Regioselective C–H Bond Oxygenation in Amides, Indoles and Isatins, and Oxidative C–C Bond Formation in Indoles by Palladium Catalyst

by

Vijaykumar M

(Registration Number: 10CC18A26058)

A thesis submitted to the
Academy of Scientific & Innovative Research
for the award of the degree of

DOCTOR OF PHILOSOPHY
in
SCIENCE

under the supervision of
Dr. Benudhar Punji

CSIR-NATIONAL CHEMICAL LABORATORY
Pune

Academy of Scientific and Innovative Research
AcSIR Headquarters, CSIR-HRDC campus
Sector 19, Kamla Nehru Nagar
Ghaziabad, U.P. - 201 002, India

December-2023

Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled, "***Regioselective C–H Bond Oxygenation in Amides, Indoles and Isatins, and Oxidative C–C Bond Formation in Indoles by Palladium Catalyst***", submitted by ***Vijaykumar M*** to the Academy of Scientific and Innovative Research (AcSIR) in fulfillment of the requirements for the award of the Degree of ***Doctor of Philosophy in Science***, embodies original research work carried-out by the student. We, further certify that this work has not been submitted to any other University or Institution in part or full for the award of any degree or diploma. Research material(s) obtained from other source(s) and used in this research work has/have been duly acknowledged in the thesis. Image(s), illustration(s), figure(s), table(s) etc., used in the thesis from other source(s), have also been duly cited and acknowledged.

Mr. Vijaykumar M
Research Student
Date: 20/12/2023

Dr. Benudhar Punji
Research Supervisor
Date: 20/12/2023

STATEMENTS OF ACADEMIC INTEGRITY

I **Vijaykumar M**, a Ph.D. student of the Academy of Scientific and Innovative Research (AcSIR) with Registration No. **10CC18A26058** hereby undertake that, the thesis entitled "**Regioselective C–H Bond Oxygenation in Amides, Indoles and Isatins, and Oxidative C–C Bond Formation in Indoles by Palladium Catalyst**" has been prepared by me and that the document reports original work carried out by me and is free of any plagiarism in compliance with the UGC Regulations on *"Promotion of Academic Integrity and Prevention of Plagiarism in Higher Educational Institutions (2018)"* and the CSIR Guidelines for "*Ethics in Research and in Governance (2020)*".

Signature of the Student
Date : 20/12/2023
Place : CSIR-NCL, Pune

It is hereby certified that the work done by the student, under my/our supervision, is plagiarism-free in accordance with the UGC Regulations on *"Promotion of Academic Integrity and Prevention of Plagiarism in Higher Educational Institutions (2018)"* and the CSIR Guidelines for "*Ethics in Research and in Governance (2020)*".

NA
Signature of the Co-supervisor (if any)
Name :
Date :
Place :

Signature of the Supervisor
Name : Dr. Benudhar Punji
Date : 20/12/2023
Place : CSIR-NCL, Pune

Dedicated to My Parents

I would like to express my sincere gratitude to all those who contributed to the work described in this thesis. First, I sincerely thank my research supervisor, ***Prof. Benudhar Punji****, for his invaluable guidance and scholarly insights. His enthusiasm, encouragement, and unwavering faith in me have been tremendously beneficial. I am thankful for the opportunity to work under his guidance, where fruitful discussions allowed me to plan and execute my research ideas without pressure. The principles he instilled in me will be a guiding force throughout my life.*

I also extend my thanks to Dr. Mahesh Dharne, Dr. Ravindar Konatham, and Dr. Sakya S. Sen for their roles as members of my doctoral advisory committee (DAC) and for providing valuable suggestions during DAC meetings. I am grateful to Prof. Ashish K. Lele, Director of CSIR-NCL, and Prof. A. K. Nangia, Former Director of NCL, for providing the necessary infrastructure and facilities. Acknowledgment is given to CSIR, New Delhi, for their financial support through junior and senior research fellowships.

I want to thank our collaborator, Dr. Rajesh Gonnade, for his assistance in the XRD analysis and Mrs. B. Santhakumari for the HRMS analysis. I also thank Dr. Rajamohanan, Dr. Ajithkumar, and Dr. Uday Kiran for the NMR facilities.

Fortunately, I have worked in a lab characterized by unity, uniformity, and cleanliness. I appreciate the cheerful cooperation and companionship of my seniors, Drs. Shrikant Khake, Hanuman Prasad Pandiri, Vineeta Soni, Ulhas Patel, Dilip Pandey, Rahul Jagtap, Abad Ali, Dipesh Sharma, Sidheshwar Ankade, ***Surydev Kumar Verma*** *and juniors, Anand Shabade, Sadhna Bansal, Chandini Pradhan, Rameshwar Pawar, Yogeshwar Ramasane, Rahul K. Singh, Shana, Pragnya, Sandip, Chandrakant, Banamali, Tamal, and Shuvajit for their valuable time and cooperation. Also, I would like to thank the research trainees of our lab, Jagnyesh, Ankita, Tejaswini, Ishita, Harshada, Vishal, Sachin Patel, Mital, and Darsana M, for their cooperation. The warm memories of my days in Polyolefin Lab, High-Pressure Lab, and Lab-226 will remain with me forever.*

Special thanks go to Dr. Samir Chikkali and his group members, Drs. Shahaji, Satej, Nilesh, Anirban, and Bhausaheb for their valuable scientific advice and help in lab practices. I greatly acknowledge other lab colleagues Dnyaneshwar, Rohit, Dr. Sandip Pawal, Amol, Kishor, Rajkumar, Tanuja, Dr. Shailaja, and Uday for keeping healthy environment in the lab and for their valuable scientific discussions.

I acknowledge colleagues' efforts in various institute divisions and SAC office staff for

cooperation. My appreciation also extends to the staff members of NMR, Mass Spectroscopy, Microanalysis, Library, Administration, and technical divisions of NCL.

I want to express my thanks to all my teachers, and all friends from my academic journey, as well as the staff of The Oxford Science College, Bengaluru, M.S Ramaiah College, Bengaluru, and First Grade College, KGF, for their support during my M. Sc. and B. Sc. days.

Special gratitude is reserved for my friends at CSIR-NCL, whose camaraderie created a wonderful atmosphere outside the lab. Further, I extend my special thanks to ***Krithika, Dr. Shailaja, Shubha Markande, Dr Nayaka G P*** *and* ***Shivamurthy B P*** *for her generous support and motivation.*

My family has been a constant inspiration and moral support throughout my education. I am profoundly grateful to my parents, ***Parvathamma*** *and* ***Muniyappa R****, for their love, sacrifices, blessings, and unwavering support. I sincerely thank my wife,* ***Shalini M****, and my son,* ***Dhruvik Vijay Naidu****, for being my pillars of strength during my Ph.D. journey. I also express heartfelt thanks to my sister,* ***Aruna****,* ***Veena****, and my brother,* ***Anil Kumar****, for their constant support and encouragement. I also express sincere gratitude to my mother-in-law,* ***Geetha,*** *and father-in-law,* ***Muniswamy,*** *for their love, blessings, and unwavering support. Lastly, I attribute all my achievements to Almighty God, thanking Him for the wisdom, health, and strength to undertake and complete this research task.*

-VIJAYKUMAR

Units

Å	Angstrom
^{o}C	Degree Celsius
g	Gram
mg	Milligram
h	Hour (s)
Hz	Hertz
mL	Millilitre
µL	Microlitre
min	Minutes
MHz	Mega Hertz
mmol	Millimole
ppm	Parts per million
m/z	Mass to charge ratio
cm	Centimetre

Chemical Notations

AcOH	Acetic acid
Ac_2O	Acetic anhydride
AdCOOH	1-Adamantanecarboxylic acid
aq	Aqueous
br s	Broad singlet
BHT	Butylated hydroxytoluene
bpy	Bipyridine
Calcd	Calculated
Cat	Catalyst
CD_3OD	Deuterated methanol
$CDCl_3$	Deuterated chloroform
Conc.	Concentrated
DCE	1,2-Dichloroethane
DG	Directing group
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
DMSO-d_6	Deuterated dimethyl sulfoxide

equiv	Equivalent
EtOH	Ethanol
EtOAc	Ethyl acetate
Galvinoxyl	2,6-Di-*tert*-butyl-α-(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadien-1- ylidene)-*p*-tolyloxy
H_2O	Water
HRMS	High resolution mass spectrometry
HFIP	Hexafluoro isopropanol
$KMnO_4$	Potassium permanganate
$K_2S_2O_8$	Potassium persulfate
M.p	Melting point
Na_2SO_4	Sodium sulfate
NaH	Sodium hydride
NMR	Nuclear Magnetic Resonance
NFSI	*N*-Fluorobenzene sulfonimide
Pd	Palladium
$Pd(OAc)_2$	Palladium(II) acetate
$PdCl_2$	Palladium(II) chloride
Ph	Phenyl
$PhI(OAc)_2$	Iodosobenzene diacetate
Piv	Pivalate
PPh_3	Triphenyl phosphine
2-py	2-Pyridinyl
rt	Room temperature
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic acid anhydride
TFE	Trifluoroethanol
TLC	Thin layer chromatography
vacuo	Vacuum

- All reagents, starting materials, and solvents were obtained from commercial suppliers and used as such without further purification. Solvents were dried using standard protocols.
- All reactions were carried out in oven-dried glassware in open air or glove box or under a positive pressure of argon unless otherwise mentioned with magnetic stirring.
- Air-sensitive reagents and solutions were transferred *via* syringe or cannula and were introduced to the apparatus *via* rubber septa.
- Progresses of reactions were monitored by thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F254). Visualization was accomplished with UV light, $KMnO_4$ stain, or Iodine adsorbed on silica gel.
- Column chromatography was performed on silica gel (100-200 or 230-400 mesh size).
- Deuterated solvents for NMR spectroscopic analyses were used as received.
- All ^{1}H NMR and ^{13}C NMR spectra were obtained using a 200 MHz, 400 MHz, and 500 MHz spectrometer. Coupling constants were measured in Hertz. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m =multiplet, br = broad.
- HRMS (ESI) were recorded on ORBITRAP mass analyzer (Thermo Scientific, QExactive).
- Chemical nomenclature (IUPAC) and structures were generated using Chem Bio Draw Ultra.

AcSIR	**Synopsis of the Thesis to be submitted to the Academy of Scientific and Innovative Research for Award of the Degree of Doctor of Philosophy in Sciences/ Engineering**
Name of the Candidate	**Mr. Vijaykumar M**
Degree Enrollment No. &Date	Ph. D. in Chemical Sciences (10CC18A26058); 1st August 2018
Laboratory	CSIR-National Chemical Laboratory
Title of the Thesis	**Regioselective C–H Bond Oxygenation in Amides, Indoles and Isatins, and Oxidative C–C Bond Formation in Indoles by Palladium Catalyst**
Research Supervisor	Dr. Benudhar Punji

1. Introduction:

The thesis entitled "**Regioselective C–H Bond Oxygenation in Amides, Indoles and Isatins, and Oxidative C–C Bond Formation in Indoles by Palladium Catalyst**" is divided into six chapters. Chapter-1 deals with the literature survey on the synthetic and biological relevance of oxygenation and selective C–C dimerization. Moreover, a comprehensive analysis on transition metal-catalyzed oxygenation of amides, isatins, indoles, and oxidative C–C coupling of indoles is highlighted.[1-7] In general, the amide is a versatile functional group with easy transformative tendencies into useful functionalities like carboxylic acid and aldehyde. Therefore, in Chapter-2, we have discussed selective C–H oxygenation of amide-containing substrates using a palladium catalyst. Similarly, the isatin framework leads to diverse privileged molecules that are entrenched as antimalarial, antifungal, antibacterial, antiviral, and potential antitumor agents. In particular, the hydroxy group-containing isatins/indoles represent an important subclass among the isatin-based natural products. Therefore, developing protocols for the efficient hydroxylation of isatins is highly indispensable. In Chapter-3, we describe the palladium-catalyzed regioselective oxygenation of $C(sp^2)$–H and $C(sp^3)$–H bonds in isatins.[8] Chapter-4, presents the palladium-catalyzed regioselective C–4 alkoxylation of indoles *via* weak chelation assistance.

The indole dimers are found in many biologically active microbial natural products and plant alkaloids. The preparation of indole dimers includes the Madelung cyclization, the intramolecular hydroamination, and the coupling of the corresponding indoles. However, these methods usually suffer from harsh reaction conditions and lengthy steps. Therefore, in Chapter-

Dr. Benudhar Punji (Supervisor)

Vijaykumar M (Candidate)

5, we discuss the Pd(II)-catalyzed intermolecular C–2/C–7 oxidative coupling of indoles. Lastly, Chapter-6 presents the overall summary of the thesis work, followed by the future direction related to the field.

2. Statement of the Problem:

The construction of C–C/C–O bonds has emerged as a powerful tool with application to material sciences, pharmaceutical industries, and natural product synthesis. Traditionally, oxygenated compounds are developed *via* the condensation of alcohols, the reaction of alkoxides with alkyl halides (Williamson synthesis), alkoxy mercuration/demercuration of alkenes, and combining carboxylic acids and alcohols. However, most of these methods are associated with limited substrate scope, harsh reaction conditions, multistep synthetic sequences, and generation of by-products. To overcome these challenges, the transition metal-catalyzed regioselective functionalization has been given significant importance, which we have emphasized in this thesis work.

3. Objectives:

As discussed, selective functionalization of inert C–H bond to C–O/C–C bonds are restricted to the use of traditional methods or limited to severe reaction conditions and the use of precise reagents. Thus, our objective is to investigate the problem related to these precedented approaches and attempt to resolve those by developing suitable catalytic systems and novel reaction methodologies to achieve mild reaction conditions by employing the palladium catalyst.

4. Methodology and Result:

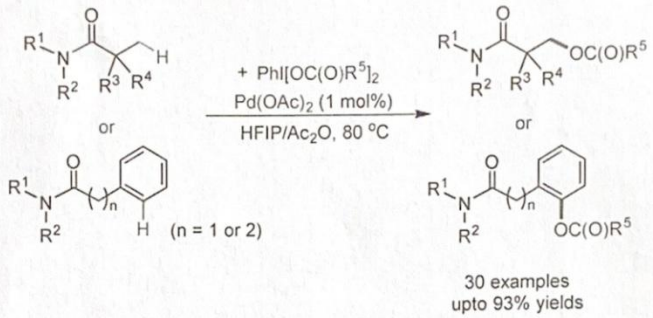
Chapter 2. A General Method for the Palladium-Catalyzed Acetoxylation of $C(sp^2)$–H and $C(sp^3)$–H Bonds in Amides

Amide represents a privileged constituent for the synthesis of many natural products and biologically active compounds.[2] Specifically, β-$C(sp^3)$–H oxygenated amides are of incredible importance because of their tremendous pharmacological activities. Precedented approaches for the synthesis are limited to harsh reaction conditions, a stoichiometric amount of catalyst loading, and the accession of directing group. To address these limitations, in this chapter,

Dr. Benudhar Punji (Supervisor)

Vijaykumar M (Candidate)

palladium-catalyzed acetoxylation of simple amides is established that proceeds *via* weak chelation assistance (Scheme 1).[8] Acetoxylation of amides provided a direct approach for synthesizing variously functionalized and pharmaceutically relevant acetoxy-amides with the tolerance of sensitive functionalities. The kinetic isotopic effect study suggested the rate-determining C(sp^3)–H bond activation. A gram-scale reaction and further functionalization into alcohols, tertiary amines, and acids exhibit synthetic utility.



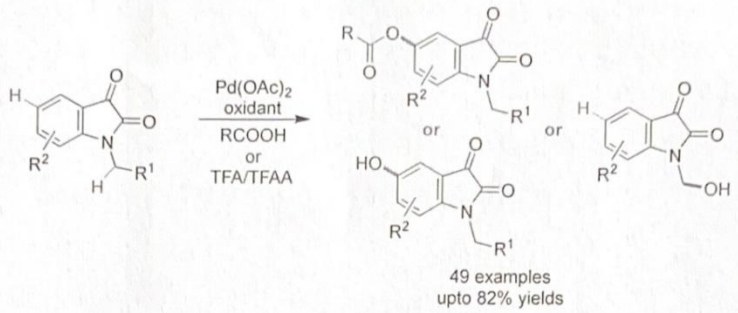
Scheme 1. Palladium-catalyzed acetoxylation of C–H bonds in amide derivatives.

Chapter 3. Palladium-Catalyzed Regioselective Oxygenation of C–H Bonds in Isatins

Isatin is an elite oxidized indole nucleus and has gained particular attention as a core motif in developing numerous pharmacologically active compounds. Notably, the hydroxy group-containing isatins represent the important subclass among the isatin-based natural products.[9] The precedented approaches for their synthesis are restricted to traditional protocol or cyclization methods. Unfortunately, the direct oxygenation at selective C–H position of isatin is not precedented. In this chapter, direct oxygenation of selective C–H bonds in isatins by palladium catalyst is discussed (Scheme 2).[10] The $PhI(OAc)_2$ or selectfluor oxidant in the Pd-catalyzed protocol in 1.0 M acidic solution exclusively provided C5 oxygenation of isatins *via* electrophilic palladation. However, the same reaction employing $K_2S_2O_8$ in a dilute solution (0.13 M) afforded *N*-methyl C(sp^3)–H oxygenation through carbonyl-assisted intramolecular –NCH_3 C(sp^3)–H radical palladation. The synthetic utility of oxygenation is exemplified by performing a gram-scale reaction, and further derivatization was exhibited by synthesizing diverse oxygenated isatins with sensitive functionalities, including bio-relevant compounds.

Dr. Benudhar Punji (Supervisor)

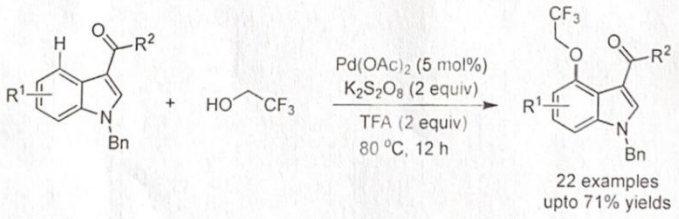
Vijaykumar M (Candidate)



Scheme 2. Palladium-catalyzed regioselective oxygenation of C5 and *N*-methyl C−H Bonds in Isatin derivatives.

Chapter 4. Palladium-Catalyzed regioselective C(4)−H Alkoxylation of Indoles *via* Weak Chelation Assistance

Indoles are the structural frame of numerous biologically active compounds and natural products. The functionalizations at selective C2 and C3 C−H bonds of indoles have been considerably reported. However, limited studies have focused on the less reactive C4-C7 C−H bonds of indoles. In particular, the C4 C−H oxygenation is provocative as C4-alkoxy-indoles are structural constituents of various drug molecules and natural products. In this chapter, palladium-catalyzed regioselective C4 alkoxylation have been adept using readily available alcohols under mild-conditions (Scheme 3). This protocol shows high regioselectivity for the selective C4-alkoxylation of indole using C3 benzoyl as a directing group. Significant features of this modification include the board substrate scope and excellent functional group tolerance.



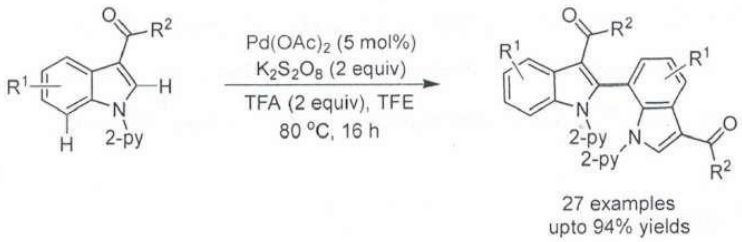
Scheme 3. The regioselective C4 alkoxylation of indoles by using palladium catalyst.

Dr. Benudhar Punji (Supervisor)

Vijaykumar M (Candidate)

Chapter 5. Palladium-Catalyzed Intermolecular C(2)–H/C(7)–H Oxidative Coupling of Indoles

Indole dimers are crucial motifs in many pharmaceutically active compounds and natural products. In last few decades, the construction of the 2,2, 2,3 and 3,3-linked dimer motifs was precedented. The enzymatic strategy and Sonogashira coupling of the indolyl halides were known to synthesize dimer motifs. However, precedented approaches are limited to traditional methods to construct 2,2, 2,3, and 3,3-linked bi-indolyl scaffolds. Thus, in this chapter, a strategic approach for the intermolecular C(2)–H/C(7)–H oxidative dimerization of indoles by using palladium catalyst is discussed (Scheme 4). The reaction shows intermolecular C(2)–H/C(7)–H dimerization of indoles using pyridine as a directing group. Significant features of this transformation include broad substrate scope and a preliminary mechanistic study.



Scheme 4. Intermolecular C(2)–H/C(7)–H oxidative coupling of indoles.

5. Summary:

In summary, we developed an efficient method for the regioselective acetoxylation of C–H bond in simple amides by palladium catalyst. The reaction provided access to synthesize diverse biologically relevant acetoxy-amides (Chapter-2). In addition, we have also optimized the reaction protocol for the regioselective oxygenation of C–H bonds in isatins by palladium catalyst. The concentration and oxidant-dependent selectivity for oxygenation of isatin is shown (Chapter-3). Further, unified protocol was developed for synthesizing C4 alkoxy-indole using alcohols. This methodology provided an efficient approach for synthesizing diversely functionalized and biologically relevant alkoxy-indoles with high tolerance of sensitive functionalities (Chapter-4). Additionally, intermolecular C(2)–H/C(7)–H oxidative dimerization of indoles by using palladium catalyst is demonstrated (Chapter-5).

Dr. Benudhar Punji (Supervisor)

Vijaykumar M (Candidate)

6. Future Directions:

We have successfully attempted to resolve the problems related to existing methodologies for the oxygenation of amides, indoles, isatins, and C(2)–H/C(7)–H oxidative dimerization of indoles. However, still, there is a scope to achieve better conditions for C–H functionalization reactions. In chapter-2, the acetoxylation of methylene β-C(sp^3)–H bond in alkyl amides and cyclic amides was unsuccessful. This protocol is limited to acetoxylation of β-C(sp^3)–H bond of amides. The focus should be given to performing the acetoxylation of methylene β-C(sp^3)–H bond and acyloxylation of amides using acids as a coupling partner. In chapter-3, a detailed mechanistic study has to be performed to know the effect of solvent concentration in selective oxygenation of C5-(sp^2)–H and *N*-methyl C(sp^3)–H bonds in isatin. Similarly, the C4 alkoxylation reaction of indoles using unactivated alcohols as a coupling partner under mild reaction conditions should be focused. The last chapter deals with intermolecular C(2)–H/C(7)–H oxidative homocoupling of indoles. The focus should be given to oxidative hetero-coupling of indole derivatives. Moreover, the use of a chiral catalyst to achieve chiral bisindole can be explored. Finally, the focus should be given to replacing palladium metal with 3d transition metals for selective oxygenation and dimerization reactions.

7. List of Publications:

1. Vijaykumar, M.; Punji, B., "Pd(II)-Catalyzed Chemoselective Acetoxylation of C(sp^2)–H and C(sp^3)–H Bonds in Tertiary Amides" *J. Org. Chem.* **2021**, *86*, 8172.
2. Vijaykumar, M.; Punji, B., "Advances in Transition-Metal-Catalyzed C–H Bond Oxygenation of Amides" *Synthesis* **2021**, *53*, 2935.
3. Vijaykumar, M.; Pradhan, C.; Gonnade, R. G.; Punji, B., "Palladium-Catalyzed Chemoselective Oxygenation of C(sp^2)–H and C(sp^3)–H Bonds in Isatins" *Org. Lett.* **2023**, *25*, 1862.
4. Vijaykumar, M.; Punji, B., "Palladium-Catalyzed Regioselective C(4)–H Alkoxylation of Indoles using Weak Chelation". (Manuscript under preparation)
5. Vijaykumar, M.; Punji, B., Pd(II)-Catalyzed Chemoselective Acetoxylation of C(sp^2)–H and C(sp^3)–H Bonds in Tertiary Amides". (Manuscript under preparation)
6. Pandey, D. K.; Vijaykumar, M.; Punji, B., "Nickel-Catalyzed C(2)–H Arylation of Indoles with Aryl Chlorides under Neat Conditions" *J. Org. Chem.* **2019**, *84*, 12800.

Dr. Benudhar Punji (Supervisor)

Vijaykumar M (Candidate)

8. References:

1. Vijaykumar, M.; Punji, B., "Advances in Transition-Metal-Catalyzed C–H Bond Oxygenation of Amides" *Synthesis* **2021**, *53*, 2935.
2. Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J., Mild Metal-Catalyzed C–H Activation: Examples and Concepts. Chem. Soc. Rev. **2016**, *45*, 2900-2936
3. Kalepu, J.; Pilarski, L. T. Weinreb Amides as Directing Groups for Transition Metal-Catalyzed C−H Functionalizations. *Molecules* **2019**, *24*, 830.
4. Moghimi, S.; Mahdavi, M.; Shafiee, A.; Foroumadi, A., Transition-Metal-Catalyzed Acyloxylation: Activation of C(sp^2)–H and C(sp^3)–H Bonds. *Eur. J. Org. Chem.* **2016**, *2016*, 3282-3299.
5. Leitch, J. A.; Bhonoah, Y.; Frost, C. G., Beyond C2 and C3: Transition-Metal-Catalyzed C–H Functionalization of Indole. *ACS Catal.* **2017**, *7*, 5618-5627.
6. Iqbal, Z.; Joshi, A.; Ranjan De, S., Recent Advancements on Transi-tion-Metal-Catalyzed, Chelation-Induced ortho-Hydroxylation of Arenes. *Adv. Synth. Catal.* **2020**, *362*, 5301-5351.
7. Jagtap, R. A.; Punji, B., C−H Functionalization of Indoles by 3d Transition-Metal Catalysis. *Asian J. Org. Chem.* **2020**, *9*, 326-342.
8. Vijaykumar, M.; Punji, B., "Pd(II)-Catalyzed Chemoselective Acetoxylation of C(sp^2)–H and C(sp^3)–H Bonds in Tertiary Amides" *J. Org. Chem.* **2021**, *86*, 8172.
9. Khan, F. A.; Maalik, A., Advances in Pharmacology of Isatin and its Derivatives: A Review. *Trop J Pharm Res.* **2015**, *14*, 1937-1942.
10. Vijaykumar, M.; Pradhan, C.; Gonnade, R. G.; Punji, B., "Palladium-Catalyzed Chemoselective Oxygenation of C(sp^2)–H and C(sp^3)–H Bonds in Isatins" *Org. Lett.* **2023**, *25*, 1862.

Dr. Benudhar Punji (Supervisor)

Vijaykumar M (Candidate)

TABLE OF CONTENTS

Chapter 1. Introduction 1

1.1 OXYGENATION OF AMIDES 3

1.1.1 Cobalt-Catalyzed Oxygenation of Amides 4

1.1.2 Nickel-Catalyzed Oxygenation of Amides 7

1.1.3 Copper-Catalyzed Oxygenation of Amides 8

1.1.4 Ruthenium-Catalyzed Oxygenation of Amides 10

1.1.5 Palladium-Catalyzed Oxygenation of Amides 14

1.1.5.1 $C(sp^2)$–H Oxygenation of Amides 14

1.1.5.2 $C(sp^3)$–H Oxygenation of Amides 18

1.2 OXYGENATION OF ISATINS 23

1.3 OXYGENATION OF INDOLES 24

1.3.1 Cobalt-Catalyzed Oxygenation of Indoles 25

1.3.2 Ruthenium-Catalyzed Oxygenation of Indoles 28

1.3.3 Palladium-Catalyzed Oxygenation of Indoles 28

1.4 DIMERIZATION OF INDOLES 33

1.4.1 Iron-Catalyzed Dimerization of Indoles 33

1.4.2 Copper-Catalyzed Dimerization of Indoles 34

1.4.3 Palladium-Catalyzed Dimerization of Indoles 35

1.5 REFERENCES 39

1.6 OBJECTIVES OF THE PRESENT STUDY 46

Chapter 2. Pd(II)-Catalyzed Acetoxylation of $C(sp^2)$−H and $C(sp^3)$−H Bonds in Amides

2.1 INTRODUCTION 49

2.2 RESULTS AND DISCUSSION 50

2.2.1 Optimization of Reaction Parameters 50

2.2.2 Scope for Acetoxylation of Tertiary Amides 53

2.2.3 Scope for Acetoxylation of Secondary Amides 57

2.2.4 Synthetic Utility and Mechanistic Perspective 57

2.2.5 Probable Catalytic Cycle 58

2.3 CONCLUSION 60

2.4 EXPERIMENTAL SECTION 60

2.4.1 General Information 60

2.4.2 Synthesis and Characterization of Starting Compounds 61

2.4.3 Procedure for Acetoxylation of Amides 66
2.4.4 Characterization Data of Acetoxylated Amides 66
2.4.5 Alcoholysis of *β*-Acetoxylated Compounds 78
2.4.6 Procedure for Kinetic Isotopic Effect Study 80
2.4.7 ^{1}H and ^{13}C NMR Spectra for Selected Acetoxy-Compounds 81
2.5 REFERENCES 87

Chapter 3. Pd-Catalyzed Regioselective Oxygenation of C(sp^2)–H and C(sp^3)–H Bonds in Isatins
3.1 INTRODUCTION 91
3.2 RESULTS AND DISCUSSION 92
3.2.1 Optimization of Reaction Parameters 92
3.2.2 Scope for C(5)–H Acetoxylation of Isatins 96
3.2.3 Scope for C(5)–H Hydroxylation of Isatins 98
3.2.4 Scope for *N*-Methyl Hydroxylation of Isatins 99
3.2.5 Synthetic Transformation of Oxygenated Isatins 100
3.2.6 Probable Catalytic Cycle 102
3.3 CONCLUSION 103
3.4 EXPERIMENTAL SECTION 104
3.4.1 General Information 104
3.4.2 Procedure for the Oxygenation of Isatins 104
3.4.3 Characterization Data of Oxygenated Isatins 106
3.4.3.1 Characterization Data of C5 Acetoxylated Isatins 106
3.4.3.2 Characterization Data of C5 Hydroxylated Isatins 121
3.4.3.3 Characterization Data of *N*-Methyl Hydroxylated Isatins 127
3.4.4 Procedures for Functionalization of Oxygenated Isatins 129
3.4.5 Procedure for *H/D* Scrambling Experiments 133
3.4.6 Procedure for External Additive Experiments 134
3.4.7 X-ray Structural Analysis 135
3.4.8 ^{1}H and ^{13}C Spectra of Selected Oxygenated Isatins 139
3.5 REFERENCES 147

Chapter 4. Palladium-Catalyzed Regioselective C(4)–H Fluoroalkoxylation of Indoles *via* Weak Chelation

4.1 INTRODUCTION 151

4.2 RESULTS AND DISCUSSION 153

4.2.1 Optimization of Reaction Parameters 153

4.2.2 Effect of C3 Substituents on Selective C(4)–H Fluoroalkoxylation 155

4.2.3 Scope for C(4)–H Fluoroalkoxylation of Indoles 155

4.2.4 Gram Scale-Synthesis and Removal of Directing and Protecting Group 158

4.2.5 Synthetic Transformation of C(4)–H Fluoroalkoxylated Indoles 159

4.2.6 Mechanistic Aspects 161

4.2.7 Probable Catalytic Cycle 162

4.3 CONCLUSION 162

4.4 EXPERIMENTAL SECTION 163

4.4.1 General Information 163

4.4.2 Synthesis and Characterization of Starting Compounds 163

4.4.3 Procedure for the C(4)–H Fluoroalkoxylation of Indoles 168

4.4.4 Characterization Data for C(4)–H Fluoroalkoxylated Indoles 169

4.4.5 Procedure for Removal of Directing and Protecting Groups 183

4.4.6 Post Synthetic Modification of Fluoroalkoxylated Indoles 186

4.4.7 Procedure for Synthesis of Palladium Complex 188

4.4.8 Procedure for *H/D* Scrambling Experiments 189

4.4.9 X-ray Structural Analysis 189

4.4.10 ^{1}H and ^{13}C Spectra of Selected Compounds 192

4.5 REFERNCES 198

Chapter 5: Palladium Catalyzed Intermolecular C(2)–H/C(7)–H Oxidative Coupling of Indoles

5.1 INTRODUCTION 202

5.2 RESULTS AND DISCUSSION 204

5.2.1 Optimization of Reaction Parameters 204

5.2.2 Effect of C3 and *N*-Substituents for C(2)–H/C(7)–H Coupling 206

5.2.3 Scope for C(2)–H/C(7)–H Homo-Coupling of Indoles 207

5.2.4 Scale-up and Synthetic Transformation of Indole Dimer 212

5.2.5 Mechanistic Aspects 213
5.2.6 Probable Catalytic Cycle 215
5.3 CONCLUSION 216
5.4 EXPERIMENTAL SECTION 216
5.4.1 General Information 216
5.4.2 Synthesis and Characterization of Starting Compounds 217
5.4.3 Procedure for the Homo-Coupling of Indoles 219
5.4.4 Characterization Data for the Coupled Indoles 220
5.4.5 Procedure for the Hetero-Coupling of Indoles 235
5.4.6 Procedures for Reduction of Carbonyl Groups 237
5.4.7 Procedure for Synthesis of Palladium Complex 238
5.4.8 Procedure for *H/D* Scrambling Experiment 239
5.4.9 X-ray Structural Analysis 239
5.4.10 ^{1}H and ^{13}C Spectra of Coupled Indoles 245
5.5 REFERNCES 251

Chapter 6. Summary and Outlook 253
6.1 SUMMARY 254
6.2 OUTLOOK 256

Abstract 257
List of Publication 259
List of Conference 260
Publications 261

Chapter 1

Introduction

This chapter has been partly adapted from the publication "Advances in Transition-Metal-Catalyzed C–H Bond Oxygenation of Amides" **Vijaykumar, M;** and Punji, B. *Synthesis* **2021**, *53*, 2935.

The advancement of scientific disciplines, including materials and pharmaceuticals, heavily relies on chemical synthesis. Transition-metal catalyzed synthetic transformations play a crucial role in discovering and developing novel molecules for diverse applications.[1-3] However, their prevalent use often relies on prefunctionalized starting materials, posing a challenge due to limited availability compared to unfunctionalized feedstock chemicals. This limitation becomes particularly pronounced when dealing with complex molecules like natural products and pharmaceuticals. Various methods have been developed to address this challenge, involving the installation of functional handles. Unfortunately, many of these multi-step methods lead to reduced sustainability, synthetic inefficiency, and increased waste. Therefore, there is a pressing need for catalytic methods enabling the direct functionalization of inert C−H bonds. Despite the challenge, significant efforts have been dedicated to developing synthetic approaches allowing direct C−H bond functionalization with a broad array of coupling partners, improving step-economy and overall sustainability. This capability opens avenues for new strategic disconnections and innovative synthetic routes, providing a valuable synthetic handle.

In the context of these challenges and opportunities, the transition-metal-catalyzed oxygenation of inert C(sp^2)–H or C(sp^3)–H bonds to C–O bonds is a powerful tool,[4-6] with wide-ranging applications in material sciences, pharmaceutical industries, and natural product synthesis.[7-10] Traditionally, the synthesis of oxygenated compounds involves several methods, such as the acid-catalyzed condensation of alcohols, the coupling of alkoxide and alkyl halides, alkoxy mercuration/demercuration of alkenes, and the combination of carboxylic acids and alcohols.[11,12] However, these methods often come with limitations, such as harsh reaction conditions, limited substrate scope, multi-step sequences for preparing starting materials, and the generation of unwanted by-products. Direct oxygenation of C–H bonds to form C–O bonds holds significant potential in organic synthesis, especially for late-stage modifications of complex molecules. This approach offers advantages in terms of step economy and versatility.[13,14]

Recent research has flourished with various effective protocols for synthesizing oxygenated amides and indole derivatives, employing 3d and 4d metal catalysts. However, the site-selective inert C(sp^2)–H or C(sp^3)–H oxygenation remains challenging due to the unique nature of C–H bonds. In this context, directing group-assisted strategy in inert C–H oxygenation has been recognized as a robust technique for constructing chemo- and regioselective C–O bonds. Directing groups facilitate the selective oxygenation of specific positions within a molecule, improving the reaction's control, efficiency, and selectivity. This approach has garnered remarkable attention in academic and industrial research, making it a

valuable tool for developing various oxygenated compounds with broad applications in diverse fields.

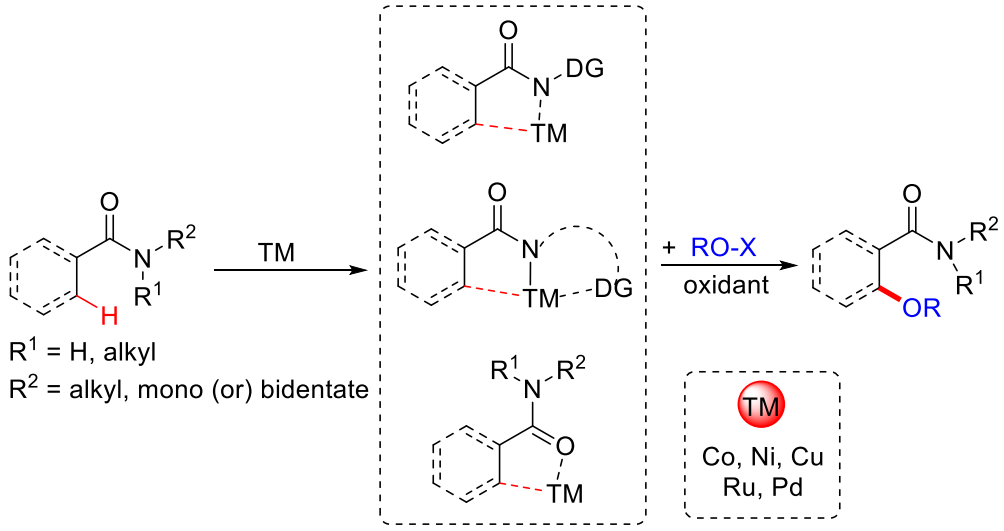
In addition to the C–H oxygenation, it is essential to highlight the significance of indole dimerization in organic synthesis and pharmaceutical industries.[15-22] Biindoles are critical structural motifs in various natural products and organic electroluminescent materials. The most systematic approach to biindole synthesis traditionally involves the acidic coupling of indoles, followed by dehydrogenation. Another approach employs transition-metal-catalyzed coupling reactions of indole halides with organo-indole metals, which have also proven to be versatile tools for biindole synthesis. However, these methods typically require prefunctionalized substrates and generate stoichiometric amounts of organometallic waste by-products. Recently, there has been a growing interest in using transition-metal-catalyzed C–H/C–H oxidative coupling of indoles. This method has gained attention as an efficient one-step route for producing biindole compounds without prefunctionalizing substrates. Over the past decade, there has been significant exploration of the coupling of indoles to create various biindole derivatives, including 2,2'-biinolyls, 3,3'-biindolyls, and 2,3'-biindolyls.[1,23-29] However, these studies have been primarily focused on the homo-coupling of indoles and carbazoles at carbon centers activated by various groups. In view of the substantial development in C–H oxygenation and indole dimerization, and thesis objectives, in this chapter, we provide a comprehensive summary of the literature on the transition metal-catalyzed oxygenation of amides, isatins and indoles, as well as the oxidative dimerization of indoles.

1.1 OXYGENATION OF AMIDES

The amide functional group is an essential moiety in synthetic organic chemistry and can be smoothly transformed into useful functionalities like aldehyde, carboxylic acid, and amines. Hence, the synthetic transformations of amides are highly desirable. In recent years, considerable attention has been directed towards the transition-metal-catalyzed C–H functionalization of amides.[30-37] Remarkably, the amide-bearing compounds' regioselective C–H oxygenation is indispensable. In this direction, diverse C–O bond formations, such as alkoxylation, acetoxylation, acyloxylation, and hydroxylation of both C(sp^2)–H and C(sp^3)–H bonds on aliphatic and aromatic amides have been extensively investigated. Notably, the C–O bond formation for the primary and secondary amides proceeds *via* the chelation-assisted coordination of *N*-amidate to the transition metal catalyst. The lone pair of electrons on amide coordinates reversibly to a transition metal, bringing the metal close to the C–H bond targeted

for functionalization. This strong coordination expedites the C–H activation by inciting thermodynamically favorable metallacycle.

Moreover, numerous reports exit on the oxygenation of C(sp^2)–H and C(sp^3)–H bonds in amides, facilitated by bidentate coordination through the introduction of ligands such as 8-amino quinolinyl, 2-(pyridine-2-yl)isopropyl, picolinamide, pyridinyl sulfoximine. In contrast to the oxygenation *via* strong *N*-amidated coordination, a few examples are also known for the oxygenation of unactivated C–H bond on privileged and multi-functional amides with a weakly coordinating carbonyl (C=O) group, which is presumed to occur *via* a less favored cyclometallated intermediate. In view of the importance of oxygenated amide derivatives and the significance of C–H bond oxygenation, this section describes the development in C(sp^2)–H and C(sp^3)–H oxygenation of amides, catalyzed by various transition metals (Scheme 1.1).

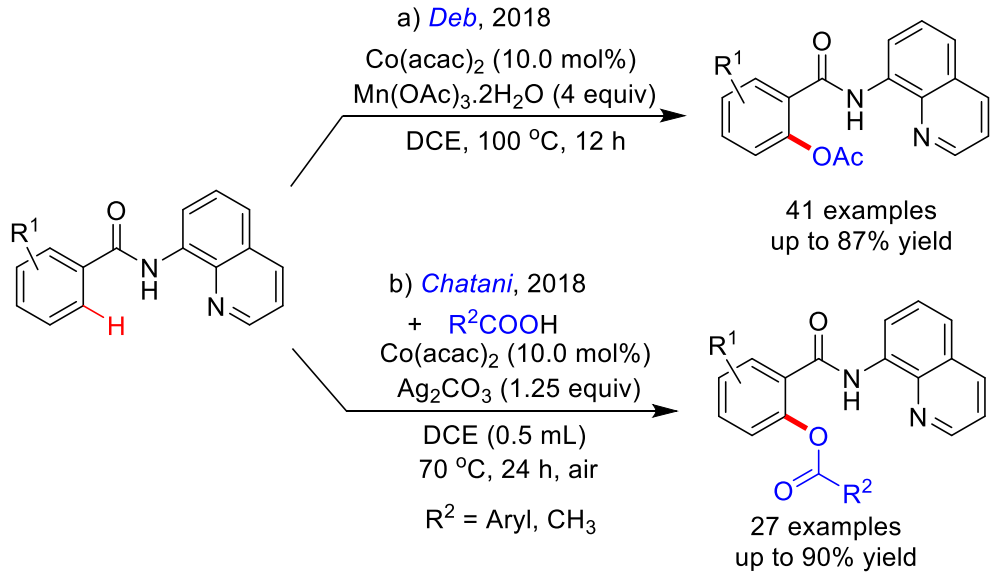


Scheme 1.1. Representation of DG Coordination and C–H Activation in Amides.

1.1.1. Cobalt-Catalyzed Oxygenation of Amides

Cobalt is an abundant transition metal with significant potential for catalysis, and its low toxicity and presence in bioactive compounds like vitamin B12 make it an attractive choice for catalytic applications. A notable achievement has been gained in the cobalt-catalyzed amide C–H bond functionalization.[38,39] However, the oxygenation of amides using cobalt as a catalyst remains relatively limited. Benzamides, in particular, are considered an essential structural framework due to their existence in pharmaceutically important compounds and bioactive natural products. In 2018, Deb described *ortho*-C(sp^2)–H acetoxylation of unactivated benzamides, employing quinoline as a directing group. In this context, a catalytic system involving $Co(acac)_2/Mn(OAc)_3.2H_2O$ facilitated the selective acetoxylation of benzamides

(Scheme 1.2a).[40] This protocol was applied to a wide range of substrates, showcasing tolerance for diverse functional groups, such as chloro, bromo, iodo, trifluoromethyl, and phenyl moieties. The role of $Mn(OAc)_3.2H_2O$ is crucial in oxidizing Co(II) to Co(III), and the latter species is responsible for the cleavage of C–H bonds. Notably, this protocol uses stoichiometric amounts of manganese metal salt, which makes it less desirable. Similarly, in 2018, the Chatani group reported the Co-catalyzed acyloxylation of benzamide with aromatic acids in the presence of Ag_2CO_3 as a base (Scheme 1.2b).[41] A wide array of aromatic and aliphatic carboxylic acids were employed as coupling partners to achieve the acyloxylation of amides. *Ortho*-substituted benzamides provided good yields of monoacyloxylation products, while those without a substituent at the *ortho*-position led to diacyloxylation. The mechanistic investigation unveiled a non-radical pathway for C–H activation and a Co(II)/Co(III) cycle (Figure 1.1). However, this protocol was limited to C(sp^2)–H bond acyloxylation and many heteroarenecarboxamides failed to give the desired products.



Scheme 1.2. Co-Catalyzed C(sp^2)–H Acyloxylation of *N*-Quinolinyl Benzamides.

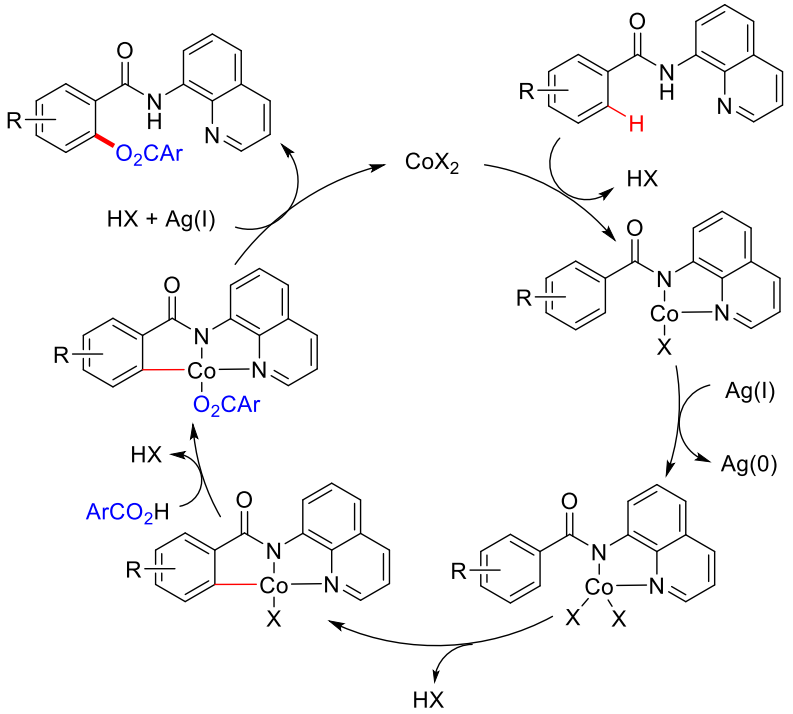
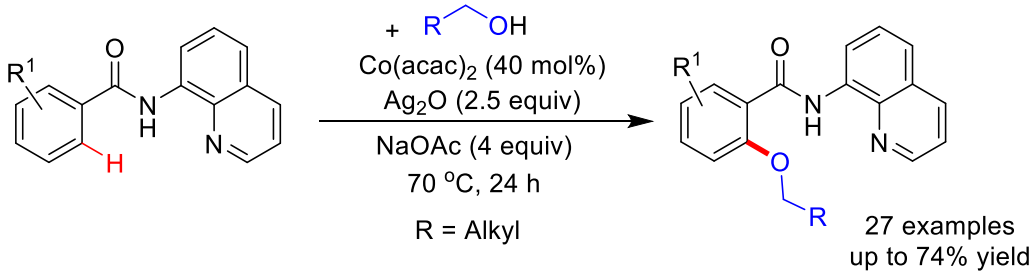


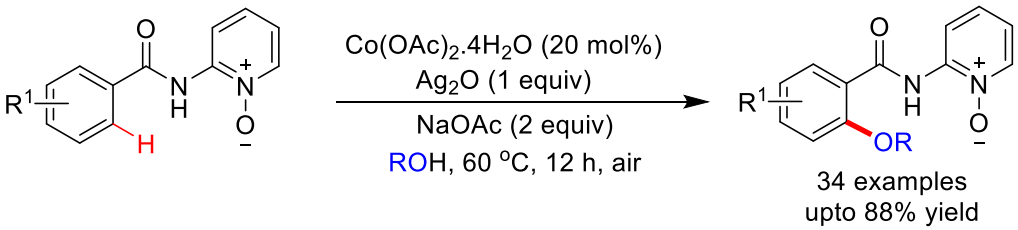
Figure 1.1. Plausible Catalytic Cycle for Co-Catalyzed C(sp^2)–H Acyloxylation of *N*-Quinolinyl Benzamides.

In the same year, Huang developed the Co-catalyzed alkoxylation of benzamides with alcohols through cross-dehydrogenative coupling, employing a bidentate directing group (Scheme 1.3).[42] In this reaction, Ag_2O serves as the oxidant, NaOAc functions as the base, and alcohol is utilized as both the solvent and the alkoxylation source under an N_2 atmosphere. The reaction demonstrated a broad scope of amides and alcohol coupling partners. Notably, heteroarenecarboxamides, such as thiophene-2-carboxamide and furan-2-carboxamide, afforded moderate yields. Aliphatic alcohols such as methanol, propanol, and trifluoroethanol were also compatible with the reaction conditions. However, bulky alcohols such as isopropyl alcohol, butanol, pentanol, cyclohexanol, and phenol did not produce the alkoxylated product. This reaction has been proposed to proceed *via* a radical pathway.



Scheme 1.3. Co-Catalyzed C(sp^2)–H Alkoxylation of *N*-Quinolinyl Benzamides.

In 2015, Song and Niu demonstrated using 2-aminopyridine 1-oxide as an *N,O*-bidentate directing group in the Co-catalyzed alkoxylation of a C(sp^2)–H bond (Scheme 1.4).[43] This method demonstrated suitability for a broad spectrum of alcohols and benzamides, encompassing diverse electron-rich and electron-poor groups, such as halogen, ether, methoxy, trifluoromethyl, and dimethylamino substituents. Furthermore, this approach was applied to the alkoxylation of alkene carboxamides featuring 2-aminopyridine 1-oxide. The reaction mechanism involved radical species, which was supported by evidence from EPR and additive experiments.



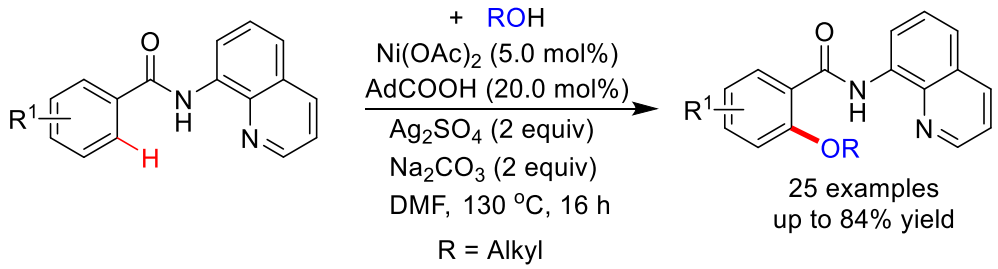
Scheme 1.4. Co-Catalyzed C(sp^2)–H Alkoxylation of 2-Aminopyridine 1-Oxide Benzamides.

Furthermore, in 2017, Ackermann extended the alkoxylation of 2-aminopyridine 1-oxide benzamides by employing cobalt catalysis with an electrochemical oxidant, an RVC anode, and a platinum cathode.[44] The electrochemical oxidation represents a unique protocol for silver-free direct oxygenation. Many arenes and alkenes underwent oxygenation with notable levels of chemo-, regio-, and diastereoselectivity under mild conditions. Mechanistic investigations unveiled a radical C–H activation pathway and a Co(II)/Co(III) cycle.

1.1.2 Nickel-Catalyzed Oxygenation of Amides

In recent decades, nickel-catalyzed C–H functionalization has been applied in diverse organic transformations through the C–H activation strategy.[45-47] However, direct oxygenation has remained relatively underdeveloped. The advantage of the 8-aminoquinolinyl chelation assistance was applied in the nickel-catalyzed C–H bond alkoxylation by Sundararaju and Rajesh (Scheme 1.5).[48] In this process, a $Ni(OAc)_2 \cdot 4H_2O$/AdCOOH catalyst system efficiently catalyzed benzamide derivatives' C–H alkoxylation with aliphatic alcohols *via* bidentate-chelation assistance. Benzamides with *para*-substituents encompassing electron-donating groups (Me, OMe, SMe) and electron-withdrawing groups (F, Cl, Br, CF_3) exhibited good compatibility in the reaction. They provided the mono-methoxylated product with good yields. Notably, the thioenyl group tolerability and the participation of amide derived from methacrylic

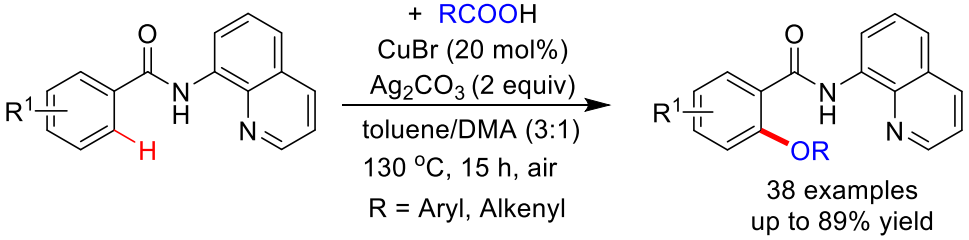
acid are noteworthy. The alkoxylation using aliphatic alcohols, such as ethanol, butanol, and benzyl alcohol, provided moderate yields. The C–H activation in this alkoxylation protocol proceeds through the concerted metalation-deprotonation pathway and is an irreversible process.



Scheme 1.5. Ni-Catalyzed C(sp^2)–H Alkoxylation of *N*-Quinolinyl Benzamides.

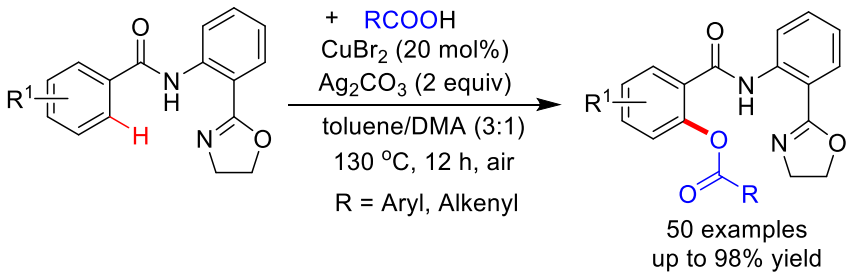
1.1.3 Copper-Catalyzed Oxygenation of Amides

Copper complexes exhibit the capability to shift between different oxidation states, encompassing Cu(0), Cu(I), Cu(II), and Cu(III). This adaptability empowers them to participate in a straightforward one-electron or two-electron process. This versatility enables the utilization of both single-electron transfer (SET) and two-electron redox routes, involving organometallic intermediates.[49,50] In this context, Zhang reported the utilization of a CuBr catalyst in the *ortho*-C–H acyloxylation of benzamides with carboxylic acid via quinoline-8-yl chelation (Scheme 1.6).[51] The reaction proceeded without additional ligands or additives, establishing a straightforward and practical method for synthesizing carboxylic esters. It is worth noting that diacyloxylation products were obtained in moderate yields when the reaction was prolonged. This reaction does not follow a radical pathway and is proposed to proceed through a facile C–H cleavage.



Scheme 1.6. Cu-Catalyzed C(sp^2)–H Acyloxylation of *N*-Quinolinyl Benzamides.

An oxazolyl functionality as a directing group was employed by Chen and co-workers in the Cu-catalyzed acyloxylation of benzamides (Scheme 1.7).[52] In this process, stable and cost-effective $CuBr_2$ coupled with various aliphatic and aromatic carboxylic acids affording acyloxylated products in good yields. Moreover, various cinnamic acids participated in the reaction, which was not feasible in the *N*-quinolinyl-directed acyloxylation. The reaction conditions were well-suited for both electron-donating and electron-withdrawing substituents. Remarkably, *o*-Cl- or *o*-Br-substituted benzamides underwent diacyloxylation by replacing Cl or Br to produce the disubstituted products, indicating activation of both C(sp^2)–H and C(sp^2)–X bonds. Notably, this reaction necessitated a relatively high temperature of 130 °C. In-depth mechanistic studies revealed that the reaction proceeds through the SET process (Figure 1.2).



Scheme 1.7. Cu-Catalyzed C(sp^2)–H Oxygenation of *N*-Oxazolyl Benzamides.

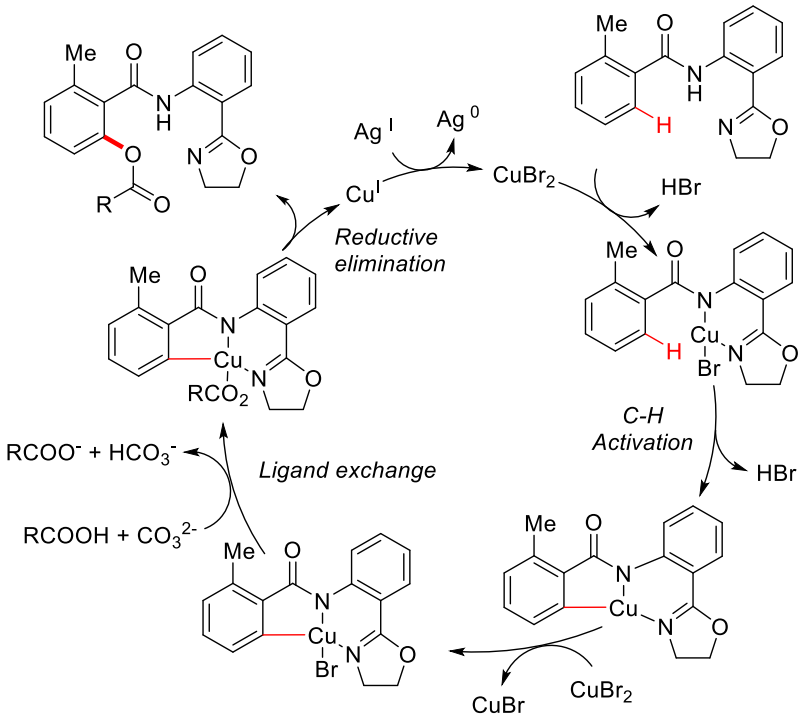
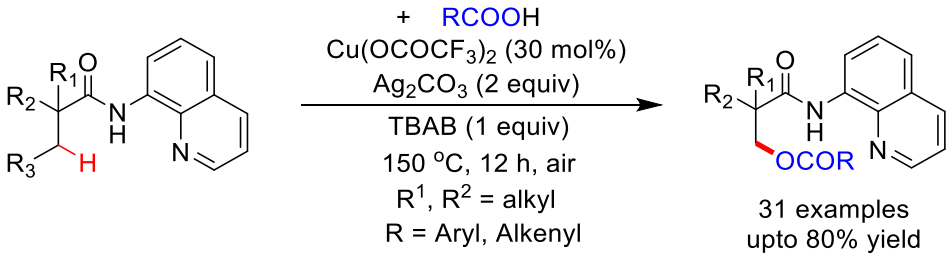


Figure 1.2. Plausible Catalytic Cycle for Cu-Catalyzed *Ortho*-Acyloxylation of *N*-Oxazolyl Benzamides.

Despite considerable advancement in the direct functionalization of C(sp^2)–H bond, examples of C(sp^3)–H functionalization are still scarce. In 2019, Zhang and co-workers harnessed the earth-abundant and cost-effective Cu catalyst for the direct C–H acyloxylation of unactivated C(sp^3)–H bonds in aliphatic amides with aromatic acids, facilitated by bidentate *N*-quinolinyl assistance (Scheme 1.8).[53] The key to their success was the utilization of $Cu(OCOCF_3)_2$ as the catalyst and tetrabutylammonium bromide (TBAB) as an additive. This combination facilitated the regioselective *α*-methyl acyloxylation over *β*- or *γ*-methyl and methylene groups. This protocol demonstrates a range of compatibility with various carboxylic acids and aliphatic amides. Primarily, the competition between intramolecular dehydrogenative amidation and acyloxylation is effectively controlled by the amount of Cu salt and additive TBAB. The reaction is proposed through a radical pathway involving the rate-influencing C–H cleavage process. However, it's worth mentioning that this approach has its drawbacks, including the requirement for high reaction temperatures and significant catalyst loadings.



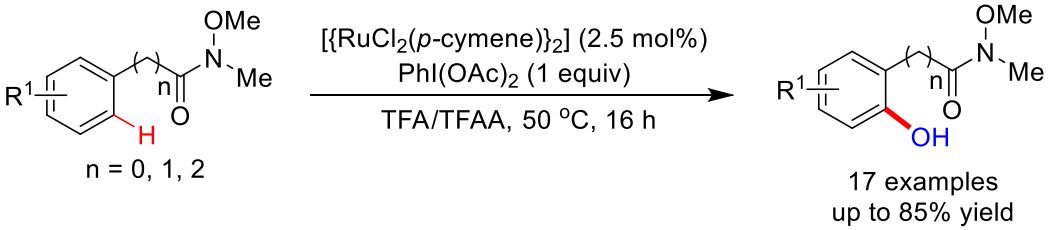
Scheme 1.8. Cu-Catalyzed C(sp^3)–H Acyloxylation of *N*-Quinolinyl Benzamides.

Recently, a pyridin-2-yl directing group was employed for the Cu-catalyzed *α*-C(sp^3)–H alkoxylation by Liu and Dong.[54] This method led to the synthesis of a series of quaternary *α*-alkoxylated amino acid derivatives in good yields. In a distinct approach to that precedented, this protocol uses $B(OR)_3$ as an alkoxylation agent and Ag_2CO_3 as an oxidant. The tolerance of sensitive functionalities and facile removal of the directing auxiliary highlights the potential of this protocol.

1.1.4 Ruthenium-Catalyzed Oxygenation of Amides

Ruthenium plays a crucial role in catalysis due to its versatility, high activity, and selectivity, contributing to efficient and sustainable processes across various industries.[55-60] In 2013, the Ackermann group disclosed versatile Ru-catalyzed *ortho*-hydroxylation of Weinreb amides with a wide range of substrates, all achieved under mild reaction conditions (Scheme

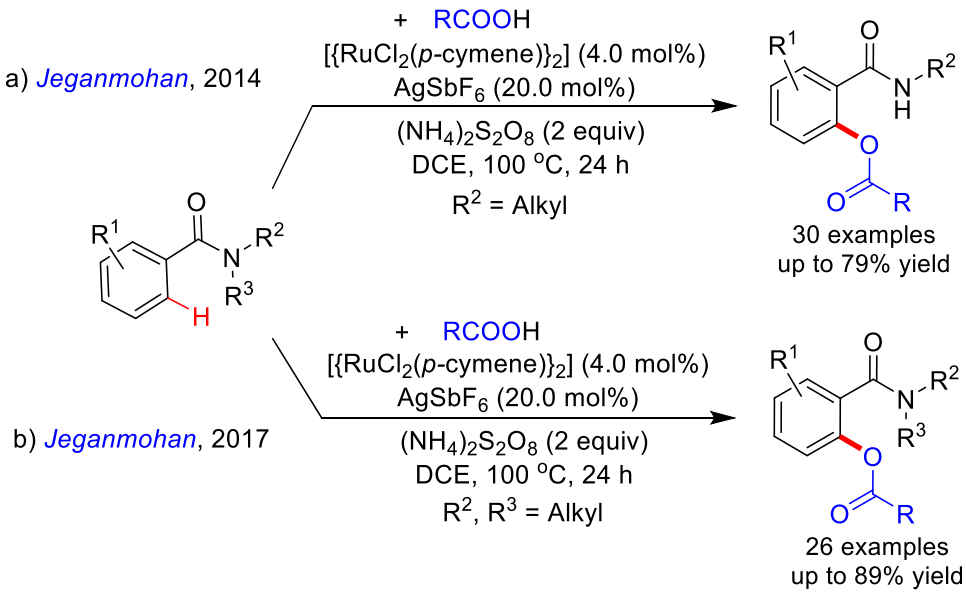
1.9).[61] Notably, electron-rich Weinreb amides reacted preferentially over electron-deficient amides. The preliminary kinetic analysis supported the irreversible and crucial C–H bond activation process. Again, the same group demonstrated an iodine(III)/Ru(II)-electrocatalyzed *ortho*-hydroxylation of synthetically useful Weinreb amides.[62] The catalytic generation of hypervalent iodine(III) reagents, facilitated by the use of sustainable electricity as an economical terminal oxidant, enabled this method. It demonstrated excellent compatibility with amides containing *para*- and *meta*-substituents, including chloro, bromo, or iodo groups, as well as sensitive benzyl chlorides. Mechanistic studies employing experiments, computation, and flow NMR spectroscopy provided evidence that supports a fast and reversible C–H ruthenation process.



Scheme 1.9. Ru-Catalyzed C(sp^2)–H Hydroxylation of Weinreb Amides.

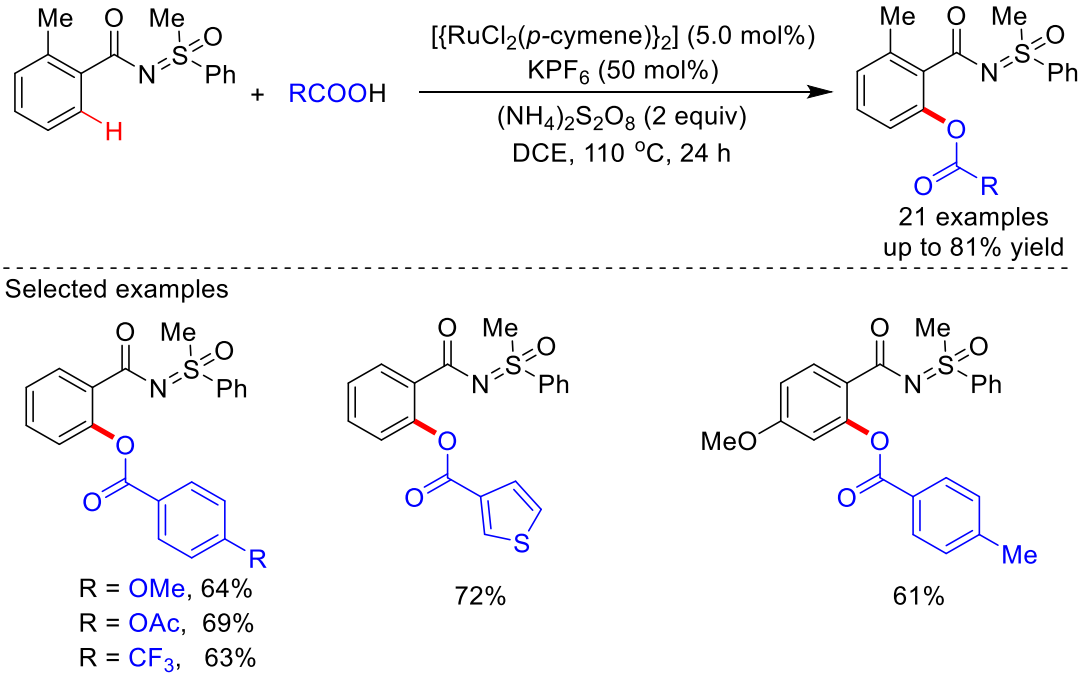
Similarly, Jeganmohan and Padala reported the *ortho*-acyloxylation of *N*-alkyl benzamides using a Ru complex as the catalyst (Scheme 1.10a).[63] The catalytic system, employing $[RuCl_2(p\text{-cymene})]_2/AgSbF_6$ in the presence of oxidant $(NH_4)_2S_2O_8$, facilitated the regioselective benzoxylation of diverse benzamides with aromatic acids. The benzoxylation occurred selectively at the less sterically hindered *ortho* position in *meta*-substituted benzamide. Important functionalities such as halides, $–CF_3$, and $–NO_2$ were effectively accommodated by the reaction conditions and provided the desired products in satisfactory yields. Notably, the benzoxylated *N*-alkylbenzamides were smoothly converted into *o*-hydroxybenzamides upon treatment with an acid or a base. This reaction is limited to aromatic acids, possibly due to the carboxylic acids' rapid complex formation with ruthenium. It is hypothesized that the reaction proceeds to form a cationic Ru species, following a Ru(II)/Ru(0) pathway. Later, the same group demonstrated the benzoxylation of *tert*-benzamide with a Ru catalyst, which is assumed to proceed by weak C=O coordination of the amide group (Scheme 1.10b).[64] The catalytic reaction was efficient in the presence of chloro, ether, ester, and nitro functionalities. Several carboxylic acids were employed as coupling partners, wherein the electron-deficient systems reacted with high efficiency. The *o*-benzoxylated benzamides can be

easily converted into *o*-benzoxylated benzaldehydes at room temperature using Cp_2ZrHCl. Notably, the attempts to perform benzoxylation with 4-methoxy benzoic acid, diphenyl acetic acid, phenylacetic acid, acetic acid, 6-bromohexanoic acid, propanoic acid, and pivalic acid were unsuccessful.



Scheme 1.10. Ru-Catalyzed C(sp^2)–H Acyloxylation of *N*-Alkyl Benzamides.

The acyloxylation of *N*-sulfoximine benzamides employing a Ru catalyst was demonstrated by Ackermann. Diversely decorated benzoic acids were used as coupling partners to achieve *ortho*-benzoxylated benzamides (Scheme 1.11).[65] The reaction proceeded with excellent chemoselectivity, facilitated by base-assisted intramolecular electrophilic substitution-type C–H activation. Notably, electron-rich benzamides reacted preferentially, and electron-rich aromatic carboxylic acids proved more reactive. However, aliphatic carboxylic acids were unsuitable for this oxygenation reaction. Both the Ru-catalyzed protocols for the oxygenation of *N*-sulfoximine benzamides are significant, considering the smooth removal of the directing group. However, the requirement for longer reaction times could be a practical challenge that requires further development. The reaction has been proposed to proceed via the Ru(II) to Ru(IV) pathway (Figure 1.3).



Scheme 1.11. Ru-Catalyzed C(sp^2)–H Acyloxylation of *N*-Sulfoximine Benzamides.

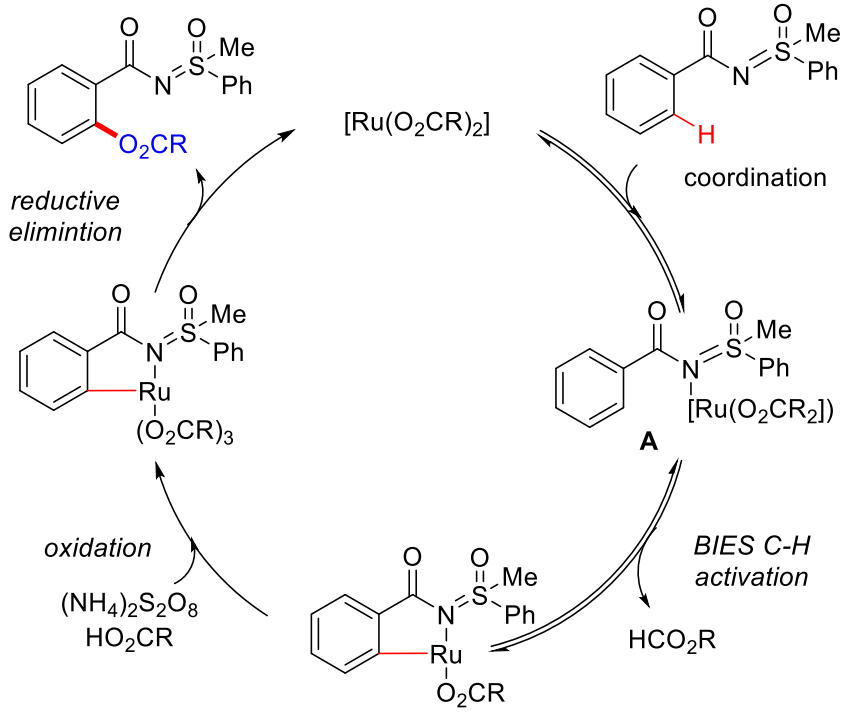
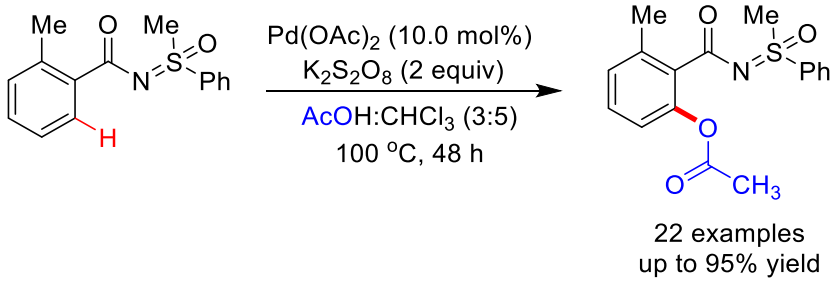


Figure 1.3. Plausible Catalytic Cycle for Ru-Catalyzed *Ortho*-Acyloxylation of *N*-Sulfoximine Benzamides.

1.1.5 Palladium-Catalyzed Oxygenation of Amides

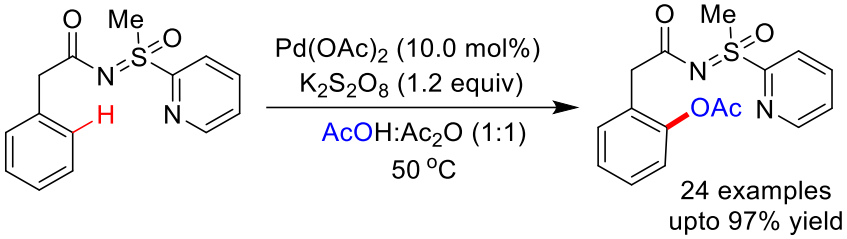
1.1.5.1 C(sp^2)–H Oxygenation of Amides

Palladium metal plays a multifaceted and essential role in various industries. Its significance lies in its function as a catalyst in palladium-catalyzed reactions, which is fundamental in organic synthesis and enables the efficient construction of complex molecules.[66-71] Over recent years, palladium-catalyzed direct C–H functionalization has been widely applied in diverse organic transformations through the C–H activation strategy. However, the direct oxygenation of amide derivatives has remained relatively underdeveloped. Sahoo has developed the regioselective *ortho* C–H acetoxylation of *N*-sulfoximine amides using palladium catalysis (Scheme 1.12).[72] This protocol employed mild inorganic oxidant $K_2S_2O_8$ and AcOH/$CHCl_3$ solvent system to acetoxylate *N*-sulfoximine benzamides. Remarkably, the *N*-sulfoximine directing group can be readily removed from the oxidation product and reused. Moreover, the *β,β'*-diacetoxylation products can be achieved under forced conditions.



Scheme 1.12. Pd-Catalyzed C(sp^2)–H Acetoxylation of *N*-Sulfoximine Benzamides.

Using a similar directing functionality, methyl-2-pyridyl sulfoximine as a bidentate Sahoo showed *ortho* C–H acetoxylation of phenylacetic acid derivatives (Scheme 1.13).[74] As a result, the oxidation of *ortho*-substituted aryl acetic acids yielded the desired *ortho*-C–H acetoxylation products in excellent yields when using a $Pd(OAc)_2$ catalyst and $K_2S_2O_8$ oxidant in acetic acid. The reaction exhibited good tolerance toward various sensitive functional groups, including chloro, bromo, ether, ester, and nitro. In some instances, a small amount of diacetoxylated product was also observed. The acetoxylated derivatives can be hydrolyzed to yield *ortho*-hydroxyarylacetic acids, and the directing group can be recovered. It is suggested that the reaction proceeds through a Pd(II)/Pd(IV) catalytic cycle involving the facile C–H palladation (Figure 1.4).



Scheme 1.13. Pd-Catalyzed Sulphoximine-Directed C(sp^2)–H Acetoxylation.

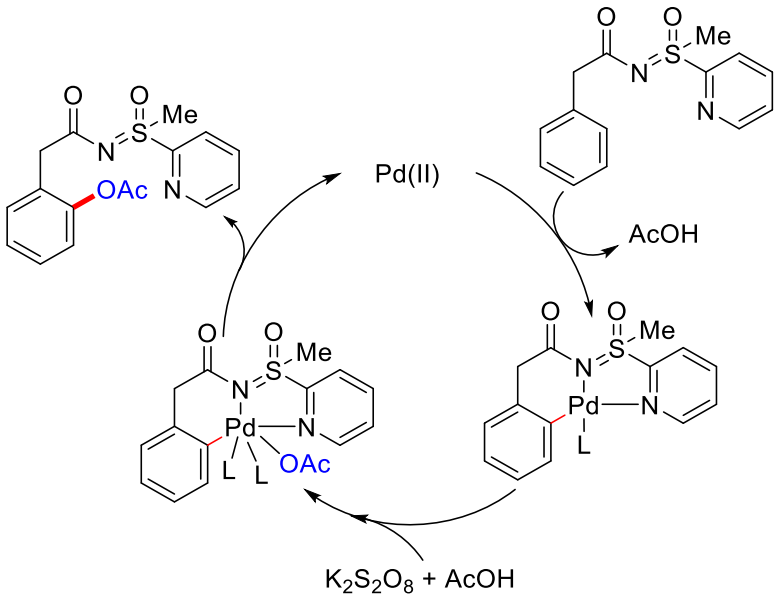
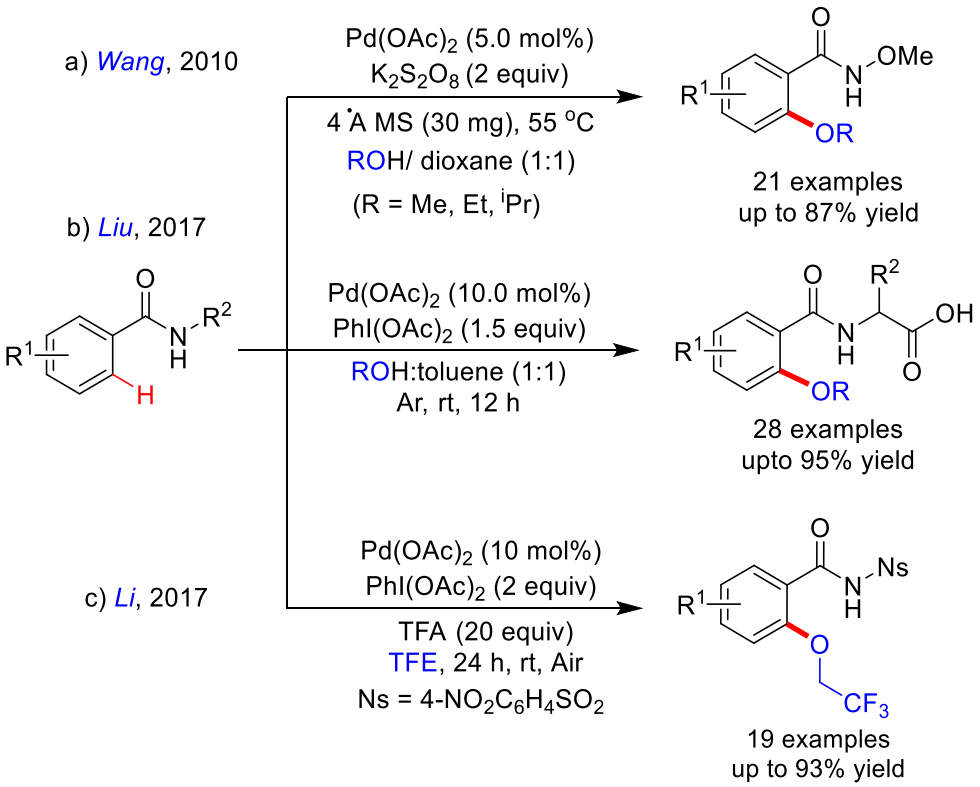


Figure 1.4. Plausible Catalytic Cycle for Pd-Catalyzed Sulphoximine-Directed C(sp^2)–H Acetoxylation.

The *ortho*-alkoxylation of *N*-methoxybenzamides using a Pd-catalyst was established by Wang (Scheme 1.14a).[76] The reaction employed $K_2S_2O_8$ as an oxidant and alcohol solvents, MeOH, EtOH, and ^{i}PrOH for the alkoxylation of benzamide. The directing group played an essential role as acetanilide gave poor yield. A variety of *N*-methoxybenzamides, including those with electron-donating and electron-withdrawing groups, could be efficiently subjected to alkoxylation. The utilization of secondary alcohols as alkoxylating reagents provided moderate yields, whereas tertiary alcohol failed to react with *N*-methoxy benzamide under optimized conditions. Notably, the reaction has been suggested to proceed through a Pd(II)/Pd(IV) catalytic cycle. A theoretical study of the reaction suggested the crucial role of alcoholic solvent, which assisted in *N*–H and C–H activation. Moreover, the transition state leading to palladacycle formation is more stable in the methanol-assisted pathway. This protocol highlighted the importance of the *N*-direction rather than the carbonyl-directed alkoxylation.

Similarly, the *ortho*-alkoxylation of *N*-benzoyl *α*-amino acid derivatives was demonstrated by Liu using Pd(II)-catalyst at room temperature (Scheme 1.14a).[75] This method shows broad applicability, high mono-selectivity, and regioselectivity. Mainly, the acid moiety of the directing group played a crucial role in the reaction, without which the reaction failed. Both these strategies provided a new approach to the oxygenation of amide derivatives. However, moderate functionality tolerance and high loading of expensive palladium are concerns and need further improvement.

In an independent development, Li has introduced trifluoroethoxy functionality at the *ortho* position of *N*-sulfonylbenzamides using a Pd(II) catalyst (Scheme 1.14c).[73] The reaction occurred at room temperature using $PhI(OAc)_2$ as the oxidant in the TFA/TFE solvent system. A Pd(II)/Pd(IV) pathway has been postulated for this reaction, involving an *N*-amido-palladium ligation that stabilizes the high-valent palladium intermediate (Figure 1.5). Though installing the fluoroalkoxy group in benzamide is significant, employing 10 mol% of Pd-catalyst is a concern in this reaction. Moreover, most of the products resulted only in moderate yields. Interestingly, the protocol was applied in the synthesis of the drug molecule Flecainide.



Scheme 1.14. Pd-Catalyzed *Ortho*-Alkoxylation of *N*-Substituted Benzamides.

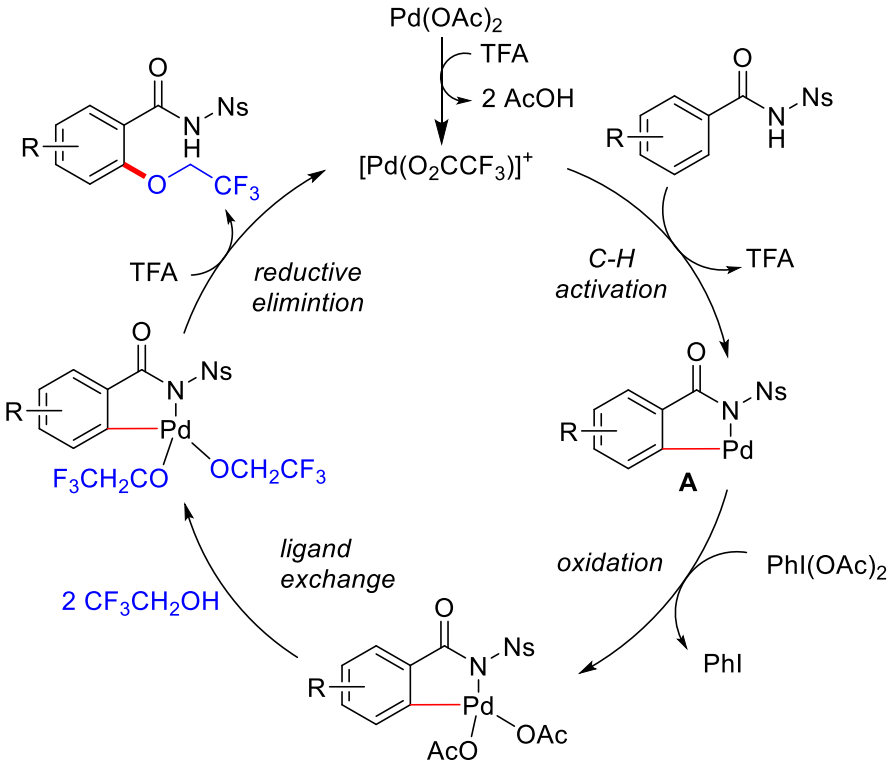
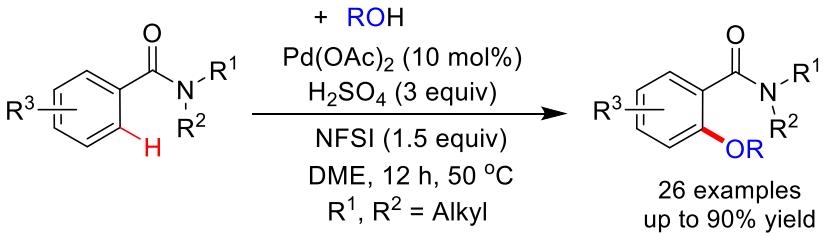


Figure 1.5. Plausible Catalytic Cycle for Pd-Catalyzed C(sp^2)–H Fluoroalkoxylation of *N*-Sulfonyl Benzamides.

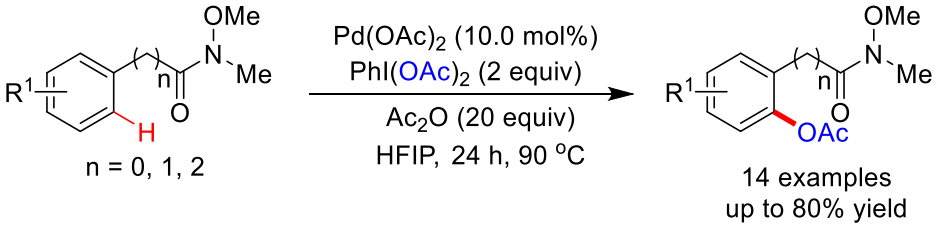
In a similar protocol, Guan showed the Pd-catalyzed *ortho*-alkoxylation of *tert*-benzamide using various alcohols (Scheme 1.15).[77] The reaction employed a NFSI (*N*-fluorobenzenesulfonimide) oxidant and was carried out under acidic conditions. Notably, the alkoxylation is limited to the use of aliphatic alcohols and the electron-rich benzamide derivatives. This alkoxylation proceeds via a Pd(II)/Pd(IV) pathway involving the rate-limiting C–H activation process.



Scheme 1.15. Pd-Catalyzed *Ortho*-Alkoxylation of *Tert*-Benzamides.

Weinreb amides are valuable synthetic functionalities known for their ease of transformation. Thus, Weinreb amide's functionalization is significant, mainly through C–H activation. In 2015, Yu developed Pd-catalyzed acetoxylation of Weinreb amides, which

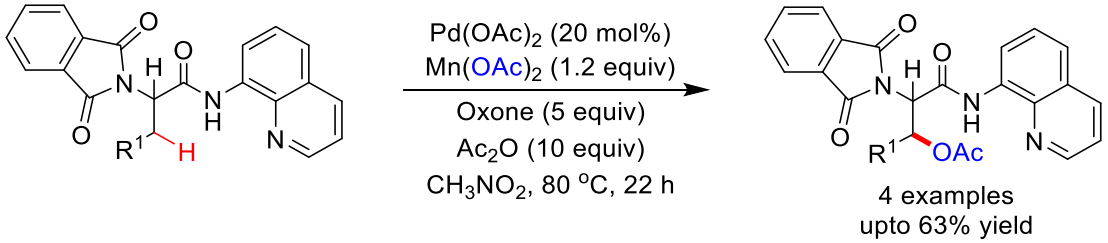
proceeds *via* distal weak coordination of C=O moiety (Scheme 1.16).[78] Notably, this protocol is remarkable for its ability to accommodate a significant distance between the target C–H bonds and the directing functional groups during the functionalization process. This reaction needed a significantly long reaction time for completion. Moreover, the high loading of precious palladium in this reaction is a concern.



Scheme 1.16. Pd-Catalyzed C(sp^2)–H Acetoxylation of Weinreb Amides.

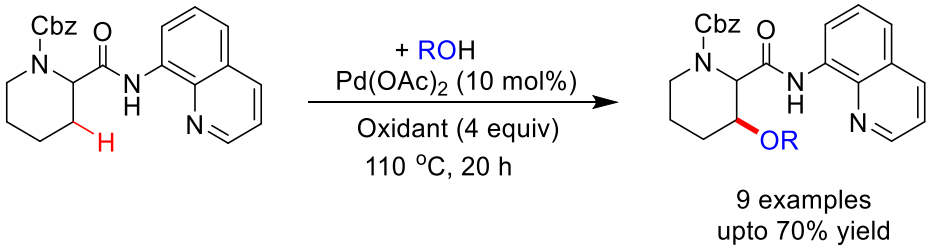
1.1.5.2 C(sp^3)–H Oxygenation of Amides

In addition to the considerable advancement in the direct functionalization of the C(sp^2)–H bond, the transition metal-catalyzed directing group-assisted oxidation of unactivated C(sp^3)–H bonds has emerged as a valuable tool in synthetic chemistry. This approach enables the selective creation of C−O bonds in aliphatic chains, allowing the introduction of oxygenated functional groups into complex molecules. However, the high bond dissociation energy and lack of π-participation in C(sp^3)−H bonds make direct oxidation challenging. While inherently reactive alkane C−H bonds are more amenable to oxidation, there is a need to develop new pathways that enable the direct oxidation of C(sp^3)−H bonds under mild catalytic conditions with reusable directing groups. Notably, the selective oxygenation of C(sp^3)−H bonds in amides has been a critical focus, involving the incorporation of monodentate and bidentate directing auxiliaries. In that context, Corey showed the palladium-catalyzed C−H bond oxygenation of *N*-phthaloyl-*α*-amino acid amides by installing an *N*-quinolinyl group (Scheme 1.17).[79] Under the optimized conditions, a diastereoselective acetoxylation could afford the expected compounds with an excellent diastereomeric excess. This protocol was applied to amide derivatives of *N*-phthaloyl-protected leucine, alanine, *α*-methyl alanine, *α*-ethylalanine, and *α*-phenylalanine. The formation of the intermediate *trans*-palladacycle could explain the diastereoselective oxidation of the C–Pd bond. Later, Daugulis showed an example of acetoxylation of unnatural amino acids by employing $PhI(OAc)_2$ oxidant in an Ac_2O solvent under mild conditions.[80]



Scheme 1.17. Pd-Catalyzed C(sp^3)–H Acetoxylation *N*-Phthaloyl-α-Amino Acid Amides.

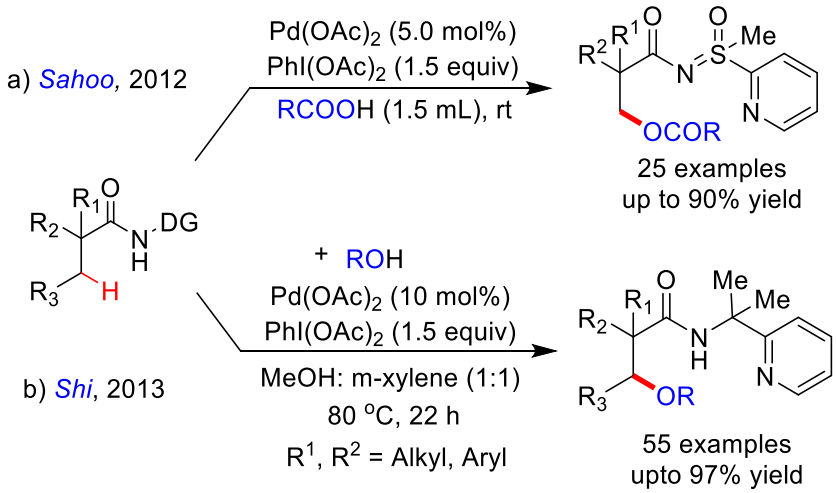
In a related investigation, Wu and Cao demonstrated the Pd-catalyzed alkoxylation and acyloxylation of *L*-pipecolinic acids at the C3 position, leading to the formation of cis-disubstituted piperidines as exclusive single stereoisomers (Scheme 1.18).[81] This protocol uses 1-methoxy-1,2-benziodoxole as an oxidant. Notably, methanol as solvent gave a mixture of methoxylated and acyloxylated products, whereas the reaction in other alcoholic solvents exclusively produced acyloxylated products. The choice of oxidant and solvent significantly influenced the success of the alkoxylation or acyloxylation reaction of a piperidine derivative.



Scheme 1.18. Pd-Catalyzed Quinoline-Directed C(sp^3)–H Alkoxylation Piperidine Derivatives.

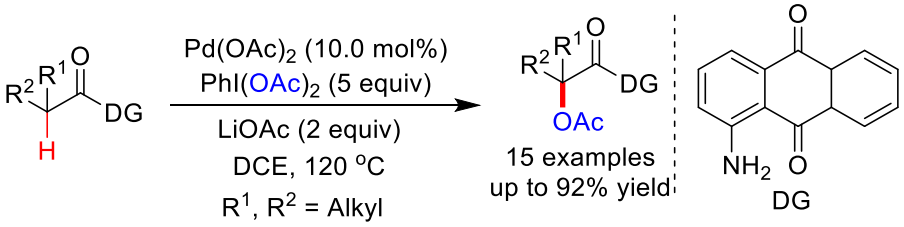
Furthermore, Sahoo successfully showed the acetoxylation of unactivated primary β-C(sp^3)–H of *N*-pivaloyl methyl-2-pyridyl sulfoximine using methyl-2-pyridyl sulfoximine as a bidentate directing group (Scheme 1.19a).[82] Notably, this reaction proceeded at room temperature, employing $Pd(OAc)_2$ catalyst and $PhI(OAc)_2$ oxidant in an AcOH medium. The practical utility of this approach was illustrated through the acetoxylation of fibrate-based drugs like gemfibrozil and clofibrate, both known for their efficacy in reducing cardiovascular risk factors. Notably, this sulfoximine-directing group can be easily removed and reused for further functionalization. This protocol is essential to note that it is limited to the primary β-C(sp^3)–H bond acetoxylation of amides. A 2-(pyridine-2-yl)isopropyl directing group was introduced for the amides alkoxylation of unactivated β-methylene C(sp^3)–H and C(sp^2)–H bonds with alkyl alcohols (Scheme 1.19b).[83] Thus, $Pd(OAc)_2$ and $PhI(OAc)_2$ enabled the regioselective alkoxylation of amide derivatives. This method showcased a broad substrate scope and

displayed tolerance toward essential functional groups, including chloro, cyano, ether, ester, olefin, and amino groups. Notably, it achieved γ-alkoxylation of the C(sp^2)–H bond without affecting the reactive β-C–H bond. A probable concerted palladation-deprotonation pathway has been suggested from the preliminary DFT calculations.



Scheme 1.19. Pd-Catalyzed C(sp^3)–H Bond Oxygenation using a 2-Pyridinyl Directing Group.

In elegant contribution, Zhang came up with a new bidentate directing group, 1-aminoanthraquinone, for the α-C(sp^3)–H acetoxylation (Scheme 1.20).[84] This directing group enabled precise control of the α-C(sp^3)–H acetoxylation through a unique [4,6]-bicyclic cyclopalladation pathway. The reaction provided excellent results with substrates containing primary α-C(sp^3)–H bonds. Moreover, even amides with α-methylene C(sp^3)–H bonds, which are typically more challenging to cleave than primary ones, proceeded smoothly under the optimal conditions. The reaction followed a Pd(II)/Pd(IV) catalytic cycle through a concerted metalation-deprotonation C(sp^3)–H activation (Figure 1.6). Density functional theory calculations supported the selective α-C(sp^3)–H acetoxylation of amides, revealing that the formation of a 5,6-fused palladacycle is a challenging step requiring significant rotation of the C(O)–C(α) bond. It is important to note that phenyl acetamide and but-3-enamide proved unstable under standard reaction conditions.



Scheme 1.20. Pd-Catalyzed 1-Aminoanthraquinone Directed α-C(sp^3)–H Oxygenation of Aliphatic Amides.

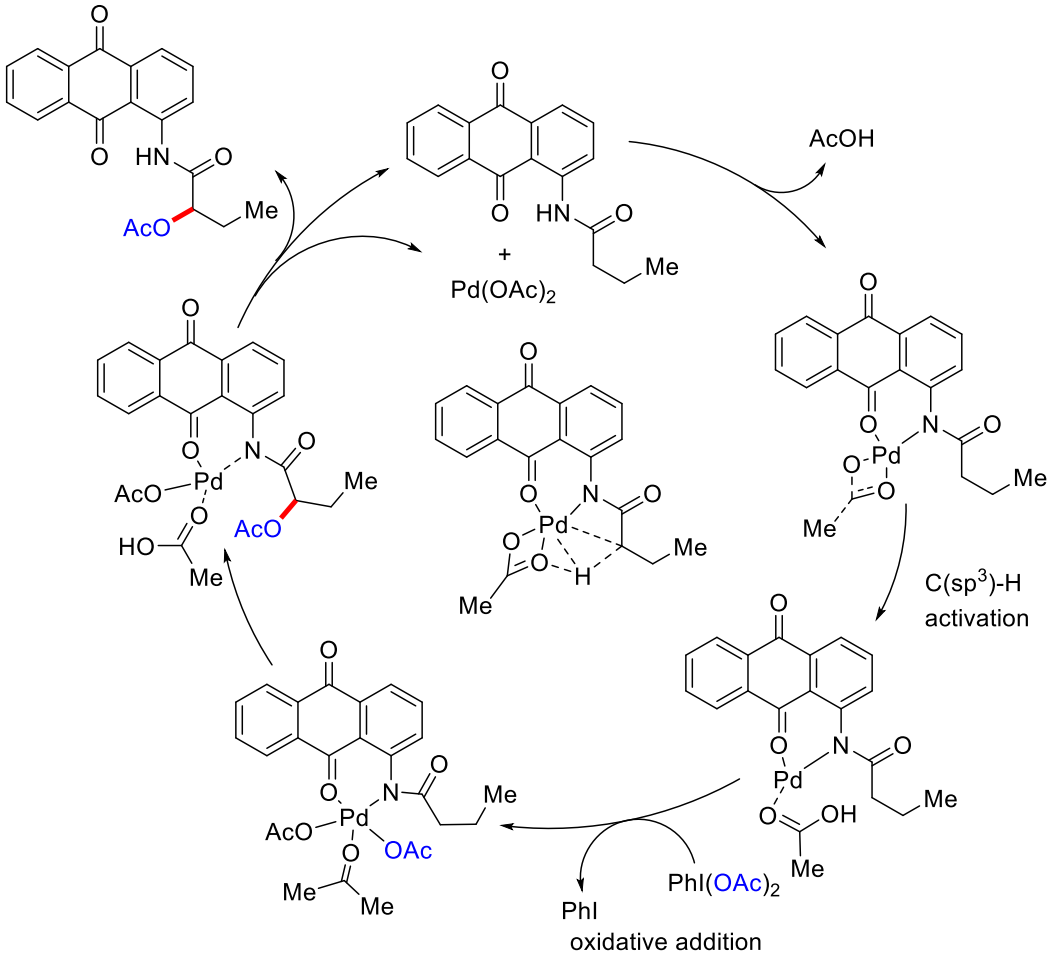
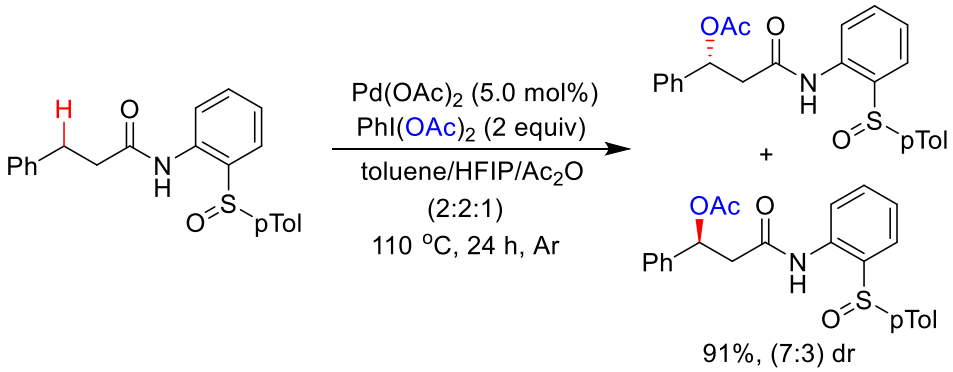


Figure 1.6. Plausible Catalytic Cycle for Pd-Catalyzed 1-Aminoanthraquinone Directed α-C(sp^3)–H Oxygenation of Aliphatic Amides.

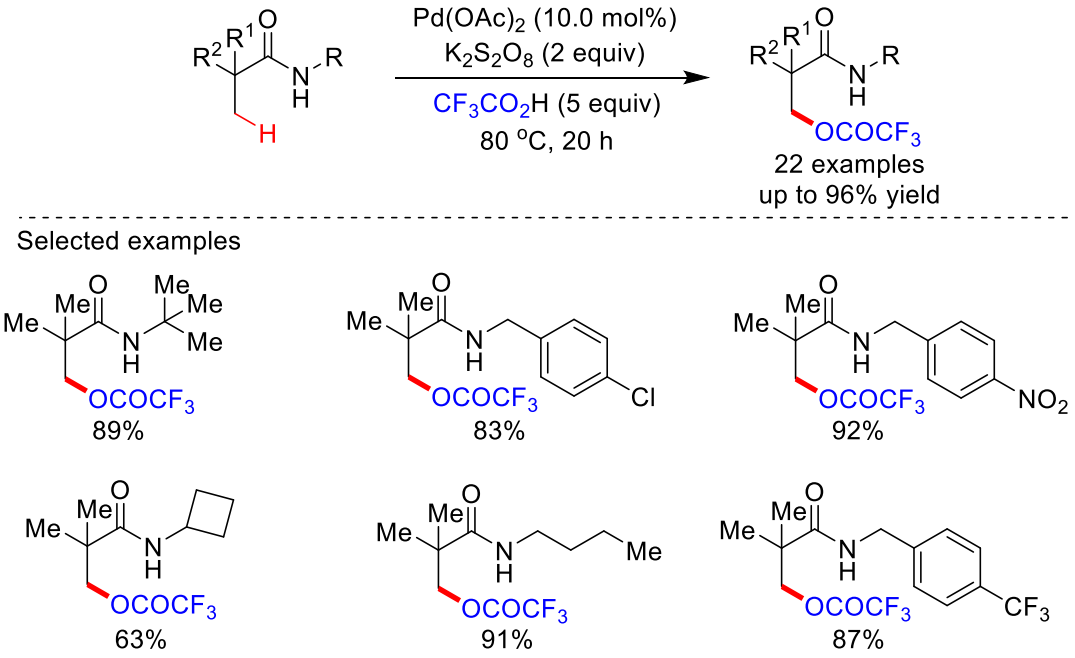
Later, Colobert and Wencel-Delord disclosed an example of 2-(*p*-tolyl sulfinyl)aniline-directed stereoselective acetoxylation using palladium catalysis (Scheme 1.21).[85] The stereoselective direct acetoxylation, which was previously considered unattainable, was successfully carried out with high efficiency, yielding the desired C–O coupling product in a high yield. Though the protocol was exclusively explored for the arylation, an example of

stereoselective acetoxylation provides a path forward for further development.



Scheme 1.21. Pd-Catalyzed 2-(*p*-Tolyl sulfinyl)aniline Directed *β*-C(sp^3)–H Acetoxylation of Aliphatic Amides.

The selective oxygenation of the C(sp^3)−H bond in amides with the assistance of monodentate amido-group is attractive as it does not need an additional directing group. Lu and Zhou demonstrated the acyloxylation of unactivated C(sp^3)−H bonds of simple amides under mild conditions using a palladium catalyst (Scheme 1.22).[86] The protocol employs a $K_2S_2O_8$ oxidant and an acidic solvent (CF_3COOH). Other oxidants such as $PhI(OAc)_2$, O_2, or oxone were ineffective. The employment of non-fluorinated solvents gave low yields. Various secondary amides were employed in this acyloxylation, demonstrating broad substrate scope and moderate functional group compatibility. However, the tertiary amide was unreactive under the present conditions. The reaction has been proposed to proceed *via* the C=O coordination, though the non-reactivity of *tert*-amides could not be explained. The *β*-acyloxyl amides can be hydrolyzed to give corresponding *β*-hydroxy amides using a standard alcoholysis method.



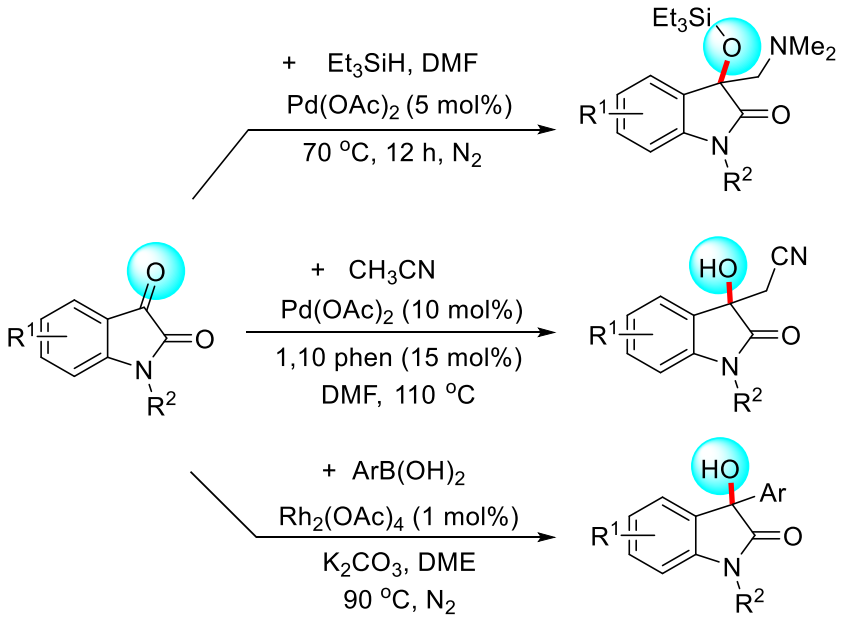
Scheme 1.22. Pd-Catalyzed C(sp^3)–H Acyloxylation of Secondary Amides.

1.2 OXYGENATION OF ISATINS

Isatin compounds are versatile and crucial in medicinal chemistry, serving as potential antiviral, anticancer, and anti-inflammatory agents.[87-94] Isatin-based derivatives promise to inhibit viral infections and cancer cell growth for drug development. They also find applications as agrochemicals, highlighting their versatility across various domains.[95-100] Consequently, significant attention has been given to their functionalization. Oxygenated isatins or indoles, particularly, form a significant subclass within the category of isatin-based natural products.[101-103] Therefore, developing unified protocols for efficient isatin functionalization is highly essential. Various groups have aimed at the selective synthesis of oxygenated isatins. However, traditional methods involve strong acid- or base-mediated condensation of oxy-substituted aniline with diethyl ketomalonate, oxalyl chloride, or chloral hydrate.[104] These approaches, while helpful, have drawbacks such as harsh reaction conditions, limited substrate range, and low yields.

Recent advancements have led to modern synthetic protocols for synthesizing oxygenated isatins and their derivatives, including C–H oxidation/acylation of formyl-*N*-aryl formamides and Suzuki cross-coupling reactions from iodoisatins.[105-110] Although the selective synthesis of C3 oxygenated isatin is well-studied (Scheme 1.23),[111-118] the site-specific modification on the benzene ring at C4, C5, C6, and C7 is relatively less explored. In addition, catalytic oxidative transformations of oxy-indoles to oxy-isatins have been disclosed.[119-121] However, all these

methods could synthesize only oxy-substituted-isatins, but to date, there is no report for the selective C–H oxygenation of isatins. Transition-metal-catalyzed, step-economic C–H activation and functionalization has recently experienced substantial expansion and development. Thus, developing a transition metal-catalyzed protocol for direct oxygenation of isatins is of great interest.



Scheme 1.23. Pd-Catalyzed C(3)–H oxygenation of Isatins.

1.3 OXYGENATION OF INDOLES

Indoles are essential heterocyclic compounds in natural chemistry and drug discovery, given their pivotal role in generating a diverse array of bioactive compounds and pharmacologically relevant substances.[122-125] In particular, oxygenated indoles play a crucial role in organic synthesis and medicinal chemistry by allowing the introduction of oxygen-containing functional groups into the indole molecule.[5,6,126] This modification can lead to significant changes in the chemical and biological properties of the indole compound, making it valuable for drug design and other synthetic applications. The traditional methods for oxygenating indoles involve metal oxides like selenium dioxide or potassium permanganate and peracids like peracetic acid. These methods have limitations such as low selectivity, the formation of unwanted by-products, and the use of toxic reagents. An alternative approach is the transition metal-catalyzed cross-coupling of organometallic substrates using various precious and inexpensive 3d metal catalysts. Despite its widespread use in academia and various industries, the traditional cross-coupling method still requires prefunctionalized

organometallic substrates. This necessitates a multi-step synthesis process and results in the generation of stoichiometric metallic waste.[11,12,127]

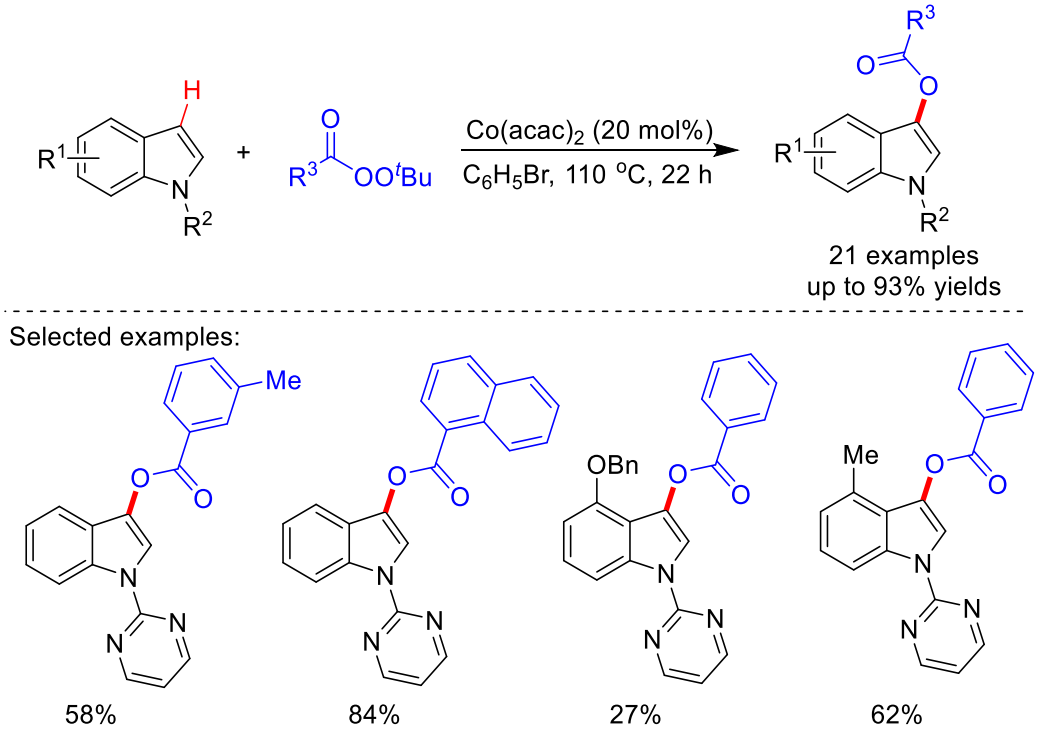
Over the past few years, transition-metal-catalyzed oxygenation of C–H bonds in indole has emerged as a potent and environmentally friendly alternative to the conventional oxygenation methods. This approach facilitates diverse C–O bond formations on indole's pyrrole and benzenoid rings, including alkoxylation, acetoxylation, acyloxylation, and hydroxylation.[5,6,126,128] Directing groups in C–H activation procedures has proven to be a valuable approach for the remote functionalization of the less reactive indole-benzenoid ring. When a directing group is positioned at the nitrogen of the indole structure, it facilitates functionalization at positions C2, C6, and C7.[129,130] Similarly, having a directing group at C3 is well-suited for functionalization at positions C4 and C2.[131,132]

Thus, researchers have reported successful indole oxygenation through monodentate- or bidentate-coordination using compounds such as pyridine derivatives or 8-aminoquinoline. In contrast to oxygenation via strong *N*-coordination, few examples exist for oxygenation of unactivated C–H bonds on versatile and multi-functional indoles through weakly coordinating carbonyl (C=O) groups. This is believed to proceed *via* less favored cyclometallated intermediates. It is worth noting that the C–O bond formation at the more reactive C(3)–H bond in indoles is well-established without installing any external directing group. However, the formation of C–O bonds in indoles at positions C2, C4, C5, C6, and C7 has recently gained significant attention. Given the importance of oxygenated indole derivatives and the significance of C–H bond oxygenation, this section describes the developments in selective C–H bond oxygenation of indoles catalyzed by different transition metal catalysts.

1.3.1. Cobalt-Catalyzed Oxygenation of Indoles

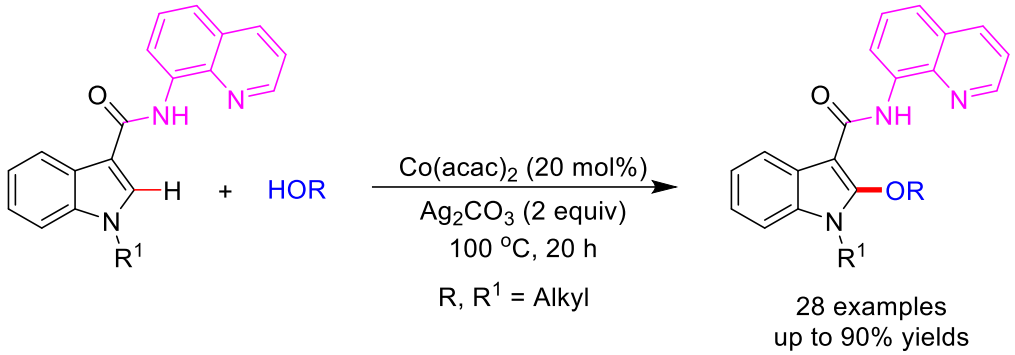
Cobalt, being both biologically relevant and cost-effective as a transition metal, has been the subject of extensive study in C–H functionalization reactions.[38,39] However, the oxygenation of heteroarenes presents a challenge due to the high electron density in their partially filled d-orbitals, rendering it energetically unfavorable for oxygen interaction. Achieving the necessary oxidation state for cobalt and controlling redox chemistry further complicates the process. Neverthless, Liu and co-workers reported a method for the direct C3-selective C–H acyloxylation of indoles, employing *tert*-butyl peresters as a coupling partner (Scheme 1.24).[133] Here, $Co(acac)_3$ catalyst and bromo benzene as the solvent were found to be best and provided the desired acyloxylation products in moderate to good yields. This versatile reaction demonstrated applicability across various *N*-substituted indoles and *tert*-butyl

peresters. A preliminary mechanistic investigation revealed a pathway involving radical C–H activation and a Co(II)/Co(III) cycle. However, it's worth mentioning that this approach has its drawbacks, such as potential over-oxidation, stability concerns, the toxicity of peresters, and significant catalyst loadings.



Scheme 1.24. Co-Catalyzed C3 Acyloxylation of Indole Derivatives.

Expanding on the exploration of 3d metals in indole oxygenation, the Wu group presented an appealing approach for the selective alkoxylation of the C(2)−H bond in indoles using an 8-amino quinoline directing group. This approach utilized a $Co(acac)_2/Ag_2CO_3$ catalyst system, providing a straightforward and highly efficient method for synthesizing 2-alkoxyindoles from alcohols (Scheme 1.25).[134] This methodology facilitated the alkoxylation of a series of 8-aminoquinoline indole derivatives with alcohols at 100 °C, affording the desired alkoxylated indoles in moderate to good yields. Notably, control experiments unveiled Co(III) as the active catalyst, revealing a radical pathway in the reaction (Figure 1.7). While these cobalt-catalyzed methods exhibit notable advancements in the selective oxygenation of indoles, some limitations persist. The dependency on *tert*-butyl peresters and specific directing groups may restrict the generality of the C3-selective C–H acyloxylation and C2 alkoxylation methods. Additionally, moderate to good yields suggest room for improvement in reaction efficiency.



Scheme 1.25. Co-Catalyzed Quinoline-Directed C(2)–H Alkoxylation of Indoles.

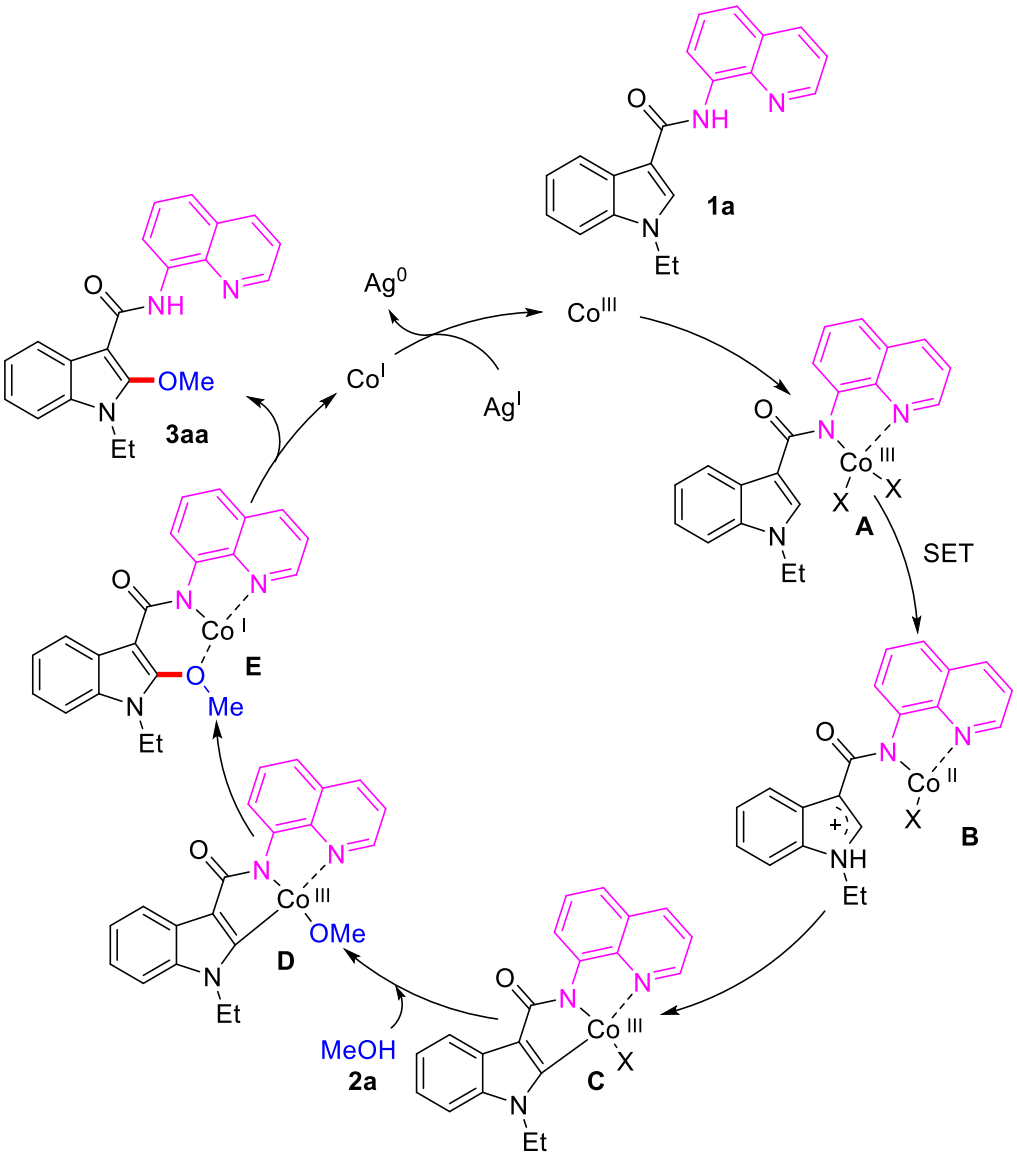
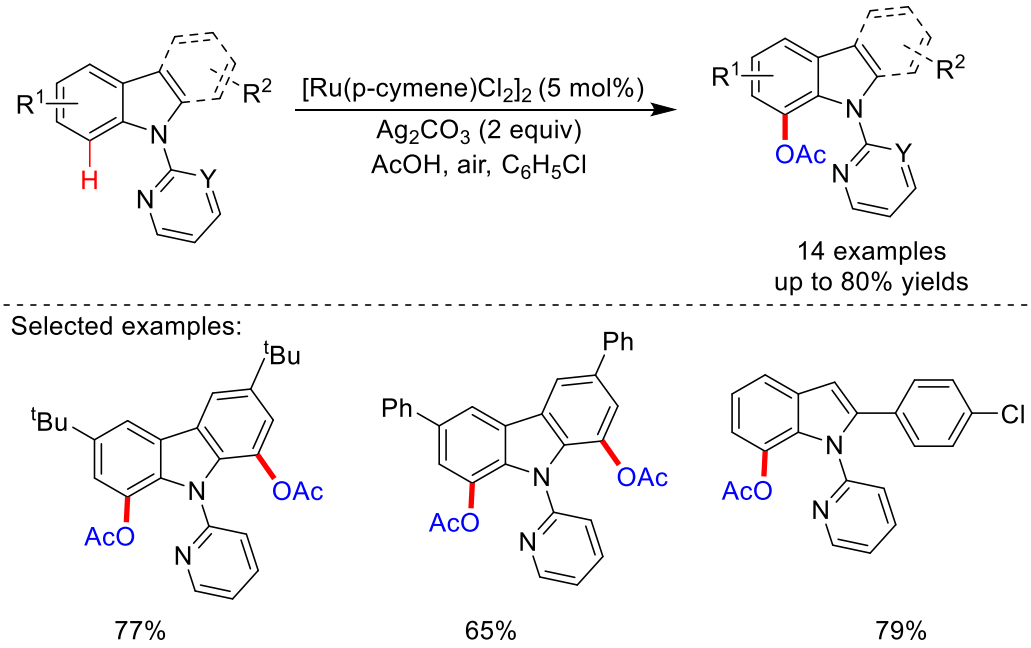


Figure 1.7. Plausible Catalytic Cycle for Co-Catalyzed Quinoline-Directed C2 Alkoxylation of Indoles.

1.3.2. Ruthenium-Catalyzed Oxygenation of Indoles

Ruthenium complexes have seen extensive use as catalysts in indoles C–H functionalization.[55-59] In a noteworthy contribution, Miura developed an efficient method that enables the selective cleavage of C–H bonds and the formation of C–O bonds regioselectively in various heteroarenes (Scheme 1.26).[135] This transformation occurs when 9-(pyridine-2-yl)carbazoles are treated with acetic acid in the presence of a silver salt oxidant under ruthenium catalysis, resulting in the synthesis of diacetoxylated products at positions C1 and C8. These reactions proceed smoothly, and the products are obtained in good yields. Notably, the same reaction conditions can also be effectively used for acetoxylation of 2-substituted-(pyridin-2-yl)indoles and 1-aryl-7-azaindoles, thereby broadening the applicability of this catalytic process. The use of acetic acid as a coupling partner and a silver salt oxidant may limit the scope of applicable substrates, while the requirement for longer reaction times could pose a practical challenge that necessitates further development.

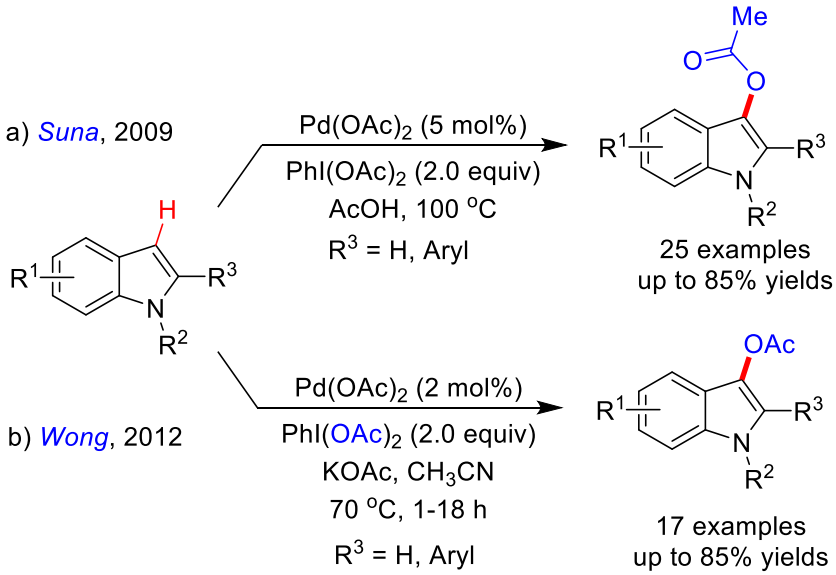


Scheme 1.26. Ru-Catalyzed C7 Acetoxylation of 2,3-Substituted 2-Pyridinyl Indoles.

1.3.3. Palladium-Catalyzed Oxygenation of Indoles

The exploration of palladium catalysts in the oxygenation of indoles has led to significant advancements in regioselective acetoxylation, acyloxylation, hydroxylation, and alkoxylation methods.[66-71] In 2009, Suna revealed a regioselective acetoxylation method for indole-2-carboxylates, explicitly targeting the C3 position and employing $PhI(OAc)_2$ as the oxidizing

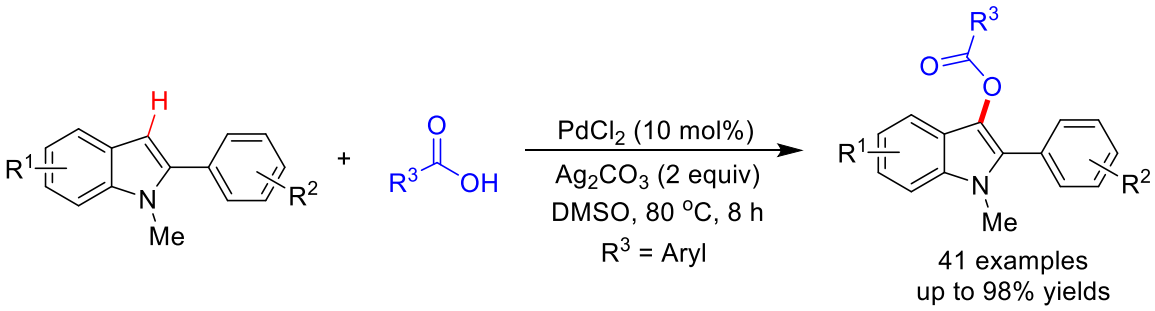
agent (Scheme 1.27a).[137] This acetoxylation reaction could be catalyzed by $Pd(OAc)_2$ and $PtCl_2$. Notably, C–H activation and subsequent oxidation predominantly occurred at the C3 position, as no products with acetoxylation at C2 were observed when employing 2-unsubstituted 3-methylindole as the substrate. The yields of the acetoxylation products were influenced by the electronic properties of the substrate. Indoles containing electron-rich substituents readily underwent acetoxylation, while those with electron-deficient analogs required higher amounts of $PhI(OAc)_2$ and longer reaction times to achieve yields suitable for synthetic purposes. Similarly, a selective acetoxylation of the C(3)−H bond in unsubstituted indoles was developed by Wong. This method, employing palladium catalysis, provided a direct acetoxylation of 2,3-unsubstituted indoles without the need for additional steps to protect reactive positions (Scheme 1.27b).[138] Wong's approach allowed for the synthesis of a variety of 3-oxindole scaffolds with pharmaceutical relevance. Importantly, this method was compatible with halide functionalities, allowing for additional structural modifications highlighting the potential of this protocol.



Scheme 1.27. Pd-Catalyzed C3 Acetoxylation of C2-Substituted Indoles.

Moreover, the Liu group introduced a novel approach for indoles' direct C3 oxidative acyloxylation, utilizing a stoichiometric quantity of carboxylic acid in the presence of a palladium catalyst (Scheme 1.28).[139] This innovative method is compatible with a wide array of indole derivatives and carboxylic acids, resulting in acyloxylated products with good yields. Both aliphatic and aromatic carboxylic acids are suitable for this reaction. Interestingly, indole starting materials lacking substitution at the C2 position undergo homocoupling with high selectivity at the C2/C3 position, and acyloxylation occurs in a single step. The inclusion of

Ag_2CO_3 plays a critical role in promoting this transformation, serving as a base and an oxidant to regenerate palladium(II). The proposed mechanism involves cationic Pd(II) catalysis, offering valuable insights into the reaction pathway (Figure 1.8).



Scheme 1.28. Pd-Catalyzed Oxidative C3 Acyloxylation of C2-Protected Indoles.

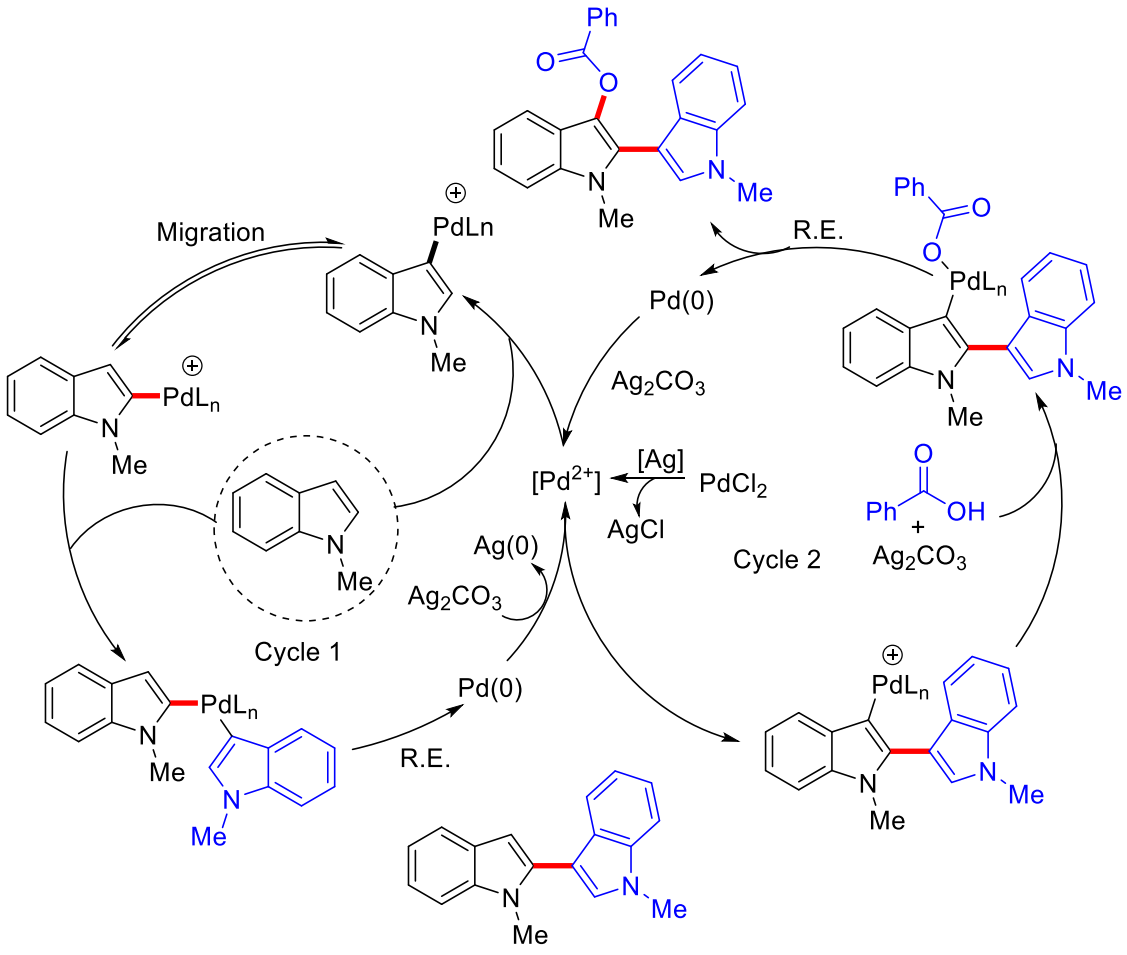
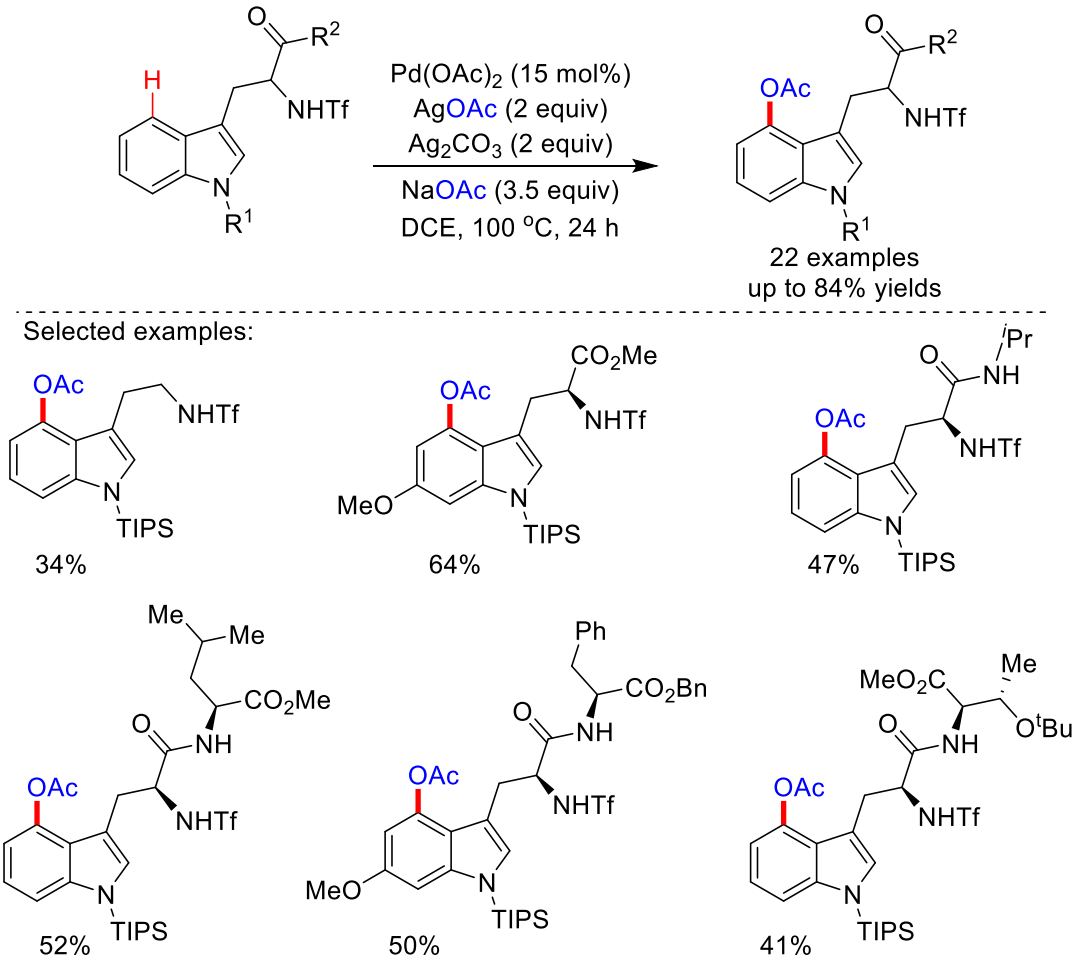


Figure 1.8. Plausible Catalytic Cycle for Pd-Catalyzed C(2)–C(3) Homocoupling and C3 Acyloxylation of Indoles.

In addition to the palladium-catalyzed C-3 oxygenation of indoles, there are a few approaches to selective C-4 oxygenation. In that direction, a palladium-catalyzed direct C-4

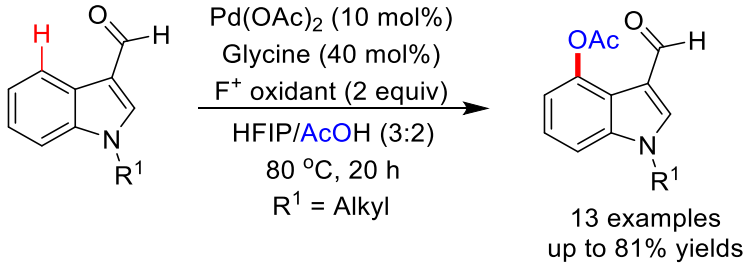
acetoxylation of tryptophan with acetic acid was described by Wang and co-workers (Scheme 1.29).[140] This method is notable for its mild reaction conditions and extensive compatibility with various functional groups. Significantly, this innovative protocol provides a straightforward strategy for synthesizing 4-substituted tryptophan derivatives, which have diverse applications in organic chemistry. Furthermore, this method enables the selective removal of the acetyl group after the C4-acetoxylation of tryptophan derivatives, producing 4-hydroxyl compounds. This step is advantageous for further modifications of tryptophan-containing peptides, opening up possibilities for the design and synthesis of complex molecules and biomolecules with tailored properties.



Scheme 1.29. Pd-Catalyzed Regioselective C(4)–H Acetoxylation of Tryptophan.

Very recently, Volla reported an efficient and convenient method for achieving regioselective C-4 acetoxylation, chlorination, and bromination of indole-3-carboxaldehyde using a Pd(II) catalyst with glycine as the transient directing group (Scheme 1.30).[141] This process relies on readily available, cost-effective, and stable CuX_2 as the source of halogens

and acetic acid to facilitate the acetoxylation. A crucial aspect of this transformation is the employment of glycine as the transient directing group, along with NFSI or 1-fluoro-2,4,6-trimethylpyridinium triflates as a bystander oxidant. This combination in the HFIP solvent is vital for successfully executing the reaction (Figure 1.9).



Scheme 1.30. Pd-Catalyzed C(4)–H Acetoxylation of Indoles using a Transient Directing Group.

