NEW STRATEGIES FOR TRANSITION METAL CATALYZED C-C AND C-N BOND

FORMATION

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NEW STRATEGIES FOR TRANSITION METAL CATALYZED C-C

AND C-N BOND FORMATION

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The Supervisory Committee certifies that this ***disquisition*** complies with North Dakota

State University's regulations and meets the accepted standards for the degree of

DOCTOR OF PHILOSOPHY

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ABSTRACT

Transition metal catalysis emerged as an essential tool in the field of organic chemistry. In this context, transition metal catalyzed C-H bond functionalization is considered as an alluring strategy as it occurs with high atom-and-step economy. In the recent years, significant attention has been paid for the conversion of C-H bond into C-X (X = C, N, O, S, P..etc) bonds using transition metal catalysts. This thesis presents the development of new catalytic systems for the construction of C-C and C-N bonds through late transition metal-mediated C-H activation and decarboxylation reactions.

Chapter 1 introduces the background of transition metal catalyzed C-H bond functionalization. This chapter provide reported catalytic methods for the conversion of arene C-H bonds into various functional groups through transition metal mediated chelation-assisted C-H bond activation.

Chapter 2 describes the development of a new method for the synthesis of oxindoles via intramolecular alkene hydroarylation with N-aryl acrylamides using a Ru(II)/N-heterocyclic carbene (NHC) catalyst system. This reaction occurs with good substrate scope and synthetically useful tolerance of functional groups and does not require the assistance of additional directing group. Preliminary mechanistic results support a tandem sequence involving amide-directed aromatic C–H bond activation and intramolecular alkene arylmetalation.

Chapter 3 describes ruthenium-based decarboxylative alkenylation of heteroarenes through carboxylate directed C-H bond functionalization. The decarboxylative functionalization of heteroarenes occurs with high regioselectivity and a broad range of functional group tolerance. This decarboxylation proceeds without stoichiometric amounts of bases or oxidants and it is applicable for functionalization of various heteroarenes such as indole, pyrrole, thiophene,

benzothiophene, and benzofuran at both C-2 and C-3 positions. The current protocol provides a straightforward approach for the synthesis of trisubstituted olefins with heteroarenes.

Chapter 4 explains the development of Rh/Ag-bimetallic catalyst system for decarboxylative amidation of *ortho*-substituted benzoic acids with 3-aryldioxazolones. The nature of *ortho*-substituents determines regioselectivity of this reaction through two forms of proposed chelation assistance: (1) A wide range of non-directing *ortho*-substituents led to *ortho*-amidation products via carboxylate-directed C-H amidation and subsequent decarboxylation. (2) 2-Pyridyl and analogous DGs led to *ipso*-amidation products via DG-assisted decarboxylation and subsequent amidation.

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DEDICATION

To my family for their love and continuous support.

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LIST OF SCHEMES

LIST OF ABBREVIATIONS

acac ....Acetylacetone

AcOH ....Acetic acid

Ag..Silver

Bn..Benzyl

Bpin...Bis(pinacolato)diboron

BPMEN...N, N'-bis(6-R-2-pyridylmethyl)-1,2-diaminoethane

bpy..Bipyridine

Bz ....Benzoyl

CMD ....Concerted metalation and deprotonation

^{13}C-NMR..Nuclear magnetic resonance (detecting carbon isotope ^{13}C)

Coe..Cyclooctene

Co..Cobalt

COD 1,5-Cyclooctadiene

Cp..Cyclopentadienyl

Cp*...Pentamethylcyclopentadienyl

Cu..Copper

DABCO...1,4-diazabicyclo [2.2.2]octane

dba...Dibenzylideneacetone

DBU ....1,8-Diazabicyclo[5.4.0]undec-7-ene

DCC ....N, N'-Dicyclohexylcarbodiimide

DCE...1,2-dichloroethane

DCM ....Dichloromethane

DG...Directing group

MeCN...Acetonitrile

Mes...Mesityl

MS..Molecular sieves

Na...Sodium

NBS...N-Bromosuccinimide.

NCTS ....N-Cyano-N-phenyl-*p*-toluenesulfonamide

NHC..N-Heterocyclic carbene

Ni..Nickel

NMP..N-Methyl-2-pyrrolidine

OAc...Acetate

OBz ....Benzoate

OPiv ....Pivalate

PCy$_3$ ....Tricyclohexyl phosphine

P^{t}Bu$_3$..Tri-*tert*-butylphosphine

Pd ....Palladium

Phen...Phenanthroline

PivOH ....Pivalic acid

PPh$_3$..Triphenylphosphine

Ru..Ruthenium

Rh..Rhodium

RT ....Room temperature

Sb ....Antimony

SIMes ....4,5-Dihydro-1,3-bis(2,4,6-trimethylphenyl)-1H-imidazolium chloride

SIPr ....*N*, *N*′-(2,6-Diisopropylphenyl)dihydroimidazolium chloride

1. TRANSITION METAL CATALYSED C-H BOND FUNCTIONALISATION

1.1. Introduction

Construction of Carbon-Carbon (C-C) and Carbon-Nitrogen (C-N) bonds are essential transformations in synthetic organic chemistry. Conventional methods such as cross-coupling reactions require pre-functionalized starting materials for the formation of C-C and C-N bonds. Additional steps are required to access these pre-functionalized substrates and therefore limits the substrate scope. The need for these substrates can be bypassed by the direct functionalization of ubiquitous C-H bonds. Hence C-H bond functionalization is considered as an allusive strategy for eco-friendly chemical synthesis with high atom efficiency and reduced waste production.

Transition metal catalysts are widely employed for the functionalization of inert C-H bonds. These catalysts react with C-H bonds to produce a C-M bond by a process known as C-H activation (Scheme 1.1). The resulting C-M bond is more reactive than C-H bond and can be easily converted into functional groups.

$$R-H \xrightarrow{\text{[M]}} R-\text{[M]}$$
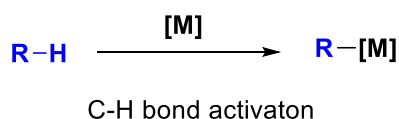
C-H bond activaton

Scheme 1.1. Transition metal catalyzed C-H bond activation.

The critical issue in C-H bond activation is selective functionalization of a C-H bond within a complex molecule which has many C-H bonds. The typical strategy employed for the selective C-H functionalization is the usage of substrates that contain coordinating ligands which are termed as directing groups (DGs). The metal center coordinates to the directing group and cleaves the proximal C-H bond to form a cyclometalated intermediate. Formation of this intermediate is the driving force for the selective functionalization of C-H bond at a precisely desired position. This is termed as chelation assisted C-H bond activation.[1, 2] The first example

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for transition metal mediated C-H bond functionalization is demonstrated by Kleiman and

Dubeck using azobenzene (**1.01**) and stoichiometric amounts of Cp$_2$Ni (**1.02**) (Scheme 1.2.).[3]

The azo functional group acts as a directing group and cleaves the *ortho* C-H bond.

Regioselectivity is achieved through the formation of 5-membered nickellacycle (**1.03**). Later in

1965, Chatt and coworkers reported C-H bond functionalization of naphthalene using ruthenium

(Scheme 1.3).[4] They demonstrated that C-H bond functionalization occurs with the formation of

naphthyl-ruthenium(ll) hydride complex (**1.05**) via C-H oxidative addition.
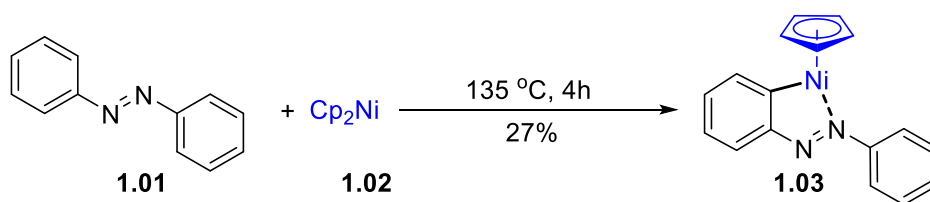
Scheme 1.2. The first example of transition metal mediated C-H bond cleavage.
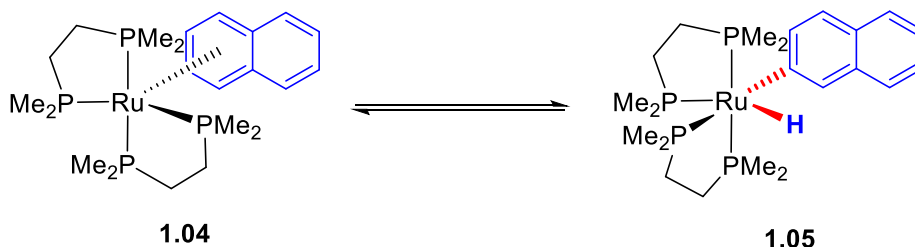
Scheme 1.3. The first example of ruthenium mediated C-H bond cleavage.

After these ground-breaking result, significant efforts were devoted to the catalytic

functionalization of unreactive C-H bonds. The first example for catalytic C-H functionalization

was reported by Murai and coworkers using ruthenium catalyst (Scheme 1.4)[5]. In their seminal

work, they described *ortho*-alkylation of aromatic ketones with terminal alkenes. This report

demonstrated the importance of a chelating group to achieve high selectivity in the C-H

activation processes.
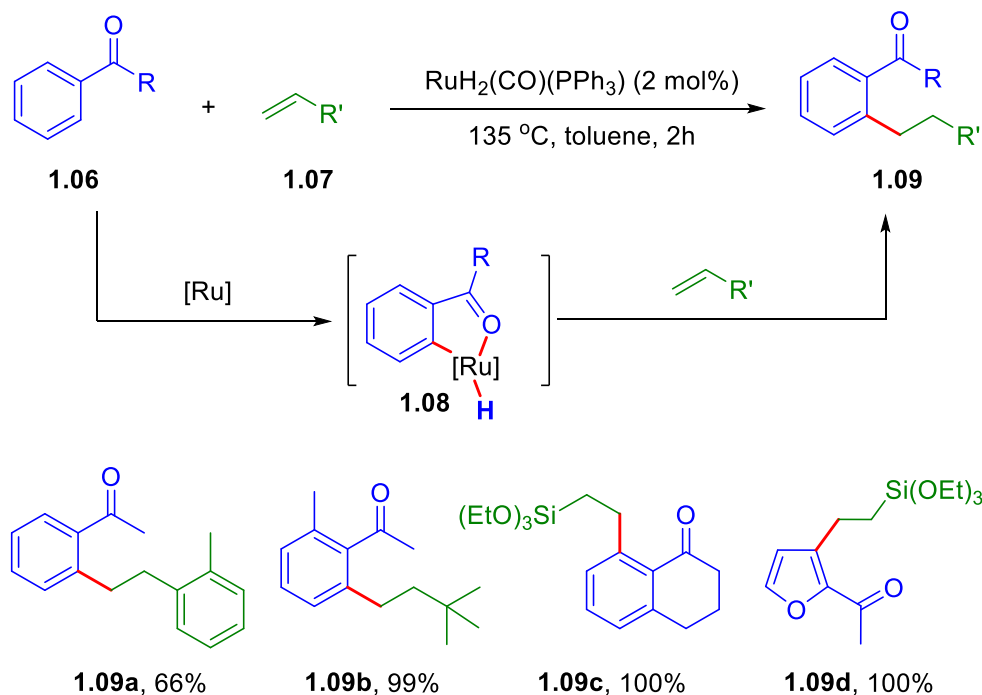
Scheme 1.4. Ruthenium catalyzed alkylation of aromatic ketones with terminal alkenes initiated by carbonyl directed C-H activation.

The proposed reaction mechanism for *ortho*-alkylation via C-H bond activation is illustrated in Scheme 1.5. First, coordination of transition metal to the chelating group or directing group enables the oxidative addition of C-H bond in the *ortho* position and generates a cyclometalated Ru-H intermediate (**1.08**). Next, olefin coordination and subsequent migratory insertion gives a metal alkyl intermediate (**1.13**). Lastly, reductive elimination produces the *ortho* alkylated product (**1.09**) and regenerates the initial catalyst. In this mechanism, reductive elimination was proposed as the rate-determining step.
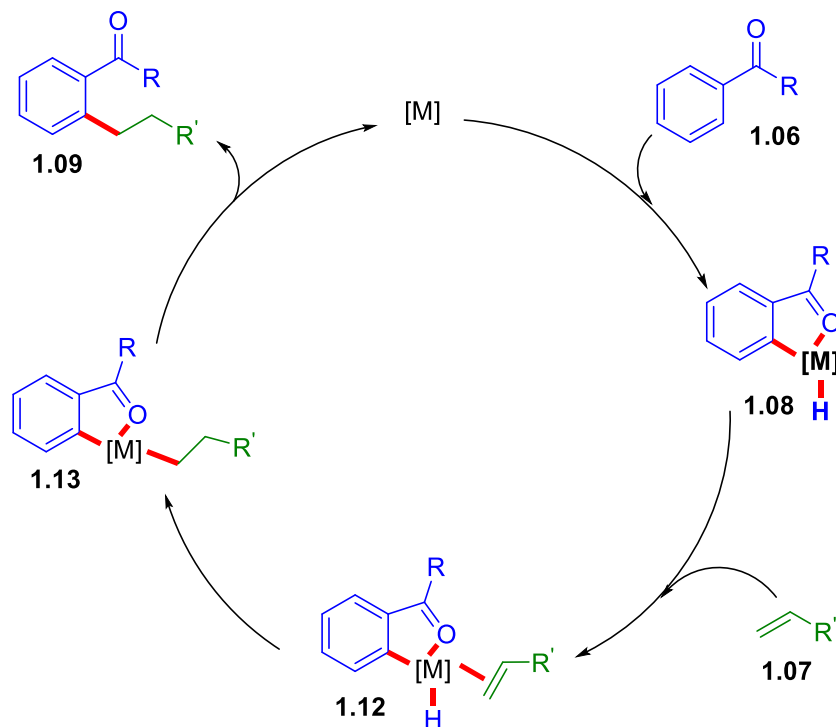
Scheme 1.5. Generally accepted reaction mechanism for murai reaction.

Following this seminal work, Murai-type C-H alkylation was extended to various

functional groups such as ester,[6] aldehydes,[7] aldimines,[8] pyridines,[9] oxazolines,[10] and nitrile.[11]

This transformation proceeds with high regioselectivity without any byproducts, and it is

considered as a typical example of the atom-, step-, and redox-economic reactions.[12] This

pioneering work blazed the trail to an important direction of organic synthesis to advance atom-,

step- and redox-economic reactions.

Later, in 1995 Murai et al. reported hydroarylation of internal alkynes using a ruthenium

catalyst to generate substituted alkene products.[13] The hydroarylation of alkynes occurred with

site selectivity *ortho* to the directing carbonyl group (Scheme 1.6). α-Tetralone (**1.06b**) was

reacted with internal alkynes (**1.14**) with a catalytic amount of $RuH_2(CO)(PPh_3)_3$ to obtain the

alkenylated arenes (**1.15**). When symmetrically substituted internal alkynes such as 4-octyne

were employed, the reaction occurred in favor of the *syn*-hydroarylation products. This result

indicated a *syn*-migratory insertion of alkynes. On the other hand, it was observed that the use of unsymmetrically substituted internal alkynes such as 1-phenyl-1-butyne produced all the four regio- and stereoisomers.
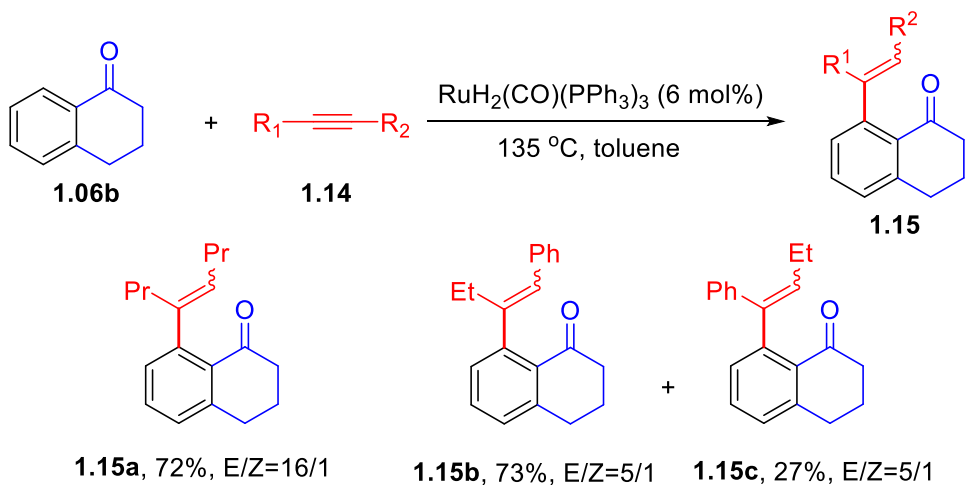
Scheme 1.6. Ruthenium-catalyzed alkyne hydroarylation with cyclic α-tetralone.

The mechanism for alkyne hydroarylation with aromatic ketones is described in the Scheme 1.7, which is analogous to the hydroarylation of olefins. The first step involves the formation of cyclometalated intermediate (**1.08**) via directed C-H bond oxidative addition. Next subsequent alkyne coordination and migratory insertion into the M-H linkage would generate alkenyl-metal intermediates **1.17** and **1.17'**. Finally, reductive elimination of alkenyl-metal intermediates delivers the product and regenerates the catalyst. Electronic and steric effects rationalize the regio- and stereochemistry results. Formation of **1.17** is more favorable than **1.17'** because it is electronically stable vinyl-metal intermediate while steric effects might favor the other regioisomer **1.17'**. Thus, the combined electronic and steric effects of alkyne substrates make the reaction relatively challenging to achieve high regioselectivity. Due to lack of strong geometry restriction, the formation of both *E* and *Z* isomers is observed.
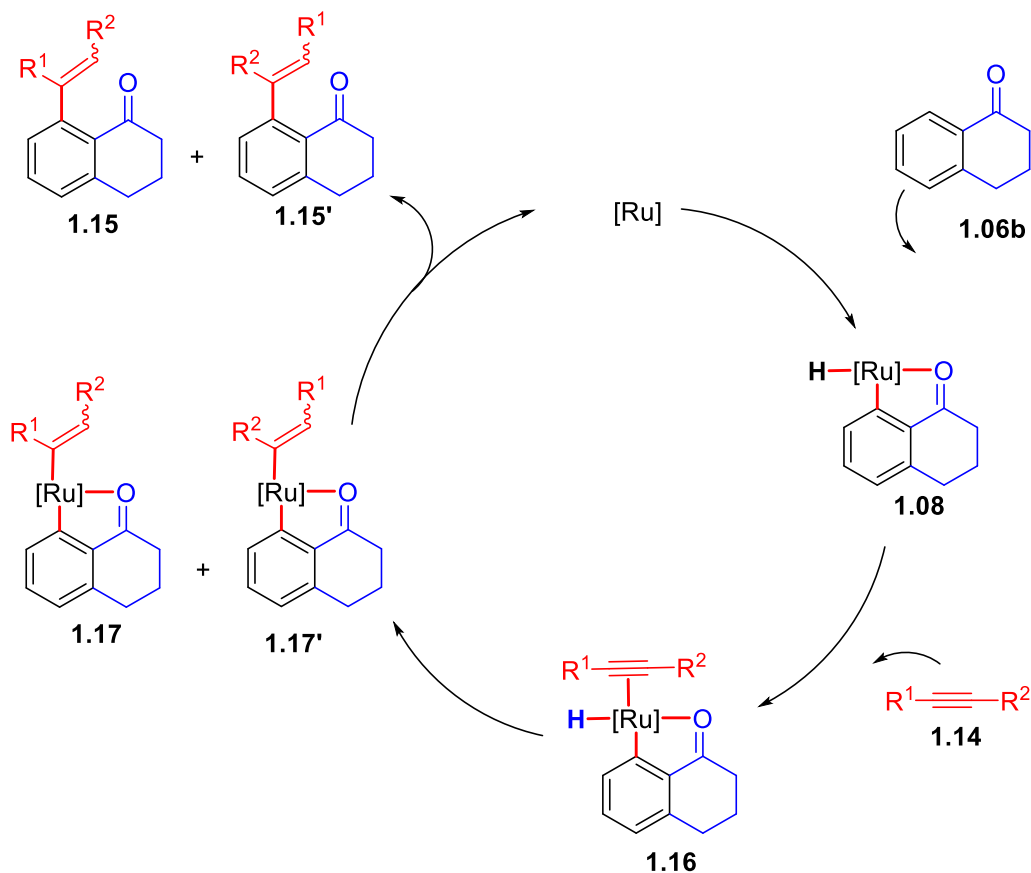
Scheme 1.7. The proposed reaction mechanism for alkyne hydroarylation with aromatic ketones initiated by C-H bond oxidative addition.

This alkyne hydroarylation represents the most straightforward and economical method to access trisubstituted styrene derivatives, which are omnipresent in biologically active compounds and used extensively as synthetic intermediates for fine chemicals and materials.[14] In 1999, the group of Miura disclosed a new method for hydroarylation of dialkyl alkynes with 1-naphthol using iridium(I)/P^{t}Bu$_3$ catalytic system in refluxing toluene (Scheme 1.8).[14a] The transformation proceeds with high regioselectivity and stereoselectivity. Hydroarylation occurred selectively at the *ortho* position of the hydroxyl group and produced only *E*-isomers. The selective formation of *E*-isomers is achieved by using bulky phosphine ligand on the catalyst. Later in 2001, Lim and co-workers discovered another example of alkyne hydroarylation with 2-phenyl pyridines (**1.20**) using rhodium(I)/PPh$_3$ catalytic system (Scheme 1.9).[14b] However, the

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formation of double alkenylated products (**1.22**) is observed when the other *ortho* C-H bond is

not blocked.
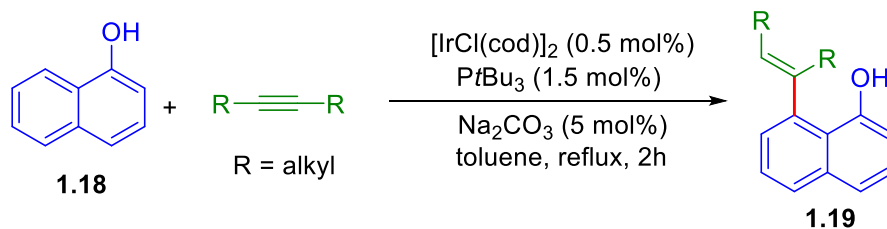
Scheme 1.8. Iridium-catalyzed alkyne hydroarylation with 1-naphthol.
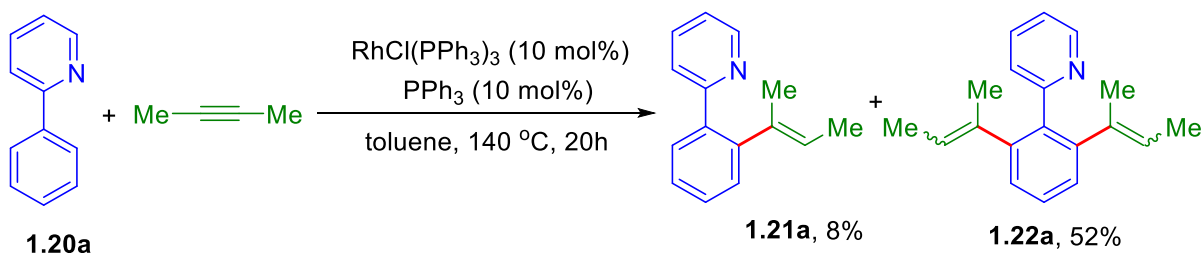
Scheme 1.9. Rhodium-catalyzed alkyne hydroarylation with 2-phenyl pyridine.

Following Murai's pioneering study, significant efforts have been devoted to the

development of directed C-H bond functionalization. C-H bond functionalization is not limited

to the hydroarylation alkene and alkynes, and it has been extended to the construction of various

Carbon-Carbon(C-C) and Carbon-Heteroatom (C-X, X= I, Br, F, N, O, P.. etc.) bonds. By

employing various transition metal catalysts, arene C-H bonds were converted to a broad range

of functional groups through chelation assisted C-H bond activation as shown in the

Scheme1.10.
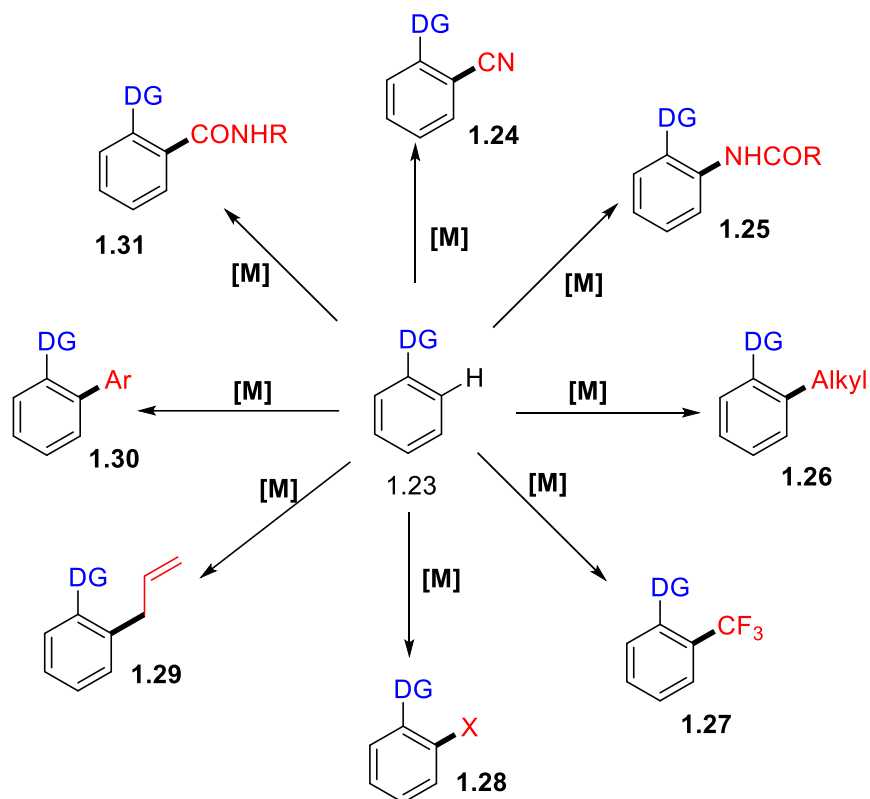
Scheme 1.10. Conversion of arene C-H bonds into various functional groups.

Nitrogen-containing molecules are widely present in many natural products, biologically active compounds and functional materials. There has been an increased interest in the construction of C-N bond in these molecules. The most reliable method for of C-N bond formation is Buchwald-Hartwig amination using pre-functionalised aryl halides. Direct C-H amination is more straightforward and presents the advantages of accessing to the broad substrate scope and minimal waste production.[15] Che and coworkers first reported the C-N formation of oximes through chelation directed/assisted C-H bond functionalization using palladium catalyst (Scheme 2.0).[16] This procedure enables the functionalization of both Sp2 and Sp3 C-H bonds and occurs with high regioselectivity.
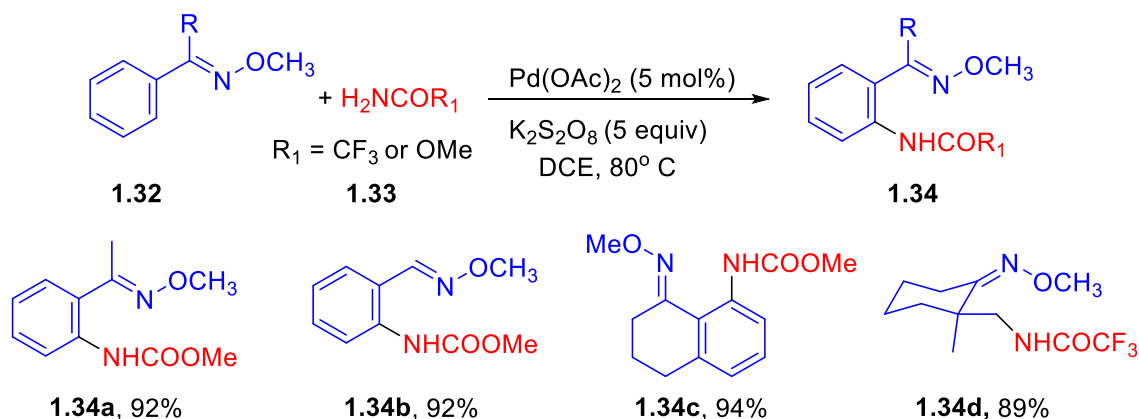
Scheme 1.11. Palladium-catalyzed direct C-H amination of oximes.

The possible mechanism for the reaction is depicted in Scheme 1.12. Formation of cyclometalated complex **1.35** through the chelation assisted C-H bond functionalization followed by insertion of nitrene (generated from the amide through the oxidation) into C-Pd leads to the formation of Carbon-nitrogen bond. Finally, upon protonation, the desired amination product is obtained (1.20b).
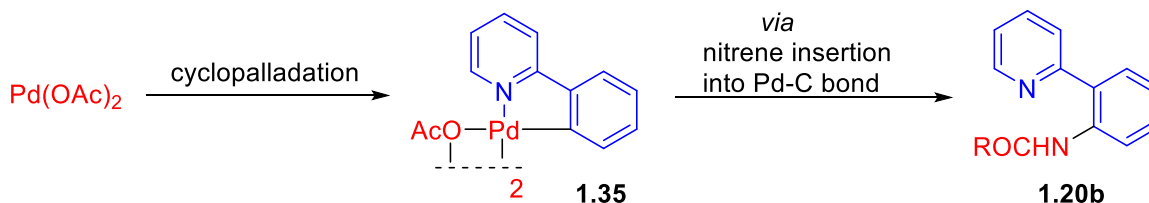
Scheme 1.12. Proposed mechanism for the C-H amidation.

For many decades cross coupling reactions have been used as a valuable tool in synthetic organic chemistry. Aryl halides are widely utilized as reaction partners in the cross-coupling reactions and precursor for the synthesis of various organometallic reagents. Developing new methods for selective bromination and iodination is highly desirable. Glorius and coworkers developed a technique for *ortho* bromination and iodination of arenes by using cationic Rh(III) through chelation assisted mechanism. The current process is compatible with the broad number of directing groups and high functional group tolerance.[17]

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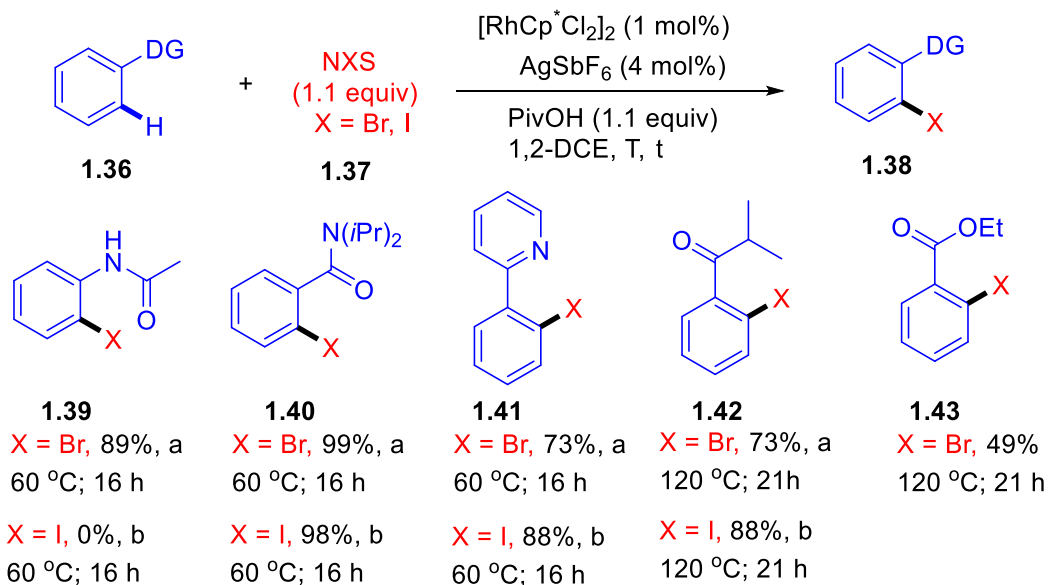
Scheme 1.13. *ortho* Bromination and iodination of various arenes.

The plausible mechanism for Rh(III) catalyzed halogenation is illustrated below (Scheme 1.14). The catalytic cycle starts with the formation of rhodacycle (**1.45**) through chelation assistance. In path A, rhodacycle reacts with NBS (**1.37**) to give the final product. Whereas in path B, rhodacycle is oxidized to Rh(V) intermediate (**1.47**). Rh(V) intermediate upon reductive elimination regenerates the catalyst and delivers the desired product.
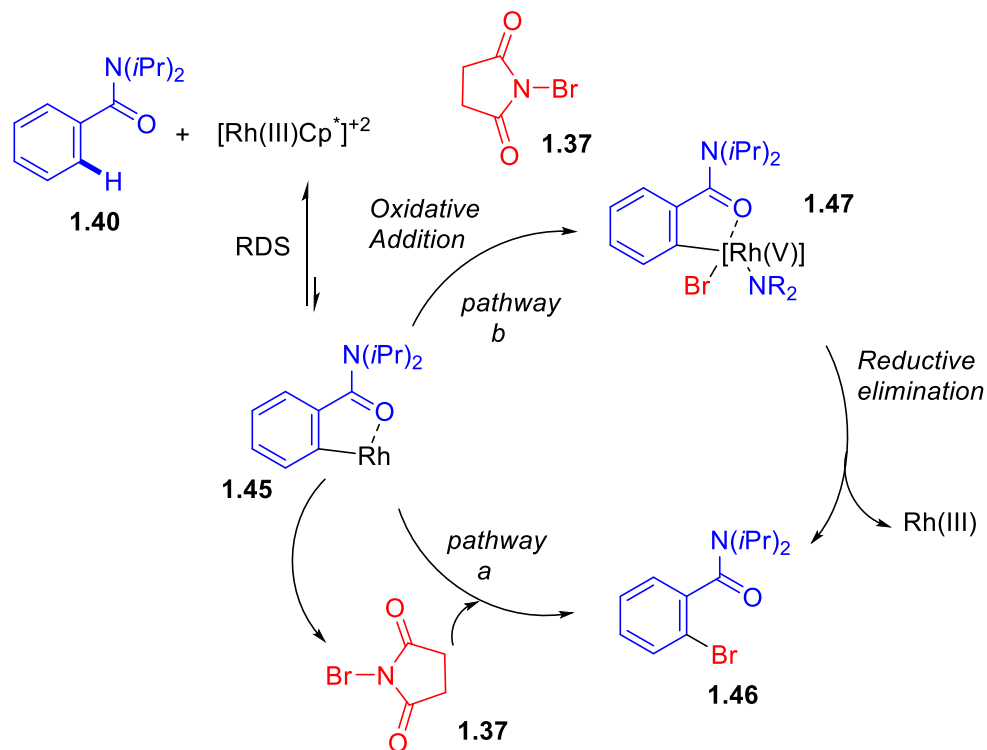
Scheme 1.14. Proposed catalytic pathways for bromination of arenes.

Biaryls are prevalent in many pharmaceuticals, agrochemicals, and functional materials. Biaryls can be accessed by the cross-coupling reactions between aryl halides and stoichiometric amounts of organometallic reagents.
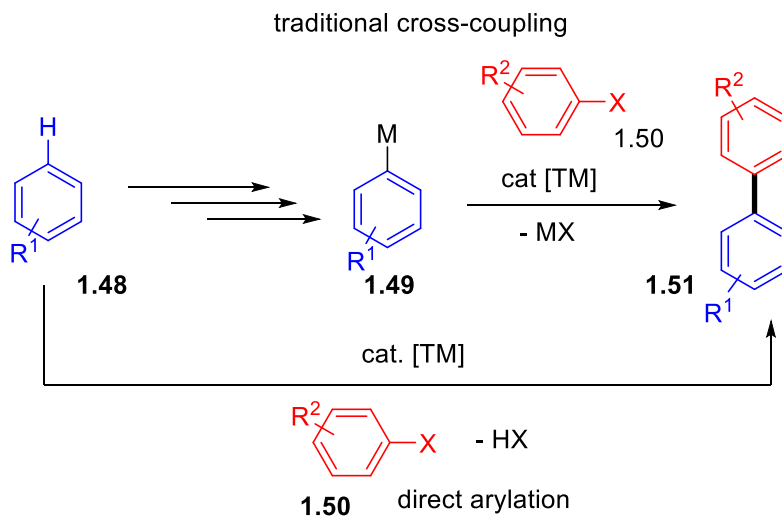
Scheme 1.15. Comparision between classical cross-coupling and direct arylation.

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The synthesis of organometallic nucleophilic reagents involves many steps which produce undesired byproducts. The direct C-H arylation represents an attractive strategy with minimization of waste production.[18]

Ames et al. first reported the transition metal catalyzed direct intramolecular arylation with aryl halides using palladium catalyst.[19] This early discovery laid the foundation for the synthesis of numerous important heterocycles through the direct C-H arylation. Later Miura and coworkers disclosed a method for intermolecular direct C-H arylation of 2-aryl phenols with aryl iodides.[20] This transformation occurs with high regioselectivity. The mechanism for the protocol is illustrated below as shown in Scheme 1.16. The reaction begins with the oxidative addition of palladium catalyst into the aryl iodide bond. The resulting palladium complex (**1.55**) reacts with 2-aryl phenol (**1.52**) and generates the palladium phenolate complex (**1.56**) which undergoes C-H bond functionalization through chelation assistance to give **1.57**. Finally, reductive elimination of **1.57** delivers the final product and regenerates the active catalyst.
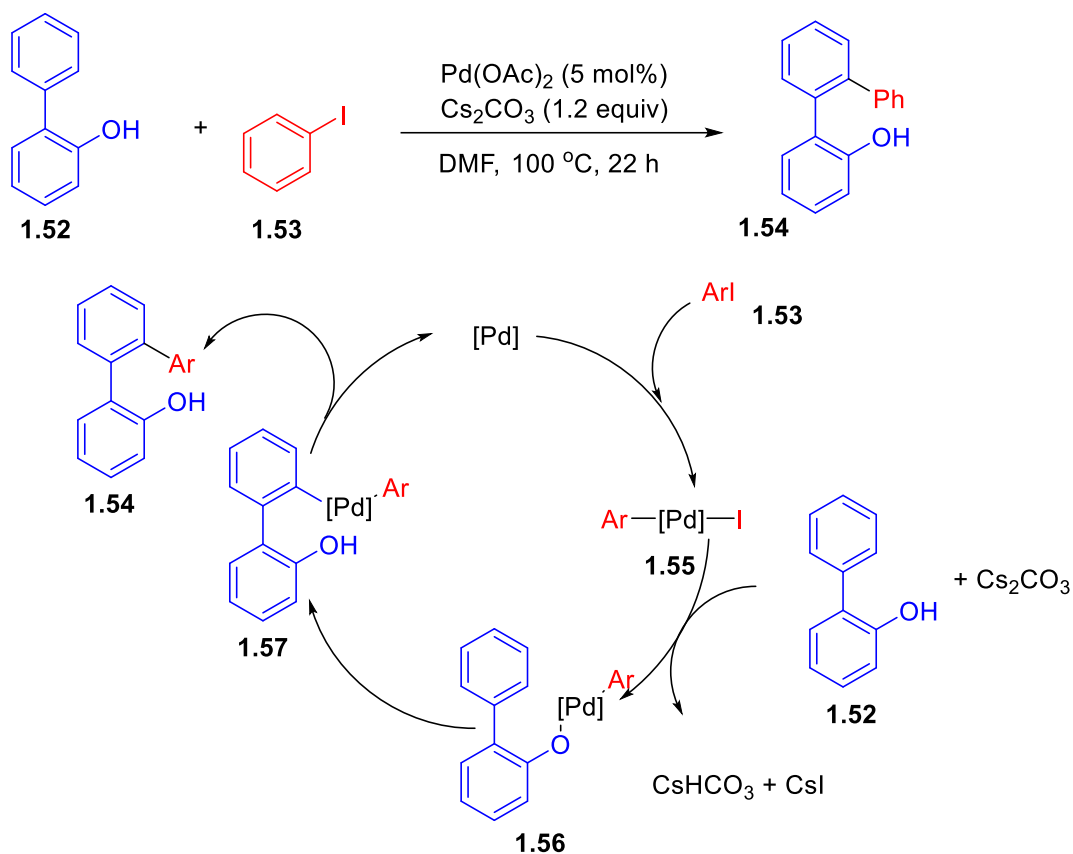
Scheme 1.16. Proposed mechanism for the palladium-catalyzed direct arylation of 2-phenyl phenol.

Further, the direct C-H arylation was extended to various directing groups such as pyridine, amide, ketone, esters, and acids with aryl bromides, aryl triflates using different transition metal catalysts.

Trifluoromethylation of arenes and heteroarenes is an essential transformation for the synthesis of agrochemicals, building blocks for the organic materials and drug candidates.[21] The incorporation of strong withdrawing trifluoromethyl group into the drug candidates has been known to remarkably improve many properties like catabolic activity, lipophilicity, transport rate and dipole moment.[22] The two-step Swarts reaction is the classical method for the synthesis of trifluoromethyl arenes from corresponding methyl arenes.[23] However, it suffers from harsh reaction conditions and limited substrate scope. Because of the high demand for the

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trifluoromethylated products, it has drawn the significant attention of synthetic chemists to develop new protocols which are practically applicable for trifluoromethylation.

Amy and coworkers developed copper catalyzed trifluoromethylation of aryl iodides by using Ruppert's Prakash reagent.[24] Later Buchwald *et. al*[25] made significant advancement by developing palladium-catalyzed trifluoromethylation of aryl chlorides. The advantage of these cross-coupling reactions is regiospecific trifluoromethylation of arenes and heteroarenes. Although considerable progress has been made, these methods require functionalization of starting materials. The direct functionalization of C-H bond bypasses the need for the preactivation of substrates. Hence, the direct trifluoromethylation of C-H bonds is an attractive strategy compared to cross-coupling reactions due to its step and atom economy. Yu et al. first developed a protocol for Pd catalyzed C-H trifluoromethylation of phenyl pyridine using electrophilic Umemoto's reagent.[26] Later, Qing et al. established a copper-catalyzed C-H trifluoromethylation of heteroarenes by using Rupert's Prakash regent.[27]
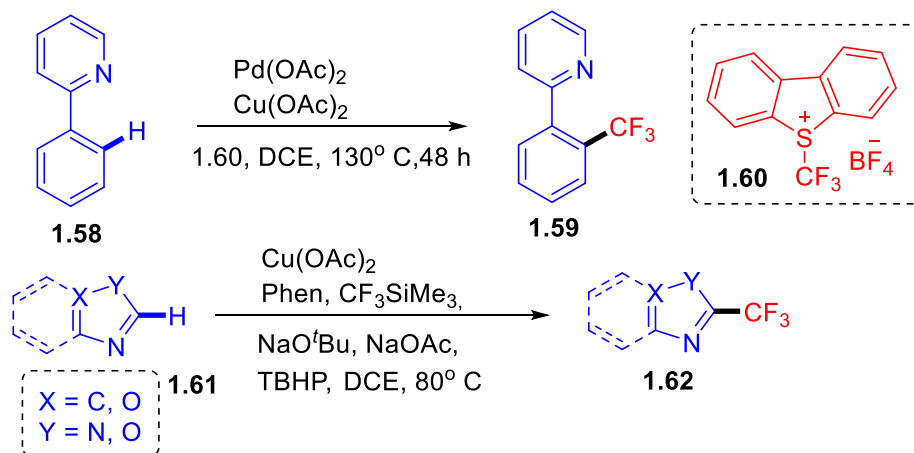
Scheme 1.17. Palladium and copper catalyzed C-H trifluoromethylation.

Amides are frequently found in many natural products, drug candidates and fundamental linkages of peptides. It is noteworthy to mention that amides were used as a precursor for the synthesis of heterocyclic compounds. In the recent years, isocyanates were utilized for atom and

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step economical synthesis of aryl amides employing transition metal catalysts. Hagihara and coworkers independently reported the amide synthesis through the direct addition of benzene C-H bond to isocyanate using $Rh_4(CO)_{12}$.[28] Later Ellman et al. established a protocol for the C-H amidation of phenyl pyridine using Rh(III) catalyst. They demonstrated the synthetical utility of this strategy by synthesizing the N-acyl anthranilamides through the C-H amidation of anilides (Scheme 1.18) which are present in many drug candidates.[29] Following this seminal report, C-H amidation was extended to various directing groups such as imines,[30] carboxylic acids,[31] diazo compounds,[32] and pyrazoles[33]. The synthesis of heterocyclic compounds frequently involved the coupling of C-H amidation with cyclisation .[34]
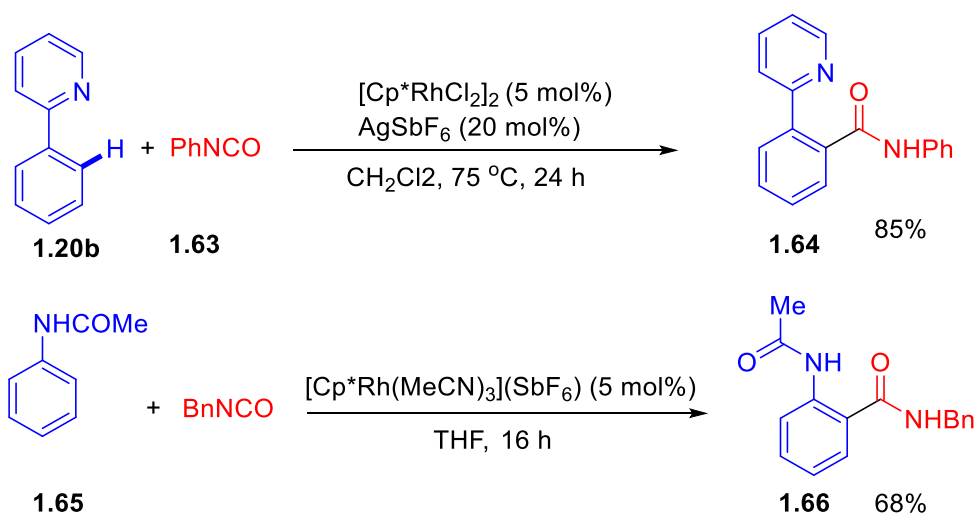
Scheme 1.18. Rhodium-catalyzed directed C-H amidation using isocyanates.

The likely mechanism for the transition metal catalyzed C-H amidation is depicted in the Scheme 1.19. The catalytic cycle is commenced by the precordination of directing the group to metal center and then the subsequent formation of cyclometalated intermediate **1.67**. Coordination and then followed by isocyanate insertion generates the metal amido intermediate. Finally, protonation of **1.68** produces the desired product and regenerates the catalyst.

