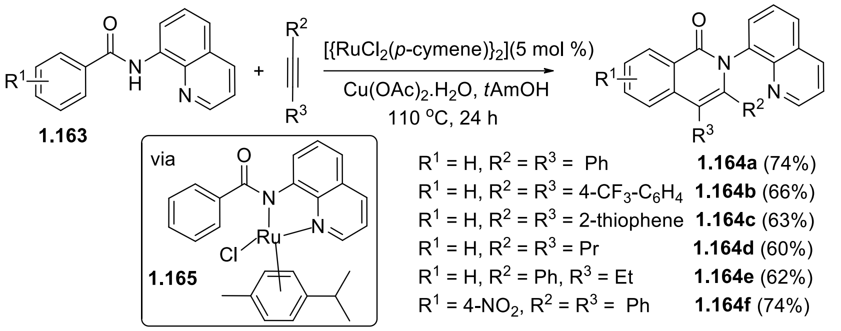
Recently, Jeganmohan *et al* reported that treatment of substituted *N*-carbamoyl indolines **1.161** with symmetrical and unsymmetrical alkynes in the presence of [{RuCl$_2$(*p*-cymene)}$_2$] (5.0 mol %), AgSbF$_6$ (20 mol %) and Ad-1-COOH (30 mol %) in *tert*-amyl alcohol at 130 °C for 24 h led to the formation of pyrroloquinolinones **1.162a-e** in good yields (Scheme 1.49).[67] They also performed the aromatization of pyrroloquinolinones into indole derivatives in the presence of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).

Scheme 1.49



From our laboratory, an efficient method for the synthesis of isoquinolones **1.164a-f** *via* the oxidative annulation of *N*-quinolin-8-yl-benzamides **1.163** with alkynes with the aid of 8-aminoquinoline as bidentate directing group in the presence of [RuCl$_2$(*p*-cymene)]$_2$ and Cu(OAc)$_2$.H$_2$O in open air has been developed (Scheme 1.50).[68a] The reaction features high regioselectivity, good substrate scope, and large functional group tolerance. This method was successfully extended to heterocyclic amides also. A ruthenium *N*-quinolin-8-yl-benzamide complex **1.165** has been isolated and characterized, illustrating the key role played by the quinoline moiety.

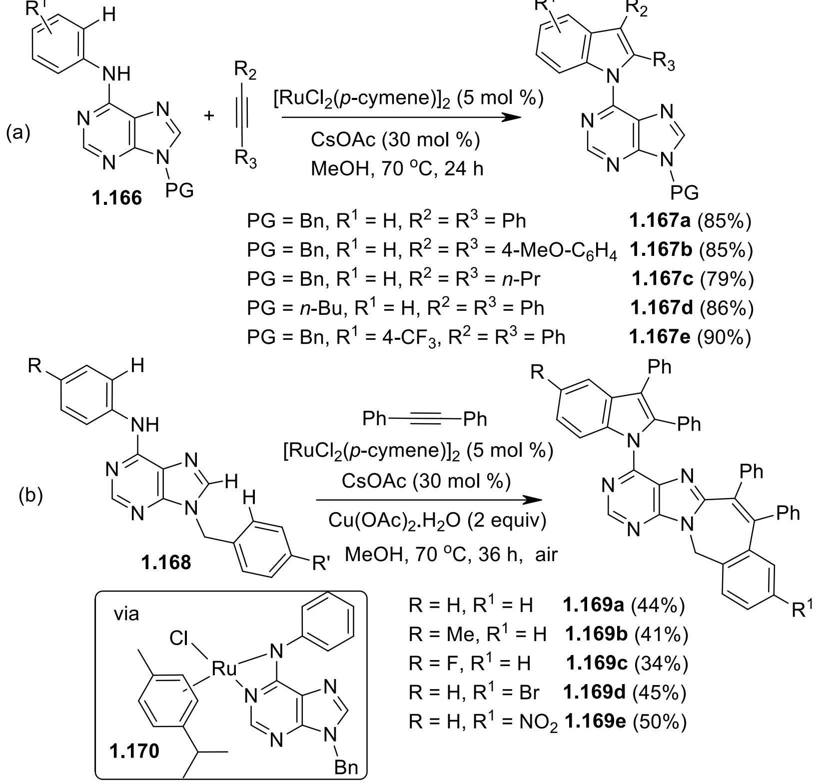
Scheme 1.50



R^1 = H, R^2 = R^3 = Ph **1.164a** (74%)
R^1 = H, R^2 = R^3 = 4-CF_3-C_6H_4 **1.164b** (66%)
R^1 = H, R^2 = R^3 = 2-thiophene **1.164c** (63%)
R^1 = H, R^2 = R^3 = Pr **1.164d** (60%)
R^1 = H, R^2 = Ph, R^3 = Et **1.164e** (62%)
R^1 = 4-NO_2, R^2 = R^3 = Ph **1.164f** (74%)

A new protocol of ruthenium-catalyzed oxidative annulation of 6-anilinopurine nucleobases **1.166** with alkynes *via* C-H activation for the synthesis of a wide range of indole substituted purines **1.167a-e** has also been discovered recently from our laboratory (Scheme 1.51a).[68b] The reaction was conducted by using [RuCl$_2$(*p*-cymene)]$_2$ as the catalyst and CsOAc as an oxidant in MeOH. The reaction is sustainable with purine nucleosides that contain a saccharide moiety. Novel purine C8 fused polycyclics **1.169a-e** formed *via* double C-H activation are also obtained in the presence of Cu(OAc)$_2$·H$_2$O in selected cases involving N(9)-benzyl purine substrates **1.168** (Scheme 1.51b). These products are endowed with fluorescence properties. A ruthenacycle intermediate **1.170** has been isolated and catalytic activity of this complex suggests that purinyl N1 chelates with the metal and directs the reaction.

Scheme 1.51



1.166

1.168

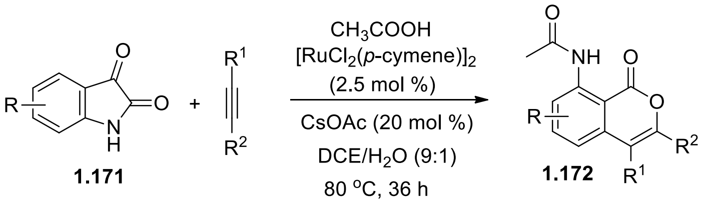
1.170

PG = Bn, R^1 = H, R^2 = R^3 = Ph **1.167a** (85%)
PG = Bn, R^1 = H, R^2 = R^3 = 4-MeO-C_6H_4 **1.167b** (85%)
PG = Bn, R^1 = H, R^2 = R^3 = *n*-Pr **1.167c** (79%)
PG = *n*-Bu, R^1 = H, R^2 = R^3 = Ph **1.167d** (86%)
PG = Bn, R^1 = 4-CF_3, R^2 = R^3 = Ph **1.167e** (90%)

R = H, R^1 = H **1.169a** (44%)
R = Me, R^1 = H **1.169b** (41%)
R = F, R^1 = H **1.169c** (34%)
R = H, R^1 = Br **1.169d** (45%)
R = H, R^1 = NO_2 **1.169e** (50%)

Very recently, Gogoi *et al* exploited the amide C-N bond of isatins as the directing group and as an internal oxidant in ruthenium-catalyzed C-H activation and annulation reaction for the synthesis of 8-amido isocoumarins. They employed various substituted isatins **1.171** along with symmetrical and unsymmetrical diaryl or dialkyl acetylenes in this redox-neutral C-H activation strategy by using inexpensive [{$RuCl_2$(*p*-cymene)}$_2$] catalyst in the presence of CsOAc and CH_3COOH in DCE-H_2O solvent mixture (9:1) that afforded the 8-amido isocoumarins **1.172a-e** in good yields (Scheme 1.52).[69] This oxidative directing group approach offered good functional group tolerance and high regioselectivity with unsymmetrical alkynes.

Scheme 1.52



1.171

1.172

R = H, R^1 = R^2 = Ph **1.172a** (84%)
R = H, R^1 = R^2 = 4-MeC_6H_4 **1.172b** (72%)
R = H, R^1 = R^2 = 4-F-C_6H_4 **1.172c** (65%)
R = H, R^1 = R^2 = *n*-Pr **1.172d** (85%)
R = 5-Cl, R^1 = R^2 = *n*-Pr **1.172e** (66%)

OBJECTIVES OF THE PRESENT WORK

The main aim of the present work was to explore the new C-C and C-N bond forming reactions and synthesis of novel indole and chromene fused nitrogen heterocycles *via* transition metal catalyzed C-H bond activation or functionalization. Specifically, it was envisioned to explore the following:

(i) To synthesize indole fused α-carbolines *via* decarboxylative nitrile insertion from indole-2-carboxylic acids in [Pd]-catalyzed reaction,

(ii) To investigate the reactivity of alkynyl-indole-2-carboxamides in [Pd]-catalyzed C-H activation and in phase transfer catalysis for the formation of pyrrolo diindolones and β-carbolinones,

(iii) To probe [Pd]-catalyzed *ortho*-amidation of indole-3-carboxylic acids with isothiocyanates using carboxyl group as traceless directing group and to investigate the utility of the indole-2-carboxamides in the [Pd]-catalyzed reaction for the formation of diindole fused 2-pyridones and

(iv) To study the reactivity of 2*H*-chromene-3-carboxamides in [Ru]-catalyzed oxidative annulation and/or hydroarylation with alkynes through C-H/N-H bond functionalizations.

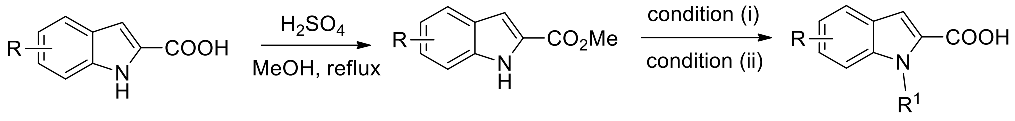
RESULTS AND DISCUSSION

The theme of this work is C-H functionalization. The first few sections (2.1-2.5) deal with the synthesis of the precursors required for this study. After this, synthesis of indolo-carbolines through palladium catalyzed decarboxylative nitrile insertion of indole-2-carboxylic acid as well as formation of triindoles is discussed. In the next section, reactivity 3-alkynyl-indole-2-carboxamides under [Pd]-catalysis *via* C-H activation and under phase transfer catalysis for the formation of pyrrolo diindolones and β-carbolinones, respectively, have been described. Palladium catalyzed amidation of indole-3-carboxylic acids with isothiocyanates using a carboxyl group as traceless directing group and the utility of the indole-2-carboxamides in the palladium-catalyzed reaction for the formation of diindole fused 2-pyridones are discussed later. In the last part of this work, ruthenium-catalyzed oxidative annulation of alkynes with 2*H*-chromene-3-carboxamides is presented. Characterization of the products is generally done by using mp (for solids), IR, NMR, LCMS/CHN, and HRMS with single crystal X-ray structure determination for representative compounds.

2.1 Synthesis of indole-2-carboxylic acid precursors 1a-j

All the indole-2-carboxylic acid reactants used in the present study have been synthesized by starting with indole-2-carboxylic acid utilizing a literature procedure with slight modification where appropriate (Scheme 1).[70] Thus esterification of indole-2-carboxylic acids with MeOH/H_2SO_4 resulted in the corresponding methyl-1*H*-indole-2-carboxylates. These esters were converted to *N*-substituted-methyl-1*H*-indole-2-carboxylates by treatment with alkyl bromides or chlorides (EOM-Cl and MOM-Cl) in the presence of NaH in DMF as the solvent.[70a,c] These esters upon hydrolysis (saponification) afford the corresponding carboxylic acids **1a-j**. Among the synthesized indole-2-carboxylic acids, **1e** is new.

Scheme 1



condition (i) : R^1Br (or) R^1Cl, NaH, DMF, 0 °C to rt
($ClCH_2OEt$ for **1i** and $ClCH_2OMe$ for **1j**)

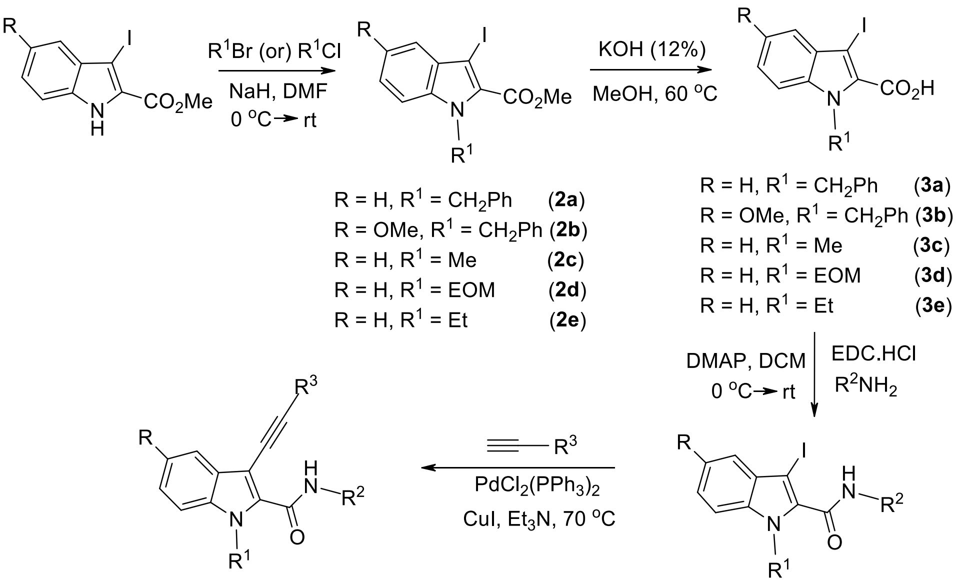
condition (ii) : KOH (12%), MeOH, reflux, 24 h

R = H, R^1 = Me (**1a**)
R = 5-OMe, R^1 = Me (**1b**)
R = 5-OBn, R^1 = Me (**1c**)
R = 5-F, R^1 = Me (**1d**)
R = 5,6-Me, R^1 = Me (**1e**)
R = 7-Cl, R^1 = Me (**1f**)
R = H, R^1 = Et (**1g**)
R = H, R^1 = Bn (**1h**)
R = H, R^1 = EOM (**1i**)
R = H, R^1 = MOM (**1j**)

2.2 Synthesis of 3-alkynyl-indole-2-carboxamides 5a-o

The 3-alkynyl-indole-2-carboxamides were prepared by starting with indole-2-carboxylic acid. Esterification of indole-2-carboxylic acid followed by iodination[70d,2a] resulted in the methyl-3-iodo-1*H*-indole-2-carboxylates. These were transformed to *N*-substituted products **2a-e** by treatment with alkyl bromides or chlorides (EOM-Cl) in the presence of NaH in DMF as the solvent.[71a] Compounds **2a-e** upon saponification afforded the corresponding acids **3a-e** (Scheme 2) which were further converted to the corresponding 3-iodo-indole-2-carboxamides **4a**-**k** by using EDC.HCl/ DMAP in DCM as the solvent.[71b] Under Sonogashira conditions[71c,d] **4a-k** were transformed to 3-alkynyl-indole-2-carboxamides **5a-o**. Precursors **2d**, **3b** and **3d** are new. All the 3-iodo-indole-2-carboxamides **4a-k** and 3-alkynyl-indole-2-carboxamides **5a-o** are also new.

Scheme 2



R = H, $R^1 = CH_2Ph$ (**2a**)
R = OMe, $R^1 = CH_2Ph$ (**2b**)
R = H, R^1 = Me (**2c**)
R = H, R^1 = EOM (**2d**)
R = H, R^1 = Et (**2e**)

R = H, $R^1 = CH_2Ph$ (**3a**)
R = OMe, $R^1 = CH_2Ph$ (**3b**)
R = H, R^1 = Me (**3c**)
R = H, R^1 = EOM (**3d**)
R = H, R^1 = Et (**3e**)

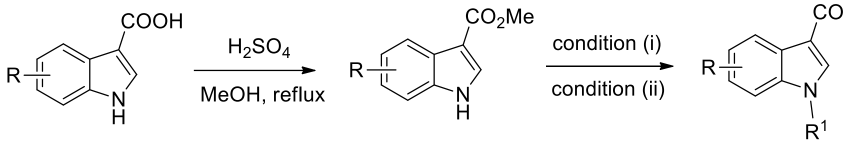
R = H, $R^1 = CH_2Ph$, R^2 = *p*-$MeOC_6H_4$, R^3 = Ph (**5a**)
R = H, $R^1 = CH_2Ph$, R^2 = *p*-MeC_6H_4, R^3 = Ph (**5b**)
R = H, $R^1 = CH_2Ph$, R^2 = *p*-MeC_6H_4, R^3 = *p*-MeC_6H_4 (**5c**)
R = OMe, $R^1 = CH_2Ph$, R^2 = *m*-MeC_6H_4, R^3 = *p*-$MeOC_6H_4$ (**5d**)
R = OMe, $R^1 = CH_2Ph$, R^2 = *p*-$MeOC_6H_4$, R^3 = Ph (**5e**)
R = H, R^1 = Me, R^2 = *p*-$MeOC_6H_4$, R^3 = *p*-$MeOC_6H_4$ (**5f**)
R = H, R^1 = Me, R^2 = *p*-$MeOC_6H_4$, R^3 = Ph (**5g**)
R = H, R^1 = Me, R^2 = *p*-$MeOC_6H_4$, R^3 = *p*-MeC_6H_4 (**5h**)
R = H, R^1 = Me, R^2 = *p*-$MeOC_6H_4$, R^3 = *p*-FC_6H_4 (**5i**)
R = H, R^1 = EOM, R^2 = *p*-ClC_6H_4, R^3 = Ph (**5j**)
R = H, $R^1 = CH_2Ph$, R^2 =Me, R^3 = Ph (**5k**)
R = H, $R^1 = CH_2Ph$, $R^2 = CH_2Ph$, R^3 = Ph (**5l**)
R = H, R^1 = Me, R^2 = 2-pyridyl, R^3 = Ph (**5m**)
R = H, R^1 = Et, R^2 = Ph, R^3 = Ph (**5n**)
R = H, $R^1 = CH_2Ph$, R^2 = *p*-$NO_2C_6H_4$, R^3 = Ph (**5o**)

R = H, $R^1 = CH_2Ph$, R^2 = *p*-$MeOC_6H_4$ (**4a**)
R = H, $R^1 = CH_2Ph$, R^2 = *p*-MeC_6H_4 (**4b**)
R = OMe, $R^1 = CH_2Ph$, R^2 = *m*-MeC_6H_4 (**4c**)
R = OMe, $R^1 = CH_2Ph$, R^2 = *p*-$MeOC_6H_4$ (**4d**)
R = H, R^1 = Me, R^2 = *p*-$MeOC_6H_4$ (**4e**)
R = H, R^1 = EOM, R^2 = *p*-ClC_6H_4 (**4f**)
R = H, $R^1 = CH_2Ph$, R^2 = Me (**4g**)
R = H, $R^1 = CH_2Ph$, $R^2 = CH_2Ph$ (**4h**)
R = H, R^1 = Me, R^2 = 2-pyridyl (**4i**)
R = H, R^1 = Et, R^2 = Ph (**4j**)
R = H, $R^1 = CH_2Ph$, R^2 = *p*-$NO_2C_6H_4$ (**4k**)

2.3 Synthesis of indole-3-caboxylic acids 6a-i

Indole-3-carboxylic acids **6a-i** were prepared from the corresponding indole-3-carboxylic acids. Esterification of indole-3-carboxylic acids followed by treatment with alkyl bromides MOM-Cl furnished *N*-substituted-methyl-1*H*-indole-3-carboxylates.[72] Hydrolysis of these esters afforded the corresponding 3-carboxylic acids **6a-i**.

Scheme 3



condition (i) : R^1Br (or) R^1Cl, NaH, DMF, 0 °C to rt
($ClCH_2OMe$ for **6d** and **6i**)

condition (ii) : KOH (12%), MeOH, reflux, 24 h

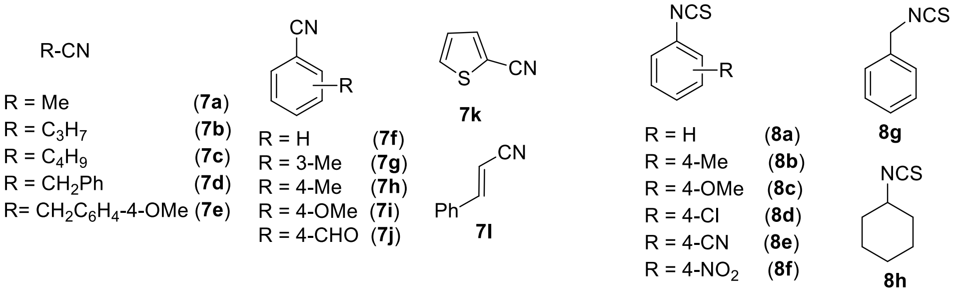
R = H, R^1 = Me (**6a**)
R = H, R^1 = *n*-Bu (**6b**)
R = H, R^1 = Bn (**6c**)
R = H, R^1 = MOM (**6d**)
R = H, R^1 = propargyl (**6e**)
R = 5,6-OMe, R^1 = Me (**6f**)
R = 5-OBn, R^1 = Me (**6g**)
R = 5-OMe, R^1 = Bn (**6h**)
R = 5-F, R^1 = MOM (**6i**)

We have also utilized various substituted nitriles and isothiocyanates shown in the Chart 1 in the present study. The nitriles **7a-l** and isothiocyanates **8a-h** are commercially available. Other hetero aromatic carboxylic acids **9**-**13** used in our reactions are also shown in Chart 1. 2*H*-Chromene-3-carboxylic acid **9**[73a] and imidazo[1,2-*a*]pyridine-2-carboxylic acid **10**[73b] were prepared by following literature procedures. The hetero-aromatic carboxylic acids benzofuran-2-carboxylic acid **11**, thiophene-2-carboxylic acid **12** and *N*-methyl-pyrrole-2-carboxylic acid **13** are commercially available.

Chart 1

(i) Nitriles used in the present study

(ii) Isothiocyanates used in the present study

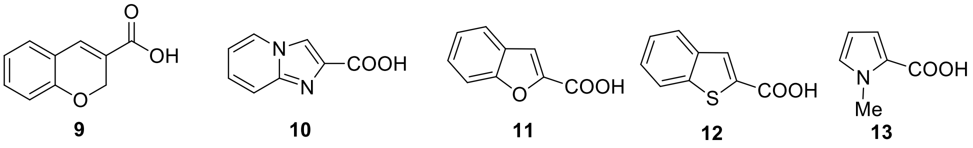


R = Me (**7a**)
R = C_3H_7 (**7b**)
R = C_4H_9 (**7c**)
R = CH_2Ph (**7d**)
R= $CH_2C_6H_4$-4-OMe (**7e**)

R = H (**7f**)
R = 3-Me (**7g**)
R = 4-Me (**7h**)
R = 4-OMe (**7i**)
R = 4-CHO (**7j**)

R = H (**8a**)
R = 4-Me (**8b**)
R = 4-OMe (**8c**)
R = 4-Cl (**8d**)
R = 4-CN (**8e**)
R = 4-NO_2 (**8f**)

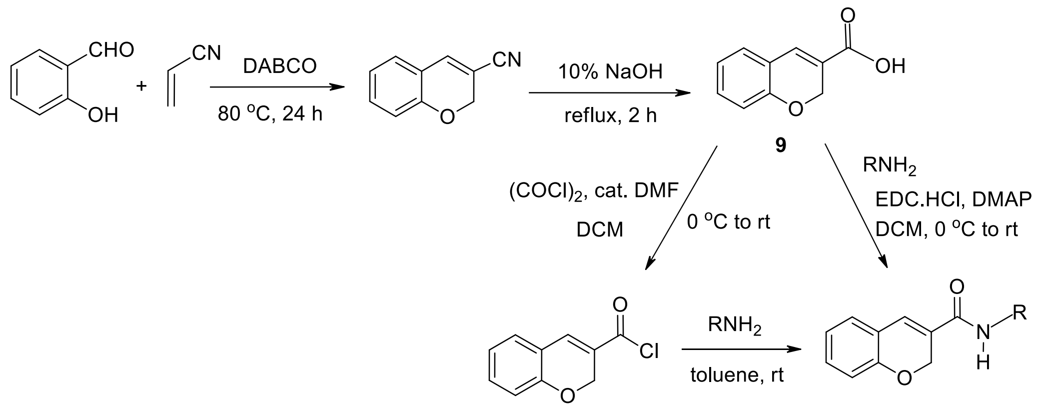
(iii) Other carboxylic acids used in the present study



2.4 Synthesis of 2*H*-chromene-3-carboxamides 14a-f

2*H*-Chromene-3-carboxylic acid **9** was prepared in a two-step sequence from salicylaldehyde using Corey's procedure (Scheme 4).[73a] Thus, the reaction of salicylaldehyde with acrylonitrile in the presence of DABCO by sequential *O*-cyanoethylation and aldol cyclization resulted in 2*H*-chromene-3-carbonitrile, which upon hydrolysis gave the acid **9**. The *N*-substituted 2*H*-chromene-3-carboxamides **14a-f** were synthesized *via* the acid chloride obtained by treating the carboxylic acid **9** with oxalyl chloride using a catalytic amount of DMF in dichloromethane (DCM). The acid chloride so obtained was converted to the corresponding amides **14a-f** by using *N*-substituted amines (cf. Scheme 4).[74a,b,c] An alternative procedure utilized to synthesize the amides **14a-f** is also shown in Scheme 4. The 2*H*-chromene-3-carboxylic acids are converted to the corresponding *N*-substituted 2*H*-chromene-3-carboxamides **14a-f** in a single step by using EDC.HCl/DMAP in DCM as the solvent.[74d,e]

Scheme 4

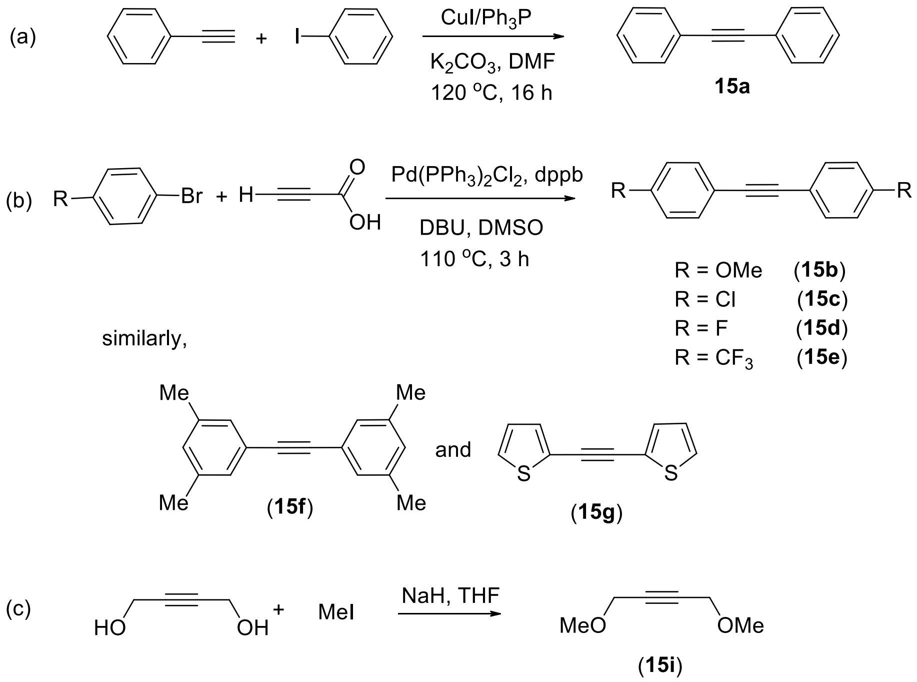


R = 4-OMe-C_6H_4 (**14a**)
R = 4-Me-C_6H_4 (**14b**)
R = 3-Me-C_6H_4 (**14c**)
R = *i*-Pr (**14d**)
R = *n*-Bu (**14e**)
R = cyclohexyl (**14f**)

2.5 Synthesis of disubstituted alkynes 15a-j

All these alkynes were synthesized by following the literature procedures with slight modifications wherever required.[75] Thus alkyne **15a** was prepared by coupling phenyl acetylene with iodobenzene in the presence of CuI/PPh_3 catalytic system using K_2CO_3 as the base (Scheme 5a).[75a] Alkynes **15b-g** were obtained from the corresponding aryl halide (iodo/bromo) and propiolic acid in the presence of dppb [1,4-bis(diphenylphosphino butane)] and DBU in DMSO *via* palladium-catalyzed decarboxylative coupling (Scheme 5b).[75b] 3-Hexyne (**15h**) and 1-phenyl-1-butyne (**15j**) are commercially available. 1,4-Bis(methoxymethoxy)-2-butyne **15i** was prepared by methylation of the corresponding 1,4-butynediol using MeI and NaH (Scheme 5c).[75c] All the alkynes **15a-j** used in the present study are known.[75]

Scheme 5



2.6 Palladium-catalyzed decarboxylative nitrile insertion *via* dual C-H activation

The development of methods for the direct conversion of C-H bonds to C-C and C-N bonds has received significant attention in organic chemistry.[2,3] Palladium catalysts are widely used for such transformations. In such cases, the nitrile group is considered to be inert and thus acetonitrile is one of the frequently used solvents.[76] To our knowledge, there is hardly any report on the incorporation of the nitrile group directly into a cyclic structure.[77] Such reactions utilizing the indole system could lead to carbolines[78] that are again another important class of medicinally useful products.[79]

2.6.1 *Synthesis of indole fused α-carbolines via decarboxylative nitrile insertion of indole-2-carboxylic acids*

This work began with a serendipitous observation that a blank reaction of 1-methyl-indole-2-carboxylic acid (**1a**) with in CH_3CN (**7a**, used actually as a solvent!) in the presence of $Pd(OAc)_2$ /Ag_2CO_3 afforded indole fused α-carboline **16** as one of the products.[80] We then surmised that it may be possible to construct indole fused α-carbolines by treating **1a-j** with various nitriles under [Pd] catalysis. For optimization of conditions, we used **1a** and benzonitrile (**7f**) (Scheme 6, Table 1). To our delight, we obtained **17** as the only fused product. The yield of the isolated product was moderate probably because of the formation of insoluble silver carboxylate salt (X-ray powder diffraction). Predictably, the reaction did not occur in the absence of Ag_2CO_3 (entry 2) or [Pd]-catalyst (entry 3); in the latter case, only the decarboxylative product *N*-methyl indole was observed. The yield of **17** was enhanced sharply to 65% with 2.0 equiv of Ag_2CO_3 (entry 4). Results identical to those with 2.0 equiv of Ag_2CO_3 were obtained when the reaction was carried out with 3.0 equiv of Ag_2CO_3 (entry 5). Subsequently, a series of other oxidants, including $Cu(OAc)_2.H_2O$, $CuCl_2$, Ag_2O, AgOAc and O_2 were examined. They were less effective than Ag_2CO_3 (entries 6−10). Extensive screening revealed that the reaction between **1a** and PhCN at 5 mol % of $Pd(OAc)_2$ worked well and gave the desired product **17** in 49% yield (entry 11). However, the yield was lowered to 36% using 2 mol % of $Pd(OAc)_2$ (entry 12). Other [Pd]-catalysts like $PdCl_2$, $Pd(dba)_2$, $Pd(TFA)_2$ and $Pd_2(dba)_3$, were less effective than $Pd(OAc)_2$ (entries 13-19). Bases like K_2CO_3 and Cs_2CO_3 (entries 20-21) gave rather low yields. No increase in the yield was observed by adding additives like $AgSbF_6$ (entry 22) and AgOTf (entry 23). Thus, the best conditions were: 10 mol % of $Pd(OAc)_2$ as catalyst, Ag_2CO_3 (2.0 equiv) as oxidant under solvent free conditions (neat) at 80 °C for 12 h (65% yield; Table 1, entry 4).

Scheme 6

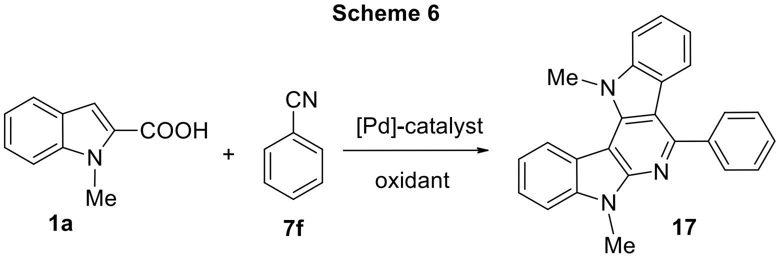


Table 1. Optimization of conditions for the synthesis of indolocarboline **17**[a]

Entry	[Pd] (mol %)	Oxidant (equiv) + base/additive (equiv)	Yield (%)[b]
1	$Pd(OAc)_2$ (10)	Ag_2CO_3 (1)	51
2	$Pd(OAc)_2$ (10)	-	-
3	-	Ag_2CO_3 (1)	-
4	**$Pd(OAc)_2$ (10)**	**Ag_2CO_3 (2)**	**65**[c]
5	$Pd(OAc)_2$ (10)	Ag_2CO_3 (3)	64
6	$Pd(OAc)_2$ (10)	$Cu(OAc)_2.H_2O$ (2)	trace
7	$Pd(OAc)_2$ (10)	$CuCl_2$ (2)	trace
8	$Pd(OAc)_2$ (10)	Ag_2O (2)	43
9	$Pd(OAc)_2$ (10)	AgOAc (2)	45
10	$Pd(OAc)_2$ (10)	O_2	10
11	$Pd(OAc)_2$ (5)	Ag_2CO_3 (2)	49
12	$Pd(OAc)_2$ (2)	Ag_2CO_3 (2)	43
13	$PdCl_2$ (10)	Ag_2CO_3 (2)	47
14	$PdCl_2$ (10)	$Cu(OAc)_2.H_2O$ (2)	trace
15	$PdCl_2$ (10)	Ag_2O (2)	21
16	$PdCl_2$ (10)	AgOAc (2)	32
17	$Pd(dba)_2$ (10)	Ag_2CO_3 (2)	40
18	$Pd(TFA)_2$ (10)	Ag_2CO_3 (2)	50

19	$Pd_2(dba)_3$ (10)	Ag_2CO_3 (2)	42
20	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2)/ K_2CO_3 (2)	37
21	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2)/ Cs_2CO_3 (2)	40
22	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2)/ $AgSbF_6$ (0.3)	48
23	$Pd(OAc)_2$ (10)	Ag_2CO_3 (2)/ AgOTf (0.3)	40

[a]Reactions were carried out using indole carboxylic acid **1a** (1.0 mmol), nitrile **7f** (20 mmol), [Pd]-catalyst (2-10 mol %), Oxidant (1-3.0 mmol) at 80 ^oC (oil bath) for 12 h. [b]Isolated yield. [c]This reaction conducted at 50 ^oC gave lower yield (ca 20%) while at 100 ^oC gave the same yield (65%) as the one at 80 ^oC.

Inspired by the above results, we next moved to investigate the scope of this decarboxylative [Pd]-catalyzed reaction with respect to both indole-2-carboxylic acids **1** and nitriles **7** (Scheme 7, Table 2). Gratifyingly, this protocol was general to a wide range of indole carboxylic acids and nitriles (48-65 %) except in the case of **16** where formation of triindoles was significant (*vide infra*). The R^2 in the nitriles include both aliphatic and aromatic moieties. Thus, irrespective of the aliphatic nitriles or aromatic nitriles, the desired indolo carbolines were isolated in good yields. Reaction of *N*-methyl-indole-2-carboxylic acid **1a** with nitriles **7a-i** resulted in the corresponding indolocarbolines **16-24** in good yields (Table 2, entries 1-9). Nitrile attached to heterocyclic moiety (**7k**) also reacted smoothly with **1a** and gave the indolocarboline **25** in 59% yield (entry 10). Importantly, a functional group like CHO attached to phenyl moiety of nitrile (**7j**) could be perfectly tolerated (compound **26**). Cinnamyl nitrile (**7l**) also afforded the expected product **27** in good yield. The substituents present on the aromatic ring of indole-2-carboxylic acid at different positions such as 5-methoxy (**1b**), 5-benzoxy (**1c**), 5-fluoro (**1d**), 5,6-dimethyl (**1e**) and 7-chloro (**f**) were well-tolerated and afforded the corresponding indolocarbolines **28-32** in good yields. The R^1 in the indole-2-carboxylic acids has been exclusively restricted to aliphatic groups like Me, Et, Bn, EOM, and MOM; all these acids reacted well with nitriles (compounds **33-37**). X-ray structures of compounds **16** and **18** have been determined (Figure 1).

Scheme 7

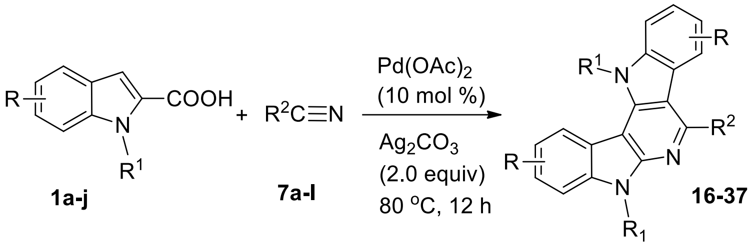
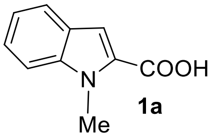
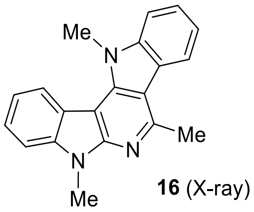
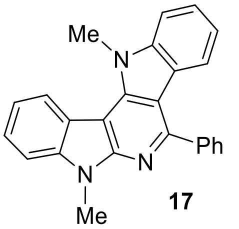
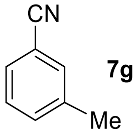
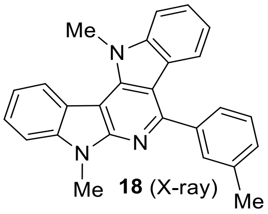
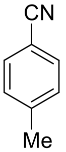
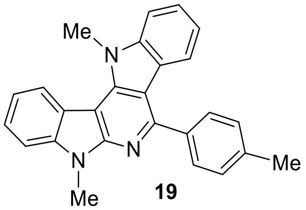
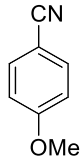
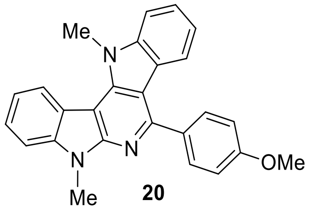
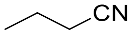
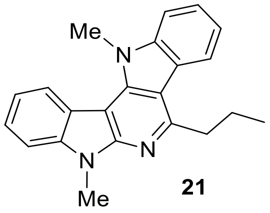
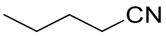
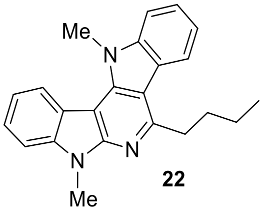
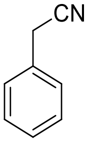
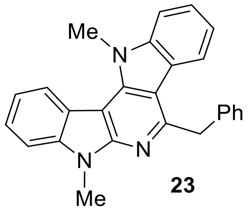
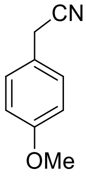
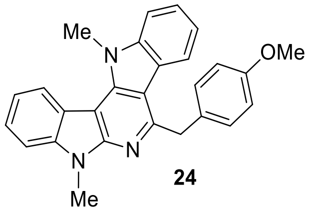
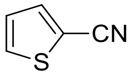
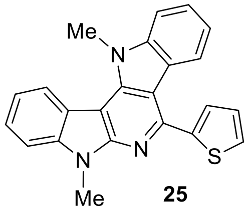
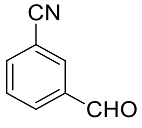
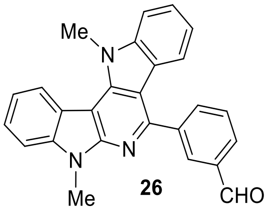
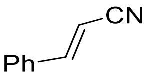
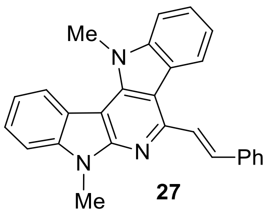
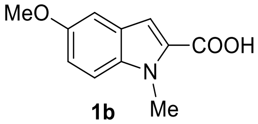
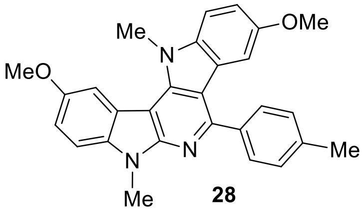
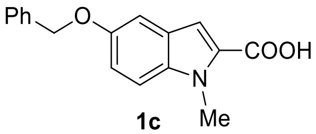
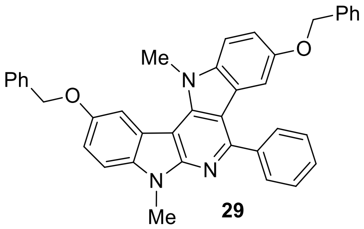
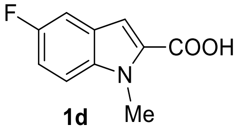
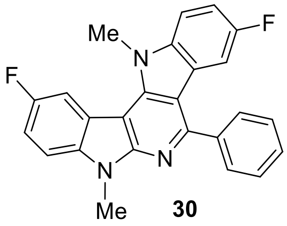
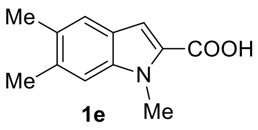
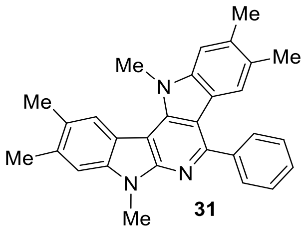
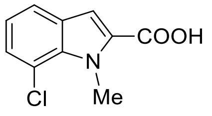
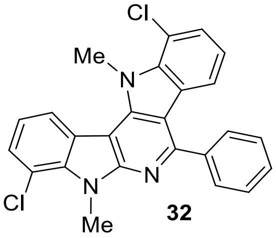
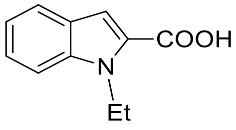
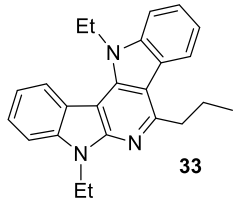
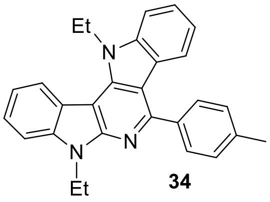
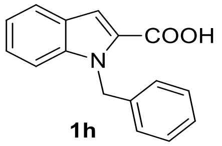
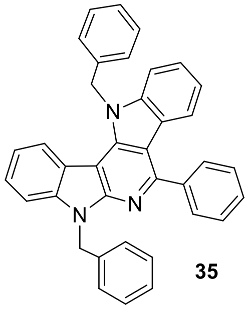
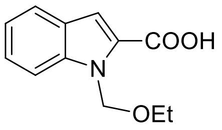
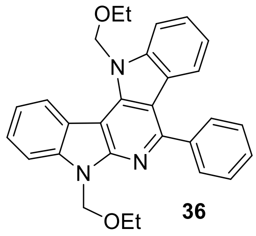
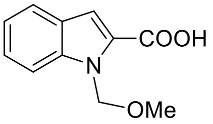
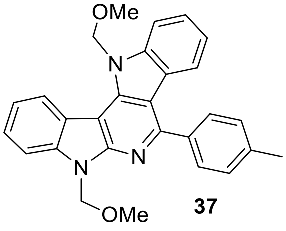


Table 2. Substrate scope of palladium-catalyzed decarboxylative nitrile insertion reaction for the synthesis indolocarbolines **16-37**[a]

Entry	Indole-2-carboxylic acid	Nitrile	Indolocarboline	Yield (%)[b]
1	 **1a**	CH_3CN **7a**	 **16** (X-ray)	38[c]
2	**1a**	PhCN **7f**	 **17**	65
3	**1a**	 **7g**	 **18** (X-ray)	61
4	**1a**	 **7h**	 **19**	57

5	**1a**	 **7i**	 **20**	59
6	**1a**	 **7b**	 **21**	56
7	**1a**	 **7c**	 **22**	53
8	**1a**	 **7d**	 **23**	60
9	**1a**	 **7e**	 **24**	55
10	**1a**	 **7k**	 **25**	59

11	**1a**	 **7j**	 **26**	60
12	**1a**	 **7l**	 **27**	63
13	 **1b**	**7h**	 **28**	58
14	 **1c**	**7f**	 **29**	64
15	 **1d**	**7f**	 **30**	51
16	 **1e**	**7f**	 **31**	62

17	 **1f**	**7f**	 **32**	56
18	 **1g**	**7b**	 **33**	55
19	**1g**	**7h**	 **34**	55
20	 **1h**	**7f**	 **35**	57
21	 **1i**	**7f**	 **36**	50
22	 **1j**	**7h**	 **37**	48

[a]Reactions were carried out using indole-2-carboxylic acid **1a-j** (1.0 mmol), nitrile **7a-l** (20 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (2.0 mmol) in neat condition under N_2 atmosphere at 80 °C (oil bath) for 12 h. [b]Isolated yield. [c]In this reaction, we isolated the triindoles (**39-40**) in ca 28% yield.

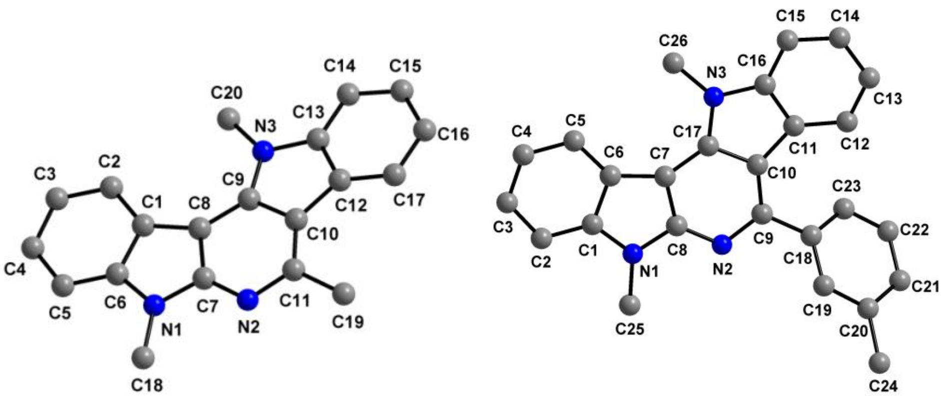
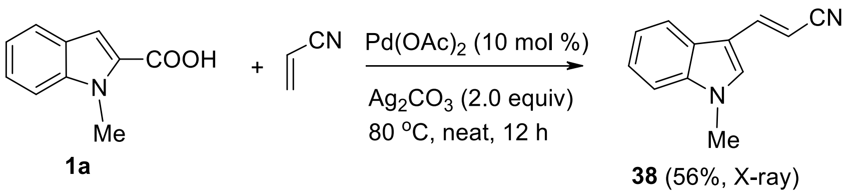


Figure 3. Ball and stick models of compounds **16** and **18**. Hydrogen atoms are omitted for clarity. Left: Compound **16**. Selected bond lengths [Å] with esds in parentheses: N(2)-C(7) 1.339(3), N(2)-C(11) 1.341(4), C(8)-C(7) 1.413(3), C(8)-C(9) 1.402(4), C(10)-C(9) 1.418(3), C(10)-C(11) 1.400(4). Right: Compound **18**. Selected bond lengths [Å] with esd's in parentheses: N(2)-C(8) 1.331(2), N(2)-C(9) 1.335(3), C(7)-C(8) 1.414(3), C(17)-C(7) 1.399(3), C(17)-C(10) 1.420(3), C(10)-C(9) 1.401(3).

2.6.2 Reaction of 1-methyl-indole-2-carboxylic acid 1a with acrylonitrile affording the C3-alkenylated product A

The reaction between 1-methyl-indole-2-carboxylic acid **1a** and acrylonitrile under conditions similar to that for **17** afforded an unexpected decarboxylative C3-alkenylated product **38** in 56% yield (Scheme 8). This Heck type coupled product has also been prepared by Wang and co-workers recently using *N*-methylindole.[81] However, our reaction conditions are different. The structure of compound **38** was further confirmed by X-ray crystallography (Figure 2).

Scheme 8



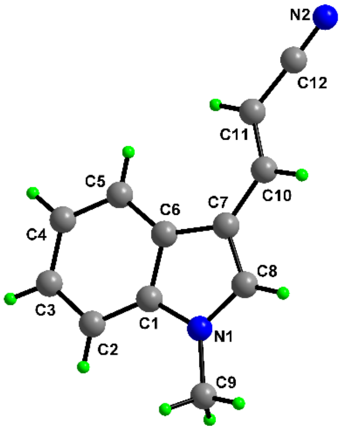
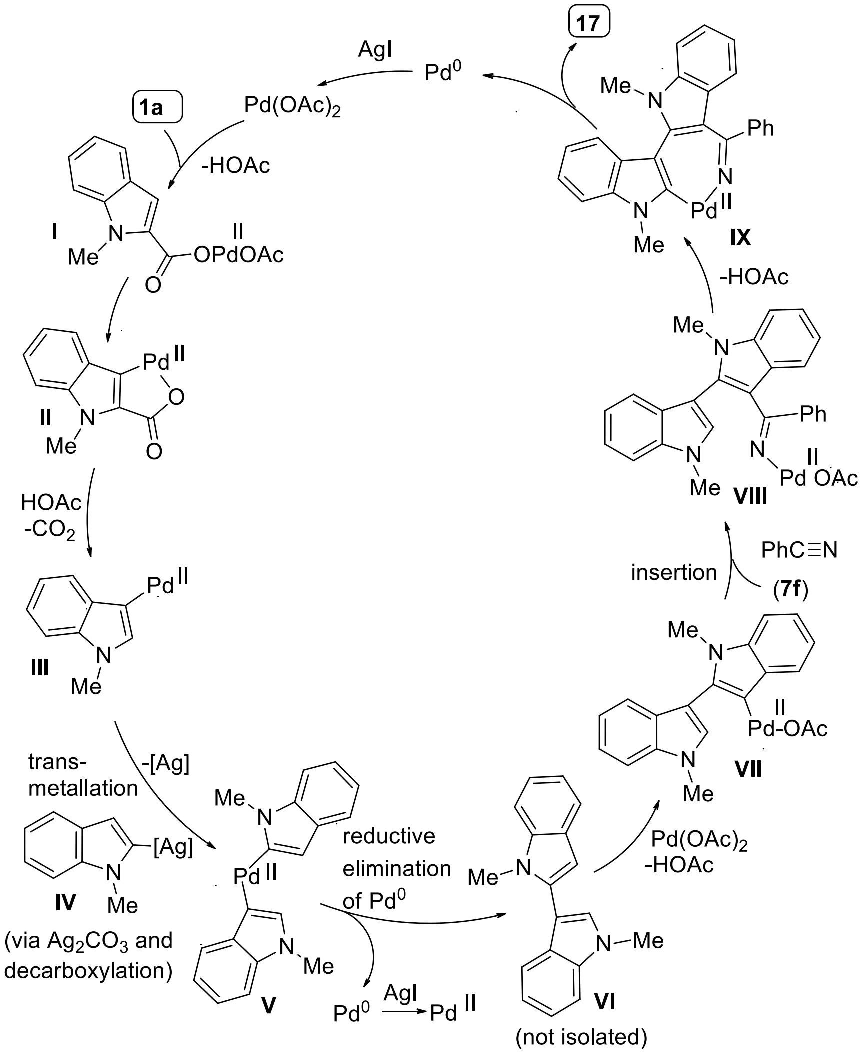


Figure 2. Ball and stick model of compound **38**. Selected bond lengths [Å] with esds in parentheses: C(7)-C(8) 1.375(2), C(7)-C(10) 1.437(2), C(10)-C(11) 1.323(2), C(11)-C(12) 1.422(2), C(12)-N(2) 1.137(2).

2.6.3 Mechanistic pathway for the formation of indolocarboline derivatives

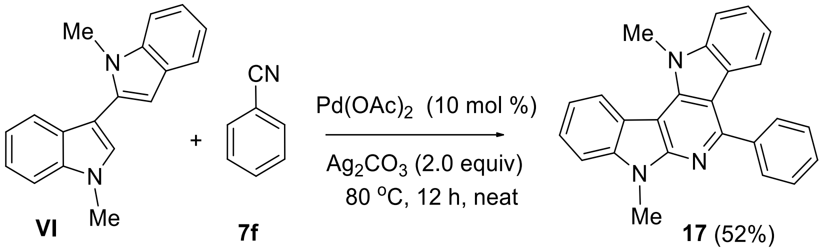
A plausible pathway for the formation of indole fused α-carboline product **17** from indole-2-carboxylic acid **1a** and benzonitrile **7f** is illustrated in Scheme 9. Initial attack of $Pd(OAc)_2$ to the carboxyl oxygen with elimination of AcOH (without undergoing decarboxylation) gives a palladium(II) carboxylate species **I** (Scheme 9). This proposal is consistent with the fact that **1a** reacts with $Pd(OAc)_2$ (1:1 stoichiometry) even at room temperature (25 ^{o}C) within 15 min with the complete consumption of **1a**. Species **I** undergoes carbo-palladation at the 3-position affording the key palladacycle intermediate **II**.[80,82] Decarboxylation of **II** results in the metallated species **III**. Meanwhile, **1a** undergoes decarboxylation in the presence of silver carbonate affording the aryl metal species **IV**,[83] which on transmetallation with the Pd^{II} species **III** gives the biaryl Pd^{II} species **V.**[82b,83,84] Intermediate **V** gives the biindolyl **VI** and Pd^0 by reductive elimination. This Pd^0 species may be oxidized in the presence of Ag^I salt to regenerate active Pd^{II} species. The *in situ* produced biindolyl **VI** undergoes palladation to give **VII**. This species has been proposed earlier by Liang et al.[85] Species **VII** upon *nitrile insertion* produces **VIII**.[86] Upon intramolecular C-H activation, **VIII** leads to the palladacycle **IX** that by reductive elimination affords indole fused α-carboline **17**. Again, Pd^0 is reoxidized to Pd^{II} via Ag^I, thus closing the catalytic cycle.

Scheme 9



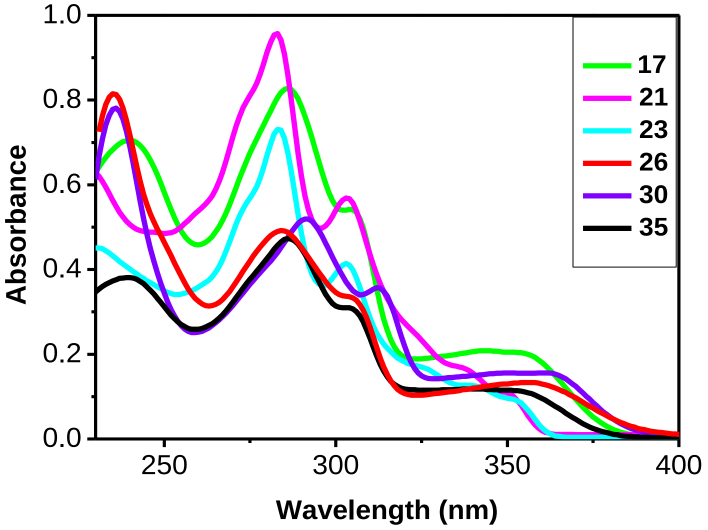
As mentioned above, the pathway for the formation of indole fused α-carboline (e.g., **17**) is assumed to take place *via* biindolyl intermediate by dual C-H activation.[86f] To confirm this, we performed a reaction between biindolyl **VI**[85,86g] and benzonitrile. Satisfyingly, this reaction afforded indole fused α-carboline **17** via double C-H activation in 52% yield (Scheme 10) vindicating our proposal. Here the yield of product **17** was low probably because of the formation of unseparable mixture of other unknown compounds. Formation of **17** from **VI** is not a simple [4+2] cycloaddition, since in the absence of the catalyst, the reaction did not take place. Also, dimethylacetylene dicarboxylate (DMAD) did not undergo [4+2] cycloaddition with **VI**. These results are also consistent with the involvement of palladium catalyst in the final steps.

Scheme 10



2.6.4 UV-Visible and Fluorescence spectra of indolocarbolines

Since our triazaindeno-fluorenes (indolocarbolines) **16-37** have a skeleton with fused indole rings similar to that of highly fluorescent triindoles, we expected that compounds **16-37** also should show good fluorescence spectra. Consistent with this prediction, indole-fused α-carbolines do show excellent fluorescence spectra (Figures 3, Table 3). The absorption and emission spectra were recorded for compounds **16-28, 30** and **33-37** in THF (10^{-5} M) and only compounds **17**, **21**, **23**, **26**, **30**, and **35** are shown in Figure 3. The absorption peak wavelengths (λ_{abs}), molar extinction coefficient (ε), emission peak wavelengths (λ_{em}) in solution are collected in Table 3.



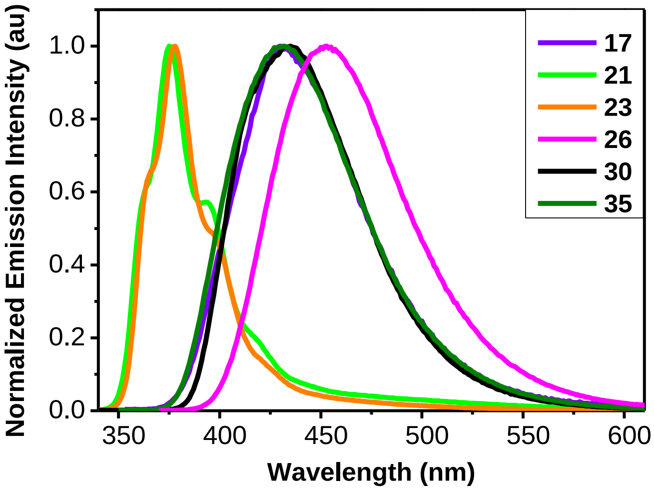


Figure 4. Top: UV-Visible spectra of **17**, **21**, **23**, **26**, **30**, and **35** in THF (10^{-5} M). Bottom: Fluorescence spectra of **17**, **21**, **23**, **26**, **30**, and **35** in THF (10^{-5} M). See Table 3 for details.

Table 3. Fluorescence spectral details on indole fused α-carbolines **16-28, 30** and **33-37**

Compound	λ_{abs} (nm)	ε (10^4 M^{-1} cm^{-1})	λ_{em} (nm)
16	282	6.2	373
17	286	8.2	430
18	286	7.2	430
19	285	6.7	427
20	285	7.0	438
21	283	9.5	375
22	283	7.6	375
23	283	7.3	378
24	283	5.4	377
25	289	7.8	450
26	284	4.9	453
27	305	6.5	468
28	296	4.9	453
30	292	5.1	435

33	283	5.6	376, 395, 425
34	286	5.4	429
35	286	4.7	432
36	281	5.2	421
37	281	5.3	426

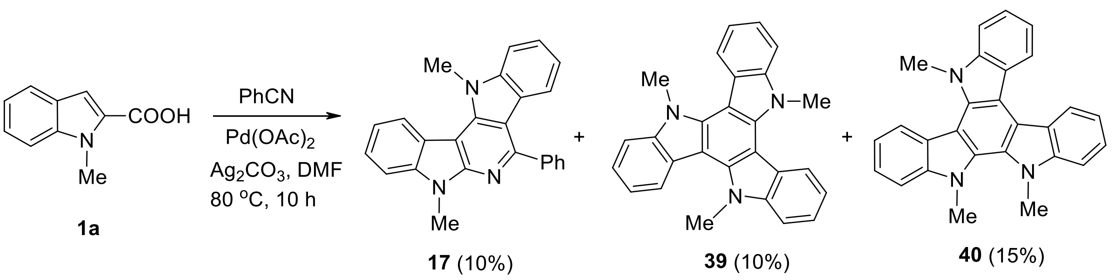
2.7 [Pd]-Catalyzed Decarboxylative Trimerization of 1-Alkyl-Indole-2-Carboxylic Acids

After successful synthesis of indole fused α-carbolines *via* decarboxylative nitrile insertion, we moved to the synthesis of triindoles *via* palladium-catalyzed decarboxylative trimerization. The results are discussed below. Another component/additive that is often used in [Pd]-catalysis as an oxidant is Ag_2CO_3. Quite often, decarboxylation in conjunction with C-H activation is the observed phenomenon.[82b,83,87] A few examples utilizing indole carboxylic acids are known.[88] Although it is possible that intermediates formed in such decarboxylations undergo self-association leading to multiply fused indoles, to this date, reports of this kind are absent in the literature. In the course of our investigations on such a system, we have discovered that indole-2-carboxylic acids lead to triindoles (diindolocarbazoles) that constitute the hot area of organic electronic materials.[89] Despite the fact that both acetonitrile and Ag_2CO_3 have been utilized in several [Pd]-catalyzed reactions involving indoles,[87e,88a,90] rather surprisingly, formation of triindoles (albeit in only moderate yield) is not mentioned in earlier reports.

