Unified Strategies for Nickel-Catalyzed and Metal-Free C–H Functionalizations of Indoles, and Mechanistic Studies

Thesis

Submitted to AcSIR for the Award of the Degree of

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by

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under the guidance of

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Dedicated to

My Beloved Parents

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Thesis Certificate

This is to certify that the work incorporated in this Ph.D. thesis entitled "**Unified Strategies for Nickel-Catalyzed and Metal-Free C–H Functionalizations of Indoles, and Mechanistic Studies**" submitted by Ms. Vineeta Soni to the Academy of Scientific and Innovative Research (AcSIR) in fulfillment of the requirements for the award of the Degree of the Doctor of Philosophy, embodies original research work under my supervision. I 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 obtained from other sources has been duly acknowledged in the thesis. Any text, illustration, table, etc., used in the thesis from other sources, have been duly cited and acknowledged.

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I hereby declare that the original research work embodied in this thesis entitled, "**Unified Strategies for Nickel-Catalyzed and Metal-Free C–H Functionalizations of Indoles, and Mechanistic Studies**" submitted to the Academy of Scientific and Innovative Research (AcSIR) for the award of the degree of the Doctor of Philosophy (Ph.D.) is the outcome of experimental investigations carried out by me under the supervision of Dr. Benudhar Punji, Senior Scientist, CSIR-National Chemical Laboratory, Pune. I affirm that the work incorporated is original, and has not been submitted to any other academy, university or institute for the award of any degree or diploma.

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Though, many have not been mentioned, none is forgotten."

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ABBREVIATIONS

BDMAE	Bis(2-dimethylaminoethyl) ether
BINOL	1,1'-Bi-2-naphthol
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bipy	2,2'-Bipyridine
Cp	Cyclopentadienyl
$(COCl)_2$	Oxalyl chloride
COD	1,5-Cyclo-octadiene
Davephos	2-Dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl
DCE	1,2-Dichloroethane
dcype	Dicyclophosphinoethane
DFT	Density Functional Theory
DMAc	*N*,*N*-dimethylacetamide
DME	Dimethoxy ethane
DMF	*N*,*N*-dimethylformamide
DMSO	Dimethyl sulfoxide
D^{t}BEDA	*N*,*N*′-Di-*tert*-butyl ethylenediamine
DTBP	Di-tert-butyl peroxide
dtbpy	4,4-Di-*tert*-butyl bipyridine
dppe	1,1-Bis(diphenylphosphino)ethane
dppm	1,1-Bis(diphenylphosphino)methane
dppb	1,4-Bis(diphenylphosphino)butane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
dppz	Dipyrido[3,2-a:2′,3′-c]phenazine
dppbz	1,2-Bis(diphenylphosphanyl)benzene
Galvinoxyl	2,6-Di-*tert*-butyl-α-(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadien-1-ylidene)-*p*-tolyloxy
IPr·HCl	1,3-Bis(2,6-diisopropylphenyl)imidazolium chloride
KTFA	Potassium trifluoroacetate
LA	Lewis Acid
LiHMDS	Lithium bis(trimethylsilyl)amide
$Me_2S·CuBr$	Copper(I) bromide dimethyl sulphide
MeSCOOH	2,4,6-trimethylbenzoic acid
MTBE	Methyl tert-butyl ether

ABBREVIATIONS

$(DME)NiCl_2$	Nickel(II) chloride ethylene glycol dimethyl ether
$(PPh_3)_2NiCl_2$	Bis(triphenylphosphine)nickel(II) dichloride
$Ni(OAc)_2$	Nickel(II) acetate
NBS	N-bromosuccinimide
NMP	1-Methyl-2-pyrrolidone
ORTEP	Oak ridge thermal-ellipsoid plot program
OTf	Trifluoromethanesulfonate
PCy_3	Tricyclohexylphosphine
$Pcyp_3$	Tricyclo pentyl phosphine
Phen	1.10-Phenanthroline
$PhI(OAc)_2$	(Diacetoxyiodo) benzene
$PhI(TFA)_2$	[Bis(trifluoroacetoxy)iodo]benzene
PIP	2-Pyridinyl isopropyl
Piv	Pivalate
$PMePh_2$	Methyldiphenylphosphane
Py	Pyridinyl
^tBu	Tertiary butyl
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
Tfacac	1,1,1-trifluoroacetylacetonate
TFE	Trifluoroethanol
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TOF	Turnover frequency
TON	Turnover number
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

ABSTRACT

This thesis is divided into six different chapters. Chapter-1 deals with the detailed literature survey on the nickel-catalyzed C–H bond activation and functionalization of arenes and heteroarenes. Various C–H bond functionalizations, such as arylation, alkenylation, benzylation, alkylation and fluoroalkylation, and C–heteroatom bond formation are discussed. Mechanistic aspects of all these C–H functionalizations are highlighted. In addition to this, the transition-metal-free C–H acetoxylation of arenes and heteroarenes is described.

Chapter-2 deals with the synthesis and characterization of (NNN)-pincer nickel complexes, and application of the Ni-complexes toward regioselective C-2 alkylation of indoles *via* a unified strategy. The nickel-catalyzed direct C-2 alkylation of indoles through monodentate-chelation assistance has been described. This reaction proceeds *via* a unique strategy by the use of well-designed and defined (quinolinyl)amido-nickel catalyst, [κ^N,κ^N,κ^N-{$Et_2NCH_2C(O)$-(μ-N)-C_9H_6N}Ni(OAc)], providing a solution to the limitations associated with the bidentate-chelate auxiliaries. This regioselective C-2 alkylation of indoles by the (NNN)-pincer nickel catalyst allows the coupling of indoles with various unactivated primary and secondary alkyl halides. Important functional groups, such as ether, nitrile, fluoro, and bromo were tolerated on the indole-moiety. Alkyl bromides with the branching at β- and γ-position were efficiently coupled with the indoles to give C-2 alkylated products in good yields. In addition, both the cyclic and acyclic secondary alkyl halides were compatible under the reaction conditions. The synthetic utility of this nickel-catalyzed protocol is demonstrated by the facile removal of 2-pyridinyl directing group, and by the convenient synthesis of the neuromodulator tryptamine alkaloid derivatives.

Chapter-3 describes the nickel-catalyzed $C(sp^2)$–H/$C(sp^3)$–H oxidative coupling of indoles with toluene derivatives. This oxidative coupling is successfully achieved in the presence of 2-iodobutane as a mild oxidant. The use of 2-iodobutane as the oxidant is very crucial, which functions as a benzyl radical originator by abstracting H-atom from the toluene derivatives. The well-defined, inexpensive nickel catalyst proved efficient for the coupling of broad indole substrates with diverse toluene derivatives. Substrates bearing both the electron-donating as well as electron-withdrawing substituent have reacted smoothly to give the regioselective C-2 benzylated products. The reaction was tolerated by ether, halides and heterocycle to afford the biologically relevant benzylated indoles. This method allows the selective C-2 benzylation of indoles with toluene derivatives over the alkylation with 2-iodobutane, and permits the coupling of diversified indoles *via* the mono-chelation assistance.

The synthetic utility of this nickel-catalyzed protocol is demonstrated by the easy removal of directing group, and by the beneficial synthesis of the melatonin receptor antagonist Luzindole derivatives.

Chapter-4 illustrates the mechanisms of C-2 alkylation and C-2 benzylation of indoles catalyzed by (quinolinyl)amido-nickel catalyst, [κ^N,κ^N,κ^N-{$Et_2NCH_2C(O)$-(μ-N)-C_9H_6N}Ni(OAc)]. Preliminary experiments have been performed to know the absolute nature of the catalyst, wherein the effect of external additives, such as Hg and TEMPO/galvinoxyl on the alkylation and benzylation were probed. Apart from these, the radical clock experiment has been performed to confirm the radical pathway of the reaction. To gain more insight into the mechanism, the electronic effect of substituents on the reaction rates has been determined by the independent kinetic experiments. The kinetic isotope effect (KIE) experiments have been performed to understand the aspects of C–H bond activation process during the reaction. The KIE value of 2.1 has been observed for the C-2 alkylation of indoles. Similarly, for the benzylation reaction the KIE value of 3.1 (for indole C–H) and 2.7 (for toluene C–H) were found, which suggest that the C–H bond nickelation on indole is significant with respect to the turnover-limiting step in both the reaction. Additionally, the H/D scrambling experiment between [1-(pyridin-2-yl)-1*H*-indole-2-*d*] and [5-methoxy-1-(pyridin-2-yl)-1*H*-indole] indicated no exchange of proton/deuterium among them. This reveals the C–H activation is irreversible, and does not proceed *via* a simple deprotonative pathway. Some of the Ni-intermediates have been detected by the MALDI-TOF mass spectroscopy. On the basis of mechanistic experiments, the catalytic cycles have been proposed for both the alkylation and benzylation of indole.

Chapter-5 describes a nickel-catalyzed method for the regioselective difluoroalkylation of indoles. The installation of fluorine into organic compounds significantly affect their properties, and thus enhances the solubility, bio-availability and metabolic stability. Herein, the in-situ generated nickel catalyst from $(DME)_2NiCl_2$ and Xantphos has been demonstrated for the regioselective C-2 difluoroalkylation of indoles with ethyl 2-bromo-2,2-difluoroacetate under mild condition. This reaction proceeded regioselectively at the C-2 position without the installation of a directing group. Broad substrate scope has been explored with diversely substituted indole derivatives. This methodology tolerates the synthetically valuable functional groups, such as –OMe, –F, –Br on indoles moiety. This represents the first report for difluoroalkylation of indoles using Ni-catalyst, without being the installation of a directing group.

ABSTRACT

The metal-free method for the regioselective C-3 acetoxylation of *N*-substituted indoles with $PhI(OAc)_2$ under the mild reaction conditions is described in chapter 6. Substrate scope has been testified with the *N*-substituted indoles having aryl and heteroaryl substitutents. This method tolerates a broad range of functional groups like –F, $–CF_3$, –C(O)Me, –C(O)OMe, –CN and $–NO_2$ with moderate to good yields. The diacetoxylated indoline is the active intermediate for the acetoxylation of the *N*-substituted indoles, where the dehydroacetoxylation is facilitated in the presence of a π-deficient arene substituent on the *N*-atom of indoles. On the basis of control experiments it has been proved that π-electron-deficient aryl-substituent on the *N*-atom of indoles and the acidic reaction medium remarkably favours the C-3 acetoxylation.

Chapter 1

Introduction

INDOLE is a heterocyclic organic compound having chemical formula C_8H_7N. It has a six-membered benzene ring fused with a five-membered nitrogen-containing pyrrole ring (Figure 1.1). The name *indole* is the combination of two words ***ind****igo* and ***ole****um*, as it was first isolated by the treatment of indigo dye with oleum.[1,2] Indole is widely dispersed in natural environment, and can be formed by various bacteria. It works as an intercellular signal molecule, and regulates the bacterial physiology, such as spore formation, plasmid stability, drug resistance, bio-film formation and virulence.[3] Amino acid tryptophan is derivative of indole, which is the precursor for neurotransmitter serotonin. Indole scaffold is encountered in a large number of drug candidates involving treatment of cancer,[4] type-2 diabetes[5] and HIV.[6] The indole backbone is also ubiquitously found in natural products,[7,8] structures that bears significant biological activities and therefore constitute targets in organic synthesis (Figure 1.2).[9-11] Furthermore, indole-based ligand can easily bind to the metal precursor, and can function as an efficient catalyst system.[12]

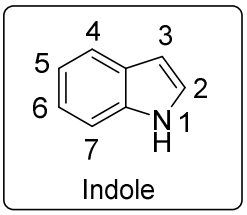


Figure 1.1 Structure and atom-numbering of indole.

Indole chemistry has given particular attention in the mid-1950s, when reserpine[13] alkaloid was used as the drugs for the treatment of central nervous system (CNS) diseases, such as anxiety and mental disorders. Indolyl alkaloids were significantly used for anti-inflammatory, ranquilizing, and antihypertensive activities. The significant applications of indole pharmacophores are in the drugs that cures CNS diseases or shows anti-inflammatory activity.[14] Indole is an electron-rich heterocycle, which has better reactivity compared to the benzene in aromatic electrophilic substitution reactions. The most reactive position of indole towards electrophilic substitution reactions is the C-3 site (about 10^{13} times more reactive than benzene);[15] and C-2 position is considered when C-3 substituted compounds are envisaged. Considering the importace of indole moiety, the regioselective and catalytic C−H bond activation and functionalization of indole is very crucial for both the academic and industrial research.

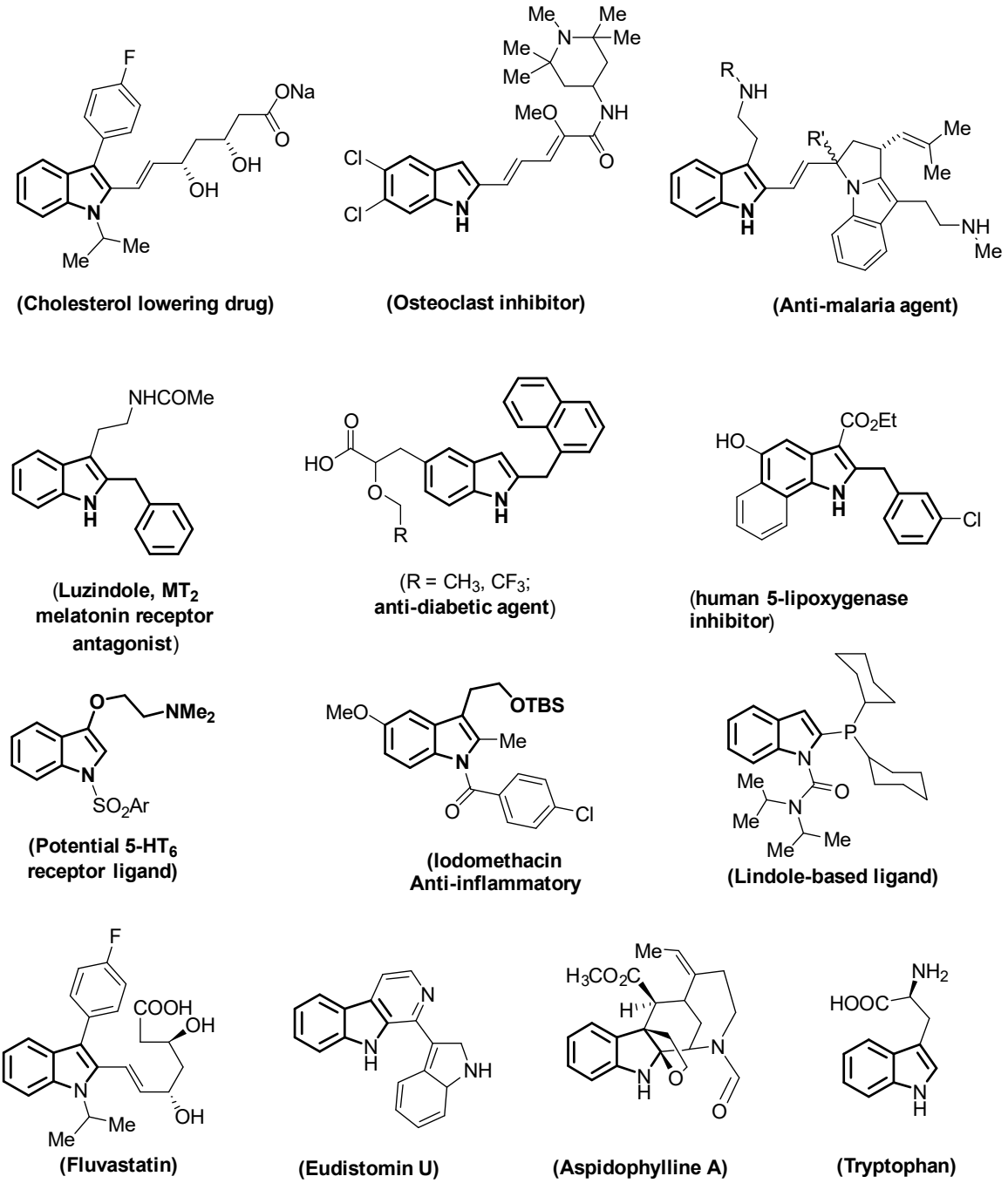
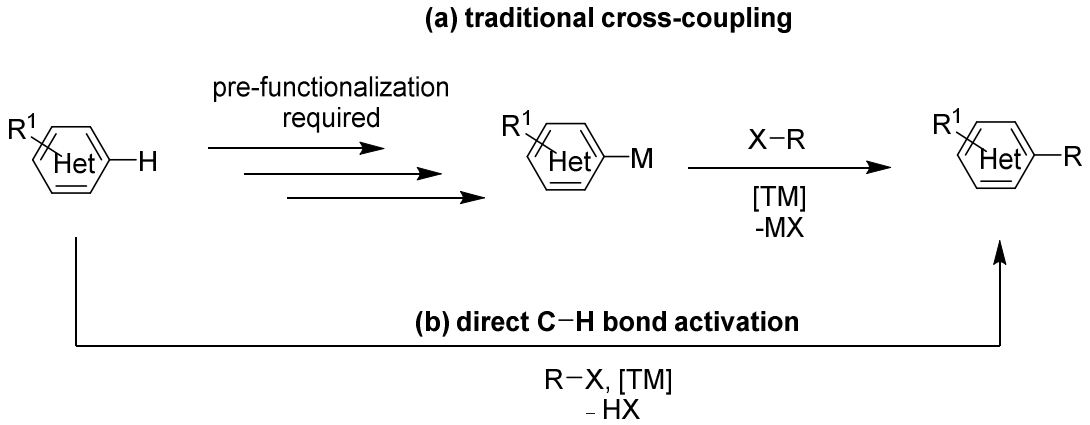


Figure 1.2 Biologically important compounds having indole backbone.

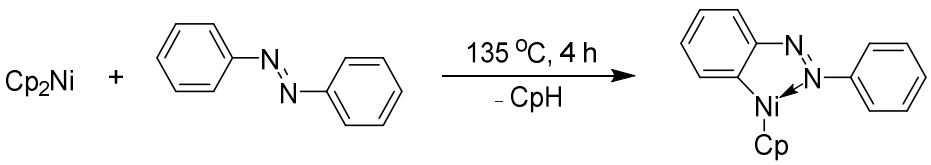
Direct C–H bond activation and functionalization is a powerful and attractive method for generating new C–C and C–heteroatom bonds.[16-26] The C–H bond functionalization of arenes and heteroarenes is considered as an alternative to the traditional cross-coupling reaction, because such a process avoids the pre-activation steps, like halogenation or metalation of arenes and heteroarenes (Scheme 1.1).[27,28] Various transition-metal-catalyzed C–H bond activation and functionalizations, such as arylation, alkenylation, benzylation, alkylation, difluoroalkylation and C–heteroatom bond formation are well precedented.[29-36]

Many late transition-metal catalysts like complexes of palladium, ruthenium, rhodium have been used to carry out these transformation efficiently. However, recently first row transition-metal catalysts have given more importance as they are readily available, less expensive and easy to handle. Particularly, the nickel-catalyzed C–H bond functionalization has given significant importance as nickel can show unique reactivity with variable oxidation states, $Ni^{I}/Ni^{II}/Ni^{III}/Ni^{IV}$, and it's chemistry is less explored. Notably, Sabatier has described that "nickel can do all kind of work and maintain it's activity for a long time". The development of organo-nickel chemistry led to the discovery of several catalytic systems and much practical application.[37-42] The nickel complexes have been used as catalyst in many organic transformations, such as cycloaddition, carbonylation, decarbonylation, alkene polymerization, which contributes both in academic as well as in the industry.[43-47]



Scheme 1.1 Traditional Cross-Coupling *versus* C−H Bond Activation.

The first nickel-mediated aromatic C–H bond activation was described by Kleinman and Dubeck in 1964.[48] They observed that the heating of dicyclopentadienyl nickel with an excess of diazo-benzene afforded purple blue organo-nickel species (Scheme 1.2). After this initial report, there are several publications appeared on the nickel-catalyzed C–H bond activation and functionalization.



Scheme 1.2 Synthesis of Organonickel Species.

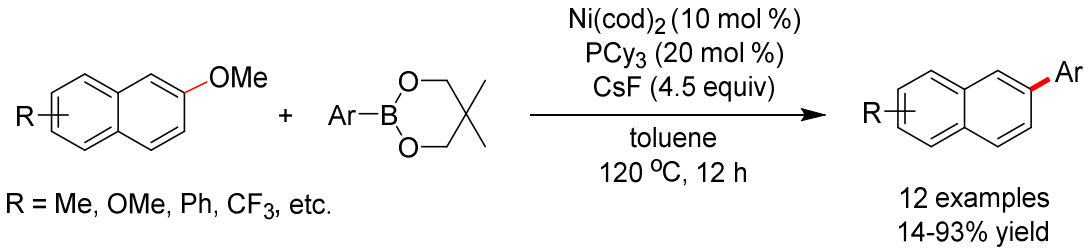
The less expensiveness, high abundance and unique reactivity of nickel make it beneficial to utilize in various organic transformation compared to the 4d and 5d transition metals. Nickel as a catalyst has been utilized in various C–C bond forming reactions, such as alkylation,[49-61] alkenylation,[46,62,63] arylation,[49,64-68] alkynylation.[66,69] This chapter deals with the detailed literature survey on the nickel-catalyzed C–H bond activation and functionalization of arenes and heteroarenes. Various C–H bond functionalizations, such as arylation, alkenylation, alkynylation, alkylation, benzylation, difluoroalkylation and C–heteroatom bond formation are discussed. Mechanistic aspects of all these C–H functionalizations are highlighted. In addition, the transition-metal-free C–H bond acetoxylation of arenes and heteroarenes is described.

1.1 Nickel-Catalyzed C–H Bond Arylation

Arylation of arenes and heteroarenes has received significant attention, as the arylated compounds are essential building units of various biological and pharmaceutical compounds.[70-73] The C−H bond arylation has widely been studied with precious 4d metal catalysts.[32,74-83] However, current research effort is being focused on the development of such transformations using naturally abundant 3d metals, such as nickel, as catalyst.[49,64,66-68]

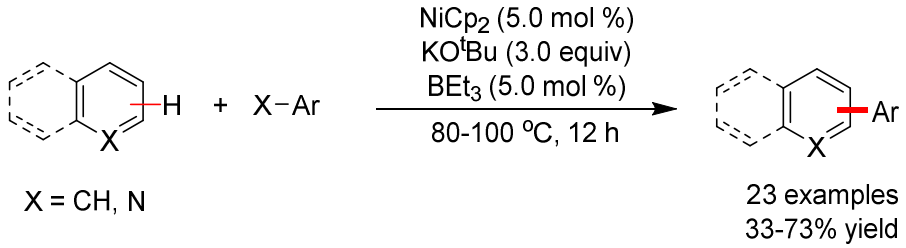
1.1.1 Arylation of Arenes

The first nickel-catalyzed arylation was documented by Wenkert *et al.* in 1979 using aryl magnesium bromide Grignard reagent as coupling partner.[84] Here, they have coupled phenyl magnesium and methyl magnesium bromide with enol and aryl ether in the presence of bis(triphenylphosphine)nickel chloride metal complex *via* the C−O bond activation. Later on, Dankwardt and Chatani independently reported the nickel-catalyzed arylation of aryl ether using Grignard reagent and boronic acid, respectively, through the C−O bond cleavage (Scheme 1.3).[85-87]



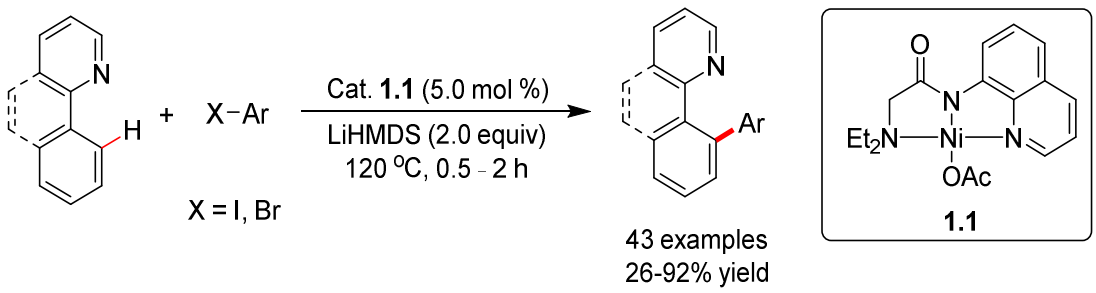
Scheme 1.3 Nickel-Catalyzed Arylation of Arene with Boronic Acid *via* C−O Bond Activation.

In 2009, Yamakawa has investigated the direct C−H bond arylation of unfunctionalized aromatic hydrocarbons, such as benzene and naphthalene with aryl halide using Cp_2Ni catalyst.[88] They found that the combination of Cp_2Ni, KO^{t}Bu and BEt_3, is an efficient catalyst system for the arylation of simple arenes (Scheme 1.4). Moreover, when PPh_3 was used instead of BEt_3, this catalyst shows efficient activity for the C−H arylation of heteroarenes like pyridine. But along with successful achievement, this methodology was limited by the regioselectivity issue *i.e.* more than one isomers were formed. Similar report has been published by the group of Mao using $Ni(OAc)_2.4H_2O$ and 1,10-phenanthroline system.[89]



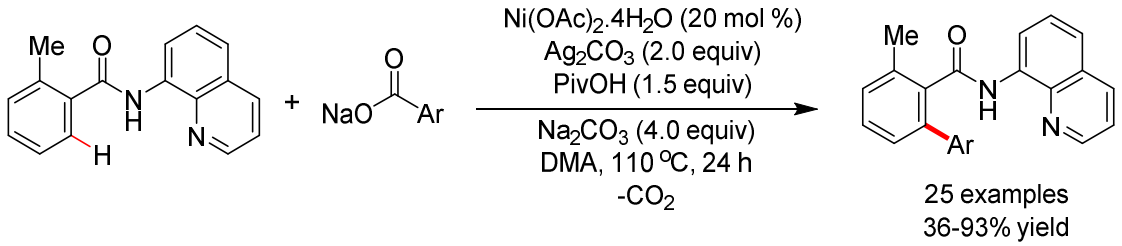
Scheme 1.4 Nickel-Catalyzed Arylation of Simple Arenes.

Recently, Punji and co-workers developed an efficient solvent-free method for the arylation of arenes and indoles using nickel catalyst through the chelation assistance (Scheme 1.5).[90] In this case, the coupling of benzo[*h*]quinoline with aryl halide was achieved using a quinolinyl-based pincer nickel complex **1.1** without the use of a solvent. This methodology also works for the arylation of indole and phenyl-pyridine derivatives. This method provided a broad substrate scope for the arylation of arenes and indoles with various aryl halides with the tolerance of functional groups. Notably, the method is highly selective for monoarylation for phenyl-pyridine derivatives.



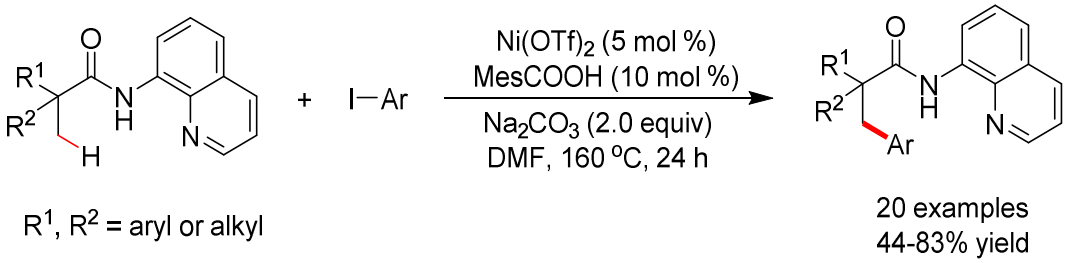
Scheme 1.5 Solvent-free Nickel-Catalyzed C(sp^2)–H Bond Arylation of Benzo[*h*]quinoline.

The nickel-catalyzed decarbonylative arylation and heteroarylation have been reported by Hoover group using 8-aminoquinoline as a bidentate auxilliary,[91] wherein the silver has been used as an oxidant that assists in decarbonylation (Scheme 1.6). Similarly, many other groups demonstrated on the arylation of azoles through bidentate-chelate assistance.[92-95]



Scheme 1.6 Nickel-Catalyzed Decarbonylative Arylation of Benzamide.

In 2014, Chatani *et al.* developed the nickel-catalyzed arylation of unactivated C(sp^3)–H bond in aliphatic amide using bidentate chelation assistance (Scheme 1.7).[96] Herein, the arylation of aliphatic amides, containing 8-aminoquinoline as directing group, with various aryl iodide was achieved using $Ni(OTf)_2$ as catalyst. This reaction is highly selective for the methyl group arylation, and the methylene and benzene C–H bond remain unreacted. Similarly, using bidentate chelation strategy You[97,98] and other groups[99-101] have reported nickel-catalyzed C(sp^3)–H bond arylation of benzamide.

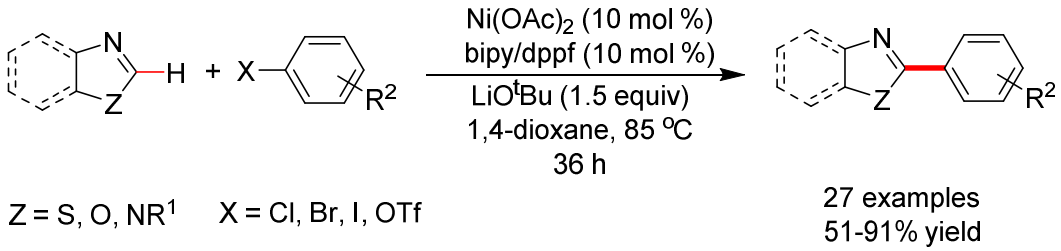


Scheme 1.7 Nickel-Catalyzed C(sp^3)–H Bond Arylation of Aliphatic Amides.

1.1.2 Arylation of Heteroarenes

The nickel-catalyzed C−H bond arylation of heteroarenes, mainly azoles with aryl halides, was reported by Itami[102] and Miura[103] independently for the first time. Itami group described the cross-coupling of azoles with aryl halides and aryl triflate using $Ni(OAc)_2$/bipy or $Ni(OAc)_2$/dppf catalyst in the presence of LiO^tBu (Scheme 1.8). A number of structurally diverse heteroarenes, such as thiazole, benzothiazole, oxazole, benzoxazole, and

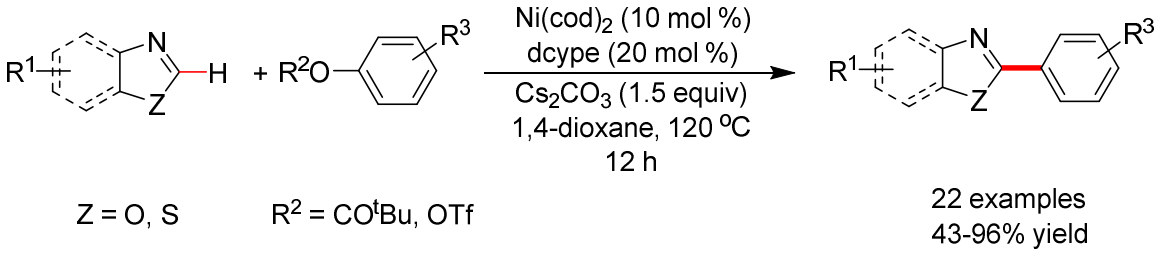
benzimidazole were efficiently coupled with differently substituted aryl halides. Similarly, Miura *et al.* demonstrated the arylation reaction of various azoles with aryl bromides.[103] They have achieved the coupling of azoles with aryl bromides using $NiBr_2$·diglyme/Phen catalyst system and LiO^tBu. It was observed that the use of Zn powder increases the reaction rate by reducing N(II) to Ni(0) active species.



Scheme 1.8 Nickel-Catalyzed Arylation of Azoles with Aryl Halide or Aryl Triflate.

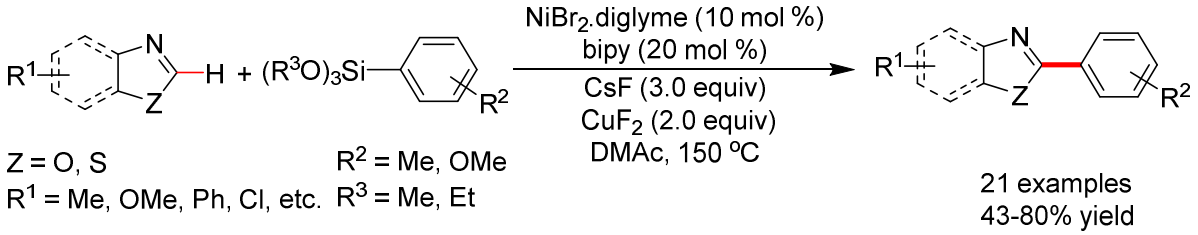
The arylation of azoles by Itami and Miura groups demonstrated that the nickel has the potential to allow the access of a wide range of 2-arylated azoles with substituted aryl halides or triflates. However, in both the cases, the utilization of strong base LiO^tBu limits the methods. Similarly, Miura group has further reported the C−H arylation of azoles with arylboronic acid, wherein, they have used $NiBr_2$ as catalyst and atmospheric air as the sole oxidant.[104] After that, Itami group has developed a new strategy for the arylation of azoles using $Mg(O^tBu)_2$ base in DMF.[65] They have developed two different conditions for the arylation of azoles using $Ni(OAc)_2$/Phen catalyst system: i) LiO^tBu/1,4-dioxane works very well for the robust substrates, ii) $Mg(O^tBu)_2$/DMF works for substrates which contain base sensitive groups like nitro and ester. This methodology also works for other heteroarenes like thiazoles, benzothiazoles, oxazoles, benzoxazoles and benzimidazoles.

Various catalytic systems were reported for the coupling reaction of (hetero)arenes with aryl halide using nickel as catalyst, but the use of aryl halide remained a drawback.[65,102,103] The coupling of arenes with phenol derivatives seems more beneficial since the phenol and their derivatives are commercially available and less expensive. In 2012, Itami group demonstrated the first nickel-catalyzed Ar–H/Ar–O coupling reaction (Scheme 1.9).[105] In this case, they have achieved the cross-coupling of variously substituted 1,3-azoles and benzoxazole with phenol derivatives using $Ni(COD)_2$/dcype as catalyst in the presence of Cs_2CO_3. This protocol provides efficient coupling of azoles with various phenol derivatives, such as pivalates, triflates, tosylates, mesylates, carbamates, carbonates, and sulfamates with the tolerance of functional groups –OMe and –COOMe on azoles.

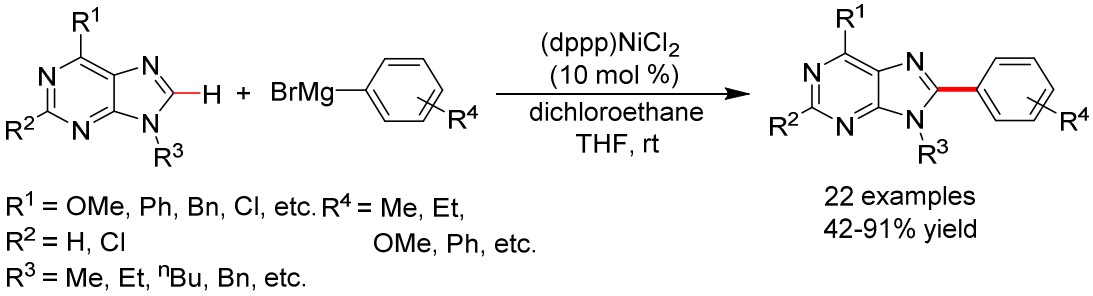


Scheme 1.9 Nickel-Catalyzed Ar–H/Ar–O Cross-Coupling Reaction.

The transition-metal-catalyzed arylation of heteroarenes has also been achieved using aryl silane or aryl boronic acid as coupling partner instead of aryl halide or triflate. In 2010, Miura *et al.* described the nickel-catalyzed cross-coupling of azoles with organosilicon as coupling reagent (Scheme 1.10).[106] Herein, the $NiBr_2$·diglyme/bipy catalyst system efficiently coupled the 1,3-azole with trimethoxyarylsilane in the presence of CsF and CuF_2 as additives. Using this strategy the coupling of various 1,3-azoles, such as benzothiazoles, benzoxazoles, benzimidazoles, thiazoles, oxazoles with aryl silane was achieved. The same group also reported the nickel-catalyzed azoles arylation using aryl boronic acid as a coupling partner in the presence of air.[104] Hence, the treatment of 1,3-azole with aryl boronic acid in the presence of $NiBr_2$/bipy catalyst and K_3PO_4 provided the desired coupled products. Guo group reported a novel strategy for the C(sp^2)–H bond arylation of purines using nickel catalyst.[107] Herein, the coupling of *N*-containing heterocycles with aryl magnesium bromide was achieved using (dppp)$NiCl_2$ catalyst in DCM/THF at room temperature (Scheme 1.11). This strategy provided excellent tolerance of electron-donating functional groups on the Grignard reagent.

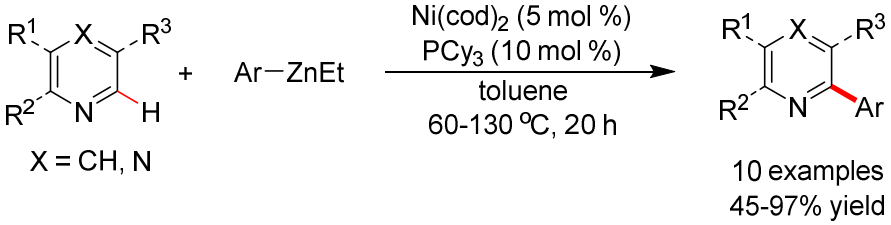


Scheme 1.10 Nickel-Catalyzed C–H Arylation of Heteroarenes with Organosilicons.



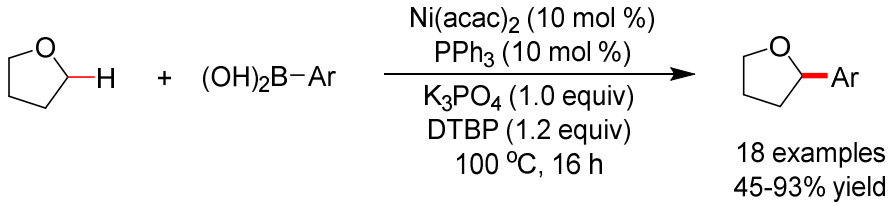
Scheme 1.11 Nickel-Catalyzed C(sp^2)–H Arylation of Purines with Aryl Magnesium Bromides.

The C−H bond arylation of electron-deficient heteroarenes, such as pyridines and quinolines is quite difficult because majority of these functionalization depend on either electrophilic substitution or concerted-metalation-deprotonation approach.[108] However, Chatani has demonstrated a Ni-catalyzed C−H bond arylation method for the electron-deficient quinoline using aryl zinc reagents (Scheme 1.12).[109,110] Herein, various substrates, such as quinoline, pyrazine, phenyl pyridine and benzo[*h*]quinoline are arylated using different substituted aryl zinc reagents.



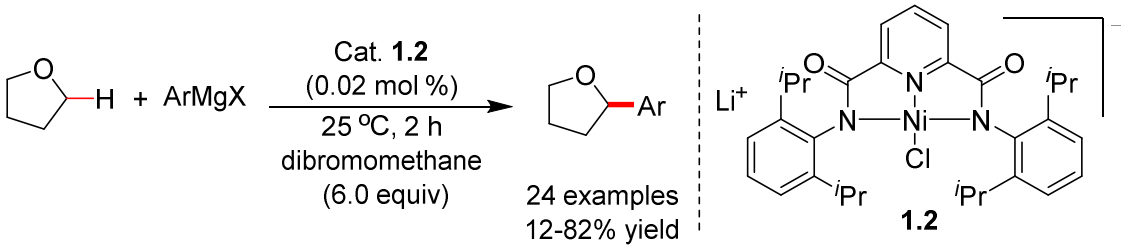
Scheme 1.12 Nickel-Catalyzed Arylation of Electron-Deficient Heteroarenes.

A wide variety of catalytic systems were developed for the C(sp^2)–H bond arylation of arenes and heteroarenes, but the C(sp^3)–H bond arylation of heteroarenes remained challenging. In 2013, for the first time Lei group has demonstrated the nickel-catalyzed oxidative arylation of the C(sp^3)–H bond on THF or 1,4-dioxane using aryl boronic acid.[111] Here, they have arylated *ortho* C–H bond adjacent to O-atom of THF and 1,4-dioxane with aryl boronic acid using $Ni(acac)_2$, PPh_3 ligand and K_3PO_4 as base in the presence of strong oxidant DTBP (Scheme 1.13). Other than this, nitrogen containing substrates like *N,N*-dimethyl aniline, *N,N*-dimethyl acetamide and *N*-methyl pyrrole have also been functionalized under the same reaction condition. The preliminary mechanistic findings demonstrated that this reaction proceeds *via* a radical pathway.



Scheme 1.13 Nickel-Catalyzed C(sp^3)−H Bond Arylation of Heteroarenes.

In 2014, Ghosh group reported the arylation of oxygen containing heterocyclic compounds, such as tetrahydrofuran and furan using Grignard reagent as an arylating reagent, wherein a pincer nickel complex of *N,N*-bis(2,6-diisopropylphenyl)-2,6-pyridinedicarboxamido ligand has been used as catalyst (Scheme 1.14).[56] The catalyst's turnover frequency is 4130 h^{-1} with the catalyst loading of 0.01 mol %. Recently, Molander group has reported photochemical nickel-catalyzed C–H arylation of THF with alkyl bromide as the coupling partner.[112]



Scheme 1.14 Nickel-Catalyzed C(sp^3)−H Arylation of THF.

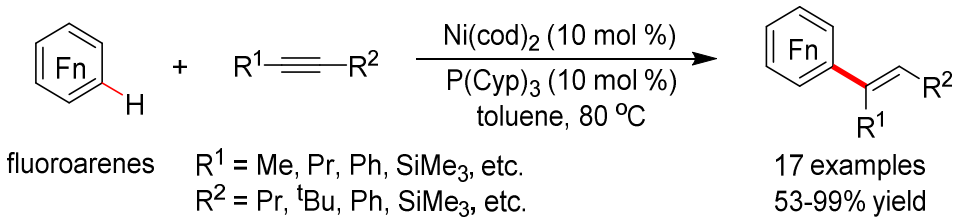
1.2 Nickel-Catalyzed C–H Bond Alkenylation

The transition-metal-catalyzed C–H bond alkenylation provides an atom and step economical approach for the synthesis of functionalized olefins. The alkenylation strategy has been applied to late-stage functionalization and total synthesis of natural products and pharmaceutical compounds.[113-120] A variety of transition-metal catalysts are known for the C–H bond alkenylation, however, the less expensive nickel catalyst is less explored for this reaction.[22,32,80,121-128]

1.2.1 Alkenylation of Arenes

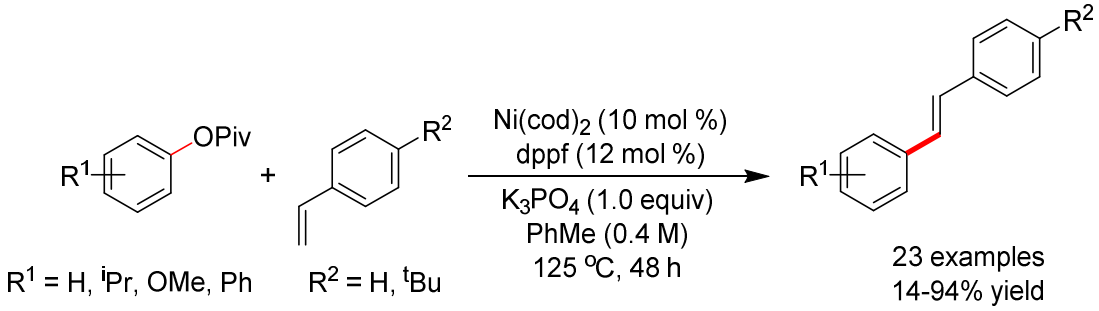
There has been great demand to develope a method for the introduction of F-containing group in organic compound due to the unique effect of F-substituent in pharmaceutical, agrochemicals and material sciences.[129] Mostly, the functionalization of polyfluoro arenes can be achieved by the deprotonation of acidic protons using the stoichiometric amount of

organometallic bases, and the reaction were followed by the electrophilic addition of electrophiles.[130] The direct C–H bond activation of polyfluoro arenes using transition metal complex appears to be the ideal catalytic approach.[131,132] Recently, Hiyama and co-workers reported the alkenylation of pentafluoro arenes *via* the C–H bond functionalization using inexpensive nickel catalyst (Scheme 1.15).[133] They observed the smooth coupling of polyfluoro arenes with symmetrical alkynes to afford good yields of the coupled products. With the excess use of alkyne and upon increasing the reaction time, they have observed dialkenylated product in good yield. The reaction shows high regio- and stereoselectivity for the insertion of alkyne to C–H bond over the C–F bond.



Scheme 1.15 Nickel-Catalyzed Alkenylation of Pentafluorobenzene.

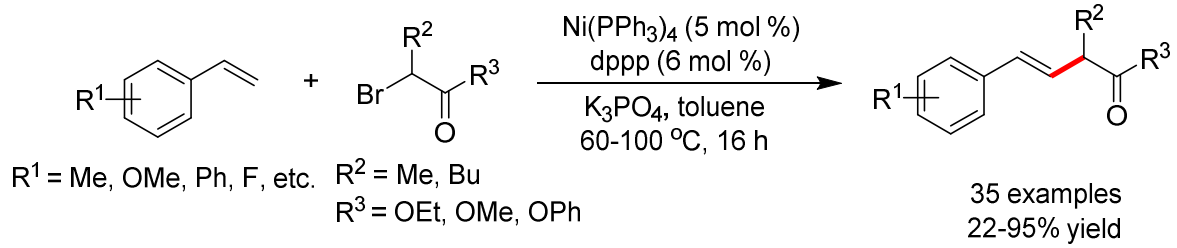
In 2012, Watson has reported the Ni-catalyzed Heck cross-coupling of aryl pivalate with olefin (Scheme 1.16).[134] Here, the C−C coupling occurs *via* the activation of strong C−O bond with the nonorganometallic coupling partner. Combination of $Ni(cod)_2$ with dppf ligand and K_3PO_4 base in toluene gave good yields of the desired products.



Scheme 1.16 Nickel-Catalyzed Alkenylation of Arenes *via* C−O Activation.

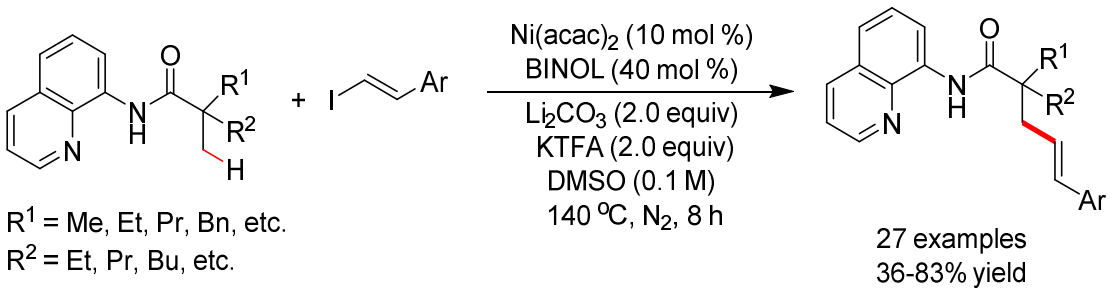
The nickel-catalyzed alkenylation of secondary and tertiary α-carbonyl bromides has been demonstrated by Lie (Scheme 1.17).[135] Here, the coupling of α-carbonyl bromide with alkene occurred in the presence of $Ni(PPh_3)_4$/dppp and K_3PO_4 base in toluene at 60-100 °C. Broad substrate scope has been explored with different functional groups on both the

coupling partner with yield up to 92%. Mechanistic studies suggested that the reaction proceeds *via* a single electron transfer pathway, with the involvement of Ni^{I}/Ni^{III} catalytic process.



Scheme 1.17 Nickel-Catalyzed Alkenylation of α-Carbonyl Bromides.

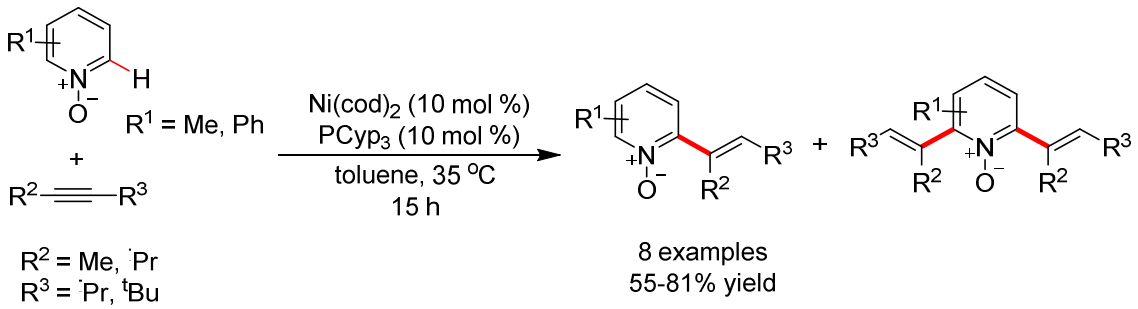
Nickel-catalyzed alkenylation of unactivated C(sp^3)−H bond remained a challenge because of the strenuous activation of C(sp^3)−H bond. Recently, there are few reports for C(sp^3)−H alkenylation of substrates having 8-aminoquinoline as a bidentate auxilliary.[136-138] Liu has reported nickel-catalyzed alkenylation of unactivated C(sp^3)−H bond with vinyl iodide.[136] They have used air-stable $Ni(acac)_2$ catalyst and BINOL ligand, wherein the combination of Li_2CO_3 and potassium trifluoroacetate base in DMSO successfully afforded the alkenylation of C(sp^3)−H bond of aliphatic carboxamide with styrenyl iodide (Scheme 1.18). A wide variety of functional groups have tolerated under the reaction condition. Synthetic utility of this protocol has been shown by synthesizing the functionalized carboxamide bearing *α*-quaternary carbon centres from simple pivalamides. Alkenylated products have been further functionalized to dihydroxylated and hydrogenated products. Similarly, the group of Maiti and You have independently demonstrated the nickel-catalyzed C(sp^3)−H alkenylation of aliphatic amides containing 8-aminoquinoline bidentate directing group, however, using the substituted alkyne coupling partner.[137,138] The insertion of alkyne in C(sp^3)−H bond of *N*-(quinolin-8-yl)pivalamide has been carried out in the presence of $Ni(OAc)_2.4H_2O$ catalyst in DMF at 140 °C. With the unsymmetrical alkynes mixtures of regioisomers have obtained. By using PPh_3 ligand under the similar reaction conditions, a number of activated olefins, such as functionalized acrylates (with –OMe, −F, −Cl groups), and acrylonitriles have been reacted successfully.



Scheme 1.18 Nickel-Catalyzed C(sp^3)–H Bond Alkenylation with Vinyl Iodides.

1.2.2 Alkenylation of Heteroarenes

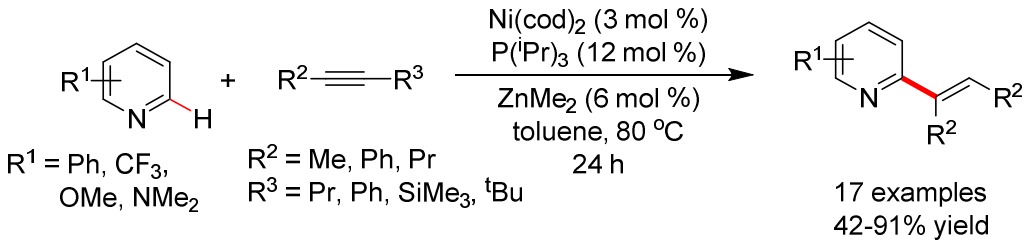
In 2007, Hiyama has reported the direct C–H bond functionalization of pyridine *N*-oxide.[139] The addition of pyridine-*N*-oxide across various alkyne was achieved using nickel as a catalyst (Scheme 1.19). This addition was chemoselective and occurred particularly at the C-2 position of the pyridine-*N*-oxide through C–H bond activation under mild reaction condition. The addition of substituted pyridine-*N*-oxides to symmetrical alkynes afforded good yield and excellent *E*/*Z* selectivity of products. Similarly, the *E*-selectivity for the product was also obtained by using unsymmetrical alkynes as coupling partner.



Scheme 1.19 Nickel-Catalyzed Addition of Pyridine-*N*-Oxide to Alkynes.

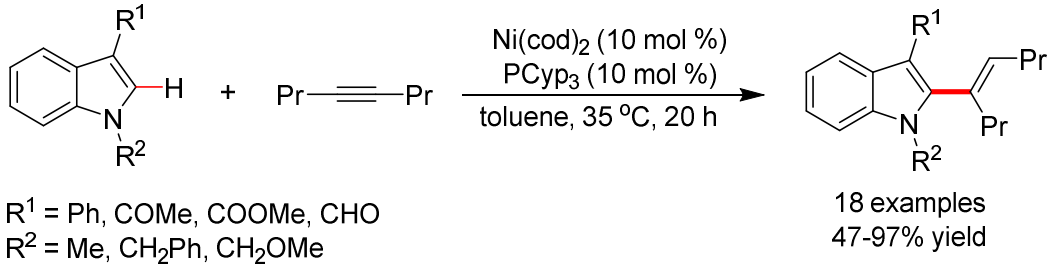
The same group has reported C(2)-selective alkenylation of pyridine, which is a difficult substrate to perform C–H functionalization.[140] They have observed that the coupling of pyridine with alkyne produces an excellent yield of coupled product using nickel and a Lewis acid catalyst (LA) (Scheme 1.20). It was assumed that the pyridine is activated by the co-ordination of pyridine nitrogen to the Lewis acid catalyst. The combination of Ni-catalyst and Lewis acid gave selective C(2)–H alkenylation product in good yield. This methodology provided a wide range of alkenylated pyridines in chemo-, regio-, and stereoselective manner under the mild reaction conditions. Similarly, nickel-catalyzed alkenylation of triazolopyridines has been demonstrated by Liu *et al.* in 2012.[141] Here, the alkenylation of

triazolopyridine with alkyne derivatives has been performed in the presence of $Ni(cod)_2$, PPh_3 Lewis acid $AlMe_3$. Kinetic isotope effect experiment revealed that C−H bond activation is turnover limiting step in the catalytic reaction (KIE = 3.0). No deuterium scrambling was observed either in substrate or in product.



Scheme 1.20 Direct C(2)–H Alkenylation of Pyridine using Nickel and Lewis Acid System.

Nickel-catalyzed C−H alkenylation of indoles and other heteroarenes with alkyne is demonstrated by Hiyama in 2006 (Scheme 1.21).[142] The reaction proceeds in the presence of $Ni(cod)_2$ and $PCyp_3$ in toluene at 35 °C. This methodology works well with diverse range of heteroarenes like indoles, benzimidazole, benzofuran, benzothiophene, benzoxazole and caffeine. Various functional groups are well tolerated. Similarly, C−H alkenylation of 1,3,4-oxadiazole with alkyne has been reported by Miura group.[51] Here, the coupling of 1,3,4-oxadiazole with alkyne is carried out in the presence of $Ni(cod)_2$ and PCy_3 in toluene at 100 °C. Both the regio-isomers were formed with unsymmetrical alkynes. With the described method, various functional groups were tolerated and afforded good yield. The alkenylation reaction proposed to proceeds *via* a Ni^0/Ni^{II} pathway.

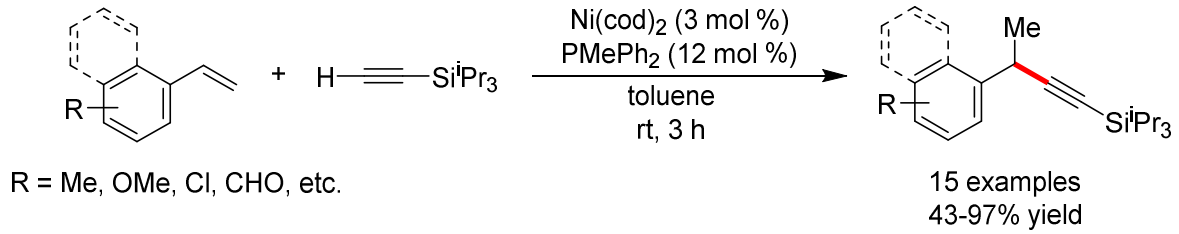


Scheme 1.21 Nickel-Catalyzed C–H Alkenylation of Indole Derivatives.

1.3 Nickel-Catalyzed C–H Bond Alkynylation

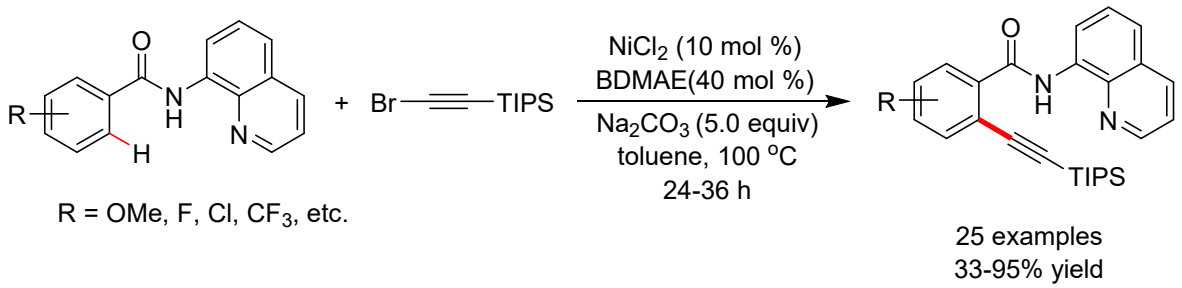
1.3.1 Alkynylation of Arenes

The alkynylated arenes and heteroarenes are the most fundamental and important composition of many natural products, materials, and pharmaceutical compounds.[143,144] Various Ni-catalyst systems were developed for the direct C(sp^2)–H arylation and alkenylation reactions; however, only few examples are known for the C(sp^2)–H alkynylation of arenes and heteroarenes using nickel catalyst.[145-149] In 2009 Suginome and co-workers reported nickel-catalyzed hydroalkynylation of styrene (Scheme 1.22).[150] Herein, addition of C(sp)−H bond of triisopropylsilylacetylene to the carbon-carbon double bonds of styrene proceeded in presence of $Ni(cod)_2$ and $PMePh_2$ in toluene. A wide variety of functional groups, such as −Me, −OMe, −Cl, −COOEt, −CHO were well tolerated on styrene under the reaction condition. Preliminary mechanistic investigation revealed the reductive elimination as the rate limiting step.



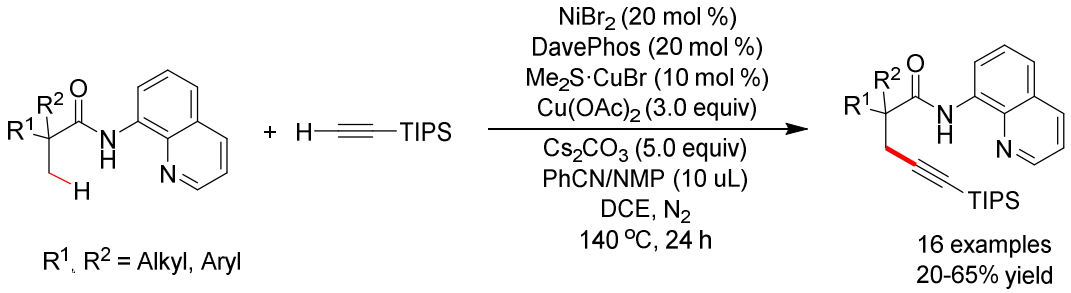
Scheme 1.22 Nickel-Catalyzed Alkynylation of C(sp^2)–H Bond of Styrene.

Recently, the C(sp^2)–H and C(sp^3)–H alkynylations are demonstrated using different alkynes source as a coupling partner.[95,146-148,151-160] In 2015, Li described an efficient method for the *ortho* C(sp^2)–H bond alkynylation of aromatic amides using nickel catalyst *via* the chelation-assistance of 8-aminoquinoline (Scheme 1.23).[147] They found that $NiCl_2$/BDMAE catalyst system efficiently catalyzes the coupling of aromatic amide with alkynyl bromides in the presence of Na_2CO_3 at 100 °C to provide desired coupled products in good yields. This protocol shows good reactivity for a range of (hetero)aryl amide, and for the α, β-unsaturated alkenyl amides. Balaraman and co-workers demonstrated the nickel-catalyzed C(sp^2)–H alkynylation of substituted benzamides with alkynyl bromides using 8-aminoquinoline as directing group and benzoic acid as a ligand.[146] In this methodology, they observed that the slight variation of substituent on aromatic ring increases the selectivity for mono alkynylation as well as dialkynylation. This methodology provided broad substrate scope and tolerance of sensitive functional group on aromatic amides.



Scheme 1.23 Nickel-Catalyzed Alkynylation of Aryl Amides.

Recently, Shi and co-worker reported the nickel-catalyzed oxidative cross-coupling of unactivated C(sp^3)–H bond in aliphatic amide with alkynes using 8-aminoquinoline directing group (Scheme 1.24).[148] The oxidative coupling was carried out by the treatment of aliphatic amide with triisopropylsilyl alkyne in the presence of $Ni(acac)_2$/DPPBz catalyst. In this reaction, the $Me_2S{\cdot}CuBr$ was used as a transmetalating reagent and $Cu(OAc)_2$ as the oxidant. This reaction shows good compatibility with differently substituted aliphatic amides. Important functional groups, such as −OMe, $-CF_3$, −Cl, −Br are well tolerated under the described condition. The reaction is stereoselective for the methyl group over the secondary C(sp^3)–H bond and benzyl methylene group.

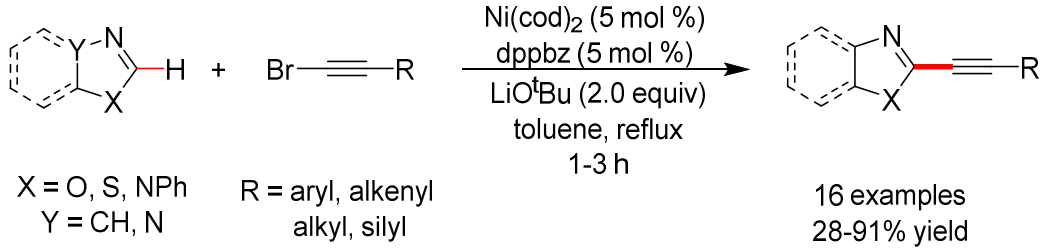


Scheme 1.24 Nickel-Catalyzed Oxidative Alkynylation of C(sp^3)–H Bond on Amides.

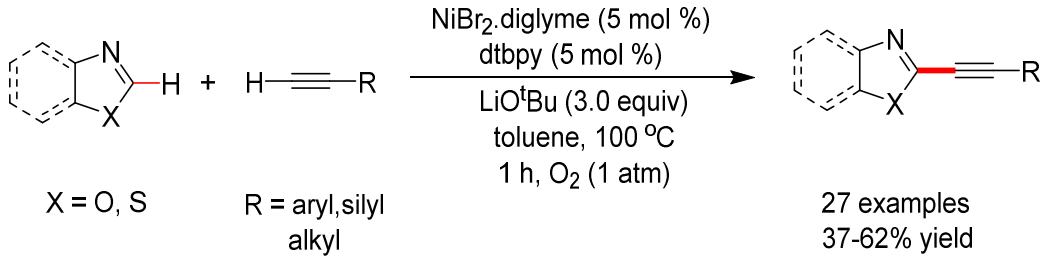
1.3.2 Alkynylation of Heteroarenes

In 2009, Miura described the nickel-catalyzed direct alkynylation of azole with alkynyl bromide (Scheme 1.25).[161] Efficient coupling of azoles with alkynyl bromides was achieved using $Ni(cod)_2$/dppz catalyst in the presence of LiO^tBu in toluene. This methodology worked well for diverse alkynyl bromides bearing aryl, alkenyl, alkyl and silyl groups. Similarly, this method was applied for the direct alkynylation of various azoles, such as benzothiazole, benzoxazole, 5-substituted oxazole and benzimidazole, and desired products were obtained in good yields with excellent functional group tolerability.

Miura also reported the nickel-catalyzed direct coupling of azoles and alkynes through double C–H bond activation, which is a highly challenging task due to the difficulties of catalyst control in activation of two different C–H bonds (Scheme 1.26).[145] Herein, various azoles were coupled with alkynes in the presence of $NiBr_2$·diglyme/dtbpy and LiO^tBu under O_2 atmosphere. This method furnishes a new approach for the direct coupling of azoles and alkynes without preactivation of the substrate under the O_2 atmosphere, which is beneficial from the economical prospective.

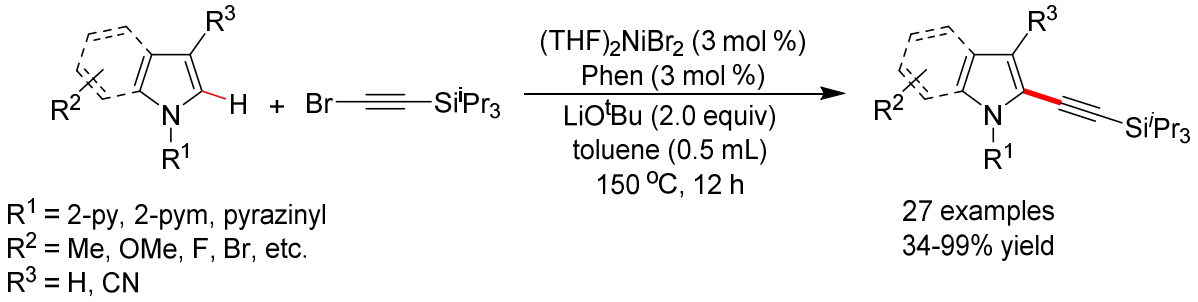


Scheme 1.25 Nickel-Catalyzed Alkynylation of Azoles with Alkynyl Bromides.



Scheme 1.26 Nickel-Catalyzed Oxidative Cross-Coupling of Azoles with Alkynes.

Recently, Punji and co-workers developed a method for the nickel-catalyzed C−H bond alkynylation of indoles and other heteroarenes through chelation assistance (Scheme 1.27).[162] Heterocycles, such as indoles, pyrroles, imidazoles, and pyrazole having monodentate directing group were coupled with (triisopropylsilyl)alkynyl bromide in the presence of low catalyst loading of $(THF)_2NiBr_2$/Phen. Synthetically important functional groups, such as halides, ether, nitrile, and nitro are tolerated under the optimized reaction condition. Synthetic utility of this method has been shown by facile removal of silyl protecting group and by synthesizing the triazolyl derivatives. A catalytically relevant nickel species is isolated and structurally characterized. Mechanistic findings demonstrated that the C−H nickelation is kinetically relevant and proceeds *via* a concerted pathway.

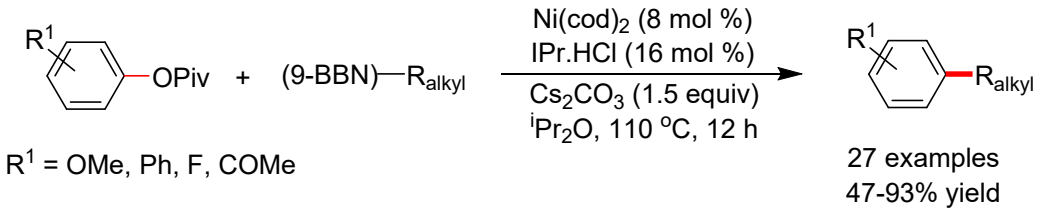


Scheme 1.27 Nickel-Catalyzed Alkynylation of Heteroarenes.

1.4 Nickel-Catalyzed C–H Bond Alkylation

1.4.1 Alkylation of Arenes

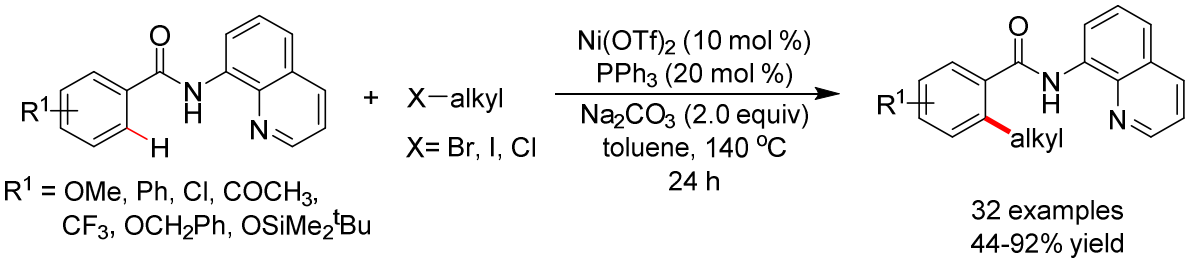
The alkylated arenes and heteroarenes are important backbone of many natural products, biologically relevant compounds, and organic materials.[163-165] During the past decade, remarkable progress has been made for the nickel-catalyzed C−H bond alkylation of arenes and heteroarenes.[45,166-168] Nickel-catalyzed alkylation of arenes with alkyl-9-BBN or Grignard reagent as a coupling partner *via* C−O bond activation has been reported.[99,169-171] The advantage of this methodology is the long chain alkylation *via* inert C−O bond activation, and high reactivity with good functional group tolerability (Scheme 1.28).[169] Combination of $Ni(cod)_2$ and carbene ligand has been used for this functionalization in the presence of Cs_2CO_3 base. Further, the utility of this method is demonstrated by sequential functionalization of aromatic rings by selective and sequential C−O bond activation.



Scheme 1.28 Nickel-Catalyzed Alkylation of Arenes.

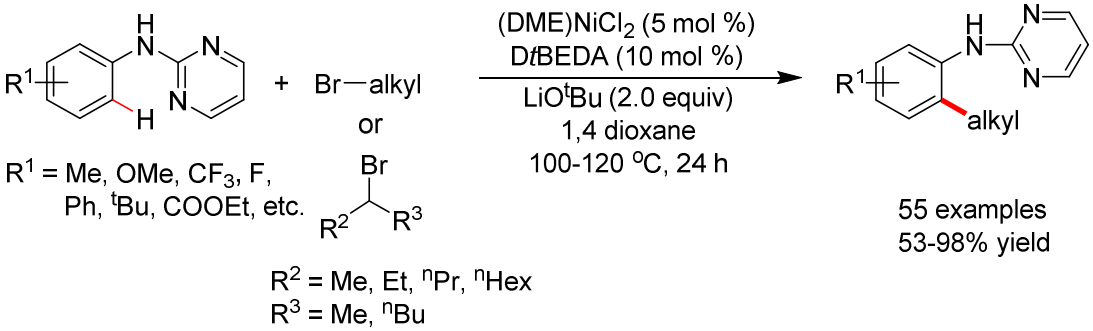
Chatani *et al.* developed a new strategy for the direct C(sp^2)−H bond alkylation of benzamides and acrylamides with alkyl halides by nickel catalyst using 8-aminoquinoline as a bidentate directing group (Scheme 1.29).[55,172] The coupling of benzamides with alkyl halides was achieved using $Ni(OTf)_2/PPh_3$ catalyst system in the presence of Na_2CO_3 in toluene. This methodology provided broad substrate scope for various benzamides, and tolerated important functional groups on both the aromatic backbone and alkyl halides. The

reaction is highly selective for less hindered C–H bond alkylation of the *meta*-substituted aromatic amides.



Scheme 1.29 Nickel-Catalyzed Alkylation of Benzamide using Bidentate Directing Group.

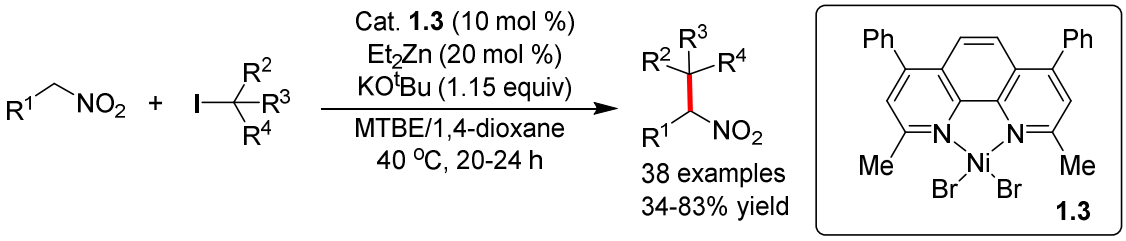
Recently, Ackermann and co-workers developed a novel methodology for *ortho* C–H alkylation of aniline with alkyl bromide using nickel catalyst *via* monodentate chelation assistance (Scheme 1.30).[58,59] Herein, the efficient cross-coupling of anilines bearing a monodentate *N*-pyrimidyl substituent with alkyl bromide was achieved using (DME)$NiCl_2$/D^{t}BEDA catalyst system. This methodology provided broad substrate scope for *ortho*, *meta* and *para*-substituted aniline with the tolerance of important functional groups, such as –OMe, –CF_3, –F, –Cl, –COOEt. This method is not only limited to the primary alkyl bromides, it also efficiently works for the secondary alkyl bromides. Mechanistic studies revealed that the C−H metalation is facile, and a SET type C−X cleavage occurs. The C−H bond activation demonstrated to proceeds *via* a six-membered nickelacycle upon dearomatization of the pyrimidinyl moiety.



Scheme 1.30 Nickel-Catalyzed *ortho*-Alkylation of Aniline *via* Monodentate Chelation.

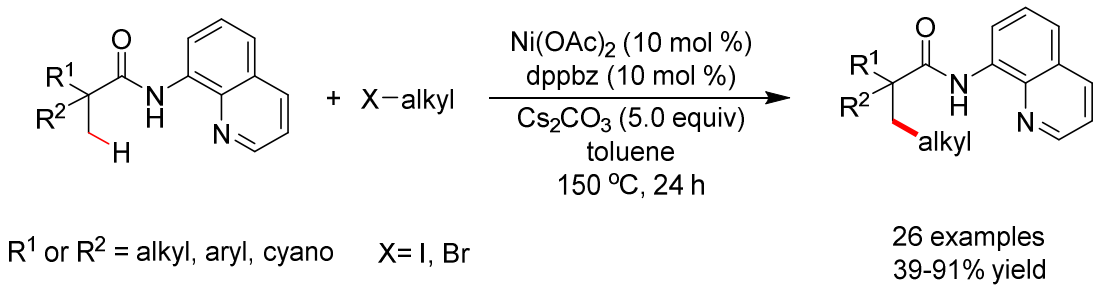
The nickel-catalyzed C(sp^3)–C(sp^2) bond formation is well-known by the traditional coupling of C(sp^3)–X using dialkyl zinc,[173-178] alkyl boranes,[179,180] allylic carbonate,[181] alkyl Grignard reagent,[182] alkyl halides, tosylates,[183,184] and carbocationic salts.[185] However,

alkylation *via* the C(sp^3)–H bond activation and coupling with alkyl halide is more challenging. Recently, Watson has reported nickel-catalyzed C(sp^3)–H alkylation of nitroalkanes with alkyl iodide (Scheme 1.31).[183] Here, the complex of $NiBr_2$.diglyme with 2,9-dimethyl-1,10-phenanthroline has been synthesized and used for the alkylation of nitroalkane employing catalytic amount of Et_2Zn as a reductant. They have developed broad substrate scope having different substituent on both the substrates. This methodology works with all the primary, secondary and tertiary alkyl iodides. Wide ranges of functional groups are tolerated under the optimal reaction condition. This method was demonstrated for the synthesis of an anti-viral drug adpromine.



Scheme 1.31 Nickel-Catalyzed Alkylation of Nitroalkanes.

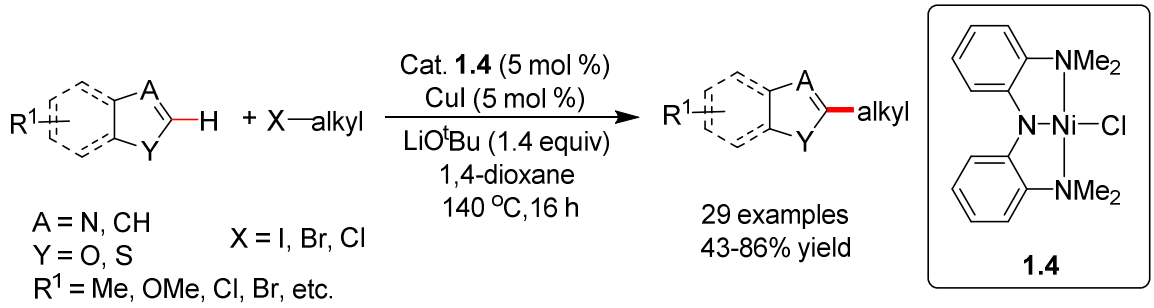
In 2014, Ge *et al.* showed the nickel-catalyzed direct alkylation of unactivated C(sp^3)–H bond of alkyl amides with alkyl halides *via* the bidentate chelation assistance (Scheme 1.32).[186] This method is highly selective for C–H bond alkylation of methyl group over the methylene C–H bond of the aliphatic amide. Important functional groups like alkenyl, cyano, ester and trifluoromethyl were tolerated on aliphatic amides.



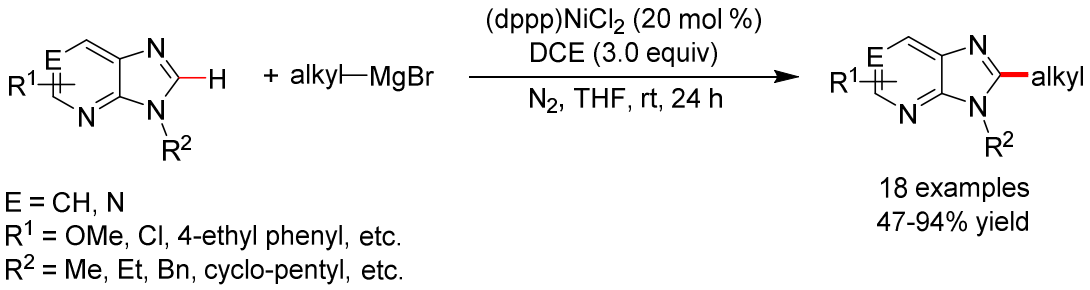
Scheme 1.32 Nickel-Catalyzed Alkylation of C(sp^3)–H Bond on Aliphatic Amides.

1.4.2 Alkylation of Heteroarenes

Nickel-catalyzed C–H alkylation of heteroarenes is widely explored because the alkylated heteroarenes are essential part of many pharmaceutical drugs. There exist a number of reports on C–H alkylation of heteroarenes employing various transition-metal catalysts.[52-54,176,187-193] In 2010, Hu group reported the nickel-catalyzed C–H bond alkylation of aromatic heterocycles with unactivated alkyl halides containing the *β*-hydrogens (Scheme 1.33).[52] With the optimization conditions, the coupling of various substituted heterocycles with diversely substituted alkyl iodides was achieved using catalyst **1.4** and CuI co-catalyst in the presence of LiO^{t}Bu. This method tolerates various functional groups, such as –OMe, –Cl, –Br on oxazole and –OAr, –OCOAr, –SAr, –CO, –CN groups on alkyl halide moiety, and shows excellent chemo- and regioselectivity for the product formation. Similarly, Miura has reported nickel-catalyzed C–H alkylation of azoles employing alkyl bromides, chlorides and *N*-tosylhydrazones as a coupling partner.[53,188] They have used $NiBr_2$/phen catalyst system in the presence of LiO^{t}Bu base. Broad substrate scope has been developed with the tolerance of various functional groups. Catalytic cycle has been proposed, which proceeds *via* Ni^0/Ni^{II} pathway. Nickel-catalyzed alkylation of pyridone and pyridine derivatives has been developed with α-bromo carbonyl compound and olefin as coupling partner.[54,189,192,194] Similarly, report on Ni-catalyzed alkylation of *N*-aromatic heterocycles with alkyl halide or Grignard reagent as an alkylating agent is also well precedented.[176,190,193] Different benzimidazole and purine derivatives are alkylated using alkyl Grignard reagent in the presence of (dppp)$NiCl_2$ catalyst (Scheme 1.34).[190] Catalytic cycle has been proposed the proceeds *via* the oxidative addition, transmetalation and reductive elimination steps involving Ni^0/Ni^{II} process.

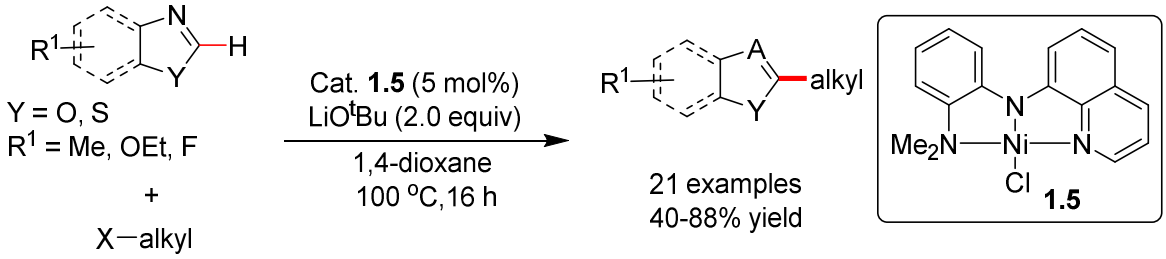


Scheme 1.33 Nickel-Catalyzed Alkylation of Aromatic Heterocycle with Alkyl Halides.



Scheme 1.34 Nickel-Catalyzed Alkylation of Heteroarenes with Alkyl Grignard Reagents.

Recently, Punji and co-workers developed a quinolinyl-based (NNN)-pincer nickel catalyst **1.5** for the direct C–H bond alkylation of azole under mild reaction conditions; wherein the coupling of azoles with alkyl halide achieved without the use of CuI co-catalyst (Scheme 1.35).[61] The catalyst **1.5** is robust in nature, which was recycled and reused five time for the alkylation without affecting the catalytic activity. This catalysis showed broad substrate scope for differently substituted azoles and alkyl halides.



Scheme 1.35 Alkylation of Azoles using (NNN)Ni-Pincer Complex.

Miura and co-worker reported the C–H bond alkylation of benzothiazole with alkyl bromide using nickel catalyst; wherein they have carried out preliminary experiments to know the working mode of the catalyst.[53] On the basis of the preliminary experiments and previous report, they have proposed a catalytic cycle for the alkylation of azoles as shown in Figure 1.3. First, the formation electron-rich heteroaryl nickel [Ni(0)] **A** occurs by the combination of $NiBr_2$·diglyme, benzothiazole, and LiO^tBu. The generation of an alkyl radical by the single electron transfer takes place from the species **A.** The species **B** on recombination with an alkyl radical forms Ni(II) species **C**, which upon reductive elimination produces the alkylated coupled product with the regeneration of species **A**.