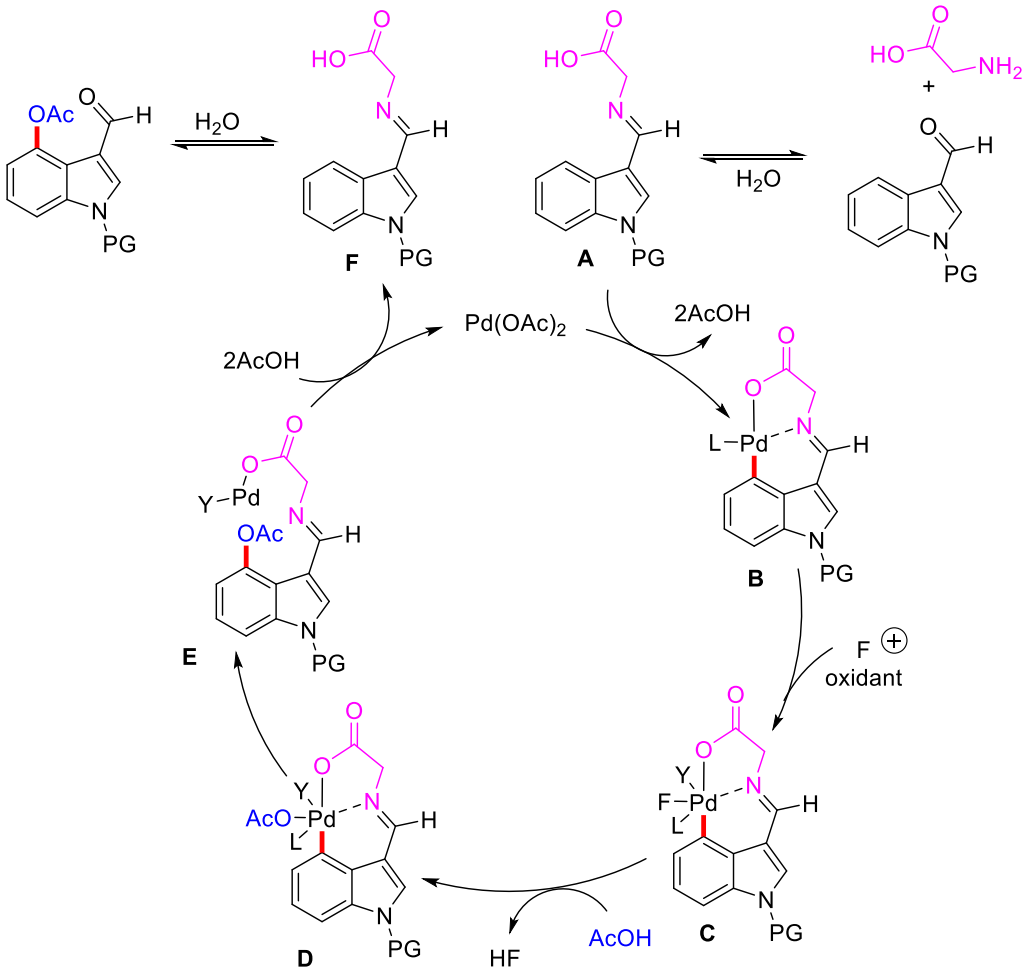


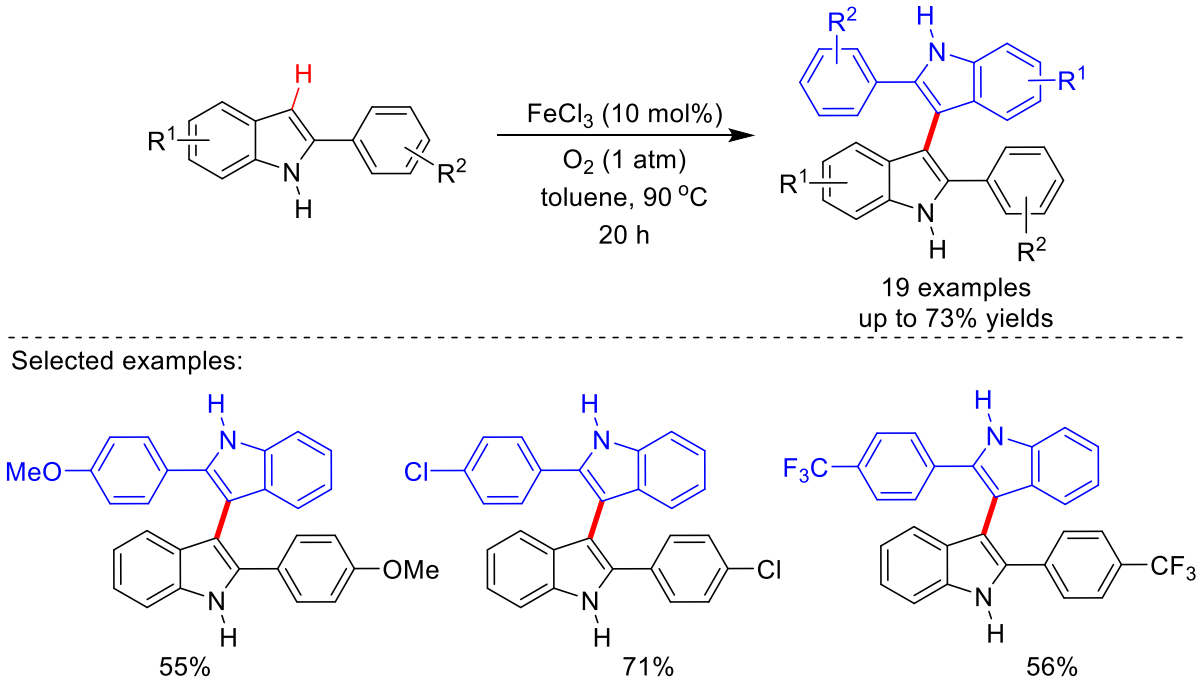
Figure 1.9. Plausible Catalytic Cycle for Pd-Catalyzed C(4)–H Acetoxylation of Indoles.

1.4 DIMERIZATION OF INDOLES

Indoles are privileged structural motifs that have gained significant attention due to their presence in numerous biologically active compounds.[122-125] Similarly, biindoles play a vital role in the development of various natural products, organic electroluminescent materials, pharmaceuticals, and in material science.[15-22] Their importance lies in their diverse applications and potential to contribute to more sustainable and efficient chemical processes. Therefore, the development of standardized protocols for synthesizing biindoles is of utmost importance. The most systematic approach to synthesizing biindolyls involves the acidic dimerization of indoles followed by dehydrogenation. Furthermore, the transition metal-catalyzed coupling of indole halides with organo-indole metals has emerged as a versatile technique for biindole synthesis.[15,18,122,123,142,143] However, these methods require prefunctionalized substrates and generate stoichiometric amounts of organometallic waste as by-products. Recently, the C−H/C−H oxidative coupling of indoles has gained attention as an efficient, step-economic method to generate biindole compounds without the need for prefunctionalization. Over the past decade, the homocoupling of indole to approach 2,2-biinolyls, 3,3-biindolyls, and 2,3-biindolyls catalyzed by palladium or copper *via* C–H bond cleavage has been well explored.[1,23-29] However, it is worth noting that dimerization of indoles is limited to more reactive sites, with the dimerization of the benzenoid site of indole being a particular challenge. Given the importance of biindole derivatives and the significance of C−H bond dimerization, this section outlines the advancements in indole dimerization catalyzed by transition metals.

1.4.1. Iron-Catalyzed Dimerization of Indoles

Iron, an economical, abundantly available, and less toxic transition metal, is extensively used in various chemical transformations. Although notable progress has been made in the iron-catalyzed C–H bond functionalization of indoles,[144-146] its application in the dimerization of indoles has been significantly limited. Zhang introduced an innovative chemical process for the direct synthesis of 3,3-biindolyls (Scheme 1.31).[24] This method utilizes iron as a catalyst and molecular oxygen as the exclusive oxidizing agent. Remarkably, it demonstrates versatility by accommodating a wide range of 2-aryl indoles, irrespective of whether they possess electron-rich or electron-poor substituents. Additionally, it exhibits tolerance for functional groups such as chloride, bromide, and iodide. Recognized for its simplicity and efficiency, this reaction stands out as a practical and effective approach for producing 3-biindolyl compounds.



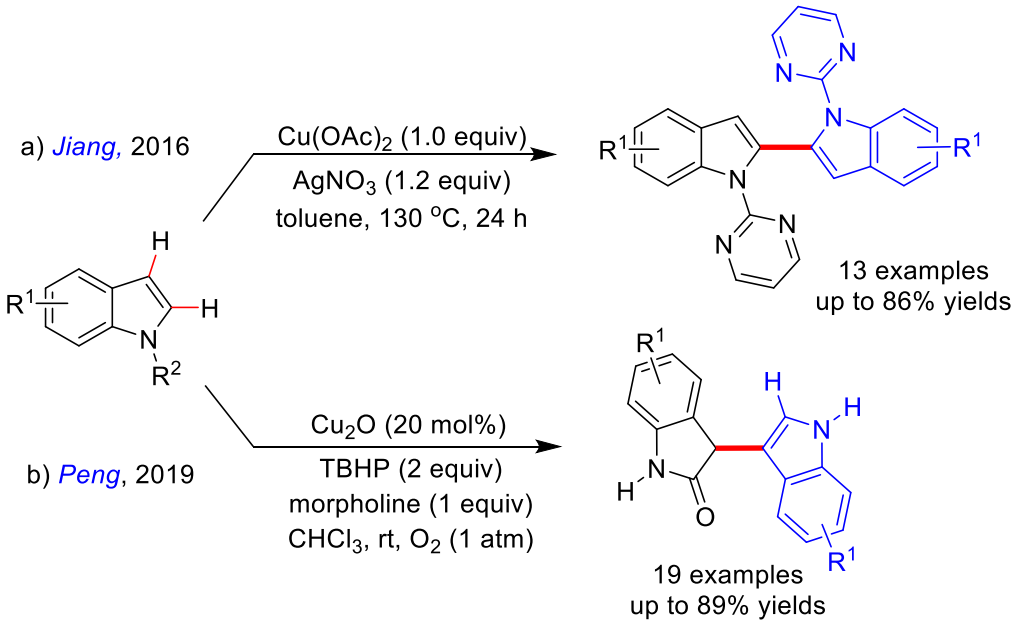
Scheme 1.31. Iron-Catalyzed Oxidative C(3)–C(3) Homocoupling of Indoles.

1.4.2. Copper-Catalyzed Dimerization of Indoles

Copper catalysts have been extensively employed for the oxidative coupling of arenes and heteroarenes.[49,50] Jiang described the C–H activation method that enables the selective coupling of indoles and substituted indoles at the C2 position using stoichiometric copper acetate (Scheme 1.32a).[26] This strategy used pyrimidine as a directing group to achieve high regioselectivity. Additionally, it is noteworthy that the pyrimidine group can be easily removed during the deprotection process. The resulting biindole compounds are crucial starting materials for synthesizing various bioactive indolocarbazoles. This method holds significant importance in pharmaceutical chemistry due to its potential for facilitating the production of valuable compounds with pharmaceutical applications. These approaches, while helpful, have drawbacks such as harsh reaction conditions, limited substrate range, and a significant amount of catalyst loading.

In a similar line, Peng developed a straightforward and practical procedure for synthesizing 3,3-biindolin-2-ones (Scheme 1.32b).[28] This synthesis method employs copper catalysis to enable the oxidative homocoupling of indoles in the presence of TBHP and morpholine. Notably, this innovative approach offers versatility by accommodating a broad range of functional groups, utilizes readily available and cost-effective starting materials, demonstrates both chemo- and regioselectivity, and can be carried out under mild reaction conditions. Another remarkable aspect of this method is its capability to selectively introduce

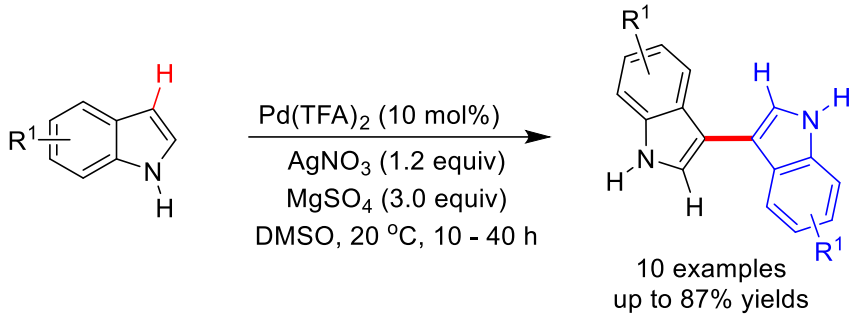
carbonyl groups at the C2 position of indoles with multiple reactive sites. The copper-catalyzed oxidative homocoupling of indoles to produce 3,3-biindolin-2-ones holds promise for various applications in synthetic chemistry.



Scheme 1.32. Cu-Mediated Oxidative C(2)–C(2) and C(3)–C(3) Homocoupling of Indoles.

1.4.3. Palladium-Catalyzed Dimerization of Indoles

Palladium catalysts have been extensively employed for the functionalization of heteroarenes.[66-71] Thus, developing a palladium catalyst for selective C–H dimerization of indoles would be a step towards sustainable synthesis. Shi has pioneered in showcasing the oxidative homo dimerization of both *N*-protected and free indole derivatives to create 3,3-linked biindolyl scaffolds through the use of palladium catalysis (Scheme 1.33).[147] The involvement of $AgNO_3$ and $MgSO_4$ proved crucial in modulating the coupling pathway and facilitating the formation of the 3,3-dimer. This innovative method showcases notable versatility in accommodating diverse chemical groups, establishing it as a valuable tool for constructing these distinct scaffolds with readily accessible indole and its derivatives. Furthermore, the homocoupling technique has been successfully applied in the synthesis of biologically active compounds, such as *β*-vulgaris. The proposed mechanism suggests a Pd(II)/Pd(0) catalytic cycle involving facile C–H palladation (Figure 1.10).



Scheme 1.33. Pd-Catalyzed Oxidative C(3)–C(3) Homocoupling of Indoles.

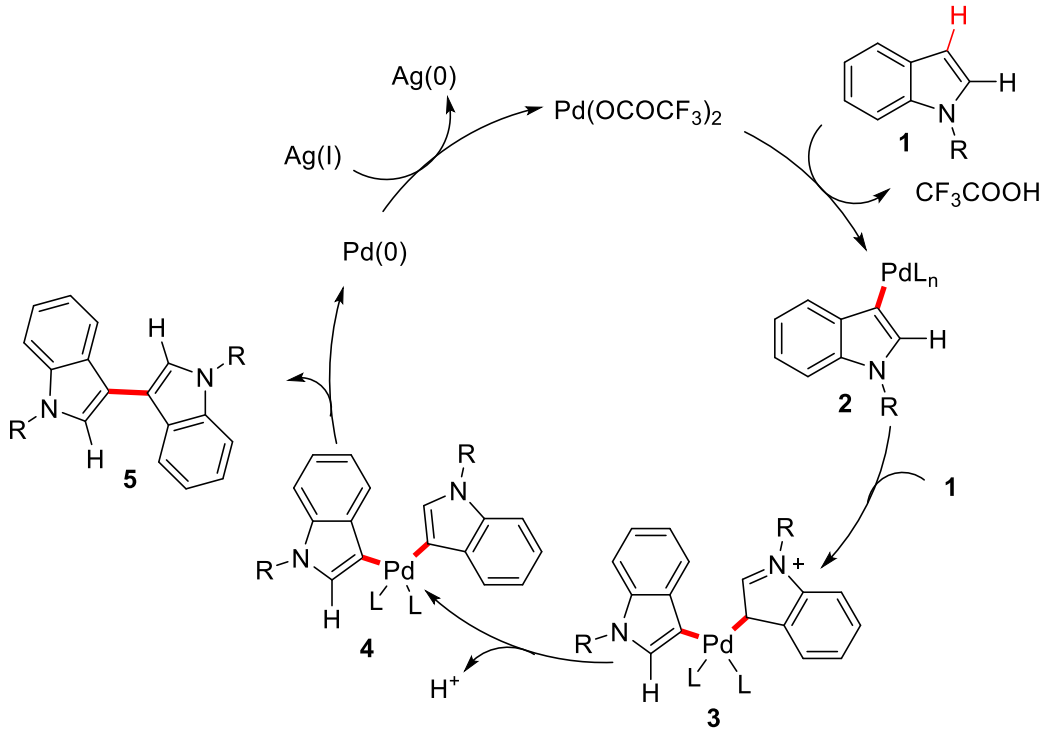
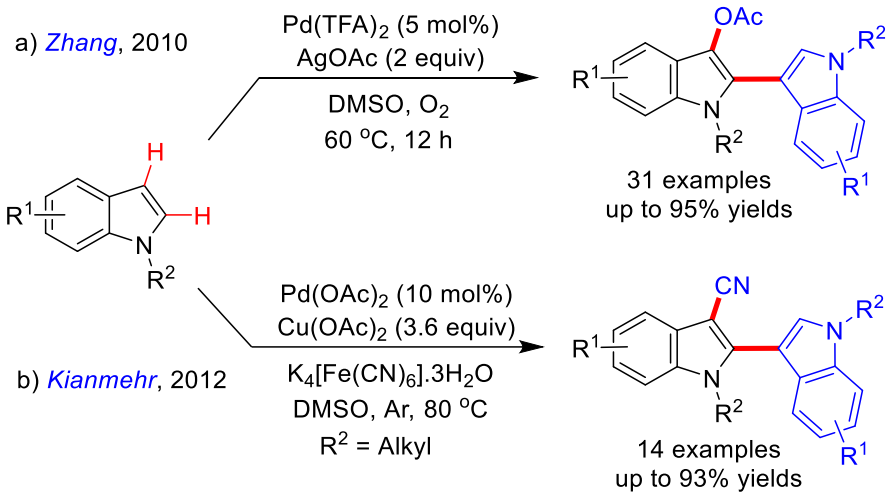


Figure 1.10. Plausible Catalytic Cycle for Pd-Catalyzed Oxidative C(3)–C(3) Homocoupling of Indoles.

In a similar vein, Zhang and co-workers developed palladium-catalyzed homocoupling of indoles to synthesize 2,3-indolyl (Scheme 1.34a).[23] This method involves the use of catalytic $Pd(TFA)_2$ in combination with $Cu(OAc)_2 \cdot 3H_2O$ (1.5 equiv) and shows tolerance towards halide-substituted indoles. This novel protocol offered a straightforward route to synthesizing 2,3-indolyl under exceptionally mild reaction conditions. Additionally, C3-position acetoxylated biindolyls could be prepared in a one-pot sequence using catalytic $Pd(TFA)_2$, AgOAc (2 equiv), and the presence of molecular oxygen. It is worth mentioning that only electron-rich indoles exhibited reactivity in this process. The proposed mechanism suggests a Pd(0)/Pd(II) catalytic cycle involving facile C–H palladation (Figure 1.11). Later, Kianmehr

demonstrated a palladium-catalyzed method for 2,3-homocoupling and C-3 cyanation of indoles (Scheme 1.34b).[25] This reaction employs $K_4[Fe(CN)_6].3H_2O$, a safe and non-toxic cyanating agent. The novel protocol provides a straightforward route to the desired products through a one-pot sequence, making it a practical and convenient method for achieving these chemical transformations.



Scheme 1.34. Pd-Catalyzed Oxidative C(2)–C(3) Homocoupling and C3 Acetoxylation and Cyanation of Indoles.

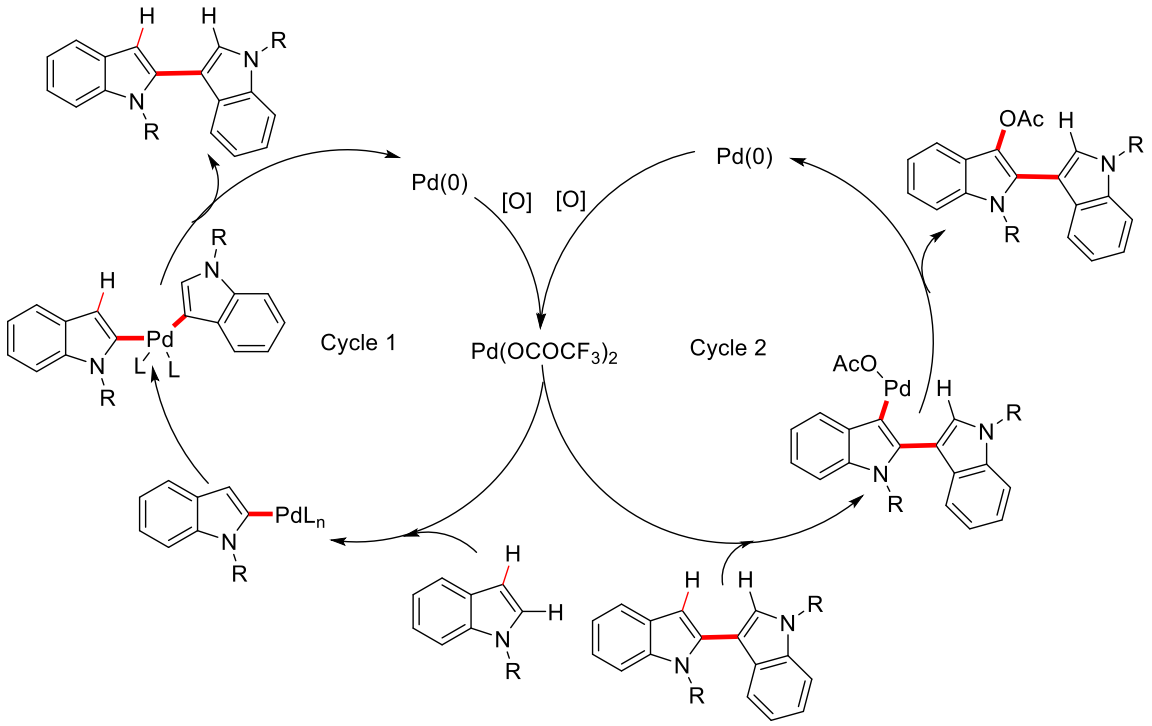
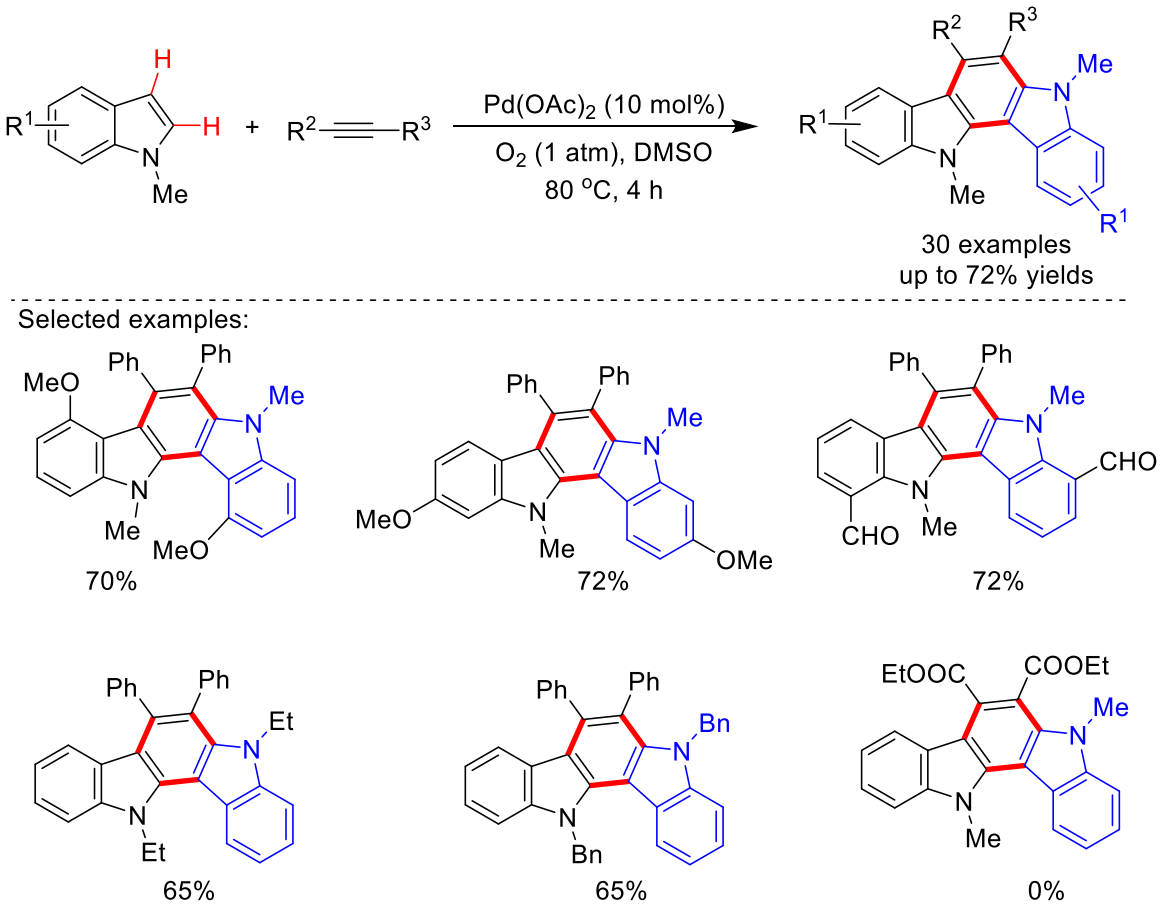


Figure 1.11. Plausible Catalytic Cycle for Pd-Catalyzed C(2)–C(3) Homocoupling and Acetoxylation of Indoles.

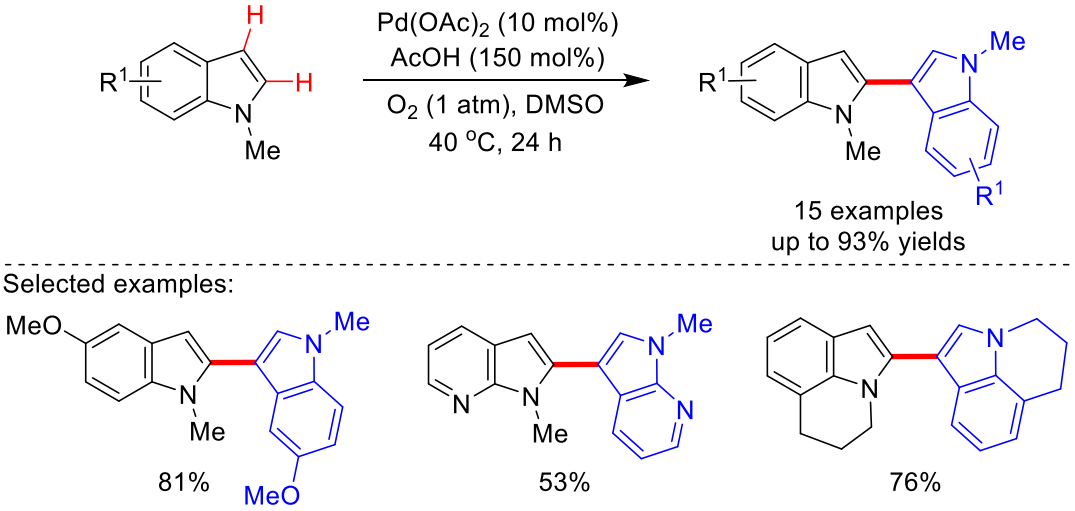
In 2018, Kumar and co-workers developed a pioneering one-pot, metal-based, and oxidant-free method for indolo[3,2] carbazole synthesis (Scheme 1.35).[27] This protocol represents the first instance of using multiple Pd-catalyzed C–H transformations and annulations to create these compounds. The reaction utilizes readily available indoles and alkynes, and notably, it does not require oxygen as an oxidizing agent. Importantly, this methodology is adaptable to azaindoles as well. The versatility of this approach holds promise for a broad range of applications, particularly in constructing libraries of indolo[3,2]carbazole-based compounds, which could be significant in medicinal research or natural product synthesis.



Scheme 1.35. Pd-catalyzed C(2)–C(3) Annulations of Indoles.

In 2021, Vos and co-workers developed a highly selective Pd-catalyzed method that involves cross-coupling C–H bonds in *N*-substituted indoles using molecular oxygen (Scheme 1.36).[29] This approach significantly simplifies the synthetic process for creating 2,3-bisindole scaffolds, which are known for their noteworthy medicinal properties. The study provides valuable insights into the selectivity of indole C–H activation, supported by density functional theory calculations, kinetic isotope studies, and Hammett investigation. This predictive

capability allows for the design of C–H/C–H coupling, offering a more efficient and environmentally friendly approach to producing bisindole compounds with medicinal significance.



Scheme 1.36. Pd-Catalyzed Oxidative C(2)–C(3) Homocoupling of Indoles.

1.5 REFERENCES

1. Alonso, D. A.; Nájera, C.; Pastor, I. M.; Yus, M., *Chem. Eur. J.* **2010**, *16*, 5274-5284.
2. Neufeldt, S. R.; Sanford, M. S., *Acc. Chem. Res.* **2012**, *45*, 936-946.
3. Thirunavukkarasu, V. S.; Kozhushkov, S. I.; Ackermann, L., *Chem. Commun.*, **2014**, *50*, 29-39.
4. Liu, B.; Shi, B. F., *Tetrahedron Letters* **2015**, *56*, 15-22.
5. Moghimi, S.; Mahdavi, M.; Shafiee, A.; Foroumadi, A., *Eur. J. Org. Chem.*, **2016**, *2016*, 3282-3299.
6. Iqbal, Z.; Joshi, A.; Ranjan De, S., *Adv. Synth. Catal.* **2020**, *362*, 5301-5351.
7. Davies, H. M. L.; Sorensen, E. J., *Chem. Soc. Rev.* **2009**, *38*, 2981-2982.
8. McMurray, L.; O'Hara, F.; Gaunt, M. J., *Chem. Soc. Rev.* **2011**, *40*, 1885-1898.
9. Roughley, S. D.; Jordan, A. M., *J. Med. Chem.* **2011**, *54*, 3451-3479.
10. Gutekunst, W. R.; Baran, P. S., *Chem. Soc. Rev.* **2011**, *40*, 1976-1991.
11. Ley, S. V.; Thomas, A. W., *Angew. Chem. Int. Ed.* **2003**, *42*, 5400-5449.
12. Hartwig, J. F., *Nature* **2008**, *455*, 314-322.
13. Dick, A. R.; Sanford, M. S., *Tetrahedron* **2006**, *62*, 2439-2463.
14. Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F., *Chem. Soc. Rev.* **2011**, *40*, 4740-4761.

15. Forke, R.; Jäger, A.; Knölker, H. J., *Org. Biomol. Chem.*, **2008**, *6*, 2481-2483.
16. Bertinetti, B. V.; Rodriguez, M. A.; Godeas, A. M.; Cabrera, G. M., *J. Antibiot.* **2010**, *63*, 681-683.
17. Shintani, A.; Toume, K.; Rifai, Y.; Arai, M. A.; Ishibashi, M., *J. Nat. Prod.* **2010**, *73*, 1711-1713.
18. Erenler, R.; Kul Köprülü, T.; Ökten, S.; tekin, s., *Turk. J. Biol.* **2015**, *39*, 15-22.
19. Micillo, R.; Panzella, L.; Koike, K.; Monfrecola, G.; Napolitano, A.; D'Ischia, M., *Int. J. Mol. Sci.* **2016**, *17*, 746.
20. Maeda, C.; Todaka, T.; Ueda, T.; Ema, T., *Chem. Eur. J.* **2016**, *22*, 7508-7513.
21. Tadano, S.; Sugimachi, Y.; Sumimoto, M.; Tsukamoto, S.; Ishikawa, H., *Chem. Eur. J.* **2016**, *22*, 1277-1291.
22. Šachlevičiūtė, U.; Varvuolytė, G.; Bieliauskas, A.; Kleizienė, N.; Žukauskaitė, A.; Šačkus, A., *Molbank* **2020**, *2020*, M1146.
23. Liang, Z.; Zhao, J.; Zhang, Y., *J. Org. Chem.* **2010**, *75*, 170-177.
24. Niu, T.; Zhang, Y., *Tetrahedron Lett.* **2010**, *51*, 6847-6851.
25. Kianmehr, E.; Ghanbari, M.; Faghih, N.; Rominger, F., *Tetrahedron Lett.* **2012**, *53*, 1900-1904.
26. Besset, T.; Jubault, P.; Pannecoucke, X.; Poisson, T., *Org. Chem. Front.*, **2016**, *3*, 1004-1010.
27. Kumar, K. S.; Meesa, S. R.; Naikawadi, P. K., *Org. Lett.* **2018**, *20*, 6079-6083.
28. Peng, X.; Zeng, Y.; Liu, H.; Xu, X.; Zhang, M.; Liu, Q., *New J. Chem.* **2019**, *43*, 15153-15160.
29. Beckers, I.; Krasniqi, B.; Kumar, P.; Escudero, D.; De Vos, D., *ACS Catal.*, **2021**, *11*, 2435-2444.
30. Engle, K. M.; Mei, T. S.; Wasa, M.; Yu, J. Q., *Acc. Chem. Res.* **2012**, *45*, 788-802.
31. De Sarkar, S.; Liu, W.; Kozhushkov, S. I.; Ackermann, L., *Adv. Synth. Catal.* **2014**, *356*, 1461-1479.
32. Zhu, R. Y.; Farmer, M. E.; Chen, Y. Q.; Yu, J. Q., *Angew. Chem. Int. Ed.* **2016**, *55*, 10578-10599.
33. Das, R.; Kumar, G. S.; Kapur, M., *Eur. J. Org. Chem.*, **2017**, *2017*, 5439-5459.
34. Muthukumar, A.; Sangeetha, S.; Sekar, G., *Org. Biomol. Chem.* **2018**, *16*, 7068-7083.
35. Bisht, R.; Hoque, M. E.; Chattopadhyay, B., *Angew. Chem. Int. Ed.* **2018**, *57*, 15762-15766.
36. Kalepu, J.; Pilarski, L. T., *Molecules* **2019**, *24*, 830.

37. Zheng, Q.; Liu, C. F.; Chen, J.; Rao, G. W., *Adv. Synth. Catal.* **2020**, *362*, 1406-1446.
38. Moselage, M.; Li, J.; Ackermann, L., *ACS Catal.* **2016**, *6*, 498-525.
39. Chandra, D.; Manisha; Sharma, U., *Chem. Rec.* **2022**, *22*, e202100271.
40. Sarkar, W.; Bhowmik, A.; Mishra, A.; Vats, T. K.; Deb, I., *Adv. Synth. Catal.* **2018**, *360*, 3228-3232.
41. Ueno, R.; Natsui, S.; Chatani, N., *Org. Lett.*, **2018**, *20*, 1062-1065.
42. Liu, S. K.; Cui, X. F.; Liu, X. X.; Ma, H. J.; Wei, D. D.; Luo, X. L.; Huang, G. S., *ChemistrySelect* **2018**, *3*, 3989-3992.
43. Zhang, L. B.; Hao, X. Q.; Zhang, S. K.; Liu, Z. J.; Zheng, X. X.; Gong, J. F.; Niu, J. L.; Song, M. P., *Angew. Chem. Int. Ed.* **2015**, *54*, 272-275.
44. Kawamata, Y.; Yan, M.; Liu, Z.; Bao, D. H.; Chen, J.; Starr, J. T.; Baran, P. S., *J. Am. Chem. Soc.* **2017**, *139*, 7448-7451.
45. Harry, N. A.; Saranya, S.; Ujwaldev, S. M.; Anilkumar, G., *Catal. Sci. Technol* **2019**, *9*, 1726-1743.
46. Khake, S. M.; Chatani, N., *Chem* **2020**, *6*, 1056-1081.
47. Chatani, N., *Acc. Chem. Res.* **2023**, *56*, 3053-3064.
48. Rajesh, N.; Sundararaju, B., *Asian J. Org. Chem.* **2018**, *7*, 1368-1371.
49. Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C., *Chem. Rev.* **2013**, *113*, 6234-6458.
50. Yang, F.; Li, J.; Xie, J.; Huang, Z.-Z., *Org. Lett.* **2010**, *12*, 5214-5217.
51. Wang, F.; Hu, Q.; Shu, C.; Lin, Z.; Min, D.; Shi, T.; Zhang, W., *Org. Lett.*, **2017**, *19*, 3636-3639.
52. Li, G. J.; Pan, Y. L.; Liu, Y. L.; Xu, H. F.; Chen, J. Z., *Org. Lett.*, **2019**, *21*, 1740-1743.
53. Wang, F.; Li, X.; Li, Z.; Zhou, S.; Zhang, W., *ACS Omega* **2019**, *4*, 331-343.
54. Wei, Q.; Ma, Y.; Dong, Y.; Liu, G., *Org. Lett.*, **2020**, *22*, 5796-5800.
55. Shan, C.; Zhu, L.; Qu, L. B.; Bai, R.; Lan, Y., *Chem. Soc. Rev.* **2018**, *47*, 7552-7576.
56. Xu, X.; Cui, X., In *Handbook of CH-Functionalization*, pp 1-39.
57. Duarah, G.; Kaishap, P. P.; Begum, T.; Gogoi, S., *Adv. Synth. Catal.* **2019**, *361*, 654-672.
58. Singh, K. S., *Catal.* **2019**, *9*, 173.
59. Gramage-Doria, R.; Bruneau, C., *Coord. Chem. Rev.* **2021**, *428*, 213602.
60. Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H., *Chem. Rev.* **2012**, *112*, 5879-5918.
61. Yang, F.; Ackermann, L., *Org. Lett.*, **2013**, *15*, 718-720.
62. Massignan, L.; Tan, X.; Meyer, T. H.; Kuniyil, R.; Messinis, A. M.; Ackermann, L.,

Angew. Chem. Int. Ed. **2020**, *59*, 3184-3189.

63. Padala, K.; Jeganmohan, M., *Chem. Eur. J.* **2014**, *20*, 4092-4097.
64. More, N. Y.; Padala, K.; Jeganmohan, M., *J. Org. Chem.* **2017**, *82*, 12691-12700.
65. Raghuvanshi, K.; Zell, D.; Ackermann, L., *Org. Lett.*, **2017**, *19*, 1278-1281.
66. Lyons, T. W.; Sanford, M. S., *Chem. rev.* **2010**, *110 2*, 1147-69.
67. He, J.; Wasa, M.; Chan, K. S. L.; Shao, Q.; Yu, J. Q., *Chem. Rev.* **2017**, *117*, 8754-8786.
68. Ramachandiran, K.; Sreelatha, T.; Lakshmi, V. N.; Babu, H. T.; Muralidharan, D.; Perumal, T. P., *Curr. Org. Chem.* **2013**, *17*, 2001-2024.
69. Panda, P.; Pal, K.; Chakroborty, S., *Results Chem.* **2021**, *3*, 100154.
70. Dey, A.; Agasti, S.; Maiti, D., *Org. Biomol. Chem.* **2016**, *14*, 5440-5453.
71. Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J. Q., *Angew. Chem. Int. Ed.* **2009**, *48*, 5094-115.
72. Yadav, M. R.; Rit, R. K.; Sahoo, A. K., *Chem. Eur. J.* **2012**, *18*, 5541-5545.
73. Yang, L.; Li, S.; Cai, L.; Ding, Y.; Fu, L.; Cai, Z.; Ji, H.; Li, G., *Org. Lett.*, **2017**, *19*, 2746-2749.
74. Rit, R. K.; Yadav, M. R.; Sahoo, A. K., *Org. Lett.*, **2014**, *16*, 968-971.
75. Li, S.; Zhu, W.; Gao, F.; Li, C.; Wang, J.; Liu, H., *J. Org. Chem.* **2017**, *82*, 126-134.
76. Wang, G. W.; Yuan, T. T., *J. Org. Chem.* **2010**, *75*, 476-479.
77. Qiu, F. C.; Xie, Q.; Guan, B. T., *Asian J. Org. Chem.* **2018**, *7*, 107-110.
78. Li, G.; Wan, L.; Zhang, G.; Leow, D.; Spangler, J.; Yu, J. Q., *J. Am. Chem. Soc.* **2015**, *137*, 4391-4397.
79. Reddy, B. V. S.; Reddy, L. R.; Corey, E. J., *Org. Lett.*, **2006**, *8*, 3391-3394.
80. Tran, L. D.; Daugulis, O., *Angew. Chem. Int. Ed.* **2012**, *51*, 5188-5191.
81. Yu, Q. Y.; Zhong, H. M.; Sun, W. W.; Zhang, S. J.; Cao, P.; Dong, X. P.; Qin, H. B.; Liu, J. K.; Wu, B., *Asian J. Org. Chem.* **2016**, *5*, 608-612.
82. Rit, R. K.; Yadav, M. R.; Sahoo, A. K., *Org. Lett.*, **2012**, *14*, 3724-3727.
83. Chen, F. J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S. Q.; Shi, B. F., *Chem. Sci.*, **2013**, *4*, 4187-4192.
84. Wang, M.; Yang, Y.; Fan, Z.; Cheng, Z.; Zhu, W.; Zhang, A., *Chem. Commun.*, **2015**, *51*, 3219-3222.
85. Jerhaoui, S.; Djukic, J. P.; Wencel-Delord, J.; Colobert, F., *Chem. Eur. J.* **2017**, *23*, 15594-15600.
86. Zhou, L.; Lu, W., *Org. Lett.*, **2014**, *16*, 508-511.

87. Zhou, G.; Wu, D.; Snyder, B.; Ptak, R. G.; Kaur, H.; Gochin, M., *J. Med. Chem.* **2011**, *54*, 7220-7231.
88. Varun; Sonam; Kakkar, R., *Med. Chem. Comm.* **2019**, *10*, 351-368.
89. Aboul-Fadl, T.; Mohammed, F. A. H.; Hassan, E. A. S., *Arch Pharm Res* **2003**, *26*, 778-784.
90. AbdEl-Halim, H. F.; Mohamed, G. G., *J. Mol. Struct.* **2016**, *1104*, 91-95.
91. Ferraz de Paiva, R. E.; Vieira, E. G.; Rodrigues da Silva, D.; Wegermann, C. A.; Costa Ferreira, A. M., *Front. Mol. Biosci.* **2021**, *7*.
92. Kumar, S.; Nair, A. S.; Abdelgawad, M. A.; Mathew, B., *ACS Omega* **2022**, *7*, 16244-16259.
93. Galliford, C. V.; Scheidt, K. A., *Angew. Chem. Int. Ed.* **2007**, *46*, 8748-8758.
94. Smith, G.; Glaser, M.; Perumal, M.; Nguyen, Q.-D.; Shan, B.; Årstad, E.; Aboagye, E. O., *J. Med. Chem.* **2008**, *51*, 8057-8067.
95. Krishnegowda, G.; Prakasha Gowda, A. S.; Tagaram, H. R. S.; Carroll, K. F. S. O.; Irby, R. B.; Sharma, A. K.; Amin, S., *Bioorg. Med. Chem.* **2011**, *19*, 6006-6014.
96. Glaser, M.; Goggi, J.; Smith, G.; Morrison, M.; Luthra, S. K.; Robins, E.; Aboagye, E. O., *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6945-6949.
97. Prakash, C. R.; Raja, S., *Eur. J. Med. Chem.* **2011**, *46*, 6057-6065.
98. Prakash, C. R.; Raja, S., *J Saudi Chem Soc.* **2013**, *17*, 337-344.
99. Zhang, Y.; Wang, R.; Zhang, T.; Yan, W.; Chen, Y.; Zhang, Y.; Zhou, M., *Chin. Chem. Lett.* **2019**, *30*, 653-655.
100. Kakkar, R. V. S., *Med. Chem. Commun.*, **2019**, *10*, 351.
101. Bridges, T. M.; Kennedy, J. P.; Cho, H. P.; Breininger, M. L.; Gentry, P. R.; Hopkins, C. R.; Conn, P. J.; Lindsley, C. W., *Bioorg. Med. Chem. Lett.* **2010**, *20*, 558-562.
102. Ewang-Emukowhate, M.; Nair, D.; Caplin, M., *Int. J. Endocr. Oncol.* **2019**, *6*, IJE17.
103. Du, F.; Zhou, Q.; Sun, W.; Yang, C.; Wu, C.; Wang, L.; Chen, G., *Molecules* **2020**, *25*, 2059.
104. Varun; Sonam; Kakkar, R., *Med. Chem. Commun.*, **2019**, *10*, 351-368.
105. Tang, B. X.; Song, R. J.; Wu, C. Y.; Liu, Y.; Zhou, M. B.; Wei, W. T.; Deng, G. B.; Yin, D. L.; Li, J. H., *J. Am. Chem. Soc.* **2010**, *132*, 8900-8902.
106. Satish, G.; Polu, A.; Ramar, T.; Ilangovan, A., *J. Org. Chem.* **2015**, *80*, 5167-5175.
107. Wang, C.; Liu, L., *Org. Chem. Front.* **2021**, *8*, 1454-1460.
108. Jaegli, S.; Dufour, J.; Wei, H. l.; Piou, T.; Duan, X. H.; Vors, J. P.; Neuville, L.; Zhu, J., *Org. Lett.* **2010**, *12*, 4498-4501.

109. Sun, J.; Liu, B.; Xu, B., *RSC Adv.*, **2013**, *3*, 5824-5827.
110. Wang, Y.; Cheng, X.; Zhan, Z.; Ma, X.; Nie, R.; Hai, L.; Wu, Y., *RSC Adv.* **2016**, *6*, 2870-2874.
111. Zeng, R.; Dong, G., *J. Am. Chem. Soc.* **2015**, *137*, 1408-1411.
112. Liu, Y.; Xia, Y. T.; Cui, S. H.; Ji, Y. G.; Wu, L., *Adv. Synth. Catal.* **2020**, *362*, 2632-2636.
113. Pawar, A. P.; Yadav, J.; Mir, N. A.; Iype, E.; Rangan, K.; Anthal, S.; Kant, R.; Kumar, I., *Chem. Commun.* **2021**, *57*, 251-254.
114. Chen, Q.; Teng, Y.; Xu, F., *Org. Lett.* **2021**, *23*, 4785-4790.
115. Klein, J. E. M. N.; Taylor, R. J. K., *Eur. J. Org. Chem.* **2011**, *2011*, 6821-6841.
116. Mohammadi Ziarani, G.; Moradi, R.; Lashgari, N., *Tetrahedron* **2018**, *74*, 1323-1353.
117. Saranya, P. V.; Neetha, M.; Aneeja, T.; Anilkumar, G., *RSC Adv.*, **2021**, *11*, 7146-7179.
118. Shen, J.; Zhang, L.; Meng, X., *Org. Chem. Front.* **2021**, *8*, 6433-6451.
119. Luo, J.; Zhao, Y.; Xu, X.; Zheng, J.; Liang, H., *Tetrahedron Lett.* **2017**, *58*, 4591-4594.
120. Luo, J.; Gao, S.; Ma, Y.; Ge, G., *Synlett* **2018**, *29*, 969-973.
121. Zhuang, W.; Zhang, J.; Ma, C.; Wright, J. S.; Zhang, X.; Ni, S. F.; Huang, Q., *Org. Lett.* **2022**, *24*, 4229-4233.
122. Robinson, B., *Chem. Rev.* **1963**, *63*, 373-401.
123. Cacchi, S.; Fabrizi, G., *Chem. Rev.* **2011**, *111*, PR215-PR283.
124. Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A. K.; Choi, E. H., *Molecules* **2013**, *18*, 6620-6662.
125. Kumar, S.; Ritika., *Future J. Pharm. Sci.* **2020**, *6*, 121.
126. Enthaler, S.; Company, A., *Chem. Soc. Rev.* **2011**, *40*, 4912-4924.
127. Cao, T.; Deitch, J.; Linton, E. C.; Kozlowski, M. C., *Angew. Chem. Int. Ed.* **2012**, *51*, 2448-2451.
128. Taskesenligil, Y.; Saracoglu, N., *Synthesis* **2023**, *55*, 3417-3433.
129. Kumar, P.; Nagtilak, P. J.; Kapur, M., *New J. Chem.* **2021**, *45*, 13692-13746.
130. Leitch, J. A.; Bhonoah, Y.; Frost, C. G., *ACS Catal.* **2017**, *7*, 5618-5627.
131. Huw M. L. D.; Daniel M., *J. Org. Chem.* **2016**, *81*, 343-350.
132. Silin Chen, Y. Y., Chao Chen., Congyang Wang., *Chinese J. Org. Chem.* **2023**, *43*, 1-16.
133. Zhou, Y.; Chen, G.; Li, C.; Liu, X.; Liu, P., *Synth. Commun.* **2018**, *48*, 2912-2922.
134. Wei, P.; Zhu, Y.; Ying, J.; Wu, X. F., *J. Org. Chem.* **2023**, *88*, 6274-6280.
135. Okada, T.; Nobushige, K.; Satoh, T.; Miura, M., *Org. Lett.* **2016**, *18*, 1150-1153.
136. Zhou, X. Y.; Chen, X.; Lei, Y. Z., *Synth. Commun.* **2021**, *51*, 943-951.

137. Mutule, I.; Suna, E.; Olofsson, K.; Pelcman, B., *J. Org.Chem.* **2009**, *74*, 7195-7198.
138. Choy, P. Y.; Lau, C. P.; Kwong, F. Y., *J. Org. Chem.* **2011**, *76*, 80-84.
139. Song, J.; Cui, J.; Liang, H.; Liu, Q.; Dong, Y.; Liu, H., *Asian J. Org. Chem.* **2018**, *7*, 341-345.
140. Jin, L.; Zhang, X. L.; Guo, R. L.; Wang, M. Y.; Gao, Y. R.; Wang, Y. Q., *Org. Lett.* **2021**, *23*, 1921-1927.
141. Singh, A.; Dey, A.; Pal, K.; Dash, O. P.; Volla, C. M. R., *Org. Lett.* **2022**, *24*, 1941-1946.
142. Lin, F.; Chen, Y.; Wang, B.; Qin, W.; Liu, L., *RSC Adv.* **2015**, *5*, 37018-37022.
143. Lei, H.; Wang, L.; Xu, Z.; Ye, T., *Org. Lett.* **2017**, *19*, 5134-5137.
144. Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E., *J. Am. Chem. Soc.* **2008**, *130*, 5858-5859.
145. Bera, A.; Kabadwal, L. M.; Bera, S.; Banerjee, D., *Chem. Commun.* **2022**, *58*, 10-28.
146. Cai, Y.; Zhu, S. F.; Wang, G. P.; Zhou, Q. L., *Adv. Synth. Catal.* **2011**, *353*, 2939-2944.
147. Li, Y.; Wang, W. H.; Yang, S. D.; Li, B. J.; Feng, C.; Shi, Z. J., *Chem. Commun.* **2010**, *46*, 4553-4555.

1.6 OBJECTIVES OF THE PRESENT STUDY

In the last few years, significant efforts have been devoted to the C–H oxygenation of amides and indole derivatives and dimerization of indoles using palladium and other 3d metal catalysts. However, most of the presented methods require harsh reaction conditions, using activated substrates, bidentate directing groups, or stoichiometric amount catalysts. Hence, the objective of the present work was to develop environmentally benign, efficient and novel protocols for the C–H oxygenation of amides and indole derivatives. In particular, C–H oxygenations of amide and indole derivatives are significant, as they are considered privileged structural motifs in many biologically active compounds and natural products. Furthermore, the dimerization of indoles at less reactive C–H bonds was another objective of the present work.

The results obtained from the present study are discussed in Chapters 2 to 5. Chapter 2 establishes a palladium-catalyzed acetoxylation of C(sp^2)−H and C(sp^3)−H bonds in simple amides, which proceeds *via* weak chelation assistance. This reaction provides a direct method for synthesizing diversely functionalized, pharmaceutically relevant acetoxy-amides while tolerating sensitive functionalities. Kinetic isotopic effect studies have highlighted that the C−H activation is the rate-limiting step. A gram-scale reaction and further functionalization into alcohols, tertiary amines, and acids demonstrate the synthetic utility.

Chapter 3 describes the direct oxygenation of C(sp^2)−H and C(sp^3)−H bonds in isatins using a palladium catalyst. This chapter discusses that using $PhI(OAc)_2$ or selectfluor oxidant in the Pd-catalyzed protocol in a 1.0 M acidic solution exclusively provides C5 oxygenation of isatins via electrophilic palladation. However, when the same reaction employs $K_2S_2O_8$ in a dilute solution (0.13 M), it selectively affords *N*-methyl C(sp^3)–H oxygenation through carbonyl-assisted intramolecular *N*-CH_3 C(sp^3)–H radical palladation. The synthetic utility of this oxygenation is exemplified by performing a gram-scale reaction, and further derivatization is demonstrated by synthesizing diverse oxygenated isatins with sensitive functionalities, including biologically relevant compounds.

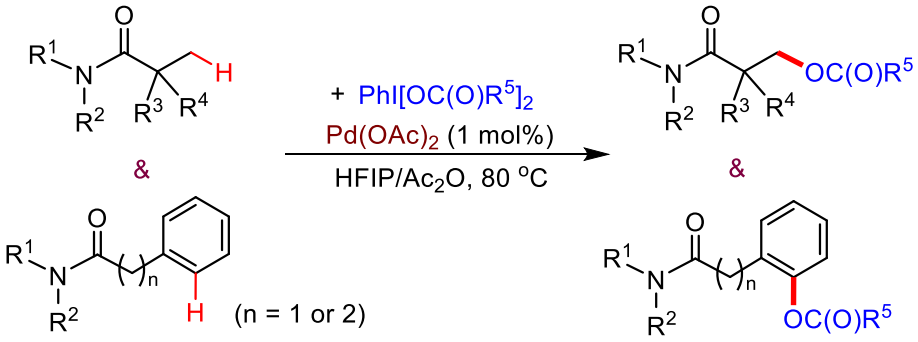
Further, Chapter 4 discusses the C(4)–H fluoroalkoxylation of indoles using a palladium catalyst. This reaction exhibits high regioselectivity, leading to the selective C4-fluoroalkoxylation of indoles, while C3 benzoyl is used as a directing group. Notable features of this transformation include the selective formation of a six-membered palladacycle and excellent tolerance for various functional groups.

Chapter 5 discusses a strategic approach to unprecedented intermolecular C(2)−H/ C(7)−H oxidative coupling of indoles using a palladium catalyst. The reaction exhibited high regioselectivity for the intermolecular C(2)−H/C(7)−H dimerization of indoles when pyridine

was employed as a directing group. Notable features of this protocol include broad substrate scope and outstanding tolerance for diverse functional groups.

Chapter 2

Palladium-Catalyzed Acetoxylation of C(sp^2)–H and C(sp^3)–H Bonds in Amides



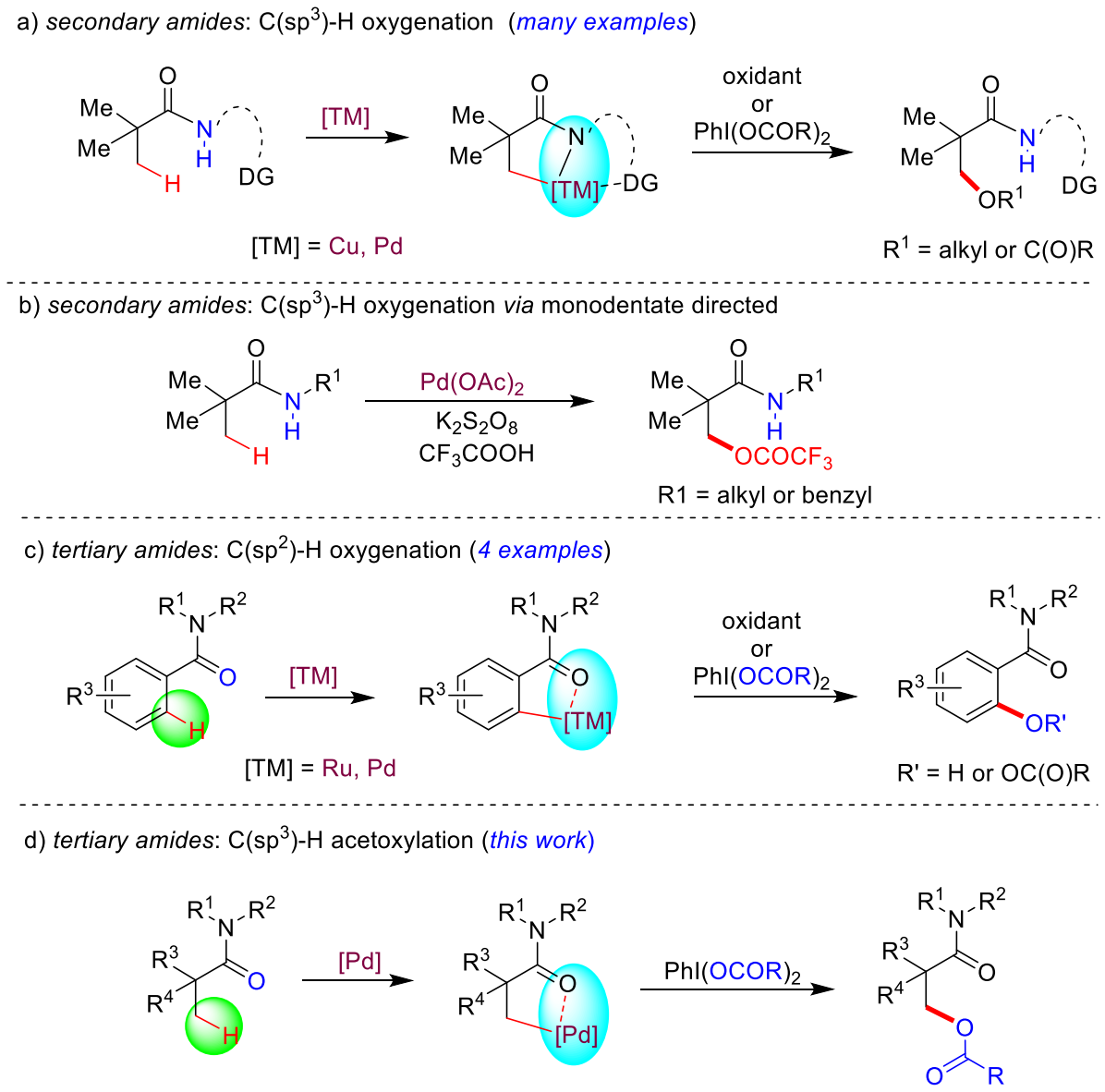
This chapter has been adapted from the publication "Pd(II)-Catalyzed Chemoselective Acetoxylation of C(sp^2)−H and C(sp^3)−H Bonds in Tertiary Amides" **Vijaykumar**, **M** and Punji, B. *J. Org. Chem*. **2021**, *86*, 8172–8181.

2.1 INTRODUCTION

Transition-metal-catalyzed C–H bond functionalization has emerged as an elegant and effective tool for molecular sciences, empowering application towards pharmaceuticals and functional materials. In this context, the directing group-assisted C–H oxygenation has been recognized as a robust technique for constructing chemo- and regioselective C–O bonds.[1] Amide being a versatile functional group with an easy transformative tendency into useful functionalities like carboxylic acid and aldehyde, the selective C–H oxygenation of amide-containing substrates becomes imperative. In that direction, with the support of monodentate or bidentate auxiliaries, diverse C–O bond formations such as alkoxylation,[2-9] acetoxylation,[10,11] acyloxylation,[12-18] and hydroxylation[19] of C(sp^2)–H bond on aromatic amides have been extensively studied. Most of these oxygenations are particularly demonstrated for the primary and secondary amides, wherein the strong coordination of *N*-amidate facilitates the C–H activation by instigating thermodynamically stable metallacycle. Moreover, several research groups have independently demonstrated the *β*-C(sp^3)–H acyloxylation/alkoxylation with the help of strong *N*-coordination by introducing 8-aminoquinolinyl,[20-23] 2-(pyridine-2-yl)isopropyl (PIP),[2] picolinamide,[24] sulfoximine[25] and sulfinyl aniline[26] directing groups (Scheme 2.1a).[27-29] Similarly, Lu has demonstrated the C(sp^3)–H acyloxylation of secondary amides *via* -CONHR coordination (Scheme 2.1b).[30] Unfortunately, this protocol failed to give acyloxylation of tertiary amides. Recently, Yu disclosed a palladium-catalyzed *β*-C(sp^3)–H acyloxylation of free carboxylic acids, wherein a well-designed mono-*N*-protected *β*-amino acid ligand is essential.[31]

Though the C(sp^2)–H and C(sp^3)–H oxygenations for strongly coordinating secondary amide (–CONHR) is well known, the oxygenation of unactivated *β*-C(sp^3)–H bond on privileged and multi-functional tertiary amides with a weakly coordinating group (C=O) is less explored.[32] The primary difficulty associated with the weaker coordinating directing groups is the hardship in generating less favored cyclometallated intermediate.[33-41] Nevertheless, the groups of Ackermann,[42-43] Jeganmohan[44,] and Yu[45] have independently established the C(sp^2)–H oxygenation of tertiary benzamides (Scheme 2.1c). In contrast, thus far, the unactivated C(sp^3)–H oxygenation of native tertiary amides by weak coordination assistance is unprecedented, and attempts were unsuccessful. Considering all these aspects and challenges, in this chapter, we discuss the palladium-catalyzed selective C(sp^3)–H acetoxylation of tertiary amides under relatively mild conditions that proceeds *via* a weakly

coordinated *O*-chelation (Scheme 2.1d). Notable features of this protocol are (i) C(sp^3)–H and C(sp^2)–H acetoxylation of tertiary amides, (ii) low catalyst loading and mild conditions, (iii) excellent regio- and chemoselectivity, and (iv) a preliminary reaction mechanism.



Scheme 2.1 C(sp^2)–H and C(sp^3)–H Bonds Oxygenation on Amides

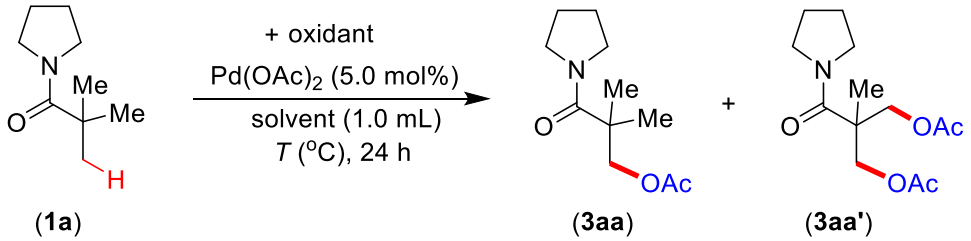
2.2 RESULTS AND DISCUSSION

2.2.1 Optimization of Reaction Parameters

The screening of reaction parameters for the acetoxylation of C(sp^3)–H bond in tertiary amide, 2,2-dimethyl-1-(pyrrolidin-1-yl)propan-1-one (**1a**) with diacetoxyiodobenzene (**2a**) was initiated employing $Pd(OAc)_2$ as a catalyst (Table 2.1). The reaction could afford both

the mono acetoxylated product 2,2-dimethyl-3-oxo-3-(pyrrolidin-1-yl)propyl acetate (**3aa**) and diacetoxylated product **3aa'** in 44% and 12% yields, respectively, when the reaction was performed in the acetic acid solvent at 120 ^{o}C (Table 2.1, entry 1). Notably, the reaction in the mixture of AcOH and Ac_2O (9:1) improved the yield and selectivity of mono acetoxylation to 68% (entry 2). Relatively mild inorganic oxidants, such as $Na_2S_2O_8$, $K_2S_2O_8$, and AgOAc, were less effective and provided moderate yield (35-56%) of **3aa** (entries 3-7). The use of other Pd(II) or Pd(0) precursors, such as $PdCl_2$, $Pd(cod)Cl_2$, $Pd_2(dba)_3$, $Pd(PPh_3)_4$ as catalysts afforded low to a moderate yield (entry 8-11). The acetoxylation reaction in toluene, DCE or methanol solvents was inefficient, whereas the reaction in TFA/TFAA led to the decomposition of **1a** (entries 12-15). Notably, the acetoxylation in the solvent HFIP/Ac_2O resulted in quantitative conversion, and **3aa** was isolated in a 69% yield (entries 16, 17). Surprisingly, upon lowering the reaction temperature to 80 ^{o}C in the HFIP/Ac_2O solvent system, the reaction provided 94% of **3aa** with high selectivity for monoacetoxylation (entry 18). The acetoxylation progressed effortlessly even with 1.0 mol% loading of $Pd(OAc)_2$ (entry 19); however, further lowering of catalyst loading to 0.5 mol% led to low conversion (entry 20). The employment of low catalyst loading is significant and could be beneficial for large-scale synthesis. The use of 2.0 equiv of $PhI(OAc)_2$ in place of 3.0 equiv resulted in incomplete conversion (entry 21). The reaction proceeded smoothly even with 0.7 mL of solvent and 20 h of reaction time (entries 22, 23). The acetoxylation failed in the absence of an external oxidant or Pd catalyst (entries 24, 25), indicating the essential role of these components. Thus, the optimal reaction conditions were found to be as follows: **1a** (0.3 mmol), **2a** (0.9 mmol), $Pd(OAc)_2$ (1 mol%) in HFIP/Ac_2O (0.7 mL) at 80 ^{o}C for 20 h.

Table 2.1 Optimization of Reaction Parameters. [a]



Entry	[Pd]	Oxidant	*T* (°C)	Solvent	Yield (%)[b]	
					3aa	**3aa'**
1	$Pd(OAc)_2$	$PhI(OAc)_2$	120	AcOH	47 (44)	12
2	$Pd(OAc)_2$	$PhI(OAc)_2$	120	$AcOH/Ac_2O$	70 (68)	8
3	$Pd(OAc)_2$	$K_2S_2O_8$	120	$AcOH/Ac_2O$	42	--
4	$Pd(OAc)_2$	$Na_2S_2O_8$	120	$AcOH/Ac_2O$	56	--
5	$Pd(OAc)_2$	AgOAc	120	$AcOH/Ac_2O$	35	--
6	$Pd(OAc)_2$	Oxone	120	$AcOH/Ac_2O$	16	2
7	$Pd(OAc)_2$	$Cu(OAc)_2$	120	$AcOH/Ac_2O$	15	--
8	$PdCl_2$	$PhI(OAc)_2$	120	$AcOH/Ac_2O$	53 (51)	5
9	$Pd_2(dba)_3$	$PhI(OAc)_2$	120	$AcOH/Ac_2O$	23	8
10	$Pd(cod)Cl_2$	$PhI(OAc)_2$	120	$AcOH/Ac_2O$	42	2
11	$Pd(PPh_3)_4$	$PhI(OAc)_2$	120	$AcOH/Ac_2O$	43	3
12	$Pd(OAc)_2$	$PhI(OAc)_2$	120	Toluene	25	--
13	$Pd(OAc)_2$	$PhI(OAc)_2$	120	MeOH	--	--
14	$Pd(OAc)_2$	$PhI(OAc)_2$	120	DCE	4	5
15	$Pd(OAc)_2$	$PhI(OAc)_2$	120	TFA/TFAA	--	--
16	$Pd(OAc)_2$	$PhI(OAc)_2$	120	HFIP	65 (62)	10
17	$Pd(OAc)_2$	$PhI(OAc)_2$	120	$HFIP/Ac_2O$	72 (69)	8
18	$Pd(OAc)_2$	$PhI(OAc)_2$	80	$HFIP/Ac_2O$	98 (94)	--
19[c]	$Pd(OAc)_2$	$PhI(OAc)_2$	80	$HFIP/Ac_2O$	97 (93)	--
20[d]	$Pd(OAc)_2$	$PhI(OAc)_2$	80	$HFIP/Ac_2O$	57	--
21[c,e]	$Pd(OAc)_2$	$PhI(OAc)_2$	80	$HFIP/Ac_2O$	86 (83)	--
22[c,f]	$Pd(OAc)_2$	$PhI(OAc)_2$	80	$HFIP/Ac_2O$	95 (94)	--
23[c,f,g]	**$Pd(OAc)_2$**	**$PhI(OAc)_2$**	**80**	**$HFIP/Ac_2O$**	**96 (93)**	--
24	$Pd(OAc)_2$	--	80	$HFIP/Ac_2O$	--	--

25	--	$PhI(OAc)_2$	80	$HFIP/Ac_2O$	--	--

[a] Reaction Conditions: 2,2-Dimethyl-1-(pyrrolidin-1-yl)propan-1-one (**1a**; 0.047 g, 0.30 mmol), oxidant (0.90 mmol), [Pd] (0.015 mmol, 5.0 mol%), solvent (1.0 mL). [b] GC yield using *n*-dodecane as internal standard, isolated yield is in parenthesis. [c] 1.0 mol% of $Pd(OAc)_2$ was used. [d] 0.5 mol% of $Pd(OAc)_2$ was used. [e] 2 equiv of $PhI(OAc)_2$ was used. [f] Reaction performed for 20 h. [g] Solvent (0.7 mL; HFIP:Ac_2O = 9:1, v/v). HFIP = Hexafluoro-2-propanol.

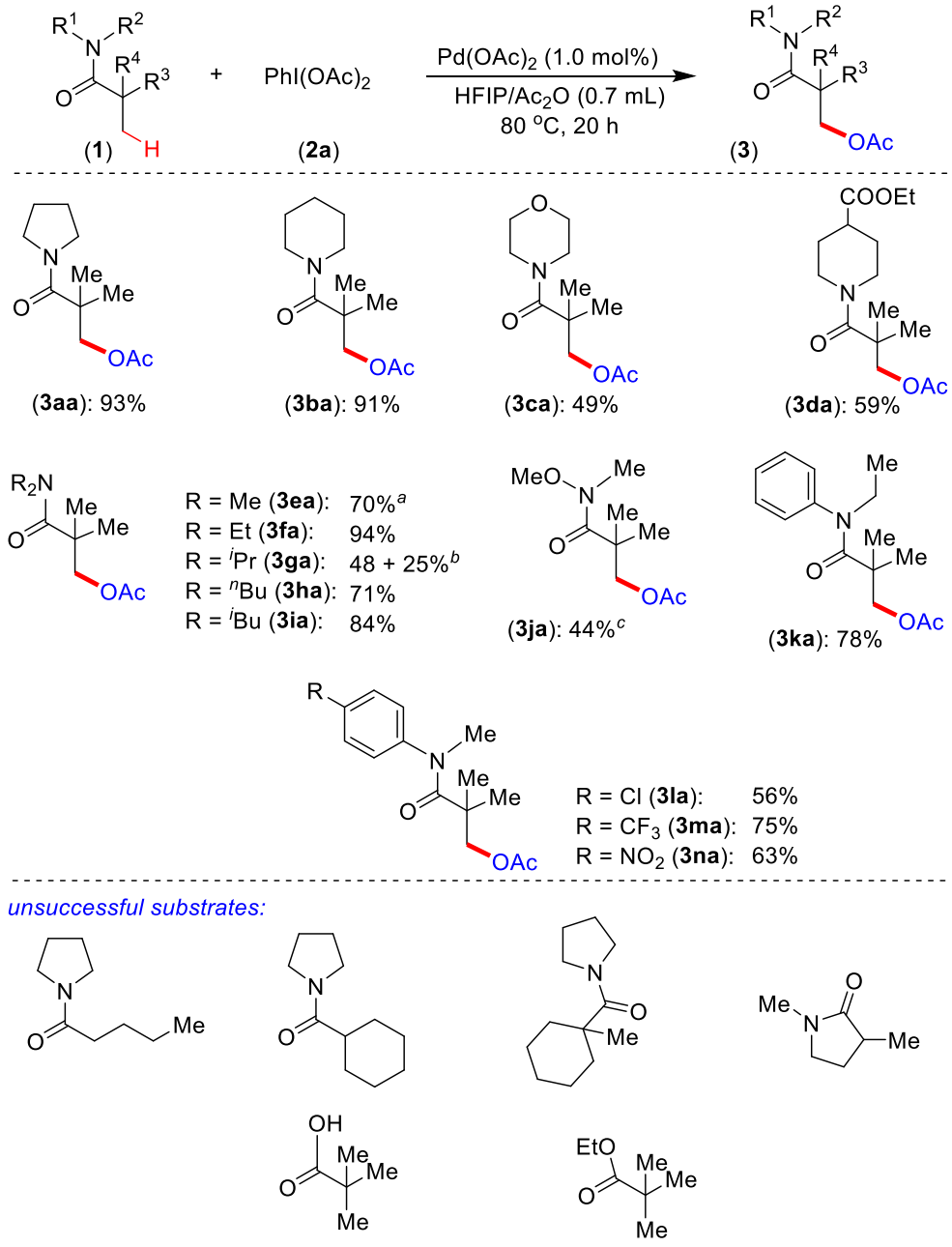
2.2.2 Scope for Acetoxylation of Tertiary Amides

After successfully optimizing the reaction parameters for the Pd-catalyzed C(sp^3)–H acetoxylation of the tertiary amide with $PhI(OAc)_2$, we have investigated the scope and limitations of acetoxylation of diverse aliphatic as well as aromatic amides. First, various *N*,*N*-disubstituted pivalamides were tested for the acetoxylation with $PhI(OAc)_2$ (Scheme 2.2). Amides with cyclic substituents, such as pyrrolidinyl, piperidinyl pivalamides, gave excellent yields of desired acetoxylated products (**3aa**, **3ba**). The pivalamides containing morpholinyl and ester groups were tolerated under the reaction conditions and provided 49% and 59% yields (**3ca**, **3da**), respectively. Simple dialkyl amides with varying steric underwent the acetoxylation to generate the *β*-acetoxy amides, **3ea**-**3ia**, in good to excellent yields.

Notably, the *N*,*N*-diisopropylpivalamide (**1g**) afforded a significant amount of diacetoxylated compound **3ga'** (25%) in addition to the mono-acetoxylated **3ga**. The steric feature of isopropyl on amide might help bring a second methyl group of the mono-acetoxylated product (**3ga**) close to the palladium center for further functionalization. It should be noted that the acetoxylation of *N*,*N*-dialkyl substituted tertiary amides using Pd was previously unsuccessful.[30] The Weinreb amide **1j** provided acetoxylated product **3ja** in 44% yield at 120 ^oC. The aryl-substituted pivalamides also reacted smoothly, affording desired acetoxylated compounds in good yields (**3ka**-**3na**). Synthetically essential functionalities, such as −Cl, $-CF_3$, and $-NO_2$ groups, were well tolerated under the reaction conditions. Interestingly, except for **1g**, the diacetoxylation was not detected or observed only in a negligible amount in most of the pivalamides. Moreover, acetoxylation of the C(sp^3)–H bonds on *N*-alkyl substituents of amide was not observed, even though a five-membered palladacycle involving this carbon center is feasible. Remarkably, the acetoxylation of methylene C(sp^3)–H bond on tertiary amides and cyclic amides was unsuccessful (Scheme

2.2). Similarly, simple carboxylic acid and esters were failed to undergo acetoxylation under the present conditions.

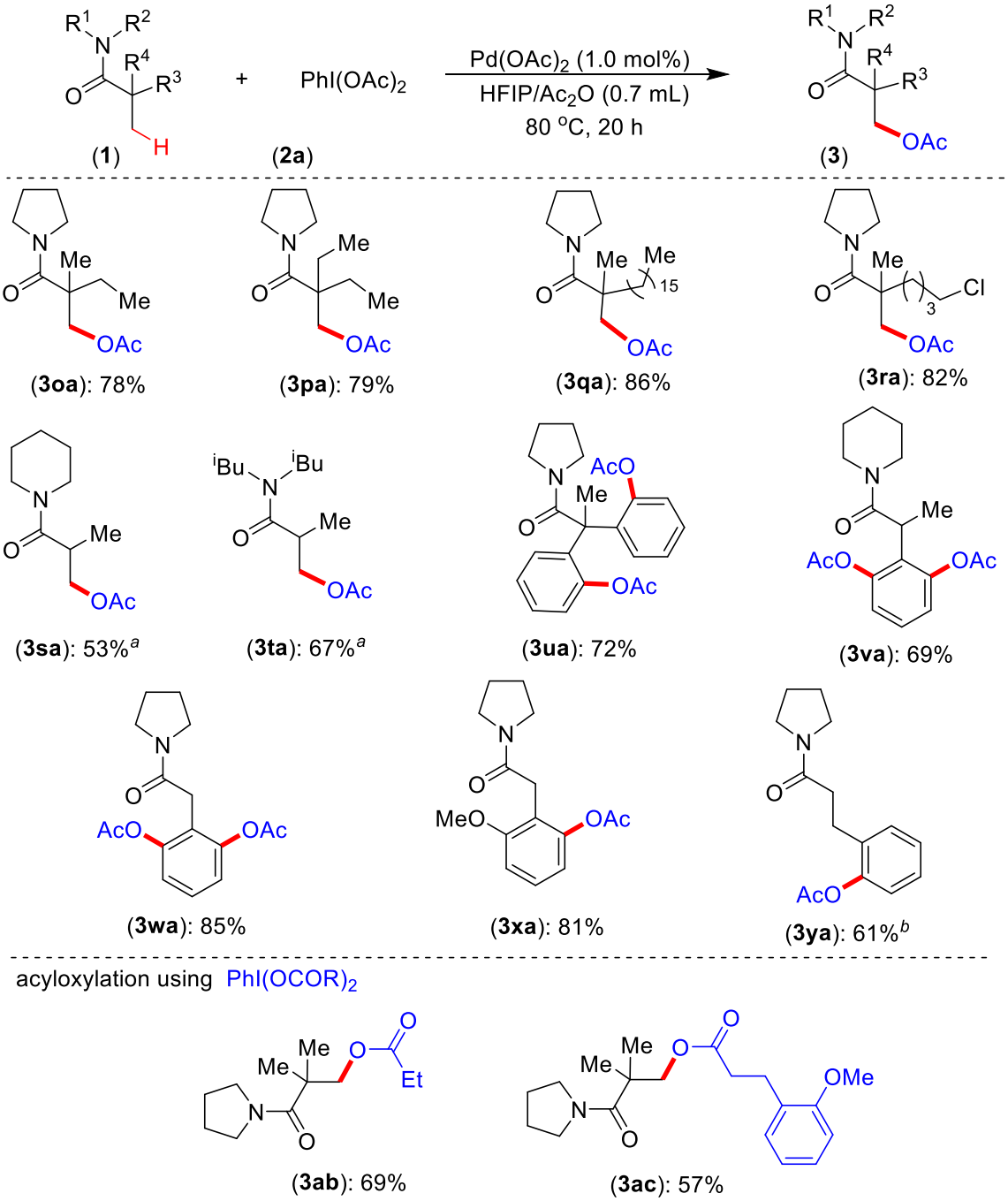
The acetoxylation protocol was applied to the tertiary amides bearing a methyl group and two different alkyl substituents (Scheme 2.3). Notably, the present protocol was selective for the acetoxylation of the primary β-C(sp^3)−H bond over the γ- or δ-C(sp^3)−H bonds or the secondary β-C(sp^3)−H (methylene) bond of amides (**3oa-3ra**). The long alkyl chain and aliphatic halide substituents like chloride were tolerated and provided an excellent yield of products, **3qa** and **3ra**. The *iso*-butyramide containing piperidinyl and di-*iso*-butyl substituents afforded **3sa** and **3ta** in 53% and 67% yields, respectively, albeit at an elevated temperature of 120 ^{o}C. When both the β-C(sp^3)−H and γ-C(sp^2)−H bonds were present on amides (**1u**, **1v**), the γ-C(sp^2)−H bonds selectively acetoxylated over β-C(sp^3)−H bond (**3ua**, **3va**). We have extended this protocol to the C(sp^2)–H acetoxylation of phenyl acetyl amide and pyrrolidine hydrocinnamic amide to achieve an excellent yield of mono or diacetoxylation (**3wa-3ya**). The distal remote *ortho* C–H bond acetoxylation, **3ya**, is notable under the present reaction protocol.



Scheme 2.2 *β*-C(sp^3)–H Acetoxylation of Tertiary Amides. Conditions: Substrate **1** (0.30 mmol), **2a** (0.29 g, 0.9 mmol), HFIP:Ac_2O (9:1, 0.7 mL). [a] NMR yield. [b] Diacetoxylated compound was obtained in 25%. [c] Reaction was performed at 120 °C.

The current methodology was further extended to the acyloxylation using diversely substituted iodonium oxidants, $PhI(OCOR)_2$ (Scheme 2.3). Thus, the acyloxylated compounds, 2,2-dimethyl-3-oxo-3-(pyrrolidin-1-yl)propyl propionate (**3ab**) and 2,2-dimethyl-3-oxo-3-(pyrrolidin-1-yl)propyl 3-(2-methoxyphenyl)propanoate (**3ac**) were synthesized in good yields using desired iodonium salts under the optimized conditions.

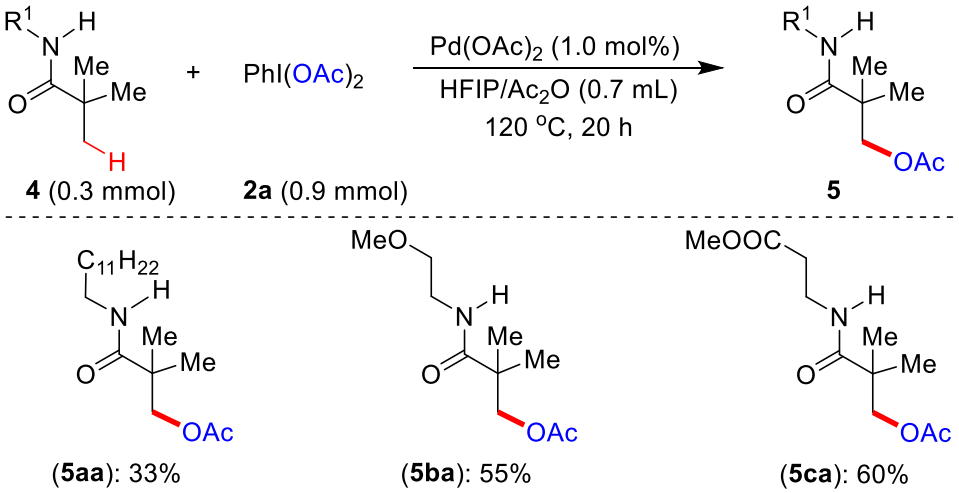
Notably, we did not observe acetoxylated (-OAc) products in these reactions, though Ac_2O was used in the reaction.



Scheme 2.3 Scope for C(sp^3)–H and C(sp^2)–H Acyloxylation of Tertiary Amides. Conditions: Substrate **1** (0.30 mmol), **2a** (0.29 g, 0.9 mmol), HFIP:Ac_2O (9:1, 0.7 mL). [a] Reaction performed at 120 °C. [b] NMR yield.

2.2.3 Scope for Acetoxylation of Secondary Amides

The substrate scope could be expanded to the acetoxylation of β-C(sp^3)–H bonds on secondary amides (Scheme 2.4). Thus, the secondary pivalamides with *N*-alkyl, methoxy-alkyl, and alkyl-ester substituents underwent acetoxylation at 120 ^oC to produce desired products in moderate to good yields. Remarkably, tertiary amides reactivity is superior to the secondary pivalamides, as seen from the product yields and employed reaction conditions.

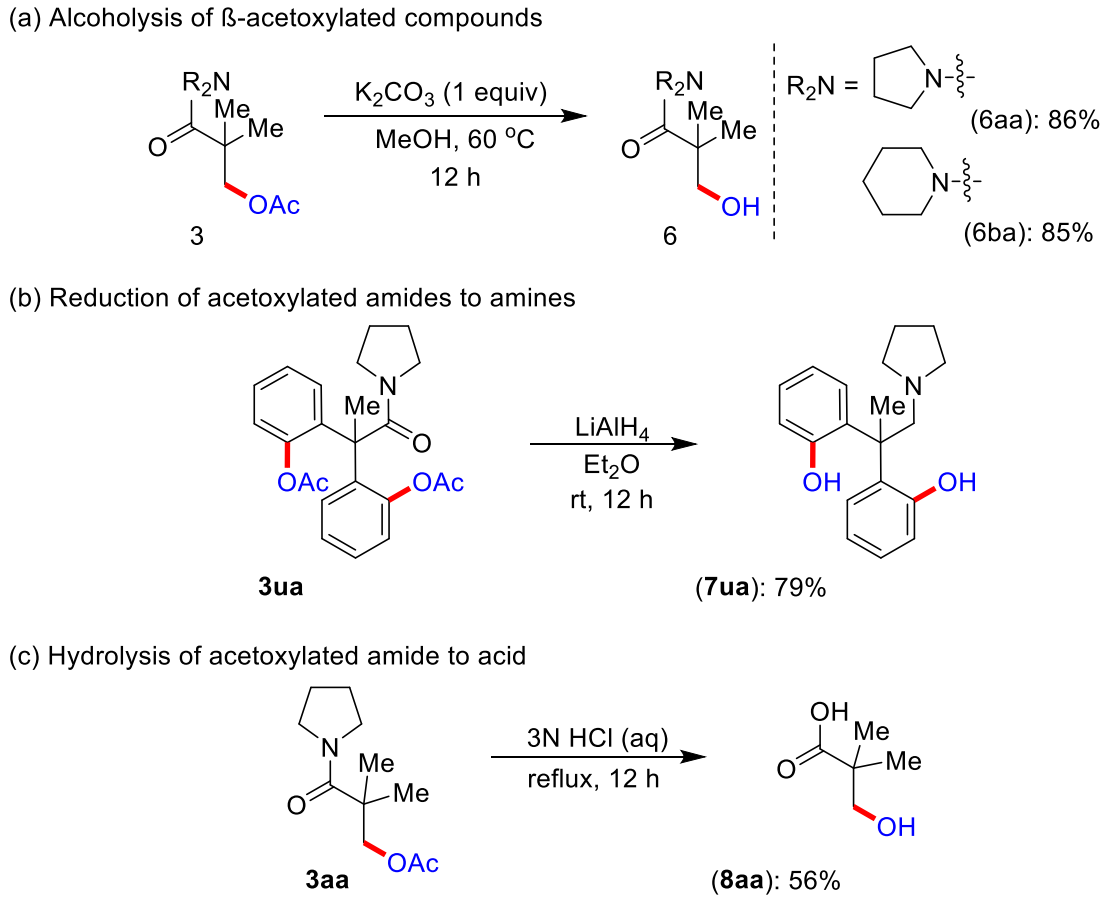


Scheme 2.4 Scope for β-C(sp^3)–H Acetoxylation of Secondary Amides.

A gram-scale acetoxylation reaction was performed to demonstrate the practical utility of this Pd-catalyzed method. Thus, the treatment of 1.2 g substrate **1a** with $PhI(OAc)_2$ (7.46 g) under the standard reaction conditions using 1.0 mol% of $Pd(OAc)_2$ and HFIP:Ac_2O [9:1] (25.0 mL) afforded 1.41 g (86%) of **3aa**.

2.2.4 Synthetic Utility and Mechanistic Perspective

We have demonstrated the synthetic utility of acetoxylated tertiary amides by converting them into valuable compounds. The acetyl group of **3aa** and **3ba** was smoothly removed by treating with K_2CO_3 in methanol to achieve β-hydroxy amides **6aa** and **6ba** in 86% and 85% yields, respectively (Scheme 2.5a). The acetoxylated amide **3ua** can be reduced to hydroxylamine **7ua** in 79% by $LiAlH_4$ in diethyl ether (Scheme 2.5b). Pleasingly, the acetoxylated amide **3aa** was hydrolyzed with HCl (3 N) at 100 ^oC to afford 3-hydroxy-2,2-dimethyl-propanoic acid (**8aa**) in 56% yield (Scheme 2.5c).[25] These transformations highlight the importance of acetoxylated tertiary amides in generating privileged functionalities.



Scheme 2.5 Functionalizations of Acetoxylated Amides.

2.2.5 Probable Catalytic Cycle

The mechanism of the Pd-catalyzed acetoxylation reaction using $PhI(OAc)_2$ is well precedented.[52-56] Controlled studies suggested that the Pd(II) is a much effective catalyst than the Pd(0), tentatively highlighting the direct participation of a Pd(II) species. Independent reaction rates determination using amide **1p** and [D]-**1p** provided a significant kinetic isotopic effect (KIE; k_H/k_D = 5.6) (Figure 2.1), which supports the probable involvement of C–H bond activation in the rate-limiting step.[57] Based on our preliminary study, and with the support of literature precedents,[52-56] we assume that the reaction begins with tertiary amide coordination to Pd(II) species through carbonyl-oxygen followed by the C–H cleavage leading to an alkyl-Pd(II) intermediate **A** (Figure 2.2). Next, the oxidation of Pd(II) to Pd(IV) by $PhI(OAc)_2$ would result in the formation of intermediate **B**.[58-59] Subsequent reductive elimination of **3** will lead to the regeneration of Pd(II) for further catalysis.

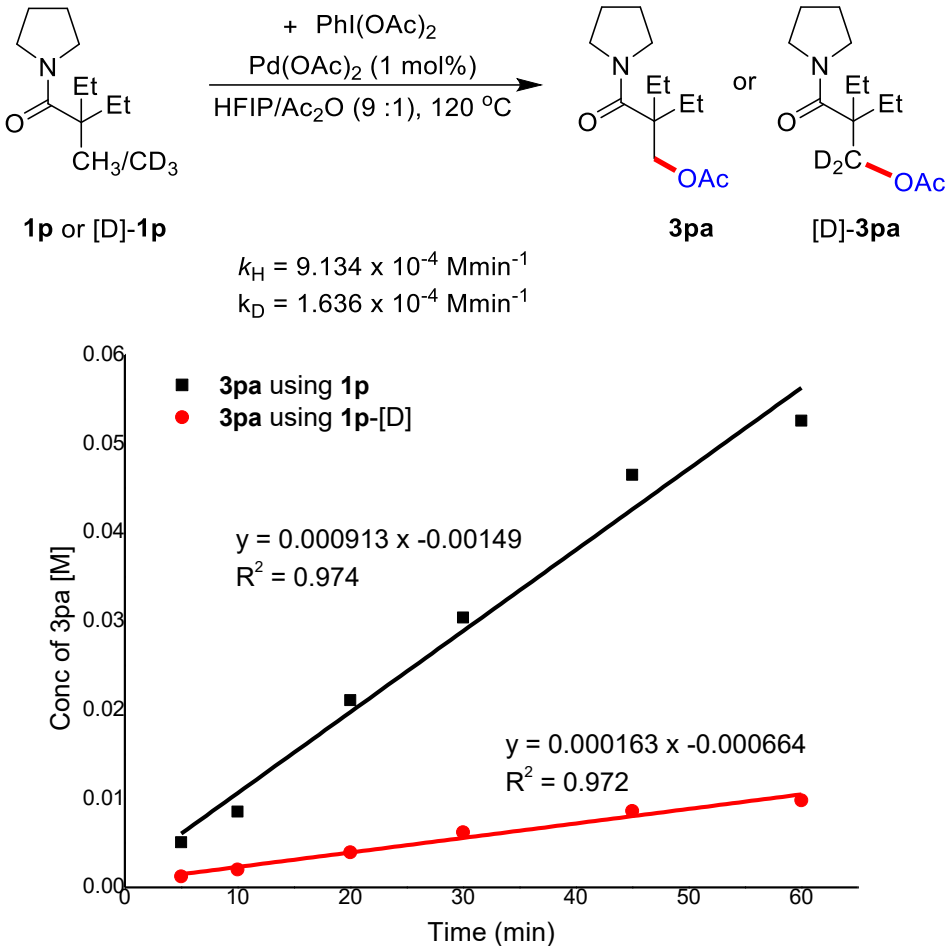


Figure 2.1 Time-dependent Formation of **3pa** using Substrates **1p** and [D]-**1p.**

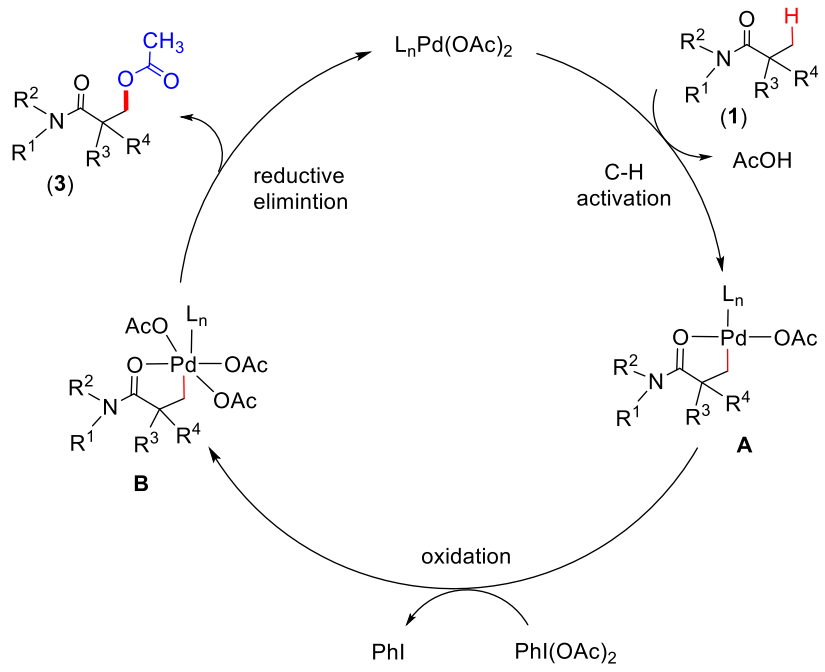


Figure 2.2 Plausible Reaction Mechanism.

2.3 CONCLUSION

In summary, we have developed a Pd(II)-catalyzed protocol for the chemoselective C(sp^2)–H and C(sp^3)–H acetoxylation of diverse tertiary amides through the weak coordination of the C=O group. Notably, the reaction uses a low loading of palladium, unlike the precedented strong *N*-chelating acetoxylation that employs a substantial loading of Pd (> 5 mol%). The reaction demonstrated the tolerability of synthetically important functionalities, like chloro, fluoro-alkyl, fluoro-arene, ester, and nitro groups, in addition to the heterocycles. The synthetic utility is demonstrated by a gram-scale reaction and further functionalization into alcohols, tertiary amines, and alcohol-acids. A preliminary KIE study indicated that the C–H activation step is rate-limiting.

2.4 EXPERIMENTAL SECTION

2.4.1 General Information

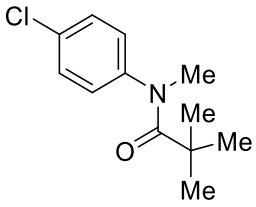
All manipulations were conducted under an argon atmosphere either in a glove box or using standard Schlenk techniques in pre-dried glasswares. The catalytic reactions were performed in flame-dried reaction vessels with a Teflon screw cap. Solvents were dried over Na/benzophenone or CaH_2 and distilled prior to use. Liquid reagents were flushed with argon prior to use. The secondary and tertiary amides,[29] and iodonium salts[41] were synthesized according to the previously described procedures. High-resolution mass spectrometry (HRMS) mass spectra were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump. NMR: (^{1}H and ^{13}C) spectra were recorded at 400 or 500 MHz (^{1}H), 100 or 125 MHz {^{13}C, DEPT (distortionless enhancement by polarization transfer)}, 377 MHz (^{19}F), respectively in $CDCl_3$ solutions, if not otherwise specified; chemical shifts (δ) are given in ppm. The ^{1}H and ^{13}C NMR spectra are referenced to residual solvent signals ($CDCl_3$: δ H = 7.26 ppm, δ C = 77.2 ppm).

GC Method. Gas Chromatography analyses were performed using a Shimadzu GC-2010 gas chromatograph equipped with a Shimadzu AOC-20s autosampler and a Restek RTX-5 capillary column (30 m x 0.25 mm x 0.25 μm). The instrument was set to an injection volume of 1 μL, an inlet split ratio of 10:1, and inlet and detector temperatures of 250 and 320 ^{o}C, respectively. UHP-grade argon was used as carrier gas with a 30 mL/min flow rate. The temperature program used for all the analyses is as follows: 80 °C, 1 min; 30 ^{o}C/min to 200 ^{o}C, 2 min; 30 ^{o}C/min to 260 ^{o}C, 3 min; 30 ^{o}C/min to 300 ^{o}C, 3 min. Response factors for

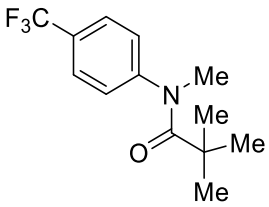
all the necessary compounds with respect to standard *n*-dodecane were calculated from the average of three independent GC runs.

2.4.2 Synthesis and Characterization of Starting Compounds

***Representative Procedure A*. Synthesis of *N*-(4-chlorophenyl)-*N*-methylpivalamide (1l):** In an oven-dried Schlenk flask, a solution of *N*-(4-chlorophenyl)pivalamide (1.0 g, 4.72 mmol) in DMF (10 mL) was slowly added to NaH (60% dispersion in mineral oil, 0.283 g, 7.10 mmol) in DMF (5.0 mL) at 0 ^{o}C, and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was further cooled to 0 ^{o}C, and iodomethane (1.01 g, 7.11 mmol) was added dropwise. The resultant reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched with the addition of NH_4Cl (aq), and diluted with EtOAc, and washed with water and brine. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude residue was purified by column chromatography on neutral alumina (petroleum ether/EtOAc: 10/1), and yielded **1l** (0.81 g, 76%) as a white solid. M.p = 83-85 ^{o}C.

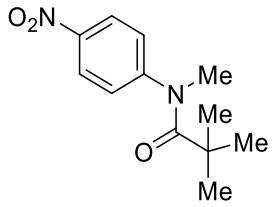


***N*-(4-chlorophenyl)-*N*-methylpivalamide (1l):** ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37-7.34 (m, 2H), 7.17-7.14 (m, 2H), 3.18 (s, 3H), 1.04 (s, 9H). $^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$): δ = 178.2, 144.0, 133.7, 130.3, 129.7, 41.5, 41.0, 29.6. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{16}NOCl$ 226.0993; Found 226.0994.



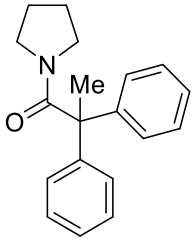
***N*-Methyl-*N*-(4-(trifluoromethyl)phenyl)pivalamides (1m):** The representative procedure **A** was followed, using *N*-(4-(trifluoromethyl)phenyl)pivalamide (1.0 g, 4.10 mmol), NaH (60%; 0.245 g, 6.12 mmol), and iodomethane (0.87 g, 6.12 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 10/1) yielded **1m**

(0.72 g, 68%) as a white solid. M.p = 83-85 ^{o}C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.66 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 3.23 (s, 3H), 1.06 (s, 9H). $^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$): δ = 178.2, 148.8, 130.0, 129.3, 126.6, 123.9, 41.4, 41.1, 29.6. ^{19}F-NMR (377 MHz, $CDCl_3$): δ = –62.5 (s). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{16}NOF_3$ 260.1257; Found 260.1254.

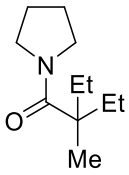


***N*-Methyl-*N*-(4-nitrophenyl)pivalamides (1n):** The representative procedure **A** was followed, using *N*-(4-nitrophenyl)pivalamide (1.0 g, 4.50 mmol), NaH (60%; 0.270 g, 6.75 mmol), and iodomethane (0.96 g, 6.75 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 10/1) yielded **1n** (0.80 g, 75%) as yellow solid. M.p = 101-103 ^{o}C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.25 (d, J = 9.2 Hz, 2H), 7.38 (d, J = 9.2 Hz, 2H), 3.26 (s, 3H), 1.10 (s, 9H). $^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$): δ = 178.2, 151.5, 146.6, 129.3, 124.9, 41.1, 41.0, 29.4. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{16}N_2O_3$ 237.1234; Found 237.1232.

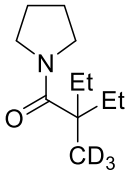
***Representative Procedure B*. Synthesis of 2,2-Diphenyl-1-(pyrrolidin-1-yl)propan-1-one (1u):** To a stirring solution of 2,2-diphenylpropanoic acid (1.0 g, 4.42 mmol) and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.93 g, 4.86 mmol) in CH_2Cl_2 (20 mL) was added pyrrolidine (0.40 mL, 4.86 mmol) and 4-(dimethylamino)pyridine (0.027 g, 0.22 mmol, 5 mol%). The reaction was allowed to stir at room temperature for 24 h. The reaction was quenched with water (15 mL) and extracted with ethyl acetate (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in *vacuo*. The crude residue was purified by column chromatography on neutral alumina (petroleum ether/EtOAc: 10/1) yielded **1u** (0.88 g, 71%) as a white solid. M. p = 115-117 ^{o}C.



2,2-Diphenyl-1-(pyrrolidin-1-yl)propan-1-one (1u): ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.36-7.23 (m, 10H), 3.62 (vt, J = 7.3 Hz, 2H), 2.53 (t, J = 6.5 Hz, 2H), 1.92 (s, 3H), 1.74-1.67 (m, 2H), 1.60-1.54 (m, 2H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 173.4, 143.4, 128.5, 128.2, 126.7, 57.6, 48.0, 47.8, 31.8, 26.7, 23.5. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{21}NO$ 280.1696; Found 280.1695.

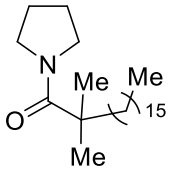


2-Ethyl-2-methyl-1-(pyrrolidin-1-yl)butan-1-one (1p): The representative procedure **B** was followed, using 2-ethyl-2-methylbutanoic acid (0.50 g, 3.84 mmol), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimidehydrochloride (0.81 g, 4.22 mmol) and pyrrolidine (0.35 mL, 4.22 mmol), 4-(dimethylamino)pyridine (0.023 g, 0.19 mmol, 5 mol%). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 10/1) yielded **1p** (0.61 g, 87%) as a light yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.50 (vt, J = 6.9 Hz, 4H), 1.80-1.71 (m, 6H), 1.44-1.35 (m, 2H), 1.14 (s, 3H), 0.81 (t, J = 7.6 Hz, 6H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 175.0, 48.1, 47.5, 31.1, 27.6, 23.2, 22.5, 9.2. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{21}NO$ 184.1701; Found 184.1698.

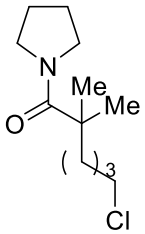


2-Ethyl-2-(methyl-d$_3$)-1-(pyrrolidin-1-yl)butan-1-one ([D]-1p): The representative procedure **B** was followed, using 2-ethyl-2-deuterated methylbutanoic acid (0.50 g, 3.75 mmol) and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.79 g, 4.13 mmol), pyrrolidine (0.34 mL, 4.13 mmol) and 4-(dimethylamino)pyridine (0.023 g, 0.188 mmol, 5 mol%). Purification by column chromatography on neutral alumina (petroleum

ether/EtOAc: 10/1) yielded [D]-**1p** (0.57 g, 82%) as a light yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.51 (vt, J = 6.7 Hz, 4H), 1.80-1.71 (m, 6H), 1.44-1.35 (m, 2H), 0.82 (t, J = 7.5 Hz, 6H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 175.1, 48.0, 47.3, 31.1, 27.4, 23.1, 21.6, 9.2. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{18}D_3NO$ 187.1813; Found 187.1808.

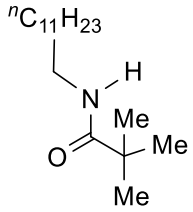


2,2-Dimethyl-1-(pyrrolidin-1-yl)octadecan-1-one (1q): The representative procedure **B** was followed, using 2,2-dimethyloctadecanoic acid (0.50 g, 1.60 mmol) and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.34 g, 1.76 mmol), 4-(dimethylamino)pyridine (0.0098 g, 0.08 mmol, 5 mol%) and pyrrolidine (0.145 mL, 1.76 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 10/1) yielded **1q** (0.42 g, 72%) as a light yellow liquid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.52 (br s, 4H), 1.86-1.81 (m, 4H), 1.56-1.53 (m, 2H), 1.30-1.24 (m, 28H), 1.22 (s, 6H), 0.87 (t, J = 6.9 Hz, 3H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 176.0, 47.6, 42.9, 40.2, 32.1, 30.5, 29.9, 29.7, 29.6, 26.4, 25.1, 22.9, 14.3. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{47}NO$ 366.3730; Found 366.3739.

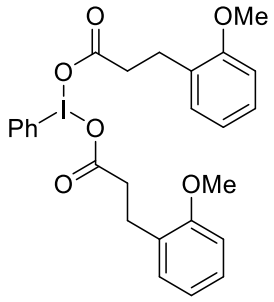


6-Chloro-2,2-dimethyl-1-(pyrrolidin-1-yl)hexan-1-one (1r): The representative procedure **B** was followed, using 6-chloro-2,2-dimethylhexanoic acid (0.50 g, 2.80 mmol) and *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.60 g, 3.08 mmol), 4-(dimethylamino)pyridine (0.019 g, 0.154 mmol, 5 mol%) and pyrrolidine (0.25 mL, 3.08 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 10/1) yielded **1r** (0.55 g, 85%) as a light yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.52-3.49 (m, 6H), 1.94-1.80 (m, 4H), 1.77-1.70 (m, 2H), 1.59-1.54 (m, 2H), 1.42-1.35 (m, 2H), 1.22 (s, 6H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 175.5, 48.0, 44.9, 42.7, 39.7, 33.2,

26.1, 22.4. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{22}NOCl$ 232.1463; Found 232.1469.



Synthesis of *N*-n-dodecylpivalamide (4a): In an oven-dried Schlenk flask, pivaloyl chloride (0.80 mL, 6.50 mmol) was dissolved in DCM (20 mL), and *n*-dodecylamine (1.0 g, 5.40 mmol) and triethylamine (1.5 mL, 10.80 mmol) in DCM (10 mL) were added dropwise at 0 ^oC. The reaction mixture was warm to room temperature and was stirred for 8 h. Upon completion of the reaction, the organic layer was washed with 0.1 M HCl (aq) and $NaHCO_3$ (aq). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in *vacuo*. The crude residue was purified by column chromatography on neutral alumina (petroleum ether/EtOAc: 10/1) yielded **4a** (1.30 g, 89%) as a white solid. M.p = 38-40 ^oC. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.61 (br s, 1H), 3.22 (q, J = 6.6, 2H), 1.50-1.46 (m, 2H), 1.29-1.23 (m, 18H), 1.18 (s, 9H), 0.87 (t, J = 6.8 Hz, 3H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 178.5, 39.8, 38.8, 32.1, 29.8, 29.8, 29.7, 29.5, 27.8, 27.1, 22.9, 14.3. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{35}NO$ 270.2791; Found 270.2790.

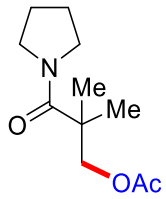


Synthesis of phenyl-iodanediyl bis(3-(2-methoxyphenyl)propanoate) (2c): In a round bottom flask, $PhI(OAc)_2$ (3.23 g, 10.03 mmol) and (2-methoxyphenyl)propanoic acid (3.61 g, 20.06 mmol) were dissolved in $CHCl_3$ (20 mL), and heated at 50 °C for 3 h. At ambient temperature, the volatiles were evaporated under reduced pressure, and the resulting solid was washed with a cold solvent mixture (pentane : CH_2Cl_2 = 10 : 1). The colorless solid was dried under high vacuum to yield **2c**, which was used without further purification. Yield: 3.56 g (63%). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.98-7.95 (m, 2H), 7.56 (tt, J = 7.5, 1.5 Hz,

1H), 7.45 (vt, *J* = 7.7 Hz, 2H), 7.18 (td, *J* = 7.8, 1.6 Hz, 2H), 7.08 (dd, *J* = 7.5, 1.7 Hz, 2H), 6.86-6.80 (m, 4H), 3.78 (s, 6H), 2.87 (vt, *J* = 7.7 Hz, 4H), 2.57 (vt, *J* = 7.7 Hz, 4H). $^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$): δ = 178.6, 157.6, 137.7, 135.0, 131.7, 131.0, 130.1, 129.3, 127.6, 120.5, 110.3, 55.3, 34.1, 27.0. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{27}O_6I$ 563.0925; Found 563.0871.

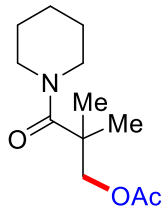
2.4.3 Procedure for Acetoxylation of Amides

***Representative Procedure C*. Synthesis of 2,2-Dimethyl-3-oxo-3-(pyrrolidin-1-yl)propyl acetate (3aa):** To an oven-dried screw-cap tube equipped with magnetic stir bar were introduced 2,2-dimethyl-1-(pyrrolidin-1-yl)propan-1-one (**1a**; 0.047 g, 0.302 mmol), $PhI(OAc)_2$ (0.292 g, 0.908 mmol), $Pd(OAc)_2$ (0.00068 g, 0.00302 mmol, 1.0 mol%; from a stock solution in HFIP) and HFIP/Ac_2O (9:1; 0.7 mL). The resultant reaction mixture was immersed in a preheated oil bath at 80 ^{o}C and stirred for 20 h. The reaction mixture was allowed to cool to room temperature, and all the volatiles were removed under reduced pressure. The remaining residue was purified by column chromatography on neutral alumina (petroleum ether/EtOAc: 5/1) yielding **3aa** (0.060 g, 93%) as a yellow liquid.



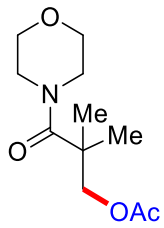
2.4.4 Characterization Data of Acetoxylated Amides

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.17 (s, 2H), 3.52 (br s, 4H), 2.03 (s, 3H), 1.84 (br s, 4H), 1.25 (s, 6H). $^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$): δ = 173.5, 171.2, 70.9, 48.1, 42.8, 27.3, 23.2, 22.5, 21.1. HRMS (ESI-TOF): *m/z* Calcd for $C_{11}H_{19}NO_3 + H^+$ $[M + H]^+$ 214.1438; Found 214.1439.

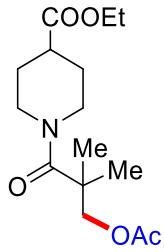


2,2-Dimethyl-3-oxo-3-(piperidin-1-yl)propyl acetate (3ba): Compound **3ba** was isolated as

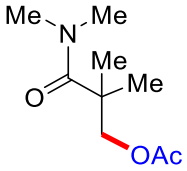
a light yellow liquid (0.062 g, 91%) by a column chromatography on neutral alumina (eluents: petroleum ether/ ethyl acetate = 5/1); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.15 (s, 2H, CH_2), 3.52 (vt, J = 5.3 Hz, 4H), 2.03 (s, 3H), 1.64-1.59 (m, 2H), 1.55-1.49 (m, 4H), 1.27 (s, 6H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 173.3, 171.3, 71.2, 46.2, 42.4, 26.2, 24.7, 23.1, 21.1. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{21}NO_3$ 228.1594; Found 228.1595.



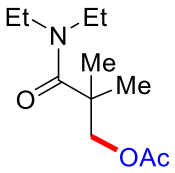
2,2-Dimethyl-3-morpholino-3-oxopropyl acetate (3ca): Compound **3ca** was isolated as a light yellow liquid (0.034 g, 49%) by column chromatography on neutral alumina (eluents: petroleum ether/ ethyl acetate = 5/1); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.16 (s, 2H), 3.68-3.63 (m, 8H), 2.06 (s, 3H), 1.29 (s, 6H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 173.8, 171.2, 70.9, 67.0, 45.8, 42.4, 23.2, 21.1. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{19}NO_4$ 230.1387; Found 230.1386.



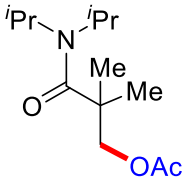
Ethyl-1-(3-acetoxy-2,2-dimethylpropanoyl)piperidine-4-carboxylate (3da): Compound **3da** was isolated as a light yellow liquid (0.053 g, 59%) by column chromatography on neutral alumina (eluents: petroleum ether/ ethyl acetate = 5/1); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.22 (d, J = 13.5 Hz, 2H), 4.14 (s, 2H), 4.12-4.09 (m, 2H), 2.96 (t, J = 12.2 Hz, 2H), 2.54-2.49 (m, 1H), 2.03 (s, 3H), 1.90 (d, J = 12.5 Hz, 2H), 1.63 (q, J = 10.9 Hz, 2H), 1.27 (s, 6H), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 174.3, 173.5, 171.2, 71.1, 60.7, 44.5, 42.4, 41.2, 28.4, 23.1, 21.1, 14.3. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{25}NO_5$ 300.1805; Found 300.1807.



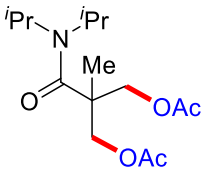
3-(Dimethylamino)-2,2-dimethyl-3-oxopropyl acetate (3ea): Compound **3ea** was (70%, ^{1}H NMR yield; a volatile compound). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.19 (s, 2H), 3.04 (s, 6H), 2.06 (s, 3H), 1.30 (s, 6H). $^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$): δ = 174.8, 171.3, 71.2, 42.5, 38.4, 23.1, 21.2. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_9H_{17}NO_3$ 188.1281; Found 188.1282.



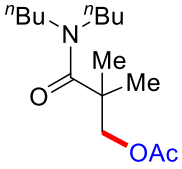
3-(Diethylamino)-2,2-dimethyl-3-oxopropyl acetate (3fa): Compound **3fa** was isolated as a light yellow liquid (0.061 g, 94%) by column chromatography on neutral alumina (eluents: petroleum ether/ ethyl acetate = 5/1); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.16 (s, 2H), 3.37 (q, J = 6.8 Hz, 4H), 2.04 (s, 3H), 1.27 (s, 6H), 1.12 (t, J = 7.0 Hz, 6H). $^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$): δ = 173.8, 171.2, 71.4, 42.7, 41.7, 23.3, 21.1, 13.5. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{21}NO_3$ 216.1595; Found 216.1594.



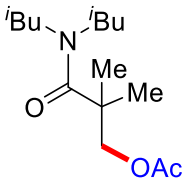
3-(Diisopropylamino)-2,2-dimethyl-3-oxopropyl acetate (3ga): Compound **3ga** was isolated as a light yellow solid (0.035 g, 48%) by column chromatography on neutral alumina (eluents: petroleum ether/ ethyl acetate = 5/1); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.24 (br s, 1H), 4.15 (s, 2H), 3.28 (br s, 1H), 2.05 (s, 3H), 1.38 (d, J = 5.3 Hz, 6H), 1.27 (s, 6H), 1.19 (d, J = 6.2 Hz, 6H). $^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$): δ = 173.4, 171.3, 71.4, 48.2, 47.0, 43.1, 23.3, 21.1, 20.8. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{25}NO_3$ 244.1907; Found 244.1909.



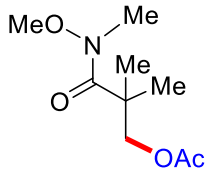
2-(Diisopropylcarbamoyl)-2-methylpropane-1,3-diyl diacetate (3ga'): Compound **3ga'** was isolated as a yellow solid (0.023 g, 25%) by a column chromatography on neutral alumina (eluents: petroleum ether/ ethyl acetate = 5/1). M.p = 66-68 ^{o}C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.31-4.14 (m, 5H), 3.31 (br s, 1H), 2.04 (s, 6H), 1.36 (br s, 6H), 1.27 (s, 3H), 1.19 (br s, 6H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 170.9, 170.3, 66.3, 47.9, 47.2, 46.6, 21.0, 20.7, 17.9. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{27}NO_5$ 302.1962; Found 302.1963.



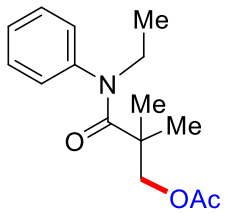
3-(Dibutylamino)-2,2-dimethyl-3-oxopropyl acetate (3ha): Compound **3ha** was isolated as a light yellow liquid (0.058 g, 71%) by column chromatography on neutral alumina (eluents: petroleum ether/ ethyl acetate = 5/1);. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.16 (s, 2H), 3.28 (t, *J* = 8.0 Hz, 4H), 2.04 (s, 3H), 1.55-1.47 (m, 4H), 1.34-124 (m, 4H), 1.27 (s, 6H), 0.92 (t, *J* = 7.3 Hz, 6H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 174.0, 171.3, 71.5, 47.6, 42.8, 30.4, 23.4, 21.1, 20.4, 14.1. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{29}NO_3$ 272.2220; Found 272.2223.



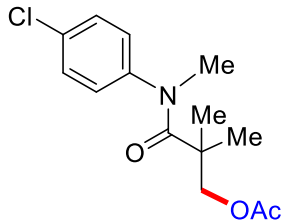
3-(Di-iso-butylamino)-2,2-dimethyl-3-oxopropyl acetate (3ia): Compound **3ia** was isolated as a light yellow liquid (0.068 g, 84%) by a column chromatography on neutral alumina (eluents: petroleum ether/ ethyl acetate = 5/1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.15 (s, 2H), 3.20 (d, *J* = 7.6 Hz, 4H), 2.01 (s, 3H), 1.98-1.91 (m, 2H), 1.28 (s, 6H), 0.85 (d, *J* = 6.9 Hz, 12H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 175.3, 171.2, 71.8, 53.1, 43.2, 26.3, 24.0, 21.1, 20.1. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{29}NO_3$ 272.2220; Found 272.2223.



3-(Methoxy(methyl)amino)-2,2-dimethyl-3-oxopropyl acetate (3ja): Compound **3ja** was isolated as a light yellow liquid (0.027 g, 44%) by a column chromatography on neutral alumina (eluents: petroleum ether/ ethyl acetate = 5/1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.20 (s, 2H), 3.68 (s, 3H), 3.19 (s, 3H), 2.05 (s, 3H), 1.27 (s, 6H). $^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$): δ = 176.1, 171.3, 70.5, 60.9, 43.4, 33.9, 22.5, 21.1. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_9H_{17}NO_4$ 204.1230; Found 204.1230.

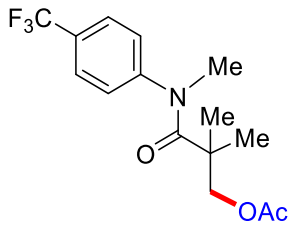


3-(Ethyl(phenyl)amino)-2,2-dimethyl-3-oxopropyl acetate (3ka): Compound **3ka** was isolated as a light yellow liquid (0.062 g, 78%) by column chromatography on neutral alumina (eluents: petroleum ether/ ethyl acetate = 5/1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.41-7.33 (m, 3H), 7.20-7.18 (m, 2H), 3.86 (s, 2H), 3.66 (q, *J* = 6.9 Hz, 2H), 2.06 (s, 3H), 1.11 (t, *J* = 6.9 Hz, 3H), 0.98 (s, 6H). $^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$): δ = 174.1, 171.0, 142.9, 129.7, 129.3, 128.4, 72.0, 48.1, 44.6, 24.7, 21.1, 12.8. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{21}NO_3$ 264.1594; Found 264.1589.

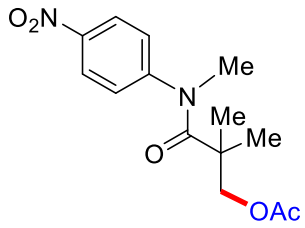


3-(4-Chlorophenyl)(methyl)amino)-2,2-dimethyl-3-oxopropyl acetate (3la): Compound **3la** was isolated as a light yellow solid (0.048 g, 56%) by a column chromatography on neutral alumina (eluents: petroleum ether/ ethyl acetate = 5/1). M.p = 39-41 ^{o}C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 3.93 (s, 2H), 3.19 (s, 3H), 2.06 (s, 3H), 1.00 (s, 6H). $^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$): δ = 175.0, 171.0, 143.2, 134.2, 130.0, 129.8, 71.9, 44.5, 41.6, 24.6, 21.1. HRMS (ESI-TOF) *m/z*: $[M + H]^+$

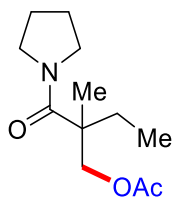
Calcd for $C_{14}H_{18}NClO_3$ 284.1048; Found 284.1045.



2,2-Dimethyl-3-(methyl(4-(trifluoromethyl)phenyl)amino)-3-oxopropyl acetate (3ma): Compound **3ma** was isolated as a light yellow liquid (0.071 g, 75%) by column chromatography on neutral alumina (eluents: petroleum ether/ ethyl acetate = 5/1); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H), 3.97 (s, 2H), 3.24 (s, 3H), 2.07 (s, 3H), 1.01 (s, 6H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 175.0, 170.9, 148, 130.5, 129 1, 126.8, 123.8, 71.9, 44.6, 41.5, 24.6, 21.1. ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −62.5 (s). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{18}NF_3O_3$ 318.1312; Found 318.1307.

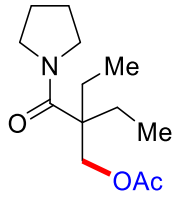


2,2-Dimethyl-3-(methyl(4-nitrophenyl)amino)-3-oxopropyl acetate (3na): Compound **3na** was isolated as a light yellow solid (0.056 g, 63%) by a column chromatography on neutral alumina (eluents: petroleum ether/ ethyl acetate = 5/1). M.p = 78-80 ^{o}C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.28 (d, J = 9.2 Hz, 2H), 7.43 (d, J = 9.2 Hz, 2H), 4.01 (s, 2H), 3.28 (s, 3H), 2.08 (s, 3H), 1.06 (s, 6H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 175.1, 170.9, 150.8, 147.0, 129.3, 125.1, 71.8, 44.8, 41.3, 24.6, 21.1. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{18}N_2O_5$ 295.1288; Found 295.1283.

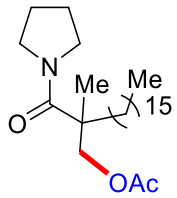


2-Methyl-2-(pyrrolidine-1-carbonyl)butyl acetate (3oa): Compound **3oa** was isolated as a

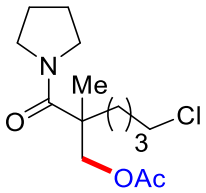
light yellow liquid (0.053 g, 78%) by column chromatography on neutral alumina (eluents: petroleum ether/ ethyl acetate = 5/1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.28 (d, J = 11.1 Hz, 1H), 4.12 (d, J = 11.1 Hz, 1H), 3.51 (vt, J = 6.2 Hz, 4H), 2.02 (s, 3H), 1.86-1.83 (m, 4H), 1.75-1.66 (m, 1H), 1.58-1.49 (m, 1H), 1.24 (s, 3H), 0.83 (t, J = 7.5 Hz, 3H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ =172.7, 171.2, 68.9, 47.1, 46.9, 27.6, 21.1, 20.8, 8.9. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{21}NO_3$ 228.1594; Found 228.1595.



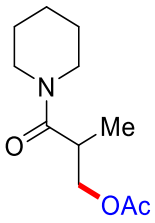
2-Ethyl-2-(pyrrolidine-1-carbonyl)butyl acetate (3pa): Compound **3pa** was isolated as a light yellow liquid (0.057 g, 79%) by column chromatography on neutral alumina (eluents: petroleum ether/ ethyl acetate = 5/1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.32 (s, 2H), 3.53 (t, J = 6.8 Hz, 4H), 2.04 (s, 3H), 1.85 (br s, 4H), 1.68-1.61 (m, 4H), 0.83 (t, J = 7.5 Hz, 6H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 172.3, 171.1, 63.6, 50.8, 47.7, 27.5, 25.5, 23.1, 21.2, 8.9. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{23}NO_3$ 242.1756; Found 242.1747.



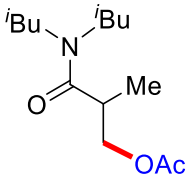
2-Methyl-2-(pyrrolidine-1-carbonyl)octadecyl acetate (3qa): Compound **3qa** was isolated as a white solid (0.109 g, 86%) by a column chromatography on neutral alumina (eluents: petroleum ether/ ethyl acetate = 5/1). M.p = 43-45 ^{o}C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.32 (d, J = 11.1 Hz, 1H, CH_2), 4.11 (d, J = 11.1 Hz, 1H), 3.53 (br s, 4H), 2.04 (s, 3H), 1.86 (br s, 4H), 1.69-1.62 (m, 1H), 1.52-1.45 (m, 1H), 1.28-1.23 (m, 31H), 0.87 (t, J = 6.8 Hz, 3H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 173.1, 171.3, 69.3, 47.9, 46.7, 35.1, 32.09, 30.3, 29.9, 29.8, 29.8, 29.7, 29.6, 29.5, 24.4, 22.9, 21.4, 21.2, 14.3. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{49}NO_3$ 424.3785; Found 424.3793.



6-Chloro-2-methyl-2-(pyrrolidine-1-carbonyl)hexyl acetate (3ra). Compound **3ra** was isolated as a light yellow liquid (0.071 g, 82%) by column chromatography on neutral alumina (eluents: petroleum ether/ ethyl acetate = 5/1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.28 (d, J = 11.1 Hz, 1H), 4.15 (d, J = 11.1 Hz, 1H), 3.53-3.49 (m, 6H), 2.04 (s, 3H), 1.88 (br s, 4H), 1.78-1.48 (m, 4H), 1.43-1.37 (m, 2H), 1.29 (s, 3H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 172.7, 171.2, 69.0, 47.8, 46.5, 44.7, 34.4, 32.9, 27.3, 23.3, 21.8, 21.1. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{24}NClO_3$ 290.1517; Found 290.1522.

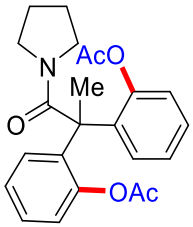


2-Methyl-3-oxo-3-(piperidin-1-yl)propyl acetate (3sa): Compound **3sa** was isolated as a light yellow liquid (0.034 g, 53%) by a column chromatography on neutral alumina (eluents: petroleum ether/ ethyl acetate = 5/1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.28-4.23 (m, 1H), 4.07-4.03 (m, 1H), 3.56-3.52 (m, 2H), 3.46-3.43 (m, 2H), 3.11-3.03 (m, 1H), 2.01 (s, 3H), 1.64-1.61 (m, 2H), 1.59-1.51 (m, 4H), 1.11 (d, J = 6.9 Hz, 3H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 172.3, 171.2, 66.7, 46.9, 43.3, 35.0, 26.9, 25.8, 24.7, 21.1, 14.6. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{19}NO_3$ 214.1438; Found 214.1438.

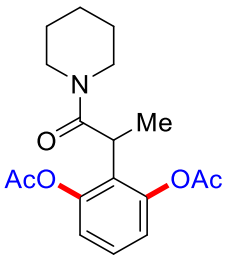


3-(Di-iso-butylamino)-2-methyl-3-oxopropyl acetate (3ta): Compound **3ta** was isolated as a light yellow liquid (0.052 g, 67%) by a column chromatography on neutral alumina (eluents: petroleum ether/ ethyl acetate = 5/1); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.24-4.19 (m, 1H), 4.09-4.05 (m, 1H), 3.26-3.20 (m, 1H), 3.13-3.02 (m, 4H), 1.99-1.95 (m, 1H), 1.97 (s, 3H), 1.90-1.85 (m, 1H), 1.08 (d, J = 6.9 Hz, 3H). 0.89 (dd, J = 6.9, 1.5 Hz, 6H), 0.84 (dd,

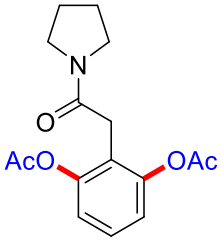
J = 6.9, 3.1 Hz, 6H). $^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$): δ = 174.4, 170.9, 67.0, 55.5, 53.8, 35.3, 28.4, 26.7, 20.9, 20.2, 20.2, 19.9, 14.7. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{27}NO_3$ 258.2064; Found 258.2065.



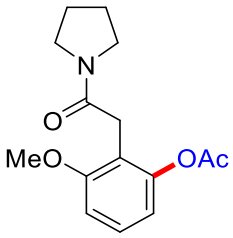
(1-Oxo-1-(pyrrolidin-1-yl)propane-2,2-diyl)bis(2,1 phenylene) diacetate (3ua): Compound **3ua** was isolated as a light yellow liquid (0.085 g, 72%) by column chromatography on neutral alumina (eluents: petroleum ether/ ethyl acetate = 5/1); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.34-7.29 (m, 2H), 7.19 (d, *J* = 7.6 Hz, 2H), 7.14-7.10 (m, 2H), 7.04-7.02 (m, 2H), 3.50 (t, *J* = 6.9 Hz, 2H), 2.42 (br s, 2H), 2.11 (s, 6H), 2.07 (s, 3H), 1.68-1.64 (m, 2H), 1.57-1.53 (m, 2H). $^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$): δ = 171.3, 169.1, 149.0, 133.7, 129.6, 128.1, 125.6, 124.7, 55.6, 48.2, 26.9, 25.9, 23.3, 21.6. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{25}NO_5$ 396.1805; Found 396.1810.



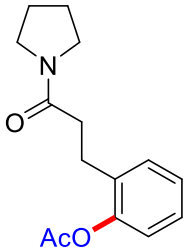
2-(1-Oxo-1-(piperidin-1-yl)propan-2-yl)-1,3-phenylene diacetate (3va): Compound **3va** was isolated as a light yellow liquid (0.069 g, 69%) by a column chromatography on neutral alumina (eluents: petroleum ether/ ethyl acetate = 5/1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.23 (t, *J* = 8.4 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 2H), 3.76 (q, *J* = 7.1 Hz, 1H), 3.55-3.52 (m, 1H), 3.40-3.37 (m, 1H), 3.06-2.96 (m, 2H), 2.26 (s, 6H), 1.43 (br s, 4H), 1.29 (d, *J* = 7.6 Hz, 3H), 1.21-1.17 (m, 1H), 1.0-0.97 (m, 1H). $^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$): δ = 170.5, 169.3, 148.9, 127.7, 127.5, 121.1, 46.2, 43.3, 35.3, 25.5, 25.3, 24.5, 20.8, 17.1. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{23}NO_5$ 334.1649; Found 334.1643.



2-(2-Oxo-2-(pyrrolidin-1-yl)ethyl)-1,3-phenylene diacetate (3wa): Compound **3wa** was isolated as a light yellow liquid (0.078 g, 85%) by a column chromatography on neutral alumina (eluents: petroleum ether/ ethyl acetate = 5/1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.29 (t, J = 8.2 Hz, 1H), 7.01 (d, J = 8.1 Hz, 2H), 3.53 (s, 2H), 3.42 (t, J = 6.9 Hz, 2H), 3.20 (t, J = 6.9 Hz, 2H), 2.30 (s, 6H), 1.89-1.85 (m, 2H), 1.82-1.78 (m, 2H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 169.0, 168.0, 150.0, 128.0, 121.1, 120.4, 46.8, 46.4, 32.4, 26.4, 24.3, 21.1. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{19}NO_5$ 306.1336; Found 306.1332.

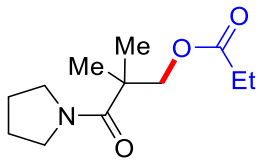


3-Methoxy-2-(2-oxo-2-(pyrrolidin-1-yl)ethyl)phenyl acetate (3xa): Compound **3xa** was isolated as a light yellow liquid (0.067 g, 81%) by a column chromatography on neutral alumina (eluents: petroleum ether/ ethyl acetate = 5/1); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.03 (t, J = 8.3 Hz, 1H), 6.53 (d, J = 8.4 Hz, 1H), 6.49-6.47 (m, 1H), 3.59 (s, 3H), 3.35 (s, 2H), 3.21 (vt, J = 6.9 Hz, 2H), 3.13 (vt, J = 6.7 Hz, 2H), 2.05 (s, 3H), 1.69-1.66 (m, 2H), 1.61-1.57 (m, 2H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 169.6, 169.2, 158.3, 150.4, 128.0, 117.1, 115.1, 108.2, 56.1, 46.7, 46.2, 31.0, 26.4, 24.5, 21.1. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{19}NO_4$ 278.1387; Found 278.1384.

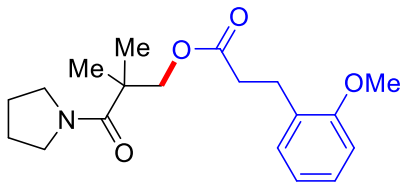


2-(3-Oxo-3-(pyrrolidin-1-yl)propyl)phenyl acetate (3ya): Compound **3ya** was light yellow liquid (61%, ^{1}H NMR yield); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.30-7.28 (m, 1H), 7.25-7.21

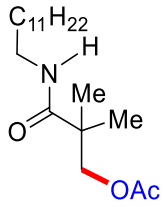
(m, 1H), 7.19-7.15 (m, 1H), 7.03-6.99 (m, 1H), 3.46 (t, *J* = 6.6 Hz, 2H), 3.27 (t, *J* = 6.5 Hz, 2H), 2.91 (t, *J* = 7.8 Hz, 2H), 2.51 (t, *J* = 7.8 Hz, 2H), 2.33 (s, 3H), 1.90-1.80 (m, 4H, CH_2). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 170.7, 169.8, 149.0, 133.4, 130.5, 127.5, 126.3, 122.5, 46.7, 45.8, 35.2, 26.1, 25.6, 24.5, 21.1. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{19}NO_3$ 262.1438; Found 262.1435.



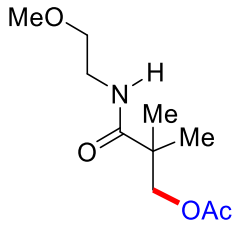
2,2-Dimethyl-3-oxo-3-(pyrrolidin-1-yl)propyl propionate (3ab): Compound **3ab** was isolated as a light yellow liquid (0.047 g, 69%) by a column chromatography on neutral alumina (eluents: petroleum ether/ ethyl acetate = 5/1); ^1H-NMR (400 MHz, $CDCl_3$): δ = 4.17 (s, 2H), 3.51 (br s, 4H), 2.30 (q, *J* = 7.6 Hz, 2H), 1.83 (br s, 4H), 1.25 (s, 6H), 1.09 (t, *J* = 7.6 Hz, 3H). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 174.5, 173.4, 70.5, 48.0, 42.9, 27.7, 27.3, 23.1, 22.6, 9.3. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{21}NO_3$ 228.1594; Found 228.1590.



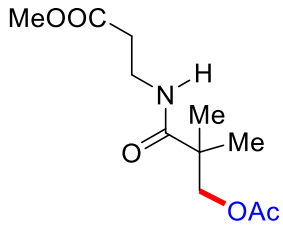
2,2-Dimethyl-3-oxo-3-(pyrrolidin-1-yl)propyl 3-(2-methoxyphenyl)propanoate (3ac): Compound **3ac** was isolated as a light yellow liquid (0.057 g, 57%) by a column chromatography on neutral alumina (eluents: petroleum ether/ ethyl acetate = 5/1); ^1H-NMR (400 MHz, $CDCl_3$): δ = 7.19-7.11 (m, 2H), 6.85-6.81 (m, 2H), 4.19 (s, 2H), 3.80 (s, 3H), 3.51 (t, *J* = 6.1 Hz, 4H), 2.92 (t, *J* = 8.0 Hz, 2H), 2.61 (t, *J* = 8.0 Hz, 2H), 1.83 (br s, 4H), 1.24 (s, 6H). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 173.5, 173.5, 157.6, 130.0, 128.9, 127.7, 120.5, 110.3, 70.7, 55.3, 47.9, 42.9, 34.3, 27.4, 26.2, 23.4, 22.7. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{27}NO_4$ 334.2013; Found 334.2014.



3-(Dodecylamino)-2,2-dimethyl-3-oxopropyl acetate (5aa): Compound **5aa** was isolated as a light yellow liquid (0.032 g, 33%) by column chromatography on neutral alumina (eluents: petroleum ether/ ethyl acetate = 5/1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.77 (br s, 1H), 4.08 (s, 2H), 3.24 (q, J = 5.9 Hz, 2H), 2.05 (s, 3H), 1.50-1.46 (m, 2H), 1.30-1.24 (m, 18H) 1.19 (s, 6H), 0.86 (t, J = 6.9 Hz, 3H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 175.3, 170.9, 70.7, 42.4, 39.8, 32.0, 29.8, 29.7, 29.5, 29.5, 27.0, 22.8, 21.0, 14.3. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{37}NO_3$ 328.2846; Found 328.2849.

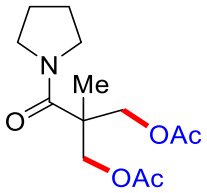


3-(Methoxyamino)-2,2-dimethyl-3-oxopropyl acetate (5ba): Compound **5ba** was isolated as a light yellow liquid (0.036 g, 55%) by a column chromatography on neutral alumina (eluents: petroleum ether/ ethyl acetate = 5/1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 6.22 (br s, 1H), 4.08 (s, 2H), 3.46-3.42 (m, 4H), 3.35 (s, 3H), 2.05 (s, 3H), 1.20 (s, 6H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 175.6, 170.8, 71.3, 70.6, 59.0, 42.4, 39.5, 22.8, 21.0. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{19}NO_4$ 218.1387; Found 218.1387.



3-(Methoxycarbonyl)amino)-2,2-dimethyl-3-oxopropyl acetate (5ca): Compound **5ca** was isolated as a light yellow liquid (0.044 g, 60%) by column chromatography on neutral alumina (eluents: petroleum ether/ ethyl acetate = 5/1); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 6.54 (br s, 1H), 4.05 (s, 2H), 3.68 (s, 3H), 3.51 (q, J = 5.9 Hz, 2H), 2.52 (t, J = 5.9 Hz, 2H), 2.04 (s, 3H), 1.17 (s, 6H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 175.5, 173.4, 170.8, 70.5, 51.9,

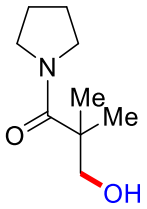
42.3, 35.1, 33.7, 22.7, 20.9. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{19}NO_5$ 246.1336; Found 246.1336.



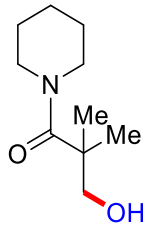
2-Methyl-2-(pyrrolidine-1-carbonyl)propane-1,3-diyl diacetate (3aa'): Compound **3aa'** as a light yellow liquid; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.38-4.18 (m, 4H), 3.54 (br s, 4H), 2.04 (s, 6H), 1.88 (br s, 4H), 1.28 (s, 3H). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 171.0, 170.6, 65.8, 47.9, 46.6, 27.2, 23.3, 21.0, 17.3. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{21}NO_5$ 272.1492; Found 272.1489.

2.4.5 Alcoholysis of *β*-Acetoxylated Compounds

Procedure for Synthesis of 3-Hydroxy-2,2-dimethyl-1-(pyrrolidin-1-yl)propan-1-one (6aa):[60] In an oven-dried Schlenk flask, a mixture of 2-methyl-3-(pyrrolidin-1-yl)but-3-en-2-yl acetate (**3aa**; 0.10 g, 0.469 mmol) and K_2CO_3 (0.065 g, 0.47 mmol) in MeOH (3 mL) was refluxed for 12 h. At ambient temperature, the solvent was evaporated under reduced pressure, quenched with H_2O (15 mL), and extracted with EtOAc (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in *vacuo*. The crude residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **6aa** (0.069 g, 86%) as a white solid.

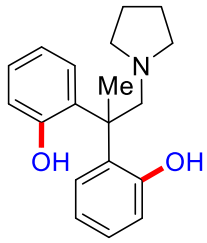


3-Hydroxy-2,2-dimethyl-1-(pyrrolidin-1-yl)propan-1-one (6aa): ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.96 (s, 1H), 3.60-3.48 (m, 6H), 1.85 (br s, 4H), 1.24 (s, 6H). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 176.9, 72.7, 47.9, 43.4, 27.1, 23.2, 21.2. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_9H_{17}NO_2$ 172.1332; Found 172.1331.



