C3 FUNCTIONALIZATION OF 2-OXINDOLE TOWARDS DRUGS AND NATURAL PRODUCTS USING METAL AND METAL-FREE APPROACHES

A THESIS

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BY

GIRISH SINGH BISHT

(ID: 20142009)

UNDER THE SUPERVISION OF Dr. BOOPATHY GNANAPRAKASAM

AT

DEPARTMENT OF CHEMISTRY
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This Thesis is Dedicated to My Family, Teachers, and Friends

CERTIFICATE

This is to certify that the work incorporated in this thesis entitled *"C3 Functionalization of 2-Oxindole Towards Drugs and Natural Products Using Metal and Metal-Free Approaches"* submitted by Girish Singh Bisht has been carried out by the candidate, under my supervision at Indian Institute of Science Education and Research, Pune. The work presented in this thesis or any part of it has not been included in any other thesis submitted previously for the award of any degree or diploma from any other university or institution.

Date: 4/12/2020

Place: Pune

Research Supervisor

Dr. Boopathy Gnanaprakasam

Email: gnanaprakasam@iiserpune.ac.in

DECLARATION

I hereby declare that the written submission represents my ideas in my own words and wherever other's ideas have been included, I have adequately cited and referenced the original sources. I also declare that I have adhered to all principles of academic honesty and integrity and have not misrepresented or fabricated or falsified any idea/data/fact/source in my submission. I understand that the violation of the above will cause for disciplinary action by the institute and also evoke penal action from the sources which have thus not been properly cited or from whom proper permission has not been taken when needed.

Girish Bisht

Date: 4/12/2020

Girish Singh Bisht

ID. 20142009

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Girish Singh Bisht

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List of Abbreviation

Ac	Acetyl
AD	Acceptorless dehydrogenation
AcOH	Acetic acid
ACN	Acetonitrile
Ar	Aryl
Atm	Atmospheric
ATR	Attenuated total reflection
Aq	Aqueous
BH	Borrowing hydrogen
Bn	Benzyl
BPY	2,2'-Bipyridine
Bs	Broad singlet
Bu	Butyl
BuLi	Butyllithium
Calcd.	Calculated
Cat.	Catalytic
CCDC	Cambridge crystallographic data centre
Conc.	Concentrated
^{o}C	Degree Celsius
δ	Chemical shift in ppm
d	Doublet in NMR
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
dba	Dibenzylideneacetone
DCM	Dichloromethane
DCE	Dichloroethane
DEPT	Distortionless enhancement by polarization transfer
DMF	*N, N*-Dimethyl formamide
DMSO	Dimethyl sulfoxide
DMA	*N,N*-Dimethylacetamide
Dppf	1,1'-Bis(diphenylphosphino)ferrocene
ee	Enantiomeric excess
EI	Electron impact
EtOAc	Ethyl acetate
Equiv.	Equivalent
ESI TOF	Electrospray ionization time-of-flight
FTIR	Fourier-transform infrared spectroscopy

g	Grams
GC	Gas chromatography
GC-MS	Gas chromatography-mass spectrometry
Hrs	Hours
Hz	Hertz
HRMS	High-resolution mass spectroscopy
IC_{50}	The half maximal inhibitory concentration
IR	Infra-red
J	Coupling constant in NMR
L	Liter
LDA	Lithium diisopropylamide
$LiAlH_4$	Lithium aluminium hydride
M	Molar (mol L^{-1})
m/z	Mass to charge ratio
Me	Methyl
m	Multiplet in NMR
mg	Milligram
min	Minutes
mL	Millilitre
mmol	Millimoles
MS	Mass spectroscopy
NBS	*N*-bromosuccinimide
NMR	Nuclear magnetic resonance
Nu	Nucleophile
NHC	*N*-heterocyclic carbene
Pd/C	Palladium on carbon
p	Pentet in NMR
ppm	Parts per million
q	Quartet in NMR
s	Singlet in NMR
Temp	Temperature
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TMS	Tetramethylsilane
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
Ts	*p*-toluenesulfonyl (tosyl)
UV	Ultraviolet-visible spectroscopy
X	Halides

PREFACE

2-Oxindole is an important scaffold in various drugs, pharmaceutical and natural products. Due to their wide range of bioactivity and synthetic application, these derivatives have received significant attention among biologists and synthetic chemists. Biological activities of oxindole derivatives includes, anti-cancer, antiviral, Aurora B Inhibitor, anti-oxidant, neuroprotective agent, treatment of idiopathic pulmonary fibrosis (IPF), and antimicrobial etc. In these derivatives 2-oxindole is often connected to another partner at C-3 position *via* C−C, C=C, C−N, and C−O bond. Consequently, the functionalization of 2-oxindole at C3 position *via* catalytic/non-catalytic method is important in organic synthesis. In this context, the present research analysis of my thesis focus on domino C−C and C−O bond formation reaction of cyclic amides *i.e.* 2-oxindole, C=C bond formation *via* acceptorless dehydrogenation, metal-free synthesis of Z-3-(aminobenzylidene/aminoalkylidene)indolin-2-ones derivatives and synthesis of quaternary spirooxindole *2H*-azirines derivatives under batch and continuous flow.

In this thesis, we have illustrated the research findings in the establishment of "C3 functionalization of 2-oxindole towards drugs and natural products using metal and metal-free approaches". All the research outcomes are divided into five chapters.

Chapter 1: Introduction to C3 Functionalization of 2-Oxindole using Different Approaches

At the outset, a summary of various C3 substituted oxindole is described. We have discussed different types of transformations on its various positions. A detailed description of its reactive position is provided. Further, the strategy used to get functionalized oxindole derivatives is demonstrated. In Addition, selected examples for various C3 substituted oxindole *via* metal and metal-free approaches are presented.

Chapter 2: One-Pot Ru-NHC Catalyzed C−H Alkylation and Base Mediated Aerobic C−H Hydroxylation

In this chapter, we have developed the Ru-NHC catalyzed direct α-alkylation of unactivated amides and one-pot hydroxylation of 2-oxindole/1-tetralone derivatives using alcohol as a coupling partner. Chapter 2 is further divided into two segments. Section 2A describes an efficient method for direct α-alkylation of amides using alcohol and subsequent hydroxylation. In this chapter, various Ru catalysts and other reaction conditions were

examined for this transformation, and resulted; Ru-NHC catalyst was excellent for this transformation. Later, in section 2B, synthetic studies toward the total synthesis of hydroxy oxindole based natural product Arundaphine using borrowing hydrogen concept is presented. In this section, we have synthesized two synthons in 18 and 43% yields respectively. In addition, optimization of the final step is under progress in our laboratory.

Chapter 3: Ru-Catalyzed Direct Synthesis of Antimalarial Bis-Arylideneoxindoles from 2-Oxindole and Diaryl Methanols

In this chapter we have demonstrated Ru-NHC catalyzes olefination of 2-oxindoles by using diaryl methanols in the absence of an acceptor. Extensive screening of solvent, base and catalyst has been presented. Several diaryl methanol derivatives undergoes dehydrogenative coupling with 2-oxindole and its derivatives selectively to generate various substituted 3-(diphenylmethylene)indolin-2-one compounds in good yields and generate environmentally benign and valuable by-products namely, H_2 and H_2O. Moreover, by using this method we successfully prepared a bioactive drug *i.e.* TAS-301. A detailed experiment-based mechanism was reported for this transformation. To confirm the mechanism, we detected the dissociated ligand, hydride intermediate by using NMR spectroscopy and liberation of molecular hydrogen was confirmed by GC analysis. Besides, the biological activities of the 3-(diphenylmethylene)indolin-2-one derivatives were tested against the Plasmodium falciparum parasite and found to exhibit a significant activity with IC_{50} = 2.24 μM.

Chapter 4: Transition-Metal-Free Addition Reaction of 2-Oxindole to Nitrile: A Synthetic Application towards Fluorination and C=C Cleavage

In this chapter, we have developed a novel, elegant, efficient and transition-metal-free approach for the synthesis of Z-3-(aminobenzylidene/aminoalkylidene)indolin-2-ones derivatives in good to excellent yield from feedstock chemicals 2-oxindole and nitrile derivatives in the conjunction of LiO*t*Bu and 2,2'-bipyridine base-ligand system. In synthetic application of synthesized compounds we have demonstrated an additive and base-free method for the synthesis of 3-substituted-3-fluoro-2-oxindole derivatives by using selectfluor. In addition, we have demonstrated oxidative cleavage of C=C bond by using CuI and environmentally benign O_2 as an oxidant. Furthermore, the free amine group was functionalized *via* Cu-catalyzed Ullmann coupling.

Chapter 5: Synthesis of Quaternary Spirooxindole *2H*-Azirines Derivatives under Batch and Continuous Flow and its Synthetic Application towards Ring-Opening Reaction

In the final chapter, we have demonstrated a simple, and efficient method for the synthesis of spirooxindole *2H*-azirines *via* intramolecular oxidative cyclization of 3-(amino(phenyl)methylene)-indolin-2-one derivatives in the presence of I_2 and Cs_2CO_3. This method was also successfully transformed in continuous flow and respective azirine derivatives have been synthesized in a shorter duration. This method is mild and facile to synthesize a variety of spirooxindole *2H*-azirines derivatives in good to excellent yield.. To our delight, this transformation proceeds well in large scale in batch for the generation of spirooxindole *2H*-azirine. Furthermore, we have synthesized spiroaziridine by using Grignard reagent. Interestingly, in presence of additive formation of ring-opening product *N*-substituted 3-(aminobenzylidene)indolin-2-ones was observed.

LIST OF PUBLICATIONS

(1) **Bisht, G. S.;** Chaudhari, M. B.; Gupte, V. S.; Gnanaprakasam, B. Ru-NHC Catalysed Domino Reaction of Carbonyl Compounds and Alcohols: A Short Synthesis of Donaxaridine. *ACS Omega* **2017**, *2*, 8234-8252.

(2) **Bisht, G. S.;** Pandey, A. M.; Chaudhari, M. B.; Agalave, S. G.; Kanyal, A.; Karmodiya, K.; Gnanaprakasam, B. Ru-Catalyzed Dehydrogenative Synthesis of Antimalarial Arylidene Oxindoles. *Org. Biomol. Chem.* **2018,** *16*, 7223-7229.

(3) **Bisht, G. S.;** Gnanaprakasam, B. Transition-Metal-Free Addition Reaction for the Synthesis of 3-(Aminobenzylidene/aminoalkylidene)indolin-2-ones and Its Synthetic Applications. *J. Org. Chem.* **2019,** *84*, 13527-13527.

(4) **Bisht, G. S.;** Dunchu, D. T.; Gnanaprakasam, B. Continuous-Flow Synthesis of Quaternary Spirooxindole *2H*-azirines *via* Intramolecular Oxidative Cyclization and Its Synthetic Application Manuscript communicated.

(5) Chaudhari, M. B.; **Bisht, G. S.;** Kumari, P.; Gnanaprakasam, B. Ruthenium-Catalyzed Direct α-Alkylation of Amides Using Alcohols. *Org. Biomol. Chem.* **2016**, *14*, 9215-9220.

(6) Chaudhari, M. B.; Moorthy S.; Patil, S.; **Bisht, G. S.;** Haneef, M.; Gnanaprakasam, B. Iron-Catalyzed Batch/Continuous Flow C-H Functionalization Module for the Synthesis of Anticancer Peroxides. *J. Org. Chem.* **2018**, *83*, 1358-1368.

(7) Agalave, S. G.; Chaudhari, M. B.; **Bisht, G. S.;** Gnanaprakasam, B. Additive Free Fe-Catalyzed Conversion of Nitro to Aldehyde under Continuous Flow Module. *ACS Sustainable Chem. Eng*. **2018**, *6*, 12845-12854.

Chapter 1

Introduction to C3 Functionalization of 2-Oxindole using Different Approaches

Introduction to C3 Functionalization of 2-Oxindole using Different Approaches

1.1. Abstract

2-Oxindole and its derivatives possessing heterocyclic ring represent the basic scaffold in many biologically active alkaloids and drugs. This thesis describes new approaches for the synthesis of C3-functionalized 2-oxindole towards natural products and biologically active compounds *via* C−C, C=C, and C−N bond formation. In this general introduction, a summary of the various synthetic approaches for the functionalization of 2-oxindole derivatives has been outlined. At first, the general chemical properties of 2-oxindole molecules such as molecular properties, natural abundance, and reactivity with various electrophiles or nucleophiles have been described. Subsequently, various chemical transformations for the functionalization of different positions in 2-oxindole have been presented. Further, selected literature reports for various C−C, C−O, C−N, C−X, and C−S bond-forming reactions using metal-catalyst or metal-free conditions have been presented. Finally, the synthetic development required in this area has been discussed. After having the detailed literature accounts on the C3-functionalization, the rationale and objective of the research work will be presented at the end of this chapter.

1.2. Introduction to 2-oxindole and its properties

Indole alkaloids are heterocyclic compounds having indole in their core. In this context, Indolin-2-one or 2-oxindole could be categorized as a subclass of indole alkaloid.

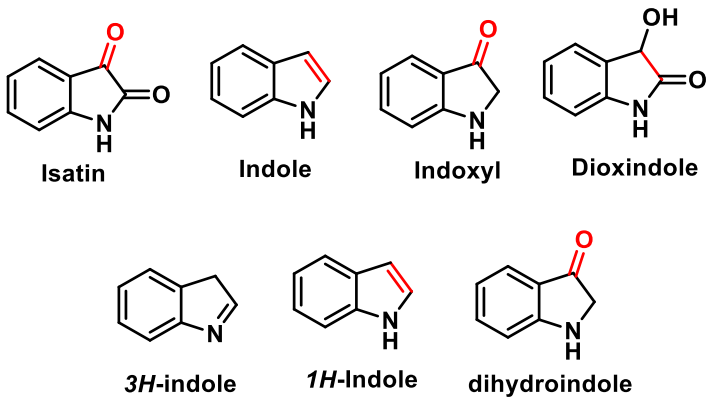


Figure 1.1. Examples of the oxidized and reduced form of indole and its isomers

The structure of 2-oxindole comprises of a benzene ring fused with a pyrrole ring having a carbonyl group at the second position. The chemical formula of oxindole is C_8H_7NO and the molecular weight is 133.05 gm/mol. 2-oxindole can be converted to other oxidized or reduced forms to afford other moieties such as isatin or indole (Figure 1.1). Additionally, isatin and indole derived compounds are starting materials in many synthetic transformations for the synthesis of alkaloids and drugs.[1] First four naturally occurring 2-oxindole alkaloids were initially isolated from the root of the plant *Gelsemium sempervirens*.[2] Later various other derivatives were isolated from the tropical Cat's claw plant *Uncaria tomentosa*, flowering plant *Kartom*, *Mitragyna*, *Rauwolfia*, and *Vinca*.[3] Some representative examples of 2-oxindole alkaloid isolated from various natural sources are shown in figure 1.2.

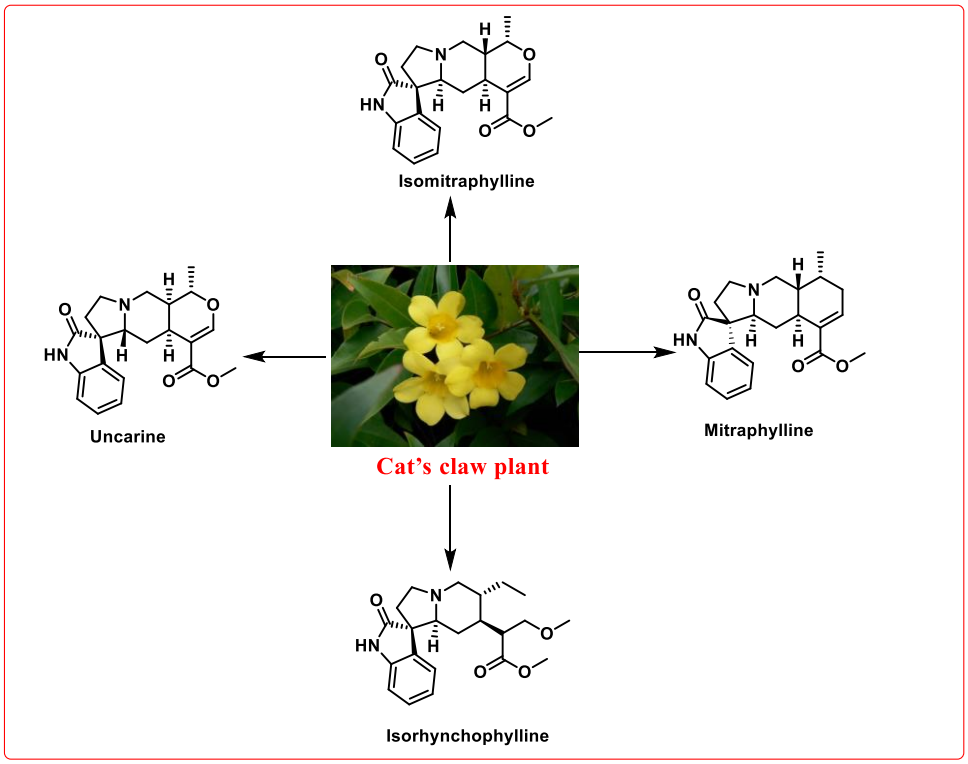
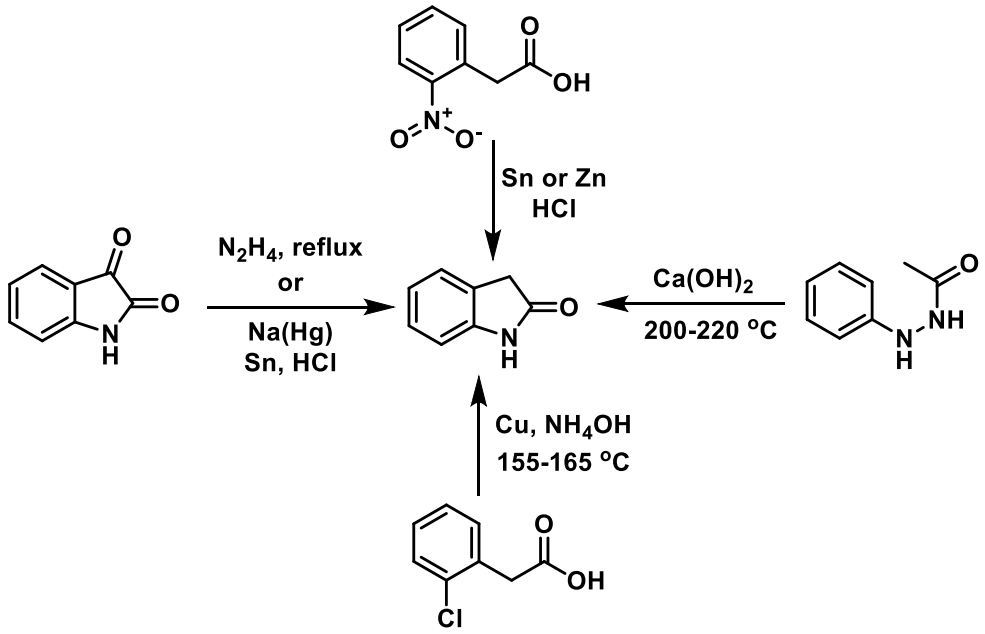


Figure 1.2. 2-Oxindole derivatives isolated from Cat's claw plant

In literature, many diversified methods are available for the synthesis of 2-oxindole. In this regard, the pioneering method for the synthesis of 2-oxindole was developed by Baeyer and Knop group in 1866 by the reduction of isatin using hydrazine hydrate. Later, the same group developed an additional route *via* the reduction of 2-nitrophenylacetic acid with Sn and hydrochloric acid. Later, Brunner and co-workers synthesized 2-oxindole by heating *N'*-phenylacetohydrazide in the presence of calcium hydroxide at a high temperature. In 1952, 2-oxindole was

synthesized by heating 2-(2-chlorophenyl)acetic acid, copper powder, and ammonium hydroxide at 155 ^{o}C in a sealed tube (Scheme 1.1).[4]



Scheme 1.1. Few of the pioneering approaches for the preparation of 2-oxindole

1.3. Reactive sites on 2-oxindole

As presented in figure 1.3, 2-oxindole has mainly four reactive positions, i) aromatic ring, ii) nitrogen atom, iii) carbonyl position, and iv) C3 position. Delocalization of the lone pair of electron from nitrogen to the benzene ring of oxindole results in electrophilic aromatic substitution reaction at the aromatic position.

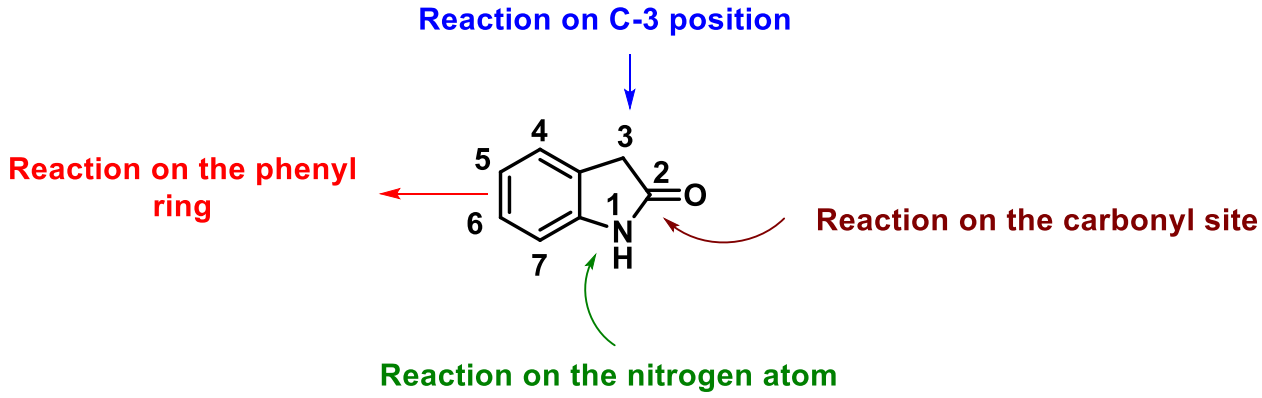


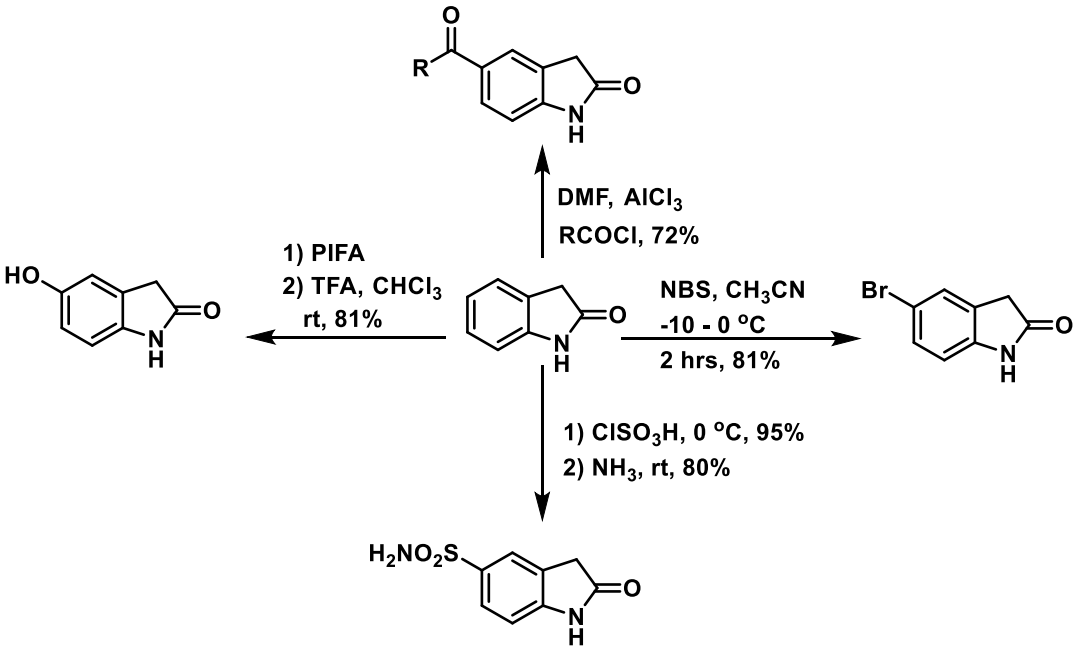
Figure 1.3. Four different reactive positions of 2-oxindole

Similarly, the lone pair of electrons on the nitrogen atom can act as a nucleophile and can undergo several nucleophilic substitution and addition reactions.[5] The pK_a of the

hydrogen at the C3 position of 2-oxindole is 18.5.[6] Therefore, bases such as isopropoxide, *tert*-butoxide, *NaH*, and KOH *etc.* can abstract the proton leading to the availability of a nucleophile for alkylation and olefination reactions.[7, 19]

1.3.1. Reaction on the aromatic position of 2-oxindole

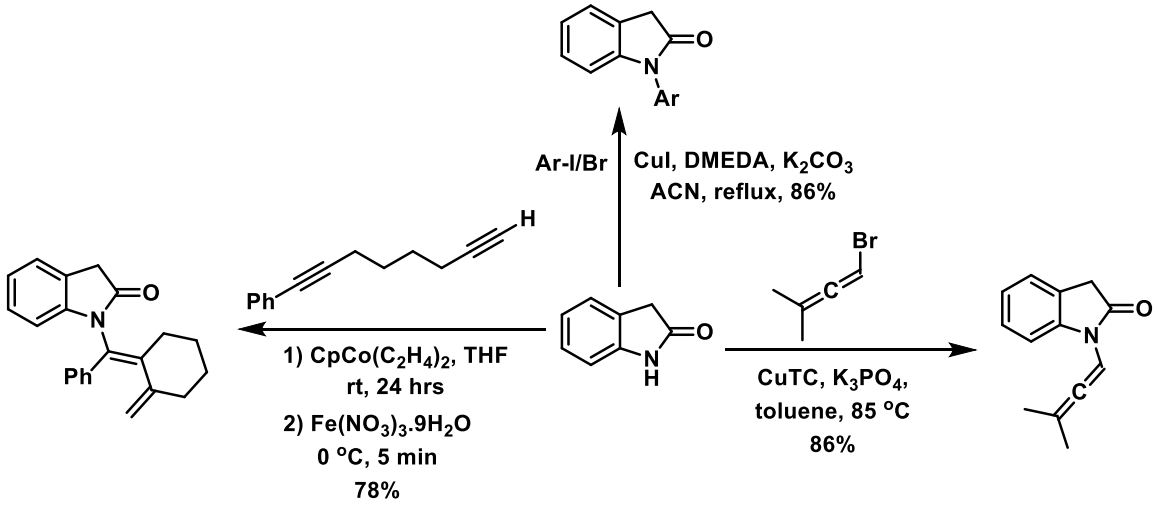
The aromatic position of 2-oxindole is known for its reactions with an electrophile. For instance, 2-oxindole can react with halogen derivatives to generate respective mono, di, and trihalogen substituted 2-oxindole derivatives under different reaction conditions.[8a] Further, it can undergo an alkylation/acylation reaction on the aromatic position.[8b] In 2002, Kikugawa and co-workers reported the addition of a hydroxyl group on the aromatic ring of 2-oxindole under acidic conditions.[9] On the other hand, Laing's research group developed a method for the synthesis of 2-oxoindoline-5-sulfonamide by using ammonia and chlorosulfonic acid (Scheme 1.2).[10]



Scheme 1.2. State-of-the-art of reaction on the aromatic position of 2-oxindole

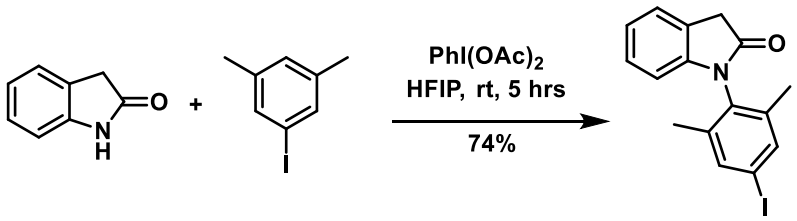
1.3.2. Reaction on the nitrogen atom of 2-oxindole

The nitrogen atom of 2-oxindole usually acts as a nucleophile and gives rise to nucleophilic substitution reactions with halides, anhydrides, acid chloride *etc.* Also, in regards to metal-mediated reactions, the N atom can undergo several coupling reactions with various coupling partners under different reaction conditions to generate *N*-substituted 2-oxindole products (Scheme 1.3).[11]



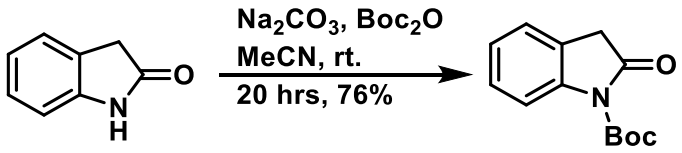
Scheme 1.3. Various reactions on the nitrogen atom of 2-oxindole using metal-catalysts

In literature, several reports are available on the reaction of the nitrogen atom with an alkyl halide, anhydride or, activated alcohol under metal-free conditions to generate the respective *N*-substituted product. In this context, in 2011, Antonchick research group developed a cross-amination reaction of 2-oxindole and unactivated arene under metal-free conditions by using (Diacetoxyiodo)benzene to generate *N*-phenyl derivatives of oxindole (Scheme 1.4).[12]



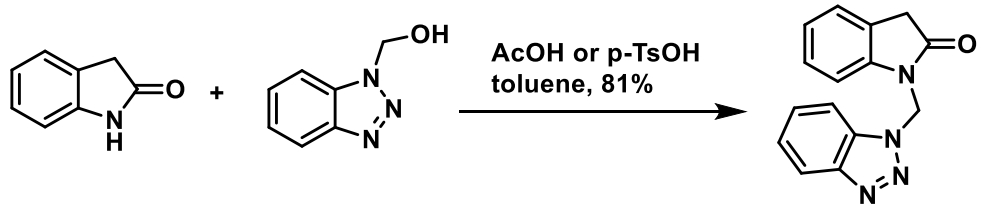
Scheme 1.4. Antonchick's approach for the *N*-protection of 2-oxindole

Moreover, the protection of free *N*−H of 2-oxindole was performed by Rajeswaran and co-workers to generate the respective *N*-substituted oxindole derivatives (Scheme 1.5).[13]



Scheme 1.5. Rajeswaran's method for the *N*-protection of 2-oxindole

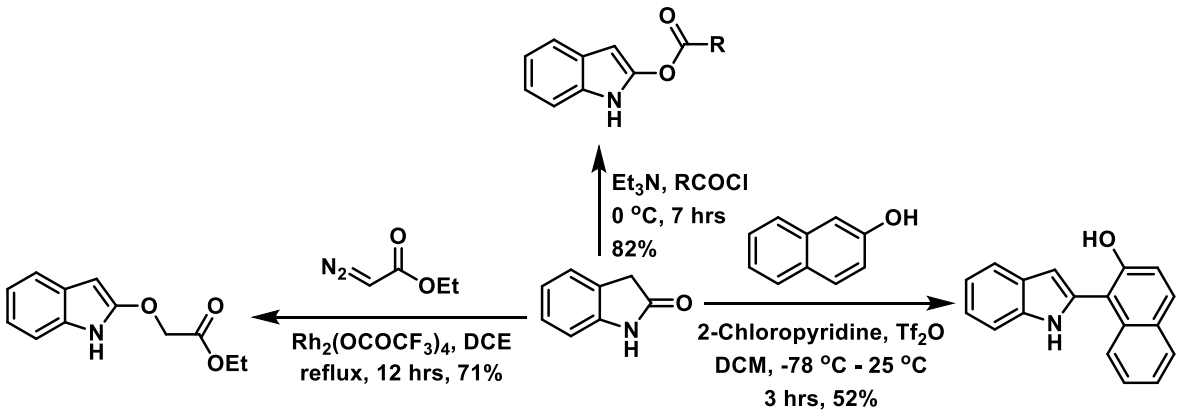
Later in 1993, Katritzky and co-workers developed the synthesis of tertiary amides by the reaction of 2-oxindole with (1H-benzo[d][1,2,3]triazol-1-yl)methanol under acidic conditions (Scheme 1.6).[14]



Scheme 1.6. Katritzky's strategy for the generation of *N*-substituted oxindole

1.3.3. Reaction on the carbonyl carbon/oxygen atom of 2-oxindole

The carbonyl site of 2-oxindole has two reactive positions, namely the carbon and oxygen atoms. Based on the reaction conditions, 2-oxindole can generate the respective C or O substituted 2-oxindole derivative. In 2000, Corey and co-workers reported the Rh-catalysed synthesis of enol ether by using 2-oxindole and diazoacetic ester.[15] Later in 2002, Yamada and co-workers developed a method for the O-acylation of 2-oxindole in the presence of acid chloride and triethylamine under mild reaction conditions.[16] Similarly, in 2011, Ghandi's research group reported the synthesis of 1-(*1H*-indol-2-yl)naphthalene-2-ol by the reaction 2-oxindole and 2-naphthol in the presence of triflic anhydride and 2-chloropyridine (Scheme 1.7).[17]



Scheme 1.7. Various reactions on the carbonyl position of 2-oxindole

1.4. Classification of the transformations at the C3 position of 2-oxindole

Transformations at the C3 position of 2-oxindole have been widely investigated in the literature. Moreover, C3 substituted derivatives are key synthons for the generation of numerous 2-oxindole based drugs and natural products.[18] A plethora of reports are available on the C3 functionalization of 2-oxindole. On the basis of atom

attached at the C3 position, based on the literature reports. These are mainly divided into four sections (Figure 1.4): **(I)** C−C and C=C bond-forming reactions at C3 position is mainly divided into the categories of condensation reaction, alkylation reaction, and Michael addition reaction. The moderate pKa of the two acidic hydrogens of 2-oxindole at the C3 position leads to the generation of a nucleophile in the presence of a suitable base. The nucleophile can attack various carbonyl compounds, alkyl halides, acyl chloride to generate C=C/C−C bond-forming products.[19] Moreover, in some cases, 2-oxindole undergoes a multicomponent reaction or metal assisted coupling reaction in the presence of alcohols or nitriles as a coupling partner.[20] **(II)** C−O bond-forming reactions - in contrast to the C=C/C−C bond reactions, the C−O bond-forming reactions at the C3 position of 2-oxindole is relatively less documented in the literature.

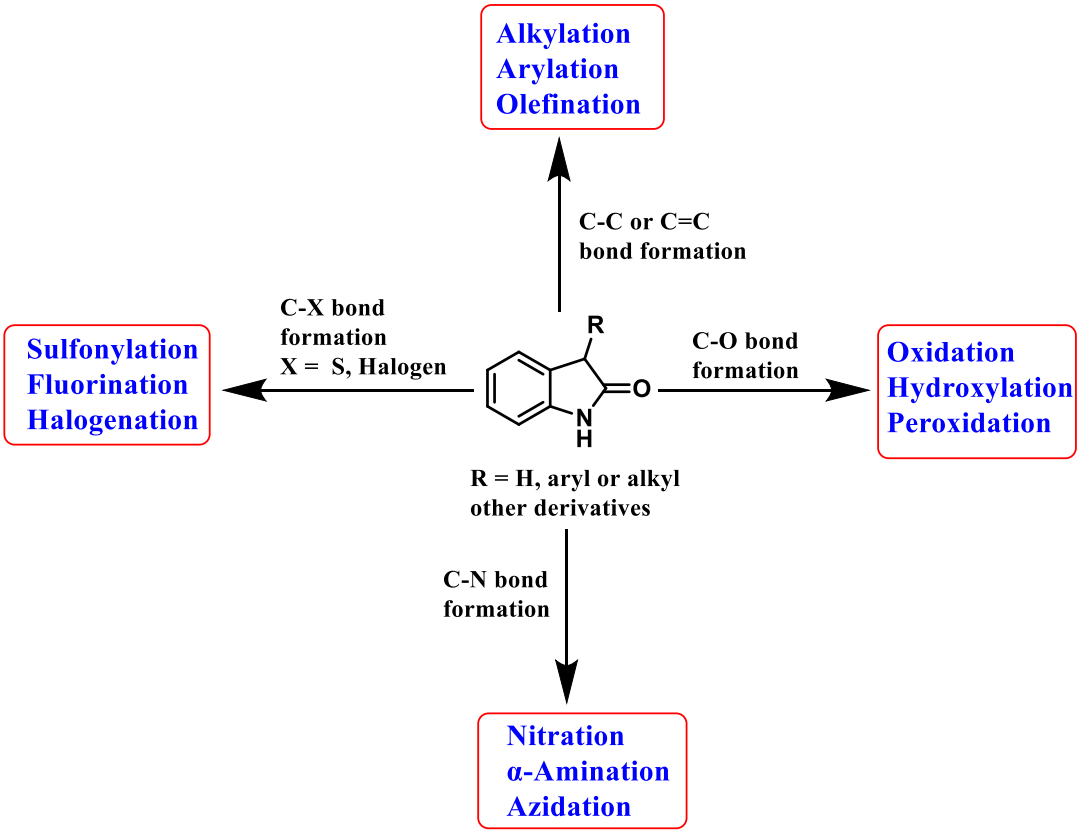


Figure 1.4. General overview on C3 functionalization of 2-oxindole

However, numerous approaches have been reported for the C−H hydroxylation/ peroxidation of 2-oxindole derivatives *via* oxidation chemistry for the generation of a C−O bond at the C3 position.[21] **(III)** C−N bond-forming reactions - the presence of carbon-nitrogen bond is frequently found in the structural units of 2-oxindole based natural products and pharmaceuticals. Hence, the construction of a C−N bond at the C3 position is of considerable significance in organic synthesis. In literature,

generation of C−N bond at C3 position of 2-oxindole can be accomplished through various nitrogen sources such as azide, amine, nitro, and sulphonamides *etc.* Moreover, the method used to get C−N bond at C3 positions of 2-oxindole are nitration, amination, and azidation respectively.[22] **(IV)** C-X bond-forming reaction - formation of C−X bond at C3 position of 2-oxindole derivatives can be subdivided into carbon halogen and C−S bond-forming reactions. Several methods for halogenation and sulfonylation have been reported for the generation of a C−X bond at the C3 position of oxindole.[23]

1.5. Different approaches for the C3 functionalization of 2-oxindole

In academia, numerous well-defined approaches are reported to generate functionalized 2-oxindole derivatives under different reaction conditions. Furthermore, all of these methods can be broadly classified into metal-assisted and metal-free methods (Figure 1.5). **(I)** Metal-mediated methods, in this class well-defined strategies such as borrowing hydrogen, C−H arylation, and C−H activation have been studied in the literature for the generation of C3 substituted 2-oxindole derivatives in the presence of a metal catalyst and the respective coupling partner.

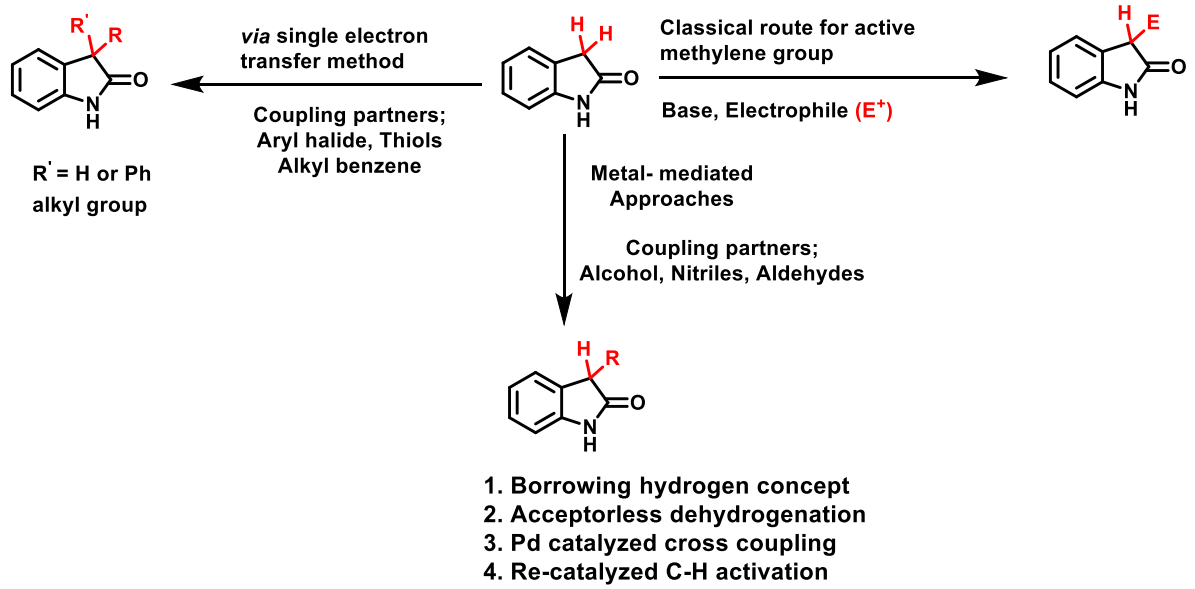


Figure 1.5. Various approaches for the functionalization of 2-oxindole

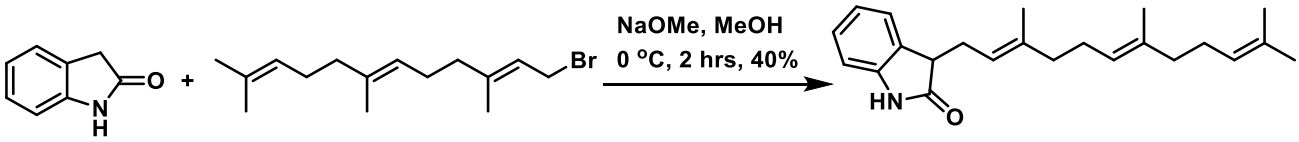
(II) Metal-free methods - this class can be further divided into the classical route wherein 2-oxindole carbanion is generated from 2-oxindole in the presence of base. The carbanion further reacts with various electrophiles to generate the respective functionalized 2-oxindole product. Another metal-free path for the generation of C3 substituted 2-oxindole involves using 2-oxindole and a variety of coupling partners in

the presence of single-electron transfer reagents such as iodine, (diacetoxyiodo)benzene, and organocatalyst. Since it is difficult to summarise the entire literature on the C3 functionalization of 2-oxindole under different reaction conditions, in this section we have focused on the recent important reports related to our studies on oxindole functionalization under metal and metal-free conditions.

1.5.1. C3 Functionalization of 2-oxindole using metal-free approaches

Since the last few decades, transition-metal-free reactions have gained popularity and are very useful in organic synthesis due to various advantages. In metal-assisted reactions, one of the major challenges is the separation of trace metal from the product. Owing to the toxicity of some metals, the use of transition metals for the synthesis of pharmaceuticals is not safe. Additionally, transition-metal catalysts are expensive and some reactions require stabilizing coordinating ligands that can sometimes add to the cost. Most of the transition metals are sensitive to air/moisture. In addition, some of the transition metal assisted reactions require additives and co-catalysts, which is not an atom-economical process.[24] Hence, the development of transition metal-free processes is immensely valuable in organic synthesis. In context to 2-oxindole functionalization, several methods for the construction of C−C, C−O, C−S, and C−X bonds have been developed under transition metal-free conditions. Based on the literature survey and the reaction mechanisms, these methods can be divided into the following categories. 1) Classical electrophilic/nucleophilic pathway. 2) SET pathway. 3) Organocatalysis pathway.[25]

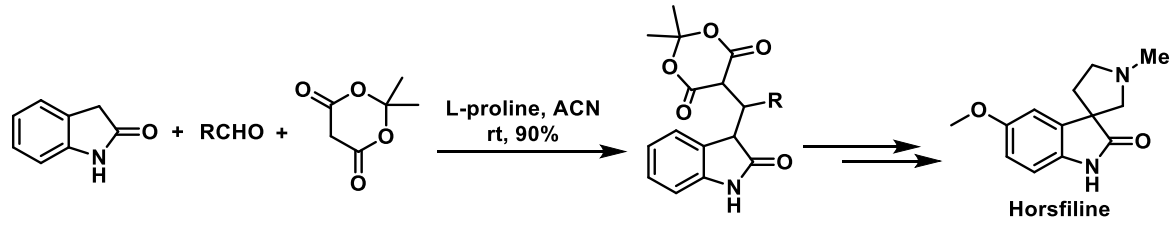
In 1985, Catherine group reported synthesis of 3-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trien-1-yl)indolin-2-one. Further, this intermediate was used for the generation of indoloterpene alkaloids (Scheme 1.8).[26]



Scheme 1.8. Catherine's method for the synthesis of 3-((2E,6E)-3,7,11 trimethyldodeca-2,6,10-trien-1-yl)indolin-2-one

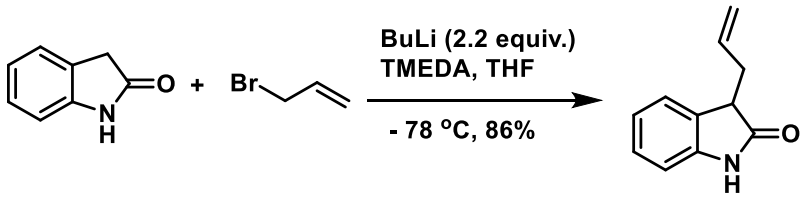
In 2002, Laronge and co-workers developed a one-pot multi-component reaction of benzaldehyde, Meldrum's acid, and 2-oxindole in the presence of L-proline for the generation of C3 substituted 2-oxindole derivative. Further, this intermediate

was used for the synthesis of spiro oxindole based natural product Horsfiline (Scheme 1.8).[27]



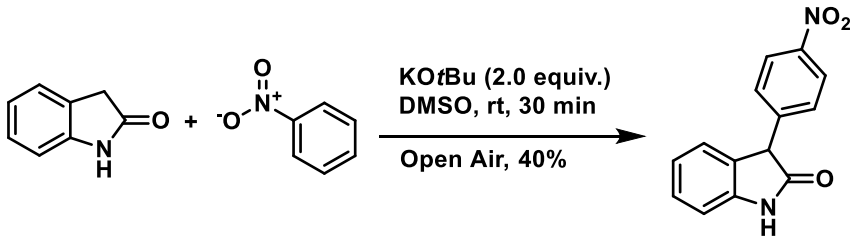
Scheme 1.9. Laronge's approach for the generation of 2-oxindole based trimolecular adduct.

In 2009, Trost and co-workers prepared C3 alkylated oxindole using base and alkyl halide. Further, this compound has been used for the generation of *N*-carbamoyl-3-monosubstituted oxindole derivatives (Scheme 1.10).[28]



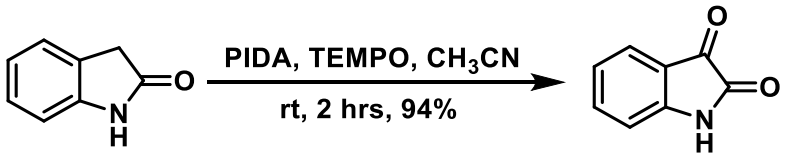
Scheme 1.10. Trost's approach for the C3 arylation of 2-oxindole

In 2018, Gao and co-workers reported a metal-free approach for the C3 arylation of carbonyl compound. This reaction was generalized with various substrates such as amides, nitriles, α-arylated esters, triarylmethane, and sulfone derivatives. This reaction was promoted by excess KO*t*Bu as a base. The report demonstrated the synthesis of more than 60 products with a detailed mechanism using DFT calculations (Scheme 1.11).[29]



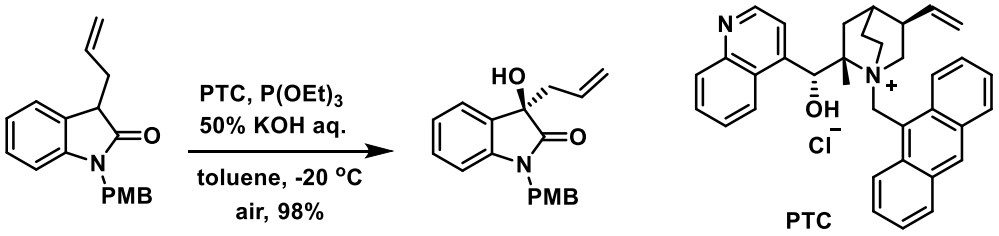
Scheme 1.11. Gao's approach for the C3 arylation of 2-oxindole

Various methods are reported for the direct oxidation of 2-oxindole using metal-free conditions. In this context, Rao and co-workers reported hypervalent iodine/TEMPO mediated oxidation of various 2-oxindole derivatives under mild reaction condition (Scheme 1.12).[30]



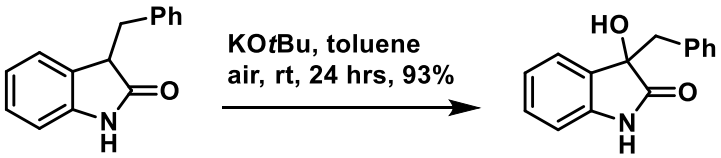
Scheme 1.12. Rao's approach for the synthesis of isatin from 2-oxindole

In 2008, Itoh's research group developed a process for the enantioselective hydroxylation of C3 substituted 2-oxindole by using a chiral ligand in the presence of a base, molecular oxygen, and external reductant triethyl phosphite (Scheme 1.10).[31]



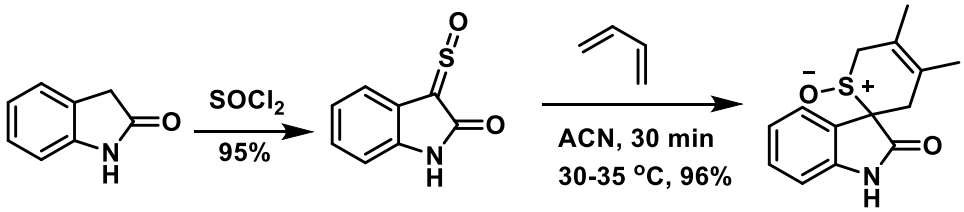
Scheme 1.13. Itoh's approach for the enantioselective hydroxylation of 2-oxindole derivatives

In 2017, our research group developed metal-free C−H hydroxylation of carbonyl compounds using KO*t*Bu. In this method, air has been used as a source of oxygen (Scheme 1.14).[32]



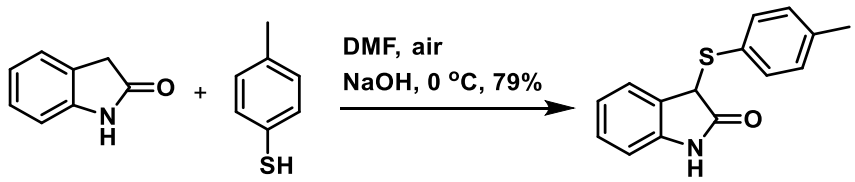
Scheme 1.14. Gnanaprakasam's approach for the hydroxylation of 2-oxindole derivatives

In 2010, Bergman and Romero collectively developed a method for the synthesis of sulfaneylidene 2-oxindole in the presence of thionyl chloride. Further, this product was used in a [3+2] cycloaddition reaction to generate spiro oxindole product (Scheme 1.15).[33]



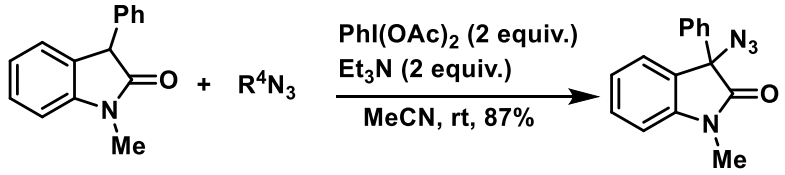
Scheme 1.15. Bergman's approach for the synthesis of sulfaneylidene oxindole

Recently, Feng and co-workers proposed a methodology for the sulfenation of 2-oxindole under transition metal-free conditions, assisted by sodium hydroxide and green atmospheric air as an oxidant. This strategy provided a straightforward method for the construction of C−S bond at the C3 position of 2-oxindole (Scheme 1.16).[34]



Scheme 1.16. Feng's approach for sulfenation of 2-oxindoles

Similarly, in 2018, Wei's research group reported the C−(sp^3)−H azidation of 2-oxindole derivatives by using a substoichiometric amount of triethylamine as a base and (diacetoxyiodo)benzene as a SET source. By using this method, several compounds have been synthesized under mild reaction conditions *via* a SET approach. In this study, the synthetic application of azide derivatives has been investigated towards reduction and cycloaddition reactions (Scheme 1.17).[35]



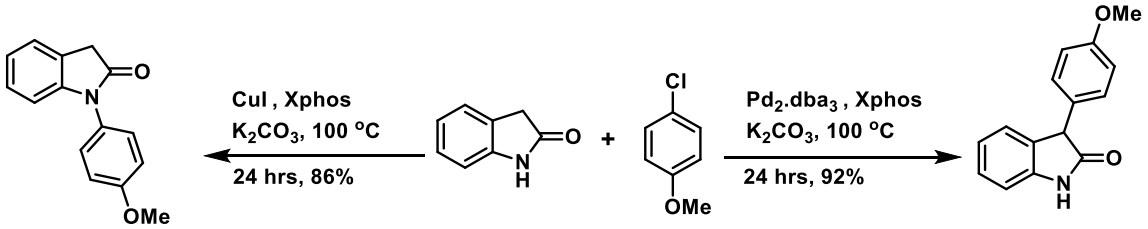
Scheme 1.17. Wei's method for the C3 azidation of 2-oxindole derivatives

1.5.2. C3 Functionalization of 2-oxindole assisted by metal-catalysts

The transition-metal catalyst drives a vast number of transformations in organic synthesis and has been the theme of passionate research in modern synthesis. Metal-assisted reactions gained widespread success towards the construction of challenging organic molecules with atom-economy and less number of steps. Moreover, metal-assisted reactions have been studied since the very beginning of the past century.[36] During the past 50 years, transition-metal assisted reactions have been used as a key step for the synthesis of several natural products, pharmaceutical, and biologically active molecules.[37] Moreover, transition-metal catalyzed reactions have been used as a powerful tool for the late-stage transformations of well-known heterocyclic core indole and its derivatives. Similarly, in the context of transformations at the C3 position of 2-oxindole several metal-assisted methodologies have been used for the construction of C−C, C−N, C−O, and C−X/S bonds in the presence/absence of additives. Moreover, several metal-catalyzed reactions play a crucial role in one of the

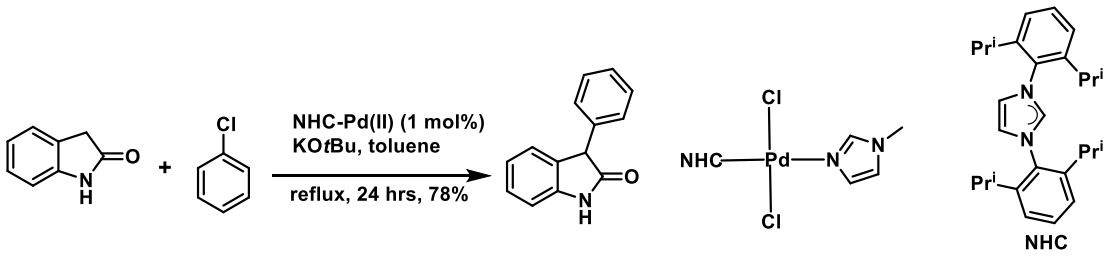
important steps for the synthesis of 2-oxindole based bioactive natural products and drugs. In the past, numerous methodologies have been developed for the synthesis of C3 substituted 2-oxindole using metal as a catalyst. Some of the selected methods pertaining to our studies have been described in this section.

In 2008, Buchwald and co-workers achieved selective coupling of oxindole with aryl halides in the presence of palladium catalyst and phosphine ligand. In this report, Buchwald and co-workers observed C and *N*-arylation of oxindole by switching the catalyst and reaction conditions (Scheme 1.18).[11c]



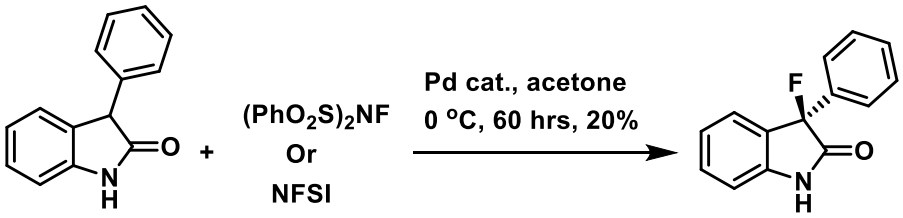
Scheme 1.18. Buchwald's approach for the C3 arylation of 2-oxindole

Similarly, Shao and co-workers did C3 arylation of 2-oxindole with aryl halides in the presence of Pd-NHC catalyst. Furthermore, this arylated product can be converted into hydroxy product under ambient conditions at room temperature in a one-pot (Scheme 1.19).[38]



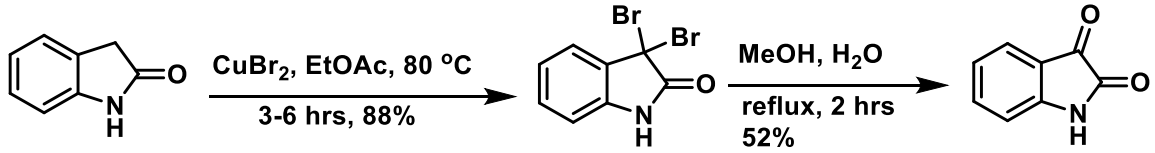
Scheme 1.19. Shao's approach for the C3 arylation of 2-oxindole

In 2005, Sodeoka and co-workers developed an efficient enantioselective C3 fluorination of 2-oxindole. This method has provided several fluorinated derivatives in good to excellent yield in enantioselective fashion (Scheme 1.20).[39]



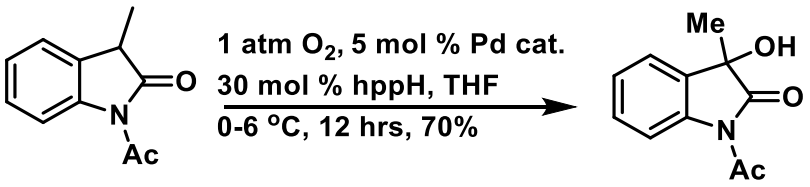
Scheme 1.20. Sodeoka's method for the fluorination of 2-oxindole derivatives

Oxidation is valuable and extensively used transformation in organic synthesis. In context to direct oxidation of 2-oxindole, Kraynack and co-workers developed regiospecific synthesis of substituted isatin derivatives. Several known and unknown derivatives has been synthesized using this method (Scheme 1.21).[40]



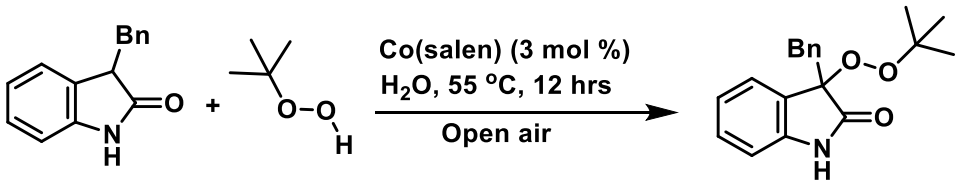
Scheme 1.21. Kraynack's approach for the metal-assisted oxidation of 2-oxindole.

Later in 2011, Ritter and co-workers developed regio- and chemoselective hydroxylation in the presence of molecular oxygen as an oxidant. Several hydroxyl derivatives have been synthesized by using this method and this reaction is considered as the first example of bimetallic binuclear Pd(III)−Pd(III) catalysis (Scheme 1.22).[41]



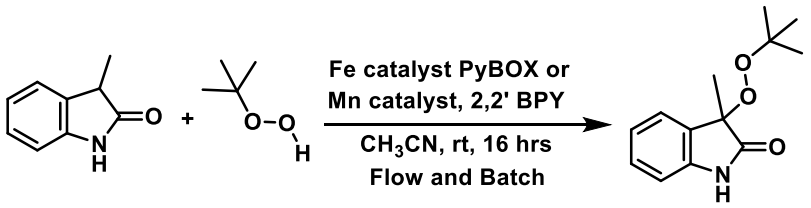
Scheme 1.22. Ritter's approach for the regioselective hydroxylation of 2-oxindole derivatives

To the direct C−O bond formation at C3 position of 2-oxindole, the pioneering work was done by Liu and co-workers. In which they performed Co(salen) complex assisted C-H peroxidation of 2-oxindole in the presence of TBHP (Scheme 1.23).[42]



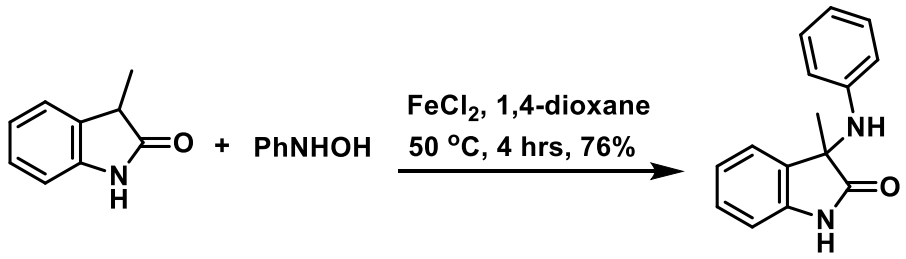
Scheme 1.23. Liu's approach for the peroxidation of 2-oxindole derivatives

Similarly, our group developed a strategy for the peroxidation of 2-oxindole derivatives by using homogeneous and heterogeneous catalysts. Further, our group extended this transformation in continuous flow conditions (Scheme 1.24).[43]



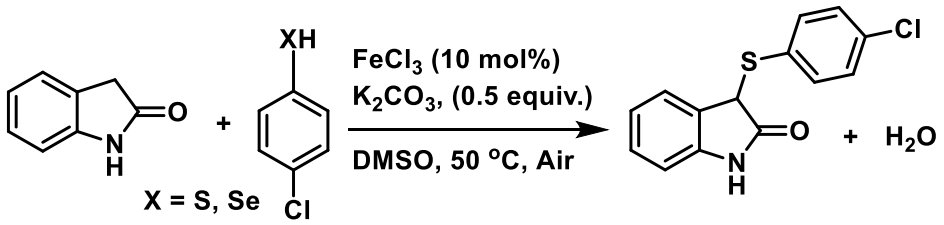
Scheme 1.24. Gnanaprakasam's approach for the peroxidation of 2-oxindole derivatives

In 2015, Srivastava's group disclosed the C−H amination of oxindole by using the iron catalyst ferrous chloride and arylhydroxylamine as a coupling partner. This reaction proceeded in mild conditions and proved to be efficient method to afford α-amino carbonyl compound in excellent yield (Scheme 1.25).[44]



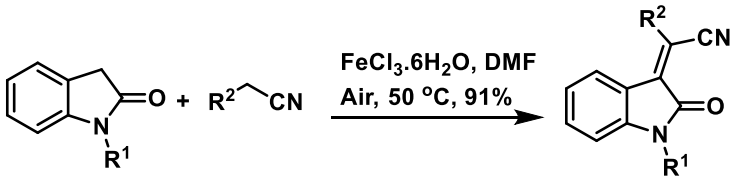
Scheme 1.25. Srivastava's approach for the C3 amination of oxindole

In 2019, Hu research group developed iron-catalyzed cross-dehydrogenative coupling for the generation of C(sp^3)−S/Se bonds at the C3 position of oxindole. The reaction was executed under mild conditions by using air as a green reagent. Moreover, a broad range of substrates including oxindole, pyrazolones, phenylacetonitrile, and phenylacetamide were well coupled with thiols and selenols (Scheme 1.26).[45]



Scheme 1.26. Hu's approach for the coupling of oxindole with thiols/selenols

Recently, Xu and co-workers developed a Fe-catalyzed dehydrogenative coupling for the formation of C−C bond by using oxindole and active methylene groups. This method is mild, ligand and base free, has a good functional group tolerance, and requires inexpensive catalysts (Scheme 1.27).[46]



Scheme 1.27. Xu's approach for the coupling of 2-oxindole with active methylene derivatives.

1.6. Rationale behind the thesis work

In the literature, various methods including metal catalyst and metal-free conditions are reported for the C−C, C−O, C−N, and C−X bond-forming reactions. The coupling partners used during the transformation ranges from an alkyl halide, alcohol, carbonyl compounds, nitriles, nitro *etc*. Besides, the various functionalization of 2-oxindole and C3 substituted 2-oxindole towards the formation of C−C, C−O, C−N, and C−X bond have been extensively studied in the literature. Derivatives of functionalized 2-oxindole are known for their various biological properties and they are key intermediates in the synthesis of various natural products. Various well-known methods have been used to generate C3 substituted oxindole derivatives. However, to generate functionalized 2-oxindole derivatives requires i) the use of toxic reagents such as, halogenated reagents and isocyanates, ii) sensitive catalysts, iii) expensive metal catalysts iv) multi-step synthesis, which limits their utilization in several organic transformations.

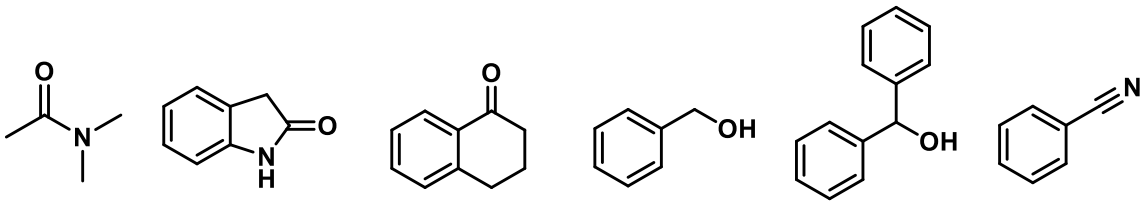


Figure 1.6. Various carbonyl compound and coupling partner for metal/metal-free functionalization reactions in our studies.

In this context, our research group has been focused on developing a mild, efficient, metal-assisted/metal-free, and elegant method for the C3 functionalization of 2-oxindole derivatives. Further our objective is to generalize the protocol with other carbonyl derivatives, to investigate the synthetic application, and transfer the developed method in continuous flow.

1.7. Objectives of our projects

✓ One-pot Ru-NHC catalyzed C−H alkylation and base mediated aerobic C−H hydroxylation

The α-alkylation reaction of carbonyl compounds and the C3 alkylation reaction are valuable in organic synthesis. Hence, many classical methods have been developed for the alkylation reaction of carbonyl compounds to overcome limitations such as, the use of toxic halogen derived alkyl halides as a coupling partner, multistep synthesis, and the use of additives. Owing to the lower Brønsted acidity of the carbonyl compounds, this transformation requires strong bases namely, BuLi, *NaH*, LDA, and $NaNH_2$. However, these bases can generate a sub stoichiometric amount of undesirable waste, which makes it less efficient process. A few of the catalytic methods are reported for the α-alkylation of carbonyl compounds having drawbacks such as the use of air-sensitive catalysts, the use of expensive catalytic systems, and the requirement of additives. Moreover, the creation of quaternary α-hydroxy oxindole, mainly achieved from indole/isatin/2-oxindole as the starting material, necessitates multistep syntheses involving stepwise C3-substitution followed by C−H hydroxylation. Considering the above drawbacks, the main objective of this chapter is to develop an efficient and environmentally benign catalytic approach for the C3-alylation of 2-oxindole and the one-pot access to C3-alkylated 3-hydroxyindolin-2-one directly from 2-oxindole. Further, the developed methodology has been used for the total synthesis of hydroxy oxindole based natural products such as, donaxaridine and arundaphine.

✓ Ru-catalyzed direct synthesis of antimalarial bis-arylideneoxindoles from 2-oxindole and diaryl methanols

The derivatives of arylidene oxindole are known for several therapeutic applications such as they act as synthetic inhibitors of neointimal thickening after balloon injury, they inhibit calcium-dependent signal transduction, and possess anti-breast-cancer activity. In the literature, few methods have been proposed for the synthesis of bis-arylidene oxindole derivatives. However, these methods have certain limitations such as the use of toxic starting material, the use of expensive and specially synthesized organometallic compounds as catalysts, and pre-functionalized starting materials that require many steps. Thus, we have envisioned a straight-forward generalized approach for the α-olefination of 2-oxindole using alcohols in the presence of air-stable Ru-NHC as a catalyst for the synthesis of bis-arylidene 2-oxindole derivatives. In this context, various Ru-NHC catalysts have been evaluated and the

optimal reaction conditions developed with a broader substrate scope. Finally, the biological activity of bis-arylidene 2-oxindole derivatives was evaluated against the malaria pathogens.

- ✓ **Transition-metal-free addition reaction of 2-oxindole to nitrile: A synthetic application towards fluorination and C=C Cleavage**

3-(Aminomethyl)indolin-2-one derivatives are cyclic enamides and these derivatives are synthetically useful intermediates in natural product and drug synthesis. These derivatives are also known for various biological applications. Several approaches were developed by various chemists for the construction of 3-(aminomethyl)indolin-2-one derivatives. In the reported method for the synthesis of 3-(aminomethyl)indolin-2-one derivatives, transition metals such as Pd, Rh, Fe, and Ru are popularly used. Moreover, in some synthetic approaches, toxic isocyanate starting materials have been used that need to be synthesized. Thus, the objective of this chapter is to develop a metal-free method for the synthesis of 3-(aminobenzylidene/aminoalkylidene)indolin-2-ones derivatives directly from 2-oxindole and nitrile *via* an addition reaction. To evaluate this objective, several bases and ligands were screened for the addition reaction of 2-oxindole radical or carbanion addition with nitriles. Another objective of this chapter was to study the reactivity of the cyclic enamides towards oxidation, fluorination, and coupling reactions.

- ✓ **Synthesis of quaternary spirooxindole 2*H*-azirines derivatives under batch and continuous flow and its synthetic applications**

Azirines are reactive intermediates due to highly strained ring structure. As a result, it has tendency to undergo several chemical transformations. Spirocyclic oxindoles containing three member spiro rings fused at the C3 position of oxindole moiety represents an important core structure in a variety of natural products and exhibits broad biological activities. Limited reports exist for the synthesis of spirooxindole having three and four-member heterocyclic rings fused at the C3 position of oxindole. Although various approaches are available for the formation of a simple azirine ring, few of these approach for the synthesis of spirooxindole *2H*-azirines *via* Neber reaction involve multistep synthesis and specially designed starting materials. Spiroazirines are one of the important compounds that exhibit many applications. However, their synthesis is extremely challenging due to the lack of an efficient method as seen in the literature. Therefore, the objectives of the present work are mainly focussed on the synthesis of spiroazirination using an oxidative approach under the batch/flow mode. In synthetic application we disclosed the synthesis of

spiroaziridines and *N*-substituted enamide in presence of Grignard reagent. The objectives of the present work were to optimize the reaction conditions using iodine and a base under batch and flow mode to get the spiroazirination. The scope of this reaction has been further expanded for the generalization of spiroaziridine and ring-opening reactions using Grignard reagent.

1.8. References:

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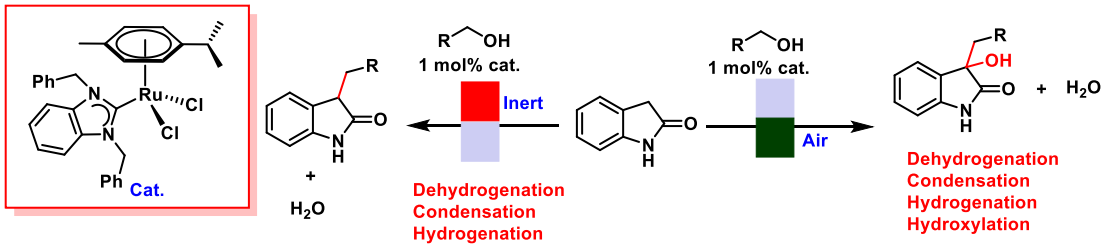
Chapter 2A

One-Pot Ru-NHC Catalyzed C−H Alkylation and Base Mediated Aerobic C−H Hydroxylation

One Pot Ru-NHC Catalyzed C−H Alkylation and Base Mediated Aerobic C−H Hydroxylation

2A.1. Abstract

In this chapter, we have developed a method for the direct α-alkylation of unactivated amide and one-pot synthesis of C3-alkylated 3-hydroxyindolin-2-one/2-substituted-2-hydroxy-3,4-dihydronaphthalen-1(2H)-one derivatives from 2-oxindole/1-teralone by using less expensive and easily available primary alcohols in the presence of well-defined Ru-NHC catalyst following the borrowing hydrogen concept. In case of inert condition, the reaction of 2-oxindole/estrone with alcohols exclusively forms the C3-alkylated product. On varying the reaction condition from inert to air atmosphere formation of a different product was observed in the reaction mixture. Thus under air atmosphere, the mixture containing C3-alkylated product predominantly gives rise to C3-alkylated 3-hydroxyindolin-2-one *via* C−H alkylation followed by aerobic C−H hydroxylation reaction sequences in a domino manner. The Ru-NHC catalyst used during this transformation has the advantages of being easily accessible, air/moisture stable, and phosphine free.



2A.2. Introduction

2A.2.1 Borrowing hydrogen concept and its literature background

Atom economy, a well-known concept in chemistry, was established by Barry M. Trost in the year 1991[1]. Later, in 1998 it was included in the twelve principles of green chemistry.[2] Atom economy is defined as the percentage ratio of the weight of the desired product to the mass of all the reactants. The parameter allows the measurement of the efficiency or effectiveness of any chemical reaction. In this context, reactions such as addition & rearrangement reactions are highly atom economical or efficient. The alkylation reaction is one of the fundamental and widely used reactions in organic synthesis. The α-alkylation reaction of carbonyl compounds

requires a strong base such as, *n*-BuLi, LDA, *NaH*, and $NaNH_2$ because of the less acidic nature of α-C−H proton. Base mediated deprotonation generates a nucleophile, which can react with a variety of electrophiles like, alkyl halide, or carbonyl derivatives to generate the desired product. This classical concept is extensively used in organic synthesis. However, these methods have some limitations such as, the necessity of genotoxic alkyl halides, cryogenic reaction conditions as well as the use of highly explosive and air/moisture sensitive bases and additives. As a result, sub-stoichiometric amount of waste is generated while using this method.[3] To overcome these challenges, readily available, environmentally benign, and easy to handle alcohols have been successfully used as an alkylating reagent in several borrowing hydrogen transformations in the last two decades.[4] In these transformations, alcohol acts as a latent aldehyde and water is the only by-product, making this operation sustainable and environmentally benign.

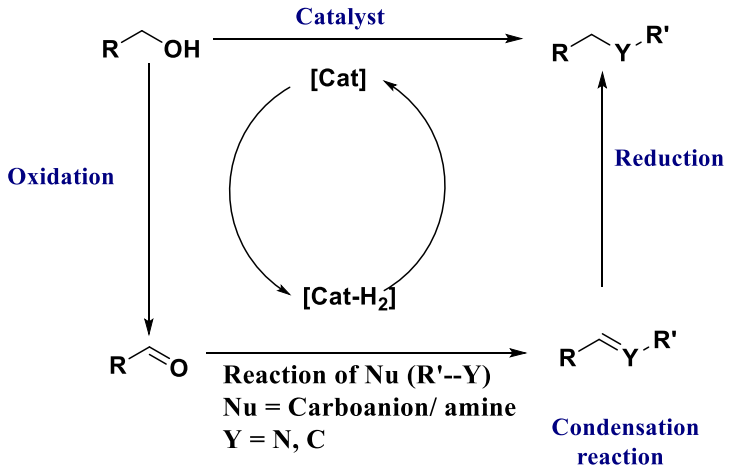
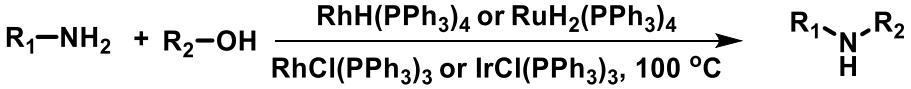


Figure 2A.1. General catalytic cycle for borrowing hydrogen (BH) methodology

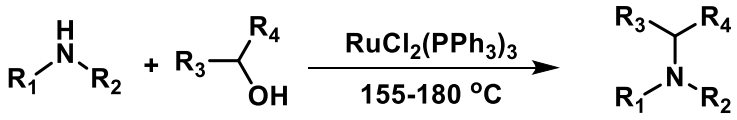
Borrowing hydrogen (BH) method, also familiarly known as dehydrogenative activation or hydrogen auto transfer, is an important catalytic cycle in organometallic chemistry. This catalytic cycle proceeds with the oxidation of alcohol by metal complex to generate an intermediate aldehyde/ketone along with intermediate metal hydride complex. Further, the aldehyde/ketone reacts with an external carbon or nitrogen nucleophile namely enolates or amines to generate an unsaturated intermediate. The in situ generated metal hydride complex reduce the unsaturated compound to afford the desired C−C or C−N bond-forming product. At the end of the process, the only by-product formed is water. There are several advantages associated with this concept - namely, i) due to the formation of less by-products, this transformation is atom-economical; ii) environment-friendly due to the use of non-toxic alcohols and generation of water as the only by-product; iii) reduction in the

number of steps in chemical transformations (Figure 2A.1). Borrowing hydrogen method is not new in the field of catalysis. Pioneering work on borrowing hydrogen method was done by Charles F. Winans and Homer Adkins in the year 1932 wherein they reported an amination reaction catalyzed by heterogeneous nickel catalysts.[5] In 1981 Grigg and co-workers developed a homogeneous catalytic system of Rh, Ir, and Ru metals for the amination of alcohols *via* BH (Scheme 2A.1).[6]



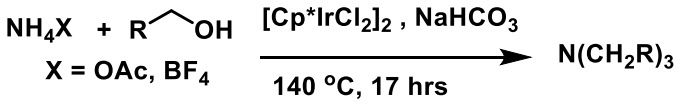
Scheme 2A.1. Grigg's approach for *N*-alkylation of amines using alcohols

Later in 1984, Watanabe and co-workers also reported the *N*-alkylation of amines by utilizing alcohol as a coupling partner in the presence of Ru catalyst.[7] Similarly, Murahashi and co-workers synthesized tertiary and secondary amines by using Ru-catalyst (Scheme 2A.2).[8]



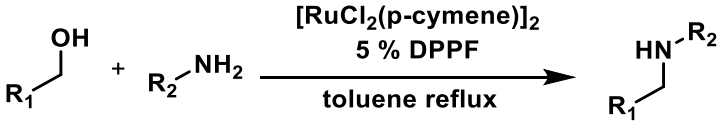
Scheme 2A.2. Murahashi's approach for the synthesis of secondary/tertiary amine

Likewise, Yamaguchi and Fujita collectively reported the synthesis of secondary and tertiary amines from ammonium salt and alcohol using Ir catalyst under a solvent-free condition (Scheme 2A.3).[9]



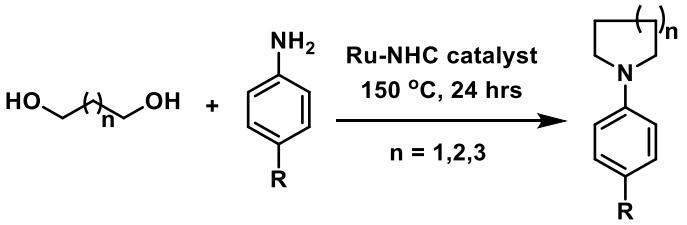
Scheme 2A.3. Yamaguchi and Fujita's approach for the synthesis of tertiary amine

William's research group reported the *N*-alkylation of amines by using bench stable and easily synthesizable $[RuCl_2(p\text{-cymene})]_2$ complex (Scheme 2A.4).[10]



Scheme 2A.4. Williams's approach for *N*-alkylation of amines using alcohols

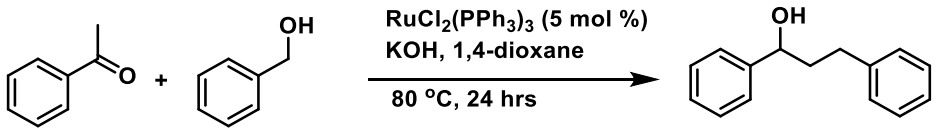
Interestingly, in 2015 Seayad and co-workers reported the *N*-alkylation of amines by using alcohol and bench stable, well-defined Ru-NHC catalyst under solvent-free conditions (Scheme 2A.5).[11]



Scheme 2A.5. Seayad's approach for *N*-alkylation of amines using alcohols

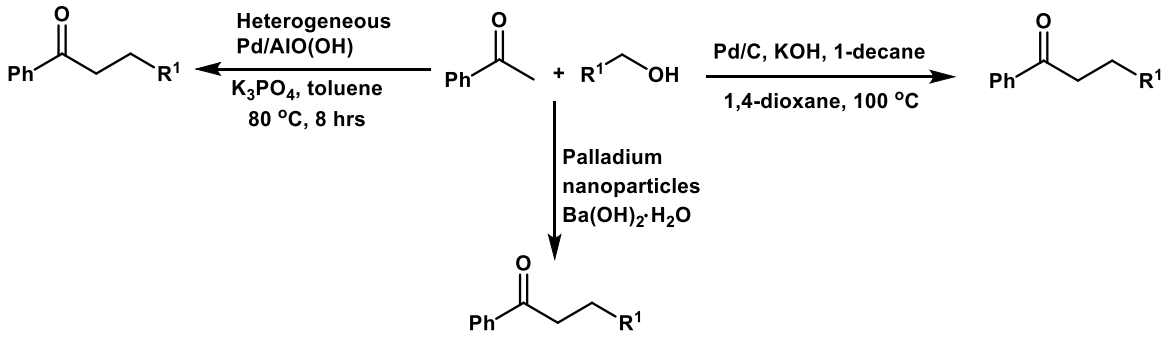
2A.2.2. Literature background on α-alkylation of carbonyl compounds

In addition to the C−N bond-forming reaction, the borrowing hydrogen method is also used for the α-alkylation of carbonyl *i.e.* C−C bond forming reactions. In 2001 Shim research group have reported the C−C bond-forming reaction of acetophenone by using $RuCl_2(PPh_3)_3$ (Scheme 2A.6).[12]



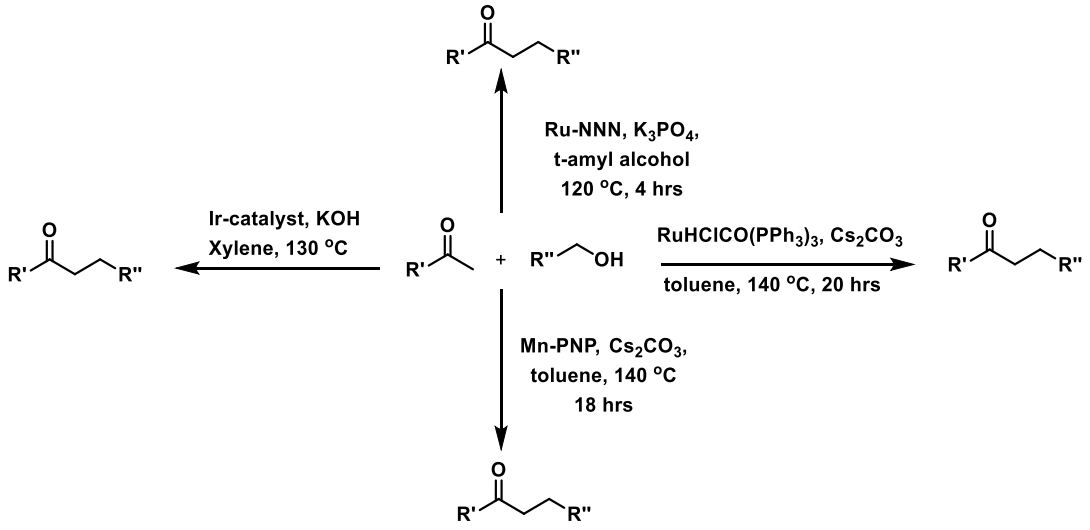
Scheme 2A.6. Shim's approach for alkylation reaction of acetophenone

Later the regioselective α-alkylation of carbonyl compounds was reported by using $RuCl_2(PPh_3)_3$ with the loading of a less amount of catalyst.[13] In 2006, Martinez and co-workers performed the same transformation by using $Ru(DMSO)_4Cl_2$ as a catalyst.[14] Additionally, apart from Ru catalyst, homogeneous and heterogeneous Pd-catalyst have also been used for the α-alkylation reactions of carbonyl compounds under different reaction conditions (Scheme 2A.7).[15]



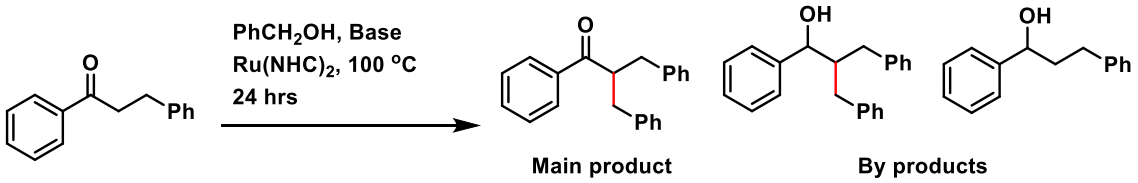
Scheme 2A.7. Palladium assisted α-alkylation reaction of carbonyl compound using alcohols

Ryu, Glorious, and several other research groups have recently explored different strategies for the α-alkylation reaction of carbonyl compounds (Scheme 2A.8).[16]



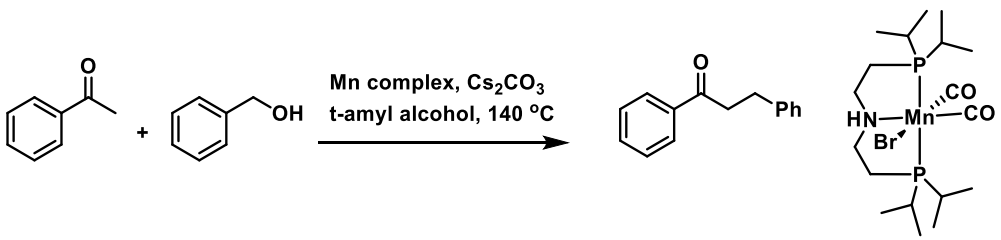
Scheme 2A.8. State-of-the-art on α-alkylation of carbonyl compound using alcohols

With respect to complexes containing NHC ligand, in 2017 Glorius and co-workers reported an in situ generated Ru-NHC catalyst for the synthesis of branched ketones (Scheme 2A.9).[17]



Scheme 2A.9. Glorius's approach for α-alkylation of ketones using alcohol

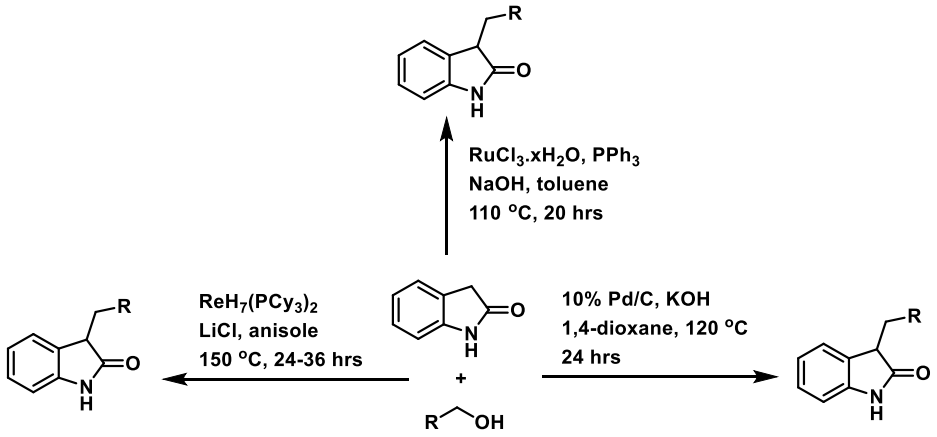
Also, in the same year Beller and co-workers reported an Mn-PNP assisted alkylation of ketones (Scheme 2A.10).[18]



Scheme 2A.10. Bellers's approach for direct α-alkylation of ketones

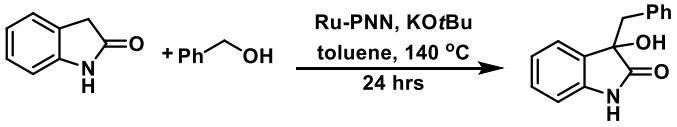
Limited reports are available for the α-alkylation of amides and ester catalyzed by air-sensitive cooperative pincer-type complexes.[19] On the other hand, a few methods have been reported for the C3 alkylation of 2-oxindole including the use of

homogeneous and heterogeneous Rh, Ru, Pd/C, and Pt/CeO_2 catalytic systems (Scheme 2A.11).[20]



Scheme 2A.11. Diverse strategy for C3 alkylation of 2-oxindole using alcohols

In the past decade, several synthetic approaches have been developed for the synthesis of quaternary α-hydroxy carbonyl compounds, centered on isatin/indole/2-oxindole as the starting material, which requires multistep syntheses involving stepwise C3-substitution and subsequent C−H hydroxylation.[21] However, the direct synthesis of quaternary α-hydroxyl amides from cyclic amide such as, 2-oxindole using alcohols as alkylating reagents had not been explored. In 2016, our research group developed the Ru-PNN catalyzed alkylation and hydroxylation of amides using alcohols (Scheme 2A.12).[22]



Scheme 2A.12. Our previous work on synthesis of C3-alkylated 3-hydroxy oxindole

2A.3 Rationale behind the present work

The α-alkylation reaction of carbonyl compounds such as, amide, ketone, and esters is one of the most useful transformations in organic chemistry and has several applications for the synthesis of pharmaceutical, natural products, and peptides modification.[23] In addition, quaternary α-hydroxy carbonyl compounds are one of the important moieties found in a class of natural indole alkaloids, drug candidates, and metabolic intermediates.[24] Moreover, C3-hydroxy functionalized 2-oxindoles are well known to be versatile compounds in terms of synthetic applicability and have attracted immense attention as these compounds have been found in number of important synthetic intermediates and biologically active molecules (Figure 2A.2.).[25]

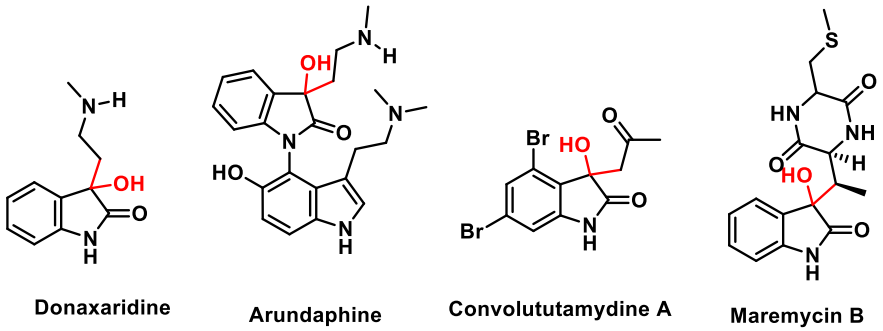


Figure 2A.2. Bioactive 3-hydroxy-2-oxindole based natural products

Traditionally, the α-alkylation of carbonyl compounds was accomplished by the transformation of the respective compounds to its enolates or enamines.[26] Due to the lower Brønsted acidity of hydrogen, strong bases such as n-BuLi, LDA is required, which typically generates sub-stoichiometric amounts of unwanted waste. Hence, in order to overcome this problem, a few methods have been reported for the α-alkylation reaction of amide. However, these methods involve severe limitations such as, the requirement of additives, activation of reagents, less atom economy, and use of expensive and highly air-sensitive complexes, making it a less efficient process. In the last 25 years, the application of *N*-heterocyclic carbene (NHC) ligands in synthetic chemistry have been studied extensively. It has been observed that certain modifications in the structure, electronic, and spectroscopic properties of such ligands can be manifold.[27] Moreover, NHC ligand's has been used in designing several metal catalysts and in various transformations.[28] Interestingly, literature reports indicate that Ru-NHC/Ir-NHC catalyst has proven to be efficient for the *N*-alkylation of amines *via* BH. Moreover, these catalytic systems exhibits excellent catalytic properties due to the strong σ-donation from NHC ligand.[29] Keeping this in mind, a phosphine free, stable, and inexpensive catalytic system is required for the α-alkylation of amides and C3 alkylation reaction of oxindole. Although Ru-complexes having PNN pincer ligands have shown astonishing catalytic activity with a high-turnover number, still it has some limitations like, this PNN catalyst is difficult to synthesize in the lab which restricts it's practical utility. In addition, the catalyst contains an electron-rich phosphine ligand backbone, which is highly air sensitive. Beside, C−H hydroxylation of carbonyl compounds is considered as an important organic transformation, and it has been well studied in literature as individual reaction steps in several multistep syntheses.[30] Although two different reaction steps for the C−H alkylation and hydroxylation are known in the literature, the Ru-NHC catalyzed one-pot C−H alkylation followed by C−H hydroxylation of amide/ketone to get quaternary α-hydroxy ketones/amides has not studied so far.

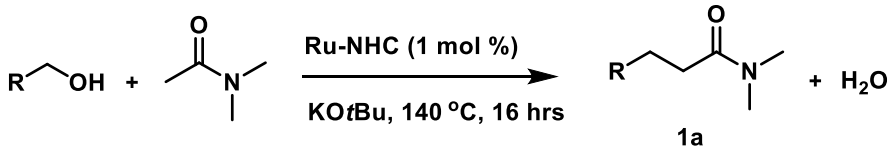
2A.4. Results and discussion

In this chapter, we have developed a straightforward and efficient method for α-alkylation of unactivated amides by using alcohol and Ru-NHC catalyst. In addition, we have developed a new method for the tandem C−H alkylation and subsequent base-mediated aerobic C−H hydroxylation in a complete atom economical manner.

2A.4.1. Optimization studies

To develop a method for α-alkylation reaction of unactivated amide, we have performed the initial optimization by heating a toluene solution containing *N*,*N*-dimethylacetamide, benzyl alcohol, base, and Ru-NHC as a preferred model reaction. Upon taking 0.1-0.5 equiv. of KO*t*Bu with respect to amide and 1.0 mol % of catalyst **2a** results either no reaction or only formation of benzyl benzoate (Table 2A.1, entries 1-3).

Table 2A.1 Optimization of reaction conditions[a]



1a

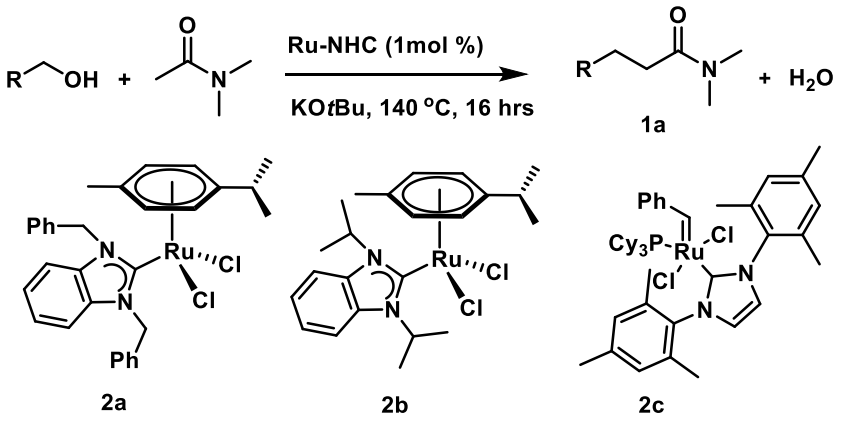
Entry	Base/amide (equiv.)	Temp(°C)	Conv. % of alcohol	Isolated yield (%) of amide
1	0:1 or 0.1 : 1	140	0	no reaction
2	0.2:1	140	70	benzyl benzoate
3	0.5:1	140	25	benzyl benzoate
4	1:1	90	47	amide **1a** (21)
5	2:2	90	72	amide **1a** (40)
6	2:2	140	100	amide **1a** (48)
7[c]	1.3:23	90	60	amide **1a** (57)
8[c]	**1.3:23**	**140**	**80**	**amide 1a (71)**

Reaction conditions: Complex **2a** (0.01 mmol), benzyl alcohol (1.0 mmol), *N*,*N*-dimethylacetamide (see table), KO*t*Bu (see table), and toluene (1 mL) were heated in a sealed tube for 16 hrs. [b]Gas chromatography (GC) conversion using mesitylene as an internal standard. [c]Neat conditions.

Later, various conditions were probed for this reaction, for instance, a decrease in temperature with a sub-stoichiometric amount of KO*t*Bu results in a lower conversion/yield of product **1a** (Table 2A.1, entries 4 & 5). Interestingly, upon

increasing the temperature with a sub-stoichiometric amount of KO*t*Bu to *N*,*N*-dimethylacetamide provided 48% isolated yield of product **1a** with complete conversion of the benzyl alcohol (Table 2A.1, entry 6). Significant improvement was obtained upon heating the reaction mixture under neat conditions at 90 ^{o}C to afford **1a** in 57% yield (Table 2A.1, entry 7). Best optimized conditions were achieved by heating the reaction mixture under neat conditions at 140 ^{o}C to furnish **1a** in 71% yield (Table 2A.1, entry 8). Further, a range of Ru-NHC catalysts was investigated under the optimized conditions (Table 2A.2). First, the α-alkylation reaction in the presence of 1.0 mol % complex **2b** afforded the product **1a** as the sole product in 56% yield (Table 2A.2, entry 2). Use of Grubbs' I and II generation catalysts led to the significant conversion of benzyl alcohol and resulted in respective yields of 47 and 59% of amides isolated by silica-gel column chromatography purification (Table 2A.2, entries 3 and 4).

Table 2A.2 Catalyst screening for α-alkylation of *N*,*N*-dimethylacetamide



Entry	Catalyst (1 mol %)	Conv. % of alcohol	Isolated yield (%) of amide	TON
1	**catalyst 2a**	**80**	**71**	**71**
2	catalyst **2b**	67	56	56
3	Grubbs'I	71	47	47
4	Grubbs'II **2c**	81	59	59

Reaction conditions: Ru-Catalyst (see table), benzyl alcohol (1 mmol), *N*,*N*-dimethylacetamide (2 mL), and KO*t*Bu (1.3 mmol) were heated at 140 ^{o}C for 16 hrs.

In contrast to the Grubbs' catalysts, the catalysts **2a** and **2b** were easily synthesizable and air and moisture stable and did not undergo any reactivity changes over a long period of time when exposed to the air atmosphere. After having optimization conditions in hand, a range of alcohol was tested under optimized reaction condition to afforded the respective α-alkylated products **1b-k** in moderate

yield (Figure 2A.3). Additionally, the *N*-acetyl derivatives of pyrrolidine, pyridine, and morpholine were also subjected under optimized reaction condition and successfully afforded the respective alkylated products **1l-n** in 38-48% yields.

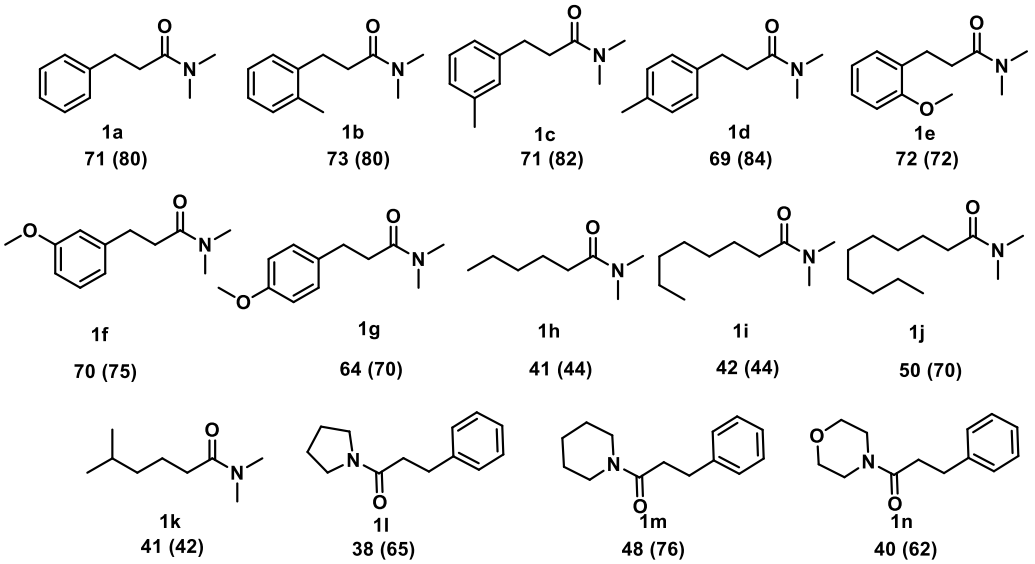


Figure 2A.3. Substrate scope for α-alkylation of *N*,*N*-dimethylacetamide

Reaction conditions: complex **2a** (0.01 mmol), alcohol (1.0 mmol), KO*t*Bu (1.3 mmol), and *N*,*N*-dimethylacetamide (23.0 mmol) were heated at 140 ^{o}C in a sealed tube for 16 hrs.

Further, the scope of this α-alkylation reaction was further explored with 2-oxindole.

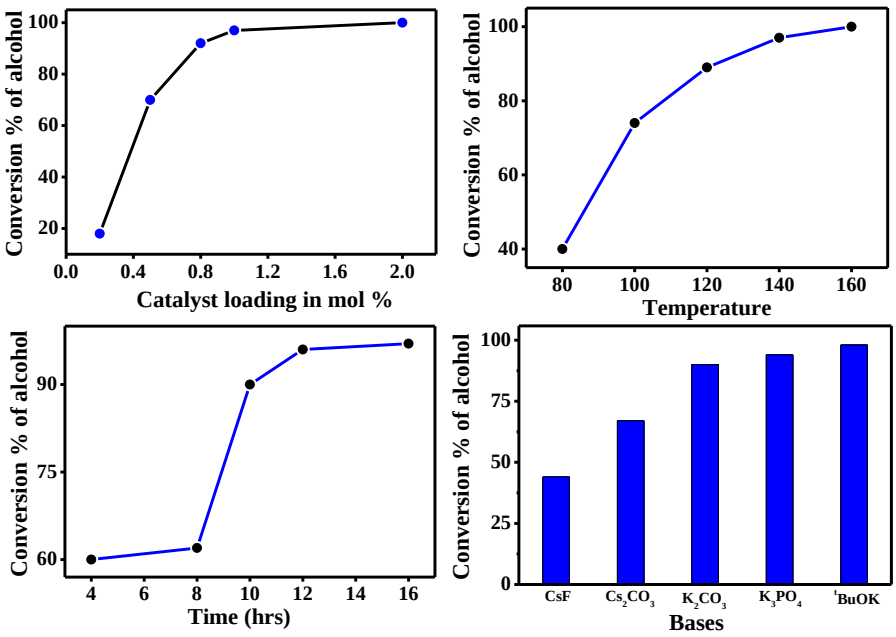
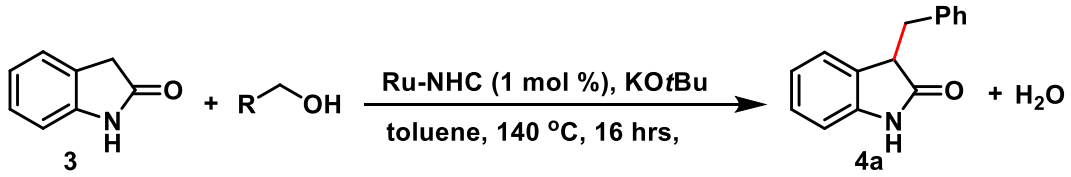


Figure 2A.4. Reaction profile under various reaction parameters

A toluene solution containing 2-oxindole, benzyl alcohol, complex **2a** and base was taken as a model reaction and several reaction parameters such as catalyst loading, temperature, time, and base has been screened (Figure 2A.4). Initially, the reaction was performed in the presence of different concentrations of the Ru-NHC catalyst **2a**, complete conversion of benzyl alcohol was observed with 1.0 mol% catalyst and conversion of alcohol was observed by GC analysis. Upon lowering the catalyst loading from 1 mol% to 0.8 & 0.4% drop in the conversion of benzyl alcohol was observed. Also, this reaction was performed at various temperatures, revealing that performing the reaction at 140-160 ^{o}C led to the complete conversion of the alcohol. Moreover, less conversion of alcohol was observed when the reaction was performed at lower temperature (Figure 2A.4). Later, the reaction was monitored at different time intervals. From these studies, it was noticed that the complete conversion of benzyl alcohol was found after heating at 140 ^{o}C for 16 hrs. When the reaction was performed under nitrogen atmosphere in sealed tube, formation of C3-benzylated 2-oxindole was observed in the reaction mixture and respective product **4a** was isolated in 94% yield.

Table 2A.3. Effect of KO*t*Bu concentration on C-3 alkylation of 2-oxindole



Entry	2-Oxindole (equiv.)	KO*t*Bu (equiv.)	Isolated yield (%) of 4a
1	2	0.2	49
2	2	0.4	60
3	2	0.6	62
4	2	0.8	74
5	**2**	**1.3**	**94**
6	1.5	1.3	73
7	1	1.3	57

Reaction conditions: benzyl alcohol (1 mmol), oxindole (see table), base (see table), and 1 mol % catalyst **2a** in toluene were heated in sealed tube at 140 ^{o}C for 16 hrs.

Screening the effect of base for this reaction revealed that KO*t*Bu is efficient base for this transformation and higher conversion was observed in the case of KO*t*Bu

(Figure 2A.4). Further, this reaction was also investigated with different concentrations of KO*t*Bu (Table 2A.3), by taking 0.2 equiv of base poor yield was observed. Moderate to good yield was observed when the 0.4, 0.6 and 0.8 equiv. of base was used (Table 2A.3, entries 2, 3 and 4). Excellent yield of C3 alkylated product was isolated by using 1.3 equiv. of KO*t*Bu. Furthermore, this reaction requires an excess of 2-oxindole to get the product **4a** in better yield. On lowering the amount of 2-oxindole in reaction mixture decrease in the yield of the product was observed (Table 2A.3, entries 6 and 7). After having optimized reaction condition in hand, several other alcohols were tested under optimized condition. Substituted aromatic alcohols reacted smoothly to give the C3-alkylated 2-oxindole **4b-g** in excellent yields. Interestingly, aliphatic alcohols were also effective for this C3 alkylation to give the corresponding products **4h-l** in moderate to good yields, but this required 2 mol% of the Ru-NHC catalyst for better yields.