2.7.1 Synthesis of triindoles

Initially, we investigated the reaction of 1-methyl-indole-2-carboxylic acid **1a** with benzonitrile **7f** using 10 mol % of $Pd(OAc)_2$ catalyst and 2 equiv of Ag_2CO_3 as the oxidant in DMF solvent under N_2 atmosphere at 80 °C (Scheme 11). Surprisingly, this reaction afforded a mixture of three products (TLC). These products were isolated by flash chromatography using EtOAc/hexane as eluent. We found that one of the products was the indole fused α-carboline (**17**; ~10 %). Other two were the trimerization products, the heptacyclic triindoles (diindolocarbazoles) **39-40**. After careful chromatographic separation, both symmetrical and unsymmetrical triindoles (overall yield 35 %, Scheme 11) were isolated, thus revealing a new type of reaction in indole chemistry. Such products must have been formed in several reactions of indole substrates (albeit in small quantities) where $Pd(OAc)_2/Ag_2CO_3$ system is utilized, but to our knowledge, are not reported thus far.

Scheme 11



It may be noticed that in the above reaction, benzonitrile is not required for the formation of triindoles. Since such compounds are of significant interest as electronic materials,[89] we moved our attention to intentionally synthesize these heptacyclic triindoles. To our delight, even the blank reaction of **1a** with $Pd(OAc)_2$/ Ag_2CO_3 in DMF led to the symmetrical (**39**) and unsymmetrical triindoles (**40**) in an overall yield of 48 % (Table 4, entry 4). Inspired by this result, we synthesized various triindoles using the same protocol. For this purpose, we established reaction conditions for the decarboxylative trimerization of **1a** (Scheme 12) and the results are summarized in Table 4. In the presence of 1.0 equiv of Ag_2CO_3, compounds **39** and **40** were isolated in lower yield (entry 1). The reaction did not occur in the absence of Ag_2CO_3 (entry 2) or Pd catalyst (entry 3). For this purpose, we screened various oxidants like $Cu(OAc)_2.H_2O$, Ag_2O, and AgOAc, but no improvement in the yield was observed (entries 5-7). By switching solvent from DMF to DMA, the overall yield decreased slightly (45 %, entry 8). Solvents like toluene, THF and DME were also screened (entries 9-11), but they were less effective than DMF. When the catalyst was changed to $PdCl_2$, the overall yield of **39** and **40** was lower (entry 12). Two other Pd catalysts, $Pd(dba)_2$ and $Pd(TFA)_2$, were checked, but they were less active than $Pd(OAc)_2$ (entries 13-14). Use of additives $AgSbF_6$ (entry 15) and AgOTf (entry 16) decreased the yield of the reaction. Thus the best conditions were: $Pd(OAc)_2$(10 mol %) as catalyst, Ag_2CO_3 (2.0 equiv) as the oxidant, DMF as solvent at 80 ^{0}C for 10 h (48 % overall yield; Table 4, entry 4).

Scheme 12

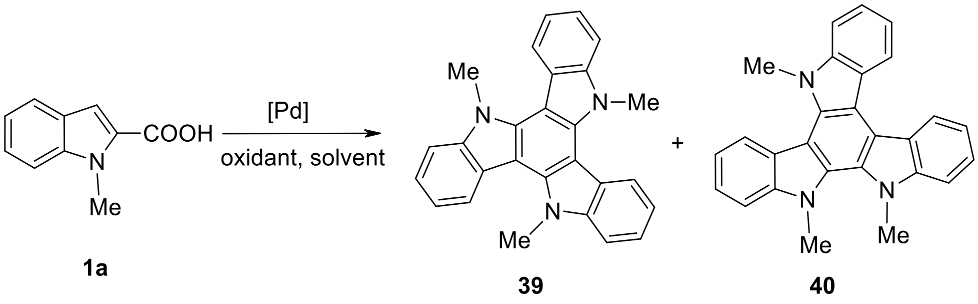


Table 4: Optimization of conditions for trimerization of indole **1a** to lead to **39** and **40**[a]

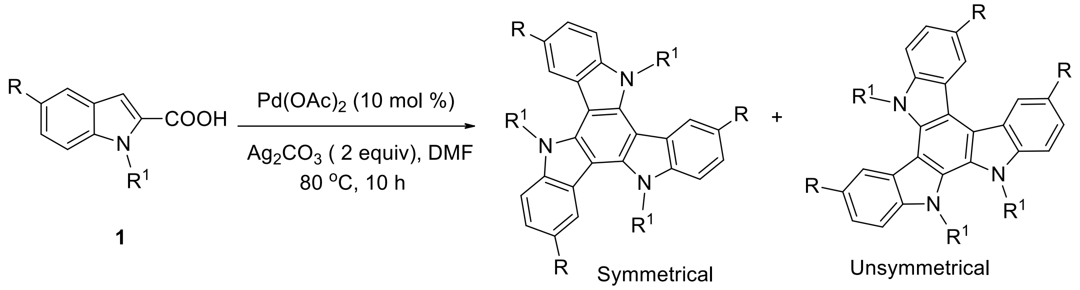
Entry	[Pd] catalyst	Oxidant	Solvent	Overall Yield (%)[b]
1	$Pd(OAc)_2$	Ag_2CO_3[a]	DMF	38
2	$Pd(OAc)_2$	-	DMF	-
3	-	Ag_2CO_3	DMF	-
4	**$Pd(OAc)_2$**	**Ag_2CO_3**	**DMF**	**48**
5	$Pd(OAc)_2$	$Cu(OAc)_2.H_2O$	DMF	trace
6	$Pd(OAc)_2$	Ag_2O	DMF	36
7	$Pd(OAc)_2$	AgOAc	DMF	39
8	$Pd(OAc)_2$	Ag_2CO_3	DMA	45
9	$Pd(OAc)_2$	Ag_2CO_3	Toluene	40
10	$Pd(OAc)_2$	Ag_2CO_3	THF	28

11	Pd(OAc)$_2$	Ag$_2$CO$_3$	DME	trace
12	PdCl$_2$	Ag$_2$CO$_3$	DMF	41
13	Pd(dba)$_2$	Ag$_2$CO$_3$	DMF	35
14	Pd(TFA)$_2$	Ag$_2$CO$_3$	DMF	35
15	Pd(OAc)$_2$	Ag$_2$CO$_3$+ AgSbF$_6$ (0.3)	DMF	37
16	Pd(OAc)$_2$	Ag$_2$CO$_3$+ AgOTf (0.3)	DMF	34

[a] Reactions were carried out using **1a** (1.0 mmol), [Pd]-catalyst (10 mol %), oxidant (2.0 mmol except for entry 1 where 1.0 mmol was used) and DMF (5.0 mL) for 10 h. [b] Isolated yield.

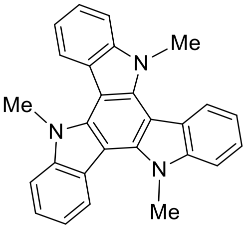
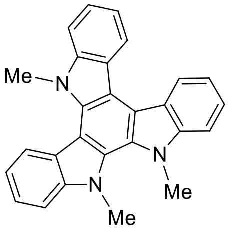
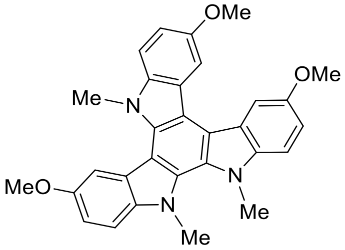
The above information was utilized in the synthesis of triindoles **39-47** (Scheme 13, Table 5). As expected, R_f values of the symmetrical and unsymmetrical triindoles are very close. Hence we were able to separate both the isomers only in selected cases. The unsymmetrical triindoles were obtained in a pure state in all the cases except when R = OMe and R^1 = Bn. Overall, four symmetrical triindoles (**39, 43, 45,** and **46**) and five unsymmetrical triindoles (**40**, **41**, **42**, **44**, and **47**) have been obtained in a pure state. Triindoles **39, 40** and **46** are reported in the literature.[91] Quite pleasingly though, the yield (after isolation) and selectivity of **40** was dramatically increased to 50% by keeping the reaction for 12 h at 30 ^{o}C and then slowly raising the temperature to 50 ^{o}C over a period of 12 h (Table 5, entry 2). This observation may be related to kinetic/steric parameters. Inspired by this, we prepared compound **42** also as the exclusive product in 42% yield (entry 5). In other cases though, both the isomers were formed under these conditions. The structures of the unsymmetrical triindole **41** and the symmetrical triindole **45** were confirmed by single crystal X-ray analysis (Figure 5).

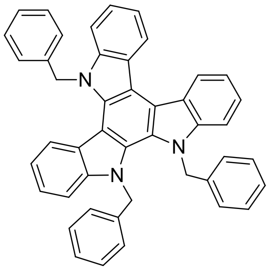
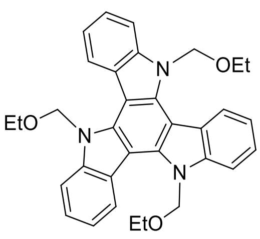
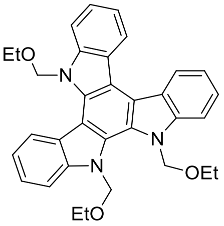
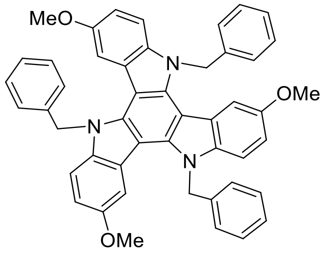
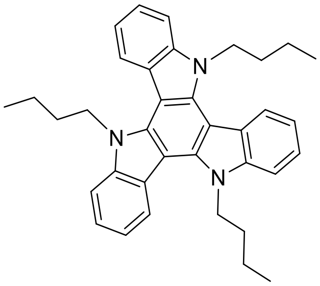
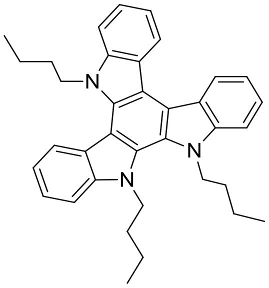
Scheme 13



Compounds **39-47**

Table 5. Synthesis of triindoles (diindolocarbazoles) **39-47**[a]

Entry	Indole-2-carboxylic acid	Symmetrical triindole	Unsymmetrical triindole	Overall yield (%)[b]
1	**1a**	 **39** (20%)	 **40** (28%)	48
2[c]	**1a**	-	**40** (50%)	50
3[d]	**1b**	Not isolated	 **41** (30%, X-ray)	45

4[d]	**1h**	Not isolated	 **42** (32%)	43
5[c]	**1h**	-	**42** (42%)	42
6	**1i**	 **43** (21%)	 **44** (31%)	52
7[d]	**1k**	 **45** (35%, X-ray)	Not isolated	44
8	**1l**	 **46** (20%)	 **47** (30%)	50

[a]Reaction conditions: indole-2-carboxylic acid (1.0 mmol)/ Pd(OAc)$_2$ (10 mol %)/ Ag$_2$CO$_3$ (2.0 mmol)/ DMF(5 mL) under N$_2$ atmosphere. [b] Isolated yield. [c]Reactions were performed at rt for 12 h and then heated to 50 °C (oil bath) for 12 h. [d]In these cases, only one isomer was isolated in a pure state. The other isomer was eluted along with the first one (very close R$_f$ values); this was obtained only as the isomeric mixture. The combined weight (isomeric mixture + pure isomer) corresponds to the total yield.

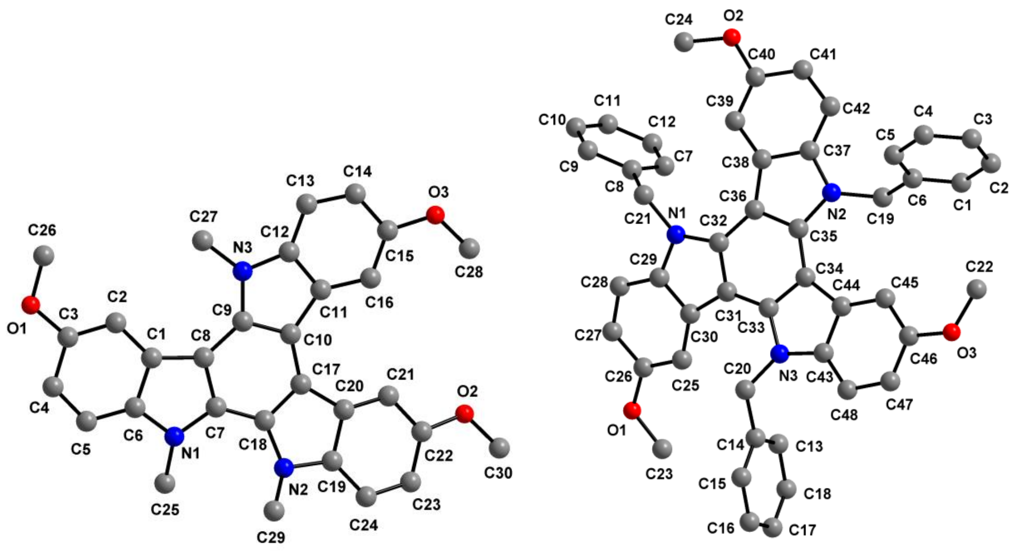


Figure 5. Ball and stick models of compounds **41** and **45**. Hydrogen atoms are omitted for clarity. Left: Compound **41**. Selected bond lengths [Å] with esds in parentheses: C(7)-N(1) 1.378(4), C(7)-C(8) 1.416(4), C(9)-C(8) 1.430(4), N(3)-C(9) 1.388(3), C(9)-C(10) 1.414(4), C(17)-C(10) 1.424(4), C(17)-C(18) 1.398(4), N(2)-C(18) 1.406(4). Right: Compound **45**. Selected bond lengths [Å] with esd's in parentheses: C(31)-C(32) 1.404(3), N(1)-C(32) 1.396(2), C(36)-C(32) 1.418(3), C(36)-C(35) 1.412(3), N(2)-C(35) 1.379(2), C(34)-C(35) 1.406(3), C(34)-C(33) 1.399(3), N(3)-C(33) 1.379(3).

Formation of the above triindoles is possible through the diindole and an *in situ* formed *N*-methylindole *via* cycloaddition followed by aromatization. At least in the reaction of biindole **VI** with **7a** or *N*-methylindole, we have been able to isolate the symmetrical triindole **39**, albeit in 25% yield, but this could also be due to self-reaction involving **7a** or *N*-methylindole. We are investigating this aspect further.

2.7.2 UV-Visible and Fluorescence spectra of triindoles

As a measure of comparison to the α-carbolines discussed earlier, the UV-Vis and fluorescence spectra of chromophores **41-45** and **47** were recorded in THF solvent at 1 X 10^{-5} M concentration and the data are shown in Figure 6 (further details in Table 6). These data are consistent with those reported for compounds **39**, **40** and **46** (these are well known triindoles).[88b,89a,c,d,91a,b] The absorption peak wavelengths (λ_{abs}), molar extinction coefficient (ε), emission peak wavelengths (λ_{em}) in solution are depicted in Table 6.

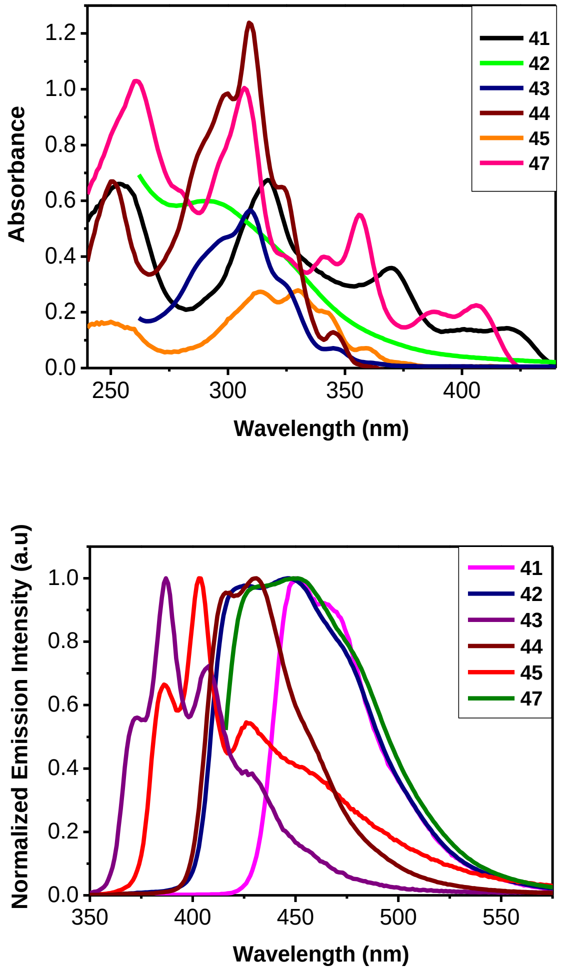


Figure 6. Top: Absorption spectra of compounds **41-45** and **47** in THF (10^{-5} M). Bottom: Fluorescence spectra of compounds **41-45** and **47** in THF (10^{-5} M), excited at the λ_{abs} of their absorption spectra.

Table 6. Fluorescence spectral details on triindoles (diindolocarbazoles) **41-45** and **47**

Compound	λ_{abs} (nm)	ε (10^4 M^{-1} cm^{-1})	λ_{em} (nm)
41	317	6.7	450, 464
42	291	5.9	425, 447
43	330	2.7	386, 403, 426

44	307	10.0	451
45	309	5.6	373, 387, 408
47	309	12.3	416, 431

2.7.3 Reaction of Triindoles with HCl: Observation of Radical Cations

While recording the NMR spectra for the unsymmetrical triindole **40** in $CDCl_3$, it was noticed that after a period of ca 1 h, the spectra were broad and the color of solution in the NMR tube turned green. We suspected that this feature may be due to traces of HCl present in the $CDCl_3$. Hence dry HCl was passed into a toluene solution of **40** upon which a green precipitate formed. This solid, interestingly, showed a nice EPR spectrum (solid state). Similarly, we also recorded the EPR spectra for the green solids obtained by using the triindoles **39**, **41** and **43**. The spectra for **39-40** are reproduced in Figure 7 and the spectra for **41** and **43** shown in Figure 8. There is one report in the literature in which the authors obtained green colored EPR active solids from unsubstituted triindoles in the presence of nitrosobenzene and carboxylic acids.[91b] The solids were proposed to contain radical cations. However, in our case, no external reagent like nitrosobenzene was used. We surmise that the species formed in our reaction (in the case of **40**) has also radical cation shown in the structure **X**. This is based on an earlier assignment from other workers. If this is so, the proton presumably has been oxidized by adventitious oxygen. However, the problem was that the HRMS data was rather unexpected. Attempts to obtain single crystals of this species are yet to meet with success though. However, we believe that this is an interesting observation which needs to be investigated further.

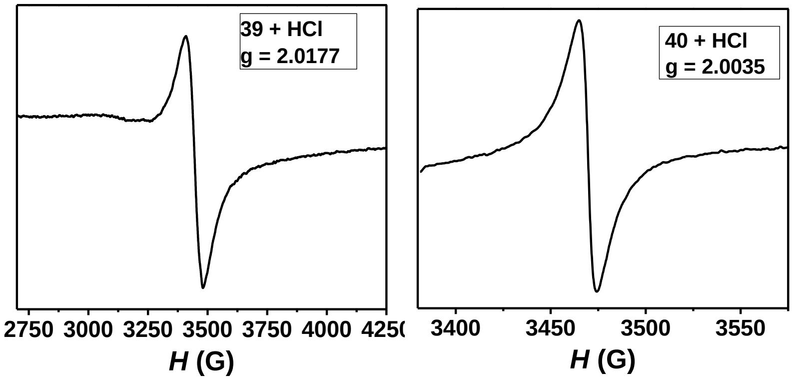
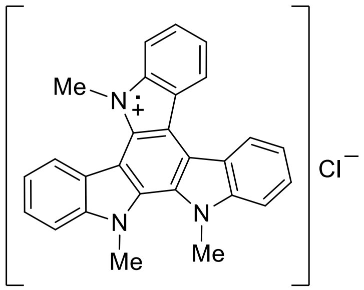


Figure 7. EPR spectra of the species obtained by adding dry HCl to the triindoles **39** and **40** (in toluene solution) suggesting the formation of radical cations.



X

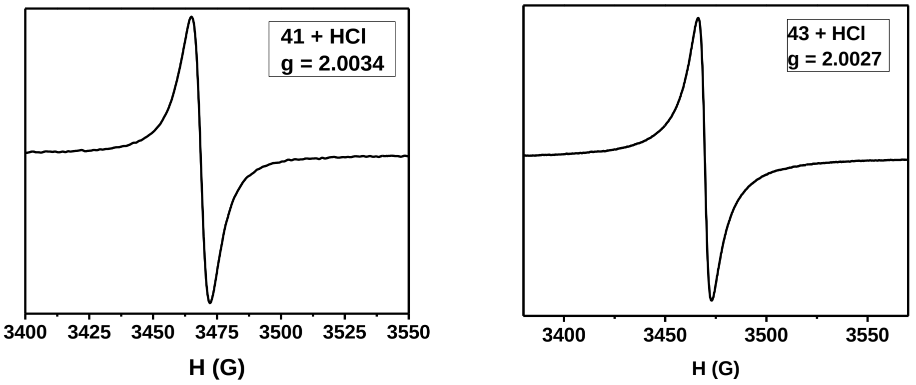


Figure 8. EPR spectra for the compounds **41** (left) and **43** (right)

2.8 Palladium catalyzed oxidative double cyclization of 3-alkynylindole-2-carboxamides involving C-H activation

2.8.1 Synthesis of pyrrolodiindolones by palladium-catalyzed oxidative cyclization using 3-alkynylindole-2-carboxamides that involves C-H activation

After the synthesis of indole fused α-carbolines and triindoles using simple indole-2-carboxylic acid, we investigated the reactivity of 3-alkynylindole-2-carboxamides in the palladium catalyzed reaction for the synthesis of pyrrolodiindolones. The pyrrolo-3-indolone moiety, that is relevant to the present study, appear in a significant number of synthetic targets and clinically useful agents.[92]

Our investigations began by using 1-benzyl-*N*-(4-methoxyphenyl)-3-(phenylethynyl)-1*H*-indole-2-carboxamide **5a** as the substrate for the optimization of the palladium-catalyzed cyclization and C-H activation. Treatment of **5a** with $Pd(OAc)_2$ (10 mol %) and Ag_2CO_3 (2.0 equiv) in CH_3CN at 90 ^oC for 8 h afforded the pyrrolodiindolone **48** in 68% yield (Table 7, entry 1). Addition of a base like K_2CO_3 improved the yield (entry 2). We then screened bases like Cs_2CO_3, K_3PO_4 and KO^tBu (entries 3-5), but these did not improve the yield of **48**. Gratifyingly, a drastic improvement was observed when the solvent was changed from CH_3CN to PhCN. Thus, in PhCN solvent, the yield of pyrrolo[1,2-a:4,3-b']diindol-6(5H)-one **48** was increased to 87% (entry 6). The structure of **48** was confirmed by single crystal X-ray analysis (Figure 9). Other nitriles such as ^{n}BuCN and acrylonitrile were less effective than PhCN (entries 8-9). Changing the solvent to DMF decreased the yield of **48** to 66% (entry 10). Other solvents like DMA and TFE did not improve the yield (entries 11-12). Subsequently, a series of other oxidants that include $Cu(OAc)_2{\cdot}H_2O$, $CuCl_2$, Ag_2O, AgOAc and $K_2S_2O_8$ were examined. They were less effective than Ag_2CO_3 (entries 13−17). A series of control experiments were conducted to check the role of both [Pd]-catalyst and oxidant. In the absence of Ag_2CO_3, the desired product **48** (entry 18) was not formed. Next, the reaction was conducted in the presence of Ag_2CO_3, without the Pd catalyst. In this case also, the desired product could not be observed (entry 19). In the absence of both $Pd(OAc)_2$ and Ag_2CO_3, instead of **48**, we isolated the isoquinolinone (β-carbolinone) **58** in 46% yield (*vide infra*). Other Pd catalysts like $Pd(OTf)_2$, $PdCl_2(CH_3CN)_2$, $PdCl_2$, $Pd(dba)_2$, and $Pd(dba)_3$ were evaluated, but they were less effective than $Pd(OAc)_2$ (entries 21-25). Thus, the combination of 10 mol % of $Pd(OAc)_2$ as catalyst, 2.0 equiv of Ag_2CO_3 as oxidant and 1.0 equiv of K_2CO_3 in PhCN at 90 ^oC for 8 h (87 % yield; Table 7, entry 6) was found to be the optimum condition.

Scheme 14

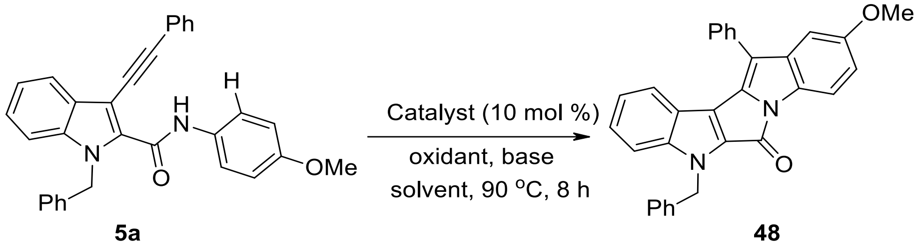


Table 7. Optimization study for palladium catalyzed cyclization of 3-alkynylindole-2-carboxamide **5a** for the synthesis of pyrrolodiindolone **48**[a]

Entry	[Pd]-catalyst	Oxidant	Base	Solvent	Yield of **48** (%)[b]
1	$Pd(OAc)_2$	Ag_2CO_3	-	CH_3CN	68
2	$Pd(OAc)_2$	Ag_2CO_3	K_2CO_3	CH_3CN	76
3	$Pd(OAc)_2$	Ag_2CO_3	Cs_2CO_3	CH_3CN	65
4	$Pd(OAc)_2$	Ag_2CO_3	K_3PO_4	CH_3CN	57
5	$Pd(OAc)_2$	Ag_2CO_3	KO^tBu	CH_3CN	61
6	**$Pd(OAc)_2$**	**Ag_2CO_3**	**K_2CO_3**	**PhCN**	**87**
7	$Pd(OAc)_2$	Ag_2CO_3	K_2CO_3	PhCN	n.d.[c]
8	$Pd(OAc)_2$	Ag_2CO_3	K_2CO_3	BuCN	65
9	$Pd(OAc)_2$	Ag_2CO_3	K_2CO_3	$CH_2=CHCN$	49
10	$Pd(OAc)_2$	Ag_2CO_3	K_2CO_3	DMF	66
11	$Pd(OAc)_2$	Ag_2CO_3	K_2CO_3	DMA	65
12	$Pd(OAc)_2$	Ag_2CO_3	K_2CO_3	TFE	25[d]
13	$Pd(OAc)_2$	Ag_2O	K_2CO_3	PhCN	62
14	$Pd(OAc)_2$	AgOAc	K_2CO_3	PhCN	64
15	$Pd(OAc)_2$	$Cu(OAc)_2\cdot H_2O$	K_2CO_3	PhCN	trace
16	$Pd(OAc)_2$	$CuCl_2$	K_2CO_3	PhCN	trace
17	$Pd(OAc)_2$	$K_2S_2O_8$	K_2CO_3	PhCN	trace
18	$Pd(OAc)_2$	-	K_2CO_3	PhCN	n.d.

19	-	Ag_2CO_3	K_2CO_3	PhCN	n.d.
20	-	-	K_2CO_3	PhCN	n.d.[e]
21	$Pd(OTf)_2$	Ag_2CO_3	K_2CO_3	PhCN	76
22	$PdCl_2(CH_3CN)_2$	Ag_2CO_3	K_2CO_3	PhCN	69
23	$PdCl_2$	Ag_2CO_3	K_2CO_3	PhCN	58
24	$Pd(dba)_2$	Ag_2CO_3	K_2CO_3	PhCN	45[d]
25	$Pd(dba)_3$	Ag_2CO_3	K_2CO_3	PhCN	49[d]

[a]Reaction conditions: alkynylamide **5a** (0.4 mmol), [Pd]-catalyst (10 mol %), oxidant (0.8 mmol), base (0.4 mmol), solvent (2 mL), 90 ^{o}C (oil bath temperature) for 8 h. [b]Isolated yields. [c]Reaction was performed at rt (25 ^{o}C). [d]Starting material remained. [e]β-Carbolinone **58** was isolated in 46% yield in this case.

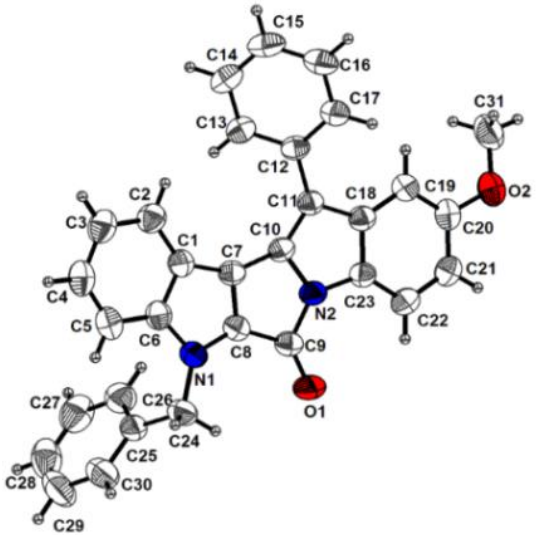


Figure 9. ORTEP (ellipsoid contour probability 50%) of compound **48**. Selected bond lengths [Å] with esds in parentheses: N(2)-C(10) 1.4065(19), C(10)-C(11) 1.363(2), N(2)-C(23) 1.394(2), C(18)-C(11) 1.466(2), C(11)-C(12) 1.466(2).

With the above optimized reaction conditions in hand, we moved further to investigate the substrate scope in the palladium catalyzed C-H activation with the 3-alkynylindole-3-carboxamides (**5a-5j**). In all the cases, good to excellent yields of the pyrrolodiindolones **48-57** were obtained (Scheme 15, Table 8). The reaction worked well with a wide variety of substituents that included 4-Me, 4-OMe, 3-Me, 4-Cl, and 4-F, affording the pyrrolodiindolone derivatives **48-57** in 75-86% yield. Electron releasing substituents on the phenyl rings of alkyne or amide moiety gave excellent results (compounds **48-55**). Substrates with R^1 being benzyl, methyl and ethoxymethylether (EOM) also worked well.

Scheme 15

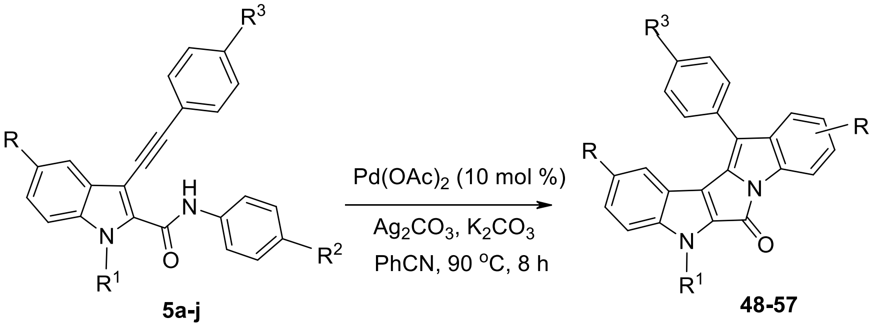
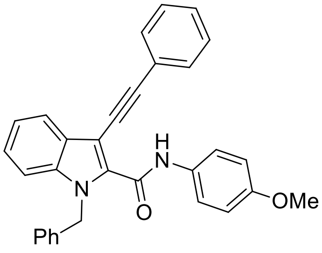
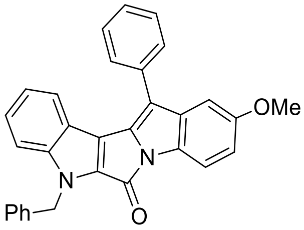
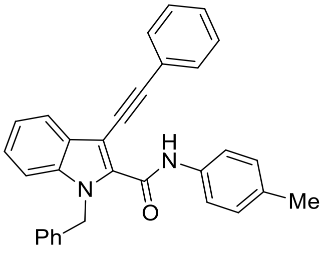
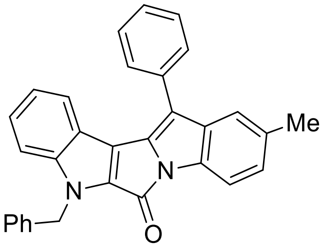
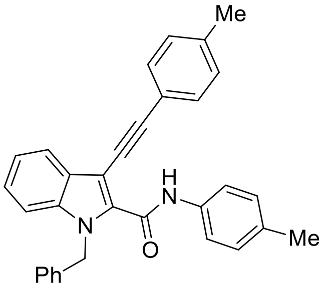
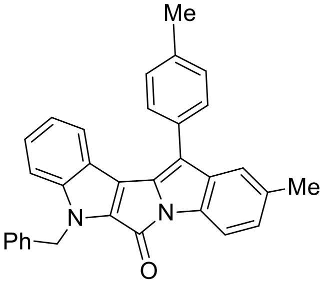
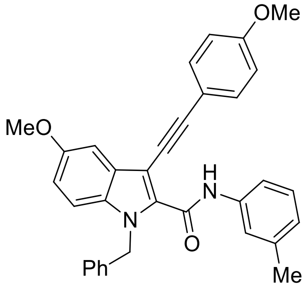
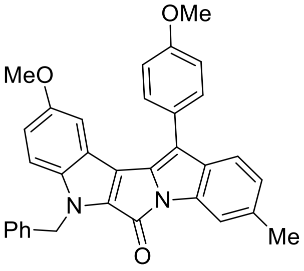
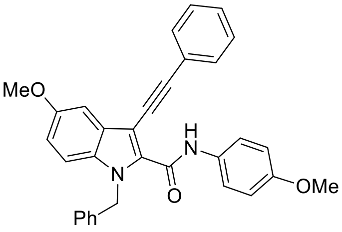
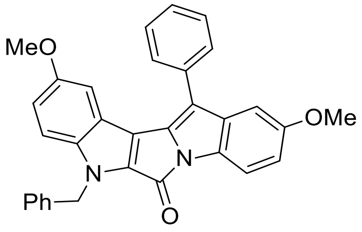
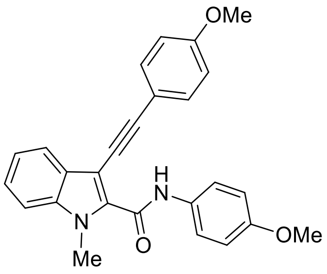
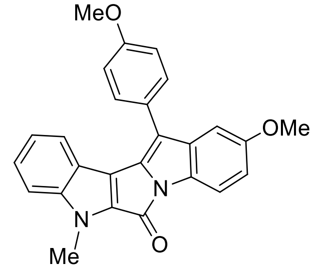
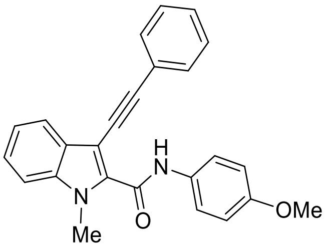
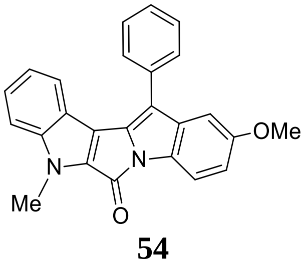
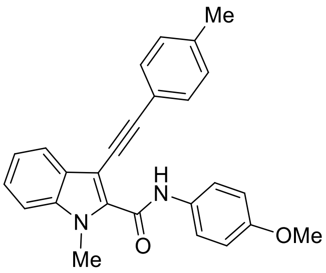
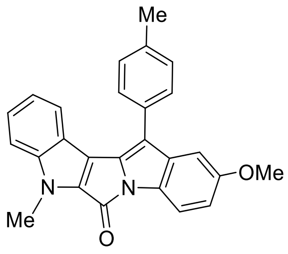
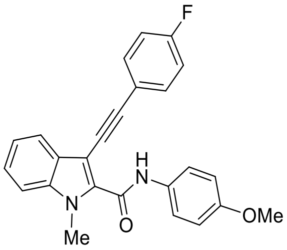
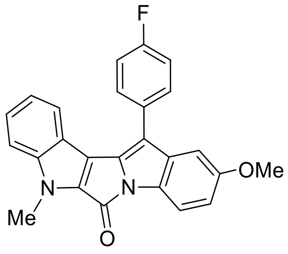
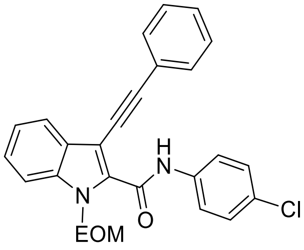
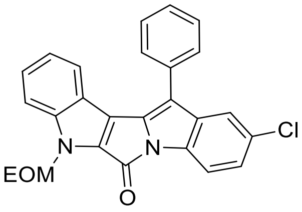


Table 8. Substrate scope for the palladium-catalyzed cyclization and C-H activation of 3-alkynylindole-2-carboxamides (**5**)^a

Entry	3-Alkynyl-indole-2-carboxamides	Pyrrolodiindolones	Yield (%)^b
1	 **5a**	 **48** (X-ray)	82

2	 **5b**	 **49**	80
3	 **5c**	 **50**	85
4	 **5d**	 **51**	86
5	 **5e**	 **52**	79
6	 **5f**	 **53**	81

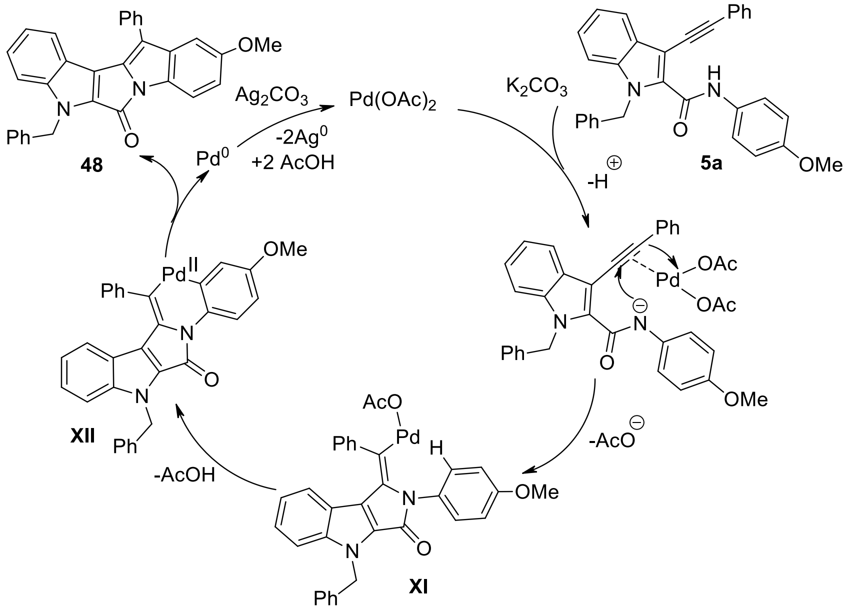
7	 **5g**	 **54**	75
8	 **5h**	 **55**	78
9	 **5i**	 **56**	76
10	 **5j**	 **57**	75

[a]Reaction conditions: alkynylamide **5** (0.4 mmol), Pd(OAc)$_2$ (10 mol %), Ag$_2$CO$_3$ (0.8 mmol), K$_2$CO$_3$ (0.4 mmol), PhCN (2 mL), 90 ^{o}C (oil bath temperature) for 8 h. [b]Isolated yields.

2.8.2 Plausible reaction pathway for the formation of pyrrolodiindolone 48

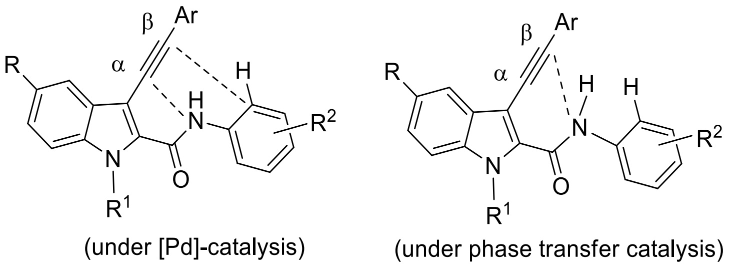
A plausible pathway for the formation of pyrrolodiindolone product **48** is shown in Scheme 16. First, the NH group in the amide moiety may undergo deprotonation in the presence of base to produce an anion which attacks $Pd(OAc)_2$ activated alkynic π-bond[93] to generate the vinylpalladium species[93a,f,g,k] **XI** *via* 5-*endo-dig* mode of cyclization (Scheme 16). Species **XI** may undergo intramolecular C-H activation leading to the palladacycle intermediate **XII**. Finally, **XII** upon reductive elimination may yield pyrrolodiindolone **48** and Pd^0 species. Later, Pd^0 is reoxidized to Pd^{II} by Ag^I in the next step.

Scheme 16



2.9 Phase transfer (solid-liquid) catalyzed intramolecular cyclization of 3-alkynylindole-2-carboxamides

In contrast to the above reaction, when we used tetra-*n*-butyl ammonium bromide (TBAB) as the catalyst, the 3-alkynylindole-2-carboxamides underwent intramolecular cyclization to produce β-carbolinones with remarkable regio- and chemo-selectivity. Thus, as shown below, the cyclization using the precursor 3-alkynylindole-2-carboxamide need not always lead to the formation of the five-membered ring by 5-*exo-dig* cyclization that connects the *N*-end to the α-carbon of the alkyne. Under simple phase transfer catalytic conditions, cyclization utilizing the *N*-end and the β-carbon of the alkyne leading to β-carbolinones by 6-*endo-dig* cyclization may be readily effected. This type of reaction is described below. The resulting β-carbolinone moiety is present various bioactive molecules that have immense medicinal value and hence this system is of some practical significance.[94]



2.9.1 Synthesis of β-carbolinones via phase transfer catalyzed cyclization

Initially, we started by treating 1-benzyl-*N*-(4-methoxyphenyl)-3-(phenylethynyl)-1*H*-indole-2-carboxamide **5a** with K_2CO_3 (2.0 equiv) in CH_3CN solvent at 80 °C (Scheme 17, Table 9, entry 1) that afforded the corresponding β-carbolinone **58** in 48% yield (starting material was not completely consumed). A simple switch from K_2CO_3 to Cs_2CO_3 resulted in increase in the yield of compound **58** upto 56% (Table 9, entry 2). Interestingly, complete consumption of starting material was observed and the yield of **58** dramatically increased to 90% when TBAB (10 mol %) was used as the catalyst and Cs_2CO_3 as the base (entry 3). The product yield decreased and the starting material was not consumed completely when the reaction was conducted at rt for 24 h (entry 4). The yield was lower when the catalyst loading was decreased to 5 mol % (entry 5) or by using one equiv of Cs_2CO_3 (entry 6). When other phase transfer catalysts such as tetrabutylammonium chloride (TBAC), tetrabutylammonium fluoride (TBAF), tetrabutylammonium iodide (TBAI) or tetraethylammonium bromide (TEAB) were applied to this process, the yield was not better than that by using TBAB (entries 7-10). Bases such as Li_2CO_3, K_3PO_4, KO^{t}Bu and KOAc gave lower yields than Cs_2CO_3 (entries 11-14). Solvents like PhCN, DMF, DMSO and DMA were less effective than CH_3CN (entries 15-18).

Scheme 17

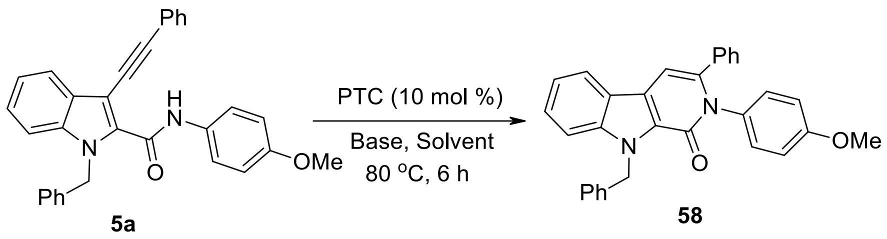


Table 9. Optimization study for the phase transfer catalyzed intramolecular cyclization of **5a** for the synthesis of β-carbolinone **58**^{a}

Entry	PTC	Base	Solvent	Yield of **58** (%)^b
1	-	K_2CO_3	CH_3CN	48
2	-	Cs_2CO_3	CH_3CN	56
3	**TBAB**	$\mathbf{Cs_2CO_3}$	$\mathbf{CH_3CN}$	**90**
4	TBAB	Cs_2CO_3	CH_3CN	45^c
5	TBAB	Cs_2CO_3	CH_3CN	65^d
6	TBAB	Cs_2CO_3	CH_3CN	73^e
7	TBAC	Cs_2CO_3	CH_3CN	79
8	TBAF	Cs_2CO_3	CH_3CN	80
9	TBAI	Cs_2CO_3	CH_3CN	72
10	TEAB	Cs_2CO_3	CH_3CN	81
11	TBAB	Li_2CO_3	CH_3CN	70
12	TBAB	K_3PO_4	CH_3CN	55
13	TBAB	KO^{t}Bu	CH_3CN	68
14	TBAB	KOAc	CH_3CN	58
15	TBAB	Cs_2CO_3	PhCN	70

16	TBAB	Cs_2CO_3	DMF	85
17	TBAB	Cs_2CO_3	DMSO	74
18	TBAB	Cs_2CO_3	DMA	81

[a]Reaction conditions: alkynylamide **5a** (0.4 mmol), PTC (10 mol %), base (0.8 mmol), solvent (2 mL), 80 °C (oil bath temperature) for 6 h. [b]Isolated yields. [c]Reaction was performed at rt (25 °C) for 24 h. [d]5 mol% of TBAB was used. [e]One equiv of Cs_2CO_3 was used.

Following the above optimized reaction conditions, we examined the scope of phase transfer catalyzed intramolecular cyclization for highly regio- and chemo-selective formation of β-carbolinones (**58-72**). The results are summarized in Scheme 18. The yields were, in general, very good. On introducing aryl groups on the amide moiety, the desired products (**58-67** and **70-72**) were isolated in good to excellent yields irrespective of the presence of electron-withdrawing or electron-donating groups. Furthermore, we evaluated the effect of various substituents on the remote end of the alkyne moiety. A variety of groups like 4-Me, 4-OMe, 3-Me and 4-F worked well and afforded the corresponding β-carbolinone derivatives in 74-85% yield. Importantly, alkyl substituents such as methyl and benzyl attached to nitrogen of the amide moiety resulted in β-carbolinones (**68-69**) with excellent yields. The structure of 2-(4-methoxyphenyl)-9-methyl-3-(*p*-tolyl)-2,9-dihydro-1*H*-pyrido[3,4-b]indol-1-one **65** was confirmed by X-ray crystallography (Figure 10).

Scheme 18

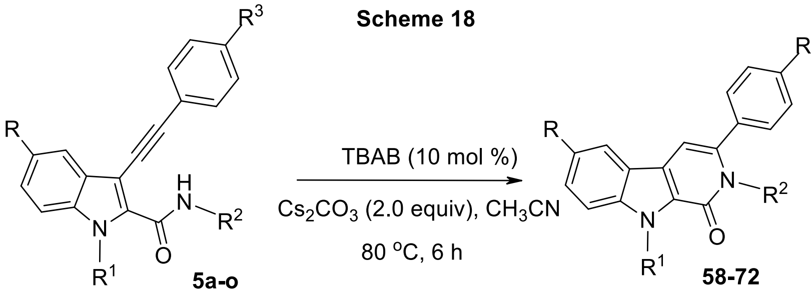
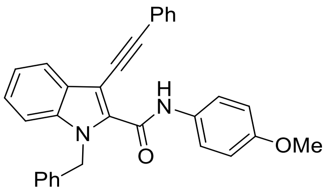
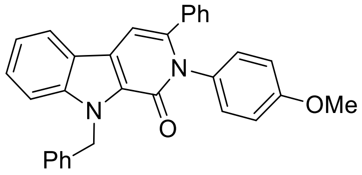
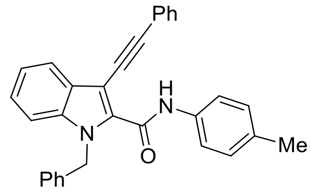
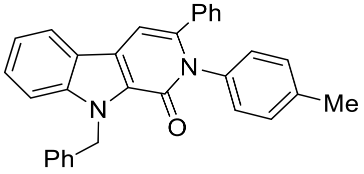
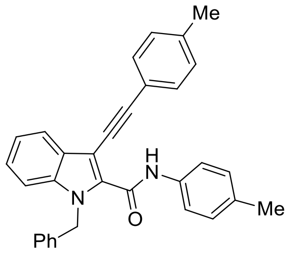
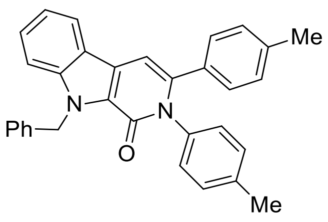
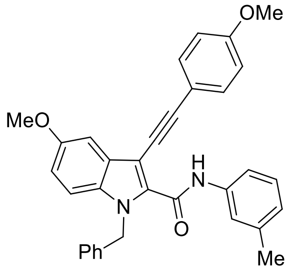
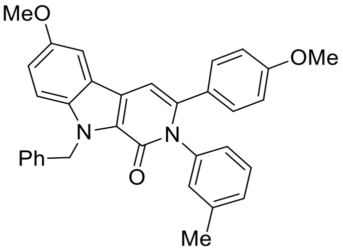
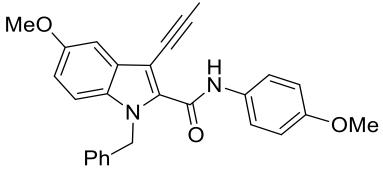
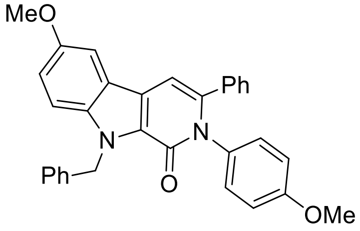
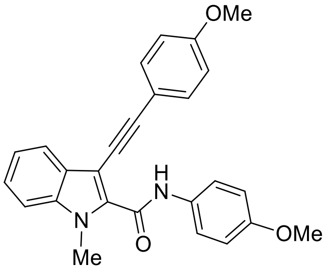
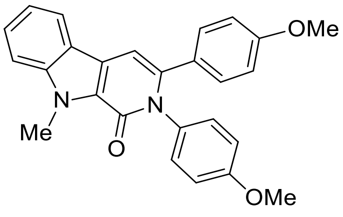
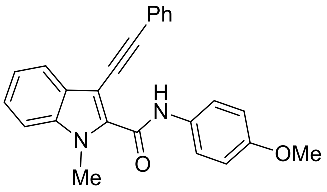
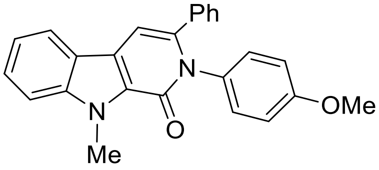
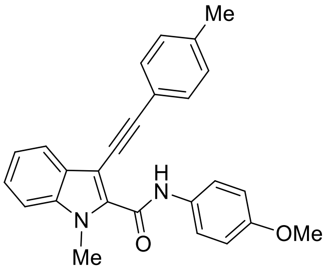
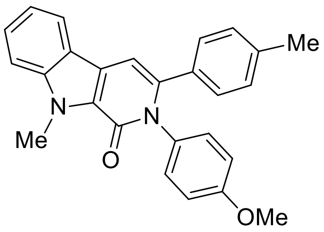
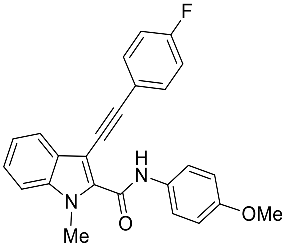
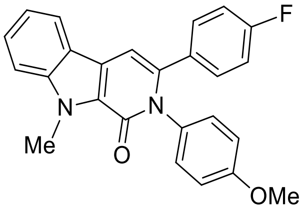
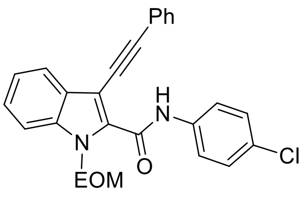
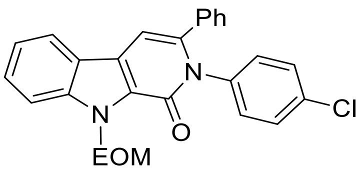
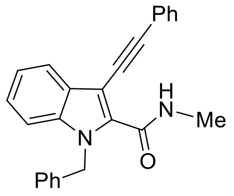
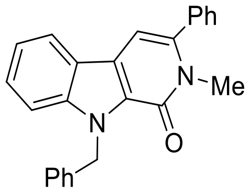
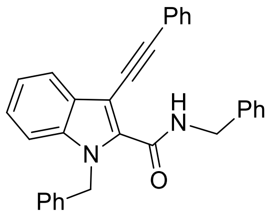
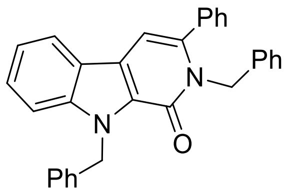
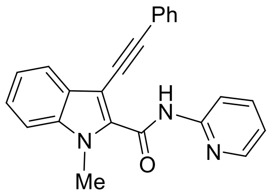
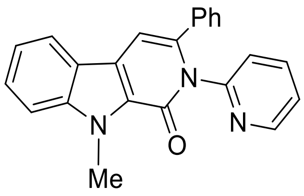
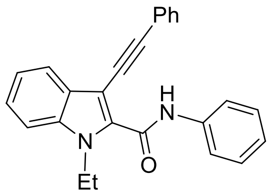
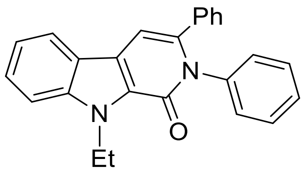
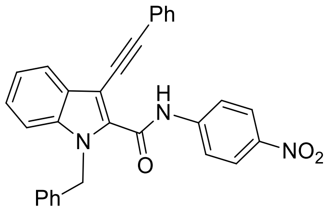
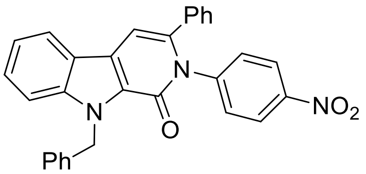


Table 10. Phase transfer catalyzed synthesis of β-carbolinones **58-72**[a]

Entry	3-alkynyl-indole-2-carboxamides	β-carbolinones	Yield (%)[b]
1	 **5a**	 **58**	94
2	 **5b**	 **59**	85
3	 **5c**	 **60**	76
4	 **5d**	 **61**	85
5	 **5e**	 **62**	89

6	 **5f**	 **63**	80
7	 **5g**	 **64**	91
8	 **5h**	 **65** (X-ray)	83
9	 **5i**	 **66**	74
10	 **5j**	 **67**	78

11	 **5k**	 **68**	93
12	 **5l**	 **69**	90
13	 **5m**	 **70**	88
14	 **5n**	 **71**	91
15	 **5o**	 **72**	70

[a]Reaction conditions: alkynylamide **5a-o** (0.4 mmol), TBAB (10 mol %), Cs_2CO_3 (0.8 mmol), CH_3CN (2 mL), 80 °C (oil bath temperature) for 6 h. [b]Isolated yields.

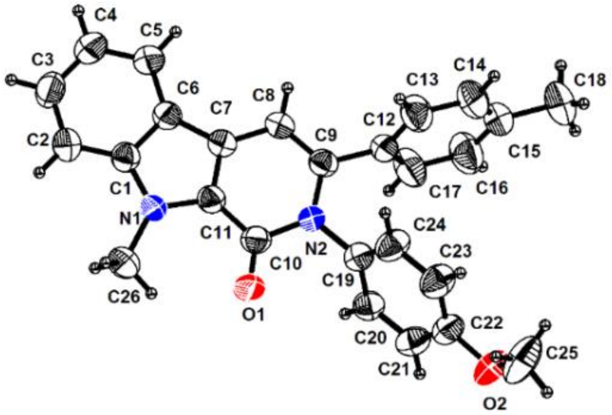
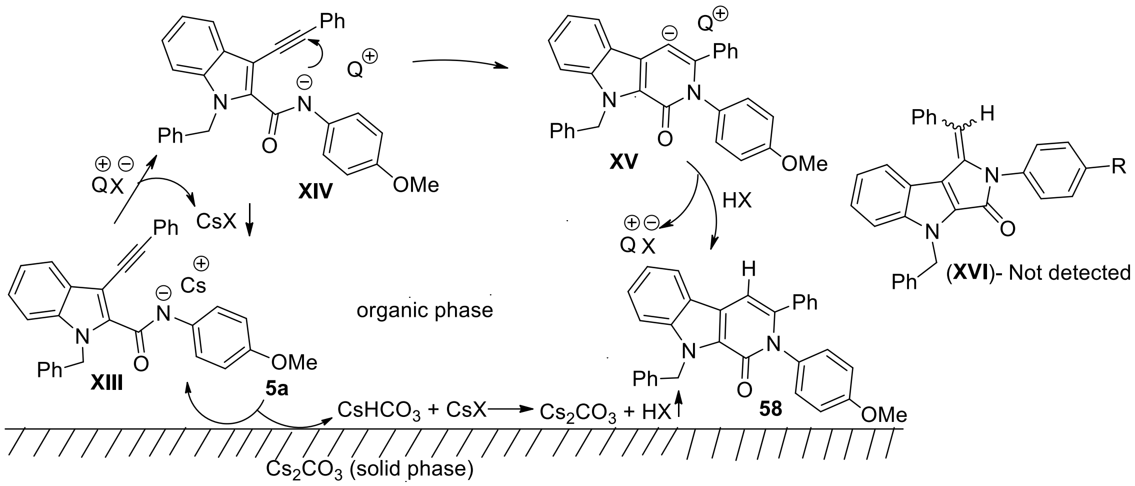


Figure 10. ORTEP (ellipsoid contour probability 50%) of compound **65**. Selected bond lengths [Å] with esds in parentheses: N(2)-C(9) 1.406(2), C(8)-C(9) 1.351(2), C(9)-C(12) 1.492(2), N(2)-C(19) 1.442(2).

2.9.2 Plausible reaction pathway for the formation of β-carbolinones 58

Formation of β-carbolinone **58** may be rationalized by solid-liquid phase transfer catalytic (SL-PTC) mechanism (Scheme 19).[95] 3-Alkynyl-indole-2-carboxamide **5a** reacts with solid Cs_2CO_3 at the interphase, giving the caesium salt **XIII**.[95a,d,e,f] In the presence of PTC (Q^+X^-), salt **XIII** is transferred into the bulk of the organic phase where exchange of cations results in species **XIV**.[95a,d,e,f] The amidic anion in the species **XIV** readily attacks the β-carbon of the alkyne via 6-*endo-dig* cyclisation producing species **XV**. In the [Pd]-catalyzed reaction, the palladium moiety prefers the alkynyl carbon close to the aryl group, but in the reaction using TBAB, the corresponding end is more readily available (or sterically favored) for the nucleophilic attack of the amidic anion leading to the formation of the six-membered ring. The anionic species **XV** present in the organic phase reacts with HX leads to the formation of β-carbolinone **58** and a Q^+X^- is regenerated. It is possible that there is a 'co-solvent' effect by TBAB, but we have not studied this aspect further. Finally, a species like **XVI** with a new five-membered ring was not detected in the reaction using TBAB, although in principle, traces of this compound could have been formed.