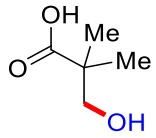
Synthesis of 3-Hydroxy-2,2-dimethyl-1-(piperidin-1-yl)propan-1-one) (6ba): The representative was followed, using 2,2-dimethyl-3-oxo-3-(piperidin-1-yl)propyl acetate (**3ba**; 0.10 g, 0.44 mmol) and K_2CO_3 (0.061 g, 0.44 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **6ba** (0.069 g, 85%) as a white solid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.55 (t, J = 5.7 Hz, 4H), 3.48 (s, 2H), 1.68-1.64 (m, 2H), 1.59-1.54 (m, 4H), 1.27 (s, 6H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 176.4, 73.2, 46.0, 43.2, 26.2, 24.7, 22.1. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{19}NO_2$ 186.1489; Found 186.1484.

Procedure for Reduction of Acetoxylated Compound. **Synthesis of 2,2'-(1-(Pyrrolidin-1yl)propane-2,2-diyl)diphenol) (7ua):**



A solution of (1-oxo-1-(pyrrolidin-1-yl)propane-2,2-diyl)bis(2,1 phenylene) diacetate (**3ua**; 0.10 g, 0.252 mmol) in Et_2O (10 mL) was added to $LiAlH_4$ (0.096 g, 2.52 mmol) at 0 ^{o}C and the reaction mixture was stirred for 12 h at room temperature. The reaction was slowly quenched with cold water (15 mL) at 0 ^{o}C, and the product was extracted with diethyl ether (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in *vacuo*. The crude residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **7ua** (0.059 g, 79%) as a white solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.20-7.11 (m, 4H), 6.88-6.81 (m, 4H), 3.26 (s, 2H), 3.77 (br s, 4H), 1.85-1.82 (m, 4H), 1.77 (s, 3H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 156.1, 131.4, 129.1, 127.9, 120.3, 119.2, 65.0, 56.0, 49.2, 27.0, 23.9. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{24}NO_2$ 298.1807; Found 298.1788.

***Procedure for Hydrolysis of β-Acetoxylated Compound*. Synthesis of 3-hydroxy-2,2-dimethylpropanoic acid (8aa):**[25]

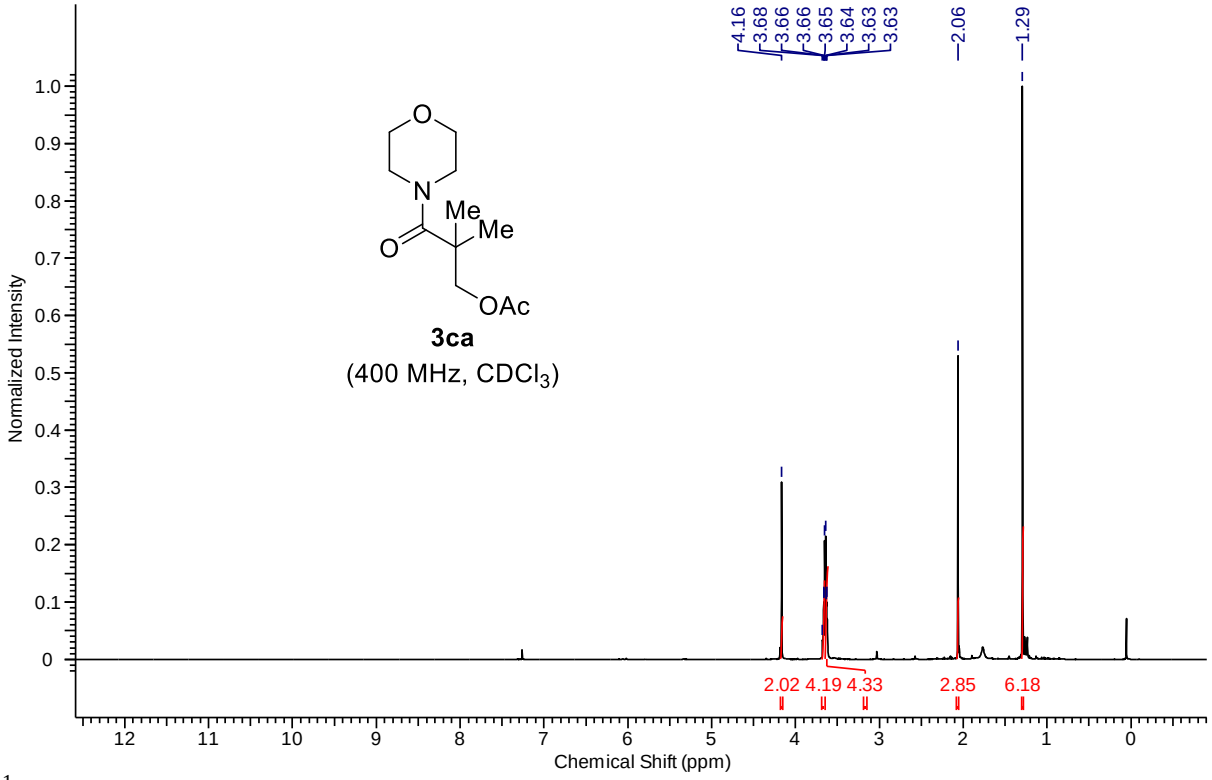


In a Schlenk flask, the mixture of 2-methyl-3-(pyrrolidin-1-yl)but-3-en-2-yl acetate (0.10 g, 0.47 mmol) and 3N HCl (aq, 3 mL) was refluxed for 12 h. The reaction mixture was neutralized and extracted with ethyl acetate (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in *vacuo*. The crude residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **8aa** (0.031 g, 56%) as a white solid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 3.60 (s, 2H), 1.24 (s, 6H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 183.4, 69.5, 44.2, 22.1. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_5H_{10}O_3$ 119.0710; Found 119.0709.

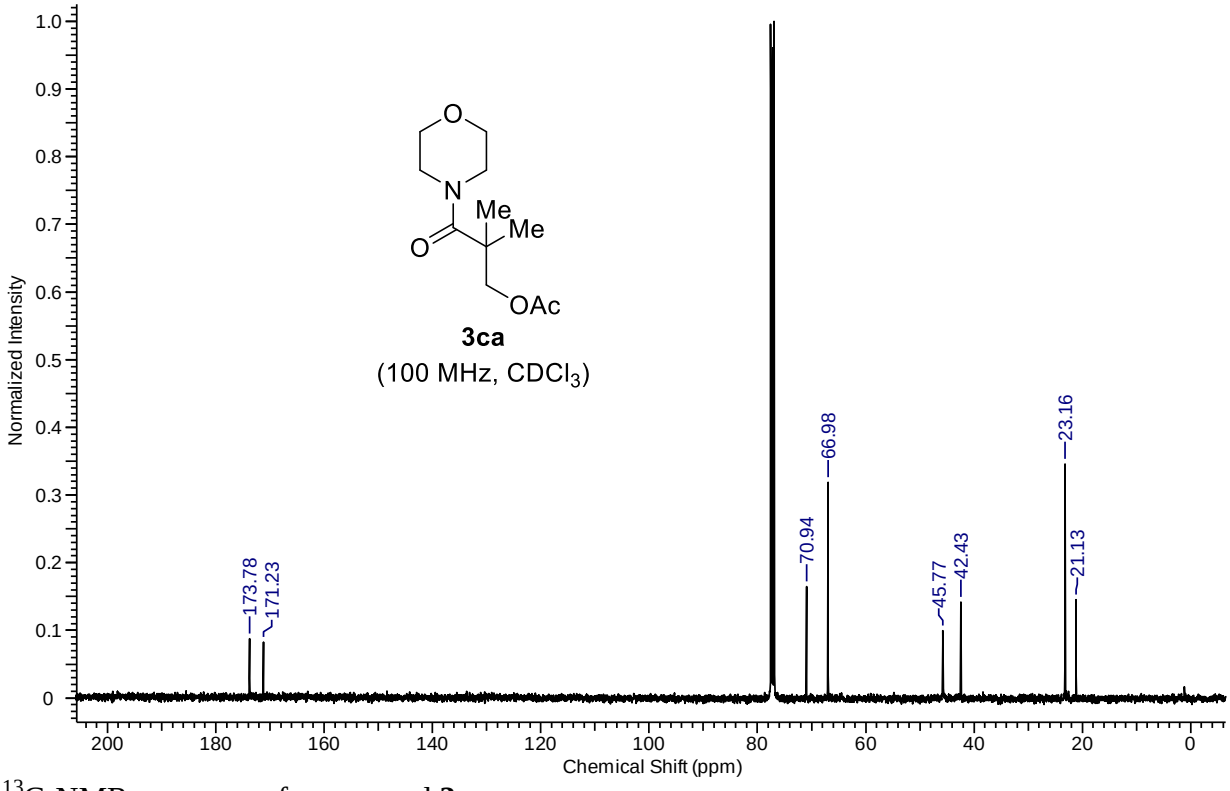
2.4.6 Procedure for Kinetic Isotope Effect Study

To a flame dried screw-cap tube equipped with magnetic stir bar was introduced $Pd(OAc)_2$ (0.0047 g, 0.002 mmol, 1.0 mol%, 100 µL from stock solution), 2-ethyl-2-methyl-1-(pyrrolidin-1-yl)butan-1-one (**1p**; 0.037 g, 0.20 mmol), {or [D]-**1p** (0.038 g, 0.20 mmol)}, $PhI(OAc)_2$ (**2a**; 0.193 g, 0.60 mmol), and *n*-dodecane (0.020 mL, 0.088 mmol, 0.088 M, internal standard), and HFIP/Ac_2O (9:1) (0.88 mL) was added to make the total volume to 1.0 mL. The reaction mixture was then stirred at 120 ^{o}C in a pre-heated oil bath. At regular intervals (5, 10, 20, 30, 45, 60 mins), the reaction vessel was cooled to ambient temperature, and an aliquot of sample was withdrawn to the GC vial. The sample was diluted with EtOAc and subjected to GC analysis. The concentration of product **3pa** (or D-**3pa**) obtained in each sample was determined with respect to the internal standard *n*-dodecane. The data of the concentration of the product *vs* time (min) plot was drawn (Figure 1) with Origin Pro 8, and the rate was determined by the initial rate method (up to 60 minutes). The data's were taken from the average of two independent experiments.

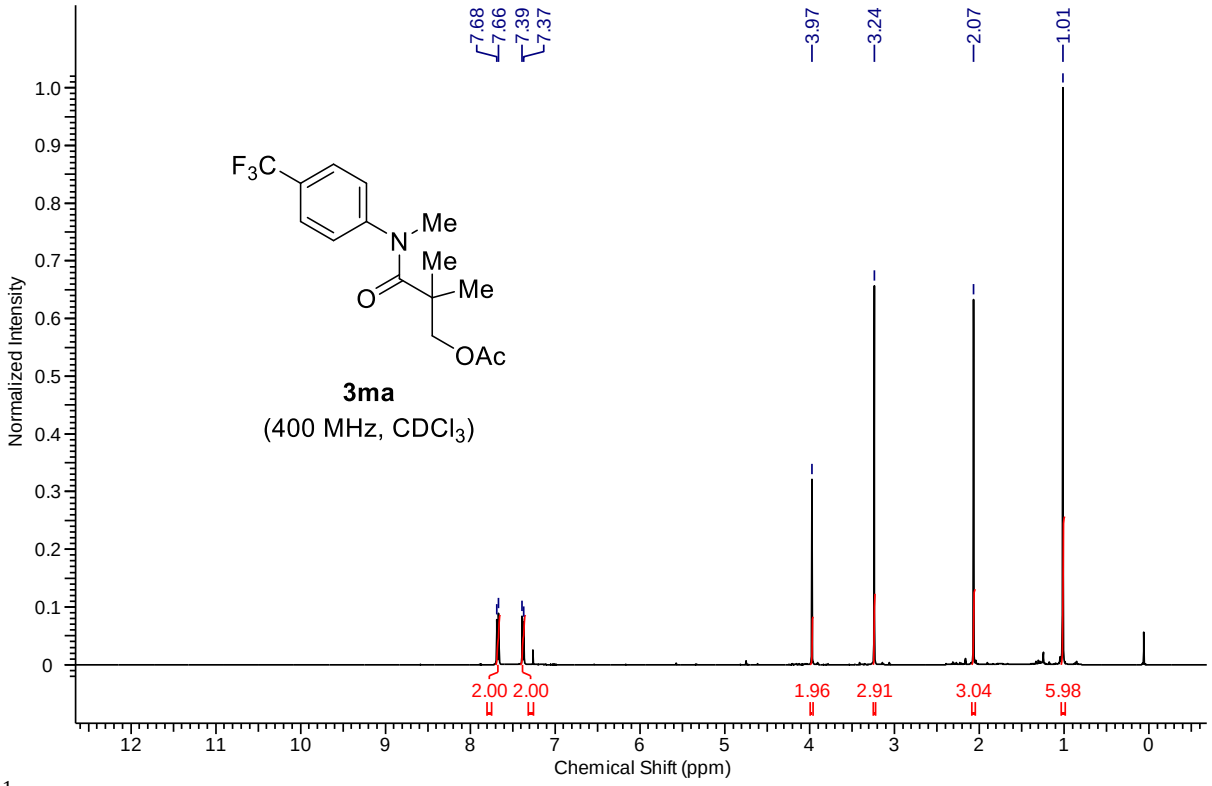
2.4.7 ^{1}H and ^{13}C NMR Spectra for Selected Acetoxy Compounds



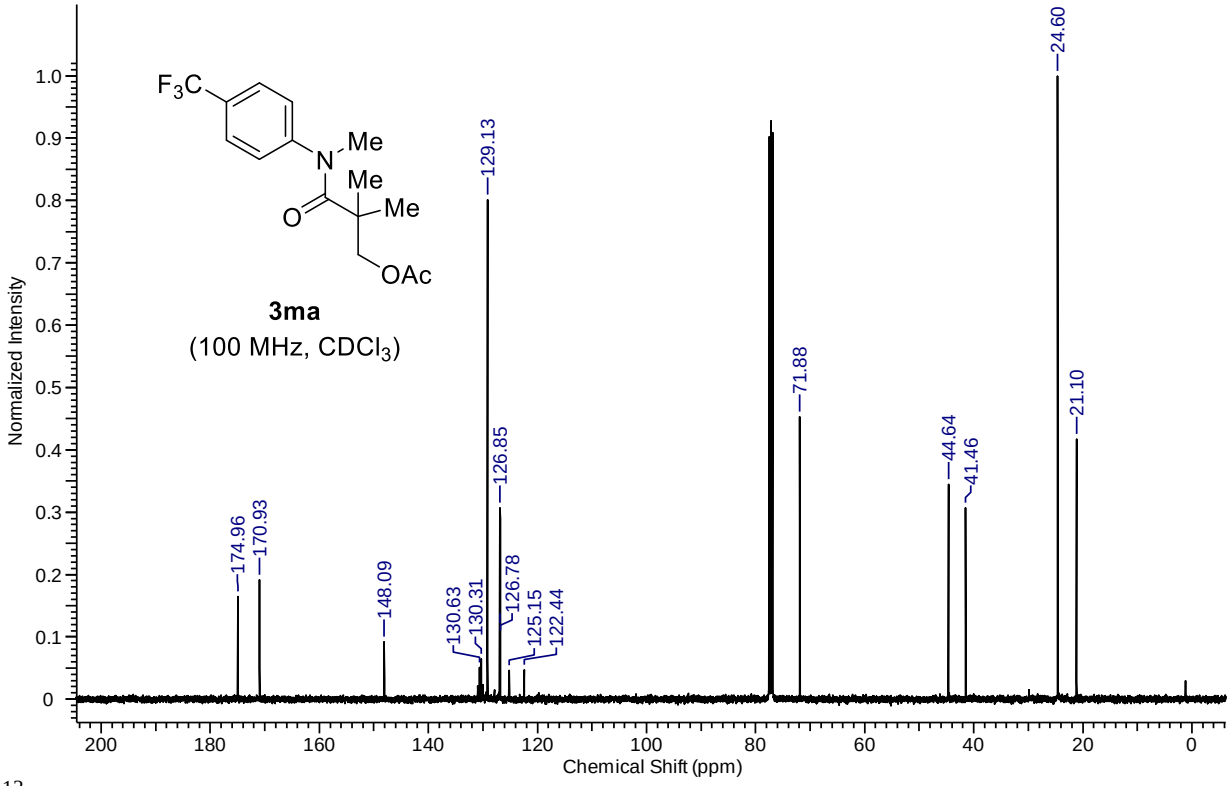
^{1}H-NMR spectrum of compound **3ca**



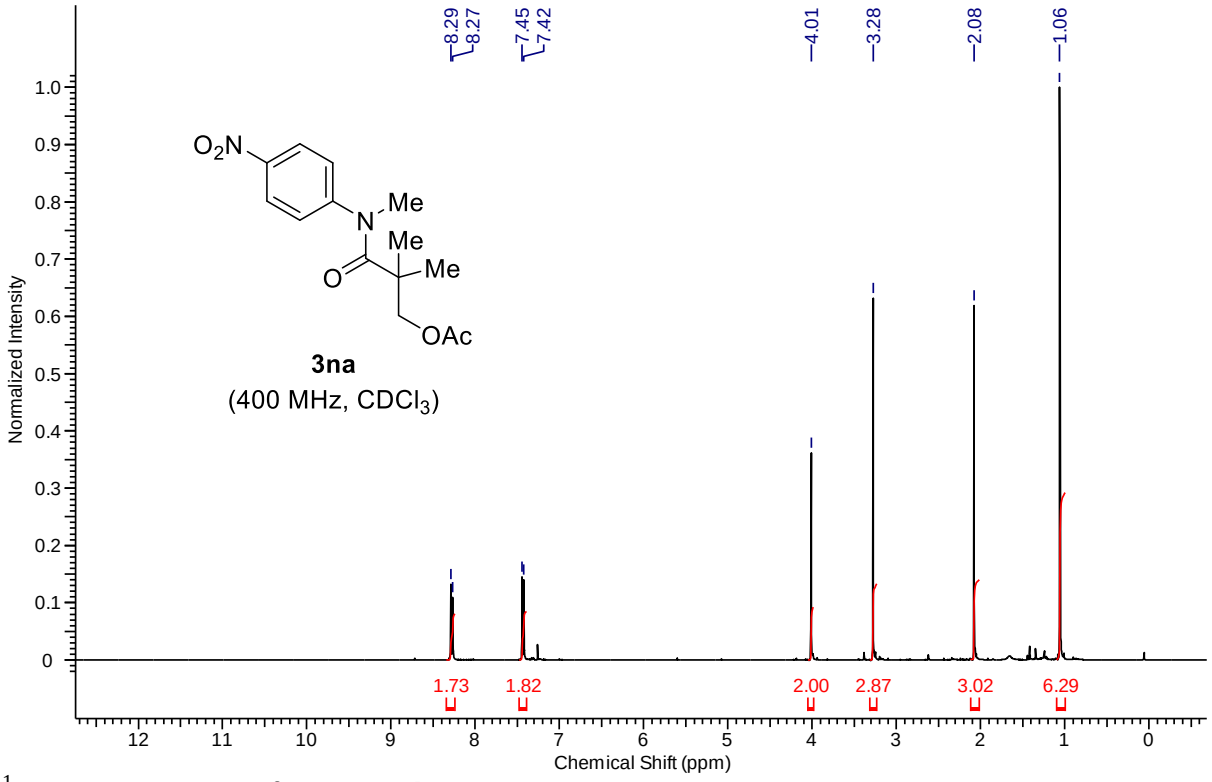
^{13}C-NMR spectrum of compound **3ca**



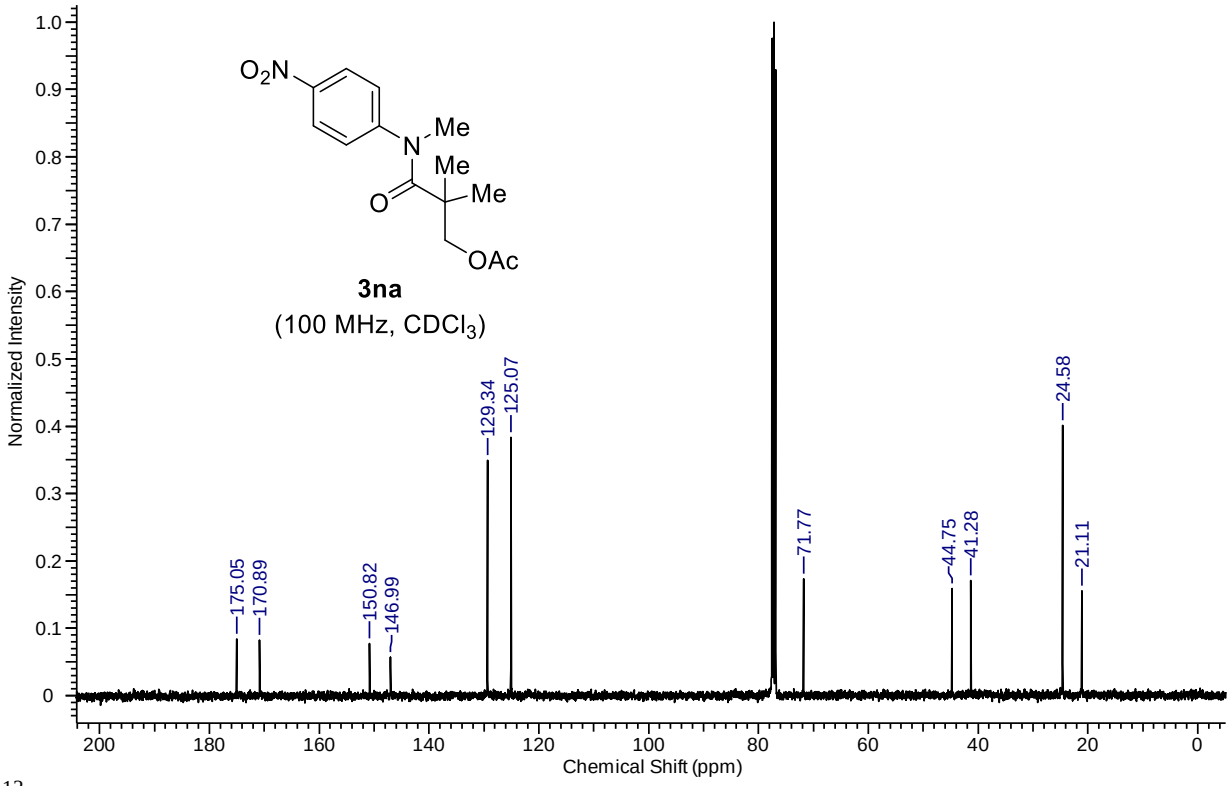
^{1}H-NMR spectrum of compound **3ma**



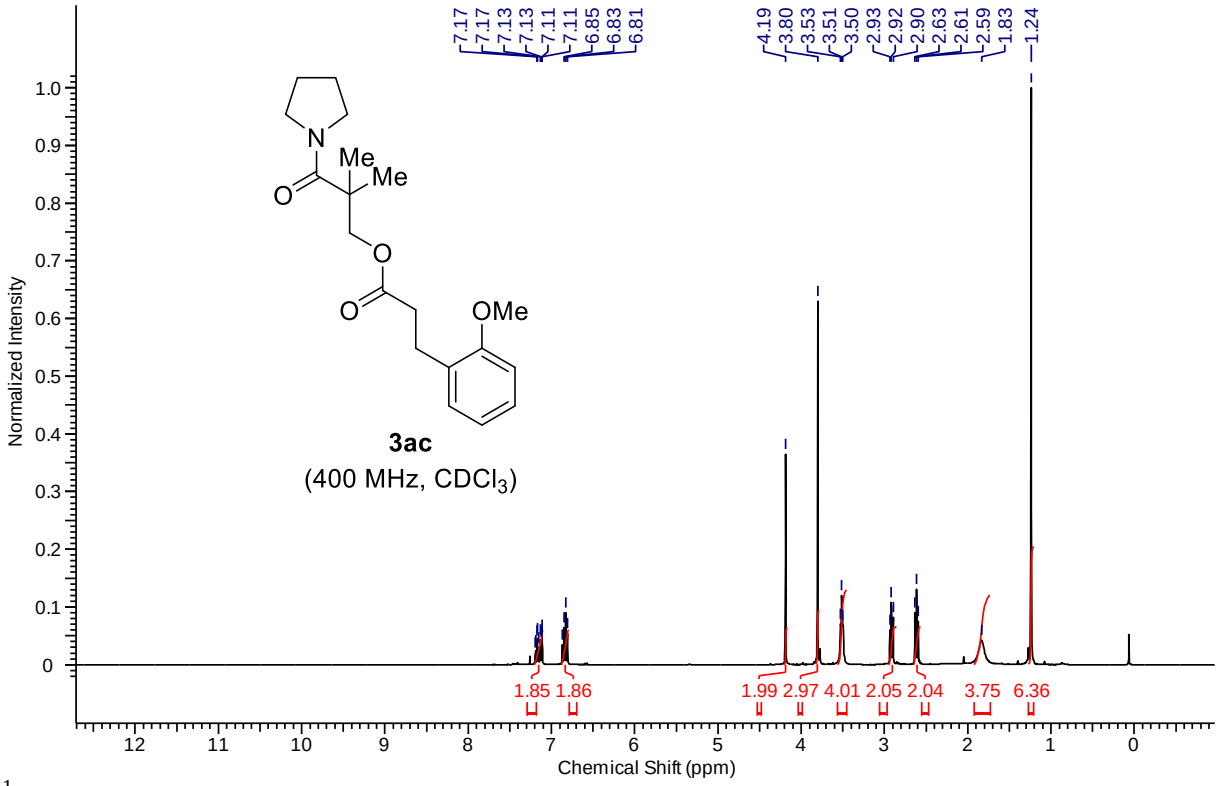
^{13}C-NMR spectrum of compound **3ma**



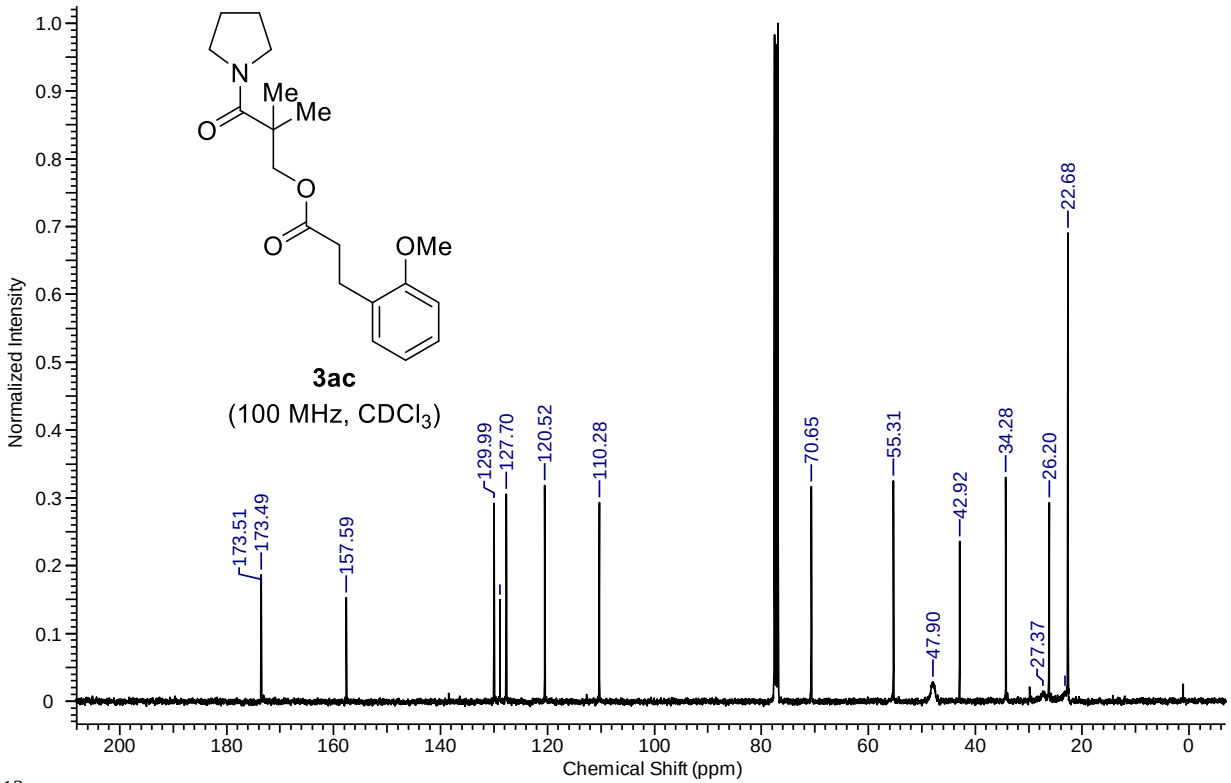
^{1}H-NMR spectrum of compound **3na**



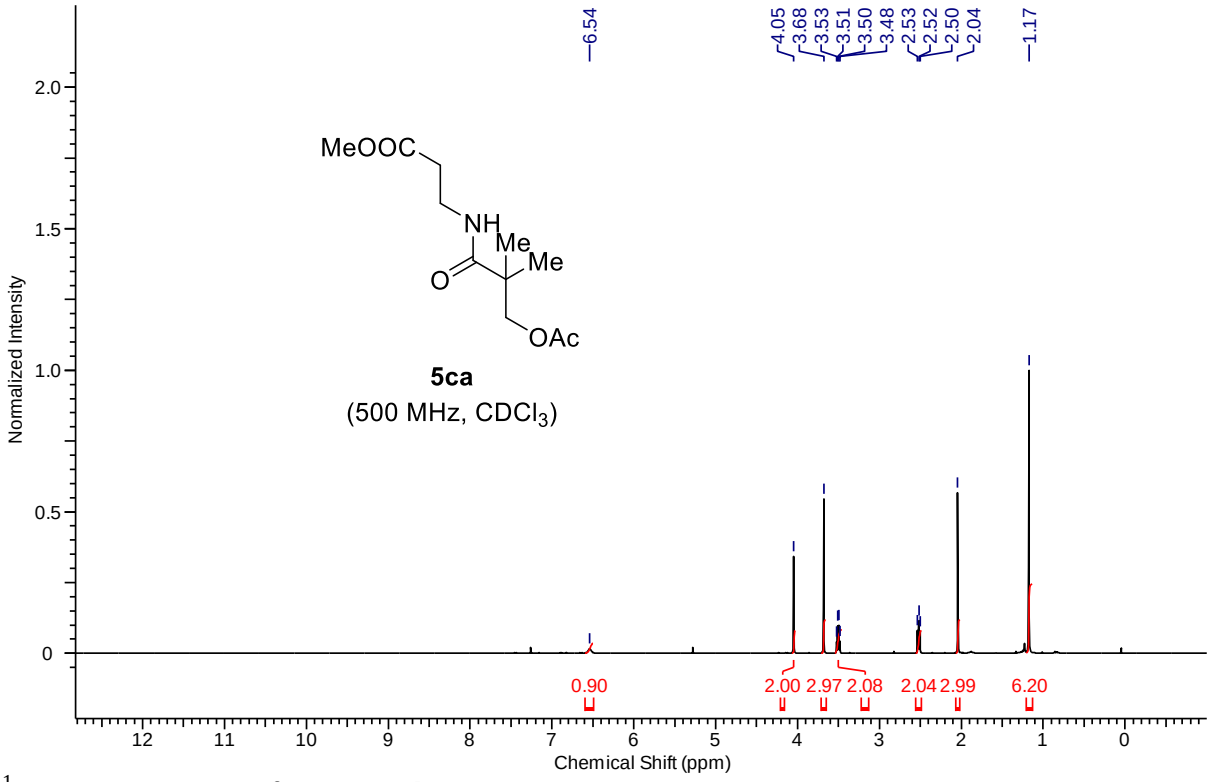
^{13}C-NMR spectrum of compound **3na**



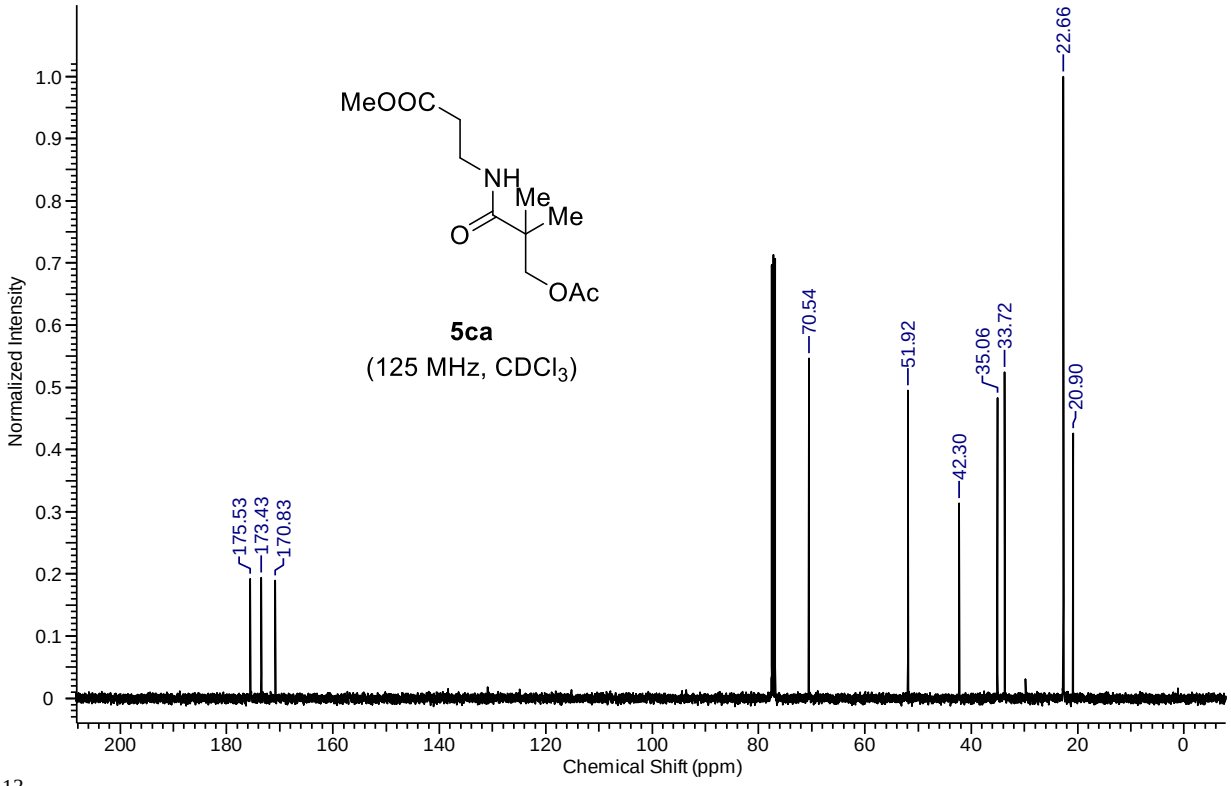
^{1}H-NMR spectrum of compound **3ac**



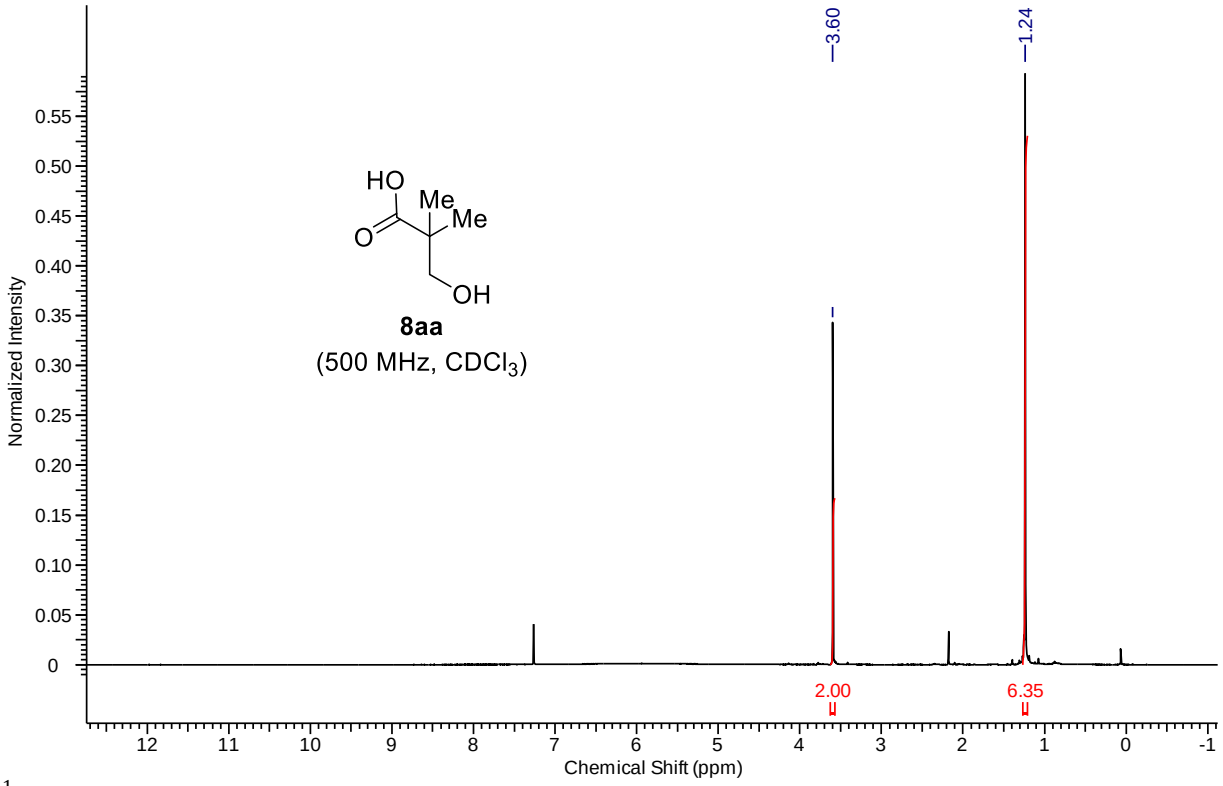
^{13}C-NMR spectrum of compound **3ac**



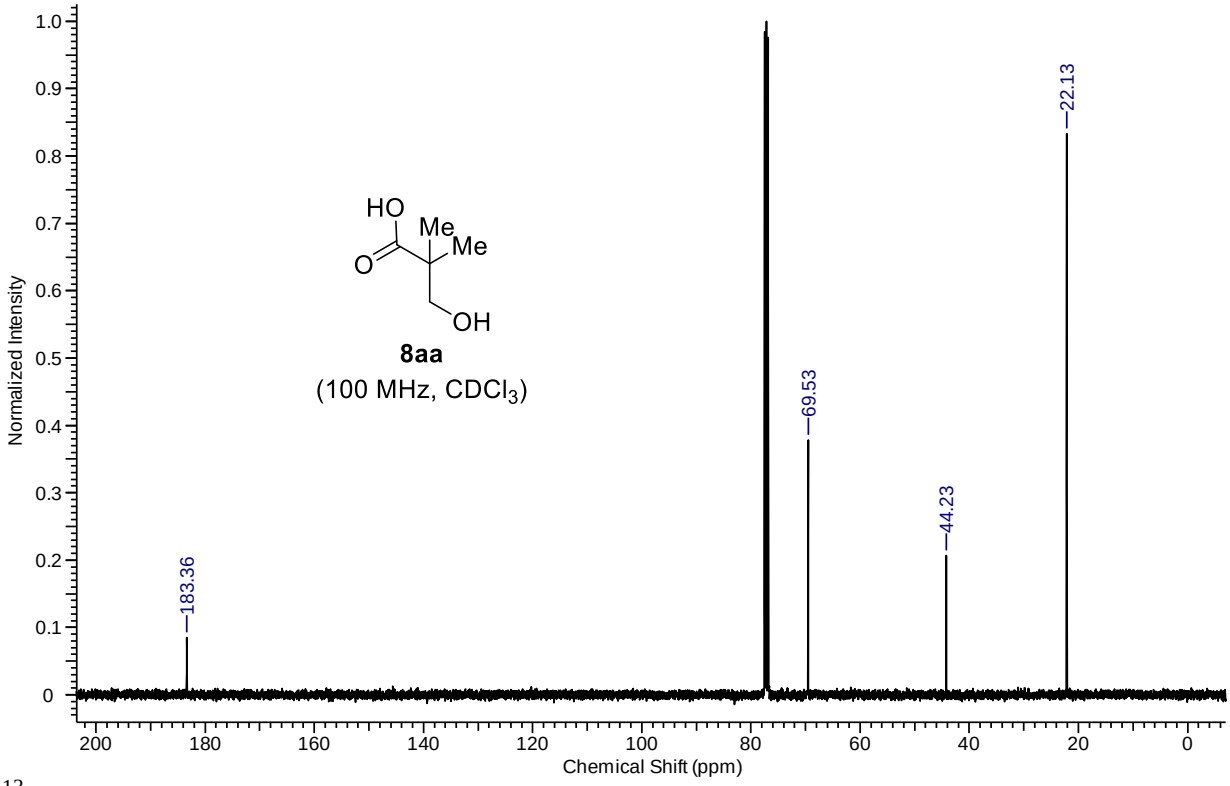
^{1}H-NMR spectrum of compound **5ca**



^{13}C-NMR spectrum of compound **5ca**



^{1}H-NMR spectrum of compound **8aa**



^{13}C-NMR spectrum of compound **8aa**

2.5 REFERENCES

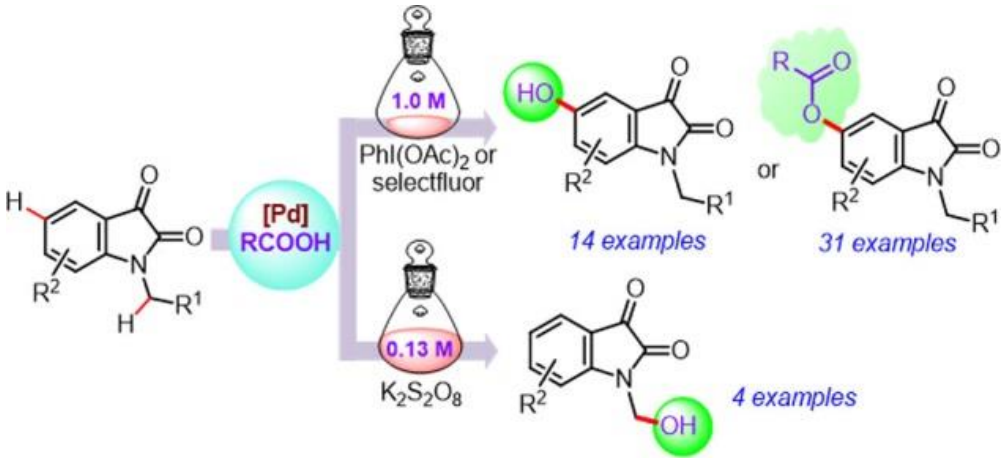
1. Alonso, D. A.; Nájera, C.; Pastor, I. M.; Yus, M., *Chem. Eur. J.* **2010**, *16*, 5274-5284.
2. Wang, G. W.; Yuan, T. T., *J. Org. Chem.* **2010**, *75*, 476-479.
3. Chen, F. J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S. Q.; Shi, B. F., *Chem. Sci.* **2013**, *4*, 4187-4192.
4. Zhang, L. B.; Hao, X. Q.; Zhang, S. K.; Liu, K.; Ren, B.; Gong, J. F.; Niu, J. L.; Song, M. P., *J. Org. Chem.* **2014**, *79*, 10399-10409.
5. Zhang, L. B.; Hao, X. Q.; Zhang, S. K.; Liu, Z. J.; Zheng, X. X.; Gong, J. F.; Niu, J. L.; Song, M. P., *Angew. Chem. Int. Ed.* **2015**, *54*, 272-275.
6. Li, S.; Zhu, W.; Gao, F.; Li, C.; Wang, J.; Liu, H., *J. Org. Chem.* **2017**, *82*, 126-134.
7. Rajesh, N.; Sundararaju, B., *Asian J. Org. Chem.* **2018**, *7*, 1368-1371.
8. Liu, S. K.; Cui, X. F.; Liu, X. X.; Ma, H. J.; Wei, D. D.; Luo, X. L.; Huang, G. S., *Chem. Select* **2018**, *3*, 3989-3992.
9. Yadav, M. R.; Rit, R. K.; Sahoo, A. K., *Chem. Eur. J.* **2012**, *18*, 5541-5545.
10. Rit, R. K.; Yadav, M. R.; Sahoo, A. K., *Org. Lett.* **2014**, *16*, 968-971.
11. Zhou, L.; Lu, W., *Org. Lett.* **2014**, *16*, 508-511.
12. Wu, X.; Zhao, Y.; Ge, H., *Chem. Asian J.* **2014**, *9*, 2736-2739.
13. Padala, K.; Jeganmohan, M., *Chem. Eur. J.* **2014**, *20*, 4092-4097.
14. Lan, J.; Xie, H.; Lu, X.; Deng, Y.; Jiang, H.; Zeng, W., *Org. Lett.* **2017**, *19*, 4279-4282.
15. Wang, F.; Hu, Q.; Shu, C.; Lin, Z.; Min, D.; Shi, T.; Zhang, W., *Org. Lett.* **2017**, *19*, 3636-3639.
16. Raghuvanshi, K.; Zell, D.; Ackermann, L., *Org. Lett.* **2017**, *19*, 1278-1281.
17. Ueno, R.; Natsui, S.; Chatani, N., *Org. Lett.* **2018**, *20*, 1062-1065.
18. Li, G. J.; Pan, Y. L.; Liu, Y. L.; Xu, H. F.; Chen, J. Z., *Org. Lett.* **2019**, *21*, 1740-1743.
19. Li, X.; Liu, Y. H.; Gu, W. J.; Li, B.; Chen, F. J.; Shi, B. F., *Org. Lett.* **2014**, *16*, 3904-3907.
20. Reddy, B. V. S.; Reddy, L. R.; Corey, E. J., *Org. Lett.* **2006**, *8*, 3391-3394.
21. Wang, Z.; Kuninobu, Y.; Kanai, M., *Org. Lett.* **2014**, 16, 4790-4793.
22. Chen, K.; Zhang, S. Q.; Jiang, H. Z.; Xu, J. W.; Shi, B. F., *Chem. Eur. J.* **2015**, *21*, 3264-3270.
23. Wang, F.; Li, X.; Li, Z.; Zhou, S.; Zhang, W., *ACS Omega* **2019**, *4*, 331-343.
24. Zhang, S.-Y.; He, G.; Zhao, Y.; Wright, K.; Nack, W. A.; Chen, G., *J. Am. Chem. Soc.* **2012**, *134*, 7313-7316.

25. Rit, R. K.; Yadav, M. R.; Sahoo, A. K., *Org. Lett.* **2012**, *14*, 3724-3727.
26. Jerhaoui, S.; Djukic, J. P.; Wencel-Delord, J.; Colobert, F., *Chem. Eur. J.* **2017**, *23*, 15594-15600.
27. Zhao, R.; Lu, W., *Organometallics* **2018**, *37*, 2188-2192.
28. Park, H.; Chekshin, N.; Shen, P. X.; Yu, J. Q., *ACS Catal.* **2018**, *8*, 9292-9297.
29. Park, H.; Li, Y.; Yu, J.-Q., *Angew. Chem. Int. Ed.* **2019**, *58*, 11424-11428.
30. Zhou, L.; Lu, W., *Org. Lett.* **2014**, *16*, 508-511
31. Zhuang, Z.; Herron, A. N.; Fan, Z.; Yu, J.-Q., *J. Am. Chem. Soc.* **2020**, *142*, 6769-6776.
32. Kalepu, J.; Pilarski, L. T., *Molecules* **2019**, *24*, 830.
33. Yang, Y.; Lin, Y.; Rao, Y., *Org. Lett.* **2012**, *14*, 2874-2877.
34. Thirunavukkarasu, V. S.; Ackermann, L., *Org. Lett.* **2012**, *14*, 6206-6209.
35. Mo, F.; Trzepkowski, L. J.; Dong, G., *Angew. Chem. Int. Ed.* **2012**, *51*, 13075-13079.
36. Shan, G.; Yang, X.; Ma, L.; Rao, Y., *Angew. Chem. Int. Ed.* **2012**, *51*, 13070-13074.
37. Bhadra, S.; Dzik, W. I.; Gooben, L. J., *Angew. Chem., Int. Ed.* **2013**, *52*, 2959-2962.
38. Yang, X.; Shan, G.; Rao, Y., *Org. Lett.* **2013**, *15*, 2334-2337.
39. Yu, W.; Chen, J.; Gao, K.; Liu, Z.; Zhang, Y., *Org. Lett.* **2014**, *16*, 4870-4873.
40. Yang, F.; Rauch, K.; Kettelhoit, K.; Ackermann, L., *Angew. Chem. Int. Ed.* **2014**, *53*, 11285-11288.
41. Ghosh, K. K.; Uttry, A.; Koldemir, A.; Ong, M.; van Gemmeren, M., *Org. Lett.* **2019**, *21*, 7154-7157.
42. Thirunavukkarasu, V. S.; Hubrich, J.; Ackermann, L., *Org. Lett.* **2012**, *14*, 4210-4213.
43. Yang, F.; Ackermann, L., *Org. Lett.* **2013**, *15*, 718-720.
44. More, N. Y.; Padala, K.; Jeganmohan, M., *J. Org. Chem.* **2017**, *82*, 12691-12700.
45. Li, G.; Wan, L.; Zhang, G.; Leow, D.; Spangler, J.; Yu, J.-Q., *J. Am. Chem. Soc.* **2015**, *137*, 4391-4397.
46. Pandey, D. K.; Ankade, S. B.; Ali, A.; Vinod, C. P.; Punji, B., *Chem. Sci.* **2019**, *10*, 9493-9500.
47. Jagtap, R. A.; Samal, P. P.; Vinod, C. P.; Krishnamurty, S.; Punji, B., *ACS Catal*. **2020**, *10*, 7312-7321.
48. Jagtap, R. A.; Verma, S. K.; Punji, B., *Org. Lett*. **2020**, *22*, 4643-4647.
49. Jagtap, R. A.; Punji, B., *Asian J. Org. Chem*. **2020**, *9*, 326-342.
50. Ankade, S. B.; Shabade, A. B.; Soni, V.; Punji, B., *ACS Catal*. **2021**, *11*, 3268-3292.
51. Bansal, S.; Shabade, A. B.; Punji, B., *Adv. Synth. Catal*. **2021**, *363*, 1998-2022.

52. Dick, A. R.; Hull, K. L.; Sanford, M. S., *J. Am. Chem. Soc.* **2004**, *126*, 2300-2301.
53. Desai, L. V.; Hull, K. L.; Sanford, M. S., *J. Am. Chem. Soc.* **2004**, *126*, 9542-9543.
54. Giri, R.; Liang, J.; Lei, J. G.; Li, J. J.; Wang, D. H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J. Q., *Angew. Chem. Int. Ed.* **2005**, *44*, 7420-7424.
55. Desai, L. V.; Malik, H. A.; Sanford, M. S., *Org. Lett.* **2006**, *8*, 1141-1144.
56. Cook, A. K.; Sanford, M. S., *J. Am. Chem. Soc.* **2015**, *137*, 3109-3118.
57. Yan, J. X.; Li, H.; Liu, X. W.; Shi, J. L.; Wang, X.; Shi, Z. J., *Angew. Chem. Int. Ed.* **2014**, *53*, 4945-4949.
58. Dick, A. R.; Kampf, J. W.; Sanford, M. S., *J. Am. Chem. Soc.* **2005**, *127*, 12790-12791.
59. Racowski, J. M.; Dick, A. R.; Sanford, M. S., *J. Am. Chem. Soc.* **2009**, *131*, 10974-10983.
60. Barwick-Silk, J.; Hardy, S.; Willis, M. C.; Weller, A. S., *J. Am. Chem. Soc.* **2018**, *140*, 7347-7357.

Chapter 3

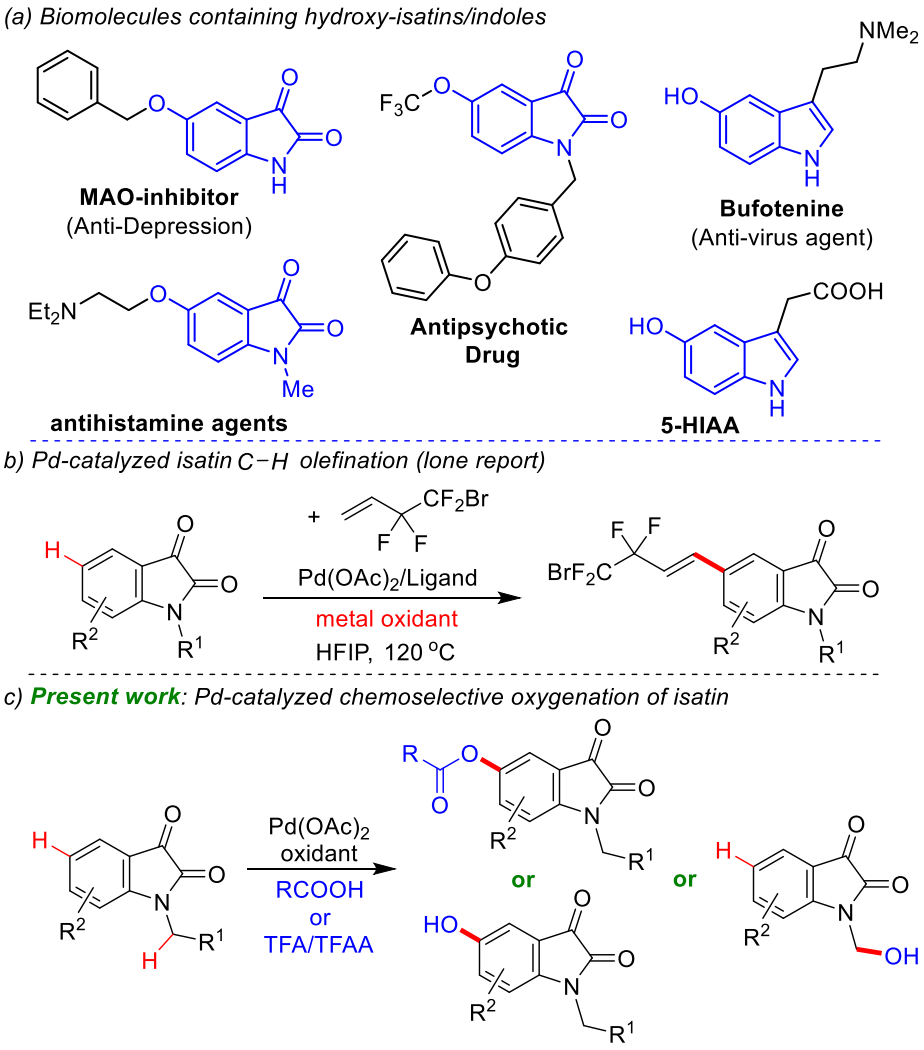
Pd(II)-Catalyzed Regioselective Oxygenation of C(sp^2)–H and C(sp^3)–H Bonds in Isatins



This chapter has been adapted from the publication "Palladium-Catalyzed Chemoselective Oxygenation of C(sp^2)–H and C(sp^3)–H Bonds in Isatins" **Vijaykumar**, **M**; Pradhan, C; Gonnade, R. G.; and Punji, B. *Org. Lett.* **2023**, *25*, 1862−1867.

3.1 INTRODUCTION

Isatin, the 2,3-dioxindole, is an elite oxidized indole nucleus and has gained particular attention as a core motif in the development of numerous pharmacologically active compounds.[1-8] The precise decoration of the isatin framework leads to diverse privileged molecules that are entrenched as antimalarial, antifungal, antibacterial, antiviral, and potential antitumor agents.[9-14] Particularly, the hydroxy group-containing isatins/indoles represent the important subclass among the isatin-based natural products (Scheme 3.1a).[3,7,15-18] Therefore, developing unified protocols for the efficient functionalization of isatins is highly indispensable. Notably, the strategic functionalization of isatins at the activated C2 and C3 carbonyl centers is widely explored;[19-26] however, the site-selective derivatization on the benzenoid moiety at C4, C5, C6, and C7 is scarce.



Scheme 3.1 Bioactive Molecules Containing C5 Oxygenated Isatin/Indole Core and C–H Functionalization of Isatin

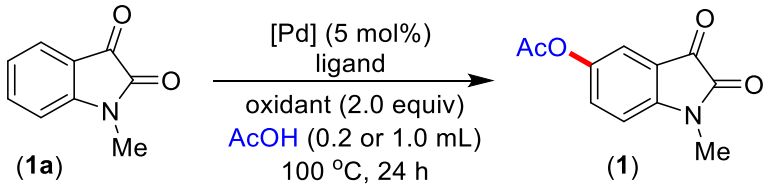
In recent years, the transition-metal-catalyzed step-economic C–H activation/ functionalization has seen tremendous growth.[27-29] In view of the prevailing applications and existence of isatins in bioactive molecules, the straightforward chemoselective C–H functionalization of benzenoid-ring in isatin is highly imperative.[30-35] Li and Zhao demonstrated the C5 selective fluorinated-olefination of isatins using a palladium catalyst via the C–H activation strategy (Scheme 3.1b), wherein a specific oxalyl amide ligand and an excess of metal-oxidant is essential.[38] Notably, this represents a lone precedent for the chemoselective C–H functionalization of isatins. Considering the existence of hydroxy-isatin moiety in diverse pharmacological compounds, we aimed to develop a straightforward protocol for the chemoselective oxygenation of isatins using a step-economical direct C–H activation strategy.[39-45] With this target, in this chapter, we demonstrate a Pd-catalyzed chemoselective oxygenation of isatin derivatives to obtain C5 C(sp^2)–H acetoxylation/hydroxylation and –*N*CH_3 C(sp^3)–H hydroxylation (Scheme 3.1c).

3.2 RESULTS AND DISCUSSION

3.2.1 Optimization of Reaction Parameters

We began the screening of reaction parameters for the acetoxylation of 1-methylindoline-2,3-dione (**1a**) with $PhI(OAc)_2$ employing $Pd(OAc)_2$ as a catalyst (Table 3.1). We assumed that the reaction might provide carbonyl-directed C(4)–H or –*N*CH_3 C(sp^3)–H acetoxylation or an electrophilic non-directed C(5)–H acetoxylation. Interestingly, this palladium-catalyzed reaction using acetic acid (1.0 mL) exclusively provided C(5)–H acetoxylation in 43% yield at 100 ^oC (Table 3.1, entry 1). The use of oxidants $K_2S_2O_8$, selectfluor, or $Cu(OAc)_2$ gave only a trace of **1**, whereas NFSI and oxone were incompetent (entries 2-6). The acetoxylation reaction in TFE, HFIP, toluene, or DCE solvents was inefficient (entry 7-10). Notably, the reaction in 0.2 mL of AcOH (1.0 M) instead of 1.0 mL provided **1** in 59% yield (entry 11). The use of a PPh_3 ligand along with $Pd(OAc)_2$ gave an 82% yield of **1** (entry 12). Bidentate ligand xantphos provided a slightly lower yield, whereas the *N*-donor ligands, like bpy or phen, were inefficient (entries 13-15).

Table 3.1. Optimization of Reaction Parameters for C(5)–H Acetoxylation [a]



Entry	[Pd]	Ligand	Oxidant	Solvent	**1** (%) [b]
1	$Pd(OAc)_2$	--	$PhI(OAc)_2$	AcOH	43
2	$Pd(OAc)_2$	--	$K_2S_2O_8$	AcOH	trace
3	$Pd(OAc)_2$	--	selectfluor	AcOH	trace
4	$Pd(OAc)_2$	--	NFSI	AcOH	NR
5	$Pd(OAc)_2$	--	$Cu(OAc)_2$	AcOH	trace
6	$Pd(OAc)_2$	--	oxone	AcOH	NR
7	$Pd(OAc)_2$	--	$PhI(OAc)_2$	TFE	trace
8	$Pd(OAc)_2$	--	$PhI(OAc)_2$	HFIP	trace
9	$Pd(OAc)_2$	--	$PhI(OAc)_2$	toluene	trace
10	$Pd(OAc)_2$	--	$PhI(OAc)_2$	DCE	trace
11	$Pd(OAc)_2$	--	$PhI(OAc)_2$	AcOH	59
12	**$Pd(OAc)_2$**	**PPh_3**	**$PhI(OAc)_2$**	**AcOH**	**82**
13	$Pd(OAc)_2$	xantphos	$PhI(OAc)_2$	AcOH	74
14	$Pd(OAc)_2$	bpy	$PhI(OAc)_2$	AcOH	NR
15	$Pd(OAc)_2$	phen	$PhI(OAc)_2$	AcOH	NR
16	$PdCl_2$	PPh_3	$PhI(OAc)_2$	AcOH	43
17	$Pd_2(dba)_3$	PPh_3	$PhI(OAc)_2$	AcOH	NR
18 [c]	$Pd(OAc)_2$	PPh_3	$PhI(OAc)_2$	AcOH	66
19 [d]	$Pd(OAc)_2$	PPh_3	$PhI(OAc)_2$	AcOH	54
20 [e]	$Pd(OAc)_2$	PPh_3	$PhI(OAc)_2$	AcOH	77
21 [f]	$Pd(OAc)_2$	PPh_3	$PhI(OAc)_2$	AcOH	61
22	$Pd(OAc)_2$	PPh_3	--	AcOH	NR
23	--	PPh_3	$PhI(OAc)_2$	AcOH	NR

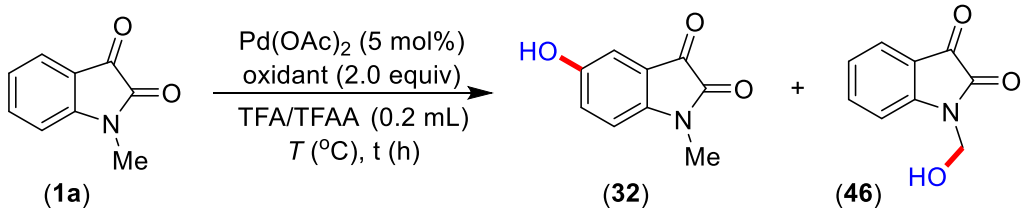
[a] Reaction Conditions: **1a** (0.032 g, 0.20 mmol), oxidant (0.40 mmol), [Pd] (0.01 mmol, 5.0 mol %), ligand (10 mol% for monodentate, 5 mol% for bidentate). Entries 1-10: 1.0 mL of solvent used. Entries 11-23: 0.2 mL of solvent was used. [b] Yield of isolated compound. [c] 15 mol% PPh_3 ligand used. [d] 1.5 equiv of $PhI(OAc)_2$ was used. [e] Reaction performed at 120 °C. [f] 3 mol% of $Pd(OAc)_2$ was used.

The acetoxylation was sluggish using $PdCl_2$ as a catalyst and provided a 43% yield of **1**; however, $Pd_2(dba)_3$ was ineffective (entries 16, 17). The use of 15 mol% of PPh_3 in place of 10.0 mol% resulted in lower conversion (entry 18). Moreover, reducing the loading of $PhI(OAc)_2$ or increasing the temperature resulted in a diminished yield (entries 19, 20). The lowering of catalyst loading to 3.0 mol% led to a lower conversion of the desired yield (entry 21). The acetoxylation was failed in the absence of an external oxidant or Pd catalyst (entries 22, 23), indicating the essential role of these components. After an exhaustive screening, the C5 acetoxylation of isatins has effectively occurred under the following conditions: $Pd(OAc)_2$ (5.0 mol%), $PhI(OAc)_2$ (2.0 equiv), PPh_3 (10.0 mmol%), and AcOH (0.2 mL) at 100 ^oC for 24 h.

The oxygenation reaction using $PhI(OAc)_2$ in TFA/TFAA (0.2 mL, 1.0 M) gave hydroxylated product **32** in 10% (Table 3.2, entry 1). Interestingly, the use of $K_2S_2O_8$ in TFA/TFAA (0.2 mL) provided **32** in 49% and a trace amount of –*N*CH_3 C(sp^3)–H hydroxylation **46** (Table 3.2, entry 2). The use of oxidants NFSI gave only a trace of **32**, whereas AgOAc was incompetent (entries 3, 4). The C5 hydroxylation reaction gave 72% of **32** when selectfluor was employed as an oxidant (entry 5). The hydroxylation was slightly improved to provide a 79% yield of **32** at 80 ^oC (entry 6). This reaction was sluggish using $PdCl_2$ as a catalyst and provided a 23% yield of **32**; however, $Pd_2(dba)_3$ was ineffective (entries 7, 8). Moreover, the use of 10 mol% of PPh_3 ligand or reducing the loading of selecfluor or lowering of loading of $Pd(OAc)_2$ (3.0 mol%) resulted in a diminished yield.

We assumed the product **32** could form *via* direct electrophilic C(5)–H activation (a more reactive site), and a concentrated solution should be ideal for this intermolecular reaction. While the formation of **46** could be a –CO-directed intramolecular reaction between coordinated Pd(II) and –*N*CH_3 C(sp^3)–H and might favor even in the dilute solution by restricting intermolecular C(5)–H palladation. With this, we checked the oxygenation of isatin in 1.0 mL of TFA/TFAA (0.2 M) (Table 3.2, entries 12). Thus, the use of selectfluor gave 36% of **32**, whereas $K_2S_2O_8$ provided 17% of **32** and 48% of **46** (Table 3.2, entries 13). Notably, using 1.5 mL of TFA/TFAA in the presence of $K_2S_2O_8$ improved the yield of **46** to 71% (entry 14); however, using 2 mL of TFA/TFAA in the presence of $K_2S_2O_8$ resulted in low conversion (entry 15). The reaction provided 93% of **46** upon performing for a short time (entry 8). Thus, the reaction selectively gave **46** in the presence of $K_2S_2O_8$ and 1.5 mL of TFA/TFAA (9:1) in 1 h (entries 16, 17). In contrast, the C5 hydroxylated product **32** was selectively obtained in 0.2 mL of TFA/TFAA (9:1) in the presence of a selectfluor.

Table 3.2. Optimization of Reaction Parameters for Hydroxylation [a]



(**1a**) (**32**) (**46**)

Entry	[Pd]	Oxidant	*T* (°C)/ t (h)	Yield (%) [b] **32**	**46**
1	$Pd(OAc)_2$	$PhI(OAc)_2$	100/20	10	trace
2	$Pd(OAc)_2$	$K_2S_2O_8$	100/20	49	trace
3	$Pd(OAc)_2$	NFSI	100/20	trace	--
4	$Pd(OAc)_2$	AgOAc	100/20	--	--
5	$Pd(OAc)_2$	selectfluor	100/20	72	trace
6	**$Pd(OAc)_2$**	**selectfluor**	**80/20**	**79**	--
7	$PdCl_2$	selectfluor	80/20	23	trace
8	$Pd_2(dba)_3$	selectfluor	80/20	--	--
9 [c]	$Pd(OAc)_2$	selectfluor	80/20	63	trace
10 [d]	$Pd(OAc)_2$	selectfluor	80/20	67	trace
11 [e]	$Pd(OAc)_2$	selectfluor	80/20	64	trace
12 [f]	$Pd(OAc)_2$	selectfluor	80/20	36	--
13 [f]	$Pd(OAc)_2$	$K_2S_2O_8$	100/20	17	48
14 [g]	$Pd(OAc)_2$	$K_2S_2O_8$	100/20	trace	71
15 [h]	$Pd(OAc)_2$	$K_2S_2O_8$	100/20	trace	65
16 [g]	$Pd(OAc)_2$	$K_2S_2O_8$	100/8	--	82
17 [g]	**$Pd(OAc)_2$**	**$K_2S_2O_8$**	**100/1**	**--**	**93**
18 [g]	$Pd(OAc)_2$	--	100/1	--	--
19 [g]	--	selectfluor	100/1	--	--

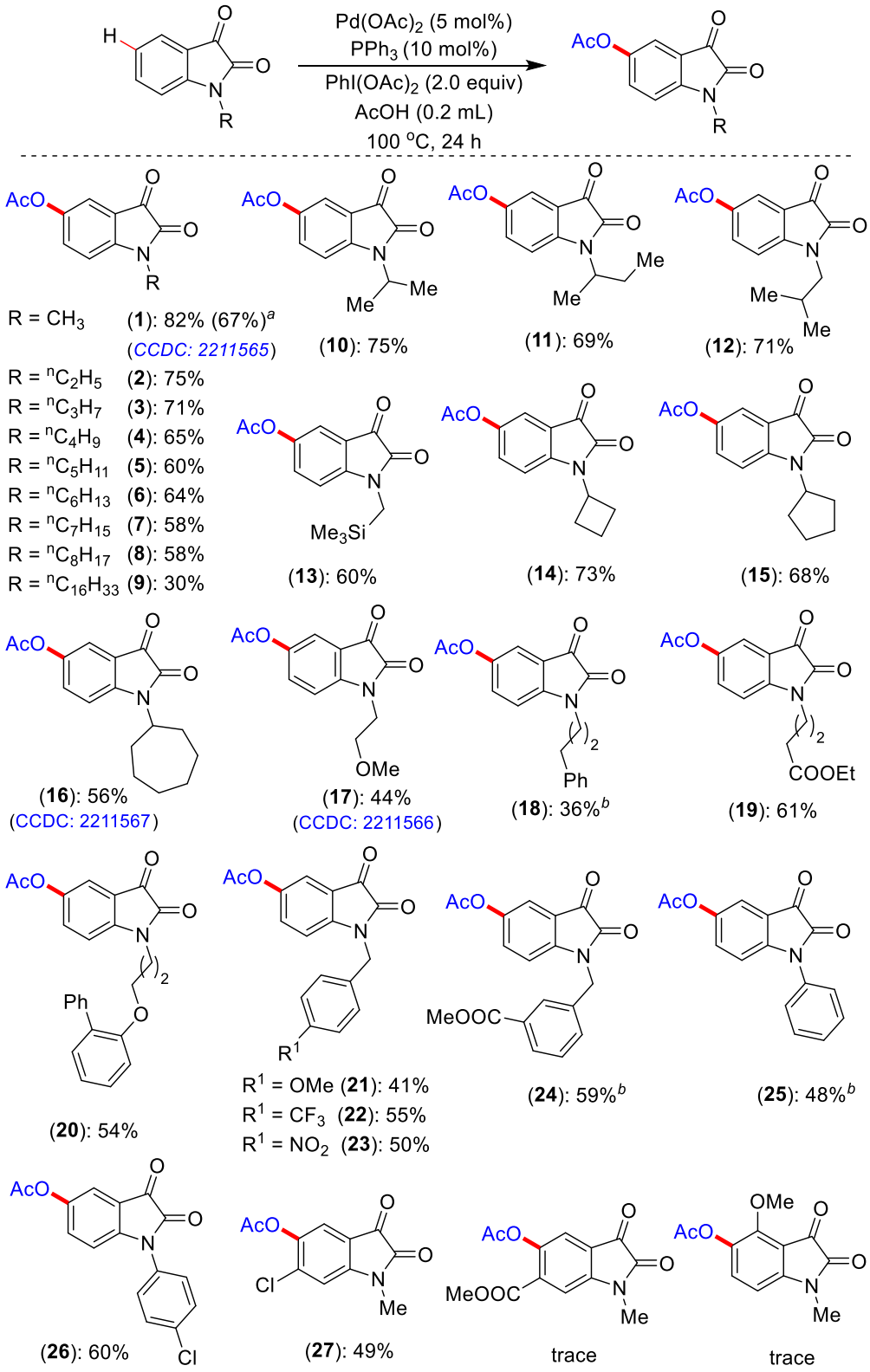
[a] Reaction Conditions: **1a** (0.032 g, 0.20 mmol), oxidant (0.40 mmol), [Pd] (0.01 mmol, 5.0 mol %). Entries 1-11: 0.2 mL of solvent was used. [b] Yields of isolated compounds. [c] 10 mol% of PPh_3 was used. [d] 1.5 equiv of selectfluor was used. [e] 3 mol% of $Pd(OAc)_2$ used. [f] 1.0 mL of TFA/TFAA solvent was used. [g] 1.5 mL of TFA/TFAA solvent was used. [h] 2.0 mL of TFA/TFAA solvent was used. TFA = Trifluoroacetic acid. TFAA = Trifluoroacetic anhydride.

The hydroxylation failed without an external oxidant or Pd catalyst (entries 18, 19). After an exhaustive screening, the C5 hydroxylation of isatins has effectively occurred under the following conditions: $Pd(OAc)_2$ (5.0 mol%), selectfluor (2.0 equiv), and TFA/TFAA (0.2 mL) at 80 ^oC for 20 h. Similarly, the *N*-methyl hydroxylation has effectively occurred under the following conditions: $Pd(OAc)_2$ (5.0 mol%), $K_2S_2O_8$ (2.0 equiv), and TFA/TFAA (1.5 mL) at 100 ^oC for 1 h.

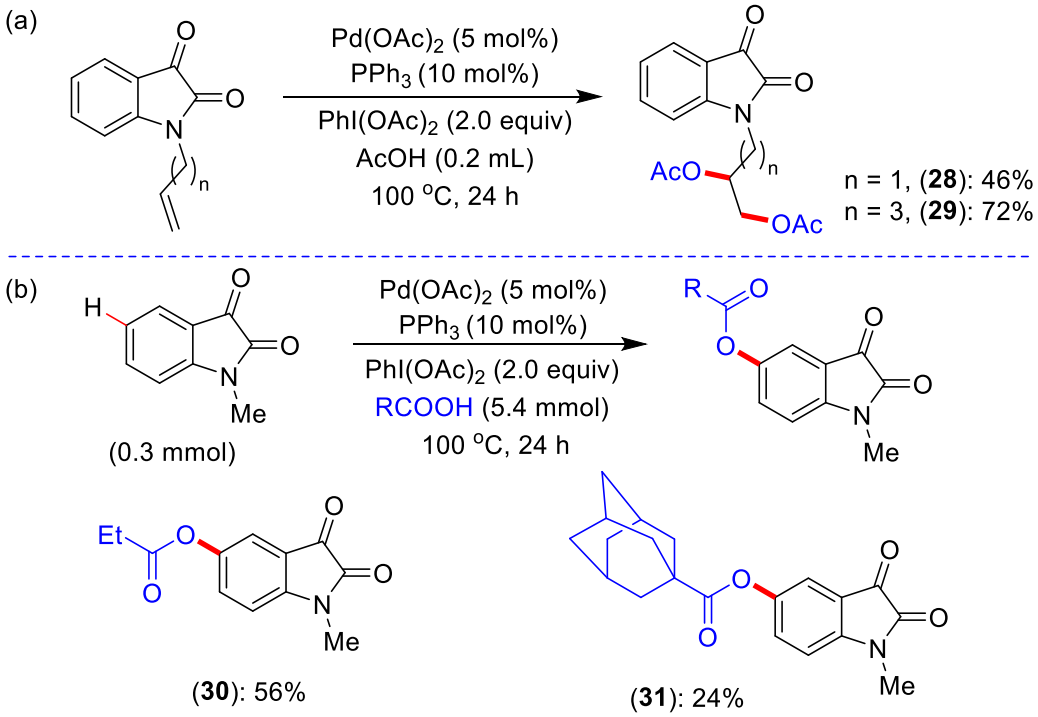
3.2.2 Scope for C(5)–H Acetoxylation of Isatins

Next, we started investigating the scope and limitations of the C5 acetoxylation of diverse isatins (Scheme 3.2). The isatins containing *N*-alkyl with different chain lengths reacted smoothly to give C5 acetoxylated products, **2**-**8**. The branched alkyl and cyclo-alkyl groups were also compatible (**10**-**16**). A synthetically important silyl moiety is tolerated on isatin and provided **13** in 60%. The isatins containing notable functionalities, such as −OMe, −Ph, −COOEt, and alkyl ether, reacted with low efficacy to afford compounds **17**-**20**. Similarly, functional groups like –OMe, $–CF_3$, $–NO_2$, and –COOMe at different positions of the *N*-benzyl isatins were well tolerated (**21**-**24**). The compatibility of such moieties is crucial for synthetic perspective and further derivatizations. In addition to the *N*-alkyl and *N*-benzyl isatins, the *N*-aryl substituted isatins were acetoxylated at the C5 position to give **25** and **26**. The C6-chloro-substituted *N*-methyl isatin yielded 49% of **27**, whereas the C6 ester substituted *N*-methylisatin was unreactive. Unfortunately, an isatin derivative having a C4 methoxy substituent could not participate in the reaction. The structures of **1**, **16,** and **17** were confirmed by X-ray diffraction study. Interestingly, the alkenyl-substituted isatins provided the diacetoxylation at the alkenyl C(sp^2)–H position leading to **28** and **29** in 46% and 72% yields, respectively (Scheme 3.3a). In fact, these two diacetoxylations were also observed under the Pd-free conditions.[46,47] Unfortunately, the free *NH* isatin and isatins containing –CN, –OH, or heterocycle groups remained unreacted.

The acyloxylated compounds, **30** and **31**, were obtained in low to moderate yields using the propionic and adamantine carboxylic acids, respectively (Scheme 3.3b). Notably, a trace amount of acetoxylated (−OAc) product was also observed in both cases that might originate from $PhI(OAc)_2$.



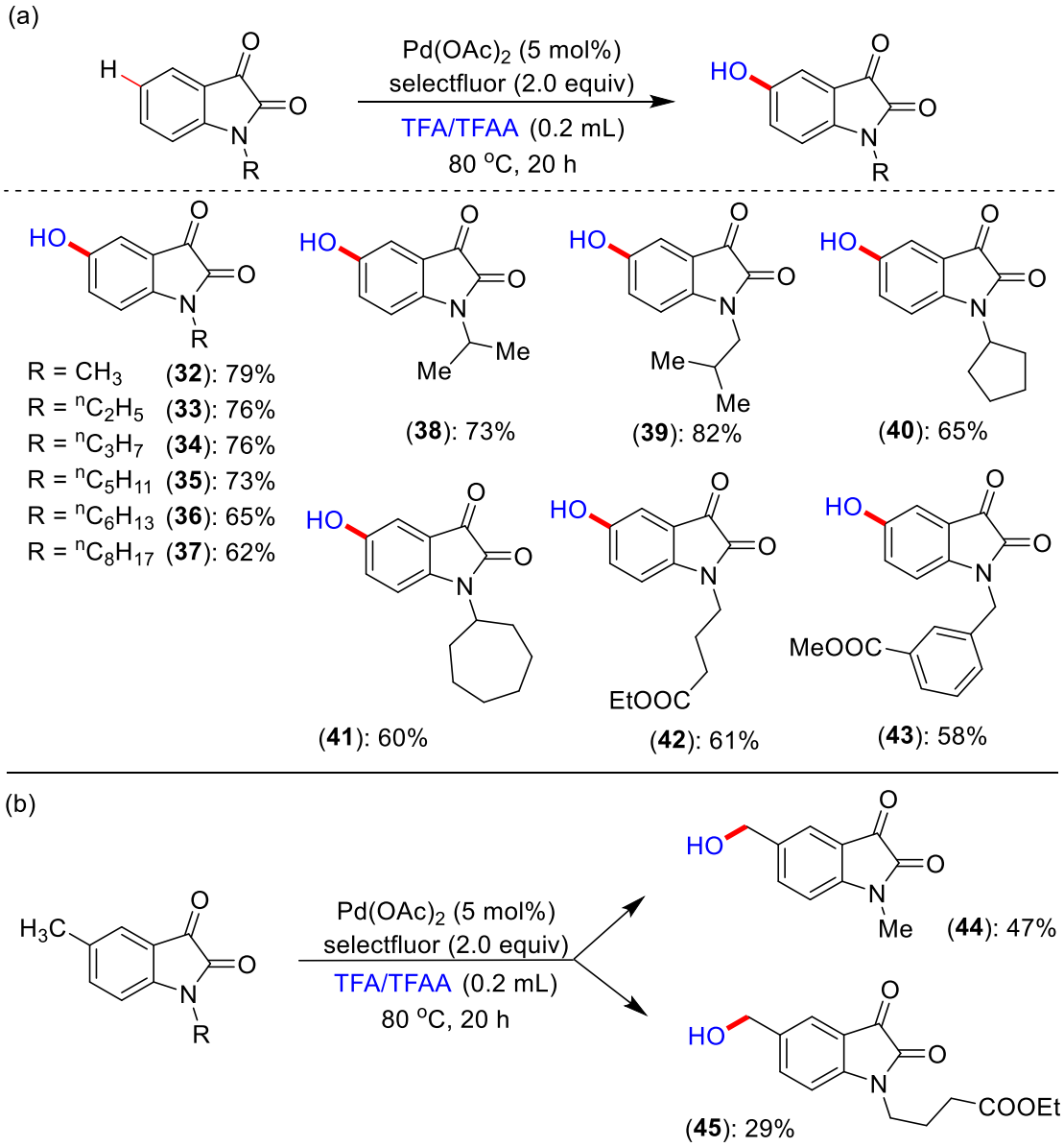
Scheme 3.2. Scope for C5 C(sp^2)–H Acetoxylation of Isatins. Conditions: Isatin (0.20 mmol), $PhI(OAc)_2$ (0.40 mmol), $Pd(OAc)_2$ (0.0022 g, 0.01 mmol), PPh_3 (0.02 mmol, 10 mol%), and AcOH (0.2 mL). [a] Yield for 3.1 mmol scale. [b] Yield by ^1H NMR.



Scheme 3.3 (a) Acetoxylation of *N*-Alkenyl Isatins (with or without Pd), (b) Acyloxylation of Isatins.

3.2.3 Scope for C(5)–H Hydroxylation of Isatins

Like the acetoxylation, various isatins participated in the hydroxylation using selectfluor in TFA/TFAA to afford moderate to good yields of the C5 hydroxylated isatins (Scheme 3.4a). The alkyl, cycloalkyl, and benzyl substitutions at the *N*-position of isatin were tolerated. The compatibility of synthetically useful functionalities like −COOEt and −COOMe is notable (**42**, **43**). To our surprise, when C5 methylated isatins were subjected to oxygenation, the C5-CH_3 C(sp^3)−H hydroxylation was observed, albeit in low to moderate yields (**44** and **45**; Scheme 3.4b).

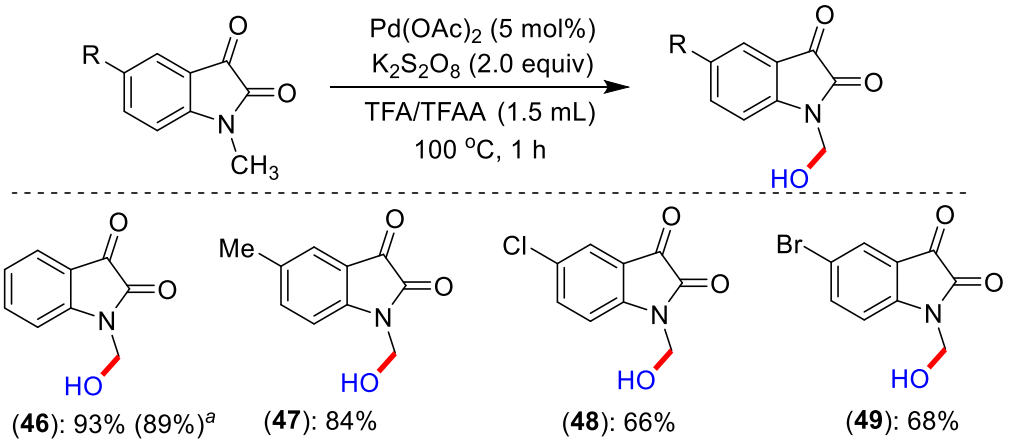


Scheme 3.4 Scope for (a) C5 C(sp^2)–H Hydroxylation, and (b) C5-CH_3 C(sp^3)–H Hydroxylation of Isatins.

3.2.4 Scope for *N*-Methyl Hydroxylation of Isatins

The $Pd(OAc)_2$-catalyzed reaction using $K_2S_2O_8$ as an oxidant and 1.5 mL of TFA/TFAA at 100 °C for 1 h afforded selective *N*-methyl C(sp^3)–H bond hydroxylation (Scheme 3.5). The unsubstituted C5 methyl and halides (Cl, Br) substituted *N*-methyl isatins gave *N*-methyl C(sp^3)–H bond hydroxylated products **46-49** in good yields. Notably, the *N*-methyl hydroxylated products are considerably unstable, resulting in decomposition. The *N*-ethyl isatin as substrate did not provide CH_2 C(sp^3)–H or the C5 C(sp^2)–H hydroxylation under this reaction condition. Isatins bearing –F, $–NO_2$, –OH, or –OAc at the C5 position

failed to participate in the reaction. The site-selective hydroxylation of the –*N*CH_3 C(sp^3)–H bond in the presence of activated C5 C(sp^2)–H bond is remarkable. This chemoselective hydroxylation is phenomenal, as such an approach can be applied in synthesizing crucial molecules of choice.

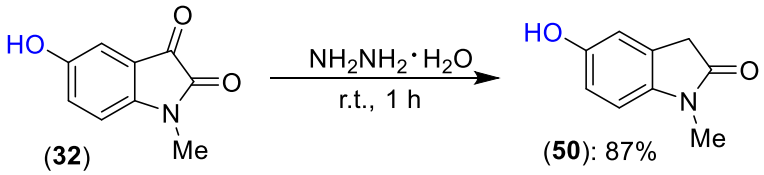


Scheme 3.5 Scope for *N*-CH_3 C(sp^3)–H Hydroxylation (Conditions: Isatin (0.20 mmol), $K_2S_2O_8$ (0.40 mmol), $Pd(OAc)_2$ (0.0022 g, 0.01 mmol), and TFA/TFAA (1.5 mL, 9:1 ratio). [a] Reaction performed under argon atmosphere.)

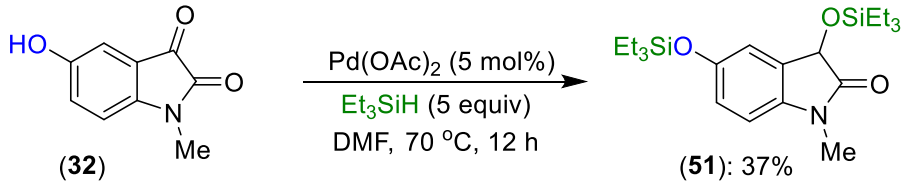
3.2.5 Synthetic Transformation of Oxygenated Isatins

A 3.1 mmol scale reaction of 1-methylindoline-2,3-dione (**1a**) afforded **1** in 67% yield (Scheme 3.2). The hydroxylated isatin **32** could undergo semi-reduction to oxindole **50** in 87% yield (Scheme 3.6a). Moreover, compound **32** could be converted to highly functionalized **51**, albeit in moderate yield (Scheme 3.6b).[23] In an attempt to synthesize *MAO inhibitor* (anti-depression agent, shown in Scheme 1a), we obtained (benzyloxy)oxindole **52** (Scheme 3.6c). Similarly, the C3 carbonyl in **32** can be smoothly functionalized to obtain (benzyloxy)imino-5-hydroxy-1-methylindolin-2-one, **53** in 49% yield (Scheme 3.6d). Finally, the biologically relevant compound *bufotenine derivative*, **56** was synthesized in three steps starting from **32** in good yield (Scheme 3.6e).[48-49]

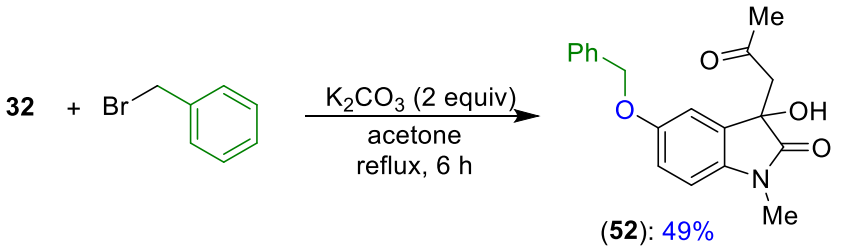
a) Reduction of C5 hydroxylated isatin to C5 hydroxylated oxindole



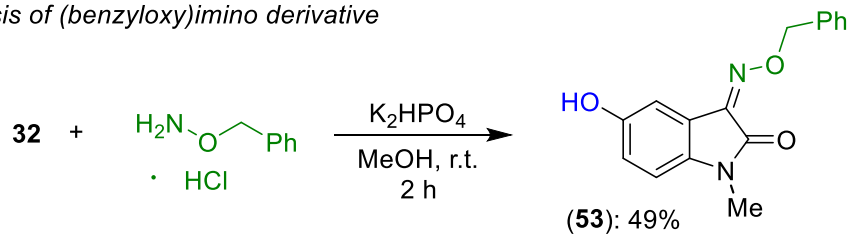
b) Silylation of C5 hydroxylated isatin



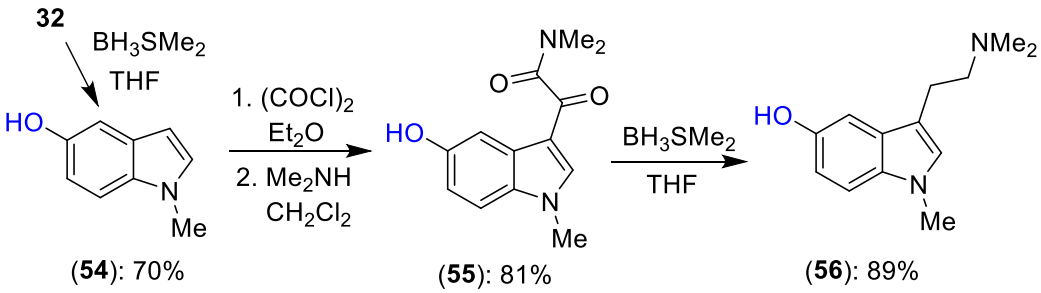
*c) Synthesis of (benzyloxy)oxindolinone: (**MAO inhibitor** derivative)*



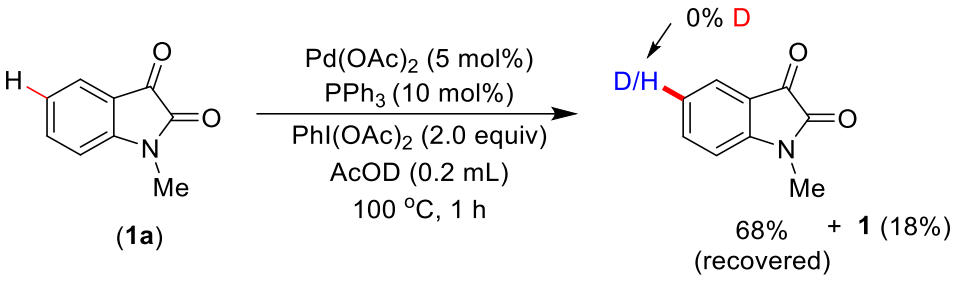
d) Synthesis of (benzyloxy)imino derivative



*e) Synthesis of **bufotenine drug** derivative*

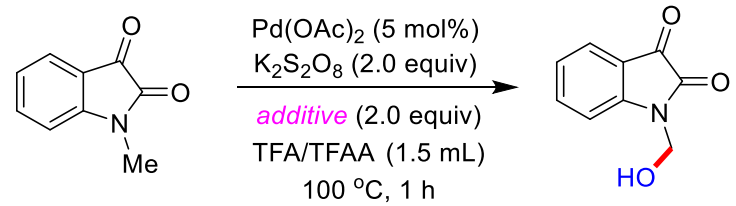


Scheme 3.6. Synthetic Transformation of C5 Hydroxy-Isatin.



Scheme 3.7 *H/D* Scrambling Experiment.

The ineffectiveness of Pd(0) and the high efficiency of Pd(II) as a catalyst suggest that Pd(II) could be an active catalyst. A greater reactivity of isatin with $Pd(OAc)_2$ over $PdCl_2$ supports an electrophilic-type C(5)–H activation. The use of CH_3COOD in the acetoxylation did not show *H/D* scrambling at the C5 position of **1a**, indicating the irreversible C5 C(sp^2)–H palladation (Scheme 3.7). This C–H oxygenation also proceeded quantitatively under an argon atmosphere, ruling out the atmospheric O_2 or H_2O as the oxygen source for the reaction. Further, the radical scavenger/inhibition experiments suggested the involvement of a radical intermediate for the *N*-CH_3 C–H hydroxylation of isatin (Scheme 3.8).



additive	(**46**)	recover (**1a**)
Tempo	--	0.18 mmol
Galvinoxy	--	0.17 mmol
BHT	--	0.16 mmol

Scheme 3.8 External Additive Experiments for *N*-Methyl Hydroxylated Isatins.

3.2.6 Probable Catalytic Cycle

Based on preliminary observations and literature,[41,50,51] we have proposed two catalytic cycles (Figure 3.1). For the C5 acetoxylation (path I), the reaction would be initiated by electrophilic C(5)–H activation of **1a** with $Pd(OAc)_2$ to form **A**. The intermediate **A** will undergo oxidation to **B**, followed by the reductive elimination to afford **1** and Pd(II). For –*N*CH_3 C(sp^3)–H hydroxylation (path II), the radical intermediate **D** is generated in situ by hydrogen-atom abstraction by sulfate radical anion produced from $K_2S_2O_8$. Next, the radical

combination leads to Pd(IV) species **E**, followed by the reductive elimination of **46**. We believe that both the reaction concentrations and the type of oxidants play a significant role in the selectivity of oxygenation.

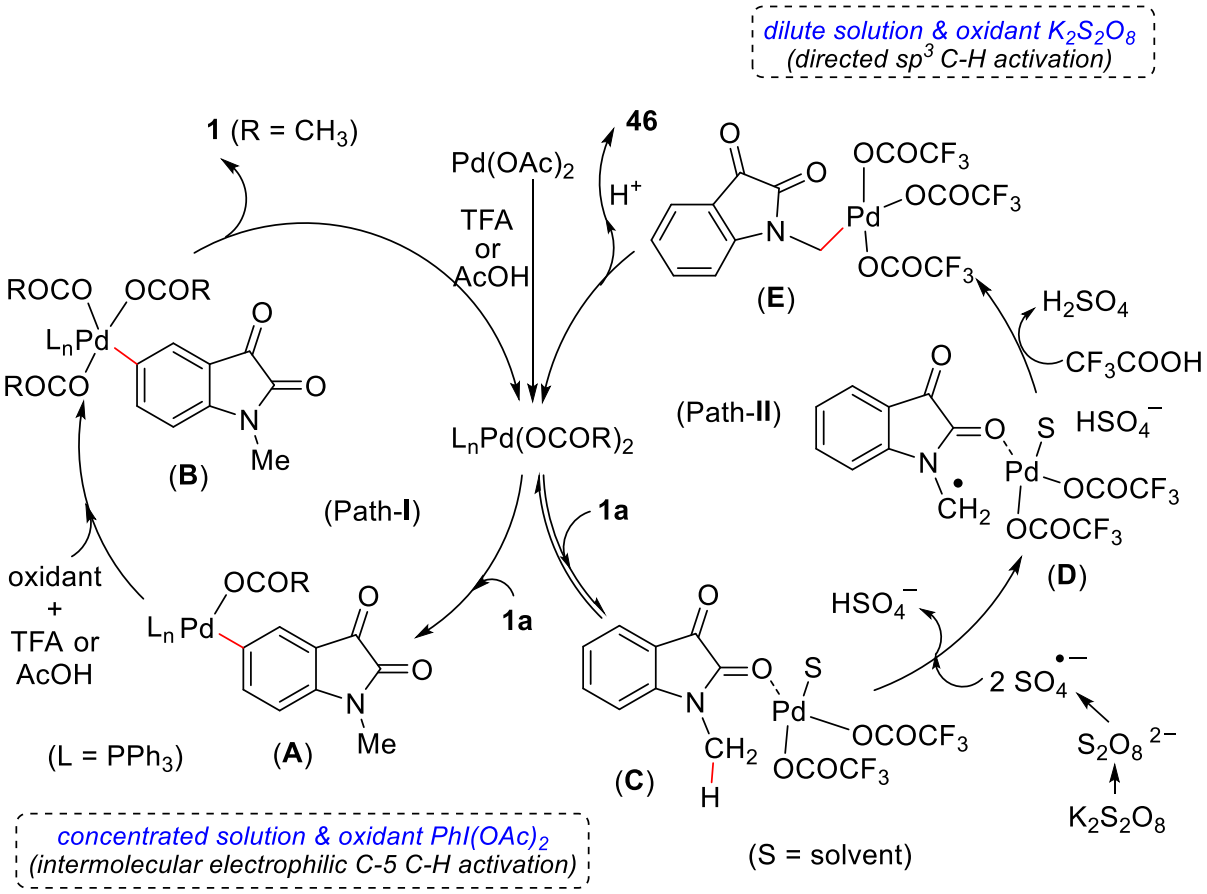


Figure 3.1 Plausible Catalytic Cycles for C5 C(sp^2)–H and –*N*CH_3 C(sp^3)–H Oxygenation.

3.3 CONCLUSION

In summary, we developed an efficient and unified protocol for the palladium-catalyzed chemoselective C5 C(sp^2)–H and *N*-methyl C(sp^3)–H oxygenation of isatin derivatives employing user-friendly oxidants. The use of $PhI(OAc)_2$ or selectfluor oxidant in the Pd-catalyzed protocol in 1.0 M acidic solution exclusively provided C5 oxygenation of isatins via electrophilic palladation, whereas the same reaction employing $K_2S_2O_8$ in dilute solution (0.13 M) selectively afforded *N*-methyl C(sp^3)–H oxygenation through carbonyl-assisted intramolecular –*N*CH_3 C(sp^3)–H radical palladation. The synthetic utility of oxygenation is exemplified by performing a gram-scale reaction, and further derivatization was demonstrated by synthesizing hydroxylated oxindole, silylated isatins, (benzyloxy)oxindolinone, (benzyloxy)imino derivative, and a bufotenine drug compound.

3.4 EXPERIMENTAL SECTION

3.4.1 General Information

The catalytic reactions were performed in oven-dried reaction vessels with a Teflon screw cap under an air atmosphere. The isatin derivatives were synthesized according to the previously described procedures.[52-54] All other chemicals were obtained from commercial sources and were used without further purification. High-resolution mass spectrometry (HRMS) mass spectra were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump. NMR: (^{1}H and ^{13}C{^{1}H}) spectra were recorded at 400 or 500 MHz (^{1}H), 100 or 125 MHz {^{13}C{^{1}H}, DEPT (distortionless enhancement by polarization transfer)}, 377 MHz (^{19}F), respectively in $CDCl_3$ and DMSO-d_6 solutions, if not otherwise specified; chemical shifts (δ) are given in ppm. The ^{1}H and ^{13}C{^{1}H} NMR spectra are referenced to residual solvent signals ($CDCl_3$: δ H = 7.26 ppm, δ C = 77.2 ppm; DMSO-d_6: δ H = 2.50 ppm, δ C = 39.5 ppm). The splitting patterns of NMR are abbreviated as follows: s = singlet; br s = broad singlet; d = doublet; t = triplet; q = quartet; sept = septet; dd = doublet of doublets; td = triplet of doublets; m = multiplet.

3.4.2 Procedure for the Oxygenation of Isatins

Representative Procedure A. **Synthesis of C-5 Acetoxylated Isatin:** To an oven-dried screw-cap tube equipped with magnetic stir bar were introduced 1-methylindoline-2,3-dione (**1a**; 0.032 g, 0.20 mmol), $PhI(OAc)_2$ (0.129 g, 0.40 mmol), $Pd(OAc)_2$ (0.0022 g, 0.01 mmol, 5.0 mol%) and PPh_3 (0.0053 g, 0.02 mmol, 10.0 mol%). To the resulting mixture, AcOH (0.2 mL) was added and stirred at 100 °C in a preheated oil bath for 24 h. At ambient temperature, the reaction mixture was quenched with $NaHCO_3$ (aq) solution, and the crude product was extracted with EtOAc (10 mL x 3). The combined organic extract was dried over Na_2SO_4, and the volatiles were evaporated in *vacuo*. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) to yield compound **1** (0.036 g, 82%) as an orange solid. M.p: 140-143 ^{o}C.

Representative Procedure B. **Synthesis of C-5 Hydroxylated Isatin:** To an oven-dried screw-cap tube equipped with magnetic stir bar were introduced 1-methylindoline-2,3-dione (**1a**; 0.032 g, 0.20 mmol), selectfluor (0.142 g, 0.40 mmol), and $Pd(OAc)_2$ (0.0022 g, 0.01 mmol, 5.0 mol%). To the resulting mixture, TFA/TFAA (9:1) (0.2 mL) was added and stirred at 80 °C in a preheated oil bath for 20 h. At ambient temperature, the reaction mixture was

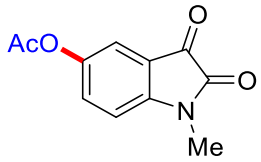
quenched with $NaHCO_3$ (aq) solution, and the crude product was extracted with EtOAc (10 mL x 3). The combined organic extract was dried over Na_2SO_4, and the volatiles were evaporated in vacuo. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 2/1) to yielded **32** (0.028 g, 79%) as a dark red solid. M.p: 125-128 ^oC.

Representative Procedure C. **Synthesis of *N*-Methyl Hydroxylated Isatin:** To an oven-dried screw-cap tube equipped with magnetic stir bar were introduced 1-methylindoline-2,3-dione (**1a**; 0.032 g, 0.20 mmol), $K_2S_2O_8$ (0.108 g, 0.40 mmol), and $Pd(OAc)_2$ (0.0022 g, 0.01 mmol, 5.0 mol%). To the resulted mixture, TFA/TFAA (9:1) (1.5 mL) was added and stirred at 100 °C in a preheated oil bath for 1 h. At ambient temperature, the reaction mixture was quenched with $NaHCO_3$ (aq) solution and the crude product was extracted with EtOAc (10 mL x 3). The combined organic extract was dried over Na_2SO_4, and the volatiles were evaporated in *vacuo*. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 3/1), yielding **46** (0.033 g, 93%) as a yellow solid. M.p: 119-122 ^oC.

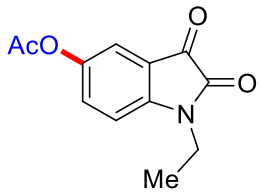
Procedure for Gram Scale. **Synthesis of Compound 1:** To an oven-dried screw-cap tube (15 ml) equipped with magnetic stir bar were introduced 1-methylindoline-2,3-dione (**1a**; 0.50 g, 3.10 mmol), $PhI(OAc)_2$ (2.0 g, 6.20 mmol), $Pd(OAc)_2$ (0.035 g, 0.15 mmol, 5.0 mol%) and PPh_3 (0.081 g, 0.31 mmol, 10.0 mol%). To the resulted mixture, AcOH (2.5 mL) was added and stirred at 100 °C in a preheated oil bath for 24 h. At ambient temperature, the reaction mixture was quenched with $NaHCO_3$ (aq) solution, and the crude product was extracted with EtOAc (10 mL x 3). The combined organic extract was dried over Na_2SO_4, and the volatiles were evaporated in *vacuo*. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) to yield compound **1** (0.453 g, 67%) as an orange solid.

3.4.3 Characterization Data of Oxygenated Isatins

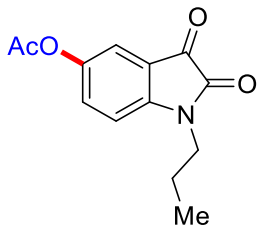
3.4.3.1 Characterization Data of C5 Acetoxylated Isatins



1-Methyl-2,3-dioxoindolin-5-yl acetate (1): ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.34-7.32 (m, 2H, Ar–H), 6.90 (d, J = 8.2 Hz, 1H, Ar–H), 3.25 (s, 3H, CH_3), 2.30 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 182.8 (CO), 169.4 (CO), 158.3 (CO), 149.0 (C_q), 147.1 (C_q), 131.4 (CH), 119.0 (CH), 118.0 (C_q), 110.7 (CH), 26.5 (CH_3), 21.1 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{10}NO_4^+$ 220.0604; Found 220.0600.

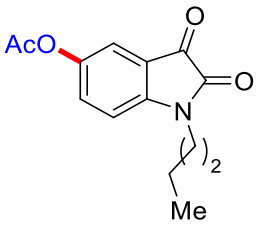


1-Ethyl-2,3-dioxoindolin-5-yl acetate (2): The representative procedure **A** was followed, using substrate **2a** (0.035 g, 0.20 mmol) and $PhI(OAc)_2$ (0.129 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **2** (0.035 g, 75%) as a light orange solid. M.p: 146-149 ^{o}C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.33 (d, J = 2.4 Hz, 1H, Ar–H), 7.31 (dd, J = 8.4, 2.4 Hz, 1H, Ar–H), 6.90 (d, J = 8.4 Hz, 1H, Ar–H), 3.78 (q, J = 7.3 Hz, 2H, CH_2), 2.30 (s, 3H, CH_3), 1.30 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 183.2 (CO), 169.4 (CO), 157.9 (CO), 148.2 (C_q), 146.9 (C_q), 131.4 (CH), 119.2 (CH), 118.1 (C_q), 110.8 (CH), 35.2 (CH_2), 21.1 (CH_3), 12.6 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{12}NO_4^+$ 234.0761; Found 234.0757.

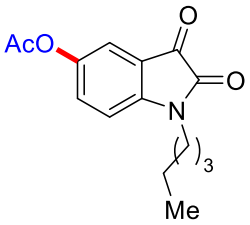


2,3-Dioxo-1-propylindolin-5-yl acetate (3): The representative procedure **A** was followed, using substrate **3a** (0.038 g, 0.20 mmol) and $PhI(OAc)_2$ (0.129 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **3** (0.035 g, 71%)

as a light orange solid. M.p: 103-106 ^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, J = 2.0 Hz, 1H, Ar–H), 7.30 (dd, J = 8.5, 2.4 Hz, 1H, Ar–H), 6.89 (d, J = 8.5 Hz, 1H, Ar–H), 3.69 (t, J = 7.3 Hz, 2H, CH_2), 2.30 (s, 3H, CH_3), 1.77-1.68 (m, 2H, CH_2), 0.99 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 183.1 (CO), 169.5 (CO), 158.3 (CO), 148.7 (C_q), 146.9 (C_q), 131.4 (CH), 119.1 (CH), 118.1 (C_q), 111.0 (CH), 42.1 (CH_2), 21.1 (CH_3), 20.8 (CH_2), 11.5 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{14}NO_4^+$ 248.0917; Found 248.0914.

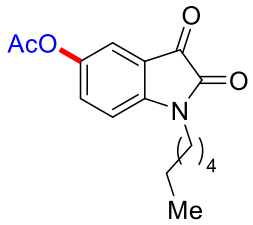


1-Butyl-2,3-dioxoindolin-5-yl acetate (4): The representative procedure **A** was followed, using substrate **4a** (0.041 g, 0.20 mmol) and $PhI(OAc)_2$ (0.129 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **4** (0.034 g, 65%) as an orange liquid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.33 (d, J = 2.3 Hz, 1H, Ar–H), 7.30 (dd, J = 8.5, 2.5 Hz, 1H, Ar–H), 6.89 (d, J = 8.4 Hz, 1H, Ar–H), 3.71 (t, J = 7.2 Hz, 2H, CH_2), 2.30 (s, 3H, CH_3), 1.70-1.63 (m, 2H, CH_2), 1.42-1.37 (m, 2H, CH_2), 0.96 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 183.1 (CO), 169.5 (CO), 158.2 (CO), 148.6 (C_q), 146.9 (C_q), 131.3 (CH), 119.1 (CH), 118.1 (C_q), 111.0 (CH), 40.3 (CH_2), 29.4 (CH_2), 21.1 (CH_3), 20.8 (CH_2), 13.8 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{16}NO_4^+$ 262.1074; Found 262.1070.

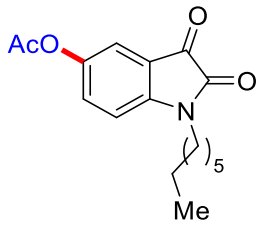


2,3-Dioxo-1-pentylindolin-5-yl acetate (5): The representative procedure **A** was followed, using substrate **5a** (0.044 g, 0.20 mmol) and $PhI(OAc)_2$ (0.129 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **5** (0.033 g, 60%) as an orange liquid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.33 (d, J = 2.4 Hz, 1H, Ar–H), 7.30 (dd, J = 8.4, 2.4 Hz, 1H, Ar–H), 6.89 (d, J = 8.4 Hz, 1H, Ar–H), 3.70 (t, J = 7.4 Hz, 2H,

CH_2), 2.30 (s, 3H, CH_3), 1.72-1.65 (m, 2H, CH_2), 1.36-1.33 (m, 4H, $2CH_2$), 0.89 (t, J = 6.8 Hz, 3H, CH_3). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 183.1 (CO), 169.5 (CO), 158.2 (CO), 148.6 (C_q), 146.9 (C_q), 131.3 (CH), 119.1 (CH), 118.1 (C_q), 111.0 (CH), 40.5 (CH_2), 29.1 (CH_2), 27.0 (CH_2), 22.4 (CH_2), 21.1 (CH_3), 14.0 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{18}NO_4^+$ 276.1230; Found 276.1225.

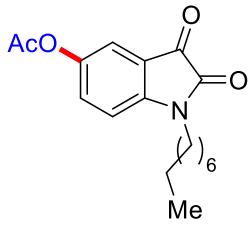


1-Hexyl-2,3-dioxoindolin-5-yl acetate (6): The representative procedure **A** was followed, using substrate **6a** (0.046 g, 0.20 mmol) and $PhI(OAc)_2$ (0.129 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **6** (0.037 g, 64%) as a dark orange liquid. ^1H-NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, J = 2.3 Hz, 1H, Ar–H), 7.30 (dd, J = 8.5, 2.4 Hz, 1H, Ar–H), 6.89 (d, J = 8.5 Hz, 1H, Ar–H), 3.71 (t, J = 7.4 Hz, 2H, CH_2), 2.30 (s, 3H, CH_3), 1.72-1.64 (m, 2H, CH_2), 1.40-1.29 (m, 6H, $3CH_2$), 0.88 (t, J = 6.9 Hz, 3H, CH_3). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 183.1 (CO), 169.5 (CO), 158.2 (CO), 148.7 (C_q), 146.9 (C_q), 131.3 (CH), 119.1 (CH), 118.1 (C_q), 111.0 (CH), 40.6 (CH_2), 31.5 (CH_2), 27.3 (CH_2), 26.7 (CH_2), 22.7 (CH_2), 21.1 (CH_3), 14.1 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{20}NO_4^+$ 290.1387; Found 290.1381.

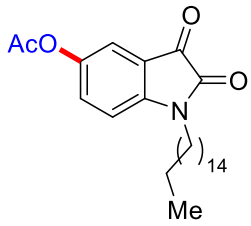


1-Heptyl-2,3-dioxoindolin-5-yl acetate (7): The representative procedure **A** was followed, using substrate **7a** (0.049 g, 0.20 mmol) and $PhI(OAc)_2$ (0.129 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **7** (0.035 g, 58%) as an orange liquid. ^1H-NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, J = 2.3 Hz, 1H, Ar–H), 7.30 (dd, J = 8.4, 2.4 Hz, 1H, Ar–H), 6.89 (d, J = 8.4 Hz, 1H, Ar–H), 3.71 (t, J = 7.4 Hz, 2H, CH_2), 2.30 (s, 3H, CH_3), 1.72-1.65 (m, 2H, CH_2), 1.35-1.25 (m, 8H, $4CH_2$), 0.87 (t, J = 6.8 Hz, 3H, CH_3). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 183.1 (CO), 169.5 (CO), 158.2 (CO),

148.7 (C_q), 146.9 (C_q), 131.3 (CH), 119.1 (CH), 118.1 (C_q), 111.0 (CH), 40.6 (CH_2), 31.8 (CH_2), 29.0 (CH_2), 27.4 (CH_2), 27.0 (CH_2), 22.7 (CH_2), 21.1 (CH_3), 14.2 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{22}NO_4^+$ 304.1543; Found 304.1538.

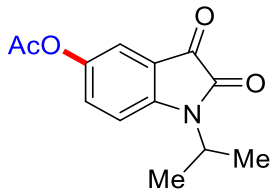


1-Octyl-2,3-dioxoindolin-5-yl acetate (8): The representative procedure **A** was followed, using substrate **8a** (0.052 g, 0.20 mmol) and $PhI(OAc)_2$ (0.129 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **8** (0.037 g, 58%) as an orange liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 2.4 Hz, 1H, Ar–H), 7.30 (dd, *J* = 8.5, 2.4 Hz, 1H, Ar–H), 6.89 (d, *J* = 8.4 Hz, 1H, Ar–H), 3.70 (t, *J* = 7.4 Hz, 2H, CH_2), 2.30 (s, 3H, CH_3), 1.71-1.64 (m, 2H, CH_2), 1.40-1.26 (m, 10H, $5CH_2$), 0.87 (t, *J* = 6.8 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 183.1 (CO), 169.5 (CO), 158.2 (CO), 148.7 (C_q), 146.9 (C_q), 131.3 (CH), 119.1 (CH), 118.1 (C_q), 111.0 (CH), 40.6 (CH_2), 31.9 (CH_2), 29.3 (2C, CH_2), 27.4 (CH_2), 27.0 (CH_2), 22.7 (CH_2), 21.1 (CH_3), 14.2 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{24}NO_4^+$ 318.1700; Found 318.1693.

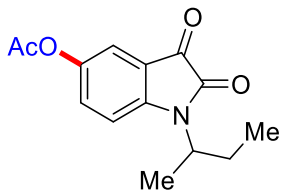


1-Hexadecyl-2,3-dioxoindolin-5-yl acetate (9): The representative procedure **A** was followed, using substrate **9a** (0.074 g, 0.20 mmol) and $PhI(OAc)_2$ (0.129 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **9** (0.026 g, 30%) as an orange solid. M.p: 83-86 ^{o}C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 2.3 Hz, 1H, Ar–H), 7.30 (dd, *J* = 8.4, 2.5 Hz, 1H, Ar–H), 6.89 (d, *J* = 8.4 Hz, 1H, Ar–H), 3.70 (t, *J* = 7.5 Hz, 2H, CH_2), 2.31 (s, 3H, CH_3), 1.69-1.65 (m, 2H, CH_2), 1.38-1.25 (m, 26H, $13CH_2$), 0.87 (t, *J* = 6.8 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 183.1 (CO), 169.5 (CO), 158.2 (CO), 148.7 (C_q), 146.9 (C_q), 131.3 (CH), 119.1 (CH), 118.2 (C_q), 111.0 (CH), 40.6 (CH_2), 32.1 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2),

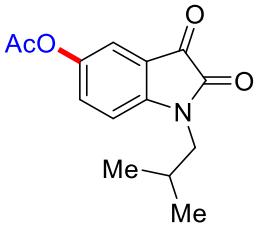
29.3 (5C, CH_2), 27.4 (CH_2), 27.1 (CH_2), 22.9 (CH_2), 21.1 (CH_3), 14.3 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{40}NO_4^+$ 430.2952; Found 430.2945.



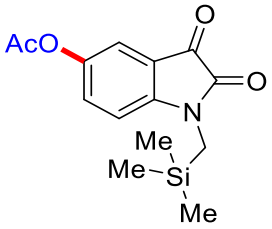
1-Isopropyl-2,3-dioxoindolin-5-yl acetate (10): The representative procedure **A** was followed, using substrate **10a** (0.038 g, 0.20 mmol) and $PhI(OAc)_2$ (0.129 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **10** (0.037 g, 75%) as an orange solid. M.p: 98-101 ^oC. ^1H-NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 2.4 Hz, 1H, Ar–H), 7.28 (dd, *J* = 8.8, 2.5 Hz, 1H, Ar–H), 7.02 (d, *J* = 8.6 Hz, 1H, Ar–H), 4.53 (sept, *J* = 7.0 Hz, 1H, CH), 2.31 (s, 3H, CH_3), 1.51 (d, *J* = 7.0 Hz, 6H, $2CH_3$). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 183.3 (CO), 169.5 (CO), 158.1 (CO), 148.1 (C_q), 146.6 (C_q), 131.1 (CH), 119.2 (CH), 118.6 (C_q), 112.2 (CH), 45.1 (CH), 21.1 (CH_3), 19.5 (2C, CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{14}NO_4^+$ 248.0917; Found 248.0914.



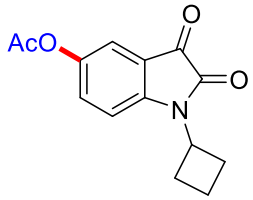
1-(sec-Butyl)-2,3-dioxoindolin-5-yl acetate (11): The representative procedure **A** was followed, using substrate **11a** (0.041 g, 0.20 mmol) and $PhI(OAc)_2$ (0.129 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **11** (0.036 g, 69%) as a dark orange liquid. ^1H-NMR (500 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 2.5 Hz, 1H, Ar–H), 7.27 (dd, *J* = 8.6, 2.5 Hz, 1H, Ar–H), 7.01 (d, *J* = 8.5 Hz, 1H, Ar–H), 4.33-4.24 (m, 1H, CH), 2.31 (s, 3H, CH_3), 2.06-1.94 (m, 1H, CH_2), 1.87-1.76 (m, 1H, CH_2), 1.48 (d, *J* = 7.0 Hz, 3H, CH_3), 0.93 (t, *J* = 7.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 183.2 (CO), 169.5 (CO), 158.2 (CO), 148.3 (C_q), 146.6 (C_q), 131.1 (CH), 119.2 (CH), 118.5 (C_q), 112.3 (CH), 51.2 (CH), 26.5 (CH_2), 21.1 (CH_3), 17.7 (CH_3), 11.5 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{16}NO_4^+$ 262.1074; Found 262.1073.



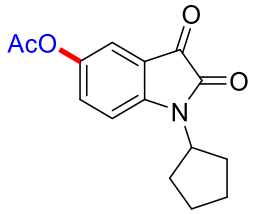
1-Isobutyl-2,3-dioxoindolin-5-yl acetate (12): The representative procedure **A** was followed, using substrate **12a** (0.041 g, 0.20 mmol) and $PhI(OAc)_2$ (0.129 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **12** (0.037 g, 71%) as an orange solid. M.p: 94-97 ^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, J = 2.4 Hz, 1H, Ar–H), 7.29 (dd, J = 8.4, 2.4 Hz, 1H, Ar–H), 6.89 (d, J = 8.5 Hz, 1H, Ar–H), 3.53 (d, J = 7.5 Hz, 2H, CH_2), 2.31 (s, 3H, CH_3), 2.16-2.09 (m, 1H, CH), 0.99 (d, J = 6.6 Hz, 6H, $2CH_3$). $^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$): δ = 183.1 (CO), 169.5 (CO), 158.5 (CO), 149.0 (C_q), 146.9 (C_q), 131.3 (CH), 119.1 (CH), 118.1 (C_q), 111.2 (CH), 48.0 (CH_2), 27.2 (CH), 21.1 (CH_3), 20.4 (2C, CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{16}NO_4^+$ 262.1074; Found 262.1073.



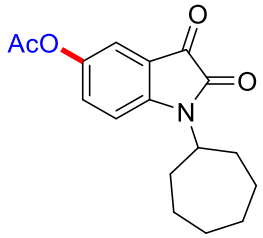
2,3-Dioxo-1-((trimethylsilyl)methyl)indolin-5-yl acetate (13): The representative procedure **A** was followed, using substrate **13a** (0.047 g, 0.20 mmol) and $PhI(OAc)_2$ (0.129 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **13** (0.035 g, 60%) as a red liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.23-7.19 (m, 2H, Ar–H), 6.73 (d, J = 8.3, 1H, Ar–H), 3.12 (s, 2H, CH_2), 2.23 (s, 3H, CH_3), 0.07 (s, 9H, $3CH_3$). $^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$): δ = 183.1 (CO), 169.4 (CO), 158.0 (CO), 149.4 (C_q), 146.8 (C_q), 131.0 (CH), 118.8 (CH), 118.3 (C_q), 110.9 (CH), 32.0 (CH_2), 21.1 (CH_3), –1.34 (3C, CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{18}NSiO_4^+$ 292.1000; Found 292.0995.



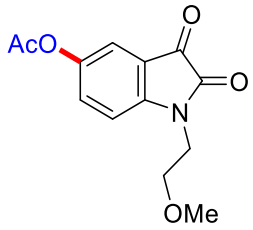
1-Cyclobutyl-2,3-dioxoindolin-5-yl acetate (14): The representative procedure **A** was followed, using substrate **14a** (0.041 g, 0.20 mmol) and $PhI(OAc)_2$ (0.129 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **14** (0.038 g, 73%) as an orange solid. M.p: 138-141 ^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, J = 2.4 Hz, 1H, Ar–H), 7.29 (dd, J = 8.5, 2.5 Hz, 1H, Ar–H), 7.07 (d, J = 8.5 Hz, 1H, Ar–H), 4.63-4.55 (m, 1H, CH), 2.87-2.76 (m, 2H, CH_2), 2.43-2.35 (m, 2H, CH_2), 2.31 (s, 3H, CH_3), 1.99-1.86 (m, 2H, CH_2). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 183.2 (CO), 169.5 (CO), 158.2 (CO), 148.7 (C_q), 146.8 (C_q), 131.1 (CH), 119.1 (CH), 118.4 (C_q), 112.1 (CH), 47.7 (CH), 27.6 (2C, CH_2), 21.1 (CH_3), 15.6 (CH_2). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{14}NO_4^+$ 260.0917; Found 260.0916.



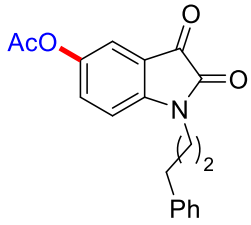
1-Cyclopentyl-2,3-dioxoindolin-5-yl acetate (15): The representative procedure **A** was followed, using substrate **15a** (0.043 g, 0.20 mmol) and $PhI(OAc)_2$ (0.129 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **15** (0.037 g, 68%) as a red solid. M.p: 110-113 ^{o}C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.34 (d, J = 2.5 Hz, 1H, Ar–H), 7.28 (dd, J = 8.5, 2.5 Hz, 1H, Ar–H), 6.96 (d, J = 8.5 Hz, 1H, Ar–H), 4.71-4.62 (m, 1H, CH), 2.30 (s, 3H, CH_3), 2.08-2.01 (m, 2H, CH_2), 2.00-1.90 (m, 4H, $2CH_2$), 1.75-1.69 (m, 2H, CH_2). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 183.1 (CO), 169.5 (CO), 158.2 (CO), 148.0 (C_q), 146.7 (C_q), 131.0 (CH), 119.1 (CH), 118.6 (C_q), 112.2 (CH), 53.3 (CH), 27.9 (2C, CH_2), 25.1 (2C, CH_2), 21.1 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{16}NO_4^+$ 274.1074; Found 274.1074.



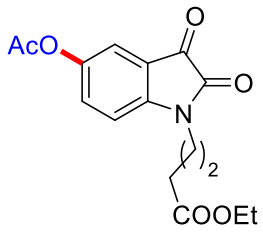
1-Cycloheptyl-2,3-dioxoindolin-5-yl acetate (16): The representative procedure **A** was followed, using substrate **16a** (0.049 g, 0.20 mmol) and $PhI(OAc)_2$ (0.129 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **16** (0.034 g, 56%) as a light red liquid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.33 (d, J = 2.5 Hz, 1H, Ar–H), 7.26 (dd, J = 8.5, 2.5 Hz, 1H, Ar–H), 7.00 (d, J = 8.5 Hz, 1H, Ar–H), 4.35-4.30 (m, 1H, CH), 2.30 (s, 3H, CH_3), 2.19-2.09 (m, 2H, CH_2), 1.92-1.78 (m, 4H, $2CH_2$), 1.74-1.66 (m, 2H, CH_2), 1.64-1.56 (m, 4H, $2CH_2$). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 183.5 (CO), 169.5 (CO), 157.5 (CO), 148.1 (C_q), 146.6 (C_q), 131.0 (CH), 119.1 (CH), 118.5 (C_q), 112.6 (CH), 54.8 (CH), 31.7 (2C, CH_2), 27.7 (2C, CH_2), 25.9 (2C, CH_2), 21.1 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{20}NO_4^+$ 302.1387; Found 302.1387.



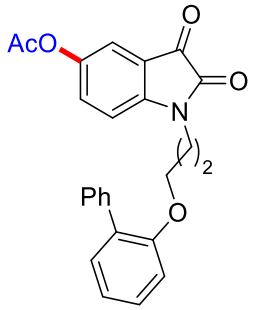
1-(2-Methoxyethyl)-2,3-dioxoindolin-5-yl acetate (17): The representative procedure **A** was followed, using substrate **17a** (0.041 g, 0.20 mmol) and $PhI(OAc)_2$ (0.129 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **17** (0.023 g, 44%) as a light yellow solid. M.p: 110-113 ^{o}C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.32 (d, J = 2.3 Hz, 1H, Ar–H), 7.29 (dd, J = 8.5, 2.5 Hz, 1H, Ar–H), 7.06 (d, J = 8.5 Hz, 1H, Ar–H), 3.90 (t, J = 5.2 Hz, 2H, CH_2), 3.63 (t, J = 5.1 Hz, 2H, CH_2), 3.33 (s, 3H, CH_3), 2.30 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 182.9 (CO), 169.5 (CO), 158.5 (CO), 149.2 (C_q), 146.9 (C_q), 131.4 (CH), 118.7 (CH), 118.0 (C_q), 112.2 (CH), 70.4 (CH_2), 59.2 (CH_3), 40.9 (CH_2), 21.1 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{14}NO_5^+$ 264.0866; Found 264.0867



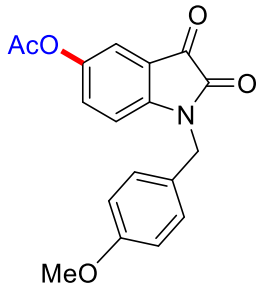
2,3-Dioxo-1-(3-phenylpropyl)indolin-5-yl acetate (18): The representative procedure **A** was followed, using substrate **18a** (0.053 g, 0.20 mmol) and $PhI(OAc)_2$ (0.129 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) **18** obtained as an orange liquid (36%, ^{1}H NMR yield). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.58-7.54 (m, 2H, Ar–H), 7.48-7.46 (m, 1H, Ar–H), 7.44-7.39 (m, 3H, Ar–H), 7.26 (dd, J = 8.5, 2.5 Hz, 1H, Ar–H), 6.72 (d, J = 8.4 Hz, 1H, Ar–H), 3.75 (t, J = 7.3 Hz, 2H, CH_2), 2.73 (t, J = 7.6 Hz, 2H, CH_2), 2.31 (s, 3H, CH_3), 2.05-1.96 (m, 2H, CH_2). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 182.9 (CO), 169.4 (CO), 158.3 (CO), 148.4 (C_q), 146.9 (C_q), 140.6 (C_q), 131.3 (CH), 128.7 (2C, CH), 128.5 (2C, CH), 126 (CH), 119.1 (CH), 118.1 (C_q), 110.9 (CH), 40.0 (CH_2), 33.2 (CH_2), 28.5 (CH_2), 21.1 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{18}NO_4^+$ 324.1230; Found 324.1226.



Ethyl 4-(5-acetoxy-2,3-dioxoindolin-1-yl)butanoate (19): The representative procedure **A** was followed, using substrate **19a** (0.052 g, 0.20 mmol) and $PhI(OAc)_2$ (0.129 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **19** (0.039 g, 61%) as an orange liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.34 (d, J = 2.3 Hz, 1H, Ar–H), 7.31 (dd, J = 8.4, 2.3 Hz, 1H, Ar–H), 7.06 (d, J = 8.4 Hz, 1H, Ar–H), 4.13 (q, J = 7.1 Hz, 2H, CH_2), 3.77 (t, J = 7.4 Hz, 2H, CH_2), 2.41 (t, J = 6.8 Hz, 2H, CH_2), 2.30 (s, 3H, CH_3), 2.03-1.96 (m, 2H, CH_2), 1.25 (t, J = 6.8 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 182.9 (CO), 172.8 (CO), 169.4 (CO), 158.3 (CO), 148.3 (C_q), 147.0 (C_q), 131.5 (CH), 119.1 (CH), 118.1 (C_q), 111.3 (CH), 60.9 (CH_2), 39.6 (CH_2), 31.0 (CH_2), 22.3 (CH_2), 21.1 (CH_3), 14.3 (CH_3) HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{18}NO_6^+$ 320.1129; Found 320.1129.

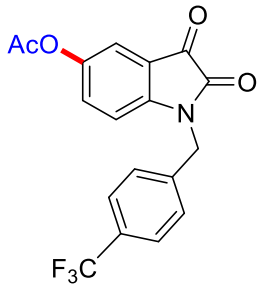


1-(4-([1,1'-Biphenyl]-2-yloxy)butyl)-2,3-dioxoindolin-5-yl acetate (20): The representative procedure **A** was followed, using substrate **20a** (0.074 g, 0.20 mmol) and $PhI(OAc)_2$ (0.129 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **20** (0.046 g, 54%) as an oily liquid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.58 (dd, J = 7.4, 0.9 Hz, 1H, Ar–H), 7.53-7.47 (m, 3H, Ar–H), 7.34-7.24 (m, 3H, Ar–H), 7.12 (t, J = 7.5 Hz, 1H, Ar–H), 7.05-7.00 (m, 2H, Ar–H), 6.94 (d, J = 8.8 Hz, 1H, Ar–H), 6.67 (d, J = 8.0 Hz, 1H, Ar–H), 3.99 (t, J = 5.4 Hz, 2H, CH_2), 3.65 (t, J = 6.9 Hz, 2H, CH_2), 2.29 (s, 3H, CH_3), 1.81-1.72 (m, 4H, $2CH_2$). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 183.7 (CO), 170.1 (CO), 158.3 (CO), 153.6 (C_q), 150.9 (C_q), 144.5 (C_q), 138.5 (CH), 137.8 (C_q), 132.0 (C_q), 129.6 (2C, CH), 128.1 (2C, CH), 127.3 (CH), 125.6 (CH), 124.0 (CH), 123.8 (CH), 121.3 (CH), 117.7 (C_q), 113.3 (CH), 110.3 (CH), 68.2 (CH_2), 40.0 (CH_2), 26.7 (CH_2), 24.3 (CH_2), 21.2 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{24}NO_5^+$ 430.1649; Found 430.1639.

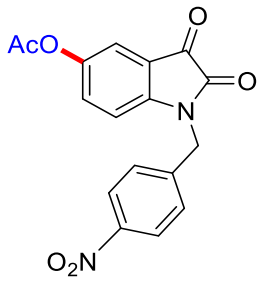


1-(4-Methoxybenzyl)-2,3-dioxoindolin-5-yl acetate (21): The representative procedure **A** was followed, using substrate **21a** (0.054 g, 0.20 mmol) and $PhI(OAc)_2$ (0.129 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **21** (0.027 g, 41%) as a dark orange solid. M.p: 120-123 ^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.60 (dd, J = 7.5, 0.8 Hz, 1H, Ar–H), 7.49 (td, J = 7.8, 1.3 Hz, 1H, Ar–H), 7.18 (dd, J = 8.4, 2.3 Hz, 1H, Ar–H), 7.09 (td, J = 7.6, 0.6 Hz, 1H, Ar–H), 7.04 (d, J = 2.3 Hz, 1H, Ar–H), 6.92 (d, J = 8.5 Hz, 1H, Ar–H), 6.80 (d, J = 8.0 Hz, 1H, Ar–H), 4.84 (s, 2H, CH_2), 3.80 (s, 3H, CH_3), 2.29 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 183.4 (CO), 169.0 (CO),

158.4 (CO), 151.2 (C_q), 150.7 (C_q), 140.2 (C_q), 138.5 (CH), 127.2 (C_q), 126.2 (CH), 125.6 (CH), 124.1 (CH), 122.5 (CH), 117.8 (C_q), 112.9 (CH), 111.1 (CH), 56.1 (CH_3), 43.4 (CH_2), 20.8 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{16}NO_5^+$ 326.1023; Found 326.1020.

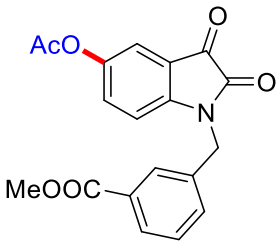


2,3-Dioxo-1-(4-(trifluoromethyl)benzyl)indolin-5-yl acetate (22): The representative procedure **A** was followed, using substrate **22a** (0.061 g, 0.20 mmol) and $PhI(OAc)_2$ (0.129 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **22** (0.04 g, 55%) as a yellow solid. M.p: 124-127 ^oC. ^1H-NMR (400 MHz, $CDCl_3$): δ = 7.62 (d, J = 8.1 Hz, 2H, Ar–H), 7.45 (d, J = 8.1 Hz, 2H, Ar–H), 7.39 (d, J = 2.4 Hz, 1H, Ar–H), 7.22 (dd, J = 8.5, 2.5 Hz, 1H, Ar–H), 6.72 (d, J = 8.5 Hz, 1H, Ar–H), 5.00 (s, 2H, CH_2), 2.29 (s, 3H, CH_3). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 182.3 (CO), 169.4 (CO), 158.3 (CO), 147.8 (C_q), 147.3 (C_q), 138.5 (C_q), 131.5 (CH), 131.0 (q, $^2J_{C–F}$ = 32.8 Hz, C_q), 127.9 (2C, CH), 126.4 (q, $^3J_{C–F}$ = 3.8 Hz, 2C, CH), 124.0 (q, $^1J_{C–F}$ = 272.4 Hz, CF_3), 119.4 (CH), 118.3 (C_q), 111.5 (CH), 43.9 (CH_2), 21.1 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −62.7 (s). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{13}NF_3O_4^+$ 364.0791; Found 364.0791.

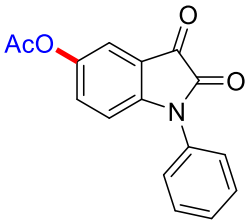


1-(4-Nitrobenzyl)-2,3-dioxoindolin-5-yl acetate (23): The representative procedure **A** was followed, using substrate **23a** (0.057 g, 0.20 mmol) and $PhI(OAc)_2$ (0.129 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **23** (0.034 g, 50%) as a red liquid. ^1H-NMR (500 MHz, $CDCl_3$): δ = 8.23 (d, J = 8.8 Hz, 2H, Ar–H), 7.51 (d, J = 8.8 Hz, 2H, Ar–H), 7.41 (d, J = 2.4 Hz, 1H, Ar–H), 7.24 (dd, J = 8.5, 2.4 Hz, 1H, Ar–H), 6.71 (d, J = 8.5 Hz, 1H, Ar–H), 5.03 (s, 2H, CH_2), 2.30 (s, 3H, CH_3).

$^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$): δ = 182.0 (CO), 169.3 (CO), 158.3 (CO), 148.1 (C_q), 147.5 (2C, C_q), 141.7 (C_q), 131.6 (CH), 128.4 (2C, CH), 124.6 (2C, CH), 119.6 (CH), 118.3 (C_q), 111.4 (CH), 43.7 (CH_2), 21.1 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{13}N_2O_6^+$ 341.0768; Found 341.0762.

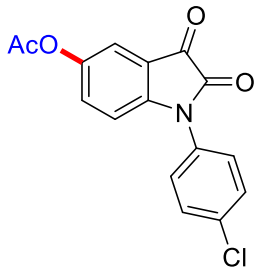


Methyl 3-(5-acetoxy-2,3-dioxoindolin-1-yl)methyl)benzoate (24): The representative procedure **A** was followed, using substrate **24a** (0.059 g, 0.20 mmol) and $PhI(OAc)_2$ (0.129 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) **24** obtained as a yellow solid (59%, ^{1}H NMR yield). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.99-7.97 (m, 2H, Ar–H), 7.52-7.51 (m, 1H, Ar–H), 7.43 (t, *J* = 7.6 Hz, 1H, Ar–H), 7.36 (d, *J* = 2.4 Hz, 1H, Ar–H), 7.20 (dd, *J* = 8.5, 2.4 Hz, 1H, Ar–H), 6.74 (d, *J* = 8.5 Hz, 1H, Ar–H), 4.96 (s, 2H, CH_2), 3.91 (s, 3H, CH_3), 2.28 (s, 3H, CH_3). $^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$): δ = 182.5 (CO), 169.4 (CO), 166.6 (CO), 158.3 (CO), 147.9 (C_q), 147.2 (C_q), 135.0 (C_q), 132.0 (CH), 131.4 (CH), 131.2 (C_q), 129.7 (CH), 129.5 (CH), 128.6 (CH), 119.2 (CH), 118.2 (C_q), 111.7 (CH), 52.5 (CH_3), 44.0 (CH_2), 21.1 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{16}NO_6^+$ 354.0972; Found 354.0969.

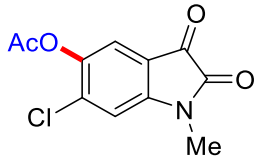


2,3-Dioxo-1-phenylindolin-5-yl acetate (25): The representative procedure **A** was followed, using substrate **25a** (0.045 g, 0.20 mmol) and $PhI(OAc)_2$ (0.129 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) **25** obtained as a yellow solid (48%, ^{1}H NMR yield). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.58-7.54 (m, 2H, Ar–H), 7.48-7.46 (m, 1H, Ar–H), 7.44-7.39 (m, 3H, Ar–H), 7.26 (dd, *J* = 8.5, 2.5 Hz, 1H, Ar–H), 6.90 (d, *J* = 8.6 Hz, 1H, Ar–H), 2.32 (s, 3H, CH_3). $^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$): δ = 182.4 (CO), 169.4 (CO), 157.3 (CO), 149.3 (C_q), 147.3 (C_q), 132.9 (C_q), 131.5 (CH), 130.2

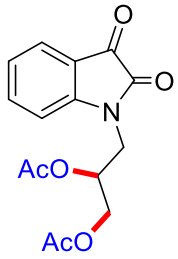
(2C, CH), 129.2 (CH), 126.1 (2C, CH), 119.1 (CH), 118.0 (C_q), 112.2 (CH), 21.1 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$Calcd for $C_{16}H_{12}NO_4^+$ 282.0761; Found 282.0756.



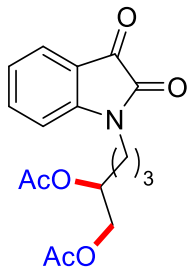
1-(4-Chlorophenyl)-2,3-dioxoindolin-5-yl acetate (26): The representative procedure **A** was followed, using substrate **26a** (0.052 g, 0.20 mmol) and $PhI(OAc)_2$ (0.129 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **26** (0.038 g, 60%) as a yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 8.8 Hz, 2H, Ar–H), 7.37 (d, 2.4 Hz, 1H, Ar–H), 7.30 (d, *J* = 8.6 Hz, 2H, Ar–H), 7.21 (dd, *J* = 8.6, 2.5 Hz, 1H, Ar–H), 6.82 (d, *J* = 8.6 Hz, 1H, Ar–H), 2.25 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 182.0 (CO), 169.4 (CO), 157.2 (CO), 148.7 (C_q), 147.5 (C_q), 134.9 (C_q), 131.6 (CH), 131.4 (C_q), 130.5 (2C, CH), 127.4 (2C, CH), 119.3 (CH), 118.1 (C_q), 112.0 (CH), 21.1 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{11}NO_4Cl^+$ 316.0371; Found 316.0374.