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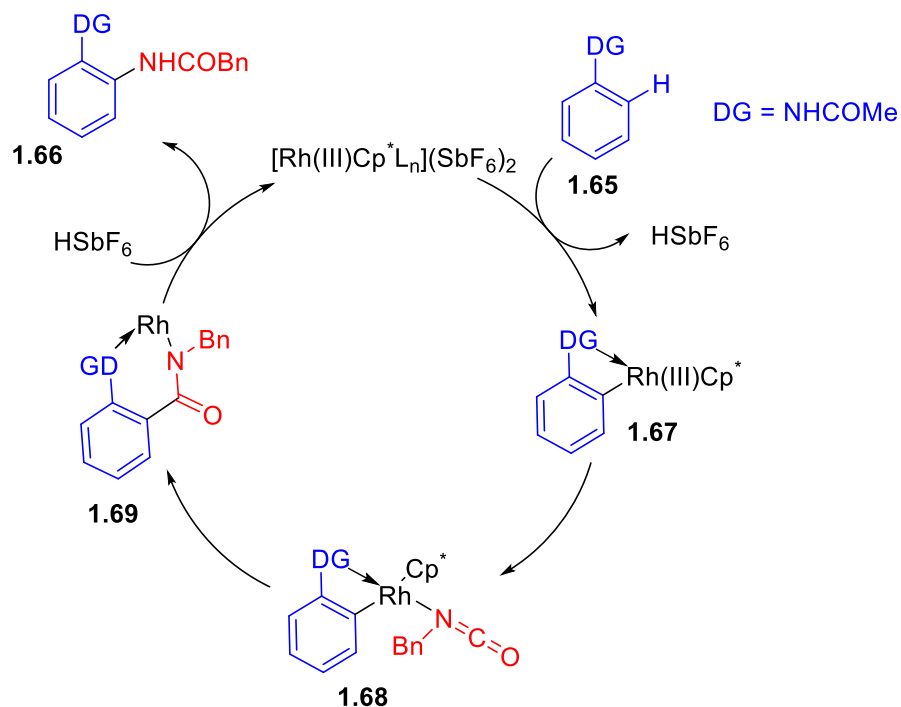
Scheme 1.19. A plausible mechanism for the rhodium-catalyzed C-H amidation.

Cyano group serves as an essential functional group in the organic synthesis, and it can be easily converted into various functional groups such as imines, amines, esters aldehydes and carboxylic acids. Benzonitriles are ubiquitous in many natural products, drugs, and agrochemicals.[35] Classical methods for the synthesis of benzonitriles are Sandmayers[36] reaction and Rosenmund–von Braun[37] reaction. However, these reactions suffer from harsh reaction conditions and the need for stoichiometric amounts of metal cyanides. Buchwald reported the conversion of aryl halides and aryl boronic acids into benzonitriles by employing transition metal catalysts. However, these transformations require pre-functionalised substrates and generates stoichiometric amounts of waste. Introduction of cyano group in arenes through transition metal catalyzed C-H bond activation is an elegant approach to reduce the number of steps and waste production. Recently Fu and coworkers accomplished rhodium catalyzed directed C-H cyanation using less toxic and readily available N-cyano-N-phenyl-p-toluene sulfonamide (NCTS) as the

cyanation reagent (Scheme 1.20). This protocol applies to various directing groups such as pyridine, pyrazole, dihydroimidazole, dihydro oxazole, and oxime.[38] Later, Ackermann et al. reported the cobalt catalyzed C-H cyanation using NCTS. This reaction proceeds efficiently over a broad range of substrates with excellent functional group tolerance.[39]
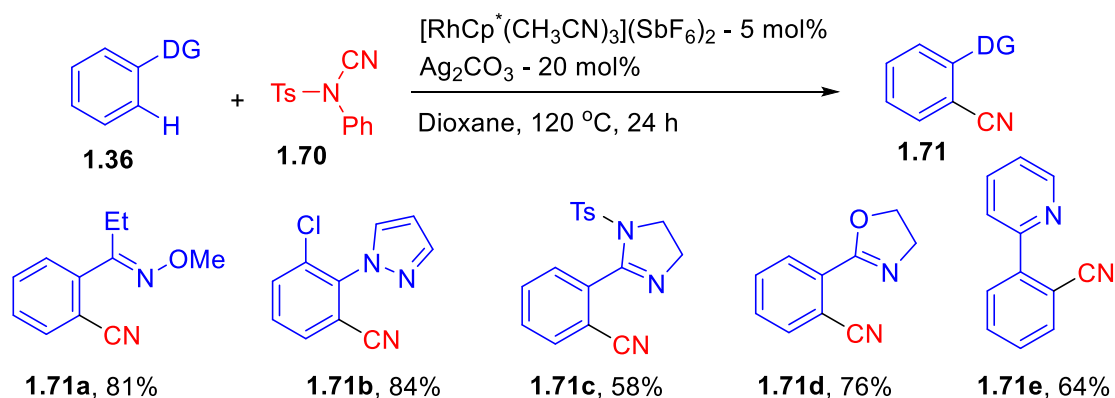
Scheme 1.20. Rhodium-catalyzed directed C-H cyanation of various directing groups.

The plausible mechanism for the directed C-H cyanation is illustrated in Scheme 1.21. In the first step, the reaction of Rh(III) with substrates generate the cyclometalated intermediate **1.72** via concerted metalation-deprotonation. Coordination of NCTS (**1.70**) and then insertion of CN produces rhodacycle **1.73**. Elimination of tosyl anline from intermediate **1.73** delivers the final product and rhodium amido complex **1.74.** Upon protonation of **1.74** regenerates the catalyst.
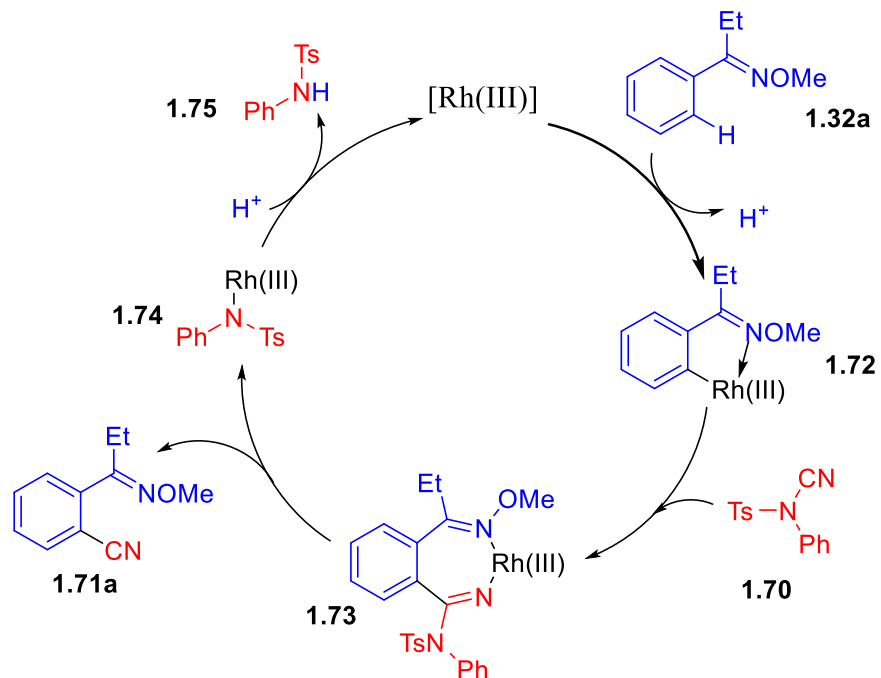
Scheme 1.21. Proposed reaction mechanism for rhodium-catalyzed directed C-H cyanation.

Allylation of arenes is considered as an essential transformation in organic synthesis because allyl benzene is a central structural motif found in many natural products and bioactive compounds.[40] Allyl group serves as a versatile intermediate in organic synthesis and can be quickly transformed into various functional groups. The most reliable method for the allylation of arenes is transition metal mediated coupling of allyl framework with aryl metal units such as boron, zinc, magnesium and aluminum reagents. However, the main drawback of these methods is the need for stoichiometric metal reagents which are prepared from the corresponding aryl halides. Although Lewis acid promoted Friedel-Crafts allylation is considered as a straightforward approach for allylation, it is limited to electron rich arenes and often produces a mixture of products. In this context, transition metal catalyzed direct C-H allylation has gained significant attention because of it's synthetic and atom efficiency.[41]

a) Conventional allylation with aryl metals

1.76　　　　　Stoichiometric metalation　　　　　M = Mg, Zn, Al, B etc.
1.77　　　　　(1.78)　　　cat. [M]　　　**1.79**
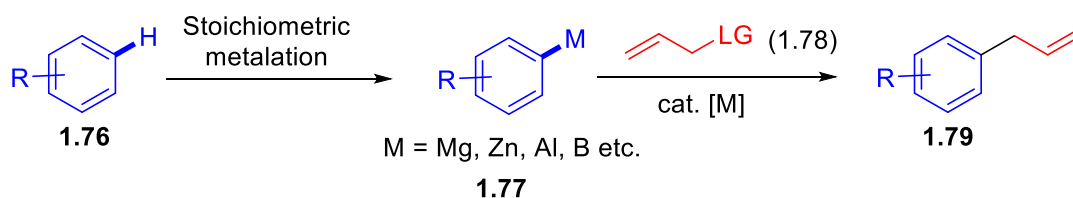
b) Friedel-Crafts-type allylations

1.80　　　Lewis acids　　　**1.81**
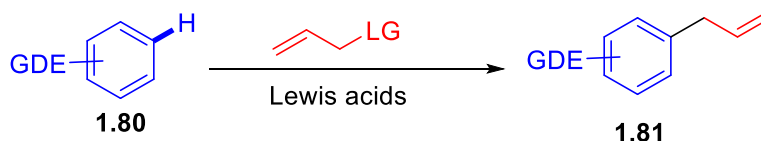
c) Directing group assisted C-H allylation

1.82　　　cat. [M]　　　**1.83**　　　allyl sources　　　**1.84**
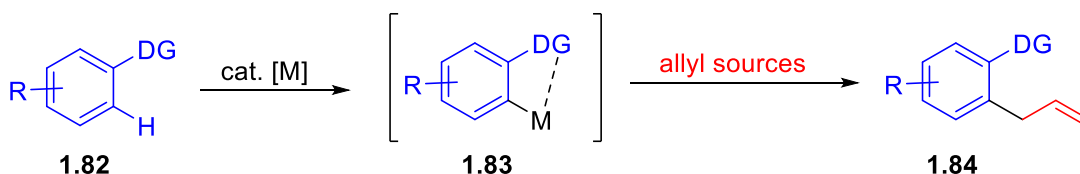
Scheme 1.22. Traditional vs. Catalytic $C(sp^2)$-H allylation reactions.

In 2011, Inoue and coworkers demonstrated the ruthenium catalyzed C-H allylation of phenyl pyridine using readily available allyl acetate as a reaction partner.[42] This reaction proceeds with broad substrate scope and good yields. With linear allyl acetate, a mixture of linear and branched products was obtained, whereas with branched allyl acetate selective linear products were obtained.

$[RuCl_2(COD)]_n$
PPh_3
Xylene/2-picoline
$K_2CO_3,$ 120 °C, 20 h

1.20　　　**1.85**　　　**1.86**, 73%　　　**1.87**, 13%
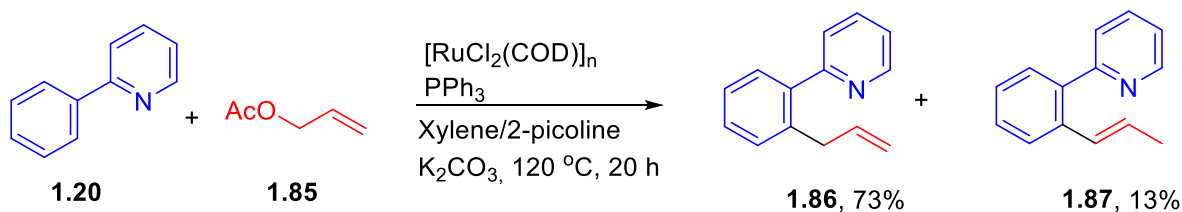
Scheme 1.23. Ruthenium-catalyzed directed C-H allylation of phenyl pyridine.

The catalytic cycle involves the first formation of sigma-allylruthenium intermediate through oxidative addition. Sigma allyl ruthenium intermediate upon reaction with phenyl pyridine generates ruthenacycle **1.90** with the elimination of AcOH. Finally, the product is formed through the reductive elimination and regenerates the catalyst.

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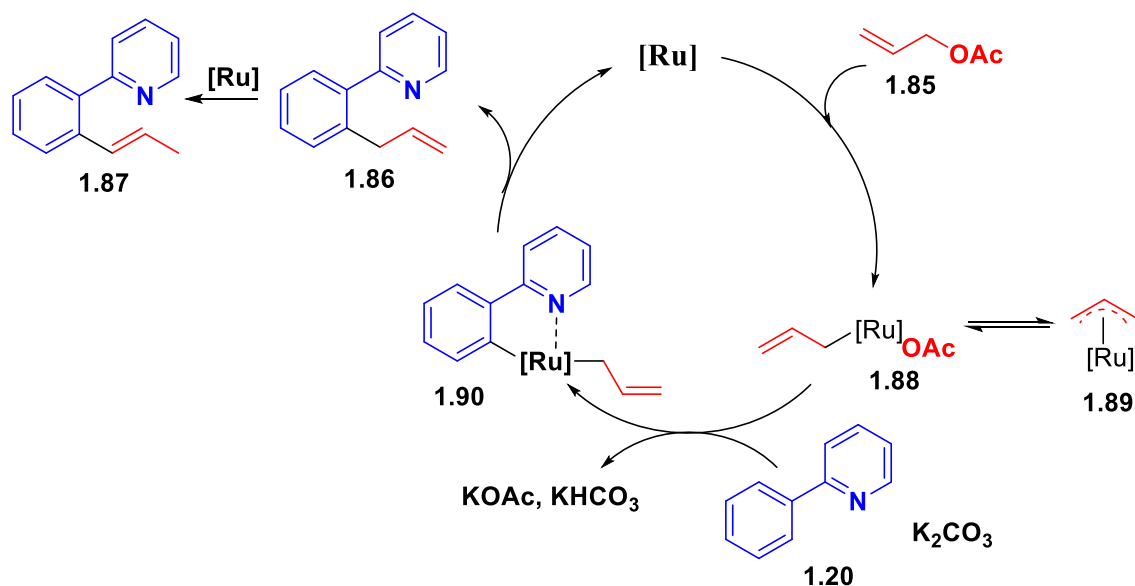
Scheme 1.24. Proposed mechanism for ruthenium catalyzed directed C-H allylation.

Selective hydroxylation of arene or alkane C-H bonds is considered as a challenging transformation in organometallic chemistry. The early example for hydroxylation of arene C-H bond was first revealed by Fujiwara using $Pd(OAc)_2$.[43] In 2005, Rybak-Akimova and Que demonstrated *ortho*-hydroxylation of benzoic acid with hydrogen peroxide using stoichiometric nonheme iron complex $[Fe(II)(BPMEN)(CH_3CN)_2](ClO4)_2$.[44]
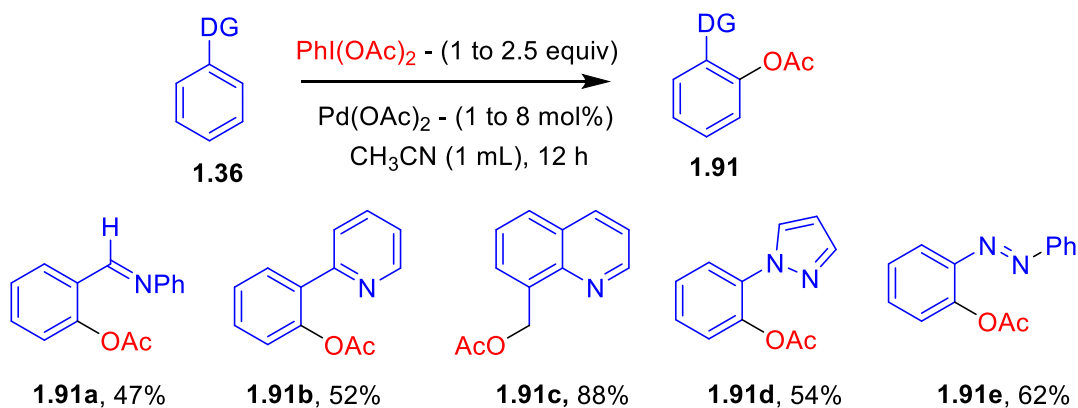
Scheme 1.25. Palladium-catalyzed directed the C-O bond formation.

Sanford et al. reported operationally simple Pd-catalyzed oxidative functionalization of Sp2 and Sp3 C-H bonds through chelation assisted C-H mechanism. This reaction proceeds with

high levels of efficiency and selectivity. This protocol applies to various directing groups such as pyridine, quinoline, imine, pyrazole and azobenzene.[45]

The proposed catalytic cycle is described in the following Scheme 1.26. The catalytic cycle starts with the formation of cyclopalladation intermediate through the chelation assisted C-H activation followed by oxidation Pd(II) to give Pd(IV) intermediate **1.95**. Reductive elimination of carbon-heteroatom gives the final product and regenerates the catalyst. Reductive elimination occurs via intramolecular C-X bond elimination from the metal center or by the attack of an external nucleophile (X) in an S_N2-like reaction.
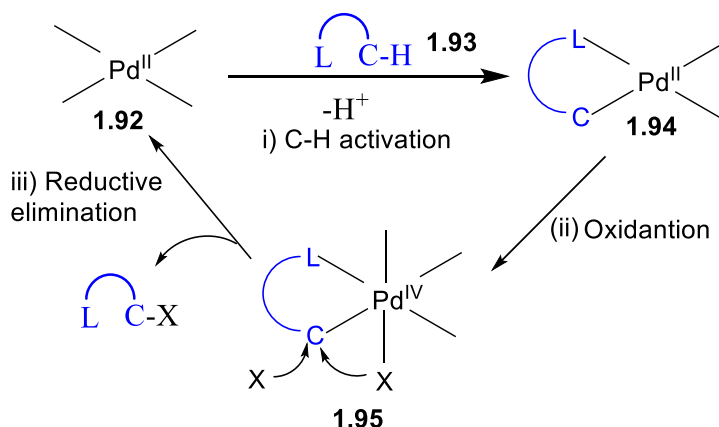
Scheme 1.26. Proposed mechanism for the oxidative functionalization of C-H bond.

Arylboran reagents serve as synthetic building blocks in the transition metal catalyzed cross-coupling reactions. Conventional methods for the synthesis of these reagents is an addition of organolithium or magnesium species to borates. Direct borylation of arene C-H bonds is an elegant approach for the synthesis of aryl boron reagents, and it is thermodynamically & kinetically favorable based on the bond energies.[46] C-H borylation of arenes was first reported using HBpin, in the presence of rhodium and iridium half sandwich complexes such as Cp*Rh(η4-C_6Me_6), Cp*Ir(PMe_3)(H)(Bpin) and (Cp*RhCl$_2$)$_2$. However, these reactions are limited by the harsh reaction conditions and low turn over numbers.[47, 48, 49, 50]

Recently Ishima, Miyaura, and Hartwig groups disclosed a mild protocol for the C-H

borylation using air stable, commercially available Ir(I) precursor in conjunction with bipyridyl

ligands.[51] This reaction proceeds with regioselectivity when arene is symmetrically substituted

at 1,2 and 1,4 position. Whereas, in the case of 1,3-disubstituted arenes borylation occurred at the

common meta position. The steric factors control regioselectivity of this C-H borylation.

$$2ArH \quad + \quad B_2pin_2 \quad \xrightarrow[\text{bpy (3 mol\%), 80 °C, 16 h}]{\text{[IrCl(cod)]}_2 \text{ (1.5 mol\%)}} \quad 2ArBpin \quad + \quad H_2$$

1.96　　　**1.97**　　　　　　　　　　　　　　　　**1.98**

1.98a, 83%　　**1.98b**, 86%　　**1.98c**,58%　　**1.98d,** 86%　　**1.98e**, 73%
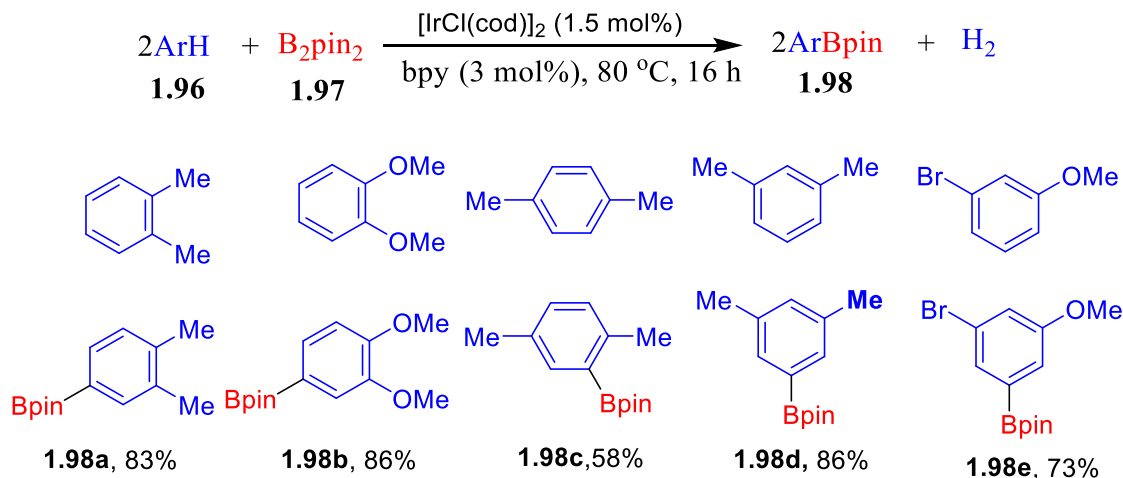
Scheme 1.27. Iridium catalyzed C-H borylation of arenes.

Stoichiometric study of this C-H borylation reaction using [IrCl(coe)$_2$]$_2$, 2 equiv of dtbpy,

and 10 equiv of B$_2$pin$_2$in mesitylene solvent revealed the formation of tris-boryl complex

[Ir(dtbpy)(coe)(Bpin)$_3$] **2.01** as shown in Scheme 1.28. The reaction of **2.01** with deuterated

benzene afforded C$_6$D$_5$-Bpin in 80% yield. [IrCl(coe)$_2$]$_2$ is showed high catalytic activity for C-

H borylation of arenes. This is the first example for C-H borylation of arenes at room

temperature.

1.99　　　　**2.0**　　　　　　　　　　　　　**2.01**　　　　**2.02**
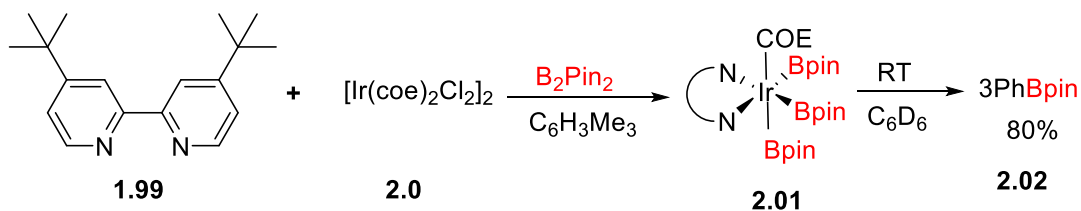
Scheme 1.28. The mechanism for the iridium-catalyzed C-H borylation of arenes.

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But this protocol is not suitable for selective borylation of monosubstituted arenes. Later, in 2008 Hartwig et al. reported *ortho* borylation of arenes using hydrosilanes as a directing group. This approach can also be used for *ortho* borylation of phenol and aniline derivatives.[52]
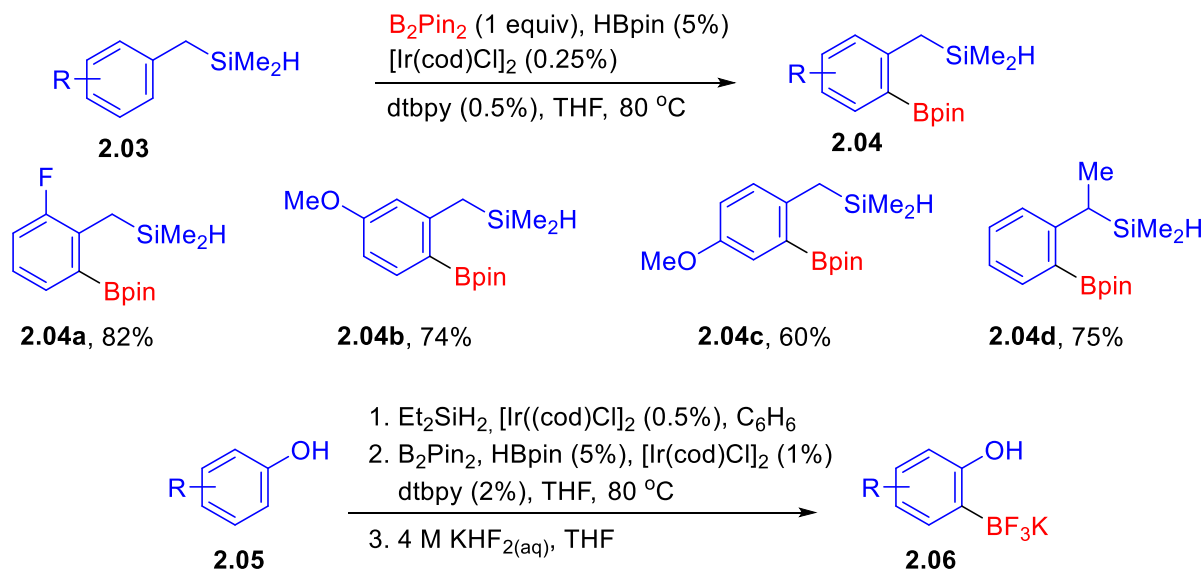
Scheme 1.29. Iridium-catalyzed directed borylation of arenes.

While working for the development of this thesis, various methods have been developed for transition metal catalyzed C-H bond functionalization of arenes using ruthenium, rhodium, iridium, manganese and cobalt catalysts.[19] Despite the significant advancements in transition metal catalyzed C-H bond functionalization, many catalytic systems require harsh reaction conditions such as high reaction temperatures and heavy salt additives which limits the synthetic utility and functional group compatibility. In most cases, regioselectivity is achieved through the assistance of directing groups. Although chelation assisted C-H bond functionalization occurs with regioselectivity, it is accompanied by several challenges or limitations. First, additional steps are required to install and remove the directing groups. Second, the directing group on the product carried over to the product structure after the reaction which could cause over-reaction leads to a mixture of mono-and difunctionalised products. Third, directed C-H bond activation is

well known for *ortho* C-H bond functionalization, but meta and *para* C-H bond functionalization remained as significant challenge.

These challenges have provoked us to develop new catalytic methods for transition metal catalyzed C-H functionalization using directing groups which can be easily removed or incorporated into the product backbone. The following chapters describe our research on the development of new and improved catalytic methods for construction of C-C and C-N bond formations through activation of sp^2 C-H bonds using ruthenium and rhodium catalysts. Results from the following three major projects are summarized: (1) A tethering directing Group strategy for ruthenium-catalyzed intramolecular alkene hydroarylation (2) Rhodium-catalyzed decarboxylative amination (3) Ruthenium(II)-catalyzed decarboxylative hydroheteroarylation of internal alkynes with heteroarene carboxylic Acids.

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2. RUTHENIUM-CATALYSED INTRAMOLECULAR ALKENE HYDROARYLATION FOR OXINDOLE SYNTHESIS

2.1. Background and Significance

An important transformation in the field of synthetic organic chemistry for construction of Carbon-Carbon bonds is alkyaltion of arenes. Conventional method for the alkylation of arenes is electrophilic aromatic substitution (Scheme 2.1 a) which relies on alkylating agents such as alkyl halides and alkyl sulfonates. Though the transformation is highly efficient, it suffers from some drawbacks namely generation of stoichiometric amounts of byproducts and achieving regio and, stereo selectivity.[1]
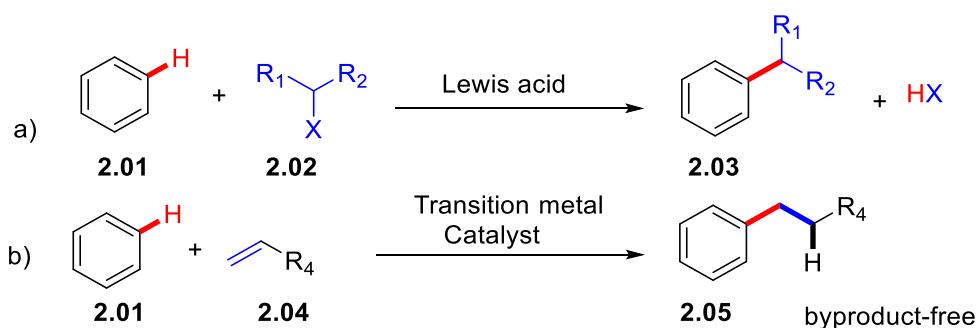
Scheme 2.1. a) Friedel-Crafts alkylation b) Transition metal catalyzed hydroarylation.

With the advances in the field of transition metal chemistry, transition metal catalyzed addition of aromatic C-H bond across the carbon-carbon double bond (Hydroarylation) has become an important strategy for the alkylation of arenes and heteroarenes (Scheme 2.1 b). Hydroarylation proceeds with high regioselectivity and occurs without byproducts. Olefins used in hydroarylation are relatively inexpensive and more readily available unlike alkyl halides and sulfonates which are generally synthesized from olefins.[2, 3] Murai et al first revealed a protocol for the ruthenium catalyzed C-H alkylation of ketones using vinyl silanes as coupling partners. Alkylation occurs selectively at *ortho* position to the aromatic ketones with high atom efficiency.[4] After Murai's poinnering work, transition metal-catalyzed hydroarylation of alkenes,

the formal alkene addition by an aromatic C−H bond, has become a powerful strategy for atom-efficient C−H alkylation of arenes and heteroarenes. Inspired by Murai's C-H alkylation, many research groups explored broad range of Ru, Rh, Ir, Co and Ni catlysts improving scope and efficiency of the hydroarylation.[5] In 2002, Jun and coworkers revealed a new protocol for the alkyaltion of ketimines using alkenes in the presence of Rh(I) catalyst (Scheme 2.2). This transformation is suitable for 1-alkenes and dienes whcich were causing problems in ruthenium catalysed Murai's alkylation.[6]
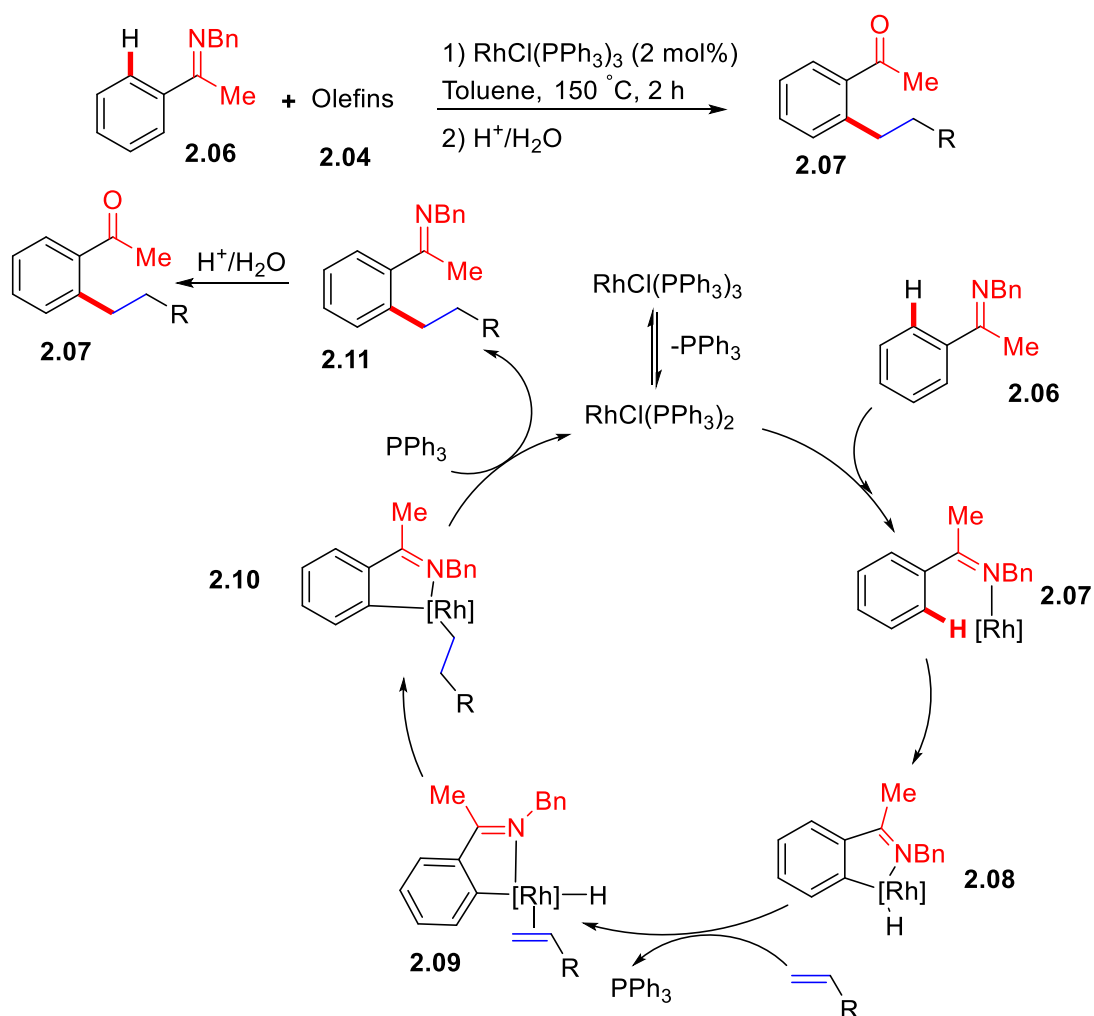
Scheme 2.2. Rh(I) catalyzed C-H alkylation of ketimines with olefins.

The catalytic cycle starts with the dissociation of ligand followed by coordination of substrate gives **2.07**. Subsequent oxidative addition of C-H bond generates Rh-H intermediate **2.08** which coordinates with the olefin followed by insertion into the C-Rh bond producing **2.10**. Finally, reductive elimination of **2.10** affords *ortho* alkylation of ketimine (**2.11**). Authours proposed that the reductive elimination is the rate determining step which was supported by deuterium labelling studies. Later, the Rh(I) catalysed intermolecular C-H hydroarylation was extended to directing groups such as ketone[7], phenyl pyridine[8], phenol and aniline[9] derivatives.
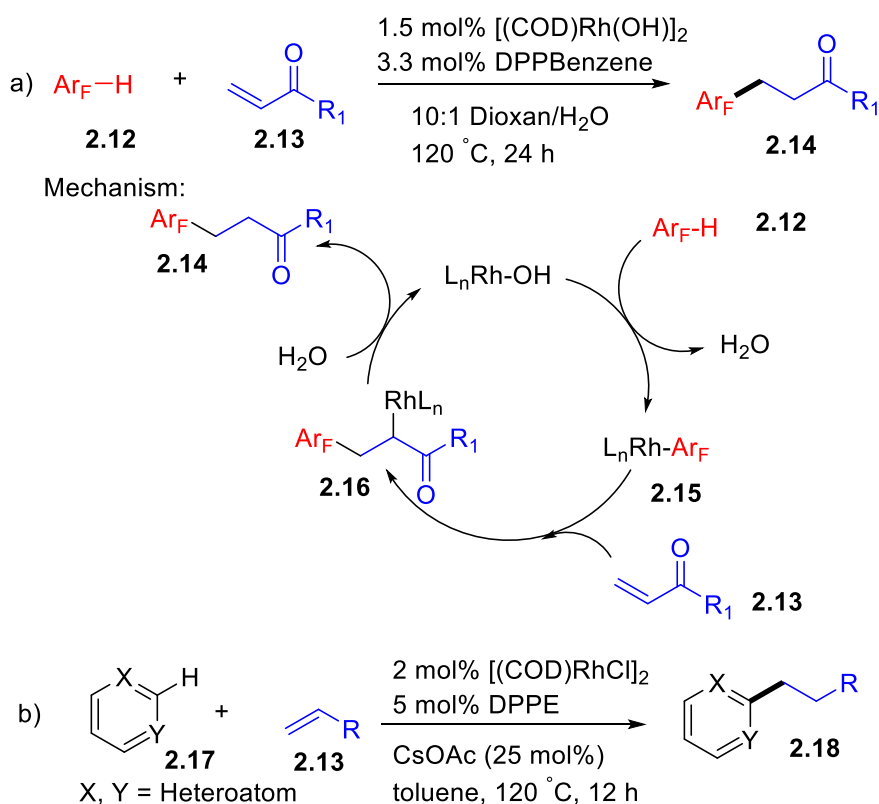
Scheme 2.3. a) Rh(I) catalysed hydroarylation of activated olefins with perfluoro arenes b) Rh(I) catalysed hydroheteroarylation of activated olefins with heteroarenes.

Nakao and Hiyama reported a protocol for the hydroarylation of 2-vinylnaphthalene or buta-1,3-dienylbenzene with perfuoroarenes using Ni-catalyst.[10] In 2008, Zhao and coworkers disclosed a new Rh(I) catalytic system for hydroarylation of activated olefins (**2.13**) with perfluoro arenes (**2.12**) (Scheme 2.3. a). This Rh(I) catalysis occurs with high catalytic efficiency

and is compatible with broad range of functional groups.[11] The reaction proceeds via formation

of C-Rh intermediate **2.15** through C-H bond functionalization. Subsequent olefin insertion into

the carbon metal bond leads to the formation of Rh-alkyl intermediate **2.16**. Upon protonolysis of

intermediate **2.16** delivers the desired product and regenerates the final product. This catalytic

reaction works well without *ortho* directing group and C-H bond functionalization occurs at the

most acidic position. In 2013 Chang et al developed a new method for hydroheteroarylation of

activated olefins (**2.13**) with heteroarenes. The substrate scope of this protocol is broad and it is

suitable for both electron deficient pyridine oxide and electron rich azoles (Scheme 2.3. b).[12]
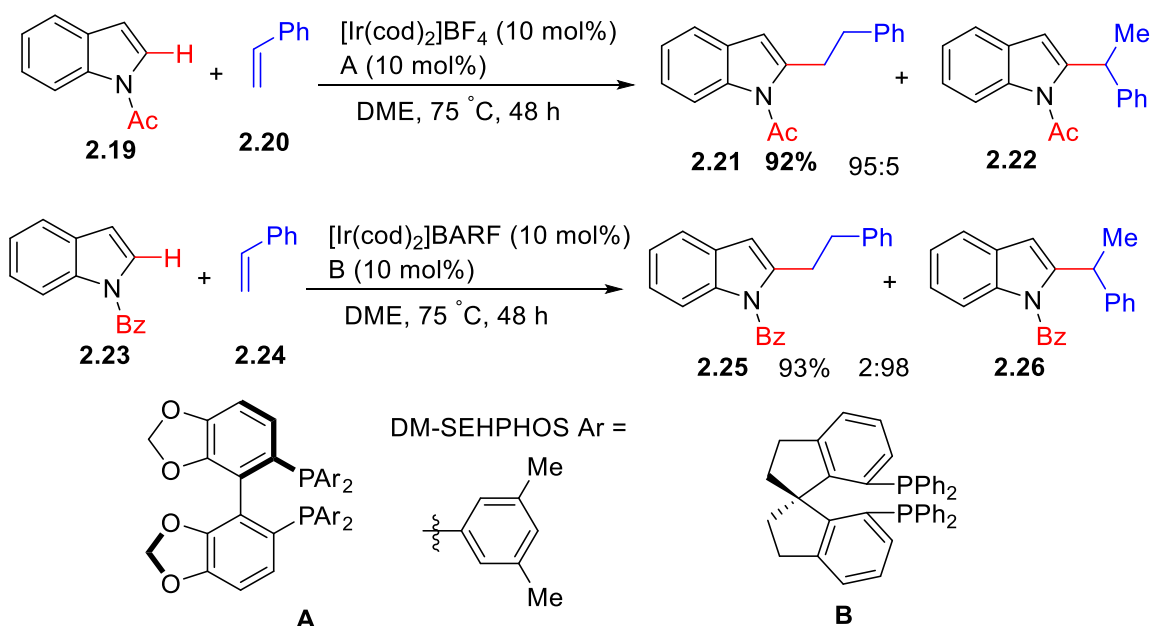
Scheme 2.4. Iridium catalysed regioselective hydroheteroarylation of styrene derivatives.

In 2008 Shibata and coworkers revealed a protocol for Ir(I) catalysed C-H alkylation of

ketones through directed C-H activation mechanism.[13] This particular reaction is highly effecient

in the presence of bidentate phosphine ligand and enanatioselective alkylation was acheived. The

same group extended the Iridium catalysed hydroarylation to the N-protected indoles (**2.19 or

2.23**) and regioselectivity was regulated by the combination of protecting group and ligand as

depicted in Scheme 2.4.[14] The Iridium catalysed hydroarylation of alkenes is compatible with various arenes such as ary amides amides, pyridine derivatives, aniline..etc.[15]

Another protocol for Ir(I) catalysed hydroheteroarylation of norbornene (**2.28**) was revealed by Hartwig's group which is suitable for various heteroarenes (**2.27**) such as Indole, benzofuran, benzothiophene, pyrrole, furan occuring with high yields and excellent enantiomeric excess (Scheme 2.5).[16] This protocol proceeds without any directing group and alkyaltion occurs at *ortho* to the heteroatom. Deuterium labelling study reveals that the reaction goes through the oxidative addition of C-H bond.
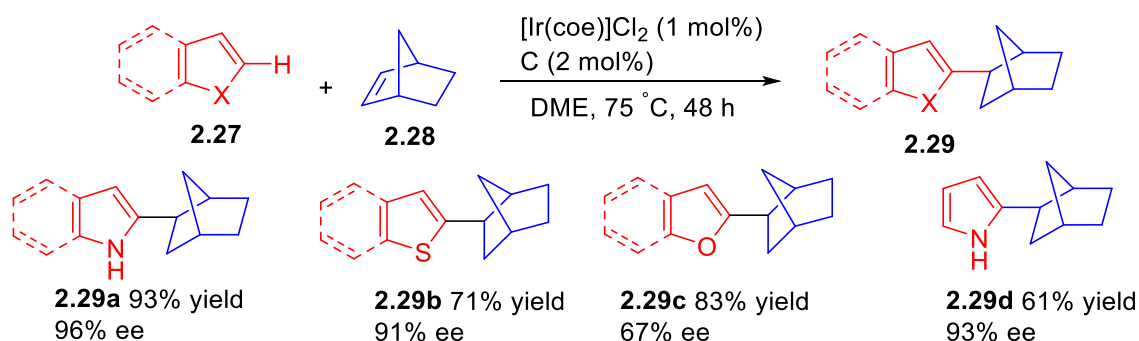
Scheme 2.5. Iridium catalyzed enantioselective hydroheteroarylation of norbornene.

In 2015, Chang and coworkers reported a protocol for C-H hydroarylation of activated olefins using directing group in presence of Ir(III) catalyst (Scheme 2.6).[17] Unlike Murai type alkylation the transformation proceeds via concerted metalation and deprotonation mechanism through the assistance of a directing group. The plausible mechanism for this reaction is depicted in the following Scheme 2.6. The catalytic cycle begins with the formation of cyclometalated intermediate **2.32** through concerted metalation and deprotonation. Coordination of olefin followed by migratory insertion into C-M bond generates seven membered cyclic intermediate **2.34**. Protonolysis of intermediate **2.34** affords final product and regenerates the final product.
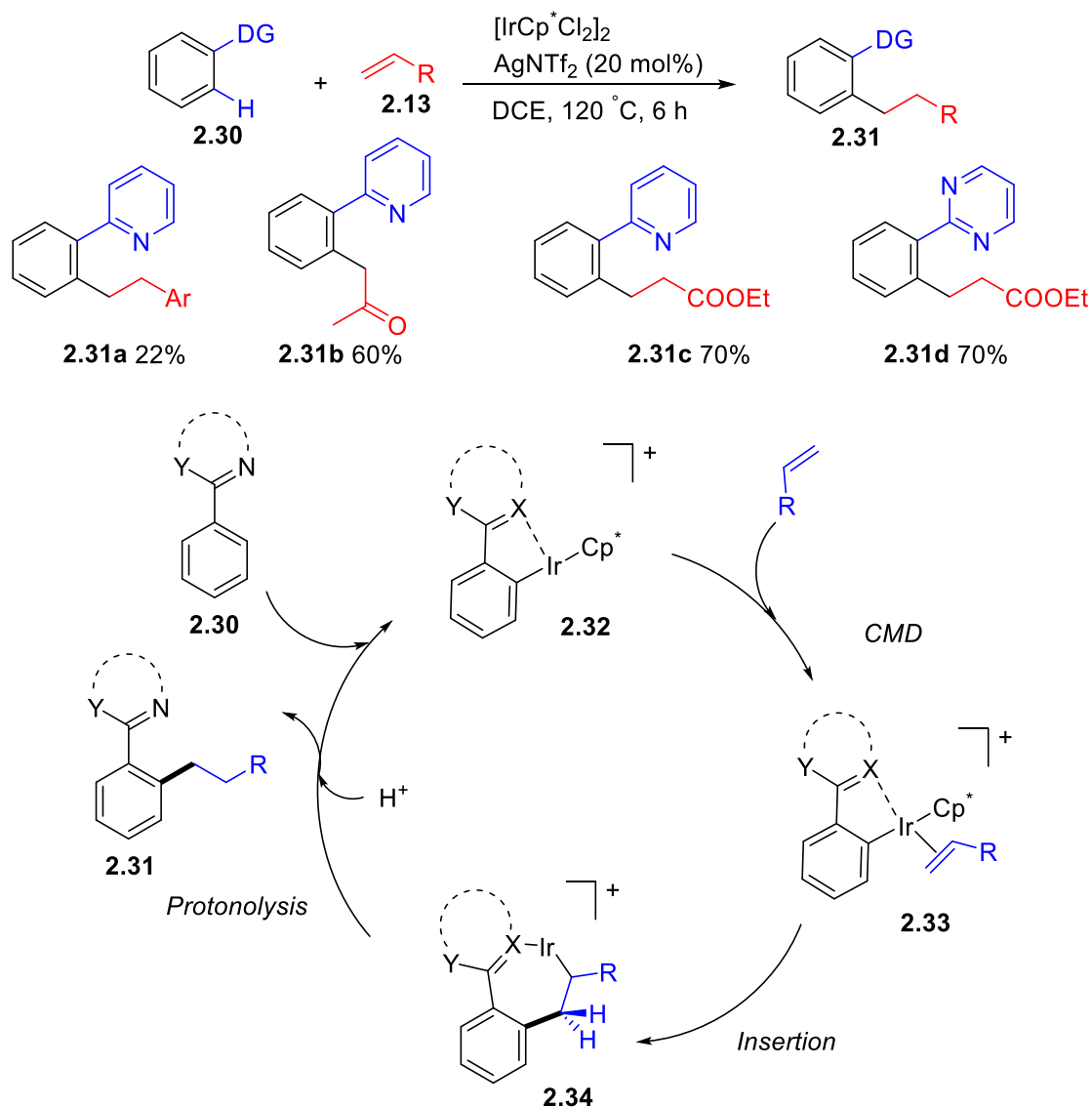
Scheme 2.6. Ir(III) catalyzed hydroarylation of activated olefins.