Scheme 19



2.10 Palladium-catalyzed decarboxylative *ortho*-amidation of indole-3-carboxylic acids by using the carboxylic acid as a traceless directing group

After successful study of decarboxylative nitrile insertion reactions of indole-2-carboxylic acids as described in previous sections, we thought that this decarboxylative coupling is an equally interesting approach for *ortho* C-H functionalization also. Notably, this carboxyl group can direct the regioselectivity and the only waste product from the reaction is CO_2. This indicates that the carboxyl group may act as a unique, traceless directing group (or removable directing group). With this in mind, we have chosen indole-3-carboxylic acid as a precursor for C-H functionalization, especially for C-H amidation, where carboxyl group can act as traceless directing group.

2.10.1 Synthesis of indole-2-carboxamides by decarboxylative ortho-amidation of indole-3-carboxylic acids with isothiocyanates

We commenced our studies by employing 1-methyl-1*H*-indole-3-carboxylic acid **6a** and phenylisothiocyanate **8a** as model substrates. Thus the reaction of **6a** with 3 equiv of **8a** was performed in the presence of 10 mol % of $Pd(OAc)_2$ and 2.0 equiv of Ag_2CO_3 in CH_3CN solvent at 80 ^{o}C in open air. This reaction afforded the desired C2-amidation product **73** in 45% yield (Scheme 20, Table 9, entry 1). Addition of a base like K_2CO_3 (2.0 equiv) led to further improvement of yield (entry 2). A sequence of control experiments were performed to check the role of both [Pd]-catalyst and Ag_2CO_3.

In the absence of $Pd(OAc)_2$, the desired product **73** (entry 3) was not formed. Next, the reaction was conducted in the presence of $Pd(OAc)_2$ catalyst, without Ag_2CO_3. In this case, we observed 61 % of the desired product (entry 4). From this experiment, we concluded that there was no role for Ag_2CO_3 in the reaction. Further investigation on the effect of bases on the reaction outcome showed that Cs_2CO_3 provided the best result (Table 9, entries 5-9). Gratifyingly, a drastic improvement in the yield was observed when we added the additive TBAB (tetrabutyl ammonium bromide). Thus the yield of **73** was increased to 83% (entry 10). A slight decrease in the yield was observed when we used O_2 (balloon) instead of open air condition (entry 11). The yield was lowered when the reaction was performed at room temperature (25 ^{o}C; entry 12). Screening of additives KOAc, AcOH and $AgSbF_6$ revealed that they were not much effective compared to TBAB (entries 13-15). Changing the solvent to DMF decreased the yield of **73** to 77% (entry 16). Other solvents like DCE and DMA did not improve the yield (entries 17–18). The [Pd] catalysts like $PdCl_2$, $Pd(OTf)_2$ were less effective than $Pd(OAc)_2$ (entries 19–20). The desired product was obtained in 40% yield when we used $Pd_2(dba)_3$ in the presence of Ag_2CO_3 (entry 21). The conclusion for this study was that the combination of 10 mol % of $Pd(OAc)_2$ as the catalyst, 1.0 equiv of Cs_2CO_3 and 0.5 equiv of TBAB in CH_3CN solvent at 80 °C for 6 h in open air (83% yield; Table 1, entry 10) was the optimum condition.

Scheme 20

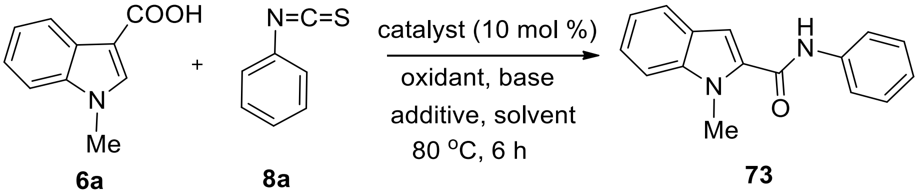


Table 11. Optimization Study for Palladium Catalyzed Decarboxylative Amidation[a]

Entry	Catalyst	Oxidant	Base	Additive	Solvent	Yield of **73** (%)[b]
1	$Pd(OAc)_2$	Ag_2CO_3	-	-	CH_3CN	45

2	$Pd(OAc)_2$	Ag_2CO_3	K_2CO_3	-	CH_3CN	63
3	-	Ag_2CO_3	K_2CO_3	-	CH_3CN	n.d.
4	$Pd(OAc)_2$	-	K_2CO_3	-	CH_3CN	61
5	$Pd(OAc)_2$	-	Cs_2CO_3	-	CH_3CN	70
6	$Pd(OAc)_2$	-	K_3PO_4	-	CH_3CN	58
7	$Pd(OAc)_2$	-	KO^tBu	-	CH_3CN	53
8	$Pd(OAc)_2$	-	NEt_3	-	CH_3CN	trace
9	$Pd(OAc)_2$	-	LiO^tBu		CH_3CN	
10	**$Pd(OAc)_2$**	**-**	**Cs_2CO_3**	**TBAB**	**CH_3CN**	**83**
11	$Pd(OAc)_2$	-	Cs_2CO_3	TBAB	CH_3CN	80[c]
12	$Pd(OAc)_2$	-	Cs_2CO_3	TBAB	CH_3CN	32[d,e]
13	$Pd(OAc)_2$	-	Cs_2CO_3	KOAc	CH_3CN	65
14	$Pd(OAc)_2$	-	Cs_2CO_3	AcOH	CH_3CN	78
15	$Pd(OAc)_2$	-	Cs_2CO_3	$AgSbF_6$	CH_3CN	70
16	$Pd(OAc)_2$	-	Cs_2CO_3	TBAB	DMF	77
17	$Pd(OAc)_2$	-	Cs_2CO_3	TBAB	DCE	trace
18	$Pd(OAc)_2$	-	Cs_2CO_3	TBAB	DMA	70
19	$PdCl_2$	-	Cs_2CO_3	TBAB	CH_3CN	67
20	$Pd(OTf)_2$	-	Cs_2CO_3	TBAB	CH_3CN	78
21	$Pd_2(dba)_3$	Ag_2CO_3	Cs_2CO_3	TBAB	CH_3CN	40[e]

[a] Reaction conditions: indole-3-carboxylicacid **6a** (0.5 mmol), isothiocyanate **8a (**1.5 mmol), [Pd]-catalyst (10 mol%), oxidant (1.0 mmol), base (0.5 mmol), additive (0.25 mmol), solvent (2 mL), 80 °C (oil bath temperature) for 6 h in open air. [b] Isolated yields. [c] O_2 (balloon) was used. [d] Reaction was performed at rt (28 °C). [e] Starting material remained.

Encouraged by the above results, we evaluated the substrate scope for this protocol. As shown by the examples in Table 10 (Scheme 21), this method was applicable to the C2-amidation of a broad array of indole-3-carboxylic acids with various isothiocyanates affording good to excellent yields of indole-2-carboxamides. The scope of isothiocyanates was investigated first by using 1-methyl-indole-3-carboxylic acid **6a** as the partner. Phenylisothiocyanates bearing electron-rich, electron neutral or electron-deficient groups reacted well with **6a** and afforded the corresponding indole-2-carboxamides **73-78** in excellent yields (71-90%). The structure of compound **77** was confirmed by single crystal X-ray analysis (Figure 11). We then examined the scope of the reaction with respect to the indole partner. *N*-Protected indole-3-carboxylic acids were thus evaluated, and the substrates with protecting groups *n*-Bu, benzyl (Bn), MOM and propargyl provided the indole-2-carboxamides **79-81, 84, 85** and **87**, respectively, in good yields. Interestingly, tolerance of the terminal triple bond in the product (**81**) enhances the utility of this protocol. Indole-3-carboxylic acids with substituents at 5- and 6-positions on the phenyl ring of indole moiety also reacted smoothly with phenylisothiocyanate **8a**. Thus, 5,6-dimethoxy-1-methyl-indole-3-carboxylic acid **(6f)**, 5-benzoxy-1-methyl-indole-3-carboxylic acid (**6g**) and 5-methoxy-1-benzyl-indole-3-carboxylic acid **(6h)** reacted well with **8a** affording the corresponding 2-amides **82-84** in excellent yields. The reaction of 5-fluoro-1-methoxymethyl-indole-3-carboxylic acid (**6i**) with **8c** also gave the corresponding amide **85** in good yields. We were pleased to find that the amidation reaction of indole-3-carboxylic acids with alkylisothiocyanates (**8g-h**) afforded the indole-2-carboxamides (**85-88**) in excellent yields (83–90%).

Scheme 21

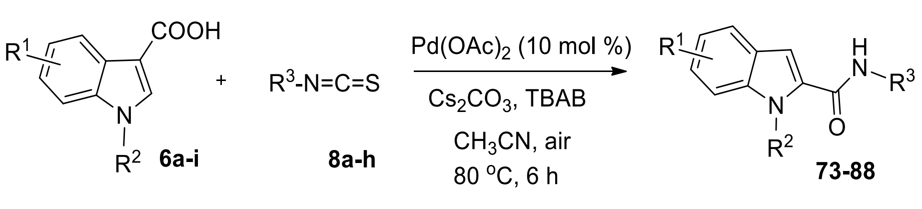
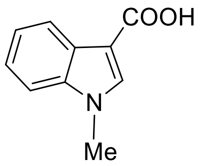
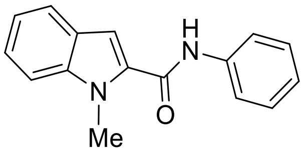
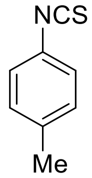
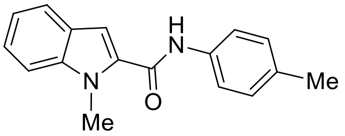
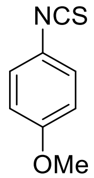
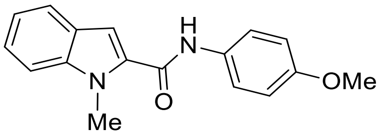
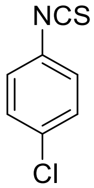
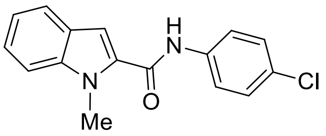
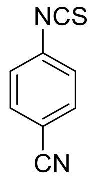
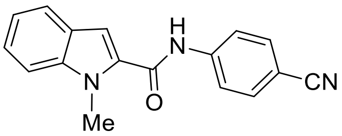
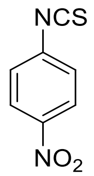
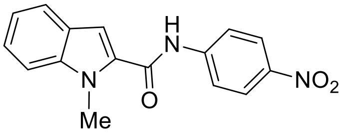
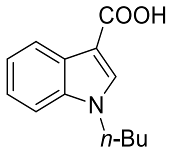
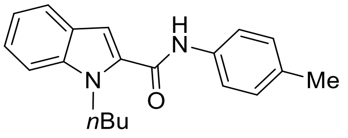
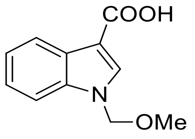
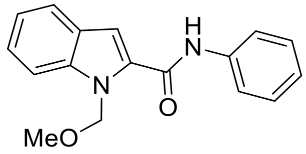
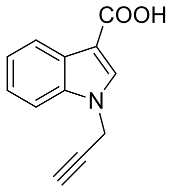
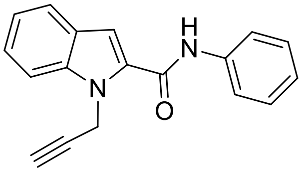
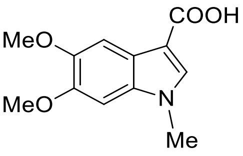
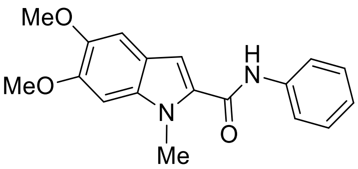
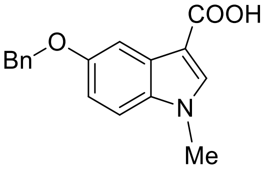
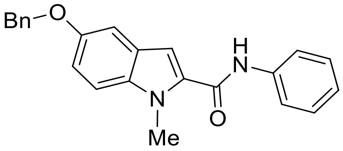
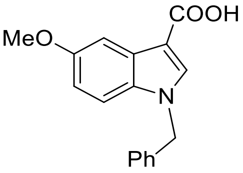
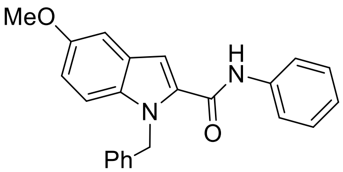
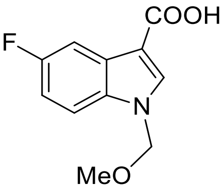
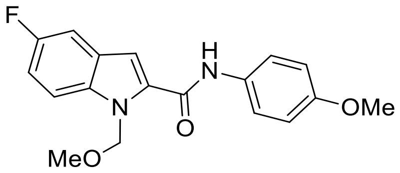
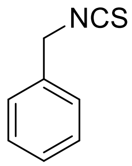
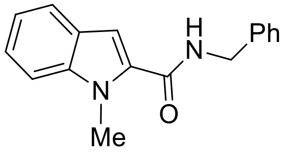
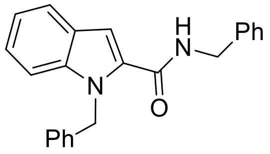
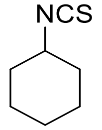
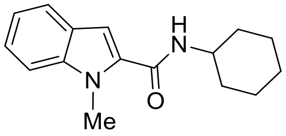


Table 12. Substrate Scope for the Palladium-catalyzed Decarboxylative Amidation by C-H Activation of indole-3-carboxylic acids (**6a-i**) with isothiocyanates (**8a-h**).[a]

Entry	Indole acid	Isothiocyanate	Indole-2-carboxamide	Yield (%)[b]
1	 **6a**	PhNCS **8a**	 **73**	83
2	**6a**	 **8b**	 **74**	85
3	**6a**	 **8c**	 **75**	90
4	**6a**	 **8d**	 **76**	78
5	**6a**	 **8e**	 **77** (X-ray)	75
6	**6a**	 **8f**	 **78**	71

7	 **6b**	**8b**	 **79**	80
8	 **6d**	**8a**	 **80**	70
9	 **6e**	**8a**	 **81**	76
10	 **6f**	**8a**	 **82**	87
11	 **6g**	**8a**	 **83**	86
12	 **6h**	**8a**	 **84**	87
13	 **6i**	**8c**	 **85**	68

14	**6a**	 **8g**	 **86**	90
15	**6c**	**8g**	 **87**	87
16	**6a**	 **8h**	 **88**	83

[a]Reaction conditions: **6a-i** (0.5 mmol), isothiocyanate **8a-h (**1.5 mmol), $Pd(OAc)_2$ (10 mol %), Cs_2CO_3 (0.5 mmol), TBAB (0.25 mmol), CH_3CN (2 mL), 80 °C (oil bath temperature) for 6 h in open air. [b]Isolated yields.

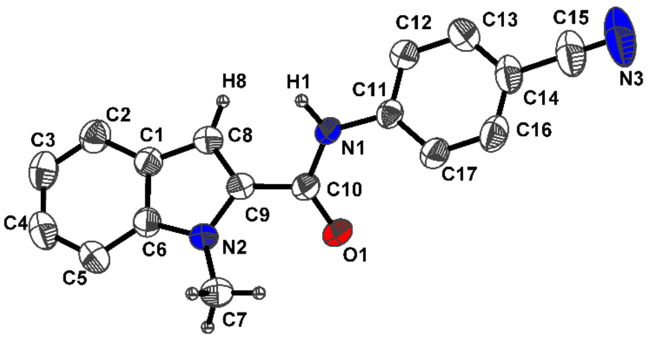


Figure 11. ORTEP (ellipsoid contour probability 50%) of compound **77**. Selected bond lengths [Å] with esds in parentheses: C(9)-C(10) 1.468(2), N(1)-C(10) 1.360(2), N(1)-C(11) 1.405(2), C(15)-N(3) 1.144(3). Hydrogen atoms are omitted for clarity.

2.10.2 Palladium-catalyzed decarboxylative ortho-amidation of heteroaromatic carboxylic acids

To extend the reaction scope of above amidation reaction, we proceeded to study the decarboxylative amidation of heteroaromatic carboxylic acids with phenylisothiocyanate under the above optimized reaction conditions. The results are summarized in Table 11 (Scheme 22). As shown in the Table, 2*H*-chromene-3-carboxylic acid **9** reacted with **8a** *via* C3-amidation and decarboxylation to afford compound **89** (*N*-phenyl-2*H*-chromene-4-carboxamide) in 85% yield (entry 1). This is a rare example of amidation as this chromene-4-carboxamide is not known in the literature. Imidazo[1,2-*a*]pyridine-2-carboxylic acid **10** also reacted well with **8a** to give *N*-phenylimidazo[1,2-*a*]pyridine-3-carboxamide **90** in 75% yield. As expected, 1-methyl-indole-2-carboxylic acid **1a** underwent decarboxylative amidation with phenylisothiocyanate resulting in C3-amidation product **91** in excellent yield (88%, entry 3). Benzofuran-2-carboxylic acid **11** and thiophene-2-carboxylic acid **12** also reacted smoothly under the optimized conditions to afford the corresponding 3-substituted amides (**92** & **93**) in good yields (entries 4-5). Pyrrole-2-carboxylic acid **13** also produced the amidation product **94** in moderate yield (entry 6).

Scheme 22

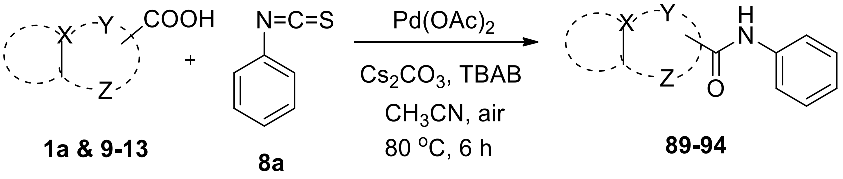
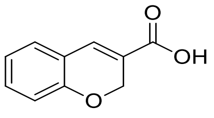
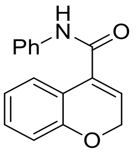
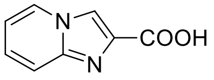
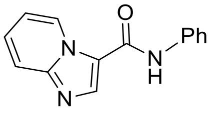
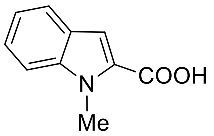
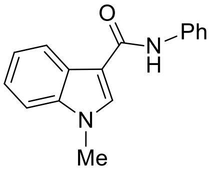
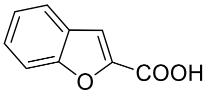
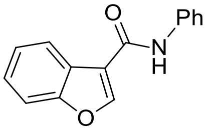
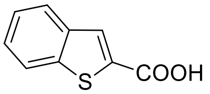
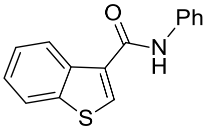
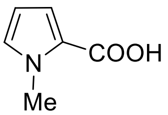
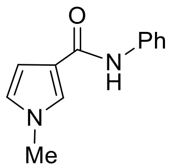


Table 11. Study of Decarboxylative Amidation Reaction of Heteroaromatic Systems.[a]

Entry	Carboxylic acids	Products	Yield[b]
1	 **9**	 **89**	85
2	 **10**	 **90**	84

3	 **1a**	 **91**	88
4	 **11**	 **92**	76
5	 **12**	 **93**	70
6	 **13**	 **94**	65

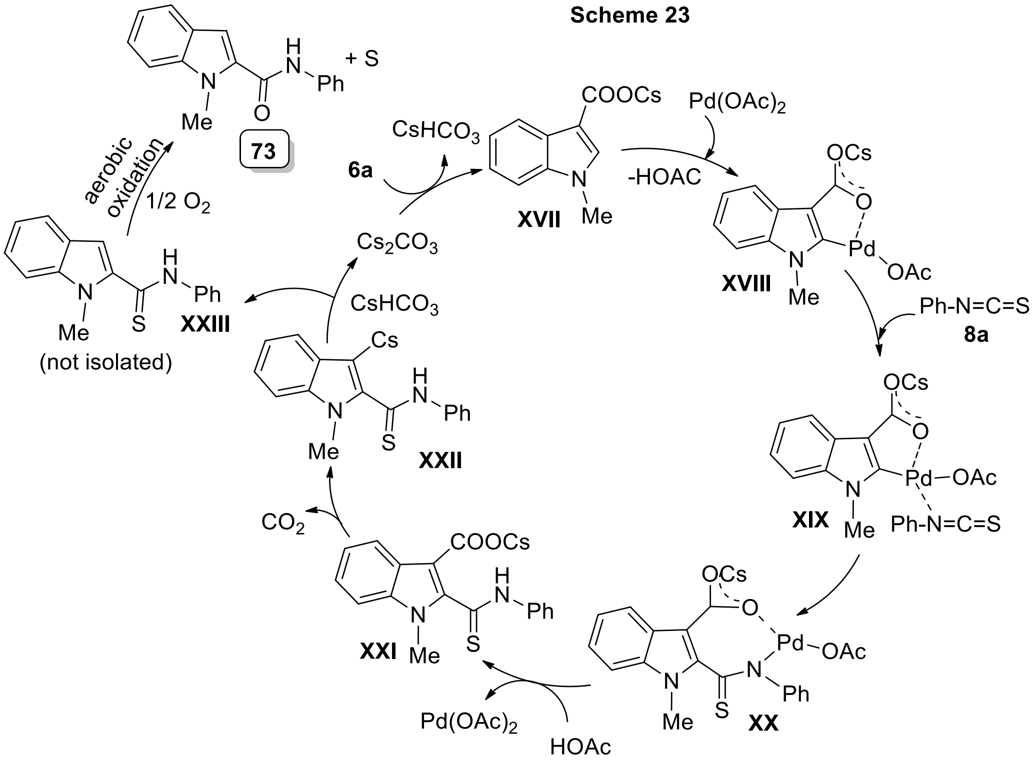
[a]Reaction conditions: carboxylic acid (0.5 mmol), phenylisothiocyanate **8a (**1.5 mmol), $Pd(OAc)_2$ (10 mol %), Cs_2CO_3 (0.5 mmol), TBAB (0.25 mmol), CH_3CN (2 mL), 80 °C (oil bath temperature) for 6 h in open air. [b]Isolated yields.

2.10.3 Plausible pathway for the formation C2-amidation product 73 using the carboxyl group as traceless directing group

To the best of our knowledge, there are no previous reports on the palladium catalyzed decarboxylative *ortho*-amidation of indole-3-carboxylic acids using isothiocyanates. It is important to note that in these reactions, ***decarboxylation takes place at C-3, but amidation takes place at C-2 carbon*** of the heterocyclic carboxylic acid. To propose the mechanistic pathway, we followed the recent literature reports on transition metal catalyzed amidation reactions using isocyanates.[96] Based on these reports, a few palladium catalyzed decarboxylative reactions,[84a,b,97] and recent literature on metal catalyzed decarboxylation through carboxyl group as traceless directing group,[98] a tentative mechanism to rationalize the decarboxylative amidation is depicted in Scheme 23. Initially, carboxylic acid **6a** reacts with Cs_2CO_3 to afford cesium carboxylate **XVII**, which is further converted to a five membered palladacycle **XVIII**.

This palladacycle **XVIII** is expected to be derived from the coordination of $Pd(OAc)_2$ to the carboxylic oxygen followed by subsequent *ortho*-C-H bond activation with the elimination of AcOH. Now, phenylisothiocyanate **8a** will enter into the catalytic cycle and coordinates to the palladium resulting in intermediate **XIX**.[96,97a] Subsequently, the seven membered palladacycle complex **XX** is generated by insertion of the C=N double bond into the Pd-C bond of intermediate **XIX**. A new C-C bond is formed in this step. Next, in the presence of AcOH, the cesium carboxylate species **XXI**[98a] is generated with protonation at amidic nitrogen, thus regenerating $Pd(OAc)_2$ for the next catalytic cycle. Finally, decarboxylation of **XXI** followed by protonation provides the indole-2-thioamide **XXIII** and Cs_2CO_3. Thioamide **XXIII** may further be transformed to indole-2-carboxamide **73** by aerobic oxidation with elemental sulfur as by product.[99] It is true that indole-2-carboxamides may be accessible by the corresponding acid chlorides, but from the chemistry point of view, the route described here is interesting in its own right. The same product may be obtainable by using isocyanates, but this aspect yet to be investigated.

Scheme 23



2.11 Utility of Indole-2-carboxamides: Synthesis of Diindole-fused Pyridones *via* Palladium-Catalyzed C-H bond activation

After the synthesis of indole-2-carboxamides using carboxylic acid as the traceless directing group, we aimed for the [Pd]-catalyzed nitrile insertion reaction using indole-2-carboxamides by C-H and N-H bond cleavage. We started our reaction by using *N*-(4-methoxyphenyl)-1-methyl-1*H*-indole-2-carboxamide **75** in the presence of $Pd(OAc)_2$ as catalyst, Ag_2CO_3 as the oxidant and Cs_2CO_3 as the base in benzonitrile at 90 ^oC/ 14 h. Surprisingly, we did not observe nitrile inserted product but instead obtained the diindole fused 2-pyridone **95** (58% yield) by C-C and C-N bond formation (Scheme 24). This unusual formation of diindole fused 2-pyridone may be feasible by combining two molecules of indole moiety attached at C3-position for the C-C and C-N bond formation with the elimination of one of the amide group (*via* amine and CO_2). The structure of this diindole fused 2-pyridone **95** was confirmed by X-ray crystallography (Figure 12). To maximize the yield of diindole fused pyridone **95**, we screened several reaction conditions as shown in Table 12. As was mentioned before, by using PhCN as the solvent 58% of the desired product was formed (Table 12, entry 1). By changing the solvent from PhCN to CH_3CN and keeping the temperature at 80 ^oC, the yield of **95** was increased to 66% (entry 2). Pleasingly, the yield of **95** after isolation was increased to 75% when DMF was used as the solvent at 110 ^oC (entry 3). Addition of an additive like TBAB decreased the yield (entry 4). Alternative bases, such as K_2CO_3, KO^tBu and K_3PO_4, provided lower yields when compared to Cs_2CO_3 (entries 5-8). Other oxidants like $Cu(OAc)_2$ did not improve the yield of **95** (entry 9). There was no improvement in the yield when Pd(0) complex $Pd_2(dba)_3$ was used instead of $Pd(OAc)_2$ (entry 10).

Scheme 24

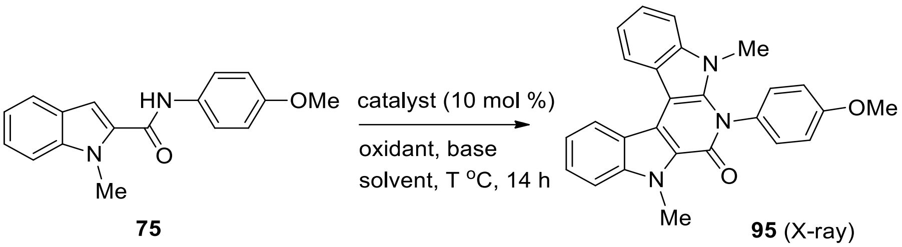


Table 12. Optimization Study for Palladium Catalyzed Formation of Diindole Fused 2-Pyridone **95**[a]

Entry	Catalyst	Oxidant	Base	Solvent, T (°C)[b]	Yield of **95** (%)[c]
1	$Pd(OAc)_2$	Ag_2CO_3	Cs_2CO_3	PhCN, 90	58
2	$Pd(OAc)_2$	Ag_2CO_3	Cs_2CO_3	CH_3CN, 80	66
3	**$Pd(OAc)_2$**	**Ag_2CO_3**	**Cs_2CO_3**	**DMF, 110**	**78**
4	$Pd(OAc)_2$	Ag_2CO_3	Cs_2CO_3	DMF, 110	56[d]
5	$Pd(OAc)_2$	Ag_2CO_3	K_2CO_3	DMF, 110	60
6	$Pd(OAc)_2$	Ag_2CO_3	K_2CO_3	CH_3CN, 80	58
7	$Pd(OAc)_2$	Ag_2CO_3	KO^tBu	DMF, 110	50
8	$Pd(OAc)_2$	Ag_2CO_3	K_3PO_4	DMF, 110	46
9	$Pd(OAc)_2$	$Cu(OAC)_2$	Cs_2CO_3	DMF, 110	51
10	$Pd_2(dba)_3$	Ag_2CO_3	Cs_2CO_3	DMF	32[e]

[a]Reaction conditions: indole-2-carboxamide **75** (0.5 mmol), [Pd]-catalyst (10 mol%), oxidant (1.0 mmol), base (0.5 mmol), solvent (DMF or CH_3CN; 3 mL) for.14 h. [b]oil bath temperature [c]Isolated yields. [d]TBAB (0.25 mmol) was used. [e]Starting material remained.

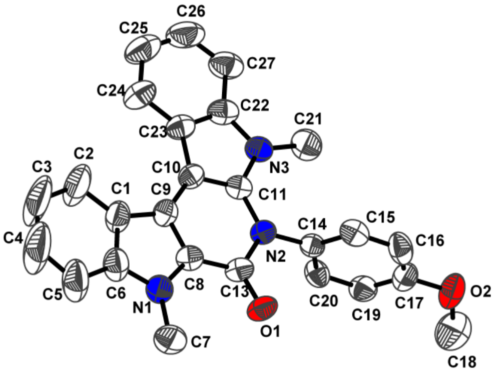
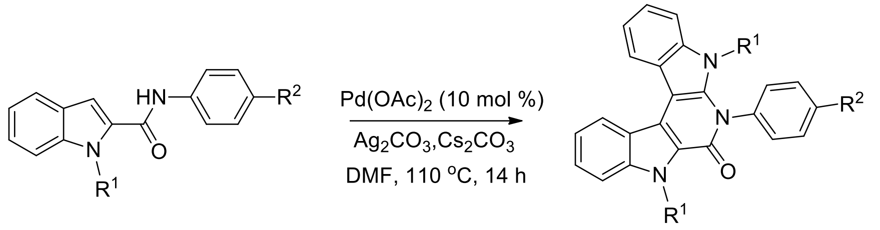


Figure 12. ORTEP (ellipsoid contour probability 50%) of compound **95**. Selected bond lengths [Å] with esds in parentheses: N(2)-C(11) 1.398(5), C(9)-C(10) 1.428(5), C(10)-C(111) 1.373(5), C(9)-C(8) 1.395(5). C(13)-O(1) 1.231(4), O(2)-C(18) 1.533(7). Hydrogen atoms are omitted for clarity.

Under the above optimized conditions, we have also synthesized compound **96** in 70% yield as shown in Scheme 25. We are still working on this system to examine the substrate scope by using diverse indole-2-carboxamides.

Scheme 25



R^1 = Me, R^2 = OMe; **75**
R^1 = *n*-Bu, R^2 = Me; **79**

R^1 = Me, R^2 = OMe; **95** (78%, X-ray)
R^1 = *n*-Bu, R^2 = Me; **96** (70%)

2.12 Ruthenium-catalyzed oxidative annulation *via* C-H functionalization

Ruthenium-catalyzed oxidative annulation with alkynes by C-H functionalizations has attracted recent interest as they avoid the multistep synthesis of pre-activated starting materials. To achieve this, we have chosen a benzopyran moiety with an amide functionality at the 3rd position. C-H functionalization on this benzopyran ring system with amide directing group has not reported so far. Benzopyran ring system is an ubiquitous substructural motif observed in many natural products, plays a pivotal role in the regulation of the activity in various biopolymers[100-101] and shows potent anti-HIV and anti-inflammatory activities.[102]

2.12.1 Ruthenium-catalyzed synthesis of benzopyran-fused 2-pyridones via C-H/N-H bond functionalization

In this part, we report the synthesis of benzopyran-fused 2-pyridones *via* ruthenium catalyzed oxidative annulation of chromene-3-carboxamides with alkynes through C-H and N-H bond cleavage. Our investigation began with the reaction of equimolar *N*-(4-methoxyphenyl)-2*H*-chromene-3-carboxamide **14a** with diphenylacetylene **15a** in the presence of $[RuCl_2(p\text{-cymene})]_2$ and $Cu(OAc)_2{\cdot}H_2O$ in *t*AmOH at 100 ºC. To our delight, this reaction afforded the desired cyclization product **97** in 50% yield (cf. Scheme 26 and Table 13, entry 1). Other oxidants like Ag_2CO_3, AgOAc and $CuCl_2$ did not improve the yield (entries 2-4). Gratifyingly, additives like NaOAc and KPF_6 improved the yield of **97** (entries 5-6). Subsequently, a series of other additives that include $AgSbF_6$, $AgBF_4$, AgOTf and $AgNTf_2$ were examined. Among these, $AgNTf_2$ was the most effective for the annulation (entries 7–10). In this case, we isolated **97** in 88% yield.

A series of control experiments were conducted to check the role of both [Ru]-catalyst and oxidant. In the absence of $Cu(OAc)_2{\cdot}H_2O$, the desired product **97** (entry 11) was not formed. Next, the reaction was conducted in the presence of $Cu(OAc)_2{\cdot}H_2O$, without the [Ru] catalyst. In this case also, the desired product could not be observed (entry 12). Changing the solvent to *t*BuOH decreased the yield of **97** to 69% (entry 13). Other solvents like *n*BuOH, DCE, DMF and H_2O did not improve the yield (entries 14–17). It is noteworthy that under the same catalytic conditions in open air also the reaction afforded the product in 65% yield (entry 18). Other [Ru]-catalysts like $[CpRuCl(PPh_3)_2]$, $[Ru(OAc)_2(p\text{-cymene})]$ and $[RuCl_2(benzene)]_2$ were evaluated, but they were less effective than $[RuCl_2(p\text{-cymene})]_2$ (entries 21–25). Thus, the combination of 5.0 mol % of $[RuCl_2(p\text{-cymene})]_2$ as the catalyst, 2 equiv of $Cu(OAc)_2{\cdot}H_2O$ as the oxidant and 30 mol % of $AgNTf_2$ as additive in *t*AmOH solvent at 100 °C for 14 h (88% yield; Table 13, entry 10) was found to be the optimum condition.

Scheme 26

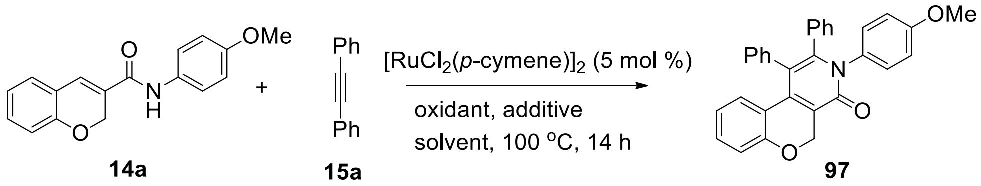


Table 13: Optimization study for the [Ru]-catalyzed oxidative annulation[a]

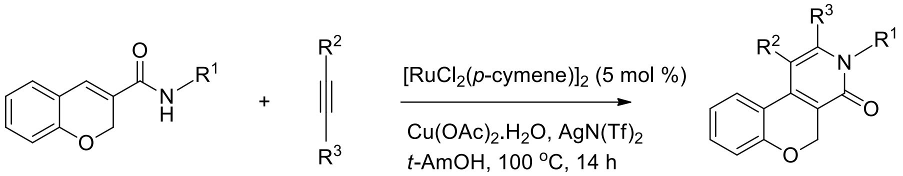
Entry	Oxidant	Additive	Solvent	Yield of **97** (%)[b]
1	$Cu(OAc)_2.H_2O$	-	*t*AmOH	50
2	Ag_2CO_3	-	*t*AmOH	trace
3	AgOAc	-	*t*AmOH	trace
4	$CuCl_2$	-	*t*AmOH	36
5	$Cu(OAc)_2.H_2O$	NaOAc	*t*AmOH	55
6	$Cu(OAc)_2.H_2O$	KPF_6	*t*AmOH	62
7	$Cu(OAc)_2.H_2O$	$AgSbF_6$	*t*AmOH	73
8	$Cu(OAc)_2.H_2O$	$AgBF_4$	*t*AmOH	71
9	$Cu(OAc)_2.H_2O$	AgOTf	*t*AmOH	77
10	**$Cu(OAc)_2.H_2O$**	**$AgNTf_2$**	***t*AmOH**	**88**
11	-	$AgNTf_2$	*t*AmOH	n.d.
12	$Cu(OAc)_2.H_2O$	$AgNTf_2$	*t*AmOH	n.d[c]
13	$Cu(OAc)_2.H_2O$	$AgNTf_2$	*t*BuOH	69

14	$Cu(OAc)_2.H_2O$	$AgNTf_2$	*n*BuOH	65
15	$Cu(OAc)_2.H_2O$	$AgN(Tf)_2$	DCE	52
16	$Cu(OAc)_2.H_2O$	$AgNTf_2$	DMF	48
17	$Cu(OAc)_2.H_2O$	$AgNTf_2$	H_2O	26
18	$Cu(OAc)_2.H_2O$	$AgNTf_2$	*t*AmOH	65[d]
19	$Cu(OAc)_2.H_2O$	$AgNTf_2$	*t*AmOH	trace[e]
20	$Cu(OAc)_2.H_2O$	$AgNTf_2$	*t*AmOH	75[f]
21	$Cu(OAc)_2.H_2O$	$AgNTf_2$	*t*AmOH	58[g]

[a]Reaction conditions: 2*H*-chromene-3-carboxamide **14a** (0.5 mmol), alkyne **15a** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), oxidant (1.0 mmol), additive (30 mol %), solvent (2 mL), 100 °C (oil bath temperature) for 14 h. [b]Isolated yields. [c]No catalyst was added. [d]In open air. [e]5.0 mol % of $CpRuCl(PPh_3)_2$ catalyst was used. [f]10.0 mol % of $[Ru(OAc)_2(p\text{-cymene})]$ catalyst was used. [g]5.0 mol % of $[RuCl_2(benzene)]_2$ catalyst was used.

With the optimal catalytic system in hand, we moved on to investigate its scope in ruthenium catalyzed C-H/N-H bond functionalizations by employing various 2*H*-chromene-3-carboxamides and alkynes (Scheme 27). Satisfyingly, the present reaction proved broadly applicable and good to excellent yields of benzopyran fused 2-pyridones were obtained. The scope of alkynes was investigated first using *N*-(4-methoxyphenyl)-2*H*-chromene-3-carboxamide **14a** as the partner. These results indicated that symmetrical diarylacetylenes with electron-donating or electron-withdrawing groups proceeded well and gave excellent yields to afford the benzopyran fused 2-pyridone derivatives (**97-102**, 75-86%). The reaction of **14a** with heteroarylalkyne (**15g**) under the same catalytic conditions produced **102** in good yield. Moreover, dialkylacetylenes such as 3-hexyne (**15h)** and 1,4-dimethoxybut-2-yne (**15i)** reacted smoothly and furnished the corresponding 2-pyridone derivatives **104-105** in good yield. To understand the regioselectivity of the present reaction, unsymmetrical alkyne was employed as the substrate for the reaction with **14a**. Thus, 1-phenyl-1-butyne **15j** gave product **106** in 75% yield. Only one isomer in which C-aryl carbon occurred adjacent to amide nitrogen was obtained in a highly ***regioselective*** manner. The regiochemistry of the product **106** was confirmed by X-ray crystallography (Figure 13, left). We also evaluated the effect of substituents on the nitrogen atom of amide in the reaction with diphenylacetylene. Amides bearing *N*-aryl or *N*-alkyl substituents were effectively converted to the corresponding benzopyran fused 2-pyridones (**107-111**) in excellent yields (81-90%). The structure of the product **107** was further confirmed by single crystal X-ray analysis (Figure 13, right).

Scheme 27

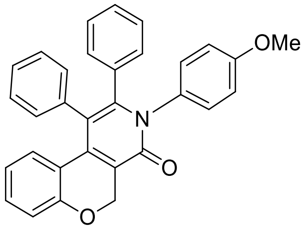
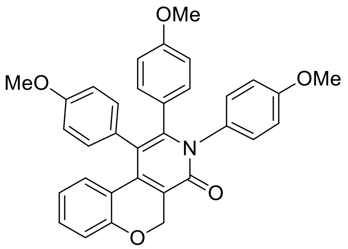


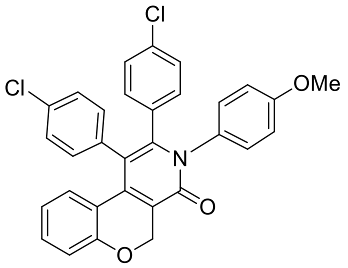
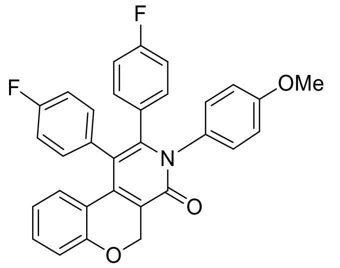
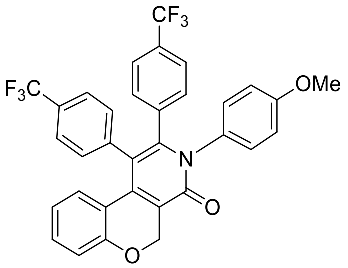
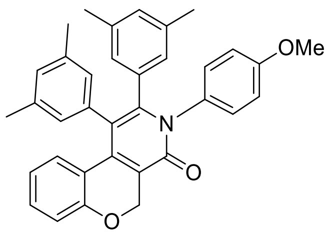
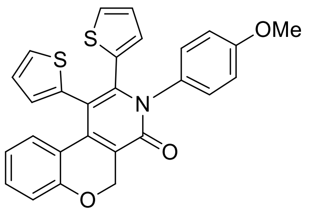
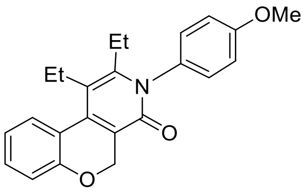
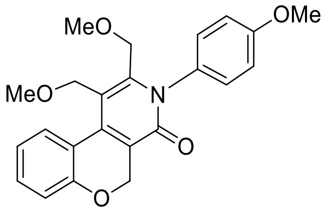
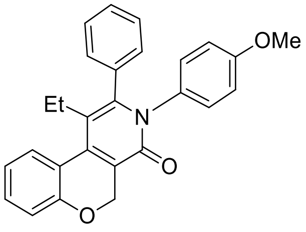
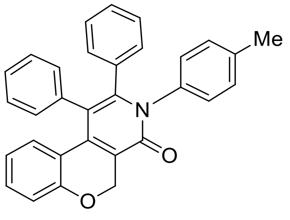
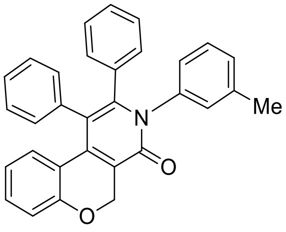
97-111

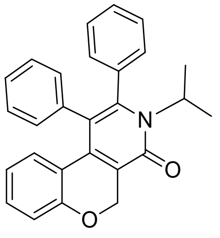
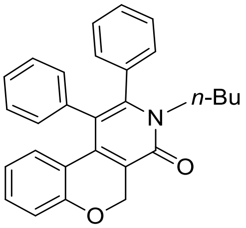
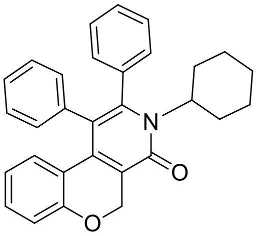
R^1 = *p*-anisyl (**14a**)
R^1 = *p*-tolyl (**14b**)
R^1 = *m*-tolyl (**14c**)
R^1 = *i*-Pr (**14d**)
R^1 = *n*-Bu (**14e**)
R^1 = cyclohexyl (**14f**)

R^2, R^3 = Ph (**15a**)
R^2, R^3 = 4-MeO-C_6H_4 (**15b**)
R^2, R^3 = 4-Cl-C_6H_4 (**15c**)
R^2, R^3 = 4-F-C_6H_4 (**15d**)
R^2, R^3 = 4-CF_3-C_6H_4 (**15e**)
R^2, R^3 = 3,5-Me-C_6H_3 (**15f**)
R^2, R^3 = 2-thiophene (**15g**)
R^2, R^3 = Et (**15h**)
R^2, R^3 = MOM (**15i)**
R^2 = Et, R^3 = Ph (**15j)**

Table 14. Substrate Scope for the Ruthenium-Catalyzed C-H Activation of 2*H*-chromene-3-carboxamides (**14a-f**)^a

Entry	Benzopyran fused 2-pyridone	Entry	Benzopyran fused 2-pyridone
1	 **97** (88%)	2	 **98** (92%)

3	 **99** (86%)	4	 **100** (83%)
5	 **101** (78%)	6	 **102** (90%)
7	 **103** (83%)	8	 **104** (76%)
9	 **105** (78%)	10	 **106** (75%, X-ray)
11	 **107** (86%, X-ray)	12	 **108** (81%)

13	 **109** (90%)	14	 **110** (88%)
15	 **111** (87%)		

[a]Reaction conditions: 2*H*-chromene-3-carboxamide **14a-f** (0.5 mmol), alkyne **15a-j** (0.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), $Cu(OAc)_2.H_2O$ (1.0 mmol), $AgNTf_2$ (30 mol %), *t*-AmOH (2 mL), 100 °C (oil bath temperature) for 14 h. [b]Isolated yield. [c]We used 0.6 mmol (1.2 equiv) of alkyne.

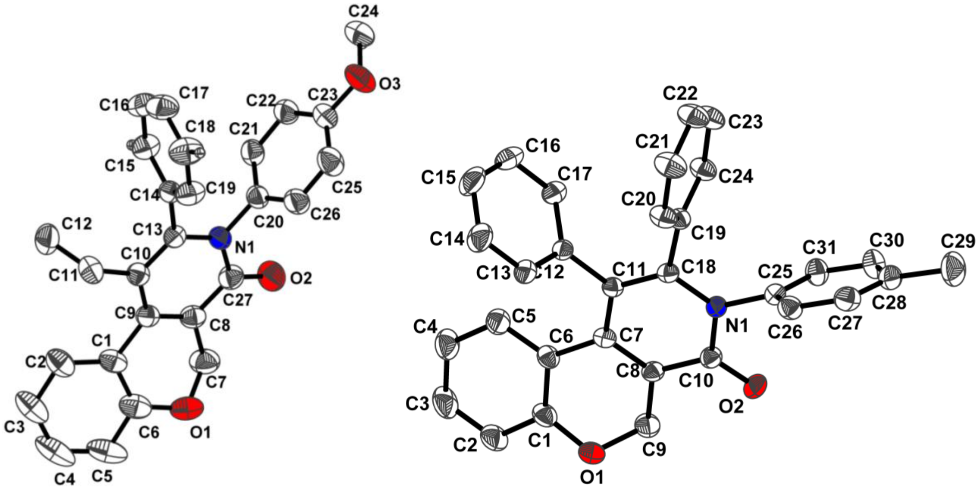


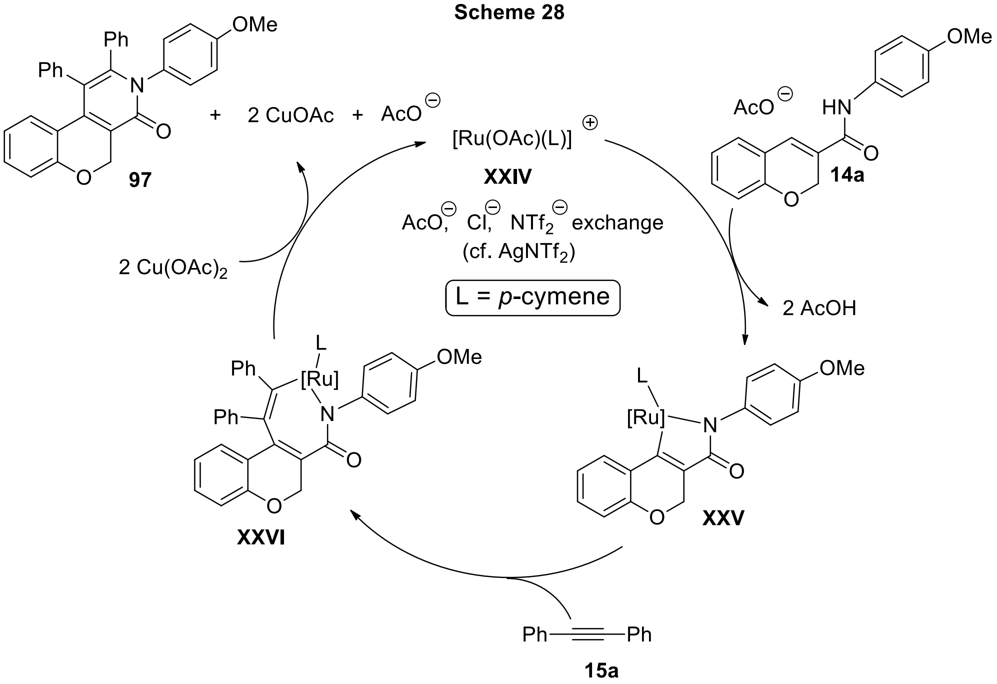
Figure 13. ORTEP (ellipsoid contour probability 50%) of compounds **106-107**. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] with esd's in parentheses: Compound **106** N(1)-C(13) 1.390(2), C(10)-C(13) 1.366(2), C(10)-C(9) 1.439(2), C(9)-C(8) 1.369(2), C(8)-C(27) 1.433(2), N(1)-C(27) 1.397(2). Compound **107**. Selected bond lengths [Å] with esd's in parentheses: N(1)-C(18) 1.382(3), C(11)-

C(18) 1.357(3), C(7)-C(11) 1.442(3), C(7)-C(8) 1.367(3), C(8)-C(10) 1.416(3), N(1)-C(10) 1.403(3).

2.12.2 Plausible mechanistic pathway for the formation of benzopyran-fused 2-pyridone 97

A plausible reaction pathway based on literature reports[103] to account for the annulation reaction leading to benzopyran fused 2-pyridones is proposed in Scheme 28. Initially, $[RuCl_2(p\text{-cymene})]_2$ undergoes ligand exchange with $Cu(OAc)_2$ to give the mono-acetate [RuCl(OAc)(*p*-cymene)]. This proposal is based on previous reports from our laboratory.[104] The active cationic ruthenium species **XXIV** is generated by the ligand exchange reaction between [RuCl(OAc)(*p*-cymene)] and $AgNTf_2$. Here the role of $AgNTf_2$ is to remove the Cl^- ligand from the mono-acetate [RuCl(OAc)(*p*-cymene)] complex providing a cationic ruthenium species **XXIV**. Coordination of the nitrogen of the amide in chromene-3-carboxamide **14a** to ruthenium species followed by subsequent N-H bond cleavage and ortho metalation at C(4)-H of the chromene moiety affording the five-membered ruthenacycle **XXV** with elimination of AcOH. Complex **XXV** subsequently undergoes migratory insertion with alkyne **15a** into the Ru-C bond leading to the seven-membered ruthenium intermediate **XXVI**. Finally, intermediate **XXVI** undergoes reductive elimination in the presence of $Cu(OAc)_2$ providing the benzopyran fused 2-pyridone **97** and regenerating the active ruthenium(II) catalyst. In the case of the unsymmetrical alkyne **15j**, the regioselective formation of the benzopyran fused 2-pyridone **106** is explained by intramolecular coordination of the phenyl group to the Ru metal that could stabilize intermediate **XXVI** shown in Scheme 28.[105] Hence the phenyl group always tends to stay close to the Ru metal in intermediate **XXVI**.

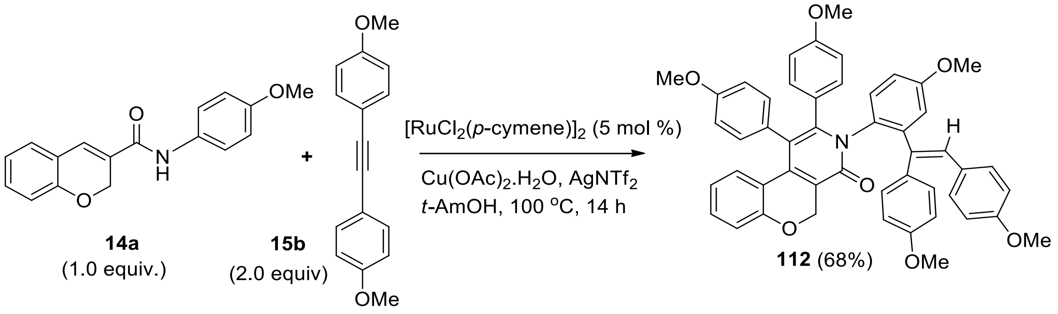
Scheme 28



2.12.3 *Ruthenium-Catalyzed Double C-H Activation of 2H-chromene-3-carboxamides: Annulation along with Hydroarylation*

While studying the above reaction, we onserved formation of a double C-H activation product **112** when we treated *N*-(4-methoxyphenyl)-2*H*-chromene-3-carboxamide **14a** with 2.0 equiv of alkyne **15b** in the presence of $[RuCl_2(p\text{-cymene})]_2$, $Cu(OAc)_2$ and $AgNTf_2$ in *t*-AmOH at 100 °C/ 14 h (Scheme 29). We isolated product **112** in 68% yield along with traces of the mono-activated product **96**. We confirmed this double C-H activation product by ^{1}H-NMR and HRMS data. The ^{1}H-NMR spectrum of compound **112** showed a singlet at δ 6.0 indicating that an olefinic proton is present; five singlets for OMe groups in at δ ~3.8-3.7 suggested that two alkyne moieties are present. HRMS data was also consistent with the double C-H activated product. We believe that one alkyne moiety underwent oxidative annulation *via* C-H and N-H bond cleavage, while the other alkyne moiety was attached as vinylic group *via* hydroarylation. Both of these took place in a single pot reaction.

Scheme 29



We next focused on to improve the yield of **112**. As shown in the Table 15, we varied catalyst loading, temperature and duration of time by keeping the oxidant, additive and solvent constant. A slight increase in the yield was observed with 10 °C increase in the reaction temperature (entry 2). Change of alkyne equiv from 2 to 2.5 afforded the product in 76% yield (entry 3). Less reaction time had marginal negative effect on the yield of the product (entries 4-5). Gratifyingly, the product was isolated in 88% yield (entry 6) when we increased the catalyst loading from 5 mol% to 8.0 mol%. A slight decrease in the yield was observed when 8 mol % of catalyst and 3.0 equiv of alkyne (entry 7) were used. We obtained almost the same yield with 10 mol% of catalyst loading (entry 8). Thus the optimum conditions were found to be 8 mol % of $[RuCl_2(p\text{-cymene})]_2$, $Cu(OAc)_2$ (2.0 equiv) and $AgNTf_2$ (30 mol %), in *t*-AmOH at 110 °C for 12h.

Table 15. Optimization Study for Ruthenium-Catalyzed Double C-H activation[a]

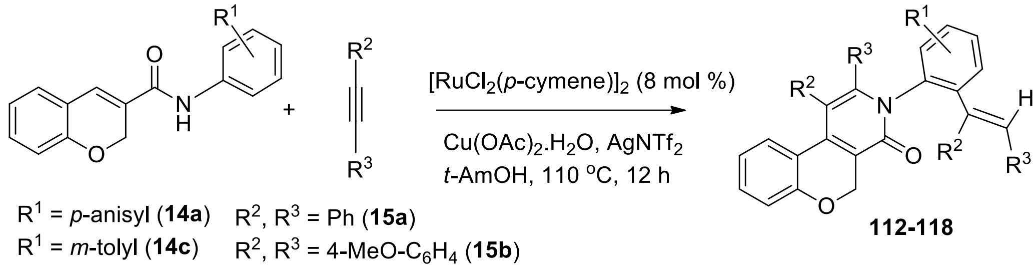
Entry	[Ru] (mol %)[b]	Alkyne **15b** (equiv)	T (0 °C)[c]	Time (h)	Yield of **112** (%)[d]
1	5	2.0	100	14	68
2	5	2.0	110	14	70
3	5	2.5	110	14	76
4	5	2.5	110	12	75

5	5	2.5	110	10	66
6	**8**	**2.5**	**110**	**12**	**88**
7	8	3.0	110	12	86
8	10	2.5	110	12	88

[a]Reaction conditions: 2*H*-chromene-3-carboxamide **14a** (0.5 mmol), alkyne **15b** (1.0-1.5 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0-10 mol %), oxidant (1.0 mmol), additive (30 mol %), solvent (2 mL) for 12-14 h. [b]$[RuCl_2(p\text{-cymene})]_2$. [c]Oil bath temperature. [d]Isolated yields.

Having the optimized reaction conditions in hand, the substrate scope was studied by using differently substituted alkynes (Scheme 30 and Table 16). Diaryl alkynes bearing electron donating groups as well as withdrawing groups reacted smoothly with chromene-3-carboxamide **14a** and afforded the double C-H activation products **112-114** in excellent yields (76-88%). The structure of compound **113** was confirmed by X-ray crystallography (Figure 14, left). This protocol was compatible with the presence of synthetically important functional groups such as fluoro and chloro, producing the corresponding double C-H activation products **115-116** in good yields, which should prove useful for further functionalization by cross-coupling chemistry. Moreover, dialkylacetylene such as 3-hexyne (**15h**) was also converted to the corresponding double C-H activation product **117** in good yield (78%). 3-Methyl substituted chromene-3-carboxamide (**14c**) underwent the C-H functionalization with diphenyl acetylene (**15a**) exclusively at the less hindered position and produced the desired product in good yields (**118**, 80%). The structure of compound **118** was also confirmed by X-ray crystallography (Figure 14, right).

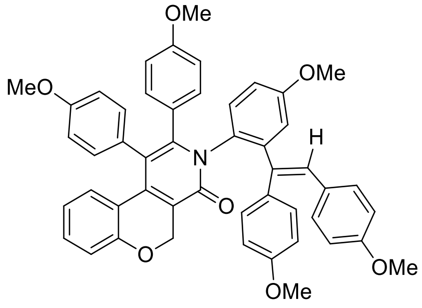
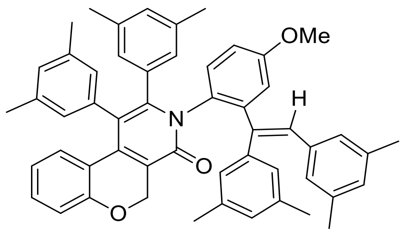
Scheme 30

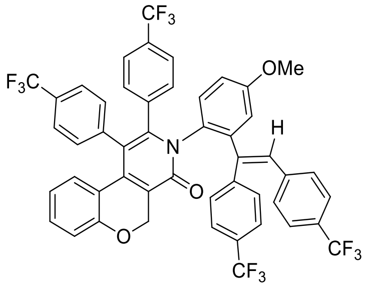
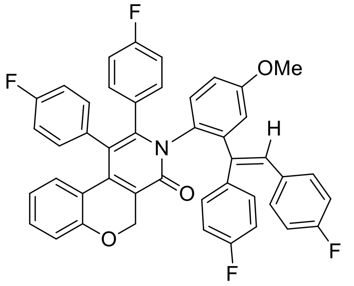
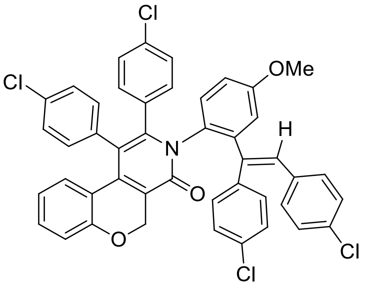
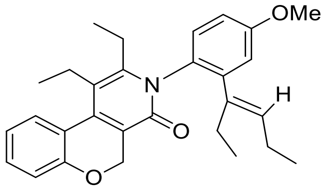
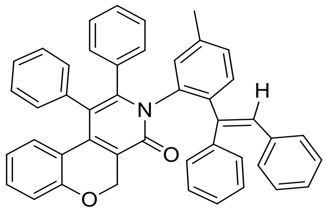


R^1 = *p*-anisyl (**14a**)
R^1 = *m*-tolyl (**14c**)

R^2, R^3 = Ph (**15a**)
R^2, R^3 = 4-MeO-C_6H_4 (**15b**)
R^2, R^3 = 4-Cl-C_6H_4 (**15c**)
R^2, R^3 = 4-F-C_6H_4 (**15d**)
R^2, R^3 = 4-CF_3-C_6H_4 (**15e**)
R^2, R^3 = 3,5-Me-C_6H_3 (**15f**)

Table 16. Substrate Scope for the Ruthenium-Catalyzed Double C-H Activation of 2*H*-chromene-3-carboxamides (**14a** or **14c**) with alkynes (**15a-f**)[a]

Entry	Product	Yield (%)[b]
1	 **112**	88
2	 **113** (X-ray)	86

3	 **114**	76
4	 **115**	75
5	 **116**	82
6	 **117**	78
7	 **118** (X-ray)	80

[a]Reaction conditions: 2*H*-chromene-3-carboxamide **14a** or **14c** (0.5 mmol), alkyne **15a-f** (1.25 mmol), $[RuCl_2(p\text{-cymene})]_2$ (8.0 mol %), $Cu(OAc)_2.H_2O$(1.0 mmol), $AgNTf_2$ (30.0 mol %), *t*-AmOH (2mL), 110 °C (oil bath temperature) for 12 h. [b]Isolated yields.