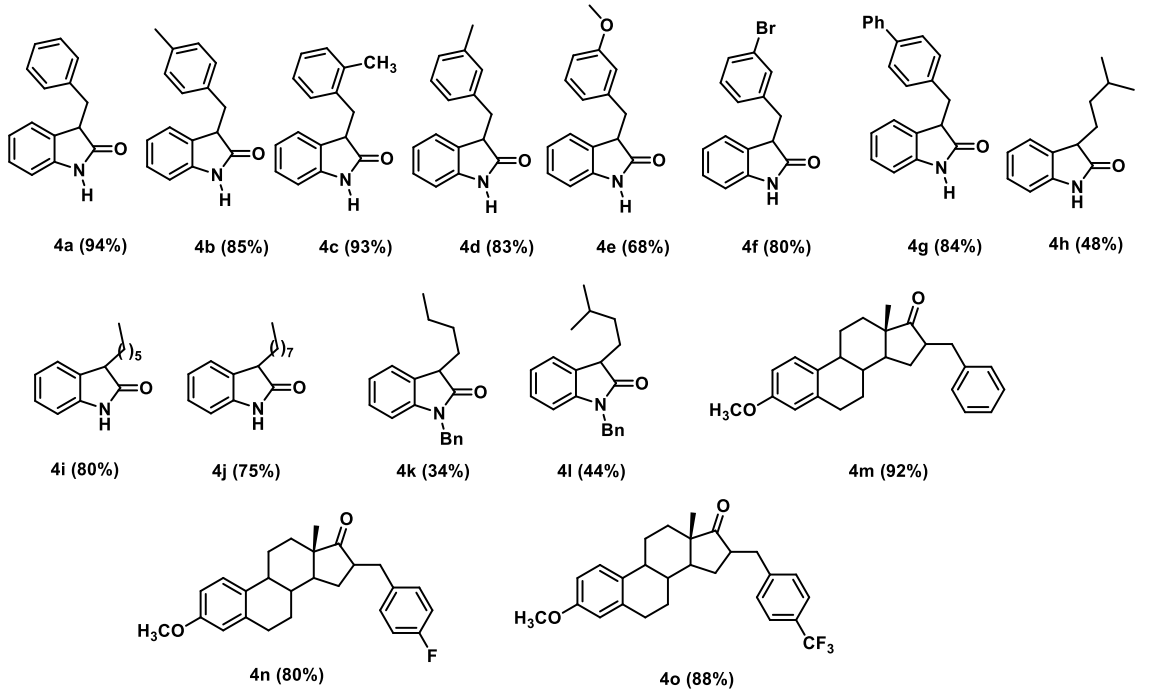


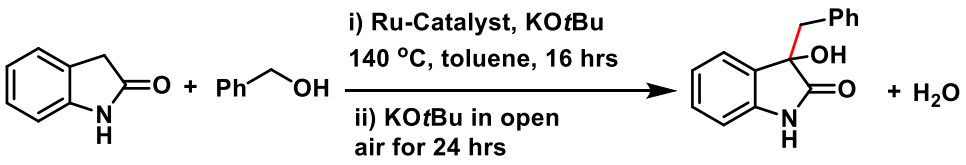
Figure 2A.5. Substrate scope for C3 alkylation of oxindole

Reaction conditions: alcohol (1 mmol), 2-oxindole (2 mmol), KO*t*Bu (1.3 mmol), and catalyst **2a** (1 mol %) in toluene were heated at 140 °C for 16 hrs.

Further, this reaction was extended with steroid substrate such as estrone. Hence, the reaction of estrone with benzyl alcohol, 4-fluorobenzyl alcohol, and trifluorobenzyl alcohol afforded the corresponding alkylated products **4m-o** in very good yield (Figure 2A.5). We further developed double functionalization of 2-oxindole to synthesize quaternary hydroxyl C3-alkylated 2-oxindole. This allows

rapid access to double functionalized 2-oxindole in one pot. To achieve the domino C−H alkylation and subsequent aerobic C−H hydroxylation, a set of conditions was established after a series of experiments, which includes temperature, time, base concentration, and various catalysts (Table 2A.4).

Table 2A.4 Optimization of reaction condition for the synthesis of 3-benzyl-3-hydroxyindolin-2-one[a]



Entry	Catalyst (1 mol%)	KO*t*Bu (in equiv.)	Temp (°C)	Time in hrs	Isolated yield of 5a (%)
1	Catalyst **2a**	2.3	50	24	NR
2	Catalyst **2a**	2.3	80	24	31
3	Catalyst **2a**	2.3	100	24	45
4	Catalyst **2a**	2.3	140	24	69
5[b]	Catalyst **2a**	2.3	140	24	40
6	Catalyst **2a**	2.0	140	24	58
7	Catalyst **2a**	1.9	140	24	49
8	Catalyst **2a**	1.6	140	24	37
9	Catalyst **2a**	1	140	24	10
10	Catalyst **2a**	0	140	24	NR
11	Catalyst **2a**	1.3	140	16	59
12	Catalyst **2a**	1.3	140	8	45
13	Catalyst **2b**	1.3	140	24	54
14	Grubbs' I	1.3	140	24	43
15	Grubbs' II **2c**	1.3	140	24	55

[a]**Reaction conditions:** alcohol (1 mmol), 2-oxindole (2 mmol), KO*t*Bu (1.3 mmol), and 1 mol% catalyst **2a** in toluene were heated at 140 °C for 16 hrs followed by addition of 1 mmol of KO*t*Bu and kept at rt for 24 hrs. [b]2-oxindole (1 mmol) used.

Thus, heating the reaction mixture containing 2-oxindole, benzyl alcohol, catalyst **2a**, and KO*t*Bu in toluene solution at 50, 80, 100, and 140 °C and further exposing to atmospheric air for 24 hrs at room temperature afforded the product **5a** in 0, 31, 45, and 69% yield respectively (Table 2A.4, entries 1-4), indicating that higher temperature is crucial for this transformation. Interestingly, this reaction (Table 2A.4, entry 4) afforded quaternary hydroxyl C3-benzylated 2-oxindole **5a** (69%) as the major product along with a minor amount (10%) of the C3-alkylated product **4a**. Lowering the amount of 2-oxindole led to a decrease in the yield of product **5a** to 40% (Table 2.4, entry 5). In addition, by lowering the amount of base from 2.3

to 0 equiv. decreases in product yield was observed (Table 4, entries 6-10). Upon decreasing reaction time, product **5a** was isolated in fewer amounts (Table 2A.4, entries 11 and 12). The reaction was also performed by using other Ru catalyst such as, catalysts **2b,** Grubbs' I, and Grubbs' II resulted in lower yield of the product **5a** (Table 2.4, entries 13-15). To expand the scope of this approach, a range of aromatic alcohols were reacted with 2-oxindole (Figure 2A.6). Methyl substitution on para/meta to benzyl alcohol gave similar yields of **5b**/**c** (50/45%). In the case of 2-methoxybenzyl alcohol, a moderate yield of the product **5d** (55%) was observed. Methoxy substitution on the meta position gave **5e** in poor yield (25%). Biphenyl methanol gave **5f** in 42% yield.

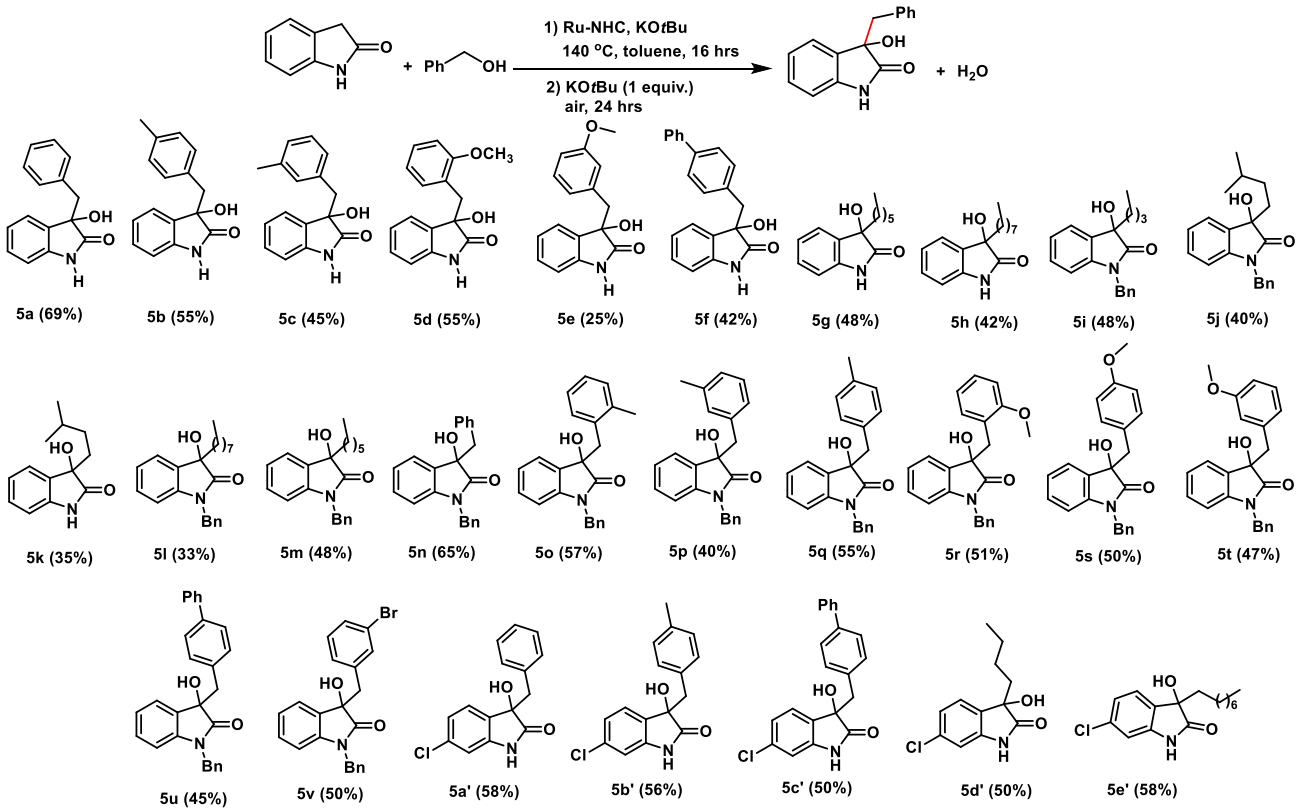


Figure 2A.6. Substrate scope for C3-hydroxy functionalized 2-oxindole

Reaction conditions: alcohol (1 mmol), 2-oxindole (2 mmol), KO*t*Bu (1.3 mmol), and 1 mol % catalyst **2a** in toluene were heated at 140 ^{o}C for 16 hrs followed by addition of 1 mmol of KO*t*Bu and kept at rt for 24 hrs.

Aliphatic alcohols such as hexanol, octanol, butanol, and iso-amyl alcohol were also reacted to give the respective quaternary hydroxy C3-alkylated products **5g-k** in moderate yield (Figure 2A.6). Next, *N*-benzylated 2-oxindole was prepared and reacted with a variety of aromatic and aliphatic alcohols. All aliphatic alcohols gave the corresponding product and did not display any improvement in the yield of the

products **5l, m** in 33, 48% yield (Figure 2A.6). Reaction with benzyl alcohol gave the corresponding product **5n** in 65% yield. A slight decrease in yield was observed for aromatic alcohols with ortho/para methoxy/methyl substituents to afford quaternary C3-hydroxy products **5o-t** in 40-57% yields (Figure 2A.6). This reaction was also successful with biphenyl methanol to give the highly aromatic ring centered quaternary hydroxylated product **5u** (45%). Interestingly, this reaction was functional group tolerant, upon reaction with 3-bromobenzyl alcohol, to afford the bromo functionalized product **5v** in 50% yield (Figure 2A.6). Interestingly, these domino reactions were also successful with substituted 2-oxindole. Upon reaction of 6-chloro-2-oxindole with benzyl alcohol, 4-methylbenzyl alcohol, biphenyl methanol, 1-butanol, and 1-octanol in the presence of Ru-NHC catalyst afforded the respective products **5a'-e'** in moderate yield (Figure 2A.6). Further, the scope of this domino reaction was also attempted with 1-tetralone to get α-hydroxy-1-tetralone (Figure 2A.7). Upon heating the toluene solution containing benzyl alcohol, 1-tetralone, KO*t*Bu, and 1 mol % of the Ru-NHC catalyst for 16 hrs, followed by exposure to air for 24 hrs, afforded the respective product **7a** in 69% yield.

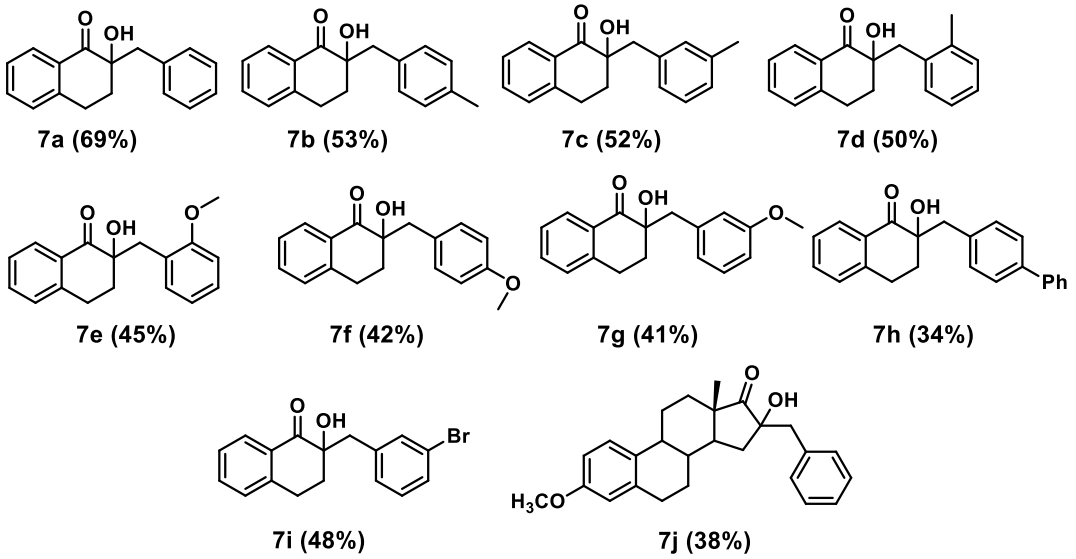


Figure 2A.7. Substrate scope for tetralone and estrone

Reaction conditions: alcohol (1 mmol), ketone (2 mmol), KO*t*Bu (1.3 mmol), and 1 mol % catalyst **2a** in toluene were heated at 140 ^{o}C for 16 hrs followed by addition of 1 mmol of KO*t*Bu and kept at rt for 24 hrs.

Substituted benzyl alcohols such as 2/3/4-methylbenzyl alcohol, 2/3/4-methoxybenzyl alcohol, biphenyl methanol, and 3-bromobenzyl alcohol also successfully afforded the appropriate substituted hydroxy functionalized 1-tetralone **7b-i** in moderate yield. This approach was also successfully applied to one of the

steroid, estrone, to get the D-ring functionalization. Estrone was subjected to C−H alkylation using benzyl alcohol, and subsequent aerial oxidation under the optimized reaction conditions afforded the respective quaternary hydroxyl functionalized product **7j** in 38 % yield (Figure 2A.7).

2A.5 Mechanistic investigation

To investigate the mechanism for the formation of hydroxyl compound, complex **2a** (0.01 mmol), KO*t*Bu (1.3 mmol), alcohol (1 mmol), and 2-oxindole (2 mmol) were added to an oven-dried 20 mL resealable pressure tube (equipped with rubber septum) under an N_2 atmosphere using a balloon. Then, the tube was purged with N_2, and the septum was quickly removed and the tube was sealed with a cap using a crimper. The reaction mixture was stirred at 140 ^{o}C for 16 hrs. After cooling to room temperature, KO*t*Bu was added to the reaction mixture and after 4 hrs crude reaction mixture was frozen by using liquid N_2 followed by immediate injection into HRMS instrument which observed the mass value of 294.0537, which corresponds to the intermediate **G** (Figure 2A.8.) as a potassium adduct.

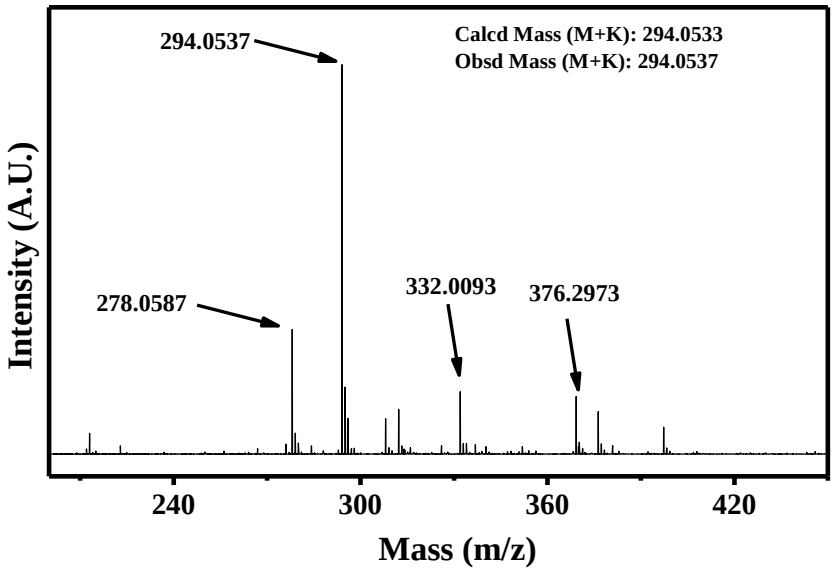


Figure2A.8. Detection of intermediate using HRMS

This evidenced that the C−H hydroxylation is facilitated by atmospheric oxygen. Based on our experimental observations and literature background,[22,30,31] the possible mechanism for the formation of the quaternary hydroxyl C3-alkylated 2-oxindole (**H**) is proposed (Figure 2A.9). Initially, the alcohol (**A**) forms the aldehyde *via* Ru-catalyzed dehydrogenation, which further undergoes base-mediated condensation with 2-oxindole to give the unsaturated intermediate **C**. The unsaturated intermediate **C** is

undergoing hydrogenation in the presence of Ru-H intermediate to give the C3-alkylated product **D**.

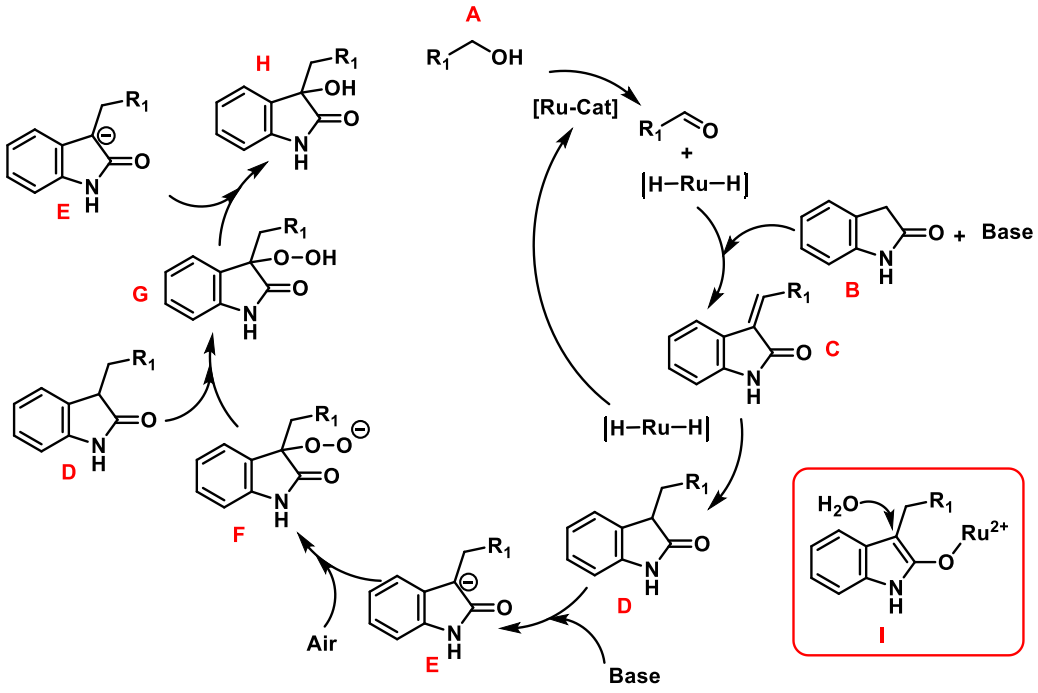


Figure 2A.9. Plausible mechanism

Because the reaction was performed under inert conditions, exclusive formation of the intermediate **D** ruled out the water addition across the Ru-alkoxy intermediate **I**.[22] Further, by adding base to the reaction mixture it generate intermediate **E**. In addition, allowing the reaction mixture under air generates the intermediate **F** which further reacts with product **D** generate peroxy intermediate **G** *via* C−H peroxidation. Moreover, formation of intermediate was confirmed by HRMS analysis, further peroxide cleavage by enolate[31] to afford the product **H**.

2A.6 Conclusion

In summary, this chapter established Ru-NHC catalyzed domino C−H alkylation reaction of amides using alcohols. In addition, the catalyst used in this transformation is air-stable and phosphine free. During the complete transformations, reactions proceeded *via* dehydrogenation-condensation-hydrogenation and hydroxylation steps in a domino manner. Moreover, a new approach for the tandem C−H alkylation followed by an aerobic base-mediated C−H hydroxylation was achieved with a complete atom economical approach. Swapping the reaction conditions between that under air or inert, the reaction product can be switched to C3 alkylation or C3 alkylation followed by C−H hydroxylation.

2A.7. Experimental section and characterization data

2A.7.1. General information and data collection

All experiments with Ru-catalyst were carried out under an atmosphere of nitrogen. All alcohols and amides were purchased from Sigma-Aldrich or Alfa-Aesar and stored over molecular sieves. Deuterated solvents were used as received. All the solvents used were dry grade and stored over 4Å molecular sieves. Column chromatographic separation was performed over 100-200 mesh size silica-gel. Visualization was accomplished with UV light and iodine. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded on 400 and 100 MHz respectively, using a Bruker or JEOL spectrometers. The chemical shift (δ) and coupling constant (J) values are given in parts per million and Hertz, respectively. Abbreviations used in the NMR follow-up experiments: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; td, dd doublet of triplet and double doublet; m, multiplet, tt, triplet of triplets and ddd, doublet of doublet of doublets. Tetramethylsilane (TMS) was used as an internal standard for all ^{1}H NMR studies. High-resolution mass spectra were obtained with Waters-synapt G2 using electrospray ionization (ESI-TOF). Infrared (ATR) spectra were obtained with a Bruker Alpha-E infrared spectrometer.

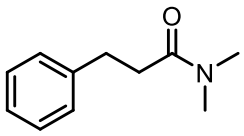
A) General experimental procedure for the α-alkylation of unactivated amides (method A): Complex **2a** (0.01 mmol), KO*t*Bu (1.3 mmol), alcohol (1 mmol), and *N*,*N*-dimethylacetamide (2 mL) was added to an oven dried 20 mL resealable pressure tube (equipped with rubber septum) under N_2 atmosphere using N_2 balloon. Then, the tube was purged with N_2 and the septum was quickly removed, then the tube was sealed with a cap using a crimper. The reaction mixture was stirred at 140 °C for 16 h. After cooling to room temperature, mesitylene (1.0 mmol) was added, and the products were analyzed by GC. The reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (3×20 mL). The entire ethyl acetate layer was combined, washed with brine (30 mL), and then dried over Na_2SO_4. After concentration under reduced pressure, the residue was purified by 100−200 mesh silica-gel column chromatography. (In the case of aliphatic alcohols, 0.02 mmol of Ru-NHC catalyst was used and heated for 24 h. In the case of cyclic amides, the reaction was heated for 24 hrs.)

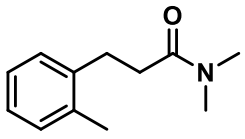
B) General experimental procedure for C3 alkylation of 2-oxindole and *N*-protected 2-oxindole (method B) Complex **2a** (0.01 mmol), KO*t*Bu (1.3 mmol), alcohol (1 mmol), and 2-oxindole (2 mmol) were added to an oven-dried 20 mL resealable pressure tube (equipped with rubber septum) under N_2 atmosphere using a

balloon. Then, the tube was purged with N_2, and the septum was quickly removed. The tube was sealed with a cap using a crimper. The reaction mixture was stirred at 140 ^oC for 16 hrs. After cooling to room temperature, the reaction mixture was passed through a celite bed. After concentration under reduced pressure, the residue was purified by 100-200 mesh silica-gel column chromatography to afford the pure product. (In the case of aliphatic alcohols, 0.02 mmol of Ru-NHC catalyst was used and heated for 24 hrs).

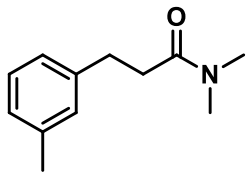
C) Experimental procedure for C−H alkylation and aerobic C−H hydroxylation of 2-oxindole, α-tetralone and *N*-protected 2-oxindole (method C): Complex **2a** (0.01 mmol), KO*t*Bu (1.3 mmol), alcohol (1 mmol), and 2-oxindole (2 mmol) were added to an oven-dried 20 mL resealable pressure tube (equipped with rubber septum) under N_2 atmosphere using a balloon. Then, the tube was purged with N_2, and the septum was quickly removed and the tube was sealed with a cap using a crimper. The reaction mixture was stirred at 140 ^oC for 16 hrs. After cooling to room temperature tube was unsealed and KO*t*Bu (1 mmol) was added to reaction mixture and stirred under open air at room temperature for 24 hrs. The reaction mixture was passed through celite bed (200 nm). After concentration under reduced pressure, residue was purified by 100-200 mesh silica-gel column chromatography using ethyl acetate/petroleum ether to afford the pure product. (In case of aliphatic alcohols reaction mixture was heated for 24 hours).

D) Analytical data for the products:

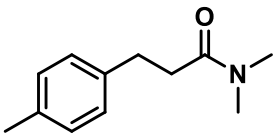
***N*,*N*-Dimethyl-3-phenylpropanamide (1a).**[22] Complex **2a** (6.05 mg, 0.01 mmol), KO*t*Bu (146 mg, 1.3 mmol), benzyl alcohol (108 mg, 1 mmol), and *N*,*N*-dimethylacetamide (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method A to afford the amide 1a (125 mg, 71%) as a colorless liquid. 
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.21 (m, 5H), 3.02-2.96 (m, 8H), 2.64 (t, *J* = 8 Hz, 2H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 172.33, 141.62, 128.58, 128.54, 128.45, 127.16, 126.21, 37.28, 35.56, 35.42, 31.51. **IR** (neat) 1642 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{11}H_{15}NO$ $(M+H)^+$: 178.1232, found: 178.1235.

***N*,*N*-Dimethyl-3-o-tolylpropanamide (1b).**[22] Complex **2a** (6.05 mg, 0.01 mmol), KO*t*Bu (146 mg, 1.3 mmol), 2-methylbenzyl alcohol (122 mg, 1 mmol), and *N*,*N*-dimethylacetamide (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method A to afford the amide **1b** (140 mg, 73%) as a pale yellow liquid. 
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17-7.09 (m, 4H), 2.98-2.93 (m, 8H), 2.56 (t, *J* = 8 Hz, 2H), 2.33 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 172.48, 139.67, 136.1, 130.39, 128.89,

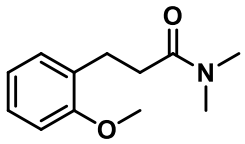
126.39, 126.22, 37.27, 35.57, 34.04, 28.82, 19.41. **IR** (neat) 1641 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{12}H_{17}NO$ $(M+H)^+$: 192.1388, found: 192.1391.

***N*,*N*-Dimethyl-3-m-tolylpropanamide** (**1c**).[22] Complex **2a** (6.05 mg, 0.01 mmol), KO*t*Bu (146 mg, 1.3 mmol), 3-methylbenzyl alcohol (122 mg, 1 mmol), and *N*,*N*-dimethylacetamide (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method A to afford the amide **1c** (135 mg, 71%) as a pale yellow liquid. 

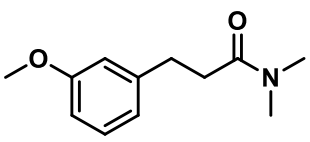
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (m, 1H), 7.03-7.01 (m, 3H), 2.95−2.90 (m, 8H), 2.60 (t, *J* = 8 Hz, 2H), 2.33 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 172.43, 141.57, 138.17, 129.36, 126.96, 125.52, 37.31, 35.52, 35.57, 31.45, 21.51. **IR** (neat) 1642 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{12}H_{17}NO$ $(M+H)^+$: 192.1388, found: 192.1390.

***N*,*N*-Dimethyl-3-p-tolylpropanamide** (**1d**).[22] Complex **2a** (6.05 mg, 0.01 mmol), KO*t*Bu (146 mg, 1.3 mmol), 4-methylbenzyl alcohol (122 mg, 1 mmol), and *N*,*N*-dimethylacetamide (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method A to afford the amide **1d** (132 mg, 69%) as a pale yellow liquid. 

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13−7.08 (m, 4H), 2.95−2.90 (m, 8H), 2.59 (t, *J* = 8 Hz 2H), 2.32 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 172.42, 138.52, 135.69, 129.25, 128.41, 37.29, 35.61, 35.55, 31.06, 21.12. **IR** (neat) 1641 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{12}H_{17}NO$ $(M + H)^+$: 192.1388, found: 192.1393.

3-(2-Methoxyphenyl)-N,N-dimethylpropanamide (**1e**).[22] Complex **2a** (6.05 mg, 0.01 mmol), KO*t*Bu (146 mg, 1.3 mmol), 2-methoxybenzyl alcohol (138 mg, 1 mmol), and *N*,*N*-dimethylacetamide (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method A to afford the amide **1e** (150 mg, 72%) as a pale yellow liquid. 

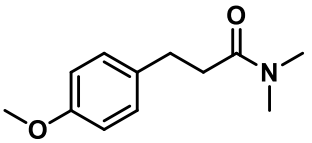
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21−7.16 (m, 2H), 6.89−6.83 (m, 2H), 3.82 (s, 3H), 2.95−2.94 (m, 8H), 2.59 (t, *J* = 8 Hz, 2H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 173.04, 157.59, 130.3, 127.58, 120.63, 114.32, 110.29, 55.30, 37.28, 35.49, 33.84, 26.80. **IR** (neat) 1643 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{12}H_{17}NO_2$ $(M+H)^+$:208.1337, found: 208.1340.

3-(3-Methoxyphenyl)-N,N-dimethylpropanamide (**1f**).[22] Complex **2a** (6.05 mg, 0.01 mmol), KO*t*Bu (146 mg, 1.3 mmol), 3-methoxybenzyl alcohol (138 mg, 1 mmol), and *N*,*N*-dimethylacetamide (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method A to afford the amide **1f** (145 mg, 70%) as a pale yellow liquid. 

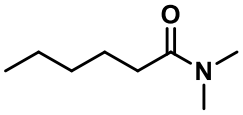
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22−7.18 (m, 1H), 6.82−6.73 (m, 3H), 3.79 (s, 3H), 2.95−2.93 (m, 8H), 2.60 (t, *J* = 8 Hz, 2H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 172.30, 159.81, 143.26, 129.57, 120.89, 114.30, 111.50, 55.29, 37.30, 35.58, 35.35, 31.55. **IR** (neat) 1640 cm^{-1}. HRMS (ESI) m/z calculated for $C_{12}H_{17}NO_2$ $(M+H)^+$: 208.1337, found: 208.1344.

3-(4-Methoxyphenyl)-N,N-dimethylpropanamide (**1g**).[22] Complex **2a** (6.05 mg, 0.01 mmol), KO*t*Bu (146 mg, 1.3 mmol), 4-methoxybenzyl alcohol (138 mg, 1

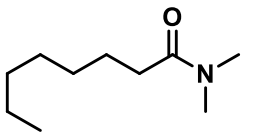
mmol), and *N*,*N*-dimethylacetamide (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method A to afford the amide **1g** (133 mg, 64%) as a pale yellow liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8 Hz, 2H), 6.82 (d, *J* = 8 Hz, 2H), 3.78 (s, 3H), 2.94−2.92 (m, 8H), 2.58 (t, *J* = 8 Hz, 2H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 172.54, 158.08, 133.61, 129.48, 113.98, 55.38, 37.34, 35.69, 35.58, 30.62. **IR** (neat) 1640 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{12}H_{17}NO_2$ $(M+H)^+$: 208.1337, found: 208.1339.



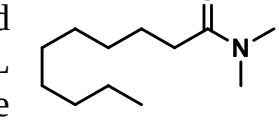
***N*,*N*-Dimethylhexanamide** (**1h**).[22] Complex **2a** (12.10 mg, 0.02 mmol), KO*t*Bu (146 mg, 1.3 mmol), butanol (74 mg, 1 mmol), and *N*,*N*-dimethylacetamide (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method A to afford the amide **1h** (59 mg, 41%) as a colorless liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.99 (s, 3H), 2.93 (s, 3H), 2.29 (t, *J* = 8 Hz, 2H), 1.62 (quintet, *J* = 8 Hz, 2H), 1.30−1.33 (m, 4H), 0.89 (m, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) 173.55, 37.46, 35.51, 33.51, 31.81, 25.01, 22.62, 14.1. **IR** (neat) 1643 cm^{-1}. HRMS (ESI) m/z calculated for $C_8H_{17}NO$ $(M+H)^+$: 144.1388, found: 144.1390.



***N*,*N*-Dimethyloctanamide** (**1i**).[22] Complex **2a** (12.10 mg, 0.02 mmol), KO*t*Bu (146 mg, 1.3 mmol), hexanol (102 mg, 1 mmol), and *N*,*N*-dimethylacetamide (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method A to afford the amide 1i (71 mg, 42%) as a colorless liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.99 (s, 3H), 2.93 (s, 3H), 2.29 (t, *J* = 8 Hz, 2H), 1.61 (quintet, *J* = 8 Hz, 2H), 1.30−1.27 (m, 8H), 0.86 (m, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) 173.44, 37.44, 35.49, 33.57, 31.87, 29.62, 29.25, 22.76, 14.21. **IR** (neat) 1642 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{10}H_{21}NO$ $(M+H)^+$: 172.1701, found: 172.1701.

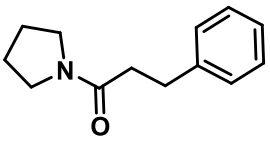


***N*,*N*-Dimethyldecanamide** (**1j**).[22] Complex **2a** (12.10 mg, 0.02 mmol), KO*t*Bu (146 mg, 1.3 mmol), octanol (130 mg, 1 mmol), and *N*,*N*-dimethylacetamide (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method A to afford the amide **1J** (100.5 mg, 50%) as a colorless liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.99 (s, 3H), 2.92 (s, 3H), 2.28 (t, *J* = 8 Hz, 2H), 1.60 (quintet, *J* = 8 Hz, 2H), 1.28−1.24 (m, 12H), 0.86 (m, 3H). **^{13}C{^{1}H} NMR** (100 MHz, CDC_{l3}) 173.48, 37.43, 33.55, 31.99, 29.64, 29.6, 29.58, 29.4, 25.33, 22.77, 14.19. **IR** (neat) 1645 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{12}H_{25}NO$ $(M+H)^+$: 200.2014, found: 200.2016.

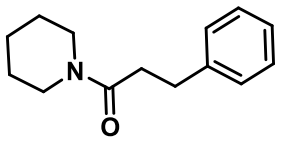


***N*,*N*-Dimethyl-5-methylhexanamide** (**1k**).[22] Complex **2a** (12.10 mg, 0.02 mmol), KO*t*Bu (146 mg, 1.3 mmol), iso-amyl alcohol (88 mg, 1 mmol), and *N*,*N*-dimethylacetamide (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method A to afford the amide **1k** (65 mg, 41%) as a colorless liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.00 (s, 3H), 2.94 (s, 3H), 2.28 (t, *J* = 8 Hz, 2H), 1.66−1.56 (m, 5H), 1.21 (m, 2H), 0.88 (d, *J* = 6H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 173.45, 38.88, 37.43, 35.49, 33.77, 28.03, 23.18,

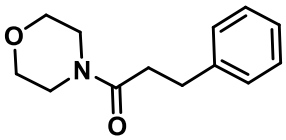
22.67. **IR** (neat) 1644 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_9H_{19}NO$ $(M+H)^+$: 158.1545, found: 158.1548.

3-Phenyl-1-(pyrrolidin-1-yl)propan-1-one (**1l**).[22] Complex **2a** (6.05 mg, 0.01 mmol), KO*t*Bu (146 mg, 1.3mmol), benzyl alcohol (108 mg, 1 mmol), and Nacetylpyrrolidine (226 mg, 2 mmol) were allowed to react ina 20 mL resealable pressure tube according to method A to afford the cyclic amide **1l** (78 mg, 38%) as a yellow liquid. 

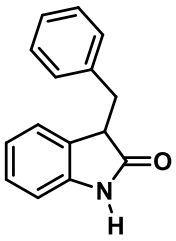
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.21 (m, 5H), 3.46 (t, *J* = 6.7 Hz, 2H), 3.28 (t, *J* = 6.6 Hz 2H), 2.98 (t, *J* = 8 Hz, 2H), 2.56 (t, *J* = 8.0 Hz, 2H), 1.89−1.80 (m, 4H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 170.97, 141.64, 128.88, 128.57, 127.96, 126.19, 46.71, 45.79, 36.89, 31.36, 26.18, 24.51. **IR** (neat) 1641 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{13}H_{17}NO$ $(M+H)^+$: 204.1388, found: 204.1389.

3-Phenyl-1-(piperidin-1-yl)propan-1-one (**1m**).[22] Complex **2a** (6.05 mg, 0.01 mmol), KO*t*Bu (146 mg, 1.3 mmol), benzyl alcohol (108 mg, 1 mmol), and *N*-acetylpiperidine (254 mg, 2 mmol) were allowed to react in a 20 mL resealable pressure tube according to method A to afford the cyclic amide **1m** (105 mg, 48%) as a yellow liquid. 

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18−7.05 (m, 5H), 3.43 (m, 2H), 3.20 (m, 2H), 2.84 (t, *J* = 8 Hz, 2H), 2.49 (t, *J* = 8.0 Hz, 2H), 1.31−1.48 (m, 6H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 170.58, 141.63, 128.6, 128.58, 126.93, 126.22, 46.77, 42.87, 35.33, 31.77, 26.54, 25.69, 24.76, 24.68. **IR** (neat) 1633 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{14}H_{19}NO$ $(M+H)^+$: 218.1545, found: 218.1547.

1-Morpholino-3-phenylpropan-1-one (**1n**).[22] Complex **2a** (6.05 mg, 0.01 mmol), KO*t*Bu (146 mg, 1.3 mmol), benzyl alcohol (108 mg, 1 mmol), and *N*-acetyl morpholine (258 mg, 2 mmol) were allowed to react in a 20 mL resealable pressure tube according to method A to afford the cyclic amide **1n** (88 mg, 40%) as a pale yellow liquid. 

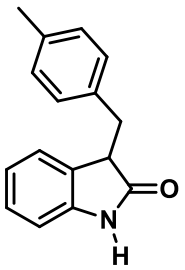
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16−7.05 (m, 5H), 3.47 (s, 4H), 3.35 (t, *J* = 4 Hz, 2H), 3.2 (t, *J* = 4 Hz, 2H), 2.82 (t, *J* = 8 Hz, 2H), 2.46 (t, *J* = 8 Hz, 2H). **^{13}C{^{1}H} NMR** (100 Hz, $CDCl_3$) δ 171.05, 141.16, 128.68, 128.59, 127.21, 126.41, 66.98, 66.59, 46.1, 42.07, 34.94, 31.61. **IR** (neat) 1639 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{13}H_{17}NO_2$ $(M+H)^+$: 220.1337, found: 220.1343.

3-Benzylindolin-2-one (**4a**).[20a] Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (146 mg, 1.3 mmol), benzyl alcohol (108 mg, 1 mmol), oxindole (266 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method B to afford 3-benzylindolin-2-one (209 mg, 94%) as a yellow solid. 

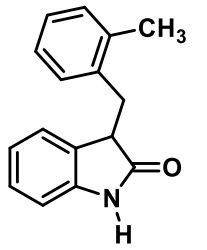
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (bs, 1H), 7.29−7.27 (m, 1H), 7.25−7.22 (m, 2H), 7.20−7.15 (m, 3H), 6.92−6.89 (dt, *J* = 4 Hz, 1H), 6.86 (d, *J* = 8 Hz, 1H), 6.75 (d, *J* = 8 Hz, 1H), 3.76 (dd, *J* = 9.2, 4.6 Hz, 1H), 3.51 (dd, *J* = 13.7, 4.6 Hz, 1H), 2.95 (dd, *J* = 13.7, 9.3 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 179.77, 141.50, 137.88, 129.52, 129.05, 128.43, 128.05, 126.77,

124.94, 122.11, 109.81, 47.63, 36.71. **IR** (neat) 1705 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{15}H_{13}NO$ $(M+H)^+$: 224.1075, found: 224.1085.

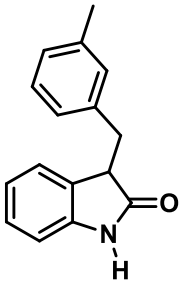
3-(4-Methylbenzyl)indolin-2-one (**4b**).[20a] Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (146 mg, 1.3 mmol), 4-methyl benzyl alcohol (122 mg, 1 mmol), oxindole (266 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method B to afford 3-(4-methylbenzyl)indolin-2-one (201 mg, 85%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.16 (dd, *J* = 12, 4 Hz, 1H), 7.11−7.03 (m, 4H), 6.94−6.83 (m, 2H), 6.77 (d, *J* = 8 Hz, 1H), 3.74 (dd, *J* = 8, 4 Hz, 1H), 3.47 (dd, *J* = 12, 4 Hz, 1H), 2.91 (dd, *J* = 12, 8 Hz, 1H), 2.31 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 180.01, 141.62, 136.27, 134.81, 129.61, 29.02, 128.01, 124.96, 122.08, 109.88, 47.77, 36.33, 21.18. **IR** (neat) 1703 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{16}H_{15}NO$ $(M+H)^+$: 238.1232, found: 238.1241.



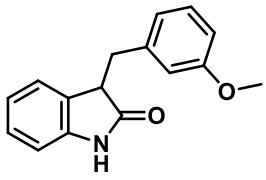
3-(2-Methylbenzyl)indolin-2-one (**4c**).[20a] Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (146 mg, 1.3 mmol), 3-methyl benzyl alcohol (122 mg, 1 mmol), oxindole (266 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method B to afford 3-(2-methylbenzyl)indolin-2-one (220 mg, 93%) as a yellow crystalline solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.34 (bs, 1H), 7.36−7.28 (m, 1H), 7.20−7.17 (m, 4H), 6.95−6.92 (m, 1H), 6.85 (t, *J* = 8 Hz, 1H), 6.54 (d, *J* = 8 Hz, 1H), 3.72 (dd, *J* = 10.9, 4.5 Hz, 1H), 3.52 (dd, *J* = 13, 4.0 Hz, 1H), 2.81 (dd, *J* = 12, 8 Hz, 1H), 2.31 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 180.34, 141.58, 136.80, 136.67, 130.62, 130.16, 129.30, 128.04, 126.98, 125.97, 125.10, 122.02, 110.17, 46.41, 34.40, 19.90. **IR** (neat) 1704 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{16}H_{15}NO$ $(M+H)^+$: 238.1232, found: 238.1245.



3-(3-Methylbenzyl)indolin-2-one (**4d**).[20a] Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (146 mg, 1.3 mmol), 3-methyl benzyl alcohol (122 mg, 1 mmol), oxindole (266 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method B to afford 3-(3-methylbenzyl)indolin-2-one (196 mg, 83%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.68 (bs, 1H), 7.21−7.16 (t, *J* = 8 Hz, 2H), 7.07−7.01 (m, 3H), 6.94−6.92 (t, *J* = 8 Hz, 2H), 6.76−6.74 (d, *J* = 8 Hz, 1H), 3.77 (dd, *J* = 9.5, 4.4 Hz, 1H), 3.51 (dd, *J* = 13.7, 4.0 Hz, 1H), 2.88 (dd, *J* = 13.6, 9.7 Hz, 1H), 2.01 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 180.57, 141.98, 138.05, 131.17, 129.87, 129.44, 128.36, 128.06, 127.54, 126.55, 124.93, 121.98, 111.00, 47.78, 36.73, 21.51. **IR** (neat) 1714 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{16}H_{15}NO$ $(M+H)^+$: 238.1232, found: 238.1242.

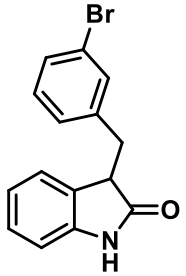


3-(3-Methoxybenzyl)indolin-2-one (**4e**). Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (146 mg, 1.3 mmol), 3-methoxybenzyl alcohol (138 mg, 1 mmol), oxindole (266 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method B to afford 3-(3-methoxybenzyl)indolin-2-one **4e** (172 mg, 68%) as

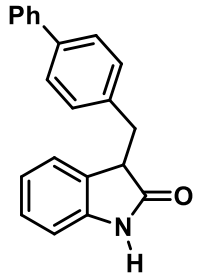


a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.93 (bs, 1H), 7.17 (t, *J* = 8 Hz, 2H), 6.91 (td, *J* = 7.6, 1.0 Hz, 1H), 6.66 (d, *J* = 8 Hz, 1H), 6.80−6.73 (m, 4H), 3.75 (dd, *J* = 9.3, 4.5 Hz, 1H), 3.72 (s, 3H), 3.48 (dd, *J* = 13.7, 4.5 Hz, 1H), 2.91 (dd, *J* = 13.7, 9.3 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 179.83, 159.64, 141.59, 139.51, 129.43, 129.12, 128.10, 125.00, 122.16, 121.95, 114.85, 112.56, 109.89, 55.25, 47.60, 36.80. **IR** (neat) 1707 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{16}H_{15}NO_2$ $(M+H)^+$: 254.1181, found: 254.1188.

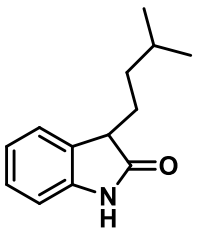
3-(3-Bromobenzyl)indolin-2-one (**4f**). Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (146 mg, 1.3 mmol), biphenyl-4-methanol (185 mg, 1 mmol), oxindole (266 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method B to afford 3-(3-Bromobenzyl)indolin-2-one **4f** (240 mg, 80%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 7.37−7.32 (m, 2H), 7.17 (tt, *J* = 6.8, 3.0 Hz, 1H), 7.04−7.00 (m, 2H), 6.93 (tt, *J* = 8.4, 4.1 Hz, 1H), 6.84 (dd, *J* = 7.6, 2.9 Hz, 2H), 3.73 (dd, *J* = 8.5, 4.6 Hz, 1H), 3.39 (dd, *J* = 13.8, 4.7 Hz, 1H), 2.98 (dd, *J* = 8, 4 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 179.49, 141.55, 136.65, 131.46, 131.26, 128.52, 128.26, 124.73, 122.26, 120.72, 109.98, 47.37, 35.95. **IR** (neat) 1707 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{15}H_{12}BrNO$ $(M+H)^+$: 302.0180, found: 302.0189.

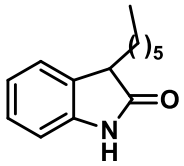


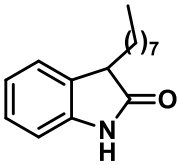
3-([1,1'-Biphenyl]-4-ylmethyl)indolin-2-one (**4g**). Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (146 mg, 1.3 mmol), biphenyl-4-methanol (184 mg, 1 mmol), oxindole (266 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method B to afford 3-([1,1'-biphenyl]-4-ylmethyl)indolin-2-one (252 mg, 84%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.63−7.58 (m, 2H), 7.54−7.50 (m, 2H), 7.48−7.43 (m, 2H), 7.40−7.32 (m, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.23−7.18 (m, 1H), 6.96 (td, *J* = 7.5, 0.9 Hz, 1H), 6.89 (dd, *J* = 11.0, 7.6 Hz, 2H), 3.82 (dd, *J* = 9.1, 4.5 Hz, 1H), 3.56 (dd, *J* = 13.7, 4.6 Hz, 1H), 3.03 (dd, *J* = 13.7, 9.1 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 179.78, 141.57, 140.80, 139.52, 136.97, 129.94, 129.08, 128.84, 128.12, 127.20, 127.07, 127.03, 124.94, 122.18, 109.91, 47.60, 36.34. **IR** (neat) 1706 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{21}H_{17}NO$ $(M+H)^+$: 300.1388, found: 300.1394.

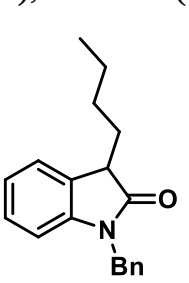


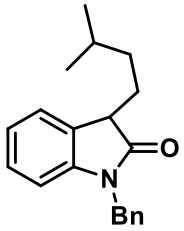
3-Isopentylindolin-2-one (**4h**). Complex **2a** (12 mg, 0.02 mmol), KO*t*Bu (146 mg, 1.3 mmol), amyl alcohol (88 mg, 1 mmol), oxindole (266 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method B to afford 3-isopentylindolin-2-one (98 mg, 48%) as a colorless liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.58 (bs, 1H), 7.24−7.19 (m, 2H), 7.04−7.00 (m, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 3.47 (t, *J* = 8 Hz, 1H), 2.05−1.92 (m, 2H), 1.58−1.52 (m, 1H), 1.35−1.16 (m, 2H), 0.87 (d *J* = 8 Hz, 6H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 181.44, 141.97, 130.02, 127.85, 124.11, 122.29, 110.01, 46.43, 34.71, 28.50, 28.21, 22.51. **IR** (neat) 1701 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{13}H_{17}NO$ $(M+H)^+$: 204.1388, found: 204.1391.



3-Hexylindolin-2-one (**4i**). Complex **2a** (12 mg, 0.02 mmol), KO*t*Bu (146 mg, 1.3 mmol), 1-hexanol (102 mg, 1 mmol), oxindole (266 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method B to 3-hexylindolin-2-one (174 mg, 80%) as a colorless liquid. 
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 7.24−7.18 (m, 2H), 7.01 (dd, *J* = 11.0, 4.1 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 3.47 (t, *J* = 6.0 Hz, 1H), 2.07−1.87 (m, 2H), 1.44−1.25 (m, 8H), 0.85 (t, *J* = 6.9 Hz, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 181.06, 141.78, 130.03, 127.83, 124.17, 122.27, 109.85, 46.27, 31.64, 30.62, 29.35, 25.82, 22.66, 14.11. **IR** (neat) 1701 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{14}H_{19}NO$ $(M+H)^+$: 218.1545, found: 218.1552.

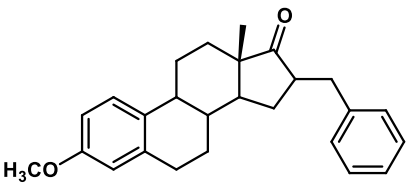
3-Octylindolin-2-one (**4j**). Complex **2a** (12 mg, 0.02 mmol), KO*t*Bu (146 mg, 1.3 mmol), 1-octanol (130 mg, 1 mmol), oxindole (266 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method B to afford 3-octylindolin-2-one (183 mg, 75%) as a yellow liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.90 (s, 1H), 7.23 (dd, *J* = 13.7, 7.4 Hz, 2H), 7.07−7.01 (m, 1H), 6.98 (d, *J* = 7.7 Hz, 1H), 3.50 (t, *J* = 6.0 Hz, 1H), 2.08−1.90 (m, 2H), 1.52−1.20 (m, 12H), 0.89 (t, *J* = 6.9 Hz, 3H). 
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 181.66, 142.07, 130.07, 127.83, 124.07, 122.21, 110.07, 46.41, 31.91, 30.62, 29.72, 29.42, 29.33, 25.88, 22.72, 14.18. **IR** (neat) 1715 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{16}H_{23}NO$ $(M+H)^+$: 246.1858, found: 246.1861.

1-Benzyl-3-butylindolin-2-one (**4k**). Complex **2a** (12 mg, 0.02 mmol), KOtBu (146 mg, 1.3 mmol), iso-amyl alcohol (88 mg, 1 mmol), *N*-benzyl oxindole (446 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method B to 1-benzyl-3- butylindolin-2-one (94 mg, 34%) as a yellow liquid. 
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.29 (m, 5H), 7.29−7.27 (m, 1H), 7.20−7.14 (m, 1H), 7.03 (td, *J* = 8, 0.9 Hz, 1H), 6.73 (d, *J* = 7.7 Hz, 1H), 4.99 (d, *J* = 16 Hz, 1H), 4.87 (d, *J* = 16 Hz, 1H), 3.55 (t, *J* = 6.0 Hz, 1H), 2.06−2.00 (m, 2H), 1.47−1.24 (m, 5H), 0.90 (t, *J* = 8 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.20, 143.59, 136.15, 129.41, 128.82, 127.77, 127.63, 127.39, 124.00, 122.36, 109.03, 45.66, 43.74, 30.64, 28.09, 22.82, 13.98. **IR** (neat) 1703, 3031 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{19}H_{22}NO$ $(M+H)^+$: 280.1701, found: 280.1707.

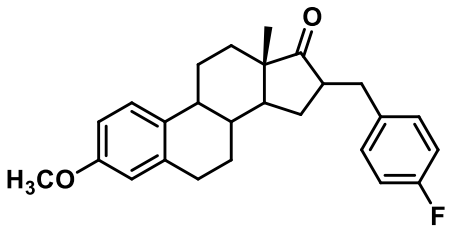
1-Benzyl-3-isopentylindolin-2-one (**4l**). Complex **2a** (12 mg, 0.02 mmol), KO*t*Bu (146 mg, 1.3 mmol), iso-amyl alcohol (88 mg, 1 mmol), N-benzyl oxindole (446 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method B to 1-benzyl-3-isopentylindolin-2-one (128 mg, 44%) as a colorless liquid. 
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.27 (m, 4H), 7.23−7.21 (m, 2H), 7.14−7.10 (m, 1H), 6.98 (dd, *J* = 7.6, 6.6 Hz, 1H), 6.68 (d, *J* = 8 Hz, 1H), 4.95 (d, *J* = 16 Hz, 1H), 4.82 (d, *J* = 16 Hz, 1H), 3.50 (t, *J* = 4 Hz, 1H), 2.05−1.94 (m, 2H), 1.56−1.49 (m, 1H), 1.28−1.14 (m, 2H), 0.85 (d, *J* = 8 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.13, 143.58, 136.13, 129.35, 128.78, 127.76, 127.61,

127.38, 123.95, 122.35, 109.00, 45.72, 43.70, 34.79, 28.76, 28.19, 22.52. **IR** (neat) 1704 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{20}H_{23}NO$ $(M+H)^+$: 294.1858, found: 294.1873.

(8R,9S,13S,14S)-16-Benzyl-3-methoxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]-phenanthren-17-one (**4m**).[18] Complex **2a** (1.5 mg, 0.0025 mmol), KO*t*Bu (36 mg, 0.32 mmol), benzyl alcohol (27 mg, 0.25 mmol), and estron 3-methyl ether (72 mg, 0.25 mmol) were allowed to react in a 20 mL resealable pressure tube according to method B to afford the product (8R,9S,13S,14S)-16-Benzyl-3-methoxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]-phenanthren-17-one **4m** (85 mg, 92%) as a white crystalline solid with a mixture of diastereoisomers based on ^{1}H NMR spectra. Spectral data for maior diastereoisomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.3 Hz, 1H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.31 (t, *J* = 7.3 Hz, 3H), 6.77−6.70 (m, 2H), 6.64 (d, *J* = 2.7 Hz, 2H), 3.78 (s, 3H), 3.24 (dd, *J* = 13.6, 4.1 Hz, 1H), 3.04−2.84 (m, 6H), 2.70 (dd, *J* = 13.6, 9.8 Hz, 1H), 2.15−2.03 (m, 3H), 1.70−1.53 (m, 5H), 0.73 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 157.62, 139.90, 137.74, 136.04, 133.21, 132.06, 130.35, 129.03, 128.71, 128.44, 126.29, 113.89, 111.56, 55.22, 51.37, 49.00, 48.58, 46.42, 44.13, 37.86, 37.62, 29.66, 27.94, 26.76, 13.65. **IR** (neat) 1732 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{26}H_{30}O_2$ $(M+H)^+$: 375.2324, found: 375.2326.

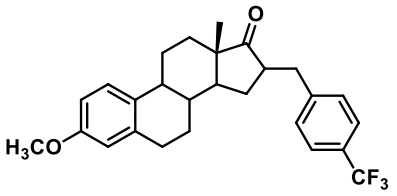


(8R,9S,13S,14S)-16-(4-Fluorobenzyl)-3-methoxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17Hcyclopenta[a]phenanthren-17-one (**4n**). Complex **2a** (1.5 mg, 0.0025 mmol), KO*t*Bu (36 mg, 0.32 mmol), 4- fluorobenzyl alcohol (32 mg, 0.25 mmol), and estron 3-methyl ether (71 mg, 0.25 mmol) were allowed to react in a 20 mL resealable pressure tube according to method B to afford the product (8R,9S,13S,14S)-16-(4-Fluorobenzyl)-3-methoxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17Hcyclopenta[a]phenanthren-17-one **4n** (77 mg, 80%) as a white crystalline solid with a mixture of diastereoisomers based on ^{1}H NMR spectra. Spectral data for major diastereoisomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22−7.18 (m, 2H), 7.04−7.01 (m, 2H), 6.77 (d, *J* = 2.8 Hz, 1H), 6.70 (d, *J* = 2.6 Hz, 2H), 3.83 (s, 3H), 3.23 (dd, *J* = 13.8, 4.2 Hz, 1H), 2.99−2.89 (m, 4H), 2.77 (dd, *J* = 13.8, 9.4 Hz, 1H), 2.50−2.40 (m, 2H), 2.03−2.00 (m, 3H), 1.57 (d, *J* = 9.2 Hz, 3H), 0.76 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 161.57 (d, *J* = 242 Hz), 157.65, 137.73, 135.81, 135.78 (d, *J* = 3.18 Hz), 135.51, 135.47 (d, J = 3.18), 132.02, 130.47, 126.32, 115.34, 115.20 (d, *J* = 20.99), 115.13, 113.93, 111.62, 55.23, 51.39, 49.01, 48.58, 44.16, 37.87, 36.63, 32.03, 29.69, 27.81, 26.81, 25.92, 13.62. **IR** (neat) 1733 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{26}H_{29}FO_2$ $(M+H)^+$: 393.2230, found: 393.2232.

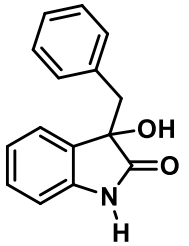


(8R,9S,13S,14S)-3-Methoxy-13-methyl-16-(4-(trifluoromethyl)benzyl)-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one (**4o**).

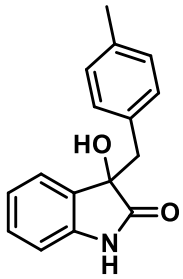
Complex **2a** (1.5 mg, 0.0025 mmol), KO*t*Bu (36 mg, 0.32 mmol), 4-trifluorobenzyl alcohol (44 mg, 0.25 mmol), and estron 3-methyl ether (71 mg, 0.25 mmol) were allowed to react in a 20 mL resealable pressure tube according to method B to afford the product (8R,9S,13S,14S)-3-Methoxy-13-methyl-16-(4-(trifluoromethyl)benzyl)-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one **4o** (92 mg, 88%) as a white crystalline solid with a mixture of diastereoisomers based on ^{1}H NMR spectra. Spectral data for major diastereoisomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 (s, 2H), 7.32 (s, 2H), 7.19 (s, 1H), 6.72 (d, *J* = 2.1 Hz, 1H), 6.65 (s, 1H), 3.78 (s, 3H), 3.29 (dd, *J* = 13.7, 4.1 Hz, 1H), 2.88 (dd, *J* = 9.9, 4.7 Hz, 4H), 2.48−2.35 (m, 3H), 2.02−1.91 (m, 3H), 1.59−1.34 (m, 6H), 0.76 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 171.14, 157.69, 144.16, 137.73, 131.97, 129.35, 128.68 (q, *J* = 32 Hz), 126.32, 125.86 (q, *J* = 3.6 Hz), 124.30 (q, *J* = 270 Hz), 113.95, 111.64, 55.23, 51.03, 49.01, 48.61, 44.17, 37.88, 32.02, 29.68, 28.00, 26.85, 25.91, 13.82. **IR** (neat) 1733, cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{27}H_{29}F_3O_2$ $(M+H)^+$: 443.2198, found: 443.2206.



3-Benzyl-3-hydroxyindolin-2-one (**5a**).[22] Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), benzyl alcohol (108 mg, 1 mmol), oxindole (266 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 3-benzyl-3-hydroxyindolin-2-one (166 mg, 69%) as a white crystalline solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.17 (d, *J* = 7.7 Hz, 1H), 7.12 (d, *J* = 6.8 Hz, 3H), 7.02 (d, *J* = 7.4 Hz, 1H), 6.98 (t, *J* = 6.4 Hz, 3H), 6.70 (d, *J* = 7.7 Hz, 1H), 3.71 (s, 1H), 3.30 (d, *J* = 13.0 Hz, 1H), 3.12 (d, *J* = 13.0 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 179.69, 140.27, 133.92, 130.57, 129.84, 128.81, 128.0, 127.11, 125.10, 122.98, 110.21, 44.75. **IR** (neat) 3264, 1710 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{15}H_{13}NO_2$ $(M+Na)^+$: 262.0843, found: 262.0841.

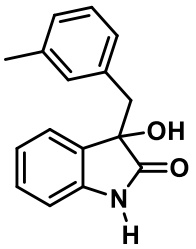


3-Hydroxy-3-(4-methylbenzyl)indolin-2-one (**5b**).[22] Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), 4-methylbenzyl alcohol (122 mg, 1 mmol), oxindole (266 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 3-hydroxy-3-(4-methylbenzyl)indolin-2-one (130 mg, 55%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (bs, 1H), 7.22−7.13 (m, 2H), 7.05−7.03 (t, 1H), 6.95−6.93 (d, *J* = 8 Hz, 2H), 6.88−6.86 (d, *J* = 8 Hz, 2H), 6.72−6.70 (d, *J* = 8 Hz 1H), 3.28−3.24 (d, *J* = 8 Hz, 1H), 3.18 (s, 1H), 3.11−3.08 (d, *J* = 12 Hz, 1H), 2.24 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 179.69, 140.31, 136.69, 130.72, 130.42, 129.78, 129.50, 128.79, 125.34, 125.08, 122.95, 110.19, 44.35, 21.19. **IR** (neat) 3320, 2942, 1729 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{16}H_{15}NO_2$ $(M + Na)^+$: 276.1000, found: 276.1000.

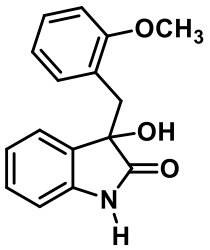


3-Hydroxy-3-(3-methylbenzyl)indolin-2-one (**5c**). Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), 3-methylbenzyl alcohol (122 mg, 1 mmol), oxindole (266 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 3-hydroxy-3-(3-methylbenzyl)indolin-2-one

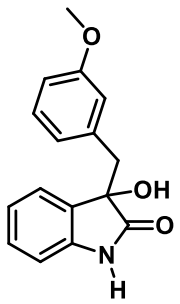
(114 mg, 45%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.24−7.14 (m, 2H), 7.03 (t, *J* = 8 Hz, 2H), 6.97 (d, *J* = 8 Hz, 1H), 6.83−6.75 (m, 2H), 6.72 (d, *J* = 8 Hz, 1H), 3.27 (d, *J* = 12 Hz, 1H), 3.19 (s, 1H), 3.09 (d, *J* = 12 Hz, 1H), 2.20 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 179.72, 140.31, 137.59, 133.79, 131.38, 129.83, 127.88, 127.58, 125.14, 122.91, 110.19, 44.72, 21.41. **IR** (neat) 3262, 2923, 1715 cm^{-1}. HRMS (ESI) m/z calculated for $C_{16}H_{15}NO_2$ $(M+Na)^+$: 276.1000, found: 276.1000.



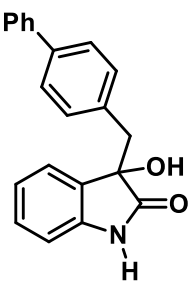
3-Hydroxy-3-(2-methoxybenzyl)indolin-2-one (**5d**). Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), 2-methoxylbenzyl alcohol (122 mg, 1 mmol), oxindole (266 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 3-hydroxy-3-(2-methoxylbenzyl)indolin-2-one (147 mg, 55%) as a yellow liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.26−7.22 (m, 1H), 7.18 (td, *J* = 7.7, 1.2 Hz, 1H), 6.93 (dd, *J* = 8 Hz, 2H), 6.90−6.85 (m, 2H), 6.84−6.79 (m, 2H), 4.36 (bs, 1H), 3.77 (s, 3H), 3.63 (d, *J* = 13.8 Hz, 1H), 2.86 (dd, *J* = 13.8, 1.3 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 180.86, 157.86, 140.17, 132.86, 130.39, 129.36, 128.81, 125.53, 123.06, 122.36, 120.73, 110.74, 110.17, 77.66, 55.53, 38.52. IR (neat) 3256.92, 2928.24, 1715.51 cm^{-1}. HRMS (ESI) m/z calculated for $C_{16}H_{15}NO_2$ $(M+H)^+$: 270.1130, found: 270.1134.



3-Hydroxy-3-(3-methoxybenzyl)indolin-2-one (**5e**).[23] Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), 3-methoxylbenzyl alcohol (122 mg, 1 mmol), oxindole (266 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 3-hydroxy-3-(3-methoxylbenzyl)indolin-2-one (67 mg, 25%) as a light brown solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (bs, 1H), 7.20−7.17 (m, 2H), 7.05−7.01 (m, 2H), 6.70−6.68 (m, 2H), 6.57 (m, 1H), 6.48 (m, 1H), 3.61 (s, 3H), 3.43 (bs, 1H), 3.38 (d, *J* = 12 Hz, 1H), 3.11 (d, *J* = 16 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 180.23, 159.08, 140.46, 135.45, 129.98, 129.80, 128.96, 125.01, 123.02, 122.98, 115.59, 113.11, 110.43, 77.69, 55.17, 44.68, 29.83. **IR** (neat) 3228, 1704 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{16}H_{15}NO_3$ $(M+Na)^+$: 292.0949, found: 292.0948.

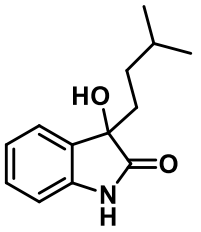


3-([1,1'-Biphenyl]-4-ylmethyl)-3-hydroxyindolin-2-one (**5f**). Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), biphenyl-4-methanol (184 mg, 1 mmol), oxindole (266 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 3-([1,1'-biphenyl]-4-ylmethyl)-3-hydroxyindolin-2-one (133 mg, 42%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57−7.50 (m, 2H), 7.43−7.38 (m, 3H), 7.35−7.28 (m, 1H), 7.20 (dd, *J* = 8, 5.0 Hz, 3H), 7.11−7.01 (m, 3H), 6.72 (d, *J* = 8 Hz, 2H), 3.35 (d, *J* = 12 Hz, 1H), 3.18 (d, *J* = 12 Hz, 1H), 2.81 (bs, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 130.66, 128.55, 126.69, 126.18, 124.56, 122.35,

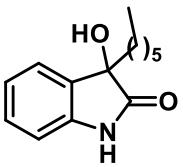


109.93, 77.42, 77.20, 76.78, 49.81, 49.37, 49.09, 48.83, 48.18, 48.18, 45.57, 43.58, 29.53. **IR** (neat) 3335, 1715 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{21}H_{17}NO_2$ $(M+Na)^+$: 338.1156, found: 338.1163.

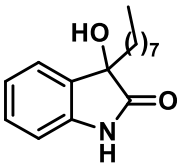
3-Hydroxy-3-isopentylindolin-2-one (**5g**).[22] Complex **2a** (12 mg, 0.02 mmol), KO*t*Bu (258 mg, 2.3 mmol), isoamyl alcohol (88 mg, 1 mmol), oxindole (266 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 3-hydroxy-3-isopentylindolin-2-one (77 mg, 35%) as a pale yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.77 (bs, 1H), 7.33 (d, *J* = 6.6 Hz, 1H), 7.25−7.19 (m, 1H), 7.11−7.02 (m, 1H), 6.88 (d, *J* = 7.5 Hz, 1H), 3.37 (bs, 1H), 2.04−1.89 (m, 2H), 1.45 (dt, *J* = 12.9, 6.4 Hz, 1H), 1.15−0.88 (m, 2H), 0.79 (d, *J* = 6.3 Hz, 6H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 190.73, 140.72, 129.67, 124.35, 123.24, 110.67, 36.49, 31.86, 28.21, 22.53, 22.44. **IR** (neat) 3389, 3680, 1711 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{13}H_{17}NO_2$ $(M+Na)^+$: 242.1156, found: 242.1161.



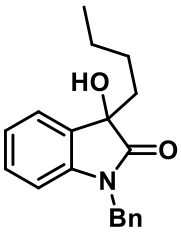
3-Hexyl-3-hydroxyindolin-2-one (**5h**).[22] complex **2a** (12 mg, 0.02 mmol), KO*t*Bu (258 mg, 2.3 mmol), 1-hexanol (102 mg, 1 mmol), oxindole (266 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 3-hexyl-3-hydroxyindolin-2-one **5h** (115 mg, 48%) as a pale yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.11 (s, 1H), 7.31 (d, *J* = 7.3 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 7.7 Hz, 1H), 4.16 (s, 1H), 1.91 (dt, *J* = 13.0, 7.3 Hz, 2H), 1.14 (m, 8H), 0.80 (t, *J* = 6.9 Hz, 3H). **^{13}C{^{1}H} NMR** (400 MHz, $CDCl_3$) δ 181.64, 140.76, 130.98, 129.53, 124.22, 123.13, 110.70, 77.28, 38.37, 31.60, 29.39, 23.09, 22.61, 14.11. **IR** (neat) 3678, 3324, 1711, cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{14}H_{20}NO_2$ $(M+H)^+$: 234.1494, found: 234.1486.



3-Hydroxy-3-octylindolin-2-one (**5i**).[22] Complex **2a** (12 mg, 0.02 mmol), KO*t*Bu (258 mg, 2.3 mmol), 1-hexanol (130 mg, 1 mmol), oxindole (266 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealabl pressure tube according to method C to afford 3-hydroxy-3-octylindolin-2-one **5i** (110 mg, 42%) as a pale yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.69 (bs, 1H), 7.35−7.25 (m, 1H), 7.22−7.25 (m, 1H), 6.87 (d, *J* = 12 Hz, 1H), 2.76 (bs, 1H), 1.96−1.94 (m, 2H), 1.25−1.19 (m, 12H), 0.85 (t, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 180.31, 140.51, 130.56, 129.75, 124.46, 123.28, 110.29, 77.07, 38.72, 31.91, 29.74, 29.41, 29.28, 23.20, 22.75, 14.23. **IR** (neat) 3267, 1713 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{16}H_{22}NO_2$ $(M+Na)^+$: 284.1626, found: 284.1626.

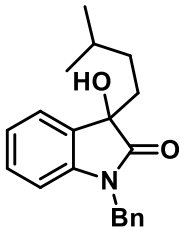


1-Benzyl-3-butyl-3-hydroxyindolin-2-one (**5j**).[22] Complex **2a** (12 mg, 0.02 mmol), KO*t*Bu (258 mg, 2.3 mmol), 1-butanol (74 mg, 1 mmol), *N*-benzyl-2-oxindole (446 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 1-benzyl-3-butyl-3-hydroxyindolin-2-one **5j** (141 mg, 48%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36−7.34

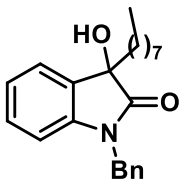


(d, *J* = 8 Hz, 1H), 7.30−7.27 (m, 3H), 7.25−7.20 (m, 2H), 7.17 (dt, *J* = 8 Hz, 1H), 7.03 (dt, *J* = 8 Hz, 1H), 7.69 (d, *J* = 8 Hz, 1H), 4.97 (d, *J* = 16 Hz, 1H), 4.73 (d, *J* = 16 Hz, 1H), 3.11 (s, 1H), 2.02−1.97 (m, 2H), 1.26−1.03 (m, 4H), 0.88 (t, *J* = 8 Hz, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 179.03, 143.09, 135.98, 130.54, 129.24, 127.74, 124.39, 123.60, 109.19, 44.26, 38.97, 25.88, 23.18, 14.28. **IR** (neat) 3338, 2930, 1696 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{19}H_{21}NO_2$ $(M+Na)^+$: 318.1469, found: 318.1472.

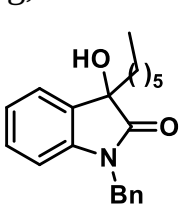
1-Benzyl-3-hydroxy-3-isopentylindolin-2-one (**5k**). Complex **2a** (12 mg, 0.02 mmol), KO*t*Bu (258 mg, 2.3 mmol), iso-amyl alcohol (88 mg, 1 mmol), *N*-benzyl-2-oxindole (446 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 1-benzyl-3-hydroxy-3-isopentylindolin-2-one **5k** (123 mg, 40%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 4 Hz, 1H), 7.31−7.27 (m, 3H), 7.24−7.12 (m, 3H), 7.03 (t, *J* = 8 Hz, 1H), 6.69 (d, *J* = 8 Hz, 1H), 5.98 (d, *J* = 16 Hz, 1H), 4.73 (d, *J* = 16 Hz, 1H), 3.60 (s, 1H), 2.05−1.99 (m, 2H), 1.45−1.42 (m, 1H), 1.06−1.02 (m, 1H), 0.94−0.83 (m, 1H), 0.78 (dd, *J* = 4 Hz, 6H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 178.86, 142.68, 135.64, 130.31, 129.91, 129.19, 127.78, 127.41, 124.03, 123.28, 109.53, 76.88, 43.88, 36.75, 32.17, 28.17, 22.55, 22.37. **IR** (neat) 3390, 2954, 1705 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{20}H_{23}NO_2$ $(M+Na)^+$: 332.1626, found: 332.1625.



1-Benzyl-3-hydroxy-3-octylindolin-2-one (**5l**). Complex **2a** (12 mg, 0.02 mmol), KO*t*Bu (258 mg, 2.3 mmol), octanol (130 mg, 1 mmol), N-benzyl-2-oxindole (446 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 1-benzyl-3-hydroxy-3-octylindolin-2-one **5l** (115 mg, 33%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 8 Hz, 1H), 7.31−7.26 (m, 2H), 7.23 (m, 3H), 7.17 (td, *J* = 8, 1.3 Hz, 1H), 7.03 (td, *J* = 8, 0.7 Hz, 1H), 6.68 (d, *J* = 8 Hz, 1H), 4.98 (d, *J* = 16 Hz, 1H), 4.72 (d, *J* = 16 Hz, 1H), 3.09 (s, 1H), 2.03−1.88 (m, 2H), 1.22−1.15 (m, 12H), 0.82 (t, *J* = 8 Hz, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 178.71, 142.77, 135.66, 130.21, 129.62, 128.92, 127.83, 127.41, 124.06, 123.28, 109.58, 43.94, 38.91, 31.92, 29.73, 29.32, 23.44, 22.74, 14.23. **IR** (neat) 3377, 3056, 1704 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{23}H_{29}NO_2$ $(M+Na)^+$: 374.2095, found: 374.2097.

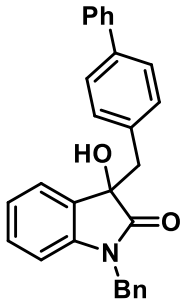


1-Benzyl-3-hexyl-3-hydroxyindolin-2-one (**5m**). Complex **2a** (12 mg, 0.02 mmol), KO*t*Bu (258 mg, 2.3 mmol), hexanol (103 mg, 1 mmol), *N*-protected-2-oxindole (446 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 1-benzyl-3-hexyl-3-hydroxyindolin-2-one **5m** (155 mg, 48%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37−7.35 (d, *J* = 8 Hz, 1H), 7.24−7.27 (m, 2H), 7.25−7.15 (m, 1H), 7.03 (t, *J* = 8 Hz, 3H), 6.68 (d, *J* = 8 Hz, 1H), 5.98 (d, *J* = 16 Hz, 1), 4.70 (d, *J* = 16 Hz, 1H), 3.72 (s, 1H), 2.03−1.99 (m, 2H), 1.24−1.16 (m, 8H), 0.80 (t, *J* = 8 Hz, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 178.95, 142.69, 135.66, 130.40, 129.48, 128.86, 127.76, 127.38,

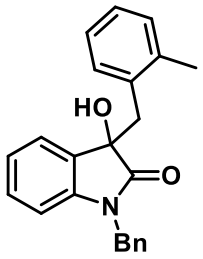


124.04, 123.24, 109.52, 76.87, 43.89, 38.85, 31.61, 29.35, 23.38, 22.53, 14.10. **IR** (neat) 3377, 3056, 1704 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{21}H_{25}NO_2$ $(M+H)^+$: 324.1963, found: 324.1967.

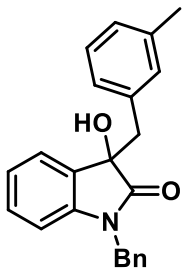
1,3-Dibenzyl-3-hydroxyindolin-2-one (**5n**). Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), benzyl alcohol (108 mg, 1 mmol), N-benzyl-2-oxindole (446 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 1,3-dibenzyl-3-hydroxyindolin-2-one **5n** (213 mg, 65%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41−7.36 (m, 1H), 7.22−7.05 (m, 8H), 6.97−6.92 (m, 2H), 6.71 (d, *J* = 7.1 Hz, 2H), 6.43 (d, *J* = 7.7 Hz, 1H), 5.00 (d, *J* = 16.0 Hz, 1H), 4.45 (d, *J* = 15.9 Hz, 1H), 3.44 (dd, *J* = 12.7, 2.2 Hz, 1H), 3.32 (dd, *J* = 12.7, 3.7 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 177.88, 142.81, 135.01, 133.99, 130.55, 129.86, 129.38, 128.77, 128.21, 127.43, 127.04, 126.76, 124.52, 123.11, 109.72, 77.76, 44.92, 43.84. **IR** (neat) 3325, 3031, 1690 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{22}H_{19}NO$ $(M+H)^+$: 330.1494, found: 330.1501.



1-Benzyl-3-hydroxy-3-(2-methylbenzyl)indolin-2-one (**5p**). Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), 3-methyl benzyl alcohol (122 mg, 1 mmol), *N*-benzyl-2-oxindole (446 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 1-benzyl-3-hydroxy-3-(2-methylbenzyl)indolin-2-one **5p** (195 mg, 57%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24−7.17 (m, 3H), 7.16−7.12 (m, 3H), 7.08 (d, *J* = 7.3 Hz, 1H), 7.04−6.95 (m, 3H), 6.88 (dd, *J* = 6.5, 3.0 Hz, 2H), 6.54 (d, *J* = 7.8 Hz, 1H), 5.05 (d, *J* = 15.9 Hz, 1H), 4.54 (d, *J* = 15.8 Hz, 1H), 3.39 (d, *J* = 13.6 Hz, 1H), 3.29 (d, *J* = 13.6 Hz, 1H), 2.93 (s, 1H), 2.10 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 178.23, 142.66, 137.85, 135.25, 132.53, 131.22, 130.62, 129.88, 129.57, 128.88, 127.58, 127.28, 126.91, 125.68, 124.75, 122.99, 109.61, 43.92, 41.02, 20.05. **IR** (neat) 3364, 3059, 1700 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{23}H_{21}NO_2$ $(M+Na)^+$: 366.1469, found: 366.1462.

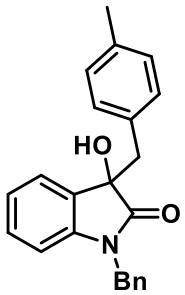


1-Benzyl-3-hydroxy-3-(3-methylbenzyl)indolin-2-one (**5q**). Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), 3-methyl benzyl alcohol (122 mg, 1 mmol), *N*-benzyl-2-oxindole (446 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 1-benzyl-3-hydroxy-3-(3-methylbenzyl)indolin-2-one **5q** (137 mg, 40%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 8 Hz, 1H), 7.21−7.07 (m, 5H), 7.01−6.97 (m, 2H), 6.77 (s, 1H), 7.01− 6.97 (m, 3H), 6.72−6.66 (m, 1H), 6.43 (d, *J* = 12, 1H), 5.05 (d, *J* = 16 Hz, 1H), 4.42 (d, *J* = 16 Hz, 1H), 3.42 (d, *J* = 16 Hz, 1H), 3.31 (d, *J* = 12 Hz, 1H), 2.15 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 178.15, 142.80, 137.74, 135.02, 133.87, 131.27, 129.75, 129.55, 128.72, 128.04, 127.75, 127.54, 127.38, 126.61, 124.53, 123.08, 109.68, 77.85, 44.84,

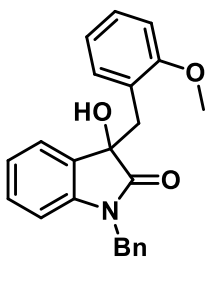


43.82, 21.36. **IR** (neat) 3377, 1704 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{23}H_{21}NO_2$ $(M+Na)^+$: 366.1469, found: 366.1475.

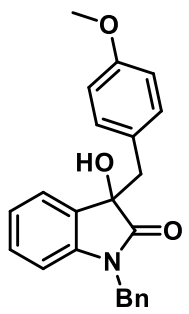
1-Benzyl-3-hydroxy-3-(4-methylbenzyl)indolin-2-one (**5r**). Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), 4-methyl benzyl alcohol (122 mg, 1 mmol), *N*-benzyl-2-oxindole (446 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 1-benzyl-3-hydroxy-3-(4-methylbenzyl)-indolin-2-one **5r** (189 mg, 55%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 7.2, 1.1 Hz, 1H), 7.19−7.01 (m, 5H), 6.92 (d, *J* = 8 Hz, 2H), 6.83 (d, *J* = 8.0 Hz, 2H), 6.72 (d, *J* = 8 Hz, 2H), 6.46−6.40 (m, 1H), 5.05 (d, *J* = 16.0 Hz, 1H), 4.41 (d, *J* = 16.0 Hz, 1H), 4.09 (s, 1H), 3.42 (d, *J* = 12.7 Hz, 1H), 3.34 (d, *J* = 12.7 Hz, 1H), 2.29 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 178.19, 142.79, 136.44, 135.03, 130.88, 130.40, 129.71, 129.61, 128.87, 128.60, 127.37, 126.81, 124.50, 123.08, 109.66, 77.83, 44.42, 43.83, 21.25. **IR** (neat) 3292, 2943, 1737 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{23}H_{21}NO_2$ $(M+H)^+$: 344.1650, found: 344.1652.



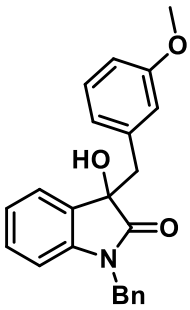
1-Benzyl-3-(2-methoxybenzyl)indoline (**5s**). Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), 2-methoxy benzyl alcohol (138 mg, 1 mmol), *N*-benzyl-2-oxindole (446 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 1-benzyl-3-hydroxy-3-(2-methoxylbenzyl)indolin-2-one **5s** (183 mg, 51%) as a yellow liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 8.8, 2.5 Hz, 2H), 7.24 (dd, *J* = 4.6, 3.6 Hz, 2H), 7.17−7.09 (m, 3H), 6.97 (dd, *J* = 14.8, 8.0, Hz, 3H), 6.85 (t, *J* = 7.1 Hz, 2H), 6.59 (d, *J* = 7.8 Hz, 1H), 5.04 (d, *J* = 15.8 Hz, 1H), 4.66 (d, *J* = 15.9 Hz, 1H), 3.74−3.70 (m, 5H), 2.97 (d, *J* = 16 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 178.61, 157.86, 142.31, 135.59, 132.59, 129.27, 129.06, 128.47, 128.18, 127.43, 127.09, 125.07, 122.97, 122.45, 120.60, 110.68, 109.22, 108.81, 55.31, 43.82, 38.46. **IR** (neat) 3375.29, 1708.59 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{23}H_{21}NO_3$ $(M+Na)^+$: 382.1418, found: 382.1418.



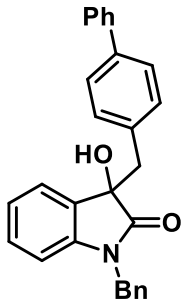
1-Benzyl-3-hydroxy-3-(4-methoxybenzyl)indolin-2-one (**5t**). Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), 4-methoxy benzyl alcohol (138 mg, 1 mmol), N-benzyl-2-oxindole (446 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 1-benzyl-3-hydroxy-3-(4-methoxylbenzyl)indolin-2-one **5t** (179 mg, 50%) as a green solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.40 (d, *J* = 12 Hz, 1H), 7.34−7.30 (m, 1H), 7.16−7.08 (m, 4H), 6.82 (d, *J* = 8 Hz, 2H), 6.67−6.61 (m, 4H), 6.44−6.42 (m, *J* = 8 Hz, 1H), 5.05 (d,*J* = 8 Hz, 1H), 4.05 (s, 1H), 4.40 (d, *J* = 16 Hz, 1H), 3.72 (s, 3H), 3.40−3.37 (d, *J* = 12 Hz, 1H), 3.30−3.27 (d, *J* = 12 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 178.35, 158.72, 142.77, 135.15, 131.51, 129.78, 129.60, 128.7, 127.45, 126.97, 126.74, 125.96, 124.45, 123.19,



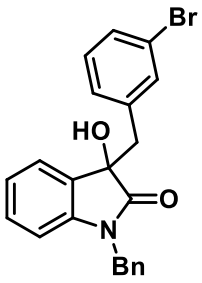
113.63, 109.47, 77.97, 55.16, 43.93, 43.68. **IR** (neat) 1703, 2924, 3369 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{23}H_{21}NO_3$ $(M+Na)^+$: 382.1418, found: 382.1423.

1-Benzyl-3-hydroxy-3-(3-methoxybenzyl)indolin-2-one (**5u**). Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), 3-methoxy benzyl alcohol (138 mg, 1 mmol), N-benzyl-2-oxindole (446 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 1-benzyl-3-hydroxy-3-(3-methoxylbenzyl)indolin-2-one **5u** (168 mg, 47%) as a white solid. 

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 8, 1.2 Hz, 1H), 7.21−7.08 (m, 5H), 7.02 (d, *J* = 8 Hz, 1H), 6.75 (d, *J* = 2.4 Hz, 1H), 6.74−6.69 (m, 2H), 6.57 (d, *J* = 8 Hz, 1H), 6.44 (d, *J* = 8 Hz, 1H), 6.42−6.40 (m, 1H), 5.03 (d, *J* = 16.0 Hz, 1H), 4.43 (d, *J* = 16.0 Hz, 1H), 3.64 (s, 1H), 3.52 (s, 3H), 3.42 (d, *J* = 12 Hz, 1H), 3.32 (d, *J* = 12.7 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 177.86, 159.31, 142.94, 135.41, 135.02, 129.86, 129.48, 129.17, 128.79, 127.46, 126.68, 124.49, 123.03, 115.12, 113.58, 109.76, 77.69, 55.13, 44.97, 43.85. **IR** (neat) 1705, 2922, 3380 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{23}H_{21}NO_3$ $(M+H)^+$: 360.1599, found: 360.1607.

3-([1,1'-Biphenyl]-4-ylmethyl)-1-benzylindolin-3-ol (**5v**). Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), 2-methoxy biphenyl-4-methanol (185 mg, 1 mmol), N-benzyl-2-oxindole (446 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 3-([1,1'-biphenyl]-4-ylmethyl)-1-benzylindolin-3-ol **5v** (182 mg, 45%) as a white solid. 

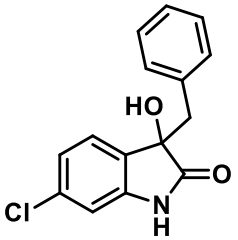
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, 2H), 7.44−7.33 (m, 6H), 7.06−7.00 (m, 7H), 6.73 (d, *J* = 8 Hz, 2H), 6.45 (d, *J* = 8 Hz, 1H), 5.06 (d, *J* = 16 Hz, 1H), 4.44 (d, *J* = 12 Hz, 1H), 3.49 (d, *J* = 12 Hz, 1H), 3.37 (d, *J* = 16 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 177.89, 142.88, 140.64, 139.77, 134.97, 133.08, 130.99, 129.94, 129.37, 128.83, 127.44, 127.04, 126.76, 124.53, 123.17, 109.83, 77.69, 44.57, 43.93. **IR** (neat) 3373, 1701 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{28}H_{23}NO_2$ $(M+H)^+$: 406.1807, found: 406.1814.

1-Benzyl-3-(3-bromobenzyl)-3-hydroxyindolin-2-one (**5w**). Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), 3-bromobenzyl alcohol (185 mg, 1 mmol), N-benzyl-2-oxindole (446 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 1-benzyl-3-(3-bromobenzyl)-3-hydroxyindolin-2-one **5w** (204 mg, 50%) as a yellow solid. 

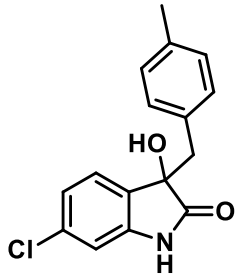
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 12 Hz, 1H), 7.35−7.29 (m, 2H), 7.24−7.18 (m, 5H), 7.04 (d, *J* = 8 Hz, 2H), 6.80 (d, *J* = 8 Hz, 1H), 6.53 (d, *J* = 8 Hz, 1H), 5.10 (d, *J* = 16 Hz, 1H), 4.53 (d, *J* = 16 Hz, 1H), 4.23 (bs, 1H), 3.55 (d, *J* = 12 Hz, 1H), 3.46 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 178.05, 142.67, 134.82, 133.93, 132.10, 131.19, 130.44, 129.69, 129.40, 128.88, 128.43, 128.72, 128.08, 127.50, 127.31, 126.90, 126.65, 124.39, 123.10, 109.67, 77.62, 44.80, 43.78. **IR** (neat)

3367, 2923, 1708 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{22}H_{18}BrNO_2$ $(M+H)^+$: 408.0599, found: 408.0597.

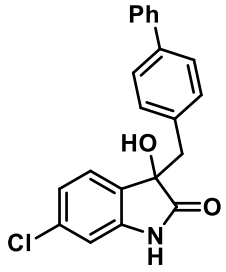
3-Benzyl-6-chloro-3-hydroxyindolin-2-one (**5a'**). Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), benzyl alcohol (108 mg, 1 mmol), 6-chloro-2-oxindole (335 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 3-benzyl-6-chloro-3-hydroxyindolin-2-one **5a'** (158 mg, 58%) as a white solid. **^{1}H NMR** [400 MHz, $CDCl_3$+ CD_3CN (3:2)] δ 8.00 (s, 1H), 6.92 (d, *J* = 1.5 Hz, 3H), 6.75 (dd, *J* = 19.9, 6.2 Hz, 4H), 6.48 (s, 1H), 3.81 (s, 1H), 3.00 (d, *J* = 12.8 Hz, 1H), 2.85 (d, *J* = 13.0 Hz, 1H). **^{13}C{^{1}H} NMR** [100 MHz, $CDCl_3$+CD_3CN (3:2)] δ 179.08, 142.75, 134.83, 134.64, 130.74, 129.13, 128.15, 127.13, 126.34, 122.19, 110.54, 77.04, 44.12. **IR** (neat) 3315, 2943, 1665 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{15}H_{12}ClNO_2$ $(M+Na)^+$: 274.0635, found: 274.0629.



6-Chloro-3-hydroxy-3-(4-methylbenzyl)indolin-2-one (**5b'**). Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), 4-methyl-benzyl alcohol (122 mg, 1 mmol), 6-chloro-2-oxindole (335 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 6-chloro-3-hydroxy-3-(4-methylbenzyl)indolin-2-one **5b'** (160 mg, 56%) as a white solid. **^{1}H NMR** [400 MHz, $CDCl_3$+CD_3OD (3:2)] δ 7.02 (dd, *J* = 7.8, 4.2 Hz, 1H), 6.93 (d, *J* = 7.9 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 2H), 6.80 (d, *J* = 7.4 Hz, 2H), 6.66 (s, 1H), 4.31 (bs, 1H), 3.18 (d, *J* = 12.9 Hz, 1H), 3.03 (d, *J* = 12.9, 1H), 2.20 (s, 3H). **^{13}C{^{1}H} NMR** [100 MHz, $CDCl_3$+CD_3OD (3:2)] δ 180.85, 142.78, 136.67, 135.19, 131.28, 130.51, 129.39, 128.82, 126.01, 122.45, 110.92, 43.80, 21.08. **IR** (neat) 3323, 2942, 1663 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{16}H_{14}ClNO_2$ $(M+H)^+$: 288.0791, found: 288.0783.

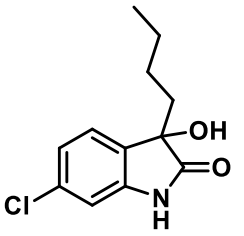


3-([1,1'-Biphenyl]-4-ylmethyl)-6-chloro-3-hydroxyindolin-2-one (**5c'**). Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), biphenyl methanol (184 mg, 1 mmol), 6-chloro-2-oxindole (335 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 3-([1,1'-biphenyl]-4-ylmethyl)-6-chloro-3-hydroxyindolin-2-one **5c'** (174 mg, 50%) as a yellow solid. **^{1}H NMR** [400 MHz, $CDCl_3$+CD_3OD (3:2)]: δ 7.49 (d, *J* = 6.8 Hz, 2H), 7.35 (d, *J* = 7.7 Hz, 4H), 7.27 (d, *J* = 6.9 Hz, 1H), 7.08 (d, *J* = 7.8 Hz, 1H), 7.04−6.93 (m, 3H), 6.68 (s, 1H), 3.27 (d, *J* = 12.9 Hz, 1H), 3.12 (d, *J* = 12.8 Hz, 1H). **^{13}C{^{1}H} NMR** [100 MHz, CDCl3 + CD3OD (3:2)] δ 180.92, 143.15, 141.23, 140.16, 135.48, 133.85, 131.32, 129.22, 127.69, 127.31, 126.87, 126.22, 122.67, 111.13, 77.71, 44.02. **IR** (neat) 3339, 2947, 1670cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{21}H_{16}ClNO_2$ $(M+H)^+$: 350.0948, found: 350.0940.

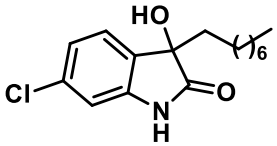


3-Butyl-6-chloro-3-hydroxyindolin-2-one (**5d'**). Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), 1-butanol (74 mg, 1 mmol), 6-chloro-2-oxindole (334 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure

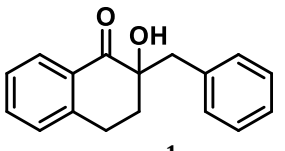
tube according to method C to afford 3-butyl-6-chloro-3-hydroxyindolin-2-one **5d'** (119 mg, 50%) as a white solid. **^{1}H NMR** (400 MHz, CD_3OD) δ 7.28 (d, *J* = 7.9 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.91 (s, 1H), 1.95−1.87 (m, 2H), 1.26 (dt, *J* = 14.4, 7.2 Hz, 2H), 1.16−0.91 (m, 2H), 0.83 (t, *J* = 7.3 Hz, 3H). **^{13}C{^{1}H} NMR** (100 MHz, CD_3OD) δ 182.07, 144.26, 135.87, 131.59, 126.18, 123.40, 111.53, 77.51, 38.55, 26.46, 23.77, 14.17. **IR** (neat) 1708.33, 2830.98, 3317.44 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{12}H_{14}ClNO_2$ $(M+H)^+$: 240.0791, found: 240.0797.



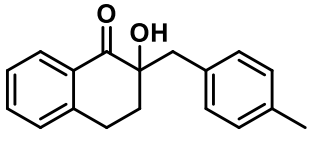
6-Chloro-3-hydroxy-3-octylindolin-2-one (**5e'**). Complex **2a** (12 mg, 0.02 mmol), KO*t*Bu (258 mg, 2.3 mmol), 1-octanol (130 mg, 1 mmol), 6-chloro-2-oxindole (335 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 6-chloro-3-hydroxy-3-octylindolin-2-one **5e'** (171 mg, 58%) as a white solid. **^{1}H NMR** [400 MHz, $CDCl_3$ + CD_3CN (3:2)] δ 7.28 (d, *J* = 2.3 Hz, 1H), 7.06 (dd, *J* = 7.9, 1.7 Hz, 1H), 6.91 (d, *J* = 1.6 Hz, 1H), 2.08−1.86 (m, 2H), 1.27 (m, 12H), 0.86 (t, *J* = 8 Hz, 3H). **^{13}C{^{1}H} NMR** [100 MHz, $CDCl_3$+CD_3CN (3:2)] δ 180.17, 143.53, 134.89, 130.97, 126.03, 122.75, 110.97, 76.72, 38.28, 32.25, 30.00, 29.62, 23.59, 23.09, 14.14. **IR** (neat) 3319, 1618 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{16}H_{22}ClNO_2$ $(M+H)^+$: 296.1417, found: 296.1408.



2-Benzyl-2-hydroxy-3,4-dihydronaphthalen-1(2H)-one (**7a**).[31]10a Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), benzyl alcohol (108 mg, 1 mmol), α-tetralone (292 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 2-benzyl-2-hydroxy-3,4-dihydronaphthalen- 1(2H)-one (173 mg, 69%) as a white crystalline solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04−8.02 (d, *J* = 8 Hz, 1H), 7.59−7.55 (dt, 1H), 7.39 (t, *J* = 8 Hz, 1H), 7.32−7.28 (m, 3H), 7.15 (d, *J* = 4 Hz, 2H), 3.78 (s, 1H), 3.31−3.23 (m, 1H), 3.02−2.91 (m, 3H), 2.27−2.19 (m, 2H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 200.98, 143.28, 135.42, 134.23, 130.45, 129.21, 128.19, 128.09, 127.16, 126.96, 76.13, 42.02, 33.90, 26.46. **IR** (neat) 1683, 3028, 3477 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{17}H_{16}O_2$ $(M+Na)^+$: 275.1047, found: 275.1047. 4.3.29.

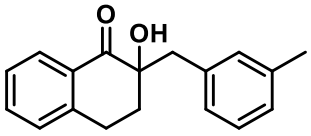


2-Hydroxy-2-(4-methylbenzyl)-3,4-dihydronaphthalen-1(2H)-one (**7b**).[31] Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), 4-methylbenzyl alcohol (122 mg, 1 mmol), α-tetralone (292 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 2-hydroxy-2-(4-methylbenzyl)-3,4-dihydronaphthalen-1(2H)-one (143 mg, 53%) as a pale yellow liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8 Hz, 1H), 7.55 (dt, 1H), 7.41 (t, *J* = 8 Hz, 1H), 7.31 (d, *J* = 8 Hz, 1H), 7.12−7.03 (m, 2H), 3.75 (s, 1H), 3.30-3.22 (m, 1H), 3.07−2.87 (m, 3H), 2.32 (s, 1H), 2.29−2.17 (m, 3H), 2.20 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) 201.09, 143.33, 136.53, 134.22, 132.26, 130.34,

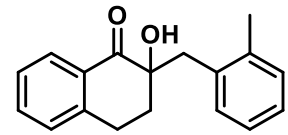


129.23, 128.96, 128.11, 127.17, 76.20, 41.64, 33.95, 26.51, 21.22. **IR** (neat) 3490, 2929, 1685 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{18}H_{18}O_2$ $(M+Na)^+$: 289.1204, found: 289.1205.

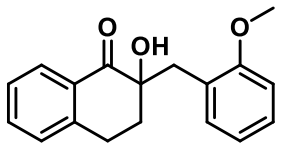
2-Hydroxy-2-(3-methylbenzyl)-3,4-dihydronaphthalen-1(2H)-one (**7c**).[31] Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), 3-methylbenzyl alcohol (122 mg, 1 mmol), α-tetralone (292 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 2-hydroxy-2-(3-methylbenzyl)-3,4-dihydronaphthalen-1(2H)-one (138 mg, 52%) as a yellow liquid. **^{1}H NMR** (400 MHz, CDCl3) δ 8.03 (d, *J* = 8 Hz, 1H), 7.57 (dt, 1H), 7.39 (d, *J* = 8 Hz, 1H), 7.31 (d, *J* = 8 Hz, 1H), 7.16 (t, *J* = 8 Hz, 1H), 7.06 (d, *J* = 8 Hz, 1H), 6.99 (s, 1H), 6.93 (d, *J* = 8 Hz, 1H), 3.77 (s, 1H), 3.31−3.22 (m, 1H), 3.07−2.87 (m, 3H), 2.32 (s, 3H), 2.27−2.15 (m, 2H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 201.06, 143.34, 137.75, 135.36, 134.22, 131.35, 130.60, 129.24, 128.11, 128.09, 127.77, 127.45, 127.18, 76.20, 42.01, 33.93, 26.53, 21.56. **IR** (neat) 3499, 3052, 2940, 1734 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{18}H_{18}O_2$ $(M+Na)^+$: 289.1204, found: 289.1205.



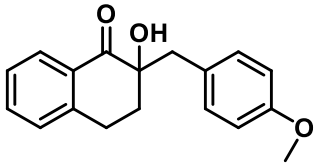
2-Hydroxy-2-(2-methylbenzyl)-3,4-dihydronaphthalen-1(2H)-one (**7d**).[31] Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), 2-methylbenzyl alcohol (122 mg, 1 mmol), α-tetralone (292 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 2-hydroxy-2-(2-methylbenzyl)-3,4-dihydronaphthalen-1(2H)-one **7d** (133 mg, 50%) as a pale yellow liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.57 (td, *J* = 7.5, 1.4 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.15−7.05 (m, 3H), 6.96 (d, *J* = 7.2 Hz, 1H), 3.71 (s, 1H), 3.32 (ddd, *J* = 18.0, 12.8, 5.3 Hz, 1H), 3.15 (d, *J* = 14.0 Hz, 1H), 3.12−3.06 (m, 1H), 3.01 (d, *J* = 13.9 Hz, 1H), 2.48−2.41 (m, 1H), 2.35-2.25 (m, 1H), 2.20 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 200.78, 143.21, 137.97, 134.23, 133.56, 131.16, 130.58, 129.26, 128.20, 127.26, 127.05, 125.52, 76.68, 38.54, 35.43, 26.58, 20.29. **IR** = 1686, 2935, 3496 cm^{-1} **HRMS** (ESI) m/z calculated for $C_{18}H_{18}O_2$ $(M+Na)^+$: 289.1204, found: 289.1201.



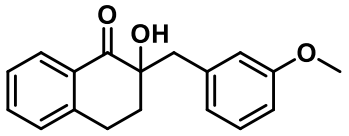
2-Hydroxy-2-(2-methoxybenzyl)-3,4-dihydronaphthalen-1(2H)-one (**7e**). Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), 2-methoxybenzyl alcohol (138 mg, 1 mmol), α-tetralone (292 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 2-hydroxy-2-(2-methoxybenzyl)-3,4-dihydronaphthalen-1(2H)-one **7e** (126 mg, 45%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03−8.01 (dd, 1H), 7.56−7.52 (dt, 1H), 7.37 (t, *J* = 8 Hz, 1H), 7.32−7.27 (m, 2H), 7.24 (dd, *J* = 8 Hz, 1H), 6.93 (td, 8 Hz, 1.3 Hz, 1H), 6.78 (d, *J* = 8 Hz, 3H), 3.74 (s, 1H), 3.50 (s, 1H), 3.44−3.38 (m, 2H), 3.08−3.01 (m, 1H), 2.86 (d, *J* = 16 Hz, 1H), 2.34−2.28 (m, 2H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 200.12, 157.46, 143.23, 133.64, 132.97, 131.12, 129.10, 128.42, 127.89, 126.66, 123.46, 120.37, 110.06, 75.96, 54.66, 36.31, 35.30, 26.50. **IR** (neat)



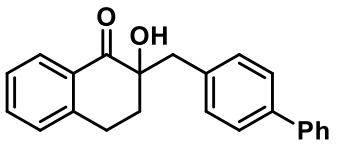
1737, 2930, 3501 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{18}H_{18}O_3$ $(M+Na)^+$: 305.1153, found: 305.1158.

2-Hydroxy-2-(4-methoxybenzyl)-3,4-dihydronaphthalen-1(2H)-one (**7f**). Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), 4-methoxybenzyl alcohol (138 mg, 1 mmol), α-tetralone (292 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 2-hydroxy-2-(4-methoxybenzyl)-3,4-dihydronaphthalen-1(2H)-one **7f** (118 mg, 42%) as a white solid. 

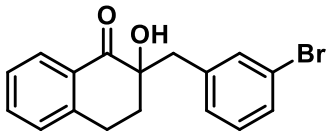
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8 Hz, 1H), 7.56 (td, *J* = 7.5, 1.4 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 7.7 Hz, 1H), 7.07 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 3.79 (s, 3H), 3.76 (s, 1H), 3.30−3.21 (m, 1H), 3.06 (dd, *J* = 5.5, 2.0 Hz, 1H), 2.91 (q, *J* = 14.0 Hz, 2H), 2.32-2.14 (m, 2H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 201.16, 158.68, 143.33, 134.23, 131.43, 130.55, 129.24, 128.09, 127.38, 127.18, 113.68, 76.23, 55.31, 41.20, 33.89, 26.50. **IR** (neat) 3493, 3610, 1735 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{18}H_{18}O_3$ $(M+Na)^+$: 305.1153, found: 305.1151.

2-Hydroxy-2-(4-methoxybenzyl)-3,4-dihydronaphthalen-1(2H)-one (**7g**). Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), 4-methoxybenzyl alcohol (138 mg, 1 mmol), α-tetralone (292 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 2-hydroxy-2-(4-methoxybenzyl)-3,4-dihydronaphthalen-1(2H)-one **7g** (116 mg, 41%) as a pale yellow liquid. 

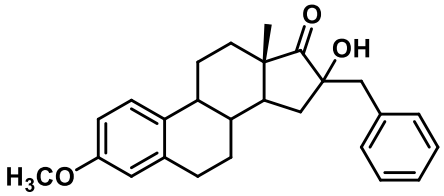
^{1}H NMR (400 MHz, CDCl3) δ 8.02 (d, *J* = 8 Hz, 1H), 7.56 (dt, 1H), 7.38 (t, 1H), 7.30 (d, 1H), 7.18 (t, 1H), 6.80−6.71 (m, 3H), 3.81 (s, 1H), 3.77 (s, 3H), 3.25−3.21 (m, 1H), 3.07−2.88 (m, 3H), 2.30−2.17 (m, 2H). **^{13}C{^{1}H} NMR** (100 MHz, CDCl3) δ 200.95, 159.37, 143.28, 136.99, 134.24, 130.50, 129.17, 128.07, 127.17, 122.80, 116.17, 112.40, 76.16, 55.21, 42.09, 33.91, 26.49. **IR** (neat) 3490, 2935, 1686 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{18}H_{18}O_3$ $(M+Na)^+$: 305.1153, found: 305.1161.

2-([1,1'-Biphenyl]-4-ylmethyl)-2-hydroxy-3,4-dihydronaphthalen-1(2H)-one (**7h**). Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), biphenyl-4-methanol (185 mg, 1 mmol), α-tetralone (292 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 2-([1,1′-biphenyl]-4-ylmethyl)-2-hydroxy-3,4-dihydronaphthalen-1(2H)-one **7h** (112 mg, 34%) as an orange crystalline solid. 

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 8 Hz, 1H), 7.61−7.57 (m, 3H), 7.52 (d, *J* = 8 Hz, 2H), 7.46−7.41 (m, 4H), 7.35−7.33 (m, 2H), 7.24 (s, 1H), 3.85 (s, 1H), 3.31−3.26 (m, 1H), 3.09−2.97 (m, 3H), 2.36−2.19 (m, 2H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 201.06, 143.36, 134.55, 134.33, 130.92, 129.29, 128.85, 128.17, 127.17, 76.23, 41.70, 33.92, 26.54. **IR** (neat) 3456.99, 3029.72, 1677.58 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{23}H_{20}O_2$ $(M+Na)^+$: 351.1360, found: 351.1367.

2-(3-bromobenzyl)-2-hydroxy-3,4-dihydronaphthalen-1(2H)-one (**7i**).[31] Complex **2a** (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), 3-bromobenzyl alcohol (185 mg, 1 mmol), α-tetralone (292 mg, 2 mmol), and toluene (2 mL) were allowed to react in a 20 mL resealable pressure tube according to method C to afford 2-(3-bromobenzyl)-2-hydroxy-3,4-dihydronaphthalen-1(2H)-one **7i** (168 mg, 48%) as a white solid. 