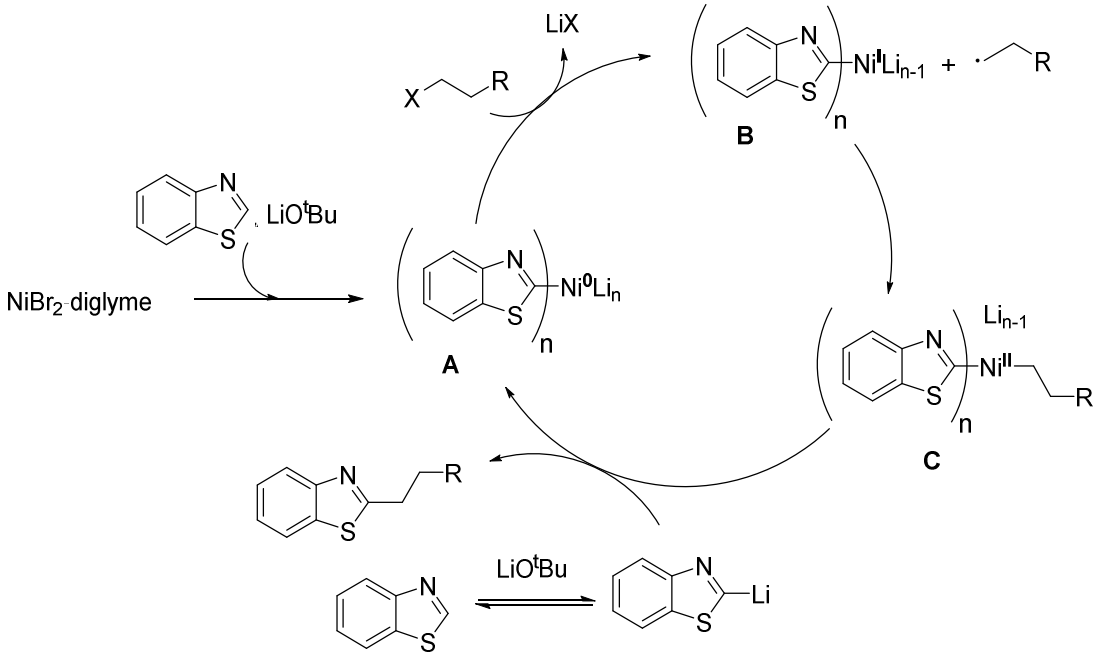
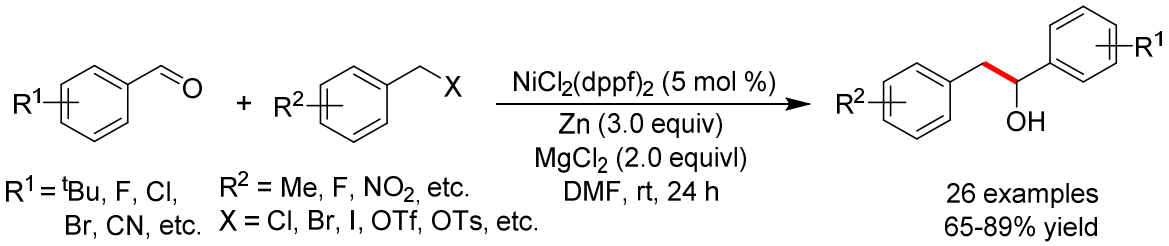


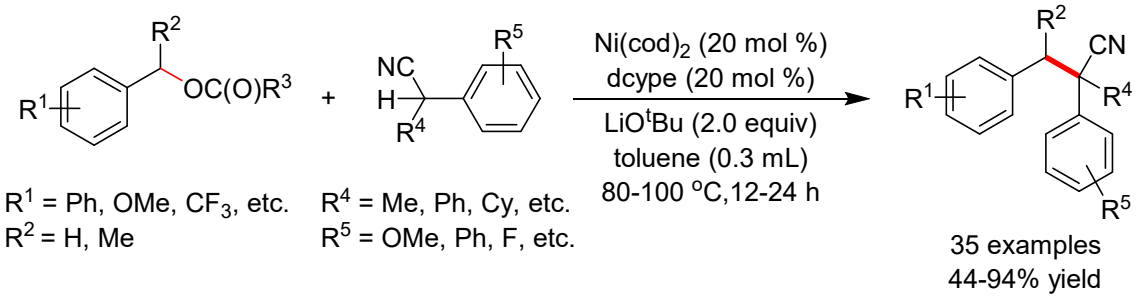
Figure 1.3 Plausible mechanism for nickel-catalyzed alkylation of azoles.

1.5 Nickel-Catalyzed C–H Bond Benzylation of Arenes

Nickel-catalyzed benzylation of (hetero)arenes is relatively less explored.[195-199] Recently, nickel-catalyzed benzylation of aldehyde has been reported with benzyl halides and pseudohalides.[198] The combination of $(dppf)_2NiCl_2$, Zn and $MgCl_2$ has efficiently been employed for such benzylation at room temperature (Scheme 1.36). Various functional groups are tolerated under the optimized reaction condition. Catalytic cycle goes *via* Ni^0/Ni^{II}, wherein Zn works as a reductant. In 2016, Xiao *et al.* has described the direct cross-coupling of benzyl alcohol derivatives with arylacetonitriles *via* C−O bond activation (Scheme 1.37).[197] Various α-benzylated arylacetonitriles are prepared using this methodology.

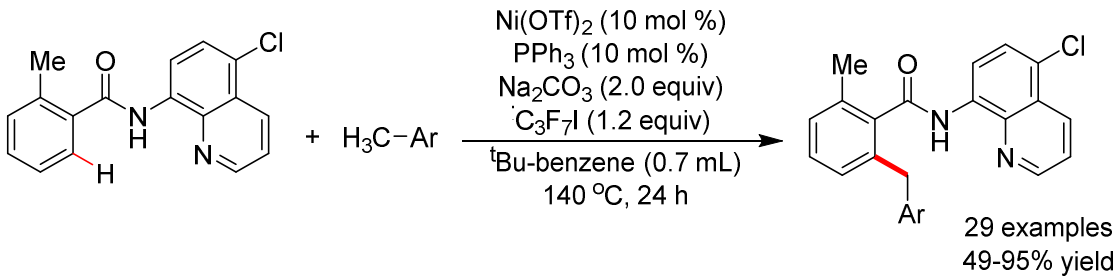


Scheme 1.36 Nickel-Catalyzed Benzylation of Aldehydes.



Scheme 1.37 Nickel-Catalyzed Benzylation of Benzyl Alcohols.

Chatani and co-workers demonstrated the Ni-catalyzed benzylation *via* C(sp^2)–H/C(sp^3)–H oxidative coupling between benzamide and toluene derivatives through chelation assistance (Scheme 1.38).[200] In benzamide substrates, 8-aminoquinoline has been used as a bidentate directing group. Reaction is catalyzed by $Ni(OTf)_2$ with PPh_3 ligand, and heptafluoro isopropyl iodide was used as an oxidant in ^{t}Bu-benzene solvent. Mainly, 5-substituted benzamides have been explored with wide functional group tolerance. Reaction proceeds *via* a single electron transfer mechanism. On the basis of preliminary mechanistic experiments, they have proposed a catalytic cycle (Figure 1.4). First, the metal coordinates to substrate **A** to gives Ni(II) complex **B** with the generation of HX, which is trapped by Na_2CO_3. Then the reversible cleavage of C–H bond in complex **B** leads to the formation of nickelacycle **C**. Base-promoted single-electron transfer (SET) of $^iC_3F_7I$ (R_f–I)[201,202] followed by a hydrogen abstraction from toluene leads to the formation of benzyl radical and R_f–H. The complex **C** reacts with benzyl radical to afford Ni(III) species **D**. Further, reductive elimination followed by protonation leads to the benzylated product with generation of the Ni(I) complex. The reaction of R_f–I with Ni(I)X produces the Ni(II) complex with the generation of R_f radical.[203] Xu *et al.* performed thorough DFT study on this reaction, and suggested that iodine-atom transfer (IAT) mechanism is energetically more feasible.[204]



Scheme 1.38 Nickel-Catalyzed Benzylation of Benzamides *via* C(sp^2)–H/C(sp^3)–H Oxidative Coupling.

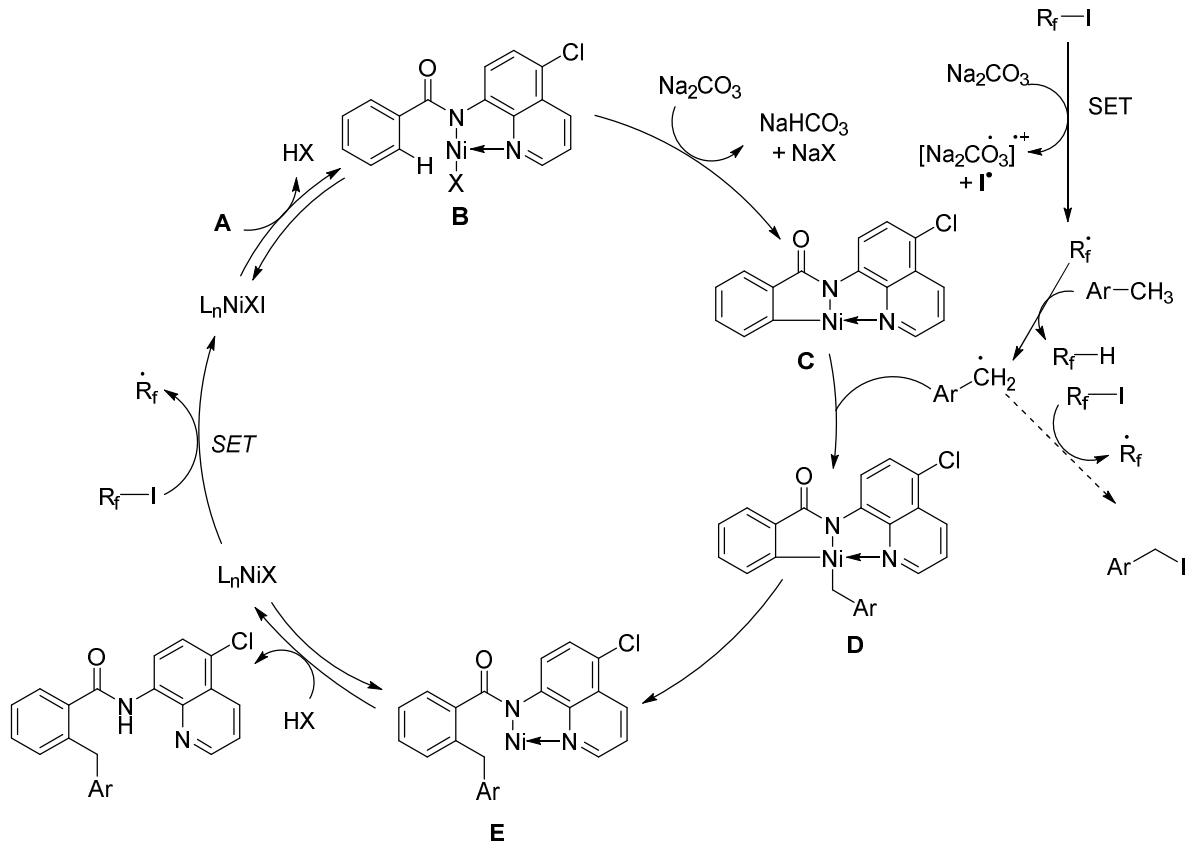
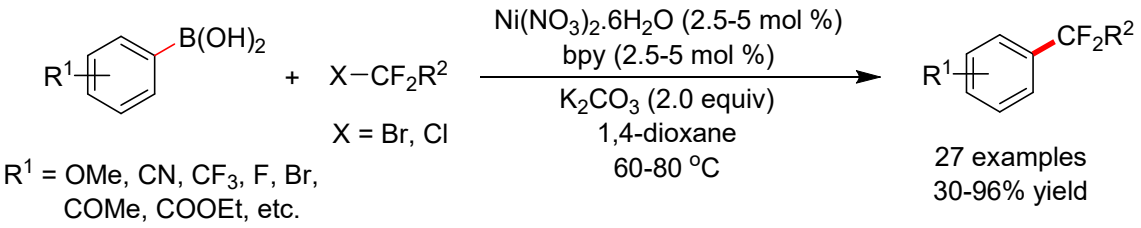


Figure 1.4 Mechanism of Ni-catalyzed C(sp^2)–H/C(sp^3)–H oxidative benzylation of benzamides.

1.6 Nickel-Catalyzed C–H Bond Difluoroalkylation

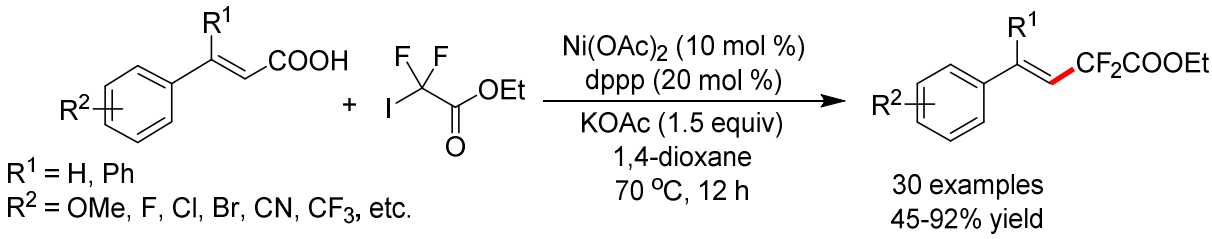
Organofluorine chemistry has emerged as a power tool in the elaboration of new bioactive molecules, pharmaceuticals, agrochemicals and materials.[205-209] Introduction of fluorine(s) into a organic molecule significantly affect its physical and biological properties, like metabolic stability and lipophilicity. From the synthetic point of view, further functionalization can be achieved from fluorinated moieties. Difluoroalkylation has mostly been explored by using late transition metals,[210-216] however, limited reports are known with the first-row transition metals, such as copper,[210-215,217] and nickel[60,218-227] In 2000, Whitten *et al.* demonstrated the difluoroalkylation of vinyl zirconium with α-bromo-α,α-difluoro esters using $Ni(PPh_3)_4$ catalyst.[228] Recently, Zhang and co-workers have demonstrated the Ni-catalyzed difluoroalkylation of aryl boronic acid with different fluoroalkylated coupling partners (Scheme 1.39).[224,226,229] Different substituted boronic acids have been difluoroalkylated using $Ni(NO_3)_2.6H_2O$ catalyst and 3,3'-dimethyl-2,2'-bipyridine ligand in the presence of K_2CO_3 under mild condition. Variety of difluoromethyl bromides and chlorides has been used as coupling partner. Functional group compatibility is very good in

the substrates delivering the desired products up to 96% yields. Zhang group further reported on nickel-catalyzed coupling between aryl boronic acid and fluoromethyl bromide under mild reaction condition.[229] Similar report has been known for hetero-aryl boronic acid with 1-bromo-1,1-difluoroalkanes. Synthetic utility of this method is shown by synthesizing some biologically active compounds. Wang group reported the monofluoromethylation of aryl boronic acids with ((fluoroiodomethyl)sulfonyl)benzene as coupling partner.[230] Both the electron-rich and electron-deficient aryl boronic acids are compatible under the reaction condition. Mechanistic investigation revealed that a fluoromethyl radical is participated in the catalytic cycle, and it proceeds through the Ni^{I}/Ni^{III} pathway.



Scheme 1.39 Nickel-Catalyzed Difluoroalkylation of Aryl Boronic Acids.

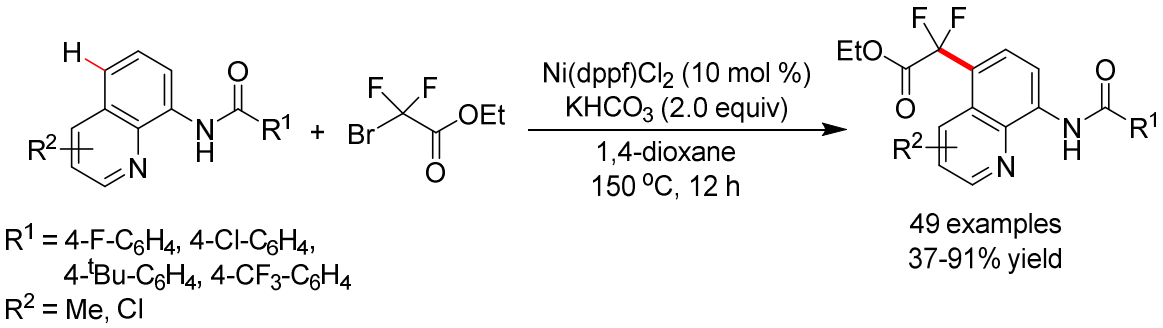
Wang and co-workers demonstrated the nickel-catalyzed decarboxylative difluoroalkylation of *α,β*-unsaturated carboxylic acids (Scheme 1.40).[227] Herein, cinnamic acid derivatives have been coupled with iododifluoroacetate using $Ni(OAc)_2$/dppp catalyst system in the presence of KOAc in 1,4-dioxane. Wide substrate scope has been developed and exceptional functional group tolerability has been shown under the reaction condition. Both electron-withdrawing and electron-donating groups are well tolerated and provided excellent yields of the products. Mechanistic study reveals a radical pathway for the reaction.



Scheme 1.40 Nickel-Catalyzed Difluoroalkylation of *α,β*-Unsaturated Carboxylic Acids.

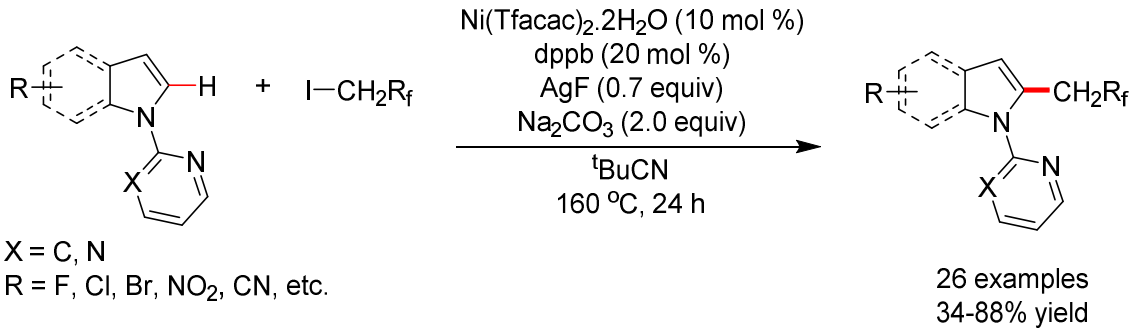
In 2016, Wang has reported the nickel-catalyzed C−H difluoroalkylation of 8-aminoquinoline moiety (Scheme 1.41).[60] Here, regioselectively C-5 position of 8-

aminoquinoline is difluoroalkylated instead of amide moiety *via* the remote C−H functionalization. Broad substrate scope has been developed with different aminoquinolinyl-benzamide compounds. Various functional groups, such as −OCH_3, −F, −Cl, −Br, −CF_3 are well tolerated under the optimized reaction conditions. Reaction is proposed to proceeds *via* a single electron transfer (SET) mechanism, wherein, the involvement of a cationic quinolinyl radical species and difluoromethyl radical is hypothesized.



Scheme 1.41 Nickel-Catalyzed Site-Selective Difluoromethylation of 8-Aminoquinoline.

Fluoroalkylation of heteroarenes, such as indole is also well documented with various metal catalysts, however, the regioselectivity is the major issue (both C-2 and C-3 functionalization occurs). Recently, Shi has reported nickel-catalyzed C−H trifluoroethylation of indoles and other heteroarenes with the assistance of monodentate directing group (Scheme 1.42).[231] Herein, $Ni(Tfacac)_2.2H_2O$ and dppb catalyzes the reaction in presence of silver salt in ^{t}BuCN solvent. Various functional groups, such as −F, −Cl, −NO_2, −CN, −CH_2COOEt are well tolerated under the reaction condition. The reaction proceeds *via* a SET process with the involvement of CF_3CH_2 radical. Similarly, trifluoromethylation has been reported by Wang group.[225] They have functionalized different electron-rich heteroarenes like imidazopyridines, indoles and thiophenes.

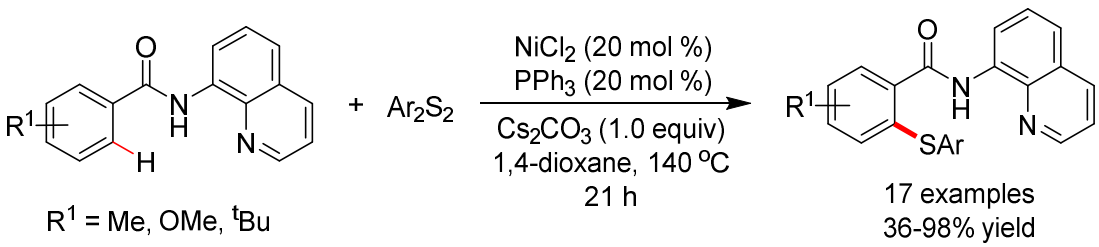


Scheme 1.42 Nickel-Catalyzed Trifluoroethylation of Heteroarenes.

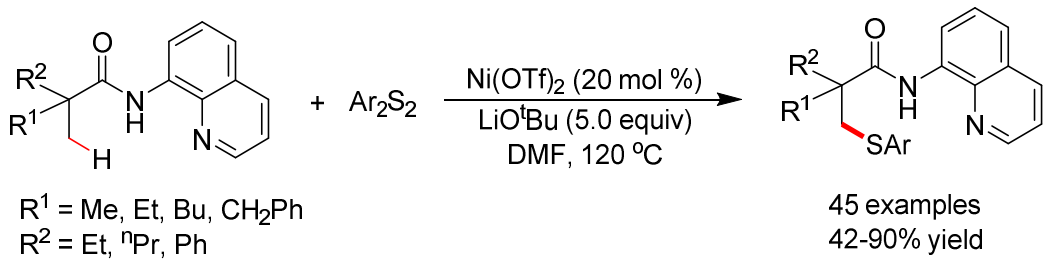
1.7 Nickel-Catalyzed C–Heteroatom Bond Forming Reactions

1.7.1 Carbon–Sulphur Bond Forming Reactions

Diaryl sulphide and their derivatives are found in many biologically active compounds, natural products and pharmaceuticals compounds.[232-234] There are various synthetic routes known to synthesize the diarylsulfide, among them the transition-metal-catalyzed cross-coupling aryl thiols or their metal salts (ArSM) with aryl–X (X = Cl, Br, I, OTf) is one of the most convenient and effective method.[232,235,236] In 2015, Reddy *et al.* reported the sulfenylation of C(sp^2)–H bond of benzamide with nickel catalyst using 8-aminoquinolinyl moiety as a bidentate directing group (Scheme 1.43).[237] The sulfenylation of benzamide was achieved using $NiCl_2$ as catalyst with diaryl sulfides in the presence of Cs_2CO_3. This protocol provided broad substrate scope for benzamide derivatives, and tolerated diverse functional groups on diaryldisulfide electrophiles. Similarly, Shi group developed a new method for the sulfenylation of C(sp^3)–H bond of aliphatic amides *via* bidentate chelation assistance (Scheme 1.44).[238] Herein, efficient coupling of the aliphatic amide with diaryldisulfide was achieved using $Ni(OTf)_2$ catalyst in DMF. Other metals, such as Cu, Fe, Rh, Pd, Co are ineffective to give the desired sulfenylated product under the identical condition. This protocol is also applied for the oxidative cross-coupling of C(sp^2)–H bond of benzamides and ArSH in the presence of air. This methodology has broad substrate scope for the aliphatic and aromatic amides, and tolerates the important functional groups, such as –OMe, $–CF_3$, –Cl, –F on amide. Shi and co-worker also reported the sulfenylation of unactivated arenes bearing PIP as the directing group using the nickel catalyst.[239] Similarly, thiolation of heteroarenes like indoles,[240] anilines[241] and azoles[242] are also demonstrated in very effective manners.



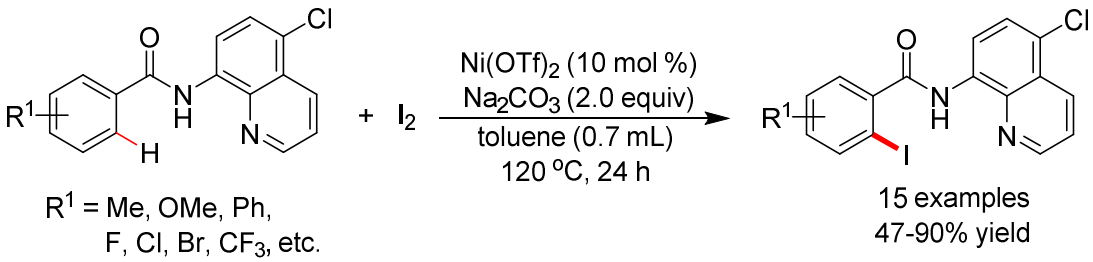
Scheme 1.43 Nickel-Catalyzed Sulfenylation of C(sp^2)–H Bond of Benzamide with Diaryldisulfide.



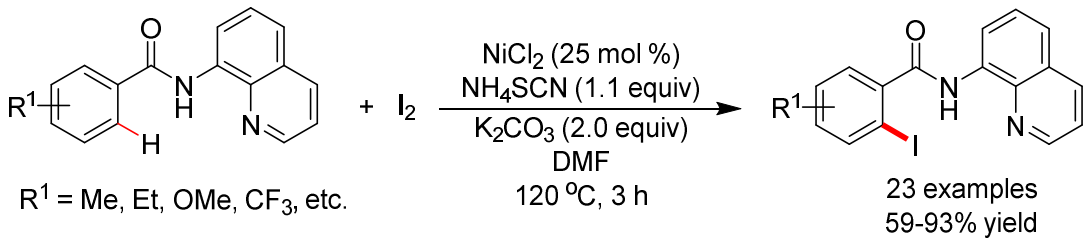
Scheme 1.44 Nickel-Catalyzed Sulfenylation of C(sp^3)–H Bond of Aliphatic Amides.

1.7.2 Carbon–Halogen Bond Forming Reactions

Aryl halides are widely used in organic synthesis as important starting materials for constructing a variety of useful compounds in the fields of material science and medicinal chemistry.[243-246] In 2016, Chatani has reported the nickel-catalyzed iodination of benzamide containing 8-aminoquinoline as a bidentate directing group (Scheme 1.45).[247] This strategy works *via* bidentate chelation assistance of directing group.[95] Herein, the benzamides with 5-substituted aminoquinolinyl moiety are used with readily available iodine employing $Ni(OTf)_2$ catalyst in the presence of Na_2CO_3. Controlled study of the reaction confirmed that electronics of the substituent has no significant effect on the efficiency of the reaction. Deuterium labeling experiments highlighted the cleavage of C−H bonds is irreversible, and is most likely the rate-determining step. This methodology is also applicable to the synthesis of *β*-lactams from aliphatic amides as the substrate. Interestingly, the group of Koley demonstrated the iodination of benzamides containing C-5 unsubstituted 8-aminoquinolinyl directing (Scheme 1.46).[248] The reaction has been performed employing $NiCl_2$ precursor and NH_4SCN ligand in the presence of K_2CO_3 base in DMF. Notably, the use of NH_4SCN inhibits the iodination at C(5)−H position of quinoline ring. Various substrate scope have been generated to produce the desired compounds in moderate to good yields.

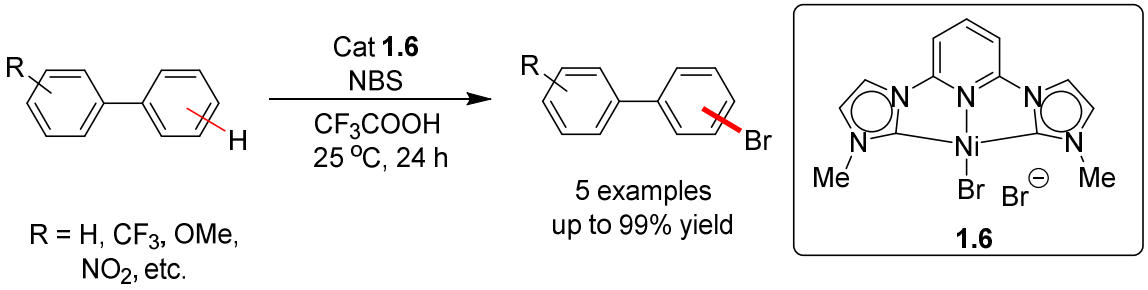


Scheme 1.45 Nickel-Catalyzed Iodination of Benzamides.



Scheme 1.46 Nickel-Catalyzed Iodination of Benzamides.

In 2014, Das and co-workers reported the bromination of unactivated aromatic C–H bond employing a *N*-heterocyclic carbene (NHC)-base pincer Ni(II) complex **1.6** (Scheme 1.47). The $PhI(OAC)_2$ is used as an oxidizing agent and *N*-bromosuccinimide (NBS) as a bromine source for the reaction. Bromination reactions were effective with both the electron-deficient and electron-rich substrates. However, high yield and good selectivity was observed towards the C–halogenation of electron-deficient substrates.



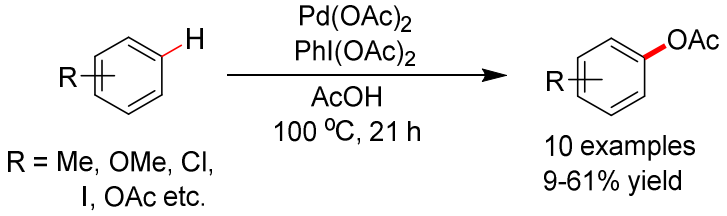
Scheme 1.47 Nickel-Catalyzed Bromination of Aryl C−H Bond.

1.8 Transition-Metal Catalyzed C−H Bond Oxygenation

1.8.1 Palladium-Catalyzed Oxygenation

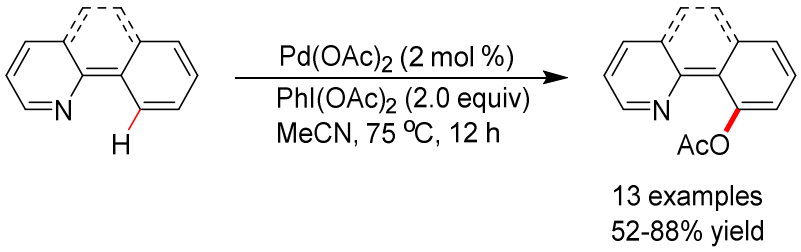
Selective C−H bond hydroxylation of arenes has gained increased attention, because oxygenated arenes and heteroarenes are important compounds in pharmaceuticals and medicinal chemistry as they possess unique biological activities. Oxygenated arenes also play the role of intermediates in many organic synthesis due to their high reactivity.[249-251] In this regard, the development of efficient transition-metal-catalyzed C–O bond-forming reactions is very important. In general, palladium catalysts are very efficiently employed for the direct C–H bond oxygenation of arenes. In 1971, Henry has reported the first Pd^{II}-catalyzed oxygenation of arenes using various oxidants. By employing $K_2Cr_2O_7$ as oxidant, the turnover numbers obtained were 10-55 for different substituted arenes. In the absence of oxidant, the formation of biphenyl product was observed.[252,253] In 1996, Crabtree *et al.*

reported the $Pd(OAc)_2$-catalyzed C–H bond acetoxylation of arenes using $PhI(OAc)_2$ as an oxidant, which largely avoided the formation of biphenyl (Scheme 1.48).[254] Unfortunately, this method is limited with the regioselectivity issue. This acetoxylation reaction was proposed to proceed *via* a Pd^{IV} intermediate with the C−H bond palladation being the rate-determining step.[255,256]



Scheme 1.48 $Pd(OAc)_2$-Catalyzed C−H Bond Acetoxylation of Arenes with $PhI(OAc)_2$.

Sanford and co-workers reported the *ortho*-regioselective C–H bond acetoxylation of arenes bearing a nitrogen-directing group that can coordinate to the palladium center, and directs the cyclopalladation-oxidation to a specific C–H bond of the arene (Scheme 1.49).[257-260] This transformation proceeded under mild reaction conditions with high regioselectivity for the *ortho* acetoxylation. A wide variety of nitrogen heterocycles, such as pyridine,[261,262] pyrazole as well as various functional groups like azo, amide, imine, oxime-ether[260,263] were employed as directing group. After these initial studies, palladium-catalyzed oxygenation of aromatic ketone,[264] phosphine oxides,[265] carboxylic acids,[266-269] anilides,[270] benzothiazole[271] and indoles[272,273] has also been reported with various organic and inorganic oxidants.

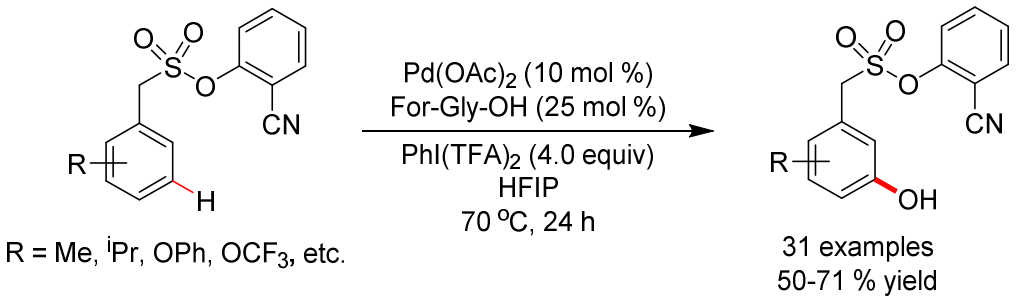


Scheme 1.49 Regioselective $Pd(OAc)_2$-Catalyzed Acetoxylation of Benzo[*h*]-quinoline.

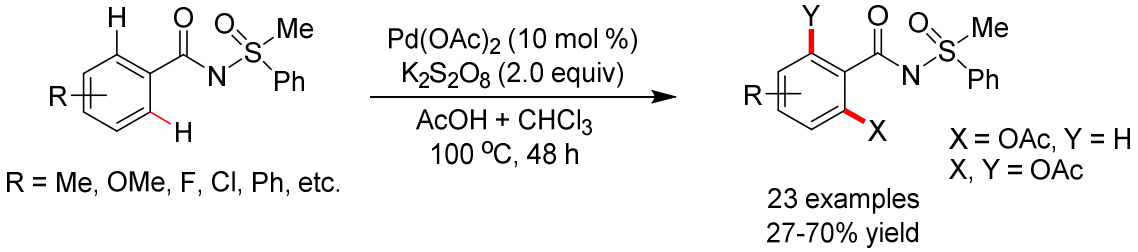
Sanford group has carried out detailed mechanistic study for the Pd-catalyzed *ortho*-oxygenation of functionalized arenes employing $PhI(OAc)_2$ as the oxidant.[257-260] This reaction is proposed to proceed *via* a Pd^{II}/Pd^{IV} catalytic cycle[254,257-260] involving five steps: (i) first substrate coordinates to the Pd^{II} precursor; (ii) cyclopalladation (rate limiting step); (iii)

two-electron oxidation to generate Pd^{IV} intermediate; (iv) reductive C–O elimination; and finally, (v) ligand exchange takes place to release the product. The formation of the Pd^{IV} intermediate has been confirmed by the X-ray characterization.[259,274]

The group of Maiti successfully demonstrated the palladium-catalyzed *meta*-hydroxylation of arenes that proceed *via* a template directed C–H activation (Scheme 1.50).[275] Herein, sulfonyl group is used as a directing group. Palladium-catalyzed acetoxylation is also reported using 8-aminoquinoline as a bidentate directing group.[95] Recently, palladium-catalyzed acetoxylation of arylacetic acid has been reported by Sahoo group, wherein sulfoxime directing group is employed (Scheme 1.51).[276-278]



Scheme 1.50 $Pd(OAc)_2$-Catalyzed *meta*-Hydroxylation.

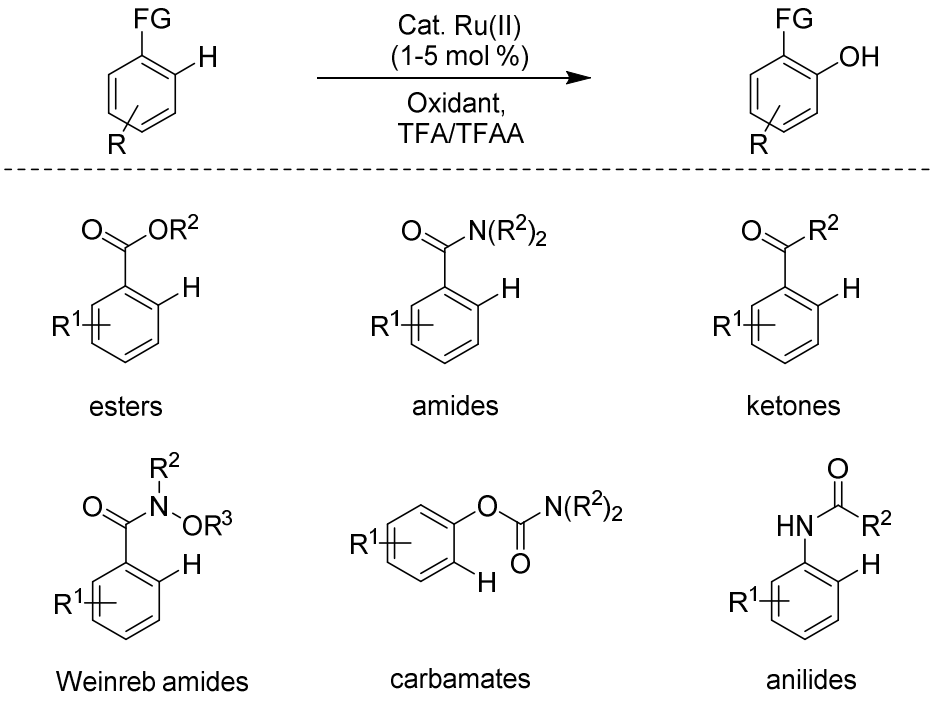


Scheme 1.51 $Pd(OAc)_2$-Catalyzed Acetoxylation.

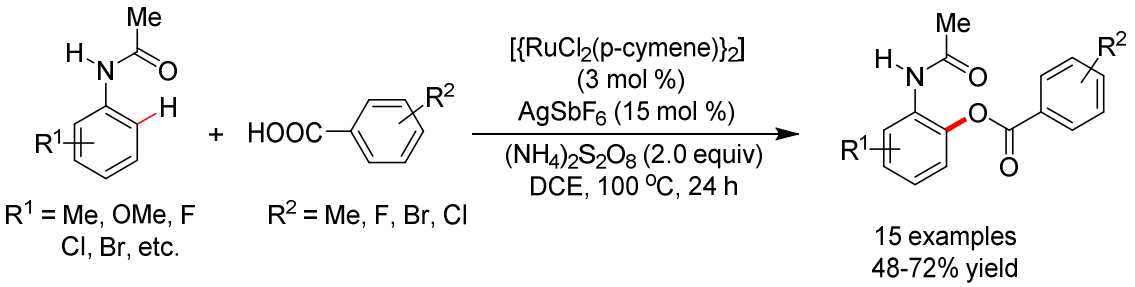
1.8.2 Ruthenium-Catalyzed Oxygenation

In past few years, remarkable progress have witnessed in the development of direct oxygenation of $C(sp^2)$–H bond in arenes and heteroarenes with comparatively less expensive and readily accessible ruthenium catalysts (Scheme 1.52). Rao and co-workers used the complex $[RuCl_2(p\text{-cymene})]_2$ as the precatalyst and $K_2S_2O_8$ or HIO_3 as the oxidant for the *ortho*-hydroxylation of arene containing ester as a directing group.[279] Similarly, Ackermann and co-workers have employed $[RuCl_2(p\text{-cymene})]_2$ as well as the defined ruthenium(II) biscarboxylate $[Ru(O_2CMes)_2(p\text{-cymene})]$[280,281] or inexpensive $[RuCl_3 \cdot nH_2O]$, and $PhI(OAc)_2$ as the oxidant for the chelation-assisted C–O bond formation on arenes. Notably, the mixture

of solvents comprising of TFA and TFAA plays very important role, which enables successful oxygenation of electron-deficient and electron-rich arenes as well as heteroarenes. A variety of weakly coordinated directing groups, such as ketones, esters are effectively employed in the substrates for C–H bond oxygenation.[279-290] In 2013, Jeganmohan and co-workers have reported ruthenium-catalyzed benzoxylation of acetanilide with aromatic acids (Scheme 1.53).[290] Various functional groups, such as −OMe, −F, −Cl, −Br are tolerated with moderate to good yields. Electronic effect of substituents on aromatic acid played very important role. Moderate electron-donating and electron-withdrawing groups, such as −Me, −F, −Cl, −Br nicely participated in the reaction as compared to strong electron-donating and electron-withdrawing groups.



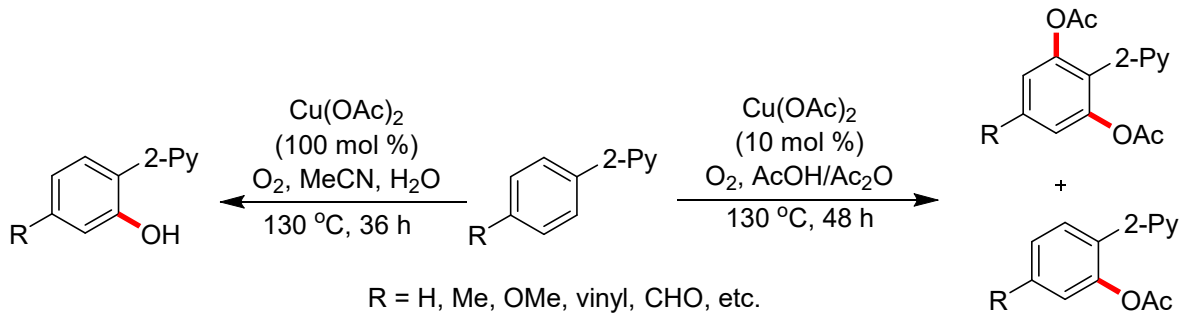
Scheme 1.52 Overview of Ruthenium-Catalyzed Direct Hydroxylation of C(sp^2)−H Bonds.



Scheme 1.53 Ru-Catalyzed Acetoxylation of Acetanilide.

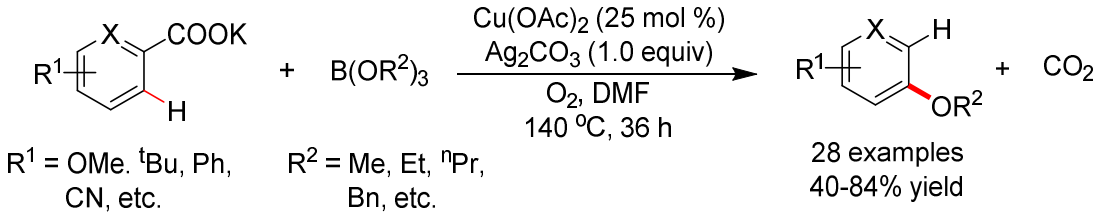
1.8.3 Copper-Catalyzed Oxygenation

Copper-catalyzed oxidation of aryl C–H bond to obtain hydroxylated arenes and heteroarenes has recently being progressed.[291] Initially, *ortho*-acetoxylation of phenols was performed using stoichiometric amounts of Cu(II) salt.[292] Chen and Yu group reported a $Cu(OAc)_2$-catalyzed *ortho*-selective hydroxylation of 2-phenylpyridines, wherein O_2 (1 atm) was used as an oxidant (Scheme 1.54).[293] The reaction is performed with 1.0 equiv of $Cu(OAc)_2$ in acetonitrile at 130 ^oC in the presence of one equiv of water, generating the desired phenols in good yields upon the in-situ hydrolysis. Stoichiometric amounts of $Cu(OAc)_2$ is accountable for the oxygen incorporation, and further oxidation reaction of the product was prevented by the hydroxyl and pyridinyl groups coordination. However, this product coordination inhibits the reaction and prevents the catalytic turnover. This limitation was overcome by adding acetic anhydride to the reaction to acetylate the hydroxylated product. As a result, the Cu loading was reduced to 10 mol % instead of stoichiometric amounts (Scheme 1.54).[293]

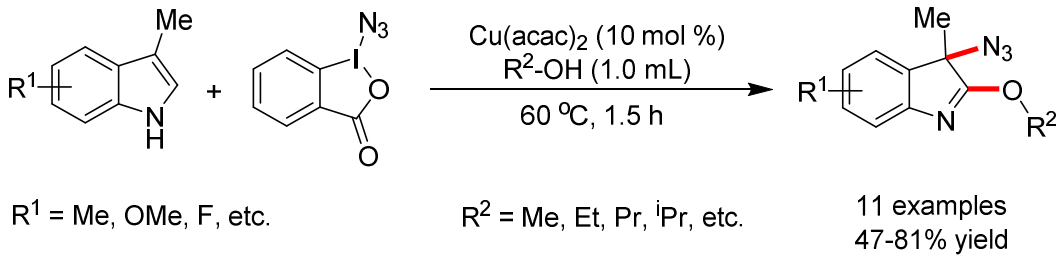


Scheme 1.54 Copper(II)-Catalyzed Acetoxylation of 2-Phenyl Pyridine.

In 2013, Gooßen group reported the formation of aryl ethers from benzoates *via* carboxylate-directed C–H bond activating alkoxylation with successive decarboxylation (Scheme 1.55).[294] The reaction consists of a silver/copper-mediated oxidative *ortho* alkoxylation cycle of the benzoate followed by a decarboxylation cycle. Recently, Jiao and co-workers reported the copper-catalyzed oxoazidation and alkoxyazidation of indoles through dearomatization (Scheme 1.56).[295] The dearomatized derivatives of indoles are important structural moieties in various natural products and bioactive molecules. The 3-azido indolenine and oxindole derivatives can be used for further transformation by oxoazidation and alkoxyazidation.



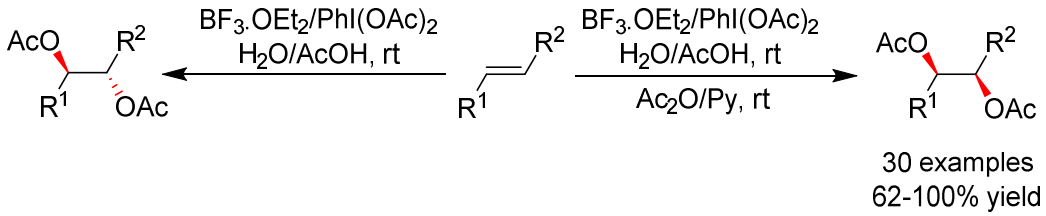
Scheme 1.55 Carboxylate Directed C−H Alkoxylation.



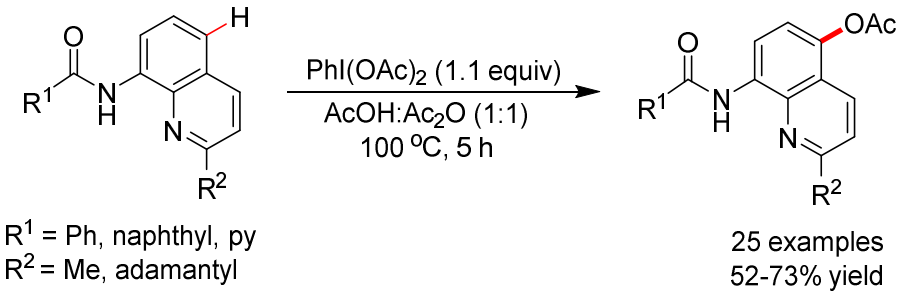
Scheme 1.56 Oxoazidation and Alkoxyazidation of Indoles.

1.9 Transition-Metal-Free C−H Oxygenation

Recently, transition-metal-free catalytic reactions have given particular attention. In that direction, transition-metal-free acetoxylation of different arenes like phenol,[296] alcohol[297] and sulphonamide[298] and aldoximes[299] has been reported with $PhI(OAc)_2$ oxidant under acidic condition.[300] Metal-free oxygenation of cyclohexane has been reported by Fukuzumi.[300] Herein, 9-mesityl-10-methylacridinium catalyzes the reaction in acidic medium under visible light. In 2011, Li and co-workers have reported the disteroselective diacetoxylation of alkene (Scheme 1.57).[301] Herein, selective *syn* and *anti* diacetoxylated alkenes were formed in the presence of $PhI(OAc)_2/BF_3.OEt_2$. Broad range of substrate scope has been developed in this methodology furnishing the desired product in good to excellent yields with excellent diastereoselectivity. This methodology provided an alternative route for the preparation of various 1,2-diols. Similarly, Chiba also reported diastereoselective aminooxygenation and diamination of alkenes with amidines by employing a hypervalent iodine(III) precursor.[302] Recently, Volla and co-workers demonstrated the remote C−H bond acetoxylation of 8-aminoquinoline under metal free condition (Scheme 1.58).[303] This methodology shows high conversion efficiency, broad substrate scope and excellent functional group tolerance giving access to various C-5 acetoxylated carboxamides, sulphonamides or phosphinamides.

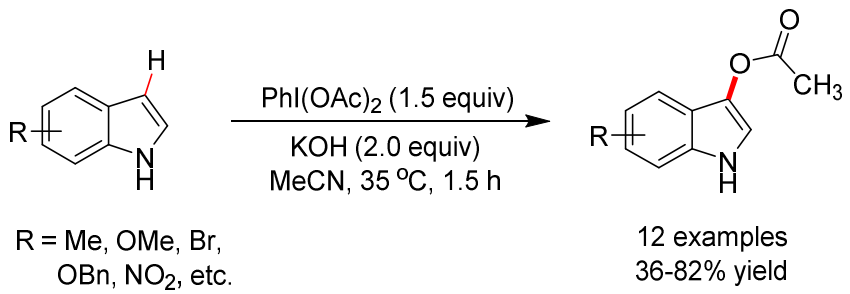


Scheme 1.57 Transition-Metal-Free Acetoxylation of Alkenes.



Scheme 1.58 Remote C−H Acetoxylation of 8-Aminoquinoline.

Recently, the group of Huang reported a transition-metal-free method for the C-3 acetoxylation of 1*H*-indole (Scheme 1.59).[304,305] Notably, the presence of –NH is important for the reaction, and the *N*-substituted indole derivatives are unreactive. The C-3 acetoxylated *N*-substituted indole has also been reported by Lei *et al.* upon elimination of acetic acid from the diacyloxylated indolines during their studies directed towards synthesis of *trans*-diacyloxylated indoline.[306] Similarly, iodine-mediated α-acetoxylation of 2,3-disubstituted indoles has been demonstrated under acidic conditions.[307,308] Many other nitrogen-containing heteroarenes are also subjected for the acetoxylation under transition-metal-free conditions.[309]



Scheme 1.59 Transition-Metal-Free C-3 Acetoxylation of *NH*-Indoles.

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Objectives of the Present Study

Literature survey shows that there is tremendous effort in the development of nickel-chemistry and nickel-catalyzed reactions. Nickel complexes are highly active and efficient catalyst system for various organic transformations. The nickel catalysts have been used for many C–H bond functionalization reactions, such as arylation, alkenylation, alkynylation, and alkylation as well as for C−X bond forming reactions of (hetero)arenes. However, majority of the nickel-catalyzed processes have been employed for the C–H bond functionalization of activated substrates or for the substrates containing an expensive bidentate-chelate motif. Hence, one of the major objectives of the present work was to design and develop the novel nickel-catalyst systems for the C–H functionalization of unactivated substrates without being the assistance of bidentate chelation motif. Particularly, the C–H bond functionalization of indoles is significant as they are the building blocks of various biologically active and pharmaceutical compounds. Hence, selective functionalization of indoles using the well-defined nickel-catalysts *via* the unified strategies was another objective of the present work.

The results obtained from the investigation are discussed in Chapters 2 and 3. In Chapter 2, the design and development of novel nickel catalyst systems is described. These nickel-catalysts efficiently catalyze the direct C-2 alkylation of indoles through monodentate-chelation assistance. The reaction proceeded *via* a unique strategy by the use of well-designed and defined (quinolinyl)amido-based nickel catalyst, thus, providing a solution to the limitations associated with the bidentate-chelate auxiliaries. This regioselective C-2 alkylation of indoles by the (NNN)-pincer nickel catalyst allowed the coupling of indoles with various unactivated primary and secondary alkyl halides. In Chapter 3, the $C(sp^2)$–H/$C(sp^3)$–H oxidative coupling of indoles with toluene derivatives is discussed employing the well-defined nickel catalyst. This coupling is successfully achieved in the presence of 2-iodobutane as a mild oxidant, which proceeds *via* a unique strategy, wherein the 2-iodobutane functions as a benzyl radical originator by abstracting H-atom from the toluene derivatives. This method allows the selective C-2 benzylation of indoles with toluene derivatives over the alkylation with 2-iodobutane, and permits the coupling of diversified indoles *via* the mono-chelation assistance.

Another objective of the work was to perform the detail mechanistic study of the described nickel-catalyzed C−H functionalizations. Thus, in Chapter 4, detail mechanisms of the C-2 alkylation and C-2 benzylation of indoles by the (quinolinyl)amido-nickel catalyst is described. Preliminary experiments have been performed to know the absolute nature of the

catalyst, wherein the effect of external additives, such as Hg and TEMPO/galvinoxyl on alkylation and benzylation was probed. Apart from this, the radical clock experiment has been performed to confirm the radical pathway of the reaction. To gain more insight into the mechanism, the electronic effect of substituents on the reaction rates has been determined by the independent kinetic experiments. The kinetic isotope effect (KIE) experiments have been performed to understand the aspects of C–H bond activation process during the reaction. Mechanistic cycles are proposed for the nickel-catalyzed regioselective alkylation and benzylation of indoles.

Further, literature reports show that the regioselective C–H bond fluoroalkylation of indoles is more challenging for the C-3 unsubstituted indoles, and for the indoles without bearing a directing group. Herein, the objective was to develop a suitable catalyst system for the regioselective difluoroalkylation of such challenging indoles. Thus, Chapter 5 describes a general nickel-catalyzed method for the regioselective difluoroalkylation of indoles. Herein, the in-situ generated nickel catalyst (DME)$NiCl_2$/Xantphos system C-2 selectively catalyzes the difluoroalkylation of indoles, without the assistance of a directing group. Broad substrate scope has been explored with diversely substituted indoles.

Last chapter of the thesis deals with the metal-free approach for the regioselective C-3 acetoxylation of *N*-substituted indoles with $PhI(OAc)_2$ under the mild reaction conditions. This method tolerates a broad range of functional groups, such as –F, $–CF_3$, –C(O)Me, –C(O)OMe, –CN and $–NO_2$ with moderate to good yields. The diacetoxylated indoline is the active intermediate for the acetoxylation of the *N*-substituted indoles, wherein the dehydroacetoxylation is facilitated in the presence of a π-deficient arene substituent on the *N*-atom of indoles. On the basis of control experiments it has been proved that π-electron-deficient aryl-substituent on the *N*-atom of indoles and the acidic reaction medium remarkably favours the reaction**.**

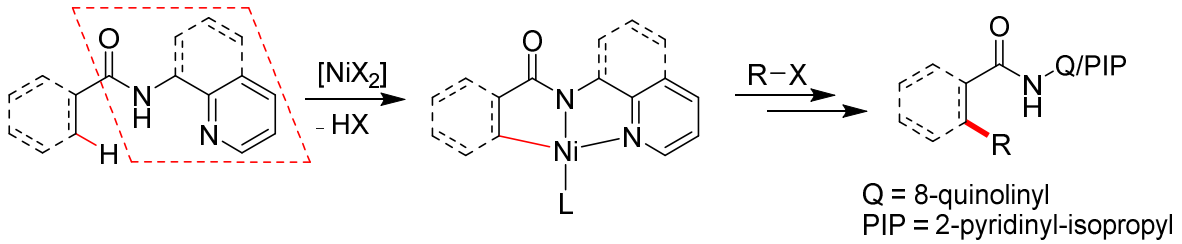
Chapter 2

Unified Strategy for Nickel-Catalyzed C-2 Alkylation of Indoles with Alkyl Halides

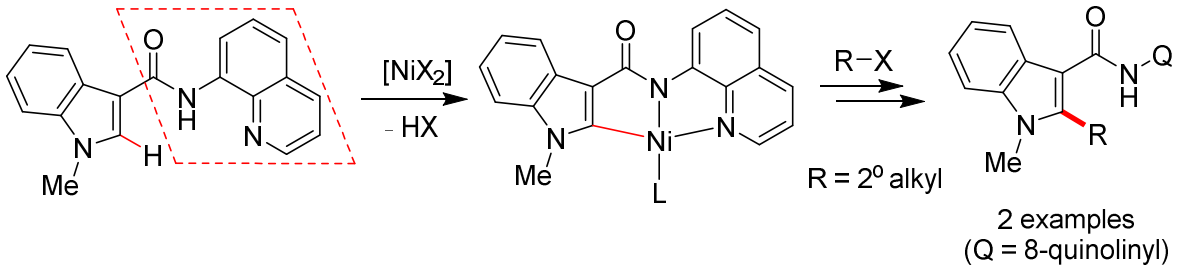
2.1 INTRODUCTION

Indoles are indispensable substructures of various natural products, drugs and biologically active compounds.[1-8] Thus, there is a growing interest in the efficient and selective functionalization of indoles,[9-12] particularly, by developing the strategies based on transition-metal-catalyzed direct C–H bond activation.[13-21] While various effective methods were devised for the regioselective arylations[22-31] and alkenylations[32-36] of indoles, significantly more challenging C–H bond alkylation with unactivated alkyl halides containing *β*-hydrogen is very scarce;[37-43] which is mainly due to the difficulty in oxidative addition of alkyl halides onto the transition metals and their tendency to the *β*–hydride eliminations. Indeed, only a few methods for direct alkylation of indoles with alkyl halides have reported with the precious Pd-metal catalyst.[44-47] In light of the beneficial features of earth-abundant 3d transition metals, Ackermann *et al.* described an inexpensive Co-catalyzed C-2 alkylation of indoles with primary alkyl chlorides.[48-51] However, the use of strong base, Grignard reagent (CyMgCl), is the major limitation associated with this method.

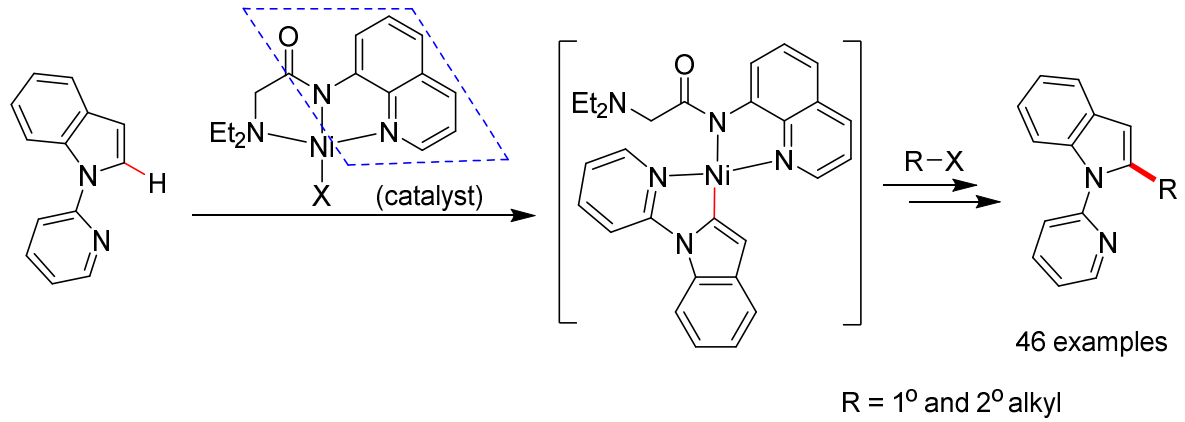
A variety of nickel-catalyzed C–H functionalizations have been established and found beneficial for organic synthesis. In general, the Ni-catalyzed regioselective C–H functionalization has thus far been limited, with few exceptions,[52-58] to the arenes containing a *N,N*-bidentate auxiliary, (quinolin-8-yl)amide or (pyridin-2-yl)isopropyl amide (Scheme 2.1).[59-67] Along those lines, Ackermann *et al.* reported a Ni-catalyzed alkylation of indole-3-carboxamide with secondary alkyl halides through bidentate-chelate assistance, only with the limited scope (Scheme 2.2).[64] The bidentate directing group largely binds the Ni-center more tightly and lowers the C–H activation barrier to facilitates the (hetero)arene C–H functionalization.[68] Unfortunately, this bidentate-chelate strategy is confined only to the carboxylamides, and needed the installation of an expensive bidentate auxiliary on each substrate before the C–H functionalization,[59-67] which are the major disadvantages associated with it. To address these drawbacks, strategically, a Ni-catalyst system with (quinolin-8-yl)amido ligand was developed (bidentate-chelate motif in the form of ligand on Ni to achieve the desired electronic requirements; Scheme 2.3), that regioselectively catalyzes the alkylation of indoles with various primary and secondary alkyl halides through a monodentate chelate assistance.[69] In this chapter, the synthesis and characterization of novel nickel catalysts, scope of the nickel-catalyzed alkylation of indoles using monodentate chelation, and the synthetic utility of the developed methodology are discussed.



Scheme 2.1 Regioselective C−H Functionalization *via N,N*-Bidentate-Chelate Strategy.



Scheme 2.2 C-2 Alkylation of Indole through *N,N*-Bidentate-Chelate Assistance.



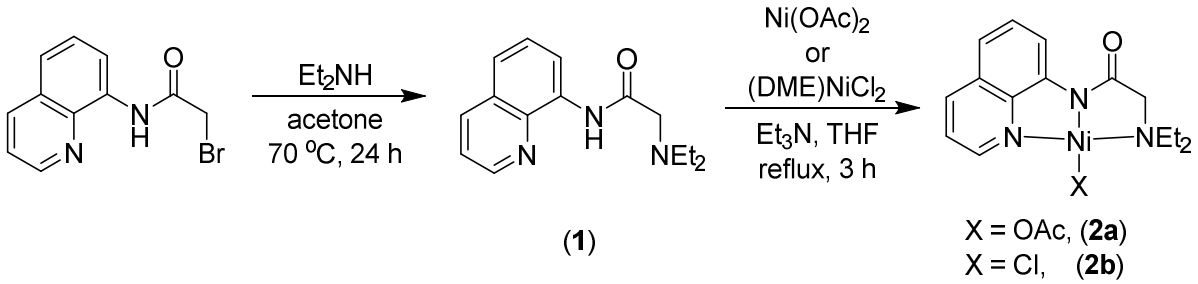
Scheme 2.3 Strategy without Bidentate Chelate Auxiliary.

2.2 RESULTS AND DISCUSSION

2.2.1 Synthesis and Characterization of Ligand Precursor and Nickel Complexes

The 2-(diethylamino)-*N*-(quinolin-8-yl)acetamide ligand, $Et_2NCH_2C(O)$-(NH)-C_9H_6N (**1**) was synthesized in excellent yield from the reaction of 2-bromo-*N*-(quinolin-8-yl)acetamide with diethyl amine at mild reaction conditions (Scheme 2.4). Metalation reactions of the ligand **1** with $Ni(OAc)_2$ and $(DME)NiCl_2$ in the presence of triethylamine afforded the complexes, $\kappa^N,\kappa^N,\kappa^N$-{$Et_2NCH_2C(O)$-($\mu$-N)-$C_9H_6N$}NiX, [($^{Q}NNN^{Et2}$)NiX; X = OAc, **2a** and X = Cl, **2b**], respectively. Both the nickel complexes were characterized by the

NMR spectroscopy as well as by the elemental analysis. Notably, in the ^{1}H NMR spectrum of **2a** and **2b**, the methylene (–CH_2) protons of –Et groups displayed two sets of apparent sextet (δ 2.86, 2.21 ppm for **2a** and δ 3.15, 2.06 ppm for **2b**) in comparison to a single quartet for the same in the ligand **1**, which could be due to the diastereotopic induction of the methylene protons upon coordination of –NEt_2 arm to the Ni-center. Further, the molecular structures of complexes **2a** and **2b** were established by the X-ray crystallography.



Scheme 2.4 Synthesis of Pincer Ligand and Nickel Complexes.

The ORTEP diagrams of complexes **2a** and **2b** are shown in Figures 2.1 and 2.2, respectively. Selected bond lengths and bond angles are listed in Table 2.1. For both the complexes, distorted square planar geometry is observed around the Ni-centers. The Ni(1)–N(1), Ni(1)–N(2) and Ni(1)–N(3) bond lengths around the nickel in **2a** and **2b** are comparable with the bond lengths in a similar complex, (^{Me2}NNN^{Q})NiCl.[70] Similarly, the N(2)–Ni(1)–N(3) bond angles (170.89(7)º for **2a**, 170.13(6)º for **2b**) are almost same as that observed in (^{Me2}NNN^{Q})NiCl (170.77 (8)º).[70] In addition, both the five-membered rings bearing Ni are almost planar with the quinolinyl ring.

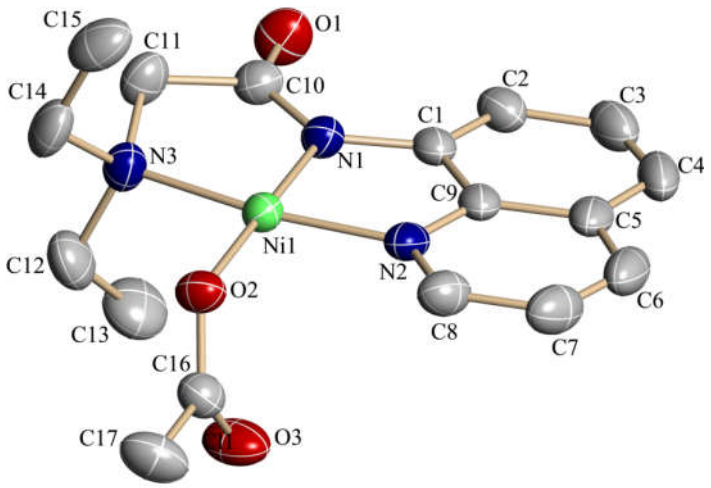


Figure 2.1 Thermal ellipsoid plot of **2a**. All hydrogen atoms are omitted for clarity.

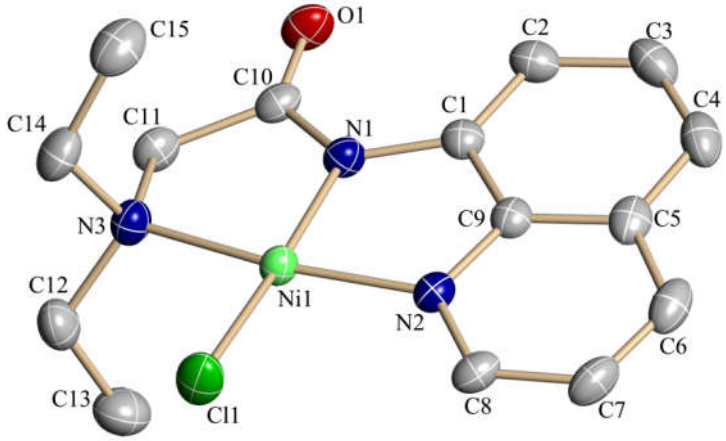


Figure 2.2 Thermal ellipsoid plot of **2b**. All hydrogen atoms are omitted for clarity.

Table 2.1 Selected bond lengths (Å) and bond angles (°) for **2a** and **2b**

Bond length (Å)		**Bond angles (°)**	
Complex **2a**			
Ni(1)–N(1)	1.8364(17)	N(1)–Ni(1)–O(2)	178.67(7)
Ni(1)–N(2)	1.8962(17)	N(1)–Ni(1)–N(2)	85.10(7)
Ni(1)–N(3)	1.9443(18)	O(2)–Ni(1)–N(2)	95.06(7)
Ni(1)–O(2)	1.8801(14)	N(2)–Ni(1)–N(3)	170.89(7)
		C(10)–N(1)–C(1)	125.35(18)
Complex **2b**			
Ni(1)–N(1)	1.8427(13)	N(1)–Ni(1)–Cl(1)	173.81(5)
Ni(1)–N(2)	1.9107(13)	N(1)–Ni(1)–N(2)	84.39(6)
Ni(1)–N(3)	1.9668(14)	N(2)–Ni(1)– Cl(1)	95.50(4)
Ni(1)–Cl(1)	2.1818(5)	N(2)–Ni(1)–N(3)	170.13(6)
		C(10)–N(1)–C(1)	124.27(14)

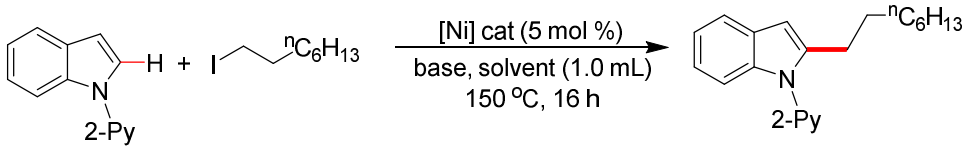
2.2.2 Catalytic Activity of (^{Q}NNN^{Et2})NiX Complexes for C–H Bond Alkylation

2.2.2.1 Optimization of Catalytic Condition

The optimization studies for the cross-coupling of indole **3a** with 1-iodooctane (**4a**) employing the Ni-catalyst (^{Q}NNN^{Et2})NiOAc (**2a**) was initiated (Table 2.2). The use of LiO^{t}Bu or NaO^{t}Bu as base gave only trace amount of product, 2-octyl-1-(pyridin-2-yl)-1*H*-indole (**5aa)**, whereas LiHMDS base was very efficient and gave 70% coupled product (entries 1-3). Surprisingly, the employment of catalytic amount of LiHMDS (20 mol %) in addition to the

LiO^{t}Bu was also effective and showed the complete conversion.[71] Other mild bases in combination with the LiHMDS were less effective (entries 5-11). Most effective solvent was toluene and the alkylation in other solvents or in absence of solvent was less efficient (entries 12-21). Notably, the use of 1.0 mL of toluene resulted in the partial formation of benzylated product, 2-benzyl-1-(pyridin-2-yl)-1*H*-indole (15%) in addition to the desired compound **5aa** (75%), whereas the reaction with 0.15 mL of toluene gave 82% yield of **5aa** (entries 4 and 22). Reaction at lower temperatures was less effective (entries 23-24). The nickel derivative **2b** as catalyst produced 53% of **5aa** (entry 25). The catalyst **2a** was essential for achieving the alkylation, without that no coupling occurred (entry 26). The employment of other Ni^{II} precursors with or without ligand, such as Ni(OAc)$_2$, (DME)NiCl$_2$, (DME)NiCl$_2$/Phen or (DME)NiCl$_2$/BDMAE gave poor yield of **5aa** (< 43%, entries 27-30). The mixture of Ni(OAc)$_2$ and ligand **1** afforded moderate yield of product **5aa** (entry 31). In addition to the iodide, the more challenging 1-bromooctane or 1-chlorooctane can also be employed for the coupling reaction with **3a**, however, the addition of KI (2.0 equiv) was necessary (Table 2.3). Various iodide sources were screened and the KI was found to be beneficial.

Table 2.2 Optimization of reaction conditions for alkylation of indole.[a]



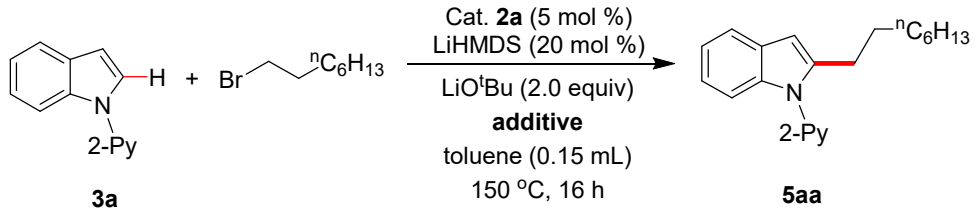
3a **4a** **5aa**

Entry	[Ni] cat	Base (equiv)	Solvent	Yield [%][b]
1	**2a**	LiO^{t}Bu (2.0)	toluene	12
2	**2a**	NaO^{t}Bu (2.0)	toluene	8
3	**2a**	LiHMDS (2.0)	toluene	70[c]
4	**2a**	LiHMDS (0.2) + LiO^{t}Bu (2.0)	toluene	**75**[c,d]
5	**2a**	LiHMDS (0.2) + NaO^{t}Bu (2.0)	toluene	45
6	**2a**	LiHMDS (0.2) + Li_2CO_3 (2.0)	toluene	22
7	**2a**	LiHMDS (0.2) + Na_2CO_3 (2.0)	toluene	12
8	**2a**	LiHMDS (0.2) + K_2CO_3 (2.0)	toluene	15
9	**2a**	LiHMDS (0.2) + Cs_2CO_3 (2.0)	toluene	22
10	**2a**	LiHMDS (0.2) + NaOAc (2.0)	toluene	26
11	**2a**	LiHMDS (0.2) + KOAc (2.0)	toluene	44

12	**2a**	LiHMDS (0.2) + LiO^{t}Bu (2.0)	*o*-xylene	30
13	**2a**	LiHMDS (0.2) + LiO^{t}Bu (2.0)	*m*-xylene	9
14	**2a**	LiHMDS (0.2) + LiO^{t}Bu (2.0)	*p*-xylene	13
15	**2a**	LiHMDS (0.2) + LiO^{t}Bu (2.0)	mesitylene	18
16	**2a**	LiHMDS (0.2) + LiO^{t}Bu (2.0)	^{t}Bu-benzene	57
17	**2a**	LiHMDS (0.2) + LiO^{t}Bu (2.0)	1,4-dioxane	9
18	**2a**	LiHMDS (0.2) + LiO^{t}Bu (2.0)	chlorobenzene	61
19	**2a**	LiHMDS (0.2) + LiO^{t}Bu (2.0)	1,2-dichlorobenzene	55
20	**2a**	LiHMDS (0.2) + LiO^{t}Bu (2.0)	toluene[e]	79[c]
21	**2a**	LiHMDS (0.2) + LiO^{t}Bu (2.0)	-	47[g]
22	**2a**	**LiHMDS (0.2) + LiO^{t}Bu (2.0)**	**toluene**[f]	**82**[c]
23	**2a**	LiHMDS (0.2) + LiO^{t}Bu (2.0)	toluene[f]	78[c,h]
24	**2a**	LiHMDS (0.2) + LiO^{t}Bu (2.0)	toluene[f]	60[c,i]
25	**2b**	LiHMDS (0.2) + LiO^{t}Bu (2.0)	toluene[f]	53[c]
26	-	LiHMDS (0.2) + LiO^{t}Bu (2.0)	toluene	NR
27	$Ni(OAc)_2$	LiHMDS (0.2) + LiO^{t}Bu (2.0)	toluene[f]	33[c]
28	$(DME)NiCl_2$	LiHMDS (0.2) + LiO^{t}Bu (2.0)	toluene[f]	43[c]
29	$(DME)NiCl_2$/Phen	LiHMDS (0.2) + LiO^{t}Bu (2.0)	toluene[f]	38[c]
30	$(DME)NiCl_2$/ BDMAE	LiHMDS (0.2) + LiO^{t}Bu (2.0)	toluene[f]	21
31	$Ni(OAc)_2$/ligand **1**	LiHMDS (0.2) + LiO^{t}Bu (2.0)	toluene[f]	62

[a] Reaction conditions: **3a** (0.058 g, 0.3 mmol), **4a** (0.144 g, 0.6 mmol), [Ni] cat (0.015 mmol, 5 mol %), LiHMDS (0.010 g, 0.06 mmol, 20 mol %), base (0.6 mmol), 150 °C, 16 h. [b] GC yield using *n*-dodecane as internal standard. [c] Isolated yield. [d] Benzylated product *i.e.* 2-benzyl-1-(pyridin-2-yl)-1*H*-indole (coupling with solvent toluene) was observed in 15%. [e] 0.2 mL toluene used. [f] 0.15 mL toluene used. [g] Neat reaction (without solvent). [h] Reaction at 140 °C for 24 h. [i] Reaction at 120 °C for 24 h.

Table 2.3 Optimization of reaction parameters for C–H alkylation of indole with alkyl bromides/chlorides.[a]

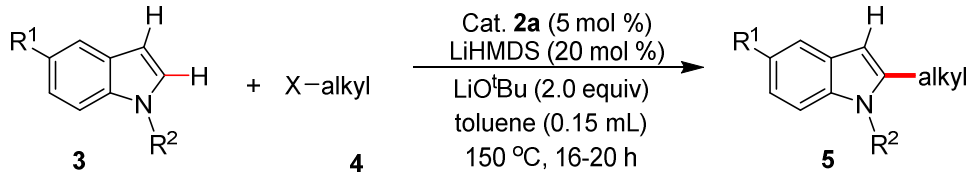


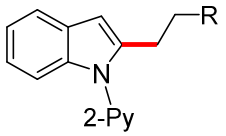
Entry	Additive (equiv)	Yield [%][b]
1	-	51
2	NaI (2.0)	21
3	Bu_4NI (2.0)	39
4	KI (1.0)	79
5	KI (1.5)	86
6	KI (2.0)	89 (79)
7[c]	KI (2.0)	86 (76)

[a] Reaction conditions: **3a** (0.058 g, 0.3 mmol), 1-bromooctane (0.116 g, 0.6 mmol), cat **2a** (0.0056 g, 0.015 mmol, 5 mol %), LiHMDS (0.010 g, 0.06 mmol, 20 mol %), LiO^tBu (0.048 g, 0.6 mmol), 150 °C, 16 h. [b] GC yield using *n*-dodecane as internal standard. Isolated yield in parenthesis. [c] Using 1-chlorooctane (0.089 g, 0.6 mmol).

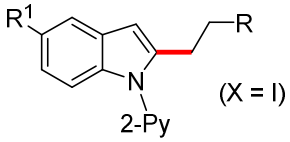
2.2.2.2 Substrate Scope for Alkylation of Indoles

The optimized reaction condition with the catalyst **2a** was applied to the alkylation of indoles with various unactivated primary alkyl halides (Scheme 2.5). Alkyl halides with different chain lengths were coupled to give the desired C-2 alkylation products (**5aa-5aj**) in good to excellent yields. Important functional groups, such as ether, nitrile, fluoro, and bromo groups were tolerated on the indole moiety (**3b-3f**). The aryl–Br moiety of the indole did not pose problem for the coupling reaction. Notably, the indole substrates containing ether, fluoro, and bromo groups show full conversion, though the isolated yields were modest. The sterically hindered C-3 substituted indole **3g** could be alkylated with moderate reactivity. Alkyl bromides with branching at the β- and γ-position were tolerated and efficiently coupled with the indole to give good yields of the C-2 alkylated products (**5ak-5an, 5bl** and **5bn**). It is noteworthy that a sterically hindered neopentyl bromide **4o** could be coupled by this **2a**-catalyzed C–H functionalization approach. The aryl-substituted alkyl bromides **4p**,**q** were also conveniently coupled. Interestingly, the coupling of alkyl iodide site was selective in the



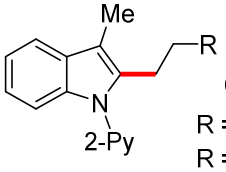


R = ^{n}C$_6$H$_{13}$ (**5aa**): 82% (X = I)
76% (X = Cl)
R = ^{n}C$_2$H$_5$ (**5ab**): 92% (X = I)
R = ^{n}C$_3$H$_7$ (**5ac**): 62% (X = I)
R = ^{n}C$_4$H$_9$ (**5ad**): 78% (X = Br)
R = ^{n}C$_8$H$_{17}$ (**5ae**): 72% (X = Br)
R = ^{n}C$_{10}$H$_{21}$ (**5af**): 86% (X = I)
65% (X = Br)
R = ^{n}C$_{11}$H$_{23}$ (**5ag**): 70% (X = Br)
R = ^{n}C$_{12}$H$_{25}$ (**5ah**): 86% (X = Br)
R = ^{n}C$_{14}$H$_{29}$ (**5ai**): 60% (X = Br)
R = ^{n}C$_{16}$H$_{33}$ (**5aj**): 56% (X = Br)



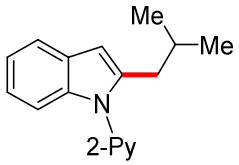
(X = I)

R^1 = Me, R = ^{n}C$_{10}$H$_{21}$ (**5bf**): 93%
R^1 = OMe, R = ^{n}C$_6$H$_{13}$ (**5ca**): 53%
R^1 = OMe, R = ^{n}C$_{10}$H$_{21}$ (**5cf**): 61%
R^1 = F, R = ^{n}C$_6$H$_{13}$ (**5da**): 53%
R^1 = F, R = ^{n}C$_{10}$H$_{21}$ (**5df**): 43%
R^1 = Br, R = ^{n}C$_{10}$H$_{21}$ (**5ef**): 56%
R^1 = CN, R = ^{n}C$_6$H$_{13}$ (**5fa**): 38%
R^1 = CN, R = ^{n}C$_{10}$H$_{21}$ (**5ff**): 45%

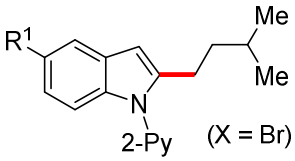


(X = I)

R = ^{n}C$_6$H$_{13}$ (**5ga**): 46%
R = ^{n}C$_{10}$H$_{21}$ (**5gf**): 38%

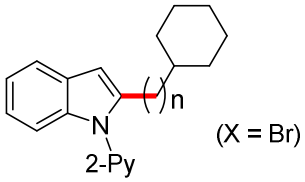


5ak: 80% (X = Br)



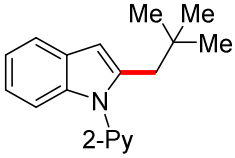
(X = Br)

R^1 = H (**5al**): 88%
R^1 = Me (**5bl**): 77%

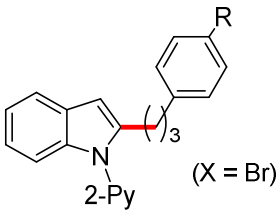


(X = Br)

R = H, n = 1 (**5am**): 85%
R = H, n = 2 (**5an**): 67%
R = Me, n = 2 (**5bn**): 70%

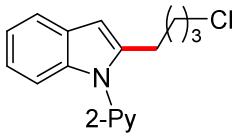


5ao: 52% (X = Br)

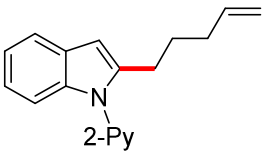


(X = Br)

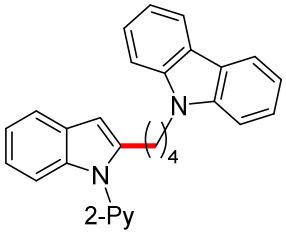
R = H, (**5ap**): 75%
R = OMe, (**5aq**): 68%



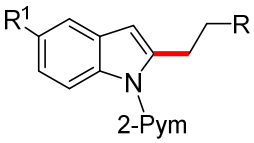
5ar: 52% (X = I)



5as: 47% (X = Br)



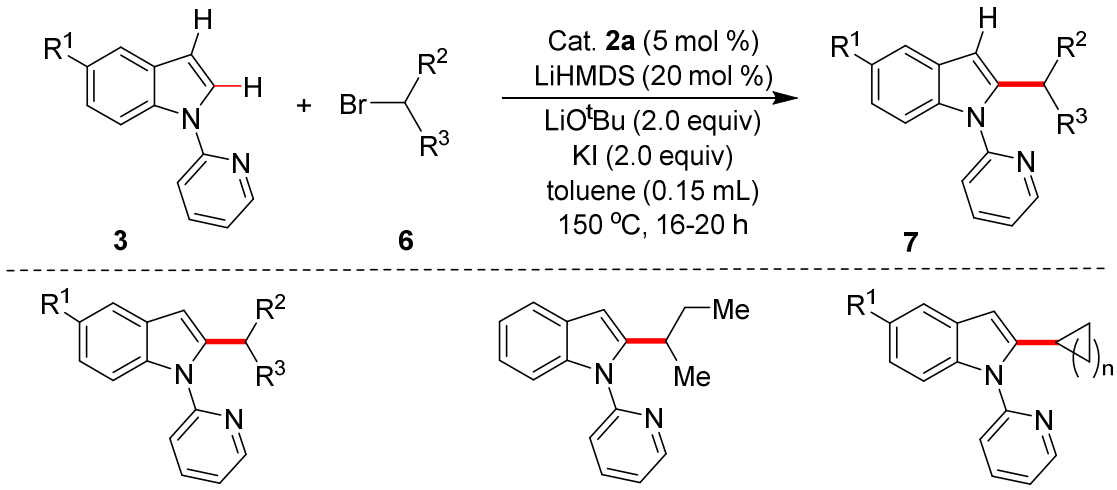
5at: 57% (X = I)



R^1 = H, R = ^{n}C$_{12}$H$_{25}$ (**5hh**): 56% (X = Br)
R^1 = H, R = ^{n}C$_{16}$H$_{33}$ (**5hj**): 56% (X = Br)
R^1 = OMe, R = ^{n}C$_6$H$_{13}$ (**5ia**): 61% (X = I)

Scheme 2.5 Scope of the Ni-Catalyzed C-2 Alkylation of Indoles with Primary Alkyl Halides. KI (2.0 equiv) was used while employing coupling partners alkyl chloride and alkyl bromide.

presence of alkyl–Cl bond (**4r**), which is significant as this can further be used for functionalization. The substrate containing alkene moiety **4s**, as well as heterocycle carbazole **4t** were coupled with moderate yields. Encouragingly, the substrates bearing easily removable 2-pyrimidinyl group, **3h**,**i** could be employed for this strategy, albeit in modest yield. However, indoles having $–C(O)CH_3$, $–C(O)^tBu$, $–OSO_2Ph$ as directing group at the N-center of indole were not reactive.