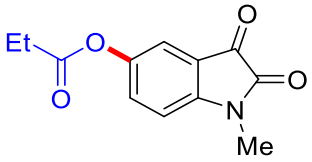
6-Chloro-1-methyl-2,3-dioxoindolin-5-yl acetate (27): The representative procedure **A** was followed, using substrate **27a** (0.039 g, 0.20 mmol) and $PhI(OAc)_2$ (0.129 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **27** (0.025 g, 49%) as a yellow liquid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 7.56 (s, 1H, Ar–H), 7.47 (s, 1H, Ar–H), 3.14 (s, 3H, CH_3), 2.32 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 181.8 (CO), 168.5 (CO), 158.2 (CO), 149.5 (C_q), 142.2 (C_q), 134.9 (C_q), 119.8 (CH), 116.9 (C_q), 112.1 (CH), 26.3 (CH_3), 20.3 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_9NClO_4^+$ 254.0215; Found 254.0217.



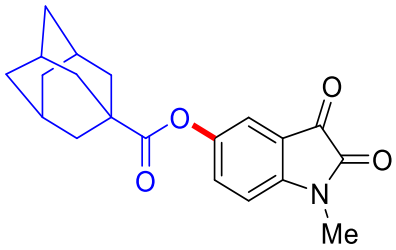
3-(2,3-Dioxoindolin-1-yl)propane-1,2-diyl diacetate) (28): The representative procedure **A** was followed, using substrate **28a** (0.038 g, 0.20 mmol) and $PhI(OAc)_2$ (0.129 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 2/1) yielded **28** (0.028 g, 46%) as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.64-7.59 (m, 2H, Ar–H), 7.14 (t, *J* = 7.6 Hz, 1H, Ar–H), 7.08 (d, *J* = 8.3 Hz, 1H, Ar–H), 5.32-5.27 (m, 1H, CH), 4.31 (dd, *J* = 12.3, 3.9 Hz, 1H, CH_2), 4.18 (dd, *J* = 12.3, 5.4 Hz, 1H, CH_2), 4.18 (dd, *J* = 14.6, 5.5 Hz, 1H, CH_2), 3.87 (dd, *J* = 14.6, 6.8 Hz, 1H, CH_2), 2.08 (s, 3H, CH_3), 2.02 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 182.7 (CO), 170.6 (CO), 170.5 (CO), 158.6 (CO), 150.8 (C_q), 138.6 (CH), 125.8 (CH), 124.3 (CH), 117.8 (C_q), 110.6 (CH), 69.0 (CH), 63.1 (CH_2), 40.6 (CH_2), 21.0 (CH_3), 20.8 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{16}NO_6^+$ 306.0972; Found 306.0969.



5-(2,3-Dioxoindolin-1-yl)pentane-1,2-diyl diacetate (29): The representative procedure **A** was followed, using substrate **29a** (0.043 g, 0.20 mmol) and $PhI(OAc)_2$ (0.129 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 2/1) yielded **29** (0.048 g, 72%) as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.60-7.56 (m, 2H, Ar–H), 7.11 (t, *J* = 7.5 Hz, 1H, Ar–H), 6.90 (d, *J* = 8.1 Hz, 1H, Ar–H), 5.10 (br s, 1H, CH), 4.20 (dd, *J* = 11.9, 3.3 Hz, 1H, CH_2), 4.02-3.98 (m, 1H, CH_2), 3.79-3.67 (m, 2H, CH_2), 2.04-2.02 (m, 6H, $2CH_3$), 1.77-1.63 (m, 4H, $2CH_2$). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 183.5 (CO), 170.8 (CO), 170.8 (CO), 158.4 (CO), 150.8 (C_q), 138.6 (CH), 125.7 (CH), 124.0 (CH), 117.8 (C_q), 110.2 (CH), 70.8 (CH), 64.9 (CH_2), 39.9 (CH_2), 28.2 (CH_2), 23.2 (CH_2), 21.1 (CH_3), 20.9 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{20}NO_6^+$ 334.1285; Found 334.1283.

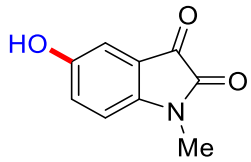


1-Methyl-2,3-dioxoindolin-5-yl propionate (30): The representative procedure **A** was followed, using substrate **1a** (0.048 g, 0.30 mmol), $PhI(OAc)_2$ (0.193 g, 0.6 mmol) and propionic acid (0.40 g, 5.4 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **30** (0.039 g, 56%) as a red solid. M.p: 122-125 ^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.35-7.31 (m, 2H, Ar–H), 6.89 (dd, J = 8.2, 0.6 Hz, 1H, Ar–H), 3.26 (s, 3H, CH_3), 2.60 (q, J = 7.5 Hz, 2H, CH_2), 1.26 (t, J = 7.5 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 182.9 (CO), 173.0 (CO), 158.3 (CO), 149.0 (C_q), 147.2 (C_q), 131.5 (CH), 119.1 (CH), 118.0 (C_q), 110.7 (CH), 27.8 (CH_2), 26.5 (CH_3), 9.1 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{12}NO_4^+$ 234.0761; Found 234.0760.

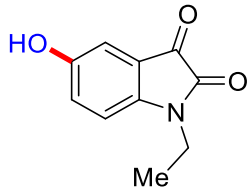


1-Ethyl-2,3-dioxoindolin-5-yl (1s,3s)-adamantane-1-carboxylate (31): The representative procedure **A** was followed, using substrate **1a** (0.048 g, 0.30 mmol), $PhI(OAc)_2$ (0.193 g, 0.60 mmol) and adamantane carboxylic acid (0.973 g, 5.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **31** (0.024 g, 24%) as a yellow solid. M.p: 130-133 ^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, J = 7.9 Hz, 1H, Ar–H), 7.12 (dd, J = 7.9, 1.5 Hz, 1H, Ar–H), 6.84 (d, J = 1.3 Hz, 1H, Ar–H), 3.25 (s, 3H, CH_3), 2.14 (br s, 3H, 3 CH), 1.92-1.90 (m, 6H, $3CH_2$), 1.84-1.71 (m, 6H, $3CH_2$). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 183.0 (2C, CO), 164.1 (CO), 159.1 (C_q), 152.0 (C_q), 125.3 (CH), 120.7 (CH), 115.5 (C_q), 107.0 (CH), 42.8 (3C, CH_2), 38.8 (C_q), 36.6 (3C, CH_2), 28.8 (3C, CH), 26.3 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{22}NO_4^+$ 340.1543; Found 340.1542.

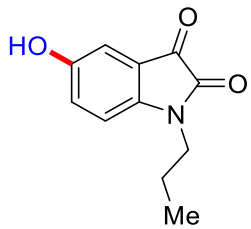
3.4.3.2 Characterization Data of C5 Hydroxylated Isatins



5-Hydroxy-1-methylindoline-2,3-dione (**32**)**:** ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 9.65 (s, 1H, OH), 7.07-7.04 (m, 1H, Ar–H), 6.96 (d, J = 8.5 Hz, 1H, Ar–H), 6.89 (d, J = 2.5 Hz, 1H, Ar–H), 3.08 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, DMSO-d_6): δ = 184.0 (CO), 158.1 (CO), 153.7 (C_q), 143.8 (C_q), 124.3 (CH), 117.9 (C_q), 111.5 (CH), 110.6 (CH), 26.0 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_9H_8NO_3^+$ 178.0499; Found 178.0499.

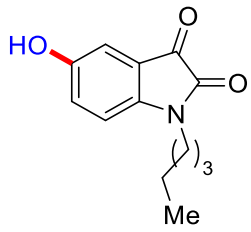


1-Ethyl-5-hydroxyindoline-2,3-dione (33): The representative procedure **B** was followed, using substrate **2a** (0.035 g, 0.20 mmol) and selectfluor (0.142 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 2/1) yielded **33** (0.029 g, 76%) as a red solid. M.p: 129-132 ^{o}C. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 9.63 (s, 1H, OH), 7.06-7.00 (m, 2H, Ar–H), 6.90 (d, J = 2.3 Hz, 1H, Ar–H), 3.64 (q, J = 7.3 Hz, 2H, CH_2), 1.15 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, DMSO-d_6): δ = 184.2 (CO), 157.7 (CO), 153.6 (C_q), 142.7 (C_q), 124.3 (CH), 118.0 (C_q), 111.6 (CH), 110.8 (CH), 34.2 (CH_2), 12.0 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{10}NO_3^+$ 192.0655; Found 192.0658.

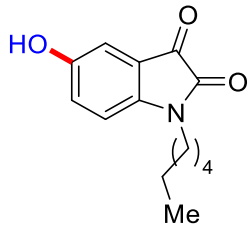


5-Hydroxy-1-propylindoline-2,3-dione (34): The representative procedure **B** was followed using substrate **3a** (0.038 g, 0.20 mmol) and selectfluor (0.142 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 2/1) yielded **34** (0.031 g, 76%) as a red solid. M.p: 121-124 ^{o}C. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 9.63 (s, 1H, OH), 7.05-6.99 (m, 2H, Ar–H), 6.89 (d, J = 2.3 Hz, 1H, Ar–H), 3.56 (t, J = 7.1 Hz, 2H, CH_2), 1.64-

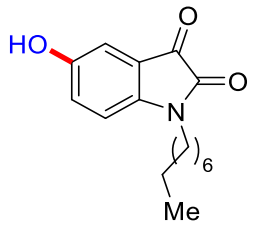
1.55 (m, 2H, CH_2), 0.88 (t, J = 7.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$-NMR (100 MHz, DMSO-d_6): δ = 184.1 (CO), 158.0 (CO), 153.6 (C_q), 143.2 (C_q), 124.3 (CH), 118.0 (C_q), 111.8 (CH), 110.8 (CH), 41.0 (CH_2), 20.2 (CH_2), 11.1 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{12}NO_3^+$ 206.0812; Found 206.0814.



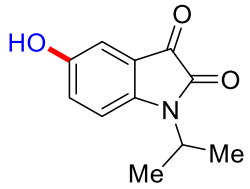
5-Hydroxy-1-pentylindoline-2,3-dione (35): The representative procedure **B** was followed using substrate **5a** (0.044 g, 0.20 mmol) and selectfluor (0.142 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **35** (0.034 g, 73%) as a light red liquid. ^1H-NMR (500 MHz, DMSO-d_6): δ = 9.64 (s, 1H, OH), 7.07-6.99 (m, 2H, Ar–H), 6.90 (d, J = 2.4 Hz, 1H, Ar–H), 3.59 (t, J = 7.1 Hz, 2H, CH_2), 1.61-1.54 (m, 2H, CH_2), 1.33-1.27 (m, 4H, $2CH_2$), 0.85 (t, J = 6.9 Hz, 3H, CH_3). $^{13}C\{^1H\}$-NMR (125 MHz, DMSO-d_6): δ = 184.1 (CO), 157.9 (CO), 153.6 (C_q), 143.1 (C_q), 124.3 (CH), 118.0 (C_q), 111.7 (CH), 110.8 (CH), 28.4 (2C, CH_2), 26.4 (CH_2), 21.8 (CH_2), 13.8 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{16}NO_3^+$ 234.1125; Found 234.1123.



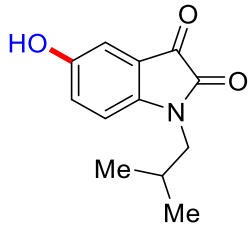
1-Hexyl-5-hydroxyindoline-2,3-dione (36): The representative procedure **B** was followed using substrate **6a** (0.046 g, 0.20 mmol) and selectfluor (0.142 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **36** (0.032 g, 65%) as a red liquid. ^1H-NMR (500 MHz, DMSO-d_6): δ = 9.63 (s, 1H, OH), 7.06-6.99 (m, 2H, Ar–H), 6.89 (d, J = 2.4 Hz, 1H, Ar–H), 3.59 (t, J = 7.1 Hz, 2H, CH_2), 1.60-1.53 (m, 2H, CH_2), 1.31-1.23 (m, 6H, $3CH_2$), 0.84 (t, J = 6.8 Hz, 3H, CH_3). $^{13}C\{^1H\}$-NMR (125 MHz, DMSO-d_6): δ = 184.1 (CO), 157.9 (CO), 153.6 (C_q), 143.1 (C_q), 124.3 (CH), 118.0 (C_q), 111.7 (CH), 110.8 (CH), 39.4 (CH_2), 30.9 (CH_2), 26.8 (CH_2), 25.9 (CH_2), 22.0 (CH_2), 13.9 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{18}NO_3^+$ 248.1281; Found 248.1281.



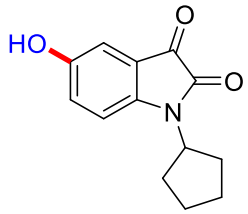
5-Hydroxy-1-octylindoline-2,3-dione (37): The representative procedure **B** was followed using substrate **8a** (0.052 g, 0.20 mmol) and selectfluor (0.142 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **37** (0.034 g, 62%) as a red liquid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 9.63 (s, 1H, OH), 7.05 (dd, J = 8.5, 2.4 Hz, 1H, Ar–H), 6.99 (d, J = 8.5 Hz, 1H, Ar–H), 6.89 (d, J = 2.4 Hz, 1H, Ar–H), 3.58 (t, J = 7.1 Hz, 2H, CH_2), 1.60-1.50 (m, 2H, CH_2), 1.27-1.22 (m, 10H, $5CH_2$), 0.84 (t, J = 6.7 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, DMSO-d_6): δ = 184.1 (CO), 157.9 (CO), 153.6 (C_q), 143.1 (C_q), 124.3 (CH), 117.9 (C_q), 111.7 (CH), 110.8 (CH), 39.4 (CH_2), 31.2 (CH_2), 28.6 (CH_2), 28.6 (CH_2), 26.7 (CH_2), 26.2 (CH_2), 22.1 (CH_2), 13.9 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{22}NO_3^+$ 276.1594; Found 276.1593.



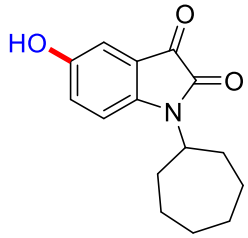
5-Hydroxy-1-isopropylindoline-2,3-dione (38): The representative procedure **B** was followed using substrate **10a** (0.038 g, 0.20 mmol) and selectfluor (0.142 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **38** (0.030 g, 73%) as a red liquid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 9.77 (br s, 1H, OH), 7.12-7.10 (m, 1H, Ar–H), 7.04-7.01 (m, 1H, Ar–H), 6.90 (d, J = 2.4 Hz, 1H, Ar–H), 4.37 (sept, J = 6.9 Hz, 1H, CH), 1.38 (d, J = 6.9 Hz, 6H, $2CH_3$). ^{13}C{^{1}H}-NMR (100 MHz, DMSO-d_6): δ = 184.3 (CO), 157.6 (CO), 153.5 (C_q), 142.4 (C_q), 124.3 (CH), 118.4 (C_q), 112.8 (CH), 111.0 (CH), 43.8 (CH), 19.0 (2C, CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{12}NO_3^+$ 206.0812; Found 206.0811.



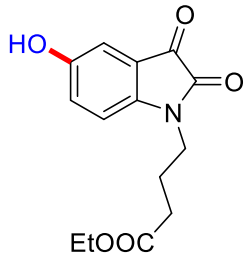
5-Hydroxy-1-isobutylindoline-2,3-dione (39): The representative procedure **B** was followed using substrate **12a** (0.041 g, 0.20 mmol) and selectfluor (0.142 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **39** (0.036 g, 82%) as a light red liquid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 9.64 (s, 1H, OH), 7.05-7.00 (m, 2H, Ar–H), 6.89 (d, J = 2.1 Hz, 1H, Ar–H), 3.41 (d, J = 7.4 Hz, 2H, CH_2), 2.04-1.97 (m, 1H, CH), 0.90 (d, J = 6.8 Hz, 6H, 2 CH_3). ^{13}C{^{1}H}-NMR (100 MHz, DMSO-d_6): δ = 184.0 (CO), 158.2 (CO), 153.6 (C_q), 143.5 (C_q), 124.3 (CH), 118.0 (C_q), 112.0 (CH), 110.8 (CH), 46.9 (CH), 26.6 (CH_2), 20.0 (2C, CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{14}NO_3^+$ 220.0968; Found 220.0965.



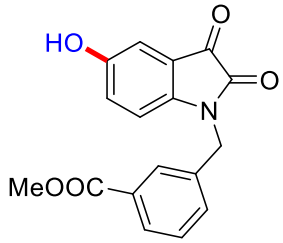
1-Cyclopentyl-5-hydroxyindoline-2,3-dione (40): The representative procedure **B** was followed using substrate **15a** (0.043 g, 0.20 mmol) and selectfluor (0.142 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **40** (0.030 g, 65%) as a red liquid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 9.65 (s, 1H, OH), 7.04-7.03 (m, 2H, Ar–H), 6.90-6.89 (m, 1H, Ar–H), 4.55-4.46 (m, 1H, CH), 2.0-2.94 (m, 2H, CH_2), 1.91-1.80 (m, 4H, 2CH_2), 1.66-1.57 (m, 2H, CH_2). ^{13}C{^{1}H}-NMR (100 MHz, DMSO-d_6): δ = 184.1 (CO), 157.8 (CO), 153.4 (C_q), 142.6 (C_q), 124.2 (CH), 118.4 (C_q), 112.5 (CH), 110.8 (CH), 52.4 (CH), 27.5 (2C, CH_2), 24.5 (2C, CH_2). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{14}NO_3^+$ 232.0968; Found 232.0964.



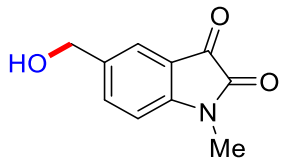
1-Cycloheptyl-5-hydroxyindoline-2,3-dione (41): The representative procedure **B** was followed, using substrate **16a** (0.049 g, 0.20 mmol) and selectfluor (0.142 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **41** (0.031 g, 60%) as a light red liquid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 9.69 (s, 1H, OH), 7.10-7.07 (m, 1H, Ar–H), 7.03-7.00 (m, 1H, Ar–H), 6.89 (d, J = 2.6 Hz, 1H, Ar–H), 4.17-4.09 (m, 1H, CH), 2.12-2.02 (m, 2H, CH_2), 1.79-1.73 (m, 4H, $2CH_2$), 1.62-1.47 (m, 6H, $3CH_2$). ^{13}C{^{1}H}-NMR (125 MHz, DMSO-d_6): δ = 184.4 (CO), 157.3 (CO), 153.5 (C_q), 142.5 (C_q), 124.3 (CH), 118.4 (C_q), 113.1 (CH), 111.0 (CH), 53.7 (CH), 31.0 (2C, CH_2), 27.2 (2C, CH_2), 25.3 (2C, CH_2). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{18}NO_3^+$ 260.1281; Found 260.1277.



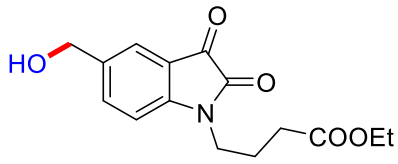
Ethyl 4-(5-hydroxy-2,3-dioxoindolin-1-yl)butanoate (42): The representative procedure **B** was followed, using substrate **19a** (0.052 g, 0.20 mmol) and selectfluor (0.142 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **42** (0.034 g, 61%) as a red liquid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 9.66 (br s, 1H, OH), 7.06 (dd, J = 8.5, 2.4 Hz, 1H, Ar–H), 7.01 (d, J = 8.4 Hz, 1H, Ar–H), 6.90 (d, J = 2.4 Hz, 1H, Ar–H), 4.01 (q, J = 7.1 Hz, 2H, CH_2), 3.63 (t, J = 6.9 Hz, 2H, CH_2), 2.39 (t, J = 7.3 Hz, 2H, CH_2), 1.86-1.79 (m, 2H, CH_2), 1.14 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, DMSO-d_6): δ = 184.0 (CO), 172.5 (CO), 158.2 (CO), 153.8 (C_q), 143.0 (C_q), 124.3 (CH), 118.1 (C_q), 111.6 (CH), 110.8 (CH), 59.9 (CH_2), 38.7 (CH_2), 30.7 (CH_2), 22.1 (CH_2), 14.1 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{16}NO_5^+$ 278.1023; Found 278.1020.



Methyl 3-((5-hydroxy-2,3-dioxoindolin-1-yl)methyl)benzoate (43): The representative procedure **B** was followed, using substrate **24a** (0.059 g, 0.20 mmol) and selectfluor (0.142 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **43** (0.036 g, 58%) as a red liquid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 9.65 (s, 1H, OH), 8.0 (s, 1H, Ar–H), 7.87 (d, J = 7.4 Hz, 1H, Ar–H), 7.69 (d, J = 7.5 Hz, 1H, Ar–H), 7.49 (t, J = 7.6 Hz, 1H, Ar–H), 6.97 (d, J = 8.4 Hz, 1H, Ar–H), 6.93 (s, 1H, Ar–H), 6.81 (d, J = 8.4 Hz, 1H, Ar–H), 4.93 (s, 2H, CH_2), 3.84 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, DMSO-d_6): δ = 183.5 (CO), 166.0 (CO), 158.4 (CO), 153.9 (C_q), 142.5 (C_q), 136.6 (C_q), 132.2 (CH), 130.1 (C_q), 129.1 (CH), 128.3 (CH), 128.1 (CH), 124.1 (CH), 118.0 (C_q), 112.0 (CH), 110.8 (CH), 52.2 (CH_3), 42.6 (CH_2). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{14}NO_5^+$ 312.0866; Found 312.0864.



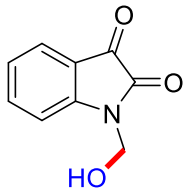
5-(Hydroxymethyl)-1-methylindoline-2,3-dione (44): The representative procedure **B** was followed, using substrate **44a** (0.035 g, 0.20 mmol) and selectfluor (0.142 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **44** (0.018 g, 47%) as a light red liquid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 7.60 (d, J = 8.0 Hz, 1H, Ar–H), 7.45 (s, 1H, Ar–H), 7.09 (d, J = 8.0 Hz, 1H, Ar–H), 5.32 (br s, 1H, OH), 4.46 (s, 2H, CH_2), 3.13 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, DMSO-d_6): δ = 183.7 (CO), 158.3 (CO), 150.2 (C_q), 137.9 (C_q), 136.3 (CH), 122.4 (CH), 117.2 (C_q), 110.3 (CH), 62.0 (CH_2), 26.1 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{10}NO_3^+$ 192.0655; Found 192.0653.



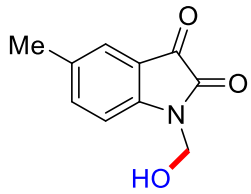
Ethyl 4-(5-(hydroxymethyl)-2,3-dioxoindolin-1-yl)butanoate (45): The representative

procedure **B** was followed, using substrate **45a** (0.055 g, 0.20 mmol) and selectfluor (0.142 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **45** (0.017 g, 29%) as a red liquid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 7.59 (d, J = 8.1 Hz, 1H, Ar–H), 7.46 (s, 1H, Ar–H), 7.15 (d, J = 8.1 Hz, 1H, Ar–H), 5.32 (br s, 1H, OH), 4.45 (s, 2H, CH_2), 4.01 (q, J = 7.1 Hz, 2H, CH_2), 3.68 (t, J = 6.8 Hz, 2H, CH_2), 2.41 (t, J = 7.4 Hz, 2H, CH_2), 1.89-1.82 (m, 2H, CH_2), 1.15 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, DMSO-d_6): δ = 183.6 (CO), 172.5 (CO), 158.4 (CO), 149.5 (C_q), 137.7 (C_q), 136.1 (CH), 122.5 (CH), 117.4 (C_q), 110.3 (CH), 62.0 (CH_2), 59.8 (CH_2), 38.8 (CH_2), 30.6 (CH_2), 22.1 (CH_2), 14.1 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{18}NO_5^+$ 292.1179; Found 292.1176.

3.4.3.3 Characterization Data of *N*-Methyl Hydroxylated Isatins

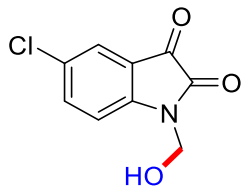


1-(Hydroxymethyl)indoline-2,3-dione (46): ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 7.70 (dd, J = 7.8, 1.1 Hz, 1H, Ar–H), 7.58 (d, J = 6.8 Hz, 1H, Ar–H), 7.25 (d, J = 8.0 Hz, 1H, Ar–H), 7.17 (vt, J = 7.5 Hz, 1H, Ar–H), 6.41 (t, J = 7.1 Hz, 1H, OH), 5.09 (d, J = 7.1 Hz, 2H, CH_2). ^{13}C{^{1}H}-NMR (125 MHz, DMSO-d_6): δ = 183.6 (CO), 157.7 (CO), 150.3 (C_q), 138.3 (CH), 124.6 (CH), 123.6 (CH), 117.3 (C_q), 111.7 (CH), 63.0 (CH_2). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_9H_8NO_3^+$ 178.0499; Found 178.0498. The ^{1}H and ^{13}C spectra are consistent with those reported in the literature.[55]

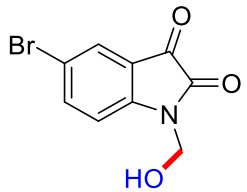


1-(Hydroxymethyl)-5-methylindoline-2,3-dione (**47**)**:** The representative procedure **C** was followed, using substrate **44a** (0.035 g, 0.20 mmol) and $K_2S_2O_8$ (0.108 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **47** (0.032 g, 84%) as a yellow liquid. ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 7.78 (dd, J = 8.1, 1.6 Hz, 1H, Ar–H), 7.67 (d, J = 1.5 Hz, 1H, Ar–H), 7.19 (d, J = 8.1 Hz, 1H, Ar–H), 5.40 (s,

2H, CH_2), 3.14 (s, 3H, CH_3). $^{13}C\{^1H\}$-NMR (125 MHz, DMSO-d_6): δ = 183.1 (CO), 158.4 (CO), 151.9 (C_q), 139.2 (CH), 128.5 (C_q), 125.3 (CH), 117.7 (C_q), 110.8 (CH), 69.2 (CH_2), 26.2 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{10}NO_3^+$ 192.0655; Found 192.0653.



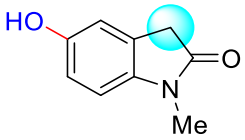
5-Chloro-1-(hydroxymethyl)indoline-2,3-dione (48): The representative procedure **C** was followed, using substrate **48a** (0.039 g, 0.20 mmol) and $K_2S_2O_8$ (0.108 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **48** (0.028 g, 66%) as a yellow liquid. ^1H-NMR (400 MHz, DMSO-d_6): δ = 7.75 (dd, *J* = 8.4, 2.3 Hz, 1H, Ar–H), 7.64 (d, *J* = 2.0 Hz, 1H, Ar–H), 7.29 (d, *J* = 8.4 Hz, 1H, Ar–H), 6.47 (t, *J* = 7.1 Hz, 1H, OH), 5.09 (d, *J* = 7.0 Hz, 2H, CH_2). $^{13}C\{^1H\}$-NMR (100 MHz, DMSO-d_6): δ = 182.5 (CO), 157.4 (CO), 148.8 (C_q), 137.2 (CH), 127.8 (C_q), 124.1 (CH), 118.7 (C_q), 113.5 (CH), 63.1 (CH_2).



5-Bromo-1-(hydroxymethyl)indoline-2,3-dione (49): The representative procedure **C** was followed, using substrate **49a** (0.048 g, 0.20 mmol) and $K_2S_2O_8$ (0.108 g, 0.40 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **49** (0.035 g, 68%) as a yellow liquid. ^1H-NMR (500 MHz, DMSO-d_6): δ = 7.87 (dd, *J* = 8.4, 1.8 Hz, 1H, Ar–H), 7.73 (d, *J* = 1.8 Hz, 1H, Ar–H), 7.23 (d, *J* = 8.5 Hz, 1H, Ar–H), 6.45 (t, *J* = 7.1 Hz, 1H, OH), 5.08 (d, *J* = 6.9 Hz, 2H, CH_2). $^{13}C\{^1H\}$-NMR (125 MHz, DMSO-d_6): δ = 182.3 (CO), 157.2 (CO), 149.1 (C_q), 140.0 (CH), 126.8 (CH), 119.1 (C_q), 115.3 (C_q), 113.9 (CH), 63.1 (CH_2).

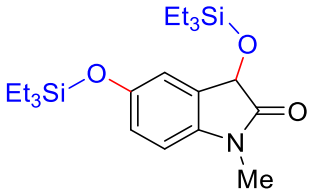
3.4.4 Procedures for Functionalization of Oxygenated Isatins

Reduction of Oxygenated Isatin to 5-Hydroxy-1-methylindolin-2-one (50):



To an oven-dried Schlenk flask equipped with a magnetic stir bar was introduced 5-hydroxy-1-methylindoline-2,3-dione (**32**; 0.030 g, 0.169 mmol) and hydrazine hydrate (0.5 mL) was added into it. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched at ambient temperature with water (10 mL) and extracted with EtOAc (20 mL x 3). The combined organic extract was dried over Na_2SO_4, and the volatiles were evaporated in vacuo. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 5/1), yielding **50** (0.024 g, 87%) as a yellow solid. M.p: 71-74 ^{o}C. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 9.04 (s, 1H, OH), 6.75-6.72 (m, 2H, Ar–H), 6.64 (dd, J = 8.3, 2.5 Hz, 1H, Ar–H), 3.45 (s, 2H, CH_2), 3.05 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, DMSO-d_6): δ = 173.8 (CO), 152.9 (C_q), 137.1 (C_q), 125.8 (C_q), 113.2 (CH), 112.4 (CH), 108.5 (CH), 35.5 (CH_2), 25.8 (CH_3). HRMS (ESI) *m/z*: [M + H]$^+$ Calcd for $C_9H_{10}NO_2^+$ 164.0706; Found 164.0704. The ^{1}H and ^{13}C{^{1}H} spectra are consistent with those reported in the literature.[56]

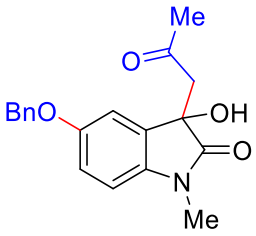
Synthesis of 1-Methyl-3,5-bis((triethylsilyl)oxy)indolin-2-one (51):



To an oven-dried screw-cap tube equipped with a magnetic stir bar was introduced 5-hydroxy-1-methylindoline-2,3-dione (**32**; 0.050 g, 0.282 mmol) and $Pd(OAc)_2$ (0.0063 g, 0.028 mmol) in DMF (2 mL). The Et_3SiH (0.163 g, 1.4 mmol) was added at room temperature under the nitrogen atmosphere.[57] The resultant reaction mixture was stirred at 70 °C in a preheated oil bath for 12 h. At ambient temperature, the reaction mixture was poured into brine (10 mL) and extracted with EtOAc (5 mL × 3). The combined organic phase was dried over anhydrous Na_2SO_4, and the volatiles were evaporated in vacuo. The crude product was purified by column chromatography on silica gel (petroleum ether/ EtOAc=5/1) to yielded **51** (0.042 g, 37%) as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.86 (dd, J =

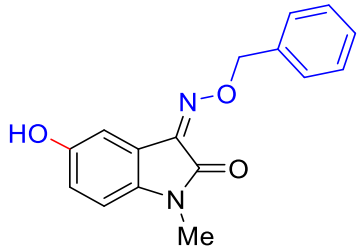
2.4, 0.8 Hz, 1H, Ar–H), 6.77 (dd, *J* = 8.5, 2.5 Hz, 1H, Ar–H), 6.61 (d, *J* = 8.3 Hz, 1H, Ar–H), 4.97 (s, 1H, CH), 3.10 (s, 3H, CH_3), 1.06-0.98 (m, 18H, $6CH_3$), 0.79-0.69 (m, 12H, $6CH_2$). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 175.5 (CO), 151.8 (C_q), 137.7 (C_q), 129.3 (C_q), 120.3 (CH), 117.3 (CH), 108.8 (CH), 70.9 (CH), 26.2 (CH_3), 6.8 (3C, CH_3), 6.7 (3C, CH_3), 5.2 (3C, CH_2), 5.0 (3C, CH_2). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{38}NSi_2O_3^+$ 408.2385; Found 408.2385.

Procedure for Synthesis of 5-(Benzyloxy)-1-methylindoline-2,3-dione (52):



To an oven-dried round bottom flask equipped with a magnetic stir bar were introduced 5-hydroxy-1-methylindoline-2,3-dione (**32**; 0.030 g, 0.169 mmol) and K_2CO_3 (0.0468 g, 0.338 mmol), and acetone (2 mL) was added into it. The resulting reaction mixture was stirred at room temperature for 30 min and benzyl bromide (0.0318 g, 0.186 mmol) was added into it, and continued stirring at 65 ^oC for 6 h. The volatiles were removed under vacuum and the reaction mixture was quenched with 10 mL of water and extracted with EtOAc (20 mL x 3). The combined organic extract was dried over Na_2SO_4, and the volatiles were evaporated in vacuo. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) to yielded **52** (0.027 g, 49%) as a viscous liquid. ^1H-NMR (500 MHz, $CDCl_3$): δ = 7.42-7.29 (m, 5H, Ar–H), 7.07 (d, *J* = 2.5 Hz, 1H, Ar–H), 6.91 (dd, *J* = 8.5, 2.5 Hz, 1H, Ar–H), 6.72 (d, *J* = 8.4 Hz, 1H, Ar–H), 5.02 (s, 2H, CH_2), 4.62 (s, 1H, OH), 3.17 (d, *J* = 17.0 Hz, 1H, CH_2), 3.16 (s, 3H, CH_3), 2.94 (d, *J* = 17.0 Hz, 1H, CH_2), 2.12 (s, 3H, CH_3). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 207.5 (C_q), 176.2 (C_q), 155.6 (C_q), 137.3 (C_q), 137.0 (C_q), 131.1 (C_q), 128.7 (2 CH), 128.2 (CH), 127.6 (2 CH), 115.6 (CH), 112.5 (CH), 109.2 (CH), 74.6 (C_q), 70.9 (CH_2), 49.1 (CH_2), 31.5 (CH_3), 26.5 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{20}NO_4^+$ 326.1387; Found 326.1371.

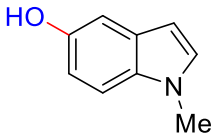
Synthesis of (Z)-3-((Benzyloxy)imino)-5-hydroxy-1-methylindolin-2-one (53):



To an oven-dried round bottom flask equipped with a magnetic stir bar was introduced 5-hydroxy-1-methylindoline-2,3-dione (**32**; 0.050 g, 0.282 mmol), *O*-benzylhydroxylamine hydrochloride (0.0494 g, 0.310 mmol) and K_2HPO_4 (0.049 g, 0.282 mmol) and methanol (3 mL) was added into it. The reaction mixture was stirred at room temperature for 2 h, and the solvent was removed in vacuo. The reaction mixture was quenched with 10 mL of water and extracted with EtOAc (20 mL x 3). The combined organic extract was dried over Na_2SO_4, and the volatiles were evaporated in vacuo. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 2/1) to yielded **53** (0.0391 g, 49%) as a yellow solid. M.p: 135-138 ^oC. ^1H-NMR (500 MHz, DMSO-d_6): δ = 9.40 (s, 1H, OH), 7.46-7.37 (m, 6H, Ar–H), 6.88-6.87 (m, 2H, Ar–H), 5.47 (s, 2H, CH_2), 3.09 (s, 3H, CH_3). $^{13}C\{^1H\}$-NMR (125 MHz, DMSO-d_6): δ = 162.1 (CO), 153.2 (C_q), 144.4 (C_q), 136.9 (C_q), 136.7 (C_q), 128.6 (2C, CH), 128.3 (CH), 128.2 (2C, CH), 119.0 (CH), 115.3 (C_q), 114.8 (CH), 110.0 (CH), 78.2 (CH_2), 26.0 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{15}N_2O_3^+$ 283.1077; Found 283.1076.

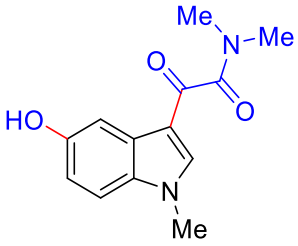
Synthesis of 3-(2-(Dimethylamino)ethyl)-1-methyl-1*H*-indol-5-ol (56):

To an oven-dried Schlenk flask equipped with a magnetic stir bar was introduced 5-hydroxy-1-methylindoline-2,3-dione (**32**; 0.050 g, 0.282 mmol) in THF (2 mL) under an argon atmosphere and the reaction mixture was cooled to 0 ^oC. The BH_3-SMe_2 (169 µL, 5M solution in Et_2O) was added to the mixture, and the resultant reaction mixture was stirred at room temperature for 6 h.[58] At ambient temperature, the reaction mixture was quenched with MeOH (1 mL) and 1N HCl (2 mL) at 0 ^oC. The crude product was extracted with EtOAc (10 mL x 3). The combined organic extract was dried over Na_2SO_4, and the volatiles were evaporated in *vacuo*. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) to yielded 1-methyl-1*H*-indol-5-ol (**54**) (0.029 g, 70%) as a white liquid.



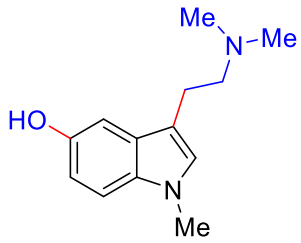
1-Methyl-1*H*-indol-5-ol (54): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (br s, 1H, OH), 7.23 (d, *J* = 8.8 Hz, 1H, Ar–H), 7.09 - 7.14 (m, 2H, Ar–H), 6.86 (dd, *J* = 8.8, 2.4 Hz, 1H, Ar–H), 6.46 (br. s, 1H), 3.84 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 154.3 (C_q), 131.1 (C_q), 128.4 (C_q), 125.1 (CH), 112.5 (CH), 111.9 (CH), 102.5 (CH), 102.5 (CH), 56.0 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_9H_{10}NO^+$ 148.0757; Found 148.0758.

The compound **54** (0.10 g, 0.67 mmol) was dissolved in Et_2O (5 mL), and oxalyl chloride (0.07 mL, 0.815 mmol) was added at 0 ^{o}C and stirred at room temperature for 2 h. The yellow solid obtained was collected by filtration and washed with diethyl ether. Further, the crude reaction residue was dissolved in DCM (10 mL), and Me_2NH (54 µL, 0.815 mmol) was added to the reaction mixture at 0 ^{o}C. The resultant reaction mixture was stirred at room temperature for 12 h, and the volatiles were evaporated under vacuum. The reaction mixture was quenched with water, and the crude product was extracted with EtOAc (10 mL x 3). The combined organic extract was dried over Na_2SO_4, and the volatiles were evaporated in *vacuo*. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 1/5) to yielded 2-(5-hydroxy-1-methyl-1*H*-indol-3-yl)-*N*,*N*-dimethyl-2-oxoacetamide (**55**) (0.134 g, 81%) as a pale yellow solid.



2-(5-Hydroxy-1-methyl-1*H*-indol-3-yl)-*N*,*N*-dimethyl-2-oxoacetamide (**55**): ^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.18 (br.s, 1H, OH), 8.02 (s, 1H, Ar–H), 7.60 (d, *J* = 2.3 Hz, 1H, Ar–H), 7.42 (d, *J* = 8.9 Hz, 1H, Ar–H), 6.90 (dd, *J* = 8.8, 2.6 Hz, 1H, Ar–H), 3.80 (s, 3H, CH_3), 2.98 (s, 3H, CH_3), 2.91 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, DMSO-d_6): δ = 186.5 (CO), 167.4 (CO), 155.9 (CO), 136.9 (CH), 131.6 (C_q), 125.8 (C_q), 113.4 (CH), 113.3 (CH), 112.8 (C_q), 102.5 (CH), 55.3 (CH_3), 36.8 (CH_3), 33.4 (CH_3). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{15}N_2O_3^+$ 247.1083; Found 247.1075.

The crude residual 2-(5-hydroxy-1-methyl-1*H*-indol-3-yl)-*N*,*N*-dimethyl-2-oxoacetamide (**55**) was redissolved in THF (3 mL), and BH_3-SMe_2 (243 µL, 1.21 mmol, 5M solution in Et_2O) was added at 0 °C. The resultant reaction mixture was stirred at room temperature for 6 h. The reaction mixture was quenched at ambient temperature with MeOH (1 mL) and 1 N HCl (2 mL) at 0 °C. The crude product was extracted with EtOAc (20 mL x 3). The combined organic extract was dried over Na_2SO_4, and the volatiles were evaporated in vacuo. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) to yielded **56** (0.0791 g, 89%) as a white liquid.



3-(2-(Dimethylamino)ethyl)-1-methyl-1*H*-indol-5-ol (56): ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 10.7 (br s, 1H, OH), 7.24 (d, J = 8.8 Hz, 1H, Ar–H), 7.14 (d, J = 2.3 Hz, 1H, Ar–H), 7.03 (d, J = 2.3 Hz, 1H, Ar–H), 6.73 (dd, J = 8.8, 2.3 Hz, 1H, Ar–H), 3.76 (s, 3H, CH_3), 3.08-3.04 (m, 2H CH_2), 2.96-2.92 (m, 2H, CH_2), 2.60 (s, 6H, 2 CH_3). ^{13}C{^{1}H}-NMR (100 MHz, DMSO-d_6): δ = 153.0 (C_q), 131.4 (C_q), 127.2 (C_q), 123.5 (CH), 112.2 (CH), 111.1 (CH), 110.3 (C_q), 100.1 (CH), 64.0 (CH_2), 55.4 (CH_3), 51.0 (2C, CH_3), 19.7 (CH_2). HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{19}N_2O^+$ 219.1492; Found 219.1492.

3.4.5 Procedure for *H/D* Scrambling Experiment

To an oven-dried screw-cap tube equipped with magnetic stir bar were introduced 1-methylindoline-2,3-dione (**1a**; 0.032 g, 0.20 mmol), $PhI(OAc)_2$ (0.129 g, 0.40 mmol), $Pd(OAc)_2$ (0.0022 g, 0.01 mmol, 5.0 mol%) and PPh_3 (0.0053 g, 0.02 mmol, 10.0 mol%). To the resulted mixture, AcOD (0.2 mL) was added and stirred at 100 °C in a preheated oil bath for 1 h. At ambient temperature, the reaction mixture was quenched with $NaHCO_3$ (aq) solution and the crude product was extracted with EtOAc (10 mL x 3). The combined organic extract was dried over Na_2SO_4 and the volatiles were evaporated in *vacuo*. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) to recover the starting compound. The ^{1}H NMR analysis of the recovered compound have not

shown incorporation of deuterium at the C(5)–H position (Scheme 3.7).

3.4.6 Procedure for External Additive Experiments

C-5 Hydroxylated Isatin: To an oven-dried screw-cap tube equipped with magnetic stir bar were introduced 1-methylindoline-2,3-dione (**1a**; 0.032 g, 0.20 mmol), selectfluor (0.142 g, 0.40 mmol), $Pd(OAc)_2$ (0.0022 g, 0.01 mmol, 5.0 mol%) and TEMPO (0.063 g, 0.40 mmol) [or galvinoxyl (0.169 g, 0.40 mmol) or BHT (0.088 g, 0.40 mmol]. To the resulted mixture, TFA/TFAA (9:1) (0.2 mL) was added and stirred at 80 °C in a preheated oil bath for 20 h. At ambient temperature, the reaction mixture was quenched with $NaHCO_3$ (aq) solution and the crude product was extracted with EtOAc (10 mL x 3). The combined organic extract was dried over Na_2SO_4 and the volatiles were evaporated in vacuo. The formation of oxygenated product **32** was not observed in any of these external additive reactions in TLC analysis (Figure 3.2).

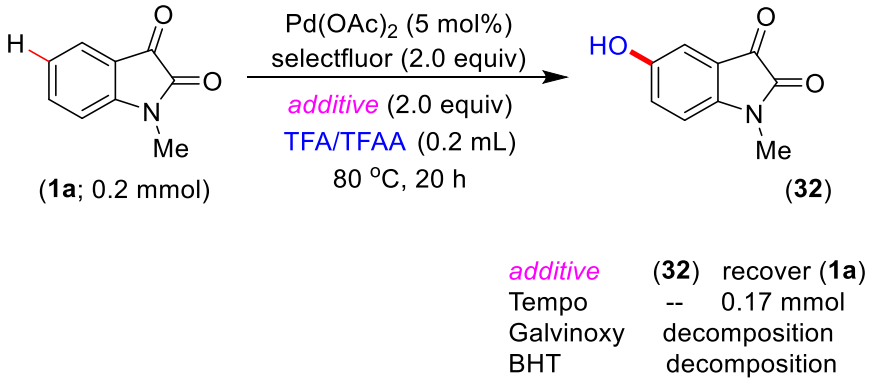


Figure 3.2. External Additive Experiments for C5 Hydroxylated Isatins.

***N*-Methyl Hydroxylated Isatin:** To an oven-dried screw-cap tube equipped with magnetic stir bar were introduced 1-methylindoline-2,3-dione (**1a**; 0.032 g, 0.20 mmol), $K_2S_2O_8$ (0.108 g, 0.40 mmol), $Pd(OAc)_2$ (0.0022 g, 0.01 mmol, 5.0 mol%) and TEMPO (0.063 g, 0.40 mmol) [or galvinoxyl (0.169 g, 0.40 mmol) or BHT (0.088 g, 0.40 mmol]. To the resulted mixture, TFA/TFAA (9:1) (1.5 mL) was added and stirred at 100 °C in a preheated oil bath for 1 h. At ambient temperature, the reaction mixture was quenched with $NaHCO_3$ (aq) solution and the crude product was extracted with EtOAc (10 mL x 3). The combined organic extract was dried over Na_2SO_4, and the volatiles were evaporated in *vacuo*. The formation of oxygenated product **46** was not observed in any of these external additive reactions in TLC analysis, and starting compounds were recovered quantitative amount (Scheme 3.8).

3.4.7 X-ray Structural Analysis

Crystal of compounds **1**, **16** and **17** were grown by slow vapourization of ethylacetate. X-ray intensity data measurements of compounds **1**, **16** and **17** were carried out on a Bruker D8 VENTURE Kappa Duo PHOTON II CPAD diffractometer equipped with Incoatech multilayer mirrors optics. The intensity measurements were carried out with Mo micro-focus sealed tube diffraction source (MoK_α= 0.71073 Å) at low temperature. The X-ray generator was operated at 50 kV and 1.4 mA. A preliminary set of cell constants and an orientation matrix were calculated from three matrix sets of 36 frames (each matrix run consists of 12 frames). Data were collected with ω scan width of 0.5° at different settings of φ and 2θ with a frame time of 10-20 sec depending on the diffraction power of the crystals keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX3 program (Bruker, 2016).[59] All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2016). Using the APEX3 (Bruker) program suite, the structure was solved with the ShelXS-97 (Sheldrick, 2008)[60] structure solution program, using direct methods. The model was refined with a version of ShelXL-2018/3 (Sheldrick, 2015)[61] using Least Squares minimization. All the hydrogen atoms were placed in a geometrically idealized position and constrained to ride on their parent atoms. An *ORTEP* III[62] view of the compounds was drawn with 50% probability displacement ellipsoids, and H atoms are shown as small spheres of arbitrary radii.

Table 3.3. Crystal Data for Compounds 1, 16 and 17.

Crystal Data	Comp **1**	Comp **16**	Comp **17**
Formula	$C_{11}H_9NO_4$	$C_{17}H_{19}NO_4$	$C_{13}H_{13}NO_5$
Molecular weight	219.19	301.33	263.24
Crystal Size, mm	0.29 × 0.23 × 0.17	0.41× 0.36 × 0.26	0.37 × 0.27 × 0.11
Temp. (K)	100(2)	100(2)	123(2)
Wavelength (Å)	0.71073	0.71073	0.71073
Crystal Syst.	monoclinic	triclinic	triclinic
Space Group	*C*2/*c*	*P*-1	*P*-1
a/Å	12.6762(16)	7.8951(7)	8.3471(4)
b/Å	12.2110(13)	7.9666(8)	10.7335(5)
c/Å	12.8540(13)	12.2714(11)	14.7742(6)
α/°	90	87.093(3)	103.781(2)
β/°	101.871(4)	87.780(3)	102.3030(10)
γ/°	90	77.617(3)	99.4370(10)
V/Å^3	1947.1(4)	752.60(12)	1223.47(10)
Z	8	2	4
D_{calc}/g cm^{-3}	1.495	1.330	1.429
μ/mm^{-1}	0.116	0.095	0.111
F(000)	912	320	552
Ab. Correct.	multi-scan	multi-scan	multi-scan
T_{min}/ T_{max}	0.6864/0.7461	0.7164/0.7462	0.7059/0.7467
$2\theta_{max}$	56	56	60
Total reflns.	11945	41101	38088
Unique reflns.	2354	3638	7073
Obs. reflns.	2155	3135	6564
h, *k*, *l* (min, max)	(-16, 13), (-16, 16), (-16, 16)	(-10, 10), (-10, 10), (-16, 16)	(-11, 11), (-15, 13), (-19, 20)
R_{int} / R_{sig}	0.0403/ 0.0336	0.0557/0.0252	0.0408/0.0272
No. of parameters	147	222	356
R1 [$I > 2\sigma(I)$]	0.0423	0.0446	0.0409
wR2[$I > 2\sigma(I)$]	0.1127	0.1117	0.1090
R1 [all data]	0.0456	0.0525	0.0435
wR2 [all data]	0.1162	0.1181	0.1112
goodness-of-fit	1.081	1.028	1.039
$\Delta\rho_{max}$, $\Delta\rho_{min}$(eÅ^{-3})	+0.344, -0.253	+0.387, -0.252	+0.431, -0.276
CCDC	2211565	2211567	2211566

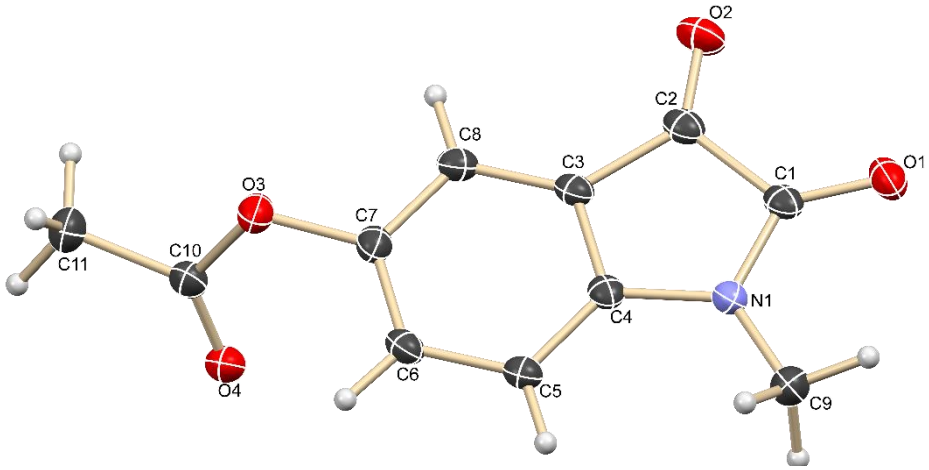


Figure 3.2 ORTEP of compound **1** showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres with arbitrary radii.

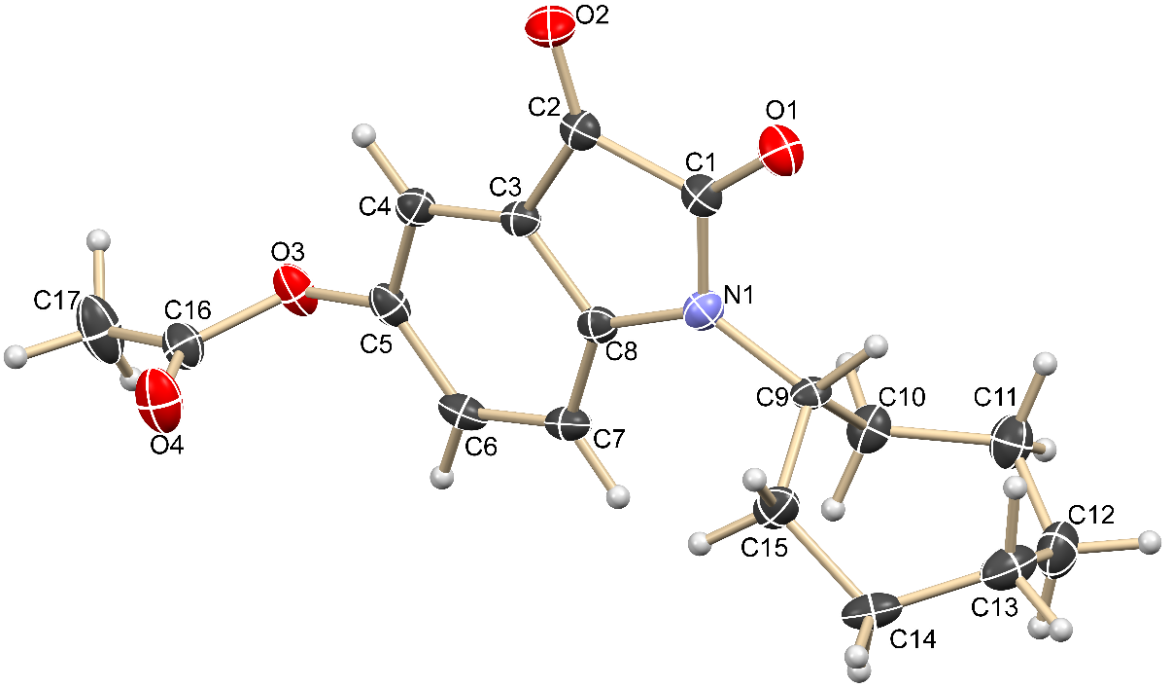


Figure 3.3 ORTEP of compound **16** showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres with arbitrary radii.

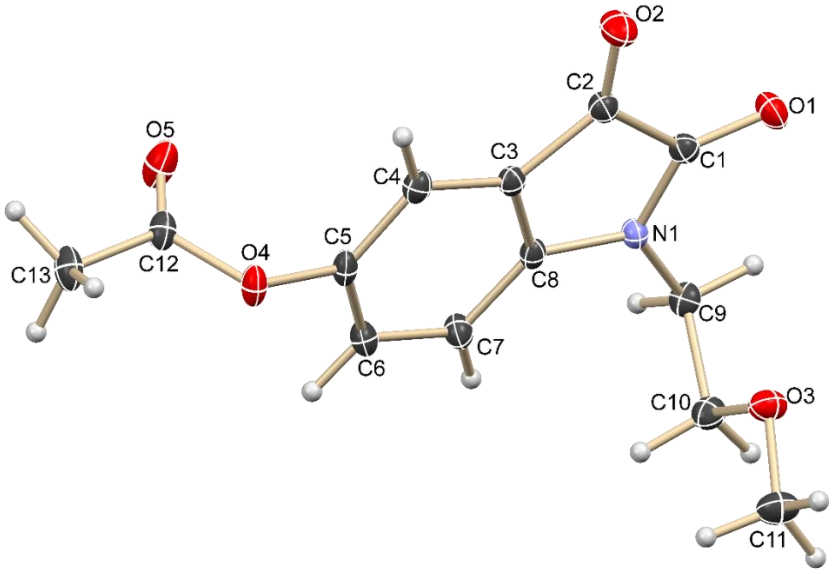
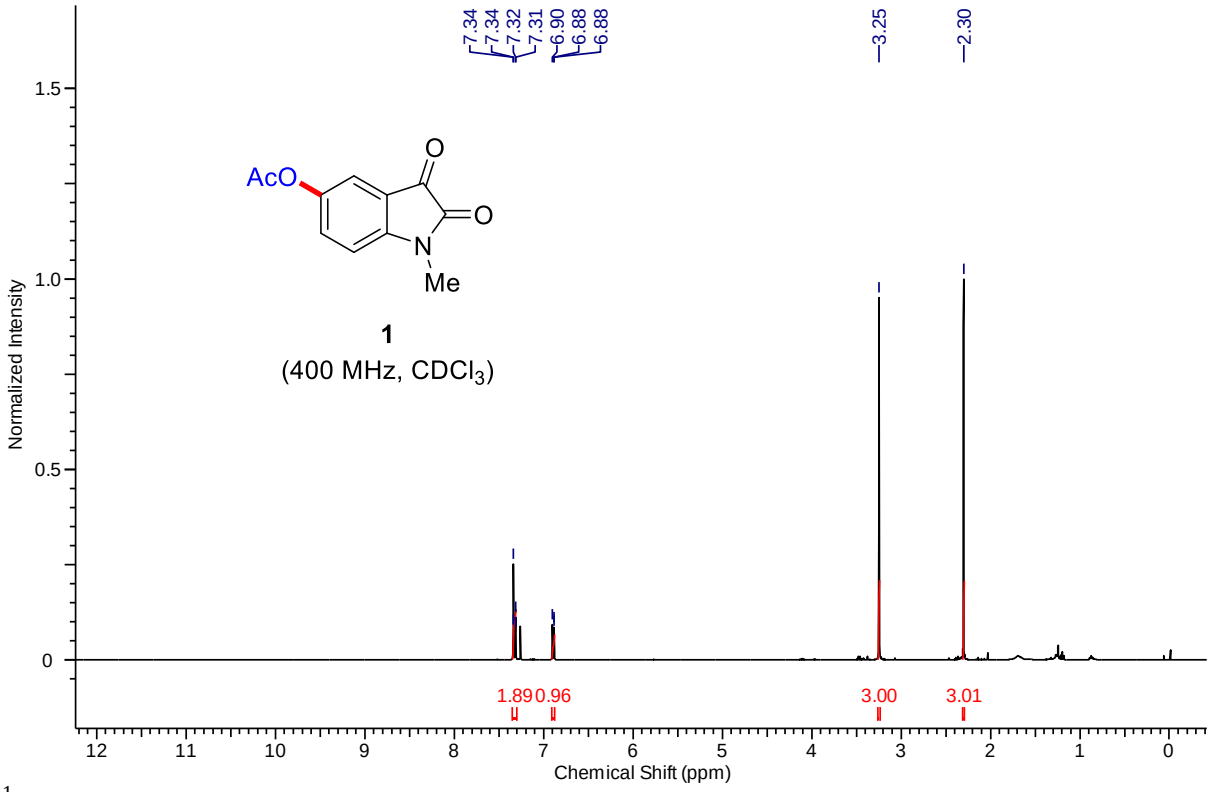
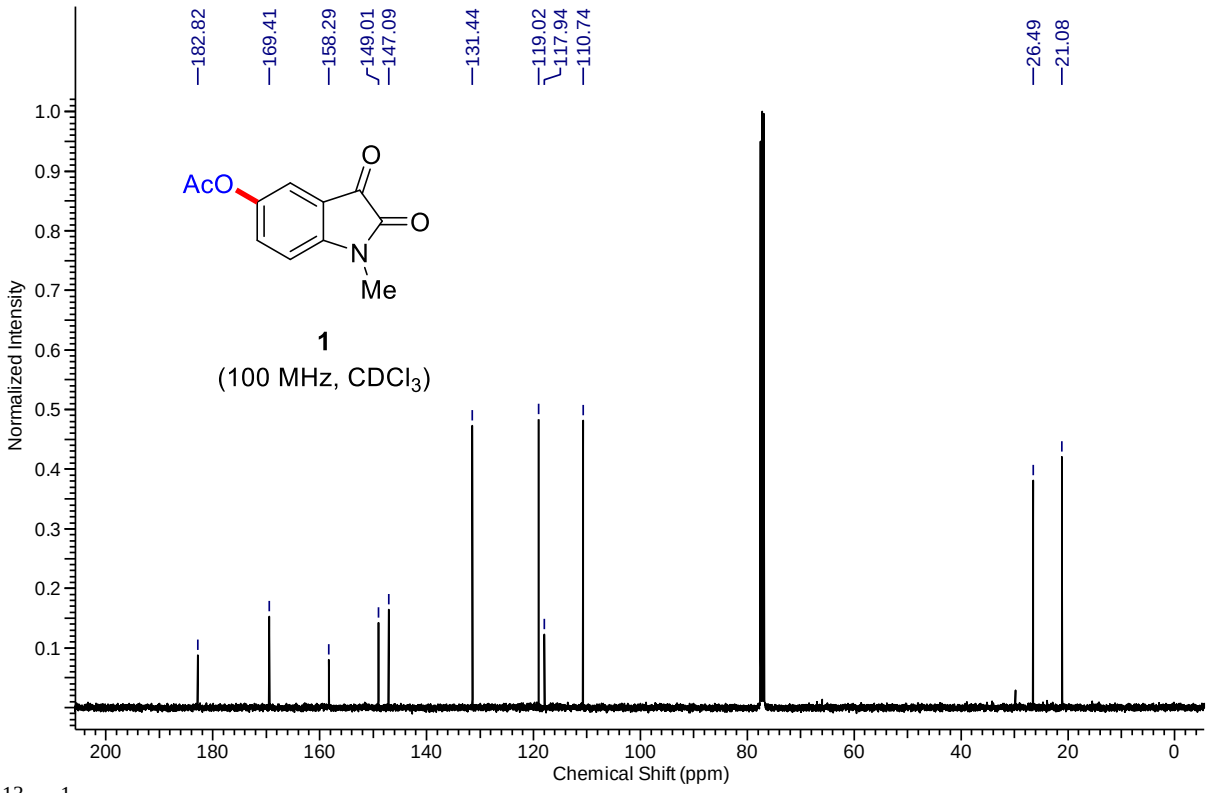


Figure 3.4. ORTEP of compound **17** showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres with arbitrary radii. Two molecules are present in the asymmetric unit. Only the unprimed molecule is displayed here.

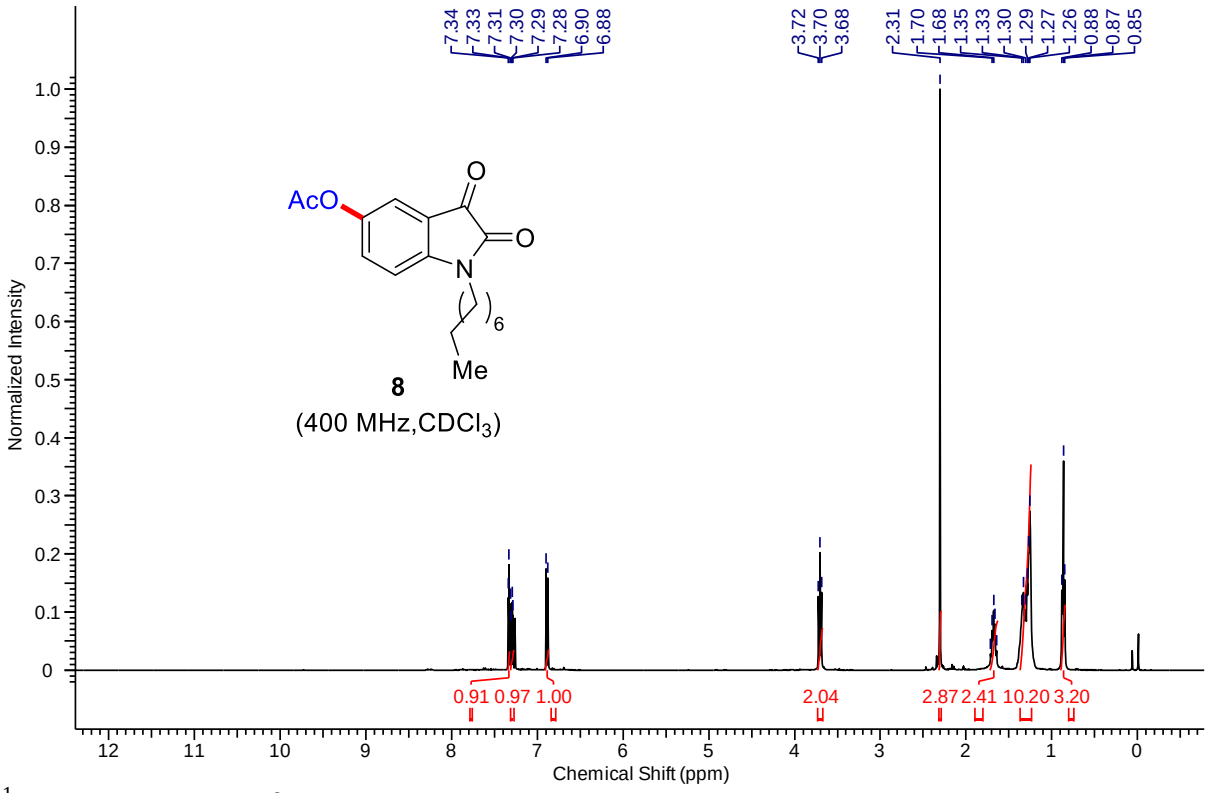
3.4.8 ^{1}H and ^{13}C Spectra of Selected Oxygenated Isatins



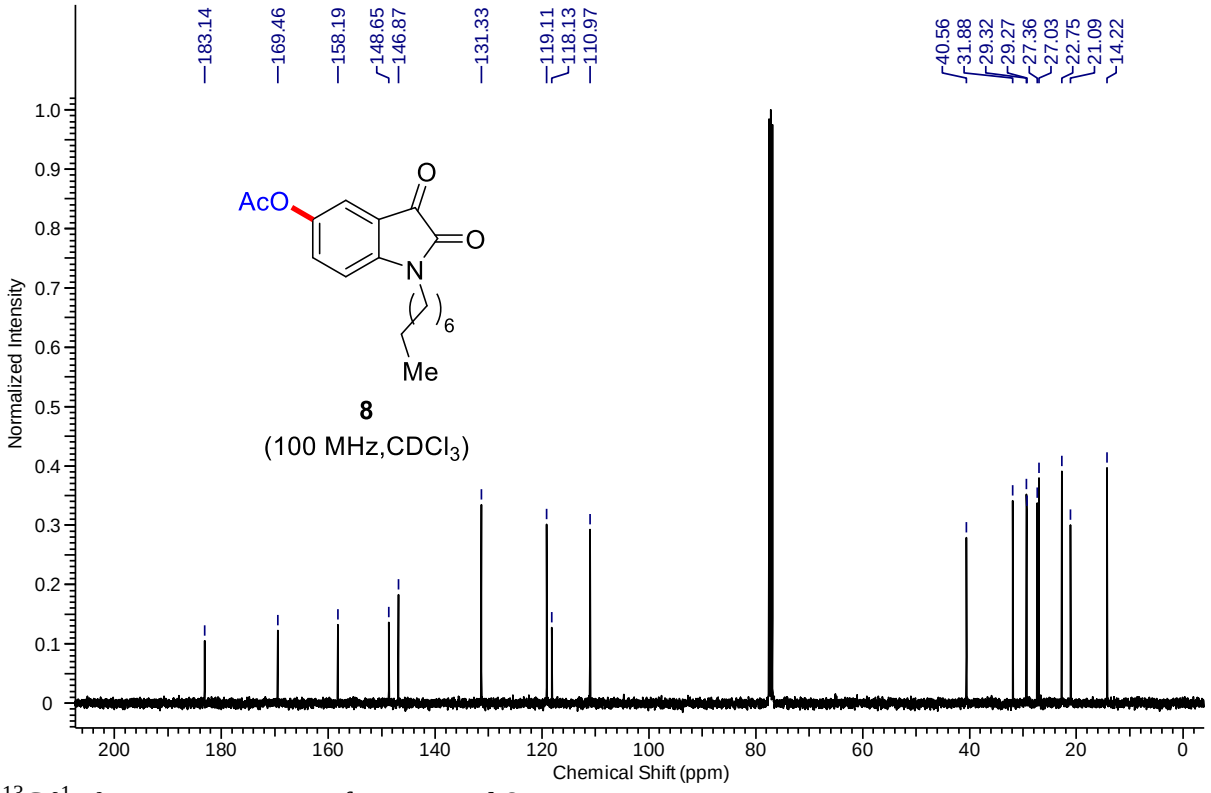
^{1}H-NMR spectrum of compound **1**



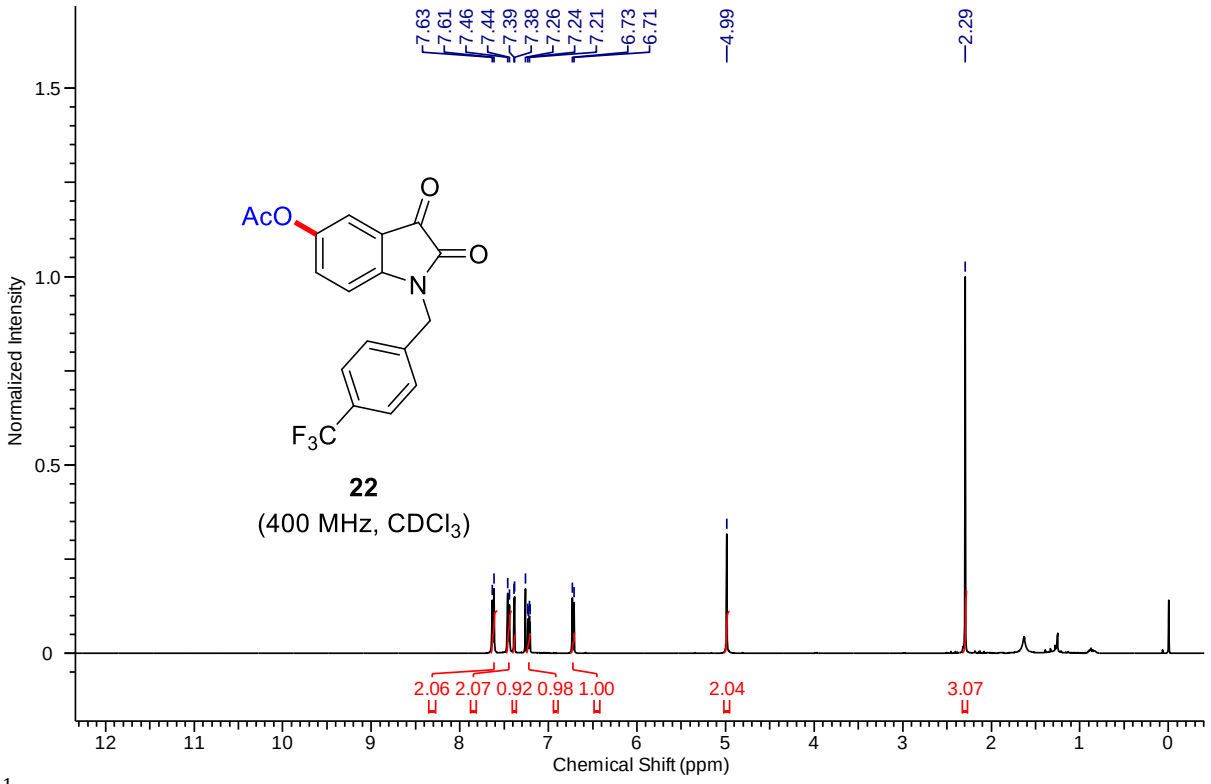
^{13}C{^{1}H}-NMR spectrum of compound **1**



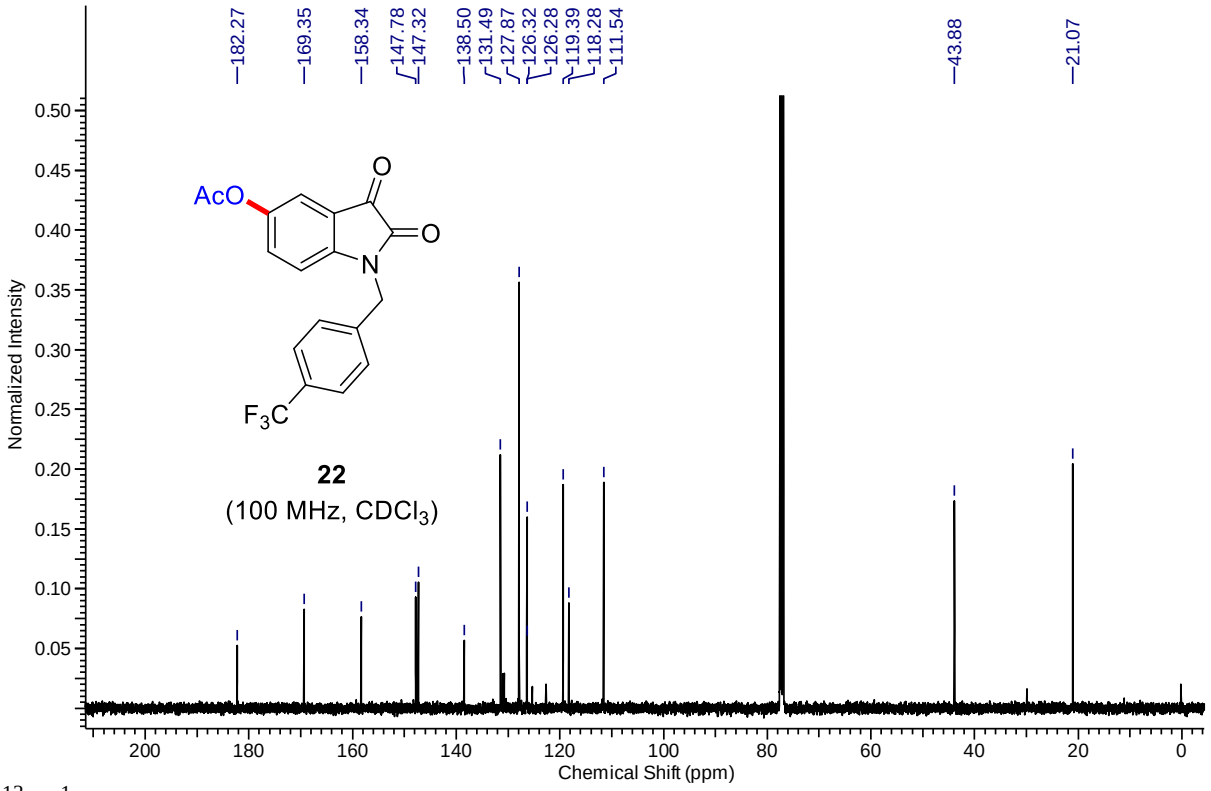
^{1}H-NMR spectrum of compound **8**



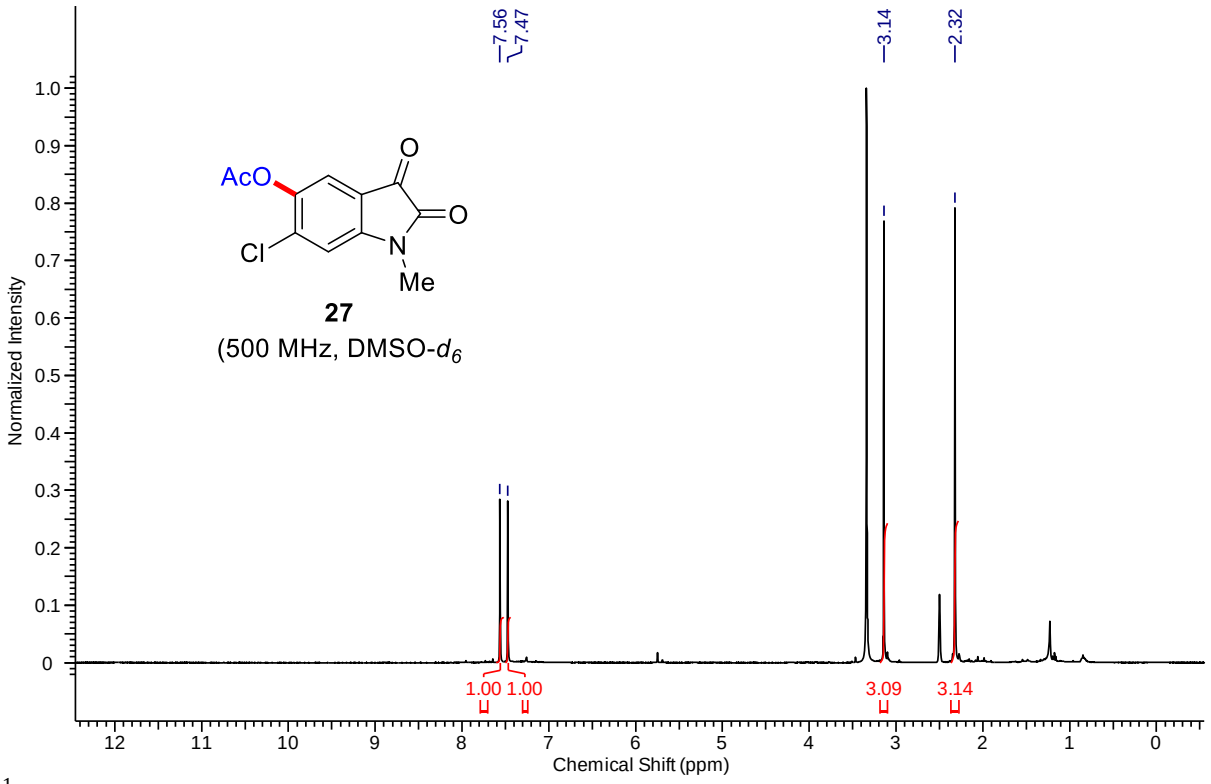
^{13}C{^{1}H}-NMR spectrum of compound **8**



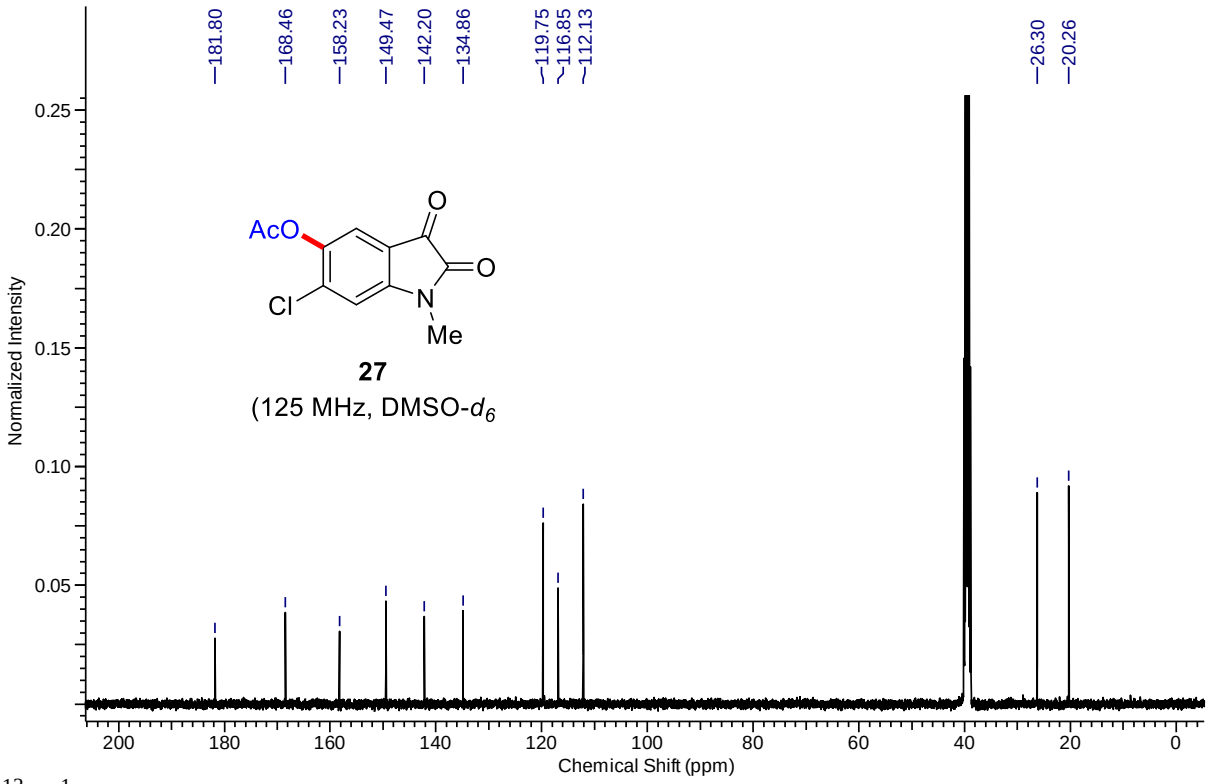
^{1}H-NMR spectrum of compound **22**



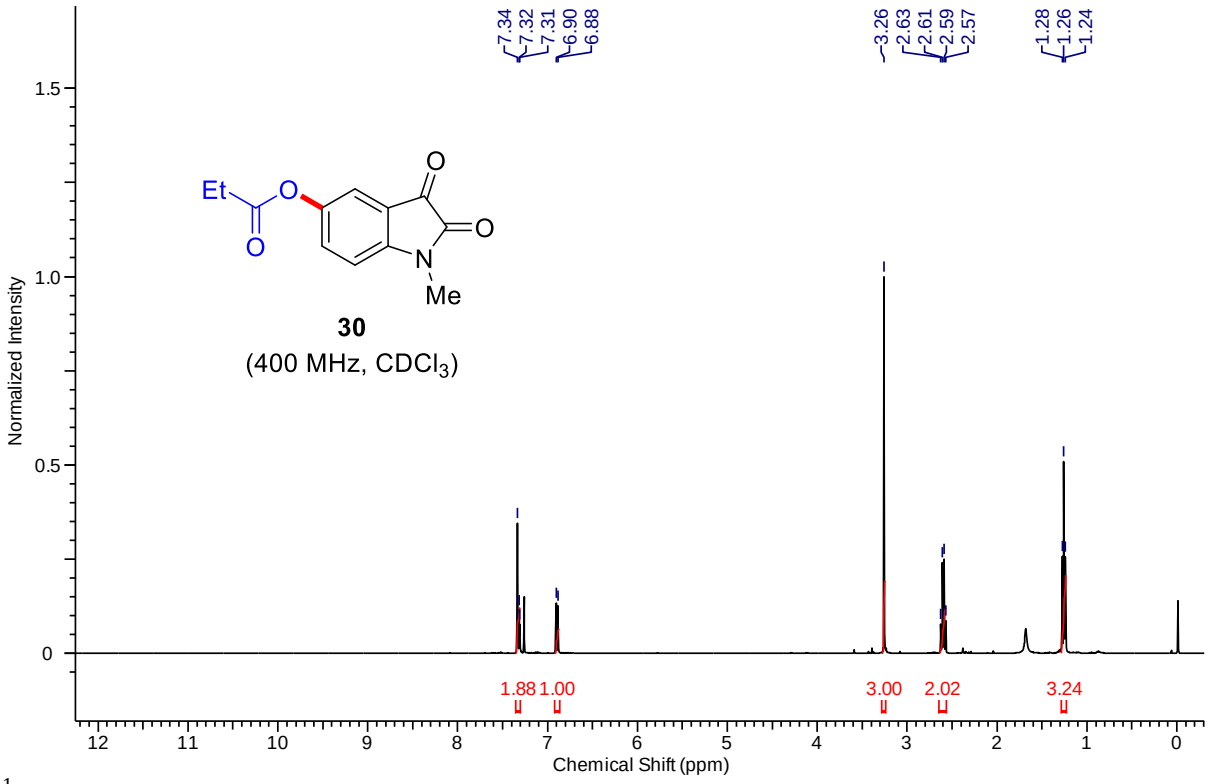
^{13}C{^{1}H}-NMR spectrum of compound **22**



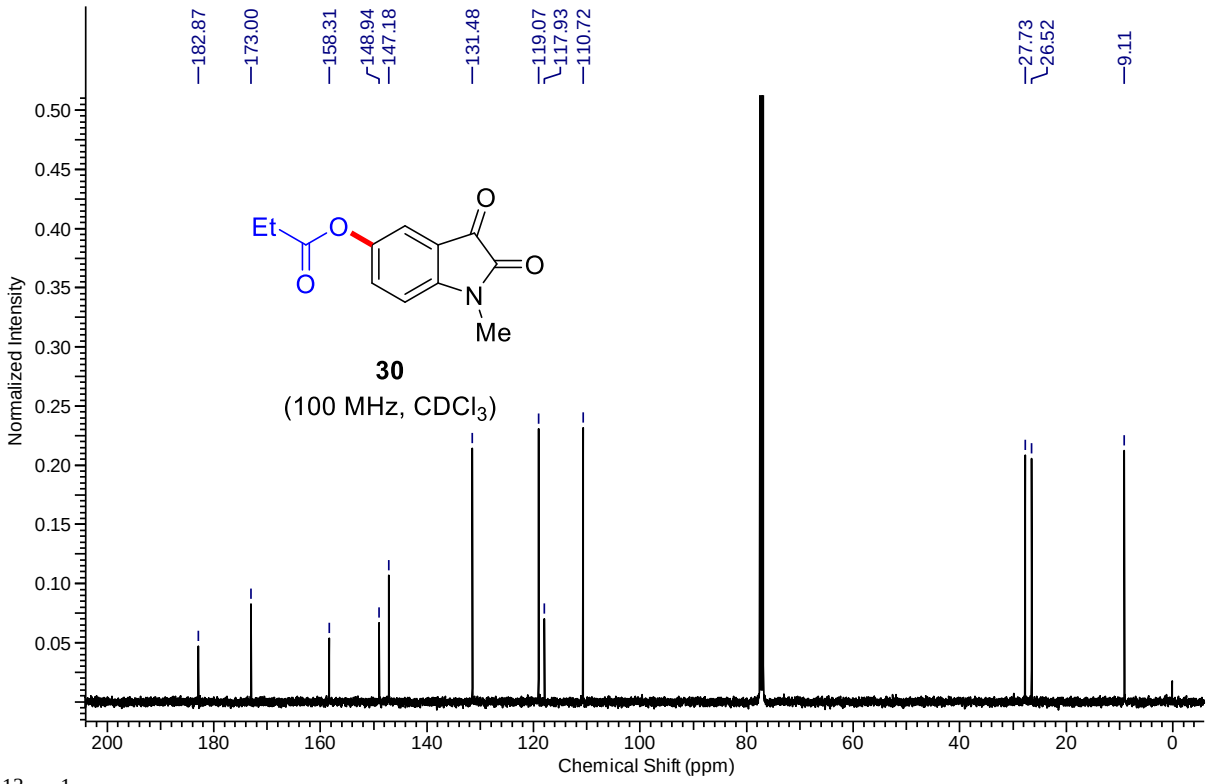
^{1}H-NMR spectrum of compound **27**



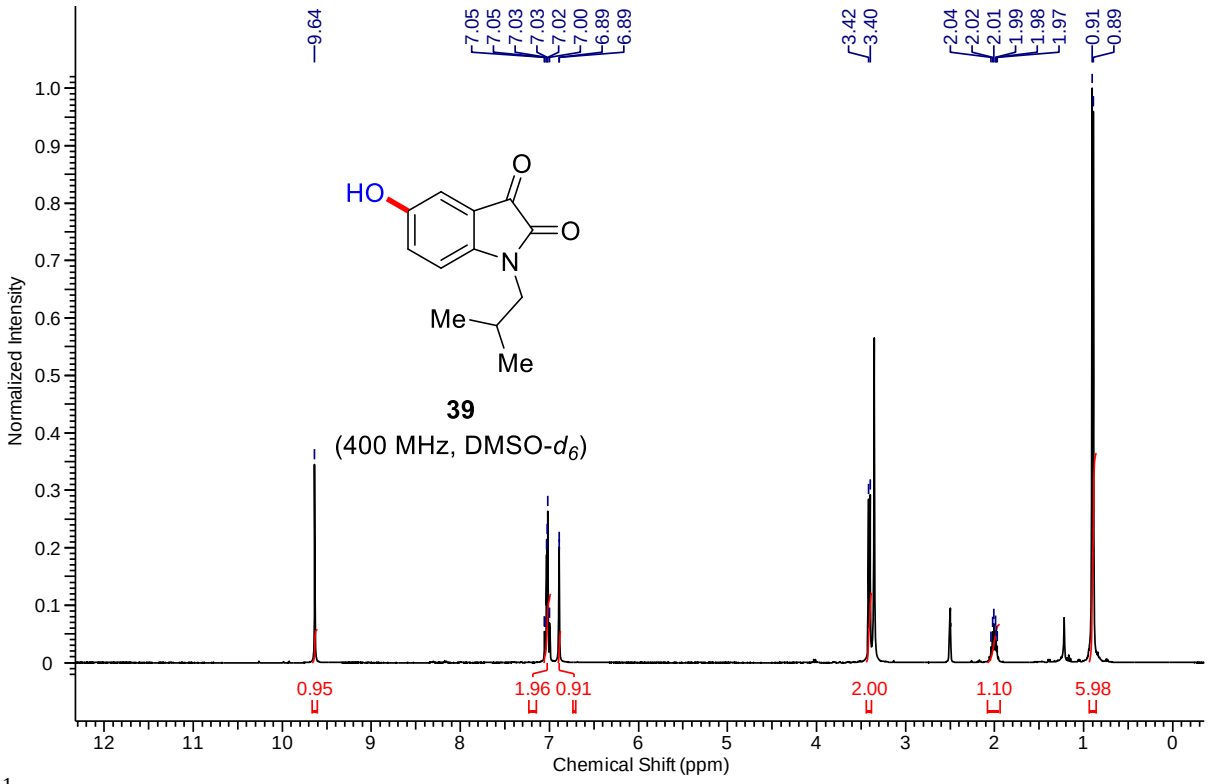
^{13}C{^{1}H}-NMR spectrum of compound **27**



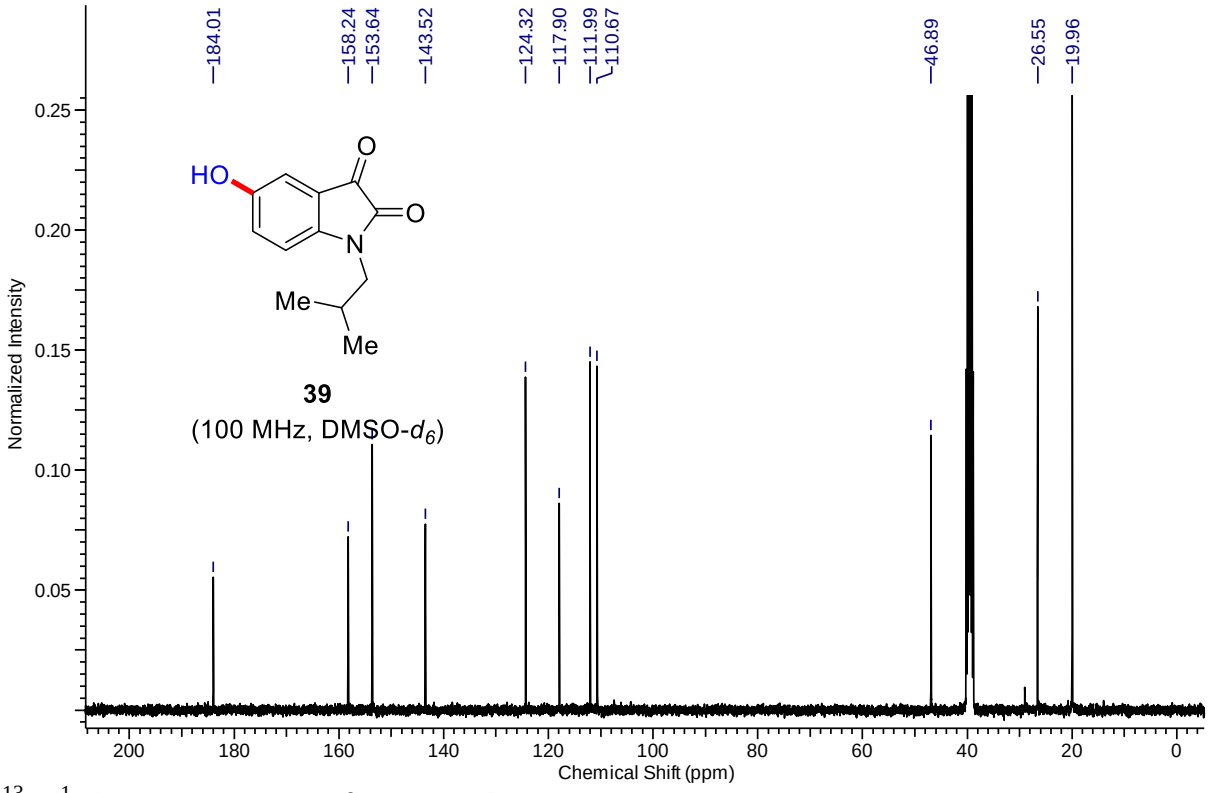
^{1}H-NMR spectrum of compound **30**



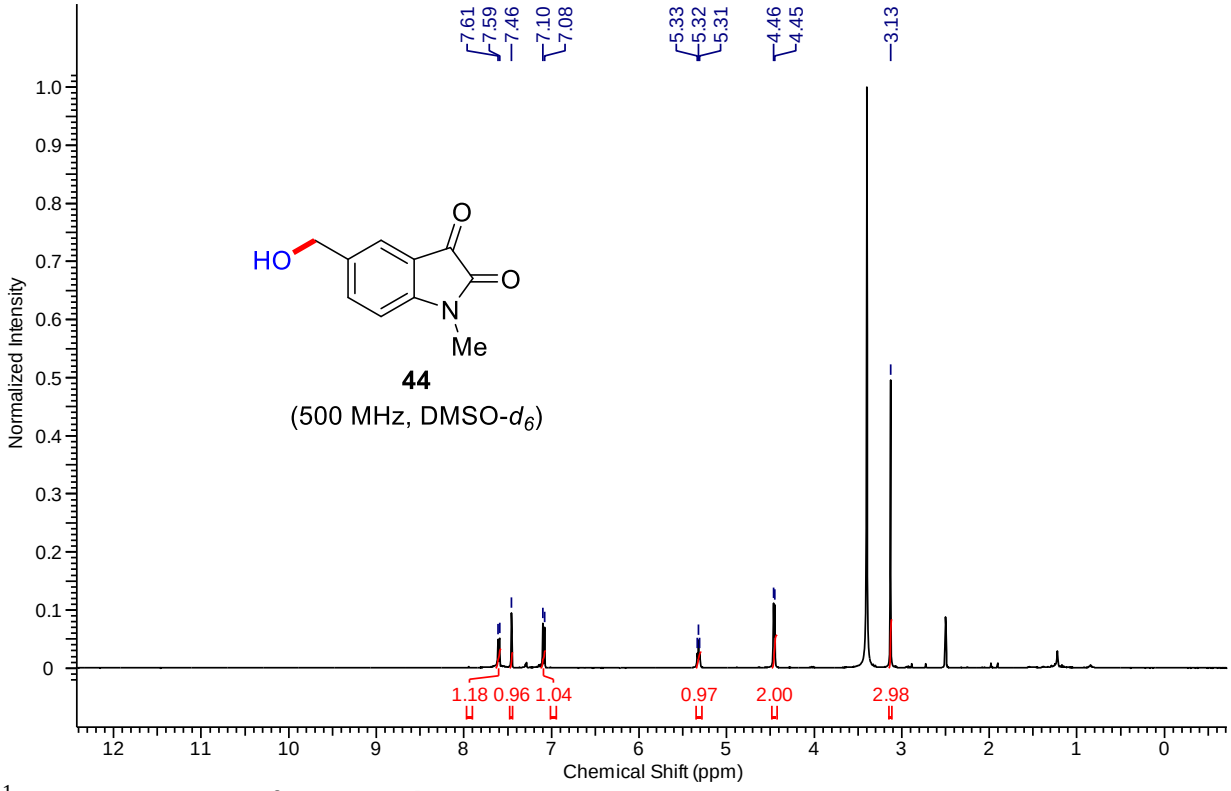
^{13}C{^{1}H}-NMR spectrum of compound **30**



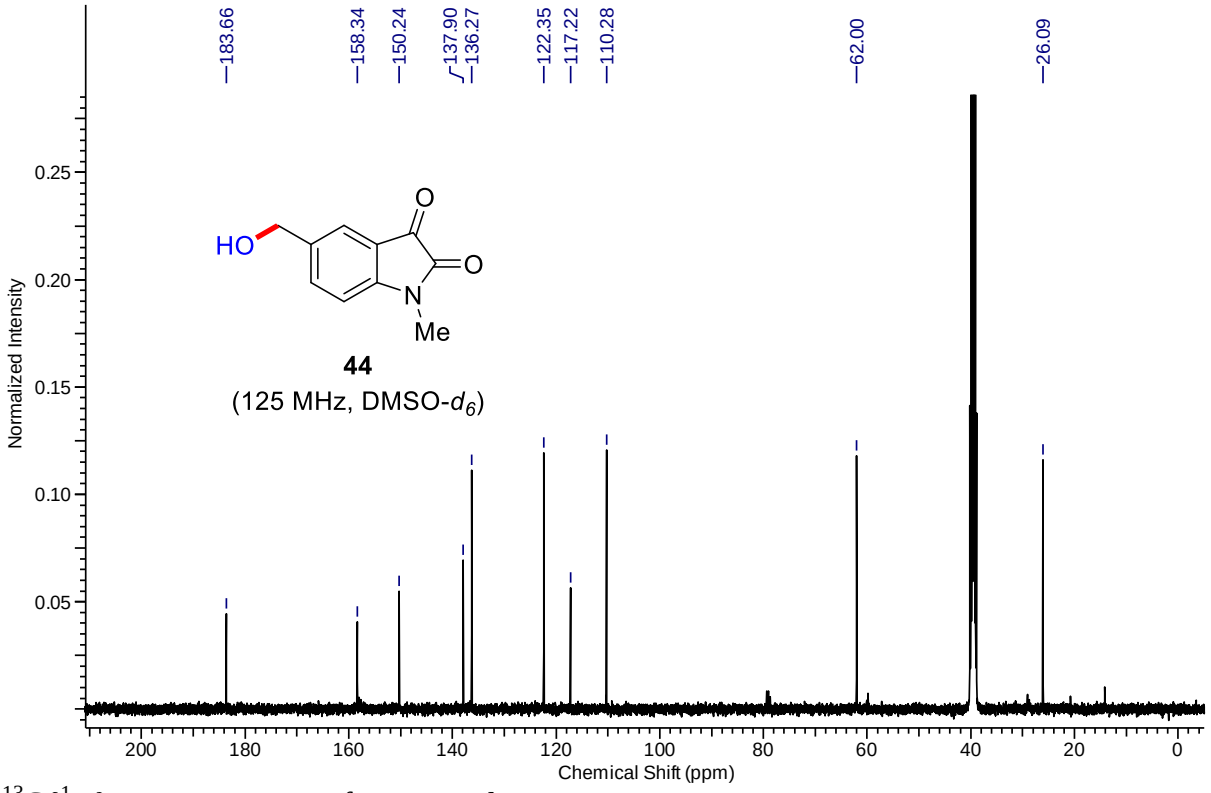
^{1}H-NMR spectrum of compound **39**



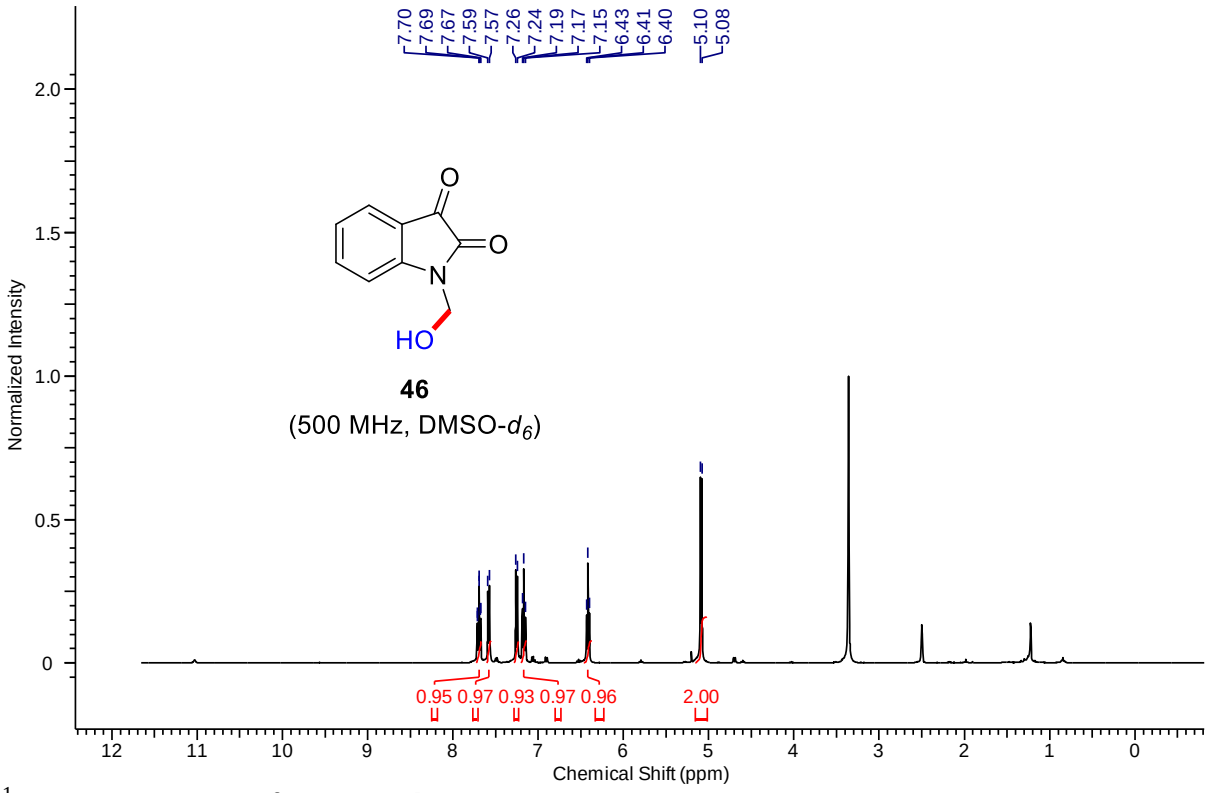
^{13}C{^{1}H}-NMR spectrum of compound **39**



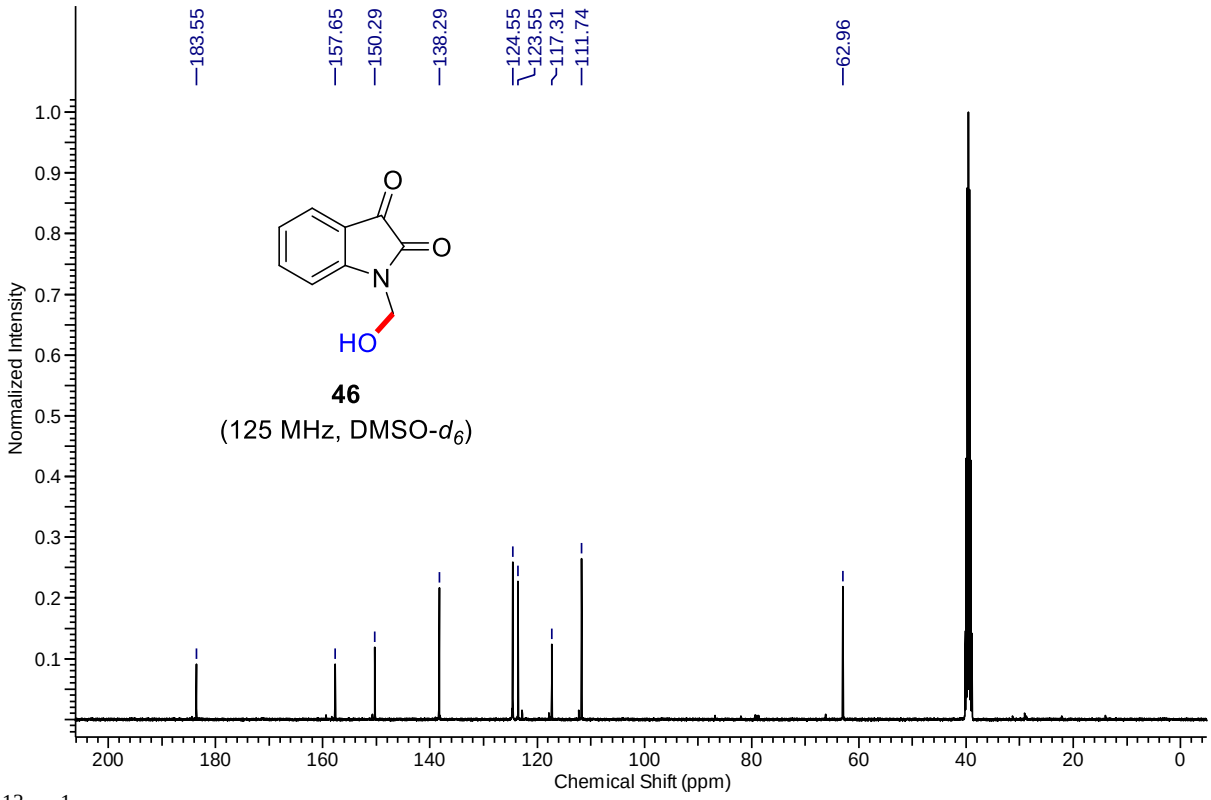
^{1}H-NMR spectrum of compound **44**



^{13}C{^{1}H}-NMR spectrum of compound **44**



^{1}H-NMR spectrum of compound **46**



^{13}C{^{1}H}-NMR spectrum of compound **46**

3.5 REFERENCES

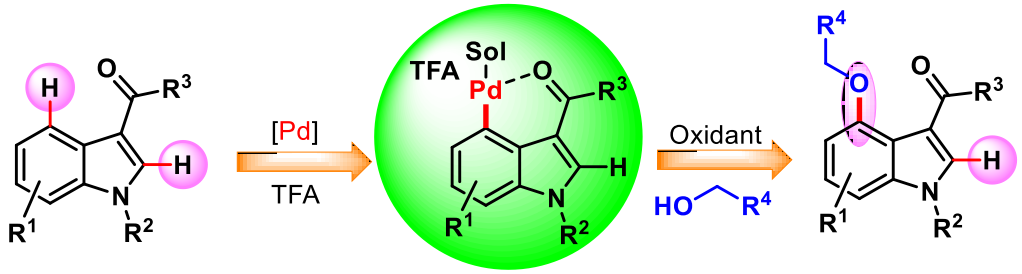
1. Khan, F. A.; Maalik, A., *Trop J Pharm Res.* **2015**, *14*, 1937-1942.
2. Kaur, M.; Singh, M.; Chadha, N.; Silakari, O., Oxindole: A Chemical Prism Carrying Plethora of Therapeutic Benefits. *Eur. J. Med. Chem.* **2016**, *123*, 858-894.
3. Nautiyal, O. H., Synthesis of Oxindoles, Spirooxindoles, and Isatins with Prominent Bioactive Probes Review. *Org. Med. Chem. IJ* **2018**, *5*, 126-137.
4. Shukla, P. K.; Singh, M. K.; Patel, R., *J. Appl. Pharm. Sci. Res.* **2018**, *1*, 16-22.
5. Varun; Sonam; Kakkar, R., *Med. Chem. Comm.* **2019**, *10*, 351-368.
6. Brandao, P.; Marques, C.; Burke, A. J.; Pineiro, M., *Eur. J. Med. Chem.* **2021**, *211*, 113102.
7. Kumar, S.; Nair, A. S.; Abdelgawad, M. A.; Mathew, B., *ACS Omega* **2022**, *7*, 16244-16259.
8. Chowdhary, S.; Shalini; Arora, A.; Kumar, V., *Pharmaceuticals.* **2022**, *15*, 536.
9. Galliford, C. V.; Scheidt, K. A., *Angew. Chem. Int. Ed.* **2007**, *46*, 8748-8758.
10. Smith, G.; Glaser, M.; Perumal, M.; Nguyen, Q. D.; Shan, B.; Ãrstad, E.; Aboagye, E. O., *J. Med. Chem.* **2008**, *51*, 8057-8067.
11. Krishnegowda, G.; Prakasha Gowda, A. S.; Tagaram, H. R. S.; Carroll, K. F. S.-O.; Irby, R. B.; Sharma, A. K.; Amin, S., *Bioorg. Med. Chem.* **2011**, *19*, 6006-6014.
12. Glaser, M.; Goggi, J.; Smith, G.; Morrison, M.; Luthra, S. K.; Robins, E.; Aboagye, E. O., *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6945-6949.
13. Prakash, C. R.; Raja, S., *Eur. J. Med. Chem.* **2011**, *46*, 6057-6065.
14. Ferraz de Paiva, R. E.; Vieira, E. G.; Rodrigues da Silva, D.; Wegermann, C. A.; Costa Ferreira, A. M., *Front. Mol. Biosci.* **2021**, 7:627272.
15. Bridges, T. M.; Kennedy, J. P.; Cho, H. P.; Breininger, M. L.; Gentry, P. R.; Hopkins, C. R.; Conn, P. J.; Lindsley, C. W., *Bioorg. Med. Chem. Lett.* **2010**, *20*, 558-562.
16. Konda, S.; Srinivas, A.; Sarangapani, M., *J. Chem. Pharm. Res.* **2010**, *2*, 220-225.
17. Ewang-Emukowhate, M.; Nair, D.; Caplin, M., *Int. J. Endo. Oncol.* **2019**, *6*, IJE17.
18. Du, F.; Zhou, Q.; Sun, W.; Yang, C.; Wu, C.; Wang, L.; Chen, G., *Molecules* **2020**, *25*, 2059.
19. Zeng, R.; Dong, G., *J. Am. Chem. Soc.* **2015**, *137*, 1408-1411.
20. Liu, Y.; Xia, Y. T.; Cui, S.-H.; Ji, Y. G.; Wu, L., *Adv. Synth. Catal.* **2020**, *362*, 2632-2636.

21. Pawar, A. P.; Yadav, J.; Mir, N. A.; Iype, E.; Rangan, K.; Anthal, S.; Kant, R.; Kumar, I., *Chem. Commun.* **2021**, *57*, 251-254.
22. Chen, Q.; Teng, Y.; Xu, F., *Org. Lett.* **2021**, *23*, 4785-4790.
23. Klein, J. E. M. N.; Taylor, R. J. K., *Eur. J. Org. Chem.* **2011**, *2011*, 6821-6841.
24. Mohammadi Ziarani, G.; Moradi, R.; Lashgari, N., *Tetrahedron.* **2018**, *74*, 1323-1353.
25. Shen, J.; Zhang, L.; Meng, X., *Org. Chem. Front.* **2021**, *8*, 6433-6451.
26. Saranya, P. V.; Neetha, M.; Aneeja, T.; Anilkumar, G., *RSC Adv.*, **2021**, *11*, 7146-7179.
27. Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J., *Chem. Soc. Rev.* **2016**, *45*, 2900-2936.
28. Wedi, P.; van Gemmeren, M., *Angew.Chem. Int. Ed.* **2018**, *57*, 13016-13027.
29. Rogge, T.; Kaplaneris, N.; Chatani, N.; Kim, J.; Chang, S.; Punji, B.; Schafer, L. L.; Musaev, D. G.; Wencel-Delord, J.; Roberts, C. A.; Sarpong, R.; Wilson, Z. E.; Brimble, M. A.; Johansson, M. J.; Ackermann, L., *Nat. Rev. Methods Primers* **2021**, *1*, 43.
30. Sandtorv, A. H., *Adv. Synth. Catal.* **2015**, *357*, 2403-2435.
31. Leitch, J. A.; Bhonoah, Y.; Frost, C. G., *ACS Catal.* **2017**, *7*, 5618-5627.
32. Jagtap, R. A.; Punji, B., *Asian J. Org. Chem.* **2020**, *9*, 326-342.
33. Jagtap, R. A.; Punji, B., *Chem. Rec.* **2021**, *21*, 3573-3588.
34. Bansal, S.; Shabade, A. B.; Punji, B., *Adv. Synth. Catal.* **2021**, *363*, 1998-2022.
35. Pradhan, C.; Punji, B., *SynLett* **2022**, *33*, 10.1055/a-1890-8503.
36. Jagtap, R. A.; Samal, P. P.; Vinod, C. P.; Krishnamurty, S.; Punji, B., *ACS Catal.* **2020**, *10*, 7312-7321.
37. Verma, S. K.; Punji, B., *Chem. Asian J.* **2022**, *17*, e202200103.
38. Zhou, K.; Wang, D.; Ju, G.; Deng, Z.; Huang, P.; Huang, Z.; Li, B.; Zhao, Y., *Org. Lett.* **2022**, *24*, 5568-5572.
39. Dick, A. R.; Hull, K. L.; Sanford, M. S., *J. Am. Chem. Soc*. **2004**, *126*, 2300-301.
40. Zhang, Y.-H.; Yu, J. Q., *J. Am. Chem. Soc.* **2009**, *131*, 14654-14655.
41. Emmert, M. H.; Cook, A. K.; Xie, Y. J.; Sanford, M. S., *Angew. Chem., Int. Ed.* **2011**, *50*, 9409-9412.
42. Enthaler, S.; Company, A., *Chem. Soc. Rev.* **2011**, *40*, 4912-4924.
43. Valderas, C.; Naksomboon, K.; Fernández-Ibáñez, M. Á., *ChemCatChem* **2016**, *8*, 3213-3217.
44. Iqbal, Z.; Joshi, A.; Ranjan De, S., *Adv. Synth. Catal.* **2020**, *362*, 5301-5351.
45. Vijaykumar, M.; Punji, B., *Synthesis* **2021**, *53*, 2935-2946.

46. Kang, Y.B.; Gade, L. H., *J. Am. Chem. Soc.* **2011**, *133*, 3658-3667.
47. Wang, A.; Jiang, H.; Chen, H., *J. Am. Chem. Soc.* **2009**, *131*, 3846-3847.
48. Dou, X.; Yao, W.; Jiang, C.; Lu, Y., *Chem. Commun.* **2014**, *50*, 11354-11357.
49. Wang, Y. Y.; Chen, C., *J. Chin. Chem. Soc.* **2007**, *54*, 1363-1368.
50. Cook, A. K.; Emmert, M. H.; Sanford, M. S., *Org. Lett.* **2013**, *15*, 5428-5431.
51. Cook, A. K.; Sanford, M. S., *J. Am. Chem. Soc.* **2015**, *137*, 3109-3118.
52. Hebda, M. B., M.; Wieckowska, A.; Szalaj, N.; Pasieka, A.; Panek, D.; Godyn, J.; Wichur, T.; Knez, D.; Gobec, S.; Malawska, B., *Molecules* **2016**, *21*, 410.
53. Nyantakyi, S. A.; Li, M.; Gopal, P.; Zimmerman, M.; Dartois, V.; Gengenbacher, M.; Dick, T.; Go, M., *J. Med. Chem.* **2018**, *61*, 5733-5750.
54. Jagtap, R. A.; Pradhan, C.; Gonnade, R. G.; Punji, B., *Chem. Asian J.* **2022**, doi.org/10.1002/asia.202200414.
55. Aboul-Fadl, T.; Mohammed, F. A. H.; Hassan, E. A. S., *Arch Pharm Res* **2003**, *26*, 778-784
56. Chambers, R. J.; Abrams, K.; Garceau, N. Y.; Kamath, A. V.; Manley, C. M.; Lilley, S. C.; Otte, D. A.; Scott, D. O.; Sheils, A. L.; Tess, D. A.; Vellekoop, A. S.; Zhang, Y.; Lam, K. T., *Bioorg. Med. Chem. Lett.* **2006**, *16*, 307-310.
57. Liu, Y.; Xia, Y. T.; Cui, S. H.; Ji, Y. G.; Wu, L., *Adv. Synth. Catal.* **2020**, *362*, 2632-2636.
58. Wang, Y. Y.; Chen, C., *J. Chin. Chem. Soc.* **2007**, *54*, 1363-1368.
59. Bruker, *APEX3, SAINT and SADABS.* Bruker AXS Inc., Madison, Wisconsin, USA. **2016**.
60. Sheldrick, G. M., *Acta Crystallogr.* **2008**, *A64*, 112-122.
61. Sheldrick, G. M., *Acta Crystallogr.* **2015**, *C71*, 3-8.
62. Farrugia, L. J., *J. Appl. Crystallogr.* **2012**, *45*, 849-854.

Chapter 4

Palladium-Catalyzed Regioselective C(4)–H Fluoroalkoxylation of Indoles *via* Weak Chelation-Assistance

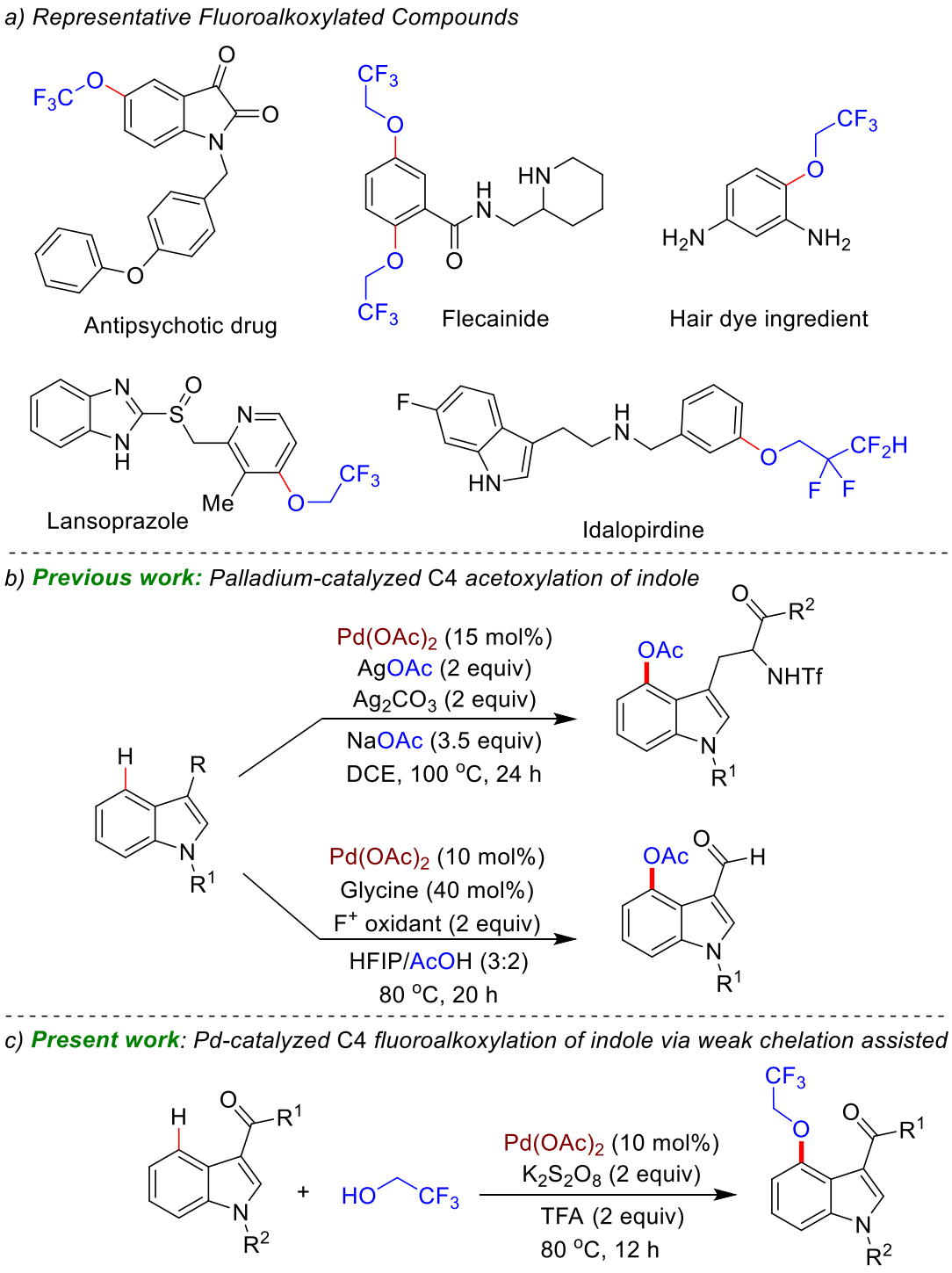


4.1 INTRODUCTION

Organic compounds containing fluorine have significant implication in the fields of drug discovery and medicinal chemistry. In particular, fluoroalkyl aryl ethers are widely used in agrochemical and pharmaceutical products due to their unique drug-kinetic and chemical properties, including electron withdrawal effect, high metabolic stability, and the extended lipophilicity (Scheme 4.1a).[1-5] Considering its broad importance, it is highly desirable to develop efficient synthetic method to integrate fluoroalkoxy groups into (hetero)arene. Conventional approaches to the synthesizing of fluoroalkoxy (hetero)arenes usually involve the cross-coupling of phenols or aromatic halides with reagents containing fluorine through nucleophilic substitution or transition-metal-mediation.[6-14] However, these methods require prefunctionalized substrates and generate stoichiometric amounts of organometallic waste as byproducts. The fluoroalkoxylation of the direct C–H bond has recently brought clear advantages to the step and the atomic economy. In that direction, the fluoroalkoxylation methods are widely explored for simple arenes using amide-based (or) transient directing groups *via* C–H activation strategy.[14,17-19] However, the site-selective fluoroalkoxylation of synthetically important *N*-containing heteroarenes is scarce.

The *N*-(hetero)arenes, such as functionalized indole core, are crucial structural motifs in various biologically active compounds and drugs.[20-25] The functionalization of C4 CH is of great interest due to the fact that indoles replaced at the C4 position serve as integral components in various natural products and pharmaceutical molecules.[26-29] Introducing a directing group at the C3 position to facilitate access to the C4 position poses a practical challenge, as there is a potential for the formation of a five-member metal cycle at C2 compared to a six-member metal cycle at C4. Therefore, the necessity for a flexible and easily attachable guiding group at the C3 site becomes crucial to overcome the competition with C2 metals and achieve exclusive C4 selectivity. Recent investigations have explored transition metal-catalyzed group-assisted regioselective CH functionalization at the C4 position of indole.[30-35] Additionally, given the widespread applications of 4-oxyindole in biology and medicine, C4-oxygenation holds significant importance.[36-38] More recently, Wang reported an efficient Pd-catalyzed regioselective C4 acetoxylation of tryptophan indoles.[39] Similarly, Volla and co-workers have shown that the Pd-catalyzed C4 acetoxylation of indole through a transient directing group (Scheme 4.1b).[40] However, these reports are restricted to acetoxylation, whereas C4 fluoroalkoxylation of indole is not yet precedented. Considering the properties of indoles and the fluorinated organic compounds,

we were keen to explore fluoroalkoxylation at the C4-position of indole. In this chapter, we develop a Pd-catalyzed regioselective C4 fluoroalkoxylation of indole derivatives with fluorinated alcohol *via* weak chelation-assistance (Scheme 4.1c).



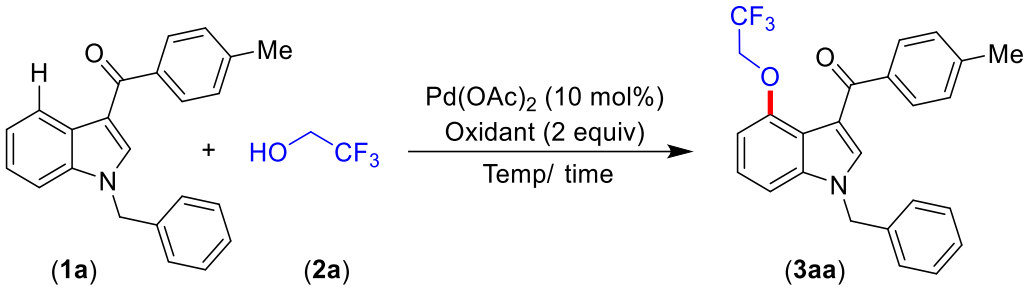
Scheme 4.1. Selective C(4)–H Oxygenation of Indoles.

4.2 RESULTS AND DISCUSSION

4.2.1 Optimization of Reaction Parameters

We initiated the screening of reaction parameters for the fluoroalkoxylation of (1-benzyl-1*H*-indol-3-yl)(*p*-tolyl)methanone (**1a**) using trifluoroethanol as a model substrate, employing toluoyl as the directing group, and testing various Pd sources, oxidants, and additives (Table 4.1). In the initial attempt, When **1a** was stirred with $Pd(OAc)_2$ (10 mol%) at 100 °C for 12 h in the presence of $PhI(OAc)_2$ and TFA (2.0 equiv), only a trace of the product was obtained (Table 4.1, entry 1). Subsequent screening of oxidants, including metal salts, NFSI, selectfluor, and benzoquinone resulted in incomplete conversion (entries 2-6). The utilization of metal persulphate, specifically $(NH_4)_2S_2O_8$, led to a diminished yield (entry 7). Encouragingly, $Na_2S_2O_8$ and $K_2S_2O_8$ proved to be effective oxidants, providing the desired trifluoroalkoxylated product **3aa** in 47% and 58% yield, respectively (entries 8, 9). Among the additives examined, water, triflic acid, and acetic acid, former TFA provided the best results (entries 10, 11). The alkoxylation was sluggish using $PdCl_2$ as a catalyst and provided a 19% yield of **3aa**; however, $Pd_2(dba)_3$ as a catalyst was ineffective (entries 12, 13). The use of 5.0 mol% of the catalyst led to a decrease in conversion (entry 14). Surprisingly, the C4 fluoroalkoxylation progressed effortlessly even at 80 °C, yielding a 64% yield (entry 15); however, further decreasing the temperature lowered the conversion (entry 16). Moreover, reducing the loading of $K_2S_2O_8$ or TFA and lowering solvent loading resulted in a low yield (entries 17-19). Achieving the selective C(4)−H fluoroalkoxylation of indoles relies on the essential Pd(II) catalyst, $K_2S_2O_8$, as the oxidant and the required additive (entries 20, 21). After exhaustive screening, the conditions for the C(4)−H fluoroalkoxylation are as follows: $Pd(OAc)_2$ (10 mol%), $K_2S_2O_8$ (2.0 equiv), TFA (2.0 equiv), in TFE (1.0 mL) at 80 °C for 12 h.

Table 4.1. Optimization of Reaction Parameters for C4 Fluoroalkoxylation of Indoles.[a]

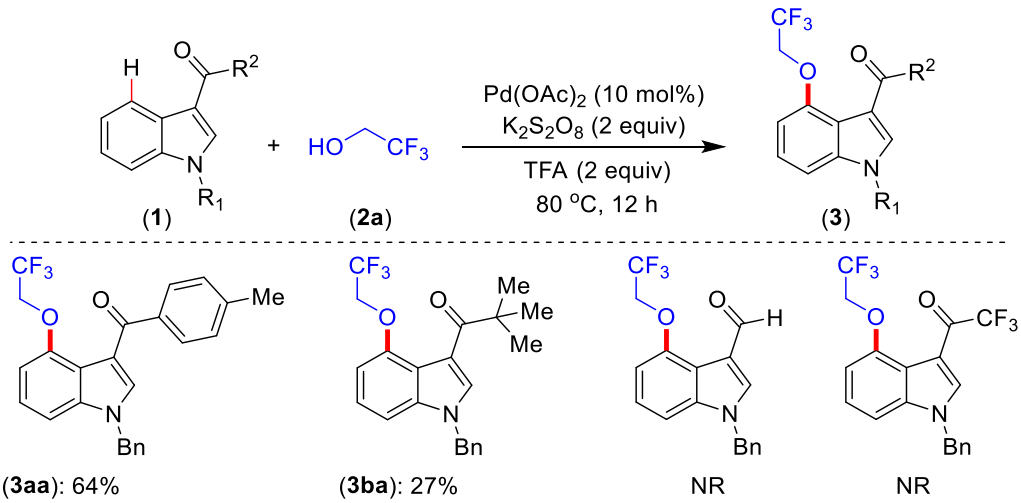


Entry	[Pd]	Oxidant	Additive	Solvent	Yield (%)[b] 3aa
1	$Pd(OAc)_2$	$PhI(OAc)_2$	TFA	TFE	trace
2	$Pd(OAc)_2$	$Cu(OAc)_2$	TFA	TFE	trace
3	$Pd(OAc)_2$	AgOAc	TFA	TFE	NR
4	$Pd(OAc)_2$	NFSI	TFA	TFE	trace
5	$Pd(OAc)_2$	Selecfluor	TFA	TFE	NR
6	$Pd(OAc)_2$	BQ	TFA	TFE	trace
7	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	TFA	TFE	NR
8	$Pd(OAc)_2$	$Na_2S_2O_8$	TFA	TFE	47
9	$Pd(OAc)_2$	$K_2S_2O_8$	TFA	TFE	58
10	$Pd(OAc)_2$	$K_2S_2O_8$	TfOH	TFE	NR
11	$Pd(OAc)_2$	$K_2S_2O_8$	AcOH	TFE	trace
12	$PdCl_2$	$K_2S_2O_8$	TFA	TFE	19
13	$Pd_2(dba)_3$	$K_2S_2O_8$	TFA	TFE	NR
14[c]	$Pd(OAc)_2$	$K_2S_2O_8$	TFA	TFE	52
15[d]	**$Pd(OAc)_2$**	**$K_2S_2O_8$**	**TFA**	**TFE**	**64**
16[e]	$Pd(OAc)_2$	$K_2S_2O_8$	TFA	TFE	45
17[d,f]	$Pd(OAc)_2$	$K_2S_2O_8$	TFA	TFE	53
18[d,g]	$Pd(OAc)_2$	$K_2S_2O_8$	TFA	TFE	57
19[d,h]	$Pd(OAc)_2$	$K_2S_2O_8$	TFA	TFE	48
20[d]	$Pd(OAc)_2$	$K_2S_2O_8$	--	TFE	NR
21[d]	$Pd(OAc)_2$	--	TFA	TFE	NR
22[d]	--	$K_2S_2O_8$	TFA	TFE	NR

[a] Reaction Conditions: **1a** (0.065 g, 0.20 mmol), oxidant (0.40 mmol), [Pd] (0.02 mmol, 10.0 mol%), additive (0.40 mmol), TFE (1 mL), 100 °C, 12 h. [b] Yield of isolated compound **3aa**. [c]5.0 mol% of $Pd(OAc)_2$ used. [d] Reaction performed at 80 °C, [e] Reaction performed at 60 °C, [f] 1.5 equiv of $K_2S_2O_8$ was used. [g]1.5 equiv of TFA was used. [h] 0.5 mL of TFE was used. NR = No Reaction. TFA = Trifluoroacetic acid. TFE = Trifluoroethanol.

4.2.2 Effect of C3 Substituents on Selective C(4)−H Fluoroalkoxylation

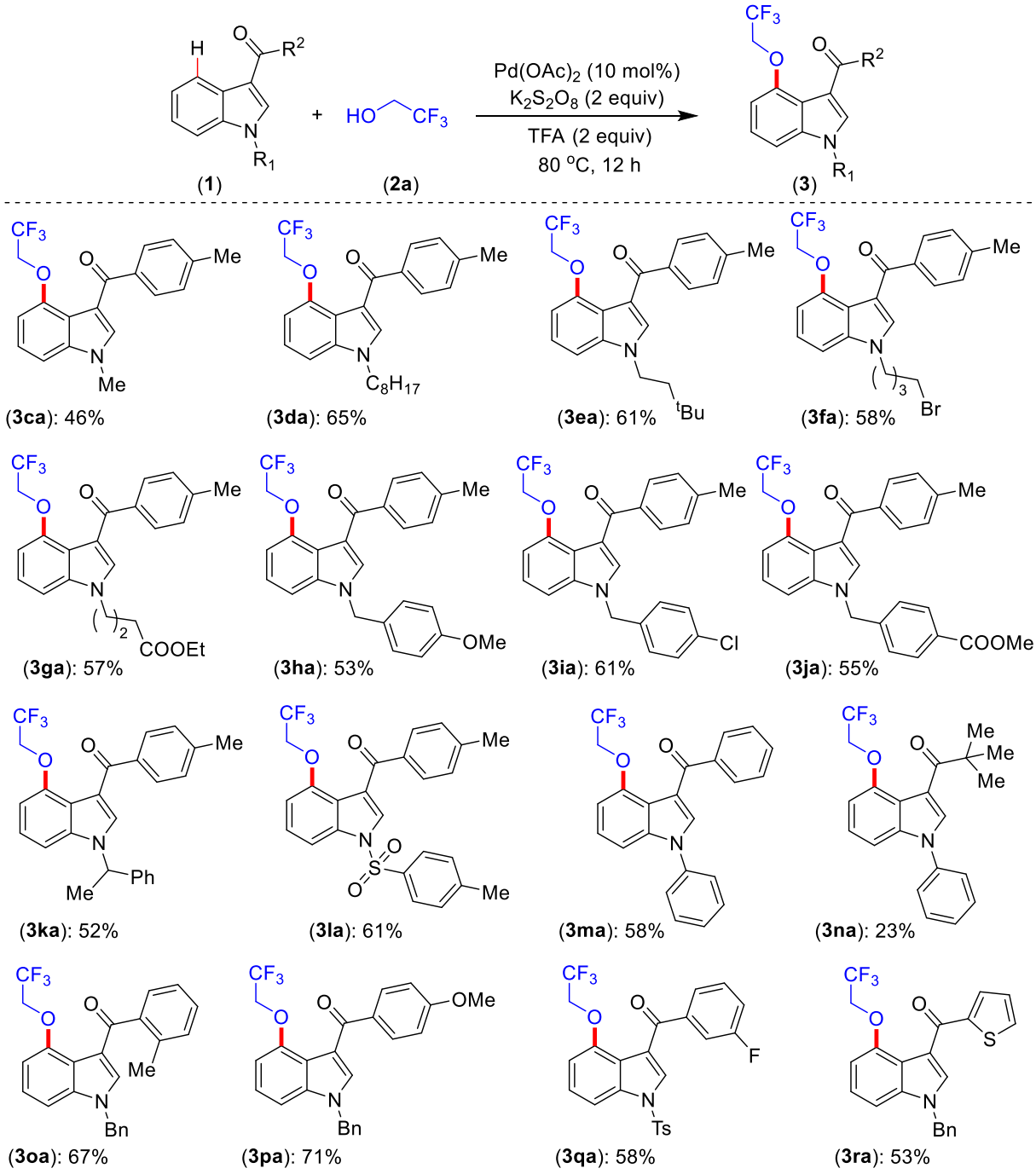
Using the optimal reaction condition, we investigated the influence of C3 substituents on indole derivative in selective C(4)−H fluoroalkoxylation (Scheme 4.2). The reaction involving the fluoroalkoxylation of (1-benzyl-1*H*-indol-3-yl)(*p*-tolyl)methanone (**1a**) afforded product **3aa** in 64% yield. Similarly, 1-(1-benzyl-1*H*-indol-3-yl)-2,2-dimethylpropan-1-one (**1b**) reacted moderately, resulting in the desired product **3ba** in 27% yield. Notably, no alkoxylation was observed when employing directing groups like –CHO, –$COCF_3$, and –COOMe. These results strongly indicate that the electronic characteristics of chelated carbonyl groups play a vital role in the selective activation of C(4)−H.



Scheme 4.2. Effect of C3 Directing Group for C(4)−H Fluoroalkoxylation of Indoles.

4.2.3 Scope for C(4)–H Fluoroalkoxylation of Indoles

We investigated the scope and limitations of the current protocol for synthesizing C4 fluoroalkoxylation products in various indoles (Scheme 4.3). Initially, we screened *N*-substituted indole substrates. The (1*H*-indol-3-yl)(*p*-tolyl)methanone, bearing *N*-methyl and octyl substituents, demonstrated smooth reactivity, leading to the formation of C4 fluoroalkoxylated products **3ca** and **3da** with good yields. Even a branched alkyl substituent was compatible, resulting in the desired product **3ea** in 61% yield. Indoles with notable functionalities, such as −Br and –COOEt, reacted with low efficacy to afford fluoroalkoxylated compounds **3fa** and **3ga** in moderate yields. Similarly, functional groups like –OMe, –Cl, and –COOMe at the *para* position of the *N*-benzyl indoles were well tolerated (**3ha**-**3ja**), demonstrating their compatibility, which is essential for synthetic versatility and subsequent derivatizations.

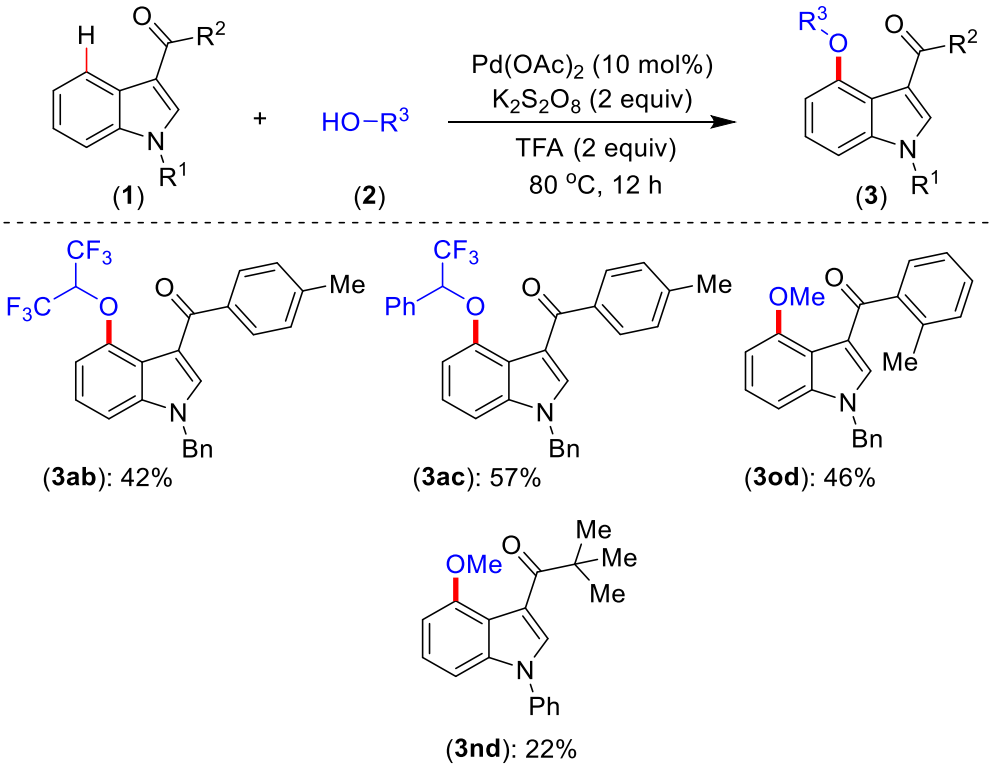


Scheme 4.3. Scope for C(4)−H Fluoroalkoxylation of C3 and *N*-Substituted Indoles. Reaction conditions: **1** (0.20 mmol), $K_2S_2O_8$ (0.40 mmol), $Pd(OAc)_2$ (0.02 mmol, 10 mol%), TFA (0.40 mmol), TFE (1.0 mL).