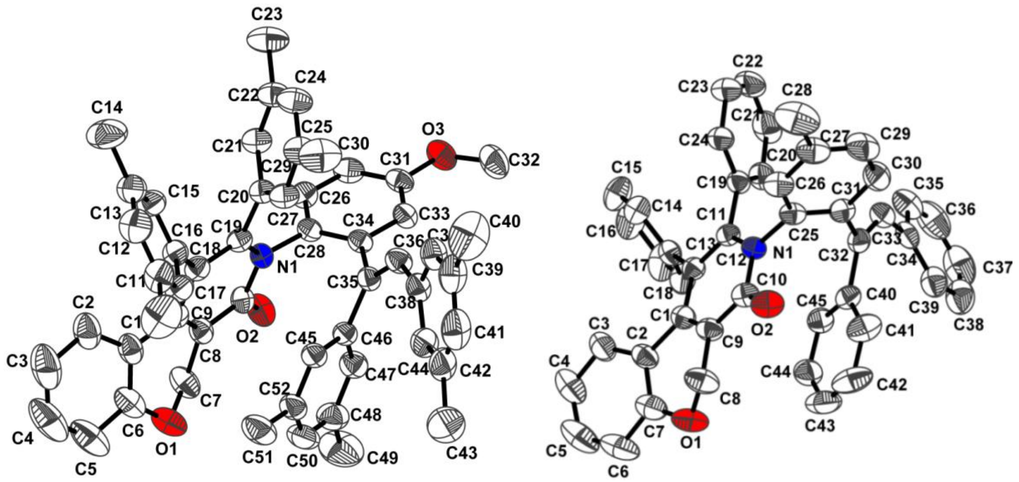


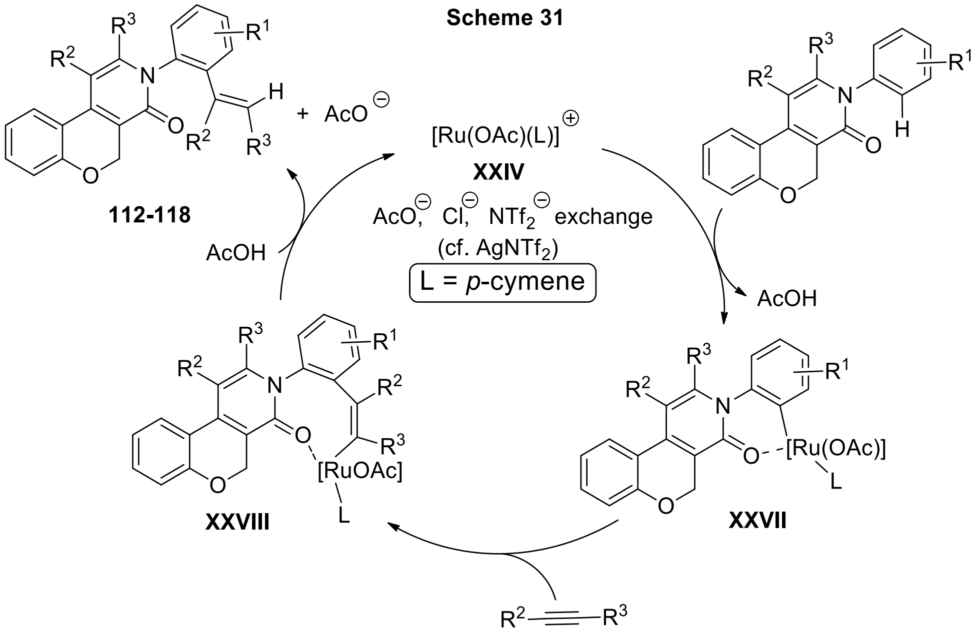
Figure 15. ORTEP (ellipsoid contour probability 50%) of compounds **113** and **118**. H-atoms are not shown for clarity. Selected bond lengths [Å] with esds in parentheses: Compound **113** N(1)-C(19) 1.391(2), C(19)-C(10) 1.376(3), C(8)-C(9) 1.363(3), C(10)-C(9) 1.442(3), C(34)-C(35) 1.500(2), C(35)-C(36) 1.340(3). Compound **118** N(1)-C(11) 1.385(3), C(11)-C(12) 1.373(3), C(12)-C(1) 1.437(3), C(1)-C(9) 1.361(3), C(9)-C(10) 1.428(3), N(1)-C(10) 1.398(3).

2.12.4 Plausible mechanistic pathway for the formation of double C-H activation products (annulation along with hydroarylation) 112-118

On the basis of previous reports on metal catalyzed C-H bond activation (annulation as well as hydroarylation)[105b,106], we propose a possible pathway for the formation of double C-H activation products *via* the annulated products (Scheme 31). The active cationic ruthenium species **XXIV** is generated by the ligand exchange reaction between $\{RuCl(OAc)(p\text{-cymene})\}$[104]and $AgNTf_2$. This active ruthenium(II) species undergoes coordination with the oxygen atom (of C=O) followed by *ortho* metalation at phenyl ring of amide moiety with subsequent elimination of AcOH providing the ruthenium complex **XXVII**. Migratory insertion of alkyne moiety into the

Ru-C bond furnishes ruthenium intermediate **XXVIII**. Finally, intermediate **XXVIII** undergoes protonation in the presence of AcOH affording the double C-H activation products and regenerating the active ruthenium (II) catalyst.

Scheme 31



SUMMARY

1) The simple [Pd]-catalyzed reaction of indole-2-carboxylic acids in the presence of Ag_2CO_3 leads to triindoles. This reaction acts as a caveat while using the common [Pd]-catalyst/Ag_2CO_3 system. To our knowledge, there is no previously recorded report of this type. The triindoles so obtained give green radical cationic species upon treatment with gaseous HCl, as evidenced by EPR spectra Along with [Pd]-catalyst/Ag_2CO_3/ indole carboxylic acid, when a ***nitrile*** is present even as a solvent (e.g., acetonitrile or benzonitrile), a new cyclization reaction with ***nitrile insertion*** leading to fluorescence active indolocarbolines is discovered. This result is also significant because acetonitrile or benzonitrile is often used as a solvent in [Pd]-catalyzed reactions involving indoles. A possible pathway involving biindoles is proposed for the formation of these indolocarbolines.
2) An efficient method for the synthesis of pentacyclic pyrrolodiindolone derivatives in good to excellent yields by using 3-alkynylindole-2-carboxamides *via* palladium-catalyzed intramolecular C-N and C-C bond formation in a single step has been developed. We have also successfully utilized the same 3-alkynylindole-2-carboxamides for phase-transfer catalyzed high yield synthesis of tricyclic 3-substituted β-carbolinones. The reaction features high regio- and chemo-selectivity, good substrate scope, is atom economical and provides a new strategy for the synthesis of synthetically and medicinally useful β-carbolinone derivatives. Notably, depending on the catalyst, a switch to trigger different reaction pathways affording two types of products from the same starting material is demonstrated.
3) A palladium-catalyzed ***ortho***-amidation of indole-3-carboxylic acids with isothiocyanates resulting in indole-2-carboxamides is achieved *via* C-H bond activation/functionalization using carboxylic group as traceless directing group. This protocol has high functional group tolerance in terms of isothiocyanate substrates. Other heteroaromatic carboxylic acids are also successfully converted to amidation products under this protocol. We have also utilized indole-2-carboxamides for the synthesis of diindole fused 2-pyridones by palladium-catalyzed C-H activation.

4) A new protocol of ruthenium-catalyzed oxidative annulation of 2*H*-chromene-3-carboxamides with alkynes for the synthesis of a wide range of benzopyran fused 2-pyridones *via* C-H activation has been discovered. The reaction features high regioselectivity, good substrate scope, and large functional group tolerance. In addition, we have also studied the formation of ***double C-H activation*** products in excellent yields when an excess of alkyne is used. In these reactions, one alkyne moiety undergoes annulation with chromene-3-carboxamides and other alkyne moiety is used up for hydroarylation.

EXPERIMENTAL SECTION

General: Chemicals and solvents were procured from Aldrich/Alfa Aesar or local manufacturers. Further purification was done according to standard procedures wherever required.[107] All operations, unless otherwise specified, were carried out under dry nitrogen atmosphere using standard vacuum and Schlenk line techniques.[108]

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: ^{1}H and ^{13}C 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: $\delta = 0$). 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.

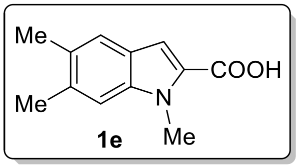
Absorbance and Fluorescence Spectroscopy: Steady state absorption and fluorescence spectra were recorded on UV-Vis-NIR scanning spectrophotometer (Shimadzu, model no. UV-3101PC) and SPEX FLUOROMAX-3 spectrofluorimeter respectively.

Precursors **7a-l** (nitriles), **8a-h** (isothiocyanates) and **11-13** (heteroaromatic carboxylic acids) are commercially available. The substituted indole-3-carboxylic acids **6a-i** were prepared according to the literature procedure.[72] 2*H*-Chromene-3-carboxylic acid **9** was prepared in a two-step sequence from salicylaldehyde using Corey's protocol.[74a] The compound imidazo[1,2-*a*]pyridine-2-carboxylic acid **10** was synthesized according to the literature procedure.[73] The *N*-substituted 2*H*-chromene-3-carboxamides **14a-f** and the disubstituted alkynes (**15a-j**) were synthesized by following known literature reports.[74b-f, 75]

3.1 Synthesis of indole-2-carboxylic acid precursors 1a-j

All the indole-2-carboxylic acid derivatives used in the present study have been synthesized by starting with indole-2-carboxylic acid with slight modification of a literature procedure as appropriate.[70] Among these, the acid **1e** is new.

Compound 1e



Yield: 0.8 g (95%, white solid).

Mp: 226-228 ^{0}C.

IR (KBr): 2965, 2598, 1681, 1519, 1474, 1444, 1261, 1235, 1134, 1062, 997, 843 cm^{-1}.

^{1}H NMR (DMSO-d$_6$): δ 12.74 (br s, 1H, COO*H*), 7.39 (s, 1H, Ar-*H*), 7.32 (s, 1H, Ar-*H*), 7.14-7.07 (m, 1H, Ar-*H*), 3.96 (s, 3H, NCH_3), 2.35 (s, 3H, CH_3), 2.28 (s, 3H, CH_3).

^{13}C NMR (DMSO-d$_6$): δ 163.6, 138.9, 134.4, 129.3, 128.0, 124.2, 122.2, 111.1, 109.4, 31.8, 20.9, 20.1.

LC-MS: *m/z* 204 [M+1]$^+$.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.85; H, 6.51; N, 6.79.

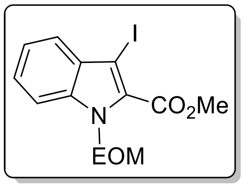
3.2 Synthesis of 3-alkynyl-indole-2-carboxamides 5a-o

These precursors were prepared by following literature procedures via **2a-e**, **3a-e** and **4a-k** (*cf* Scheme 2) by starting with methyl-3-iodo-1*H*-indole-2-carboxylates.[70d,71a-d] Compounds **2d**, **3b**, **3d**, **4a-k** and **5a-5o** are new. Details are given in the following subsections.

3.2.1 Synthesis of 1-alkyl-3-iodo-indole-2-carboxylate esters (2a-e), 1-alkyl-3-iodo-indole-2-carboxylic acids (3a-e)

These compounds were prepared by starting with indole-2-carboxylic acid. Esterification of indole-2-carboxylic acid (MeOH/ and Conc. H_2SO_4) followed by iodination[70d,71a] using *N*-chlorosuccinimide (1.2 equiv) and NaI (1.2 equiv) in DMF solvent at 0 °C to rt (25 °C), resulted in the methyl-3-iodo-1*H*-indole-2-carboxylates. These were transformed to *N*-substituted products **2a-e** by using different alkyl bromides or EOM-Cl (1.3 equiv) in the presence of NaH (60% in oil, 1.1 equiv) with DMF as the solvent by following standard literature procedure.[71a] These esters upon saponification (12% KOH/ MeOH) afforded the corresponding acids **3a-e**. Among these, **2d**, **3b** and **3d** are new.

Compound 2d



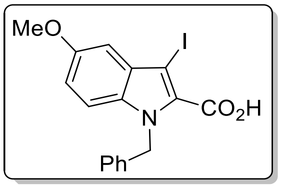
Yield:	3.6 g (95%, white solid; using 2.5 g (8.3 mmol) of methyl-3-iodo-1*H*-indole-2-carboxylate).
Mp:	153-155 °C.
IR (KBr):	2970, 1699, 1610, 1452, 1386, 1337, 1293, 1249, 1222, 1096, 1057, 745, 668 cm^{-1}.
^{1}H NMR (500 MHz):	δ 7.59 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.40 (~t, *J* = 7.8 Hz, 1H), 7.27 (~t, *J* = 7.5 Hz, 1H), 5.93 (s, 2H), 4.00 (s, 3H), 3.46 (qrt, *J* = 7.0 Hz, 2H), 1.13 (t, *J* = 7.0 Hz, 3H).
^{13}C NMR (125 MHz):	δ 161.3, 138.7, 130.3, 128.4, 126.4, 123.8, 122.0, 111.2, 74.0,

69.9, 63.8, 51.6, 14.9.

LC-MS: *m/z* 360 $[M+1]^+$.

Anal. Calcd. for $C_{13}H_{14}INO_3$: C, 43.47; H, 3.93; N, 3.90. Found: C, 43.40; H, 3.89; N, 3.86.

Compound 3b



Yield: 4.46 g (93%, white solid; using 15.1 mmol of methyl-1-benzyl-3-iodo-5-methoxy-1*H*-indole-2-carboxylate **2b**).

Mp: 178-180 °C.

IR (KBr): 2960, 1666, 1501, 1447, 1419, 1381, 1266, 1200, 1019, 800, 729, 652 cm^{-1}.

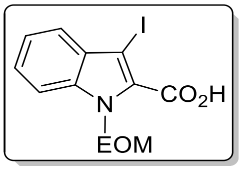
^1H NMR (500 MHz, DMSO-d_6): δ 7.48 (d, *J* = 8.0 Hz, 1H), 7.27-7.17 (m, 3H), 7.02-6.99 (m, 3H), 6.89 (d, *J* = 2.5 Hz, 1H), 5.84 (s, 2H), 3.81 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 162.7, 155.7, 138.9, 134.0, 130.8, 130.0, 129.0, 127.6, 126.7, 117.7, 113.4, 103.6, 67.5, 55.9, 48.8.

LC-MS: *m/z* 406 $[M-1]^+$.

Anal. Calcd. for $C_{12}H_{12}INO_3$: C, 41.76; H, 3.50; N, 4.06. Found: C, 41.65; H, 3.56; N, 4.12.

Compound 3d



Yield: 4.46 g (93%, white solid; using 9.7 mmol of methyl-1-(ethoxymethyl)-3-iodo-1*H*-indole-2-carboxylate **2d**).

Mp: 178-180 °C.

IR (KBr): 2960, 1666, 1501, 1447, 1419, 1381, 1266, 1200, 1019, 800, 729, 652 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ 7.48 (d, *J* = 8.0 Hz, 1H), 7.27-7.17 (m, 3H), 7.02-6.99 (m, 3H), 6.89 (d, *J* = 2.5 Hz, 1H), 5.84 (s, 2H), 3.81 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d$_6$): δ 162.7, 155.7, 138.9, 134.0, 130.8, 130.0, 129.0, 127.6, 126.7, 117.7, 113.4, 103.6, 67.5, 55.9, 48.8.

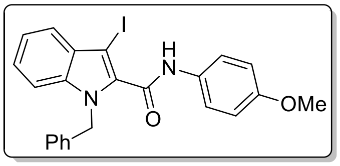
LC-MS: *m/z* 406 [M-1]$^+$.

Anal. Calcd. for $C_{12}H_{12}INO_3$: C, 41.76; H, 3.50; N, 4.06. Found: C, 41.65; H, 3.56; N, 4.12.

3.2.2 Synthesis of N-Alkyl-3-Iodo-indole-2-carboxamides (4a-k): General Procedure

To a stirred solution of corresponding 3-iodo-indole-2-carboxylic acid (one of **3a-k**, 1.0 equiv) in DCM (60 mL per 21.2 mmol of **3a**) at 0 °C, EDC.HCl (1.2 equiv) and DMAP (2.0 equiv) were added. Alkyl or aryl amine (1.2 equiv) was added after 10 min to the above solution, the mixture was kept at 0 °C for 1h and then at rt (25 °C) for 2-3 h. After the completion of the reaction (TLC), the solvent was removed using rotary evaporator and then water (2 x 20 mL per 21.2 mmol of **3a**) was added. The mixture was extracted with ethyl acetate (2 x 40 mL per 21.2 mmol of **3a**), washed with brine (2 x 10 mL per 21.2 mmol of **3a)**, dried over Na_2SO_4 and filtered. The solvent was removed by rotary evaporator. The crude product was purified by column chromatography by using silica gel with ethyl acetate/hexane mixture (ratio *ca* 1:9) as the eluent to afford the corresponding *N*-alkyl-3-iodo-indole-2-carboxamides **4a-k**.

Compound 4a



Yield: 9.4 g (92%, pale yellow solid; using 21.2 mmol of 1-benzyl-3-iodo-1*H*-indole-2-carboxylic acid **3a** and 25.4 mmol of *p*-anisidine).

Mp: 160-163 °C.

IR (KBr): 3260, 1638, 1523, 1452, 1408, 1342, 1249, 1173, 1112, 1030, 822, 740, 696 cm^{-1}.

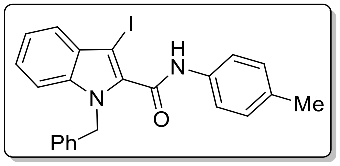
^{1}H NMR: δ 8.09 (s, 1H), 7.58 (d, *J* = 7.6 Hz, 3H), 7.37 (s, 2H), 7.28-7.17 (m, 6H), 6.92 (d, J = 6.0 Hz, 2H), 5.76 (s, 2H), 3.84 (s, 3H).

^{13}C NMR: δ 159.2, 156.9, 138.1, 137.7, 133.7, 130.3, 129.7, 128.7, 127.5, 126.8, 125.5, 123.0, 122.0, 121.7, 114.2, 111.0, 61.1, 55.5, 48.6.

LC-MS: *m/z* 406 [M-1]$^+$.

Anal. Calcd. for $C_{23}H_{19}IN_2O_2$: C, 57.28; H, 3.97; N, 5.81. Found: C, 57.36; H, 3.92; N, 5.73.

Compound 4b



Yield: 3.34 g (90%, pale yellow solid; using 8.0 mmol of 1-benzyl-3-iodo-1*H*-indole-2-carboxylic acid **3a** and 9.7 mmol of *p*-toluidine).

Mp: 158-160 °C.

IR (KBr): 3260, 1638, 1589, 1529, 1447, 1337, 1310, 1249, 1173, 1101, 926, 817, 740, 701 cm^{-1}.

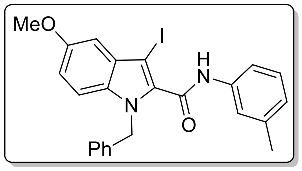
^{1}H NMR: δ 8.09 (s, 1H), 7.59-7.56 (m, 3H), 7.38 (~d, J = ~3.6 Hz, 2H), 7.32-7.17 (m, 8H), 5.78 (s, 2H), 2.40 (s, 3H).

^{13}C NMR: δ 159.3, 138.2, 137.7, 134.8, 134.7, 133.6, 129.8, 129.7, 128.7, 127.6, 126.8, 125.6, 123.1, 121.8, 120.3, 111.1, 61.2, 48.7, 21.0.

LC-MS: *m/z* 467 [M+1]$^+$.

Anal. Calcd. for $C_{23}H_{19}IN_2O$: C, 59.24; H, 4.11; N, 6.01. Found: C, 59.16; H, 4.18; N, 6.12.

Compound 4c



Yield: 1.60 g (88%, pale yellow solid; using 3.7 mmol of 1-benzyl-3-iodo-5-methoxy-1*H*-indole-2-carboxylic acid **3b** and 4.4 mmol of *m*-toluidine).

Mp: 170-172 °C.

IR (KBr): 3271, 1638, 1589, 1534, 1490, 1447, 1375, 1288, 1205, 1030, 964, 778 cm^{-1}.

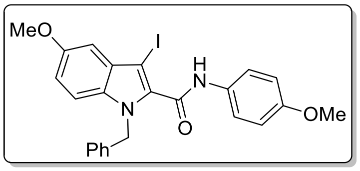
^{1}H NMR (500 MHz, DMSO-d$_6$): δ 10.57 (s, 1H), 7.64 (s, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.50 (d, *J* = 9.0 Hz, 1H), 7.29-7.20 (m, 6H), 6.98-6.96 (m, 2H), 6.87 (d, *J* = 2.0 Hz, 1H), 5.60 (s, 2H), 3.82 (s, 3H), 2.32 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d$_6$): δ 160.4, 155.5, 138.9, 138.5, 138.1, 137.1, 132.3, 130.3, 129.1, 129.0, 127.9, 127.5, 125.4, 120.9, 117.6, 115.6, 113.0, 103.1, 61.2, 55.9, 48.3, 21.7.

LC-MS: *m/z* 497 [M+1]$^+$.

Anal. Calcd. for $C_{24}H_{21}IN_2O_2$: C, 58.08; H, 4.26; N, 5.64. Found: C, 58.16; H, 4.23; N, 5.71.

Compound 4d



Yield: 1.8 g (95%, pale yellow solid; using 3.7 mmol of 1-benzyl-3-iodo-5-methoxy-1*H*-indole-2-carboxylic acid **3b** and 4.4 mmol of *p*-anisidine).

Mp: 174-176 °C.

IR (KBr): 3260, 2926, 1638, 1529, 1441, 1348, 1233, 1205, 1162, 1025, 827, 696 cm^{-1}.

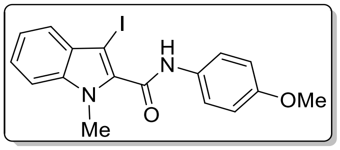
^{1}H NMR: δ 8.0 (s, 1H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.29-7.23 (m, 4H), 7.15-7.13 (m, 2H), 7.00 (dd, *J* = 8.8 Hz and 2.4 Hz, 1H), 6.95-6.92 (m, 3H), 5.77 (s, 2H), 3.93 (s, 3H), 3.84 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d$_6$): δ 160.0, 156.4, 155.5, 138.2, 132.3, 132.1, 130.3, 129.0, 127.9, 127.5, 121.9, 115.5, 114.4, 113.0, 103.1, 60.9, 55.9, 55.7, 48.3.

LC-MS: *m/z* 511 [M+1]$^+$.

Anal. Calcd. for $C_{24}H_{21}IN_2O_3$: C, 56.26; H, 4.13; N, 5.47. Found: C, 56.14; H, 4.18; N, 5.42.

Compound 4e



Yield: 2.55 g (93%, pale yellow solid; using 6.6 mmol of 1-methyl-3-iodo-1*H*-indole-2-carboxylic acid **3c** and 7.9 mmol of *p*-anisidine).

Mp: 176-178 °C.

IR (KBr): 3255, 1638, 1595, 1540, 1501, 1458, 1403, 1244, 1107, 1030, 838, 751 cm^{-1}.

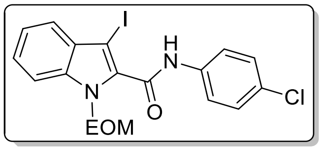
^{1}H NMR (500 MHz, DMSO-d_6): δ 10.5 (s, 1H), 7.76 (d, *J* = 9.0 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.38 (t, *J* = 7.3 Hz, 1H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.00 (d, *J* = 9.0 Hz, 2H), 3.89 (s, 3H), 3.78 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6): δ 159.9, 156.4, 137.7, 137.4, 132.2, 129.5, 124.7, 122.0, 121.8, 121.6, 114.5, 111.3, 59.9, 55.8, 32.1.

LC-MS: *m/z* 407 $[\text{M}+1]^+$.

Anal. Calcd. for $C_{17}H_{15}IN_2O_2$: C, 50.26; H, 3.72; N, 6.90. Found: C, 50.36; H, 3.65; N, 6.98.

Compound 4f



Yield: 2.28 g (87%, white solid; using 5.7 mmol of 1-(ethoxymethyl)-3-iodo-1*H*-indole-2-carboxylic acid **3d** and 6.9 mmol of *p*-chloroaniline).

Mp: 144-146 °C.

IR (KBr): 3271, 2356, 2340, 1644, 1589, 1534, 1490, 1452, 1337, 1304, 1238, 1205, 1090, 1008, 827, 734 cm^{-1}.

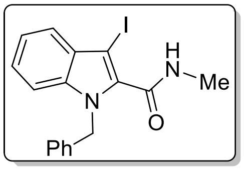
^{1}H NMR: δ 8.67 (s, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.58-7.52 (m, 2H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 1H), 5.85 (s, 2H), 3.63 (qrt, *J* = 6.9 Hz, 2H), 1.22 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR: δ 159.0, 138.2, 136.2, 133.2, 129.9, 129.2, 126.1, 123.2, 122.3, 121.3, 110.9, 74.0, 65.1, 64.5, 15.1.

LC-MS: *m/z* 453 $[M-1]^+$.

Anal. Calcd. for $C_{18}H_{16}ClIN_2O_2$: C, 47.55; H, 3.55; N, 6.16. Found: C, 47.61; H, 3.58; N, 6.09.

Compound 4g



Yield: 1.65 g (96%, pale yellow solid; using 5.3 mmol of 1-benzyl-3-iodo-1*H*-indole-2-carboxylic acid **3a** and 7.9 mmol of methylamine).

Mp: 156-158 °C.

IR (KBr): 3304, 1638, 1573, 1452, 1392, 1353, 1288, 1211, 1145, 1030, 871, 745, 718, 685, 630 cm^{-1}.

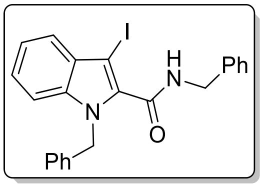
^1H NMR (500MHz): δ 7.53 (d, *J* = 8.0 Hz, 1H), 7.35-7.23 (m, 6H), 7.11 (d, *J* = 6.5 Hz, 2H), 6.49 (s, 1H), 5.70 (s, 2H), 2.99 (d, *J* = 4.5 Hz, 3H).

^{13}C NMR (125 MHz): δ 162.0, 137.8, 137.7, 133.9, 129.7, 128.5, 127.3, 126.6, 125.1, 122.8 121.5, 110.9, 60.2, 48.5, 26.4.

LC-MS: *m/z* 391 $[M+1]^+$.

Anal. Calcd. for 162.0, 137.8, 137.7, 133.9, 129.7, 128.5, 127.3, 126.6, 125.1, 122.8 121.5, 110.9, 60.2, 48.5, 26.4.

Compound 4h



Yield: 2.32 g (94%, pale yellow solid; using 5.3 mmol of 1-benzyl-3-iodo-1*H*-indole-2-carboxylic acid **3a** and 6.4 mmol of benzyl amine).

Mp: 148-151 °C.

IR (KBr): 3271, 2356, 2340, 1644, 1589, 1534, 1490, 1452, 1337, 1304, 1238, 1205, 1090, 1008, 827, 734 cm^{-1}.

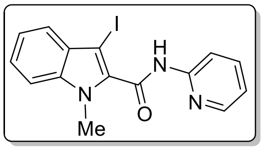
^1H NMR (500 MHz): δ 7.53 (d, *J* = 8.0 Hz, 1H), 7.39-7.25 (m, 11H), 7.10 (t, *J* = 3.5 Hz, 2H), 6.69 (s, 1H), 5.78 (s, 2H), 4.67 (d, *J* = 5.5 Hz, 2H).

^{13}C NMR (125 MHz): δ 161.4, 138.1, 137.9, 137.5, 133.4, 129.8, 128.8, 128.7, 128.0, 127.6, 127.5, 126.7, 125.4, 123.1, 121.6, 110.8, 60.7, 48.5, 43.9.

LC-MS: *m/z* 467 [M+1]$^+$.

Anal. Calcd. for $C_{23}H_{19}IN_2O$: C, 59.24; H, 4.11; N, 6.01. Found: C, 59.36; H, 4.18; N, 5.92.

Compound 4i



Yield: 2.72 g (90%, yellow solid; using 6.6 mmol of 1-methyl-3-iodo-1*H*-indole-2-carboxylic acid **3c** and 7.9 mmol of 2-aminopyridine).

Mp: 146-148 °C.

IR (KBr): 3112, 1671, 1584, 1534, 1436, 1386, 1310, 1227, 1151, 992, 784, 740, 625 cm^{-1}.

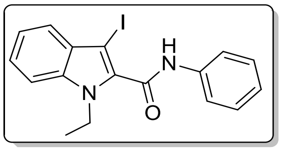
^{1}H NMR (500 MHz): δ 9.51 (s, 1H), 8.38 (d, *J* = 8.5 Hz, 1H), 8.07-8.06 (m, 1H), 7.73-7.70 (m, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.41-7.38 (m, 1H), 7.32-7.24 (m, 2H), 6.95-6.92 (m, 1H), 3.99 (s, 3H).

^{13}C NMR (125 MHz): δ 9.51 (s, 1H), 8.38 (d, *J* = 8.5 Hz, 1H), 8.07-8.06 (m, 1H), 7.73-7.70 (m, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.41-7.38 (m, 1H), 7.32-7.24 (m, 2H), 6.95-6.92 (m, 1H), 3.99 (s, 3H).

LC-MS: *m/z* 457 [M+1]$^+$.

Anal. Calcd. for $C_{15}H_{12}IN_3O$: C, 47.77; H, 3.21; N, 11.14. Found: C, 47.83; H, 3.26; N, 11.26.

Compound 4j



Yield: 3.45 g (93%, pale yellow solid; using 9.5 mmol of 1-ethyl-3-iodo-1*H*-indole-2-carboxylic acid **6e** and 11.4 mmol of aniline).

Mp: 134-136 °C.

IR (KBr): 3277, 2356, 1644, 1594, 1540, 1490, 1441, 1386, 1342, 1310, 1249, 1200, 1107, 1074, 1008, 745 cm^{-1}.

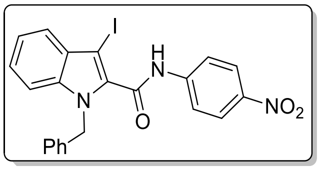
^{1}H NMR: δ 8.20 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.47-7.42 (m, 4H), 7.32-7.22 (m, 2H), 4.60 (qrt, *J* = 7.1 Hz, 2H), 1.49 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz): δ 159.4, 137.5, 132.9, 129.7, 129.2, 125.4, 125.0, 123.2, 121.6, 120.2, 110.5, 60.3, 40.7, 16.0.

LC-MS: *m/z* 391 [M+1]$^+$.

Anal. Calcd. for $C_{17}H_{15}IN_2O$: C, 52.33; H, 3.87; N, 7.18. Found: C, 52.45; H, 3.84; N, 7.23.

Compound 4k



Yield: 5.25 g (80%, yellow solid; using 13.2 mmol of 1-benzyl-3-iodo-1*H*-indole-2-carboxylic acid **3a** and 15.9 mmol of *p*-nitroaniline).

Mp: 192-194 °C.

IR (KBr): 3337, 2915, 1660, 1611, 1540, 1496, 1452, 1332, 1249, 1189, 1112, 937, 740 cm^{-1}.

^{1}H NMR: δ 8.47 (s, 1H), 8.27 (d, *J* = 9.2 Hz, 2H), 7.84 (d, *J* = 9.2 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.42-7.39 (m, 2H), 7.34-7.24 (m, 4H), 7.14-7.12 (m, 2H), 5.82 (s, 2H).

^{13}C NMR: δ 159.3, 144.0, 143.0, 138.7, 137.4, 132.0, 129.7, 128.8, 127.7, 126.6, 126.4, 125.2, 123.4, 122.2, 119.3, 111.2, 62.7, 48.9.

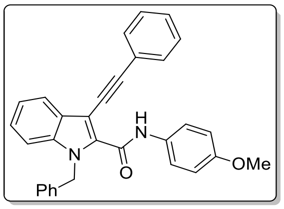
LC-MS: *m/z* 498 [M+1]$^+$.

Anal. Calcd. for $C_{22}H_{16}IN_3O_3$: C, 53.14; H, 3.24; N, 8.45. Found: C, 53.21; H, 3.28; N, 8.36.

3.2.3 Synthesis of 3-Alkynyl-indole-2-carboxamides 5a-o: General procedure

To a solution of 3-iodo-indole-2-carboxamide (one of **4a-k**, 1.0 equiv) and the terminal alkyne (1.2 equiv) in excess of Et_3N (20 mL per 6.2 mmol of **4a**) were added $PdCl_2(PPh_3)_2$ (2.5 mol %) and CuI (5 mol %). The resulting mixture was then heated under N_2 atm at 70 °C. When the reaction was complete (TLC), the mixture was allowed to cool to rt (25 °C), and the ammonium salt was removed by filtration. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using ethyl acetate/hexane mixture (ratio *ca* 1:9) as the eluent to afford the corresponding 3-alkynyl-indole-2-carboxamide (one of **5a-o**).

Compound 5a



Yield: 2.55 g (85%, white solid; using 6.2 mmol of 1-benzyl-3-iodo-*N*-(4-methoxyphenyl)-1*H*-indole-2-carboxamide **4a** and 6.6 mmol of phenylacetylene).

Mp: 148-150 °C.

IR (KBr): 3359, 2197, 1655, 1595, 1534, 1512, 1457, 1332, 1244, 1178, 1123, 1025, 827, 734, 696 cm^{-1}.

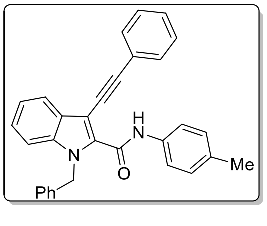
^{1}H NMR (500 MHz): δ 9.44 (s, 1H), 7.97 (d, *J* = 6.4 Hz, 1H), 7.68-7.65 (m, 4H), 7.47-7.26 (m, 9H), 7.23 (d, *J* = 6.0 Hz, 2H), 6.95 (d, *J* = 7.2 Hz, 2H), 6.03 (s, 2H), 3.84 (s, 3H).

^{13}C NMR (125 MHz): δ 158.8, 156.6, 137.9, 132.6, 131.4, 131.0, 128.8, 128.7, 128.6, 127.9, 127.2, 126.6, 125.7, 122.7, 121.9, 121.6, 121.2, 114.3, 111.2, 99.7, 98.4, 82.4, 55.5, 48.6.

LC-MS: *m/z* 457 [M+1]$^+$.

Anal. Calcd. for $C_{31}H_{24}N_2O_2$: C, 81.56; H, 5.30; N, 6.14. Found: C, 81.47; H, 5.21; N, 6.23.

Compound 5b



Yield: 2.35 g (83%, pale yellow solid; using 6.4 mmol of 1-Benzyl-3-iodo-*N*-(*p*-tolyl)-1*H*-indole-2-carboxamide **4b** and 7.7 mmol of phenylacetylene).

Mp: 154-156 ^{o}C.

IR (KBr): 3364, 3014, 2942, 2192, 1666, 1595, 1523, 1457, 1332, 1315, 1244, 1178, 1118, 1019, 816, 734, 690, 570 cm^{-1}.

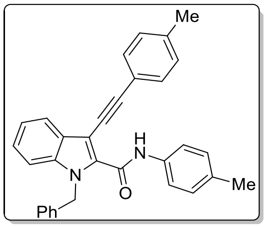
^{1}H NMR (500 MHz): δ 9.53 (s, 1H), 8.01 (d, *J* = 7.5 Hz, 1H), 7.72-7.67 (m, 4H), 7.50-7.30 (m, 10H), 7.25 (~t, *J* = 9.0 Hz, 3H), 6.06 (s, 2H), 2.43 (s, 3H).

^{13}C NMR (125 MHz): δ 158.8, 137.8_3, 137.8_2, 135.3, 134.0, 132.4, 131.4, 129.6, 128.8, 128.7, 128.6, 127.9, 127.2, 126.6, 125.7, 122.6, 121.9, 121.2, 119.9, 111.2, 99.8, 98.5, 82.3, 48.5, 20.9.

LC-MS: *m/z* 441 [M+1]$^{+}$.

Anal. Calcd. for $C_{31}H_{24}N_2O$: C, 84.52; H, 5.49; N, 6.36. Found: C, 84.42; H, 5.56; N, 6.31.

Compound 5c



Yield: 2.51 g (86%, pale yellow solid; using 6.4 mmol of 1-benzyl-3-iodo-*N*-(*p*-tolyl)-1*H*-indole-2-carboxamide **4b** and 7.7 mmol of 1-ethynyl-4-methylbenzene).

Mp: 154-156 ^{o}C.

IR (KBr): 3310, 2378, 2190, 1644, 1600, 1523, 1452, 1244, 1167, 1008, 805, 735, 707 cm^{-1}.

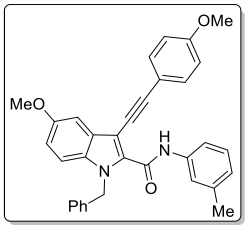
^{1}H NMR: δ 9.57 (s, 1H), 7.99 (d, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 7.45-7.22 (m, 12H), 6.06 (s, 2H), 2.48 (s, 3H), 2.42 (s, 3H).

^{13}C NMR: δ 158.9, 139.1, 137.9, 135.4, 134.0, 132.3, 131.3, 129.6, 129.4, 128.6, 127.9, 127.2, 126.6, 125.7, 121.8, 121.2, 119.9, 119.6, 111.2, 100.1, 98.8, 81.7, 48.6, 21.6, 20.9.

LC-MS: *m/z* 453 $[M-1]^+$.

Anal. Calcd. for $C_{32}H_{26}N_2O$: C, 84.55; H, 5.77; N, 6.16. Found: C, 84.46; H, 5.82; N, 6.07.

Compound 5d



Yield: 0.55 g (92%, pale yellow solid; using 1.21 mmol of 1-benzyl-3-iodo-5-methoxy-*N*-(*m*-tolyl)-1*H*-indole-2-carboxamide **4c** and 1.45 mmol of 1-ethynyl-4-methoxybenzene).

Mp: 134-136 °C.

IR (KBr): 3360, 2850, 2362, 2199, 1666, 1605, 1540, 1479, 1447, 1282, 1249, 1162, 1025, 822, 767, 696 cm^{-1}.

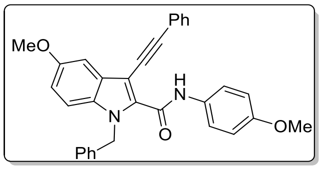
^{1}H NMR: δ 9.59 (s, 1H), 7.60 (d, *J* = 8.8 Hz, 2H), 7.51 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.31-7.21 (m, 6H), 7.15 (d, *J* = 7.2 Hz, 2H), 7.02 (dd, *J* = 8.8 Hz and 2.4 Hz, 1H), 6.98-6.95 (m, 3H), 6.03 (s, 2H), 3.93 (s, 3H), 3.90 (s, 3H), 2.33 (s, 3H).

^{13}C NMR: δ 160.1, 158.9, 155.6, 138.9, 137.9, 133.1, 133.0, 132.1, 128.9, 128.6, 128.3, 127.2, 126.4, 125.0, 120.4, 116.9, 116.8, 114.6, 114.3, 112.1, 101.4, 99.6, 98.6, 81.1, 55.7, 55.3, 48.6, 21.4.

LC-MS: *m/z* 501 $[M+1]^+$.

Anal. Calcd. for $C_{33}H_{28}N_2O_3$: C, 79.18; H, 5.64; N, 5.60. Found: C, 79.23; H, 5.56; N, 5.68.

Compound 5e



Yield: 1.02 g (90%, pale yellow solid; using 2.3 mmol of 1-benzyl-3-iodo-5-methoxy-*N*-(4-methoxyphenyl)-1*H*-indole-2-carboxamide **4d** and 2.8

mmol of phenylacetylene).

Mp: 166-168 ^{o}C.

IR (KBr): 3288, 2932, 2827, 2197, 1633, 1534, 1496, 1452, 1244, 1205, 1173, 1036, 822, 756, 690 cm^{-1}.

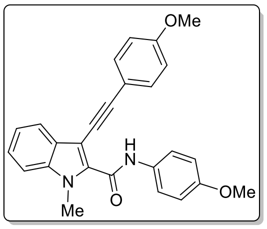
^{1}H NMR: δ 9.42 (s, 1H), 7.66-7.59 (m, 4H), 7.45-7.22 (m, 8H), 7.17 (d, *J* = 8.5 Hz, 2H), 7.03 (dd, *J* = 9.2 Hz and 2.4 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.99 (s, 2H), 3.93 (s, 3H), 3.83 (s, 3H).

^{13}C NMR: δ 158.8, 156.5, 155.8, 137.9, 133.1, 132.6, 131.4, 131.1, 128.8, 128.7, 128.6, 128.5, 127.3, 126.6, 122.8, 121.6, 116.9, 114.3, 112.3, 101.5, 99.1, 98.4, 82.6, 55.8, 55.5, 48.7.

LC-MS: *m/z* 487 [M+1]$^{+}$.

Anal. Calcd. for $C_{32}H_{26}N_2O_3$: C, 78.99; H, 5.39; N, 5.76. Found: C, 78.85; H, 5.32; N, 5.83.

Compound 5f



Yield: 1.3 g (88%, pale yellow solid; using 3.7 mmol of 1-methyl-3-iodo-*N*-(4-methoxyphenyl)-1*H*-indole-2-carboxamide **4e** and 4.4 mmol of 1-ethynyl-4-methoxybenzene).

Mp: 160-162 ^{o}C.

IR (KBr): 3381, 2932, 2838, 2190, 1671, 1605, 1534, 1507, 1468, 1370, 1288, 1238, 1030, 816, 734 cm^{-1}.

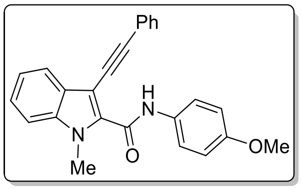
^{1}H NMR (500 MHz): δ 9.46 (s, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.41-7.26 (m, 3H), 6.92 (~t, *J* = 8.8 Hz, 4H), 4.16 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H).

^{13}C NMR (125 MHz): δ 160.0, 159.2, 156.5, 138.1, 132.9, 132.4, 131.2, 127.7, 125.4, 121.5_1, 121.4_6, 121.2, 114.8, 114.3_2, 114.2_9, 110.5, 99.4, 98.3, 81.1, 55.5, 55.4, 32.6.

LC-MS: *m/z* 409 [M-1]$^{+}$.

Anal. Calcd. for $C_{26}H_{22}N_2O_3$: C, 76.08; H, 5.40; N, 6.82. Found: C, 76.18; H, 5.45; N, 6.76.

Compound 5g



Yield: 0.77 g (83%, pale yellow solid; using 2.5 mmol of 1-methyl-3-iodo-*N*-(4-methoxyphenyl)-1*H*-indole-2-carboxamide **4e** and 3.0 mmol of phenylacetylene).

Mp: 158-160 °C.

IR (KBr): 3380, 2210, 1671, 1605, 1540, 1507, 1468, 1326, 1238, 1036, 816, 723, 679 cm^{-1}.

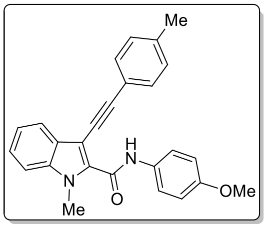
^{1}H NMR: δ 9.41 (s, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.64-7.60 (m, 4H), 7.49-7.41 (m, 5H), 7.33-7.31 (m, 1H), 6.94 (d, *J* = 9.2 Hz, 2H), 4.23 (s, 3H), 3.85 (s, 3H).

^{13}C NMR (125 MHz): δ 159.1, 156.6, 138.1, 132.8, 131.3, 131.1, 128.7, 127.7, 125.4, 122.8, 121.6, 121.1, 114.3, 110.5, 98.9, 98.2, 82.5, 55.5, 32.6.

LC-MS: *m/z* 381 $[M+1]^+$.

Anal. Calcd. for $C_{25}H_{20}N_2O_2$: C, 78.93; H, 5.30; N, 7.36. Found: C, 78.81; H, 5.35; N, 7.29.

Compound 5h



Yield: 0.825 g (85%, pale yellow solid; using 2.5 mmol of 1-methyl-3-iodo-*N*-(4-methoxyphenyl)-1*H*-indole-2-carboxamide **4e** and 2.9 mmol of 1-ethynyl-4-methylbenzene).

Mp: 160-162 °C.

IR (KBr): 3380, 2200, 1660, 1611, 1540, 1512, 1457, 1114, 1370, 1332, 1244, 1025, 822, 740 cm^{-1}.

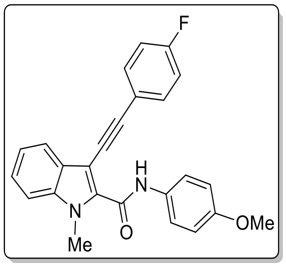
^{1}H NMR (500 MHz): δ 9.45 (s, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.45-7.41 (m, 2H), 7.31-7.27 (m, 1H), 7.23 (d, *J* = 7.5 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H), 4.19 (s, 3H), 3.84 (s, 3H), 2.42 (s, 3H).

^{13}C NMR (125 MHz): δ 159.1, 156.5, 139.0, 138.1, 132.5, 131.3, 131.1, 129.5, 127.7, 125.4, 121.6, 121.5, 121.2, 119.7, 114.3, 110.5, 99.2, 98.5, 81.8, 55.5, 32.7, 21.6.

LC-MS: *m/z* 395 [M+1]$^{+}$.

Anal. Calcd. for $C_{26}H_{22}N_2O_2$: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.08; H, 5.56; N, 7.23.

Compound 5i



Yield: 0.79 g (81%, pale yellow solid; using 2.4 mmol of 1-methyl-3-iodo-*N*-(4-methoxyphenyl)-1*H*-indole-2-carboxamide **4e** and 2.9 mmol of 1-ethynyl-4-fluorobenzene).

Mp: 162-165 °C.

IR (KBr): 3381, 2980, 2202, 1682, 1611, 1540, 1496, 1337, 1244, 1041, 921, 816, 740, 575 cm^{-1}.

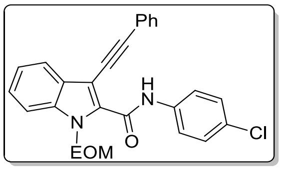
^{1}H NMR: δ 9.32 (s, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.60-7.30 (m, 7H), 7.11 (~t, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 4.20 (s, 3H), 3.84 (s, 3H).

^{13}C NMR (125 MHz): δ 163.7, 161.7, 159.0, 156.6, 138.0, 135.2, 133.3, 133.2, 132.9, 131.0, 130.3, 127.7, 127.6, 125.4, 121.8, 121.6, 121.5, 121.1, 118.9_0, 118.8_7, 116.1, 116.0, 114.4, 110.5, 98.7, 97.0, 82.2, 55.5_3, 55.5_2, 32.6.

LC-MS: *m/z* 399 [M+1]$^{+}$.

Anal. Calcd. for $C_{25}H_{19}FN_2O_2$: C, 75.36; H, 4.81; N, 7.03. Found: C, 75.48; H, 4.76; N, 7.12.

Compound 5j



Yield: 0.65 g (87%, white solid; using 1.75 mmol of *N*-(4-chlorophenyl)-1-(ethoxymethyl)-3-iodo-1*H*-indole-2-carboxamide **4f** and 2.1 mmol of phenylacetylene).

Mp: 166-169 °C.

IR (KBr): 3348, 2981, 2197, 1649, 1595, 1523, 1490, 1386, 1326, 1107, 1003, 915, 833, 756, 690 cm^{-1}.

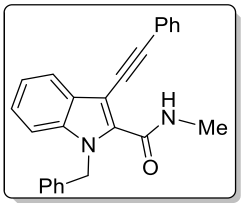
^{1}H NMR: δ 9.52 (s, 1H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 3H), 7.63-7.61 (m, 2H), 7.49-7.44 (m, 4H), 7.37-7.33 (m, 3H), 6.19 (s, 2H), 3.61 (qrt, *J* = 7.0 Hz, 2H), 1.18 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR: δ 158.9, 138.2, 136.5, 132.0, 131.4, 129.5, 129.2, 129.1, 128.8, 127.8, 126.2, 122.4, 121.2, 121.1, 111.8, 101.4, 99.1, 81.9, 74.1, 64.2, 15.1.

LC-MS: *m/z* 429 $[M+1]^{+}$.

Anal. Calcd. for $C_{26}H_{21}ClN_2O_2$: C, 72.81; H, 4.94; N, 6.54. Found: C, 72.68; H, 4.89; N, 6.61.

Compound 5k



Yield: 0.99 g (90%, pale yellow solid; using 3.0 mmol of 1-benzyl-3-iodo-*N*-methyl-1*H*-indole-2-carboxamide **4g** and 3.6 mmol of phenylacetylene).

Mp: 124-126 °C.

IR (KBr): 3309, 2290, 2180, 1666, 1633, 1540, 1463, 1332, 1282, 1200, 1156, 1014, 844, 745, 701 cm^{-1}.

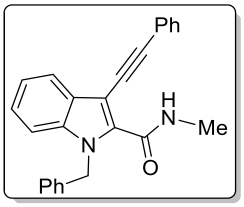
^{1}H NMR (500 MHz): δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.62-7.60 (m, 3H), 7.47-7.34 (m, 5H), 7.31-7.22 (m, 4H), 7.14 (d, *J* = 7.5 Hz, 2H), 6.00 (s, 2H), 3.09 (d, *J* = 5.0 Hz, 3H).

^{13}C NMR (125 MHz): δ 161.8, 138.0, 137.6, 132.8, 131.3, 128.7, 128.6_2, 128.5_9, 127.9, 127.2, 126.5, 125.4, 123.0, 121.7, 121.1, 111.2, 99.3, 97.3, 82.5, 48.5, 26.4.

LC-MS: *m/z* 365 [M+1]$^+$.

Anal. Calcd. for $C_{25}H_{20}N_2O$: C, 82.39; H, 5.53; N, 7.69. Found: C, 82.23; H, 5.58; N, 7.61.

Compound 5k



Yield: 0.99 g (90%, pale yellow solid; using 3.0 mmol of 1-benzyl-3-iodo-*N*-methyl-1*H*-indole-2-carboxamide **4g** and 3.6 mmol of phenylacetylene).

Mp: 124-126 °C.

IR (KBr): 3309, 2290, 2180, 1666, 1633, 1540, 1463, 1332, 1282, 1200, 1156, 1014, 844, 745, 701 cm^{-1}.

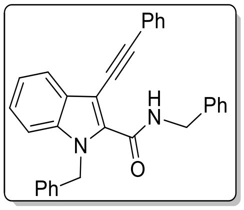
^{1}H NMR (500 MHz): δ 7.90 (d, J = 8.0 Hz, 1H), 7.62-7.60 (m, 3H), 7.47-7.34 (m, 5H), 7.31-7.22 (m, 4H), 7.14 (d, J = 7.5 Hz, 2H), 6.00 (s, 2H), 3.09 (d, J = 5.0 Hz, 3H).

^{13}C NMR (125 MHz): δ 161.8, 138.0, 137.6, 132.8, 131.3, 128.7, 128.6_2, 128.5_9, 127.9, 127.2, 126.5, 125.4, 123.0, 121.7, 121.1, 111.2, 99.3, 97.3, 82.5, 48.5, 26.4.

LC-MS: *m/z* 365 [M+1]$^+$.

Anal. Calcd. for $C_{25}H_{20}N_2O$: C, 82.39; H, 5.53; N, 7.69. Found: C, 82.23; H, 5.58; N, 7.61.

Compound 5l



Yield: 0.844 g (89%, pale yellow solid; using 2.1 mmol of *N*,1-dibenzyl-3-iodo-

1*H*-indole-3-carboxamide **4h** and 2.5 mmol of phenylacetylene).

Mp: 104-106 °C.

IR (KBr): 3382, 3063, 3030, 2921, 2200, 1638, 1545, 1452, 1337, 1277, 1195, 1079, 1019, 844, 740, 702 cm^{-1}.

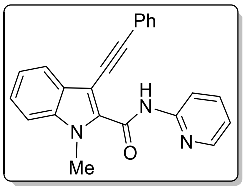
^{1}H NMR (500 MHz): δ 8.00 (s, 2H), 7.46-7.24 (m, 18H), 6.07 (s, 2H), 4.77 (s, 2H).

^{13}C NMR (125 MHz): δ 160.9, 137.9, 137.6$_3$, 137.5$_8$, 132.1, 131.1, 128.7, 128.5, 128.3, 128.0, 127.8, 127.5, 127.1, 126.5, 125.4, 122.6, 121.6, 121.0, 111.1, 99.6, 97.6, 82.3, 48.4, 43.8.

LC-MS: *m/z* 442 [M+2]$^+$.

Anal. Calcd. for $C_{31}H_{24}N_2O$: C, 84.52; H, 5.49; N, 6.36. Found: C, 84.63; H, 5.41; N, 6.42.

Compound 5m



Yield: 0.84 g (90%, yellow solid; using 2.6 mmol of 3-iodo-1-methyl-*N*-(pyridin-2-yl)-1*H*-indole-2-carboxamide **4i** and 3.1 mmol of phenylacetylene).

Mp: 140-142 °C.

IR (KBr): 3315, 3047, 2200, 1666, 1584, 1534, 1468, 1425, 1370, 1304, 1211, 926, 745, 652 cm^{-1}.

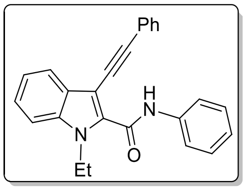
^{1}H NMR: δ 10.26 (s, 1H), 8.42 (~t, *J* = 6.6 Hz, 2H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.89-7.77 (m, 3H), 7.47-7.29 (m, 6H), 7.14-7.11 (m, 1H), 4.23 (s, 3H).

^{13}C NMR: δ 159.1, 151.6, 148.0, 138.1, 137.9, 131.4, 128.2, 127.4, 125.6, 122.9, 121.4, 121.2, 119.6, 114.0, 110.3, 99.4, 82.0, 32.6.

LC-MS: *m/z* 352 [M+1]$^+$.

Anal. Calcd. for $C_{23}H_{17}N_3O$: C, 78.61; H, 4.88; N, 11.96. Found: C, 78.69; H, 4.82; N, 11.85.

Compound 5n



Yield: 0.65 g (88%, white solid; using 2.0 mmol of 1-ethyl-3-iodo-*N*-phenyl-1*H*-indole-2-carboxamide **4j** and 2.4 mmol of phenylacetylene).

Mp: 110-113 °C.

IR (KBr): 3359, 3299, 2959, 2150, 1671, 1644, 1595, 1540, 1441, 1348, 1315, 1244, 1205, 1074, 899, 745, 685 cm^{-1}.

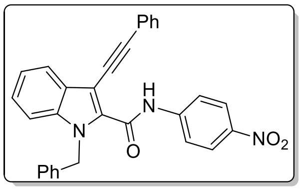
^{1}H NMR: δ 9.56 (s, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 2H), 7.64-7.62 (m, 2H), 7.52-7.29 (m, 8H), 7.18 (~t, *J* = 7.4 Hz, 1H), 4.79 (qrt, *J* = 7.1 Hz, 2H), 1.53 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz): δ 158.9, 138.0, 137.1, 131.8, 131.3, 129.1, 128.7, 128.6, 127.9, 125.5, 124.4, 122.7, 121.6, 121.2, 119.9, 110.5, 99.3, 98.4, 82.5, 40.6, 15.7.

LC-MS: *m/z* 365 [M+1]$^+$.

Anal. Calcd. for $C_{25}H_{20}N_2O$: C, 82.39; H, 5.53; N, 7.69. Found: C, 82.26; H, 5.58; N, 7.61.

Compound 5o



Yield: 0.58 g (62%, yellow solid; using 2.0 mmol of 1-benzyl-3-iodo-*N*-(4-nitrophenyl)-1*H*-indole-2-carboxamide **4k** and 2.4 mmol of phenylacetylene).

Mp: 174-176 °C.

IR (KBr): 3326, 3057, 2931, 1676, 1556, 1512, 1457, 1336, 1298, 1260, 1177, 1112, 925, 854, 750, 695 cm^{-1}.

^{1}H NMR (500 MHz): δ 9.90 (s, 1H), 8.20 (d, *J* = 9.0 Hz, 2H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 9.0 Hz, 2H), 7.65-7.63 (m, 2H), 7.49-7.46 (m, 3H), 7.44-7.40

(m, 2H), 7.35-7.25 (m, 4H), 7.15 (d, *J* = 7.5 Hz, 2H), 6.00 (s, 2H).

^{13}C NMR (125 MHz): δ 159.1, 143.8, 143.5, 138.7, 137.5, 131.4, 131.0, 129.4, 129.0, 128.7, 127.8, 127.5, 126.6, 126.4, 125.2, 122.3, 122.1, 121.5, 119.1, 111.3, 101.1, 99.6, 82.0, 48.7.

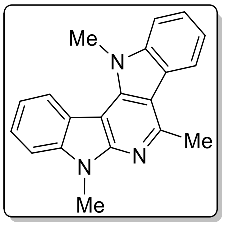
LC-MS: *m/z* 470 [M-1]$^+$.

Anal. Calcd. for $C_{30}H_{21}N_3O_3$: C, 76.42; H, 4.49; N, 8.91. Found: C, 76.58; H, 4.42; N, 9.06.

3.3 Synthesis of indole fused α-carbolines (16-37) by decarboxylative coupling of indole-2-carboxylic acids 1a-j with nitriles 7a-l: General procedure

In an oven dried round-bottomed flask (25 mL), silver carbonate (2.0 mmol) was dried in *vacuo* while heating (ca 100 °C) using a hot air gun for 0.5 h. To this, Pd(OAc)$_2$ (10 mol %), 1-alkylindole-2-carboxylic acid (1.0 mmol) and nitrile (20 mmol) were added. The mixture was stirred at 80 °C (oil bath) for 12 h. After the completion of the reaction (TLC), the excess of nitrile was removed in *vacuo* (for liquid nitriles) and the mixture was subjected to column chromatography (ethyl acetate/hexane) to afford the desired products in 40-65 % yield. Compounds **16-37** and **38** were prepared by this procedure. The synthesis of C3-alkenylated product **38** was reported by Wang and co–workers recently by following a different route.[81] For compounds **20** and **26**, only 2.5 mmol of nitrile was used.

Compound 16



Yield: 0.057 g (38%; brown solid)

Mp: 204-206 °C

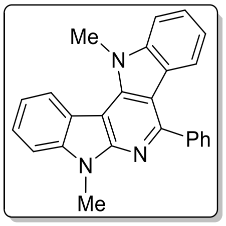
IR (KBr): 3054, 2939, 1618, 1593, 1481, 1325, 1257, 1024, 721, 698 cm^{-1}.