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02−7.98 (m, 1H), 7.57−7.53 (m, 1H), 7.38−7.36 (m, 2H), 7.29 (d, *J* = 8 Hz, 1H), 7.23−7.21 (m, 1H), 7.13 (dd, 1H), 7.00 (d, *J* = 12 Hz, 1H), 3.79−3.77 (d, *J* = 8 Hz, 1H), 3.25−3.18 (m, 1H), 3.00−2.88 (m, 3H), 2.26−2.17 (m, 2H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 200.77, 143.22, 135.46, 134.39, 132.15, 131.32, 130.50, 129.29, 128.22, 127.24, 126.99, 121.10, 75.96, 42.06, 33.96, 26.48. **IR** (neat) 3486, 2926, 1684 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{17}H_{15}BrO_2$ $(M+H)^+$: 331.0333, found: 331.0330.

(8R,9S,13S,14S)-16-Benzyl-16-hydroxy-3-methoxy-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17Hcyclopenta[a]phenanthren-17-one (**7j**). Complex **2a** (1.5 mg, 0.0025 mmol), KO*t*Bu (64 mg, 0.57 mmol), benzyl alcohol (27 mg, 0.25 mmol), and estron 3-methyl ether (71 mg 0.25 mmol) were allowed to react in a 20 mL resealable pressure tube according to method C to afford the product **7j** (37 mg, 38%) as a colorless thick liquid with a mixture of diastereoisomers based on ^{1}H NMR spectra. Selected spectral data for major diastereoisomer: 

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* = 7.1 Hz, 3H), 7.24−7.17 (m, 3H), 6.75−6.69 (m, 1H), 6.63 (d, *J* = 1.6 Hz, 1H), 3.78 (d, *J* = 0.8 Hz, 3H), 3.42 (d, *J* = 8 Hz, 1H), 2.95−2.81 (m, 3H), 2.70 (dd, *J* = 12, 8 Hz, 1H), 2.35−2.14 (m, 3H), 1.97−1.78 (m, 4H), 1.59−1.45 (m, 3H), 0.81 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 157.56, 141.43, 138.08, 132.76, 128.91, 128.55, 126.41, 126.14, 113.94, 111.59, 87.79, 55.32, 48.33, 45.63, 44.20, 41.73, 38.65, 36.98, 30.12, 29.91, 27.39, 26.33, 12.06. **IR** (neat) 3386, 2923, 1736 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{26}H_{31}O_3$ $(M+H)^+$: 391.2273, found: 391.2272.

2A.8. Appendix I: Copies of ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of representative compounds

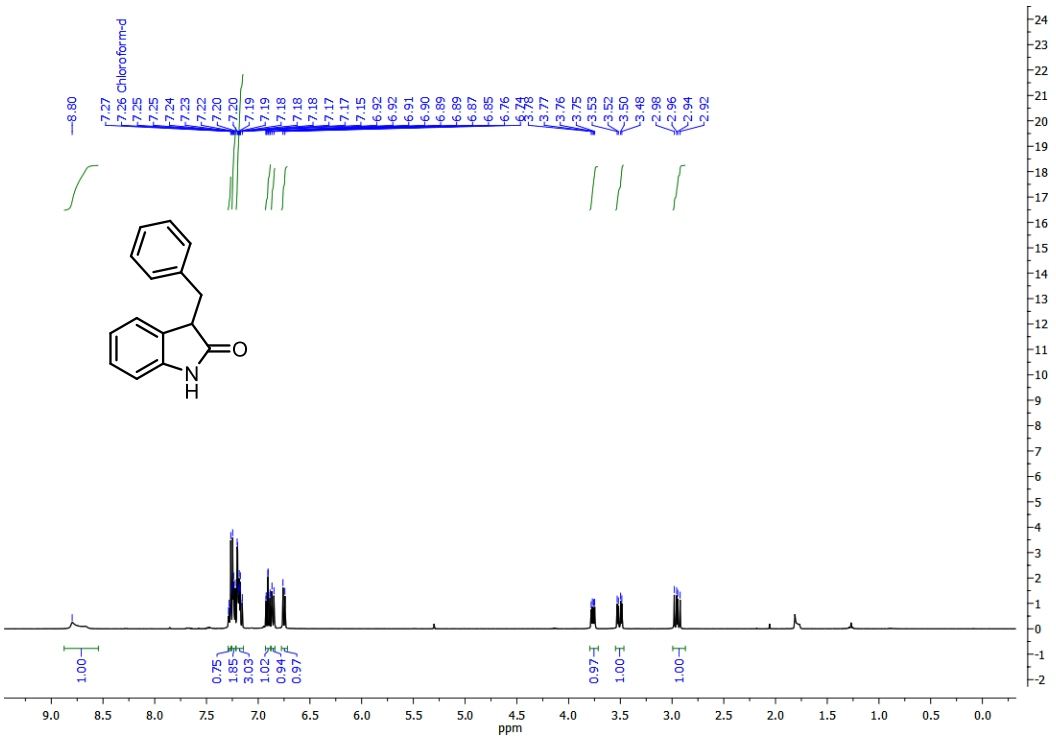


Figure 2A.10. ^{1}H NMR of compound **4a**

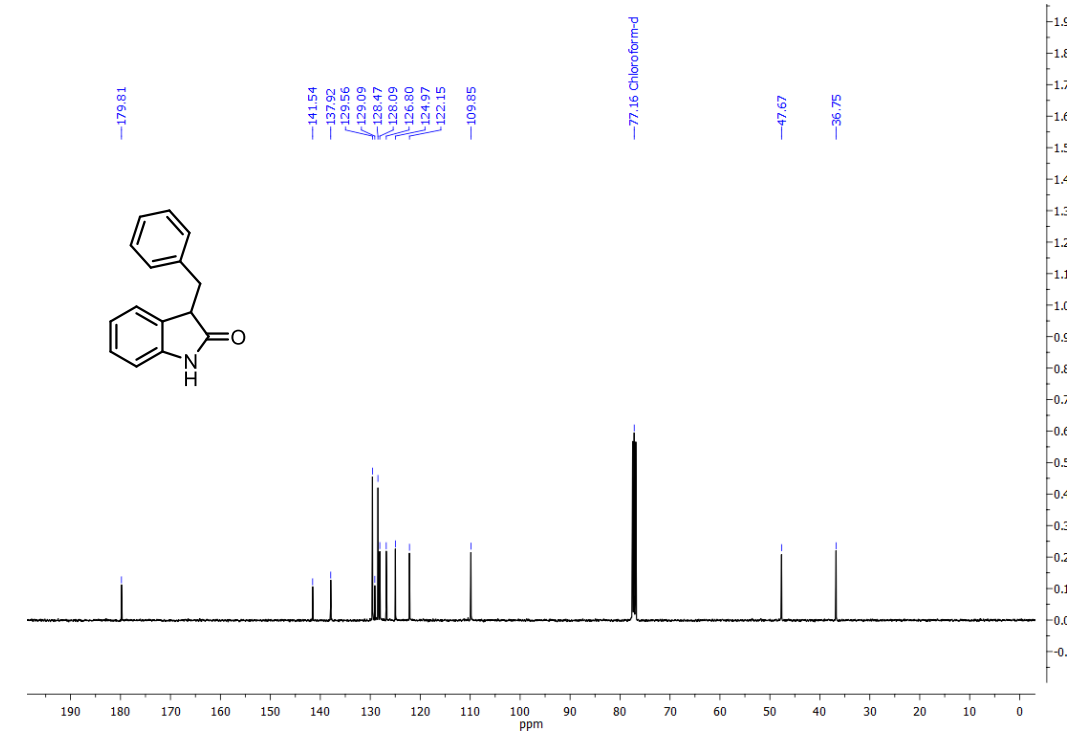


Figure 2A.11. ^{13}C{^{1}H} NMR of compound **4a**

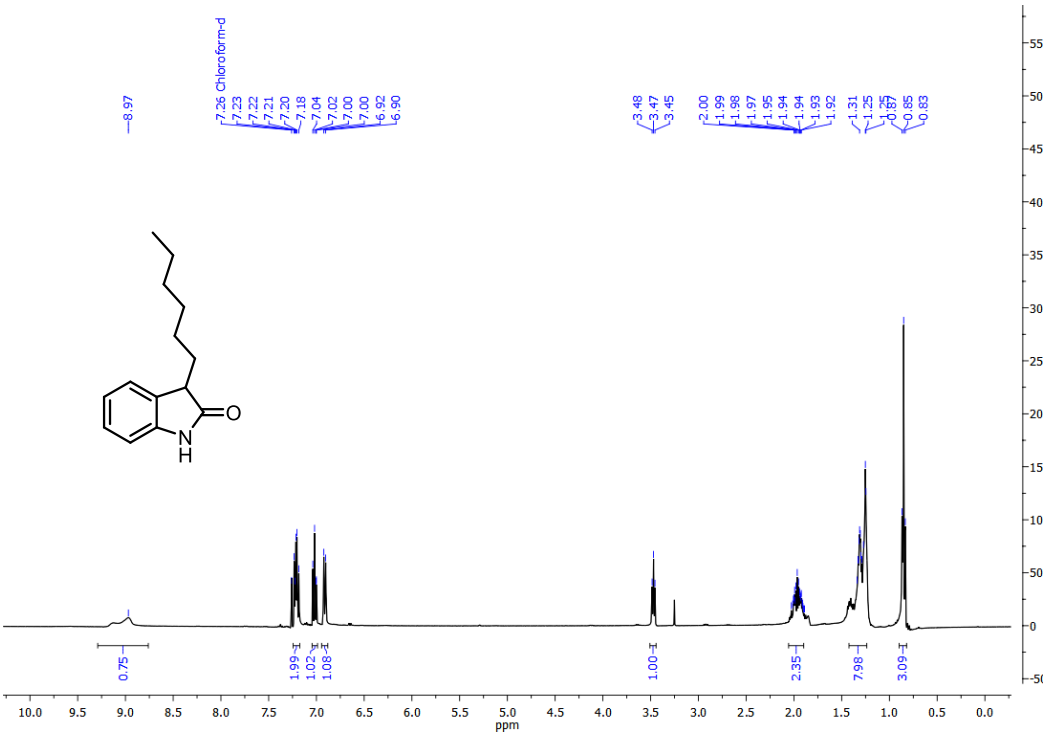


Figure 2A.12. ^{1}H NMR of compound **4j**

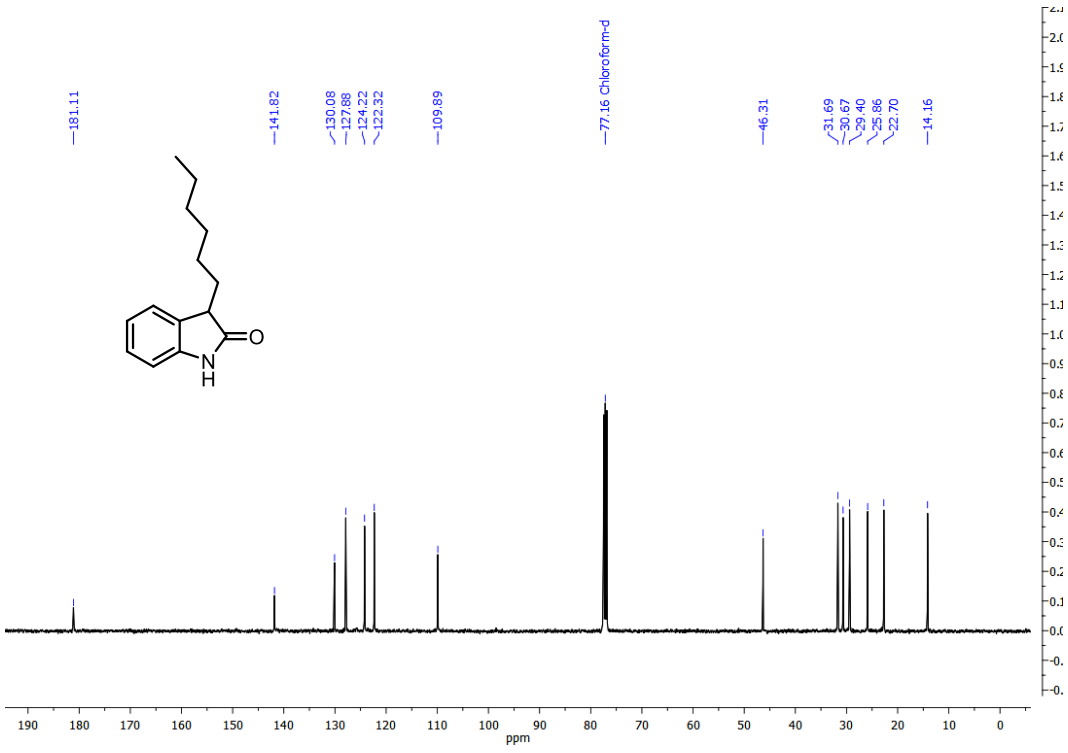


Figure 2A.13. ^{13}C{^{1}H} NMR of compound **4j**

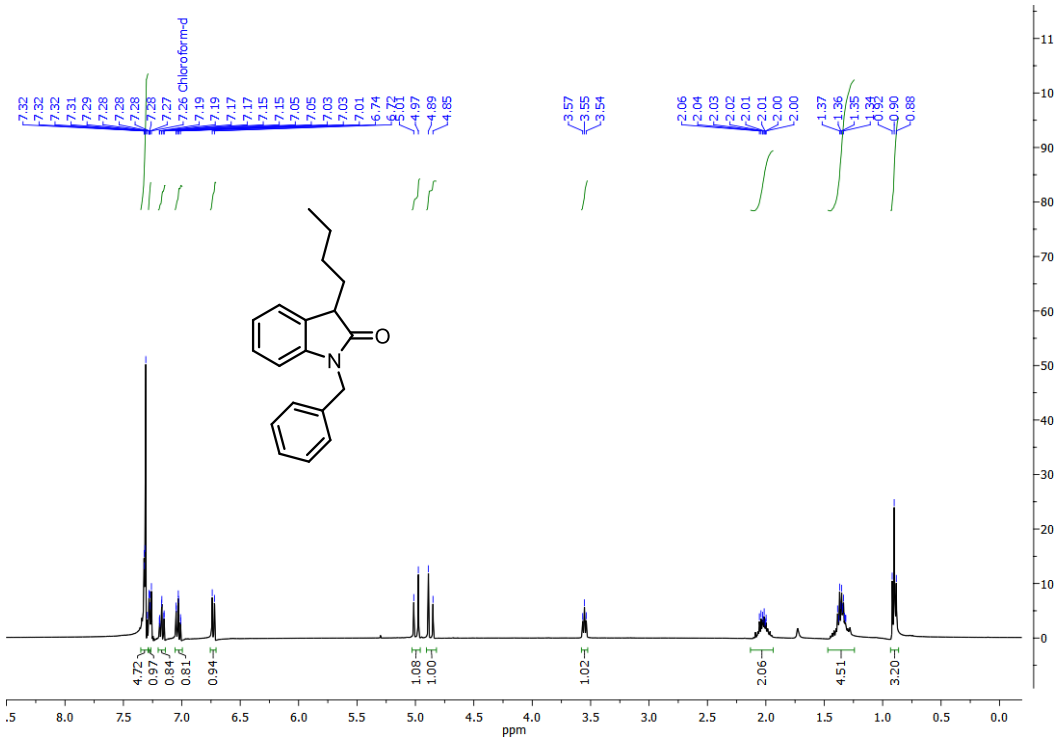


Figure 2A.14. ^{1}H NMR of compound **4k**

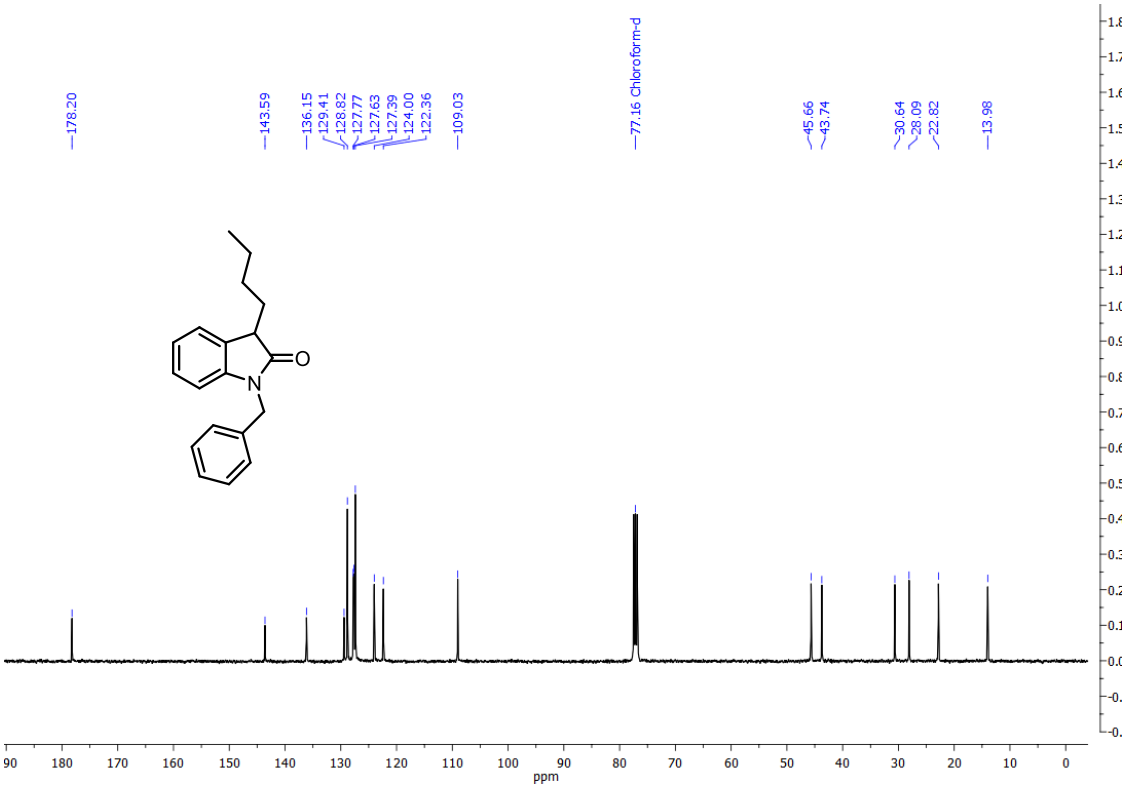


Figure 2A.15. ^{13}C{^{1}H} NMR of compound **4k**

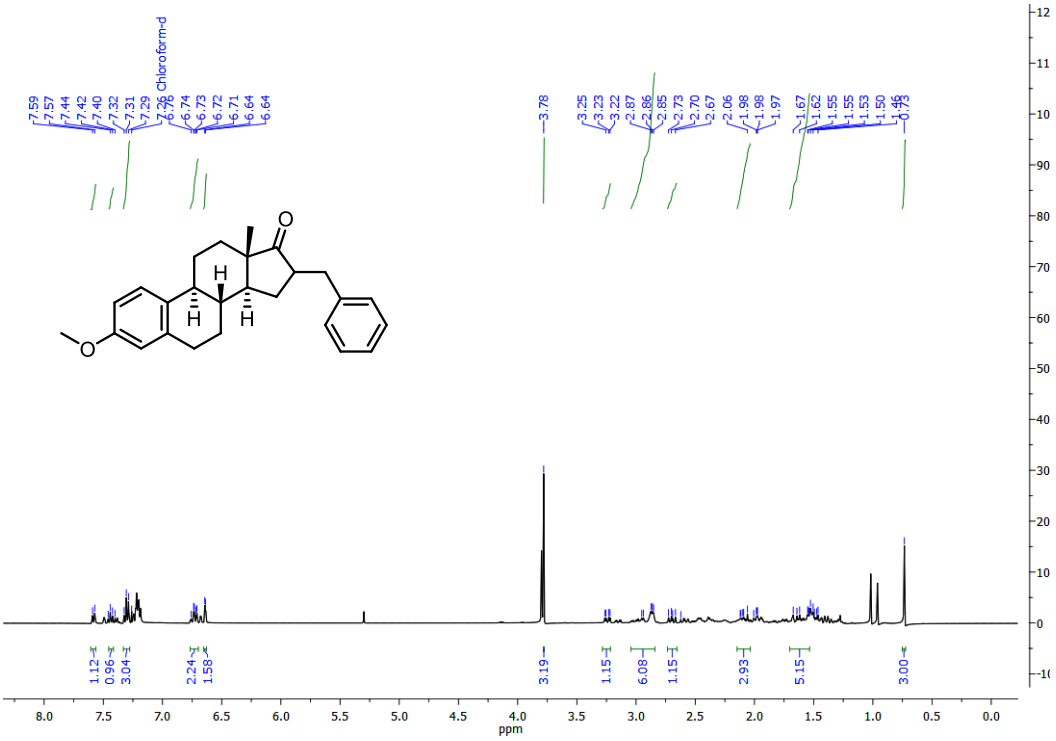


Figure 2A.16. ^{1}H NMR of compound **4m**

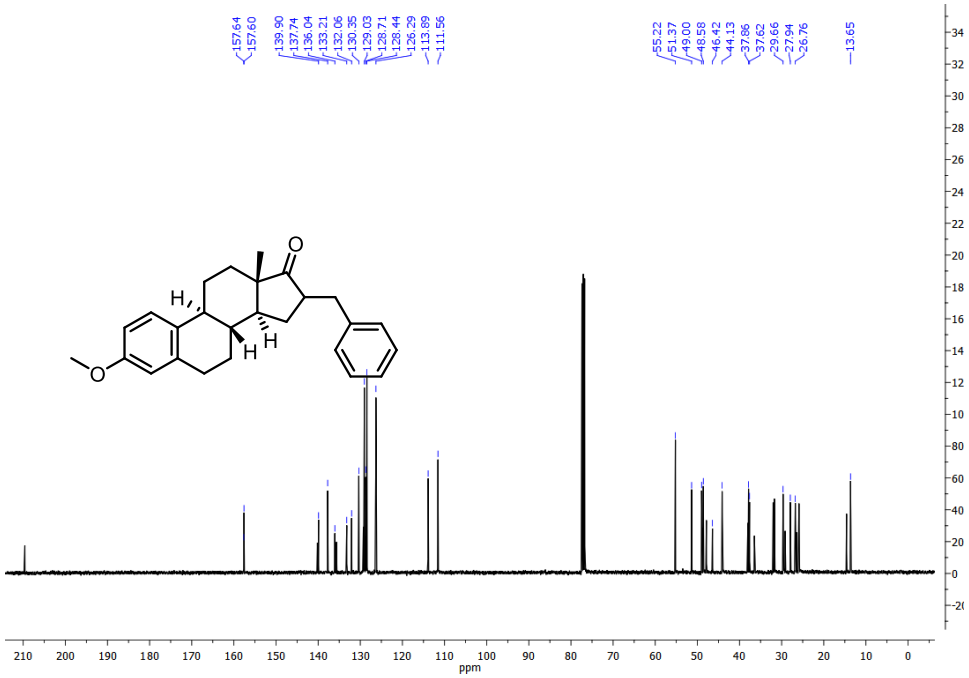


Figure 2A.17. ^{13}C{^{1}H} NMR of compound **4m**

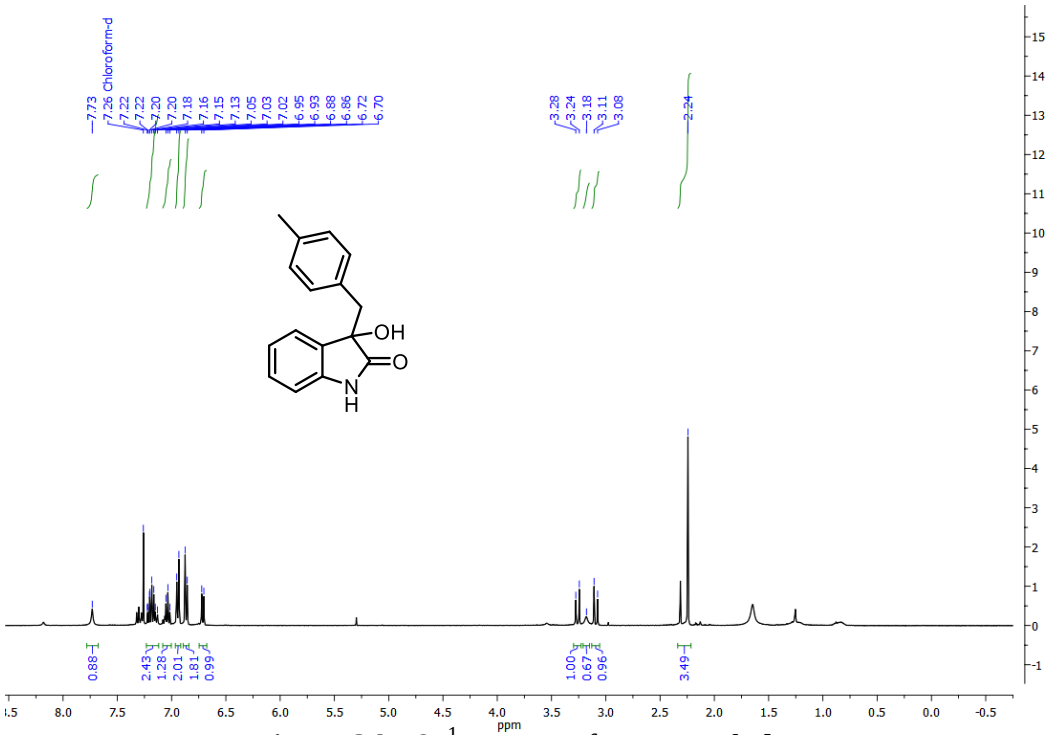


Figure 2A.18. ^{1}H NMR of compound **5b**

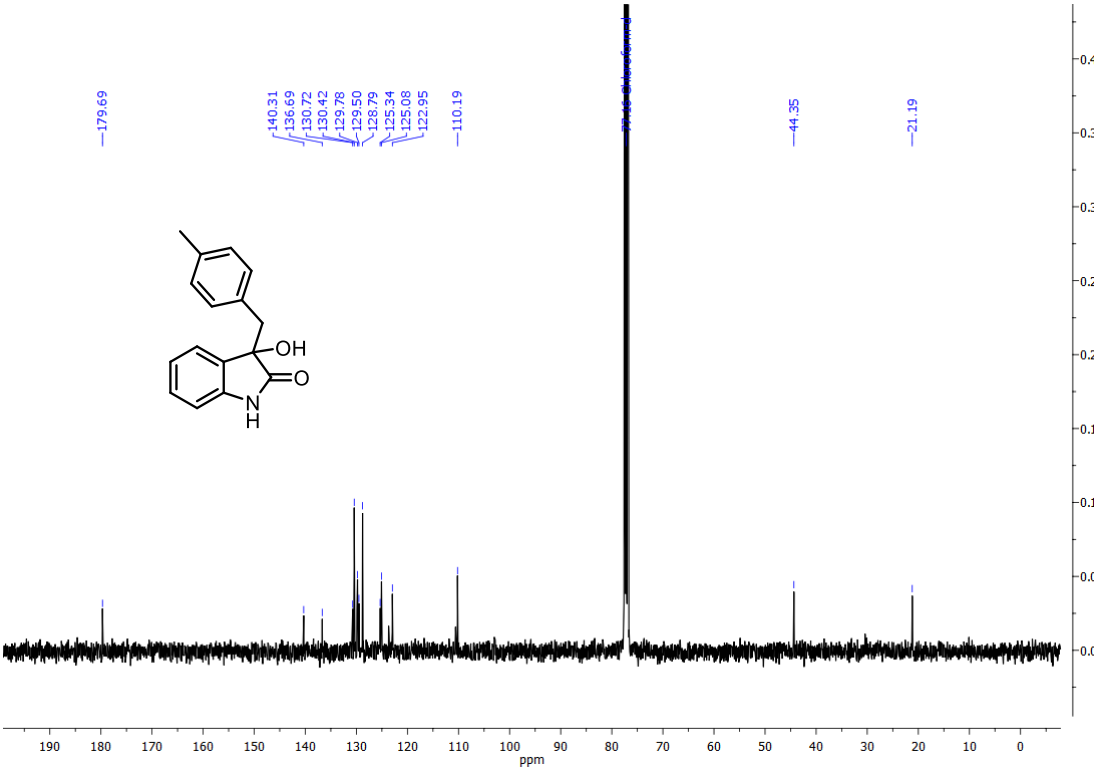


Figure 2A.19. ^{13}C{^{1}H} NMR of compound **5b**

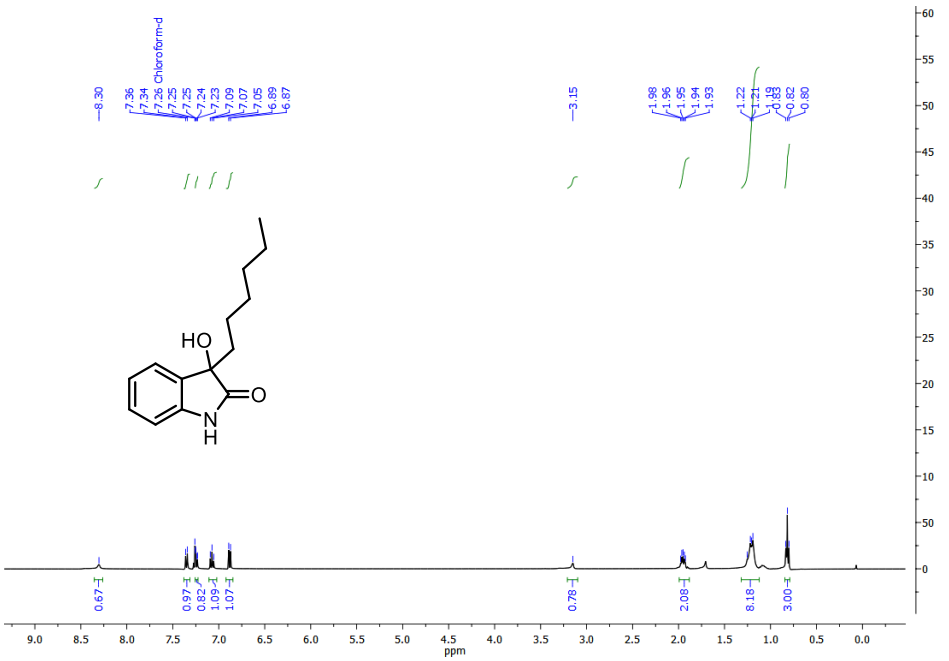


Figure 2A.20. ^{1}H NMR of compound **5h**

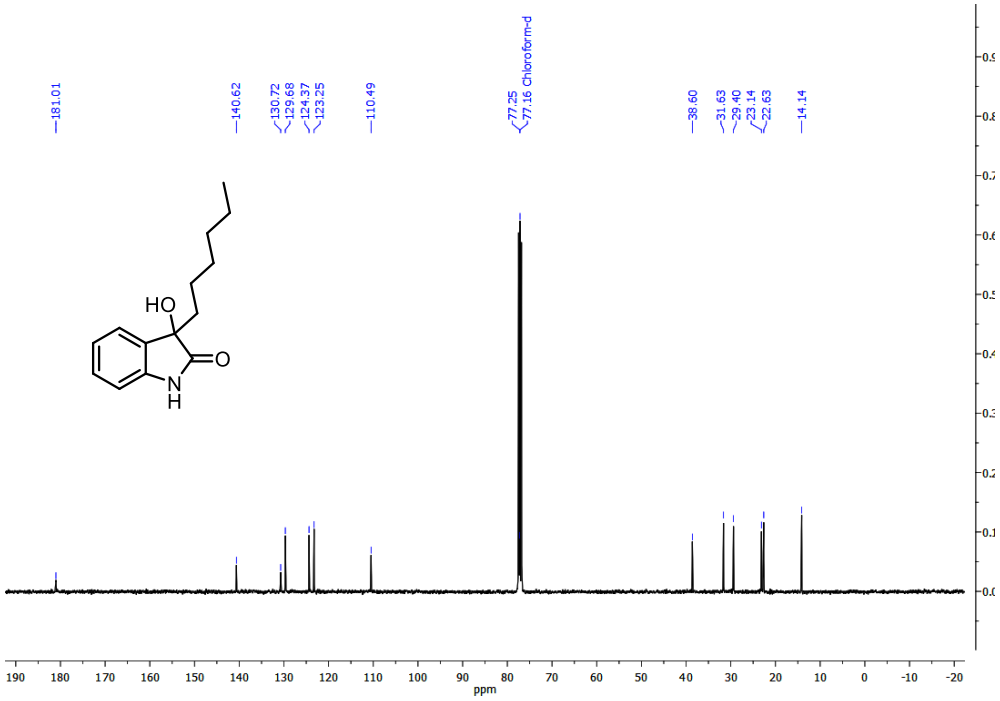


Figure 2A.21. ^{13}C{^{1}H} NMR of compound **5h**

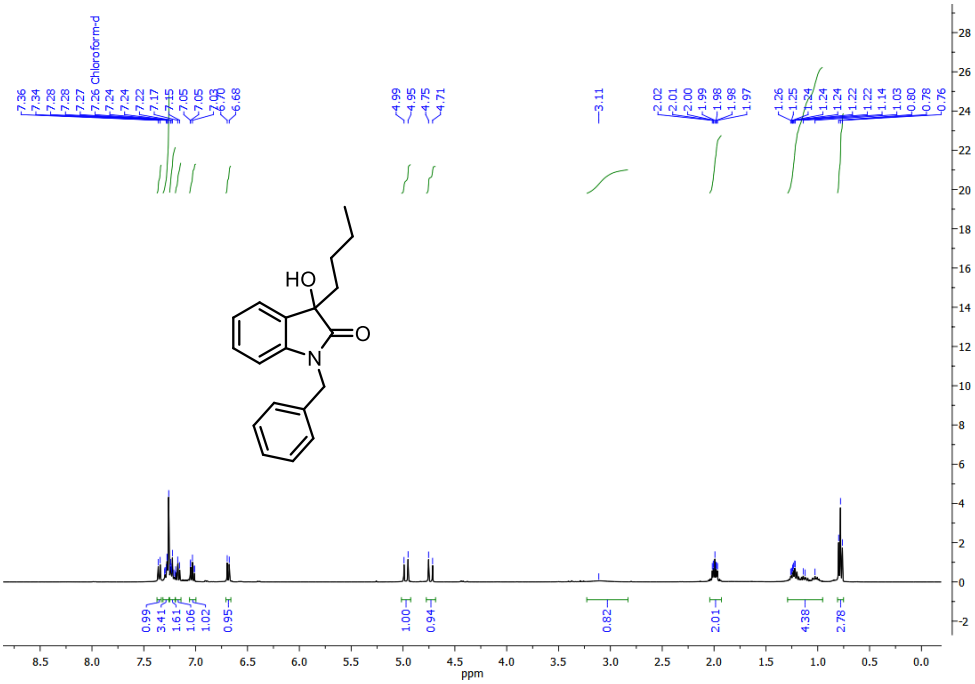


Figure 2A.22. ^{1}H NMR of compound **5i**

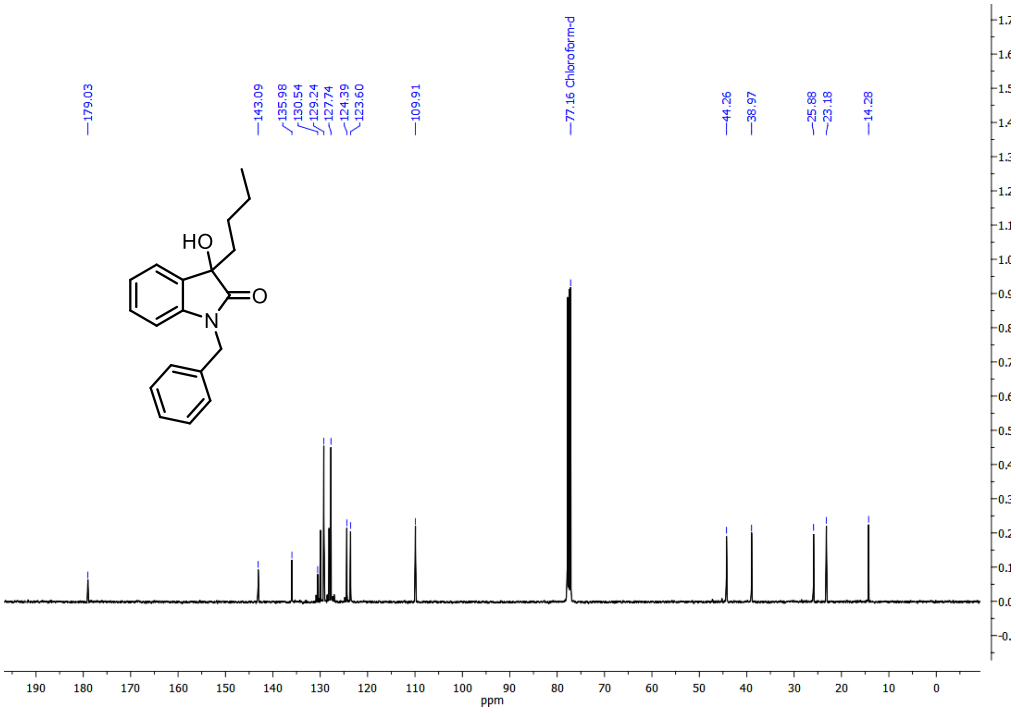


Figure 2A.23. ^{13}C{^{1}H} NMR of compound **5i**

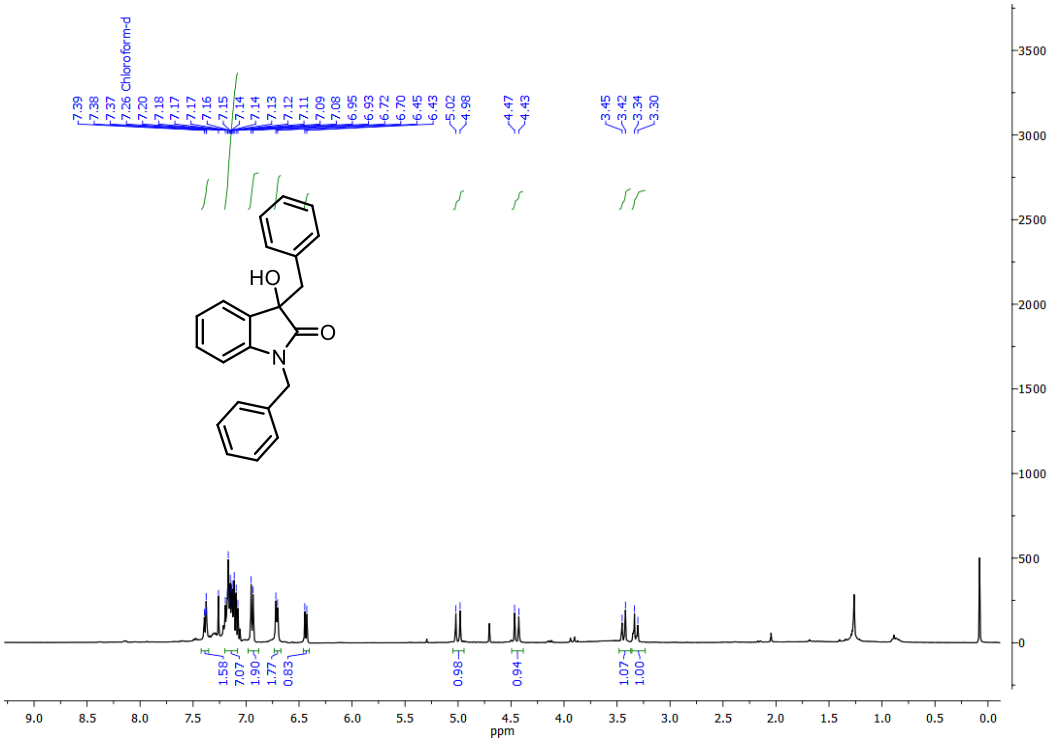


Figure 2A.24. ^{1}H NMR of compound **5n**

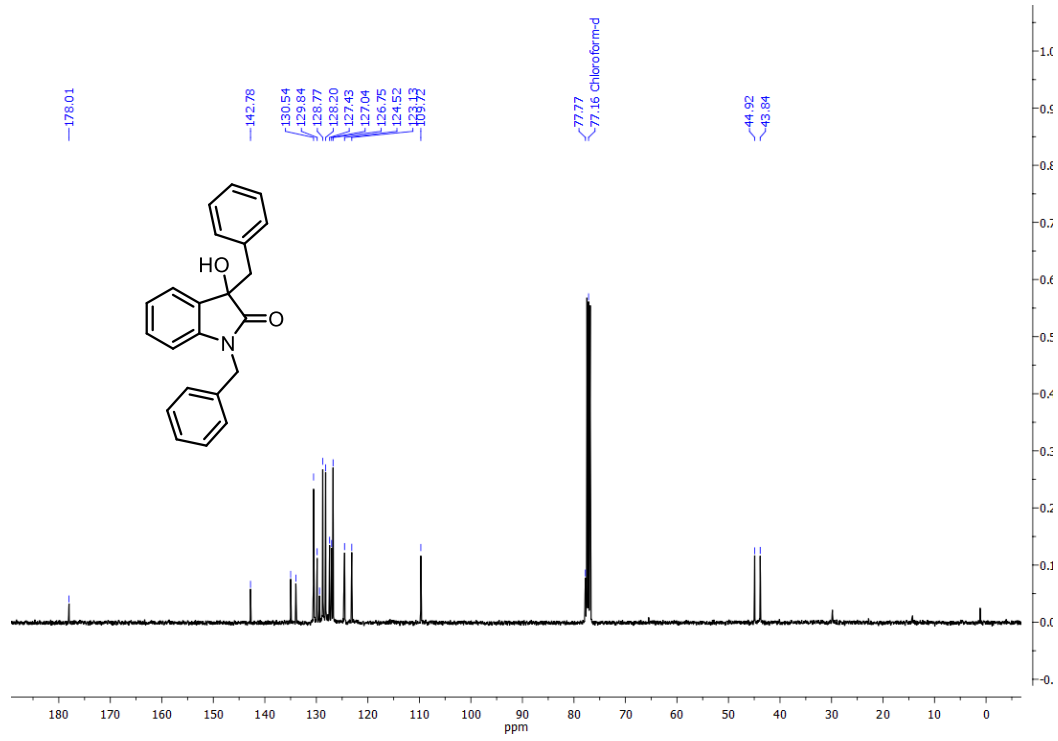


Figure 2A.25. ^{13}C{^{1}H} NMR of compound **5n**

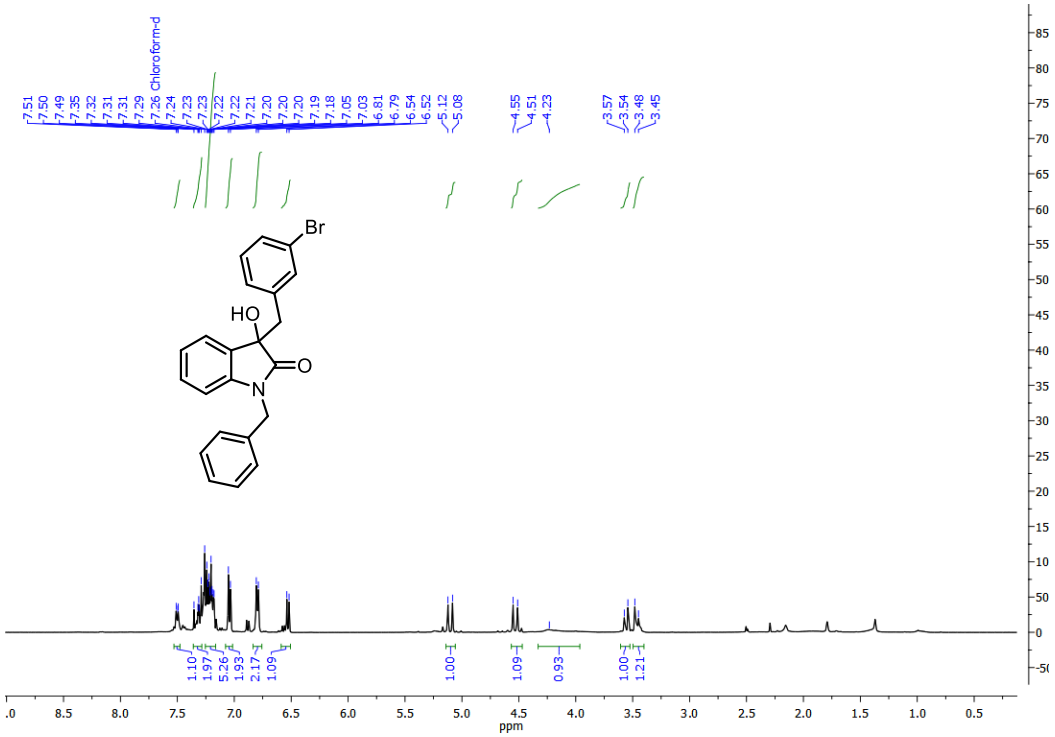


Figure 2A.26. ^{1}H NMR of compound **5v**

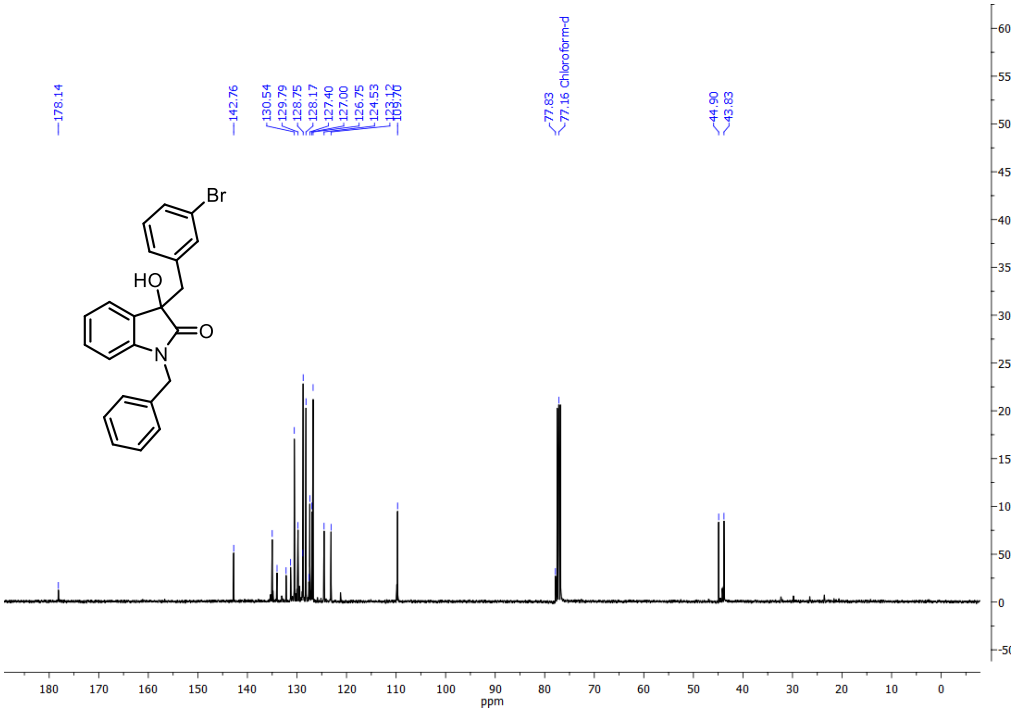


Figure 2A.27. ^{13}C{^{1}H} NMR of compound **5v**

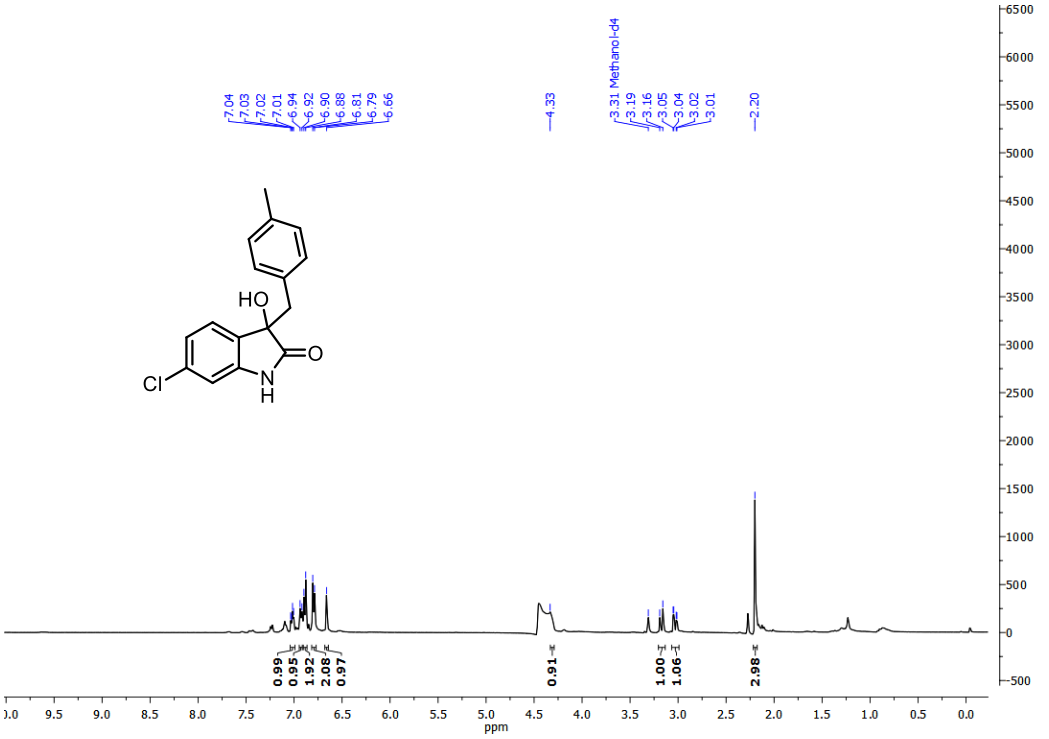


Figure 2A.28. ^{1}H NMR of compound **5b'**

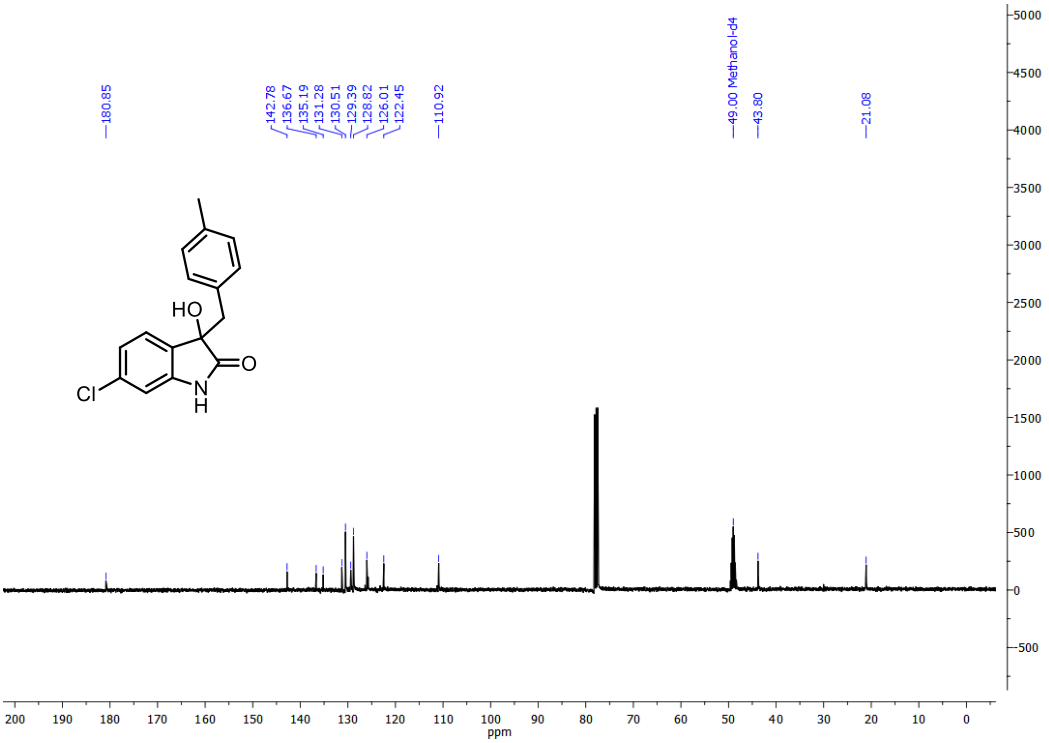


Figure 2A.29. ^{13}C{^{1}H} NMR of compound **5b'**

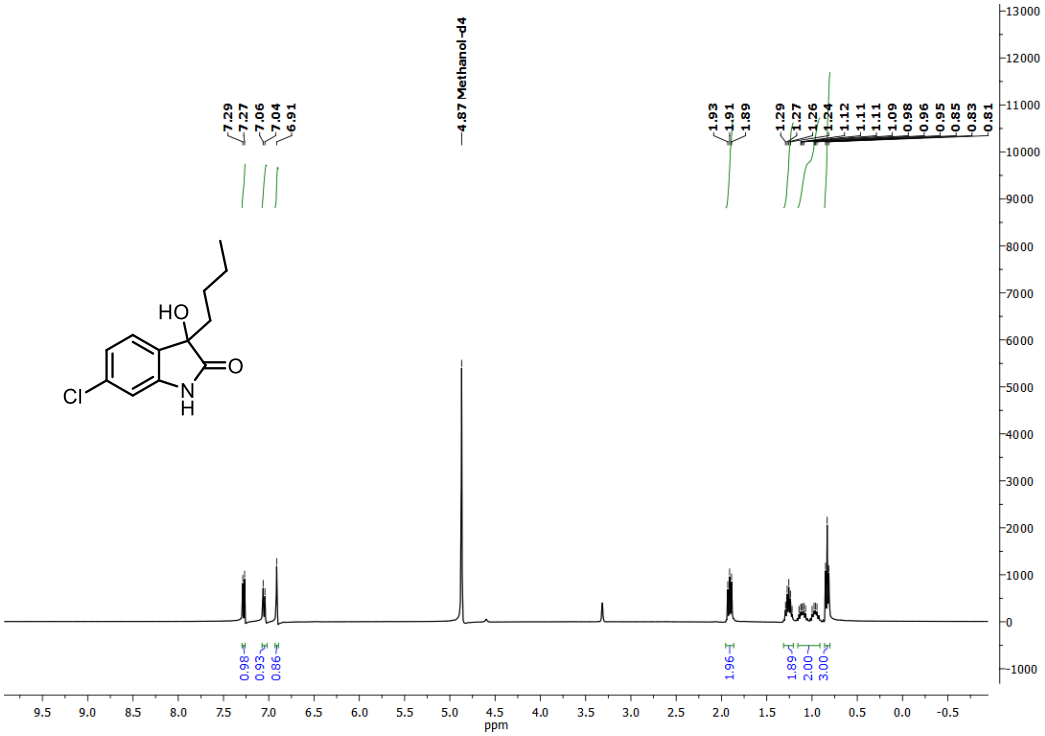


Figure 2A.30. ^{1}H NMR of compound **5d'**

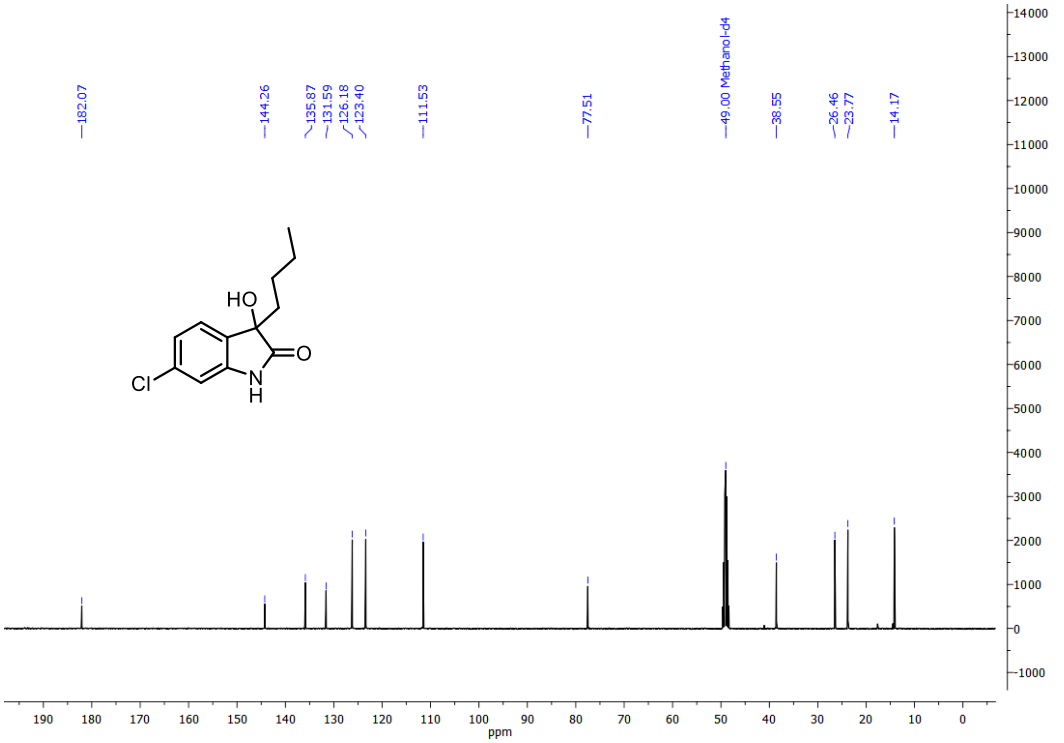


Figure 2A.31. ^{13}C{^{1}H} NMR of compound **5d'**

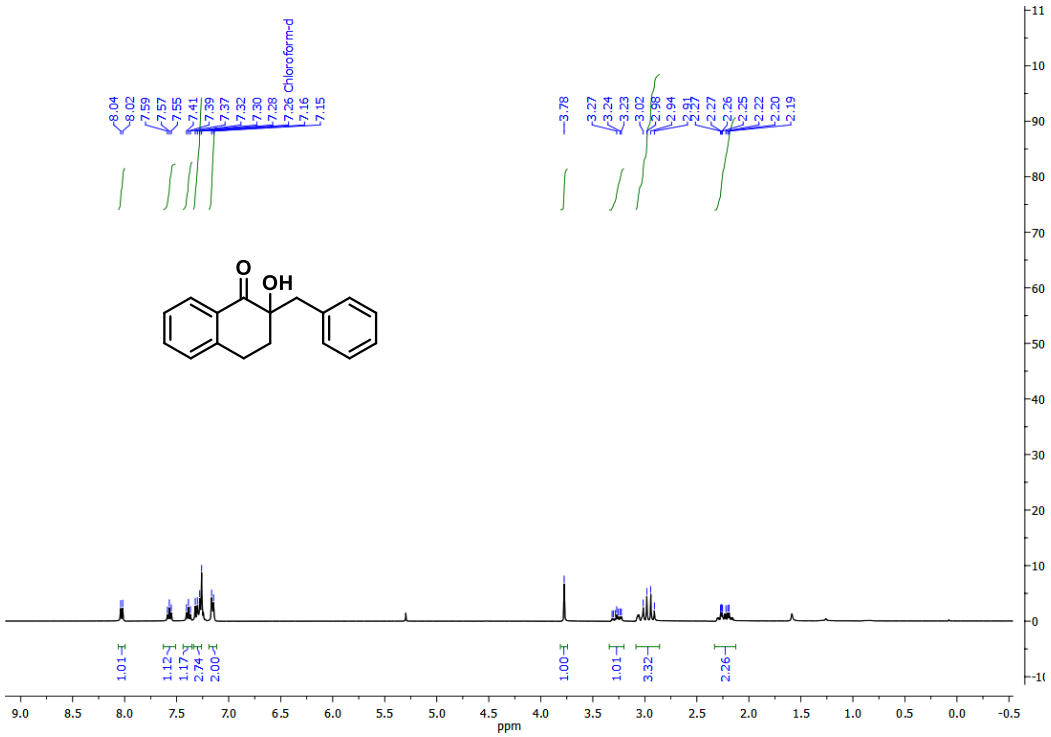


Figure 2A.32. ^{1}H NMR of compound **7a**

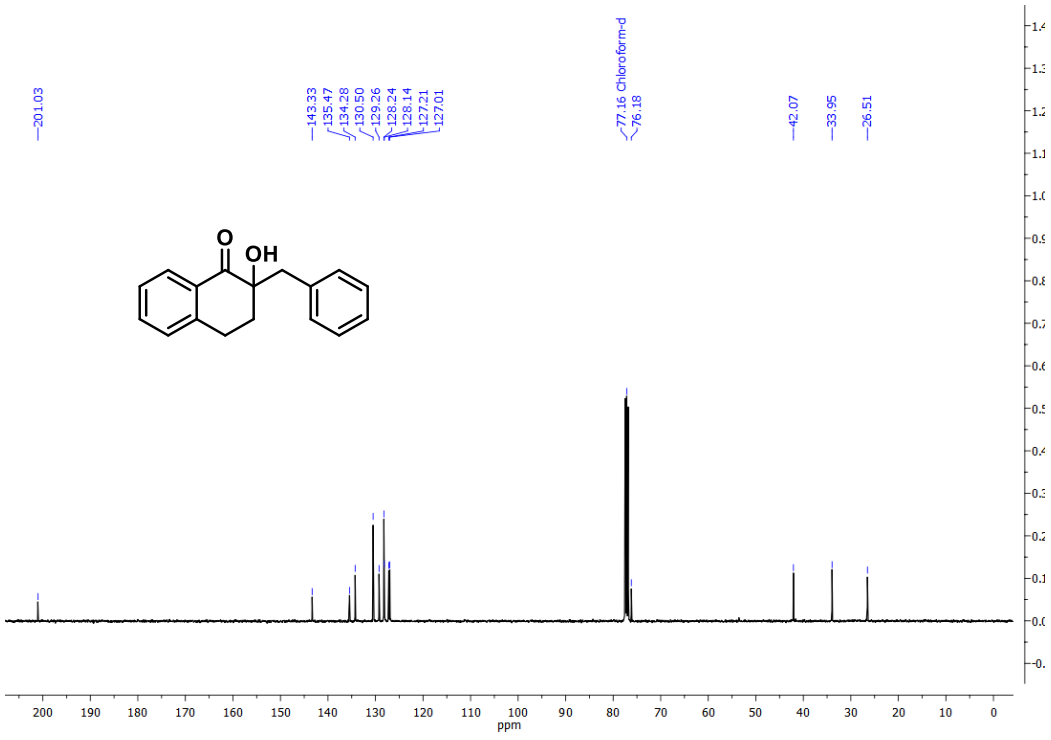


Figure 2A.33. ^{13}C{^{1}H} NMR of compound **7a**

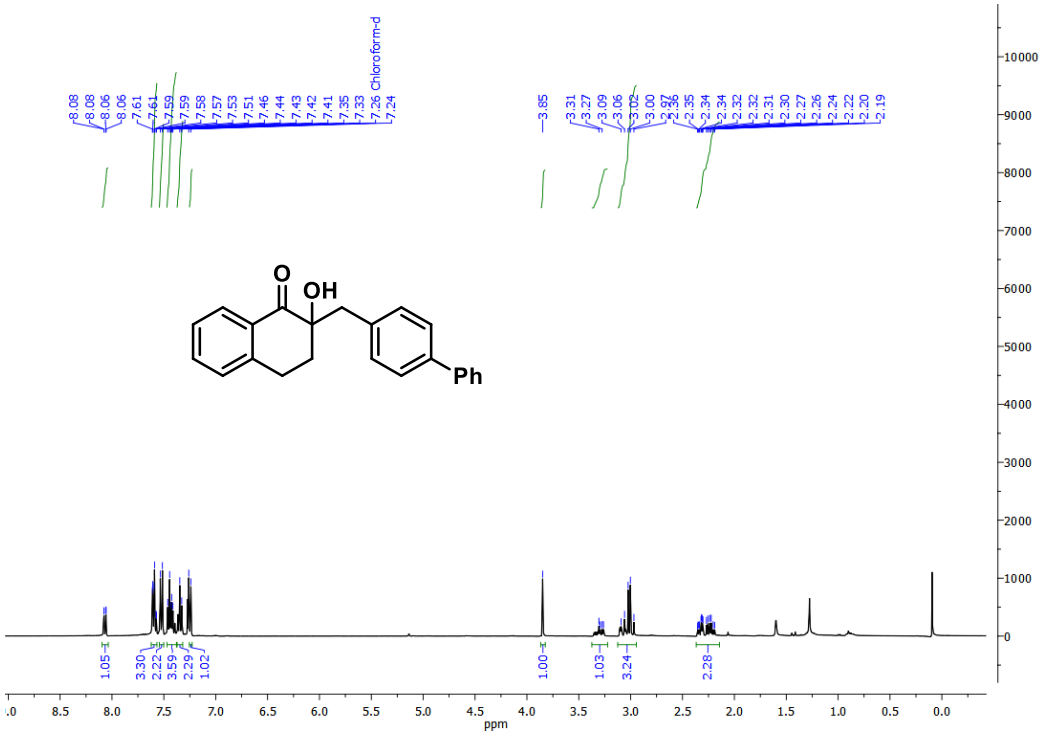


Figure 2A.34. ^{1}H NMR of compound **7h**

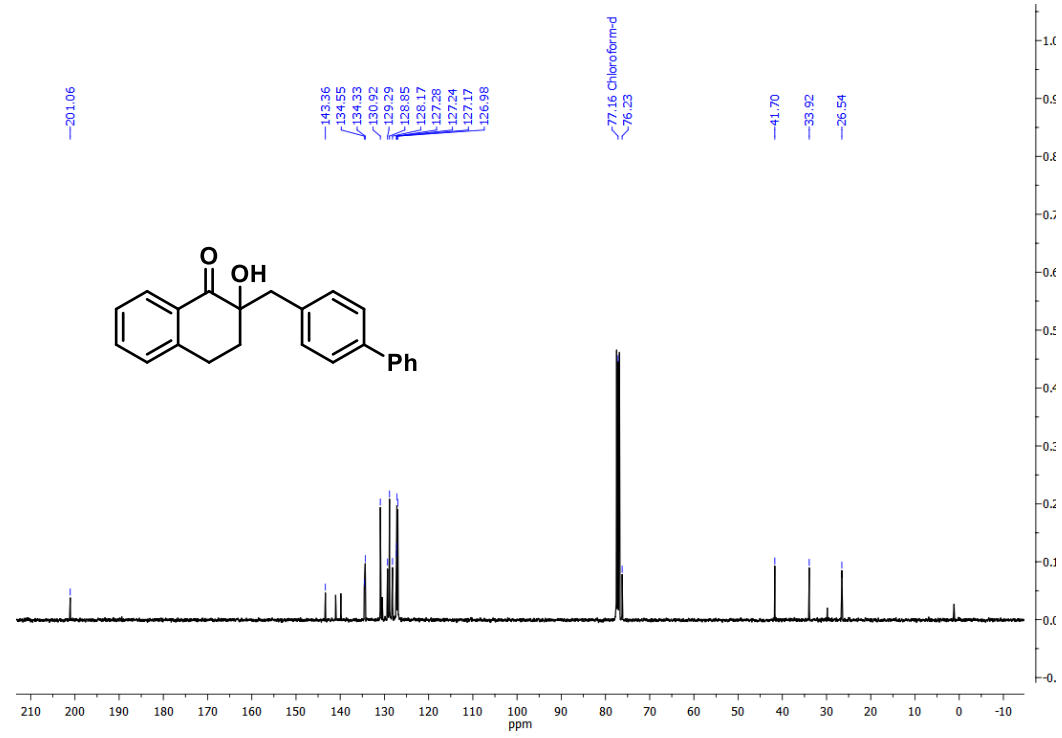


Figure 2A.35. ^{13}C{^{1}H} NMR of compound **7h**

2A.9. References:

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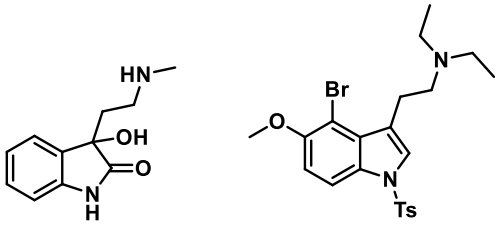
Chapter 2B

Progress Towards Total Synthesis of Arundaphine Using Borrowing Hydrogen Methodology

Progress towards Total Synthesis of Arundaphine Using Borrowing Hydrogen Methodology

2B.1. Abstract

In this chapter, progress toward the total synthesis of 2-oxindole based natural product Arundaphine is presented. Retrosynthetic analysis delineate, Arundaphine can be approached using the key synthons **5** and **10'**. Herein, we have successfully synthesized both the synthons for natural product Arundaphine. The synthon **5** (Donaxaridine) has been synthesized in three steps with overall yield of 43%. Second important synthon **10'** has been completed in five steps with overall yield 18%. The key step during the synthesis of synthon **5** was C3 alkylation followed by one-pot hydroxylation. Similarly, for synthon **10'** selective bromination at C4 position of indole was key step.



Donaxaridine (5) 10'

2B.2. Introduction

2B.2.1 Introduction to Arundaphine Alkaloid

Indole is an aromatic heterocyclic compound having molecular formula C_8H_7N and one of the most studied core in heterocyclic chemistry. Moreover, indole alkaloid is a class of natural product having indole moiety in its core and known for its structural diversity.[1] In literature around 4000 natural products are known which belong to the class of indole alkaloids.[2] based on their biosynthesis it can be classified into two classes such as isoprenoids and non-isoprenoids. Further, it can be categorized into sub-class such as, simple derivatives of indole, tryptamines, carbazoles, vinca, strychnine. Due to structural complexity and unanticipated biological properties, isoprenoid and bisindole alkaloids are fascinated by biologists and synthetic chemists.[3] Also, indole alkaloid is known for various biological

activities such as, anti-cholinesterase activity, anti-viral, anti-tumor, anti-depressant, antimicrobial activity, anti-inflammatory activity, anti-cholinergic *etc*.[4] *Arundo donax* is usually known as giant reed or Spanish cane, it belongs to family poaceae. It is native plant of Asian region due to human intervention it is also found in the southern part of USA. Traditionally this plant has been used in various therapeutic applications.[5]

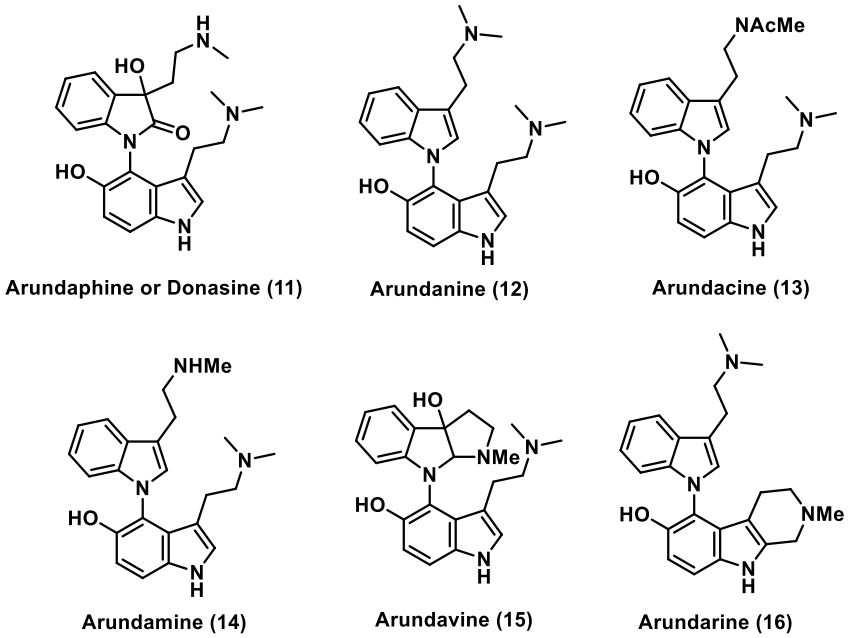


Figure 2B.1. Arundaphine and its derivatives isolated from *Arunda donax*

Furthermore, this plant has been used in several other objectives such as, for the construction of musical instrument, useful chemicals and biofuel.[6] Also, this plant found to be an excellent source of several natural products for instance, in 2004 Khuzhaev research group isolated 6 different derivatives of bis indole alkaloid from the root of giant reed arunda donax (Figure 2B.1).[7] Traditionally, the rhizomes of Arundaphine can act as diuretic medicine and antifebrile for curing disease such as, fever and headache.[8] Later in 2008, a group of chinese scientist reisolated arundaphine from the rhizomes of Arundo donax L. and confirmed the structure by single crystal and other spectroscopic analysis.[9] Arundaphine is a dimeric alkaloid having molecular formula $C_{23}H_{28}N_4O_3$ and molecular weight 408.2161. Arundaphine consists of indole and oxindole ring connected through C4 atom of indole and N1 atom of amide bond of oxindole and related by a pseudo-center of symmetry.

2B.3. Objective of the present work

Natural products having quaternary 3-alkyl-3-hydroxy-2-oxindole skeleton is known for various biological activities for instance, anti-oxidant, exhibit cytotoxicity

and inhibits specific cytokines.[10] Moreover, Arundaphine is 3-alkyl-3-hydroxy-2-oxindole based natural product, and there is no report for the synthesis of arundaphine. In present chapter, our objective is to accomplish total synthesis of arundaphine by using borrowing hydrogen concept. Moreover, we envisioned that the route should be efficient and short.

2B.4. Retrosynthesis of Arundaphine

Retrosynthetic analysis of arundaphine **11** using disconnection approach is shown in figure 2B.2. From retrosynthesis analysis, the key steps for the total synthesis of arundaphine involves. I) C−C bond formation using borrowing hydrogen concept. II) Selective C4 bromination of 5-methoxy indole. III) C−N bond-forming reaction. Since, two indole moieties in Arudnaphine are connected through C−N bond, we realized that Ullmann type or Buchwald- Hartwig coupling reaction could generate the desired intermediate. Further, boron tribromide demethylation could give the final product arundaphine. One of the synthon **5** (Donaxaridine) can be synthesized by selective tosylation of the compound **4** followed by substitution reaction in the presence of methylamine.

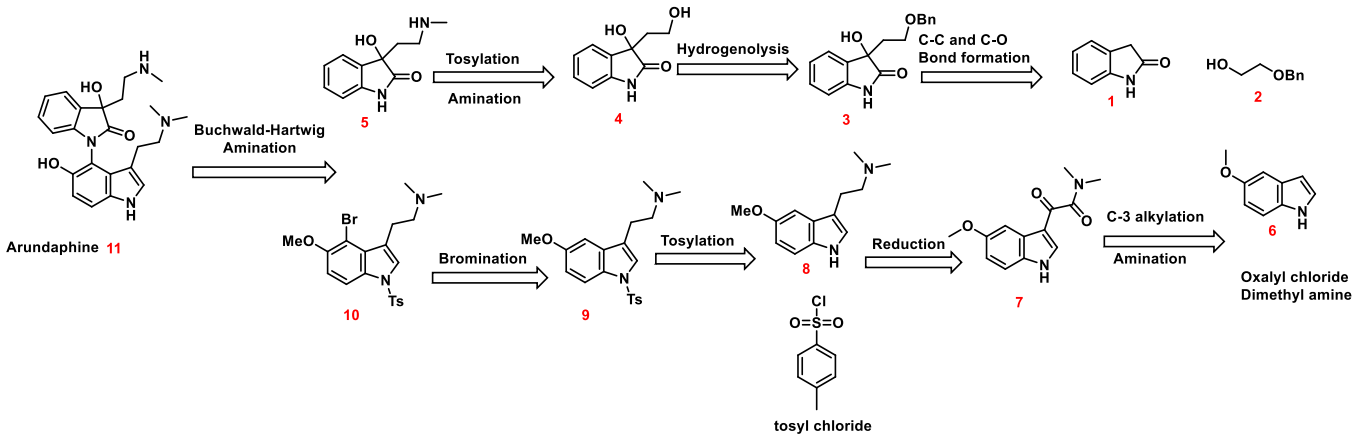


Figure 2B.2. Retrosynthetic analysis of Arundaphine

Generation of dihydroxy compound, 3-hydroxy-3-(2-hydroxyethyl)indolin-2-one **4** is expected to be very simple *via* deprotection of benzyl group through hydrogenolysis. Similarly, in order to get compound **3**, we anticipated that 2-oxindole can easily couple with 2-(benzyloxy)ethan-1-ol *via* borrowing hydrogen concept followed by one-pot hydroxylation reaction. On other hand, to develop a procedure for the synthesis of compounds **10,** we envision the selective bromination reaction of compound **9** under suitable reaction condition. Beside, formation of 2-(5-methoxy-1-tosyl-1H-indol-3-yl)-*N*,*N*-dimethylethan-1-amine **9** was expected to be straightforward

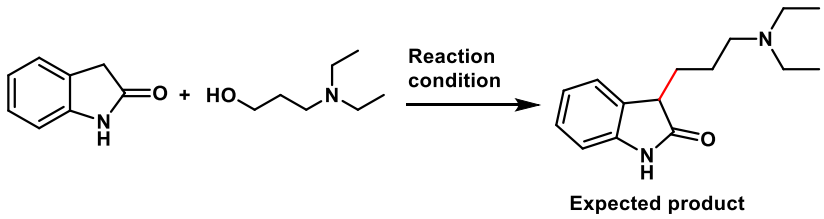
through *N*-toslylation of compound **8**. Similarly, compound **8** can be easily generated from intermediate **7** with help of well-known carbonyl reduction using lithium aluminium hydride as a reducing agent. Finally, compound **7** could be synthesized from commercially available starting material 5-methoxy indole, oxalyl chloride, and dimethylamine.

2B.5. Results and discussion

2B.5.1 Forward synthesis of synthon 5 (Donaxaridine)

Donaxaridine is hydroxyl oxindole based natural product and isolated along with arundaphine, in 1997. MacLeod and co-workers reported first total synthesis of donaxaridine comprises of multi-step.[11]

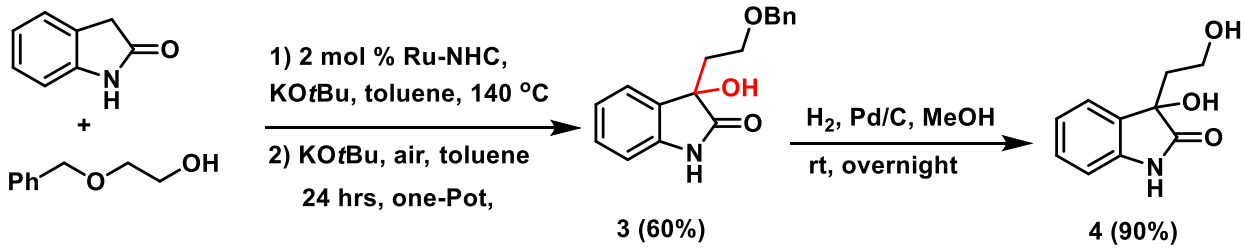
Table 2B.1. Optimization for C−C bond forming reaction



Entry	Catalyst (in mol %)	Temp.	Time	Result
1	Ru-PNN (2.2)	140 °C	24 hrs.	No reaction
2	Ru-PNN (4)	160 °C	24 hrs.	Multiple spots on TLC
3	Ru-NHC (2)	140 °C	24 hrs.	No reaction
4	Ru-NHC (5)	190 °C	16 hrs.	Multiple spots on TLC
5	$FeCl_3$ (20)	140 °C	24 hrs.	No reaction
6	$RuCl_3$ (10) PPh_3 (20)	110 °C	24 hrs.	No reaction
7	Ru-MACHO (3)	120 °C	24 hrs.	No reaction
8	$RuHClCOPPh_3$ (1)	120 °C	24 hrs.	No reaction

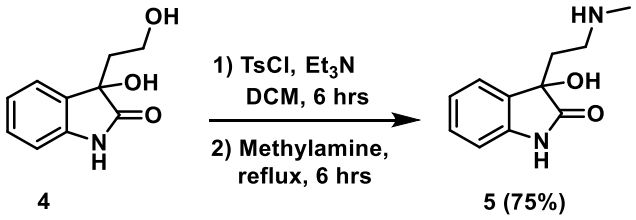
Initially, we thought to couple 2-oxindole and amino alcohol 2-(methylamino)ethan-1-ol *via* borrowing hydrogen concept in presence of suitable catalyst to get synthon **5** directly in single step. To establish a procedure of the generation of synthon **5**, reaction of oxindole and with 3-(diethylamino)propan-1-ol was taken as a model reaction. Several reaction conditions have been screened and results are summarized in table 2B.1. When the reaction was performed in presence of Ru-PNN catalyst and heated at 140 °C for 24 hrs resulted no reaction. Complicated reaction mixture was observed when reaction was heated at a higher temperature (Table 2B.1 entries 1 & 2).

Similarly, no reaction was observed when we have taken Ru-NHC as a catalyst for this transformation. Further, a range of Ru catalyst has been screened in order to get optimized reaction condition. $RuCl_3$, Ru-MACHO and $RuHClCO(PPh_3)$ was failed to give the desired product (Table 2B.1 entries 6-8). Moreover, no progress in the reaction was observed when the reaction was performed with ferric chloride. Unfortunately, no reaction was observed after several attempts. Hence alternative approach was considered with other protected alcohol as a coupling partner shown in figure 2B.2. Thus, we started the reaction of commercially available 2-oxindole and 2-(benzyloxy)ethan-1-ol by using our reported procedure generated compound **3** in 65% yield.[12] Further, to get compound **4,** compound **3** was subjected to hydrogenolysis reaction by using hydrogen gas-balloon over Pd/C to generate 3-hydroxy-3-(2-hydroxyethyl)indolin-2-one **4** in excellent yield (Scheme 2B.1).[13]



Scheme 2B.1. Synthesis of compounds **3** and **4**

Next, primary alcohol of compound **4** was selectively converted into good leaving group by using *p*-toluenesulfonyl chloride provided the tosylated intermediate. Next, we performed amination reaction without purifying the crude reaction mixture. Interestingly, when the reaction mixture was subjected to reflux condition in presence of 6M methylamine in ethanol furnished product **5** (donaxaridine) in good yield (Scheme 2B.2).[10]

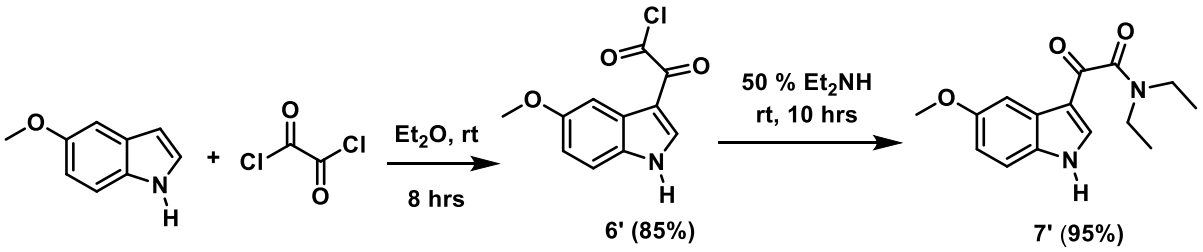


Scheme 2B.2. Synthesis of compound **5** (donaxaridine)

2B.5.2. Forward synthesis of synthon 10'

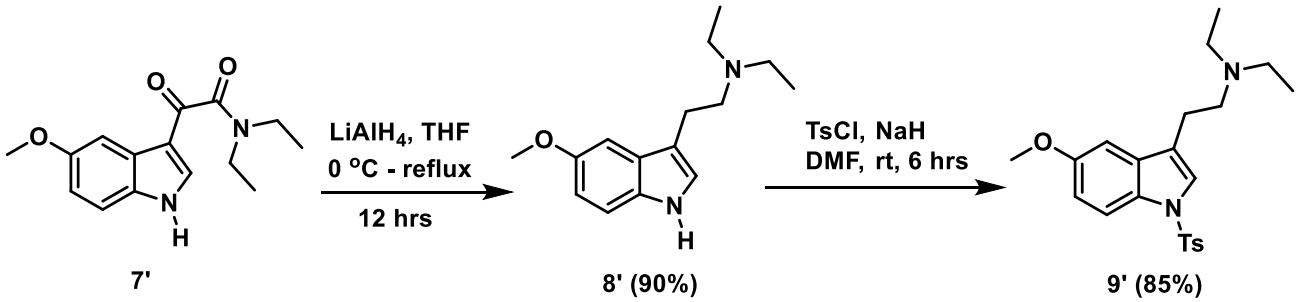
In order to get compound **10'**, the reaction of 5-methoxyindole was performed with oxalylchloride to get the acylated intermediate **6'**. Further reaction of compound

6' with diethylamine generated compound **7'** for the further transformation according to modified literature procedure (Scheme 2B.3).[14]



Scheme 2B.3. Synthesis of synthon **6'** and **7'**

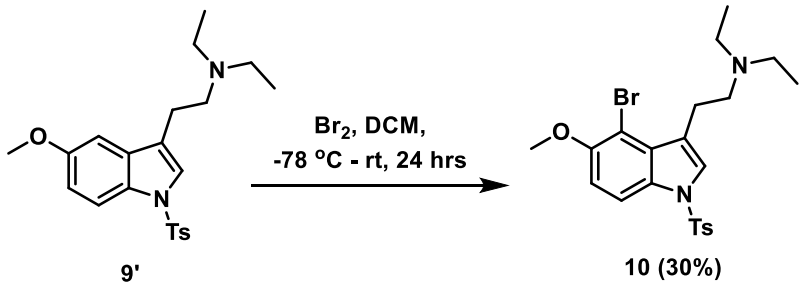
Further, the carbonyl of compound **7'** was reduced by using lithium aluminium hydride under reflux condition to generate compound **8'**.[13] In final stage, bromination is required at C4 position of indole. Thus, we thought to protect free NH by tosyl group in order to avoid bromination at C3 position of indole. Thus, *N*-tosylated compound **9'**was prepared from compound **8'** *via* tosylation reaction (Scheme 2B.4).[15]



Scheme 2B.4. Synthesis of compound **8'** and **9'**

To perform a selective bromination at C4 position of synthon **9'**, a set of reaction conditions has been studied and the results are discussed in table 2B.2.

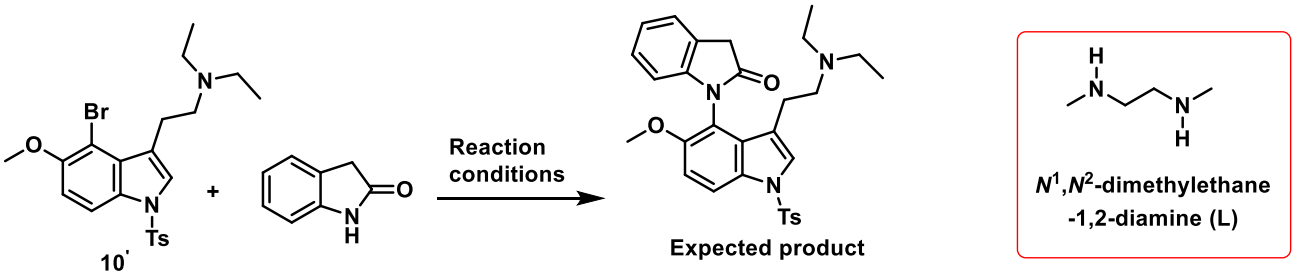
Table 2B.2. Optimization for bromination reaction



Entry	Reagent	Solvent	Temp (°C)	Time	Result
1	Br_2	AcOH	rt.	6	NR
2	NBS	CCl_4	rt.	8	NR
3	Br_2	DCM	-78 °C - rt.	24	30

Initially, when the bromine was added to acetic acid solution containing compound **9'** resulted no reaction. Further, when NBS was taken as a halogenated source no improvement in the reaction was observed. Interestingly, as per literature procedure[16] when bromine was added to lower temperature and kept for longer time. This reaction indicates formation of product **10'** and isolated in 30% yield after column purification.

Table 2B.3. Optimization for C−N bond forming reaction



S.N.	Catalyst (mol%)	Base	Temp.	Ligand	Solvent	Time	Result
1	CuI (10)	K_3PO_4	130 °C	Glycine	DMF	24 hrs	Multiple spot
2	CuI (10)	K_3PO_4	90 °C	Glycine	DMF	24 hrs	NR
3	CuI (10)	K_3PO_4	110 °C	L	Toluene	24 hrs	NR
4	CuI (10)	K_2CO_3	80 °C	L	CH_3CN	21 hrs	NR
5	$Pd(PPh_3)_4$ (5)	Cs_2CO_3	100 °C	Xantphos	1,4-Dioxane	16 hrs	NR
6	$Pd(OAc)_2$ (5)	Cs_2CO_3	100 °C	Xantphos	1,4-Dioxane	16 hrs	NR
7	$Pd(OAc)_2$ (5)	Cs_2CO_3	80 °C	Xantphos	1,4-Dioxane	16 hrs	NR
8	$Pd(dba_3)_2$ (5)	Cs_2CO_3	100 °C	Xantphos	1,4-Dioxane	37 hrs	Multiple spot

After synthesizing both substrate **5** and **10'**, reaction optimization was performed for the C−N bond-forming reaction. Initial reaction was performed with compounds **5** and **10'** using CuI as a catalyst in the presence of ligand **A** and K_3PO_4 base in DMF as a solvent. When the reaction mixture was heated at 140 °C for 24 hrs resulted no reaction (Table 2B.3, entry 1). To identify the optimized reaction condition for the C−N bond formation, we investigated this reaction with 2-oxindole. Various reaction conditions attempted are shown in Table 2B.3. No progress in the reaction was observed when the reaction performed by decreasing the temperature (Table 2B.3 entry 2). Later to achieve the reaction condition several parameters such as base, ligand and solvent has been screened resulted no reaction (Table 2B.3 entries 3 & 4). Since, there was no reaction in presence of CuI at this moment, we realised that it is requisite to change the catalyst. In this regard, on switching the catalyst from CuI to tetrakis(triphenylphosphine)palladium(0) did not generate any product (Table 2B.3 entry 5). Furthermore, changing the Pd catalyst to $Pd(OAc)_2$ or $Pd(dba_3)_2$ results no

reaction (Table 2B.3. entries 6-8). Unfortunately, no C−N bond forming reaction was observed in reaction mixture. Still optimization for this reaction condition is under progress in our laboratory.

2B.6 Conclusion

In this chapter, we have successfully used BH concept and one-pot hydroxylation reaction as a key step toward the synthesis of natural product Arundaphine. During the forward synthesis of synthon **10'**, selective bromination at C4 position of indole was developed. While performing the synthesis of arundaphine natural product, we have completed the total synthesis of oxindole based natural product donaxaridine in short route with overall yield 43%. In order to complete the total synthesis of arundaphine, optimization for the key C−N bond-forming step is under progress in our research group.

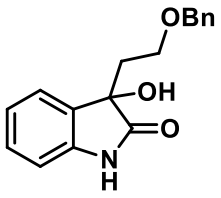
2B.7. Experimental section and characterization data

2B.7.1. General information and data collection

All the starting material was prepared according to the reported literature procedures. All the chemicals were purchased from Sigma-Aldrich or Alfa-Aesar. Deuterated solvents were used as received. As per reaction requirement solvents were dried and stored over 4Å molecular sieves. Column chromatographic separation was performed over 100-200 mesh size silica-gel. Visualization was accomplished with UV light and iodine. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded on 400 and 100 MHz respectively, using a Bruker or JEOL spectrometers. The chemical shift (δ) and coupling constant (J) values are given in parts per million and Hertz, respectively. Abbreviations used in the NMR follow-up experiments: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; td, dd doublet of triplet and double doublet; m, multiplet, tt, triplet of triplets and ddd, doublet of doublet of doublets. High-resolution mass spectra were obtained with Waters-synapt G2 using electrospray ionization (ESI-TOF). Infrared (ATR) spectra were obtained with a Bruker Alpha-E infrared spectrometer.

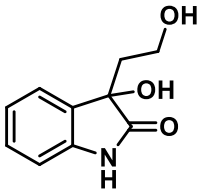
2B.7.2. Experimental procedure and analytical data for the synthons

3-(2-(benzyloxy)ethyl)-3-hydroxyindolin-2-one (3): Ru-NHC (6 mg, 0.01 mmol), KO*t*Bu (258 mg, 2.3 mmol), 2-(benzyloxy)ethan-1-ol (154 mg, 1 mmol), oxindole (266 mg, 2 mmol) and toluene (2 mL) were added to an oven-dried 20 mL resealable pressure tube (equipped with rubber septum) under N_2 atmosphere using a nitrogen balloon. Then, the tube was purged with N_2, and the septum was quickly removed

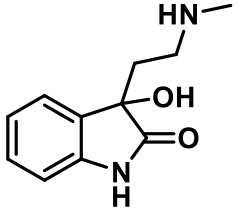


and the tube was sealed with a cap using a crimper. The reaction mixture was stirred at 140 ^{o}C for 16 hrs. After cooling to room temperature, the tube was unsealed and KO*t*Bu (1 mmol) was added to reaction mixture and stirred under open air at room temperature for 24 hrs. The reaction mixture was passed through celite bed (200 nm). After concentration under reduced pressure, residue was purified by 100-200 mesh silica-gel column chromatography using ethyl acetate/petroleum ether to afford the 3-(2-(benzyloxy)ethyl)-3-hydroxyindolin-2-one (175 mg, 60%) as a white solid. **^{1}H NMR** (400 MHz, acetone-D_6) δ 9.24 (bs, 1H), 7.31-7.20 (m, 7H), 7.00 (t, *J* = 8, 1H), 6.89 (d, *J* = 8 Hz, 1H), 4.94 (s, 1H), 4.41-4.34 (m, 2H), 3.54-3.50 (m, 2H), 2.29-2.23 (m, 1H), 2.21-2.19 (m, 1H). **^{13}C{^{1}H} NMR** (100 MHz, acetone-D_6) δ 179.65, 142.79, 139.62, 132.48, 130.00, 129.00, 128.26, 128.09, 125.16, 122.70, 110.56, 75.81, 73.35, 66.69, 38.52. **IR** (neat) = 3308, 2943, 1658 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{21}H_{17}NO_2$ $(M+Na)^+$: 306.1106, found: 306.1102.

3-hydroxy-3-(2-hydroxyethyl)indolin-2-one (4): In a 100 ml round-bottom flask, to methanol solution containing 3-(2-(benzyloxy)ethyl)-3-hydroxyindolin-2-one (1mmol, 283mg), 5 % palladium on carbon was added. Further, the system was purged with nitrogen. Later, the mixture was charged with hydrogen by using hydrogen-balloon and kept overnight at room temperature. At ice cold temperature, the reaction mixture was diluted with 30 mL DCM and filtered through celite bed. Subsequently, the residue was washed three times with 1:1 MeOH-DCM (30 mL). The filtrate was concentrated under reduced pressure to afford the 3-hydroxy-3-(2-hydroxyethyl)indolin-2-one (173 mg, 90%) as a colorless thick liquid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 4 Hz, 1H), 7.25 (td, *J* = 8, 1 Hz, 1H), 7.05 (t, *J* = 8 Hz, 1H), 6.89 (d, *J* = 8 Hz, 1H), 3.51 (t, *J* = 8 Hz, 2H), 3.35 (s, 1H), 2.24 – 2.11 (m, 2H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 181.99, 142.66, 132.70, 130.56, 125.12, 123.65, 111.26, 76.43, 58.41, 41.21. **IR** (neat) = 3309.16, 2943.66, 1718.32 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{10}H_{11}NO_3$ $(M+Na)^+$: 216.0636, found: 216.0642.

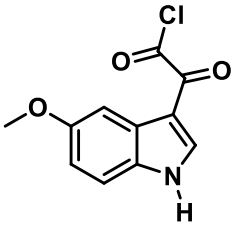


3-Hydroxy-3-(2-(methylamino)ethyl)indolin-2-one (Donaxaridine): To the 3-hydroxy-3-(2-hydroxyethyl)indolin-2-one (193 mg, 1 mmol,) in solution of DCM (2 mL), triethylamine (2 mL) and *p*-toluenesulfonyl chloride (190 mg, 1 mmol) was added and stirred for 6 h at room temperature. The reaction mixture was poured into a mixture of ice and 5% aqueous HCl (100 mL) and extracted with EtOAc. The extract was washed with brine, dried, and evaporated. The crude reaction mixture was added to a 30% solution of methylamine in ethanol (20 mL) and the mixture stirred under reflux for 5 h. The volatiles were evaporated, H_2O was added,

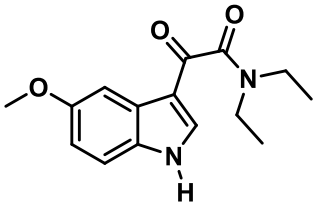


and the mixture was extracted with EtOAc. The organic extract was washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4 and evaporated. Further the crude reaction mixture was purified by column chromatography to afford the 3-hydroxy-3-(2-(methylamino)ethyl)indolin-2-one (Donaxaridine) in 75% yield as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$ δ 7.08 (td, *J* = 7.9, 1.5 Hz, 1H), 6.83 (dd, *J* = 7.7, 1.4 Hz, 1H), 6.71 – 6.63 (m, 2H), 4.68 (s, 2H), 3.26 (dtd, *J* = 16.0, 9.8, 4.0 Hz, 2H), 2.93 (s, 3H), 2.74 – 2.67 (m, 1H), 2.44 – 2.37 (m, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 175.36, 145.97, 129.21, 125.80, 125.22, 118.27, 118.04, 79.54, 45.78, 33.06, 30.26. **IR** (neat) = 3335, 3057, 2923, 1668 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{11}H_{14}N_2O_2$ $(M+H)^+$: 207.1133, found: 207.1132.

2-(5-methoxy-1H-indol-3-yl)-2-oxoacetyl chloride (6'): 5-Methoxyindole (147 mg, 1 mmol) was taken in diethyl ether (10 mL) and oxalyl chloride (250 mg, 2 mmol) was slowly added to it and stirred at reflux for 6 hrs. Further, the solid from reaction mixture was filtered and residue collected was evaporated the solvent to afford 2-(5-methoxy-1H-indol-3-yl)-2-oxoacetyl chloride (201 mg, 85%) as a yellow solid. **^{1}H NMR** (400 MHz, DMSO-D_6) δ 12.28 (s, 1H), 8.33 (d, *J* = 3.0 Hz, 1H), 7.67 (s, 1H), 7.44 (d, *J* = 8.8 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 1H), 3.80 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 181.09, 165.78, 156.50, 138.30, 131.86, 126.96, 113.82, 113.54, 113.52, 112.62, 103.49, 55.77. **IR**: 3226, 1697 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{11}H_8ClNO_3$ $(M+H)^+$: 238.0271, found: 238.0278.

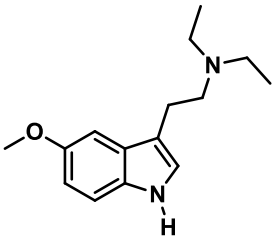


***N,N*-diethyl-2-(5-methoxy-1H-indol-3-yl)-2-oxoacetamide (7'):** A solution of 2-(5-methoxy-1H-indol-3-yl)-2-oxoacetyl chloride (237 mg, 1 mmol) in water was treated with diethyl amine in water (25 mL) and stirred at room temperature for 10 hrs. The aqueous layer was extracted with EtOAc or DCM and the combined organic layers were evaporated by reduced pressure afforded *N,N*-diethyl-2-(5-methoxy-1H-indol-3-yl)-2-oxoacetamide (260 mg, 95 %) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.74 (s, 1H), 7.74 (d, *J* = 1.9 Hz, 1H), 7.51 (d, *J* = 3.2 Hz, 1H), 7.15 (d, *J* = 8.9 Hz, 1H), 6.81 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.84 (s, 3H), 3.32 (q, *J* = 7.1 Hz, 2H), 1.14 (t, *J* = 7.1 Hz, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 186.21, 168.20, 156.72, 135.77, 131.79, 126.14, 114.49, 113.92, 113.23, 103.17, 55.84, 42.68, 39.23, 14.34, 12.86. **IR**: 2926, 1614, 1516, 1372 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{15}H_{18}N_2O_3$ $(M+H)^+$: 275.1396, found: 275.1390.

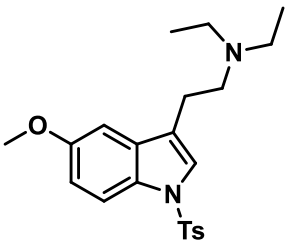


***N,N*-diethyl-2-(5-methoxy-1H-indol-3-yl)-2-oxoacetamide (8'):** *N,N*-diethyl-2-(5-methoxy-1H-indol-3-yl)-2-oxoacetamide (274 mg, 1 mmol) was taken in dry THF and lithium aluminum hydride (74 mg, 2 mmol) was added slowly under nitrogen

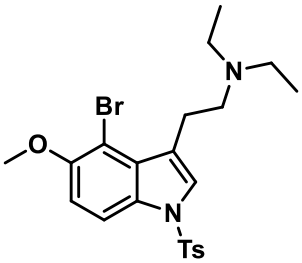
atmosphere at 0 ^{o}C. After 5 min. stirring at ice cold temperature, reaction mixture heated at reflux for 8 hrs. The reaction was cooled to room temperature and 1 mL 3N KOH, 2 mL H_2O, was added slowly. The residue was filtered and the organic layer was removed. The aqueous layer was extracted with DCM and the combined organic layers were evaporated in reduced pressure to afforded the desired product *N*,*N*-diethyl-2-(5-methoxy-1H-indol-3-yl)ethan-1-amine in (221 mg, 90%) as a yellow semi solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.22 (d, *J* = 8.8 Hz, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 6.96 (d, *J* = 1.8 Hz, 1H), 6.84 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.86 (s, 3H), 2.92 (ddd, *J* = 6.9, 6.2, 2.7 Hz, 2H), 2.84 (ddd, *J* = 12.7, 6.8, 2.9 Hz, 2H), 2.72 (q, *J* = 7.2 Hz, 4H), 1.13 (t, *J* = 7.2 Hz, 6H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 153.77, 131.58, 127.82, 122.60, 111.97, 100.65, 55.97, 53.15, 46.73, 22.45, 12.03, 11.30. **IR**: 3223 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{15}H_{22}N_2O$ $(M+H)^+$: 247.1810, found: 247.1008.



***N*,*N*-diethyl-2-(5-methoxy-1-tosyl-1H-indol-3-yl)ethan-1-amine (9'):** In dry DMF *N*,*N*-diethyl-2-(5-methoxy-1H-indol-3-yl)ethan-1-amine (1 mmol, 246 mg) taken and Na*H* (60 % in mineral oil, 2 mmol, 46 mg) was added portionwise at 0 ^{o}C. The resultant mixture was stirred for 5-10 min at 0 ^{o}C. Further, *p*-toluenesulfonyl chloride was added to the reaction mixture and kept it at room temperature for 6 hrs. Later, the reaction mixture was diluted with saturated solution of ammonium chloride solution, organic layer extracted with DCM and washed with brine several times. The combined organic layers were evaporated by using reduced pressure and purified by column chromatography afforded *N*,*N*-diethyl-2-(5-methoxy-1-tosyl-1H-indol-3-yl)ethan-1-amine (340 mg, 85 %) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 8.6, 0.8 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.32 (s, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 6.91 (dt, *J* = 8.6, 2.1 Hz, 2H), 3.81 (s, 3H), 2.81 - 2.73 (m, 4H), 2.64 (q, *J* = 7.2 Hz, 4H), 2.32 (s, 3H), 1.08 (t, *J* = 7.2 Hz, 6H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 156.47, 144.76, 135.39, 132.23, 130.04, 129.87, 126.82, 123.90, 121.45, 114.81, 113.57, 102.14, 55.82, 52.38, 47.00, 22.92, 21.67, 11.74. **IR**: 3103 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{22}H_{28}N_2O_3S$ $(M+H)^+$: 401.1899, found: 401.1892.



2-(4-bromo-5-methoxy-1-tosyl-1H-indol-3-yl)-N,N-diethylethan-1-amine (10'): To a solution of *N,N*-diethyl-2-(5-methoxy-1-tosyl-1H-indol-3-yl)ethan-1-amine (400 mg, 1 mmol) in DCM (10 mL), solution of bromine in DCM (2 mmol, 104 µl) was added dropwise at -78 ^{o}C by using cooling bath. The mixture was stirred overnight, and quenched by washing with solution of $Na_2S_2O_3$. After drying over sodium sulphate, the organic layers were evaporated in reduced pressure. The column purification of the crude reaction mixture afforded 2-(4-bromo-5-methoxy-1-tosyl-1H-indol-3-yl)-N,N-diethylethan-1-amine (143 mg, 30 %) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 9.0 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.52 (s, 1H), 7.23 (d, *J* = 8.1 Hz, 2H), 6.95 (d, *J* = 9.1 Hz, 1H), 3.90 (s, 3H), 3.37 (dd, *J* = 10.3, 6.2 Hz, 2H), 3.10 (ddd, *J* = 21.8, 11.6, 6.1 Hz, 6H), 2.35 (s, 3H), 1.30 (t, *J* = 7.3 Hz, 6H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 152.63, 145.47, 134.74, 131.14, 130.15, 129.73, 127.41, 126.99, 118.85, 113.53, 110.45, 102.96, 57.43, 53.26, 46.71, 22.11, 21.75, 9.50. **IR**: 3032 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{22}H_{27}N_2O_3BrS$ $(M+H)^+$: 479.1004, found: 479.1005.