R^1 = H, R^2 = R^3 = Me (**7aa**): 73%[a]
R^1 = H, R^2 = Me, R^3 = Ph (**7ab**): 75%
R^1 = H, R^2 = R^3 = Ph (**7ac**): 75%
R^1 = Me, R^2 = R^3 = Me (**7ba**): 82%[a]
R^1 = Me, R^2 = R^3 = Ph (**7bc**): 84%

7ad: 51%[a]

R^1 = H, n = 1 (**7ae**): 64%[b]
R^1 = H, n = 3 (**7af**): 48%[a]
R^1 = H, n = 4 (**7ag**): 76%
R^1 = H, n = 5 (**7ah**): 38%
R^1 = Me, n = 4 (**7bg**): 63%

Scheme 2.6 Scope of the Ni-Catalyzed C-2 Alkylation of Indoles with Secondary Alkyl Halides. Yields refer to isolated product. [a] Employing alkyl iodides. [b] Yield by ^{1}H NMR.

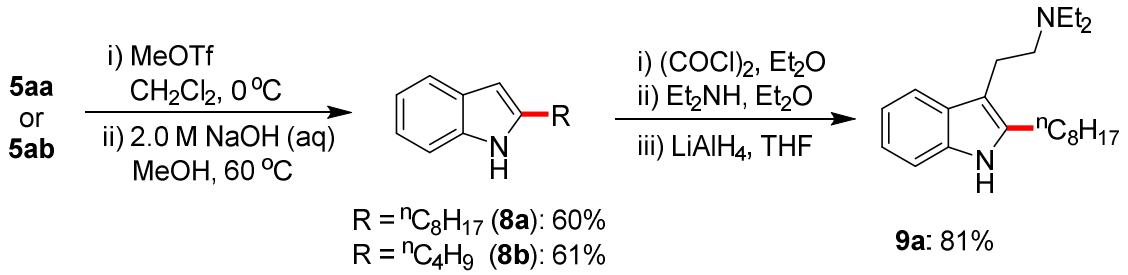
The same optimized reaction conditions can be used for the coupling of secondary alkyl halides with various indole substrates (Scheme 2.6). Hence, the acyclic alkyl-substituted secondary alkyl halides **6a**,**b**,**d** as well as the phenyl-substituted secondary alkyl halide **6c** were selectively and efficiently coupled at the C-2 position of the indole to give the desired products in good yields. Further the cyclic secondary alkyl halides **6e-h** reacted in moderate to good activity. No coupling occurred with the tertiary alkyl halides, such as *tert*-butyl iodide and 1-bromoadamantane.

This uniquely strategized Ni-catalyst **2a** facilitates the coupling of both the primary and secondary alkyl halides with indoles having monodentate directing group under a single optimized condition. Further, the **2a**-catalyzed C-2 alkylation process of indole was tolerated

by ether, nitrile, olefin, carbazole, alkyl-chloro and aryl-bromo groups. For all substrates, the regioselective C-2 alkylation was accomplished, and neither the C-3 alkylation nor the C-2, C-3 double alkylation observed, which is very significant as the C(3)–H can be further functionalized *via* the electrophilic metalation.

2.2.3 Synthetic Utility of Alkylation Method

We demonstrated the synthetic utility of our strategy by the removal of pyridinyl group in a facile manner, affording the corresponding C-2 alkylated free-*NH*-indoles **8a**,**b** (Scheme 2.7). The compound **8a** was further functionalized at C(3)–H, yielding a neuromodulator tryptamine alkaloid derivative **9a** in very excellent yield.[72,73]



Scheme 2.7 Removal of Directing Group and Synthesis of Tryptamine Alkaloid.

2.3 CONCLUSION

In this chapter, the synthesis and characterization of new pincer nickel complexes (quinolinyl)amido-nickel catalysts, [κ^N,κ^N,κ^N-{$Et_2NCH_2C(O)$-(μ-N)-C_9H_6N}Ni(OAc)] and [κ^N,κ^N,κ^N-{$Et_2NCH_2C(O)$-(μ-N)-C_9H_6N}NiCl] is described. Both the complexes were fully characterized by ^1H, ^{13}C spectroscopy, X-ray analysis and elemental analyses. These complexes have been employed for the C–H bond alkylation reaction of indoles, which proceeded through monodenate-chelation assistance. This unified stratagy represents the first pincer-nickel complex that has been employed for the C–H bond alkylation of indoles having monodentate directing group. This approach unfolded the Ni-catalyzed C–H functionalization beyond the commonly used carboxamides, and without the installation of a bidentate auxiliary. The inexpensive nickel-catalyst proved highly efficient for the coupling of unactivated primary and secondary alkyl halides, including the inexpensive bromides and chlorides with indoles. Various functional groups, such as –Me, –OMe, –Br, –CN were tolerated on the indole backbone to give the coupled products in moderate to excellent yields.

Especially, the regio- and chemo-selectivities are excellent. The synthetic applicability of this Ni-catalyzed strategy is established by the facile removal of directing groups and by synthesizing the biologically active tryptamine derivatives.

2.4 EXPERIMENTAL SECTION

General Experimental

All manipulations were conducted under an argon atmosphere either in the glove box or using standard Schlenk techniques in pre-dried glass wares. The catalytic reactions were performed in the 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 2-bromo-*N*-(quinolin-8-yl)acetate,[74,75] 5-substituted 1-(pyridin-2-yl)-1*H*-indole,[76,77] 1-(pyrimidin-2-yl)-1*H*-indole,[78,79] 1-(pyridin-2-yl)-1*H*-indole-2-*d*,[80] 9-(4-iodobutyl)-8a,9a-dihydro-9*H*-carbazole,[81] were synthesized according to previously described procedures. All other chemicals were obtained from commercial sources and were used without further purification. Yields refer to isolated compound estimated to be > 95% pure as determined by ^{1}H-NMR. TLC: TLC Silica gel 60 F_{254}. Detection under UV light at 254 nm. Chromatography: Separations were carried out on Spectrochem silica gel (0.120-0.250 mm, 100-200 mesh) or neutral alumina (Al_2O_3). High resolution mass spectroscopy (HRMS) mass spectra were recorded on a Thermo Scientific Q-Exactive, Accela 1250 pump. M. p.: Büchi 540 capillary melting point apparatus, values are uncorrected. NMR (^{1}H and ^{13}C) spectra were recorded at 400 or 500 MHz (^{1}H), 100 or 125 {^{13}C, DEPT (distortionless enhancement by polarization transfer)} and 377 MHz (^{19}F) on Bruker AV 400 and AV 500 spectrometers 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 ($CDCl_3$: δH = 7.26 ppm, δC = 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 250 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 °C, respectively. UHP-grade argon was used as carrier gas with a flow rate of 30 mL/min. The temperature program used for all the analyses is as follows: 80 °C, 1 min; 30 °C/min to 200 °C, 2 min; 30 °C/min to 260 °C, 3 min; 30 °C/min to 300 °C, 3 min.

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

2.4.1 Synthesis of 2-Bromo-*N*-(quinolin-8-yl)acetamide

To a solution of 8-aminoquinoline (1.0 g, 6.94 mmol) in CH_2Cl_2 (40 mL), Et_3N (1.02 mL, 7.32 mmol) was added at 0 ^oC and stirred for 20 min. To the resulted reaction mixture, bromo acetyl chloride (1.20 g, 7.64 mmol) was added dropwise *via* a syringe. The reaction mixture was then allowed to warm to room temperature and continued stirring for 24 h. At ambient temperature, the reaction mixture was quenched with water (20 mL) and extracted with CH_2Cl_2 (15 mL x 3). The combined organic phase was washed with H_2O (15 mL x 3) and dried over Na_2SO_4. After filtration and evaporation of the solvents in *vacuo*, the crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded the desired product as a light yellow solid. Yield: 1.30 g, 71%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.89 (br s, 1H, N–H), 8.85 (dd, J = 4.2, 1.5 Hz, 1H, Ar–H), 8.74 (dd, J = 6.1, 2.9 Hz, 1H, Ar–H), 8.17 (dd, J = 8.3, 1.5 Hz, 1H, Ar–H), 7.57-7.54 (m, 2H, Ar–H), 7.47 (dd, J = 8.3, 4.2 Hz, 1H, Ar–H), 4.32 (s, 2H, CH_2). ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 164.6 (CO), 148.8 (CH), 138.8 (C_q), 136.6 (CH), 133.7 (C_q), 128.1 (C_q), 127.4 (CH), 122.7 (CH), 121.9 (CH), 116.9 (CH), 43.5 (CH_2). HRMS (ESI): *m/z* Calcd for $C_{11}H_9BrN_2O+H^+$ $[M+H]^+$ 264.9971 and 266.9953; Found 264.9966 and 266.9945. The ^{1}H and ^{13}C spectra are consistent with those reported in the literature.[74,75]

2.4.2 Synthesis of 2-(Diethylamino)-*N*-(quinolin-8-yl)acetamide Ligand (1)

A mixture of 2-bromo-*N*-(quinolin-8-yl)acetamide (1.0 g, 3.77 mmol) and Et_2NH (0.83 g, 11.35 mmol) in acetone (30 mL) was refluxed for 24 h. The reaction mixture was then cooled to room temperature and quenched with distilled H_2O (20 mL). The crude aminated product was extracted with EtOAc (15 mL × 3), and the combined organic extract was washed with H_2O (15 mL × 3) and dried over Na_2SO_4. After filtration and evaporation of the volatiles in *vacuo*, the crude product was purified by column chromatography on silica gel (petroleum ether/EtOAc/Et_3N: 5/1/0.5) to yield the ligand precursor **1**. Yield: 0.95 g, 98%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 11.56 (br s, 1H, N–H), 8.85-8.79 (m, 2H, Ar–H), 8.12 (dd, J = 8.3, 1.6 Hz, 1H, Ar–H), 7.57-7.46 (m, 2H, Ar–H), 7.41 (dd, J = 8.3, 4.2 Hz, 1H, Ar–H), 3.29 (s, 2H, CH_2), 2.70 (q, J = 7.2 Hz, 4H, CH_2), 1.16 (t, J = 7.2 Hz, 6H, CH_3). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 171.3 (CO), 148.6 (CH), 139.3 (C_q), 136.2 (CH), 134.7 (C_q), 128.2

(C_q), 127.4 (CH), 121.7 (CH), 121.6 (CH), 116.6 (CH), 59.2 (CH_2), 48.9 (2C, CH_2), 12.7 (2C, CH_3). HRMS (ESI): *m/z* Calcd for $C_{15}H_{19}N_3O+H^+$ $[M+H]^+$ 258.1601; Found 258.1599.

2.4.3 Synthesis ($^{Q}NNN^{Et2}$)NiX Complexes and Characterization Data

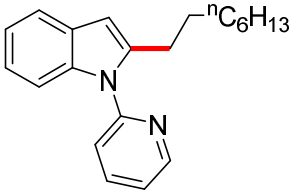
Synthesis of $\kappa^N,\kappa^N,\kappa^N$-{$Et_2NCH_2C(O)$-($\mu$-N)-$C_9H_6N$}Ni-OAc (2a): To a Schlenk flask equipped with magnetic stir bar was introduced ligand **1** (0.3 g, 1.166 mmol) and $Ni(OAc)_2$ (0.216 g, 1.222 mmol), and THF (20 mL) was added into it. Then, the Et_3N (0.16 mL, 1.148 mmol) was added and the reaction mixture was heated to reflux for 3 h. The reaction mixture was cooled to ambient temperature and the volatiles were evaporated under vacuum. The resultant residue was washed with *n*-hexane (10 mL × 3) and the product was extracted with toluene (10 mL × 2). The toluene extract was concentrated and *n*-hexane was added to precipitate the pure product of **2a**. The compound was recrystallized from toluene/*n*-hexane mixture to obtain the crystals of **2a**. Yield: 0.362 g, 83%. M.P. = 140-144 ^oC. ^1H-NMR (500 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 7.5 Hz, 1H, Ar–H), 8.19 (d, *J* = 7.8 Hz, 1H, Ar–H), 7.55 (d, *J* = 4.5 Hz, 1H, Ar–H), 7.42 (vt, *J* = 7.9 Hz, 1H, Ar–H), 7.32-7.22 (m, 2H, Ar–H), 3.22 (s, 2H, CH_2), 2.86 (app. sextet, *J* = 5.1 Hz, 2H, CH_2), 2.34 (t, *J* = 6.7 Hz, 6H, CH_3), 2.21 (app. sextet, *J* = 6.1 Hz, 2H, CH_2), 1.98 (s, 3H, CH_3). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 178.6 (CO), 175.2 (CO), 148.7 (CH), 145.6 (C_q), 143.4 (C_q), 138.7 (CH), 129.4 (CH), 128.8 (C_q), 121.4 (CH), 119.7 (CH), 119.0 (CH), 62.6 (CH_2), 56.1 (2C, CH_2), 24.5 ($COCH_3$), 13.1 (2C, CH_3). Anal. Calcd for $C_{17}H_{21}N_3O_3Ni$: C, 54.59; H, 5.66; N, 11.23. Found: C, 54.02; H, 5.33; N, 10.98.

Synthesis of $\kappa^N,\kappa^N,\kappa^N$-{$Et_2NCH_2C(O)$-($\mu$-N)-$C_9H_6N$}NiCl (2b): This complex was synthesized following the procedure similar to the synthesis of **2a**, using ligand precursor **1** (0.3 g, 1.166 mmol), (DME)$NiCl_2$ (0.27 g, 1.229 mmol) and Et_3N (0.16 mL, 1.148 mmol). Yield: 0.375 g, 92%. M.P. = 168-170 ^oC. ^1H-NMR (500 MHz, $CDCl_3$): δ = 8.59 (d, *J* = 7.9 Hz, 1H, Ar–H), 8.54 (dd, *J* = 5.2, 0.9 Hz, 1H, Ar–H), 8.17 (dd, *J* = 8.2, 1.2 Hz, 1H, Ar–H), 7.43 (vt, *J* = 7.9 Hz, 1H, Ar–H), 7.29-7.25 (m, 2H, Ar–H), 3.20 (s, 2H, CH_2), 3.15 (app. sextet, *J* = 4.9 Hz, 2H, CH_2), 2.38 (t, *J* = 7.0 Hz, 6H, CH_3), 2.06 (app. sextet, *J* = 5.5 Hz, 2H, CH_2). ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 176.3 (CO), 151.4 (CH), 145.9 (C_q), 143.7 (C_q), 138.8 (CH), 129.4 (CH), 128.7 (C_q), 121.2 (CH), 119.6 (CH), 119.3 (CH), 63.5 (CH_2), 57.8 (2C, CH_2), 13.7 (2C, CH_3). Anal. Calcd for $C_{15}H_{18}ClN_3ONi$: C, 51.41; H, 5.18; N, 11.99. Found: C, 51.73; H, 5.00; N, 11.91.

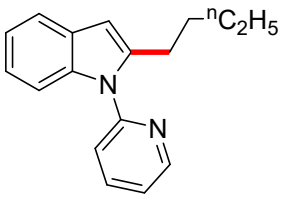
2.4.4 Procedure for Alkylation of Indoles

Representative Procedure: Synthesis of 2-Octyl-1-(pyridine-2-yl)-1*H*-indole (5aa): To a flame-dried screw-cap tube (5 mL) equipped with magnetic stir bar was introduced 1-pyridine-2-yl-1*H*-indole (**3a**; 0.058 g, 0.3 mmol), 1-iodooctane (**4a**; 0.144 g, 0.6 mmol), cat **2a** (0.0056 g, 0.015 mmol, 5.0 mol %), LiHMDS (0.010 g, 0.06 mmol, 20 mol %) and LiO^tBu (0.048 g, 0.6 mmol) inside the glove-box. To the above mixture in the tube, toluene (0.15 mL) was added and the resultant reaction mixture was stirred at 150 °C in a preheated oil bath for 16 h. At ambient temperature, the reaction mixture was quenched with distilled H_2O (10 mL) and then neutralized with 2N HCl (0.5 mL). The crude product was then extracted with CH_2Cl_2 (20 mL × 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 neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) to yield **5aa** as a light yellow liquid. Yield: 0.075 g, 82%.

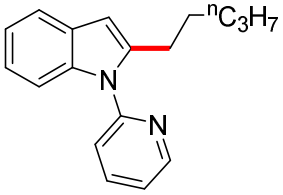
2.4.5 Characterization Data for Compounds 5



2-Octyl-1-(pyridin-2-yl)-1*H*-indole (5aa): Yield: 0.075 g, 82%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.68 (d, J = 5.0 Hz, 1H, Ar–H), 7.88 (td, J = 7.6, 1.8 Hz, 1H, Ar–H), 7.60-7.58 (m, 1H, Ar–H), 7.44 (d, J = 8.0 Hz, 1H, Ar–H), 7.35-7.31 (m, 2H, Ar–H), 7.16-7.12 (m, 2H, Ar–H), 6.47 (s, 1H, Ar–H), 2.85 (t, J = 7.6 Hz, 2H, CH_2), 1.61-1.55 (m, 2H, CH_2), 1.31-1.24 (m, 10H, CH_2), 0.89 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 151.8 (C_q), 149.8 (CH), 141.9 (C_q), 138.4 (CH), 137.4 (C_q), 128.8 (C_q), 122.1 (CH), 121.7 (CH), 121.3 (CH), 120.7 (CH), 120.0 (CH), 110.2 (CH), 102.2 (CH), 32.0 (CH_2), 29.5 (2C, CH_2), 29.3 (CH_2), 28.7 (CH_2), 27.6 (CH_2), 22.8 (CH_2), 14.3 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{21}H_{26}N_2$+H^+ $[M+H]^+$ 307.2169; Found 307.2172.

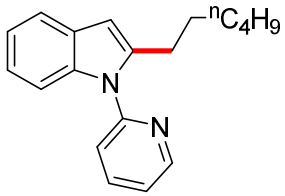


2-Butyl-1-(pyridin-2-yl)-1*H*-indole (5ab): The representative procedure was followed, using substrate **3a** (0.058 g, 0.3 mmol) and 1-iodobutane (**4b**; 0.110 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) yielded **5ab** as a light yellow liquid. Yield: 0.069 g, 92%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.67 (d, J = 3.4 Hz, 1H, Ar–H), 7.89 (t, J = 7.3 Hz, 1H, Ar–H), 7.57 (d, J = 4.9 Hz, 1H, Ar–H), 7.44 (d, J = 7.8 Hz, 1H, Ar–H), 7.34-7.30 (m, 2H, Ar–H), 7.14-7.11 (m, 2H, Ar–H), 6.46 (s, 1H, Ar–H), 2.85 (t, J = 7.3 Hz, 2H, CH_2), 1.59 (pent, J = 7.3 Hz, 2H, CH_2), 1.38-1.31 (m, 2H, CH_2), 0.87 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 151.8 (C_q), 149.8 (CH), 141.9 (C_q), 138.4 (CH), 137.4 (C_q), 128.8 (C_q), 122.2 (CH), 121.7 (CH), 121.3 (CH), 120.7 (CH), 120.0 (CH), 110.2 (CH), 102.2 (CH), 30.9 (CH_2), 27.3 (CH_2), 22.6 (CH_2), 14.0 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{17}H_{18}N_2$+H^+ $[M+H]^+$ 251.1543; Found 251.1545. The ^{1}H and ^{13}C spectra are consistent with those reported in the literature.[47]

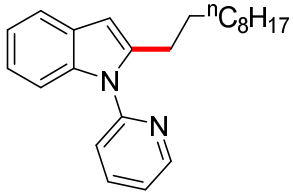


2-Pentyl-1-(pyridin-2-yl)-1*H*-indole (5ac): The representative procedure was followed, using substrate **3a** (0.058 g, 0.3 mmol) and 1-iodopentane (**4c**; 0.119 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) yielded **5ac** as a light yellow liquid. Yield: 0.049 g, 62%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.67 (dd, J = 4.9, 1.1 Hz, 1H, Ar–H), 7.88 (td, J = 7.8, 1.9 Hz, 1H, Ar–H), 7.61-7.56 (m, 1H, Ar–H), 7.44 (dt, J = 7.9, 0.9 Hz, 1H, Ar–H), 7.36-7.29 (m, 2H, Ar–H), 7.18-7.08 (m, 2H, Ar–H), 6.46 (s, 1H, Ar–H), 2.85 (t, J = 7.6 Hz, 2H, CH_2), 1.65-1.51 (m, 2H, CH_2), 1.33-1.24 (m, 4H, CH_2), 0.85 (t, J = 6.8 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 151.8 (C_q), 149.8 (CH), 142.0 (C_q), 138.4 (CH), 137.5 (C_q), 128.8 (C_q), 122.2 (CH), 121.7 (CH), 121.3 (CH), 120.7 (CH), 120.0 (CH), 110.2 (CH), 102.2 (CH), 31.7 (CH_2), 28.4 (CH_2), 27.6 (CH_2), 22.5 (CH_2), 14.1 (CH_3). HRMS

(ESI): *m/z* Calcd for $C_{18}H_{20}N_2+H^+$ $[M+H]^+$ 265.1699; Found 265.1701. The ^1H and ^{13}C spectra are consistent with those reported in the literature.[47]

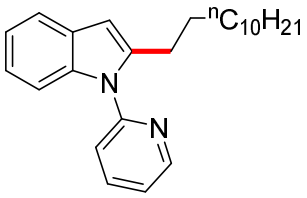


2-Hexyl-1-(pyridin-2-yl)-1*H*-indole (5ad): The representative procedure was followed, using substrate **3a** (0.058 g, 0.3 mmol), 1-bromohexane (**4d**; 0.099 g, 0.6 mmol) and KI (0.1 g, 0.6 mmol), and the reaction mixture was stirred for 20 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) yielded **5ad** as a light yellow liquid. Yield: 0.065 g, 78%. ^1H-NMR (500 MHz, $CDCl_3$): δ = 8.68 (d, J = 4.2 Hz, 1H, Ar–H), 7.89 (vt, J = 7.6 Hz, 1H, Ar–H), 7.60-7.59 (m, 1H, Ar–H), 7.44 (d, J = 8.0 Hz, 1H, Ar–H), 7.35-7.31 (m, 2H, Ar–H), 7.16-7.12 (m, 2H, Ar–H), 6.47 (s, 1H, Ar–H), 2.86 (t, J = 7.6 Hz, 2H, CH_2), 1.58 (app. pent, J = 7.3 Hz, 2H, CH_2), 1.35-1.22 (m, 6H, CH_2), 0.87 (t, J = 6.3 Hz, 3H, CH_3). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 151.8 (C_q), 149.8 (CH), 141.9 (C_q), 138.4 (CH), 137.4 (C_q), 128.8 (C_q), 122.2 (CH), 121.7 (CH), 121.3 (CH), 120.7 (CH), 120.0 (CH), 110.2 (CH), 102.2 (CH), 31.7 (CH_2), 29.2 (CH_2), 28.7 (CH_2), 27.6 (CH_2), 22.7 (CH_2), 14.2 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{19}H_{22}N_2+H^+$ $[M+H]^+$ 279.1856; Found 279.1856. The ^1H and ^{13}C spectra are consistent with those reported in the literature.[48]

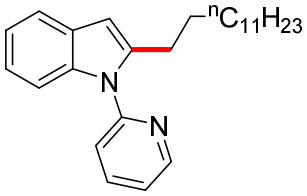


2-Decyl-1-(pyridin-2-yl)-1*H*-indole (5ae): The representative procedure was followed, using substrate **3a** (0.058 g, 0.3 mmol), 1-bromodecane (**4e**; 0.133 g, 0.6 mmol) and KI (0.1 g, 0.6 mmol), and the reaction mixture was stirred for 20 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) yielded **5ae** as a light yellow liquid. Yield: 0.072 g, 72%. ^1H-NMR (500 MHz, $CDCl_3$): δ = 8.68 (dd, J = 4.9, 1.2 Hz, 1H, Ar–H), 7.88 (td, J = 7.3, 1.8 Hz, 1H, Ar–H), 7.62-7.58 (m, 1H, Ar–H), 7.44 (d, J = 7.9 Hz, 1H, Ar–H), 7.36-7.31 (m, 2H, Ar–H), 7.16-7.14 (m, 2H, Ar–H), 6.48 (s, 1H, Ar–H), 2.86 (t, J = 7.6 Hz, 2H, CH_2), 1.62-1.56 (m, 2H, CH_2), 1.33-1.26 (m, 14H, CH_2), 0.92 (t, J = 6.7 Hz, 3H, CH_3). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 151.7 (C_q), 149.8 (CH),

141.9 (C_q), 138.4 (CH), 137.4 (C_q), 128.8 (C_q), 122.1 (CH), 121.6 (CH), 121.3 (CH), 120.7 (CH), 120.0 (CH), 110.2 (CH), 102.2 (CH), 32.0 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (2C, CH_2), 29.4 (CH_2), 28.7 (CH_2), 27.6 (CH_2), 22.8 (CH_2), 14.3 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{23}H_{30}N_2+H^+$ $[M+H]^+$ 335.2482; Found 335.2486.

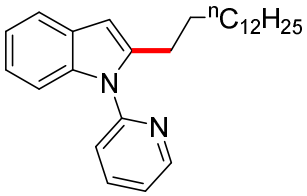


2-Dodecyl-1-(pyridin-2-yl)-1*H*-indole (5af): The representative procedure was followed, using substrate **3a** (0.058 g, 0.3 mmol) and 1-iodododecane (**4f**; 0.178 g, 0.6 mmol), and the reaction mixture was stirred for 20 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) yielded **5af** as a light yellow liquid. Yield: 0.093 g, 86%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.67 (dd, *J* = 4.6, 0.9 Hz, 1H, Ar–H), 7.89 (td, *J* = 7.6, 1.8 Hz, 1H, Ar–H), 7.60-7.58 (m, 1H, Ar–H), 7.44 (d, *J* = 7.9 Hz, 1H, Ar–H), 7.35-7.31 (m, 2H, Ar–H), 7.16-7.12 (m, 2H, Ar–H), 6.46 (s, 1H, Ar–H), 2.85 (t, *J* = 7.6 Hz, 2H, CH_2), 1.60-1.54 (m, 2H, CH_2), 1.31-1.24 (m, 18H, CH_2), 0.91 (t, *J* = 7.0 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 151.8 (C_q), 149.8 (CH), 141.9 (C_q), 138.4 (CH), 137.4 (C_q), 128.8 (C_q), 122.2 (CH), 121.7 (CH), 121.3 (CH), 120.7 (CH), 120.0 (CH), 110.2 (CH), 102.2 (CH), 32.1 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (2C, CH_2), 29.5 (CH_2), 28.7 (CH_2), 27.6 (CH_2), 22.9 (CH_2), 14.3 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{25}H_{34}N_2+H^+$ $[M+H]^+$ 363.2795; Found 363.2798.

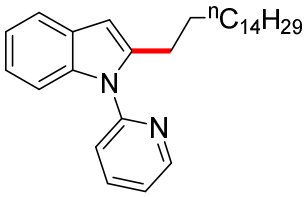


1-(Pyridin-2-yl)-2-tridecyl-1*H*-indole (5ag): The representative procedure was followed, using substrate **3a** (0.058 g, 0.3 mmol), 1-bromotridecane (**4g**; 0.16 g, 0.6 mmol) and KI (0.1 g, 0.6 mmol), and the reaction mixture was stirred for 20 h. Purification by column chromatography on neutral alumina (petroleum ether/Et_3N: 50/1/0.5) yielded **5ag** as a light yellow liquid. Yield: 0.079 g, 70%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.68 (dd, *J* = 4.9, 1.8 Hz, 1H, Ar–H), 7.88 (td, *J* = 7.6, 1.8 Hz, 1H, Ar–H), 7.60-7.59 (m, 1H, Ar–H), 7.44 (d, *J*

= 7.9 Hz, 1H, Ar–H), 7.35-7.31 (m, 2H, Ar–H), 7.16-7.12 (m, 2H, Ar–H), 6.47 (s, 1H, Ar–H), 2.85 (t, J = 7.9 Hz, 2H, CH_2), 1.61-1.55 (m, 2H, CH_2), 1.34-1.22 (m, 20H, CH_2), 0.91 (t, J = 6.7 Hz, 3H, CH_3). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 151.8 (C_q), 149.8 (CH), 141.9 (C_q), 138.4 (CH), 137.4 (C_q), 128.8 (C_q), 122.1 (CH), 121.7 (CH), 121.3 (CH), 120.7 (CH), 120.0 (CH), 110.2 (CH), 102.2 (CH), 32.1 (CH_2), 29.9 (CH_2), 29.8 (2C, CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 28.7 (CH_2), 27.6 (CH_2), 22.9 (CH_2), 14.3 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{26}H_{36}N_2$+H^+ $[M+H]^+$ 377.2951; Found 377.2947.

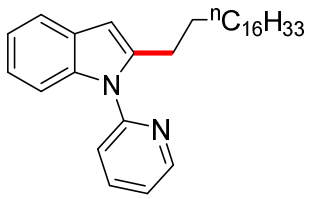


1-(Pyridin-2-yl)-2-tetradecyl-1*H*-indole (5ah): The representative procedure was followed, using substrate **3a** (0.058 g, 0.3 mmol), 1-bromotetradecane (**4h**; 0.166 g, 0.6 mmol) and KI (0.1 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) yielded **5ah** as a light yellow liquid. Yield: 0.101 g, 86%. ^1H-NMR (500 MHz, $CDCl_3$): δ = 8.68 (dd, J = 4.6, 0.9 Hz, 1H, Ar–H), 7.88 (td, J = 7.9, 1.8 Hz, 1H, Ar–H), 7.60-7.58 (m, 1H, Ar–H), 7.44 (d, J = 7.9 Hz, 1H, Ar–H), 7.34-7.31 (m, 2H, Ar–H), 7.16-7.12 (m, 2H, Ar–H), 6.47 (s, 1H, Ar–H), 2.85 (t, J = 6.7 Hz, 2H, CH_2), 1.61-1.54 (m, 2H, CH_2), 1.35-1.21 (m, 22H, CH_2), 0.91 (t, J = 7.0 Hz, 3H, CH_3). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 151.8 (C_q), 149.8 (CH), 141.9 (C_q), 138.4 (CH), 137.4 (C_q), 128.8 (C_q), 122.2 (CH), 121.7 (CH), 121.3 (CH), 120.7 (CH), 120.0 (CH), 110.2 (CH), 102.2 (CH), 32.1 (CH_2), 29.8 (4C, CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 28.7 (CH_2), 27.6 (CH_2), 22.9 (CH_2), 14.3 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{27}H_{38}N_2$+H^+ $[M+H]^+$ 391.3108; Found 391.3116.

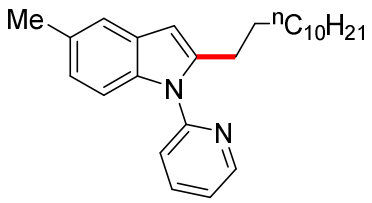


2-Hexadecyl-1-(pyridin-2-yl)-1*H*-indole (5ai): The representative procedure was followed, using substrate **3a** (0.058 g, 0.3 mmol), 1-bromohexadecane (**4i**; 0.183 g, 0.6 mmol) and KI (0.1 g, 0.6 mmol), and the reaction mixture was stirred for 20 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5)

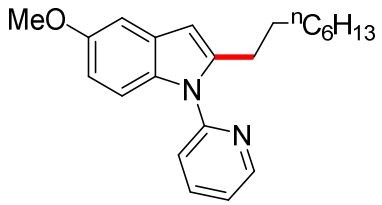
yielded **5ai** as a light yellow liquid. Yield: 0.075 g, 60%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.67 (dd, *J* = 4.9, 1.2 Hz, 1H, Ar–H), 7.88 (td, *J* = 7.9, 1.8 Hz, 1H, Ar–H), 7.60-7.58 (m, 1H, Ar–H), 7.44 (d, *J* = 7.9 Hz, 1H, Ar–H), 7.35-7.31 (m, 2H, Ar–H), 7.16-7.12 (m, 2H, Ar–H), 6.46 (s, 1H, Ar–H), 2.85 (t, *J* = 7.6 Hz, 2H, CH_2), 1.60-1.54 (m, 2H, CH_2), 1.34-1.24 (m, 26H, CH_2), 0.91 (t, *J* = 6.9 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 151.8 (C_q), 149.8 (CH), 141.9 (C_q), 138.4 (CH), 137.4 (C_q), 128.8 (C_q), 122.1 (CH), 121.7 (CH), 121.3 (CH), 120.7 (CH), 120.0 (CH), 110.2 (CH), 102.2 (CH), 32.1 (CH_2), 29.9 (4C, CH_2), 29.8 (2C, CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 28.7 (CH_2), 27.6 (CH_2), 22.9 (CH_2), 14.3 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{29}H_{42}N_2$+H^+ $[M+H]^+$ 419.3421; Found 419.3424.



2-Octadecyl-1-(pyridin-2-yl)-1*H*-indole (5aj): The representative procedure was followed, using substrate **3a** (0.058 g, 0.3 mmol), 1-bromooctadecane (**4j**; 0.20 g, 0.6 mmol) and KI (0.1 g, 0.6 mmol), and the reaction mixture was stirred for 20 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) yielded **5aj** as a light yellow solid. Yield: 0.075 g, 56%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.68 (dd, *J* = 5.0, 1.8 Hz, 1H, Ar–H), 7.92-7.87 (m, 1H, Ar–H), 7.61-7.57 (m, 1H, Ar–H), 7.44 (d, *J* = 8.2 Hz, 1H, Ar–H), 7.35-7.32 (m, 2H, Ar–H), 7.15-7.12 (m, 2H, Ar–H), 6.46 (s, 1H, Ar–H), 2.85 (t, *J* = 7.3 Hz, 2H, CH_2), 1.60-1.58 (m, 2H, CH_2), 1.36-1.24 (m, 30H, CH_2), 0.91 (t, *J* = 6.4 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 151.8 (C_q), 149.8 (CH), 142.0 (C_q), 138.4 (CH), 137.4 (C_q), 128.8 (C_q), 122.2 (CH), 121.7 (CH), 121.3 (CH), 120.7 (CH), 120.0 (CH), 110.2 (CH), 102.2 (CH), 32.1 (CH_2), 29.9 (8C, CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (2C, CH_2), 29.5 (CH_2), 28.8 (CH_2), 27.6 (CH_2), 22.9 (CH_2), 14.3 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{31}H_{46}N_2$+H^+ $[M+H]^+$ 447.3734; Found 447.3730.

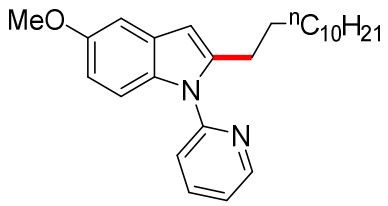


2-Dodecyl-5-methyl-1-(pyridin-2-yl)-1*H*-indole (5bf): The representative procedure was followed using, 5-methyl-1-(pyridine-2-yl)-1*H*-indole (**3b**; 0.062 g, 0.3 mmol) and iodide **4f** (0.178 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 20/1/0.5) yielded **5bf** as a light yellow liquid. Yield: 0.105 g, 93%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.67 (dd, J = 5.0, 1.5 Hz, 1H, Ar–H), 7.87 (td, J =7.6, 1.9 Hz, 1H, Ar–H), 7.42 (d, J = 8.0 Hz, 1H, Ar–H), 7.37 (s, 1H, Ar–H), 7.31-29 (m, 1H, Ar–H), 7.24 (d, J = 8.4 Hz, 1H, Ar–H), 6.96 (dd, J = 8.3, 1.1 Hz, 1H, Ar–H), 6.38 (s, 1H, Ar–H), 2.84 (t, J = 7.6 Hz, 2H, CH_2), 2.45 (s, 3H, CH_3), 1.59-1.53 (m, 2H, CH_2), 1.34-1.23 (m, 18H, CH_2), 0.91 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): 152.0 (C_q), 149.7 (CH), 142.0 (C_q), 138.3 (CH), 135.8 (C_q), 129.9 (C_q), 129.1 (C_q), 123.1 (CH), 121.9 (CH), 121.1 (CH), 119.8 (CH), 109.9 (CH), 101.9 (CH), 32.1 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (2C, CH_2), 29.5 (CH_2), 28.8 (CH_2), 27.7 (CH_2), 22.9 (CH_2), 21.5 (CH_3), 14.3 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{26}H_{36}N_2$+H^+ $[M+H]^+$ 377.2946; Found 377.2951.

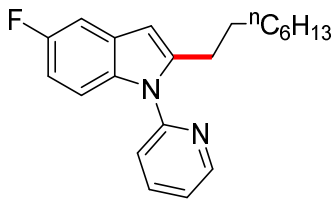


5-Methoxy-2-octyl-1-(pyridin-2-yl)-1*H*-indole (5ca): The representative procedure was followed, using 5-methoxy-1-(pyridine-2-yl)-1*H*-indole (**3c**; 0.067 g, 0.3 mmol) and iodide **4a** (0.144 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 10/1/0.5) yielded **5ca** as a light yellow liquid. Yield: 0.053 g, 53%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.63 (dd, J = 4.4, 1.0 Hz, 1H, Ar–H), 7.85 (td, J = 7.8, 1.8 Hz, 1H, Ar–H), 7.38 (d, J = 8.3 Hz, 1H, Ar–H), 7.29-26 (m, 1H, Ar–H), 7.22 (d, J = 8.8 Hz, 1H, Ar–H), 7.04 (d, J = 2.5 Hz, 1H, Ar–H), 6.76 (dd, J = 8.8, 2.5 Hz, 1H, Ar–H), 6.36 (s, 1H, Ar–H), 3.84 (s, 3H, CH_3), 2.81 (t, J = 7.3 Hz, 2H, CH_2), 1.58-1.50 (m, 2H, CH_2), 1.31-1.21 (m, 10H, CH_2), 0.86 (t, J = 6.6 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): 154.9 (C_q), 151.9 (C_q), 149.7 (CH), 142.6 (C_q), 138.4 (CH), 132.6 (C_q), 129.4 (C_q), 121.9 (CH), 121.0 (CH), 111.2 (CH), 111.0 (CH), 102.3

(CH), 102.1 (CH), 56.0 (CH_3), 32.0 (CH_2), 29.5 (2C, CH_2), 29.3 (CH_2), 28.8 (CH_2), 27.7 (CH_2), 22.8 (CH_2), 14.3 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{22}H_{28}N_2O+H^+$ $[M+H]^+$ 337.2274; Found 337.2273. The ^1H and ^{13}C spectra are consistent with those reported in the literature.[48]

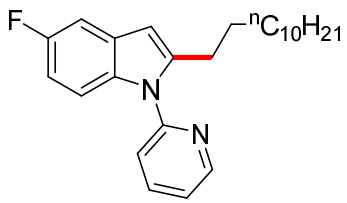


2-Dodecyl-5-methoxy-1-(pyridin-2-yl)-1*H*-indole (5cf): The representative procedure was followed using, substrate **3c** (0.067 g, 0.3 mmol) and iodide **4f** (0.178 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 20/1/0.5) yielded **5cf** as a light yellow liquid. Yield: 0.072 g, 61%. ^1H-NMR (500 MHz, $CDCl_3$): δ = 8.64 (dd, *J* = 5.0, 1.1 Hz, 1H, Ar–H), 7.84 (td, *J* = 8.0, 1.9 Hz, 1H, Ar–H), 7.38 (d, *J* = 7.6 Hz, 1H, Ar–H), 7.29-7.26 (m, 1H, Ar–H), 7.23 (d, *J* = 9.2 Hz, 1H, Ar–H), 7.04 (d, *J* = 2.3 Hz, 1H, Ar–H), 6.76 (dd, *J* = 9.2, 2.7 Hz, 1H, Ar–H), 6.37 (s, 1H, Ar–H), 3.84 (s, 3H, CH_3), 2.82 (t, *J* = 7.6 Hz, 2H, CH_2), 1.57-1.52 (m, 2H, CH_2), 1.30-1.22 (m, 18H, CH_2), 0.88 (t, *J* = 6.9 Hz, 3H, CH_3). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): 154.9 (C_q), 151.9 (C_q), 149.7 (CH), 142.5 (C_q), 138.3 (CH), 132.5 (C_q), 129.4 (C_q), 121.9 (CH), 121.0 (CH), 111.1 (CH), 111.0 (CH), 102.3 (CH), 102.1 (CH), 56.0 (CH_3), 32.1 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.5 (2C, CH_2), 29.5 (CH_2), 28.8 (CH_2), 27.7 (CH_2), 22.8 (CH_2), 14.3 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{26}H_{36}N_2O+H^+$ $[M+H]^+$ 393.2900; Found 393.2898.

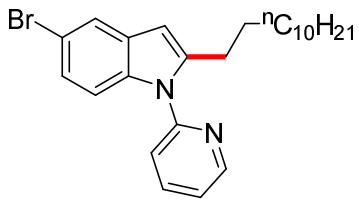


5-Fluoro-2-octyl-1-(pyridin-2-yl)-1*H*-indole (5da): The representative procedure was followed, using 5-fluoro-1-(pyridin-2-yl)-1H-indole (**3d**; 0.064 g, 0.3 mmol) and iodide **4a** (0.144 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) yielded **5da** as a light yellow liquid. Yield: 0.052 g, 53%. ^1H-NMR (400 MHz, $CDCl_3$): δ = 8.70 (d, *J* = 4.3

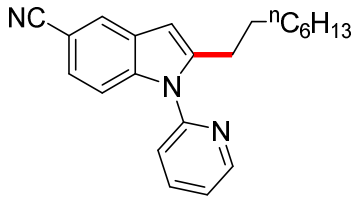
Hz, 1H, Ar–H), 7.93 (t, J = 7.3 Hz, 1H, Ar–H), 7.43 (d, J = 7.9 Hz, 1H, Ar–H), 7.37 (dd, J = 5.5, 4.9 Hz, 1H, Ar–H), 7.28-7.23 (m, 2H, Ar–H), 6.89 (td, J = 9.2, 2.4 Hz, 1H, Ar–H), 6.44 (s, 1H, Ar–H), 2.84 (t, J = 7.9 Hz, 2H, CH_2), 1.64-1.56 (m, 2H, CH_2), 1.35-1.27 (m, 10H, CH_2), 0.91 (t, J = 6.7 Hz, 3H, CH_3). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 158.6 (d, J_{C-F} = 235.0 Hz, C_q), 151.6 (C_q), 149.9 (CH), 143.6 (C_q), 138.5 (CH), 134.0 (C_q), 129.3 (d, J_{C-F} = 10.0 Hz, C_q), 122.4 (CH), 121.2 (CH), 110.9 (d, J_{C-F} = 10.0 Hz, CH), 109.6 (d, J_{C-F} = 26.2 Hz, CH), 105.0 (d, J_{C-F} = 23.9 Hz, CH), 102.1 (d, J_{C-F} = 4.6 Hz, CH), 32.0 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.7 (CH_2), 27.7 (CH_2), 22.8 (CH_2), 14.3 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = –124.2 (s). HRMS (ESI): *m/z* Calcd for $C_{21}H_{25}N_2F+H^+$ $[M+H]^+$ 325.2075; Found 325.2077.



2-Dodecyl-5-fluoro-1-(pyridin-2-yl)-1*H*-indole (5df): The representative procedure was followed using, substrate **3d** (0.042 g, 0.2 mmol) and iodide **4f** (0.118 g, 0.4 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) yielded **5df** as a light yellow liquid. Yield: 0.033 g, 43%. ^1H-NMR (400 MHz, $CDCl_3$): δ = 8.67 (d, J = 4.4 Hz, 1H, Ar–H), 7.89 (t, J = 7.3 Hz, 1H, Ar–H), 7.39 (d, J = 7.8 Hz, 1H, Ar–H), 7.33 (dd, J = 7.3, 5.4 Hz, 1H, Ar–H), 7.24-7.19 (m, 2H, Ar–H), 6.84 (td, J = 9.3, 2.5 Hz, 1H, Ar–H), 6.40 (s, 1H, Ar–H), 2.80 (t, J = 7.3 Hz, 2H, CH_2), 1.59-1.52 (m, 2H, CH_2), 1.32-1.19 (m, 18H, CH_2), 0.89 (t, J = 6.6 Hz, 3H, CH_3). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): 158.6 (d, J_{C-F} = 235 Hz, C_q), 151.6 (C_q), 149.9 (CH), 143.6 (C_q), 138.5 (CH), 134.0 (C_q), 129.2 (d, J_{C-F} = 10.0 Hz, C_q), 122.4 (CH), 121.2 (CH), 111.0 (d, J_{C-F} = 9.3 Hz, CH), 109.5 (d, J_{C-F} = 25.4 Hz, CH), 105.0 (d, J_{C-F} = 23.1 Hz, CH), 102.2 (d, J_{C-F} = 3.9 Hz, CH), 32.1 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 28.7 (CH_2), 27.7 (CH_2), 22.9 (CH_2), 14.3 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = –124.2 (s). HRMS (ESI): *m/z* Calcd for $C_{25}H_{33}N_2F+H^+$ $[M+H]^+$ 381.2701; Found 381.2695.

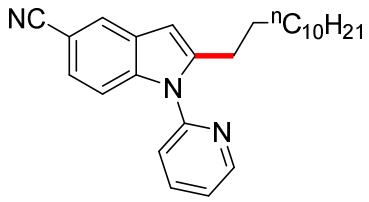


5-Bromo-2-dodecyl-1-(pyridin-2-yl)-1*H*-indole (5ef): The representative procedure was followed using, 5-bromo-1-(pyridine-2-yl)-1*H*-indole (**3e**; 0.082 g, 0.3 mmol) and iodide **4f** (0.178 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 20/1/0.5) yielded **5ef** as a light yellow liquid. Yield: 0.074 g, 56%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.66 (dd, J = 5.0, 1.1 Hz, 1H, Ar–H), 7.91-7.86 (m, 2H, Ar–H), 7.38-7.34 (m, 3H, Ar–H), 7.08 (d, J = 8.4 Hz, 1H, Ar–H), 6.36 (s, 1H, Ar–H), 2.79 (t, J = 7.6 Hz, 2H, CH_2), 1.57-1.51 (m, 2H, CH_2), 1.31-1.18 (m, 18H, CH_2), 0.88 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): 151.2 (C_q), 149.9 (CH), 142.9 (C_q), 138.6 (CH), 136.6 (C_q), 131.3 (C_q), 129.9 (CH), 128.7 (CH), 122.5 (CH), 121.3 (CH), 112.2 (CH), 101.3 (CH), 84.2 (C_q), 32.1 (CH_2), 29.8 (2C, CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 28.6 (CH_2), 27.5 (CH_2), 22.9 (CH_2), 14.3 (CH_3). LC-MS: *m/z* (%): 441 (100) $[M+H]^+$, 443 (100) $[M+H]^+$. HRMS (ESI): *m/z* Calcd for $C_{25}H_{33}N_2Br^+$ $[M]^+$ 440.1822, 442.1807; Found 440.1845, 442.1843.

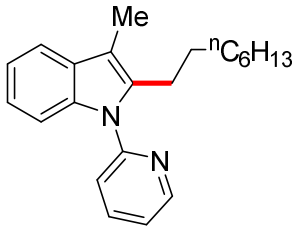


2-Octyl-1-(pyridin-2-yl)-1*H*-indole-5-carbonitrile (5fa): The representative procedure was followed using, 1-(pyridin-2-yl)-1*H*-indole-5-carbonitrile (**3f**; 0.066 g, 0.3 mmol) and iodide **4a** (0.144 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 20/1/0.5) yielded **5fa** as a light yellow liquid. Yield: 0.038 g, 38%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.69 (dd, J = 4.4, 1.0 Hz, 1H, Ar–H), 7.95 (td, J = 7.8, 2.0 Hz, 1H, Ar–H), 7.90 (s, 1H, Ar–H), 7.43-7.39 (m, 2H, Ar–H), 7.36-7.29 (m, 2H, Ar–H), 6.50 (s, 1H, Ar–H), 2.78 (t, J = 7.3 Hz, 2H, CH_2), 1.56 (pent, J = 7.3 Hz, 2H, CH_2), 1.30-1.22 (m, 10H, CH_2), 0.86 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): 150.7 (CN), 150.2 (CH), 144.6 (C_q), 139.1 (C_q), 138.8 (CH), 128.6 (C_q), 125.3 (CH), 124.9 (CH), 123.2 (CH), 121.6 (CH), 120.9 (C_q), 111.1 (CH), 103.7 (C_q), 102.4 (CH), 32.0 (CH_2), 29.4 (2C, CH_2), 29.3 (CH_2), 28.5

(CH_2), 27.5 (CH_2), 22.8 (CH_2), 14.3 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{22}H_{25}N_3$+H^+ $[M+H]^+$ 332.2121; Found 332.2119.

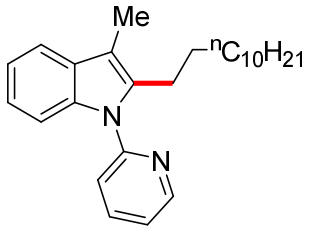


2-Dodecyl-1-(pyridin-2-yl)-1*H*-indole-5-carbonitrile (5ff): The representative procedure was followed using, substrate **3f** (0.066 g, 0.3 mmol) and iodide **4f** (0.178 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 20/1/0.5) yielded **5ff** as a light yellow liquid. Yield: 0.052 g, 45%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.69 (d, J = 4.2 Hz, 1H, Ar–H), 7.94 (td, J = 7.6, 1.5 Hz, 1H, Ar–H), 7.89 (s, 1H, Ar–H), 7.42-7.38 (m, 2H, Ar–H), 7.34-7.29 (m, 2H, Ar–H), 6.49 (s, 1H, Ar–H), 2.78 (t, J = 7.6 Hz, 2H, CH_2), 1.56 (pent, J = 7.4 Hz, 2H, CH_2), 1.34-1.22 (m, 18H, CH_2), 0.88 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): 150.7 (CN), 150.1 (CH), 144.6 (C_q), 139.1 (C_q), 138.8 (CH), 128.6 (C_q), 125.2 (CH), 124.8 (CH), 123.2 (CH), 121.5 (CH), 120.9 (C_q), 111.1 (CH), 103.7 (C_q), 102.3 (CH), 32.1 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 28.5 (CH_2), 27.5 (CH_2), 22.8 (CH_2), 14.3 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{26}H_{33}N_3$+H^+ $[M+H]^+$ 388.2747; Found 388.2744.

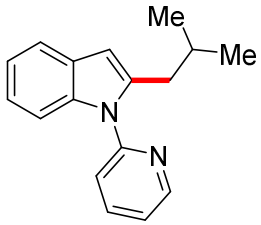


3-Methyl-2-octyl-1-(pyridin-2-yl)-1*H*-indole (5ga): The representative procedure was followed, using 3-methyl-1-(pyridine-2-yl)-1*H*-indole (**3g**) (0.062 g, 0.3 mmol) and iodide **4a** (0.144 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) yielded **5ga** as a light yellow liquid. Yield: 0.044 g, 46%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.67 (d, J = 3.9 Hz, 1H, Ar–H), 7.90 (t, J = 7.7 Hz, 1H, Ar–H), 7.55 (d, J = 6.8 Hz, 1H, Ar–H), 7.44 (d, J = 7.8 Hz, 1H, Ar–H), 7.33-7.29 (m, 2H, Ar–H), 7.18-7.12 (m, 2H, Ar–H), 2.91 (t, J = 7.8 Hz, 2H, CH_2), 2.33 (s, 3H, CH_3), 1.35-1.17 (m, 12H), 0.87 (t, J = 6.8 Hz, 3H, CH_3). ^{13}C{^{1}H}-

NMR (100 MHz, $CDCl_3$): δ = 152.1 (C_q), 149.7 (CH), 138.3 (CH), 137.5 (2C, C_q), 136.7 (C_q), 129.7 (C_q), 121.8 (CH), 121.8 (CH), 121.2 (CH), 120.2 (CH), 118.3 (CH), 109.9 (CH), 32.0 (CH_2), 29.6 (CH_2), 29.3 (2C, CH_2), 29.3 (CH_2), 24.9 (CH_2), 22.8 (CH_2), 14.3 (CH_3), 9.0 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{22}H_{28}N_2+H^+$ $[M+H]^+$ 321.2325; Found 321.2323. The ^1H and ^{13}C spectra are consistent with those reported in the literature.[48]

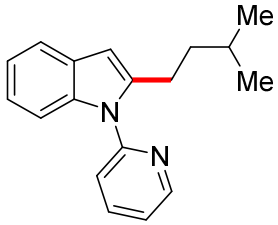


2-Dodecyl-3-methyl-1-(pyridin-2-yl)-1*H*-indole (5gf): The representative procedure was followed, using substrate **3g** (0.062g, 0.3 mmol) and iodide **4f** (0.178 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1) yielded **5gf** as a light yellow liquid. Yield: 0.043 g, 38%. ^1H-NMR (400 MHz, $CDCl_3$): δ = 8.66 (d, *J* = 3.4 Hz, 1H, Ar–H), 7.88 (td, *J* = 7.8, 1.5 Hz, 1H, Ar–H), 7.55 (d, *J* = 6.9 Hz, 1H, Ar–H), 7.43 (d, *J* = 7.8 Hz, 1H, Ar–H), 7.33-7.29 (m, 2H, Ar–H), 7.18-7.12 (m, 2H, Ar–H), 2.91 (t, *J* = 7.6 Hz, 2H, CH_2), 2.33 (s, 3H, CH_3), 1.34-1.16 (m, 20H, CH_2), 0.90 (t, *J* = 6.6 Hz, 3H, CH_3). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): 152.2 (C_q), 149.8 (CH), 138.3 (CH), 137.5 (2C, C_q), 136.7 (C_q), 129.7 (C_q), 121.8 (CH), 121.8 (CH), 121.2 (CH), 120.2 (CH), 118.3 (CH), 109.9 (CH), 32.1 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.8 (CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 24.9 (CH_2), 22.9 (CH_2), 14.3 (CH_3), 9.0 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{26}H_{36}N_2+H^+$ $[M+H]^+$ 377.2938; Found 377.2951.

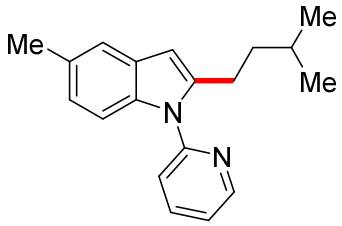


2-Isobutyl-1-(pyridin-2-yl)-1*H*-indole (5ak): The representative procedure was followed, using substrate **3a** (0.058 g, 0.3 mmol), 1-bromo-2-methylpropane (**4k**; 0.082 g, 0.6 mmol) and KI (0.1 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) yielded **5ak** as a light yellow liquid. Yield: 0.060 g, 80%. ^1H-NMR (400 MHz, $CDCl_3$): δ =

8.68 (d, J = 4.4 Hz, 1H, Ar–H), 7.89 (t, J = 7.8 Hz, 1H, Ar–H), 7.61-7.59 (m, 1H, Ar–H), 7.43 (d, J = 8.3 Hz, 1H, Ar–H), 7.35-7.31 (m, 2H, Ar–H), 7.17-7.12 (m, 2H, Ar–H), 6.47 (s, 1H, Ar–H), 2.77 (d, J = 6.8 Hz, 2H, CH_2), 1.73 (sept, J = 6.8 Hz, 1H, CH), 0.88 (d, J = 6.4 Hz, 6H, CH_3). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 151.8 (C_q), 149.8 (CH), 140.7 (C_q), 138.4 (CH), 137.5 (C_q), 128.8 (C_q), 122.2 (CH), 121.7 (CH), 121.4 (CH), 120.7 (CH), 120.0 (CH), 110.2 (CH), 103.4 (CH), 36.7 (CH_2), 28.2 (CH), 22.7 (2C, CH_3). HRMS (ESI): *m/z* Calcd for $C_{17}H_{18}N_2+H^+$ $[M+H]^+$ 251.1543; Found 251.1545.

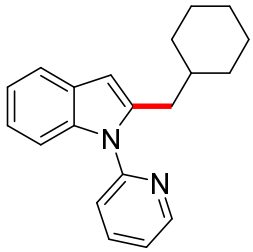


2-Isopentyl-1-(pyridin-2-yl)-1*H*-indole (5al): The representative procedure was followed, using substrate **3a** (0.058 g, 0.3 mmol), 1-bromo-3-methylbutane (**4l**; 0.090 g, 0.6 mmol) and KI (0.1 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) yielded **5al** as a light yellow liquid. Yield: 0.070 g, 88%. ^1H-NMR (500 MHz, $CDCl_3$): δ = 8.68 (dd, J = 4.9, 1.8 Hz, 1H, Ar–H), 7.89 (td, J = 7.9, 2.1 Hz, 1H, Ar–H), 7.60-7.59 (m, 1H, Ar–H), 7.45 (d, J = 7.9 Hz, 1H, Ar–H), 7.35-7.32 (m, 2H, Ar–H), 7.16-7.12 (m, 2H, Ar–H), 6.47 (s, 1H, Ar–H), 2.87 (t, J = 7.9 Hz, 2H, CH_2), 1.57 (sept, J = 6.4 Hz, 1H, CH), 1.49-1.43 (m, 2H, CH_2), 0.86 (d, J = 6.4 Hz, 6H, CH_3). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 151.7 (C_q), 149.8 (CH), 142.1 (C_q), 138.4 (CH), 137.4 (C_q), 128.8 (C_q), 122.2 (CH), 121.7 (CH), 121.3 (CH), 120.7 (CH), 120.0 (CH), 110.2 (CH), 102.2 (CH), 37.9 (CH_2), 27.8 (CH), 25.5 (CH_2), 22.6 (2C, CH_3). HRMS (ESI): *m/z* Calcd for $C_{18}H_{20}N_2+H^+$ $[M+H]^+$ 265.1699; Found 265.1701.

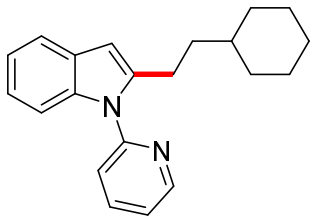


2-Isopentyl-5-methyl-1-(pyridin-2-yl)-1*H*-indole (5bl): The representative procedure was followed, using substrate **3b** (0.062 g, 0.3 mmol), bromide **4l** (0.090 g, 0.6 mmol) and KI (0.1 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column

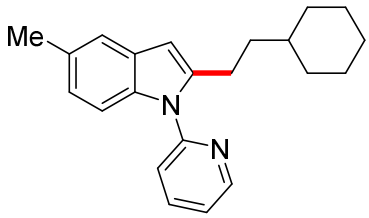
chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) yielded **5bl** as a light yellow liquid. Yield: 0.064 g, 77%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.67 (dd, *J* = 5.0, 1.1 Hz, 1H, Ar–H), 7.87 (td, *J* = 8.0, 1.9 Hz, 1H, Ar–H), 7.43 (d, *J* = 8.0 Hz, 1H, Ar–H), 7.37 (s, 1H, Ar–H), 7.32-7.30 (m, 1H, Ar–H), 7.24 (d, *J* = 8.4 Hz, 1H, Ar–H), 6.96 (d, *J* = 8.4 Hz, 1H, Ar–H), 6.38 (s, 1H, Ar–H), 2.87 (t, *J* = 7.8 Hz, 2H, CH_2), 2.46 (s, 3H, CH_3), 1.56 (sept, *J* = 6.5 Hz, 1H, CH), 1.47-1.42 (m, 2H, CH_2), 0.85 (d, *J* = 6.5 Hz, 6H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 151.9 (C_q), 149.7 (CH), 142.1 (C_q), 138.3 (CH), 135.7 (C_q), 129.9 (C_q), 129.1 (C_q), 123.1 (CH), 121.9 (CH), 121.1 (CH), 119.8 (CH), 109.9 (CH), 101.9 (CH), 38.0 (CH_2), 27.8 (CH), 25.6 (CH_2), 22.6 (2C, CH_3), 21.6 (CH_3) . HRMS (ESI): *m/z* Calcd for $C_{19}H_{22}N_2$+H^+ $[M+H]^+$ 279.1856; Found 279.1856.



2-(Cyclohexylmethyl)-1-(pyridin-2-yl)-1*H*-indole (5am): The representative procedure was followed, using substrate **3a** (0.058 g, 0.3 mmol), (bromomethyl)cyclohexane (**4m**; 0.106 g, 0.6 mmol) and KI (0.1 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 40/1/0.5) yielded **5am** as a light yellow liquid. Yield: 0.074 g, 85%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.68 (dd, *J* = 5.0, 2.3 Hz, 1H, Ar–H), 7.88 (td, *J* = 8.2, 1.8 Hz, 1H, Ar–H), 7.61-7.57 (m, 1H, Ar–H), 7.42 (d, *J* = 8.7 Hz, 1H, Ar–H), 7.34-7.31 (m, 2H, Ar–H), 7.17-7.11 (m, 2H, Ar–H), 6.45 (s, 1H, Ar–H), 2.77 (d, *J* = 6.9 Hz, 2H, CH_2), 1.68-1.61 (m, 5H, CH_2), 1.45-1.33 (m, 1H, CH), 1.17-1.06 (m, 3H, CH_2), 0.91-0.82 (m, 2H, CH_2). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 151.9 (C_q), 149.8 (CH), 140.4 (C_q), 138.4 (CH), 137.5 (C_q), 128.8 (C_q), 122.2 (CH), 121.6 (CH), 121.5 (CH), 120.7 (CH), 119.9 (CH), 110.2 (CH), 103.4 (CH), 37.8 (CH), 35.2 (CH_2), 33.4 (2C, CH_2), 26.6 (CH_2), 22.3 (2C, CH_2). HRMS (ESI): *m/z* Calcd for $C_{20}H_{22}N_2$+H^+ $[M+H]^+$ 291.1856; Found 291.1857.

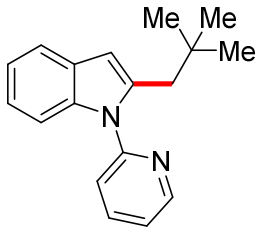


2-(2-Cyclohexylethyl)-1-(pyridin-2-yl)-1*H*-indole (5an): The representative procedure was followed, using substrate **3a** (0.058 g, 0.3 mmol), (2-bromoethyl)cyclohexane (**4n**; 0.115 g, 0.6 mmol) and KI (0.1 g, 0.6 mmol), and the reaction mixture was stirred for 24 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 40/1/0.5) yielded **5an** as a light yellow liquid. Yield: 0.061 g, 67%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.67 (dd, J = 4.6, 1.1 Hz, 1H, Ar–H), 7.89 (td, J = 7.6, 1.9 Hz, 1H, Ar–H), 7.60-7.56 (m, 1H, Ar–H), 7.44 (d, J = 8.0 Hz, 1H, Ar–H), 7.35-7.31 (m, 2H, Ar–H), 7.15-7.11 (m, 2H, Ar–H), 6.45 (s, 1H, Ar–H), 2.86 (t, J = 8.0 Hz, 2H, CH_2), 1.69-1.59 (m, 5H, CH_2), 1.48-1.44 (m, 2H, CH_2), 1.25-1.08 (m, 4H, CH_2), 0.90-0.80 (m, 2H, CH_2). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 151.8 (C_q), 149.8 (CH), 142.2 (C_q), 138.4 (CH), 137.4 (C_q), 128.8 (C_q), 122.2 (CH), 121.7 (CH), 121.3 (CH), 120.7 (CH), 120.0 (CH), 110.2 (CH), 102.1 (CH), 37.4 (CH), 36.5 (CH_2), 33.3 (2C, CH_2), 26.8 (CH_2), 26.4 (2C, CH_2), 25.0 (CH_2). HRMS (ESI): *m/z* Calcd for $C_{21}H_{24}N_2$+H^+ $[M+H]^+$ 305.2012; Found 305.2014.

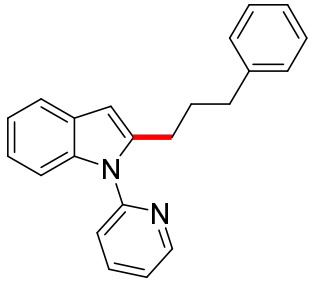


2-(2-Cyclohexylethyl)-5-methyl-1-(pyridin-2-yl)-1*H*-indole (5bn): The representative procedure was followed, using substrate **3b** (0.062 g, 0.3 mmol), bromide **4n** (0.115 g, 0.6 mmol) and KI (0.1 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 40/1/0.5) yielded **5bn** as a light yellow liquid. Yield: 0.067 g, 70%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.66 (dd, J = 4.6, 1.1 Hz, 1H, Ar–H), 7.87 (td, J = 8.0, 1.9 Hz, 1H, Ar–H), 7.42 (d, J = 8.0 Hz, 1H, Ar–H), 7.36 (s, 1H, Ar–H), 7.31-7.29 (m, 1H, Ar–H), 7.22 (d, J = 8.4 Hz, 1H, Ar–H), 6.94 (d, J = 8.4 Hz, 1H, Ar–H), 6.36 (s, 1H, Ar–H), 2.85 (t, J = 7.6 Hz, 2H, CH_2), 2.44 (s, 3H, CH_3), 1.67-1.59 (m, 5H, CH_2), 1.47-1.41 (m, 2H, CH_2), 1.26-1.10 (m, 4H, CH_2), 0.89-0.80 (m, 2H, CH_2). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 152.0 (C_q), 149.7 (CH), 142.3 (C_q), 138.3 (CH), 135.8 (C_q), 129.9 (C_q), 129.1 (C_q), 123.1 (CH), 121.9 (CH), 121.1

(CH), 119.8 (CH), 109.9 (CH), 101.8 (CH), 37.4 (CH), 36.6 (CH_2), 33.4 (2C, CH_2), 26.8 (CH_2), 26.4 (2C, CH_2), 25.1 (CH_2), 21.6 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{22}H_{26}N_2$+H^+ $[M+H]^+$ 319.2169; Found 319.2168.

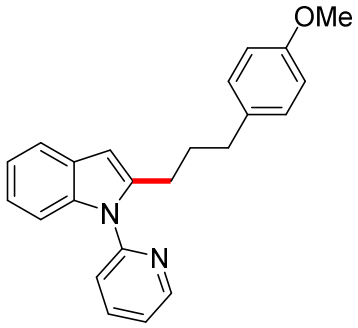


2-Neopentyl-1-(pyridin-2-yl)-1*H*-indole (5ao): The representative procedure was followed, using substrate **3a** (0.058 g, 0.3 mmol), 1-bromo-2,2-dimethylpropane (**4o**; 0.09 g, 0.6 mmol), KI (0.1 g, 0.6 mmol) and the reaction mixture was stirred for 24 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) yielded **5ao** as a light yellow liquid. Yield: 0.041 g, 52%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.68 (dd, *J* = 4.6, 1.8 Hz, 1H, Ar–H), 7.89 (t, *J* = 7.8 Hz, 1H, Ar–H), 7.62-7.59 (m, 1H, Ar–H), 7.41 (d, *J* = 7.8 Hz, 1H, Ar–H), 7.34-7.30 (m, 2H, Ar–H), 7.17-7.10 (m, 2H, Ar–H), 6.49 (s, 1H, Ar–H), 2.91 (s, 2H, CH_2), 0.76 (s, 9H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 152.2 (C_q), 149.7 (CH), 139.1 (C_q), 138.3 (CH), 137.5 (C_q), 128.6 (C_q), 122.4 (CH), 121.2 (CH), 121.7 (CH), 120.7 (CH), 120.0 (CH), 110.3 (CH), 105.3 (CH), 40.1 (CH_2), 32.4 (C_q), 29.6 (3C, CH_3). HRMS (ESI): *m/z* Calcd for $C_{18}H_{20}N_2$+H^+ $[M+H]^+$ 265.1699; Found 265.1700.

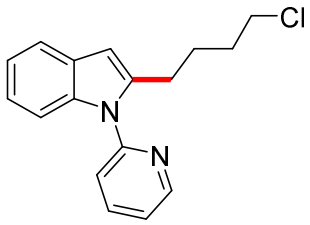


2-(3-Phenylpropyl)-1-(pyridin-2-yl)-1*H*-indole (5ap): The representative procedure was followed, using substrate **3a** (0.058 g, 0.3 mmol), (3-bromopropyl)benzene (**4p**; 0.119 g, 0.6 mmol) and KI (0.1 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 20/1/0.5) yielded **5ap** as a light yellow liquid. Yield: 0.070 g, 75%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.66 (dd, *J* = 4.6, 1.1 Hz, 1H, Ar–H), 7.87 (td, *J* = 7.6, 1.9 Hz, 1H, Ar–H), 7.63-7.62 (m, 1H, Ar–H), 7.42 (d, *J* = 8.0 Hz, 1H, Ar–H), 7.38-7.36 (m, 1H, Ar–H), 7.33-7.27 (m,

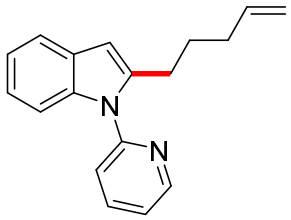
3H, Ar–H), 7.22-7.13 (m, 5H, Ar–H), 6.52 (s, 1H, Ar–H), 2.94 (t, J = 7.6 Hz, 2H, CH_2), 2.66 (t, J = 7.6 Hz, 2H, CH_2), 1.93 (pent, J = 7.6 Hz, 2H, CH_2). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 151.6 (C_q), 149.8 (CH), 142.1 (C_q), 141.3 (C_q), 138.4 (CH), 137.4 (C_q), 128.8 (C_q), 128.6 (2C, CH), 128.4 (2C, CH), 125.9 (CH), 122.2 (CH), 121.8 (CH), 121.2 (CH), 120.8 (CH), 120.1 (CH), 110.2 (CH), 102.5 (CH), 35.5 (CH_2), 30.5 (CH_2), 27.2 (CH_2). HRMS (ESI): *m/z* Calcd for $C_{22}H_{20}N_2+H^+$ $[M+H]^+$ 313.1699; Found 313.1700. The ^1H and ^{13}C spectra are consistent with those reported in the literature.[48]



2-(3-(4-Methoxyphenyl)propyl)-1-(pyridin-2-yl)-1*H*-indole (5aq): The representative procedure was followed, using substrate **3a** (0.058 g, 0.3 mmol), 1-(3-bromopropyl)-4-methoxybenzene (**4q**; 0.137 g, 0.6 mmol) and KI (0.1 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 5/1/0.5) yielded **5aq** as a light yellow liquid. Yield: 0.070 g, 68%. ^1H-NMR (500 MHz, $CDCl_3$): δ = 8.66 (d, J = 4.6 Hz, 1H, Ar–H), 7.86 (td, J = 7.3, 1.0 Hz, 1H, Ar–H), 7.63-7.61 (m, 1H, Ar–H), 7.42 (d, J = 7.9 Hz, 1H, Ar–H), 7.38-7.35 (m, 1H, Ar–H), 7.33-7.30 (m, 1H, Ar–H), 7.19-7.15 (m, 2H, Ar–H), 7.05 (d, J = 8.3 Hz, 2H, Ar–H), 6.83 (d, J = 8.3 Hz, 2H, Ar–H), 6.51 (s, 1H, Ar–H), 3.81 (s, 3H, CH_3), 2.92 (t, J = 7.6 Hz, 2H, CH_2), 2.60 (t, J = 7.6 Hz, 2H, CH_2), 1.89 (pent, J = 7.6 Hz, 2H, CH_2). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 157.8 (C_q), 151.6 (C_q), 149.7 (CH), 141.3 (C_q), 138.4 (CH), 137.4 (C_q), 134.2 (C_q), 129.4 (2C, CH), 128.7 (C_q), 122.1 (CH), 121.7 (CH), 121.2 (CH), 120.7 (CH), 120.0 (CH), 113.8 (2C, CH), 110.2 (CH), 102.5 (CH), 55.4 (OCH_3), 34.6 (CH), 30.7 (CH_2), 27.1 (CH_2). HRMS (ESI): *m/z* Calcd for $C_{23}H_{22}N_2O+H^+$ $[M+H]^+$ 343.1805; Found 343.1805.

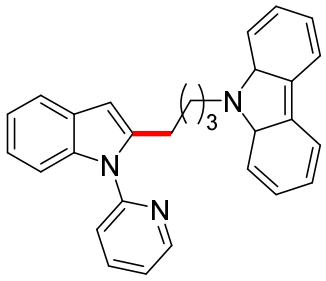


2-(4-Chlorobutyl)-1-(pyridin-2-yl)-1*H*-indole (5ar): The representative procedure was followed, using substrate **3a** (0.058 g, 0.3 mmol), 1-chloro-4-iodobutane (**4r**; 0.14 g, 0.6 mmol) and KI (0.1 g, 0.6 mmol), and the reaction mixture was stirred for 24 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) yielded **5ar** as a light yellow liquid. Yield: 0.047 g, 52%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.55 (dd, J = 5.0, 2.3 Hz, 1H, Ar–H), 8.16 (d, J = 8.7 Hz, 1H, Ar–H), 7.85 (d, J = 8.2 Hz, 1H, Ar–H), 7.79 (td, J = 7.8, 1.8 Hz, 1H, Ar–H), 7.50-7.48 (m, 2H, Ar–H), 7.30-7.27 (m, 1H, Ar–H), 7.19 (t, J = 7.8 Hz, 1H, Ar–H), 7.14-7.11 (m, 1H, Ar–H), 1.51 (s, 8H, CH_2). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 152.7 (C_q), 149.2 (CH), 138.4 (CH), 136.4 (C_q), 129.3 (C_q), 129.0 (C_q), 122.8 (CH), 121.8 (CH), 121.5 (CH), 120.5 (CH), 119.8 (CH), 114.9 (CH), 113.0 (CH), 31.9 (CH_2), 30.7 (2C, CH_2), 29.9 (CH_2). LC-MS: *m/z* (%): 251.1 (100) $[(M+2H)–Cl]^+$. HRMS (ESI): *m/z* Calcd for $[(C_{17}H_{17}ClN_2+2H)–Cl]^+$ $[(M+2H)–Cl]^+$ 251.1543; Found 251.1542.

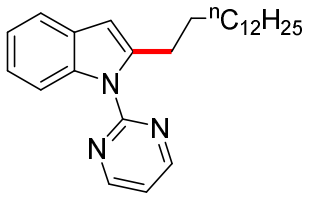


2-(Pent-4-en-1-yl)-1-(pyridin-2-yl)-1*H*-indole (5as): The representative procedure was followed, using substrate **3a** (0.058 g, 0.3 mmol), 5-bromopent-1-ene (**4s**; 0.089 g, 0.6 mmol) and KI (0.1 g, 0.6 mmol), and the reaction mixture was stirred for 20 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) yielded **5as** as a light yellow liquid. Yield: 0.037 g, 47%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.67 (dd, J = 5.0, 0.9 Hz, 1H, Ar–H), 7.89 (td, J = 7.8, 1.8 Hz, 1H, Ar–H), 7.59-7.55 (m, 1H, Ar–H), 7.43 (d, J = 8.2 Hz, 1H, Ar–H), 7.34-7.31 (m, 2H, Ar–H), 7.15-7.11 (m, 2H, Ar–H), 6.46 (s, 1H, Ar–H), 5.79-5.69 (m, 1H, CH), 4.99-4.92 (m, 2H, CH_2), 2.86 (t, J = 7.3 Hz, 2H, CH_2), 2.10-2.04 (m, 2H, CH_2), 1.70-1.65 (m, 2H, CH_2). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 151.7 (C_q), 149.8 (CH), 141.5 (C_q), 138.5 (CH), 138.4 (CH), 137.4 (C_q), 128.8 (C_q), 122.2 (CH), 121.8 (CH), 121.3 (CH), 120.8 (CH), 120.1 (CH), 115.0 (CH_2), 110.2 (CH), 102.4

(CH), 33.4 (CH_2), 28.0 (CH_2), 27.0 (CH_2). HRMS (ESI): *m/z* Calcd for $C_{18}H_{18}N_2+H^+$ $[M+H]^+$ 263.1543; Found 263.1542.

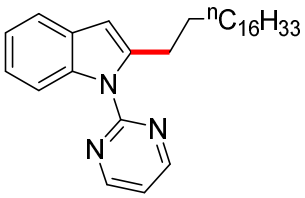


9-(4-(1-(Pyridin-2-yl)-1H-indol-2-yl)butyl)-9*H*-carbazole (5at): The representative procedure was followed, using substrate **3a** (0.058 g, 0.3 mmol) and 9-(4-iodobutyl)-8a,9a-dihydro-9*H*-carbazole (**4t**; 0.21 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 10/1/0.5) yielded **5at** as an off white liquid. Yield: 0.071 g, 57%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.57 (d, *J* = 4.6 Hz, 1H, Ar–H), 8.13 (d, *J* = 7.6 Hz, 2H, Ar–H), 7.76 (vt, *J* = 8.0 Hz, 1H, Ar–H), 7.59 (d, *J* = 6.9 Hz, 1H, Ar–H), 7.46 (vt, *J* = 7.6 Hz, 2H, Ar–H), 7.35 (d, *J* = 8.4 Hz, 2H, Ar–H), 7.32-7.22 (m, 5H, Ar–H), 7.18-7.13 (m, 2H, Ar–H), 6.41 (s, 1H, Ar–H), 4.28 (t, *J* = 6.9 Hz, 2H, CH_2), 2.91 (t, *J* = 7.4 Hz, 2H, CH_2), 1.92 (pent, *J* = 7.6 Hz, 2H, CH_2), 1.61 (pent, *J* = 7.6 Hz, 2H, CH_2). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 151.5 (C_q), 149.7 (CH), 140.9 (C_q), 140.5 (2C, C_q), 138.4 (CH), 137.4 (C_q), 128.7 (C_q), 125.8 (2C, CH), 123.0 (2C, C_q), 122.1 (CH), 121.9 (CH), 121.0 (CH), 120.8 (CH), 120.5 (2C, CH), 120.1 (CH), 118.9 (2C, CH), 110.2 (CH), 108.8 (2C, CH), 102.6 (CH), 42.9 (CH_2), 28.8 (CH_2), 27.4 (CH_2), 26.4 (CH_2). HRMS (ESI): *m/z* Calcd for $C_{29}H_{25}N_3+H^+$ $[M+H]^+$ 416.2121; Found 416.2120.

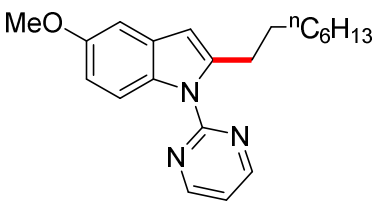


1-(Pyrimidin-2-yl)-2-tetradecyl-1*H*-indole (5hh): The representative procedure was followed, using 1-(pyrimidin-2-yl)-1*H*-indole (**3h**; 0.039 g, 0.2 mmol), bromide **4h** (0.111 g, 0.4 mmol) and KI (0.067 g, 0.4 mmol), and the reaction mixture was stirred for 24 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) yielded **5hh** as a light yellow liquid. Yield: 0.044 g, 56%. ^{1}H-NMR (500 MHz,

$CDCl_3$): δ = 8.80 (d, J = 5.0 Hz, 2H, Ar–H), 8.21 (d, J = 8.0 Hz, 1H, Ar–H), 7.53 (d, J = 7.2 Hz, 1H, Ar–H), 7.22-7.14 (m, 3H, Ar–H), 6.47 (s, 1H, Ar–H), 3.15 (t, J = 7.8 Hz, 2H, CH_2), 1.61 (pent, J = 7.6 Hz, 2H, CH_2), 1.39-1.33 (m, 2H, CH_2), 1.31-1.22 (m, 20H, CH_2), 0.88 (t, J = 6.9 Hz, 3H, CH_3). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): 158.5 (C_q), 158.3 (2C, CH), 142.6 (C_q), 137.1 (C_q), 129.6 (C_q), 122.5 (CH), 121.9 (CH), 119.8 (CH), 117.2 (CH), 113.7 (CH), 105.6 (CH), 32.1 (CH_2), 29.9 (3C, CH_2), 29.8 (2C, CH_2), 29.8 (CH_2), 29.7 (2C, CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 22.9 (CH_2), 14.3 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{26}H_{37}N_3+H^+$ $[M+H]^+$ 392.3060; Found 392.3053.

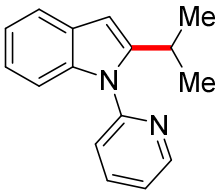


2-Octadecyl-1-(pyrimidin-2-yl)-1*H*-indole (5hj): The representative procedure was followed, using substrate **3h** (0.059 g, 0.3 mmol), bromide **4j** (0.20 g, 0.6 mmol) and KI (0.1 g, 0.6 mmol), and the reaction mixture was stirred for 24 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 40/1/0.5) yielded **5hj** as a light yellow liquid. Yield: 0.075 g, 56%. ^1H-NMR (500 MHz, $CDCl_3$): δ = 8.80 (d, J = 4.6 Hz, 2H, Ar–H), 8.22 (d, J = 7.9 Hz, 1H, Ar–H), 7.54 (dd, J = 7.0, 1.2 Hz, 1H, Ar–H), 7.23-7.16 (m, 2H, Ar–H), 7.14 (t, J = 4.6 Hz, 1H, Ar–H), 6.48 (s, 1H, Ar–H), 3.16 (t, J = 7.6 Hz, 2H, CH_2), 1.65-1.59 (m, 2H, CH_2), 1.40-1.35 (m, 2H, CH_2), 1.32-1.20 (m, 28H, CH_2), 0.90 (t, J = 6.9 Hz, 3H, CH_3). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 158.5 (C_q), 158.3 (2C, CH), 142.6 (C_q), 137.1 (C_q), 129.5 (C_q), 122.5 (CH), 121.8 (CH), 119.8 (CH), 117.2 (CH), 113.7 (CH), 105.6 (CH), 32.1 (CH_2), 29.9 (7C, CH_2), 29.8 (2C, CH_2), 29.8 (CH_2), 29.6 (2C, CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.2 (CH_2), 22.9 (CH_2), 14.3 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{30}H_{45}N_3+H^+$ $[M+H]^+$ 448.3686; Found 448.3672.