^{1}H NMR: δ 8.50 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 8.19 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 7.55-7.49 (m, 4H, Ar-*H*), 7.40-7.30 (m, 2H, Ar-*H*), 4.52 (s, 3H, NCH_3), 4.10 (s, 3H, NCH_3), 3.18 (s, 3H, CH_3).

^{13}C NMR: δ 151.0 (*C*=N), 150.3 (C=N-*C*), 142.6, 140.5, 138.7, 124.2, 123.6, 122.2, 121.3, 120.5, 119.4, 119.2, 111.9, 109.2, 108.6, 97.2 (C=N-C=*C*), 33.8, 28.1 (N$C\mathrm{H}_3$), 24.5 (N$C\mathrm{H}_3$).

HRMS (ESI): Calcd. for $C_{20}H_{18}N_3$ [M$^+$+H]: *m/z* 300.1501. Found: 300.1506.

Compound 17



Yield: 0.117 g (65%; white solid).

Mp: 188-190 °C.

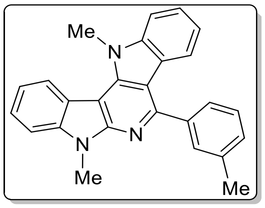
IR (KBr): 3053, 2924, 1616, 1591, 1483, 1323, 1265, 1176, 1091, 731, 698 cm^{-1}.

^{1}H NMR: δ 8.55 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.88 (d, *J* = 6.8 Hz, 2H, Ar-*H*), 7.63-7.50 (m, 7H, Ar-*H*), 7.44 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 7.36-7.32 (m, 1H, Ar-*H*), 7.09 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 4.55 (s, 3H, NCH_3), 4.10 (s, 3H, NCH_3).

^{13}C NMR: δ 152.1 (*C*=N), 150.3 (C=N-*C*), 143.2, 141.2, 140.7, 139.1, 129.4, 128.6, 128.5, 124.6, 124.5, 122.9, 122.4, 121.2, 120.0, 119.5, 119.5, 119.0, 111.4, 108.6, 97.7 (C=N-C=*C*), 33.8 (N$C\mathrm{H}_3$), 28.2 (N$C\mathrm{H}_3$).

HRMS (ESI): Calcd. for $C_{25}H_{20}N_3$ [M$^+$+H]: *m/z* 362.1658. Found: 362.1657.

Compound 18



Yield: 0.114 g (61%; white solid).

Mp: 206-208 °C.

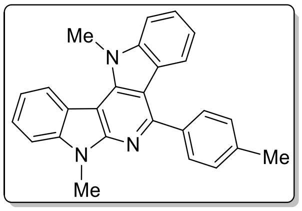
IR (KBr): 3051, 2925, 1615, 1593, 1544, 1478, 1319, 1276, 1089, 744, 722 cm^{-1}.

^{1}H NMR: δ 8.55 (d, *J* = 8 Hz, 1H, Ar-*H*), 7.69-7.34 (m, 10H, Ar-*H*), 7.10 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 4.55 (s, 3H, NCH_3), 4.11 (s, 3H, NCH_3), 2.51 (s, 3H, CH_3).

^{13}C NMR: δ 152.4 (*C*=N), 150.4 (C=N-*C*), 143.2, 142.3, 140.7, 139.1, 138.2, 130.1, 129.4, 128.5, 126.7, 124.7, 124.5, 123.1, 122.5, 121.4, 120.1, 119.5, 119.0, 111.4, 109.2, 108.7, 97.7 (C=N-C=*C*), 33.8 (NCH_3), 28.3 (NCH_3), 21.7 (CH_3).

HRMS (ESI): Calcd. for $C_{26}H_{22}N_3$ [M^++H]: *m/z* 376.1814. Found: 376.1814.

Compound 19



Yield: 0.107 g (57%; yellow solid).

Mp: 234-236 °C.

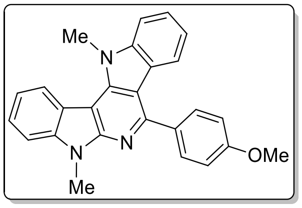
IR (KBr): 2953, 2909, 2860, 1616, 1589, 1479, 1391, 1254, 1194, 1090, 728, 690 cm^{-1}

^{1}H NMR: δ 8.54 (d, *J* = 8 Hz, 1H, Ar-*H*), 7.79 (d, *J* = 7.6 Hz, 2H, Ar-*H*), 7.60 (d, *J* = 3.8 Hz, 1H, Ar-*H*), 7.54-7.32 (m, 7H, Ar-*H*), 7.11 (t, *J* = 14.8 Hz, 1H, Ar-H), 4.54 (s, 3H, NCH_3), 4.09 (s, 3H, NCH_3), 2.53 (s, 3H, CH_3).

^{13}C NMR: δ 152.4 (*C*=N), 150.5 (C=N-*C*), 143.4, 140.9, 139.2, 138.5, 129.3, 129.2, 124.7, 124.6, 123.1, 122.5, 121.4, 120.1, 119.6, 119.2, 111.5, 109.3, 108.7, 97.7 (C=N-C=*C*), 34.0 (NCH_3), 28.4 (NCH_3), 21.6 (CH_3).

HRMS (ESI): Calcd. for $C_{26}H_{22}N_3$ [M^++H]: *m/z* 376.1814. Found: 376.1811.

Compound 20



Yield: 0.115 g (59%; yellow solid).

Mp: 240-244 °C.

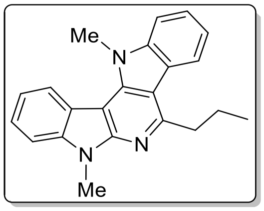
IR (KBr): 3046, 2926, 2832, 1621, 1589, 1506, 1468, 1326, 1265, 1243, 1178, 1024, 838, 728 cm^{-1}.

^{1}H NMR: δ 8.55 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.85-7.83 (m, 2H, Ar-*H*), 7.64 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.56-7.32 (m, 5H, Ar-*H*), 7.15-7.10 (m, 3H, Ar-*H*), 4.55 (s, 3H, OC*H*$_3$), 4.10 (s, 3H, NC*H*$_3$), 3.96 (s, 3H, NC*H*$_3$).

^{13}C NMR: δ 160.1 (*C*-OCH$_3$), 152.1 (*C*=N), 150.6 (C=N-*C*), 143.5, 140.9, 139.2, 133.8, 130.8, 124.7, 124.6, 123.2, 122.5, 121.4, 120.1, 119.6, 119.2, 113.9, 111.5, 109.3, 108.7, 97.6 (C=N-C=*C*), 55.5 (O*C*H$_3$), 34.1 (N*C*H$_3$), 28.4 (N*C*H$_3$).

HRMS (ESI): Calcd. for $C_{26}H_{22}N_3O$ [M$^+$+H]: *m/z* 392.1764. Found: 392.1761.

Compound 21



Yield: 0.092 g (56%; white solid).

Mp 170-173 °C.

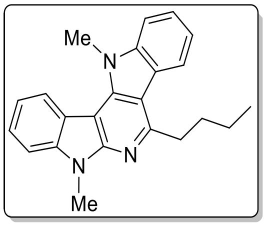
IR (KBr): 3051, 2951, 1616, 1587, 1552, 1477, 1396, 1255, 1089, 746, 729 cm^{-1}.

^{1}H NMR: δ 8.49 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 8.13 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.54-7.29 (m, 6H, Ar-*H*), 4.50 (s, 3H, NC*H*$_3$), 4.09 (s, 3H, NC*H*$_3$), 3.45 (t, *J* = 7.8 Hz, 2H, C*H*$_2$-CH$_2$-CH$_3$), 2.08-2.02 (m, 2H, C*H*$_2$-CH$_3$), 1.19 (t, *J* = 7.6 Hz, 3H, C*H*$_3$).

^{13}C NMR: δ 155.0 (*C*=N), 150.2 (C=N-*C*), 142.7, 140.5, 138.7, 124.0, 123.1, 122.2, 121.8, 121.3, 120.4, 119.3, 119.2, 111.2, 109.1, 108.6, 97.0 (C=N-C=*C*), 39.4 (*C*H$_2$-CH$_2$-CH$_3$), 33.6 (N*C*H$_3$), 28.1 (N*C*H$_3$), 21.6 (*C*H$_2$-CH$_3$), 14.6 (CH$_2$-*C*H$_3$).

HRMS (ESI): Calcd. for $C_{22}H_{22}N_3$ [M$^+$+H]: *m/z* 328.1814. Found: 328.1813.

Compound 22



Yield: 0.090 g (53%; white solid).

Mp 196-198 ^{o}C.

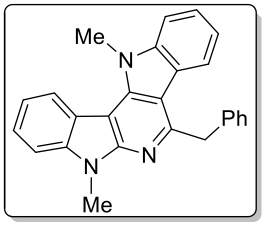
IR (KBr): 3051, 2953, 1621, 1593, 1473, 1325, 1259, 1133, 1089, 717 cm^{-1}.

^{1}H NMR: δ 8.50 (d, *J* = 8 Hz, 1H, Ar-*H*), 8.14 (d, *J* = 8 Hz, 1H, Ar-*H*), 7.55-7.27 (m, 6H, Ar-*H*), 4.52 (s, 3H, NC*H*$_3$), 4.09 (s, 3H, NC*H*$_3$), 3.48 (t, *J* = 8.4 Hz, 2H, C*H*$_2$-CH$_2$-CH$_2$-CH$_3$), 2.02-1.98 (m, 2H, C*H*$_2$-CH$_2$-CH$_3$), 1.67-1.56 (m, 2H, C*H*$_2$-CH$_3$), 1.06 (t, *J* = 7.4 Hz, 3H, C*H*$_3$).

^{13}C NMR: δ 155.3 (*C*=N), 150.3 (C=N-*C*), 142.8, 140.5, 138.7, 124.1, 123.1, 122.2, 121.4, 120.4, 119.3, 119.2, 111.2, 109.1, 108.7, 97.0 (C=N-C=*C*), 37.2 (NCH$_3$), 33.8 (*C*H$_2$CH$_2$CH$_2$CH$_3$), 30.4 (*C*H$_2$CH$_2$CH$_3$), 28.1 (NCH$_3$), 23.2 (*C*H$_2$-CH$_3$), 14.3 (CH$_2$-*C*H$_3$).

HRMS (ESI): Calcd. for $C_{23}H_{24}N_3$ [M$^+$+H]: *m/z* 342.1971. Found: 342.1970.

Compound 23



Yield: 0.113 g (60%; yellow solid).

Mp 208-210 ^{o}C.

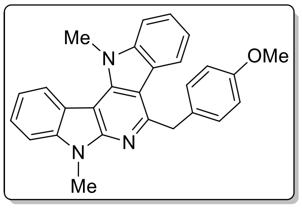
IR (KBr): 3068, 3024, 2915, 1616, 1589, 1473, 1326, 1254, 1106, 980, 723, 695 cm^{-1}.

^{1}H NMR: δ 8.52 (d, *J* = 8 Hz, 1H, Ar-*H*), 8.06 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 7.56-7.30 (m, 7H, Ar-*H*), 7.24-7.15 (m, 4H, Ar-*H*), 4.89 (s, 2H, C*H*$_2$), 4.53 (s, 3H, NC*H*$_3$), 4.09 (s, 3H, NC*H*$_3$).

^{13}C NMR: δ 152.1 (CH_2-*C*=N), 150.4 (CH_2-C=N-*C*), 143.2, 140.7, 139.1, 139.0, 128.7, 128.4, 126.0, 124.4_2, 122.9, 122.4, 121.5, 120.5, 119.5, 119.2, 112.2, 109.2, 108.7, 97.5 (C=N-C=*C*), 43.0, 33.9 (N*C*H_3), 28.2 (N*C*H_3).

HRMS (ESI): Calcd. for $C_{26}H_{22}N_3$ [M^++H]: *m/z* 376.1814. Found: 376.1813.

Compound 24



Yield: 0.112 g (55%; white solid).

Mp: 182-184 ^{o}C.

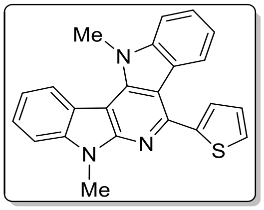
IR (KBr): 3057, 2909, 2832, 1615, 1588, 1511, 1473, 1391, 1325, 1243, 1106, 1029, 804, 739 cm^{-1}.

^{1}H NMR: δ 8.51 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 8.08 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 7.53-7.24 (m, 8H, Ar-*H*), 6.79 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 4.81 (s, 2H, C*H*$_2$), 4.52 (s, 3H, C*H*$_3$), 4.08 (s, 3H, C*H*$_3$), 3.74 (s, 3H, C*H*$_3$).

^{13}C NMR: δ 158.0 (*C*-OCH_3), 152.7 (*C*=N), 150.4, 143.3, 140.8 (C=N-*C*), 139.0, 131.2, 129.6, 126.2, 124.4, 123.0, 122.4, 121.6, 120.6, 119.6, 119.2, 113.9, 112.2, 109.3, 108.8, 97.6 (C=N-C=*C*), 55.2 (O*C*H_3), 42.1 (*C*H_2), 34.0 (N*C*H_3), 28.3 (N*C*H_3).

HRMS (ESI):Calcd. for $C_{27}H_{24}N_3O$ [M^++H]: *m/z* 406.1920. Found: 406.1919.

Compound 25



Yield: 0.108 g (59%; yellow solid).

Mp: 216-218 ^{0}C.

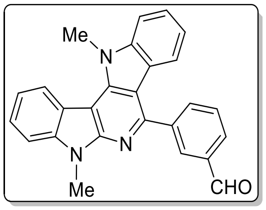
IR (KBr): 3079, 2920, 2843, 1610, 1588, 1473, 1319, 1259, 1095, 733, 700 cm^{-1}.

^{1}H NMR: δ 8.53 (d, *J* = 8 Hz, 1H, Ar-*H*), 8.03 (d, *J* = 8 Hz, 1H, Ar-*H*), 7.74-7.48 (m, 6H, Ar-*H*), 7.33-7.19 (m, 3H, Ar-*H*), 4.54 (s, 3H, NC*H*$_3$), 4.10 (s, 3H, NC*H*$_3$).

^{13}C NMR: δ 150.0 (*C*=N), 145.1 (C=N-*C*), 143.7, 143.3, 140.7, 139.2, 127.7, 127.2, 127.0, 124.9, 124.7, 122.6, 122.5, 121.1, 120.1, 119.6, 118.9, 111.6, 109.2, 108.7, 98.0 (C=N-C=*C*), 33.9 (N*C*H$_3$), 28.2 (N*C*H$_3$).

HRMS (ESI): Calcd. for $C_{23}H_{18}N_3S$ [M$^+$+H]: *m/z* 368.1222. Found: 368.1224.

Compound 26



Yield: 0.117 g (60%; yellow solid).

Mp 232-234 °C.

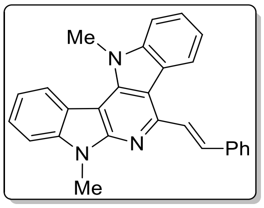
IR (KBr): 3046, 2920, 2848, 1714, 1582, 1473, 1374, 1325, 1276, 1155, 1089, 733 cm^{-1}.

^{1}H NMR: δ 10.17 (s, 1H, C*H*O), 8.56 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 8.42 (s, 1H, Ar-*H*), 8.18 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 8.10 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 7.77 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 7.57-7.34 (m, 6H, Ar-*H*), 7.10 (t, *J* = 7.4 Hz, 1H, Ar-*H*), 4.55 (s, 3H, NC*H*$_3$), 4.09 (s, 3H, NC*H*$_3$).

^{13}C NMR: δ 192.3 (*C*HO), 150.5 (*C*=N), 150.4 (C=N-*C*), 143.5, 142.3, 141.0, 139.4, 136.8, 135.6, 131.6, 129.2, 125.1, 125.0, 122.7, 122.6, 120.9, 120.3, 119.8, 119.0, 111.5, 109.4, 109.0, 98.2 (C=N-C=*C*), 34.1 (N*C*H$_3$), 28.4 (N*C*H$_3$).

HRMS (ESI): Calcd. for $C_{26}H_{20}N_3O$ [M$^+$+H]: *m/z* 390.1607. Found: 390.1606.

Compound 27



Yield: 0.122 g (63%; yellow solid).

Mp: 228-230 ^{o}C.

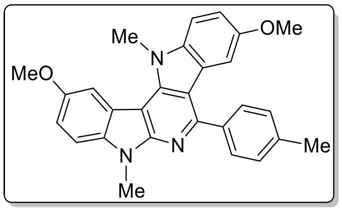
IR (KBr) 2920, 1632, 1583, 1467, 1319, 1254, 1095, 963, 788, 728 cm^{-1}.

^{1}H NMR: δ 8.40 (d, *J* = 8 Hz, 1H, Ar-*H*), 8.25 (d, *J* = 8 Hz, 1H, Ar-*H*), 8.16 (d, *J* = 4.8 Hz, 2H, Ar-*H*), 7.78 (d, *J* = 7.6 Hz, 2H, Ar-*H*), 7.49-7.28 (m, 9H, Ar-*H*), 4.36 (s, 3H, NC*H*$_3$), 4.04 (s, 3H, NC*H*$_3$).

^{13}C NMR: δ 150.3 (*C*=N), 147.2 (C=N-*C*), 143.1, 140.9, 139.5, 137.5, 133.9, 128.8, 128.2, 127.5, 125.9, 124.5, 122.9, 122.4, 121.9, 120.5, 119.4, 119.2, 112.0, 109.1, 108.8, 98.2 (C=N-C=*C*), 33.8 (N*C*H$_3$), 28.0 (N*C*H$_3$).

HRMS (ESI): Calcd. for $C_{27}H_{22}N_3$ [M$^+$+H]: *m/z* 388.1814. Found: 388.1817.

Compound 28



Yield: 0.127 g (58%; white solid).

Mp: 180-182 ^{o}C.

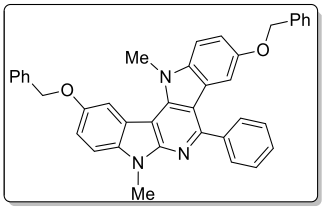
IR (KBr): 2997, 2926, 2827, 1621, 1600, 1578, 1490, 1304, 1216, 1139, 1041, 778 cm^{-1}.

^{1}H NMR: δ 8.03 (s, 1H, Ar-*H*), 7.76 (d, *J* = 8 Hz, 2H, Ar-*H*), 7.44-7.34 (m, 4H, Ar-*H*), 7.18-7.03 (m, 3H, Ar-*H*), 4.48 (s, 3H, NC*H*$_3$), 4.05 (s, 3H, OC*H*$_3$), 3.97 (s, 3H, OC*H*$_3$), 3.69 (s, 3H, NC*H*$_3$), 2.51 (s, 3H, C*H*$_3$).

^{13}C NMR: δ 154.0 and 153.7 (*C*-OCH$_3$), 152.5 (*C*=N), 150.8 (C=N-*C*), 143.6, 138.4, 138.2, 135.6, 134.3, 129.3, 129.0, 123.7, 119.4, 112.7, 112.0, 110.9, 109.4, 109.0, 107.3, 105.1, 97.5 (C=N-C=*C*), 56.2 (O*CH*$_3$), 55.6 (O*CH*$_3$), 33.9 (N*C*H$_3$), 28.3 (N*C*H$_3$), 21.5 (*C*H$_3$).

HRMS (ESI): Calcd. for $C_{28}H_{26}N_3O_2$ [M$^+$+H] *m/z* 436.2026. Found: 436.2029.

Compound 29



Yield: 0.183 g (64%; white solid).

Mp: 178-180 ^{o}C.

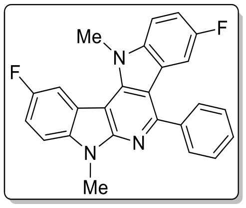
IR (KBr): 2943, 2850, 1622, 1593, 1489, 1330, 1293, 1142, 1029, 790, 715 cm^{-1}.

^{1}H NMR: δ 8.02 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 7.85-7.83 (m, 2H, Ar-*H*), 7.58-7.54 (m, 5H, Ar-*H*), 7.47-7.32 (m, 10H, Ar-H), 7.25 (dd, *J* = 8.8 Hz, *J* = 2.0 Hz, 1H), 7.11 (dd, *J* = 8.6 Hz, *J* = 2.2 Hz, 1H, Ar-*H*), 7.04 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 5.24 (s, 2H, OCH_2), 4.90 (s, 3H, OCH_2), 4.31 (s, 3H, CH_3), 4.03 (s, 3H, CH_3).

^{13}C NMR: δ 153.0, 152.7, 152.1, 150.5, 143.3, 141.1, 137.6, 137.4, 135.5, 134.2, 129.5, 128.6, 128.5, 128.4, 127.9, 127.8, 127.6, 127.4, 123.2, 119.1, 114.1, 113.3, 110.8, 109.3, 109.2, 108.6, 105.7, 97.5 (C=N-C=*C*), 71.3, 70.3, 33.7, 28.2.

HRMS (ESI): Calcd. for $C_{39}H_{32}N_3\,O_2$ [M^{+}+H]: *m/z* 574.2494. Found: 574.2494.

Compound 30



Yield: 0.101 g (51%; yellow solid).

Mp 258-261 ^{0}C.

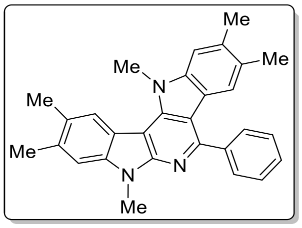
IR (KBr): 2920, 2827, 1621, 1600, 1490, 1298, 1123, 947, 767, 706 cm^{-1}.

^{1}H NMR: δ 8.13 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 8.11-7.58 (m, 5H, Ar-*H*), 7.43-7.12 (m, 5H, Ar-*H*), 4.43 (s, 3H, NCH_3), 4.04 (s, 3H, NCH_3).

^{13}C NMR: δ 153.3, 151.2, 144.0, 140.6, 137.1, 135.6, 129.2, 129.0, 128.7, 112.5, 112.4, 112.3, 112.2, 109.8, 109.7, 109.3, 109.2, 108.5, 108.3, 107.5, 107.3, 34.2 (N*C*H$_3$), 28.5 (N*C*H$_3$).

HRMS (ESI): Calcd. for $C_{25}H_{18}F_2N_3$ [M^{+}+H]: *m/z* 398.1470. Found: 398.1468.

Compound 31



Yield: 0.130 g (62%; pale yellow solid).

Mp: 256-258 °C.

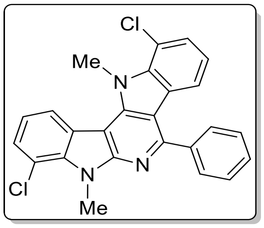
IR (KBr): 2917, 2851, 1610, 1594, 1448, 1393, 1295, 1050, 753, 700 cm^{-1}.

^{1}H NMR (500 MHz): δ 8.27 (s, 1H, Ar-*H*), 7.91-7.90 (m, 2H, Ar-*H*), 7.63-7.57 (m, 3H, Ar-*H*), 7.33 (s, 1H, Ar-H), 7.29 (s, 1H, Ar-H), 7.27 (s, 1H, Ar-H), 4.51 (s, 3H, NC*H*3), 4.06 (s, 3H, NC*H*3), 2.53 (d, *J* = 2.0 Hz, 6H, C*H*3), 2.46 (s, 3H, C*H*3), 2.26 (s, 3H, C*H*3).

^{13}C NMR (125 MHz): δ 153.1, 150.3, 143.1, 141.5, 139.8, 138.2, 133.8, 133.7, 129.5, 128.5, 128.4, 128.3, 127.8, 123.1, 121.9, 121.1, 117.2, 111.3, 109.9, 109.4, 97.7 (C=N-C=*C*), 34.1, 28.4, 20.8, 20.6 and 20.2.

HRMS (ESI): Calcd. for $C_{29}H_{28}N_3$ [M^++H]:*m/z* 418.2283. Found: 418.2287.

Compound 32



Yield: 0.122 g (56%; white solid).

Mp: 224-226 °C.

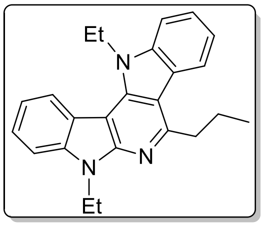
IR (KBr): 2947, 2824, 1666, 1611, 1582, 1551, 1476, 1400, 1348, 1294, 1209, 1182, 1099, 786, 727 cm^{-1}.

^{1}H NMR (500 MHz, C_6D_6): δ 8.37 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.84-7.82 (m, 2H, Ar-*H*), 7.64-7.58 (m, 3H, Ar-*H*), 7.49 (dd, *J* = 9.75 Hz, *J* = 1.25 Hz, 1H), 7.41-7.36 (m, 2H, Ar-H), 7.27-7.23 (m, 1H, Ar-H), 7.00 (t, *J* = 10.25 Hz, 1H, Ar-H), 4.67 (s, 3H, NCH_3), 4.53 (s, 3H, NCH_3).

^{13}C NMR (125 MHz, C_6D_6): δ 153.1, 151.3, 145.6, 141.3, 138.0, 135.2, 129.5, 128.6, 128.4, 128.0, 127.9, 127.7, 127.5, 127.0, 126.6, 126.5, 122.1, 121.7, 121.5, 120.1, 120.0, 116.9, 112.1, 97.9 (C=N-C=*C*), 37.5, 31.2.

HRMS (ESI): Calcd. for $C_{25}H_{18}Cl_2N_3$ [M^++H]: *m/z* 430.0878. Found: 430.0873.

Compound 33



Yield: 0.098 g (55%; yellow solid).

Mp: 130-132 °C.

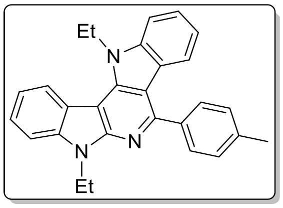
IR (KBr): 3051, 2958, 2865, 1610, 1600, 1588, 1473, 1325, 1248,749, 728 cm^{-1}.

^{1}H NMR: δ 8.30 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 8.16 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.60-7.27 (m, 6H, Ar-*H*), 4.98 (qrt, 2H, NCH_2CH_3), 4.72 (qrt, 2H, NCH_2CH_3), 3.49-3.45 (m, 2H, CH_2), 2.10-2.04 (m, 2H, CH_2-CH_3), 1.78 (t, *J* = 8.0 Hz, 3H, CH_3) 1.52 (t, *J* = 6.0 Hz, 3H, CH_3), 1.20 (t, *J* = 8.0 Hz, 3H, CH_3).

^{13}C NMR: δ 155.0, 149.5, 142.0, 139.4, 137.6, 124.0, 123.3, 122.8, 122.1, 121.4, 120.5, 119.5, 119.4, 112.7, 111.3, 109.6, 109.2, 108.6, 96.7 (C=N-C=*C*-), 40.4, 39.2, 36.6, 21.5, 16.1, 14.4, 14.0.

HRMS (ESI): Calcd. for $C_{24}H_{26}N_3$ [M^++H]: *m/z* 356.2127. Found: 356.2126.

Compound 34



Yield: 0.111 g (55%; white solid).

Mp 148-150 °C.

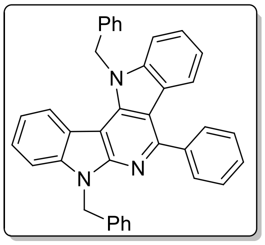
IR (KBr): 2969, 2920, 1610, 1578, 1468, 1326, 1254,794, 734 cm^{-1}.

^{1}H NMR: δ 8.36 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.77 (d, *J* = 7.6 Hz, 2H, Ar-*H*), 7.62-7.35 (m, 8H, Ar-*H*), 7.10 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 5.05-5.00 (m, 2H, NCH_2), 4.77-4.74 (m, 2H, NCH_2), 2.54 (s, 3H, CH_3), 1.81 (t, *J* = 7.2 Hz, 3H, NCH_2CH_3), 1.50 (t, *J* = 7.2 Hz, 3H, NCH_2CH_3).

^{13}C NMR: δ 152.5 (*C*=N), 149.8 (C=N-*C*), 142.6, 139.7, 138.4, 138.2, 129.3, 129.2, 124.7, 124.5, 123.3, 122.5, 121.5, 120.1, 119.7, 119.4, 111.5, 109.6, 109.4, 108.5, 97.4 (C=N-C=*C*), 40.6 (NCH_2CH_3), 36.7 (NCH_2CH_3), 21.6 (CH_3), 16.2 (NCH_2CH_3), 14.1 (NCH_2CH_3).

HRMS (ESI): Calcd. for $C_{28}H_{26}N_3$ [M^++H]: *m/z* 404.2127. Found: 404.2124.

Compound 35



Yield: 0.146 g (57%; white solid).

Mp: 236-238 °C.

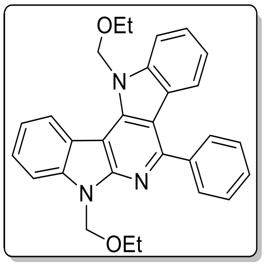
IR (KBr): 2920, 2848, 1621, 1593, 1544, 1467, 1402, 1325, 1243, 1177, 739, 711 cm^{-1}.

^{1}H NMR: δ 7.98 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.94 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 7.62-7.22 (m, 18H, Ar-*H*), 7.10-7.07 (m, 2H, Ar-*H*), 6.16 (s, 2H, CH_2), 5.91 (s, 2H, CH_2).

^{13}C NMR: δ 152.5 (*C*=N), 150.7 (C=N-*C*), 144.0, 141.2, 140.8, 138.6, 137.9, 137.4, 129.6, 129.2, 128.7, 128.6, 128.5, 127.8, 127.3, 127.2, 126.5, 125.0, 124.7, 123.4, 122.8, 121.4, 120.6, 120.1, 119.2, 112.0, 110.1, 109.6, 97.6 (C=N-C=*C*), 50.0, 45.5.

HRMS (ESI): Calcd. for $C_{37}H_{28}N_3$ [M^++H]: *m/z* 514.2284. Found: 514.2282.

Compound 36



Yield: 0.113 g (50%; yellow solid).

Mp 158-160 °C.

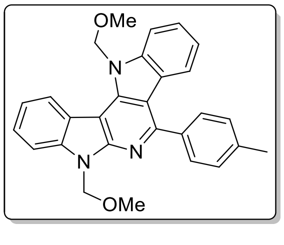
IR (KBr): 3057, 2969, 2893, 1616, 1589, 1473, 1380, 1326, 1260, 728 cm^{-1}.

^{1}H NMR: δ 8.69 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.88-7.40 (m, 11H, Ar-*H*), 7.12 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 6.23 (s, 2H, NCH_2), 6.14 (s, 2H, NCH_2), 3.86 (qrt, 2H, CH_2CH_3), 3.60 (qrt, 2H, CH_2CH_3), 1.31 (t, *J* = 7.0 Hz, 3H, CH_2CH_3), 1.17 (t, *J* = 7.2 Hz, 3H, CH_2CH_3).

^{13}C NMR: δ 152.1 (*C*=N), 150.8 (C=N-*C*), 142.8, 141.0, 138.6, 129.4, 128.7, 128.5, 125.3, 125.2, 123.4, 123.2, 121.6, 121.0, 120.9, 120.0, 112.6, 110.4, 109.1, 98.6 (C=N-C=*C*), 73.9 (O*C*H_2), 71.2 (O*C*H_2), 64.4 (N*C*H_2), 64.0 (N*C*H_2), 15.2 (CH_2CH_3), 15.0 (CH_2CH_3).

HRMS (ESI): Calcd. for $C_{29}H_{28}N_3O_2$ [M^++H]: *m/z* 450.2182. Found: 450.2182.

Compound 37



Yield: 0.105 g (48%; white solid).

Mp 170-172 °C.

IR (KBr): 3046, 2947, 2821, 1610, 1593, 1473, 1330, 1259, 1182, 1062, 793, 728 cm^{-1}.

^{1}H NMR: δ 8.63 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.78-7.52 (m, 6H, Ar-*H*), 7.47-7.41 (m, 4H, Ar-*H*), 7.12 (t, *J* = 6.6 Hz, 1H, Ar-H), 6.20 (s, 2H, NC*H*$_2$), 6.09 (s, 2H, NC*H*$_2$), 3.62 (s, 3H, OC*H*$_3$), 3.38 (s, 3H, OC*H*$_3$), 2.54 (s, 3H, C*H*$_3$).

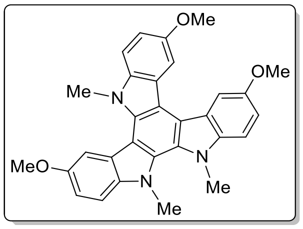
^{13}C NMR: δ 152.3 (*C*=N), 150.9 (C=N-*C*), 142.9, 141.1, 138.6$_2$, 138.5$_7$, 138.1, 129.3, 129.2, 125.4, 125.2, 123.4, 123.2, 121.8, 121.0$_3$, 120.9$_8$, 120.0$_0$, 112.7, 110.3, 109.0, 98.5 (C=N-C=*C*), 75.1 (N*C*H$_2$OCH$_3$), 72.7 (NCH$_2$O*C*H$_3$), 56.4 (O*C*H$_3$), 21.5 (*C*H$_3$).

HRMS (ESI): Calcd. for $C_{28}H_{26}N_3O_2$ [M^++H]: *m/z* 436.2026. Found: 436.2024.

3.4 Synthesis of triindoles (39-47) by [Pd]-catalyzed decarboxylative trimerization of indole-2-carboxylic acids 1a-b, 1h-i and 1k-l: General procedure

In an oven dried round-bottomed flask (25 mL), silver carbonate (2.0 mmol) was dried in *vacuo* while heating (ca 100 °C) using a hot air gun for 0.5 h. To this, Pd(OAc)$_2$ (10 mol %), 1-alkylindole-2-carboxylic acid (1.0 mmol) and DMF (5.0 mL) were added. The mixture was stirred at rt (25 °C) for 10 min. The RBF was flushed with N$_2$ and sealed with a stopper. Then the contents were stirred at 80 ^{0}C (oil bath) for 10 h. After the completion of the reaction as monitored by TLC, the mixture was cooled to rt, filtered and extracted with diethyl ether (3 x 25 mL). The combined organic extracts were washed with brine solution (4 x 10 mL). The organic part was dried over anhy. Na$_2$SO$_4$, and the solvent was removed using a rotary evaporator. The crude product was purified by column chromatography (230-400 mesh silica) using hexane/ EtOAc as eluent to afford the final products **39-47**. Triindoles **39, 40** and **46** are known.[91]

Compound 41



Yield: 0.048 g (30%; yellow solid).

Mp 118-121 ^{o}C.

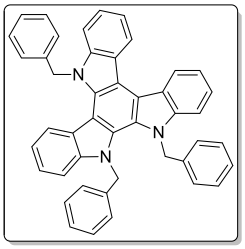
IR (KBr): 2920, 2832, 1616, 1567, 1484, 1386, 1304, 1221, 1030, 909, 783 cm^{-1}.

^{1}H NMR (C_6D_6): δ 8.85 (d, *J* = 2.0 Hz, 1H, Ar-*H*), 8.80 (d, *J* = 2.8 Hz, 1H, Ar-*H*), 8.20 (d, *J* = 2.4 Hz, 1H, Ar-*H*), 7.51-7.31 (m, 6H, Ar-*H*), 4.00 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.78 (s, 3H, NCH_3), 3.51 (s, 3H, NCH_3), 3.46 (s, 3H, NCH_3).

^{13}C NMR (C_6D_6): δ 155.4, 155.3, 155.0, 141.7, 140.3, 138.4, 136.1, 133.3, 128.6, 126.8, 125.5, 125.2, 119.8, 115.1, 113.2_2, 113.1_9, 112.4_9, 112.4_5, 111.8, 111.1, 110.1, 107.5, 106.5, 105.8, 55.9, 55.8_2, 55.7_8 (OCH_3), 36.9, 35.1, 36.1 (NCH_3).

HRMS (ESI): Calcd. for $C_{30}H_{28}N_3O_3$ [M^{+}+H]: *m/z* 478.2131. Found: 478.2130.

Compound 42



Yield: 0.066 g (32%; yellow solid).

Mp 107-109 ^{o}C.

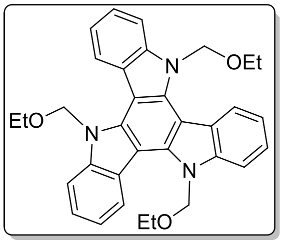
IR (KBr): 3024, 2926, 1715, 1578, 1331, 1194, 1167, 1019, 739, 690 cm^{-1}.

^{1}H NMR (C_6D_6): δ 9.33 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 9.27 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 8.33 (d, *J* = 7.6 Hz, 1H, Ar-*H*), 7.48-7.23 (m, 9H, Ar-*H*), 7.11-6.92 (m, 11H, Ar-*H*), 6.80-6.76 (m, 4H, Ar-*H*), 5.82 (s, 2H, NCH_2), 5.11 (s, 2H, NCH_2), 5.03 (s, 2H, NCH_2).

^{13}C NMR (C_6D_6): δ 146.1, 144.6, 143.7, 139.4, 138.0, 137.7, 136.1, 132.2, 129.6, 128.9, 128.5, 128.2, 127.8, 127.7, 127.3, 127.2, 126.8, 126.6, 126.5, 125.9, 125.8, 125.1, 124.9, 124.7, 124.0, 123.3, 123.2, 121.5, 121.3, 120.9, 120.7, 113.8, 113.1, 112.8, 112.0, 110.8, 52.9, 52.3, 52.0.

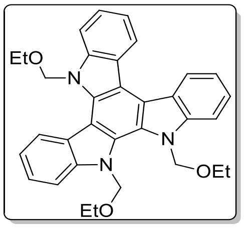
HRMS (ESI): Calcd. for $C_{45}H_{34}N_3$ [M^{+}+H]: *m/z* 616.2753. Found: 616.2752.

Compound 43



Yield:	0.037 g (21%; white solid).
Mp:	119-121 ^{o}C.
IR (KBr):	2920, 2849, 1583, 1473, 1385, 1325, 1226, 1078, 1013, 755, 722 cm^{-1}.
^{1}H NMR (C_6D_6):	δ 9.05-9.02 (m, 3H, Ar-*H*), 7.73-7.70 (m, 3H, Ar-*H*), 7.58-7.53 (m, 6H, Ar-*H*), 5.78 (s, 6H, NC*H*$_2$), 3.45 (qrt, 6H, C*H*$_2$), 1.17 (t, 9H, C*H*$_3$).
^{13}C NMR (C_6D_6):	δ 142.7, 139.0, 124.8, 124.4, 122.4, 121.6, 111.2, 105.2, 76.1, 64.2, 15.5.
HRMS (ESI):	Calcd. for $C_{33}H_{33}N_3O_3$ [M^{+}+Na]: *m/z* 542.2420. Found: 542.2420.

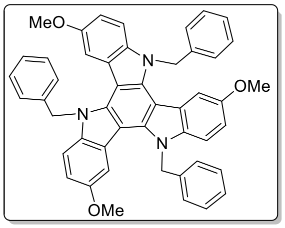
Compound 44



Yield:	0.054 g (31%; white solid).
Mp:	119-121 ^{o}C.
IR (KBr):	2920, 2849, 1583, 1473, 1385, 1325, 1226, 1078, 1013, 755, 722 cm^{-1}.
^{1}H NMR (C_6D_6):	δ 9.30-9.20 (m, 3H, Ar-*H*), 7.92 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.87-7.85 (m, 1H, Ar-*H*), 7.75 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 7.64-7.52 (m, 6H, Ar-*H*), 5.85-5.66 (m, 6H, NC*H*$_2$), 3.50-3.44 (m, 2H, OC*H*$_2$), 3.17-3.08 (m, 4H, OC*H*$_2$), 1.22-1.13 (m, 3H, OCH$_2$C*H*$_3$), 1.01-0.93 (m, 6H, OCH$_2$C*H*$_3$).

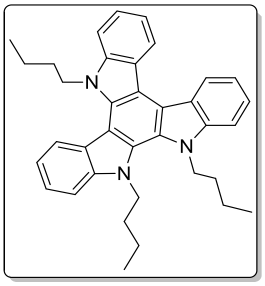
^{13}C NMR (C_6D_6):	δ 145.3, 144.1, 143.2, 134.7,130.7, 128.6, 127.0, 126.6, 126.0, 125.7, 125.6, 124.8, 124.0, 123.7, 123.1, 122.2, 121.8, 121.2, 120.1, 114.0, 113.3, 112.8, 111.2, 110.9, 77.8, 77.5, 76.0, 64.2, 64.1, 64.0, 15.5, 15.3.
HRMS (ESI):	Calcd. for $C_{33}H_{33}N_3O_3$ [M^++Na]: *m/z* 542.2420. Found: 542.2420.

Compound 45



Yield:	0.082 g (35%; yellow solid).
Mp:	132-134 °C.
IR (KBr):	2909, 2843, 1615, 1566, 1489, 1451, 1319, 1232, 1040, 914, 739 cm^{-1}.
^{1}H NMR (C_6D_6):	δ 7.74 (s, 3H, Ar-*H*), 7.46 (d, *J* = 7.6 Hz, 6H, Ar-*H*), 7.18-7.07 (m, 15H, Ar-*H*), 5.80 (s, 6H, NC*H*$_2$), 3.14 (s, 9H, OC*H*$_3$).
^{13}C NMR (C_6D_6):	δ 155.4, 140.8, 138.9, 137.1, 129.0, 127.2, 126.7, 124.3, 113.3, 111.9, 104.4, 104.2, 54.2, 51.7.
HRMS (ESI):	Calcd. for $C_{48}H_{40}N_3O_3$ [M^++H]: *m/z* 706.3070. Found: 706.3069.

Compound 47



Yield:	0.052 g (30%; yellow solid).
Mp:	131-133 °C.
IR (KBr):	2920, 2860, 1572, 1456, 1402, 1336, 1128, 1024, 744, 667 cm^{-1}.

^{1}H NMR (C_6D_6): δ 9.37-9.31 (m, 2H, Ar-*H*), 8.58 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.67-7.47 (m, 9H, Ar-*H*), 4.77 (t, *J* = 8.0 Hz, 2H, NC*H*$_2$), 4.63 (t, *J* = 8.0 Hz, 2H, NC*H*$_2$), 4.54 (t, *J* = 8.0 Hz, 2H, NC*H*$_2$), 1.90-1.82 (m, 2H), 1.29-1.21 (m, 4H), 1.19-1.09 (m, 2H), 0.71-0.64 (m, 7H), 0.45-0.40 (m, 6H).

^{13}C NMR (C_6D_6): δ 145.8, 144.4, 142.0, 135.0, 132.8, 128.6, 128.1, 127.9, 126.3, 125.4, 125.3, 124.7, 124.6, 124.0, 123.8, 123.2, 121.2, 121.1, 120.9, 120.1, 113.6, 113.4, 113.2, 110.9, 49.0, 48.4, 46.9, 32.7, 30.3, 29.9, 20.4$_4$, 20.3$_8$, 20.2, 14.1, 13.7$_4$, 13.7$_1$.

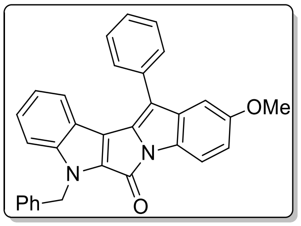
HRMS (ESI): Calcd. for $C_{36}H_{40}N_3$ [M$^+$+H] 514.3223. Found: 514.3223.

The green colored solid obtained on passing dry HCl gas into a toluene solution of compound **40** (see text, section 2.7.3) show peaks at *m/z* values 477.2069, 490.2145 and 560.1521 in the HRMS.

3.5 Synthesis of Pyrrolodiindolones 48-57 by the [Pd]-catalyzed intramolecular cyclization and C-H activation: General Procedure

In an oven dried 25 mL round-bottomed flask, silver carbonate (1.0 mmol) was dried *in vacuo* while heating (ca 100 °C) for 0.5 h. To this, Pd(OAc)$_2$ (10 mol%), 3-alkynyl-indole-2-carboxamide (one of **8a-8j**, 0.5 mmol), K_2CO_3 (0.5 mmol) and PhCN (4 mL) were added. The vessel was stoppered and the mixture was stirred at 90 °C (oil bath) for 8h. After the completion of the reaction (TLC), excess of the nitrile was removed *in vacuo* and the mixture was subjected to column chromatography using silica gel with ethyl acetate/hexane mixture (ca 1:19) as the eluent to afford the desired products in 75-86 % yield. Compounds **48-57** were prepared by this procedure.

Compound 48



Yield: 0.186 g (82%; orange red solid; using 0.5 mmol of precursor **5a**).

Mp: 198-200 ^{o}C.

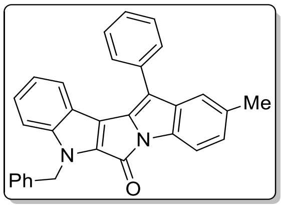
IR (KBr): 2362, 1712, 1590, 1521, 1479, 1378, 1249, 1145, 1090, 904, 822, 732, 696 cm^{-1}.

^{1}H NMR (500 MHz): δ 7.77-7.75 (m, 2H), 7.62-7.50 (m, 4H), 7.38-7.30 (m, 7H), 7.26-7.22 (m, 1H), 7.10-7.06 (m, 1H), 6.99 (d, *J* = 2.5 Hz, 1H), 6.82 (dd, *J* = 11.0 Hz and 3.0 Hz, 1H), 5.56 (s, 2H), 3.83 (s, 3H).

^{13}C NMR (125 MHz): δ 156.5$_3$, 156.4$_5$, 142.4, 136.5, 135.7, 134.4, 133.2, 132.8, 129.9, 129.2, 129.0, 128.9, 128.4, 128.1, 127.4, 125.3, 122.5, 122.0, 120.5, 120.1, 119.1, 113.1, 112.5, 112.0, 106.0, 55.9, 48.0.

HRMS (ESI): $C_{31}H_{23}N_2O_2$ [M$^+$+H]: *m/z* 455.1759. Found: 455.1755.

Compound 49



Yield: 0.175 g (80%, orange red solid; using 0.5 mmol of precursor **5b**).

Mp: 202-204 ^{o}C.

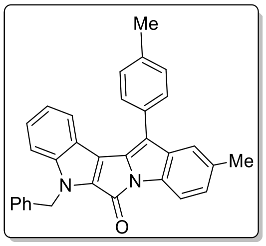
IR (KBr): 2959, 2926, 2855, 1715, 1518, 1468, 1381, 1173, 1085, 893, 811, 740, 702 cm^{-1}.

^{1}H NMR: δ 7.77-7.75 (m, 2H), 7.62-7.58 (m, 3H), 7.53-7.49 (m, 1H), 7.38-7.21 (m, 9H), 7.09-7.04 (m, 2H), 5.56 (s, 2H), 2.36 (s, 3H).

^{13}C NMR (125 MHz): δ 156.6, 142.5, 136.5, 135.6, 133.5, 133.4, 133.0, 132.8, 132.4, 129.2, 129.0, 128.9, 128.4, 128.0, 127.6, 127.4, 125.4, 122.6, 122.0, 121.2, 120.5, 120.3, 119.2, 112.0, 111.8, 48.0, 21.5.

HRMS (ESI): Calc. for $C_{31}H_{23}N_2O$ [M$^+$+H]: *m/z* 439.1810. Found: 439.1803.

Compound 50



Yield: 0.192 g (85%, orange red solid; using 0.5 mmol of precursor **5c**).

Mp: 193-195 °C.

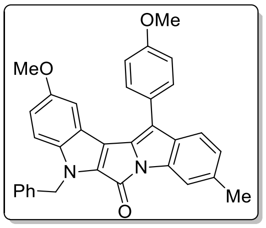
IR (KBr): 3030, 2921, 2855, 1715, 1523, 1474, 1370, 1173, 1085, 893, 811, 740, 702 cm^{-1}.

^1H NMR: δ 7.66 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.42 (~t, *J* = 7.2 Hz, 3H), 7.38-7.28 (m, 6H), 7.25-7.21 (m, 2H), 7.11-7.04 (m, 2H), 5.53 (s, 2H), 2.53 (s, 3H), 2.37 (s, 3H).

^{13}C NMR: δ 156.5, 142.5, 138.2, 136.6, 135.6, 133.7, 133.4, 132.7, 132.0, 130.0, 129.7, 129.1, 128.9, 128.0, 127.5, 127.4, 125.3, 122.6, 121.9, 121.2, 120.6, 120.4, 119.3, 111.9, 111.8, 47.9, 21.6, 21.5.

HRMS (ESI): Calc. for $C_{32}H_{25}N_2O$ [M^++H]: *m/z* 453.1967. Found: 453.1966.

Compound 51



Yield: 0.215 g (86%, orange red solid; using 0.5 mmol of precursor **5d**).

Mp: 134-136 °C.

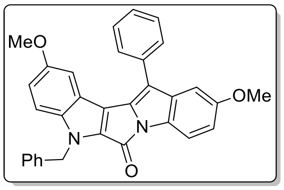
IR (KBr): 2915, 2849, 2367, 2340, 1715, 1605, 1523, 1502, 1452, 1337, 1260, 1151, 1030, 833, 701 cm^{-1}.

^1H NMR (500 MHz, C_6D_6): δ 7.95 (d, *J* = 8.0 Hz, 1H), 7.39-7.36 (m, 2H), 7.13 (s, 1H), 7.02-6.93 (m, 5H), 6.85 (dd, *J* = 9.0 Hz and 2.5 Hz, 1H), 6.80-6.70 (m, 2H), 6.75-6.70 (m, 2H), 6.22 (d, *J* = 9.0 Hz, 1H), 5.02 (s, 2H), 3.33 (s, 3H), 3.26 (s, 3H), 2.13 (s, 3H).

^{13}C NMR (125 MHz, C_6D_6): δ 159.6, 156.3, 155.6, 137.6, 136.9, 135.6, 135.2, 132.0_1, 131.9_5, 131.9, 130.6, 128.6, 128.0, 127.2, 126.4, 125.3, 120.9, 120.1, 118.5, 116.7, 114.2, 113.4, 112.7, 110.2, 102.3, 54.7, 54.5, 47.6, 19.7.

HRMS (ESI): Calc. for $C_{33}H_{26}N_2O_3$ [M^+]: *m/z* 498.1943. Found 498.1946.

Compound 52



Yield: 0.192 g (79%, orange red solid; using 0.5 mmol of precursor **5e**).

Mp: 254-258 °C.

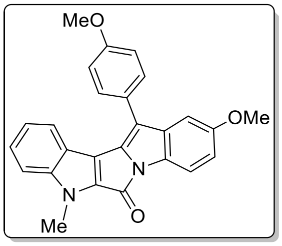
IR (KBr): 2921, 2855, 2329, 1710, 1622, 1518, 1479, 1447, 1370, 1233, 1145, 1079, 1030, 937, 696 cm^{-1}.

^{1}H NMR: δ 7.82-7.77 (m, 2H), 7.63-7.48 (m, 4H), 7.34 (d, *J* = 4.0 Hz, 5H), 7.21 (d, *J* = 8.8 Hz, 1H), 7.01 (s, 1H), 6.89 (d, *J* = 9.2 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.75 (s, 1H), 5.53 (s, 2H), 3.84 (s, 3H), 3.69 (s, 3H).

^{13}C NMR (125 MHz): δ 156.5, 155.5, 137.7, 136.5, 135.7, 134.3, 133.5, 133.0, 129.8, 129.3, 128.9, 128.7, 128.2, 128.0, 127.3, 120.8, 119.4, 118.8, 116.7, 112.9, 112.8, 112.5, 105.8, 102.9, 55.9, 55.4, 48.1.

HRMS (ESI): Calc. for $C_{32}H_{24}N_2O_3Na$ [M^++Na]: *m/z* 507.1685. Found: 507.1688.

Compound 53



Yield: 0.165 g (81%, orange red solid; using 0.5 mmol of precursor **5f**).

Mp: 226-228 °C.

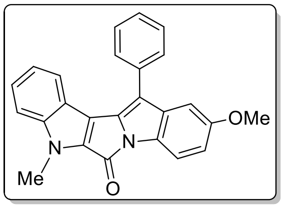
IR (KBr): 2950, 2860, 1704, 1605, 1474, 1260, 1090, 1036, 899, 740 cm^{-1}.

^{1}H NMR (500 MHz): δ 7.69-7.66 (m, 2H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.32-7.29 (m, 2H), 7.15-7.08 (m, 3H), 6.96 (d, *J* = 2.5 Hz, 1H), 6.80 (dd, *J* = 8.5 Hz and 2.5 Hz, 1H), 3.96_1 (s, 3H), 3.95_6 (s, 3H), 3.83 (s, 3H).

^{13}C NMR (125 MHz): δ 159.7, 156.4, 156.3, 143.0, 135.9, 134.6, 132.6, 130.3, 129.8, 125.2, 125.0, 122.3, 121.7, 120.2, 119.4, 118.4, 114.4, 112.7, 112.4, 111.4, 105.9, 55.9, 55.5, 30.5.

HRMS (ESI): Calc. for $C_{26}H_{21}N_2O_3$ [M^++H]: *m/z* 409.1552. Found: 409.1553.

Compound 54



Yield: 0.142 g (75%, orange red solid; using 0.5 mmol of precursor **5g**).

Mp: 236-238 ^{o}C.

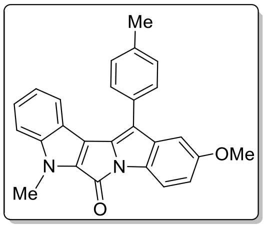
IR (KBr): 3056, 2948, 2833, 1715, 1584, 1534, 1479, 1386, 1282, 1222, 1151, 1090, 893, 734, 702 cm^{-1}.

^{1}H NMR: δ 7.75-7.73 (m, 2H), 7.62-7.49 (m, 4H), 7.37-7.29 (m, 3H), 7.11-7.07 (m, 1H), 6.98 (d, *J* = 2.4 Hz, 1H), 6.81 (dd, *J* = 8.4 Hz and 2.4 Hz, 1H), 3.96 (s, 3H), 3.82 (s, 3H).

^{13}C NMR (125 MHz): δ 156.4, 143.0, 136.0, 134.3, 133.2, 132.8, 129.8, 129.1, 129.0, 128.3, 125.1, 122.4, 121.8, 120.2, 119.3, 118.6, 112.9, 112.4, 111.2, 105.8, 55.9, 30.5.

HRMS (ESI): Calc. for $C_{25}H_{19}N_2O_2$ [M^++H]: *m/z* 379.1446. Found: 379.1449.

Compound 55



Yield: 0.149 g (78%, orange red solid; using 0.5 mmol of precursor **5h**).

Mp: 256-258 ^{o}C.

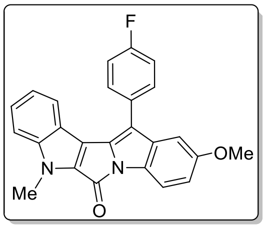
IR (KBr): 2932, 2833, 1710, 1584, 1529, 1474, 1375, 1343, 1211, 1151, 1085, 1041, 899, 800, 734.

^{1}H NMR (500 MHz): δ 7.62 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.5 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 3H), 7.30-7.25 (m, 2H), 7.11-7.08 (m, 1H), 6.96 (d, *J* = 2.0, 1H), 6.79 (dd, *J* = 8.5 Hz and 2.5 Hz, 1H), 3.92 (s, 3H), 3.81 (s, 3H), 2.52 (s, 3H).

^{13}C NMR (125 MHz): δ 156.4, 143.0, 138.2, 136.0, 134.5, 133.0, 129.9, 129.7, 129.0, 125.1, 122.4, 121.8, 120.2, 119.4, 118.8, 112.9, 112.4, 111.2, 105.9, 55.9, 30.5, 21.6.

HRMS (ESI): Calc. for $C_{26}H_{21}N_2O_2$ [M^++H]: *m/z* 393.1603. Found: 393.1600.

Compound 56



Yield: 0.150 g (76%, orange red solid; using 0.5 mmol of precursor **5i**).

Mp: 228-230 °C.

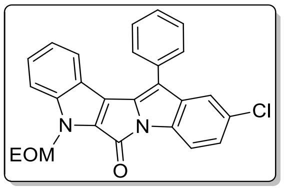
IR (KBr): 2921, 2838, 1715, 1584, 1512, 1485, 1238, 1167, 1036, 904, 795, 734 cm^{-1}.

^{1}H NMR: δ 7.72-7.68 (m, 2H), 7.59 (d, *J* = 8.8 Hz, 1H), 7.32-7.30 (m, 5H), 7.13-7.09 (m, 1H), 6.91 (d, *J* = 2.4 Hz, 1H), 6.81 (dd, *J* = 8.8 Hz and 2.4 Hz, 1H), 3.95 (s, 3H), 3.82 (s, 3H).

^{13}C NMR (125 MHz): δ 163.9, 161.5, 156.4, 156.3, 143.0, 136.0, 134.2, 133.2, 130.8, 130.7, 129.6, 128.8$_3$, 128.8$_0$, 125.1, 124.4, 122.0$_1$, 121.9$_8$, 121.9, 120.0, 119.0, 117.4, 116.1, 115.9, 114.3, 112.8, 112.4, 111.2, 105.6, 55.9, 30.4.

HRMS (ESI): Calc. for $C_{25}H_{18}FN_2O_2$ [M^++H]: *m/z* 397.1352. Found: 397.1353.

Compound 57



Yield: 0.160 g (75%, orange red solid; using 0.5 mmol of precursor **5j**).

Mp: 156-158 °C.

IR (KBr): 3030, 2975, 2926, 1710, 1655, 1523, 1490, 1452, 1370, 1266, 1184, 1090, 1014, 790 cm^{-1}.

^{1}H NMR: δ 7.89 (d, *J* = 6.4 Hz, 1H), 7.71-7.68 (m, 3H), 7.52 (~t, *J* = 6.2 Hz, 1H), 7.43-7.32 (m, 7H), 7.22 (s, 1H), 6.40 (s, 1H), 3.70 (qrt, *J* = 5.6 Hz, 2H), 1.20 (t, *J* = 5.6 Hz, 3H).

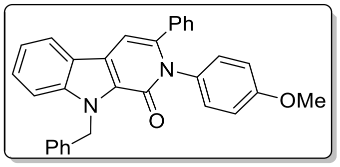
^{13}C NMR (125 MHz): δ 150.9, 145.3, 144.8, 140.9, 132.7, 128.9, 128.8_4, 128.8_2, 128.4, 126.9, 124.4, 124.2, 123.8, 122.4, 121.6, 121.3, 120.4, 112.0, 96.4, 73.4, 63.4, 15.2.

HRMS (ESI): Calc. for $C_{26}H_{20}ClN_2O_2$ [M^++H]: *m/z* 427.1213. Found: 427.1215.

3.6 Synthesis of β-carbolinones 58-72 by phase-transfer catalysis: General procedure

To a solution of 3-alkynylindole-2-carboxamide (one of **5a-5o**, 0.5 mmol) in dry CH_3CN (4 mL) was added TBAB (10 mol %) and Cs_2CO_3 (1.0 mmol) at rt. The reaction vessel was stoppered and the contents were stirred for 6 h at 80 °C. The progress of the reaction was monitored by TLC. Later, the solvent was removed under vacuum, and crude product was purified by column chromatography by using silica gel with ethyl acetate/hexane (1:9) mixture as the eluent to afford the corresponding β-carbolinones **58-72**.

Compound 58



Yield: 0.215 g (94%, yellow solid; using 0.5 mmol of precursor **5a**).

Mp: 160-162 °C.

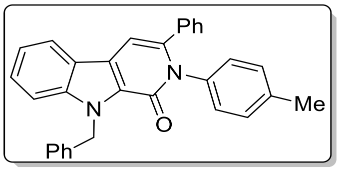
IR (KBr): 2926, 2849, 1737, 1655, 1501, 1452, 1238, 1085, 1019, 795, 745, 701 cm^{-1}.

^{1}H NMR: δ 8.00 (d, *J* = 8.0 Hz, 1H), 7.49 (s, 2H), 7.29-7.22 (m, 11H), 7.10 (d, *J* = 7.6 Hz, 2H), 7.05 (s, 1H), 6.81 (d, *J* = 7.6 Hz, 2H), 6.16 (s, 2H), 3.76 (s, 3H).