In the recent years significant attention has been diverted towards the development of new and efficient catalytic systems using 3d transition metal catalysts because of their high abundance and low cost compared to 4d and 5d transition metals. Among the first-row metals, cobalt catalysts have gained special interest for the directed C-H bond functionalization.[18] Yoshikai and coworkers developed a cobalt(II)/phenanthroline catalytic system for *ortho* alkylation of aromatic imines (**2.35**) with broad range of olefins (Scheme 2.7 a).[19] The present cobalt catalysis proceeds at room temperature with good yields and high functional group

tolerance, and it is complementary to the rhodium and ruthenium catalysed hydroarylation which occurs at high reaction temperatures. In 2013 Kannai et al demonstrated the hydroarylation of activated olefins with phenyl pyridine (**2.37**) derivatives using a cationic, high-valent Co catalyst (Scheme 2.7 b).[20] Authors proposed that C-H bond functionalisation of arenes proceeds via concerted metalation and deprotonation through the assistance of directing group. In 2017, Li and coworkers revealed another protocol for C-2 selective alkylation of indoles with activated olefins using cobalt(III) catalysts.[21] Inaddition to atom and step economy, cobalt(III) catalytic systems occured with high regioselectivity through the assistance of directing groups pyridine, pyrimidine, pyrazole, ketone and amides.
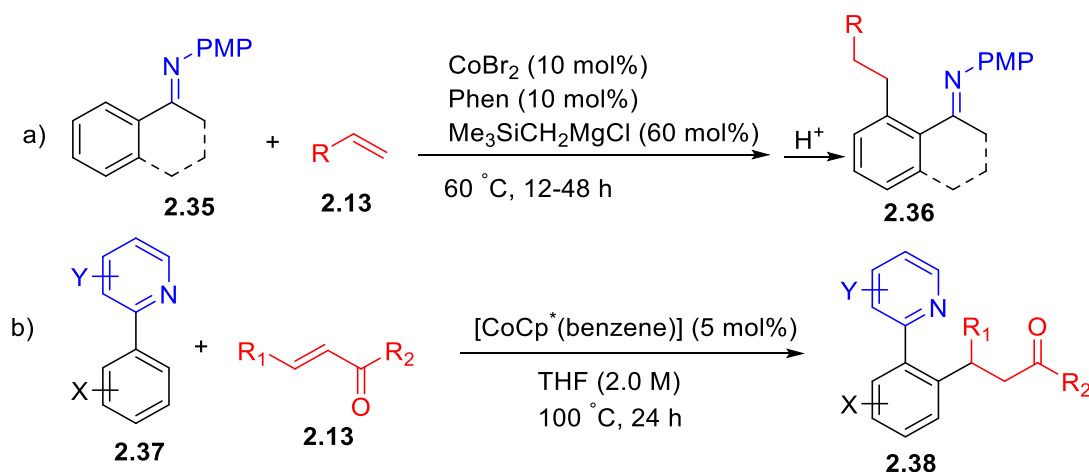
Scheme 2.7. a) Co(II) catalyzed hydroarylation of olefins b) Co(III) catalyzed hydroarylation of activated olefins.

Nickel catalysts were considered as a replacement for the palladium catalysed cross coupling reactions becuase of high abundance and low cost of the nickel. Recently, nickel complexes have been explored for the C-H bond functionalisation of arenes and heteroarenes. Hartwig et al reported a new protocol for hydroarylations of unactivated olefins (**2.13**) with trifluoromethyl-substituted arenes (**2.39**) without a directing group (Scheme 2.8).[22] The reaction is compatible with both terminal and internal alkenes and it exhibited high selectivity to yield

linear alkylarene products. From experimental observations, authours proposed that reductive

elimination of an alkylnickel−aryl intermediate to form C-C bond was the rate determining step.

The linear selectivity is acheived because of the high difference in energy between the

corresponding transition states for C-C bond formation step.
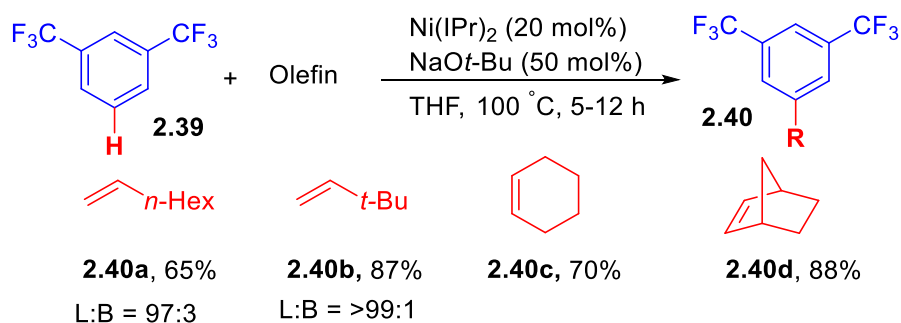
Scheme 2.8. Ni catalysed hydroarylation of unactivated olefins with trifluoromethyl-substituted arenes.

In 2015, the same group disclosed another method for C_2 alkylation of heteroarenes

(**2.27**) with unactivated terminal and internal alkenes using Nickel catalytic system (Scheme 2.

9).[23] The reaction is compatible with various heteroarenes such as Indole, Pyrrole, furan, and

benzofuran and it occurs with broad functional group tolerance.
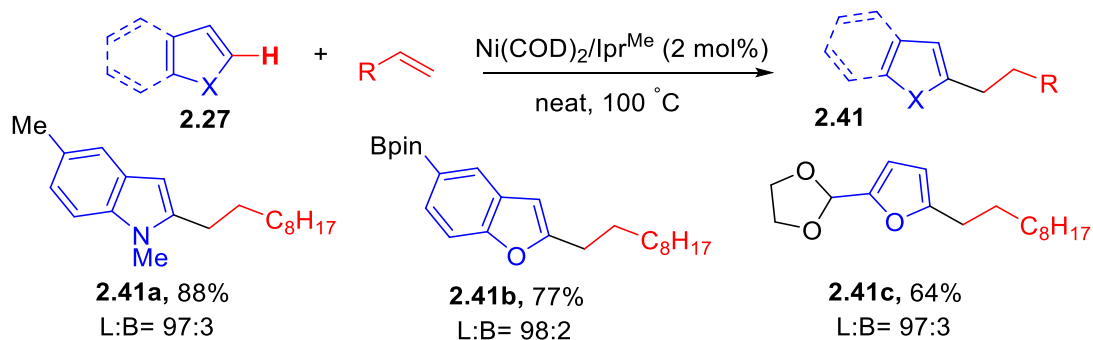
Scheme 2.9. Ni catalysed hydroheteroarylation of unactivated alkenes.

Authors proposed that the reaction proceeds through the direct transfer of hydrogen from

arene to alkene without formation of Ni-H intermediate which is termed as ligand-to-ligand

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hydrogen transfer. Reductive elimination of alkylnickel heteroaryl intermediate leads to the formation of desired alkylated heteroarene.

Recently, applications of intramolecular alkene hydroarylation towards heterocycle synthesis have drawn significant attention.[24,25] Reports on such cyclization of arenes containing heteroatom-tethered alkene moiety have focused on two general approaches: (1) electrophilic aromatic substitution (EAS) that involves alkene activation by a Lewis-acidic metal catalyst and subsequent intramolecular alkene attack by the arene nucleophile (Scheme 2.10 a);[24,26] (2) aromatic C–H activation/cyclometalation assisted by an *ortho*-directing group (DG) and subsequent intramolecular alkene insertion into the metal-aryl linkage (Scheme 2.10 b).[25,27,28]

Scheme 2.10. (a) Electrophilic aromatic substitution (b) Directing group (DG)-assisted tandem C-H activation/cyclometallation.

Sames and coworkers reported a Ru(III)/Ag(I) catalytic system for an intramolecular hydroarylation of arene-ene substrates (Scheme 2.11).[29] This protocol works under mild reaction conditions with good yields and it enables the easy access of various heterocycles and carbocycles such as chromane, tetralin, terpenoid, dihydrocoumarin, tetrahydroquinoline, and indolocyclohexane and cyclopentane systems. Authors proposed that the reaction occurs via an electrophilic C-H activation pathway as discussed earlier in the Scheme 2.10 a. In 2016,

Shigehisa et al reported a new protocol for intramolecular hydroarylation of unactivated olefins using Co(salen) complex.[30]
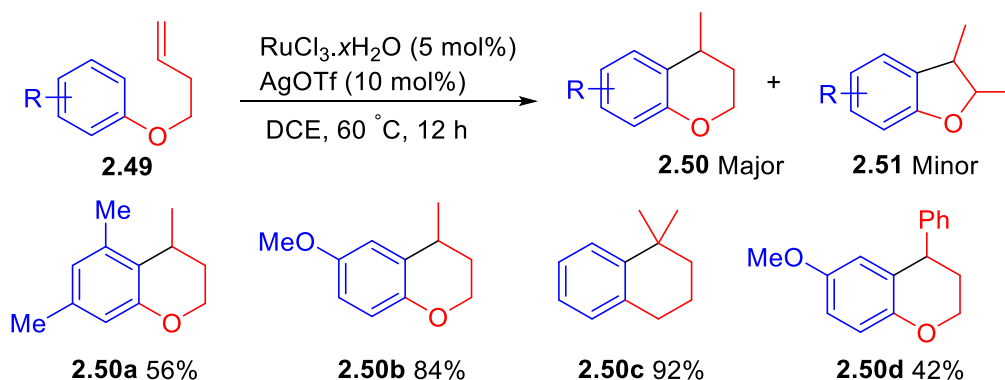
Scheme 2.11. Ru(III) catalyzed intramolecular hydroarylation.

Guosheng Liu et al used the olefin activation strategy for the aryl trifluormethylation of activated olefins using Pd(II) catalyst as shown in Scheme 2.12.[31] This protocol provides a straightforward access to the trifluormethylated oxindole derivatives. Based on preliminary mechanistic studies authors proposed that the reaction is initiated by the activation of olefin through the coordination with palladium catalyst. Nucleophilic attack of arene on olefin produces Pd intermediate **2.56**.
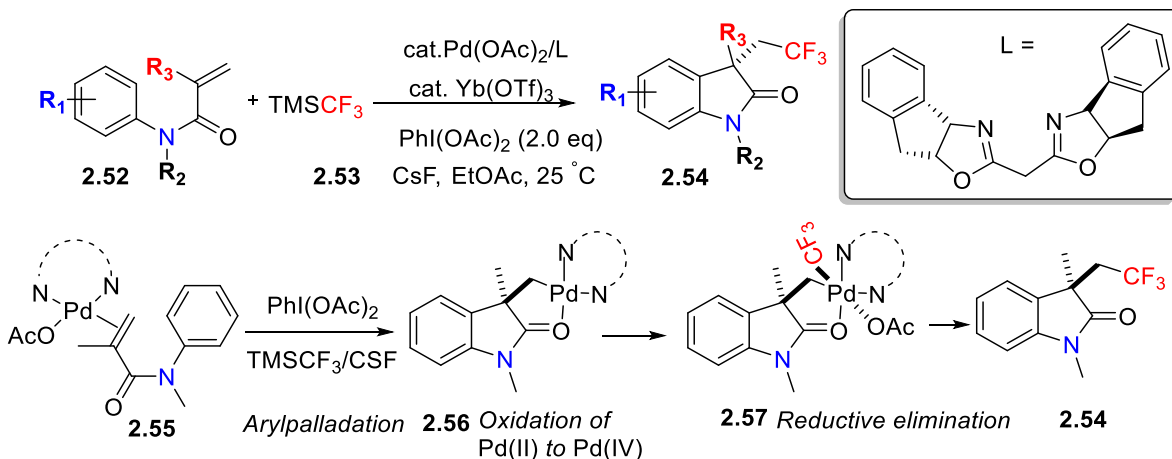
Scheme 2.12. Palladium-catalyzed oxidative aryltrifluoromethylation of activated alkenes.

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The intermediate **2.56** undergoes oxidation in presence of I(III) reagent and leads to formation of

Pd(IV) intermediate **2.57** which upon reductive elimination delivers the final product

trifluoromethylated oxindole (**2.54**) and regenerates catalyst.

Notably, these specific hydroarylation pathways have led to inherent limitations on

substrate scopes. For example, the EAS approach suffers significant loss of reactivity with

electron-poor arenes and prefers electron-donating aromatic substituents.[26] In comparison, the

cyclometalation approach reduces reactivity dependence on electronic properties of arenes and

has more success with asymmetric catalysis.[25c,25d,25h]
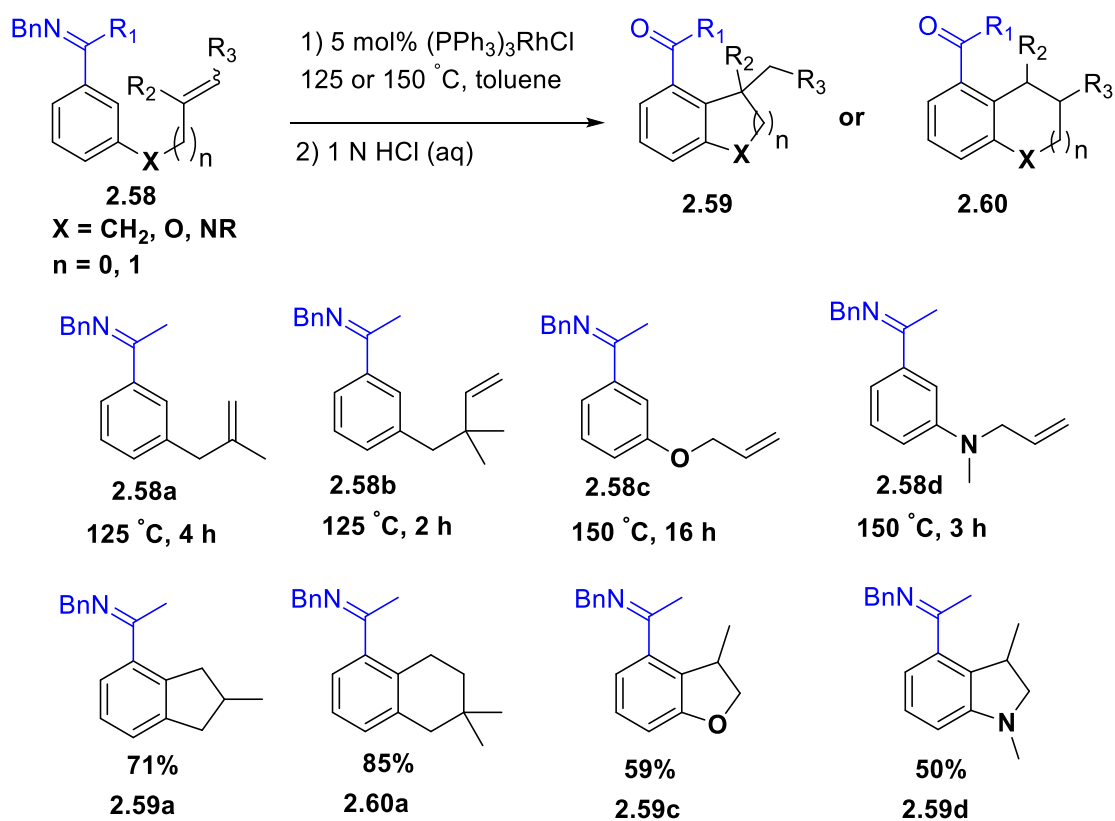
Scheme 2.13. Annulation of aromatic imines via directed C-H activation.

In 2001, Ellman et al reported a method for intramolecular hydroarylation of aroatic

imines in which alkene is tethered *meta* to the imine (Scheme 2.13).[25a] Annulation occurs

selectively to the more hindered *ortho* site to furnish functionalized bicyclic ring systems. This

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protocol is useful for synthesis of functionalized indane, tetralane, dihydrobenzofuran, and dihydroindole derivatives from simple starting materials.

Later in 2004, Ellman et al reported the a highly enantioselective and efficient protocol for the intramolecular imine-directed C-H/olefin coupling reaction using Rh(I) catalytst in presence of chiral phosphoramidite ligands as shown in Scheme 2.14.[25c] This methodolgy was used for the synthesis of biologically active molecules possessing dihydropyrroloindole cores.[25d]
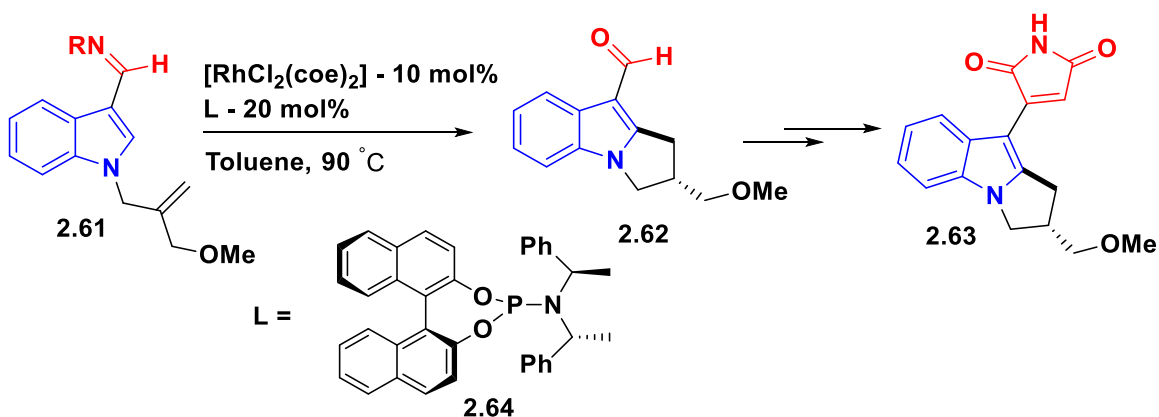
Scheme 2.14. Enantioselective synthesis of biologically active molecules possessing dihydropyrroloindole via catalytic C−H bond activation.

In 2013, Ding and cowrkers disclosed a cobalt-NHC-catalytic system for intramolecular olefin hydroarylation of N-allyl indole derivatives (Scheme 2.15).[32] The reaction proceeds via rate limiting C-H bond activation through chelation assistance of imine directing group. This reaction provides staightforward approach for synthesis of dihydropyrroloindole and tetrahydropyridoindole derivatives under mild conditions. The regioselectivity of intramolecular
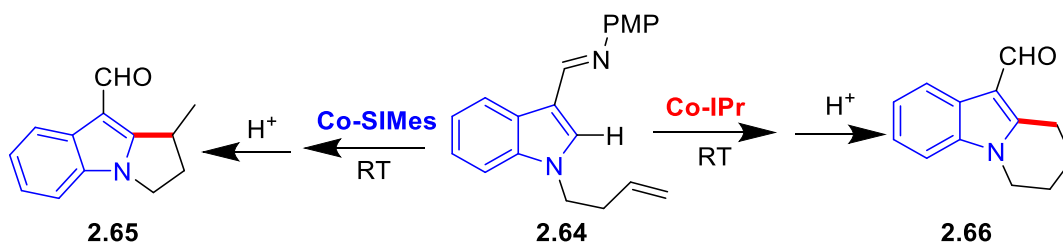
Scheme 2.15. Cobalt-catalyzed intramolecular olefin hydroarylation.

hydroarylation was acheived by the steric nature of the NHC ligand as depicted in Scheme 2.15.

However, in cyclometalation approach the substrate structures are limited by the requirement of having carbonyl derivative-based DGs *meta* to the tethered alkene moiety. We hypothesize that incorporation of DGs into the tethered alkene moiety would eliminate the need for additional DGs and achieve broader substrate scopes (Scheme 2.16). This modified cyclometalation approach requires that the metal coordination by tethered DG to be strong enough to promote *ortho*-aromatic C−H activation, yet weak enough to allow the resulting metallacycle (**A**) to undergo facile ligand substitution via DG dissociation and alkene coordination (**A→B**). Subsequent ring-closure via intramolecular alkene arylmetalation (**B→C**) is envisioned to occur without DG assistance.
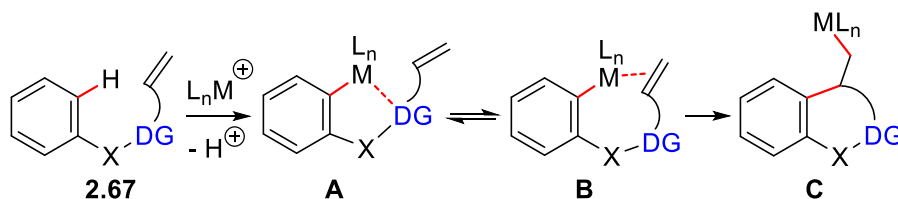
Scheme 2.16. This study: alkene-tethered directing group for C-H activation.

We herein report the first demonstration of this catalysis design with intramolecular alkene hydroarylation of N-aryl acrylamides (**2.68**) to form oxindoles (**2.70**), which are important synthetic targets due to their biological activities (Scheme 2.17).[33] Utilizing the amide carbonyl as a tethered DG for aromatic C−H activation (**2.68→2.69**), this Ru-catalyzed cyclization process does not require additional DG assistance and tolerates a broad range of aromatic and vinyl substituents. With the redox-neutral nature and high atom-efficiency of alkene hydroarylation, the current method for oxindole synthesis complements existing strategies such as N-aryl acrylamide cyclizations via free radical processes an Heck-type oxidative alkene functionalizations.[25e, 33-35]
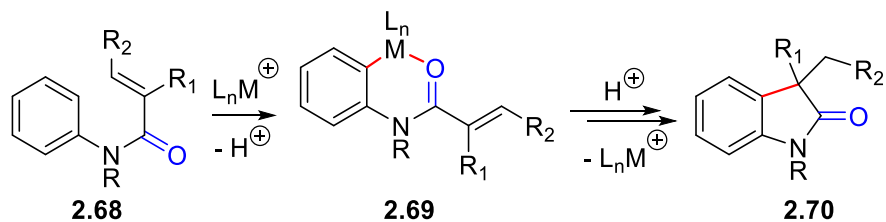
Scheme 2.17. Target catalytic process for oxindole synthesis.

2.2. Optimization of Reaction Conditions

Current catalyst development was guided by results from our previous report on Ru/N-heterocyclic carbene (NHC)-catalyzed [3+2] annulation between N-H aromatic ketimines and alkynes, which was promoted by [Ru(cod)(η^3-methallyl)$_2$] pre-catalyst and IPr ligand.[36] The proposed mechanism shared key common features with the envisioned pathway for target oxindole synthesis, which included DG assistance for aromatic C-H activation (imine C=N vs. amide C=O) and *5-exo-trig* ring-closure by intramolecular 1,2-insertion (imine into M-alkenyl vs. alkene into M-aryl). Thus, we focused our attention on Ruthenium catalysts to evaluate conditions for a model reaction with N-methyl-N-phenyl methacrylamide (**2.68a**).

Table 2.1. Development of catalytic reaction conditions (Part I).
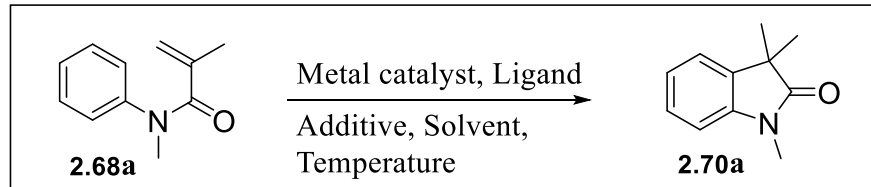
Catalyst	Additive	Solvent	Temp ($^\circ$C)	Yield (%)
[RuH$_2$(CO)(PPh$_3$)$_3$]	-	Dioxane	120	0
[Ru$_3$(CO)$_{12}$]	-	Dioxane	120	0
[RuCl$_2$(p-cymene)]$_2$	-	Dioxane	120	0
[Ru(COD)(Methallyl)$_2$]	NaOAc	Dioxane	120	0
[RuCl$_2$(cod)]$_2$	NaOAc	Dioxane	120	43[a]
[RuCl$_2$(cod)]$_2$	AgOAc	Dioxane	120	20[b]
[RuCl$_2$(p-cymene)]$_2$[c]	NaOAc	Dioxane	120	61[a]
[RuCl$_2$(p-cymene)]$_2$[c]	AgOAc	Dioxane	120	55[a]
[RuCl$_2$(p-cymene)]$_2$[c]	K$_2$CO$_3$	Dioxane	120	20[b]
[RuCl$_2$(p-cymene)]$_2$[c]	AgSbF$_6$ + Pivalic aicd	Dioxane	120	10[b]
[RuCl$_2$(p-cymene)]$_2$[c]	NaOAc	Toluene	120	60[a]
[RuCl$_2$(p-cymene)]$_2$[c]	NaOAc	THF	120	30[b]
[RuCl$_2$(p-cymene)]$_2$[c]	NaOAc	DCE	120	<20[b]
[RuCl$_2$(p-cymene)]$_2$[c]	NaOAc	DME	120	<20[b]
[RuCl$_2$(p-cymene)]$_2$[c]	NaOAc	DMF	120	<10[b]
[RuCl$_2$(p-cymene)]$_2$[c]	NaOAc	CH$_3$CN	120	<5[b]

0.17 mmol of Substarte, 10 mol% Catalyst, 20 mol% additive, 1 mL of Solvent.

a = Isolated yield. b = estimated based on TLC. c = 5 mol% of the catalyst

Table 2.2. Development of catalytic reaction conditions (Part II).
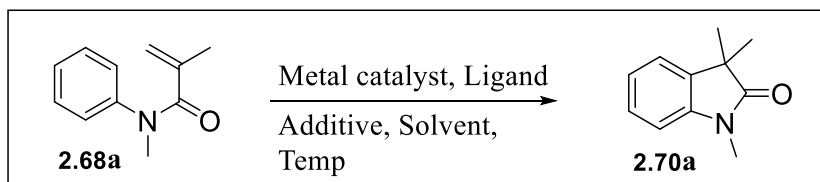
Catalyst	Additive	Ligand	Solvent	Temp (° C)	Yield (%)
[RuCl$_2$(p-cymene)]$_2$	NaOAc(20mol%)	-	Dioxane	140	73[a,c]
[RuCl$_2$(p-cymene)]$_2$	NaOAc(20mol%)	Phen	Dioxane	140	82[a,c]
[Ru(COD)(Methallyl)$_2$]			Dioxane	120	0[b]
[Ru(COD)(Methallyl)$_2$]		PPh$_3$	Dioxane	120	<5[b]
[Ru(COD)(Methallyl)$_2$]		PCy$_3$	Dioxane	120	<10
[Ru(COD)(Methallyl)$_2$]		PMe$_3$	Dioxane	120	0[b]
[Ru(COD)(Methallyl)$_2$]		Phen	Dioxane	120	0[b]
[Ru(COD)(Methallyl)$_2$]		IPr	Dioxane	120	28[a]
[Ru(COD)(Methallyl)$_2$]		SIPr	Dioxane	120	25[a]
[Ru(COD)(Methallyl)$_2$]	AcOH (1equiv)	IPr	Dioxane	120	46[a]
[Ru(COD)(Methallyl)$_2$]	AcOH(2equiv)	IPr	Dioxane	120	**81[a]**
-	AcOH(2equiv))	-	Dioxane	120	0
[Ru(COD)(Methallyl)$_2$]	AcOH(2equiv)	SIPr	Dioxane	120	80[a]
[Ru(COD)(Methallyl)$_2$]	AcOH(2equiv)	SIMes	Dioxane	120	78[a]
[Ru(COD)(Methallyl)$_2$]	AcOH(2equiv)	IMes	Dioxane	120	75[a]
[Ru(COD)(Methallyl)$_2$]	Pivalic acid(2equiv)	IMes	Dioxane	120	<50[b]
[Ru(COD)(Methallyl)$_2$]	CF$_3$COOH(2equiv)	IMes	Dioxane	120	<70[b]
[Ru(COD)(Methallyl)$_2$]	AcOH(2equiv)	IPr	Dioxane	120	54[c]
[Ru(COD)(Methallyl)$_2$]	AcOH(2equiv)	IPr	Toluene	120	79[a]
[Ru(COD)(Methallyl)$_2$]	AcOH(2equiv)	IPr	DCE	120	<60[b]
[Ru(COD)(Methallyl)$_2$]	AcOH(2equiv)	IPr	THF	120	<60[b]

0.17mmol of Substarte, 10mol% Catalyst, 20 mol% additive, 1mL of Solvent.
a = Isolated yield   b = estimated based on TLC   c = 5mol% catalyst and Ligand

We found that intramolecular alkene hydroarylation with **2.68a** was promoted by 10 mol% [Ru(cod)(η³-C₄H₇)₂]/IPr and 2 equivalents of acetic acid at 120 °C and in dioxane solvent. Under these conditions, the oxindole product **2.70a** was formed in 81% yield over 24 hours and no other byproducts were detected. [37]
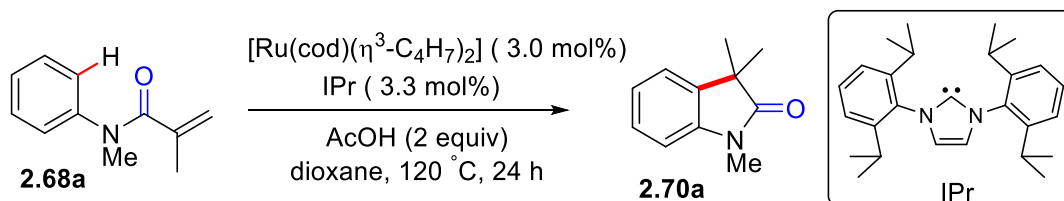
Scheme 2.18. Optimized Ru/NHC catalyst system for current study.

2.3. Substrate Scope

With the standard reaction conditions established, various N-aryl acrylamides (**2.68**) were studied for Ru(II)-catalyzed intramolecular hydroarylation (Scheme 2.19). In general, oxindole products were formed without the detection of 2-quinolone byproducts.[37] Scope of the N-aryl moiety was studied with N-aryl-N-methylmethacrylates to generate products **2.70a-I′**. Good yields were acquired for substrates with *para*-electron-withdrawing groups including halogens, CF_3, NO_2, acyl, and ester groups (products **2.70d**-**j**), although *para*-iodine and cyano functionality led to no product formation. In comparison, reduced reactivity was observed for substrates with *para*-electron-donating groups. The *p*-anisyl substrate led to product **2.70c** in a moderate yield of 65%, while the *p*-tolyl substrate required the use of CF_3CO_2H additive in place of acetic acid to form **2.70b** in 61% yield. With *ortho*-fluoro substituent, harsher reaction conditions of 140 °C over 48 h was necessary to give product **2.70k** in 73% yield. With *meta*-fluoro substituent, mixed regioisomers **2.70I**/**2.70I′** corresponding to C–H activation *para*- vs. *ortho*-to-F were formed in 84% combined yield and 9:1 selectivity favoring the *ortho*-isomer **2.70I′**. Replacing N-methyl with another N-phenyl or N-benzyl moiety led to products **2.70m**

and **2.70n** in satisfactory yields, with the latter providing a convenient synthetic handle for oxindole N-deprotection.
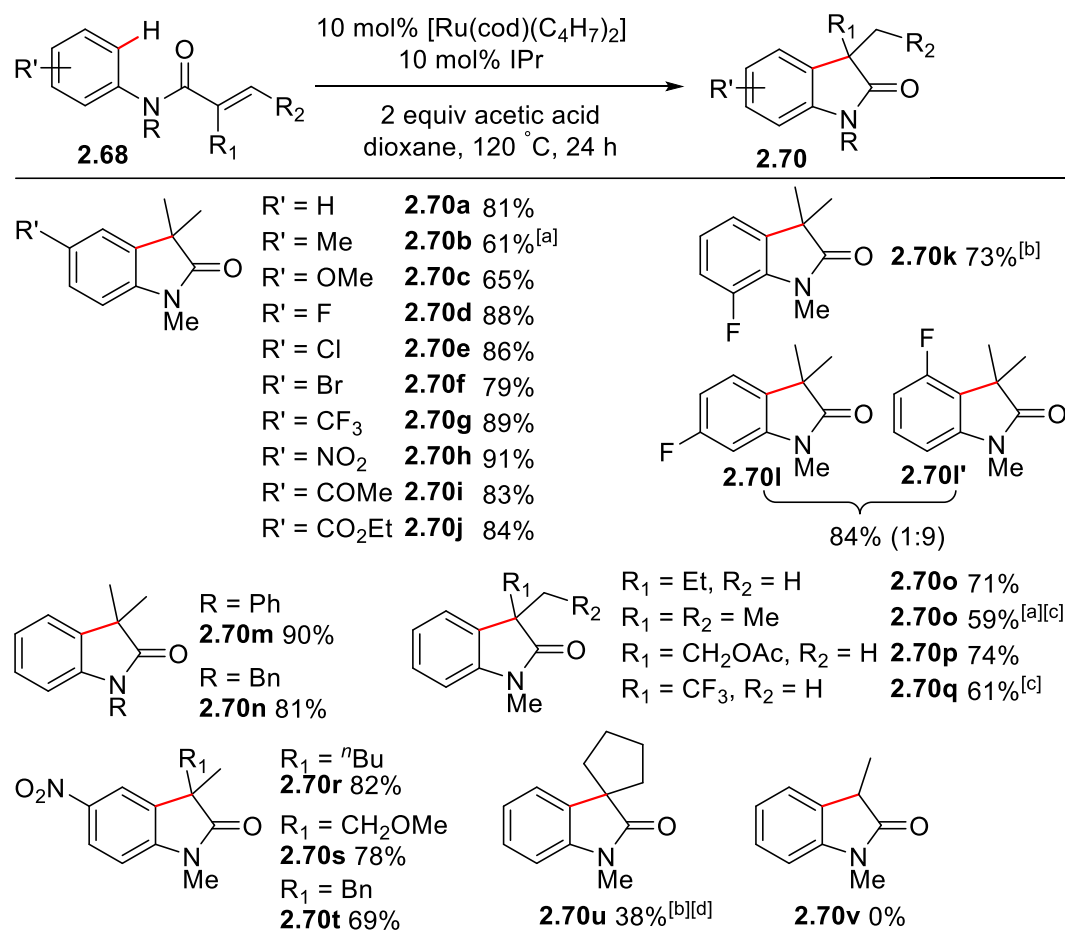
General reaction conditions: 2.68 (0.17 mmol, 1.0 equiv), 2.71 (0.10 equiv), 2.72 (0.10 equiv), AcOH (2.0 equiv), dioxane (1.0 mL), 120 °C, 24h; averaged isolated yields of two runs. [a] Using CF_3CO_2H in place of AcOH. [b] Reaction at 140 °C for 48 h. [c] Using 0.20 equiv 3a and 4a; reaction at 155 °C for 72 h. [d] Using 10 mol % [Ru(p-cymene)Cl$_2$] as Ru catalyst precursor and 2 0 mol% 1,10-phenanthroline ligand.

Figure 2.1. Scope of the intramolecular alkene hydroarylation for oxindole synthesis.

Scope of the alkene moiety was studied by modification of α- and β-substituents in N-aryl-N-methyl substrates to form products **2.70o-v**. Replacing α-methyl with ethyl and acetoxymethyl groups in methacrylamide backbone did not cause major loss of reactivity and

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gave products **2.70o** and **2.70p** in 71% and 74% yield respectively. In contrast, the cis-2,3-dimethylacrylamide analog was much less reactive and required the use of CF_3CO_2H additive, 20 mol% Ru/NHC catalyst loading, as well as 155 °C over 72 h to give 2.70o in 59% yield. Such harsher conditions were also required for the α-CF_3 analog of **2.68a** to form product **2.70q** in 61% yield, giving a rare example of synthesizing 3-CF_3-substituted oxindoles that were not accessible via established methods such as free radical cyclization.[34] The scope of α-substituents was further explored with N-4-nitrophenyl-N-methyl acrylamides to afford products **2.70r-t** in 69-82% yields containing 3-butyl, -methoxymethyl, and -benzyl groups. Considering the high values of spirooxindoles in drug development,[33] we attempted the synthesis of product **2.70u** with a 1-cyclopentenecarboxylic amide substrate. However, only trace amount of **2.70u** was formed under standard conditions. A modified catalyst-ligand combination of 10 mol% [Ru(p-cymene)Cl$_2$] and 20 mol% 1,10-phenanthroline ligand allowed **2.70u** to be synthesized in 38% yield over 48 h of heating at 140 °C. Lastly, removing α-methyl from substrate **2.68a** led to total loss of reactivity and failure to form corresponding oxindole product **2.70v**.[38]

2.4. Proposed Mechanism

Current results on structure-reactivity correlations provide several important mechanistic insights as follows: (1) The general higher reactivity for electron-poor arene substrates than electron-rich arenes (products **2.70a-j**) suggests that the hydroarylation process does not occur via electrophilic aromatic substitution. Thus, we propose an amide-directed C–H activation that occurs by a proton abstraction pathway such as concerted metalation-deprotonation (CMD),[39] and is either the rate-limiting step or a pre-rate-limiting equilibrium. This hypothesis resonantes with the proposed C–H activation mechanism in our prior report on Ru/NHC-catalyzed imine/alkyne [3+2] annulation.[36] (2) The significantly lower reactivity for substrates with
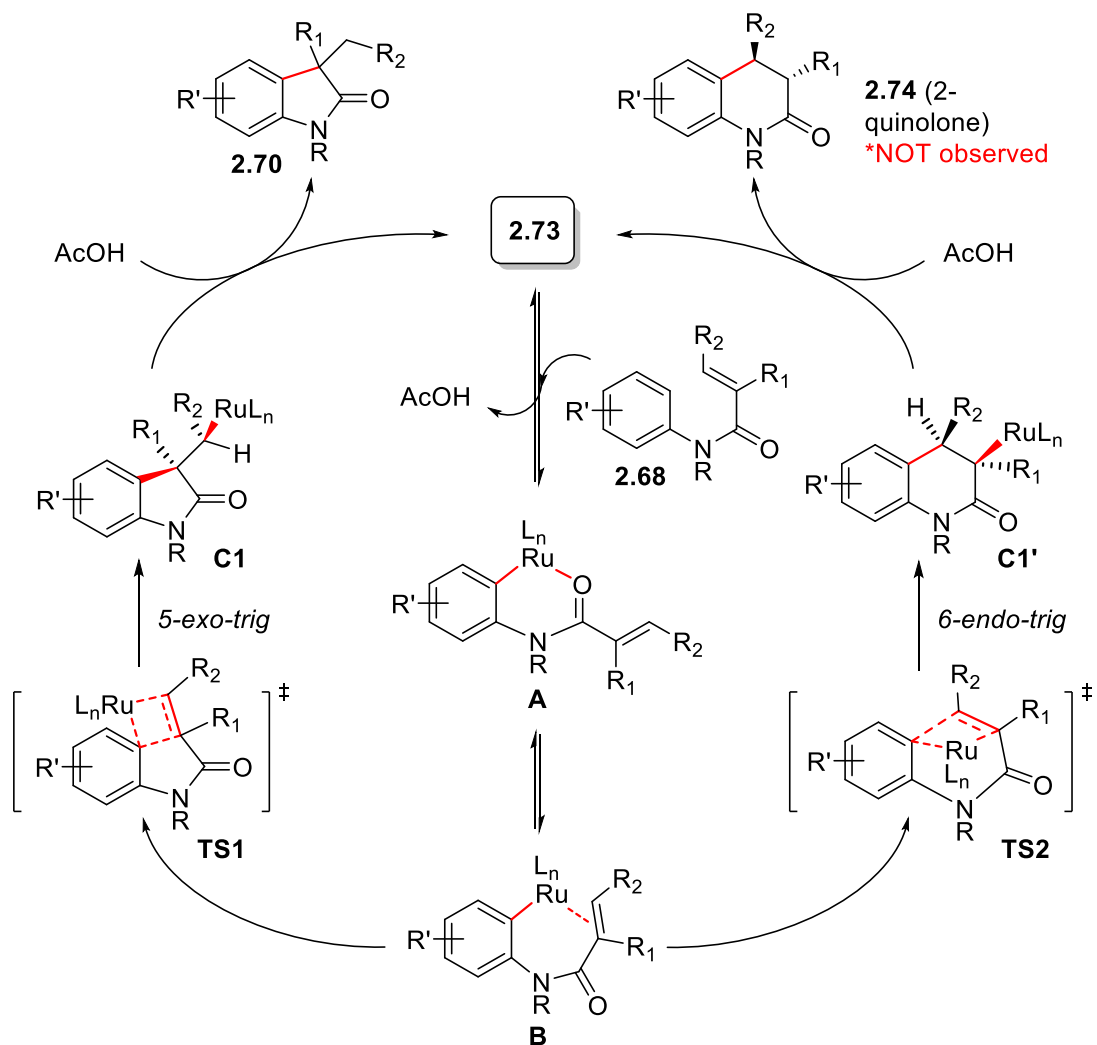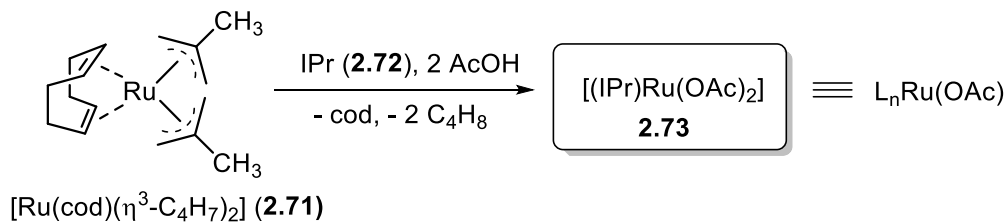
Scheme 2.19. Proposed catalyst activation process and catalytic cycles.

ortho-F substitution or larger alkene substituents (products **2.70k**, **2.70o**, **2.70q** and **2.70u**)

suggests that the cyclization step by intramolecular alkene arylmetalation sterically inhibited by

bulky alkene or arene moieties. (3) The exclusive formation of 5-membered oxindoles over 6-

membered 2-quinolones further supports a pronounced steric effect on the cyclization process,

with the former favored by formation of a less crowded alkyl C−Ru bond and the later favored

by electronic stabilization of the resulting enolate C−Ru bond (see Scheme 2.20 for a more

detailed mechanism description).

With a major focus of current study on new method development for C−H

functionalization, we carried out a series of kinetic experiments to explore details of the

proposed deprotonation pathway for C−H activation (Scheme 2.21). Firstly, intramolecular

competition with unsymmetrical N,N-diaryl substrates **2.68w** and **2.68x** under standard catalytic

conditions showed slightly higher C−H alkylation reactivity for more electron-deficient aryls

based on yield comparison (1.2:1 for phenyl vs. *p*-anisyl, and 1.1:1 for 4-fluorophenyl vs. phenyl

moiety) (Scheme 2.21a). Such reactivity differences were smaller than expected and may be

cuased by intramolecular electronic effects with the non-transformed aryl on reacted aryl.

Secondly, initial-rate ^{1}H NMR kinetics with electronically differentiated substrates **2.68a**, **2.68c**

and **2.68g** showed a clear reactivity disparity that favors more electron-deficient aryls, with

roughly 8:5:1 relative rate for 4-trifluoromethylphenyl vs. phenyl vs. *p*-anisyl moiety (Scheme

2.21b). Lastly, reaction rate comparison between **2.68a** and its C_6D_5-analog (***d5*-2.68a**) led to the

determination of a normal isotope effect (k_H/k_D=2.1) (Scheme 2.21c). Notably, the initial-rate

kinetic experiment with ***d5*-2.68a** led to a 1.2:1 product mixture of ***d4*-2.70a** and ***d3*-2.70a**. Neither

product incorporated deuterium at 3,3-dimethyl substituents, which supports the involvement of

acetic acid additive as an external proton source in the hydroarylation process.[40] Compared to ***d4*-**

2.70a, ***d3*-2.70a** contained one less aromatic deuterium, which can be attibuted to *ortho*-H/D

exchange of ***d5*-2.68a** via an equilibrium of Ru-mediated C−H activation/cyclometalation and

protonation of Ru-aryl linkage (likely by acetic acid). Overall, results from these studies are

consistent with a reversible, amide-directed aromatic C–H activation via proton abstraction, which precedes the rate-limiting alkene arylmetalation via insertion into the Ru-aryl linkage.[41]
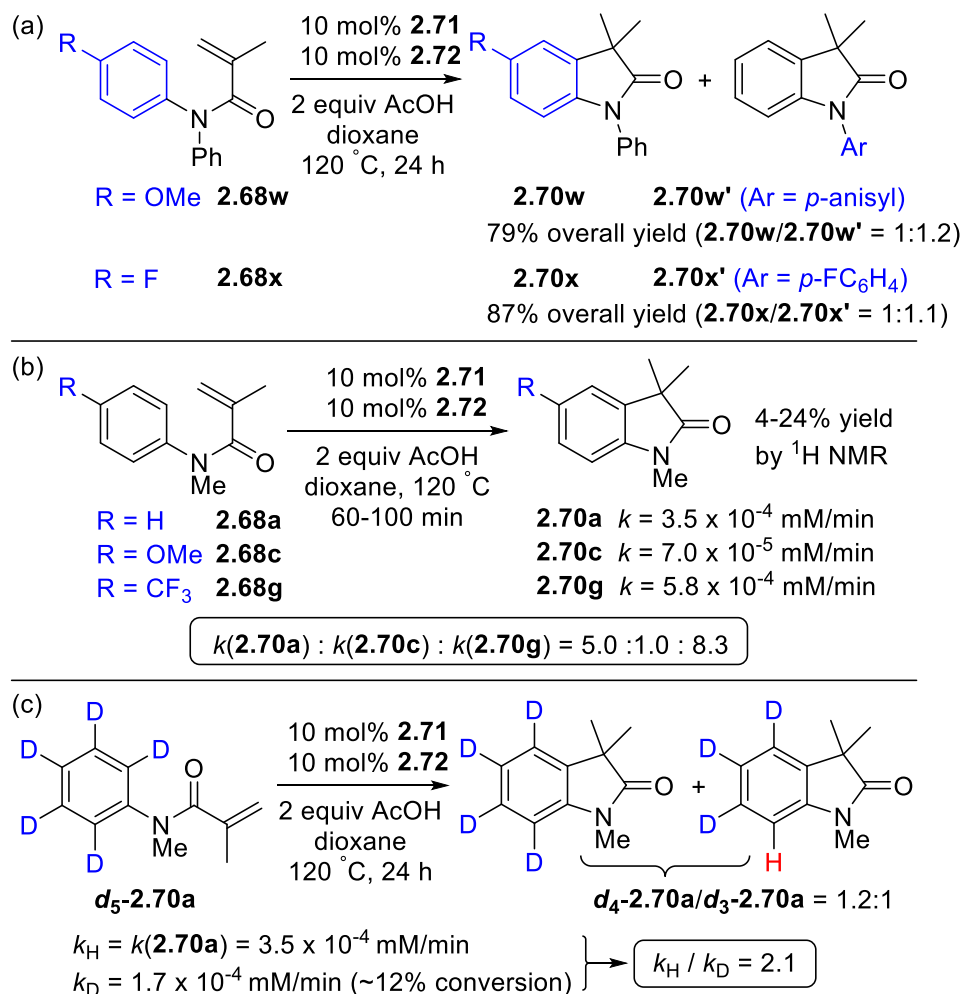
Scheme 2.20. Results from reaction mechanism studies. (a) Intramolecular competition experiments. (b) Comparing rate constants at early conversions to determine aromatic substitution effect on reactivity. (c) Deuterium labeling study and measurement of the kinetic isotope effect.