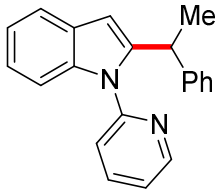


5-Methoxy-2-octyl-1-(pyrimidine-2-yl)-1*H*-indole (5ia): The representative procedure was followed, using 5-methoxy-1-(pyrimidin-2-yl)-1*H*-indole (**3i**; 0.044 g, 0.2 mmol) and

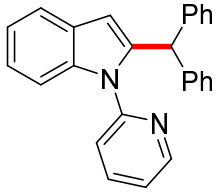
iodide **4a** (0.096 g, 0.4 mmol), and the reaction mixture was stirred for 16 h. Column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) afforded the mixture of **3i** and **5ia**. ^{1}H NMR yield of **5ia**: 61%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.76 (d, J = 5.0 Hz, 2H, Ar–H), 8.19 (d, J = 8.8 Hz, 1H, Ar–H), 7.10 (t, J = 4.6 Hz, 1H, Ar–H), 7.01 (d, J = 2.3 Hz, 1H, Ar–H), 6.85 (dd, 1H, J = 9.2, 2.1 Hz, Ar–H), 6.40 (s, 1H, Ar–H), 3.87 (s, 3H, CH_3), 3.16 (t, J = 7.6 Hz, 2H, CH_2), 1.63 (pent, J = 7.6 Hz, 2H, CH_2), 1.39-1.27 (m, 10H, CH_2), 0.89 (t, J = 6.6 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): 158.5 (C_q), 158.2 (2C, CH), 155.5 (C_q), 143.4 (C_q), 132.0 (C_q), 130.3 (C_q), 116.9 (CH), 115.0 (CH), 111.3 (CH), 105.7 (CH), 102.3 (CH), 55.9 (CH_3), 32.0 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 22.9 (CH_2), 14.3 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{21}H_{27}N_3O+H^+$ $[M+H]^+$ 338.2227; Found 338.2221.



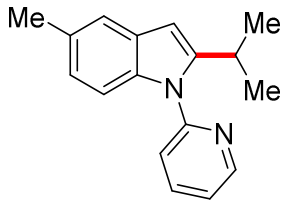
2-Isopropyl-1-(pyridin-2-yl)-1*H*-indole (7aa): The representative procedure was followed using, substrate **3a** (0.058 g, 0.3 mmol) and 2-iodopropane (**6a**; 0.101 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1) yielded **7aa** as a light yellow liquid. Yield: 0.052 g, 73%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.69 (dd, J = 5.0, 1.1 Hz, 1H, Ar–H), 7.91 (td, J = 7.6, 1.9 Hz, 1H, Ar–H), 7.64-7.60 (m, 1H, Ar–H), 7.47 (d, J = 8.0 Hz, 1H, Ar–H), 7.35 (dd, J = 7.3, 5.0 Hz, 1H, Ar–H), 7.30-7.27 (m, 1H, Ar–H), 7.17-7.13 (m, 2H, Ar–H), 6.51 (s, 1H, Ar–H), 3.44 (sept, J = 6.9 Hz, 1H, CH), 1.23 (d, J = 6.9 Hz, 6H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): 151.8 (C_q), 149.9 (CH), 148.3 (C_q), 138.5 (CH), 137.6 (C_q), 128.6 (C_q), 122.3 (CH), 121.7 (CH), 121.6 (CH), 120.6 (CH), 120.1 (CH), 110.0 (CH), 99.6 (CH), 25.9 (CH), 22.6 (2C, CH_3). HRMS (ESI): *m/z* Calcd for $C_{16}H_{16}N_2+H^+$ $[M+H]^+$ 237.1386; Found 237.1386.



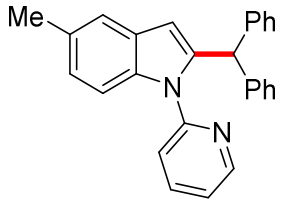
2-(1-Phenylethyl)-1-(pyridin-2-yl)-1*H*-indole (7ab): The representative procedure was followed, using substrate **3a** (0.058 g, 0.3 mmol), (1-bromoethyl)benzene (**6b**; 0.11 g, 0.6 mmol) and KI (0.1 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) yielded **7ab** as a light yellow liquid. Yield: 0.067 g, 75%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.57 (d, J = 3.8 Hz, 1H, Ar–H), 8.16 (d, J = 8.4 Hz, 1H, Ar–H), 7.79 (td, J = 8.4, 1.9 Hz, 1H, Ar–H), 7.62 (s, 1H, Ar–H), 7.50 (d, J = 8.4 Hz, 1H, Ar–H), 7.39-7.34 (m, 3H, Ar–H), 7.31-7.28 (m, 2H, Ar–H), 7.25-7.24 (m, 1H, Ar–H), 7.20 (t, J = 7.3 Hz, 1H, Ar–H), 7.13 (dd, J = 5.3, 1.5 Hz, 1H, Ar–H), 7.09 (t, J = 7.6 Hz, 1H, Ar–H), 4.40 (q, J = 7.3 Hz, 1H, CH), 1.76 (d, J = 7.3 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 152.7 (C_q), 149.1 (CH), 146.4 (C_q), 138.5 (CH), 135.9 (C_q), 129.9 (C_q), 128.6 (2C, CH), 127.7 (2C, CH), 126.3 (CH), 124.2 (C_q), 123.3 (CH), 123.1 (CH), 121.0 (CH), 120.2 (CH), 119.8 (CH), 114.5 (CH), 113.0 (CH), 37.1 (CH), 22.5 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{21}H_{18}N_2$+H^+ $[M+H]^+$ 299.1543; Found 299.1541.



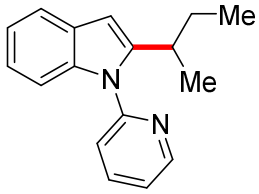
2-Benzhydryl-1-(pyridin-2-yl)-1*H*-indole (7ac): The representative procedure was followed using, substrate **3a** (0.058 g, 0.3 mmol), (bromoethylene)dibenzene (**6c**; 0.148 g, 0.6 mmol) and KI (0.1 g 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) yielded **7ac** as a pale yellow solid. Yield: 0.081 g, 75%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.65 (d, J = 3.4 Hz, 1H, Ar–H), 8.37 (d, J = 8.3 Hz, 1H, Ar–H), 7.87-7.83 (m, 1H, Ar–H), 7.49-7.36 (m, 14H, Ar–H), 7.25-7.21 (m, 2H, Ar–H), 5.86 (s, 1H, CH). ^{13}C{^{1}H}-NMR(125 MHz, $CDCl_3$): 152.6 (C_q), 149.0 (CH), 143.5 (2C, C_q), 138.4 (CH), 136.0 (C_q), 129.8 (C_q), 129.2 (4C, CH), 128.6 (4C, CH), 126.6 (2C, CH), 125.8 (CH), 123.5 (CH), 122.8 (C_q), 121.2 (CH), 120.4 (CH), 119.9 (CH), 114.6 (CH), 113.3 (CH), 48.9 (CH). HRMS (ESI): *m/z* Calcd for $C_{26}H_{20}N_2$+H^+ $[M+H]^+$ 361.1701; Found 361.1699.



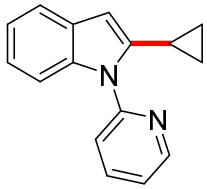
2-Isopropyl-5-methyl-1-(pyridin-2-yl)-1*H*-indole (7ba): The representative procedure was followed, using substrate **3b** (0.042 g, 0.2 mmol) and iodide **6a** (0.067 g, 0.4 mmol), and the reaction mixture was stirred for 24 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) yielded **7ba** as a light yellow liquid. Yield: 0.041 g, 82%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.66 (dd, J = 4.6, 1.0 Hz, 1H, Ar–H), 7.89 (td, J = 7.6, 1.5 Hz, 1H, Ar–H), 7.44 (d, J = 8.0 Hz, 1H, Ar–H), 7.37 (s, 1H, Ar–H), 7.32 (dd, J = 6.9, 5.3 Hz, 1H, Ar–H), 7.16 (d, J = 8.4 Hz, 1H, Ar–H), 6.93 (d, J = 8.4 Hz, 1H, Ar–H), 6.39 (s, 1H, Ar–H) 3.41 (sept, J = 6.9 Hz, 1H, CH), 2.4.3 (s, 3H, CH_3), 1.18 (d, J = 6.9 Hz, 6H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): 152.1 (C_q), 149.8 (CH), 148.4 (C_q), 138.4 (CH), 136.0 (C_q), 129.9 (C_q), 128.9 (C_q), 123.2 (CH), 122.1 (CH), 121.5 (CH), 120.0 (CH), 109.7 (CH), 99.4 (CH), 26.0 (CH), 22.7 (2C, CH_3), 21.6 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{17}H_{18}N_2$+H^+ $[M+H]^+$ 251.1546; Found 251.1543.



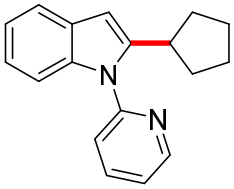
2-Benzhydryl-5-methyl-1-(pyridin-2-yl)-1*H*-indole (7bc): The representative procedure was followed using, substrate **3b** (0.042 g, 0.2 mmol), bromide **6c** (0.098 g, 0.4 mmol) and KI (0.066 g 0.4 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) yielded **7bc** as a pale yellow solid. Yield: 0.063 g, 84%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.49 (d, J = 5.0 Hz, 1H, Ar–H), 8.09 (d, J = 8.4 Hz, 1H, Ar–H), 7.71 (td, J = 7.3, 1.9 Hz, 1H, Ar–H), 7.34-7.21 (m, 11H, Ar–H), 7.09-7.05 (m, 4H, Ar–H), 5.67 (s, 1H, CH), 2.34 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): 152.7 (C_q), 149.0 (CH), 143.6 (2C, C_q), 138.4 (CH), 134.3 (C_q), 130.5 (C_q), 130.1 (C_q), 129.2 (4C, CH), 128.5 (4C, CH), 126.5 (2C, CH), 125.8 (CH), 125.0 (CH), 122.4 (C_q), 119.9 (CH), 119.7 (CH), 114.3 (CH), 113.0 (CH), 48.8 (CH), 21.6 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{27}H_{22}N_2$+H^+ $[M+H]^+$ 375.1861; Found 375.1856.



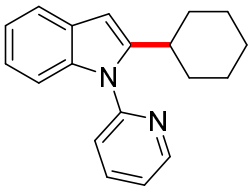
2-(Sec-butyl)-1-(pyridin-2-yl)-1*H*-indole (7ad): The representative procedure was followed, using substrate **3a** (0.058 g, 0.3 mmol) and 2-iodobutane (**6d**; 0.11 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) yielded **7ad** as a light yellow liquid. Yield: 0.038 g, 51%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.67 (dd, J = 5.0, 0.9 Hz, 1H, Ar–H), 7.91-7.86 (m, 1H, Ar–H), 7.61-7.57 (m, 1H, Ar–H), 7.42 (d, J = 7.3 Hz, 1H, Ar–H), 7.35-7.31 (m, 1H, Ar–H), 7.26-7.24 (m, 1H, Ar–H), 7.14-7.08 (m, 2H, Ar–H), 6.46 (s, 1H, Ar–H), 3.12 (app. sextet, J = 6.9 Hz, 1H, CH), 1.73-1.62 (m, 1H, CH_2), 1.50-1.37 (m, 1H, CH_2), 1.24 (d, J = 6.9 Hz, 3H, CH_3), 0.82 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 151.9 (C_q), 149.9 (CH), 147.3 (C_q), 138.4 (CH), 137.6 (C_q), 128.7 (C_q), 122.4 (CH), 121.9 (CH), 121.6 (CH), 120.7 (CH), 120.1 (CH), 110.2 (CH), 100.1 (CH), 32.5 (CH), 29.9 (CH_2), 20.2 (CH_3), 11.8 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{17}H_{18}N_2$+H^+ $[M+H]^+$ 251.1543; Found 251.1546.



2-Cyclopropyl-1-(pyridin-2-yl)-1*H*-indole (7ae): The representative procedure was followed, using substrate **3a** (0.058 g, 0.3 mmol) and bromocyclopropane (**6e**; 0.073 g, 0.6 mmol) and KI (0.1 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 40/1/0.5) afforded the mixture of **3a** and **7ae**. ^{1}H NMR yield of **7ae**: 64%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.70 (d, J = 4.6 Hz, 1H, Ar–H), 7.88 (td, J = 8.0, 1.9 Hz, 1H, Ar–H), 7.57-7.53 (m, 2H, Ar–H), 7.47 (d, J = 6.9 Hz, 1H, Ar–H), 7.33-7.30 (m, 1H, Ar–H), 7.18-7.12 (m, 2H, Ar–H), 6.29 (s, 1H, Ar–H), 2.08-2.00 (m, 1H, CH), 0.91-0.88 (m, 2H, CH_2), 0.81-0.78 (m, 2H, CH_2). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 151.9 (C_q), 149.6 (CH), 143.4 (C_q), 138.2 (CH), 137.4 (C_q), 128.6 (C_q), 121.9 (CH), 121.9 (CH), 121.2 (CH), 120.9 (CH), 120.1 (CH), 110.7 (CH), 100.0 (CH), 8.8 (CH), 8.4 (2C, CH_2). HRMS (ESI): *m/z* Calcd for $C_{16}H_{14}N_2$+H^+ $[M+H]^+$ 235.1230; Found 235.1227. The ^{1}H and ^{13}C spectra are consistent with those reported in the literature.[47]

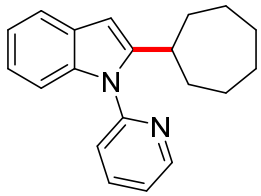


2-Cyclopentyl-1-(pyridin-2-yl)-1*H*-indole (7af): The representative procedure was followed, using substrate **3a** (0.058 g, 0.3 mmol) and iodocyclopentane (**6f**; 0.118 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) yielded **7af** as a light yellow liquid. Yield: 0.038 g, 48%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.67 (dd, J = 4.6, 0.9 Hz, 1H, Ar–H), 7.89 (td, J = 7.9, 1.8 Hz, 1H, Ar–H), 7.59-7.57 (m, 1H, Ar–H), 7.44 (d, J = 7.9 Hz, 1H, Ar–H), 7.35-7.33 (m, 1H, Ar–H), 7.25-7.23 (m, 1H, Ar–H), 7.14-7.09 (m, 2H, Ar–H), 6.48 (s, 1H, Ar–H), 3.43 (pent, J = 7.9 Hz, 1H, CH), 1.88-1.81 (m, 2H, CH_2), 1.77-1.70 (m, 2H, CH_2), 1.67-1.60 (m, 2H, CH_2), 1.59-1.53 (m, 2H, CH_2). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 152.1 (C_q), 149.9 (CH), 146.4 (C_q), 138.5 (CH), 137.8 (C_q), 128.6 (C_q), 122.3 (CH), 121.8 (CH), 121.7 (CH), 120.6 (CH), 120.1 (CH), 110.0 (CH), 99.8 (CH), 37.6 (CH), 33.1 (2C, CH_2), 25.4 (2C, CH_2). HRMS (ESI): *m/z* Calcd for $C_{18}H_{18}N_2$+H^+ $[M+H]^+$ 263.1543; Found 263.1545. The ^{1}H and ^{13}C spectra are consistent with those reported in the literature.[47]

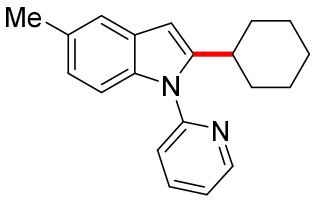


2-Cyclohexyl-1-(pyridin-2-yl)-1*H*-indole (7ag): The representative procedure was followed, using substrate **3a** (0.058 g, 0.3 mmol), bromocyclohexane (**6g**; 0.098 g, 0.6 mmol) and KI (0.1 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) yielded **7ag** as a light yellow liquid. Yield: 0.063 g, 76%. ^{1}H-NMR (500 MHz, ($CDCl_3$): δ = 8.68 (dd, J = 4.9, 1.2 Hz, 1H, Ar–H), 7.90 (td, J = 7.9, 2.1 Hz, 1H, Ar–H), 7.61-7.58 (m, 1H, Ar–H), 7.44 (d, J = 7.9 Hz, 1H, Ar–H), 7.34 (ddd, J = 7.6, 4.9, 0.9 Hz, 1H, Ar–H), 7.29-7.27 (m, 1H, Ar–H), 7.15-7.10 (m, 2H, Ar–H), 6.47 (s, 1H, Ar–H), 3.01 (tt, J = 11.6, 3.1 Hz, 1H, CH), 1.92 (d, J = 12.8 Hz, 2H, CH_2), 1.77-1.69 (m, 2H, CH_2), 1.45-1.38 (m, 2H, CH_2), 1.30-1.22 (m, 4H, CH_2). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 151.9 (C_q), 149.8 (CH), 147.4 (C_q), 138.5 (CH), 137.5 (C_q), 128.7 (C_q), 122.3 (CH), 121.7 (CH), 121.6 (CH), 120.6 (CH), 120.1

(CH), 110.1 (CH), 100.0 (CH), 35.8 (CH), 33.4 (2C, CH_2), 26.6 (2C, CH_2), 26.4 (CH_2). HRMS (ESI): *m/z* Calcd for $C_{19}H_{20}N_2+H^+$ $[M+H]^+$ 277.1699; Found 277.1699. The ^1H and ^{13}C spectra are consistent with those reported in the literature.[48]



2-Cycloheptyl-1-(pyridin-2-yl)-1*H*-indole (7ah): The representative procedure was followed, using substrate **3a** (0.058 g, 0.3 mmol), bromocycloheptane (**6h**; 0.106 g, 0.6 mmol) and KI (0.1 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) yielded **7ah** as a light yellow liquid. Yield: 0.033 g, 38%. ^1H-NMR (500 MHz, ($CDCl_3$): δ = 8.69 (dd, *J* = 4.6, 0.8 Hz, 1H, Ar–H), 7.90 (td, *J* = 8.0, 1.9 Hz, 1H, Ar–H), 7.59-7.57 (m, 1H, Ar–H), 7.44 (d, *J* = 8.0 Hz, 1H, Ar–H), 7.35-7.33 (m, 1H, Ar–H), 7.25 (d, *J* = 8.0 Hz, 1H, Ar–H), 7.14-7.09 (m, 2H, Ar–H), 6.47 (s, 1H, Ar–H), 3.24-3.19 (m, 1H, CH), 2.00-1.95 (m, 2H, CH_2), 1.72-1.64 (m, 4H, CH_2), 1.60-1.52 (m, 4H, CH_2), 1.39-1.33 (m, 2H, CH_2). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 152.0 (C_q), 149.9 (CH), 148.5 (C_q), 138.4 (CH), 137.5 (C_q), 128.7 (C_q), 122.3 (CH), 121.9 (CH), 121.6 (CH), 120.6 (CH), 120.1 (CH), 110.1 (CH), 100.0 (CH), 37.0 (CH), 35.0 (2C, CH_2), 28.4 (2C, CH_2), 26.8 (2C, CH_2). HRMS (ESI): *m/z* Calcd for $C_{20}H_{22}N_2+H^+$ $[M+H]^+$ 291.1856; Found 291.1855.

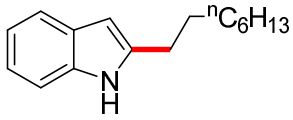


2-Cyclohexyl-5-methyl-1-(pyridin-2-yl)-1*H*-indole (7bg): The representative procedure was followed, using substrate **3b** (0.062 g, 0.3 mmol), bromide **6g** (0.098 g, 0.6 mmol) and KI (0.1 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) yielded **7bg** as a light yellow liquid. Yield: 0.055 g, 63%. ^1H-NMR (500 MHz, ($CDCl_3$): δ = 8.67 (d, *J* = 4.6 Hz, 1H, Ar–H), 7.88 (td, *J* = 7.6, 1.5 Hz, 1H, Ar–H), 7.42 (d, *J* = 8.0 Hz, 1H, Ar–H), 7.38 (s, 1H, Ar–H), 7.32 (dd, *J* = 5.0, 1.5 Hz, 1H, Ar–H), 7.17 (d, *J* = 8.4 Hz, 1H, Ar–H), 6.94 (d, *J* = 8.4 Hz, 1H, Ar–H), 6.38 (s, 1H, Ar–H), 3.02 (t, *J* = 11.4 Hz, 1H, CH),

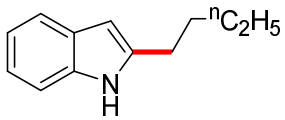
2.44 (s, 3H, CH_3), 1.90 (d, J = 12.2 Hz, 2H, CH_2), 1.77-1.65 (m, 3H, CH_2), 1.43-1.37 (m, 2H, CH_2), 1.28-1.20 (m, 3H, CH_2). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 152.1 (C_q), 149.8 (CH), 147.5 (C_q), 138.4 (CH), 135.8 (C_q), 129.9 (C_q), 129.0 (C_q), 123.1 (CH), 122.1 (CH), 121.5 (CH), 120.0 (CH), 109.9 (CH), 99.7 (CH), 35.8 (CH), 33.4 (2C, CH_2), 26.7 (2C, CH_2), 26.4 (CH_2), 21.5 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{20}H_{22}N_2+H^+$ $[M+H]^+$ 291.1856; Found 291.1857.

2.4.6 Removal of Directing Group and Functionalization

Procedure for Removal of Directing Group:[80] In an oven dried Schlenk flask, **5aa** (0.049 g, 0.16 mmol) or **5ab** (0.04 g, 0.16 mmol) was introduced and CH_2Cl_2 (5 mL) was added into it. Methyl trifluoromethanesulfonate, MeOTf (0.031 g, 0.19 mmol) was added dropwise via a syringe to the reaction mixture at 0 °C, and the resultant reaction mixture was stirred at room temperature for 12 h. Then the volatiles were removed under vacuum and the residue was redissolved in MeOH (2 mL). To the resultant mixture, 2M aq. NaOH (2 mL) solution was added and the reaction mixture was stirred at 60 °C for 10 h. At ambient temperature, the volatiles were evaporated under reduced pressure, and the resulting residue was extracted with EtOAc (15 mL x 3). The combined organic extract was washed with brine, dried over Na_2SO_4 and the volatiles were evaporated in *vacuo*. The remaining residue was purified by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 5/1/0.5) to yield **8a** or **8b** as a light yellow liquid.

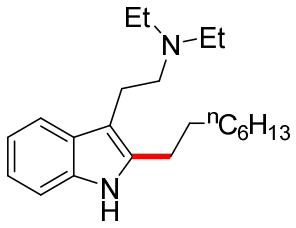


2-Octyl-1*H*-indole (8a): Yield: 0.022 g, 60%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.78 (br s, 1H, N–H), 7.61 (d, J = 7.6 Hz, 1H, Ar–H), 7.31 (d, J = 8.0 Hz, 1H, Ar–H), 7.21-7.14 (m, 2H, Ar–H), 6.31 (s, 1H, Ar–H), 2.76 (t, J = 7.6 Hz, 2H, CH_2), 1.76 (app. pent, J = 7.6 Hz, 2H, CH_2), 1.47-1.34 (m, 10H, CH_2), 0.98 (t, J = 6.9 Hz, 3H, CH_3). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): 140.3 (C_q), 136.0 (C_q), 129.0 (C_q), 121.0 (CH), 119.9 (CH), 119.7 (CH), 110.5 (CH), 99.5 (CH), 32.1 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 28.4 (CH_2), 22.8 (CH_2), 14.3 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{16}H_{23}N+H^+$ $[M+H]^+$ 230.1903; Found 230.1902.



2-Butyl-1*H*-indole (8b): Yield: 0.017 g, 61%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.87 (br s, 1H, N–H), 7.53 (d, J = 7.6 Hz, 1H, Ar–H), 7.30 (d, J = 8.0 Hz, 1H, Ar–H), 7.13-7.05 (m, 2H, Ar–H), 6.24 (s, 1H, Ar–H), 2.76 (t, J = 7.6 Hz, 2H, CH_2), 1.71 (app. pent, J = 7.6 Hz, 2H, CH_2), 1.43 (app. sextet, J = 7.6 Hz, 2H, CH_2), 0.96 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 140.2 (C_q), 136.0 (C_q), 129.0 (C_q), 121.1 (CH), 119.9 (CH), 119.7 (CH), 110.4 (CH), 99.6 (CH), 31.5 (CH_2), 28.1 (CH_2), 22.6 (CH_2), 14.1 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{12}H_{15}N+H^+$ $[M+H]^+$ 174.1277; Found 174.1277. The ^{1}H and ^{13}C spectra are consistent with those reported in the literature.[44]

Procedure for Functionalization:[72] To an oven dried Schlenk flask, **8a** (0.019 g, 0.083 mmol) was introduced and dissolved in Et_2O (5 mL). To the above solution, oxalyl chloride (0.021 g, 0.165 mmol) in Et_2O was added at 0 °C and stirred for 2 h. After that Et_2NH was added to the reaction mixture until the pH reached 9-10 at 0 °C. The resultant reaction mixture was stirred at room temperature for 12 h and the volatiles were evaporated under vacuum. The crude residual product was redissolved in THF (5 mL), and $LiAlH_4$ (0.047 g, 1.24 mmol) in THF (10 mL) was added *via* a cannula. The resultant reaction mixture was refluxed for 5 h. At ambient temperature, the reaction was quenched with H_2O (20 mL) and extracted with EtOAc (10 mL x 3). The combined organic extract was washed with H_2O, dried over Na_2SO_4 and the volatiles were evaporated in *vacuo*. The remaining residue was purified by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 5/1/0.5) to yield **9a** a light yellow liquid.



***N,N*-Diethyl-2-(2-octyl-1*H*-indol-3-yl)ethan-1-amine (9a):** Yield: 0.022 g, 81%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.87 (br s, 1H, N–H), 7.52 (d, J = 7.3 Hz, 1H, Ar–H), 7.28 (d, J = 7.8 Hz, 1H, Ar–H), 7.13-7.05 (m, 2H, Ar–H), 3.64 (app. t, J = 6.5 Hz, 1H, CH_2), 3.26 (app. q, J = 7.3 Hz, 1H, CH_2), 2.90-2.85 (m, 2H, CH_2), 2.74-2.68 (m, 6H, CH_2), 1.69-1.61

(m, 2H, CH_2), 1.33-1.26 (m, 10H, CH_2), 1.13 (t, J = 7.1 Hz, 6H, CH_3), 0.88 (t, J = 6.6 Hz, 3H, CH_3). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): 136.0 (C_q), 135.4 (C_q), 128.8 (C_q), 121.1 (CH), 119.2 (CH), 118.2 (CH), 110.5 (CH), 109.6 (C_q), 53.8 (CH_2), 47.0 (2C, CH_2), 32.0 (CH_2), 30.3 (CH_2), 29.9 (CH_2), 29.6 (2C, CH_2), 29.4 (CH_2), 26.4 (CH_2), 22.8 (CH_2), 14.3 (CH_3), 11.8 (2C, CH_3). HRMS (ESI): *m/z* Calcd for $C_{22}H_{36}N_2+H^+$ $[M+H]^+$ 329.2951; Found 329.2946.

2.4.7 X-ray Structure Determination

X-ray intensity data measurements of compounds **2a** and **2b** were carried out on a Bruker SMART APEX II CCD diffractometer with graphite-monochromatized (MoK_α= 0.71073 Å) radiation. The X-ray generator was operated at 50 kV and 30 mA. A preliminary set of cell constants and an orientation matrix were calculated from three sets of 12 frames (total 36 frames). Data were collected with ω scan width of 0.5° at eight different settings of φ and 2θ keeping the sample-to-detector distance fixed at 5.00 cm for both compounds. The X-ray data collection was monitored by APEX2 program (Bruker, 2006).[82] All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2006). SHELX-97 was used for structure solution and full matrix least-squares refinement on F^2.[83] Hydrogen atoms were placed in geometrically idealized position and constrained to ride on their parent atoms. An ORTEP III[84] view of both compounds was drawn with 50% probability displacement ellipsoids and H atoms are shown as small spheres of arbitrary radii (Figures 2.1 and 2.2). CCDC-1472403 (**2a**) and CCDC-1472402 (**2b**).

Table 2.4 Crystal data and structure refinement for complexes **2a** and **2b**

	2a	**2b**
Empirical formula	$C_{17}H_{21}N_3NiO_3$, 0.5 (H_2O)	$C_{15}H_{18}ClN_3NiO$
Formula weight	383.08	350.48
Temperature, K	200(2)	200(2)
Cryst. Syst.	Monoclinic	Monoclinic
Space group	$P2_1/c$	C2/c
a (Å)	15.7724(4)	14.6259(3)
b (Å)	14.0286(3)	13.2292(3)
c (Å)	16.1653(4)	16.0114(3)
α (°)	90	90
β (°)	101.2360(10)	101.1540(10)
γ (°)	90	90
V ($Å^3$)	3508.25(15)	3039.51(11)
Z	8	8
$\rho_{cald.}$ g/cm^3	1.451	1.532
ε (mm^{-1})	1.129	1.454
F (000)	1608	1456
Crystal size (mm)	0.47 x 0.32 x 0.26	0.45 x 0.35 x 0.25
θ (min, max) (°)	1.94, 25.00	2.09, 24.99
R(int)	0.0199	0.0143
Independent reflections	6182	2682
Completeness to θ	100.0 %	100.0 %
Max. and min. transmission	0.7579, 0.6189	0.7126, 0.5608
Data / restraints / parameters	6182 / 0 / 448	2682 / 0 / 192
GOF on F^2	1.038	1.078
R1, wR2 ($I>2\sigma(I)$)	0.0283, 0.0673	0.0219, 0.0547
R1, wR2 (all data)	0.0360, 0.0723	0.0240, 0.0559

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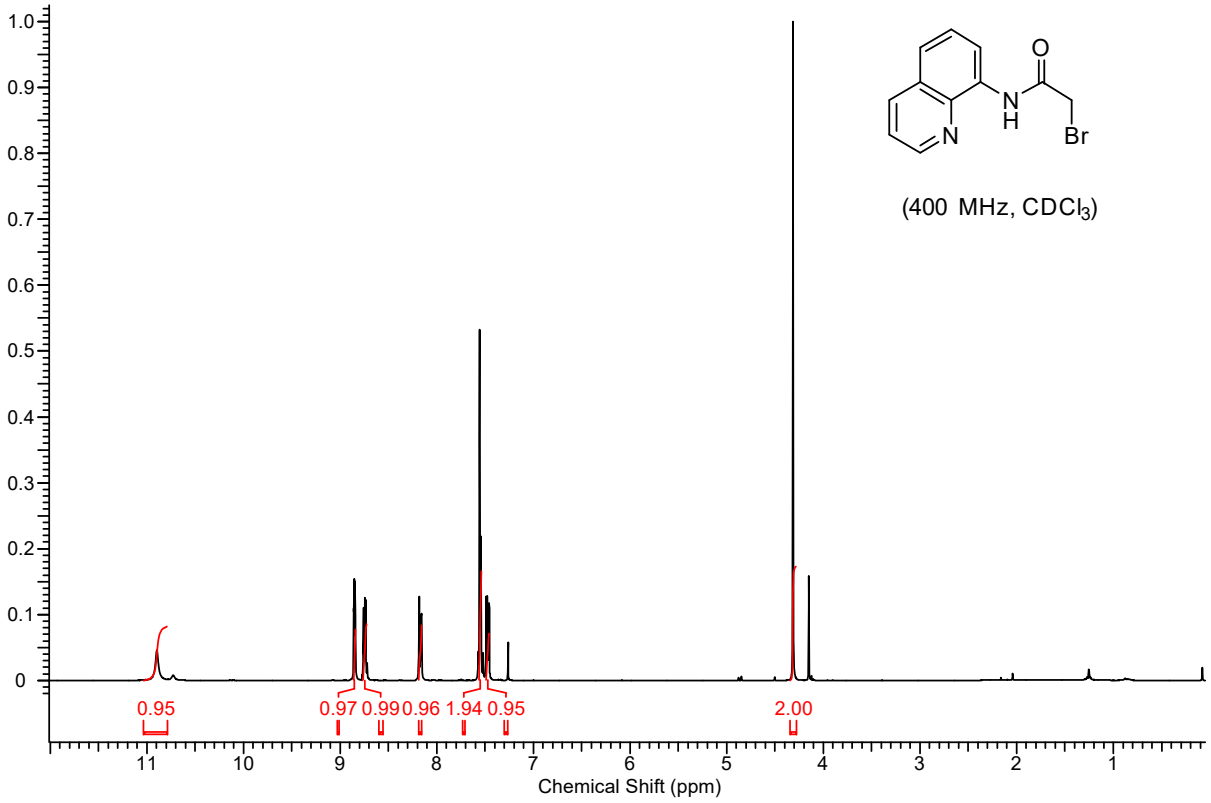
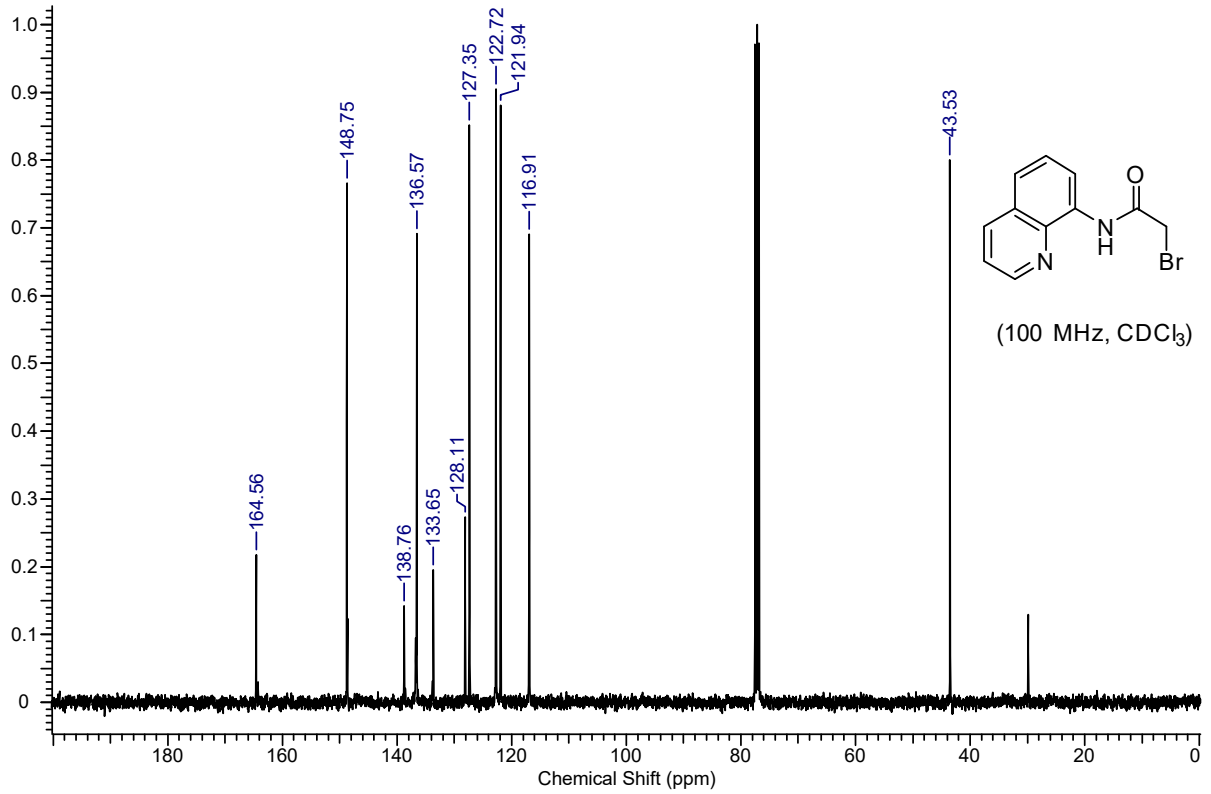
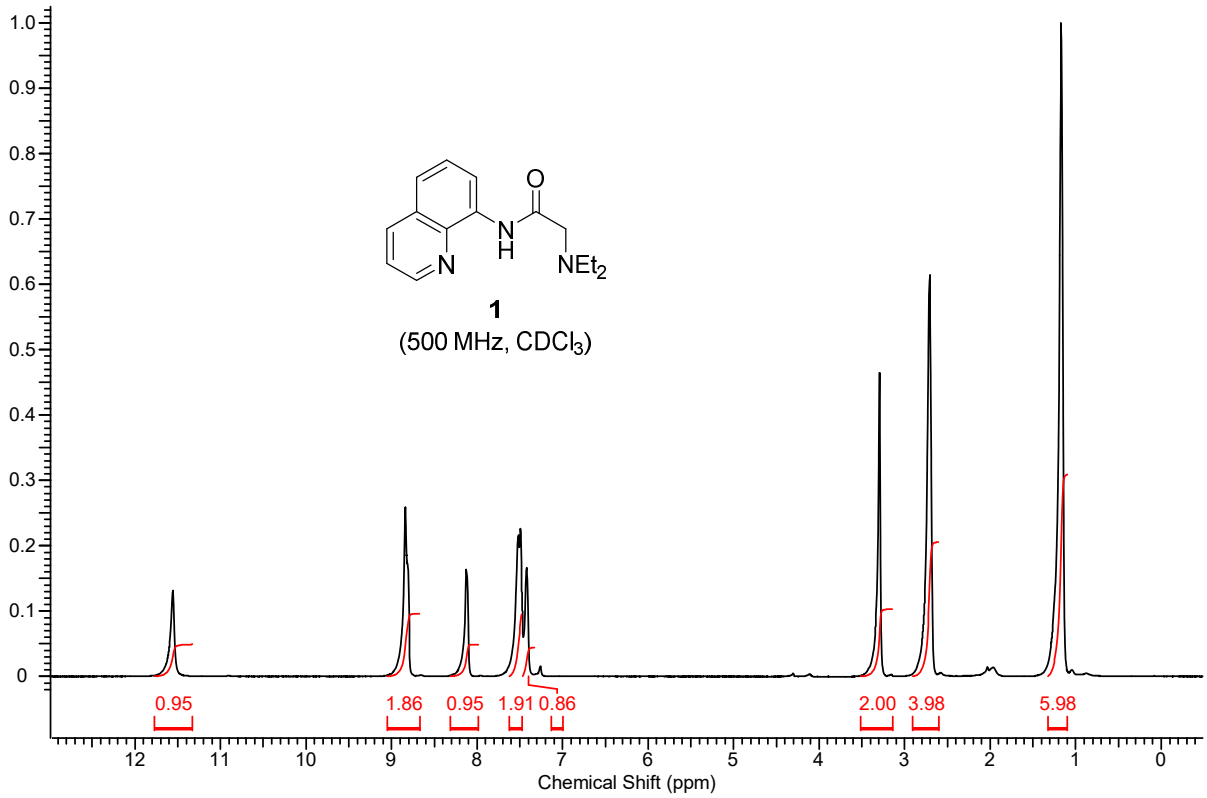
NMR Spectra of Selected Compounds



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0.95
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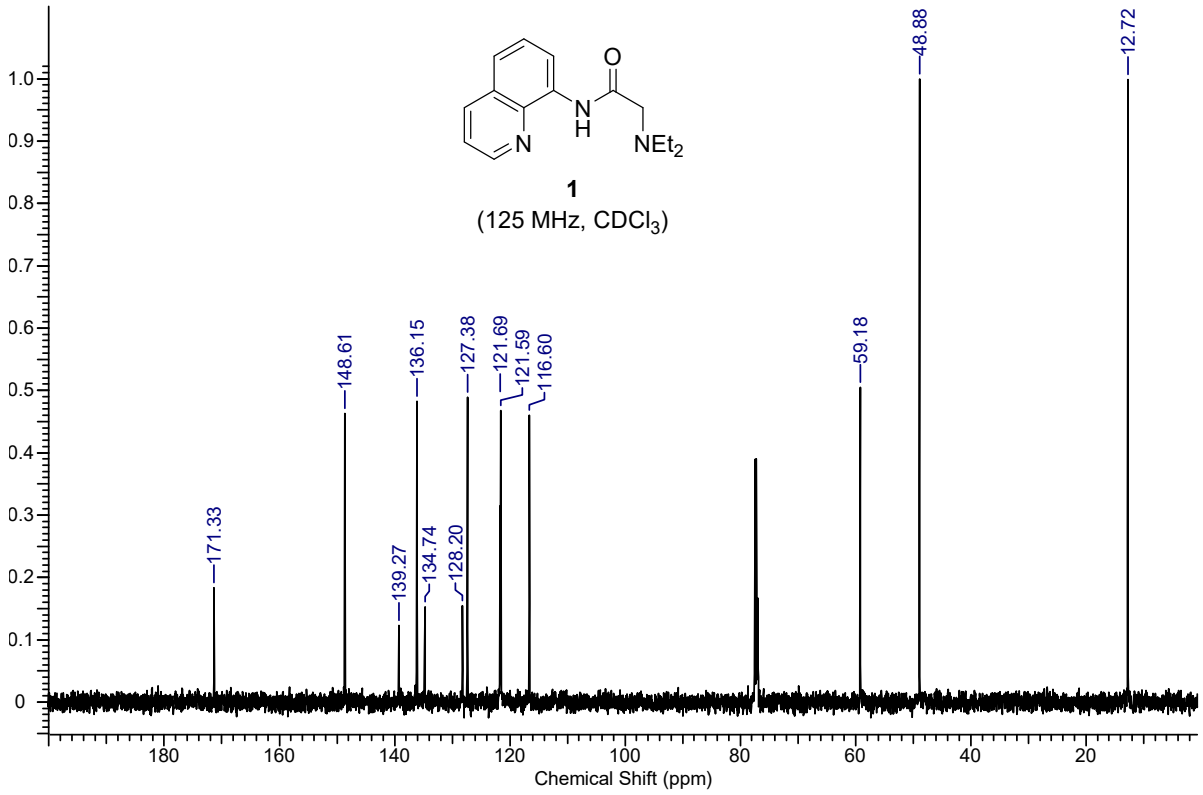
0.86
2.00
3.98
5.98
Chemical Shift (ppm)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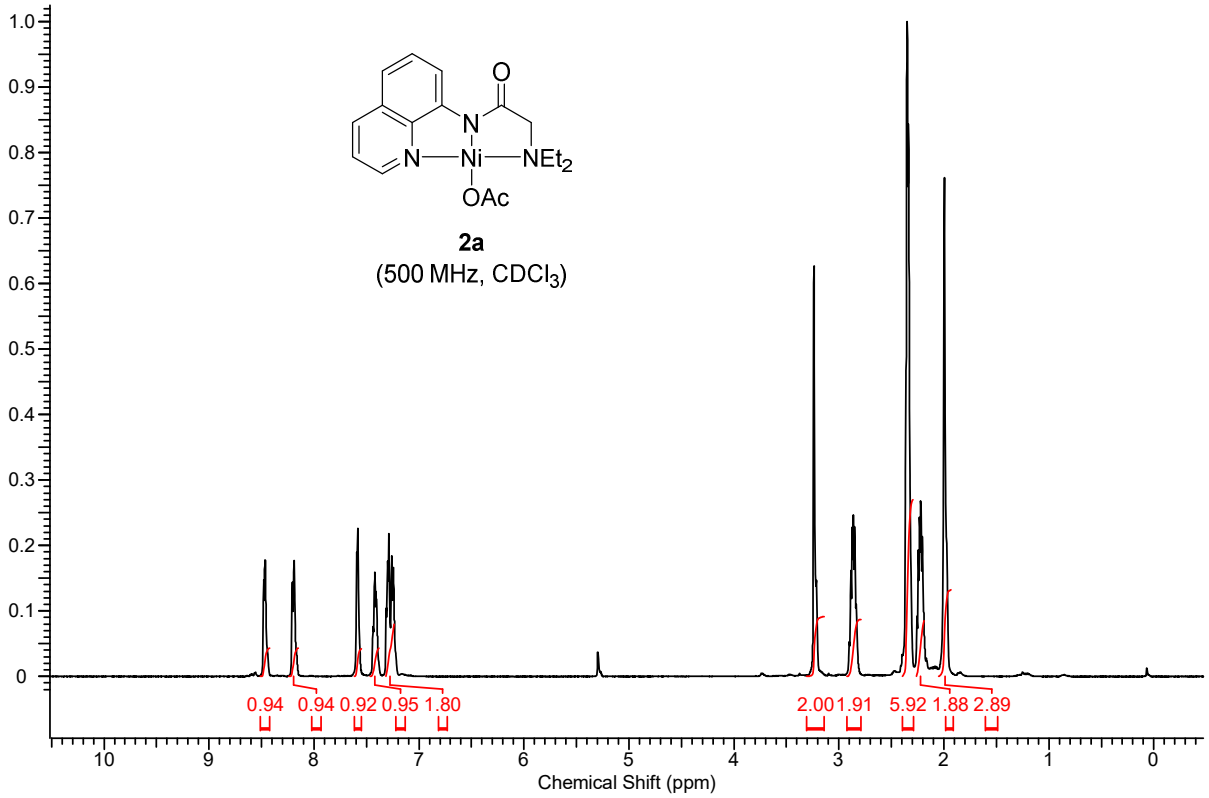
Chemical Shift (ppm)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N
N
Ni
NEt2
OAc
2a
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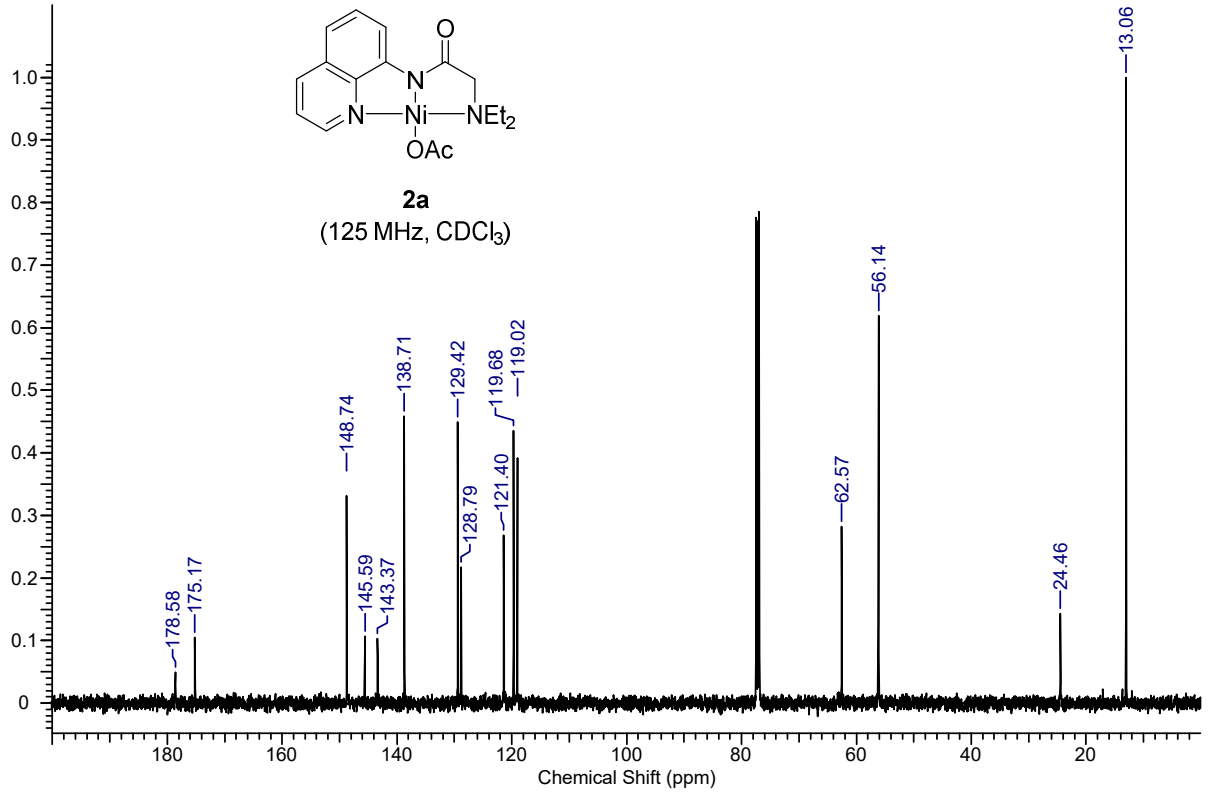
2.00 1.91 5.92 1.88 2.89
Chemical Shift (ppm)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Ni
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OAc
2a
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148.74
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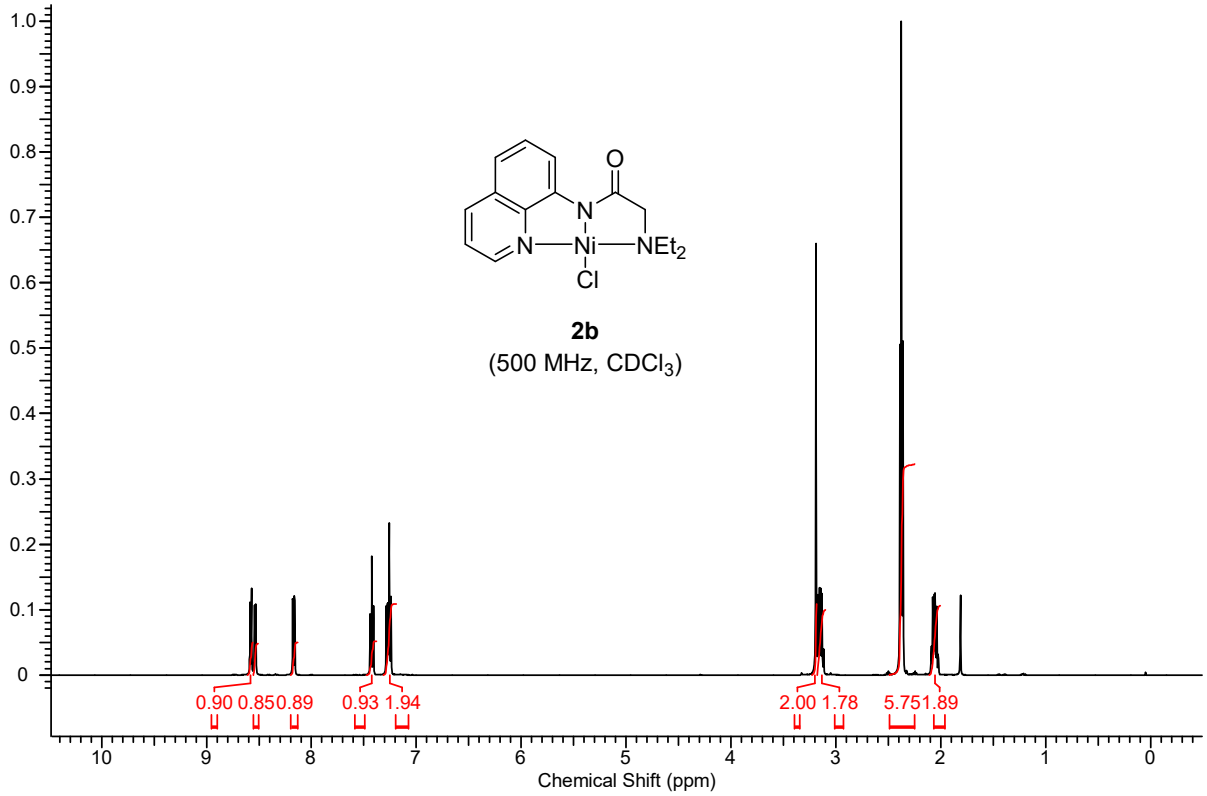
62.57
56.14
24.46
13.06
Chemical Shift (ppm)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Ni
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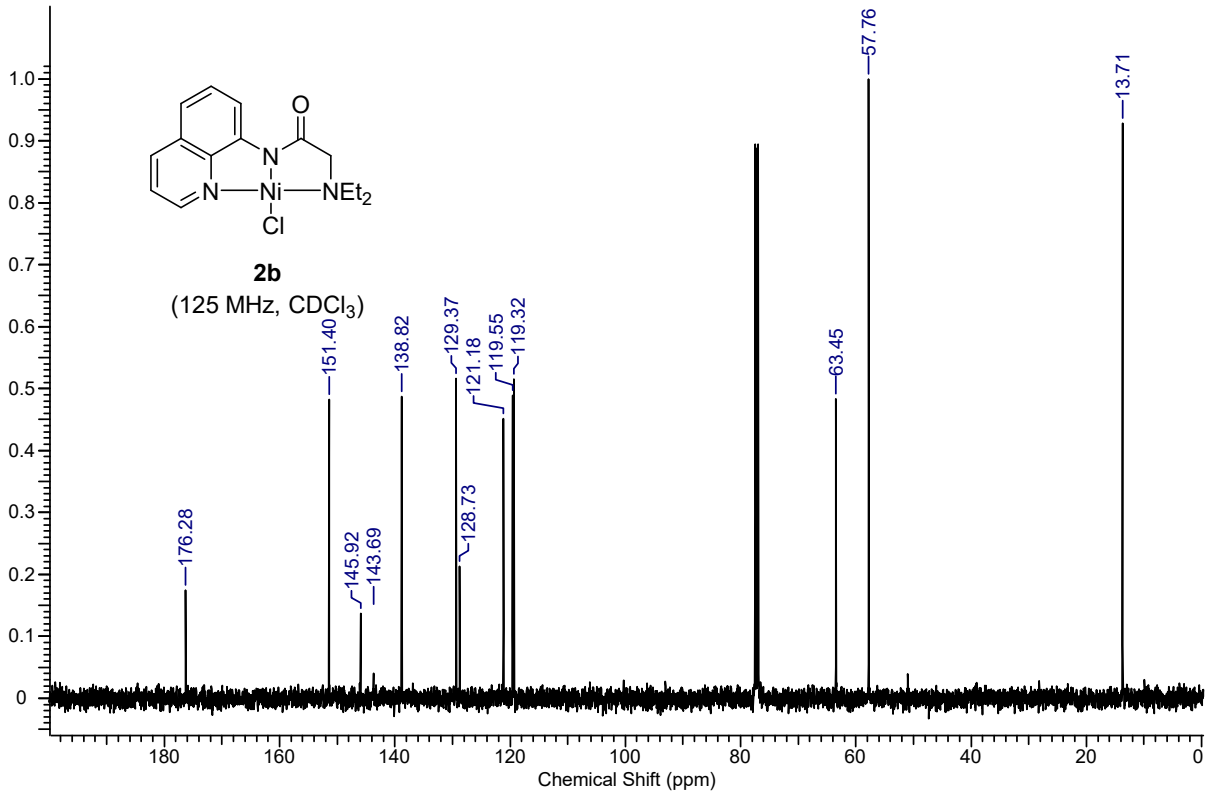
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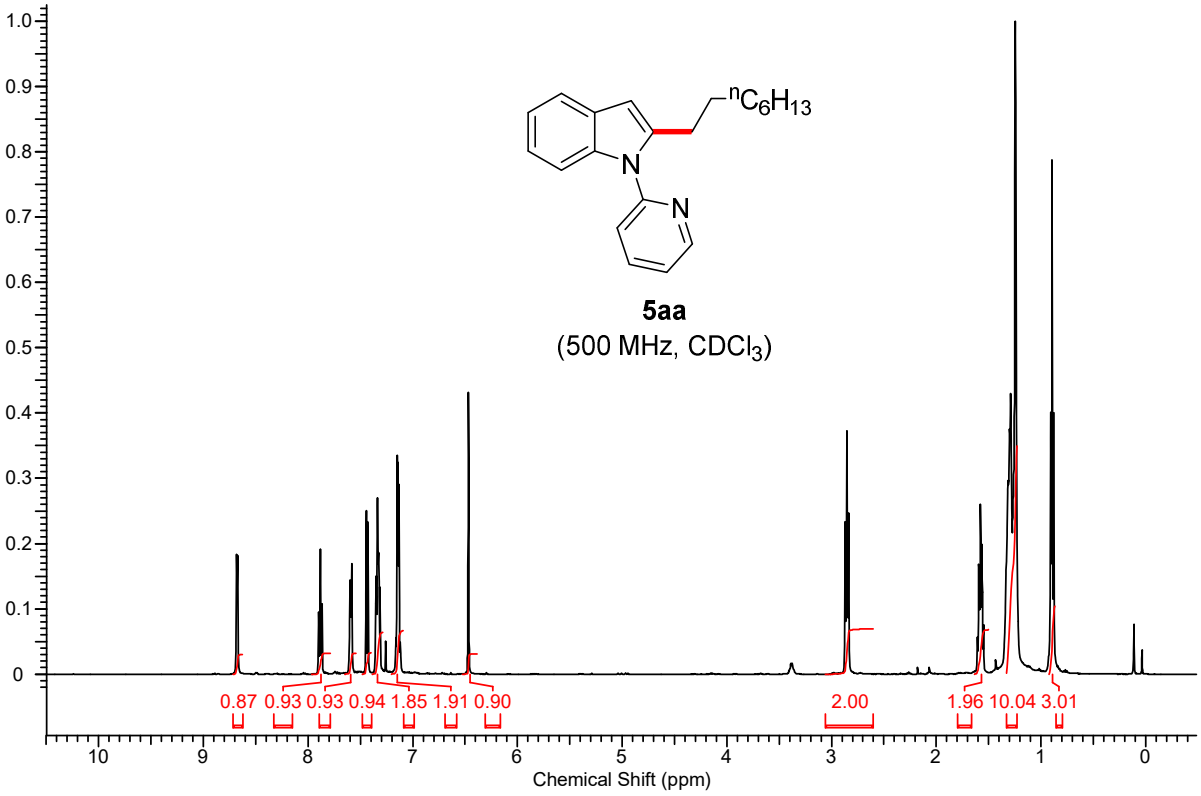
13.71
Chemical Shift (ppm)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N
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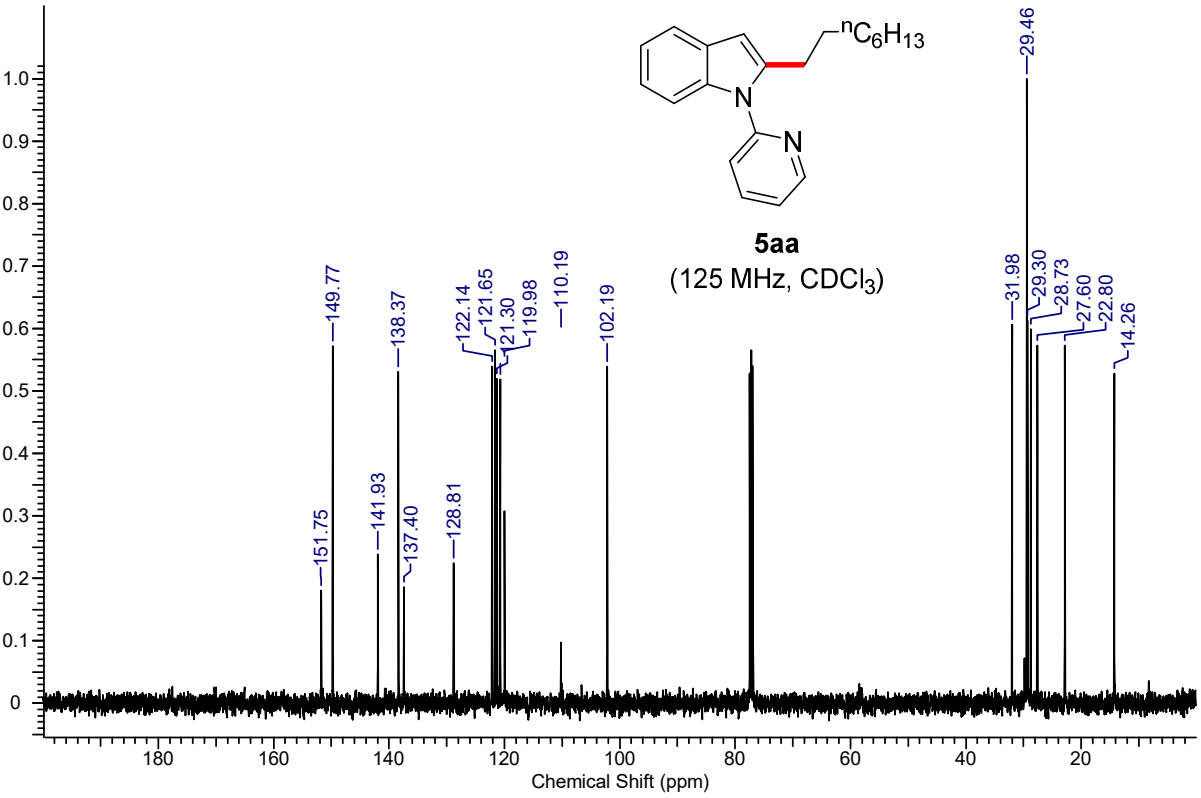
2.00
1.96 10.04 3.01
Chemical Shift (ppm)


$^{n}C_6H_{13}$
N
N
5aa
(125 MHz, $CDCl_3$)
151.75
149.77
141.93
138.37
137.40
128.81
122.14
121.65
121.30
119.98
110.19
102.19
31.98
29.46
29.30
28.73
27.60
22.80
14.26
Chemical Shift (ppm)

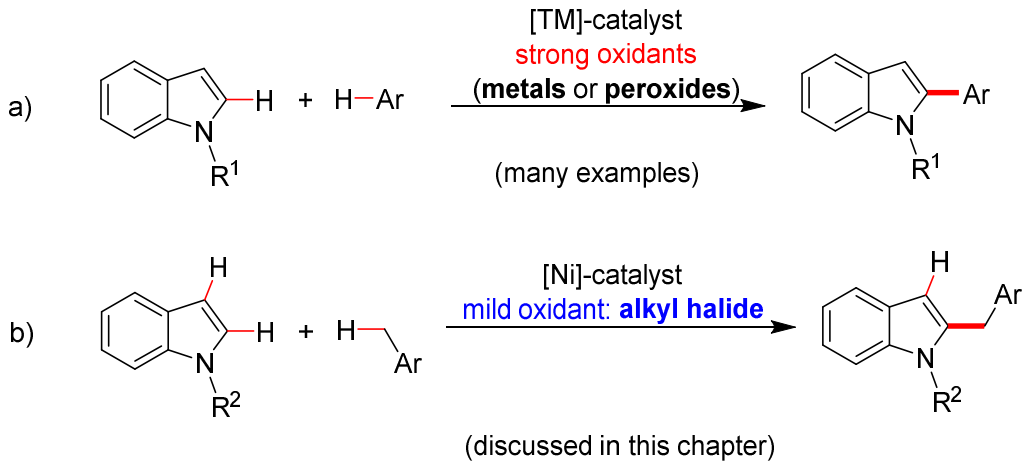
Chapter 3

Nickel-Catalyzed C(sp^2)–H/C(sp^3)–H Oxidative Coupling of Indoles with Toluene Derivatives

3.1 INTRODUCTION

Selective functionalization of indole has attracted considerable attention owing to the ubiquitous nature of this heterocycle in natural products, pharmaceuticals and biologically active compounds.[1-8] Particularly, the direct C–H bonds functionalization to construct C–C bonds by the transition-metal-catalysts, using various organic halides and organometallic compounds as the coupling partner, has proven a versatile technique for step-economical synthesis, and has significantly been progressed.[9-19] In contrast, the oxidative C–H/C–H coupling of indoles with the organic coupling partners is relatively less explored,[20-23] though it is an ideal and environmentally benign strategy because the prefunctionalization of substrates is not necessary in this case, and the reaction would not generate halogenated or organometallic by-products. In the pioneering work, Fagnou reported on the palladium-catalyzed oxidative coupling of indoles with arenes *via* the $C(sp^2)$–H/$C(sp^2)$–H bonds activation resulting in the arylation products.[24] Subsequently, a number of reactions on indoles have been reported involving the oxidative $C(sp^2)$–H/$C(sp^2)$–H coupling (Scheme 3.1a).[25-36] On the contrary, the $C(sp^2)$–H coupling of indoles with more strenuous $C(sp^3)$–H bond remains challenging.[37-62]

Nevertheless, all the $C(sp^2)$–H/$C(sp^2)$–H and $C(sp^2)$–H/$C(sp^3)$–H oxidative couplings of indoles reported till date use either noble metal catalysts and/or excess amount of strong oxidants, such as peroxides or secondary transition-metals, which remains the critical drawback. Oxidative $C(sp^2)$–H/$C(sp^3)$–H coupling without the use of strong oxidants and precious metals is the most challenging task. In particular, the $C(sp^2)$–H/$C(sp^3)$–H coupling of indoles with toluene derivatives leading to the selective C-2 benzylation,[63] under such conditions, would be an ideal strategy to synthesize the biologically active benzylated-indoles (Figure 3.1).[64-68] Thus, in this chapter the Ni-catalyzed benzylation of indoles with toluene derivatives through the oxidative $C(sp^2)$–H/$C(sp^3)$–H cross-coupling using 2-iodobutane as the oxidant is discussed (Scheme 3.1b).[69] A variety of indoles were benzylated regioselectively at the C-2 position with numerous functionalized toluene derivatives *via* the chelation assistance. Further, the practical applicability of this approach is demonstrated by synthesizing some pharmaceutically relevant compound.



Scheme 3.1 Oxidative C–H/C–H Bonds Cross-Couplings.

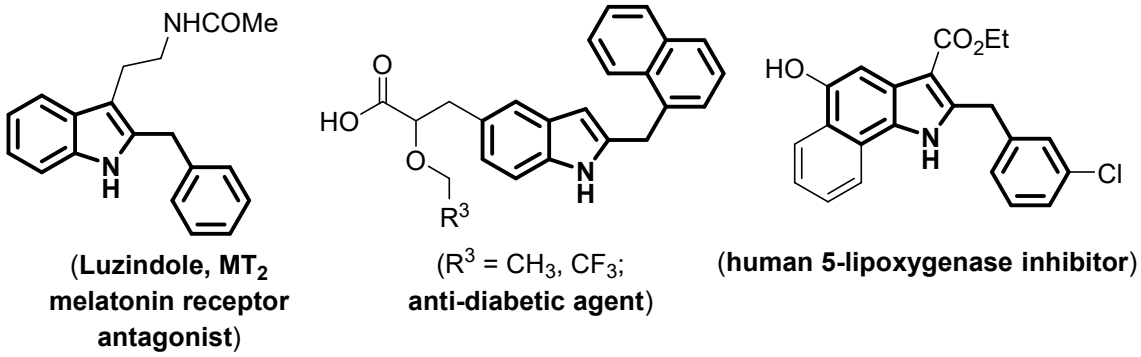


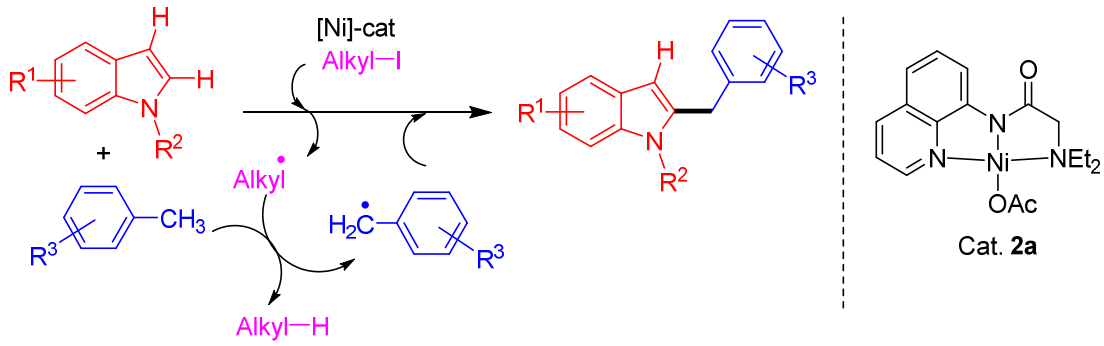
Figure 3.1 Biologically active 2-benzylated indoles.

3.2 RESULTS AND DISCUSSION

3.2.1 Optimization of Reaction Conditions for C(sp^2)–H/C(sp^3)–H Coupling

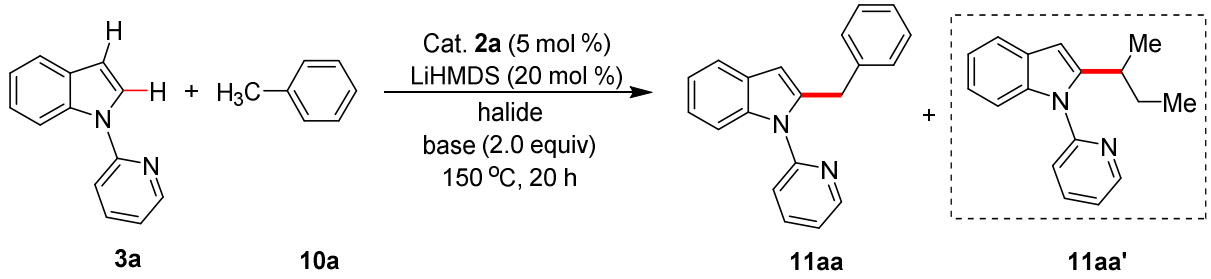
During the nickel-catalyzed C–H bond alkylation of indole with alkyl halide (Chapter-2), it was found that the alkylation reaction involves an alkyl radical intermediate.[70] In order to employ alkyl halide as an oxidant for achieving indole benzylation, *via* the oxidative C(sp^2)–H/C(sp^3)–H coupling with toluene derivatives, a key point would be how to expedite the radical transfer from alkyl to toluene so that selective benzylation can be obtained rather than the alkylation (Scheme 3.2). Thus, our initial investigation centered on the employment of a suitable halide source as well as the perfect combination of halide and toluene. The reaction of indole **3a** with toluene (10 equiv) and 2-iodobutane (2 equiv), in the presence of nickel catalyst **2a**, catalytic amount of LiHMDS and LiO^tBu, afforded the benzylated product 2-benzyl-1-(pyridin-2-yl)-1*H*-indole (**11aa)** in 32% and alkylated product **11aa'** in 63% yield (Table 3.1, entry 1). Upon increasing the toluene concentration, the selectivity for benzylation

was enhanced, and with the 30 equiv of toluene the product **11aa** was isolated in 69% yield (entries 2,3). Reducing the concentration of 2-iodobutane to 1.5 equiv, the product **11aa** was obtained in 70% yield (entry 4); however, further reducing the halide concentration or increasing the toluene concentration resulted with lowering in yield of benzylation (entries 5-7). The employment of other primary and secondary alkyl iodides as oxidant gave lower yield of **11aa**, whereas the electron-deficient halide $^{i}C_3F_7$-I or aryl iodides afforded a small amount of benzylation (entries 8-14). The benzylation using ancillary non-polar solvents, in addition to toluene (30 equiv), did not help in improving the selectivity of benzylation (Table 3.2). Surprisingly, the reaction in the presence of a small amount of chlorobenzene (10 equiv) as the solvent afforded **11aa** in 82% yield (Table 3.2, entry 7). We assume that the chlorobenzene enhances the solubility of reaction components, hence favors the reaction. The benzylation in the presence of mild bases, such as Na_2CO_3, K_2CO_3, Cs_2CO_3 produces trace amount of **11aa** (Table 3.1, entries 15-17). Other nickel precursors [$(DME)NiCl_2$, $(THF)_2NiBr_2$ or $Ni(OAc)_2$] as catalyst were less efficient for the benzylation and produced low to moderate yield of **11aa** (entries 18-20); however, in the absence of nickel catalyst benzylation was not observed (entry 21). The use of base $LiO^{t}Bu$, catalytic amount of LiHMDS, and a relatively higher reaction temperature of 150 ^{o}C for 20 h are essential for the benzylation reaction to obtained good yield (entries 22,23). Though the reaction condition seems severe, this challenging oxidative coupling reaction in the presence of mild oxidant 2-iodobutane has significant advantage.



Scheme 3.2 Hypothesis on Oxidative Coupling of Indole with Toluene.

Table 3.1 Optimization of Reaction Conditions for Benzylation of Indole.[a]

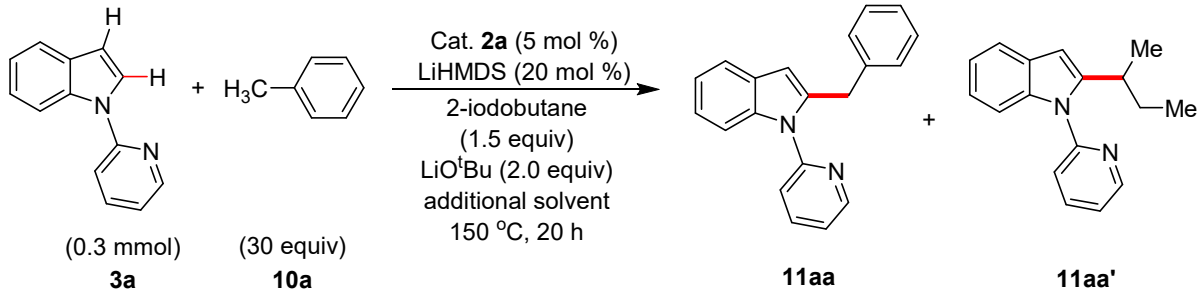


3a **10a** **11aa** **11aa'**

Entry	Halide (equiv)	Toluene (equiv)	Base	Solvent	**11aa** (%)[b]	**11aa'** (%)[b]
1	2-iodobutane (2.0)	10	LiO^{t}Bu	--	32	63
2	2-iodobutane (2.0)	20	LiO^{t}Bu	--	60	34
3	2-iodobutane (2.0)	30	LiO^{t}Bu	--	74 (69)	23
4	**2-iodobutane (1.5)**	**30**	**LiO^{t}Bu**	--	**76 (70)**	21
5	2-iodobutane (1.2)	30	LiO^{t}Bu	--	67	24
6	2-iodobutane (1.0)	30	LiO^{t}Bu	--	60	19
7	2-iodobutane (1.5)	60	LiO^{t}Bu	--	67	14
8	^{i}C$_3$H$_7$I (1.5)	30	LiO^{t}Bu	--	56	n.d.
9	Cyp-I (1.5)	30	LiO^{t}Bu	--	39	n.d.
10	1-iodobutane (1.5)	30	LiO^{t}Bu	--	41	n.d.
11	^{i}C$_3$F$_7$I (1.5)	30	LiO^{t}Bu	--	5	n.d.
12	C$_6$H$_5$I (1.5)	30	LiO^{t}Bu	--	27	n.d.
13	4-MeO-C$_6$H$_4$I (1.5)	30	LiO^{t}Bu	--	9	n.d.
14	4-CF$_3$-C$_6$H$_4$I (1.5)	30	LiO^{t}Bu	--	10	n.d.
15	2-iodobutane (1.5)	30	Na_2CO_3	--	5	5
16	2-iodobutane (1.5)	30	Cs_2CO_3	--	2	6
17	2-iodobutane (1.5)	30	K_2CO_3	--	10	5
18[c]	2-iodobutane (1.5)	30	LiO^{t}Bu	--	18	8
19[d]	2-iodobutane (1.5)	30	LiO^{t}Bu	--	20	7
20[e]	2-iodobutane (1.5)	30	LiO^{t}Bu	--	48	20
21[f]	2-iodobutane (1.5)	30	LiO^{t}Bu	--	--	--
22[g]	2-iodobutane (1.5)	30	LiO^{t}Bu	--	24	5
23[h]	2-iodobutane (1.5)	30	LiO^{t}Bu	--	32	12

[a] Reaction conditions: **3a** (0.058 g, 0.3 mmol), halides and toluene equivalents are w.r.t. substrate **3a**, [Ni] cat (0.015 mmol), LiHMDS (0.01 g, 0.06 mmol) and base (0.6 mmol), heated at 150 °C for 20 h. [b] GC yields using *n*-dodecane as internal standard. Values in parentheses are isolated yields. [c] Employing $(DME)_2NiCl_2$. [d] Employing $(THF)_2NiBr_2$. [e]Employing $Ni(OAc)_2$. [f] In the absence of [Ni] catalyst. [g] Without using LiHMDS. [h] Reaction performed at 130 °C. n.d. = Corresponding couple products with the halide compounds are not determined.

Table 3.2 Screening of Solvents for the Benzylation Reaction.[a]



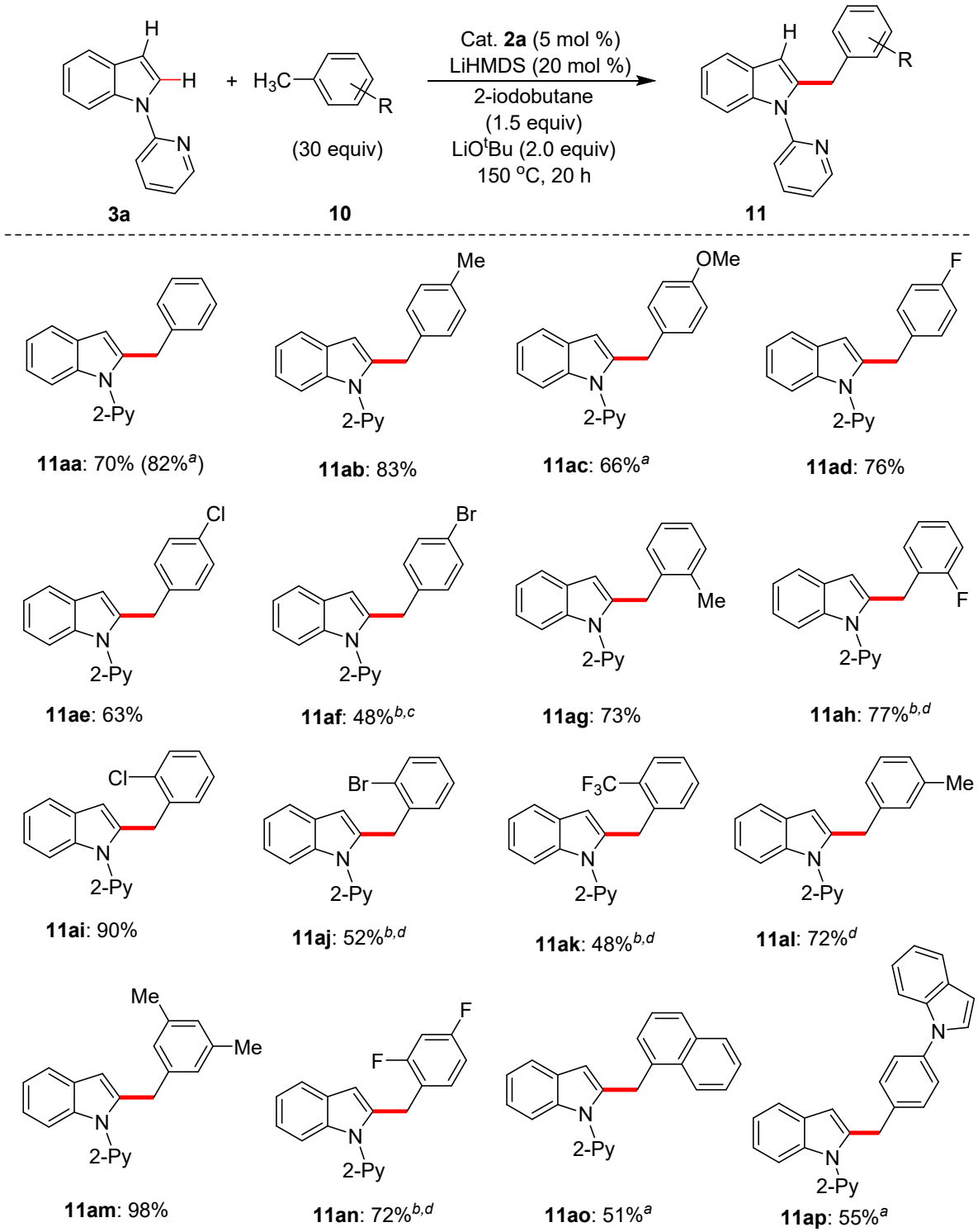
(0.3 mmol) **3a** (30 equiv) **10a** **11aa** **11aa'**

Entry	Additional Solvent	Additional Solvent (equiv)	**11aa** (%)[b]	**11aa'** (%)[b]
1	--	--	**76 (70)**	21
2	^{t}Bu-C_6H_5	30	57	29
3	^{i}Pr-C_6H_5	30	19	21
4	Et-C_6H_5	30	61	20
5	C_6H_5-Cl	30	66	16
6	C_6H_5-Cl	20	82 (70)	15 (11)
7	**C_6H_5-Cl**	**10**	**86 (82)**	7

[a] Reaction conditions: **3a** (0.058 g, 0.3 mmol), toluene (**10a**; 0.96 mL, 9.0 mmol), cat **2a** (0.0056 g, 0.015 mmol, 5.0 mol %), LiHMDS (0.010 g, 0.06 mmol, 20 mol %), LiO^{t}Bu (0.048 g, 0.6 mmol) and heated at 150 °C for 20 h. [b] GC yields using *n*-dodecane as internal standard. Values in parentheses are isolated yields. Chlorobenzene (10 equiv, 0.304 mL) is used as solvent in addition to toluene (30 equiv).

3.2.2 Substrate Scope of the Benzylation of Indoles

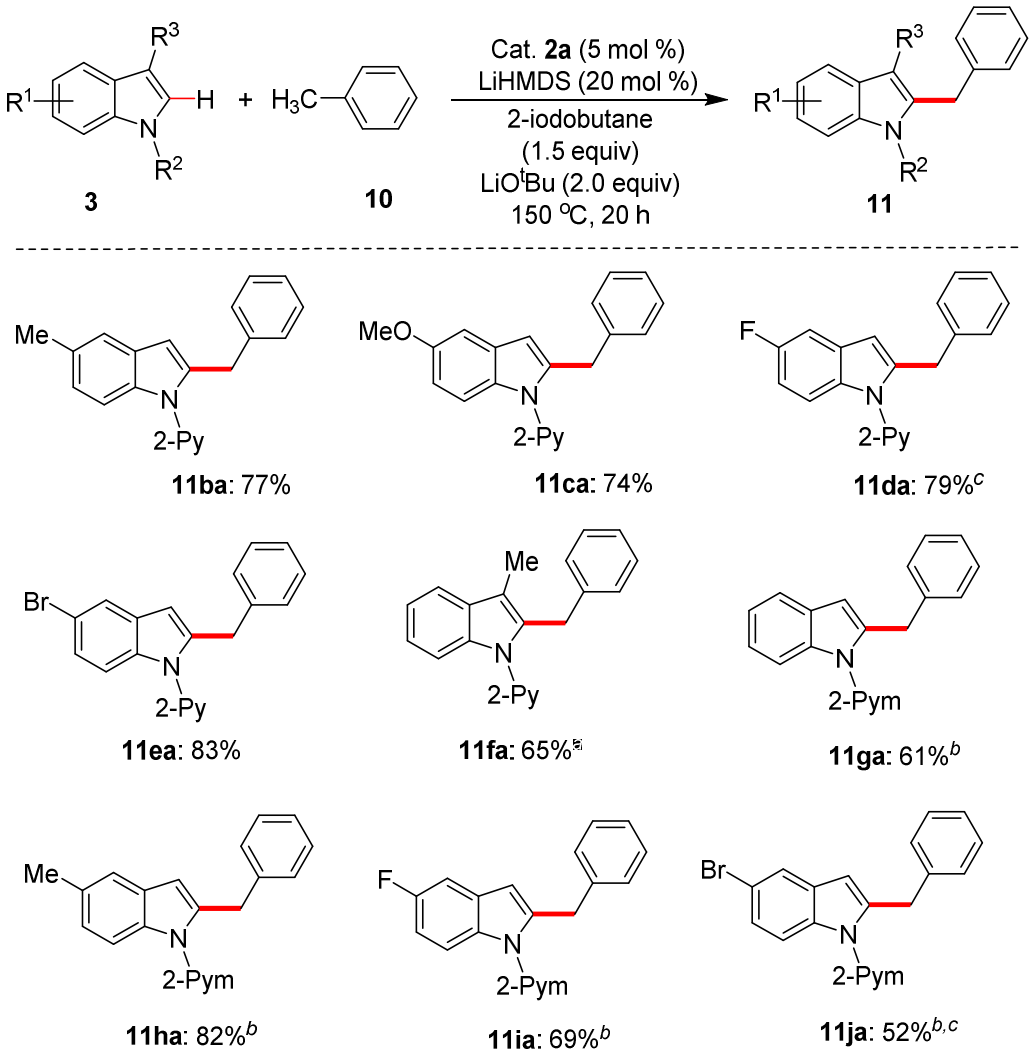
With the optimized reaction conditions in hand, the benzylation of various indoles was examined either in neat condition (using 30 equiv of toluene derivatives) or employing 10 equiv of chlorobenzene in addition to toluene derivatives, and the best results obtained were tabulated. As shown in Scheme 3.3, the toluene derivatives containing a variety of functional groups were efficiently reacted with indole *via* oxidative C(sp^2)–H/C(sp^3)–H coupling. Notably, selective C(2)–H benzylation was observed in all the cases, and the C(3)–H bond remained untouched. Substrates bearing both the electron-donating as well as electron-withdrawing substituents reacted smoothly to give the desired benzylation products **11aa-11af**. The halide functionality in the toluene derivatives mostly remained unaffected, and the C(sp^3)–H bond selectively involved in the couplings. The *ortho* or *meta* substitutions on toluene did not stage problem for the benzylation, and delivered the products **11ag-11an** in



Scheme 3.3 Ni(II)-Catalyzed C-2 Benzylation of Indole with Toluene Derivatives. [a]Employing chlorobenzene (10 equiv). [b] Employing cat **2a** (10 mol %) and chlorobenzene (10 equiv). [c] 8% arylation was observed *via* C–Br coupling. [d] Compound isolated as a mixture with starting precursor; hence yield was determined and verified by ^{1}H NMR.

moderate to excellent yields. The substrate 1-methylnaphthalene reacted with low pace to give **11ao** in 51% yield. We were pleased to show that the toluene derivative containing a heterocycle indole moiety coupled moderately to afford product **11ap**. However, toluene derivatives bearing ester, aldehyde, nitrile or nitro functionality reacted sluggishly to give traces of products. Other substrates bearing benzylic C–H bond, such as ethyl benzene and isopropyl benzene did not couple with the indole derivatives under the standard reaction conditions. Interestingly, in all the benzylation reactions, the oxidative coupling between $C(sp^2)$–H in indoles and $C(sp^2)$–H in toluene derivatives was not observed, and the competitive alkylation with 2-iodobutane was detected only in trace amounts.