2B.8. Appendix II: Copies of ^{1}H and ^{13}C{^{1}H} NMR spectra of representative compounds

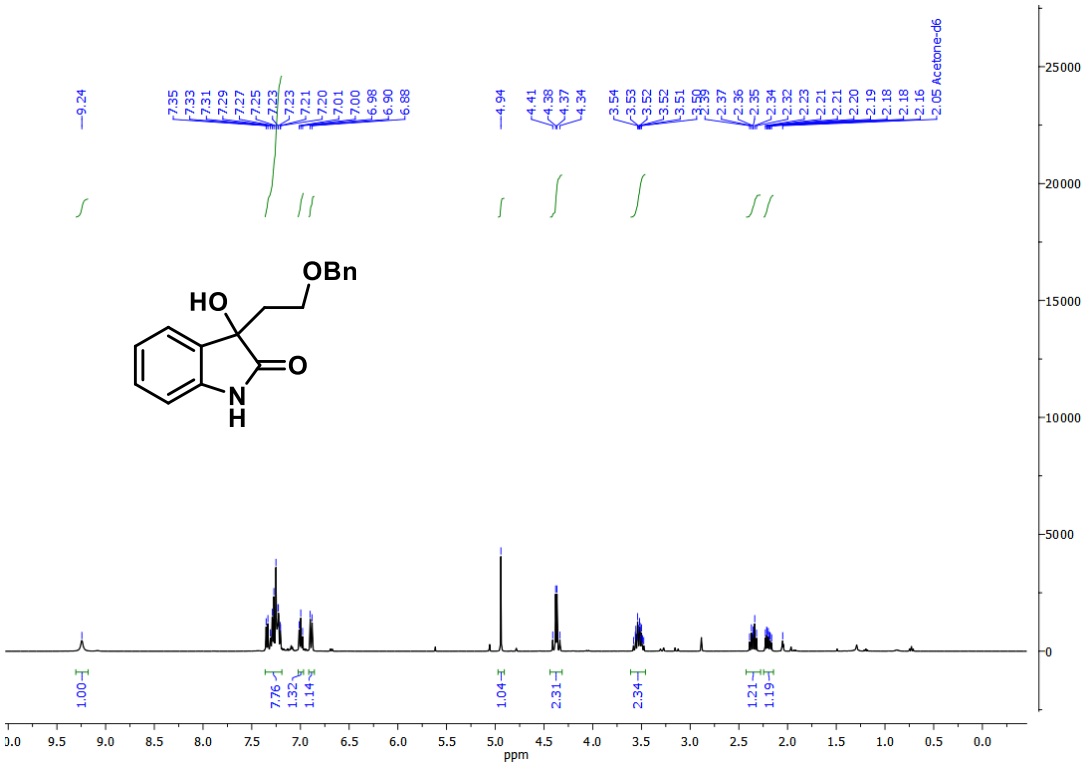


Figure 2B.3. ^{1}H NMR of compound **3**

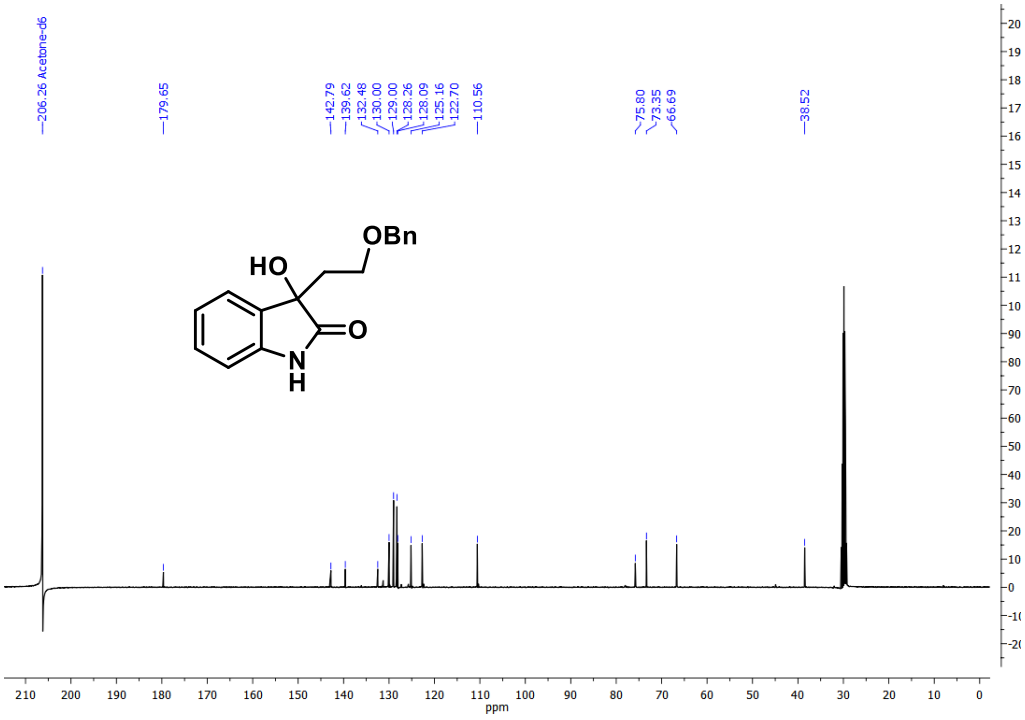


Figure 2B.4. ^{13}C{^{1}H} NMR of compound **3**

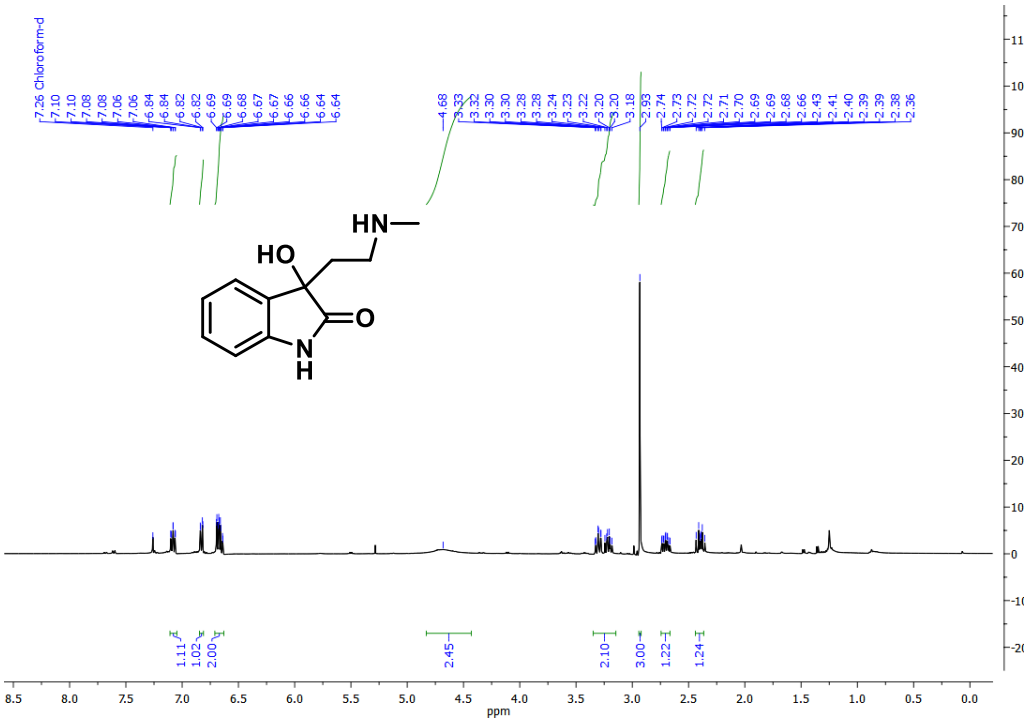


Figure 2B.5. ^{1}H NMR of compound **5**

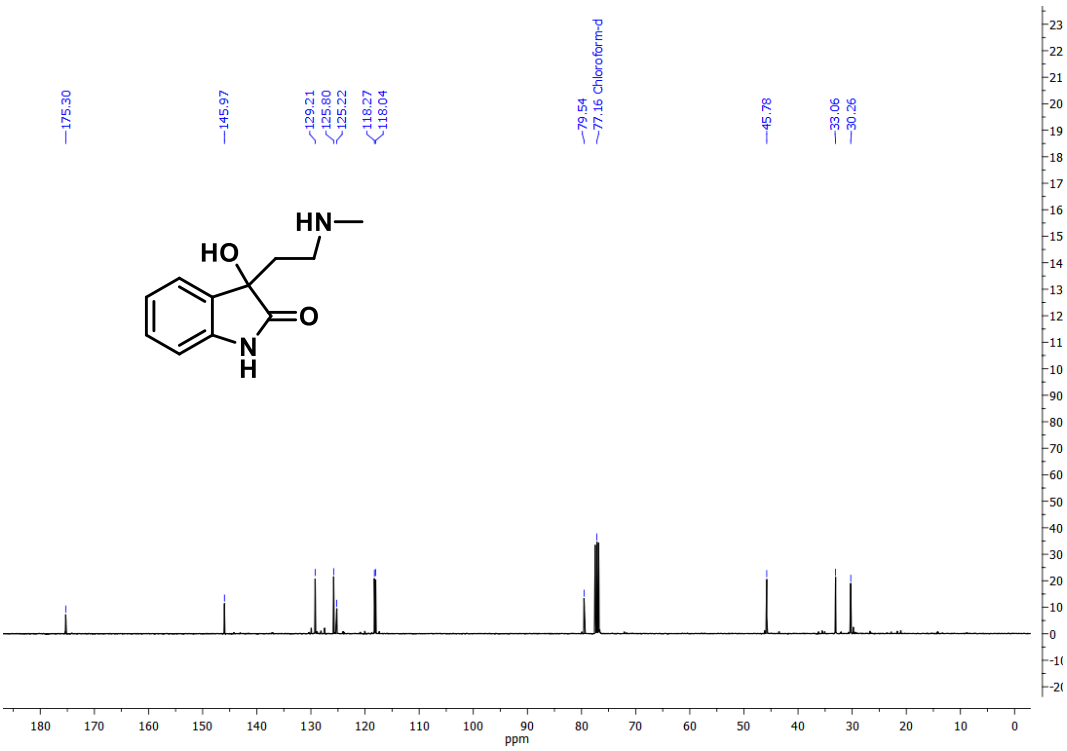


Figure 2B.6. ^{13}C{^{1}H} NMR of compound **5**

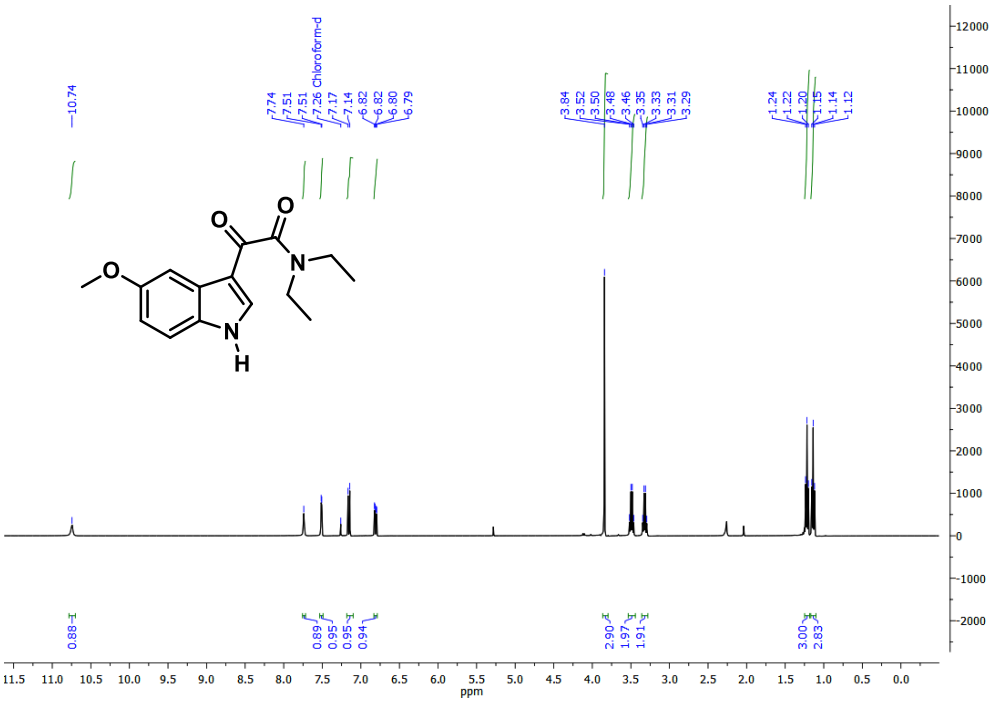


Figure 2B.7. ^{1}H NMR of compound **7'**

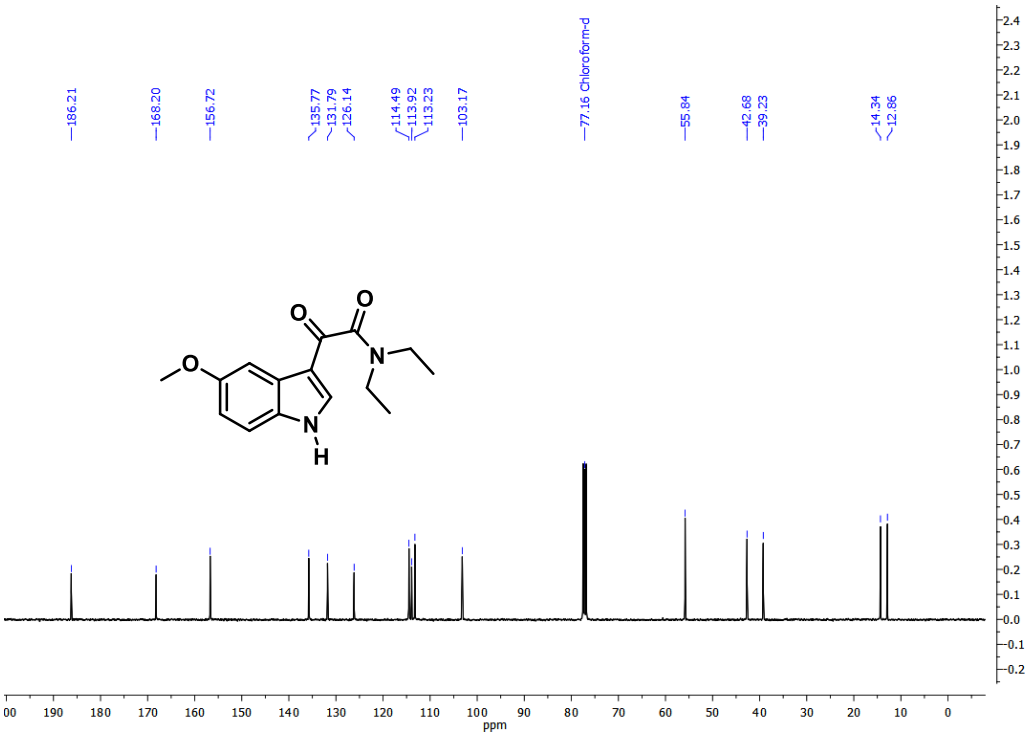


Figure 2B.8. ^{13}C{^{1}H} NMR of compound **7'**

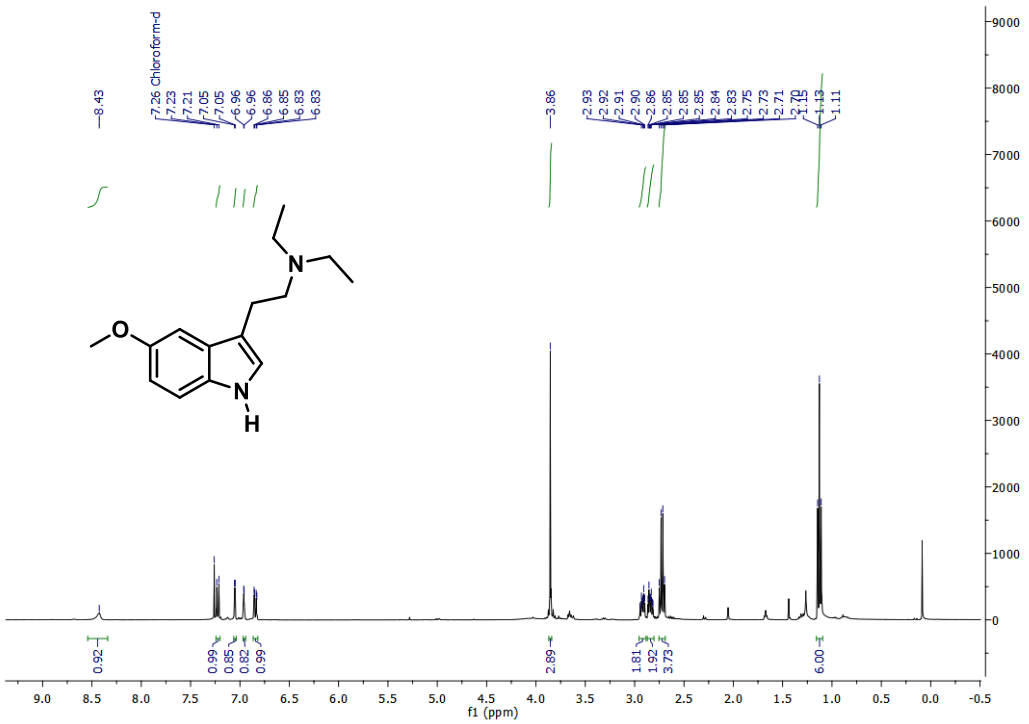


Figure 2B.9. ^{1}H NMR of compound **8'**

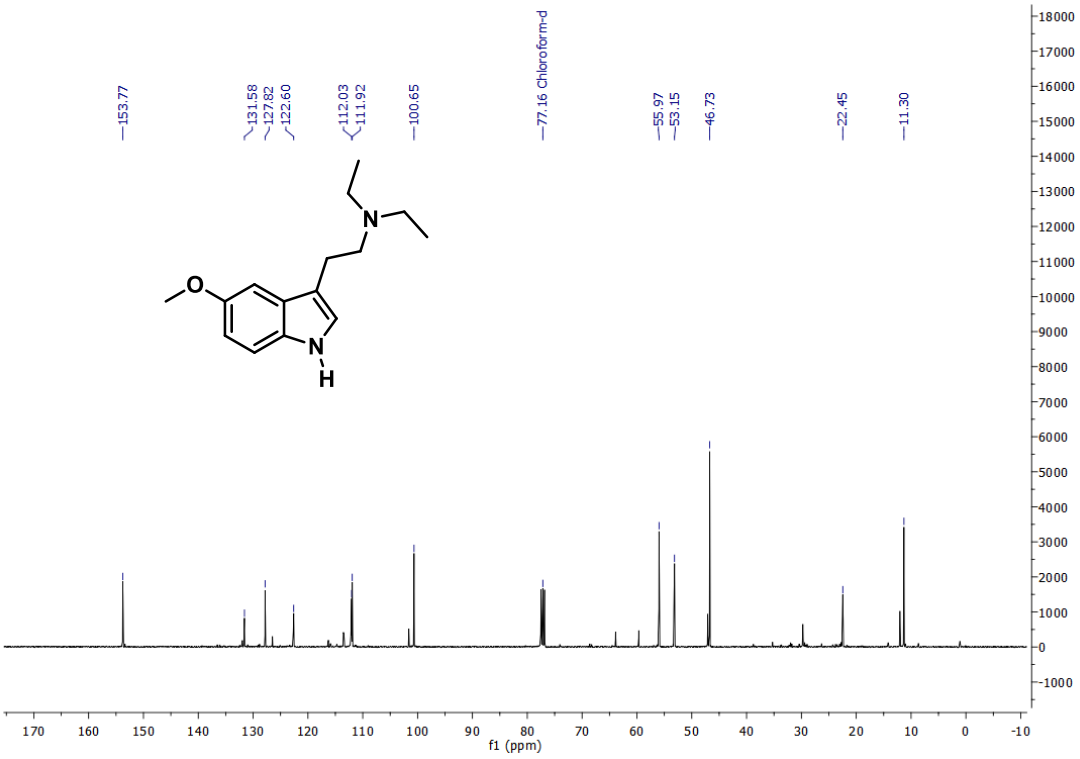


Figure 2B.10. ^{13}C{^{1}H} NMR of compound **8'**

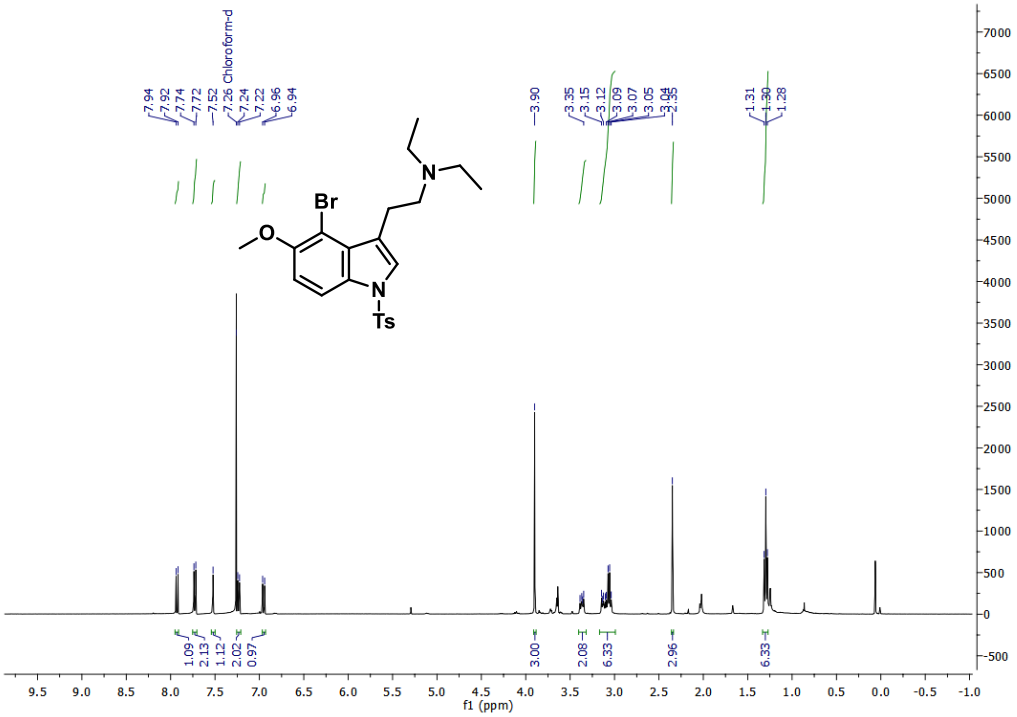


Figure 2B.11. ^{1}H NMR of compound **10'**

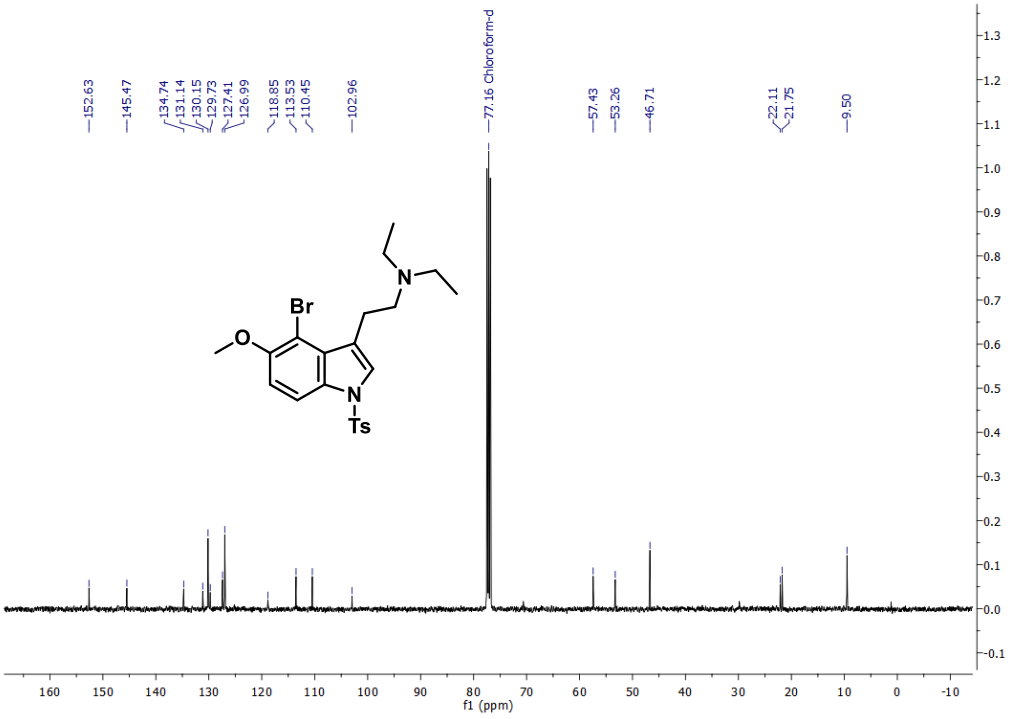


Figure 2B.12. ^{13}C{^{1}H} NMR of compound **10'**

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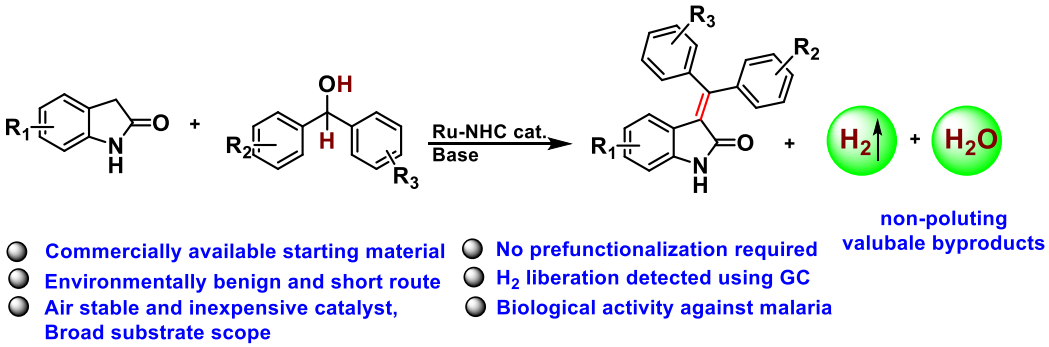
Chapter 3

Ru-Catalyzed Direct Synthesis of Antimalarial Bis-Arylideneoxindoles from 2-Oxindole and Diaryl Methanols

Ru-Catalyzed Direct Synthesis of Antimalarial Bis-Arylideneoxindoles from 2-Oxindole and Diaryl Methanols

3.1. Abstract

In this chapter we have developed a method for the α-olefination of 2-oxindoles by using diaryl methanols and Ru-NHC catalyst in the absence of an acceptor. A wide range of symmetrical and unsymmetrical diaryl methanols undergoes dehydrogenative coupling with 2-oxindole and its derivatives selectively to generate a library of substituted 3-(diphenylmethylene)indolin-2-one in good yields. This process generates environmentally benign and valuable by-products such as molecular hydrogen and water. In addition, this method was successfully applied for the preparation of a bioactive drug, TAS-301. Moreover, the biological activities of the 3-(diphenylmethylene)indolin-2-one derivatives were tested against the *Plasmodium falciparum* parasite. The derivatives were found to exhibit a significant activity with IC_{50} = 2.24 μM.



3.2. Acceptorless dehydrogenation and its literature background

The oxidation of alcohols to carbonyl compounds is one of the fundamental and foremost transformations in organic chemistry. Conventionally, this oxidation process has been accomplished by using stoichiometric amounts of inorganic oxidants such as, chromium (IV) salts, an oxidizing agent or peroxides, along with additives that result in the generation of a large amount of unpleasant waste, which is usually toxic for humans as well as environment.[1] To avoid these shortcomings, metal promoted oxidation process was developed by several research groups. Based on the pathway of complete transformation and mechanism, these modern methods of oxidation of

alcohols using metal catalyst can be divided into two categories, namely i) Acceptorless dehydrogenation (AD) and ii) Borrowing hydrogen methodology.

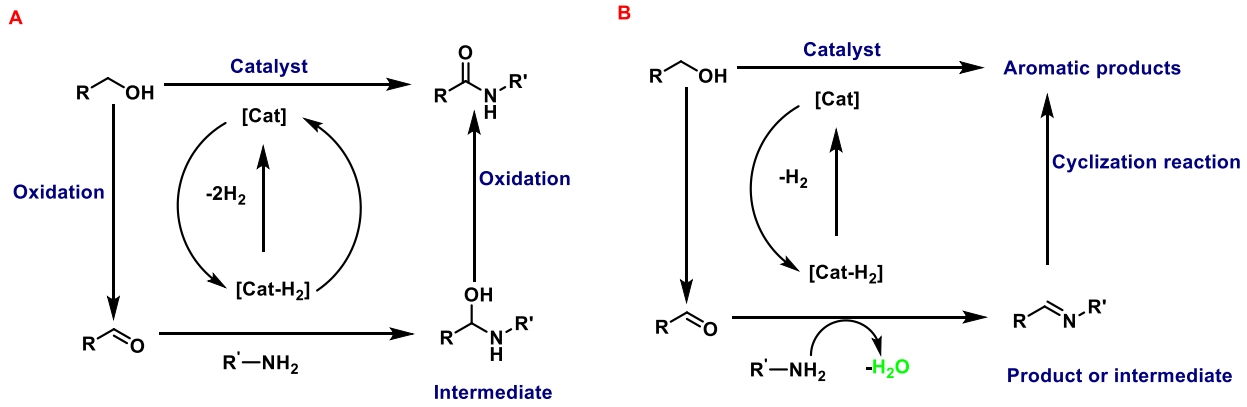
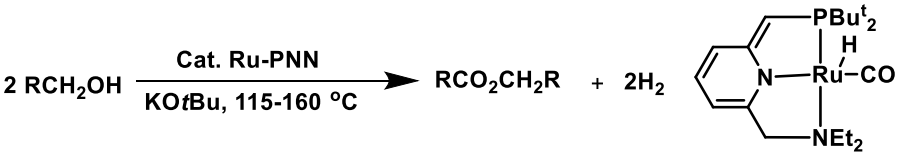


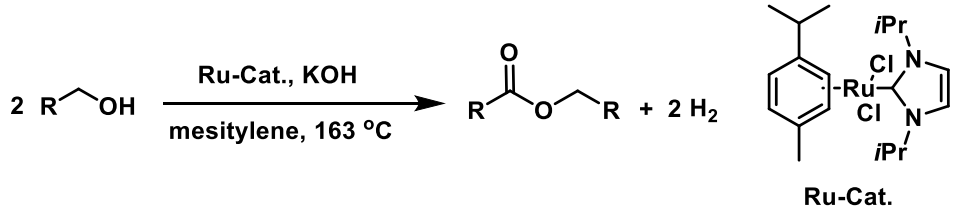
Figure 3.1. General scheme for acceptorless dehydrogenation concept

Acceptorless dehydrogenation AD can be classified mainly in two categories (Figure 3.1). (A) The first category is the sequential dehydrogenation with the release of hydrogen gas, wherein the catalyst oxidizes both the starting material and the intermediate and liberates hydrogen. For instance, the formation of amide from alcohol and amine follows this cycle. (B) The second category involves the acceptorless dehydrogenation with the release of water and molecular hydrogen. In this case, first starting material reacts with the catalyst to generate intermediate and molecular hydrogen and subsequently the intermediate reacts with an external nucleophile to give the final product. A good example of this is the formation of imine or α-alkylation of carbonyl compound from alcohol and amine/carbonyl compound. In the last two decades, several homogeneous and heterogeneous catalytic systems have been developed for the generation of useful products such as ester, amide, α-alkylated carbonyl compound, and imine with high efficiency and atom-economically *via* the process of acceptorless dehydrogenation.[2] In this regard, several efforts have been made by Murahashi and Shavo. However, they have faced certain limitations such as less reaction efficiency, harsh reaction conditions, longer reaction times, and poor yields.[3] Later in 2005, Milstein and co-workers reported the synthesis of esters from alcohol by a newly developed Ru-PNN complex under mild and redox neutral conditions (Scheme 3.1).[4]



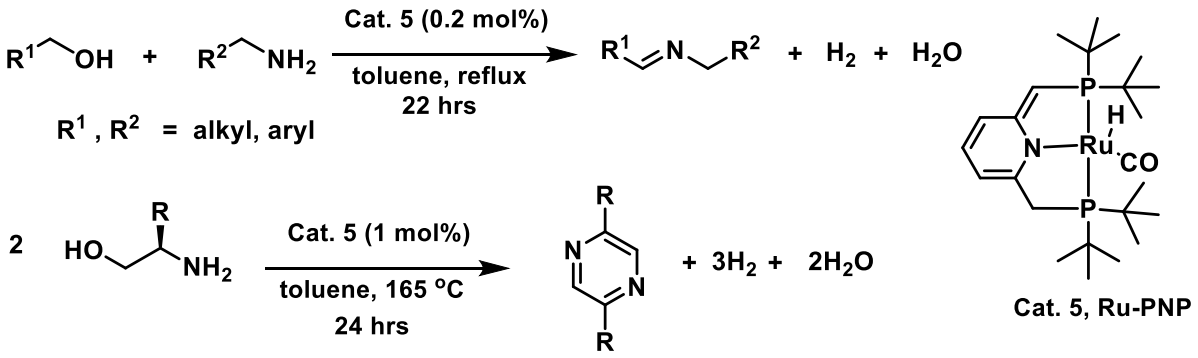
Scheme 3.1. Direct conversion of alcohol into ester by using Ru-PNN catalyst

In the same year, Madsen and co-workers reported the synthesis of ester/lactones from primary alcohols with the liberation of molecular hydrogen by using Ru-NHC catalyst (Scheme 3.2).[5]



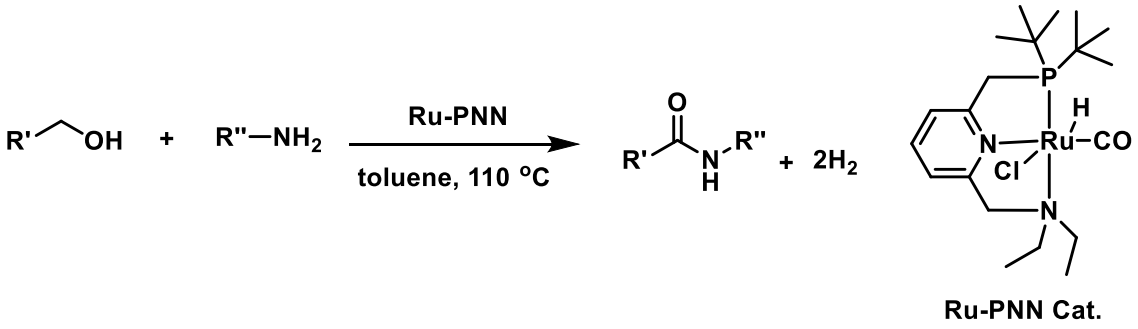
Scheme 3.2. Ru-NHC catalyzed direct synthesis of ester/lactones by using alcohol

Moreover, Ru-PNS and Ir catalysts have proved to be efficient for this transformation.[6] In 2010, Milstein's group reported the direct synthesis of imines from amines and alcohols by using a Ru-PNP pincer complex. The same catalyst has also been used for the synthesis of pyrazine from β-amino alcohols (Scheme 3.3).[7]



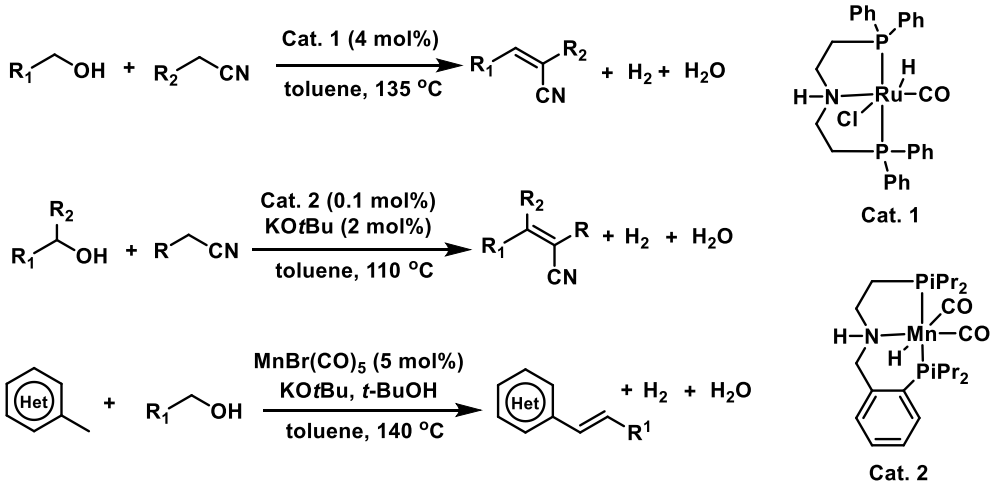
Scheme 3.3. Direct synthesis of imine by using amine and alcohol *via* AD

Interestingly, in 2007 Milstein and co-workers came up with path-breaking research, involving a direct, efficient, and atom-economical synthesis of an amide from alcohols and amines by a Ru-PNN complex (Scheme 3.4).[8]



Scheme 3.4. Milstein approach for the synthesis of amide using Ru-PNN complex

After this remarkable research by Milstein, Madsen, Crabtree, and Hong research group developed the same transformation by using a variety of other ruthenium complexes containing carbene or phosphine ligands. Although these methods were efficient for the production of amide, a large amount of base was required during these transformation.[9] Similarly, for the synthesis of amide from amine and alcohol, several efforts have been made by various groups. Interestingly, Milstein's group developed a method for the synthesis of amides directly from esters and amines by using a Ru-PNN complex with excellent turnover number under neutral conditions.[10] In the last few decades, the acceptorless dehydrogenation (AD) strategy has been used for the α-alkylation and olefination of various carbonyl compounds in the presence of Ru, Rh, and earth-abundant metals such as Mn as a catalyst.[11] While these methods were efficient for the production of olefinated products, the methods were restricted to C−H bond connected with nitrile functionality.[11] Recently, Kempe and Maji groups reported the AD reaction of methyl arenes with primary alcohols with the liberation of H_2 (Scheme 3.5).[12]



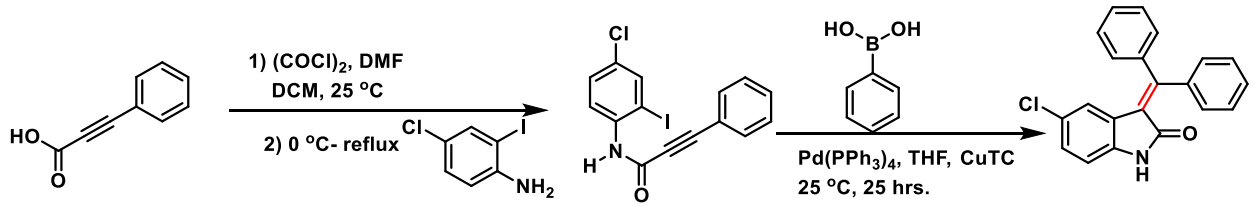
Scheme 3.5. Olefination of nitrile and methyl arene using alcohols

Moreover, there are only a few literature reports for the synthesis of C-alkylated oxindoles by using metal catalysts such as Ru, Ir, and Pd/C.[13]

3.3. Literature reports for the synthesis of 3-arylideneoxindoles derivatives

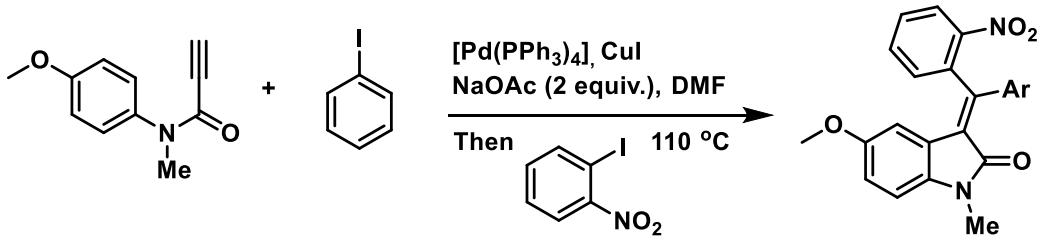
Construction of the C=C bond at α-position of oxindole, which generates the arylidieneoxindole derivatives is extremely useful in organic synthesis towards the synthesis of natural products and synthetic intermediates.[14] In this regard, in 2005 Player and co-workers reported a domino method for the stereoselective synthesis of (*E*)-3,3-(diarylmethylene)indolinones. This transformation was catalyzed by palladium

in presence of copper(I)thiophene-2-carboxylate as an additive, involving a tandem Heck-carbocyclization/Suzuki coupling sequence (Scheme 3.6).[15]



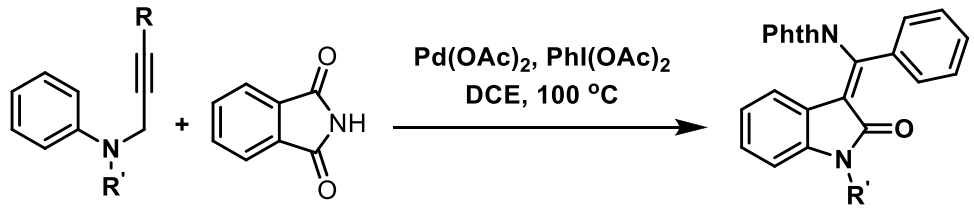
Scheme 3.6. Players's approach for synthesis of (*E*)-3,3-(diarylmethylene)indolinones

In 2007, Zhu and co-workers reported a three-component method for the synthesis 3-(diarylmethylene)indolinones derivatives. The reaction proceeded in domino fashion, involving the Sonagashira reaction/carbopalladation/C−H Activation followed by a C−C bond-formation reaction sequence (Scheme 3.7).[16]



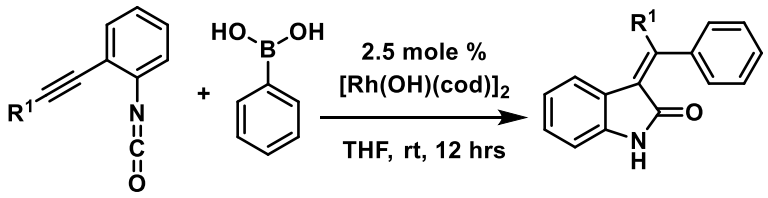
Scheme 3.7. Zhu's method for the synthesis of 3-(diarylmethylene)indolinones derivatives

In 2008, Li and co-workers developed a palladium-catalyzed sequential method for the selective preparation of (*E*)-(2-oxoindolin-3-ylidene)phthalimides from *N*-phenylpropiolamides and phthalimide *via* intermolecular aminopalladation/C−H activation. In this reaction, a catalytic amount of palladium was used along with (diacetoxyiodo)benzene as an additive (Scheme 3.8).[17]



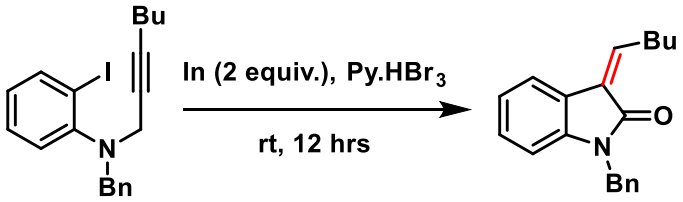
Scheme 3.8. Li's approach for the synthesis of 2-oxindolin-3-ylidene-phthalimides

Murakami and co-workers have reported a rhodium-catalyzed cyclization of 2-alkynylaryl isocyanates in the presence of aryl/alkenylboronic acids derivatives to generate 3-alkylideneoxindoles in stereoselective fashion (Scheme 3.9).[18]



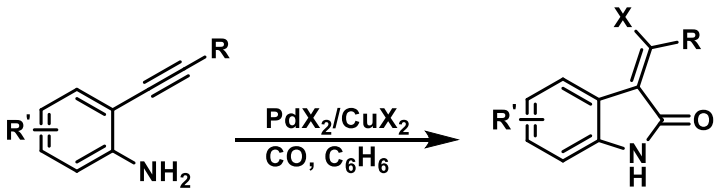
Scheme 3.9. Murakami's approach for the synthesis of 3-alkylideneoxindoles

Takemoto and co-workers developed a tandem approach for the stereoselective synthesis of several disubstituted and monosubstituted E/Z isomers of 3-alkylideneoxindoles through radical cyclization (Scheme 3.10).[19]



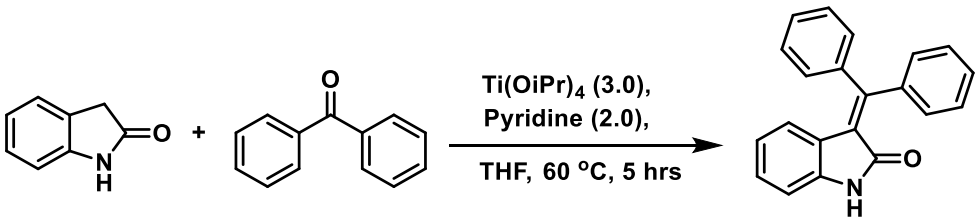
Scheme 3.10. Takemoto's method for the preparation of 3-alkylideneoxindole derivatives

Similarly, Li's research group put forth a palladium-assisted carbonylative annulation method for the generation of 3-(halomethylene)oxindole derivatives.[20]



Scheme 3.11. Li's method for the preparation of 3-(halomethylene)oxindoles

In 2014, Kim and co-workers reported the synthesis of 3-alkylideneoxindoles derivatives from oxindole and carbonyl derivatives by using titanium isopropoxide as an additive and pyridine as a base (Scheme 3.12).[21]



Scheme 3.12. Kim's method for the generation of 3-alkylideneoxindole derivatives

3.4. The rationale of present work

Malaria, a lethal disease of worldwide concern, is caused by the fatal parasite *Plasmodium falciparum* and spreads to humans by the bite of female Anopheles mosquitoes. Although there are numerous drugs available for the therapy of malaria, their complex structures necessitate multiple steps in their synthesis process. Additionally, malaria parasite has a tendency to develop resistance to the major existing antimalarial drugs because of its highly adaptive nature. Hence, it is crucial to develop an alternative and effective drug for malaria. Additionally, the derivative of arylidene oxindole is a privileged scaffold in medicinal chemistry, and biologically active molecules. For instance, TAS-301 exhibits inhibitory activity of neointimal thickening following single balloon injury[22], AMPK activation[23], and anti-breast cancer activity (Figure 3.2).[24]

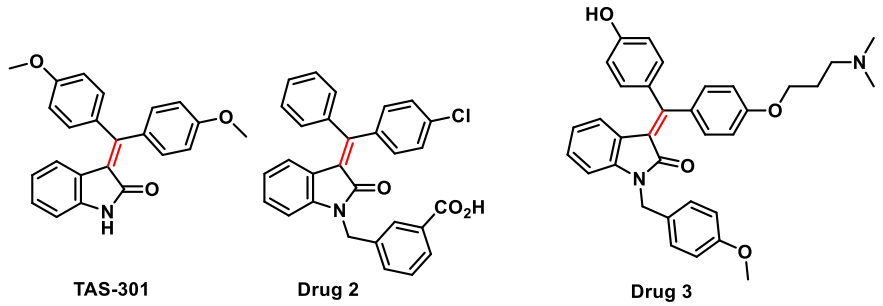


Figure 3.2. Bioactive arylidene-2-oxindole derivatives drug

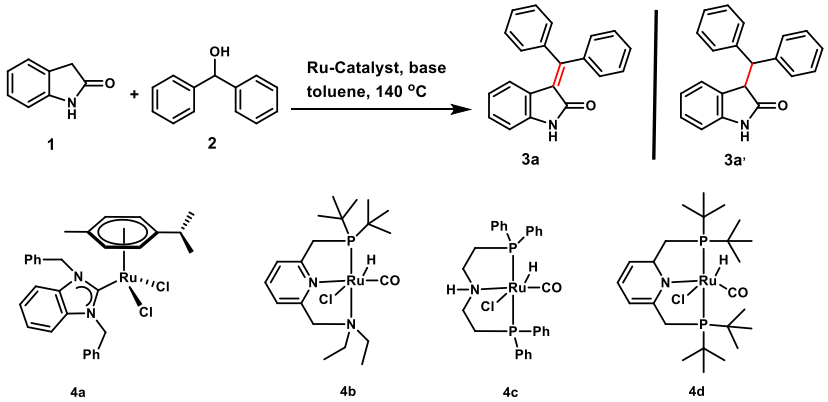
Consequently, the development of efficient and short methods for the fabrication of these compounds is highly desirable in organic synthesis. Although, several methods are available for the preparation of bis-arylidene derivatives, there are various shortcomings. Some of the drawbacks include the use of toxic reagents isocyanate, production of stoichiometric amounts of waste, poor atom economy, use of catalysts comprising expensive metals,[17] multistep syntheses, and pre-functionalization of the starting material, which limits their practical utility. Hence, we aim to develop an effective method for the synthesis of olefin derivatives of 2-oxindole by using inexpensive, easily accessible, cheap reagents, and air-stable Ru-NHC catalyst.

3.5. Results and discussion

To establish a procedure for the synthesis of bis-arylidene oxindole through α-olefination reaction of 2-oxindole, a toluene solution containing diphenylmethanol and 2-oxindole was heated at 140 ^{o}C. A control experiment was performed by heating a reaction mixture containing 2-oxindole, diphenyl methanol, and a stoichiometric

amount of Cs_2CO_3 in the absence of a ruthenium catalyst resulted in no reaction (Table 3.1, entry 1).

Table. 3.1. Screening of various Ru catalyst for olefination reaction of 2-oxindole



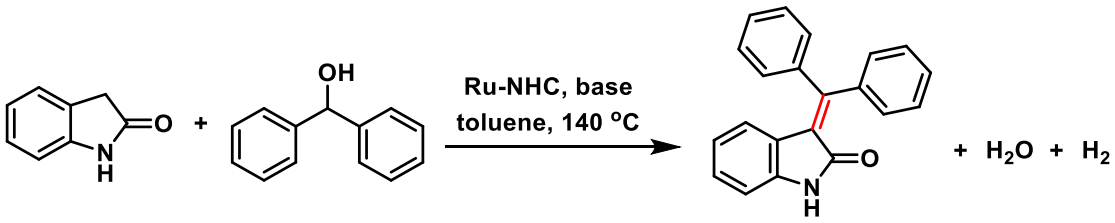
Entry	Catalyst (equiv.)	Base	Yield (%)
1	-	Cs_2CO_3	no reaction
2	$RuCl_3$	Cs_2CO_3	no reaction
3	$RuCl_3$ (4 mol%) + PPh_3 (8 mol%)	Cs_2CO_3	no reaction
4	$RuHClCO(PPh_3)_2$ (2.5 mol%)	Cs_2CO_3	-
5	$RuH_2CO(PPh_3)_2$ (2.5 mol%)	Cs_2CO_3	-
6	$RuCl_2(PPh_3)_2$ (2.5 mol%)	Cs_2CO_3	40
7	Dichloro(p-cymene)Ru(II) dimer (2.5 mol%)	Cs_2CO_3	40
8	$RuH_2CO(PPh_3)_3$ (2.5 mol%) + xantphos (3 mol%)	Cs_2CO_3	59
9	**Ru-NHC 4a (2.5 mol%)**	**Cs_2CO_3**	**65**
10	Ru-PNN **4b** (1 mol%)	Cs_2CO_3	46
11	Ru-MACHO **4c** (1 mol%)	Cs_2CO_3	13
12	Ru-PNPtBu **4d** (1 mol%)	Cs_2CO_3	27
13	Grubbs' II generation	Cs_2CO_3	15

Reaction condition: Ru-complex (see table), diphenylmethanol (0.25 mmol), 2-oxindole (0.5 mmol), Cs_2CO_3 (0.5 mmol) and toluene (2 mL) were heated in a sealed tube for 30 hrs at 140 °C.

Furthermore, different Ru catalysts that are regularly used in the borrowing hydrogen method were screened to get optimized reaction condition. Catalysts such as $RuCl_3$, $RuHClCO(PPh_3)_2$, and $RuH_2CO(PPh_3)_2$ failed to generate the 3-(diphenylmethylene)indolin-2-one **3a** (Table 3.1, entries 2-5). Later, $RuCl_2(PPh_3)_2$ and

dichloro(*p*-cymene)Ru(II)dimer were tested and product **3a** was isolated in 40% yield in each case (Table 3.1, entries 6 and 7). Moreover, when ligand, such as xantphos was taken along with $RuH_2CO(PPh_3)_3$, resulted in a significant improvement in yield of product **3a** to 59% yield (Table 3.1, entry 8). Based on the mentioned findings, we investigated this transformation with robust well-defined catalysts Ru-PNN **4b**, Ru-MACHO **4c**, and Ru-PNP **4d** for α-olefination of 2-oxindole, which resulted in 46%, 13%, and 27% yield (Table 3.1, entries 10-12), respectively. Since, these catalysts are sensitive to air, which might lower the catalytic activity and decrease the yield for reactions having longer durations. Then, we screened air-stable catalysts derived from *N*-heterocyclic carbenes. Grubbs' second-generation catalyst provided product **3a** in poor yield (Table 3.1, entry 13).

Table 3.2. Base optimization for α-olefination reaction[a]



Entry	Base (eq. equiv.)	Time	Yield (%)
1[b]	K_2CO_3 (2 equiv.)	30	no reaction
2[b]	*NaH* (2 equiv.)	30	no reaction
3[b]	K_3PO_4 (1.3 equiv.)	30	40
4[b]	Cs_2CO_3 (1.3 equiv.)	30	58
5[b]	Cs_2CO_3 (2 equiv.)	30	60
6[c]	Cs_2CO_3 (2 equiv.)	30	65
7[c]	Cs_2CO_3 (2 equiv.)	48	70
8[c]	KO*t*Bu (0.1 equiv.)	16	17
9[c]	KO*t*Bu (2 equiv.)	30	85
10[c]	**KO*t*Bu (3 equiv.)**	**48**	**87**
11[c,d]	K_3PO_4 (3 equiv.)	48	75

[a]**Reaction condition:** Catalyst **4a** (0.0025 mmol), diphenylmethanol (0.25 mmol), 2-oxindole (0.5 mmol), base (see table) and toluene (2 mL) were heated in a sealed tube at 140 °C; [b]1 mol% of catalyst was used; [c]2.5 mol% of catalyst **4a** (0.00625 mmol) were used; [d]1,4-dioxane was used as a solvent.

However, Ru-NHC **4a** provided product **3a** in 65% yield (Table 3.1, entry 9). After having ideal catalyst in hand, a series of bases were investigated. Bases such as, K_2CO_3 and *NaH* failed to give product **3a** (Table 3.2, entries 1 and 2). Further, reaction with dibasic and tribasic bases such as Cs_2CO_3 and K_3PO_4 afforded product **3a** in moderate yield (Table 3.2, entries 3 and 4). Upon increasing the amount of Cs_2CO_3, a slight increase in the product yield was observed (Table 3.2, entry 5). Further, improvement in product yield was observed when the catalyst loading and time was increased (Table 3.2, entries 6-7). The best-optimized conditions were obtained when the reaction was carried out using 3 equivalents of KO*t*Bu and reaction mixture kept for 48 hrs, leading to 87% yield of the product **3a** (Table 3.2, entry 10). Moreover, this olefination reaction was performed with K_3PO_4 base, 1,4-dioxane was taken as a solvent and the product **3a** was isolated in 75% yield. The formation of α-alkylated product **3a′** was not observed in the reaction mixture under this reaction condition. A control experiment was performed by heating the toluene solution of **3a′** and catalyst **4a** in the presence/absence of KO*t*Bu resulted in no reaction, which ruled out the possibility of the formation of **3a** from **3a′**. After having optimized reaction condition in hand, further we explored the scope for this transformation.

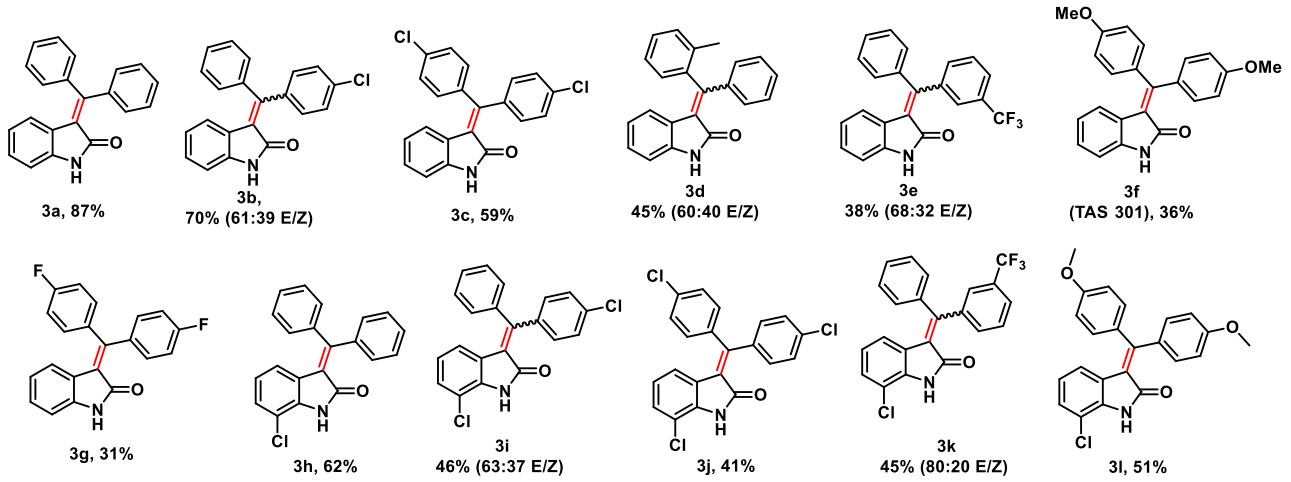


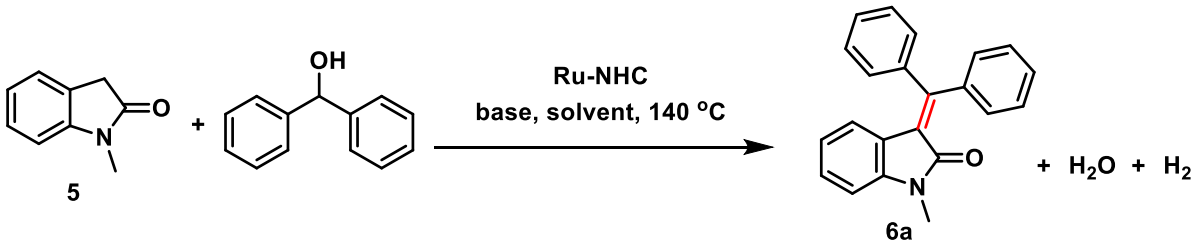
Figure 3.3. Substrate scope for α-olefination with 2-oxindole and 7-chloro-2-oxindole

Reaction condition: catalyst **4a** (2.5 mol %), diarylmethanol (0.25 mmol), 2-oxindole (0.5 mmol), KO*t*Bu (0.75 mmol) and toluene (2 mL) were heated in a sealed tube at 140 ^{o}C. For compounds **3f** and **3g**, Cs_2CO_3 (0.75 mmol) was used; for compound **3f**, 1,4-dioxane was used as a solvent.

Several diaryl methanols were also reacted well using optimized condition. The reaction of (4-chlorophenyl)(phenyl)methanol, bis(4-chlorophenyl)methanol, and phenyl(*o*-tolyl)methanol proceeded smoothly and successfully to afford the desired

olefinated products **3b**, **3c**, and **3d** in 70%, 59%, and 45% yield respectively (Figure 3.3). To our delight, this transformation was tolerant to a highly electron-withdrawing CF_3 group and led to the formation of respective 3-(phenyl(3-(trifluoromethyl)phenyl)methylene)indolin-2-one **3e** in 38% yield. Unfortunately, di-substituted diphenyl methanol derivatives, bis(4-methoxyphenyl)methanol, and bis(4-fluorophenyl)methanol, were unsuccessful in giving the desired products **3f** (TAS-301) and **3g**. This might be due to the strong nucleophilicity of bases, which can substitute the fluorine present in the aromatic ring. Interestingly, the addition of Cs_2CO_3 was successful to give products **3f** and **3g** in 36% and 31% yield, respectively. Moreover, in case of less yield of product, an unreacted intermediate ketone was observed in the reactions. Furthermore, the reaction of 7-chloro-2-oxindole with a range of diaryl methanols afforded the respective products **3h-l** in moderate yield. Although reactions with 2-oxindole and 7-chloro-2-oxindole were successful, unfortunately, 6-chloro and *N*-substituted 2-oxindole failed to furnish arylidene-2-oxindole derivatives after subjected to optimized conditions.

Table 3.3 Optimization of base for *N*-protected and 6-chloro-2-oxindole



Entry	Base (equiv.)	Solvent	Yield (%)
1	KO*t*Bu (3 equiv.)	toluene	traces
2	KOH (2 equiv.)	toluene	no reaction
3	KO*t*Bu (2 equiv.)	THF	no reaction
4	Cs_2CO_3 (3 equiv.)	DMSO	no reaction
5	Cs_2CO_3 (3 equiv.)	DMF	no reaction
6	K_2PO_4 (3 equiv.)	1,4-dioxane	78

Reaction condition: catalyst (2.5 mol%), diphenylmethanol (0.25 mmol), 1-methyl-2-oxindole (0.5 mmol), base (see table) and solvent (see table) were heated in a sealed tube for 48 hrs at 140 ^{o}C.

Therefore, further optimization was carried out by replacing the solvent and base (Table 3.3). Hence, the reaction of *N*-methyl-oxindole and diphenylmethanol was

taken as a model reaction. When the reaction was performed with bases such as KO*t*Bu, Cs_2CO_3 and KOH resulted in no reaction. Moreover, when the reaction performed with the solvents such as THF, DMF, DMSO, and toluene, failed to give the desired product **6a** (Table 3.3, entries 1-5). Interestingly, when the reaction performed with K_3PO_4 as a base and 1,4-dioxane as a solvent afforded the desired product **6a** in 78% yield (Table 3.3, entry 6). Similarly, reaction of 1-methyl-2-oxindole with various diaryl methanols afforded the corresponding products **6b–f** in moderate yield.

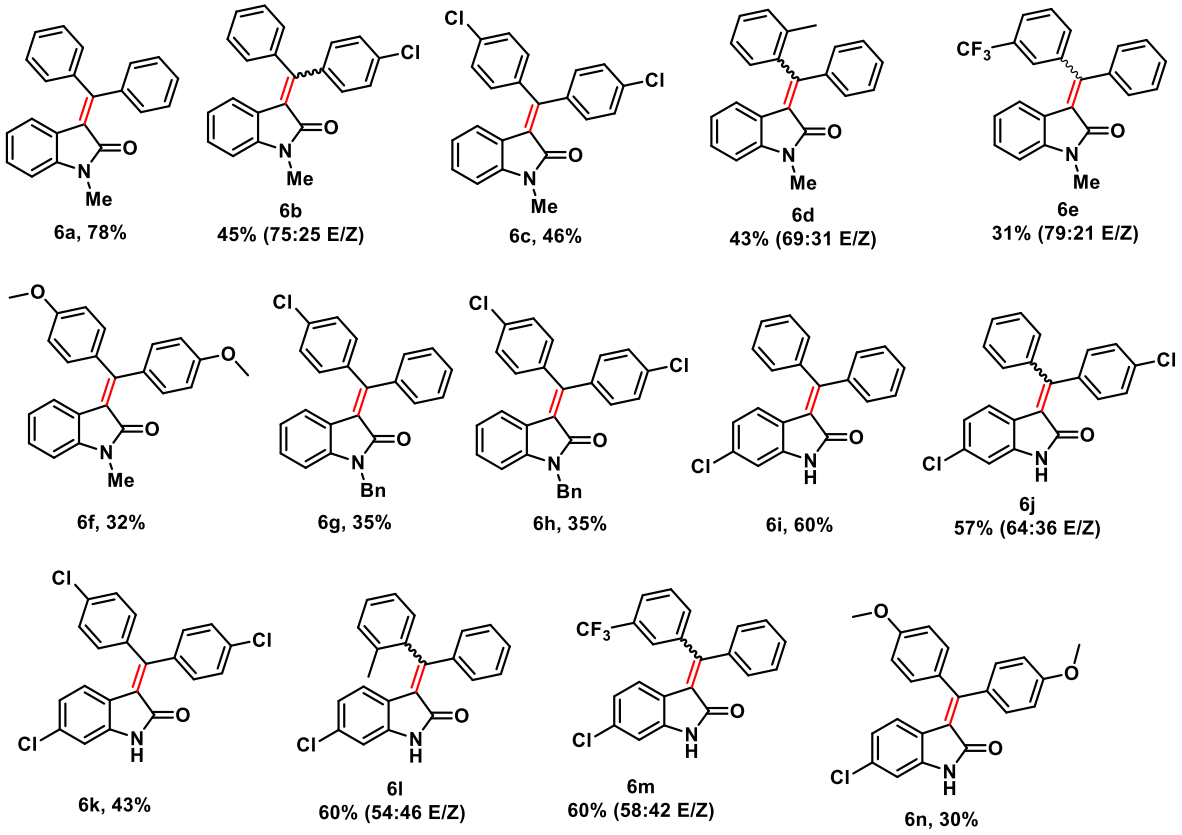
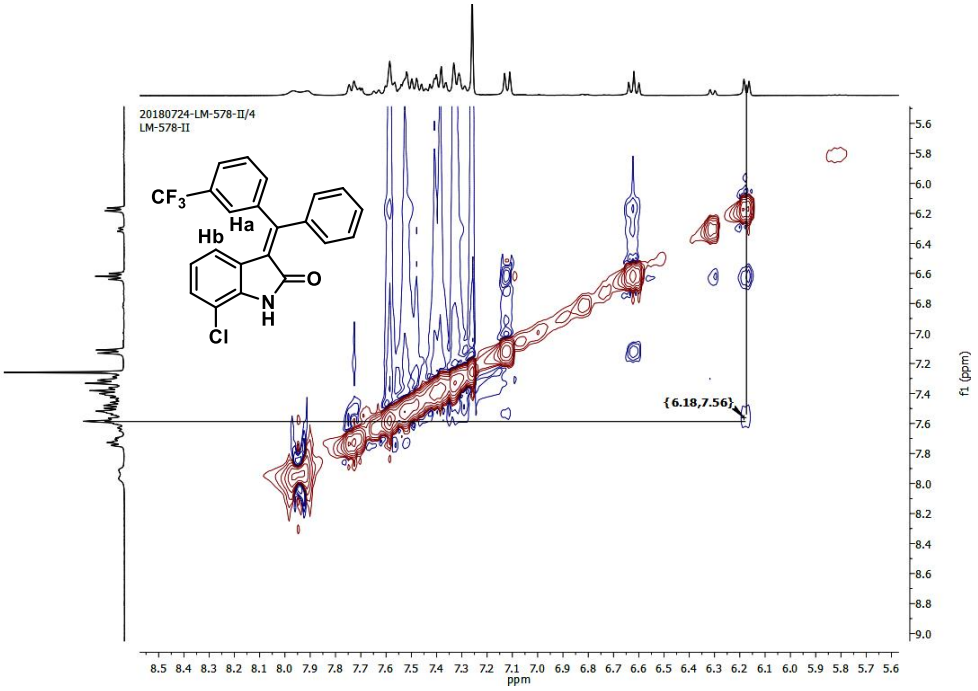


Figure 3.4. Substrate scope of olefination reaction with 1-methyl/7-chloro-2-oxindole

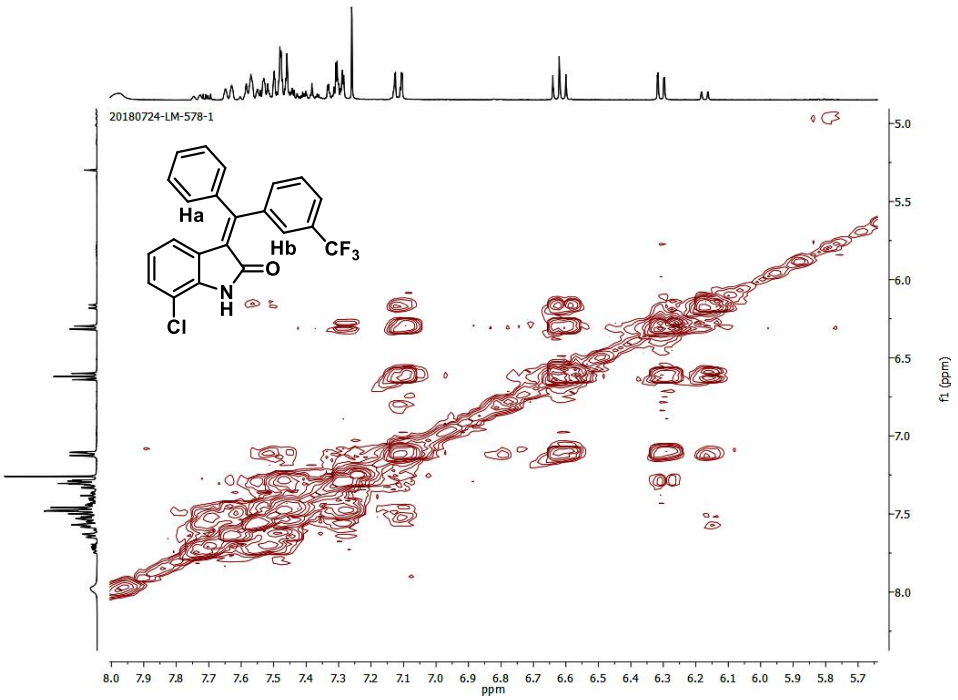
Reaction condition for *N*-protected-2-oxindole: Catalyst **4a** (0.01 mmol), diarylmethanol (0.25 mmol), *N*-protected-2-oxindole or 6-chloro-2-oxindole (0.5 mmol) and K_3PO_4 (0.75 mmol) in 1,4-dioxane were heated in a sealed tube for 48 hrs at 140 ^oC. In case of 6-chloro-2-oxindole (0.5 mmol), KO*t*Bu was taken as a base.

Similarly, the reaction of 1-benzyl-2-oxindole with (4-chlorophenyl)(phenyl)methanol and bis(4-chlorophenyl)methanol under the same experimental condition afforded bis-arylidene oxindole products **6g** and **6h** in 35% yield (Figure 3.4). Moreover, the reaction of 6-chloro-2-oxindole with various diphenylmethanol derivatives afforded corresponding arylidene products **6i-n** in 30-

60% yield. Furthermore, *E* and *Z* isomer of **3k** & **6e** was separated by preparative TLC and characterized by NOESY experiment (Figure 3.5).



3.5a)



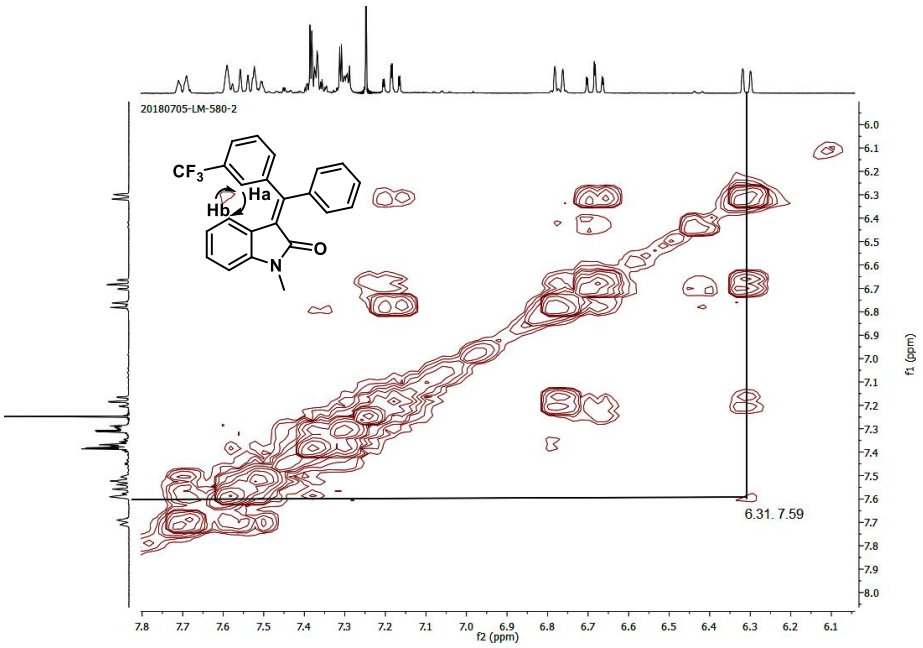
3.5b)

Figure 3.5. NOESY Spectra of isomer E (Figure 3.5a) and Z (Figure 3.5b) of compound **3k**

The major isolated compound **3k** (Figure 3.5a) clearly shows that there is a correlation between protons H_a (6.18 ppm) and H_b (7.56) confirms the *E* isomer. However, the

minor isolated compound of **3k** showing (Figure 3.5b) the absence of interaction between H_a and H_b indicating the Z isomer.

3.6a)



3.6b)

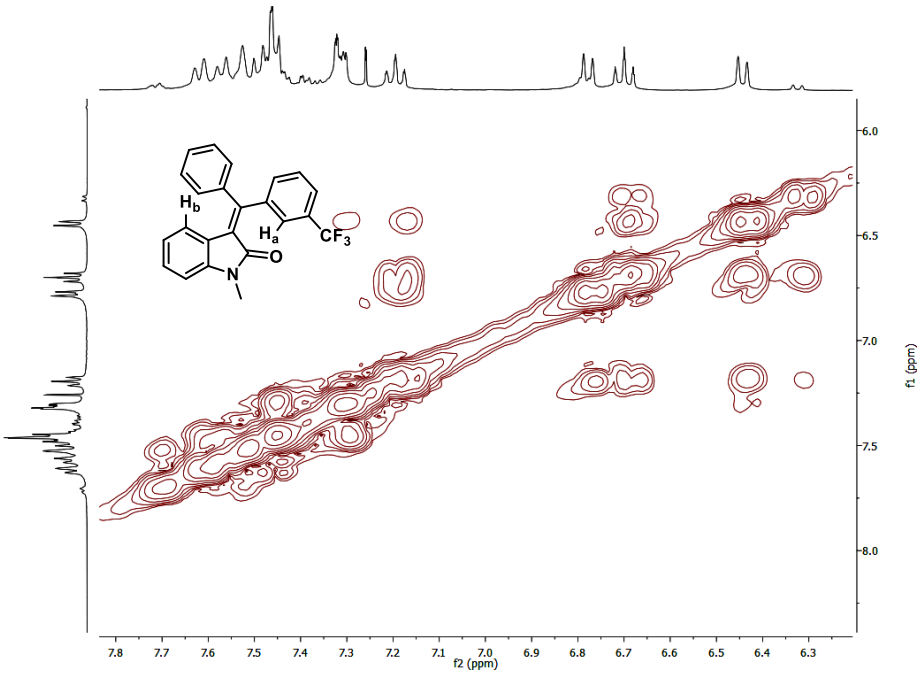


Figure 3.6. NOESY Spectra of isomer E (Figure 3.6a) and Z (Figure 3.6b) of compound **6e**

Similarly in case of compound **6e** (Figure 3.6a) clearly shows that there is a correlation between protons H_a (6.31 ppm) and H_b (7.59) confirms the *E* isomer.

However, the minor isolated compound of **6e** showing (Figure 3.6b) the absence of interaction between H_a and H_b indicating the *Z* isomer.

3.6. Mechanistic investigations

3.6.1. Detection of dissociated *para*-cymene using NMR spectroscopy

To understand the reaction mechanism for this transformation, initially, dissociation of paracymene ligand from the original catalyst was studied. To probe the dissociation of ligand, we have performed the reaction in the NMR tube. Thus, in a dry NMR tube 2-oxindole (0.1 mmol, 13.3 mg), diphenyl methanol (0.1 mmol, 18.4 mg) complex **4a** (0.02 mmol, 20 mol %), KO*t*Bu (0.1 mmol, 11.2 mg) was taken in benzene-d_6. The NMR tube was then kept in a preheated oil bath at 80 ^oC for 10 min. Subsequently, the sample was analyzed by ^1H NMR spectroscopy, dissociation of *p*-cymene ligand from the metal complex was observed and confirmed by NMR (Figure 3.7a & 3.7b), which shows peak at δ 2.74 (H, *J* = 6.5 Hz, 1H), 2.16 (s, 3H), 1.16 (d, *J* = 7.9 Hz, 6H) for dissociated ligand. In addition, the aromatic peaks of Ru attached *p*-cymene [δ 5.37 (d, *J* = 6.1 Hz, 2H), 5.08 (d, *J* = 6.1 Hz, 2H)] were missing which supports for the dissociation of para-cymene ligand while heating (Figure 3.8).

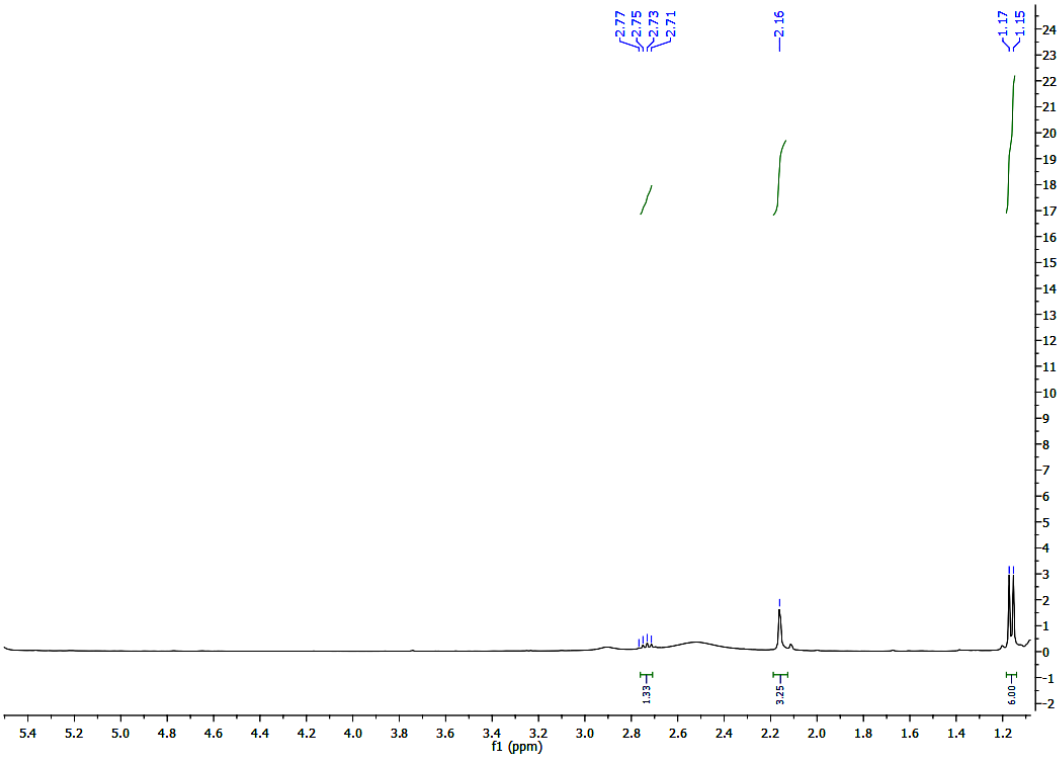


Figure 3.7a. ^1H NMR of ligand *p*-cymene before heating the catalyst

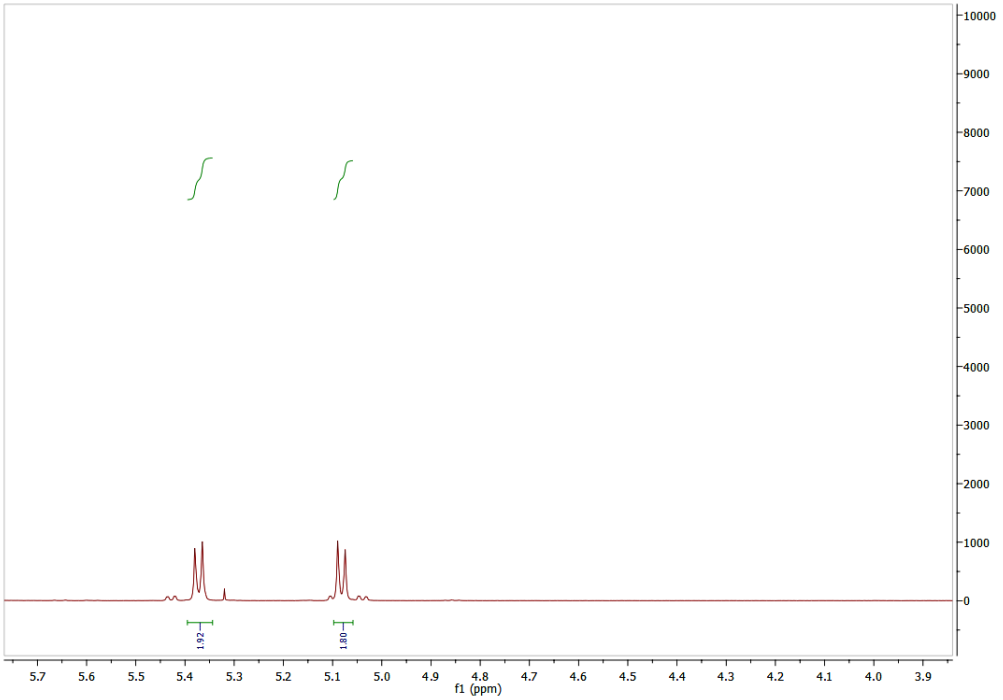


Figure 3.7b. ^{1}H NMR of the aromatic region of *p*-cymene before heating

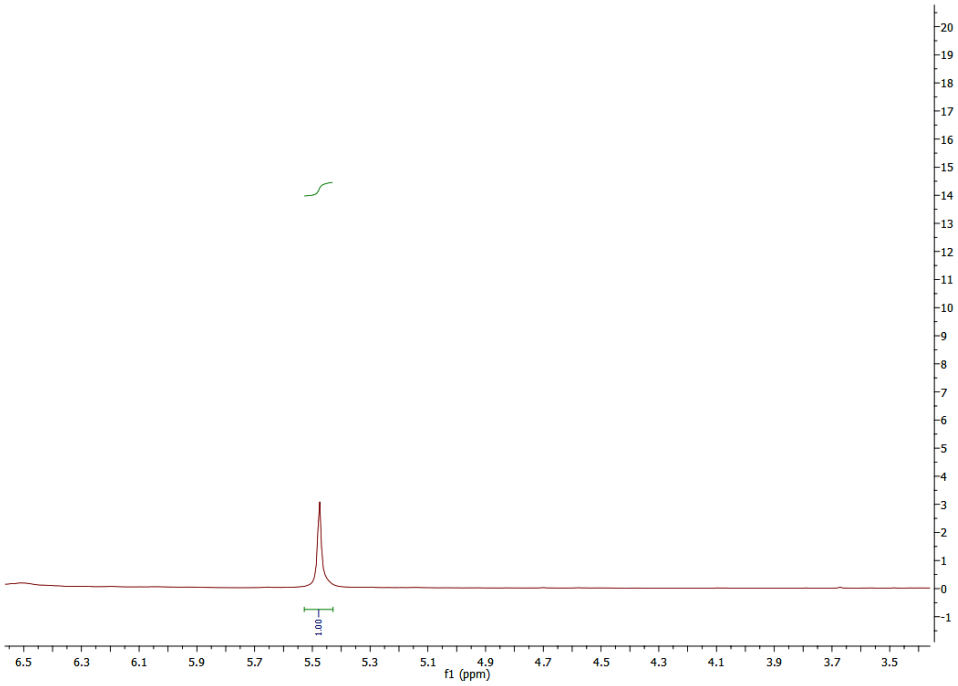


Figure 3.8. ^{1}H NMR of the aromatic region of *p*-cymene after heating

3.6.2. Hydride detection in the reaction mixture

In the same reaction mixture some hydride signals were detected in the range from -6 to -9 ppm (Figure 3.9). This is previously observed by Madsen's and Huynh.[25a,b] Similar observation was observed when the NMR sample was heated at 110 ^{o}C for 1 hrs followed by NMR analysis.

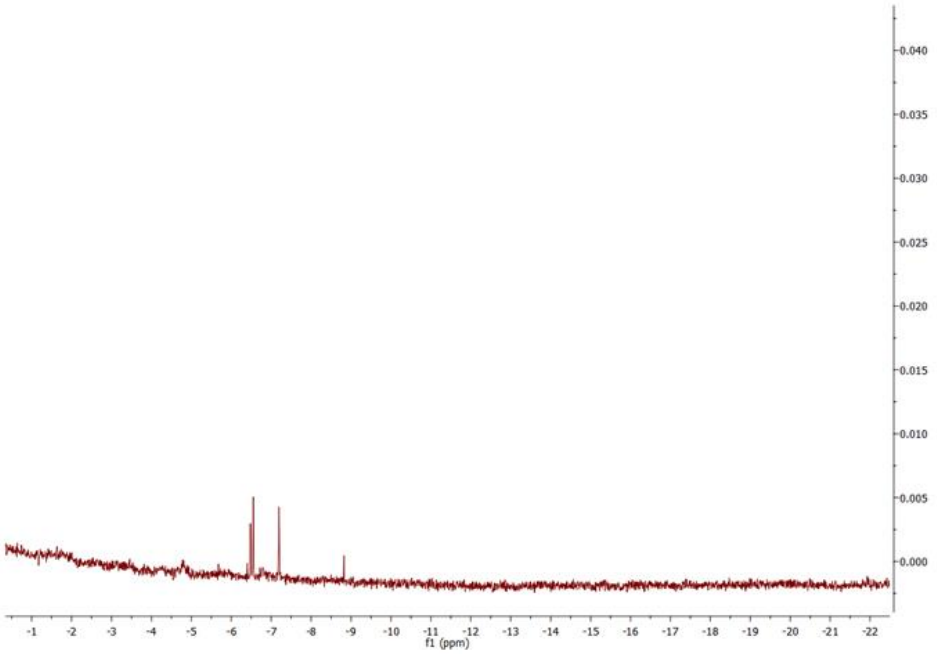


Figure 3.9. ^{1}H NMR of the reaction mixture at 110 ^{o}C

3.6.3. Molecular hydrogen detection using GC analysis

To investigate the formation of molecular hydrogen, the same reaction was performed in the sealed tube. After 48 hrs, the gaseous component of the reaction mixture inside the sealed tube was taken using a gas-tight syringe and injected to the gas chromatography (GC) instrument. The formation of molecular hydrogen was confirmed by GC analysis (Figure 3.10).

Data File: C:\EZChrom Elite\Data\kshirodra\060118 lm564.dat
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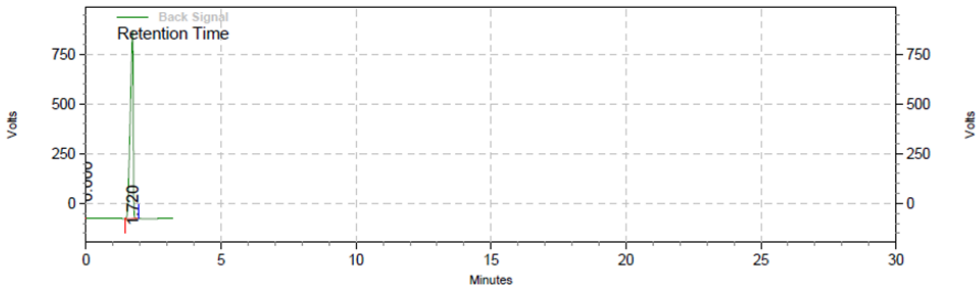
Acquired: 1/6/2018 2:47:26 PM
Printed: 6/9/2018 12:48:40 PM



Back Signal
Results

Retention Time	Area	Area %	Height	Height %
0.000	0	0.00	0	0.00
1.720	54595256	100.00	7266938	100.00
Totals	54595256	100.00	7266938	100.00

Figure 3.10. Detection of molecular hydrogen liberation using GC analysis

3.7. The possible reaction mechanism

Based on our experimental observations and previous literature reports,[25] the possible mechanism for the α-olefination of 2-oxindole is proposed (Figure 3.11). At first, Ru-NHC catalyst **4a** reacts with secondary alcohol **2** in the presence of a base to generate alkoxy-coordinated intermediate **A** *via* dissociation of the p-cymene ligand (confirmed by ^{1}H NMR analysis).

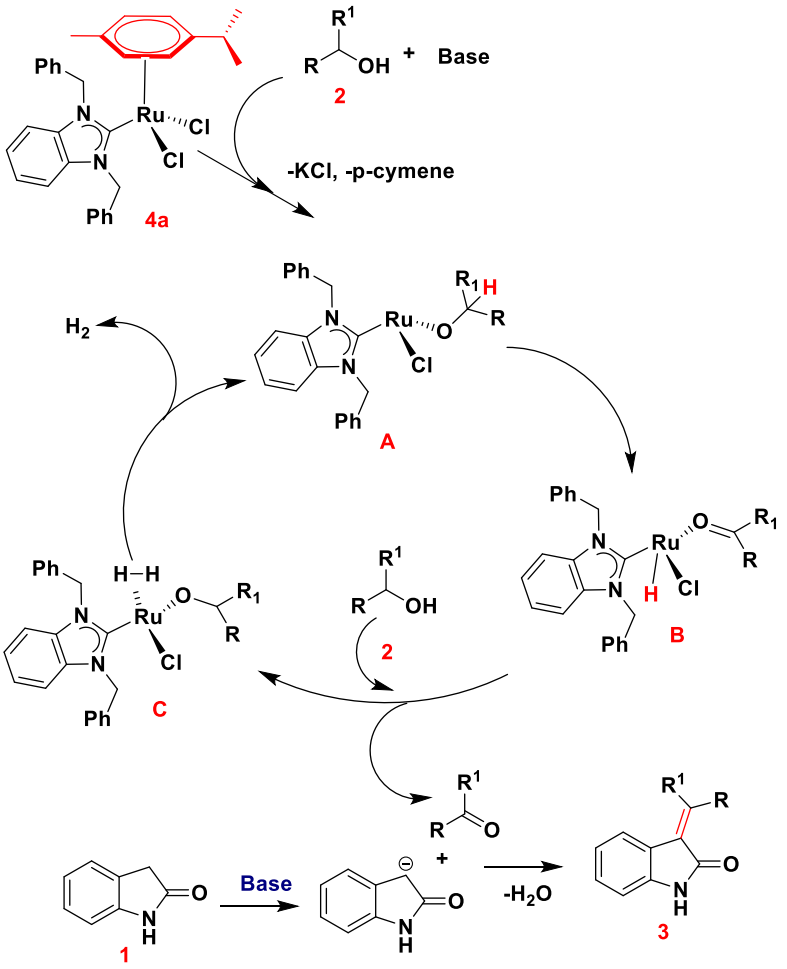


Figure 3.11. The possible reaction mechanism

Further, intermediate **A** undergoes β-hydride elimination to form the carbonyl compound attached Ru-H intermediate **B**. Moreover, the formation of hydride intermediate was confirmed by NMR analysis. The intermediate **B** reacts with the alcohol to generate intermediate **C** with the release of the free carbonyl compound. Finally, the intermediate **C** releases molecular H_2 to generate the active catalyst **A**. Base-generated enolate of oxindole undergoes aldol condensation with the carbonyl compound to form tetra substituted vinyl alkene **3**. Furthermore, the gas phase of the reaction mixture analyzed by using gas chromatography (Figure 3.10) indicated the liberation of H_2, which suggests a possible catalytic cycle. However, further reduction

of alkene **3** by in situ generated H_2 in the presence of catalyst **A** was not observed, this might be due to the sterically hindered alkene **3** and it may not be possible to coordinate with the intermediate **B**. A control experiment was performed by the reaction of 2-oxindole and benzophenone in the presence of KO*t*Bu generate the product **3** which confirm the intermediate ketone in the reaction mixture.

3.8. Biological screening against malaria

Although the biological activities of 3-arylideneindolin-2-one derivatives against cancer were studied, so far their activity against malaria is not studied. Hence, we have collaborated with Dr. Krishanpal Karmodiya of Biology department IISER, Pune and screened the antimalarial activity against parasite *Plasmodium falciparum* culture (infected RBCs in RPMI-1640 medium) at 2% parasitemia and 2% haematocrit was incubated in 96 well plates with different concentrations of the various bis-arylidene compounds.

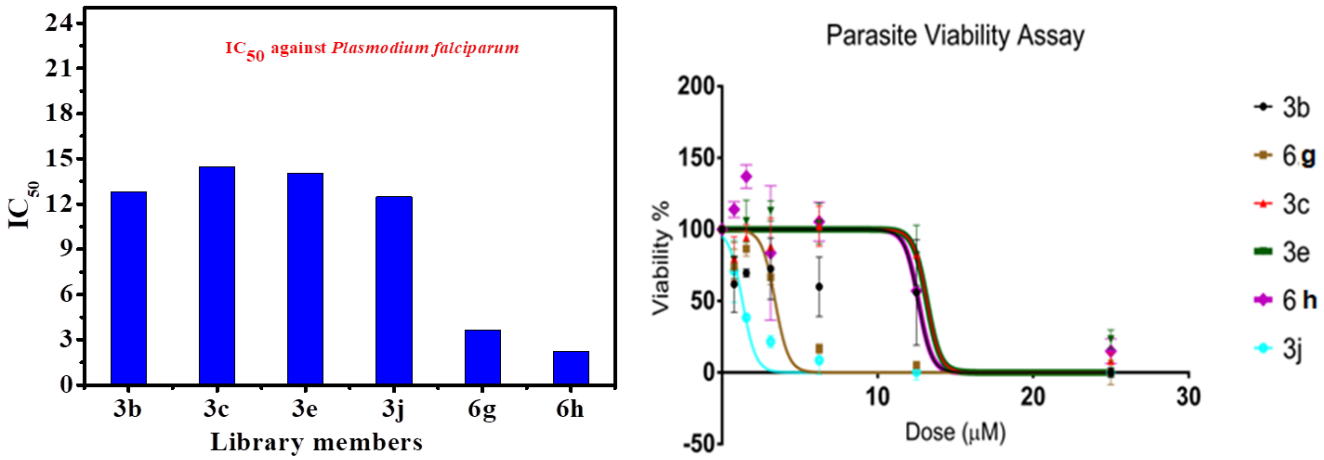


Figure 3.12. IC_{50} values and parasite viability assay of library members

The range of concentrations tested for the several compounds was from 25µM to 781 nM with a twofold serial dilution across the plate. Each concentration was tested for in duplicate for its effect on parasite viability. The parasites were cultured in presence of drug for 48 hours after which the plate was frozen at -80 ^{o}C for one hour and subsequently thawed at room temperature to enable the lysis of parasitized RBCs. The SYBR green lysis buffer was added to the wells to lyse the RBCs completely and enable incorporation of the SYBR green I fluorochrome into the released parasite DNA. Post 45 minute incubation in dark the plate was processed for SYBR Green I fluorescence readout on a varioscan plate reader. The readout for SYBR green I

fluorescence was considered as representative of the viable count of the parasite in a particular dosed well. The readout from the RPMI control (non-drugged) wells was considered as 100% (maximum) viability (Figure 3.12). The readout was then plotted for various dosages of the drug tested. The IC_{50} value for each drug was calculated as the drug concentration for which the parasite viability was registered at 50% as per the curve structure (Figure 3.12). The IC_{50} was estimated using the IC_{50} estimator online tool which employs the non-linear regression method for estimation of IC_{50}.

3.9. Conclusion

In conclusion, in this chapter we have disclosed a simple and efficient method for the α-olefination of 2-oxindole and its various derivatives with diaryl methanol by using an inexpensive Ru-NHC catalyst to synthesize a wide variety of arylidene-2-oxindole derivatives. This transformation follows acceptorless dehydrogenation pathway and the liberation of H_2 was confirmed by GC analysis. Detailed mechanism has been investigated for this transformation and supported by ^1H NMR and GC analysis. A plausible mechanism has been proposed to rationalize the formation of tetra-substituted alkenes. This method is direct, atom economical, general to all diaryl methanols, and valuable by-products such as H_2 and H_2O generated during this transformation. The biological activities of synthesized 3-(diphenylmethylene)indolin-2-one compounds were evaluated against the parasite *Plasmodium falciparum* and few compounds have shown significant activity with IC_{50} = 2.24 μM.

3.10. Experimental details and characterization data

3.10.1. General information and data collection

All the secondary alcohols and oxindole derivatives were purchased from Sigma-Aldrich. Ru-NHC catalyst was prepared according to the known literature procedure.[26] Deuterated solvents were used as received. All the solvents used were dry grade and stored over 4Å molecular sieves. Column chromatographic separation was performed over 100-200 mesh size silica-gel. Visualization was accomplished with UV light and iodine. The ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on 400 and 100 MHz respectively, using a Bruker or JEOL spectrometers. Abbreviations used in the NMR follow-up experiments: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; td, dd doublet of triplet and double doublet; m, multiplet, tt, triplet of triplets and ddd, doublet of doublet of doublets. High-resolution mass spectra were obtained with Waters-synapt G2 using electrospray ionization (ESI-TOF). Infrared (ATR) spectra were obtained with a Bruker Alpha-E infrared spectrometer and FTIR spectra were

recorded on pressed pellets of powder samples diluted with KBr on NICOLET 6700 spectrophotometer.

A) General experimental procedure for the synthesis of bis-arylidene oxindoles (3 or 6): To an oven dried 20 mL resealable pressure tube (equipped with a rubber septum), Ru-NHC complex **4a** (0.00625 mmol), KO*t*Bu (0.75 mmol), diaryl methanol (0.25 mmol) and 2-oxindole (0.5 mmol) were added in toluene/1,4-dioxane under an N_2 atmosphere using an N_2 balloon. Then, the tube was purged with N_2 and the septum was quickly removed and sealed with a cap using a crimper. The reaction mixture was stirred at 140 ^oC for 48 h. After cooling to room temperature, the reaction mixture was diluted with DCM and MeOH. After concentrating under reduced pressure, the residue was purified by 100–200 mesh silica-gel column chromatography by using ethyl acetate and hexane to obtain the pure compound **3** or **6**.

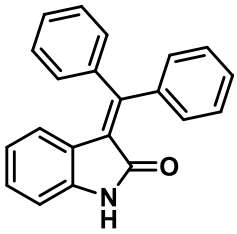
B) General experimental procedure for the synthesis of *N*-protected bis-arylidene oxindoles (6): To an oven dried 20 mL resealable pressure tube (equipped with a rubber septum), Ru-NHC complex **4a** (0.01 mmol), K_3PO_4 (0.75 mmol), diaryl methanol (0.25 mmol) and 2-oxindole (0.5 mmol) were added in 1,4-dioxane under an N_2 atmosphere using an N_2 balloon. Then, the tube was purged with N_2 and the septum was quickly removed and sealed with a cap using a crimper. The reaction mixture was stirred at 140 ^oC for 48 hrs. After cooling to room temperature, the reaction mixture was diluted with DCM and MeOH. After concentrating under reduced pressure, the residue was purified by using column chromatography (EtOAc:hexane = 15:85 to 25:75).

C) Experimental procedure for the detection of H_2 gas using GC analysis: To an oven dried 20 mL resealable pressure tube (equipped with a rubber septum), Ru-NHC complex **4a** (0.01 mmol), K_3PO_4 (0.75 mmol), bis(4-methoxyphenyl)methanol or diphenylmethanol (0.25 mmol) and 1-methyl 2-oxindole (0.5 mmol) were added in 1,4-dioxane under an N_2 atmosphere. Then, the tube was purged with N_2 and the septum was quickly removed and sealed with a cap using a crimper. The reaction mixture was stirred at 140 ^oC for 48 hrs. The gas phase of the reaction mixture was taken out by a gas tight glass syringe and immediately injected into an injector. A similar experiment in the absence of 2-oxindole was performed exhibiting the formation of benzophenone with the liberation of H_2 detected by GC analysis.

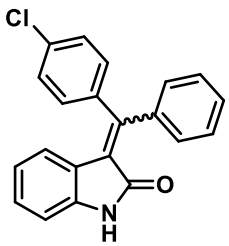
3.10.2. Spectroscopic data for the products

3-(diphenylmethylene)indolin-2-one (3a)[27]. Ru-NHC complex **4a** (3.78 mg, 0.00625 mmol), KO*t*Bu (84 mg, 0.75 mmol), diphenylmethanol (46 mg, 0.25 mmol), 2-

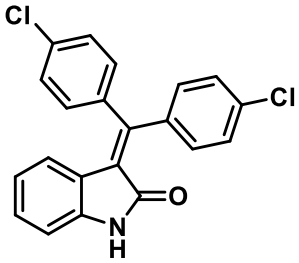
oxindole (66 mg, 0.5 mmol) and toluene (2 ml) were allowed to react in 20 mL resealable pressure tube according to method A to afford 3-(diphenylmethylene)indolin-2-one **3a** (64 mg, 87 %) as a pale yellow crystalline solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.95 (s, 1H), 7.36 - 7.27 (m, 4H), 7.26 -7.19 (m, 6H), 6.94 (td, *J* = 7.6, 1.0 Hz, 1H), 6.53 (d, *J* = 7.7 Hz, 2H), 6.26 (d, *J* = 7.7 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 168.85, 155.02, 141.50, 140.96, 139.94, 130.52, 129.62, 129.15, 128.93, 127.87, 124.85, 124.14, 123.33, 121.27, 109.86; **IR** (neat) 1615, 1699, 3392 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{21}H_{15}NO$ $(M+H)^+$: 298.1232, found: 298.1228.



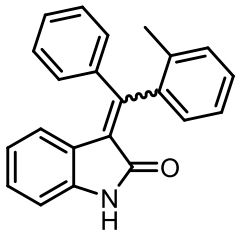
3-((4-chlorophenyl)(phenyl)methylene)indolin-2-one (3b)[28]. Ru-NHC complex **4a** (3.78 mg, 0.00625 mmol), KOtBu (84 mg, 0.75 mmol), (4-chlorophenyl)(phenyl)methanol (54 mg, 0.25 mmol), 2-oxindole (66 mg, 0.5 mmol) and toluene (2 ml) were allowed to react in 20 mL resealable pressure tube according to method A to afford isomeric mixture of 3-((4-chlorophenyl)(phenyl)methylene)indolin-2-one **3b** (57 mg, 70%) in the ratio of E/Z = (61:39)% as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) for major isomer δ 8.91 (bs, 1H), 7.47–7.37 (m, 3H), 7.36 – 7.32 (m, 2H), 7.31–7.25 (m, 4H), 7.07 (dt, *J* = 7.9, 4.4 Hz, 1H), 6.72 – 6.59 (m, 2H), 6.41 (dd, *J* = 47.5, 7.8 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) for major isomer δ 168.81, 153.30, 141.06, 139.82, 138.27, 135.49, 132.02, 131.18, 129.55, 129.33, 129.13, 128.05, 123.89, 123.36, 121.38, 109.99; **IR** (neat) = 1616, 1696, 2854, 2924, 3060, 3216 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{21}H_{14}ClNO$ $(M+H)^+$: 332.0842, found: 332.0849.



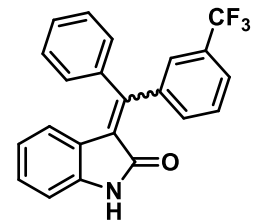
3-(bis(4-chlorophenyl)methylene)indolin-2-one (3c). Ru-NHC complex **4a** (3.78 mg, 0.00625 mmol), KO*t*Bu (84 mg, 0.75 mmol), bis(4-chlorophenyl)methanol (63 mg, 0.25 mmol), 2-oxindole (66 mg, 0.5 mmol) and toluene (2 ml) were allowed to react in 20 mL resealable pressure tube according to method A to afford 3-(bis(4-chlorophenyl)methylene)indolin-2-one **3c** (53 mg, 59%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.95 (s, 1H), 7.43 – 7.39 (m, 2H), 7.33 – 7.28 (m, 3H), 7.26 – 7.23 (m, 3H), 7.12 – 7.07 (m, 1H), 6.68 (td, *J* = 7.8, 0.8 Hz, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 6.45 (d, *J* = 7.7 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 168.58, 151.65, 141.10, 139.37, 137.92, 135.78, 135.64, 132.07, 131.22, 129.48, 128.27, 125.57, 123.57, 123.30, 121.56, 110.10; **IR** (neat) = 1452, 1650, 2831, 2941, 3321 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{21}H_{13}Cl_2NO$ $(M+H)^+$: 366.0452, found: 366.0452.



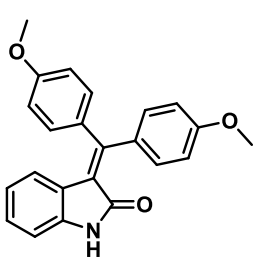
3-(phenyl(o-tolyl)methylene)indolin-2-one (3d)[31]. Ru-NHC complex **4a** (3.78 mg, 0.00625 mmol), KOtBu (84 mg, 0.75 mmol), phenyl(o-tolyl)methanol (49 mg, 0.25 mmol), 2-oxindole (66 mg, 0.5 mmol) and toluene (2 ml) were allowed to react in 20 mL resealable pressure tube according to method A to afford isomeric mixture of 3-(phenyl(o-tolyl)methylene)indolin-2-one **3d** (45 mg, 45%) in the ratio of E/Z = (60:40)% as a yellow crystalline solid. **^{1}H NMR** (400 MHz, $CDCl_3$) for major isomer δ 8.73 (s, 1H), 7.34 – 7.31 (m, 1H), 7.22–7.18 (m, 2H), 7.12 – 7.07 (m, 3H), 7.01 (dd, J = 7.8, 1.6 Hz, 2H), 6.90 (td, J = 7.7, 1.1 Hz, 1H), 6.50 – 6.43 (m, 2H), 5.78 (d, J = 7.7 Hz, 1H), 1.99 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) for major isomer δ 168.44, 154.25, 141.13, 140.91, 140.18 138.32, 135.44, 131.17, 130.26, 129.27, 129.16, 128.89, 128.49, 127.75, 126.86, 125.88, 124.36, 123.39, 123.31, 121.77, 109.57, 19.69; **IR** (neat) = 1465, 1613, 1696, 3221 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{22}H_{17}NO$ $(M+H)^+$: 312.1388, found: 312.1389.



3-(phenyl(2-(trifluoromethyl)phenyl)methylene)indolin-2-one (3e). Ru-NHC complex **4a** (3.78 mg, 0.00625 mmol), KO*t*Bu (84 mg, 0.75 mmol), phenyl(3-(trifluoromethyl)phenyl)methanol (63 mg, 0.25 mmol), 2-oxindole (66 mg, 0.5 mmol) and toluene (2 ml) were allowed to react in 20 mL resealable pressure tube according to method A to afford isomeric mixture of 3-(phenyl(3-(trifluoromethyl)phenyl)methylene)indolin-2-one **3e** (34 mg, 38%) separated by preparative TLC in the ratio of E/Z = (68:32)% as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) for E isomer δ 8.57 (s, 1H), 7.62 (s, 1H), 7.52-7.55 (s, 1H), 7.45 (t, *J* = 6.8 Hz, 2H), 7.37 (d, *J* = 5.9 Hz, 2H), 7.30 (d, *J* = 7.8 Hz, 3H), 7.01 (t, *J* = 7.7 Hz, 1H), 6.60 (d, *J* = 7.8 Hz, 2H), 6.18 (d, *J* = 7.8 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) for *E* isomer δ 168.16, 152.52, 142.01, 140.90, 139.02, 132.91, 130.29, 129.58, 129.54, 129.35, 128.57, 128.44, 128.02, 127.05, 126.29 (q, *J* = 3.7 Hz), 125.90 (q, *J* = 3.7 Hz), 125.51, 125.23, 125.07, 123.40, 123.09, 121.47, 109.84; IR (neat) = 2831, 2941 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{22}H_{14}F_3NO$ $(M+H)^+$: 366.1105, found: 366.1104.

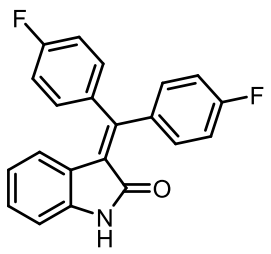


3-(bis(4-methoxyphenyl)methylene)indolin-2-one (3f)[31]**.** Ru-NHC complex **4a** (3.78 mg, 0.00625 mmol), Cs_2CO_3 (162 mg, 0.5 mmol), bis(4-methoxyphenyl)methanol (61 mg, 0.25 mmol), 2-oxindole (66 mg, 0.5 mmol) and 1,4-Dioxane (2 ml) were allowed to react in 20 mL resealable pressure tube according to method A to afford 3-(bis(4-methoxyphenyl)methylene)indolin-2-one **3f** (34 mg, 38%) as a yellow semi solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92

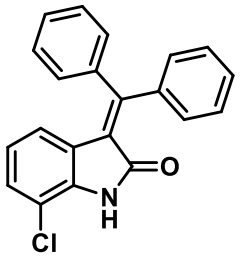


(s, 1H), 7.34 – 7.30 (m, 2H), 7.28 (d, *J* = 2.5 Hz, 2H), 7.09 (td, *J* = 7.6, 1.1 Hz, 1H), 6.97 – 6.93 (m, 2H), 6.91 – 6.86 (m, 2H), 6.78 (d, *J* = 7.7 Hz, 1H), 6.69 (td, *J* = 7.7, 1.0 Hz, 1H), 6.54 (d, *J* = 7.7 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 168.80, 161.20, 160.96, 155.69, 139.97, 133.89, 133.25, 132.26, 132.16, 128.05, 125.20, 122.88, 121.26, 114.26, 113.25, 109.77, 109.39, 55.52, 55.40; **IR** (neat) = 1606, 1695, 2831, 2942 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{23}H_{19}NO_3$ $(M+H)^+$: 358.1443, found: 358.1446.