To explore the potential of current method towards practical synthetic applications, we first studied hydroarylation of **2.68a** under scale-up conditions (Scheme 2.22a). Gratifyingly, solvent volume reduction enabled scale-up reactions to proceed smoothly at reduced catalyst loadings. Thus, gram-scale synthesis of **2.68a** was successfully carried out with 0.70 mM substrate concentration and 2.5 or 5 mol% catalyst loading to achieve 80% and 92% isolated

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yield respectively. Next, we incorporated the hydroarylation method into a new synthetic route

for an oxindole-based progesterone receptor antagonist (**2.75**) (Scheme 2.22b).[42]

Substrate Quantity	Solvent Volume	Substrate Concentration	Catalyst/Ligand Loading	Isolated Yield
300 mg	10 mL	0.17 mM	10 mol%	66%
300 mg	5 mL	0.34 mM	5 mol%	82%
1.0 g	8 mL	0.70 mM	5 mol%	92%
1.0 g	8 mL	0.70 mM	2.5 mol%	80%
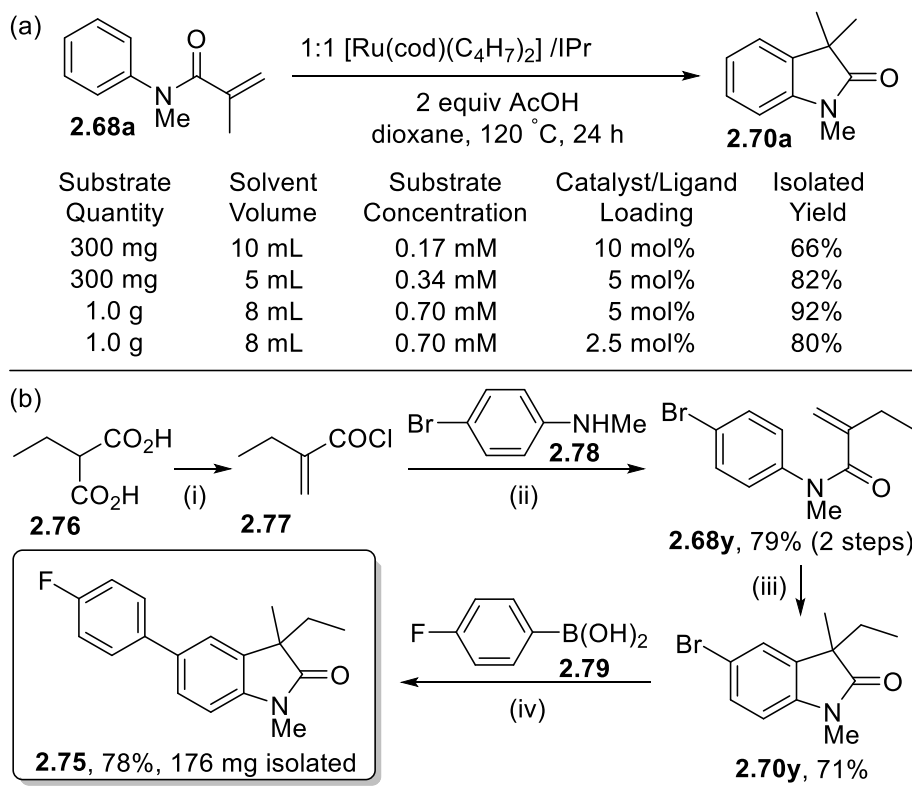
(i) Stage 1: 1.5 equiv Et_2NH, AcOEt solvent, 0 C, 5 min; then 1.5 equiv
(HCHO)n, reflux for 2 h. Stage 2: $SOCl_2$, N_2, 50 C, 5 h. (ii) 2 equiv Et_3N,
CH_2Cl_2, 0 °C to r.t., 6 h. (iii) 10 mol% 2.71/2.72, 2 equiv AcOH, dioxane,
120 °C, 24 h. (iv) 5 mol% $PdCl_2$, 1 equiv 4-$FC_6H_4B(OH)_2$, 2 equiv K_2CO_3,
50% $EtOH/H_2O$, r.t., 24 h.

Scheme 2.21. Studies towards practical synthetic applications. (a) Reactions under scale-up
conditions. (b) New synthesis of a progesterone receptor antagonist.

The synthesis started with turning ethylmalonic acid into 2-ethylacryloyl chloride via an

established procedure.[43] The crude product was subjected to Et_3N-mediated amidation with 4-

bromo-N-methylaniline to afford N-4-bromophenyl-N-methyl-2-ethylacrylamide (**2.68y**) in 79%

yield over two steps. Intramolecular hydroarylation with **2.68y** was carried out using 10 mol%

Ru/NHC catalyst to form oxindole product **2.70y** in 71% yield. Lastly, Pd-catalyzed Suzuki

coupling between **2.70y** and 4-fluorophenylboronic acid gave desired product **2.75** in 78% yield.

Although **2.75** was acquired as a racemic mixture, the current method has the potential to be further developed into an enantioselective catalysis based on the proposed catalyst-enabled construction of quaternary chiral center at the oxindole 3-position.

2.5. Conclusion

In summary, we have developed a Ru-catalyzed intramolecular alkene hydroarylation with N-aryl acrylamides for oxindole synthesis. This redox-neutral, 5-exo-trig cyclization occurs via a proposed tandem sequence of aromatic C–H activation and intramolecular alkene arylmetalation. The amide-directed C–H activation is promoted by electron-withdrawing aromatic substituents and does not require the assistance of additional directing groups.

2.6. General Experimental Procedures and Reagent Availability

Unless otherwise noted, all manipulations were carried out under a nitrogen atmosphere using standard Schlenk-line or glove box techniques. All glassware was oven-dried for at least 1 h prior to use. Toluene and hexane solvents were degassed by purging with nitrogen for 45 min and dried with a solvent purification system (MBraun MB-SPS). THF and dichloromethane were dried over activated 3Å molecular sieves and degassed by purging with nitrogen. Other reagents and starting materials for substrate synthesis were purchased from commercial vendors and used as received. TLC plates were visualized by exposure to ultraviolet light.

Organic solutions were concentrated by rotary evaporation at ~10 torr. Flash column chromatography was performed with 40–63 microns silica gel. ^{1}H NMR and ^{13}C NMR spectra were obtained on a 400 MHz spectrometer, and chemical shifts were recorded relative to residual protiated solvent. Both ^{1}H and ^{13}C NMR chemical shifts were reported in parts per million downfield from tetramethylsilane (δ = 0 ppm). ^{19}F NMR spectra were obtained at 282.4

MHz, and all chemical shifts were reported in parts per million upfield of CF_3COOH ($\delta = -78.5$ ppm). High resolution mass spectra were obtained at a Waters HRMS spectrometer.

2.6.1. Experimental Procedure for Preparation of Acrylamide Substrates

2.6.1.1. *General Procedure for Preparation of Substrates 2.68a- 2.68g and 2.68i- 2.68n[44, 45]*
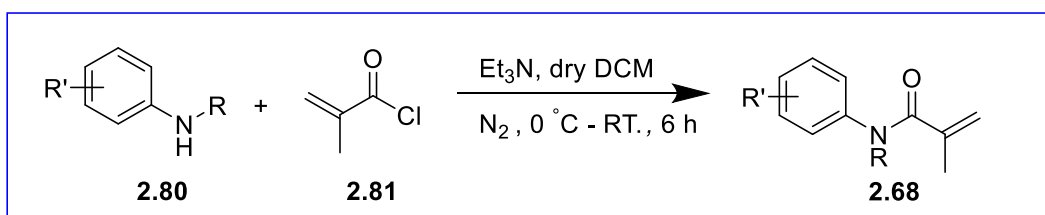
R = Me   R' = *p*-H   **2.68a** - 84% (white solid)   R' = *p*-CF$_3$ **2.68g** - 76% (yellow liquid)
         R' = *p*-Me   **2.68b** - 87% (yellow liquid) R' = *p*-COMe   **2.68i** - 78% (yellow liquid)
         R' = *p*-OMe **2.68c** - 94% (yellow liquid) R' = *p*-CO$_2$Et **2.68j** - 75% (yellow liquid)
         R' = *p*-F   **2.68d** - 79% (yellow liquid) R' = *o*-F   **2.68k** - 73% (yellow liquid)
         R' = *p*-Cl   **2.68e** - 81% (white solid)   R' = *m*-F   **2.68l** - 79% (yellow liquid)
         R' = *p*-Br   **2.68f** - 85% (white solid)

         R' = *p*-H   R = Ph   **2.68m** - 92% (white solid)
         R' = *p*-H   R = Bn   **2.68n** - 94% (white solid)

Scheme 2.22. Synthesis of acryl amides (Procedure 1).

Into a 250 mL round-bottom flask equipped with a magnetic stir-bar was added solution of aniline **2.80** (1.0 g, 1 equiv) in DCM (60 mL) and triethylamine (2 equiv). The mixture was stirred at 0 °C, and methacryloyl chloride **2.81** (1.5 equiv) was added under nitrogen atmosphere. The resulting solution was allowed to warm up to room temperature and stirred for 6 hours, followed by the addition of H_2O (150 mL) to quench excess acyl chloride. The mixture was settled in a separation funnel, and the organic layer was extracted, washed with brine (3 x 100 mL), and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (0 to 6% ethyl acetate in hexanes).

2.6.1.2. *Preparation of Substrates 2.68o and 2.68u*
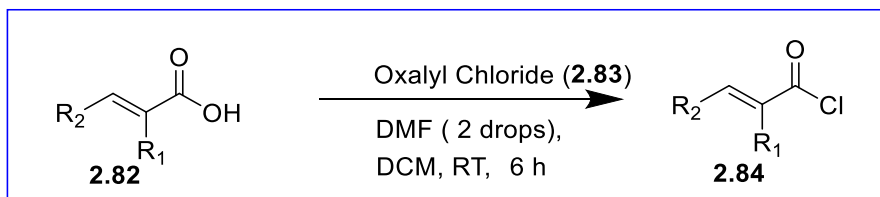
Scheme 2.23. Synthesis of acryloyl chlorides (Procedure 1).

Into a 50 mL round-bottom flask equipped with a magnetic stir-bar was added solution of

acrylic acid **2.82** (1.5 g, 1 equiv) in dichloromethane (DCM, 20 mL), followed by dropwise

addition of oxalyl chloride (2 equiv) and 2 drops of DMF under nitrogen atmosphere. The

mixture was stirred at room temperature for 6 hours before removing all volatiles under reduced

pressure. The crude product was used for the next step without purification.

The general procedure for acrylamide synthesis was applied for the reaction between

corresponding N-methylaniline and crude acryloyl amide compounds.

Compound **2.68o** is isolated in 76% yield as a white solid.

Compound **2.68u** is isolated in 71% yield as a white solid.

2.6.1.3. *Preparation of Substrates 2.68h and 2.68t[45]*

Scheme 2.24. Synthesis of acryl amides (Procedure 2).

Into a 250 mL round-bottom flask equipped with Liebig condenser and a magnetic stir-

bar was added a solution of N-methyl- 4-nitroaniline **S1a** (1.0 g, 1 equiv) in benzene (100 mL)

and potassium carbonate (1.82 g, 2 equiv). Under N_2 atmosphere, the reaction mixture was added

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with acryloyl chloride **2.84** (1.5 equiv), transferred to an oil bath, and refluxed under stirring for

24h. After cooling to room temperature, the reaction mixture was added with water (150 mL)

and continued to with stirring for 30 min. The reaction mixture was then extracted with ethyl

acetate (3 x 100 mL), and the combined organic phases were evaporated under reduced pressure

to remove all volatiles. The resulting crude product was purified by column chromatography (0

to 8% ethyl acetate in hexanes).

The compound **2.68h** is isolated in 69% yield as a yellow solid.

The compound **2.68t** is isolated in 63% yield as a yellow solid.

2.6.1.4. *Preparation of Substrate 2.68s[46]*
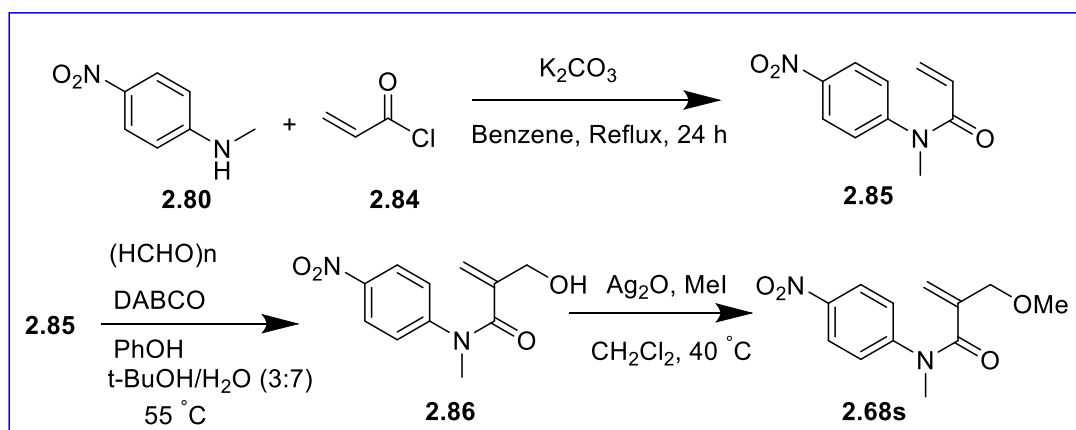
Scheme 2.25. Synthesis of acryl amides (Procedure 3).

i) Synthesis of intermediate **2.85**: the synthetic procedure for substrate **2.68h**

2.68h and **2.68ht** was applied for the reaction between **2.80** and parent acryloyl chloride

(**2.84**) to obtain **2.85**.

ii) Synthesis of intermediate **2.86**: Into a 10 mL Schlenk tube equipped with a magnetic

stir-bar was added paraformaldehyde (5 equiv), DABCO (1 equiv), phenol (0.25 equiv) and 4

mL of mixed solvent (3:7 *t*-BuOH/H$_2$O). The mixture was stirred at 55 °C until all reactants were

dissolved. Intermediate **2.85** (1.0 g, 1 equiv) was then added slowly for 5 min, and the reaction

mixture was stirred at 55 °C for three days. After cooling to room temperature, the mixture was evaporated under reduced pressure to remove t-BuOH and extracted with ethyl acetate (3 x 100 mL). The combined organic phases was dried over anhydrous sodium sulfate and concentrated over rotary evaporator to remove all volatiles. The resulting crude mixture was subjected to column chromatography (0 to 17% ethyl acetate in hexanes) to obtain the desired intermediate **2.86** in 45% yield as light yellow oil.

iii) Methylation of **2.86** to synthesize substrate **2.68s:** Into a 100 mL round-bottom flask equipped with a magnetic stir-bar was added a solution of intermediate **2.86** (1.5 g, 1 equiv) in DCM (40 mL), Ag$_2$O (2 equiv), and iodomethane (3 equiv). The resulting mixture was stirred at 40 ºC and monitored by TLC to ensure the complete conversion of **2.86**. The reaction mixture was cooled to room temperature and filtered. The filtrate was evaporated under reduced pressure to remove all volatiles. The resulting crude mixture was purified by column chromatography (0 to 10% ethyl acetate in hexanes) to afford compound **2.68s** in 71% yield as a yellow solid.

2.6.1.5. *Preparation of Substrate 2.68r*
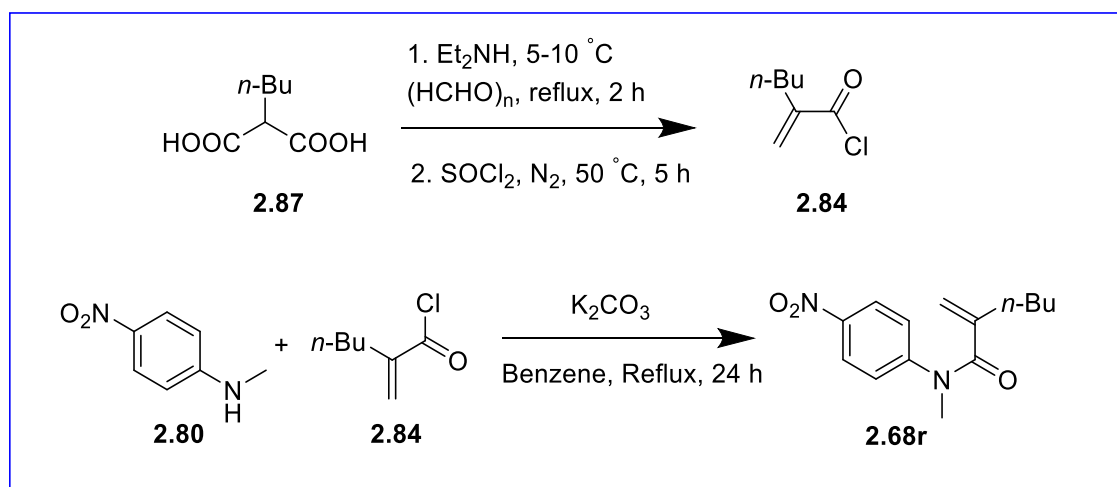
Scheme 2.26. Synthesis of acryl amides (Procedure 4).

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Into a 100 mL round-bottom flask equipped with a magnetic stir-bar was added a solution of butyl malonic acid **2.87** (2.0 g, 1 equiv) in dry ethyl acetate (50 mL). The solution was cooled to 5 °C and added with diethyl amine (1.5 equiv) under nitrogen atmosphere. After stirring the mixture for 5 min, paraformaldehyde (1.5 equiv) was added slowly and the resulting mixture was refluxed for 2 h. The reaction mixture was cooled to room temperature and quenched with water (100 mL). The p^H value of the solution was brought to ~1 by adding concentrated HCl before being extracted with ethyl acetate (3 x 75 mL). The combined organic phases were dried over anhydrous sodium sulfate and concentrated at rotary evaporator to remove all volatiles. The crude 2-butyl acryloyl chloride was acquired as a pale-yellow liquid and used for the next step without purification.

Synthesis of substrate **2.68r**: the synthetic procedure for substrate **2.68h** and **2.68t** was applied for the reaction between **2.80** and **2.84** to obtain **2.68r**. The compound **2.68r** is purified by column chromatography (0 to 8% ethyl acetate in hexanes) in 65% yield as yellow solid.

2.6.1.6. *Preparation of Substrate 2.68p[46]*
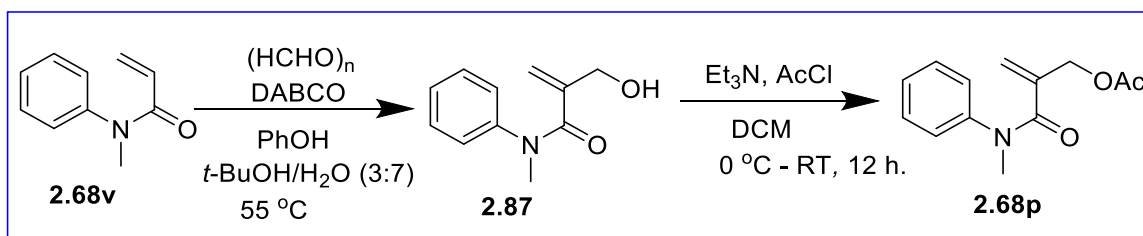
Scheme 2.27. Synthesis of acryl amides (Procedure 5).

➤ Synthesis of intermediate **2.87**: the synthetic procedure for intermediate **S4** was applied for the reaction with N-methyl-N-phenyl acrylamide (**2.68**) to afford intermediate **2.87**.

➤ Acetylation of **2.87** to synthesize substrate **2.68p**
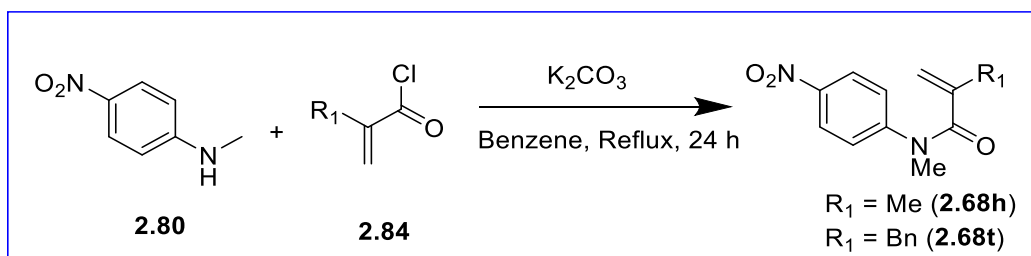
Into a 100 mL round-bottom flask equipped with a magnetic stir-bar was added a solution

of **2.87** (1.0 g, 1 equiv) in DCM (30 mL) and triethylamine (2 equiv). The mixture was cooled to

0 °C and added with acetyl chloride (1.5 equiv) under nitrogen atmosphere, then stirred at room

temperature for 12h. The reaction mixture was then added with water (100 mL) to quench the

excess acetyl chloride and settled in a separation funnel. The organic layer was collected, washed

with brine (3 x 50 mL), and dried over anhydrous sodium sulfate. All volatiles were removed

under reduced pressure and the resulting crude product was purified by column chromatography

(0 to 10% ethyl acetate in hexanes) to afford the compound **2.68p** in yield 55% as a white solid.

2.6.1.7. *Preparation of Substrate 2.68q*
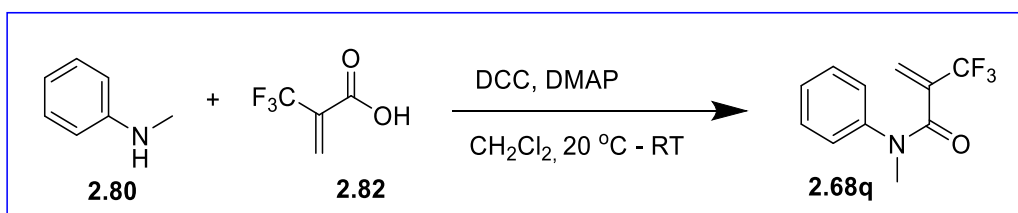
Scheme 2.28. Synthesis of acryl amides (Procedure 6).

Into a 100 mL round-bottom flask equipped with a magnetic stir-bar was added N-methyl

aniline **2.80** (2 equiv), acrylic acid **2.82** (1.0 g, 1 equiv) and dichloromethane (40 mL). The

mixture was cooled to -20 °C before the addition of a solution of DCC (1.3 equiv) and DMAP

(0.2 equiv) in dichloromethane (10 mL). The resulting mixture was stirred overnight at room

temperature, and then evaporated under reduced pressure to remove all volatiles. The crude

product was subjected to column chromatography (6% ethyl acetate in hexanes) to obtain

compound **2.68q** in 62% yield as a white solid.

2.6.2. General Procedure for Ru-Catalyzed Intramolecular Alkene Hydroarylation

Into a 4 mL scintillation vial equipped with a magnetic stir bar was placed [Ru(cod)(η^3-

C$_4$H$_7$)$_2$] (0.017 mmol), IPr (0.017 mmol), and N-aryl acrylamide substrate (0.17 mmol). Dioxane

(1.0 mL) and acetic acid (0.34 mmol) were subsequently added. The reaction mixture was stirred at room temperature for 5 minutes and the vial was sealed with a silicone-lined screw-cap and electrical tape before being transferred out of the glovebox and stirred at 120 °C for 24 hours. The reaction mixture was cooled to room temperature and evaporated under reduced pressure to remove all volatiles. Further purification was achieved by flash-column chromatography on silica.

2.6.3. ^{1}H NMR-Based Initial-Rate Kinetic Studies

General Procedure: Into a 4 mL scintillation vial equipped with a magnetic stir bar was placed [Ru(cod)(η^3-C$_4$H$_7$)$_2$] (0.017 mmol), IPr (0.017 mmol), acrylamide substrate (0.17 mmol), and triphenylmethane (internal standard, 41.5 mg). Deuterated toluene (C$_7$D$_8$, 99.94% D, 1.0 mL) and acetic acid (2 equiv) was subsequently added, and the mixture was stirred at room temperature for 5-10 minutes to get a homogeneous solution. The reaction mixture was transferred into a screw-cap NMR tube and analyzed by ^{1}H NMR to determine initial substrate concentration. The NMR tube was placed in a 120 °C oil bath and the reaction progress was monitored by ^{1}H NMR by taking the NMR tube out of the oil bath every 20 minutes, immediately transferring to a cold water bath to cool to room temperature, and analyzed by ^{1}H NMR to get relative integration values of substrate and product signals against the internal standard. The resulting product concentrations were plotted against time to determine the reaction rates at early conversions (<25% conversion).
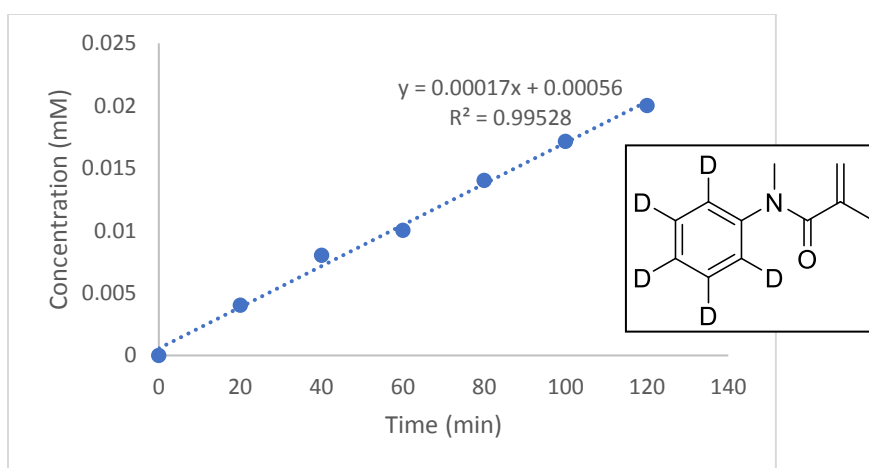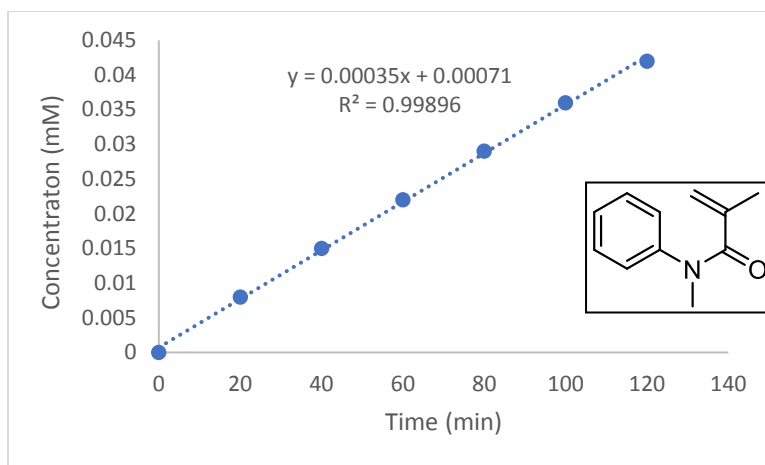
$$\frac{K_H}{K_D} = \frac{0.00035}{0.00017} = 2.1$$

Figure 2.2. Kinetic isotope effect measurement through ^{1}H NMR-based initial-rate kinetic studies.
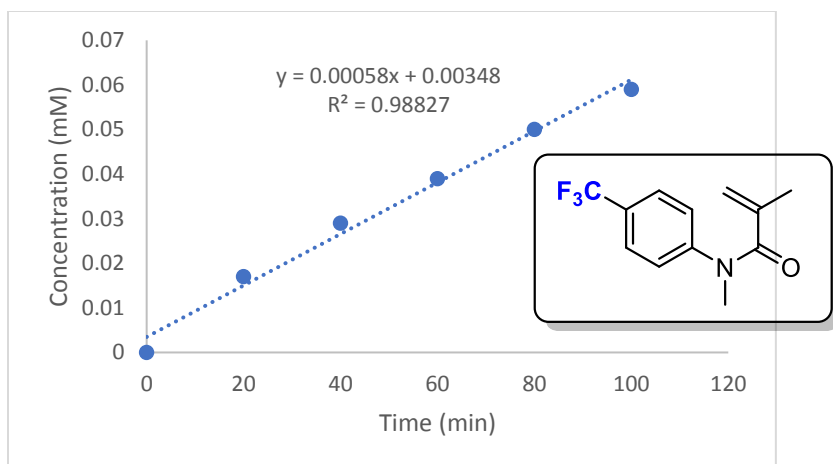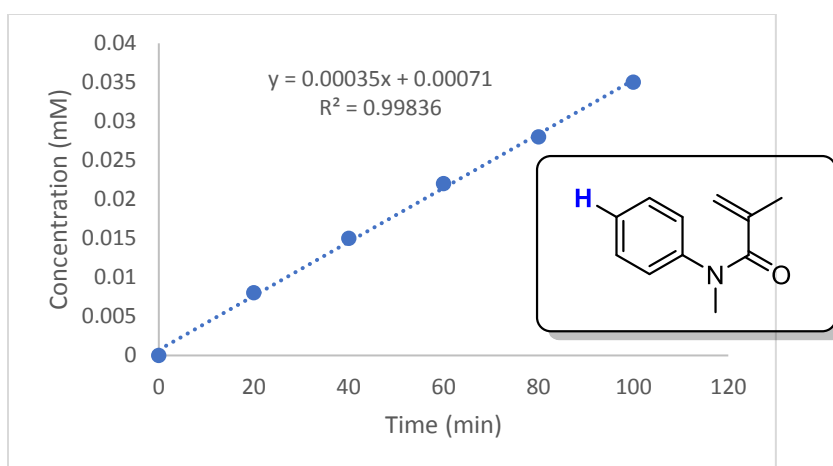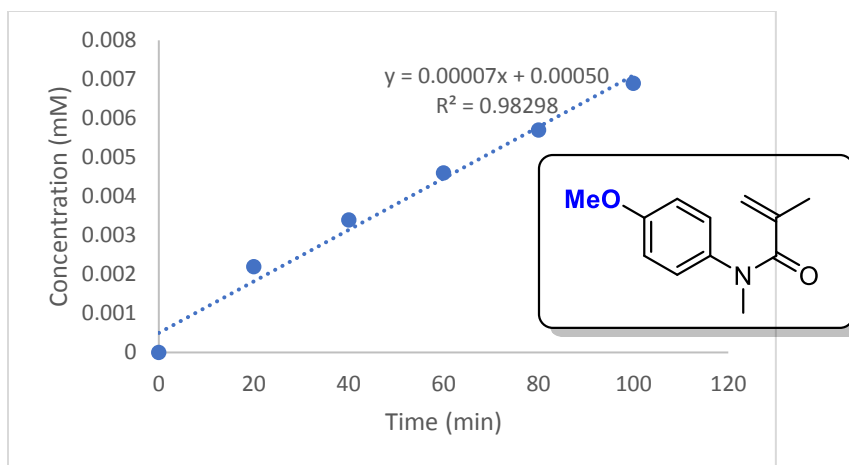
Figure 2.3. Reactivity comparison through ^{1}H NMR-based initial-rate kinetic studies.

2.6.4. Procedure for Synthesis of the Progesterone Receptor Antagonist (2.75)

➢ Synthesis of N-Aryl Acrylamide Compound **2.68y**

➢ Synthesis of acyl chloride intermediate **2.77**

In a 250 mL round bottom flask equipped with a magnetic stir bar was placed

ethylmalonic acid **2.76** (2.0 g, 1 equiv) and dry ethyl acetate (50 mL). Diethylamine (1.5 equiv)

was subsequently added at 5 °C under nitrogen atmosphere. After stirring the mixture at 5 °C for

5 min, paraformaldehyde (1.5 equiv) was slowly added over 5 min and then the mixture was

refluxed for 2 h. The reaction mixture was cooled to room temperature and quenched with water

(150 mL). The P^H value of the solution was brought to ~1 by adding concentrated HCl, and the

resulting mixture was settled in a separation funnel and extracted with ethyl acetate (3 x 75 mL).

The combined organic phases were dried over anhydrous sodium sulfate and evaporated under

reduced pressure to remove all volatiles. The crude compound **2.77** was acquired as a pale-

yellow liquid and used for the next step without further purification.
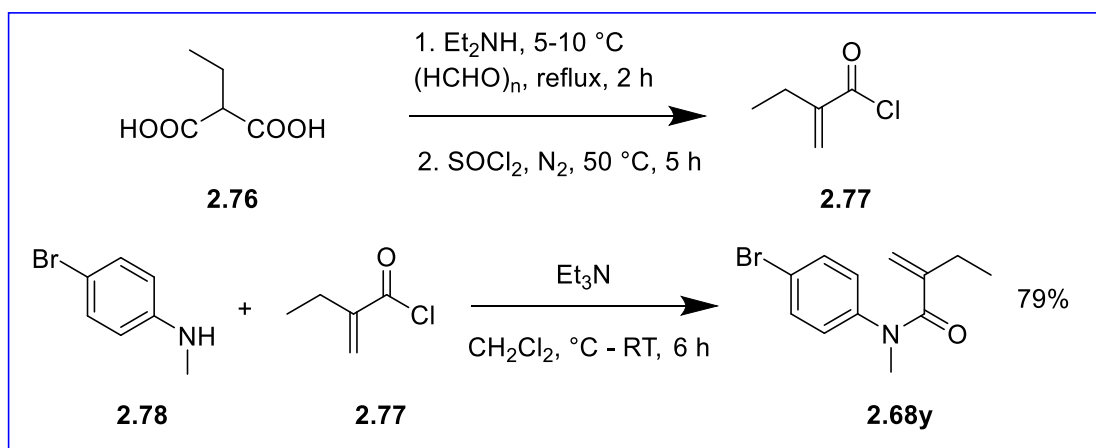
Scheme 2.29. Synthesis of the progesterone receptor antagonist (Step i and ii).

2.6.4.1. *Synthesis of 2.68y by N-acylation with 2.77*

In a 250 mL round bottom flask equipped with a magnetic stir bar was placed 4–bromo-

N-methylaniline **2.78** (1.0 g, 1 equiv), dichloromethane (60 mL) and triethylamine (2 equiv). A

solution of crude 2-ethylacryloyl chloride **2.77** (~2 equiv) in dry dichloromethane (10 mL) was

subsequently added dropwise at 0 °C under nitrogen atmosphere. The resulting solution was

stirred at room temperature for 6 hours, followed by addition of water (150 mL) to quench the

excess acryl chloride. The mixture was settled in a separation funnel and extracted with

dichloromethane (3 x 50 mL). The combined organic layers was washed with brine (3 x 100 mL)

and then dried over anhydrous Na_2SO_4. Szolvent was removed under reduced pressure and the

crude product was purified by column chromatography (0 to 5% ethyl acetate in hexanes) to give

2.68y as white solid in 79% yield.

2.6.4.2. *Synthesis of Oxindole 2.70y by Intramolecular Hydroarylation with 2.68y*
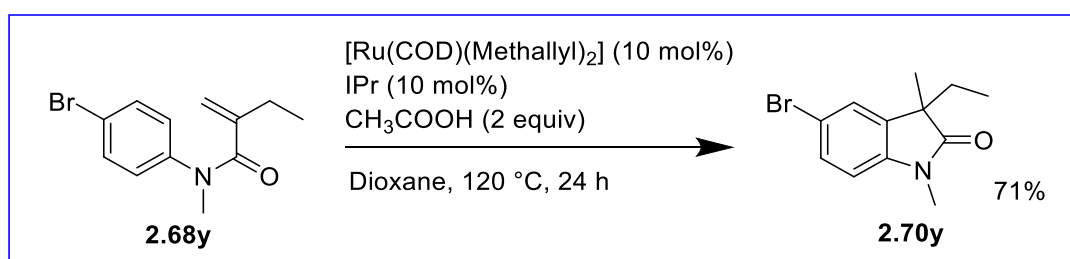
Scheme 2.30. Synthesis of the progesterone receptor antagonist (Step iii).

In a 20 mL scintillation vial equipped with a magnetic stir-bar was placed

[Ru(COD)(methallyl)$_2$] (0.10 equiv), IPr (0.10 equiv) and **2.68y** (300 mg, 1.0 equiv, 1.12 mmol).

Dioxane (5 mL) was added, followed by the addition of acetic acid (2 equiv). The reaction

mixture was stirred at room temperature for five minutes and the vial was sealed with a silicone-

lined screw-cap before transferring out of the glove box. The mixture was stirred in a 120° C oil

bath for 24 hours. After the reaction mixture was cooled to room temperature, all volatiles were

removed under reduced pressure. Further purification was achieved by column chromatography

(0 to 4% ethyl acetate in hexanes) to give **2.70y** as colorless oil in 71% yield.

2.6.4.3. *Synthesis of Compound 2.75 by Suzuki Coupling with 2.70y*
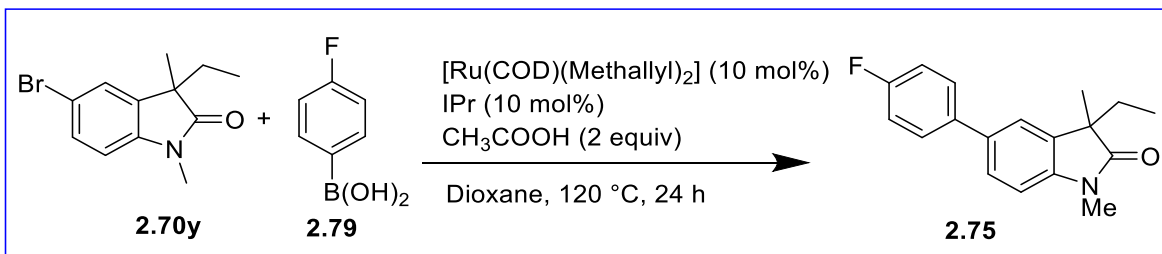
Scheme 2.31. Synthesis of the progesterone receptor antagonist (Step iv).

In a 10 mL round bottom flask equipped with a magnetic stir bar was placed **2.70y** (213 mg, 1.0 equiv), 50% ethanol (4 mL), and $PdCl_2$ (0.05 equiv). The mixture was stirred at room temperature for 5 min to give a homogeneous solution, and subsequently added with potassium carbonate (2.0 equiv) and $4\text{-}FC_6H_5B(OH)_2$ **2.79** (1.0 equiv). The mixture was stirred at room temperature under air for 24 hours, mixed with brine (50 mL), and settled in a separation funnel. After extraction with dichloromethane (3 x 50 mL), the combined organic layers were dried over sodium sulfate and evaporated under reduced pressure to remove all volatiles. Further purification by column chromatography (0 to 3% ethyl acetate in hexanes) gave **2.75** as colorless oil in 78% yield.

2.7. Spectral Data for Reported Compounds
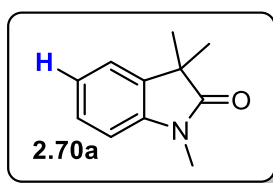
1, 3, 3-trimethylindolin-2-one (2.70a): The compound **2.70a** was prepared according to the general method described above and purified by flash column chromatography (0 to 3% ethyl acetate in hexanes) in 81% yield as a light-yellow oil. 1H NMR (400 MHz, CDCl3): δ 7.24 – 7.16 (m, 2H), 7.02 (td, J = 7.5, 1.0 Hz, 1H), 6.82 (d, J = 7.8 Hz, 1H), 3.18 (s, 3H), 1.34 (s, 6H).

13C NMR (100 MHz, CDCl3): δ 181.2, 142.5, 135.7, 127.6, 122.4, 122.2, 108.0, 77.6, 77.2, 76.9, 44.0, 26.1, 24.3. HRMS: m/z calcd for $C_{11}H_{13}NO$: 176.1075; found: 176.1076.
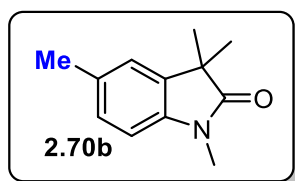
2.70b

1,3,3,5-tetramethylindolin-2-one (2.70b) : The compound **2.70b** was prepared according to the general method described above and purified by flash column chromatography (0 to 3% ethyl acetate in hexanes) in 61% yield as a light-yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.09 − 7.05 (m, 2H), 6.77 (d, J = 7.8 Hz, 1H), 3.22 (s, 3H), 2.36 (s, 3H), 1.38 (s, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 181.7, 140.0, 135.8, 132.2, 127.9, 123.1, 107.9, 77.4, 77.1, 76.8, 44.4, 26.3, 24.3, 21.1. HRMS: m/z calcd for $C_{12}H_{15}NO$: 190.1232; found: 190.1239.

2.70c

5-methoxy-1, 3, 3-trimethylindolin-2-one (2.70c): The compound **2.70c** was prepared according to the general method described above and purified by flash column chromatography (0 to 5% ethyl acetate in hexanes) in 65% yield as a light-yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.82 − 6.81 (m, 1H), 6.78 − 6.72 (m, 2H), 3.79 (s, 3H), 3.18 (s, 3H), 1.35 (s, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 180.9, 156.07, 137.2, 136.1, 111.5, 110.0, 108.2, 77.4, 77.1, 76.8, 55.7, 44.5, 26.2, 24.3. HRMS: m/z calcd for $C_{12}H_{16}NO_2$: 206.1181; found: 206.1181.
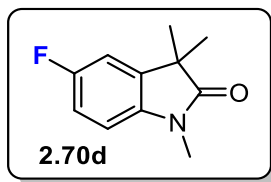
2.70d

5-fluoro-1, 3, 3-trimethylindolin-2-one (2.70d): The compound **2.70d** was prepared according to the general method described above and purified by flash column chromatography (0 to 3% ethyl acetate in hexanes) in 88% yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.95 – 6.90 (m, 2H), 6.74 (dd, J = 9.1, 4.2 Hz, 1H), 3.18 (s, 3H), 1.34 (s, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 180.8 δ 159.3 (d, J = 240.3 Hz), 138.5 , 137.4 (d, J = 7.8 Hz), 113.7 (d, J = 23.4 Hz), 110.5 (d, J = 24.5 Hz), 108.4 (d, J = 8.1 Hz). 77.4, 77.1, 76.8, 44.6, 26.2, 24.2. ^{19}F NMR (376 MHz, CDCl$_3$): δ -120.9. HRMS: m/z calcd for C$_{11}$H$_{12}$FNO: 194.0981; found: 194.0989.
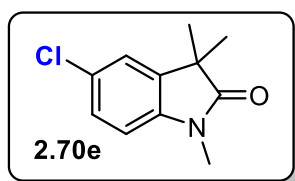
2.70e

5-chloro-1, 3, 3-trimethylindolin-2-one (2.70e): The compound **2.70e** was prepared according to the general method described above and purified by flash column chromatography (0 to 3% ethyl acetate in hexanes) in 86% yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.21 – 7.15 (m, 2H), 6.75 (d, J = 8.2 Hz, 1H), 3.18 (s, 3H), 1.34 (s, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 180.7, 141.1, 137.4, 127.7, 127.5, 122.8, 108.9, 77.4, 77.1, 76.8, 44.3, 26.2, 24.2. HRMS: m/z calcd for C$_{11}$H$_{12}$ClNO: 210.0686; found: 210.0690.
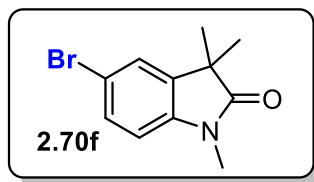
5-bromo-1, 3, 3-trimethylindolin-2-one (2.70f): The compound **2.70f** was prepared

according to the general method described above and purified by flash column chromatography

(0 to 3% ethyl acetate in hexanes) in 79% yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ

7.35 (dd, J = 8.2, 2.0 Hz, 1H), 7.29 (d, J = 1.9 Hz, 1H), 6.71 (d, J = 8.2 Hz, 1H), 3.17 (s, 3H),

1.34 (s, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 180.5, 141.6, 137.8, 130.4, 125.6, 115.1, 109.4,

77.4, 77.1, 76.8, 44.3, 26.2, 24.2. HRMS: m/z calcd for C$_{11}$H$_{12}$BrNO: 254.0181; found:

254.0180.
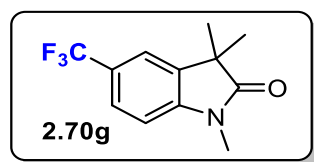
1, 3, 3-trimethyl-5-(trifluoromethyl) indolin-2-one (2.70g): The compound **2.70g** was

prepared according to the general method described above and purified by flash column

chromatography (0 to 3% ethyl acetate in hexanes) in 89% yield as a light-yellow oil. ^{1}H NMR

(400 MHz, CDCl3): δ 7.53 (ddd, J = 8.2, 1.7, 0.8 Hz, 1H), 7.43 – 7.32 (m, 1H), 6.91 (d, J = 8.2

Hz, 1H), 3.24 (s, 3H), 1.38 (s, 6H). ^{13}C NMR (100 MHz, CDCl3): δ 181.1, 145.6, 136.2, 125.4

(q, J = 4 Hz), 124.6 (q, J = 32.4 Hz), 124.4 (q, J = 270 Hz), 119.2 (q, J = 3.7 Hz) 107.6, 77.4,

77.0, 76.7, 44.1, 26.3, 24.1. ^{19}F NMR (376 MHz, CDCl3) δ -61.3. HRMS: m/z calcd for

C$_{12}$H$_{12}$F$_3$NO: 244.0949; found: 244.0953.
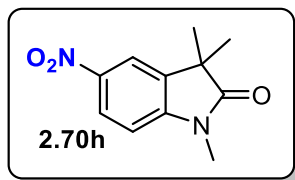
1,3,3-trimethyl-5-nitroindolin-2-one (2.70h): The compound **2.70h** was prepared

according to the general method described above and purified by flash column chromatography

(0 to 6% ethyl acetate in hexanes) in 91% yield as a yellow solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ

8.21 (dd, J = 8.6, 2.3 Hz, 1H), 8.07 (d, J = 2.2 Hz, 1H), 6.93 (d, J = 8.6 Hz, 1H), 3.27 (s, 3H),

1.40 (s, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 181.2, 148.4, 143.4, 136.4, 125.1, 118.2, 107.6,

77.4, 77.1, 76.8, 44.1, 26.6, 24.0. HRMS: m/z calcd for C$_{11}$H$_{12}$N$_2$O$_3$: 221.0926; found: 221.0929.

5-acetyl-1, 3, 3-trimethylindolin-2-one (2.70i): The compound **2.70i** was prepared

according to the general method described above and purified by flash column chromatography

(0 to 5% ethyl acetate in hexanes) in 83% yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ

7.83 (dd, J = 8.2, 1.7 Hz, 1H), 7.75 (d, J = 1.5 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 3.15 (s, 3H),

2.47 (s, 3H), 1.28 (s, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 196.7, 181.4, 146.9, 135.8, 132.0,

129.8, 122.0, 107.4, 77.5, 77.2, 76.9, 43.8, 26.3, 26.3, 24.1. HRMS: m/z calcd for C$_{13}$H$_{15}$NO$_2$:

218.1181; found: 218.1190.