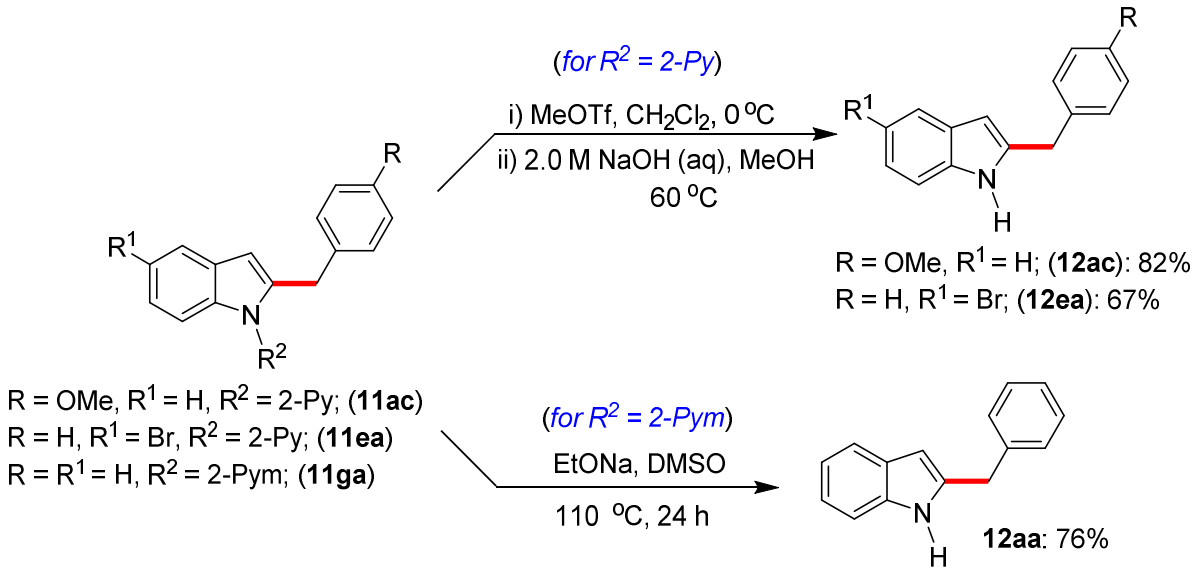
Electronically distinct groups on the indole moiety, such as ether and halides are also well tolerated (Scheme 3.4). The sterically hindered C-3 substituted indole **3f** was benzylated with good yield to deliver **11fa**. Unfortunately, the indoles bearing electron-withdrawing groups, such as –CN, –CHO at the C-3 position did not undergo benzylation with toluene substrate. Notably, the indoles bearing easily removable 2-pyrimidinyl group reacted smoothly with toluene to afford moderate to good yields of the benzylated products **11ga-11ja**. However, indoles containing $–C(O)CH_3$, $–C(O)^tBu$ and $–OSO_2Ph$ at the *N*-center as the directing group were not reactive. This suggests that the nitrogen as chelate directing group is essential for the benzylation reaction. In general, the nickel-catalyzed regioselective C−H functionalizations are well represented, with few exceptions,[71-74] employing the bidentate chelation-assisted strategy.[75-78] However, herein the benzylation reaction smoothly proceeded *via* the monochelate assistance. This nickel-catalyzed protocol facilitates the coupling of $C(sp^3)$–H bond of toluene derivatives in the presence of a mild oxidant, and the reaction was tolerated by ether, halides and heterocycle to afford the biologically relevant benzylated indoles. Notably, for all the substrates regioselective C-2 benzylation was observed, and neither C-3 nor C-2/C-3 double benzylation encountered, which is significant as the C(3)–H can further be functionalized.



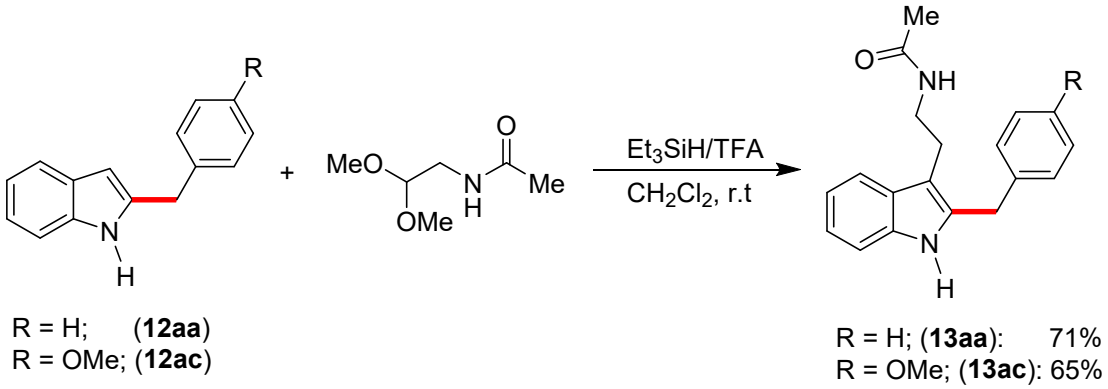
Scheme 3.4 Ni(II)-Catalyzed C-2 Benzylation of Substituted Indoles. [a] Using 10 mol % of cat **2a**. [b] Employing cat **2a** (10 mol %) and chlorobenzene (10 equiv). [c] Compound isolated as a mixture with starting precursor; hence yield was determined and verified by ^{1}H NMR.

3.2.3 Removal of Directing Group and Synthesis of Luzindole Derivatives

Considering the high synthetic value of free *N-H* benzylated indoles, we have demonstrated the removal of 2-pyridinyl and 2-pyrimidinyl groups from the benzylated products. Hence, the treatments of **11ac** and **11ea** with MeOTf and NaOH (aq. 2.0 M) afforded the desired free *NH* indoles **12ac** and **12ea**, respectively, in good yields (Scheme 3.5).[79] Similarly, the 2-pyrimidinyl group was easily removed from **11ga** by the reaction with EtONa at 110 °C in DMSO affording the indole **12aa** in 76% yield (Scheme 3.5).[80] The compounds **12aa** and **12ac** upon treatment with *N*-(2,2-dimethoxyethyl)acetamide produced the melatonin receptor antagonist,[81,82] Luzindole derivatives **13aa** and **13ac**, respectively, in good yields (Scheme 3.6).[66]



Scheme 3.5 Removal of Directing Group.



Scheme 3.6 Synthesis of Luzindole Derivatives.

3.3 CONCLUSION

In this chapter, we have described a unified strategy for the C(sp^2)–H/C(sp^3)–H oxidative coupling of indoles with toluene derivatives using mild oxidant and a Ni(II)-pincer catalyst. The use of 2-iodobutane as the oxidant is very crucial, which functions as a benzyl radical originator by abstracting H-atom from the toluene derivatives. The well-defined, inexpensive nickel catalyst proved efficient for the coupling of broad indole substrates with diverse toluene derivatives. Various functional groups, such as –Me, –OMe, –Br, –CN were tolerated on the indole backbone to give the coupled products in moderate to excellent yields. Especially, the regio- and chemo-selectivities are excellent. The synthetic applicability of this Ni-catalyzed strategy is established by the facile removal of directing groups and by synthesizing the biologically active Luzindole derivatives.

3.4 EXPERIMENTAL SECTION

General Experimental

All manipulations were conducted under an argon atmosphere in the glove box using pre-dried glassware. The catalytic reactions were performed in flame-dried reaction vessels with Teflon screw caps. Toluene was dried over Na/benzophenone and distilled under argon. Liquid reagents were flushed with argon prior to use. Indole derivatives, 5-substituted 1-(pyridin-2-yl)-1*H*-indole,[80,83] 1-(pyrimidin-2-yl)-1*H*-indole,[84,85] 1-(pyridin-2-yl)-1*H*-indole-2-*d*,[79] compound **11p**,[86] and *N*-(2,2-dimethoxyethyl)acetamide[87] were synthesized according to previously described procedures. All other chemicals were obtained from commercial sources and were used without further purification. High resolution mass spectroscopy (HRMS) mass spectra were recorded on a Thermo Scientific Q-Exactive instrument with Accela 1250 pump. Melting points: Büchi 540 capillary melting point apparatus; values are uncorrected. NMR (^{1}H and ^{13}C) spectra were recorded at 400 or 500 (^{1}H), 100 or 125 {^{13}C, DEPT (distortionless enhancement by polarization transfer)}, 377 (^{19}F) on Bruker AV 400 and AV 500 spectrometers 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 250 µm). The instrument was set to an injection volume of 1.0 µL, an inlet split ratio of 10:1, and inlet and detector temperatures of 250 and 320 °C, respectively. UHP-grade argon was used as carrier gas with a flow rate of 30 mL/min. The temperature program used for all the analyses is as follows: 80 °C, 1 min; 30 °C/min to 200 °C, 2 min; 30 °C/min to 260 °C, 3 min; 30 °C/min to 300 °C, 3 min.

Response factors for all the necessary compound, with respect to standard *n*-dodecane or *n*-hexadecane, were calculated from the average of three independent GC runs.

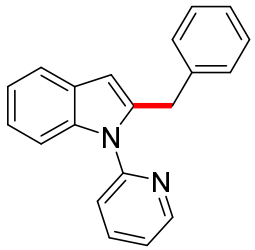
3.4.1 Procedure for Benzylation of Indoles

Representative Procedure: Synthesis of 2-Benzyl-1-(pyridin-2-yl)-1*H*-indole (11aa). Procedure A. To a flame dried screw-cap tube (5 mL) equipped with magnetic stir bar was introduced 1-pyridine-2-yl-1*H*-indole (**3a**; 0.058 g, 0.3 mmol), 2-iodobutane (0.083 g, 0.45 mmol), cat **2a** (0.0056 g, 0.015 mmol, 5.0 mol %), LiHMDS (0.010 g, 0.06 mmol, 20 mol %), LiO^{t}Bu (0.048 g, 0.6 mmol) and toluene (**10a**; 0.96 mL, 9.0 mmol) inside the glove-box. The resultant reaction mixture was stirred at 150 °C in a preheated oil bath for 20 h. At

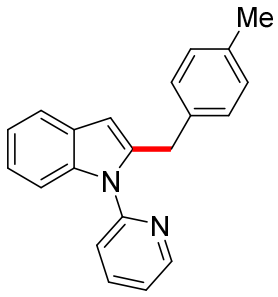
ambient temperature, the reaction mixture was quenched with distilled H_2O (10 mL) and then neutralized with 2N HCl (0.5 mL). The crude product was then extracted with CH_2Cl_2 (20 mL x 3). The combined organic extract was dried over Na_2SO_4 and the volatiles were evaporated in *vacuo*. The remaining residue was purified by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 20/1/0.5) yielded **11aa** as a light yellow liquid. Yield : 0.060 g, 70%.

Procedure B. This procedure was similar to procedure **A**, except the solvent chlorobenzene (0.304 mL, 3.0 mmol, 10 equiv) was added in addition to the toluene (0.96 mL, 9.0 mmol, 30 equiv). The yield of the product **11aa** obtained by this procedure was 82% (0.070 g).

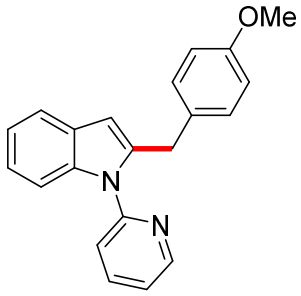
3.4.2 Characterization Data for Benzylated Indoles



2-Benzyl-1-(pyridin-2-yl)-1*H*-indole (11aa): ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.66 (dd, J = 3.8, 0.8 Hz, 1H, Ar–H), 7.77 (td, J = 8.0, 1.7 Hz, 1H, Ar–H), 7.62-7.56 (m, 1H, Ar–H), 7.36-7.31 (m, 1H, Ar–H), 7.29-7.26 (m, 2H, Ar–H), 7.20-7.13 (m, 5H, Ar–H), 7.06 (d, J = 6.9 Hz, 2H, Ar–H), 6.40 (s, 1H, Ar–H), 4.28 (s, 2H, CH_2). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 151.5 (C_q), 149.7 (CH), 140.3 (C_q), 138.9 (C_q), 138.3 (CH), 137.6 (C_q), 129.0 (2C, CH), 128.6 (C_q), 128.3 (2C, CH), 126.3 (CH), 122.2 (CH), 122.0 (CH), 121.3 (CH), 120.8 (CH), 120.3 (CH), 110.2 (CH), 104.3 (CH), 34.2 (CH_2). HRMS (ESI): *m/z* Calcd for $C_{20}H_{16}N_2$+H^+ $[M+H]^+$ 285.1386; Found 285.1386.

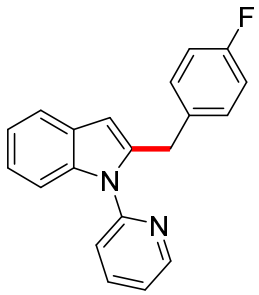


2-(4-Methylbenzyl)-1-(pyridin-2-yl)-1*H*-indole (11ab): The representative procedure **A** was followed, using substrate **3a** (0.058 g, 0.3 mmol) and *p*-xylene (**10b**; 1.1 mL, 9.0 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 30/1/0.5) yielded **11ab** as a light yellow liquid. Yield: 0.074 g, 83%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.68 (d, *J* = 4.2 Hz, 1H, Ar–H), 7.78 (td, *J* = 8.0, 1.3 Hz, 1H, Ar–H), 7.60 (dd, *J* = 5.7, 3.1 Hz, 1H, Ar–H), 7.37-7.35 (m, 1H, Ar–H), 7.32-7.28 (m, 2H, Ar–H), 7.19-7.16 (m, 2H, Ar–H), 7.03 (d, *J* = 8.0 Hz, 2H, Ar–H), 6.99 (d, *J* = 7.9 Hz, 2H, Ar–H), 6.40 (s, 1H, Ar–H), 4.25 (s, 2H, CH_2), 2.32 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 151.5 (C_q), 149.6 (CH), 140.6 (C_q), 138.3 (CH), 137.6 (C_q), 135.8 (C_q), 135.7 (C_q), 129.0 (2C, CH), 128.9 (2C, CH), 128.6 (C_q), 122.1 (CH), 121.9 (CH), 121.3 (CH), 120.8 (CH), 120.3 (CH), 110.2 (CH), 104.1 (CH), 33.7 (CH_2), 21.1 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{21}H_{18}N_2$+H^+ $[M+H]^+$ 299.1543; Found 299.1542.

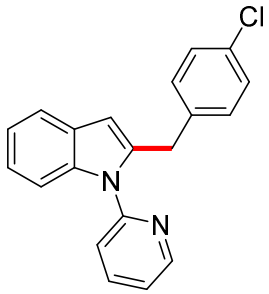


2-(4-Methoxybenzyl)-1-(pyridin-2-yl)-1*H*-indole (11ac): The representative procedure **B** was followed, using substrate **3a** (0.058 g, 0.3 mmol) and 1-methoxy-4-methylbenzene (**10c**; 1.13 mL, 9.0 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 10/1/0.5) yielded **11ac** as a light yellow liquid. Yield: 0.062 g, 66%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.65 (dd, *J* = 4.6, 0.8 Hz, 1H, Ar–H), 7.77 (td, *J* = 7.6, 1.9 Hz, 1H, Ar–H), 7.57 (dd, *J* = 5.7, 3.1 Hz, 1H, Ar–H), 7.32 (dd, *J* = 5.7, 3.1 Hz, 1H, Ar–H), 7.29-7.25 (m, 2H, Ar–H), 7.15-7.12 (m, 2H, Ar–H), 6.97 (d, *J* = 8.8 Hz, 2H, Ar–H), 6.73 (d, *J* = 8.8 Hz, 2H, Ar–H), 6.37 (s, 1H, Ar–H), 4.19 (s, 2H, CH_2), 3.75 (s, 3H,

CH_3). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 158.1 (C_q), 151.5 (C_q), 149.6 (CH), 140.8 (C_q), 138.3 (CH), 137.6 (C_q), 130.9 (C_q), 130.0 (2C, CH), 128.6 (C_q), 122.2 (CH), 122.0 (CH), 121.4 (CH), 120.8 (CH), 120.3 (CH), 113.8 (2C, CH), 110.2 (CH), 104.1 (CH), 55.4 (CH_2), 33.3 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{21}H_{18}N_2O+H^+$ $[M+H]^+$ 315.1492; Found 315.1489.

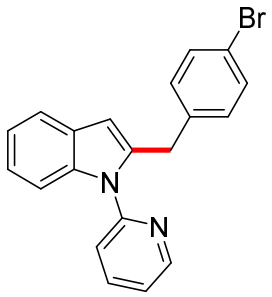


2-(4-Fluorobenzyl)-1-(pyridin-2-yl)-1*H*-indole (11ad): The representative procedure **A** was followed, using substrate **3a** (0.058 g, 0.3 mmol) and 1-fluoro-4-methylbenzene (**10d**; 0.99 mL, 9.0 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 20/1/0.5) yielded **11ad** as a light yellow liquid. Yield: 0.069 g, 76%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.64 (dd, J = 5.7, 1.9 Hz, 1H, Ar–H), 7.77 (td, J = 7.6, 1.9 Hz, 1H, Ar–H), 7.59 (dd, J = 5.7, 3.1 Hz, 1H, Ar–H), 7.33-7.30 (m, 1H, Ar–H), 7.28-7.26 (m, 2H, Ar–H), 7.17-7.14 (m, 2H, Ar–H), 7.00-6.97 (m, 2H, Ar–H), 6.89-6.80 (m, 2H, Ar–H), 6.39 (s, 1H, Ar–H), 4.24 (s, 2H, CH_2). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 161.5 (d, $^1J_{C-F}$ = 244.1 Hz, C_q), 151.4 (C_q), 149.7 (CH), 140.2 (C_q), 138.4 (CH), 137.6 (C_q), 134.6 (d, $^4J_{C-F}$ = 2.9 Hz, C_q), 130.4 (d, $^3J_{C-F}$ = 7.6 Hz, 2C, CH), 128.5 (C_q), 122.2 (CH), 122.2 (CH), 121.3 (CH), 120.9 (CH), 120.4 (CH), 115.1 (d, $^2J_{C-F}$ = 21.0 Hz, 2C, CH), 110.2 (CH), 104.3 (CH), 33.4 (CH_2). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = –117.0 (s). HRMS (ESI): *m/z* Calcd for $C_{20}H_{15}FN_2+H^+$ $[M+H]^+$ 303.1292; Found 303.1293.

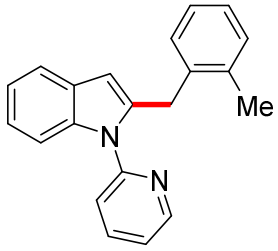


2-(4-Chlorobenzyl)-1-(pyridin-2-yl)-1*H*-indole (11ae): The representative procedure **A** was followed, using substrate **3a** (0.058 g, 0.3 mmol) and 1-chloro-4-methylbenzene (**10e**; 1.1 mL, 9.0 mmol). Purification by column chromatography on neutral alumina (petroleum

ether/EtOAc/Et_3N: 20/1/0.5) yielded **11ae** as a light yellow liquid. Yield: 0.060 g, 63%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.63 (d, J = 3.8 Hz, 1H, Ar–H), 7.78 (td, J = 7.6, 1.5 Hz, 1H, Ar–H), 7.59 (dd, J = 5.7, 3.4 Hz, 1H, Ar–H), 7.32 (dd, J = 5.7, 3.1 Hz, 1H, Ar–H), 7.28 (d, J = 7.6 Hz, 2H, Ar–H), 7.19-7.13 (m, 4H, Ar–H), 6.97 (d, J = 8.0 Hz, 2H, Ar–H), 6.39 (s, 1H, Ar–H), 4.24 (s, 2H, CH_2). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 151.4 (C_q), 149.7 (CH), 139.7 (C_q), 138.4 (CH), 137.6 (C_q), 137.4 (C_q), 132.1 (C_q), 130.3 (2C, CH), 128.5 (C_q), 128.4 (2C, CH), 122.3 (2C, CH), 121.2 (CH), 121.0 (CH), 120.4 (CH), 110.2 (CH), 104.5 (CH), 33.5 (CH_2). HRMS (ESI): *m/z* Calcd for $C_{20}H_{15}ClN_2$+H^+ $[M+H]^+$ 319.0997; Found 319.0994.

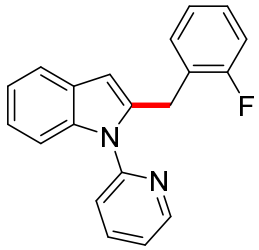


2-(4-Bromobenzyl)-1-(pyridin-2-yl)-1*H*-indole (11af): The representative procedure **B** was followed, using substrate **3a** (0.058 g, 0.3 mmol), 1-bromo-4-methylbenzene (**10f**; 1.1 mL, 9.0 mmol) and cat **2a** (0.0112 g, 0.03 mmol, 10.0 mol %). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 10/1/0.5) yielded **11af** as a light yellow liquid. Yield: 0.052 g, 48%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.65 (d, J = 3.8 Hz, 1H, Ar–H), 7.81 (vt, J = 7.6 Hz, 1H, Ar–H), 7.61-7.59 (m, 1H, Ar–H), 7.35-7.28 (m, 5H, Ar–H), 7.18-7.16 (m, 2H, Ar–H), 6.93 (d, J = 8.0 Hz, 2H, Ar–H), 6.40 (s, 1H, Ar–H), 4.24 (s, 2H, CH_2). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 151.4 (C_q), 149.7 (CH), 139.6 (C_q), 138.4 (CH), 138.0 (C_q), 137.6 (C_q), 131.4 (2C, CH), 130.7 (2C, CH), 128.5 (C_q), 122.3 (2C, CH), 121.2 (CH), 121.0 (CH), 120.4 (CH), 120.2 (C_q), 110.2 (CH), 104.5 (CH), 33.6 (CH_2). $C_{20}H_{15}N_2Br$+H^+ $[M+H]^+$ *m/z* Calcd for 363.0491, 365.0471; Found 363.0495, 365.0468.

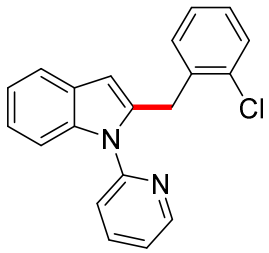


2-(2-Methylbenzyl)-1-(pyridin-2-yl)-1*H*-indole (11ag): The representative procedure **A** was followed, using substrate **3a** (0.058 g, 0.3 mmol) and *ortho*-xylene (**10g**; 1.1 mL, 9.0

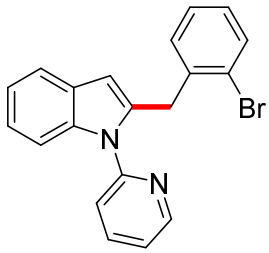
mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 30/1/0.5) yielded **11ag** as a light yellow liquid. Yield: 0.065 g, 73%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.67 (dd, J = 4.6, 1.1 Hz, 1H, Ar–H), 7.83 (vt, J = 7.6 Hz, 1H, Ar–H), 7.57-7.51 (m, 1H, Ar–H), 7.41-7.36 (m, 2H, Ar–H), 7.32-7.27 (m, 1H, Ar–H), 7.18-7.12 (m, 4H, Ar–H), 7.11-7.04 (m, 2H, Ar–H), 6.18 (s, 1H, Ar–H), 4.21 (s, 2H, CH_2), 2.24 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 151.6 (C_q), 149.8 (CH), 139.9 (C_q), 138.4 (CH), 137.6 (C_q), 137.2 (C_q), 136.7 (C_q), 130.3 (CH), 129.8 (CH), 128.7 (C_q), 126.7 (CH), 126.1 (CH), 122.2 (CH), 122.0 (CH), 121.2 (CH), 120.8 (CH), 120.3 (CH), 110.3 (CH), 104.2 (CH), 32.0 (CH_2), 19.5 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{21}H_{18}N_2$+H^+ $[M+H]^+$ 299.1543; Found 299.1542.



2-(2-Fluorobenzyl)-1-(pyridin-2-yl)-1*H*-indole (11ah): The representative procedure **B** was followed, using substrate **3a** (0.058 g, 0.3 mmol), 1-fluoro-2-methylbenzene (**10h**; 0.99 mL, 9.0 mmol) and cat **2a** (0.0112 g, 0.03 mmol, 10.0 mol %). Upon column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 20/1/0.5) yielded **11ah** as a light yellow liquid along with trace of starting compound. Yield (by ^{1}H NMR): 77%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.59 (d, J = 3.8 Hz, 1H, Ar–H), 7.75 (vt, J = 6.3 Hz, 1H, Ar–H), 7.52 (d, J = 5.0 Hz, 1H, Ar–H), 7.31-7.29 (m, 2H, Ar–H), 7.24-7.20 (m, 1H, Ar–H), 7.12-7.09 (m, 3H, Ar–H), 6.99 (vt, J = 7.3 Hz, 1H, Ar–H), 6.93-6.88 (m, 2H, Ar–H), 6.32 (s, 1H, Ar–H), 4.24 (s, 2H, CH_2). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 160.9 (d, $^1J_{C-F}$ = 246.1 Hz, C_q), 151.4 (C_q), 149.8 (CH), 138.8 (C_q), 138.4 (CH), 137.6 (C_q), 131.1 (d, $^4J_{C-F}$ = 3.8 Hz, CH), 128.6 (C_q), 128.2 (d, $^3J_{C-F}$ = 7.6 Hz, CH), 126.0 (d, $^2J_{C-F}$ = 15.3 Hz, C_q), 124.0 (d, $^3J_{C-F}$ = 3.8 Hz, CH), 122.2 (CH), 122.2 (CH), 121.1 (CH), 120.9 (CH), 120.4 (CH), 115.1 (d, $^2J_{C-F}$ = 21.0 Hz, CH), 110.3 (CH), 104.5 (CH), 27.0 (d, $^3J_{C-F}$ = 3.8 Hz, CH_2). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = –118.0 (s). HRMS (ESI): *m/z* Calcd for $C_{20}H_{15}FN_2$+H^+ $[M+H]^+$ 303.1292; Found 303.1292.

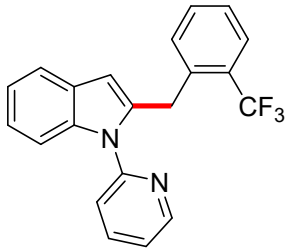


2-(2-Chlorobenzyl)-1-(pyridin-2-yl)-1*H*-indole (11ai): The representative procedure **A** was followed, using substrate **3a** (0.058 g, 0.3 mmol) and 1-chloro-2-methylbenzene (**10i**; 1.1 mL, 9.0 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 20/1/0.5) yielded **11ai** as a light yellow liquid. Yield: 0.086 g, 90%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.64 (dd, J = 4.8, 1.3 Hz, 1H, Ar–H), 7.81 (td, J = 7.6, 1.9 Hz, 1H, Ar–H), 7.58-7.55 (m, 1H, Ar–H), 7.40-7.36 (m, 2H, Ar–H), 7.32-7.27 (m, 2H, Ar–H), 7.17-7.14 (m, 2H, Ar–H), 7.13 (vt, J = 2.7 Hz, 1H, Ar–H), 7.12-7.09 (m, 2H, Ar–H), 6.31 (s, 1H, Ar–H), 4.37 (s, 2H, CH_2). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 151.4 (C_q), 149.8 (CH), 138.6 (C_q), 138.4 (CH), 137.5 (C_q), 136.8 (C_q), 134.2 (C_q), 131.0 (CH), 129.5 (CH), 128.6 (C_q), 127.9 (CH), 126.9 (CH), 122.2 (2C, CH), 121.0 (CH), 120.9 (CH), 120.4 (CH), 110.4 (CH), 104.7 (CH), 31.8 (CH_2). HRMS (ESI): *m/z* Calcd for $C_{20}H_{15}ClN_2$+H^+ $[M+H]^+$ 319.0997; Found 319.0998.

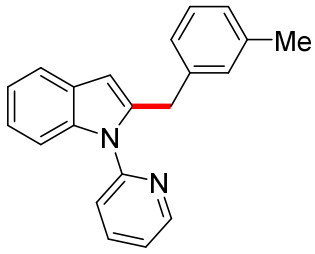


2-(2-Bromobenzyl)-1-(pyridin-2-yl)-1*H*-indole (11aj): The representative procedure **B** was followed, using substrate **3a** (0.058 g, 0.3 mmol), 1-bromo-2-methylbenzene (**10j**; 1.1 mL, 9.0 mmol), and cat **2a** (0.0112 g, 0.03 mmol, 10.0 mol %). Upon column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 20/1/0.5) yielded **11aj** as a light yellow liquid along with trace of starting compound. Yield (by ^{1}H NMR): 52%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.79 (d, J = 3.8 Hz, 1H, Ar–H), 7.96 (vt, J = 7.6 Hz, 1H, Ar–H), 7.74-7.70 (m, 1H, Ar–H), 7.64 (d, J = 7.6 Hz, 1H, Ar–H), 7.54-7.52 (m, 2H, Ar–H), 7.43-7.41 (m, 1H, Ar–H), 7.33-7.26 (m, 4H, Ar–H), 7.20 (vt, J = 7.6 Hz, 1H, Ar–H), 6.45 (s, 1H, Ar–H), 4.51 (s, 2H, CH_2). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 151.4 (C_q), 149.8 (CH), 138.6 (C_q), 138.6 (C_q), 138.4 (CH), 137.5 (C_q), 132.8 (CH), 131.0 (CH), 128.7 (C_q), 128.2 (CH), 127.5 (CH), 124.7 (C_q), 122.2 (CH), 122.2 (CH), 121.0 (CH), 120.9 (CH), 120.4

(CH), 110.4 (CH), 104.8 (CH), 34.5 (CH_2). HRMS (ESI): *m/z* Calcd for $C_{20}H_{15}N_2Br+H^+$ $[M+H]^+$ *m/z* Calcd for 363.0491, 365.0471; Found 363.0498, 365.0469.

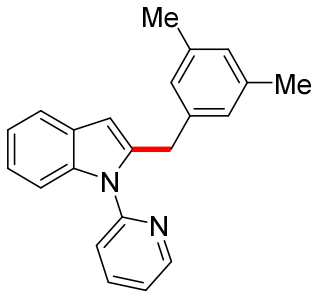


1-(Pyridin-2-yl)-2-(2-(trifluoromethyl)benzyl)-1*H*-indole (11ak): The representative procedure **B** was followed, using substrate **3a** (0.019 g, 0.1 mmol), 1-methyl-2-(trifluoromethyl)benzene (**10k**; 0.41 mL, 3.0 mmol) and cat **2a** (0.0037 g, 0.01 mmol, 10.0 mol %). Upon column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 20/1/0.5) yielded **11ak** along with trace of starting compound. Yield (by ^1H NMR): 48%. ^1H-NMR (500 MHz, $CDCl_3$): δ = 8.60 (d, *J* = 2.3 Hz, 1H, Ar–H), 7.81 (vt, *J* = 6.9 Hz, 1H, Ar–H), 7.65-7.56 (m, 2H, Ar–H), 7.39 (vt, *J* = 8.8 Hz, 2H, Ar–H), 7.32-7.25 (m, 3H, Ar–H), 7.24-7.17 (m, 3H, Ar–H), 6.34 (s, 1H, Ar–H), 4.47 (s, 2H, CH_2). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 151.3 (C_q), 149.8 (CH), 138.4 (CH), 137.7 (C_q), 137.5 (C_q), 135.3 (C_q), 131.9 (CH), 131.3 (CH), 129.6 (q, $^1J_{C-F}$ = 236.5 Hz, C_q), 128.6 (C_q), 128.4 (q, $^3J_{C-F}$ = 3.8 Hz, C_q), 126.6 (CH), 125.9 (q, $^3J_{C-F}$ = 5.7 Hz, CH), 122.3 (CH), 122.2 (CH), 121.0 (CH), 120.9 (CH), 120.4 (CH), 110.5 (CH), 105.4 (CH), 30.7 (CH_2). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = –60.4 (s). HRMS (ESI): *m/z* Calcd for $C_{21}H_{15}N_2F_3+H^+$ $[M+H]^+$ 353.1260; Found 353.1262.

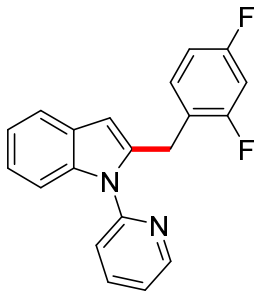


2-(3-Methylbenzyl)-1-(pyridin-2-yl)-1*H*-indole (11al): The representative procedure **A** was followed, using substrate **3a** (0.058 g, 0.3 mmol) and *m*-xylene (**10l**; 1.1 mL, 9.0 mmol). Upon column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 30/1/0.5) yielded **11al** as a light yellow liquid along with trace of starting compound. Yield (by ^1H NMR): 72%. ^1H-NMR (500 MHz, $CDCl_3$): δ = 8.69 (d, *J* = 3.4 Hz, 1H, Ar–H), 7.78 (dd, *J* = 8.8, 1.1 Hz, 1H, Ar–H), 7.62 (d, *J* = 3.4 Hz, 1H, Ar–H), 7.35 (br s, 1H, Ar–H), 7.30 (d, *J* = 7.6 Hz, 2H, Ar–H), 7.19 (br s, 2H, Ar–H), 7.10 (t, *J* = 7.3 Hz, 1H, Ar–H), 6.99 (d, *J* =

7.3 Hz, 1H, Ar–H), 6.93-6.85 (m, 2H, Ar–H), 6.42 (s, 1H, Ar–H), 4.25 (s, 2H, CH_2), 2.27 (s, 3H, CH_3). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 151.5 (C_q), 149.7 (CH), 140.5 (C_q), 138.8 (C_q), 138.3 (CH), 137.9 (C_q), 137.6 (C_q), 129.8 (CH), 128.6 (C_q), 128.2 (CH), 127.0 (CH), 126.1 (CH), 122.2 (CH), 122.0 (CH), 121.4 (CH), 120.8 (CH), 120.3 (CH), 110.2 (CH), 104.2 (CH), 34.1 (CH_2), 21.4 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{21}H_{18}N_2+H^+$ $[M+H]^+$ 299.1543; Found 299.1541.

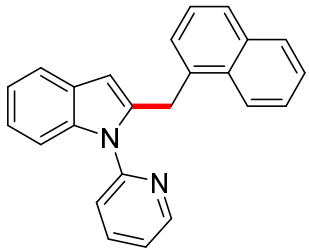


2-(3,5-Dimethylbenzyl)-1-(pyridin-2-yl)-1*H*-indole (11am): The representative procedure **A** was followed, using substrate **3a** (0.058 g, 0.3 mmol) and mesitylene (**10m**; 1.25 mL, 9.0 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 30/1/0.5) yielded **11am** as a light yellow liquid. Yield: 0.092 g, 98%. ^1H-NMR (500 MHz, $CDCl_3$): δ = 8.69 (d, *J* = 4.6 Hz, 1H, Ar–H), 7.79 (td, *J* = 7.6, 1.9 Hz, 1H, Ar–H), 7.63-7.60 (m, 1H, Ar–H), 7.37-7.32 (m, 1H, Ar–H), 7.31-7.27 (m, 2H, Ar–H), 7.20-7.14 (m, 2H, Ar–H), 6.81 (s, 1H, Ar–H), 6.69 (s, 2H, Ar–H), 6.42 (s, 1H, Ar–H), 4.20 (s, 2H, CH_2), 2.23 (s, 6H, CH_3). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 151.6 (C_q), 149.6 (CH), 140.7 (C_q), 138.7 (C_q), 138.2 (CH), 137.7 (2C, C_q), 137.6 (C_q), 128.6 (C_q), 127.9 (CH), 126.9 (2C, CH), 122.1 (CH), 121.9 (CH), 121.5 (CH), 120.8 (CH), 120.3 (CH), 110.2 (CH), 104.1 (CH), 33.9 (CH_2), 21.3 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{22}H_{20}N_2+H^+$ $[M+H]^+$ 313.1699; Found 313.1697.

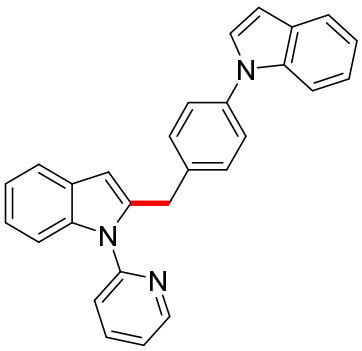


2-(2,4-Difluorobenzyl)-1-(pyridin-2-yl)-1*H*-indole (11an): The representative procedure **B** was followed, using substrate **3a** (0.019 g, 0.1 mmol), 2,4-difluoro-1-

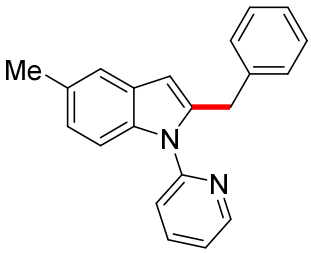
methylbenzene (**10n**; 0.34 mL, 3.0 mmol), cat **2a** (0.0037 g, 0.01 mmol, 10.0 mol %) and chlorobenzene (0.101 mL, 1 mmol). Upon column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 10/1/0.5) yielded **11an** as a light yellow liquid along with trace of starting compound. Yield (by ^1H NMR): 72%. ^1H-NMR (500 MHz, $CDCl_3$): δ = 8.63 (br s, 1H, Ar–H), 7.82 (vt, J = 7.4 Hz, 1H, Ar–H), 7.56 (d, J = 5.3 Hz, 1H, Ar–H), 7.36-7.26 (m, 3H, Ar–H), 7.17-7.13 (m, 2H, Ar–H), 6.99 (d, J = 7.6 Hz, 1H, Ar–H), 6.70 (vt, J = 9.0 Hz, 2H, Ar–H), 6.36 (s, 1H, Ar–H), 4.24 (s, 2H, CH_2). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 161.8 (dd, $^1J_{C-F}$ = 247.0 Hz, $^3J_{C-F}$ = 11.9 Hz, C_q), 160.7 (dd, $^1J_{C-F}$ = 249.0 Hz, $^3J_{C-F}$ = 11.4 Hz, C_q), 151.4 (C_q), 149.8 (CH), 138.5 (CH), 137.6 (C_q), 131.7 (dd, $^3J_{C-F}$ = 9.5, 6.7 Hz, CH), 128.5 (C_q), 128.3 (C_q), 122.3 (CH), 122.3 (CH), 121.9 (dd, $^2J_{C-F}$ = 15.8, $^4J_{C-F}$ = 3.4 Hz, C_q), 121.0 (CH), 121.0 (CH), 120.4 (CH), 111.1 (dd, $^2J_{C-F}$ = 21.0, $^4J_{C-F}$ = 3.8 Hz, CH), 110.3 (CH), 104.5 (CH), 103.6 (t, $^2J_{C-F}$ = 25.8 Hz, CH), 26.6 (d, $^3J_{C-F}$ = 2.9 Hz, CH_2). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = –112.8 (d, $^4J_{F-F}$ = 6.9 Hz), –113.8 (d, $^4J_{F-F}$ = 6.9 Hz). HRMS (ESI): *m/z* Calcd for $C_{20}H_{14}N_2F_2+H^+$ $[M+H]^+$ 321.1198; Found 321.1202.



2-(Naphthalen-1-ylmethyl)-1-(pyridin-2-yl)-1*H*-indole (11ao): The representative procedure **B** was followed, using substrate **3a** (0.058 g, 0.3 mmol) and 1-methylnaphthalene (**10o**; 1.28 mL, 9.0 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 10/1/0.5) yielded **11ao** as a light yellow solid. Yield: 0.051 g, 51%. M.p. = 112-114 °C. ^1H-NMR (500 MHz, $CDCl_3$): δ = 8.67 (dd, J = 5.0, 1.1 Hz, 1H, Ar–H), 8.03 (d, J = 8.0 Hz, 1H, Ar–H), 7.88-7.85 (m, 1H, Ar–H), 7.83 (td, J = 7.6, 2.0 Hz, 1H, Ar–H), 7.76 (d, J = 8.0 Hz, 1H, Ar–H), 7.51-7.42 (m, 4H, Ar–H), 7.40-7.35 (m, 2H, Ar–H), 7.31-7.27 (m, 2H, Ar–H), 7.18-7.11 (m, 2H, Ar–H), 6.17 (s, 1H, Ar–H), 4.70 (s, 2H, CH_2). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 151.6 (C_q), 149.8 (CH), 140.0 (C_q), 138.5 (CH), 137.5 (C_q), 135.0 (C_q), 133.9 (C_q), 132.2 (C_q), 128.7 (C_q), 128.7 (CH), 127.4 (CH), 127.3 (CH), 126.1 (CH), 125.7 (CH), 125.6 (CH), 124.4 (CH), 122.2 (CH), 122.1 (CH), 121.2 (CH), 120.9 (CH), 120.3 (CH), 110.3 (CH), 104.7 (CH), 31.7 (CH_2). HRMS (ESI): *m/z* Calcd for $C_{24}H_{18}N_2+H^+$ $[M+H]^+$ 335.1543; Found 335.1545.

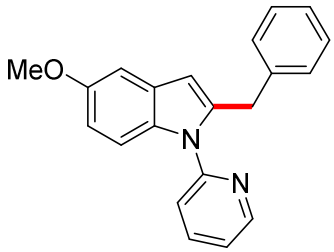


2-(4-(1*H*-Indol-1-yl)benzyl)-1-(pyridin-2-yl)-1*H*-indole (11ap): The representative procedure **B** was followed, using substrate **3a** (0.019 g, 0.1 mmol), 1-(*p*-tolyl)-1*H*-indoletoluene (**10p**; 0.62 g, 3.0 mmol) and chlorobenzene (0.101 mL, 1.0 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 5/1/0.5) yielded **11ap** as a light yellow liquid. Yield: 0.022 g, 55%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.68 (dd, *J* = 5.0, 1.1 Hz, 1H, Ar–H), 8.28 (dd, *J* = 5.0, 1.1 Hz, 1H, Ar–H), 7.79 (td, *J* = 7.7, 1.7 Hz, 1H, Ar–H), 7.70-7.65 (m, 2H, Ar–H), 7.62 (dd, *J* = 5.7, 3.1 Hz, 1H, Ar–H), 7.51-7.47 (m, 2H, Ar–H), 7.35-7.28 (m, 3H, Ar–H), 7.18-7.14 (m, 3H, Ar–H), 7.08 (dd, *J* = 7.1, 5.1 Hz, 1H, Ar–H), 6.92 (s, 1H, Ar–H), 6.82 (d, *J* = 8.0 Hz, 1H, Ar–H), 6.67 (d, *J* = 3.1 Hz, 1H, Ar–H), 6.49 (s, 1H, Ar–H), 4.36 (s, 2H, CH_2). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 151.5 (C_q), 151.1 (C_q), 149.7 (CH), 148.6 (CH), 139.9 (C_q), 138.4 (CH), 138.0 (CH), 137.3 (C_q), 136.0 (C_q), 131.1 (C_q), 130.1 (2C, CH), 129.4 (C_q), 128.6 (C_q), 124.2 (2C, CH), 123.6 (CH), 122.3 (CH), 121.6 (CH), 121.4 (CH), 121.3 (CH), 120.4 (CH), 120.0 (CH), 112.1 (CH), 110.6 (CH), 104.5 (CH), 103.5 (CH), 33.7 (CH_2). HRMS (ESI): *m/z* Calcd for $C_{28}H_{21}N_3$+H^+ $[M+H]^+$ 400.1808; Found 400.1811.

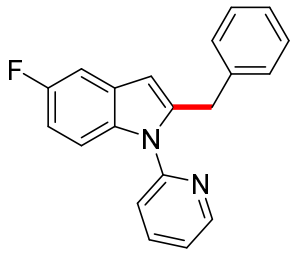


2-Benzyl-5-methyl-1-(pyridin-2-yl)-1*H*-indole (11ba): The representative procedure **A** was followed, using substrate **3b** (0.063 g, 0.3 mmol) and toluene (**10a**; 0.96 mL, 9.0 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 20/1/0.5) yielded **11ba** as a light yellow liquid. Yield: 0.069 g, 77%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.77 (d, *J* = 4.3 Hz, 1H, Ar–H), 7.87 (vt, *J* = 7.6 Hz, 1H, Ar–H), 7.51 (s, 1H, Ar–H), 7.39-7.35 (m, 3H, Ar–H), 7.31-7.27 (m, 3H, Ar–H), 7.19-7.17

(m, 2H, Ar–H), 7.11 (d, J = 8.5 Hz, 1H, Ar–H), 6.46 (s, 1H, Ar–H), 4.40 (s, 2H, CH_2), 2.59 (s, 3H, CH_3). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$): δ = 151.6 (C_q), 149.5 (CH), 140.3 (C_q), 139.0 (C_q), 138.2 (CH), 135.9 (C_q), 130.1 (C_q), 128.9 (2C, CH), 128.8 (C_q), 128.3 (2C, CH), 126.2 (CH), 123.5 (CH), 121.9 (CH), 121.1 (CH), 120.1 (CH), 109.9 (CH), 104.0 (CH), 34.2 (CH_2), 21.5 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{21}H_{18}N_2+H^+$ $[M+H]^+$ 299.1543; Found 299.1544.

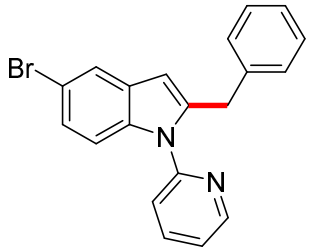


2-Benzyl-5-methoxy-1-(pyridin-2-yl)-1*H*-indole (11ca): The representative procedure **A** was followed, using substrate **3c** (0.067 g, 0.3 mmol) and toluene (**10a**; 0.96 mL, 9.0 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 10/1/0.5) yielded **11ca** as a light yellow liquid. Yield: 0.070 g, 74%. ^1H-NMR (500 MHz, $CDCl_3$): δ = 8.71 (dd, J = 4.6, 1.1 Hz, 1H, Ar–H), 7.83 (td, J = 8.0, 1.9 Hz, 1H, Ar–H), 7.35-7.31 (m, 3H, Ar–H), 7.28-7.20 (m, 3H, Ar–H), 7.16-7.13 (m, 3H, Ar–H), 6.88 (dd, J = 8.8, 2.3 Hz, 1H, Ar–H), 6.39 (s, 1H, Ar–H), 4.33 (s, 2H, CH_2), 3.93 (m, 3H, CH_3). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 155.0 (C_q), 151.6 (C_q), 149.6 (CH), 140.9 (C_q), 139.0 (C_q), 138.3 (CH), 132.7 (C_q), 129.2 (C_q), 129.0 (2C, CH), 128.3 (2C, CH), 126.3 (CH), 122.0 (CH), 121.0 (CH), 111.6 (CH), 111.1 (CH), 104.2 (CH), 102.5 (CH), 56.0 (CH_3), 34.2 (CH_2). HRMS (ESI): *m/z* Calcd for $C_{21}H_{18}N_2O+H^+$ $[M+H]^+$ 315.1492; Found 315.1493.

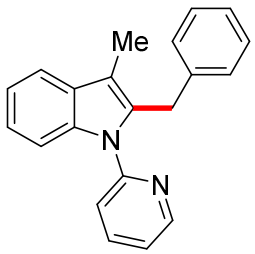


2-Benzyl-5-fluoro-1-(pyridin-2-yl)-1*H*-indole (11da): The representative procedure **A** was followed, using substrate **3d** (0.064 g, 0.3 mmol) and toluene (**10a**; 0.96 mL, 9.0 mmol). Upon column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 10/1/0.5) yielded **11da** as a light yellow liquid along with trace of starting compound. Yield (by ^1H NMR): 79%. ^1H-NMR (500 MHz, $CDCl_3$): δ = 8.71 (dd, J = 5.0, 1.1 Hz, 1H, Ar–H), 7.85 (td,

J = 7.6, 2.0 Hz, 1H, Ar–H), 7.37-7.34 (m, 1H, Ar–H), 7.32- 7.21 (m, 6H, Ar–H), 7.12 (d, J = 6.9 Hz, 2H, Ar–H), 6.94 (td, J = 9.2, 2.4 Hz, 1H, Ar–H), 6.40 (s, 1H, Ar–H), 4.30 (s, 2H, CH_2). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 158.6 (d, $^1J_{C-F}$ = 235.6 Hz, C_q), 151.3 (C_q), 149.7 (CH), 149.1 (C_q), 142.0 (C_q), 138.5 (CH), 134.2 (C_q), 129.0 (2C, CH), 128.4 (2C, CH), 127.4 (C_q), 126.4 (CH), 122.4 (CH), 121.3 (CH), 111.0 (d, $^3J_{C-F}$ = 9.5 Hz, CH), 110.0 (d, $^2J_{C-F}$ = 25.8 Hz, CH), 105.3 (d, $^2J_{C-F}$ = 23.8 Hz, CH), 104.2 (d, $^4J_{C-F}$ = 3.8 Hz, CH), 34.2 (CH_2). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = –123.9 (s). HRMS (ESI): *m/z* Calcd for $C_{20}H_{15}N_2F+H^+$ $[M+H]^+$ 303.1292; Found 303.1294.

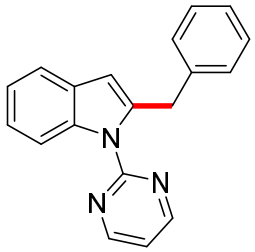


2-Benzyl-5-bromo-1-(pyridin-2-yl)-1*H*-indole (11ea): The representative procedure **A** was followed, using substrate **3e** (0.082 g, 0.3 mmol) and toluene (**10a**; 0.96 mL, 9.0 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 15/1/0.5) yielded **11ea** as a light yellow liquid. Yield: 0.090 g, 83%. ^1H-NMR (500 MHz, $CDCl_3$): δ = 8.64 (d, J = 3.4 Hz, 1H, Ar–H), 7.90 (s, 1H, Ar–H), 7.77 (vt, J = 6.9 Hz, 1H, Ar–H), 7.38 (d, J = 8.4 Hz, 1H, Ar–H), 7.30-7.28 (m, 1H, Ar–H) 7.22-7.14 (m, 4H, Ar–H), 7.07 (d, J = 8.4 Hz, 1H, Ar–H), 7.02 (d, J = 6.9 Hz, 2H, Ar–H), 6.31 (s, 1H, Ar–H) 4.23 (s, 2H, CH_2). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 151.0 (C_q), 149.8 (CH), 141.3 (2C, C_q), 138.5 (CH), 136.8 (C_q), 131.1 (C_q), 130.3 (CH), 129.1 (CH), 128.9 (2C, CH), 128.4 (2C, CH), 126.5 (CH), 122.6 (CH), 121.3 (CH), 112.3 (CH), 103.4 (CH), 84.3 (C_q), 34.0 (CH_2). HRMS (ESI): *m/z* Calcd for $C_{20}H_{15}N_2Br+H^+$ $[M+H]^+$ 363.0491, 365.0471; Found 363.0496, 365.0468.

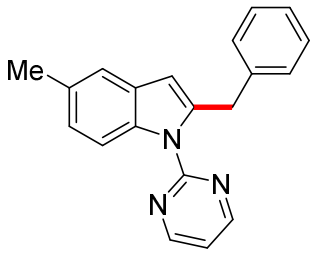


2-Benzyl-3-methyl-1-(pyridin-2-yl)-1*H*-indole (11fa): The representative procedure **A** was followed, using substrate **3f** (0.062 g, 0.3 mmol), toluene (**10a**; 0.96 mL, 9.0 mmol), and

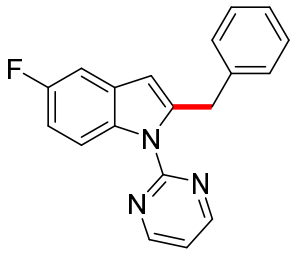
cat **2a** (0.0112 g, 0.03 mmol, 10.0 mol %). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 20/1/0.5) yielded **11fa** as a light yellow liquid. Yield: 0.058 g, 65%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.60 (d, J = 3.8 Hz, 1H, Ar–H), 7.67 (td, J = 8.0, 1.7 Hz, 1H, Ar–H), 7.61 (d, J = 6.9 Hz, 1H, Ar–H), 7.31 (d, J = 7.3 Hz, 1H, Ar–H), 7.22-7.16 (m, 3H, Ar–H), 7.12 (d, J = 8.0 Hz, 1H, Ar–H), 7.10-7.04 (m, 3H, Ar–H), 6.87 (d, J = 7.3 Hz, 2H, Ar–H), 4.32 (s, 2H, CH_2), 2.40 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 151.8 (C_q), 149.5 (CH), 139.5 (C_q), 138.2 (CH), 136.9 (C_q), 135.1 (C_q), 129.5 (C_q), 128.3 (4C, CH), 126.0 (CH), 122.3 (CH), 121.9 (CH), 121.4 (CH), 120.4 (CH), 118.7 (CH), 111.3 (C_q), 110.1 (CH), 30.9 (CH_2), 9.2 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{21}H_{18}N_2$+H^+ $[M+H]^+$ 299.1543; Found 299.1544.



2-Benzyl-1-(pyrimidin-2-yl)-1*H*-indole (11ga): The representative procedure **B** was followed, using substrate **3g** (0.058 g, 0.297 mmol), toluene (**10a**; 0.96 mL, 9.0 mmol) and cat **2a** (0.0112 g, 0.03 mmol, 10.0 mol %). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 20/1/0.5) yielded **11ga** as a light yellow liquid. Yield: 0.052 g, 61%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.78 (d, J = 4.6 Hz, 2H, Ar–H), 8.35 (d, J = 8.0 Hz, 1H, Ar–H), 7.59 (d, J = 7.3 Hz, 1H, Ar–H), 7.33-7.21 (m, 7H, Ar–H), 7.12 (t, J = 4.8 Hz, 1H, Ar–H), 6.41 (s, 1H, Ar–H), 4.66 (s, 2H, CH_2). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 158.3 (C_q), 158.2 (2C, CH), 140.7 (C_q), 139.5 (C_q), 137.3 (C_q), 129.3 (C_q), 129.2 (2C, CH), 128.4 (2C, CH), 126.2 (CH), 122.9 (CH), 122.0 (CH), 120.1 (CH), 117.1 (CH), 114.1 (CH), 108.0 (CH), 36.1 (CH_2). HRMS (ESI): *m/z* Calcd for $C_{19}H_{15}N_3$+H^+ $[M+H]^+$ 286.1339; Found 286.1341. The ^{1}H and ^{13}C spectra are consistent with those reported in the literature.[63]

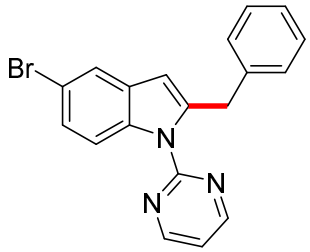


2-Benzyl-5-methyl-1-(pyrimidin-2-yl)-1*H*-indole (11ha): The representative procedure **B** was followed, using substrate **3h** (0.063 g, 0.3 mmol), toluene (**10a**; 0.96 mL, 9.0 mmol) and cat **2a** (0.0112 g, 0.03 mmol, 10.0 mol %). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 10/1/0.5) yielded **11ha** as a light yellow liquid. Yield: 0.074 g, 82%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.70 (d, J = 4.6 Hz, 2H, Ar–H), 8.20 (d, J = 8.4 Hz, 1H, Ar–H), 7.31 (s, 1H, Ar–H), 7.21 (d, J = 7.3 Hz, 2H, Ar–H), 7.18-7.14 (m, 3H, Ar–H), 7.07 (d, J = 8.0 Hz, 1H, Ar–H), 7.03 (t, J = 4.8 Hz, 1H, Ar–H), 6.27 (s, 1H, Ar–H), 4.58 (s, 2H, CH_2), 2.45 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 158.4 (C_q), 158.1 (2C, CH), 140.7 (C_q), 139.7 (C_q), 135.6 (C_q), 131.4 (C_q), 129.5 (C_q), 129.1 (2C, CH), 128.3 (2C, CH), 126.2 (CH), 124.3 (CH), 119.9 (CH), 116.9 (CH), 114.0 (CH), 108.0 (CH), 36.3 (CH_2), 21.5 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{20}H_{17}N_3$+H^+ $[M+H]^+$ 300.1495; Found 300.1497.

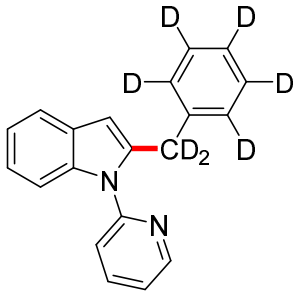


2-Benzyl-5-fluoro-1-(pyrimidin-2-yl)-1*H*-indole (11ia): The representative procedure **B** was followed, using substrate **3i** (0.064 g, 0.3 mmol), toluene (**10a**; 0.96 mL, 9.0 mmol) and cat **2a** (0.0112 g, 0.03 mmol, 10.0 mol %). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 10/1/0.5) yielded **11ia** as a light yellow liquid. Yield: 0.063 g, 69%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.71 (d, J = 5.0 Hz, 2H, Ar–H), 8.24 (dd, J = 9.0, 4.8 Hz, 1H, Ar–H), 7.25-7.22 (m, 2H, Ar–H), 7.18-7.13 (m, 4H, Ar–H), 7.08 (t, J = 5.0 Hz, 1H, Ar–H), 6.96 (td, J = 9.2, 2.7 Hz, 1H, Ar–H), 6.27 (s, 1H, Ar–H), 4.57 (s, 2H, CH_2). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 159.1 (d, $^1J_{C-F}$ = 236.5 Hz, C_q), 158.5 (C_q), 158.2 (2C, CH), 142.5 (C_q), 139.3 (C_q), 133.7 (C_q), 130.0 (d, $^4J_{C-F}$ = 9.5 Hz, C_q), 129.2 (2C, CH), 128.5 (2C, CH), 126.4 (CH), 117.3 (CH), 115.2 (d, $^3J_{C-F}$ = 8.6 Hz, CH), 110.6 (d, $^2J_{C-F}$ = 24.8 Hz, CH), 107.8 (d, $^4J_{C-F}$ = 3.8 Hz, CH), 105.2 (d, $^2J_{C-F}$ = 23.8 Hz, CH), 36.3 (CH_2).

^{19}F-NMR (377 MHz, $CDCl_3$): δ = –122.5 (s). HRMS (ESI): *m/z* Calcd for $C_{19}H_{14}N_3F+H^+$ $[M+H]^+$ 304.1245; Found 304.1248.



2-Benzyl-5-bromo-1-(pyrimidin-2-yl)-1*H*-indole (11ja): The representative procedure **B** was followed, using substrate **3j** (0.082 g, 0.3 mmol), toluene (**10a**; 0.96 mL, 9.0 mmol) and cat **2a** (0.0112 g, 0.03 mmol, 10.0 mol %). Upon column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 10/1/0.5) yielded **11ja** as a light yellow solid along with trace of starting compound. Yield (by ^{1}H NMR): 52%. M.p. = 98-100 ^{o}C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.72 (d, *J* = 4.6 Hz, 2H, Ar–H), 8.05 (d, *J* = 8.8 Hz, 1H, Ar–H), 7.83 (s, 1H, Ar–H), 7.48 (d, *J* = 8.8 Hz, 1H, Ar–H), 7.24-7.21 (m, 2H, Ar–H), 7.17-7.14 (m, 3H, Ar–H), 7.09 (t, *J* = 4.6 Hz, 1H, Ar–H), 6.24 (s, 1H, Ar–H), 4.56 (s, 2H, CH_2). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 158.2 (2C, CH), 158.1 (C_q), 141.8 (C_q), 139.1 (C_q), 136.6 (C_q), 131.7 (C_q), 131.3 (CH), 129.1 (2C, CH), 128.8 (CH), 128.5 (2C, CH), 126.4 (CH), 117.5 (CH), 116.3 (CH), 107.0 (CH), 85.8 (C_q), 36.1 (CH_2). HRMS (ESI): *m/z* Calcd for $C_{19}H_{14}N_3Br+H^+$ $[M+H]^+$ 364.0444, 366.0423; Found 364.0444, 366.0422.



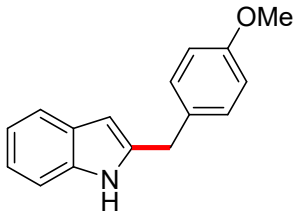
2-((phenyl-d5)methyl-d2)-1-(pyridin-2-yl)-1*H*-indole ([D$_7$]-11aa): The representative procedure **A** was followed, using substrate **3a** (0.058 g, 0.3 mmol) and toluene-d_8 ([D_8]-**10a**; 0.96 mL, 9.0 mmol). Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 20/1/0.5) yielded [D_7]-**11aa** as a light yellow liquid. Yield: 0.030 g, 34%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.64 (dd, *J* = 5.0, 1.5 Hz, 1H, Ar–H), 7.75 (td, *J* = 7.8, 1.7 Hz, 1H, Ar–H), 7.57 (dd, *J* = 6.1, 3.1 Hz, 1H, Ar–H), 7.31 (dd, *J* = 5.9, 3.2 Hz, 1H, Ar–H), 7.28-7.24 (m, 2H, Ar–H), 7.15-7.11 (m, 2H, Ar–H), 6.38 (s, 1H, Ar–H). ^{13}C{^{1}H}-NMR (125

MHz, $CDCl_3$): δ = 151.5 (C_q), 149.7 (CH), 140.3 (C_q), 138.7 (C_q), 138.3 (CH), 137.6 (C_q), 128.6 (C_q), 128.6 (t, J = 24.8 Hz, 2C, CD), 127.8 (t, J = 23.8 Hz, 2C, CD), 125.8 (t, J = 24.8 Hz, CD), 122.2 (CH), 122.0 (CH), 121.4 (CH), 120.8 (CH), 120.3 (CH), 110.2 (CH), 104.3 (CH), 33.6 (pent, J = 19.1 Hz, CD_2). HRMS (ESI): *m/z* Calcd for $C_{20}H_9D_7N_2+H^+$ $[M+H]^+$ 292.1826; Found 292.1828.

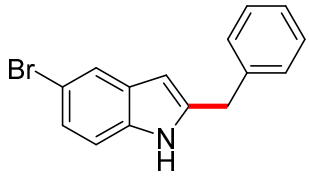
3.4.3 Procedure for Removal of Directing Group and Characterization Data

Removal of 2-Pyrimidinyl Group: To an oven dried Schlenk flask, **11ga** (0.049 g, 0.172 mmol) and EtONa (0.047g, 0.688 mmol) was introduced and DMSO (2 mL) was added into it. The resultant reaction mixture was stirred at 110 ^oC for 24 h. At ambient temperature, the reaction mixture was quenched with distilled H_2O (10 mL) and extracted with EtOAc (15 mL x 3). The combined organic layer was washed with H_2O (15 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 neutral alumina (petroleum ether/EtOAc/Et_3N: 3/1/0.5) to yielded **12aa** as a light yellow liquid. Yield: 0.027 g, 76%. ^1H-NMR (500 MHz, $CDCl_3$): δ = 7.80 (br s, 1H, NH), 7.57 (d, J = 7.6 Hz, 1H, Ar–H), 7.39-7.32 (m, 2H, Ar–H), 7.32-7.23 (m, 4H, Ar–H), 7.16-7.07 (m, 2H, Ar–H), 6.36 (s, 1H, Ar–H), 4.16 (s, 2H, CH_2). $^{13}C\{^1H\}$-NMR (125 MHz, $CDCl_3$): δ = 138.7 (C_q), 138.0 (C_q), 136.5 (C_q), 129.0 (2C, CH), 128.9 (2C, CH), 128.9 (C_q), 126.9 (CH), 121.5 (CH), 120.2 (CH), 119.9 (CH), 110.6 (CH), 101.3 (CH), 34.9 (CH_2). HRMS (ESI): *m/z* Calcd for $C_{15}H_{13}N+H^+$ $[M+H]^+$ 208.1121; Found 208.1124.

Removal of 2-Pyridinyl Group: In an oven dried Schlenk tube, the compound **11ac** (0.042 g, 0.134 mmol) or **11ea** (0.049 g, 0.135 mmol) was introduced and CH_2Cl_2 (5 mL) was added into it. Methyl trifluoromethanesulfonate, MeOTf (0.018 mL, 0.027 g, 0.16 mmol) was added dropwise *via* a syringe to the reaction mixture at 0 ^oC, and the resultant reaction mixture was stirred at room temperature for 12 h. Then the volatiles were evaporated under vacuum and the residue was redissolved in MeOH (3.0 mL). To the resultant mixture, 2M aq. NaOH (2.0 mL) solution was added and the reaction mixture was stirred at 60 ^oC for 10 h. At ambient temperature, the volatiles were evaporated under reduced pressure, and the resulting residue was extracted with EtOAc (15 mL x 3). The combined organic extract was washed with brine, dried over Na_2SO_4 and the volatiles were evaporated in *vacuo*. The remaining residue was purified by preparative TLC (petroleum ether/EtOAc: 5/1) to yield **12ac** or **12ea** as liquid.



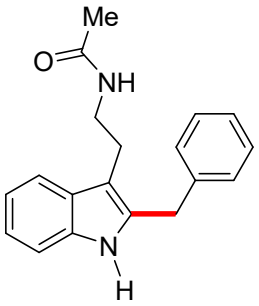
2-(4-Methoxybenzyl)-1*H*-indole (12ac): Yield: 0.026 g, 82%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.77 (br s, 1H, N–H), 7.55 (d, J = 7.2 Hz, 1H, Ar–H), 7.25 (d, J = 8.0 Hz, 1H, Ar–H), 7.18 (d, J = 8.0 Hz, 2H, Ar–H), 7.15-7.04 (m, 2H, Ar–H), 6.88 (d, J = 7.6 Hz, 2H, Ar–H), 6.32 (s, 1H, Ar–H), 4.08 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3). $^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$): δ = 158.6 (C_q), 138.5 (C_q), 136.4 (C_q), 130.7 (C_q), 130.0 (2C, CH), 128.9 (C_q), 121.4 (CH), 120.1 (CH), 119.9 (CH), 114.3 (2C, CH), 110.6 (CH), 101.0 (CH), 55.5 (CH_3), 34.0 (CH_2). HRMS (ESI): *m/z* Calcd for $C_{16}H_{15}NO+H^+$ $[M+H]^+$ 238.1226; Found 238.1225.



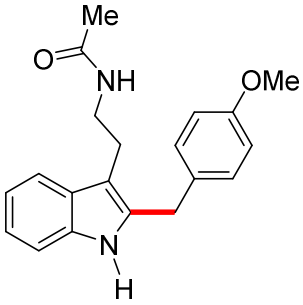
2-Benzyl-5-bromo-1*H*-indole (12ea): Yield: 0.026 g, 67%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.90 (s, 1H, Ar–H), 7.83 (br s, 1H, N–H), 7.40-7.35 (m, 3H, Ar–H), 7.32-7.26 (m, 3H, Ar–H), 7.05 (d, J = 8.5 Hz, 1H, Ar–H), 6.29 (s, 1H, Ar–H), 4.15 (s, 2H, CH_2). $^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$): δ = 139.0 (C_q), 138.2 (C_q), 135.5 (C_q), 131.5 (C_q), 129.8 (CH), 129.0 (4C, CH), 128.9 (CH), 127.1 (CH), 112.6 (CH), 100.6 (CH), 83.3 (C_q), 34.8 (CH_2). HRMS (ESI): *m/z* Calcd for $C_{15}H_{12}BrN+H^+$ $[M+H]^+$ 286.0226, 288.0205; Found 286.0225, 288.0204.

3.4.4 Procedure for Synthesis of Luzindole Derivatives and Characterization Data

A solution of **12aa** (0.022 g, 0.106 mmol) [or **12ac** (0.025 g, 0.105 mmol)] and *N*-(2,2-dimethoxyethyl)acetamide (0.017 g, 0.116 mmol) in CH_2Cl_2 (2.0 mL) was added to the mixture of trifluoroacetic acid (0.06 g, 0.525 mmol) and triethylsilane (0.037g, 0.318 mmol) in CH_2Cl_2 (1.0 mL), and the resulted reaction mixture was stirred at room temperature for 4 h. The reaction mixture was cooled to 0 °C, neutralized with saturated aqueous solution of $NaHCO_3$ and diluted with CH_2Cl_2. Aqueous layer was extracted with CH_2Cl_2 (20 mL x 3). The combined organic extract was washed with brine, dried over Na_2SO_4 and the volatiles were evaporated in *vacuo*. The remaining residue was purified by preparative TLC (EtOAc) to yield the compound **13aa** or **13ac**.



***N*-(2-(2-Benzyl-1*H*-indol-3-yl)ethyl)acetamide (13aa):** Yield: 0.022 g, 71%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.79 (br s, 1H, N–H), 7.57 (d, J = 7.6 Hz, 1H, Ar–H), 7.35-7.30 (m, 2H, Ar–H), 7.31-7.28 (m, 2H, Ar–H), 7.21 (d, J = 7.2 Hz, 2H, Ar–H), 7.16-7.12 (m, 2H, Ar–H), 5.46 (br s, 1H, N–H), 4.14 (s, 2H, CH_2), 3.55 (q, J = 6.4 Hz, 2H, CH_2), 3.02 (vt, J = 6.5 Hz, 2H, CH_2), 1.81 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 170.3 (CO), 138.8 (C_q), 135.8 (C_q), 134.4 (C_q), 129.1 (2C, CH), 128.7 (2C, CH), 128.1 (C_q), 127.0 (CH), 121.9 (CH), 119.8 (CH), 118.5 (CH), 110.8 (CH), 109.7 (C_q), 40.3 (CH_2), 32.4 (CH_2), 24.4 (CH_2), 23.5 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{19}H_{20}N_2O+H^+$ $[M+H]^+$ 293.1648; Found 293.1645. The ^{1}H and ^{13}C spectra are consistent with those reported in the literature.[66]



***N*-(2-(2-(4-Methoxybenzyl)-1*H*-indol-3-yl)ethyl)acetamide (13ac):** Yield: 0.022 g, 65%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.80 (br s, 1H, N–H), 7.57 (d, J = 7.3 Hz, 1H, Ar–H), 7.28 (br s, 1H, Ar–H), 7.20-7.07 (m, 4H, Ar–H), 6.87 (d, J = 7.9 Hz, 2H, Ar–H), 5.48 (br s, 1H, N–H), 4.08 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3), 3.55 (q, J = 6.3 Hz, 2H, CH_2), 3.01 (vt, J = 6.4 Hz, 2H, CH_2), 1.84 (s, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 170.2 (CO), 158.7 (C_q), 135.7 (C_q), 134.9 (C_q), 130.7 (C_q), 129.7 (2C, CH), 128.7 (C_q), 121.8 (CH), 119.7 (CH), 118.4 (CH), 114.5 (2C, CH), 110.8 (CH), 109.3 (C_q), 55.5 (OCH_3), 40.3 (CH_2), 31.5 (CH_2), 24.4 (CH_2), 23.5 (CH_3). HRMS (ESI): *m/z* Calcd for $C_{20}H_{22}N_2O_2+H^+$ $[M+H]^+$ 323.1754; Found 323.1750.

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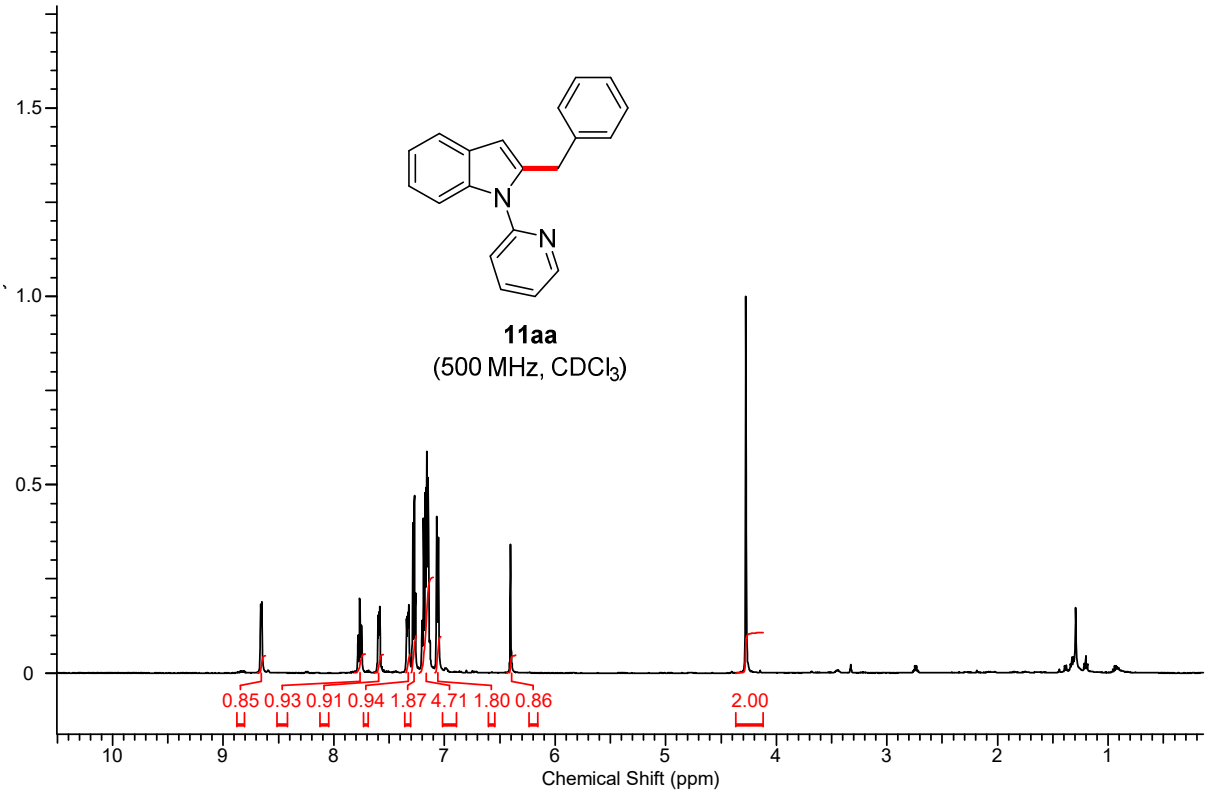
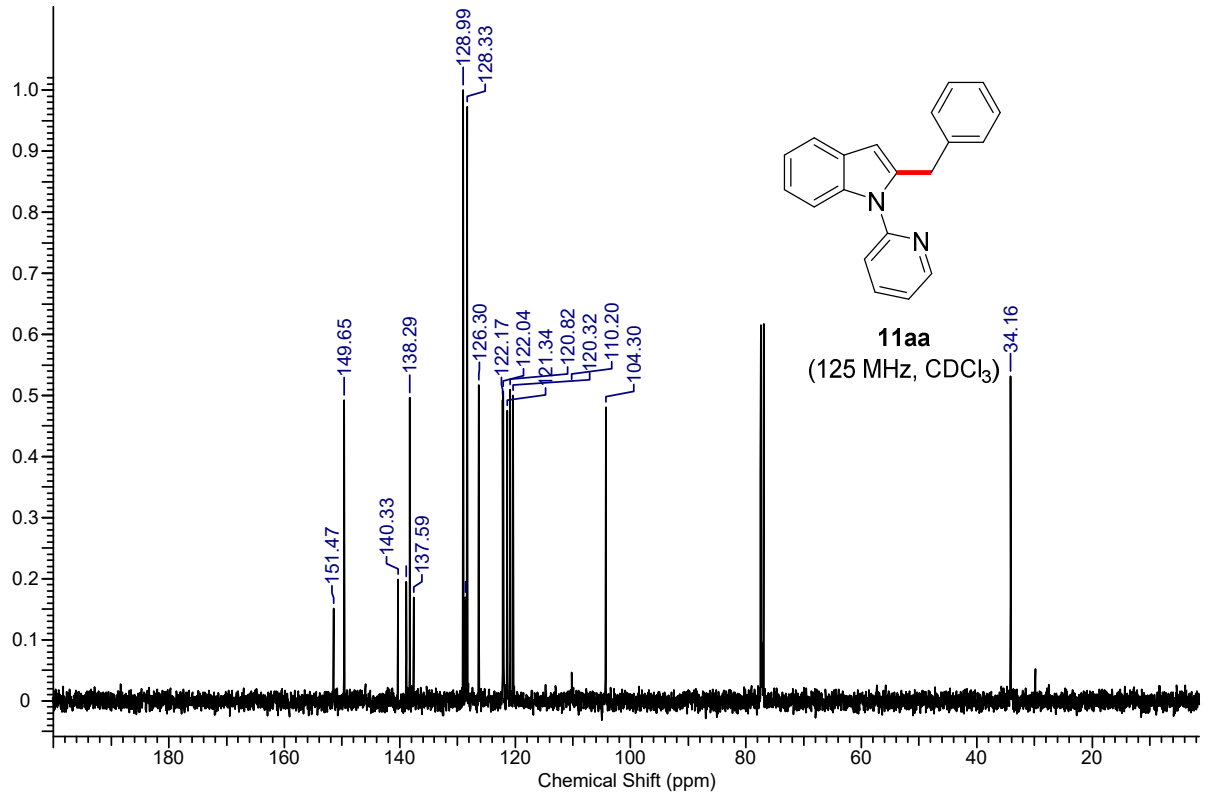
NMR Spectra of Representative Benzylated Indole





Chapter 4

Mechanistic Aspects of Nickel-Catalyzed Alkylation and Benzylation of Indoles

4.1 INTRODUCTION

Transition-metal-catalyzed C–H bond alkylation of heteroarenes with unactivated alkyl halides bearing *β*-hydrogen is one of the most promising and challenging reaction, because of the trivial *β*-hydride elimination and/or hydrodehalogenation of the alkyl electrophiles upon oxidative addition to the transition metal.[1-7] Regardless of this, few methods are known for the alkylation of indoles employing precious Pd-metal catalyst.[8-11] Considering the importance of earth-abundant 3d transition metals, Ackermann *et al.* described an inexpensive Co-catalyzed C-2 alkylation of indoles with primary alkyl chlorides, however, the use of strong base Grignard reagent (CyMgCl) limits this methodology.[12-15] Particularly, the alkylation of indoles by the nickel is significant because of the unique reactivity of this inexpensive and earth-abundant metal. In this direction, Ackermann and co-worker reported the Ni-catalyzed alkylation of indole-3-carboxamide with secondary alkyl halides through the bidentate-chelate assistance, however, with the limited scope.[16]

Despite some progress on methodology, the detailed mechanistic insight for the nickel-catalyzed C−H bond alkylation is not well understood, which enforce the assumption of various catalytic pathways. For example, Chatani has hypothesized a Ni^{II}/Ni^{IV} catalytic cycle for the alkylation of benzamide that proceeds *via* bidentate-chelation assistance.[17,18] Similary Ge proposed a Ni^{II}/Ni^{IV} catalytic pathway for the alkylation of $C(sp^3)$−H bond on amides.[19] A Ni^{0}/Ni^{II} catalytic cycle has been hypotheiszed for the nickel-catalyzed alkylation of azoles.[20] Notably, all these proposals don't have much experimental evidences to support the mechanism. With regards to the nickel-catalyzed benzylation, Fu *et al.* has performed the mechanistic studies for the oxidative coupling of benzamide with toluene,[21] the reaction that was originally reported by Chatani.[22] The reaction has been proposed to proceed through Ni^{II}/Ni^{III} pathway *via* iodine-atom-transfer (IAT) mechanism. However, the mechanistic detail of the nickel-catalyzed benzylation of indole is not known.

In chapter 2, the nickel-catalyzed regioselective C(2)-alkylation of indoles is described using monodentate directing group, wherein the well-defined pincer nickel catalyst efficiently catalyzes the reaction. Chapter 3 detailed the nickel-catalyzed $C(sp^2)$–H/$C(sp^3)$–H oxidative coupling of indoles with toluene derivatives. This chapter describes the mechanistic study of nickel-catalyzed alkylation as well as benzylation of indole by the well-defined pincer nickel complex. Various reactivity studies, detailed kinetic experiments and isotope labeling experiments have been performed to get more mechanistic insights. Mechanistic cycles have been drawn for both the alkylation and benzylation reactions.

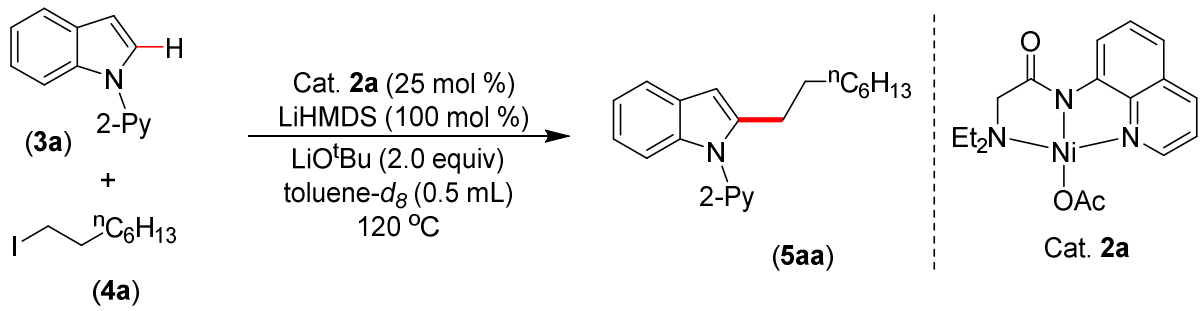
4.2 RESULTS AND DISCUSSION

4.2.1 MECHANISTIC ASPECTS OF INDOLE ALKYLATION

Considering the well-defined nature of catalyst $\kappa^N,\kappa^N,\kappa^N$-{$Et_2NCH_2C(O)$-($\mu$-N)-$C_9H_6N$}NiOAc (**2a**) and unique versatility of the C–H alkylation of indoles, we have performed mechanistic experiments for the alkylation of indole. Various controlled experiments were carried out to know the working mode of the catalyst. External additive experiment and radical clock experiments were executed to understand the status of active catalyst. Deuterium labeling experiments and kinetic studies were performed to know the C−H activation process during the reaction.