Furthermore, 1-methyl benzyl and tosyl substituents on the nitrogen of C3-toluoylindoles yielded 52% and 61% of products **3ka** and **3la**, respectively. Apart from *N*-alkyl and *N*-benzyl indoles, *N*-aryl substituted indoles were also subjected to

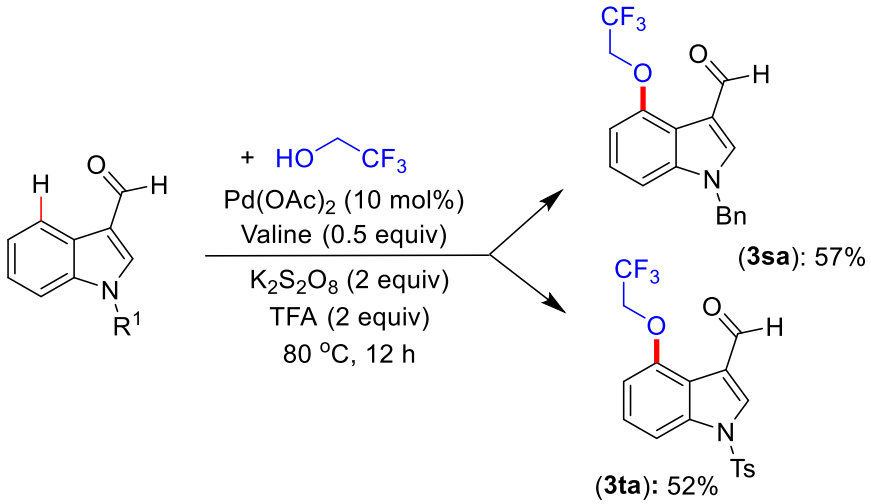
fluoroalkoxylation at the C4 position, forming **3ma** and **3na** with moderate yields. Furthermore, the functional groups such as –Me, –OMe, and –F at different positions of C3-benzoyl *N*-substituted indoles were well tolerated and provided moderate to good yields (**3oa-3qa**). Additionally, a synthetically important thiophene-2-carbonyl moiety onto the indole compound proceeded smoothly, resulting **3ra** in 53% yield.

Subsequently, we explored the range of alcohols that can be used in the alkoxylation with (1-benzyl-1*H*-indol-3-yl)(tolyl)methanone (Scheme 4.4). We were pleased to observe that 1,1,1,3,3,3-hexafluoropropan-2-ol and 2,2,2-trifluoro-1-phenylethan-1-ol exhibited excellent reactivity under the optimal reaction conditions, providing the corresponding fluoroalkoxylated products **3ab** and **3ac** with yields of 42% and 57%, respectively. Notably, the reaction with methanol demonstrated favorable tolerance to the reaction conditions, proceeding smoothly to give products (**3od**, **3nd**) in moderate yields. However, the reaction with ethanol and isopropanol only resulted in a trace amount of product. Further, electron-rich alcohols were tested, and only trace products were observed.



Scheme 4.4. Scope for C(4)−H Alkoxylation of Indoles using Alcohols. Reaction conditions: **1** (0.20 mmol), $K_2S_2O_8$ (0.40 mmol), $Pd(OAc)_2$ (0.02 mmol, 10 mol%), TFA (0.40 mmol), alcohol (1.0 mL).

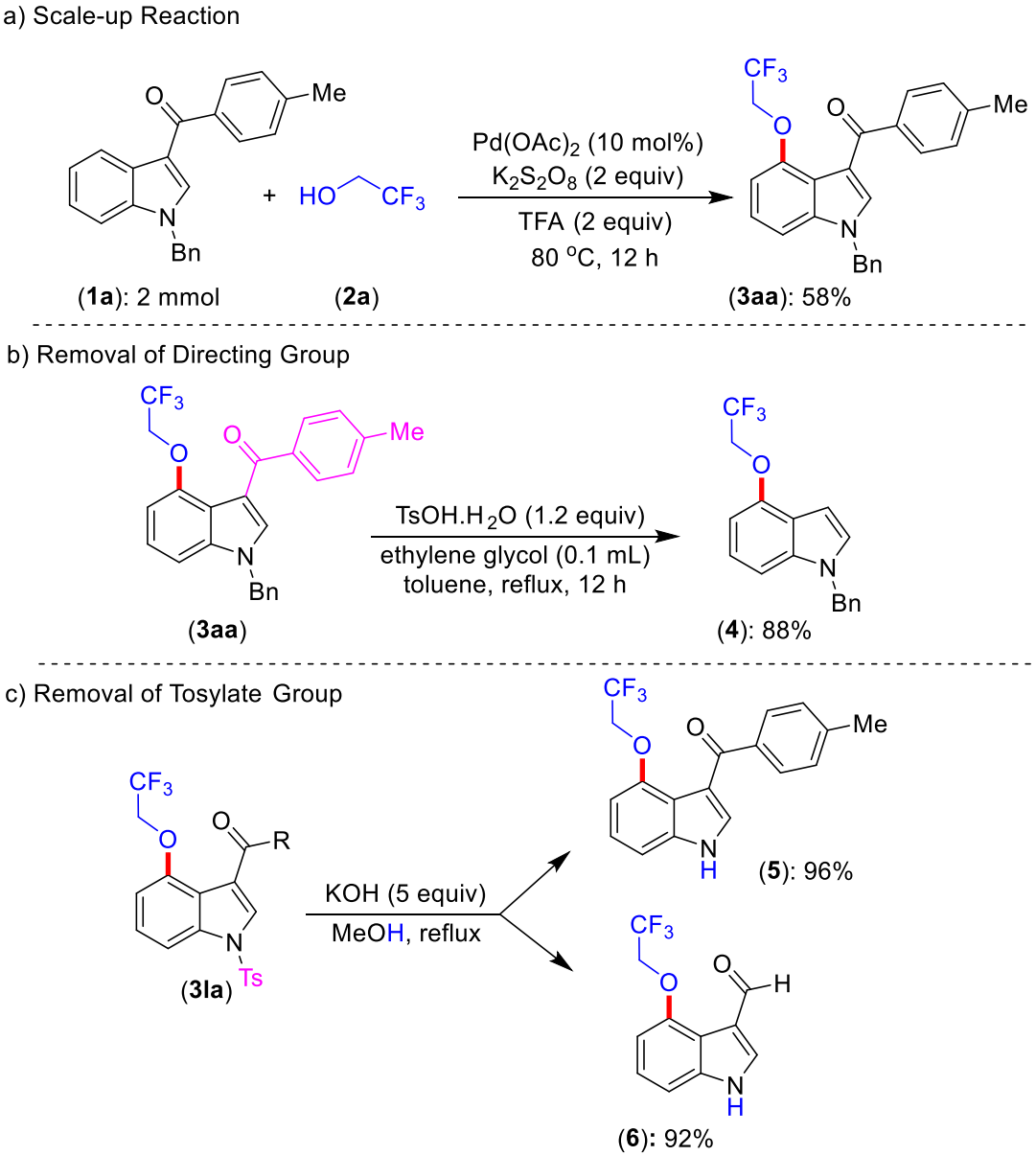
In addition to the keto group at position C3, we investigated the fluoroalkoxylation of aldehydes substituted at C3. However, these attempts do not result in the desired product under standard reaction conditions. Upon making slight modifications to the standard conditions, such as using valine as a transient directing group, we observed that *N*-substituted 1*H*-indole-3-carbaldehyde substrates facilitated the formation of selective C4 fluoroalkoxylation products **3sa** and **3ta** in moderate yields (Scheme 4.5). The structure of compound **3sa** was confirmed by single crystal X-ray diffraction study (Figure **3sa**).



Scheme 4.5. Scope using Transient Directing Group for C(4)−H Fluoroalkoxylation of Indoles.

4.2.4 Gram Scale-Synthesis and Removal of Directing and Protecting Group

A scale-up reaction was conducted to exhibit the practical applicability of the palladium-catalyzed method. Thus, the reaction of 2.0 mmol of indole **1a** was subjected to the standard catalytic conditions with trifluoroethanol, forming **3aa** with a yield of 58% (Scheme 4.6a). Subsequently, we tried to remove the touloyl directing group from **3aa** using TsOH and ethylene glycol to give **4** in 88% of yield (Scheme 4.6b). Likewise, the deprotection of the tosyl group from compounds **3la** and **3ta** in the presence of KOH provided the *NH*-trifluoroalkoxy indoles **5** and **6** with yields of 96% and 92%, respectively (Scheme 4.6c).

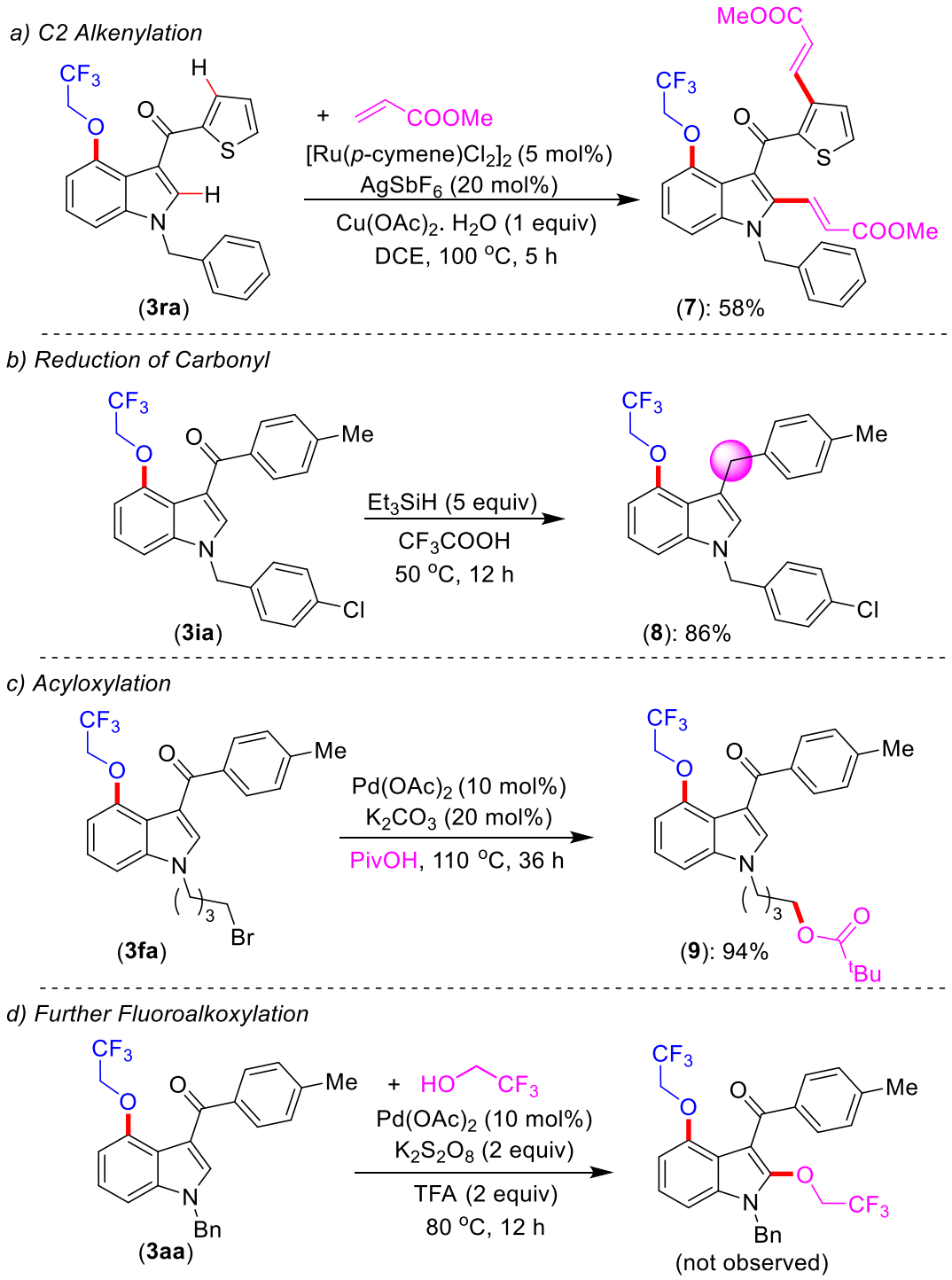


Scheme 4.6. Removal of Benzoyl Directing and Tosyl Protecting Group.

4.2.5 Synthetic Transformation of C(4)–H Fluoroalkoxylated Indoles

Furthermore, the fluoroalkoxylated indoles at the C4 position exhibited versatility in expanding the molecular frameworks (Scheme 4.7). The catalytic C2-alkenylation, facilitated by ruthenium in **3ra** with methyl acrylate, resulted in the production of compound **7** with a yield of 58% (Scheme 4.7a). Reducing the carbonyl group of **3ia** using excess Et_3SiH and trifluoroacetic acid furnished **8** in 86% yield (Scheme 4.7b). The reaction of **3fa** with a Pd-catalyst and pivalic acid at 110 ^oC provided the carboxylated compound **9** with a 94% yield (Scheme 4.7c). However, an attempt to perform a C(2)–H fluoroalkoxylation of compound **3aa** with trifluoroethanol under the standard Pd-catalyzed conditions could not deliver the

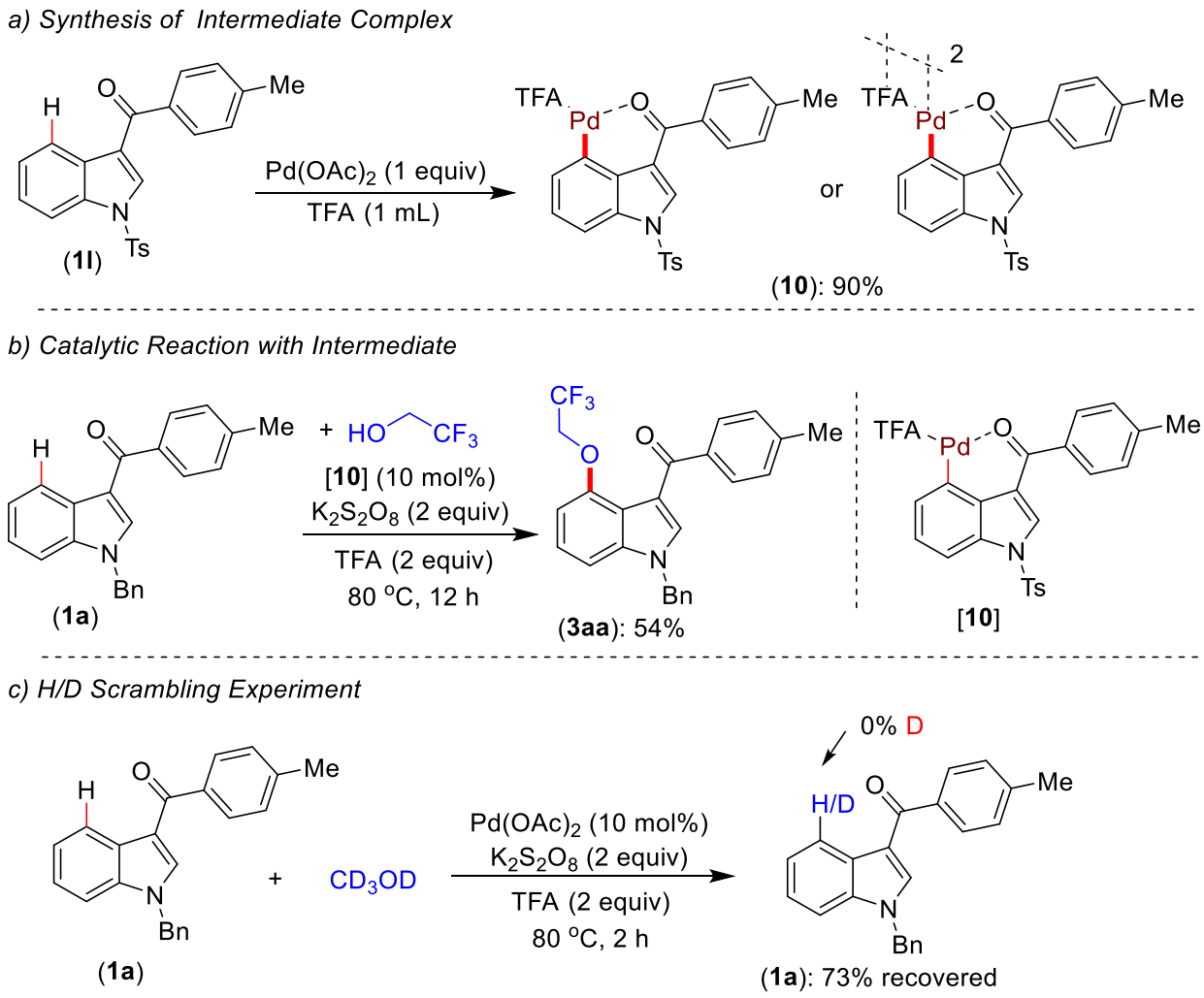
expected C2 fluoroalkoxylated product (Scheme 4.7d). The demonstrated synthetic modifications of the C4 fluoroalkoxylated indole highlight the protocol's usefulness and its potential for future synthetic applications.



Scheme 4.7. Synthetic Transformation of C4 Fluoroalkoxylated Indoles.

4.2.6 Mechanistic Aspects

A preliminary mechanistic investigation was conducted to identify the active Pd-catalytic species and to understand the indole's fluoroalkoxylation pathway. The treatment of *p*-tolyl(1-tosyl-1*H*-indol-3-yl)methanone (**1l**) with $Pd(OAc)_2$ using trifluoroacetic acid resulted the complex (3-(4-methylbenzoyl)-1-tosyl-1*H*-indol-4-yl)(2,2,2-trifluoroacetoxy)palladium (**10**) in excellent yield (Scheme 4.8a).[41,29] The structure of **10** was confirmed by the single-crystal X-ray analysis (Figure 4.3). The complex **10** served as a catalyst for the C-4 fluoroalkoxylation of indole, producing the desired product **3aa** in 54% of yield (Scheme 4.8b). Further, we conducted control experiments, such as the *H/D* scrambling experiment, to better understand the reaction mechanism (Scheme 4.8c). The reaction with CD_3OD as a solvent does not exhibit *H/D* scrambling at positions C4 or C2 of **1a**, which indicates that the C−H cleavage is irreversible.



Scheme 4.8. Preliminary Mechanistic Study.

4.2.7 Probable Catalytic Cycle

Based on literature precedents[29,33] and preliminary mechanistic observations, we propose a probable catalytic cycle (Figure 4.1). The activation of C(sp^2)–H directed by carbonyl at the C-4 position of **1l** occurs by the active Pd(II) complex **A**, resulting in the formation of a six-membered palladacycle **10**. Subsequently, the coordination of alcohol with the metal center leads to the formation of **B**, followed by proton exchange leads to intermediate **C**. Further, reductive elimination leads to the formation of C4-fluoroalkoxylated indole **3la** and Pd(0) species. The Pd(0) species oxidizes with $K_2S_2O_8$ in the presence of TFA, thereby regenerating active Pd(II) catalysts and completing the catalytic cycle.

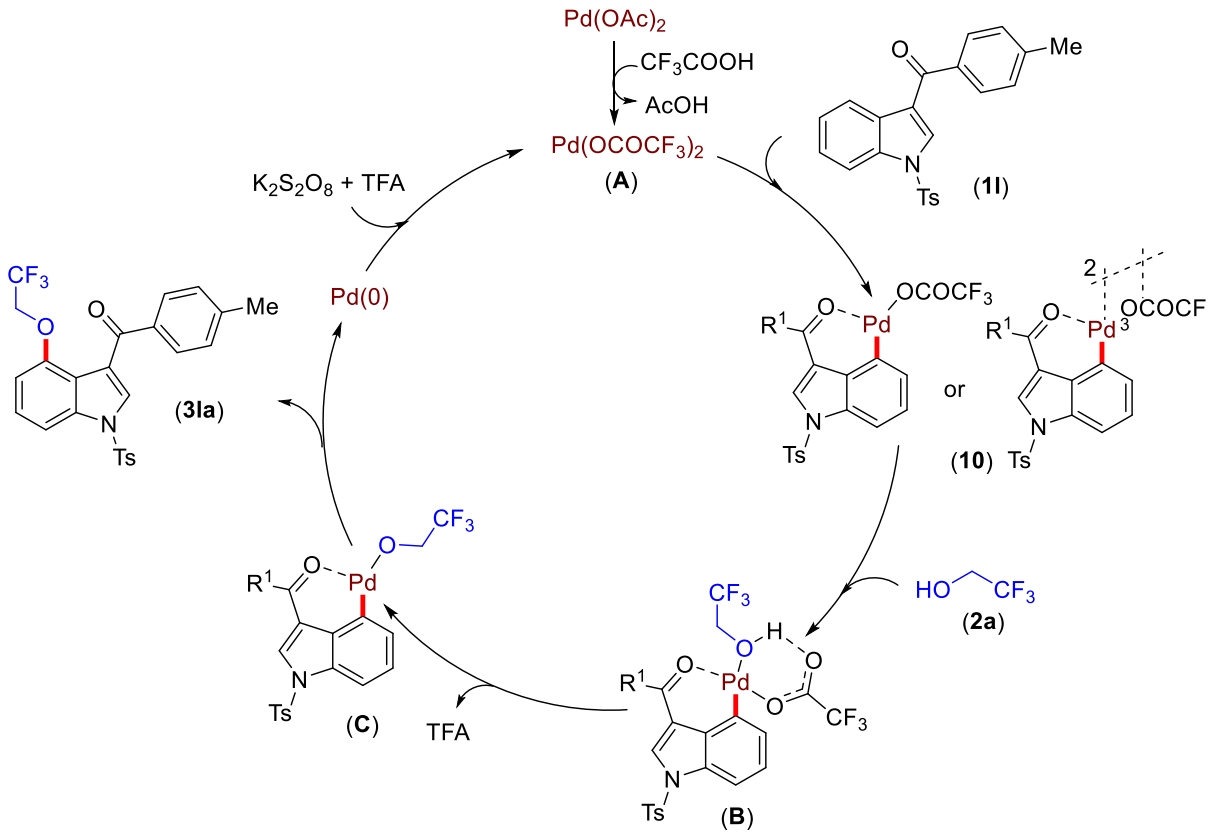


Figure 4.1. Plausible Catalytic Cycle for Fluoroalkoxylation of Indoles.

4.3 CONCLUSION

In summary, we have successfully achieved a Pd-catalyzed C4-fluoroalkoxylation of indoles with the assistance of weak chelation using fluoroalcohols. The fluoroalkoxylation protocol demonstrates extensive applicability, accommodating diverse functional groups like halides, esters, and thiophene. The practicality of the palladium-catalyzed method is

illustrated by the facial removal of the tosyl group, carbonyl directing group, gram scale synthesis, and highlighting its applicability in late-stage modifications of fluoroalkoxylated products. The catalytically active intermediates were isolated and structurally characterized. The preliminary reaction mechanism demonstrate that the reaction proceed via initial C4–H activation. Due to the significant role of the trifluoroethoxyl group in enhancing the bioavailability of organic molecules in medicinal chemistry, we expect that this reaction will garner considerable attention in the field of drug discovery.

4.4 EXPERIMENTAL SECTION

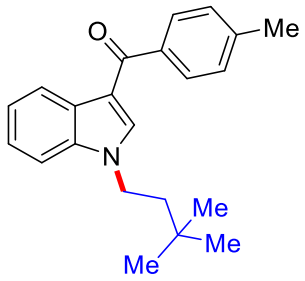
4.4.1 General Information

All manipulations were conducted under an argon atmosphere either in a glove box or using standard Schlenk techniques in pre-dried glasswares. The catalytic reactions were performed in oven-dried reaction vessels with a Teflon screw cap under open air. Solvents were dried over Na/benzophenone or CaH_2 and distilled prior to use. Liquid reagents were flushed with argon prior to use. The starting compounds **1a-1d**, **1i**, **1l-1p**, **1s,** and **1t** were synthesized according to the previously described procedures.[33,42,43] All other chemicals were obtained from commercial sources and were used without further purification. High-resolution mass spectrometry (HRMS) mass spectra were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump. NMR: (^{1}H and ^{13}C{^{1}H}) spectra were recorded at 400 or 500 MHz (^{1}H), 100 or 125 MHz {^{13}C{^{1}H}, DEPT (distortionless enhancement by polarization transfer)}, 377 MHz (^{19}F), respectively in $CDCl_3$ and DMSO-d_6 solutions, if not otherwise specified; chemical shifts (δ) are given in ppm. The ^{1}H and ^{13}C{^{1}H} NMR spectra are referenced to residual solvent signals ($CDCl_3$: δ H = 7.26 ppm, δ C = 77.2 ppm; DMSO-d_6: δ H = 2.50 ppm, δ C = 39.5 ppm). The splitting pattern of NMR is abbreviated as follows: s = singlet; br s = broad singlet; d = doublet; t = triplet; q = quartet; sept = septet; dd = doublet of doublets; td = triplet of doublets; m = multiplet.

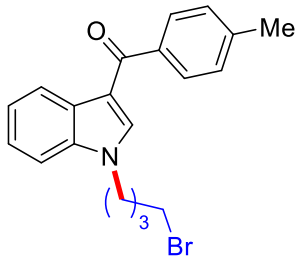
4.4.2 Synthesis and Characterization of Starting Compounds

***Representative Procedure A*. Synthesis of (1-(3,3-Dimethylbutyl)-1*H*-indol-3-yl)(*p*-tolyl)methanone (1e):** In an oven-dried Schlenk flask, a solution of (1*H*-indol-3-yl)(*p*-tolyl)methanone (0.50 g, 2.13 mmol) in DMF (10 mL) was slowly added to NaH (0.077 g, 3.20 mmol) in DMF (5.0 mL) at 0 ^{o}C, and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was further cooled to 0 ^{o}C, and 1-bromo-3,3-

dimethylbutane (0.527 g, 3.2 mmol) was added dropwise. The resultant reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched with the addition of sat. NH_4Cl (aq), diluted with EtOAc and washed with ice-cold water and brine. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude residue was purified by column chromatography on silica gel (petroleum ether/ EtOAc: 10/1) to yield **1e** (0.61 g, 90%) as a pale yellow solid. M.pt: 122-126 ^oC.

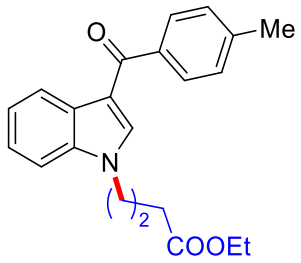


(1-(3,3-Dimethylbutyl)-1*H*-indol-3-yl)(*p*-tolyl)methanone (1e): ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.42-8.40 (m, 1H, Ar–H), 7.74 (d, J = 8.0 Hz, 2H, Ar–H), 7.58 (s, 1H, Ar–H), 7.37-7.29 (m, 5H, Ar–H), 4.19-4.14 (m, 2H, CH_2), 2.45 (s, 3H, CH_3), 1.80-1.75 (m, 2H, CH_2), 1.03 (s, 9H, CH_3). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 190.8 (CO), 141.7 (C_q), 138.4 (C_q), 136.9 (C_q), 136.6 (CH), 129.1 (2C, CH), 129.1 (2C, CH), 127.6 (C_q), 123.6 (CH), 123.1 (CH), 122.7 (CH), 116.0 (C_q), 109.8 (CH), 43.9 (CH_2), 43.8 (CH_2), 30.2 (C_q), 29.4 (3C, CH_3), 21.7 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{22}H_{25}NO + H^+$ $[M + H]^+$ 320.2009; Found 320.2010.

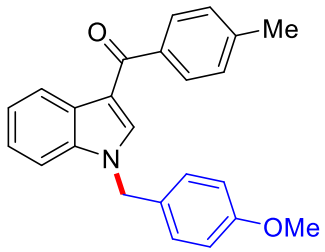


(1-(4-Bromobutyl)-1*H*-indol-3-yl)(*p*-tolyl)methanone (1f): The representative procedure **A** was followed, using (1*H*-indol-3-yl)(*p*-tolyl)methanone (0.50 g, 2.13 mmol), NaH (0.077 g, 3.20 mmol), and 1,4-dibromobutane (0.690 g, 3.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **1f** (0.59 g, 76%) as a red solid. M.pt: 104-108 ^oC. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.43-8.40 (m, 1H, Ar–H), 7.74 (d, J = 8.0 Hz, 2H, Ar–H), 7.57 (s, 1H, Ar–H), 7.40-7.32 (m, 3H, Ar–H), 7.30 (d, J = 7.9 Hz, 2H, Ar–H), 4.20 (t, J = 7.0 Hz, 2H, CH_2), 3.38 (t, J = 6.4 Hz, 2H, CH_2), 2.45 (s, 3H, CH_3), 2.09-

2.02 (m, 2H, CH_2), 1.90-1.83 (m, 2H, CH_2). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 190.8 (CO), 141.7 (C_q), 138.1 (C_q), 136.8 (C_q), 136.3 (CH), 129.1 (2C, CH), 128.9 (2C, CH), 127.5 (C_q), 123.6 (CH), 122.9 (CH), 122.6 (CH), 116.0 (C_q), 109.7 (CH), 46.4 (CH_2), 32.7 (CH_2), 29.9 (CH_2), 28.6 (CH_2), 21.7 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{20}H_{20}NO^{79}Br + H^+$ $[M + H]^+$ 370.0801; Found 370.0807, *m/z* Calcd for $C_{20}H_{20}NO^{81}Br + H^+$ $[M + H]^+$ 372.0781; Found 372.0774.

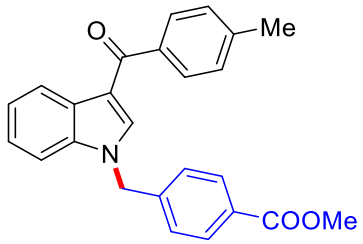


Ethyl 4-(3-(4-methylbenzoyl)-1*H*-indol-1-yl)butanoate (1g): The representative procedure **A** was followed, using (1*H*-indol-3-yl)(*p*-tolyl)methanone (0.50 g, 2.13 mmol), NaH (0.077 g, 3.20 mmol), and ethyl 4-bromobutanoate (0.624 g, 3.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **1g** (0.65 g, 89%) as a yellow liquid. ^1H-NMR (500 MHz, $CDCl_3$): δ = 8.38-8.36 (m, 1H, Ar–H), 7.43-7.38 (m, 2H, Ar–H), 7.36-7.24 (m, 6H, Ar–H), 4.19 (t, *J* = 7.1 Hz, 2H, CH_2), 4.10 (q, *J* = 7.1 Hz, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.29 (t, *J* = 6.9 Hz, 2H, CH_2), 2.19-2.12 (m, 2H, CH_2), 1.21 (t, *J* = 7.1 Hz, 3H, CH_3). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 193.0 (CO), 172.5 (CO), 141.2 (C_q), 137.7 (CH), 137.1 (C_q), 136.0 (C_q), 131.0 (CH), 129.5 (CH), 127.7 (CH), 127.0 (C_q), 125.3 (CH), 123.8 (CH), 123.0 (CH), 123.0 (CH), 117.4 (C_q), 110.1 (CH), 60.9 (CH_2), 46.2 (CH_2), 30.9 (CH_2), 25.1 (CH_2), 19.8 (CH_3), 14.3 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{22}H_{23}NO_3 + H^+$ $[M + H]^+$ 350.1751; Found 350.1739.

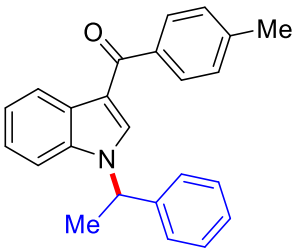


(1-(4-Methoxybenzyl)-1*H*-indol-3-yl)(*p*-tolyl)methanone (1h): The representative procedure **A** was followed, using (1*H*-indol-3-yl)(*p*-tolyl)methanone (0.50 g, 2.1 mmol), NaH (0.077 g, 3.20 mmol), and 1-(chloromethyl)-4-methoxybenzene (0.501 g, 3.20 mmol).

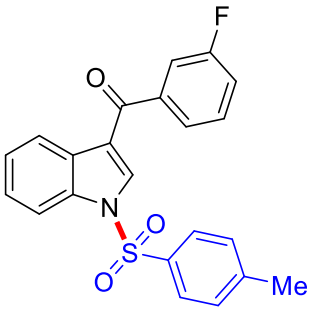
Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **1h** (0.65 g, 87%) as a yellow solid. M.pt: 118-122 ^{o}C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.41 (d, J = 8.0 Hz, 1H, Ar–H), 7.73 (d, J = 8.0 Hz, 2H, Ar–H), 7.60 (s, 1H, Ar–H), 7.32-7.25 (m, 5H, Ar–H), 7.08 (d, J = 8.8 Hz, 2H, Ar–H), 6.85-6.81 (m, 2H, Ar–H), 5.27 (s, 2H, CH_2), 3.76 (s, 3H, CH_3), 2.42 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 190.9 (CO), 159.6 (C_q), 141.8 (C_q), 138.2 (C_q), 137.2 (C_q), 136.9 (CH), 129.1 (2C, CH), 129.1 (2C, CH), 128.5 (2C, CH), 127.9 (C_q), 127.7 (C_q), 123.8 (CH), 122.9 (CH), 122.8 (CH), 116.2 (C_q), 114.5 (2C, CH), 110.4 (CH), 55.4 (CH_3), 50.5 (CH_2), 21.7 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{24}H_{21}NO_2 + H^+$ $[M + H]^+$ 356.1645; Found 356.1642.



Methyl 4-((3-(4-methylbenzoyl)-1*H*-indol-1-yl)methyl)benzoate (1j): The representative procedure **A** was followed, using (1*H*-indol-3-yl)(*p*-tolyl)methanone (0.50 g, 2.13 mmol), NaH (0.077 g, 3.20 mmol), and methyl 4-(bromomethyl)benzoate (0.733 g, 3.2 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **1j** (0.67 g, 83%) as an orange solid. M.pt: 136-140 ^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.43 (d, J = 7.6 Hz, 1H, Ar–H), 7.98 (d, J = 8.4 Hz, 2H, Ar–H), 7.75 (d, J = 8.1 Hz, 2H, Ar–H), 7.64 (s, 1H, Ar–H), 7.35-7.31 (m, 1H, Ar–H), 7.30-7.25 (m, 4H, Ar–H), 7.18 (d, J = 8.3 Hz, 2H, Ar–H), 5.42 (s, 2H, CH_2), 3.89 (s, 3H, CH_3), 2.43 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 190.9 (CO), 166.7 (CO), 142.0 (C_q), 141.1 (C_q), 138.1 (C_q), 137.1 (C_q), 136.9 (CH), 130.5 (2C, CH), 130.3 (C_q), 129.2 (2C, CH), 129.1 (2C, CH), 127.7 (C_q), 126.8 (2C, CH), 124.1 (CH), 123.1 (CH), 123.0 (CH), 116.7 (C_q), 110.2 (CH), 52.4 (CH_3), 50.7 (CH_2), 21.7 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{25}H_{21}NO_3 + H^+$ $[M + H]^+$ 384.1594; Found 384.1581.

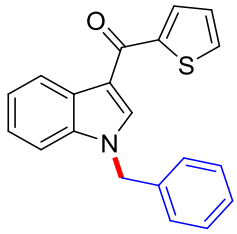


(1-(1-Phenylethyl)-1*H*-indol-3-yl)(*p*-tolyl)methanone (1k): The representative procedure **A** was followed, using (1*H*-indol-3-yl)(*p*-tolyl)methanone (0.50 g, 2.13 mmol), NaH (0.077 g, 3.20 mmol), and (1-bromoethyl)benzene (0.592 g, 3.2 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **1k** (0.63 g, 88%) as a brown solid. M.pt: 90-94 ^{o}C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.39 (d, J = 7.8 Hz, 1H, Ar–H), 7.77-7.74 (m, 3H, Ar–H), 7.32-7.25 (m, 6H, Ar–H), 7.24-7.20 (m, 2H, Ar–H), 7.13 (d, J = 7.1 Hz, 2H, Ar–H), 5.69 (q, J = 7.0 Hz, 1H, CH), 2.43 (s, 3H, CH_3), 1.92 (d, J = 7.0 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): = 191.0 (CO), 141.8 (C_q), 141.3 (C_q), 138.3 (C_q), 137.1 (C_q), 134.0 (CH), 129.2 (2C, CH), 129.1 (4C, CH), 128.1 (CH), 127.7 (C_q), 126.0 (2C, CH), 123.6 (CH), 122.8 (2C, CH), 116.2 (C_q), 110.8 (CH), 55.9 (CH), 21.9 (CH_3), 21.7 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{24}H_{21}NO + H^+$ $[M + H]^+$ 340.1696; Found 340.1690.



(3-Fluorophenyl)(1-tosyl-1*H*-indol-3-yl)methanone (1q): The representative procedure **A** was followed, using (3-fluorophenyl)(1*H*-indol-3-yl)methanone (0.50 g, 2.09 mmol), NaH (0.075 g, 3.14 mmol), and *p*-toluenesulfonyl chloride (0.598 g, 3.14 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **1q** (0.67 g, 82%) as a grey solid. M.pt: 86-90 ^{o}C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.30-8.28 (m, 1H, Ar–H), 8.04 (s, 1H, Ar–H), 7.99 (d, J = 7.8 Hz, 1H, Ar–H), 7.81 (d, J = 8.4 Hz, 2H, Ar–H), 7.64 (d, J = 7.6 Hz, 1H, Ar–H), 7.55-7.50 (m, 2H, Ar–H), 7.42-7.35 (m, 2H, Ar–H), 7.33-7.29 (m, 1H, Ar–H), 7.26 (d, J = 8.0 Hz, 2H, Ar–H), 2.35 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 189.5 (d, $^{4}J_{C-F}$ = 2.3 Hz, CO), 162.8 (d, $^{1}J_{C-F}$ = 248.0 Hz, C_q), 146.2 (C_q), 141.3 (d, $^{3}J_{C-F}$ = 6.1 Hz, C_q), 135.1 (C_q), 134.5 (C_q), 133.8 (CH), 130.5 (d, $^{3}J_{C-F}$ = 7.6 Hz,

CH), 130.4 (2C, CH), 128.4 (C_q), 127.3 (2C, CH), 126.2 (CH), 125.1 (CH), 124.8 (d, $^4J_{C–F}$ = 3.0 Hz, CH), 123.0 (CH), 120.1 (C_q), 119.5 (d, $^2J_{C–F}$ = 21.4 Hz, CH), 115.9 (d, $^2J_{C–F}$ = 22.9 Hz, CH), 113.3 (CH), 21.7 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −111.4 (s). HRMS (ESI): *m/z* Calcd for $C_{22}H_{16}NO_3FS + H^+$ $[M + H]^+$ 394.0908; Found 394.0894.



(1-Benzyl-1*H*-indol-3-yl)(thiophen-2-yl)methanone (1r): The representative procedure **A** was followed, using (1*H*-indol-3-yl)(thiophen-2-yl)methanone (0.50 g, 2.20 mmol), NaH (0.079 g, 3.30 mmol), and (bromomethyl)benzene (0.564 g, 3.30 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **1r** (0.63 g, 90%) as a brown solid. M.pt: 124-128 ^oC. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.46-8.44 (m, 1H, Ar–H), 7.88 (s, 1H, Ar–H), 7.72 (dd, *J* = 3.8, 1.0 Hz, 1H, Ar–H), 7.59 (dd, *J* = 5.0, 1.0 Hz, 1H, Ar–H), 7.36-7.29 (m, 6H, Ar–H), 7.18-7.16 (m, 2H, Ar–H), 7.14 (dd, *J* = 4.9, 3.8 Hz, 1H, Ar–H), 5.38 (s, 2H, CH_2). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 181.6 (CO), 145.5 (C_q), 137.2 (C_q), 136.0 (C_q), 135.5 (CH), 131.6 (CH), 131.3 (CH), 129.2 (2C, CH), 128.4 (CH), 127.7 (CH), 127.6 (C_q), 127.1 (2C, CH), 124.0 (CH), 122.9 (2C, CH), 116.2 (C_q), 110.4 (CH), 51.0 (CH_2). HRMS (ESI): *m/z* Calcd for $C_{20}H_{15}NOS + H^+$ $[M + H]^+$ 318.0947; Found 318.0947.

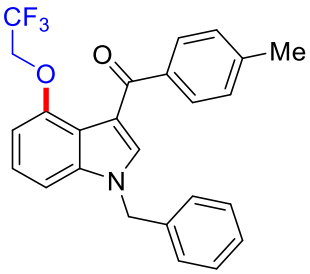
4.4.3 Procedure for the C(4)–H Fluoroalkoxylation of Indoles

Representative Procedure B. **Synthesis of (1-Benzyl-4-(2,2,2-trifluoroethoxy)-1*H*-indol-3-yl)(*p*-tolyl)methanone (3aa):** To an oven-dried screw-cap tube equipped with magnetic stir bar were introduced (1-benzyl-1*H*-indol-3-yl)(*p*-tolyl)methanone (**1a**; 0.065 g, 0.20 mmol), $K_2S_2O_8$ (0.108 g, 0.40 mmol), and $Pd(OAc)_2$ (0.0045 g, 0.02 mmol, 10 mol%), followed by the addition of TFA (0.046 g, 0.40 mmol) and TFE (1.0 mL). The resultant reaction mixture was immersed in a preheated oil bath at 80 °C and stirred for 12 h. The reaction mixture was allowed to cool to room temperature, and all the volatiles were removed under reduced pressure. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) to yield compound **3aa** (0.054 g, 64%) as a yellow liquid.

Procedure for Scale-up Synthesis of Compound 3aa: To an oven-dried screw-cap tube equipped with magnetic stir bar were introduced (1-benzyl-1*H*-indol-3-yl)(*p*-tolyl)methanone (**1a**; 0.650 g, 2.0 mmol), $K_2S_2O_8$ (1.08 g, 4.0 mmol), and $Pd(OAc)_2$ (0.045 g, 0.2 mmol, 10.0 mol%), followed by the addition of TFA (0.456 g, 4.0 mmol) and TFE (10 mL). The resultant reaction mixture was immersed in a preheated oil bath at 80 ^oC and stirred for 12 h. The reaction mixture was allowed to cool to room temperature, and all the volatiles were removed under reduced pressure. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) to yield compound **3aa** (0.490 g, 58%) as a yellow liquid.

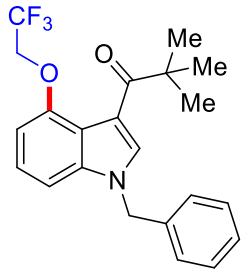
Procedure for Fluoroalkoxylation of Indole using Palladium Complex B: To an oven-dried screw-cap tube equipped with magnetic stir bar were introduced (1-benzyl-1*H*-indol-3-yl)(*p*-tolyl)methanone (**1a**; 0.033 g, 0.1 mmol), $K_2S_2O_8$ (0.054 g, 0.2 mmol), and (3-(4-methylbenzoyl)-1-tosyl-1*H*-indol-4-yl)(2,2,2-trifluoroacetoxy)palladium (**10**; 0.0061 g, 0.01 mmol, 10.0 mol%), followed by the addition of TFA (0.023 g, 0.2 mmol) and TFE (0.5 mL). The resultant reaction mixture was immersed in a preheated oil bath at 80 ^oC and stirred for 12 h. The reaction mixture was allowed to cool to room temperature, and all the volatiles were removed under reduced pressure. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) to yield compound **3aa** (0.023 g, 54%) as a yellow liquid.

4.4.4 Characterization Data for C(4)–H Fluoroalkoxylation of Indoles

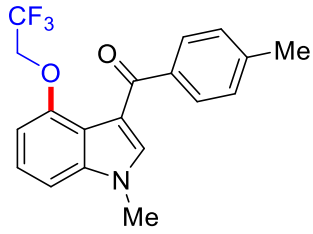


(1-Benzyl-4-(2,2,2-trifluoroethoxy)-1*H*-indol-3-yl)(*p*-tolyl)methanone (3aa): ^1H-NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, J = 8.0 Hz, 2H, Ar–H), 7.51 (s, 1H, Ar–H), 7.34-7.29 (m, 3H, Ar–H), 7.23-7.17 (m, 3H, Ar–H), 7.14 (d, J = 6.8 Hz, 2H, Ar–H), 7.06 (d, J = 8.4 Hz, 1H, Ar–H), 6.69 (d, J = 7.9 Hz, 1H, Ar–H), 5.34 (s, 2H, CH_2), 4.32 (q, J = 8.3 Hz, 2H, CH_2), 2.41 (s, 3H, CH_3). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 190.7 (CO), 152.3 (C_q), 142.6 (C_q),

139.0 (C_q), 137.7 (C_q), 136.0 (C_q), 134.8 (CH), 129.9 (2C, CH), 129.2 (2C, CH), 128.8 (2C, CH), 128.3 (CH), 127.0 (2C, CH), 124.2 (CH), 123.4 (q, $^1J_{C–F}$ = 278.0 Hz, CF_3), 117.8 (C_q), 117.0 (C_q), 106.3 (CH), 105.8 (CH), 67.4 (q, $^2J_{C–F}$ = 35.8 Hz, CH_2), 51.0 (CH_2), 21.7 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −73.5 (s). HRMS (ESI): *m/z* Calcd for $C_{25}H_{20}NO_2F_3$ + H^+ $[M + H]^+$ 424.1519; Found 424.1516.

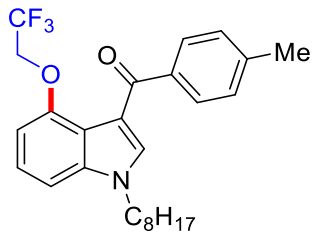


1-(1-Benzyl-4-(2,2,2-trifluoroethoxy)-1*H*-indol-3-yl)-2,2-dimethylpropan-1-one (3ba): The representative procedure **B** was followed, using substrate **1b** (0.058 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **3ba** (0.021 g, 27%) as a brown solid. M.pt: 88-92 ^{o}C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.33-7.30 (m, 3H, Ar–H), 7.16 (s, 1H, Ar–H), 7.16-7.10 (m, 3H, Ar–H), 6.98 (d, *J* = 8.3 Hz, 1H, Ar–H), 6.55 (d, *J* = 7.9 Hz, 1H, Ar–H), 5.31 (s, 2H, CH_2), 4.45 (q, *J* = 8.0 Hz, 2H, CH_2), 1.29 (s, 9H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 207.2 (CO), 151.5 (C_q), 138.0 (C_q), 136.7 (C_q), 129.1 (2C, CH), 128.1 (CH), 126.9 (2C, CH), 126.4 (CH), 123.7 (CH), 123.5 (q, $^1J_{C–F}$ = 277.7 Hz, CF_3), 118.1 (C_q), 115.4 (C_q), 105.1 (CH), 103.3 (CH), 66.6 (q, $^2J_{C–F}$ = 35.9 Hz, CH_2), 50.6 (CH_2), 45.3 (C_q), 27.0 (3C, CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −73.7 (s). HRMS (ESI): *m/z* Calcd for $C_{22}H_{22}NO_2F_3$ + H^+ $[M + H]^+$ 390.1675; Found 390.1673.

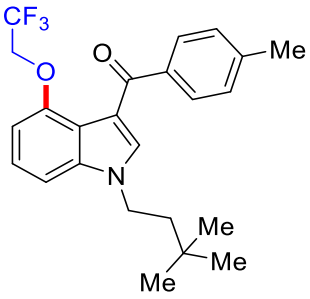


(1-Methyl-4-(2,2,2-trifluoroethoxy)-1*H*-indol-3-yl)(*p*-tolyl)methanone (3ca): The representative procedure **B** was followed, using substrate **1c** (0.050 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **3ca** (0.032 g, 46%) as a brown solid. M.pt: 84-88 ^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.73

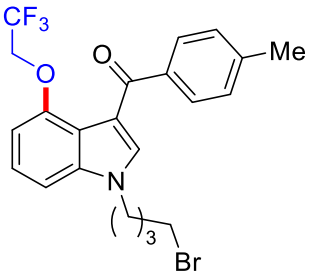
(d, *J* = 8.1 Hz, 2H, Ar–H), 7.41 (s, 1H, Ar–H), 7.24-7.19 (m, 3H, Ar–H), 7.09 (d, *J* = 8.1 Hz, 1H, Ar–H), 6.71 (d, *J* = 7.8 Hz, 1H, Ar–H), 4.31 (q, *J* = 8.4 Hz, 2H, CH_2), 3.80 (s, 3H, CH_3), 2.40 (s, 3H, CH_3). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 190.7 (CO), 152.3 (C_q), 142.5 (C_q), 139.5 (C_q), 137.9 (C_q), 135.7 (CH), 129.9 (2C, CH), 128.8 (2C, CH), 124.1 (CH), 123.5 (q, $^1J_{C-F}$ = 279.2 Hz, CF_3), 117.6 (C_q), 116.5, (C_q) 106.6 (CH), 105.3 (CH), 67.4 (q, $^2J_{C-F}$ = 35.1 Hz, CH_2), 33.8 (CH_3), 21.7 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −73.7 (s). HRMS (ESI): *m/z* Calcd for $C_{19}H_{16}NO_2F_3 + H^+$ $[M + H]^+$ 348.1206; Found 348.1200.



(1-Octyl-4-(2,2,2-trifluoroethoxy)-1*H*-indol-3-yl)(*p*-tolyl)methanone (3da): The representative procedure **B** was followed, using substrate **1d** (0.070 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3da** (0.058 g, 65%) as a yellow liquid. ^1H-NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.45 (s, 1H, Ar–H), 7.25-7.21 (m, 3H, Ar–H), 7.12 (d, *J* = 8.1 Hz, 1H, Ar–H), 6.71 (d, *J* = 7.9 Hz, 1H, Ar–H), 4.32 (q, *J* = 8.4 Hz, 2H, CH_2), 4.11 (t, *J* = 7.2 Hz, 2H, CH_2), 2.41 (s, 3H, CH_3), 1.88-1.81 (m, 2H, CH_2), 1.31-1.24 (m, 10H, CH_2), 0.87 (vt, *J* = 6.9 Hz, 3H, CH_3). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 190.7 (CO), 152.4 (C_q), 142.4 (C_q), 138.8 (C_q), 137.9 (C_q), 134.8 (CH), 129.9 (2C, CH), 128.8 (2C, CH), 123.9 (CH), 123.5 (q, $^1J_{C-F}$ = 278.5 Hz, CF_3), 117.7 (C_q), 116.4 (C_q), 106.4 (CH), 105.5 (CH), 67.4 (q, $^2J_{C-F}$ = 35.9 Hz, CH_2), 47.3 (CH_2), 31.9 (CH_2), 30.0 (CH_2), 29.2 (2C, CH_2), 27.0 (CH_2), 22.7 (CH_2), 21.7 (CH_3), 14.2 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −73.7 (s). HRMS (ESI): *m/z* Calcd for $C_{26}H_{30}NO_2F_3 + H^+$ $[M + H]^+$ 446.2301; Found 446.2300.

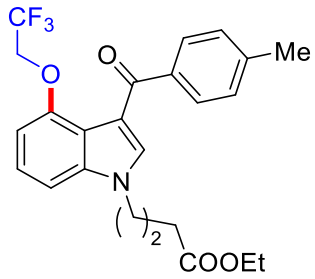


(1-(3,3-Dimethylbutyl)-4-(2,2,2-trifluoroethoxy)-1*H*-indol-3-yl)(*p*-tolyl)methanone (3ea): The representative procedure **B** was followed using substrate **1e** (0.064 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **3ea** (0.051 g, 61%) as a yellow solid. M. pt: 120-124 ^{o}C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.75 (d, J = 8.1 Hz, 2H, Ar–H), 7.47 (s, 1H, Ar–H), 7.23 (dd, J = 8.0, 2.3 Hz, 3H, Ar–H), 7.11 (d, J = 8.3 Hz, 1H, Ar–H), 6.71 (d, J = 7.8 Hz, 1H, Ar–H), 4.32 (q, J = 8.5 Hz, 2H, CH_2), 4.16-4.12 (m, 2H, CH_2), 2.42 (s, 3H, CH_3), 1.79-1.75 (m, 2H, CH_2), 1.03 (s, 9H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 190.7 (CO), 152.5 (C_q), 142.5 (C_q), 138.7 (C_q), 138.0 (C_q), 134.5 (CH), 129.9 (2C, CH), 128.8 (2C, CH), 123.9 (CH), 123.5 (q, $^{1}J_{C–F}$ = 278.5 Hz, CF_3), 117.8 (C_q), 116.6 (C_q), 106.4 (CH), 105.4 (CH), 67.3 (q, $^{2}J_{C–F}$ = 35.8 Hz, CH_2), 44.0 (CH_2), 43.7 (CH_2), 30.2 (C_q), 29.4 (3C, CH_3), 21.7 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −73.7 (s). HRMS (ESI): *m/z* Calcd for $C_{24}H_{26}NO_2F_3$ + H^+ $[M + H]^+$ 418.1988; Found 418.1990.

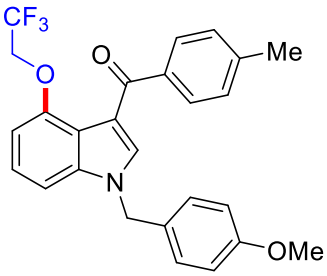


(1-(4-Bromobutyl)-4-(2,2,2-trifluoroethoxy)-1*H*-indol-3-yl)(*p*-tolyl)methanone (3fa): The representative procedure **B** was followed, using substrate **1f** (0.074 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **3fa** (0.054 g, 58%) as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, J = 8.1 Hz, 2H, Ar–H), 7.44 (s, 1H, Ar–H), 7.25-7.21 (m, 3H, Ar–H), 7.12 (d, J = 8.1 Hz, 1H, Ar–H), 6.70 (d, J = 7.8 Hz, 1H, Ar–H), 4.31 (q, J = 8.4 Hz, 2H, CH_2), 4.17 (t, J = 7.0 Hz, 2H, CH_2), 3.38 (t, J = 6.4 Hz, 2H, CH_2), 2.41 (s, 3H, CH_3), 2.08-2.00 (m, 2H, CH_2), 1.90-1.83 (m, 2H,

CH_2). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 190.7 (CO), 152.4 (C_q), 142.6 (C_q), 138.7 (C_q), 137.7 (C_q), 134.2 (CH), 129.9 (2C, CH), 128.8 (2C, CH), 124.2 (CH), 123.4 (q, $^1J_{C-F}$ = 278.5 Hz, CF_3), 117.7 (C_q), 116.8 (C_q), 106.2 (CH), 105.3 (CH), 67.2 (q, $^2J_{C-F}$ = 35.8 Hz, CH_2), 46.4 (CH_2), 32.7 (CH_2), 29.9 (CH_2), 28.6 (CH_2), 21.7 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −73.7 (s). HRMS (ESI): *m/z* Calcd for $C_{22}H_{21}NO_2BrF_3$ + H^+ $[M + H]^+$ 468.0781; Found 468.0786.

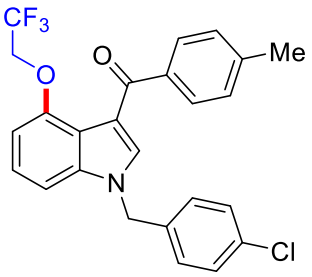


Ethyl 4-(3-(4-methylbenzoyl)-4-(2,2,2-trifluoroethoxy)-1*H*-indol-1-yl)butanoate (3ga): The representative procedure **B** was followed, using substrate **1g** (0.070 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **3ga** (0.051 g, 57%) as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* =7.6 Hz, 1H, Ar–H), 7.37-7.34 (m, 1H, Ar–H), 7.33 (s, 1H, Ar–H), 7.30-7.28 (m, 2H, Ar–H), 7.22-7.17 (m, 2H, Ar–H), 6.82 (d, *J* = 7.8 Hz, 1H, Ar–H), 4.39 (q, *J* = 8.5 Hz, 2H, CH_2), 4.20 (t, *J* = 7.1 Hz, 2H, CH_2), 4.13 (q, *J* = 7.2 Hz, 2H, CH_2), 2.46 (s, 3H, CH_3), 2.31 (t, *J* = 6.8 Hz, 2H, CH_2), 2.20-2.13 (m, 2H, CH_2), 1.25 (t, *J* = 7.1 Hz, 3H, CH_3). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 192.1 (CO), 172.5 (CO), 152.9 (C_q), 141.5 (C_q), 139.4 (C_q), 137.1 (CH), 137.0 (C_q), 131.0 (CH), 129.8 (CH), 128.8 (CH), 125.1 (CH), 124.5 (CH), 123.5 (q, $^1J_{C-F}$ = 278.4 Hz, CF_3), 118.4 (C_q), 117.4 (C_q), 108.3 (CH), 105.7 (CH), 68.4 (q, $^2J_{C-F}$ = 35.8 Hz, CH_2), 60.9 (CH_2), 46.3 (CH_2), 30.9 (CH_2), 25.1 (CH_2), 20.1 (CH_3), 14.3 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −73.7 (s). HRMS (ESI): *m/z* Calcd for $C_{24}H_{24}NO_4F_3$ + H^+ $[M + H]^+$ 448.1730; Found 448.1729.



(1-(4-Methoxybenzyl)-4-(2,2,2-trifluoroethoxy)-1*H*-indol-3-yl)(*p*-tolyl)methanone

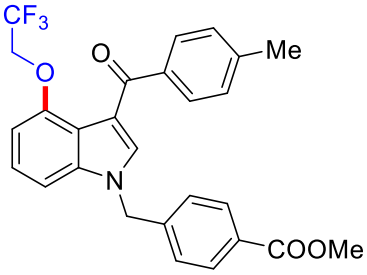
(3ha): The representative procedure **B** was followed, using substrate **1h** (0.071 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **3ha** (0.048 g, 53%) as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, J = 8.0 Hz, 2H, Ar–H), 7.48 (s, 1H, Ar–H), 7.22-7.17 (m, 3H, Ar–H), 7.11-7.07 (m, 3H, Ar–H), 6.85 (d, J = 8.6 Hz, 2H, Ar–H), 6.69 (d, J = 7.8 Hz, 1H, Ar–H), 5.26 (s, 2H, CH_2), 4.31 (q, J = 8.4 Hz, 2H, CH_2), 3.78 (s, 3H, CH_3), 2.41 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 190.8 (CO), 159.6 (C_q), 152.3 (C_q), 142.6 (C_q), 138.9 (C_q), 137.7 (C_q), 134.7 (CH), 129.9 (2C, CH), 128.8 (2C, CH), 128.6 (2C, CH), 127.9 (C_q), 124.1 (CH), 123.5 (q, $^{1}J_{C–F}$ = 278.5 Hz, CF_3), 117.8 (C_q), 116.9 (C_q), 114.6 (2C, CH), 106.3 (CH), 105.8 (CH), 67.2 (q, $^{2}J_{C–F}$ = 35.1 Hz, CH_2), 55.5 (CH_3), 50.6 (CH_2), 21.7 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −73.5 (s). HRMS (ESI): *m/z* Calcd for $C_{26}H_{22}NF_3O_3 + H^+$ $[M + H]^+$ 454.1625; Found 454.1628.



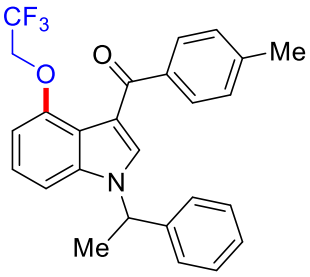
(1-(4-Chlorobenzyl)-4-(2,2,2-trifluoroethoxy)-1*H*-indol-3-yl)(*p*-tolyl)methanone

(3ia): The representative procedure **B** was followed using substrate **1i** (0.072 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **3ia** (0.056 g, 61%) as a yellow liquid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.44-7.43 (m, 2H, Ar–H), 7.40-7.37 (m, 1H, Ar–H), 7.34-7.31 (m, 3H, Ar–H), 7.24-7.21 (m, 2H, Ar–H), 7.07 (d, J = 8.2 Hz, 2H, Ar–H), 7.02 (d, J = 8.2 Hz, 1H, Ar–H), 6.81 (d, J = 7.9 Hz, 1H, Ar–H), 5.31 (s, 2H, CH_2), 4.39 (q, J = 8.4 Hz, 2H, CH_2), 2.50 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 192.3 (CO), 152.8 (C_q), 141.2 (C_q), 139.3 (C_q), 137.1 (C_q), 137.0 (CH), 134.3 (C_q), 134.2 (C_q), 131.1 (CH), 130.0 (CH), 129.4 (2C, CH), 128.9 (CH), 128.1 (2C,

CH), 125.1 (CH), 124.7 (CH), 123.4 (q, $^{1}J_{C-F}$ = 278.5 Hz, CF_3), 118.9 (C_q), 117.4 (C_q), 107.8 (CH), 105.9 (CH), 67.9 (q, $^{2}J_{C-F}$ = 35.3 Hz, CH_2), 50.4 (CH_2), 20.2 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −73.7 (s). HRMS (ESI): *m/z* Calcd for $C_{25}H_{19}NO_2ClF_3$ + H^+ $[M + H]^+$ 458.1129; Found 458.1129.

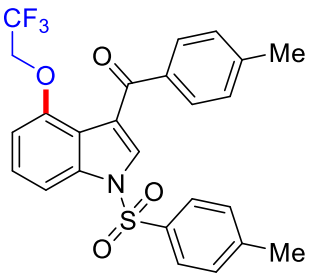


Methyl 4-((3-(4-methylbenzoyl)-4-(2,2,2-trifluoroethoxy)-1*H*-indol-1-yl)methyl)benzoate (3ja): The representative procedure **B** was followed, using substrate **1j** (0.077 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **3ja** (0.053 g, 55%) as an orange solid. M.pt: 118-122 ^{o}C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.4 Hz, 2H, Ar–H), 7.76 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.50 (s, 1H, Ar–H), 7.24-7.16 (m, 5H, Ar–H), 6.98 (d, *J* = 8.3 Hz, 1H, Ar–H), 6.69 (d, *J* = 7.8 Hz, 1H, Ar–H), 5.39 (s, 2H, CH_2), 4.32 (q, *J* = 8.3 Hz, 2H, CH_2), 3.89 (s, 3H, CH_3), 2.41 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 190.7 (CO), 166.7 (CO), 152.3 (C_q), 142.8 (C_q), 141.1 (C_q), 138.8 (C_q), 137.6 (C_q), 134.5 (CH), 130.5 (2C, CH), 130.2 (C_q), 129.9 (2C, CH), 128.8 (2C, CH), 126.8 (2C, CH), 124.4 (CH), 123.4 (q, $^{1}J_{C-F}$ = 279.0 Hz, CF_3), 117.8 (C_q), 117.4 (C_q), 106.1 (CH), 105.6 (CH), 67.1 (q, $^{2}J_{C-F}$ = 35.8 Hz, CH_2), 52.4 (CH_3), 50.7 (CH_2), 21.7 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −73.73 (s). HRMS (ESI): *m/z* Calcd for $C_{27}H_{22}NO_4F_3$ + H^+ $[M + H]^+$ 482.1574; Found 482.1556.

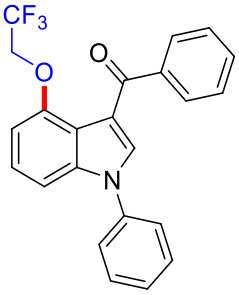


(1-(1-Phenylethyl)-4-(2,2,2-trifluoroethoxy)-1*H*-indol-3-yl)(*p*-tolyl)methanone (3ka): The representative procedure **B** was followed, using substrate **1k** (0.068 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1)

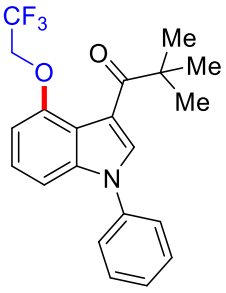
yielded **3ka** (0.045 g, 52%) as a pale yellow liquid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.77 (d, J = 8.1 Hz, 2H, Ar–H), 7.68 (s, 1H, Ar–H), 7.34-7.24 (m, 3H, Ar–H), 7.22 (d, J = 7.9 Hz, 2H, Ar–H), 7.15-7.11 (m, 3H, Ar–H), 6.99 (d, J = 8.3 Hz, 1H, Ar–H), 6.65 (d, J = 7.9 Hz, 1H, Ar–H), 5.66 (q, J = 7.0 Hz, 1H, CH), 4.27 (q, J = 8.4 Hz, 2H, CH_2), 2.41 (s, 3H, CH_3), 1.93 (d, J = 7.0 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 191.1 (CO), 152.2 (C_q), 142.6 (C_q), 141.4 (C_q), 138.8 (C_q), 137.8 (C_q), 131.6 (CH), 130.0 (2C, CH), 129.2 (2C, CH), 128.8 (2C, CH), 128.1 (CH), 126.0 (2C, CH), 124.0 (CH), 123.4 (q, $^{1}J_{C–F}$ = 278.5 Hz, CF_3), 117.9 (C_q), 116.8 (C_q), 106.2 (CH), 106.1 (CH), 67.1 (q, $^{2}J_{C–F}$ = 35.8 Hz, CH_2), 56.1 (CH), 22.0 (CH_3), 21.8 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −73.7 (s). HRMS (ESI): *m/z* Calcd for $C_{26}H_{22}NF_3O_2$ + H^+ $[M + H]^+$ 438.1675; Found 438.1659.



***p*-Tolyl(1-tosyl-4-(2,2,2-trifluoroethoxy)-1*H*-indol-3-yl)methanone (3la):** The representative procedure **B** was followed, using substrate **1l** (0.078 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **3la** (0.059 g, 61%) as a yellow liquid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.81-7.79 (m, 3H, Ar–H), 7.74 (d, J = 8.1 Hz, 3H, Ar–H), 7.31 (t, J = 8.2 Hz, 1H, Ar–H), 7.28-7.22 (m, 4H, Ar–H), 6.69 (d, J = 8.0 Hz, 1H, Ar–H), 4.25 (q, J = 8.1 Hz, 2H, CH_2), 2.42 (s, 3H, CH_3), 2.37 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 190.5 (CO), 151.5 (C_q), 146.0 (C_q), 144.1 (C_q), 136.4 (C_q), 135.9 (C_q), 134.7 (C_q), 130.3 (2C, CH), 130.0 (2C, CH), 129.2 (2C, CH), 128.7 (CH), 127.3 (2C, CH), 126.7 (CH), 123.4 (q, $^{1}J_{C–F}$ = 278.5 Hz, CF_3), 121.6 (C_q), 119.3 (C_q), 108.4 (CH), 107.2 (CH), 66.5 (q, $^{2}J_{C–F}$ = 35.8 Hz, CH_2), 21.8 (CH_3), 21.8 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −73.7 (s). HRMS (ESI): *m/z* Calcd for $C_{25}H_{20}NO_4F_3S$ + H^+ $[M + H]^+$ 488.1138; Found 488.1137.

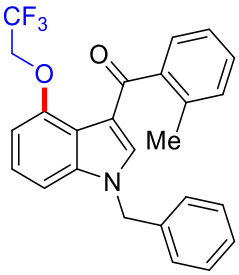


Phenyl(1-phenyl-4-(2,2,2-trifluoroethoxy)-1*H*-indol-3-yl)methanone (3ma): The representative procedure **B** was followed, using substrate **1m** (0.060 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **3ma** (0.046 g, 58%) as an orange solid. M.pt: 90-94 ^{o}C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.93-7.90 (m, 2H, Ar–H), 7.67 (s, 1H, Ar–H), 7.57-7.50 (m, 5H, Ar–H), 7.47-7.42 (m, 3H, Ar–H), 7.26-7.24 (m, 2H, Ar–H), 6.75-6.73 (m, 1H, Ar–H), 4.37 (q, J = 8.4 Hz, 2H, CH_2). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 191.2 (CO), 152.3 (C_q), 140.2 (C_q), 138.9 (C_q), 138.6 (C_q), 134.2 (CH), 132.2 (CH), 130.1 (2C, CH), 129.8 (2C, CH), 128.2 (4C, CH), 125.2 (2C, CH), 124.8 (CH), 123.4 (q, $^{1}J_{C-F}$ = 281.2 Hz, CF_3), 118.3 (C_q), 118.0 (C_q), 106.5 (CH), 67.0 (q, $^{2}J_{C-F}$ = 35.9 Hz, CH_2). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −73.7 (s). HRMS (ESI): *m/z* Calcd for $C_{23}H_{16}NO_2F_3 + H^+$ $[M + H]^+$ 396.1206; Found 396.1203.

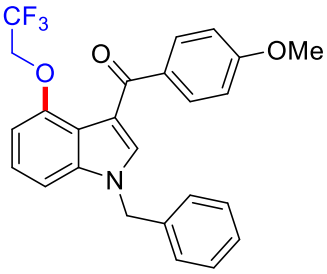


2,2-Dimethyl-1-(1-phenyl-4-(2,2,2-trifluoroethoxy)-1*H*-indol-3-yl)propan-1-one (3na): The representative procedure **B** was followed, using substrate **1n** (0.056 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **3na** (0.017 g, 23%) as a brown solid. M. pt: 136-140 ^{o}C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.56-7.52 (m, 2H, Ar–H), 7.49-7.47 (m, 2H, Ar–H), 7.42 (vt, J = 7.3 Hz, 1H, Ar–H), 7.33 (s, 1H, Ar–H), 7.21-7.16 (m, 2H, Ar–H), 6.61 (d, J = 6.8 Hz, 1H, Ar–H), 4.47 (q, J = 8.2 Hz, 2H, CH_2), 1.34 (s, 9H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 207.5 (CO), 151.4 (C_q), 139.0 (C_q), 137.7 (C_q), 130.0 (2C, CH), 127.6 (CH), 125.7 (CH), 125.0 (2C, CH), 124.2 (CH), 123.4 (q, $^{1}J_{C-F}$ = 278.5 Hz, CF_3), 118.5 (C_q), 116.8 (C_q), 105.8 (CH), 103.7 (CH), 66.6 (q, $^{2}J_{C-F}$ = 35.8 Hz, CH_2), 45.4 (C_q), 26.9 (3C, CH_3). ^{19}F-NMR (377 MHz,

$CDCl_3$): δ = −73.1 (s). HRMS (ESI): *m/z* Calcd for $C_{21}H_{20}NO_2F_3$ + H^+ $[M + H]^+$ 376.1519; Found 376.1516.

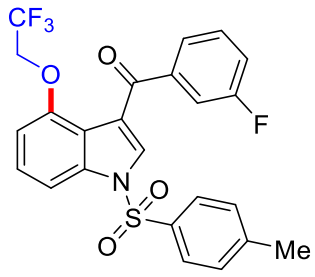


(1-Benzyl-4-(2,2,2-trifluoroethoxy)-1*H*-indol-3-yl)(*o*-tolyl)methanone (3oa): The representative procedure **B** was followed, using substrate **1o** (0.065 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **3oa** (0.057 g, 67%) as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.43-7.39 (m, 2H, Ar–H), 7.34-7.24 (m, 5H, Ar–H), 7.17 (q, *J* = 8.3 Hz, 2H, Ar–H), 7.09 (d, *J* = 7.1 Hz, 2H, Ar–H), 7.03 (d, *J* = 8.3 Hz, 1H, Ar–H), 6.77 (d, *J* = 7.9 Hz, 1H, Ar–H), 5.28 (s, 2H, CH_2), 4.35 (q, *J* = 8.5 Hz, 2H, CH_2), 2.44 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 192.2 (CO), 152.8 (C_q), 141.4 (C_q), 139.6 (C_q), 137.4 (CH), 137.1 (C_q), 135.8 (C_q), 131.1 (CH), 129.9 (CH), 129.2 (2C, CH), 128.9 (CH), 128.3 (CH), 126.9 (2C, CH), 125.1 (CH), 124.6 (CH), 123.4 (q, $^1J_{C–F}$ = 278.8 Hz, CF_3), 118.7 (C_q), 117.5 (C_q), 108.1 (CH), 106.1 (CH), 68.0 (q, $^2J_{C–F}$ = 35.8 Hz, CH_2), 51.1 (CH_2), 20.2 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −73.5 (s). HRMS (ESI): *m/z* Calcd for $C_{25}H_{20}NO_2F_3$ + H^+ $[M + H]^+$ 424.1519; Found 424.1515.

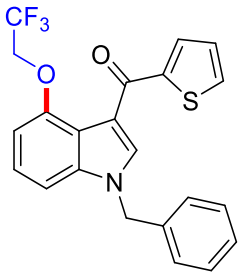


(1-Benzyl-4-(2,2,2-trifluoroethoxy)-1*H*-indol-3-yl)(4-methoxyphenyl)methanone (3pa): The representative procedure **B** was followed, using substrate **1p** (0.068 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **3pa** (0.062 g, 71%) as a pale yellow solid. M. pt: 96-100 ^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 7.8 Hz, 2H, Ar–H), 7.50 (s, 1H, Ar–H), 7.35-7.29 (m, 3H, Ar–H),

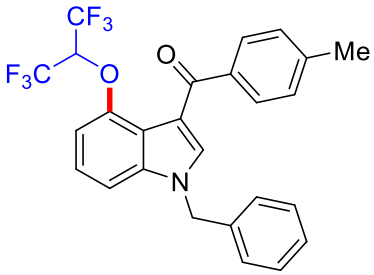
7.21-7.14 (m, 3H, Ar–H), 7.06 (d, J = 8.3 Hz, 1H, Ar–H), 6.90 (d, J = 7.8 Hz, 2H, Ar–H), 6.67 (d, J = 7.8 Hz, 1H, Ar–H), 5.34 (s, 2H, CH_2), 4.31 (q, J = 8.3 Hz, 2H, CH_2), 3.86 (s, 3H, CH_3). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 190.1 (CO), 163.0 (C_q), 152.2 (C_q), 138.9 (C_q), 136.1 (C_q), 134.0 (CH), 133.1 (C_q), 132.0 (2C, CH), 129.2 (2C, CH), 128.3 (CH), 127.1 (2C, CH), 124.1 (CH), 123.4 (q, $^1J_{C–F}$ = 278.5 Hz, CF_3), 117.8 (C_q), 117.0 (C_q), 113.4 (2C, CH), 105.7 (CH), 105.7 (CH), 67.0 (q, $^2J_{C–F}$ = 35.8 Hz, CH_2), 55.6 (CH_3), 51.0 (CH_2). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −73.5 (s). HRMS (ESI): *m/z* Calcd for $C_{25}H_{20}NO_3F_3$ + H^+ $[M + H]^+$ 440.1468; Found 440.1466.



(3-Fluorophenyl)(1-tosyl-4-(2,2,2-trifluoroethoxy)-1*H*-indol-3-yl)methanone (3qa): The representative procedure **B** was followed, using substrate **1q** (0.079 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **3qa** (0.057 g, 58%) as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.85 (s, 1H, Ar–H), 7.82 (d, J = 8.4 Hz, 2H, Ar–H), 7.74 (d, J = 8.1 Hz, 1H, Ar–H), 7.59 (dt, J = 7.8, 1.2 Hz, 1H, Ar–H), 7.53-7.50 (m, 1H, Ar–H), 7.41-7.37 (m, 1H, Ar–H), 7.33 (t, J = 8.3 Hz, 1H, Ar–H), 7.30-7.27 (m, 3H, Ar–H), 6.69 (d, J = 8.0 Hz, 1H, Ar–H), 4.21 (q, J = 8.1 Hz, 2H, CH_2), 2.38 (s, 3H, CH_3). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 189.6 (d, $^4J_{C–F}$ = 2.3 Hz, CO), 162.8 (d, $^1J_{C–F}$ = 247.2 Hz, C_q), 151.3 (C_q), 146.2 (C_q), 140.5 (d, $^3J_{C–F}$ = 6.1 Hz, C_q), 136.4 (C_q), 134.6 (C_q), 130.4 (2C, CH), 130.1 (d, $^3J_{C–F}$ = 7.6 Hz, CH), 129.2 (CH), 127.3 (2C, CH), 126.9 (CH), 125.7 (d, $^4J_{C–F}$ = 3.1 Hz, CH), 122.9 (q, $^1J_{C–F}$ = 277.7 Hz, CF_3), 121.1 (C_q), 120.2 (d, $^2J_{C–F}$ = 21.4 Hz, CH), 118.8 (C_q), 116.3 (d, $^2J_{C–F}$ = 22.1 Hz, CH), 108.4 (CH), 106.8 (CH), 66.4 (q, $^2J_{C–F}$ = 35.8 Hz, CH_2), 21.8 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −74.0 (s), −112.6 (s). HRMS (ESI): *m/z* Calcd for $C_{24}H_{17}NO_4F_4S$ + H^+ $[M + H]^+$ 492.0887; Found 492.0885.

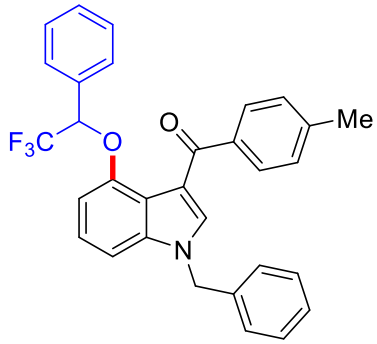


(1-Benzyl-4-(2,2,2-trifluoroethoxy)-1*H*-indol-3-yl)(thiophen-2-yl)methanone (3ra): The representative procedure **B** was followed, using substrate **1r** (0.064 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **3ra** (0.044 g, 53%) as a yellow solid. M. pt: 104-108 ^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.62-7.60 (m, 2H, Ar–H), 7.59 (dd, J = 3.8, 1.0 Hz, 1H, Ar–H), 7.35-7.29 (m, 3H, Ar–H), 7.20 (t, J = 7.2 Hz, 1H, Ar–H), 7.16-7.14 (m, 2H, Ar–H), 7.10-7.06 (m, 2H, Ar–H), 6.72 (d, J = 7.9 Hz, 1H, Ar–H), 5.35 (s, 2H, CH_2), 4.43 (q, J = 8.3 Hz, 2H, CH_2). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 182.3 (CO), 152.3 (C_q), 146.2 (C_q), 139.0 (C_q), 136.0 (C_q), 133.9 (CH), 133.5 (CH), 132.9 (CH), 129.2 (2C, CH), 128.4 (CH), 127.7 (CH), 127.1 (2C, CH), 124.4 (CH), 123.5 (q, $^{1}J_{C–F}$ = 278.5 Hz, CF_3), 117.6 (C_q), 116.5 (C_q), 106.3 (CH), 105.8 (CH), 67.2 (q, $^{2}J_{C–F}$ = 35.8 Hz, CH_2), 51.0 (CH_2). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −73.7 (s). HRMS (ESI): *m/z* Calcd for $C_{22}H_{16}NSO_2F_3 + H^+$ $[M + H]^+$ 416.0927; Found 416.0925.

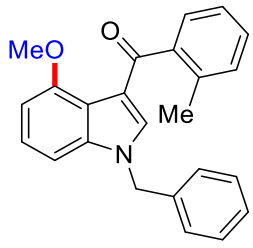


(1-Benzyl-4-((1,1,1,3,3,3-hexafluoropropan-2-yl)oxy)-1*H*-indol-3-yl)(*p*-tolyl)methanone (3ab): The representative procedure **B** was followed using substrate **1a** (0.065 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3ab** (0.041 g, 42%) as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, J = 8.1 Hz, 2H, Ar–H), 7.53 (s, 1H, Ar–H), 7.35-7.30 (m, 3H, Ar–H), 7.21-7.12 (m, 6H, Ar–H), 6.74 (d, J = 7.9 Hz, 1H, Ar–H), 5.35 (s, 2H, CH_2), 4.94 (sept, J = 5.8 Hz, 1H, CH), 2.40 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 190.7 (CO), 151.8 (C_q), 142.8 (C_q), 139.0 (C_q), 137.4 (C_q), 135.9 (C_q), 134.6 (CH), 130.0 (2C, CH), 129.2 (2C, CH), 128.8 (2C, CH), 128.4 (CH), 127.1 (2C, CH), 124.0 (CH), 125.0-116.0 (m, 2C,

CF_3), 118.1 (C_q), 117.0 (C_q), 106.9 (CH), 105.5 (CH), 77.0-75.8 (m, CH), 51.1 (CH_2), 21.7 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −73.1 (s). HRMS (ESI): *m/z* Calcd for $C_{26}H_{19}NO_2F_6$ + H^+ $[M + H]^+$ 492.1393; Found 492.1389.

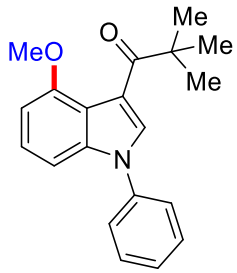


(1-Benzyl-4-(2,2,2-trifluoro-1-phenylethoxy)-1*H*-indol-3-yl)(*p*-tolyl)methanone (3ac): The representative procedure **B** was followed, using substrate **1a** (0.065 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **3ac** (0.057 g, 57%) as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 8.0 Hz, 2H, Ar–H), 7.47 (s, 1H, Ar–H), 7.34-7.29 (m, 8H, Ar–H), 7.27-7.24 (m, 2H, Ar–H), 7.15-7.13 (m, 2H, Ar–H), 7.01 (t, *J* = 8.1 Hz, 1H, Ar–H), 6.94 (d, *J* = 8.0 Hz, 1H, Ar–H), 6.39 (d, *J* = 7.8 Hz, 1H, Ar–H), 5.41 (q, *J* = 6.4 Hz, 1H, CH), 5.29 (s, 2H, CH_2), 2.43 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 191.3 (CO), 151.3 (C_q), 142.7 (C_q), 138.7 (C_q), 137.8 (C_q), 136.1 (C_q), 133.3 (CH), 132.4 (C_q), 130.2 (2C, CH), 129.6 (CH), 129.1 (2C, CH), 128.8 (2C, CH), 128.7 (2C, CH), 128.2 (CH), 128.1 (2C, CH), 127.1 (2C, CH), 123.9 (CH), 123.2 (q, $^1J_{C–F}$ = 282.5 Hz, CF_3), 117.6 (C_q), 117.2 (C_q), 104.9 (CH), 104.5 (CH), 78.3 (q, $^2J_{C–F}$ = 32.0 Hz, CH), 50.9 (CH_2), 21.8 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −73.75 (s). HRMS (ESI): *m/z* Calcd for $C_{31}H_{24}NO_2F_3$ + H^+ $[M + H]^+$ 500.1832; Found 500.1828.

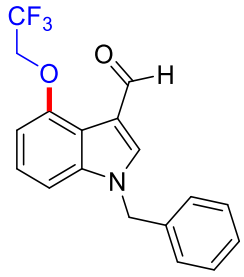


(1-Benzyl-4-methoxy-1*H*-indol-3-yl)(*o*-tolyl)methanone (3od): The representative procedure **B** was followed, using substrate **1o** (0.065 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **3od** (0.033 g, 46%) as a yellow liquid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.42 (s, 1H, Ar–H), 7.39 (d, *J* = 7.6 Hz, 1H,

Ar–H), 7.33-7.27 (m, 4H, Ar–H), 7.26-7.23 (m, 1H, Ar–H), 7.20-7.15 (m, 2H, Ar–H), 7.13-7.09 (m, 2H, Ar–H), 6.90 (d, J = 8.3 Hz, 1H, Ar–H), 6.63 (d, J = 8.0 Hz, 1H, Ar–H), 5.28 (s, 2H, CH_2), 3.72 (s, 3H, CH_3), 2.44 (s, 3H, CH_3). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 192.8 (CO), 154.8 (C_q), 142.0 (C_q), 139.3 (C_q), 137.0 (C_q), 136.4 (CH), 136.1 (C_q), 130.7 (CH), 129.7 (CH), 129.1 (2C, CH), 129.1 (CH), 128.2 (CH), 126.9 (2C, CH), 124.9 (CH), 124.7 (CH), 119.3 (C_q), 116.5 (C_q), 103.6 (CH), 103.1 (CH), 55.7 (CH_3), 51.0 (CH_2), 20.3 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{24}H_{21}NO_2 + H^+$ $[M + H]^+$ 356.1645; Found 356.1639.

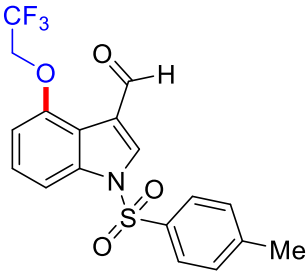


1-(4-Methoxy-1-phenyl-1*H*-indol-3-yl)-2,2-dimethylpropan-1-one (3nd): The representative procedure **B** was followed, using substrate **1n** (0.056 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **3nd** (0.013 g, 22%) as a brown solid. M.pt: 72-76 ^oC. ^1H-NMR (500 MHz, $CDCl_3$): δ = 7.54-7.48 (m, 4H, Ar–H), 7.41-7.37 (m, 1H, Ar–H), 7.25 (s, 1H, Ar–H), 7.18 (t, J = 8.0 Hz, 1H, Ar–H), 7.11 (d, J = 7.8 Hz, 1H, Ar–H), 6.60 (d, J = 7.6 Hz, 1H, Ar–H), 3.91 (s, 3H, CH_3), 1.32 (s, 9H, CH_3). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 209.3 (CO), 153.8 (C_q), 139.3 (C_q), 137.3 (C_q), 129.9 (2C, CH), 127.3 (CH), 124.9 (2C, CH), 124.7 (CH), 124.5 (CH), 118.0 (C_q), 117.2 (C_q), 104.0 (CH), 101.6 (CH), 55.6 (CH_3), 45.4 (C_q), 27.2 (3C, CH_3). HRMS (ESI): *m/z* Calcd for $C_{20}H_{21}NO_2 + H^+$ $[M + H]^+$ 308.1645; Found 308.1633.



1-Benzyl-4-(2,2,2-trifluoroethoxy)-1*H*-indole-3-carbaldehyde (3sa): The representative procedure **B** was followed, using substrate **1s** (0.047 g, 0.20 mmol) and valine (0.012 g, 0.1 mmol). Purification by column chromatography on silica gel (petroleum

ether/EtOAc: 5/1) yielded **3sa** (0.038 g, 57%) as a yellow liquid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 10.43 (s, 1H, CH), 7.89 (s, 1H, Ar–H), 7.34-7.31 (m, 3H, Ar–H), 7.21-7.15 (m, 3H, Ar–H), 7.07 (d, J = 8.3 Hz, 1H, Ar–H), 6.67 (d, J = 7.9 Hz, 1H, Ar–H), 5.33 (s, 2H, CH_2), 4.54 (q, J = 8.0 Hz, 2H, CH_2). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 187.7 (CHO), 152.1 (C_q), 138.7 (C_q), 135.2 (C_q), 132.4 (CH), 129.3 (2C, CH), 128.6 (CH), 127.4 (2C, CH), 123.9 (CH), 123.4 (q, $^{1}J_{C–F}$ = 277.7 Hz, CF_3), 118.3 (C_q), 117.2 (C_q), 106.0 (CH), 103.7 (CH), 65.9 (q, $^{2}J_{C–F}$ = 35.8 Hz, CH_2), 51.4 (CH_2). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −73.7 (s). HRMS (ESI): *m/z* Calcd for $C_{18}H_{14}NO_2F_3$ + H^+ $[M + H]^+$ 334.1049; Found 334.1048.

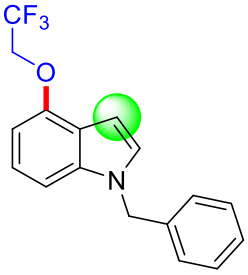


1-Tosyl-4-(2,2,2-trifluoroethoxy)-1*H*-indole-3-carbaldehyde (3ta): The representative procedure **B** was followed, using substrate **1t** (0.060 g, 0.20 mmol) and valine (0.012 g, 0.1 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **3ta** (0.041 g, 52%) as a brown solid. M. pt: 142-145 ^{o}C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.35 (s, 1H, CH), 8.19 (s, 1H, Ar–H), 7.75 (d, J = 8.4 Hz, 2H, Ar–H), 7.63 (d, J = 8.4 Hz, 1H, Ar–H), 7.24-7.17 (m, 3H, Ar–H), 6.67 (d, J = 8.1 Hz, 1H, Ar–H), 4.42 (q, J = 7.9 Hz, 2H, CH_2), 2.29 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 187.8 (CHO), 151.7 (C_q), 146.4 (C_q), 136.6 (C_q), 134.3 (C_q), 130.5 (2C, CH), 129.7 (CH), 127.5 (2C, CH), 126.5 (CH), 123.2 (q, $^{1}J_{C–F}$ = 277.7 Hz, CF_3), 121.9 (C_q), 117.8 (C_q), 108.5 (CH), 105.8 (CH), 65.9 (q, $^{2}J_{C–F}$ = 35.8 Hz, CH_2), 21.8 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −73.7 (s). HRMS (ESI): *m/z* Calcd for $C_{18}H_{14}NO_4F_3S$ + H^+ $[M + H]^+$ 398.0668; Found 398.0669.

4.4.5 Procedure for Removal of Benzoyl Directing and Tosyl Protecting Group

***Removal of Benzoyl Directing Group*. Synthesis of Compound 4:** To the mixture (1-benzyl-4-(2,2,2-trifluoroethoxy)-1*H*-indol-3-yl)(*p*-tolyl)methanone (**3aa**; 0.042 g, 0.1 mmol) and *p*-toluenesulfonic acid monohydrate (0.023 g, 0.12 mmol) in toluene (5 mL), the ethylene glycol (0.1 mL) was added. The resultant reaction mixture was stirred at 110 ^{o}C for 16 h. At ambient temperature, the reaction mixture was quenched with saturated $NaHCO_3$ (10 mL)

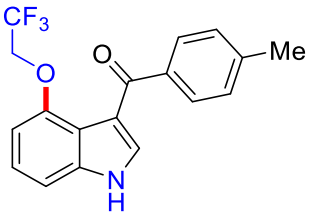
and extracted with EtOAc (10 mL x 3). The combined organic extract was dried over Na_2SO_4, and the volatiles were evaporated in *vacuo*. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) to yield **4** (0.027 g, 88%) as a pale yellow solid. M.pt: 71-74 ^oC.



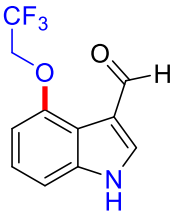
1-Benzyl-4-(2,2,2-trifluoroethoxy)-1*H*-indole (4): ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.31-7.24 (m, 3H, Ar–H), 7.09-7.05 (m, 4H, Ar–H), 7.00 (d, J = 8.3 Hz, 1H, Ar–H), 6.68-6.67 (m, 1H, Ar–H), 6.51 (d, J = 7.6 Hz, 1H, Ar–H), 5.30 (s, 2H, CH_2), 4.49 (q, J = 8.3 Hz, 2H, CH_2). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 151.3 (C_q), 138.3 (C_q), 137.5 (C_q), 129.0 (2C, CH), 127.9 (CH), 127.7 (CH), 126.9 (2C, CH), 123.4 (q, $^1J_{C-F}$ = 277.7 Hz, CF_3), 122.4 (CH), 119.7 (C_q), 105.1 (CH), 101.6 (CH), 99.1 (CH), 66.3 (q, $^2J_{C-F}$ = 35.1 Hz, CH_2), 50.5 (CH_2). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −73.9 (s). HRMS (ESI): *m/z* Calcd for $C_{17}H_{14}NOF_3 + H^+$ $[M + H]^+$ 306.1100; Found 306.1098.

***Representative Procedure for Removal of Tosyl Protecting Group*. Synthesis of 5:**

To an oven-dried round-bottom flask, *p*-tolyl(1-tosyl-4-(2,2,2-trifluoroethoxy)-1*H*-indol-3-yl)methanone (**3la**; 0.05 g, 0.103 mmol) and KOH (0.029 g, 0.515 mmol) were introduced, and MeOH (10 mL) was added into it. The resultant reaction mixture was refluxed for 3 h. The volatiles were evaporated under reduced pressure at ambient temperature, and the resulting residue was extracted with EtOAc (10 mL x 3). The combined organic extract was dried over Na_2SO_4, and the volatiles were evaporated in vacuo. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) to yield **5** (0.033 g, 96%) as a yellow liquid.



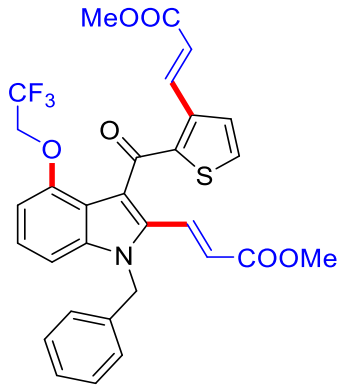
***p*-Tolyl(4-(2,2,2-trifluoroethoxy)-1*H*-indol-3-yl)methanone (5):** ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.78 (br s, 1H, *NH*), 7.73 (d, *J* = 8.1 Hz, 2H, Ar–H), 7.38 (d, *J* = 2.9 Hz, 1H, Ar–H), 7.20 (d, *J* = 7.9 Hz, 2H, Ar–H), 7.14 (t, *J* = 7.9 Hz, 1H, Ar–H), 7.08 (d, *J* = 7.5 Hz, 1H, Ar–H), 6.65 (d, *J* = 7.5 Hz, 1H, Ar–H), 4.29 (q, *J* = 8.4 Hz, 2H, CH_2), 2.41 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 191.7 (CO), 152.0 (C_q), 142.8 (C_q), 138.7 (C_q), 137.5 (C_q), 132.2 (CH), 130.0 (2C, CH), 128.9 (2C, CH), 124.3 (CH), 123.3 (q, $^{1}J_{C–F}$ = 278.5 Hz, CF_3), 117.4 (C_q), 116.8 (C_q), 107.4 (CH), 106.2 (CH), 67.3 (q, $^{2}J_{C–F}$ = 35.1 Hz, CH_2), 21.7 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −73.7 (s). HRMS (ESI): *m/z* Calcd for $C_{18}H_{14}NO_2F_3$ + H^+ $[M + H]^+$ 334.1049; Found 334.1047.



4-(2,2,2-Trifluoroethoxy)-1*H*-indole-3-carbaldehyde (6): The representative procedure was followed, using substrate **3ta** (0.05 g, 0.126 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **6** (0.028 g, 92%) as a yellow liquid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 12.34 (br s, 1H, *NH*), 10.29 (s, 1H, CH), 8.12 (d, *J* = 3.0 Hz, 1H, Ar–H), 7.24-7.16 (m, 2H, Ar–H), 6.89 (d, *J* = 7.4 Hz, 1H, Ar–H), 4.92 (q, *J* = 8.8 Hz, 2H, CH_2). ^{13}C{^{1}H}-NMR (100 MHz, DMSO-d_6): δ = 185.8 (CHO), 151.2 (C_q), 138.1 (C_q), 130.5 (CH), 124.1 (q, $^{1}J_{C–F}$ = 278.5 Hz, CF_3), 123.4 (CH), 117.7 (C_q), 115.6 (C_q), 107.4 (CH), 104.1 (CH), 64.9 (q, $^{2}J_{C–F}$ = 35.8 Hz, CH_2). ^{19}F-NMR (377 MHz, DMSO-d_6): δ = −67.9 (s). HRMS (ESI): *m/z* Calcd for $C_{11}H_8NF_3O_2$ + H^+ $[M + H]^+$ 244.0580; Found 244.0578.

4.4.6 Post Synthetic Modification of Fluoroalkoxylated Indoles

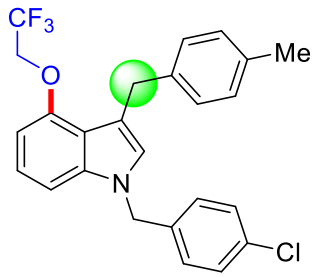
Procedure for Synthesis of Methyl (*E*)-3-(2-(1-benzyl-2-((*E*)-3-methoxy-3-oxoprop-1-en-1-yl)-4-(2,2,2-trifluoroethoxy)-1*H*-indole-3-carbonyl)thiophen-3-yl)acrylate (7): To an oven-dried screw-cap tube equipped with magnetic stir bar were introduced (1-benzyl-4-(2,2,2-trifluoroethoxy)-1*H*-indol-3-yl)(thiophen-2-yl)methanone (**3ra**; 0.042 g, 0.10 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (0.003 g, 0.005 mmol), $AgSbF_6$ (0.0068 g, 0.02 mmol), $Cu(OAc)_2.H_2O$ (0.020 g, 0.1 mmol) and methyl acrylate (0.026 g, 0.30 mmol), followed by the addition of DCE (1.0 mL). The resultant reaction mixture was immersed in a preheated oil bath at 100 °C and stirred for 12 h. The reaction mixture was allowed to cool to room temperature, and the volatiles were removed under reduced pressure. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) to yield compound **7** (0.034 g, 58%) as a yellow liquid.



Methyl (*E*)-3-(2-(1-benzyl-2-((*E*)-3-methoxy-3-oxoprop-1-en-1-yl)-4-(2,2,2-trifluoroethoxy)-1*H*-indole-3-carbonyl)thiophen-3-yl)acrylate (7): ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, J = 16.0 Hz, 1H, CH), 7.68 (d, J = 16.1 Hz, 1H, CH), 7.45 (d, J = 5.1 Hz, 1H, Ar–H), 7.36-7.28 (m, 4H, Ar–H), 7.19 (t, J = 8.1 Hz, 1H, Ar–H), 7.07 (d, J = 6.8 Hz, 2H, Ar–H), 7.00 (d, J = 8.4 Hz, 1H, Ar–H), 6.48 (d, J = 7.9 Hz, 1H, Ar–H), 6.36 (d, J = 5.9 Hz, 1H, CH), 6.32 (d, J = 5.9 Hz, 1H, CH), 5.50 (s, 2H, CH_2), 4.21 (q, J = 8.1 Hz, 2H, CH_2), 3.73 (s, 3H, CH_3), 3.69 (s, 3H, CH_3). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 185.8 (CO), 167.3 (CO), 166.8 (CO), 151.2 (C_q), 143.1 (C_q), 141.1 (C_q), 139.2 (C_q), 137.7 (CH), 136.2 (C_q), 133.6 (C_q), 131.9 (CH), 130.9 (CH), 129.3 (2C, CH), 128.1 (CH), 127.6 (CH), 126.0 (2C, CH), 125.8 (CH), 123.0 (q, $^1J_{C-F}$ = 277.7 Hz, CF_3), 122.9 (CH), 121.7 (CH), 118.9 (C_q), 117.3 (C_q), 105.3 (CH), 102.7 (CH), 65.6 (q, $^2J_{C-F}$ = 36.6 Hz, CH_2), 52.0 (CH_3), 51.9 (CH_3),

48.1 (CH_2). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −74.0 (s). HRMS (ESI): *m/z* Calcd for $C_{30}H_{24}NSO_6F_3 + H^+$ $[M + H]^+$ 584.1349; Found 584.1348.

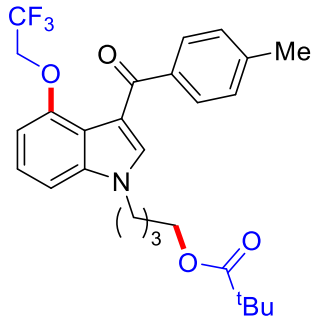
Procedure for Synthesis of Compound 1-(4-chlorobenzyl)-3-(4-methylbenzyl)-4-(2,2,2-trifluoroethoxy)-1*H*-indole (8): To a solution of (1-(4-chlorobenzyl)-4-(2,2,2-trifluoroethoxy)-1*H*-indol-3-yl)(*p*-tolyl)methanone (**3ia**; 0.046 g, 0.1 mmol) in trifluoroacetic acid (0.5 mL) was added Et_3SiH (0.08 mL, 0.5 mmol) under argon at room temperature. The reaction mixture was stirred at 50 ^oC for 3 h. The resultant mixture was quenched at ambient temperature with aqueous sodium bicarbonate and saturated brine solution. The crude product was extracted with EtOAc (10 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) to yield **8** (0.038 g, 86%) as a yellow liquid.



1-(4-Chlorobenzyl)-3-(4-methylbenzyl)-4-(2,2,2-trifluoroethoxy)-1*H*-indole (8): ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.24-7.21 (m, 2H, Ar–H), 7.19-7.13 (m, 4H, Ar–H), 7.05 (t, *J* = 8.0 Hz, 1H, Ar–H), 6.92 (d, *J* = 8.5 Hz, 2H, Ar–H), 6.85 (d, *J* = 8.3 Hz, 1H, Ar–H), 6.42 (d, *J* = 7.8 Hz, 1H, Ar–H), 6.38 (s, 1H, Ar–H), 5.13 (s, 2H, CH_2), 4.39 (q, *J* = 8.1 Hz, 2H, CH_2), 4.27 (s, 2H, CH_2), 2.30 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 152.8 (C_q), 139.9 (C_q), 138.7 (C_q), 136.7 (C_q), 136.3 (C_q), 133.5 (C_q), 130.2 (CH), 129.6 (CH), 129.1 (2C, CH), 127.9 (2C, CH), 126.2 (CH), 126.1 (CH), 126.0 (CH), 123.7 (q, $^1J_{C–F}$ = 277.7 Hz, CF_3), 122.6 (CH), 118.3 (C_q), 115.4 (C_q), 104.8 (CH), 100.5 (CH), 65.8 (q, $^2J_{C–F}$ = 35.8 Hz, CH_2), 49.6 (CH_2), 30.9 (CH_2), 19.5 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −73.7 (s). HRMS (ESI): *m/z* Calcd for $C_{25}H_{21}NOClF_3 + H^+$ $[M + H]^+$ 444.1337; Found 444.1327.

Procedure for Synthesis of 4-(3-(4-methylbenzoyl)-4-(2,2,2-trifluoroethoxy)-1*H*-indol-1-yl)butyl pivalate (9): To an oven-dried round-bottom flask equipped with a magnetic stir bar were introduced (1-(4-bromobutyl)-4-(2,2,2-trifluoroethoxy)-1*H*-indol-3-

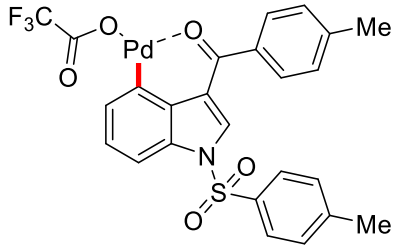
yl)(*p*-tolyl)methanone (**3fa**; 0.047 g, 0.1 mmol), $Pd(OAc)_2$ (0.0023 g, 0.01 mmol), K_2CO_3 (0.003 g, 0.02 mmol), and pivalic acid (0.051 g, 0.5 mmol). The reaction mixture was stirred at 110 ^oC for 30 h. At ambient temperature, the reaction mixture was quenched with saturated Na_2CO_3 (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic extract was dried over Na_2SO_4, and the volatiles were evaporated in vacuo. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) to yield **9** (0.046 g, 94%) as a yellow liquid.



4-(3-(4-methylbenzoyl)-4-(2,2,2-trifluoroethoxy)-1*H*-indol-1-yl)butyl pivalate (9): ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, J = 8.0 Hz, 2H, Ar–H), 7.46 (s, 1H, Ar–H), 7.24-7.21 (m, 3H, Ar–H), 7.12 (d, J = 8.3 Hz, 1H, Ar–H), 6.71 (d, J = 7.8 Hz, 1H, Ar–H), 4.31 (q, J = 8.3 Hz, 2H, CH_2), 4.18 (t, J = 7.2 Hz, 2H, CH_2), 4.08 (t, J = 6.3 Hz, 2H, CH_2), 2.42 (s, 3H, CH_3), 1.98-1.91 (m, 2H, CH_2), 1.70-1.60 (m, 2H, CH_2), 1.17 (s, 9H, CH_3). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 190.8 (CO), 178.7 (CO), 152.5 (C_q), 142.6 (C_q), 138.7 (C_q), 137.8 (C_q), 134.4 (CH), 129.9 (2C, CH), 128.8 (2C, CH), 124.1 (CH), 123.7 (q, $^1J_{C–F}$ = 279.2 Hz, CF_3), 117.7 (C_q), 116.8 (C_q), 106.3 (CH), 105.3 (CH), 67.2 (q, $^2J_{C–F}$ = 35.8 Hz, CH_2), 63.5 (CH_2), 46.9 (CH_2), 38.9 (C_q), 27.3 (3C, CH_3), 26.6 (CH_2), 26.3 (CH_2), 21.8 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −73.7 (s). HRMS (ESI): *m/z* Calcd for $C_{27}H_{30}NO_4F_3 + H^+$ $[M + H]^+$ 490.2200; Found 490.2200.

4.4.7 Procedure for Synthesis of Palladium Complex

To a Schleck tube were added phenyl(1-tosyl-1*H*-indol-3-yl)methanone (0.078 g, 0.20 mmol), $Pd(OAc)_2$ (0.046 g, 0.20 mmol) and TFA (1.0 mL). The reaction mixture was stirred at room temperature for 24 h. The resultant precipitate was washed with hexane and dried under vacuum to obtain the desired palladacycle product **10** (0.110 g, 90%) as a light yellow solid.



(3-(4-Methylbenzoyl)-1-tosyl-1*H*-indol-4-yl)(2,2,2-trifluoroacetoxy)palladium (10): ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.46 (s, 1H, Ar–H), 8.07 (d, J = 8.5 Hz, 2H, Ar–H), 7.94 (d, J = 8.1 Hz, 2H, Ar–H), 7.71 (d, J = 8.1 Hz, 1H, Ar–H), 7.59 (d, J = 7.6 Hz, 1H, Ar–H), 7.49 (d, J = 8.0 Hz, 2H, Ar–H), 7.43 (d, J = 8.1 Hz, 2H, Ar–H), 7.23 (t, J = 7.9 Hz, 1H, Ar–H), 2.47 (s, 3H, CH_3), 2.34 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, DMSO-d_6): 189.8 (CO), 146.7 (C_q), 146.7 (C_q), 144.2 (C_q), 144.2 (C_q), 136.8 (CH), 133.8 (C_q), 132.9 (C_q), 131.8 (C_q), 130.5 (2C, CH), 130.0 (2C, CH), 129.6 (2C, CH), 129.4 (CH), 127.7 (2C, CH), 125.1 (CH), 121.7 (C_q), 110.4 (CH), 21.3 (CH_3), 21.1 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −73.5 (s).

4.4.8 Procedure for *H/D* Scrambling Experiment

To an oven-dried screw-cap tube equipped with magnetic stir bar were introduced (1-benzyl-1*H*-indol-3-yl)(*p*-tolyl)methanone (**1a**; 0.065 g, 0.20 mmol), $K_2S_2O_8$ (0.108 g, 0.40 mmol), and $Pd(OAc)_2$ (0.0045 g, 0.02 mmol, 10 mol%), followed by the addition of TFA (0.046 g, 0.4 mmol) and CD_3OD (1.0 mL). The resultant reaction mixture was immersed in a preheated oil bath at 80 °C and stirred for 2 h. The reaction mixture was allowed to cool to room temperature, and all the volatiles were removed under reduced pressure. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) to recover the starting compound. The ^{1}H NMR analysis of the recovered compound **1a** has not shown the incorporation of deuterium at the C(4)–H or C(2)–H position (Scheme 4.8d).

4.4.9 X-ray Structural Analysis

Crystal of compounds **3sa,** and **10** were grown by slow vaporization of DCE/Hexane. X-ray intensity data measurements of compounds **3sa** and **10** were carried out on a Bruker D8 VENTURE Kappa Duo PHOTON II CPAD diffractometer equipped with Incoatech multilayer mirrors optics. The intensity measurements were carried out with Mo micro-focus sealed tube diffraction source (MoK_α= 0.71073 Å) at low temperature. The X-ray generator was operated at 50 kV and 1.4 mA. A preliminary set of cell constants and an orientation matrix were calculated from three matrix sets of 36 frames (each matrix run consists of 12

frames). Data were collected with ω scan width of 0.5° at different settings of φ and 2θ with a frame time of 10-20 sec depending on the diffraction power of the crystals keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX3 program (Bruker, 2016).[44] All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2016). Using the APEX3 (Bruker) program suite, the structure was solved with the ShelXS-97 (Sheldrick, 2008)[45] structure solution program, using direct methods. The model was refined with a version of ShelXL-2018/3 (Sheldrick, 2015[46] using Least Squares minimization. All the hydrogen atoms were placed in a geometrically idealized position and constrained to ride on their parent atoms. An *ORTEP* III[47] view of the compounds was drawn with 50% probability displacement ellipsoids, and H atoms are shown as small spheres of arbitrary radii.

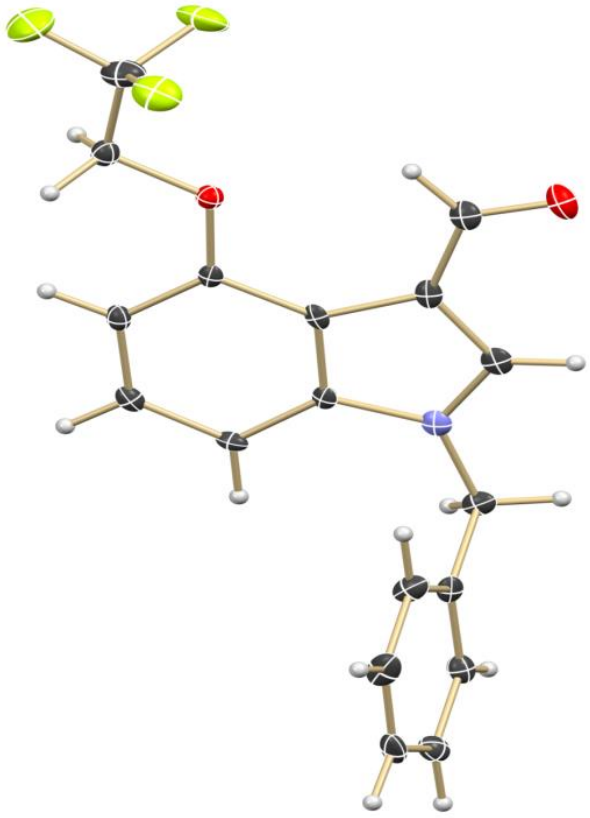


Figure 4.2 ORTEP of compound **3sa** showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres with arbitrary radii.

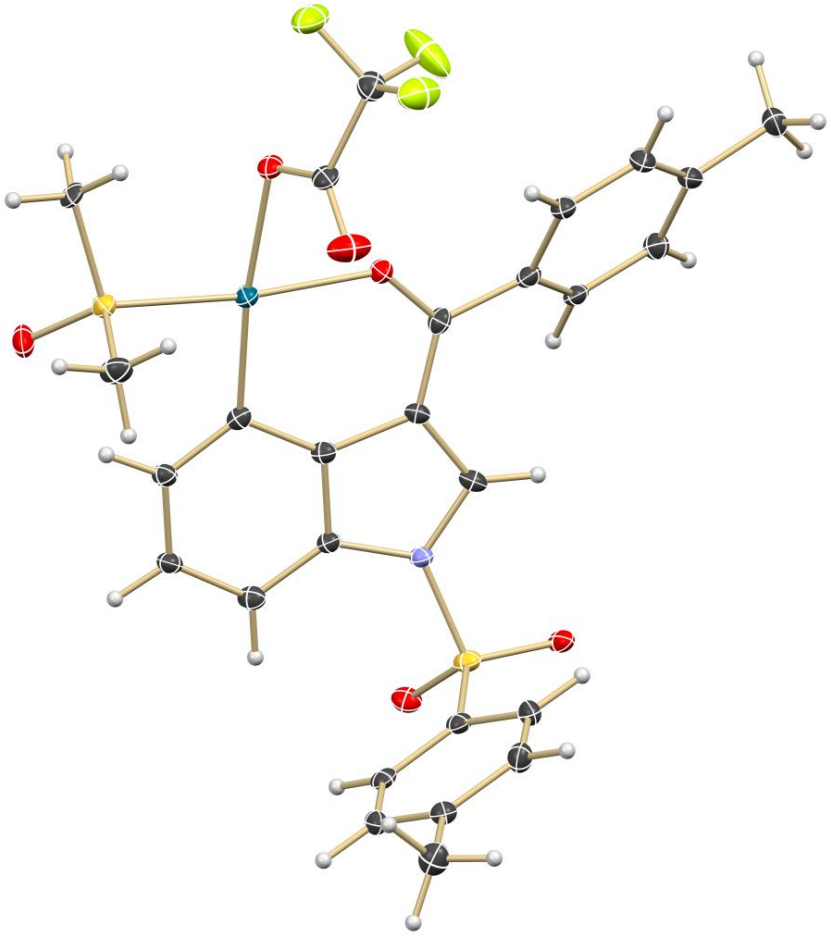
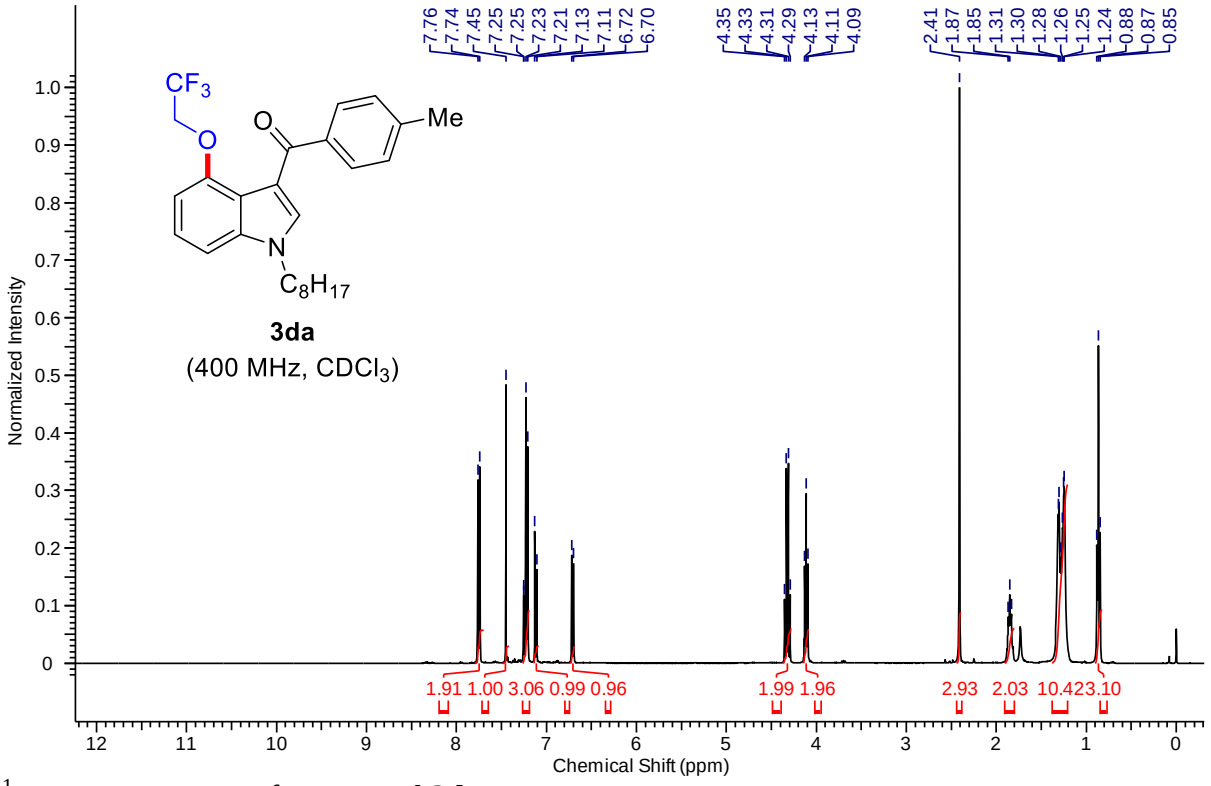
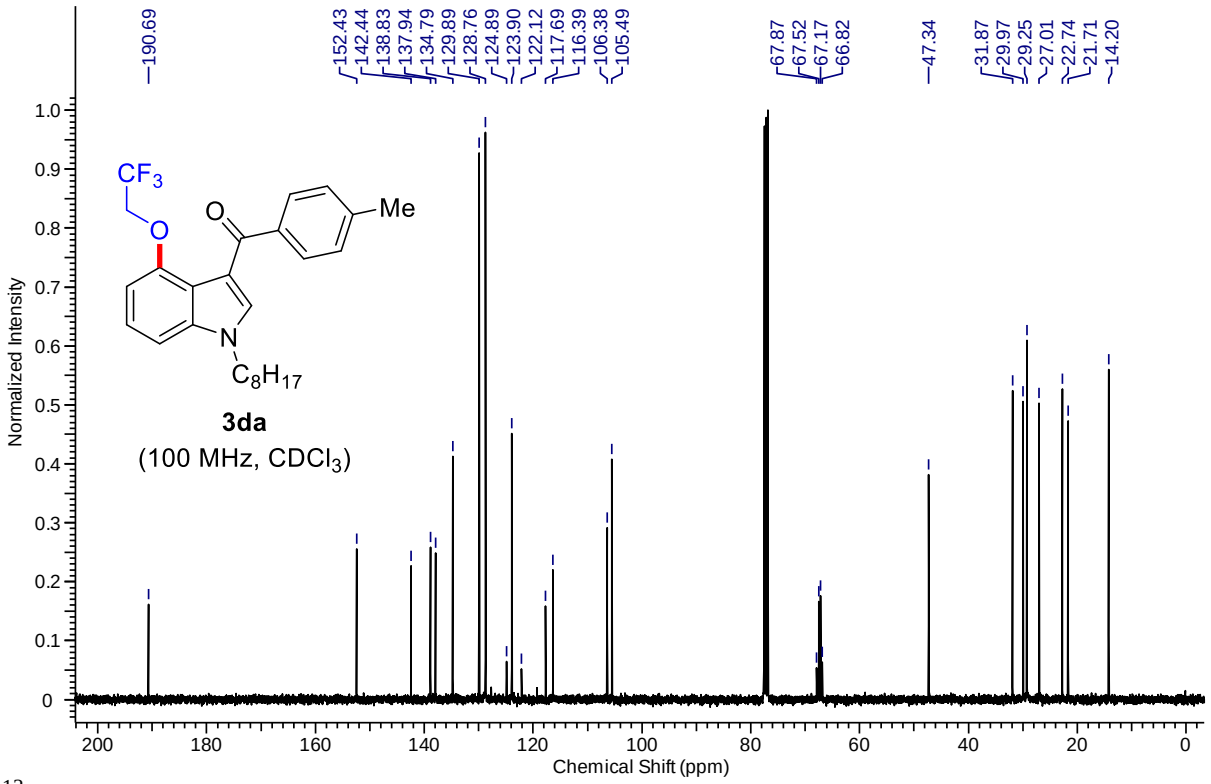


Figure 4.3 ORTEP of compound **10** showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres with arbitrary radii.

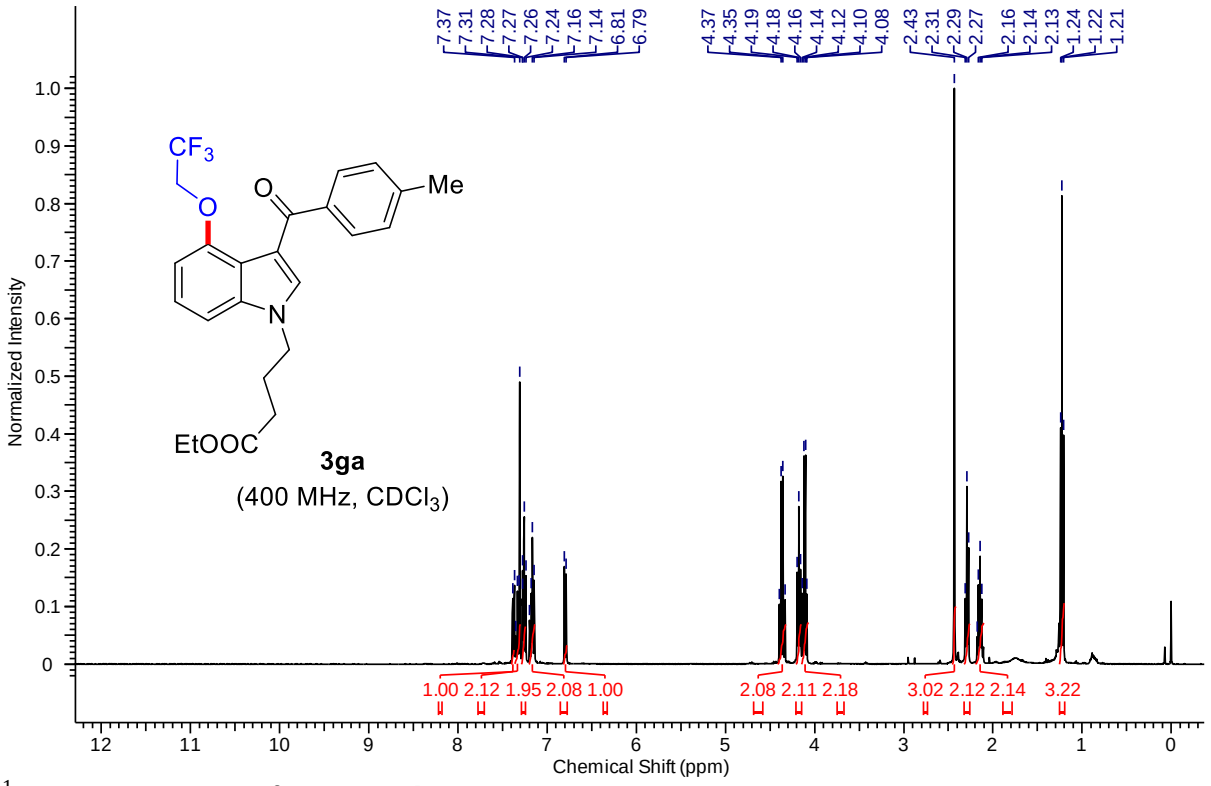
4.4.10 ^{1}H NMR and ^{13}C NMR for Selected Compounds



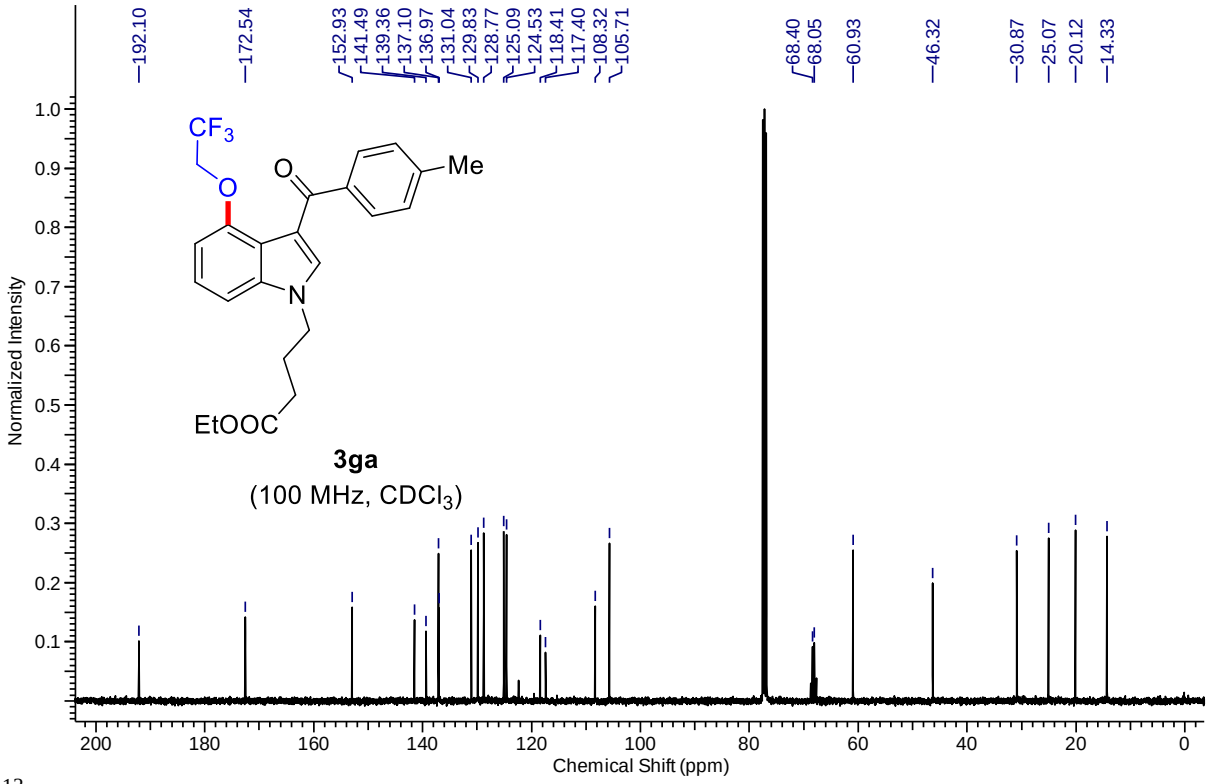
^{1}H-NMR spectrum of compound **3da**



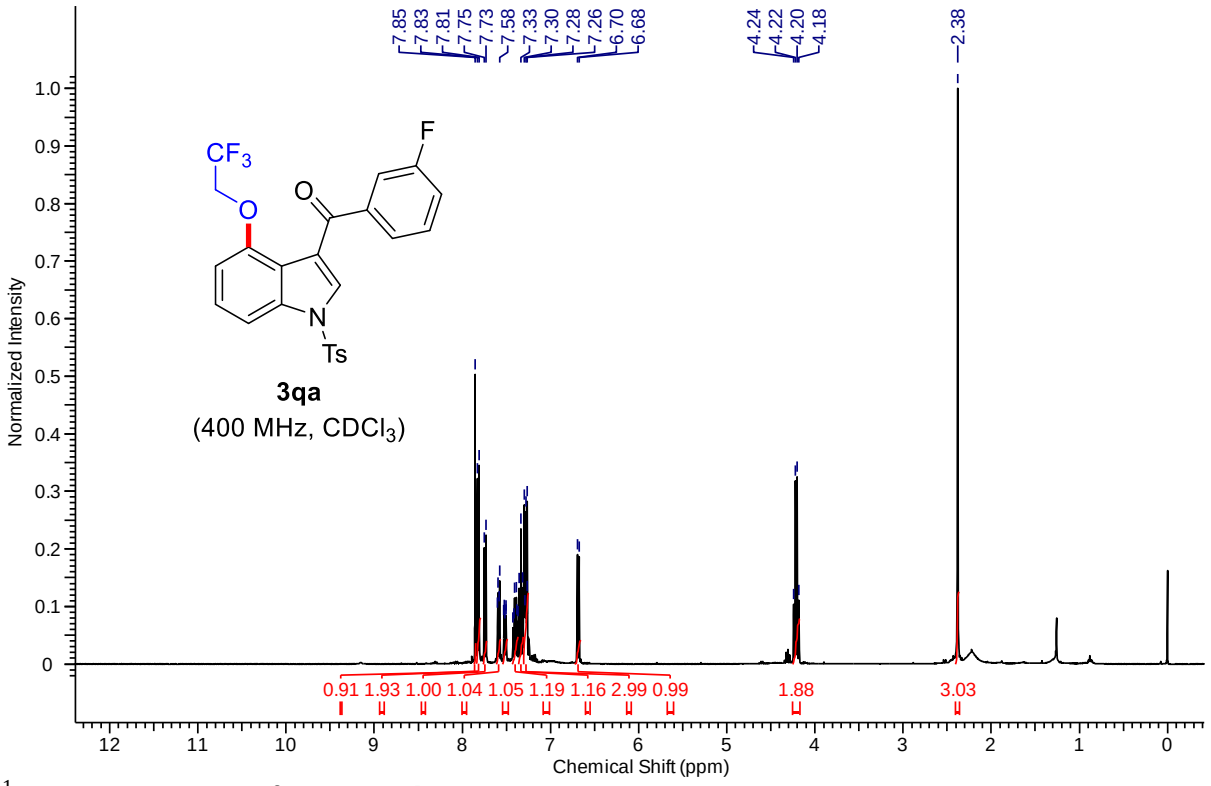
^{13}C-NMR spectrum of compound **3da**



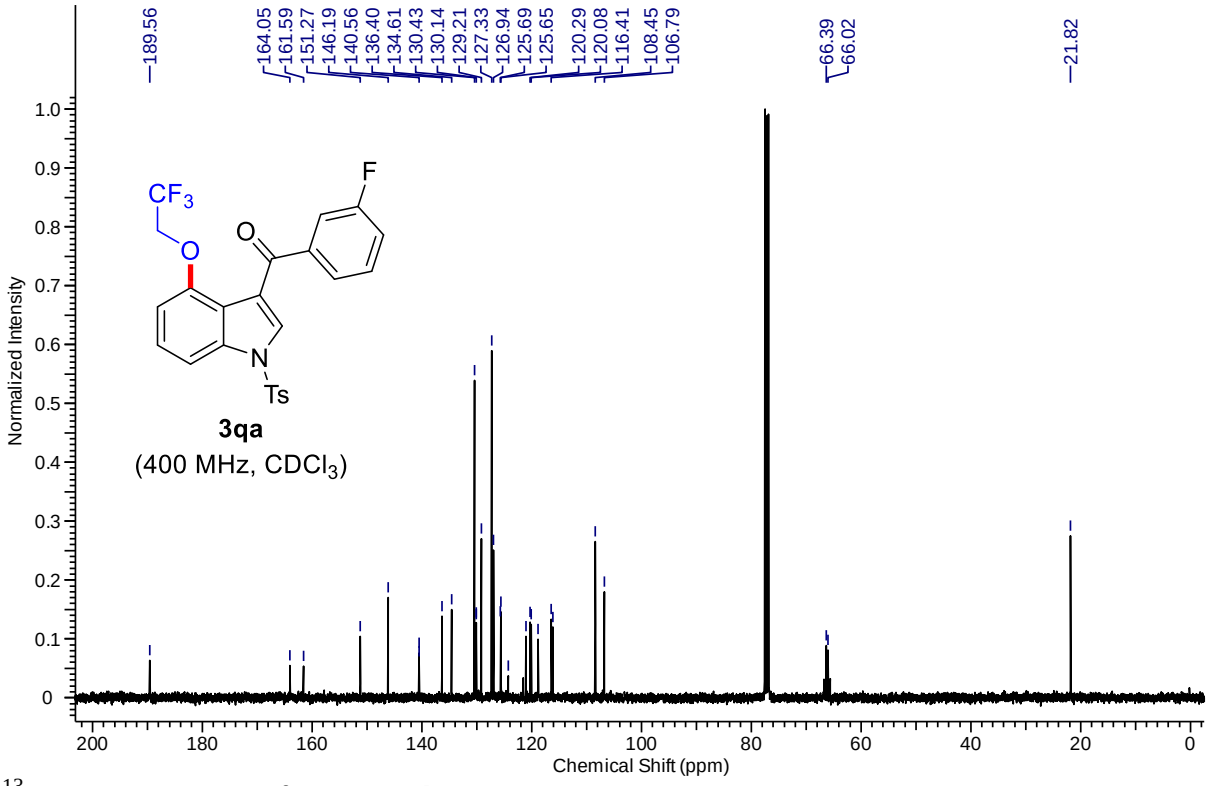
^{1}H-NMR spectrum of compound **3ga**



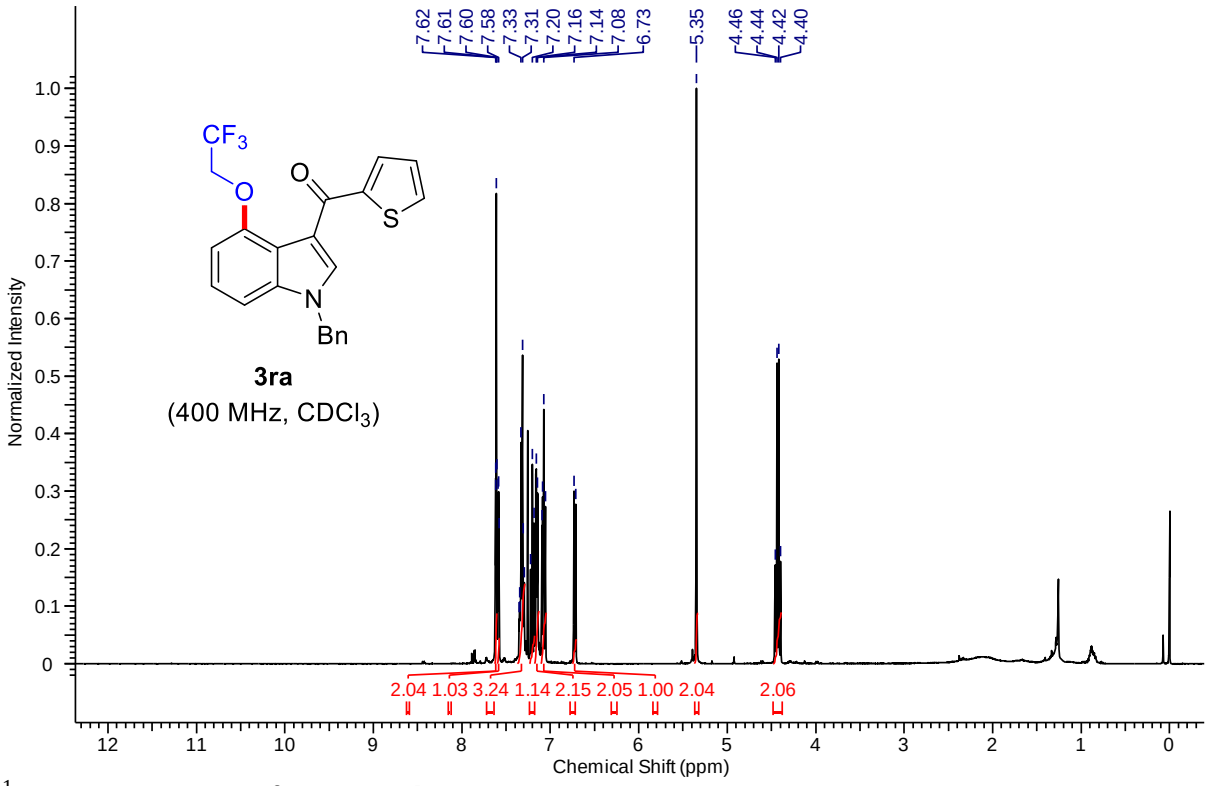
^{13}C-NMR spectrum of compound **3ga**



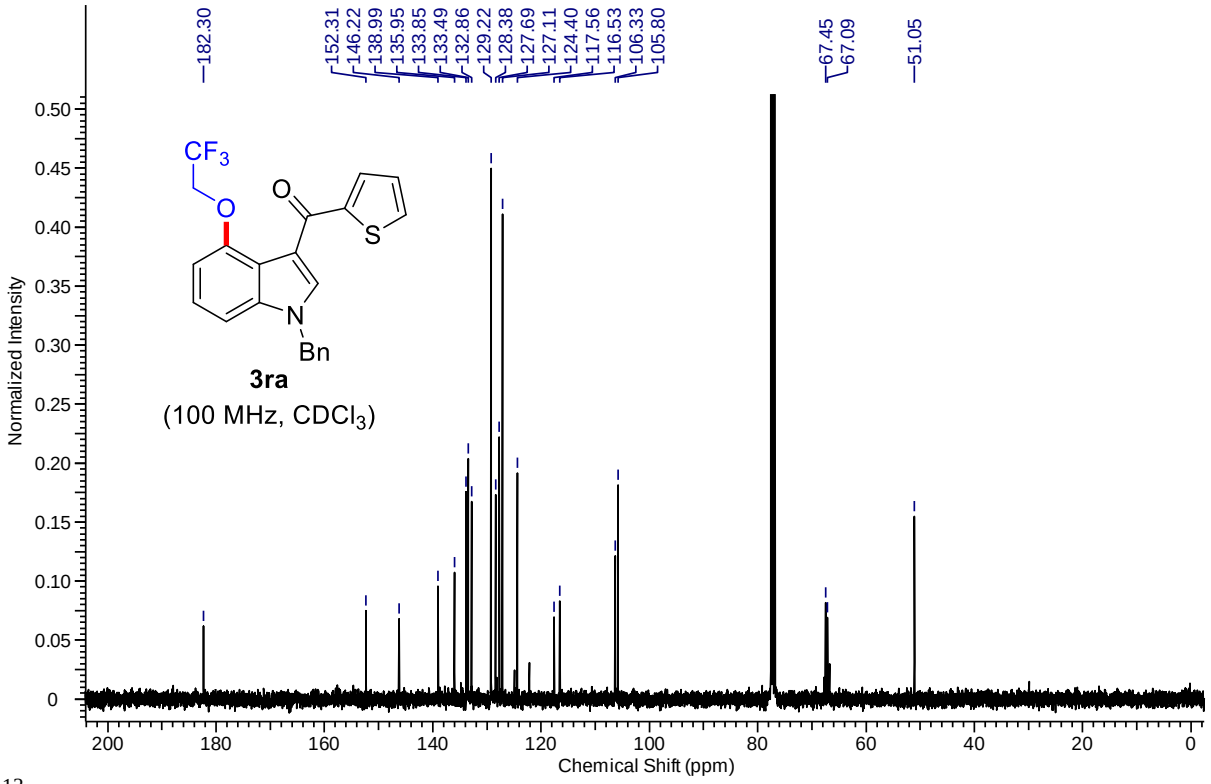
^{1}H-NMR spectrum of compound **3qa**



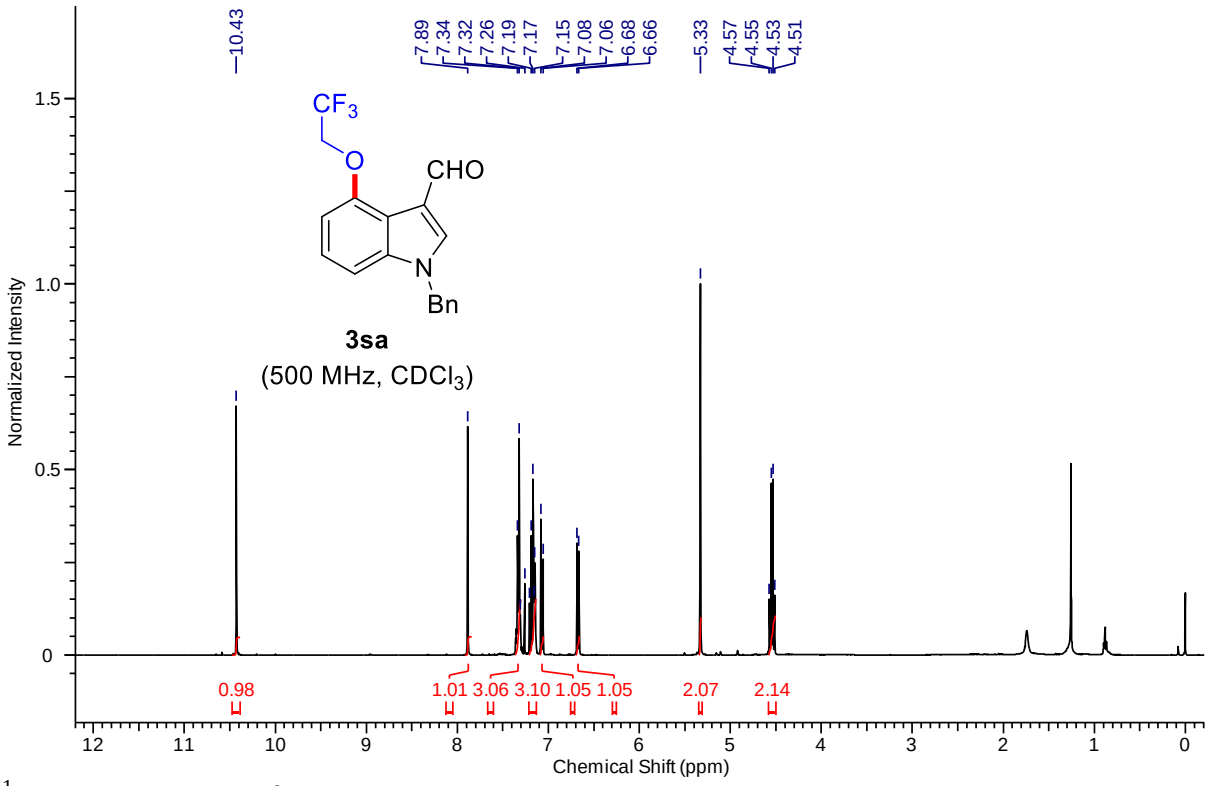
^{13}C-NMR spectrum of compound **3qa**



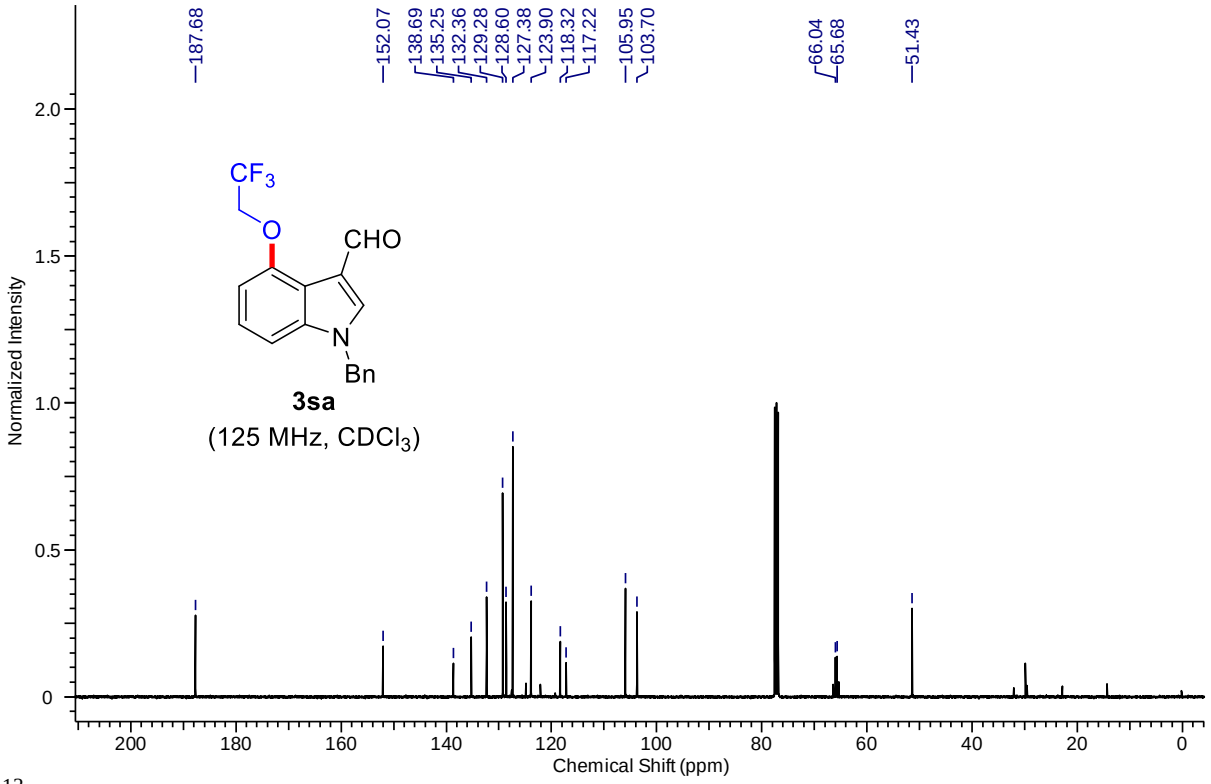
^{1}H-NMR spectrum of compound **3ra**



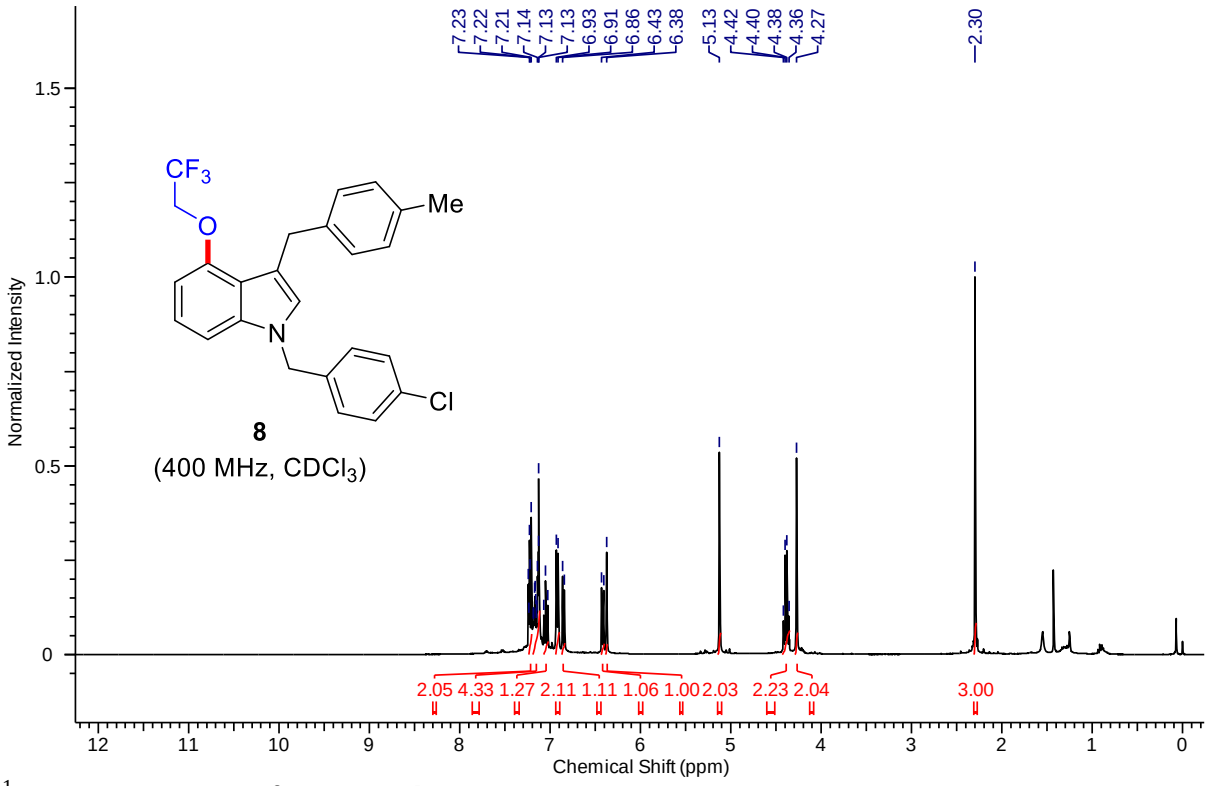
^{13}C-NMR spectrum of compound **3ra**



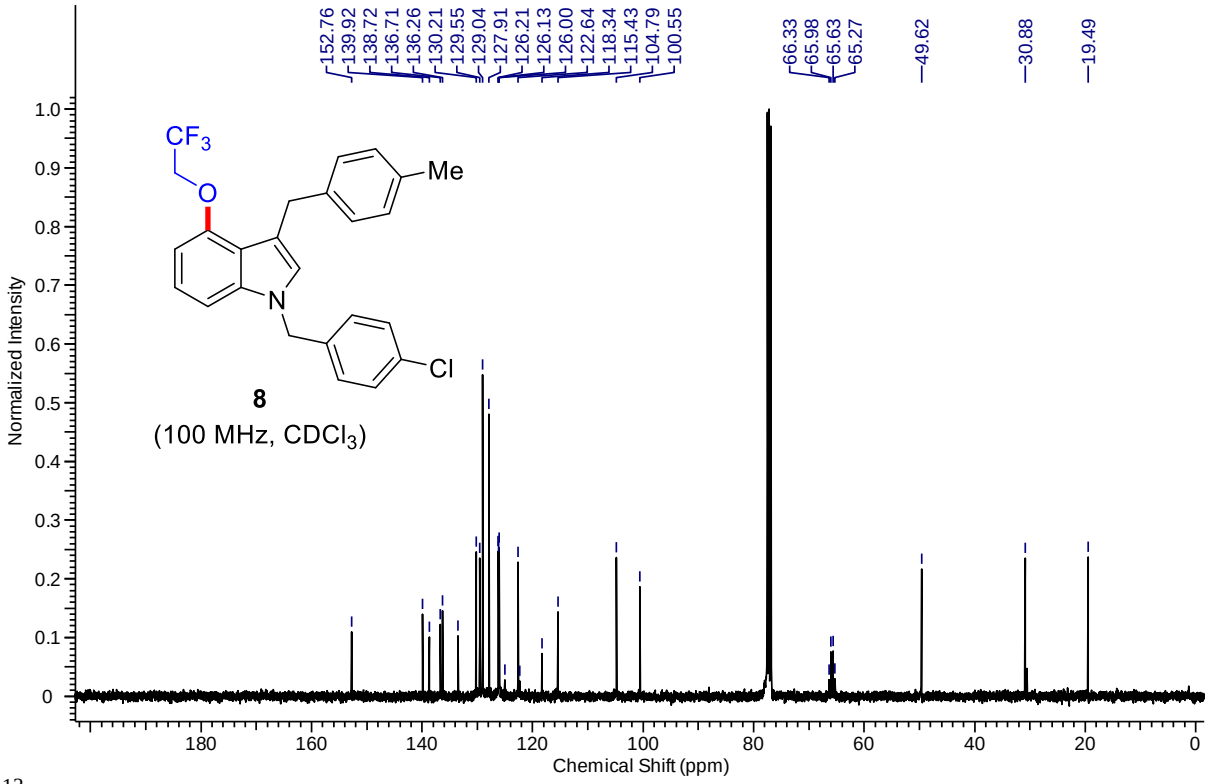
^{1}H-NMR spectrum of compound **3sa**



^{13}C-NMR spectrum of compound **3sa**



^{1}H-NMR spectrum of compound **8**



^{13}C-NMR spectrum of compound **8**

4.5 References

1. Jimonet, P.; Audiau, F.; Barreau, M.; Blanchard, J.C.; Boireau, A.; Bour, Y.; Coléno, M.A.; Doble, A.; Doerflinger, G.; Do Huu, C.; Donat, M.H.; Duchesne, J. M.; Ganil, P.; Guérémy, C.; Honoré, E.; Just, B.; Kerphirique, R.; Gontier, S.; Hubert, P.; Laduron, P. M.; Le Blevec, J.; Meunier, M.; Miquet, J.M.; Nemecek, C.; Pasquet, M.; Piot, O.; Pratt, J.; Rataud, J.; Reibaud, M.; Stutzmann, J.M.; Mignani, S., Riluzole Series., *J. Med. Chem.* **1999**, *42*, 2828-2843.
2. Batool, F.; Parveen, S.; Emwas, A.H.; Sioud, S.; Gao, X.; Munawar, M. A.; Chotana, G. A., *Org. Lett.* **2015**, *17*, 4256-4259.
3. Besset, T.; Jubault, P.; Pannecoucke, X.; Poisson, T., *Org. Chem. Front.*, **2016**, *3*, 1004-1010.
4. Fu, M. L.; Liu, J. B.; Xu, X. H.; Qing, F. L., *J. Org. Chem.* **2017**, *82*, 3702-3709.
5. Granados, A.; Ballesteros, A.; Vallribera, A., *J. Org. Chem.* **2020**, *85*, 10378-10387.
6. Nakai, T.; Tanaka, K.; Ishikawa, N., *J. Fluor. Chem.* **1977**, *9*, 89-93.
7. Camps, F.; Coll, J.; Messeguer, A.; Pericàs, M. A., *Synthesis* **1980**, *1980*, 727-728.
8. Kamal, A.; Pratap, T. B.; Ramana, K. V.; Ramana, A. V.; Babu, A. H., *Tetrahedron Lett.* **2002**, *43*, 7353-7355.
9. Vuluga, D.; Legros, J.; Crousse, B.; Bonnet-Delpon, D., *Eur. J. Org. Chem.* **2009**, *2009*, 3513-3518.
10. Huang, R.; Huang, Y.; Lin, X.; Rong, M.; Weng, Z., *Angew. Chem. Int. Ed.* **2015**, *54*, 5736-5739.
11. Zhang, K.; Xu, X.H.; Qing, F. L., *J. Fluor. Chem.* **2017**, *196*, 24-31.
12. Zhang, H.; Ruiz-Castillo, P.; Buchwald, S. L., *Org. Lett.* **2018**, *20*, 1580-1583.
13. Chen, Z.; Jiang, Y.; Zhang, L.; Guo, Y.; Ma, D., *J. Am. Chem. Soc.* **2019**, *141*, 3541-3549.
14. Szpera, R.; Isenegger, P. G.; Ghosez, M.; Straathof, N. J. W.; Cookson, R.; Blakemore, D. C.; Richardson, P.; Gouverneur, V., *Org. Lett.* **2020**, *22*, 6573-6577.
15. Yang, L.; Li, S.; Cai, L.; Ding, Y.; Fu, L.; Cai, Z.; Ji, H.; Li, G., *Org. Lett.* **2017**, *19*, 2746-2749.
16. Jin, L.; Zhang, X. L.; Guo, R. L.; Wang, M. Y.; Gao, Y. R.; Wang, Y. Q., *Org. Lett.* **2021**, *23*, 1921-1927.
17. Sato, T.; Nogi, K.; Yorimitsu, H., *ChemCatChem* **2020**, *12*, 3467-3471.
18. Tian, M.; Shao, L.; Su, X.; Zhou, X.; Zhang, H.; Wei, K.; Sun, R.; Wang, J., *RSC Adv.*,

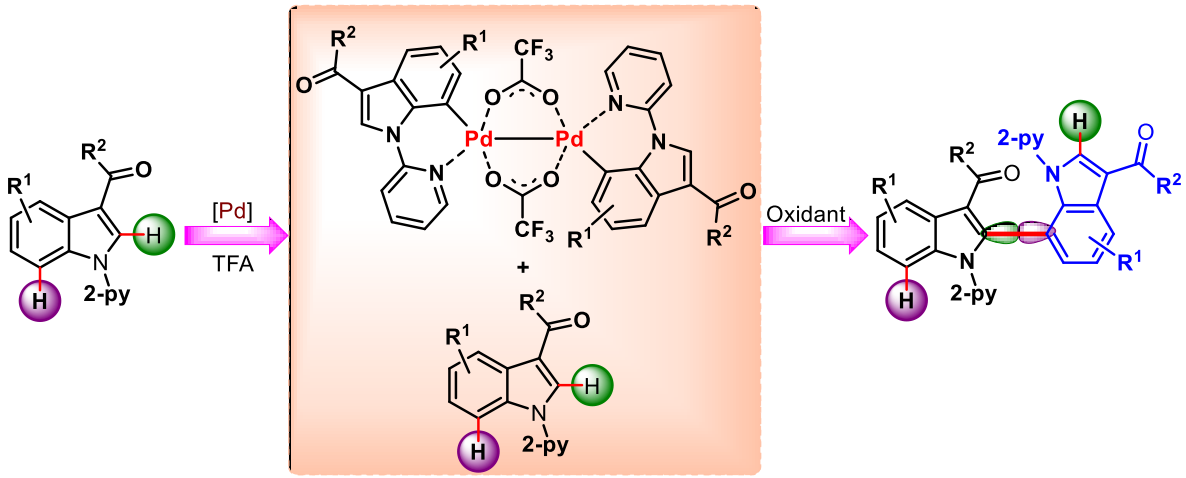
2022, *12*, 18722-18727.