3-(bis(4-fluorophenyl)methylene)indolin-2-one (3g). Ru-NHC complex **4a** (3.78 mg, 0.00625 mmol), Cs_2CO_3 (162 mg, 0.5 mmol), bis(4-fluorophenyl)methanol (55 mg, 0.25 mmol), 2-oxindole (66 mg, 0.5 mmol) and toluene (2 ml) were allowed to react in 20 mL resealable pressure tube according to method A to afford 3-(bis(4-fluorophenyl)methylene)indolin-2-one **3g** (26 mg, 31%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.35 – 7.28 (m, 4H), 7.17 – 7.13 (m, 2H), 7.11 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.07 – 7.01 (m, 2H), 6.73 (d, *J* = 7.7 Hz, 1H), 6.69 (td, *J* = 7.7, 1.0 Hz, 1H), 6.43 (d, *J* = 7.8 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 168.36, 163.95 (d, *J* = 249 Hz), 152.60, 140.64, 137.16, 135.49, 132.85 (d, *J* = 8.5 Hz), 131.91 (d, *J* = 8.2 Hz), 129.14, 124.84, 124.00, 123.26, 121.56, 116.59, 116.48, 116.35 (d, *J* = 21.7 Hz), 115.23, 115.01, 109.78; **IR** (neat) = 1601, 1699, 2856, 2926, 3076, 3241 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{21}H_{13}F_2NO$ $(M+H)^+$: 334.1043, found: 334.1045.

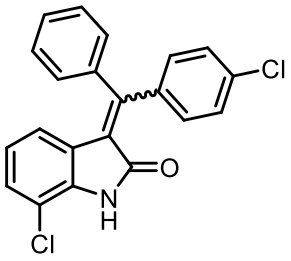


7-chloro-3-(diphenylmethylene)indolin-2-one (3h). Ru-NHC complex **4a** (3.78 mg, 0.00625 mmol), KO*t*Bu (84 mg, 0.75 mmol), diphenylmethanol (46 mg, 0.25 mmol), 7-chloro-2-oxindole (83 mg, 0.5 mmol) and toluene (2 ml) were allowed to react in 20 mL resealable pressure tube according to method A to afford 7-chloro-3-(diphenylmethylene)indolin-2-one **3h** (51 mg, 62%) as a pale yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 7.50-7.42 (m, 4H), 7.38-7.36 (m, 4H), 7.34-7.29 (m, 2H), 7.09 (dd, *J* = 8.1, 0.7 Hz, 1H), 6.60 (t, *J* = 8.0 Hz, 1H), 6.28 (d, *J* = 7.8 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 167.85, 157.14, 141.01, 139.33, 138.37, 130.54, 129.66, 129.53, 129.09, 128.60, 128.31, 127.93, 126.65, 124.44, 122.05, 121.59, 115.04; **IR** (neat) = 1584, 1696, 3061 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{21}H_{14}ClNO$ $(M+H)^+$: 332.0842, found: 332.0847.

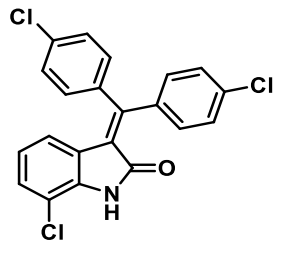


7-chloro-3-((4-chlorophenyl)(phenyl)methylene)indolin-2-one (3i). Ru-NHC complex **4a** (3.78 mg, 0.00625 mmol), KOtBu (84 mg, 0.75 mmol), (4-chlorophenyl)(phenyl)methanol (54 mg, 0.25 mmol), 7-chloro-2-oxindole (83 mg, 0.5 mmol) and toluene (2 ml) were allowed to react in 20 mL resealable pressure tube

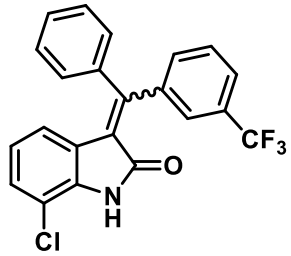
according to method A to afford 7-chloro-3-((4-chlorophenyl)(phenyl)methylene)indolin-2-one **3i** (41 mg, 46%) in the ratio of *E*/Z = (63:37%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.47 – 7.44 (m, 2H), 7.41 (dd, *J* = 4.1, 1.9 Hz, 2H), 7.37 (dd, *J* = 5.6, 4.0 Hz, 3H), 7.29 (t, *J* = 2.2 Hz, 2H), 7.13 (d, *J* = 8.1 Hz, 1H), 6.67 (t, *J* = 8.0 Hz, 1H), 6.41 (d, *J* = 7.8 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 167.44, 155.46, 139.36, 139.04, 135.91, 131.19, 130.58, 129.91, 129.67, 129.53, 129.45, 129.11, 128.63, 128.26, 128.07, 125.27, 122.21, 121.52, 115.18. **IR** (neat) = 1584, 1697, 3062 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{21}H_{13}Cl_2NO$ $(M+H)^+$: 366.0452, found: 366.0457.



3-(bis(4-chlorophenyl)methylene)-7-chloroindolin-2-one (3j). Ru-NHC complex **4a** (3.78 mg, 0.00625 mmol), KO*t*Bu (84 mg, 0.75 mmol), bis(4-chlorophenyl)methanol (63 mg, 0.25 mmol), 7-chloro-2-oxindole (83 mg, 0.5 mmol) and toluene (2 ml) were allowed to react in 20 mL resealable pressure tube according to method A to afford 3-(bis(4-chlorophenyl)methylene)-7-chloroindolin-2-one **3j** (41 mg, 41%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.48-7.44 (m, 2H), 7.38-7.34 (m, 3H), 7.28 (dt, *J* = 6.3, 2.3 Hz, 3H), 7.15 (dd, *J* = 8.2, 0.9 Hz, 1H), 6.68 (t, *J* = 8.0 Hz, 1H), 6.41 (d, *J* = 7.8 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 167.31, 153.81, 138.89, 138.36, 137.30, 136.20, 132.07, 131.24, 129.59, 128.89, 128.39, 125.04, 122.36, 121.60, 115.25; **IR** (neat) = 1589, 1702, 2857, 2925, 3067, 3135 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{21}H_{12}Cl_3NO$ $(M+H)^+$: 400.0062, found: 400.0058.

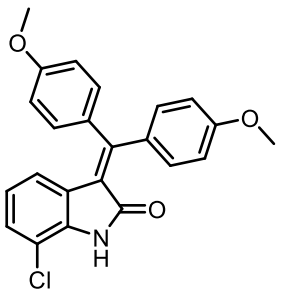


7-chloro-3-(phenyl(3-(trifluoromethyl)phenyl)methylene)indolin-2-one (3k). Ru-NHC complex **4a** (3.78 mg, 0.00625 mmol), KO*t*Bu (84 mg, 0.75 mmol), phenyl(3-(trifluoromethyl)phenyl)methanol (63 mg, 0.25 mmol), 7-chloro-2-oxindole (83 mg, 0.5 mmol) and toluene (2 ml) were allowed to react in 20 mL resealable pressure tube according to method A to afford 7-chloro-3-(phenyl(3-(trifluoromethyl)phenyl)methylene)indolin-2-one **3k** (44 mg, 45%) separated by preparative TLC in the ratio of E/Z = (80:20)% as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.74 (d, *J* = 7.3 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 3H), 7.53 – 7.46 (m, 2H), 7.41 (dt, *J* = 3.2, 2.0 Hz, 1H), 7.35 – 7.31 (m, 2H), 7.12 (dd, *J* = 8.2, 0.8 Hz, 1H), 6.62 (t, *J* = 8.0 Hz, 1H), 6.18 (d, *J* = 7.8 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 167.17, 154.63, 141.71, 138.61, 138.52, 133.04, 130.47, 130.04, 129.79, 129.43, 129.37, 128.92, 128.20, 126.43 (q, *J* = 4 Hz), 126.32 (q, *J* = 4

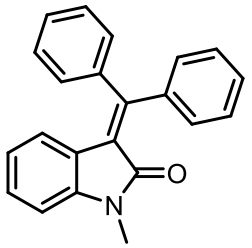


Hz), 122.29, 121.42, 115.28; IR (neat) = 1604, 1701, 3066, 3142 cm^{-1}. HRMS (ESI) m/z calculated for $C_{22}H_{13}ClF_3NO$ $(M+H)^+$: 400.0716, found: 400.0715.

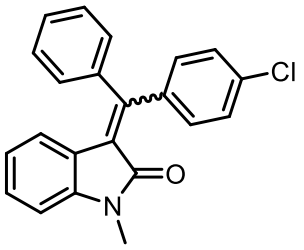
3-(bis(4-methoxyphenyl)methylene)-7-chloroindolin-2-one (3l). Ru-NHC complex **4a** (3.78 mg, 0.00625 mmol), KO*t*Bu (84 mg, 0.75 mmol), bis(4-methoxyphenyl)methanol (61 mg, 0.25 mmol), 7-chloro-2-oxindole (83 mg, 0.5 mmol) and toluene (2 ml) were allowed to react in 20 mL resealable pressure tube according to method A to afford 3-(bis(4-methoxyphenyl)methylene)-7-chloroindolin-2-one **3l** (50 mg, 25%) as a yellow semi solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.26 – 7.21 (m, 2H), 7.06 (d, *J* = 8.1 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 1H), 6.62 (t, *J* = 8.0 Hz, 1H), 6.41 (d, *J* = 7.8 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 167.71, 161.59, 161.24, 157.70, 137.31, 133.48, 1233.42, 132.32, 131.74, 127.36, 126.68, 122.13, 121.94, 121.02, 114.68, 114.30, 113.32, 55.54, 55.43; **IR** (neat) = 1563, 1611, 1698, 2924, 3435 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{23}H_{18}ClNO_3$ $(M+H)^+$: 391.0975, found: 391.0979.



3-(diphenylmethylene)-1-methylindolin-2-one (6a)[29]. Ru-NHC complex **4a** (6.05 mg, 0.01 mmol), K_3PO_4 (159 mg, 0.75 mmol), diphenylmethanol (46 mg, 0.25 mmol), 1-methylindolin-2-one (73 mg, 0.5 mmol) and 1,4-dioxane (2 ml) were allowed to react in 20 mL resealable pressure tube according to method B to afford 3-(diphenylmethylene)-1-methylindolin-2-one **6a** (36 mg, 46%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 3H), 7.39 – 7.35 (m, 3H), 7.35 – 7.31 (m, 4H), 7.21 – 7.13 (m, 1H), 6.77 (d, *J* = 7.7 Hz, 1H), 6.69 (td, *J* = 7.8, 1.0 Hz, 1H), 6.43 (d, *J* = 7.7 Hz, 1H), 3.21 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 166.95, 154.72, 143.42, 141.41, 140.07, 130.12, 129.80, 128.63, 127.94, 124.33, 123.27, 121.51, 107.82, 25.98; **IR** (neat) = 1599, 1683, 3063, 3397 cm^{-1}; **HRMS** (ESI) m/z calculated for $C_{22}H_{17}NO$ $(M+H)^+$: 312.1388, found: 312.1389.

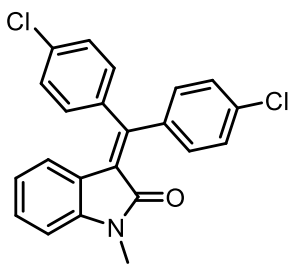


3-((4-chlorophenyl)(phenyl)methylene)-1-methylindolin-2-one (6b)[30]. Ru-NHC complex **4a** (6.05 mg, 0.01 mmol), K_3PO_4 (159 mg, 0.75 mmol), (4-chlorophenyl)(phenyl)methanol (54 mg, 0.25 mmol), 1-methylindolin-2-one (73 mg, 0.5 mmol) and 1,4-Dioxane (2 ml) were allowed to react in 20 mL resealable pressure tube according to method B to afford isomeric mixture of 3-((4-chlorophenyl)(phenyl)methylene)-1-methylindolin-2-one **6b** (36 mg, 41%) in the ratio of E/Z = (75:25)% as a yellow semi

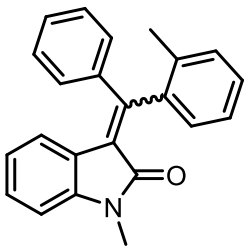


solid. **^{1}H NMR** (400 MHz, $CDCl_3$) for major isomer δ 7.46 – 7.43 (m, 3H), 7.35 (d, *J* = 4.5 Hz, 7H), 6.72 – 6.65 (m, 1H), 5.82 (d, *J* = 3.4 Hz, 2H), 3.21 (s, 3H); **^{13}C{^{1}H} NMR** (400 MHz, $CDCl_3$) for major isomer δ 166.88, 153.04, 143.59, 142.37, 133.41, 131.66, 130.19, 129.44, 128.97, 128.73, 128.23, 128.01, 127.71, 126.66, 123.34, 121.64, 107.92, 26.01; **IR** (neat) = 1091, 1605, 1687, 3061 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{22}H_{16}ClNO$ $(M+H)^+$: 346.0998, found: 346.1001.

3-(bis(4-chlorophenyl)methylene)-1-methylindolin-2-one (6c)[30]. Ru-NHC complex **4a** (6.05 mg, 0.01 mmol), K_3PO_4 (159 mg, 0.75 mmol), bis(4-chlorophenyl)methanol (63 mg, 0.25 mmol), 1-methylindolin-2-one (73 mg, 0.5 mmol) and 1,4-dioxane (2 ml) were allowed to react in 20 mL resealable pressure tube according to method B to afford 3-(bis(4-chlorophenyl)methylene)-1-methylindolin-2-one **6c** (43 mg, 46%) as a yellow semi solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 – 7.44 (m, 2H), 7.38 – 7.35 (m, 3H), 7.33 (d, *J* = 4.3 Hz, 4H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.77 (td, *J* = 7.7, 1.0 Hz, 1H), 6.56 (d, *J* = 7.7 Hz, 1H), 3.21 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 166.68, 151.37, 143.56, 142.01, 139.31, 138.01, 135.74, 135.60, 133.70, 131.72, 131.17, 129.49, 129.44, 128.88, 128.34, 127.99, 126.65, 125.07, 123.23, 122.84, 121.75, 108.10, 26.04; **IR** (neat) = 1600, 1692, 3058, 3407 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{22}H_{15}Cl_2NO$ $(M+H)^+$: 380.0609, found: 380.0609.

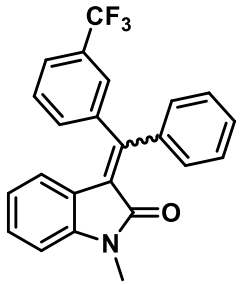


1-methyl-3-(phenyl(o-tolyl)methylene)indolin-2-one (6d)[29]. Ru-NHC complex **4a**(6.05 mg, 0.01 mmol), K_3PO_4 (159 mg, 0.75 mmol), phenyl(o-tolyl)methanol (49 mg, 0.25 mmol), 1-methylindolin-2-one (73 mg, 0.5 mmol) and 1,4-dioxane (2 ml) were allowed to react in 20 mL resealable pressure tube according to method B to afford isomeric mixture of 1-methyl-3-(phenyl(o-tolyl)methylene)indolin-2-one **6d** (35 mg, 43%) in the ratio of E/Z = (69:31)% as a yellow semi solid. **^{1}H NMR** (400 MHz, $CDCl_3$) for major isomer δ 7.48 – 7.47 (m, 1H), 7.39 – 7.35 (m, 4H), 7.31 (s, 2H), 7.19 – 7.14 (m, 2H), 6.83 – 6.75 (m, 3H), 6.01 (dd, *J* = 7.7, 0.6 Hz, 3H), 3.24 (s, 3H), 2.17 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) for major isomer δ 166.65, 153.83, 140.85, 138.44, 131.13, 129.95, 129.14, 128.85, 128.40, 127.73, 126.83, 125.92, 123.09, 121.90, 107.67, 53.56, 25.94; **IR** (neat) = 1702, 1607, 2927, 3058 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{23}H_{19}NO$ $(M+H)^+$: 326.1545, found: 326.1549.

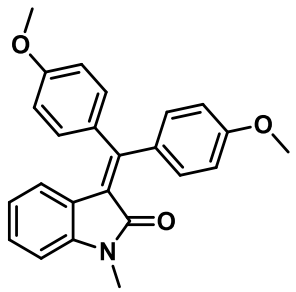


1-methyl-3-(phenyl(3-(trifluoromethyl)phenyl)methylene)indolin-2-one (6e). Ru-NHC complex **4a** (6.05 mg, 0.01 mmol), K_3PO_4 (159 mg, 0.75 mmol), phenyl(3-(trifluoromethyl)phenyl)methanol (63 mg, 0.25 mmol), 1-methyl-2-oxindole (83 mg,

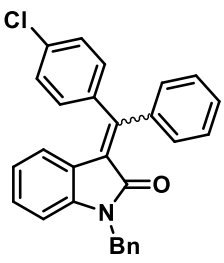
0.5 mmol) and 1,4-dioxane (2 ml) were allowed to react in 20 mL resealable pressure tube according to method B to afford isomeric mixture of 1-methyl-3-(phenyl(3-(trifluoromethyl)phenyl)methylene)indolin-2-one **6e** (30 mg, 31%) separated by preparative TLC in the ratio of E/Z = (79:21)% as a blood red semi solid. **^{1}H NMR** (400 MHz, $CDCl_3$) for major isomer δ 7.58 (d, *J* = 7.8 Hz, 1H), 7.53 (s, 1H), 7.48 – 7.45 (m, 3H), 7.41 – 7.37 (m, 1H), 7.35 – 7.29 (m, 3H), 7.20 (td, *J* = 7.7, 1.1 Hz, 1H), 6.78 (d, *J* = 7.7 Hz, 1H), 6.71 (dt, *J* = 7.8, 4.0 Hz, 1H), 6.47 – 6.43 (m, 1H), 3.20 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) for major isomer δ 166.69, 152.14, 143.70, 140.27, 140.63, 133.49, 129.62, 129.43, 129.35, 129.29, 128.31, 126.76 (q, *J* = 4 Hz), 125.70 (q, *J* = 4 Hz), 125.42, 123.50, 122.88, 121.70, 107.98, 26.05; **IR** (neat) = 1609, 1704, 2931, 3489 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{23}H_{16}F_3NO$ $(M+H)^+$: 380.1262, found: 380.1263.



3-(bis(4-methoxyphenyl)methylene)-1-methylindolin-2-one (6f)[27]. Ru-NHC complex **4a** (6.05 mg, 0.01 mmol), K_3PO_4 (159 mg, 0.75 mmol), bis(4-methoxyphenyl)methanol (61 mg, 0.25 mmol), 1-methylindolin-2-one (73 mg, 0.5 mmol) and 1,4-dioxane (2 ml) were allowed to react in 20 mL resealable pressure tube according to method B to afford 3-(bis(4-methoxyphenyl)methylene)-1-methylindolin-2-one **6f** (30 mg, 32%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (dd, *J* = 15.2, 8.6 Hz, 4H), 7.15 (t, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.77 (d, *J* = 7.7 Hz, 1H), 6.71 (t, *J* = 7.6 Hz, 1H), 6.57 (d, *J* = 7.7 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.23 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 167.28, 161.05, 160.84, 155.10, 142.83, 133.87, 132.93, 132.41, 132.09, 128.04, 124.26, 122.67, 122.45, 121.29, 114.20, 113.20, 107.67, 55.49, 55.38, 26.00; **IR** (neat) = 1605, 1696, 2850, 2925, 3056 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{24}H2_1NO_3$ $(M+H)^+$: 372.1599, found: 372.1598.

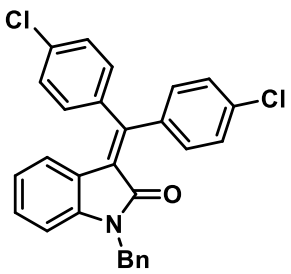


1-benzyl-3-((4-chlorophenyl)(phenyl)methylene)indolin-2-one (6g)[27]. Ru-NHC complex **4a** (6.05 mg, 0.01 mmol), K_3PO_4 (159 mg, 0.75 mmol), (4-chlorophenyl)(phenyl)methanol (54 mg, 0.25 mmol), 1-benzylindolin-2-one (111 mg, 0.5 mmol) and 1,4-dioxane (2 ml) were allowed to react in 20 mL resealable pressure tube according to method B to afford 1-benzyl-3-((4-chlorophenyl)(phenyl)methylene)indolin-2-one **6g** (36 mg, 35 %) as a pale yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 8.6, 3.5 Hz, 3H), 7.43 – 7.39 (m, 3H), 7.35 (dd, *J* = 13.1, 7.4 Hz, 7H), 7.10 (dd, *J* = 14.3, 7.6 Hz, 2H),

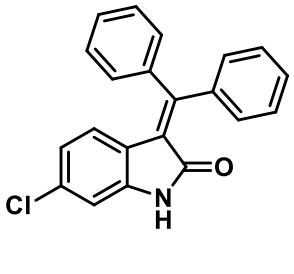


6.71 (dt, *J* = 15.4, 6.6 Hz, 2H), 6.52 (dd, *J* = 44.5, 7.9 Hz, 1H), 4.96 (s, 2H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 166.68, 153.38, 142.56, 140.98, 139.76, 136.29, 135.42, 131.79, 131.10, 130.34, 129.17, 128.76, 128.76, 128.20, 127.77, 123.28, 121.62, 43.58; **IR** (neat) = 1608, 1703, 2853, 2920, 3057 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{28}H_{20}ClNO$ $(M+H)^+$: 422.1311, found: 422.1318.

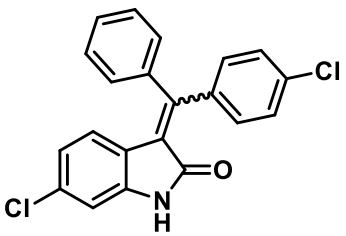
1-benzyl-3-(bis(4-chlorophenyl)methylene)indolin-2-one (6h). Ru-NHC complex **4a** (6.05 mg, 0.01 mmol), K_3PO_4 (159 mg, 0.75 mmol), bis(4-chlorophenyl)methanol (63 mg, 0.25 mmol), 1-benzylindolin-2-one (111 mg, 0.5 mmol) and 1,4-dioxane (2 ml) were allowed to react in 20 mL resealable pressure tube according to method B to afford 1-benzyl-3-(bis(4-chlorophenyl)methylene)indolin-2-one **6h** (40 mg, 35%) as a pale yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.45 – 7.41 (m, 2H), 7.37 – 7.34 (m, 2H), 7.33 – 7.30 (m, 4H), 7.30 (t, *J* = 2.0 Hz, 3H), 7.27 (d, *J* = 2.2 Hz, 2H), 7.09 (td, *J* = 7.7, 1.0 Hz, 1H), 6.73 – 6.67 (m, 2H), 6.52 (dd, *J* = 8.0, 0.9 Hz, 1H), 4.91 (s, 2H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 166.69, 151.79, 142.72, 139.37, 137.95, 136.23, 135.80, 135.73, 131.89, 131.19, 129.52, 129.36, 128.85, 128.39, 127.68, 127.59, 124.84, 123.28, 122.97, 121.79, 109.06, 43.69; **IR** (neat) = 1453, 1649, 2942, 3328 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{28}H_{19}Cl_2NO$ $(M+H)^+$: 456.0922, found: 456.0923.



6-chloro-3-(diphenylmethylene)indolin-2-one (6i). Ru-NHC complex **4a** (6.05 mg, 0.01 mmol), KO*t*Bu (84 mg, 0.75 mmol), diphenylmethanol (46 mg, 0.25 mmol), 6-chloro-2-oxindole (83 mg, 0.5 mmol) and 1,4-dioxane (2 ml) were allowed to react in 20 mL resealable pressure tube according to method A to afford 6-chloro-3-(diphenylmethylene)indolin-2-one **6i** (49 mg, 60%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 7.46 – 7.41 (m, 3H), 7.37 (dd, J = 11.8, 4.1 Hz, 5H), 7.30 (d, J = 6.3 Hz, 2H), 6.74 (d, J = 1.7 Hz, 1H), 6.62 (dd, J = 8.4, 1.8 Hz, 1H), 6.27 (d, J = 8.4 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 168.25, 155.97, 141.42, 141.20, 139.52, 134.37, 130.50, 129.71, 129.66, 129.17, 127.99, 124.34, 123.55, 122.78, 121.54, 109.97; **IR** (neat) = 1510, 1694, 1707, 2925 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{21}H_{14}ClNO$ $(M+H)^+$: 332.0842, found: 332.0849.

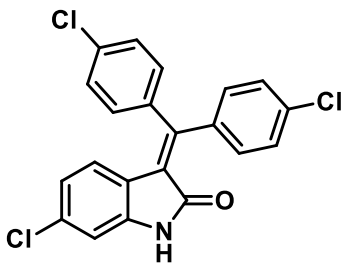


(6-chloro-3-((4-chlorophenyl)(phenyl)methylene)indolin-2-one (6j). Ru-NHC complex **4a** (6.05 mg, 0.01 mmol), KOtBu (84 mg, 0.75 mmol), (4-chlorophenyl)(phenyl)methanol (54 mg, 0.25 mmol), 6-chloro-2-oxindole (83 mg, 0.5 mmol) and 1,4-dioxane (2 ml) were allowed to react in 20 mL resealable

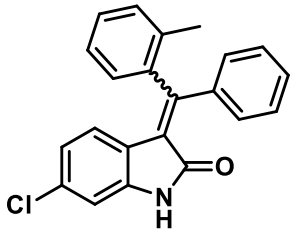


pressure tube according to method A to afford isomeric mixture of 6-chloro-3-((4-chlorophenyl)(phenyl)methylene)indolin-2-one **6j** (52 mg, 57%) in the ratio of E/Z = 64:36% as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) for major isomer δ 8.55 (s, 1H), 7.45 (dd, *J* = 4.5, 2.1 Hz, 2H), 7.40 – 7.37 (m, 2H), 7.35-7.33 (m, 2H) 7.31 (t, *J* = 1.9 Hz, 2H), 7.25 (d, *J* = 1.1 Hz, 1H), 6.72 – 6.63 (m, 2H), 6.25 (dd, *J* = 8.3, 6.0 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) for major isomer δ 167.78, 155.45, 140.57, 139.34, 138.47, 137.65, 135.89, 132.01, 131.19, 130.59, 129.89, 129.57, 129.44, 129.22, 128.64 128.23, 128.05, 125.36, 125.23, 124.76, 122.19, 121.49, 115.23; **IR** (neat) = 1657, 1703, 2853, 2922, 3066, 3221. cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{21}H_{13}Cl_2NO$ $(M+H)^+$: 366.0452, found: 366.0449.

3-(bis(4-chlorophenyl)methylene)-6-chloroindolin-2-one (6k). Ru-NHC complex **4a** (6.05 mg, 0.01 mmol), KOtBu (84 mg, 0.75 mmol), bis(4-chlorophenyl)methanol (63 mg, 0.25 mmol), 6-chloro-2-oxindole (83 mg, 0.5 mmol) and 1,4-dioxane (2 ml) were allowed to react in 20 mL resealable pressure tube according to method A to afford 3-(bis(4-chlorophenyl)methylene)-6-chloroindolin-2-one **6k** (43 mg, 43%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.42 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.24 (dd, *J* = 8.4, 3.9 Hz, 4H), 6.76 (d, *J* = 1.8 Hz, 1H), 6.68 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.38 (d, *J* = 8.4 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 167.88, 152.53, 141.55, 139.09, 137.49, 136.15, 136.10 135.00, 132.04, 131.21, 129.64, 128.43, 124.30, 124.21, 122.22, 121.80, 110.23; **IR** (neat) = 1611, 1705, 2855, 2925, 3243 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{21}H_{12}Cl_3NO$ $(M+H)^+$: 400.0062, found: 400.0061.

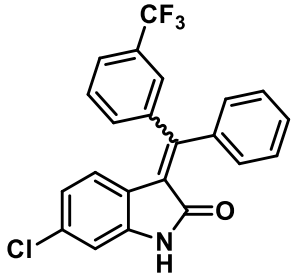


6-chloro-3-(phenyl(o-tolyl)methylene)indolin-2-one (6l). Ru-NHC complex **4a** (6.05 mg, 0.01 mmol), KO*t*Bu (84 mg, 0.75 mmol), phenyl(o-tolyl)methanol (49 mg, 0.25 mmol), 6-chloro-2-oxindole (83 mg, 0.5 mmol) and 1,4-dioxane (2 ml) were allowed to react in 20 mL resealable pressure tube according to method A to afford isomeric mixture of 6-chloro-3-(phenyl(o-tolyl)methylene)indolin-2-one **6l** (44 mg, 51%) in the ratio of E/Z = 54:46% as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) for major isomer δ 8.24 (bs, 1H), 7.43 (ddd, *J* = 10.1, 5.6, 1.4 Hz, 4H), 7.29 (dd, *J* = 6.8, 4.5 Hz, 2H), 7.18 – 7.12 (m, 2H), 6.70 (dd, *J* = 15.3, 7.3 Hz, 2H), 6.63 (s, 1H), 5.81 (d, *J* = 8.4 Hz, 1H), 2.11 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) for major isomer δ 168.19, 155.04, 141.92, 140.63, 137.98, 135.38, 134.44, 131.28, 130.25, 129.63, 129.14, 128.53, 127.84, 125.95, 124.17, 121.88, 121.46, 109.93, 19.66; **IR** (neat) = 1608, 1703, 2856,

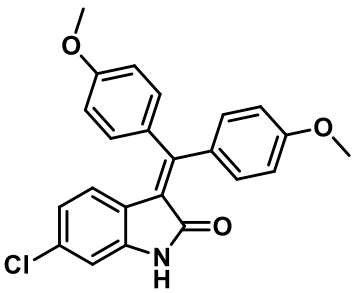


2926, 3067, 3231 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{22}H_{16}ClNO$ $(M+H)^+$: 346.0998, found: 346.0994.

6-chloro-3-(phenyl(3-(trifluoromethyl)phenyl)methylene)indolin-2-one (6m). Ru-NHC complex **4a** (6.05 mg, 0.01 mmol), KO*t*Bu (84 mg, 0.75 mmol), phenyl(3-(trifluoromethyl)phenyl)methanol (63 mg, 0.25 mmol), 6-chloro-2-oxindole (83 mg, 0.5 mmol) and 1,4-dioxane (2 ml) were allowed to react in 20 mL resealable pressure tube according to method A to afford isomeric mixture of 6-chloro-3-(phenyl(3-(trifluoromethyl)phenyl)methylene)indolin-2-one **6m** (40 mg, 40%) separated by preparative TLC in the ratio of E/Z = (58:42)% as a yellow semi solid. **^{1}H NMR** (400 MHz, $CDCl_3$) for major isomer δ 8.88 (bs, 1H), 7.65 (d, *J* = 4.0 Hz, 2H), 7.50 (dd, *J* = 5.5, 4.0 Hz, 3H), 7.38 (dd, *J* = 6.6, 1.8 Hz, 1H), 7.33 – 7.28 (m, 3H), 6.68 (s, 1H), 6.62 (d, *J* = 1.9 Hz, 1H), 6.30 (d, *J* = 8.4 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) for major isomer δ 168.48, 153.35, 141.88, 140.38, 140.10, 135.00, 133.63, 130.51, 129.97, 129.41, 128.48, 128.22, 127.36 (q, *J* = 4 Hz), 126.12 (q, *J* = 4 Hz), 124.80, 124.50, 124.97, 122.16, 121.81, 110.31; **IR** (neat) = 1692, 2831, 2942 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{22}H_{14}ClF_3NO$ $(M+H)^+$: 400.0761, found: 400.0716.



3-(bis(4-methoxyphenyl)methylene)-6-chloroindolin-2-one (6n). Ru-NHC complex **4a** (6.05 mg, 0.01 mmol), KO*t*Bu (84 mg, 0.75 mmol), bis(4-methoxyphenyl)methanol (63 mg, 0.25 mmol), 6-chloro-2-oxindole (83 mg, 0.5 mmol) and 1,4-dioxane (2 ml) were allowed to react in 20 mL resealable pressure tube according to method A to afford 3-(bis(4-methoxyphenyl)methylene)-6-chloroindolin-2-one **6n** (50 mg, 60%) as a yellow semi solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.33 – 7.28 (m, 2H), 7.25 – 7.21 (m, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.90 – 6.85 (m, 2H), 6.71 (dd, *J* = 3.1, 1.6 Hz, 1H), 6.62 (dd, J = 8.4, 2.0 Hz, 1H), 6.40 (d, *J* = 8.4 Hz, 1H), 3.89 (s, 3H), 3.84 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 169.11, 161.42, 161.10, 156.39, 141.04, 133.43, 133.30, 132.27, 123.66, 123.48, 121.15, 114.27, 113.25, 110.00, 55.51, 55.41; **IR** (neat) = 1507, 1612, 1705, 3212 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{23}H_{18}ClNO_3$ $(M+H)^+$: 392.1052, found: 392.1050.



3.11. Appendix III: Copies of ^{1}H & $^{13}C\{^{1}H\}$ NMR spectra of representative compounds

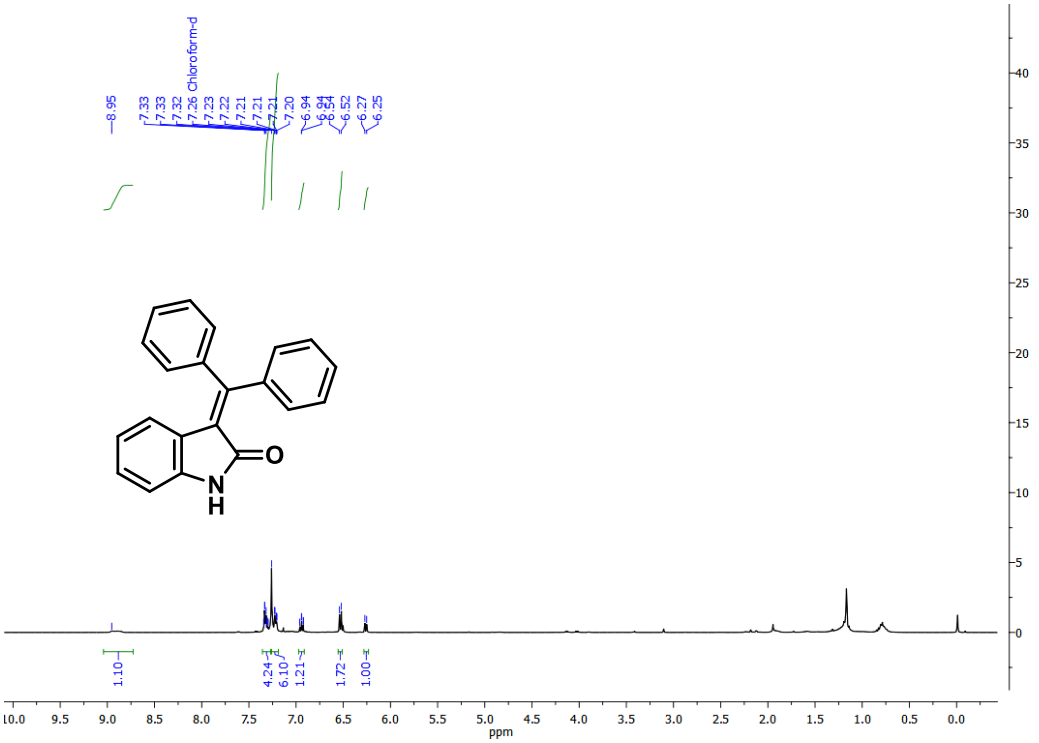


Figure 3.13. ^{1}H NMR of compound **3a**

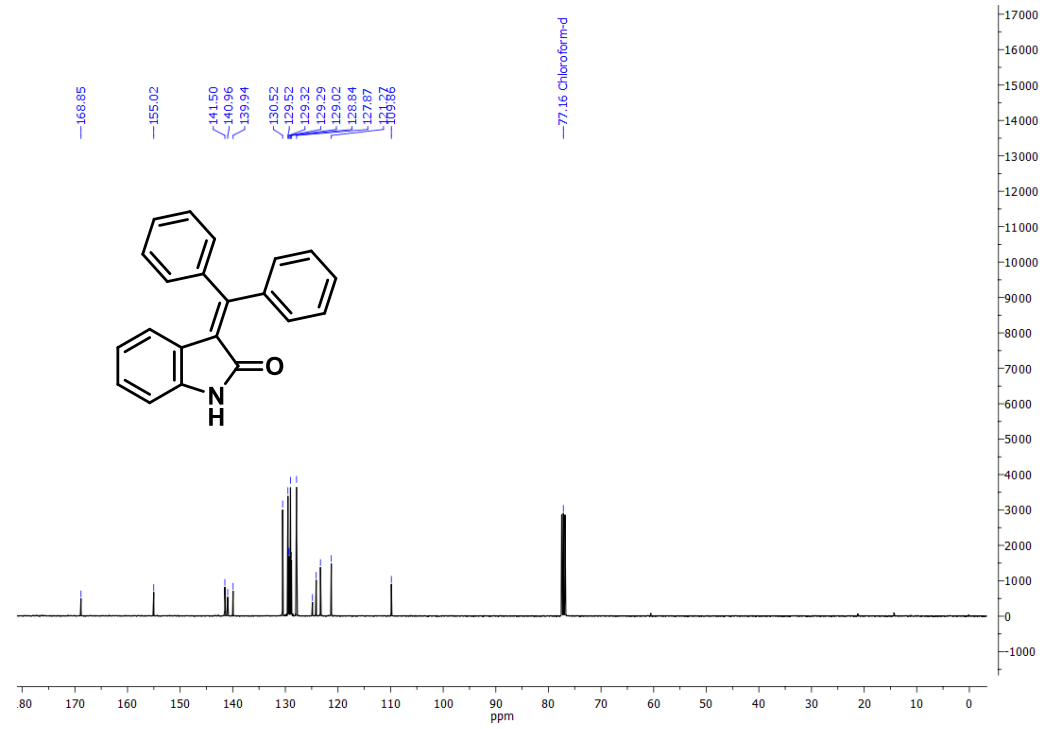


Figure 3.14. ^{13}C{^{1}H} NMR of compound **3a**

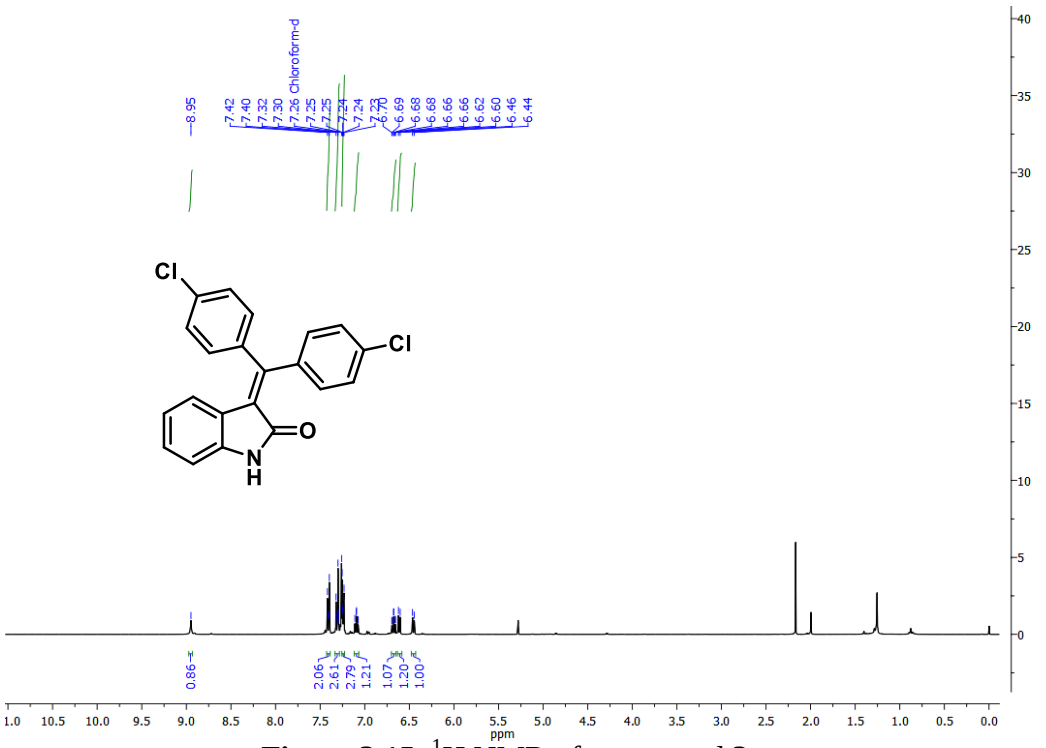


Figure 3.15. ^{1}H NMR of compound **3c**

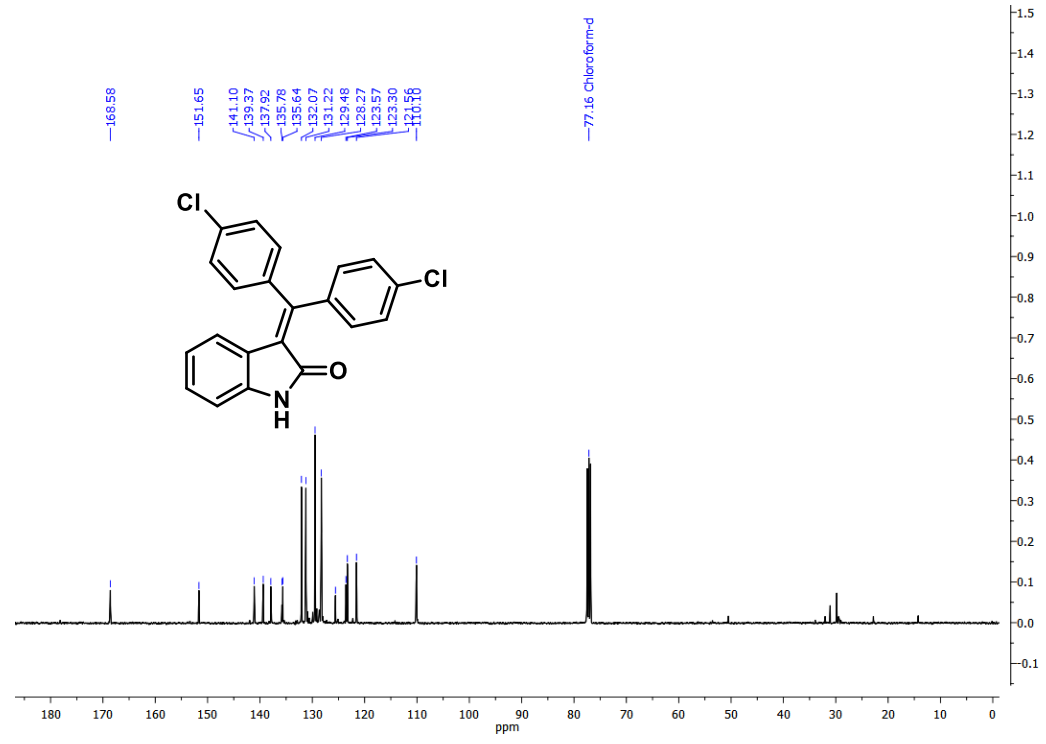


Figure 3.16. ^{13}C{^{1}H} NMR of compound **3c**

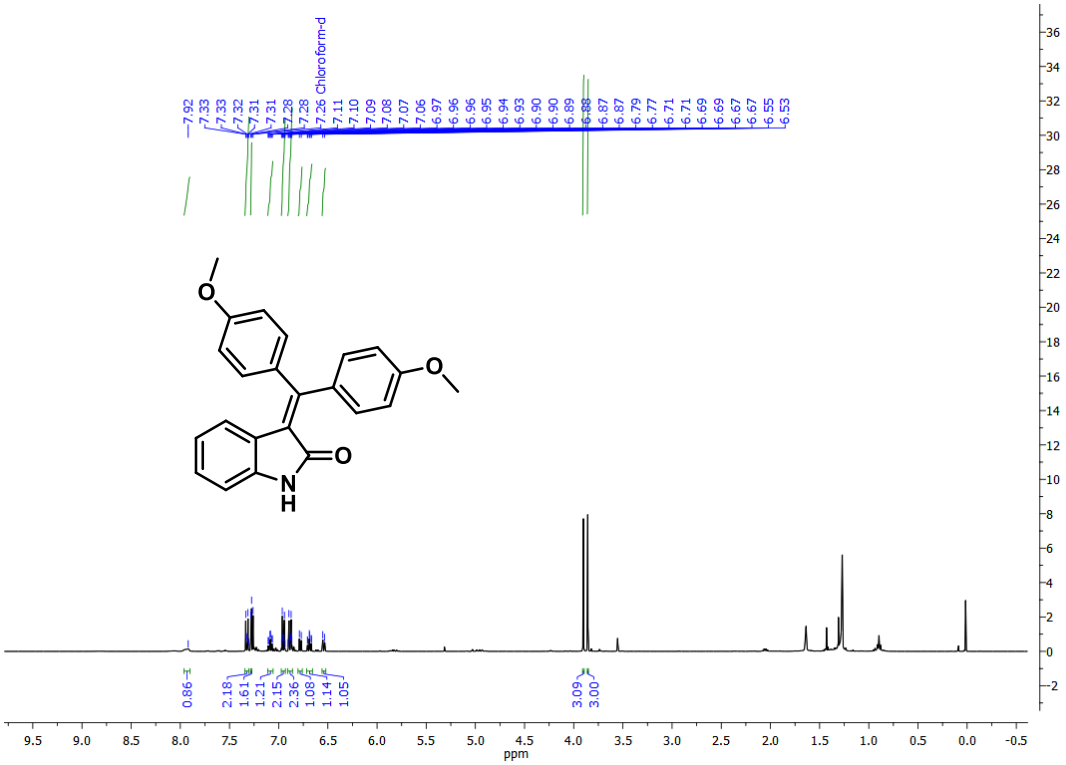


Figure 3.17. ^{1}H NMR of compound **3f**

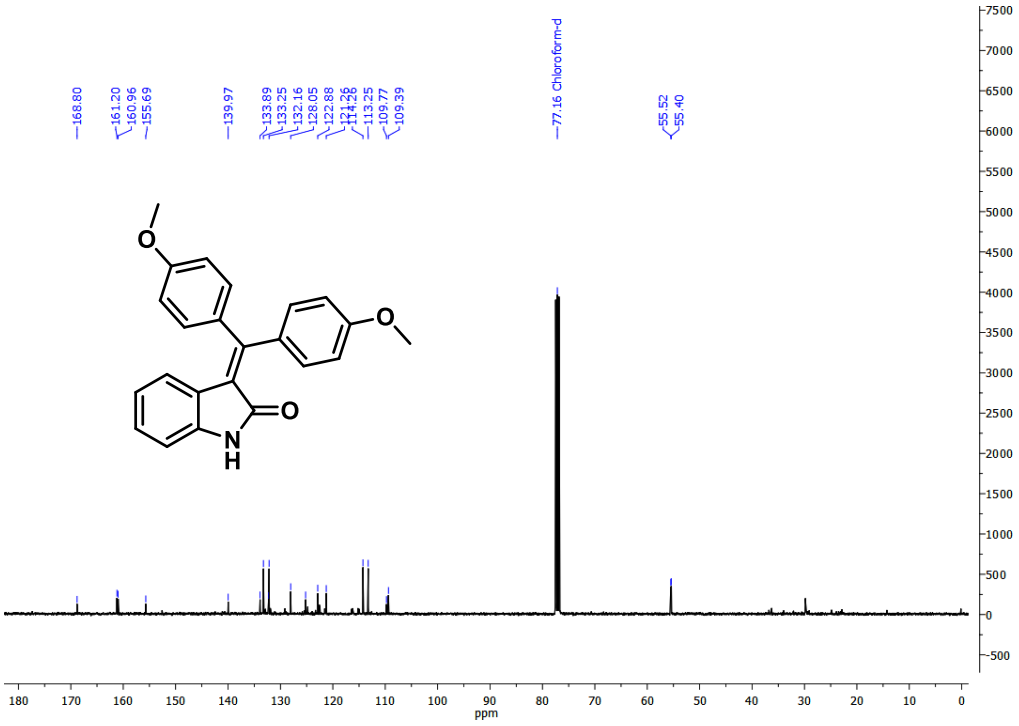


Figure 3.18. ^{13}C{^{1}H} NMR of compound **3f**

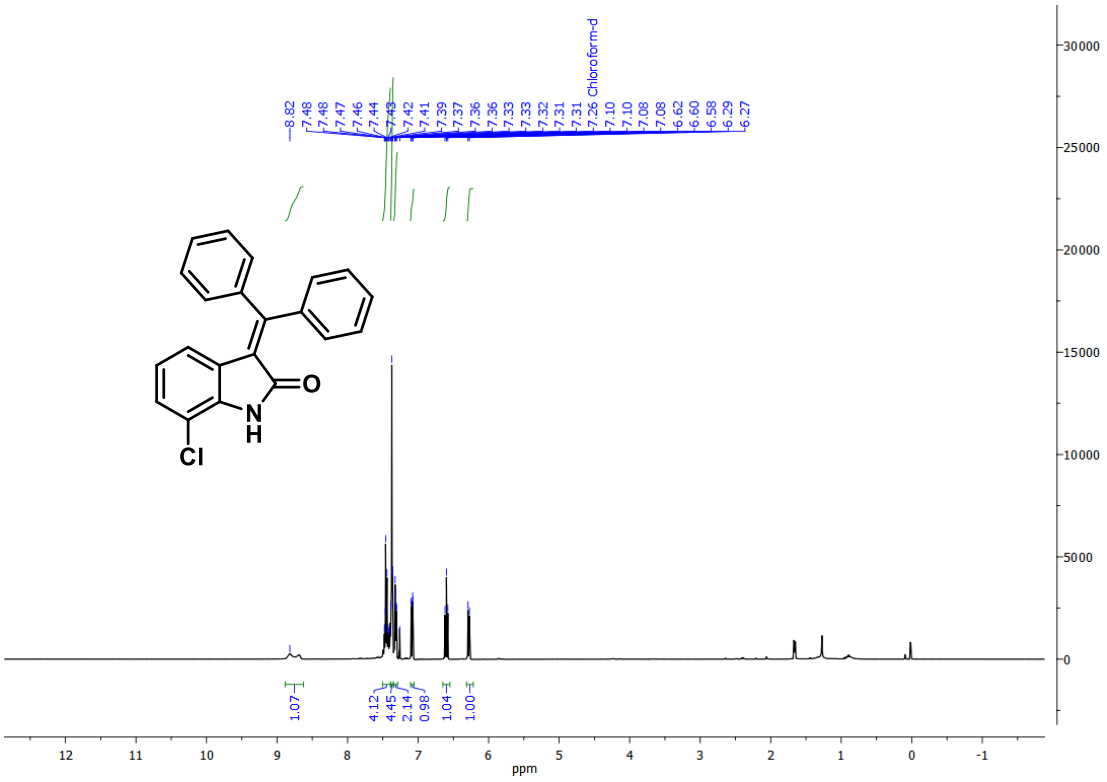


Figure 3.19. ^{1}H NMR of compound **3h**

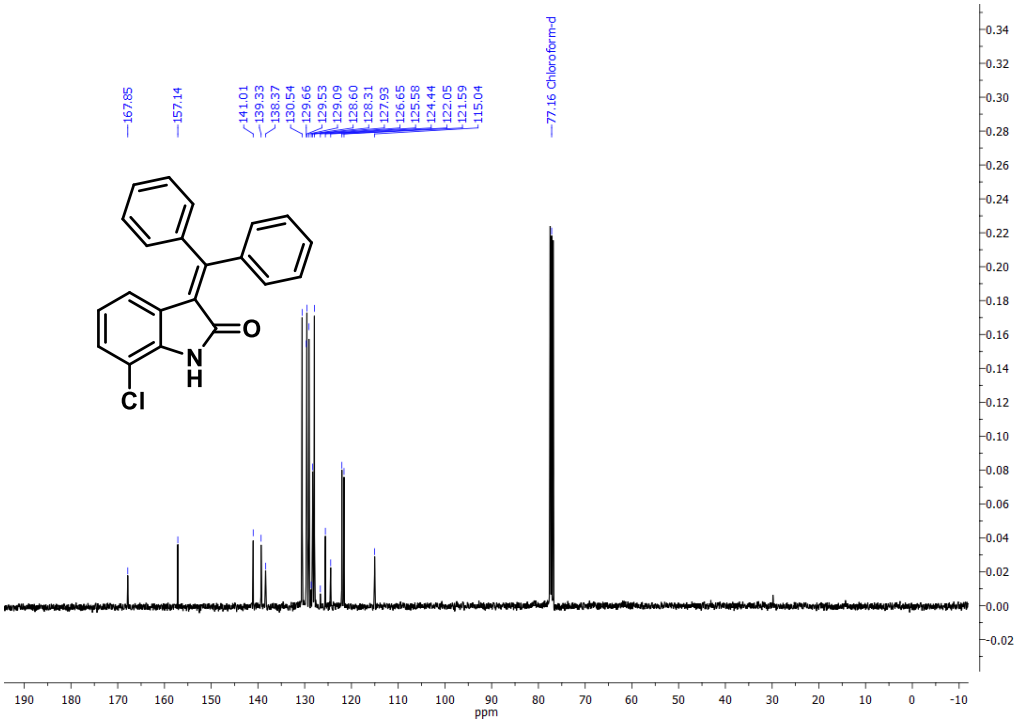


Figure 3.20. ^{13}C{^{1}H} NMR of compound **3h**

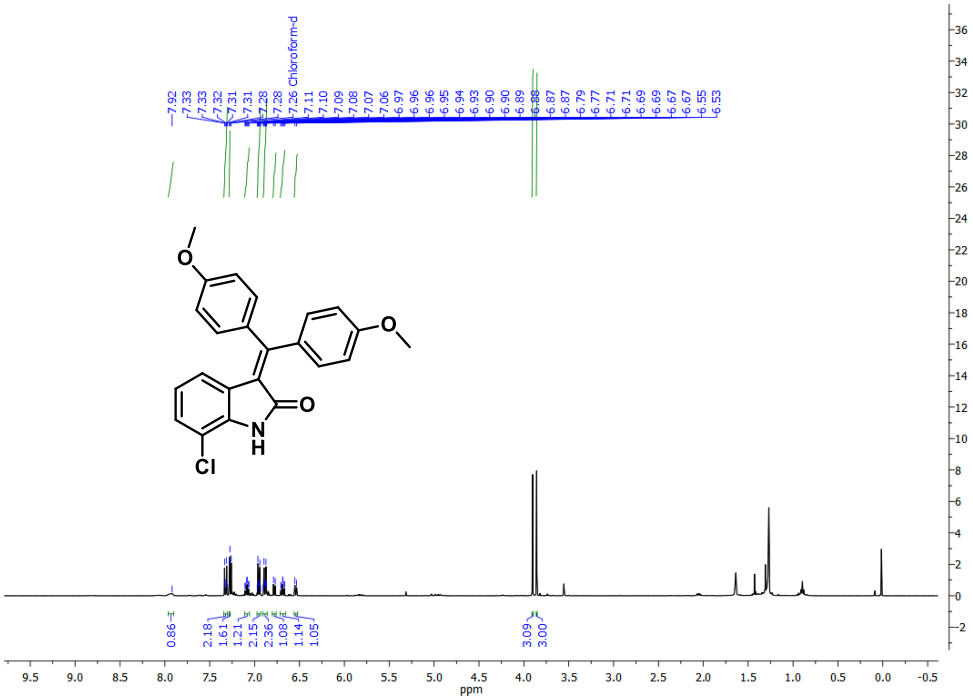


Figure 3.21. ^{1}H NMR of compound **3j**

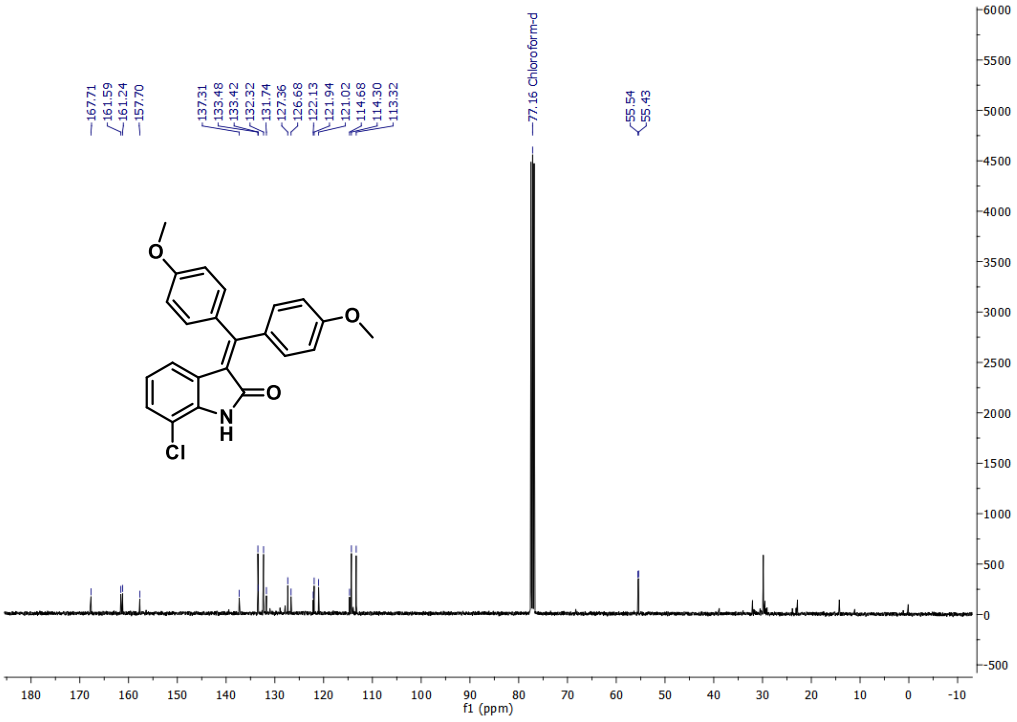


Figure 3.22. ^{13}C{^{1}H} NMR of compound **3j**

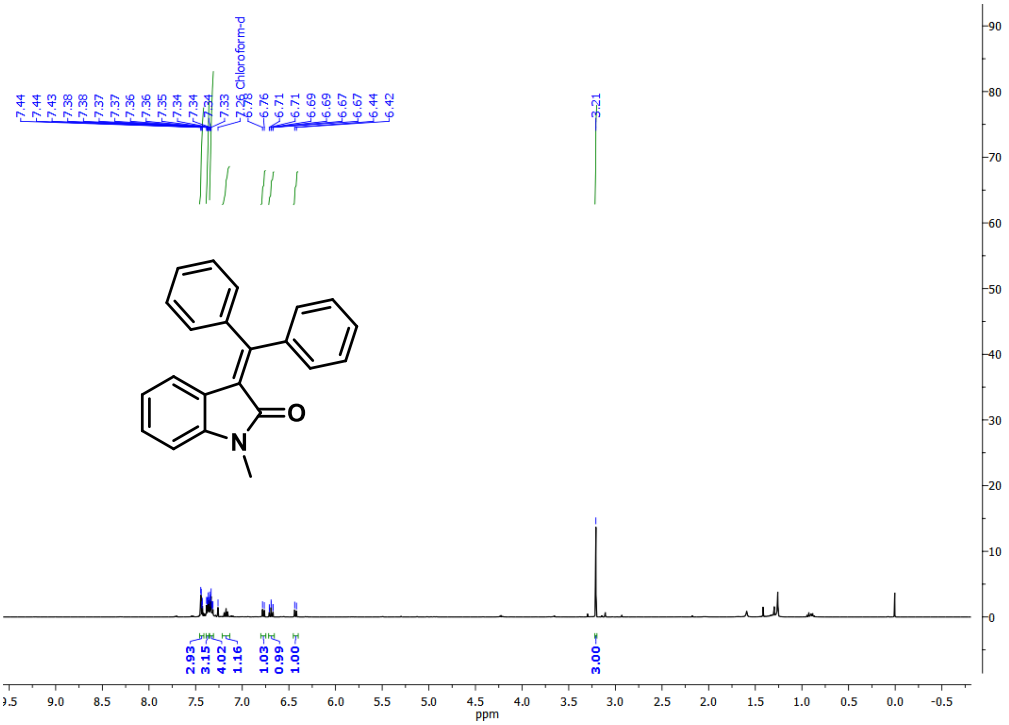


Figure 3.23. ^{1}H NMR of compound **6a**

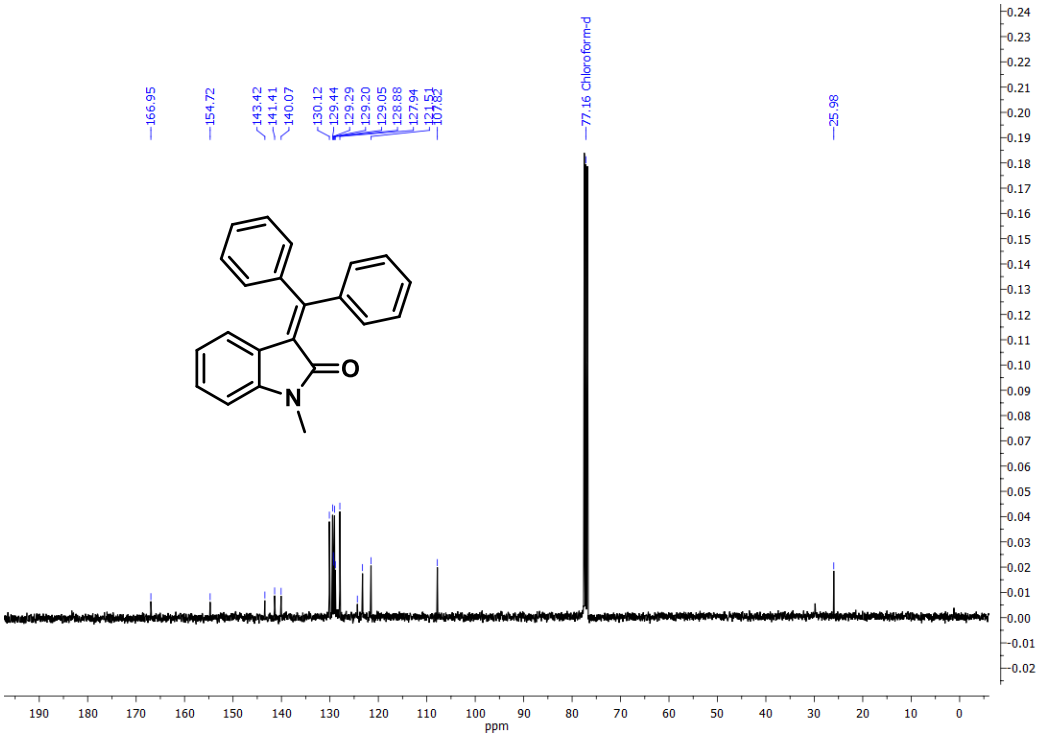


Figure 3.24. ^{13}C{^{1}H} NMR of compound **6a**

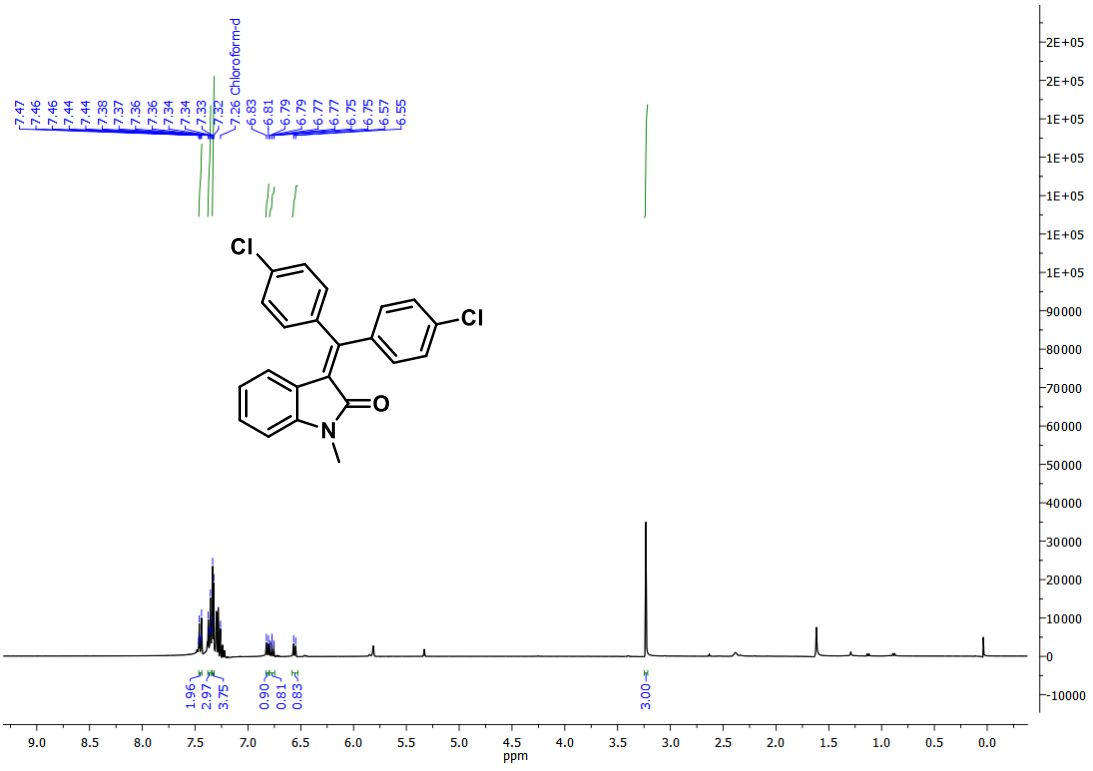


Figure 3.25. ^{1}H NMR of compound **6c**

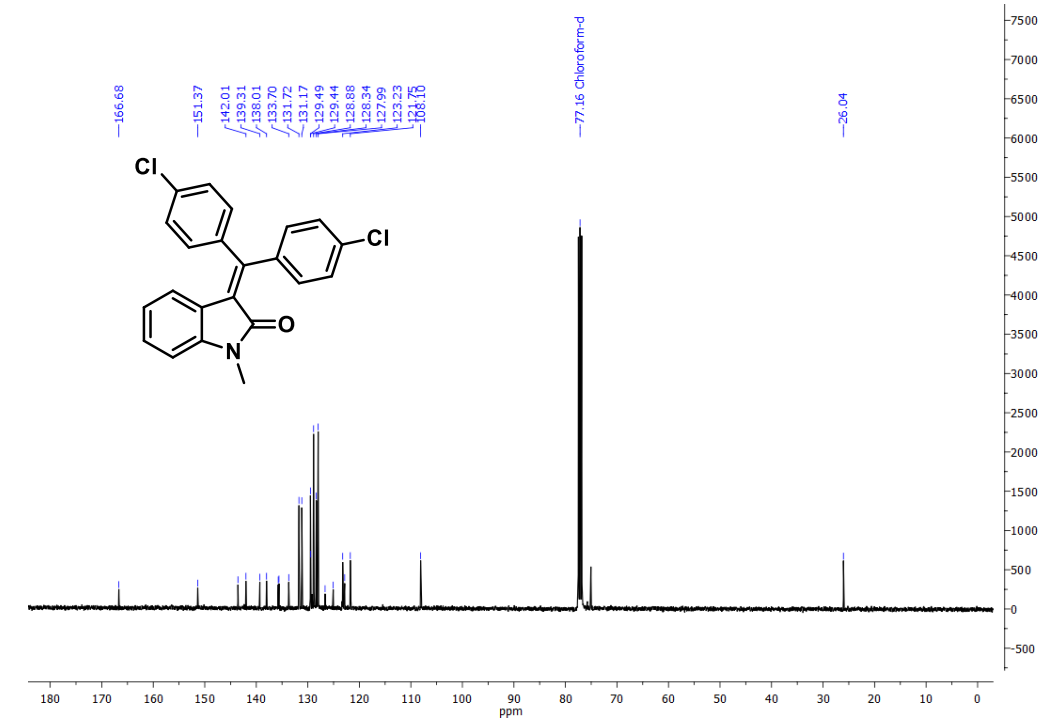


Figure 3.26. ^{13}C{^{1}H} NMR of compound **6c**

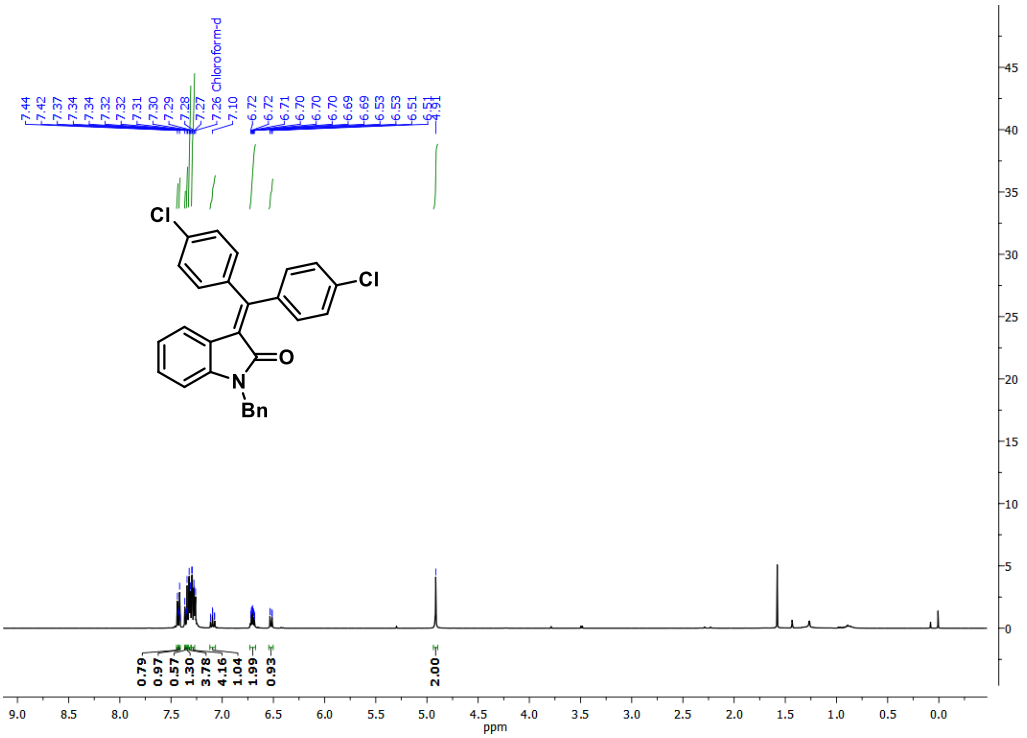


Figure 3.27. ^{1}H NMR of compound **6h**

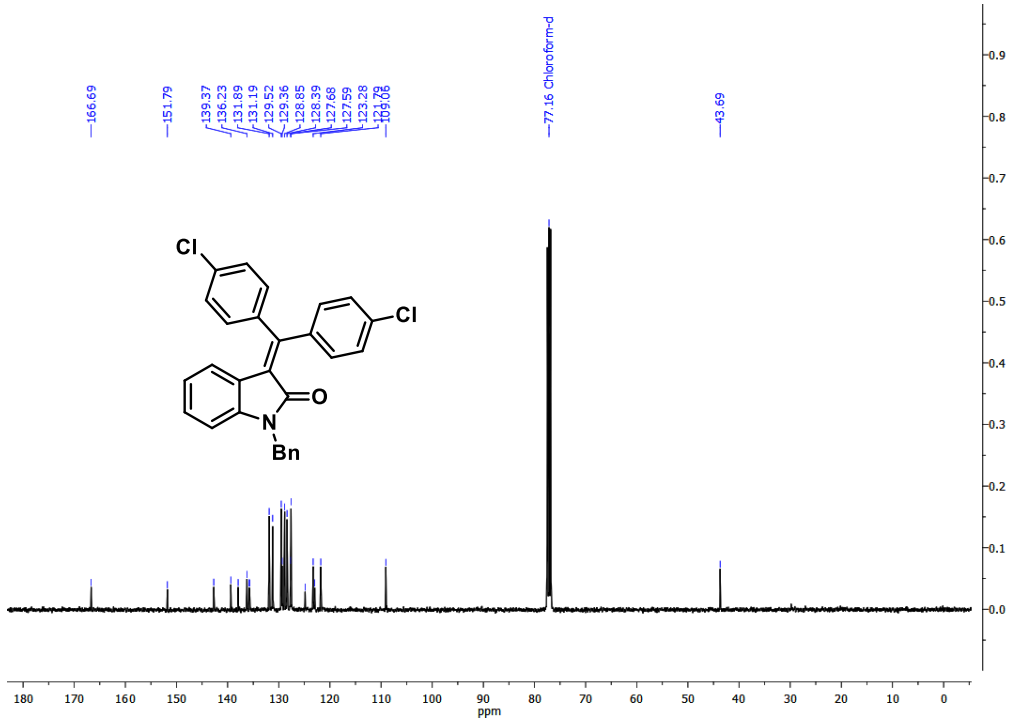


Figure 3.28. ^{13}C{^{1}H} NMR of compound **6h**

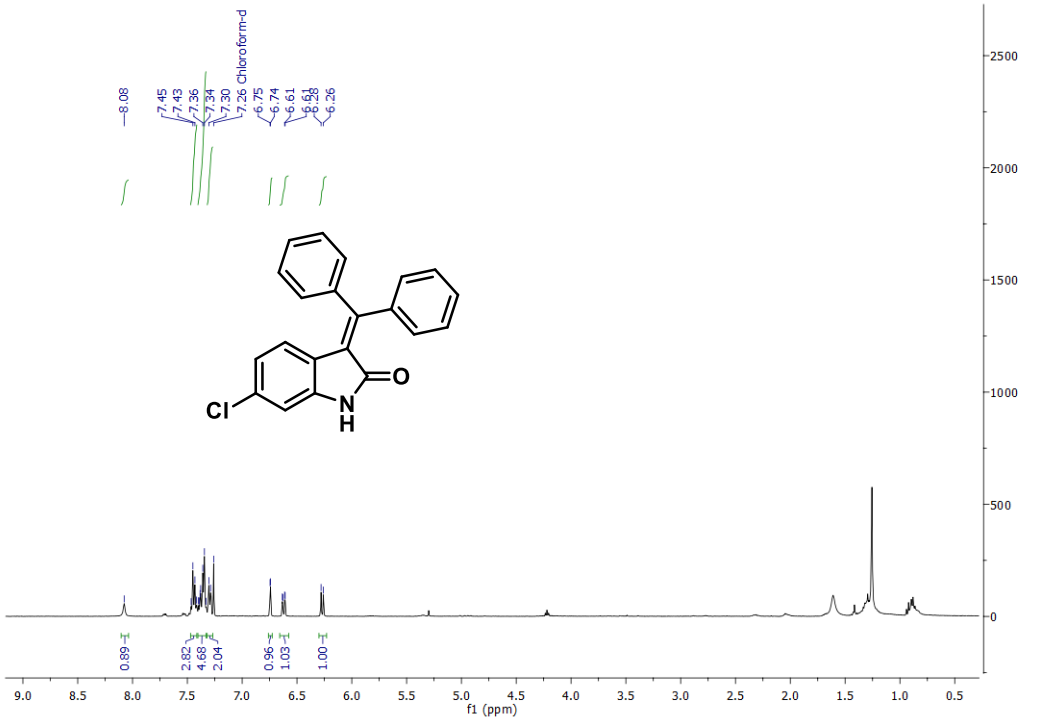


Figure 3.29. ^{1}H NMR of compound **6i**

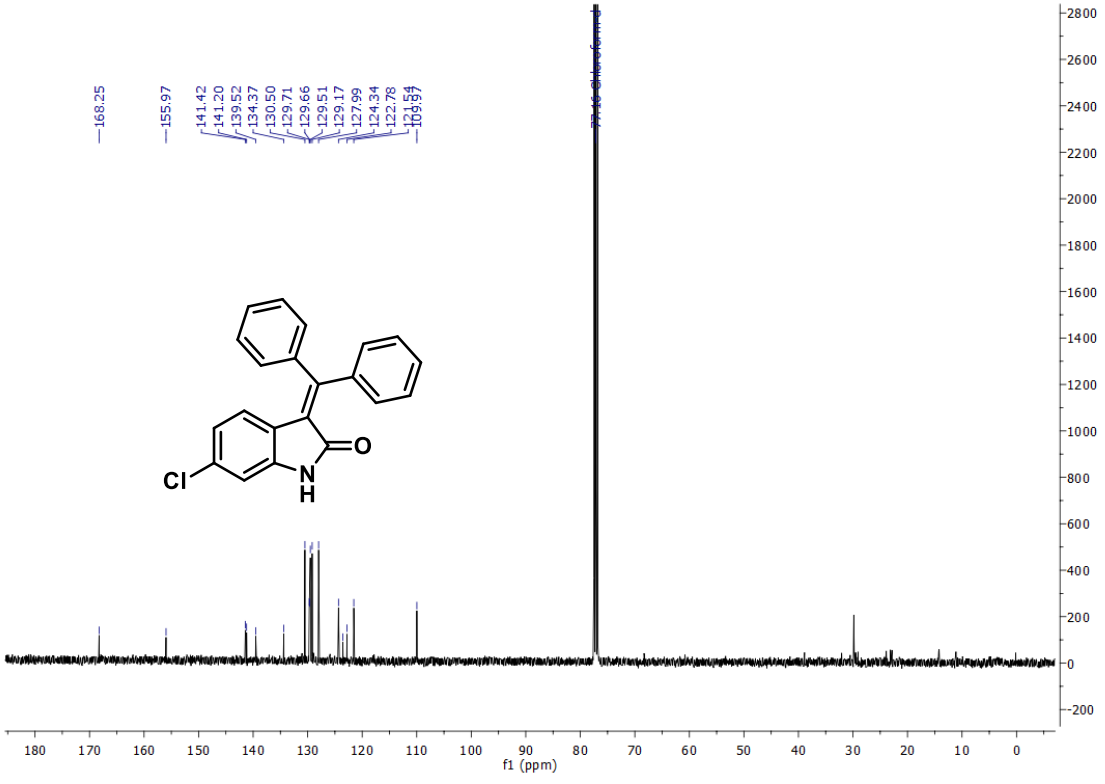


Figure 3.30. ^{13}C{^{1}H} NMR of compound **6i**

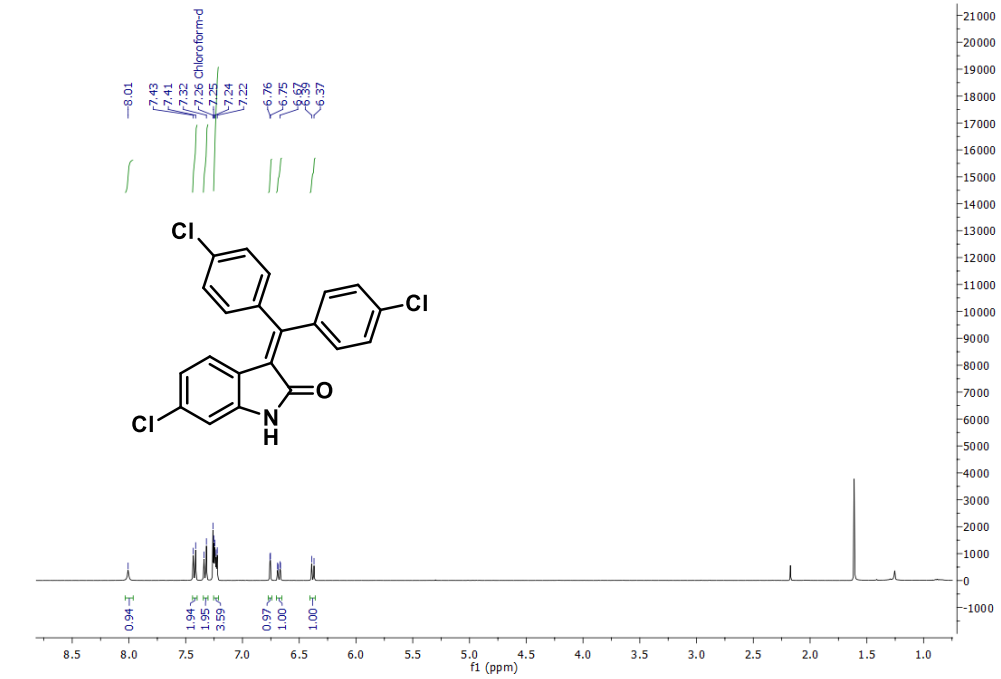


Figure 3.31. ^{1}H NMR of compound **6k**

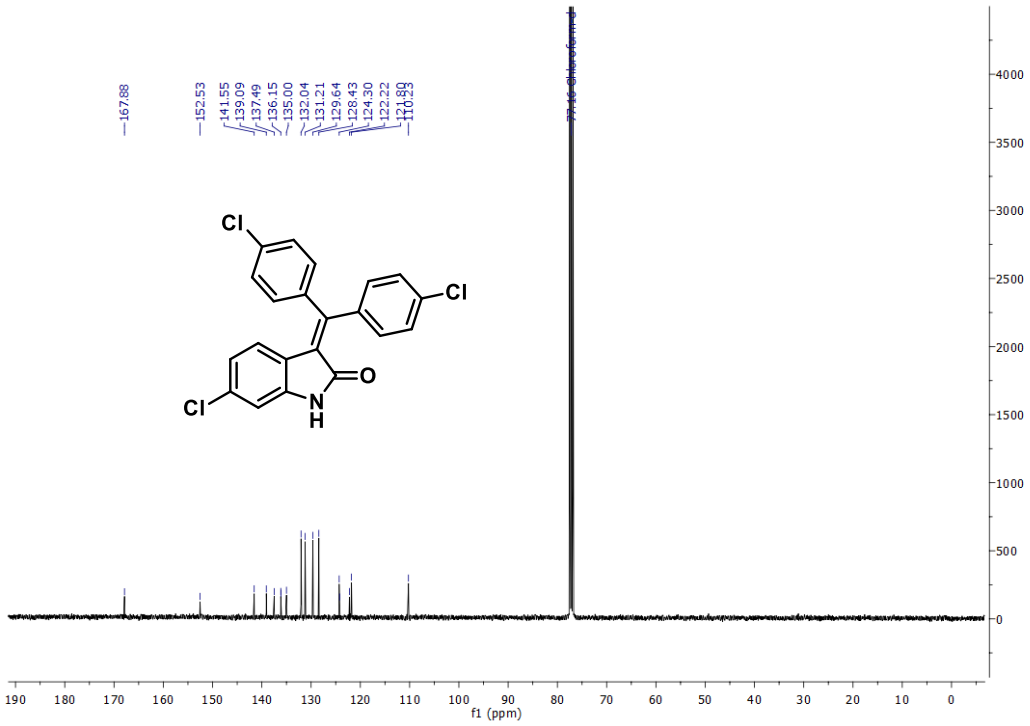


Figure 3.32. ^{13}C{^{1}H} NMR of compound **6k**

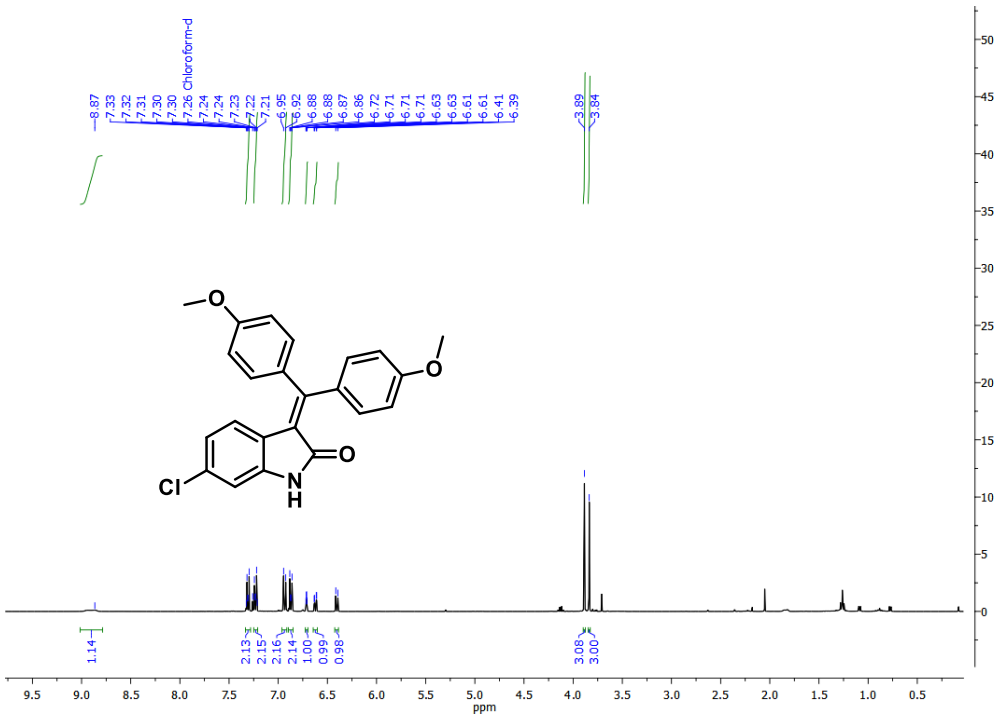


Figure 3.33. ^{1}H NMR of compound **6n**

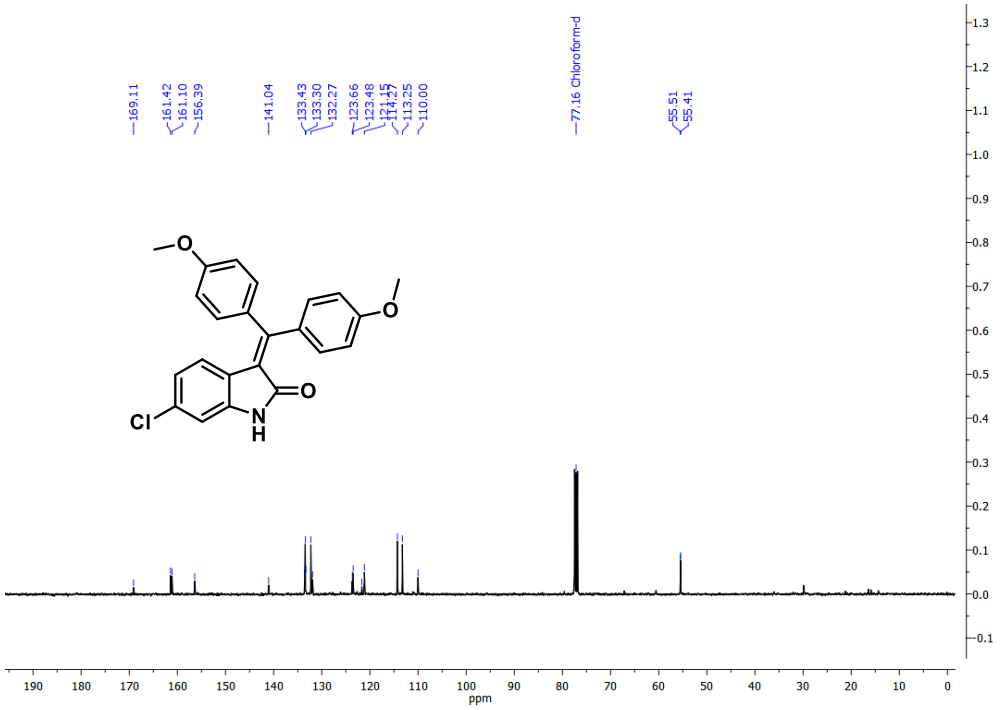


Figure 3.34. ^{13}C{^{1}H} NMR of compound **6n**

3.12. References:

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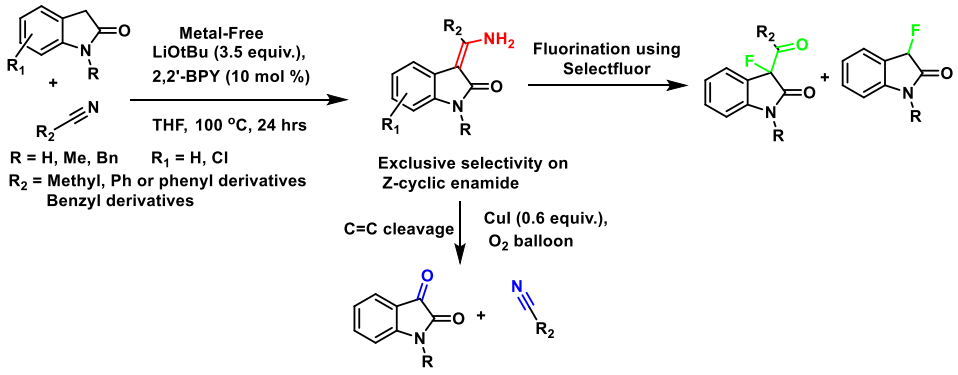
Chapter 4

Transition-Metal-Free Addition Reaction of 2-Oxindole to Nitrile: A Synthetic Application towards Fluorination and C=C Cleavage

Transition-Metal-Free Addition Reaction of 2-Oxindole to Nitrile: A Synthetic Application towards Fluorination and C=C Cleavage

4.1. Abstract

In the present chapter, we have developed a novel, efficient, and transition-metal-free method for the synthesis of *Z*-3-(aminobenzylidene/aminoalkylidene)indolin-2-one derivatives in good to excellent yields from 2-oxindole and aryl/alkyl nitrile by using LiO*t*Bu and 2,2'-bipyridine system. The application of these compounds was demonstrated towards the base and additive-free fluorination by using selectfluor as well as the oxidative cleavage of C=C bond using CuI in the presence of environmentally benign molecular oxygen as an oxidant. Additionally, Cu-catalyzed Ullmann coupling was demonstrated by using enaminones and aryl bromide towards the synthesis of the drug skeleton.



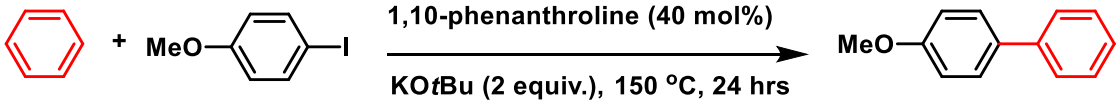
4.2. General introduction

Nitriles are abundant, inexpensive, and structurally distinctive, making them one of the most frequently used precursors in a myriad number of chemical transformations. Nitriles are important in both academic and industrial applications owing to their well-recognized diverse chemical reactivity.[1] Addition reaction is one of the basic, important, and widely used reactions in organic chemistry. Also, it is considered as a green reaction since it leads to the formation of less number of byproducts and has a high atom economy.[2] Among several reactions, the addition reaction of nucleophilic carbon to nitrile has been used extensively in synthetic organic chemistry. In particular, the addition reaction of α-carbon nucleophiles,

generated from carbonyl compounds, with nitriles to construct bioactive enaminones is an appealing transformation for the construction of heterocyclic compounds.[3] In literature, numerous protocols have been reported for the synthesis of enaminones by C-nucleophilic addition to nitriles such as - i) *via* C−H activation by using Iridium complexes;[4] ii) Lewis acid assisted reaction of 1,3-dicarbonyl and nitriles[5]; iii) Zn and Ti catalyzed addition reaction[6] and other miscellaneous reactions.[7] Interestingly, in 2013, Yu and co-workers developed a CuI-2,2'-BPY metal-ligand assisted synthesis of enaminones.[8] Recently, Rao and Hilt's group reported the synthesis of enaminones by a modification of the classical Blaise reaction *via* in situ generations of organo Zn nucleophiles.[9] Additionally, the transition metal-mediated addition reaction of nitrogen nucleophile to nitrile for accessing synthetic intermediates, common building blocks, and materials are also well studied.[10]

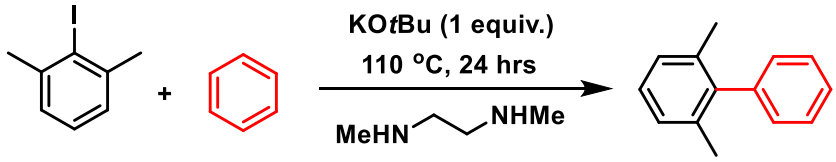
4.3. KO*t*Bu: A well-known base and reagent for SET reactions

Alkali metal *tert*-butoxides bases such as KO*t*Bu, LiO*t*Bu, and NaO*t*Bu are typically used as a powerful base in organic synthesis. KO*t*Bu has been frequently used for assisting many chemical transformations such as, alkylation, condensations, and rearrangement reactions.[11] Additionally, it has been used as an additive in many transition metal-mediated coupling reactions.[12] Interestingly, in recent years, KO*t*Bu base has been identified as a reagent for single electron transfer reactions.[13] For instance, in 2010 Shi and co-workers developed a metal-free cross-coupling reaction of aryl halide and arenes in the presence of KO*t*Bu base and 1,10-phenanthroline ligand (Scheme 4.1).



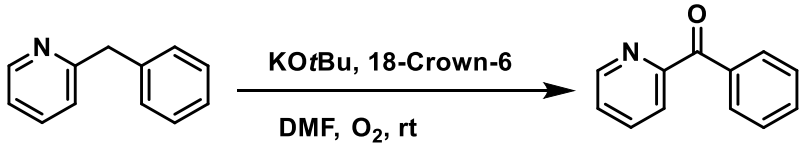
Scheme 4.1. Shi's approach for the coupling of aryl halide with benzene

In the mechanistic investigation, it was identified that the reaction proceeded *via* a single electron transfer pathway (Scheme 4.2).[14]



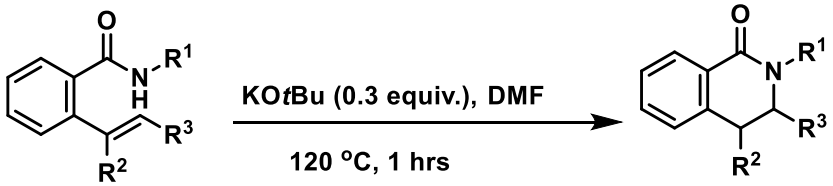
Scheme 4.2. Murphy's approach for the coupling of haloarenes with arenes

Later in 2014, Murphy and co-workers reported the coupling of haloarenes to arenes in the presence of KO*t*Bu or NaO*t*Bu.[15] In addition to coupling reactions, KO*t*Bu has been used in oxidation chemistry. In 2016, Xu and co-workers reported benzylic oxidation reaction in the presence of a green oxidant such as, oxygen and the additive potassium *tert*-butoxide (Scheme 4.3).[16]



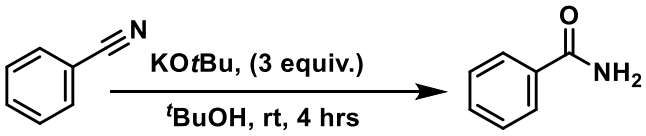
Scheme 4.3. Xu's approach for the benzylic oxidation using KO*t*Bu

In 2017 Zhang and co-workers reported the transition metal-free intramolecular hydroamidation reaction of 2-vinyl benzamide derivatives assisted by KO*t*Bu and DMF (Scheme 4.4).[17]



Scheme 4.4. Zhang's method for the transition metal-free C−N bond forming reaction

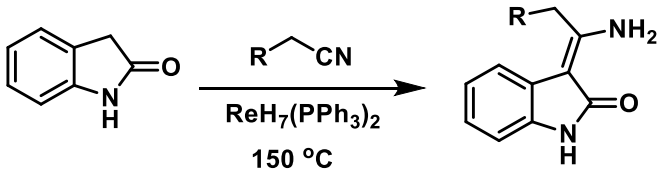
Recently, Dash and co-workers reported the metal-free conversion of nitrile to amide by using KO*t*Bu under anhydrous condition (Scheme 4.5).[18]



Scheme 4.5. Dash's approach for the conversion of nitrile to amide

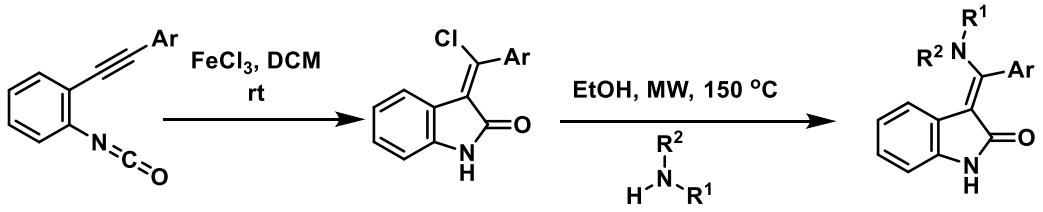
4.4. Literature background for the synthesis of 3-(aminomethyl)indolin-2-one derivatives

3-(aminobenzylene)indolin-2-one derivatives has been found in the core of several bioactive compounds. Considering the importance of the synthesis 3-(aminobenzylene)indolin-2-one, various methods were reported in the literature. In 2009, C−H activation strategy was used by Murahashi research group by using a hydride complex of Re for the generation of 3-(1-amino-2-methoxyethylidene)indolin-2-one. In this transformation, they used a catalyst comprising an expensive metal (Scheme 4.6).[19]



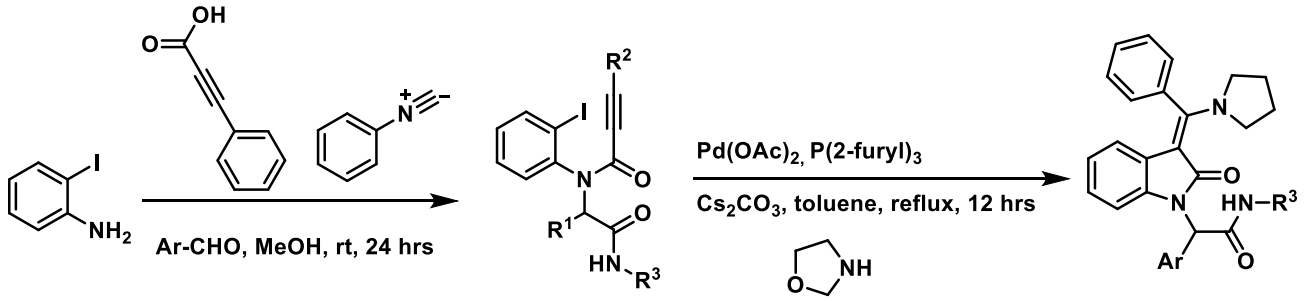
Scheme 4.6. Murahashi's approach for the synthesis of 3-(1-amino-2-methoxyethylidene)indolin-2-one *via* C−H activation

Later, in the same year, Cossy and Meyer collectively reported a $FeCl_3$ assisted cyclization of *o*-(arylethynyl)aryl isocyanates to generate 3-(arylchloromethylene)oxindoles, which were further treated with an amine derivative under microwave condition to produce stereoselective (*Z*)-3-(aminoarylmethylene)oxindoles derivatives. In this report, isocyanides were taken as the starting material and multiple steps were required for the generation of (aminoarylmethylene)oxindoles (Scheme 4.7).[20]



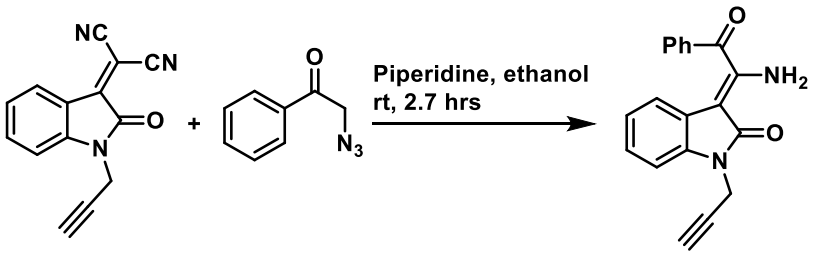
Scheme 4.7. Cossy's strategy for the synthesis of 3-(aminoarylmethylene)oxindoles

In 2010, Balalaie and co-workers reported palladium assisted multi-component reaction strategy for the stereoselective synthesis of 3-(aminoarylmethylene)oxindoles. In this context, Ugi 4-component reaction adducts were used as starting materials, involving carbopalladative cyclization-Buchwald reaction sequences (Scheme 4.8).[21]



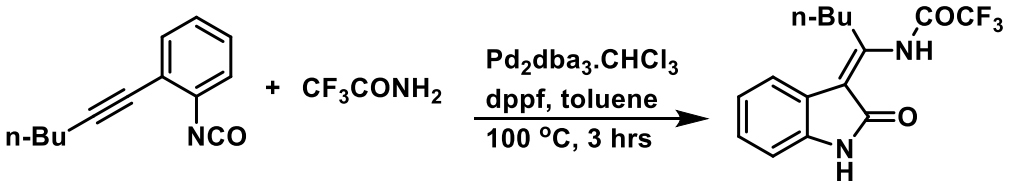
Scheme 4.8. Balalie's method for the synthesis of 3-(aminoarylmethylene)oxindoles

Later in 2012, Perumal and co-workers prepared 3-(aminomethylene)oxindoles by using prefunctionalized oxindole and α-azido ketones *via* the Michael addition subsequent to the conversion of azide to amine (Scheme 4.9).[22]



Scheme 4.9. Perumal's method for the synthesis of 3-(aminomethylene)oxindoles

In 2013, Murakami and co-workers achieved the stereoselective synthesis of 3-(amidoalkylidene)oxindoles, using 2-(alkynyl)aryl isocyanates with amides in the presence of a palladium(0)/diphosphine ligand system. Metal catalyst and air-sensitive phosphine ligand were used in this transformation (Scheme 4.10).[23]



Scheme 4.10. Murakami's method for 3-(amidoalkylidene)oxindoles synthesis

4.5. The rationale behind the present work

Derivatives of 3-(aminomethyl)indolin-2-one are used as useful intermediates in the synthesis of natural products.[24] Moreover, it has been found that the application of such analogs is immensely valuable in medicinal chemistry. For instance, this scaffold is responsible for various biological activities such as anticancer, antiviral intoxicating antifungal, *etc.* Hesperidin molecule identified Aurora B inhibitor and Nintedanib (Ofev) and BIBF 1000 used for the treatment of idiopathic pulmonary fibrosis (IPF) (Figure 4.1).[25]

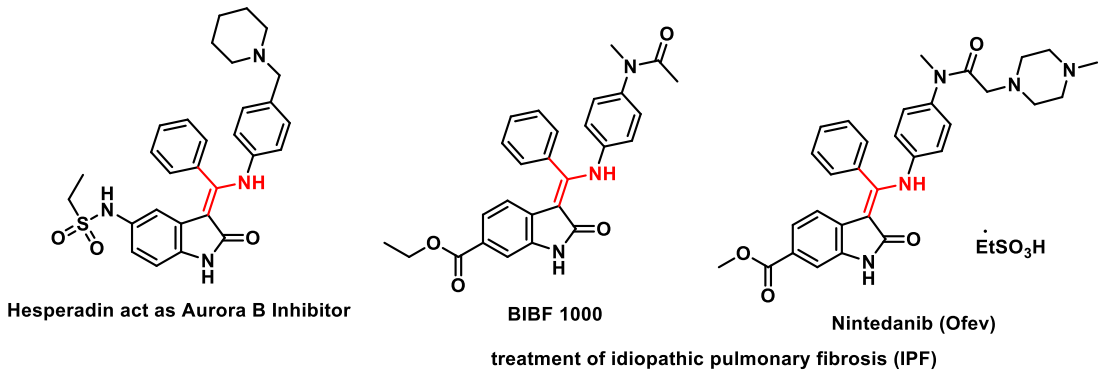


Figure 4.1. Bioactive derivatives of 3-(aminoarylidene)indolin-2-one

Many literature reports are available for the synthesis of 3-(aminomethyl)indolin-2-one derivatives. Although the reported methods were efficient, the methods have certain shortcomings, such as, the use of pre-functionalized starting materials, the use of toxic starting materials like isocyanate, the requirement of transition-metals, and the necessity of multiple steps.[19-22] Moreover, organic moieties containing fluorine atom have drawn the attention of synthetic chemists, due to their importance in agrochemical and pharmaceutical fields.[26] In literature, there are a few methods reported for the synthesis of 3-fluoro-2-oxindoles and its derivatives.[27] However, there is no report for the synthesis of 3-acetyl/benzoyl-3-fluoroindolin-2-one derivatives. In modern chemical synthesis, transition-metal-free reactions are of considerable importance due to their many advantages over metal-mediated reactions.[28] Metal-mediated reactions face several limitations such as, i) transition metal complexes are usually expensive; ii) metal-mediated reactions are not suitable for pharmaceuticals because of the separation difficulty of transition-metal residues from desired products; iii) less natural abundance, and a high sensitivity toward air/moisture. Keeping these disadvantages in mind, there is a demand for a new and metal-free practice for the synthesis of 3-(aminoalkylidene)oxindoles. Besides, there is a need for an additive-free approach for the synthesis of 3-acetyl/benzoyl-3-fluoroindolin-2-one derivatives.

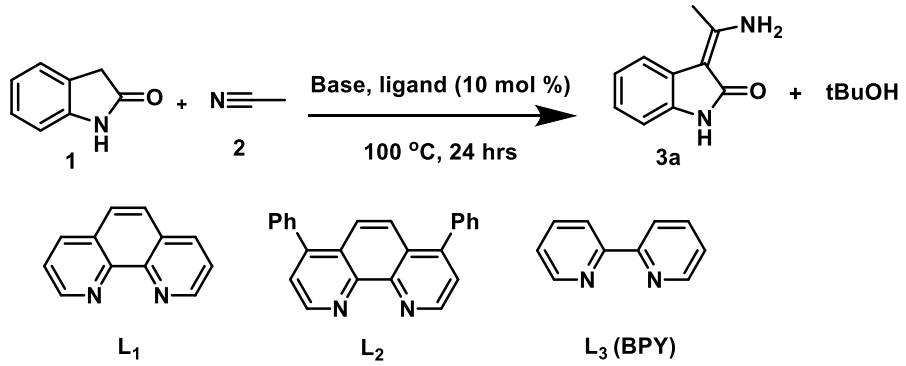
4.6. Results and discussion

Herein, we have reported a transition metal-free synthesis of 3-(aminobenzylidene/aminoalkylidene)indolin-2-ones from 2-oxindole and nitrile using LiO*t*Bu/2,2′-bipyridine base ligand system. This method provides direct synthesis of the cyclic enamide without pre-functionalization of starting material 2-oxindole. This method allowed us to use easily accessible, inexpensive starting material, commercially available base, and bench stable ligand.

4.6.1. Optimization studies

To establish a procedure for the synthesis of 3-(aminobenzylidene/aminoalkylidene)indolin-2-ones, we started optimization by heating a ACN solution to 100 ^{o}C containing 2-oxindole and LiO*t*Bu/2,2′-bipyridine as a model reaction. A control experiment was performed by heating the reaction mixture containing 2-oxindole, acetonitrile (ACN), and a catalytic amount of phenanthroline or 2,2′-BPY, in absence of a base, results in no reaction (Table 4.1, entry 1).

Table 4.1. Optimization for the addition reaction of 2-oxindole and acetonitrile[a]



Entry	Base (equiv.)	Ligand (mol %)	Yield (%)
1	—	Phenanthroline/2,2′-Bipyridine	no reaction
2	Cs_2CO_3 (1 equiv.)	Phenanthroline	no reaction
3	K_2CO_3 (1 equiv.)	Phenanthroline	no reaction
4	KOH (1 equiv.)	Phenanthroline	Traces
5	KO*t*Bu (1 equiv.)	Phenanthroline	25
6	KO*t*Bu (1 equiv.)	Bathophenanthroline	10
7	KO*t*Bu (1 equiv.)	2,2′-Bipyridine	30
8	KO*t*Bu (2 equiv.)	2,2′-Bipyridine	35
9	NaO*t*Bu (2 equiv.)	2,2′-Bipyridine	40
10	LiO*t*Bu (2 equiv.)	2,2′-Bipyridine	60
11	LiO*t*Bu (3.5 equiv.)	2,2′-Bipyridine	65
12[b]	LiO*t*Bu (3.5 equiv.)	2,2′-Bipyridine	no reaction
13[c]	LiOtBu (3.5 equiv.)	2,2′-Bipyridine	no reaction
14[d]	LiOtBu (3.5 equiv.)	2,2′-Bipyridine	15
15[e]	LiOtBu (3.5 equiv.)	2,2′-Bipyridine	Traces
16[f]	**LiOtBu (3.5 equiv.)**	**2,2′-Bipyridine**	**65**
17[f]	LiO*t*Bu (3.5 equiv.)	-	46

Reaction Conditions: [a]ligand (0.025 mmol), 2-oxindole (0.25 mmol), base (see table) and dry acetonitrile (2 mL) were heated in a sealed tube for 24 hrs. [b]2 mL of DMF was used as a solvent. [c]2 mL of DMSO was used as a solvent. [d] 2 mL of 1,4-dioxane was taken as a solvent. [e]2 mL of toluene was taken as a solvent. [f]2 mL of THF was taken as a solvent.