^{13}C NMR: δ 158.7, 157.2, 141.0, 140.9, 138.4, 137.1, 131.9, 130.6, 129.7, 128.6, 127.9, 127.7, 127.2, 127.1, 125.9, 124.8, 122.1, 121.3, 120.4, 114.0, 111.2, 102.4, 55.4, 47.9.

HRMS (ESI): Calc. for $C_{31}H_{25}N_2O_2$ [M^++H]: *m/z* 457.1916. Found: 457.1919.

Compound 59



Yield: 0.187 g (85%, yellow solid; using 0.5 mmol of precursor **5b**).

Mp: 98-100 °C.

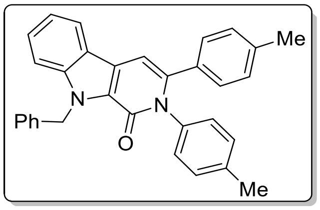
IR (KBr): 3030, 2915, 1655, 1562, 1507, 1457, 1326, 1260, 1205, 1140, 1074, 1030, 904, 805, 734, 696 cm^{-1}.

^{1}H NMR: δ 8.01 (d, *J* = 8.0 Hz, 1H), 7.50 (s, 2H), 7.29-7.23 (m, 11H), 7.09-7.06 (m, 5H), 6.17 (s, 2H), 2.30 (s, 3H).

^{13}C NMR: δ 157.1, 140.9, 140.8, 138.5, 137.5, 137.1, 136.5, 129.7, 129.4, 129.3, 128.5, 127.8, 127.6, 127.2, 127.1_3, 127.0_8, 125.9, 124.8, 122.1, 121.3, 120.4, 111.2, 102.5, 47.9, 21.2.

HRMS (ESI): Calc. for $C_{31}H_{25}N_2O$ [M^++H]: *m/z* 441.1967. Found: 441.1966.

Compound 60



Yield: 0.173 g (76%, yellow solid; using 0.5 mmol of precursor **5c**).

Mp: 148-150 °C.

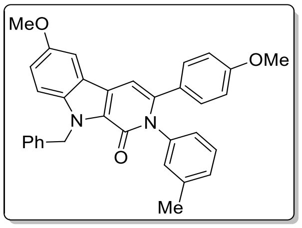
IR (KBr): 3030, 2920, 1649, 1507, 1468, 1326, 1266, 1211, 1134, 1025, 811, 734 cm^{-1}.

^{1}H NMR: δ 8.01 (d, *J* = 8.0 Hz, 1H), 7.50-7.47 (m, 2H), 7.30-7.21 (m, 6H), 7.15-7.09 (m, 6H), 7.04-7.00 (m, 3H), 6.18 (s, 2H), 2.33 (s, 3H), 2.32 (s, 3H).

^{13}C NMR: δ 157.1, 140.9, 138.5, 137.4, 136.6, 134.2, 130.0, 129.5, 129.3, 128.5, 127.2, 127.1, 127.0, 125.8, 124.8, 122.1, 121.3, 120.3, 115.3, 111.2, 102.3, 47.8, 21.2_1, 21.1_8.

HRMS (ESI): Calc. for $C_{32}H_{27}N_2O$ [M^++H]: *m/z* 455.2123. Found: 455.2127.

Compound 61



Yield: 0.213 g (85%, yellow solid; using 0.5 mmol of precursor **5d**).

Mp: 198-200 °C.

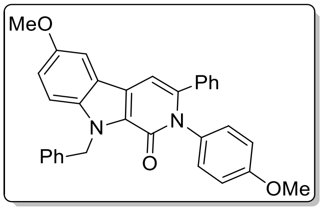
IR (KBr): 3002, 2931, 2833, 1649, 1554, 1512, 1490, 1468, 1288, 1255, 1167, 1030, 822, 701 cm^{-1}.

^{1}H NMR (500 MHz): δ 7.43 (d, *J* = 2.5 Hz, 1H), 7.38 (d, *J* = 9.0 Hz, 1H), 7.28-7.26 (m, 4H), 7.24-7.19 (m, 2H), 7.18-7.14 (m, 3H), 7.06-7.02 (m, 3H), 7.00 (s, 1H), 6.74 (d, *J* = 9.0 Hz, 2H), 6.16 (s, 2H), 3.92 (s, 3H), 3.77 (s, 3H), 2.31 (s, 3H).

^{13}C NMR (125 MHz) δ 158.9, 157.0, 154.5, 140.0, 139.2, 138.5, 138.4, 136.2, 130.8, 130.2, 129.6, 128.5, 128.4$_3$, 128.3$_8$, 127.0$_3$, 127.0$_0$, 126.7, 126.1, 124.2, 122.2, 117.8, 113.1, 112.1, 102.2$_4$, 102.1$_8$, 55.9, 55.2, 47.9, 21.3.

HRMS (ESI): Calc. for $C_{33}H_{29}N_2O_3$ [M$^+$+H]: *m/z* 501.2178. Found: 501.2177.

Compound 62



Yield: 0.218 g (89%, yellow solid; using 0.5 mmol of precursor **5e**).

Mp: 92-94 °C.

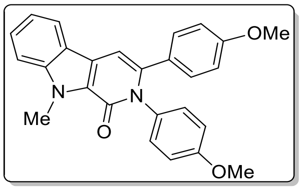
IR (KBr): 3063, 2958, 2821, 1655, 1512, 1249, 1162, 1025, 915, 805, 751, 696 cm^{-1}.

^{1}H NMR (500 MHz): δ 7.41-7.38 (m, 2H), 7.27-7.20 (m, 10H), 7.16-7.10 (m, 3H), 7.01 (s, 1H), 6.82 (d, *J* = 9.0 Hz, 2H), 6.13 (s, 2H), 3.91 (s, 3H), 3.76 (s, 3H).

^{13}C NMR (125 MHz): δ 158.7, 157.3, 154.7, 140.5, 138.6, 137.2, 136.3, 132.0, 130.6, 129.7, 128.6, 127.8, 127.6, 127.1, 126.3, 124.2, 122.3, 117.9, 114.0, 112.2, 102.4, 102.3, 56.0, 55.4, 48.0.

HRMS (ESI): Calc. for $C_{32}H_{27}N_2O_3$ [M$^+$+H]: *m/z* 487.2021. Found: 487.2020.

Compound 63



Yield: 0.165 g (80%, yellow solid; using 0.5 mmol of precursor **5f**).

Mp: 156-158 ^{o}C.

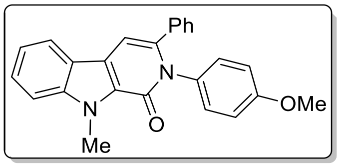
IR (KBr): 3068, 3003, 2937, 2833, 1649, 1605, 1567, 1479, 1233, 1173, 1036, 822, 740 cm^{-1}.

^{1}H NMR: δ 7.98 (d, *J* = 8.0 Hz, 1H), 7.57-7.50 (m, 2H), 7.31-7.27 (m, 1H), 7.14-7.08 (m, 5H), 6.99 (s, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.73 (d, *J* = 8.8 Hz, 2H), 4.35 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H).

^{13}C NMR: δ 158.9, 158.7, 157.6, 141.4, 140.4, 132.1, 130.9, 130.5, 129.6, 126.9, 126.2, 124.4, 121.6, 121.3, 120.1, 114.0, 113.3, 110.2, 102.3, 55.5, 55.3, 31.3.

HRMS (ESI): Calc. for $C_{26}H_{23}N_2O_3$ [M$^+$+H]: *m/z* 411.1708. Found: 411.1709.

Compound 64



Yield: 0.173 g (91%, yellow solid; using 0.5 mmol of precursor **5g**).

Mp: 184-186 ^{o}C.

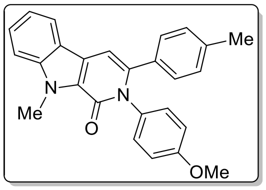
IR (KBr): 3030, 2915, 2334, 1655, 1584, 1501, 1457, 1326, 1244, 1068, 823, 745 cm^{-1}.

^{1}H NMR (500 MHz): δ 7.99 (d, *J* = 8.0 Hz, 1H), 7.58-7.51 (m, 2H), 7.32-7.28 (m, 1H), 7.22-7.21 (m, 5H), 7.11 (d, *J* = 8.5 Hz, 2H), 7.03 (s, 1H), 6.83 (d, *J* = 9.0 Hz, 2H), 4.37 (s, 3H), 3.78 (s, 3H).

^{13}C NMR (125 MHz): δ 158.7, 157.6, 141.4, 140.6, 137.1, 132.0, 130.5, 129.7, 127.8, 127.6, 126.9, 126.3, 124.3, 121.7, 121.3, 120.2, 114.0, 110.2, 102.5, 55.4, 31.3.

HRMS (ESI): Calc. for $C_{25}H_{21}N_2O_2$ [M$^+$+H]: *m/z* 381.1603. Found: 381.1604.

Compound 65



Yield: 0.163 g (83%, yellow solid; using 0.5 mmol of precursor **5h**).

Mp: 226-228 °C.

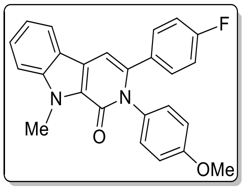
IR (KBr): 3014, 2970, 2931, 1666, 1567, 1507, 1337, 1238, 1178, 1074, 827, 745 cm^{-1}.

^{1}H NMR: δ 7.98 (d, *J* = 8.0 Hz, 1H), 7.58-7.50 (m, 2H), 7.31-7.27 (m, 1H), 7.11-7.00 (m, 7H), 6.84 (d, *J* = 8.8 Hz, 2H), 4.36 (s, 3H), 3.79 (s, 3H), 2.30 (s, 3H).

^{13}C NMR: δ 158.7, 157.6, 141.4, 140.7, 137.4, 134.2, 132.1, 130.5, 129.5, 128.6, 126.9, 126.3, 124.4, 121.7, 121.3, 120.1, 114.0, 110.2, 102.4, 55.5, 31.3, 21.2.

HRMS (ESI): Calc. for $C_{26}H_{23}N_2O_2$ [M$^+$+H]: *m/z* 395.1759. Found: 395.1761.

Compound 66



Yield: 0.148 g (74%, yellow solid; using 0.5 mmol of precursor **5i**).

Mp: 198-200 °C.

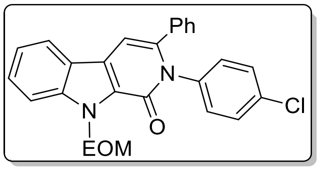
IR (KBr): 3068, 2921, 2827, 1655, 1600, 1507, 1463, 1332, 1244, 1173, 1025, 822, 734 cm^{-1}.

^{1}H NMR: δ 8.00 (d, *J* = 8.0 Hz, 1H), 7.59-7.52 (m, 2H), 7.33-7.29 (m, 1H), 7.21-7.18 (m, 2H), 7.08 (d, *J* = 8.8 Hz, 2H), 7.00 (s, 1H), 6.93-6.84 (m, 4H), 4.36 (s, 3H), 3.80 (s, 3H).

^{13}C NMR: δ 163.0, 161.1, 158.8, 157.5, 141.4, 139.5, 133.2$_0$, 133.1$_8$, 131.5, 131.4, 130.5, 127.0, 126.4, 124.1, 121.6, 121.2, 120.3, 115.0, 114.8, 114.1, 110.3, 102.6, 55.4, 31.3.

HRMS (ESI): Calc. for $C_{25}H_{20}FN_2O_2$ [M^++H]: *m/z* 399.1509. Found: 399.1506.

Compound 67



Yield: 0.167 g (78%, yellow solid; using 0.5 mmol of precursor **5j**).

Mp: 170-172 °C.

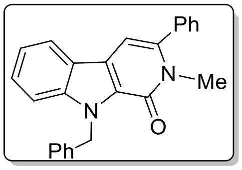
IR (KBr): 3096, 3063, 2981, 2915, 1649, 1567, 1490, 1463, 1392, 1271, 1216, 1085, 1014, 821, 751 cm^{-1}.

^{1}H NMR: δ 7.99 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.58 (~t, *J* = 7.6 Hz, 1H), 7.35 (~t, *J* = 7.6 Hz, 1H), 7.30-7.20 (m, 7H), 7.14 (d, *J* = 8.8 Hz, 2H), 7.05 (s, 1H), 6.33 (s, 2H), 3.68 (qrt, *J* = 7.0 Hz, 2H), 1.18 (~t, *J* = 7.0 Hz, 3H).

^{13}C NMR: δ 156.6, 141.2, 140.9, 137.6, 136.5, 133.7, 131.0, 129.6, 128.9, 128.1, 127.6, 125.7$_0$, 125.6$_6$, 122.3, 121.2$_3$, 121.1$_6$, 111.8, 102.7, 73.6, 63.8, 15.2.

HRMS (ESI): Calc. for $C_{26}H_{21}ClN_2O_2Na$ [M^++Na]: *m/z* 451.1190. Found: 451.1187.

Compound 68



Yield: 0.169 g (93%, yellow solid; using 0.5 mmol of precursor **5k**).

Mp: 154-156 °C.

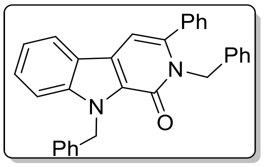
IR (KBr): 3068, 2986, 2931, 1688, 1545, 1479, 1320, 1162, 1025, 827, 756, 707 cm^{-1}.

^{1}H NMR: δ 7.86 (d, *J* = 8.0 Hz, 1H), 7.46-7.44 (m, 5H), 7.39-7.27 (m, 8H), 6.75 (s, 1H), 5.61 (s, 2H), 3.08 (s, 3H).

^{13}C NMR: δ 162.7, 142.6, 137.0, 135.4, 134.2, 132.9, 130.3, 129.9, 128.8, 128.2, 127.8, 127.5, 127.3, 124.8, 123.6, 121.5, 120.7, 112.0, 109.2, 48.0, 31.0.

HRMS (ESI): Calc. for $C_{25}H_{21}N_2O$ [M$^+$+H]: *m/z* 365.1654. Found: 365.1659.

Compound 69



Yield: 0.199 g (90%, yellow solid; using 0.5 mmol of precursor **5l**).

Mp: 128-130 °C.

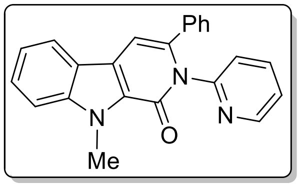
IR (KBr): 3057, 3025, 2942, 1715, 1649, 1540, 1480, 1337, 1178, 948, 745, 696 cm^{-1}.

^{1}H NMR (500 MHz): δ 7.81 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 1H), 7.37-7.23 (m, 10H), 7.18-7.16 (m, 2H), 7.11-7.07 (m, 3H), 6.66-6.64 (m, 3H), 5.65 (s, 2H), 4.87 (s, 2H).

^{13}C NMR (125 MHz): δ 162.9, 142.8, 137.7, 137.0, 135.2, 132.6$_1$, 132.5$_6$, 129.9, 128.8, 128.1, 128.0, 127.9, 127.5, 127.3, 126.7, 126.5, 125.0, 124.6, 121.6, 120.9, 120.8, 112.1, 110.4, 48.1, 45.6.

HRMS (ESI): Calc. for $C_{31}H_{25}N_2O$ [M$^+$+H]: *m/z* 441.1967. Found: 441.1969.

Compound 70



Yield: 0.154 g (88%, yellow solid; using 0.5 mmol of precursor **5m**).

Mp: 170-172 °C.

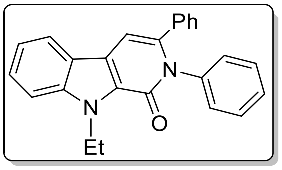
IR (KBr): 3074, 2953, 1655, 1584, 1468, 1326, 1271, 1145, 959, 1025, 734, 690 cm^{-1}.

^{1}H NMR: δ 8.53-8.51 (m, 1H), 7.99 (d, *J* = 7.6 Hz, 1H), 7.69-7.64 (m, 1H), 7.57-7.49 (m, 2H), 7.31-7.26 (m, 4H), 7.19-7.16 (m, 4H), 7.04 (s, 1H), 4.34 (s, 3H).

^{13}C NMR: δ 157.2, 152.7, 149.0, 141.3, 139.5, 137.5, 136.5, 129.4, 127.8, 127.6, 126.9, 126.1, 124.9, 124.5, 123.0, 121.6, 121.2, 120.2, 110.2, 102.7, 31.3.

HRMS (ESI): Calc. for $C_{23}H_{18}N_3O$ [M^++H]: *m/z* 352.1450. Found: 352.1455.

Compound 71



Yield: 0.167 g (91%, yellow solid; using 0.5 mmol of precursor **5n**).

Mp: 124-126 °C.

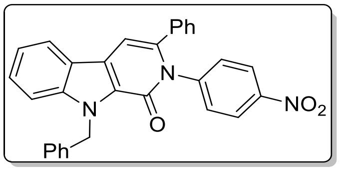
IR (KBr): 3052, 2986, 2931, 1655, 1490, 1463, 1326, 1255, 1211, 1090, 751, 696 cm^{-1}.

^{1}H NMR: δ 8.02 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 3.6 Hz, 2H), 7.35-7.20 (m, 11H), 7.07 (s, 1H), 4.94 (qrt, *J* = 7.0 Hz, 2H), 1.53 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR: δ 156.8, 140.2, 139.2, 137.0, 129.7, 129.6, 128.6, 127.7, 127.6$_4$, 127.5$_7$, 126.9, 125.6, 124.4, 121.8, 121.3, 120.1, 110.3, 102.6, 39.5, 16.1.

HRMS (ESI): Calc. for $C_{25}H_{21}N_2O$ [M^++H]: *m/z* 365.1654. Found 365.1658.

Compound 72



Yield: 0.165 g (70%, yellow solid; using 0.5 mmol of precursor **5n**).

Mp: 247-250 °C.

IR (KBr): 2932, 2849, 1666, 1578, 1468, 1342, 1320, 1271, 1205, 1145, 1008, 964, 849, 745, 701 cm^{-1}.

^{1}H NMR (500 MHz): δ 8.16 (d, *J* = 9.0 Hz, 2H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.52 (d, *J* = 3.5 Hz, 2H), 7.40 (d, *J* = 9.0 Hz, 2H), 7.34-7.31 (m, 1H), 7.27-7.23 (m, 8H), 7.22-7.19 (m, 2H), 7.12 (s, 1H), 6.12 (s, 2H).

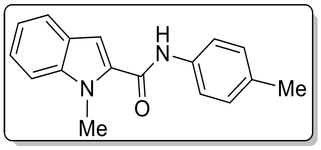
^{13}C NMR (125 MHz): δ 156.5, 146.6, 145.1, 141.0, 139.6, 138.1, 136.1, 130.9, 129.4, 128.6, 128.3$_0$, 128.2$_8$, 127.6, 127.3, 127.0, 125.4, 125.0, 123.8, 121.9, 121.4, 120.8, 111.3, 103.5, 47.9.

HRMS (ESI): Calc. for $C_{30}H_{22}N_3O_3$ [M$^+$+H]: *m/z* 472.1661. Found: 472.1659.

3.7 Synthesis of indole-2-carboxamide derivatives 73-88 by the [Pd]-catalyzed *ortho*-amidation of indole-3-carboxylic acid derivatives with isothiocyanates: General procedure

A mixture of indole-3-carboxylic acid (one of **6a-i**, 0.5 mmol), isothiocyanate (one of **8a-h**, 1.5 mmol), Pd(OAc)$_2$ (10 mol %), Cs_2CO_3 (0.5 mmol), and TBAB (0.25 mmol) was taken in a 10 mL round bottomed flask. To this, CH_3CN (2 mL) was added and the contents were heated at 80 °C for 6 h in open air. The progress of the reaction was monitored by TLC. After cooling to rt, the solvent was removed under vacuum, and the crude product was purified by column chromatography by using silica gel with ethyl acetate/hexane (1:9) mixture as the eluent to afford the corresponding indole-2-carboxamides **73-88**. Compounds **73**, **75**, **86** and **87** are known.

Compound 74



Yield: 0.112 g (85 %, white solid; using precursors **6a** and **8b**).

Mp: 154–156 °C.

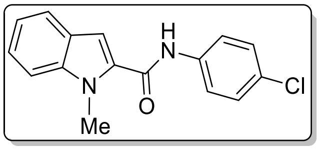
IR (KBr): 3251, 2352, 1639, 1598, 1541, 1458, 1386, 1314, 1246, 1091, 1014, 926, 818, 740 cm^{-1}.

^{1}H NMR: δ 8.00 (s, 1H, N*H*), 7.66 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.54 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.43-7.36 (m, 2H, Ar-*H*), 7.22-7.18 (m, 3H, Ar-*H*), 6.18 (s, 1H, Ar-*H*), 4.07 (s, 3H, NC*H*$_3$), 2.37 (s, 3H, C*H*$_3$).

^{13}C NMR: δ 160.6, 139.3, 135.2, 134.2, 132.2, 129.7, 126.0, 124.4, 122.0, 120.7, 120.2, 110.3, 104.3, 31.6, 21.0.

HRMS (ESI): Calcd. for $C_{17}H_{16}N_2ONa$ [M$^+$+Na]: *m/z* 287.1161. Found: 287.1160.

Compound 76



Yield: 0.111 g (78 %, white solid; using precursors **6a** and **8d**)

Mp: 216–218 °C.

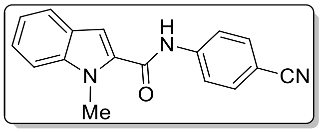
IR (KBr): 3292, 2352, 1645, 1516, 1464,1387, 1314, 1247, 824, 746 cm^{-1}.

^{1}H NMR: δ 7.93 (s, 1H, N*H*), 7.69 (dd, *J* = 8.0 Hz and 0.8 Hz, 1H, Ar-*H*), 7.61 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 7.46-7.36 (m, 4H, Ar-*H*), 7.23-7.19 (m, 1H, Ar-*H*), 7.03 (s, 1H, Ar-*H*), 4.11 (s, 3H, NCH_3).

^{13}C NMR: δ 160.5, 139.4, 136.3, 131.6, 129.5, 129.2, 125.9, 124.7, 122.0, 121.3, 120.9, 110.3, 104.5, 31.7.

HRMS (ESI): Calcd. for $C_{16}H_{14}ClN_2O$ [M$^+$+H]: *m/z* 285.0794. Found: 285.0791.

Compound 77



Yield: 0.103g (75 %, white solid; using precursors **6a** and **8e**).

Mp: 218–220 °C.

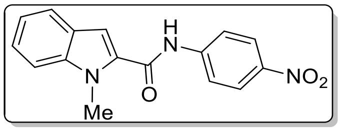
IR (KBr): 3313, 2228, 1645, 1583, 1505, 1459, 1407, 1387, 1309, 1242, 1216, 839, 751, 669 cm^{-1}.

^{1}H NMR (500 MHz): δ 8.13 (s, 1H, N*H*), 7.79 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 7.70-7.67 (m, 3H, Ar-*H*), 7.46-7.39 (m, 2H, Ar-*H*), 7.24-7.21 (m, 1H, Ar-*H*), 7.08 (s, 1H, Ar-*H*), 4.11 (s, 3H, NCH_3).

^{13}C NMR (125 MHz): δ 160.6, 142.0, 139.8, 133.5, 131.1, 125.9, 125.2, 122.3, 121.2, 119.8, 118.9, 110.5, 107.4, 105.3, 31.8.

HRMS (ESI): Calcd. for $C_{17}H_{14}N_3O$ [M$^+$+H]: *m/z* 276.1137. Found: 276.1138.

Compound 78



Yield: 0.105 g (71 %, white solid; using precursors **6a** and **8f**).

Mp: 232–234 °C.

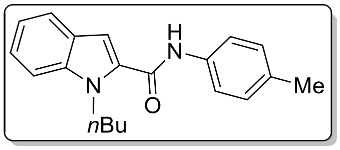
IR (KBr): 3313, 1650, 1609, 1542, 1505, 1340, 1247, 1216, 1175, 1108, 855, 762 cm^{-1}.

^{1}H NMR: δ 8.30 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 8.18 (s, 1H, N*H*), 7.85 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 7.72 (d, *J* = 6.4 Hz, 1H, Ar-*H*), 7.47-7.41 (m, 1H, Ar-*H*), 7.25-7.21 (m, 1H, Ar-*H*), 7.11 (s, 1H, Ar-*H*), 4.13 (s, 3H, NCH_3).

^{13}C NMR: δ 160.5, 143.8, 139.8, 130.9, 125.9, 125.4, 124.2, 122.3, 121.2, 119.3, 110.5, 105.4, 31.9.

HRMS (ESI): Calcd. for $C_{16}H_{14}N_3O_3$ [M$^+$+H]: *m/z* 295.0957. Found: 295.0955.

Compound 79



Yield: 0.122 g (80 %, white solid; using precursors **6b** and **8b**).

Mp: 138–140 °C.

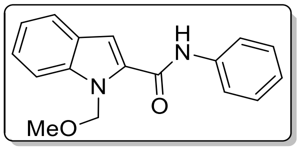
IR (KBr): 3298, 2957, 2921, 2864, 1645, 1593, 1516, 1454, 1402, 1314, 1242, 1195, 813, 736 cm^{-1}.

^{1}H NMR: δ 7.86 (s, 1H, N*H*), 7.68 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.51 (d, *J* = 7.6 Hz, 2H, Ar-*H*), 7.44 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.34 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 7.21-7.16 (m, 3H, Ar-*H*), 6.98 (s, 1H, Ar-*H*), 4.59 (t, *J* = 7.4 Hz, 2H, NCH_2), 2.36 (s, 3H, CH_3), 1.87-1.80 (m, 2H, CH_2), 1.43-1.33 (m, 2H, CH_2), 0.94 (t, *J* = 7.2 Hz, 3H, CH$_2$CH_3).

^{13}C NMR: δ 160.6, 138.6, 135.2, 134.2, 131.8, 129.6, 126.1, 124.2, 122.0, 120.5, 120.3, 110.5, 104.5, 44.5, 32.8, 20.9, 20.2, 13.9.

HRMS (ESI): Calcd. for $C_{20}H_{23}N_2O$ [M$^+$+H]: *m/z* 307.1810. Found: 307.1806.

Compound 80



Yield: 0.098g (70 %, white solid; using precursors **6d** and **8a**).

Mp: 188–190 °C.

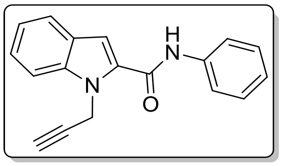
IR (KBr): 3302, 1644, 1593, 1525, 1443, 1345, 1314, 1246, 1086, 910, 761 cm^{-1}.

^{1}H NMR: δ 8.45 (s, 1H, N*H*), 7.72-7.67 (m, 3H, Ar-*H*), 7.59 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.41 (t, *J* = 7.6 Hz, 3H, Ar-*H*), 7.29-7.17 (m, 3H, Ar-*H*), 5.92 (s, 2H, NCH_2), 3.43 (s, 3H, OCH_3).

^{13}C NMR: δ 159.9, 139.3, 137.8, 132.9, 129.2, 126.4, 125.2, 124.6, 122.2, 121.6, 120.1, 110.8, 107.9, 74.9, 56.2.

HRMS (ESI): Calcd. for $C_{17}H_{17}N_2O_2$ [M$^+$+H]: *m/z* 280.1290. Found: 280.1293.

Compound 81



Yield: 0.104 g (76 %, white solid; using precursors **6e** and **8a**).

Mp: 151–153 °C.

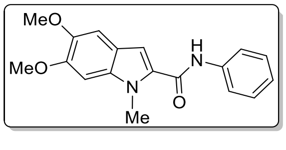
IR (KBr): 3365, 3267, 3225, 1640, 1526, 1433, 1309, 1247, 1159, 927, 756, 694 cm^{-1}.

^{1}H NMR: δ 7.97 (s, 1H, N*H*), 7.72-7.67 (m, 3H, Ar-*H*), 7.57 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.46-7.40 (m, 3H, Ar-*H*), 7.29-7.18 (m, 2H, Ar-*H*), 7.08 (s, 1H, Ar-*H*), 5.50 (s, 2H, NCH_2), 2.30 (s, 1H, alkyne *H*).

^{13}C NMR: δ 160.2, 138.6, 137.6, 130.9, 129.2, 126.3, 125.1, 124.7, 122.2, 121.4, 120.1, 110.6, 105.7, 78.8, 72.3, 33.9.

HRMS (ESI): Calcd. for $C_{18}H_{15}N_2O$ [M$^+$+H]: *m/z* 275.1184. Found: 275.1189.

Compound 82



Yield: 0.135 g (87 %, white solid; using precursors **6f** and **8a**).

Mp: 198–200 °C.

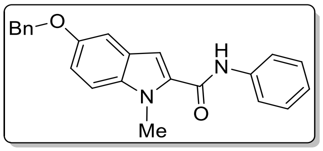
IR (KBr): 3308, 1650, 1593, 1526, 1500, 1464, 1438, 1304, 1252, 1216, 1097, 999, 839, 818, 756 cm^{-1}.

^{1}H NMR: δ 7.87 (s, 1H, N*H*), 7.64 (d, *J* = 7.6 Hz, 2H, Ar-*H*), 7.40 (t, *J* = 7.8 Hz, 2H, Ar-*H*), 7.17 (t, *J* = 7.4 Hz, 1H, Ar-*H*), 7.06 (s, 1H, Ar-*H*), 6.93 (s, 1H, Ar-*H*), 6.82 (s, 1H, Ar-*H*), 4.08 (s, 3H, NC*H*$_3$), 4.01 (s, 3H, OC*H*$_3$), 3.96 (s, 3H, OC*H*$_3$).

^{13}C NMR (125 MHz): δ 160.6, 149.6, 146.2, 138.0, 134.7, 130.3, 124.4, 120.1, 118.7, 104.4, 102.3, 92.5, 56.3, 56.2, 32.0.

HRMS (ESI): Calcd. for $C_{18}H_{18}N_2O_3Na$ [M$^+$+Na]: *m/z* 333.1215. Found: 333.1212.

Compound 83



Yield: 0.153 g (86 %, white solid; using precursors **6g** and **8a**).

Mp: 194–196 °C.

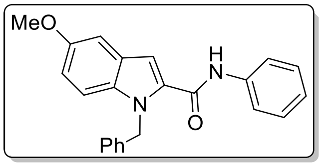
IR (KBr): 3267, 3065, 2921, 1640, 1593, 1531, 1464, 1438, 1381, 1319, 1237, 1201, 1009, 844, 746, 684 cm^{-1}.

^{1}H NMR: δ 7.90 (s, 1H, N*H*), 7.65 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 7.51 (d, *J* = 7.2 Hz, 2H, Ar-*H*), 7.43-7.34 (m, 6H, Ar-*H*), 7.21-7.14 (m, 3H, Ar-*H*), 6.92 (s, 1H, Ar-*H*), 5.15 (s, 2H, OC*H*$_2$), 4.09 (s, 3H, NC*H*$_3$).

^{13}C NMR: δ 160.6, 155.4, 138.6, 137.5, 134.4, 132.2, 129.1, 128.7, 127.3, 126.6, 124.5, 120.7, 120.2, 116.0, 111.9, 104.8, 102.6, 71.3, 33.1.

HRMS (ESI): Calcd. for $C_{23}H_{21}N_2O_2$ [M$^+$+H]: *m/z* 357.1603. Found: 357.1601.

Compound 84



Yield: 0.155g (87 %, white solid; using precursors **6h** and **8a**).

Mp: 168–170 °C.

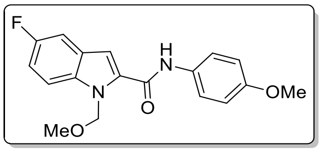
IR (KBr): 3337, 3129, 3025, 2932, 2367, 1649, 1595, 1518, 1441, 1359, 1315, 1222, 1025, 855, 756 cm^{-1}.

^{1}H NMR: δ 7.88 (s, 1H, N*H*), 7.62-7.59 (m, 2H, Ar-*H*), 7.40-7.31 (m, 3H, Ar-*H*), 7.28-7.21 (m, 3H, Ar-*H*), 7.18-7.11 (m, 4H, Ar-*H*), 7.01 (s, 1H, Ar-*H*), 6.98 (dd, *J* = 9.2 Hz and *J* = 2.4 Hz, 1H, Ar-*H*), 5.85 (s, 2H, NCH_2), 3.88 (s, 3H, OCH_3).

^{13}C NMR: δ 160.4, 155.0, 138.3, 137.8, 134.6, 132.2, 129.1, 128.7, 127.3, 126.6, 124.5, 120.7, 120.2, 116.0, 111.9, 104.8, 102.6, 55.8, 48.1.

HRMS (ESI): Calcd. for $C_{23}H_{20}N_2O_2Na$ [M^++Na]: *m/z* 379.1423. Found: 379.1422.

Compound 85



Yield: 0.112g (68 %, white solid; using precursors **6i** and **8c**).

Mp: 188–190 °C.

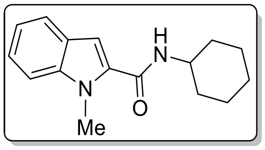
IR (KBr): 3282, 2936, 2848, 1645, 1531, 1448, 1392, 1257, 1185, 1108, 1077, 1030, 963, 865, 823 cm^{-1}.

^{1}H NMR: δ 8.28 (s, 1H, N*H*), 7.56 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 7.52-7.49 (m, 1H, Ar-*H*), 7.32-7.30 (m, 1H, Ar-*H*), 7.16-7.11 (m, 1H, Ar-*H*), 7.07 (s, 1H, Ar-*H*), 6.93 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 5.88 (s, 2H, NCH_2), 3.84 (s, 3H, OCH_3), 3.39 (s, 3H, OCH_3).

^{13}C NMR: δ 159.7, 157.5, 156.9, 135.8, 134.4, 130.7, 126.8, 122.1, 114.4, 114.0, 113.8, 112.0, 111.9, 107.0_2, 106.9_7, 106.7, 106.5, 75.2, 56.2, 55.6.

HRMS (ESI): Calcd. for $C_{18}H_{18}FN_2O_3$ [M^++H]: *m/z* 329.1301 Found: 329.1301.

Compound 88



Yield: 0.106 g (83 %, white solid; using precursors **6a** and **8h**).

Mp: 175–177 °C.

IR (KBr): 3282, 2931, 2848, 1629, 1536, 1464, 1387, 1247, 1144, 751 cm^{-1}.

^{1}H NMR: δ 7.62 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.39 (d, *J* = 8.4 Hz, 1H, Ar-*H*), 7.32 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 7.15 (t, *J* = 7.4 Hz, 1H, Ar-*H*), 6.81 (s, 1H, Ar-*H*), 6.08 (s, 1H, N*H*), 4.06 (s, 3H, NCH_3), 4.00-3.93 (m, 1H, C*H*), 2.07-

2.04 (m, 2H, C*H*$_2$), 1.80-1.76 (m, 2H, CH$_2$), 1.49-1.40 (m, 2H, CH$_2$), 1.31-1.22 (m, 4H, C*H*$_2$).

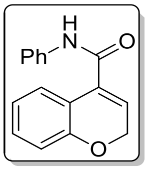
^{13}C NMR: δ 161.9, 139.0, 132.6, 126.4, 126.1, 124.0, 123.9, 121.7, 120.5, 110.2, 52.7, 48.5, 33.3, 32.5, 31.6, 25.6, 25.0.

HRMS (ESI): Calcd. for $C_{16}H_{21}N_2O$ [M^++H]: *m/z* 257.1654. Found: 257.1654.

3.8 Synthesis of heteroarene-2-carboxamides 89-94 by the [Pd]-catalyzed *ortho*-amidation of heteroaromatic carboxylic acids with phenylisothiocyanate: General procedure

A mixture of heteroarene-2-carboxylic acid (**1a** and **9-13**, 0.5 mmol), phenylisothiocyanate (**8a**, 1.5 mmol), Pd(OAc)$_2$ (10 mol %), Cs_2CO_3 (0.5 mmol), and TBAB (0.25 mmol) was taken in a 10 mL round-bottomed flask. To this, CH_3CN (2 mL) was added and the contents were heated at 80 °C for 6 h in open air. The progress of the reaction was monitored by TLC. After cooling to rt, the solvent was removed under vacuum, and the crude product was purified by column chromatography by using silica gel with ethyl acetate/hexane (1:9) mixture as the eluent to afford the corresponding indole-2-carboxamides **89-94**. Compounds **90-93** are reported in the literature,[109] only **89** and **94** are new.

Compound 89



Yield: 0.107 g, 85 % (white solid; using precursors **9** and **8a**).

Mp: 136–138 °C.

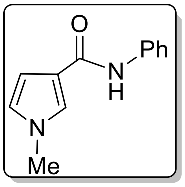
IR (KBr): 3255, 3118, 3058, 1742, 1649, 1595, 1523, 1447, 1332, 1249, 1041, 904, 762 cm^{-1}.

^{1}H NMR (500 MHz): δ 7.69 (s, 1H, N*H*), 7.60-7.58 (m, 2H, Ar-*H*), 7.38-7.35 (m, 2H, Ar-*H*), 7.27-7.24 (m, 1H, Ar-*H*), 7.18-7.15 (m, 1H, Ar-*H*), 7.13 (dd, *J* = 7.5 Hz and *J* = 1.5 Hz, 1H, Ar-*H*), 7.10 (s, 1H, Ar-*H*), 6.97-6.94 (m, 1H, Ar-*H*), 6.90 (d, *J* = 8.0 Hz, 1H, NC*H*$_2$), 5.09 (d, *J* = 1.0 Hz, 2H, OC*H*$_2$).

^{13}C NMR: δ 163.5, 154.9, 137.5, 131.6, 129.1, 128.5, 127.7, 127.1, 124.7, 121.9, 120.8, 120.3, 116.2, 64.8.

HRMS (ESI): Calcd. for $C_{16}H_{14}NO_2$ [M$^+$+H]: *m/z* 252.1024. Found: 252.1024.

Compound 94



Yield: 0.065 g (65 %, white solid; using precursors **13** and **8a**).

Mp: 105–107 ^{o}C.

IR (KBr): 3303, 1640, 1593, 1531, 1443, 1340, 1247, 1113, 901, 870, 751 cm^{-1}.

^{1}H NMR: δ 7.64 (s, 1H, N*H*), 7.58 (d, *J* = 7.6 Hz, 2H, Ar-*H*), 7.37 (t, *J* = 8.0 Hz, 2H, Ar-*H*), 7.14 (t, *J* = 7.4 Hz, 1H, Ar-*H*), 6.81-6.72 (m, 2H, Ar-*H*), 6.18-6.16 (m, 1H, Ar-*H*), 4.00 (s, 3H, NCH_3).

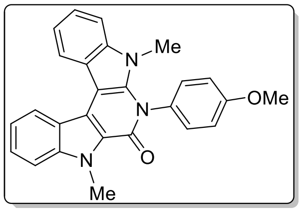
^{13}C NMR: δ 160.0, 138.1, 129.1, 128.8, 125.8, 124.0, 120.1, 112.3, 107.5, 36.9.

HRMS (ESI): Calcd. for $C_{12}H_{13}N_2O$ [M$^+$+H]: *m/z* 201.1028. Found: 201.1029.

3.9 Synthesis of diindole-fused pyridones (95-96) *via* palladium-catalyzed C-H bond activation: General procedure

In an oven dried round-bottomed flask (10 mL), silver carbonate (1.0 mmol) was dried in *vacuo* (ca 0.2 mm Hg) while heating (ca 100 ^{o}C) using a hot air gun for 0.5 h. To this, $Pd(OAc)_2$ (10 mol %), indole-2-carboxamide (**75** or **79**, 1.0 mmol), Cs_2CO_3 (0.5 mmol) and DMF (3.0 mL) were added. The RBF was sealed with a stopper and the contents were stirred at 110 ^{o}C (oil bath temperature) for 14 h. After the completion of the reaction as monitored by TLC, the mixture was cooled to rt, filtered and extracted with diethyl ether (3 x 25 mL). The combined organic extract was washed with brine solution (4 x 10 mL). The organic part was dried over anhy. Na_2SO_4, and the solvent was removed using a rotary evaporator. The crude products were purified by column chromatography (100-200 mesh silica) using hexane/ EtOAc (9:1) as eluent to afford the final products **95-96**.

Compound 95



Yield: 0.079 g (78 %, yellow solid; using compound **74**).

Mp: 245– 247 °C.

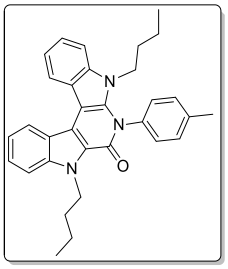
IR (KBr): 3055, 2931, 1640, 1552, 1516, 1469, 1237, 1108, 1025, 839, 736 cm^{-1}.

^{1}H NMR (C_6D_6): δ 9.06 (d, 1H, *J* = 8.0 Hz, Ar-*H*), 8.88 (d, 1H, *J* = 7.6 Hz, Ar-*H*), 7.51 (qrt, 2H, *J* = 7.2 Hz, Ar-H), 7.40 (d, 2H, *J* = 7.6 Hz, Ar-*H*), 7.10-7.06 (m, 4H, Ar-*H*), 6.83-6.79 (m, 2H, Ar-*H*), 4.23 (s, 3H, NC*H*$_3$), 3.35 (s, 3H, NC*H*$_3$), 2.64 (s, 3H, OC*H*$_3$).

^{13}C NMR (C_6D_6): δ 160.1, 158.7, 144.3, 140.1, 136.3, 136.1, 135.0, 133.2, 128.4, 128.0, 125.3, 123.9, 123.0, 121.7, 119.8, 119.4, 115.0, 114.3, 109.5, 109.1, 98.6, 55.5, 34.1, 28.4.

HRMS (ESI): Calcd. for $C_{26}H_{22}N_3O_2$ [M$^+$+H]: *m/z* 408.1712. Found: 408.1712.

Compound 96



Yield: 0.083 g (70 %, yellow solid; using compound **78**).

Mp: 110–112 °C.

IR (KBr): 3050, 2962, 2936, 2864, 1650, 1609, 1464, 1350, 1257, 1102, 1025, 787, 736 cm^{-1}.

^{1}H NMR (C_6D_6): δ 9.11 (d, 1H, *J* = 8.0 Hz, Ar-*H*), 8.93 (d, 1H, *J* = 7.6 Hz, Ar-*H*), 7.55-7.50 (m, 2H, Ar-H), 7.43-7.41 (m, 3H, Ar-*H*), 7.25 (s, 1H, Ar-*H*), 7.18 (d, 2H, *J* = 8.0 Hz, Ar-*H*), 7.01 (d, 2H, *J* = 8.0 Hz, Ar-*H*), 3.27 (t, 2H, *J* = 8.0 Hz, NC*H*$_2$), 2.15 (s, 3H, C*H*$_3$), 1.99-1.93 (m, 2H, C*H*$_2$), 1.47-

1.38 (m, 2H, C*H*$_2$), 1.22-1.18 (m, 2H, C*H*$_2$), 0.90 (t, 3H, *J* = 7.4 Hz, CH_2CH_3), 0.79-0.72 (m, 2H, C*H*$_2$), 0.62 (t, 3H, *J* = 7.2 Hz, CH_2CH_3).

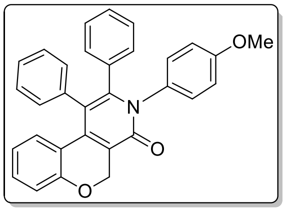
^{13}C NMR (C_6D_6): δ 156.7, 141.6, 139.0, 137.6_4, 137.6_2, 136.1, 130.3, 130.0, 128.1, 126.8, 125.3, 123.9, 123.0, 122.6, 122.2_4, 122.1_6, 121.5, 120.2, 111.2, 110.5, 98.5, 44.9, 44.7, 33.7, 31.4, 21.3, 20.8, 20.3, 14.4, 13.9.

HRMS (ESI): Calcd. for $C_{32}H_{34}N_3O$ [M^++H]: *m/z* 476.2702. Found: 476.2706.

3.10 Synthesis of benzopyran fused 2-pyridone derivatives 97-111 by the [Ru]-catalyzed coupling of 2*H*-chromene-3-carboxamides (14a-f) with alkynes: General procedure

Into a 10 mL round-bottomed flask, 2*H*-chromene-3-carboxamide (one of **14a-f**, 0.5 mmol), diaryl or dialkyl acetylene (one of **15a-j**, 0.5 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (5 mol %), $Cu(OAc)_2.H_2O$ (1.0 mmol) and $AgNTf_2$ (30 mol %) were added under N_2 atmosphere. To this, *t*AmOH (2 mL) was added and the mixture stirred at 100 °C (oil bath temperature) for 14 h. After cooling to rt, saturated NH_4Cl solution (50 mL) was added and the contents extracted with EtOAc (3 x 30 mL). The combined organic phase was washed with brine solution (2x25 mL), dried over anh. Na_2SO_4 and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel using *n*-hexane-EtOAc (4:1) mixture as the eluent.

Compound 97



Yield: 0.201 g (88%, pale yellow solid; using precursors **14a** and **15a**).

Mp: 228–230 °C.

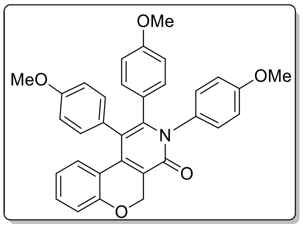
IR (KBr): 3055, 2828, 1650, 1511, 1490, 1438, 1242, 1025, 839, 798, 762, 694 cm^{-1}.

^{1}H NMR: δ 7.15 (~t, *J* = 7.0 Hz, 2H, Ar-*H*), 7.10-7.09 (m, 2H, Ar-*H*), 7.03-6.92 (m, 8H, Ar-*H*), 6.83-6.82 (m, 2H, Ar-*H*), 6.73 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 6.52 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 6.45 (~d, 1H, *J* = 8.0 Hz, Ar-*H*), 5.19 (s, 2H, OC*H*$_2$), 3.71 (s, 3H, OC*H*$_3$).

^{13}C NMR: δ 160.1, 158.7, 157.5, 147.4, 139.7, 137.4, 134.4, 131.5, 130.8, 130.7, 129.9, 128.9, 128.1, 127.5, 127.3, 126.9, 122.4, 121.4, 120.9, 117.7, 117.5, 114.0, 64.1, 55.3.

HRMS (ESI): Calcd. for $C_{31}H_{24}NO_3$ [M$^+$+H]: *m/z* 458.1756. Found: 458.1756.

Compound 98



Yield: 0.238 g (92%, pale yellow solid; using precursors **14a** and **15b**).

Mp: 215–217 ^{o}C.

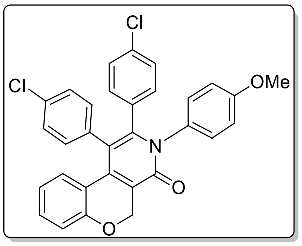
IR (KBr): 3008, 2838, 1644, 1605, 1501, 1293, 1244, 1184, 1041, 838, 756 cm^{-1}.

^{1}H NMR: δ 7.18-7.14 (m, 1H, Ar-*H*), 7.03-7.01 (m, 1H, Ar-*H*), 6.97 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 6.86 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 6.76-6.71 (m, 4H, Ar-*H*), 6.66 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 6.59-6.55 (m, 1H, Ar-*H*), 6.52-6.50 (m, 1H, Ar-*H*), 6.47 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 5.18 (s, 2H, OC*H*$_2$), 3.74 (s, 3H, OC*H*$_3$), 3.73 (s, 3H, OC*H*$_3$), 3.64 (s, 3H, OC*H*$_3$).

^{13}C NMR: δ 160.1, 158.6, 158.3, 157.5, 147.5, 139.9, 132.5, 131.9, 131.8, 130.6, 129.9, 129.8, 128.8, 126.9, 122.3, 121.7, 120.9, 117.6, 117.5, 114.1, 113.6, 112.7, 64.2, 55.3, 55.1, 55.0.

HRMS (ESI): Calcd. for $C_{34}H_{27}NO_5$ [M$^+$+H]: *m/z* 518.1967. Found: 518.1965.

Compound 99



Yield: 0.225 g (86%, pale yellow solid; using precursors **14a** and **15c**).

Mp: 260–262 ^{o}C.

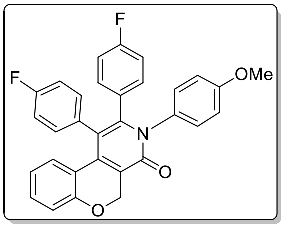
IR (KBr): 2932, 2833, 2362, 1644, 1595, 1512, 1485, 1392, 1238, 1090, 1008, 762 cm^{-1}.

^{1}H NMR: δ 7.21-7.17 (m, 1H, Ar-*H*), 7.12 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.04 (dd, *J* = 1.2 Hz and *J* = 8.0 Hz, 1H, Ar-*H*), 6.98-6.94 (m, 4H, Ar-*H*), 6.89 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 6.78-6.75 (m, 4H, Ar-*H*), 6.62-6.58 (m, 1H, Ar-*H*), 6.44 (dd, *J* = 1.6 Hz and *J* = 8.0 Hz, 1H, Ar-*H*), 5.17 (s, 2H, OCH_2), 3.75 (s, 3H, OCH_3).

^{13}C NMR: δ 159.0, 157.5, 146.3, 139.5, 135.8, 133.9, 133.3, 132.8, 132.7, 131.9, 131.2, 131.1, 129.9, 128.6, 127.9, 123.1, 121.1$_0$, 121.0$_8$, 117.8, 116.6, 114.3, 64.1, 55.4.

HRMS (ESI): Calcd. for $C_{32}H_{21}Cl_2NO_3$ [M$^+$+H]: *m/z* 526.0976. Found: 526.0973.

Compound 100



Yield: 0.205g (83%, pale brown solid; using precursors **14a** and **15d**).

Mp: 276–278 °C.

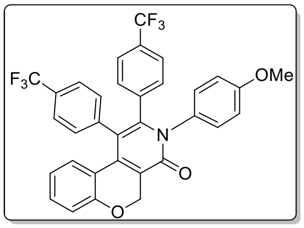
IR (KBr): 3052, 2997, 2959, 2833, 1644, 1595, 1496, 1299, 1238, 1211, 1156, 1008, 767 cm^{-1}.

^{1}H NMR: δ 7.21-7.16 (m, 1H, Ar-*H*), 7.04 (dd, *J* = 8.2 Hz and *J* = 0.6 Hz, 1H, Ar-*H*), 6.97-6.91 (m, 4H, Ar-*H*), 6.85-6.75 (m, 6H, Ar-*H*), 6.67 (t, *J* = 8.6 Hz, 2H, Ar-*H*), 6.61-6.56 (m, 1H, Ar-*H*), 6.45 (dd, *J* = 8.0 Hz and *J* = 1.2 Hz, 1H, Ar-*H*), 5.18 (s, 2H, OCH_2), 3.74 (s, 3H, OCH_3).

^{13}C NMR: δ 163.0, 162.8, 160.5, 160.3, 160.0, 158.9, 157.5, 146.7, 139.6, 133.4, 133.3, 133.1, 133.0, 132.5, 132.4, 131.4, 131.0, 130.4$_3$, 130.4$_0$, 129.9, 128.6, 122.9, 121.2, 121.0, 117.7, 116.9, 115.5, 115.3, 114.9, 114.6, 114.2, 64.1, 55.4.

HRMS (ESI): Calcd. for $C_{31}H_{22}F_2NO_3$ [M$^+$+H]: *m/z* 494.1567. Found: 494.1563.

Compound 101



Yield: 0.232 g (78%, brown solid; using precursors **14a** and **15e**).

Mp: 241–243 °C.

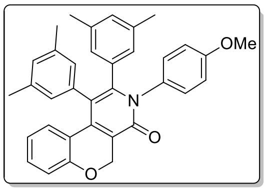
IR (KBr): 3008, 2953, 2844, 2367, 1644, 1512, 1321, 1249, 1162, 1134, 1068, 1014, 855, 773 cm^{-1}.

^{1}H NMR: δ 7.39 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 7.25 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.22-7.17 (m, 1H, Ar-*H*), 7.11-7.04 (m, 3H, Ar-*H*), 6.97 (d, *J* = 8.8 Hz, 4H, Ar-*H*), 6.76 (d, *J* = 9.2 Hz, 2H, Ar-*H*), 6.58-6.54 (m, 1H, Ar-*H*), 6.34 (dd, *J* = 1.6 Hz and *J* = 8.0 Hz, 1H, Ar-*H*), 5.19 (s, 2H, OCH_2), 3.73 (s, 3H, OCH_3).

^{13}C NMR: δ 159.9, 159.2, 157.6, 146.1, 141.0, 139.4, 137.7, 131.9, 131.3, 131.1, 130.9, 130.1, 129.9, 129.8, 129.7, 129.4, 128.5, 125.3, 125.2, 124.8, 124.6, 124.5, 123.6, 122.5, 122.1, 121.1, 120.8, 117.9, 116.4, 114.4, 64.0, 55.4.

HRMS (ESI): Calcd. for $C_{34}H_{21}F_6NO_3$ [M^++H]: *m/z* 594.1504. Found: 594.1508.

Compound 102



Yield: 0.232g (90%, pale yellow solid; using precursors **14a** and **15f**).

Mp: 216–218 °C.

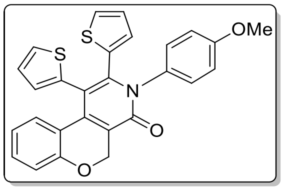
IR (KBr): 3057, 2997, 2915, 2838, 1649, 1605, 1512, 1463, 1249, 1030, 822, 844, 750 cm^{-1}.

^{1}H NMR: δ 7.18-7.14 (m, 1H, Ar-*H*), 7.03-6.97 (m, 3H, Ar-*H*), 6.75-6.71 (m, 3H, Ar-*H*), 6.60-6.53 (m, 5H, Ar-*H*), 6.44 (s, 2H, Ar-*H*), 5.19 (s, 2H, OCH_2), 3.72 (s, 3H, OCH_3), 2.10 (s, 6H, CH_3), 2.01 (s, 6H, CH_3).

^{13}C NMR: δ 160.1, 158.7, 157.4, 147.7, 139.7, 137.1$_2$, 137.0$_9$, 136.3, 134.1, 131.8, 130.7, 129.9, 129.3, 129.1, 128.8, 128.6, 128.3, 121.7, 121.6, 120.8, 117.9, 117.4, 113.8, 64.1, 55.4, 21.1, 21.0.

HRMS (ESI): Calcd. for $C_{36}H_{31}NO_3$ [M^++H]: *m/z* 514.2382. Found: 514.2385.

Compound 103



Yield: 0.195 g (83%, pale yellow solid; using precursors **14a** and **15g**).

Mp: 256–258 °C.

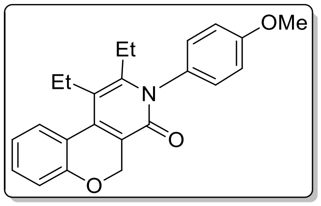
IR (KBr): 3074, 2833, 1496, 1436, 1249, 1162, 1123, 1019, 838, 756, 701 cm^{-1}.

^{1}H NMR: δ 7.24-7.20 (m, 2H, Ar-*H*), 7.12 (d, *J* = 4.5 Hz, 1H, Ar-*H*), 7.05 (t, *J* = 9.5 Hz, 3H, Ar-*H*), 6.86-6.85 (m, 1H, Ar-*H*), 6.81 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.72 (d, *J* = 3.0 Hz, 1H, Ar-*H*), 6.70-6.64 (m, 3H, Ar-*H*), 6.61 (d, *J* = 3.0 Hz, 1H, Ar-*H*), 5.17 (s, 2H, OCH_2), 3.77 (s, 3H. OCH_3).

^{13}C NMR (125 MHz): δ 160.0, 159.1, 157.4, 142.4, 140.0, 138.6, 134.3, 131.4, 131.2, 131.1, 129.9, 129.7, 128.1, 128.0, 127.0, 126.8, 125.8, 123.4, 121.2, 121.1, 117.5, 114.1, 112.4, 64.0, 55.4.

HRMS (ESI): Calcd. for $C_{28}H_{19}NO_3S_2$ [M^++H]: *m/z* 470.0884. Found: 470.0887.

Compound 104



Yield: 0.138g (76%, pale yellow solid; using precursors **14a** and **15h**).

Mp: 198–200 °C.

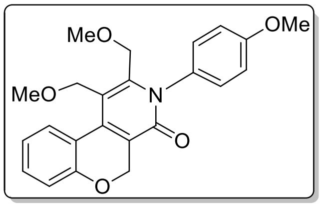
IR (KBr): 2975, 2844, 2362, 1879, 1638, 1501, 1457, 1293, 1249, 1025, 767 cm^{-1}.

^{1}H NMR (500 MHz): δ 7.77 (dd, *J* = 1.3 Hz and *J* = 9.8 Hz, 1H, Ar-*H*), 7.37-7.33 (m, 1H, Ar-*H*), 7.18 (d, *J* = 11.0 Hz, 2H, Ar-*H*), 7.12-7.08 (m, 2H, Ar-*H*), 7.04 (d, *J* = 11.0 Hz, 2H, Ar-*H*), 5.00 (s, 2H, OCH_2), 3.88 (s, 3H, OCH_3), 2.79 (qrt, *J* = 9.3 Hz, 2H, CH_2), 2.54 (qrt, *J* = 9.3 Hz, 2H, CH_2), 1.34 (t, *J* = 9.3 Hz, 3H, CH_3), 1.00 (t, 3H, *J* = 9.3 Hz, CH_3).

^{13}C NMR (125 MHz): δ 160.4, 159.5, 157.9, 148.7, 141.1, 131.5, 130.8, 129.4, 127.4, 122.5, 121.8, 121.6, 118.1, 115.6, 114.8, 55.6, 23.3, 21.6, 15.9, 13.7.

HRMS (ESI): Calcd. for $C_{24}H_{23}NO_3$ [M$^+$+H]: *m/z* 362.1756. Found: 362.1759.

Compound 105



Yield: 0.153 g(78%, gummy liquid; using precursors **14a** and **15i**).

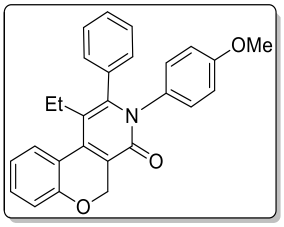
IR (neat): 2921, 2833, 1721, 1644, 1605, 1518, 1463, 1397, 1299, 1244, 1085, 942, 762 cm^{-1}.

^{1}H NMR: δ 7.91 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.38 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 7.22 (d, *J* = 8.4 Hz, 2H, Ar-*H*), 7.16-7.10 (m, 2H, Ar-*H*), 7.04 (d, *J* = 8.8 Hz, 2H, Ar-*H*), 5.04 (s, 2H, OCH_2), 4.36 (s, 2H, MeOCH_2), 4.12 (s, 2H, MeOCH_2), 3.89 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 3.10 (s, 3H, OCH_3).

^{13}C NMR: δ 160.3, 159.8, 157.5, 146.1, 141.6, 131.4, 129.6, 127.6, 123.7, 122.2, 121.8, 121.6, 117.9, 114.5, 112.4, 68.2, 67.2, 64.1, 58.7, 58.2, 55.6.

HRMS (ESI): Calcd. for $C_{24}H_{23}NO_5$ [M$^+$+H]: *m/z* 394.1654. Found: 394.1652.

Compound 106



Yield: 0.153 g (75%, yellow solid; using precursors **14a** and **15j**).

Mp: 216–218 °C.

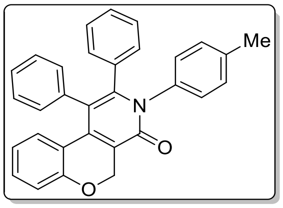
IR (KBr): 2964, 2838, 1638, 1551, 1512, 1299, 1244, 1030, 827, 762, 707 cm^{-1}.

^{1}H NMR (500 MHz): δ 7.84 (dd, *J* = 8.0 Hz and *J* = 1.5 Hz, 1H, Ar-*H*), 7.39-7.35 (m, 1H, Ar-*H*), 7.25-7.20 (m, 3H, Ar-*H*), 7.15 (dd, *J* = 8.3 Hz and *J* = 1.3 Hz, 1H, Ar-*H*), 7.11-7.08 (m, 3H, Ar-*H*), 6.92 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 6.72 (d, *J* = 9.0 Hz, 2H, Ar-*H*), 5.11 (s, 2H, OC*H*$_2$), 3.72 (s, 3H, OC*H*$_3$), 2.57 (qrt, *J* = 7.3 Hz, 2H, C*H*$_2$), 0.97 (t, *J* = 7.5 Hz, 3H, C*H*$_3$).