19. Jiang, Y.; Pan, C.; Tang, T.; Liu, M.; *Org. Biomol. Chem.*, **2023**, *21*, 2748-2753.
20. Mutule, I.; Suna, E.; Olofsson, K.; Pelcman, B., *J. Org.Chem.* **2009**, *74*, 7195-7198.
21. Soni, V.; Patel, U. N.; Punji, B., *RSC Adv.*, **2015**, *5*, 57472-57481.
22. Sandtorv, A. H., *Adv. Synth. Catal.* **2015**, *357*, 2403-2435.
23. Okada, T.; Nobushige, K.; Satoh, T.; Miura, M., *Org. Lett.* **2016**, *18*, 1150-1153.
24. Kumar, P.; Nagtilak, P. J.; Kapur, M., *New J. Chem.* **2021**, *45*, 13692-13746.
25. Wei, P.; Zhu, Y.; Ying, J.; Wu, X. F., *J. Org. Chem.* **2023**, *88*, 6274-6280.
26. Kalepu, J.; Gandeepan, P.; Ackermann, L.; Pilarski, L. T., *Chem. Sci.*, **2018**, *9*, 4203-4216.
27. Basak, S.; Paul, T.; Maharana, P. K.; Debnath, B.; Punniyamurthy, T., *Synlett* **2022**, *34*, 759-776.
28. Thrimurtulu, N.; Dey, A.; Singh, A.; Pal, K.; Maiti, D.; Volla, C. M. R., *Adv. Synth. Catal.* **2019**, *361*, 1441-1446.
29. Zhang, J.; Wu, M.; Fan, J.; Xu, Q.; Xie, M., *Chem. Commun.* **2019**, *55*, 8102-8105.
30. Pan, C.; Huang, G.; Shan, Y.; Li, Y.; Yu, J. T., *Org. Biomol. Chem.*, **2020**, *18*, 3038-3042.
31. Kuang, G.; Liu, D.; Chen, X.; Liu, G.; Fu, Y.; Peng, Y.; Li, H.; Zhou, Y., *Org. Lett.* **2021**, *23*, 8402-8406.
32. Cheng, Y.; Yu, S.; He, Y.; An, G.; Li, G.; Yang, Z., *Chem. Sci.*, **2021**, *12*, 3216-3225.
33. Basak, S.; Paul, T.; Punniyamurthy, T., *Org. Lett.* **2022**, *24*, 554-558.
34. Liu, Y.Z.; Zeng, Y.F.; Shu, B.; Zheng, Y.C.; Xiao, L.; Chen, S.Y.; Song, J.L.; Zhang, X.; Zhang, S.S., *Org. Chem. Front.*, **2022**, *9*, 4287-4293.
35. Gupta, S. K.; Panda, N., *J. Org. Chem.* **2023**, *88*, 4254-4263.
36. Enthaler, S.; Company, A., *Chem. Soc. Rev.* **2011**, *40*, 4912-4924.
37. Moghimi, S.; Mahdavi, M.; Shafiee, A.; Foroumadi, A., *Eur. J. Org. Chem.* **2016**, *2016*, 3282-3299.
38. Iqbal, Z.; Joshi, A.; Ranjan De, S., *Adv. Synth. Catal.* **2020**, *362*, 5301-5351.
39. Zhang, Q.; Xie, X.; Peng, J.; Chen, F.; Ma, J.; Li, C.; Liu, H.; Wang, D.; Wang, J., *Org. Lett.* **2021**, *23*, 4699-4704.
40. Singh, A.; Dey, A.; Pal, K.; Dash, O. P.; Volla, C. M. R., *Org. Lett.* **2022**, *24*, 1941-1946.
41. Shan, G.; Yang, X.; Ma, L.; Rao, Y., *Angew. Chem. Int. Ed.* **2012**, *51*, 13070-13074.

42. Ankade, S. B.; Samal, P. P.; Soni, V.; Gonnade, R. G.; Krishnamurty, S.; Punji, B., *ACS Catal.* **2021**, *11*, 12384-12393.
43. Pradhan, C.; Jagtap, R. A.; Samal, P. P.; Krishnamurty, S.; Punji, B., *Green Chem.* **2023**.
44. Bruker, *APEX3, SAINT and SADABS*. Bruker AXS Inc., Madison, Wisconsin, USA. **2016**.
45. Sheldrick, G. M., *Acta Crystallogr.* **2008**, *A64*, 112-122.
46. Sheldrick, G. M., *Acta Crystallogr.* **2015**, *C71*, 3-8.
47. Farrugia, L. J., *J. Appl. Crystallogr.* **2012**, *45*, 849-854.

Chapter 5

Palladium-Catalyzed Intermolecular C(2)−H/C(7)−H Oxidative Coupling of Indoles



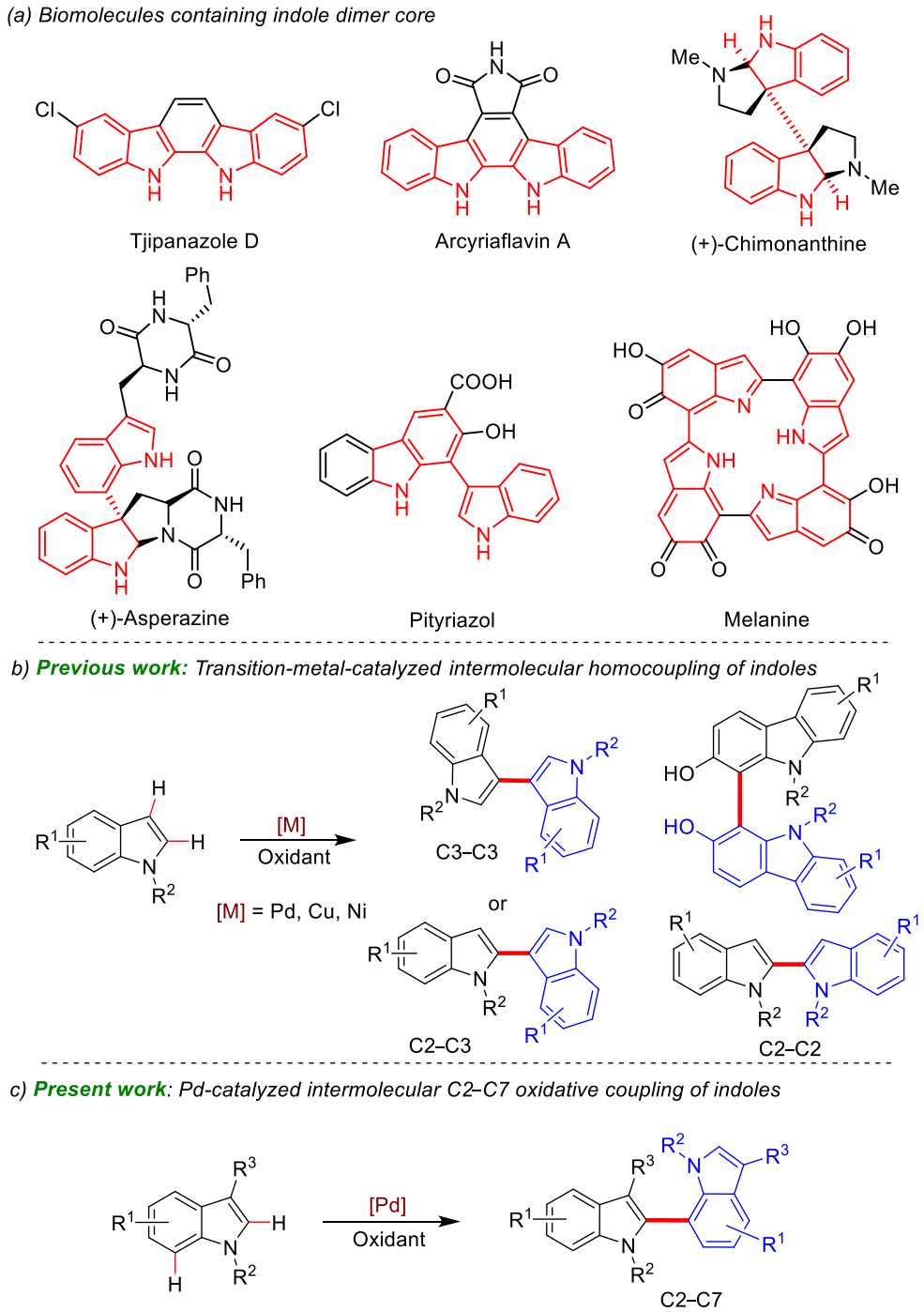
5.1 INTRODUCTION

Indoles are highly significant heterocyclic constituents in the realm of natural chemistry and drug discovery, given their pivotal role in generating a diverse array of bioactive compounds and pharmacologically relevant substances.[1-4] In particular, biindoles serve as crucial motifs representing a large class of interesting natural products and organic electroluminescent gadget materials (Scheme 5.1a).[5-12] Therefore, the development of unified protocols for the efficient synthesis of biindole is vital. Existing literature reveals that only a few methods are available for synthesizing biindoles.[11,13-20] The most systematic approach for synthesizing biindolyls involves the acidic coupling of indoles followed by dehydrogenation.[21] The versatile synthesis of biindoles has been facilitated by coupling indole halides with organo-indole catalyzed by transition metals.[1,3,5,21-23] However, these methods necessitate prefunctionalized substrates and generate stoichiometric amounts of organometallic waste as byproducts.

Recently, the C−H/C−H oxidative coupling of indoles has gained attention as an efficient one-step method for producing biindole compounds without prefunctionalizing substrates.[24,25] Over the past decade, homocoupling of indole to approach the 2,2-biinolyls, 3,3-biindolyls, and 2,3-biindolyls catalyzed by palladium, $Cu(OAc)_2$ or $AgNO_3$ *via* C–H bond cleavage has been well explored (Scheme 5.1b).[13-19,26] A recent development by Li and coworkers involves an efficient strategy for synthesizing 2,3-biindoles by merging C–H activation with nucleophilic cyclization, using alkynylanilines and indoles.[27] However, these reports are restricted to the homocoupling of indoles and carbazoles at activated carbonyl centers. Unfortunately, the selective coupling of C2 and C7 in indole remains unexplored. However, achieving selectivity at the C7 position has proven challenging. Typically, functionalization here requires strategic substitutions at the C2 position or a multi-step process involving indole reduction to indoline derivatives. In 2010, a breakthrough occurred with Hartwig and team's Ir-catalyzed C−H borylation at the elusive C7 position, controlled by an N-silyl DG.[28] This ground breaking method paved the way for synthesizing valuable C7-functionalized indoles through subsequent Suzuki−Miyaura coupling. Despite this progress, the quest for a direct C−H functionalization at C7 persists due to challenges arising from the preferred formation of a five-membered metallacycle at C2. In recent study propose an innovative strategy: enhancing C7 selectivity by using a bulkier and more electron-withdrawing DG on the N-atom.

The 2,7-biindoles are in high demand as they are important natural products and pharmaceutical drug molecule scaffolds.[29,30] Considering the importance of selective 2,7-

biindoles, we were keen to perform the C2–C7 coupling of indole. In this chapter, we describe a palladium-catalyzed C(2)−H/C(7)−H oxidative coupling of indoles, employing pyridine as a directing group and $K_2S_2O_8$ as an oxidant. This reaction demonstrates remarkable selectivity in producing biindoles linked at the C2 and C7 positions (Scheme 5.1c).



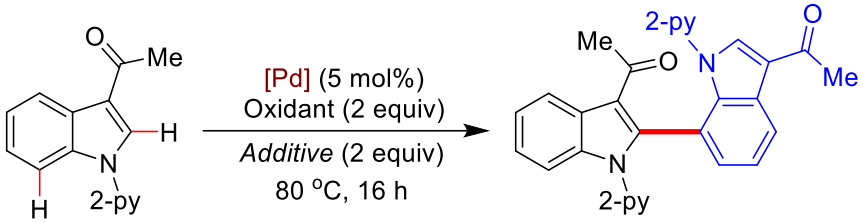
Scheme 5.1 Bioactive Molecules Containing Biindole Scaffolds and C2/C7 Oxidative Coupling of Indoles.

5.2 RESULTS AND DISCUSSION

5.2.1 Optimization of Reaction Parameters

We have commenced a systematic exploration of reaction parameters for the oxidative coupling of 1-(1-(pyridin-2-yl)-1*H*-indol-3-yl)ethan-1-one (**1a**) as a model substrate, utilizing various Pd sources, oxidants, and additives (Table 5.1). In the initial attempt, When **1a** was stirred with $Pd(OAc)_2$ (5 mol%) at 80 °C for 16 h in the presence of $PhI(OAc)_2$ and TFA (2.0 equiv), only a trace of the product was obtained (Table 5.1, entry 1). Subsequent screening of oxidants, including metal salts, and NFSI resulted in incomplete conversion (entries 2-5). The utilization of metal persulphate, specifically $(NH_4)_2S_2O_8$, led to a diminished yield (entry 6). Encouragingly, $Na_2S_2O_8$ and $K_2S_2O_8$ proved to be effective oxidants, providing the desired C2-C7 homo-coupled product **1** in 81% and 94% yield, respectively (entries 7, 8). The reaction was carried out in other solvents, including HFIP and AcOH, which afforded lower yields, whereas TFA as solvent was incompetent (entries 9-11). Additionally, a range of additives were examined, including triflic acid, water, and acetic acid; among these, trifluoroacetic acid yielded the most favorable results (entries 12-14). The homo-coupling reaction exhibited sluggish progress, using $PdCl_2$ as a catalyst and providing a 41% yield of **1**; however, $Pd_2(dba)_3$ as catalyst was ineffective (entries 15, 16). The homo-coupling progressed effortlessly even with 3.0 mol% loading of $Pd(OAc)_2$ (entry 17); however, further lowering of catalyst loading led to low conversion. The use of 1.5 equiv of $K_2S_2O_8$ instead of 2.0 equiv resulted in incomplete conversion (entry 18). Substituting 5.0 equiv of TFA instead of 2.0 equiv resulted in low yield (entry 19). Increasing in the temperature did not significantly impact the selective homocoupling of indole (entries 20, 21). The homocoupling failed in the absence of an external oxidant, additive, or Pd catalyst (entries 22-24), indicating the essential role of these components. Thus, the optimal reaction condition was found to be as follows: **1a** (0. 2 mmol), $K_2S_2O_8$ (0.4 mmol), $Pd(OAc)_2$ (3 mol%), TFA (0.2 mmol) in TFE (1 mL) at 80 ^oC for 16 h.

Table 5.1. Optimization of Reaction Condition for C(2)−H/C(7)−H Oxidative Coupling [a]



(**1a**) (**1**)

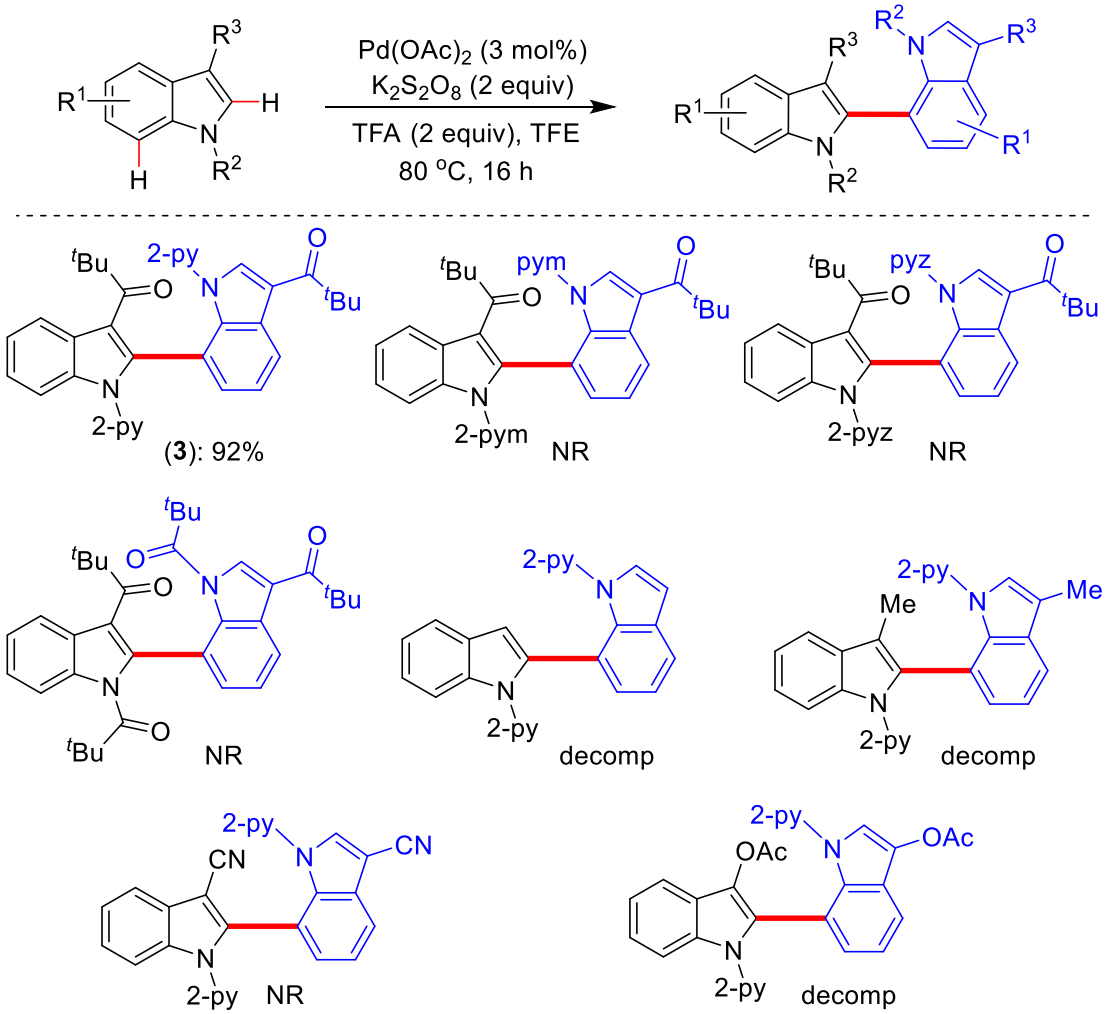
Entry	[Pd]	Oxidant	Additive	Solvent	Yield (%) [b] **1**
1	$Pd(OAc)_2$	$PhI(OAc)_2$	TFA	TFE	trace
2	$Pd(OAc)_2$	AgTFA	TFA	TFE	trace
3	$Pd(OAc)_2$	AgOAc	TFA	TFE	trace
4	$Pd(OAc)_2$	$Cu(OAc)_2$	TFA	TFE	trace
5	$Pd(OAc)_2$	NFSI	TFA	TFE	trace
6	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	TFA	TFE	NR
7	$Pd(OAc)_2$	$Na_2S_2O_8$	TFA	TFE	81
8	$Pd(OAc)_2$	$K_2S_2O_8$	TFA	TFE	94 (91)
9	$Pd(OAc)_2$	$K_2S_2O_8$	TFA	HFIP	68
10	$Pd(OAc)_2$	$K_2S_2O_8$	TFA	AcOH	trace
11	$Pd(OAc)_2$	$K_2S_2O_8$	--	TFA	ND
12	$Pd(OAc)_2$	$K_2S_2O_8$	AcOH	TFE	trace
13	$Pd(OAc)_2$	$K_2S_2O_8$	H_2O	TFE	NR
14	$Pd(OAc)_2$	$K_2S_2O_8$	TfOH	TFE	NR
15	$PdCl_2$	$K_2S_2O_8$	TFA	TFE	41
16	$Pd_2(dba)_3$	$K_2S_2O_8$	TFA	TFE	NR
17[c]	**$Pd(OAc)_2$**	**$K_2S_2O_8$**	**TFA**	**TFE**	**87**
18[c,d]	$Pd(OAc)_2$	$K_2S_2O_8$	TFA	TFE	(76)
19[c,e]	$Pd(OAc)_2$	$K_2S_2O_8$	TFA	TFE	65
20[c,f]	$Pd(OAc)_2$	$K_2S_2O_8$	TFA	TFE	(79)
21[c,g]	$Pd(OAc)_2$	$K_2S_2O_8$	TFA	TFE	83
22[c]	$Pd(OAc)_2$	$K_2S_2O_8$	--	TFE	NR
23[c]	--	$K_2S_2O_8$	TFA	TFE	NR
24[c]	$Pd(OAc)_2$	--	TFA	TFE	NR

[a] Conditions: Substrate **1a** (0.047 g, 0.20 mmol), oxidant (0.40 mmol), [Pd] (0.01 mmol, 5 mol%), TFA (0.40 mmol), solvent (1.0 mL). [b] isolated yield, ^{1}H NMR yield (using

dibromometane as internal standard) in parenthesis. [c] 3.0 mol% of $Pd(OAc)_2$ used. [d] 1.5 equiv of $K_2S_2O_8$ was used. [e] 5.0 equiv of TFA was used. [f] Reaction performed at 70 ^oC. [g] Reaction performed at 100 ^oC. ND = Not Determined. NR = No Reaction. TFA = Trifluoroacetic acid. TFE = Trifluoroethanol.

5.2.2 Effect of C3 and *N*-Substituents for C(2)−H/C(7)−H Coupling of Indoles

Using the optimal reaction condition, the study delved into the impact of C3 and *N*-substituents on oxidative coupling in indole derivatives (Scheme 5.2). In the initial screening phase with *N*-substituents of 3-pivaloyl-indole, it was observed that the coupling with *N*-2-pyridinyl-3-pivaloyl-indole (**3a**) resulted in 92% yield of product **3**. Surprisingly, attempts with substrates such as *N*-2-pyrimidinyl-3-pivaloyl-indole and *N*-2-pyrazinyl-3-pivaloyl-indole did not yield the desired coupled product. Additionally, the inclusion of a −CO^{t}Bu as an *N*-substituent also failed to produce the desired outcome, highlighting the crucial role of σ-donor nitrogen coordination in this intermolecular oxidative coupling. Furthermore, the screening extended to C3-substituents of 1-(pyridin-2-yl)-*1H*-indole. It was observed that both 1-(pyridin-2-yl)-*1H*-indole and 3-methyl-1-(pyridin-2-yl)-*1H*-indole decomposed under the established protocol. Likewise, the cyano and acetate group at the C3 position was not tolerated under the standard conditions. Indeed, C3 carbonyl and pyridine groups play a pivotal role in facilitating selective C2–C7 coupling reactions.



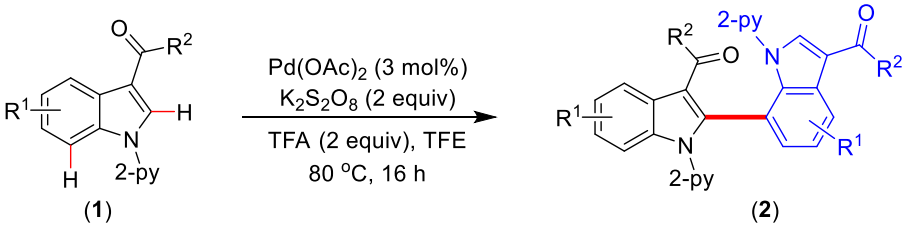
Scheme 5.2. Effect of C3 and *N*-Substituents for C(2)−H/C(7)−H Coupling of Indoles.

5.2.3 Scope for C(2)−H/C(7)−H Homo-Coupling of Indoles

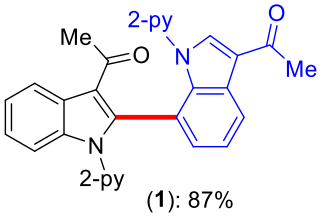
With the best condition in hand, we explored the current protocol's applicability and limitations for synthesizing diverse C2–C7 coupled biindoles (Scheme 5.3). The results indicated a wide substrate tolerance for indoles containing diverse C3 carbonyl functionalities. Notably, indoles with keto moieties carrying various substituents such as methyl, isopropyl, *tert*-butyl, neopentyl, cyclohexyl, and adamantly groups were well tolerated and afforded good to excellent yields of desired products (**1**-**6**). Interestingly, even an aldehyde and ester group at the C3 position were found to be compatible with the reaction conditions, yielding products **7** and **8** with 81% and 65% yields, respectively. Additionally, trace amounts of C2–C2 homo-coupled compounds were obtained along with C2–C7 homo-coupled compounds. Indoles bearing C3 substituents such as 2-(dimethylamino)-2-oxoacetyl and 2-morpholino-2-oxoacetyl groups were found to be well-tolerated, yielding good results at 120 °C (**9**, **10**). Likewise, indoles featuring C3-positioned such as 4-methylbenzoyl, 4-

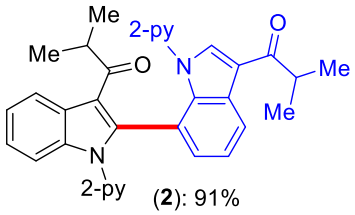
trifluoromethylbenzoyl, 3-fluorobenzoyl, and thiophene-2-carbonyl groups were well tolerated and provided good yields (**11**-**14**). Notably, (1-(pyridin-2-yl)-1*H*-indol-3-yl)(*p*-tolyl)methanone (**11a**) produced a notable quantity of C2–C2 homo-coupled compound **11'** (18%) alongside the C2–C7 homo-coupled product **11** in 71% yield. The relatively lower steric hindrance of the C3 benzoyl group on indole might favor the initial C(2)–H activation over C(7)–H activation.

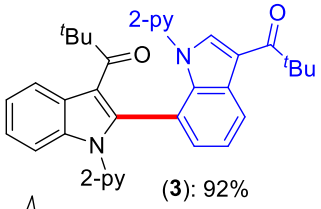
Indoles substituted with the C3 pivaloyl group, incorporating notable functionalities such as −Me and −Cl at the C5 position, yielded moderate to good yields of **15, 16**. Likewise, C3 aldehyde-substituted indoles featuring significant functionalities like −OMe and −Br at the C5 position resulted in the formation of C2–C7 homo-coupled products in good yields (**17, 18**), with trace amounts of C2–C2 coupled compounds. Similarly, the C3 pivaloyl group, incorporating functional group such as −COOMe at C4 position resulted in the formation of C2–C7 homo-coupled product **19** in 73% of yield. The compatibility of these functional groups suggests the possibility of additional derivatization to create more complex organic compounds. In addition, indoles with C2-blocked substrates produced selective C7–C7 coupled products (**20**, **21**) with moderate to good yields (Scheme 5.4). A single-crystal X-ray analysis verified the molecular structure of compounds **2**, **7**, **16**, **20**, and **21** (Figures 5.2-5.6).

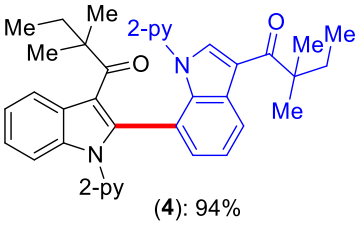


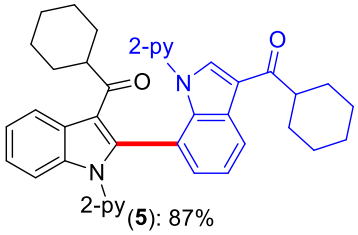
(**1**) (**2**)

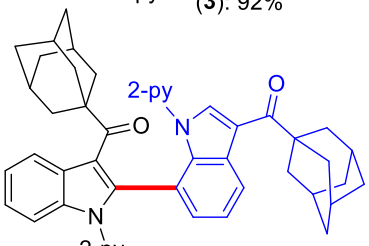

(**1**): 87%

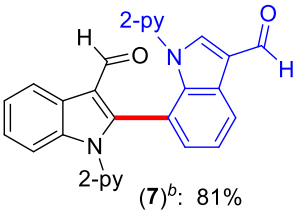

(**2**): 91%

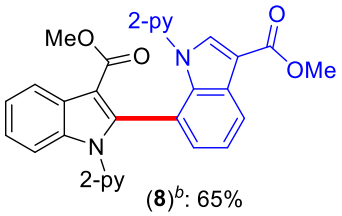

(**3**): 92%

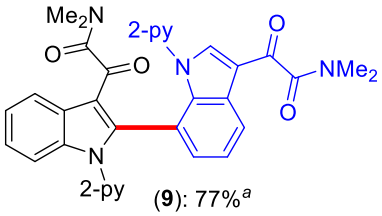

(**4**): 94%

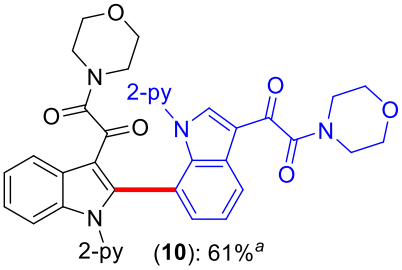

(**5**): 87%

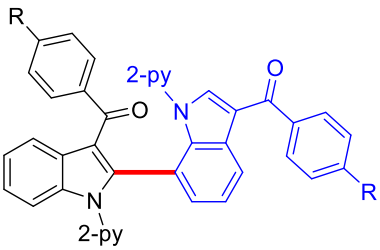

(**6**): 82%

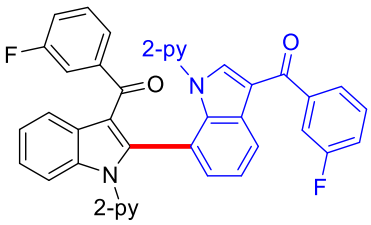

(**7**)[b]: 81%

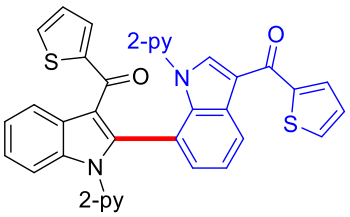

(**8**)[b]: 65%

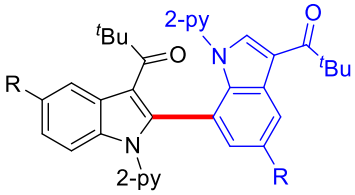

(**9**): 77%[a]

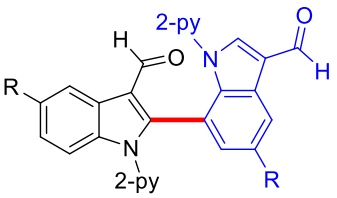

(**10**): 61%[a]

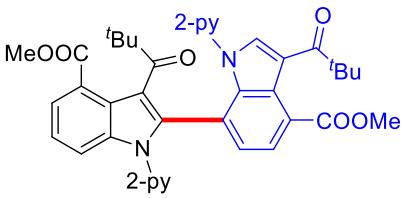

R = Me; (**11**)[b]: 71% + 18%
R = CF_3; (**12**): 57%


(**13**)[b]: 65%

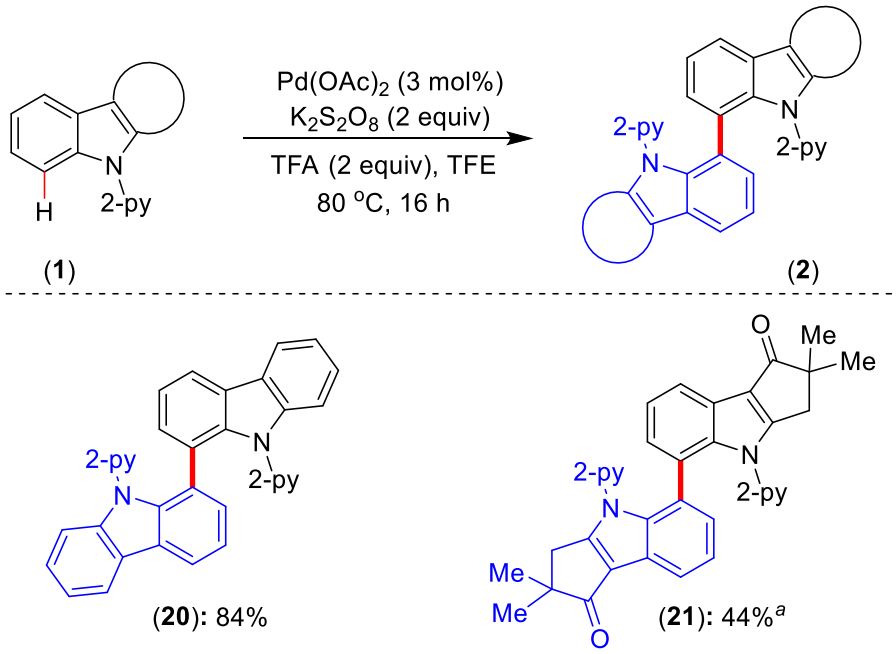

(**14**): 53%


R = Me; (**15**): 94%
R = Cl; (**16**): 83%


R = OMe; (**17**)[b]: 62%
R = Br; (**18**)[b]: 78%

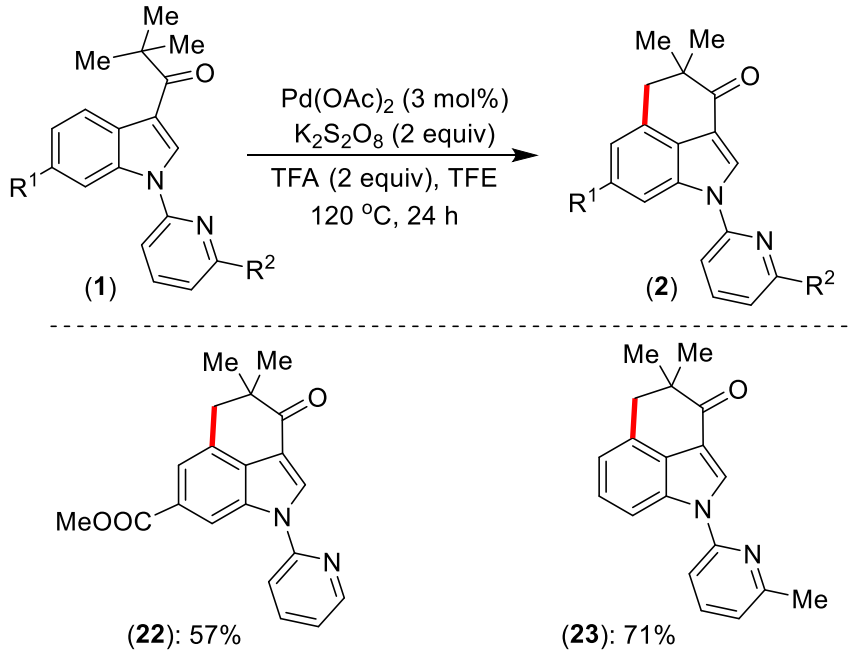

(**19**): 73%

Scheme 5.3. Scope for C(2)/C(7) Oxidative Homo-Coupling of Indole Pyridine. Conditions: Indole (0.20 mmol), $K_2S_2O_8$ (0.40 mmol), $Pd(OAc)_2$ (0.006 mmol, 3 mol%), TFA (0.40 mmol), solvent (1.0 mL). [a] Reaction performed at 120 °C for 24 h. [b] C2–C2 homo-coupled compound was obtained in minor amounts (<10%).



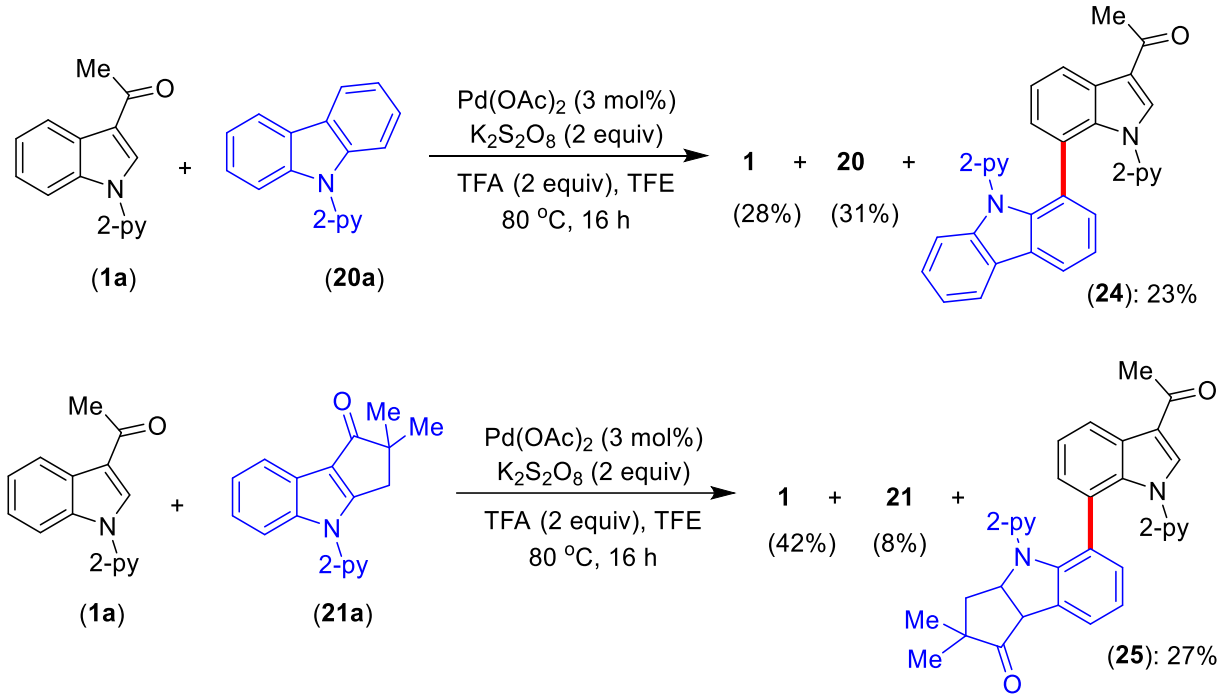
Scheme 5.4 Scope for C(7)/C(7) Oxidative Coupling of C2, C3 Substituted Indole Pyridine. Conditions: Indole (0.20 mmol), $K_2S_2O_8$ (0.40 mmol), $Pd(OAc)_2$ (0.006 mmol, 3 mol%), TFA (0.40 mmol), solvent (1.0 mL). [a] Reaction performed at 120 °C for 24 h.

Remarkably, when an ester group was placed at the C6 position or methyl group was positioned adjacent to the pyridine nitrogen of an *N*-2-pyridinyl-3-pivaloyl-indole, an intramolecular $C(sp^2)$–H/$C(sp^3)$–H oxidative coupling reaction was initiated at 120 °C, resulting in a 4,4-dimethyl-1-(pyridin-2-yl)-4,5-dihydrobenzo[*cd*]indol-3(1*H*)-one derivative (**22**, **23**) with good yields (Scheme 5.5). The steric hindrance posed by the ester and methyl groups was inhibiting the activation of C7 or C2 CH of indole. Consequently, this hindrance diverted the reaction pathway towards C4 CH activation through C3 carbonyl-directed processes, steering away from the conventional C2-C7 homocoupling route.



Scheme 5.5. Scope for Intramolecular C(sp^2)–H/C(sp^3)–H Oxidative Coupling of Indole Pyridine.

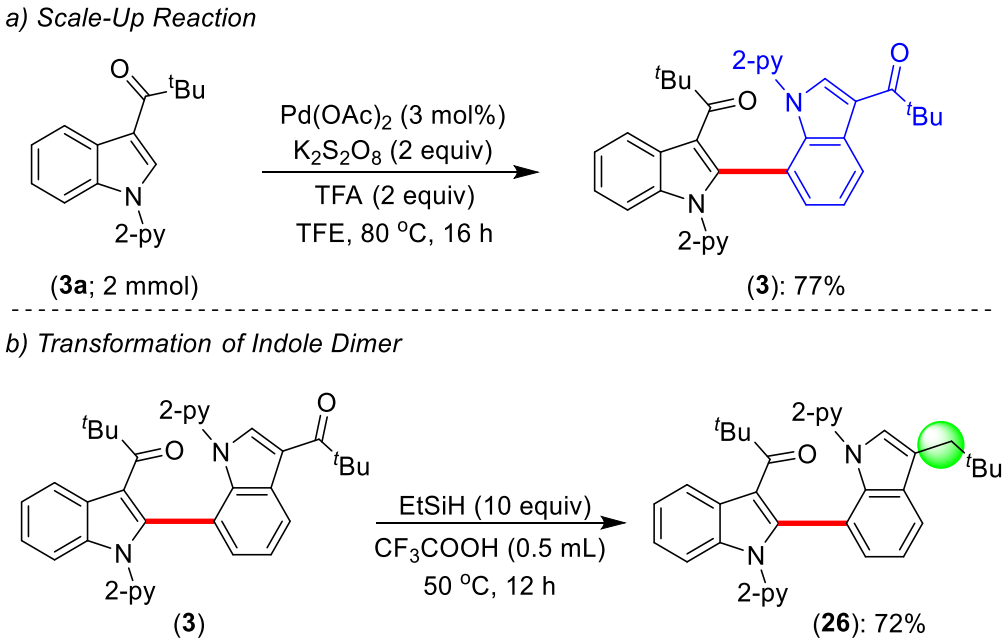
The focus then shifted to the cross-coupling of indoles (Scheme 5.6). The selective hetero-coupling of indoles holds great promise as it introduces distinct functionalities to each indole unit. However, achieving the desired hetero-coupled selectivity can pose notable challenges. Subsequently, we applied the established protocol to the hetero-coupling of substituted indole derivatives to obtain the desired products. For instance, 1-(1-(pyridin-2-yl)-1*H*-indol-3-yl)ethan-1-one (**1a**) was treated with either 9-(pyridin-2-yl)-9*H*-carbazole (**20a**) or 2,2-dimethyl-4-(pyridin-2-yl)-3,4-dihydrocyclopenta[*b*]indol-1(2*H*)-one (**21a**), resulting in the formation of the respective hetero-coupled products, **24** and **25**, with 23% and 27% yields, respectively. Notably, in addition to hetero-coupled product, homo-coupled **2** and **20** were obtained in 28% and 31% yields, respectively. The hetero-coupling reactions are attributed to the formation of two possible homo-coupled products. Nevertheless, despite the moderate yields in the hetero-coupling of indoles, the synthesis of such compounds remains profoundly significant, owing to their potential applications across various fields. The structure of compound **25** was confirmed through single-crystal X-ray analysis (Figure 5.7).



Scheme 5.6 Scope for C(2)−H/C(7)−H Hetero-Coupling of Indoles. Conditions: Both the indole derivatives were used in 1:1 ratio (0.20 mmol each), $K_2S_2O_8$ (0.216 g, 0.80 mmol), $Pd(OAc)_2$ (0.0027 g, 0.012 mmol, 3 mol%), TFA (0.091 g, 0.80 mmol), solvent (2.0 mL).

5.2.4 Scale-Up and Synthetic Transformation of Indole Dimer

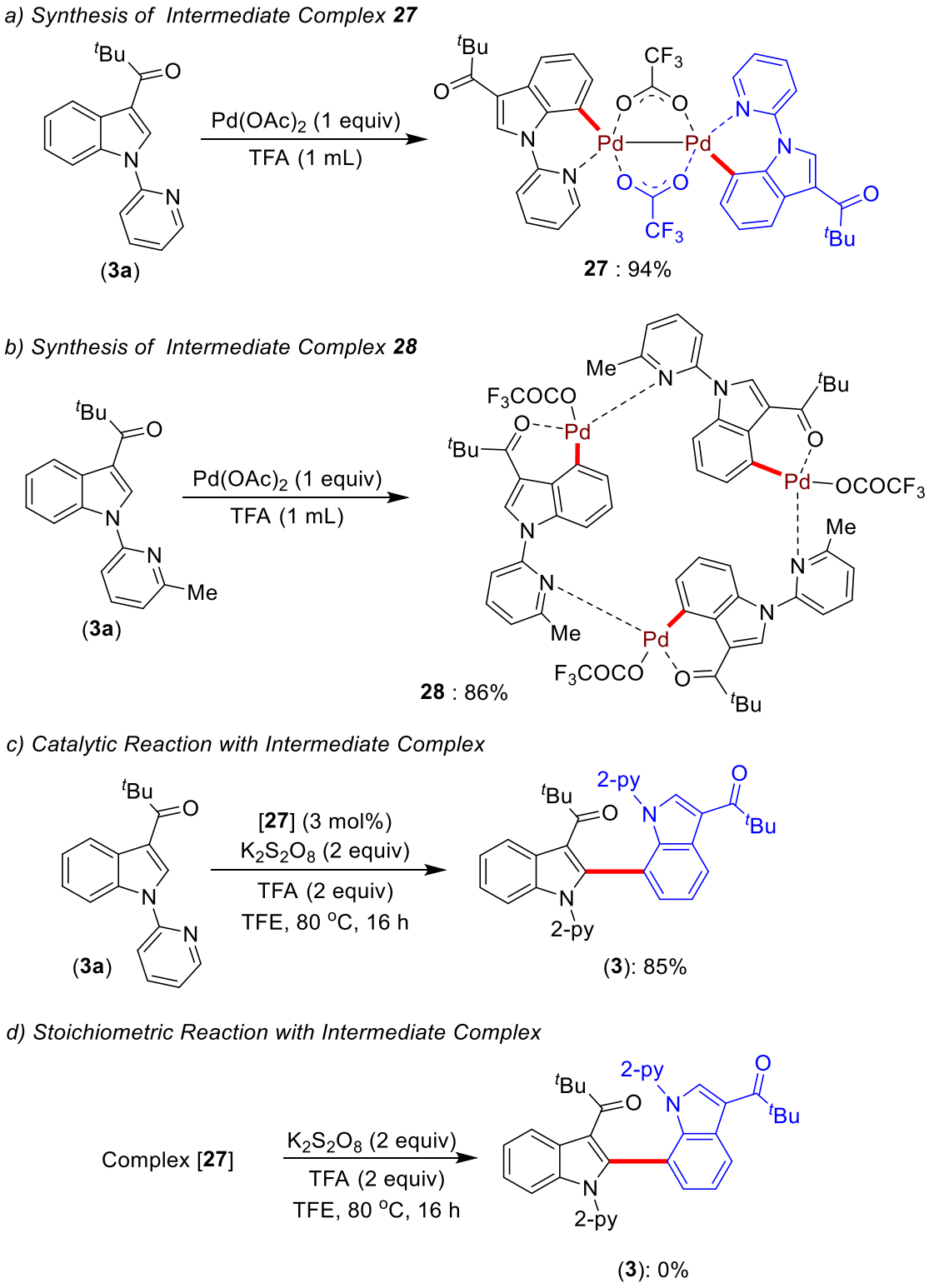
Moreover, a gram-scale reaction involving compound **3a** (2.0 mmol) furnished the homocoupled product **3** with a yield of 77%, suggesting the potential scalability of this protocol (Scheme 5.7a). Furthermore, recognizing the synthetic significance of C3 alkyl biindole, the carbonyl group of compound **3** was effectively reduced by using triethylsilyl hydride and trifluoroacetic acid, leading to the formation of **26** in 72% yield (Scheme 5.7b). The structure of compound **26** was confirmed through a single-crystal X-ray analysis (Figure 5.8).



Scheme 5.7 Gram Scale Reaction and Transformation of C(2)−H/C(7)−H Indole Dimer.

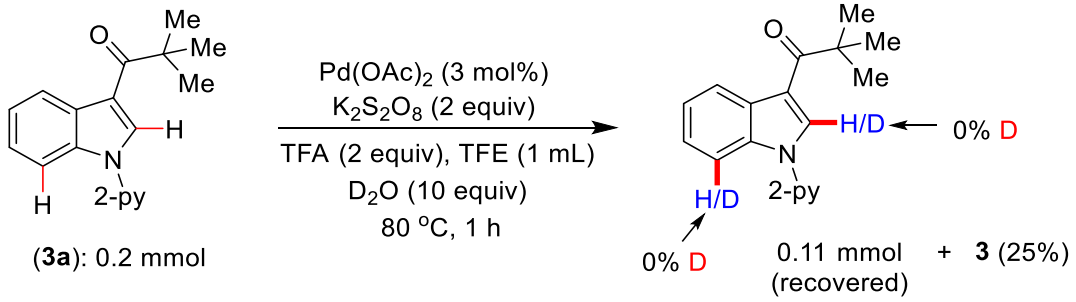
5.2.5 Mechanic Aspects

A preliminary mechanistic investigation was conducted to elucidate the active Pd-catalytic species and better understand the pathway involved in indoles C2–C7 coupling. The reaction of 2,2-dimethyl-1-(1-(pyridin-2-yl)-1*H*-indol-3-yl)propan-1-one (**3a**) with $Pd(OAc)_2$ in the presence of trifluoroacetic acid resulted in the formation of the complex (3-pivaloyl-1-(pyridin-2-yl)-1*H*-indol-2-yl)(2,2,2-trifluoroacetyl)palladium (**27**), in 94% of yield (Scheme 5.8a).[31] Likewise, the treatment of 2,2-dimethyl-1-(1-(6-methylpyridin-2-yl)-1*H*-indol-3-yl)propan-1-one (**23a**) with $Pd(OAc)_2$ in the presence of trifluoroacetic acid yielded complex **28** in good yield (Scheme 5.8b). The structures of compounds **27** and **28** were confirmed through a single-crystal X-ray analysis (Figures 5.9, 5.10). Interestingly, the catalytic reaction in the presence of complex **27** resulted in a quantitative yield of the desired product **3** (Scheme 5.8c). However, it is worth noting that the attempt to utilize a stoichiometric amount of complex **27** alone failed to produce the desired coupled product in the absence of **3a** (Scheme 5.8d)



Scheme 5.8. Preliminary Mechanistic Study.

To gain more insight into the reaction mechanism, we performed control experiments, such as *H/D* scrambling (Scheme 5.9). The use of D_2O as a co-solvent in the reaction did not show any *H/D* scrambling at C2 or C7 for compound **3a**. This observation suggests that the initial C–H cleavage is irreversible.



Scheme 5.9. *H/D* Scrambling Experiment.

5.2.6 Probable Catalytic Cycle.

We have proposed a catalytic cycle based on preliminary observation and literature precedents[13,16,17] (Figure 5.1). The process initiates with the in situ formation of the active Pd(II) complex **A**, followed by pyridine-directed C−H activation at the more nucleophilic C7 position of **1a**. This is facilitated by the resulting in the formation of a six-membered binuclear **27,** which may transform in to the mono-nuclear Pd-catalyst **27'**. We assume that steric crowding inhibits the C2−H activation due to the presence of C3 substitution. Subsequent to this, the second activation of the C−H bond at the C2 position of substrate **1a** towards the metal center results in the formation of **B** *via* a five-membered palladacycle. Further, **B** can provide C2−C7 homocoupled product and Pd(0) species upon reductive elimination. Finally, the active Pd(II) catalyst will regenerate in the presence of $K_2S_2O_8$ and TFA.

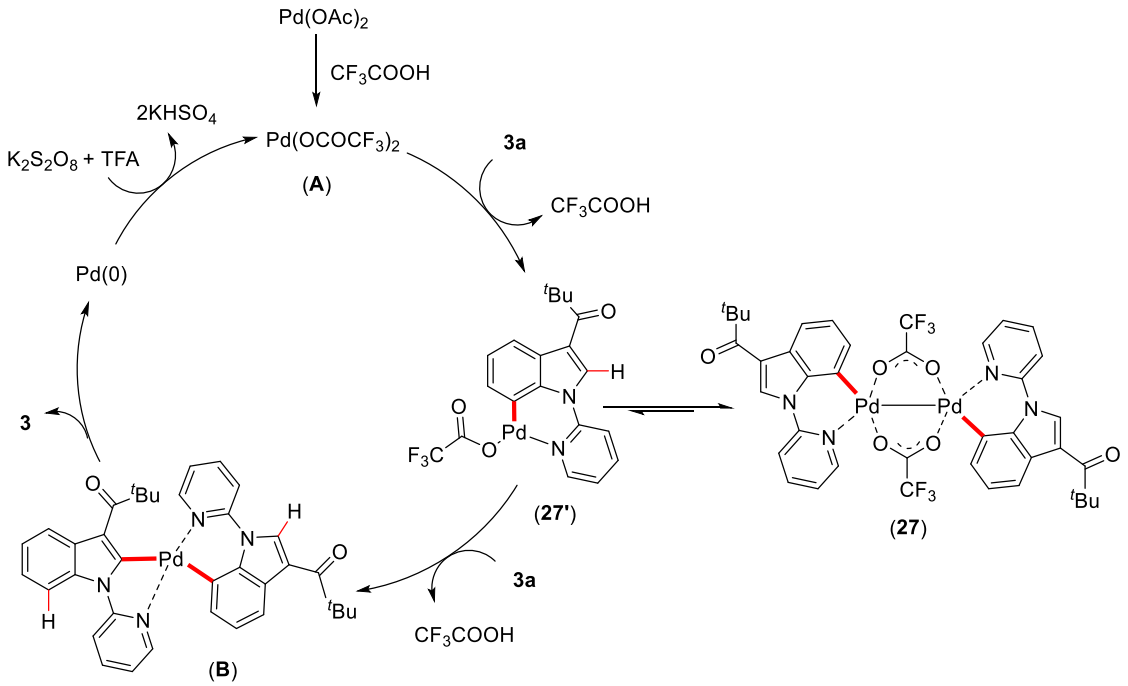


Figure 5.1. Plausible Catalytic Cycle for C(2)−H/C(7)−H Oxidative Coupling of Indoles.

5.3 CONCLUSION

In summary, we have shown the first Pd(II)-catalyzed regioselective oxidative coupling at the C2–C7 positions of C3 substituted indoles, with pyridine serving as a directing group. The C3-substituted carbonyl and *N*-pyridinyl groups emerged as pivotal factors in achieving the selective formation of C2–C7 biindoles. The reaction protocol is compatible with indole substrates having numerous functionalities at C3, C4, and C5 positions, such as halides, aldehydes, ester, trifluoromethane, as well as heteroarenes such as morpholinyl, and thiophene are well tolerated under the standard conditions. The practicality of this Pd-catalyzed method was demonstrated by reducing the carbonyl group and gram scale synthesis. The catalytically active intermediates were isolated and structurally characterized. The preliminary reaction mechanism demonstrate that the reaction proceed via initial C7–H activation follow by C2–H activation.

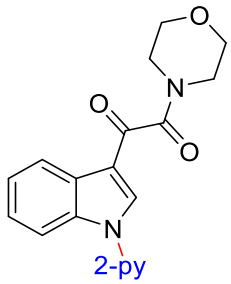
5.4 EXPERIMENTAL SECTION

5.4.1 General Information

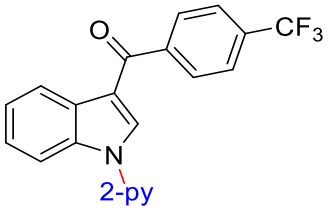
All manipulations were conducted under an argon atmosphere in a glove box or using standard Schlenk techniques in pre-dried glassware. The catalytic reactions were performed in oven-dried reaction vessels with a Teflon screw cap under open air. Solvents were dried over Na/benzophenone or CaH_2 and distilled before use. Liquid reagents were flushed with argon prior to use. The starting compounds **1a-9a**, **11a**, **13a, 15a-18a**, **and 20a-25a** were synthesized according to the previously described procedures.[31-34] All other chemicals were obtained from commercial sources and were used without further purification. High-resolution mass spectrometry (HRMS) mass spectra were recorded on a Thermo Scientific Q-Exactive Accela 1250 pump. NMR: (^{1}H and ^{13}C{^{1}H}) spectra were recorded at 400 or 500 MHz (^{1}H), 100 or 125 MHz {^{13}C{^{1}H}, DEPT (distortionless enhancement by polarization transfer)}, 377 MHz (^{19}F), respectively in $CDCl_3$ and DMSO-d_6 solutions, if not otherwise specified; chemical shifts (δ) are given in ppm. The ^{1}H and ^{13}C{^{1}H} NMR spectra are referenced to residual solvent signals ($CDCl_3$: δ H = 7.26 ppm, δ C = 77.2 ppm; DMSO-d_6: δ H = 2.50 ppm, δ C = 39.5 ppm). The splitting patterns of NMR are abbreviated as follows: s = singlet; br s = broad singlet; d = doublet; t = triplet; q = quartet; sept = septet; dd = doublet of doublets; ddd = doublet of doublet of doublets; td = triplet of doublets; m = multiplet.

5.4.2 Synthesis and Characterization of Starting Compounds

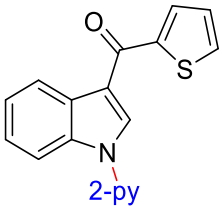
***Representative Procedure A*. Synthesis of 1-Morpholino-2-(1-(pyridin-2-yl)-1*H*-indol-3-yl)ethane-1,2-dione (10a):** In an oven-dried Schlenk flask, a solution of 1-(1*H*-indol-3-yl)-2-morpholinoethane-1,2-dione (0.50 g, 1.94 mmol) in DMF (10 mL) was slowly added to NaH (0.070 g, 2.91 mmol) in DMF (5.0 mL) at 0 ^{o}C, and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was further cooled to 0 ^{o}C, and 2-fluoropyridine (0.282 g, 2.91 mmol) was added dropwise. The resultant reaction mixture was immersed in a preheated oil bath at 100 ^{o}C and stirred for 16 h. The reaction mixture was allowed to cool to room temperature, and the reaction was quenched with the addition of sat. NH_4Cl (aq), diluted with EtOAc and washed with ice-cold water and brine. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in *vacuo*. The crude residue was purified by column chromatography on silica gel (petroleum ether/ EtOAc: 1/1) to yield **10a** (0.58 g, 89%) as a pale yellow solid.



1-Morpholino-2-(1-(pyridin-2-yl)-1*H*-indol-3-yl)ethane-1,2-dione (10a): ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.64-8.63 (m, 1H, Ar–H), 8.50 (s, 1H, Ar–H), 8.45-8.42 (m, 1H, Ar–H), 8.03 (dd, J = 6.2, 3.2 Hz, 1H, Ar–H), 7.94-7.90 (m, 1H, Ar–H), 7.61 (d, J = 8.1 Hz, 1H, Ar–H), 7.42-7.40 (m, 2H, Ar–H), 7.36 (dd, J = 7.4, 4.9 Hz, 1H, Ar–H), 3.82-3.76 (m, 4H, CH_2), 3.72-3.70 (m, 2H, CH_2), 3.60-3.58 (m, 2H, CH_2). $^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$): δ = 185.8 (CO), 165.8 (CO), 151.0 (C_q), 149.7 (CH), 139.1 (CH), 137.0 (CH), 136.2 (C_q), 127.3 (C_q), 125.3 (CH), 124.4 (CH), 122.7 (CH), 122.6 (CH), 116.4 (CH), 116.0 (C_q), 113.0 (CH), 67.2 (CH_2), 66.9 (CH_2), 46.8 (CH_2), 42.1 (CH_2). HRMS (ESI): *m/z* Calcd for $C_{19}H_{17}N_3O_3$ + H^+ $[M + H]^+$ 336.1343; Found 336.1334.

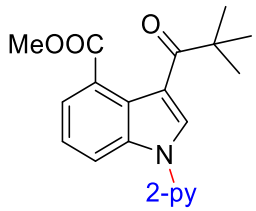


(1-(Pyridin-2-yl)-1*H*-indol-3-yl)(4-(trifluoromethyl)phenyl)methanone (12a): The representative procedure **A** was followed, using (1*H*-indol-3-yl)(4-(trifluoromethyl)phenyl)methanone (0.50 g, 1.73 mmol), NaH (0.062 g, 2.6 mmol), and 2-fluoropyridine (0.252 g, 2.60 mmol), and stirred at 100 ^{o}C in a preheated oil bath for 16 h. Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) to yield **12a** (0.61 g, 96%) as a yellow solid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.62 (dd, J = 4.8, 1.1 Hz, 1H, Ar–H), 8.53-8.50 (m, 1H, Ar–H), 8.15 (s, 1H, Ar–H), 8.04-8.01 (m, 1H, Ar–H), 7.99 (d, J = 8.1 Hz, 2H, Ar–H), 7.92 (td, J = 7.8, 1.8 Hz, 1H, Ar–H), 7.78 (d, J = 8.1 Hz, 2H, Ar–H), 7.61 (d, J = 8.1 Hz, 1H, Ar–H), 7.45-7.41 (m, 2H, Ar–H), 7.33 (dd, J = 7.4, 4.8 Hz, 1H, Ar–H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 190.2 (CO), 151.1 (C_q), 149.8 (CH), 143.7 (C_q), 139.1 (CH), 136.0 (C_q), 135.6 (CH), 133.1 (q, $^{2}J_{C–F}$ = 32.8 Hz, C_q), 129.2 (2C, CH), 128.3 (C_q), 125.7 (q, $^{3}J_{C–F}$ = 3.8 Hz, 2C, CH), 125.2 (CH), 124.1 (CH), 124.0 (q, $^{1}J_{C–F}$ = 272.4 Hz, CF_3), 123.1 (CH), 122.4 (CH), 118.1 (C_q), 116.3 (CH), 112.5 (CH). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −62.7 (s). HRMS (ESI): *m/z* Calcd for $C_{21}H_{13}N_2OF_3$ + H^+ $[M + H]^+$ 367.1053; Found 367.1040.



(1-(Pyridin-2-yl)-1*H*-indol-3-yl)(thiophen-2-yl)methanone (14a): The representative procedure **A** was followed, using (1*H*-indol-3-yl)(thiophen-2-yl)methanone (0.5 g, 2.20 mmol), NaH (0.079 g, 3.3 mmol), and 2-fluoropyridine (0.320 g, 3.30 mmol), and stirred at 100 ^{o}C in a preheated oil bath for 16 h. Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) to yield **14a** (0.55 g, 82%) as a yellow liquid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.87 (s, 1H, Ar–H), 8.66-8.64 (m, 1H, Ar–H), 8.63-8.59 (m, 1H, Ar–H), 8.04-8.01 (m, 1H, Ar–H), 7.93 (td, J = 7.8, 1.8 Hz, 1H, Ar–H), 7.66-7.64 (m, 2H, Ar–H), 7.41-7.37 (m, 3H, Ar–H), 7.33 (dd, J = 7.3, 5.1 Hz, 1H, Ar–H), 6.60 (dd, J = 3.5, 1.6 Hz, 1H, Ar–H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 176.9 (CO), 154.4 (C_q), 151.4 (C_q), 149.7

(CH), 145.4 (CH), 139.0 (CH), 135.5 (C_q), 134.5 (CH), 128.9 (C_q), 124.8 (CH), 123.8 (CH), 123.3 (CH), 122.1 (CH), 117.1 (CH), 117.0 (C_q), 116.3 (CH), 112.4 (CH), 112.3 (CH).



Methyl 3-pivaloyl-1-(pyridin-2-yl)-1*H*-indole-4-carboxylate (19a): The representative procedure **A** was followed, using methyl 3-pivaloyl-1*H*-indole-4-carboxylate (0.50 g, 1.93 mmol), NaH (0.070 g, 2.89 mmol), and 2-fluoropyridine (0.282 g, 2.90 mmol), and stirred at 100 ^{o}C in a preheated oil bath for 16 h. Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) to yield **19a** (0.57 g, 88%) as a pale yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.61 (dd, J = 4.8, 1.1 Hz, 1H, Ar–H), 8.21 (d, J = 8.4 Hz, 1H, Ar–H), 8.09 (s, 1H, Ar–H), 7.88 (td, J = 7.8, 1.8 Hz, 1H, Ar–H), 7.71-7.69 (m, 1H, Ar–H), 7.50 (d, J = 8.3 Hz, 1H, Ar–H), 7.36 (t, J = 7.9 Hz, 1H, Ar–H), 7.29-7.27 (m, 1H, Ar–H), 3.90 (s, 3H, CH_3), 1.40 (s, 9H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 205.6 (CO), 168.6 (CO), 151.4 (C_q), 149.6 (CH), 139.0 (CH), 135.6 (C_q), 128.5 (CH), 126.1 (C_q), 125.9 (C_q), 124.2 (CH), 123.6 (CH), 121.8 (CH), 119.0 (C_q), 116.1 (CH), 116.0 (CH), 52.2 (CH_3), 44.9 (C_q), 27.9 (3C, CH_3). HRMS (ESI): *m/z* Calcd for $C_{20}H_{20}N_2O_3$ + H^+ $[M + H]^+$ 337.1547; Found 337.1544.

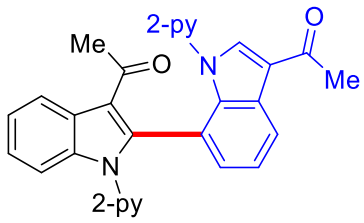
5.4.3 Procedure for the Homo-Coupling of Indoles

***Representative Procedure B*. Synthesis of 1,1'-(1,1'-Di(pyridin-2-yl)-1*H*, 1'*H*-[2,7'-biindole]-3,3'-diyl)bis(ethan-1-one) (1):** To an oven-dried screw-cap tube equipped with magnetic stir bar were introduced 1-(1-(pyridin-2-yl)-1*H*-indol-3-yl)ethan-1-one (**1a**; 0.047 g, 0.20 mmol), $K_2S_2O_8$ (0.108 g, 0.40 mmol), and $Pd(OAc)_2$ (0.0014 g, 0.006 mmol, 3.0 mol%), followed by the addition of TFA (0.046 g, 0.40 mmol) and TFE (1.0 mL). The resultant reaction mixture in the tube was immersed in a preheated oil bath at 80 °C and stirred for 16 h. The reaction mixture was allowed to cool to room temperature, and all the volatiles were removed under reduced pressure. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) to yield compound **1** (0.041 g, 87%) as a brown solid.

Procedure for Scale-up Synthesis of 3: To an oven-dried screw-cap tube equipped with a magnetic stir bar was introduced 2,2-dimethyl-1-(1-(pyridin-2-yl)-1*H*-indol-3-yl)propan-1-one (**3a**; 0.557 g, 2.0 mmol), $K_2S_2O_8$ (1.08 g, 4.0 mmol), and $Pd(OAc)_2$ (0.014 g, 0.06 mmol, 3.0 mol%), followed by the addition of TFA (0.456 g, 4.0 mmol) and TFE (10 mL). The resultant reaction mixture in the tube was immersed in a preheated oil bath at 80 °C and stirred for 16 h. The reaction mixture was allowed to cool to room temperature, and all the volatiles were removed under reduced pressure. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) to yield compound **3** (0.428 g, 77%) as an orange solid.

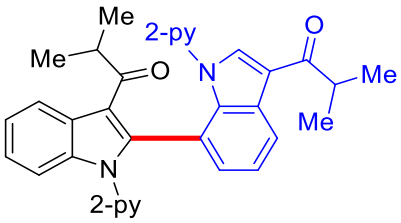
Procedure for Homocoupling of Indoles using Palladium Complex 27: To an oven-dried screw-cap tube equipped with a magnetic stir bar were introduced 2,2-dimethyl-1-(1-(pyridin-2-yl)-1*H*-indol-3-yl)propan-1-one (**3a**; 0.056 g, 0.20 mmol), $K_2S_2O_8$ (0.108 g, 0.40 mmol), and **27** (0.006 g, 0.006 mmol, 3.0 mol%), followed by the addition of TFA (0.046 g, 0.40 mmol) and TFE (1.0 mL). The resultant reaction mixture was immersed in a preheated oil bath at 80 °C and stirred for 16 h. The reaction mixture was allowed to cool to room temperature, and all the volatiles were removed under reduced pressure. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) to yield compound **3** (0.047 g, 85%) as a brown solid.

5.4.4 Characterization Data for C2–C7 Coupled Indoles

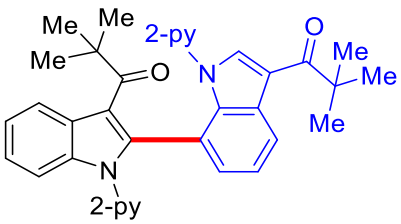


1,1'-(1,1'-Di(pyridin-2-yl)-1*H*, 1'*H*-[2,7'-biindole]-3,3'-diyl)bis(ethan-1-one) (1): ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.62 (dd, *J* = 8.1, 0.9 Hz, 1H, Ar–H), 8.56-8.54 (m, 1H, Ar–H), 8.20-8.18 (m, 1H, Ar–H), 8.12 (s, 1H, Ar–H), 7.90 (dd, *J* = 4.5, 1.3 Hz, 1H, Ar–H), 7.71 (td, *J* = 7.6, 1.9 Hz, 1H, Ar–H), 7.62-7.59 (m, 2H, Ar–H), 7.43-7.41 (m, 1H, Ar–H), 7.36-7.28 (m, 5H, Ar–H), 7.08 (d, *J* = 7.4 Hz, 1H, Ar–H), 6.84 (dd, *J* = 7.4, 4.9 Hz, 1H, Ar–H), 2.66 (s, 3H, CH_3), 1.83 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 194.4 (CO), 193.6 (CO), 151.1 (C_q), 150.5 (C_q), 149.3 (CH), 148.2 (CH), 141.3 (C_q), 138.3 (CH), 137.9 (CH), 136.6 (C_q), 136.2 (C_q), 136.1 (CH), 127.5 (C_q), 127.3 (CH), 126.6 (C_q), 124.3 (CH), 124.0 (CH),

123.2 (CH), 123.2 (CH), 123.0 (CH), 122.9 (CH), 122.5 (CH), 122.3 (CH), 119.4 (CH), 118.8 (C_q), 118.2 (C_q), 116.7 (C_q), 111.0 (CH), 29.6 (CH_3), 27.8 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{30}H_{22}N_4O_2 + H^+$ $[M + H]^+$ 471.1816; Found 471.1805.

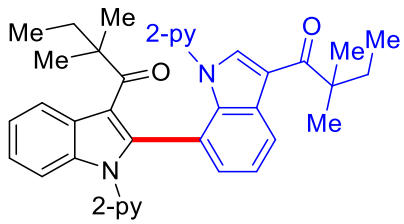


1,1'-(1,1'-Di(pyridin-2-yl)-1*H*, 1'*H*-[2,7'-biindole]-3,3'-diyl)bis(2-methylpropan-1-one) (2): The representative procedure **B** was followed, using substrate **2a** (0.053 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **2** (0.048 g, 91%) as a pale yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 8.0 Hz, 1H, Ar–H), 8.50 (d, *J* = 4.5 Hz, 1H, Ar–H), 8.04 (s, 1H, Ar–H), 7.99-7.97 (m, 1H, Ar–H), 7.73 (d, *J* = 4.6 Hz, 1H, Ar–H), 7.59 (t, *J* = 7.6 Hz, 1H, Ar–H), 7.54 (d, *J* = 7.9 Hz, 1H, Ar–H), 7.43 (d, *J* = 7.9 Hz, 1H, Ar–H), 7.37-7.30 (m, 2H, Ar–H), 7.24-7.16 (m, 4H, Ar–H), 7.00 (d, *J* = 7.3 Hz, 1H, Ar–H), 6.77-6.74 (m, 1H, Ar–H), 3.38 (sept, *J* = 6.8 Hz, 1H, CH), 2.47 (sept, *J* = 6.8 Hz, 1H, CH), 1.37-1.27 (m, 6H, CH_3), 0.81 (d, *J* = 6.6 Hz, 3H, CH_3), 0.78 (d, *J* = 7.0 Hz, 3H, CH_3).^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 201.7 (CO), 201.0 (CO), 151.2 (C_q), 150.7 (C_q), 149.2 (CH), 147.8 (CH), 140.6 (C_q), 138.3 (CH), 137.9 (CH), 136.8 (C_q), 136.2 (C_q), 135.2 (CH), 128.0 (C_q), 127.4 (CH), 126.8 (C_q), 124.3 (CH), 123.8 (CH), 123.1 (CH), 123.0 (CH), 122.8 (CH), 122.6 (CH), 122.6 (CH), 121.9 (CH), 119.3 (CH), 117.3 (C_q), 116.9 (C_q), 116.8 (C_q), 111.2 (CH), 37.7 (CH), 37.5 (CH), 20.2 (CH_3), 20.0 (CH_3), 19.8 (CH_3), 17.8 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{34}H_{30}N_4O_2 + H^+$ $[M + H]^+$ 527.2442; Found 527.2446.

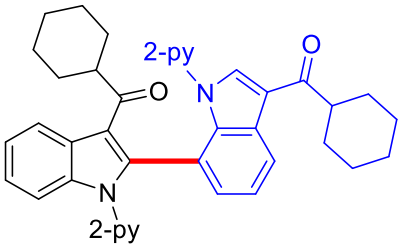


1,1'-(1,1'-Di(pyridin-2-yl)-1*H*,1'*H*-[2,7'-biindole]-3,3'-diyl)bis(2,2-dimethylpropan-1-one) (3): The representative procedure **B** was followed, using substrate **3a** (0.056 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **3** (0.051 g, 92%) as a brown solid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.67 (d, *J* = 8.0

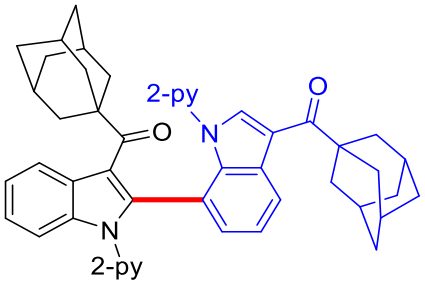
Hz, 1H, Ar–H), 8.51 (d, *J* = 4.5 Hz, 1H, Ar–H), 8.18 (s, 1H, Ar–H), 8.05 (d, *J* = 4.6 Hz, 1H, Ar–H), 7.71 (d, *J* = 8.0 Hz, 1H, Ar–H), 7.59-7.55 (m, 2H, Ar–H), 7.47 (d, *J* = 7.5 Hz, 1H, Ar–H), 7.34-7.15 (m, 7H, Ar–H), 6.88 (t, *J* = 6.1 Hz, 1H, Ar–H), 1.49 (s, 9H, CH_3), 1.08 (s, 9H, CH_3). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 210.1 (CO), 203.0 (CO), 150.5 (C_q), 150.2 (C_q), 148.8 (CH), 146.6 (CH), 138.2 (CH), 137.9 (CH), 136.1 (C_q), 135.4 (C_q), 134.7 (CH), 134.6 (C_q), 130.4 (C_q), 128.1 (CH), 126.6 (C_q), 124.6 (CH), 123.5 (CH), 122.9 (CH), 122.3 (CH), 122.1 (CH), 121.9 (CH), 121.2 (CH), 120.4 (CH), 119.5 (CH), 119.5 (C_q), 116.7 (C_q), 115.1 (C_q), 111.8 (CH), 44.8 (C_q), 44.7 (C_q), 28.9 (3C, CH_3), 27.4 (3C, CH_3). HRMS (ESI): *m/z* Calcd for $C_{36}H_{34}N_4O_2 + H^+$ $[M + H]^+$ 555.2755; Found 555.2759.



1,1'-(1,1'-Di(pyridin-2-yl)-1*H*, 1'*H*-[2,7'-biindole]-3,3'-diyl)bis(2,2-dimethylbutan-1-one) (4): The representative procedure **B** was followed, using substrate **4a** (0.059 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **4** (0.055 g, 94%) as a yellow liquid. ^1H-NMR (500 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 8.0 Hz, 1H, Ar–H), 8.47 (d, *J* = 4.5 Hz, 1H, Ar–H), 8.11 (s, 1H, Ar–H), 7.97 (d, *J* = 4.6 Hz, 1H, Ar–H), 7.68 (d, *J* = 8.1 Hz, 1H, Ar–H), 7.56 (t, *J* = 7.7 Hz, 1H, Ar–H), 7.46 (d, *J* = 8.1 Hz, 1H, Ar–H), 7.38-7.11 (m, 7H, Ar–H), 7.06 (d, *J* = 7.4 Hz, 1H, Ar–H), 6.81 (t, *J* = 6.0 Hz, 1H, Ar–H), 1.87 (q, *J* = 7.5 Hz, 2H, CH_2), 1.42 (m, 8H, CH_2, CH_3), 0.93 (s, 3H, CH_3), 0.85 (t, *J* = 7.4 Hz, 3H, CH_3), 0.83 (s, 3H, CH_3), 0.56 (t, *J* = 7.4 Hz, 3H, CH_3). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 209.8 (CO), 203.0 (CO), 150.5 (C_q), 150.1 (C_q), 148.8 (CH), 146.3 (CH), 138.4 (CH), 138.2 (CH), 136.2 (C_q), 135.0 (C_q), 134.8 (C_q), 134.1 (CH), 130.4 (C_q), 128.2 (CH), 126.7 (C_q), 124.5 (CH), 123.5 (CH), 123.0 (CH), 122.5 (CH), 122.1 (CH), 121.9 (CH), 121.6 (CH), 120.4 (CH), 119.7 (C_q), 119.6 (CH), 116.8 (C_q), 115.9 (C_q), 111.5 (CH), 48.6 (C_q), 48.4 (C_q), 34.9 (CH_2), 32.8 (CH_2), 26.3 (CH_3), 26.2 (CH_3), 24.6 (CH_3), 24.4 (CH_3), 9.4 (CH_3), 8.9 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{38}H_{38}N_4O_2 + H^+$ $[M + H]^+$ 583.3068; Found 583.3054.

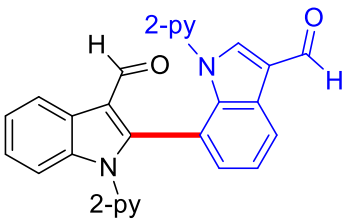


(1,1'-Di(pyridin-2-yl)-1*H*,1'*H*-[2,7'-biindole]-3,3'-diyl)bis(cyclohexylmethanone) (5): The representative procedure **B** was followed, using substrate **5a** (0.061 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **5** (0.053 g, 87%) as a yellow liquid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.58 (d, J = 8.0 Hz, 1H, Ar–H), 8.51 (br s, 1H, Ar–H), 8.09 (s, 1H, Ar–H), 8.06-8.04 (m, 1H, Ar–H), 7.81 (br s, 1H, Ar–H), 7.68-7.59 (m, 2H, Ar–H), 7.51 (d, J = 7.9 Hz, 1H, Ar–H), 7.35-7.18 (m, 6H, Ar–H), 6.99 (d, J = 7.3 Hz, 1H, Ar–H), 6.78-6.75 (m, 1H, Ar–H), 3.31-3.07 (m, 1H, CH), 2.11-1.85 (m, 4H, CH_2), 1.76-1.50 (m, 4H, CH_2), 1.45-1.21 (m, 8H, CH_2), 1.05-0.86 (m, 3H, CH_2, CH), 0.59-0.42 (m, 2H, CH_2). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 201.0 (CO), 200.4 (CO), 151.0 (C_q), 150.6 (C_q), 149.3 (CH), 147.8 (CH), 140.4 (C_q), 138.5 (CH), 138.1 (CH), 136.7 (C_q), 136.3 (C_q), 135.2 (CH), 128.1 (C_q), 127.4 (CH), 127.0 (C_q), 124.4 (CH), 123.9 (CH), 123.2 (CH), 123.1 (CH), 122.9 (CH), 122.7 (2C, CH), 122.2 (CH), 119.5 (CH), 117.5 (C_q), 117.0 (C_q), 116.8 (C_q), 111.0 (CH), 48.3 (CH), 48.1 (CH), 30.8 (CH_2), 30.0 (CH_2), 30.0 (CH_2), 27.7 (CH_2), 26.1 (CH_2), 26.1 (2C, CH_2), 26.1 (CH_2), 25.8 (CH_2), 25.7 (CH_2). HRMS (ESI): *m/z* Calcd for $C_{40}H_{38}N_4O_2 + H^+$ $[M + H]^+$ 607.3068; Found 607.3054.

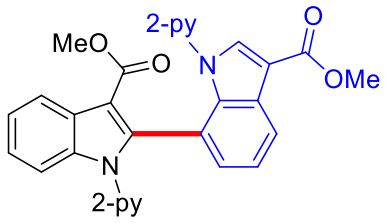


(1,1'-Di(pyridin-2-yl)-1*H*,1'*H*-[2,7'-biindole]-3,3'-diyl)bis(((3r,5r,7r)-adamantan-1-yl)methanone) (6): The representative procedure **B** was followed, using substrate **6a** (0.071 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **6** (0.058 g, 82%) as a pale yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.62 (dd, J = 8.1, 1.2 Hz, 1H, Ar–H), 8.51-8.49 (m, 1H, Ar–H), 8.26 (s, 1H, Ar–H), 7.96-7.94 (m, 1H, Ar–H), 7.64 (d, J = 8.0 Hz, 1H, Ar–H), 7.58 (d, J = 8.0 Hz, 1H, Ar–H), 7.54 (td, J = 7.8, 1.9 Hz, 1H, Ar–H), 7.43-7.40 (m, 1H, Ar–H), 7.32-7.27 (m, 3H, Ar–H), 7.25-7.20 (m, 1H,

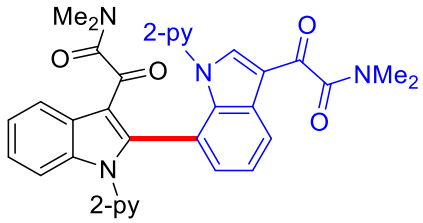
Ar–H), 7.19-7.13 (m, 3H, Ar–H), 6.80 (ddd, *J* = 7.4, 4.9, 0.9 Hz, 1H, Ar–H), 2.21-2.16 (m, 6H, CH_2, 3H, CH), 1.96-1.93 (m, 2H, CH_2), 1.91-1.80 (m, 6H, CH_2, 3H, CH), 1.79-1.73 (m, 2H, CH_2), 1.70-1.64 (m, 4H, CH_2), 1.57-1.49 (m, 4H, CH_2). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 209.9 (CO), 203.0 (CO), 150.8 (C_q), 150.8 (C_q), 148.8 (CH), 147.1 (CH), 138.0 (CH), 137.3 (CH), 136.0 (C_q), 134.7 (C_q), 134.5 (C_q), 134.5 (CH), 130.6 (C_q), 128.3 (CH), 126.9 (C_q), 124.4 (CH), 123.3 (CH), 122.7 (CH), 122.1 (CH), 121.9 (CH), 121.6 (CH), 121.1 (CH), 120.3 (CH), 119.3 (C_q), 119.2 (CH), 116.8 (C_q), 115.0 (C_q), 111.8 (CH), 47.5 (C_q), 47.2 (C_q), 40.6 (3C, CH_2), 38.5 (3C, CH_2), 37.0 (3C, CH_2), 36.6 (3C, CH_2), 28.6 (3C, CH), 28.2 (3C, CH). HRMS (ESI): *m/z* Calcd for $C_{48}H_{46}N_4O_2 + H^+$ $[M + H]^+$ 711.3694; Found 711.3691.



1,1'-Di(pyridin-2-yl)-1*H*, 1'*H*-[2,7'-biindole]-3,3'-dicarbaldehyde (7): The representative procedure **B** was followed, using substrate **7a** (0.045 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **7** (0.036 g, 81%) as a pale yellow solid. ^1H-NMR (400 MHz, $CDCl_3$): δ = 10.16 (s, 1H, CHO), 9.50 (s, 1H, CHO), 8.57 (dd, *J* = 4.8, 1.3 Hz, 1H, Ar–H), 8.51 (dd, *J* = 7.9, 1.0 Hz, 1H, Ar–H), 8.11-8.08 (m, 1H, Ar–H), 8.06 (s, 1H, Ar–H), 7.79 (dd, *J* = 4.7, 1.0 Hz, 1H, Ar–H), 7.62 (td, *J* = 7.8, 1.9 Hz, 1H, Ar–H), 7.53-7.41 (m, 4H, Ar–H), 7.33-7.25 (m, 4H, Ar–H), 7.14 (dd, *J* = 7.4, 1.0 Hz, 1H, Ar–H), 6.82-6.79 (m, 1H, Ar–H). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 186.3 (CO), 185.3 (CO), 150.9 (C_q), 150.2 (C_q), 149.3 (CH), 148.1 (CH), 146.1 (C_q), 139.7 (CH), 138.6 (CH), 138.5 (CH), 137.0 (C_q), 136.1 (C_q), 129.0 (CH), 127.0 (C_q), 125.0 (C_q), 124.7 (CH), 124.1 (CH), 123.9 (CH), 123.5 (CH), 123.2 (CH), 123.0 (CH), 121.8 (CH), 121.7 (CH), 120.1 (C_q), 118.7 (CH), 117.3 (C_q), 114.3 (C_q), 111.7 (CH). HRMS (ESI): *m/z* Calcd for $C_{28}H_{18}N_4O_2 + H^+$ $[M + H]^+$ 443.1503; Found 443.1486.

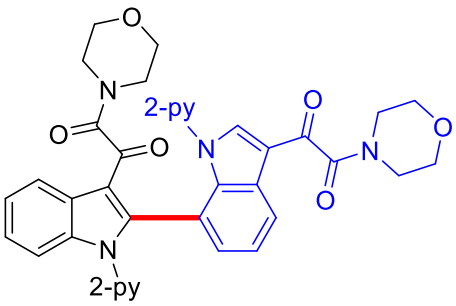


Dimethyl 1,1'-di(pyridin-2-yl)-1*H*, 1'*H*-[2,7'-biindole]-3,3'-dicarboxylate (8): The representative procedure **B** was followed, using substrate **8a** (0.076 g, 0.30 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **8** (0.049 g, 65%) as a brown solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.57 (d, *J* = 4.6 Hz, 1H, Ar–H), 8.28 (d, *J* = 8.0 Hz, 1H, Ar–H), 8.10 (s, 1H, Ar–H), 7.91 (d, *J* = 7.6 Hz, 1H, Ar–H), 7.66-7.61 (m, 2H, Ar–H), 7.57 (t, *J* = 7.7 Hz, 1H, Ar–H), 7.50-7.45 (m, 2H, Ar–H), 7.38 (d, *J* = 8.0 Hz, 1H, Ar–H), 7.24-7.19 (m, 3H, Ar–H), 7.14 (t, *J* = 7.7 Hz, 1H, Ar–H), 6.90 (d, *J* = 7.3 Hz, 1H, Ar–H), 6.75 (t, *J* = 6.0 Hz, 1H, Ar–H), 3.95 (s, 3H, CH_3), 3.51 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 165.4 (CO), 164.7 (CO), 151.7 (C_q), 150.9 (C_q), 149.1 (CH), 147.4 (CH), 142.1 (C_q), 138.3 (CH), 138.0 (CH), 136.5 (C_q), 135.5 (C_q), 135.0 (CH), 127.6 (C_q), 127.0 (CH), 126.7 (C_q), 123.7 (CH), 122.9 (CH), 122.7 (CH), 122.7 (CH), 122.6 (CH), 122.4 (CH), 122.1 (CH), 121.5 (CH), 118.7 (CH), 117.1 (C_q), 111.5 (CH), 109.8 (C_q), 108.2 (C_q), 51.4 (CH_3), 50.8 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{30}H_{22}N_4O_4$ + H^+ $[M + H]^+$ 503.1714; Found 503.1700.

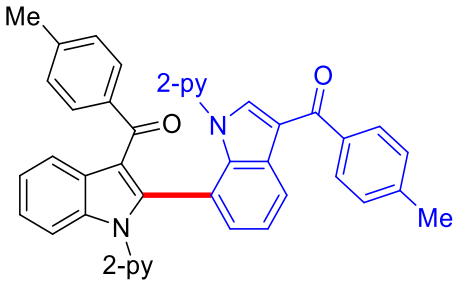


2,2'-(1,1'-Di(pyridin-2-yl)-1*H*, 1'*H*-[2,7'-biindole]-3,3'-diyl)bis(*N*,*N*-dimethyl-2-oxoacetamide) (9): The representative procedure **B** was followed, using substrate **9a** (0.059 g, 0.20 mmol) at 120 ^{o}C for 24 h. Purification by column chromatography on silica gel (petroleum ether/EtOAc: 1/2) yielded **9** (0.045 g, 77%) as a brown solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.56-8.54 (m, 1H, Ar–H), 8.52 (dd, *J* = 8.0, 1.1 Hz, 1H, Ar–H), 8.19 (s, 1H, Ar–H), 8.13-8.10 (m, 1H, Ar–H), 7.78 (d, *J* = 7.9 Hz, 1H, Ar–H), 7.61-7.54 (m, 4H, Ar–H), 7.43-7.41 (m, 1H, Ar–H), 7.30-7.27 (m, 2H, Ar–H), 7.26-7.21 (m, 1H, Ar–H), 7.19-7.22 (m, 1H, Ar–H), 7.06 (dd, *J* = 7.4, 1.1 Hz, 1H, Ar–H), 6.75 (ddd, *J* = 7.5, 4.8, 0.9 Hz, 1H, Ar–H), 3.15 (s, 3H, CH_3), 3.10 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 2.24 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 187.5 (CO), 186.3 (CO), 167.1 (CO), 167.1 (CO), 150.9 (C_q), 150.1 (C_q),

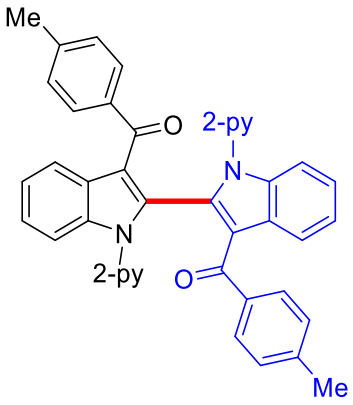
149.1 (CH), 146.9 (CH), 143.8 (C_q), 140.3 (CH), 138.6 (CH), 138.6 (CH), 136.9 (C_q), 136.2 (C_q), 127.7 (C_q), 127.5 (CH), 126.4 (C_q), 124.8 (CH), 124.4 (CH), 124.0 (CH), 123.5 (CH), 122.8 (CH), 122.4 (CH), 122.3 (CH), 121.7 (CH), 120.6 (CH), 114.8 (C_q), 114.8 (C_q), 114.2 (C_q), 111.8 (CH), 37.9 (CH_3), 36.8 (CH_3), 34.8 (CH_3), 33.2 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{34}H_{28}N_6O_4 + H^+$ $[M + H]^+$ 585.2245; Found 585.2241.



2,2'-(1,1'-Di(pyridin-2-yl)-1*H*, 1'*H*-[2,7'-biindole]-3,3'-diyl)bis(1-morpholinoethane-1,2-dione) (10): The representative procedure **B** was followed, using substrate **10a** (0.067 g, 0.20 mmol) at 120 ^oC for 24 h. Purification by column chromatography on silica gel (petroleum ether/EtOAc: 1/3) yielded **10** (0.041 g, 61%) as a pale yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.57 (d, *J* = 4.9 Hz, 1H, Ar–H), 8.51 (dd, *J* = 8.0, 0.9 Hz, 1H, Ar–H), 8.19 (s, 1H, Ar–H), 8.06-8.03 (m, 1H, Ar–H), 7.72 (d, *J* = 7.9 Hz, 1H, Ar–H), 7.59-7.53 (m, 4H, Ar–H), 7.42-7.39 (m, 1H, Ar–H), 7.31-7.24 (m, 4H, Ar–H), 7.08 (d, *J* = 6.8 Hz, 1H, Ar–H), 6.77 (dd, *J* = 6.9, 5.1 Hz, 1H, Ar–H), 3.80-3.72 (m, 6H, CH_2), 3.70-3.59 (m, 2H, CH_2), 3.50-3.43 (m, 2H, CH_2), 3.36-3.27 (m, 2H, CH_2), 3.25-3.14 (m, 2H, CH_2), 3.05-2.99 (m, 1H, CH_2), 2.65-2.61 (m, 1H, CH_2). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 186.7 (CO), 185.4 (CO), 165.7 (CO), 165.5 (CO), 150.9 (C_q), 150.0 (C_q), 149.2 (CH), 147.1 (CH), 143.7 (C_q), 140.2 (CH), 138.6 (2C, CH), 136.9 (C_q), 136.4 (C_q), 128.0 (CH), 127.5 (C_q), 126.1 (C_q), 124.9 (CH), 124.4 (CH), 124.1 (CH), 123.6 (CH), 123.0 (CH), 122.7 (CH), 122.3 (CH), 121.5 (CH), 120.5 (CH), 114.9 (C_q), 114.8 (C_q), 114.2 (C_q), 111.8 (CH), 67.1 (CH_2), 66.9 (CH_2), 66.3 (CH_2), 66.1 (CH_2), 46.8 (CH_2), 45.8 (CH_2), 42.2 (CH_2), 40.6 (CH_2). HRMS (ESI): *m/z* Calcd for $C_{38}H_{32}N_6O_6 + H^+$ $[M + H]^+$ 669.2456; Found 669.2451.

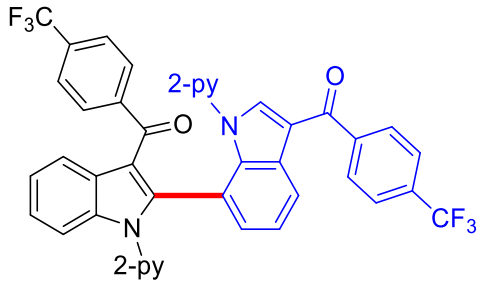


(1,1'-Di(pyridin-2-yl)-1*H*,1'*H*-[2,7'-biindole]-3,3'-diyl)bis(*p*-tolylmethanone) (11): The representative procedure **B** was followed, using substrate **11a** (0.063 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **11** (0.044 g, 71%) as a pale yellow solid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.59 (d, J = 4.5 Hz, 1H, Ar–H), 8.23 (d, J = 8.0 Hz, 1H, Ar–H), 7.79-7.77 (m, 3H, Ar–H), 7.73-7.68 (m, 3H, Ar–H), 7.63 (t, J = 7.8 Hz, 1H, Ar–H), 7.53 (d, J = 8.0 Hz, 2H, Ar–H), 7.39 (t, J = 7.7 Hz, 1H, Ar–H), 7.33 (d, J = 7.6 Hz, 2H, Ar–H), 7.27-7.23 (m, 2H, Ar–H), 7.20-7.16 (m, 3H, Ar–H), 7.10 (t, J = 7.6 Hz, 1H, Ar–H), 6.94 (d, J = 7.4 Hz, 1H, Ar–H), 6.75 (t, J = 6.1 Hz, 1H, Ar–H), 6.71 (d, J = 7.6 Hz, 2H, Ar–H), 2.46 (s, 3H, CH_3), 2.13 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 192.3 (CO), 190.9 (CO), 151.0 (C_q), 150.9 (C_q), 149.2 (CH), 147.3 (CH), 142.3 (C_q), 141.9 (C_q), 141.4 (C_q), 138.4 (CH), 138.0 (CH), 137.8 (C_q), 137.1 (CH), 136.7 (C_q), 136.5 (2C, C_q), 135.8 (C_q), 129.3 (2C, CH), 129.1 (2C, CH), 129.0 (C_q), 128.3 (CH), 128.1 (2C, CH), 127.6 (2C, CH), 124.0 (CH), 123.3 (CH), 123.0 (CH), 122.8 (2C, CH), 122.6 (CH), 122.0 (CH), 121.8 (CH), 118.1 (CH), 117.7 (C_q), 117.1 (C_q), 116.9 (C_q), 111.3 (CH), 21.8 (CH_3), 21.5 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{42}H_{30}N_4O_2 + H^+$ $[M + H]^+$ 623.2442; Found 623.2444.

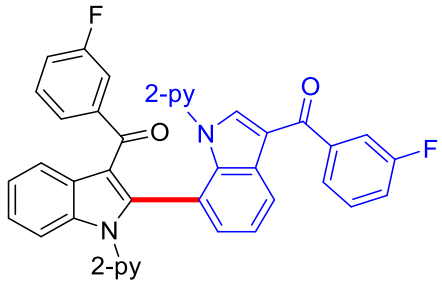


(1,1'-Di(pyridin-2-yl)-1*H*,1'*H*-[2,2'-biindole]-3,3'-diyl)bis(*p*-tolylmethanone) (11'): Yield **11'** (0.011 g, 18%) as a yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.34 (d, J = 4.6 Hz, 2H, Ar–H), 7.56-7.48 (m, 10H, Ar–H), 7.34 (d, J = 8.0 Hz, 2H, Ar–H), 7.19 (t, J = 7.7 Hz,

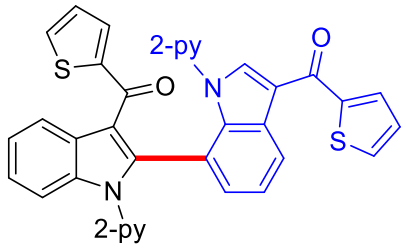
2H, Ar–H), 7.14-7.07 (m, 4H, Ar–H), 6.97 (d, J = 7.9 Hz, 4H, Ar–H), 2.25 (s, 6H, CH_3). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 191.7 (2C, CO), 150.4 (2C, C_q), 148.9 (2C, CH), 142.8 (2C, C_q), 138.3 (2C, CH), 136.7 (2C, C_q), 136.4 (2C, C_q), 133.1 (2C, C_q), 130.0 (4C, CH), 128.5 (4C, CH), 127.1 (2C, C_q), 124.2 (2C, CH), 122.6 (2C, CH), 122.4 (2C, CH), 121.6 (2C, CH), 121.5 (2C, CH), 120.2 (2C, C_q), 112.0 (2C, CH), 21.7 (2C, CH_3). HRMS (ESI): *m/z* Calcd for $C_{42}H_{30}N_4O_2 + H^+$ $[M + H]^+$ 623.2442; Found 623.2432.



(1,1'-Di(pyridin-2-yl)-1*H*,1'*H*-[2,7'-biindole]-3,3'-diyl)bis((4-(trifluoromethyl)phenyl)methanone) (12): The representative procedure **B** was followed, using substrate **12a** (0.073 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **12** (0.042 g, 57%) as a brown solid. ^1H-NMR (500 MHz, $CDCl_3$): δ = 8.58-8.54 (m, 1H, Ar–H), 8.21 (dd, J = 8.0, 1.0 Hz, 1H, Ar–H), 7.93-7.91 (m, 3H, Ar–H), 7.87 (dd, J = 4.8, 1.1 Hz, 1H, Ar–H), 7.80 (d, J = 8.1 Hz, 2H, Ar–H), 7.77-7.75 (m, 2H, Ar–H), 7.73 (s, 1H, Ar–H), 7.60 (d, J = 8.0 Hz, 1H, Ar–H), 7.48 (d, J = 8.1 Hz, 1H, Ar–H), 7.34-7.25 (m, 6H, Ar–H), 7.13-7.09 (m, 3H, Ar–H), 6.92-6.90 (m, 1H, Ar–H), 6.80 (dd, J = 6.9, 5.2 Hz, 1H, Ar–H). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 191.2 (CO), 189.4 (CO), 150.6 (C_q), 150.6 (C_q), 149.6 (CH), 147.9 (CH), 143.5 (C_q), 142.3 (C_q), 142.1 (C_q), 138.7 (CH), 138.0 (CH), 137.4 (CH), 137.3 (C_q), 136.9 (C_q), 135.8 (C_q), 133.3 (q, $^2J_{C–F}$ = 32.8 Hz, C_q), 131.8 (q, $^2J_{C–F}$ = 32.8 Hz, C_q), 129.0 (CH), 128.9 (2C, CH), 128.5 (C_q), 128.2 (CH), 127.8 (2C, CH), 127.2 (C_q), 125.8 (q, $^3J_{C–F}$ = 3.2 Hz, 2C, CH), 124.5 (CH), 124.0 (q, $^1J_{C–F}$ = 273.1 Hz, CF_3), 124.0 (CH), 123.7 (q, $^1J_{C–F}$ = 273.1 Hz, CF_3), 123.5 (q, $^3J_{C–F}$ = 3.2 Hz, 2C, CH), 123.5 (CH), 123.1 (CH), 122.7 (CH), 122.5 (CH), 122.0 (CH), 118.3 (CH), 117.4 (C_q), 116.7 (C_q), 111.1 (CH). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −62.9 (s), −63.3 (s). HRMS (ESI): *m/z* Calcd for $C_{42}H_{24}N_4O_2F_6 + H^+$ $[M + H]^+$ 731.1876; Found 731.1856.

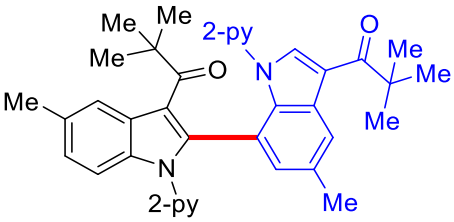


(1,1'-Di(pyridin-2-yl)-1*H*,1'*H*-[2,7'-biindole]-3,3'-diyl)bis((3-fluorophenyl)methanone) (13): The representative procedure **B** was followed, using substrate **13a** (0.063 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **13** (0.041 g, 65%) as a yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.58 (dd, *J* = 4.8, 0.9 Hz, 1H, Ar–H), 8.21 (dd, *J* = 8.0, 1.1 Hz, 1H, Ar–H), 7.86 (d, *J* = 7.6 Hz, 1H, Ar–H), 7.80-7.74 (m, 3H, Ar–H), 7.70 (td, *J* = 7.7, 1.8 Hz, 1H, Ar–H), 7.65 (d, *J* = 7.6 Hz, 1H, Ar–H), 7.57-7.54 (m, 2H, Ar–H), 7.52-7.48 (m, 2H, Ar–H), 7.38 (td, *J* = 7.8, 1.8 Hz, 1H, Ar–H), 7.32-7.26 (m, 3H, Ar–H), 7.22 (vt, *J* = 7.5 Hz, 1H, Ar–H), 7.11 (t, *J* = 7.8 Hz, 1H, Ar–H), 7.00-6.97 (m, 1H, Ar–H), 6.93 (d, *J* = 7.5, 2H, Ar–H), 6.84-6.71 (m, 3H, Ar–H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 191.0 (d, $^{4}J_{C-F}$ = 2.3 Hz, CO), 189.6 (d, $^{4}J_{C-F}$ = 2.3 Hz, CO), 162.8 (d, $^{1}J_{C-F}$ = 257.9 Hz, C_q), 161.8 (d, $^{1}J_{C-F}$ = 246.4 Hz, C_q), 150.8 (C_q), 149.5 (CH), 147.6 (CH), 142.5 (C_q), 142.4 (d, $^{3}J_{C-F}$ = 6.1 Hz, C_q), 142.1 (C_q), 141.3 (d, $^{3}J_{C-F}$ = 6.1 Hz, C_q), 138.5 (CH), 138.1 (CH), 137.4 (CH), 136.8 (C_q), 135.8 (C_q), 130.4 (d, $^{3}J_{C-F}$ = 7.6 Hz, CH), 128.7 (C_q), 128.4 (d, $^{3}J_{C-F}$ = 7.6 Hz, CH), 128.2 (CH), 127.3 (C_q), 124.6 (d, $^{4}J_{C-F}$ = 2.3 Hz, CH), 124.3 (CH), 123.8 (CH), 123.6 (d, $^{4}J_{C-F}$ = 2.3 Hz, CH), 123.3 (CH), 123.3 (CH), 123.0 (CH), 122.7 (CH), 122.3 (CH), 121.8 (CH), 118.8 (d, $^{2}J_{C-F}$ = 21.4 Hz, CH), 118.1 (CH), 117.6 (d, $^{2}J_{C-F}$ = 21.3 Hz, CH), 117.4 (C_q), 116.9 (C_q), 116.5 (C_q), 115.8 (d, $^{2}J_{C-F}$ = 22.1 Hz, CH), 114.5 (d, $^{2}J_{C-F}$ = 22.1 Hz, CH), 111.2 (CH). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −111.9 (s), –113.6 (s). HRMS (ESI): *m/z* Calcd for $C_{40}H_{24}N_4O_2F_2 + H^+$ $[M + H]^+$ 631.1940; Found 631.1926.

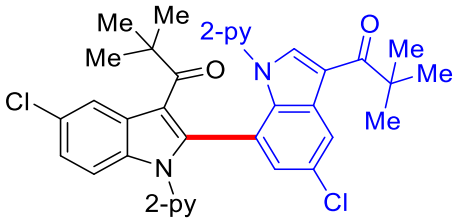


(1,1'-Di(pyridin-2-yl)-1*H*,1'*H*-[2,7'-biindole]-3,3'-diyl)bis(thiophen-2-ylmethanone) (14): The representative procedure **B** was followed, using substrate **14a** (0.061 g, 0.20 mmol).

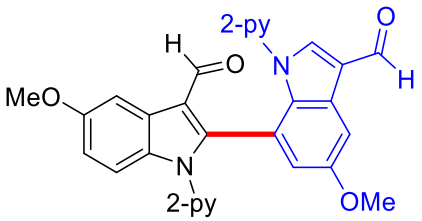
Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **14** (0.032 g, 53%) as a brown solid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.59-8.57 (m, 1H, Ar–H), 8.54 (dd, *J* = 8.0, 1.3 Hz, 1H, Ar–H), 8.51 (s, 1H, Ar–H), 7.75-7.73 (m, 2H, Ar–H), 7.62 (dd, *J* = 1.7, 0.8 Hz, 1H, Ar–H), 7.59-7.52 (m, 4H, Ar–H), 7.47 (td, *J* = 7.8, 1.9 Hz, 1H, Ar–H), 7.35 (dd, *J* = 3.5, 0.8 Hz, 1H, Ar–H), 7.25-7.17 (m, 4H, Ar–H), 7.14 (dd, *J* = 1.6, 0.6 Hz, 1H, Ar–H), 7.07 (dd, *J* = 7.4, 1.1 Hz, 1H, Ar–H), 6.80 (ddd, *J* = 7.4, 4.8, 0.9 Hz, 1H, Ar–H), 6.66 (dd, *J* = 3.6, 0.7 Hz, 1H, Ar–H), 6.59 (dd, *J* = 3.6, 1.7 Hz, 1H, Ar–H), 6.12 (dd, *J* = 3.6, 1.7 Hz, 1H, Ar–H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 178.5 (CO), 176.7 (CO), 154.3 (C_q), 152.8 (C_q), 151.1 (C_q), 150.8 (C_q), 149.1 (CH), 147.2 (CH), 145.5 (CH), 145.4 (CH), 141.1 (C_q), 138.3 (CH), 138.2 (CH), 137.3 (CH), 136.7 (C_q), 135.3 (C_q), 129.3 (C_q), 128.4 (CH), 127.2 (C_q), 124.0 (CH), 123.9 (CH), 123.0 (CH), 122.9 (CH), 122.7 (CH), 122.3 (CH), 122.2 (CH), 121.2 (CH), 118.8 (CH), 117.7 (CH), 117.1 (CH), 116.7 (C_q), 116.4 (C_q), 116.2 (C_q), 112.3 (CH), 111.7 (CH), 111.5 (CH).



1,1'-(5,5'-Dimethyl-1,1'-di(pyridin-2-yl)-1*H*,1'*H*-[2,7'-biindole]-3,3'-diyl)bis(2,2-dimethylpropan-1-one) (15): The representative procedure **B** was followed, using substrate **15a** (0.059 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **15** (0.055 g, 94%) as a pale yellow solid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.41 (br s, 2H, Ar–H), 8.08 (s, 1H, Ar–H), 7.94 (d, *J* = 4.8 Hz, 1H, Ar–H), 7.50-7.42 (m, 3H, Ar–H), 7.21 (t, *J* = 7.8 Hz, 1H, Ar–H), 7.17 (s, 1H, Ar–H), 7.10-7.05 (m, 2H, Ar–H), 6.99 (d, *J* = 8.5 Hz, 1H, Ar–H), 6.93 (s, 1H, Ar–H), 6.80 (t, *J* = 6.0 Hz, 1H, Ar–H), 2.42 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 1.41 (s, 9H, CH_3), 1.02 (s, 9H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 210.6 (CO), 203.2 (CO), 150.9 (C_q), 150.6 (C_q), 148.7 (CH), 147.2 (CH), 137.7 (CH), 137.3 (CH), 135.5 (C_q), 134.8 (CH), 134.4 (C_q), 132.7 (C_q), 132.5 (C_q), 131.1 (C_q), 130.8 (C_q), 129.5 (CH), 127.0 (C_q), 124.9 (CH), 124.3 (CH), 121.8 (2C, CH), 120.7 (CH), 119.9 (CH), 119.3 (C_q), 118.7 (CH), 116.7 (C_q), 114.6 (C_q), 111.7 (CH), 44.8 (C_q), 44.6 (C_q), 29.0 (3C, CH_3), 27.4 (3C, CH_3), 21.8 (CH_3), 21.4 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{38}H_{38}N_4O_2 + H^+$ $[M + H]^+$ 583.3068; Found 583.3068.

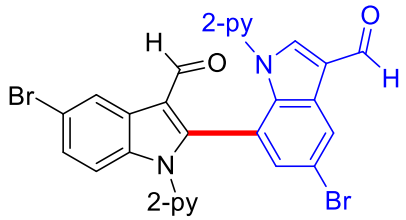


1,1'-(5,5'-Dichloro-1,1'-di(pyridin-2-yl)-1*H*,1'*H*-[2,7'-biindole]-3,3'-diyl)bis(2,2-dimethylpropan-1-one) (16): The representative procedure **B** was followed, using substrate **16a** (0.063 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **16** (0.052 g, 83%) as a colorless solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.62 (d, *J* = 2.1 Hz, 1H, Ar–H), 8.47 (dd, *J* = 4.8, 1.2 Hz, 1H, Ar–H), 8.08 (s, 1H, Ar–H), 7.81 (dd, *J* = 4.8, 1.1 Hz, 1H, Ar–H), 7.53 (td, *J* = 7.8, 1.9 Hz, 1H, Ar–H), 7.48-7.45 (m, 2H, Ar–H), 7.34-7.30 (m, 2H, Ar–H), 7.24 (s, 1H, Ar–H), 7.17 (ddd, *J* = 7.4, 4.9, 0.9 Hz, 1H, Ar–H), 7.13 (dd, *J* = 8.9, 2.0 Hz, 1H, Ar–H), 7.02 (d, *J* = 2.1 Hz, 1H, Ar–H), 6.84-6.80 (m, 1H, Ar–H), 1.39 (s, 9H, CH_3), 0.96 (s, 9H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 209.0 (CO), 202.6 (CO), 150.5 (C_q), 150.2 (C_q), 149.1 (CH), 147.2 (CH), 138.3 (CH), 137.7 (CH), 135.6 (CH), 135.4 (C_q), 134.5 (C_q), 133.1 (C_q), 131.4 (C_q), 128.5 (C_q), 127.6 (CH), 127.5 (C_q), 127.3 (C_q), 124.3 (CH), 124.0 (CH), 122.7 (CH), 122.3 (CH), 121.0 (CH), 119.8 (CH), 119.0 (C_q), 118.9 (CH), 117.7 (C_q), 114.5 (C_q), 113.2 (CH), 44.9 (C_q), 44.7 (C_q), 28.8 (3C, CH_3), 27.3 (3C, CH_3). HRMS (ESI): *m/z* Calcd for $C_{36}H_{32}N_4O_2Cl_2$ $[M]^+$ 623.1975; Found 623.1965.

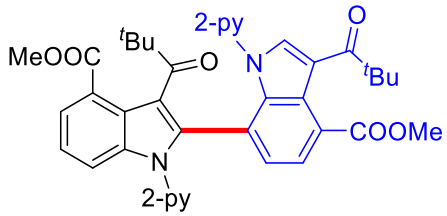


5,5'-Dimethoxy-1,1'-di(pyridin-2-yl)-1*H*, 1'*H*-[2,7'-biindole]-3,3'-dicarbaldehyde (17): The representative procedure **B** was followed, using substrate **17a** (0.051 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **17** (0.031 g, 62%) as a brown solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.09 (s, 1H, CHO), 9.49 (s, 1H, CHO), 8.53 (dd, *J* = 4.8, 1.1 Hz, 1H, Ar–H), 8.00 (s, 1H, Ar–H), 7.98 (d, *J* = 2.5 Hz, 1H, Ar–H), 7.82-7.79 (m, 1H, Ar–H), 7.63-7.58 (m, 2H, Ar–H), 7.46-7.40 (m, 3H, Ar–H), 7.33 (d, *J* = 8.0 Hz, 1H, Ar–H), 7.26-7.23 (m, 1H, Ar–H), 6.89 (dd, *J* = 9.0, 2.6 Hz, 1H, Ar–H), 6.83 (dd, *J* = 7.3, 4.9 Hz, 1H, Ar–H), 6.78 (d, *J* = 2.5 Hz, 1H, Ar–H), 3.86 (s, 3H, CH_3), 3.83 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 186.4 (CO), 185.4 (CO),

157.1 (C_q), 156.3 (C_q), 150.7 (C_q), 150.1 (C_q), 149.2 (CH), 148.0 (CH), 145.5 (C_q), 140.0 (CH), 138.5 (CH), 138.5 (CH), 131.8 (C_q), 130.9 (C_q), 128.0 (C_q), 125.8 (C_q), 123.1 (CH), 122.8 (CH), 121.3 (CH), 119.8 (C_q), 118.6 (CH), 118.2 (CH), 117.1 (C_q), 115.2 (C_q), 115.0 (CH), 112.9 (CH), 105.7 (CH), 102.6 (CH), 56.0 (CH_3), 55.9 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{30}H_{22}N_4O_4 + H^+$ $[M + H]^+$ 503.1714; Found 503.1710.

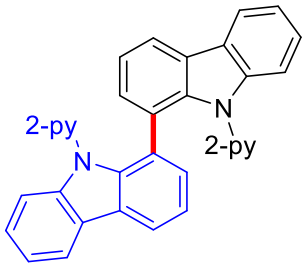


5,5'-Bibromo-1,1'-di(pyridin-2-yl)-1*H*, 1'*H*-[2,7'-biindole]-3,3'-dicarbaldehyde (18): The representative procedure **B** was followed, using substrate **18a** (0.060 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 2/1) yielded **18** (0.047 g, 78%) as a yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.12 (s, 1H, CHO), 9.46 (s, 1H, CHO), 8.68 (d, *J* = 2.0 Hz, 1H, Ar–H), 8.58 (dd, *J* = 4.9, 1.3 Hz, 1H, Ar–H), 8.25 (s, 1H, Ar–H), 8.04 (s, 1H, Ar–H), 7.78 (dd, *J* = 4.8, 1.2 Hz, 1H, Ar–H), 7.68 (td, *J* = 7.8, 1.9 Hz, 1H, Ar–H), 7.51 (td, *J* = 7.8, 1.9 Hz, 1H, Ar–H), 7.48 (d, *J* = 8.0 Hz, 1H, Ar–H), 7.39-7.37 (m, 3H, Ar–H), 7.34-7.31 (m, 1H, Ar–H), 7.25 (d, *J* = 1.9 Hz, 1H, Ar–H), 6.91-6.88 (m, 1H, Ar–H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 185.5 (CO), 184.9 (CO), 150.5 (C_q), 149.6 (CH), 149.5 (C_q), 148.2 (CH), 144.7 (C_q), 140.2 (CH), 138.9 (CH), 138.8 (CH), 135.7 (C_q), 134.8 (C_q), 131.2 (CH), 128.4 (C_q), 128.0 (CH), 127.0 (CH), 126.4 (C_q), 124.2 (CH), 123.7 (CH), 123.4 (CH), 121.6 (CH), 119.4 (C_q), 118.7 (CH), 117.5 (C_q), 116.7 (C_q), 116.7 (C_q), 115.5 (C_q), 113.4 (CH). HRMS (ESI): *m/z* Calcd for $C_{28}H_{16}N_4O_2Br_2$ $[M]^+$ 600.9692; Found 600.9675.



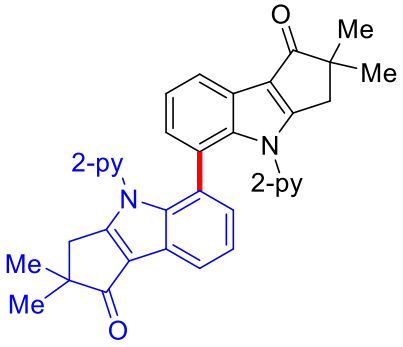
Dimethyl 3,3'-dipivaloyl-1,1'-di(pyridin-2-yl)-1*H*, 1'*H*-[2,7'-biindole]-4,4'-dicarboxylate (19): The representative procedure **B** was followed, using substrate **19a** (0.067 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **19** (0.049 g, 73%) as a yellow solid. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.62 (d, *J* = 4.6

Hz, 1H, Ar–H), 7.86 (s, 1H, Ar–H), 7.81 (d, *J* = 7.6 Hz, 1H, Ar–H), 7.79-7.76 (m, 2H, Ar–H), 7.74 (d, *J* = 8.2 Hz, 1H, Ar–H), 7.57 (t, *J* = 7.8 Hz, 1H, Ar–H), 7.53 (t, *J* = 7.5 Hz, 1H, Ar–H), 7.39 (d, *J* = 7.6 Hz, 1H, Ar–H), 7.32 (d, *J* = 4.6 Hz, 1H, Ar–H), 7.27-7.23 (m, 2H, Ar–H), 6.94 (d, *J* = 7.6 Hz, 1H, Ar–H), 6.56 (dd, *J* = 7.2, 5.0 Hz, 1H, Ar–H), 3.89 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 1.43 (s, 9H, CH_3), 0.72 (s, 9H, CH_3). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 208.0 (CO), 204.5 (CO), 168.7 (CO), 167.6 (CO), 152.1 (C_q), 150.8 (C_q), 148.9 (CH), 145.8 (CH), 138.8 (CH), 137.8 (CH), 137.0 (C_q), 136.6 (C_q), 135.6 (C_q), 132.7 (CH), 127.6 (CH), 127.2 (C_q), 126.3 (C_q), 125.0 (C_q), 124.7 (CH), 122.8 (CH), 122.6 (CH), 122.4 (CH), 122.3 (CH), 122.1 (C_q), 121.8 (C_q), 121.5 (CH), 120.8 (CH), 118.8 (C_q), 117.6 (C_q), 116.7 (CH), 52.3 (CH_3), 51.9 (CH_3), 46.6 (C_q), 44.8 (C_q), 28.3 (3C, CH_3), 27.2 (3C, CH_3). HRMS (ESI): *m/z* Calcd for $C_{40}H_{38}N_4O_6 + H^+$ $[M + H]^+$ 671.2864; Found 671.2840.

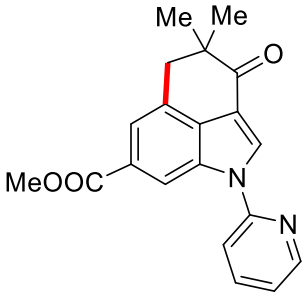


9,9'-Di(pyridin-2-yl)-9*H*, 9'*H*-1,1'-bicarbazole (20): The representative procedure **B** was followed, using substrate **20a** (0.049 g, 0.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **20** (0.041 g, 84%) as a white solid. ^1H-NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 7.6 Hz, 2H, Ar–H), 7.94 (d, *J* = 7.4 Hz, 2H, Ar–H), 7.67 (d, *J* = 4.4 Hz, 2H, Ar–H), 7.36-7.33 (m, 2H, Ar–H), 7.30-7.23 (m, 4H, Ar–H), 7.18 (t, *J* = 7.5 Hz, 4H, Ar–H), 7.07 (br s, 2H, Ar–H), 6.99 (t, *J* = 6.9 Hz, 2H, Ar–H), 6.74-6.72 (m, 2H, Ar–H). HRMS (ESI): *m/z* Calcd for $C_{34}H_{22}N_4 + H^+$ $[M + H]^+$ 487.1917; Found 487.1911.

(Note: Compound **20** is partially soluble in $CDCl_3$, DMSO-d_6 and acetone, and the compound **20** structure is confirmed by X-ray analysis (Figure 5.5)).

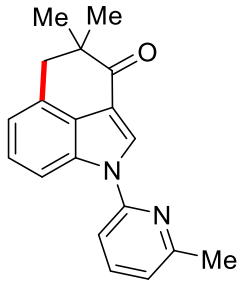


2,2,2',2'-Tetramethyl-4,4'-di(pyridin-2-yl)-3,3',4,4'-tetrahydro-[5,5'-bi(cyclopenta[*b*]indole)]-1,1' (2*H*, 2'*H*)-dione (21): The representative procedure **B** was followed, using substrate **21a** (0.055 g, 0.20 mmol) at 120 ^{o}C for 24 h. Purification by column chromatography on silica gel (petroleum ether/EtOAc: 2/1) yielded **21** (0.024 g, 44%) as a brown solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, J = 3.9 Hz, 2H, Ar–H), 7.67 (dd, J = 7.8, 1.3 Hz, 2H, Ar–H), 7.35-7.3 (m, 2H, Ar–H), 7.27 (t, J = 7.6 Hz, 2H, Ar–H), 7.10-7.07 (m, 2H, Ar–H), 6.82-6.79 (m, 4H, Ar–H), 3.12 (d, J = 17.9 Hz, 2H, CH_2), 2.51 (d, J = 17.9 Hz, 2H, CH_2), 1.39 (s, 6H, CH_3), 1.18 (s, 6H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 201.2 (2C, CO), 165.5 (2C, C_q), 148.4 (2C, C_q), 147.1 (2C, CH), 138.9 (2C, C_q), 135.8 (2C, CH), 126.0 (2C, CH), 124.7 (2C, C_q), 123.3 (2C, CH), 122.7 (2C, C_q), 122.3 (2C, CH), 120.6 (2C, CH), 118.6 (2C, CH), 118.6 (2C, C_q), 51.3 (2C, C_q), 38.2 (2C, CH_2), 26.3 (2C, CH_3), 25.6 (2C, CH_3). HRMS (ESI): *m/z* Calcd for $C_{36}H_{30}N_4O_2 + H^+$ $[M + H]^+$ 551.2442; Found 551.2440.



Methyl 4,4-dimethyl-3-oxo-1-(pyridin-2-yl)-1,3,4,5-tetrahydrobenzo[*cd*]indole-7-carboxylate (22): The representative procedure **B** was followed, using substrate **22a** (0.067 g, 0.20 mmol) at 120 ^{o}C for 24 h. Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **22** (0.038 g, 57%) as a brown solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.68-8.66 (m, 1H, Ar–H), 8.47 (t, J = 1.0 Hz, 1H, Ar–H), 8.02 (d, J = 1.0 Hz, 2H, Ar–H), 8.01-7.97 (m, 1H, Ar–H), 7.61 (d, J = 8.1 Hz, 1H, Ar–H), 7.40 (ddd, J = 7.4, 4.9, 0.9 Hz, 1H, Ar–H), 3.94 (s, 3H, CH_3), 3.22 (s, 2H, CH_2), 1.36 (s, 6H, CH_3). ^{13}C{^{1}H}-

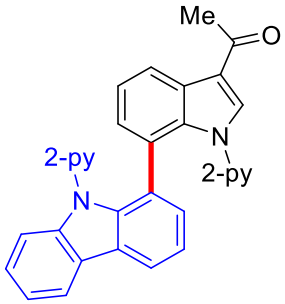
NMR (100 MHz, $CDCl_3$): δ = 201.5 (CO), 167.6 (CO), 166.6 (C_q), 150.2 (C_q), 150.0 (CH), 141.5 (C_q), 139.3 (CH), 126.4 (C_q), 126.1 (C_q), 124.7 (CH), 122.8 (CH), 121.0 (CH), 120.1 (C_q), 117.8 (CH), 114.4 (CH), 52.4 (CH_3), 51.6 (C_q), 39.8 (CH_2), 25.8 (2C, CH_3). HRMS (ESI): *m/z* Calcd for $C_{20}H_{18}N_2O_3 + H^+$ $[M + H]^+$ 335.1390; Found 335.1386.