Reaction with carbonate salts such as Cs_2CO_3, K_2CO_3, failed to give 3-(aminoethylidene)indolin-2-one **3a** (Table 4.1, entries 2 & 3). While this reaction with

KOH results in a trace amount of desired product **3a**. Interestingly, the addition of KO*t*Bu results in a slight improvement in the yield of product **3a** (Table 4.1, entry 5). On changing ligand to bathophenanthroline (**L_2**) a decrease in yield was noticed (Table 4.1, entry 6). Interestingly, the addition of 2,2′-bipyridine ligand (**L_3**), product **3a** was isolated in 30% yield (Table 4.1, entry 7). Further increasing the quantity of base a slight increase in yield was observed (Table 4.1, entry 8). After finding satisfactory results with *tert*-butoxide base, we further change the counter cation of base. Thus when the reaction was performed with 2 equiv. of NaO*t*Bu & LiO*t*Bu, 40% & 60% yield was observed respectively (Table 4.1, entries 9 and 10). Upon increasing the amount of LiO*t*Bu from 2 to 3.5 equiv., a slight increase in yield was observed (Table 4.1, entry 11). After obtaining satisfactory yield with acetonitrile, the solvent study was performed by heating a reaction mixture containing 0.6 ml of acetonitrile, oxindole, ligand, and base. Polar solvents such as DMF and DMSO was inefficient to give the desired product **3a** (Table 4.1, entries 12 & 13). The poor yield was observed in the case of 1,4-dioxane as a solvent (Table 4.1, entry 14). Trace amount of product was observed when toluene was taken as a solvent. Gratifyingly, by using THF as a solvent in this addition reaction afforded 65% yield of the product **3a** (Table 4.1, entry 16). Moreover, 46% yield was observed when the reaction was performed in absence of ligand. With optimized conditions in hand, we started to survey the substrate scope for the transition-metal-free addition reaction. Thus, the reaction of 2-oxindole with ACN provided 3-(1-aminoethylidene)indolin-2-one **3a** in 65% yield. The product **3a** was well characterized by spectroscopic techniques and x-ray analysis (Figure 4.2). To our delight, this reaction afforded exclusively Z-selective product **3a** which might be due to the hydrogen bonding of amine with amide carbonyl group. Furthermore, deuterated acetonitrile afforded corresponding deuterated derivative **3a'** in 62% yield. Upon reaction of 2-oxindole with benzonitrile, product **3b** was isolated in 70% yield. Moreover, in case of (4-chlorophenyl)acetonitrile, addition reaction proceeded smoothly to yield the desired product **3c** in 74%. Likewise, when this reaction was examined with substituted oxindole, for instance, 7-chloro-2-oxindole and 6-chloro-2-oxindole proceeded smoothly. Thus, the reaction of 7-chloro-2-oxindole with benzonitrile and 3-bromobenzonitrile afforded the respective products **3d, 3e** in 60% and 84% yield respectively. Furthermore, this transformation was tolerant to a functional group, for instance, highly electron-withdrawing -CF_3 group to afford product 3-(amino(4-(trifluoromethyl)phenyl)methylene)-7-chloroindolin-2-one **3f** in 83% yield. Similarly, the reaction of 6-chloro-2-oxindole with acetonitrile, 3-bromobenzonitrile, and 4-(trifluoromethyl)benzonitrile afforded corresponding products **3g**, **3h, 3i** in 30%, 75%, and 30% yield respectively.

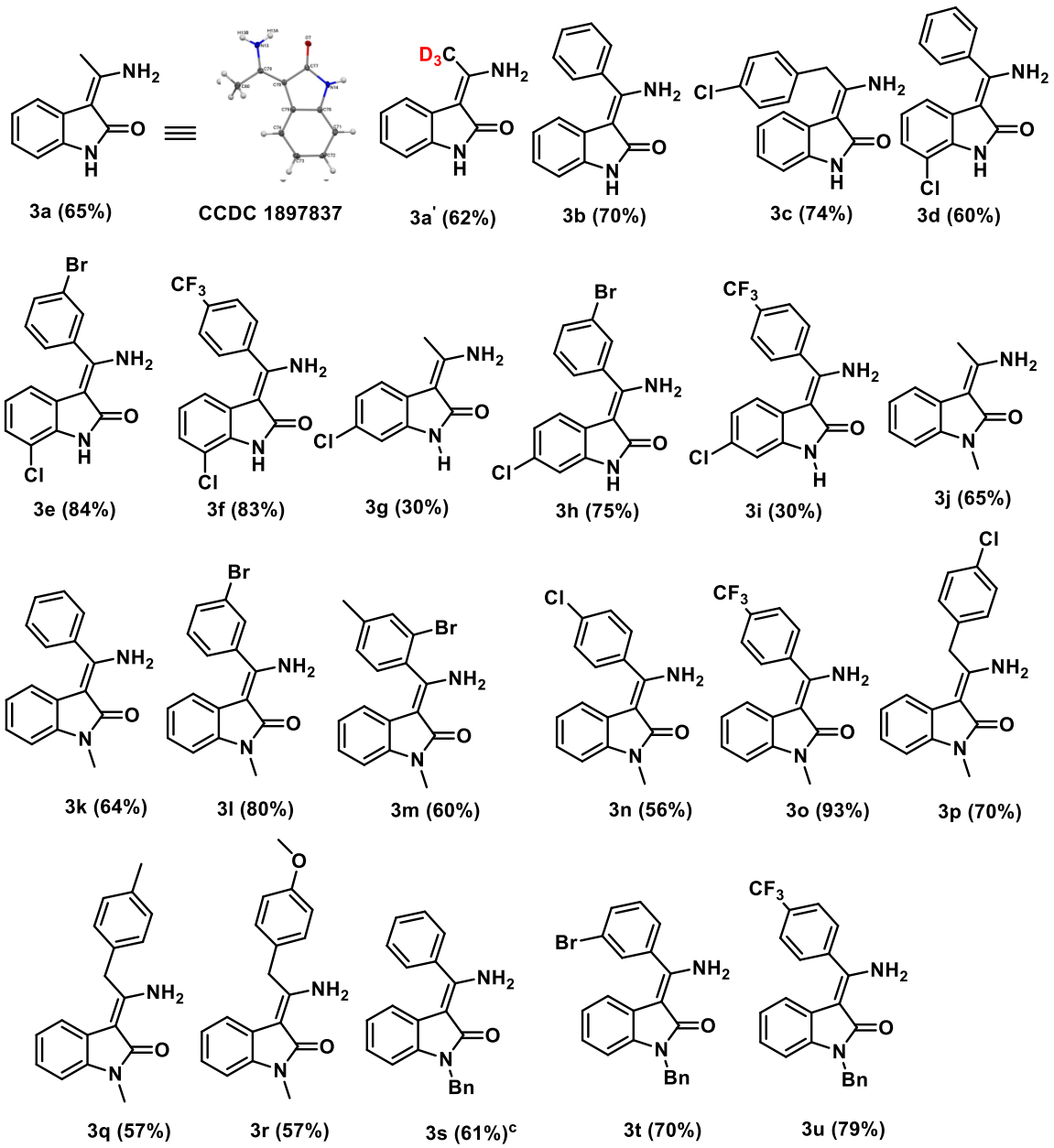


Figure 4.2. Substrate scope for base assisted addition reaction[a]

[a]**Reaction conditions:** 2-oxindole (0.25 mmol), nitrile (0.5 mmol), 2,2′-bipyridine (0.025 mmol) and THF (2 mL) were heated in a sealed tube at 100 [o]C for 24 h. [b]In case of substrate **3b**, **3k**, and **3s**, 4 equiv. of benzonitrile has been taken. [c]In case of substrate **3s** large-scale synthesis (i.e., 223 mg, 1 mmol scale) has been performed.

In the case of lower yield reactions, the starting material was recovered. The generality of this reaction was then investigated with *N*-protected oxindole. This approach was highly efficient for *N*-methyl-2-oxindole. Addition reaction of *N*-methyl-2-oxindole with acetonitrile, benzonitrile, and 3-bromobenzonitrile afforded corresponding products **3j, 3k, 3l** in 65%, 64%, and 80% yield respectively. Besides, substituted

nitrile such as 2-bromo-4-methylbenzonitrile afforded corresponding product **3m** in 60% yield. Further, when 4-(t rifluoromethyl)benzonitrile was treated with *N*-methyl oxindole afforded corresponding product **3o** in 93% yield. Moreover, the addition reaction was performed with aryl methyl nitriles namely, (4-chlorophenyl)acetonitrile, *p*-tolylacetonitrile and 4-methoxyphenylacetonitrile to furnish corresponding products **3p, 3q,** and **3r** in good yields. The transition metal-free reaction of 1-benzylindolin-2-one with nitriles proceeds smoothly to afford (*Z*)-3-(amino(aryl)methylene)-1-benzylindolin-2-one derivatives **3s-3u** in good yields.

4.6.2. Chemical reactivity of cyclic enamide

Next, we have investigated the reactivity of cyclic enamide. Installation of fluorine at 3-position of 2-oxindole represents a prime approach for the preparation of biologically active 3-fluorooxindole derivatives.

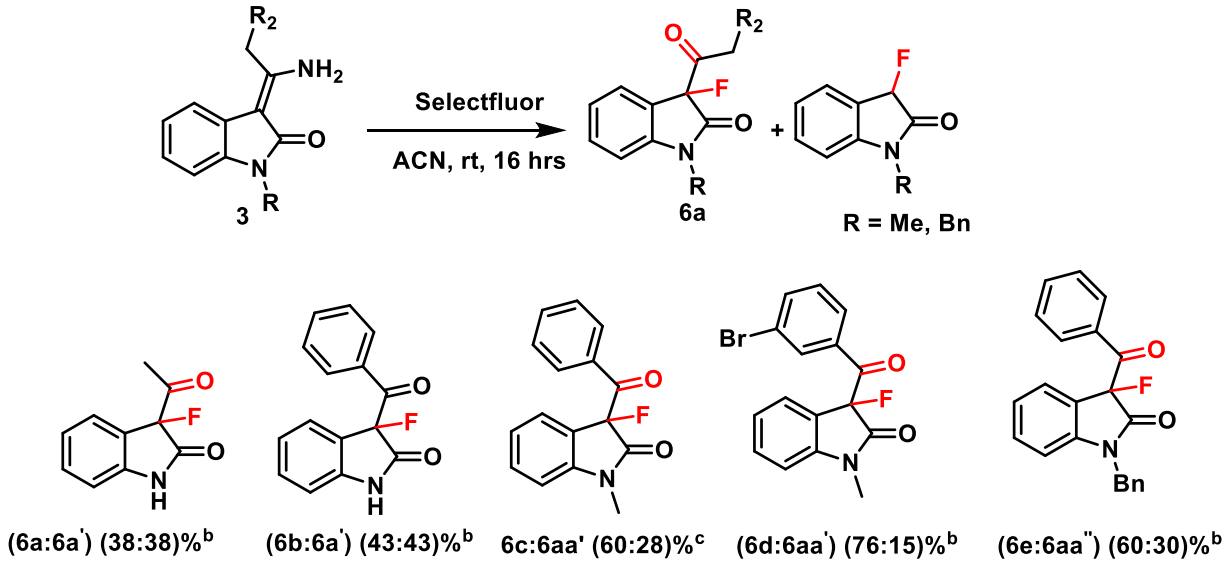


Figure 4.3a. Additive and base-free fluorination[a]

[a]**Reaction conditions for fluorination:** 3-(aminobenzylidene/aminoalkylidene)indolin-2-ones **3** (0.3 mmol), selectfluor (0.45 mmol) were kept at rt for 16 h. (In the case of **3a** methanol and ACN used as a solvent). [b]Mixture of product isolated and % yield calculated from NMR. [c]3-fluoro-1-methylindolin-2-one was separated from the mixture after washing with n- pentane.

In this regard, we examine synthetic applicability of synthesized 3-(aminobenzylidene/aminoalkylidene)indolin-2-ones for the synthesis of 3-fluoro-2-oxindole derivatives *via* sp^2 C=C functionalization. To our delight, when the selectfluor was added in acetonitrile (ACN) containing 3-

(amino(phenyl)methylene)indolin-2-one, after 16 hrs complete conversion of starting material was observed. The reaction mixture was purified by column chromatography to afford inseparable products **6a** and **6a'** (Figure 4.3a). The yield of the **6a** and **6a'** was determined from ^{1}H NMR.

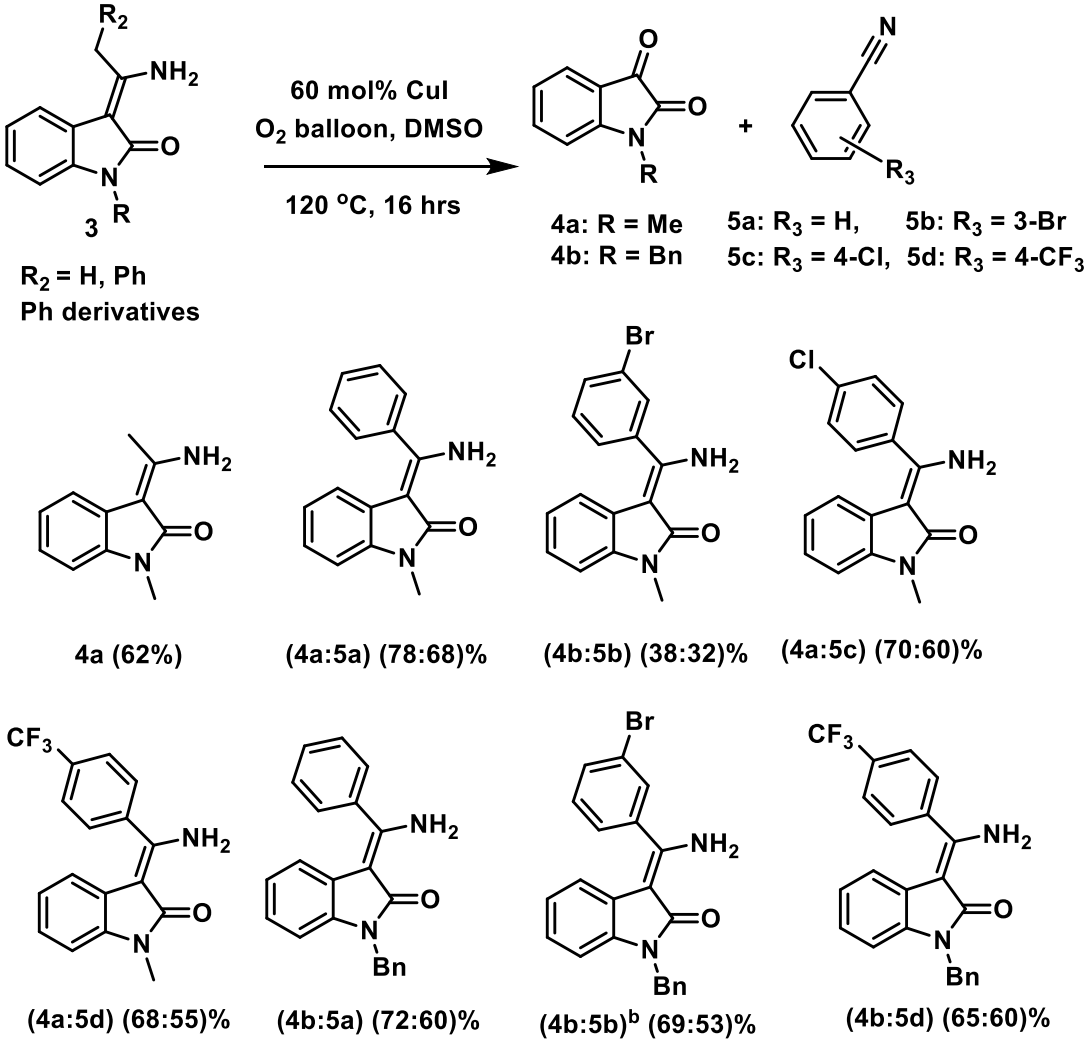


Figure 4.3b. C=C bond cleavage of using CuI and molecular oxygen[a]

[a]**Reaction conditions for the oxidative cleavage of C=C:** 3-(aminobenzylidene/aminoalkylidene)indolin-2-ones **3** (0.1 mmol), CuI (0.06 mmol), and DMSO (2 mL) were heated in a 10 mL round-bottom flask at 120 ^{o}C under an O_2 balloon for 16 h. The isolated yield of the corresponding *N*-protected isatin **4** is given. [b]Large-scale synthesis (i.e., 500 mg, 1.5 mmol scale) has been performed with these substrates.

To expand the scope of this method, other 3-(aminobenzylidene/aminoalkylidene)indolin-2-ones derivatives were subjected under similar reaction conditions to obtain corresponding products **6b, 6c,** and **6d** in

moderate to good yields (Figure 4.3a). The pure product of **6c** was obtained by recrystallization and confirmed by spectroscopic analysis.

The oxidative cleavage of C=C to provide corresponding carbonyl derivatives is one of the most fundamental transformation and ubiquitous approach used in organic chemistry. This transformation is well explored using various oxidants by using both metal and metal-free approaches to afford only carbonyl compounds.[29] To study the oxidative cleavage of the 3-(aminobenzylidene/aminoalkylidene)indolin-2-ones derivatives to get carbonyl compounds and nitrile, a set of reaction was studied by using metal and oxidants.

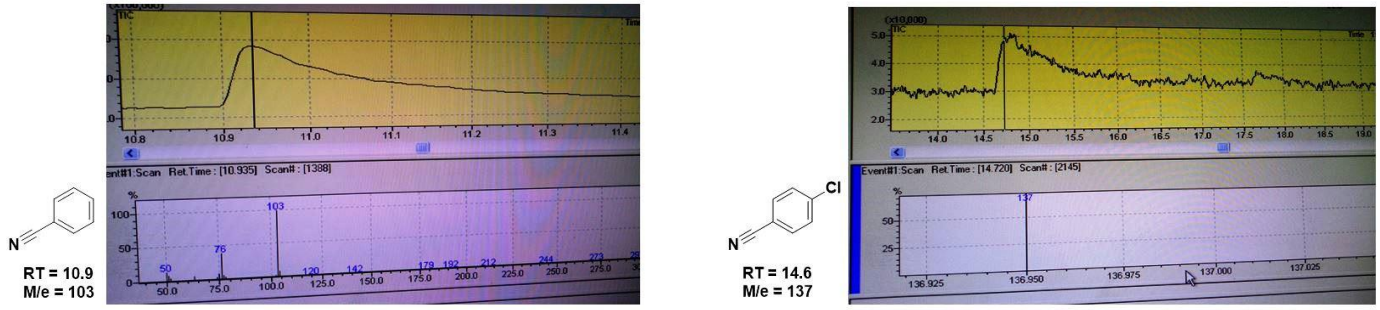


Figure 4.4. GC-MS spectra for benzonitrile and 4-chloro benzonitrile

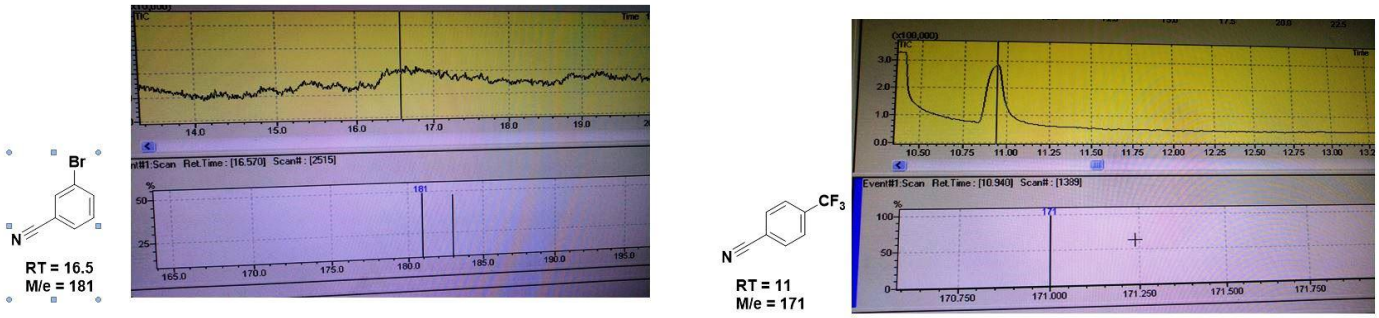


Figure 4.5. GC-MS spectra for 3-bromo benzonitrile and 4-trifluoro benzonitrile

Hence, we investigated Cu-mediated C=C bond cleavage of 3-(aminobenzylidene/aminoalkylidene)indolin-2-ones derivatives by using green and environmentally benign oxidant such as, O_2. A control experiment was performed in the absence of catalyst, no reaction was observed. To our surprise, the solution of compound **3j** in DMSO was treated with 60 mol% of CuI in presence of molecular oxygen by using oxygen balloon, oxidative C=C bond cleavage of **3j** was observed (Figure 4.3b). After completion of this reaction, 1-methylindoline-2,3-dione **4a** and 1-benzylindoline-2,3-dione **4b** were isolated in moderate to good yield (Figure 4.3b). Further, the formation of the corresponding nitrile as the other fragment product for the C=C cleavage was isolated and confirmed by GC-MS analysis (Figure 4.4 &

Figure 4.5). The scope of this novel approach was further studied with other substrates **3k, 3l, 3n, 3o, 3s, 3t,** and **3u** under similar reaction condition (Figure 4.3b). Further, the synthetic application of 3-(aminobenzylidene/aminoalkylidene)indolin-2-ones derivatives have been investigated toward the C−N bond formation through Ullmann coupling reaction. To perform this coupling reaction, compounds **3j, 3o** with bromobenzene and 4-methoxy bromobenzene in the presence of CuI and BPY led to the products **8a, 8b,** and **8c** in 65%, 71% and 66% isolated yields, respectively (Figure 4.6).

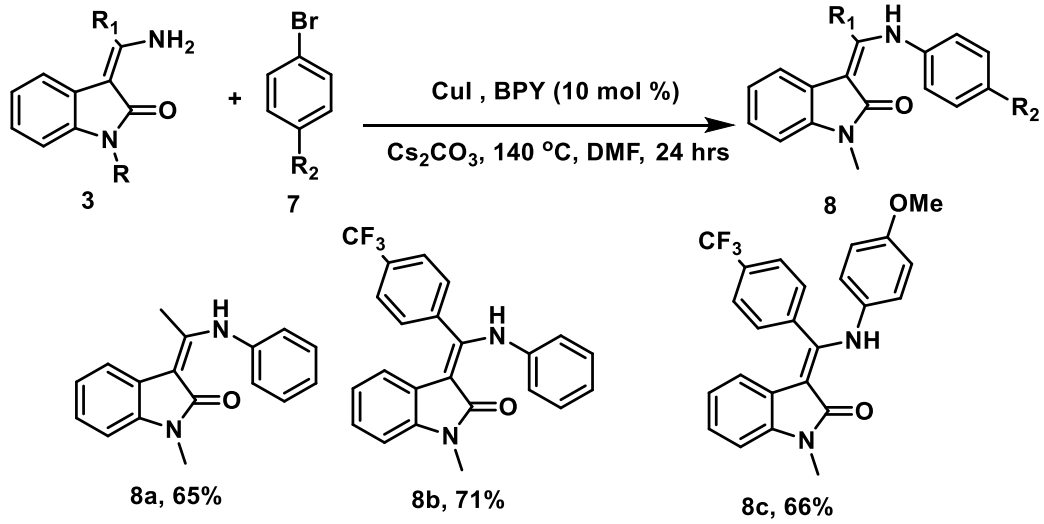


Figure 4.6. Substrate scope for Cu-catalyzed C−N bond formation reaction

Reaction conditions: Cyclic enamide (0.1 mmol), bromobenzene (0.15 mmol), 2,2′-bipyridine (0.01 mmol), CuI (0.01 mmol), Cs_2CO_3 (0.15 mmol) and DMF (2 mL) were heated in a sealed tube at 140 ^oC for 24 hrs.

4.7. Mechanistic investigations

4.7.1. Confirmation of intermediate using HRMS

To investigate the reaction mechanism for the addition reaction, reaction was monitored by HRMS analysis. Thus, we performed the reaction by heating an acetonitrile solution containing 2-oxindole, LiO*t*Bu and 2,2'-BPY ligand to 100 ^oC. After 4 hrs, the reaction mixture was injected into HRMS instrument. The HRMS of the reaction mixture indicates m/z 296.1373 which corresponds to the mass of intermediate **B** (Figure 4.7).

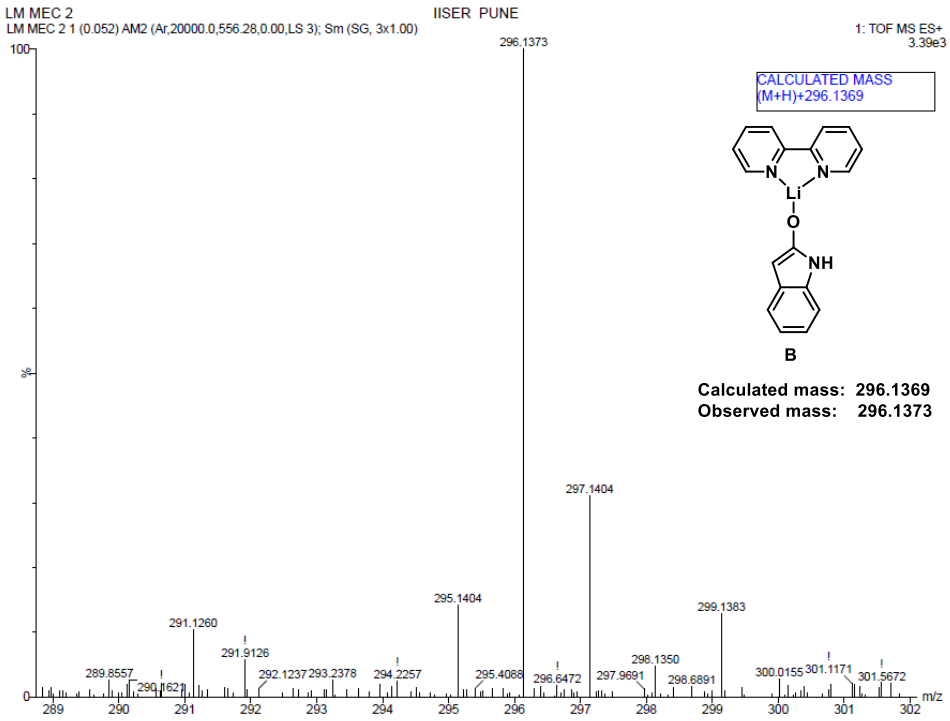
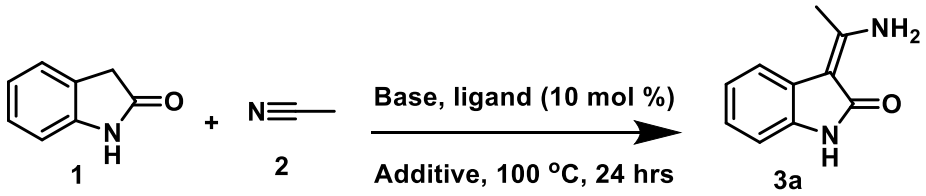


Figure 4.7. HRMS spectra of the intermediate **B**

4.7.2. Radical quenching experiments

Since the addition of ligand has a decisive role in the product yield. Hence, the product **3b** can be formed *via* the SET mechanism.

Table 4.2. Radical quenching experiments



Additive	yield of 3a %
None	65
TEMPO (1 equiv.)	0
TEMPO (0.6 equiv.)	0
α-methylstyrene	40
TEMPO (0.3 equiv.)	15

To understand SET mechanism, an addition reaction of 2-oxindole with acetonitrile was performed with radical-quenchers. In the case of the 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) quencher, no reaction was observed (Table 4.2, entries 1 & 2). The use of α-methylstyrene resulted in a decrease in the yield significantly (Table 4.2, entry 3). Further, these reactions were performed with radical quencher TEMPO or α-methylstyrene in the absence of the bipyridine (BPY), which results in product **3a** in 15 and 40% yield, respectively.

4.8. Plausible mechanisms

Mechanistically, there is two possible way for the formation of 3-(aminobenzylidene)indolin-2-ones derivatives. The first pathway involves ligand exchange followed by the nucleophilic attack (Figure 4.8).

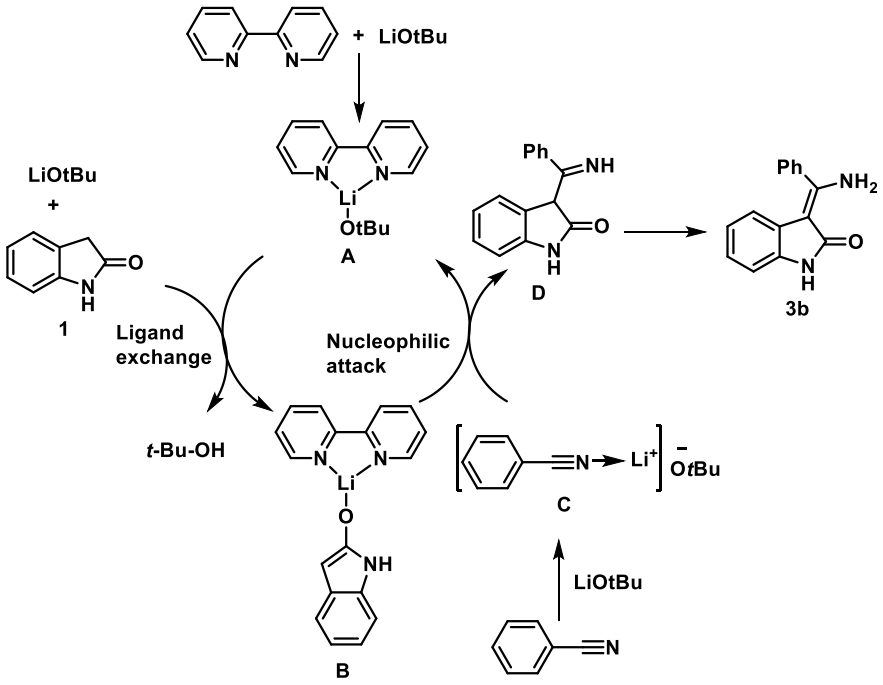


Figure 4.8. Plausible mechanism *via* ligand exchange followed by nucleophilic attack

Initially, 2,2′-bipyridine (BPY) in the presence of LiO*t*Bu generates complex **A**[13a,28a]. Next ligand exchange in the complex **A** between coordinated $^{-}$O*t*Bu and the nucleophile generated from 2-oxindole and LiO*t*Bu to form complex **B**. To analyze the reaction intermediate, the crude reaction mixture was examined in HRMS after 4 hrs. The HRMS of the reaction mixture indicates m/z 296.1373 which corresponds to the intermediate **B** as $(M+H)^{+}$. The oxindole in complex **B** could attack the electrophilic nitrile group of the intermediate **C**[29h] and subsequent proton abstraction from the *t*-

BuOH results in intermediate **D**. Finally, intermediate **D** isomerizes to form the product **3b**. In the second pathway, the product **3b** can be formed *via* SET mechanism.

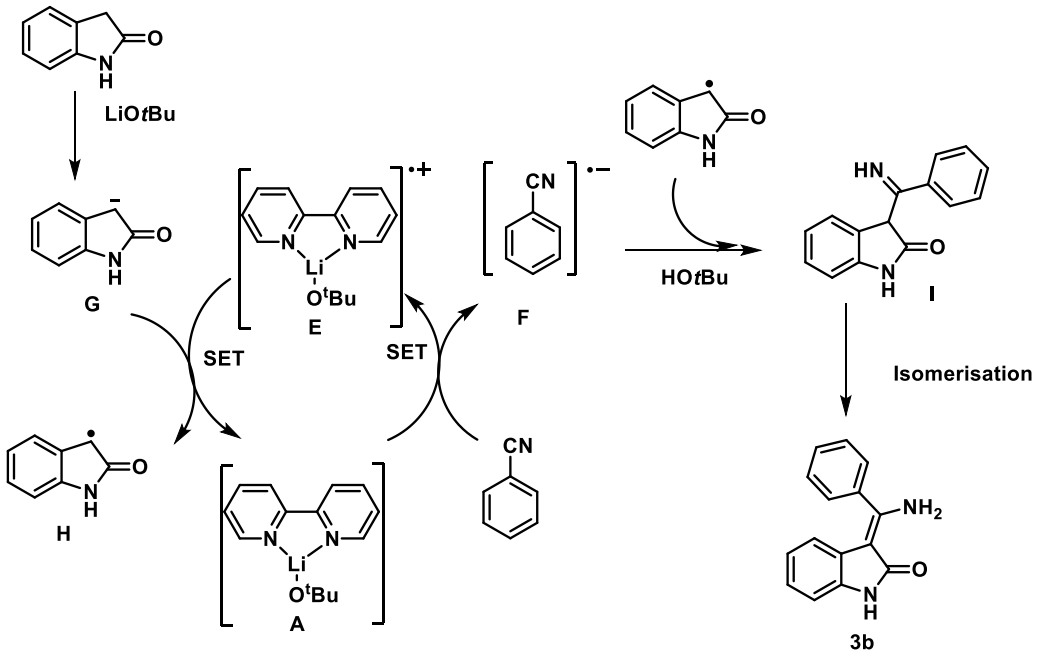


Figure 4.9. Plausible mechanism *via* a single-electron transfer pathway

Based on our experimental observation and from the literature precedence,[13-18,28a] a plausible SET mechanism is proposed (Figure 4.9). Initially, the complex **A** undergoes the SET process in presence of nitrile to generate complex **E** and the intermediate **F**. The intermediate **G** generated by the reaction of 2-oxindole and LiO*t*Bu reacts with complex **E** *via* SET process to generate the 2-oxindole radical **H** and the intermediate **A**. Further, upon the reaction of 2-oxindole radical **H** with nitrile radical **F** subsequent proton abstraction from the *t*-BuOH results the intermediate **I**. The isomerization of intermediate **I** deliver the product **3b**. Although this mechanism was tentatively proposed, further investigation about this mechanism is under progress.

4.9. Conclusion

Herein, we have depicted a transition metal-free approach for the synthesis of *Z*-3-(aminobenzylidene/aminoalkylidene)indolin-2-one by using LiO*t*Bu-BPY base ligand system in good to excellent yield by using feedstock chemicals such as, nitriles and 2-oxindole. The addition of oxindole to aromatic/aliphatic nitriles proceeded smoothly to afford exclusively selective *Z*-3-(aminobenzylidene/aminoalkylidene)indolin-2-ones derivatives in excellent yields. This addition reaction proceeded *via* direct nucleophilic or SET mechanism proven by

experimental evidences. Moreover, synthetic applications of synthesized compounds 3-(aminobenzylidene/aminoalkylidene)indolin-2-one derivatives investigated towards base and additive-free fluorination to generate C3-fluorinated 2-oxindole derivatives. Additionally, we have developed a Cu/O_2 mediated approach for the C=C bond cleavage. Finally, the free amine group of 3-(aminobenzylidene/aminoalkylidene)indolin-2-one derivatives were functionalized *via* Cu-catalyzed Ullmann coupling to afford the drug scaffold.

4.10. Experimental details and characterization data

4.10.1. General information and data collection:

All the nitriles and oxindole derivatives were purchased from Sigma-Aldrich. Deuterated solvents were used as received. All the solvents used were dry grade and stored over 4Å molecular sieves. Column chromatographic separation was performed over 100-200 mesh size silica-gel. Visualization was accomplished with UV light and iodine. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded on 400 and 100 MHz respectively, using a Bruker or JEOL spectrometers. Abbreviations used in the NMR follow-up experiments: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; td, dd doublet of triplet and double doublet; m, multiplet, tt, triplet of triplets and ddd, doublet of doublet of doublets. High-resolution mass spectra were obtained with Waters-synapt G2 using electrospray ionization (ESI-TOF). Infrared (ATR) spectra were obtained with a Bruker Alpha-E infrared spectrometer and FTIR spectra were recorded on pressed pellets of powder samples diluted with KBr on NICOLET 6700 spectrophotometer.

A) General experimental procedure for the synthesis of 3-(aminobenzylidene/aminoalkylidene)indolin-2-ones: To an oven dried 20 mL resealable pressure tube (equipped with rubber septum), 2-oxindole (0.25 mmol), LiO*t*Bu (0.875 mmol), nitrile (0.5 mmol) and 2,2'-bipyridine (0.025 mmol) was added in THF under N_2 atmosphere using N_2 balloon. Then, the tube was purged with N_2 and quickly removed septum and sealed with a cap using a crimper. The reaction mixture was stirred at 100 ^{o}C for 24 hrs on a preheated oil bath. After cooling to room temperature, the reaction mixture was diluted by DCM and MeOH. After concentration under reduced pressure, the residue was purified by 100-200 mesh silica-gel column chromatography (EtOAc:hexane= 35:65 to 65:35) for substrates **3a-3i** and (EtOAc:hexane = 20:80 to 40:60) for substrates **3j-3u**.

B) General experimental procedure for C=C bond cleavage using CuI/O_2: 3-(Aminobenzylidene/aminoalkylidene)indolin-2-ones (0.1 mmol), CuI (0.06 mmol)

were charged in a 10 mL round bottom flask equipped with stirring bar. DMSO (2 mL) was added and the mixture was stirred at 120 ^{o}C on preheated oil bath for 16 hrs under oxygen atmosphere by using an oxygen balloon. After cooling down to room temperature, water was added, and the resulting mixture was extracted with ethyl acetate three times using 50 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc:hexane = 15:85 to 25:75).

C) General experimental procedure for synthesis of 3-subsitituted-3-fluoro-oxindoles: 3-(Aminobenzylidene/aminoalkylidene)indolin-2-ones (0.3 mmol), selectfluor (0.45 mmol) were charged in a 10 mL round bottom flask equipped with stirring bar. Acetonitrile (2 mL) was added and the mixture was stirred at rt for 16 hrs. After 16 hrs, water was added in the reaction mixture and the resulting mixture was extracted with ethyl acetate three times using 50 mL of solvent each time. Further, solvent was dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc:hexane = 10:90 to 15:85).

D) General experimental procedure for radical inhibition: To an oven dried 20 mL resealable pressure tube (equipped with rubber septum), 2-oxindole (0.25 mmol), LiO*t*Bu (0.875 mmol), nitrile (2 ml), 2,2'-bipyridine (0.025 mmol) and 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (1 equiv.) or α-methylstyrene (1 equiv.) were added under N_2 atmosphere using N_2 balloon. Then, the tube was purged with N_2 and quickly removed septum and sealed with a cap using a crimper. The reaction mixture was stirred at 100 ^{o}C for 24 hrs on a preheated oil bath. After cooling to room temperature, the reaction mixture was diluted by DCM and MeOH. After concentration under reduced pressure, the residue was purified by 100-200 mesh size silica-gel column chromatography.

E) General experimental procedure for Ullmann coupling reaction: To a solution of 3-(aminobenzylidene/aminoalkylidene)indolin-2-ones (0.1 mmol) in dry DMF, CuI (0.01 mmol), Cs_2CO_3 (0.15 mmol), 2,2′-bipyridine (0.01 mmol) and bromobenzene (0.15 mmol) was added in inert atmosphere and the mixture was stirred at 140 ^{o}C for 24 hrs on a preheated oil bath. After cooling to room temperature, brine solution was added, and the mixture was extracted with CH_2Cl_2 three times using 50 mL of solvent each time and washed with brine solution 5-6 times. Further solvent was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (EtOAc:hexane = 15:85 to 20:80).

F) Analytical data for the product:

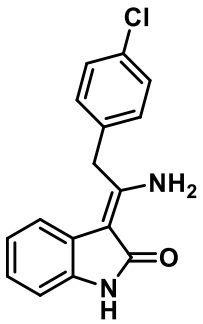
3-(1-aminoethylidene)indolin-2-one (**3a**): Prepared according to general procedure A, using 2-oxindole (33 mg, 0.25 mmol), LiO*t*Bu (70 mg, 0.8 ml, 0.875 mmol), dry acetonitrile (0.6 ml) and 2,2'-bipyridine (3.9 mg, 0.025 mmol) to afford 3-(1-aminoethylidene)indolin-2-one **3a** (28 mg, 65%) as a yellow crystalline solid. **^{1}H NMR** (400 MHz, Methanol-d_4): δ 7.32–7.28 (m, 1H), 7.00–6.90 (m, 3H), 4.61 (s, 1H), 2.44 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, Methanol-d_4) δ 163.1, 136.5, 126.8, 123.2, 121.7, 119.4, 110.1, 95.1, 21.1. **FTIR** (neat): 3342, 3182, 1618, 1535, 1459 cm^{-1}. **HRMS**: (ESI-TOF) m/z: $(M+H)^+$ calculated for $C_{10}H_{11}N_2O$ 175.0871; found: 175.0870. **Crystal Data:** compound **3a** were grown by slow evaporation from a solution of methanol. A single crystal (0.13×0.09×0.04 mm) was mounted on loop with a small amount of the paraffin oil. The X-ray data were collected at 100K temperature on a Bruker APEX(II) DUO CCD diffractometer using Cu Kα radiation (λ = 1.54 Å), ω-scans (2θ = 130.64), for a total of 98429 independent reflections. Space group P 21, a = 45.984(3) Å, b = 14.1262(9) Å, c = 15.9483(10) Å, α =90°, β = 92.210 (3)°, γ = 90°, V = 4151.68Å3, monoclinic, Z = 48 for chemical formula $C_{10}H_{10}N_2O$, with 12 molecule in asymmetric unit; ρ calcd = 1.341gcm-3 , μ = 0.721 mm-1, F (000) = 4416.0. The final R value was 0.0465 (wR2 = 0.1495) 17685 observed reflections (F0 ≥ 4σ (|F0|)) and 1417 variables, S = 1.130.

3-(1-aminoethylidene-2,2,2-d_3)indolin-2-one (3a'): Prepared according to general procedure A, using 2-oxindole (33 mg, 0.25 mmol), LiO*t*Bu in THF 1M (0.8 ml, 0.875 mmol), acetonitrile-d_3 (0.6 ml) and 2,2'-bipyridine (3.9 mg, 0.025 mmol) to afford 3-(1-aminoethylidene-2,2,2-d_3)indolin-2-one **3a'** (27 mg, 62%) as a white solid. **^{1}H NMR** (400 MHz, Methanol-d_4): δ 7.28 (d, *J* = 6.5 Hz, 1H), 6.99 – 6.88 (m, 3H), 2.41 (s, 1H). **^{13}C{^{1}H} NMR** (100 MHz, Methanol-d_4) δ 171.8, 163.0, 136.6, 126.8, 123.2, 121.7, 119.3, 110.1, 95.1, 21.1. **FTIR** (neat): 3343, 3197, 1653, 1537, 1463 cm^{-1}. **HRMS**: (ESI-TOF) m/z: $(M+H)^+$ calculated for $C_{10}H_8D_3N_2O$ 178.1059; found: 178.1057.

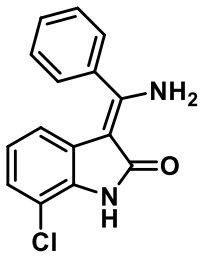
3-(amino(phenyl)methylene)indolin-2-one (3b)[30]: Prepared according to general procedure A, using 2-oxindole (33 mg, 0.25 mmol), LiO*t*Bu (70 mg, 0.875 mmol), benzonitrile (103 mg, 1 mmol) and 2,2'-bipyridine (3.9 mg, 0.025 mmol) to afford 3-(amino(phenyl)methylene)indolin-2-one **3b** (41 mg, 70%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.52 (s, 1H), 8.14 (s, 1H), 7.61 – 7.50 (m, 5H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 8 Hz, 1H), 6.66 (t, *J* = 8 Hz, 1H), 6.29 (d, *J* = 8 Hz, 1H), 5.20 (s, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 171.0, 159.7, 136.0, 135.7, 130.6, 129.3, 127.9,

124.7, 123.6, 120.7, 118.6, 109.2, 96.0. **FTIR** (neat): 3353, 3186, 1735, 1617, 1545, 1470 cm^{-1}. **HRMS**: (ESI-TOF) m/z: $(M+H)^+$ calculated for $C_{15}H_{13}N_2O$ 237.1027; found: 237.1030.

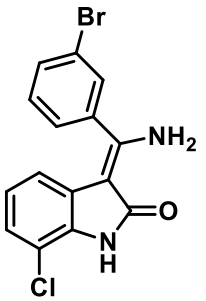
3-(1-amino-2-(4-chlorophenyl)ethylidene)indolin-2-one (3c): Prepared according to general procedure A, using 2-oxindole (33 mg, 0.25 mmol), Li*O*tBu (70 mg, 0.875 mmol), 2-(4-chlorophenyl)acetonitrile (75.5 mg, 0.5 mmol) and 2,2'-bipyridine (3.9 mg, 0.025 mmol) to afford 3-(1-amino-2-(4-chlorophenyl)ethylidene)indolin-2-one **3c** (52 mg, 74%) as a white solid partially soluble in chloroform. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 8.45 (s, 1H), 7.41 - 7.37 (m, 2H), 7.30 - 7.27 (m, 3H), 7.08 (td, *J* = 7.6, 1.1 Hz, 1H), 7.01- 6.96 (m, 2H), 5.06 (s, 1H), 4.16 (s, 2H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 170.6, 159.6, 135.6, 134.0, 132.2, 131.0, 129.5, 124.8, 123.4, 121.2, 118.9, 109.4, 95.7, 39.3. **FTIR** (neat): 3350, 3122, 1653, 1614, 1534, 1462 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calculated for $C_{16}H_{14}ClN_2O$ 285.0794; found: 285.0793.



3-(amino(phenyl)methylene)-7-chloroindolin-2-one (3d): Prepared according to general procedure A, using 7-chloro-2-oxindole (41 mg, 0.25 mmol), Li*O*tBu (70 mg, 0.875 mmol), benzonitrile (104 mg, 1 mmol) and 2,2'-bipyridine (3.9 mg, 0.025 mmol) to afford to 3-(amino(phenyl)methylene)-7-chloroindolin-2-one **3d** (40 mg, 60%) as a yellow solid partially soluble in chloroform. **^{1}H NMR** (400 MHz, $CDCl_3$+CCl_4) δ 9.62 (s, 1H), 8.28 (s, 1H), 7.63 – 7.47 (m, 5H), 6.94 (d, *J* = 8 Hz, 1H), 6.59 (t, *J* = 8 Hz, 1H), 6.16 (d, *J* = 8 Hz, 1H), 5.35 (s, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$+CCl_4) δ 160.7, 135.7, 133.1, 130.8, 129.4, 127.8, 126.2, 123.1, 121.4, 116.8, 114.6, 96.2. **FTIR** (KBr) 3452, 3166, 1654, 1608, 1528, 1491, 1479 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calculated for $C_{15}H_{12}ClN_2O$ 271.0638; found: 271.0647.

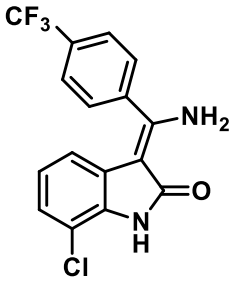


3-(amino(3-bromophenyl)methylene)-7-chloroindolin-2-one (3e): Prepared according to general procedure A, using 7-chloro-2-oxindole (41 mg, 0.25 mmol), Li*O*tBu (70 mg, 0.875 mmol), 3-bromobenzonitrile (91 mg, 0.5 mmol) and 2,2'-bipyridine (3.9 mg, 0.025 mmol) to afford 3-(amino(3-bromophenyl)methylene)-7-chloroindolin-2-one **3e** (73 mg, 84%) as a yellow solid partially soluble in chloroform. **^{1}H NMR** (400 MHz, CDCl3) δ 9.56 (s, 1H), 7.98 (s, 1H), 7.73 (dt, *J* = 2.8, 1.7 Hz, 2H), 7.50 (dt, *J* = 8, 1.4 Hz, 1H), 7.44 (t, *J* = 8 Hz, 1H), 6.97 (dd, *J* = 8, 0.8 Hz, 1H), 6.65 (t, *J* = 8.0 Hz, 1H), 6.19 (d, *J* = 8 Hz, 1H), 5.25 (s, 1H). **^{13}C{^{1}H} NMR** (100 MHz, CDCl3) δ 169.6, 158.0, 136.8, 133.3, 132.6, 130.4, 130.2, 126.0,

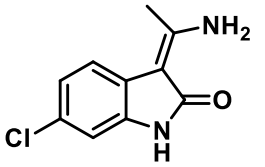


125.1, 122.8, 121.1, 116.2, 116.1, 114.2, 95.8. **FTIR** (KBr) = 3385, 3199, 1653, 1625, 1536, 1470 cm^{-1} **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calculated for $C_{15}H_{11}BrClN_2O$ 348.9743; found: 348.9739.

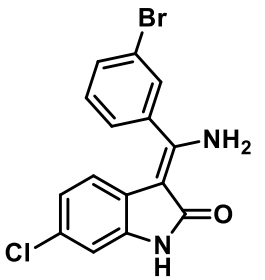
3-(amino(4-(trifluoromethyl)phenyl)methylene)-7-chloroindolin-2-one (3f): Prepared according to general procedure A, using 7-chloro-2-oxindole (41 mg, 0.25 mmol), Li*O*tBu (70 mg, 0.875 mmol), 4-(trifluoromethyl)benzonitrile (85.5 mg, 0.5 mmol) and 2,2'-bipyridine (3.9 mg, 0.025 mmol) to afford 3-(amino(4-(trifluoromethyl)phenyl)methylene)-7-chloroindolin-2-one **3f** (70 mg, 83%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 8.04 (s, 1H), 7.84 (d, *J* = 8 Hz, 2H), 7.70 (d, *J* = 8 Hz, 2H), 6.98 (dd, *J* = 8, 1 Hz, 1H), 6.64 (t, *J* = 8.0 Hz, 1H), 6.10 (d, *J* = 8 Hz, 1H), 5.28 (s, 1H). **^{13}C{^{1}H} NMR** (100 MHz, Methanol-d4) δ 171.8, 161.9, 140.3, 134.2, 133.1 (q, *J* = 32.4 Hz), 129.7, 127.3, 126.9 (q, *J* = 3.7 Hz), 123.9 (q, *J* = 269.8 Hz), 123.5, 122.0, 116.9, 115.4, 95.5 **FTIR** (KBr) 3474, 2926, 1667, 1605, 1545, 1440 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calculated for $C_{16}H_{11}ClF_3N_2O$: 339.0512; found: 339.0520.



3-(1-aminoethylidene)-6-chloroindolin-2-one (3g): Prepared according to general procedure A, using 6-chloro-2-oxindole (41 mg, 0.25 mmol), Li*O*tBu in THF 1M (0.8 ml, 0.875 mmol), dry acetonitrile (1 ml), and 2,2'-bipyridine (3.9 mg, 0.025 mmol) to afford 3-(1-aminoethylidene)-6-chloroindolin-2-one **3g** (15 mg, 30%) as a light red color solid. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.34 (s, 1H), 9.34 (s, 1H), 8.14 (s, 1H), 7.19 (d, *J* = 8 Hz, 1H), 6.87 (dd, *J* = 7.6, 2.0 Hz, 1H), 6.81 (d, *J* = 4 Hz, 1H), 2.36 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 169.5, 161.4, 136.5, 125.5, 124.4, 119.3, 118.7, 108.2, 92.5, 20.5. **FTIR** (KBr) = 3485, 3140, 1639, 1540, 1469 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calculated for $C_{10}H_{10}ClN_2O$ 209.0481; found: 209.0482.

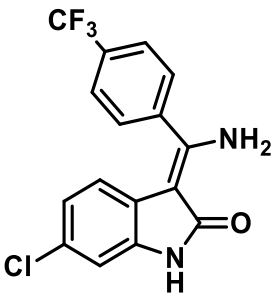


3-(amino(3-bromophenyl)methylene)-6-chloroindolin-2-one (3h): Prepared according to general procedure A, using 6-chloro-2-oxindole (41 mg, 0.25 mmol), Li*O*tBu (70 mg, 0.875 mmol), 3-bromobenzonitrile (91 mg, 0.5 mmol) and 2,2'-bipyridine (3.9 mg, 0.025 mmol) to afford 3-(amino(3-bromophenyl)methylene)-6-chloroindolin-2-one **3h** (65 mg, 75%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.44 (s, 1H), 9.33 (s, 1H), 7.74 – 7.67 (m, 2H), 7.48 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.42 (t, *J* = 7.7 Hz, 1H), 6.94 (d, *J* = 1.9 Hz, 1H), 6.67 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.19 (d, *J* = 8.3 Hz, 1H), 5.36 (s, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 171.0, 157.7, 137.5, 136.7, 133.9, 131.0, 130.8, 129.3, 126.6,



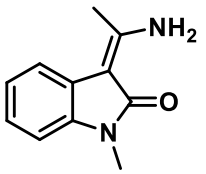
123.4, 122.8, 120.9, 119.2, 109.8, 95.7. **FTIR** (KBr) = 3382, 3180, 1643, 1610, 1544, 1484 cm^{-1} **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calculated for $C_{15}H_{11}BrClN_2O$ 348.9733; found: 348.9726.

3-(amino(4-(trifluoromethyl)phenyl)methylene)-6-chloroindolin-2-one (3i):



Prepared according to general procedure A, using 6-chloro-2-oxindole (41 mg, 0.25 mmol), LiO*t*Bu (70 mg, 0.875 mmol), 4-(trifluoromethyl)benzonitrile (85.5 mg, 0.5 mmol) and 2,2'-bipyridine (3.9 mg, 0.025 mmol) to afford 3-(amino(4-(trifluoromethyl)phenyl)methylene)-6-chloroindolin-2-one (25 mg, 30%) as a yellow solid partially soluble in chloroform. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.57 (s, 1H), 8.27 (s, 1H), 7.72 (m, 2H), 7.50 (d, *J* = 8 Hz, 1H), 7.43 (t, *J* = 8 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.64 (t, *J* = 8 Hz, 1H), 6.18 (d, *J* = 8 Hz, 1H), 5.30 (s, 1H). **^{13}C{^{1}H} NMR** (100 MHz, Acetone-d6) 171.3, 159.6, 140.5, 138.5, 132.3 (q, *J* = 32.2), 129.8, 129.1, 128.8, 126.9 (q, *J* = 3.8), 126.1 (q, *J* = 3.9), 124.2, 120.5, 119.3, 109.8, 95.2 **FTIR** (KBr) = 3398, 3161, 1665, 1605, 1574, 1555 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calculated for $C_{16}H_{11}ClF_3N_2O$ 339.0512; found: 339.0511.

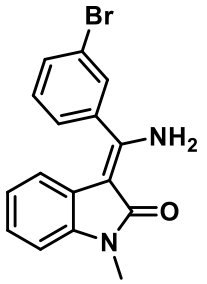
3-(1-aminoethylidene)-1-methylindolin-2-one (3j): Prepared according to general procedure A, using 1-methylindolin-2-one (36 mg, 0.25 mmol), LiO*t*Bu in THF 1M (70 mg, 0.875 mmol), dry acetonitrile (0.6 ml), and 2,2'-bipyridine (3.9 mg, 0.025 mmol) to afford 3-(1-aminoethylidene)-1-methylindolin-2-one **3j** (30 mg, 65%) as a light red solid. **^{1}H NMR** (400 MHz, Methanol-d_4) δ 7.31–7.27 (m, 1H), 7.02 (td, *J* = 7.5, 1.3 Hz, 1H), 6.96 (dd, *J* = 7.6, 1.3 Hz, 1H), 6.94–6.90 (m, 1H), 4.59 (s, 2H), 3.27 (s, 3H), 2.41 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, Methanol-d_4) δ 170.0, 162.7, 138.2, 126.0, 123.2, 122.1, 119.2, 108.5, 94.5, 25.8, 21.1. **IR** (neat) = 3282, 3124, 1700, 1623, 1532, 1464 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calculated for $C_{11}H_{13}N_2O$ 189.1028; found: 189.1033.



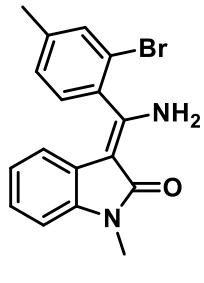
3-(amino(phenyl)methylene)-1-methylindolin-2-one (3k)[31]: Prepared according to general procedure A, using 1-methylindolin-2-one (36 mg, 0.25 mmol), LiO*t*Bu (70 mg, 0.875 mmol), benzonitrile (103 mg, 1 mmol), and 2,2'-bipyridine (3.9 mg, 0.025 mmol) to afford 3-(amino(phenyl)methylene)-1-methylindolin-2-one **3k** (40 mg, 64%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.64 – 7.48 (m, 5H), 7.03 (td, *J* = 7.7, 1.0 Hz, 1H), 6.86 (d, *J* = 8 Hz, 1H), 6.70 (td, *J* = 7.7, 1.0 Hz, 1H), 6.32 (d, *J* = 8 Hz, 1H), 5.17 (s, 1H), 3.37 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 169.6, 159.0, 138.4, 136.1, 130.5, 129.2, 127.9, 123.8,

123.5, 120.6, 118.3, 107.4, 95.8, 25.7. **IR** (Neat) = 3339, 3178, 1606, 1542, 1473 cm^{-1} **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calculated for $C_{16}H_{15}N_2O$ 251.1184; found: 251.1182.

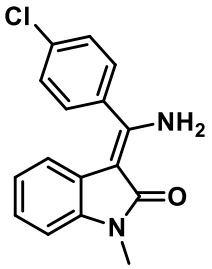
3-(amino(3-bromophenyl)methylene)-1-methylindolin-2-one (3l): Prepared according to general procedure A, using 1-methylindolin-2-one (36 mg, 0.25 mmol), LiOtBu (70 mg, 0.875 mmol), 3-bromobenzonitrile (91 mg, 0.5 mmol) and 2,2'-bipyridine (3.9 mg, 0.025 mmol) to afford 3-(amino(3-bromophenyl)methylene)-1-methylindolin-2-one **3l** (65 mg, 80%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.46 (s, 1H), 7.72 – 7.67 (m, 2H), 7.50 (dd, *J* = 8, 3.9 Hz, 1H), 7.43 – 7.38 (m, 1H), 7.06 (td, *J* = 8, 0.8 Hz, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 6.77 – 6.69 (m, 1H), 6.33 (d, *J* = 8 Hz, 1H), 5.19 (s, 1H), 3.36 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 169.4, 156.7, 138.6, 137.9, 133.5, 130.93, 130.90, 126.7, 123.9, 123.4, 123.2, 120.9, 118.3, 107.6, 96.1, 25.7. **IR** (neat) = 3450, 3267, 1604, 1532, 1459 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calculated for $C_{16}H_{14}BrN_2O$ 329.0289; found: 329.0290.



3-(amino(2-bromo-4-methylphenyl)methylene)-1-methylindolin-2-one (3m): Prepared according to general procedure A, using 1-methylindolin-2-one (36 mg, 0.25 mmol), LiO*t*Bu (70 mg, 0.875 mmol), 2-bromo-4-methylbenzonitrile (98 mg, 0.5 mmol), and 2,2'-bipyridine (3.9 mg, 0.025 mmol) to afford 3-(amino(2-bromo-4-methylphenyl)methylene)-1-methylindolin-2-one **3m** (51 mg, 60%) as a light red solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 7.58 (s, 1H), 7.28 (dd, *J* = 8, 4.4 Hz, 2H), 7.03 (td, *J* = 8, 1.1 Hz, 1H), 6.85 (d, *J* = 8 Hz, 1H), 6.71 (td, *J* = 8, 1.0 Hz, 1H), 5.93 (d, *J* = 8 Hz, 1H), 5.13 (s, 1H), 3.36 (s, 3H), 2.45 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 169.4, 156.5, 142.0, 138.5, 134.1, 133.8, 129.5, 129.1, 123.7, 123.6, 121.08, 121.04, 118.0, 107.5, 96.8, 25.7, 21.2. **FTIR** (KBr) = 3475, 3274, 2924, 1662, 1628, 1613, 1555, 1466, 1432 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calculated for $C_{17}H_{16}BrN_2O$ 343.0446; found: 343.0442.

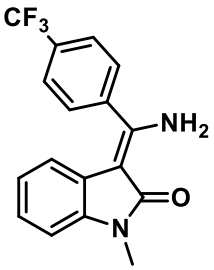


3-(amino(4-chlorophenyl)methylene)-1-methylindolin-2-one (3n)[31]: Prepared according to general procedure A, using 1-methylindolin-2-one (36 mg, 0.25 mmol), LiO*t*Bu (70 mg, 0.875 mmol), 4-chlorobenzonitrile (68.5 mg, 0.5 mmol), and 2,2'-bipyridine (3.9 mg, 0.025 mmol) to afford 3-(amino(4-chlorophenyl)methylene)-1-methylindolin-2-one **3n** (39 mg, 56%) as a yellow color solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.58 – 7.43 (m, 4H), 7.05 (td, *J* = 7.7, 1.0 Hz, 1H), 6.86 (d, *J* = 8 Hz, 1H), 6.73 (td, *J* = 7.6, 1.0 Hz, 1H), 6.36 (d, *J* = 8 Hz, 1H), 5.12

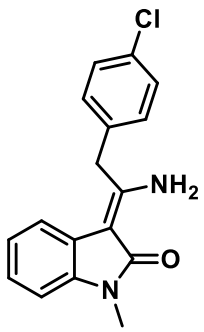


(s, 1H), 3.36 (s, 3H). **$^{13}C\{^{1}H\}$ NMR** (100 MHz, $CDCl_3$) δ 169.5, 157.4, 138.5, 136.6, 134.5, 129.56, 129.51, 123.8, 123.5, 120.8, 118.3, 107.6, 96.1, 25.7. **IR** (neat) = 3312, 3152, 1632, 1535, 1482, 1466 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calculated for $C_{16}H_{14}ClN_2O$ 285.0794; found: 285.0790.

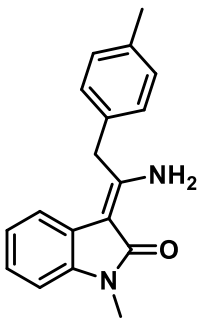
3-(amino(4-(trifluoromethyl)phenyl)methylene)-1-methylindolin-2-one (3o)[31]: Prepared according to general procedure A, using 1-methylindolin-2-one (36 mg, 0.25 mmol), LiO*t*Bu (70 mg, 0.875 mmol), 4-(trifluoromethyl)benzonitrile (85.5 mg, 0.5 mmol) and 2,2'-bipyridine (3.9 mg, 0.025 mmol) to afford 3-(amino(4-(trifluoromethyl)phenyl)methylene)-1-methylindolin-2-one **3o** (74 mg, 93%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.53 (s, 1H), 7.82 (d, *J* = 8 Hz, 2H), 7.70 (d, *J* = 8 Hz, 2H), 7.05 (td, *J* = 7.6, 1.1 Hz, 1H), 6.86 (d, *J* = 8 Hz, 1H), 6.71 (td, *J* = 7.7, 1.0 Hz, 1H), 6.23 (d, *J* = 8 Hz, 1H), 5.07 (s, 1H), 3.37 (s, 3H). **$^{13}C\{^{1}H\}$ NMR** (100 MHz, $CDCl_3$) δ 169.4, 156.8, 139.6, 138.6, 133.5(q, *J* = 32.6 Hz), 128.6, 126.36 (q, *J* = 3.7 Hz), 124.1, 123.8 (q, *J* = 270.8 Hz), 123.2, 120.9, 118.2, 107.7, 96.34, 25.73. **FTIR** (KBr) = 3350, 3189, 1626, 1556, 1469 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calculated for $C_{17}H_{14}F_3N_2O$: 319.1058; found: 319.1058.



(3-(1-amino-2-(4-chlorophenyl)ethylidene)-1-methylindolin-2-one (3p): Prepared according to general procedure A, using 1-methylindolin-2-one (36 mg, 0.25 mmol), LiO*t*Bu (70 mg, 0.875 mmol), 2-(4-chlorophenyl)acetonitrile (75.5 mg, 0.5 mmol) and 2,2'-bipyridine (3.9 mg, 0.025 mmol) to afford (3-(1-amino-2-(4-chlorophenyl)ethylidene)-1-methylindolin-2-one **3p** (52 mg, 70%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.40–7.35 (m, 2H), 7.32–7.28 (m, 3H), 7.16 (td, *J* = 7.7, 1.1 Hz, 1H), 7.03 (td, *J* = 7.6, 1.1 Hz, 1H), 6.95 (d, *J* =8 Hz, 1H), 5.00 (s, 1H), 4.16 (s, 2H), 3.39 (s, 3H). **$^{13}C\{^{1}H\}$ NMR** (100 MHz, $CDCl_3$) δ 169.2, 158.9, 138.3, 133.9, 132.4, 130.9, 129.5, 123.9, 123.3, 121.1, 118.6, 107.7, 95.6, 39.2, 25.7. **FTIR** (KBr) = 3306, 3137, 1625, 1606, 1537, 1488 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calculated for $C_{17}H_{16}ClN_2O$ 299.0951; found: 299.0951.

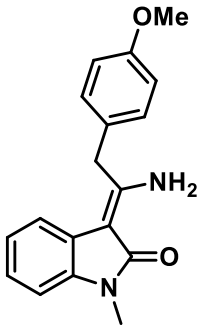


3-(1-amino-2-(p-tolyl)ethylidene)-1-methylindolin-2-one (3q): Prepared according to general procedure A, using 1-methylindolin-2-one (36 mg, 0.25 mmol), LiO*t*Bu (70 mg, 0.875 mmol), 2-(p-tolyl)acetonitrile (65.5 mg, 0.5 mmol), and 2,2'-bipyridine (3.9 mg, 0.025 mmol) to afford 3-(1-amino-2-(p-tolyl)ethylidene)-1-methylindolin-2-one **3q** (39 mg, 57%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$+CCl_4) δ 9.71 (s, 1H), 7.33 (d, *J* = 8 Hz, 1H), 7.18 (s,

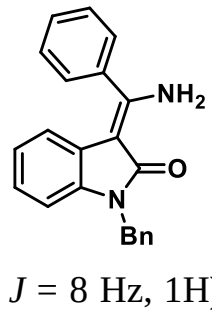


4H), 7.11 (dt, *J* = 7.7, 4.0 Hz, 1H), 7.00 (td, *J* = 7.7, 1.1 Hz, 1H), 6.91 (d, *J* = 8 Hz, 1H), 5.14 (s, 1H), 4.13 (s, 2H), 3.36 (s, 3H), 2.37 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$+CCl_4) δ 169.1, 160.2, 138.1, 137.5, 130.5, 130.0, 129.7, 124.2, 122.9, 121.0, 118.6, 107.5, 95.0, 39.4, 25.6, 21.2. **IR** (neat) = 3392, 3186, 1634, 1528, 1466 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calculated for $C_{18}H_{19}N_2O$ 279.1497; found: 279.1500.

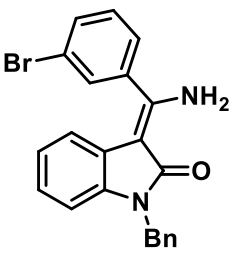
3-(1-amino-2-(4-methoxyphenyl)ethylidene)-1-methylindolin-2-one (3r): Prepared according to general procedure A, using 1-methylindolin-2-one (36 mg, 0.25 mmol), Li*O*t*Bu (70 mg, 0.875 mmol), 2-(4-methoxyphenyl)acetonitrile (73.5 mg, 0.5 mmol), and 2,2'-bipyridine (3.9 mg, 0.025 mmol) to afford 3-(1-amino-2-(4-methoxyphenyl)ethylidene)-1-methylindolin-2-one **3r** (42 mg, 57%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$+CCl_4) δ 9.71 (s, 1H), 7.33 (d, *J* = 8 Hz, 1H), 7.23 – 7.18 (m, 2H), 7.11 (td, *J* =7.5, 0.9 Hz, 1H), 7.00 (td, *J* =7.7, 1.1 Hz, 1H), 6.93 – 6.87 (m, 3H), 5.12 (s, 1H), 4.11 (s, 2H), 3.81 (s, 3H), 3.36 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$+CCl_4) δ 169.1, 160.4, 159.3, 138.1, 130.9, 125.3, 124.2, 122.9, 121.0, 118.6, 114.7, 107.5, 94.9, 55.3, 39.0, 25.6. **FTIR** (KBr) = 3403, 3328, 3202, 1616, 1510, 1439 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calculated for $C_{18}H_{19}N_2O_2$ 295.1446; found: 295.1449.



3-(amino(phenyl)methylene)-1-benzylindolin-2-one (3s): Prepared according to general procedure A, using 1-benzylindolin-2-one (55.7 mg, 0.25 mmol), Li*O*t*Bu (70 mg, 0.875 mmol), benzonitrile (103 mg, 1 mmol) and 2,2'-bipyridine (3.9 mg, 0.025 mmol) to afford 3-(amino(phenyl)methylene)-1-benzylindolin-2-one **3s** (49 mg, 61%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.62–7.50 (m, 5H), 7.35 – 7.28 (m, 4H), 7.21-7.25 (m, 1H), 6.91 (td, *J* = 8, 1.0 Hz, 1H), 6.74 (d, *J* = 8 Hz, 1H), 6.66 (td, *J* = 8, 0.9 Hz, 1H), 6.31 (d, *J* = 8 Hz, 1H), 5.22 (s, 1H), 5.09 (s, 2H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 169.5, 159.3, 137.6, 137.2, 136.1, 130.6, 129.3, 128.7, 127.9, 127.3, 124.0, 123.5, 120.7, 118.4, 108.4, 95.7, 43.3. **FTIR** (KBr) = 3367, 3188, 1715, 1644, 1623, 1549, 1467 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calculated for $C_{22}H_{19}N_2O$: 327.1497; found: 327.1495.

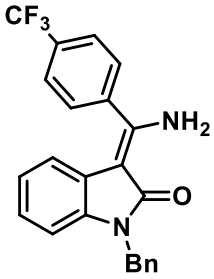


3-(amino(3-bromophenyl)methylene)-1-benzylindolin-2-one (3t): Prepared according to general procedure A, using 1-benzylindolin-2-one (55.7 mg, 0.25 mmol), Li*O*t*Bu (70 mg, 0.875 mmol), 3-bromobenzonitrile (91 mg, 0.5 mmol) and 2,2'-bipyridine (3.9 mg, 0.025 mmol) to afford 3-(amino(3-bromophenyl)methylene)-1-benzylindolin-2-one **3t** (70 mg, 70%) as a yellow solid. **^{1}H NMR**



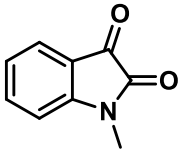
(400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.72–7.66 (m, 2H), 7.52–7.48 (m, 1H), 7.40 (t, *J* = 8 Hz, 1H), 7.31–7.27 (m, 4H), 7.24 – 7.19 (m, 1H), 6.93 (td, *J* = 8, 1.0 Hz, 1H), 6.74 (d, *J* = 8 Hz, 1H), 6.72–6.65 (td, *J* = 8, 1.0 Hz, 1H), 6.32 (d, *J* = 8 Hz, 1H), 5.17 (s, 1H), 5.06 (s, 2H). **$^{13}C\{^1H\}$ NMR** (100 MHz, $CDCl_3$) δ 169.4, 157.0, 137.9, 137.8, 137.0, 133.6, 130.9, 128.7, 127.4, 127.3, 126.7, 123.9, 123.5, 123.2, 120.9, 118.4, 108.5, 96.0, 43.3. **IR** (neat) 3347, 3185, 1620, 1548, 1479 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M)^+$ calculated for $C_{22}H_{18}BrN_2O$: 404.0524; found: 404.0519.

3-(amino(4-(trifluoromethyl)phenyl)methylene)-1-benzylindolin-2-one (3u): Prepared according to general procedure A, using 1-benzylindolin-2-one (55.7 mg, 0.25 mmol), LiO*t*Bu (70 mg, 0.875 mmol), 4-(trifluoromethyl)benzonitrile (85.5 mg, 0.5 mmol), and 2,2'-bipyridine (3.9 mg, 0.025 mmol) to afford 3-(amino(4-(trifluoromethyl)phenyl)methylene)-1-benzylindolin-2-one **3u** (78 mg, 79%) as a yellow solid.



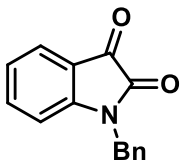
^1H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8 Hz, 2H), 7.35 - 7.30 (m, 4H), 7.26 – 7.22 (m, 1H), 6.96 (td, *J* = 7.7, 1.0 Hz, 1H), 6.78 (d, *J* = 7.7 Hz, 1H), 6.70 (td, *J* =7.7, 1.0 Hz, 1H), 6.25 (d, *J* = 8 Hz, 1H), 5.19 (s, 1H), 5.09 (s, 2H). **$^{13}C\{^1H\}$ NMR** (100 MHz, $CDCl_3$) δ 169.3, 157.2, 139.4, 137.7, 136.9, 132.4 (q, *J* = 32.6), 130.0, 128.7, 128.6, 127.4, 127.2, 126.30 (q, *J* = 3.7 Hz), 123.9, 123.8(q, *J* = 270.7 Hz), 123.4, 120.9, 118.2, 108.6, 95.9, 43.2. **IR** (neat) = 3312, 3152, 1632, 1604, 1565, 1426 $cm^{-1.}$ **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calculated for $C_{23}H_{18}F_3N_2O$: 395.1371; found: 395.1372.

1-methylindoline-2,3-dione (4a)[32]: 3-(aminobenzylidene/aminoalkylidene)indolin-2-ones (**3j, 3k, 3l, 3n, 3o**) (0.1 mmol) and CuI (11 mg, 0.06 mmol) were allowed to react in 10 mL round bottom flask according to method B to afford 1-methylindoline-2,3-dione (for yield see scheme 3) red solid



4a. ^1H NMR (400 MHz, $CDCl_3$+CCl_4) δ 7.60 (dd, *J* = 12.1, 4.4 Hz, 2H), 7.12 (t, *J* = 8 Hz, 1H), 6.88 (d, *J* = 8 Hz, 1H), 3.25 (s, 3H). **$^{13}C\{^1H\}$ NMR** (100 MHz, $CDCl_3$+CCl_4) δ 183.3, 158.2, 151.6, 138.4, 125.4, 123.9, 117.6, 109.9, 26.3. **IR** (Neat) 1721 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calculated for $C_9H_8NO_2$: 162.0555; found: 162.0560.

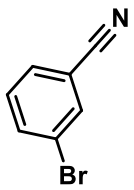
1-benzylindoline-2,3-dione (4b)[32]: 3-(aminobenzylidene/aminoalkylidene)indolin-2-ones (**3s, 3t, 3u**) (0.1 mmol) and CuI (11 mg, 0.06 mmol) were allowed to react in 10 mL round bottom flask according to method B to afford 1-benzylindoline-2,3-dione (for yield see scheme 3 main article) red solid



4b. ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.5 Hz, 1H), 7.47 (td, *J* = 7.8, 1.4 Hz, 1H), 7.38 – 7.28 (m, 5H), 7.09 (td, *J* = 7.6, 0.8 Hz, 1H),

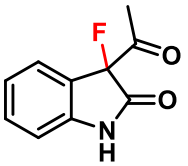
6.77 (d, *J* = 8.0 Hz, 1H), 4.93 (s, 2H). **$^{13}C\{^{1}H\}$ NMR** (100 MHz, $CDCl_3$+CCl_4) δ 183.2, 158.3, 150.9, 138.3, 134.6, 129.2, 128.3, 127.5, 125.5, 123.9, 117.9, 111.1, 44.2. **IR** (Neat) 1732 cm^{-1}. **HRMS** (ESI-TOF) m/z $(M+H)^+$ calculated for $C_{15}H_{12}NO_2$ 238.0868; found: 238.0871.

3-bromobenzonitrile (**5b**): 3-(aminobenzylidene)indolin-2-ones (**3l** or **3t**) (0.1 mmol) and CuI (11 mg, 0.06 mmol) were allowed to react in 10 mL round bottom flask according to method B to afford 3-bromobenzonitrile (for yield see scheme 3 main article) white solid **5b**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 – 7.77 (m, 1H), 7.75 (dd, *J* = 8.1, 1.0 Hz, 1H), 7.63 – 7.57 (m, 1H), 7.36 (t, *J* = 7.9 Hz, 1H). **$^{13}C\{^{1}H\}$ NMR** (100 MHz, $CDCl_3$) δ 136.2, 134.8, 130.8, 130.7, 122.9, 117.3, 114.2.

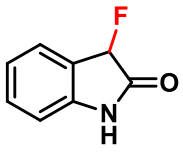


3-acetyl-3-fluoroindolin-2-one (6a). 3-(1-aminoethylidene)indolin-2-one (52 mg, 0.3 mmol), selectfluor (159.3 mg, 0.45 mmol), were allowed to react in 10 mL round-bottom flask according to method **C** to afford inseparable mixture of 3-fluorooxindole[33] (17 mg, 38%) and 3-acetyl-3-fluoroindolin-2-one (22 mg, 38%) as a white solid.

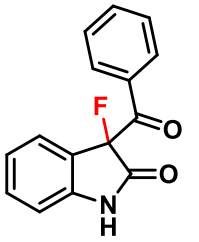
3-acetyl-3-fluoroindolin-2-one (6a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.29 (s, 1H), 7.25 - 7.29 (m, 2H), 7.11 (tt, *J* = 7.6 Hz, *J* = 0.8 Hz 1H), 6.99 (d, *J* = 7.9 Hz, 1H), 2.40 (d, *J* = 3.6 Hz, 3H). **$^{13}C\{^{1}H\}$ NMR** (100 MHz, $CDCl_3$) δ 200.0 (d, *J* = 30 Hz), 174.0 (d, *J* = 17.7 Hz), 142.7 (d, *J* = 5.3 Hz), 132.5 (d, *J* = 2.9 Hz), 125.1, 123.8 (d, *J* = 2.5 Hz), 123.5 (d, *J* = 14.9 Hz), 111.7, 96.3 (d, *J* = 203 Hz), 25.9. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -165; **IR** (Neat) = 1721, 1620 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calculated for $C_{10}H_9FNO_2$ 194.0617; found: 194.0626.



3-fluorooxindole (**6a'**).[33] **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.10 (s, 1H), 7.43 (d, *J* = 7.4 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.11 (tt, *J* = 7.6 Hz, *J* = 0.8 Hz 1H), 6.92 (dd, *J* = 7.9, 0.4 Hz, 1H), 5.69 (d, *J* = 50.8 Hz, 1H). **$^{13}C\{^{1}H\}$ NMR** (100 MHz, $CDCl_3$) 171.7 (d, *J* = 20 Hz), 142.1 (d, *J* = 5.4 Hz), 131.6 (d, *J* = 3.3 Hz), 126.4 (d, *J* = 0.9 Hz), 123.4 (d, *J* = 2.8 Hz), 123.3 (d, *J* = 12 Hz), 111.1 (d, *J* = 1.2 Hz), 86.0 (d, *J* = 188.09 Hz). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -193.8.



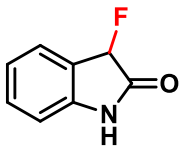
3-benzoyl-3-fluoroindolin-2-one (**6b**)**:** 3-(amino(phenyl)methylene)indolin-2-one (70 mg, 0.3 mmol), selectfluor (159.3 mg, 0.45 mmol), were allowed to react in 10 mL round-bottom flask according to method C to afford inseparable mixture of 3-fluorooxindole (19 mg, 43%) and 3-benzoyl-3-fluoroindolin-2-one **6b** (33 mg, 43%) as a white solid.



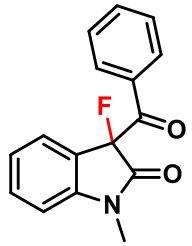
3-benzoyl-3-fluoroindolin-2-one (**6b**): ^{1}H NMR for (400 MHz,

$CDCl_3$) δ 8.66 (s, 1H), 8.12 (dt, *J* = 8.5, 1.2 Hz, 2H), 7.67 – 7.60 (m, 1H), 7.53 – 7.48 (m, 2H), 7.41 – 7.35 (m, 1H), 7.35 – 7.31 (m, 1H), 7.13 – 7.09 (m, 1H), 7.00 (d, *J* = 7.9 Hz, 1H). **^{13}C{^{1}H}NMR** (100 MHz, $CDCl_3$) δ 192.3 (d, *J* = 27 Hz), 173.4 (d, *J* = 17 Hz), 141.8 (d, J = 5.2 Hz), 134.3, 133.9 (d, *J* = 3.8 Hz), 132.5 (d, *J* = 3.2), 129.9 (d, *J* = 5.9 Hz), 128.9 (d, *J* = 0.6 Hz), 126.5 (d, *J* = 1.1 Hz), 124.5 (d, *J* = 18.3 Hz), 123.7 (d, *J* = 2.8 Hz), 111.5 (d, *J* = 1.2 Hz), 96.9 (d, *J* = 204.23). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -156.61. **IR** (Neat) = 1740, 1623 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+Na)^+$ calculated for $C_{15}H_{11}FNO_2$: 278.0593; found: 278.0599.

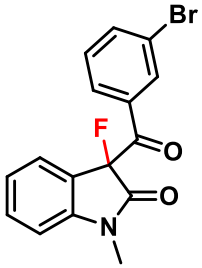
3-fluorooxindole (**6a'**) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.46 (d, *J* = 7.4 Hz, 1H), 7.35 – 7.31 (m, 1H), 7.09 – 7.04 (m, 1H), 6.89 (d, *J* = 7.9 Hz, 1H), 5.70 (d, *J* = 50.8 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 171.6 (d, *J* = 21 Hz), 142.6 (d, *J* = 5.3 Hz), 131.6 (d, *J* = 3.3 Hz), 126.3 (d, *J* = 0.5 Hz), 123.5 (d, *J* = 2.9 Hz), 123.1 (d, *J* = 16 Hz), 110.8 (d, *J* = 1.3 Hz), 85.8 (d, *J* = 188 Hz). **^{19}F NMR** (377 MHz, $CDCl_3$) -193.56.



3-benzoyl-3-fluoro-1-methylindolin-2-one (**6c**). (3-(amino(phenyl)methylene)-1-methylindolin-2-one (75 mg, 0.3 mmol), selectfluor (159.3 mg, 0.45 mmol), were allowed to react in 10 mL round-bottom flask according to method C to afford mixture of 3-fluoro-1-methylindolin-2-one and 3-benzoyl-3-fluoro-1-methylindolin-2-one, recrystallized using n-pentane afforded pure product 3-benzoyl-3-fluoro-1-methylindolin-2-one (50 mg, 62%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.12 (dt, *J* = 8.6, 1.3 Hz, 2H), 7.65 – 7.60 (m, 1H), 7.52 – 7.47 (m, 2H), 7.44 (td, *J* = 7.8, 2.0, 1.3 Hz, 1H), 7.36 – 7.31 (m, 1H), 7.08 (tt, *J* = 7.7, 0.9 Hz, 1H), 6.92 (d, *J* = 7.9 Hz, 1H), 3.27 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 192.8 (d, *J* = 28 Hz), 169.7 (d, *J* = 21 Hz), 145.5 (d, *J* = 5.0 Hz), 134.2, 134.1 (d, *J* = 4 Hz), 132.4 (d, *J* = 3.2 Hz), 130.0 (d, *J* = 6.2 Hz), 128.8 (d, *J* = 0.8), 125.8 (d, *J* = 0.8 Hz), 124.2 (d, *J* = 18.6 Hz), 123.6 (d, *J* = 2.8 Hz), 109.5 (d, *J* = 1.3 Hz), 96.9 (d, *J* = 203 Hz), 26.7. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -157.11. **IR** (Neat) = 1733, 1609 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calculated for $C_{16}H_{13}FNO_2$ 270.0930; found: 270.0920.

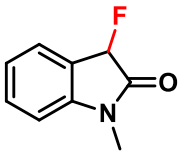


3-(3-bromobenzoyl)-3-fluoro-1-methylindolin-2-one (**6d**). 3-(amino(3-bromophenyl)methylene)-1-methylindolin-2-one (98.4 mg, 0.3 mmol), selectfluor (159.3 mg, 0.45 mmol), were allowed to react in 10 mL round-bottom flask according to method C to afford inseparable mixture of 3-fluoro-1-methylindolin-2-one[33] (7.4 mg, 15%) and 3-(3-bromobenzoyl)-3-fluoro-1-methylindolin-2-one **6d** (78 mg, 76%) as a white solid.

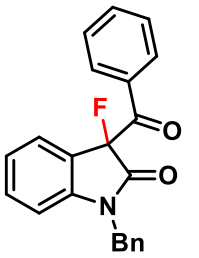


3-(3-bromobenzoyl)-3-fluoro-1-methylindolin-2-one (**6d**): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 8.09 (d, *J* = 7.9 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 7.9 Hz, 1H), 3.25 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 191.7 (d, *J* = 30 Hz), 169.3 (d, *J* = 21 Hz), 145.4 (d, *J* = 5.0 Hz), 136.9, 136.7, 132.8 (d, *J* = 5.8 Hz), 132.6 (d, *J* = 3 Hz), 128.5 (d, *J* = 7.1 Hz), 125.8 (d, *J* = 0.8 Hz), 123.8 (d, *J* = 2.7 Hz), 123.7 (d, *J* = 18 Hz), 122.9 (d, *J* = 0.9 Hz), 122.6, 109.6 (d, *J* = 1.2 Hz), 96.8 (d, *J* = 203 Hz), 26.8. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -157.25. **IR** (Neat) = 1730, 1612 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calculated for $C_{16}H_{12}BrFNO_2$: 348.0035; found: 348.0037.

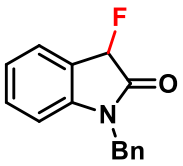
3-fluoro-1-methylindolin-2-one (6aa') ^{1}H NMR (400 MHz, $CDCl_3$) 7.44 (t, *J* = 7.7 Hz, 0.23 H), 7.38 (t, *J* = 7.9 Hz, 0.26 H), 7.09 (t, *J* = 7.6 Hz, 0.22 H), 6.81 (d, *J* = 7.8 Hz, 0.21 H), 5.65 (d, *J* = 51.0 Hz, 0.23 H), 3.18 (s, 0.69 H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 171.2 (d, *J* = 18 Hz), 144.7 (d, *J* = 5.1 Hz), 131.5 (d, *J* = 3.3Hz), 126.0 (d, *J* = 1.2 Hz), 123.4 (d, *J* = 2.8 Hz), 122.8 (d, *J* = 16 Hz), 108.8 (d, *J* = 1.3 Hz), 85.5 (d, *J* = 187.09 Hz), 26.3. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -193.29.



3-benzoyl-1-benzyl-3-fluoroindolin-2-one (**6e**): 3-(amino(phenyl)methylene)-1-benzylindolin-2-one (491 mg, 1.5 mmol), selectfluor (796 mg, 3 mmol), were allowed to react in 10 mL round-bottom flask according to method C to afford inseparable mixture of 1-benzyl-3-fluoroindolin-2-one (108 mg, 30%) and 3-benzoyl-1-benzyl-3-fluoroindolin-2-one **6e** (310 mg, 60%) as a white solid. **^{1}H NMR** for 3-benzoyl-1-benzyl-3-fluoroindolin-2-one **6e** (400 MHz, $CDCl_3$) δ 8.17 – 8.11 (m, 5H), 7.65 – 7.59 (m, 3H) 7.48 – 7.50 (m, 3H), 7.37 – 7.31 (m, 13H), 7.09 – 7.04 (m, 2H), 6.76 (d, *J* = 7.9 Hz, 2H), 5.12 (d, *J* = 15.7 Hz, 2H), 4.78 (d, *J* = 15.7 Hz, 2H). **^{13}C{^{1}H} NMR** δ 192.5 (d, *J* = 27.8 Hz), 170.0 (d, *J* = 21.6 Hz), 144.6 (d, *J* = 5.0 Hz), 134.6, 134.2, 134.0 (d, *J* = 3.8), 133.8, 132.3 (d, *J* =3.1 Hz), 130.2, 129.9 (d, *J* = 5.9 Hz), 129.1, 129.0, 128.5, 125.9 (d, *J* = .75), 124.1 (d, *J* = 18.5), 123.7 (d, *J* = 2.7 Hz), 110.6 (d, *J* = 1.1 Hz), 96.88 (d, *J* = 204, Hz), 44.3. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -157.31. **HRMS** (ESI-TOF) m/z: calculated for $(M+H)^+$ $C_{22}H_{17}FNO_2$ 346.1243; found: 346.1259.

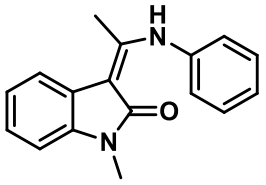


1-benzyl-3-fluoroindolin-2-one (**6ab'**).[33] **^{1}H NMR** for (400 MHz, $CDCl_3$) (400 MHz, $CDCl_3$) δ 7.46 (d, J = 7.6, 1H), 7.31-7.25 (m, 6H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.71 (d, *J* = 7.9 Hz, 3H), 5.73 (d, *J* = 51.0 Hz, 1H), 4.86 (q, *J* = 25.88 Hz, 2H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 171.3 (d, *J* = 17.9 Hz), 143.9 (d, *J* = 5.1 Hz), 135.0, 131.5 (d, *J* = 3.4 Hz), 128.8, 128.0

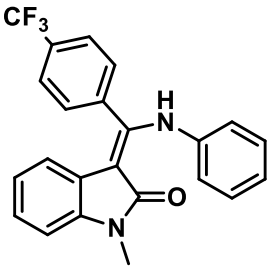


(d, *J* = 6.5 Hz), 127.4, 126.2 (d, *J* = 1.2 Hz), 123.4 (d, *J* = 2.9 Hz), 122.9 (d, *J* = 16.4 Hz), 109.9 (d, *J* = 1.4 Hz), 85.5 (d, *J* = 188 Hz), 43.9. **^{19}F NMR** (377 MHz, CDCl3) δ -192.35.

1-methyl-3-(1-(phenylamino)ethylidene)indolin-2-one (8a): 3-(1-aminoethylidene)-1-methylindolin-2-one (18.8 mg, 0.1 mmol), Cs_2CO_3 (48.7 mg, 0.15 mmol), bromobenzene (23.5 mg, 0.15 mmol), and 2,2'-bipyridine (1.6 mg, 0.01 mmol) and CuI (1.9 mg, 0.01 mmol) were allowed to react in 20 mL resealable pressure tube according to method E to afford 1-methyl-3-(1-(phenylamino)ethylidene)indolin-2-one **8a** (17 mg, 65%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.12 (s, 1H), 7.46 – 7.41 (m, 3H), 7.31 – 7.27 (m, 1H), 7.22 (d, *J* = 8 Hz, 2H), 7.16 (td, *J* = 8, 1.1 Hz, 1H), 7.08 (td, *J* = 8, 1.1 Hz, 1H), 6.97 (d, *J* = 8 Hz, 1H), 3.43 (s, 3H), 2.57 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 168.8, 157.2, 138.1, 137.9, 129.4, 125.9, 125.2, 124.6, 123.0, 121.1, 118.9, 107.7, 96.9, 25.6, 17.6. **IR** (neat) = 3049, 2928, 1627, 1582, 1469 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calculated for $C_{17}H_{17}N_2O$ 265.1341; found: 265.1343.

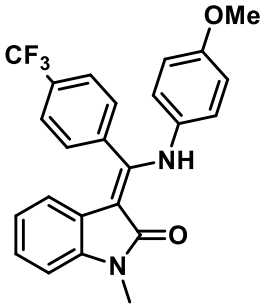


1-methyl-3-((phenylamino)(4-(trifluoromethyl)phenyl)methylene)indolin-2-one (**8b**): 3-(amino(4-(trifluoromethyl)phenyl)methylene)-1-methylindolin-2-one (31.8 mg, 0.1 mmol), Cs_2CO_3 (48.7 mg, 0.15 mmol), bromobenzene (23 mg, 0.15 mmol), and 2,2'-bipyridine (1.6 mg, 0.01 mmol) and CuI (1.9 mg, 0.01 mmol) were allowed to react in 20 mL resealable pressure tube according to method E to afford 1-methyl-3-((phenylamino)(4-(trifluoromethyl)phenyl)methylene)indolin-2-one **8b** (28 mg, 71%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.00 (s, 1H), 7.76 (d, *J* = 8.1 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.12 (t, *J* = 7.8 Hz, 2H), 7.05 (td, *J* = 7.7, 1.0 Hz, 1H), 6.99 (t, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 7.7 Hz, 1H), 6.73 (d, *J* = 7.6 Hz, 2H), 6.69 (td, *J* = 7.7, 1.0 Hz, 1H), 5.95 (d, *J* = 7.7 Hz, 1H), 3.41 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 169.2, 154.5, 138.60, 138.5, 136.8, 132.53 (q, *J* = 32.71 Hz), 129.7, 129.0, 126.36 (q, *J* = 3.7 Hz), 124.7, 124.1, 123.8 (q, *J* = 270.8 Hz), 123.3, 123.2, 122.4, 121.1, 119.7, 118.5, 107.8, 98.1, 25.8. **IR** (neat) = 2982, 2926, 1736, 1457 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calculated for $C_{23}H_{18}F_3N_2O$ 395.1371; found: 395.1372.



3-(((4-methoxyphenyl)amino)(4-(trifluoromethyl)phenyl)methylene)-1-methylindolin-2-one (8c): 3-(amino(4-(trifluoromethyl)phenyl)methylene)-1-methylindolin-2-one (31.8 mg, 0.1 mmol), Cs_2CO_3 (48.7 mg, 0.15 mmol), 4-methoxy-bromobenzene (28 mg, 0.15 mmol), 2,2'-bipyridine (1.6 mg, 0.01 mmol) and CuI (1.9 mg, 0.01 mmol) were allowed to react in 20 mL resealable pressure tube according to

method E to afford 3-(((4-methoxyphenyl)amino)(4-(trifluoromethyl)phenyl)methylene)-1-methylindolin-2-one **8c** (28 mg, 66%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.85 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 7.9 Hz, 2H), 7.05 (td, *J* = 7.7, 1.1 Hz, 1H), 6.89 (d, *J* = 7.7 Hz, 1H), 6.71 (ddd, *J* = 10.5, 7.1, 1.6 Hz, 3H), 6.68 – 6.64 (m, 2H), 5.93 (d, *J* = 7.4 Hz, 1H), 3.72 (s, 3H), 3.41 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 169.3, 157.0, 155.6, 138.4, 136.8, 131.8 (q, *J* = 32.6 Hz), 131.3, 129.7, 126.21 (q, *J* = 3.7 Hz), 125.6, 123.83 (q, *J* = 270.7 Hz), 123.82, 123.5, 120.9, 118.3, 114.2, 107.7, 97.2, 55.4, 25.7. **IR** (neat) = 2922, 2856, 1725, 1610, 1512, 1462 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calculated for $C_{24}H_{20}F_3N_2O_2$ 424.1477; found: 424.1479.