^{13}C NMR (125 MHz): δ 159.8, 158.6, 157.8, 147.3, 140.7, 134.8, 131.9, 131.2, 131.0, 130.2, 130.0, 128.2, 128.0, 127.4, 123.4, 122.5, 121.7, 118.1, 116.9, 114.0, 64.2, 55.3, 22.8, 15.3.

HRMS (ESI): Calcd. for $C_{28}H_{23}NO_3$ [M$^+$+H]: *m/z* 410.1756. Found: 410.1758.

Compound 107



Yield: 0.190 g (86%, pale yellow solid; using precursors **14b** and **15a**).

Mp: 234–236 °C.

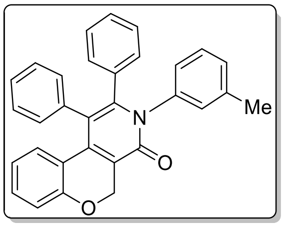
IR (KBr): 2992, 2838, 2236, 1649, 1485, 1441, 1348, 1271, 1238, 1123, 1014, 762 cm^{-1}.

^{1}H NMR: δ 7.19-7.14 (m, 1H, Ar-*H*), 7.11-7.08 (m, 3H, Ar-*H*), 7.05-7.02 (m, 3H, Ar-*H*), 6.99-6.97 (m, 3H, Ar-*H*), 6.96-6.92 (m, 4H, Ar-*H*), 6.85-6.82 (m, 2H, Ar-*H*), 6.56-6.51 (m, 1H, Ar-*H*), 6.46 (dd, *J* = 8.0 Hz and *J* = 1.6 Hz, 1H, Ar-*H*), 5.20 (s, 2H, OC*H*$_2$), 2.25 (s, 3H, C*H*$_3$).

^{13}C NMR: δ 159.9, 157.5, 147.2, 139.7, 137.7, 137.4, 136.2, 134.3, 131.6, 130.8, 129.4, 128.8, 128.7, 128.1, 127.4, 127.2, 126.9, 122.5, 121.5, 120.9, 117.6, 117.5, 64.1, 21.1.

HRMS (ESI): Calcd. for $C_{31}H_{24}NO_2$ [M$^+$+H]: *m/z* 442.1807. Found: 442.1805.

Compound 108



Yield: 0.179 g (81%, yellow solid; using precursors **14c** and **15a**).

Mp: 246–248 °C.

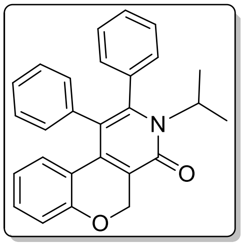
IR (KBr): 3052, 3025, 2921, 2849, 1638, 1485, 1342, 1244, 1205, 1129, 1019, 762 cm^{-1}.

^{1}H NMR: δ 7.19-7.15 (m, 1H, Ar-*H*), 7.13-7.09 (m, 4H, Ar-*H*), 7.04 (dd, *J* = 8.0 Hz and *J* = 1.2 Hz, 1H, Ar-*H*), 6.99-6.96 (m, 3H, Ar-*H*), 6.94-6.87 (m, 5H, Ar-*H*), 6.85-6.84 (m, 2H, Ar-*H*), 6.56-6.52 (m, 1H, Ar-*H*), 6.46 (dd, *J* = 8.0 Hz and *J* = 1.6 Hz, 1H, Ar-*H*), 5.21 (s, 2H, OCH_2), 2.23 (s, 3H, CH_3).

^{13}C NMR: δ 159.8, 157.5, 147.1, 139.7, 138.7, 138.6, 137.4, 134.3, 130.8_1, 130.7_6, 129.6, 128.9, 128.7, 128.5, 128.1, 127.5, 127.2, 127.1, 126.9, 126.0, 122.5, 121.5, 120.9, 117.7, 117.6, 64.1, 21.1.

HRMS (ESI): Calcd. for $C_{31}H_{24}NO_2$ [M^++H]: *m/z* 442.1807. Found: 442.1801.

Compound 109



Yield: 0.177 g (90%, yellow solid; using precursors **14d** and **15a**).

Mp: 262–264 °C.

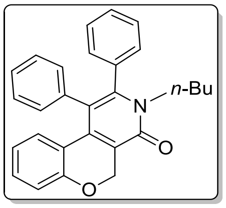
IR (KBr): 2995, 2843, 1619, 1531, 1469, 1443, 1386, 1237, 1240, 1113, 1012, 890, 760 cm^{-1}.

^{1}H NMR (500 MHz): δ 7.24-7.20 (m, 3H, Ar-*H*), 7.10-7.04 (m, 6H, Ar-*H*), 6.97 (dd, *J* = 8.0 Hz and *J* = 1.0 Hz, 1H, Ar-*H*), 6.91-6.89 (m, 2H, Ar-*H*), 6.48-6.44 (m, 1H, Ar-*H*), 6.38 (dd, *J* = 8.0 Hz and *J* = 1.5 Hz, 1H, Ar-*H*), 5.17 (s, 2H, OCH_2), 4.14-4.09 (m, 1H, $(CH_3)_2CH$), 1.56 (d, *J* = 6.5 Hz, 6H, CH_3).

^{13}C NMR (125 MHz): δ 159.9, 157.2, 147.4, 138.1, 138.0, 135.2, 131.5, 130.4, 129.4, 128.5, 128.3, 128.1, 127.9, 126.7, 122.8, 121.3, 120.8, 117.9, 117.3, 63.9, 54.5, 19.3.

HRMS (ESI): Calcd. for $C_{27}H_{24}NO_2$ [M^++H]: *m/z* 394.1807. Found: 394.1805.

Compound 110



Yield: 0.180 g (88%, pale yellow solid; using precursors **14e** and **15a**).

Mp: 196–198 °C.

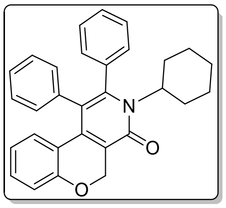
IR (KBr): 2994, 2843, 2235, 1655, 1489, 1445, 1344, 1276, 1243, 1129, 1015, 761 cm^{-1}.

^{1}H NMR (500 MHz): δ 7.26-7.23 (m, 3H, Ar-*H*), 7.15-7.07 (m, 6H, Ar-*H*), 7.00 (dd, *J* = 8.0 Hz and *J* = 1.0 Hz, 1H, Ar-*H*), 6.93-6.91 (m, 2H, Ar-*H*), 6.51-6.48 (m, 1H, Ar-*H*), 6.41 (dd, *J* = 8.5 Hz and *J* = 1.5 Hz, 1H, Ar-*H*), 5.20 (s, 2H, OCH_2), 3.82-3.79 (m, 2H, NCH_2), 1.64-1.61 (m, 2H, NCH_2CH_2), 1.20-1.12 (m, 2H, $N(CH_2)_2CH_2$), 0.75 (t, *J* = 7.5 Hz, 3H, CH_3).

^{13}C NMR: δ 159.3, 157.3, 147.2, 138.6, 137.7, 134.3, 131.5, 130.6, 129.9, 128.7, 128.4, 128.0, 127.9, 126.8, 121.5, 121.4, 120.8, 117.9, 117.4, 64.1, 46.6, 30.7, 20.1, 13.4.

HRMS (ESI): Calcd. for $C_{28}H_{26}NO_2$ [M^++H]: *m/z* 408.1963. Found: 408.1966.

Compound 111



Yield: 0.202 g (93%, white solid; using precursors **14f** and **15a**).

Mp: 218–220 °C.

IR (KBr): 2931, 2848, 1634, 1521, 1485, 1443, 1402, 1247, 1113, 1056, 751, 710 cm^{-1}.

^{1}H NMR: δ 7.25-7.23 (m, 3H, Ar-*H*), 7.14-7.06 (m, 6H, Ar-*H*), 6.99 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 6.93-6.91 (m, 2H, Ar-*H*), 6.51-6.47 (m, 1H, Ar-*H*), 6.38 (dd, *J* = 8.0 Hz and *J* = 1.2 Hz, 1H, Ar-*H*), 5.17 (s, 2H, OCH_2), 3.62-3.59 (m, 1H, C*H*), 2.90-2.82 (m, 2H, CH_2), 1.76-1.63 (m, 4H, CH_2), 1.53-1.21 (m, 2H, CH_2), 0.91-0.79 (m, 2H, CH_2).

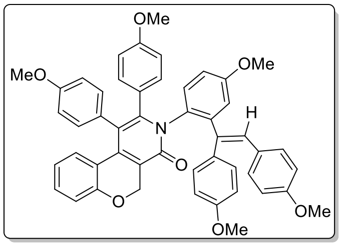
^{13}C NMR (125 MHz): δ 160.1, 159.1, 157.2, 147.6, 138.1, 135.3, 131.5, 130.5, 129.3, 128.5, 128.3, 128.1, 127.9, 126.7, 122.9, 121.4, 120.8, 117.9, 117.4, 64.0, 48.8, 32.6, 26.2, 25.4, 25.0, 24.7.

HRMS (ESI): Calcd. for $C_{30}H_{28}NO_2$ [M^++H]: *m/z* 434.2120. Found: 434.2123.

3.11 Synthesis of annulation along with hydroarylation products 112-118 by the [Ru]-catalyzed double C-H activation of 2*H*-chromene-3-carboxamides with alkynes: General procedure

Into a 10 mL round-bottomed flask, a mixture of 2*H*-chromene-3-carboxamide (**14a** or **14c**, 0.5 mmol), diaryl or dialkyl acetylene (one of **15a-f**, 1.25 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (8 mol %), $Cu(OAc)_2.H_2O$ (1.0 mmol) and $AgNTf_2$ (30 mol %) was taken under N_2 atmosphere. To this, *t*AmOH (2 mL) was added and the mixture was stirred at 110 °C (oil bath temperature) for 12 h. After cooling to rt, saturated NH_4Cl solution (50 mL) was added and the contents extracted with EtOAc (3 x 30 mL). The combined organic phase was washed with brine solution (2 x 15 mL), dried over anh. Na_2SO_4 and concentrated *in vacuo.* The crude product was purified by column chromatography on silica gel using *n*-hexane-EtOAc (4:1) mixture as the eluent.

Compound 112



Yield: 0.332 g (88 %, brown solid; using precursors **14a** and **15b**).

Mp: 166–168 °C.

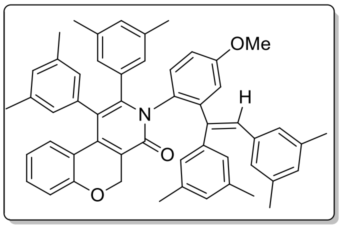
IR (KBr): 2932, 2827, 2044, 1715, 1638, 1611, 1496, 1348, 1293, 1249, 1030, 833, 745 cm^{-1}.

^{1}H NMR (500 MHz): δ 7.17 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.11-7.08 (m, 1H, Ar-*H*), 6.98-6.93 (m, 5H, Ar-*H*), 6.86 (d, *J* = 8.5 Hz, 2H, Ar-*H*), 6.81-6.78 (m, 3H, Ar-*H*), 6.71-6.66 (m, 5H, Ar-*H*), 6.56-6.46 (m, 5H, Ar-*H*), 6.33 (dd, *J* = 8.0 Hz and *J* = 1.5 Hz, 1H, Ar-*H*), 6.00 (s, 1H, olefinic *H*), 4.75-4.66 (m, 2H, OCH_2), 3.80 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3).

^{13}C NMR: δ 159.1, 159.0, 158.5, 158.4, 158.2, 157.3, 146.8, 142.7, 139.0, 138.3, 132.8, 132.4, 132.3, 131.9, 130.6, 130.2, 130.0, 129.9, 129.8_3, 129.8_0, 128.7, 126.3, 121.6, 120.6, 117.4, 117.3, 116.8, 113.5, 113.2, 113.0, 111.9, 111.7, 63.9, 55.4, 55.2, 55.1, 55.0, 54.9.

HRMS (ESI): Calcd. for $C_{49}H_{42}NO_7$ [M$^+$+H]: *m/z* 756.2961. Found: 756.2966.

Compound 113



Yield: 0.321 g (86 %, pale yellow solid; using precursors **14a** and **15f**).

Mp: 242–244 ^{o}C.

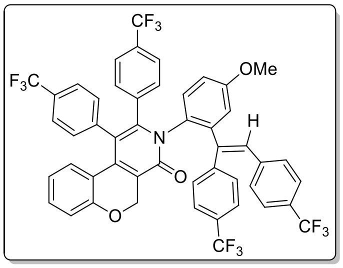
IR (KBr): 3025, 2964, 2921, 2860, 2356, 1638, 1595, 1507, 1260, 1200, 1030, 1101, 1030, 805 cm^{-1}.

^{1}H NMR (500 MHz): δ 7.12-7.08 (m, 2H, Ar-*H*), 6.95 (dd, *J* = 8.0 Hz and *J* = 1.0 Hz, 1H, Ar-*H*), 6.88 (s, 1H, Ar-*H*), 6.85-6.81 (m, 2H, Ar-*H*), 6.79 (s, 1H, Ar-*H*), 6.68 (d, *J* = 9.5 Hz, 5H, Ar-*H*), 6.59 (s, 1H, Ar-*H*), 6.56 (d, *J* = 8.0 Hz, 2H, Ar-*H*), 6.49-6.45 (m, 1H, Ar-*H*), 6.42-6.40 (m, 2H, Ar-*H*), 6.26 (s, 1H, Ar-*H*), 6.17 (s, 1H, olefinic *H*), 4.84 (d, *J* = 14.0 Hz, 1H, OCH_2), 4.66 (d, *J* = 14.0 Hz, 1H, OCH_2), 3.79 (s, 3H, OCH_3), 2.15-2.14 (m, 15H, CH_3), 2.06 (s, 6H, CH_3), 1.99 (s, 3H, CH_3).

^{13}C NMR: δ 158.9, 157.2, 147.2, 142.8, 140.8, 138.3, 137.4, 137.2, 136.9, 136.6, 135.5, 135.2, 133.7, 132.5, 132.0, 130.3, 130.2, 129.8, 129.2_3, 129.1_7, 129.1, 128.9, 128.8, 128.7, 128.0, 127.7, 127.1, 121.8, 121.6, 120.3, 117.5, 117.0, 116.6, 112.9, 63.8, 55.4, 21.3, 21.2, 21.1, 21.0.

HRMS (ESI): Calcd. for $C_{53}H_{50}NO_3$ [M$^+$+H]: *m/z* 748.3790. Found: 748.3790.

Compound 114



Yield: 0.345 g (76 %, white solid; using precursors **14a** and **15e**).

Mp: 255-258 °C.

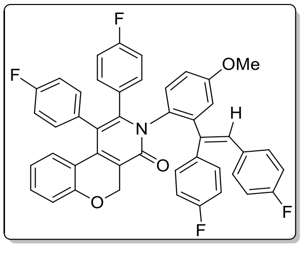
IR (KBr): 3068, 3008, 2937, 2838, 1929, 1649, 1605, 1496, 1414, 1315, 1167, 1118, 1063, 1019, 849, 756 cm^{-1}.

^{1}H NMR (500 MHz): δ 7.49-7.44 (m, 5H, Ar-*H*), 7.34 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.30 (d, *J* = 7.0 Hz, 1H, Ar-*H*), 7.24 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.17-7.13 (m, 4H, Ar-*H*), 7.07-6.98 (m, 5H, Ar-*H*), 6.93 (dd, *J* = 8.8 Hz and *J* = 2.8 Hz, 1H, Ar-*H*), 6.87 (d, *J* = 3.0 Hz, 1H, Ar-*H*), 6.82 (d, *J* = 6.0 Hz, 1H, Ar-*H*), 6.77 (d, *J* = 7.5 Hz, 1H, Ar-*H*), 6.51-6.47 (m, 1H, Ar-*H*), 6.30 (s, 1H, olefinic *H*), 6.16 (dd, *J* = 8.0 Hz and *J* = 1.0 Hz, 1H, Ar-*H*), 4.77-4.69 (m, 2H, OCH_2), 3.83 (s, 3H, OCH_3).

^{13}C NMR (125 MHz): δ 159.8, 158.6, 157.4, 145.2, 141.4, 141.0, 140.9, 140.5, 139.3, 138.8, 136.9, 132.6, 132.5, 132.1, 131.6, 131.5, 131.2, 130.7, 130.3$_9$, 130.3$_6$, 130.1, 130.0, 129.8, 129.7, 129.5, 129.4, 129.2, 129.0, 128.1, 125.4$_2$, 125.3$_9$, 125.2$_9$, 125.2$_7$, 125.1, 125.0, 124.8, 124.5, 124.2$_4$, 124.2$_1$, 123.6, 123.4$_2$, 123.3$_9$, 122.8$_0$, 122.7$_9$, 122.7, 122.4, 120.8, 120.2, 117.8, 117.1, 116.6, 114.1, 63.3, 55.6.

HRMS (ESI): Calcd. for $C_{49}H_{30}F_{12}NO_3$ [M$^+$+H]: *m/z* 908.2034. Found: 908.2030.

Compound 115



Yield: 0.266 g (75 %, pale yellow solid; using precursors **14a** and **15d**).

Mp: 256-258 °C.

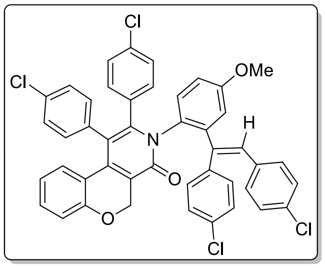
IR (KBr): 2838, 2329, 1907, 1644, 1595, 1501, 1227, 1151, 1041, 997, 805 cm^{-1}.

^{1}H NMR (500 MHz): δ 7.17-7.12 (m, 2H, Ar-*H*), 7.00-6.97 (m, 3H, Ar-*H*), 6.94-6.85 (m, 10H, Ar-*H*), 6.83 (d, *J* = 3.0 Hz, 1H, Ar-*H*), 6.76-6.71 (m, 3H, Ar-*H*), 6.69-6.65 (m, 2H, Ar-*H*), 6.53-6.50 (m, 1H, Ar-*H*), 6.27 (dd, *J* = 8.0 Hz and *J* = 1.0 Hz, 1H, Ar-*H*), 6.12 (s, 1H, olefinic *H*), 4.79-4.69 (m, 2H, OCH_2), 3.81 (s, 3H, OCH_3).

^{13}C NMR (125 MHz): δ 163.4, 162.8, 162.7, 162.6, 161.4, 160.8, 160.6_9, 160.6_6, 159.5, 158.7, 157.4, 145.9, 142.0, 139.2, 138.9, 133.3_8, 133.3_5, 133.2_4, 133.1_7, 133.0_2, 132.9_9, 132.9_2, 132.8_9, 132.8, 132.7, 132.5, 131.9, 131.1_2, 131.0_6, 131.0, 130.9, 130.8, 129.7, 129.6, 129.4, 128.3, 122.8, 120.9, 120.7, 117.7, 116.8_4, 116.8_1, 115.4, 115.3_2, 115.2_6, 115.2, 114.4, 114.3, 113.5_4, 113.4_9, 113.3, 63.7, 55.5.

HRMS (ESI): Calcd. for $C_{45}H_{30}F_4NO_3$ [M^++H]: *m/z* 708.2162. Found: 708.2164.

Compound 116



Yield: 0.317 g (82 %, white solid; using precursors **14a** and **15c**).

Mp: 264–266 °C.

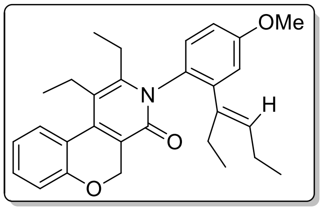
IR (KBr): 2838, 1644, 1595, 1485, 1392, 1288, 1085, 1008, 822, 751 cm^{-1}.

^{1}H NMR (500 MHz): δ 7.17-7.12 (m, 7H, Ar-*H*), 7.03-6.96 (m, 4H, Ar-*H*), 6.93 (s, 1H, Ar-*H*), 6.91-6.88 (m, 4H, Ar-*H*), 6.83-6.80 (m, 3H, Ar-*H*), 6.67 (dd, *J* = 8.0 Hz and *J* = 2.0 Hz, 1H, Ar-*H*), 6.61 (d, *J* = 7.5 Hz, 1H, Ar-*H*), 6.55-6.52 (m, 1H, Ar-*H*), 6.27 (dd, *J* = 8.0 Hz and *J* = 1.5 Hz, 1H, Ar-*H*), 6.14 (s, 1H, olefinic *H*), 4.75 (s, 2H, OCH_2), 3.82 (s, 3H, OCH_3).

^{13}C NMR (125 MHz): δ 159.6, 158.7, 157.5, 145.6, 141.8, 139.9, 138.8, 135.9, 135.5, 134.8, 134.2, 134.1, 133.4, 133.3, 132.5, 132.4, 132.3, 132.1, 132.0, 130.9, 130.8, 130.5, 129.4, 128.7, 128.5, 128.3, 127.6, 126.7, 123.3, 120.9, 120.8, 117.8, 117.0, 116.7, 113.8, 63.7, 55.6.

HRMS (ESI): Calcd. for $C_{45}H_{32}Cl_4NO_3$ [M^++2+H]: *m/z* 774.0950. Found: 774.0952, 772.0969, 773.0998, 775.0975, 776.0932, 777.0951 and 778.0917 (multiple chlorine pattern).

Compound 117



Yield: 0.173 g (78 %, white solid; using precursors **14a** and **15h**).

Mp: 125–127 °C.

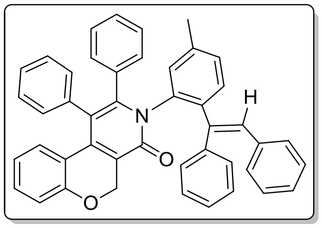
IR (KBr): 2970, 2926, 2367, 1742, 1638, 1518, 1447, 1299, 1233, 1036, 756 cm^{-1}.

^{1}H NMR (500 MHz): δ 7.73 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.34 (t, *J* = 7.5 Hz, 1H, Ar-*H*), 7.21 (d, *J* = 8.5 Hz, 1H, Ar-*H*), 7.12-7.08 (m, 2H, Ar-*H*), 6.93 (dd, *J* = 8.5 Hz and *J* = 3.0 Hz, 1H, Ar-*H*), 6.84 (d, *J* = 2.5 Hz, 1H, Ar-*H*), 5.34-5.28 (m, 2H, OCH_2), 4.68 (d, *J* = 7.0 Hz, 1H, olefinic *H*), 3.88 (s, 3H, OCH_3), 2.85-2.78 (m, 1H), 2.69-2.58 (m, 2H, $CHCH_aH_b$), 2.23-2.10 (m, 2H, CH_2), 2.05-1.99 (m, 2H, CH_2), 1.97-1.90 (m, 1H, $CHCH_aH_b$), 1.33 (t, *J* = 7.3 Hz, 3H, CH_3), 0.95 (t, *J* = 7.5 Hz, 3H, CH_3), 0.91-0.85 (m, 6H, CH_3).

^{13}C NMR (125 MHz): δ 160.5, 159.4, 157.9, 149.3, 143.0, 140.9, 139.1, 132.8, 130.7, 130.4, 129.3, 127.4, 122.6, 121.8, 121.5, 118.1, 116.2, 115.4, 112.4, 64.4, 55.5, 23.7, 23.3, 21.4_1, 21.3_5, 16.1, 14.3, 13.7, 13.4.

HRMS (ESI): Calcd. for $C_{29}H_{34}NO_3$ [M^++H]: *m/z* 444.2538. Found: 444.2539.

Compound 118



Yield:	0.247 g (80 %, pale yellow solid; using precursors **14b** and **15a**).
Mp:	208–208 °C
IR (KBr):	3052, 3025, 2838, 1737, 1633, 1512, 1490, 1441, 1244, 1025, 756 cm^{-1}.
^{1}H NMR:	δ 7.25-7.22 (m, 1H, Ar-*H*), 7.19-7.12 (m, 7H, Ar-*H*), 7.10-7.04 (m, 7H, Ar-*H*), 7.00-6.86 (m, 9H, Ar-*H*), 6.65 (d, *J* = 7.2 Hz, 1H, Ar-*H*), 6.43 (t, *J* = 7.6 Hz, 1H, Ar-*H*), 6.25 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 6.08 (s, 1H, olefinic *H*), 4.71 (s, 2H, OCH_2), 2.35 (s, 3H, CH_3).
^{13}C NMR:	δ 158.5, 157.3, 146.3, 140.4, 138.8, 138.6, 137.9, 137.8, 137.7, 137.1, 136.6, 133.6, 132.4, 132.1, 131.9, 131.5, 131.2, 131.1, 130.3, 129.6, 129.4, 128.6, 128.1, 128.0, 127.7, 127.6, 127.0, 126.7, 126.5, 126.1, 122.6, 121.3, 120.6, 117.6, 117.4, 63.8, 21.0.
HRMS (ESI):	Calcd. for $C_{45}H_{34}NO_2$ [M$^+$+H]: *m/z* 720.2589. Found: 720.2586.

3.12 X-ray crystallography

A suitable crystal was mounted on a glass fiber (for **16**, **18**, **38**, **41**, **45**, **48**, **65**, **77**, **95**, **106**, **107**, **113** and **118**) and X-ray data were collected at 298 K on a Bruker AXS-SMART or on an OXFORD diffractometer using Mo-K$_\alpha$ radiation (for **18**, **38**, **41**, **45**, **77**, **95**, **106**, **107**, **113** and **118**, λ = 0.71073 Å) or Cu-K$_\alpha$ (for **16**, **48**, **65**, λ = 1.54184 Å). Structures were solved and refined using standard methods.[110] Absorption corrections, where applicable, were done using SADABS program, 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 17-20.

Table 17: Crystal data for compounds **16**, **18**, **38** and **41**[a]

Compound	**16**	**18**	**38**	**41**
CCDC no.	1029448	1029449	1029452	1029450
Emp. formula	$C_{20}H_{17}N_3$	$C_{26}H_{21}N_3$	$C_{12}H_{10}N_2$	$C_{30}H_{27}N_3O_3$
Formula wt	299.37	375.46	182.22	477.55
Crystal system	Monoclinic	Monoclinic	Monoclinic	Orthorhombic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$	$Pca2_1$
a /Å	17.0546(9)	13.1017(10)	9.0822(11)	21.214(3)
b /Å	5.5978(2)	20.7038(19)	14.3844(18)	8.2654(11)
c /Å	16.1901(6)	7.3429(6)	7.6234(10)	27.017(4)

α/deg	90	90	90	90
β/deg	105.328(4)	100.921(9)	92.165(2)	90
γ/deg	90	90	90	90
V /Å^3	1490.66(11)	1915.4(3)	995.2(2)	4737.3(11)
Z	4	4	4	8
Dcalc /g cm^{-3}]	1.344	1.302	1.216	1.339
μ /mm^{-1}	0.625	0.077	0.074	0.088
F(000)	632	792	384	2016
Data/ restraints/ parameters	2844/0/212	3032/0/265	1750/0/129	8319/1/661
S	1.070	1.017	1.070	1.056
R1 [I>2σ(I)]	0.0583	0.0507	0.0458	0.0534
wR2 [all data]	0.1492	0.1190	0.1329	0.1193
Max./min. residual electron dens. [eÅ^{-3}]	0.216/-0.277	0.147/-0.164	0.167/-0.122	0.167/-0.146

[a] $R1 = \Sigma||Fo| - |Fc||/\Sigma|Fo|$ and $wR2 = [\Sigma w(Fo^2-Fc^2)^2/\Sigma wFo^4]^{0.5}$

Table 18: Crystal data for compounds **45**, **48**, **65** and **77**[a]

Compound	**45**	**48**	**65**	**77**
CCDC No.	1029451	1453189	1453190	-
Emp. formula	$C_{48}H_{39}N_3O_3$	$C_{31}H_{22}N_2O_2$	$C_{26}H_{22}N_2O_2$	$C_{17}H_{13}N_3O$
Formula wt	705.82	454.51	394.46	275.30
Crystal system	Monoclinic	Triclinic	Triclinic	Triclinic
Space group	$C2/c$	$P\bar{1}$	$P\bar{1}$	$P2_1/n$
a /Å	14.8372(17)	9.4276(5)	11.5059(4)	16.2541(13)
b /Å	26.503(3)	11.2761(9)	12.8459(6)	5.0990(3)
c /Å	18.224(2)	11.6981(10)	15.6020(8)	16.9467(11)
α/deg	90	112.674(8)	106.081(4)	90
β/deg	96.420(11)	90.151(5)	93.226(4)	96.534(3)
γ/deg	90	96.976(5)	70.104(8)	90
V /Å^3	7121.3(17)	1137.32(14)	109.728(4)	1395.41(17)
Z	8	2	4	4
D_{calc} /g cm^{-3}	1.317	1.327	1.274	1.434
μ /mm^{-1}	0.082	0.660	0.643	0.129
F(000)	2976	476	858	616

Data/ restraints/ parameters	6266/0/490	4333/0/317	7879/0/547	3047/0/195
S	1.011	1.029	1.034	1.023
R1 [I>2σ(I)]	0.0531	0.0449	0.0488	0.0521
wR2 [all data]	0.1239	0.1166	0.1277	0.1242
Max./min. residual electron dens. [eÅ^{-3}]	0.152/-0.179	0.158/-0.197	0.193/-0.260	0.189/-0.272

[a]R1 = Σ||Fo| - |Fc||/Σ|Fo| and wR2 = $[\Sigma w(Fo^2-Fc^2)^2/\Sigma wFo^4]^{0.5}$

Table 19: Crystal data for compounds **95**, **106** and **107**[a]

Compound	**95**	**106**	**107**
CCDC No.	-	-	-
Emp. formula	$C_{26}H_{21}N_3O_2$	$C_{27}H_{23}NO_3$	$C_{31}H_{23}NO_2$
Formula wt	407.1634	409.46	441.52
Crystal system	Monoclinic	Triclinic	Monoclinic
Space group	$C2/c$	$P\bar{1}$	$P2_1$
a /Å	17.005(3)	11.1487(5)	10.930(4)
b /Å	15.917(2)	13.6771(7)	14.661(5)
c /Å	30.298(5)	15.2660(7)	14.878(5)
α/deg	90	71.218(2)	90
β/deg	99.023(3)	75.407(2)	98.110(7)
γ/deg	90	73.308(2)	90
V /Å^3	8099(2)	2078.08(17)	2360.2(13)
Z	4	4	4
D_{calc} /g cm^{-3}	1.429	1.444	1.423
μ /mm^{-1}	0.128	0.130	0.128
F(000)	3654	924	1034
Data/ restraints/ parameters	9774/0/565	9638/0/563	4156/0/309
S	1.180	1.016	1.146
R1 [I>2σ(I)]	0.1278	0.0528	0.0619
wR2 [all data]	0.2763	0.1119	0.1285

Max./min. residual electron dens. [eÅ^{-3}]	1.102/-0.343	1.168/-0.277	0.154/-0.157

[a]R1 = Σ||Fo| - |Fc||/Σ|Fo| and wR2 = $[\Sigma w(Fo^2-Fc^2)^2/\Sigma wFo^4]^{0.5}$

Table 20: Crystal data for compound **113** and **118**[a]

Compound	**113**	**118**
CCDC No.	-	-
Emp. formula	$C_{53}H_{49}NO_3$	$C_{45}H_{33}NO_2$
Formula wt	747.96	619.75
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
a /Å	11.300(2)	10.3589(5)
b /Å	23.294(6)	17.6488(6)
c /Å	16.578(4)	36.7182(15)
α/deg	90	90
β/deg	94.778(8)	91.708(2)
γ/deg	90	90
V /Å^3	4348.4(18)	6709.9(5)
Z	4	8
D_{calc} /g cm^{-3}	1.430	1.427
μ /mm^{-1}	0.128	0.128
F(000)	1914	2948
Data/restraints/ parameters	9941/0/523	14825/0/867
S	1.069	1.168
R1 [I>2σ(I)]	0.0668	0.0758
wR2 [all data]	0.1364	0.1354
Max./min. residual electron dens. [eÅ^{-3}]	0.226/-0.231	0.211/-0.230

[a]R1 = Σ||Fo| - |Fc||/Σ|Fo| and wR2 = $[\Sigma w(Fo^2-Fc^2)^2/\Sigma wFo^4]^{0.5}$

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A) Copies of ^{1}H/^{13}C NMR spectra for representative compounds 16, 26, 41, 43, 48, 65, 77, 89, 96, 98, 106 and 113.