4.2.1.1 NMR Study of Alkylation Reaction

The NMR experiment was performed to know about the possible intermediate species that might form during the reaction. In a J-Young NMR tube, 1-(pyridin-2-yl)-1*H*-indole (**3a**), 1-iodooctane (**4a**), catalyst **2a** (25 mol %), LiHMDS (4.0 equiv w.r.t. **2a**) and LiO^tBu were introduced, and toluene-d_8 was added to it (Scheme 4.1). The resultant reaction mixture was heated at 120 °C in a preheated oil bath and the ^{1}H NMR was recorded at different time interval (1 h, 3 h, and 16 h). In all the run, ^{1}H NMR showed the signals correspond to the coupled alkylated product **5aa**; however, neither the complex **2a** or its derivative, or the formation of free-ligand was observed. In addition, the GC analysis of this reaction mixture did not show the formation of free-ligand, which suggests the probable involvement of a paramagnetic catalytic species.

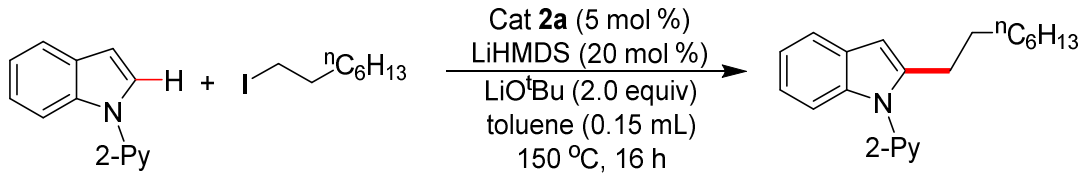


Scheme 4.1 NMR Tube Experiment.

4.2.1.2 External Additive Studies

The alkylation reaction of indole **3a** with alkyl iodide **4a** in the presence of 200 equiv and 600 equiv of Hg with respect to catalyst under the standard catalytic conditions afforded the product **5aa** in 40% and 38% yield, respectively (Scheme 4.2). The addition of Hg led to the lowering in yield of **5aa** (~ 40%), however, the reaction was not completely shutdown;

indicating the probable homogeneous character of nickel catalyst. The standard alkylation reaction in the presence of 2.0 equiv of TEMPO suppressed the catalysis completely, which suggests the involvement of radical intermediate during the reaction. Unfortunately, the coupling of TEMPO with any of the organic intermediate was not detected.



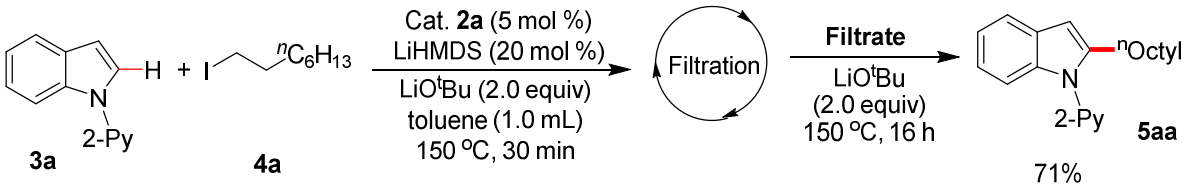
3a **4a** **5aa**

Additive	Yield (%)
No additive:	82
Hg (200 equiv):	40
Hg (600 equiv):	38
TEMPO:	0

Scheme 4.2 Alkylation Reaction in Presence of External Additives.

4.2.1.3 Filtration Study

Filtration experiment was performed to know the nature of the catalyst during the reaction. In a screw-capped tube 1-(pyridin-2-yl)-1*H*-indole (**3a**), 1-iodooctane (**4a**), catalyst **2a,** LiHMDS and LiO^{t}Bu were taken inside the glove-box (Scheme 4.3). To the above mixture, toluene and internal standard *n*-dodecane were added, and the resultant reaction mixture was stirred at 150 °C in a preheated oil bath for 30 min, wherein GC analysis of the reaction mixture shows 14% yield of **5aa**. The reaction mixture was filtered inside the glove-box to another screw cap tube containing LiO^{t}Bu (2.0 equiv) and the resultant reaction mixture was stirred at 150 °C for 16 h. The GC analysis of the reaction mixture showed 71% yield of **5aa** w.r.t. internal standard. This experiment demonstrated that the alkylation proceeded even after the initial filtration, suggesting that heterogeneous particles may not be the active catalyst during the reaction.



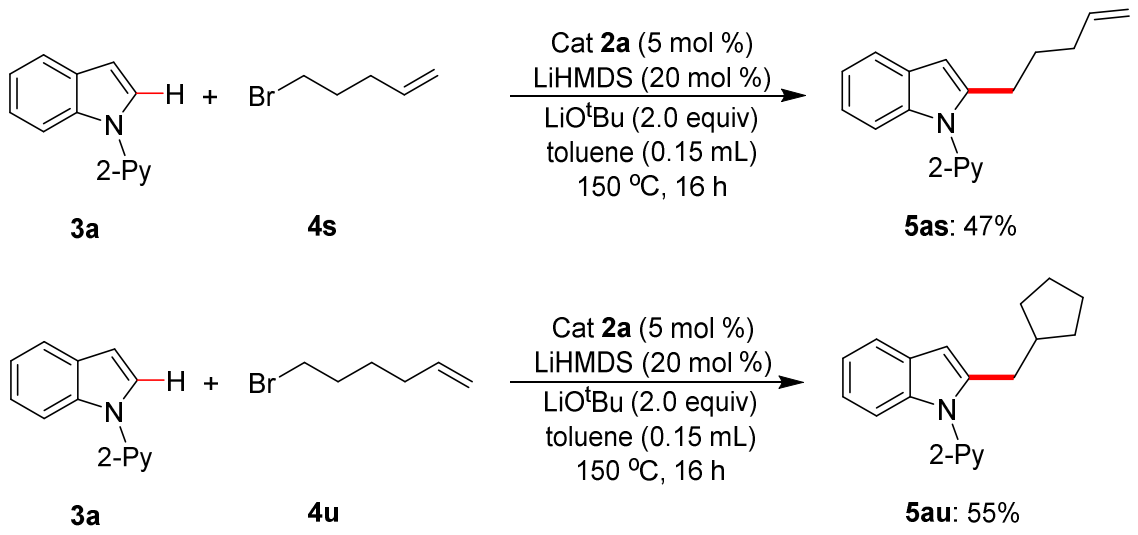
3a **4a** **5aa**

71%

Scheme 4.3 Filtration Experiment.

4.2.1.4 Radical Clock Studies of Alkylation

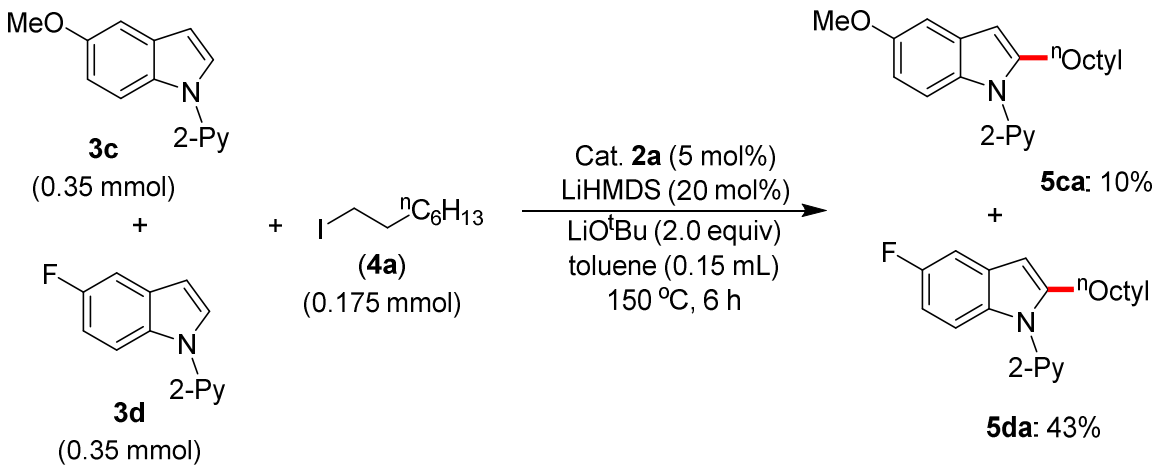
Radical clock experiment was performed to support the preliminary observation of radical pathway for the alkylation reaction. Two independent reactions were carried out with 5-bromopent-1-ene (**4s**) and 6-bromohex-1-ene (**4u**) under the standard reaction condition (Scheme 4.4). The reaction of **3a** with **4s** resulted in the formation of expected alkylated product **5as**, while the reaction of **3a** with **4u** gave alkylated product **5au** resulting from the radical cyclization. This observation clearly confirms the involvement of an alkyl radical intermediate during the **2a**-catalyzed alkylation reaction.



Scheme 4.4 Nickel-Catalyzed Radical Clock Experiment.

4.2.1.5 Intermolecular Competition Studies

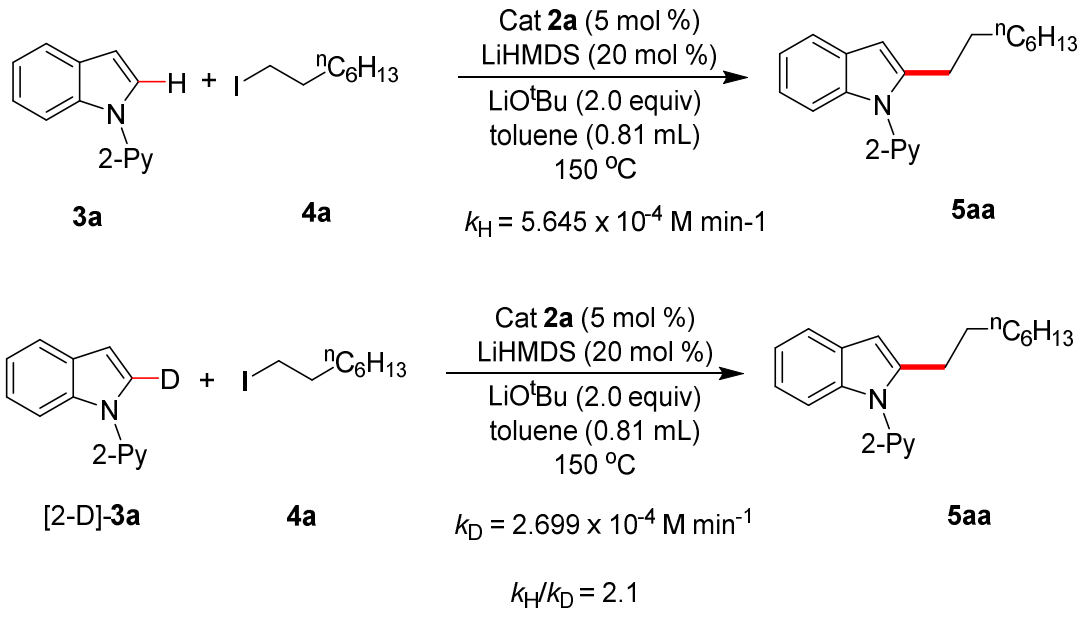
An intermolecular competition experiment was performed between electronically distinct substrates 5-methoxy-1-(pyridin-2-yl)-1*H*-indole (**3c**) and 5-fluoro-1-(pyridin-2-yl)-1*H*-indole (**3d**) using the standard reaction conditions for 6 h (Scheme 4.5). Both the expected products were isolated by column chromatography and found that the product **5da** obtained in 43%, while **5ca** obtained in 10%. This result highlights that the electron-withdrawing substituent on indole significantly favors the reaction, which manifest the importance of C–H acidity during the reaction.



Scheme 4.5 Intermolecular Competition Experiment.

4.2.1.6 Isotope Labeling Studies

4.2.1.6.1 Kinetic Isotope Effect (KIE) Study: To know whether the C–H bond breaking is involved in the rate determining step, the kinetic isotope effect (KIE) study was carried out using 1-(pyridin-2-yl)-1*H*-indole (**3a**) and 1-(pyridin-2-yl)-1*H*-indole-2-*d* ([2-D]-**3a**) (Scheme 4.6). The rate of alkylation of **3a** with alkyl iodide **4a** was calculated to be 5.645 x 10^{-4} $Mmin^{-1}$. Similarly, the rate of alkylation reaction of [2-D]-**3a** with iodide **4a** was 2.699 x 10^{-4} $Mmin^{-1}$. From these two reaction rates, the kinetic isotope effect (KIE) value calculated as k_H/k_D = 2.1 (Figure 4.1). This indicates that the C–H bond nickelation is significant with respect to the turnover-limiting step.



Scheme 4.6 Kinetic Isotope Effect Experiment.

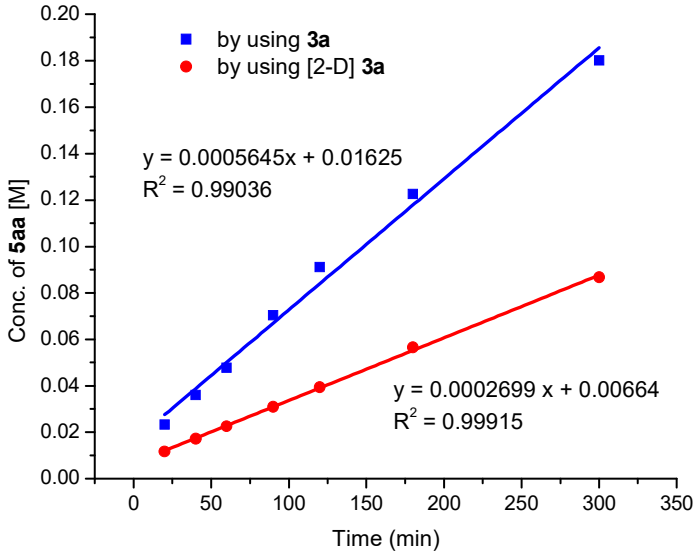
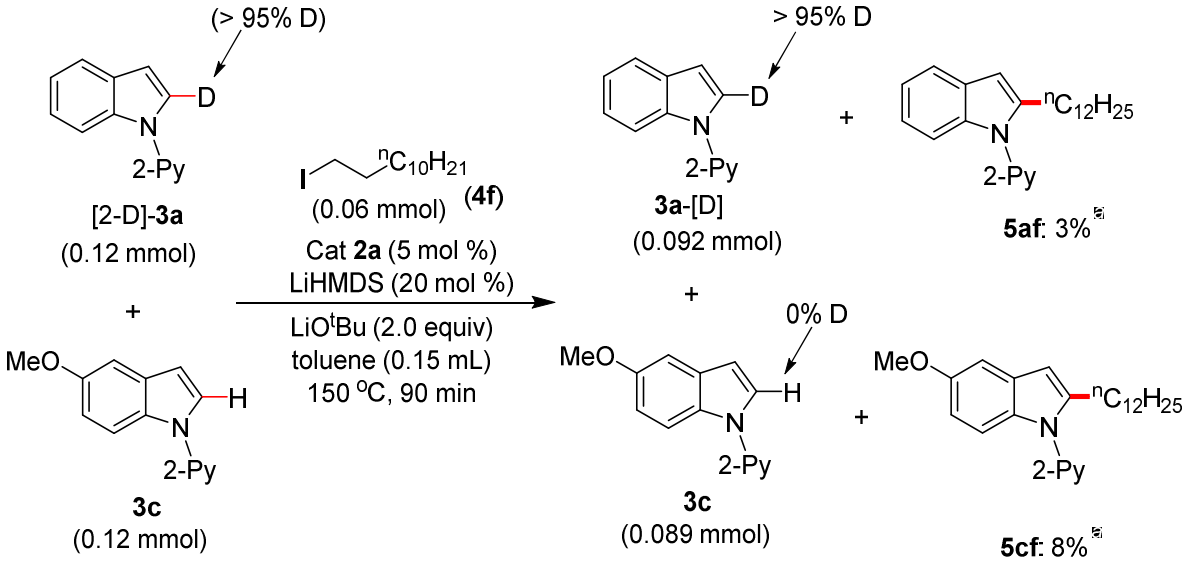


Figure 4.1 Time-dependent formation of product **5aa** using catalyst **2a**.

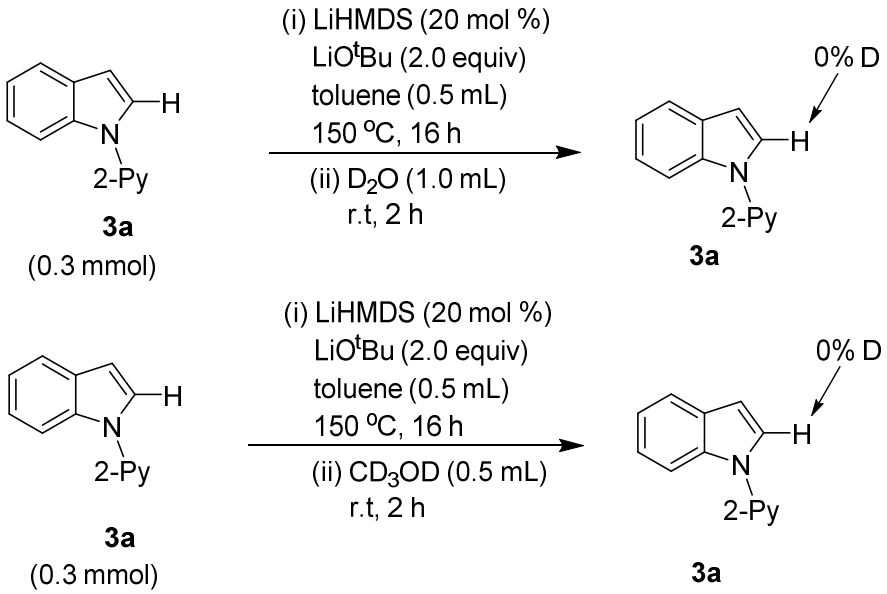


Scheme 4.7 H/D Scrambling Experiment. [a] GC conversion.

4.2.1.6.2. *H/D* Scrambling Study: The deuterium scrambling experiment was carried out to understand the nature of C–H bond metalation process. Hence, the compounds 1-(pyridin-2-yl)-1*H*-indole-2-*d* [2-D]-**3a** (0.12 mmol) and 5-methoxy-1-(pyridin-2-yl)-1*H*-indole **3c** (0.12 mmol) were treated with alkyl iodide **4f** (0.06 mmol) under the optimized reaction condition for 90 min (Scheme 4.7). The starting substrates 1-(pyridin-2-yl)-1*H*-indole-2-*d* and 5-methoxy-1-(pyridin-2-yl)-1*H*-indole were recovered. The ^{1}H NMR analysis of the recovered substrates suggest that the *H/D* has not occurred at the C(2) positions. This

scrambling experiment indicates that the C–H bond metalation is the irreversible process during the alkylation reaction.

4.2.1.6.3 Deuterium Incorporation Studies: Further to understand the deprotonation pathway on indole C–H bond, two independent experiments were performed following the optimized reaction conditions (without using alkyl iodide and catalyst **2a**) (Scheme 4.8). The reactions were quenched with CD_3OD or D_2O and the starting compound was recovered. The ^1H NMR analysis of the recovered substrate **3a** doesn't show the deuterium incorporation at the C(2)–H of **3a**. This finding clearly suggests that the indole C–H bond nickelation is very crucial and does not occur *via* a simple deprotonative pathway involving the base.



Scheme 4.8 Deuterium Incorporation Experiment.

4.2.1.7 Proposed Catalytic Cycle for Ni-Catalyzed Alkylation of Indoles

Based on our preliminary mechanistic findings and literature reports,[17,19,23-25] a probable mechanism for the **2a**-catalyzed alkylation is shown in Figure 4.2. Presumably, catalyst **2a** is first transformed to the active amido-complex **A**. Thereafter, coordination of the substrate **3a** to the [Ni] followed by crucial C–H nickelation delivers the nickelacycle **B**. This nickel species is suggested to triggers the formation of alkyl radical, followed by radical rebound to generate the intermediate species **C**. At the end, the reductive elimination will deliver the alkylated product, and the reaction of Ni-halide with LiHMDS would regenerate the active catalyst species.[26-29] The C−H activation step might involved in the rate-limiting step, as was

observed from the KIE study. Further, the involvement of alkyl radical was confirmed by radical clock experiments.

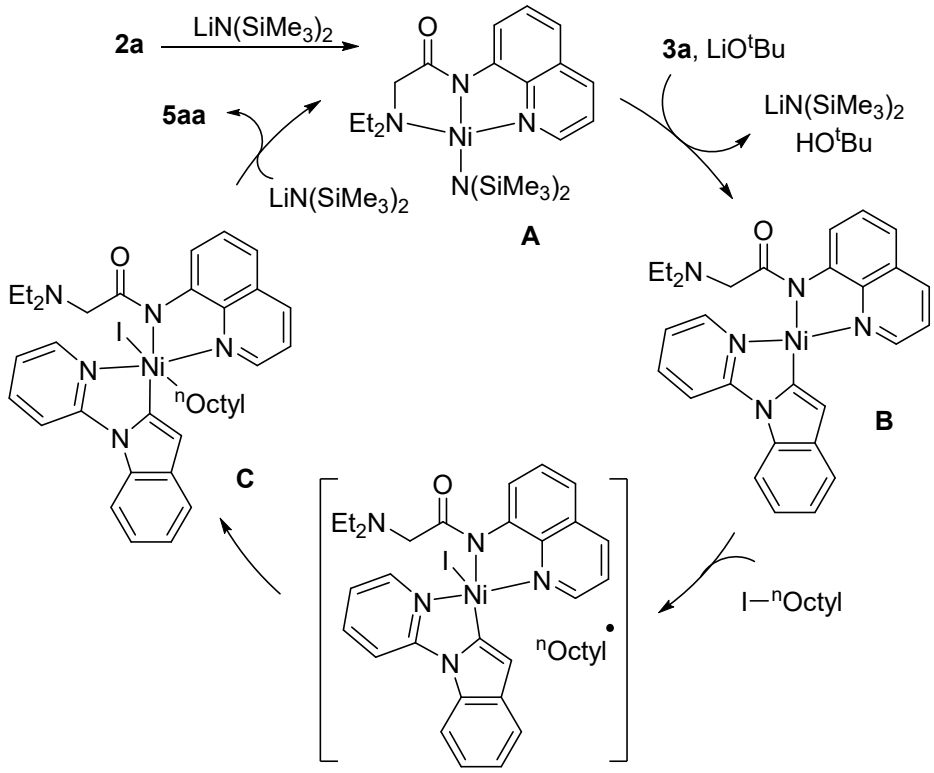


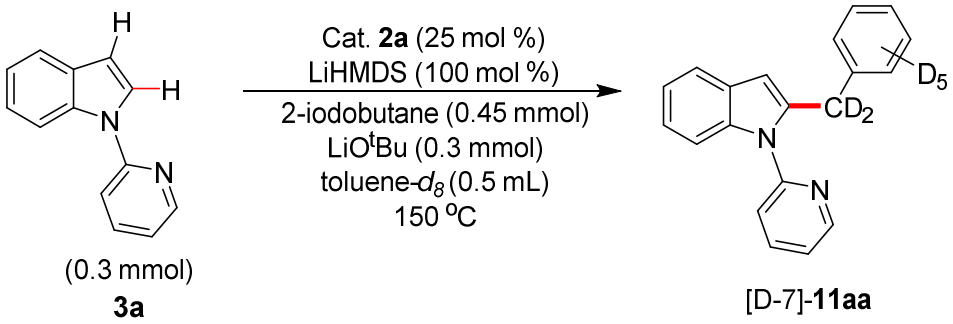
Figure 4.2 Proposed catalytic cycle for Ni-catalyzed alkylation of indoles.

4.2.2 MECHANISTIC ASPECTS OF OXIDATIVE INDOLES BENZYLATION

Mechanistic experiments were performed to know the mechanism of Ni-catalyzed regioselective benzylation of indoles that proceeds through the C(sp^2)−H/C(sp^3)−H oxidative coupling of indoles with toluene derivatives. Various controlled studies were carried out to obtain information about the working mode of catalyst. External additive experiments were performed to understand the status of active catalyst. Deuterium labeling experiments and kinetic studies were done to know the importance of C−H activation process.

4.2.2.1 NMR Study of Benzylation Reaction

The ^{1}H NMR experiment was performed to detect the existence of any active intermediate species during the oxidative coupling reaction (Scheme 4.9). In a standard reaction, the substrate 1-(pyridin-2-yl)-1*H*-indole (**3a**), 2-iodobutane, catalyst **2a** (25 mol %), LiHMDS (4.0 equiv w.r.t. **2a**) and LiO^tBu were introduced into a J-Young NMR tube inside the glove-box. To the above mixture in the tube, toluene-d_8 (0.5 mL) was added and the resultant reaction mixture was heated at 150 °C in a preheated oil bath. The ^{1}H NMR was recorded at different time intervals (1 h, 3 h, and 16 h). In all the run, ^{1}H NMR analysis showed the signals correspond to the couple product [D-7]-**11aa**; however, neither the complex **2a** nor it's derivative, nor the formation of free-ligand was observed. In addition, the GC analysis of this reaction mixture did not show the formation of free-ligand. This experiment suggests the probable involvement of a paramagnetic catalytic species during the benzylation reaction.

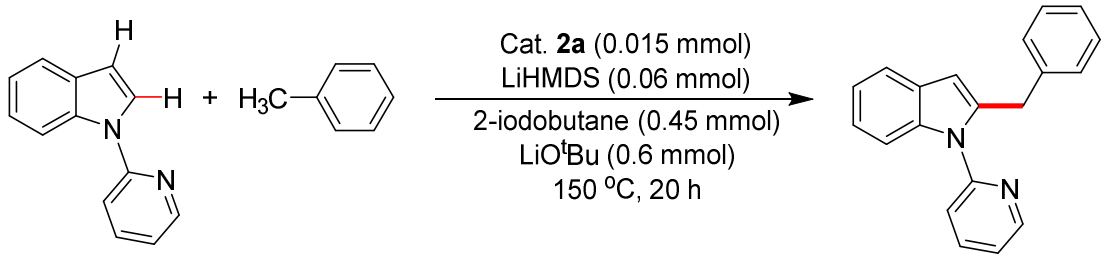


Scheme 4.9 ^{1}H NMR Experiment for Benzylation Reaction.

4.2.2.2 External Additive Studies

In order to know the nature of active catalyst species, the mercury drop experiment was performed for the **2a**-catalyzed benzylation reaction under standard reaction conditions (Scheme 4.10). Hence, the benzylation reaction of indole **3a** with toluene **10a** in the presence

of 7.5 mmol of Hg (500 equiv w.r.t. cat **2a**) afforded the product **11aa** in 66%. The benzylation was slightly affected in the presence of mercury and did not shutdown completely, which indicates the homogeneous character of active nickel catalyst. Similarly, the standard benzylation reaction was performed in the presence of TEMPO (2.0 equiv) or galvinoxyl (2.0 equiv). Notably, the benzylation was completely quenched in the presence of these radical inhibitors, which strongly suggests the involvement of a radical intermediate during the reaction.

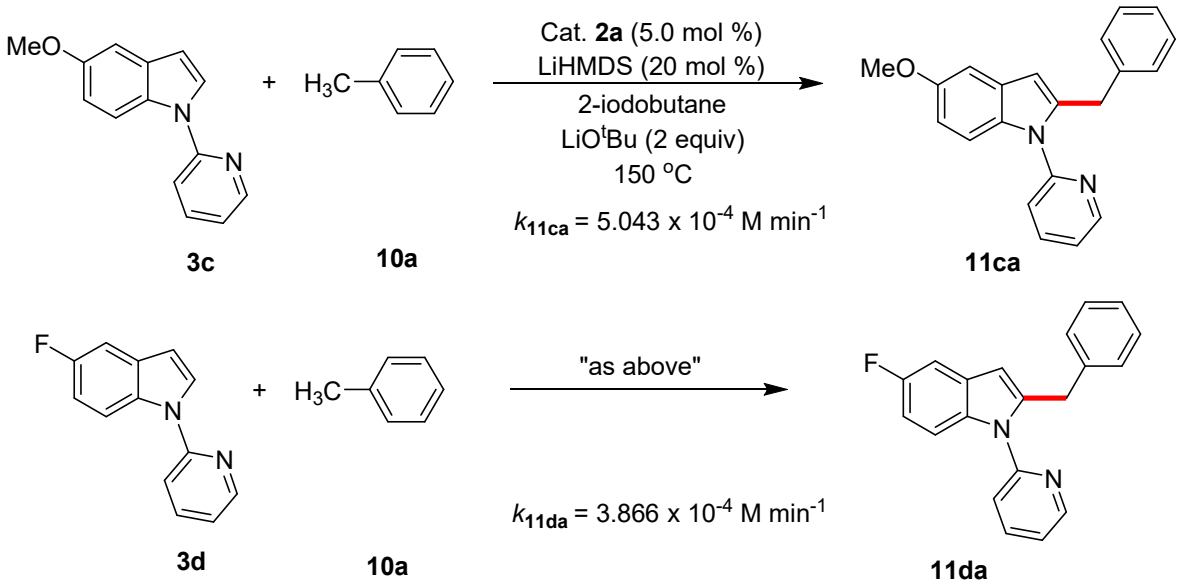


Additives	Yield (%)
No additive:	82
Hg (500 equiv):	66
TEMPO (2 equiv):	0
Galvinoxyl (2 equiv):	0

Scheme 4.10 External Additive Experiments.

4.2.2.3 Kinetic Analysis of Benzylation Reaction

Reaction Rates for Formation of Products 11ca and 11da: The standard benzylation reactions have been performed independently with electronically distinct indoles, 5-methoxy-1-(pyridin-2-yl)-1*H*-indole (**3c**) and 5-fluoro-1-(pyridin-2-yl)-1*H*-indole (**3d**), and the rates of the reactions were measured by initial rate method (Scheme 4.11, Table 4.1). The rate constants of these two reactions are found to be $k_{\mathbf{11ca}}$ = 5.043 x 10^{-4} Mmin^{-1} and $k_{\mathbf{11da}}$ = 3.866 x 10^{-4} Mmin^{-1} respectively (Figures 4.3, 4.4). Ratio of these two rates $k_{\mathbf{11ca}}/k_{\mathbf{11da}}$ = 1.3. This suggests that the electronic-factor has little influence on the benzylation (the reaction rates are almost similar). These findings rule out the possibility of electrophilic-type C–H activation on the indole moiety.



Scheme 4.11 Benzylation Reaction with Electronically Distinct Indoles.

Table 4.1 Concentrations of **11ca** and **11da** at different time intervals.

Entry	Time (min)	Conc. of **11ca** [M] (average of three experiments)	Conc. of **11da** [M] (average of three experiments)
1	20	0.0034	0.0067
2	40	0.0148	0.0133
3	60	0.0236	0.0218
4	90	0.0385	0.0319
5	120	0.0555	0.0452

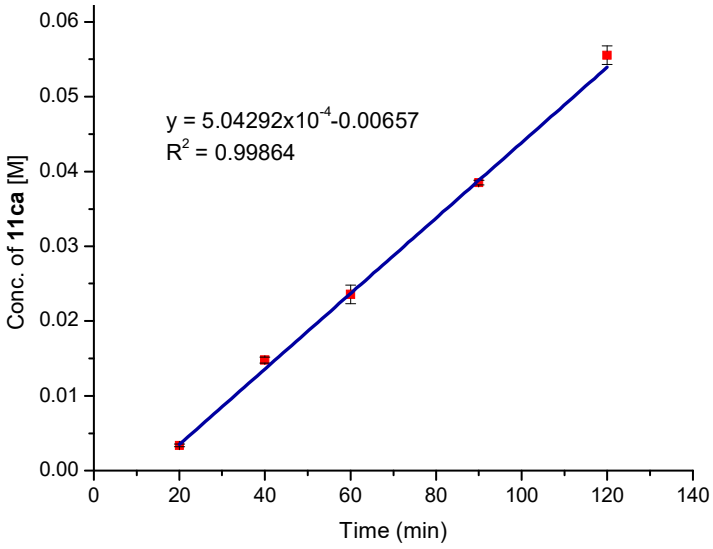


Figure 4.3 Time-dependent formation of **11ca**. The error bar represents the standard deviation of the results from three independent measurements.

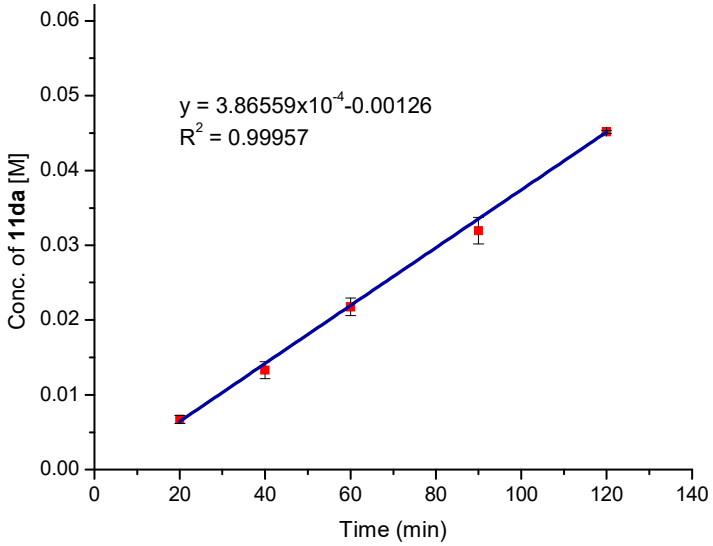
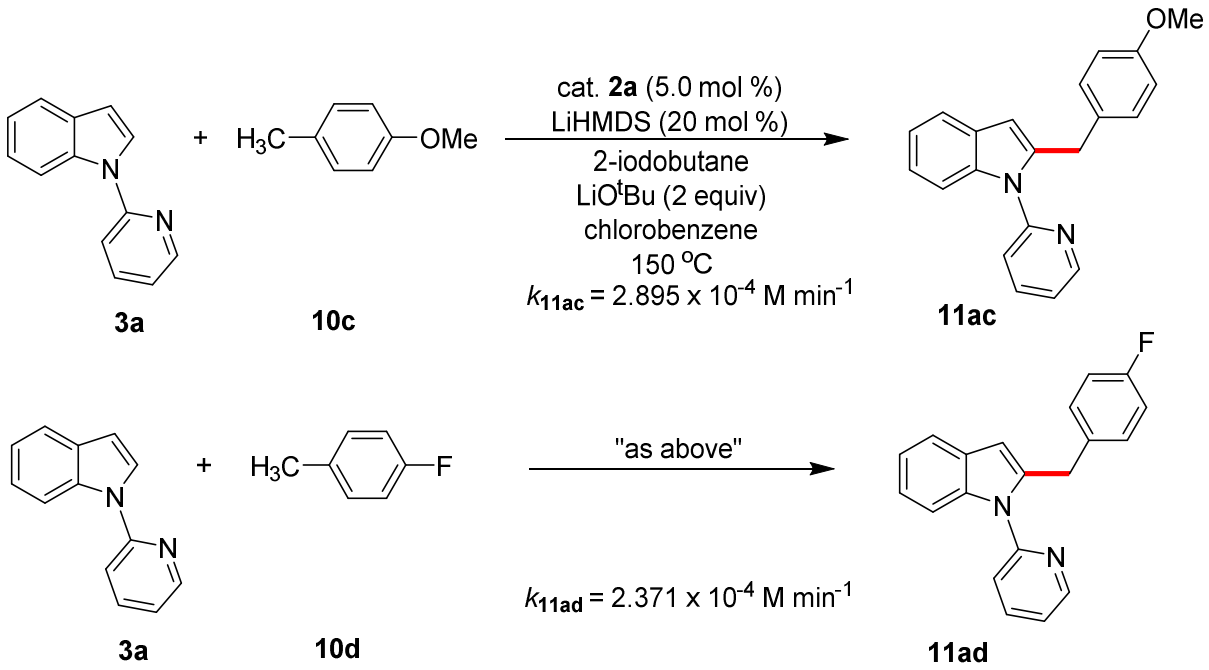


Figure 4.4 Time-dependent formation of **11da**. The error bar represents the standard deviation of the results from three independent measurements.



Scheme 4.12 Benzylation Reaction with Electronically Distinct Toluene Derivatives.

Reaction Rates for Formation of 11ac and 11ad: The standard benzylation reactions have been carried out independently with electronically distinct toluene derivatives, 1-methoxy-4-methylbenzene (**10c**) and 1-fluoro-4-methylbenzene (**10d**), and rates of the reactions were measured (Scheme 4.12, Table 4.2). The rate constants of the reactions employing **10c** and **10d** are found to be k_{11ac} = 2.895 x 10^{-4} $Mmin^{-1}$ and k_{11ad} = 2.371 x 10^{-4}

$Mmin^{-1}$, respectively (Figures 4.5, 4.6). Ratio of these two rates k_{11ac}/k_{11ad} = 1.22. These kinetics analysis suggests that the electronic factor on toluene derivatives has little influence on the benzylation (the reaction rates are almost similar). This finding dismissed the possibility of electrophilic-type C–H activation of the toluene derivatives.

Table 4.2 Concentrations of **11ac** and **11ad** at different time intervals.

Entry	Time (min)	Conc. of **11ac** [M] (average of three experiments)	Conc. of **11ad** [M] (average of three experiments)
1	20	0.0031	0.0046
2	40	0.0062	0.0085
3	60	0.0151	0.0138
4	90	0.0210	0.0208
5	120	0.0326	0.0286

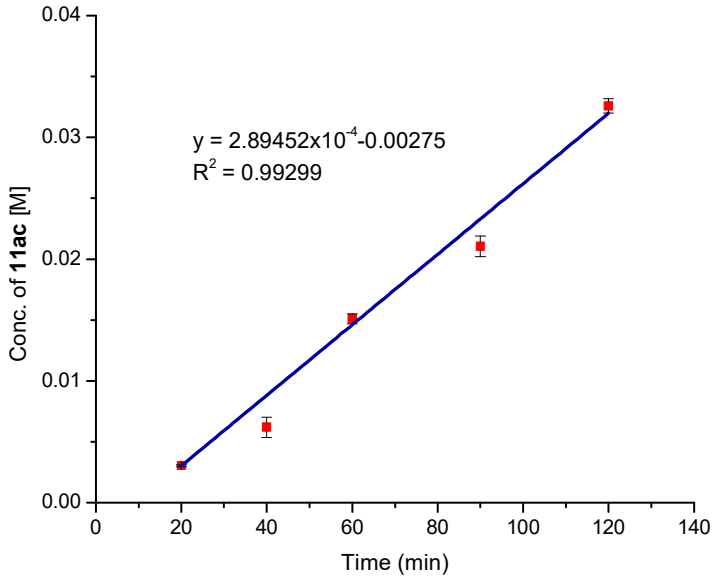


Figure 4.5 Time-dependent formation of **11ac**. The error bar represents the standard deviation of the results from three independent measurements

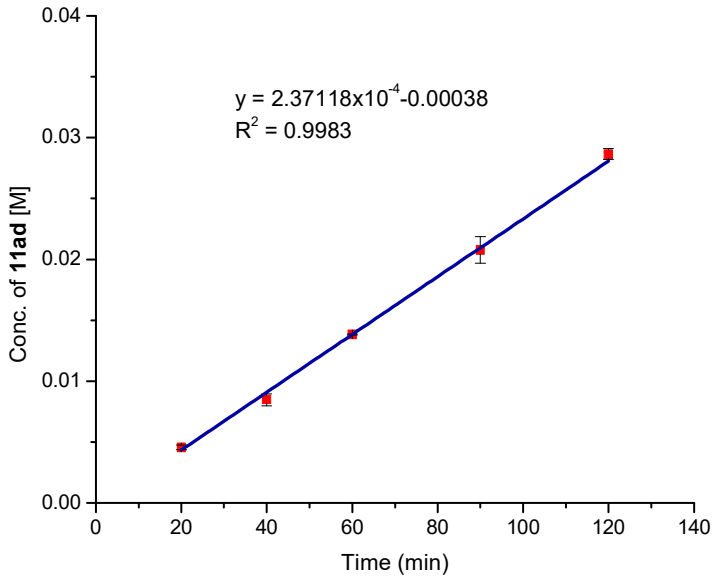


Figure 4.6 Time-dependent formation of **11ad**. The error bar represents the standard deviation of the results from three independent measurements

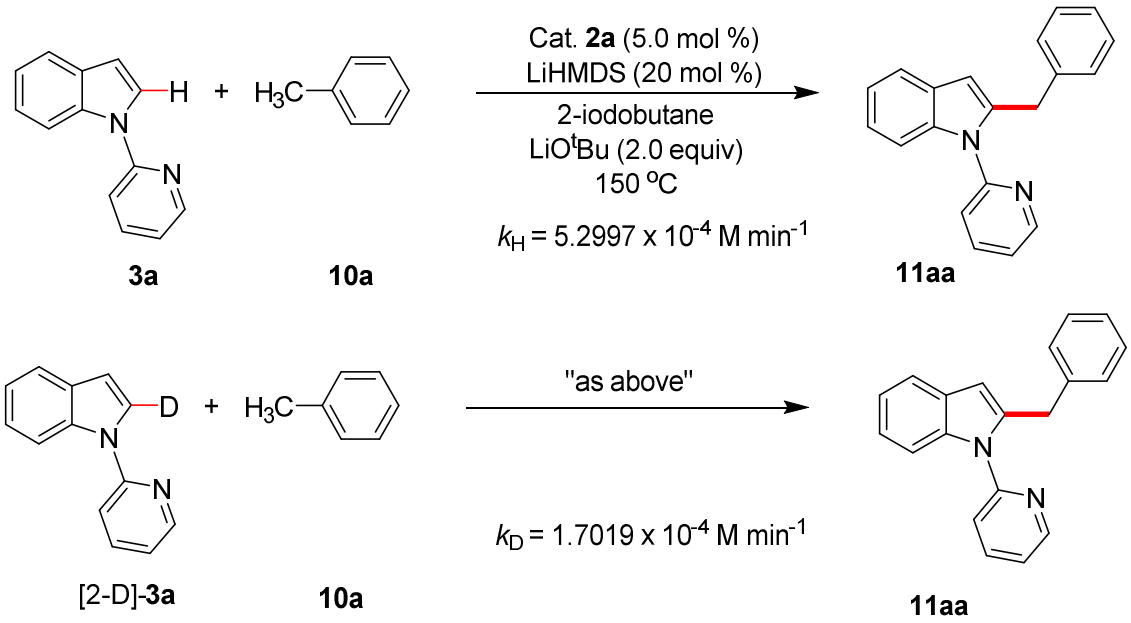
4.2.2.4 Isotope Labeling Studies

4.2.2.4.1 Kinetic Isotope Effect (KIE) Study

Determination of k_H/k_D (for C–H of Indole): To know whether the indole C–H bond breaking is involved in the rate determining step, the kinetic isotope effect (KIE) study was carried out using 1-(pyridin-2-yl)-1*H*-indole (**3a**) and 1-(pyridin-2-yl)-1*H*-indole-2-*d* ([2-D]-**3a**) (Scheme 4.13, Table 4.3). The rate of benzylation of **3a** with toluene **10a** was calculated as 5.2997 x 10^{-4} M min^{-1} (Figure 4.7). Similarly, the rate of benzylation reaction of [2-D]-**3a** was measured to be 1.7019 x 10^{-4} M min^{-1} (Figure 4.8). From these two reaction rates, the kinetic isotope effect (KIE) calculated as k_H/k_D = 3.1. This indicates that the C–H bond nickelation of indole is most likely involved in the turnover-limiting step.[30]

Table 4.3 Concentration of **11aa** Employing **3a** and [2-D]-**3a**.

Entry	Time (min)	Conc. of **11aa** [M] using **3a** (average of three experiments)	Conc. of **11aa** [M] using [2-D]-**3a** (average of three experiments)
1	20	0.00745	0.00185
2	40	0.01345	0.00420
3	60	0.02795	0.00645
4	90	0.04030	0.01305
5	120	0.05990	0.01820



Scheme 4.13 Rates of Benzylation Reactions for Indoles **3a** and [2-D]-**3a**.

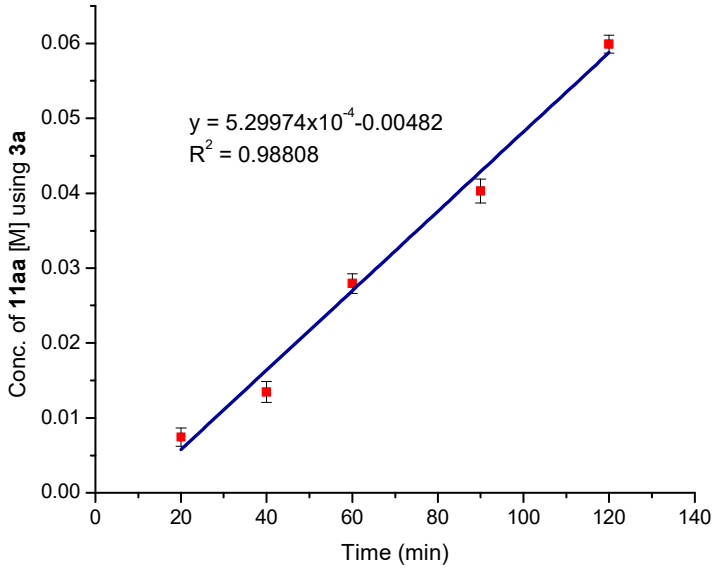


Figure 4.7 Time-dependent formation of **11aa** employing **3a.** The error bar represents the standard deviation of the results from three independent measurements

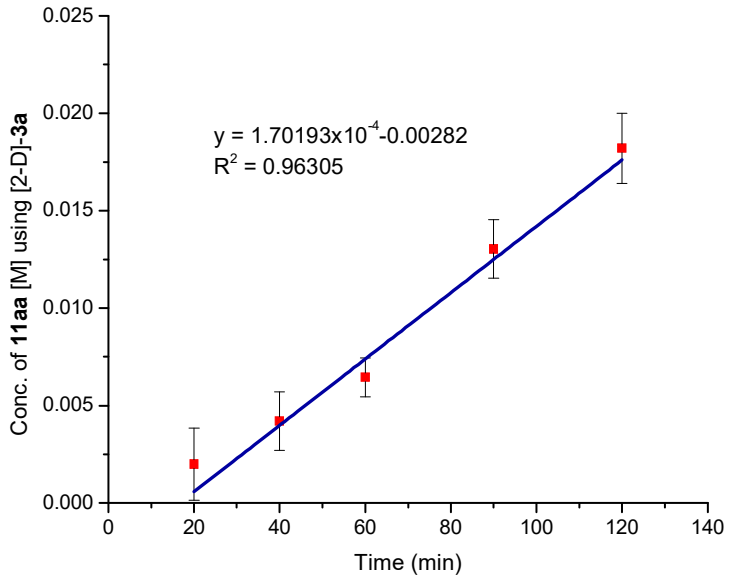
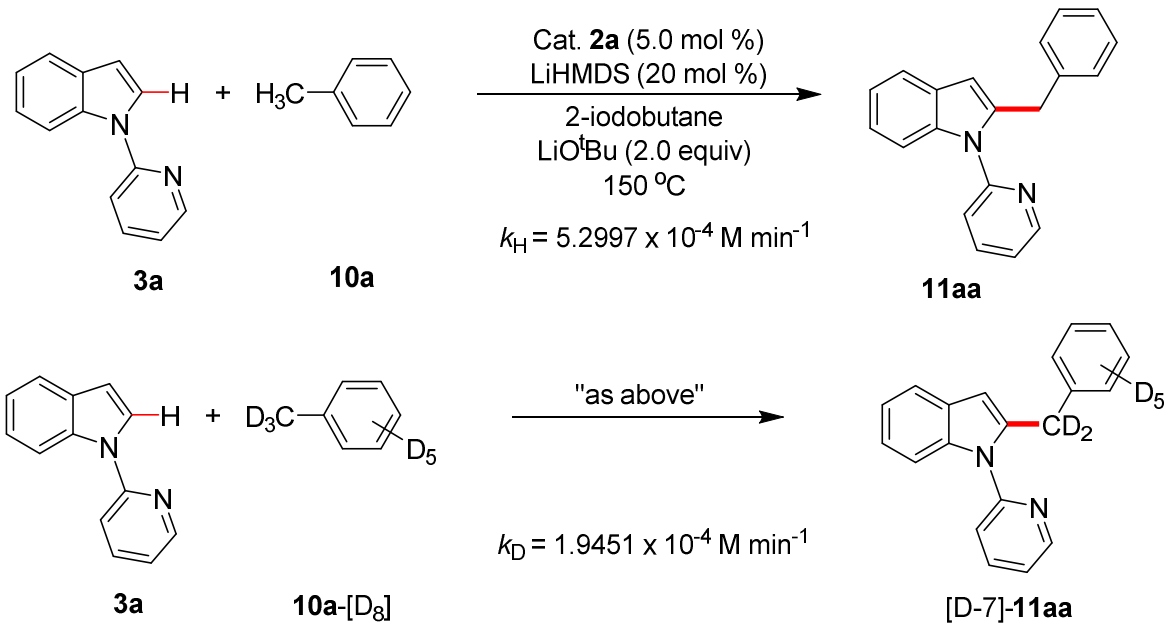


Figure 4.8 Time-dependent formation of **11aa** employing [2-D]**-3a.** The error bar represents the standard deviation of the results from three independent measurements

Determination of k_H/k_D (for C–H of Toluene): Similar to the above experiments, the initial rates of the benzylation reactions with toluene and toluene-d_8 were determined by independent experiments (Scheme 4.14, Table 4.4). The rates of benzylation of **3a** with toluene **10a** was calculated as 5.2997 x 10^{-4} Mmin^{-1} (Figure 4.7). Similarly, the rate of benzylation reaction of **3a** with toluene-d_8 was found to be 1.9451 x 10^{-4} Mmin^{-1} (Figure 4.9). From these two reaction rates, the kinetic isotope effect (KIE) calculated as $k_{tol}/k_{tol\text{-}d8} = 2.7$.



Scheme 4.14 Rates of Benzylation Reactions with Toluene and Toluene-d_8.

Table 4.4 Concentrations of **11aa** and [D_7]-**11aa** at different time intervals.

Entry	Time (min)	Conc. of **11aa** [M] (average of three experiments)	Conc. of **[D-7]-11aa** [M] (average of three experiments)
1	20	0.00745	0.00244
2	40	0.01345	0.00575
3	60	0.02795	0.01120
4	90	0.04030	0.01560
5	120	0.05990	0.02183

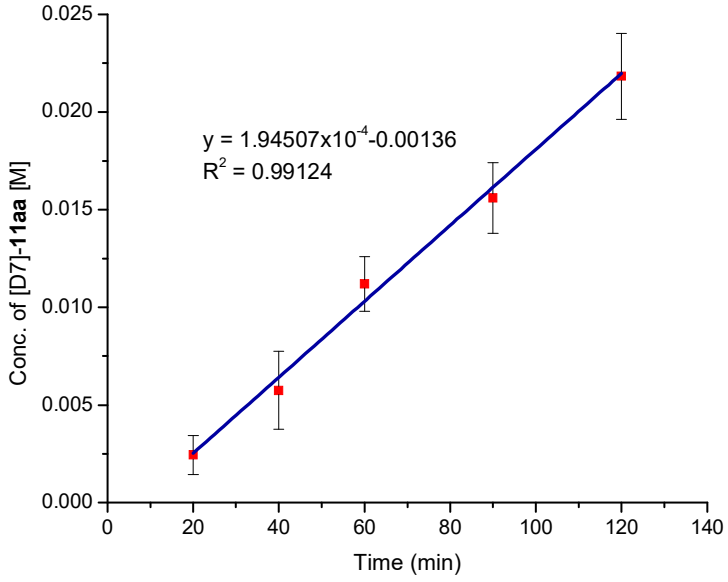
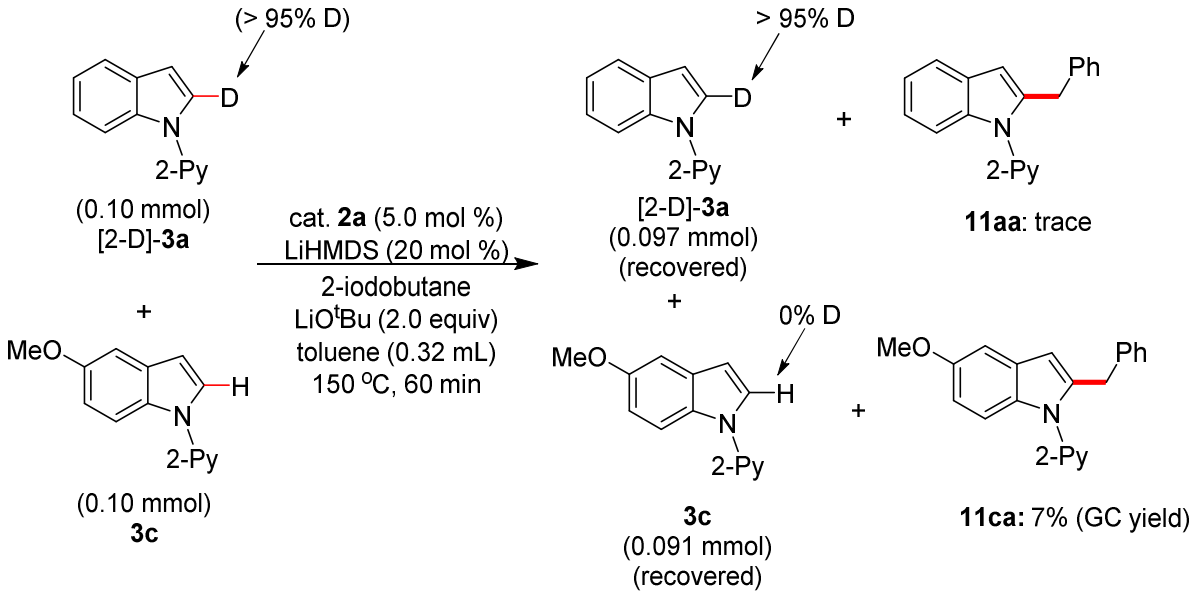


Figure 4.9 Time-dependent formation of [D-7]-**11aa** employing toluene-d_8. The error bar represents the standard deviation of the results from three independent measurements

4.2.2.4.2 H/D Scrambling Study

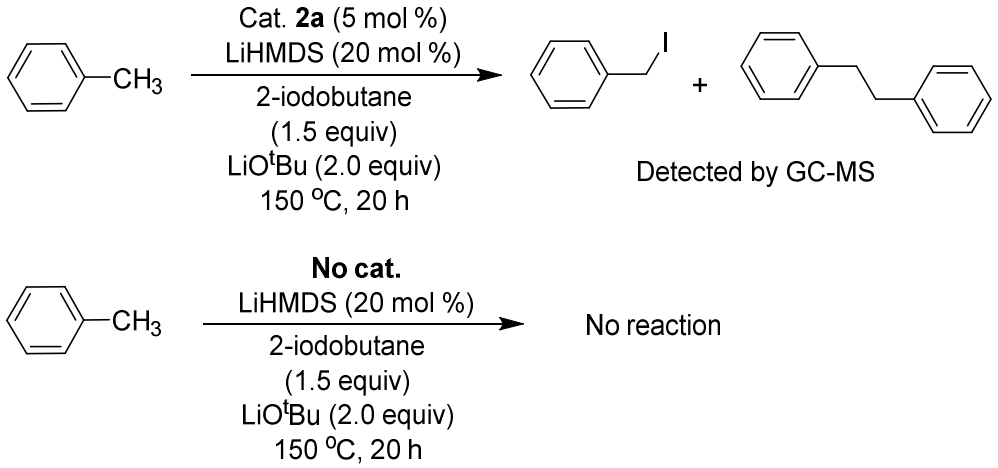
The deuterium scrambling experiment was carried out to understand the nature of C–H bond metalation process. Hence, the compounds 1-(pyridin-2-yl)-1*H*-indole-2-*d* ([2-D]-**3a**; 0.10 mmol) and 5-methoxy-1-(pyridin-2-yl)-1*H*-indole (**3c**; 0.10 mmol) were treated with toluene (3.0 mmol) under the standard reaction condition for 60 min (Scheme 4.15). Both the starting substrates 1-(pyridin-2-yl)-1*H*-indole-2-*d* and 5-methoxy-1-(pyridin-2-yl)-1*H*-indole were recovered. The ^{1}H NMR analysis of the recovered substrates suggest that the H/D scrambling has not occurred at the C(2) positions of indoles. This experiment highlights that the C–H bond nickelation is the irreversible process during the reaction.



Scheme 4.15 H/D Scrambling Studies for Benzylation Reaction.

4.2.2.5 Benzylation Under Controlled Condition

Looking at the reaction components, and findings on indole alkylation;[31] it was assumed that a benzyl radical could be the actual benzylation species, which might evolve by the radical transfer from the initially formed 2-butyl radical to toluene. With this in mind, a standard catalytic benzylation reaction was performed in the absence of substrate **3a** (Scheme 4.16). This reaction produced benzyl iodide and 1,2-diphenylethane ($PhCH_2CH_2Ph$) (Figure 4.10). Notably, in the absence of nickel catalyst **2a**, neither the benzyl iodide nor the 1,2-diphenylethane was formed. These investigations revealed that the nickel catalyst **2a** is essential for the generation of 2-butyl radical, which is then involved in the production of benzyl radical. In the absence of coupling partner **3a**, the benzyl radical dimerized to 1,2-diphenylethane. All the findings further suggest that the benzyl radical is generated from the toluene by radical transfer with butyl radical, and the benzyl radical is the coupling partner during the reaction. Since, the benzyl iodide formation was not efficient under the reaction condition, the contribution of benzyl iodide to the benzylation of indole as the major species is unlikely.



Scheme 4.16 Benzylation Reaction under Controlled Conditions.

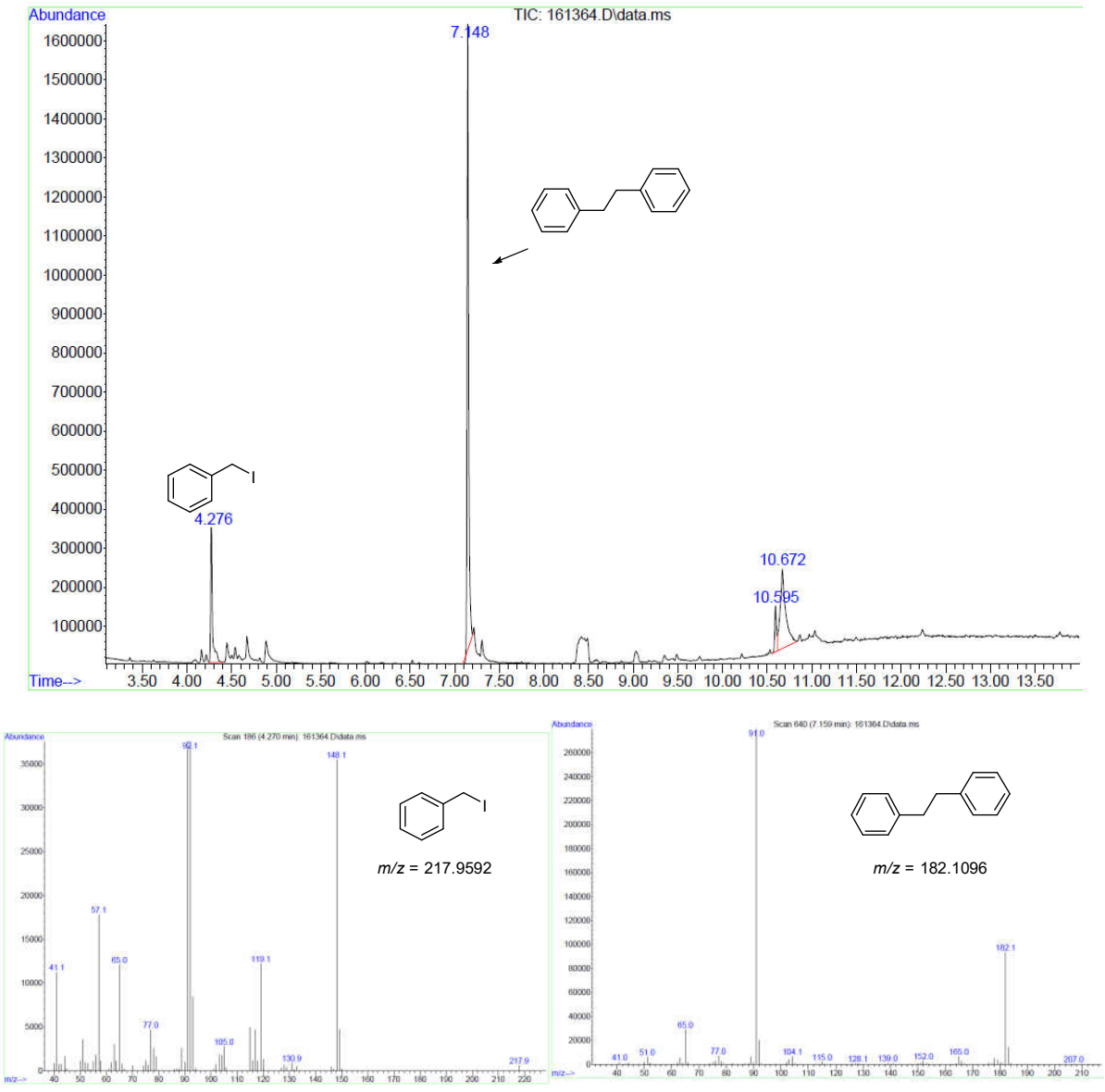


Figure 4.10 GC-MS spectra of controlled benzylation reaction.

4.2.2.6 Proposed Catalytic Cycle for Ni-Catalyzed Benzylation of Indoles

On the basis of preliminary mechanistic findings and literature reports,[21,22] a plausible mechanism for the **2a**-catalyzed benzylation of indole is presented in Figure 4.12. Reaction of **2a** with LiHMDS gives the active amido Ni(II) complex **A**. Coordination of indole **3a** to **A** followed by the rate-limiting C–H nickelation would produce species **B**. The C–H activation process pressumed to proceeds *via* a concerted-metalation-deprotonation (CMD) approach as the electronic has no influence on the benzylation reaction. The complex **B** would trigger the generation of 2-butyl radical by the iodine atom transfer (IAT) mechanism *via* a single-electron-transfer (SET) process.[21,31] Next, the butyl radical can have two competing reactions: first the butyl radical can abstract a hydrogen from toluene to produce the benzyl radical (radical transfer),[32] which is then reacts with species **C** to afford Ni(IV) complex **D**. Reductive elimination of the benzylated product **11aa** will deliver Ni(II) species **E**, which is then reacts with LiHMDS to complete the cycle. The MALDI-TOF-MS analysis of a catalytic reaction provided evidence for the existance of species **D** (Figure 4.11). In the second case, the butyl radical can rebound with **C** to produce the Ni(IV) species **F**, which leads to undesired alkylation **11aa'**. Alternately, the formation of 2-butyl radical can be presumed from an oxidatively added species **F**. However, such a path would lead to the major alkylation (**11aa'**) rather than the radical creation; hence the production of butyl radical by this mechanism is unlikely. Although our findings support a Ni(II)/Ni(III) pathway, probability of a Ni(I)/Ni(III) catalytic cycle cannot be ruled out at this stage.[28,29]

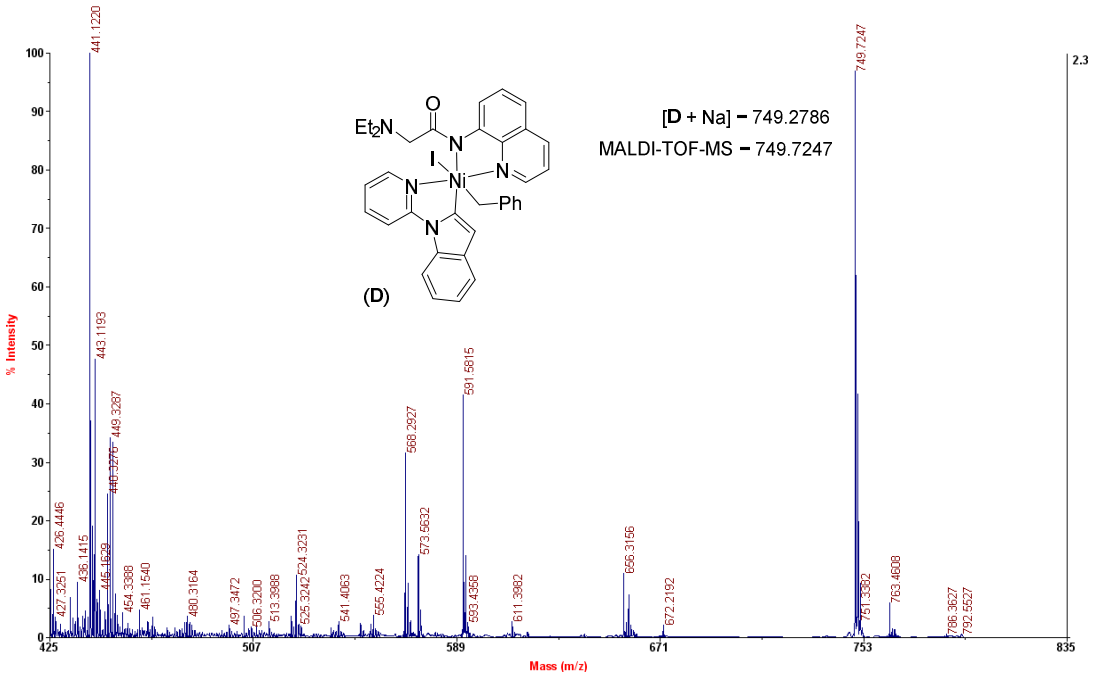


Figure 4.11 MOLDI-TOF-MS spectrum of benzylation reaction.

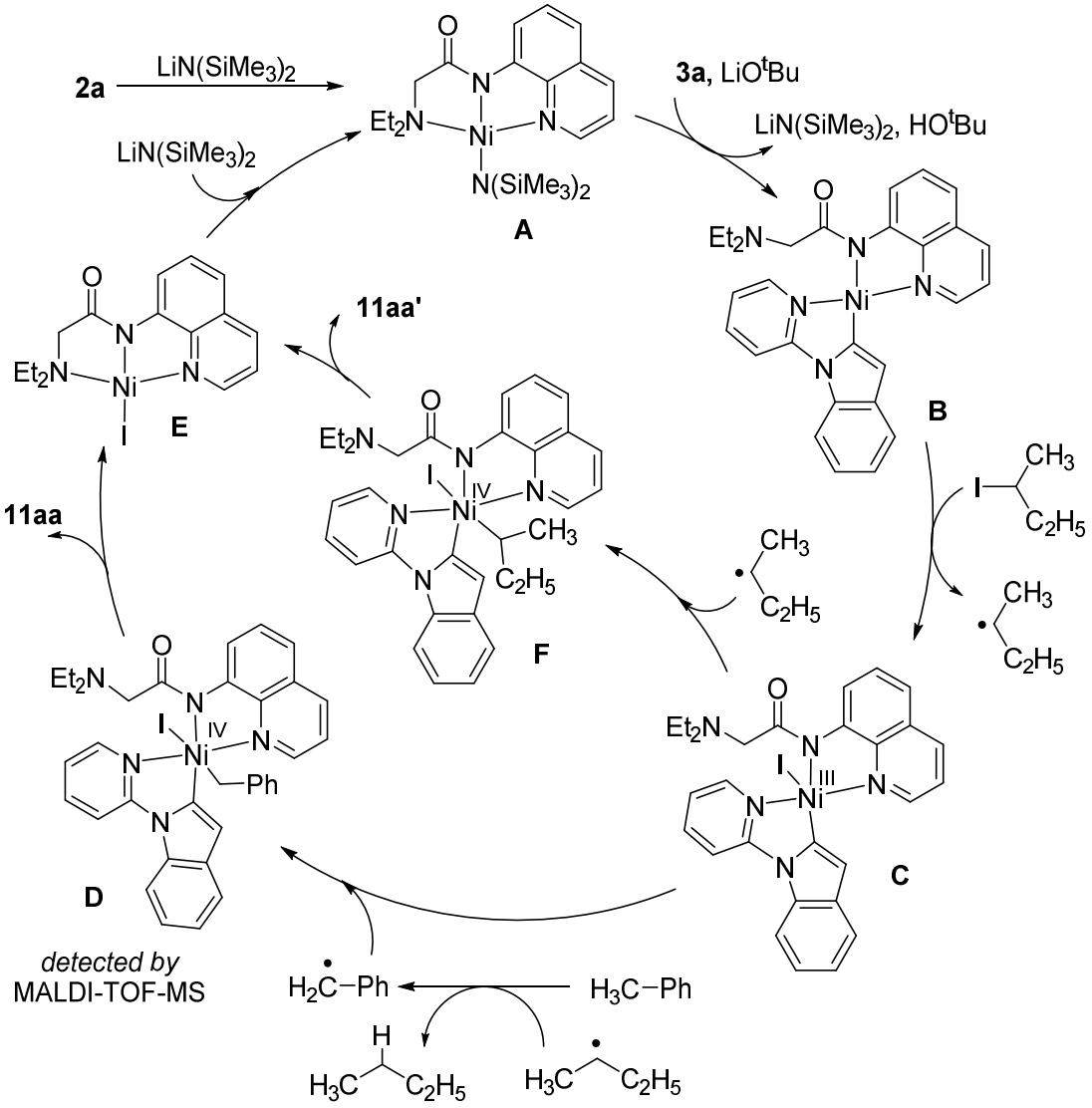


Figure 4.12 Proposed catalytic cycle for benzylation of indoles.

4.3 CONCLUSION

In this chapter, the detailed mechanism of the **2a**-catalyzed alkylation and benzylation of indoles with alkyl halide and toluene derivatives, respectively, are described. The external additive experiments ruled out the involvement of heterogeneous catalytic species and reveal the involvement of free-radical intermediates for both the reaction. Formation of alkyl radical has been confirmed by radical clock experiments during the alkylation. Similarly, benzyl radical is detected by the controlled studies. The kinetic analyses of the reactions suggest that the C–H bond nickelation is most likely the turnover limiting step in both cases. Deuterium scrambling experiment reveals that C–H activation is irreversible and does not proceed *via* a simple deprotonative pathway. The generation of alkyl radical and radical transfer from alkyl to benzyl is very crucial to obtained either alkylation or benzylation. Considering all these

experimental findings, catalytic cycles for the nickel-catalyzed alkylation as well as benzylation of indole is drawn, both of which occur through Ni(II)/Ni(III)/Ni(IV) pathway.

4.4 EXPERIMENTAL SECTION

4.4.1 Experimental for Mechanistic Aspects of Alkylation

4.4.1.1 Procedure for ^{1}H NMR Experiment: To a J-Young NMR tube was introduced compound **3a** (0.023 g, 0.12 mmol), 1-iodooctane (**4a**; 0.028 g, 0.12 mmol), cat **2a** (0.011 g, 0.03 mmol), LiHMDS (0.02 g, 0.12 mmol, 4.0 equiv w.r.t. **2a**) and LiO^tBu (0.01 g, 0.12 mmol) inside the glove-box. To the above mixture in the tube, toluene-d_8 (0.5 mL) was added and the resultant reaction mixture was heated at 120 °C in a preheated oil bath. The ^{1}H NMR was recorded at different interval of time (1 h, 3 h, and 16 h). In all the run, ^{1}H NMR showed the signals correspond to the couple product **5aa**; however, neither the complex **2a** or its derivative, or the formation of free-ligand was observed.

4.4.1.2 Representative Procedure for External Additive Experiment: To a flame-dried screw-cap tube (5 mL) equipped with magnetic stir bar was introduced 1-pyridine-2-yl-1*H*-indole (**3a**; 0.058 g, 0.3 mmol), 1-iodooctane (**4a**; 0.144 g, 0.6 mmol), cat **2a** (0.0056 g, 0.015 mmol, 5.0 mol %), LiHMDS (0.010 g, 0.06 mmol, 20 mol %), LiO^tBu (0.048 g, 0.6 mmol) and additive [mercury (0.60 g, 3.0 mmol or 1.8 g, 9.0 mmol) /TEMPO (0.094 g, 0.6 mmol)] inside the glove-box. To the above mixture in the tube, toluene (0.15 mL) was added and the resultant reaction mixture was stirred at 150 °C in a preheated oil bath for 16 h. Yield of the product **5aa** was determined by the GC analysis of crude reaction mixture using *n*-dodecane as an internal standard.

4.4.1.3 Procedure for Filtration Experiment: To a flame-dried screw-cap tube (5 mL) equipped with magnetic stir bar was introduced substrate **3a** (0.058 g, 0.3 mmol), 1-iodooctane (**4a**; 0.144 g, 0.6 mmol), cat **2a** (0.0056 g, 0.015 mmol, 5.0 mol %), LiHMDS (0.010 g, 0.06 mmol, 20 mol %) and LiO^tBu (0.048 g, 0.6 mmol) inside the glove-box. To the above mixture in the tube, toluene (1.0 mL) and *n*-dodecane (0.025 mL, 0.11 mmol) were added, and the resultant reaction mixture was stirred at 150 °C in a preheated oil bath for 30 min. The reaction vessel was cooled to ambient temperature and an aliquot of the sample was drawn in-side the box, whose GC analysis shown 14% yield of **5aa**. After that the reaction mixture was filtered inside the glove-box to an another screw cap tube containing LiO^tBu (0.048 g, 0.6 mmol) and the resultant reaction mixture in the new tube was stirred at 150 °C in a preheated oil bath for 16 h. The GC analysis of the reaction mixture showed 71% yield of **5aa** w.r.t. internal standard.

4.4.1.4 Procedure for Radical Clock Experiment: Representative procedure of the catalytic alkylation reaction was followed, using substrate **3a** (0.058 g, 0.3 mmol), 6-bromo-1-hexene (**4u**; 0.098 g, 0.6 mmol) and KI (0.1 g, 0.6 mmol), and the reaction mixture was stirred for 16 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) yielded **5au** as a light yellow liquid. Yield: 00.046 g, 55%.

4.4.1.5 Procedure for Intermolecular Competition Experiment: The representative procedure of the catalytic alkylation reaction was followed, using substrate **3c** (0.078 g, 0.35 mmol), substrate **3d** (0.074 g, 0.35 mmol), 1-iodooctane (**4a**; 0.042 g, 0.175 mmol), cat **2a** (0.0033 g, 0.0088 mmol), LiHMDS (0.00586 g, 0.035 mmol), LiO^tBu (0.028 g, 0.35 mmol), and the reaction mixture was heated for 6 h. Purification by column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 50/1/0.5) yielded **5ca** (10%) and **5da** (43%) as yellow liquids.

4.4.1.6 Procedure for KIE Study: To the teflon-screw capped tube equipped with magnetic stir bar was introduced catalyst **2a** (0.0056 g, 0.015 mmol, 0.015 M), LiHMDS (0.010 g, 0.06 mmol), LiO^tBu (0.048 g, 0.6 mmol), substrate **3a** (0.058 g, 0.3 mmol, 0.3 M) or [2-D]-**3a** (0.0586 g, 0.3 mmol, 0.3 M), and 1-iodooctane (0.144 g, 0.6 mmol, 0.6 M), and toluene (0.81 mL) was added to make the total volume 1.0 mL. To the reaction mixture *n*-dodecane (0.025 mL, 0.11 mmol, 0.11 M) was added as an internal standard. The reaction mixture was then stirred at 150 ^oC in a pre-heated oil bath. At regular intervals (20, 40, 60, 90, 120, 180, 300 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 acetone and subjected to GC analysis. The concentration of the product **5aa** 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 and fitted linear with Origin Pro 8, and the rate was determined by initial rate method (up to 300 minutes). The slope of the linear fitting represents the reaction rate.

4.4.1.7 Procedure for H/D Scrambling Experiment: To a flame-dried screw-capped tube equipped with magnetic stir bar was introduced 1-(pyridine-2-yl)-1*H*-indole-2-*d* ([2-D]-**3a**; 0.023 g, 0.12 mmol), 5-methoxy-1-(pyridine-2-yl)-1*H*-indole (**3c**; 0.027 g, 0.12 mmol), 1-iodododecane (**4f**; 0.018 g, 0.06 mmol), cat **2a** (0.001 g, 0.003 mmol, 5.0 mol %), LiHMDS (0.002 g, 0.012 mmol, 20 mol %) and LiO^tBu (0.01 g, 0.12 mmol) inside the glove-box. To the above mixture toluene (0.15 mL) was added and the resultant reaction mixture was stirred at 150 °C in a preheated oil bath for 90 min. At ambient temperature, the reaction mixture was quenched with distilled H_2O (10 mL). The crude product was then extracted with CH_2Cl_2

(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 subjected to column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 20/1/0.5) to isolate the products (**5af** and **5cf**) and recovered the starting compounds.

4.4.1.8 Procedure for Deuterium Incorporation Experiment: To a flame-dried screw-capped tube equipped with magnetic stir bar were introduced 1-(pyridine-2-yl)-1*H*-indole (**3a**; 0.058 g, 0.3 mmol), LiHMDS (0.01 g, 0.06 mmol, 20 mol %) and LiO^tBu (0.048 g, 0.6 mmol) inside the glove-box. To the above mixture toluene (0.5 mL) was added and the resultant reaction mixture was stirred at 150 °C in a preheated oil bath for 16 h. At ambient temperature, D_2O (1.0 mL) or CD_3OD (0.5 mL) was added to the reaction mixture under argon and stirred for 2 h. Reaction mixture was quenched with distilled H_2O (10 mL). The crude product was then 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 ^1H NMR analysis of the compound does not show incorporation of deuterium at C(2)–H of indole **3a**.

4.4.2 Experimental for Mechanistic Aspects of Benzylation

4.4.2.1 Representative Procedure for External Additive Experiments: To a flame dried screw-cap tube (5 mL) equipped with magnetic stir bar was introduced 1-pyridine-2-yl-1*H*-indole (**3a**; 0.058 g, 0.3 mmol), 2-iodobutane (0.083 g, 0.45 mmol), cat **2a** (0.0056 g, 0.015 mmol, 5.0 mol %), LiHMDS (0.010 g, 0.06 mmol, 20 mol %), LiO^tBu (0.048 g, 0.6 mmol), mercury (1.5 g, 7.5 mmol)/TEMPO (0.094 g, 0.6 mmol)/galvinixyl (0.253 g, 0.6 mmol) and toluene (**10a**; 0.96 mL, 9.0 mmol) inside the glove-box. The resultant reaction mixture was stirred at 150 °C in a preheated oil bath for 20 h. Yield of the product **11aa** was determined by the GC analysis of the recation mixture using *n*-dodecane as internal standard.

4.4.2.2 Procedure for Kinetic Experiments

*Reaction Rates for the Formation of **11ca** and **11da**:* To the teflon-screw capped tube equipped with magnetic stir bar was introduced cat **2a** (0.0056 g, 0.015 mmol, 0.015 M), LiHMDS (0.010 g, 0.06 mmol), LiO^tBu (0.048 g, 0.6 mmol), substrate **3c** (0.067 g, 0.3 mmol, 0.3 M) or **3d** (0.0637 g, 0.3 mmol, 0.3 M), 2-iodobutane (0.083 g, 0.45 mmol, 0.45 M), *n*-hexadecane (0.025 mL, 0.085 mmol, 0.085 M, internal standard) and toluene (0.923 mL) was added to make the total volume 1.0 mL. The reaction mixture was then stirred at 150 ^oC in a pre-heated oil bath. At regular intervals (20, 40, 60, 90, 120 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 acetone and subjected to GC analysis. The concentration of

the product **11ca** (or **11da**) obtained in each sample was determined with respect to the internal standard *n*-hexadecane. The data of the concentration of the product *vs* time (min) plot was drawn and fitted linear with Origin Pro 8, and the rate was determined by the initial rate method (up to 120 minutes). The slope of the linear fitting represents the reaction rate. The data's were taken from the average of three independent experiments.

*Reaction Rates for the Formation of **11ac** and **11ad**:* To the teflon-screw capped tube equipped with magnetic stir bar was introduced cat **2a** (0.0056 g, 0.015 mmol), LiHMDS (0.010 g, 0.06 mmol), LiO^{t}Bu (0.048 g, 0.6 mmol), substrate **3a** (0.058 g, 0.3 mmol), 2-iodobutane (0.083 g, 0.45 mmol), **10c** (1.13 mL, 9.0 mmol) or **10d** (0.991 mL, 0.9 mmol), *n*-hexadecane (0.025 mL, 0.085 mmol, internal standard), and chlorobenzene (0.304 mL, 3.0 mmol); wherein the total volume became 1.511 mL or 1.372 mL, respectively. The reaction mixture was then stirred at 150 ^{o}C in a pre-heated oil bath. At regular intervals (20, 40, 60, 90, 120 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 acetone and subjected to GC analysis. The concentration of the product **11ac** or **11ad** obtained in each sample was determined with respect to the internal standard *n*-hexadecane. The data of the concentration of the product *vs* time (min) plot was drawn (Figures 4.5 and 4.6) and fitted linear with Origin Pro 8, and the rate was determined by initial rate method (up to 120 minutes). The slope of the linear fitting represents the reaction rate. The data's were taken from the average of three independent experiments.

4.4.2.3 Isotope Labeling Experiment: *Determination of k_H/k_D (for C–H of indole):* Representative procedure of the kinetic experiment was followed (Sec 4.4.2.2), employing cat **2a** (0.0056 g, 0.015 mmol, 0.015 M), LiHMDS (0.010 g, 0.06 mmol), LiO^{t}Bu (0.048 g, 0.6 mmol), substrate **3a** (0.058 g, 0.3 mmol, 0.3 M) or [2-D]-**3a** (0.0586 g, 0.3 mmol, 0.3 M), 2-iodobutane (0.083 g, 0.45 mmol, 0.45 M), *n*-hexadecane (0.025 mL, 0.085 mmol, 0.085 M), and toluene (0.87 mL). The concentration of the product **11aa** obtained in each sample was determined with respect to the internal standard *n*-hexadecane. The data of the concentration of the product *vs* time (min) plot was drawn and fitted linear with Origin Pro 8, and the rate was determined by the initial rate method (up to 120 minutes). The slope of the linear fitting represents the reaction rate. The data's were taken from the average of three independent experiments.

Determination of k_H/k_D (for C–H of Toluene): Representative procedure of the kinetic experiment was followed (Sec 4.4.2.2), employing cat **2a** (0.0056 g, 0.015 mmol, 0.015 M), LiHMDS (0.010 g, 0.06 mmol), LiO^{t}Bu (0.048 g, 0.6 mmol), substrate **3a** (0.058 g, 0.3

mmol, 0.3 M) and 2-iodobutane (0.083 g, 0.45 mmol, 0.45 M), *n*-hexadecane (0.025 mL, 0.085 mmol, 0.085 M) and toluene (0.87 mL) or toluene-d_8 (0.87 mL). The concentration of the product **11aa** or [D-7]-**11aa** obtained in each sample was determined with respect to the internal standard *n*-hexadecane. The data's were taken from the average of three independent experiments.

H/D Scrambling Experiment: To a flame-dried screw-capped tube equipped with magnetic stir bar was introduced 1-(pyridine-2-yl)-1*H*-indole-2-*d* ([2-D]-**3a**; 0.0195 g, 0.10 mmol), 5-methoxy-1-(pyridine-2-yl)-1*H*-indole (**3c**; 0.0224 g, 0.10 mmol), 2-iodobutane (0.056 g, 0.3 mmol), cat **2a** (0.0038 g, 0.01 mmol, 5.0 mol %), LiHMDS (0.0066 g, 0.04 mmol, 20 mol %) and LiO^tBu (0.032 g, 0.4 mmol) inside the glove-box. To the above mixture toluene (0.64 mL, 6.0 mmol) was added and the resultant reaction mixture was stirred at 150 °C in a preheated oil bath for 60 min. At ambient temperature, the reaction mixture was quenched with distilled H_2O (10 mL). The crude mixture was then extracted with CH_2Cl_2 (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 subjected to column chromatography on neutral alumina (petroleum ether/EtOAc/Et_3N: 20/1/0.5) to recovered the starting compounds, [2-D]-**3a** and **3c**.