2.70j

Ethyl 1, 3, 3-trimethyl-2-oxoindoline-5-carboxylate (2.70j): The compound **2.70j** was prepared according to the general method described above and purified by flash column chromatography (0 to 5% ethyl acetate in hexanes) in 84% yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.95 (dd, J = 8.2, 1.7 Hz, 1H), 7.82 (d, J = 1.4 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 3.18 (s, 3H), 1.37 – 1.29 (m, 9H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 181.4, 166.3, 146.6, 135.5, 130.3, 124.6, 123.4, 107.4, 77.5, 77.1, 76.8, 60.7, 43.9, 26.3, 24.1, 14.3. HRMS: m/z calcd for C$_{14}$H$_{17}$NO$_3$: 248.1287; found: 248.1292.
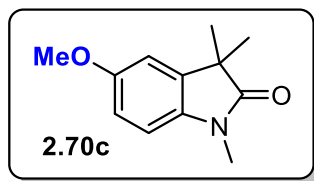

2.70k

7-fluoro-1,3,3-trimethylindolin-2-one (2.70k): The compound **2.70k** was prepared according to the general method described above and purified by flash column chromatography (0 to 3% ethyl acetate in hexanes) in 73% yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.97 – 6.90 (m, 3H), 3.39 (d, J = 2.7 Hz, 3H), 1.34 (s, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 180.7, 147.7 (d, J = 243.2 Hz), 138.7 (d, J = 3.1 Hz), 129.1 (d, J = 8.0 Hz), 122.9 (d, J = 6.3 Hz), 118.0 (d, J = 3.2 Hz), 115.5 (d, J = 19.3 Hz). 77.4, 77.1, 76.8, 44.4, 28.5, 24.4. ^{19}F NMR (376 MHz, CDCl$_3$): δ -136.9. HRMS: m/z calcd for C$_{11}$H$_{12}$FNO: 194.0981; found: 194.0978.

6-fluoro-1,3,3-trimethylindolin-2-one + 4-fluoro-1,3,3-trimethylindolin-2-one (2.70l and 2.70l'): The product mixture of **2.70l/2.70l'** was prepared according to the general method described above and purified by flash column chromatography (0 to 3% ethyl acetate in hexanes) in 84% yield as a white solid. The product ratio was determined by ^{1}H NMR. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.21 − 7.16 (m, 0.09H) (2.70I') 7.08 (dd, J = 8.1, 5.3 Hz, 0.91H) (2.70I), 6.70 − 6.61 (m, 1.09H), (2.70I + 2.70I') 6.55 (dd, J = 8.9, 2.3 Hz, 0.90H) (2.70I), 3.16 (d, J = 6.1 Hz, 3H) (2.70I+2.70I'), 1.42 (s, 0.53H) (2.70I), 1.31 (s, 5.49H) (2.70I). ^{13}C NMR (100 MHz, CDCl$_3$) (2.70I'): δ 181.4 , 162.7 (d, J = 243.8 Hz), 144.0 (d, J = 11.5 Hz), 131.0 (d, J = 2.9 Hz), 123.0 (d, J = 9.7 Hz), 108.2 (d, J = 22.3 Hz), 96.8 (d, J = 27.4 Hz). 43.7, 26.2, 24.3.

^{13}C NMR (100 MHz, CDCl$_3$)) (2.70I): δ 180.5, 158.9 (d, J = 246.9 Hz), 136.7 (d, J = 54.8 Hz), 129.2 (d, J = 8.6 Hz), 120.6 (d, J = 19.7 Hz), 110.0 (d, J = 21.0 Hz), 104.1 (d, J = 3.0 Hz), 44.0, 26.5, 22.7 . ^{19}F NMR (376 MHz, CDCl$_3$): δ -113.2, -121.9. HRMS: m/z calcd for C$_{11}$H$_{12}$FNO: 194.0981; found: 194.0986.
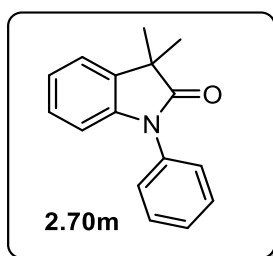
3,3-dimethyl-1-phenylindolin-2-one (2.70m): The compound **2.70m** was prepared according to the general method described above and purified by flash column chromatography

(0 to 2% ethyl acetate in hexanes) in 90% yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ

7.62 – 7.09 (m, 8H), 6.91 (d, J = 7.8 Hz, 1H), 1.56 (s, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ

180.6, 142.5, 135.6, 134.7, 129.5, 127.9, 127.6, 126.5, 123.0, 122.7, 109.4, 77.6, 77.3, 77.0, 44.3,

24.8. HRMS: m/z calcd for C$_{16}$H$_{13}$NONa: 260.1051; found: 260.1058.
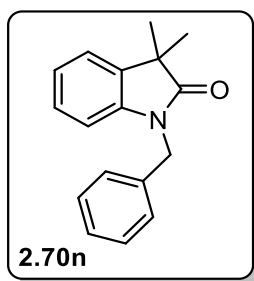
2.70n

1-benzyl-3,3-dimethylindolin-2-one (2.70n): The compound **2.70n** was prepared

according to the general method described above and purified by flash column chromatography

(0 to 2% ethyl acetate in hexanes) in 84% yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ

7.37 – 7.23 (m, 6H), 7.17 (td, J = 7.7, 1.3 Hz, 1H), 7.07 (td, J = 7.6, 1.0 Hz, 1H), 6.78 (d, J = 7.7

Hz, 1H), 4.97 (s, 2H), 1.50 (s, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 181.4, 141.7, 136.2, 135.8,

128.8, 127.6, 127.5, 127.2, 122.5, 122.3, 109.1, 77.6, 77.2, 76.9, 44.2, 43.5, 24.6. HRMS: m/z

calcd for C$_{17}$H$_{17}$NONa: 274.1208; found: 274.1221.
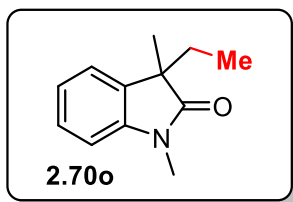
2.70o

3-ethyl-1,3-dimethylindolin-2-one (2.70o): The compound **2.70o** was prepared

according to the general method described above and purified by flash column chromatography

(0 to 3% ethyl acetate in hexanes) in 59% yield as a colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ

7.26 (t, J = 7.6 Hz, 1H), 7.17 (d, J = 7.1 Hz, 1H), 7.07 (t, J = 7.3 Hz, 1H), 6.84 (d, J = 7.6 Hz,

1H), 3.22 (s, 3H), 1.93 (dd, J = 13.6, 7.1 Hz, 1H), 1.77 (dd, J = 13.6, 7.2 Hz, 1H), 1.35 (s, 3H),

0.59 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 180.6, 143.4, 133.9, 127.6, 122.4, 122.3, 107.8, 77.4, 77.1, 76.8, 48.9, 31.4, 26.0, 23.3, 8.8. HRMS: m/z calcd for C$_{12}$H$_{15}$NO: 190.1232; found: 190.1234.

2.70p

(1,3-dimethyl-2-oxoindolin-3-yl) methyl acetate (2.70p): The compound **2.70p** was prepared according to the general method described above and purified by flash column chromatography (0 to 6% ethyl acetate in hexanes) in 74% yield as a light yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.28 – 7.20 (m, 2H), 7.03 (t, $J = 7.4$ Hz, 1H), 6.84 (d, $J = 7.8$ Hz, 1H), 4.46 (d, $J = 10.8$ Hz, 1H), 4.14 (d, $J = 10.8$ Hz, 1H), 3.21 (s, 3H), 1.83 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 178.1, 170.3, 143.3, 131.2, 128.3, 123.0, 122.5, 108.1, 77.5, 77.1, 76.8, 67.4, 47.9, 26.2, 20.5, 19.6. HRMS: m/z calcd for C$_{13}$H$_{13}$NO$_3$Na: 256.0950; found: 256.0962.
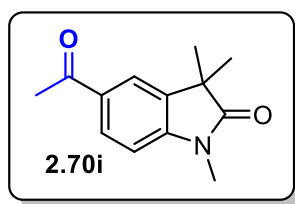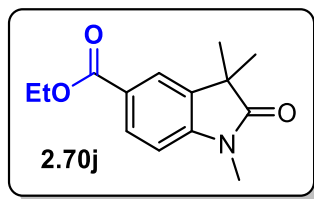

2.70q

1,3-dimethyl-3-(trifluoromethyl) indolin-2-one (2.70q): The compound **2.70q** was prepared according to the general method described above and purified by flash column chromatography (0 to 3% ethyl acetate in hexanes) in 61% yield as a light yellow oil. ^{1}H NMR (400 MHz, CDCl3): δ 7.37 – 7.36 (m, 2H), 7.11 (t, $J = 7.3$ Hz, 1H), 6.89 (d, $J = 7.7$ Hz, 1H), 3.22 (s, 3H), 1.63 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 172.2, 143.6, 129.9, 126.1, δ 125.0 (q, $J = 281.8$ Hz), 124.4, 123.1, 108.6, 77.5, 77.2, 76.8, δ 52.0 (q, $J = 27.6$ Hz), 26.4, 17.6.

<superscript>19</superscript>F NMR (376 MHz, CDCl₃): δ -73.6. HRMS: m/z calcd for $C_{11}H_{10}F_3NO$: 230.0793; found: 230.0803
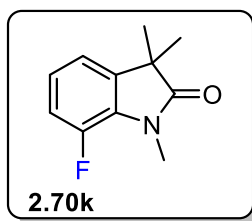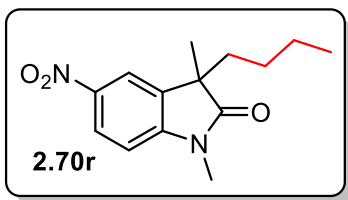

2.70r

3-butyl-1,3-dimethyl-5-nitroindolin-2-one (2.70r): The compound **2.70r** was prepared according to the general method described above and purified by flash column chromatography (0 to 6% ethyl acetate in hexanes) in 82% yield as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 8.21 (dd, J = 8.6, 2.3 Hz, 1H), 8.02 (d, J = 2.3 Hz, 1H), 6.92 (d, J = 8.6 Hz, 1H), 3.26 (s, 3H), 1.90 (td, J = 12.9, 12.4, 4.7 Hz, 1H), 1.76 (td, J = 13.4, 12.9, 4.5 Hz, 1H), 1.36 (s, 3H), 1.15 (ddd, J = 14.8, 7.6, 3.0 Hz, 2H), 0.89 (ddd, J = 10.7, 7.5, 5.4 Hz, 1H), 0.81 – 0.69 (m, 4H). ¹³C NMR (100 MHz, CDCl₃): δ 180.7, 149.0, 143.3, 135.0, 125.1, 118.2, 107.4, 77.4, 77.1, 76.8, 48.4, 38.0, 26.4, 26.4, 23.4, 22.6, 13.7. HRMS: m/z calcd for $C_{14}H_{18}N_2O_3$: 263.1396; found: 263.1408.
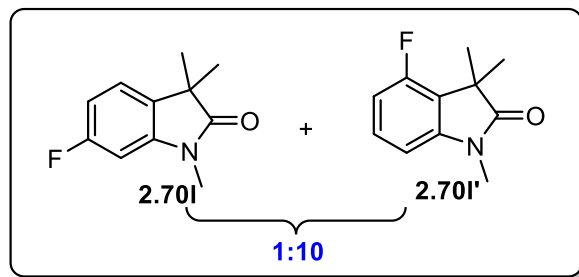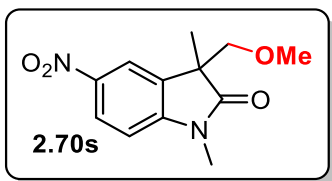

2.70s

3-(methoxymethyl)-1, 3-dimethyl-5-nitroindolin-2-one (2.70s): The compound **2.70s** was prepared according to the general method described above and purified by flash column chromatography (0 to 8% ethyl acetate in hexanes) in 78% yield as a yellow oil. ¹H NMR (400 MHz, CDCl₃): δ 8.21 (dd, J = 8.6, 2.3 Hz, 1H), 8.11 (d, J = 2.3 Hz, 1H), 6.92 (d, J = 8.6 Hz, 1H), 3.72 – 3.57 (m, 2H), 3.25 (s, 3H), 3.18(s, 3H), 1.34 (s, 3H). ¹³C NMR (100 MHz, CDCl₃): 179.1,

149.3, 143.3, 133.5, 125.4, 118.7, 107.5, 77.5, 77.2, 76.8, 76.5, 59.3, 49.3, 26.6, 19.3. HRMS:

m/z calcd for $C_{12}H_{14}N_2O_4$: 251.1032; found: 251.1036.
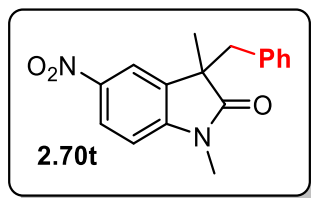
2.70t

3-benzyl-1, 3-dimethyl-5-nitroindolin-2-one (2.70t): The compound **2.70t** was prepared

according to the general method described above and purified by flash column chromatography

(0 to 5% ethyl acetate in hexanes) in 69% yield as a yellow solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ

8.14 (dd, J = 8.6, 2.3 Hz, 1H), 8.06 (d, J = 2.2 Hz, 1H), 7.07 – 7.01 (m, 3H), 6.81 (dd, J = 7.5,

1.7 Hz, 2H), 6.67 (d, J = 8.6 Hz, 1H), 3.20 (d, J = 13.1 Hz, 1H), 3.05 (d, J = 15.7 Hz, 4H), 1.54

(s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 179.9, 148.8, 143.0, 135.1, 133.8, 129.5, 127.8, 126.9,

125.2, 119.0, 107.3, 77.4, 77.1, 76.8, 50.1, 44.5, 26.2, 22.4. HRMS: m/z calcd for $C_{17}H_{16}N_2O_3$:

297.1239; found: 297.1238.
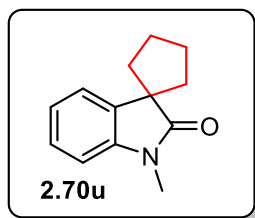
2.70u

1-methylspiro(cyclopentane-1')-indolin-2-one (2.70u): The compound **2.70u** was

prepared according to the general method described above and purified by flash column

chromatography (0 to 3% ethyl acetate in hexanes) in 38% yield as a colorless oil. ^{1}H NMR (400

MHz, CDCl$_3$): δ 7.28 – 7.23 (m, 2H), 7.08 – 7.04 (m, 1H), 6.84 (d, J = 7.7 Hz, 1H), 3.23 (s, 3H),

2.20 – 1.86 (m, 6H), 1.85 (ddd, J = 12.1, 7.0, 4.2 Hz, 2H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 181.9,

142.9, 136.8, 127.3, 122.5, 122.2, 107.6, 77.4, 77.0, 76.7, 53.9, 38.3, 26.6, 26.2. HRMS: m/z

calcd for $C_{11}H_{13}NO$: 202.1232; found: 202.1242.
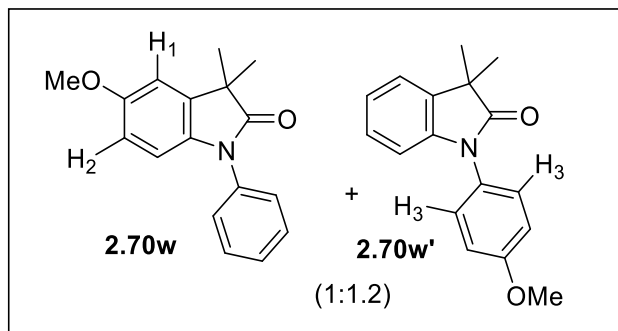
5-methoxy-3,3-dimethyl-1-phenylindolin-2-one + 1-(4-methoxyphenyl)-3,3-dimethylindolin-2-one (2.70w and 2.70w'): The product mixture of **2.70w/2.70w'** was prepared according to the general method described above and purified by flash column chromatography (0 to 5% ethyl acetate in hexanes) in 79% yield as a white solid. The product ratio was determined by ^{1}H NMR. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.54 – 7.46 (m, 3.42H), 7.40 – 7.28 (m, 4.48H), 7.21 – 7.17 (m, 1.18H), 7.04 – 7.12 (m, 3.51H), 6.94 (d, J = 2.4 Hz, 0.82H) (H$_1$), 6.82 (d, J = 8.3 Hz, 2H) (H$_3$), 6.74 (dd, J = 8.6, 2.5 Hz, 0.82H) (H$_2$), 3.84 (s, 3.44H), 3.81 (s, 2.42H), 1.52 (s, 12.28H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 180.8, 180.3, 159.0, 156.4, 142.9, 137.0, 135.8, 135.57, 135.00, 129.50, 127.94, 127.64, 127.33, 126.29, 122.86, 122.59, 114.87, 111.85, 109.9, 109.8, 109.2, 77.6, 77.3, 77.0, 55.7, 55.5, 44.7, 44.2, 24.8, 24.7.
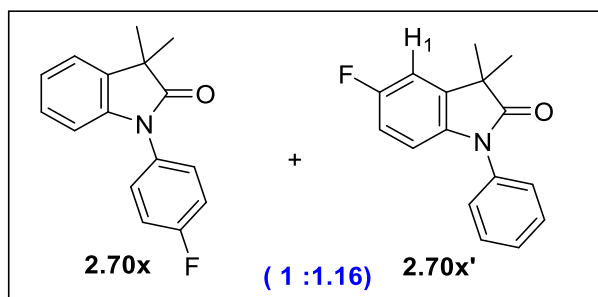
1-(4-fluorophenyl)-3,3-dimethylindolin-2-one + 5-fluoro-3,3-dimethyl-1-phenylindolin-2-one (2.70x and 2.70x'): The product mixture of **2x/2x'** was prepared according to the general method described above and purified by flash column chromatography (0 to 3%

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ethyl acetate in hexanes) in 87% combined yield as a white solid. The product ratio was determined by ^{1}H NMR. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.55 – 7.41 (m, 6.52H), 7.31 (d, J = 7.2 Hz, 1H) (H$_1$), 7.24 – 7.19 (m, 2.73H), 7.13 (t, J = 7.4 Hz,0.931H), 7.05 (dd, J = 7.8, 2.3 Hz, 0.94H), 6.90 – 6.79 (m, 2.75H), 1.56 – 1.47 (d, 10.68H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 180.7, 180.2, 162.9, 160.7, 160.5, 158.3, 142.3, 138.3, 137.3 (d, J = 7.8 Hz), 135.5, 134.6, 130.6 (d, J = 3.1 Hz), 129.6, 128.4 (d, J = 8.6 Hz), 127.8 (d, J = 27.8 Hz), 126.4 , 122.9 (d, J = 40.7 Hz), 116.5 (d, J = 22.8 Hz), 113.8 (d, J = 23.4 Hz), 110.6 (d, J = 24.4 Hz), 110.0 (d, J = 8.0 Hz), 109.2, 44.7, 44.3, 24.7 (d, J = 10.6 Hz).
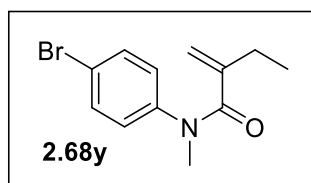
2.68y

N-(4-bromophenyl)-N-methyl-2-methylenebutanamide (2.68y): The compound **2.68y** was prepared according to the general method described above and purified by flash column chromatography (0 to 5% ethyl acetate in hexanes) in 79% yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.44 (d, J = 8 Hz 2H), 7.01 (d, J = 8 Hz, 2H), 5.01 (d, J = 30.9 Hz, 2H), 3.31 (s, 3H), 2.12 (q, J = 7.4 Hz, 2H), 0.97 (t, J = 7.4 Hz, 3H).^{13}C NMR (100 MHz, CDCl$_3$): δ 171.6, 146.1, 143.6, 132.3, 128.2, 120.3, 117.3, 77.4, 77.1, 76.8, 37.6, 26.5, 11.7.
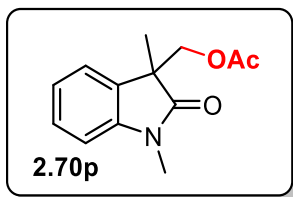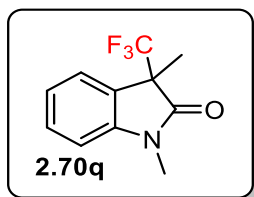

2y
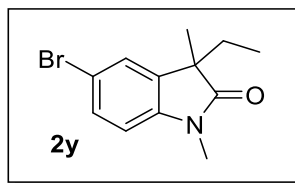
5-bromo-3-ethyl-1,3-dimethylindolin-2-one (2.70y): The compound **2.70y** was prepared according to the general method described above and purified by flash column chromatography (0 to 4% ethyl acetate in hexanes) in 71% yield as a colorless oil. ^{1}H NMR (400

MHz, CDCl$_3$): δ 7.35 (dd, J = 8.2, 1.9 Hz, 1H), 7.25 (d, J = 1.9 Hz, 1H), 6.70 (d, J = 8.2 Hz, 1H),

3.17 (s, 3H), 1.90 (dq, J = 14.8, 7.4 Hz, 1H), 1.72 (dq, J = 14.8, 7.4 Hz, 1H), 1.31 (s, 3H), 0.56

(t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 179.94, 142.53, 136.04, 130.44, 125.78,

115.11, 109.28, 77.47, 77.15, 76.83, 49.18, 31.39, 26.14, 23.23, 8.82.

2.75
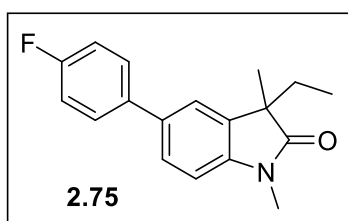
3-ethyl-5-(4-fluorophenyl)-1,3-dimethylindolin-2-one (2.75): The compound **2.75** was

prepared according to the general method described above and purified by flash column

chromatography (0 to 3% ethyl acetate in hexanes) in 78% yield as a colorless oil. ^{1}H NMR (400

MHz, CDCl$_3$): δ 7.50 – 7.34 (m, 4H), 7.08 (t, J = 7.6 Hz, 2H), 6.87 (d, J = 7.6 Hz, 1H), 3.21 (s,

3H), 2.06 – ₃1.70 (m, 2H), 1.38 (s, 3H), 0.62 (t, J = 6.3 Hz, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ

180.5, 163.4, 160.9, 142.9, 137.3 (d, J = 3.1 Hz), 134.7 (d, J = 21.1 Hz), 128.3 (d, J = 7.9 Hz),

126.4, 121.2, 115.6 (d, J = 21.4 Hz), 108.1, 49.0, 31.5, 26.0, 23.3, 8.9. ^{19}F NMR (376 MHz,

CDCl$_3$): δ -116.0.
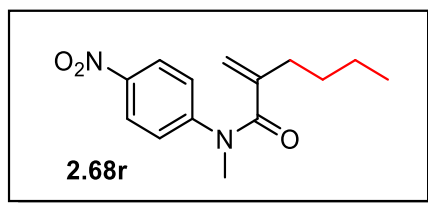
2.68r

N-methyl-N-phenyl-2-(*n*-butyl) Acrylamide (2.68r): The compound **2.68r** was

prepared according to the general method described above and purified by flash column

chromatography (0 to 8% ethyl acetate in hexanes) in 65% yield as a yellow solid. ^{1}H NMR (400

MHz, CDCl$_3$): δ 8.22 – 8.15 (m, 2H), 7.36 – 7.29 (m, 2H), 5.20 – 5.11 (m, 1H), 5.08 – 5.00 (m,

1H), 3.40 (s, 3H), 2.19 – 2.08 (m, 2H), 1.44 – 1.35 (m, 2H), 1.28 (dq, J = 14.3, 7.1 Hz, 2H), 0.86

(t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 171.6, 150.2, 145.3, 144.6, 126.3, 124.5, 119.1, 77.4, 77.1, 76.8, 37.5, 33.2, 29.6, 22.2, 13.8. HRMS: m/z calcd for C$_{14}$H$_{18}$N$_2$O$_3$Na: 285.1215; found: 285.1227.
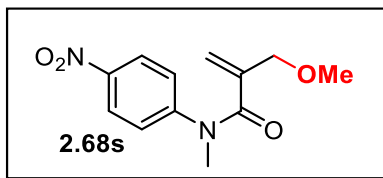
2.68s

N-methyl-N-phenyl-2-(methoxy methyl) Acrylamide (2.68s): The compound **2.68s** was prepared according to the general method described above and purified by flash column chromatography (0 to 10% ethyl acetate in hexanes) in 71% yield as a yellow solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.23 – 8.11 (m, 2H), 7.47 – 7.36 (m, 2H), 5.31 (s, 1H), 4.98 (s, 1H), 4.10 – 4.00 (m, 2H), 3.46 – 3.29 (m, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 169.62, 150.24, 145.44, 141.08, 126.72, 124.50, 120.82, 77.48, 77.16, 76.84, 73.23, 58.84, 37.38. HRMS: m/z calcd for C$_{12}$H$_{14}$N$_2$O$_4$Na: 273.0851; found: 273.0863.
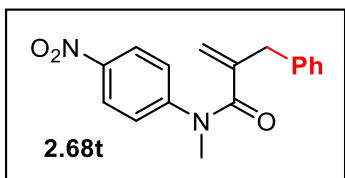
2.68t

N-methyl-N-phenyl-2-(benzyl) Acrylamide (2.68t): The compound **2.68t** was prepared according to the general method described above and purified by flash column chromatography (0 to 8% ethyl acetate in hexanes) in 63% yield as a yellow solid. ^{1}H NMR (400 MHz, CDCl$_3$): 8.11 – 8.01 (m, 2H), 7.39 – 7.24 (m, 3H), 7.22 – 7.12 (m, 2H), 6.92 – 6.82 (m, 2H), 5.20 – 5.14 (m, 1H), 4.98 – 4.90 (m, 1H), 3.60 (s, 2H), 3.32 (s, 3H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 170.6, 150.1, 145.5, 143.6, 137.4, 129.3, 128.7, 126.9, 126.5, 124.4, 120.2, 77.4, 77.1, 76.8, 40.5, 37.6. HRMS: m/z calcd for C$_{17}$H$_{16}$N$_2$O$_3$Na: 319.1059; found: 319.1066.

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3. REGIOSELECTIVE ALKENYLATION OF HETEROARENES THROUGH RUTHENIUM CATALYSED DECARBOXYLATIVE C-H BOND ACTIVATION

3.1. Introduction

Alkenyl (hetero)arenes are widely present in many useful organic compounds such as fluorescent dyes, natural products, and pharmaceuticals. Hydro(hetro)arylation of alkynes emerged as a valuable tool for the synthesis of alkenyl (Hetero)arenes.[1] Classical method for the Hydro(hetro)arylation is Lewis acid catalyzed Friedel-Crafts reaction (Scheme 3.1.). This reaction is suitable only for arenes with electron donating substituents, and it suffers from achieving regio and stereoselectivity.[2]
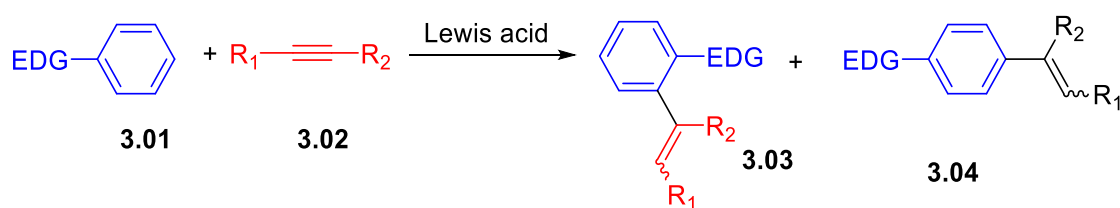
Scheme 3.1. Lewis acid mediated hydroarylation with electron-rich arenes.

Transition metal catalysts have been employed for alkyne hydroarylation (hydro heteroarylation) using aryl halides (**3.05**) and organometallic reagents (**3.08**) as coupling partners (Scheme 3.2.). The main drawback of these reactions is the generation of stoichiometric amounts of salt waste and the need for pre-functionalized substrates. [3]
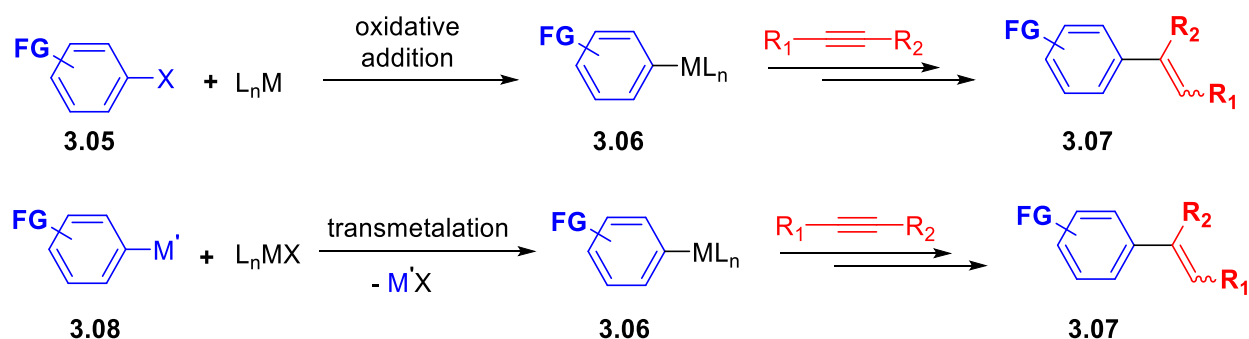
Scheme 3.2. Transition metal catalyzed hydroarlation of alkynes using aryl halides or organometallic reagents.

On the other hand, direct addition of (hetero)arenes across the alkynes through transition metal catalyzed C-H bond activation occurs with high atom and step economy. hydro(hetero)arylation of alkynes through transition metal catalyzed C-H bond functionalization represents the most straightforward method to access trisubstituted olefins which are an integral part of many biologically active compounds and used extensively as synthetic intermediates for fine chemicals and materials. Achieving regioselectivity is crucial for the practical application of transition metal catalyzed Hydro(hetero)arylation. The most reliable method for the regioselective C-H bond functionalization is the usage of directing group (Scheme 3.3.).[4] Murai and co-workers reported first example for the Hydroarylation of alkenes using ketone as a directing group.[5] Later, in 1995 they disclosed another method for Hydroarylation of alkynes using ruthenium catalyst.[6] Following Murai's pioneering work, hydroarylation was extended to many directing groups such as pyridine, imine, amides, ester, etc.[7-12]
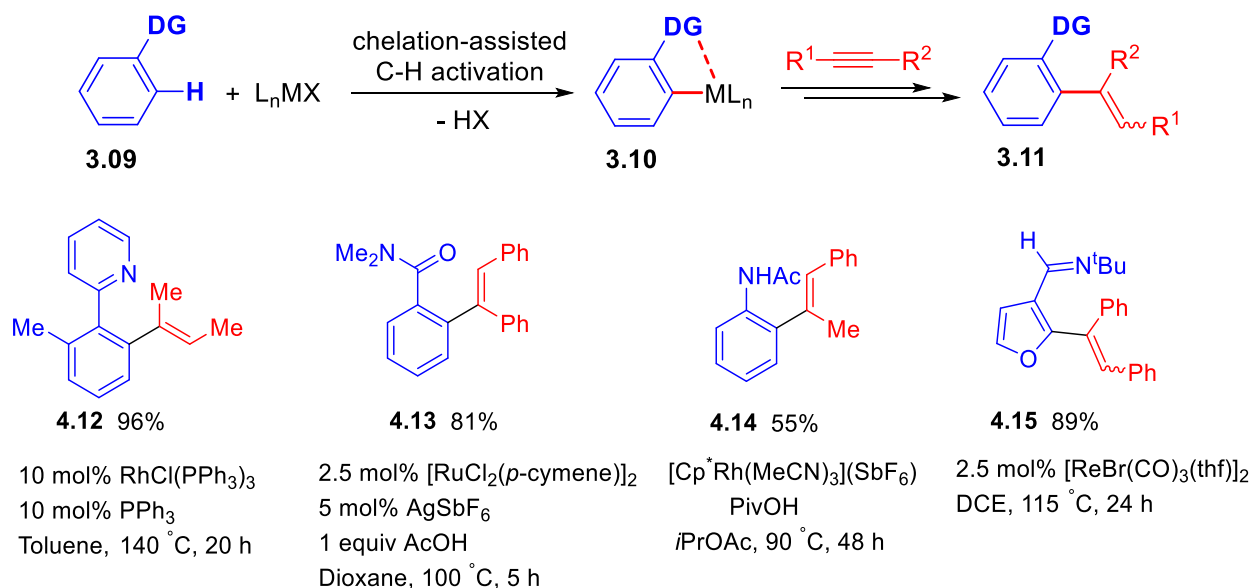
Scheme 3.3. Hydroaryation via transition metal mediated directed C-H bond activation.

Chelation assisted C-H bond activation also employed for the functionalization of heteroarenes. The group of Zeng developed a method for the ruthenium-catalyzed C-2

hydroindolation of alkynes with N-(2-pyridyl)-indoles (**3.16**), which provides access to 2-alkenyl substituted indoles (Scheme 3.4 a).[13] This approach tolerates various indole derivatives and alkynes bearing electron donating and withdrawing substituents. Recently, Yoshikai and co-workers established another protocol for alkenylation of indole via imine directed as C-H bond activation using an earth-abundant iron catalyst (Scheme 3.4 b).[14] This reaction proceeds through oxidative addition rather than concerted metalation and deprotonation.
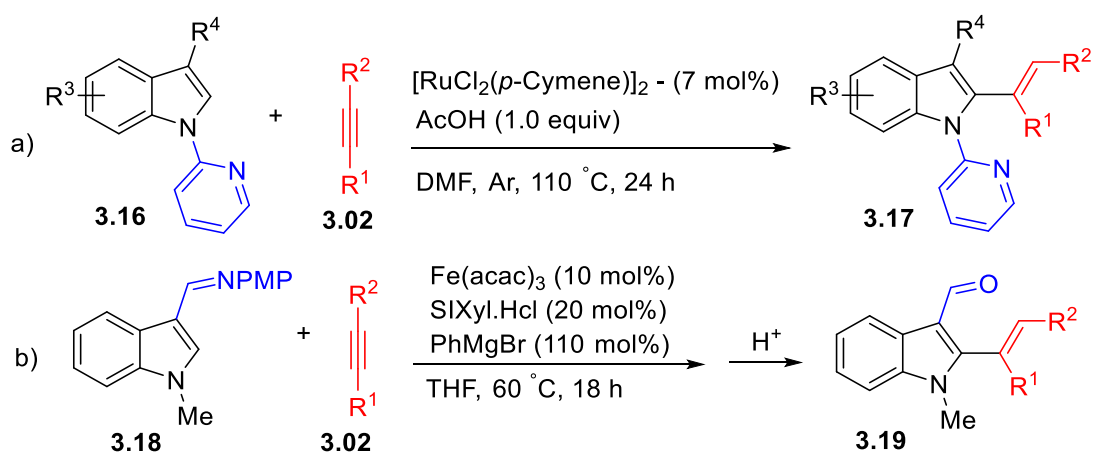
Scheme 3.4. a) Hydroindolation of alkynes with N-(2-pyridyl)-indoles b) Hydroindolation of alkynes using imine as a directing group.
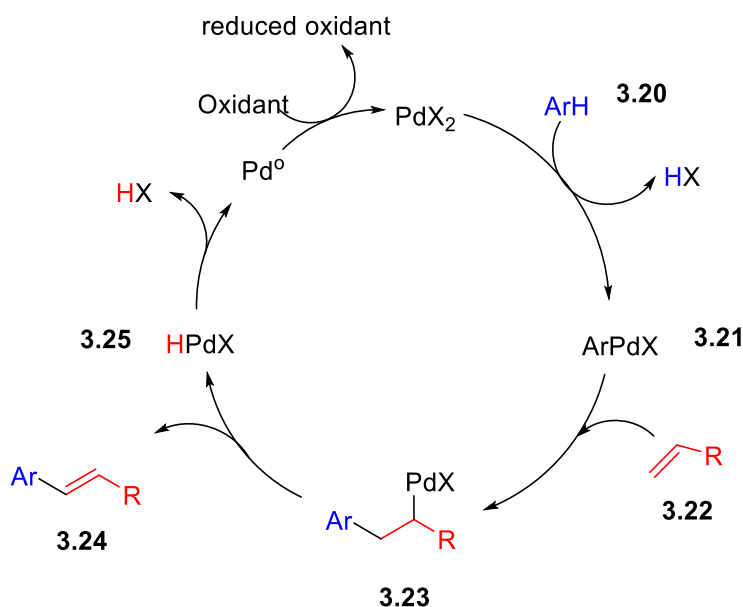
Scheme 3.5. Palladium catalyzed dehydrogenative coupling of arenes and alkenes.

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In addition to hydroarylation, dehydrogenative coupling of (hetero)arene and alkene is also emerged as a powerful tool for alkenylation of (hetero)arenes. Fujiwara's group first revealed a palladium catalyzed dehydrogenative coupling of electron-rich aromatics with styrene which proceeds through electrophilic metalation pathway.[15] Next, enormous efforts were devoted for the dehydrogenative alkenylation of arenes and heteroarenes.

In 1997, Miura et al disclosed a protocol for oxidative coupling of phenol derivatives with activated olefins using palladium catalyst in presence of stoichiometric amounts of oxidant.[16] In this example, regioselective alkenylation is achieved by the coordination of Pd catalyst to hydroxy group. Later, chelation assisted Pd-catalyzed oxidative coupling was extended to benzoic acids, aryl sulfonamides and anilides by Miura, Yu and Van Leeuwen.[17] The plausible mechanism for the dehydrogenative Heck reaction is depicted in Scheme 3.5.[18] Miura, Fagnou, Satoh and Glorius expanded the scope of dehydrogenative coupling using rhodium catalysts in presence of stoichiometric amounts of oxidant.[19] In the recent years, less expensive Ruthenium catalysts have been explored for the directed C-H alkenylation and significant advancement has been made by Milstein, Ackermann, Jagenmohan and many others.
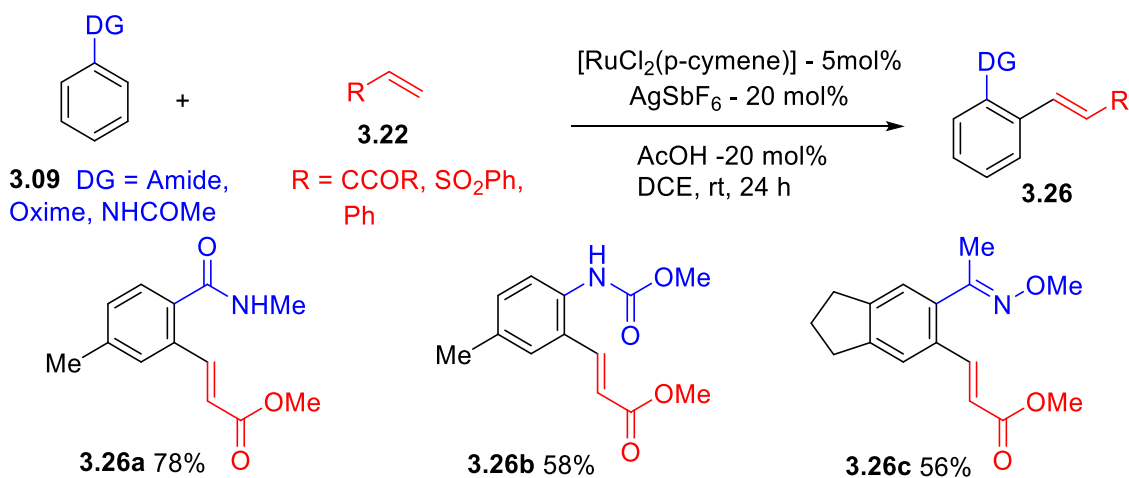
Scheme 3.6. Dehydrogenative coupling of olefin and akenes through directed C-H bond activation.

Ackermann's group established a oxidative coupling of aromatic acids and alkenes using ruthenium catalyst to produce cyclic phthalides.[20] Inspired by this work Jagenmohan and coworkers extended the ruthenium catalysed dehydrogenative coupling with broad range of arenes and olefins.[21] In their initial reports, stoichiometric amounts of copeer and silver oxidants were used for dehydrogenative heck reaction. In 2017, a new protocol was established for C-H alkenylation using Ruthenium catalyst without any external oxidant. This reaction proceeds at room temperature and suitable for *ortho* alkenylation of aromatic amides, ketoximes and anilides (Scheme 3.6.). [22]

In 2011, Miura et al developed a protocol for C-H alkenylation of various heteroarenes such as indole, pyrrole, thiophene, benzothiophene and furan through the coupling of heteroarene carboxylic acids (**3.27**) and activated olefins (**3.28**) using Ru(II)/Cu(II) catalytic system.[23] This transformation occurs via chelation assisted C-H bond activation of carboxylic acid. Recently, the group of Baidya established another method for dehydrogenative alkenylation by coupling benzoic acids (**3.30**) and styrene (**3.31**) using ruthenium catalyst in presence of copper oxidant.[24] This method enables the easy synthesis of 2-styrylbenzoic acids and it occurs with broad scope, and good yields.
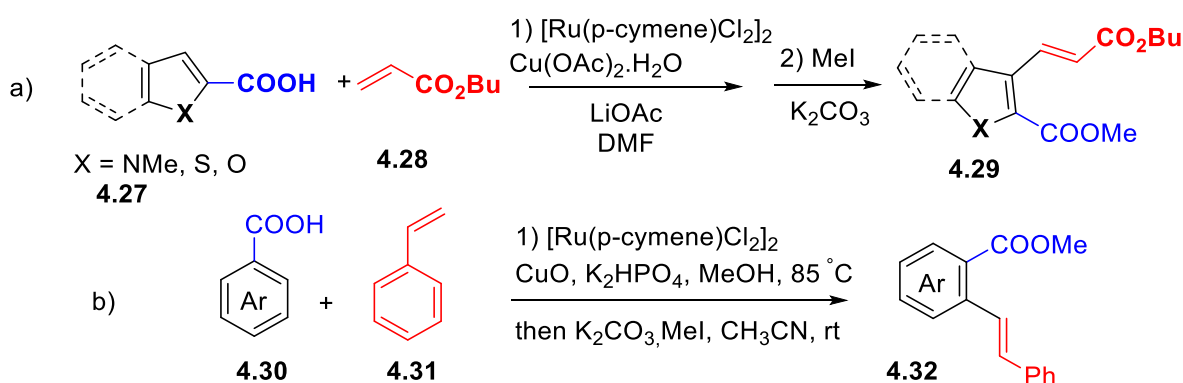
Scheme 3.7. Dehydrogenative alkenylation using COOH as a directing group.

Directed C-H bond activation is limited to functionalization of *ortho* C-H bond to a directing group and functionalization at *meta*, and *para* positions remained a challenge. Recently many methods have been developed for the *meta* C-H bond functionalization. Hartwig et al. reported a protocol for the *meta* borylation of arenes using Iridium catalyst (Scheme 3.8 a). The regioselectivity was controlled through the steric effects of the substrate. This transformation is suitable only for disubstituted arenes to achieve *meta* regioselectivity, whereas mono substituted arenes produced the mixture of isomers.[25]
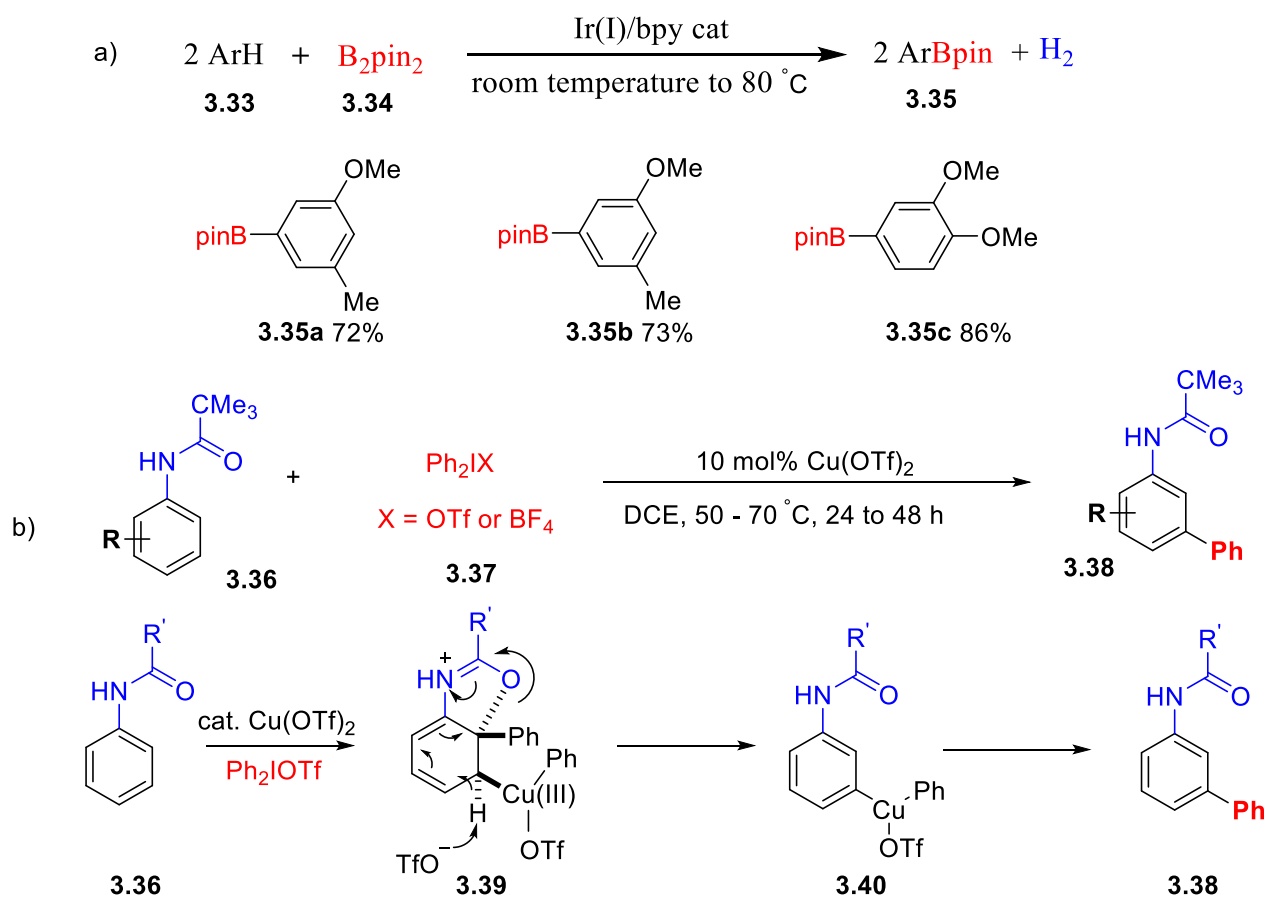
Scheme 3.8. a) Iridium catalyzed *meta* borylation of arenes. b) Cu catalyzed *meta* arylation of amides.