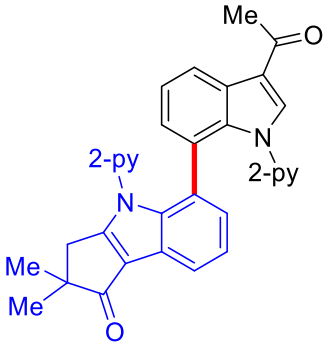
4,4-Dimethyl-1-(6-methylpyridin-2-yl)-4,5-dihydrobenzo[*cd*]indol-3(1*H*)-one (23): The representative procedure **B** was followed, using substrate **23a** (0.059 g, 0.20 mmol) at 120 ^oC for 24 h. Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **23** (0.041 g, 71%) as a yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.99-7.97 (m, 1H, Ar–H), 7.82-7.76 (m, 2H, Ar–H), 7.35 (d, *J* = 8.0 Hz, 1H, Ar–H), 7.32-7.28 (m, 2H, Ar–H), 7.19 (d, *J* = 7.6 Hz, 1H, Ar–H), 3.17 (s, 2H, CH_2), 2.63 (s, 3H, CH_3), 1.34 (s, 6H, CH_3). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 201.7 (CO), 164.5 (C_q), 159.3 (C_q), 149.8 (C_q), 141.9 (C_q), 139.1 (CH), 124.2 (CH), 123.3 (CH), 122.7 (C_q), 121.8 (CH), 121.3 (CH), 120.0 (C_q), 114.3 (CH), 112.6 (CH), 51.4 (C_q), 39.7 (CH_2), 25.9 (2C, CH_3), 24.5 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{19}H_{18}N_2O + H^+$ $[M + H]^+$ 291.1492; Found 291.1491.

5.4.5 Procedure for the Hetero-Coupling of Indoles

***Representative Procedure C*: Synthesis of 1-(1-(Pyridin-2-yl)-7-(9-(pyridin-2-yl)-9*H*-carbazol-1-yl)-1*H*-indol-3-yl)ethan-1-one (24):** To an oven-dried screw-cap tube equipped with magnetic stir bar were introduced 1-(1-(pyridin-2-yl)-1*H*-indol-3-yl)ethan-1-one (**1a**; 0.047 g, 0.20 mmol), 9-(pyridin-2-yl)-9*H*-carbazole (**20a**; 0.049 g, 0.20 mmol), $K_2S_2O_8$ (0.216 g, 0.80 mmol), and $Pd(OAc)_2$ (0.0027 g, 0.012 mmol), followed by the addition of TFE (2 mL) and TFA (0.091 g, 0.80 mmol). The resultant reaction mixture was immersed in a preheated oil bath at 80 °C and stirred for 16 h. The reaction mixture was allowed to cool to room temperature, and all the volatiles were removed under reduced pressure. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) to yield compounds **24** (0.022 g, 23%), **1** (0.026 g, 28%), and **20** (0.03 g, 31%).



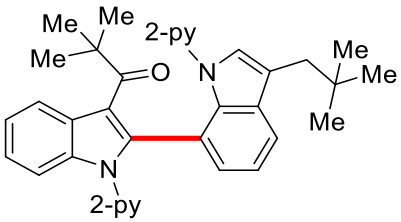
1-(1-(Pyridin-2-yl)-7-(9-(pyridin-2-yl)-9*H*-carbazol-1-yl)-1*H*-indol-3-yl)ethan-1-one (24): ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.55 (dd, *J* = 4.8, 1.3 Hz, 1H, Ar–H), 8.17-8.15 (m, 3H, Ar–H), 7.73-7.70 (m, 2H, Ar–H), 7.55-7.50 (m, 3H, Ar–H), 7.45-7.41 (m, 1H, Ar–H), 7.39-7.35 (m, 2H, Ar–H), 7.31 (d, *J* = 8.1 Hz, 1H, Ar–H), 7.24-7.22 (m, 2H, Ar–H), 7.21-7.19 (m, 1H, Ar–H), 7.17-7.15 (m, 1H, Ar–H), 7.13-7.11 (m, 1H, Ar–H), 6.72-6.68 (m, 1H, Ar–H), 1.79 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 194.6 (CO), 150.9 (C_q), 150.7 (C_q), 149.1 (CH), 148.6 (CH), 141.9 (C_q), 141.3 (C_q), 139.9 (C_q), 138.3 (CH), 138.1 (CH), 136.6 (C_q), 129.2 (CH), 126.9 (CH), 125.0 (C_q), 123.9 (CH), 123.4 (C_q), 123.2 (CH), 123.0 (CH), 122.8 (CH), 122.5 (CH), 122.3 (CH), 121.6 (2C, CH), 121.2 (CH), 120.5 (CH), 120.2 (CH), 118.0 (C_q), 115.9 (2C, C_q), 111.2 (CH), 110.2 (CH), 29.7 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{32}H_{22}N_4O + H^+$ $[M + H]^+$ 479.1866; Found 479.1870.



5-(3-Acetyl-1-(pyridin-2-yl)-1*H*-indol-7-yl)-2,2-dimethyl-4-(pyridin-2-yl)-3,4-dihydrocyclopenta[*b*]indol-1(2*H*)-one (25): The representative procedure **C** was followed, using 1-(1-(pyridin-2-yl)-1*H*-indol-3-yl)ethan-1-one (**1a**; 0.047 g, 0.20 mmol) and 2,2-dimethyl-4-(pyridin-2-yl)-3,4-dihydrocyclopenta[*b*]indol-1(2*H*)-one (**21a**; 0.055 g, 0.20 mmol. Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) to yield compounds **25** (0.028 g, 27%), **1** (0.020 g, 42%), and **21** (0.005 g, 8%). ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 7.9 Hz, 1H, Ar–H), 8.02 (d, *J* = 4.6 Hz, 1H, Ar–H), 7.92 (d, *J* = 4.3 Hz, 1H, Ar–H), 7.89 (s, 1H, Ar–H), 7.69 (d, *J* = 7.8 Hz, 1H, Ar–H), 7.38 (t, *J* = 7.2 Hz, 2H, Ar–H), 7.31 (td, *J* = 7.5, 2.7 Hz, 2H, Ar–H), 7.04 (t, *J* = 7.6 Hz, 1H, Ar–H), 7.00-6.96

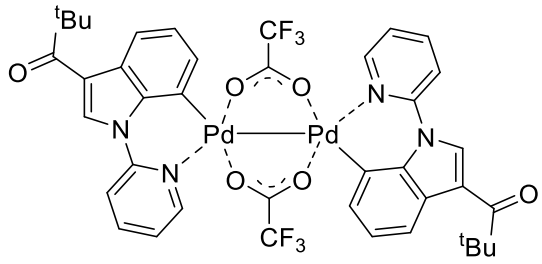
(m, 1H, Ar–H), 6.82 (dd, *J* = 7.4, 5.0 Hz, 1H, Ar–H), 6.74 (dd, *J* = 7.4, 5.0 Hz, 1H, Ar–H), 6.63 (br s, 1H, Ar–H), 6.54 (d, *J* = 7.9 Hz, 1H, Ar–H), 3.14 (d, *J* =17.9 Hz, 1H, CH_2), 2.49 (d, *J* =17.9 Hz, 1H, CH_2), 2.49 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.17 (s, 3H, CH_3). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 201.3 (CO), 193.4 (CO), 165.8 (C_q), 149.4 (C_q), 148.1 (C_q), 147.2 (2C, CH), 139.1 (C_q), 136.1 (CH), 135.6 (CH), 135.6 (CH), 132.9 (C_q), 127.4 (C_q), 125.9 (CH), 125.7 (CH), 125.1 (C_q), 123.9 (C_q), 123.6 (CH), 123.5 (CH), 122.8 (C_q), 122.5 (CH), 122.2 (CH), 121.8 (CH), 120.6 (CH), 118.6 (C_q), 118.5 (C_q), 118.0 (CH), 118.0 (CH), 51.3 (C_q), 38.2 (CH_2), 27.7 (CH_3), 26.3 (CH_3), 25.5 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{33}H_{26}N_4O_2 + H^+$ $[M + H]^+$ 511.2129; Found 511.2115.

5.4.6 *Procedure for Reduction of Carbonyl Group*.[34] Synthesis of Compound 26:

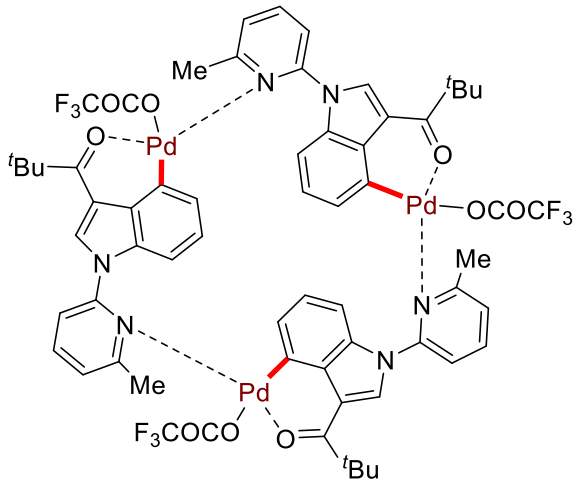


To a solution of 1,1'-(1,1'-di(pyridin-2-yl)-1*H*, 1'*H*-[2,7'-biindole]-3,3'-diyl)bis(2,2-dimethylpropan-1-one) (**3**; 0.05 g, 0.09 mmol) in trifluoroacetic acid (0.5 mL) was added Et_3SiH (0.144 mL, 0.9 mmol) under argon at room temperature. The reaction mixture was stirred at 50 ^oC for 12 h. At ambient temperature, the resultant mixture was quenched with aqueous sodium bicarbonate and saturated brine solution. The crude product was extracted with EtOAc (10 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) to yield **26** (0.035 g, 72%) as white solid. ^1H-NMR (400 MHz, $CDCl_3$): δ = 8.50 (dd, *J* = 4.9, 1.1 Hz, 1H, Ar–H), 7.66 (d, *J* = 4.5 Hz, 1H, Ar–H), 7.62-7.59 (m, 2H, Ar–H), 7.46-7.42 (m, 1H, Ar–H), 7.37-7.32 (m, 4H, Ar–H), 7.21 (s, 1H, Ar–H), 7.18-7.14 (m, 1H, Ar–H), 7.13-7.07 (m, 3H, Ar–H), 7.00-6.98 (m, 1H, Ar–H), 6.69-6.65 (m, 1H, Ar–H), 2.59-2.72 (m, 2H, CH_2), 0.96 (s, 9H, CH_3), 0.87 (s, 9H, CH_3). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 210.3 (CO), 151.5 (C_q), 151.3 (C_q), 148.6 (CH), 146.5 (CH), 137.7 (CH), 137.3 (CH), 136.1 (C_q), 135.8 (C_q), 134.5 (C_q), 132.8 (C_q), 128.4 (CH), 127.4 (C_q), 126.8 (CH), 123.1 (CH), 121.9 (CH), 121.6 (CH), 121.4 (CH), 120.7 (CH), 120.3 (CH), 120.2 (CH), 119.9 (CH), 118.7 (C_q), 117.6 (C_q), 117.4 (CH), 116.3 (C_q), 111.7 (CH), 45.0 (C_q), 38.9 (CH_2), 32.3 (C_q), 29.9 (3C, CH_3), 27.3 (3C, CH_3). HRMS (ESI): *m/z* Calcd for $C_{36}H_{36}N_4O + H^+$ $[M + H]^+$ 541.2962; Found 541.2957.

5.4.7 Procedure for Synthesis of Palladium Complex[31]



Synthesis of Palladium Complex 27: To a Schlenk tube (10 mL) was added 2,2-dimethyl-1-(1-(pyridin-2-yl)-1*H*-indol-3-yl)propan-1-one (**3a**; 0.030 g, 0.107 mmol), $Pd(OAc)_2$ (0.024 g, 0.107 mmol) and TFA (1 mL). The reaction mixture was stirred at room temperature for 24 h. Then, the reaction mixture was filtered, and the volatiles were evaporated under reduced pressure and washed with hexane to give the desired palladacycle product **27**, yielded (0.050 g, 94%) as a yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.98 (s, 2H, Ar–H), 8.80 (br s, 2H, Ar–H), 8.47 (d, J = 8.6 Hz, 2H, Ar–H), 8.20-8.17 (m, 2H, Ar–H), 7.91 (d, J = 7.1 Hz, 2H, Ar–H), 7.34 (t, J = 6.5 Hz, 2H, Ar–H), 7.05 (br s, 4H, Ar–H), 1.41 (s, 18H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 202.1 (2C, CO), 150.1 (2C, CH), 144.9 (2C, C_q), 141.0 (2C, CH), 131.0 (2C, C_q), 128.9 (2C, CH), 128.4 (2C, C_q), 125.5 (2C, C_q), 123.2 (2C, CH), 120.1 (2C, CH), 118.9 (2C, CH), 118.8 (2C, CH), 118.5 (2C, C_q), 114.9 (2C, CH), 44.0 (2C, C_q), 28.0 (6C, CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = –73.8 (s). The structure of compound **27** was confirmed through a single-crystal X-ray analysis (Figure 5.9).



Synthesis of Palladium Complex 28: To a pressure tube (10 mL) was added 2,2-dimethyl-1-(1-(6-methylpyridin-2-yl)-1*H*-indol-3-yl)propan-1-one (**23a**; 0.029 g, 0.10 mmol), $Pd(OAc)_2$ (0.023 g, 0.10 mmol) and TFA (1 mL). The reaction mixture was stirred at room temperature for 24 h. Then, the reaction mixture was filtered, and the volatiles were

evaporated under reduced pressure and washed with hexane to give the desired palladacycle product **28**, yielded (0.045 g, 88%) as a grey solid. ^{19}F-NMR (377 MHz, $CDCl_3$): δ = –73.2 (s). The structure of compound **28** was confirmed through a single-crystal X-ray analysis (Figure 5.10).

5.4.8 Procedure for *H/D* Scrambling Experiment

To an oven-dried screw-cap tube equipped with magnetic stir bar were introduced 2,2-dimethyl-1-(1-(pyridin-2-yl)-1*H*-indol-3-yl)propan-1-one (**3a**; 0.056 g, 0.20 mmol), $K_2S_2O_8$ (0.108 g, 0.40 mmol), and $Pd(OAc)_2$ (0.0014 g, 0.006 mmol, 3.0 mol%), followed by the addition of TFA (0.046 g, 0.4 mmol) and TFE (1.0 mL). To the resulting mixture, D_2O (0.040 g, 2.0 mmol) was added and stirred at 80 °C in a preheated oil bath for 1 h. The reaction mixture was allowed to cool to room temperature, and all the volatiles were removed under reduced pressure. The remaining residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) to recover the starting compound. The ^{1}H NMR analysis of the recovered compound does not show incorporation of deuterium at the C(2)–H or C(7)–H position (Scheme 5.9).

5.4.9 X-ray Structural Analysis

Crystal of compounds **2**, **7, 16, 20, 21, 25, 26, 27** and **28** were grown by slow vapourization of DCE/Hexane. X-ray intensity data measurements of compounds **2**, **7, 16, 20, 21, 25, 26, 27** and **28** were carried out on a Bruker D8 VENTURE Kappa Duo PHOTON II CPAD diffractometer equipped with Incoatech multilayer mirrors optics. The intensity measurements were carried out with Mo micro-focus sealed tube diffraction source (MoK_α= 0.71073 Å) at low temperature. The X-ray generator was operated at 50 kV and 1.4 mA. A preliminary set of cell constants and an orientation matrix were calculated from three matrix sets of 36 frames (each matrix run consists of 12 frames). Data were collected with ω scan width of 0.5° at different settings of φ and 2θ with a frame time of 10-20 sec depending on the diffraction power of the crystals keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX3 program (Bruker, 2016).[35] All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2016). Using the APEX3 (Bruker) program suite, the structure was solved with the ShelXS-97 (Sheldrick, 2008)[36] structure solution program, using direct methods. The model was refined with a version of ShelXL-2018/3 (Sheldrick, 2015)[37] using

Least Squares minimization. All the hydrogen atoms were placed in a geometrically idealized position and constrained to ride on their parent atoms. An *ORTEP* III[38] view of the compounds was drawn with 50% probability displacement ellipsoids, and H atoms are shown as small spheres of arbitrary radii.

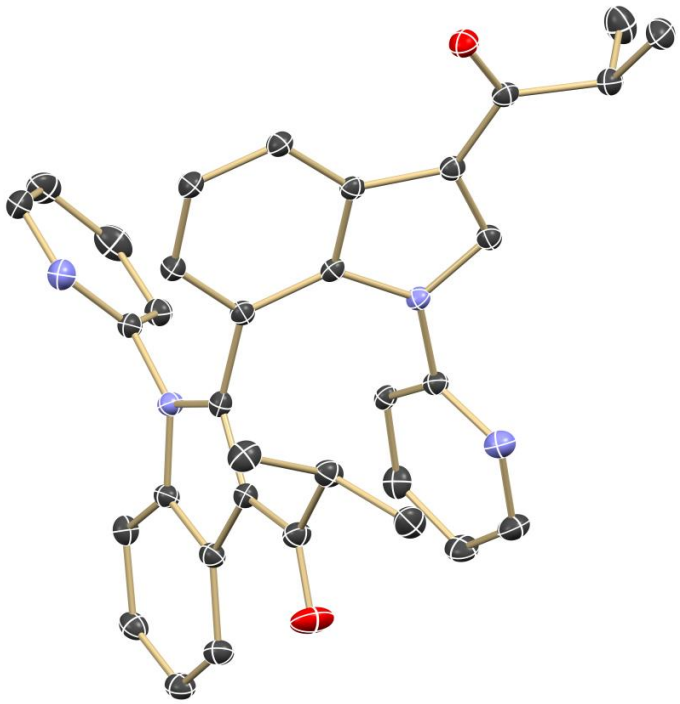


Figure 5.2 ORTEP of compound **2** showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability.

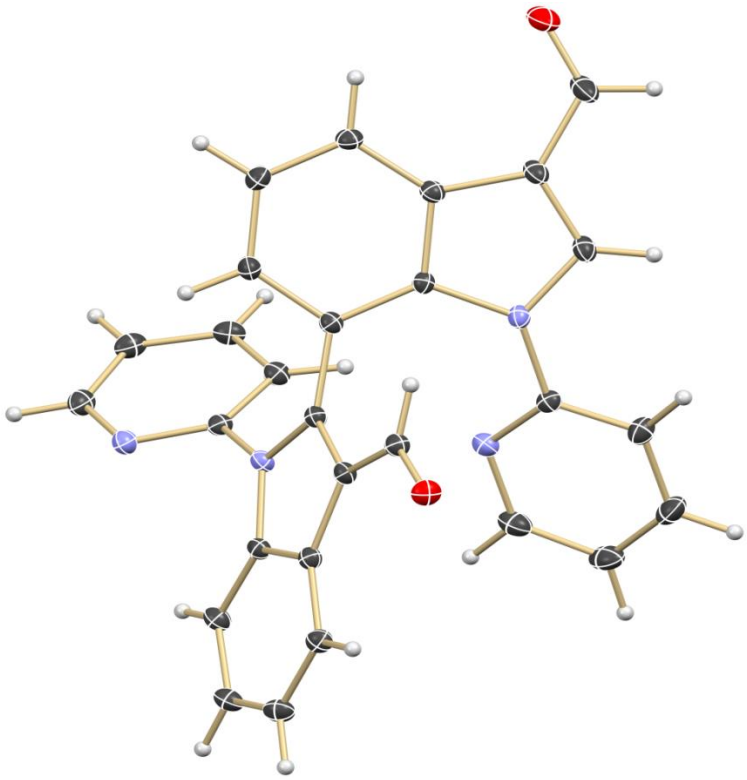


Figure 5.3 ORTEP of compound **7** showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres with arbitrary radii.

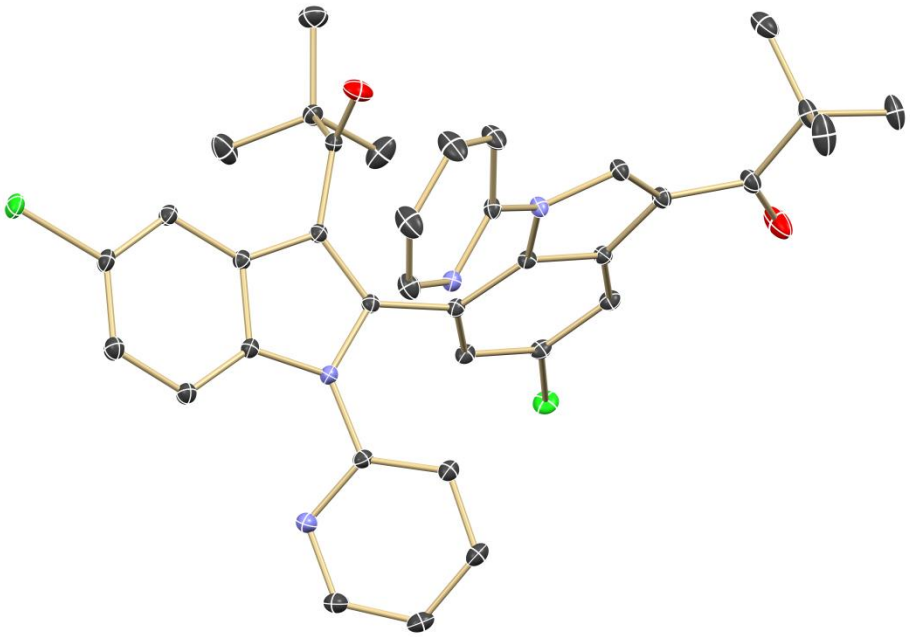


Figure 5.4 ORTEP of compound **16** showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

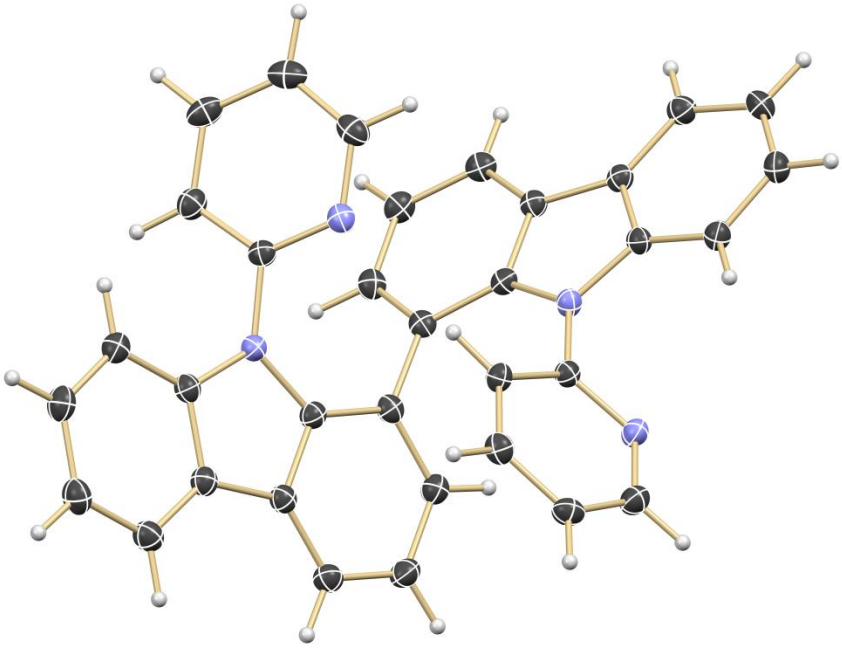


Figure 5.5 ORTEP of compound **20** showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres with arbitrary radii.

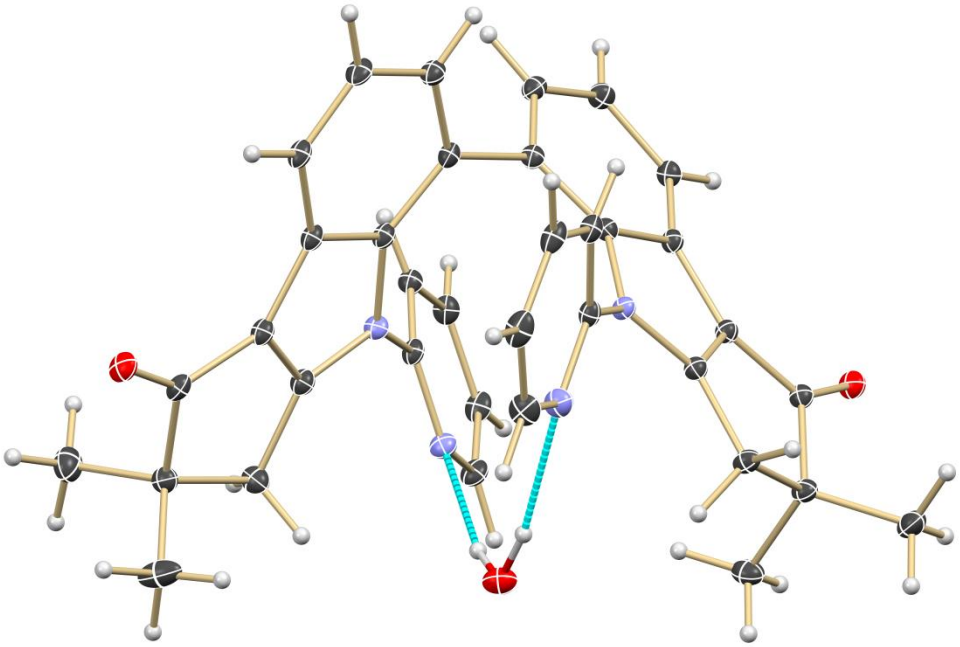


Figure 5.6 ORTEP of compound **21** showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres with arbitrary radii.

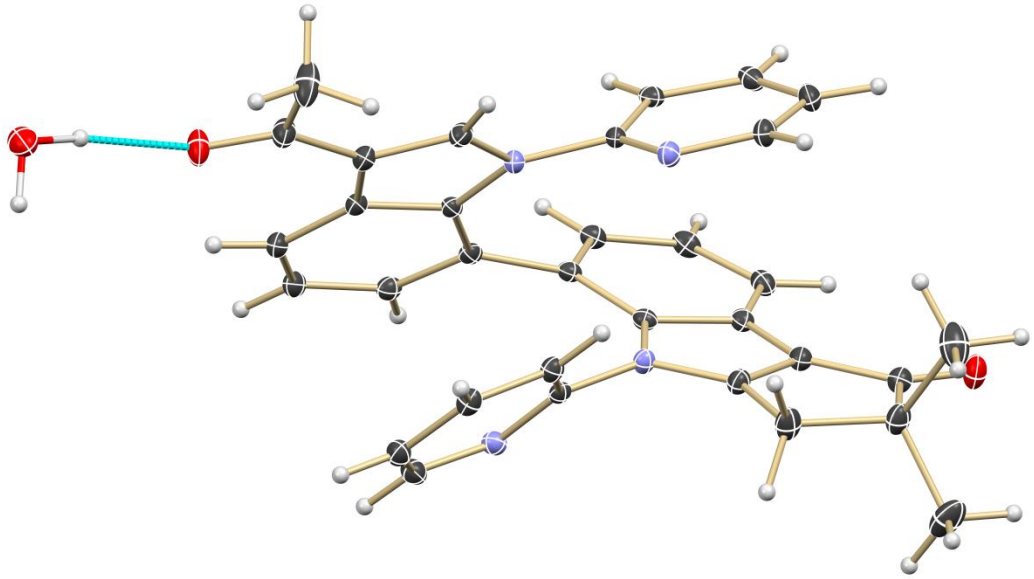


Figure 5.7 ORTEP of compound **25** showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres with arbitrary radii.

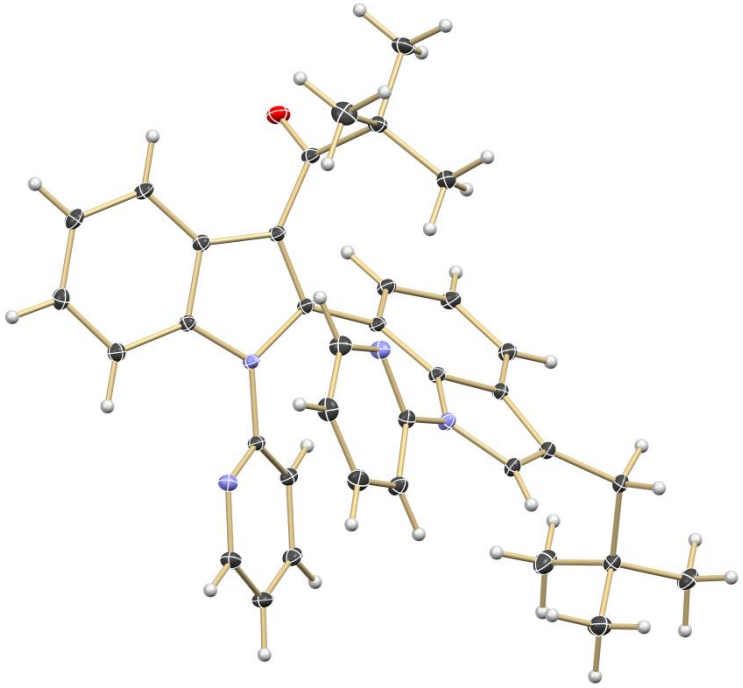


Figure 5.8 ORTEP of compound **26** showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres with arbitrary radii.

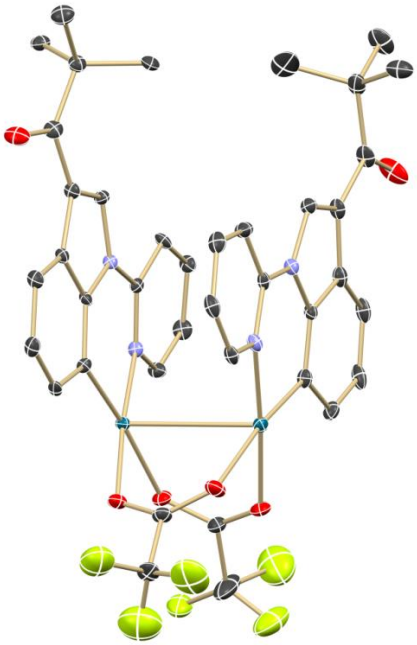


Figure 5.9 ORTEP of compound **27** showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level.

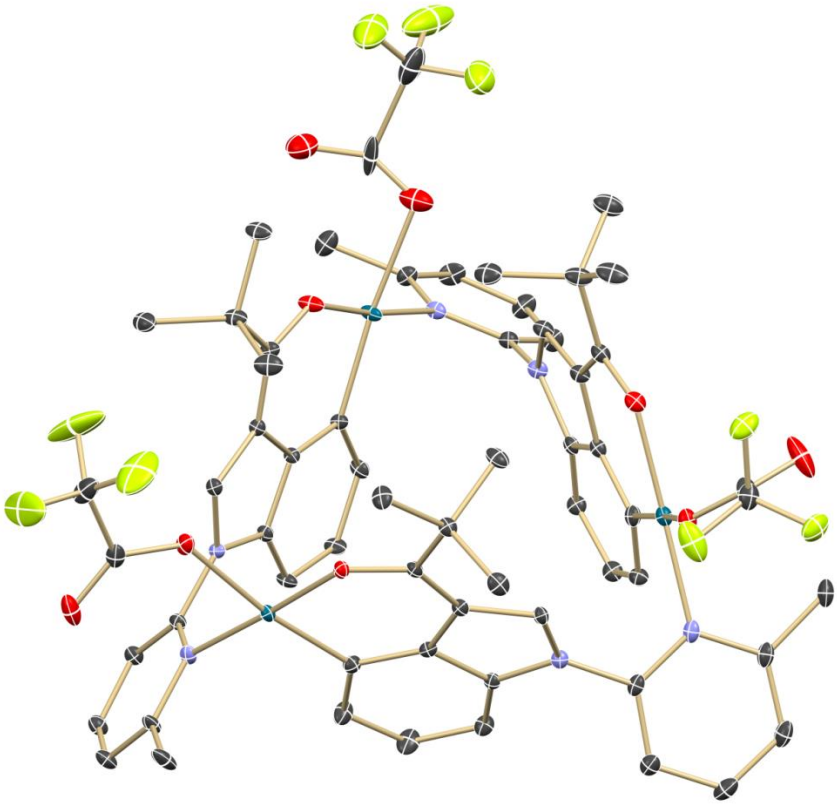
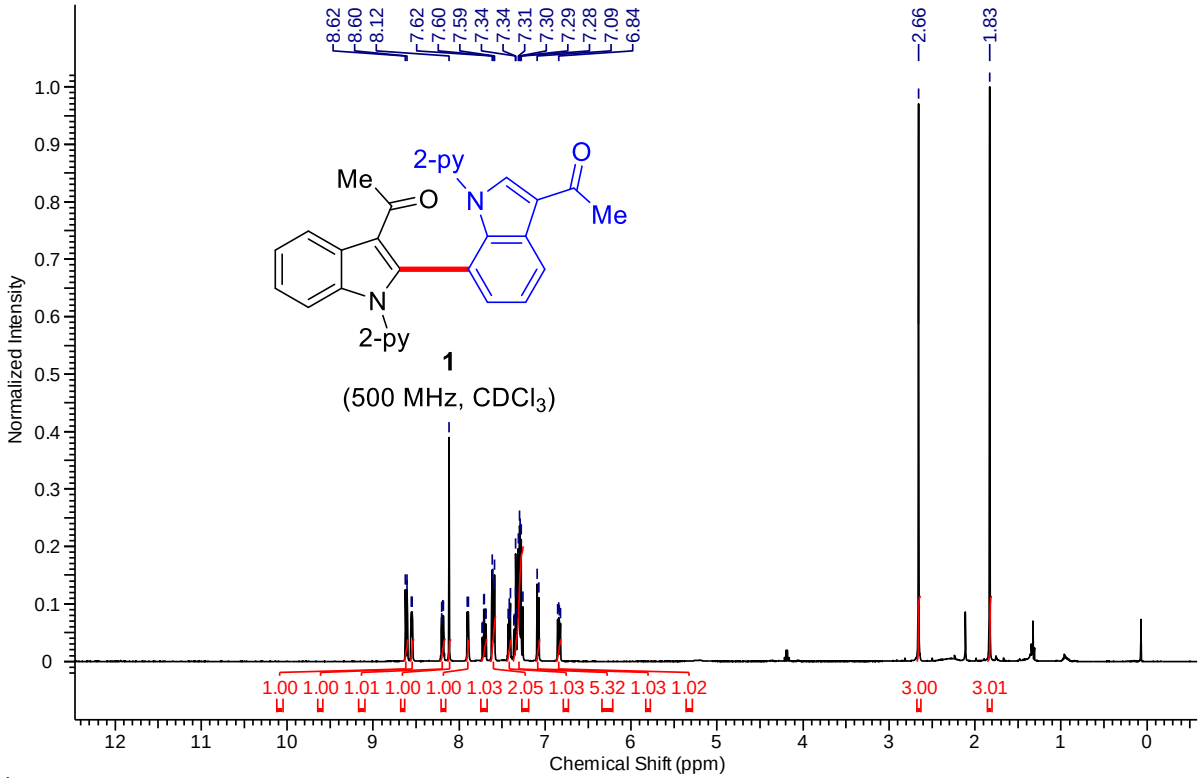
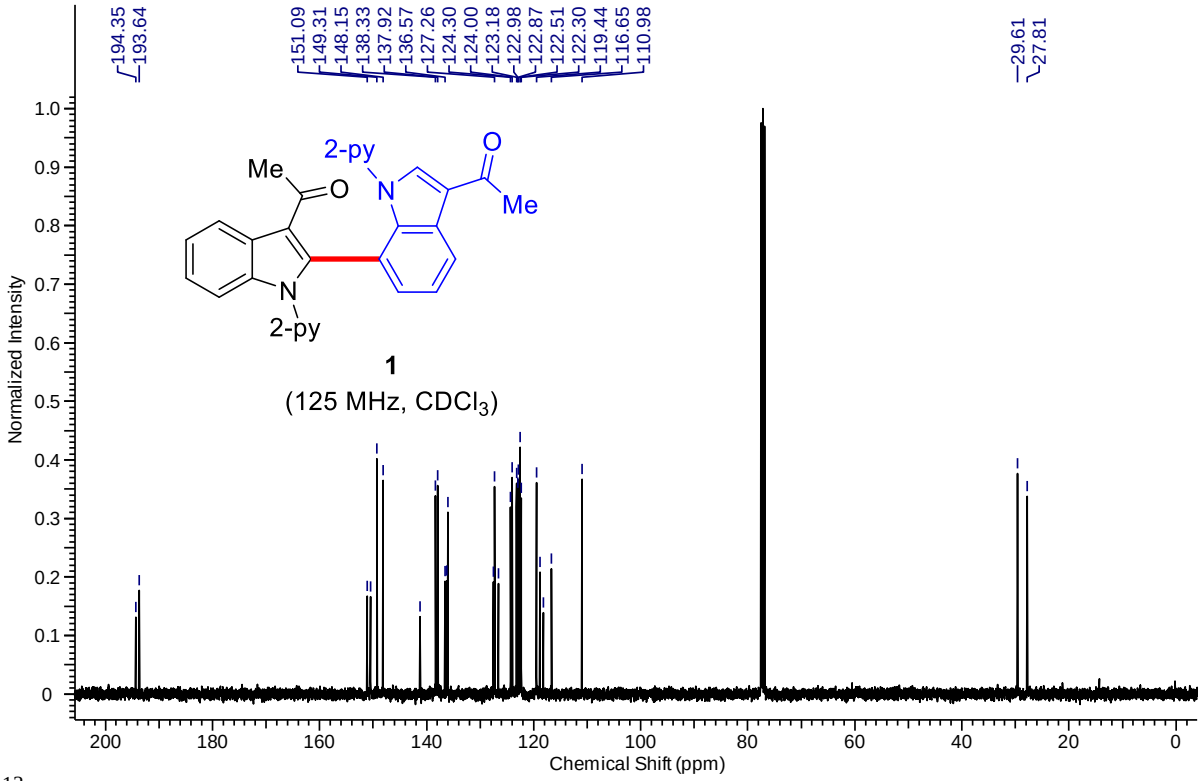


Figure 5.10 ORTEP of compound **28** showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres with arbitrary radii.

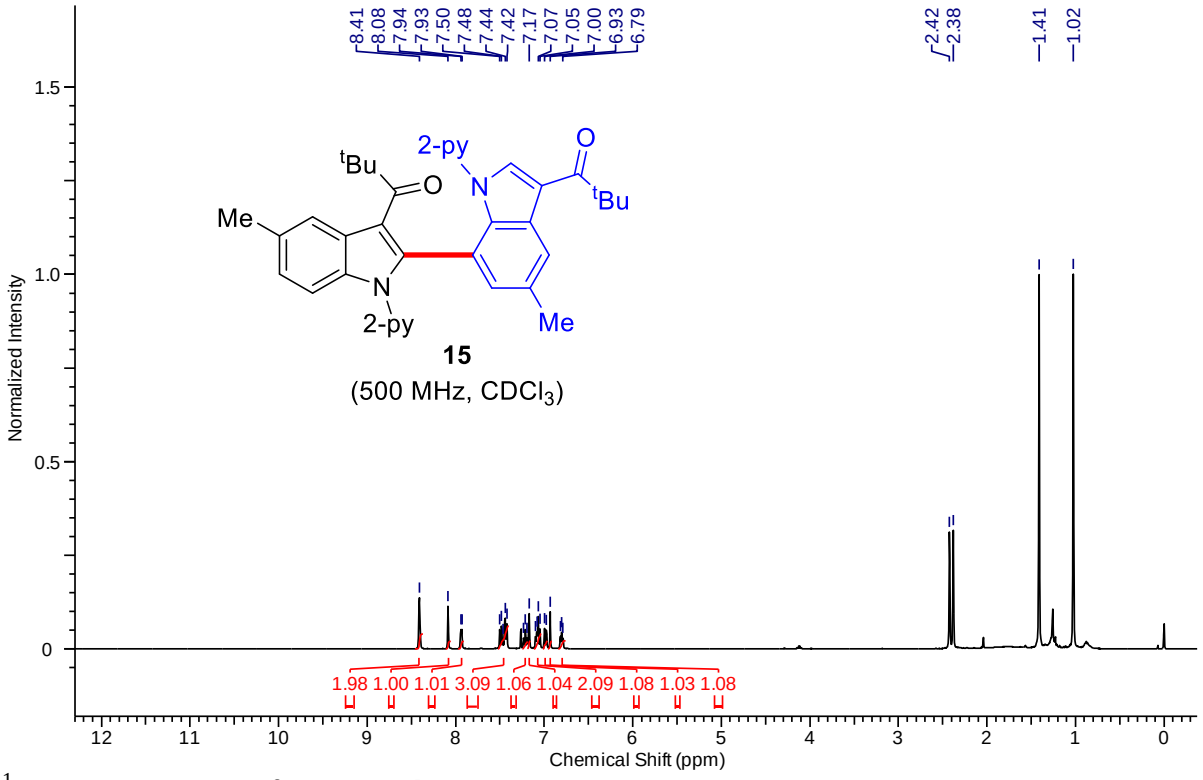
5.4.10 ^{1}H and ^{13}C Spectra for Selected C2-C7 Coupled Indoles



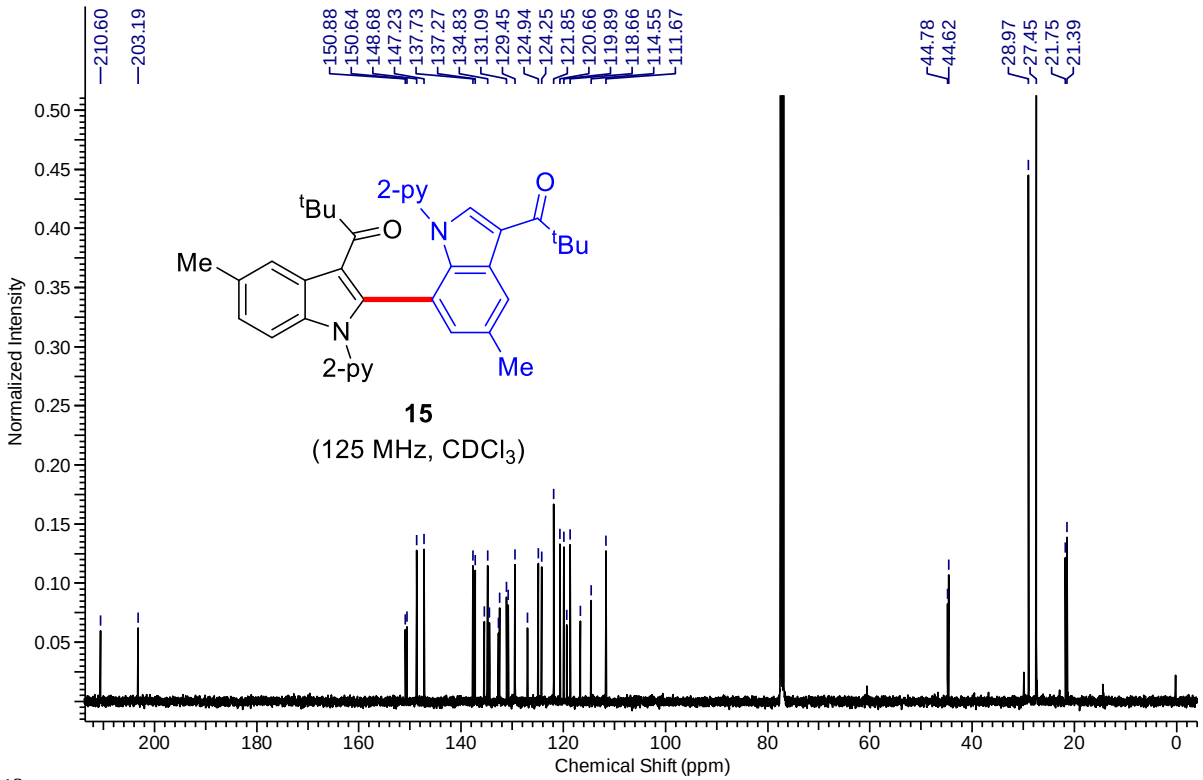
^{1}H-NMR spectrum of compound **1**



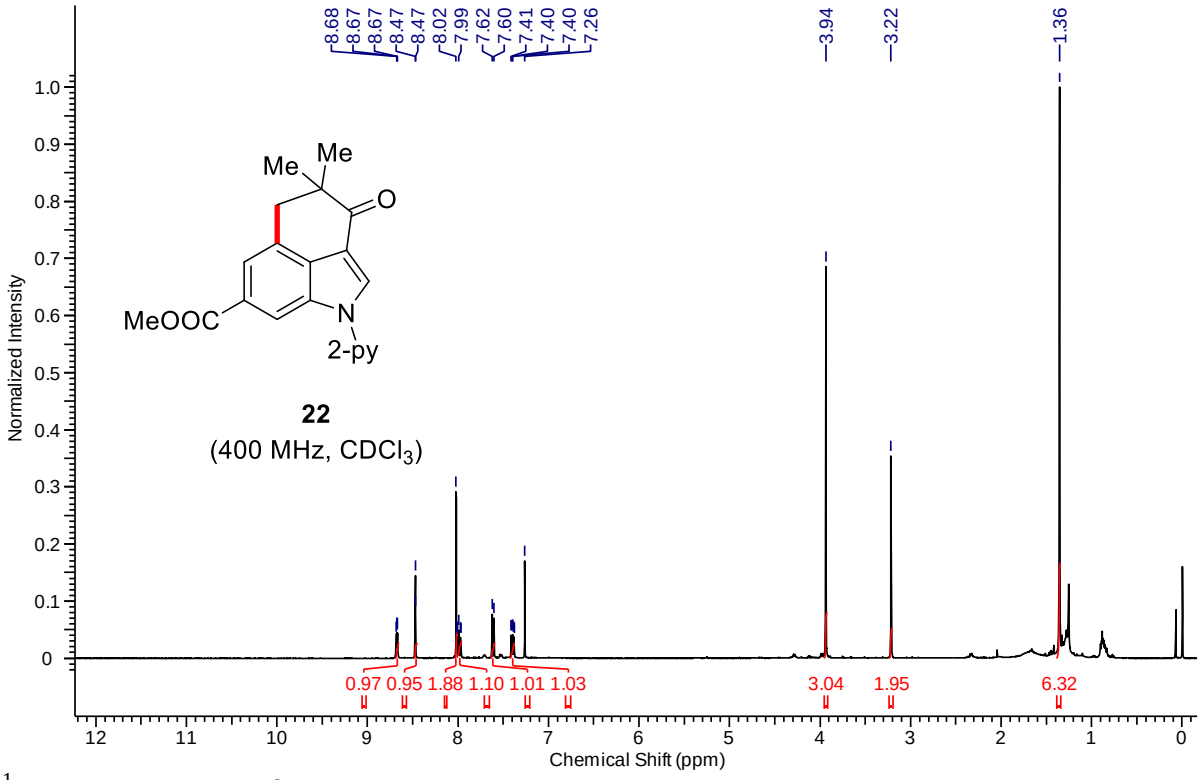
^{13}C-NMR spectrum of compound **1**



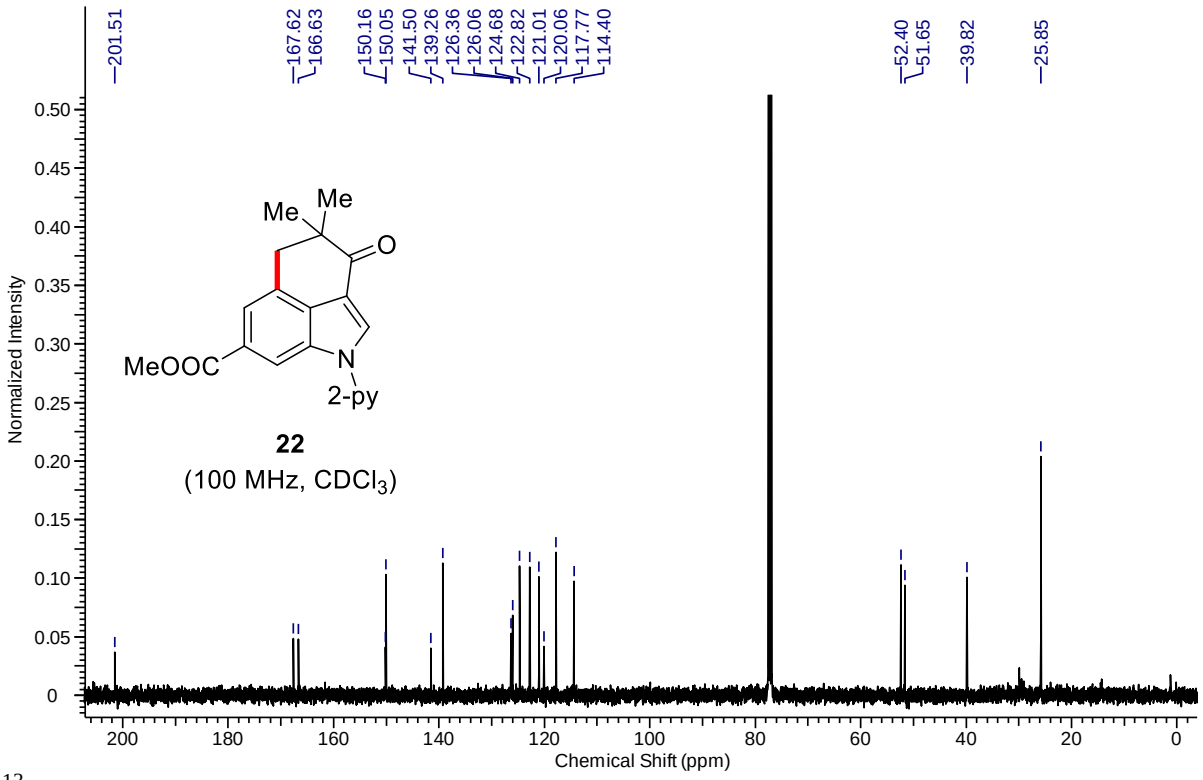
^{1}H-NMR spectrum of compound **15**



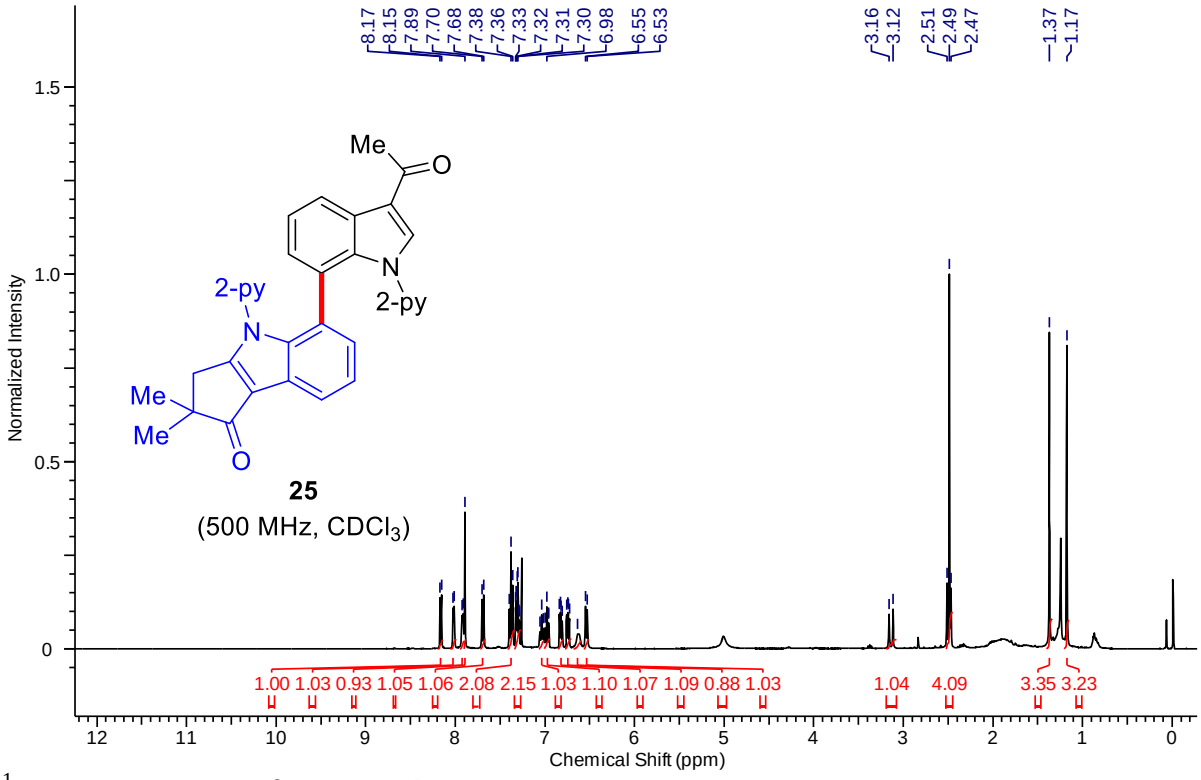
^{13}C-NMR spectrum of compound **15**



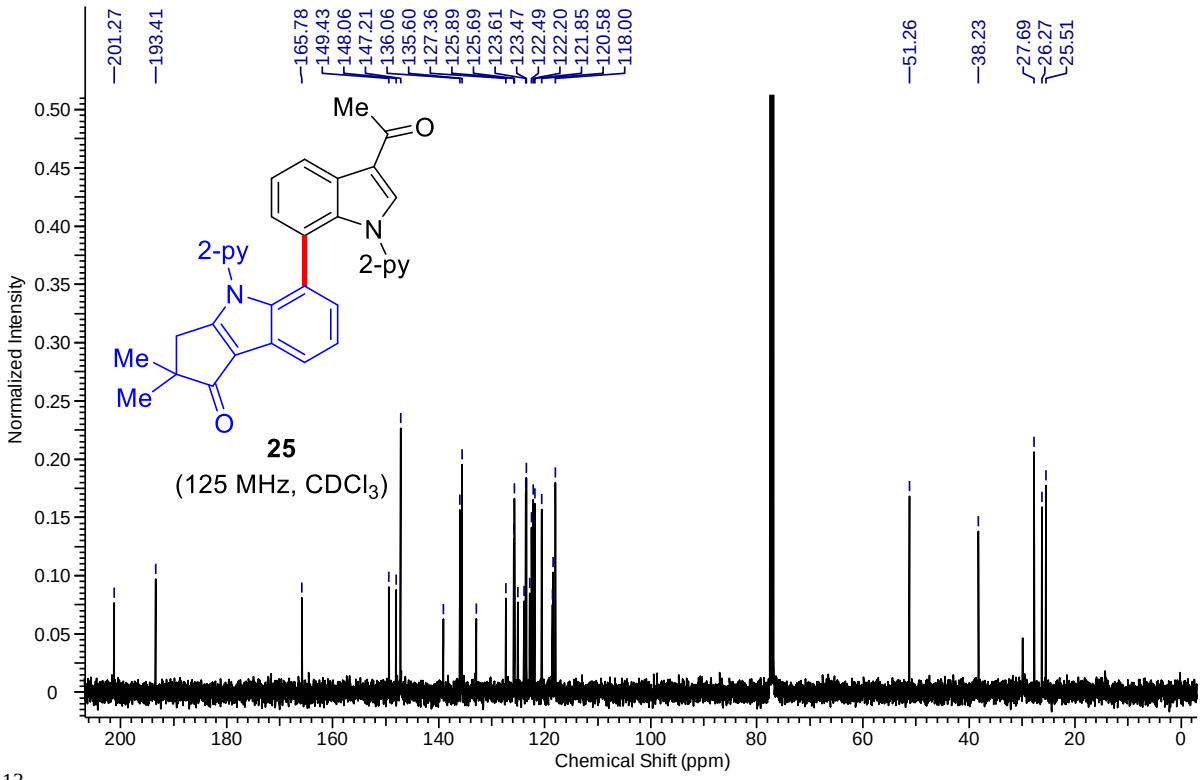
^{1}H-NMR spectrum of compound **22**



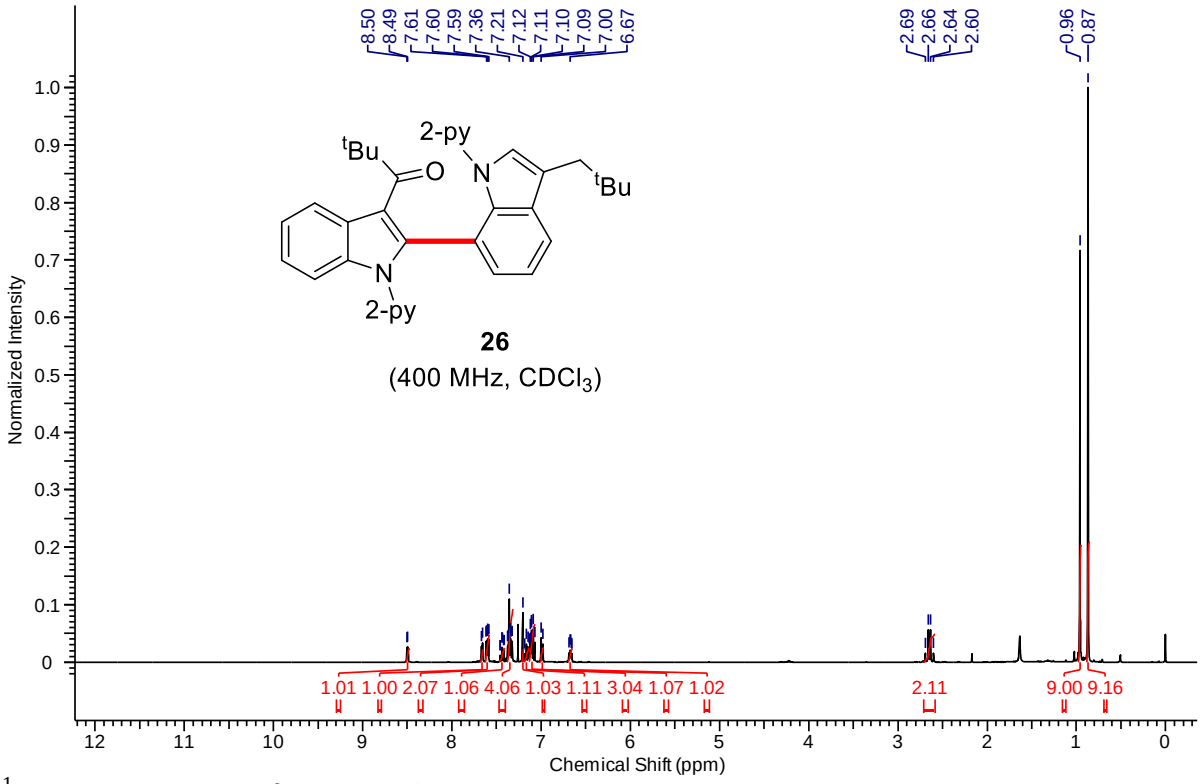
^{13}C-NMR spectrum of compound **22**



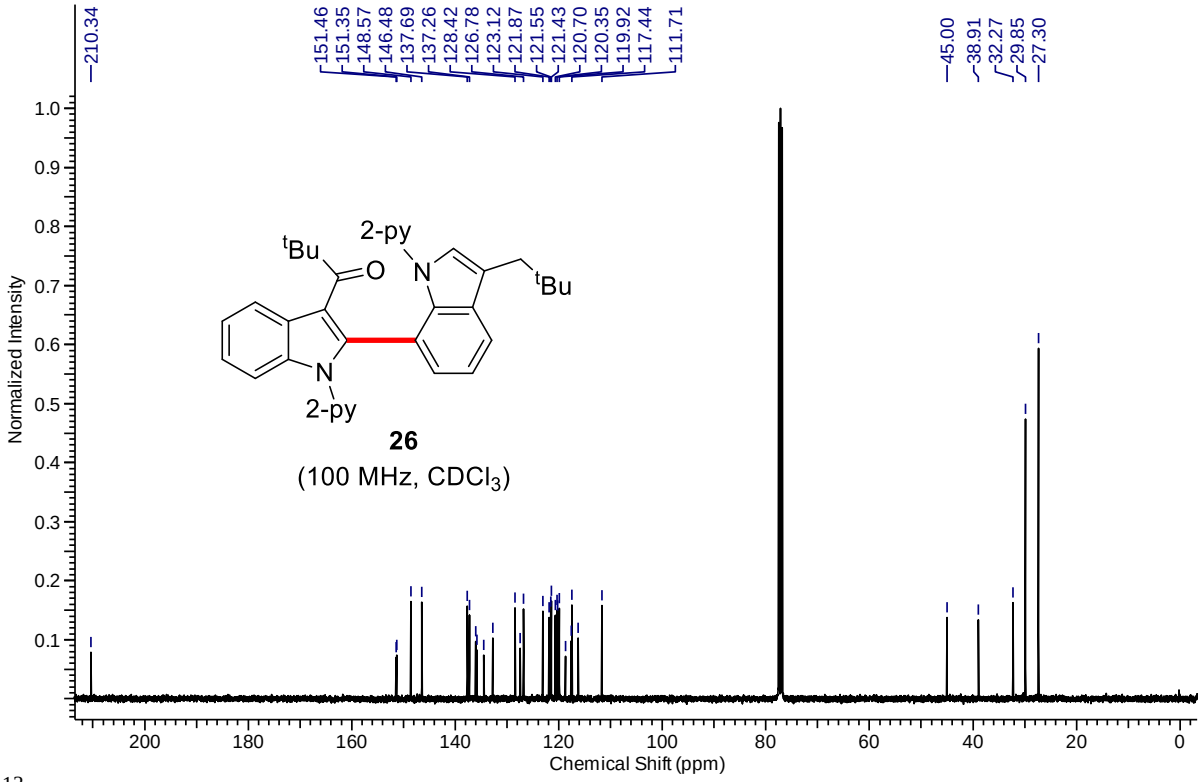
^{1}H-NMR spectrum of compound **25**



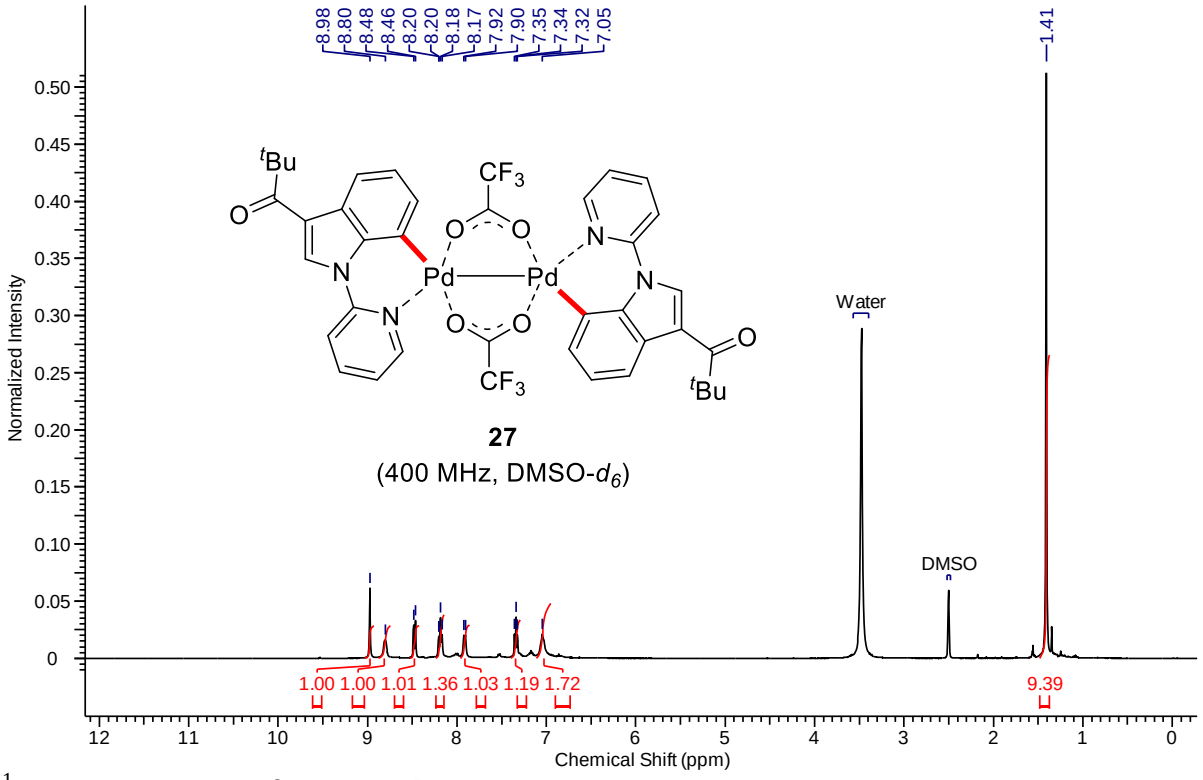
^{13}C-NMR spectrum of compound **25**



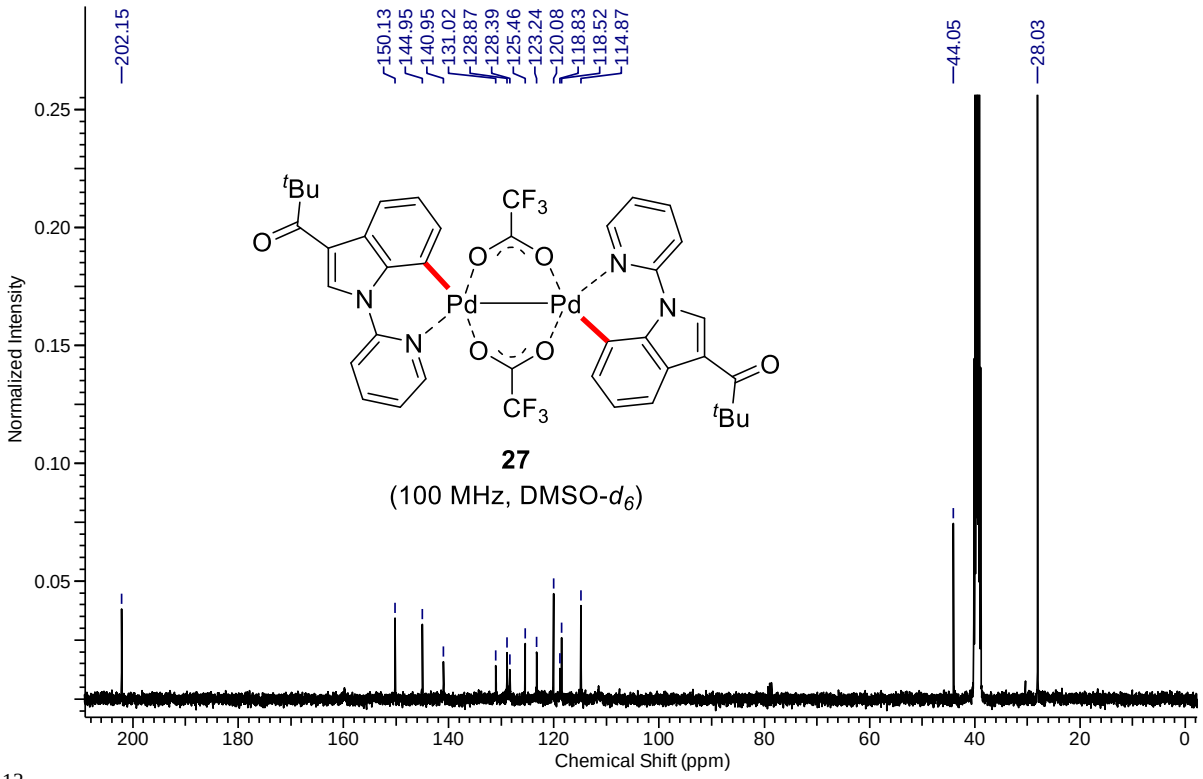
^{1}H-NMR spectrum of compound **26**



^{13}C-NMR spectrum of compound **26**



^{1}H-NMR spectrum of compound **27**



^{13}C-NMR spectrum of compound **27**

5.5 REFERENCES

1. Robinson, B., *Chem. Rev.* **1963**, *63*, 373-401.
2. Kumar, S.; Ritika,. *Future J. Pharm. Sci.* **2020**, *6*, 121.
3. Cacchi, S.; Fabrizi, G., *Chem. Rev.* **2011**, *111*, PR215-PR283.
4. Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A. K.; Choi, E. H., *Molecules* **2013**, *18*, 6620-6662.
5. Forke, R.; Jäger, A.; Knölker, H.J., *Org. Biomol. Chem.*, **2008**, *6*, 2481-2483.
6. Bertinetti, B. V.; Rodriguez, M. A.; Godeas, A. M.; Cabrera, G. M., *J. Antibiot.* **2010**, *63*, 681-683.
7. Shintani, A.; Toume, K.; Rifai, Y.; Arai, M. A.; Ishibashi, M., *J. Nat. Prod.* **2010**, *73*, 1711-1713.
8. Erenler, R.; Kul Köprülü, T.; Ökten, S.; tekin, s., *Turk. J. Biol.* **2015**, *39*, 15-22.
9. Micillo, R.; Panzella, L.; Koike, K.; Monfrecola, G.; Napolitano, A.; D'Ischia, M., *Int. J. Mol. Sci.* **2016**, *17*, 746.
10. Maeda, C.; Todaka, T.; Ueda, T.; Ema, T., *Chem. Eur. J.* **2016**, *22*, 7508-7513.
11. Tadano, S.; Sugimachi, Y.; Sumimoto, M.; Tsukamoto, S.; Ishikawa, H., *Chem. Eur. J.* **2016**, *22*, 1277-1291.
12. Šachlevičiūtė, U.; Varvuolytė, G.; Bieliauskas, A.; Kleizienė, N.; Žukauskaitė, *Molbank* **2020**, *2020*, M1146.
13. Liang, Z.; Zhao, J.; Zhang, Y., *J. Org. Chem.* **2010**, *75*, 170-177.
14. Niu, T.; Zhang, Y., *Tetrahedron Lett.* **2010**, *51*, 6847-6851.
15. Li, Y.; Wang, W.H.; Yang, S.D.; Li, B.J.; Feng, C.; Shi, Z.J., *Chem. Commun.* **2010**, *46*, 4553-4555.
16. Kianmehr, E.; Ghanbari, M.; Faghih, N.; Rominger, F., *Tetrahedron Lett.* **2012**, *53*, 1900-1904.
17. Le, J.; Gao, Y.; Ding, Y.; Jiang, C., *Tetrahedron Lett.* **2016**, *57*, 1728-1731.
18. Kumar, K. S.; Meesa, S. R.; Naikawadi, P. K., *Org. Lett.* **2018**, *20*, 6079-6083.
19. Peng, X.; Zeng, Y.; Liu, H.; Xu, X.; Zhang, M.; Liu, Q., *New J. Chem.* **2019**, *43*, 15153-15160.
20. Jagtap, R. A.; Pradhan, C.; Gonnade, R. G.; Punji, B., *Chem. Asian J.* **2022**, *17*, e202200414.
21. Lei, H.; Wang, L.; Xu, Z.; Ye, T., *Org. Lett.* **2017**, *19*, 5134-5137.
22. Lin, F.; Chen, Y.; Wang, B.; Qin, W.; Liu, L., *RSC Adv.* **2015**, *5*, 37018-37022.
23. Lu, X.M.; Cai, Z.J.; Li, J.; Wang, S.Y.; Ji, S.J., *RSC Adv.* **2015**, *5*, 51501-51507.

24. Liu, C.; Yuan, J.; Gao, M.; Tang, S.; Li, W.; Shi, R.; Lei, A., *Chem. Rev.* **2015**, *115*, 12138-12204.
25. Yang, Y.; Lan, J.; You, J., *Chem. Rev.* **2017**, *117*, 8787-8863.
26. Beckers, I.; Krasniqi, B.; Kumar, P.; Escudero, D.; De Vos, D., *ACS Catal.*, **2021**, *11*, 2435-2444.
27. Tian, M.; Bai, D.; Zheng, G.; Chang, J.; Li, X., *J. Am. Chem. Soc.* **2019**, *141*, 9527-9532.
28. Robbins, D. W.; Boebel, T. A.; Hartwig, J. F., *J. Am. Chem. Soc.* **2010,** *132*, 4068-4069.
29. Yang, Y.; Qiu, X.; Zhao, Y.; Mu, Y.; Shi, Z., *J. Am. Chem. Soc.* **2016**, *138*, 495-498.
30. Micillo, R.; Panzella, L.; Iacomino, M.; Prampolini, G.; Cacelli, I.; Ferretti, A.; Crescenzi, O.; Koike, K.; Napolitano, A.; d'Ischia, M., *Sci. Rep.* **2017**, *7*, 41532.
31. Shan, G.; Yang, X.; Ma, L.; Rao, Y., *Angew. Chem. Int. Ed.* **2012**, *51*, 13070-13074.
32. Wang, Y.T.; Qin, Y.J.; Yang, N.; Zhang, Y.L.; Liu, C.H.; Zhu, H.L., *Eur. J. Med. Chem.* **2015**, *99*, 125-137.
33. Xing, S.; Gao, T.; Jin, C.; Dong, H.; Shao, X.; Wang, K.; Zhu, B., *Adv. Synth. Catal.* **2023**, *365*, 104-109.
34. Pradhan, C.; Jagtap, R. A.; Samal, P. P.; Krishnamurty, S.; Punji, B., *Green Chem.* **2023**.
35. Bruker, *APEX3, SAINT and SADABS*. Bruker AXS Inc., Madison, Wisconsin, USA. **2016**.
36. Sheldrick, G. M., *Acta Crystallogr.* **2008**, *A64*, 112-122.
37. Sheldrick, G. M., *Acta Crystallogr.* **2015**, *C71*, 3-8.
38. Farrugia, L. J., *J. Appl. Crystallogr.* **2012**, *45*, 849-854.

Chapter 6

Summary and Outlook

6.1 SUMMARY

The establishment of C–C/C–O bonds has emerged as a powerful tool with application to material sciences, pharmaceutical industries, and the synthesis of natural products. Notably, the selective functionalization of inert C(sp^2)–H and C(sp^3)–H bonds to form C–C/C–O bonds are restricted to traditional methods or limited to harsh reaction conditions and sensitive reagents. In that context, the thesis work investigates the problem related to the precedented approaches and attempts to resolve those by developing suitable catalytic systems and novel reaction methodologies to achieve mild reaction conditions by employing the palladium catalyst.

In that context, **Chapter 1** provides an in-depth literature review on the oxygenation of synthetic and biological essential amides and indole derivatives. Additionally, it covers the selective C–C dimerization of indoles.

Chapter 2: Amide represents a privileged constituent for the synthesis of many pharmaceutical drugs and biologically active compounds. Specifically, *β*-C(sp^3)–H oxygenated amides are essential because of their tremendous pharmacological activities. Precedented approaches for their synthesis are limited to harsh reaction conditions, a stoichiometric amount of catalyst loading, and the accession of the directing group. In this project, palladium-catalyzed acetoxylation of simple amides that proceeds via weak chelation assistance is established to address these limitations. Notably, the reaction uses a low loading of palladium, unlike the precedented strong *N*-chelating acetoxylation that employs a substantial loading of Pd (> 5 mol%). The reaction demonstrated the tolerability of synthetically important functionalities, like chloro, fluoro-alkyl, fluoro-arene, ester, and nitro groups, in addition to the heterocycles. The synthetic utility is demonstrated by a gram-scale reaction and further functionalization into alcohols, tertiary amines, and alcohol-acids. A preliminary KIE study indicated that the C–H activation step is rate-limiting.

Chapter 3: Isatin is an elite oxidized indole nucleus and has gained particular attention as a core motif in developing numerous pharmacologically active compounds. Notably, the hydroxy group-containing isatins represent the important subclass among the isatin-based natural products. The precedented approaches for their synthesis are restricted to traditional protocol or cyclization methods. Unfortunately, the direct oxygenation at the selective C–H position of isatin has not been precedented yet. This project discusses the direct oxygenation of selective C–H bonds in isatins by palladium catalyst. The $PhI(OAc)_2$ or selectfluor oxidant in the Pd-catalyzed protocol in 1.0 M acidic solution exclusively provided C5 oxygenation of

isatins *via* electrophilic palladation. However, the same reaction employing $K_2S_2O_8$ in a dilute solution (0.13 M) selectively afforded *N*-methyl C(sp^3)–H oxygenation through carbonyl-assisted intramolecular –*N*CH_3 C(sp^3)–H radical palladation. The practical applicability of oxygenation is demonstrated through a gram-scale reaction, showcasing its synthetic utility. Additionally, diverse oxygenated isatins with sensitive functionalities, including bio-relevant compounds, were synthesized to illustrate the potential for further derivatization.

Chapter 4: Indoles are the structural frame of numerous biologically active compounds and natural products. The functionalizations at selective C2 and C3 C−H bonds of indoles have been extensively investigated. However, limited studies have focused on indole's less reactive C4 C−H bond functionalization. In particular, the oxygenation of the C4 C−H bond is provocative as C4-alkoxy-indoles, which serve as structural components in numerous drug molecules and natural products. In this project, we have successfully achieved a Pd-catalyzed C4-fluoroalkoxylation of indoles with the assistance of weak chelation using fluoroalcohols. The fluoroalkoxylation protocol demonstrates extensive applicability, accommodating diverse functional groups like halides, esters, and thiophene. The practicality of the palladium-catalyzed method is illustrated by the facial removal of the tosyl group, carbonyl directing group, gram scale synthesis, and highlighting its applicability in late-stage modifications of fluoroalkoxylated products. The catalytically active intermediates were isolated and structurally characterized. The preliminary reaction mechanism demonstrate that the reaction proceed via initial C4–H activation. Due to the significant role of the trifluoroethoxyl group in enhancing the bioavailability of organic molecules in medicinal chemistry, we expect that this reaction will garner considerable attention in the field of drug discovery.

Chapter 5: Indole dimers are crucial motifs in many biologically active compounds and natural products. In the last few decades, the construction of the 2,2', 2,3', and 3,3'-linked dimer motifs was precedented. However, precedented approaches are limited to traditional methods to construct 2,2', 2,3', and 3,3'-linked bi-indolyl scaffolds. Thus, in this chapter using a palladium catalyst, we have shown the regioselective oxidative coupling at the C2–C7 positions of C3 substituted indoles, with pyridine serving as a directing group. The C3-substituted carbonyl and *N*-pyridinyl groups emerged as pivotal factors in achieving the selective formation of C2–C7 biindoles. The reaction protocol is compatible with indole substrates having numerous functionalities at C3, C4, and C5 positions, such as halides, aldehydes, ester, trifluoromethane, as well as

heteroarenes such as morpholinyl, and thiophene are well tolerated under the standard conditions. The practicality of this Pd-catalyzed method was demonstrated by reducing the carbonyl group and gram scale synthesis. The catalytically active intermediates were isolated and structurally characterized. The preliminary reaction mechanism demonstrate that the reaction proceed via initial C7–H activation follow by C2–H activation.

6.2 OUTLOOK

We have successfully addressed challenges associated with existing methodologies for the oxygenation of amides, indoles, and isatins and the oxidative dimerization of indoles at C(2)−H/C(7)−H positions. Despite this progress, there is still scope for enhancing the conditions governing C−H functionalization reactions. In Chapter 2, an attempt at the acetoxylation of the methylene β-C(sp^3)−H bond in alkyl and cyclic amides proved unsuccessful, specifically in achieving acetoxylation of the primary β-C(sp^3)−H bond of amides. Our focus should now shift towards developing enhanced conditions for the acetoxylation of methylene β-C(sp^3)−H bonds and the acyloxylation of amides, utilizing acids as coupling partners. In Chapter 3, a comprehensive mechanistic study is imperative to understand the impact of solvent concentration on the selective oxygenation of C5-(sp^2)−H and *N*-methyl C(sp^3)−H bonds in isatin. Additionally, expanding the substrate scope beyond *N*-substituted isatins is crucial.

In Chapter 4, emphasis should be placed on the C4 alkoxylation reaction of indoles using unactivated alcohols as coupling partners, and this should be achieved under mild reaction conditions. Additionally, expanding the substrate scope beyond *N*-substituted indole is crucial. The final chapter focuses on the intermolecular C(2)−H/C(7)−H oxidative homocoupling of indoles. While well-functionalized indole homocoupling has been accomplished, the exploration of oxidative hetero-coupling of indole derivatives is paramount. Considering the synthesis of chiral bisindoles, the utilization of a chiral catalyst presents an avenue worth exploring. Most importantly, novel methods should be developed using inexpensive and earth-abundant 3d transition metals for selective oxygenation and dimerization reactions.

ABSTRACT

Name of the Student: Vijaykumar M **Registration No**: 10CC18A26058
Faculty of Study: Chemical Science **Year of Submission**: 2023
AcSIR academic centre/CSIR Lab: CSIR-NCL **Name of the Supervisor**: Dr. Benudhar Punji
Title of the Thesis: "Regioselective C–H Bond Oxygenation in Amides, Indoles and Isatins, and Oxidative C–C Bond Formation in Indoles by Palladium Catalyst"

The construction of C–C/C–O bonds has emerged as a powerful tool with application to material sciences, pharmaceutical industries, and the synthesis of natural products. Notably, the selective functionalization of inert C(sp^2)–H and C(sp^3)–H bonds to form C–C/C–O bonds are restricted to traditional methods or limited to harsh reaction conditions and sensitive reagents. In that context, Chapter 1 deals with the detailed literature survey on the oxygenation of synthetic and biological essential amides and indole derivatives and selective C–C dimerization of indoles.

In Chapter 2, we have discussed selective C(sp^2)–H and C(sp^3)–H oxygenation of amide-containing substrates using a palladium catalyst. Acetoxylation of amides provided a direct approach for synthesizing variously functionalized and pharmaceutically relevant acetoxy-amides with the tolerance of sensitive functionalities. The kinetic isotopic effect study suggested the rate-determining C(sp^3)−H bond activation. A gram-scale reaction and further functionalization into alcohols, tertiary amines, and acids exhibit synthetic utility.

Similarly, the isatin framework leads to diverse privileged molecules entrenched as antimalarial, antifungal, antibacterial, antiviral, and potential antitumor agents. Therefore, developing protocols for the efficient hydroxylation of isatins is highly indispensable. Chapter 3 discusses the direct oxygenation of selective C−H bonds in isatins by palladium catalyst. The $PhI(OAc)_2$ or selectfluor oxidant in the Pd-catalyzed protocol in 1.0 M acidic solution exclusively provided C5 oxygenation of isatins *via* electrophilic palladation. However, the same reaction employing $K_2S_2O_8$ in a dilute solution (0.13 M) selectively afforded *N*-methyl C(sp^3)–H oxygenation through carbonyl-assisted intramolecular –*N*CH_3 C(sp^3)–H radical palladation.

Indoles are the structural frame of numerous biologically active compounds and natural products. The functionalizations at selective C2 and C3 C−H bonds of indoles have been considerably reported. However, limited studies have focused on indole's less reactive C4 C−H bond functionalization. In particular, the C4 C−H oxygenation is provocative as C4-alkoxy-indoles, which are structural constituents of various drug molecules and natural products. In Chapter 4, palladium-catalyzed regioselective C4 alkoxylation has been adept at

using readily available alcohols under mild conditions. This protocol shows high regioselectivity for the selective C4-alkoxylation of indole using C3 benzoyl as a directing group. Significant features of this modification include the board substrate scope and excellent functional group tolerance.

Indole dimers are crucial motifs in many biologically active compounds and natural products. In the last few decades, the construction of the 2,2', 2,3', and 3,3'-linked dimer motifs was precedented. However, precedented approaches are limited to traditional methods to construct 2,2', 2,3', and 3,3'-linked bi-indolyl scaffolds. Thus, Chapter 5 discusses a strategic approach to intermolecular C(2)−H/C(7)−H oxidative dimerization of indoles using a palladium catalyst. The easily installed *N*-pyridinyl and C3 carbonyl group of indole exerted the regioselective formation of 2,7-biindoles. A wide array of indole substrates having numerous functionalities at C3, C4, and C5 positions are well tolerated under the reaction condition. This methodology has been developed as a practical approach for synthesizing the 2,7-biindole core, a structure of fundamental importance in material and pharmaceutical chemistry.

.

LIST OF PUBLICATIONS

1. **Vijaykumar, M.;** Punji, B., "Advances in Transition-Metal-Catalyzed C–H Bond Oxygenation of Amides" *Synthesis* **2021**, *53*, 2935.

2. **Vijaykumar, M.;** Punji, B., "Pd(II)-Catalyzed Chemoselective Acetoxylation of C(sp^2)–H and C(sp^3)–H Bonds in Tertiary Amides" *J. Org. Chem*. **2021**, *86*, 8172.

3. **Vijaykumar, M**.; Pradhan, C.; Gonnade, R. G.; Punji, B., "Palladium-Catalyzed Chemoselective Oxygenation of C(sp^2)–H and C(sp^3)–H Bonds in Isatins" *Org. Lett*. **2023**, *25*, 1862.

4. **Vijaykumar, M**.; Punji, B., "Palladium-Catalyzed Regioselective C(4)−H Alkoxylation of Indoles using Weak Chelation". (*Manuscript under preparation*)

5. **Vijaykumar, M**.; Punji, B., Pd(II)-Catalyzed Chemoselective Acetoxylation of C(sp^2)–H and C(sp^3)–H Bonds in Tertiary Amides". (*Manuscript under preparation*)

LIST OF NATIONAL CONFERENCES

1. **Vijaykumar, M**.; Punji, B. "Palladium-Catalyzed Solvent-Controlled Chemoselective Oxygenation of C(sp^2)-H and C(sp^3)-H Bonds in Isatins" *Poster presentation in National Conference on Contemporary Facets in Organic Synthesis (CFOS- 2022*) at Department of Chemistry, Indian Institute of Technology Roorkee.

2. **Vijaykumar, M**.; Punji, B. "Palladium-Catalyzed Chemoselective Acetoxylation of C(sp^2)-H and C(sp^3)-H Bonds in Tertiary Amides" *Poster Presentation in Science Day Celebration 2020* at CSIR- National Chemistry Laboratory, Pune.

3. **Vijaykumar, M**.; Punji, B. "Palladium-Catalyzed Chemoselective Acetoxylation of C(sp^2)-H and C(sp^3)-H Bonds in Tertiary Amides" *Poster Presentation in Science Day Celebration 2019* at CSIR- National Chemistry Laboratory, Pune.

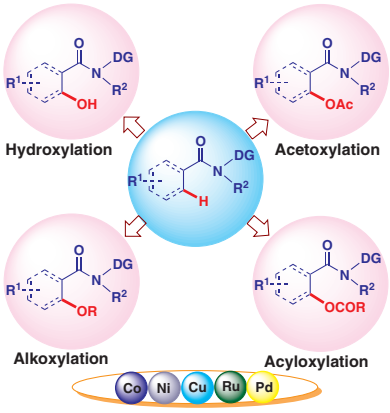
Synthesis M. Vijaykumar, B. Punji Special Topic

Advances in Transition-Metal-Catalyzed C–H Bond Oxygenation of Amides

Muniyappa Vijaykumar[a,b]
Benudhar Punji*[a,b]

[a] Organometallic Synthesis and Catalysis Lab, Chemical Engineering Division, CSIR–National Chemical Laboratory (CSIR–NCL), Dr. Homi Bhabha Road, Pune - 411 008, India
b.punji@ncl.res.in
[b] Academy of Scientific and Innovative Research (AcSIR), Ghaziabad - 201 002, India

Published as part of the Special Topic
Bond Activation – in Honor of Prof. Shinji Murai



Received: 16.03.2021
Accepted after revision: 13.04.2021
Published online: 13.04.2021
DOI: 10.1055/a-1481-2584; Art ID: ss-2021-f0146-st

Abstract C–O bond formation represents a fundamental chemical transformation in organic synthesis to develop valuably oxygenated (hetero)arenes. Particularly, the direct and regioselective C–H bond oxygenation of privileged amides, using a transition metal catalyst and a mild oxygenating source, is a step-economy and attractive approach. During the last decade, considerable progress has been realized in the direct C–H oxygenation of primary, secondary, and tertiary amides. This Short Review compiles the advances in transition-metal-catalyzed oxygenation of C(sp^2)–H and C(sp^3)–H bonds on various amides with diverse oxygenation sources. The review is categorized into two different major sections: (i) C(sp^2)–H oxygenation and (ii) C(sp^3)–H oxygenation. Each section is discussed based on the directing group (monodentate and bidentate) attached to the amide derivatives.

1 Introduction
2 C(sp^2)–H Oxygenation
2.1 Monodentate Directed
2.2 Bidentate Directed
3 C(sp^3)–H Oxygenation
3.1 Monodentate Directed
3.2 Bidentate Directed
4 Conclusion and Outlook

Key words amides, C–H activation, directing group, oxygenation, transition metal

Muniyappa Vijaykumar obtained his B.Sc. and M.Sc. degrees from Bengaluru University, Bengaluru, Karnataka, India. After qualifying CSIR-JRF in 2018, he joined Dr. Punji's group at CSIR-National Chemical Laboratory, Pune, to pursue doctoral studies. His current research focuses on transition-metal-catalyzed C–H bond functionalization of amide derivatives and mechanistic investigations.

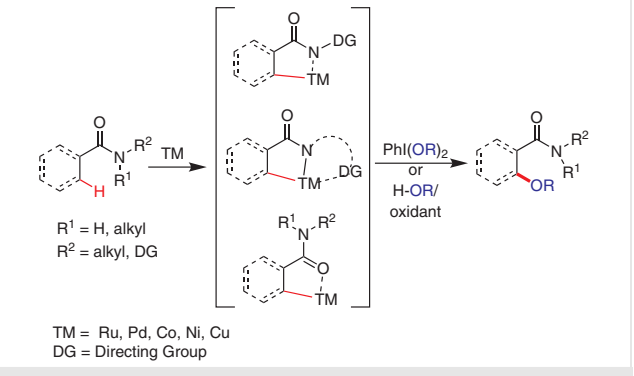
Benudhar Punji is a Principal Scientist at CSIR-National Chemical Laboratory, Pune and Associate Professor, Academy of Scientific & Innovative Research (AcSIR). Dr. Punji obtained Ph.D. from the Indian Institute of Technology, Bombay (IITB), Mumbai, under the supervision of Prof. M. S. Balakrishna. Upon graduation, he worked as an NSF-CENTC post-doctoral fellow with Prof. Alan S Goldman at Rutgers University, USA and then as a prestigious Alexander von Humboldt (AvH) post-doctoral fellow with Prof Lutz Ackermann at the University of Göttingen, Germany. As an independent investigator, Dr. Punji develops novel 3d metal-based catalysts for C–H functionalization of (hetero)arenes, and asymmetric hydrogenation of bioactive compounds. His focus is mostly on mechanistic-based homogeneous catalysis and organometallic chemistry.

1 Introduction

Transition-metal-catalyzed oxygenation of inert C(sp^2)–H and C(sp^3)–H bonds to C–O bonds has emerged as a powerful tool,[1] with application to material sciences, pharmaceutical industries, and natural product synthesis.[2] Traditionally, oxygenated compounds are developed via condensation of alcohols, reaction of alkoxides with alkyl halides (Williamson synthesis), alkoxy mercuration/demercuration of alkenes, and combining carboxylic acids and alcohols.[3] However, most of these methods are associated with limited substrate scope, harsh reaction conditions, multistep

synthetic sequences, and generation of byproducts. Thus, the direct oxygenation of a C–H bond to give a C–O bond has significant potential in chemical synthesis, particularly in terms of versatility and step-economy.[4]

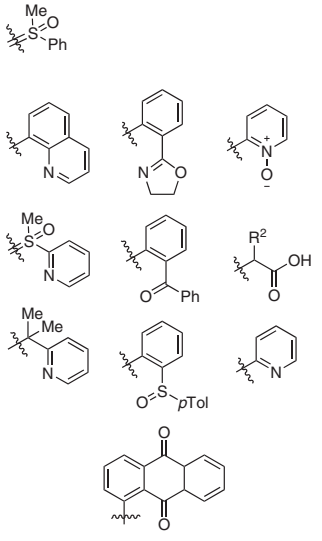
The amide functional group is an important moiety in synthetic organic chemistry and can be smoothly transformed into useful functionalities, like aldehyde, carboxylic acid, and amine. Therefore, the synthetic transformations of amides are highly desirable. In recent years, significant attention has been devoted to the transition-metal-catalyzed C–H functionalization of amides.[5] Particularly, the regioselective C–H oxygenation of amide-bearing compounds is indispensable. In this direction, diverse C–O bond formations, such as alkoxylation, acetoxylation, acyloxylation, and hydroxylation of both C(sp^2)–H and C(sp^3)–H bonds on aromatic and aliphatic amides have been extensively studied. Particularly, C–O bond formation in primary and secondary amides proceeds via the chelation-assisted coordination of *N*-amidate to the transition metal catalyst (Scheme 1). The lone pair of electrons on amide is utilized to coordinate reversibly to a transition metal, which brings the metal into proximity to the C–H bond to be functionalized. Moreover, this strong coordination expedites the C–H activation by forming a thermodynamically favorable metallacycle. A substantial number of reports on C(sp^2)–H and C(sp^3)–H oxygenation of amides with the help of bidentate-coordination by introducing 8-aminoquinolinyl, 2-(pyridin-2-yl)isopropyl (PIP), pyridine-2-carboxamide (picolinamide), *S*-(pyridin-2-yl)sulfoximine moieties, are also known. In contrast to the oxygenation via strong *N*-amidate coordination, examples of the oxygenation of unactivated C–H bonds on privileged and multifunctional amides with a weakly coordinating carbonyl (C=O) group are known, which is presumed to occur via a less favored cyclometalated intermediate.



Scheme 1 Representation of DG coordination and C–H activation in amides

Given the importance of oxygenated amide derivatives and the significance of C–H bond oxygenation, this Short Review summarizes the coupling of oxygenating nucleophiles with C–H of amide derivatives. The development in C(sp^2)–H and C(sp^3)–H oxygenation of amides, catalyzed by both first- and second-row late transition metals, such as Ru, Pd, Co, Ni, and Cu, is highlighted in this Short Review (Table 1). The review is arranged based on oxygenation of C(sp^2)–H and C(sp^3)–H bonds of amide derivatives, followed by the types of amides (native amides or directing group containing amides). The oxygenation of each of the amides is further discussed based on the type of transition metal catalyst used. Mostly, transition-metal-catalyzed oxygenations are described; thus, oxygenation via other processes would be outside the scope of this review. Attention is given to the oxygenation of C(sp^2)–H and C(sp^3)–H bond of amides, mono- and bidentate directing groups, and to the involved mechanistic pathways.

Table 1 Overview of Transition-Metal-Catalyzed C(sp^2)–H and C(sp^3)–H Oxygenation of Amide

N-Substituent (R) on amide (DG)	TM	Oxidant/oxygenating partner
R = alkyl, OMe	Ru Pd	PhI(OAc)$_2$ (or) PhI(OAc)$_2$/H-OR $K_2S_2O_8$/H-OR $(NH_4)S_2O_8$/H-OR NFSI/H-OR
	Pd Co Ni Cu	PhI(OAc)$_2$ (or) PhI(OAc)$_2$/H-OR $K_2S_2O_8$/H-OR Oxone/H-OR $(NH_4)S_2O_8$/H-OR Mn(OAc)$_3$/H-OR Ag_2CO_3/H-OR Ag_2O/H-OR Ag_2SO_4/H-OR

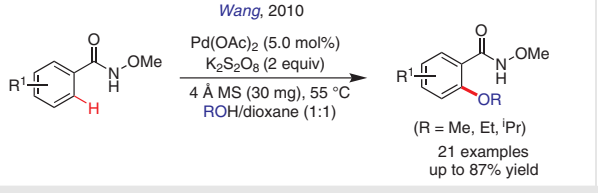
2 C(sp^2)–H Oxygenation

Classical methods to construct the C(sp^2)–O bond in arenes involve the Friedel–Crafts reaction or the traditional coupling of organometallic arenes with oxygenating nucleophiles.[3a–c] In recent years, the advancement in C–H bond functionalization has provided alternative protocols for beneficial and sustainable synthesis. In that direction, C–H bond oxygenation of diverse arenes has been demonstrated using a variety of transition-metal catalysts. The simple arenes and substituted arenes can be smoothly oxygenated employing diverse oxygenating reagents, including atmospheric air. Particularly, the regioselective C(sp^2)–H oxygenation of arenes is a challenging task, which is generally

accomplished by introducing a Lewis base directing group (DG). In the oxygenation of benzamides, the amido functionality (CONHR) in benzamides behaves as a suitable directing group because of its convenient coordinating power. Similarly, the strong N-coordination of 8-aminoquinolinyl, 2-(pyridin-2-yl)isopropyl (PIP), sulfoximine, and sulfinyl aniline moieties in benzamides facilitates regioselective C(sp^2)–H oxygenation. In this section, we have highlighted advancements in the direct oxygenation of benzamides using various oxygenating sources with monodentate and bidentate directing group assistance.

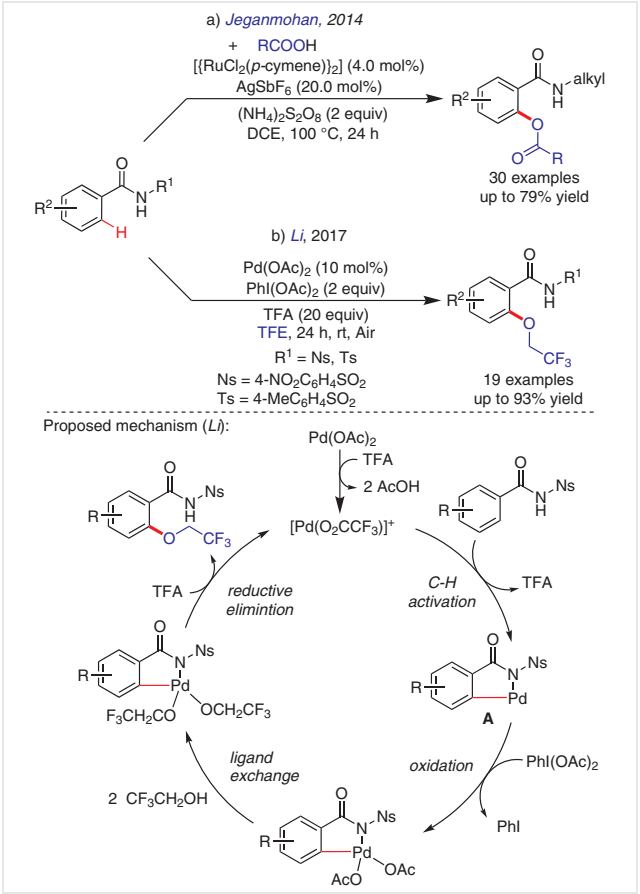
2.1 Monodentate Directed

Regioselective *ortho*-C(sp^2)–H oxygenation of benzamides has been explored employing both the precious 4d transition metals and nature-abundant 3d metal catalysts via monodentate chelation-assistance. For this purpose, various oxygenating sources, such as metal salts, $PhI(OAc)_2$, peroxides, alcohols, and acids are used. A Pd-catalyzed protocol was reported for the *ortho*-alkoxylation of *N*-methoxybenzamides by Wang and Yuan in 2010 (Scheme 2).[6] The reaction employed $K_2S_2O_8$ as an oxidant and alcohols, like MeOH, EtOH, and ^{i}PrOH, for the alkoxylation of benzamide. The amidate directing group played a crucial role, which can be ascertain from the poor reactivity of a reaction involving an acetanilide directing group for the alkoxylation. Diverse *N*-methoxybenzamides with electron-donating and electron-withdrawing groups were alkoxylated efficiently. Secondary alcohols as alkoxylating reagents provided moderate yields, whereas a tertiary alcohol failed to react with *N*-methoxybenzamide under the optimized conditions. Notably, the reaction has been proposed to proceed via Pd(II)/Pd(IV). A theoretical study of the reaction suggested the crucial role of the alcoholic solvent, which assisted in N–H and C–H activation.[7] Moreover, the transition state leading to palladacycle formation is more stable in the methanol-assisted pathway. This protocol highlighted the importance of the *N*-directed alkoxylation.



Scheme 2 Pd-catalyzed alkoxylation of *N*-methoxybenzamide

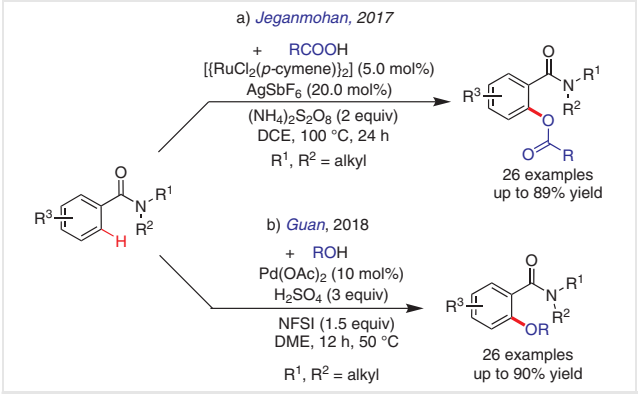
In 2014, Jeganmohan and Padala reported the *ortho*-benzoxylation of *N*-alkylbenzamides with aromatic carboxylic acid catalyzed by a Ru complex (Scheme 3a).[8] Thus, the catalytic system $[RuCl_2(p\text{-cymene})]_2/AgSbF_6$ in the presence of oxidant $(NH_4)_2S_2O_8$ facilitated the regioselective benzoxylation of diverse benzamides with aromatic acids. The benzoxylation occurred selectively at the less sterically substituted *ortho* position in a *meta*-substituted benzamide. Important functionalities like halides, CF_3, and NO_2 were well tolerated under the reaction conditions and afforded the products in good yields. Notably, the benzoxylated *N*-alkylbenzamides were smoothly converted into *o*-hydroxybenzamides upon treatment with an acid or a base. This reaction is limited to aromatic acids, which might be due to the rapid complex formation of the carboxylic acids with ruthenium. The reaction is assumed to occur via the generation of a cationic Ru species and followed a Ru(II)/Ru(0) pathway. In an independent development, Li, Ji, and coworkers have introduced the trifluoroethoxy functionality at the *ortho* position of *N*-sulfonylbenzamides using a Pd(II) catalyst (Scheme 3b).[9] The reaction occurred at room temperature using $PhI(OAc)_2$ oxidant in TFA/TFE solvent system. A Pd(II)/Pd(IV) pathway has been proposed for this reaction, wherein an *N*-amido-Pd ligation stabilizes the high-valent palladium intermediate. Though the installation of the fluoroalkoxy group in benzamide is significant, the employment of 10 mol% of Pd catalyst is a concern in this reac-



Scheme 3 Benzoxylation and trifluoroethoxylation of secondary benzamides

tion. Moreover, most of the products were obtained only in moderate yields. Interestingly, the protocol was applied in the synthesis of the drug molecule Flecainide.

In addition to the oxygenation of secondary benzamide, the C(sp^2)–H acyloxylation via *tert*-amide direction-assistance has been reported with ruthenium and rhodium catalysis.[10] Jeganmohan and co-workers have demonstrated the benzoxylation of *tert*-benzamide with a Ru catalyst, which is assumed to proceed by weak C=O coordination of the amide group (Scheme 4a).[10a] The catalytic reaction was efficient in the presence of chloro, ether, ester, and nitro functionalities. Several carboxylic acids were employed as coupling partners, wherein the electron-deficient systems reacted in high efficiency. The *o*-benzoxylated benzamides can be easily converted into *o*-benzoxylated benzaldehydes at room temperature using Cp_2ZrHCl. Notably, the attempted benzoxylation with 4-methoxybenzoic acid, diphenylacetic acid, phenylacetic acid, acetic acid, 6-bromohexanoic acid, propanoic acid, palmitic acid, pipecolic acid, isobutyric acid, isovaleric acid, and pivalic acid all failed.

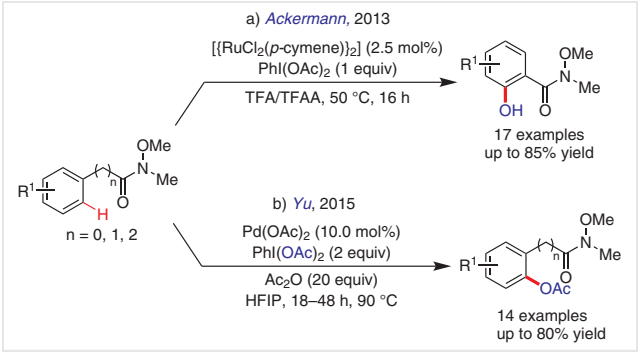


Scheme 4 Ru- and Pd-catalyzed oxygenation of *tert*-benzamides

Zhang and co-workers reported the selective acetoxylation of enamides using $[RhCp^*Cl_2]_2$ as the catalyst and $Cu(OAc)_2$ as the terminal oxidant.[10c] This method exemplified the first report on acetoxylation of the olefinic C–H bond in enamides with absolute *Z*-configuration. Though the reaction proceeded under mild conditions, it needs a significant time of 36 hours.

In a distinct protocol, Guan and co-workers reported the Pd-catalyzed *ortho*-alkoxylation of *tert*-benzamides using various alcohols (Scheme 4b).[11] The reaction employed NFSI (*N*-fluorobenzenesulfonimide) as an oxidant and was carried out under acidic conditions. Notably, the alkoxylation is limited to the use of aliphatic alcohols and electron-rich benzamide derivatives. This alkoxylation proceeds via a Pd(II)/Pd(IV) pathway involving the rate-limiting C–H activation process.

Weinreb amides are crucial synthetic functionalities due to their easy transformative tendency. Thus, the functionalization of Weinreb amide is significant, particularly by the C–H activation strategy. In 2013, the Ackermann group disclosed a versatile Ru-catalyzed *ortho*-C–H oxygenation of Weinreb amides.[12] The protocol allowed the direct synthesis of *ortho*-hydroxylated Weinreb amides with good scope under mild reaction conditions (Scheme 5a).[12a] Notably, electron-rich Weinreb amides reacted preferentially over electron-deficient examples. The preliminary kinetic analysis supported the irreversible and crucial C–H bond activation process. In 2020, the Ackermann group demonstrated an iodine(III)/Ru(II)-electrocatalyzed *ortho*-hydroxylation of synthetically useful Weinreb amides.[12b] This protocol was enabled by the catalytic generation of hypervalent iodine(III) reagents with sustainable electricity as a cost-effective terminal oxidant. The amides bearing *para*- and *meta*-substituents, such as chloro, bromo, or iodo groups, as well as sensitive benzyl chlorides were well tolerated. Mechanistic studies by experiment, computation, and flow NMR spectroscopy supported a fast and reversible C–H ruthenation.

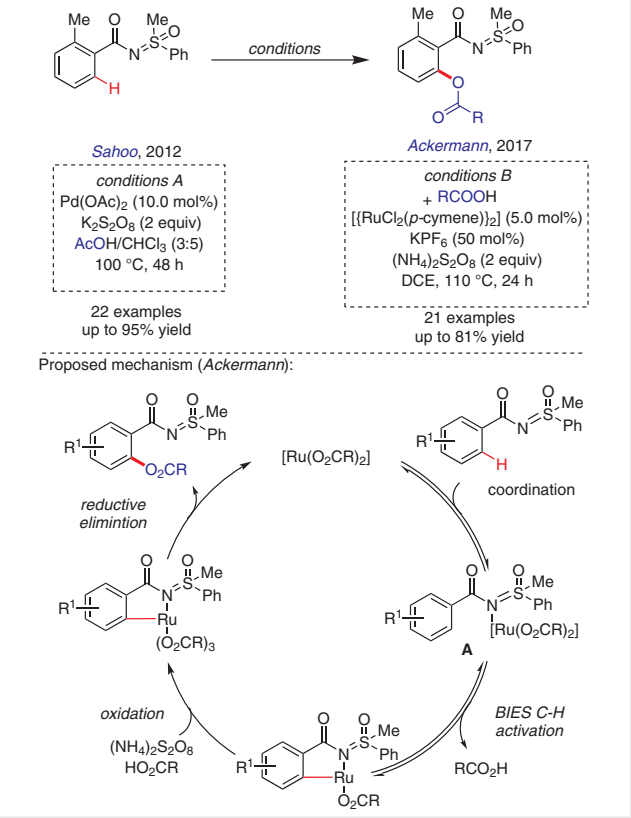


Scheme 5 Ru- and Pd-catalyzed oxygenation of Weinreb amides

Acetoxylation of similar Weinreb amides was also demonstrated by Yu and co-workers using a Pd-catalyzed protocol that proceeds via weak distal coordination of the C=O moiety (Scheme 5b).[13] Particularly, the long-distance tolerance between the directing functional group and the target C–H bond is notable in this protocol. This reaction needed a significantly long reaction time for completion. Moreover, the use of high loading (10 mol%) of palladium in this reaction is a concern.

Sulfoximines are identified as versatile directing groups in C–H functionalization reactions.[14] To this end, the Sahoo group have demonstrated the regioselective *ortho*-C–H acetoxylation of *N*-sulfoximine amides by Pd catalysis (Scheme 6).[15] This protocol employed mild inorganic oxidant $K_2S_2O_8$ and AcOH/$CHCl_3$ solvent system to acetoxylate a range of *N*-sulfoximine benzamides. Notably, the *N*-sulfoximine directing group can be smoothly detached from the oxygenation product and reused further. Moreover, the reaction can achieve β,β′-diacetoxylation products under force conditions. The Ackermann group have extended the oxygenation of *N*-sulfoximine benzamides employing a Ru catalyst,

wherein diversely decorated benzoic acids were used as coupling partners to achieve *ortho*-benzoxylated benzamides (Scheme 6).[16] The reaction proceeded with excellent chemoselectivity via base-assisted intramolecular electrophilic substitution-type C–H activation. Notably, electron-rich benzamides reacted preferentially and electron-rich aromatic carboxylic acids proved more reactive. However, aliphatic carboxylic acids were unsuitable for this oxygenation reaction. Both the Pd- and Ru-catalyzed protocols for the oxygenation of *N*-sulfoximine benzamides are significant considering the smooth removal of the directing group. However, the requirement for longer reaction times could be a practical disadvantage and needs further development.

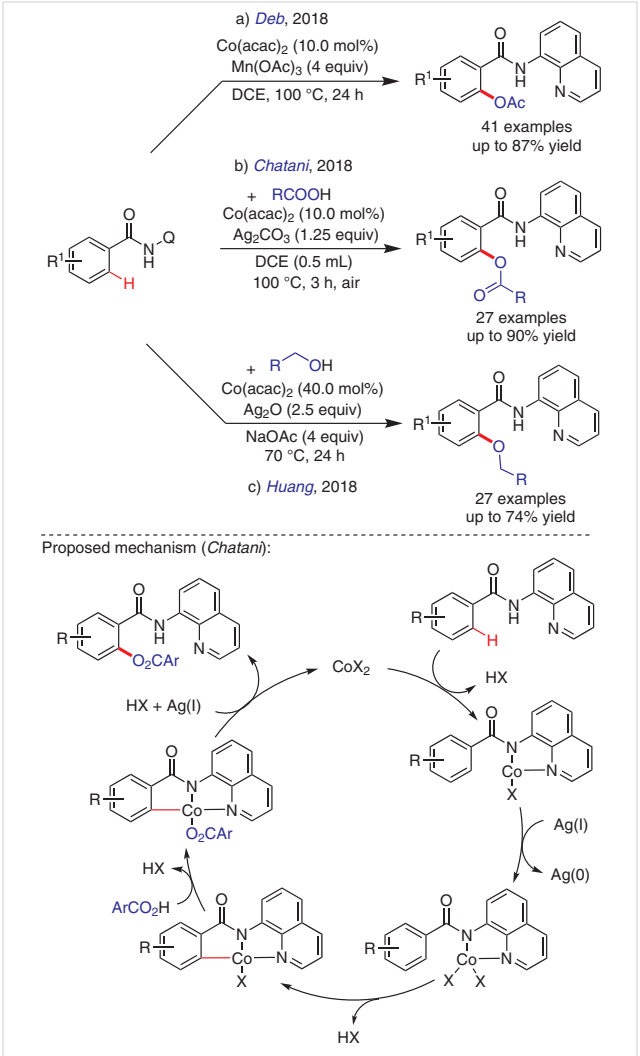


Scheme 6 Pd- and Ru-catalyzed *ortho*-C(sp^2)–H oxygenation of *N*-sulfoximine benzamides

2.2 Bidentate Directed

The chelation-assisted bidentate directing group concept of 8-aminoquinolinyl in C–H functionalization was introduced by the Daugulis group.[17] Thereafter, various research groups utilized 8-aminoquinolinyl[18] or related functionality as a bidentate chelate in diverse C–H oxygenation reactions on amides. Particularly, the *N*,*N*-bi-coordination ability of 8-aminoquinolinyl provides strong binding chelation to the transition metals, facilitating the activation of inert C(sp^2)–H bonds by stabilizing a probable high valent intermediate. Moreover, the 8-aminoquinolinyl moiety is easily incorporated into the amide molecule and readily removed from the products after the desired oxygenation reaction. This enhances the synthetic utility of the method and provides an alternate approach for the selective functionalization of amide derivatives.

Cobalt is an abundant transition metal and has significant potential for catalysis. It is also found in many bioactive compounds, including vitamin B12, thus, it is considered as a low toxic transition metal. Several groups have demonstrated the bidentate assistance of 8-aminoquinolinyl in the Co-catalyzed oxygenation of amides. In 2018, Deb and co-workers reported the Co-catalyzed *ortho*-C(sp^2)–H acetoxylation of unactivated benzamides using $Mn(OAc)_3{\cdot}2H_2O$ as an acetoxy source (Scheme 7a).[19] The methodology was applied to a wide range of substrates. It



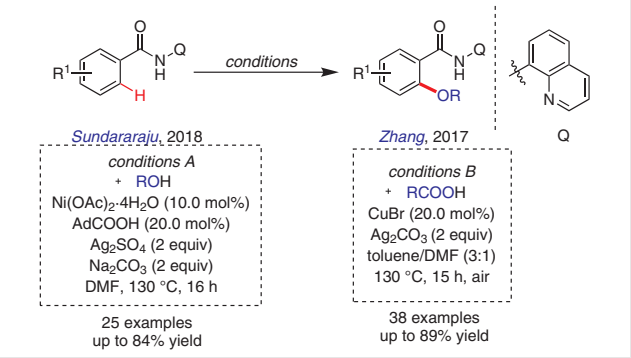
Scheme 7 Co-catalyzed C(sp^2)–H oxygenation of *N*-quinolin-8-ylbenzamides

tolerated various functional groups, such as chloro, bromo, iodo, trifluoromethyl, and phenyl moieties. The $Mn(OAc)_3{\cdot}2H_2O$ is responsible for the oxidation of Co(II) to Co(III), and the latter species is responsible for the C–H bond cleavage. Notably, this protocol uses stoichiometric amounts of manganese metal salt, which makes it less desirable.

Also in 2018, Chatani and co-workers reported the inexpensive Co-catalyzed oxygenation of benzamide with aromatic acids in the presence of Ag_2CO_3 base (Scheme 7b).[20] A variety of aromatic and aliphatic carboxylic acids were used as coupling partners to achieve acyloxylation of amides. *ortho*-Substituted benzamides gave good yields of monoacyloxylation products, whereas those without a substituent at the *ortho*-position led to diacyloxylation. Mechanistic investigation revealed a non-radical pathway for C–H activation and a Co(II)/Co(III) cycle. This protocol was limited to C(sp^2)–H bond acyloxylation, and many heteroarenecarboxamides failed to give the products.

Again in 2018, Huang and co-workers reported the Co-catalyzed alkoxylation of benzamides with alcohols via cross-dehydrogenative coupling using bidentate directing group (Scheme 7c).[21] This reaction employs Ag_2O as the oxidant, NaOAc as the base, and alcohol as the solvent as the alkoxylation source under a N_2 atmosphere. The reaction demonstrated a broad scope of amides and alcohol coupling partners. Notably, heteroarenecarboxamides, such as thiophene-2-carboxamide and furan-2-carboxamide, afforded moderate yields. Aliphatic alcohols such as methanol, propanol, and trifluoroethanol are also compatible with the reaction conditions. In contrast, bulky alcohols such as isopropyl alcohol, butanol, pentanol, cyclohexanol, and phenol did not give the alkoxylated product. This reaction has been proposed to proceed via a radical pathway.

The advantage of the 8-aminoquinolinyl chelation assistance has been implemented in the nickel-catalyzed C–H bond alkoxylation by Sundararaju and Rajesh (Scheme 8).[22] Thus, a $Ni(OAc)_2{\cdot}4H_2O$/AdCOOH catalyst system efficiently catalyzed the C–H alkoxylation of benzamides derivatives with aliphatic alcohols via bidentate-chelation assistance.



Scheme 8 Ni- and Cu-catalyzed *ortho*-oxygenation of *N*-quinolin-8-yl-benzamides

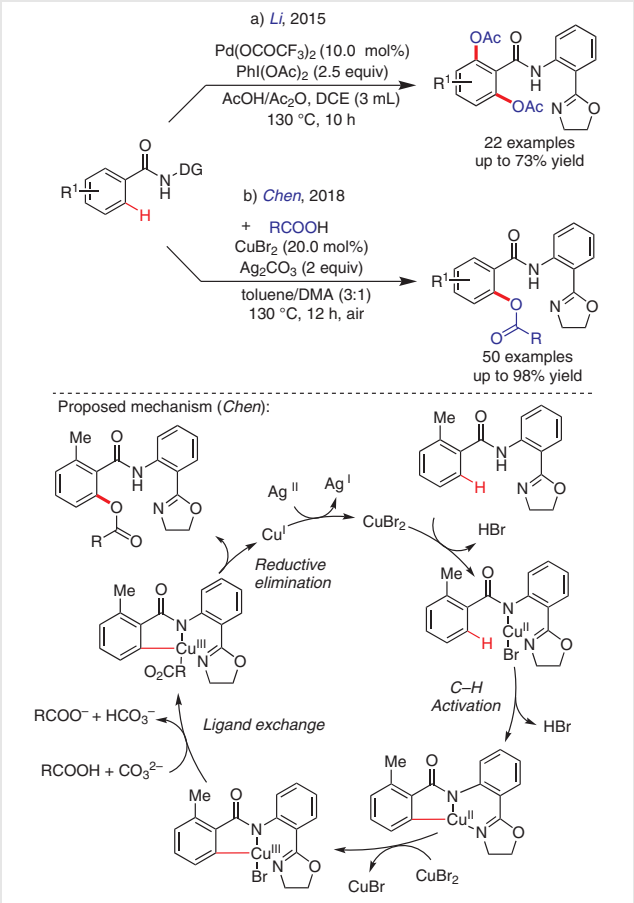
The benzamides bearing electron-donating (Me, OMe, SMe) and electron-withdrawing groups (F, Cl, Br, CF_3) at the *para*-position were well tolerated and provided the mono-methoxylated product in good yield. The tolerability of the thienyl group and participation of amide derived from methacrylic acid is notable. Alkoxylation with aliphatic alcohols, such as ethanol, butanol, and benzyl alcohol, provided moderate yields. The C–H activation in this alkoxylation protocol proceeds through the concerted metalation–deprotonation pathway and is an irreversible process.

Copper complexes can easily access variable oxidation states [Cu(0), Cu(I), Cu(II), and Cu(III)], which allows them to undergo a facile one-electron or two-electron process. Because of this, both single-electron transfer (SET) pathways and two-electron redox pathways via organometallic intermediates can be possible. In 2017, Zhang and co-workers demonstrated the use of CuBr catalyst in the *ortho*-C–H acyloxylation of benzamides with carboxylic acids via the assistance of quinolin-8-yl chelation (Scheme 8).[23] The reaction occurred without any ligand or additives, resulting in an operationally simple protocol for the synthesis of carboxylic esters. Notably, the diacyloxylation products were obtained in moderate yields upon performing the reaction for a long time. This reaction does not involve a radical pathway and is proposed to proceed via a facile C–H cleavage. Notably, compared to the Co-catalyzed oxygenations, the present Ni- and Cu-catalyzed protocols required slightly harsher conditions.

In addition to the use of *N*-quinolin-8-yl chelate, the oxazolyl functionality was also employed in the Pd-catalyzed oxygenation of benzamides by Li and co-workers (Scheme 9a).[24] Thus, the use of $Pd(OCOCF_3)_2$ along with a $PhI(OAc)_2$ afforded the regioselective diacetoxylation of benzamide derivatives. This protocol demonstrated broad substrate scope and tolerance of crucial functional groups, like aryls and heteroaryl. Notably, the *ortho*-acetoxylation of heterocycles with other directing groups had not been previously reported.

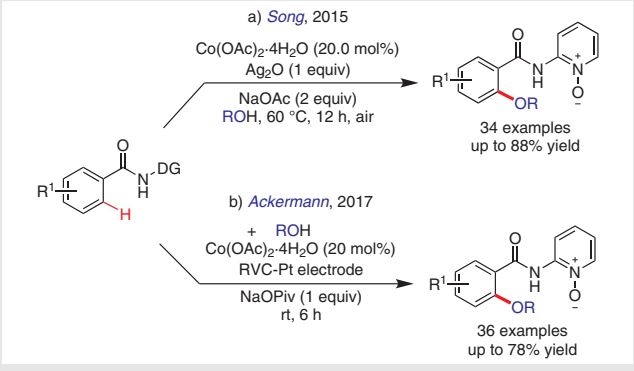
The oxazolyl functionality was also employed by Chen and co-workers in the Cu-catalyzed oxygenation of benzamides (Scheme 9b).[25] Thus, stable and cheap $CuBr_2$ coupled various aliphatic and aromatic carboxylic acids afforded acyloxylated products in good yields. Moreover, various cinnamic acids participated in the reaction which was not feasible in the *N*-quinolinyl-directed acyloxylation. Both the electron-donating and electron-withdrawing substituents were well compatible under the reaction conditions. Notably, *o*-Cl- or *o*-Br-substituted benzamides underwent diacyloxylation by replacing Cl or Br to produce the disubstituted products, indicating both C(sp^2)–H and C(sp^2)–X activation. Notably, this reaction required a high reaction temperature (130 °C).

In 2015, Song, Niu, and co-workers demonstrated the use of 2-aminopyridine 1-oxide as an *N*,*O*-bidentate directing group in the Co-catalyzed alkoxylation of a C(sp^2)–H



Scheme 9 *ortho*-Oxygenation of benzamides via oxazolyl chelation

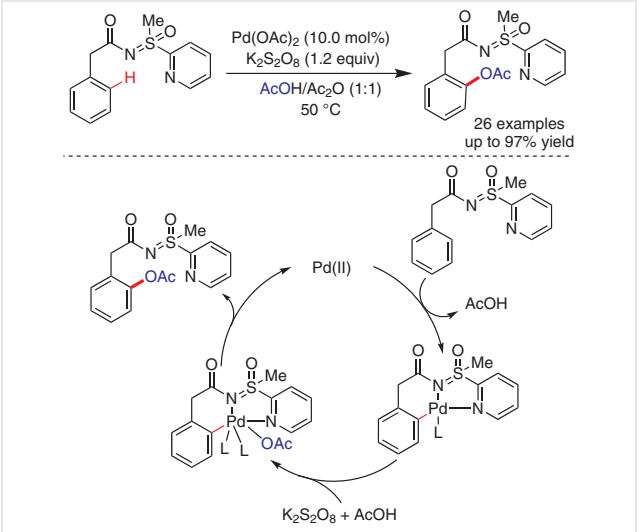
bond (Scheme 10a).[26] The method is suitable for a wide range of alcohols and benzamides bearing various electron-rich and electron-poor groups, such as halogen, ether, methoxy, trifluoromethyl, and dimethylamino substituents. In addition to aromatic amides, this method applies to the alkoxylation of 2-aminopyridine 1-oxide alkene carboxamides. The reaction occurred via the involvement of a radical species as indicated by EPR and additive experiments.



Scheme 10 Co-catalyzed aminopyridine 1-oxide directed *ortho*-alkoxylation of benzamides

Ackermann and co-workers, in 2017, extended the oxygenation of 2-aminopyridine 1-oxide benzamides by employing Co catalysis with an electrochemical oxidant RVC anode and a platinum cathode (Scheme 10b).[27] The electrochemical oxidation represents a unique protocol for silver-free direct oxygenation. Various arenes and alkenes were oxygenated with high levels of chemo-, regio-, and diastereoselectivity under mild conditions. Mechanistic investigation revealed a radical pathway for C–H activation and a Co(II)/Co(III) cycle.

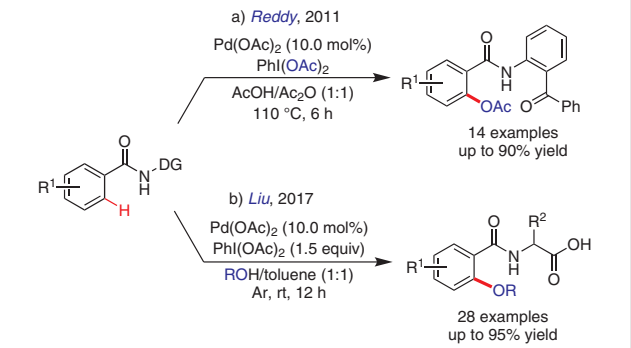
The Sahoo group reported the *ortho* C–H acetoxylation of phenylacetic acid derivatives by installing an easily accessible *S*-methyl-*S*-(pyridin-2-yl)sulfoximine as a bidentate directing group (Scheme 11).[28] Thus, the acetoxylation of α-mono- and α-unsubstituted arylacetic acid *S*-methyl-*S*-(pyridin-2-yl)sulfoximine derivatives gave excellent yields of the desired *ortho*-C–H acetoxylation products employing $Pd(OAc)_2$ catalyst and $K_2S_2O_8$ oxidant in acetic acid. Various sensitive functional groups, such as chloro, bromo, ether, ester, and nitro, were well tolerated. In some cases, a trace amount of diacetoxylated product was also observed. Notably, the acetoxylated products can be hydrolyzed into *o*-hydroxyarylacetic acid, and the directing group can be recovered. The reaction has been proposed to proceed through a Pd(II)/Pd(IV) catalytic cycle with facile a C–H palladation.



Scheme 11 Pd-catalyzed sulfoximine-directed C(sp^2)–H acetoxylation

The *ortho*-acetoxylation of *N*-(2-benzoylphenyl)benzamides via dual activation of the amide NH and chelating benzoyl carbonyl group was demonstrated by Reddy and co-workers using $Pd(OAc)_2$ catalyst and $PhI(OAc)_2$ oxidant in acidic medium (Scheme 12a).[29] Electron-rich benzamides proceeded to give the products of acetoxylation in excellent yields. Upon performing the reaction in MeOH, selective methoxylation was observed. Notably, electron-

poor benzamides were sluggish under the reaction conditions.



Scheme 12 Pd-catalyzed C(sp^2)–H oxygenation via NH and carbonyl chelation

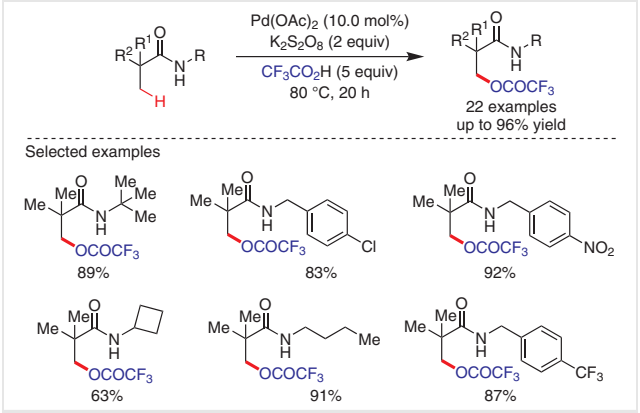
Oxygenation at the *ortho*-C(sp^2)–H bond of *N*-benzoyl-α-amino acid residues is crucial, as the resultant products help modulate the conformational and biophysical properties of the native peptide backbones. Therefore, both the design and development of efficient methods for the oxygenation of amino acids are essential. In that direction, Liu and co-workers developed a Pd(II)-catalyzed *ortho*-alkoxylation of *N*-benzoyl-α-amino acid derivatives at room temperature (Scheme 12b).[30] This novel transformation was achieved using amino acids as directing groups, $Pd(OAc)_2$ as catalyst, alcohols as the alkoxylation reagents, and $PhI(OAc)_2$ as the oxidant. This protocol showed broad generality, high monoselectivity, and high regioselectivity. Particularly, the acid moiety of the directing group was crucial to the reaction, without which the reaction failed. Both these strategies provided a new approach for the oxygenation of amide derivatives. However, moderate functionality tolerance and high loading of expensive palladium are concern and need further improvement.

3 C(sp^3)–H Oxygenation

The chemo- and regioselective C–O bond formation in aliphatic chains has been achieved by the directing group assisted, transition-metal-catalyzed oxidation of unactivated C(sp^3)–H bonds.[31] This protocol provides wide application in synthetic chemistry by installing an oxygenated functionality within a complex organic molecule. However, the high bond strength and absence of π-participation in the C(sp^3)–H bond makes the direct oxygenation of the alkane C–H bond difficult. In recent years, the development of new synthetic strategies have allowed the oxidation of the C(sp^3)–H bond with the help of suitable directing groups. Particularly, the selective oxygenation of C(sp^3)–H bonds in amides has been substantially explored by introducing both the monodentate and bidentate directing auxiliaries.

3.1 Monodentate Directed

The regioselective oxygenation of the C(sp^3)–H bond in amides with the assistance of a monodentate amido group is attractive as it does not need an additional directing group. However, reports of C(sp^3)–H bond oxygenation via monodentate chelation assistance are extremely rare. Lu and Zhou demonstrated the acyloxylation of unactivated C(sp^3)–H bonds of simple amides under mild conditions using a Pd catalyst (Scheme 13).[32] The protocol employs $K_2S_2O_8$ oxidant and an acidic solvent (CF_3COOH). The use of other oxidants, such as $PhI(OAc)_2$, O_2, or Oxone, was ineffective. The employment of non-fluorinated solvents gave low yields. Various secondary amides were employed in this acyloxylation, demonstrating broad substrate scope and moderate functional group compatibility. However, a tertiary amide was unreactive under these conditions. The reaction has been proposed to proceed via C=O coordination, though the non-reactivity of *tert*-amides could not be explained. β-Acyloxyl amides can be hydrolyzed to give the corresponding β-hydroxy amides by using a standard alcoholysis method.



Scheme 13 Pd-catalyzed C(sp^3)–H acyloxylation of secondary amides

3.2 Bidentate Directed

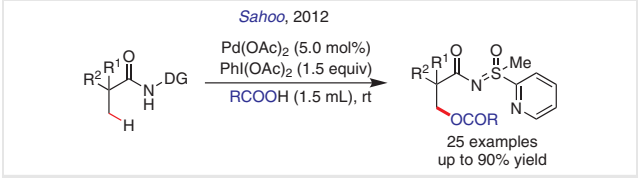
The functionalization of C(sp^3)–H bonds in amides remains a challenging task. Fortunately, the introduction of the bidentate directing group (BDG) strategy provided a new option to promote the activation of many C(sp^3)–H bonds. The pioneering study by the Daugulis group on BDG, 8-aminoquinolinyl, opened a new avenue for C(sp^3)–H activation.[17] Subsequently, a few analogous BDGs were developed and employed in numerous C(sp^3)–H activations and functionalizations.

The unnatural α-amino acids are key structural units present in peptides, peptide-mimetics, and diverse pharmaceutically beneficial compounds. Therefore, the development of effective methods for the oxygenation of amino acids is essential. In 2006, Corey and co-workers reported the Pd-catalyzed C–H bond oxygenation of *N*-phthaloyl-α-amino acid amides by installing an *N*-quinolinyl group (Scheme 14a).[33] Under the optimized conditions, a diastereoselective acetoxylation afforded the expected compounds with excellent diastereomeric excess. This protocol was applied to amide derivatives of *N*-phthaloyl-protected leucine, alanine, α-methylalanine, α-ethylalanine, and α-phenylalanine. The formation of the intermediate *trans*-palladacycle could explain diastereoselective oxidation of the C–Pd bond. In 2012, the Daugulis group reported an example of the acetoxylation of an unnatural amino acid by employing $PhI(OAc)_2$ oxidant in Ac_2O solvent under mild conditions.[34] In a similar study in 2016, Wu, Cao, and co-workers reported the Pd-catalyzed alkoxylation and acyloxylation of L-pipecolinic acids at the C3 position to afford *cis*-disubstituted piperidines as single stereoisomers (Scheme 14b).[35] This protocol uses 1-methoxy-1,2-benziodoxole as an oxidant. Notably, methanol as a solvent gave a mixture of methoxylated and acyloxylated products, whereas the reaction in other alcoholic solvents exclusively produced acyloxylated products. The alkoxylation or acyloxylation reaction of a piperidine derivative was strongly affected by both the oxidant and the solvent.

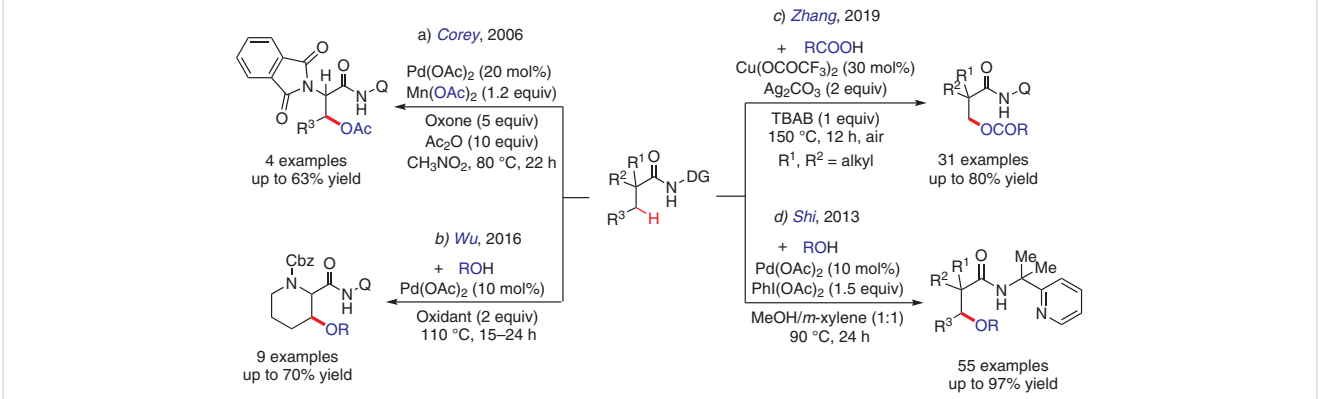
The earth-abundant and inexpensive Cu catalyst was also exploited by Zhang and co-workers in 2019 for the direct C–H acyloxylation of the unactivated C(sp^3)–H bond of aliphatic amides with aromatic acids via bidentate *N*-quinolinyl assistance (Scheme 14c).[36] Thus, the use of $Cu(OCOCF_3)_2$ as the catalyst and tetrabutylammonium bromide (TBAB) as an additive promoted the regioselective β-methyl acyloxylation over γ- or δ-methyl and methylene. This protocol exhibits a broad substrate scope of carboxylic acids and aliphatic amides. Particularly, the competing reaction of intramolecular dehydrogenative amidation over acyloxylation is efficiently controlled by the amount of Cu salt and additive TBAB. The reaction is proposed to occur through a radical pathway involving the rate-influencing C–H cleavage process. High reaction temperatures and high catalyst loadings are the drawback of this protocol.

In 2013, Shi and co-workers introduced a 2-(pyridin-2-yl)isopropyl (PIP) directing functionality on amides for the alkoxylation of unactivated β-methylene C(sp^3)–H and C(sp^2)–H bonds with alkyl alcohols (Scheme 14d).[37] Thus, the use of $Pd(OAc)_2$ along with $PhI(OAc)_2$ afforded the regioselective alkoxylation of amide derivatives. This protocol demonstrated broad substrate scope and tolerance of crucial functional groups, such as chloro, cyano, ether, ester, olefin, and amino. Notably, γ-alkoxylation of the C(sp^2)–H bond is achieved in the absence of a reactive β-C–H bond. A probable concerted palladation-deprotonation pathway has been suggested from the preliminary DFT calculations.

In 2012, the Sahoo group successfully showed the acetoxylation of the unactivated primary β-C(sp^3)–H bond of *N*-pivaloyl-*S*-methyl-*S*-(pyridin-2-yl)sulfoximines using *S*-methyl-*S*-(pyridin-2-yl)sulfoximine as a bidentate directing group (Scheme 15).[38] Notably, this reaction proceeded at room temperature employing $Pd(OAc)_2$ catalyst and $PhI(OAc)_2$ oxidant in AcOH medium. Synthetic application of this strategy was demonstrated by the acetoxylation of fibrate-based drugs, gemfibrozil and clofibrate, which effectively reduce cardiovascular risk factors. Notably, this sulfoximine directing group can be easily removed and reused for further functionalization. This protocol is limited to the primary β-C(sp^3)–H bond acetoxylation of amides.



Scheme 15 Pd-catalyzed C(sp^3)–H bond oxygenation using an *S*-(pyridin-2-yl)sulfoximine directing group

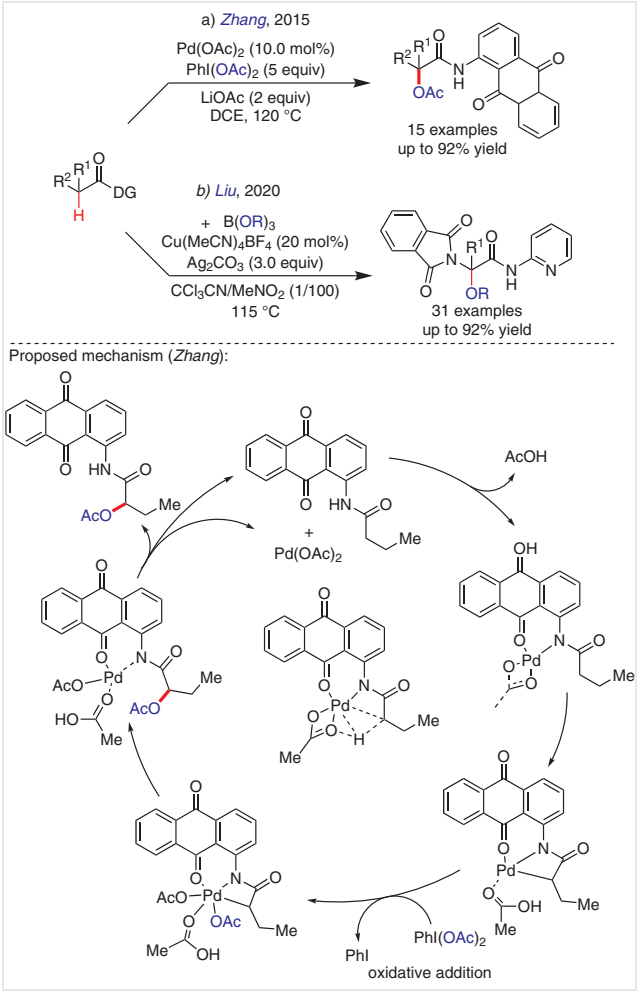


Scheme 14 Pd- and Cu-catalyzed oxygenation of C(sp^3)–H bonds via BDG

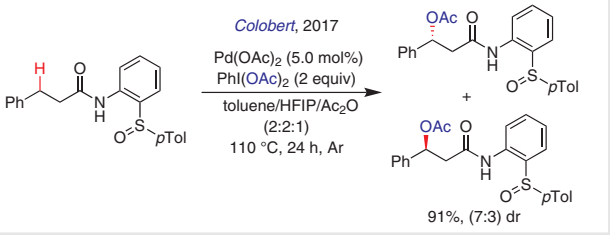
Bidentate directing groups were developed and employed in numerous C(sp^3)–H activations and subsequent chemical transformations. Notably, most BDGs prefer to assist β-C(sp^3)–H bond activation that proceeds through a fused [5,5]-bicyclic metallacycle species. However, α-C(sp^3)–H activation and oxygenations are limited. In an elegant contribution, Zhang, Cheng, Zhu, and co-workers devised a new bidentate directing group, 1-aminoanthraquinone, for α-C(sp^3)–H acetoxylation (Scheme 16a).[39] This directing group controlled the α-C(sp^3)–H acetoxylation via a less favored [4,6]-bicyclic cyclopalladation pathway. Interestingly, the substrates containing primary α-C(sp^3)–H bonds gave excellent yields. The amides containing α-methylene C(sp^3)–H bonds, which were more challenging to cleave than primary ones, also oxygenated smoothly under the optimized conditions. The reaction proceeded through a Pd(II)/Pd(IV) catalytic cycle through a concerted metalation-deprotonation C(sp^3)–H activation. DFT calculations validated the selective α-C(sp^3)–H acetoxylation of amides, which revealed that a 5,6-fused palladacycle is challenging to form as it requires a significant rotation of the C(O)–C(α) bond. Notably, phenylacetamide and but-3-enamide were unstable under the standard reaction conditions.