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Chapter 5

Nickel-Catalyzed Regioselective C−H Bond Difluoroalkylation of Indoles

5.1 INTRODUCTION

Fluorine-containing organic compounds are widely used in pharmaceuticals, agrochemicals, and in life sciences; because the presence of fluorine generally enhances the lipophilicity and metabolic stability of such compounds (Figure 1).[1-5] Hence, the selective introduction of fluorine or a fluorine-containing group into the organic molecule, relevant to drug candidate, has been recognized as a powerful strategy in drugs development. In the last few decades, transition-metal-catalyzed traditional fluoroalkylation has emerged as an efficient approach for the introduction of fluorine-containing motifs into the organic molecules.[6-32] Recently, direct C−H bond fluoroalkylation by the transition-metal-catalysts has given particular attention.[28-32] In that direction, numerous metal-catalyzed methods have been developed for the fluoroalkylation of diverse alkenes[33-37] and arenes[38,39] using various fluoroalkyl coupling partners. However, the selective C−H bond fluoroalkylation of biologically relevant and challenging heteroarenes is relatively less explored.[40-42]

Particularly, the regioselective fluoroalkylation of indoles is significant because of the biological significance of this important alkaloid heteroarene. Both the noble metals, such as palladium,[43] iridium,[44] ruthenium,[45,46] and earth-abundant copper,[47,48] nickel[49] were efficiently employed as catalyst to achieve the difluoroalkylation of indoles. Unfortunately, in all the methods a mixture of C(2)−H and C(3)−H fluoroalkylation was observed, and generally, C-3 substituted indoles are employed in order to achive the selective C(2)−H fluoroalkylation. The C-2 fluoroalkylation by protecting the C-3 position of indoles limits this methodology, because the presence of C(3)−H is very crucial for the post functionalization of C-2 fluoroalkylated indoles. Recently, Feng and Loh have demonstrated a rhodium-catalyzed C-2 selective difluoroalkylation *via* the hydroarylation approach by introducing 2-pyrimidinyl directing group at the *N*-center of indoles.[50] Similarly, Shi and co-workers reported a nickel-catalyzed 2-pyridinyl and 2-pyrimidinyl directed selective C-2 trifluoroethylation of indoles.[51] However, there is no report on the regioselective C(2)−H fluoroalkylation of C-3 unprotected indole, or for the indoles without having a directing group. In this chapter, the development and scope of the nickel-catalyzed regioselective C(2)−H ethoxycarbonyldifluoromethylation of C-3 unprotected and *N*-alkylated indoles is discussed. A variety of indoles were selectively difluoroalkylated with ethyl-2-bromo-2,2-difluoroacetate at the C-2 position. Preliminary mechanistic studies have been carried out to understand the pathway of the catalytic reaction.

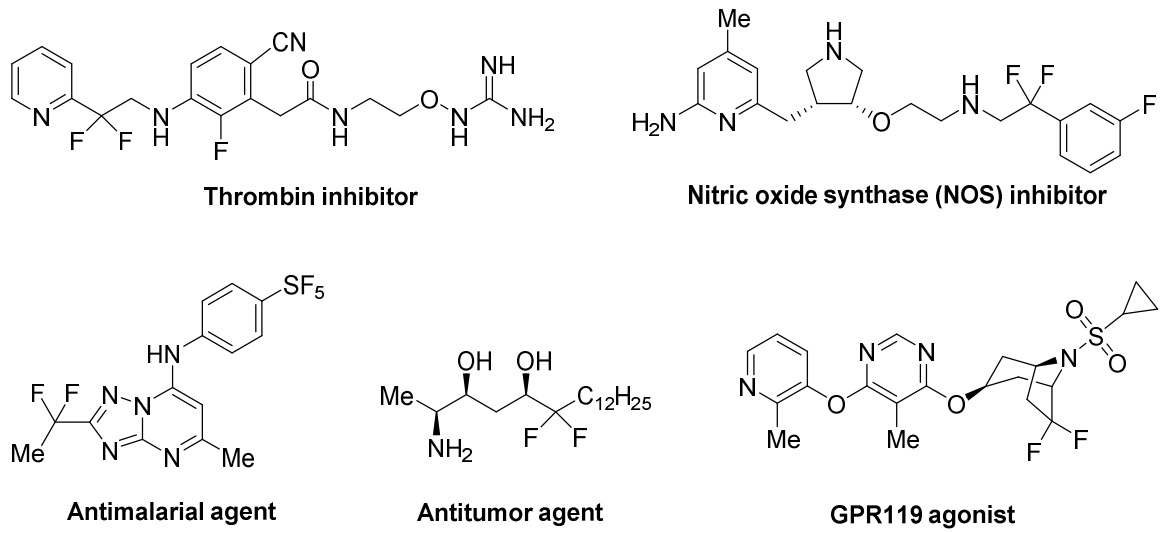


Figure 5.1 Fluorine-Containing Biologically Important Compounds.

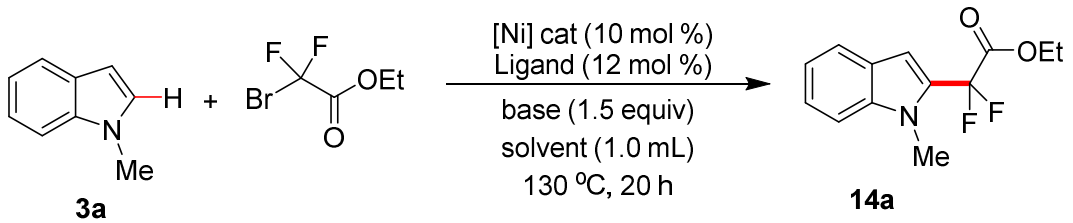
5.2 RESULTS AND DISCUSSION

5.2.1 Optimization of Reaction Conditions for Difluoroalkylation

The optimization study was initiated for the coupling of *N*-methyl indole (**3a**) with ethyl 2-bromo-2,2-difluoroacetate (Table 5.1). First, different nickel precursors were screened with or without added ligand in the presence of mild base Na_2CO_3. The reaction in the absence of ligand did not produce any coupled product, whereas the nickel precursors with the added PPh_3 ligand afforded the desired C-2 difluoroalkylated product **14a** in low to moderate yield (Table 5.1, entries 1-6). Notably, the preformed complex $(Ph_3P)_2NiCl_2$ as catalyst produce only a trace of product **14a** (entry 6). Employing the $(DME)NiCl_2$ precursor, nitrogen-containing Phen ligand as well as various bidentate phosphine ligands were screened (entries 7-13), and found that the combination of $(DME)NiCl_2$/Xantphos system afforded product **14a** in 49% yield. Surprisingly, increasing the amount of base Na_2CO_3 to 2.0 equiv the difluroalkylated compound was obtained in 61% yield (entry 14). Performing the reaction at higher temperature led to the lowring in yield, which could be due to the decomposition of substrate or product (entry 15). Similarly, the reaction at 120 ^{o}C resulted with 48% yield of difluoroalkylated product (entry 16). The catalytic reaction in toluene or polar solvents, such as DMF, DMA and diglyme is less efficient (entries 17-20). Employment of other mild inorganic bases, such as K_2CO_3, $NaHCO_3$, Cs_2CO_3 or strong base LiO^tBu resulted with very low conversion (entries 21-24). Hence, the optimized reaction condition was found to be the reaction of **3a** with ethyl 2-bromo-2,2-difluoroacetate (2.0 equiv) employing $(DME)NiCl_2$ (10 mol %)/Xantphos (12 mol %) in the presence of Na_2CO_3 (2.0 equiv) at 130 ^{o}C for 20 h.

Notably, under the optimized conditions selectively C-2 difluoroalkylated product **14a** was formed, and the C(3)−H remained unaffected.

Table 5.1 Optimization of Reaction Conditions.[a]



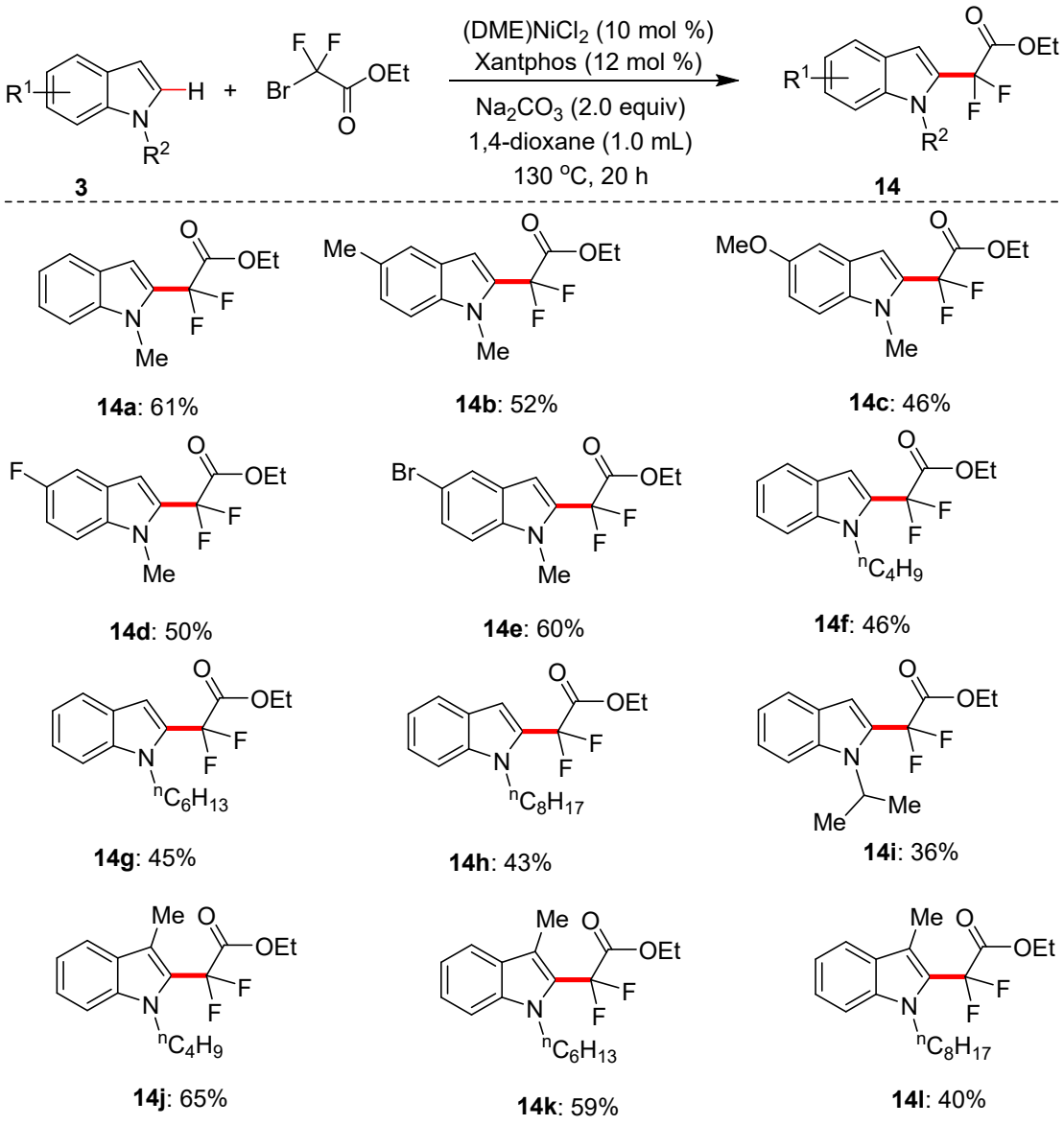
Entry	[Ni]	Ligand	Base	Solvent	Yield [%][b]
1	$Ni(OAc)_2$	-	Na_2CO_3	1,4-dioxane	-
2	$Ni(OAc)_2$	PPh_3	Na_2CO_3	1,4-dioxane	trace
3	$(THF)NiBr_2$	PPh_3	Na_2CO_3	1,4-dioxane	28
4	$(MeCN)_2NiBr_2$	PPh_3	Na_2CO_3	1,4-dioxane	32
5	$(DME)NiCl_2$	PPh_3	Na_2CO_3	1,4-dioxane	37
6	$(PPh_3)_2NiCl_2$	-	Na_2CO_3	1,4-dioxane	trace
7	$(DME)NiCl_2$	Phen	Na_2CO_3	1,4-dioxane	-
8	$(DME)NiCl_2$	BINAP	Na_2CO_3	1,4-dioxane	43
9	$(DME)NiCl_2$	dppf	Na_2CO_3	1,4-dioxane	39
10	$(DME)NiCl_2$	dppe	Na_2CO_3	1,4-dioxane	9
11	$(DME)NiCl_2$	dppm	Na_2CO_3	1,4-dioxane	38
12	$(DME)NiCl_2$	dppb	Na_2CO_3	1,4-dioxane	4
13	$(DME)NiCl_2$	Xantphos	Na_2CO_3	1,4-dioxane	49
14[c]	**$(DME)NiCl_2$**	**Xantphos**	**Na_2CO_3**	1,4-dioxane	**66 (61)**
15[d]	$(DME)NiCl_2$	Xantphos	Na_2CO_3	1,4-dioxane	44
16[e]	$(DME)NiCl_2$	Xantphos	Na_2CO_3	1,4-dioxane	48
17[c]	$(DME)NiCl_2$	Xantphos	Na_2CO_3	toluene	16
18[c]	$(DME)NiCl_2$	Xantphos	Na_2CO_3	diglyme	trace
19[c]	$(DME)NiCl_2$	Xantphos	Na_2CO_3	DMA	15
20[c]	$(DME)NiCl_2$	Xantphos	Na_2CO_3	DMF	trace
21	$(DME)NiCl_2$	Xantphos	K_2CO_3	1,4-dioxane	13
22	$(DME)NiCl_2$	Xantphos	$NaHCO_3$	1,4-dioxane	24
23	$(DME)NiCl_2$	Xantphos	Cs_2CO_3	1,4-dioxane	5
24	$(DME)NiCl_2$	Xantphos	LiO^tBu	1,4-dioxane	10

[a] Reaction conditions: **3a** (0.026 g, 0.2 mmol), ethyl 2-bromo-2,2-difluoroacetate (0.081 g, 0.4 mmol), [Ni] cat (0.02 mmol, 10 mol %), base (0.3 mmol). [b] GC yield using *n*-dodecane as internal standard. Isolated yield is in parenthesis. [c] Employing 2.0 equiv base. [d] Reaction at 150 °C. [e] Reaction at 120 °C.

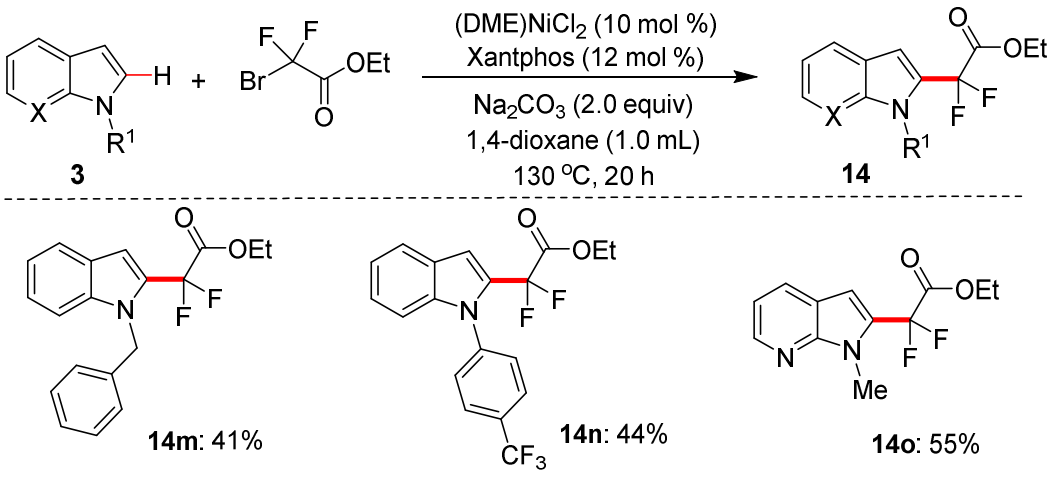
5.2.2 Substrate Scope for Difluoroalkylation of Indoles

The optimized reaction conditions with the (DME)$NiCl_2$/Xantphos catalyst system was applied to the difluoroalkylation of differently substituted *N*-methyl indoles (Scheme 5.1). Various functional groups, such as –OMe, –F, –Br are well tolerated at 5-position of indole to afford the desired difluoroalkylated products in moderate to good yields (**14c-e**). The *N*-substituents on indoles having different alkyl chain lengths are reacted efficiently to produce moderate yields of difluoroalkylation under the optimized reaction condition (**14f-h**). An isopropyl substituted indole **3i** reacted with moderate activity to yield the product **14i** in 36%. Notably, in all the cases selectively C-2 difluoroalkylation was occurred, and the C-3 difluoroalkylation or C-2/C-3 double difluoroalkylation was not observed. This is very symbolic from the synthetic aspects, as the C(3)–H can further be functionalized into important functionalities. This represents the first example of C-2 selective difluoroalkylation of indoles without the help of a chelate-assistance. Interestingly, the sterically hindered 3-methyl indoles having different *N*-alkyl substituents also reacted smoothly and produced the difluoroalkylated products in moderate to good yields (**14j-l**).

This methodology was further applied to other *N*-substituted indoles and azaindole (Scheme 5.2). Hence, indoles having benzyl or aryl substituents on nitrogen-center also reacted with good efficacy and afforded moderate yields of difluroalkylated products (**14m**,**n**). Interestingly, the azaindole substrate **3o** reacted with ethyl 2-bromo-2,2-difluoroacetate to afford the coupled product **14o** in 55% yield. Though, most of these difluoroalkylation afforded moderate yields, the excellent selectivity for C(2)–H functionalization employing an inexpensive nickel catalyst system makes this method a reliable strategy.



Scheme 5.1 Scope of the Ni-Catalyzed C-2 Difluoroalkylation of *N*-Alkyl Indoles.

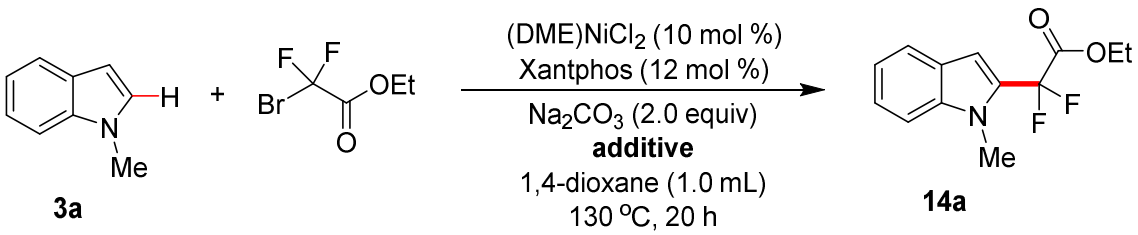


Scheme 5.2 Scope of the Ni-Catalyzed C-2 Difluoroalkylation of (Aza)indoles.

5.2.3 Mechanistic Aspects for Ni-Catalyzed Difluoroalkylation

Considering the excellent selectivity of the nickel-catalyzed difluoroalkylation of indoles, preliminary mechanistic experiments have been performed to know the working mode of the catalyst. Various external additive experiments were carried out to obtaing the information about the status of active catalyst. Deuterium labeling experiments were performed to understand the mode of C−H activation process.

5.2.3.1 External Additive Studies: The difluoroalkylation reaction of indole **3a** with ethyl 2-bromo-2,2-difluoroacetate in the presence of Hg (500 equiv w.r.t catalyst) under the standard catalytic conditions afforded the product **14a** in 40% (GC yield; Scheme 5.3). The addition of Hg led to the lowering in yield of **14a**, however, it could not quench the reaction completely. This indicates that the active nickel catalyst system is homogeneous in nature. Further, the standard difluoroalkylation reaction was performed in the presence of TEMPO (2.0 equiv) or galvinoxyl (2.0 equiv) independently. In both the cases, the difluoroalkylation was completely suppressed and did not produce the coupled product. This observation suggests the involvement of a free-radical manifold during the catalytic reaction. Unfortunately, the couple product of any expected radical intermediate with TEMPO or galvinoxyl was not observed in the reaction.

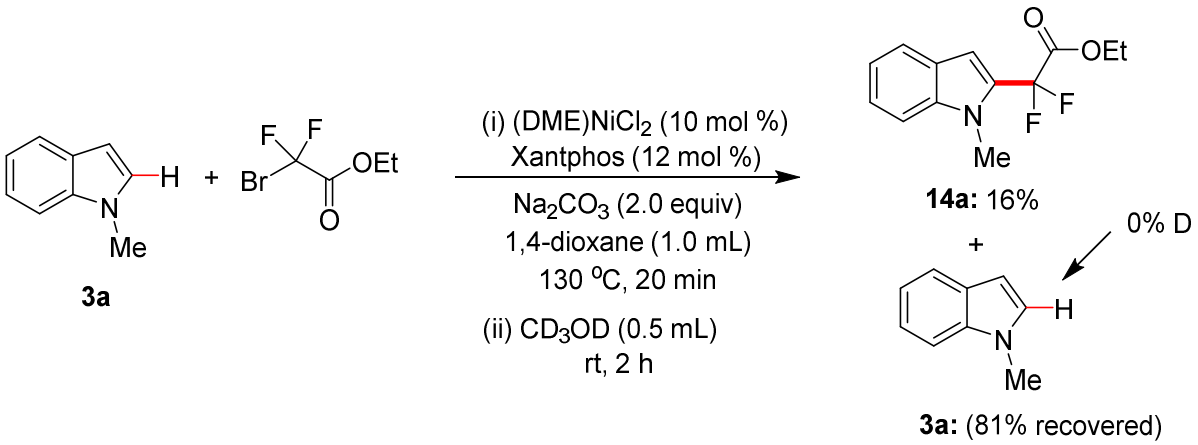


	GC Yield (%)
No additive:	66
Hg (500 equiv):	40
TEMPO:	–
Galvinoxyl	–

Scheme 5.3 Difluoalkylation in the Presence of External Additives.

5.2.3.2 H/D Scrambling Study: The difluoroalkylation reaction of indole **3a** with ethyl 2-bromo-2,2-difluoroacetate was performed for 20 min, and the reaction mixture was quenched with CD_3OD. The starting indole substrate was recovered and subjected to ^1H NMR analysis. The ^1H NMR of the recovered **3a** does not show deuterium incorporation at the C(2)–H position (Scheme 5.4). This finding clearly suggests that the indole C–H bond

activation do not occur *via* a simple deprotonative pathway, and the C–H nickelation step is irreversible.



Scheme 5.4 H/D Scrambling Experiment.

5.2.4 Mechanistic Proposal

Based on preliminary mechanistic findings and relevant literature reports,[52-55] a possible mechanistic cycle for the nickel-catalyzed difluoroalkylation of *N*-methyl indole was proposed as shown in Figure 5.2. First, the Ni-precursor will be reduced to one-electron system in the presence of Xantphos and base to generate active Ni^{I} catalyst **A**. Species **A** would activate the C(2)−H of indole *via* concerted-metalation-deprotonation (CMD) approach to produce species **B**. Compound **B** will trigger the formation of difluoroalkyl radical to form Ni^{II}-species **C** through iodine-atom-transfer (IAT) mechanism. Re-combination of radical would generate Ni^{III}-species **D**, which upon reductive elimination will produce the difluoroalkylated product and regenerate the active catalyst **A**.

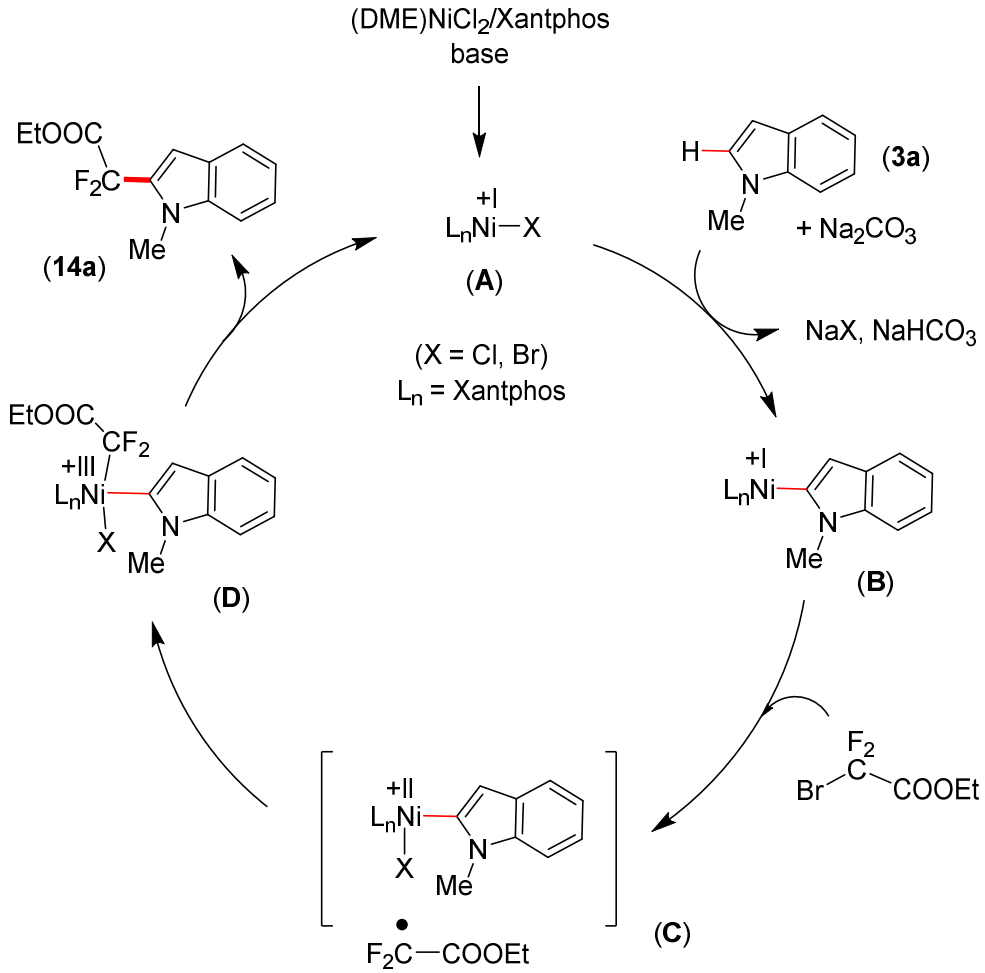


Figure 5.2 Proposed mechanistic cycle for the Ni-catalyzed difluoroalkylation of indole.

5.3 CONCLUSION

In this chapter, the nickel-catalyzed regioselective C(2)−H ethoxycarbonyldifluoromethylation of C-3 unprotected and *N*-alkylated indoles with commonly available fluoroalkyl halides is described. This methodology shows high activity, excellent regioselectivity, and broad substrate scope. Mild reaction condition has been used. Various functional groups, such as –OMe, –F, –Br are well tolerated on the indole backbone to give the coupled products in moderate to good yields. Preliminary mechanistic findings demonstrate that reaction involves a radical manifold and proceeds *via* the homogeneous pathway.

5.4 EXPERIMENTAL SECTION

General Experimental

All manipulations were conducted under an argon atmosphere either in a glove box or using standard Schlenk techniques in pre-dried glass wares. The catalytic reactions were performed in the 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 compound ethyl 2-bromo-2,2-difluoroacetate was distilled and stored under argon. The *N*-alkylated indole substrates were synthesized following the literature reported procedures. All other chemicals were obtained from commercial sources and were used without further purification. Yields refer to isolated compounds, estimated to be > 95% pure as determined by ^{1}H-NMR. TLC: TLC Silica gel 60 F_{254}. Detection under UV light at 254 nm. Separations were carried out by preparative TLC. NMR (^{1}H and ^{13}C) spectra were recorded at 400 or 500 MHz (^{1}H), 100 or 125 {^{13}C, DEPT (distortionless enhancement by polarization transfer)} and 377 MHz (^{19}F) on Bruker AV 400 and AV 500 spectrometers 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 250 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 °C, respectively. UHP-grade argon was used as carrier gas with a flow rate of 30 mL/min. The temperature program used for all the analyses is as follows: 80 °C, 1 min; 30 °C/min to 200 °C, 2 min; 30 °C/min to 260 °C, 3 min; 30 °C/min to 300 °C, 3 min.

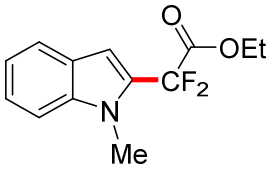
Response factors for all the required compounds with respect to standard *n*-dodecane were calculated from the average of three independent GC runs.

5.4.1 Procedure for Difluoroalkylation of Indoles

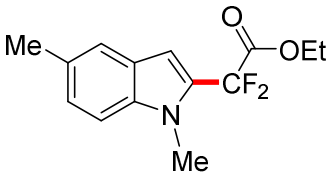
Representative Procedure: Synthesis of ethyl 2,2-difluoro-2-(1-methyl-1*H*-indol-2-yl)acetate (14a): To a flame-dried screw-cap tube (5 mL) equipped with magnetic stir bar was introduced 1-methyl-1*H*-indole (**3a**; 0.026 g, 0.2 mmol), ethyl 2-bromo-2,2-difluoroacetate (0.081 g, 0.4 mmol), (DME)$NiCl_2$ (0.0044 g, 0.02 mmol, 10.0 mol %), Xantphos (0.014 g, 0.024 mmol, 12 mol %) and Na_2CO_3 (0.042 g, 0.4 mmol) inside the

glove-box. To the above mixture in the tube, 1,4-dioxane (1.0 mL) was added and the resultant reaction mixture was stirred at 130 °C in a preheated oil bath for 20 h. At ambient temperature, the reaction mixture was diluted with EtOAc, and was filtered. The volatiles were evaporated in *vacuo*. The remaining residue was purified by preparative TLC (petroleum ether/EtOAc: 100/1) to yield **14a** as a light yellow liquid.

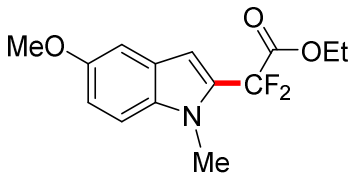
5.4.2 Characterization Data of Difluoroalkylated Indoles 14



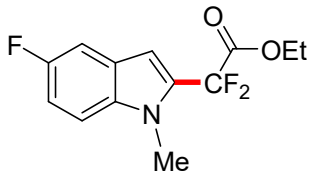
Ethyl 2,2-difluoro-2-(1-methyl-1*H*-indol-2-yl)acetate (14a): Yield: 0.031 g, 61%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.65 (d, J = 8.0 Hz, 1H, Ar–H), 7.39-7.32 (m, 2H, Ar–H), 7.17 (t, J = 7.4 Hz, 1H, Ar–H), 6.81 (s, 1H, Ar–H), 4.40 (q, J = 7.2 Hz, 2H, CH_2), 3.89 (s, 3H, CH_3), 1.38 (t, J = 7.0 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 163.4 (t, $^{2}J_{C–F}$ = 34.3 Hz, CO), 139.1 (C_q), 129.6 (t, $^{2}J_{C–F}$ = 28.6 Hz, C_q), 126.3 (C_q), 124.2 (CH), 122.1 (CH), 120.6 (CH), 111.5 (t, $^{1}J_{C–F}$ = 248.9 Hz, CF_2), 109.9 (CH), 105.0 (t, $^{3}J_{C–F}$ = 5.7 Hz, CH), 63.7 (CH_2), 31.4 (CH_3), 14.1 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = –98.4 (s). The ^{1}H and ^{13}C spectra are consistent with those reported in the literature.[43]



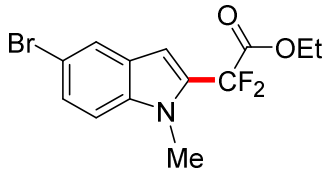
Ethyl 2-(1,5-dimethyl-1*H*-indol-2-yl)-2,2-difluoroacetate (14b): The representative procedure was followed, using substrate **3b** (0.029 g, 0.2 mmol) and ethyl 2-bromo-2,2-difluoroacetate (0.081 g, 0.4 mmol). Purification by preparative TLC (petroleum ether/EtOAc: 100/1) yielded **14b** as a light yellow liquid. Yield: 0.028 g, 52%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.42 (s, 1H, Ar–H), 7.26 (d, J = 8.4 Hz, 1H, Ar–H), 7.16 (d, J = 8.4 Hz, 1H, Ar–H), 6.71 (s, 1H, Ar–H), 4.39 (q, J = 7.1 Hz, 2H, CH_2), 3.86 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 1.37 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 163.4 (t, $^{2}J_{C–F}$ = 34.3 Hz, CO), 137.6 (C_q), 129.9 (C_q), 129.5 (t, $^{2}J_{C–F}$ = 28.6 Hz, C_q), 126.5 (C_q), 126.0 (CH), 121.5 (CH), 111.5 (t, $^{1}J_{C–F}$ = 248.0 Hz, CF_2), 109.6 (CH), 104.4 (t, $^{3}J_{C–F}$ = 6.2 Hz, CH), 63.7 (CH_2), 31.4 (CH_3), 21.5 (CH_3), 14.1 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = –98.3 (s).



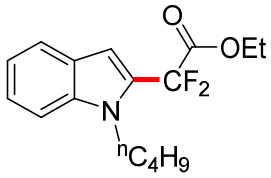
Ethyl 2,2-difluoro-2-(5-methoxy-1-methyl-1*H*-indol-2-yl)acetate (14c): The representative procedure was followed, using substrate **3c** (0.032 g, 0.2 mmol) and ethyl 2-bromo-2,2-difluoroacetate (0.081 g, 0.4 mmol). Purification by preparative TLC (petroleum ether/EtOAc: 50/1) yielded **14c** as a light yellow liquid. Yield: 0.026 g, 46%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.26 (d, J = 9.2 Hz, 1H, Ar–H), 7.07 (d, J = 1.8 Hz, 1H, Ar–H), 7.00 (dd, J = 9.2, 1.8 Hz, 1H, Ar–H), 6.71 (s, 1H, Ar–H), 4.39 (q, J = 6.9 Hz, 2H, CH_2), 3.85 (s, 6H, CH_3), 1.38 (t, J = 7.0 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 163.2 (t, $^{2}J_{C–F}$ = 34.7 Hz, CO), 154.6 (C_q), 134.3 (C_q), 129.6 (t, $^{2}J_{C–F}$ = 28.9 Hz, C_q), 126.3 (C_q), 115.0 (CH), 111.2 (t, $^{1}J_{C–F}$ = 248.9 Hz, CF_2), 110.6 (CH), 104.2 (t, $^{3}J_{C–F}$ = 6.2 Hz, CH), 102.7 (CH), 63.5 (CH_2), 55.8 (CH_3), 31.3 (CH_3), 13.9 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = –98.4 (s).



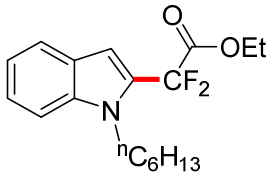
Ethyl 2,2-difluoro-2-(5-fluoro-1-methyl-1*H*-indol-2-yl)acetate (14d): The representative procedure was followed, using substrate **3d** (0.030 g, 0.2 mmol) and ethyl 2-bromo-2,2-difluoroacetate (0.081 g, 0.4 mmol). Purification by preparative TLC (petroleum ether/EtOAc: 50/1) yielded **14d** as a light yellow liquid. Yield: 0.027 g, 50%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.30-7.24 (m, 2H, Ar–H), 7.08 (td, J = 9.2, 2.3 Hz, 1H, Ar–H), 6.75 (s, 1H, Ar–H), 4.39 (q, J = 7.0 Hz, 2H, CH_2), 3.86 (s, 3H, CH_3), 1.37 (t, J = 7.2 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 163.2 (t, $^{2}J_{C–F}$ = 33.9 Hz, CO), 158.3 (d, $^{1}J_{C–F}$ = 236.5 Hz, C_q), 135.7 (C_q), 131.1 (t, $^{2}J_{C–F}$ = 29.1 Hz, C_q), 126.4 (d, $^{3}J_{C–F}$ = 9.5 Hz, C_q), 113.0 (d, $^{2}J_{C–F}$ = 26.7 Hz, CH), 111.2 (t, ^{1}J = 248.9 Hz, CF_2), 110.8 (d, $^{3}J_{C–F}$ = 9.5 Hz, CH), 106.6 (d, $^{2}J_{C–F}$ = 23.8 Hz, CH), 104.7 (virtual quartet, $J_{C–F}$ = 5.7 Hz, CH), 63.8 (CH_2), 31.6 (CH_3), 14.1 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = –98.8 (s, CF_2), –123.7 (s, Ar-F).



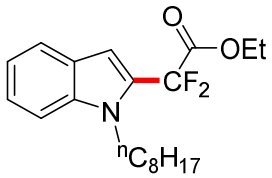
Ethyl 2,2-difluoro-2-(5-methoxy-1-methyl-1*H*-indol-2-yl)acetate (14e): The representative procedure was followed, using substrate **3e** (0.042 g, 0.2 mmol) and ethyl 2-bromo-2,2-difluoroacetate (0.081 g, 0.4 mmol). Purification by preparative TLC (petroleum ether/EtOAc: 50/1) yielded **14e** as a light yellow liquid. Yield: 0.040 g, 60%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.76 (s, 1H, Ar–H), 7.40 (d, J = 8.5 Hz, 1H, Ar–H), 7.23 (d, J = 9.2 Hz, 1H, Ar–H), 6.73 (s, 1H, Ar–H), 4.40 (q, J = 6.7 Hz, 2H, CH_2), 3.86 (s, 3H, CH_3), 1.38 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 163.1 (t, $^{2}J_{C–F}$ = 33.9 Hz, CO), 137.7 (C_q), 130.7 (t, $^{2}J_{C–F}$ = 28.9 Hz, C_q), 127.8 (C_q), 127.1 (CH), 124.5 (CH), 113.8 (C_q), 111.5 (CH), 111.1 (t, $^{1}J_{C–F}$ = 248.9 Hz, CF_2), 104.3 (t, $^{3}J_{C–F}$ = 6.2 Hz, CH), 63.9 (CH_2), 31.6 (CH_3), 14.1 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = –98.8 (s).



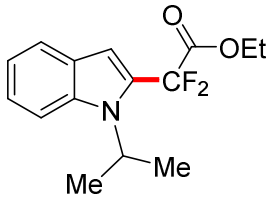
Ethyl 2-(1-butyl-1*H*-indol-2-yl)-2,2-difluoroacetate (14f): The representative procedure was followed, using substrate **3f** (0.035 g, 0.2 mmol) and ethyl 2-bromo-2,2-difluoroacetate (0.081 g, 0.4 mmol). Purification by preparative TLC (petroleum ether/EtOAc: 100/1) yielded **14f** as a light yellow liquid. Yield: 0.027g, 46%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.65 (d, J = 7.6 Hz, 1H, Ar–H), 7.38 (d, J = 8.4 Hz, 1H, Ar–H), 7.32 (*vt*, J = 7.6 Hz, 1H, Ar–H), 7.15 (t, J = 7.4 Hz, 1H, Ar–H), 6.76 (s, 1H, Ar–H), 4.40 (q, J = 7.1 Hz, 2H, CH_2), 4.24 (t, J = 8.0 Hz, 2H, CH_2), 1.80 (pent, J = 7.8 Hz, 2H, CH_2), 1.48-1.40 (m, 2H, CH_2), 1.38 (t, J = 7.3 Hz, 3H, CH_3), 0.98 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 163.5 (t, $^{2}J_{C–F}$ = 34.3 Hz, CO), 138.3 (C_q), 129.1 (t, $^{2}J_{C–F}$ = 28.1 Hz, C_q), 126.5 (C_q), 124.0 (CH), 122.2 (CH), 120.5 (CH), 111.6 (t, $^{1}J_{C–F}$ = 248.0 Hz, CF_2), 110.5 (CH), 105.1 (t, $^{3}J_{C–F}$ = 6.2 Hz, CH), 63.7 (CH_2), 45.2 (CH_2), 32.3 (CH_2), 20.4 (CH_2), 14.1 (CH_3) 13.9 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = –97.6 (s).



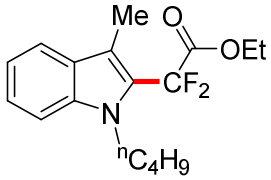
Ethyl 2,2-difluoro-2-(1-hexyl-1*H*-indol-2-yl)acetate (14g): The representative procedure was followed, using substrate **3g** (0.04 g, 0.2 mmol) and ethyl 2-bromo-2,2-difluoroacetate (0.081 g, 0.4 mmol). Purification by preparative TLC (petroleum ether/EtOAc: 100/1) yielded **14g** as a light yellow liquid. Yield: 0.029 g, 45%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, J = 7.9 Hz, 1H, Ar–H), 7.40-7.35 (m, 1H, Ar–H), 7.32 (*vt*, J = 7.3 Hz, 1H, Ar–H), 7.15 (t, J = 7.3 Hz, 1H, Ar–H), 6.76 (s, 1H, Ar–H) 4.40 (q, J = 7.0 Hz, 2H, CH_2), 4.27 (t, J = 7.9 Hz, 2H, CH_2), 1.85- 1.77 (m, 2H, CH_2), 1.44-1.28 (m, 9H, CH_2 and CH_3), 0.90 (t, J = 6.1 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 163.8 (t, $^{2}J_{C–F}$ = 37.0 Hz, CO), 138.3 (C_q), 129.1 (t, $^{2}J_{C–F}$ = 28.5 Hz, C_q), 126.5 (C_q), 124.1 (CH), 122.2 (CH), 120.5 (CH), 111.6 (t, $^{1}J_{C–F}$ = 248.2 Hz, CF_2), 110.4 (CH), 105.1 (t, $^{3}J_{C–F}$ = 6.2 Hz, CH), 63.7 (CH_2), 45.5 (CH_2), 31.6 (CH_2), 30.1 (CH_2), 26.8 (CH_2), 22.7 (CH_2), 14.2 (CH_3), 14.1 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = –97.7 (s).



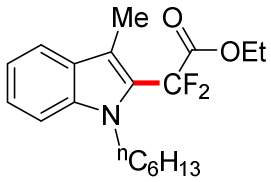
Ethyl 2,2-difluoro-2-(1-octyl-1*H*-indol-2-yl)acetate (14h): The representative procedure was followed, using substrate **3h** (0.046 g, 0.2 mmol) and ethyl 2-bromo-2,2-difluoroacetate (0.081 g, 0.4 mmol). Purification by preparative TLC (petroleum ether/EtOAc: 100/1) yielded **14h** as a light yellow liquid. Yield: 0.030 g, 43%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, J = 7.9 Hz, 1H, Ar–H), 7.37 (d, J = 7.9 Hz, 1H, Ar–H), 7.31 (t, J = 7.6 Hz, 1H, Ar–H), 7.15 (t, J = 7.3 Hz, 1H, Ar–H), 6.76 (s, 1H, Ar–H), 4.40 (q, J = 7.0 Hz, 2H, CH_2), 4.26 (t, J = 8.2 Hz, 2H, CH_2), 1.81 (pent, J = 7.3 Hz, 2H, CH_2), 1.38 (t, J = 7.0 Hz, 3H, CH_3), 1.35-1.21 (m, 10H, CH_2), 0.89 (t, J = 6.7 Hz, 3H CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 163.5 (t, $^{2}J_{C–F}$ = 34.7 Hz, CO), 138.3 (C_q), 129.1 (t, $^{2}J_{C–F}$ = 28.5 Hz, C_q), 126.5 (C_q), 124.1 (CH), 122.2 (CH), 120.5 (CH), 111.6 (t, $^{1}J_{C–F}$ = 248.9 Hz, CF_2), 110.4 (CH), 105.1 (t, $^{3}J_{C–F}$ = 6.2 Hz, CH), 63.7 (CH_2), 45.5 (CH_2), 32.0 (CH_2), 30.2 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 27.2 (CH_2), 22.8 (CH_2), 14.3 (CH_3), 14.1 (CH_3) ^{19}F-NMR (377 MHz, $CDCl_3$): δ = –97.7 (s).



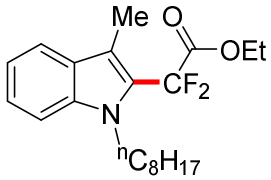
Ethyl 2,2-difluoro-2-(1-isopropyl-1*H*-indol-2-yl)acetate (14i): The representative procedure was followed, using substrate **3i** (0.032 g, 0.2 mmol) and ethyl 2-bromo-2,2-difluoroacetate (0.081 g, 0.4 mmol). Purification by preparative TLC (petroleum ether/EtOAc: 100/1) yielded **14i** as a light yellow liquid. Yield: 0.020 g, 36%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, J = 7.9 Hz, 1H, Ar–H), 7.62 (d, J = 8.6 Hz, 1H, Ar–H), 7.31-7.25 (m, 1H, Ar–H), 7.15 (t, J = 7.3 Hz, 1H, Ar–H), 6.76 (s, 1H, Ar–H), 4.94 (sept, J = 7.0 Hz, 1H, CH), 4.42 (q, J = 7.3 Hz, 2H, CH_2), 1.68 (d, J = 6.7 Hz, 6H, CH_3), 1.39 (t, J = 7.0 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 163.4 (t, $^{2}J_{C–F}$ = 34.7 Hz, CO), 136.3 (C_q), 130.1 (t, $^{2}J_{C–F}$ = 26.9 Hz, C_q), 127.4 (C_q), 123.3 (CH), 122.4 (CH), 120.0 (CH), 113.1 (CH), 111.4 (t, $^{1}J_{C–F}$ = 247.8 Hz, CF_2), 104.6 (t, $^{3}J_{C–F}$ = 6.6 Hz, CH), 63.6 (CH_2), 49.3 (CH), 21.2 (2C, CH_3), 14.0 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = –97.5 (s).



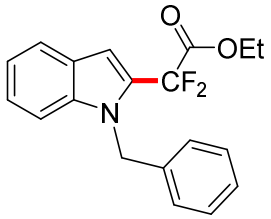
Ethyl 2-(1-butyl-3-methyl-1*H*-indol-2-yl)-2,2-difluoroacetate (14j): The representative procedure was followed, using substrate **3j** (0.037 g, 0.2 mmol) and ethyl 2-bromo-2,2-difluoroacetate (0.081 g, 0.4 mmol). Purification by preparative TLC (petroleum ether/EtOAc: 100/1) yielded **14j** as a light yellow liquid. Yield: 0.040 g, 65%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, J = 7.9 Hz, 1H, Ar–H), 7.37-7.28 (m, 2H, Ar–H), 7.16 (t, J = 7.0 Hz, 1H, Ar–H), 4.32 (q, J = 7.1 Hz, 2H, CH_2), 4.25 (t, J = 7.9 Hz, CH_2) 2.44 (s., 3H, CH_2), 1.82-1.70 (m, 2H, CH_2), 1.48-1.38 (m, 2H, CH_2), 1.33 (t, J = 7.0 Hz, 3H, CH_2), 0.98 (t, J = 7.3 Hz, 3H, CH_2). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 163.9 (t, $^{2}J_{C–F}$ = 36.2 Hz, CO), 137.5 (C_q), 128.0 (C_q), 124.5 (t, $^{2}J_{C–F}$ = 29.3 Hz, C_q), 124.0 (CH), 120.1 (CH), 119.7 (CH), 114.3 (C_q), 112.6 (t, $^{1}J_{C–F}$ = 251.2 Hz, CF_2), 110.1 (CH), 63.5 (CH_2), 45.2 (CH_2), 32.5 (CH_2), 20.4 (CH_2), 14.0 (CH_3), 9.2 (t, $^{4}J_{C–F}$ = 2.3 Hz, CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = –97.9 (s).



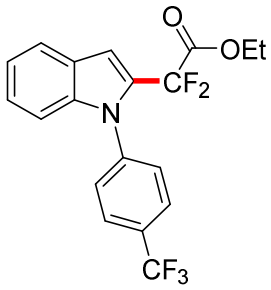
Ethyl 2,2-difluoro-2-(1-hexyl-3-methyl-1*H*-indol-2-yl)acetate (14k): The representative procedure was followed, using substrate **3k** (0.043 g, 0.2 mmol) and ethyl 2-bromo-2,2-difluoroacetate (0.081 g, 0.4 mmol). Purification by preparative TLC (petroleum ether/EtOAc: 100/1) yielded **14k** as a light yellow liquid. Yield: 0.040 g, 59%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.63 (d, J = 8.0 Hz, 1H, Ar–H), 7.35-7.29 (m, 2H, Ar–H), 7.19-7.13 (m, 1H, Ar–H), 4.32 (q, J = 7.2 Hz, 2H, CH2), 4.24 (t, J = 8.2 Hz, 2H, CH_2), 2.45 (t, J = 2.9 Hz, 3H, CH_3), 1.79 (pent, J = 7.8 Hz, 2H, CH_2), 1.43-1.32 (m, 9H, CH_2) 0.92 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 163.9 (t, $^{2}J_{C–F}$ = 35.8 Hz, CO), 137.5 (C_q), 128.0 (C_q), 124.5 (t, $^{2}J_{C–F}$ = 28.6 Hz, C_q), 124.0 (CH), 120.1 (CH), 119.7 (CH), 114.3 (C_q), 112.7 (t, $^{1}J_{C–F}$ = 250.8 Hz, CF_2), 110.1 (CH), 63.5 (CH_2), 45.5 (CH_2), 31.6 (CH_2), 30.4 (CH_2), 26.9 (CH_2), 22.8 (CH_2), 14.2 (CH_3), 14.0 (CH_3), 9.2 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = –98.0 (s).



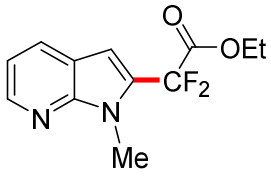
Ethyl 2,2-difluoro-2-(3-methyl-1-octyl-1*H*-indol-2-yl)acetate (14l): The representative procedure was followed, using substrate **3l** (0.049 g, 0.2 mmol) and ethyl 2-bromo-2,2-difluoroacetate (0.081 g, 0.4 mmol). Purification by preparative TLC (petroleum ether/EtOAc: 100/1) yielded **14l** as a light yellow liquid. Yield: 0.029 g, 40%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.62 (d, J = 8.0 Hz, 1H, Ar–H), 7.34-7.27 (m, 2H, Ar–H), 7.17-7.11 (m, 1H, Ar–H), 4.31 (q, J = 7.0 Hz, 2H, CH_2), 4.22 (t, J = 8.0 Hz, 2H, CH_2), 2.43 (t, J = 3.1 Hz, 3H, CH_3), 1.77 (pent, J = 7.6 Hz, 2H, CH_2), 1.40-1.27 (m, 13H, CH_2), 0.89 (t, J = 6.9 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 163.9 (t, $^{2}J_{C–F}$ = 35.3 Hz, CO), 137.5 (C_q), 130.9 (t, $^{2}J_{C–F}$ = 24.8 Hz, C_q), 128.0 (C_q), 124.0 (CH), 120.1 (CH), 119.7 (CH), 114.3 (C_q), 110.2 (CH), 112.7 (t, $^{1}J_{C–F}$ = 250.8 Hz, CF_2), 63.5 (CH_2), 45.5 (CH_2), 32.0 (CH_2), 30.4 (CH_2), 29.4 (CH_2), 29.4 (CH_2), 27.2 (CH_2), 22.8 (CH_2), 14.3 (CH_3) 14.0 (CH_3) 9.2 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = –97.9 (s).



Ethyl 2-(1-benzyl-1*H*-indol-2-yl)-2,2-difluoroacetate (14m): The representative procedure was followed, using substrate **3m** (0.041 g, 0.2 mmol) and ethyl 2-bromo-2,2-difluoroacetate (0.081 g, 0.4 mmol). Purification by preparative TLC (petroleum ether/EtOAc: 100/1) yielded **14m** as a light yellow liquid. Yield: 0.027 g, 41%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.71 (d, J = 7.6 Hz, 1H, Ar–H), 7.30-7.16 (m, 6H, Ar–H), 6.99 (d, J = 7.3 Hz, 2H, Ar–H), 6.94 (s, 1H, Ar–H), 5.58 (s, 2H, CH_2), 4.20 (q, J = 7.3 Hz, 2H, CH_2), 1.29 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 163.2 (t, $^{2}J_{C–F}$ = 34.3 Hz, CO), 138.8 (C_q), 137.4 (C_q), 130.2 (t, $^{2}J_{C–F}$ = 29.6 Hz, C_q), 128.8 (2C, CH), 127.5 (CH), 126.6 (C_q), 126.0 (2C, CH), 124.5 (CH), 122.2 (CH), 121.0 (CH), 111.4 (t, $^{1}J_{C–F}$ = 248.9 Hz, CF_2), 110.9 (CH), 105.6 (t, $^{3}J_{C–F}$ = 6.2 Hz, CH), 63.7 (CH_2), 48.5 (CH_2), 14.0 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = –98.0 (s).



Ethyl 2,2-difluoro-2-(1-(4-(trifluoromethyl)phenyl)-1*H*-indol-2-yl)acetate (14n): The representative procedure was followed, using substrate **3n** (0.052 g, 0.2 mmol) and ethyl 2-bromo-2,2-difluoroacetate (0.081 g, 0.4 mmol). Purification by preparative TLC (petroleum ether/EtOAc: 100/1) yielded **14n** as a light yellow liquid. Yield: 0.034 g, 44%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, J = 8.5 Hz, 2H, Ar–H), 7.72 (d, J = 7.9 Hz, 1H, Ar–H), 7.56 (d, J = 7.9 Hz, 2H, Ar–H), 7.30-7.20 (m, 3H Ar–H), 7.05 (s, 1H, Ar–H), 4.20 (d, J = 6.7 Hz, 2H, CH_2), 1.26 (t, J = 3.7 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 162.5 (t, $^{2}J_{C–F}$ = 33.1 Hz, CO), 140.4 (C_q), 140.0 (C_q), 130.6 (q, $^{2}J_{C–F}$ = 28.5 Hz, C_q), 129.6 (2C, CH), 126.6 (q, $^{3}J_{C–F}$ = 3.9 Hz, 2C, CH), 126.3 (t, ^{2}J = 24.7 Hz, C_q), 125.3 (C_q), 125.1 (CH), 122.6 (q, $^{1}J_{C–F}$ = 272.8 Hz, CF_3), 122.2 (CH), 121.7 (CH), 110.9 (CH), 107.2 (t, $^{3}J_{C–F}$ = 5.8 Hz, CH), 63.4 (CH_2), 14.0 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = –62.6 (s), –94.9 (s).



Ethyl 2,2-difluoro-2-(1-methyl-1*H*-pyrrolo[2,3-b]pyridin-2-yl)acetate (14o): The representative procedure was followed, using substrate **3o** (0.026 g, 0.2 mmol) and ethyl 2-bromo-2,2-difluoroacetate (0.081 g, 0.4 mmol). Purification by preparative TLC (petroleum ether/EtOAc: 100/1) yielded **14o** as a light yellow liquid. Yield: 0.028 g, 55%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.44 (d, J = 4.6 Hz, 1H, Ar–H), 7.95 (dd, J = 8.0, 1.1 Hz, 1H, Ar–H), 7.12 (dd, J = 8.0, 4.6 Hz, 1H, Ar–H), 6.77 (s, 1H, Ar–H), 4.40 (q, J = 7.0 Hz, 2H, CH_2), 3.99 (s, 3H, CH_3), 1.37 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 163.1 (t, $^{2}J_{C–F}$ = 33.4 Hz, CO), 149.3 (C_q), 145.6 (CH), 130.3 (CH), 130.2 (t, J = 28.6 Hz, C_q), 118.8 (C_q), 116.9 (CH), 111.2 (t, $^{1}J_{C–F}$ = 248.9 Hz, CF_2), 102.3 (t, $^{2}J_{C–F}$ = 6.7 Hz, CH), 63.9 (CH_2), 29.9 (CH_2), 14.1 (CH_3). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = –99.8 (s).

5.4.3 Procedure for External Additive Experiments: To a flame-dried screw-cap tube (5 mL) equipped with magnetic stir bar was introduced 1-methyl-1*H*-indole (**3a**; 0.026 g, 0.2 mmol), ethyl 2-bromo-2,2-difluoroacetate (0.081 g, 0.4 mmol), (DME)$NiCl_2$ (0.0044 g, 0.02 mmol, 10.0 mol %), Xantphos (0.014 g, 0.024 mmol, 12 mol %), Na_2CO_3 (0.042 g, 0.4 mmol) and mercury (2.0 g 10 mmol) [or TEMPO (0.063 g, 0.4 mmol) or Galvinoxyl (0.17 g, 0.4 mmol)] inside the glove-box. To the above mixture in the tube, 1,4-dioxane (1.0 mL) was added and the resultant reaction mixture was stirred at 130 °C in a preheated oil bath for 20 h. Yield of the product **14a** was determined by the GC analysis of crude reaction mixture using *n*-dodecane as an internal standard.

5.4.4 Procedure for H/D Scrambling Experiment: To a flame-dried screw-cap tube (5 mL) equipped with magnetic stir bar was introduced 1-methyl-1*H*-indole (**3a**; 0.026 g, 0.2 mmol), ethyl 2-bromo-2,2-difluoroacetate (0.081 g, 0.4 mmol), (DME)$NiCl_2$ (0.0044 g, 0.02 mmol, 10.0 mol %), Xantphos (0.014 g, 0.024 mmol, 12 mol %) and Na_2CO_3 (0.042 g, 0.4 mmol) inside the glove-box. To the above mixture in the tube, 1,4-dioxane (1.0 mL) was added and the resultant reaction mixture was stirred at 130 °C in a preheated oil bath for 20 min. At ambient temperature, CD_3OD (0.5 mL) was added to the reaction mixture under argon and stirred for 2 h. The reaction mixture was diluted with EtOAc, and was filtered. The volatiles were evaporated in *vacuo* and the crude product was subjected to preparative TLC. The product **14a** was isolated, and compound **3a** was recovered.

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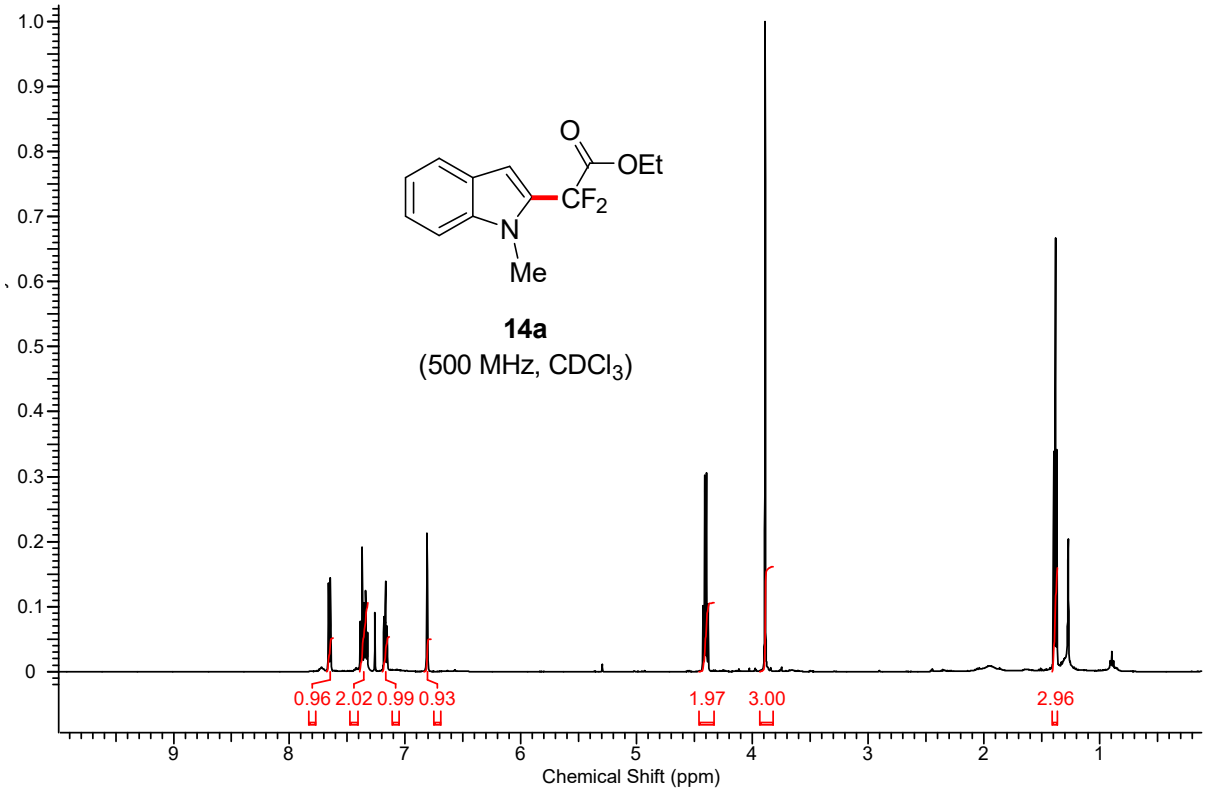
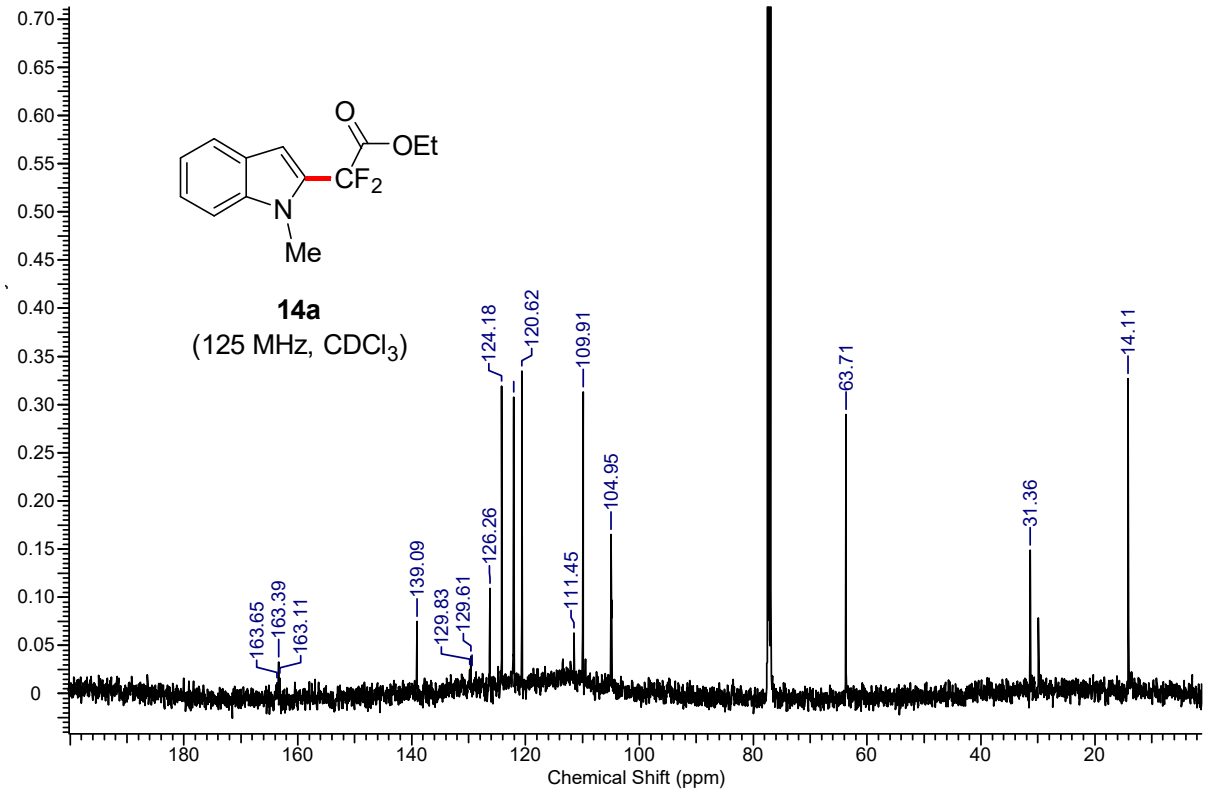
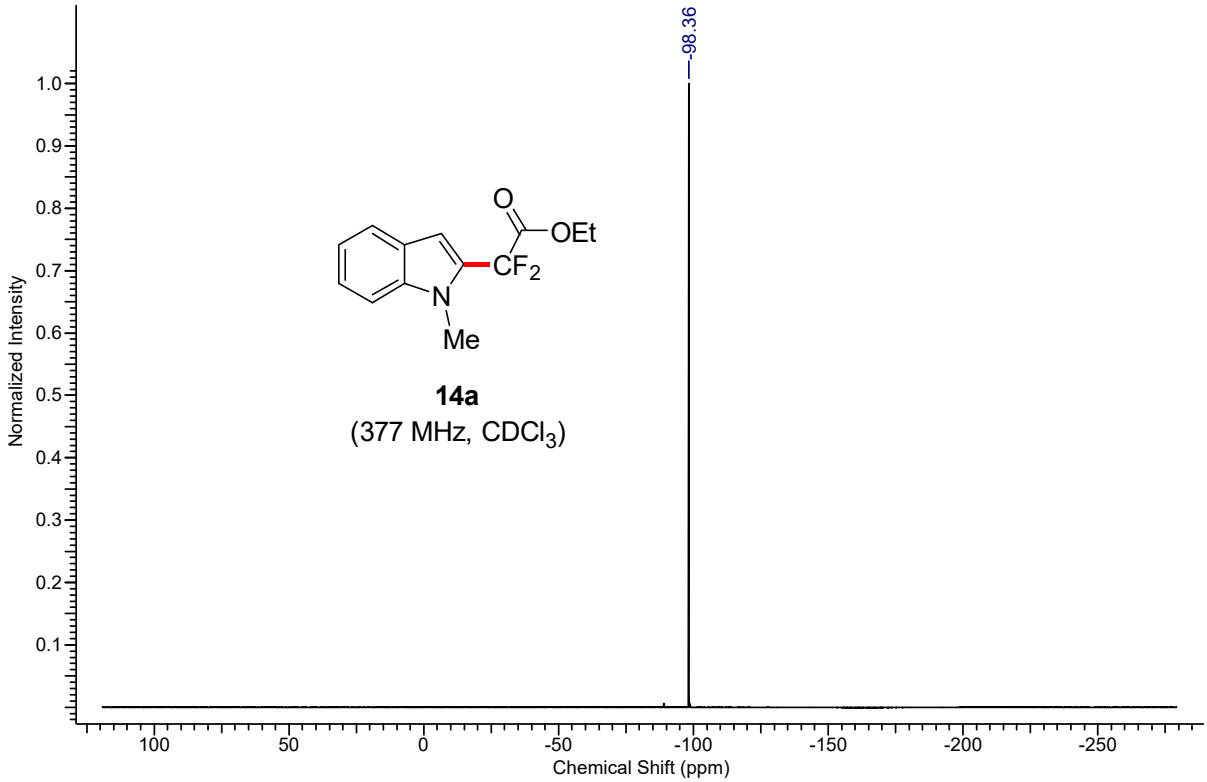
NMR Spectra of Representative Difluoroalkylated Indole







14a

(377 MHz, $CDCl_3$)

Chapter 6

Transition-Metal-Free Regioselective C-3 Acetoxylation of *N*-Substituted Indoles

6.1 INTRODUCTION

Direct functionalization of C–H bond to form C–O bond is among the most demanding chemical reaction in synthetic organic chemistry.[1-3] The C–O bond formation in arenes to obtain hydroxylated-,[4-11] alkoxylated-[12-16] or acetoxylated-arenes[17-29] are considerably explored, and the regioselectivity has been successfully achieved by the installation of a Lewis-base directing group. In contrast to many reports on the acetoxylation of arenes, the regioselective synthesis of acetoxylated heteroarenes is relatively scarce.[30,31] Among the heteroarenes, the indole derivatives are very important building blocks, found in many pharmaceuticals as well as in the biologically active compounds. In particular, 3-acetoxyindoles are potential materials, applied for the detection of acetylcholinesterase in tissue slices,[32] and they are also used as a starting precursors for the synthesis of potential 5-hydroxytryptamine$_6$ (5-HT$_6$) receptor ligand scafolds.[33,34] Hence, the efficient synthesis of 3-acetoxyindoles through the regioselective C-3 acetoxylation of indole derivatives is highly desirable. The groups of Lei,[35] Kwong[33] and Suna[36,37] have independently reported the C-3 acetoxylation of *N*-substituted indoles using Pd(OAc)$_2$ catalyst, and PhI(OAc)$_2$ as an external oxidant. This palladium-catalyzed regioselective acetoxylation process is applicable to the various indole substrates containing methyl, benzyl, aryl or arenesulfonyl groups as the nitrogen-substituent. However, the employment of the precious metal catalysts for the functionalization of probable pharmacological indole derivatives limit the advancement of these metal-catalyzed acetoxylation processes.

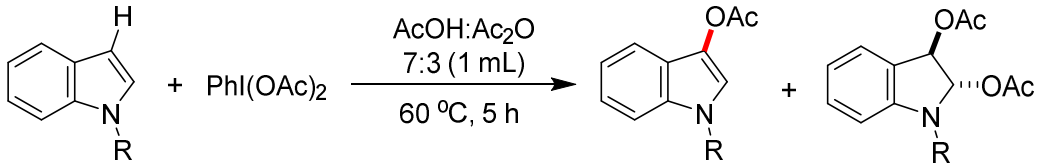
In recent years, numerous reports have been described for the C–H bond functionalization under the transition-metal-free conditions.[38,39] A transition-metal-free C-3 acetoxylation of the free *NH*-indole has been described under the strong basic condition by Huang and co-workers.[40] However, this method is not applicable to the *N*-substituted indole substrates, and has limited scope. The C-3 acetoxylation of *N*-Boc-protected indole has been observed by Lei *et.al.* during their studies directed toward the synthesis of diacetoxylated indolines.[41] However, a comprehensive approach for the metal-free C-3 acetoxylation of the *N*-substituted indoles with high regioselectivity is not known. In this chapter, the regioselective C-3 acetoxylation of *N*-substituted indoles with PhI(OAc)$_2$ as an oxidant is described under the metal-free and mild reaction conditions.[42] Moreover, the effect of *N*-substituents on reactivity and selectivity of the indole acetoxylations is demonstrated. Controlled experiments have been performed to obtain the mechanistic insight of the reaction.

6.2 RESULTS AND DISCUSSION

6.2.1 Optimization of Reaction Conditions for Acetoxylation of Indoles

During the investigation of a less expensive and earth-abundant first-row transition metal catalyst for the acetoxylation of the *N*-substituted indoles employing $PhI(OAc)_2$ in acetic acid solvent, it was observed that the C-3 acetoxylation of indole occurred in the absence of metal catalysts, when a suitable substituent on the nitrogen atom of indole is installed. For example, the reaction of 1-pyrimidinyl indole (**3a**) with $PhI(OAc)_2$ in $AcOH/Ac_2O$ solvent at 60 ^oC, exclusively produced 1-(pyrimidin-2-yl)-1*H*-indol-3-yl acetate (**15a**) in 93% isolated yield (Table 6.1, entry 1). The 1-arylindoles, like 1-phenylindole (**3n**) reacted with $PhI(OAc)_2$ under the metal-free condition to afford the corresponding C-3 acetoxylated indole **15n** in 50% yield; whereas the reaction of 1-(4-methoxypheny)indole (**3o**) with $PhI(OAc)_2$ under the same condition produced only 37% of the acetoxylated compound **15o** (Table 6.1, entries 2,3). Surprisingly, the free *NH*-indole or indoles having electron-rich substituents at the nitrogen-center, such as 1-methylindole were decomposed to the unknown compounds at room temperature (Table 6.1, entries 4,5). However, the indoles bearing strong electron-withdrawing substituents at the nitrogen-atom, such as 1-(acetyl)indole and 1-(tosyl)indole produced the diacetoxylated indolines in 91% and 28% yields, respectively (Table 6.1, entries 6,7).[41] These studies on the effect of *N*-substituents towards the acetoxylation of indoles suggested that a π-electron-deficient (hetero)arene-substituent on the nitrogen atom of indole greatly enhances the selective C-3 acetoxylation reaction.

Table 6.1 Effect of nitrogen-substituents on C-3 acetoxylation of indoles.[a]



3 **15** **16**

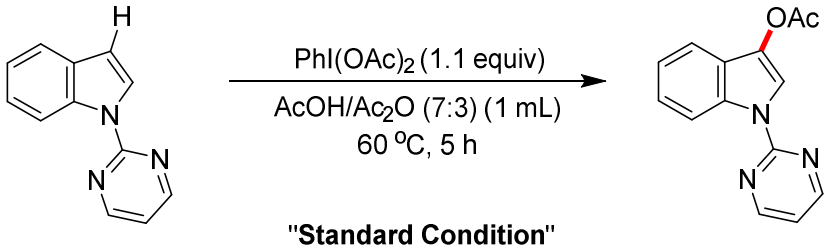
R = H, alkyl, aryl, heteroaryl, acyl, tosyl

Entry	R	Yield (%)	**16** (%)	Recovered (**3**)
1	2-Pym	93 (**15a**)	-	-
2	Ph	50 (**15n**)	-	35 (**3n**)
3	4-MeO-C_6H_4	37 (**15o**)	-	-[b]
4	H	-	-	-[c]
5	CH_3	-	-	-[c]
6	$C(O)CH_3$	-	91	5
7	Tosyl	-	28	70

[a] Reaction conditions: Compound **3** (0.30 mmol), $PhI(OAc)_2$ (0.106 g, 0.33 mmol), $AcOH/Ac_2O$ (1.0 mL), yields of isolated compounds. [b] Starting compound was not recovered. [c] Decomposed into intractable products at room temperature.

After optimizing the effect of *N*-substituent's on the metal-free acetoxylation of indoles, we have tested the impact of various solvents and oxidants on the acetoxylation reaction (Table 6.2). The use of glacial acetic acid as solvent instead of $AcOH/Ac_2O$, produced the desired acetoxylated product **15a** in 76% isolated yield (Table 6.2, entry 2). However, the complete decomposition of **3a** was observed in TFA/TFAA under the reaction conditions (entry 3). The employment of non-acid solvent 2,2,2-trifluoroethanol (TFE) gave only 20% of product **15a**, whereas the reactions in CH_3CN or 1,2-dichloroethane (DCE) did not produce any acetoxylated product (entries 4,5). The presence of strong oxidant $PhI(TFA)_2$ resulted in the decomposition of **3a**; however, other organic oxidants, such as *m*-CPBA, ^tBuOOH or inorganic oxidants like $K_2S_2O_8$ and oxone were ineffective, and most of the starting material was recovered (entries 6-8).

Table 6.2 Optimization of reaction parameters for C-3 acetoxylation of **3a**.[a]



3a **15a**

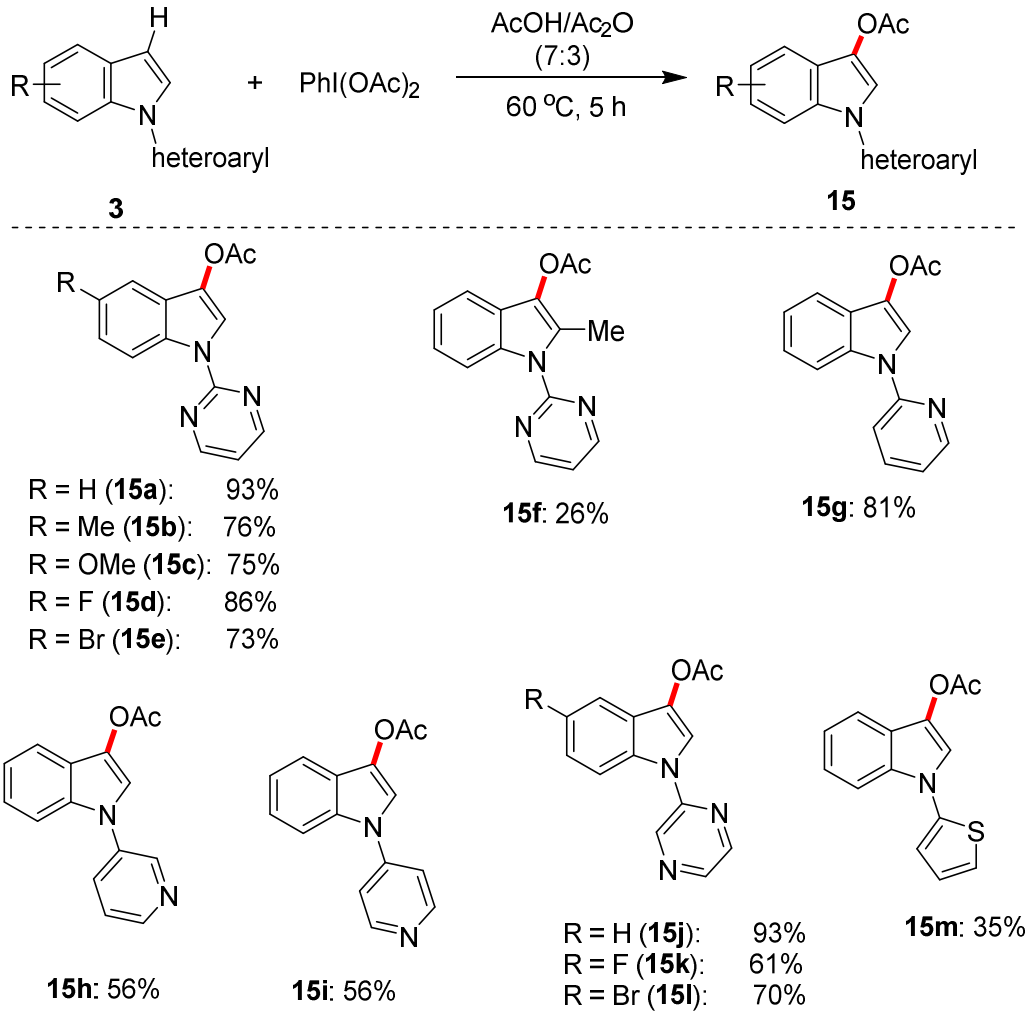
Entry	Variation from "Standard Condition"	Yield (%)[b]
1	-	93
2	AcOH instead of AcOH/Ac_2O	76
3	TFA/TFAA instead of AcOH/Ac_2O	-[c]
4	TFE instead of AcOH/Ac_2O	20
5	CH_3CN, DCE instead of AcOH/Ac_2O	NR
6	$PhI(TFA)_2$ instead of $PhI(OAc)_2$	-[c]
7	*m*-CPBA instead of $PhI(OAc)_2$	trace
8	$K_2S_2O_8$, Oxone or *t*-BuOOH instead of $PhI(OAc)_2$	NR
9	25 °C instead of 60 °C	15

[a] Reaction conditions: **3a** (0.059 g, 0.30 mmol), $PhI(OAc)_2$ (0.106 g, 0.33 mmol), AcOH/Ac_2O (1.0 mL). TFE (2,2,2-Trifluoroethanol), TFA (Trifluoroacetic acid), TFAA (Trifluoroacetic anhydride), NR = No reaction. [b] Yields of isolated compounds. [c] Decomposed into intractable compounds.

6.2.2 Scope for C-3 Acetoxylation of Indoles

Having the optimized reaction conditions in hand, we probed the scope of the metal-free C-3 acetoxylation of the *N*-heteroaryl-substituted indoles **3** employing $PhI(OAc)_2$ as the oxidant in AcOH/Ac_2O solvent (Scheme 6.1). Notably, the *N*-pyrimidinyl indoles containing electronically different functional groups reacted smoothly to produce the desired acetoxylated products **15a**-**15e** in good yields. The tolerability of the functional groups, such as –F, –Br is significant, as they can be further functionalized into important compounds. It is noteworthy that the direct acetoxylation of indoles **3** occurred with excellent regioselectivity to predominantly produce C-3 acetoxylated indoles. Particularly, by employing 2-pyrimidinyl

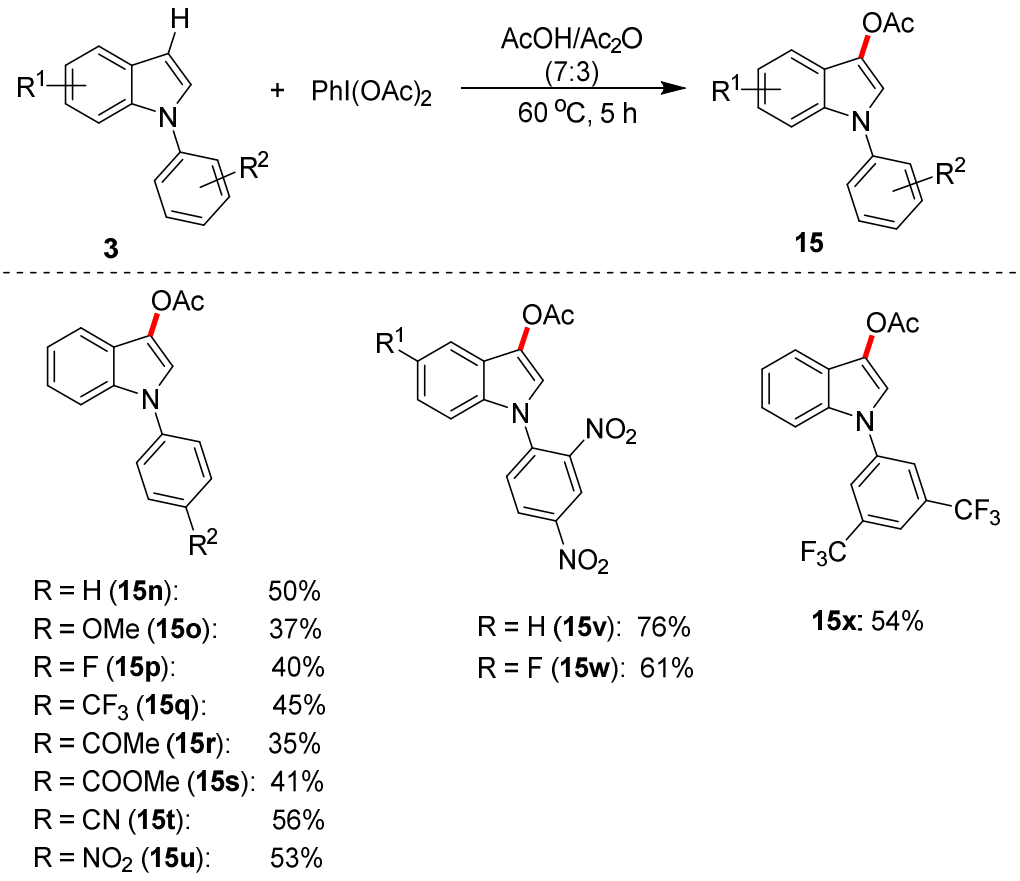
as the *N*-substituent on indoles, neither the starting compounds nor the acetoxylated products were decomposed. More hindered 2-substituted indole **3f** reacted with low efficacy to produce **15f** in 26% yield. In addition to the *N*-pyrimidinyl indoles, the indoles containing 2-pyridinyl and 2-pyrazinyl as nitrogen-substituents reacted efficiently to give the desired acetoxylated products in good yields. The pyridinyl-substituted indoles, **3h** and **3i** reacted moderately to yield the corresponding acetoxylated compounds **15h** and **15i**, respectively. Evidently, the π-electron-rich 2-thiophenyl substituted indole **3m** produced the acetoxylated compound **15m** in low yield.



Scheme 6.1 Scope of C-3 Acetoxylation of *N*-Heteroaryl Substituted Indoles.