In the year 2009, Gaunt and coworkers discovered a new method for *meta* arylation of benzanilides (**3.36**) using copper(II) catalyst. This method is complementary to both chelation

assisted C-H activation and Friedel-Crafts reaction. The reaction proceeds via *meta*-C–H bond cupration via dearomatizing oxy-cupration as described in Scheme 3.8b. Upon rearomatization followed by reductive elimination delivers the desired *meta* arylated product.[26]

Yu and coworkers described a new protocol for *meta* functionalization by cleverly designed a template as shown in Scheme 3.9. In their first report, a nitrile-based template was designed for *meta* alkenylation of toluene and hydrocinnamic acid derivatives using the catalytic amount of Pd(OPiv)$_2$. Later, template-directed C-H bond activation was extended to *meta* arylation, acetoxylation and alkylation of toluene, and amine derivatives.[27]
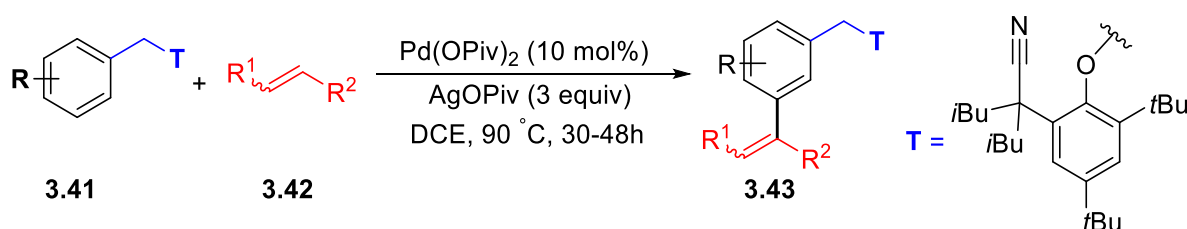
Scheme 3.9. Template-directed *meta* C-H bond functionalization of toluene derivatives.

Inspired by the success story of template-directed *meta* C-H bond activation, Maiti and coworkers devised a new template for the exclusive *para* C-H bond activation as depicted in Scheme 3.10. Authors reported an easily recyclable, biphenyl-silyl-tethered D-shaped assembly for *para* functionalization of toluene derivatives. Incorporation of biphenyl in the template regulates the chain length of the assembly and increases the strain for *ortho* and *meta* C-H bond activation, which facilitates the selective distal *para* C-H bond activation. The utility of D-shaped assembly is demonstrated by the alkenylation and acetoxylation of toluene derivatives in the presence of Pd(II) catalytic system.[28]
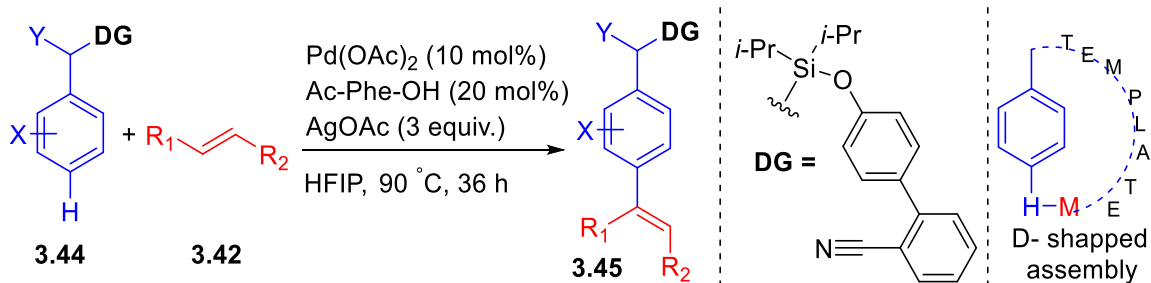
Scheme 3.10. Template-assisted *para* C−H olefination of toluene derivatives.

Although these protocols are applicable for *meta* and *para* C-H bond functionalization, covalent linkage of complex templates remained as a drawback. Recently the groups of Yu and Dong reported an elegant approach for the *meta* C-H bond functionalization using norbornene as a transient mediator (Scheme 3.11).
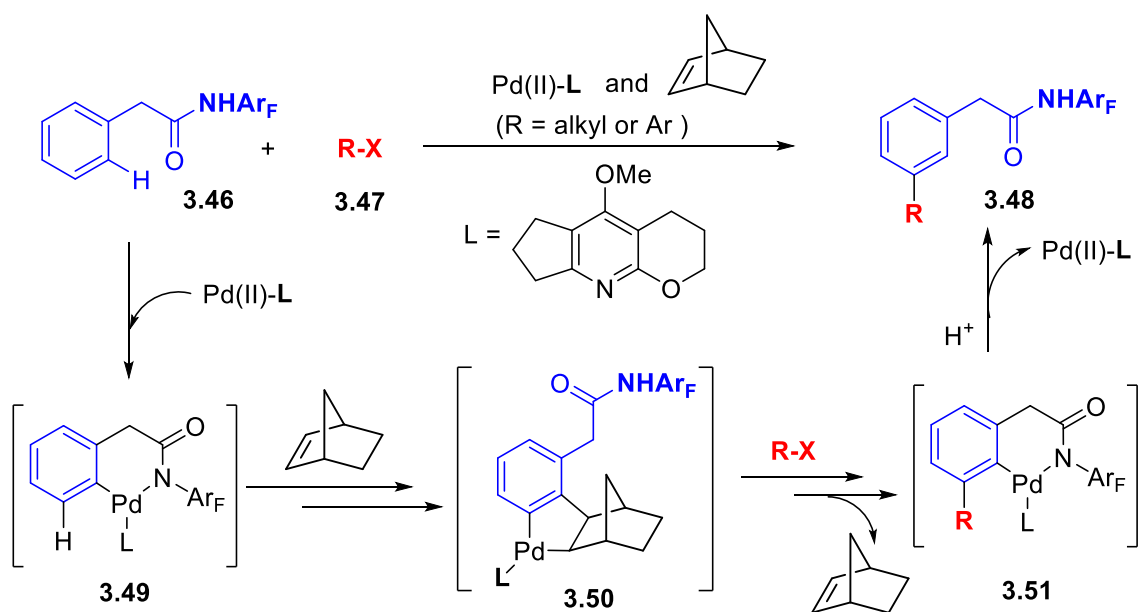
Scheme 3.11. Norbornene as a transient mediator for *meta*-C–H activation.

Yu and coworkers reported metal alkylation and arylation of phenylacetic amides, Whereas Dong et al. disclosed *meta* arylation of tertiary amine using Pd/norbornene catalysis. These protocols imply the possibility of obtaining *meta* or *ortho* selectivity through catalyst control. [29] However, transition metal catalyzed directed C-H bond activation requires extra steps

for installation and removal of directing group or template. The ideal directing group could be commercially available and readily removable after C-H bond functionalization. In this context, the traceless directing group is considered as an elusive strategy for the site-selective C-H bond functionalization. This strategy provides access to *meta* or *para* functionalized arenes with atom and step economy (Scheme 3.12).
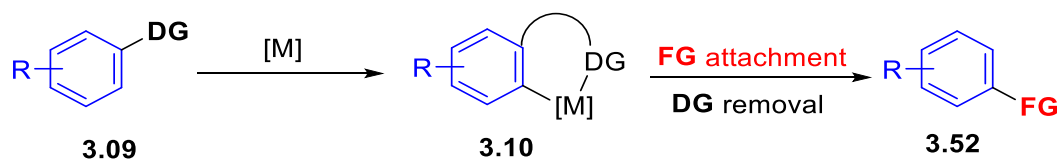
Scheme 3.12. Transition metal catalyzed C-H bond functionalization using traceless directing group.

In the recent years, -COOH has been employed as a traceless directing group because carboxylic acids are readily available, cheap, air stable and easy to remove.[30, 31] In this regard, decarboxylative C-H bond functionalization is considered as an elegant strategy for the construction of C-C bonds. Miura and coworkers reported oxidative coupling of benzoic acid with alkynes for the synthesis of coumarins (**3.54**) using Rh(III) as a catalyst and Cu(OAc)$_2$ oxidant (Scheme 3.13). This oxidative cyclization occurs via a tandem reaction of carboxylic acid directed C-H bond activation, alkyne insertion, and oxidative cyclization. Iridium-catalyzed [2+2+2] decarboxylative cyclization of benzoic acid and alkyne was also realized at elevated temperature in the presence of the Ag$_2$CO$_3$ oxidant to afford naphthalene derivatives (**3.55**) (Scheme 3.14). The reaction was proposed to proceed *via* formation of the cyclometalated complex (iridacycle), followed by alkyne insertion and decarboxylation. Second alkyne insertion and then reductive elimination furnished the cyclization product.[32]
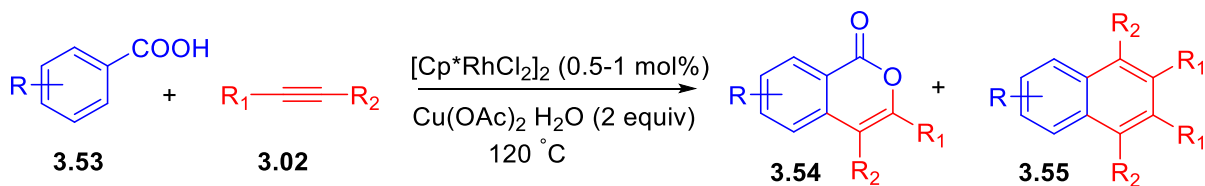
Scheme 3.13. Rhodium-catalyzed dehydrogenative coupling of carboxylic acids with alkynes.
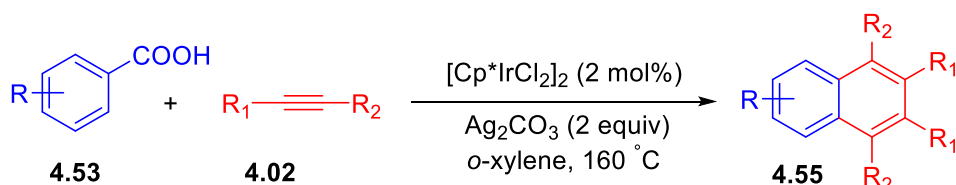
Scheme 3.14. Iridium-catalyzed decarboxylative coupling of carboxylic acids and alkynes.

Recently, Miura et al. first revealed the potential of benzoic acid as a traceless directing group in the year 2008 (Scheme 3.15 a). In the initial report, they disclosed palladium catalyzed decarboxylative alkenylation of heteroarene carboxylic acids in the presence of the stoichiometric amount of copper. The reaction occurs via carboxylic acid directed C-H bond functionalization followed by decarboxylation to produce corresponding products.[33] They subsequently developed a one-pot procedure for the decarboxylative alkenylation of styrenes with aromatic carboxylic acids using Rh(III)/Ag(I) catalytic system to obtain stilbene derivatives (Scheme 3.15 b).
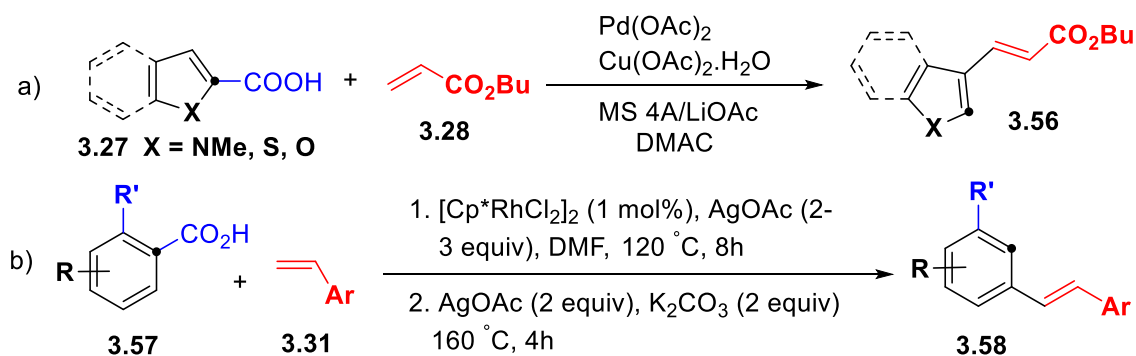
Scheme 3.15. a) Palladium-catalyzed decarboxylative alkenylation of heteroarene carboxylic acids b) Rhodium-catalyzed decarboxylative *ortho*-olefination of benzoic acids.

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The present reaction proceeds in two steps. The first step is rhodium-catalyzed C-H bond functionalization through directed C-H bond activation and the second step is silver mediated decarboxylation.[34] Larrosa et al. applied traceless directing group strategy to furnish biaryl compounds through decarboxylative coupling of *ortho*-substituted benzoic acids (**3.57**) and aryl iodides (**3.59**) using Pd catalyst (Scheme 3.16 a).[35] This reaction was performed in the presence of acetic acid and the stoichiometric amount of silver. Silver catalyzed protodecarboxylation was avoided using acetic acid. Authours demonstrated that Pd catalyst performed the protodecarboxylation of arylated product. Later in 2014, a new methodology was described using traceless directing group relay strategy for *meta* functionalization of phenol (**3.61**) (Scheme 3.16 b).[36] This transformation uses carbon dioxide as a transient directing group for *meta* arylation using aryl iodide as coupling partner. The reaction proceeds via carboxylation followed by tandem arylation and protodecarboxylation. This protocol occurs with high regioselectivity and compatible with many functional groups.
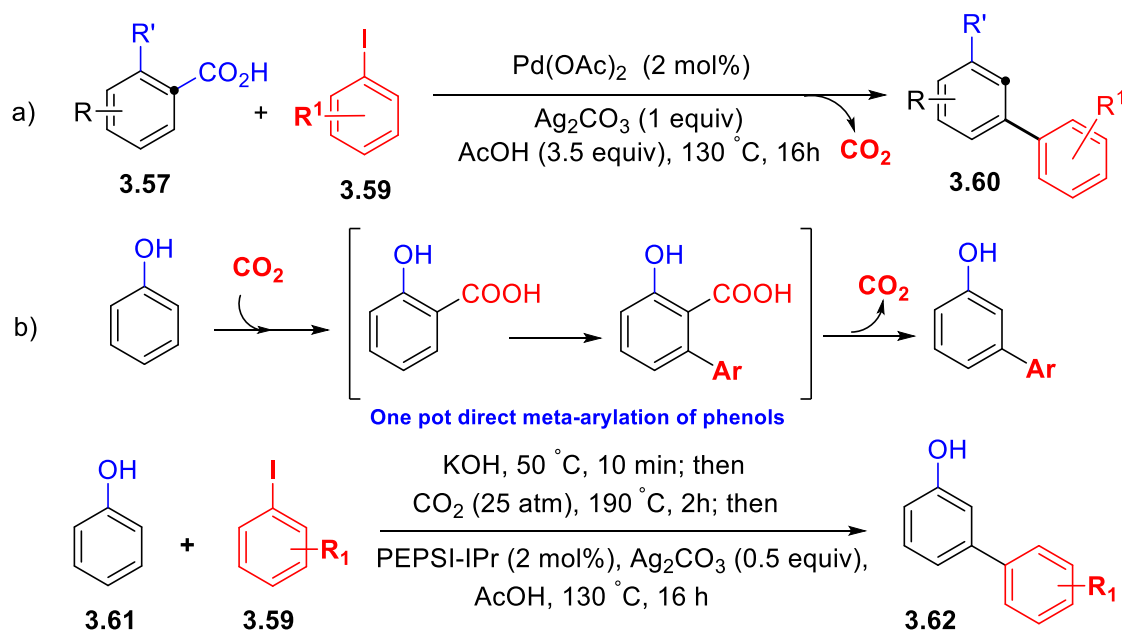
Scheme 3.16. a) Rhodium-catalyzed *ortho*-olefination and decarboxylation of benzoic acids. b) Traceless directing group relay strategy for *meta*-selective arylation of phenols.

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The group of You discovered a new catalytic method for decarboxylative cross-coupling of carboxylic acids (**3.57**) and heteroarenes (**3.63**) (Scheme 3.17). This reaction proceeds through tandem Rh(III) catalyzed carboxylic acid directed C-H arylation/Ag-catalyzed protodecarboxylation and it occurres with broad substrate scope, and functional group tolerance. This transformation enables the easy synthesis of *meta*-substituted biaryl scaffolds with heteroarenes.[37]
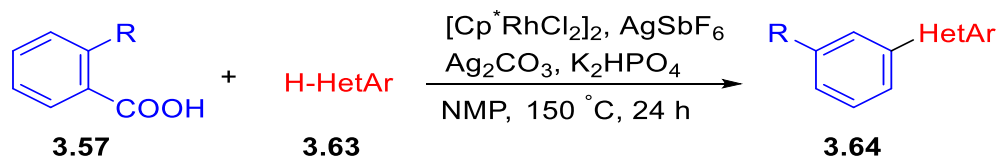
Scheme 3.17. Rh(III)-Catalyzed decarboxylative *ortho*-heteroarylation of aromatic carboxylic acids.

Recently, Li and co-workers disclosed another protocol for ruthenium catalyzed regiospecific C-H bond functionalization of carboxylic acids using isocyanate (**3.65**) as a coupling partner (Scheme 3. 18).[38] This transformation occurs via carboxylic acid directed C-H bond functionalization followed by decarboxylation. This method offers access to *meta*-substituted benzamides (**3.66**) which are difficult to synthesize in a single step.
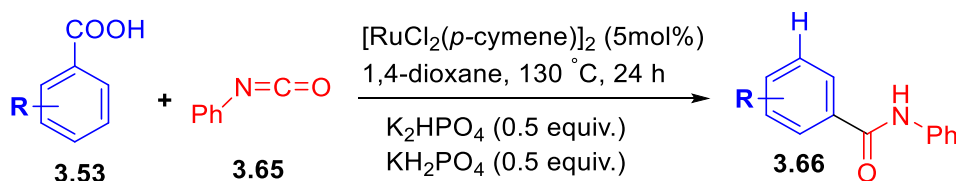
Scheme 3.18. Ru(II)-catalyzed decarboxylative *ortho*-amidation of aromatic acids.

Although numerous methods have been developed for decarboxylative functionalization of arenes using transition metal catalysts, most of them need an *ortho*-inductive electron-withdrawing aromatic substituent and stoichiometric amounts of additives, and oxidants to facilitate the transformations which limit the substrate scope and functional group tolerance.

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Zhao group et al. established a new protocol for alkyne hydroarylation using arene carboxylic acids as coupling partner.[39] Authors envisioned that the reaction proceeds in a tandem sequence of carboxylic acid directed alkenylation followed by chelation(alkenyl) assisted decarboxylation.

Scheme 3.19. Decarboxylative alkyne hydroarylation with benzoic acids via double chelation-assistance

Authors tested the proposed hypothesis by taking benzoic acid and diphenylacetylene as reaction partners. After the extensive screening of ligands and solvents decarboxylative hydroarylation is achieved in 90% yield using 10 mol% [Ru(p-cymene) (OAc)$_2$] as a catalyst in the mixed solvent system (2:2:1 dioxane, mesitylene, and heptane) at 80 $^\circ$C. In addition, formation of byproducts such as alkyne hydrocarboxylation,[40] oxidative [4+2] heterocyclization,[41] and oxidative [2+2+2] carbocyclization via decarboxylation was observed. The present reaction occurs with high regio and stereoselectivity, and high functional group tolerance.

Substrate scope of the arene carboxylic acids was studied by taking diphenyl acetylene as coupling partner. *para*-Substituted arene carboxylic acids worked well under optimized conditions and furnished *meta*-substituted alkenyl arenes. The reaction of *meta* substituted arene carboxylic acids under established conditions lead to formation *para* alkenylation products. Later alkyne scope was investigated with the model reaction between the *para* methoxy benzoic acid

and various alkynes. All internal alkynes proceeded smoothly with high yields and regio and

stereoselectivity.
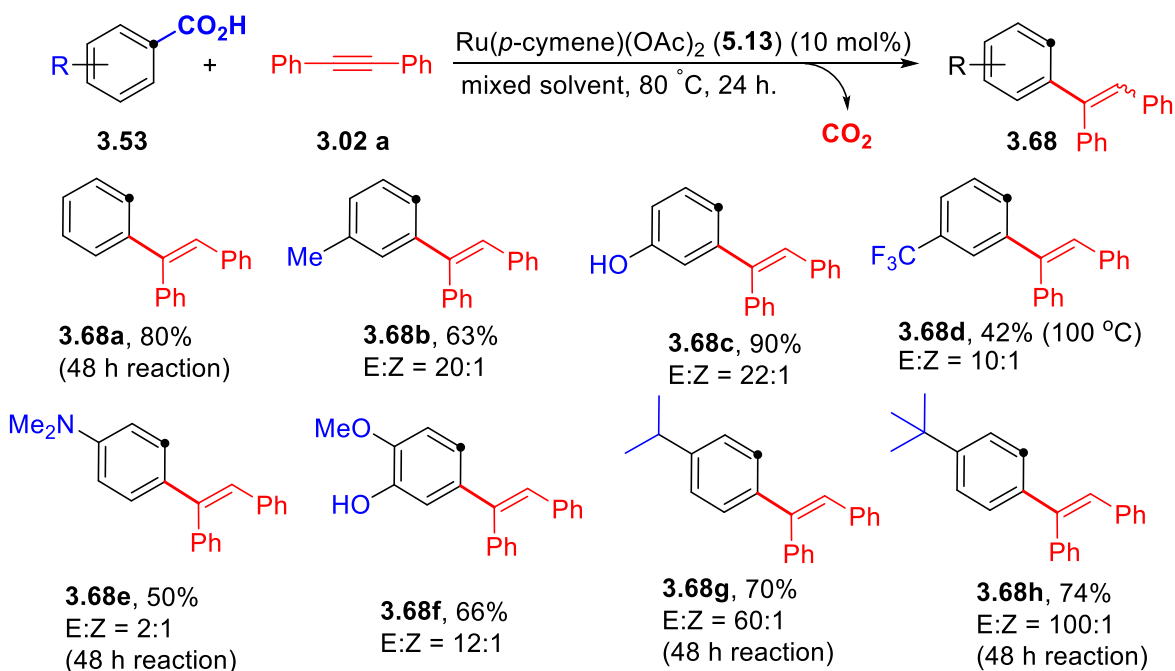
Scheme 3.20. Substrate scope of decarboxylative alkyne hydroarylation with benzoic acids.

Based on "double chelation assistance" hypothesis, authors proposed a plausible

mechanism for the decarboxylative hydroarylation as depicted in Scheme 3.21. It was proposed

that the formation of cyclometalated intermediate **II** via carboxylate directed C-H bond

activation followed by insertion of alkyne into the metal-aryl bond generates cyclometalated

alkenylruthenium (**III**). Protonation of metal alkenyl intermediate produces alkenyl-chelated

Ru(II) carboxylate intermediate (**IV**). chelation-assisted decarboxylation of intermediate **IV** leads

to the formation of aryl-ruthenium intermediate **V**. Upon protonation of **V** affords the

decarboxylative hydroarylation product.
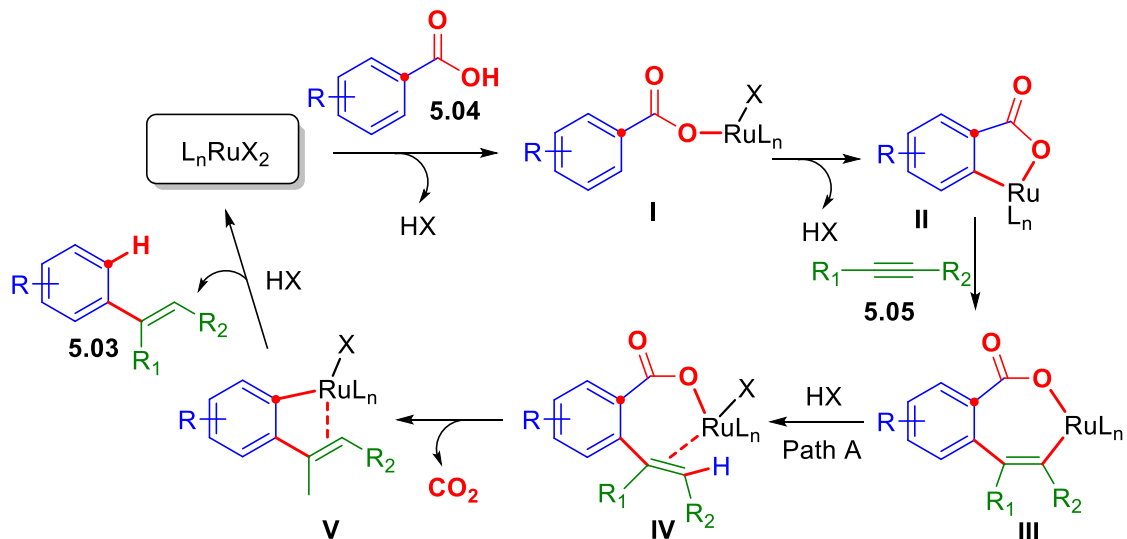
Scheme 3.21. Ruthenium catalyzed decarboxylative hydroarylation of alkynes.

The newly developed ruthenium catalyzed decarboxylative alkyne hydroarylation occurs under redox neutral conditions with broad range of functional group tolerance and substrate scope. This method also obviates the need for *ortho* substituted arene carboxylic acids and stoichiometric amounts of bases or oxidants. This protocol provides an easy route for the synthesis of various *meta, para*-substituted alkenyl arenes which are difficult to achieve via conventional Hydroarylation. This strategy demonstrates the synthetic utility of arene carboxylic acids as readily available synthons for transition metal catalyzed C-H bond functionalization.

In this chapter we describe ruthenium-based decarboxylative alkenylation of heteroarenes through directed C-H bond functionalization. The decarboxylative functionalization of heteroarenes occurs with high regioselectivity and broad range of functional group tolerance.

This decarboxylation proceeds without stoichiometric amounts of bases or Ag/Cu salts and it is applicable for functionalization of various hetero arenes such as indole, pyrrole, thiophene, benzothiophene, and benzofuran at both C-2 and C-3 positions. This protocol provides a straightforward approach for the synthesis of trisubstituted olefins with heteroarenes.

3.2. Initial Results

Recently the groups of Zhao, Gooβen and Ackermann reported decarboxylative hydroarylation of alkynes with aromatic carboxylic acids using ruthenium catalyst. Inspired by these reports and in continuation of our efforts towards development transition metal catalyzed C-H bond functionalization, we investigated decarboxylative hydroheteroarylation of alkynes with heteroarene carboxylic acids using ruthenium catalysts. After preliminary testing, we observed the formation of desired product in 38% yield using [RuCl$_2$(p-cymene)]$_2$ in the presence of AgSbF$_6$ and NaOAc in toluene at 100 $^\circ$C.
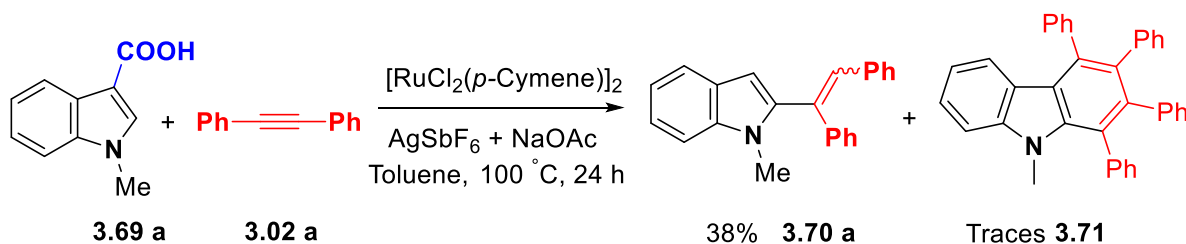
Scheme 3.22. Initial result of ruthenium catalyzed decarboxylative hydro heteroarylation with N-methyl indole-3-acid and diphenylacetylene.

3.3. Optimization of Reaction Condition

Encouraged by the initial result, we screened various ruthenium catalysts as shown in Table 1. Best result was obtained with [Ru(OAc)$_2$(p-cymene)]$_2$ in toluene at 100 $^\circ$C. After testing the several solvents, dioxane was considered as the optimal solvent. Increasing the temperature to 120 °C improved the reaction efficiency and the desired product was obtained in 84% yield. The optimized condition for decarboxylative hydro heteroarylation of alkynes with heteroarene carboxylic acids was found to be [Ru(OAc)$_2$(p-cymene)]$_2$ (10 mol%) in Dioxane at 120 $^\circ$C.

Table 3.1. Optimization of ruthenium catalysed decarboxylative hydroheteroarylation of internal alkynes.

Catalyst (mol%)	Additive	Temp	Solvent	yield(%)[a]
[RuCl$_2$(p-cymene)]$_2$	AgSbF$_6$ + NaOAc	100	Toluene	38
[RuCl$_2$(p-cymene)]$_2$	AgSbF$_6$+ Ag$_2$CO$_3$	100	Toluene	23
[RuCl$_2$(p-cymene)]$_2$	NaOAc	120	Toluene	53
[Ru(OAc)$_2$(p-cymene)]	-	120	Toluene	56
[Ru(OBz)$_2$(p-cymene)]	-	120	Toluene	48
[Ru(MesCO$_2$)$_2$(p-cymene)]	-	120	Toluene	53
[Ru(OPiv)$_2$(p-cymene)]	-	120	Toluene	45
[Ru(OAc)$_2$(p-cymene)]	Pivalic acid	120	Toluene	52
[Ru(OAc)$_2$(p-cymene)]	Acetic acid	120	Toluene	55
[Ru(OAc)$_2$(p-cymene)]	Trifluoroacetic acid	120	Toluene	0
[Ru(OAc)$_2$(p-cymene)]	K$_2$CO$_3$	120	Toluene	34
[Ru(OAc)$_2$(p-cymene)]	K$_2$HPO$_4$	100	Toluene	32
[Ru(OAc)$_2$(p-cymene)]	KH$_2$PO$_4$	120	Toluene	32
[Ru(OAc)$_2$(p-cymene)]	KH$_2$PO$_4$	120	Toluene	32
[Ru(OAc)$_2$(p-cymene)]	-	120	DCE	52
[Ru(OAc)$_2$(p-cymene)]	-	120	DME	44
[Ru(OAc)$_2$(p-cymene)]	-	120	DMF	52
[Ru(OAc)$_2$(p-cymene)]	-	120	CH$_3$CN	44
[Ru(OAc)$_2$(p-cymene)]	-	120	Xylene	52
[Ru(OAc)$_2$(p-cymene)]	-	120	Benzene	44
[Ru(OAc)$_2$(p-cymene)]	-	120	THF	59
[Ru(OAc)$_2$(p-cymene)]	-	120	Mixed	54
[Ru(OAc)$_2$(p-cymene)]	-	120	Dioxane	68
[Ru(OAc)$_2$(p-cymene)]	-	120	Dioxane	87[b]

[a] General reaction conditions: 3.69a (0.30 mmol, 1.3 equiv),
3.02a (0.15 mmol, 1.0 equiv), [Ru] (0.015mmol, 0.10 equiv), dioxane (1.0 mL),
120 °C, 48 h; NMR yields using 1,3,5-trimehoxy bezene as internal standard.
[b]: 2 equiv of 3.69a instaed of 1.3 equiv

3.4. Substrate Scope
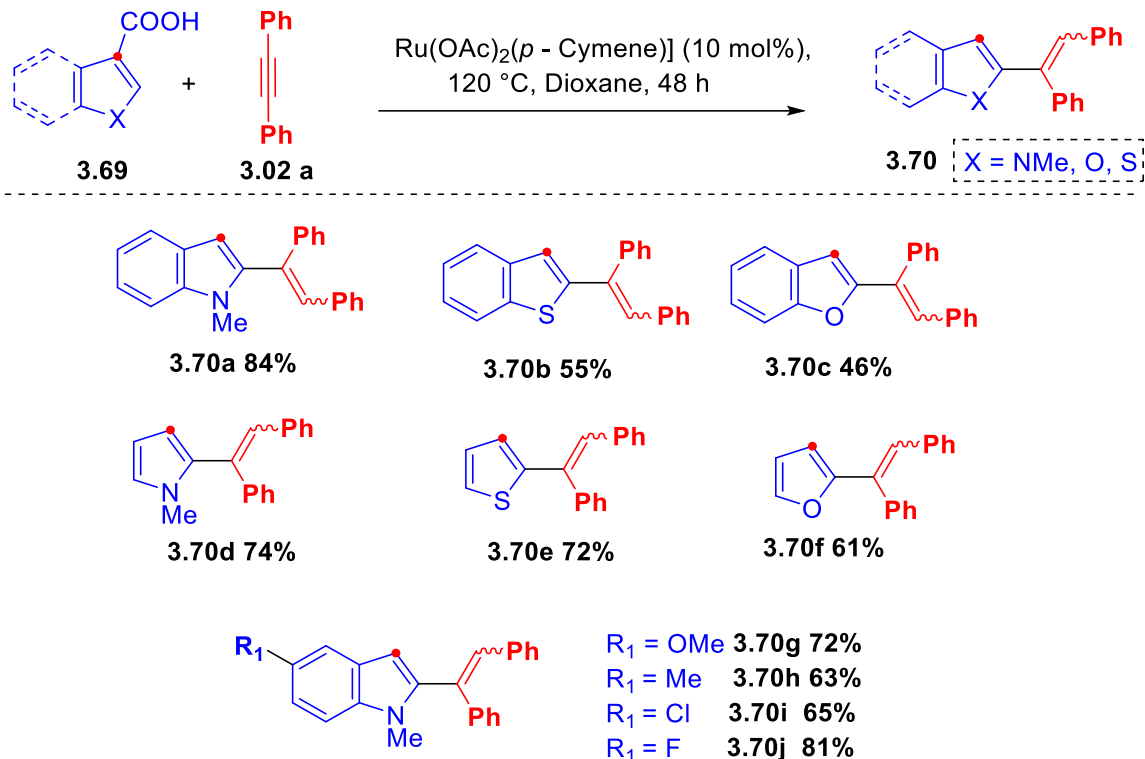
General reaction conditions: 3.69 (0.30 mmol, 2.0 equiv), 3.02a (0.15 mmol, 1.0 equiv), [Ru] (0.015mmol, 0.10 equiv), dioxane (1.0 mL), 120 °C, 48 h; averaged isolated yields of two runs.

Figure 3.1. Substrate scope of heteroarene 3-carboxylic acids in ruthenium catalyzed decarboxylative alkyne hydroheteroarylation with diarylacetylenes.

With the establishment of optimized conditions, the scope of heteroarene-3-carboxylic acids (**3.69**) was investigated using diphenylacetylene (**3.02a**) as a reaction partner. The reaction of Indole-3-carboxylic acid (**3.69a**) with diphenylacetylene (**3.02a**) proceeded smoothly, and the desired product was isolated in 84% yield. Later, various indole 3-carboxylic acids (**3.69g-j**) bearing electron donating and withdrawing groups were subjected to ruthenium catalyzed decarboxylative hydro heteroarylation. All indole-3-carboxylic acids were coupled efficiently irrespective of electronics, and corresponding products (**3.70g-j**) were obtained in 72-81% yield. All the products were afforded as a mixture of E and Z isomers. Next, established ruthenium

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catalytic system was extended to other heteroarene 3-carboxylic acids such as thiophene, furan, pyrrole, benzothiophene, benzofuran and the desired products (**3.69b-f**) were afforded in 46-83% yield. Subsequently, we also examined the reactivity of heteroarene 2-carboxylic acids (**3.72**) by taking diphenylacetylene as a coupling partner and the corresponding decarboxylative hydro heteroarylated products (**3.73a-f**) were furnished in 25-81% yield.

General reaction conditions: 3.72 (0.30 mmol, 2.0 equiv), 3.02 (0.15 mmol, 1.0 equiv), [Ru] (0.015mmol, 0.10 equiv), dioxane (1.0 mL), 120 °C, 48 h; averaged isolated yields of two runs.
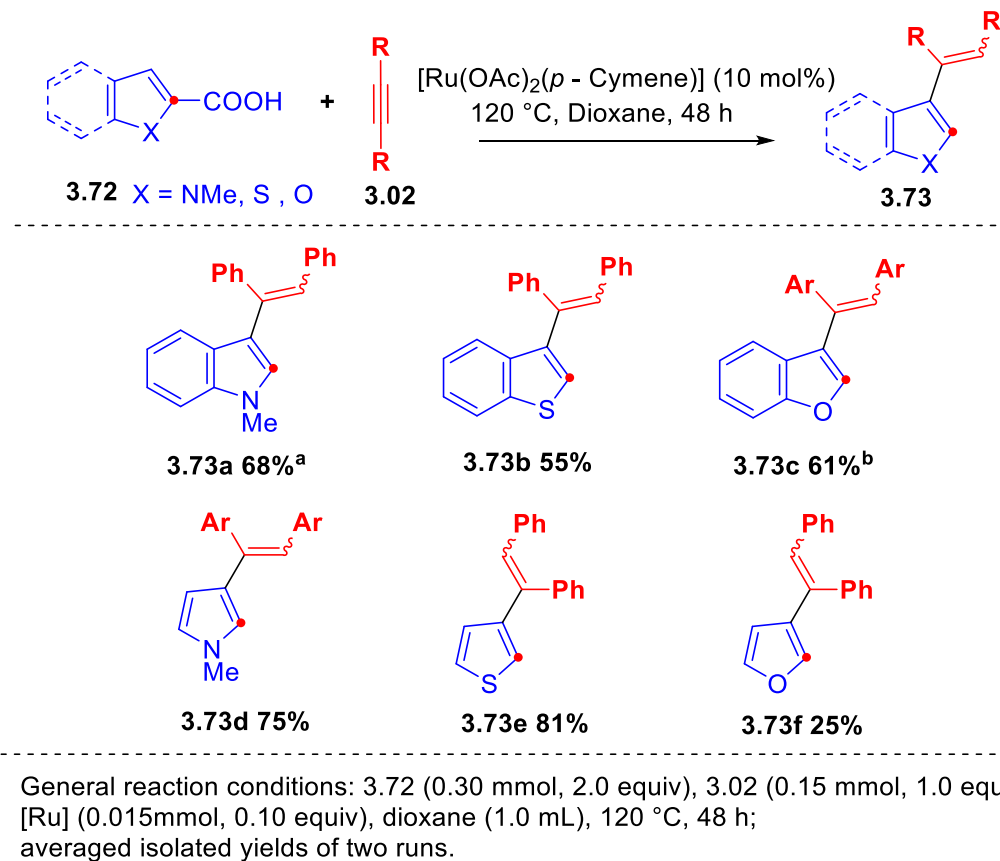
Figure 3.2. Substrate scope of heteroarene 2-carboxylic acids in ruthenium catalyzed decarboxylative alkyne hydro heteroarylation with diarylacetylenes.

Next, the scope of diarylacetylenes was examined by taking indole-3-carboxylic acid (**3.69a**) as a coupling partner. Decarboxylative hydro heteroarylation (hydroindolation) of symmetrical diarylacetylenes proceeded efficiently, and the corresponding products were afforded in good yields 62-79%. There was no loss of reactivity with the change of electronics at the *para* position. Although reactivity is good with *para* Br and *para* CF_3 substrates, to obviate

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isolation problem thiophene-2-carboxylic acid (**3.72e**) was chosen as coupling partner and desired products are furnished in 67% and 83% yields. Dimethyl acetylene dicarboxylate also coupled efficiently with thiophene-2- carboxylic acid to give the product **3.73i** in 61% yield. Upon reaction of unsymmetrical alkyne 1-phenyl-1-propyne with thiophene 2-carboxylic acids using stabilized ruthenium catalytic condition provided the desired product (**3.73j**) in 63% yield. The present catalytic system tolerates various functional groups such as methoxy, methyl, bromo, chloro, fluoro, and ester and occurred with high regioselectivity, and good yields.
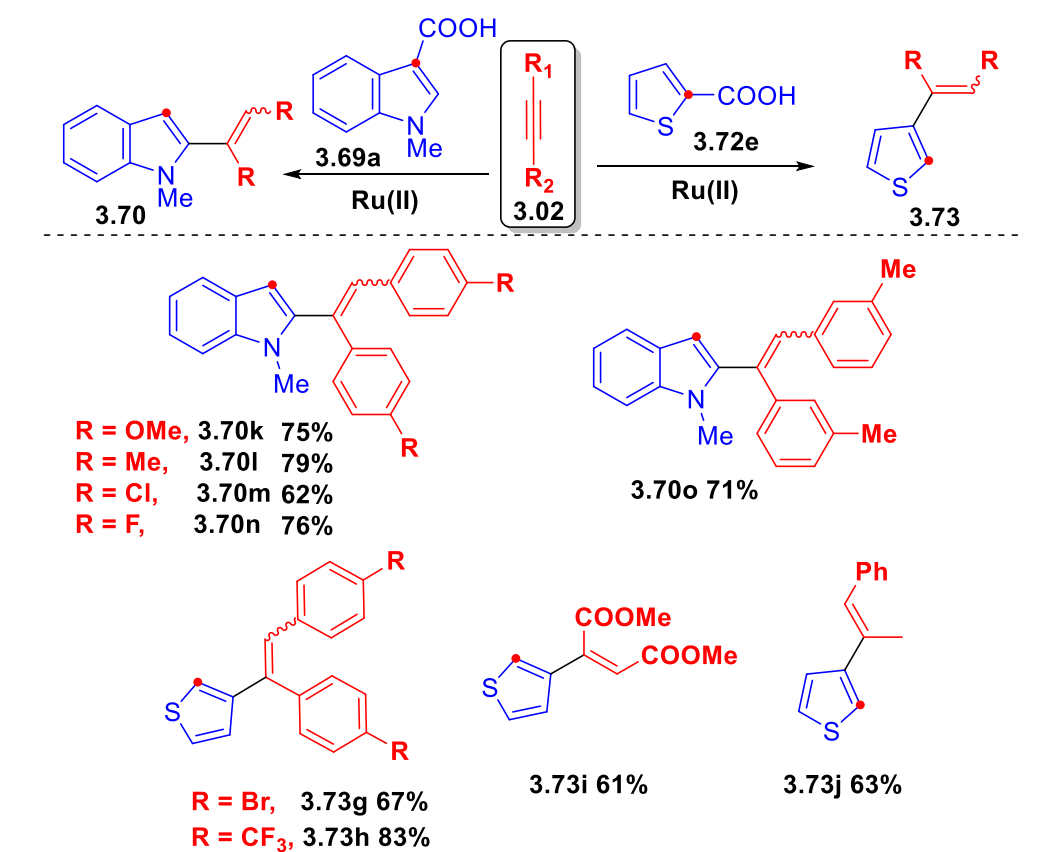
Scope of Alkynes. General reaction conditions: 3.69a or 3.72e (0.30 mmol, 2.0 equiv), 3.02 (0.15 mmol, 1.0 equiv), [Ru] (0.015mmol, 0.10 equiv), dioxane (1.0 mL), 120 °C, 48 h; averaged isolated yields of two runs

Figure 3.3. Substrate scope of alkynes in ruthenium catalyzed decarboxylative alkyne hydro heteroarylation.

3.5. Reaction Mechanism Studies

To further understand the mechanism, series of experiments were performed as shown in Scheme 3.23 a. First, intermolecular competition reaction was performed with an equimolar mixture of **3.69g** and **3.69j** by reacting with diphenylacetylene and the corresponding products were obtained in (**3.70g : 3.70j**) 1:1.3 in ratio. High reactivity of electron-deficient indole acid (**3.69j**) suggests that electrophilic C-H activation mechanism is less likely. Second, decarboxylative hydroindolation was carried out in the presence of deuterated acetic acid and incorporation of deuterium in **3.73a** demonstrates the intermolecular protonation. Overall these experiments prove the present reaction mechanism is consistent with the previously reported mechanism for decarboxylative hydroarylation which occurs through the Ruthenium catalysed chelation assisted C-H bond alkenylation followed by chelation assisted decarboxylation.
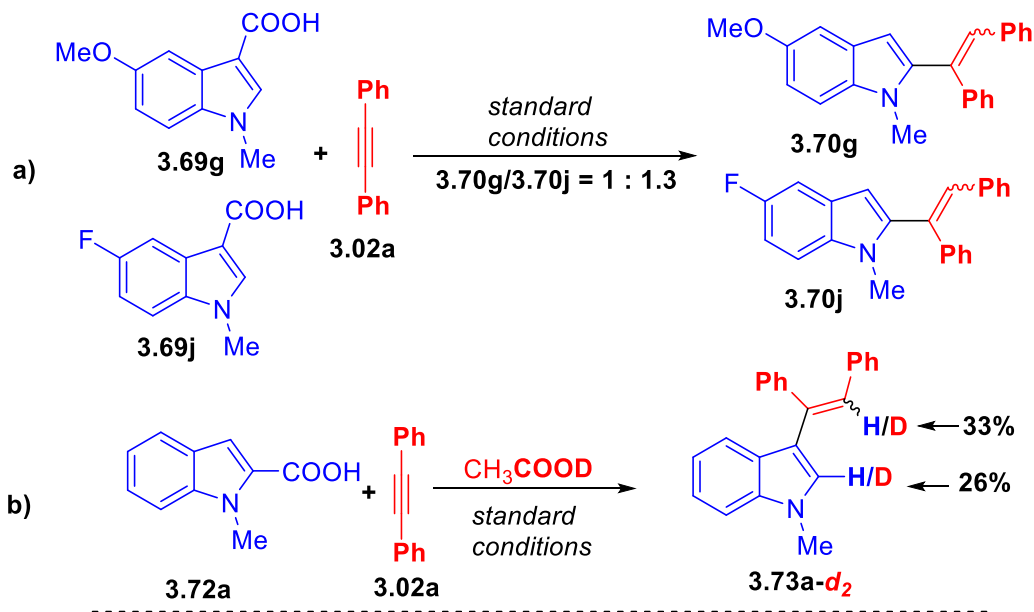
Scheme 3.23. Results from reaction mechanism studies (a) Intermolecular competition experiments (b) Deuterium labeling study.

3.6. Optimization of Reaction Condition

In addition to C-H hydro(hetero)arylation of alkynes, cross dehydrogenative coupling of arene or heteroarene C-H bonds with alkenes is also emerged as an essential tool for the synthesis of vinyl (hetero)arenes. As disucussed earlier, various ruthenium catalysts were explored for oxidative coupling of (hetero)arenes and alkenes. In the year 2011, Miura et al. reported regioselective oxidative vinylation heteroarene carboxylic acids with alkenes using ruthenium catalyst. We attempted to develop a new method for the decarboxylative oxidative coupling heteroarene carboxylic acids with activated olefins using ruthenium catalyst. We began our study by taking indole-2-carboxylic acid (**3.72**) and tertiary butyl acrylate as model substrates. After screening various oxidants in the presence of [Ru(OAc)$_2$(p-cymene)] catalyst best result was obtained with V$_2$O$_5$. Dioxane proved to be optimal solvent for this reaction.

Table 3.2. Optimization of ruthenium catalysed decarboxylative alkenylation of heteroarenes with activated olefins.