4.11. Appendix IV: Copies of ^{1}H, $^{13}C\{^{1}H\}$ and ^{19}F NMR spectra and crystal structure of representative compounds

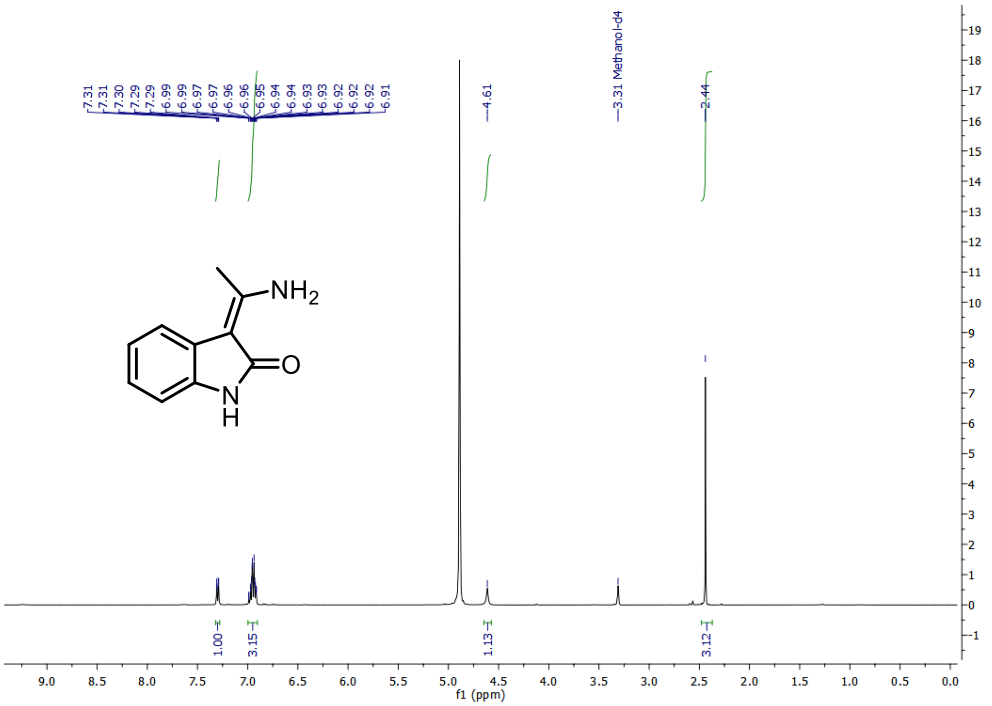


Figure 4.10. ^{1}H NMR of compound **3a**

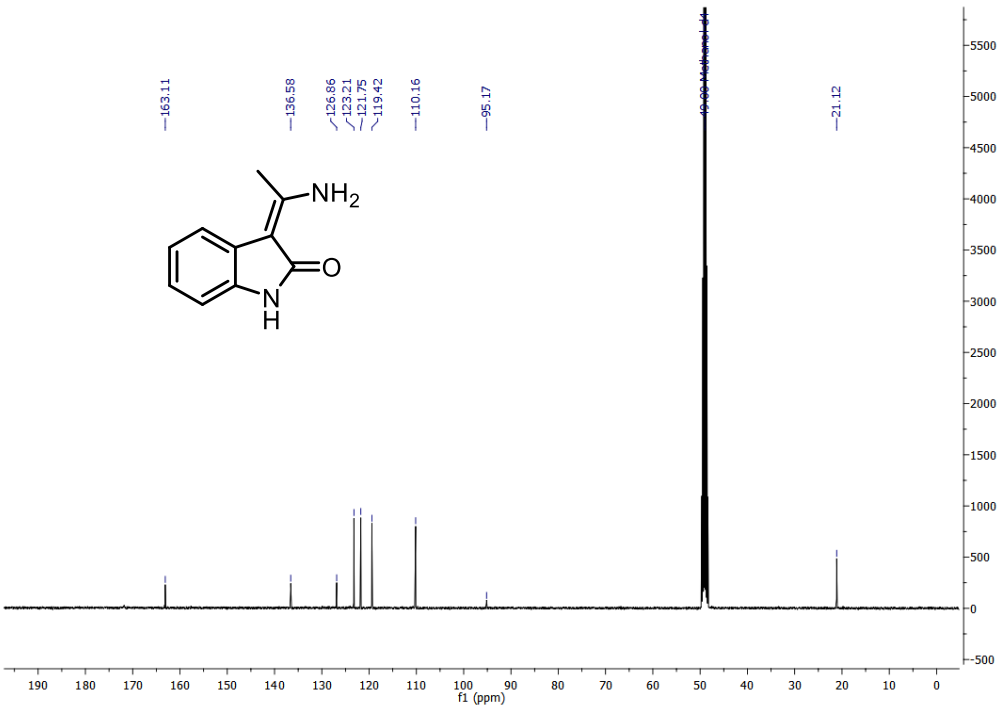


Figure 4.11. ^{13}C{^{1}H} NMR of compound **3a**

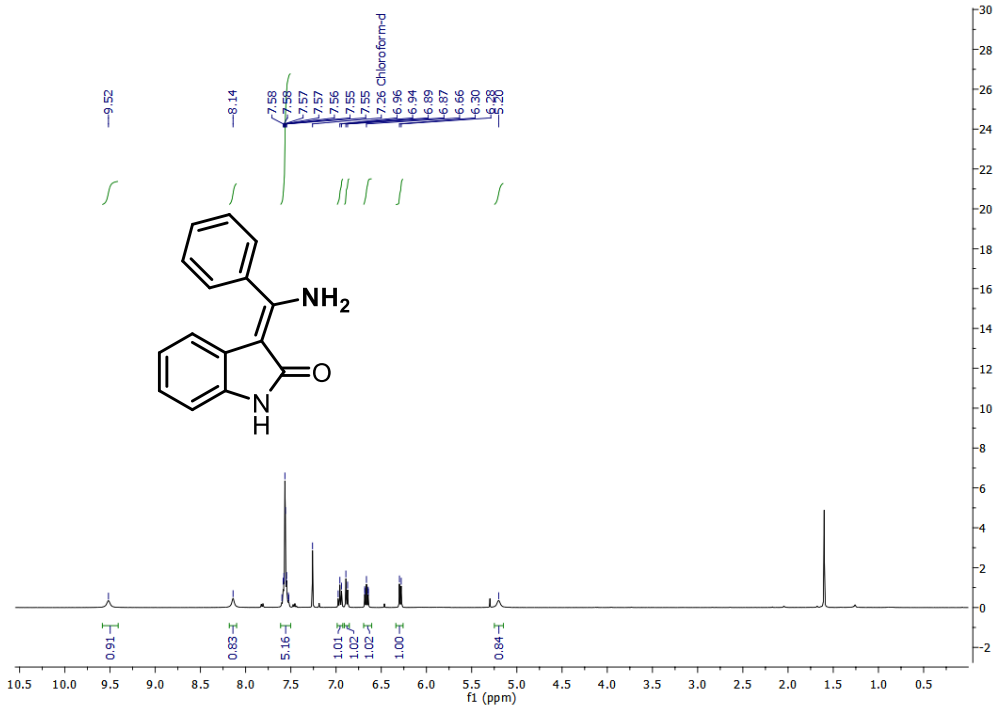


Figure 4.12. ^{1}H NMR of compound **3b**

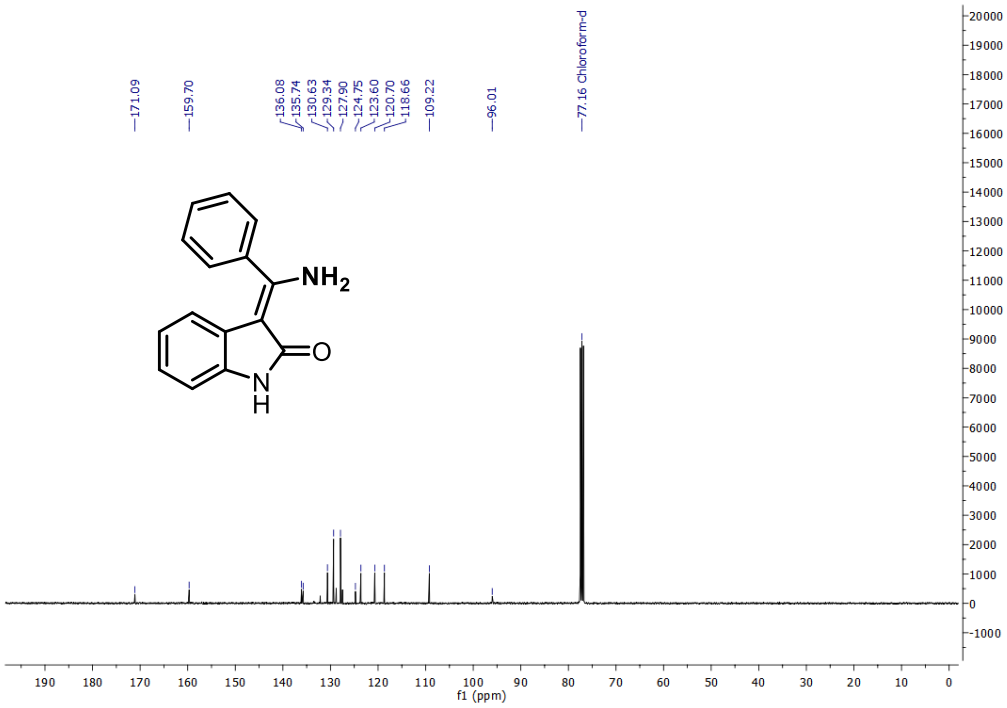


Figure 4.13. ^{13}C{^{1}H} NMR of compound **3b**

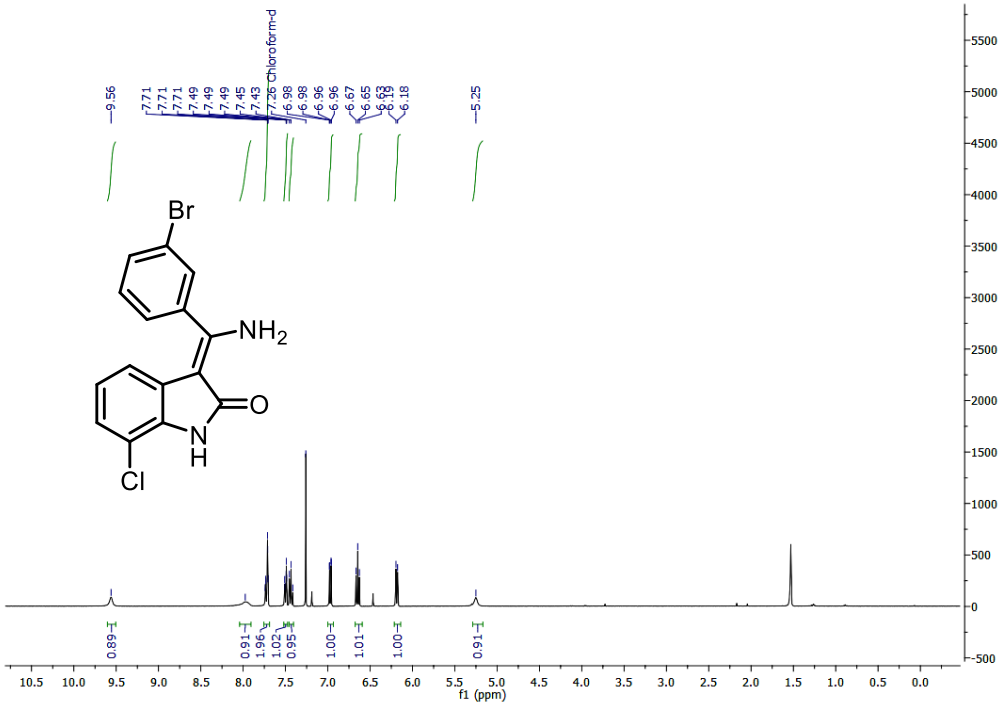


Figure 4.14. ^{1}H NMR of compound **3e**

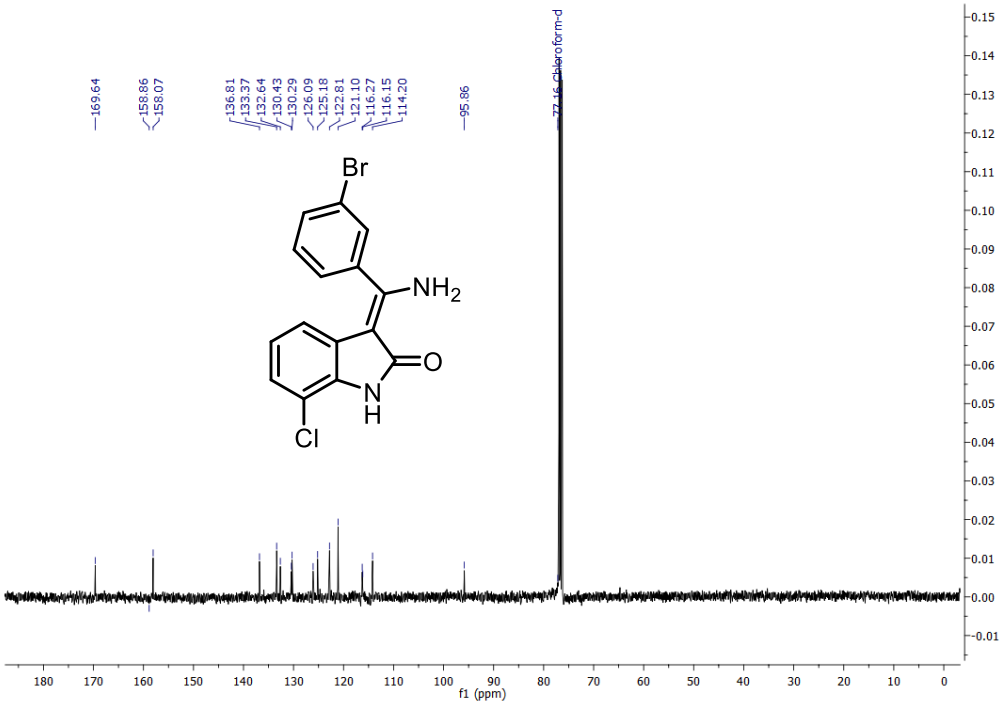


Figure 4.15. ^{13}C{^{1}H} NMR of compound **3e**

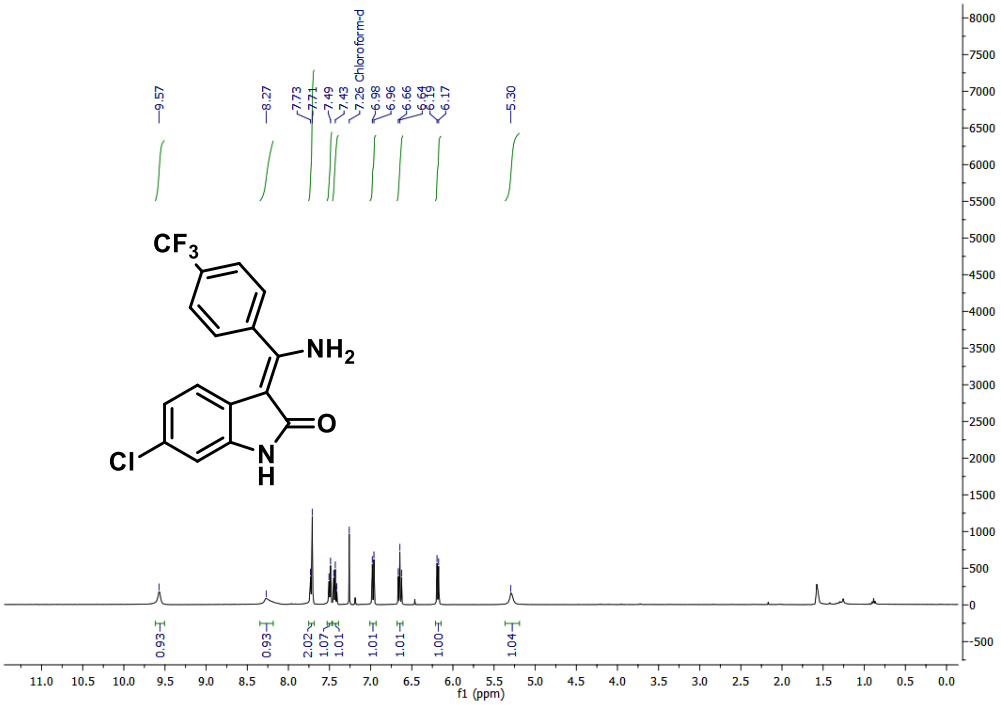


Figure 4.16. ^{1}H NMR of compound **3i**

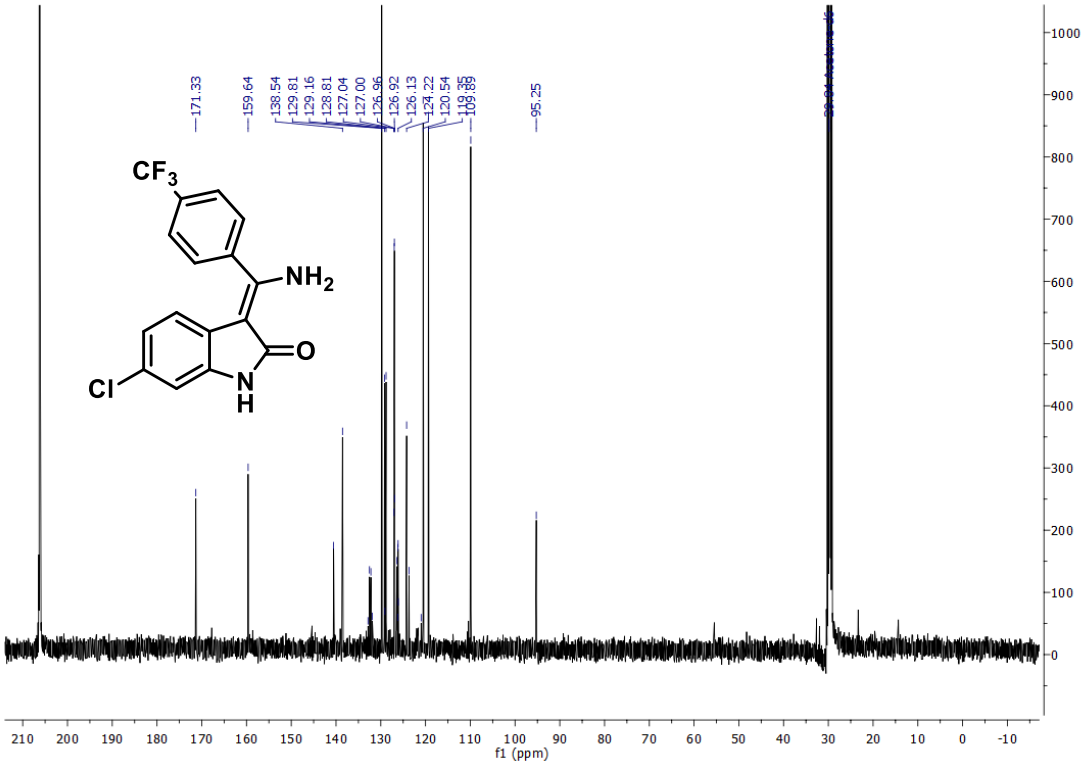


Figure 4.17. ^{13}C{^{1}H} NMR of compound **3i**

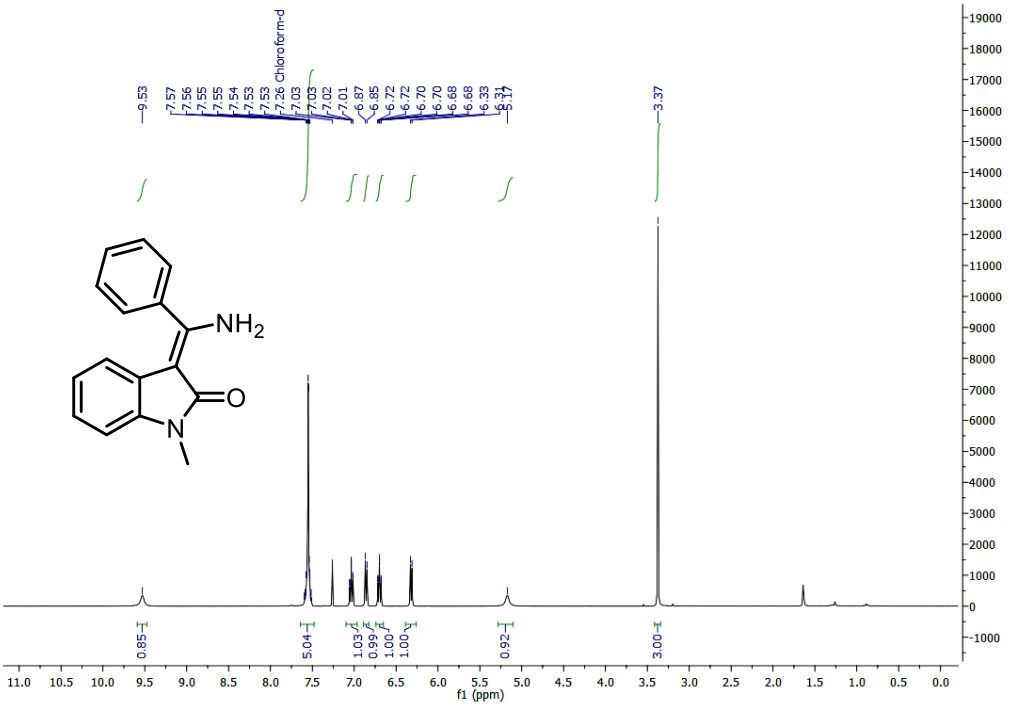


Figure 4.18. ^{1}H NMR of compound **3k**

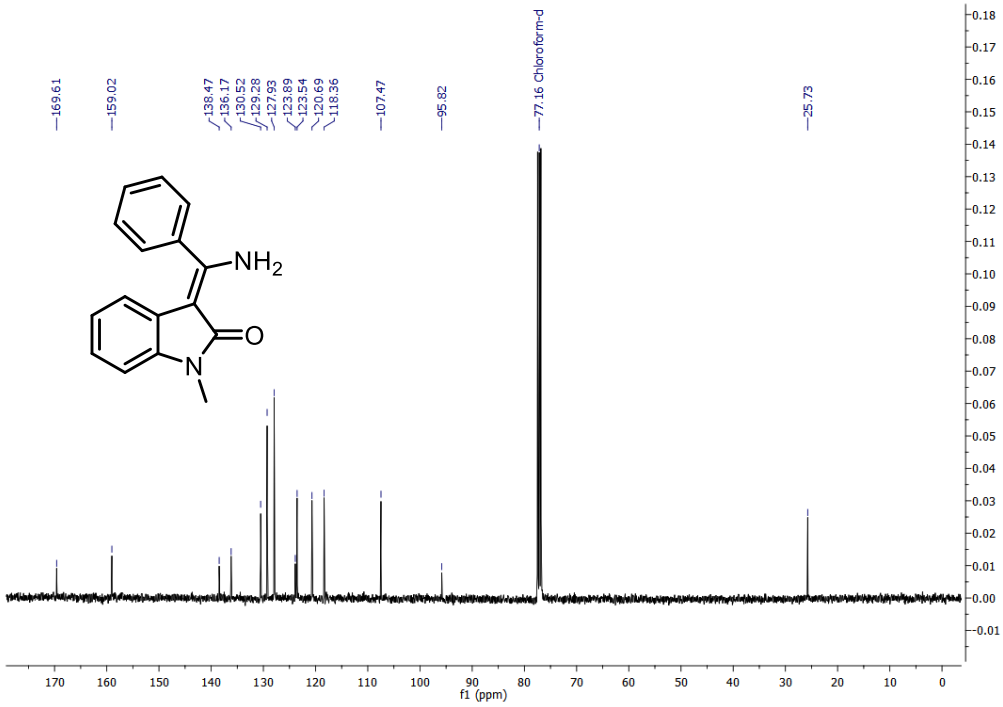


Figure 4.19. ^{13}C{^{1}H} NMR of compound **3k**

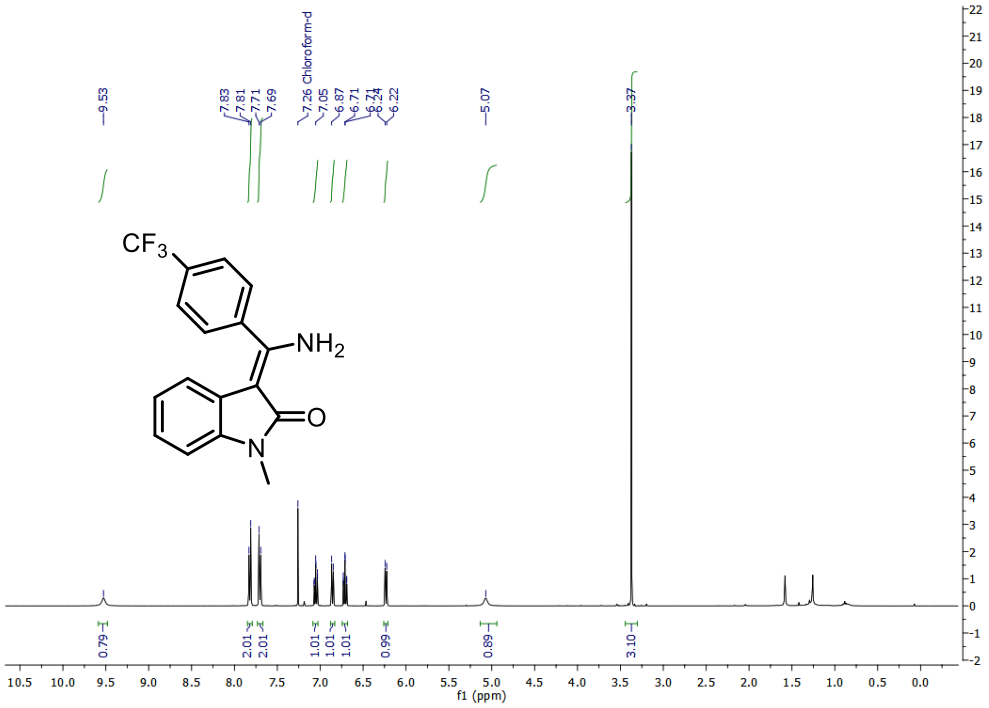


Figure 4.20. ^{1}H NMR of compound **3o**

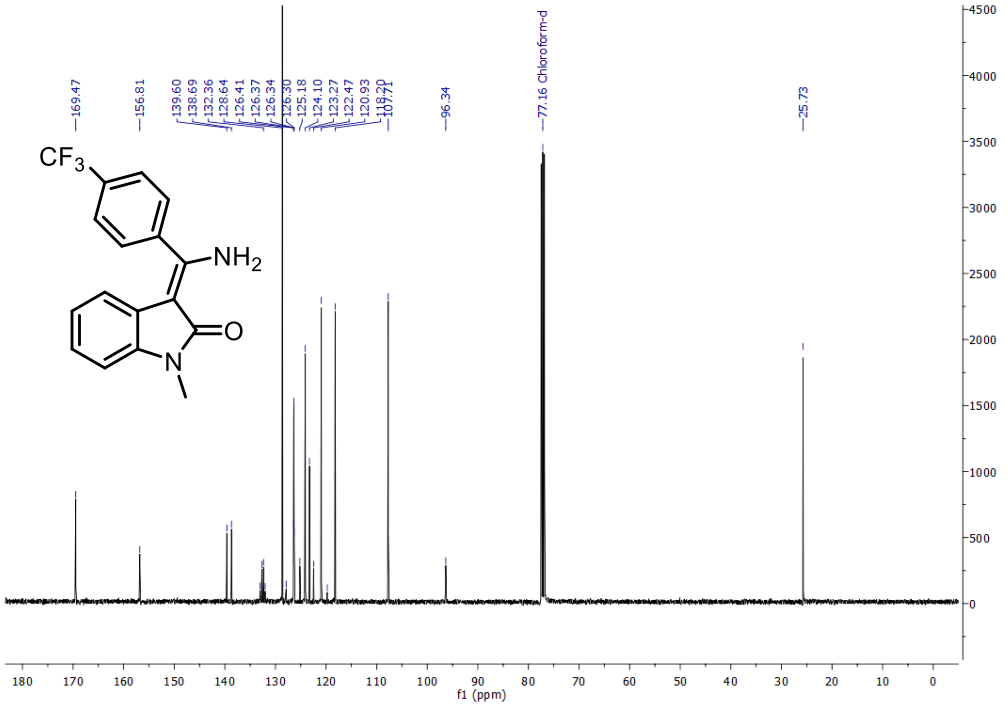


Figure 4.21. ^{13}C{^{1}H} NMR of compound **3o**

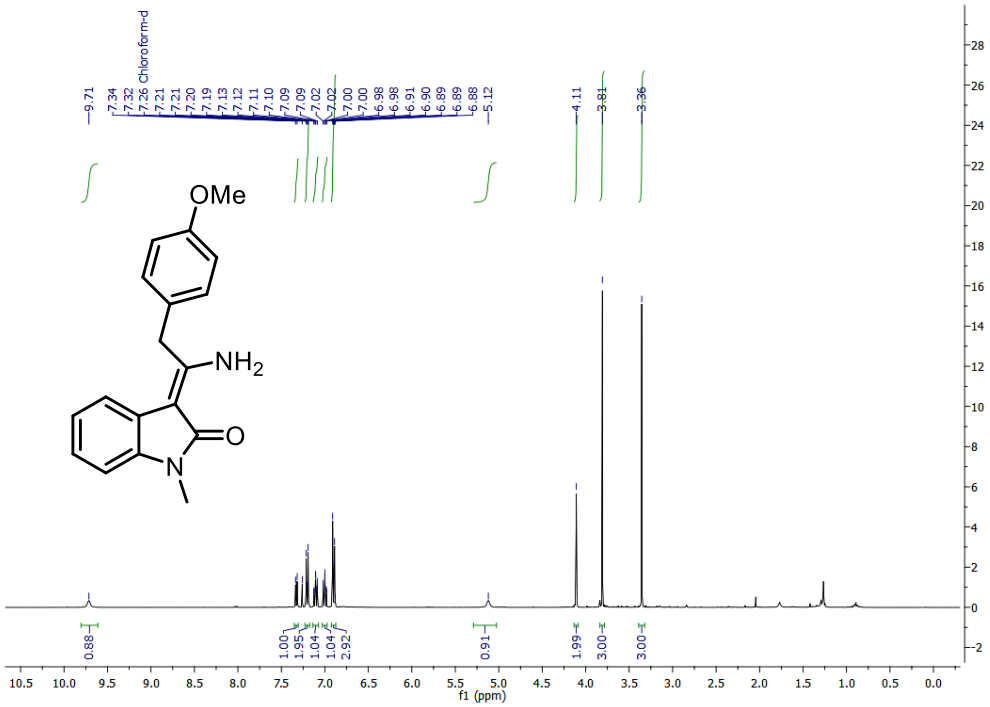


Figure 4.22. ^{1}H NMR of compound **3r**

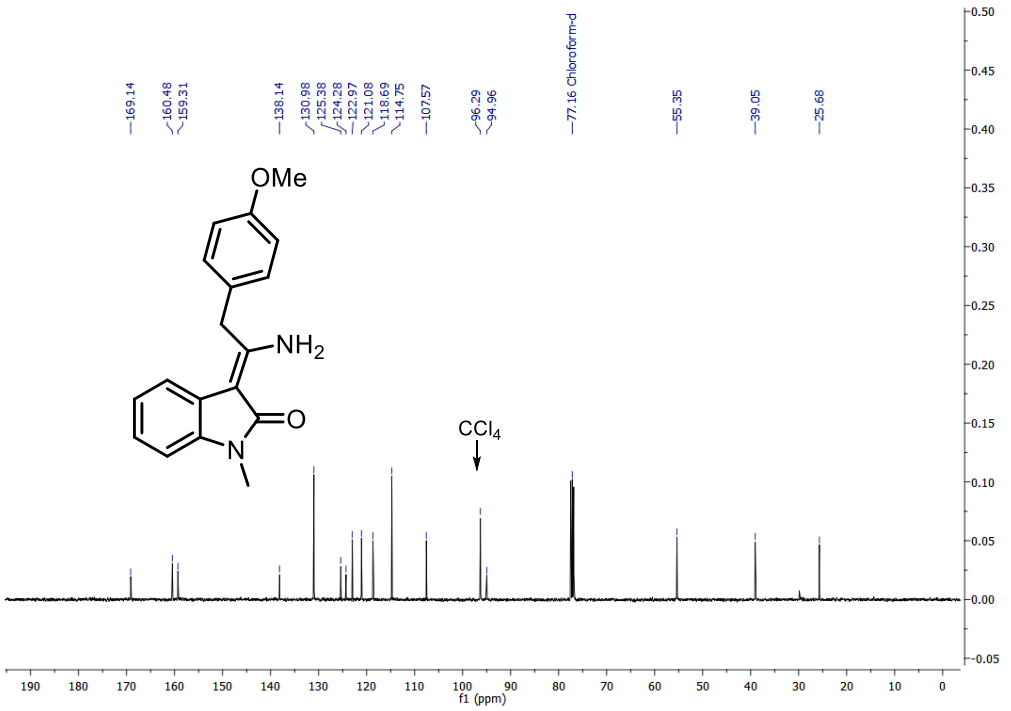


Figure 4.23. ^{13}C{^{1}H} NMR of compound **3r**

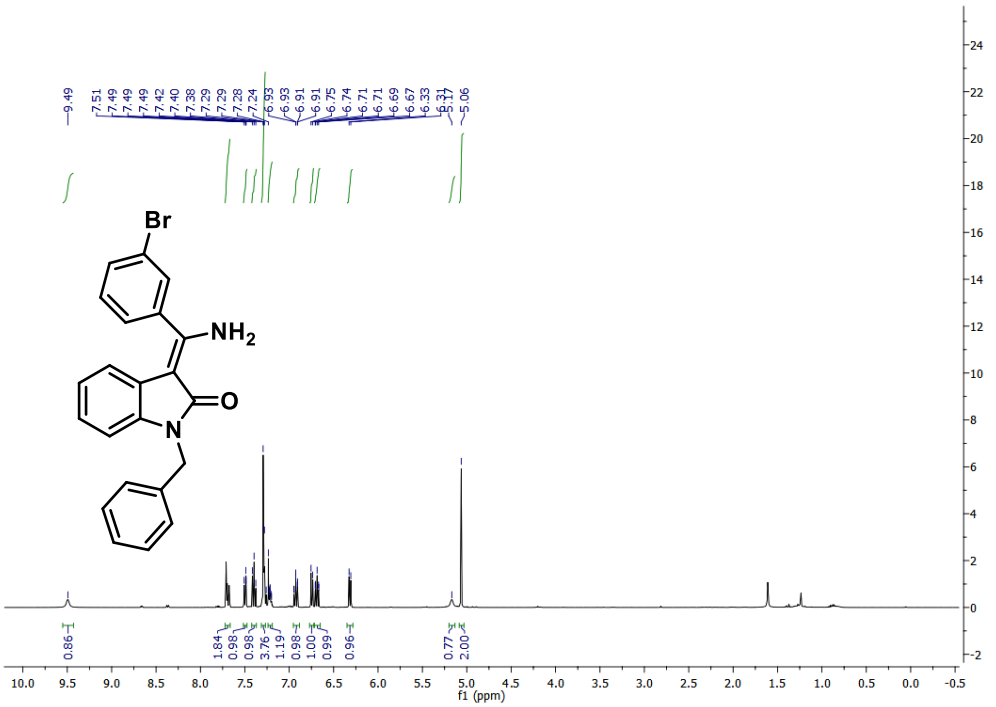


Figure 4.24. ^{1}H NMR of compound **3t**

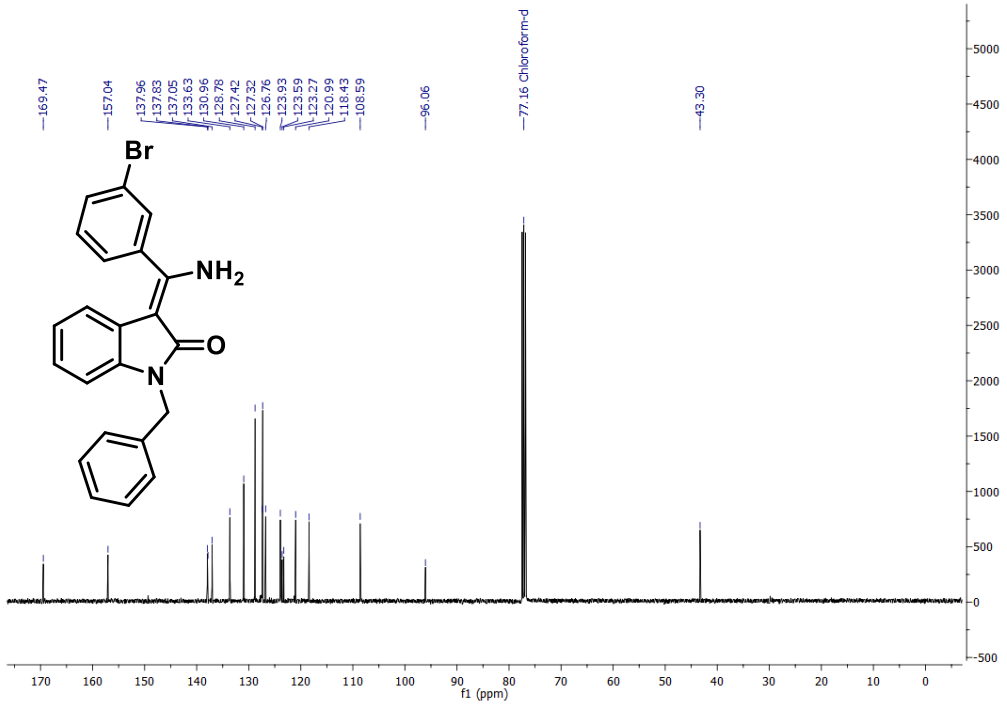


Figure 4.25. ^{13}C{^{1}H} NMR of compound **3t**

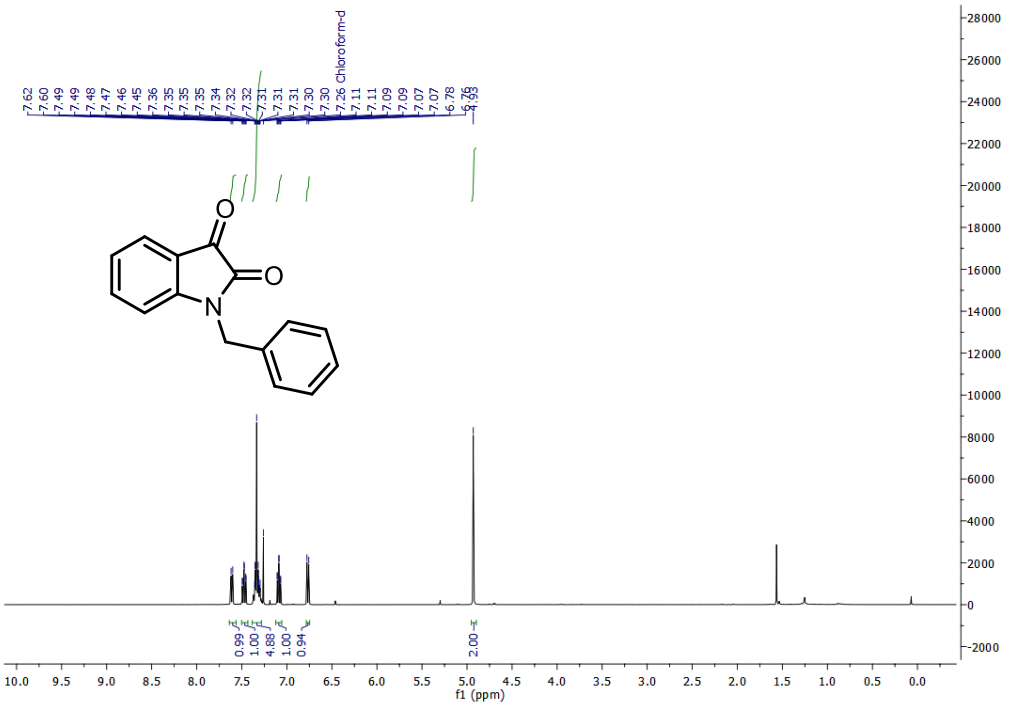


Figure 4.26. ^{1}H NMR of compound **4b**

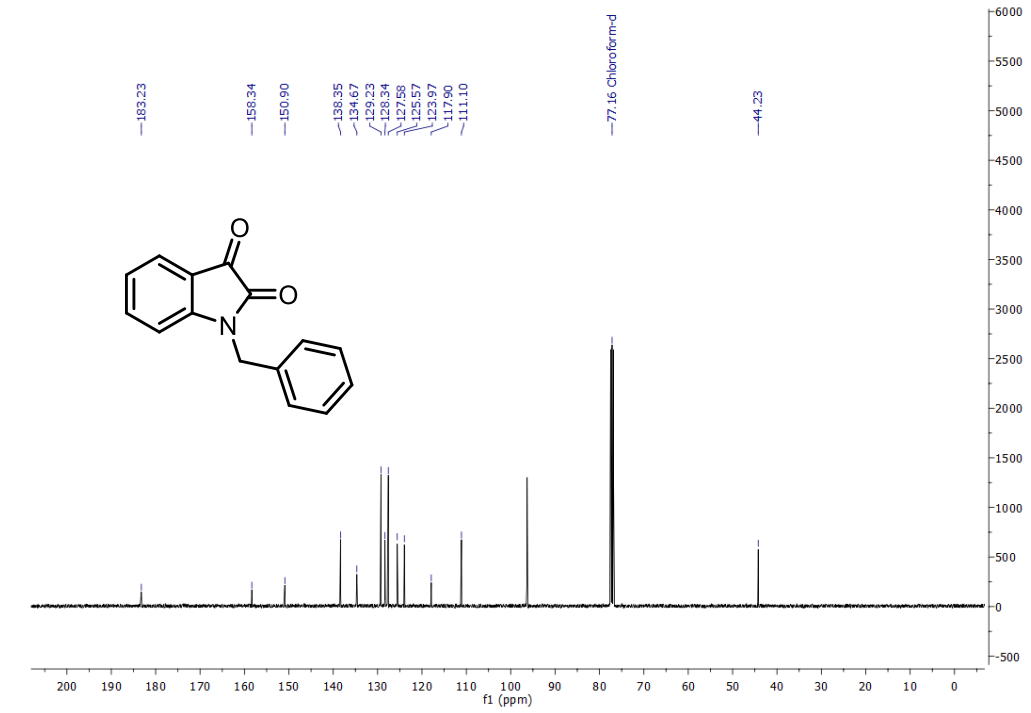


Figure 4.27. ^{13}C{^{1}H} NMR of compound **4b**

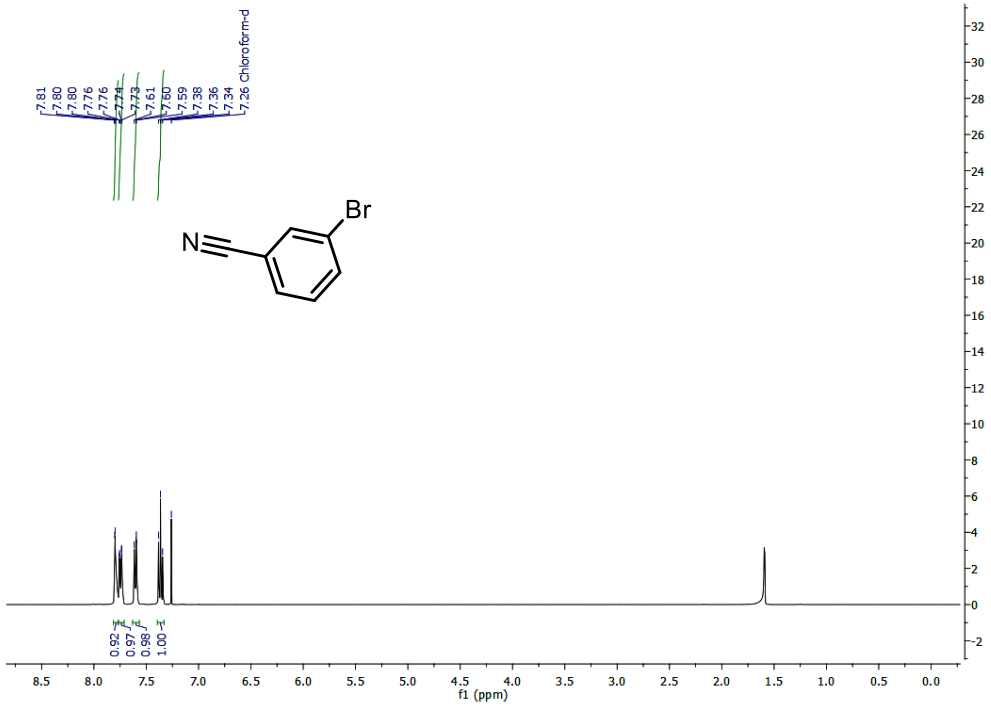


Figure 4.28. ^{1}H NMR of Compound **5b**

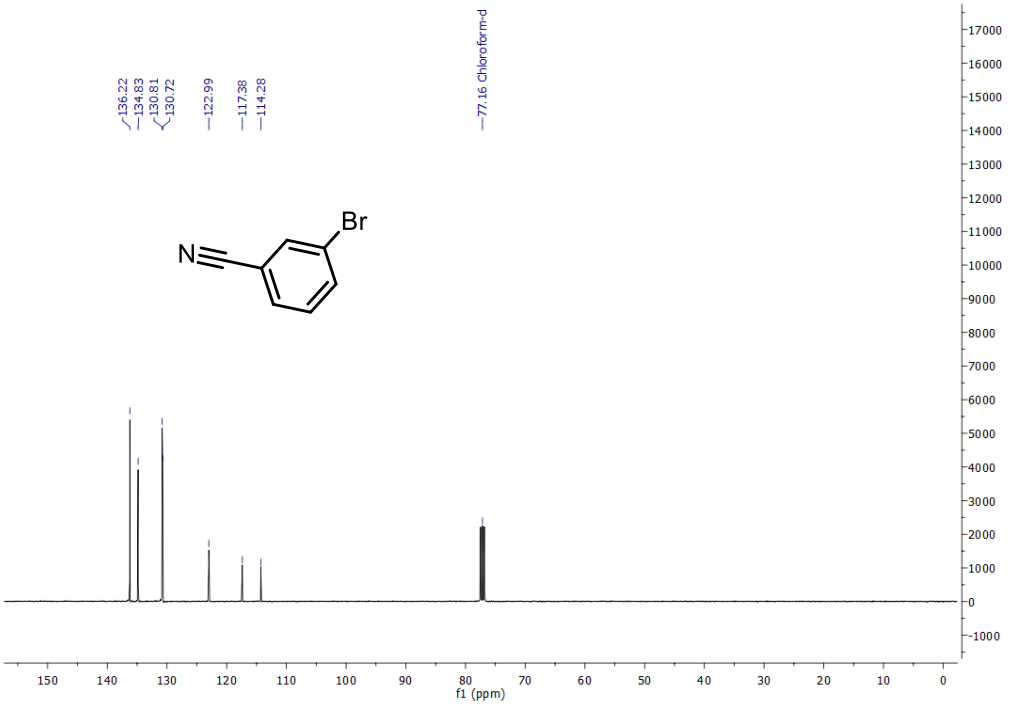


Figure 4.29. ^{13}C{^{1}H} NMR of Compound **5b**

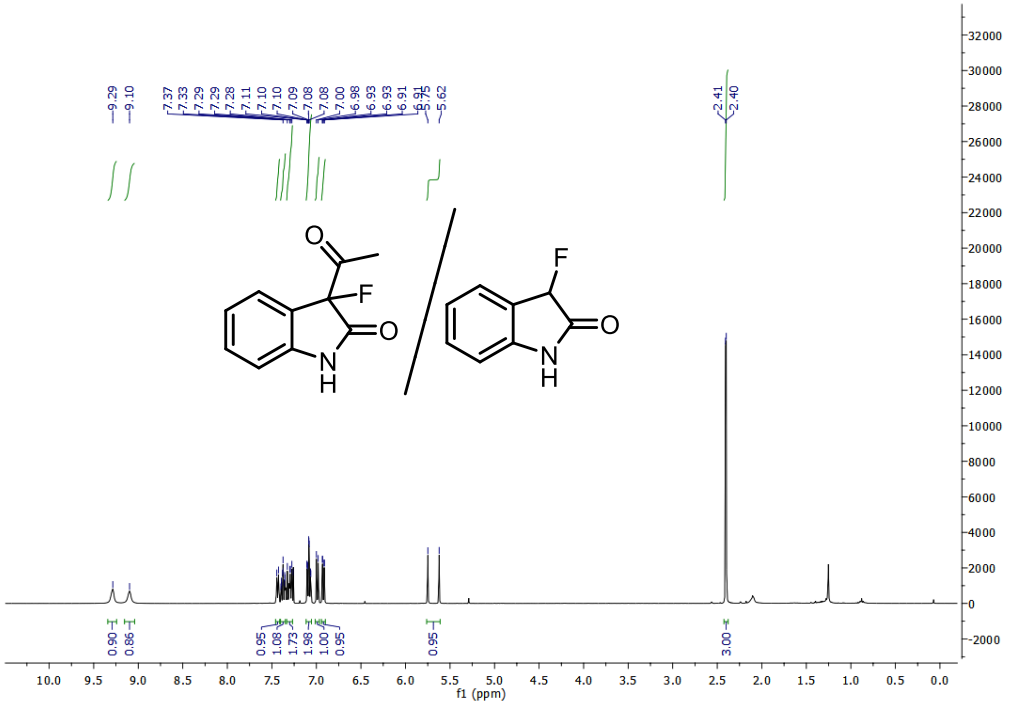


Figure 4.30. ^{1}H NMR of Compound **6a**

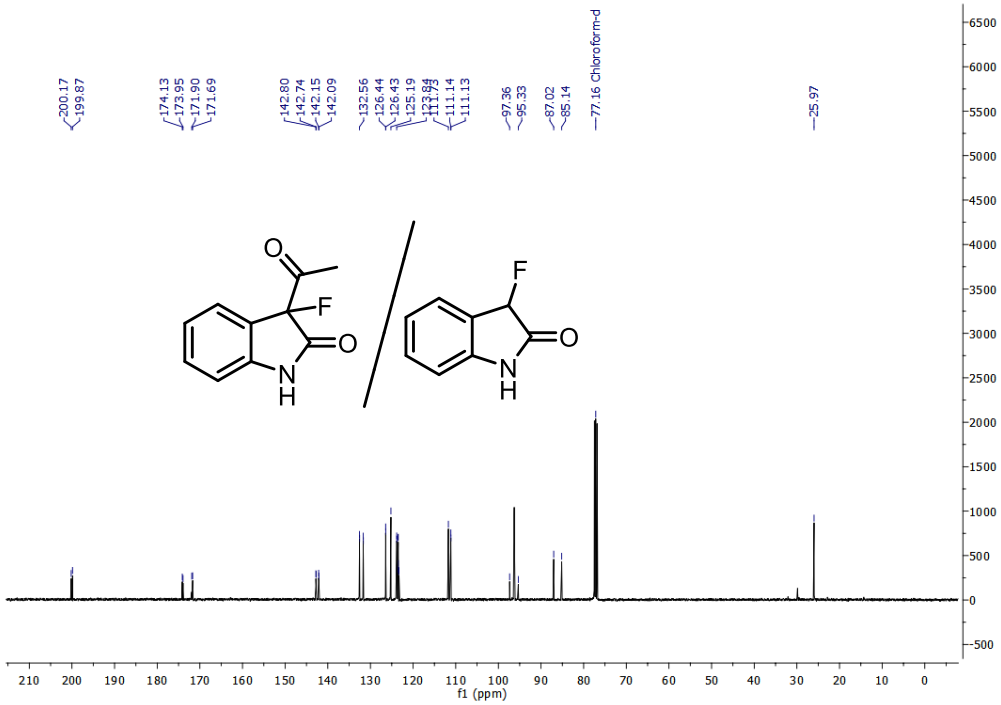


Figure 4.31. ^{13}C{^{1}H} NMR of Compound **6a**

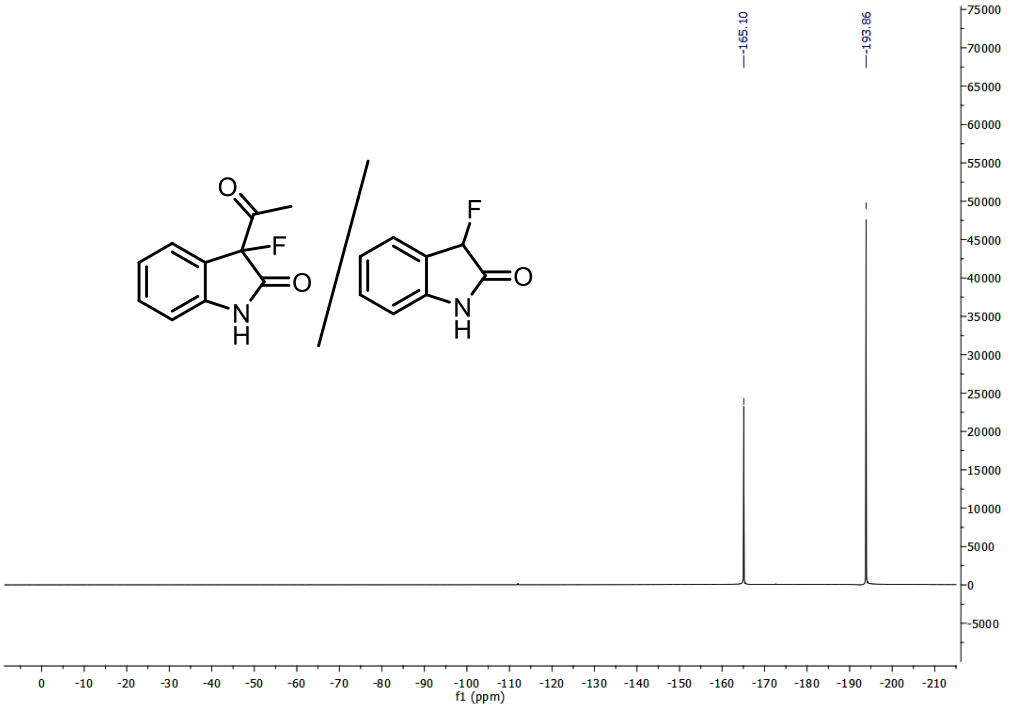


Figure 4.32. ^{19}F NMR of Compound **6a**

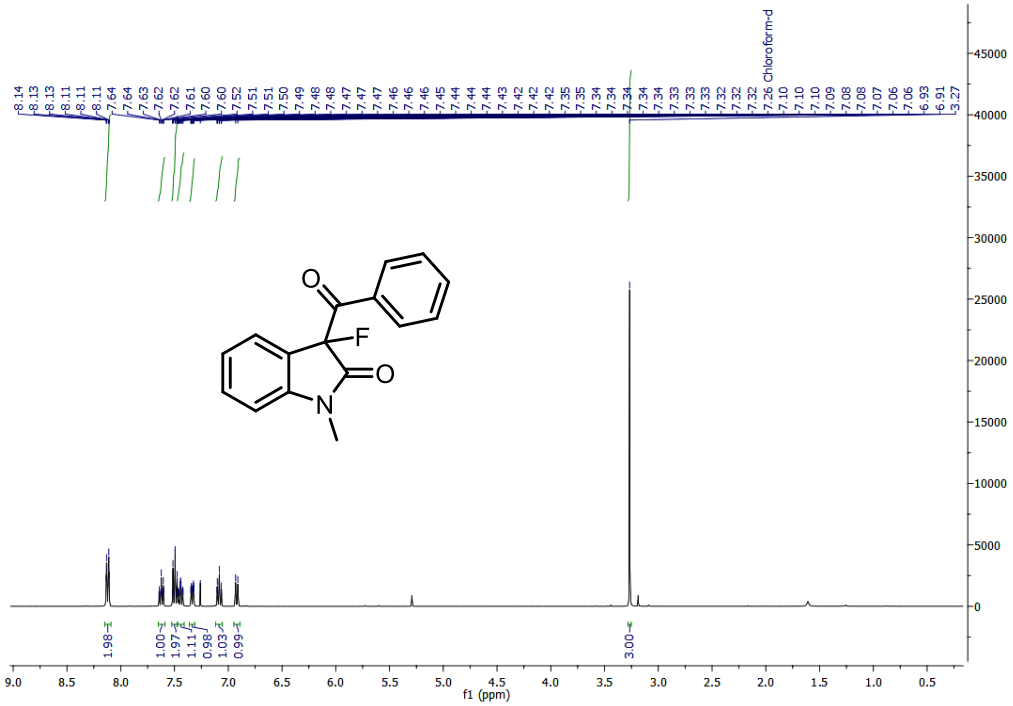


Figure 4.33. ^{1}H NMR of Compound **6c**

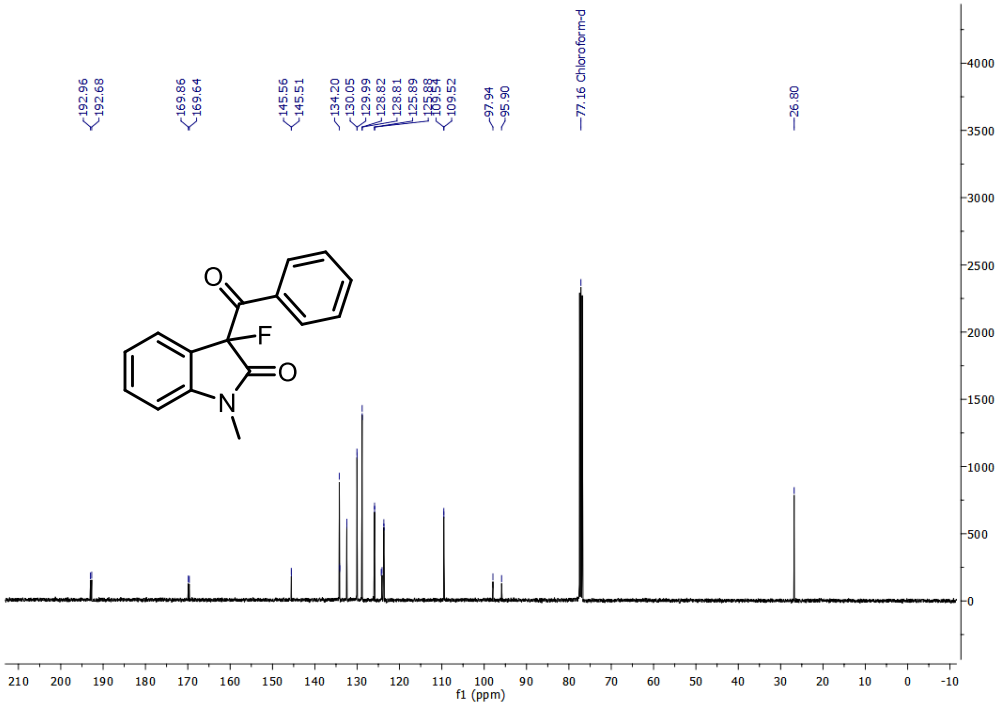


Figure 4.34. $^{13}C\{^{1}H\}$ NMR of Compound **6c**

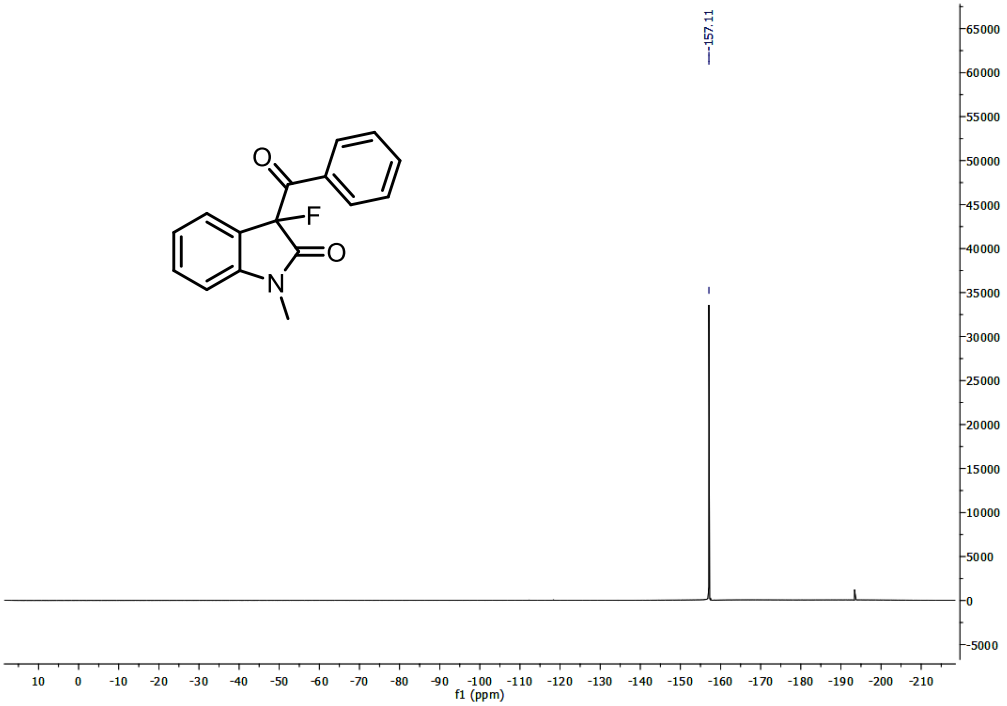


Figure 4.35. ^{19}F NMR of Compound **6c**

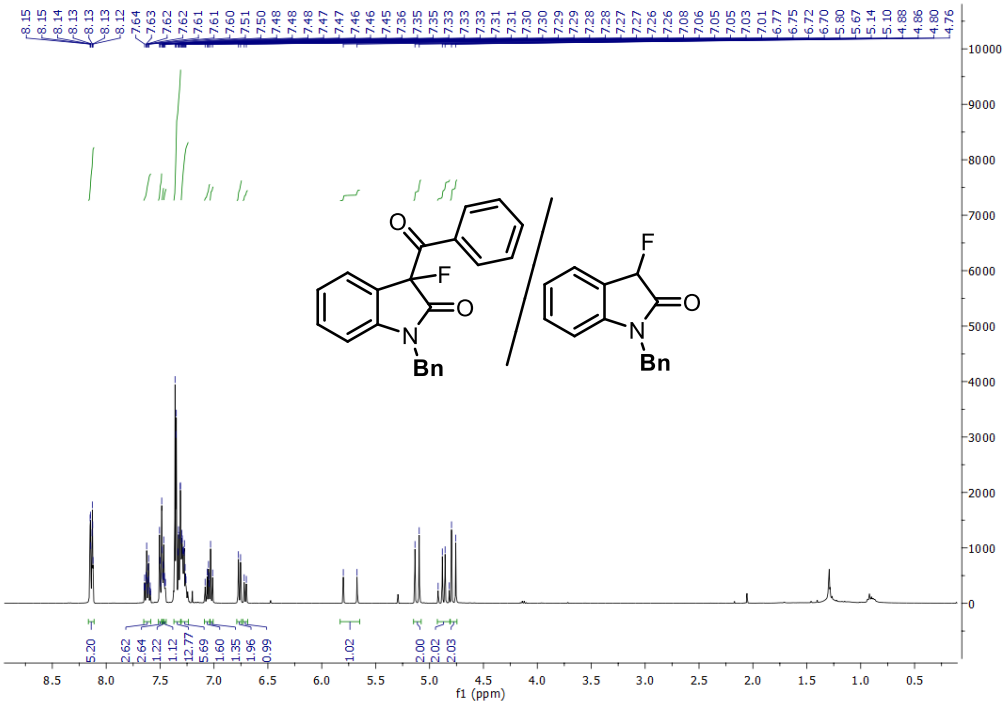


Figure 4.36. ^{1}H NMR of Compound **6e**

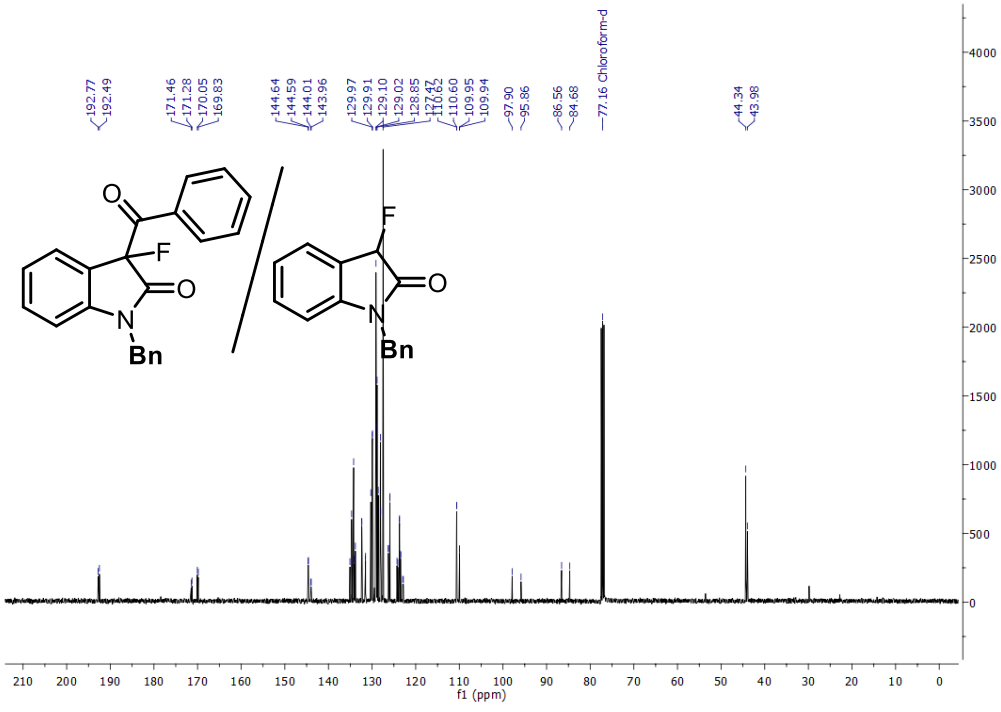


Figure 4.37. ^{13}C{^{1}H} NMR of Compound **6e**

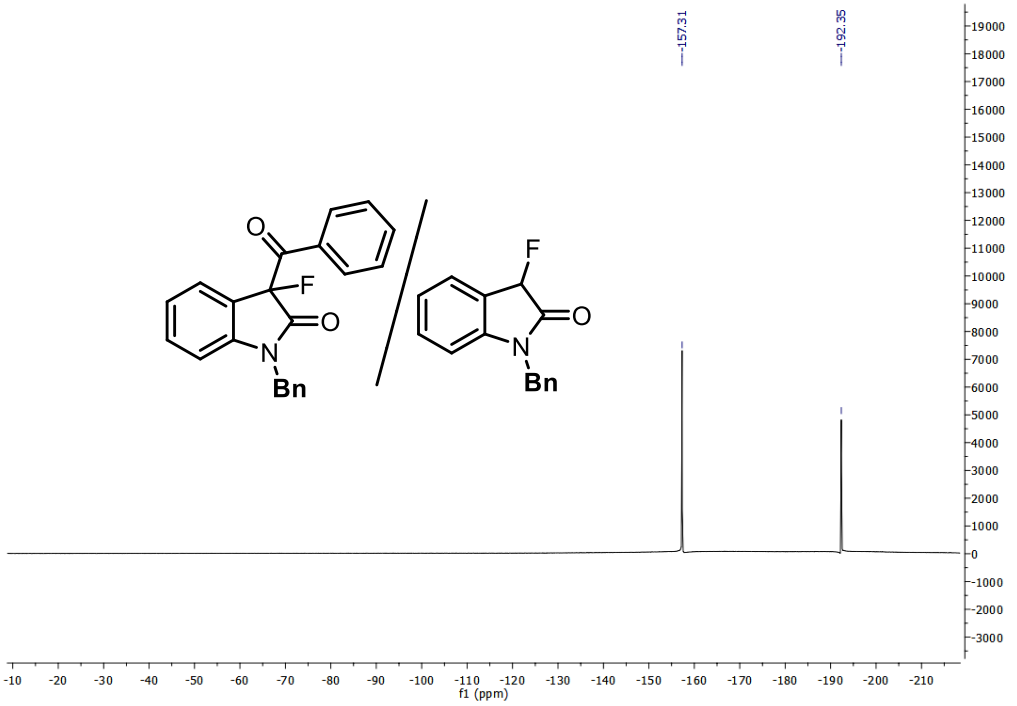


Figure 4.38. ^{19}F NMR of Compound **6e**

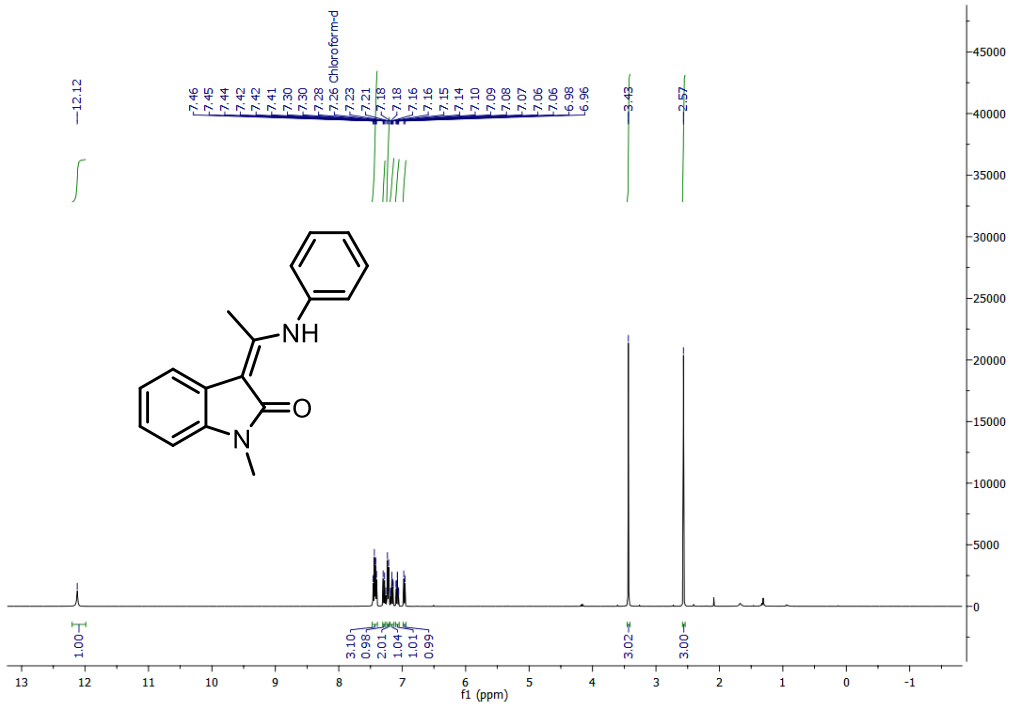


Figure 4.39. ^{1}H NMR of Compound **8a**

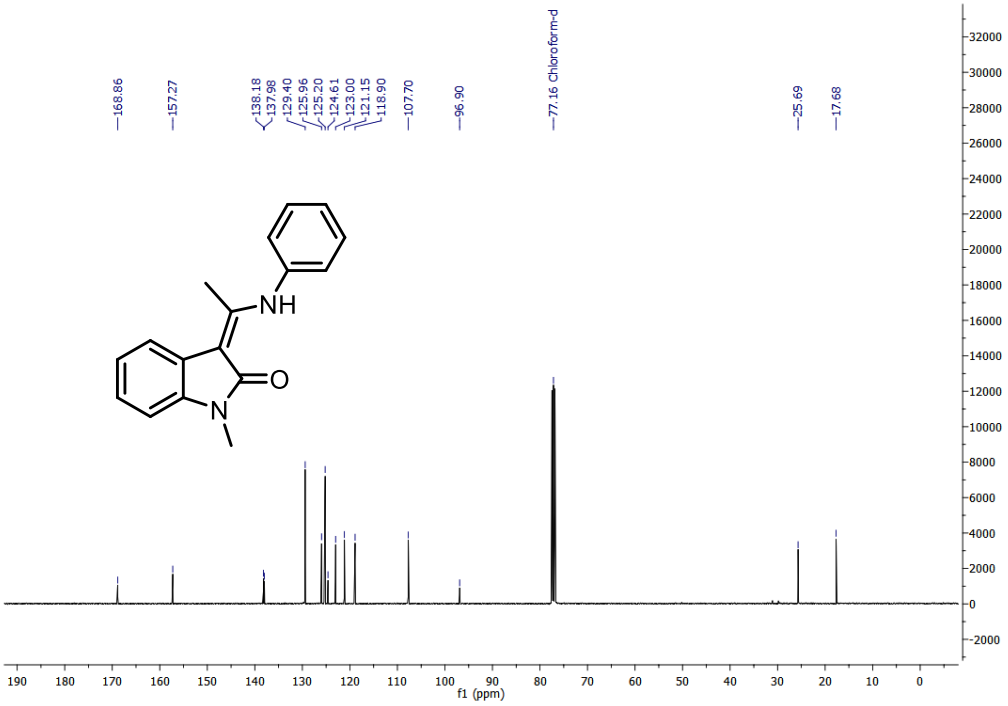


Figure 4.40. $^{13}C\{^{1}H\}$ NMR of Compound **8a**

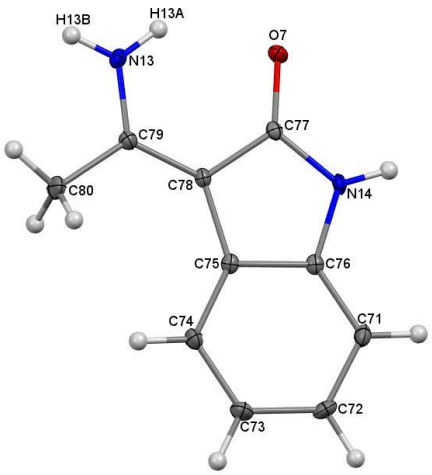


Figure 4.41. Crystal structure of compound **3a**

4.12. References

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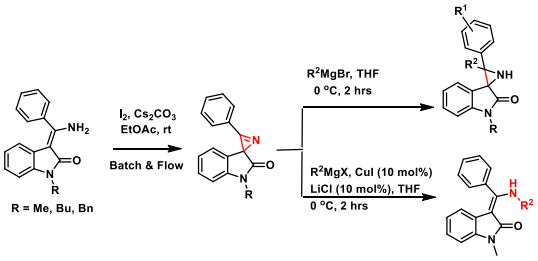
Chapter 5

Synthesis of Quaternary Spirooxindole 2*H*-Azirines Derivatives under Batch and Continuous Flow and its Synthetic Application

Synthesis of Quaternary Spirooxindole 2*H*-Azirines Derivatives under Batch and Continuous Flow and its Synthetic Application

5.1. Abstract

In this chapter, we have developed an efficient approach for the synthesis of spirooxindole 2*H*-azirines *via* the intramolecular oxidative cyclization of 3-(amino(phenyl)methylene)-indolin-2-one derivatives in the presence of I_2 and Cs_2CO_3 under batch/continuous flow. The method requires mild conditions and is facile for the synthesis of a variety of spirooxindole 2*H*-azirines derivatives. Furthermore, we have synthesized spirooxindole *2H*-aziridines and *N*-substituted 3-(aminobenzylidene)indolin-2-ones derivatives through addition of Grignard regent. On changing the reaction condition formation of different product was observed in the reaction mixture.



5.2. Introduction to continuous flow chemistry

In the last decade, flow chemistry has emerged in the field of organic synthesis with a significant pace, specifically for synthetic chemistry. It is an emerging technology for industrial applications with extensive success in both multistep and short synthesis. This technology has several advantages over batch processes such as efficient heat and mass transfer,[1] ease in carrying out high-temperature/pressure reactions with great care,[2] controlled mixing, facile scale-up, controlled addition or use of reactive and sensitive intermediates, and the replacement of toxic reagents. This chemical technology is an interface between engineering and chemistry. Further, flow chemistry can be integrated with other technologies, such as, electrochemistry and microwave irradiation, resulting in the improvement of the productivity of chemical transformations.[3] Also, the flow module is greener[4] and safer[5] than traditional batch processes. A representative continuous-flow reactor comprises of the parts as described below.

Figure 5.1. The full setup for the syringe pump in our laboratory

(a) Pumps: In continuous flow chemistry, the function of a pump is to deliver the solutions of reactant or reagents, or solvent from a reaction container/bottle into reaction loops to carry out the desired transformation. The types of pumps that are routinely used in flow chemistry are piston, peristaltic, gear centrifugal or syringe pump.

(b) Reaction loops: In flow chemistry, the reaction loops are arranged to commence a minute volume of reactants or reagents. The main role of the loops is to supply the reagents or solvent into a mixing junction.

(c) T-piece or mixing junction: T-piece or mixing junction is a crucial part of the continuous flow setup. A T-piece is the junction where the different reactants get mixed and the mixture is then passed through the reactor.

(d) Reactor: Several types of reactors are used in continuous flow chemistry whereas, coiled and column reactor being used most frequently. The coiled reactors, which are generally used in homogeneous reactions, provide the desired temperature and retention time for a reaction. On the other hand, the column reactor is used in heterogeneous reaction conditions. This type of reactor is completely different from the coiled reactor, which is made up of a hollow vertical glass or metal tube. During reaction, the solid catalyst and the reagents or scavengers are packed in hollow space.

(e) Back pressure regulator: Back pressure regulator (BPR) plays a very important role in flow chemistry by managing the pressure in the system. Superheating of a

solvent can be achieved by using BPR. For instance, in some cases, the solvent can be heated from 60 to 150 ^{o}C and even beyond its boiling point. Some excellent examples of superheating are, DCM at 158 ºC (*vs* 40 ºC at Atmospheric pressure). THF and 1,4-dioxane can be heated up to 193 ºC and 240 ºC, respectively.

(f) Downstream unit: Continuous flow chemistry can be integrated with a spectroscopic instrument such as, UV, IR, and NMR to monitor the progress of a chemical transformation. Moreover, work-up procedures can be integrated to reduce labour practices.

5.3. Introduction on *2H*-azirines and spirooxindole

2H-azirines are smallest three-membered unsaturated heterocyclic systems containing two carbon and one nitrogen atom. Owing to ring strain, the azirines have a propensity to undergo several transformations. Azirines are considered as one of the most valuable three-membered intermediates in the field of synthetic organic chemistry. In 1932, Neber and co-workers for the first time synthesized *2H*-azirines.[6] Subsequently, the chemistry of azirines became one of the most fascinating areas in organic chemistry due to its widespread application in many synthesis as an intermediate. An addition reaction on the strained three-membered ring of azirines, going from an unsaturated to a saturated three-membered ring, is accompanied by a major drop in energy (109 kJ mol^{-1})[7]. As a result, azirines can act as electrophiles.[9] Additionally, the calculated ring strain energy for these systems is around 45-48 kcal/mol.[8] The reduced azirines *i.e.* aziridines can act as dipolar species in the presence of external Lewis acid and can participate in cycloaddition reactions.[10] Furthermore, *N*-substituted aziridines undergo ring-opening reactions to afford towards the synthesis of a distinct substituted nitrogen-containing target drug and pharmaceutical compounds.[11]

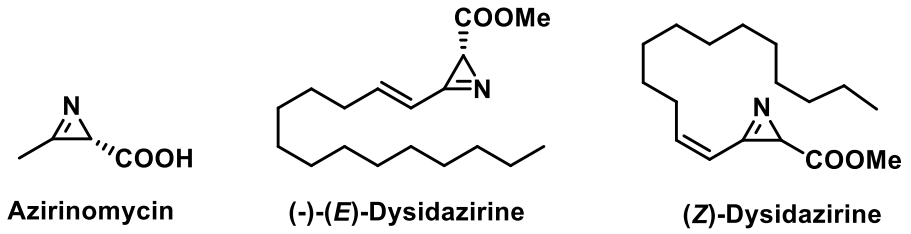


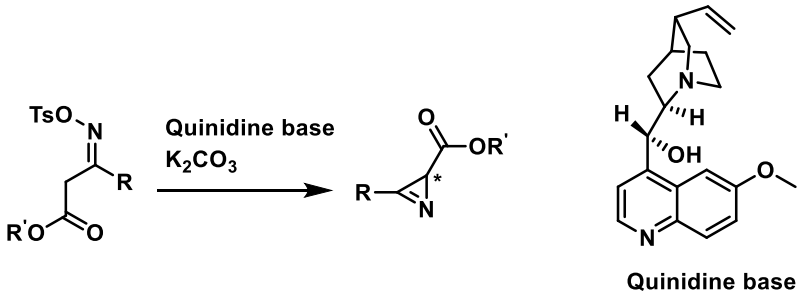
Figure 5.2. Bioactive natural products containing *2H*-azirines motifs

Azirines have also played a central role for the synthesis of heterocyclic moiety such as, pyrrole, indole, azepine, pyridine, and pyrazines.[12] On the other hand *2H*-azirine core has been found in several natural products and has a wide range of

biological activity, for instance, azirinomycin has antibiotic properties whereas, both E and Z isomer of dysidazirine are antifungal in nature (Figure 5.2).[13] Spirocyclic oxindoles can be identified by various three-, four-, five- and six-membered spiro rings fused at the C3 position of the core moiety oxindole. These compounds are significantly important because of their prevalence as structural motifs in a variety of natural products[14]. They also exhibit extensive biological activities such as, anti-HIV,[15] anticancer,[16] antiviral,[17] antimicrobial properties.[18]

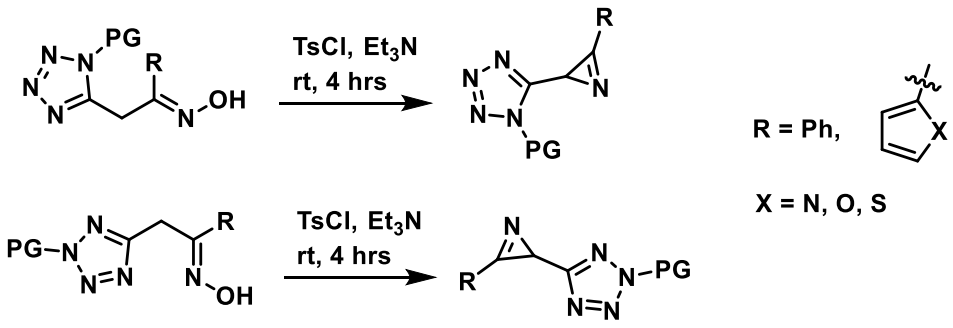
5.4. Literature background for the synthesis of *2H*-azirines and spirooxindole *2H*-azirine

In literature, several methods have been reported for the synthesis of chiral/achiral versions of azirines. The very first method was developed by Neber and co-workers in 1932. After which, several groups used this strategy for the synthesis of various natural products.[19]



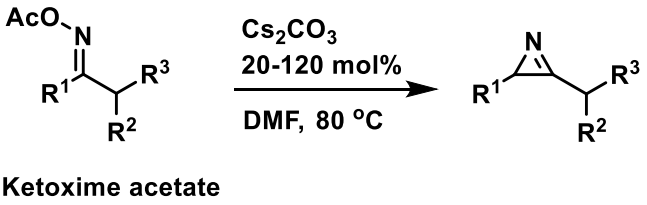
Scheme 5.1. Zwanenburg approach for asymmetric azirine synthesis

Later, several research groups used a similar strategy for the synthesis of azirine based organic moieties. For example, in 1996 by using Neber's strategy Zwanenburg and co-workers achieved an asymmetric version of azirine carboxylic ester with the help of a chiral base (Scheme 5.1).[20]



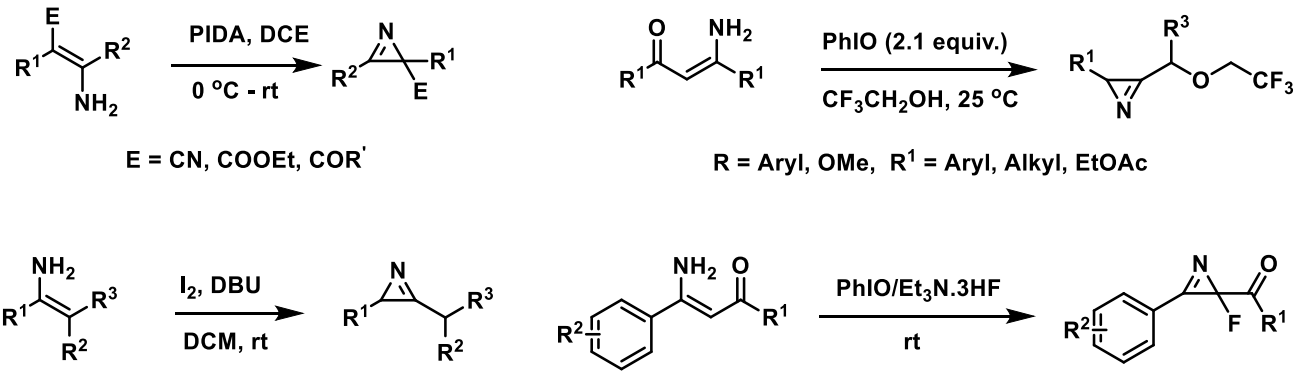
Scheme 5.2. Cardoso *et al.* approach to 2-(tetrazol-5-yl)-*2H*-azirines synthesis

Cardoso *et al.* demonstrated synthesis of novel 2-(tetrazol-5-yl)-2H-azirines having different substituents *viz* phenyl, thiophen-2-yl, furan-2-yl and pyrrol-2-yl at C3 position.[21] Recently in 2018, Guan's group established a synthesis of 2,3-diaryl-*2H*-azirines *via* Neber rearrangement, involving ketoxime acetates as starting material. The reaction proceeded through an intramolecular eliminative cyclization.[22]



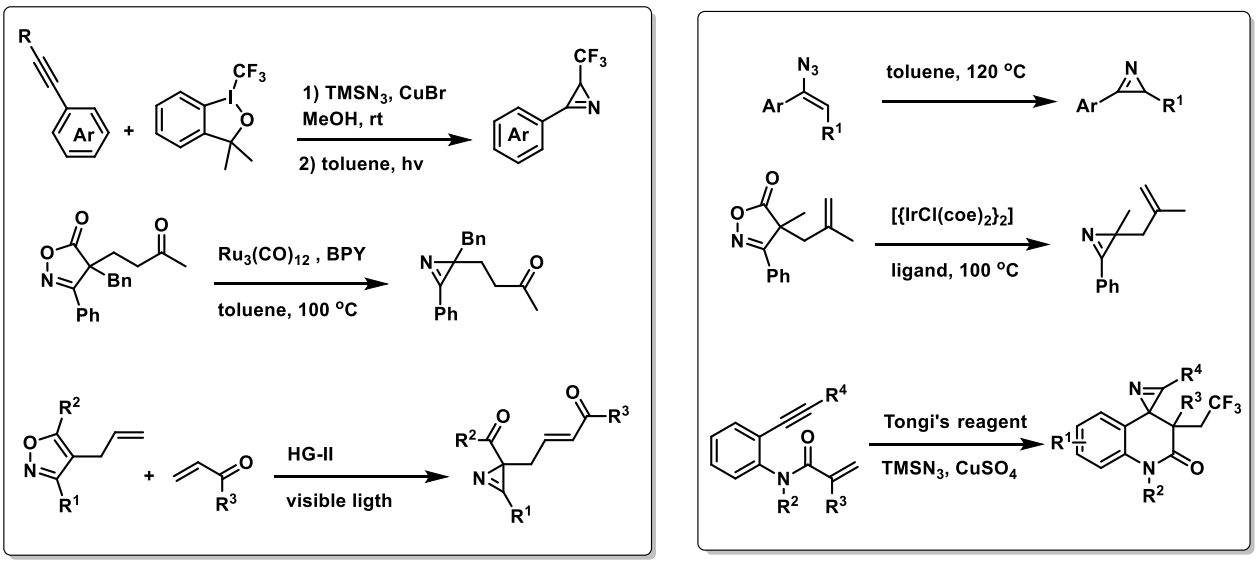
Scheme 5.3. Guan approach for the synthesis of 2,3-diaryl-*2H*-azirine

Enamine and enaminones is a versatile ingredient for the synthesis of several useful intermediates.



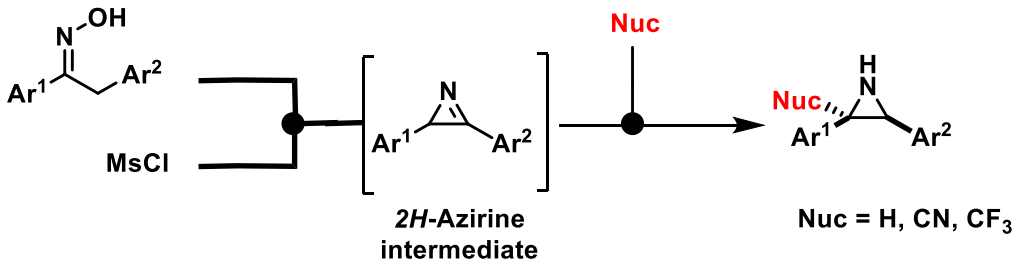
Scheme 5.4. Different approach for the synthesis of *2H*-azirines from enamine and enaminone derivatives

In the context of enamine or enaminone derivatives, several efforts have been made for the synthesis of *2H*-azirines. In 2009, for the first time, Yunfei Du and co-workers reported the synthesis of 2-aryl-2*H*-azirines from enamine derivatives by using hypervalent iodine reagent *i.e.* (diacetoxyiodo)benzene. In the same year, the same group reported the synthesis of the biologically important trifluoroethoxylated *2H*-azirines moiety from enamines and iodosobenzene in trifluoroethanol (TFE). Later in 2018, several enamines or enaminone derivatives were converted into fluoro *2H*-azirine derivatives by using PhIO and $Et_3N{\cdot}3HF$ in 1,2-dichroloethane. Subsequently, in same year, Chang's research group reported molecular iodine and base mediated synthesis of *2H*-azirines from enamines *via* oxidative cyclization method.[23]



Scheme 5.5. Miscellaneous approaches for the preparation of *2H*-azirines system

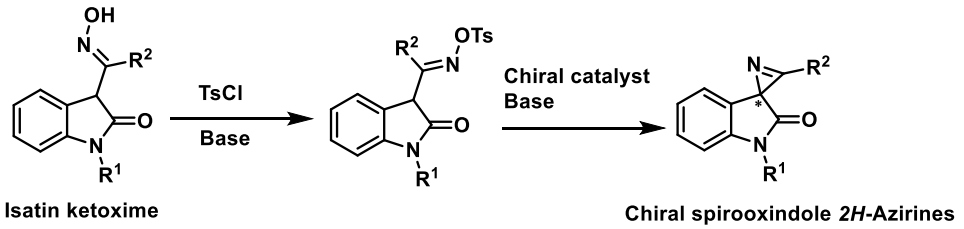
In the context of the synthesis of *2H*-aziridine in a continuous flow, Baumann and co-workers reported a protocol using oxime derivatives *via* mesylation followed by base mediated cyclization.[24]



Scheme 5.6. Synthesis of *2H*-azirine in continuous flow

Other approaches for the synthesis of azirines including photolytic or thermolytic activation of azide[25], ring contraction of isoxazol derivative,[26] from benzene-linked 1,7-enynes were extensively studied in the literature.[27]

In the context of oxindole, for the first time in year 2016, Yuan and Xu collectively reported the synthesis of enantioselective version of spirooxindole *2H*-azirines.



Scheme 5.7. Enantioselective version of spirooxindole *2H*-azirines

In this report, the reaction proceeded *via* the classical Neber rearrangement by the use of prefunctionalized oxindole *i.e.* 3-O-sulfonyl ketoxime.[28]

5.5. Rationale of present work

The high reactivity of azirines as an intermediate has gained substantial attention and consequently azirines have been used in several chemical transformations. Azirines are also an important moiety for biologists because of their presence in biologically active natural products. In literature, several methods have been reported for the generation of spirooxindoles having 5 & 6 membered rings merged at the C3 position of oxindole.[29] However, very few reports exist for the synthesis of spirooxindole having 3 and 4 member ring fused at the C3 position of oxindole.[30] However, the reported methods requires specially designed starting materials, prolonged duration and needed multistep route. Additionally, handling of large amounts of halogenated reagent in the batch process is not safe. Hence, we propose to develop an elegant and safe approach for the synthesis of spirooxindole azirines, which can be further used both as an intermediate in other reactions and for biological applications.

5.6. Results and discussions

In this chapter, we have disclosed a protocol for the synthesis of spirooxindole *2H*-azirines using 3-(amino(phenyl)methylene)-indolin-2-one derivatives in presence of cesium carbonate and molecular iodine in ethyl acetate as a green solvent. This transformation is mild and efficient as well as transformed into continuous flow conditions.

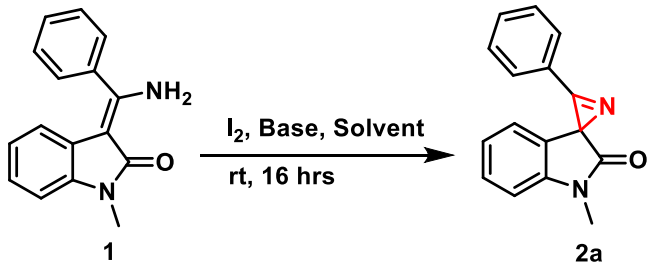
5.6.1 Optimization of reaction condition in batch

To establish the reaction condition for the synthesis of 1'-methyl-3-phenylspiro[azirine-2,3'-indolin]-2'-one **2a**, we begin the oxidative cyclization of 3-(amino(phenyl)methylene)-1-methylindolin-2-one by using iodine and base as a model reaction.

Table. 5.1. Optimization of reaction conditions in batch

Initially, a control experiment was performed by taking a DCE solution containing 3-(amino(phenyl)methylene)-1-methylindolin-2-one and base in the absence of iodine and resulted no reaction (Table 5.1, entry 1). In other experiment, the reaction was performed in the absence of base showed no reaction (Table 5.1, entry 2). Next, the

reaction was performed in presence of both base and iodine resulted the product, which indicates the requirement of both base/iodine.



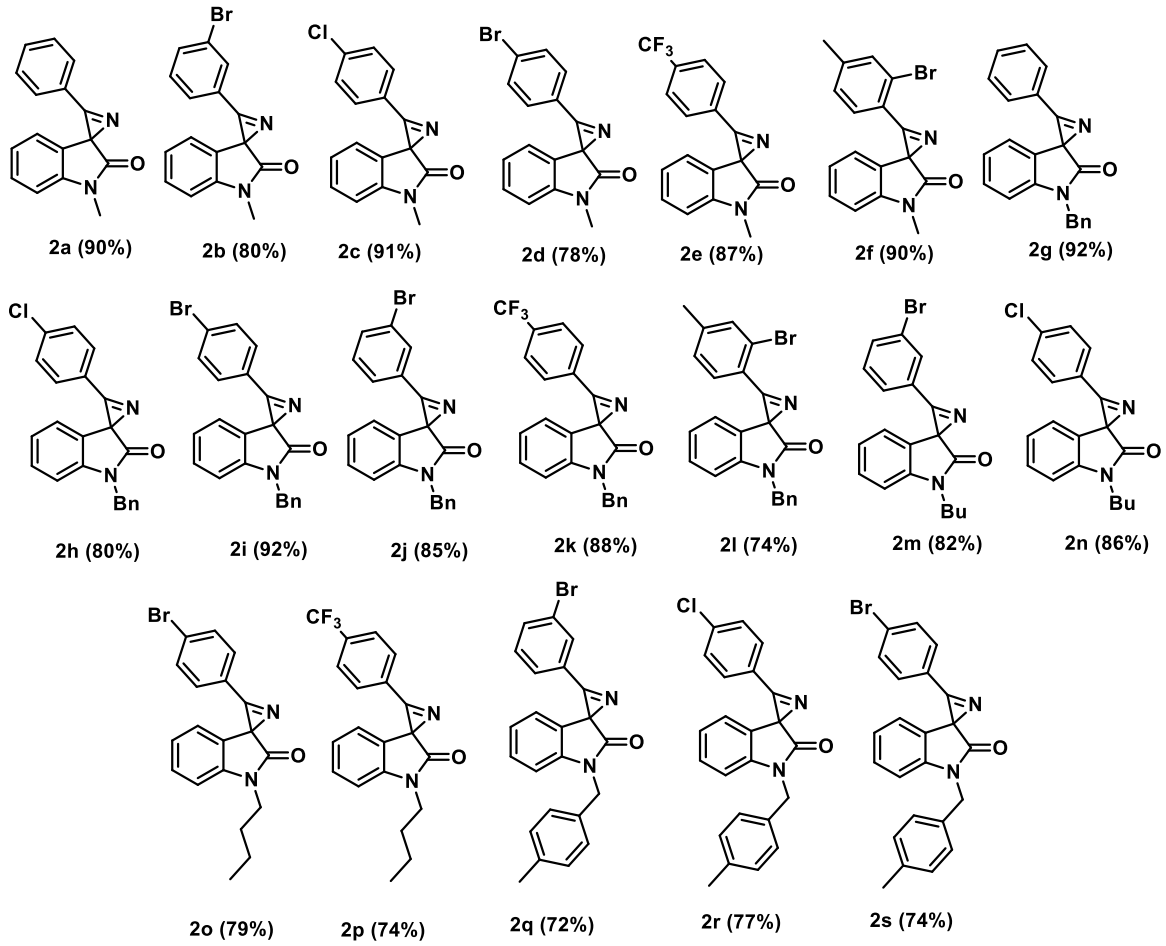
[a]Entry	Base (equiv.)	Solvent	Yield (%)
1	Cs_2CO_3	DCE (no iodine)	-
2[b]	-	DCE (no base)	-
3	DBU (2.5)	DCE	15
4	$NaHCO_3$ (2.5)	DCE	35
5	Na_2CO_3 (2.5)	DCE	45
6	K_2CO_3	DCE	50
7	Cs_2CO_3 (2.5)	DCE	75
8	Cs_2CO_3 (2.2)	Acetonitrile	68
9	Cs_2CO_3 (2.2)	DMF	85
10	**Cs_2CO_3 (2.2)**	**EtOAc**	**90**
11	Cs_2CO_3 (1)	EtOAc	40
12	Cs_2CO_3 (1.5)	EtOAc	80
13[b]	Cs_2CO_3 (1.5)	EtOAc	15
14[c]	Cs_2CO_3 (2.2)	EtOAc	40

Reaction condition: [a]3-(amino(phenyl)methylene)-indolin-2-ones (0.25 mmol), iodine (0.3 mmol), base (see table) and solvent 4 mL (see table) were stirred at room temperature in a round-bottom flasks flask for 16 hrs. [b] 30 mol% of I_2 has been used. [c] 50 mol% of I_2 has been used.

When the reaction was performed in presence of organic base such as DBU afforded the desired product **2a** in poor yield (Table 5.1, entry 3). A reaction with inorganic bases such as, $NaHCO_3$, Na_2CO_3 and K_2CO_3 results increase in the yield of product **2a** (Table 5.1, entries 4-7). Interestingly, when Cs_2CO_3 was taken as a base, 75% yield of the product **2a** was isolated (Table 5.1, entry 7). After having an efficient base on hand, solvent screening was performed. Polar solvents such as acetonitrile, DMF and ethyl acetate were turned out to be efficient for this transformation (Table 5.1, entries 8-10). Interestingly, excellent yield was noticed when inexpensive, less-toxic, and green ethyl acetate was used as a solvent.[31] Moreover, decrease in the product yield was observed when catalytic amount of iodine was used (Table 5.1, entries 13 & 14). A best optimized condition for the 1'-methyl-3-phenylspiro[azirine-2,3'-indolin]-2'-one **2a** (90%) was achieved by using I_2 (1.2 equiv.) and Cs_2CO_3 (2.2 equiv.) in ethyl

acetate as solvent. After having an optimal reaction condition in hand, we evaluated the substrate scope. In this regard, this transformation was well tolerated by other 3-(amino(phenyl)methylene)-indolin-2-one derivatives having an EWG at meta/para position, afforded respective cyclized products **2b**, **2c** and **2d** in 80, 91 and 78% respectively.

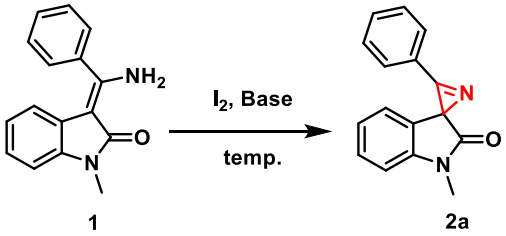
5.6.2. Substrate scope of spirooxindole *2H*-azirines in batch



Reaction condition: 3-(amino(phenyl)methylene)-indolin-2-one (0.25 mmol), iodine (0.3 mmol), Cs_2CO_3 (0.55 mmol) and EtOAc (4 mL) was stirred in a round-bottom flask at room temperature for 16 hrs. [b]In case of gram scale, reaction kept for 24 hrs.

A highly electron-withdrawing group at para position provided corresponding product **2e** in excellent yield. This transformation was also well tolerated by the electron-donating group at the para position to afford product **2f** in 90% yield. In addition, other *N*-functionalized derivatives *viz N*-benzyl, *N*-4-methyl benzyl, and *N*-butyl were also well tolerated by this transformation to provide respective products **2g-2s** in good to excellent yield. To check the scalability of this method, substrate **2c** was synthesized on a large scale (*i.e.* 900 mg, 3.17 mmol scale) with 90% isolated yield.

Table 5.2. Optimization of reaction condition in the continuous flow[a]



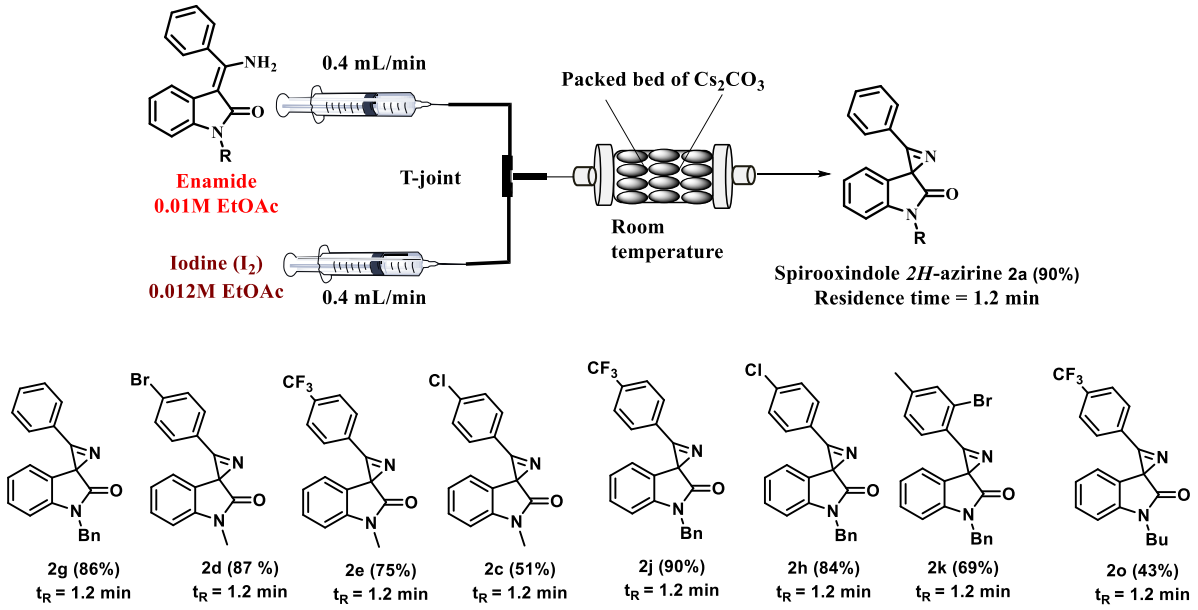
Entry	Flow rate for both (mL/min)	Conc. of compound 1 (M)	I_2 conc. (M)	Residence time (t_R)	Yield of 2a (%)
1	0.2	0.1	0.12	2.5	40
2[b]	0.2	0.1	0.12	2.5	35
3	0.1	0.1	0.12	5.1	40
4[c]	0.2	0.1	0.12	2.5	42
5	0.2	0.04	0.048	2.5	50
6	0.3	0.04	0.048	1.7	40
7	0.2	0.02	0.024	2.5	70
8	**0.4**	**0.01**	**0.012**	**1.2**	**91**
9	0.5	0.01	0.012	1.0	85

Reaction conditions: [a]Molar solution (see table) of 3-(amino(phenyl)methylene)-1-methylindolin-2-one in ethyl acetate (20 mL) and I_2 solution in ethyl acetate (20 mL) was flown through an Omnifit® (6.6 × 150 mm) packed bed (Cs_2CO_3 up to 3 cm) at room temperature with a flow rate mL min^{-1} (see table). [b]K_2CO_3 was taken as a base. [c]Heated at 50 and 70 ^oC respectively.

To perform the synthesis of spirooxindole *2H*-azirines under continuous-flow, several parameters such as, flow rate, temperature and concentration have been evaluated. Initially, a solution of 3-(amino(phenyl)methylene)-1-methylindolin-2-one (0.1 M) and iodine (0.12 M) were flown through the packed bed reactor containing Cs_2CO_3 with flow rates of 0.2 mL min^{-1} each at room temperature afforded 40% yield of desired product **2a.** Morover, decrease in product yield was observed when K_2CO_3 has been taken as a base (Table 5.2, entry 2). A slight improvnment in product yield was noticed when the flow rate was decreased to 0.1 mL/min (Table 5.2, entry 3). A slight increase in yield was observed upon increasing the temperature to 50 ^oC or 70 ^oC (Table 5.2, entry 4). Interestingly, on decreasing the concentration of enamide to 0.04 M and I_2, 50% of product **2a** was isolated. To our delight, when the 0.01 M solution of

3-(amino(phenyl)methylene)-1- methylindolin-2-one and 0.012 M solution of iodine was flown at 0.4 mL min^{-1} flow rate, an excellent yield (91%) was observed (Table 5.2, entry 8). Moreover, the drop in yield was observed when the flow rate was further increased to 0.5 mL min^{-1} (Table 5.2, entry 9).

5.6.3. Substrate scope of spirooxindole *2H*-azirines in continuous flow[a]



[a]**Reaction conditions:** 3-(amino(phenyl)methylene)-indolin-2-ones (0.01 M), iodine (0.012 M) in EtOAc was taken in two different syringes and passed through packed bed containing Cs_2CO_3 (bed height up to 3 cm).

After having flow optimized reaction condition in hand, various substrate has been tested. Thus, 3-(amino(phenyl)methylene)-1-benzylindolin-2-one and 3-(amino(phenyl)methylene)-1-benzylindolin-2-one afforded respective spirooxindole products **2g** and **2d** in 86 and 87% yield. The Cs_2CO_3 was washed with ethyl acetate, and further used for various substrates. Subsequently, the other two substrates **2e**, and **2c** synthesized in the third and fourth run with 75 and 51% yield, respectively. Drop in product yield was observed after synthesizing four substrates on a single bed which might be due to the decrease in base activity after four-run. Later, to improve the product yield a new bed of base was taken and afterwards substrates **2j**, **2h**, **2k** and **2o** were synthesized under optimized flow reaction condition.

5.6.4. Synthesis of spirooxindole *2H*-aziridines and *N*-substituted 3-(aminobenzylidene)indolin-2-ones *via* addition of Grignard reagent

To illustrate the synthetic application of spirooxindole *2H*-azirines, the azirine compound was treated with Grignard reagent such as phenyl magnesium bromide.

Column purification of reaction mixture afforded spirooxindole *2H*-aziridine.[32a] Further the respective aziridines **3a** & **3b** was isolated in 46% and 42% yield respectively. Interestingly on adding the additives such as CuI and LiCl in the reaction mixture. Umpolung addition of Grignard reagent to azirines was observed in the reaction mixture, and the corresponding ring-opening porducts *N*-substituted 3-(aminobenzylidene)indolin-2-ones derivatives **3c-h** in moderate to good yield (Figure 5.3).

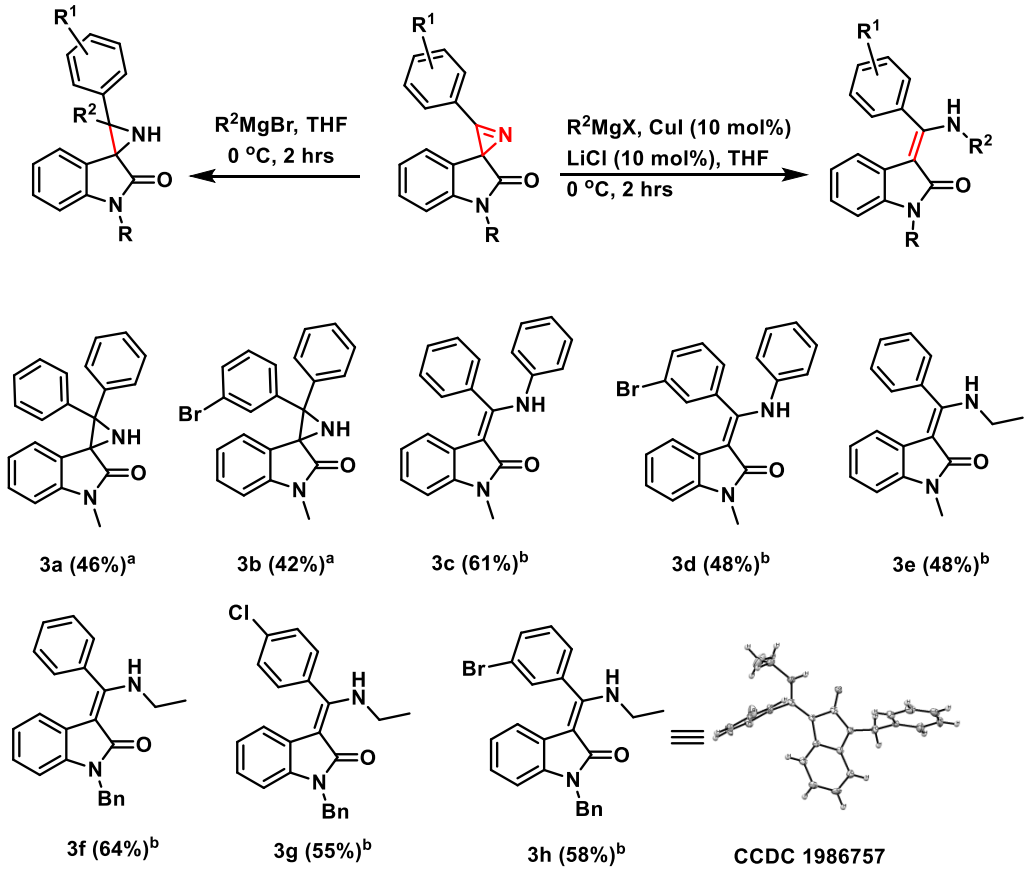


Figure 5.3. Substrate scope for spirooxindole *2H*-aziridines and *N*-substituted 3-(aminobenzylidene)indolin-2-ones.

[a]**Reaction conditions:** Spirooxindole *2H*-azirines (0.3 mmol), Grignard reagent (0.45 mmol) was added in THF at 0 °C and kept reaction in ice cold water for 2 hrs. [b]CuI (0.03 mmol) and LiCl (0.03 mmol) was added.

All the products **3a-h** were isolated and completely characterized by spectroscopic analysis. In addition, the structure of product **3h** was supported by crystal structure.

5.7. Mechanistic studies

To understand the mechansim for the formation of spirooxindole *2H*-azirine, control experiments has been performed.

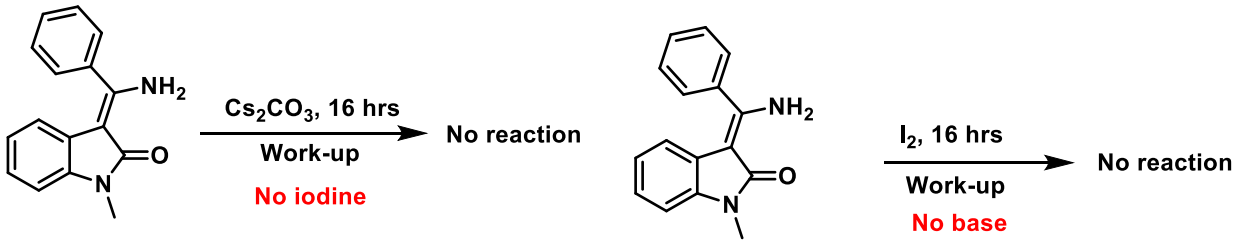


Figure 5.4. Control experiments for mechanism investigation

Initially, 3-(amino(phenyl)methylene)-indolin-2-ones was taken and kept to standard reaction condition in absence of iodine resulted no reaction. Similarly, in case of second control experiment, the reaction was performed in the absence of base resulted no reaction. Thus, it was concluded that both base and iodine is required to drive this transformation (Figure 5.4) . On the basis of our control experiment studies (Table 5.1, entries 1, 2) and based on the previous literature report,[17f] tentative reaction mechanism for the formation of spirooxindole is proposed (Figure 5.5).

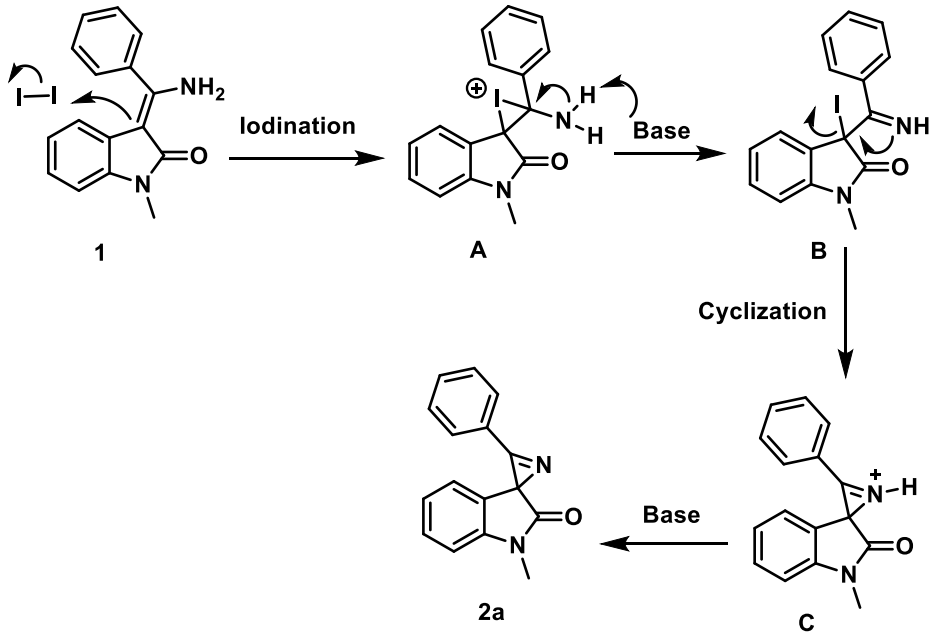


Figure 5.5. Plausible mechanism for azirination

At first, compound **1** in presence of iodine provides an intermediate **A**. Subsequently, in the presence of base intermediate **A** generate compound **B**. Further, in basic medium intermediate **B** will give compound **C**. Deprotonation of the intermediate **C** in presence of base to provide the product **2a**.

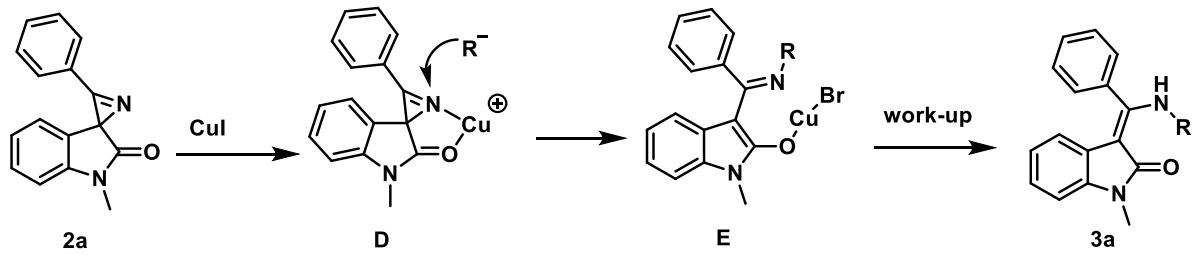


Figure 5.6. Plausible mechanism for ring opening reaction

Similarly, on the basis of previous literature report[32b] a plausable mechanism for the formation of *N*-substituted 3-(aminobenzylidene)indolin-2-ones is proposed (Figure 5.6). At first compound **2a** and Grignard reagent forms coordinated complex **D.** Further intramolecular nucleophilic attack of nucleophile to nitrogen center generate species **E**. Finally, after work-up species **E** afforded the desired product **3a**.

5.8. Conclusion

In conclusion, in this chapter we have established an efficient and scalable method for the synthesis of spirooxindole *2H*-azirines by using cesium carbonate and iodine from 3-(amino(phenyl)methylene)-indolin-2-one derivatives in good to excellent yields. Also, this reaction was successfully transformed into continuous flow and substrate scopes demonstrated by synthesizing several derivatives of spirooxindole *2H*-azirines. Moreover, we have synthesized the spirooxindole *2H*-aziridines derivatives. Interestingly, in presence of additives we developed Umpolung addition of Grignard reagent for the generation of *N*-substituted enamine derivative.

5.9. Experimental section and characterization data

5.9.1. General information and data collection: All the 3-(aminobenzylidene)oxindole derivatives were prepared according to literature procedure.[33] Deuterated solvents were used as received. Ethyl acetate was used after distillation. Column chromatographic separation was performed over 100-200 mesh size silica-gel. Visualization was accomplished with UV light and iodine. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded on 400 and 100 MHz respectively, using a Bruker or JEOL spectrometers. Abbreviations used in the NMR follow-up experiments: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; dd, double doublet; td, doublet of triplet; tt, triplet of triplets; p, pentet; ddd, doublet of doublet of doublets and m, multiplet. High-resolution mass spectra were obtained with Waters-synapt G2 using electrospray ionization (ESI-TOF). Infrared (ATR) spectra were obtained with a Bruker Alpha-E infrared spectrometer. FTIR spectra were recorded on pressed pellets of powder samples diluted with KBr on NICOLET 6700 spectrophotometer.

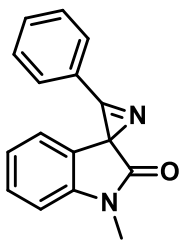
5.9.2. Experimental procedures

(A) General experimental procedure for the synthesis of spirooxindole *2H*-azirines: To an oven dried 10 mL round bottom flask, 3-(aminobenzylidene)oxindole (0.25 mmol), I_2 (0.3 mmol) and Cs_2CO_3 (0.55 mmol) was added in ethyl acetate under N_2 atmosphere using N_2 balloon. The reaction mixture was stirred at room temperature for 16 hrs. After completion of the reaction, sodium thiosulfate in water was added in the reaction mixture and the resulting mixture was extracted with ethyl acetate (3 x 40 mL). Further, all the ethyl acetate extract was combined and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by using column chromatography to afford the product **2** (EtOAc:hexane = 10:90 to 20:80).