We further extended the metal-free acetoxylation method for the selective acetoxylation of the *N*-aryl substituted indoles. Hence, the different substituted *N*-aryl indoles **3** undergo acetoxylations at C-3 position to give the desired products in moderate yields (Scheme 6.2). Interestingly, a number of important functional groups like –F, –CF_3, –C(O)Me, –C(O)OMe,

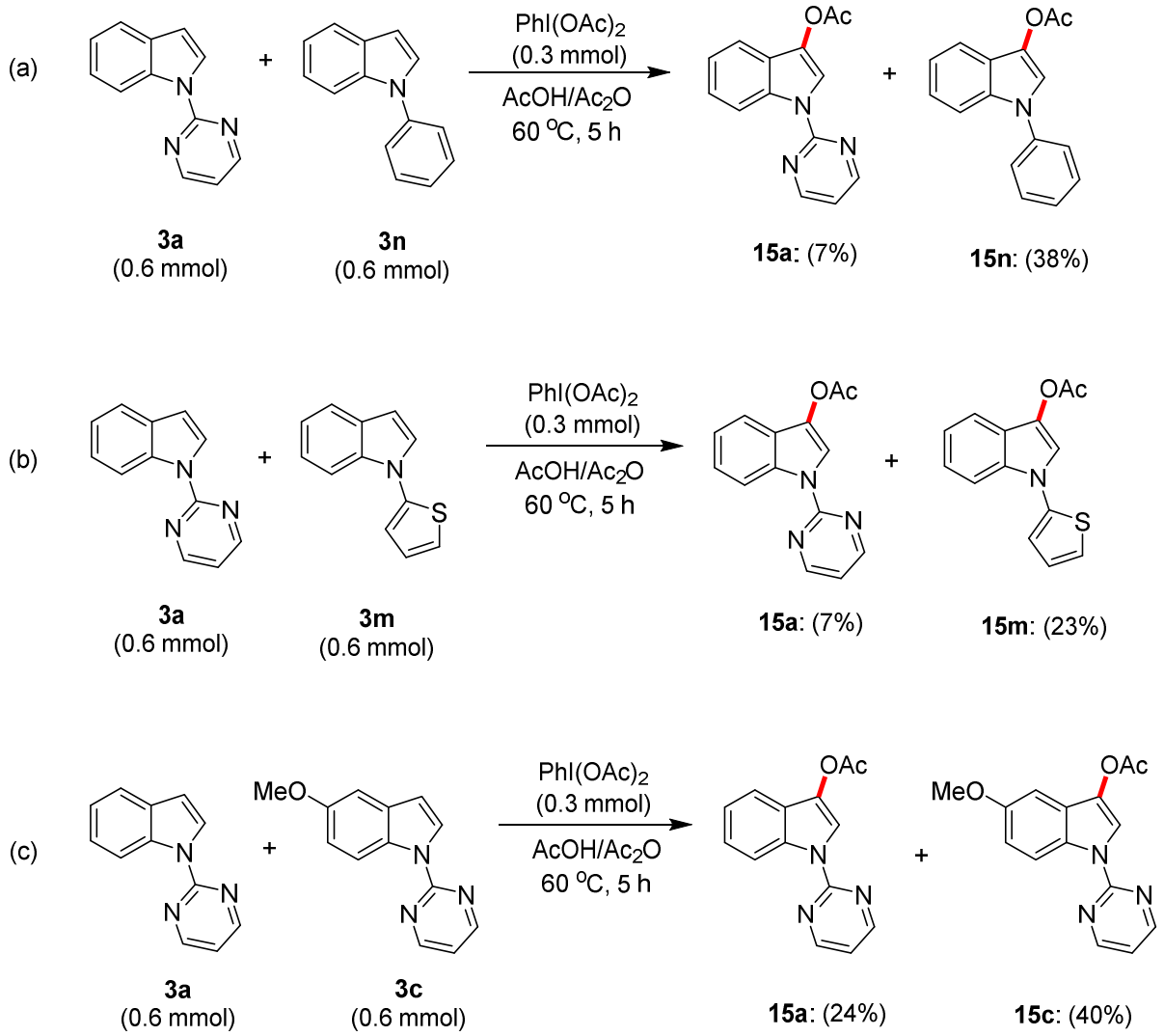
–CN and –NO_2 are well tolerated under the reaction conditions. To our surprise, the 2,4-dinitrophenyl substituted indoles **3v** and **3w** produced the acetoxylated products in good yields. The indoles containing *N*-aryl substituents with electron-withdrawing groups on the aryl backbone were found to produce improved yields of the C-3 acetoxylation than the *N*-aryl substituents bearing electron-donating groups. Unlike free-*NH*-indole or indoles bearing electron-rich *N*-protecting groups, the *N*-aryl substituted indoles do not impart decomposition; however they produced 1-aryl-indolin-3-one and 2-oxo-1-aryl-indolin-3-yl acetate as the side products in different scale, which accounts for the low yields of the C-3 acetoxylated products.[43] Most likely, these side products are formed from the hydrolysis of C-3 acetoxylated and diacetoxylated indoles.



Scheme 6.2 Scope for C-3 Acetoxylation of *N*-Aryl Substituted Indoles.

6.2.3 Mechanistic Study

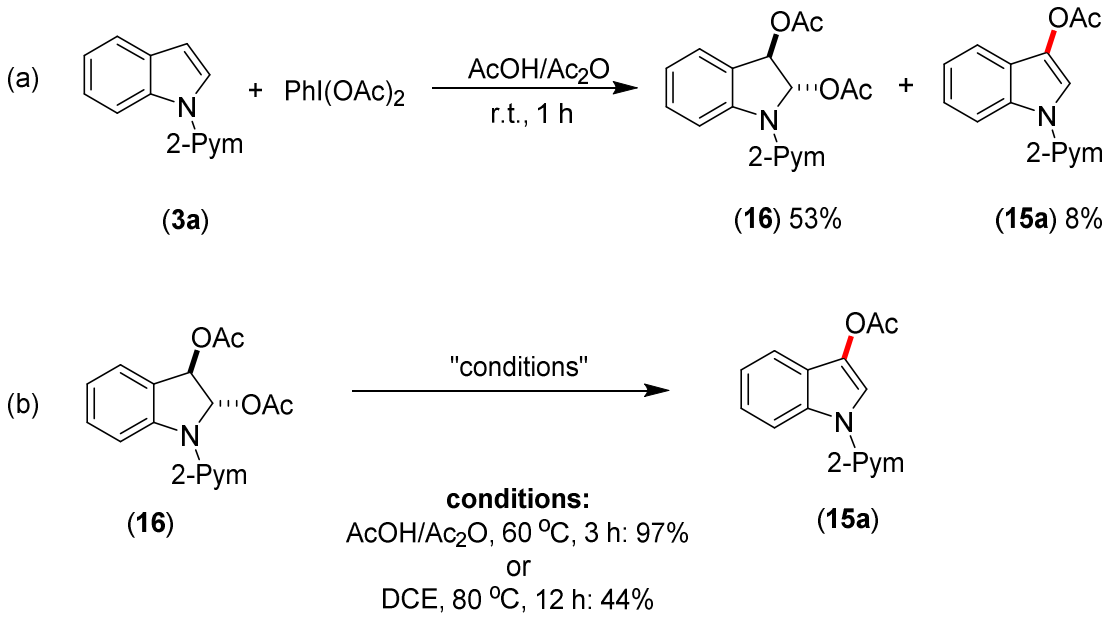
In order to obtain the mechanistic insight, the intermolecular competition experiments between the indoles **3a** and **3n** as well as between **3a** and **3m** were conducted (Scheme 6.3a,b); which highlighted that the indoles bearing π-electron-rich arene substituents were acetoxylated predominantly. Further, an additional experiment between the different substituted *N*-pyrimidinyl-indoles **3a** and **3c** clearly demonstrated that the electron-rich indole was preferentially acetoxylated (Scheme 6.3c), which revealed the nucleophilicity parameter of indoles for the acetoxylation process.[44,45]



Scheme 6.3 Intermolecular Competition Experiments.

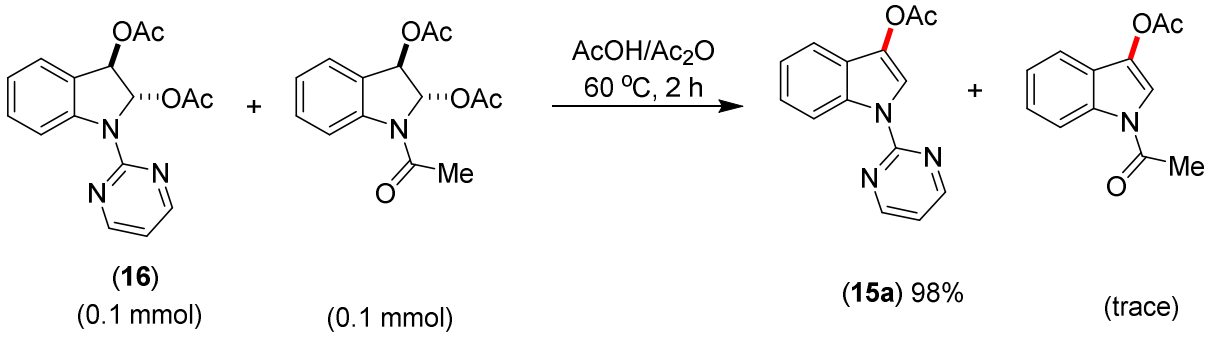
Further to isolate the probable intermediate species, an experiment of **3a** with $PhI(OAc)_2$ was carried out at room temperature, which produced the diacetoxylated indoline **16** in 53% yield after 1 h (Scheme 6.4a). The formation of **16** might follow the pathway

proposed for the similar compounds.[41] Compound **16** led to the complete conversion into the acetoxylated product **15a** upon heating in AcOH/Ac_2O solvent for 3 h (Scheme 6.4b). This clearly demonstrated that the formation of **15a** from **3a** occurred *via* the intermediacy of **16**. The dehydroacetoxylation of **16** to **15a** also occurred under non-acidic condition, however with low efficacy. Similar to the indoline **16**, the intermediate species for the indole **3m** could not be observed; instead the direct formation of **15m** was accomplished, including the intractable decomposed products.



Scheme 6.4 Synthesis and Reactivity of Intermediate Species.

To understand the dehydroacetoxylation process of the different *N*-substituted diacetoxyindolines, the compound **16** and 1-acetylindoline-2,3-diyl diacetate were heated in a single pot at 60 °C (Scheme 6.5). The compound **16** was completely converted into the C-3 acetoxylated product **15a** in 2 h, whereas a trace amount of the C-3 acetoxylated product was formed from the 1-acetylindoline-2,3-diyl diacetate, suggesting that the dehydroacetoxylation of diacetoxylated indoline is significant in the presence of 2-pyrimidinyl as the *N*-substituent. Further, looking into the excellent reactivities of the indoles containing 2-py, 2-pym, 2-pyrazinyl or 2-nitroarene as the *N*-substituents (**3a**-**3g**, **3i**-**3l**, **3v** and **3w**); we assume that the *N*-atom or *N*-group at the *ortho*-position of the substituents might have some additional influence on the dehydroacetoxylation reaction, in addition to the induced electronic of the substituent.



Scheme 6.5 Dehydroacetoxylation of Diacetoxylated Compounds.

Considering our mechanistic findings and literature precedent,[41] we have proposed a mechanistic cycle for the transition-metal-free acetoxylation of indole (Scheme 6.6). First the nucleophilic attack of **3a** towards $PhI(OAc)_2$ promoted by the proton transfer leads to the formation of intermediate **A**. Further, **A** is converted to **B** *via* intramolecular nucleophilic attack of iodine. The acetate ion attacks on C-3 position of **B** to afford *trans* intermediate **C**. The acetoxyl group attached to the iodine is then protonated to produce **D** followed by intramolecular nucleophilic attack to generate *cis* oxygen cation intermediate **E**. The acetate anion finally attacks from the opposite site of oxygen atoms of *cis* intermediate **E** to afford *trans* diacetated indoline **5a**. Further dehydroacetoxylation of **16** leads to the formation of C-**3** acetoxylated product **15a**. We assume that the 2-pyridinyl substituent greatly enhance the last step of the reaction to produce the selective C-3 acetoxylation product.

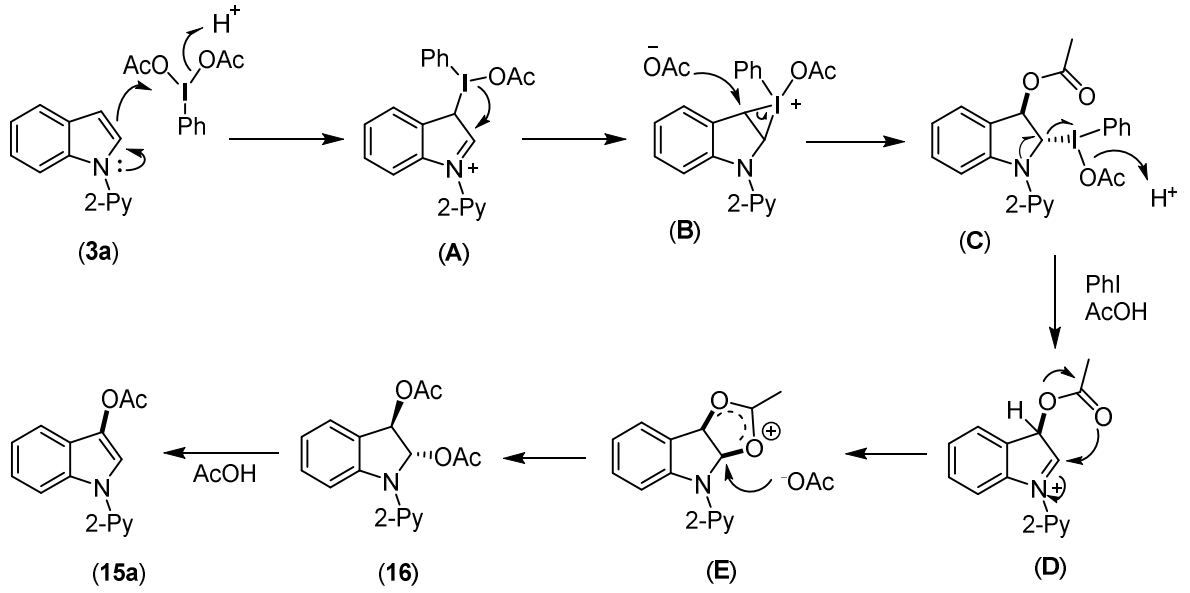


Figure 6.1 Proposed mechanism for metal-free acetoxylation of indole.

6.3 CONCLUSION

In this chapter, an efficient and regioselective method for the C-3 acetoxylation of the *N*-substituted indoles in the absence of transition-metal-catalyst is described, wherein a broad range of functional groups are tolerated. The indoles containing π-electron-deficient arene substituents on the *N*-atom are acetoxylated efficiently than the one bearing strong sigma electron-donating or sigma electron-withdrawing substituents. The diacetoxylated indoline is proposed to be the active intermediate for the acetoxylation of the *N*-substituted indoles, where the dehydroacetoxylation is facilitated in the presence of a π-deficient arene substituents on the *N*-atom of indoles.

6.4 EXPERIMENTAL SECTION

General Experimental

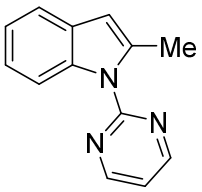
All manipulations were conducted in an argon atmosphere using standard Schlenk techniques in pre-dried glassware. Liquid reagents were flushed with argon prior to use. The starting compounds, *N*-acyl-1*H*-indole,[41] *N*-tosyl-1*H*-indole,[41] *N*-benzyl-1*H*-indole,[33] *N*-aryl-1*H*-indoles,[46-48] *N*-pyridinyl-1*H*-indole,[49,50] *N*-pyrimidinyl-1*H*-indole[46,51] and 1-acetylindoline-2,3-diyl diacetate[41] were synthesized according to the previously described procedures. All other chemicals were obtained from commercial sources and were used without further purification. Representative starting compounds **3** as well as $PhI(OAc)_2$ were analyzed by ICP-AES, which showed only trace amount of transition metals (< 0.1 ppm Fe, Co, Ni, Cu, Pd, Rh and Ru). The yields refer to isolated compound, estimated to be > 95% pure as determined by ^1H NMR. High resolution mass spectroscopy (HRMS) mass spectra were recorded on a Thermo Scientific Q-Exactive instrument with Accela 1250 pump. Melting points: Büchi 540 capillary melting point apparatus; values are uncorrected. NMR (^1H and ^{13}C) spectra were recorded at 400 or 500 (^1H), 100 or 125 {^{13}C, DEPT (distortionless enhancement by polarization transfer)}, 377 (^{19}F) on Bruker AV 400 and AV 500 spectrometers in $CDCl_3$ solutions, if not otherwise specified; chemical shifts (δ) are given in ppm. The ^1H and ^{13}C NMR spectra are referenced to residual solvent signals ($CDCl_3$: δ(H) 7.26 ppm, δ(C) 77.2 ppm).

6.4.1 Procedures for the Preparation of *N*-Substituted Indoles

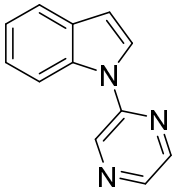
Representative Procedure A: To a stirred solution of 1*H*-indole (0.120 g, 1.00 mmol) in DMF (15 mL) at 0 °C was added NaH (0.027 g, 1.10 mmol). After stirring the reaction mixture at 0 °C for 30 min, (hetero)aryl halide (1.20 mmol) was added and the reaction mixture was heated at 130 °C for 24 h. Then the reaction mixture was cooled to ambient temperature, poured into H_2O (20 mL) and extracted with EtOAc (15 mL x 3). The combined organic phase was washed with H_2O (15 mL x 3) and dried over Na_2SO_4. After filtration and evaporation of the solvents in *vacuo*, the crude product was purified by column chromatography on silica gel.

Representative Procedure B: A mixture of 1*H*-indole (0.328 g, 2.80 mmol), (hetero)aryl halide (2.00 mmol), CuI (0.076 g, 0.40 mmol) and Cs_2CO_3 (1.30 g, 4.00 mmol) were taken in a flask and DMF (15 mL) was added into it. The reaction mixture was vigorously stirred at 120 °C under argon atmosphere for 40 h. Then the reaction mixture was cooled to ambient temperature, poured into H_2O (20 mL) and extracted with EtOAc (15 mL x 3). The combined organic phase was washed with H_2O (15 mL x 3) and dried over Na_2SO_4. After filtration and evaporation of the solvents in *vacuo*, the crude product was purified by column chromatography on silica gel.

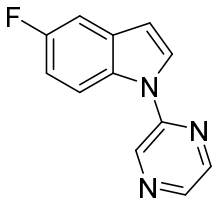
6.4.2 Characterization Data of Substituted Indoles



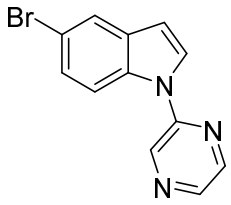
2-Methyl-1-(pyrimidin-2-yl)-1*H*-indole (3f).[52] The representative procedure **A** was followed using, 2-methyl-1*H*-indole (0.40 g, 3.05 mmol), 2-chloropyrimidine (0.489 g, 4.27 mmol), and NaH (0.095 g, 3.96 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc/Et_3N: 20/1/0.5) yielded **3f** as a brown solid. Yield: 0.153 g, 24%. M.p. = 48-50 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.79 (d, J = 4.9 Hz, 2H), 8.37 (d, J = 8.2 Hz, 1H), 7.59 (d, J = 7.3 Hz, 1H), 7.31-7.24 (m, 2H), 7.11 (t, J = 4.9 Hz, 1H), 6.50 (s, 1H), 2.78 (s, 3H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 158.5, 158.1, 137.9, 137.0, 129.6, 122.5, 121.9, 119.6, 117.0, 114.1, 106.8, 16.7. IR (neat): ν/cm^{-1} 3032, 2962, 2853, 1562, 1417, 1305, 1205, 785, 733. HRMS (ESI): *m/z* Calcd for $C_{13}H_{11}N_3$+H^+ $[M+H]^+$ 210.1026; Found 210.1024.



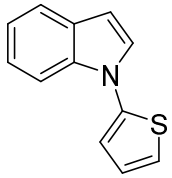
1-(Pyrazin-2-yl)-1*H*-indole (3j).[53] The representative procedure **A** was followed, using 1*H*-indole (0.120 g, 1.00 mmol), NaH (0.027 g, 1.10 mmol) and 2-iodopyrazine (0.246 g, 1.20 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 2/1) yielded **3j** as a brown solid. Yield: 0.186 g, 95%. M.p. = 77-79 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.85 (s, 1H), 8.44 (d, J = 2.1 Hz, 1H), 8.36 (d, J = 2.1 Hz, 1H), 8.26 (d, J = 8.2 Hz, 1H), 7.68 (d, J = 3.4 Hz, 1H), 7.64 (d, J = 7.6 Hz, 1H), 7.31 (dd, J = 7.9, 7.3 Hz, 1H), 7.23 (dd, J = 7.9, 7.0 Hz, 1H), 6.74 (d, J = 3.4 Hz, 1H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 149.2, 142.8, 140.0, 136.4, 135.2, 130.7, 125.0, 123.9, 122.2, 121.4, 113.5, 107.3. IR (neat): ν/cm^{-1} 3108, 3053, 1450, 1360, 839, 739. HRMS (ESI): *m/z* Calcd for $C_{12}H_9N_3$+H$^+$ $[M+H]^+$ 196.0869; Found 196.0869.



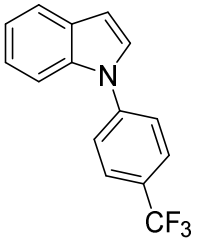
5-Fluoro-1-(pyrazin-2-yl)-1*H*-indole (3k): The representative procedure **A** was followed, using 5-fluoro-1*H*-indole (0.23 g, 1.70 mmol), NaH (0.045 g, 1.87 mmol) and 2-iodopyrazine (0.420 g, 2.04 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 2/1) yielded **3k** as a brown solid. Yield: 0.33 g, 91%. M.p. = 112-114 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.84 (d, J = 1.2 Hz, 1H), 8.47-8.46 (m, 1H), 8.41 (d, J = 2.7 Hz, 1H), 8.30 (dd, J = 9.1, 4.6 Hz, 1H), 7.72 (d, J = 3.7 Hz, 1H), 7.29 (dd, J = 9.1, 2.7 Hz, 1H), 7.06 (td, J = 9.1, 2.5 Hz, 1H), 6.71 (d, J = 3.4 Hz, 1H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 159.0 (d, J_{C-F} = 239.0 Hz), 149.1, 142.6, 140.2, 136.0, 131.8, 131.4 (d, J_{C-F} = 10.0 Hz), 126.3, 114.9 (d, J_{C-F} = 9.3 Hz), 111.9 (d, J_{C-F} = 25.4 Hz), 107.2 (d, J_{C-F} = 3.8 Hz), 106.5 (d, J_{C-F} = 23.9 Hz). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −121.6 (s). IR (neat): ν/cm^{-1} 2921, 1469, 1443, 1353, 809, 753, 714, 616. HRMS (ESI): *m/z* Calcd for $C_{12}H_8FN_3$+H$^+$ $[M+H]^+$ 214.0775; Found 214.0775.



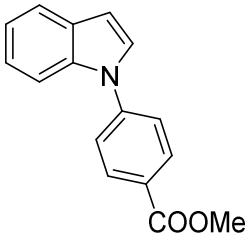
5-Bromo-1-(pyrazin-2-yl)-1*H*-indole (3l). The representative procedure **A** was followed, using 5-bromo-1*H*-indole (0.330 g, 1.70 mmol), NaH (0.045 g, 1.87 mmol) and 2-iodopyrazine (0.420 g, 2.04 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 2/1) yielded **3l** as an off-white solid. Yield: 0.44 g, 95%. M.p. = 98-100 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.84 (d, J = 1.2 Hz, 1H), 8.49-8.48 (m, 1H), 8.43 (d, J = 2.7 Hz, 1H), 8.20 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 2.0 Hz, 1H), 7.69 (d, J = 3.4 Hz, 1H), 7.40 (dd, J = 8.8, 2.0 Hz, 1H), 6.69 (d, J = 3.2 Hz, 1H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 149.0, 142.8, 140.5, 136.2, 134.0, 132.3, 126.7, 126.0, 123.9, 115.4, 115.3, 106.7. IR (neat): ν/cm^{-1} 2921, 1519, 1482, 1416, 1198, 1136, 1054, 1004, 957, 752, 709. HRMS (ESI): *m/z* Calcd for $C_{12}H_8BrN_3$+H^+ $[M+H]^+$ 273.9974, 275.9954; Found 273.9974, 275.9953.



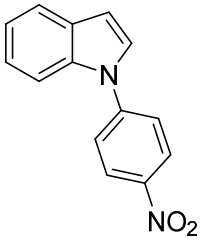
1-(Thiophen-2-yl)-1*H*-indole (3m).[48] The representative procedure **B** was followed, using 1*H*-indole (0.328 g, 2.80 mmol), 2-bromothiophene (0.326 g, 2.00 mmol), CuI (0.076 g, 0.40 mmol) and Cs_2CO_3 (1.30 g, 4.00 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 100/1) yielded **3m** as a green liquid. Yield: 0.286 g, 72%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 8.3 Hz, 1H), 7.27-7.22 (m, 2H), 7.17 (dd, J = 7.1, 6.9 Hz, 1H), 7.12 (dd, J = 5.6, 1.5 Hz, 1H), 7.03 (dd, J = 3.7, 1.5 Hz, 1H), 7.01-6.99 (m, 1H), 6.63 (d, J = 3.2 Hz, 1H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 141.8, 137.2, 129.5, 129.2, 126.2, 123.0, 121.8, 121.2, 121.0, 120.6, 110.8, 104.3. IR (neat): ν/cm^{-1} 3108, 3009, 1611, 1550, 1459, 1312, 1226, 1201, 1013, 903, 842. HRMS (ESI): *m/z* Calcd for $C_{12}H_9NS$+H^+ $[M+H]^+$ 200.0528; Found 200.0526.



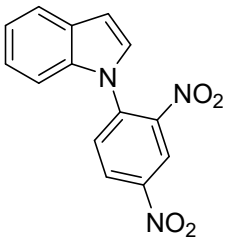
1-(4-(Trifluoromethyl)phenyl)-1*H*-indole (3q).[54] The representative procedure **B** was followed, using 1*H*-indole (0.302 g, 2.58 mmol), 1-iodo-4-(trifluoromethyl)benzene (0.50 g, 1.84 mmol), CuI (0.070 g, 0.368 mmol) and Cs_2CO_3 (1.20 g, 3.68 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 20/1) yielded **3q** as a brown solid. Yield: 0.408 g, 85%. M.p. = 50-52 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, J = 8.3 Hz, 2H), 7.68 (d, J = 7.6 Hz, 1H), 7.60-7.56 (m, 3H), 7.31 (d, J = 3.4 Hz, 1H), 7.24-7.17 (m, 2H), 6.70 (d, J = 3.2 Hz, 1H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 143.0, 135.7, 129.9, 128.3 (q, J_{C-F} = 32.4 Hz), 127.6, 127.1 (q, J_{C-F} = 3.8 Hz), 124.2 (q, J_{C-F} = 171.8 Hz), 124.1, 123.1, 121.6, 121.2, 110.5, 105.1. ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −62.2 (s). IR (neat): ν/cm^{-1} 3058, 2962, 1607, 1521, 1455, 1318, 1158, 1061, 1013, 840. HRMS (ESI): *m/z* Calcd for $C_{15}H_{10}F_3N$+H^+ $[M+H]^+$ 262.0838; Found 262.0837.



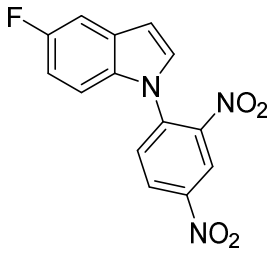
Methyl 4-(1*H*-indol-1-yl)benzoate (3s).[48] The representative procedure **B** was followed, using 1*H*-indole (0.328 g, 2.80 mmol), methyl 4-iodobenzoate (0.524 g, 2.00 mmol), CuI (0.076 g, 0.40 mmol) and K_2CO_3 (0.553 g, 4.00 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3s** as a grey solid. Yield: 0.231 g, 46%. M.p. = 55-57 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.18 (d, J = 8.5 Hz, 2H), 7.68 (d, J = 7.9 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.58 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 3.4 Hz, 1H), 7.25 (t, J = 7.3 Hz, 1H), 7.19 (t, J = 7.3 Hz, 1H), 6.71 (d, J = 3.4 Hz, 1H), 3.95 (s, 3H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 166.6, 143.9, 135.6, 131.4, 130.0, 127.8, 127.6, 123.4, 123.0, 121.5, 121.1, 110.7, 105.1, 52.4. IR (neat): ν/cm^{-1} 3106, 3049, 2947, 1707, 1602, 1509, 1455, 1433, 1281, 1117, 1097, 720. HRMS (ESI): *m/z* Calcd for $C_{16}H_{13}NO_2$+H^+ $[M+H]^+$ 252.1019; Found 252.1012.



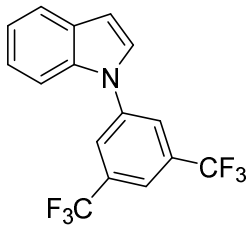
1-(4-Nitrophenyl)-1*H*-indole (3u).[53,54] The representative procedure **B** was followed, using 1*H*-indole (0.328 g, 2.80 mmol), 1-iodo-4-nitrobenzene (0.50 g, 2.00 mmol), CuI (0.076 g, 0.40 mmol) and K_2CO_3 (0.553 g, 4.00 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 20/1) yielded **3u** as a yellow solid. Yield: 0.224 g, 47%. M.p. = 132-134 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.33 (d, J = 8.9 Hz, 2H), 7.68 (d, J = 7.6 Hz, 1H), 7.62-7.60 (m, 3H), 7.33 (d, J = 3.1 Hz, 1H), 7.27 (dd, J = 7.6, 7.3 Hz, 1H), 7.21 (dd, J = 7.6, 7.3 Hz, 1H), 6.75 (d, J = 3.0 Hz, 1H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 145.3, 145.1, 135.4, 130.2, 127.2, 125.6, 123.5, 123.4, 121.8, 121.7, 110.6, 106.3. IR (neat): ν/cm^{-1} 3109, 1592, 1503, 1455, 1317, 1100, 882, 852, 690. HRMS (ESI): *m/z* Calcd for $C_{14}H_{10}N_2O_2$+H$^+$ $[M+H]^+$ 239.0815; Found 239.0811.



1-(2,4-Ninitrophenyl)-1*H*-indole (3v).[55] The representative procedure **B** was followed, using 1*H*-indole (0.351 g, 3.00 mmol), 1-chloro-2,4-dinitrobenzene (0.73 g, 3.60 mmol), CuI (0.114 g, 0.60 mmol), K_2CO_3 (0.830 g, 6.00 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **3v** as an orange solid. Yield: 0.424 g, 50%. M.p. = 96-98 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ= 8.89 (d, J = 2.5 Hz, 1H), 8.54 (dd, J = 8.8, 2.5 Hz, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.71 (d, J = 6.6 Hz, 1H), 7.30-7.21 (m, 3H), 7.15 (d, J = 3.4 Hz, 1H), 6.83 (d, J = 3.2 Hz, 1H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 145.4, 144.6, 138.0, 135.8, 129.7, 129.6, 128.1, 127.2, 123.9, 122.2, 121.9, 121.8, 109.4, 107.5. IR (neat): ν/cm^{-1} 3103, 1601, 1539, 1493, 1453, 1339, 1231, 1200, 844, 769, 752. HRMS (ESI): *m/z* Calcd for $C_{14}H_9N_3O_4$+H$^+$ $[M+H]^+$ 284.0666; Found 284.0668.



1-(2,4-Ninitrophenyl)-5-fluoro-1*H*-indole (**3w**).[56] The representative procedure **B** was followed, using 5-fluoro-1*H*-indole (0.203 g, 1.50 mmol), 1-chloro-2,4-dinitrobenzene (0.365 g, 1.80 mmol), CuI (0.057 g, 0.30 mmol), K_2CO_3 (0.415 g, 3.00 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 2/1) yielded **3w** as a yellow solid. Yield: 0.138g, 31%. M.p. = 151-153 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.90 (d, J = 2.2 Hz, 1H), 8.60 (dd, J = 8.8, 2.2 Hz, 1H), 7.84 (d, J = 8.8 Hz, 1H), 7.34 (dd, J = 9.1, 2.2 Hz, 1H), 7.17 (d, J = 3.4 Hz, 1H), 7.13-7.10 (m, 1H), 7.00 (td, J = 8.8, 2.2 Hz, 1H), 6.77 (d, J = 2.9 Hz, 1H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 159.1 (d, $J_{C–F}$ = 238.1 Hz), 145.8, 145.0, 138.0, 132.6, 130.5 (d, $J_{C–F}$ = 10.0 Hz), 129.9, 128.9, 128.4, 122.0, 112.3 (d, $J_{C–F}$ = 27.0 Hz), 110.3 (d, $J_{C–F}$ = 9.2 Hz), 107.5 (d, $J_{C–F}$ = 4.6 Hz), 107.3 (d, $J_{C–F}$ = 23.9 Hz). ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −121.5 (s). IR (neat): ν/cm^{-1} 3147, 3117, 3100, 1601, 1524, 1339, 1135, 908, 729. MS (EI): *m/z* 301 [M]$^+$, 281, 256, 226, 208, 181, 135.



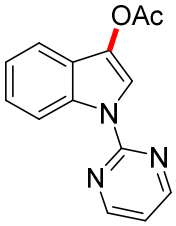
1-(3,5-Bis(trifluoromethyl)phenyl)-1*H*-indole (**3x**).[56] The representative procedure **B** was followed, using 1*H*-indole (0.328 g, 2.80 mmol), 1-bromo-3,5-bis(trifluoromethyl)benzene (0.586 g, 2.00 mmol), CuI (0.076 g, 0.40 mmol) and Cs_2CO_3 (1.30 g, 4.00 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **3x** as a light yellow liquid. Yield: 0.222 g, 34%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.97 (s, 2H), 7.84 (s, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.52 (d, J = 8.3 Hz, 1H), 7.33 (d, J = 3.4 Hz, 1H), 7.29 (dd, J = 8.0, 7.3 Hz, 1H), 7.22 (dd, J = 7.6, 7.3 Hz, 1H), 6.75 (d, J = 3.2 Hz, 1H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 141.5, 135.6, 133.6 (q, $J_{C–F}$ = 34.0 Hz), 130.0, 127.3, 124.0 (q, $J_{C–F}$ = 3.0 Hz), 123.7, 123.1 (q, $J_{C–F}$ = 272.6 Hz), 121.9,

121.7, 119.8 (q, J_{C-F} = 3.8 Hz), 109.9, 106.1. ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −63.0 (s). IR (neat): ν/cm^{-1} 3284, 3062, 2963, 1477, 1402, 1275, 1115, 1103, 890, 847, 702. MS (EI): *m/z* 329 $[M]^+$, 310, 233, 213, 116.

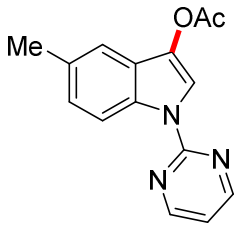
6.4.3 Procedure for C-3 Acetoxylation of *N*-Substituted Indoles

Representative Procedure: Synthesis of 1-(Pyrimidin-2-yl)-1*H*-indol-3-yl acetate (15a): To a flame-dried Schlenk tube equipped with magnetic stir bar was introduced $PhI(OAc)_2$ (0.106 g, 0.33 mmol) and 1-(pyrimidin-2-yl)-1*H*-indole (**3a**) (0.059 g, 0.30 mmol) under argon. The Schlenk tube with the mixture was evacuated and refilled with argon. To the above mixture was added acetic acid and acetic anhydride (7:3 v:v) solvent mixture (1.0 mL). The resultant reaction mixture was then degassed, refilled with argon and stirred at 60 ^{o}C in a pre-heated oil bath for 5 h. At ambient temperature, H_2O (5 mL) and saturated $NaHCO_3$ solution (15 mL) were added and the reaction mixture was extracted with ethyl acetate (15 mL x 3). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. The resultant residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) to yielded acetoxylated compound **15a** as off-white solid.

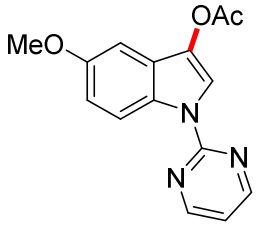
6.4.4 Characterization Data for Acetoxylated Indoles



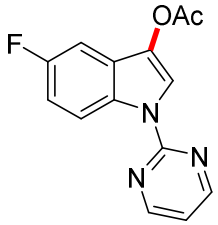
1-(Pyrimidin-2-yl)-1*H*-indol-3-yl acetate (15a): Yield: 0.071 g, 93%. M.p. = 117-119 ^{o}C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.81 (d, *J* = 8.6 Hz, 1H), 8.66 (d, *J* = 4.7 Hz, 2H), 8.43 (s, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.25 (dd, *J* = 7.6, 7.3 Hz, 1H), 7.01 (t, *J* = 4.7 Hz, 1H), 2.40 (s, 3H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 168.3, 158.3, 157.9, 133.7, 133.0, 124.8, 124.2, 122.3, 117.6, 116.6, 116.2, 114.7, 21.2. IR (neat): ν/cm^{-1} 3195, 2926, 1744, 1455, 1430, 1368, 1208, 809, 787. HRMS (ESI): *m/z* Calcd for $C_{14}H_{11}N_3O_2$+Na^+ $[M+Na]^+$ 276.0743; Found 276.0738.



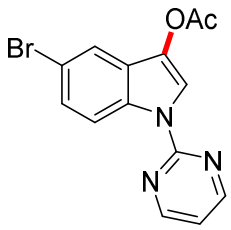
5-Methyl-1-(pyrimidin-2-yl)-1*H*-indol-3-yl acetate (15b): The representative procedure was followed, using 5-methyl-1-(pyrimidin-2-yl)-1*H*-indole (**3b**) (0.063 g, 0.30 mmol) and $PhI(OAc)_2$ (0.106 g, 0.33 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **15b** as a brown solid. Yield: 0.061 g, 76%. M.p. = 161-163 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.66 (d, J = 8.6 Hz, 1H), 8.62 (d, J = 4.9 Hz, 2H), 8.37 (s, 1H), 7.34 (s, 1H), 7.19 (d, J = 8.6, 1H), 6.95 (t, J = 4.7 Hz, 1H), 2.48 (s, 3H), 2.40 (s, 3H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 168.3, 158.1, 157.8, 133.4, 131.8, 131.3, 126.2, 124.3, 117.3, 116.3, 115.9, 114.7, 21.5, 21.1. IR (neat): ν/cm^{-1} 3202, 2917, 2851, 1747, 1579, 1451, 1430, 1206, 908, 785, 711. HRMS (ESI): *m/z* Calcd for $C_{15}H_{13}N_3O_2$+Na^+ $[M+Na]^+$ 290.0900; Found 290.0894.



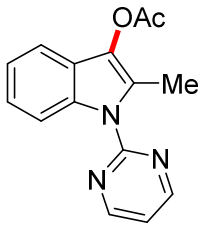
5-Methoxy-1-(pyrimidin-2-yl)-1*H*-indol-3-yl acetate (15c): The representative procedure was followed, using 5-methoxy-1-(pyrimidin-2-yl)-1*H*-indole (**3c**) (0.068 g, 0.30 mmol) and $PhI(OAc)_2$ (0.106 g, 0.33 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 2/1) yielded **15c** as a light brown crystalline solid. Yield: 0.064 g, 75%. M.p. = 166-168 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.69 (d, J = 9.5 Hz, 1H), 8.61 (d, J = 4.7 Hz, 2H), 8.39 (s, 1H), 6.99-6.95 (m, 3H), 3.89 (s, 3H), 2.40 (s, 3H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 168.2, 158.2, 157.7, 155.7, 133.5, 127.9, 124.8, 117.7, 116.0, 115.2, 114.1, 99.5, 55.8, 21.2. IR (neat): ν/cm^{-1} 3209, 2923, 1745, 1435, 1222, 1204, 911, 821, 776. HRMS (ESI): *m/z* Calcd for $C_{15}H_{13}N_3O_3$+Na^+ $[M+Na]^+$ 306.0849; Found 306.0844.



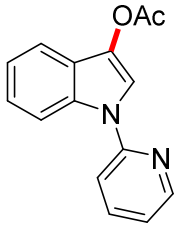
5-Fluoro-1-(pyrimidin-2-yl)-1*H*-indol-3-yl acetate (15d): The representative procedure was followed, using 5-fluoro-1-(pyrimidin-2-yl)-1*H*-indole (**3d**) (0.064 g, 0.30 mmol) and $PhI(OAc)_2$ (0.106 g, 0.33 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **15d** as an off-white solid. Yield: 0.070 g, 86%. M.p. = 173-175 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.77 (dd, J = 9.2, 4.6 Hz, 1H), 8.66 (d, J = 4.9 Hz, 2H), 8.46 (s, 1H), 7.20 (dd, J = 6.7, 1.8 Hz, 1H), 7.09 (td, J = 9.2, 1.8 Hz, 1H), 7.03 (t, J = 4.9 Hz, 1H), 2.39 (s, 3H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 168.2, 159.1 (d, $J_{C–F}$ = 239.4 Hz), 158.3, 157.7, 133.4, 129.4, 124.9 (d, $J_{C–F}$ = 9.5 Hz), 117.9 (d, $J_{C–F}$ = 9.5 Hz), 116.4, 116.3, 112.7 (d, $J_{C–F}$ = 24.8 Hz), 103.2 (d, $J_{C–F}$ = 24.8 Hz), 21.1. ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −121.0 (s). IR (neat): ν/cm^{-1} 3208, 2921, 2852, 1745, 1449, 1197, 792, 786, 588. HRMS (ESI): *m/z* Calcd for $C_{14}H_{10}FN_3O_2$+Na^+ $[M+Na]^+$ 294.0649; Found 294.0647.



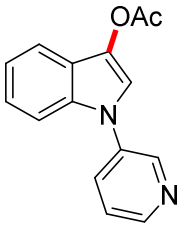
5-Bromo-1-(pyrimidin-2-yl)-1*H*-indol-3-yl acetate (15e): The representative procedure was followed, using 5-bromo-1-(pyrimidin-2-yl)-1*H*-indole (**3e**) (0.082 g, 0.30 mmol) and $PhI(OAc)_2$ (0.106 g, 0.33 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **15e** as a light brown solid. Yield: 0.073 g, 73%. M.p. = 178-179 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.68-8.65 (m, 3H), 8.42 (s, 1H), 7.67 (d, J = 2.0 Hz, 1H), 7.43 (dd, J = 9.2, 2.0 Hz, 1H), 7.04 (t, J = 4.9 Hz, 1H), 2.39 (s, 3H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 168.1, 158.3, 157.6, 132.6, 131.6, 127.6, 125.8, 120.3, 118.2, 116.5, 115.9, 115.7, 21.1. IR (neat): ν/cm^{-1} 3205, 2923, 1758, 1456, 1433, 1204, 956, 867, 784. HRMS (ESI): *m/z* Calcd for $C_{14}H_{10}BrN_3O_2$+Na^+ $[M+Na]^+$ 353.9849, 355.9828; Found 353.9848, 355.9824.



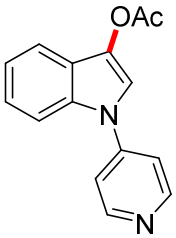
2-Methyl-1-(pyrimidin-2-yl)-1*H*-indol-3-yl acetate (15f): The representative procedure was followed, using 2-methyl-1-(pyrimidin-2-yl)-1*H*-indole (**3f**) (0.075 g, 0.358 mmol) and $PhI(OAc)_2$ (0.127 g, 0.394 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 2/1) yielded **15f** as a yellow solid. Yield: 0.025 g, 26%. M.p. = 54-56 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.75 (d, J = 4.9 Hz, 2H), 8.42 (d, J = 8.2 Hz, 1H), 7.34 (d, J = 7.6, 1H), 7.27-7.19 (m, 2H), 7.11 (t, J = 4.9 Hz, 1H), 2.59 (s, 3H), 2.42 (s, 3H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 169.2, 158.5, 158.2, 134.1, 131.4, 127.0, 123.5, 123.1, 122.2, 117.1, 116.6, 114.8, 20.8, 12.8. IR (neat): ν/cm^{-1} 2923, 2852, 1756, 1575, 1559, 1421, 1366, 1205, 733. HRMS (ESI): *m/z* Calcd for $C_{15}H_{13}N_3O_2$+Na^+ [M+Na^+] 290.0900; Found 290.0896.



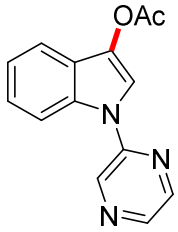
1-(Pyridin-2-yl)-1*H*-indol-3-yl acetate (15g): The representative procedure was followed, using 1-(pyridin-2-yl)-1*H*-indole (**3g**; 0.058 g, 0.30 mmol) and $PhI(OAc)_2$ (0.106 g, 0.33 mmol). Purification by preparative TLC (petroleum ether/EtOAc: 5/1) and extraction in CH_2Cl_2 (15 mL x 3) yielded **15g** as a yellow liquid. Yield: 0.061 g, 81%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.54 (dd, J = 4.9, 1.2 Hz, 1H), 8.30 (d, J = 8.3 Hz, 1H), 7.95 (s, 1H), 7.79 (dd, J = 8.3, 7.3 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.44 (dd, J = 8.3, 0.5 Hz, 1H), 7.33 (ddd, J = 8.3, 7.1, 1.2 Hz, 1H), 7.24 (ddd, J = 8.1, 7.1, 1.0 Hz, 1H), 7.14 (dd, J = 7.3, 4.9 Hz, 1H), 2.40 (s, 3H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 168.4, 152.6, 149.0, 138.6 133.0, 132.5, 124.3, 122.8, 121.5, 120.1, 117.8, 114.8, 114.4, 113.7, 21.2. IR (neat): ν/cm^{-1} 3178, 2962, 1752, 1449, 1435, 1357, 1207, 1009, 990, 799, 782. HRMS (ESI): *m/z* Calcd for $C_{15}H_{12}N_2O_2$+H^+ [M+H]$^+$ 253.0972; Found 253.0969.



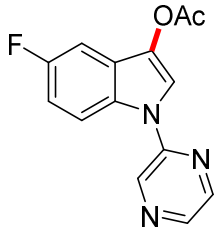
1-(Pyridin-3-yl)-1*H*-indol-3-yl acetate (15h): The representative procedure was followed, using 1-(pyridin-3-yl)-1*H*-indole (**3h**) (0.058 g, 0.30 mmol) and $PhI(OAc)_2$ (0.106 g, 0.33 mmol). Purification by preparative TLC (petroleum ether/EtOAc: 5/1) and extraction in CH_2Cl_2 (15 mL x 3) yielded **15h** as a yellow liquid. Yield: 0.042 g, 56%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.84 (d, J = 1.8 Hz, 1H), 8.60 (d, J = 4.6 Hz, 1H), 7.83 (d, J = 7.9 Hz, 1H), 7.64 (d, J = 7.9 Hz, 1H), 7.59 (s, 1H), 7.50 (d, J = 8.2 Hz, 1H), 7.47 (dd, J = 7.9, 4.6 Hz, 1H), 7.28 (dd, J = 7.9, 7.3 Hz, 1H), 7.22 (dd, J = 7.6, 7.3 Hz, 1H), 2.40 (s, 3H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 168.5, 147.5, 145.7, 136.3, 133.0, 132.5, 131.7, 124.4, 124.0, 121.8, 121.2, 118.3, 116.6, 110.2, 21.2. IR (neat): ν/cm^{-1} 3019, 3011, 1745, 1214, 746, 667. HRMS (ESI): *m/z* Calcd for $C_{15}H_{12}N_2O_2$+H^+ $[M+H]^+$ 253.0972; Found 253.0969.



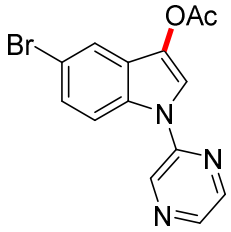
1-(Pyridin-4-yl)-1*H*-indol-3-yl acetate (15i): The representative procedure was followed, using 1-(pyridin-4-yl)-1*H*-indole (**3i**) (0.058 g, 0.30 mmol) and $PhI(OAc)_2$ (0.106 g, 0.33 mmol). Purification by preparative TLC (petroleum ether/EtOAc: 5/1) and extraction in CH_2Cl_2 (15 mL x 3) yielded **15i** as a yellow liquid. Yield: 0.042 g, 56%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.73 (d, J = 4.7 Hz, 2H), 7.75-7.66 (m, 3H), 7.49 (d, J = 4.9 Hz, 2H), 7.35 (dd, J = 7.8, 7.3 Hz, 1H), 7.29 (d, J = 7.3 Hz, 1H), 2.43 (s, 3H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 168.3, 151.4, 146.7, 133.4, 132.2, 124.5, 122.7, 121.7, 118.5, 117.4, 115.6, 111.0, 21.2. IR (neat): ν/cm^{-1} 2928, 2855, 1730, 1586, 1512, 1456, 1367, 1161, 993, 943, 807, 659. HRMS (ESI): *m/z* Calcd for $C_{15}H_{12}N_2O_2$+H^+ $[M+H]^+$ 253.0972; Found 253.0971.



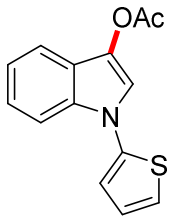
1-(Pyrazin-2-yl)-1*H*-indol-3-yl acetate (15j): The representative procedure was followed, using 1-(pyrazin-2-yl)-1*H*-indole (**3j**) (0.059 g, 0.30 mmol) and $PhI(OAc)_2$ (0.106 g, 0.33 mmol). Purification by preparative TLC (petroleum ether/EtOAc: 5/1) and extraction in CH_2Cl_2 (15 mL x 3) yielded **15j** as a brown solid. Yield: 0.071 g, 93%. M.p. = 145-147 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.86 (d, J = 1.0 Hz, 1H), 8.48 (dd, J = 2.5, 1.7 Hz, 1H), 8.40 (d, J = 2.5 Hz, 1H), 8.34 (d, J = 8.6 Hz, 1H), 8.01 (s, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.37 (dt, J = 8.1, 1.0 Hz, 1H), 7.28 (dd, J = 8.3, 7.8 Hz, 1H), 2.41 (s, 3H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 168.3, 149.3, 142.7, 140.0, 136.3, 134.1, 132.6, 125.0, 123.2, 122.3, 118.1, 114.0, 113.7, 21.2. IR (neat): ν/cm^{-1} 3021, 2961, 1737, 1449, 1425, 1365, 1210, 1123, 1013, 839, 729. HRMS (ESI): *m/z* Calcd for $C_{14}H_{11}N_3O_2$+Na^+ $[M+Na]^+$ 276.0743; Found 276.0741.



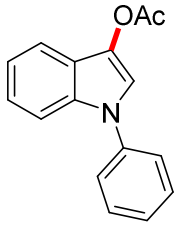
5-Fluoro-1-(pyrazin-2-yl)-1*H*-indol-3-yl acetate (15k): The representative procedure was followed, using 5-fluoro-1-(pyrazin-2-yl)-1*H*-indole (**3k**) (0.064 g, 0.30 mmol) and $PhI(OAc)_2$ (0.106 g, 0.33 mmol). Purification by column chromatography on silica gel (CH_2Cl_2/EtOAc: 15/1) yielded **15k** as an off-white solid. Yield: 0.050 g, 61%. M.p. = 166-168 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.81 (s, 1H), 8.47 (s, 1H), 8.41 (s, 1H), 8.37 (dd, J = 9.2, 4.3 Hz, 1H), 8.03 (s, 1H), 7.27-7.25 (m, 1H), 7.10 (td, J = 9.2, 2.4 Hz, 1H), 2.40 (s, 3H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 168.1, 159.0 (d, J_{C-F} = 240.3 Hz), 149.1, 142.6, 140.1, 135.8, 133.9, 129.1, 123.9 (d, J_{C-F} = 9.5 Hz), 115.7 (d, J_{C-F} = 9.5 Hz), 115.0, 113.2 (d, J_{C-F} = 24.8 Hz), 103.5 (d, J_{C-F} = 24.8 Hz), 21.2. ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −121.6 (s). IR (neat): ν/cm^{-1} 2924, 1748, 1480, 1446, 1201, 1007, 911, 839, 764. HRMS (ESI): *m/z* Calcd for $C_{14}H_{10}FN_3O_2$+H^+ $[M+H]^+$ 272.0830; Found 272.0828.



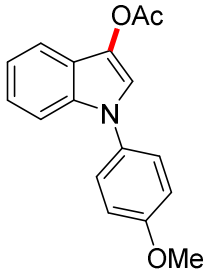
5-Bromo-1-(pyrazin-2-yl)-1*H*-indol-3-yl acetate (15l): The representative procedure was followed, using 5-bromo-1-(pyrazin-2-yl)-1*H*-indole (**3l**) (0.082 g, 0.30 mmol) and $PhI(OAc)_2$ (0.106 g, 0.33 mmol). Purification by column chromatography on silica gel (CH_2Cl_2/EtOAc: 20/1) yielded **15l** as a light brown solid. Yield: 0.069 g, 70%. M.p. = 162-164 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.81 (s, 1H), 8.48 (s, 1H), 8.42 (d, J = 2.5 Hz, 1H), 8.27 (d, J = 9.1 Hz, 1H), 8.00 (s, 1H), 7.75 (d, J = 1.7 Hz, 1H), 7.44 (dd, J = 8.8, 1.7 Hz, 1H), 2.40 (s, 3H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 168.1, 149.0, 142.6, 140.4, 136.0, 133.2, 131.2, 127.9, 124.8, 120.8, 115.9, 115.6, 114.6, 21.2. IR (neat): ν/cm^{-1} 3170, 2923, 1759, 1446, 1422, 1243, 1061, 1006, 835, 735. HRMS (ESI): *m/z* Calcd for $C_{14}H_{10}BrN_3O_2$+H^+ $[M+H]^+$ 332.0029, 334.0009; Found 332.0030, 334.0008.



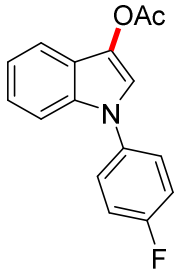
1-(Thiophen-2-yl)-1*H*-indol-3-yl acetate (15m): The representative procedure was followed, using 1-(thiophen-2-yl)-1*H*-indole (**3m**) (0.043 g, 0.22 mmol) and $PhI(OAc)_2$ (0.077 g, 0.24 mmol). Purification by preparative TLC (petroleum ether/EtOAc: 5/1) and extraction in CH_2Cl_2 (15 mL x 3) yielded **15m** as a liquid. Yield: 0.020 g, 35%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.60-7.54 (m, 3H), 7.29-7.25 (m, 1H), 7.22-7.16 (m, 2H), 7.08-7.02 (m, 2H), 2.38 (s, 3H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 168.4, 141.4, 134.4, 131.9, 126.2, 124.0, 122.0, 121.4, 121.1, 120.9, 118.5, 118.0, 110.9, 21.2. IR (neat): ν/cm^{-1} 3010, 2962, 2854, 1747, 1613, 1547, 1460, 1366, 1225, 1010, 692. HRMS (ESI): *m/z* Calcd for $C_{14}H_{11}NO_2S$+Na^+ $[M+Na]^+$ 280.0403; Found 280.0398.



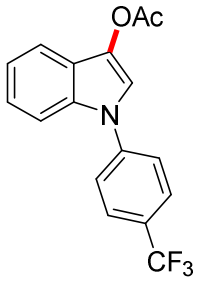
1-Phenyl-1*H*-indol-3-yl acetate (15n):[33] The representative procedure was followed, using 1-phenyl-1*H*-indole (**3n**) (0.058 g, 0.30 mmol) and $PhI(OAc)_2$ (0.106 g, 0.33 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **15n** as a liquid. Yield: 0.038 g, 50%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.61 (d, J = 7.6 Hz, 1H), 7.57 (s, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.51-7.48 (m, 4H), 7.35-7.31 (m, 1H), 7.23 (dd, J = 7.6, 7.3 Hz, 1H), 7.18 (dd, J = 7.6, 7.3 Hz, 1H), 2.38 (s, 3H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 168.6, 139.6, 133.0, 131.7, 129.8, 126.6, 124.6, 123.4, 121.4, 120.6, 118.0, 117.2, 110.8, 21.2. IR (neat): ν/cm^{-1} 3007, 2978, 2873, 1745, 1712, 1501, 1457, 1367, 1223, 1110, 696. HRMS (ESI): *m/z* Calcd for $C_{16}H_{13}NO_2$+Na^+ $[M+Na]^+$ 274.0838; Found 274.0833.



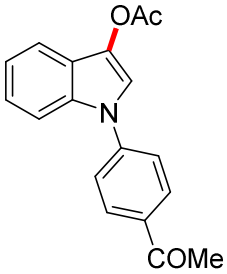
1-(4-Methoxyphenyl)-1*H*-indol-3-yl acetate (15o):[33] The representative procedure was followed, using 1-(4-methoxyphenyl)-1*H*-indole (**3o**) (0.067 g, 0.30 mmol) and $PhI(OAc)_2$ (0.106 g, 0.33 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 4/1) yielded **15o** as a liquid. Yield: 0.031 g, 37%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, J = 7.6 Hz, 1H), 7.49 (s, 1H), 7.43-7.37 (m, 3H), 7.24-7.14 (m, 2H), 7.01 (d, J = 8.6 Hz, 2H), 3.86 (s, 3H), 2.38 (s, 3H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 168.7, 158.5, 133.5, 132.5, 131.2, 126.2, 123.2, 120.9, 120.3, 117.9, 117.6, 114.9, 110.6, 55.8, 21.2. IR (neat): ν/cm^{-1} 3176, 2966, 2840, 1747, 1548, 1510, 1370, 1207, 1029, 739, 588. HRMS (ESI): *m/z* Calcd for $C_{17}H_{15}NO_3$+Na^+ $[M+Na]^+$ 304.0944; Found 304.0935.



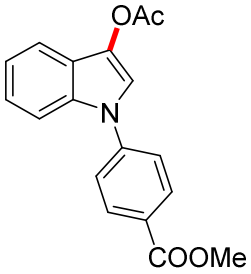
1-(4-Fluorophenyl)-1*H*-indol-3-yl acetate (15p): The representative procedure was followed, using 1-(4-fluorophenyl)-1*H*-indole (**3p**) (0.076 g, 0.36 mmol) and $PhI(OAc)_2$ (0.127 g, 0.39 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 15/1) yielded **15p** as a yellow liquid. Yield: 0.039 g, 40%. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, J = 7.6 Hz, 1H), 7.56 (s, 1H), 7.49-7.46 (m, 3H), 7.30-7.21 (m, 4H), 2.43 (s, 3H). $^{13}C\{^{1}H\}$-NMR (125 MHz, $CDCl_3$): δ = 168.6, 161.2 (d, J_{C-F} = 246.6 Hz), 135.6 (d, J_{C-F} = 2.3 Hz), 133.3, 131.7, 126.4 (d, J_{C-F} = 8.5 Hz), 123.5, 121.3, 120.6, 118.0, 117.2, 116.6 (d, J_{C-F} = 23.1 Hz), 110.4, 21.2. ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −115.1 (s). IR (neat): ν/cm^{-1} 3160, 2927, 2854, 1745, 1509, 1366, 1202, 1128, 819, 738, 558. HRMS (ESI): *m/z* Calcd for $C_{16}H_{12}FNO_2$+Na^+ $[M+Na]^+$ 292.0744; Found 292.0739.



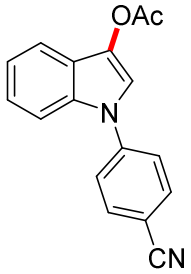
1-(4-(Trifluoromethyl)phenyl)-1*H*-indol-3-yl acetate (15q): The representative procedure was followed, using 1-(4-(trifluoromethyl)phenyl)-1*H*-indole (**3q**) (0.078 g, 0.30 mmol) and $PhI(OAc)_2$ (0.106 g, 0.33 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 10/1) yielded **15q** as a brown solid. Yield: 0.043 g, 45%. M.p. = 99-101 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.79-7.76 (m, 2H), 7.66-7.61 (m, 4H), 7.58 (dd, J = 8.3, 4.9 Hz, 1H), 7.30-7.20 (m, 2H), 2.40 (s, 3H). $^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$): δ = 168.5, 142.7, 132.8, 132.6, 128.4 (q, J_{C-F} = 33.1 Hz), 127.1 (q, J_{C-F} = 3.1 Hz), 124.2 (q, J_{C-F} = 272.0 Hz), 124.1, 124.0, 122.0, 121.2, 118.3, 116.6, 110.6, 21.2. ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −62.3 (s). IR (neat): ν/cm^{-1} 3163, 2926, 1746, 1369, 1333, 1106, 1065, 841, 763, 736. HRMS (ESI): *m/z* Calcd for $C_{17}H_{12}F_3NO_2$+Na^+ $[M+Na]^+$ 342.0712; Found 342.0706.



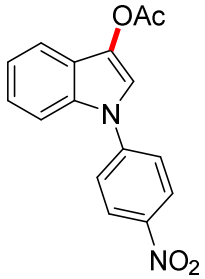
1-(4-Acetylphenyl)-1*H*-indol-3-yl acetate (15r): The representative procedure was followed, using 1-(4-(1*H*-indol-1-yl)phenyl)ethan-1-one (**3r**) (0.071 g, 0.30 mmol) and $PhI(OAc)_2$ (0.106 g, 0.33 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 3/1) yielded **15r** as a light yellow liquid. Yield: 0.031 g, 35%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.10 (d, J = 8.5 Hz, 2H), 7.64-7.58 (m, 5H), 7.28 (dd, J = 8.2, 7.0 Hz, 1H), 7.22 (dd, J = 7.6, 7.3 Hz, 1H), 2.64 (s, 3H), 2.40 (s, 3H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 197.0, 168.5, 143.6, 134.7, 132.7, 132.6, 130.2, 124.0, 123.5, 122.1, 121.3, 118.3, 116.5, 110.8, 26.8, 21.2. IR (neat): ν/cm^{-1} 2962, 2931, 2861, 1717, 1265, 1128, 1074, 736. HRMS (ESI): *m/z* Calcd for $C_{18}H_{15}NO_3$+Na$^+$ [M+Na]$^+$ 316.0944; Found 316.0938.



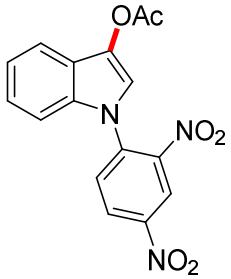
Methyl 4-(3-acetoxy-1*H*-indol-1-yl)benzoate (15s): The representative procedure was followed, using methyl 4-(1*H*-indol-1-yl)benzoate (**3s**) (0.075 g, 0.30 mmol) and $PhI(OAc)_2$ (0.106 g, 0.33 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **15s** as a liquid. Yield: 0.038 g, 41%. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.18 (d, J = 8.5 Hz, 2H), 7.64-7.60 (m, 3H), 7.57 (d, J = 8.5 Hz, 2H), 7.28 (dd, J = 8.2, 7.3 Hz, 1H), 7.22 (dd, J = 7.6, 7.3 Hz, 1H), 3.96 (s, 3H), 2.40 (s, 3H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 168.5, 166.5, 143.5, 132.7, 132.6, 131.4, 127.7, 124.0, 123.4, 122.0, 121.2, 118.2, 116.5, 110.8, 52.4, 21.2. IR (neat): ν/cm^{-1} 3028, 3012, 2954, 1717, 1605, 1515, 1457, 1437, 1365, 1280, 1206, 738, 664. HRMS (ESI): *m/z* Calcd for $C_{18}H_{15}NO_4$+Na$^+$ [M+Na]$^+$ 332.0893; Found 332.0887.



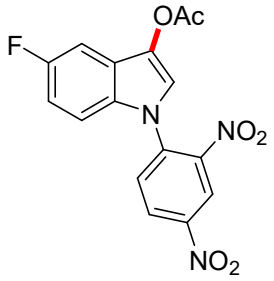
1-(4-Cynophenyl)-1*H*-indol-3-yl acetate (15t): The representative procedure was followed, using 4-(1*H*-indol-1-yl)benzonitrile (**3t**) (0.066 g, 0.30 mmol) and $PhI(OAc)_2$ (0.106 g, 0.33 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **15t** as a light brown solid. Yield: 0.046 g, 56%. M.p. = 110-112 ^{o}C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.81 (d, J = 8.2 Hz, 2H), 7.68 (d, J = 7.6 Hz, 1H), 7.66 (s, 1H), 7.63-7.60 (m, 3H), 7.33 (dd, J = 8.2, 7.3 Hz, 1H), 7.27 (dd, J = 8.2, 7.0 Hz, 1H), 2.43 (s, 3H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 168.4, 143.4, 133.9, 133.1, 132.4, 124.3, 124.0, 122.3, 121.6, 118.5, 118.4, 116.1, 110.6, 109.4, 21.2. IR (neat): ν/cm^{-1} 2921, 2851, 2225, 1776, 1562, 1509, 1366, 1211, 1126, 1012, 845, 743. HRMS (ESI): *m/z* Calcd for $C_{17}H_{12}N_2O_2$+Na^+ $[M+Na]^+$ 299.0791; Found 299.0787.



1-(4-Nitrophenyl)-1*H*-indol-3-yl acetate (15u): The representative procedure was followed, using 1-(4-nitrophenyl)-1*H*-indole (**3u**) (0.071 g, 0.30 mmol) and $PhI(OAc)_2$ (0.106 g, 0.33 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 5/1) yielded **15u** as a yellow solid. Yield: 0.047 g, 53%. M.p. = 142-144 ^{o}C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.38 (d, J = 8.9 Hz, 2H), 7.68-7.62 (m, 5H), 7.33 (dd, J = 8.2, 7.3 Hz, 1H), 7.24 (dd, J = 7.6, 7.3 Hz, 1H), 2.41 (s, 3H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 168.4, 145.2, 145.1, 133.5, 132.5, 125.7, 124.6, 123.5, 122.5, 121.8, 118.6, 116.2, 110.7, 21.2. IR (neat): ν/cm^{-1} 2923, 2852, 1746, 1592, 1524, 1222, 1129, 865, 748, 695, 528. HRMS (ESI): *m/z* Calcd for $C_{16}H_{12}N_2O_4$+Na^+ $[M+Na]^+$ 319.0689; Found 319.0688.

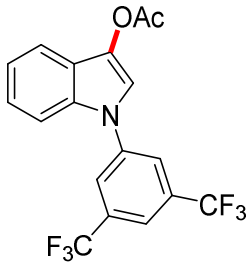


1-(2,4-Dinitrophenyl)-1*H*-indol-3-yl acetate (15v): The representative procedure was followed, using 1-(2,4-dinitrophenyl)-1*H*-indole (**3v**) (0.085 g, 0.30 mmol) and $PhI(OAc)_2$ (0.106 g, 0.33 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 4:1) yielded **15v** as an orange solid. Yield: 0.078 g, 76%. M.p. = 147-148 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.92 (d, J = 2.4 Hz, 1H), 8.57 (dd, J = 8.9, 2.4 Hz, 1H), 7.84 (d, J = 8.9 Hz, 1H), 7.68 (d, J = 7.9 Hz, 1H), 7.53 (s, 1H), 7.33-7.27 (m, 2H), 7.16 (d, J = 8.2 Hz, 1H), 2.42 (s, 3H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 168.0, 145.5, 144.7, 138.0, 134.3, 133.1, 130.0, 128.3, 125.0, 122.3, 122.2, 122.1, 118.8, 116.2, 109.5, 21.2. IR (neat): ν/cm^{-1} 3158, 3084, 2852, 1751, 1601, 1527, 1366, 1224, 1128, 748, 702, 569. HRMS (ESI): *m/z* Calcd for $C_{16}H_{11}N_3O_6$+Na^+ $[M+Na]^+$ 364.0540; Found 364.0533.



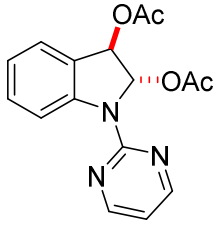
1-(2,4-Dinitrophenyl)-5-fluoro-1*H*-indol-3-yl acetate (15w): The representative procedure was followed, using 1-(2,4-dinitrophenyl)-5-fluoro-1*H*-indole (**3w**) (0.09 g, 0.30 mmol) and $PhI(OAc)_2$ (0.106 g, 0.33 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 4:1) yielded **15w** as an orange solid. Yield: 0.066 g, 61%. M.p. = 120-122 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.90 (d, J = 2.4 Hz, 1H), 8.57 (dd, J = 8.8, 2.4 Hz, 1H), 7.83 (d, J = 8.8 Hz, 1H), 7.55 (s, 1H), 7.30 (dd, J = 8.6, 2.2 Hz, 1H), 7.08-6.99 (m, 2H), 2.39 (s, 3H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 167.9, 159.0 (d, J_{C-F} = 239.7 Hz), 145.8, 144.9, 137.7, 134.0 (d, J_{C-F} = 4.6 Hz), 130.1, 129.6, 128.4, 122.9 (d, J_{C-F} = 10.8 Hz), 122.1, 117.9, 113.5 (d, J_{C-F} = 26.2 Hz), 110.7 (d, J_{C-F} = 9.3 Hz), 104.4 (d, J_{C-F} = 25.4 Hz), 21.1. ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −120.4 (s). IR (neat): ν/cm^{-1} 2922, 2852,

1754, 1452, 1338, 1202, 1188, 769, 729, 521. HRMS (ESI): *m/z* Calcd for $C_{16}H_{10}FN_3O_6$+Na^+ $[M+Na]^+$ 382.0446; Found 382.0445.



1-(3,5-Bis(trifluoromethyl)phenyl)-1*H*-indol-3-yl acetate (15x): The representative procedure was followed, using 1-(3,5-bis(trifluoromethyl)phenyl)-1*H*-indole (**3x**) (0.099 g, 0.30 mmol) and $PhI(OAc)_2$ (0.106 g, 0.33 mmol). Purification by column chromatography on silica gel (petroleum ether/EtOAc: 20/1) yielded **15x** as a light brown solid. Yield: 0.063 g, 54%. M.p. = 68-70 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.96 (s, 2H), 7.83 (s, 1H), 7.66-7.64 (m, 2H), 7.50 (d, J = 8.3 Hz, 1H), 7.32 (dd, J = 7.3, 7.1 Hz, 1H), 7.24 (dd, J = 7.6, 7.3 Hz, 1H), 2.40 (s, 3H). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ = 168.4, 141.1, 133.5 (q, J = 33.3 Hz), 133.2, 132.7, 124.6, 124.0 (q, J = 2.9 Hz), 123.1 (q, J = 272.8 Hz), 122.2, 121.7, 119.7, 118.6, 116.2, 110.0, 21.1. ^{19}F-NMR (377 MHz, $CDCl_3$): δ = −63.0 (s). IR (neat): ν/cm^{-1} 3185, 3066, 2927, 1750, 1279, 1216, 1202, 1168, 1085, 888, 737, 682. HRMS (ESI): *m/z* Calcd for $C_{18}H_{11}F_6NO_2$+H^+ $[M+H]^+$ 388.0767; Found 388.0762.

6.4.5 Procedure for Synthesis of Indoline Diacetate and Characterization Data



Synthesis of 1-(pyrimidin-2-yl)indoline-2,3-diyl diacetate (16): To a flame-dried Schlenk tube equipped with magnetic stir bar was introduced phenyl-λ^3-iodanediyl diacetate, $PhI(OAc)_2$ (0.354 g, 1.1 mmol) and 1-(pyrimidin-2-yl)-1*H*-indole (**3a**) (0.195 g, 1.0 mmol) under argon. The Schlenk tube with reaction mixture was evacuated and refilled with argon. To the above mixture was added acetic acid and acetic anhydride (7:3) solvent mixture (1.0 mL). The resultant reaction mixture was then degassed, refilled with argon and stirred at room temperature for 1 h. Then the reaction mixture was quenched with H_2O (5 mL) and saturated $NaHCO_3$ solution (15 mL) and the reaction mixture was extracted with ethyl acetate

(15 mL x 3). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. The crude residue was purified by column chromatography on silica gel (petroleum ether/EtOAc: 2/1) to yield diacyloxylated compound **16** as an off-white solid. Yield: 0.165 g, 53%. M.p. = 143-145 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.54 (d, J = 4.6 Hz, 2H), 8.45 (d, J = 8.2 Hz, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.43 (dd, J = 8.2, 7.3 Hz, 1H), 7.22 (s, 1H), 7.06 (dd, J = 7.6, 7.3 Hz, 1H), 6.85 (t, J = 4.6 Hz, 1H), 6.01 (s, 1H), 2.07 (s, 3H), 2.05 (s, 3H). ^{13}C{^{1}H}-NMR (125 MHz, $CDCl_3$): δ = 170.2, 170.1, 158.4, 158.0, 144.4, 131.0, 127.6, 127.4, 122.9, 116.2, 114.0, 87.9, 75.6, 21.1. IR (neat): ν/cm^{-1} 3735, 3015, 1734, 1730, 1585, 1488, 1444, 1227, 1014, 761, 617. HRMS (ESI): *m/z* Calcd for $C_{16}H_{15}N_3O_4$+Na^+ $[M+Na]^+$ 336.0955; Found 336.0952.

6.4.6 Representative Procedure for Competition Experiments. To a flame-dried Schlenk tube equipped with magnetic stir bar was introduced compound **3a** (0.117 g, 0.6 mmol), compound **3n** (0.116 g, 0.6 mmol) and $PhI(OAc)_2$ (0.097 g, 0.30 mmol) under argon. The Schlenk tube with the mixture was evacuated and refilled with argon. To the above mixture was added acetic acid and acetic anhydride (7:3) solvent mixture (2.0 mL). The resultant reaction mixture was then degassed, refilled with argon and stirred at 60 °C in a pre-heated oil bath for 5 h. At ambient temperature, H_2O (5 mL) and saturated $NaHCO_3$ solution (15 mL) were added and the reaction mixture was extracted with ethyl acetate (15 mL x 3). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. To the resultant residue, acetone (5 mL) and *p*-xylene (0.3 mmol) were added and injected into Gas Chromatograph. The GC yield was calculated with respect to internal standard *p*-xylene.

6.4.7 Procedure for the Dehydroacetoxylation Reaction. To a flame-dried Schlenk tube equipped with magnetic stir bar was introduced compound **16** (0.031 g, 0.1 mmol) and 1-acetylindoline-2,3-diyl diacetate (0.028 g, 0.1 mmol). To the above mixture was added acetic acid and acetic anhydride (7:3) solvent mixture (1.0 mL). The resultant reaction mixture was then degassed, refilled with argon and stirred at 60 °C in a pre-heated oil bath for 2 h. At ambient temperature, H_2O (3 mL) and saturated $NaHCO_3$ solution (10 mL) were added and the reaction mixture was extracted with ethyl acetate (10 mL x 3). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated *in vacuo*. To the resultant residue, acetone (5 mL) and *p*-xylene (0.2 mmol) were added and injected into Gas Chromatograph. The GC yield was calculated with respect to internal standard *p*-xylene.

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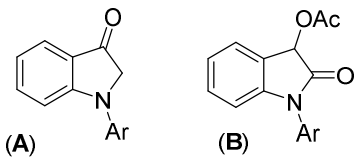

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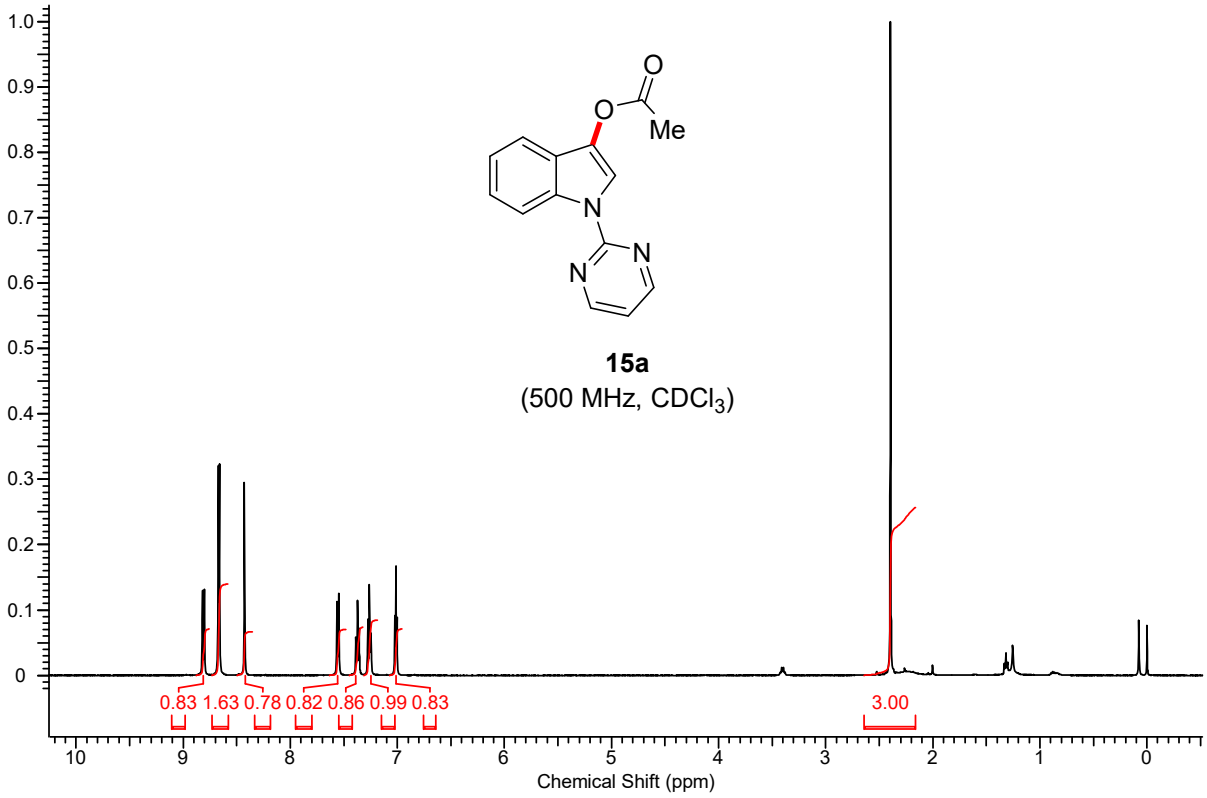
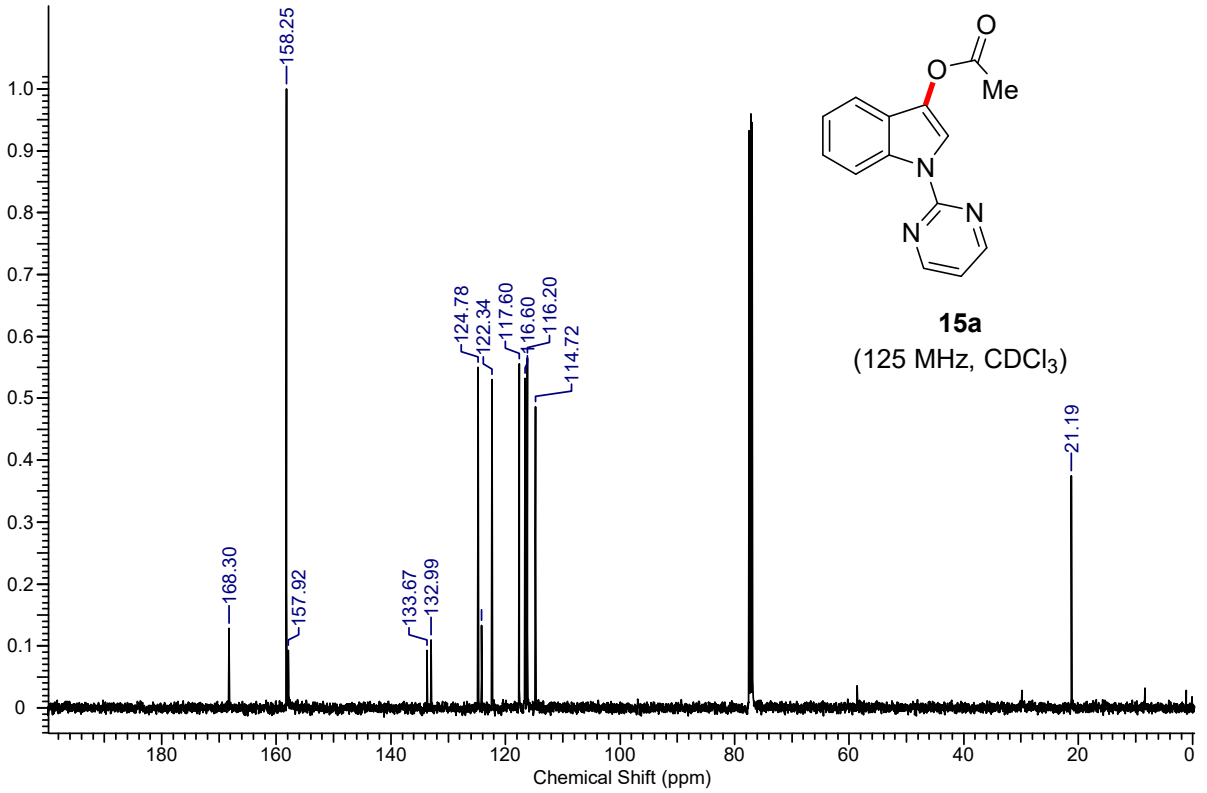
NMR Spectra of Representative Acetoxylated Indole





LIST OF PUBLICATIONS

1. Soni, V.; Sharma, D; Punji, B. "Nickel-Catalyzed Regioselective C–H Bond Difluoroalkylation of Indoles", *Manuscript under preparation*.

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Patents and Book Chapter

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1. Soni. V.; Punji, B. "*Unified Strategies for Nickel-Catalyzed and Metal-Free C–H Functionalization of Indoles, and Mechanistic Studies*" Presentation for Keerthi Sangoram Memorial Endowment Award-**2017** at CSIR-National Chemical Laboratory, Pune, India, February 14th, **2017**.

2. Soni. V.; Punji, B. "*Unified Strategies for Nickel-Catalyzed C–H Functionalization of Indoles*" Presentation in Advanced Organic Synthesis Symposium-**2017** at CSIR-National Chemical Laboratory, Pune, India, February 14th, **2017**.

3. Soni. V.; Punji, B. "*Unique Approach for the Nickel-Catalyzed C-2 Alkylation and Benzylation of Indoles*" Flash presentation in International Conference of Organic Synthesis-21, Indian Institute of Technology, Bombay, Maharashtra, India, December 11-16, **2016**.

4. Soni. V.; Punji, B. "*Unique Approach for the Nickel-Catalyzed C-2 Alkylation and Benzylation of Indoles*" International Conference of Organic Synthesis-21, Indian Institute of Technology, Bombay, Maharashtra, India, December 11-16, **2016**.

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Awards

1. NCL RF-Keerthi Sangoram Memorial Endowment Award "Best Research Scholar Award" for best research scholar in Chemical Sciences-**2017**.

2. NCL RF-Nanai Natu Award "Best Paper Published Award" for best published research paper in Organic Chemistry-**2017**.

3. Dr. Paul Ratnasamy and Dr. Ms. Suneeta B. Kulkarni "Best Paper Published Award" for best published research paper in catalysis-**2016**.

4. Best poster prize for poster presented In "International Conference of Organic Synthesis-21", Indian Institute of Technology, Bombay, Maharashtra, India, December 11-16, **2016**. entitled as "*Unique Approach for the Nickel-Catalyzed C-2 Alkylation and Benzylation of Indoles"*