Catalyst (mol%)	Additive	Temp (°C)	Solvent	yield(%)[a], [b]
[Ru(OAc)$_2$(p-cymene)]	Ag$_2$CO$_3$	100	Dioxane	31
[Ru(OAc)$_2$(p-cymene)]	AgOAc	100	Dioxane	35
[Ru(OAc)$_2$(p-cymene)]	Ag$_2$O	100	Dioxane	24
[Ru(OAc)$_2$(p-cymene)]	K$_2$S$_2$O$_8$	100	Dioxane	41
[Ru(OAc)$_2$(p-cymene)]	Benzoquinone	100	Dioxane	55
[Ru(OAc)$_2$(p-cymene)]	PhI(OAc)$_2$	100	Dioxane	55
[Ru(OAc)$_2$(p-cymene)]	CuO	100	Dioxane	34
[Ru(OAc)$_2$(p-cymene)]	Cu$_2$O	100	Dioxane	32
[Ru(OAc)$_2$(p-cymene)]	Cu(OAc)$_2$	100	Dioxane	52
[Ru(OAc)$_2$(p-cymene)]	Cu(OAc)$_2$	100	Toluene	33
[Ru(OAc)$_2$(p-cymene)]	V$_2$O$_5$	100	Dioxane	49
[Ru(OAc)$_2$(p-cymene)]	V$_2$O$_5$	120	Dioxane	87
[Ru(OAc)$_2$(p-cymene)]	Cu(OAc)$_2$	120	Toluene	85
[Ru(OAc)$_2$(p-cymene)]	V$_2$O$_5$	100	Xylene	44
[Ru(OAc)$_2$(p-cymene)]	V$_2$O$_5$	120	DCE	68
[Ru(OAc)$_2$(p-cymene)]	V$_2$O$_5$	120	Acetonitrile	37
[Ru(OAc)$_2$(p-cymene)]	V$_2$O$_5$	120	DME	59
[Ru(OAc)$_2$(p-cymene)]	V$_2$O$_5$	120	DMF	41
[Ru(OAc)$_2$(p-cymene)]	V$_2$O$_5$	120	THF	59

[a] General reaction conditions: 3.69 (0.30 mmol, 2.0 equiv), 3.74 (0.15 mmol, 1.0 equiv), [Ru] (0.015mmol, 0.10 equiv), oxidant (2 equiv), dioxane (1.0 mL), 120 °C, 48 h; [b] GC-MS yields.

3.7. Substrate Scope

With best reaction conditions in hand, we examined the scope of heteroarene-2-carboxylic acids such as indole, thiophene, pyrrole, benzothiophene and benzofuran in ruthenium catalyzed decarboxylative C-H alkenylation and the corresponding products (**4.75a-4.75f**) are furnished in 35 to 82% yield. Indole-3- carboxylic acid(**4.69a**) is also proceeded smoothly under optimized conditions to afford 2-alkenylated indole (**4.75f**). However, other heteroarene-3-carboxylic acids didn't react to give the desired products. This reaction proceeds in a tandem sequence of ruthenium catalyzed carboxylic acid directed C-H alkenylation followed by decarboxylation.
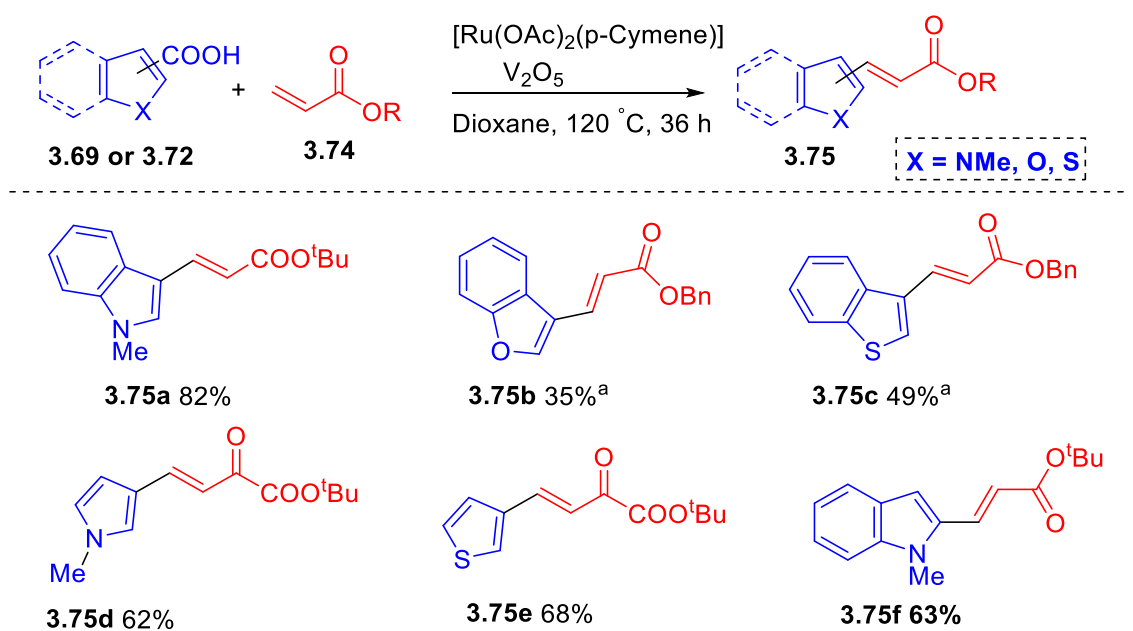

General reaction conditions: 3.69 or 3.72 (0.30 mmol, 2.0 equiv), 3.74 (0.15 mmol, 1.0 equiv), [Ru] (0.015mmol, 0.10 equiv), V_2O_5 (2.2 equiv), dioxane (1.0 mL), 120 °C, 48 h; averaged isolated yields of two runs. a: 5 equiv of acid is used

Figure 3.4. Substrate scope for ruthenium catalyzed decarboxylative alkenylation of heteroarenes.

3.8. Conclusion

In summary, we disclosed a new protocol for ruthenium catalyzed decarboxylative alkenylation of various heteroarenes through C-H bond activation. This transformation proceeds with high regioselectivity and enables alkenylation of heteroarenes at both second and third positions. Moreover, the current study demonstrates the potential of carboxylic acid as a traceless removal directing the group to achieve regioselectivity in transition metal-mediated directed C-H bond activation.

3.9. Experimental Procedures

3.9.1. General Experimental Procedures and Reagent Availability

Unless otherwise noted, all manipulations were carried out under a nitrogen atmosphere using standard Schlenk-line or glove box techniques. All glassware was oven-dried for at least one hour before use. Toluene, THF, benzene, and hexane solvents were degassed by purging with nitrogen for 45 min and dried with a solvent purification system (MBraun MB-SPS). Other reagents and starting materials for substrate synthesis were purchased from Sigma-Aldrich, VWR, Strem, Oakwood Chemical or Ark-Pharm and were used as received. TLC plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated by rotary evaporation at ~10 Torr. Flash column chromatography was performed with 40–63 microns silica gel. 1H and 13C NMR spectra were obtained on a 400 MHZ spectrometer, and chemical shifts were recorded relative residual protiated solvent. Both 1H and ^{13}C NMR chemical shifts were reported in parts per million downfield from tetramethylsilane (δ = 0 ppm). ^{19}F NMR spectra were obtained at 282.4 MHz, and all chemical shifts were reported in parts per million upfield of CF_3COOH (δ = -78.5 ppm). GC analyses were performed on a Shimadzu GC-2010

system. GC-MS data were obtained on an Agilent 7890AGC system and an Agilent 5975C mass selective detector. High-resolution mass spectra were obtained at a Waters HRMS spectrometer.

3.9.2. Experimental Procedure for Preparation of Alkyne Substrates

Diaryl alkynes were prepared by following the reported literature.[42]
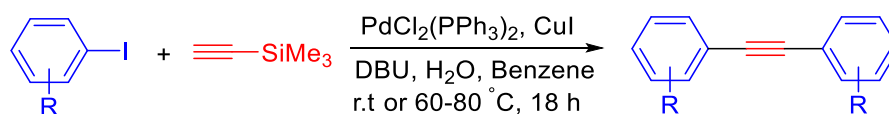
Scheme 3.24. Synthesis of internal alkynes.

i) General procedure for sonogashira coupling at room temperature (Symmetrical): Into a flame-dried 100 mL flask equipped with a magnetic stir bar was charged with $PdCl_2(PPh3)_2$(16.8 mg, 6 mol%), CuI (15.2 mg, 10 mol%) and starting material iodide. The flask was purged with nitrogen for 20 min, and then dry benzene was added. While stirring, DBU (6 equiv) was added, followed by Ice-chilled trimethylsilyl ethynylene (57 µL, 0.50 equiv) and distilled water (5.8 µL, 40 mol%) were added. The reaction mixture was purged with nitrogen, and the flask was covered in aluminum foil while stirring the mixture at room temperature for 18 hours. After that, the reaction mixture is partitioned into ethyl ether and distilled water (50 mL each). The organic layer is washed with 10% HCl (3X 75 mL), saturated aqueous NaCl (1X75 mL) and dried over $MgSO_4$. The solution was filtered, and the solvent was removed in vacuum to afford crude product. The crude product was purified by silica gel column chromatography.

ii) General procedure for sonogashira coupling at elevated temperature (Symmetrical): Oven-dried 100 mL flask was purged with nitrogen and then charged with $PdCl_2(PPh_3)_2$ (27.4 mg, 6 mol%), CuI (24.8 mg, 10 mol%), and starting material iodide (1 equiv, 1.3 mmol). While stirring, dry benzene (6.5 mL, starting material is 0.20 M in dry benzene) was added followed by dropwise addition of DBU (1.17 mL, 6 equiv) under a nitrogen atmosphere. To the resulting mixture, Distilled water (5.6 µL, 40 mol%) and ice-chilled trimethylsilyl ethynylene (92 µL, 0.50

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equiv) were added. The reaction mixture was transferred to a preheated oil bath at 60 °C and blocked from incidental light. After stirring the flask for 18 h, the reaction mixture was cooled to room temperature and partitioned in ethyl ether and distilled water (50 mL each). The organic layer was washed with 10% HCl (3X 75 mL) followed by saturated aqueous NaCl (1X 75 mL). The combined organic layers were dried over MgSO4 and the solvent removed in vacuum to obtain the crude product. The crude product is purified by silica gel column chromatography.

3.9.3. General Procedure for Synthesis of Heteroarene Carboxylic Acids[43, 44]
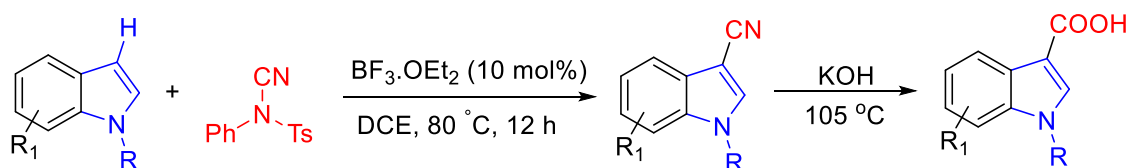
Scheme 3.25. Synthesis of indole-3-carboxylic acids.

A flame-dried vial equipped with a magnetic stir bar was charged with indole (4.8 mmol, 1.2 equiv) and N-cyano-4- methyl-N-phenyl benzene sulfonamide (NCTS, 1) (4 mmol, 1.0 equiv). After addition of anhydrous DCE (4 mL) and BF3·OEt2 (0.4 mmol) vial was sealed with a silicone-lined screw-cap and stirred at 80 °C for 12 h. The reaction mixture was concentrated under vacuum and purified by column chromatography to furnish the desired cyanated product.

Into a 10 mL vial equipped with a stir bar was charged with cyano compound (3 mmol, 1 equiv) and 4N aqueous KOH (10 equiv). The resulting mixture was moved to the preheated oil bath and stirred at 105 °C for 12 h. After completion of the reaction, the reaction mixture was neutralized by 2N HCl aq. (2.8 mL) and p^H of the solution was adjusted to 2-3. The reaction mixture was extracted with DCM (600 mL), and the combined organic layers were dried over MgSO4. The solvent was removed under reduced pressure, and the solid was washed with Et2O (3 × 10 mL) to afford the product as a colorless solid.

3.9.4. General Procedure for Ru-Catalyzed Alkyne Hydroheteroarylation

Into a 4 mL scintillation vial equipped with a magnetic stir bar was charged with [Ru(OAc)$_2$(p-cymene)] (0.017 mmol), Alkyne (0.17 mmol), and heteroarene carboxylic acid (0.34 mmol). Subsequently, Dioxane (1 mL) was added, and the vial was sealed with a silicone-lined screw-cap and electrical tape. After stirring the reaction mixture at room temperature for 5 minutes, the vial was transferred out of the glovebox and stirred at 120 $^{\circ}$C for 48 hours. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure to obtain the crude product. Further purification was achieved by flash-column chromatography on silica.

3.9.5. Intermolecular Competition Experiment

An oven dried 4 mL scintillation vial was charged with [Ru(OAc)$_2$(p-cymene)] (0.017 mmol), Alkyne (0.17 mmol), and heteroarene carboxylic acids 4.69g (0.34 mmol) and 4.69(0.34 mmol). After addition of Dioxane (1 mL) solvent, the vial was sealed with a silicone-lined screw-cap and electrical tape and the reaction mixture was stirred at room temperature for 5 minutes. The vial was transferred out of the glovebox and stirred at 120 $^{\circ}$C for 30 minutes. After completion, the reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure to obtain the crude product. The crude product was purified by flash-column chromatography on silica.

3.9.6. Deuterium Labeling Study

Alkyne (0.17 mmol), heteroarene carboxylic acid (0.34 mmol) and [Ru(OAc)$_2$(p-Cymene)] (0.017 mmol) were added into a 4 mL scintillation vial. To the above mixture, Dioxane (1 mL) and CH$_3$COOD (0.34 mmol) were added, and the vial was sealed with a silicone-lined screw-cap and electrical tape. After stirring the reaction mixture at room

temperature for 5 minutes, the vial was transferred out of the glovebox and stirred at 120 $^{\circ}$C for 24 hours. The reaction mixture was cooled to room temperature, and volatiles were removed under reduced pressure to obtain the crude product. The crude product was subjected to further purification by flash-column chromatography on silica.

3.9.7. General Procedure for Ru-Catalyzed Decarboxylative Alkenylation of Heteroarene Carboxylic Acids

An oven dried 4 mL was charged with [Ru(OAc)$_2$(p-Cymene)] (0.017 mmol), heteroarene carboxylic acid (0.34 mmol), and V$_2$O$_5$ (2 equiv). Subsequently, Dioxane (1 mL) and alkene (0.17 mmol) were added, and the vial was sealed with a silicone-lined screw-cap and electrical tape. The vial was transferred out of the glovebox and stirred at 120 $^{\circ}$C for 36 hours. The reaction mixture was brought to room temperature, and the solvent was removed in vacuo to afford the crude product. The crude mixture was purified by flash-column chromatography on silica.

3.10. Spectral Data of Isolated Products
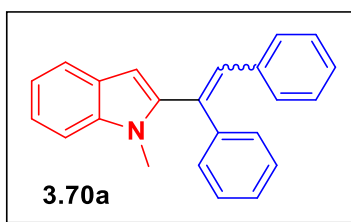
3.70a

2-(1,2-diphenylvinyl)-1-methyl-1H-indole (3.70a): The compound **3.70a** was prepared according to the general method described above and purified by flash column chromatography (0 to 0.1% ethyl acetate in hexanes) in 84% yield as a light-yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.80 − 7.72 (m, 2H), 7.55 − 7.22 (m, 25H), 7.18 − 7.12 (m, 2H), 7.09 (s, 1H), 6.72 (s, 0.7H), 6.59 (d, J = 0.8 Hz, 0.8H), 3.51 (d, J = 1.2 Hz, 6H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 143.6, 142.0, 139.1, 138.8, 138.5, 137.5, 136.9, 136.8, 134.3, 132.5, 132.0, 131.4, 130.2, 129.7,

129.1, 128.6, 128.5, 128.5, 128.4, 128.2, 128.0, 127.8, 127.7, 127.7, 127.3, 127.0, 122.0, 121.5, 120.9, 120.7, 119.8, 119.7, 109.7, 109.4, 103.8, 102.7, 77.5, 77.2, 76.8, 31.3, 30.31. HRMS: m/z calcd for $C_{23}H_{19}N$: 310.1596; found: 310.1588;
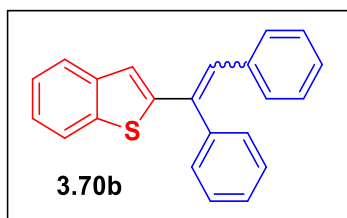
3.70b

2-(1,2-diphenylvinyl)benzo[b]thiophene (3.70b): The compound **3.70b** was prepared according to the general method described above and purified by flash column chromatography (0 to 0.1% ethyl acetate in hexanes) in 55% yield as a colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.90 – 7.80 (m, 1H), 7.76 (dd, J = 6.6, 2.0 Hz, 0.3H), 7.65 (dd, J = 6.1, 2.9 Hz, 1H), 7.58 – 7.32 (m, 10H), 7.30 – 7.03 (m, 8H), 6.93 (s, 1H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 147.6, 142.8, 142.4, 140.9, 140.3, 139.9, 139.1, 138.9, 136.8, 136.7, 136.4, 135.2, 131.5, 130.0, 129.6, 129.6, 129.0, 128.9, 128.3, 128.2, 128.1, 128.0, 128.0, 127.7, 127.5, 127.3, 125.3, 124.8, 124.5, 124.3, 124.2, 123.7, 123.6, 123.5, 122.4, 122.1, 77.4, 77.1, 76.8. HRMS: m/z calcd for $C_{22}H_{16}S$: 313.1051; found: 313.1035;

3.70c

2-(1,2-diphenylvinyl)benzofuran (3.70c): The compound **3.70c** was prepared according to the general method described above and purified by flash column chromatography (In hexanes) in 46% yield as a light-yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$)) δ 7.80 – 6.99 (m, 15H), 6.33 (s, 1H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 158.01, 155.11, 137.61, 136.32, 131.60,

130.10, 129.83, 129.26, 129.05, 128.18, 128.14, 127.42, 124.79, 122.94, 121.01, 111.02, 106.25.

HRMS: m/z calcd for $C_{22}H_{16}O$: 297.1279; found: 297.1279.

3.70d

2-(1,2-diphenylvinyl)-1-methyl-1H-pyrrole (3.70d): The compound **3.70d** was prepared according to the general method described above and purified by flash column chromatography (0 to 0.5% ethyl acetate in hexanes) in 74% yield as a light-yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.59 – 7.11 (m, 15H), 7.07 – 6.98 (m, 2H), 6.92 – 6.64 (m, 2H), 6.40 – 6.19 (m, 2H), 6.18 – 6.09 (m, 1H), 3.34 (s, 2H), 3.27 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 156.0, 142.3, 137.8, 136.6, 131.7, 129.9, 129.5, 128.8, 128.0, 127.9, 126.8, 124.5, 111.6, 109.5, 77.4, 77.1, 76.8. HRMS: m/z calcd for $C_{19}H_{17}N$: 260.1439; found: 260.1438;

3.70e

2-(1,2-diphenylvinyl)thiophene (3.70e): The compound **3.70e** was prepared according to the general method described above and purified by flash column chromatography (0 to 0.1% ethyl acetate in hexanes) in 72% yield as a colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.56 – 7.34 (m, 5H), 7.29 (dd, J = 5.2, 1.2 Hz, 1H), 7.25 – 7.15 (m, 4H), 7.06 (ddd, J = 22.4, 5.5, 3.0 Hz, 3H), 6.84 (dd, J = 3.6, 1.2 Hz, 1H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 148.0, 139.5, 136.7, 136.3, 130.0, 129.5, 128.8, 128.1, 128.0, 127.9, 127.5, 126.9, 126.4, 126.1, 124.8, 77.4, 77.1, 76.8. HRMS: m/z calcd for $C_{18}H_{14}S$: 263.0894; found: 263.0903;
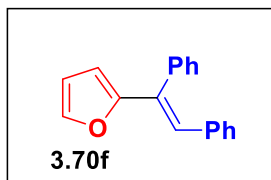
3.70f

2-(1,2-diphenylvinyl)furan(3.70f): The compound **3.70f** was prepared according to the general method described above and purified by flash column chromatography (In hexanes) in 61% yield as a light-yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.56 – 7.36 (m, 6H), 7.30 (s, 1H), 7.22 – 7.14 (m, 3H), 7.11 – 7.04 (m, 2H), 6.44 (dd, J = 3.4, 1.8 Hz, 1H), 5.99 (d, J = 3.3 Hz, 1H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 156.0, 142.3, 137.8, 136.6, 131.7, 129.9, 129.5, 128.8, 128.0, 127.9, 126.8, 124.5, 111.6, 109.5, 77.4, 77.1, 76.8. HRMS: m/z calcd for C$_{18}$H$_{14}$O: 247.1123; found: 247.1131;

3.70g

2-(1,2-diphenylvinyl)-5-methoxy-1-methyl-1H-indole (3.70g): The compound **3.70g** was prepared according to the general method described above and purified by flash column chromatography (0 to 1% ethyl acetate in hexanes) in 72% yield as a light-yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.47 – 7.17 (m, 17H), 7.13 (dd, J = 4.1, 2.4 Hz, 2H), 7.08 – 7.03 (m, 2H), 6.99 – 6.97 (m, 1H), 6.96 – 6.91 (m, 1H), 6.54 (d, J = 0.8 Hz, 1H), 6.41 (d, J = 0.8 Hz, 1H), 3.92 (d, J = 5.5 Hz, 5H), 3.41 (d, J = 9.5 Hz, 5H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 154.2, 154.2, 144.1, 141.9, 139.1, 138.9, 136.8, 136.7, 134.2, 134.1, 132.8, 132.4, 131.7, 131.1, 130.1, 129.6, 129.0, 128.5, 128.4, 128.4, 128.1, 127.9, 127.7, 127.5, 127.1, 126.9, 112.2, 111.8, 110.3, 110.1, 103.3, 102.3, 102.1, 77.3, 77.0, 76.7, 55.9, 55.8, 31.4, 30.3. HRMS: m/z calcd for C$_{24}$H$_{21}$NO: 340.1701; found: 340.1698;
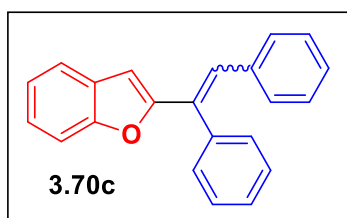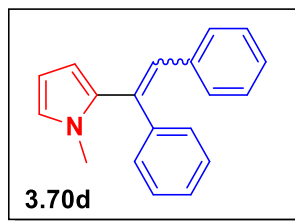
3.70h

2-(1,2-diphenylvinyl)-1,5-dimethyl-1H-indole (3.70h): The compound **3.70h** was prepared according to the general method described above and purified by flash column chromatography (0 to 0.1% ethyl acetate in hexanes) in 73% yield as a colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48 – 7.12 (m, 19H), 7.12 – 7.03 (m, 3H), 6.9 (s, 1H), 6.53 (s, 0.5H), 6.41 (s, 1H), 3.40 (d, J = 3.3 Hz, 5H), 2.52 (d, J = 12.3 Hz, 5H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 143.6, 142.1, 139.2, 138.5, 137.2, 136.9, 136.8, 135.9, 134.3, 132.5, 131.7, 131.0, 130.1, 129.7, 129.0, 128.9, 128.9, 128.5, 128.5, 128.4, 128.2, 128.1, 127.9, 127.7, 127.6, 127.2, 127.0, 123.6, 123.1, 120.5, 120.2, 109.4, 109.1, 103.3, 102.1, 77.4, 77.3, 77.1, 76.8, 31.3, 30.2, 21.5, 21.5. HRMS: m/z calcd for C$_{24}$H$_{21}$N: 324.1752; found:324.1742;

3.70i

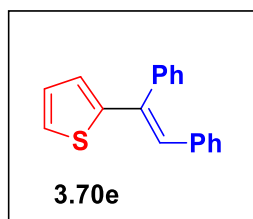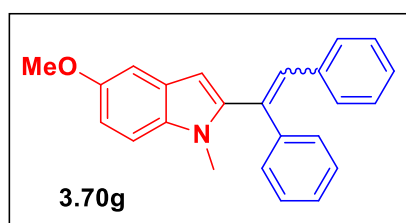**5-chloro-2-(1,2-diphenylvinyl)-1-methyl-1H-indole (3.70i):** The compound **3.70i** was prepared according to the general method described above and purified by flash column chromatography (0 to 0.1% ethyl acetate in hexanes) in 65% yield as a colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.62 (dt, J = 2.6, 1.6 Hz, 1H), 7.47 – 7.11 (m, 18H), 7.04 – 6.98 (m, 2H), 6.56 (s, 1H), 6.44 (s, 0.5H), 3.41 (d, J = 2.2 Hz, 5H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 144.8, 141.5, 139.8, 138.7, 137.0, 136.6, 136.5, 135.8, 133.7, 132.2, 131.9, 131.9, 130.0, 129.6, 129.1, 128.9, 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.7, 127.4, 126.8, 125.4, 125.3, 122.0, 121.7,

120.0, 119.8, 110.6, 110.3, 103.1, 102.2, 77.3, 77.0, 76.7, 31.4, 30.3. HRMS: m/z calcd for C$_{23}$H$_{18}$NCl: 344.1206; found: 344.1200;
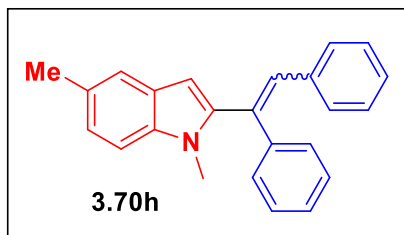

3.70j

2-(1,2-diphenylvinyl)-5-fluoro-1-methyl-1H-indole (3.70j): The compound **3.70j** was prepared according to the general method described above and purified by flash column chromatography (In hexanes) in 81% yield as a light-yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.54 – 7.20 (m, 20H), 7.16 – 7.02 (m, 4H), 6.65 (s, 1H), 6.53 (s, 0.44H), 3.49 (d, J = 4.5 Hz, 5H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 159.3 , 159.2 , 157.0 , 156.9 , 145.1 , 141.7, 140.1 , 138.9 , 136.8 , 136.6 , 135.4 , 134.1 , 134.0 , 132.2 (d, J = 2.5 Hz), 131.8 , 130.1 , 129.7 , 129.0 , 128.8 – 127.8 (m), 127.8 (d, J = 1.7 Hz), 127.4 , 126.9 , 110.4 – 109.9 (m), 109.7 , 105.6 , 105.4 , 105.2 , 103.7 (d, J = 4.6 Hz), 102.6 (d, J = 4.7 Hz), 31.5 , 30.4. ^{19}F NMR (376 MHz, CDCl$_3$) δ -124.6. HRMS: m/z calcd for C$_{23}$H$_{18}$NF:328.1501; found: 328.1500.

3.70k

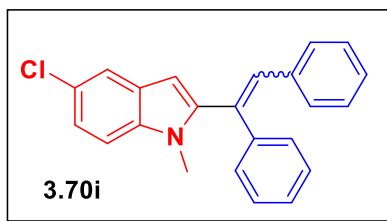**2-(1,2-di-p-anisylvinyl)-1-methyl-1H-indole (370k):** The compound **3.70k** was prepared according to the general method described above and purified by flash column chromatography (0 to 1% ethyl acetate in hexanes) in 81% yield as a colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.72 (dd, J = 11.2, 7.8 Hz, 2H), 7.46 – 7.17 (m, 11H), 7.04 – 6.72 (m, 9H), 6.66 (s, 1H), 6.54 (s, 0.5H), 3.93 – 3.83 (m, 8H), 3.79 (s, 2H), 3.48 (d, J = 9.7 Hz, 5H). ^{13}C NMR

(101 MHz, CDCl₃) δ 159.3, 159.0, 158.8, 158.6, 144.1, 138.9, 138.6, 137.4, 134.8, 131.8, 131.6, 131.3, 130.8, 130.2, 130.1, 129.8, 129.7, 129.6, 128.4, 127.9, 127.7, 121.6, 121.2, 120.7, 120.4, 119.6, 119.5, 113.9, 113.8, 113.6, 109.6, 109.3, 103.3, 102.2, 77.4, 77.1, 76.7, 55.3, 55.2, 55.1, 31.2, 30.1. HRMS: m/z calcd for $C_{25}H_{23}NO_2$: 370.1807; found: 370.1802;

3.70l

2-(1,2-di-p-tolylvinyl)-1-methyl-1H-indole (3.70I): The compound **3.70l** was prepared according to the general method described above and purified by flash column chromatography (0 to 0.1% ethyl acetate in hexanes) in 65% yield as a light yellow-oil. ¹H NMR (400 MHz, CDCl₃) δ 7.82 (t, *J* = 7.9 Hz, 2H), 7.59 – 6.98 (m, 25H), 6.78 (s, 1H), 6.65 (s, 1H), 3.58 (d, *J* = 6.4 Hz, 6H), 2.64 – 2.32 (m, 12H). ¹³C NMR (101 MHz, CDCl₃) δ 144.1, 139.4, 138.9, 138.8, 137.7, 137.5, 137.5, 137.1, 136.4, 134.3, 134.2, 133.4, 131.4, 131.2, 131.0, 130.1, 129.7, 129.4, 129.3, 129.3, 129.0, 129.0, 128.5, 127.9, 126.9, 121.9, 121.5, 120.9, 120.7, 119.8, 119.7, 109.7, 109.4, 103.7, 102.5, 77.6, 77.2, 76.9, 31.4, 30.3, 21.5, 21.4, 21.4, 21.3. HRMS: m/z calcd for $C_{25}H_{23}N$: 338.1909; found: 338.1905;
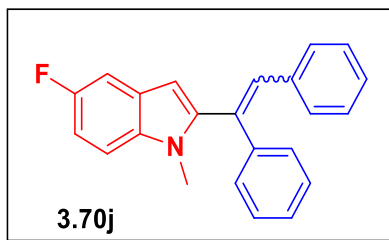

3.70m

2-(1,2-bis(4-chlorophenyl)vinyl)-1-methyl-1H-indole (3.70m): The compound **3.70m** was prepared according to the general method described above and purified by flash column chromatography (0 to 0.1% ethyl acetate in hexanes) in 65% yield as a colorless oil. ¹H NMR

123

(400 MHz, CDCl$_3$) δ 7.68 (dd, J = 7.8, 6.1 Hz, 1H), 7.45 – 7.09 (m, 16H), 6.97 (d, J = 8.6 Hz, 2H), 6.62 (s, 1H), 6.49 (s, 0H), 3.44 (d, J = 9.1 Hz, 4H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 142.6, 140.1, 138.8, 137.6, 137.4, 137.2, 135.1, 134.9, 134.0, 133.9, 133.7, 133.5, 133.1, 132.0, 131.5, 130.9, 130.7, 130.3, 130.2, 129.0, 128.7, 128.7, 128.5, 128.2, 128.2, 127.6, 122.3, 121.9, 121.0, 120.7, 120.0, 119.9, 109.8, 109.5, 104.3, 103.0, 31.4, 30.3. HRMS: m/z calcd for C$_{23}$H$_{17}$NCl$_2$: 378.0816; found: 378.0791;

3.70n

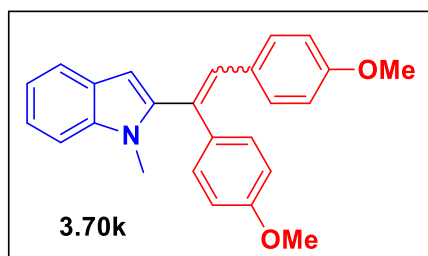**2-(1,2-bis(4-fluorophenyl)vinyl)-1-methyl-1H-indole (3.70n):** The compound **3.70n** was prepared according to the general method described above and purified by flash column chromatography (0 to 0.1% ethyl acetate in hexanes) in 65% yield as a yellow-oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.84 – 7.73 (m, 2H), 7.54 – 7.23 (m, 14H), 7.20 – 7.00 (m, 9H), 6.96 (t, J = 8.7 Hz, 2H), 6.74 (s, 1H), 6.60 (s, 1H), 3.54 (d, J = 5.7 Hz, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 163.8 (d, J = 31.2 Hz), 163.2 (d, J = 12.4 Hz), 161.3 (d, J = 31.3 Hz), 160.8 (d, J = 11.8 Hz), 143.1 , 138.9 , 138.0 (d, J = 3.2 Hz), 138.0, 137.6, 134.9 (d, J = 3.5 Hz), 133.1 (d, J = 1.5 Hz), 133.0 (d, J = 3.4 Hz), 132.8 (d, J = 3.4 Hz), 131.9 (d, J = 7.9 Hz), 131.4 (d, J = 7.9 Hz), 131.3 (d, J = 2.0 Hz), 130.8 (d, J = 7.9 Hz), 130.4 , 130.2 , 128.7 (d, J = 8.0 Hz), 128.3 , 127.7 , 122.3 , 121.9 , 120.9 (d, J = 23.4 Hz), 120.0 (d, J = 2.4 Hz), 116.0 , 115.7, 115.6 , 115.5 , 115.4 , 115.2 , 109.8 , 109.5 , 104.1 , 102.9 , 31.4 , 30.3. ^{19}F NMR (376 MHz, CDCl$_3$) δ -112.7, -113.0, -113.4, -113.7. HRMS: m/z calcd for C$_{23}$H$_{17}$NF$_2$: 346.1407; found: 346.1392;
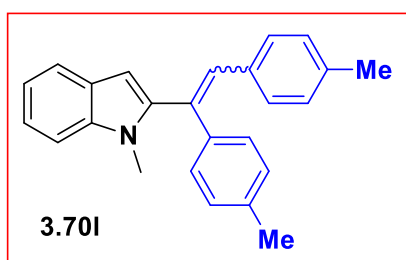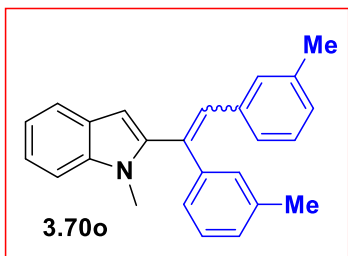
2-(1,2-di-m-tolylvinyl)-1-methyl-1H-indole (3.70o): The compound **3.70o** was prepared according to the general method described above and purified by flash column chromatography (0 to 0.1% ethyl acetate in hexanes) in 71% yield as a light yellow-oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.80 (dd, J = 7.7, 5.0 Hz, 2H), 7.53 – 7.06 (m, 22H), 7.02 (s, 1H), 6.90 – 6.82 (m, 1H), 6.75 (s, 1H), 6.62 (s, 1H), 3.56 (d, J = 7.9 Hz, 6H), 2.50 (s, 3H), 2.42 (d, J = 9.2 Hz, 6H), 2.33 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 143.9, 142.1, 139.2, 138.7, 138.7, 138.2, 138.1, 137.8, 137.7, 137.5, 136.9, 136.8, 134.2, 132.4, 132.0, 131.5, 130.6, 130.6, 130.5, 128.8, 128.6, 128.5, 128.4, 128.4, 128.4, 128.1, 128.0, 127.8, 127.6, 127.3, 126.7, 125.6, 124.3, 121.9, 121.5, 120.9, 120.7, 119.8, 119.7, 109.7, 109.5, 103.7, 102.6, 77.5, 77.2, 76.9, 31.4, 30.3, 21.6, 21.5, 21.5. HRMS: m/z calcd for C$_{25}$H$_{23}$N: 338.1909; found: 338.1906;
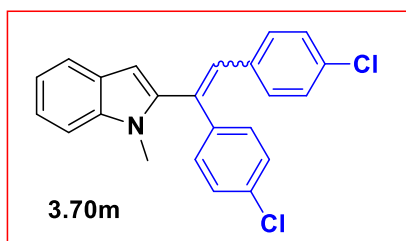

3-(1,2-diphenylvinyl)-1-methyl-1H-indole (3.73a): The compound **3.73a** was prepared according to the general method described above and purified by flash column chromatography (0 to 0.1% ethyl acetate in hexanes) in 61% yield as a light yellow-oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.86 (d, J = 8.0 Hz, 1H), 7.62 – 7.15 (m, 27H), 7.13 – 7.03 (m, 2H), 7.00 (s, 1H), 6.89 (s, 1H), 3.81 (d, J = 20.3 Hz, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 144.41, 141.50, 138.53,

138.18, 137.84, 137.26, 137.21, 135.48, 130.36, 129.76, 129.66, 129.37, 129.25, 128.63, 128.34, 128.19, 128.03, 128.01, 127.92, 127.54, 127.46, 127.41, 126.48, 126.28, 125.97, 124.49, 122.18, 121.72, 121.28, 121.11, 120.10, 119.46, 119.35, 114.02, 109.69, 109.27, 77.52, 77.20, 76.88, 32.96, 32.91. HRMS: m/z calcd for $C_{23}H_{19}N$: 310.1596; found: 310.1590;

3.73b

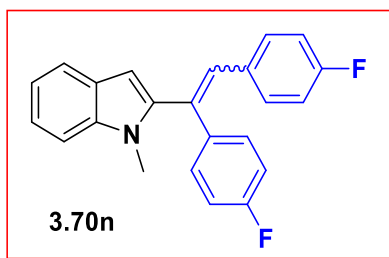**3-(1,2-diphenylvinyl)benzo[b]thiophene (3.73b):** The compound **3.73b** was prepared according to the general method described above and purified by flash column chromatography (in hexanes) in 55% yield as a colorless-oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.95 (dd, J = 15.8, 8.0 Hz, 2H), 7.65 (d, J = 8.0 Hz, 1H), 7.55 – 7.04 (m, 29H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 142.20, 140.72, 140.40, 140.20, 140.12, 138.54, 138.00, 137.28, 137.15, 135.78, 135.48, 130.85, 130.12, 129.74, 129.68, 129.12, 128.63, 128.49, 128.16, 128.14, 127.80, 127.70, 127.14, 126.99, 126.92, 125.81, 125.39, 124.47, 124.29, 124.17, 123.75, 123.56, 122.95, 122.73, 77.44, 77.12, 76.80. HRMS: m/z calcd for $C_{22}H_{16}S$: 313.1051; found: 313.1042;
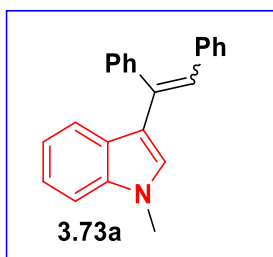

3.73c

3-(1,2-bis(4-(tert-butyl)phenyl)vinyl)benzofuran (3.73c): The compound **3.73c** was prepared according to the general method described above and purified by flash column

chromatography (in hexanes) in 61% yield as a colorless-oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.72 – 6.90 (m, 26H), 1.43 (s, 8.3H), 1.38 (s, 8.7H), 1.33 (s, 8.4H), 1.30 (s, 9H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 155.98, 155.49, 150.77, 150.69, 150.11, 149.77, 144.26, 143.76, 139.46, 136.92, 134.48, 134.25, 132.96, 130.29, 130.12, 129.39, 129.16, 129.06, 128.85, 127.71, 127.05, 126.74, 126.29, 125.61, 125.28, 125.21, 125.06, 124.99, 124.40, 124.33, 122.83, 122.64, 121.47, 121.45, 119.93, 111.75, 111.44, 77.38, 77.06, 76.74, 34.70, 34.59, 34.54, 31.48, 31.36, 31.28, 31.24. HRMS: m/z calcd for C$_{30}$H$_{32}$O: 409.2531; found: 409.2525;
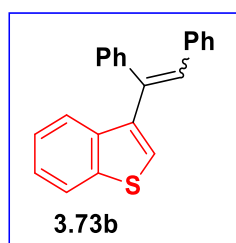

3.73d

3-(1,2-bis(4-(tert-butyl)phenyl)vinyl)-1-methyl-1H-pyrrole (3.73d): The compound **3.73d** was prepared according to the general method described above and purified by flash column chromatography 0 to 0.1% ethyl acetate in hexanes) in 71% yield as a light yellow-oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48 – 7.36 (m, 3H), 7.33 – 7.24 (m, 3H), 7.18 – 7.11 (m, 2H), 6.96 – 6.84 (m, 3H), 6.62 (t, J = 2.5 Hz, 1H), 6.48 – 6.42 (m, 1H), 6.29 (t, J = 2.0 Hz, 1H), 3.66 (s, 0.5H), 3.60 (s, 3H), 1.44 (s, 9H), 1.39 (s, 1.5H), 1.36 (s, 1.5H), 1.30 (s, 9H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 150.02, 149.88, 149.16, 148.48, 142.03, 138.06, 136.31, 136.14, 135.95, 135.12, 129.18, 128.91, 128.88, 128.69, 128.64, 128.54, 127.52, 125.99, 125.40, 125.16, 125.11, 125.06, 124.80, 124.77, 122.64, 122.44, 122.29, 121.69, 121.58, 121.52, 110.43, 105.80, 77.38, 77.06, 76.75, 36.23, 36.20, 34.63, 34.53, 34.39, 31.54, 31.43, 31.38, 31.30. HRMS: m/z calcd for C$_{27}$H$_{33}$N: 372.2691; found: 372.2681;

3.73e

3-(1,2-diphenylvinyl)thiophene (3.73e): The compound 5e was prepared according to the general method described above and purified by flash column chromatography 0 to 0.1% ethyl acetate in hexanes) in 81% yield as a light yellow-oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.67 (d, J = 7.3 Hz, 0.12H), 7.58 – 7.38 (m, 8H), 7.36 – 7.10 (m, 8H), 7.06 (dd, J = 2.9, 1.4 Hz, 1H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 145.23, 143.31, 140.46, 140.39, 137.73, 137.55, 137.44, 137.19, 130.04, 129.63, 129.58, 129.51, 129.06, 128.93, 128.88, 128.42, 128.24, 128.17, 127.84, 127.82, 127.70, 127.69, 127.10, 126.86, 126.73, 126.12, 125.81, 125.63, 125.14, 123.22, 77.60, 77.28, 76.97. HRMS: m/z calcd for C$_{18}$H$_{14}$S: 263.0894; found: 263.0884;
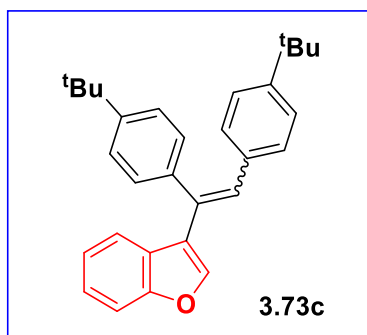

3.73g

3-(1,2-bis(4-bromophenyl)vinyl)thiophene (3.73g): The compound **3.73g** was prepared according to the general method described above and purified by flash column chromatography 0 to 0.1% ethyl acetate in hexanes) in 67% yield as a light yellow-oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.57 – 7.45 (m, 2H), 7.39 – 7.22 (m, 4H), 7.19 – 7.12 (m, 2H), 6.99 (s, 1H), 6.95 (dd, J = 3.0, 1.4 Hz, 1H), 6.91 – 6.85 (m, 2H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 144.24, 142.65, 142.26, 141.76, 139.41, 138.90, 138.71, 137.00, 136.92, 136.16, 136.01, 135.64, 132.15, 132.13, 132.02,

128

131.64, 131.43, 131.34, 131.32, 131.29, 131.07, 130.92, 130.86, 129.13, 129.11, 128.42, 128.02, 127.85, 127.68, 127.41, 126.11, 126.04, 125.88, 125.31, 123.49, 121.98, 121.91, 121.06, 120.84. HRMS: m/z calcd for $C_{18}H_{12}Br_2S$: 420.9084; found: 420.9081;
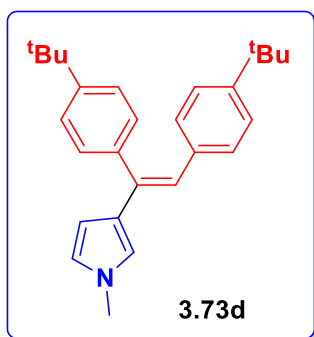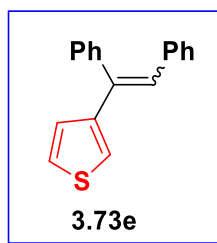

3.73h

3-(1,2-bis(4-(trifluoromethyl)phenyl)vinyl)thiophene: The compound **3.73h** was prepared according to the general method described above and purified by flash column chromatography 0 to 0.1% ethyl acetate in hexanes) in 83% yield as a light yellow-oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.75 – 7.61 (m, 3H), 7.56 – 7.30 (m, 9H), 7.30 – 7.24 (m, 0.4H), 7.20 – 7.06 (m, 4H), 7.04 (s, 0.15H), 6.97 (dd, J = 2.9, 1.4 Hz, 1H), 6.91 (dd, J = 5.0, 1.3 Hz, 0.13H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 143.7 , 143.6 , 143.5 – 143.3 (m), 140.2 – 139.5 (m), 138.2 , 130.8 , 130.3 , 130.0 , 129.6 , 129.5 (d, J = 5.3 Hz), 129.2 , 128.9 (d, J = 3.3 Hz), 128.5 (d, J = 6.0 Hz), 128.3 (d, J = 13.4 Hz), 128.1 (d, J = 2.2 Hz), 127.9 , 127.7 (d, J = 3.8 Hz), 126.4 , 126.3 , 126.0 , 125.9 (q, J = 3.7 Hz), 125.0, 125.6 , 125.4 (d, J = 2.0 Hz), 125.3 (q, J = 3.5 Hz), 125.1 (d, J = 3.7 Hz), 124.1 , 122.9 – 122.4 (m), 120.0 (d, J = 1.2 Hz), 77.3 , 77.0 , 76.7. ^{19}F NMR (376 MHz, CDCl$_3$) δ -62.48, -62.55, -62.57, -62.58. HRMS: m/z calcd for $C_{20}H_{12}F_6S$: 399.0642; found: 399.0638;
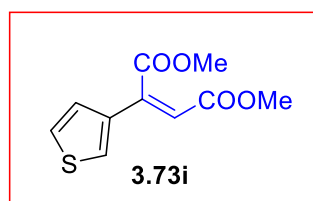
3.73i

Dimethyl 2-(thiophen-3-yl)maleate (3.73i): The compound **3.73i** was prepared according to the general method described above and purified by flash column chromato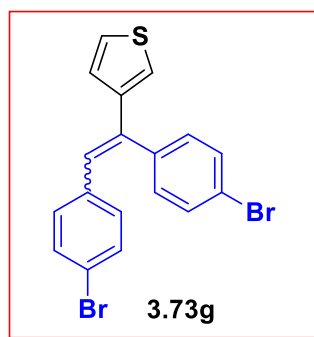graphy 0 to 0.1% ethyl acetate in hexanes) in 61% yield as a light yellow-oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48 (dd, J = 2.9, 1.4 Hz, 1H), 7.38 (dd, J = 5.1, 2.9 Hz, 1H), 7.26 (dd, J = 5.1, 1.4 Hz, 1H), 6.26 (s, 1H), 3.96 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 168.24, 165.70, 143.47, 135.12, 127.30, 127.01, 124.94, 115.42, 77.38, 77.07, 76.75, 52.78, 52.02. HRMS: m/z calcd for C$_{10}$H$_9$O$_4$SNa:249.0197; found: 249.0196;
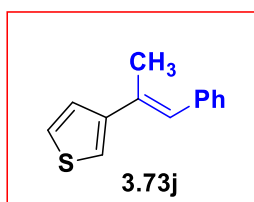
3.73j

(E)-3-(1-phenylprop-1-en-2-yl)thiophene (3.73j): The compound **3.73j** was prepared according to the general method described above and purified by flash column chromatography 0 to 0.1% ethyl acetate in hexanes) in 63% yield as a colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.55 – 7.30 (m, 8H), 7.08 (s, 1H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 145.11, 138.11, 132.11, 129.30, 128.26, 126.55, 126.49, 125.66, 125.33, 120.36, 77.47, 77.16, 76.84, 17.24. HRMS: m/z calcd for C$_{13}$H$_{12}$S: 201.0738; found: 201.0731;
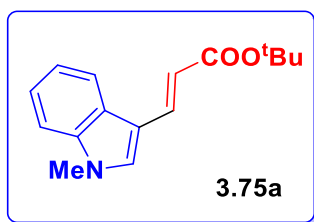
3.75a