(B) General experimental procedure for the synthesis of spirooxindole *2H*-aziridines using Grignard reagent: Spirooxindole *2H*-azirine (0.3 mmol) in 4 mL THF was kept in a 10 mL round bottom flask equipped with stirring bar. The reaction mixture was cooled to 0 ^oC and Grignard reagent (0.45) was added under nitrogen atmosphere. The reaction mixture was stirred at 0 ^oC for 5 min and further stirred at ice-cold water for 2 hrs. The resulting mixture was diluted with water and extracted with ethyl acetate (3 x 50 mL). The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using silica gel column chromatography (EtOAc:hexane = 10:90 to 20:80).

(C) General Experimental Procedure for the Synthesis of *N*-substituted 3-(aminobenzylidene)indoline-2-ones using Grignard reagent: Spirooxindole 2H-azirine (0.3 mmol), CuI (0.03 mmol) and LiCl (0.03 mmol) in 4 mL THF was kept in a 10 mL round bottom flask equipped with stirring bar. The reaction mixture was cooled to 0 ^oC and Grignard reagent (0.45 mmol) was added under nitrogen atmosphere. The reaction mixture was stirred at 0 ^oC for 5 min and further stirred at ice-cold water for 2 hrs. The resulting mixture was diluted with water and extracted with ethyl acetate (3 x 50 mL). The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using silica gel column chromatography (EtOAc:hexane = 10:90 to 20:80).

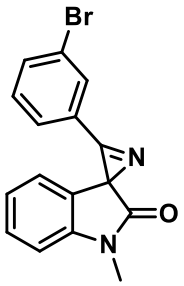
5.9.3. Analytical data for the product:



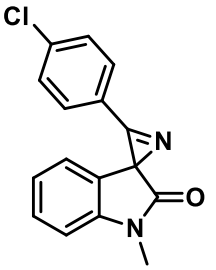
1'-methyl-3-phenylspiro[azirine-2,3'-indolin]-2'-one (2a)[28]: 3-(amino(phenyl)methylene)-1-methylindolin-2-one (62 mg, 0.25 mmol), I_2 (76 mg, 0.3 mmol), Cs_2CO_3 (178 mg, 0.55 mmol) were allowed to react according to method A to afford 1'-methyl-3-phenylspiro[azirine-2,3'-indolin]-2'-one **2a** (56 mg, 90%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 – 7.82 (m, 2H), 7.67 – 7.61 (m, 1H), 7.55 (t, *J* = 7.5 Hz, 2H),

7.34 (td, *J* = 7.8, 1.1 Hz, 1H), 7.01 (d, *J* = 7.4 Hz, 1H), 6.97 (d, *J* = 7.9 Hz, 1H), 6.85 (d, *J* = 7.3 Hz, 1H), 3.36 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 174.0, 158.6, 144.4, 134.3, 130.8, 129.5, 128.8, 126.4, 122.4, 121.2, 120.9, 108.5, 42.4, 26.9. **IR** (neat) 1714, 1614 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calcd for $C_{16}H_{13}N_2O$ 249.1028; found, 249.1032.

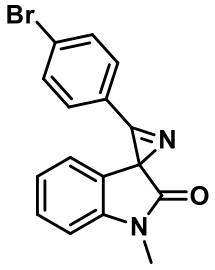
3-(3-bromophenyl)-1'-methylspiro[azirine-2,3'-indolin]-2'-one (2b): 3-(amino(3-bromophenyl)methylene)-1-methylindolin-2-one (82 mg, 0.25 mmol), I_2 (76 mg, 0.3 mmol), Cs_2CO_3 (178 mg, 0.55 mmol) were allowed to react according to method A to afford 3-(3-bromophenyl)-1'-methylspiro[azirine-2,3'-indolin]-2'-one **2b** (65 mg, 80%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (t, *J* = 1.7 Hz, 1H), 7.86 – 7.82 (m, 1H), 7.77 (ddd, *J* = 8.2, 1.8, 0.9 Hz, 1H), 7.45 (t, *J* = 7.9 Hz, 1H), 7.36 (td, *J* = 7.8, 1.0 Hz, 1H), 7.04 – 7.00 (m, 1H), 6.98 (d, *J* = 7.8 Hz, 1H), 6.85 – 6.82 (m, 1H), 3.36 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 173.6, 158.2, 144.6, 137.3, 133.4, 131.0, 129.1, 125.9, 123.5, 123.3, 122.6, 121.0, 108.6, 42.7, 26.9. **FTIR** (KBr) = 1710 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calcd for $C_{16}H_{12}BrN_2O$: 327.0139, found: 327.0139.



3-(4-chlorophenyl)-1'-methylspiro[azirine-2,3'-indolin]-2'-one (2c)[28]**:** (Z)-3-(amino(4-chlorophenyl)methylene)-1-methylindolin-2-one (71 mg, 0.25 mmol), I_2 (76 mg, 0.3 mmol), Cs_2CO_3 (178 mg, 0.55 mmol) were allowed to react according to method A to afford 3-(4-chlorophenyl)-1'-methylspiro[azirine-2,3'-indolin]-2'-one **2c** (64 mg, 91%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.7 Hz, 2H), 7.55 (d, *J* = 8.7 Hz, 2H), 7.33 (td, *J* = 7.8, 1.2 Hz, 1H), 6.99 (td, *J* = 7.6, 0.9 Hz, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.81 (dd, *J* = 7.4 Hz, 1H), 3.36 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 173.8, 158.1, 144.5, 140.9, 131.9, 130.0, 129.0, 126.1, 122.5, 120.9, 119.7, 108.6, 42.5, 26.9. **IR** (Neat) 1769, 1723 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calcd for $C_{16}H_{12}ClN_2O$: 283.0638, found: 283.0642.

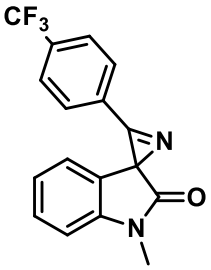


3-(4-bromophenyl)-1'-methylspiro[azirine-2,3'-indolin]-2'-one (2d)[28]**:** 3-(amino(4-bromophenyl)methylene)-1-methylindolin-2-one (82 mg, 0.25 mmol), I_2 (76 mg, 0.3 mmol), Cs_2CO_3 (178 mg, 0.55 mmol) were allowed to react according to method A to afford 3-(4-bromophenyl)-1'-methylspiro[azirine-2,3'-indolin]-2'-one **2d** (64 mg, 78%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 – 7.68 (m, 4H), 7.36 (td, *J* = 7.7, 1.1 Hz, 1H), 7.04 – 6.99 (m, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.83 (dd, *J* = 7.3, 0.8 Hz, 1H), 3.36 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz,

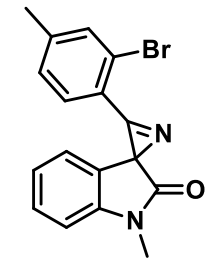


$CDCl_3$) δ 173.8, 158.3, 144.6, 133.0, 132.0, 129.6, 129.1, 126.1, 122.6, 121.0, 120.2, 108.6, 42.6, 26.9. **FTIR** (KBr) = 1667, 1605 cm^{-1}**. HRMS** (ESI) m/z calculated for $C_{16}H_{12}BrN_2O$ $(M+H)^+$: 327.0133, found: 327.0135.

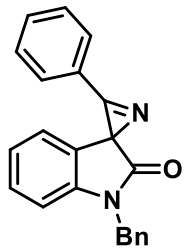
1'-methyl-3-(4-(trifluoromethyl)phenyl)spiro[azirine-2,3'-indolin]-2'-one (2e): 3-(amino(4-(trifluoromethyl)phenyl)methylene)-1-methylindolin-2-one (79 mg, 0.25 mmol), I_2 (76 mg, 0.3 mmol), Cs_2CO_3 (178 mg, 0.55 mmol) were allowed to react according to method A to afford 1'-methyl-3-(4-(trifluoromethyl)phenyl)spiro[azirine-2,3'-indolin]-2'-one **2e** (69 mg, 87%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 – 7.68 (m, 4H), 7.36 (td, *J* = 7.7, 1.1 Hz, 1H), 7.04 – 6.99 (m, 1H), 6.97 (d, *J* = 7.8 Hz, 1H), 6.83 (dd, *J* = 7.3, 0.8 Hz, 1H), 3.36 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 173.5, 158.7, 144.6, 135.7 (q, *J* = 32.4 Hz), 131.0, 129.3, 126.5 (q, *J* = 3.7 Hz), 125.8, 124.8, 123.3 (q, *J* = 271.3 Hz), 122.6, 121.0, 108.7, 42.9, 26.9. **FTIR** (KBr) = 1718, 1615 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calcd for $C_{17}H_{12}F_3N_2O$: 317.0910, found: 317.0902.



3-(2-bromo-4-methylphenyl)-1'-methylspiro[azirine-2,3'-indolin]-2'-one (2f): (Z)-3-(amino(2-bromo-4-methylphenyl)methylene)-1-methylindolin-2-one (85 mg, 0.25 mmol), I_2 (76 mg, 0.3 mmol), Cs_2CO_3 (178 mg, 0.55 mmol) were allowed to react according to method A to afford 3-(2-bromo-4-methylphenyl)-1'-methylspiro[azirine-2,3'-indolin]-2'-one **2f** (76 mg, 90%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.9 Hz, 1H), 7.56 (s, 1H), 7.33 (td, *J* = 7.8, 1.2 Hz, 1H), 7.29 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.01 (td, *J* = 7.6, 0.8 Hz, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 7.4Hz, 1H), 3.36 (s, 3H), 2.43 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 174.1, 158.7, 146.9, 144.5, 134.7, 133.3, 128.9, 128.8, 126.9, 125.9, 122.4, 121.1, 119.2, 108.4, 43.2, 26.9, 21.7. **FTIR** (neat) 1713 cm^{-1}. $C_{17}H_{14}BrN_2O$: 341.0289, found: 341.0294.

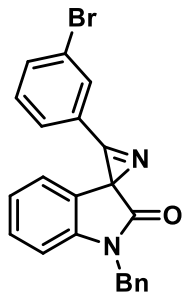


1'-benzyl-3-phenylspiro[azirine-2,3'-indolin]-2'-one (2g): (Z)-3-(amino(phenyl)methylene)-1-benzylindolin-2-one (81 mg, 0.25 mmol), I_2 (76 mg, 0.3 mmol), Cs_2CO_3 (178 mg, 0.55 mmol) were allowed to react according to method A to afford 1'-(4-methylbenzyl)-3-(4-(trifluoromethyl)phenyl)spiro[azirine-2,3'-indolin]-2'-one **2g** (75 mg, 92%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 – 7.85 (m, 2H), 7.70 – 7.63 (m, 1H), 7.57 (dd, *J* = 10.4, 4.6 Hz, 2H), 7.42 – 7.38 (m, 2H), 7.38 – 7.33 (m, 2H), 7.29 (ddd, *J* = 7.1, 3.7, 1.4 Hz, 1H), 7.22 (td, *J* = 7.8, 1.2 Hz, 1H), 6.97 (td, *J* = 7.6, 0.8 Hz, 1H), 6.88 – 6.83 (m, 2H), 5.09 (d, *J* = 15.6 Hz, 1H), 5.04 (d, *J* = 15.7 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 174.2,

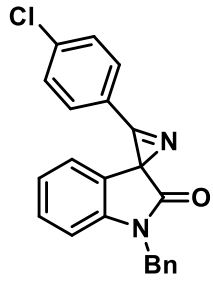


158.6, 143.6, 135.9, 134.4, 130.9, 129.6, 128.9, 128.7, 127.8, 127.5, 126.5, 122.5, 121.2, 121.0, 109.5, 44.5, 42.4. **FTIR** (KBr) = 1718 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calcd for $C_{22}H_{17}N_2O$: 325.1341, found: 325.1339.

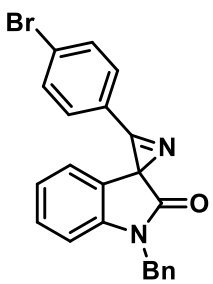
1'-benzyl-3-(3-bromophenyl)spiro[azirine-2,3'-indolin]-2'-one (2h): 3-(amino(3-bromophenyl)methylene)-1-benzylindolin-2-one (101 mg, 0.25 mmol), I_2 (76 mg, 0.3 mmol), Cs_2CO_3 (178 mg, 0.55 mmol) were allowed to react according to method A to afford 1'-benzyl-3-(3-bromophenyl)spiro[azirine-2,3'-indolin]-2'-one **2h** (85 mg, 85%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00 (t, *J* = 1.6 Hz, 1H), 7.85 (d, *J* = 7.7 Hz, 1H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.47 (t, *J* = 7.9 Hz, 1H), 7.41 – 7.33 (m, 4H), 7.30 (d, *J* = 6.9 Hz, 1H), 7.23 (dd, *J* = 7.8, 1.1 Hz, 1H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.88 – 6.83 (m, 2H), 5.11 (d, *J* = 15.6 Hz, 1H), 5.01 (d, *J* = 15.6 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 173.7, 158.1, 143.7, 137.3, 135.8, 133.4, 131.1, 129.2, 129.0, 128.9, 127.8, 127.5, 126.0, 123.5, 123.2, 122.6, 121.1, 109.7, 44.5, 42.7. **FTIR** (neat) = 1653 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calcd for $C_{22}H_{16}BrN_2O$: 403.0446, found: 403.0447.



1'-benzyl-3-(4-chlorophenyl)spiro[azirine-2,3'-indolin]-2'-one (2i): 3-(amino(4-chlorophenyl)methylene)-1-benzylindolin-2-one (90 mg, 0.25 mmol), I_2 (76 mg, 0.3 mmol), Cs_2CO_3 (178 mg, 0.55 mmol) were allowed to react according to method A to afford 1'-benzyl-3-(4-chlorophenyl)spiro[azirine-2,3'-indolin]-2'-one **2i** (72 mg, 80%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.40-7.34 (m, 4H), 7.30 (dd, *J* = 6.4, 2.0 Hz, 1H), 7.23 (td, *J* = 7.8, 1.1 Hz, 1H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 7.9 Hz, 1H), 6.84 (d, *J* = 6.9 Hz, 1H), 5.09 (d, *J* = 15.6 Hz, 1H), 5.02 (d, *J* = 15.6 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 173.9, 158.0, 143.7, 141.0, 135.9, 132.0, 130.1, 128.9, 128.9, 127.8, 127.5, 126.1, 122.6, 121.0, 119.7, 109.6, 44.5, 42.5. **IR** (neat) 1716, 1613 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calcd for $C_{22}H_{16}ClN_2O$: 359.0951, found: 359.0946.

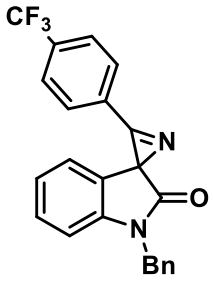


1'-benzyl-3-(4-bromophenyl)spiro[azirine-2,3'-indolin]-2'-one (2j): (Z)-3-(amino(4-bromophenyl)methylene)-1-benzylindolin-2-one (101 mg, 0.25 mmol), I_2 (76 mg, 0.3 mmol), Cs_2CO_3 (178 mg, 0.55 mmol) were allowed to react according to method A to afford 1'-benzyl-3-(4-bromophenyl)spiro[azirine-2,3'-indolin]-2'-one **2j** (92 mg, 92%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 – 7.63 (m, 4H), 7.30 (t, *J* = 8.5 Hz, 3H), 7.26 – 7.18 (m, 2H), 7.16 (t, *J* = 7.8 Hz, 1H), 6.90 (t, *J* = 7.5 Hz, 1H), 6.79 (d, *J* = 7.9 Hz, 1H), 6.76 (d, *J* = 7.4 Hz, 1H), 5.01 (d, *J* = 15.6

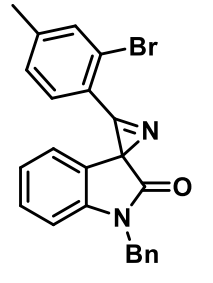


Hz, 1H), 4.95 (d, *J* = 15.6 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 173.9, 158.2, 143.7, 135.9, 133.1, 132.0, 129.7, 129.0, 128.9, 127.8, 127.6, 126.1, 122.6, 121.0, 120.1, 109.6, 44.5, 42.8. **IR** (neat) 1714, 1614 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calcd for $C_{22}H_{16}BrN_2O$: 403.0446, found: 403.0446.

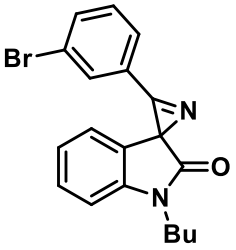
1'-benzyl-3-(4-(trifluoromethyl)phenyl)spiro[azirine-2,3'-indolin]-2'-one (2k): 3-(amino(4-(trifluoromethyl)phenyl)methylene)-1-benzylindolin-2-one (98 mg, 0.25 mmol), I_2 (76 mg, 0.3 mmol), Cs_2CO_3 (178 mg, 0.55 mmol) were allowed to react according to method A to afford 1'-benzyl-3-(4-(trifluoromethyl)phenyl)spiro[azirine-2,3'-indolin]-2'-one **2k** (86 mg, 88%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.0 Hz, 2H), 7.85 (d, *J* = 8.1 Hz, 2H), 7.41 – 7.34 (m, 4H), 7.27-7.32 (m, 1H), 7.24 (dd, *J* = 7.8, 1.3 Hz, 1H), 6.99 (td, *J* = 7.6, 0.9 Hz, 1H), 6.88 (d, *J* = 7.9 Hz, 1H), 6.86 – 6.82 (m, 1H), 5.09 (d, *J* = 15.6 Hz, 1H), 5.03 (d, *J* = 15.6 Hz, 1H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 173.6, 158.6, 143.8, 135.8, 135.7 (q, *J* = 32.9 Hz), 131.1, 129.2, 129.0, 127.9, 127.6, 126.6 (q, *J* = 3.7 Hz), 125.8, 124.7, 123.3 (q, *J* = 271.3 Hz), 122.7, 121.1, 109.7, 44.6, 42.8. **IR** (neat) = 1718, 1614 cm^{-1}. **HRMS** (ESI-TOF)m/z: $(M+H)^+$ calcd for $C_{23}H_{16}F_3N_2O$: 393.1214, found: 393.1216.



1'-benzyl-3-(2-bromo-4-methylphenyl)spiro[azirine-2,3'-indolin]-2'-one (2l): 3-(amino(2-bromo-4-methylphenyl)methylene)-1-benzylindolin-2-one (104 mg, 0.25 mmol), I_2 (76 mg, 0.3 mmol), Cs_2CO_3 (178 mg, 0.55 mmol) were allowed to react according to method A to afford 1'-benzyl-3-(2-bromo-4-methylphenyl)spiro[azirine-2,3'-indolin]-2'-one **2l** (77 mg, 74%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.9 Hz, 1H), 7.56 (s, 1H), 7.39 (d, *J* = 7.1 Hz, 2H), 7.36 – 7.28 (m, 4H), 7.24 – 7.19 (m, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.84 (dd, *J* = 7.6, 2.2 Hz, 2H), 5.14 (d, *J* = 15.6 Hz, 1H), 4.97 (d, *J* = 15.6 Hz, 1H), 2.44 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 174.2, 158.8, 147.0, 143.6, 136.1, 134.7, 133.2, 129.1, 128.8, 128.7, 127.7, 127.6, 127.0, 126.0, 122.5, 121.2, 119.1, 109.4, 44.4, 43.5, 21.7. **FTIR** (KBr) = 1704 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calcd for $C_{23}H_{18}BrN_2O$: 417.0602, found: 417.0606.

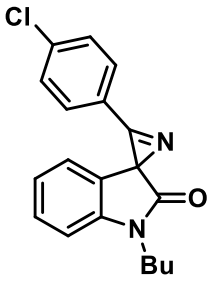


3-(3-bromophenyl)-1'-butylspiro[azirine-2,3'-indolin]-2'-one (2m): 3-(amino(3-bromophenyl)methylene)-1-butylindolin-2-one (102 mg, 0.25 mmol), I_2 (76 mg, 0.3 mmol), Cs_2CO_3 (178 mg, 0.55 mmol) were allowed to react according to method A to afford 3-(3-bromophenyl)-1'-butylspiro[azirine-2,3'-indolin]-2'-one **2m** (84 mg, 82%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (t, *J* = 1.7 Hz, 1H), 7.83 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.79 – 7.74 (m, 1H), 7.45 (t, *J* = 7.9 Hz, 1H), 7.34 (td, *J* = 7.8,

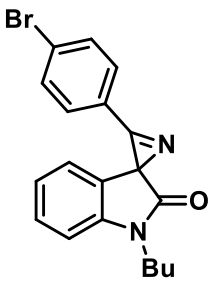


0.9 Hz, 1H), 7.00 (t, *J* = 7.7 Hz, 2H), 6.85 (d, *J* = 7.6Hz, 1H), 3.94 – 3.76 (m, 2H), 1.80 – 1.69 (m, 2H), 1.50-1.40 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H). **$^{13}C\{^{1}H\}$ NMR** (100 MHz, $CDCl_3$) δ 173.5, 158.3, 144.1, 137.2, 133.3, 131.0, 129.1, 129.0, 126.1, 123.4, 123.3, 122.3, 121.1, 108.9, 42.7, 40.5, 29.8, 20.3, 13.9. **FTIR** (KBr) = 1736 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calcd for $C_{19}H_{18}BrN_2O$: 369.0602, found: 369.0604.

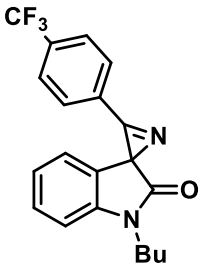
1'-butyl-3-(4-chlorophenyl)spiro[azirine-2,3'-indolin]-2'-one (2n): (Z)-3-(amino(4-chlorophenyl)methylene)-1-butylindolin-2-one (81 mg, 0.25 mmol), I_2 (76 mg, 0.3 mmol), Cs_2CO_3 (178 mg, 0.55 mmol) were allowed to react according to method A to afford 1'-butyl-3-(4-chlorophenyl)spiro[azirine-2,3'-indolin]-2'-one **2n** (69 mg, 86%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 1H), 6.99 (t, *J* = 7.7 Hz, 2H), 6.82 (d, *J* = 7.2 Hz, 1H), 3.92 – 3.75 (m, 2H), 1.81 – 1.70 (m, 2H), 1.51–1.39 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H). **$^{13}C\{^{1}H\}$ NMR** (100 MHz, $CDCl_3$) δ 173.6, 158.1, 144.1, 140.9, 132.0, 130.0, 128.9, 126.3, 122.3, 121.1, 119.8, 108.9, 42.5, 40.5, 29.8, 20.3, 13.9. **FTIR** (KBr) = 1619 cm^{-1}. **HRMS** (ESI-TOF)m/z: $(M+H)^+$ calcd for $C_{19}H_{18}ClN_2O$: 325.1107, found: 325.1114.



3-(4-bromophenyl)-1'-butylspiro[azirine-2,3'-indolin]-2'-one (2o): 3-(amino(4-bromophenyl)methylene)-1-butylindolin-2-one (92 mg, 0.25 mmol), I_2 (76 mg, 0.3 mmol), Cs_2CO_3 (178 mg, 0.55 mmol) were allowed to react according to method A to afford 3-(4-bromophenyl)-1'-butylspiro[azirine-2,3'-indolin]-2'-one **2o** (72 mg, 79%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 – 7.69 (m, 4H), 7.33 (td, *J* = 7.8, 1.3 Hz, 1H), 7.00 (dd, *J* = 11.4, 4.3 Hz, 2H), 6.84 – 6.80 (m, 1H), 3.91 – 3.76 (m, 2H), 1.80 – 1.70 (m, 2H), 1.49 – 1.40 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H). **$^{13}C\{^{1}H\}$ NMR** (100 MHz, $CDCl_3$) δ 173.6, 158.3, 144.1, 133.0, 132.0, 129.6, 129.0, 126.3, 122.3, 121.1, 120.3, 108.9, 42.5, 40.5, 29.8, 20.3, 13.9. **FTIR** (KBr) = 1713, 1618 cm^{-1}. **HRMS** (ESI-TOF) m/z: $(M+H)^+$ calcd for $C_{19}H_{18}BrN_2O$: 369.0602, found: 369.0606.

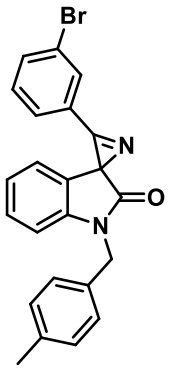


1'-butyl-3-(4-(trifluoromethyl)phenyl)spiro[azirine-2,3'-indolin]-2'-one (2p): (Z)-3-(amino(4-(trifluoromethyl)phenyl)methylene)-1-butylindolin-2-one (90 mg, 0.25 mmol), I_2 (76 mg, 0.3 mmol), Cs_2CO_3 (178 mg, 0.55 mmol) were allowed to react according to method A to afford to afford 1'-butyl-3-(4-(trifluoromethyl)phenyl)spiro[azirine-2,3'-indolin]-2'-one **2p** (66 mg, 74 %) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$ δ 8.00 (d, *J* = 8.1 Hz, 2H), 7.82 (d, *J* = 8.1 Hz, 2H), 7.34 (t, *J* = 7.8 Hz, 1H), 6.99 (t, *J* = 7.9 Hz, 2H),

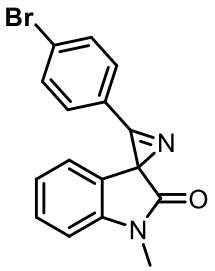


6.83 (d, *J* = 7.3 Hz, 1H), 3.92 – 3.77 (m, 2H), 1.80 – 1.71 (m, 2H), 1.50 – 1.39 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 173.3, 158.7, 144.1, 135.5 (q, *J* = 32.3 Hz), 130.9, 129.1, 126.5 (q, *J* = 3.7 Hz), 125.9, 124.8, 123.5 (q, *J* = 271.4 Hz), 122.3, 121.0, 108.9, 42.7, 40.5, 29.7, 20.2, 13.7. **FTIR** (KBr) = 1715 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{20}H_{18}F_3N_2O$ $(M+H)^+$: 359.1371, found: 359.1376.

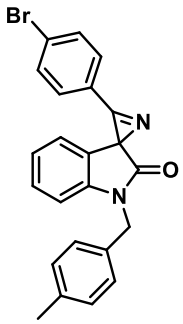
3-(3-bromophenyl)-1'-(4-methylbenzyl)spiro[azirine-2,3'-indolin]-2'-one (2q): 3-(amino(3-bromophenyl)methylene)-1-(4-methylbenzyl)indolin-2-one (104 mg, 0.25 mmol), I_2 (76 mg, 0.3 mmol), Cs_2CO_3 (178 mg, 0.55 mmol) were allowed to react according to method A to afford 3-(3-bromophenyl)-1'-(4-methylbenzyl)spiro[azirine-2,3'-indolin]-2'-one **2q** (74 mg, 72%) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 (t, *J* = 1.6 Hz, 1H), 7.87 – 7.83 (m, 1H), 7.79 (ddd, *J* = 8.1, 2.0, 1.1 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.23 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.16 (d, *J* = 7.8 Hz, 2H), 6.97 (td, *J* = 7.6, 0.9 Hz, 1H), 6.88 (d, *J* = 7.9 Hz, 1H), 6.85 – 6.81 (m, 1H), 5.06 (d, *J* = 15.5 Hz, 1H), 4.97 (d, *J* = 15.5 Hz, 1H), 2.33 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 173.7, 158.2, 143.8, 137.5, 137.3, 133.4, 132.8, 131.1, 129.6, 129.1, 129.0, 127.6, 126.0, 123.5, 123.3, 122.6, 121.1, 109.7, 44.3, 42.8, 21.2. **FTIR** (KBr) = 1617 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{23}H_{18}BrN_2O$ $(M+H)^+$: 417.0602, found: 417.0601.



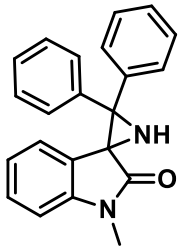
3-(4-chlorophenyl)-1'-(4-methylbenzyl)spiro[azirine-2,3'-indolin]-2'-one (2r): 3-(amino(4-chlorophenyl)methylene)-1-(4-methylbenzyl)indolin-2-one (93 mg, 0.25 mmol), I_2 (76 mg, 0.3 mmol), Cs_2CO_3 (178 mg, 0.55 mmol) were allowed to react according to method A to afford 3-(4-chlorophenyl)-1'-(4-methylbenzyl)spiro[azirine-2,3'-indolin]-2'-one **2r** (71 mg, 77%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.0 Hz, 2H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 2H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 7.3 Hz, 1H), 5.06 (d, *J* = 15.5 Hz, 1H), 5.01 (d, *J* = 15.5 Hz, 1H), 2.40 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 173.9, 158.0, 143.7, 141.0, 137.5, 132.8, 132.0, 130.1, 129.6, 128.9, 127.6, 126.2, 122.5, 121.0, 119.8, 109.7, 44.3, 42.6, 21.2. **FTIR** (KBr) = 1718, 1614 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{23}H_{18}ClN_2O$ $(M+H)^+$: 373.1107, found: 373.1105.



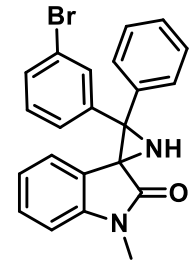
3-(4-bromophenyl)-1'-(4-methylbenzyl)spiro[azirine-2,3'-indolin]-2'-one (2s): 3-(amino(4-bromophenyl)methylene)-1-(4-methylbenzyl)indolin-2-one (104 mg, 0.25 mmol), I_2 (76 mg, 0.3 mmol), Cs_2CO_3 (178 mg, 0.55 mmol) were allowed to react according to method A to afford 3-(4-bromophenyl)-1'-(4-methylbenzyl)spiro[azirine-2,3'-indolin]-2'-one **2s** (76 mg, 74%) as a light yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 - 7.67 (m, 4H), 7.24 (d, *J* = 4.1 Hz, 2H), 7.20 (td, *J* = 7.8, 1.0 Hz, 1H), 7.13 (d, *J* = 7.9 Hz, 2H), 6.93 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 7.9 Hz, 1H), 6.79 (d, *J* = 7.0 Hz, 1H), 5.01 (d, *J* = 15.5 Hz, 1H), 4.95 (d, *J* = 15.5 Hz, 1H), 2.30 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 173.8, 158.2, 143.7, 137.5, 133.0, 132.8, 132.0, 129.6, 129.6, 128.9, 127.6, 126.1, 122.5, 121.0, 120.2, 109.7, 44.3, 42.5, 21.2. **FTIR** (KBr) = 1714.56, 1614.81 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{23}H_{17}BrN_2O$ $(M+H)^+$: 417.0602, found: 417.0600.



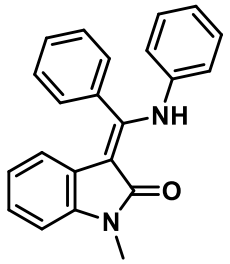
1'-methyl-3,3-diphenylspiro[aziridine-2,3'-indolin]-2'-one (**3a**): 1'-methyl-3-phenylspiro[azirine-2,3'-indolin]-2'-one (74 mg, 0.3 mmol), phenylmagnesium bromide in THF (81 mg, 0.45 mmol), were allowed to react according to method B to afford 1'-methyl-3,3-diphenylspiro[aziridine-2,3'-indolin]-2'-one **3a** (45 mg, 46%) as a red solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 – 7.63 (m, 2H), 7.57 – 7.46 (m, 5H), 7.39 (ddd, *J* = 6.5, 3.8, 1.4 Hz, 1H), 7.34 – 7.29 (m, 3H), 7.11 (d, *J* = 7.4 Hz, 1H), 7.04 (td, *J* = 7.5, 0.9 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 5.12 (s, 1H), 3.22 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 174.52, 174.20, 144.46, 139.56, 135.95, 130.70, 130.21, 129.26, 129.21, 128.85, 128.78, 128.50, 128.42, 128.18, 124.68, 122.80, 108.36, 64.83, 26.57. **FTIR** (neat) = 3057, 1613 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{24}H_{22}BrN_2O$ $(M+H)^+$: 433.0915, found: 433.0912.



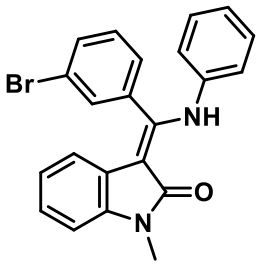
3-(3-bromophenyl)-1'-methyl-3-phenylspiro[aziridine-2,3'-indolin]-2'-one (**3b**): 3-(3-bromophenyl)-1'-methylspiro[azirine-2,3'-indolin]-2'-one (98 mg, 0.3 mmol), phenylmagnesium bromide in THF (81 mg, 0.45 mmol), were allowed to react according to method B to afford 3-(3-bromophenyl)-1'-methyl-3-phenylspiro[aziridine-2,3'-indolin]-2'-one **3b** (50 mg, 42%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (t, *J* = 1.7 Hz, 1H), 7.65 – 7.60 (m, 1H), 7.57 – 7.47 (m, 4H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.35 – 7.29 (m, 2H), 7.18 (t, *J* = 7.9 Hz, 1H), 7.10 (d, *J* = 6.7 Hz, 1H), 7.05 (tdd, *J* = 7.4, 3.3, 0.9 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 5.11 (s, 1H), 3.23 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 174.20, 172.73, 144.4, 141.54, 137.88, 135.14, 133.58, 132.42, 131.69, 130.95, 130.36, 129.57, 119.22, 129.15, 128.93, 128.73,



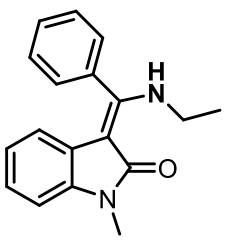
128.22, 124.68, 122.75, 108.43, 64.82, 26.58. **FTIR** (neat) = 3064, 1636 cm^{-1}. HRMS (ESI) m/z calculated for $C_{24}H_{22}BrN_2O$ $(M+H)^+$: 433.0915, found: 433.0912.

1-methyl-3-(phenyl(phenylamino)methylene)indolin-2-one (**3c**)**:** 1'-methyl-3-phenylspiro[azirine-2,3'-indolin]-2'-one (74 mg, 0.3 mmol), phenylmagnesium bromide in THF (81 mg, 0.45 mmol), CuI (5.7 mg, 0.03 mmol) and LiCl (1.23 mg, 0.03 mmol) were allowed to react according to method C to afford 1-methyl-3-(phenyl(phenylamino)methylene)indolin-2-one **3c** (59 mg, 61%) as a yellow solid. 

^{1}H NMR δ 12.03 (s, 1H), 7.55 – 7.45 (m, 3H), 7.43 (dt, *J* = 8.1, 2.0 Hz, 2H), 7.09 (dd, *J* = 11.1, 4.6 Hz, 2H), 7.03 (dd, *J* = 7.7, 1.0 Hz, 1H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.88 (d, *J* = 7.7 Hz, 1H), 6.75 (d, *J* = 7.7 Hz, 2H), 6.68 (td, *J* = 7.7, 1.0 Hz, 1H), 6.03 – 5.99 (m, 1H), 3.42 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 169.37, 156.56, 139.11, 138.42, 133.30, 130.06, 129.44, 128.91, 124.21, 123.95, 123.70, 122.82, 120.94, 118.81, 107.57, 97.88, 25.78. **FTIR** (neat) = 3056, 1616 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{24}H_{22}BrN_2O$ $(M+H)^+$: 433.0915, found: 433.0912.

3-((3-bromophenyl)(phenylamino)methylene)-1-methylindolin-2-one (**3d**): 3-(3-bromophenyl)-1'-methylspiro[azirine-2,3'-indolin]-2'-one (97 mg, 0.3 mmol), phenylmagnesium bromide in THF (81 mg, 0.45 mmol), CuI (5.7 mg, 0.03 mmol) and LiCl (1.23 mg, 0.03 mmol) were allowed to react according to method C to afford 3-((3-bromophenyl)(phenylamino)methylene)-1-methylindolin-2-one **3d** (58 mg, 48%) as a yellow solid. 

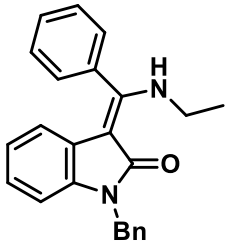
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.97 (s, 1H), 7.69 – 7.65 (m, 1H), 7.61 (s, 1H), 7.38 – 7.34 (m, 2H), 7.14 (t, *J* = 7.9 Hz, 2H), 7.07 (td, *J* = 7.7, 1.0 Hz, 1H), 7.00 (t, *J* = 7.4 Hz, 1H), 6.89 (d, *J* = 7.7 Hz, 1H), 6.77 (d, *J* = 7.7 Hz, 2H), 6.73 (t, *J* = 7.7 Hz, 1H), 6.05 (d, *J* = 7.7 Hz, 1H), 3.41 (s, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 169.31, 154.48, 138.73, 138.58, 135.22, 133.19, 131.93, 131.01, 129.07, 127.71, 124.58, 124.07, 123.50, 123.32, 123.06, 121.15, 118.73, 107.74, 98.14, 25.82. **FTIR** (neat) = 3053, 1638 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{24}H_{22}BrN_2O$ $(M+H)^+$: 433.0915, found: 433.0912.

(Z)-3-((ethylamino)(phenyl)methylene)-1-methylindolin-2-one (3e): 1'-methyl-3-phenylspiro[azirine-2,3'-indolin]-2'-one (74 mg, 0.3 mmol), ethylmagnesium bromide in diethyl ether (133 mg, 1.5 mmol), were allowed to react according to method C to afford (Z)-3-((ethylamino)(phenyl)methylene)-1-methylindolin-2-one **3e** (40 mg, 48%) as a white solid. 

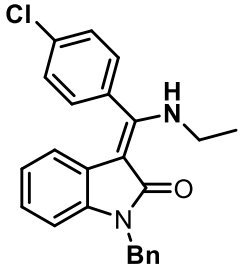
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.13 (s, 1H), 7.61 – 7.55 (m, 3H), 7.38 (dd, *J* = 6.4, 2.8 Hz, 2H), 6.96 (t, *J* = 7.6

Hz, 1H), 6.84 (d, *J* = 7.7 Hz, 1H), 6.61 (t, *J* = 7.6 Hz, 1H), 5.70 (d, *J* = 7.7 Hz, 1H), 3.38 (s, 3H), 3.15 (p, *J* = 7.0 Hz, 2H), 1.19 (t, *J* = 7.2 Hz, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 169.1, 161.3, 137.4, 133.4, 129.8, 129.5, 127.7, 124.5, 122.3, 120.5, 117.4, 107.2, 94.4, 38.8, 25.6, 16.3. **FTIR** (KBr) = 3026, 1728, 1172, 744 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{18}H_{19}N_2O$ $(M+H)^+$: 279.1497, found: 279.1499.

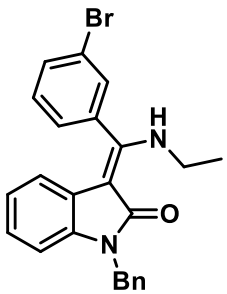
(Z)-1-benzyl-3-((ethylamino)(phenyl)methylene)indolin-2-one (**3f**): 1'-benzyl-3-phenylspiro[azirine-2,3'-indolin]-2'-one (97 mg, 0.3 mmol), ethylmagnesium bromide in diethyl ether (133 mg, 1.5 mmol), were allowed to react according to method C to afford 1-benzyl-3-((ethylamino)(phenyl)methylene)indolin-2-one **3f** (68 mg, 64%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.17 (s, 1H), 7.60 – 7.53 (m, 3H), 7.41–7.37 (m, 2H), 7.30 (t, *J* = 7.8 Hz, 4H), 7.25 – 7.18 (m, 1H), 6.87 – 6.81 (m, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 6.60 – 6.55 (m, 1H), 5.70 (d, *J* = 7.8 Hz, 1H), 5.09 (s, 2H), 3.21 – 3.09 (m, 2H), 1.20 (t, *J* = 7.2 Hz, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 169.0, 161.5, 137.4, 136.6, 133.3, 129.8, 129.5, 128.7, 127.6, 127.2, 127.2, 124.6, 122.3, 120.6, 117.4, 108.1, 94.1, 43.1, 38.9, 16.2. **FTIR** (KBr) = 3025, 1638, 1113, 742 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{24}H_{23}N_2O$ $(M+H)^+$: 355.1810, found: 355.1809.



(Z)-1-benzyl-3-((4-chlorophenyl)(ethylamino)methylene)indolin-2-one (**3g**): 1'-benzyl-3-(4-chlorophenyl)spiro[azirine-2,3'-indolin]-2'-one (107 mg, 0.3 mmol), ethylmagnesium bromide in diethyl ether (133 mg, 1.5 mmol), were allowed to react according to method C to afford 1-benzyl-3-((4-chlorophenyl)(ethylamino)methylene)indolin-2-one **3g** (64 mg, 55%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$ δ 10.13 (s, 1H), 7.59 – 7.54 (m, 2H), 7.37 – 7.33 (m, 2H), 7.29 (dd, *J* = 6.7, 2.1 Hz, 4H), 7.25 – 7.19 (m, 1H), 6.87 (td, *J* = 7.7, 1.1 Hz, 1H), 6.75 (d, *J* = 7.7 Hz, 1H), 6.63 (td, *J* = 7.7, 1.2 Hz, 1H), 5.79 (d, *J* = 7.6 Hz, 1H), 5.08 (s, 2H), 3.18 – 3.08 (m, 2H), 1.20 (t, *J* = 7.3 Hz, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 169.0, 160.0, 137.3, 136.7, 136.0, 131.7, 129.9, 129.3, 128.7, 127.3, 127.3, 124.3, 122.6, 120.7, 117.4, 108.3, 94.4, 43.2, 38.9, 16.2. **FTIR** (KBr) = 3024, 1640, 1173, 743 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{24}H_{22}ClN_2O$ $(M+H)^+$: 389.1420, found: 389.1419.



(Z)-1-benzyl-3-((3-bromophenyl)(ethylamino)methylene)indolin-2-one (**3h**): 1'-benzyl-3-(3-bromophenyl)spiro[azirine-2,3'-indolin]-2'-one (120 mg, 0.3 mmol), ethylmagnesium bromide in diethyl ether (133 mg, 1.5 mmol), were allowed to react according to method C to afford 1-benzyl-3-((3-bromophenyl)(ethylamino)methylene)indolin-2-one **3h** (75 mg, 58%) as a yellow solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ



10.13 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.58 (s, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.32 (dd, *J* = 21.5, 7.3 Hz, 5H), 7.22 (d, *J* = 5.8 Hz, 1H), 6.88 (t, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 7.7 Hz, 1H), 6.63 (dd, *J* = 9.8, 5.4 Hz, 1H), 5.77 (d, *J* = 7.4 Hz, 1H), 5.09 (s, 2H), 3.14 (p, *J* = 7.1 Hz, 2H), 1.21 (t, *J* = 7.2 Hz, 3H). **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 168.9, 159.3, 137.1, 136.7, 135.1, 132.9, 131.1, 130.6, 128.6, 127.2, 127.2, 126.4, 124.1, 123.4, 122.6, 120.7, 117.3, 108.2, 94.3, 43.1, 38.9, 16.1. **FTIR** (neat) = 2971, 1638, 1172, 748 cm^{-1}. **HRMS** (ESI) m/z calculated for $C_{24}H_{22}BrN_2O$ $(M+H)^+$: 433.0915, found: 433.0912. **Crystal Description:** An ORTEP showing the crystal structure of **3h** with displacement ellipsoids drawn at the 50% probability level: Crystals of compound **3h** were grown by slow evaporation from a mixture of $CDCl_3$:n-pentane (2:1). A single crystal (0.13×0.09×0.04 mm) was mounted on loop with a small amount of the paraffin oil. The X-ray data were collected at 100K temperature on a Bruker APEX(II) DUO CCD diffractometer using Cu Kα radiation (λ = 1.54 Å), ω-scans (2θ = 130.64), for a total of 98429 independent reflections. Space group P 21, a = 10.515 Å, b = 10.845 (9) Å, c = 17.755 (10) Å, α = 89.786°, β = 86.446°, γ = 89.978°, V = 2020.6 (12) Å, monoclinic, Z = 4 for chemical formula $C_{24}H_{21}BrN_2O$, with 7 molecule in asymmetric unit;

5.10. Appendix V: Copies of ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra and crystal structure of representative compounds

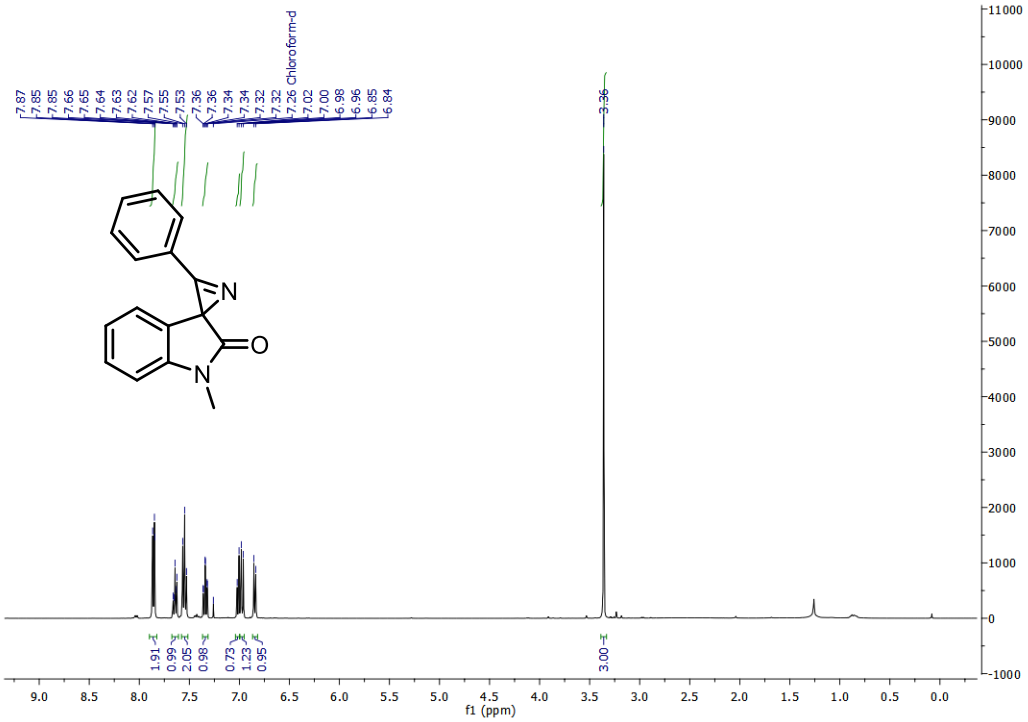


Figure 5.7. ^{1}H NMR of compound **2a**

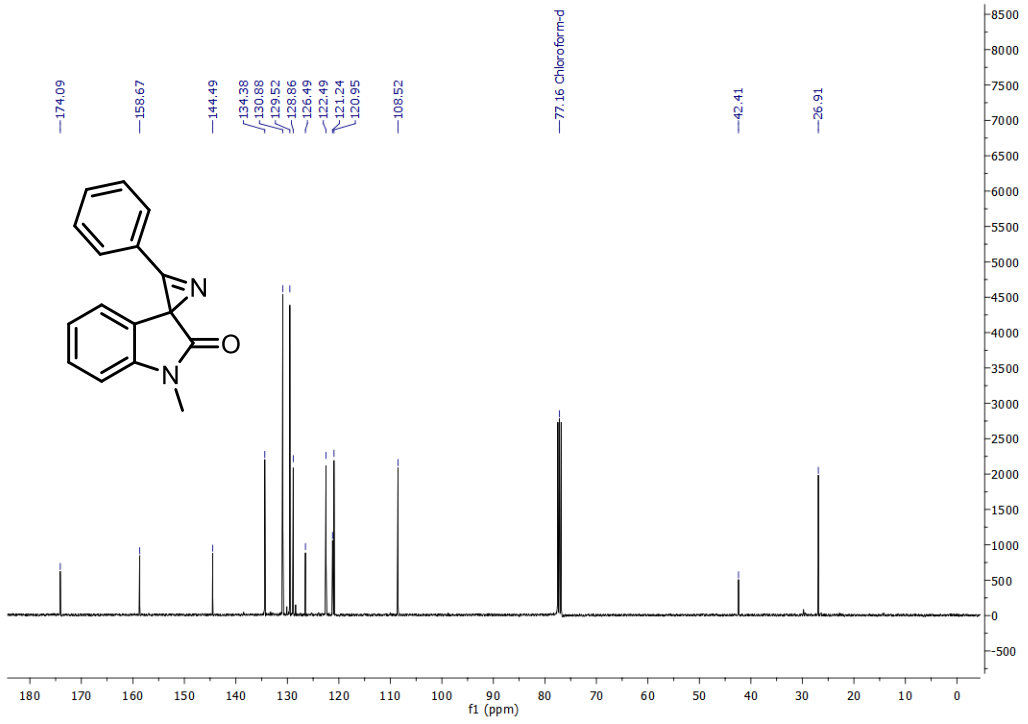


Figure 5.8. $^{13}C\{^{1}H\}$ NMR of compound **2a**

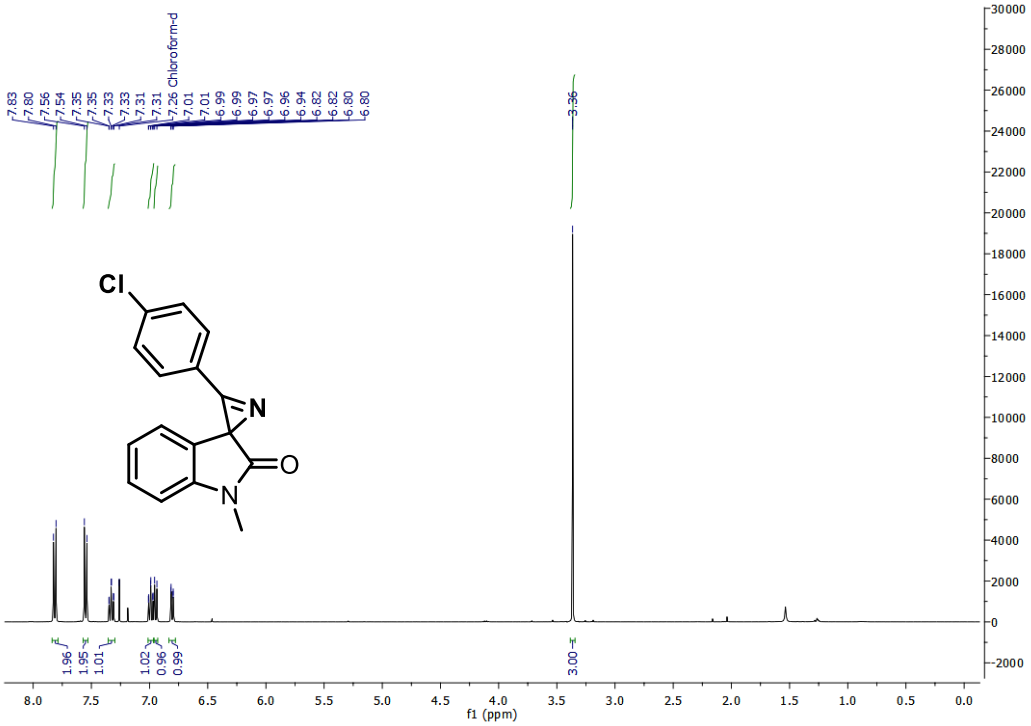


Figure 5.9. ^{1}H NMR of compound **2c**

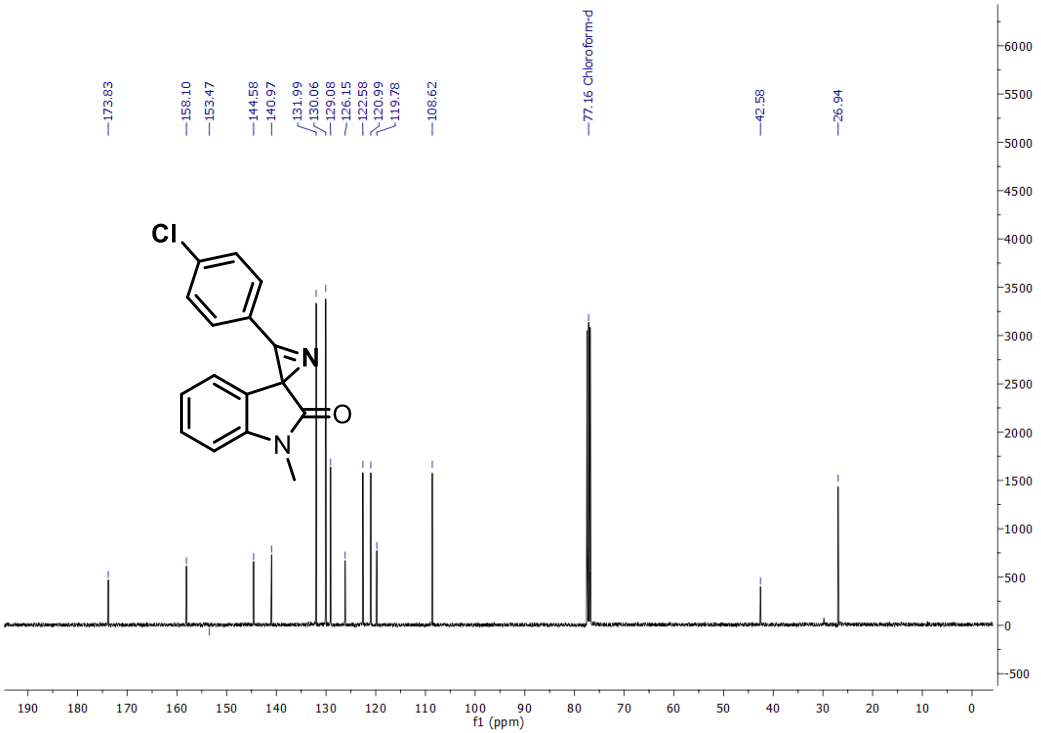


Figure 5.10. $^{13}C\{^{1}H\}$ NMR of compound **2c**

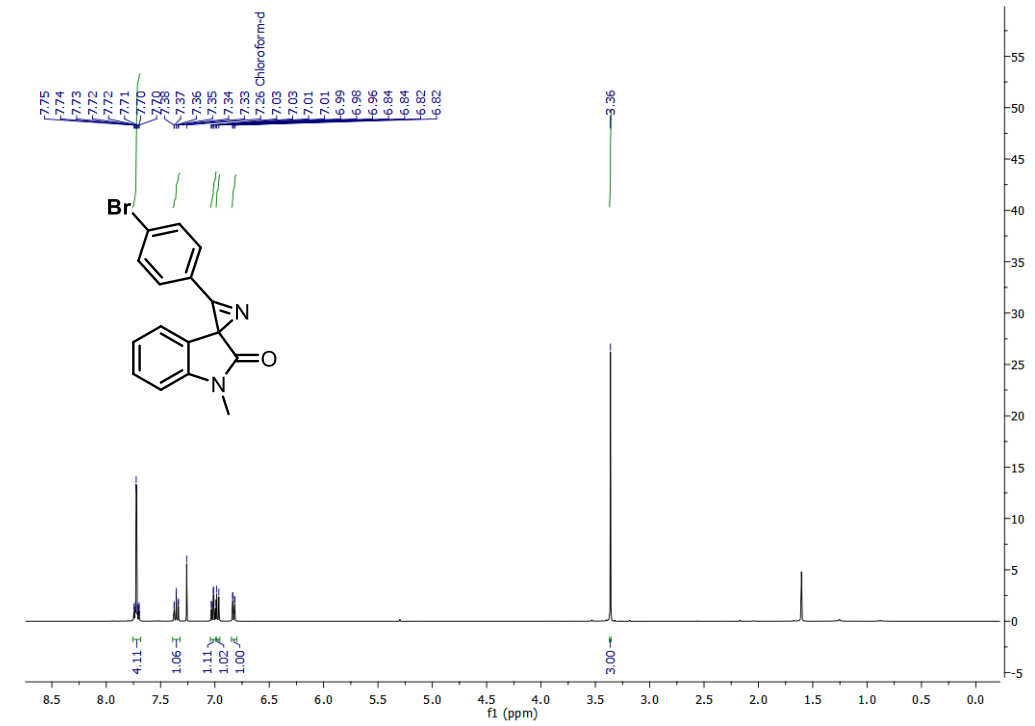


Figure 5.11. ^{1}H NMR of compound **2d**

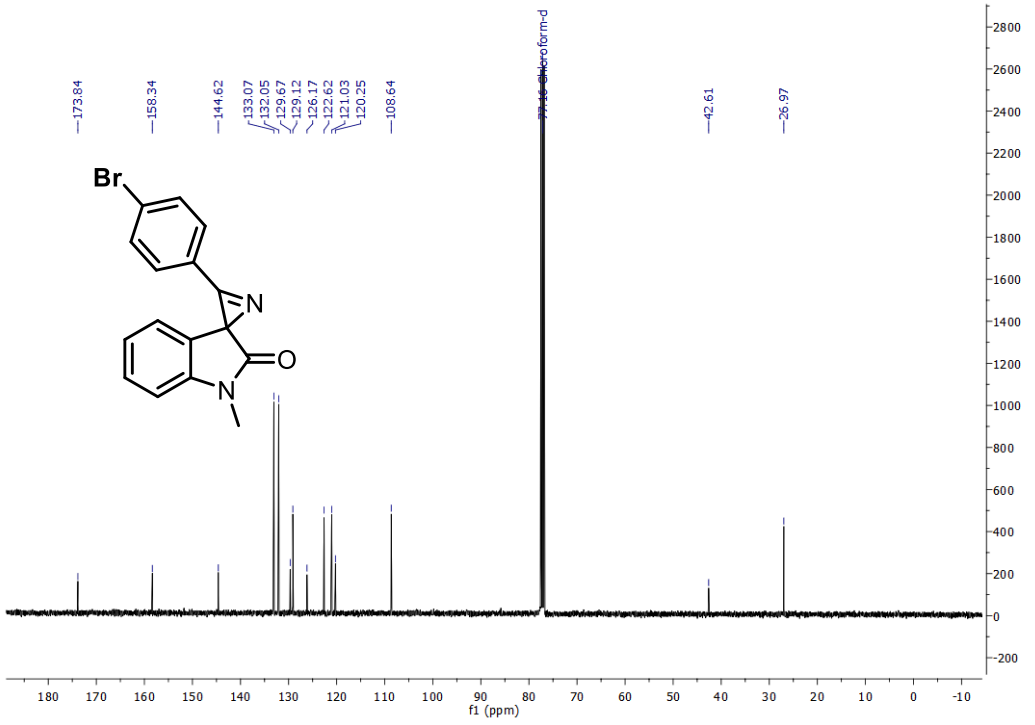


Figure 5.12. ^{13}C{^{1}H} NMR of compound **2d**

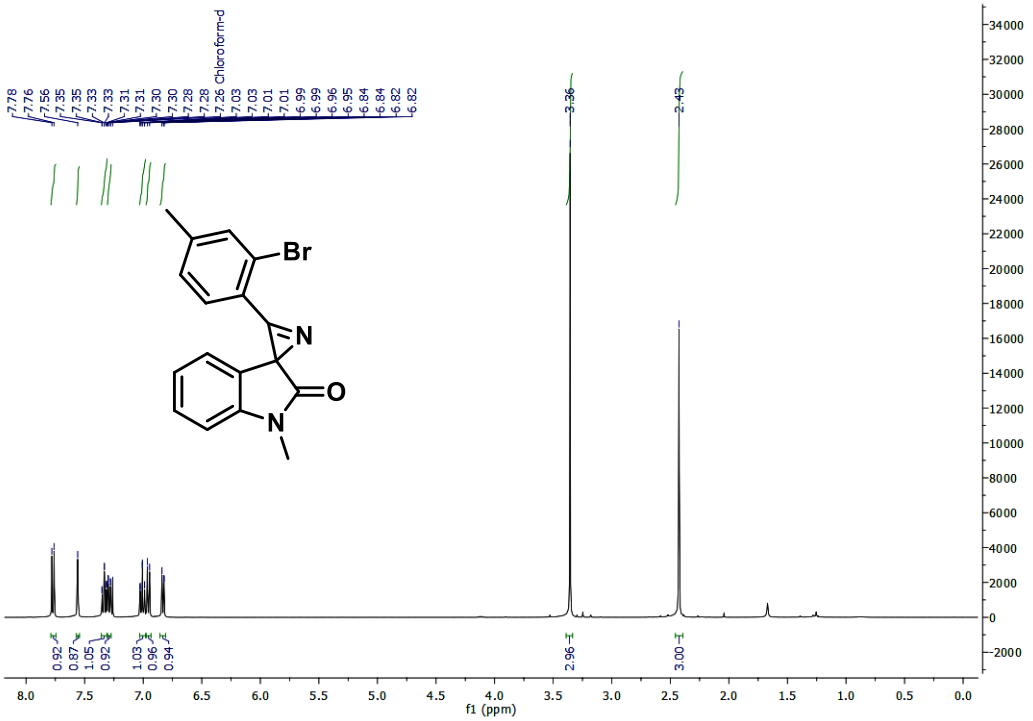


Figure 5.13. ^{1}H NMR of compound **2f**

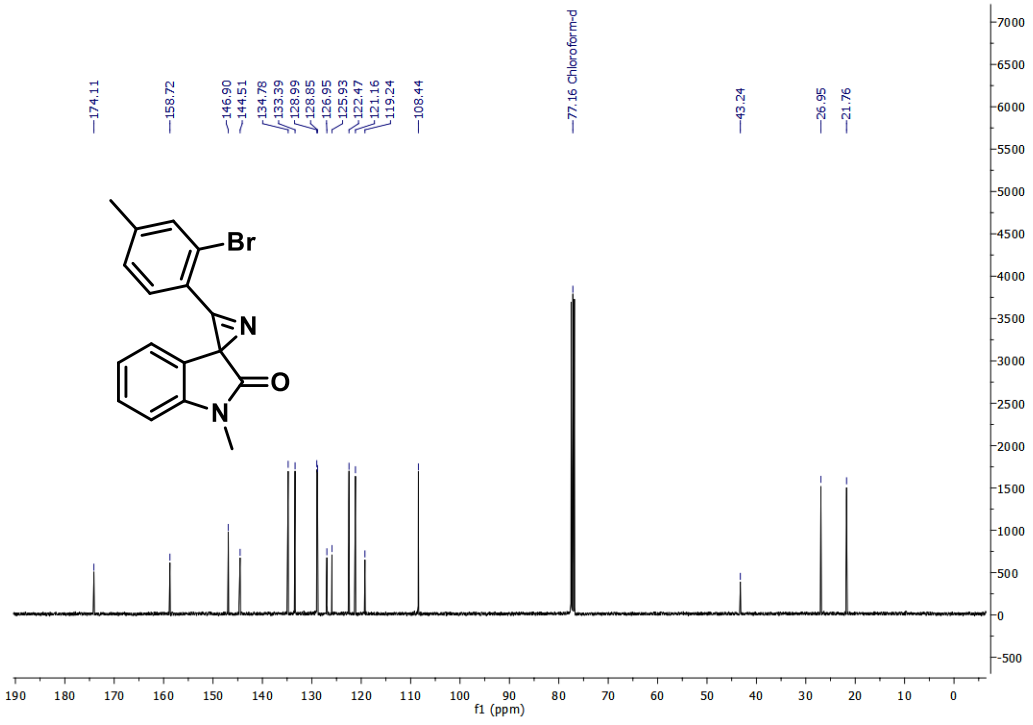


Figure 5.14. ^{13}C{^{1}H} NMR of compound **2f**

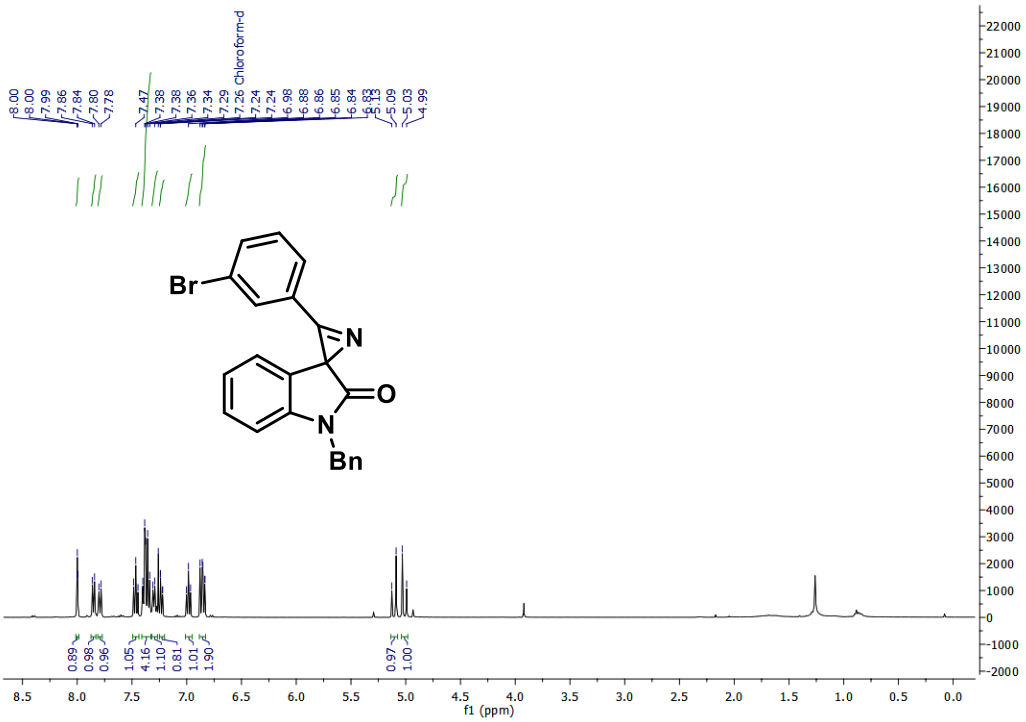


Figure 5.15. ^{1}H NMR of compound **2i**

-

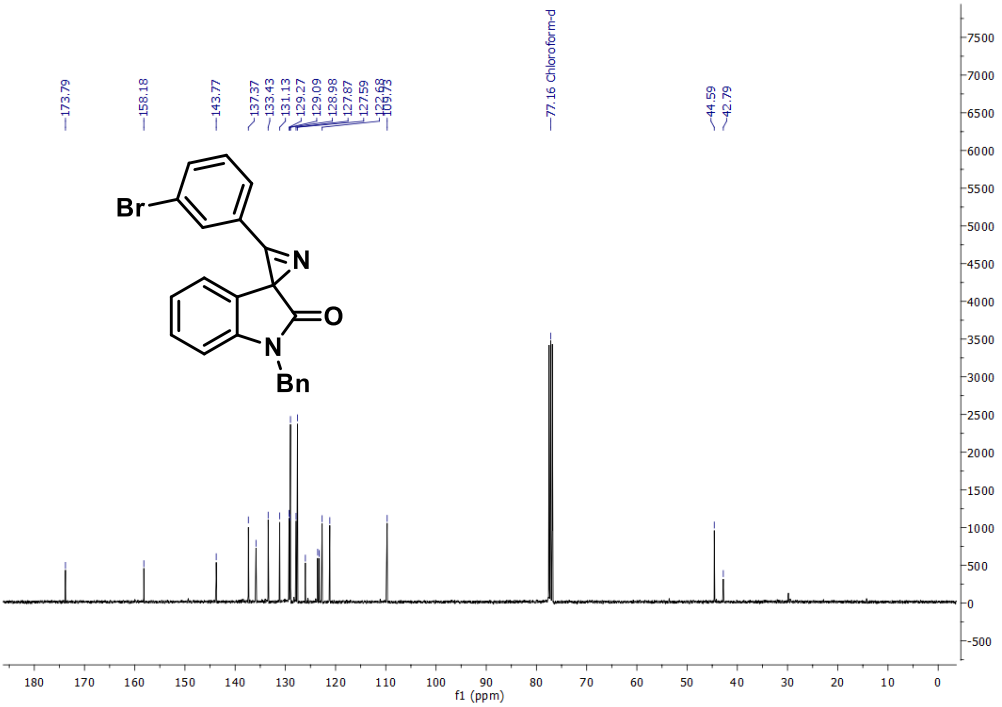


Figure 5.16. ^{13}C{^{1}H} NMR of compound **2i**

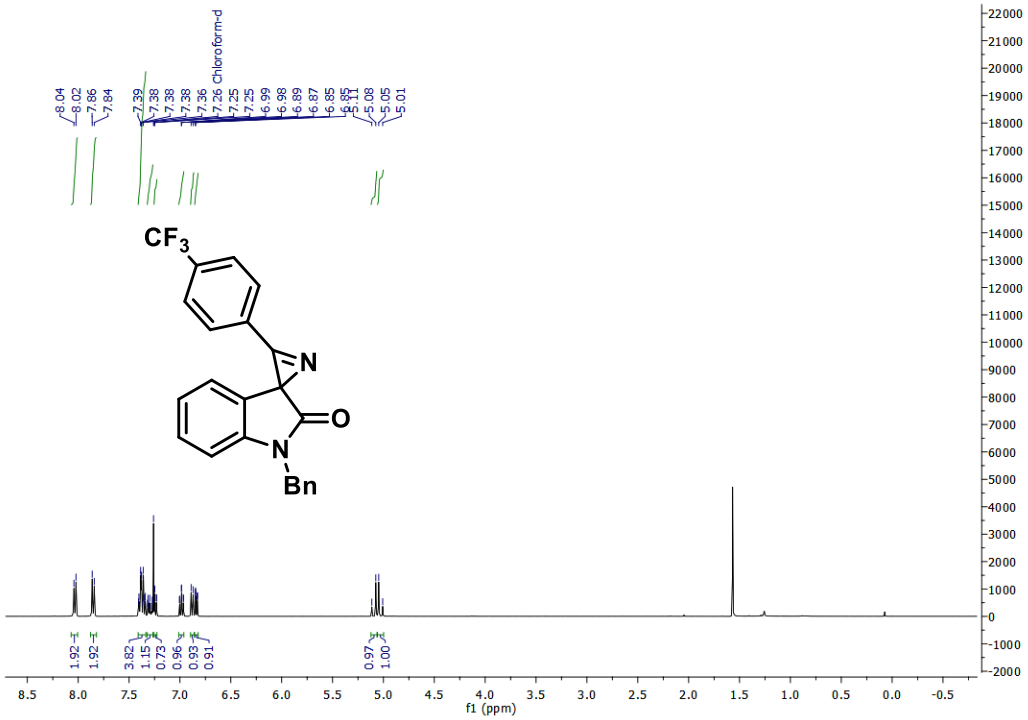


Figure 5.17. ^{1}H NMR of compound **2j**

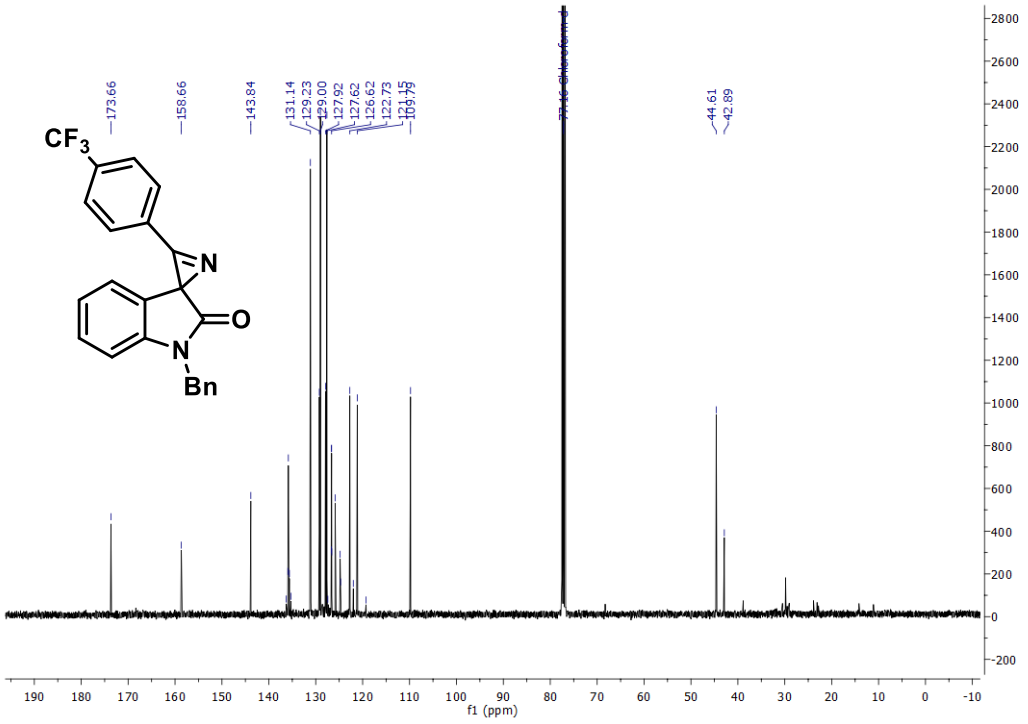


Figure 5.18. ^{13}C{^{1}H} NMR of compound **2j**

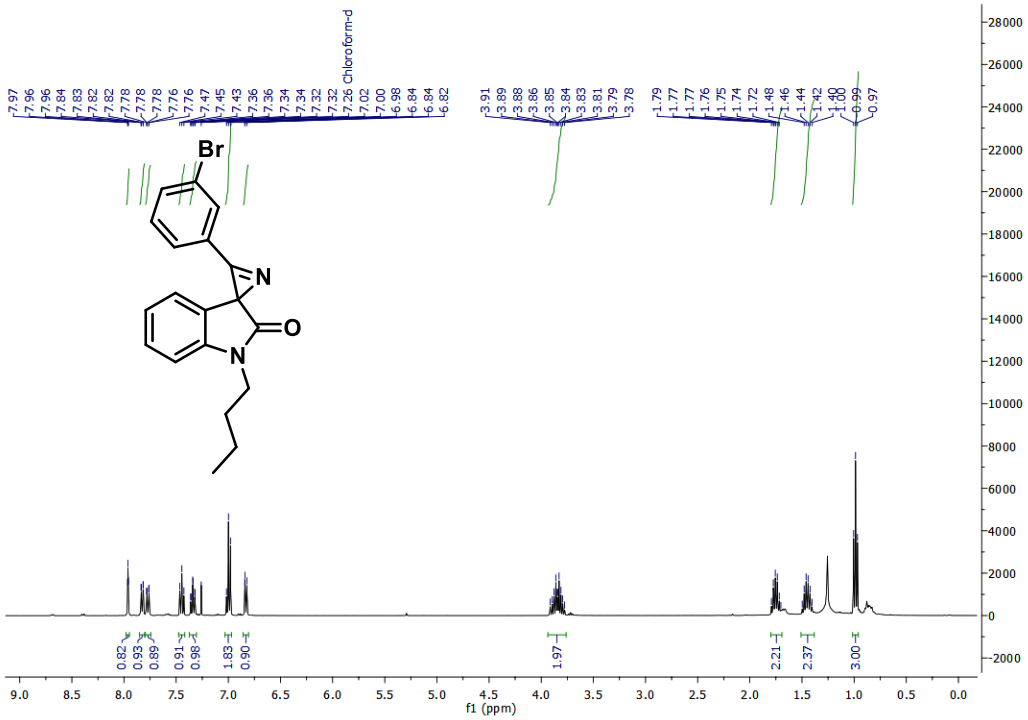


Figure 5.19. ^{1}H NMR of compound **2l**

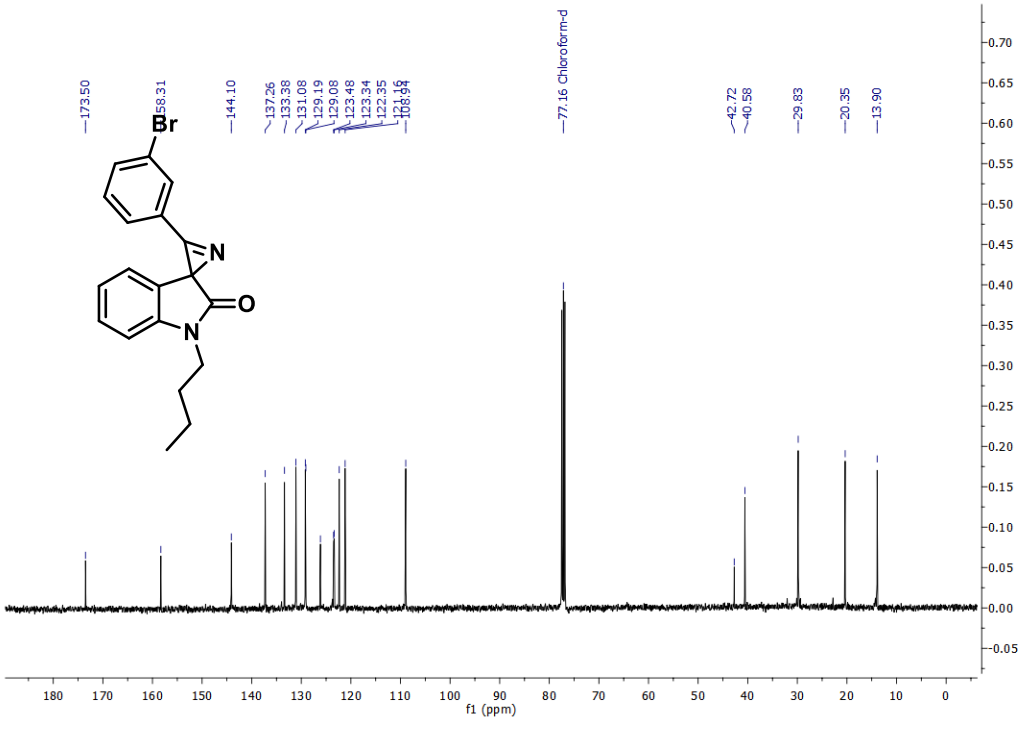


Figure 5.20. ^{13}C{^{1}H} NMR of compound **2l**

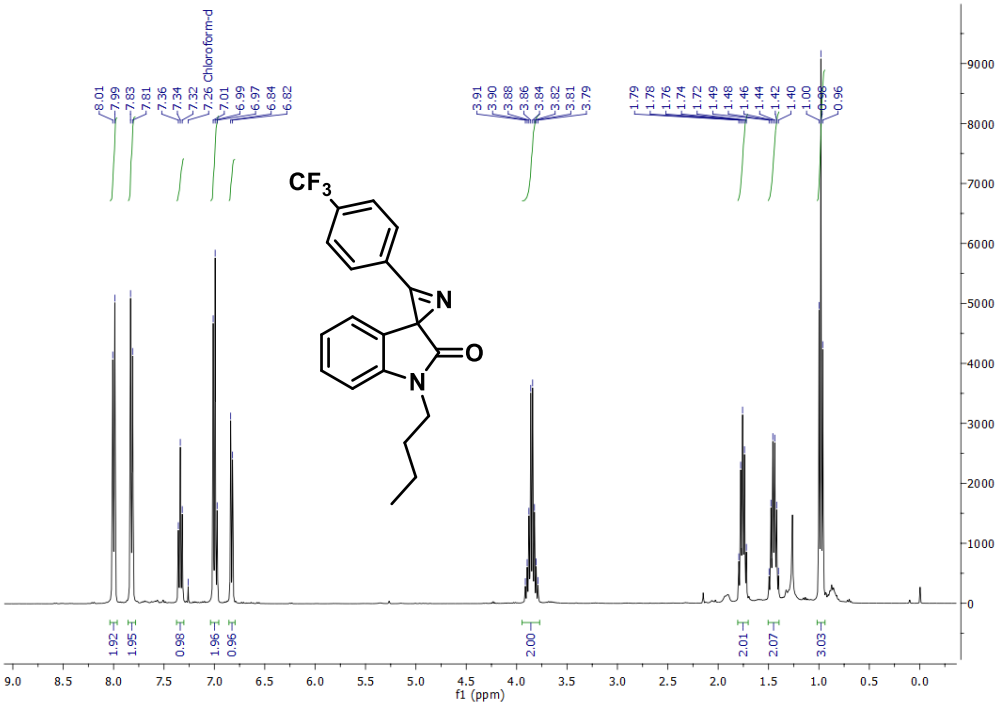


Figure 5.21. ^{1}H NMR of compound **2o**

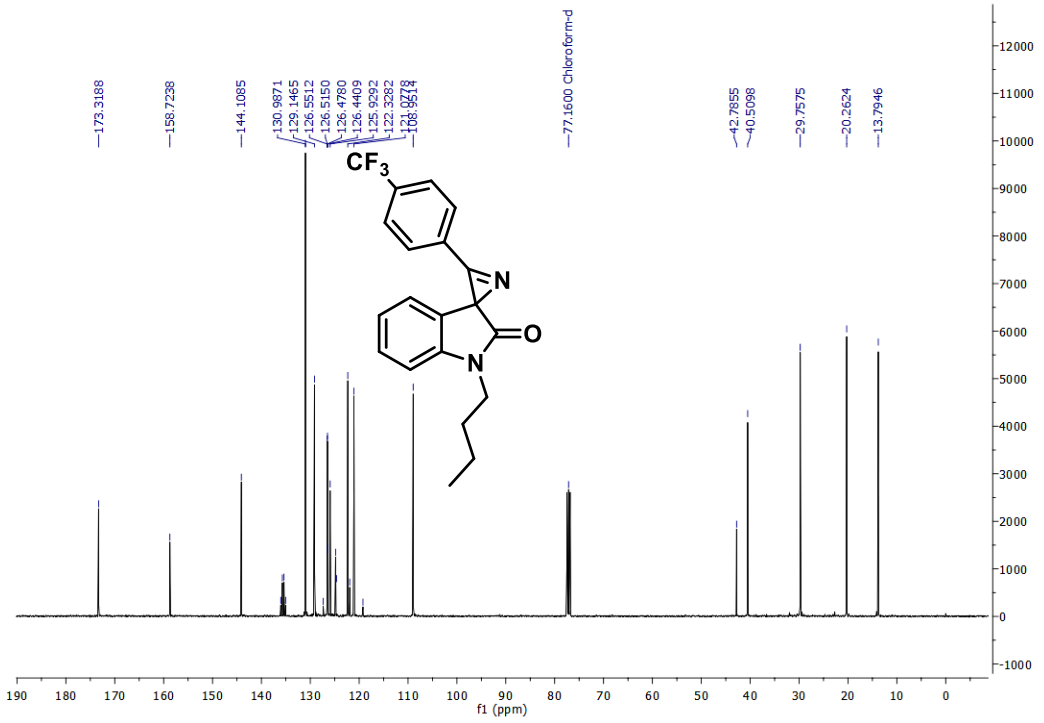


Figure 5.22. ^{13}C{^{1}H} NMR of compound **2o**

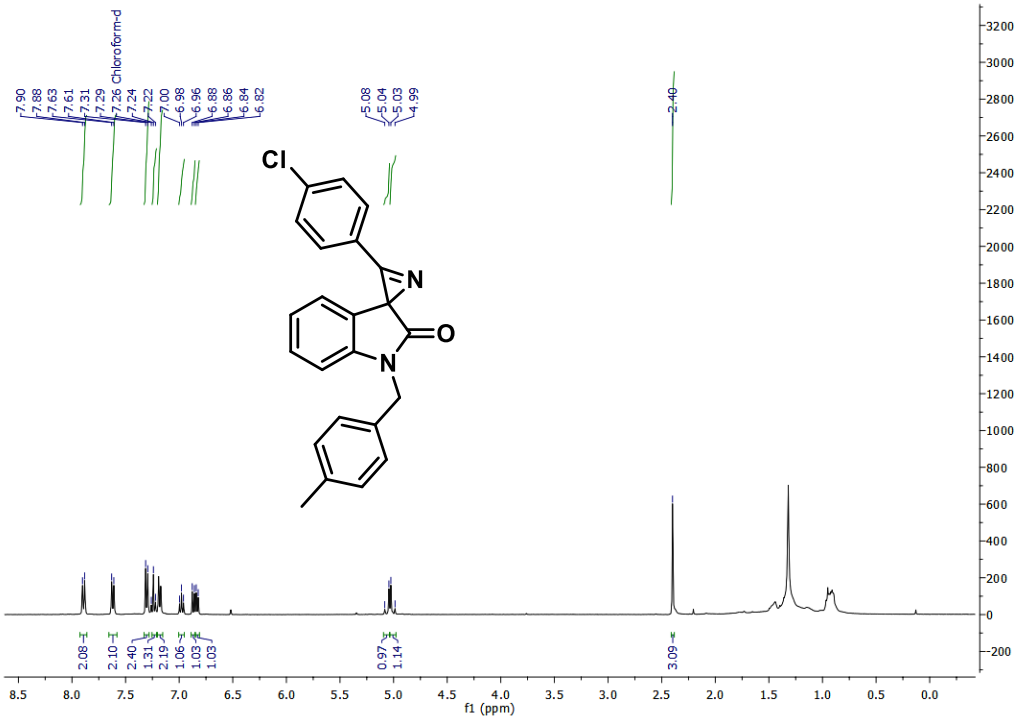


Figure 5.23. ^{1}H NMR of compound **2q**

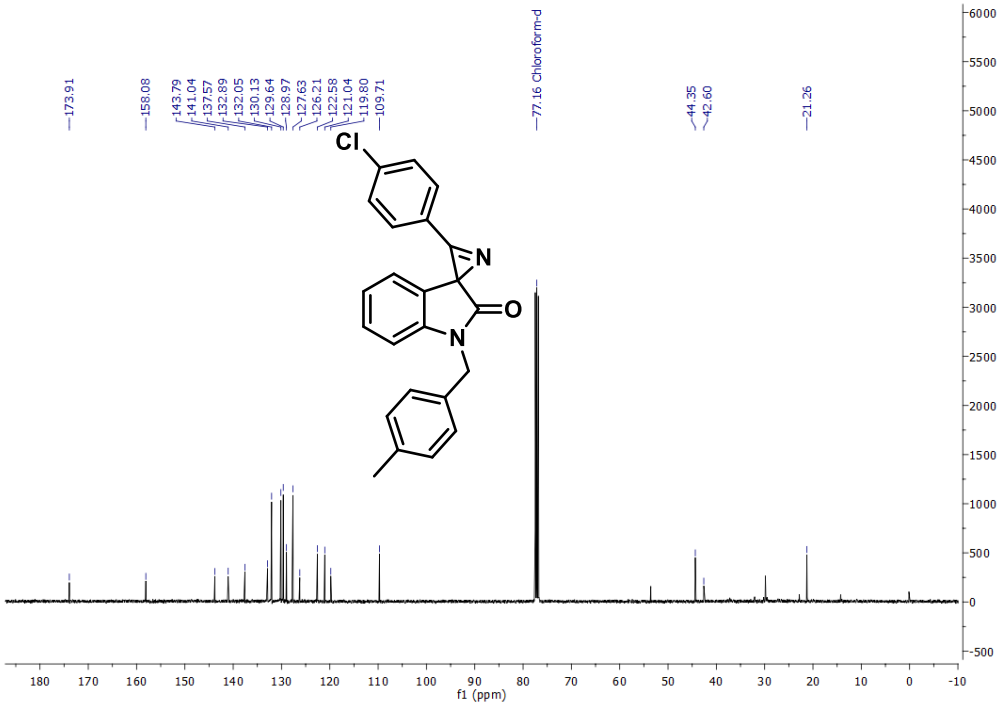


Figure 5.24. ^{13}C{^{1}H} NMR of compound **2q**

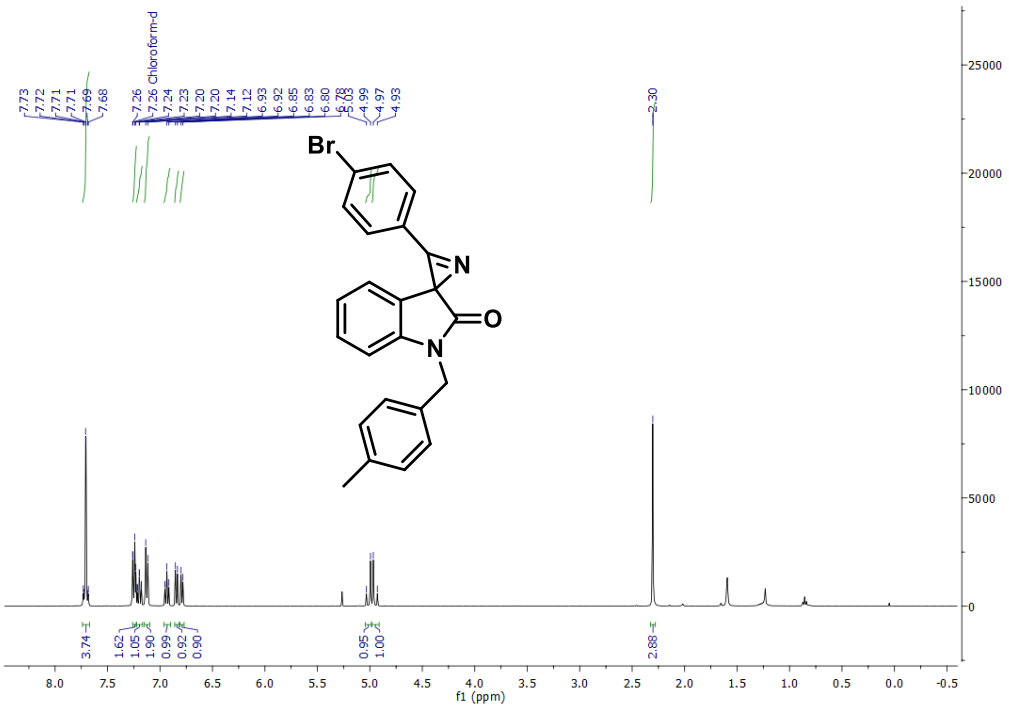


Figure 5.25. ^{1}H NMR of compound **2r**

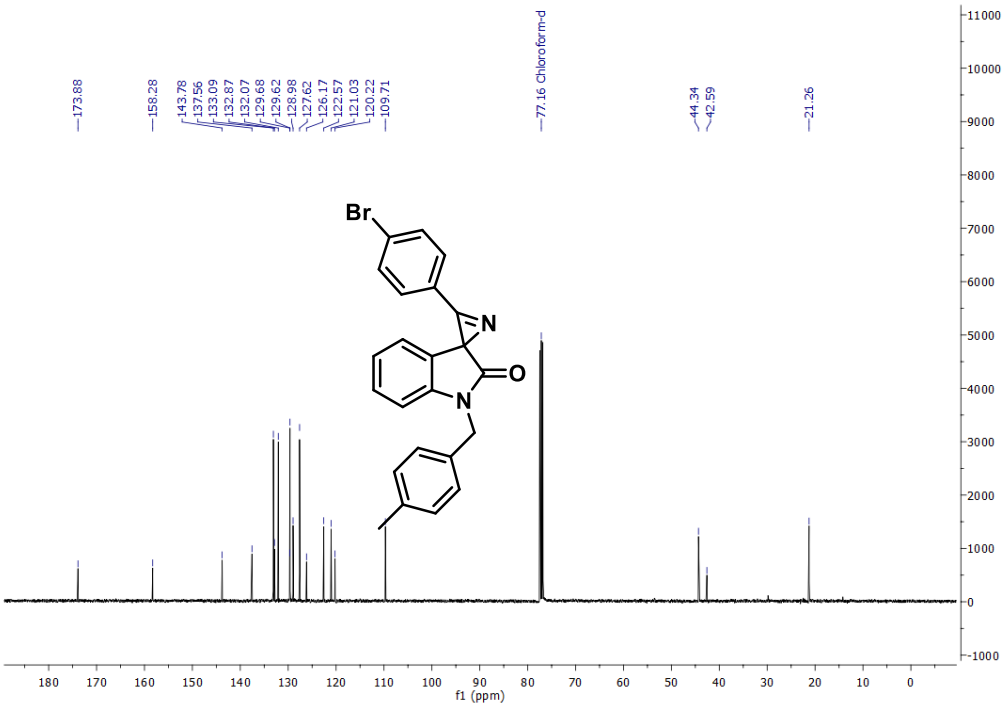


Figure 5.26. ^{13}C{^{1}H} NMR of compound **2r**

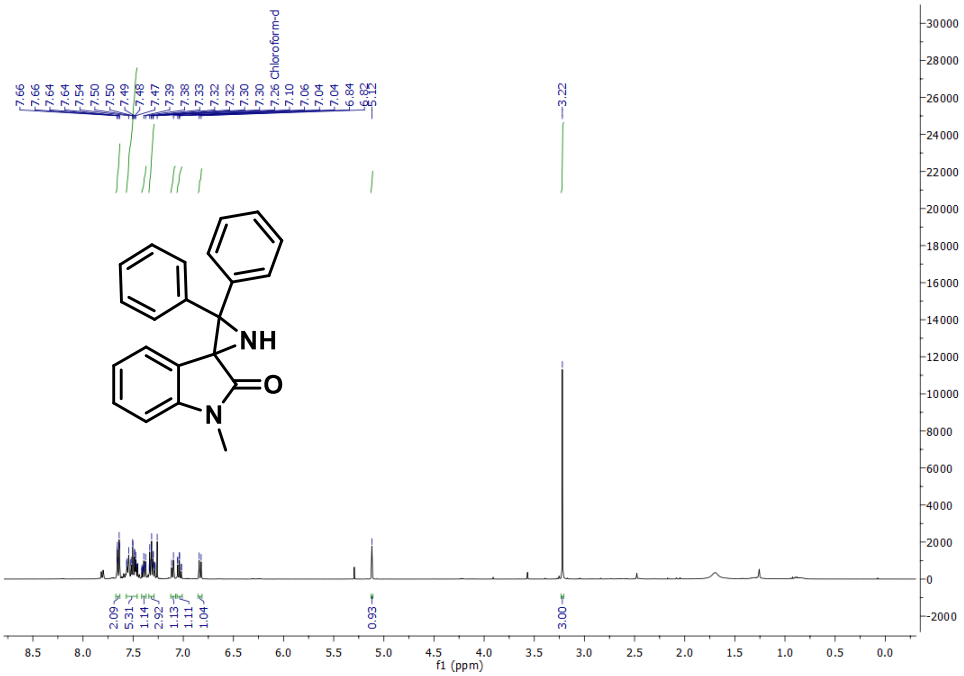


Figure 5.27. ^{1}H NMR of compound **3a**

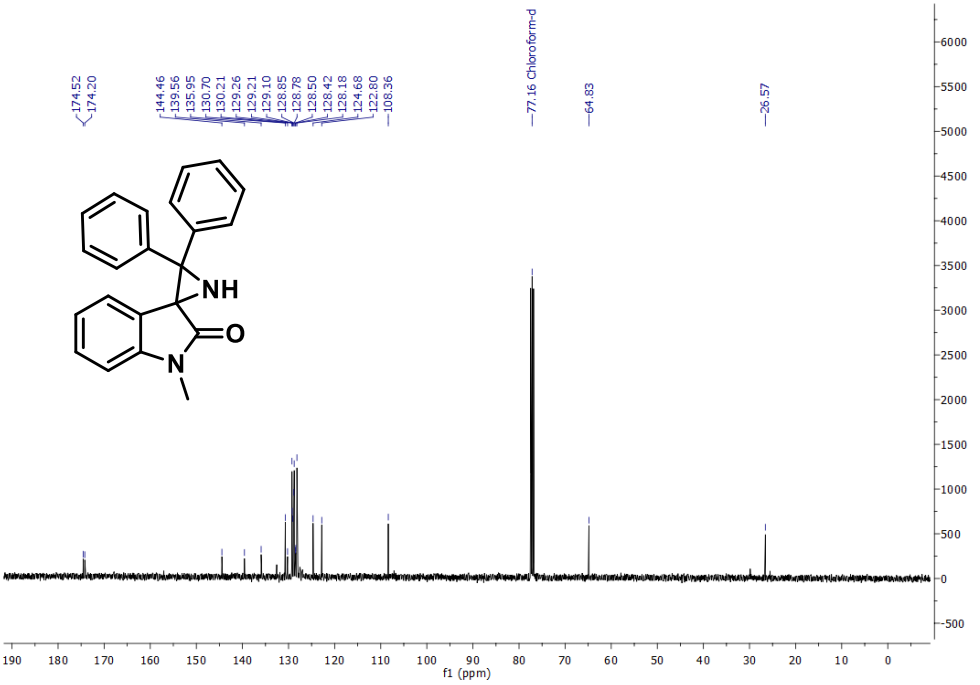


Figure 5.28. ^{13}C{^{1}H} NMR of compound **3a**

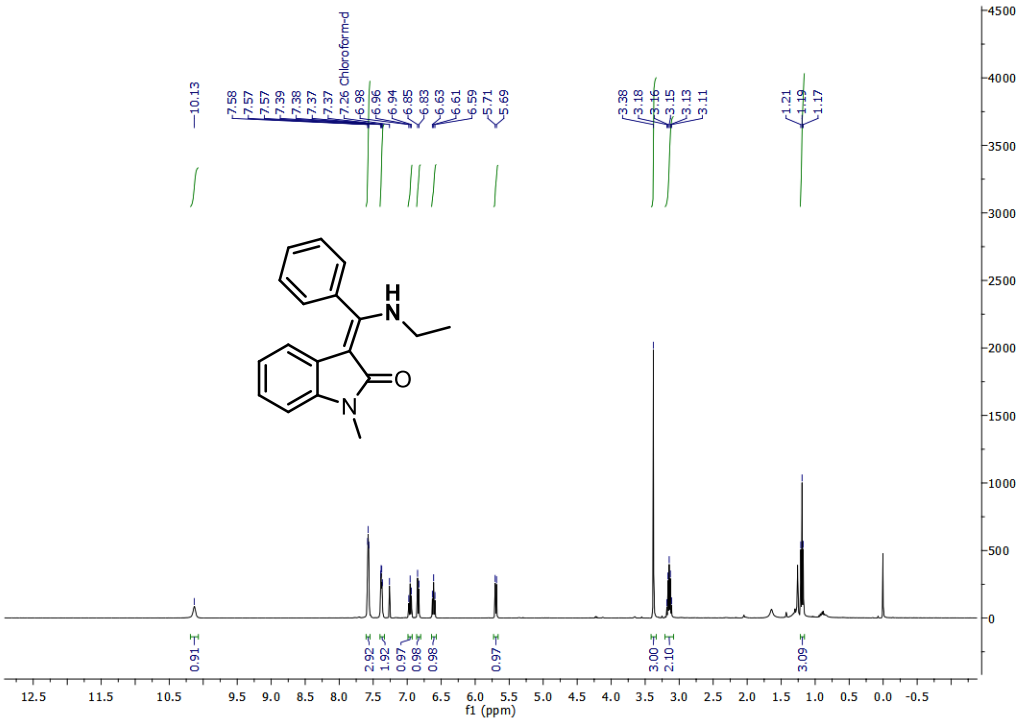


Figure 5.29. ^{1}H NMR of compound **3e**

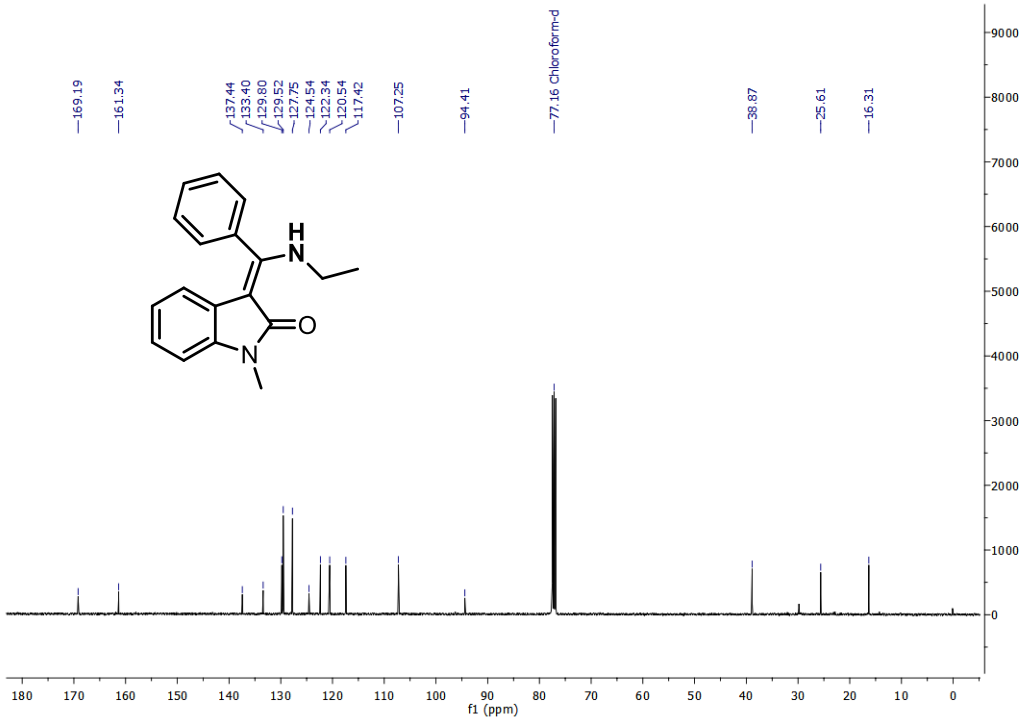


Figure 5.30. ^{13}C{^{1}H} NMR of compound **3e**

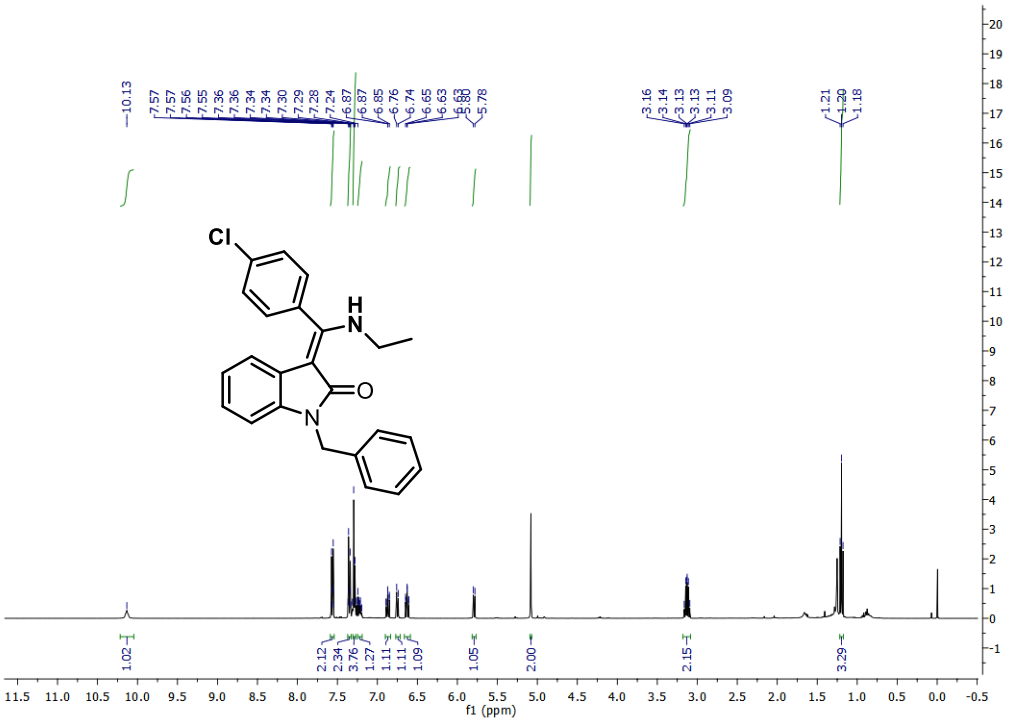


Figure 5.31. ^{1}H NMR of compound **3g**

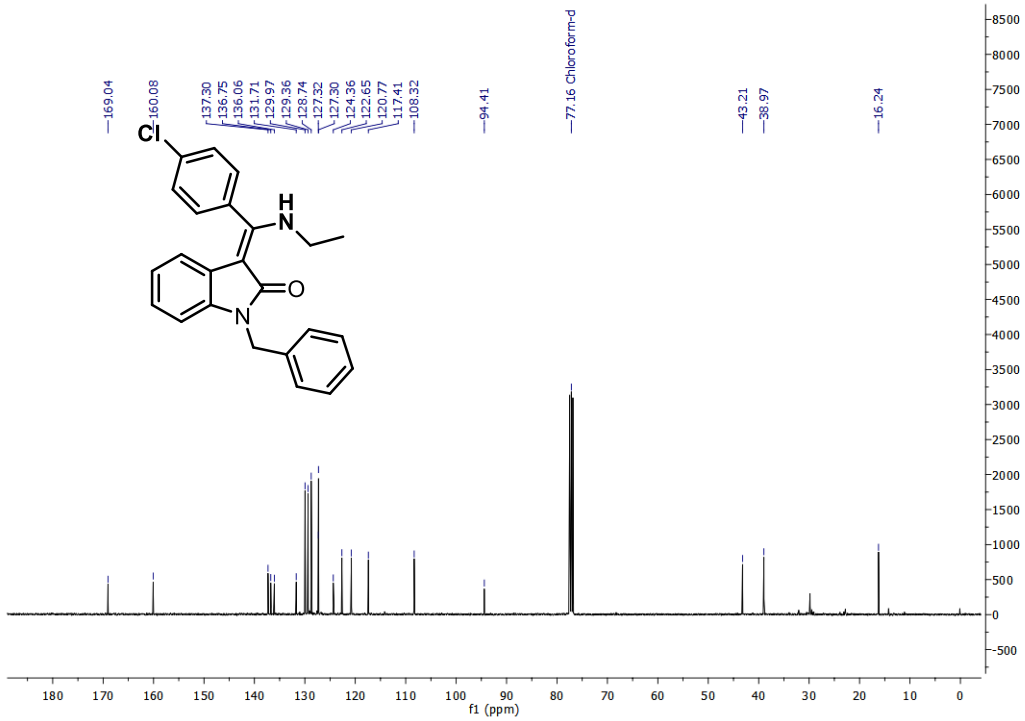


Figure 5.32. ^{13}C{^{1}H} NMR of compound **3g**

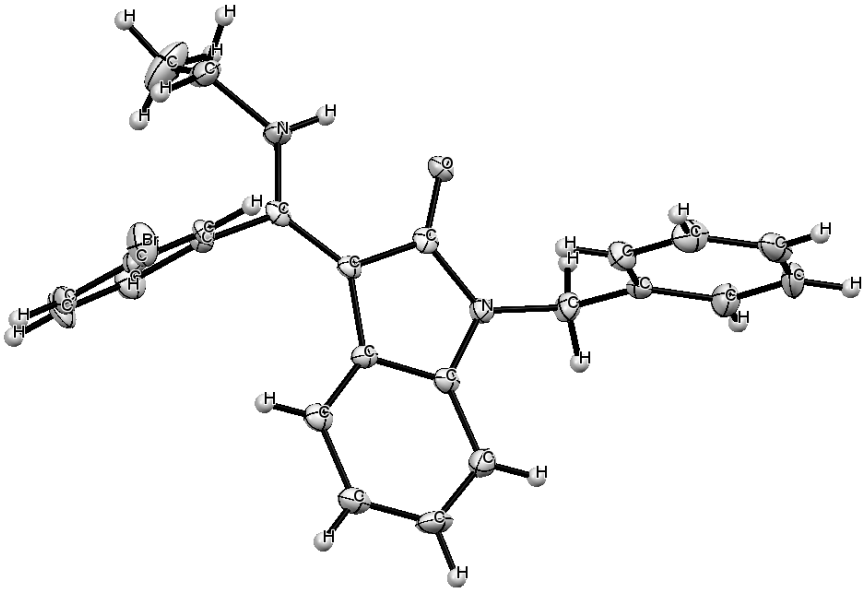


Figure 5.33. Crystal structure of compound **3h**

5.11. References:

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