In 2020, Liu, Dong, and co-workers employed a Cu-catalyzed protocol for α-C(sp^3)–H alkoxylation employing a pyridin-2-yl directing group (Scheme 16b).[40] This method led to the synthesis of a series of quaternary α-alkoxylated amino acid derivatives in good yields. In a distinct approach to that precedented, this protocol uses $B(OR)_3$ as an alkoxylation agent and Ag_2CO_3 as an oxidant. The tolerance of sensitive functionalities and facile removal of the directing auxiliary highlights the potential of this protocol.

Colobert, Wencel-Delord, and co-workers disclosed an example of 2-(*p*-tolylsulfinyl)aniline (APS)-directed stereoselective acetoxylation using Pd catalysis (Scheme 17).[41] The stereoselective direct acetoxylation could be conducted efficiently delivering the desired C–O coupling product in good yields. Though, the protocol was exclusively explored for arylation, an example of stereoselective acetoxylation provides a path forward for further development.



Scheme 16 α-C(sp^3)–H oxygenation of amide derivatives



Scheme 17 Pd-catalyzed *p*-tolylsulfinyl-directed β-C(sp^3)–H oxygenation

4 Conclusion and Outlook

Since 2020, the transition-metal-catalyzed C–H functionalization leading to C–O bond formation has emerged as an important molecular sciences tool. This Short Review highlights the transition-metal-catalyzed regioselective C–H oxygenation of privileged amide derivatives. Both C(sp^2)–H and C(sp^3)–H bond oxygenation in amides are successfully achieved by employing noble metals like ruthenium and palladium as catalysts. Besides, substantial progress has been accomplished using earth-abundant 3d metal catalysts. Particularly, the regioselectivity in amides C–H oxygenation is realized by the directing assistance of amido-functionality in native amides or installing a suitable bidentate chelate moiety on the N-center of amides. Diverse external metal oxidants and oxygenating sources are employed besides alcoholic or acidic coupling partners to achieve C–H hydroxylation, alkoxylation, acetoxylation, and acyloxylation of amides. Notably, additional metal oxidants generate stoichiometric metallic waste, which is a cause of concern. Though the reports on oxygenation of arenes employing atmospheric air/O_2 as an oxidant are known, it is underdeveloped and needs significant attention for oxygen-

ation of amides. Moreover, the expensive palladium dominated other transition metals in the oxygenations due to its unique features, and in many cases, high loading of catalyst is needed. Considering cost and sustainability, a significant development in the regioselective C–H oxygenation of amides by the earth-abundant metal catalyst is crucial. Though, cobalt, nickel, and copper-catalyzed C–H activation and oxygenation are emerging in recent years; more effort is needed to develop oxygenation under mild conditions. The demonstrated reports on amide oxygenation by 3d transition metals show their potential for further exploitation. The installation of traditional bidentate directing groups needs to be replaced with transient and/or straightforward directing groups. Mainly, the focus should be given to achieve the oxygenation of simple amides and challenging C(sp^3)–H bonds without an external directing group. The present Short Review on transition-metal-catalyzed amides oxygenation would be an informative tool for researchers interested in developing more sustainable protocols for amides oxygenation.

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

This work was financially supported by the Science and Engineering Research Board (SERB), New Delhi, India (EMR/2016/000989). V.K.M. thanks the Council of Scientific and Industrial Research, New Delhi, India for a research fellowship.

References

(1) (a) Alonso, D. A.; Nájera, C.; Pastor, I. M.; Yus, M. *Chem. Eur. J.* **2010**, *16*, 5274. (b) Neufeldt, S. R.; Sanford, M. S. *Acc. Chem. Res.* **2012**, *45*, 936. (c) Thirunavukkarasu, V. S.; Kozhushkov, S. I.; Ackermann, L. *Chem. Commun.* **2014**, *50*, 29. (d) Liu, B.; Shi, B.-F. *Tetrahedron Lett.* **2015**, *56*, 15. (e) Moghimi, S.; Mahdavi, M.; Shafiee, A.; Foroumadi, A. *Eur. J. Org. Chem.* **2016**, *2016*, 3282. (f) Iqbal, Z.; Joshi, A.; Ranjan De, S. *Adv. Synth. Catal.* **2020**, *362*, 5301.

(2) (a) Davies, H. M. L.; Sorensen, E. J. *Chem. Soc. Rev.* **2009**, *38*, 2981. (b) Jun, M.; Foote, C.; Lv, J.; Neal, B.; Patel, A.; Nicholls, S. J.; Grobbee, D. E.; Cass, A.; Chalmers, J.; Perkovic, V. *Lancet* **2010**, *375*, 1875. (c) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885. (d) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451. (e) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976.

(3) (a) Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400. (b) Theil, F. In *Organic Synthesis Highlights V*; Schmalz, H.-G.; Wirth, T., Ed.; Wiley-VCH: Weinheim, **2003**, 15. (c) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318. (d) Hartwig, J. F. *Nature* **2008**, *455*, 314.

(4) For selected examples, see: (a) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (b) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (c) Gandeepan, P.; Müller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. *Chem. Rev.* **2019**, *119*, 2192.

(5) (a) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (b) De Sarkar, S.; Liu, W.; Kozhushkov, S. I.; Ackermann, L. *Adv. Synth. Catal.* **2014**, *356*, 1461. (c) Zhu, R.-Y.; Farmer, M. E.; Chen, Y.-Q.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2016**, *55*, 10578. (d) Das, R.; Kumar, G. S.; Kapur, M. *Eur. J. Org. Chem.* **2017**, *2017*, 5439. (e) Muthukumar, A.; Sangeetha, S.; Sekar, G. *Org. Biomol. Chem.* **2018**, *16*, 7068. (f) Bisht, R.; Hoque, M. E.; Chattopadhyay, B. *Angew. Chem. Int. Ed.* **2018**, *57*, 15762. (g) Kalepu, J.; Pilarski, L. T. *Molecules* **2019**, *24*, 830. (h) Zheng, Q.; Liu, C.-F.; Chen, J.; Rao, G.-W. *Adv. Synth. Catal.* **2020**, *362*, 1406.

(6) Wang, G.-W.; Yuan, T.-T. *J. Org. Chem.* **2010**, *75*, 476.

(7) Anand, M.; Sunoj, R. B. *Org. Lett.* **2011**, *13*, 4802.

(8) (a) Padala, K.; Jeganmohan, M. *Chem. Eur. J.* **2014**, *20*, 4092. For a review see: (b) Pimparkar, S.; Padala, K.; Jeganmohan, M. *Proc. Indian Natl. Sci. Acad.* **2014**, *80*, 999.

(9) Yang, L.; Li, S.; Cai, L.; Ding, Y.; Fu, L.; Cai, Z.; Ji, H.; Li, G. *Org. Lett.* **2017**, *19*, 2746.

(10) (a) More, N. Y.; Padala, K.; Jeganmohan, M. *J. Org. Chem.* **2017**, *82*, 12691. (b) Padala, K.; Jeganmohan, M. *Chem. Commun.* **2013**, *49*, 9651. (c) Yu, W.; Chen, J.; Gao, K.; Liu, Z.; Zhang, Y. *Org. Lett.* **2014**, *16*, 4870.

(11) Qiu, F.-C.; Xie, Q.; Guan, B.-T. *Asian J. Org. Chem.* **2018**, *7*, 107.

(12) (a) Yang, F.; Ackermann, L. *Org. Lett.* **2013**, *15*, 718. (b) Massignan, L.; Tan, X.; Meyer, T. H.; Kuniyil, R.; Messinis, A. M.; Ackermann, L. *Angew. Chem. Int. Ed.* **2020**, *59*, 3184.

(13) Li, G.; Wan, L.; Zhang, G.; Leow, D.; Spangler, J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 4391.

(14) Yadav, M. R.; Rit, R. K.; Shankar, M.; Sahoo, A. K. *Asian J. Org. Chem.* **2015**, *4*, 846.

(15) Yadav, M. R.; Rit, R. K.; Sahoo, A. K. *Chem. Eur. J.* **2012**, *18*, 5541.

(16) Raghuvanshi, K.; Zell, D.; Ackermann, L. *Org. Lett.* **2017**, *19*, 1278.

(17) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154.

(18) Rouquet, G.; Chatani, N. *Angew. Chem. Int. Ed.* **2013**, *52*, 11726.

(19) Sarkar, W.; Bhowmik, A.; Mishra, A.; Vats, T. K.; Deb, I. *Adv. Synth. Catal.* **2018**, *360*, 3228.

(20) Ueno, R.; Natsui, S.; Chatani, N. *Org. Lett.* **2018**, *20*, 1062.

(21) Liu, S.-K.; Cui, X.-F.; Liu, X.-X.; Ma, H.-J.; Wei, D.-D.; Luo, X.-L.; Huang, G.-S. *ChemistrySelect* **2018**, *3*, 3989.

(22) Rajesh, N.; Sundararaju, B. *Asian J. Org. Chem.* **2018**, *7*, 1368.

(23) Wang, F.; Hu, Q.; Shu, C.; Lin, Z.; Min, D.; Shi, T.; Zhang, W. *Org. Lett.* **2017**, *19*, 3636.

(24) Liu, B.; Huang, X.; Wang, X.; Ge, Z.; Li, R. *Org. Chem. Front.* **2015**, *2*, 797.

(25) Li, G.-J.; Pan, Y.-L.; Liu, Y.-L.; Xu, H.-F.; Chen, J.-Z. *Org. Lett.* **2019**, *21*, 1740.

(26) Zhang, L.-B.; Hao, X.-Q.; Zhang, S.-K.; Liu, Z.-J.; Zheng, X.-X.; Gong, J.-F.; Niu, J.-L.; Song, M.-P. *Angew. Chem. Int. Ed.* **2015**, *54*, 272.

(27) Sauermann, N.; Meyer, T. H.; Tian, C.; Ackermann, L. *J. Am. Chem. Soc.* **2017**, *139*, 18452.

(28) Rit, R. K.; Yadav, M. R.; Sahoo, A. K. *Org. Lett.* **2014**, *16*, 968.

(29) Reddy, B. V. S.; Revathi, G.; Reddy, A. S.; Yadav, J. S. *Tetrahedron Lett.* **2011**, *52*, 5926.

(30) Li, S.; Zhu, W.; Gao, F.; Li, C.; Wang, J.; Liu, H. *J. Org. Chem.* **2017**, *82*, 126.

(31) (a) Li, H.; Li, B.-J.; Shi, Z.-J. *Catal. Sci. Technol.* **2011**, *1*, 191. (b) Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2011**, *41*, 3464. (c) Mishra, A. A.; Subhedar, D.; Bhanage, B. M. *Chem. Rec.* **2018**, *19*, 1829. (d) Tan, P. W.; Seayad, J. *Tetrahedron Lett.* **2019**, *60*, 151338.
(32) Zhou, L.; Lu, W. *Org. Lett.* **2014**, *16*, 508.
(33) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391.
(34) Tran, L. D.; Daugulis, O. *Angew. Chem. Int. Ed.* **2012**, *51*, 5188.
(35) Yu, Q.-Y.; Zhong, H.-M.; Sun, W.-W.; Zhang, S.-J.; Cao, P.; Dong, X.-P.; Qin, H.-B.; Liu, J.-K.; Wu, B. *Asian J. Org. Chem.* **2016**, *5*, 608.
(36) Wang, F.; Li, X.; Li, Z.; Zhou, S.; Zhang, W. *ACS Omega* **2019**, *4*, 331.
(37) Chen, F.-J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 4187.
(38) Rit, R. K.; Yadav, M. R.; Sahoo, A. K. *Org. Lett.* **2012**, *14*, 3724.
(39) Wang, M.; Yang, Y.; Fan, Z.; Cheng, Z.; Zhu, W.; Zhang, A. *Chem. Commun.* **2015**, *51*, 3219.
(40) Wei, Q.; Ma, Y.; Dong, Y.; Liu, G. *Org. Lett.* **2020**, *22*, 5796.
(41) Jerhaoui, S.; Djukic, J.-P.; Wencel-Delord, J.; Colobert, F. *Chem. Eur. J.* **2017**, *23*, 15594.

JOC The Journal of Organic Chemistry

pubs.acs.org/joc Article

Pd(II)-Catalyzed Chemoselective Acetoxylation of C(sp^2)−H and C(sp^3)−H Bonds in Tertiary Amides

Muniyappa Vijaykumar and Benudhar Punji*

Cite This: J. Org. Chem. 2021, 86, 8172−8181 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Palladium-catalyzed chemoselective C(sp^2)−H and C(sp^3)−H acetoxylation of synthetically useful tertiary amides is reported under relatively mild reaction conditions. This protocol proceeds through the assistance of a weakly coordinated directing group (C═O) and requires low catalyst (1.0 mol %) loading. Diverse functionalities, such as C(sp^2)−Cl, C(sp^3)−Cl, −CF_3, −COOEt, and −NO_2 groups, including morpholinyl, piperazinyl, and pyrrolidinyl heterocycles, are compatible under the reaction conditions. Further functionalization of this protocol is demonstrated by hydrolysis to alcohols, alcohol−acids, as well as reduction to tertiary amines. A preliminary kinetic isotope effect study supported the rate-limiting C−H bond activation process.

INTRODUCTION

Transition-metal-catalyzed C−H bond functionalization has emerged as an elegant and effective tool for molecular sciences, empowering application toward pharmaceuticals and functional materials. In this context, directing-group-assisted C−H oxygenation has been recognized as a robust technique for constructing chemo- and regioselective C−O bonds.[1] Since amide is a versatile functional group with easy transformative tendencies into useful functionalities like carboxylic acid and aldehyde, the selective C−H oxygenation of amide-containing substrates becomes imperative. In that direction, with the support of monodentate or bidentate auxiliaries, diverse C−O bond formations such as alkoxylation,[2] acetoxylation,[3] acyloxylation,[4] and hydroxylation[5] of C(sp^2)−H bond on aromatic amides have been extensively studied. In particular, most of these oxygenations are demonstrated for the primary and secondary amides, wherein the strong coordination of *N*-amidate efficiently facilitates the C−H activation by instigating thermodynamically stable metallacycle. Several research groups have independently demonstrated the *β*-C(sp^3)−H acyloxylation/alkoxylation with the help of strong *N*-coordination by introducing bidentate directed 8-aminoquinolinyl,[6] 2-(pyridine-2-yl)isopropyl (PIP),[2a] picolinamide,[7] sulfoximine,[8] and sulfinyl aniline[9] directing groups (Scheme 1a).[10] In a significant contribution, Lu has demonstrated the C(sp^3)−H acyloxylation of secondary amides via monodentate −CONHR coordination (Scheme 1b).[11] Unfortunately, this protocol failed to give acyloxylation of tertiary amides. Recently, Yu disclosed a palladium-catalyzed *β*-C(sp^3)−H acyloxylation of free carboxylic acids, wherein a well-designed mono-*N*-protected *β*-amino acid ligand is essential.[12]

Though the C(sp^2)−H and C(sp^3)−H oxygenations for strongly coordinating secondary amide (−CONHR) are well-known, the oxygenation of unactivated *β* C(sp^3)−H bond on privileged and multifunctional tertiary amides with a weakly coordinating group (C═O) is less explored.[13] The primary difficulty associated with the weaker coordinating directing groups is the hardship in generating the less favored cyclometalated intermediate.[14] Nevertheless, the groups of Ackermann,[15] Jeganmohan,[16] and Yu[17] have independently established the C(sp^2)−H oxygenation of tertiary benzamides (Scheme 1c). In contrast, thus far, the unactivated C(sp^3)−H oxygenation of native tertiary amides by weak coordination assistance is unprecedented, and attempts were unsuccessful. As a part of our research interest in sustainable C−H functionalization,[18] herein we report the palladium-catalyzed selective C(sp^3)−H acetoxylation of tertiary amides under relatively mild conditions that proceeds via a weakly coordinated O-chelation (Scheme 1d). Notable features of this protocol are (i) C(sp^3)−H and C(sp^2)−H acetoxylation of tertiary amides, (ii) low catalyst loading and mild conditions, (iii) excellent regio- and chemoselectivity, and (iv) a preliminary reaction mechanism.

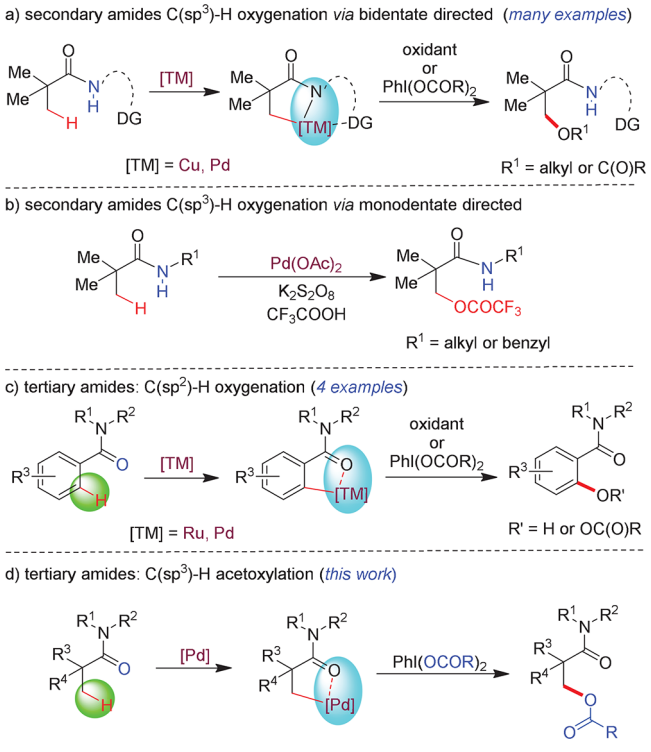
RESULTS AND DISCUSSION

Optimization of Reaction Parameters. The screening of reaction parameters for the acetoxylation of C(sp^3)−H bond in tertiary amide, 2,2-dimethyl-1-(pyrrolidin-1-yl)propan-1-one

Received: March 17, 2021
Published: May 26, 2021

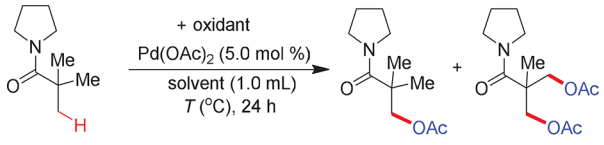
https://doi.org/10.1021/acs.joc.1c00629
J. Org. Chem. 2021, 86, 8172−8181

Scheme 1. C(sp²)−H and C(sp³)−H Bond Oxygenation on Amides



(**1a**), with diacetoxyiodobenzene (**2a**) was initiated employing $Pd(OAc)_2$ as a catalyst (Table 1, see Table S1 in the Supporting Information for details). The reaction could afford both the mono acetoxylated product 2,2-dimethyl-3-oxo-3-(pyrrolidin-1-yl)propyl acetate (**3aa**) and diacetoxylated product **3aa'** in 44% and 12% yields, respectively, when the reaction was performed in the acetic acid solvent at 120 °C (Table 1, entry 1). Notably, the reaction in the mixture of AcOH and Ac_2O (9:1) led to the improvement in yield and selectivity of monoacetoxylation to 68% (entry 2). Relatively mild inorganic oxidants, such as $Na_2S_2O_8$, $K_2S_2O_8$, and AgOAc, were less effective and provided a moderate yield (35−56%) of **3aa** (entries 3−5). The use of other Pd(II) or Pd(0) precursors, such as $PdCl_2$, $Pd(cod)Cl_2$, $Pd_2(dba)_3$, and $Pd(PPh_3)_4$ as catalysts, afforded a low to moderate yield. The acetoxylation reaction in toluene or methanol solvents was inefficient, whereas reaction in TFA/TFAA led to the decomposition of **1a** (entry 6). Notably, the acetoxylation in the solvent HFIP/Ac_2O resulted in quantitative conversion, and **3aa** was isolated in 69% yield (entry 7). Surprisingly, upon lowering the reaction temperature to 80 °C in HFIP/Ac_2O solvent system, the reaction provided 94% of **3aa** with high selectivity for monoacetoxylation (entry 8). The acetoxylation progressed effortlessly even with 1.0 mol % loading of $Pd(OAc)_2$ (entry 9); however, further lowering of catalyst loading to 0.5 mol % led to low conversion. The employment of low catalyst loading significant and could be beneficial for large-scale synthesis. The use of 2.0 equiv of $PhI(OAc)_2$ in place of 3.0 equiv resulted in incomplete conversion. Notably, the reaction proceeded smoothly even with 0.7 mL of solvent and 20 h of reaction time (entry 10). The acetoxylation was failed in the absence of an external oxidant or Pd catalyst (entries 11, 12), indicating the essential role of these components. Thus, the optimal reaction conditions were found to be as follows: **1a** (0.3 mmol), **2a** (0.9 mmol), $Pd(OAc)_2$ (1 mol %) in HFIP/Ac_2O (0.7 mL) at 80 °C for 20 h.

Table 1. Optimization of Reaction Parameters[a]



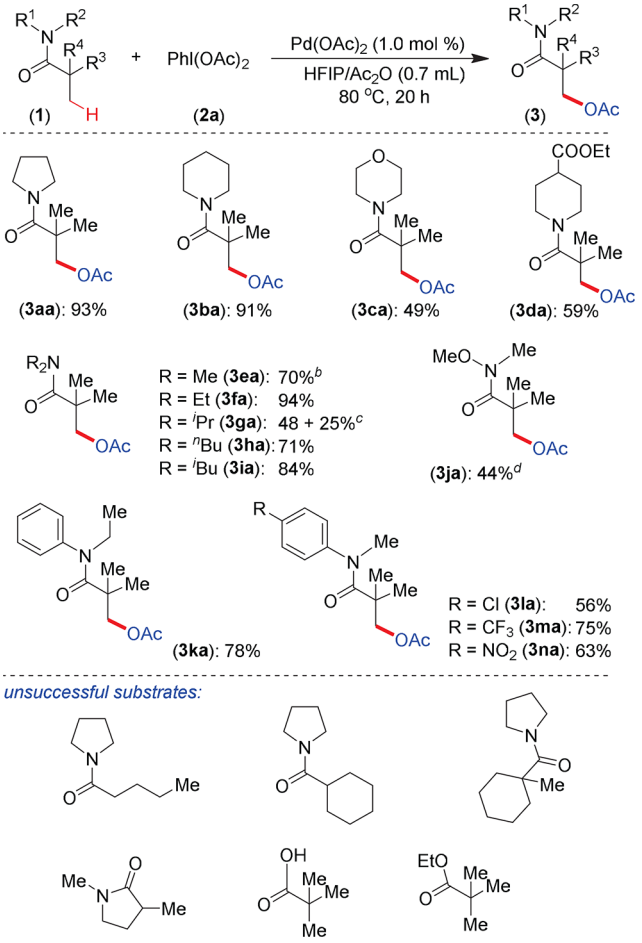
				yield[b] (%)	
entry	oxidant	T (°C)	solvent	3aa	3aa′
1	$PhI(OAc)_2$	120	AcOH	47 (44)	12
2	$PhI(OAc)_2$	120	AcOH/Ac_2O	70 (68)	8
3	$K_2S_2O_8$	120	AcOH/Ac_2O	42	–
4	$Na_2S_2O_8$	120	AcOH/Ac_2O	56	–
5	AgOAc	120	AcOH/Ac_2O	35	–
6	$PhI(OAc)_2$	120	TFA/TFAA	–	–
7	$PhI(OAc)_2$	120	HFIP/Ac_2O	72 (69)	8
8	$PhI(OAc)_2$	80	HFIP/Ac_2O	98 (94)	–
9[c]	$PhI(OAc)_2$	80	HFIP/Ac_2O	97 (93)	–
10[c,d]	$PhI(OAc)_2$	80	HFIP/Ac_2O	96 (93)	–
11	–	80	HFIP/Ac_2O	–	–
12[e]	$PhI(OAc)_2$	80	HFIP/Ac_2O	–	–

[a]Reaction conditions: **1a** (0.047 g, 0.30 mmol), oxidant (0.90 mmol), [Pd] (0.015 mmol, 5.0 mol %), solvent (1 mL; HFIP/Ac_2O = 9:1). [b]GC yield using *n*-dodecane as internal standard, isolated yield is in parentheses. [c]1.0 mol % of $Pd(OAc)_2$ used. [d]0.7 mL of solvent (HFIP:Ac_2O = 9:1) used and reaction was performed for 20 h. [e]Without $Pd(OAc)_2$ catalyst. HFIP = hexafluoro-2-propanol.

Substrate Scope of Acetoxylation. After successfully optimizing the reaction parameters for the Pd-catalyzed C(sp³)−H acetoxylation of the tertiary amide with $PhI(OAc)_2$, we have investigated the scope and limitations of acetoxylation of diverse aliphatic as well as aromatic amides. First, various *N,N*-disubstituted pivalamides were tested for the acetoxylation with $PhI(OAc)_2$ (Scheme 2). Amides with cyclic substituents, such as pyrrolidinyl and piperidinyl pivalamides, gave excellent yields of desired acetoxylated products (**3aa**, **3ba**). The pivalamides containing morpholinyl and ester groups were tolerated under the reaction conditions and provided 49% and 59% yields (**3ca**, **3da**), respectively. Simple dialkyl amides with varying steric properties smoothly underwent the acetoxylation to generate the *β*-acetoxy amides, **3ea**−**3ia**, in good to excellent yields. Notably, the *N,N*-diisopropylpivalamide (**1g**) afforded a significant amount of diacetoxylated compound **3ga′** (25%) in addition to the monoacetoxylated **3ga**. The steric feature of isopropyl on amide might help bring a second methyl group of the monoacetoxylated product (**3ga**) close to the palladium center for further functionalization. It should be noted that the acetoxylation of *N,N*-dialkyl-substituted tertiary amides using Pd was previously unsuccessful.[11] The Weinreb amide **1j** provided acetoxylated product **3ja** in 44% yield at 120 °C. The aryl-substituted pivalamides also reacted smoothly, affording the desired acetoxylated compounds in good yields (**3ka**−**3na**). Synthetically essential functionalities, such as −Cl, $-CF_3$, and $-NO_2$ groups, were well tolerated under the reaction conditions. Interestingly, except for **1g**, the diacetoxylation was not detected or observed only in a negligible amount in most

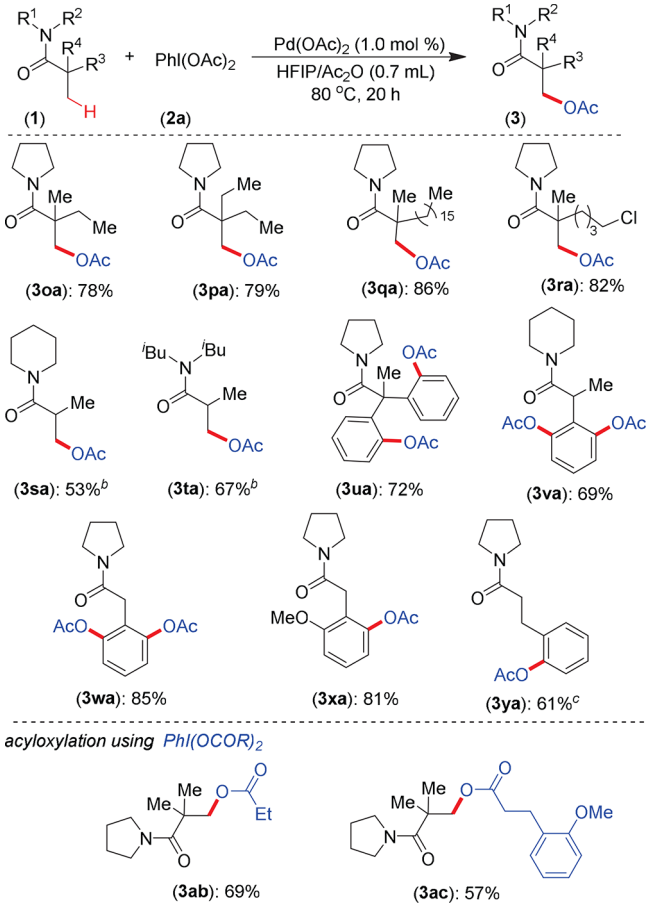
https://doi.org/10.1021/acs.joc.1c00629
J. Org. Chem. 2021, 86, 8172−8181

Scheme 2. β-C(sp^3)−H Acetoxylation of Tertiary Amides[a]



[a]Conditions: substrate **1** (0.30 mmol), **2a** (0.29 g, 0.9 mmol), HFIP/Ac_2O (9:1, 0.7 mL). [b]NMR yield. [c]Diacetoxylated compound was obtained in 25% yield. [d]Reaction was performed at 120 °C.

Scheme 3. Scope for C(sp^3)−H and C(sp^2)−H Acyloxylation of Tertiary Amides[a]



[a]Conditions: substrate **1** (0.30 mmol), **2a** (0.29 g, 0.9 mmol), HFIP/Ac_2O (9:1, 0.7 mL). [b]Reaction performed at 120 °C. [c]NMR yield.

of the pivalamides. Moreover, acetoxylation of the C(sp^3)−H bonds on *N*-alkyl substituents of amide was not observed, even though a five-membered palladacycle involving this carbon center is feasible. Particularly, the acetoxylation of methylene C(sp^3)−H bond on tertiary amides and cyclic amides was unsuccessful (Scheme 2). Similarly, simple carboxylic acid and esters were failed to undergo acetoxylation under the present conditions.

The acetoxylation protocol was applied to the tertiary amides bearing a methyl group and two different alkyl substituents (Scheme 3). Notably, the present protocol was selective for the acetoxylation of primary β-C(sp^3)−H bond over the γ- or δ-C(sp^3)−H bonds or the secondary β-C(sp^3)−H (methylene) bond of amides (**3oa**−**3ra**). The long alkyl chain and aliphatic halide substituents like chloride were tolerated and provided an excellent yield of products, **3qa** and **3ra**. The isobutyramide-containing piperidinyl and diisobutyl substituents afforded **3sa** and **3ta** in 53% and 67% yields, respectively, albeit at an elevated temperature 120 °C. When both the β-C(sp^3)−H and γ-C(sp^2)−H bonds were present on amides (**1u**, **1v**), the γ-C(sp^2)−H bonds selectively acetoxylated over the β-C(sp^3)−H bond (**3ua**, **3va**). We have extended this protocol to the C(sp^2)−H acetoxylation of phenyl acetyl amide and pyrolidinehydrocinnamic amide to achieve an excellent yield of mono- or diacetoxylation (**3wa**−**3ya**). The distal C−H bond acetoxylation, **3ya**, is notable under the present reaction protocol.

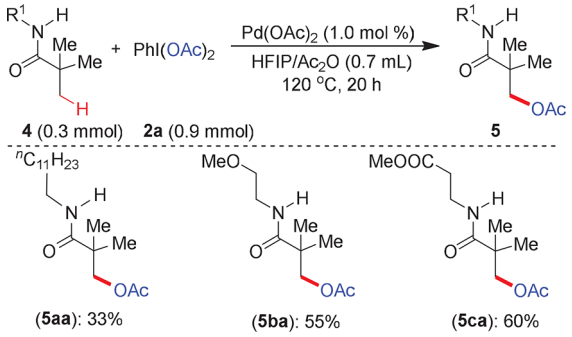
The current methodology was further extended to the acyloxylation using diversely substituted iodonium oxidants, PhI(OCOR)$_2$ (Scheme 3). Thus, the acyloxylated compounds, 2,2-dimethyl-3-oxo-3-(pyrrolidin-1-yl)propyl propionate (**3ab**) and 2,2-dimethyl-3-oxo-3-(pyrrolidin-1-yl)propyl 3-(2-methoxyphenyl)propanoate (**3ac**), were synthesized in good yields using the desired iodonium salts under the optimized conditions. Notably, we did not observe acetoxylated (−OAc) products in these reactions although Ac_2O was used in the reaction.

The substrate scope could be expanded to the acetoxylation of β-C(sp^3)−H bonds on secondary amides (Scheme 4). Thus, the secondary pivalamides with *N*-alkyl, methoxyalkyl, and alkyl ester substituents underwent acetoxylation at 120 °C to produce the desired products in moderate to good yields. Remarkably, tertiary amide reactivity is superior to the secondary pivalamides that can be seen from the product yields and employed reaction conditions.

A gram-scale acetoxylation reaction was performed to demonstrate the practical utility of this Pd-catalyzed method. Thus, the treatment of 1.2 g of substrate **1a** with PhI(OAc)$_2$ (7.46 g) under the standard reaction conditions using 1.0 mol % of Pd(OAc)$_2$ and HFIP/Ac_2O [9:1] (25.0 mL) afforded 1.41 g (86%) of **3aa**.

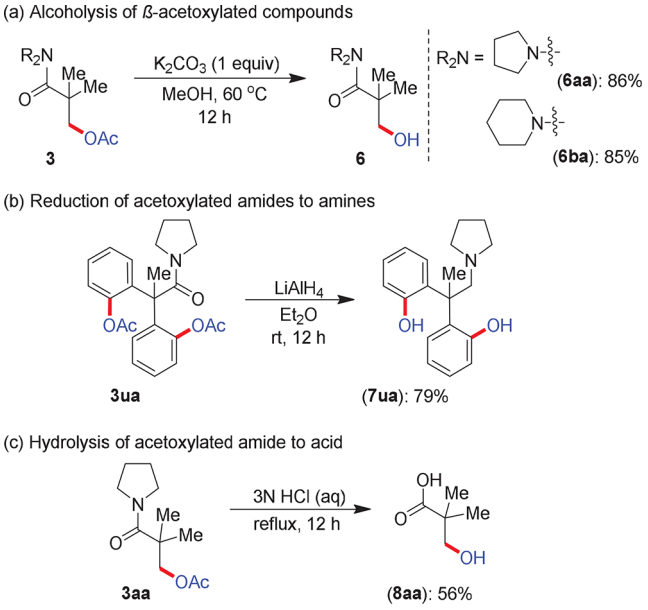
https://doi.org/10.1021/acs.joc.1c00629
J. Org. Chem. 2021, 86, 8172−8181

Scheme 4. Scope for β-C(sp^3)−H Acetoxylation of Secondary Amides



Synthetic Utility and Mechanistic Perspective. We have demonstrated the synthetic utility of acetoxylated tertiary amides by converting them to various useful compounds. The acetyl group of **3aa** and **3ba** was smoothly removed by treating with K_2CO_3 in methanol to achieve β-hydroxy amides **6aa** and **6ba** in 86% and 85% yields, respectively (Scheme 5a). The

Scheme 5. Functionalization of Acetoxylated Amides



acetoxylated amide **3ua** can be reduced to **7ua** in 79% by $LiAlH_4$ in diethyl ether (Scheme 5b). Pleasingly, the acetoxylated amide **3aa** was hydrolyzed with HCl (3 N) at 100 °C to afford 3-hydroxy-2,2-dimethylpropanoic acid (**8aa**) in 56% yield (Scheme 5c).[8] These transformations highlight the importance of acetoxylated tertiary amides in generating privileged functionalities.

The mechanism of the Pd-catalyzed acetoxylation reaction using $PhI(OAc)_2$ is well precedented.[19] Controlled studies suggested that the Pd(II) is a more effective catalyst than the Pd(0), tentatively highlighting the direct participation of a Pd(II) species. Independent reaction rate determination using amide **1p** and [D]-**1p** provided a significant kinetic isotopic effect (KIE; k_H/k_D = 5.6) (Figure S1), which supports the probable involvement of C−H bond activation in the rate-limiting step.[20] Based on our preliminary study, and with the support of literature precedents,[19] we assume that the reaction begins with tertiary amide coordination to Pd(II) species through carbonyl oxygen followed by the C−H cleavage leading to an alkyl-Pd(II) intermediate **A** (Figure 1). Next, the

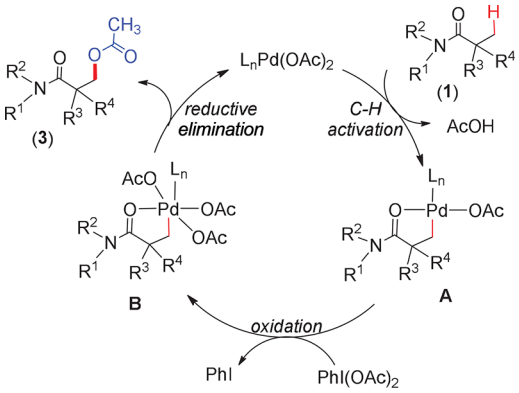


Figure 1. Plausible reaction mechanism.

oxidation of Pd(II) to Pd(IV) by $PhI(OAc)_2$ would result in the formation of intermediate **B**.[21] Subsequent reductive elimination of **3** will lead to the regeneration of Pd(II) for further catalysis.

CONCLUSION

In summary, we have developed a Pd(II)-catalyzed protocol for the chemoselective C(sp^2)−H and C(sp^3)−H acetoxylation of diverse tertiary amides through the weak coordination of the C═O group. Notably, the reaction uses a low loading of palladium unlike the precedented strong *N*-chelating acetoxylation that employs a substantial loading of Pd (>5 mol %). The reaction demonstrated the tolerability of synthetically important functionalities, like chloro, fluoroalkyl, fluoroarene, ester, and nitro groups, in addition to the heterocycles. The synthetic utility is demonstrated by a gram-scale reaction and further functionalization into alcohols, tertiary amines, and alcohol acids. A preliminary KIE study indicated that the C−H activation step is rate-limiting.

EXPERIMENTAL SECTION

General Information. All manipulations were conducted under an argon atmosphere either in a glovebox or using standard Schlenk techniques in predried glasswares. The catalytic reactions were performed in flame-dried reaction vessels with Teflon screw cap. Solvents were dried over Na/benzophenone or CaH_2 and distilled prior to use. Liquid reagents were flushed with argon prior to use. The secondary and tertiary amides[10c] and iodonium salts[14i] were synthesized according to the previously described procedures. High-resolution mass spectrometry (HRMS) mass spectra were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump. NMR: (^{1}H and ^{13}C) spectra were recorded at 400 or 500 MHz (^{1}H), 100 or 125 MHz {^{13}C, DEPT (distortionless enhancement by polarization transfer)}, 377 MHz (^{19}F), respectively in $CDCl_3$ solutions, if not otherwise specified; chemical shifts (δ) are given in ppm. The ^{1}H and ^{13}C NMR spectra are referenced to residual solvent signals ($CDCl_3$: δ H = 7.26 ppm, δ C = 77.2 ppm).

Procedure for Kinetic Isotope Effect (KIE) Study. To a flame-dried screw-cap tube equipped with a magnetic stir bar were introduced $Pd(OAc)_2$ (0.00047 g, 0.002 mmol, 1.0 mol %, 100 μL from stock solution), 2-ethyl-2-methyl-1-(pyrrolidin-1-yl)butan-1-one (**1p**; 0.037 g, 0.20 mmol), {or [D]-**1p** (0.038 g, 0.20 mmol)}, $PhI(OAc)_2$ (**2a**; 0.193 g, 0.60 mmol), and *n*-dodecane (0.020 mL, 0.088 mmol, 0.088 M, internal standard), and HFIP/Ac_2O (9:1) (0.88 mL) was added to make the total volume to 1.0 mL. The reaction mixture was then stirred at 120 °C in a preheated oil bath. At

https://doi.org/10.1021/acs.joc.1c00629
J. Org. Chem. 2021, 86, 8172−8181

regular intervals (5, 10, 20, 30, 45, 60 min), the reaction vessel was cooled to ambient temperature and an aliquot of sample was withdrawn to the GC vial. The sample was diluted with EtOAc and subjected to GC analysis. The concentration of product **3pa** (or D-**3pa**) obtained in each sample was determined with respect to the internal standard *n*-dodecane. The data of the concentration of the product vs time (min) plot was drawn (Figure 1) with Origin Pro 8, and the rate was determined by initial rate method (up to 60 min). The data were taken from the average of two independent experiments.

*Procedure A. Synthesis of N-(4-Chlorophenyl)-N-methylpivalamide (**1l**).* In an oven-dried Schlenk flask, a solution of *N*-(4-chlorophenyl)pivalamide (1.0 g, 4.72 mmol) in DMF (10 mL) was slowly added to NaH (60% dispersion in mineral oil, 0.283 g, 7.10 mmol) in DMF (5.0 mL) at 0 °C, and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was further cooled to 0 °C, and iodomethane (1.01 g, 7.11 mmol) was added dropwise. The resultant reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched with addition of NH_4Cl (aq), diluted with EtOAc, and washed with water and brine. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude residue was purified by column chromatography on neutral alumina (petroleum ether/EtOAc: 10/1) yielded **1l** (0.81 g, 76%) as a white solid. Mp = 83−85 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37−7.34 (m, 2H), 7.17−7.14 (m, 2H), 3.18 (s, 3H), 1.04 (s, 9H). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 178.2, 144.0, 133.7, 130.3, 129.7, 41.5, 41.0, 29.6. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{12}H_{16}NOCl + H^+$ 226.0993; Found 226.0994.

*N-Methyl-N-(4-(trifluoromethyl)phenyl)pivalamide (**1m**).* The representative procedure A was followed using *N*-(4-(trifluoromethyl)phenyl)pivalamide (1.0 g, 4.10 mmol), NaH (60%; 0.245 g, 6.12 mmol), and iodomethane (0.87 g, 6.12 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 10/1) yielded **1m** (0.72 g, 68%) as a white solid. Mp = 83−85 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 3.23 (s, 3H), 1.06 (s, 9H). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 178.2, 148.8, 130.0, 129.3, 126.6, 123.9, 41.4, 41.1, 29.6. ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −62.5 (s). HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{13}H_{16}NOF_3 + H^+$ 260.1257; Found 260.1254.

*N-Methyl-N-(4-nitrophenyl)pivalamides (**1n**).* The representative procedure A was followed, using *N*-(4-nitrophenyl)pivalamide (1.0 g, 4.50 mmol), NaH (60%; 0.270 g, 6.75 mmol), and iodomethane (0.96 g, 6.75 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 10/1) yielded **1n** (0.80 g, 75%) as yellow solid. Mp = 101−103 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.25 (d, *J* = 9.2 Hz, 2H), 7.38 (d, *J* = 9.2 Hz, 2H), 3.26 (s, 3H), 1.10 (s, 9H). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 178.2, 151.5, 146.6, 129.3, 124.9, 41.1, 41.0, 29.4. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{12}H_{16}N_2O_3 + H^+$ 237.1234; Found 237.1232.

*Procedure B. Synthesis of 2,2-Diphenyl-1-(pyrrolidin-1-yl)-propan-1-one (**1u**).* To a stirring solution of 2,2-diphenylpropanoic acid (1.0 g, 4.42 mmol) and *N*-(3-(dimethylamino)propyl)-*N*′-ethylcarbodiimide hydrochloride (0.93 g, 4.86 mmol) in CH_2Cl_2 (20 mL) were added pyrrolidine (0.40 mL, 4.86 mmol) and 4-(dimethylamino)pyridine (0.027 g, 0.22 mmol, 5 mol %). The reaction was allowed to stir at room temperature for 24 h. The reaction was quenched with water (15 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on neutral alumina (petroleum ether/EtOAc: 10/1) yielded **1u** (0.88 g, 71%) as a white solid. Mp = 115−117 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36−7.23 (m, 10H), 3.62 (vt, *J* = 7.3 Hz, 2H), 2.53 (t, *J* = 6.5 Hz, 2H), 1.92 (s, 3H), 1.74−1.67 (m, 2H), 1.60−1.54 (m, 2H). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 173.4, 143.4, 128.5, 128.2, 126.7, 57.6, 48.0, 47.8, 31.8, 26.7, 23.5. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{19}H_{21}NO + H^+$ 280.1696; Found 280.1695.

*2-Ethyl-2-methyl-1-(pyrrolidin-1-yl)butan-1-one (**1p**).* The representative procedure B was followed using 2-ethyl-2-methylbutanoic acid (0.50 g, 3.84 mmol), *N*-(3-(dimethylamino)propyl)-*N*′-ethylcarbodiimidehydrochloride (0.81 g, 4.22 mmol), and pyrrolidine (0.35 mL, 4.22 mmol), 4-(dimethylamino)pyridine (0.023 g, 0.19 mmol, 5 mol %). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 10/1) yielded **1p** (0.61 g, 87%) as a light-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.50 (vt, *J* = 6.9 Hz, 4H), 1.80−1.71 (m, 6H), 1.44−1.35 (m, 2H), 1.14 (s, 3H), 0.81 (t, *J* = 7.6 Hz, 6H). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 175.0, 48.1, 47.5, 31.1, 27.6, 23.2, 22.5, 9.2. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{11}H_{21}NO + H^+$ 184.1701; Found 184.1698.

*2-Ethyl-2-(methyl-d$_3$)-1-(pyrrolidin-1-yl)butan-1-one ([D]-**1p**).* The representative procedure B was followed, using 2-ethyl-2-deuterated methylbutanoic acid (0.50 g, 3.75 mmol), *N*-(3-(dimethylamino)propyl)-*N*′-ethylcarbodiimide hydrochloride (0.79 g, 4.13 mmol), pyrrolidine (0.34 mL, 4.13 mmol), and 4-(dimethylamino)pyridine (0.023 g, 0.188 mmol, 5 mol %). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 10/1) yielded [D]-**1p** (0.57 g, 82%) as a light-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.51 (vt, *J* = 6.7 Hz, 4H), 1.80−1.71 (m, 6H), 1.44−1.35 (m, 2H), 0.82 (t, *J* = 7.5 Hz, 6H). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 175.1, 48.0, 47.3, 31.1, 27.4, 23.1, 21.6, 9.2. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{11}H_{18}D_3NO + H^+$ 187.1813; Found 187.1808.

*2,2-Dimethyl-1-(pyrrolidin-1-yl)octadecan-1-one (**1q**).* The representative procedure B was followed, using 2,2-dimethyloctadecanoic acid (0.50 g, 1.60 mmol), *N*-(3-(dimethylamino)propyl)-*N*′-ethylcarbodiimide hydrochloride (0.34 g, 1.76 mmol), 4-(dimethylamino)-pyridine (0.0098 g, 0.08 mmol, 5 mol %), and pyrrolidine (0.145 mL, 1.76 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 10/1) yielded **1q** (0.42 g, 72%) as a light-yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.52 (br s, 4H), 1.86−1.81 (m, 4H), 1.56−1.53 (m, 2H), 1.30−1.24 (m, 28H), 1.22 (s, 6H), 0.87 (t, *J* = 6.9 Hz, 3H). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 176.0, 47.6, 42.9, 40.2, 32.1, 30.5, 29.9, 29.7, 29.6, 26.4, 25.1, 22.9, 14.3. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{24}H_{47}NO + H^+$ 366.3730; Found 366.3739.

*6-Chloro-2,2-dimethyl-1-(pyrrolidin-1-yl)hexan-1-one (**1r**).* The representative procedure B was followed, using 6-chloro-2,2-dimethylhexanoic acid (0.50 g, 2.80 mmol) and *N*-(3-(dimethylamino)propyl)-*N*′-ethylcarbodiimide hydrochloride (0.60 g, 3.08 mmol), 4-(dimethylamino)pyridine (0.019 g, 0.154 mmol, 5 mol %), and pyrrolidine (0.25 mL, 3.08 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc: 10/1) yielded **1r** (0.55 g, 85%) as a light-yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.52−3.49 (m, 6H), 1.94−1.80 (m, 4H), 1.77−1.70 (m, 2H), 1.59−1.54 (m, 2H), 1.42−1.35 (m, 2H), 1.22 (s, 6H). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 175.5, 48.0, 44.9, 42.7, 39.7, 33.2, 26.1, 22.4. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{12}H_{22}NOCl + H^+$ 232.1463; Found 232.1469.

*Synthesis of N-n-Dodecylpivalamide (**4a**).* In an oven-dried Schlenk flask, pivaloyl chloride (0.80 mL, 6.50 mmol) was dissolved in DCM (20 mL), and *n*-dodecylamine (1.0 g, 5.40 mmol) and triethylamine (1.5 mL, 10.80 mmol) in DCM (10 mL) were added dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 8 h. Upon completion of the reaction, the organic layer was washed with 0.1 M HCl (aq) and $NaHCO_3$ (aq). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on neutral alumina (petroleum ether/EtOAc: 10/1) yielded **4a** (1.30 g, 89%) as a white solid. Mp = 38−40 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.61 (br s, 1H), 3.22 (q, *J* = 6.6, 2H), 1.50−1.46 (m, 2H), 1.29−1.23 (m, 18H), 1.18 (s, 9H), 0.87 (t, *J* = 6.8 Hz, 3H). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 178.5, 39.8, 38.8, 32.1, 29.8, 29.8, 29.7, 29.5, 27.8, 27.1, 22.9, 14.3. HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{17}H_{35}NO + H^+$ 270.2791; Found 270.2790.

*Synthesis of Phenyl-Iodanediyl Bis(3-(2-methoxyphenyl)-propanoate) (**2c**).* In a round-bottom flask, $PhI(OAc)_2$ (3.23 g,

https://doi.org/10.1021/acs.joc.1c00629
J. Org. Chem. 2021, 86, 8172−8181

10.03 mmol) and (2-methoxyphenyl)propanoic acid (3.61 g, 20.06 mmol) were dissolved in $CHCl_3$ (20 mL) and heated at 50 °C for 3 h. At ambient temperature, the volatiles were evaporated under reduced pressure, and the resulted solid was washed with cold solvent mixture (pentane/CH_2Cl_2: 10/1). The colorless solid was dried under high vacuum to yield **2c**, which was used without further purification. Yield: 3.56 g (63%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.98−7.95 (m, 2H), 7.56 (tt, J = 7.5, 1.5 Hz, 1H), 7.45 (vt, J = 7.7 Hz, 2H), 7.18 (td, J = 7.8, 1.6 Hz, 2H), 7.08 (dd, J = 7.5, 1.7 Hz, 2H), 6.86−6.80 (m, 4H), 3.78 (s, 6H), 2.87 (vt, J = 7.7 Hz, 4H), 2.57 (vt, J = 7.7 Hz, 4H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 178.6, 157.6, 137.7, 135.0, 131.7, 131.0, 130.1, 129.3, 127.6, 120.5, 110.3, 55.3, 34.1, 27.0. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{26}H_{27}O_6I$ + H$^+$ 563.0925; Found 563.0871.

Representative Procedure for Acetoxylation. *Synthesis of 2,2-Dimethyl-3-oxo-3-(pyrrolidin-1-yl)propyl Acetate (**3aa**).* To an oven-dried screw-cap tube equipped with magnetic stir bar were introduced 2,2-dimethyl-1-(pyrrolidin-1-yl)propan-1-one (**1a**; 0.047 g, 0.302 mmol), $PhI(OAc)_2$ (0.292 g, 0.908 mmol), $Pd(OAc)_2$ (0.00068 g, 0.00302 mmol, 1.0 mol %; from a stock solution in HFIP), and HFIP/Ac_2O (9:1; 0.7 mL). The resultant reaction mixture was immersed in a preheated oil bath at 80 °C and stirred for 20 h. The reaction mixture was allowed to cool to room temperature, and all the volatiles were removed under reduced pressure. The remaining residue was purified by column chromatography on neutral alumina (petroleum ether/EtOAc: 5/1) yielding **3aa** (0.060 g, 93%) as a yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.17 (s, 2H), 3.52 (br s, 4H), 2.03 (s, 3H), 1.84 (br s, 4H), 1.25 (s, 6H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 173.5, 171.2, 70.9, 48.1, 42.8, 27.3, 23.2, 22.5, 21.1. HRMS (ESI-TOF): m/z Calcd for $C_{11}H_{19}NO_3$ + H$^+$ [M + H]$^+$ 214.1438; Found 214.1439.

*2,2-Dimethyl-3-oxo-3-(piperidin-1-yl)propyl Acetate (**3ba**).* Compound **3ba** was isolated as a light-yellow liquid (0.062 g, 91%) by a column chromatography on neutral alumina (petroleum ether/EtOAc: 5/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.15 (s, 2H, CH_2), 3.52 (vt, J = 5.3 Hz, 4H), 2.03 (s, 3H), 1.64−1.59 (m, 2H), 1.55−1.49 (m, 4H), 1.27 (s, 6H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 173.3, 171.3, 71.2, 46.2, 42.4, 26.2, 24.7, 23.1, 21.1. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{12}H_{21}NO_3$ + H$^+$ 228.1594; Found 228.1595.

*2,2-Dimethyl-3-morpholino-3-oxopropyl acetate (**3ca**).* Compound **3ca** was isolated as a light-yellow liquid (0.034 g, 49%) by a column chromatography on neutral alumina (petroleum ether/EtOAc: 5/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.16 (s, 2H), 3.68−3.63 (m, 8H), 2.06 (s, 3H), 1.29 (s, 6H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 173.8, 171.2, 70.9, 67.0, 45.8, 42.4, 23.2, 21.1. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{11}H_{19}NO_4$ + H$^+$ 230.1387; Found 230.1386.

*Ethyl-1-(3-Acetoxy-2,2-dimethylpropanoyl)piperidine-4-carboxylate (**3da**).* Compound **3da** was isolated as a light-yellow liquid (0.053 g, 59%) by a column chromatography on neutral alumina (petroleum ether/EtOAc: 5/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.22 (d, J = 13.5 Hz, 2H), 4.14 (s, 2H), 4.12−4.09 (m, 2H), 2.96 (t, J = 12.2 Hz, 2H), 2.54−2.49 (m, 1H), 2.03 (s, 3H), 1.90 (d, J = 12.5 Hz, 2H), 1.63 (q, J = 10.9 Hz, 2H), 1.27 (s, 6H), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 174.3, 173.5, 171.2, 71.1, 60.7, 44.5, 42.4, 41.2, 28.4, 23.1, 21.1, 14.3. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{15}H_{25}NO_5$ + H$^+$ 300.1805; Found 300.1807.

*3-(Dimethylamino)-2,2-dimethyl-3-oxopropyl Acetate (**3ea**).* Product **3ea** was obtained as a volatile compound (70%, ^{1}H NMR yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.19 (s, 2H), 3.04 (s, 6H), 2.06 (s, 3H), 1.30 (s, 6H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 174.8, 171.3, 71.2, 42.5, 38.4, 23.1, 21.2. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_9H_{17}NO_3$ + H$^+$ 188.1281; Found 188.1282.

*3-(Diethylamino)-2,2-dimethyl-3-oxopropyl Acetate (**3fa**).* Compound **3fa** was isolated as a light-yellow liquid (0.061 g, 94%) by a column chromatography on neutral alumina (petroleum ether/EtOAc: 10/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.16 (s, 2H), 3.37 (q, J = 6.8 Hz, 4H), 2.04 (s, 3H), 1.27 (s, 6H), 1.12 (t, J = 7.0 Hz, 6H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 173.8, 171.2, 71.4, 42.7, 41.7, 23.3, 21.1, 13.5. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{11}H_{21}NO_3$ + H$^+$ 216.1594; Found 216.1594.

*3-(Diisopropylamino)-2,2-dimethyl-3-oxopropyl Acetate (**3ga**).* Compound **3ga** was isolated as a light-yellow solid (0.035 g, 48%) by a column chromatography on neutral alumina (petroleum ether/EtOAc: 10/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.24 (br s, 1H), 4.15 (s, 2H), 3.28 (br s, 1H), 2.05 (s, 3H), 1.38 (d, J = 5.3 Hz, 6H), 1.27 (s, 6H), 1.19 (d, J = 6.2 Hz, 6H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 173.4, 171.3, 71.4, 48.2, 47.0, 43.1, 23.3, 21.1, 20.8. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{13}H_{25}NO_3$ + H$^+$ 244.1907; Found 244.1909.

*2-(Diisopropylcarbamoyl)-2-methylpropane-1,3-diyl Diacetate (**3ga′**).* Compound **3ga′** was isolated as a yellow solid (0.023 g, 25%) by column chromatography on neutral alumina (petroleum ether/EtOAc: 10/1). Mp = 66−68 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.31−4.14 (m, 5H), 3.31 (br s, 1H), 2.04 (s, 6H), 1.36 (br s, 6H), 1.27 (s, 3H), 1.19 (br s, 6H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 170.9, 170.3, 66.3, 47.9, 47.2, 46.6, 21.0, 20.7, 17.9. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{15}H_{27}NO_5$ + H$^+$ 302.1962; Found 302.1963.

*3-(Dibutylamino)-2,2-dimethyl-3-oxopropyl Acetate (**3ha**).* Compound **3ha** was isolated as a light-yellow liquid (0.058 g, 71%) by a column chromatography on neutral alumina (petroleum ether/EtOAc: 10/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.16 (s, 2H), 3.28 (t, J = 8.0 Hz, 4H), 2.04 (s, 3H), 1.55−1.47 (m, 4H), 1.34−124 (m, 4H), 1.27 (s, 6H), 0.92 (t, J = 7.3 Hz, 6H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 174.0, 171.3, 71.5, 47.6, 42.8, 30.4, 23.4, 21.1, 20.4, 14.1. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{15}H_{29}NO_3$ + H$^+$ 272.2220; Found 272.2223.

*3-(Diisobutylamino)-2,2-dimethyl-3-oxopropyl Acetate (**3ia**).* Compound **3ia** was isolated as a light-yellow liquid (0.068 g, 84%) by a column chromatography on neutral alumina (petroleum ether/EtOAc: 10/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.15 (s, 2H), 3.20 (d, J = 7.6 Hz, 4H), 2.01 (s, 3H), 1.98−1.91 (m, 2H), 1.28 (s, 6H), 0.85 (d, J = 6.9 Hz, 12H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 175.3, 171.2, 71.8, 53.1, 43.2, 26.3, 24.0, 21.1, 20.1. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{15}H_{29}NO_3$ + H$^+$ 272.2220; Found 272.2223.

*3-(Methoxy(methyl)amino)-2,2-dimethyl-3-oxopropyl Acetate (**3ja**).* Compound **3ja** was isolated as a light-yellow liquid (0.027 g, 44%) by a column chromatography on neutral alumina (petroleum ether/EtOAc: 5/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.20 (s, 2H), 3.68 (s, 3H), 3.19 (s, 3H), 2.05 (s, 3H), 1.27 (s, 6H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 176.1, 171.3, 70.5, 60.9, 43.4, 33.9, 22.5, 21.1. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_9H_{17}NO_4$ + H$^+$ 204.1230; Found 204.1230.

*3-(Ethyl(phenyl)amino)-2,2-dimethyl-3-oxopropyl Acetate (**3ka**).* Compound **3ka** was isolated as a light-yellow liquid (0.062 g, 78%) by a column chromatography on neutral alumina (petroleum ether/EtOAc: 5/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41−7.33 (m, 3H), 7.20−7.18 (m, 2H), 3.86 (s, 2H), 3.66 (q, J = 6.9 Hz, 2H), 2.06 (s, 3H), 1.11 (t, J = 6.9 Hz, 3H), 0.98 (s, 6H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 174.1, 171.0, 142.9, 129.7, 129.3, 128.4, 72.0, 48.1, 44.6, 24.7, 21.1, 12.8. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{15}H_{21}NO_3$ + H$^+$ 264.1594; Found 264.1589.

*3-(4-Chlorophenyl)(methyl)amino)-2,2-dimethyl-3-oxopropyl Acetate (**3la**).* Compound **3la** was isolated as a light-yellow solid (0.048 g, 56%) by a column chromatography on neutral alumina (petroleum ether/EtOAc: 5/1). Mp = 39−41 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 3.93 (s, 2H), 3.19 (s, 3H), 2.06 (s, 3H), 1.00 (s, 6H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 175.0, 171.0, 143.2, 134.2, 130.0, 129.8, 71.9, 44.5, 41.6, 24.6, 21.1. HRMS (ESI-TOF) m/z: [M + H]$^+$ Calcd for $C_{14}H_{18}NClO_3$ + H$^+$ 284.1048; Found 284.1045.

*2,2-Dimethyl-3-(methyl(4-(trifluoromethyl)phenyl)amino)-3-oxopropyl Acetate (**3ma**).* Compound **3ma** was isolated as a light-yellow liquid (0.071 g, 75%) by a column chromatography on neutral alumina (petroleum ether/EtOAc: 10/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 8.1 Hz, 2H), 3.97

https://doi.org/10.1021/acs.joc.1c00629
J. Org. Chem. 2021, 86, 8172−8181

(s, 2H), 3.24 (s, 3H), 2.07 (s, 3H), 1.01 (s, 6H). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 175.0, 170.9, 148, 130.5, 129 1, 126.8, 123.8, 71.9, 44.6, 41.5, 24.6, 21.1. ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −62.5 (s). HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{18}NF_3O_3 + H^+$ 318.1312; Found 318.1307.

*2,2-Dimethyl-3-(methyl(4-nitrophenyl)amino)-3-oxopropyl Acetate (**3na**).* Compound **3na** was isolated as a light-yellow solid (0.056 g, 63%) by a column chromatography on neutral alumina (petroleum ether/EtOAc: 5/1). Mp = 78−80 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.28 (d, J = 9.2 Hz, 2H), 7.43 (d, J = 9.2 Hz, 2H), 4.01 (s, 2H), 3.28 (s, 3H), 2.08 (s, 3H), 1.06 (s, 6H). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 175.1, 170.9, 150.8, 147.0, 129.3, 125.1, 71.8, 44.8, 41.3, 24.6, 21.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{18}N_2O_5 + H^+$ 295.1288; Found 295.1283.

*2-Methyl-2-(pyrrolidine-1-carbonyl)butyl Acetate (**3oa**).* Compound **3oa** was isolated as a light-yellow liquid (0.053 g, 78%) by a column chromatography on neutral alumina (petroleum ether/EtOAc: 5/1). ^1H NMR (500 MHz, $CDCl_3$): δ = 4.28 (d, J = 11.1 Hz, 1H), 4.12 (d, J = 11.1 Hz, 1H), 3.51 (vt, J = 6.2 Hz, 4H), 2.02 (s, 3H), 1.86−1.83 (m, 4H), 1.75−1.66 (m, 1H), 1.58−1.49 (m, 1H), 1.24 (s, 3H), 0.83 (t, J = 7.5 Hz, 3H). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 172.7, 171.2, 68.9, 47.1, 46.9, 27.6, 21.1, 20.8, 8.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{21}NO_3 + H^+$ 228.1594; Found 228.1595.

*2-Ethyl-2-(pyrrolidine-1-carbonyl)butyl Acetate (**3pa**).* Compound **3pa** was isolated as a light-yellow liquid (0.057 g, 79%) by a column chromatography on neutral alumina (petroleum ether/EtOAc: 5/1). ^1H NMR (500 MHz, $CDCl_3$): δ = 4.32 (s, 2H), 3.53 (t, J = 6.8 Hz, 4H), 2.04 (s, 3H), 1.85 (br s, 4H), 1.68−1.61 (m, 4H), 0.83 (t, J = 7.5 Hz, 6H). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 172.3, 171.1, 63.6, 50.8, 47.7, 27.5, 25.5, 23.1, 21.2, 8.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{23}NO_3 + H^+$ 242.1756; Found 242.1747.

*2-Methyl-2-(pyrrolidine-1-carbonyl)octadecyl Acetate (**3qa**).* Compound **3qa** was isolated as a white solid (0.109 g, 86%) by a column chromatography on neutral alumina (petroleum ether/EtOAc: 5/1). Mp = 43−45 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.32 (d, J = 11.1 Hz, 1H, CH_2), 4.11 (d, J = 11.1 Hz, 1H), 3.53 (br s, 4H), 2.04 (s, 3H), 1.86 (br s, 4H), 1.69−1.62 (m, 1H), 1.52−1.45 (m, 1H), 1.28−1.23 (m, 31H), 0.87 (t, J = 6.8 Hz, 3H). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 173.1, 171.3, 69.3, 47.9, 46.7, 35.1, 32.09, 30.3, 29.9, 29.8, 29.8, 29.7, 29.6, 29.5, 24.4, 22.9, 21.4, 21.2, 14.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{49}NO_3 + H^+$ 424.3785; Found 424.3793.

*6-Chloro-2-methyl-2-(pyrrolidine-1-carbonyl)hexyl Acetate (**3ra**).* Compound **3ra** was isolated as a light-yellow liquid (0.071 g, 82%) by a column chromatography on neutral alumina (petroleum ether/EtOAc: 5/1). ^1H NMR (500 MHz, $CDCl_3$): δ = 4.28 (d, J = 11.1 Hz, 1H), 4.15 (d, J = 11.1 Hz, 1H), 3.53−3.49 (m, 6H), 2.04 (s, 3H), 1.88 (br s, 4H), 1.78−1.48 (m, 4H), 1.43−1.37 (m, 2H), 1.29 (s, 3H). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 172.7, 171.2, 69.0, 47.8, 46.5, 44.7, 34.4, 32.9, 27.3, 23.3, 21.8, 21.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{24}NClO_3 + H^+$ 290.1517; Found 290.1522.

*2-Methyl-3-oxo-3-(piperidin-1-yl)propyl Acetate (**3sa**).* Compound **3sa** was isolated as a light-yellow liquid (0.034 g, 53%) by a column chromatography on neutral alumina (petroleum ether/EtOAc: 5/1). ^1H NMR (500 MHz, $CDCl_3$): δ = 4.28−4.23 (m, 1H), 4.07−4.03 (m, 1H), 3.56−3.52 (m, 2H), 3.46−3.43 (m, 2H), 3.11−3.03 (m, 1H), 2.01 (s, 3H), 1.64−1.61 (m, 2H), 1.59−1.51 (m, 4H), 1.11 (d, J = 6.9 Hz, 3H). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 172.3, 171.2, 66.7, 46.9, 43.3, 35.0, 26.9, 25.8, 24.7. 21.1, 14.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{19}NO_3 + H^+$ 214.1438; Found 214.1438.

*3-(Diisobutylamino)-2-methyl-3-oxopropyl Acetate (**3ta**).* Compound **3ta** was isolated as a light-yellow liquid (0.052 g, 67%) by a column chromatography on neutral alumina (petroleum ether/EtOAc: 5/1). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.24−4.19 (m, 1H), 4.09−4.05 (m, 1H), 3.26−3.20 (m, 1H), 3.13−3.02 (m, 4H), 1.99−1.95 (m, 1H), 1.97 (s, 3H), 1.90−1.85 (m, 1H), 1.08 (d, J = 6.9 Hz, 3H). 0.89 (dd, J = 6.9, 1.5 Hz, 6H), 0.84 (dd, J = 6.9, 3.1 Hz, 6H). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 174.4, 170.9, 67.0, 55.5, 53.8, 35.3, 28.4, 26.7, 20.9, 20.2, 20.2, 19.9, 14.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{27}NO_3 + H^+$ 258.2064; Found 258.2065.

*(1-Oxo-1-(pyrrolidin-1-yl)propane-2,2-diyl)bis(2,1 phenylene) Diacetate (**3ua**).* Compound **3ua** was isolated as a light-yellow liquid (0.085 g, 72%) by column chromatography on neutral alumina (petroleum ether/EtOAc: 5/1). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.34−7.29 (m, 2H), 7.19 (d, J = 7.6 Hz, 2H), 7.14−7.10 (m, 2H), 7.04−7.02 (m, 2H), 3.50 (t, J = 6.9 Hz, 2H), 2.42 (br s, 2H), 2.11 (s, 6H), 2.07 (s, 3H), 1.68−1.64 (m, 2H), 1.57−1.53 (m, 2H). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 171.3, 169.1, 149.0, 133.7, 129.6, 128.1, 125.6, 124.7, 55.6, 48.2, 26.9, 25.9, 23.3, 21.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{25}NO_5 + H^+$ 396.1805; Found 396.1810.

*2-(1-Oxo-1-(piperidin-1-yl)propan-2-yl)-1,3-phenylene Diacetate (**3va**).* Compound **3va** was isolated as a light-yellow liquid (0.069 g, 69%) by a column chromatography on neutral alumina (petroleum ether/EtOAc: 5/1). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.23 (t, J = 8.4 Hz, 1H), 6.92 (d, J = 8.4 Hz, 2H), 3.76 (q, J = 7.1 Hz, 1H), 3.55−3.52 (m, 1H), 3.40−3.37 (m, 1H), 3.06−2.96 (m, 2H), 2.26 (s, 6H), 1.43 (br s, 4H), 1.29 (d, J = 7.6 Hz, 3H), 1.21−1.17 (m, 1H), 1.0−0.97 (m, 1H). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 170.5, 169.3, 148.9, 127.7, 127.5, 121.1, 46.2, 43.3, 35.3, 25.5, 25.3, 24.5, 20.8, 17.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{23}NO_5 + H^+$ 334.1649; Found 334.1643.

*2-(2-Oxo-2-(pyrrolidin-1-yl)ethyl)-1,3-phenylene Diacetate (**3wa**).* Compound **3wa** was isolated as a light-yellow liquid (0.078 g, 85%) by a column chromatography on neutral alumina (petroleum ether/EtOAc: 5/1). ^1H NMR (500 MHz, $CDCl_3$): δ = 7.29 (t, J = 8.2 Hz, 1H), 7.01 (d, J = 8.1 Hz, 2H), 3.53 (s, 2H), 3.42 (t, J = 6.9 Hz, 2H), 3.20 (t, J = 6.9 Hz, 2H), 2.30 (s, 6H), 1.89−1.85 (m, 2H), 1.82−1.78 (m, 2H). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 169.0, 168.0, 150.0, 128.0, 121.1, 120.4, 46.8, 46.4, 32.4, 26.4, 24.3, 21.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{19}NO_5 + H^+$ 306.1336; Found 306.1332.

*3-Methoxy-2-(2-oxo-2-(pyrrolidin-1-yl)ethyl)phenyl Acetate (**3xa**).* Compound **3xa** was isolated as a light-yellow liquid (0.067 g, 81%) by a column chromatography on neutral alumina (petroleum ether/EtOAc: 5/1). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.03 (t, J = 8.3 Hz, 1H), 6.53 (d, J = 8.4 Hz, 1H), 6.49−6.47 (m, 1H), 3.59 (s, 3H), 3.35 (s, 2H), 3.21 (vt, J = 6.9 Hz, 2H), 3.13 (vt, J = 6.7 Hz, 2H), 2.05 (s, 3H), 1.69−1.66 (m, 2H), 1.61−1.57 (m, 2H). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 169.6, 169.2, 158.3, 150.4, 128.0, 117.1, 115.1, 108.2, 56.1, 46.7, 46.2, 31.0, 26.4, 24.5, 21.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{19}NO_4 + H^+$ 278.1387; Found 278.1384.

*2-(3-Oxo-3-(pyrrolidin-1-yl)propyl)phenyl Acetate (**3ya**).* Compound **3ya** was isolated as a light-yellow liquid (61%, ^1H NMR yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.30−7.28 (m, 1H), 7.25−7.21 (m, 1H), 7.19−7.15 (m, 1H), 7.03−6.99 (m, 1H), 3.46 (t, J = 6.6 Hz, 2H), 3.27 (t, J = 6.5 Hz, 2H), 2.91 (t, J = 7.8 Hz, 2H), 2.51 (t, J = 7.8 Hz, 2H), 2.33 (s, 3H), 1.90−1.80 (m, 4H, CH_2). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 170.7, 169.8, 149.0, 133.4, 130.5, 127.5, 126.3, 122.5, 46.7, 45.8, 35.2, 26.1, 25.6, 24.5, 21.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{19}NO_3 + H^+$ 262.1438; Found 262.1435.

*2,2-Dimethyl-3-oxo-3-(pyrrolidin-1-yl)propyl Propionate (**3ab**).* Compound **3ab** was isolated as a light-yellow liquid (0.047 g, 69%) by a column chromatography on neutral alumina (petroleum ether/EtOAc: 5/1). ^1H NMR (400 MHz, $CDCl_3$): δ = 4.17 (s, 2H), 3.51 (br s, 4H), 2.30 (q, J = 7.6 Hz, 2H), 1.83 (br s, 4H), 1.25 (s, 6H), 1.09 (t, J = 7.6 Hz, 3H). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 174.5, 173.4, 70.5, 48.0, 42.9, 27.7, 27.3, 23.1, 22.6, 9.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{12}H_{21}NO_3 + H^+$ 228.1594; Found 228.1590.

*2,2-Dimethyl-3-oxo-3-(pyrrolidin-1-yl)propyl 3-(2-methoxyphenyl)propanoate (**3ac**).* Compound **3ac** was isolated as a light-yellow liquid (0.057 g, 57%) by a column chromatography on neutral alumina (petroleum ether/EtOAc: 5/1). ^1H NMR (400 MHz,

https://doi.org/10.1021/acs.joc.1c00629
J. Org. Chem. 2021, 86, 8172−8181

$CDCl_3$): δ = 7.19−7.11 (m, 2H), 6.85−6.81 (m, 2H), 4.19 (s, 2H), 3.80 (s, 3H), 3.51 (t, J = 6.1 Hz, 4H), 2.92 (t, J = 8.0 Hz, 2H), 2.61 (t, J = 8.0 Hz, 2H), 1.83 (br s, 4H), 1.24 (s, 6H). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 173.5, 173.5, 157.6, 130.0, 128.9, 127.7, 120.5, 110.3, 70.7, 55.3, 47.9, 42.9, 34.3, 27.4, 26.2, 23.4, 22.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{27}NO_4 + H^+$ 334.2013; Found 334.2014.

*3-(Dodecylamino)-2,2-dimethyl-3-oxopropyl Acetate (**5aa**).* Compound **5aa** was isolated as a yellow liquid (0.032 g, 33%) by a column chromatography on neutral alumina (petroleum ether/EtOAc: 5/1). ^1H NMR (500 MHz, $CDCl_3$): δ = 5.77 (br s, 1H), 4.08 (s, 2H), 3.24 (q, J = 5.9 Hz, 2H), 2.05 (s, 3H), 1.50−1.46 (m, 2H), 1.30−1.24 (m, 18H) 1.19 (s, 6H), 0.86 (t, J = 6.9 Hz, 3H). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 175.3, 170.9, 70.7, 42.4, 39.8, 32.0, 29.8, 29.7, 29.5, 29.5, 27.0, 22.8, 21.0, 14.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{37}NO_3 + H^+$ 328.2846; Found 328.2849.

*3-(Methoxyamino)-2,2-dimethyl-3-oxopropyl Acetate (**5ba**).* Compound **5ba** was isolated as a light-yellow liquid (0.036 g, 55%) by a column chromatography on neutral alumina (petroleum ether/EtOAc: 5/1). ^1H NMR (500 MHz, $CDCl_3$): δ = 6.22 (br s, 1H), 4.08 (s, 2H), 3.46−3.42 (m, 4H), 3.35 (s, 3H), 2.05 (s, 3H), 1.20 (s, 6H). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 175.6, 170.8, 71.3, 70.6, 59.0, 42.4, 39.5, 22.8, 21.0. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{19}NO_4 + H^+$ 218.1387; Found 218.1387.

*3-(Methoxycarbonyl)amino)-2,2-dimethyl-3-oxopropyl Acetate (**5ca**).* Compound **5ca** was isolated as a light-yellow liquid (0.044 g, 60%) by a column chromatography on neutral alumina (petroleum ether/EtOAc: 5/1). ^1H NMR (500 MHz, $CDCl_3$): δ = 6.54 (br s, 1H), 4.05 (s, 2H), 3.68 (s, 3H), 3.51 (q, J = 5.9 Hz, 2H), 2.52 (t, J = 5.9 Hz, 2H), 2.04 (s, 3H), 1.17 (s, 6H). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 175.5, 173.4, 170.8, 70.5, 51.9, 42.3, 35.1, 33.7, 22.7, 20.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{11}H_{19}NO_5 + H^+$ 246.1336; Found 246.1336.

*2-Methyl-2-(pyrrolidine-1-carbonyl)propane-1,3-diyl Diacetate (**3aa′**).* Compound **3aa′** obtained as a light-yellow liquid. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.38−4.18 (m, 4H), 3.54 (br s, 4H), 2.04 (s, 6H), 1.88 (br s, 4H), 1.28 (s, 3H). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 171.0, 170.6, 65.8, 47.9, 46.6, 27.2, 23.3, 21.0, 17.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{21}NO_5 + H^+$ 272.1492; Found 272.1489.

Alcoholysis of β-Acetoxylated Compounds. *Representative Procedure: Synthesis of 3-Hydroxy-2,2-dimethyl-1-(pyrrolidin-1-yl)propan-1-one (**6aa**).*[22] In an oven-dried Schlenk flask, a mixture of 2-methyl-3-(pyrrolidin-1-yl)but-3-en-2-yl acetate (**3aa**; 0.10 g, 0.469 mmol) and K_2CO_3 (0.065 g, 0.47 mmol) in MeOH (3 mL) was refluxed for 12 h. At ambient temperature, the solvent was evaporated under reduced pressure, quenched with H_2O (15 mL), and extracted with EtOAc (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **6aa** (0.069 g, 86%) as a white solid. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.96 (s, 1H), 3.60−3.48 (m, 6H), 1.85 (br s, 4H), 1.24 (s, 6H). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 176.9, 72.7, 47.9, 43.4, 27.1, 23.2, 21.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_9H_{17}NO_2 + H^+$ 172.1332; Found 172.1331.

*Synthesis of 3-Hydroxy-2,2-dimethyl-1-(piperidin-1-yl)propan-1-one) (**6ba**).* The representative was followed, using 2,2-dimethyl-3-oxo-3-(piperidin-1-yl)propyl acetate (**3ba**; 0.10 g, 0.44 mmol) and K_2CO_3 (0.061 g, 0.44 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **6ba** (0.069 g, 85%) as a white solid. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.55 (t, J = 5.7 Hz, 4H), 3.48 (s, 2H), 1.68−1.64 (m, 2H), 1.59−1.54 (m, 4H), 1.27 (s, 6H). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 176.4, 73.2, 46.0, 43.2, 26.2, 24.7, 22.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{10}H_{19}NO_2 + H^+$ 186.1489; Found 186.1484.

*Procedure for Reduction of Acetoxylated Compound. Synthesis of 2,2′-(1-(Pyrrolidin-1yl)propane-2,2-diyl)diphenol) (**7ua**).* A solution of (1-oxo-1-(pyrrolidin-1-yl)propane-2,2-diyl)bis(2,1-phenylene) diacetate (**3ua**; 0.10 g, 0.252 mmol) in Et_2O (10 mL) was added to $LiAlH_4$ (0.096 g, 2.52 mmol) at 0 °C, and the reaction mixture was stirred for 12 h at room temperature. The reaction was slowly quenched with cold water (15 mL) at 0 °C, and the product was extracted with diethyl ether (20 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **7ua** (0.059 g, 79%) as a white solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.20−7.11 (m, 4H), 6.88−6.81 (m, 4H), 3.26 (s, 2H), 3.77 (br s, 4H), 1.85−1.82 (m, 4H), 1.77 (s, 3H). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 156.1, 131.4, 129.1, 127.9, 120.3, 119.2, 65.0, 56.0, 49.2, 27.0, 23.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{23}NO_2 + H^+$ 298.1807; Found 298.1788.

*Procedure for Hydrolysis of β-Acetoxylated Compound. Synthesis of 3-Hydroxy-2,2-dimethylpropanoic Acid (**8aa**).*[8] In a Schlenk flask the mixture of 2-methyl-3-(pyrrolidin-1-yl)but-3-en-2-yl acetate (0.10 g, 0.47 mmol) and 3 N HCl (aq, 3 mL) was refluxed for 12 h. The reaction mixture was neutralized and extracted with ethyl acetate (20 mL x 3). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **8aa** (0.031 g, 56%) as a white solid. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.60 (s, 2H), 1.24 (s, 6H). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 183.4, 69.5, 44.2, 22.1. TOF MS ES$^+$ m/z: $[M]^+$ Calcd for $C_5H_{10}O_3$ 118.0630; Found 118.0859.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00629.

^1H and ^{13}C NMR spectra of all compounds (PDF)

FAIR data, including the primary NMR FID files, for compounds **1l**−**1n**, **1p**−**1r**, **1u**, [D]−**1p**, **2c**, **4a**, **3aa**−**3ya**, **3ab**, **3ac**, **3aa′**, **5aa**−**5ca**, **6aa**, **6ba**, **7ua**, and **8aa** (ZIP)

■ AUTHOR INFORMATION

Corresponding Author

Benudhar Punji − *Organometallic Synthesis and Catalysis Lab, Chemical Engineering Division, CSIR−National Chemical Laboratory (CSIR−NCL), Pune 411 008, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India;* orcid.org/0000-0002-9257-5236; Email: b.punji@ncl.res.in

Author

Muniyappa Vijaykumar − *Organometallic Synthesis and Catalysis Lab, Chemical Engineering Division, CSIR−National Chemical Laboratory (CSIR−NCL), Pune 411 008, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad 201002, India*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.1c00629

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by SERB, New Delhi, India (EMR/2016/000989). V.K.M. thanks CSIR-New Delhi for a research fellowship.

REFERENCES

(1) Alonso, D. A.; Nájera, C.; Pastor, I. M.; Yus, M. Transition-Metal-Catalyzed Synthesis of Hydroxylated Arenes. *Chem. - Eur. J.* **2010**, *16*, 5274−5284.

(2) (a) Wang, G.-W.; Yuan, T.-T. Palladium-Catalyzed Alkoxylation of *N*-Methoxybenzamides *via* Direct sp^2 C−H Bond Activation. *J. Org. Chem.* **2010**, *75*, 476−479. (b) Chen, F.-J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S.-Q.; Shi, B.-F. Pd(II)-Catalyzed Alkoxylation of Unactivated C(sp^3)−H and C(sp^2)−H Bonds Using a Removable Directing Group: Efficient Synthesis of Alkyl Ethers. *Chem. Sci.* **2013**, *4*, 4187−4192. (c) Zhang, L.-B.; Hao, X.-Q.; Zhang, S.-K.; Liu, K.; Ren, B.; Gong, J.-F.; Niu, J.-L.; Song, M.-P. Copper-Mediated Direct Alkoxylation of Arenes Using an *N,O*-Bidentate Directing System. *J. Org. Chem.* **2014**, *79*, 10399−10409. (d) Zhang, L.-B.; Hao, X.-Q.; Zhang, S.-K.; Liu, Z.-J.; Zheng, X.-X.; Gong, J.-F.; Niu, J.-L.; Song, M.-P. Cobalt-Catalyzed C(sp^2)−H Alkoxylation of Aromatic and Olefinic Carboxamides. *Angew. Chem., Int. Ed.* **2015**, *54*, 272−275. (e) Li, S.; Zhu, W.; Gao, F.; Li, C.; Wang, J.; Liu, H. Palladium-Catalyzed *ortho*-Alkoxylation of *N*-Benzoyl α-Amino Acid Derivatives at Room Temperature. *J. Org. Chem.* **2017**, *82*, 126−134. (f) Rajesh, N.; Sundararaju, B. Nickel-catalyzed C−H bond Alkoxylation of Amides with Alcohols. *Asian J. Org. Chem.* **2018**, *7*, 1368−1371. (g) Liu, S.-K.; Cui, X.-F.; Liu, X.-X.; Ma, H.-J.; Wei, D.-D.; Luo, X.-L.; Huang, G.-S. Cobalt(II)-Catalyzed Cross-Dehydrogenative Coupling Reaction of Benzamides with Alcohols to Build C−O Bond. *Chem. Select* **2018**, *3*, 3989−3992. For a review, see: (h) Vijaykumar, M.; Punji, B. Advances in Transition-Metal-Catalyzed C−H Bond Oxygenation of Amides. *Synthesis* **2021**, DOI: 10.1055/a-1481-2584.

(3) (a) Yadav, M. R.; Rit, R. K.; Sahoo, A. K. Sulfoximines: A Reusable Directing Group for Chemo- and Regioselective *ortho*-C−H Oxidation of Arenes. *Chem. - Eur. J.* **2012**, *18*, 5541−5545. (b) Rit, R. K.; Yadav, M. R.; Sahoo, A. K. Pd(II)-Catalyzed *ortho*-C−H Oxidation of Arylacetic Acid Derivatives: Synthesis of Benzofuranones. *Org. Lett.* **2014**, *16*, 968−971.

(4) (a) Wu, X.; Zhao, Y.; Ge, H. Copper-Promoted Site-Selective Acyloxylation of Unactivated C(sp^3)−H Bonds. *Chem. - Asian J.* **2014**, *9*, 2736−2739. (b) Padala, K.; Jeganmohan, M. *ortho*-Benzoxylation of *N*-Alkyl Benzamides with Aromatic Acids Catalyzed by Ruthenium(II) Complex. *Chem. - Eur. J.* **2014**, *20*, 4092−4097. (c) Lan, J.; Xie, H.; Lu, X.; Deng, Y.; Jiang, H.; Zeng, W. Co(II)-Catalyzed Regioselective Cross-Dehydrogenative Coupling of Aryl C−H Bonds with Carboxylic Acids. *Org. Lett.* **2017**, *19*, 4279−4282. (d) Wang, F.; Hu, Q.; Shu, C.; Lin, Z.; Min, D.; Shi, T.; Zhang, W. Copper-Catalyzed Direct Acyloxylation of C(sp^2)−H Bonds in Aromatic Amides. *Org. Lett.* **2017**, *19*, 3636−3639. (e) Raghuvanshi, K.; Zell, D.; Ackermann, L. Ruthenium(II)-Catalyzed C−H Oxygenations of Reusable Sulfoximine Benzamides. *Org. Lett.* **2017**, *19*, 1278−1281. (f) Ueno, R.; Natsui, S.; Chatani, N. Cobalt(II)-Catalyzed Acyloxylation of C−H Bonds in Aromatic Amides with Carboxylic Acids. *Org. Lett.* **2018**, *20*, 1062−1065. (g) Li, G.-J.; Pan, Y.-L.; Liu, Y.-L.; Xu, H.-F.; Chen, J.-Z. Direct Acyloxylation of C(sp^2)−H and C(sp^2)−X (X = Cl, Br) Bonds in Aromatic Amides Using Copper Bromide and 2-(4,5-Dihydro-oxazol-2-yl)-phenylamine. *Org. Lett.* **2019**, *21*, 1740−1743.

(5) Li, X.; Liu, Y.-H.; Gu, W.-J.; Li, B.; Chen, F.-J.; Shi, B.-F. Copper-Mediated Hydroxylation of Arenes and Heteroarenes Directed by a Removable Bidentate Auxiliary. *Org. Lett.* **2014**, *16*, 3904−3907.

(6) (a) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. Novel Acetoxylation and C−C Coupling Reactions at Unactivated Positions in Amino Acid Derivatives. *Org. Lett.* **2006**, *8*, 3391−3394. (b) Wang, Z.; Kuninobu, Y.; Kanai, M. Copper-Mediated Direct C(sp^3)−H and C(sp^2)−H Acetoxylation. *Org. Lett.* **2014**, *16*, 4790−4793. (c) Chen, K.; Zhang, S.-Q.; Jiang, H.-Z.; Xu, J.-W.; Shi, B.-F. Practical Synthesis of anti-β-Hydroxy-α-Amino Acids by Pd(II)-Catalyzed Sequential C(sp^3)−H Functionalization. *Chem. - Eur. J.* **2015**, *21*, 3264−3270. (d) Wang, F.; Li, X.; Li, Z.; Zhou, S.; Zhang, W. Copper Salts/TBAB-Catalyzed Chemo- and Regioselective β-C(sp^3)−H Acyloxylation of Aliphatic Amides. *ACS Omega* **2019**, *4*, 331−343.

(7) Zhang, S.-Y.; He, G.; Zhao, Y.; Wright, K.; Nack, W. A.; Chen, G. Efficient Alkyl Ether Synthesis *via* Palladium-Catalyzed, Picolinamide-Directed Alkoxylation of Unactivated C(sp^3)−H and C(sp^2)−H Bonds at Remote Positions. *J. Am. Chem. Soc.* **2012**, *134*, 7313−7316.

(8) Rit, R. K.; Yadav, M. R.; Sahoo, A. K. Pd(II)-Catalyzed Primary-C(sp^3)−H Acyloxylation at Room Temperature. *Org. Lett.* **2012**, *14*, 3724−3727.

(9) Jerhaoui, S.; Djukic, J.-P.; Wencel-Delord, J.; Colobert, F. Stereoselective Sulfinyl Aniline-Promoted Pd-Catalyzed C−H Arylation and Acetoxylation of Aliphatic Amides. *Chem. - Eur. J.* **2017**, *23*, 15594−15600.

(10) For selected examples on β-C(sp^3)−H arylation and alkenylation, see: (a) Zhao, R.; Lu, W. Palladium-Catalyzed β-Arylation of Amide via Primary sp^3 C−H Activation. *Organometallics* **2018**, *37*, 2188−2192. (b) Park, H.; Chekshin, N.; Shen, P.-X.; Yu, J.-Q. Ligand-Enabled, Palladium-Catalyzed β-C(sp^3)-H Arylation of Weinreb Amides. *ACS Catal.* **2018**, *8*, 9292−9297. (c) Park, H.; Li, Y.; Yu, J.-Q. Utilizing Carbonyl Coordination of Native Amides for Palladium-Catalyzed C(sp^3)−H Olefination. *Angew. Chem., Int. Ed.* **2019**, *58*, 11424−11428.

(11) Zhou, L.; Lu, W. Palladium-Catalyzed β-Acyloxylation of Simple Amide *via* sp^3 C−H Activation. *Org. Lett.* **2014**, *16*, 508−511.

(12) Zhuang, Z.; Herron, A. N.; Fan, Z.; Yu, J.-Q. Ligand-Enabled Monoselective β-C(sp^3)-H Acyloxylation of Free Carboxylic Acids Using a Practical Oxidant. *J. Am. Chem. Soc.* **2020**, *142*, 6769−6776.

(13) For a review on Weinreb amides' C−H functionalization, see: Kalepu, J.; Pilarski, L. T. Weinreb Amides as Directing Groups for Transition Metal-Catalyzed C−H Functionalizations. *Molecules* **2019**, *24*, 830.

(14) For selected examples of C−H oxygenation for carbonyl compounds, see: (a) Yang, Y.; Lin, Y.; Rao, Y. Ruthenium(II)-Catalyzed Synthesis of Hydroxylated Arenes with Ester as an Effective Directing Group. *Org. Lett.* **2012**, *14*, 2874−2877. (b) Thirunavukkarasu, V. S.; Ackermann, L. Ruthenium-Catalyzed C−H Bond Oxygenations with Weakly Coordinating Ketones. *Org. Lett.* **2012**, *14*, 6206−6209. (c) Mo, F.; Trzepkowski, L. J.; Dong, G. Synthesis of *ortho*-Acylphenols through the Palladium-Catalyzed Ketone-Directed Hydroxylation of Arenes. *Angew. Chem., Int. Ed.* **2012**, *51*, 13075−13079. (d) Shan, G.; Yang, X.; Ma, L.; Rao, Y. Pd-Catalyzed C−H Oxygenation with TFA/TFAA: Expedient Access to Oxygen-Containing Heterocycles and Late-Stage Drug Modification. *Angew. Chem., Int. Ed.* **2012**, *51*, 13070−13074. (e) Bhadra, S.; Dzik, W. I.; Gooben, L. J. Synthesis of Aryl Ethers from Benzoates through Carboxylate-Directed C−H-Activating Alkoxylation with Concomitant Protodecarboxylation. *Angew. Chem., Int. Ed.* **2013**, *52*, 2959−2962. (f) Yang, X.; Shan, G.; Rao, Y. Synthesis of 2-Aminophenols and Heterocycles by Ru-Catalyzed C−H Mono- and Dihydroxylation. *Org. Lett.* **2013**, *15*, 2334−2337. (g) Yu, W.; Chen, J.; Gao, K.; Liu, Z.; Zhang, Y. Amide-Assisted Acetoxylation of Vinyl C(sp^2)−H Bonds by Rhodium Catalysis. *Org. Lett.* **2014**, *16*, 4870−4873. (h) Yang, F.; Rauch, K.; Kettelhoit, K.; Ackermann, L. Aldehyde-Assisted Ruthenium(II)-Catalyzed C−H Oxygenations. *Angew. Chem., Int. Ed.* **2014**, *53*, 11285−11288. (i) Ghosh, K. K.; Uttry, A.; Koldemir, A.; Ong, M.; van Gemmeren, M. Direct β-C(sp^3)−H Acetoxylation of Aliphatic Carboxylic Acids. *Org. Lett.* **2019**, *21*, 7154−7157.

(15) (a) Thirunavukkarasu, V. S.; Hubrich, J.; Ackermann, L. Ruthenium-Catalyzed Oxidative C(sp^2)−H Bond Hydroxylation: Site-Selective C−O Bond Formation on Benzamides. *Org. Lett.* **2012**, *14*, 4210−4213. (b) Yang, F.; Ackermann, L. Ruthenium-Catalyzed C−H Oxygenation on Aryl Weinreb Amides. *Org. Lett.* **2013**, *15*, 718−720.

(16) More, N. Y.; Padala, K.; Jeganmohan, M. Ruthenium-Catalyzed C−H Benzoxylation of *tert*-Benzamides with Aromatic Acids by Weak Coordination. *J. Org. Chem.* **2017**, *82*, 12691−12700.

https://doi.org/10.1021/acs.joc.1c00629
J. Org. Chem. 2021, 86, 8172−8181

(17) Li, G.; Wan, L.; Zhang, G.; Leow, D.; Spangler, J.; Yu, J.-Q. Pd(II)-Catalyzed C−H Functionalizations Directed by Distal Weakly Coordinating Functional Groups. *J. Am. Chem. Soc.* **2015**, *137*, 4391−4397.

(18) For selected recent reports, see: (a) Pandey, D. K.; Ankade, S. B.; Ali, A.; Vinod, C. P.; Punji, B. Nickel-Catalyzed C−H Alkylation of Indoles with Unactivated Alkyl Chlorides: Evidence of Ni(I)/Ni(III) Pathway. *Chem. Sci.* **2019**, *10*, 9493−9500. (b) Jagtap, R. A.; Samal, P. P.; Vinod, C. P.; Krishnamurty, S.; Punji, B. Iron-Catalyzed $C(sp^2)$−H Alkylation of Indolines and Benzo[*h*]quinoline with Unactivated Alkyl Chlorides through Chelation Assistance. *ACS Catal.* **2020**, *10*, 7312−7321. (c) Jagtap, R. A.; Verma, S. K.; Punji, B. $MnBr_2$-Catalyzed Direct and Site-Selective Alkylation of Indoles and Benzo[*h*]quinoline. *Org. Lett.* **2020**, *22*, 4643−4647. (d) Jagtap, R. A.; Punji, B. Functionalization of Indoles by 3d Transition-Metal Catalysis. *Asian J. Org. Chem.* **2020**, *9*, 326−342. (e) Ankade, S. B.; Shabade, A. B.; Soni, V.; Punji, B. Unactivated Alkyl Halides in Transition-Metal-Catalyzed C−H Bond Alkylation. *ACS Catal.* **2021**, *11*, 3268−3292. (f) Bansal, S.; Shabade, A. B.; Punji, B. Advances in $C(sp^2)$−H/$C(sp^2)$−H Oxidative Coupling of (Hetero) arenes using 3 d Transition Metal Catalysts. *Adv. Synth. Catal.* **2021**, *363*, 1998−2022.

(19) (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. A Highly Selective Catalytic Method for the Oxidative Functionalization of C-H Bonds. *J. Am. Chem. Soc.* **2004**, *126*, 2300−2301. (b) Desai, L. V.; Hull, K. L.; Sanford, M. S. Palladium-Catalyzed Oxygenation of Unactivated sp^3 C−H Bonds. *J. Am. Chem. Soc.* **2004**, *126*, 9542−9543. (c) Giri, R.; Liang, J.; Lei, J.-G.; Li, J.-J.; Wang, D.-H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J.-Q. Pd-Catalyzed Stereoselective Oxidation of Methyl Groups by Inexpensive Oxidants under Mild Conditions: A Dual Role for Carboxylic Anhydrides in Catalytic C−H Bond Oxidation. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420−7424. (d) Desai, L. V.; Malik, H. A.; Sanford, M. S. Oxone as an Inexpensive, Safe, and Environmentally Benign Oxidant for C−H Bond Oxygenation. *Org. Lett.* **2006**, *8*, 1141−1144. (e) Cook, A. K.; Sanford, M. S. Mechanism of the Palladium-Catalyzed Arene C−H Acetoxylation: A Comparison of Catalysts and Ligand Effects. *J. Am. Chem. Soc.* **2015**, *137*, 3109−3118.

(20) For a report on high KIE for $C(sp^3)$−H activation, see: Yan, J.-X.; Li, H.; Liu, X.-W.; Shi, J.-L.; Wang, X.; Shi, Z.-J. Palladium-Catalyzed $C(sp^3)$−H Activation: A Facile Method for the Synthesis of 3,4-Dihydroquinolinone Derivatives. *Angew. Chem., Int. Ed.* **2014**, *53*, 4945−4949.

(21) For examples on oxidation of Pd(II) to Pd(IV) by $PhI(OAc)_2$, see: (a) Dick, A. R.; Kampf, J. W.; Sanford, M. S. Unusually Stable Palladium(IV) Complexes: Detailed Mechanistic Investigation of C−O Bond-Forming Reductive Elimination. *J. Am. Chem. Soc.* **2005**, *127*, 12790−12791. (b) Racowski, J. M.; Dick, A. R.; Sanford, M. S. Detailed Study of C−O and C−C Bond-Forming Reductive Elimination from Stable $C_2N_2O_2$-Ligated Palladium(IV) Complexes. *J. Am. Chem. Soc.* **2009**, *131*, 10974−10983.

(22) Barwick-Silk, J.; Hardy, S.; Willis, M. C.; Weller, A. S. Rh(DPEPhos)-Catalyzed Alkyne Hydroacylation Using *β*-Carbonyl-Substituted Aldehydes: Mechanistic Insight Leads to Low Catalyst Loadings that Enables Selective Catalysis on Gram-Scale. *J. Am. Chem. Soc.* **2018**, *140*, 7347−7357.

https://doi.org/10.1021/acs.joc.1c00629
J. Org. Chem. 2021, 86, 8172−8181

OL Organic Letters

pubs.acs.org/OrgLett Letter

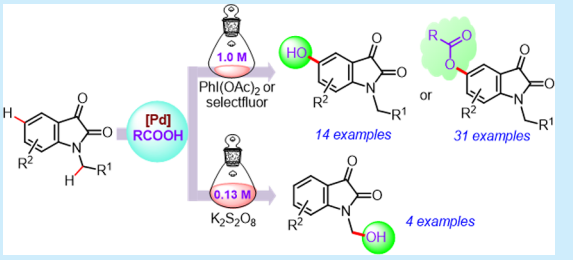
Palladium-Catalyzed Chemoselective Oxygenation of C(sp^2)−H and C(sp^3)−H Bonds in Isatins

Muniyappa Vijaykumar, Chandini Pradhan, Rajesh G. Gonnade, and Benudhar Punji*

Cite This: *Org. Lett.* 2023, 25, 1862−1867 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

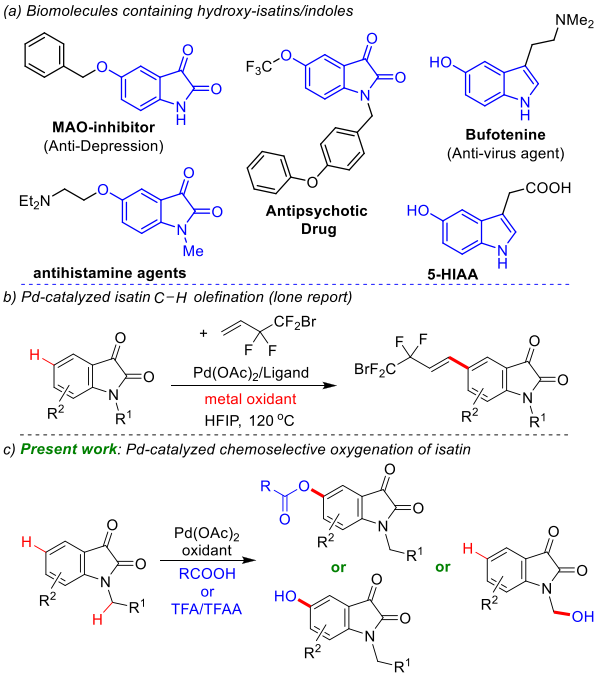
ABSTRACT: The palladium-catalyzed chemoselective C(sp^2)−H and C(sp^3)−H bond oxygenation of substituted isatin derivatives is reported. This mild protocol exhibits the C5 C(sp^2)−H oxygenation of isatins through electrophilic intermolecular C−H palladation in concentrated solutions using PhI(OAc)$_2$ or Selectfluor as an oxidant, whereas it exhibits −N−CH$_3$ C(sp^3)−H oxygenation in dilute solutions via carbonyl-assisted intramolecular palladation in the presence of $K_2S_2O_8$. This oxygenation reaction provides a direct and unified approach for synthesizing diverse oxygenated isatins with sensitive functionalities, including biorelevant compounds.



Isatin, the 2,3-dioxindole, is an elite oxidized indole nucleus and has gained particular attention as a core motif in the development of numerous pharmacologically active compounds.[1] The precise decoration of the isatin framework leads to diverse privileged molecules that are entrenched as antimalarial, antifungal, antibacterial, antiviral, and potential antitumor agents.[2] In particular, the hydroxy group-containing isatins/indoles represent an important subclass among the isatin-based natural products (Scheme 1a).[1c,g,3] Therefore, developing protocols for the efficient functionalization of isatins is highly indispensable. Notably, the strategic functionalization of isatins at the activated C2 and C3 carbonyl centers has been widely explored;[4] however, the site-selective derivatization of the benzenoid moiety at C4, C5, C6, or C7 is scarce.

In recent years, transition-metal-catalyzed step-economic C−H activation/functionalization has seen tremendous growth.[5] In view of the prevailing applications and existence of isatins in bioactive molecules, the straightforward chemoselective C−H functionalization of the benzenoid ring in isatin is highly imperative.[6] Recently, we demonstrated the C−H functionalization at the benzenoid ring of similar molecules.[7] Li and Zhao demonstrated the C5-selective fluorination/olefination of isatins using a palladium catalyst via the C−H activation strategy (Scheme 1b), wherein a specific oxalyl amide ligand and an excess of metal oxidant is essential.[8] Considering the existence of the hydroxy isatin moiety in diverse pharmacological compounds, we aimed to develop a straightforward protocol for the chemoselective oxygenation of isatins using a step-economical direct C−H activation strategy.[9] With this target, herein, we report a Pd-catalyzed chemoselective oxygenation of isatin derivatives to obtain C5 C(sp^2)−H acetoxylation/hydroxylation and −N−CH$_3$ C-(sp^3)−H hydroxylation (Scheme 1c).

Scheme 1. Bioactive Molecules Containing a C5 Oxygenated Isatin/Indole Core and C−H Functionalization of Isatin

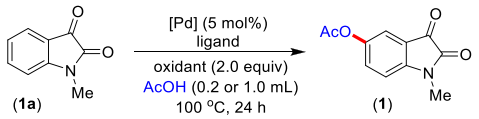


Received: February 2, 2023
Published: March 15, 2023

We began the screening of reaction parameters for the acetoxylation of 1-methylindoline-2,3-dione (**1a**) with $PhI(OAc)_2$ employing $Pd(OAc)_2$ as a catalyst (Table 1, see Tables S1 and S2 in the SI). We assumed that the reaction might provide carbonyl-directed C(4)−H, −N−CH_3 C(sp^3)−H acetoxylation, or an electrophilic nondirected C(5)−H acetoxylation. Interestingly, this palladium-catalyzed reaction using acetic acid (1.0 mL) exclusively provided the C(5)−H acetoxylation product in a 43% yield at 100 °C (Table 1, entry 1). The use of oxidants $K_2S_2O_8$, Selectfluor, and $Cu(OAc)_2$ gave only traces of **1**, whereas NFSI and oxone were incompetent (Table 1, entries 2−4, and Table S1). Notably, the reaction in 0.2 mL of AcOH (1.0 M) instead of 1.0 mL provided **1** in a 59% yield (Table 1, entry 5). The use of a PPh_3 ligand along with $Pd(OAc)_2$ gave an 82% yield of **1** (Table 1, entry 6). Using $Ph_3P{=}O$ as a ligand also provided similar yield of **1** (entry 7). Notably, the PPh_3 oxidizes to $Ph_3P{=}O$ in the presence of $PhI(OAc)_2$, which in turn can act as a stabilizing ligand via the weak O-coordination. The bidentate ligand xantphos provided a slightly lower yield, whereas the *N*-donor ligands, like pyridine, bpy, or phen, were less effective (Table 1, entries 8−10). The acetoxylation was sluggish when $PdCl_2$ was used as a catalyst and provided a 43% yield of **1**; however, $Pd_2(dba)_3$ was ineffective (Table 1, entries 11 and 12, respectively).

The oxygenation reaction using $PhI(OAc)_2$ in TFA/TFAA (0.2 mL, 1.0 M) gave hydroxylated product **32** in a 10% yield (Table 2, entry 1). This hydroxylation proceeded through acyloxylation, followed by hydrolysis. Interestingly, the use of $K_2S_2O_8$ in TFA/TFAA (0.2 mL) provided **32** in a 49% yield and a trace amount of −N−CH_3 C(sp^3)−H hydroxylation product **46** (Table 2, entry 2). This reaction gave 72% of **32** when Selectfluor was employed as an oxidant (Table 2, entry 3). The hydroxylation was slightly improved to give a 79% yield of **32** at 80 °C (Table 2, entry 4).

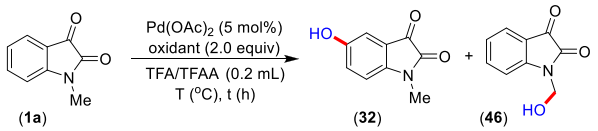
Table 1. Optimization of Reaction Parameters for C(5)−H Acetoxylation[a]



entry	[Pd]	ligand	oxidant	**1** (%)[b]
1	$Pd(OAc)_2$		$PhI(OAc)_2$	43
2	$Pd(OAc)_2$		$K_2S_2O_8$	trace
3	$Pd(OAc)_2$		Selectfluor	trace
4	$Pd(OAc)_2$		NFSI	NR
5	$Pd(OAc)_2$		$PhI(OAc)_2$	59
6	$Pd(OAc)_2$	**PPh_3**	**$PhI(OAc)_2$**	**82**
7	$Pd(OAc)_2$	$O{=}PPh_3$	$PhI(OAc)_2$	80
8	$Pd(OAc)_2$	xantphos	$PhI(OAc)_2$	74
9	$Pd(OAc)_2$	pyridine	$PhI(OAc)_2$	36
10	$Pd(OAc)_2$	bpy or phen	$PhI(OAc)_2$	trace
11	$PdCl_2$	PPh_3	$PhI(OAc)_2$	43
12	$Pd_2(dba)_3$	PPh_3	$PhI(OAc)_2$	NR

[a]Reaction conditions are as follows: **1a** (0.032 g, 0.20 mmol), oxidant (0.40 mmol), [Pd] (0.01 mmol), and ligand (10 mol % for monodentate, 5 mol % for bidentate). Entries 1−4, 1.0 mL of AcOH. Entries 5−10, 0.2 mL of AcOH. [b]Yield of isolated compound **1**.

Table 2. Optimization of Reaction Parameters for Hydroxylation[a]



			yield (%)[b]	
entry	oxidant	T (°C)/t (h)	**32**	**46**
1	$PhI(OAc)_2$	100/20	10	trace
2	$K_2S_2O_8$	100/20	49	10
3	Selectfluor	100/20	72	trace
4	**Selectfluor**	80/20	**79**	trace
5[c]	Selectfluor	80/20	36	
6[c]	$K_2S_2O_8$	100/20	17	48
7[d]	$K_2S_2O_8$	100/20	trace	71
8[d]	**$K_2S_2O_8$**	100/1		**93**

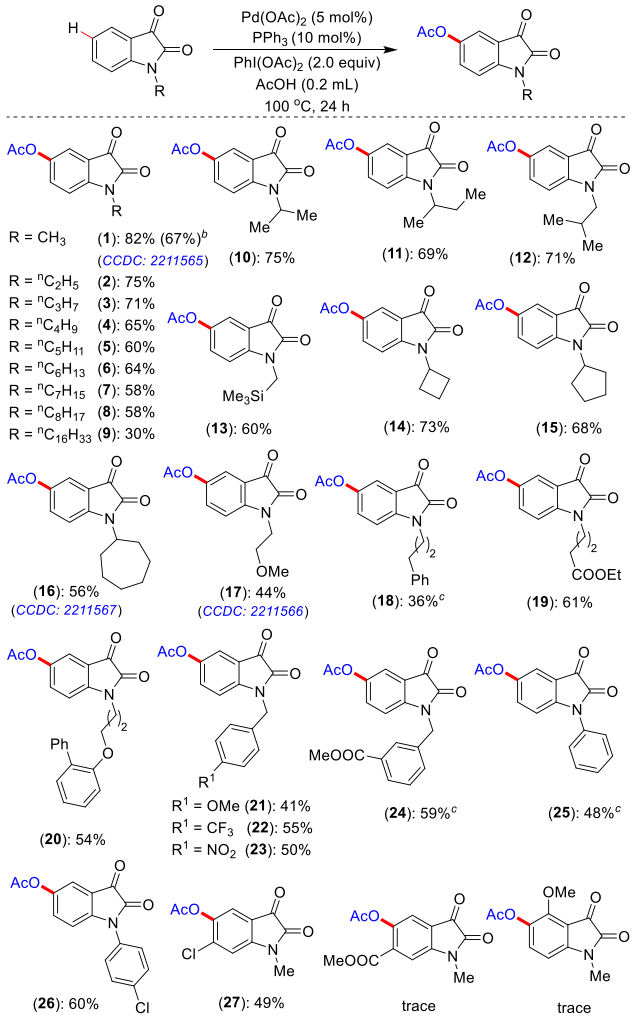
[a]Reaction conditions are as follows: **1a** (0.032 g, 0.20 mmol), oxidant (0.40 mmol), and [Pd] (0.01 mmol). [b]Isolated yields. [c]The reaction was performed with 1.0 mL of TFA/TFAA. [d]The reaction was performed with 1.5 mL of TFA/TFAA. TFA = trifluoroacetic acid, TFAA = trifluoroacetic anhydride.

We assumed the product **32** could form *via* direct electrophilic C(5)−H activation (a more reactive site), and a concentrated solution should be ideal for this intermolecular reaction. Meanwhile, the formation of **46** could be a −CO-directed intramolecular reaction between coordinated Pd(II) and −N−CH_3 C(sp^3)−H and might be favored even in the dilute solution by restricting intermolecular C(5)−H palladation. With this, we checked the oxygenation of isatin in 1.0 mL of TFA/TFAA (0.2 M) (Table 2, entries 5 and 6). Thus, the use of Selectfluor gave 36% of **32**, whereas $K_2S_2O_8$ provided 17% of **32** and 48% of **46**. Notably, using 1.5 mL of TFA/TFAA in the presence of $K_2S_2O_8$ improved the yield of **46** to 71% (Table 2, entry 7). The reaction provided 93% of **46** upon performing for a short time (Table 2, entry 8). Thus, the reaction selectively gave **46** in the presence of $K_2S_2O_8$ and 1.5 mL of TFA/TFAA (9:1) in 1 h. In contrast, the C5 hydroxylated product **32** was selectively obtained in 0.2 mL of TFA/TFAA (9:1) in the presence of Selectfluor.

Next, we started investigating the scope and limitations of the C5 acetoxylation of diverse isatins (Scheme 2). The isatins containing *N*-alkyl groups with different chain lengths reacted smoothly to give C5 acetoxylated products **2**−**8**. The branched alkyl and cycloalkyl groups were also compatible (**10**−**16**). A synthetically important silyl moiety was tolerated on isatin and provided **13** in a 60% yield. The isatins containing notable functionalities, such as −OMe, −Ph, −COOEt, and alkyl ether, reacted with low efficacy to afford compounds **17**−**20**. Similarly, functional groups like −OMe, $-CF_3$, $-NO_2$, and −COOMe at different positions of the *N*-benzyl isatins were well tolerated (**21**−**24**, respectively). The compatibility of such moieties is crucial for synthetic perspective and further derivatizations. In addition to the *N*-alkyl and *N*-benzyl isatins, the *N*-aryl-substituted isatins were acetoxylated at the C5 position to give **25** and **26**. The C6-chloro-substituted *N*-methylisatin yielded 49% of **27**, whereas the C6 ester-substituted *N*-methylisatin was unreactive. Unfortunately, an isatin derivative having a C4 methoxy substituent could not participate in the reaction. The structures of **1**, **16**, and **17** were confirmed by X-ray diffraction study. Interestingly, the alkenyl-

https://doi.org/10.1021/acs.orglett.3c00342
Org. Lett. 2023, 25, 1862−1867

Scheme 2. Scope for the C5 C(sp^2)−H Acetoxylation of Isatins[a]



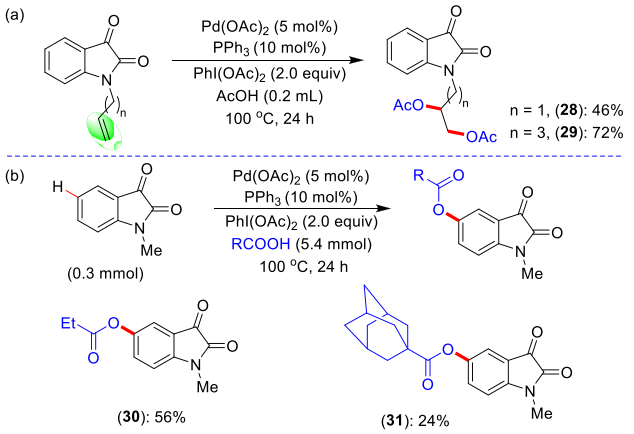
[a]Conditions are as follows: isatin (0.20 mmol), $PhI(OAc)_2$ (0.40 mmol), $Pd(OAc)_2$ (0.0022 g, 0.01 mmol), PPh_3 (0.02 mmol, 10 mol %), and AcOH (0.2 mL). [b]Yield for a 3.1 mmol scale reaction. [c]Yield determined by ^1H NMR.

substituted isatins provided the diacetoxylation at the alkenyl C(sp^2)−H position, leading to **28** and **29** in 46% and 72% yields, respectively (Scheme 3a). In fact, these two diacetoxylations were also observed under the Pd-free conditions.[10] Unfortunately, the free NH isatin and isatins containing −CN, −OH, or heterocycle groups remained unreacted.

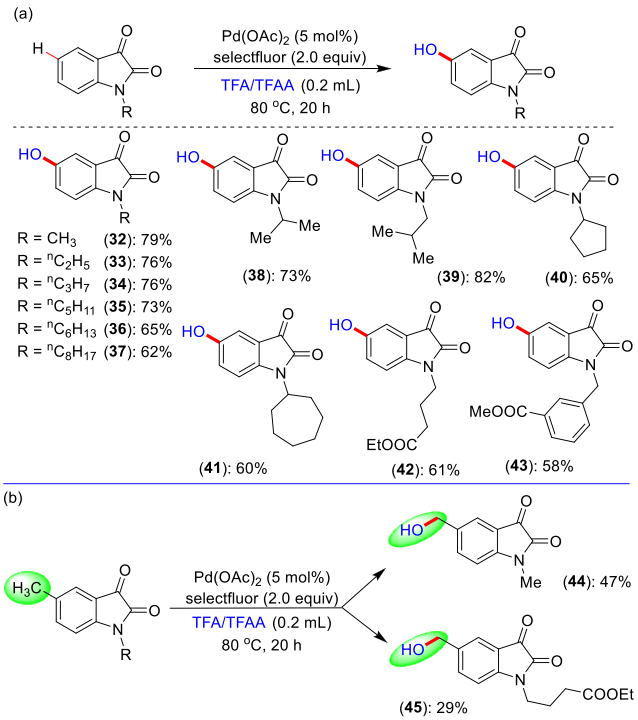
The acyloxylated compounds, **30** and **31** were obtained in low to moderate yields using the propionic and adamantine carboxylic acids, respectively (Scheme 3b). Notably, a trace amount of the acetoxylated (−OAc) product that might originate from $PhI(OAc)_2$ was also observed in both cases.

Like the acetoxylation, various isatins participated in the hydroxylation using Selectfluor in TFA/TFAA to afford moderate to good yields of the C5 hydroxylated isatins (Scheme 4a). The alkyl, cycloalkyl, and benzyl substitutions at the *N*-position of isatin were tolerated. The compatibility of synthetically useful functionalities like −COOEt and −COOMe is notable (**42** and **43**, respectively). To our surprise, when C5 methylated isatins were subjected to

Scheme 3. (a) Acetoxylation of *N*-Alkenyl Isatins (with or without Pd) and (b) Acyloxylation of Isatins



Scheme 4. Scope for the (a) C5 C(sp^2)−H Hydroxylation and (b) C5-CH_3 C(sp^3)−H Hydroxylation of Isatins

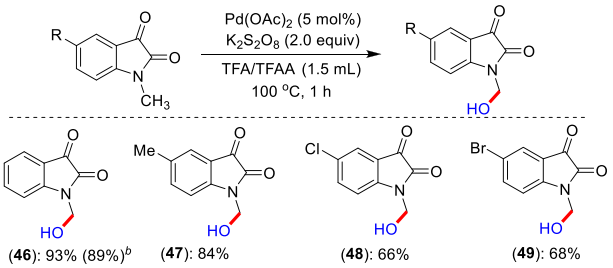


oxygenation, the C5−CH_3 C(sp^3)−H hydroxylation was observed, albeit in low to moderate yields (**44** and **45**; Scheme 4b).

The $Pd(OAc)_2$-catalyzed reaction using $K_2S_2O_8$ as an oxidant and 1.5 mL of TFA/TFAA at 100 °C for 1 h afforded selective *N*-methyl C(sp^3)−H bond hydroxylation (Scheme 5). The unsubstituted C5 methyl and halide-substituted (Cl and Br) *N*-methyl isatins gave *N*-methyl C(sp^3)−H bond hydroxylation products **46**−**49** in good yields. Notably, the *N*-methyl hydroxylated products are considerably unstable and resulted in decomposition. *N*-Ethyl isatin as the substrate did not provide CH_2 C(sp^3)−H or the C5 C(sp^2)−H hydroxylation product under this reaction condition. Isatins bearing −F, $-NO_2$, −OH, or −OAc at the C5 position failed to participate in the reaction. The site-selective hydroxylation of the −N−CH_3 C(sp^3)−H bond in the presence of activated C5

https://doi.org/10.1021/acs.orglett.3c00342
Org. Lett. 2023, 25, 1862−1867

Scheme 5. Scope for the −N−CH_3 C(sp^3)−H Hydroxylation[a]



[a]Conditions are as follows: isatin (0.20 mmol), $K_2S_2O_8$ (0.40 mmol), $Pd(OAc)_2$ (0.0022 g, 0.01 mmol), and TFA/TFAA (1.5 mL, 9:1 ratio). [b]The reaction was performed under an argon atmosphere.

C(sp^2)−H bond is remarkable. This chemoselective hydroxylation is phenomenal, as such an approach can be applied to synthesize crucial molecules of choice.

A 3.1 mmol scale reaction of 1-methylindoline-2,3-dione (**1a**) afforded **1** in a 67% yield (Scheme 2). The hydroxylated isatin **32** could undergo semireduction to oxindole **50** in an 87% yield (Figure S1a). Moreover, compound **32** could be converted to highly functionalized **51**, albeit in a moderate yield (Figure S1b).[4e] In an attempt to synthesize a MAO inhibitor (antidepression agent, shown in Scheme 1a), we obtained (benzyloxy)oxindole **52** (Figure S1c). Similarly, the C3 carbonyl in **32** can be smoothly functionalized to obtain (benzyloxy)imino-5-hydroxy-1-methylindolin-2-one **53** in a 49% yield (Figure S1d). Finally, the biologically relevant bufotenine derivative **56** was synthesized in three steps starting from **32** in a good yield (Figure S1e).[11]

The ineffectiveness of Pd(0) and the high efficiency of Pd(II) as a catalyst suggest that Pd(II) could be an active catalyst. A greater reactivity of isatin with $Pd(OAc)_2$ over $PdCl_2$ supports an electrophilic-type C(5)−H activation. The use of CH_3COOD in the acetoxylation did not show H/D scrambling at the C5 position of **1a**, indicating the irreversible C5 C(sp^2)−H palladation (section 8 in the SI). This C−H oxygenation also proceeded quantitatively under an argon atmosphere, ruling out the atmospheric O_2 or H_2O as the oxygen source for the reaction. Further, the radical scavenger/inhibition experiments (section 9 in the SI) suggested the involvement of a radical intermediate for the −N−CH_3 C−H hydroxylation of isatin.

Based on preliminary observations and literature,[9c,12] we have proposed two catalytic cycles (Figure S5). For the C5 acetoxylation (path I), the reaction would initiate by the electrophilic C(5)−H activation of **1a** with $Pd(OAc)_2$ to form **A**. The intermediate **A** will undergo oxidation to **B**, followed by the reductive elimination to afford **1** and Pd(II). Though a two-electron oxidation path is proposed, the probability of a two-step one-electron oxidation process cannot be ruled out. For −N−CH_3 C(sp^3)−H hydroxylation (path II), the radical intermediate **D** is generated in situ by hydrogen atom abstraction by a sulfate radical anion produced from $K_2S_2O_8$. Next, the radical combination leads to Pd(IV) species **E**, followed by the reductive elimination of **46**. The reaction concentrations as well as the type of oxidants play significant roles in the selectivity. A high reaction concentration would favor the intermolecular reaction between $Pd(OAc)_2$ and isatin C5 C(sp^2)−H. However, at dilution, the intermolecular reaction might be restricted; thus, isatin may coordinate to $Pd(OAc)_2$ via C2 carbonyl, which would trigger a radical path for −N−CH_3 in the presence of $K_2S_2O_8$.

In summary, we developed an efficient and unified protocol for the palladium-catalyzed chemoselective C5 C(sp^2)−H and *N*-methyl C(sp^3)−H oxygenation of isatin derivatives employing user-friendly oxidants. The use of $PhI(OAc)_2$ or Selectfluor oxidant in the Pd-catalyzed protocol in 1.0 M acidic solution exclusively provided C5 oxygenation of isatins via electrophilic palladation, whereas the same reaction employing $K_2S_2O_8$ in dilute solution (0.13 M) selectively afforded *N*-methyl C(sp^3)−H oxygenation through carbonyl-assisted intramolecular −N−CH_3 C(sp^3)−H radical palladation. The synthetic utility of oxygenation is exemplified by performing a gram-scale reaction, and further derivatization was demonstrated by synthesizing hydroxylated oxindole, silylated isatins, (benzyloxy)oxindolinone, (benzyloxy)imino derivative, and a bufotenine drug compound.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c00342.

Full experimental and characterization data, including ^1H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 2211565−2211567 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Benudhar Punji − *Organometallic Synthesis and Catalysis Lab, Organic Chemistry Division, CSIR−National Chemical Laboratory (CSIR−NCL), Pune, Maharashtra 411008, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad, Uttar Pradesh 201002, India;* orcid.org/0000-0002-9257-5236; Email: b.punji@ncl.res.in

Authors

Muniyappa Vijaykumar − *Organometallic Synthesis and Catalysis Lab, Organic Chemistry Division, CSIR−National Chemical Laboratory (CSIR−NCL), Pune, Maharashtra 411008, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad, Uttar Pradesh 201002, India*

Chandini Pradhan − *Organometallic Synthesis and Catalysis Lab, Organic Chemistry Division, CSIR−National Chemical Laboratory (CSIR−NCL), Pune, Maharashtra 411008, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad, Uttar Pradesh 201002, India*

Rajesh G. Gonnade − *Centre for Material Characterization, CSIR−National Chemical Laboratory (CSIR−NCL), Pune, Maharashtra 411008, India; Academy of Scientific and Innovative Research (AcSIR), Ghaziabad, Uttar Pradesh 201002, India;* orcid.org/0000-0002-2841-0197

https://doi.org/10.1021/acs.orglett.3c00342
Org. Lett. 2023, 25, 1862−1867

Complete contact information is available at:
https://pubs.acs.org/10.1021/acs.orglett.3c00342

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by SERB, New Delhi, India (CRG/2020/000554). M.V. and C.P. thank CSIR−New Delhi and UGC−New Delhi, respectively, for research fellowships.

■ REFERENCES

(1) (a) Khan, F. A.; Maalik, A. Advances in Pharmacology of Isatin and its Derivatives: A Review. *Trop J. Pharm. Res.* **2015**, *14*, 1937−1942. (b) Kaur, M.; Singh, M.; Chadha, N.; Silakari, O. Oxindole: A Chemical Prism Carrying Plethora of Therapeutic Benefits. *Eur. J. Med. Chem.* **2016**, *123*, 858−894. (c) Nautiyal, O. H. Synthesis of Oxindoles, Spirooxindoles, and Isatins with Prominent Bioactive Probes Review. *Org. Med. Chem. Int. J.* **2018**, *5*, 555671. (d) Shukla, P. K.; Singh, M. P.; Patel, R. A Review on Recent Advances in Chemistry, Synthesis and Biological Applications of Isatin Derivatives. *J. Appl. Pharm. Sci. Res.* **2018**, *1*, 16−22. (e) Varun; Sonam; Kakkar, R. Isatin and its derivatives: A Survey of Recent Syntheses, Reactions, and Applications. *Med. Chem. Comm.* **2019**, *10*, 351−368. (f) Brandao, P.; Marques, C.; Burke, A. J.; Pineiro, M. The Application of Isatin-Based Multicomponent-Reactions in the Quest for New Bioactive and Drug like Molecules. *Eur. J. Med. Chem.* **2021**, *211*, 113102. (g) Kumar, S.; Nair, A. S.; Abdelgawad, M. A.; Mathew, B. Exploration of the Detailed Structure−Activity Relationships of Isatin and Their Isomers as Monoamine Oxidase Inhibitors. *ACS Omega* **2022**, *7*, 16244−16259. (h) Chowdhary, S.; Shalini; Arora, A.; Kumar, V. A Mini Review on Isatin, an Anticancer Scaffold with Potential Activities Against Neglected Tropical Diseases (NTDs). *Pharmaceuticals.* **2022**, *15*, 536.

(2) For selected recent examples, see: (a) Galliford, C. V.; Scheidt, K. A. Pyrrolidinyl-Spirooxindole Natural Products as Inspirations for the Development of Potential Therapeutic Agents. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748−8758. (b) Smith, G.; Glaser, M.; Perumal, M.; Nguyen, Q.-D.; Shan, B.; Ãrstad, E.; Aboagye, E. O. Design, Synthesis, and Biological Characterization of a Caspase 3/7 Selective Isatin Labeled with 2-[18F] fluoroethylazide. *J. Med. Chem.* **2008**, *51*, 8057−8067. (c) Krishnegowda, G.; Prakasha Gowda, A. S.; Tagaram, H. R. S.; Carroll, K. F. S.-O.; Irby, R. B.; Sharma, A. K.; Amin, S. Synthesis and Biological Evaluation of a Novel Class of Isatin Analogs as Dual Inhibitors of Tubulin Polymerization and Akt Pathway. *Bioorg. Med. Chem.* **2011**, *19*, 6006−6014. (d) Glaser, M.; Goggi, J.; Smith, G.; Morrison, M.; Luthra, S. K.; Robins, E.; Aboagye, E. O. Improved Radiosynthesis of the Apoptosis Marker 18F-ICMT11 Including Biological Evaluation. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 6945−6949. (e) Prakash, C. R.; Raja, S. Design, Synthesis and Antiepileptic Properties of Novel 1-(Substituted benzylidene)-3-(1-(morpholino/piperidino methyl)-2,3-dioxoindolin-5-yl) Urea Derivatives. *Eur. J. Med. Chem.* **2011**, *46*, 6057−6065. (f) Ferraz de Paiva, R. E.; Vieira, E. G.; Rodrigues da Silva, D.; Wegermann, C. A.; Costa Ferreira, A. M. Anticancer Compounds Based on Isatin-Derivatives: Strategies to Ameliorate Selectivity and Efficiency. *Front. Mol. Biosci.* **2021**, *7*, 627272.

(3) (a) Bridges, T. M.; Kennedy, J. P.; Cho, H. P.; Breininger, M. L.; Gentry, P. R.; Hopkins, C. R.; Conn, P. J.; Lindsley, C. W. Chemical Lead Optimization of a Pan Gq mAChR M1, M3, M5 Positive Allosteric Modulator (PAM) Lead. Part I: Development of the First Highly Selective M5 PAM. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 558−562. (b) Swaithi, K.; Srinivas, A.; Sarangapani, M. Design, Synthesis and Biological Evaluation of 5-[2(3)-Dialkylaminoalkoxy] Indole 2,3-diones as New Antihistamine Agents. *J. Chem. Pharm. Res.* **2010**, *2*, 220−225. (c) Ewang-Emukowhate, M.; Nair, D.; Caplin, M. The Role of 5-Hydroxyindoleacetic Acid in Neuroendocrine Tumors: The Journey So Far. *Int. J. Endo. Oncol.* **2019**, *6*, IJE17. (d) Du, F.; Zhou, Q.; Sun, W.; Yang, C.; Wu, C.; Wang, L.; Chen, G. 5-Hydroxyindole-Based EZH2 Inhibitors Assembled via TCCA-Catalyzed Condensation and Nenitzescu Reactions. *Molecules* **2020**, *25*, 2059.

(4) For selected examples, see: (a) Zeng, R.; Dong, G. Rh-Catalyzed Decarbonylative Coupling with Alkynes via C−C Activation of Isatins. *J. Am. Chem. Soc.* **2015**, *137*, 1408−1411. (b) Liu, Y.; Xia, Y.-T.; Cui, S.-H.; Ji, Y.-G.; Wu, L. Palladium-Catalyzed Cascade Hydrosilylation and Amino-Methylation of Isatin Derivatives. *Adv. Synth. Catal.* **2020**, *362*, 2632−2636. (c) Pawar, A. P.; Yadav, J.; Mir, N. A.; Iype, E.; Rangan, K.; Anthal, S.; Kant, R.; Kumar, I. Direct Catalytic Synthesis of β-(C3)-Substituted Pyrroles: A Complementary Addition to the Paal-Knorr Reaction. *Chem. Commun.* **2021**, *57*, 251−254. (d) Chen, Q.; Teng, Y.; Xu, F. Lanthanide Silylamide-Catalyzed Synthesis of Pyrano[2,3-b]indol-2-ones. *Org. Lett.* **2021**, *23*, 4785−4790. For a review, see: (e) Klein, J. E. M. N.; Taylor, R. J. K. Transition-Metal-Mediated Routes to 3,3-Disubstituted Oxindoles Through Anilide Cyclisation. *Eur. J. Org. Chem.* **2011**, *2011*, 6821−6841. (f) Mohammadi Ziarani, G.; Moradi, R.; Lashgari, N. Asymmetric Synthesis of Chiral Oxindoles Using Isatin as Starting Material. *Tetrahedron.* **2018**, *74*, 1323−1353. (g) Shen, J.; Zhang, L.; Meng, X. Recent Advances in Cyclization Reactions of Isatins or Thioisatins via C−N or C−S Bond Cleavage. *Org. Chem. Front.* **2021**, *8*, 6433−6451. (h) Saranya, P. V.; Neetha, M.; Aneeja, T.; Anilkumar, G. Transition Metal-Catalyzed Synthesis of Spirooxindoles. *RSC Adv.* **2021**, *11*, 7146−7179.

(5) For selected reviews, see: (a) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. Mild Metal-Catalyzed C−H Activation: Examples and Concepts. *Chem. Soc. Rev.* **2016**, *45*, 2900−2936. (b) Wedi, P.; van Gemmeren, M. Arene-Limited Nondirected C−H Activation of Arenes. *Angew.Chem. Int. Ed.* **2018**, *57*, 13016−13027. (c) Rogge, T.; Kaplaneris, N.; Chatani, N.; Kim, J.; Chang, S.; Punji, B.; Schafer, L. L.; Musaev, D. G.; Wencel-Delord, J.; Roberts, C. A.; Sarpong, R.; Wilson, Z. E.; Brimble, M. A.; Johansson, M. J.; Ackermann, L. C−H activation. *Nat. Rev. Methods Primers* **2021**, *1*, 43.

(6) For reviews on the C−H functionalization of indoles, see: (a) Sandtorv, A. H. Transition Metal-Catalyzed C−H Activation of Indoles. *Adv. Synth. Catal.* **2015**, *357*, 2403−2435. (b) Leitch, J. A.; Bhonoah, Y.; Frost, C. G. Beyond C2 and C3: Transition-Metal-Catalyzed C−H Functionalization of Indole. *ACS Catal.* **2017**, *7*, 5618−5627. (c) Jagtap, R. A.; Punji, B. C−H Functionalization of Indoles by 3d Transition-Metal Catalysis. *Asian J. Org. Chem.* **2020**, *9*, 326−342. (d) Jagtap, R. A.; Punji, B. Nickel-Catalyzed C−H Bond Functionalization of Azoles and Indoles. *Chem. Rec.* **2021**, *21*, 3573−3588. (e) Bansal, S.; Shabade, A. B.; Punji, B. Advances in C(sp^2)−H/C(sp^2)−H Oxidative Coupling of (Hetero)arenes Using 3d Transition Metal Catalysts. *Adv. Synth. Catal.* **2021**, *363*, 1998−2022. (f) Pradhan, C.; Punji, B. Advances in the Iron-Catalyzed Direct Functionalizations of Heterocycles. *SynLett.* **2022**, DOI: 10.1055/a-1890-8503.

(7) (a) Jagtap, R. A.; Samal, P. P.; Vinod, C. P.; Krishnamurty, S.; Punji, B. Iron-Catalyzed C(sp^2)−H Alkylation of Indolines and Benzo[h]quinoline with Unactivated Alkyl Chlorides through Chelation Assistance. *ACS Catal.* **2020**, *10*, 7312−7321. (b) Verma, S. K.; Punji, B. Manganese-Catalyzed C(sp^2)−H Alkylation of Indolines and Arenes with Unactivated Alkyl Bromides. *Chem. Asian J.* **2022**, *17*, No. e202200103.

(8) Zhou, K.; Wang, D.; Ju, G.; Deng, Z.; Huang, P.; Huang, Z.; Li, B.; Zhao, Y. Ligand-Promoted Fluorinated Olefination of Isatins at the C5 Position via a Palladium Catalyst. *Org. Lett.* **2022**, *24*, 5568−5572.

(9) For selected early examples on Pd-catalyzed oxygenation, see: (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. A Highly Selective Catalytic Method for the Oxidative Functionalization of C−H Bonds. *J. Am. Chem. Soc.* **2004**, *126*, 2300−2301. (b) Zhang, Y.-H.; Yu, J.-Q. Pd(II)-Catalyzed Hydroxylation of Arenes with 1 atm of O_2 or Air. *J. Am. Chem. Soc.* **2009**, *131*, 14654−14655. (c) Emmert, M. H.; Cook, A. K.; Xie, Y. J.; Sanford, M. S. Remarkably High Reactivity of

$Pd(OAc)_2$/Pyridine Catalysts: Nondirected C−H Oxygenation of Arenes. *Angew. Chem., Int. Ed.* **2011**, *50*, 9409−9412. For selected reviews, see: (d) Enthaler, S.; Company, A. Palladium-Catalysed Hydroxylation and Alkoxylation. *Chem. Soc. Rev.* **2011**, *40*, 4912−4924. (e) Valderas, C.; Naksomboon, K.; Fernández-Ibáñez, M. Á. Ligand-Promoted Palladium-Catalyzed C−H Acetoxylation of Simple Arenes. *ChemCatChem.* **2016**, *8*, 3213−3217. (f) Iqbal, Z.; Joshi, A.; Ranjan De, S. Recent Advancements on Transition-Metal-Catalyzed, Chelation-Induced *ortho*-Hydroxylation of Arenes. *Adv. Synth. Catal.* **2020**, *362*, 5301−5351. (g) Vijaykumar, M.; Punji, B. Advances in Transition-Metal-Catalyzed C−H Bond Oxygenation of Amides. *Synthesis* **2021**, *53*, 2935−2946.

(10) (a) Kang, Y.-B.; Gade, L. H. The Nature of the Catalytically Active Species in Olefin Dioxygenation with $PhI(OAc)_2$: Metal or Proton? *J. Am. Chem. Soc.* **2011**, *133*, 3658−3667. (b) Wang, A.; Jiang, H.; Chen, H. Palladium-Catalyzed Diacetoxylation of Alkenes with Molecular Oxygen as Sole Oxidant. *J. Am. Chem. Soc.* **2009**, *131*, 3846−3847.

(11) (a) Dou, X.; Yao, W.; Jiang, C.; Lu, Y. Enantioselective *N*-Alkylation of Isatins and Synthesis of Chiral *N*-Alkylated Indoles. *Chem. Commun.* **2014**, *50*, 11354−11357. (b) Wang, Y.-Y.; Chen, C. Synthesis of Deuterium Labeled Tryptamine Derivatives. *J. Chin. Chem. Soc.* **2007**, *54*, 1363−1368.

(12) (a) Cook, A. K.; Emmert, M. H.; Sanford, M. S. Steric Control of Site Selectivity in the Pd-Catalyzed C−H Acetoxylation of Simple Arenes. *Org. Lett.* **2013**, *15*, 5428−5431. (b) Cook, A. K.; Sanford, M. S. Mechanism of the Palladium-Catalyzed Arene C−H Acetoxylation: A Comparison of Catalysts and Ligand Effects. *J. Am. Chem. Soc.* **2015**, *137*, 3109−3118.

https://doi.org/10.1021/acs.orglett.3c00342
Org. Lett. 2023, 25, 1862−1867