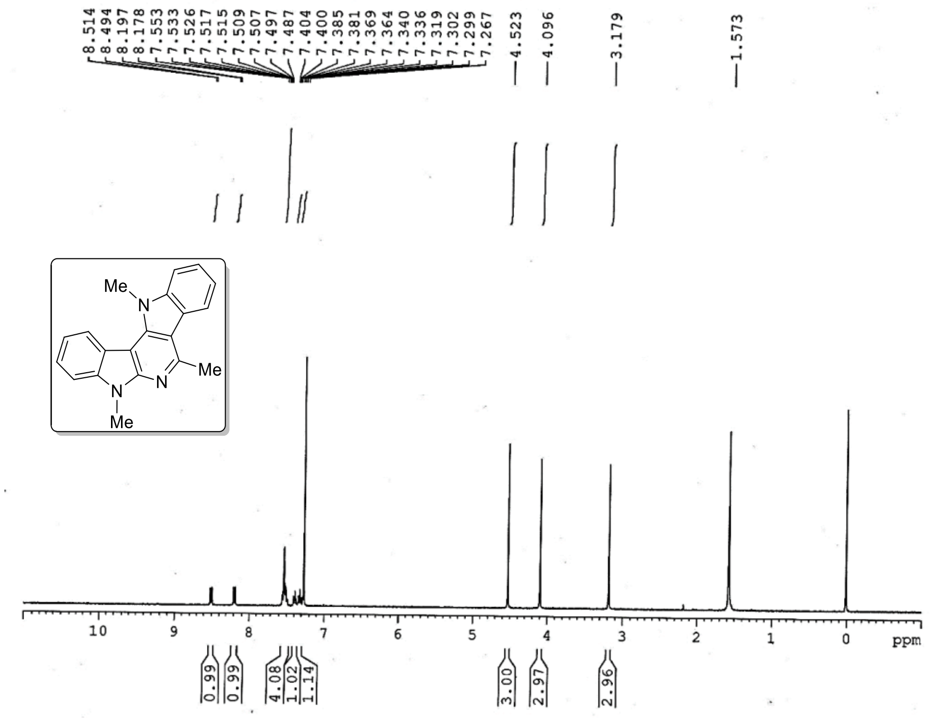

Figure A1. ^{1}H NMR spectrum of compound **16**

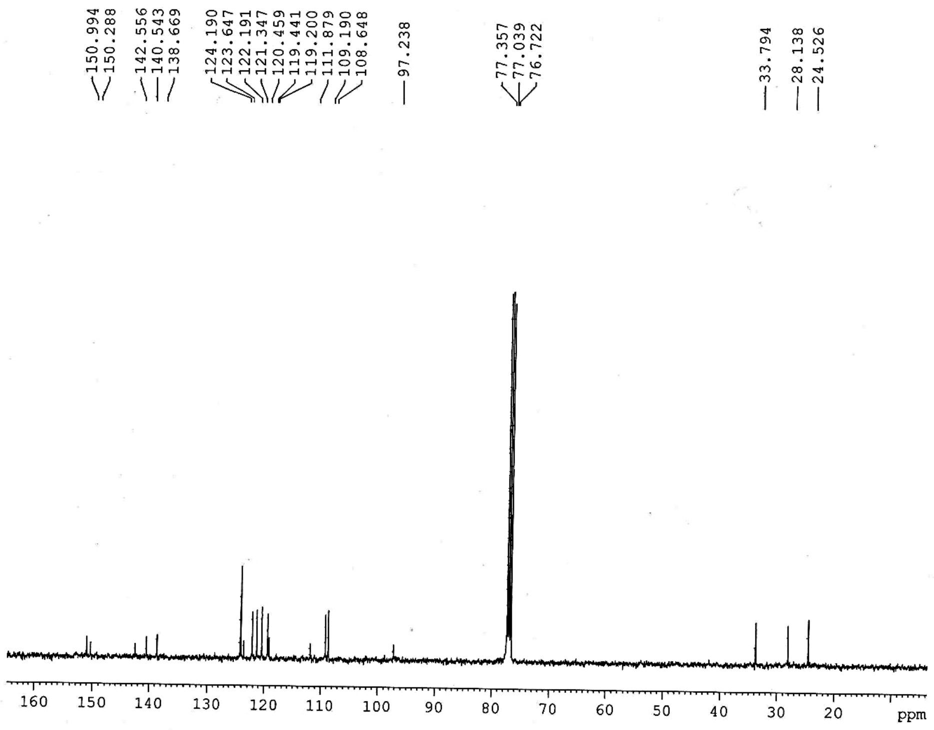

Figure A2. ^{13}C NMR spectrum of compound **16**

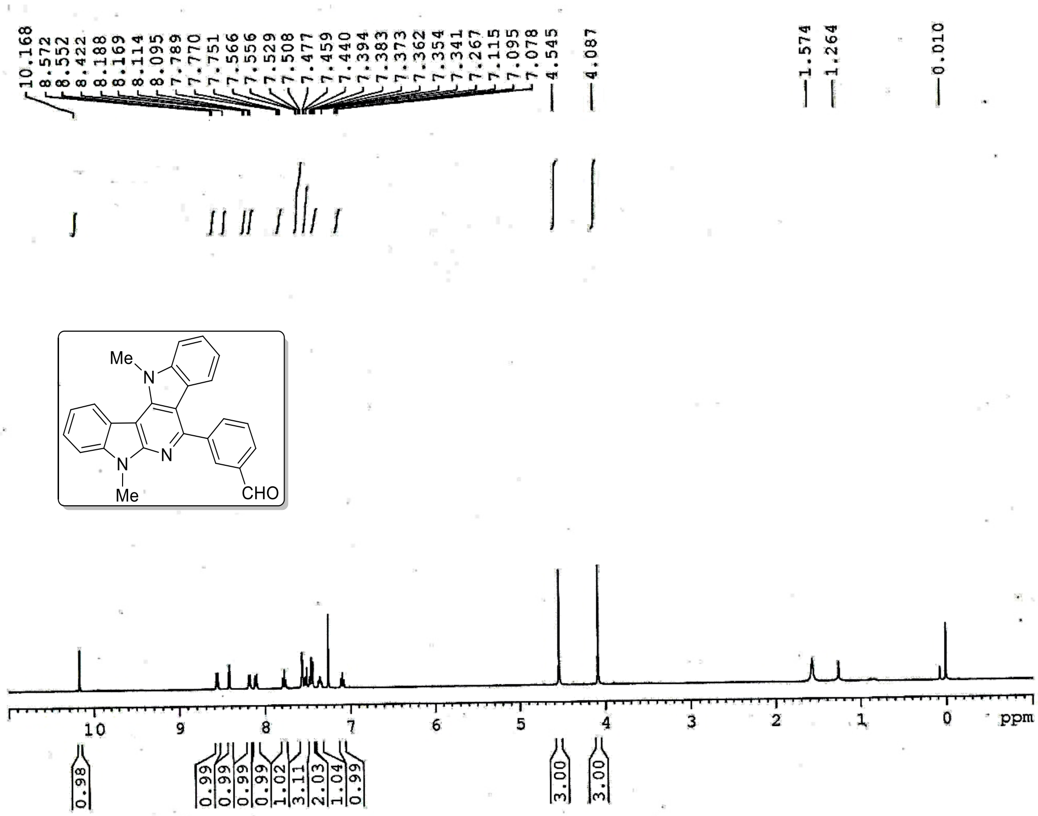

Figure A3. ^{1}H NMR spectrum of compound **26**

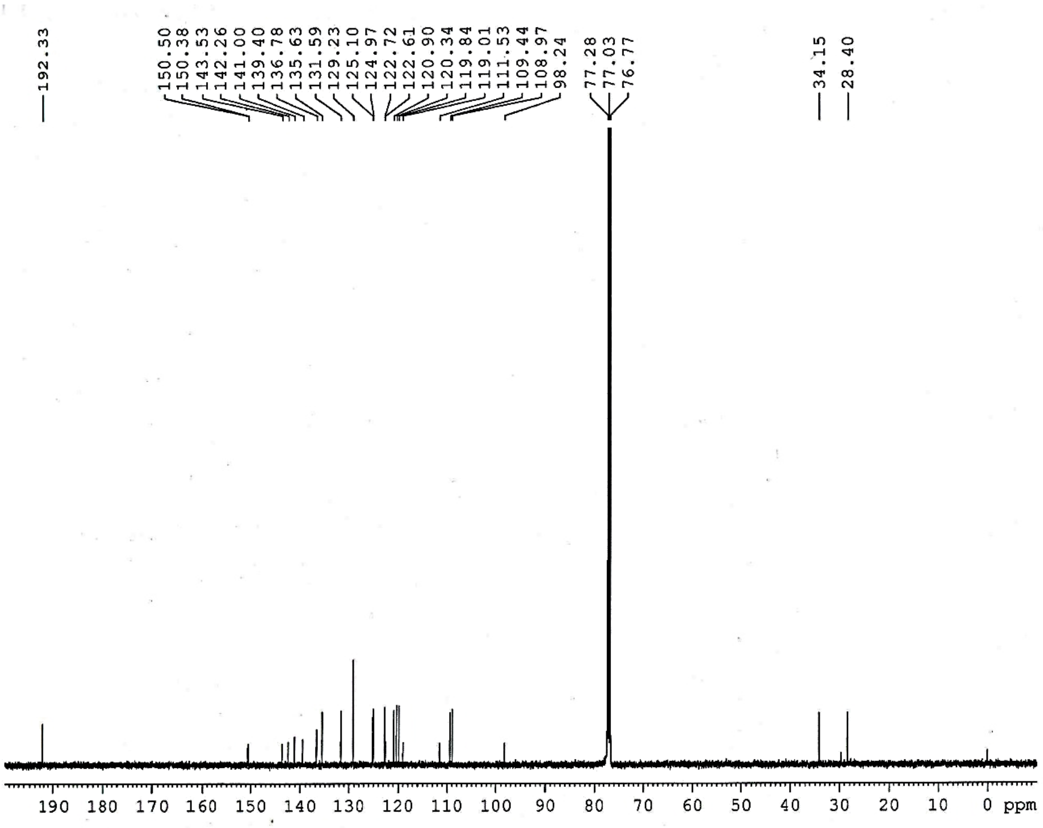

Figure A4. ^{13}C NMR spectrum of compound **26**

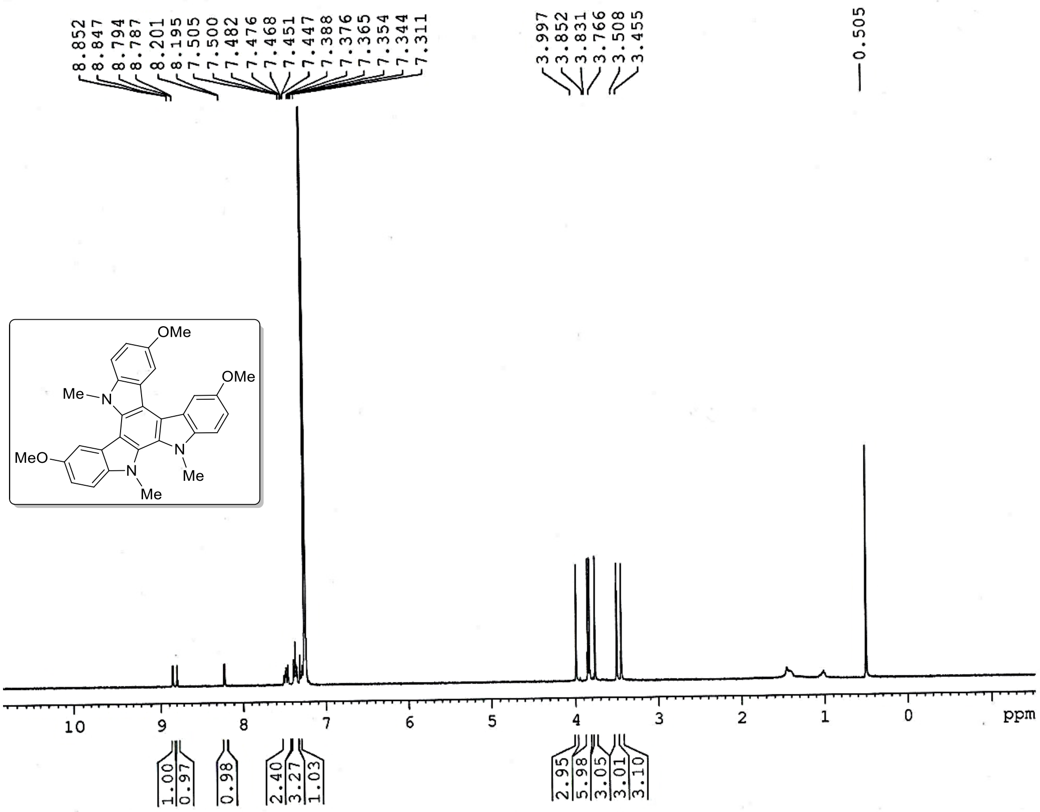

Figure A5. ^{1}H NMR spectrum of compound **41**

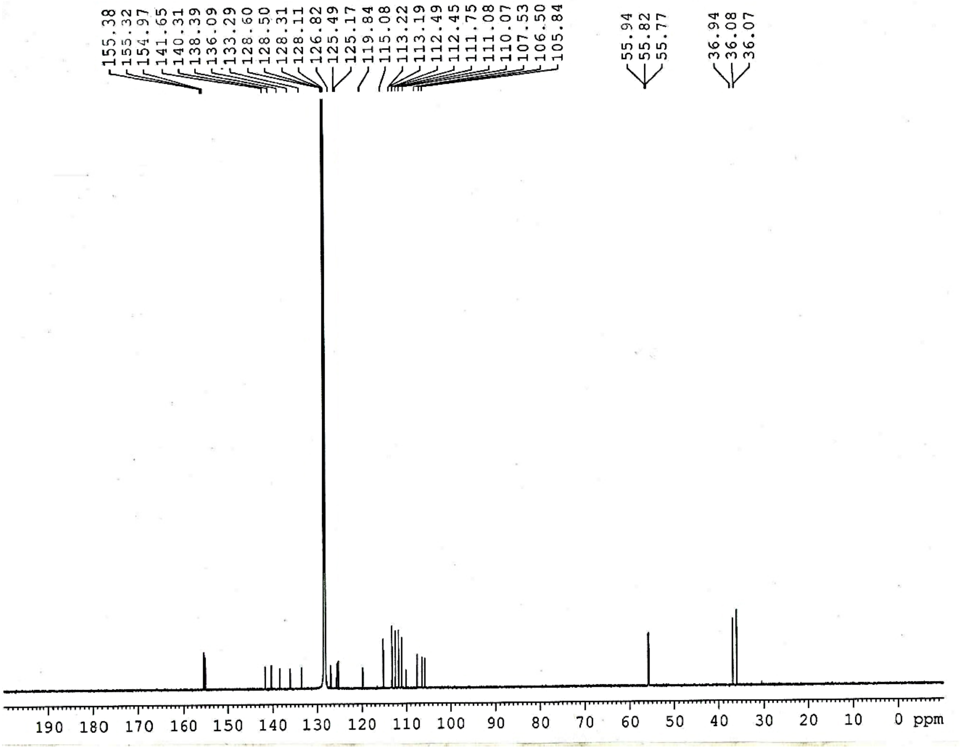

Figure A6. ^{13}C NMR spectrum of compound **41**

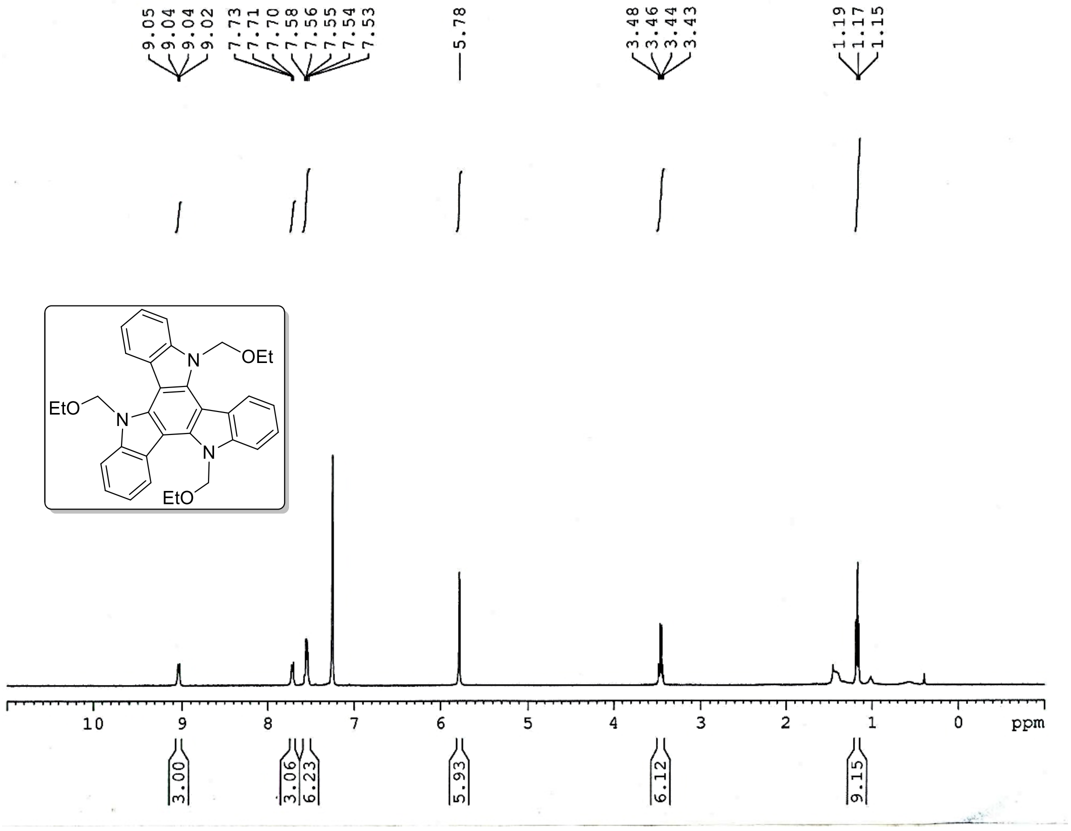

Figure A7. ^{1}H NMR spectrum of compound **43**

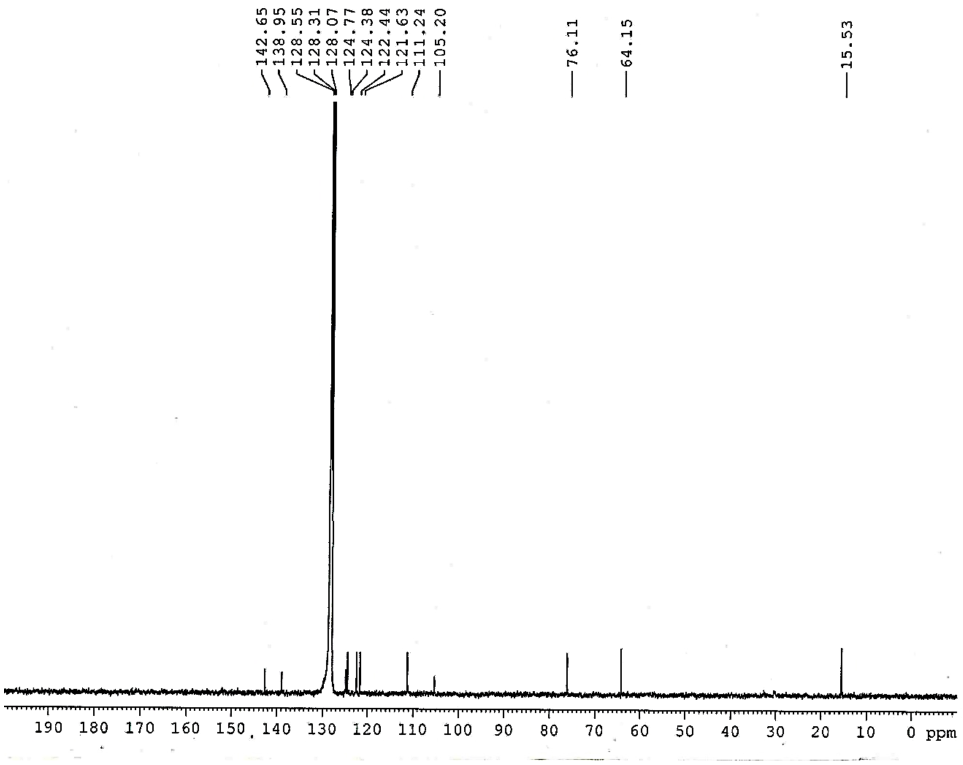

Figure A8. ^{13}C NMR spectrum of compound **43**

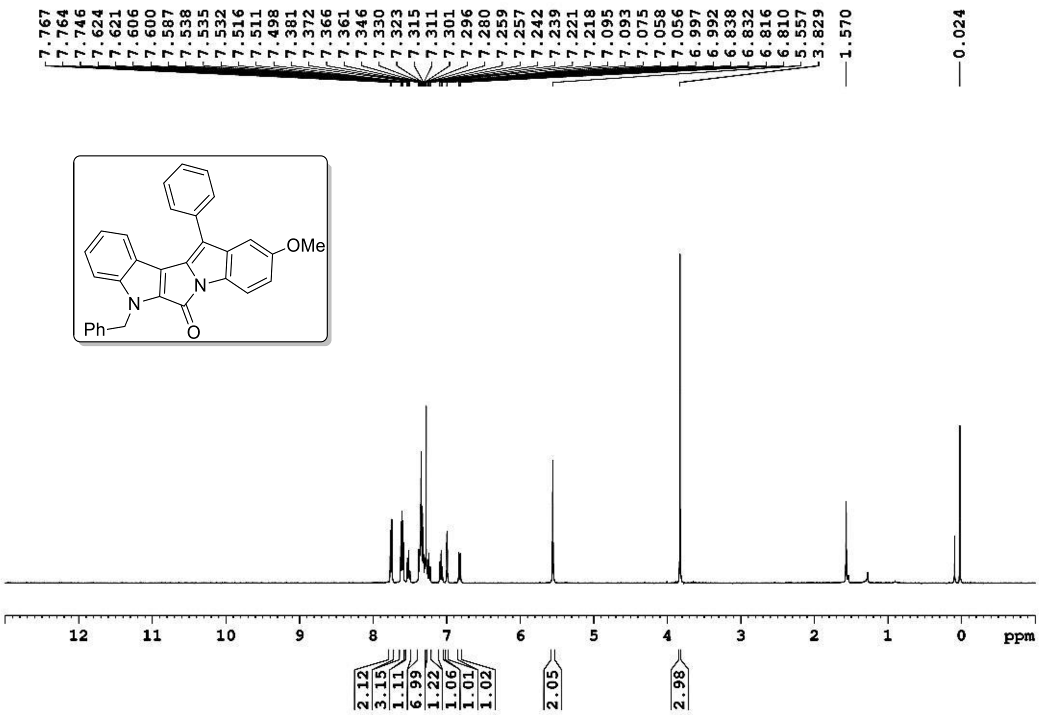

Figure A9. ^{1}H NMR spectrum of compound **48**

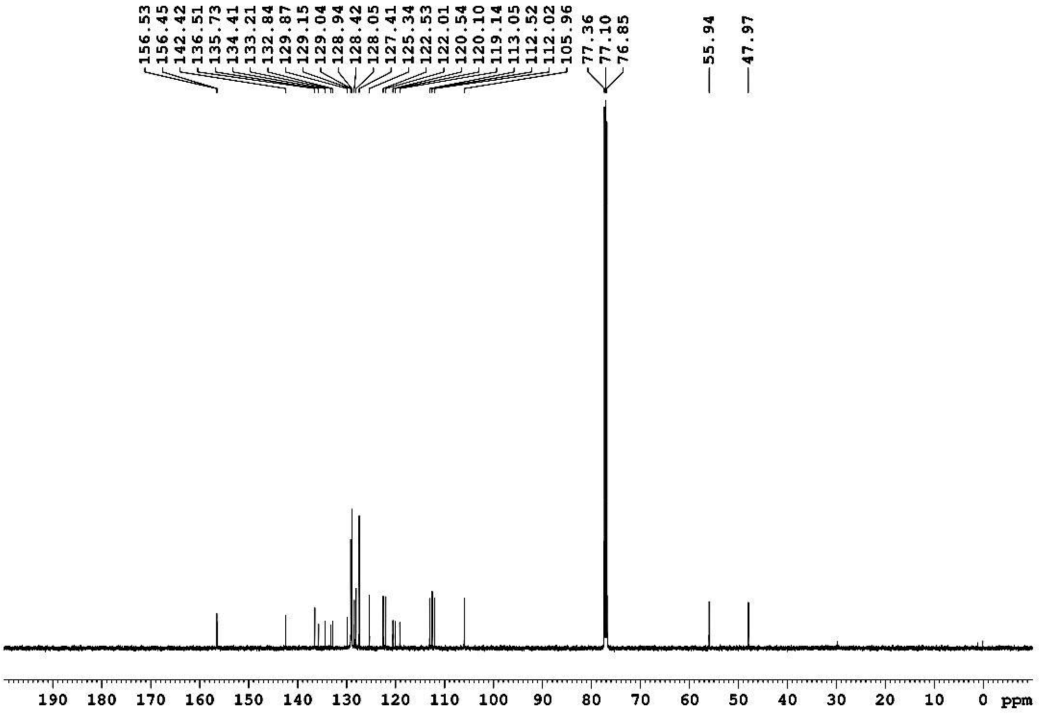

Figure A10. ^{13}C NMR spectrum of compound **48**

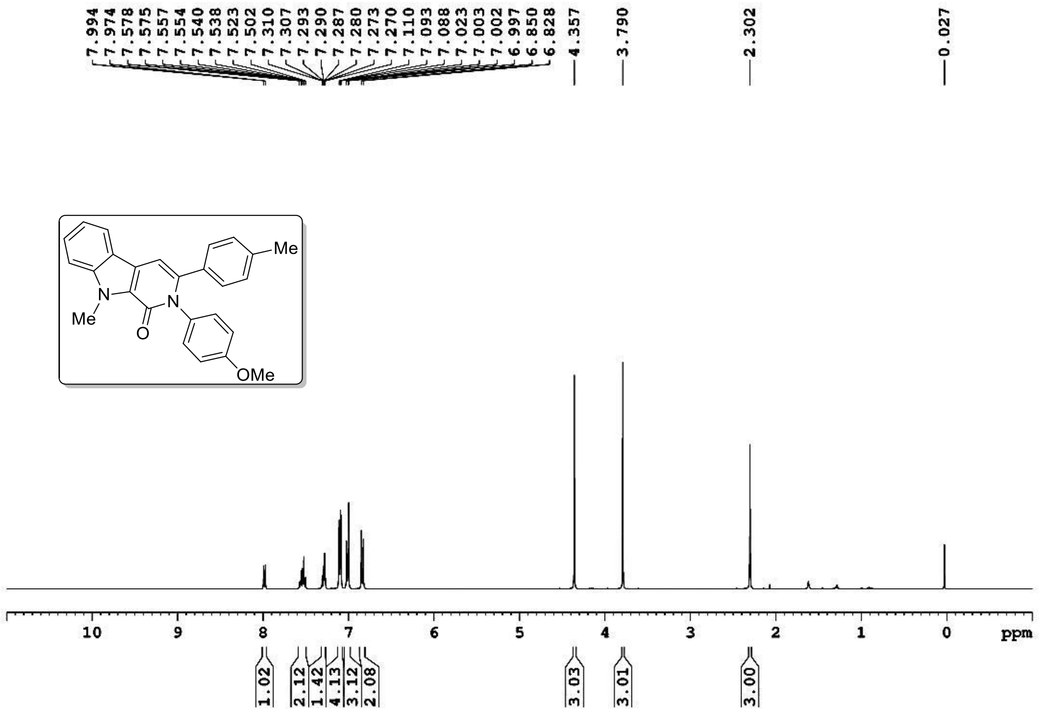

Figure A11. ^{1}H NMR spectrum of compound **65**

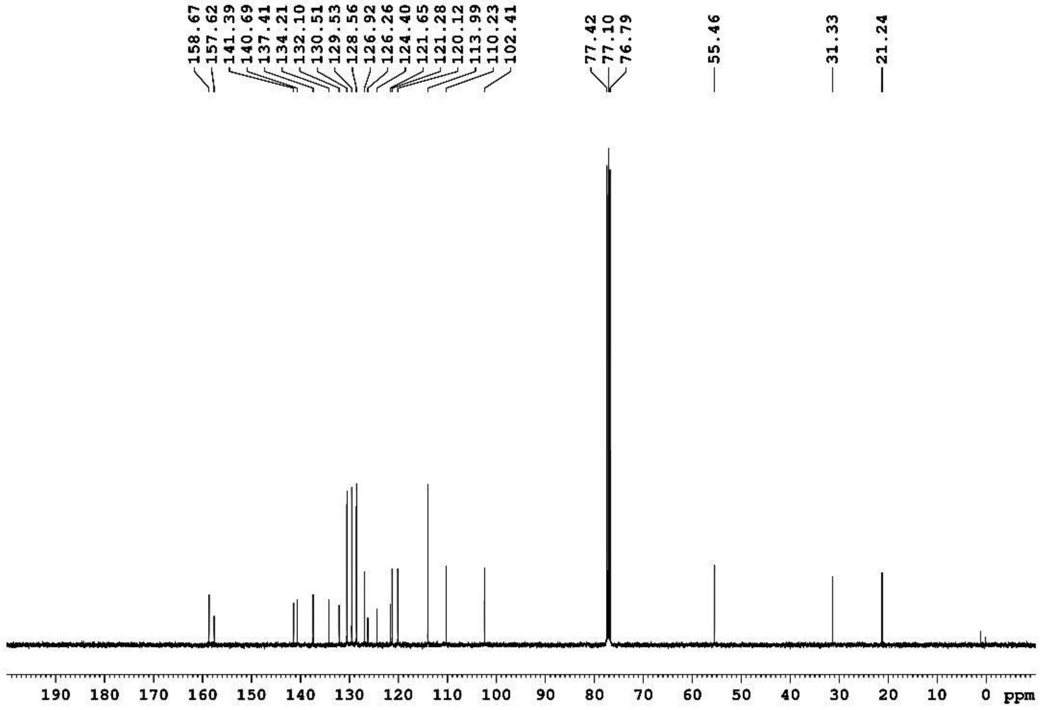

Figure A12. ^{13}C NMR spectrum of compound **65**

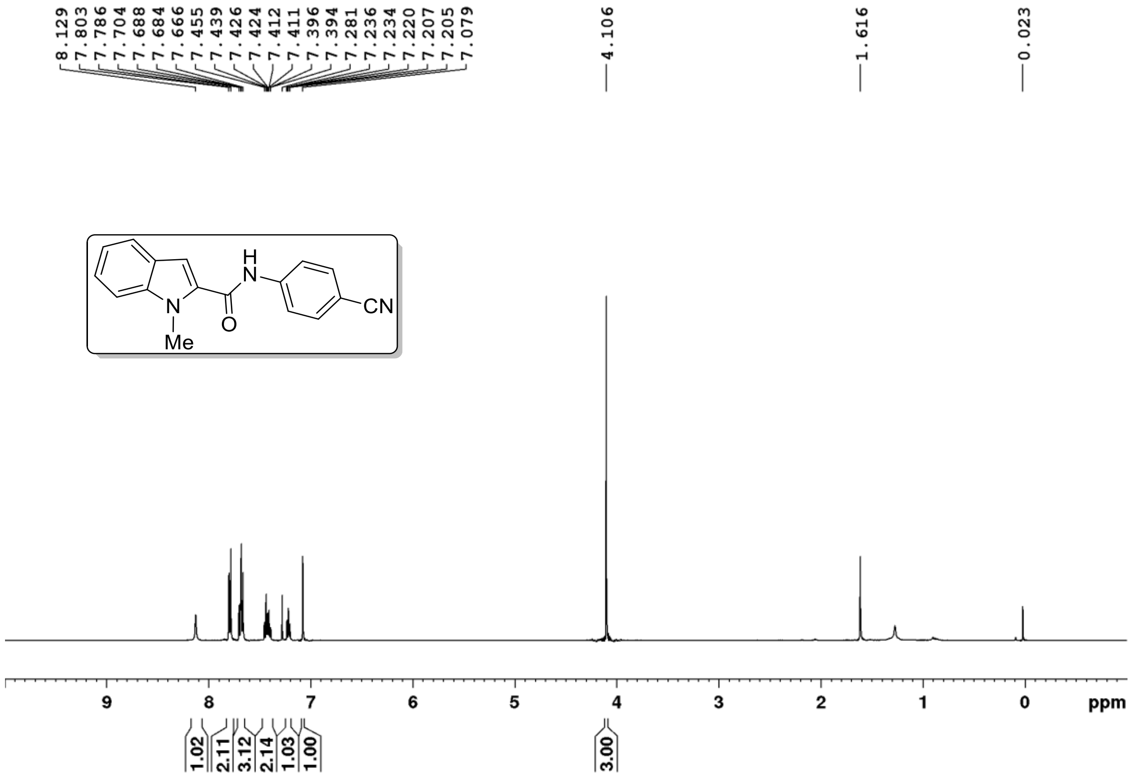

Figure A13. ^{1}H NMR spectrum of compound **77**

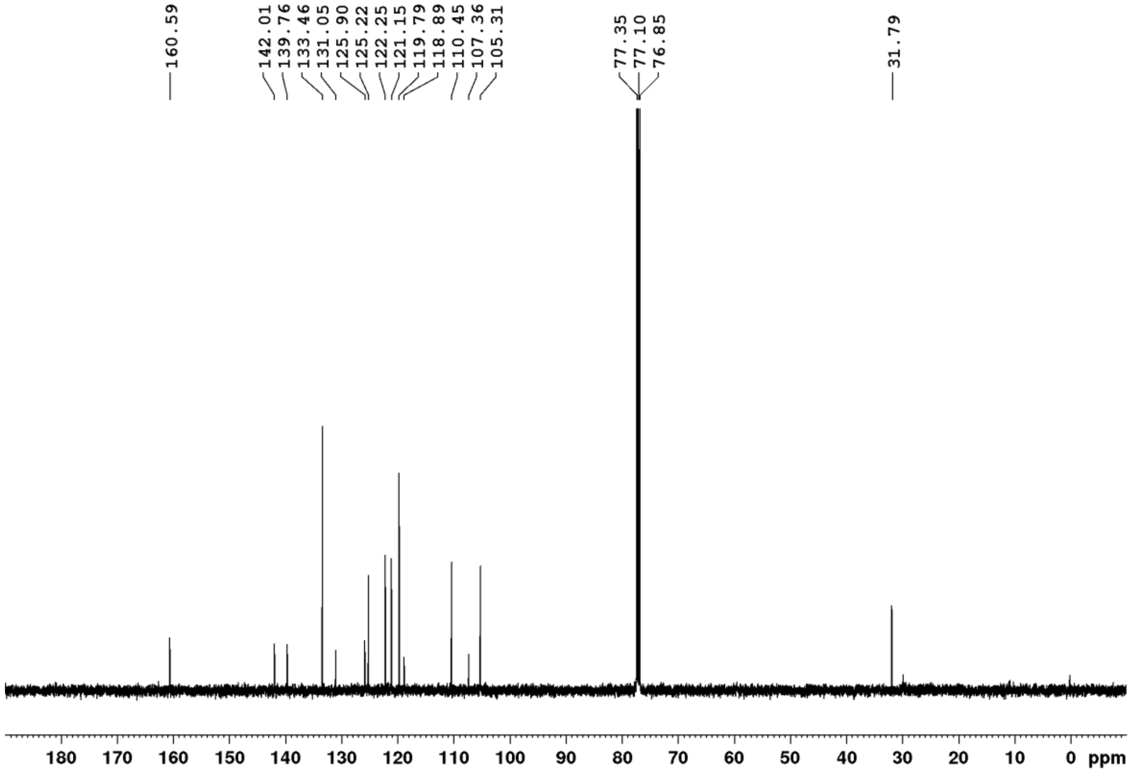

Figure A14. ^{13}C NMR spectrum of compound **77**

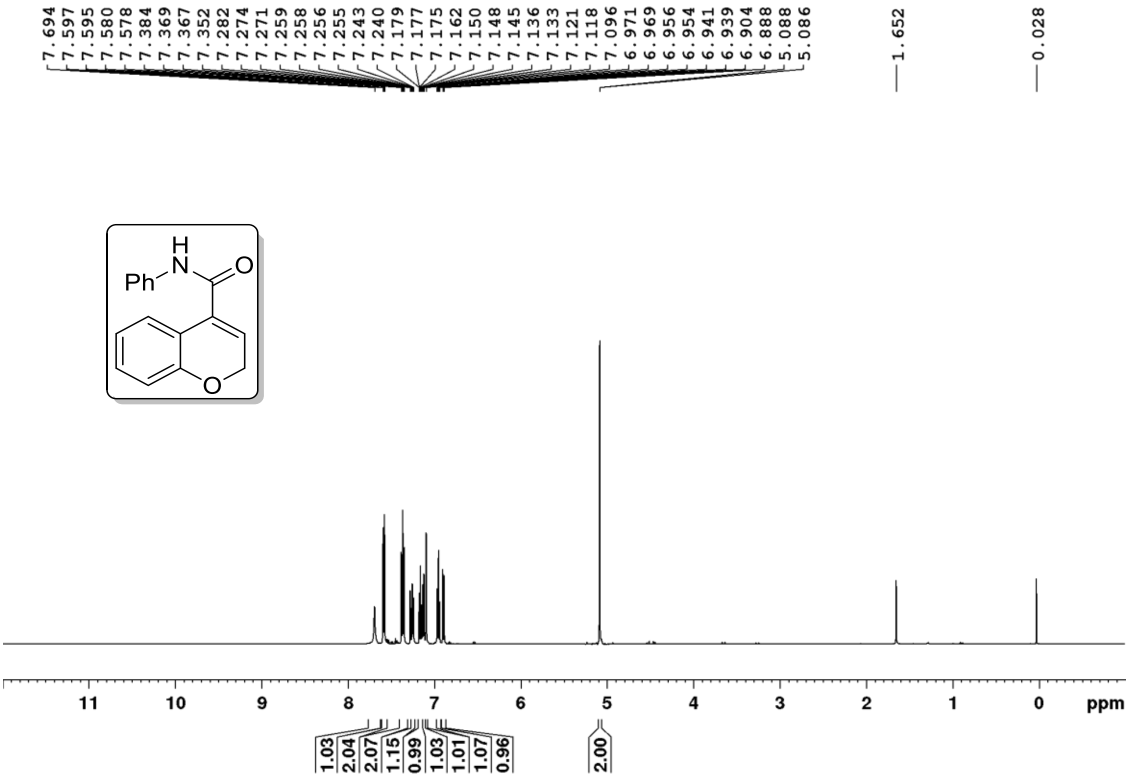

Figure A15. ^{1}H NMR spectrum of compound **89**

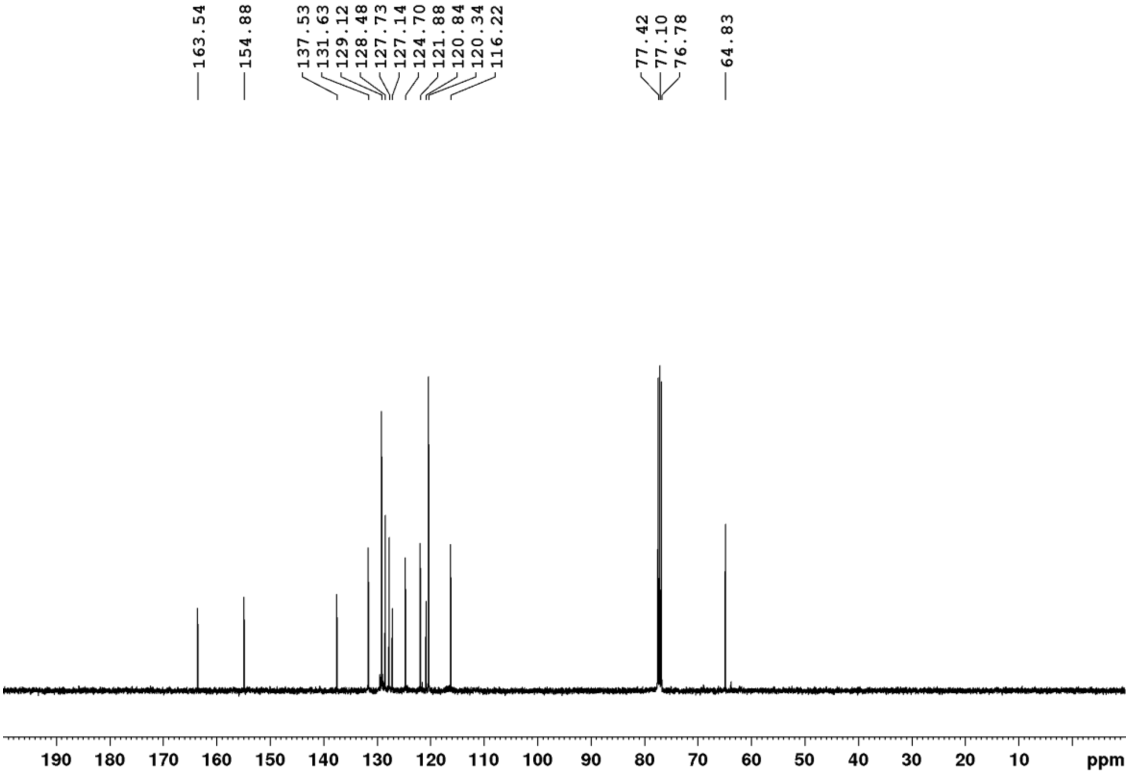

Figure A16. ^{13}C NMR spectrum of compound **89**

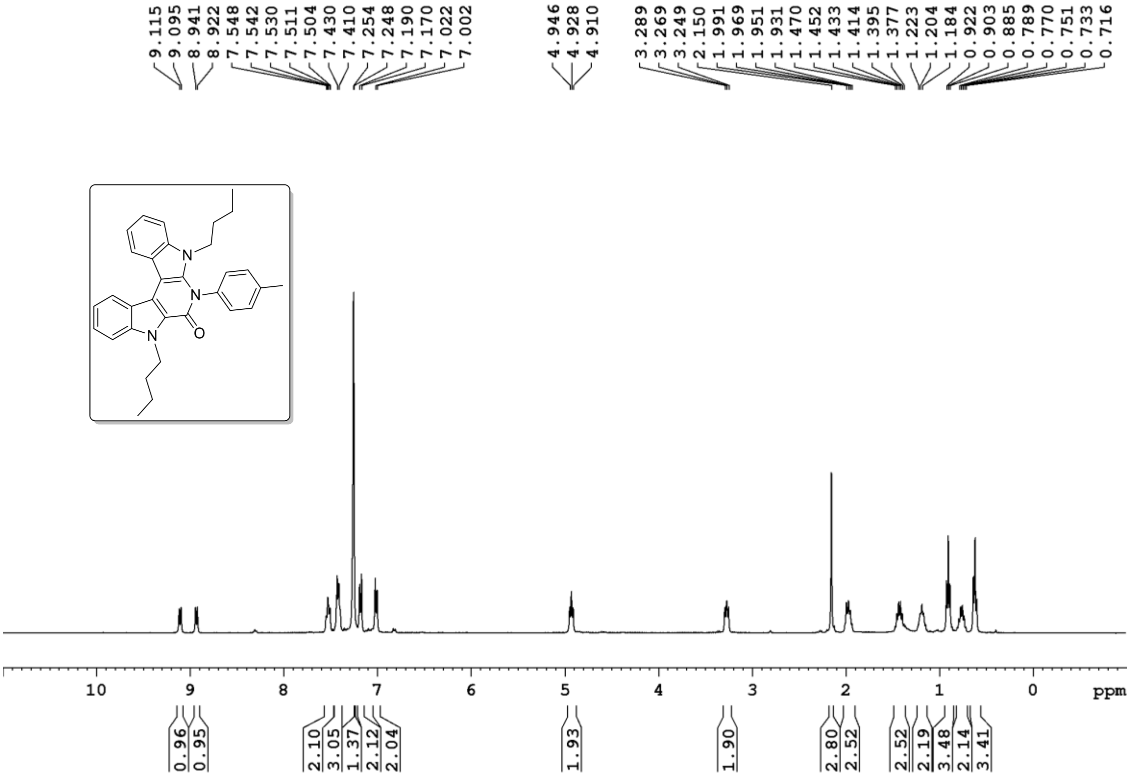

Figure A17. ^{1}H NMR spectrum of compound **96**

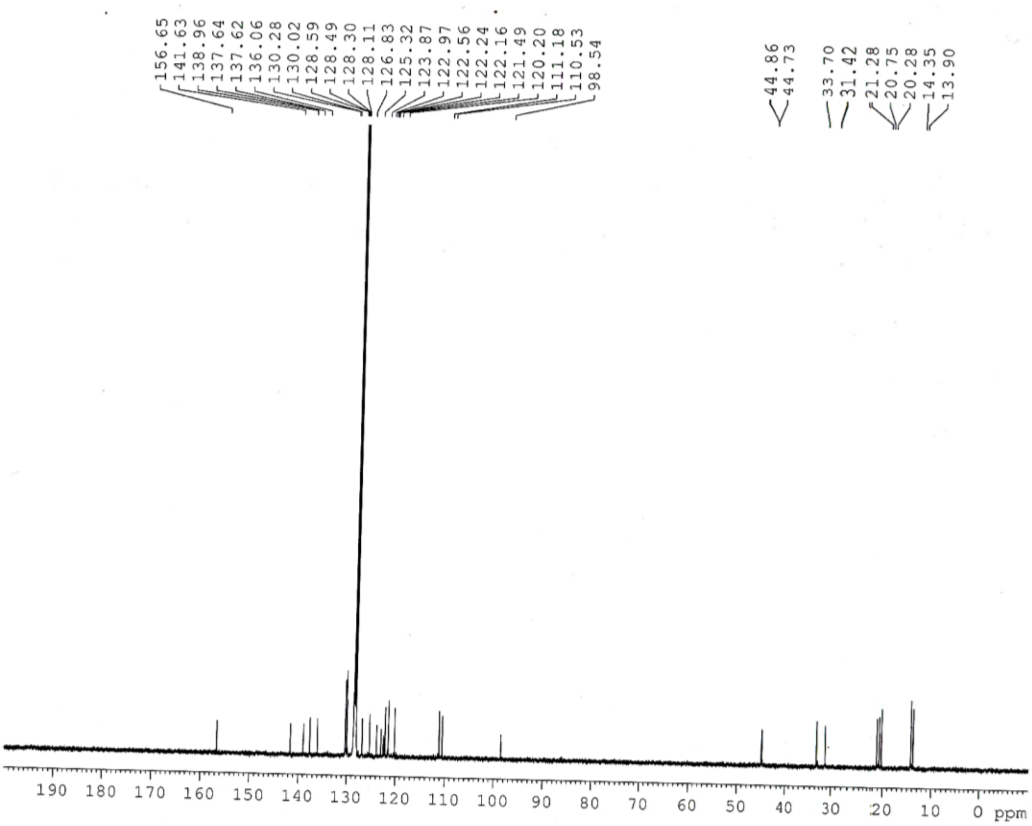

Figure A18. ^{13}C NMR spectrum of compound **96**

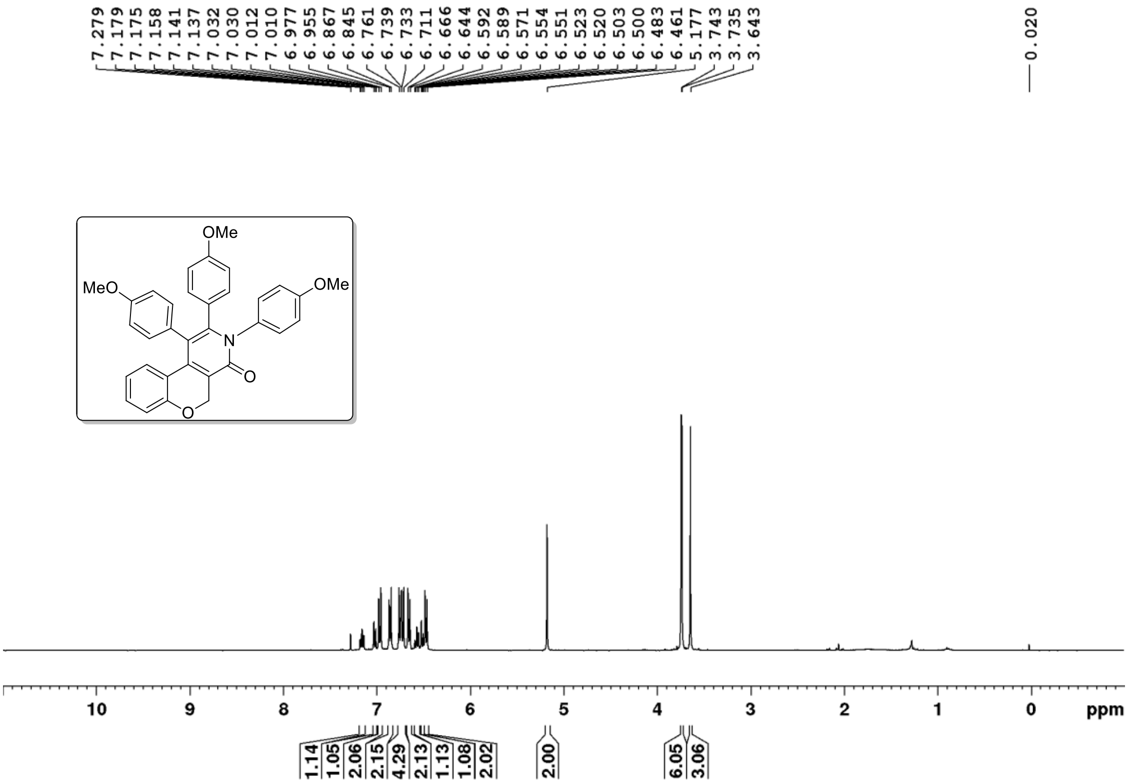

Figure A19. ^{1}H NMR spectrum of compound **98**

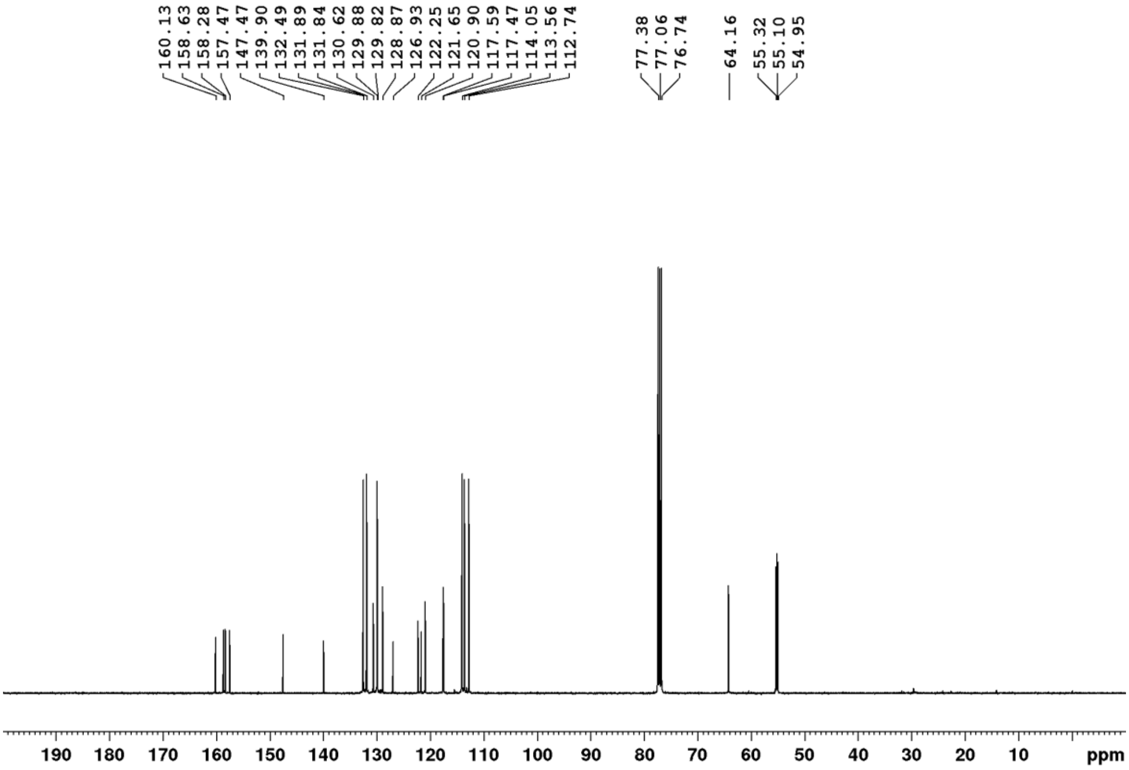

Figure A20. ^{13}C NMR spectrum of compound **98**

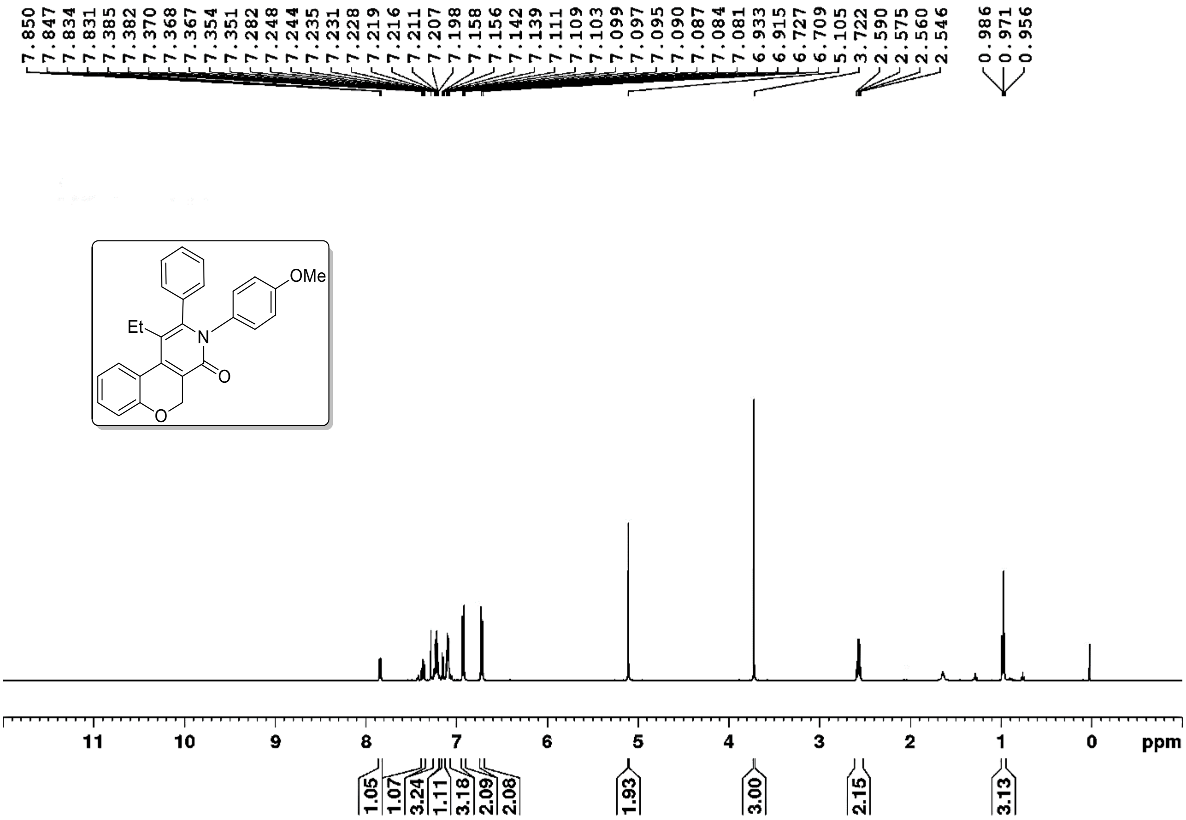

Figure A21. ^{1}H NMR spectrum of compound **106**

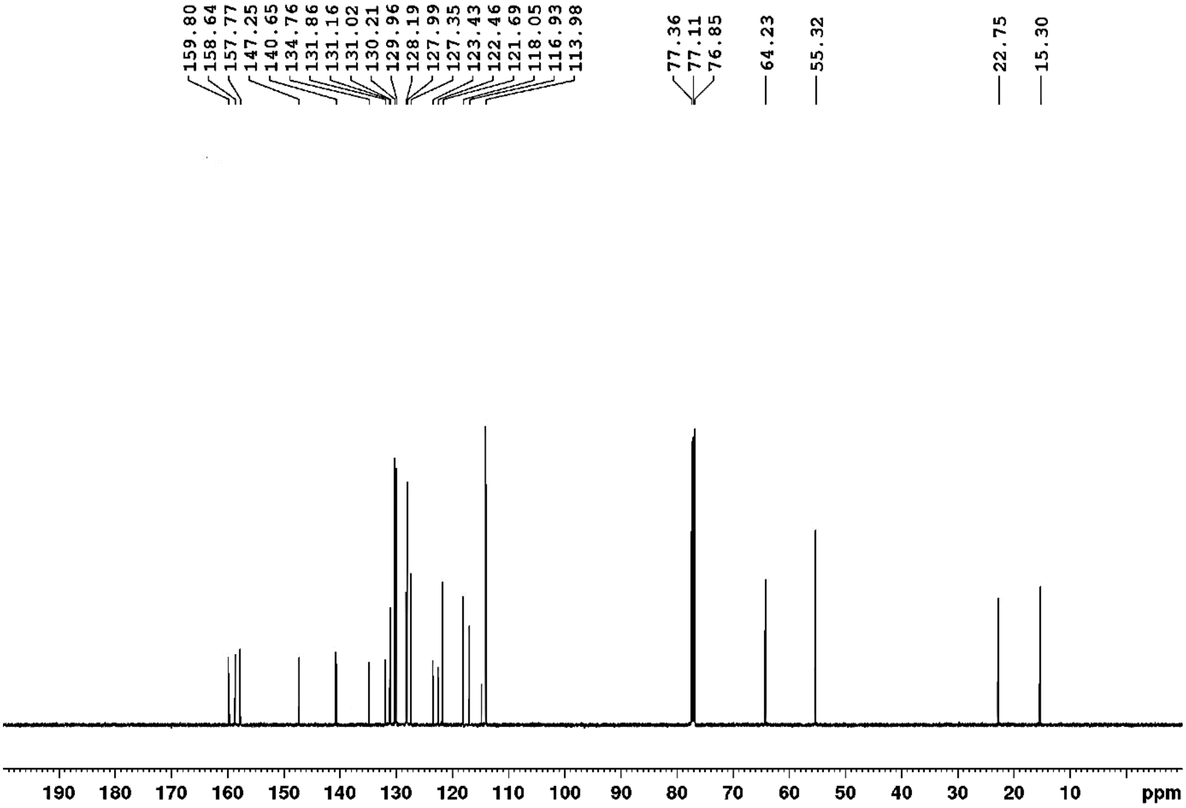

Figure A22. ^{13}C NMR spectrum of compound **106**

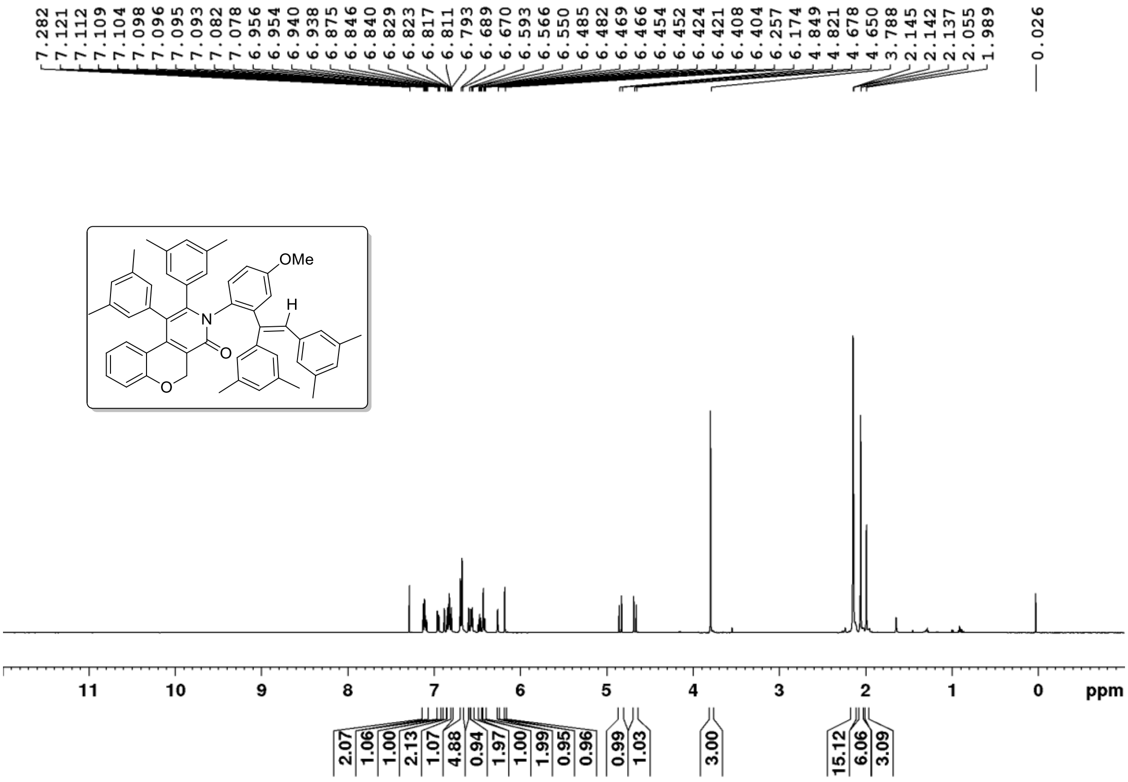

Figure A23. ^{1}H NMR spectrum of compound **113**

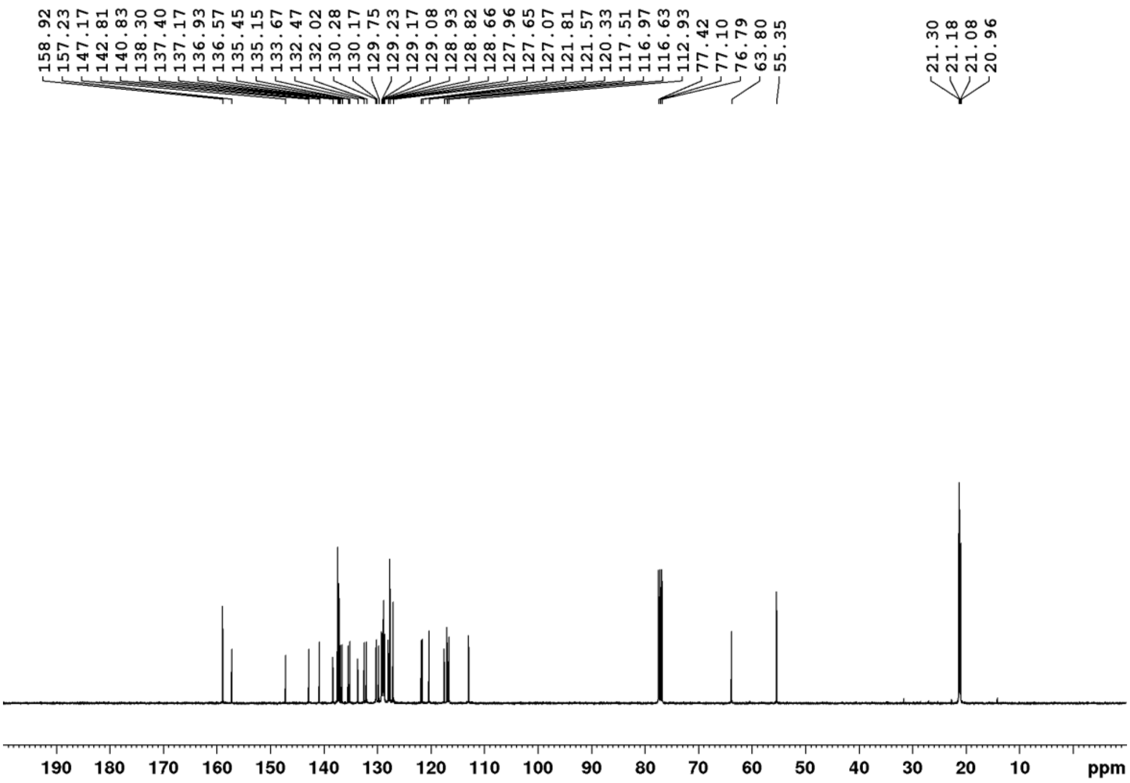

Figure A24. ^{13}C NMR spectrum of compound **113**

B) Publication numbers and atomic coordinates for X-ray structures reported in this thesis

I. Publication numbers for the published compounds

Compounds **16**, **18**, **38**, **41** and **45**: Publication no. 3
Compounds **48** and **65**: Publication no. 4 (Contents, p. xii)

II. Selected atomic coordinates for compounds 77, 95, 106, 107, 113 and 118.

Table 1. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for **Compound 77**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
N(1)	6068(1)	5002(3)	8819(1)	41(1)
O(1)	5817(1)	734(2)	8479(1)	57(1)
N(2)	5727(1)	2442(3)	6811(1)	45(1)
C(1)	6565(1)	5574(3)	6407(1)	41(1)
C(11)	6166(1)	4807(3)	9652(1)	38(1)
C(10)	5964(1)	2995(3)	8289(1)	40(1)
C(6)	6016(1)	3543(3)	6154(1)	42(1)
C(9)	6082(1)	3769(3)	7475(1)	39(1)
C(8)	6599(1)	5676(3)	7245(1)	44(1)
C(16)	5900(1)	2829(4)	10874(1)	57(1)
C(14)	6394(1)	4685(4)	11291(1)	55(1)
C(2)	6924(1)	7028(4)	5836(1)	52(1)
C(17)	5786(1)	2890(3)	10058(1)	49(1)
C(12)	6661(1)	6662(3)	10070(1)	49(1)
C(13)	6775(1)	6606(4)	10886(1)	58(1)
C(3)	6736(1)	6425(4)	5051(1)	57(1)
C(7)	5052(1)	549(4)	6772(1)	57(1)
C(4)	6198(1)	4387(4)	4816(1)	60(1)
C(15)	6503(2)	4639(5)	12146(1)	77(1)
C(5)	5834(1)	2930(4)	5355(1)	58(1)
N(3)	6578(2)	4618(6)	12825(1)	122(1)

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for **Compound 95**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
N(2)	3815(2)	5765(2)	470(1)	44(1)
O(1)	3608(2)	4383(2)	293(1)	59(1)
C(10)	3957(2)	6245(2)	1243(1)	46(1)
O(2)	3577(2)	6176(2)	-1367(1)	75(1)
N(3)	4035(2)	7234(2)	709(1)	51(1)
C(11)	3934(2)	6394(2)	795(1)	43(1)
N(1)	3610(2)	4009(2)	1243(1)	56(1)
C(14)	3757(2)	5912(2)	-3(1)	42(1)
C(13)	3700(2)	4924(2)	588(1)	47(1)
C(9)	3847(2)	5401(2)	1383(1)	47(1)
C(8)	3710(2)	4783(2)	1054(1)	46(1)
C(20)	3023(2)	6008(3)	-260(1)	50(1)
C(23)	4089(2)	7052(3)	1459(1)	53(1)
C(16)	4352(3)	5999(3)	-662(2)	63(1)
C(22)	4134(2)	7638(3)	1118(2)	56(1)
C(19)	2950(3)	6105(3)	-711(1)	55(1)
C(17)	3607(3)	6093(2)	-918(1)	56(1)

C(15)	4431(2)	5902(2)	-207(2)	52(1)
C(6)	3694(3)	4115(3)	1694(2)	67(1)
C(7)	3448(3)	3203(3)	1020(2)	71(1)
C(1)	3846(3)	4970(3)	1799(2)	64(1)
C(21)	4023(3)	7687(3)	293(2)	75(2)
C(24)	4156(3)	7345(3)	1896(2)	71(1)
C(27)	4262(3)	8497(3)	1205(2)	72(1)
C(25)	4283(4)	8185(4)	1981(2)	87(2)
C(26)	4338(4)	8752(4)	1640(2)	90(2)
C(4)	3816(7)	3758(5)	2453(2)	167(4)
C(5)	3677(4)	3500(4)	2022(2)	107(2)
C(18)	2739(5)	6091(5)	-1637(2)	117(2)
C(3)	3963(8)	4595(5)	2568(2)	189(5)
C(2)	3968(5)	5202(4)	2247(2)	126(3)
O(3)	1502(2)	5705(2)	222(1)	56(1)
C(41)	1240(2)	4201(2)	-144(1)	43(1)
N(5)	1369(2)	4306(2)	338(1)	42(1)
C(37)	1402(2)	3738(2)	1090(1)	43(1)
N(4)	1771(2)	5972(2)	1194(1)	51(1)
C(40)	1511(2)	5131(2)	494(1)	42(1)
C(35)	1626(2)	5214(2)	966(1)	44(1)
C(38)	1335(2)	3641(2)	636(1)	43(1)
O(4)	968(2)	3843(2)	-1506(1)	71(1)
N(6)	1232(2)	2808(2)	511(1)	49(1)
C(36)	1544(2)	4571(2)	1269(1)	45(1)
C(47)	1887(2)	4175(2)	-368(1)	47(1)
C(33)	1781(3)	5823(3)	1635(2)	55(1)
C(43)	369(2)	4016(3)	-835(2)	55(1)
C(44)	1013(3)	3973(3)	-1059(1)	52(1)
C(28)	1624(3)	4959(3)	1703(1)	55(1)
C(46)	1773(2)	4063(3)	-819(1)	53(1)
C(49)	1230(2)	2356(2)	905(1)	48(1)
C(48)	1273(3)	2395(3)	90(2)	67(1)
C(50)	1341(2)	2906(2)	1269(1)	50(1)
C(34)	1894(3)	6800(2)	1005(2)	66(1)
C(42)	481(2)	4138(3)	-379(1)	53(1)
C(51)	1384(3)	2567(3)	1696(2)	68(1)
C(53)	1177(3)	1184(3)	1376(2)	73(1)
C(32)	1887(3)	6387(3)	1996(2)	72(1)
C(54)	1138(3)	1487(3)	951(2)	59(1)
C(29)	1559(3)	4688(3)	2134(2)	74(1)
C(52)	1295(4)	1701(3)	1740(2)	80(2)
C(30)	1652(4)	5254(4)	2478(2)	90(2)
C(31)	1814(4)	6091(4)	2411(2)	88(2)
C(45)	211(3)	3697(4)	-1765(2)	88(2)

Table 3. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for **Compound 106**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
O(4)	3823(1)	6030(1)	4025(1)	59(1)
O(2)	361(1)	2713(1)	9339(1)	61(1)
O(1)	1784(1)	1004(1)	11738(1)	61(1)
N(1)	1651(1)	3857(1)	9022(1)	38(1)
O(3)	834(1)	5569(1)	5328(1)	65(1)
N(2)	5911(1)	8783(1)	3395(1)	40(1)
O(5)	5703(2)	7681(1)	4883(1)	70(1)
O(6)	9476(1)	10500(1)	4017(1)	74(1)
C(10)	2723(2)	3899(1)	10191(1)	36(1)
C(40)	5634(2)	9138(1)	2488(1)	36(1)
C(13)	2446(2)	4272(1)	9304(1)	35(1)
C(9)	2166(2)	3052(1)	10837(1)	36(1)
C(14)	2975(2)	5138(1)	8566(1)	37(1)
C(37)	4751(2)	8799(1)	2258(1)	37(1)
C(20)	1388(2)	4284(1)	8070(1)	37(1)
C(34)	4127(2)	8039(1)	2982(1)	39(1)
C(47)	6804(2)	9214(1)	3618(1)	40(1)
C(53)	6393(2)	10102(1)	3937(1)	41(1)
C(22)	209(2)	5614(1)	6952(1)	45(1)

C(21)	429(2)	5158(1)	7865(1)	43(1)
C(8)	1400(2)	2645(1)	10540(1)	40(1)
C(1)	2403(2)	2522(1)	11816(1)	42(1)
C(41)	6387(2)	9886(1)	1792(1)	39(1)
C(27)	1076(2)	3041(1)	9620(1)	42(1)
C(35)	4519(2)	7608(1)	3833(1)	43(1)
C(52)	7252(2)	10555(1)	4097(1)	44(1)
C(38)	4605(2)	9114(1)	1237(1)	42(1)
C(23)	965(2)	5180(2)	6247(1)	45(1)
C(28)	3117(2)	7616(2)	2854(1)	44(1)
C(54)	5403(2)	7990(2)	4099(1)	47(1)
C(42)	5941(2)	10969(2)	1629(1)	49(1)
C(33)	3047(2)	6582(2)	3371(1)	48(1)
C(15)	2343(2)	6187(1)	8482(1)	48(1)
C(50)	8531(2)	10114(2)	3920(1)	48(1)
C(6)	2213(2)	1492(2)	12217(1)	52(1)
C(11)	3619(2)	4387(2)	10423(1)	46(1)
C(26)	2138(2)	3842(2)	7366(1)	49(1)
C(2)	2799(2)	2952(2)	12378(1)	53(1)
C(19)	4078(2)	4919(2)	7939(1)	51(1)
C(25)	1929(2)	4284(2)	6458(1)	56(1)
C(48)	8086(2)	8750(2)	3473(1)	54(1)
C(16)	2812(2)	6985(2)	7786(1)	57(1)
C(17)	3915(2)	6754(2)	7175(2)	58(1)
C(49)	8943(2)	9200(2)	3624(2)	60(1)
C(36)	4024(2)	6688(2)	4515(1)	56(1)
C(12)	2974(2)	5352(2)	10791(2)	61(1)
C(29)	2217(2)	8167(2)	2269(1)	55(1)
C(7)	877(2)	1724(2)	11184(1)	56(1)
C(32)	2231(2)	6078(2)	3223(2)	65(1)
C(39)	5187(2)	8212(2)	781(1)	62(1)
C(46)	7529(2)	9500(2)	1278(2)	64(1)
C(18)	4546(2)	5722(2)	7248(2)	61(1)
C(3)	3035(2)	2382(2)	13265(1)	65(1)
C(43)	6630(2)	11651(2)	963(2)	66(1)
C(24)	-223(2)	6412(2)	5095(2)	67(1)
C(30)	1377(2)	7678(2)	2146(2)	62(1)
C(31)	1406(2)	6632(2)	2602(2)	68(1)
C(5)	2473(2)	913(2)	13102(2)	69(1)
C(4)	2884(2)	1368(2)	13622(2)	73(1)
C(44)	7762(3)	11264(2)	466(2)	78(1)
C(45)	8214(2)	10194(3)	614(2)	85(1)
C(51)	9123(3)	11416(2)	4350(2)	85(1)

Table 4. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for **Compound 107**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
N(1)	8143(2)	4728(1)	523(1)	47(1)
O(2)	8632(2)	3213(1)	525(1)	66(1)
C(10)	8057(2)	3854(2)	135(2)	49(1)
C(8)	7286(2)	3779(2)	-711(2)	48(1)
C(11)	6784(2)	5381(2)	-706(2)	45(1)
C(25)	8870(2)	4797(2)	1412(2)	48(1)
O(1)	6034(2)	2714(1)	-1663(1)	72(1)
C(18)	7521(2)	5468(2)	104(2)	44(1)
C(7)	6684(2)	4505(2)	-1150(2)	47(1)
C(12)	6089(2)	6206(2)	-1083(2)	47(1)
C(20)	6810(3)	6767(2)	973(2)	62(1)
C(6)	5989(2)	4311(2)	-2054(2)	51(1)
C(19)	7722(2)	6369(2)	568(2)	46(1)
C(26)	8309(3)	4850(2)	2172(2)	60(1)
C(31)	10127(2)	4753(2)	1493(2)	62(1)
C(1)	5697(3)	3400(2)	-2270(2)	61(1)
C(27)	9019(3)	4858(2)	3014(2)	67(1)
C(30)	10821(3)	4753(2)	2339(2)	70(1)
C(24)	8803(2)	6838(2)	536(2)	60(1)
C(13)	4842(2)	6267(2)	-1062(2)	59(1)
C(9)	7190(3)	2851(2)	-1121(2)	68(1)

C(28)	10287(3)	4797(2)	3108(2)	63(1)
C(5)	5618(3)	4954(2)	-2724(2)	66(1)
C(17)	6679(3)	6934(2)	-1425(2)	60(1)
C(21)	6972(3)	7627(2)	1346(2)	77(1)
C(14)	4187(3)	7029(2)	-1383(2)	80(1)
C(16)	6033(3)	7698(2)	-1740(2)	78(1)
C(23)	8961(3)	7698(2)	902(2)	74(1)
C(4)	4956(3)	4700(2)	-3545(2)	83(1)
C(29)	11062(3)	4788(3)	4034(2)	101(1)
C(22)	8045(3)	8089(2)	1302(2)	78(1)
C(2)	5024(3)	3150(2)	-3072(2)	77(1)
C(3)	4649(3)	3801(3)	-3709(2)	90(1)
C(15)	4788(4)	7739(2)	-1719(2)	88(1)

Table 5. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for **Compound 113**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
O(2)	3718(1)	5503(1)	6339(1)	53(1)
O(3)	4(1)	4417(1)	4103(1)	57(1)
N(1)	4199(1)	4558(1)	6139(1)	34(1)
O(1)	5978(2)	5522(1)	8439(1)	67(1)
C(19)	4969(2)	4097(1)	6287(1)	36(1)
C(34)	2122(2)	4219(1)	5913(1)	35(1)
C(28)	3093(2)	4501(1)	5628(1)	35(1)
C(10)	5951(2)	4147(1)	6831(1)	39(1)
C(20)	4709(2)	3555(1)	5820(1)	37(1)
C(35)	2144(2)	3948(1)	6735(1)	36(1)
C(00B)	4375(2)	5093(1)	6526(1)	38(1)
C(52)	3412(2)	4119(1)	8037(1)	41(1)
C(8)	5356(2)	5116(1)	7130(1)	40(1)
C(45)	2552(2)	4312(1)	7447(1)	38(1)
C(11)	6743(2)	3638(1)	7009(1)	42(1)
C(33)	1075(2)	4183(1)	5398(1)	39(1)
C(9)	6160(2)	4682(1)	7256(1)	39(1)
C(31)	1001(2)	4426(1)	4634(1)	41(1)
C(29)	3013(2)	4746(1)	4862(1)	42(1)
C(21)	4769(2)	3541(1)	4986(1)	43(1)
C(30)	1978(2)	4709(1)	4365(1)	46(1)
C(36)	1772(2)	3404(1)	6776(1)	43(1)
C(50)	3766(2)	4451(1)	8707(1)	50(1)
C(27)	4525(2)	3044(1)	6232(1)	44(1)
C(37)	1590(2)	3025(1)	7468(1)	45(1)
C(18)	6851(2)	3406(1)	7783(1)	50(1)
C(46)	2066(2)	4855(1)	7531(1)	49(1)
C(12)	7376(2)	3387(1)	6417(1)	51(1)
C(1)	7194(2)	4810(1)	7845(1)	49(1)
C(22)	4632(2)	3026(1)	4561(1)	50(1)
C(25)	4418(2)	2525(1)	5826(1)	51(1)
C(38)	1555(2)	2435(1)	7317(1)	52(1)
C(32)	-996(2)	4103(1)	4329(2)	66(1)
C(7)	5480(2)	5649(1)	7637(1)	57(1)
C(24)	4465(2)	2528(1)	4992(1)	57(1)
C(49)	3245(2)	4988(1)	8773(1)	63(1)
C(6)	7030(2)	5231(1)	8430(1)	59(1)
C(16)	7581(2)	2941(1)	7975(1)	60(1)
C(47)	2410(2)	5201(1)	8195(2)	60(1)
C(44)	1422(2)	3208(1)	8251(1)	57(1)
C(2)	8318(2)	4558(1)	7841(2)	67(1)
C(13)	8098(2)	2914(1)	6588(1)	60(1)
C(51)	4712(2)	4242(1)	9337(1)	70(1)
C(15)	8192(2)	2700(1)	7369(2)	67(1)
C(42)	1276(2)	2819(1)	8871(1)	68(1)
C(23)	4689(3)	3012(1)	3653(1)	74(1)
C(39)	1394(2)	2035(1)	7919(2)	65(1)
C(41)	1276(2)	2238(1)	8691(2)	74(1)
C(26)	4306(3)	1970(1)	6286(2)	80(1)
C(5)	7922(3)	5361(1)	9029(2)	89(1)
C(3)	9220(3)	4711(2)	8428(2)	93(1)

C(14)	8760(3)	2635(2)	5935(2)	95(1)
C(17)	7730(3)	2711(2)	8834(2)	99(1)
C(48)	1897(3)	5797(1)	8264(2)	103(1)
C(4)	9001(3)	5103(2)	9025(2)	107(1)
C(40)	1360(3)	1400(1)	7721(2)	107(1)
C(43)	1159(3)	3033(2)	9722(2)	110(1)

Table 6. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **Compound 118**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
O(001)	2308(2)	6832(1)	3983(1)	52(1)
O(002)	1365(2)	7317(1)	2903(1)	52(1)
O(2)	7501(2)	6750(1)	3755(1)	55(1)
N(2)	3803(2)	7787(1)	3994(1)	36(1)
N(1)	8863(2)	5735(1)	3724(1)	36(1)
O(1)	6900(2)	6721(1)	2641(1)	70(1)
C(11)	9622(2)	5256(1)	3522(1)	34(1)
C(12)	9660(2)	5314(1)	3150(1)	36(1)
C(46)	3581(2)	7907(1)	3245(1)	35(1)
C(57)	4440(2)	8403(1)	3447(1)	35(1)
C(56)	4544(2)	8319(1)	3818(1)	36(1)
C(19)	10432(2)	4694(1)	3730(1)	38(1)
C(54)	2808(2)	7422(1)	3428(1)	38(1)
C(13)	10445(2)	4747(1)	2950(1)	39(1)
C(25)	8764(2)	5639(1)	4114(1)	39(1)
C(58)	5141(2)	9039(1)	3270(1)	39(1)
C(1)	8920(2)	5904(1)	2972(1)	40(1)
C(70)	3851(2)	7725(1)	4389(1)	40(1)
C(47)	3482(2)	7858(1)	2842(1)	39(1)
C(64)	5469(2)	8764(1)	4052(1)	41(1)
C(32)	7275(2)	4501(1)	4024(1)	40(1)
C(31)	8012(2)	5059(1)	4255(1)	41(1)
C(55)	2917(2)	7311(1)	3814(1)	39(1)
C(10)	8123(2)	6315(1)	3563(1)	41(1)
C(9)	8163(2)	6359(1)	3176(1)	42(1)
C(76)	3230(2)	8258(1)	4602(1)	42(1)
C(40)	6446(2)	4811(1)	3722(1)	42(1)
C(34)	6706(3)	3103(1)	3947(1)	46(1)
C(77)	2512(3)	8924(1)	4452(1)	44(1)
C(45)	6585(2)	4564(1)	3365(1)	45(1)
C(26)	9452(3)	6136(1)	4338(1)	48(1)
C(24)	11467(2)	4943(2)	3947(1)	47(1)
C(52)	2356(3)	7549(1)	2686(1)	44(1)
C(85)	1593(2)	8809(1)	4136(1)	45(1)
C(48)	4463(3)	8047(1)	2608(1)	49(1)
C(33)	7402(3)	3760(1)	4101(1)	48(1)
C(14)	11776(2)	4714(1)	3001(1)	46(1)
C(53)	1827(3)	6948(1)	3229(1)	47(1)
C(2)	8913(3)	6062(1)	2573(1)	46(1)
C(20)	10234(3)	3923(1)	3686(1)	48(1)
C(59)	4441(3)	9608(1)	3093(1)	50(1)
C(71)	4515(3)	7120(1)	4541(1)	51(1)
C(63)	6474(3)	9100(2)	3288(1)	51(1)
C(65)	5322(3)	9537(2)	4099(1)	51(1)
C(27)	9418(3)	6078(2)	4712(1)	57(1)
C(69)	6523(3)	8406(2)	4217(1)	55(1)
C(78)	2729(3)	9601(1)	4606(1)	54(1)
C(7)	7861(3)	6463(2)	2425(1)	57(1)
C(30)	7987(3)	5007(2)	4634(1)	57(1)
C(18)	9849(3)	4210(2)	2727(1)	53(1)
C(90)	1672(3)	9244(2)	3821(1)	55(1)
C(39)	5416(3)	3123(2)	3835(1)	55(1)
C(51)	2177(3)	7484(2)	2313(1)	57(1)
C(3)	9875(3)	5854(2)	2334(1)	57(1)
C(75)	3345(3)	8149(2)	4979(1)	58(1)
C(44)	5863(3)	4892(2)	3083(1)	58(1)
C(79)	2059(3)	10326(2)	4539(1)	60(1)
C(86)	645(3)	8257(2)	4147(1)	57(1)

C(15)	12491(3)	4163(2)	2835(1)	61(1)
C(49)	4302(3)	7963(2)	2236(1)	59(1)
C(72)	4614(3)	7024(2)	4915(1)	59(1)
C(23)	12277(3)	4428(2)	4120(1)	62(1)
C(60)	5061(3)	10219(2)	2938(1)	62(1)
C(8)	7331(3)	6952(2)	2997(1)	62(1)
C(35)	7337(3)	2409(2)	3936(1)	62(1)
C(29)	8676(3)	5505(2)	4856(1)	64(1)
C(21)	11053(3)	3411(2)	3859(1)	64(1)
C(74)	4024(3)	7556(2)	5130(1)	65(1)
C(50)	3155(3)	7695(2)	2090(1)	64(1)
C(17)	10582(3)	3652(2)	2561(1)	68(1)
C(41)	5546(3)	5368(2)	3788(1)	61(1)
C(61)	6384(4)	10270(2)	2962(1)	70(1)
C(66)	6194(3)	9942(2)	4314(1)	67(1)
C(62)	7093(3)	9711(2)	3136(1)	67(1)
C(22)	12066(3)	3667(2)	4077(1)	69(1)
C(43)	4985(3)	5450(2)	3153(1)	70(1)
C(16)	11897(3)	3632(2)	2619(1)	72(1)
C(38)	4784(3)	2471(2)	3719(1)	71(1)
C(67)	7214(3)	9586(2)	4480(1)	76(1)
C(87)	-197(3)	8144(2)	3849(1)	68(1)
C(89)	847(3)	9117(2)	3526(1)	68(1)
C(68)	7395(3)	8820(2)	4433(1)	72(1)
C(4)	9745(4)	6005(2)	1964(1)	74(1)
C(88)	-86(3)	8568(2)	3540(1)	72(1)
C(36)	6703(4)	1761(2)	3813(1)	80(1)
C(37)	5431(4)	1793(2)	3706(1)	82(1)
C(42)	4817(3)	5676(2)	3505(1)	77(1)
C(6)	7722(4)	6594(2)	2054(1)	79(1)
C(5)	8662(4)	6359(2)	1826(1)	86(1)
C(84)	744(4)	10373(2)	4463(1)	86(1)
C(73)	5348(4)	6358(2)	5079(1)	93(1)
C(28)	10180(4)	6621(2)	4954(1)	92(1)
C(80)	2739(4)	10991(2)	4578(1)	90(1)
C(82)	837(6)	11720(2)	4455(1)	112(2)
C(81)	2125(6)	11685(2)	4536(1)	117(2)
C(83)	147(5)	11068(2)	4420(1)	108(1)

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