(E)-tert-butyl 3-(1-methyl-1H-indol-3-yl)acrylate(3.75a): The compound **3.75a** was prepared according to the general method described above and purified by flash column chromatography (0 to 4% ethyl acetate in hexanes) in 82% yield as a light-yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.95 (dt, J = 7.6, 1.1 Hz, 1H), 7.84 (d, J = 15.9 Hz, 1H), 7.37 – 7.23 (m,

4H), 6.40 (d, $J = 15.9$ Hz, 1H), 3.76 (s, 3H), 1.61 (s, 9H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 167.78, 138.04, 136.96, 132.81, 126.09, 122.84, 121.12, 120.59, 114.57, 112.10, 109.92, 79.72, 77.46, 77.14, 76.82, 33.07, 28.42. HRMS: m/z calcd for C$_{16}$H$_{19}$NO$_2$: 258.1494; found: 258.1494;
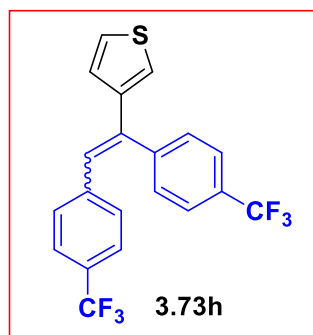

3.75b

(E)-tert-butyl 4-(1-methyl-1H-pyrrol-3-yl)-2-oxobut-3-enoate (3.75b): The compound 3.7**5b** was prepared according to the general method described above and purified by flash column chromatography (0 to 3% ethyl acetate in hexanes) in 62% yield as a light-yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.50 (d, $J = 15.7$ Hz, 1H), 6.87 − 6.74 (m, 1H), 6.62 − 6.49 (m, 1H), 6.39 − 6.28 (m, 1H), 6.02 (d, $J = 15.7$ Hz, 1H), 3.62 (s, 3H), 1.52 (s, 9H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 167.51, 137.83, 124.66, 123.73, 120.80, 114.62, 106.82, 79.52, 77.45, 77.14, 76.82, 36.30, 28.31. HRMS: m/z calcd for C$_{12}$H$_{18}$NO$_2$:208.1338; found: 208.1335;

3.73c

(E)-tert-butyl 2-oxo-4-(thiophen-3-yl)but-3-enoate (3.73c): The compound **3.73c** was prepared according to the general method described above and purified by flash column chromatography (0 to 1% ethyl acetate in hexanes) in 68% yield as a light-yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.59 (dd, $J = 15.9$, 0.7 Hz, 1H), 7.46 (dd, $J = 2.9$, 1.3 Hz, 1H), 7.37 − 7.23 (m, 2H), 6.21 (d, $J = 15.9$ Hz, 1H), 1.54 (s, 9H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 166.52, 137.75,

137.05, 127.46, 126.79, 125.18, 119.88, 80.39, 77.38, 77.07, 76.75, 28.22. HRMS: m/z calcd for C$_{11}$H$_{14}$O$_2$SNa: 233.0612; found: 233.0611;
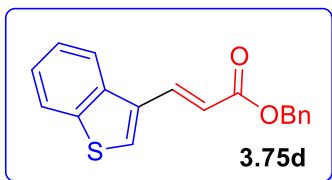
3.75d

(E)-benzyl 3-(benzo[b]thiophen-3-yl)acrylate (3.75d): The compound **3.75d** was prepared according to the general method described above and purified by flash column chromatography (0 to 1% ethyl acetate in hexanes) in 49% yield as a light-yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.11 − 7.98 (m, 2H), 7.97 − 7.83 (m, 1H), 7.78 (s, 1H), 7.56 − 7.34 (m, 7H), 6.63 (d, J = 16.1 Hz, 1H), 5.34 (s, 2H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 166.97, 140.54, 137.11, 136.92, 136.11, 131.61, 128.67, 128.40, 128.38, 128.34, 125.10, 125.01, 123.05, 122.15, 118.30, 77.43, 77.11, 76.79, 66.48. HRMS: m/z calcd for C$_{18}$H$_{14}$O$_2$S: 295.0793; found: 295.0791;
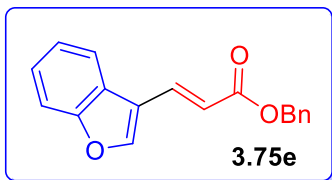
3.75e

(E)-benzyl 3-(benzofuran-3-yl)acrylate (3.75e): The compound **3.75e** was prepared according to the general method described above and purified by flash column chromatography (0 to 1% ethyl acetate in hexanes) in 35% yield as a light-yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.95 − 7.81 (m, 2H), 7.61 − 7.31 (m, 7H), 6.66 (d, J = 16.1 Hz, 1H), 5.33 (s, 2H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 166.91, 156.14, 148.02, 136.11, 135.05, 128.66, 128.41, 128.34, 125.44, 124.75, 123.83, 121.06, 118.02, 117.89, 112.04, 77.45, 77.13, 76.81, 66.45. HRMS: m/z calcd for C$_{18}$H$_{14}$O$_3$: 279.1021; found: 279.1016;
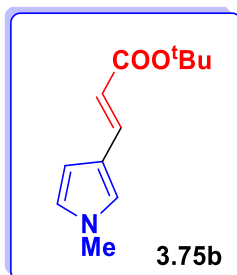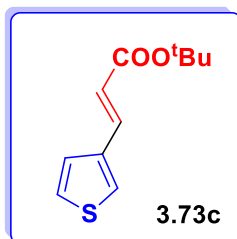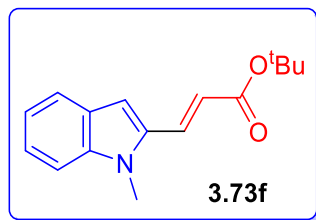
(E)-tert-butyl 3-(1-methyl-1H-indol-2-yl)acrylate (3.73f): The compound **3.75f** was prepared according to the general method described above and purified by flash column chromatography (0 to 1% ethyl acetate in hexanes) in 63% yield as a light-yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.76 (d, *J* = 15.7 Hz, 1H), 7.66 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.39 − 7.25 (m, 2H), 7.17 (ddd, *J* = 8.1, 6.3, 1.7 Hz, 1H), 6.97 (s, 1H), 6.49 (d, *J* = 15.8 Hz, 1H), 3.80 (s, 3H), 1.64 (s, 9H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 166.44, 138.97, 135.16, 131.73, 127.54, 123.42, 121.34, 120.39, 120.26, 109.63, 103.37, 80.63, 77.49, 77.17, 76.85, 29.98, 28.32. HRMS: m/z calcd for C$_{16}$H$_{19}$NO$_2$: 258.1494; found: 258.1494;

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4. CHELATION-ASSISTED DECARBOXYLATIVE ARENE AMIDATION

4.1. Introduction

Aryl amines are often found in many natural products, pharmaceutical agents, and functional materials. [1] This leads to a significant interest and desire among researchers to develop efficient and convenient methods for the construction of arene carbon-nitrogen bond.. Ullman first revealed a protocol for the synthesis of aryl amines (**4.03**) using a copper catalyst (Scheme 4.1. a)[2] ,but the current protocol suffers from certain flaws such as harsh reaction conditions and poor substrate scope. In 1994, Buchwald and Hartwig independently reported a palladium catalyzed aryl amine synthesis using aryl halides (**4.01**) as coupling partners (Scheme 4.1.b).[3]
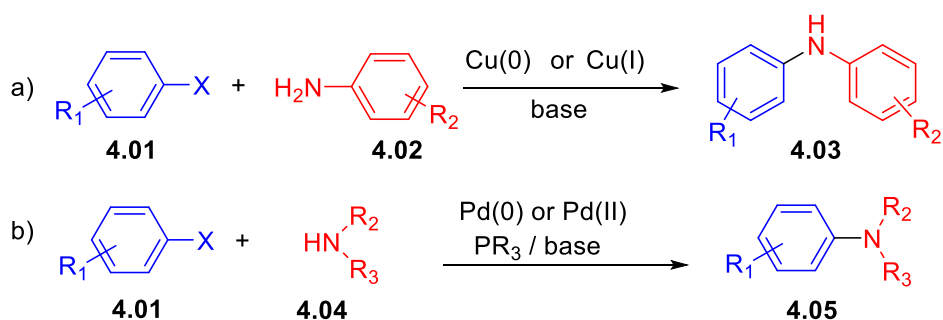
Scheme 4.1. a) Ullmann & Goldberg coupling. b) Buchwald & Hartwig coupling.

Though this transformation was significantly better in terms of the compatibility with the broad range of functional group groups and with various aryl halides, it has its own disadvantages in terms of the requirement of pre-functionalized starting materials and generation of stoichiometric amounts of metal halide waste. In contrast, direct C-H amination of arenes occurs with high step economy and reduced waste.[4] The classical method for the synthesis of aryl amines involves electrophilic nitration followed by reductive hydrogenation (Scheme 4.2). The harsh conditions such as strong acidic conditions are limiting the scope and practicality of this protocol.[5]
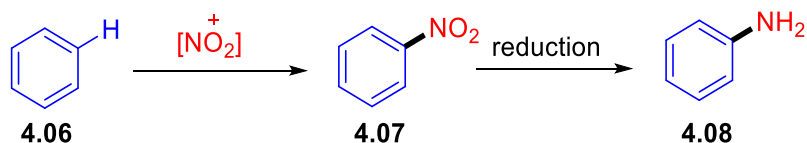
Scheme 4.2. Classical nitration pathway.

Based on the mechanism, C−H amination of arenes can be classified into three categories: (i) C−H insertion catalysis (ii) Single-electron transfer catalysis (iii) C-H activation catalysis.[6]

In C-H insertion catalysis, construction of C-N bond occurs through the catalytic transfer of nitrene moiety. The key intermediate in this reaction is metal−nitrenoid (**4.09**), which is a product of the reaction occurring between aminating agent and metal center. The interaction of metal−nitrenoid (**4.09**) species with the hydrocarbon (**4.10**) results in C-N bond formation through C-H bond functionalization. The C-H bond functionalization can occur in two different mechanisms as shown in Scheme 4.3. First one is a concerted C−H insertion and the second is a stepwise process of hydrogen atom abstraction (HAA) followed by radical recombination.[7]
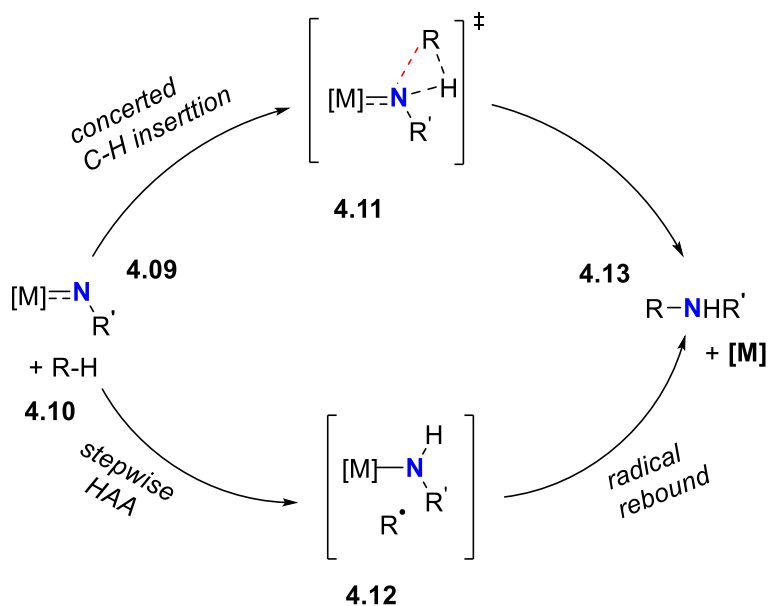
Scheme 4.3. C-H insertion catalysis.

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Breslow and coworkers first demonstrated the catalytic nitrene transfer through the amidation of cyclohexane using cytochrome P-450.[8] Later, the group of Mansuy described the nitrene transfer in the aziridination of olefins utilizing Fe and Mn porphyrin catalysts.[9] These results motivated various groups thus, diverting their attention towards the construction of C-N bond through direct functionalization of C-H bonds via insertion mechanism. In the recent years, C-H insertion catalysis has been employed for the functionalization of arene C-H bonds to construct arene C-N bond. Driver et al. reported Rh(II)-catalyzed intramolecular $C(sp^2)-H$ amination for the synthesis of indole and carbazole derivative which are often found in many biologically active compounds and functional materials (Scheme 4.4). Authors proposed that the reaction proceeded through the formation of rhodium-nitrenoid intermediate followed by C-N bond formation through 4π-electron-5-atom electrocyclization (**4.21**) which was supported by the Hammett plot and intramolecular competition experiments.[10,]
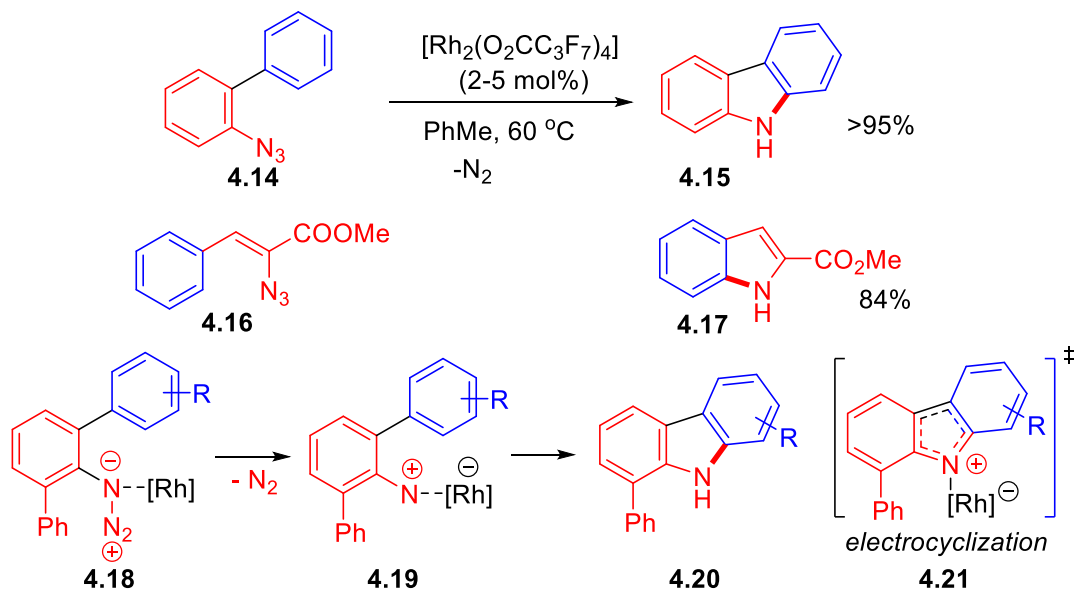
Scheme 4.4. Intramolecular C-H amination via metal-nitrenoid intermediate.

Che and coworkers demonstrated the intermolecular C−H amination of various heterocycles using Ru(II) porphyrin Catalyst.[11] Recently Falck et al. revealed $Rh_2(esp)_2$ mediated mild protocol for the synthesis of aryl amines using N-methyl-O-tosylhydroxylamine (**4.23**) as the aminating agent (Scheme 4.5).[12] Authors proposed that the reaction proceeded through the formation of rhodium-imido (**4.25**) species followed by electrophilic addition of arenes (**4.21**) furnished aryl amine product (**4.24**). This particular transformation is simple, scalable and occurs with good yields. This strategy was further extended for the synthesis of various N-heterocycles through direct intramolecular cyclization (aza-annulation) of arenes, but the drawback was that it worked only with electron-rich arenes and often produced a mixture of Regio isomers.
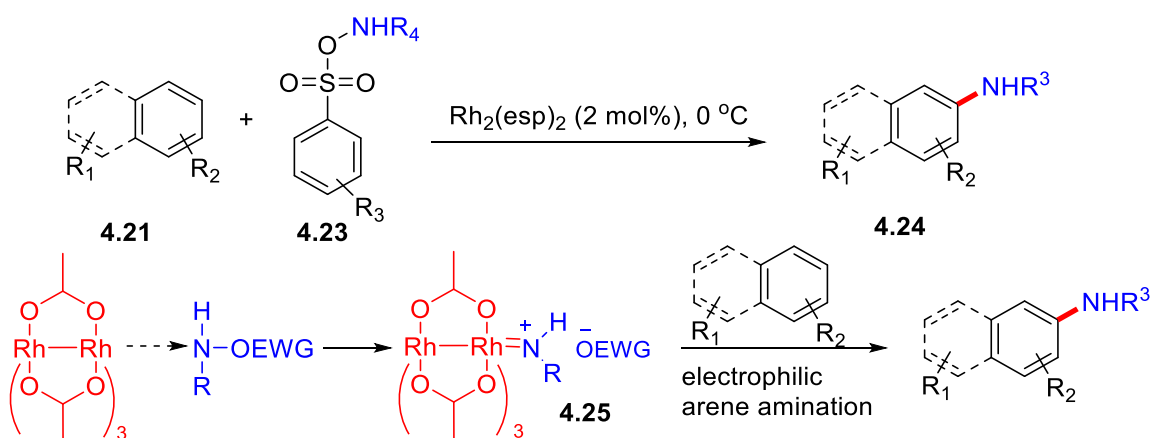
Scheme 4.5. Rh(II) Catalyzed direct intermolecular C-H amination of arenes.

In the recent years, photoredox catalysis has emerged as a valuable tool for C-H amination of arenes via single electron transfer mechanism. Significant advancements were made for the generation of nitrogen-centered radicals through visible light photo redox catalysis. Upon irradiation of visible light, organo radical species are produced in the presence of photocatalyst, which reacts with the hydrocarbon to furnish the desired aryl amine as a product (Scheme 4.6).[13,14]
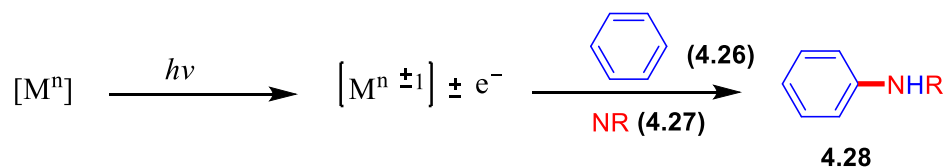
Scheme 4.6. C-H amination via photoredox catalysis.

Yu et al. reported a protocol for the synthesis of various Aza heterocycles such as phenanthridines, quinolines and pyridines through intramolecular C-H amination using iridium photocatalysis (Scheme 4.7). This transformation proceeds at room temperature with broad substrate scope and functional group tolerance. The proposed mechanism is depicted in the Scheme 4.8. [15]
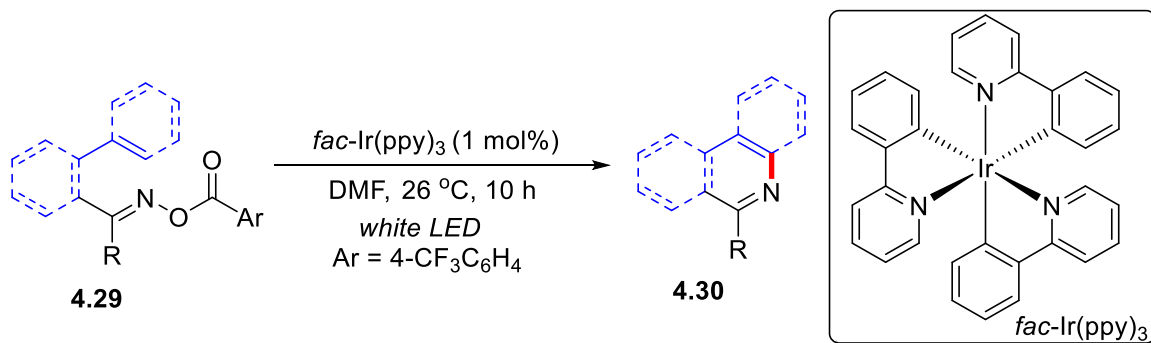
Scheme 4.7. Ir-catalysed intramolecular C-H amination via photoredox catalysis.

Upon irradiation with visible light, photocatalyst undergoes excitation and the excited species transfers a single electron to the N-acyl oxime (**4.29**) which produces nitrogen-centered radical (**4.31**), and acetate anion. The intermediate **4.31** undergoes homolytic aromatic substitution to generate radical **4.32** which is further oxidized to form cationic intermediate **4.33** and regenerate the photocatalyst. Finally, deprotonation of **4.33** delivers the final product (**4.30**).
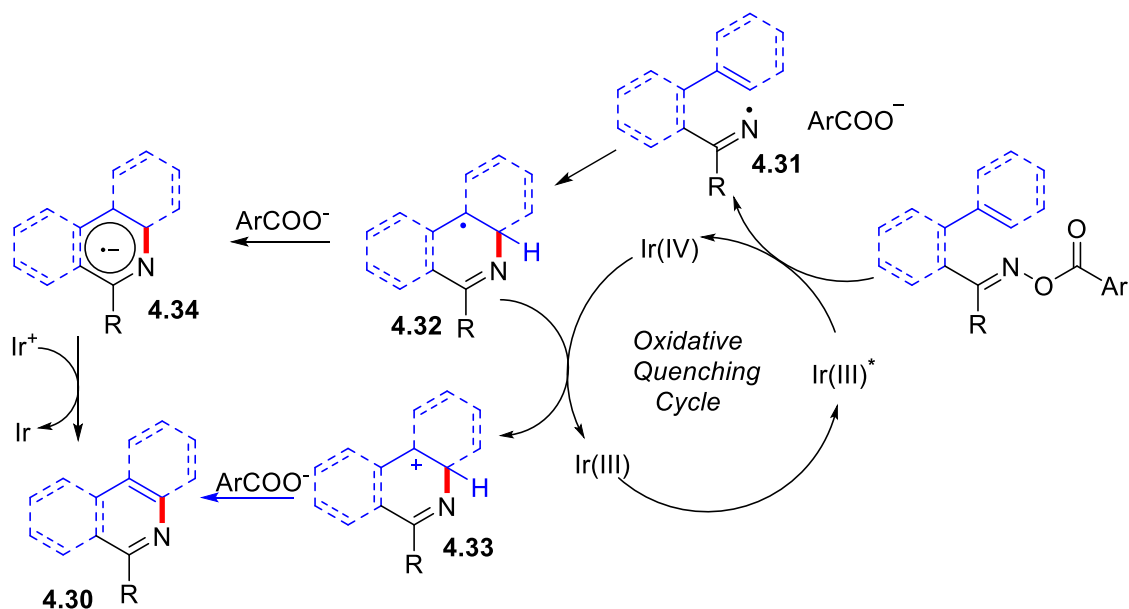
Scheme 4.8. The mechanism for intramolecular catalyzed C-H amination using a photocatalyst.

In 2014, Sanford and coworkers reported an efficient protocol for the intermolecular C-H amination of arenes and heteroarenes using N-acyloxyphthalimides as aminating agent.[16] This method enables the generation of nitrogen-based radical in the presence of photocatalyst through single electron transfer. This protocol occurs at room temperature with high functional group tolerance. Recently, the group of Konig established a new protocol for direct C-H amidation of heteroarenes using Ruthenium photocatalyst as depicted in Scheme 4.9. [17]

This protocol occurs under a mild condition and suitable for C-H amidation of various heteroarenes such as indole, furan, benzofuran, thiophene, and pyrrole. Unlike aforementioned single electron process, the present reaction occurs via energy transfer mechanism. Upon energy transfer from excited photocatalyst to benzoyl azide (**4.36**) produces benzoyl nitrene (**4.39**), which reacts with the heteroarene in the presence of an acid additive to furnish amidation product (**4.37**).
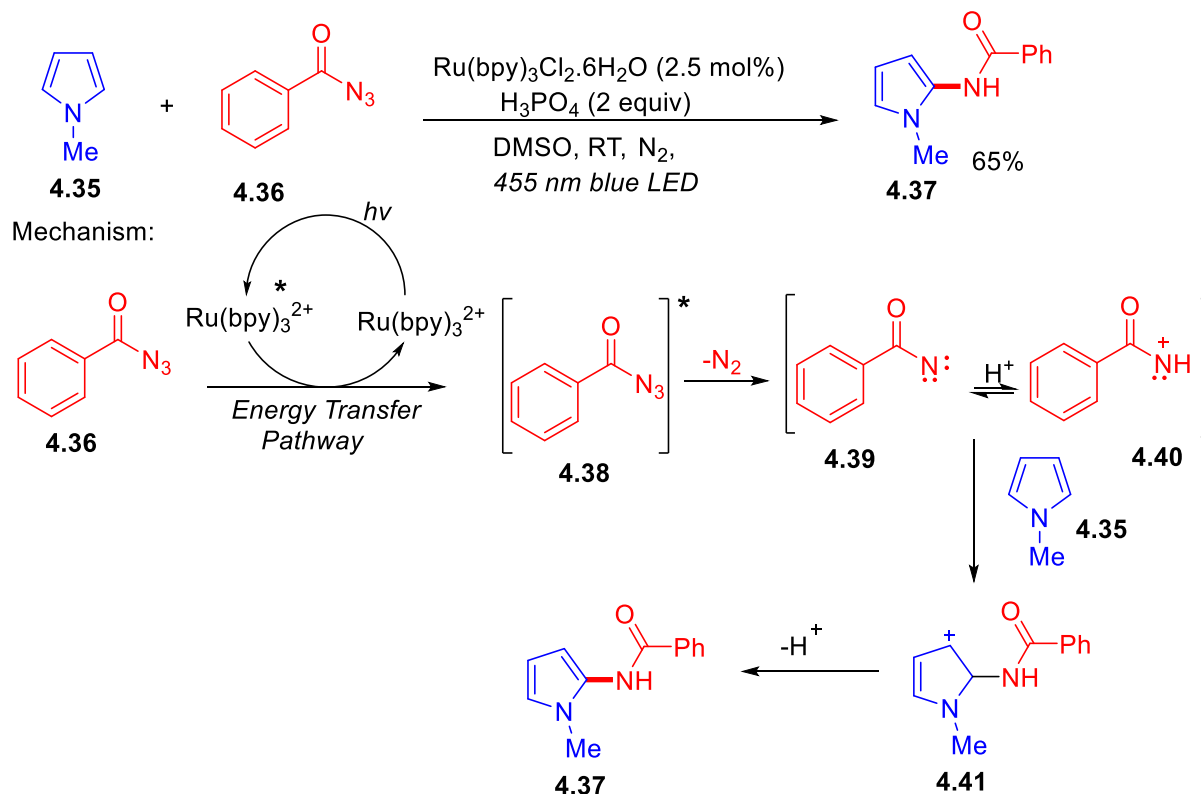
Scheme 4.9. Intermolecular C-H amination of heteroarenes via energy transfer mechanism.

Although significant advancements have been made for C-H amination through insertion catalysis or photoredox catalysis, it is still not viable for the practical applications. To counteract this, another important strategy for C-H amination is "C-H activation catalysis (Scheme 4.10)." In this mechanism, the interaction of metal catalyst with carbon-hydrogen bond of a hydrocarbon produces organometallic intermediate (C-M), which reacts with the aminating agent to furnish desired amination products. [18]
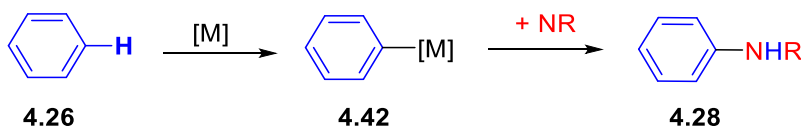
Scheme 4.10. C-H amination through transition metal catalyzed C-H activation.

The groups of Mori[19] and Schreiber[20] independently developed new protocols for the C-H amination of heterocycles such as benzimidazoles, benzoxzole and benzothiazoles in the

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presence of a copper catalyst using molecular oxygen as oxidant. The reaction proceeds via dehydrogenative coupling of heterocycles, and secondary amines and it occurs at the most acidic C-H bond. In 2011, the group of Miura established a redox neutral method using O-acylated hydroxyl amines (**4.45**) as an aminating agent which also acts as an internal oxidant and circumvents the need for eternal oxidant (Scheme 4.11).[21]
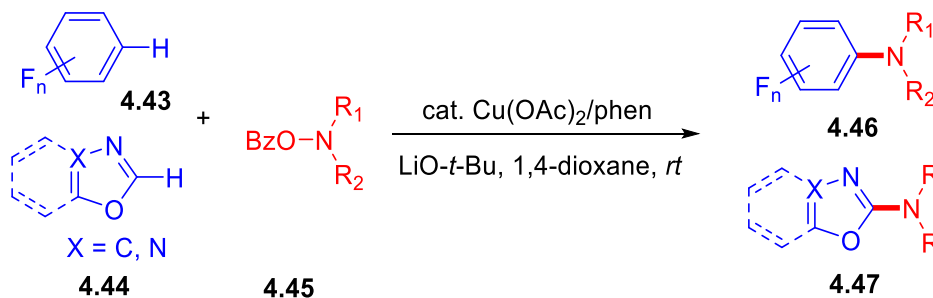
Scheme 4.11. Copper-catalyzed direct amination of electron-deficient arenes with hydroxylamines.

In addition to heterocycles, this transformation is also suitable for C-H amination of perfluoroarenes, and it works at room temperature. The proposed mechanism is depicted in the Scheme 4.12. The Cu(II) precatalyst produces Cu(I) intermediate vis disproportionation reaction. The Cu(I) active catalyst reacts with arene (**4.43**) to give Cu(I)-aryl intermediate (**4.47**) which undergoes oxidative addition with the aminating agent (**4.45**) and generates Cu(III) intermediate (**4.48**). Cu(III) intermedite upon reductive elimination produces the desired product and releases the active catalyst.
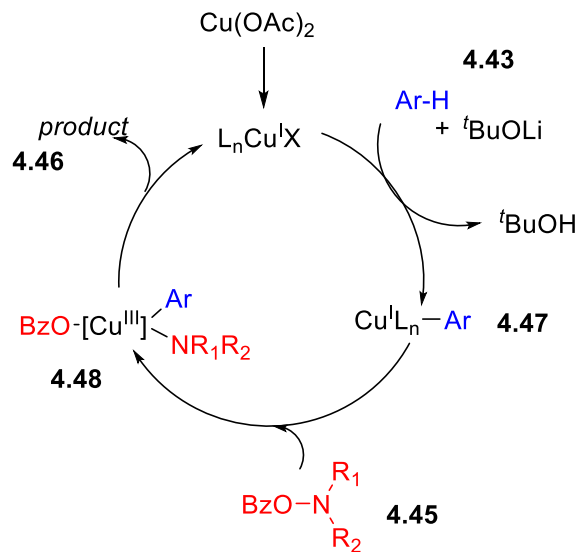
Scheme 4.12. The mechanism for copper-catalyzed intermolecular C-H amination.

In 2013, Hartwig et al. reported a palladium catalyzed intermolecular C-H amination of arenes using an N-aryl phthalimides (**4.51**) aminating agent and Diacetoxyiodobenzene oxidant. Despite the broad substrate scope and high yields, the reaction occurs with less of regioselectivity and the reaction results in a mixture of regio isomers in most of the cases as shown in Scheme 4.13.[22]

4.49a	4.49b	4.49c	4.49d	4.49e	4.49f
61%	72%	62%	76%	75%	67%
o:m:p	o:m:p	o:m:p	o:m:p	1:2:3:4	1:2:3:4
1:1:5	1:30:11	1:10:6	1:6:6	1:1:50:29	1:1:19:19
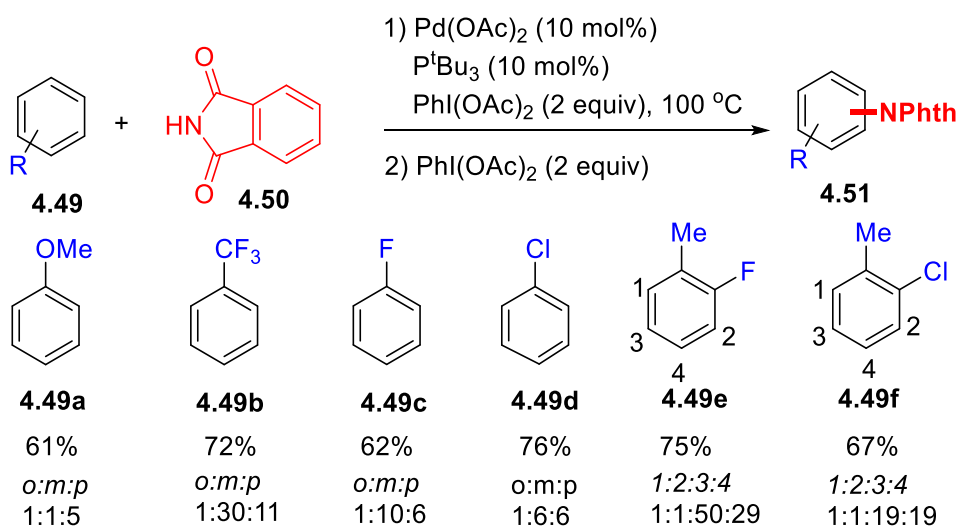
Scheme 4.13. Palladium-catalyzed intermolecular amination of arenes.

Achieving regioselectivity is a critical challenge in an intermolecular C-H amination. In this regard, chelation assisted C-H amination is an allusive strategy to achieve regioselectivity. In 2005, Buchwald revealed an efficient protocol for the synthesis of the carbazole (**4.53**) from acetaminobiphenyl (**4.52**) through intramolecular C-H amination (Scheme 4.14. b). This reaction proceeds via C-H bond activation followed by C-N formation.[23] The catalytic cycle starts with the pre-association of pd catalyst with amide to generate metal amido intermediate. Subsequently, Palladium undergoes heck type or wacker type addition on to the arene and generates corresponding Pd(II) intermediate, which upon β-hydride elimination delivers the carbazole product and Pd (0). Pd(II) catalyst can be regenerated by using copper oxidant. In 2008, Gaunt and coworkers revealed another protocol for the synthesis of carbazole using intramolecular C-H amination in the presence of palladium catalyst and PhI(OAc)$_2$ oxidant.[24] This reaction proceeds through Pd(II)/Pd(iv) catalytic system and occurs with high functional group tolerance and good yields. Later, Hartwig and co-workers established a new method for Pd (0) catalyzed Indole (**4.55**) synthesis via intramolecular C-H amination using N-acyl oxime (**4.54**) as an aminating agent and no external oxidant is required for this reaction (Scheme 4. 14. b).[25]
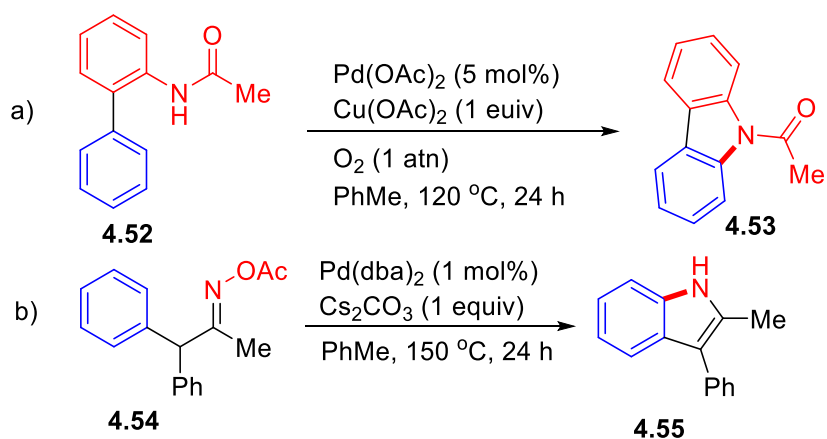
Scheme 4.14. a) Pd(II)-catalyzed carbazole synthesis through oxidative C−H bond amination b) Palladium-catalyzed intramolecular C−H amination of aromatics with oxime esters.

After these seminal reports, many research groups developed various methods for the cross dehydrogenative coupling for the synthesis of azaheterocycles (Scheme 4.15). [26, 27, 28, 29]
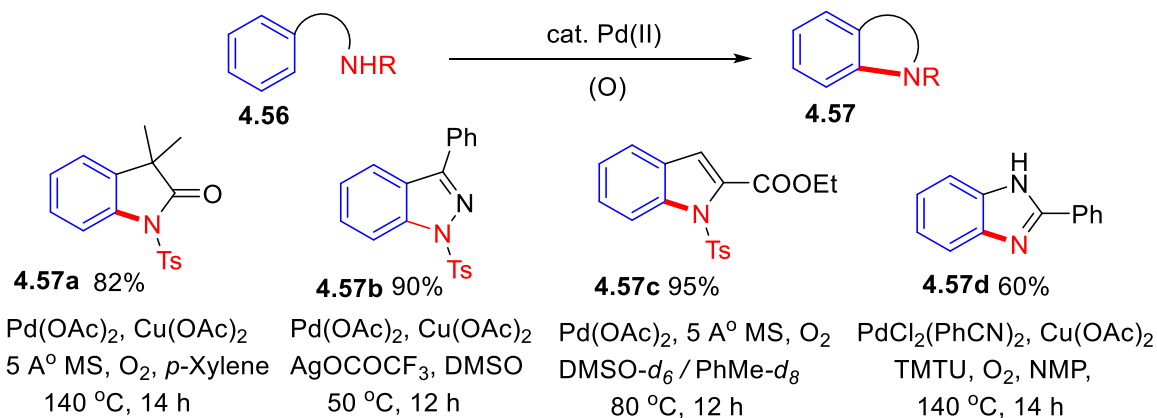
Scheme 4.15. Pd catalyzed intramolecular C-H amination for the synthesis of heterocycles.

In 2007, Sanford and coworkers demonstrated the chelation assisted intermolecular C-H amination through the stoichiometric amination of palladacyclic complexes with PhI=NTs as shown in Scheme 4.16.[30] Authors proposed that the reaction proceeds via a stepwise mechanism which involves the formation of Pd^{IV} imido intermediate (**4.59**).
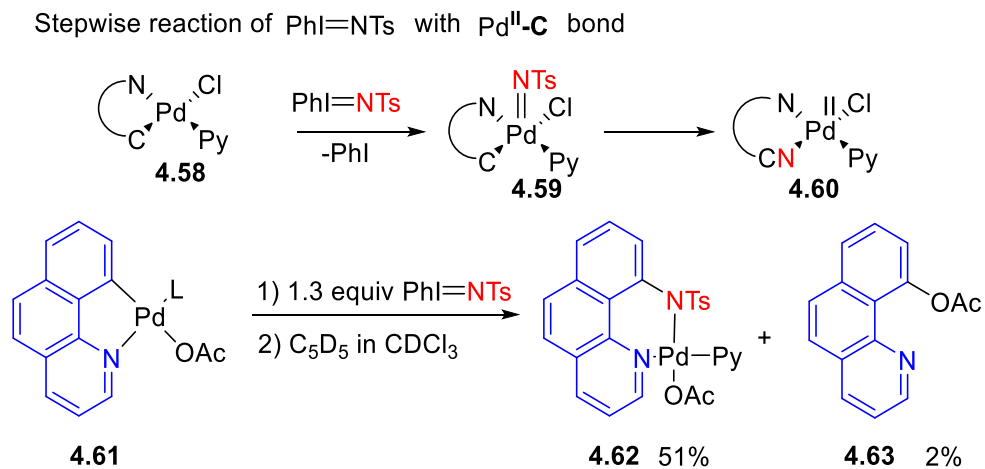
Scheme 4.16. Amination of palladacycle with an iminoiodinane reagent.

Che and coworkers first revealed a Pd-catalyzed directed oxidative C-H amination of phenyl pyridine using a stoichiometric amount of $K_2S_2O_8$ oxidant.[31] Later, Liu et al. accomplished Pd

catalyzed dehydrogenative coupling of aromatic ketones and amides for intermolecular C-N

bond formation using N-fluoro-2, 4,6-trimethyl-pyridinium triflate as oxidant.[32] Later in 2010,

the group of Yu reported a redox-neutral method for intermolecular C-H amidation of anilides

using N-Nosylcarbamates as aminating agent.[33] The reaction proceeded with good functional

group tolerance and regioselectivity. This protocol enables the facile synthesis of 2-

aminoanilines which are essential scaffolds in many biologically active compounds. The usage

of electrophilic aminating agents containing weak N-O bond is an attractive strategy as it occurs

under redox neutral conditions. This strategy was extended for the intermolecular C-H amination

of various directing groups through chelation assisted C-H bond activation (Scheme 4.17). [34]
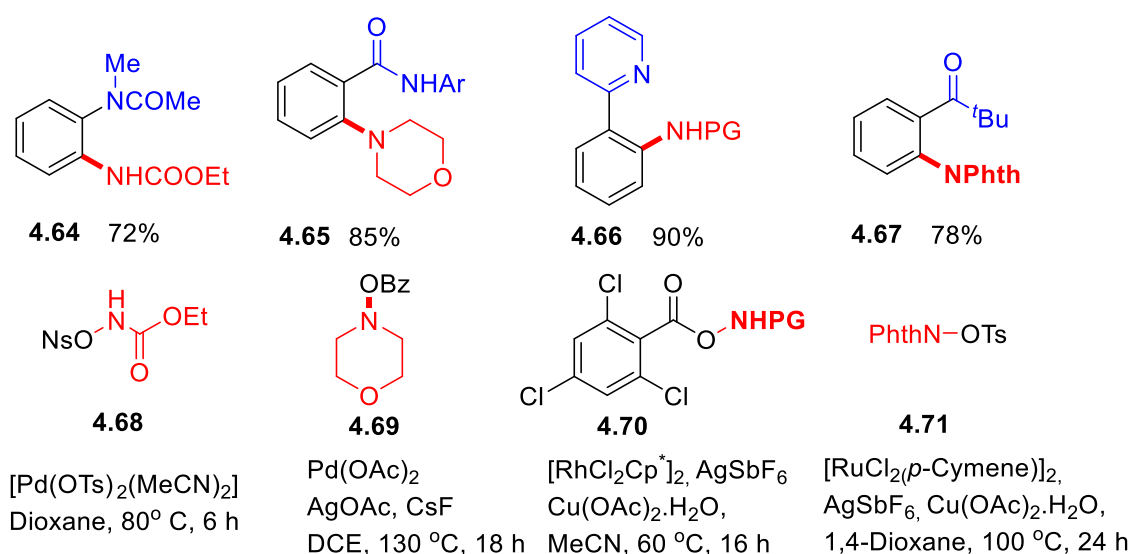
Scheme 4.17. Intermolecular C-H amination using electrophilic aminating agents.

The use of preactivated aminating agents in directed C-H amination also produces

stoichiometric amounts of byproducts. In this regard, organic azides have been considered as

efficient aminating agents for intermolecular C-H amination because of prominent features such

as i) easy synthesis of azides ii) generation of N_2 as a sole byproduct in C-N bond forming

reaction. iii) an internal oxidant which obviates the need for the external oxidant.

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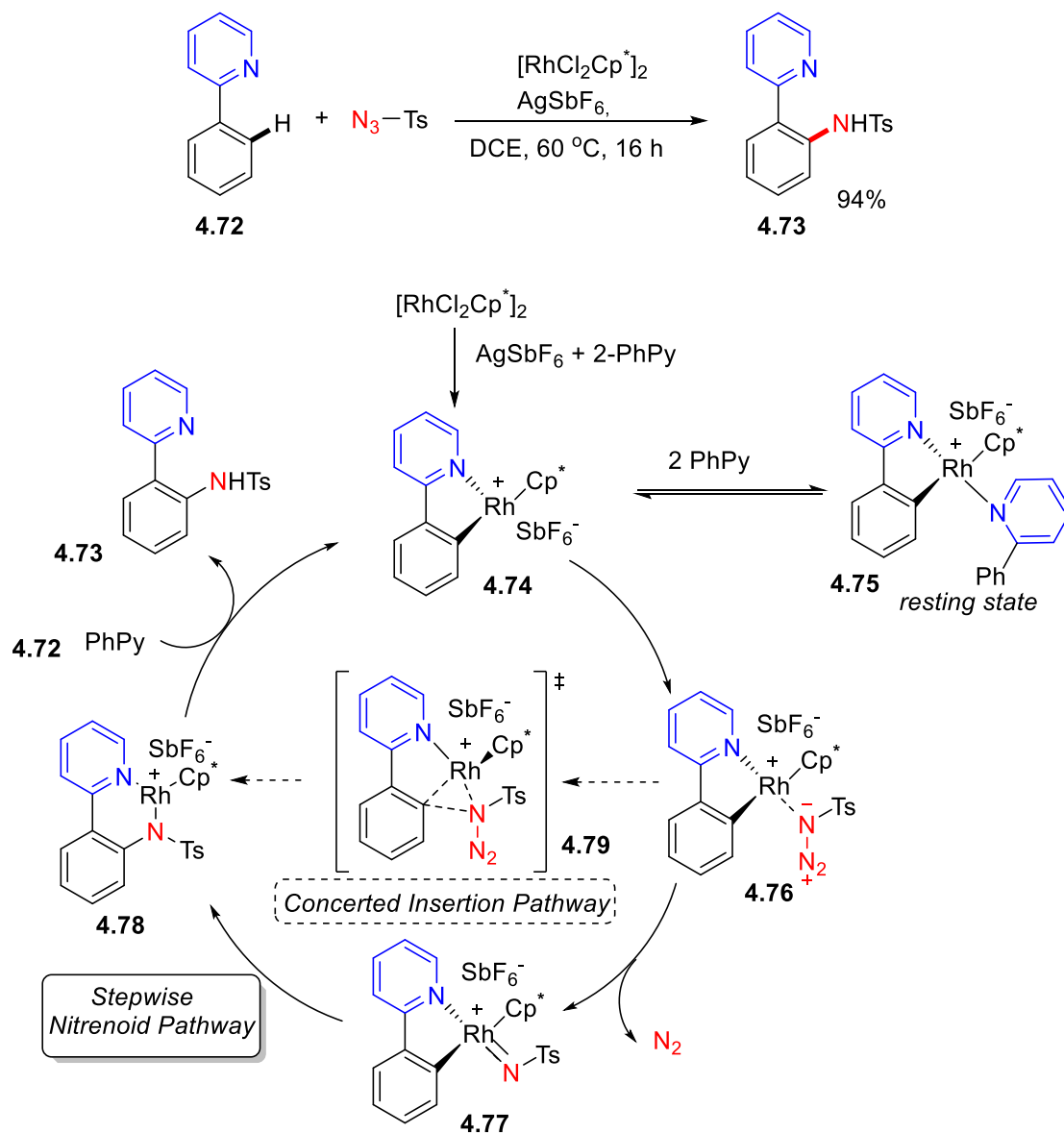
Scheme 4.18. Rhodium-catalyzed intermolecular C-H amination using tosyl azide as aminating source.

Chang and coworkers first reported a rhodium catalyzed protocol for the directed C-H amination of arenes using sulfonyl azide as an aminating source.[35] This protocol is suitable for broad range of arenes with good yield and high functional group tolerance. The mechanism of the reaction is described in the Scheme 4.18. The reaction proceeds via formation of rhodacycle **4.74** followed by addition tosyl azide coordination leads to the generation of intermediate **4.76**. Later, the formation of metal amido intermediate **4.78** can occur in two possible pathways: i)

through the stepwise formation of Rh(V) metal nitrenoid intermediate followed by insertion of a nitrenoid moiety to cyclometalate. ii) Through concerted mechanism. Depending on experimental and DFT calculations authors proposed that stepwise mechanism is more probable than concerted mechanism.[36] Finally, protonation of metal amido species releases the aminated product and regenerates the active catalyst.

Kanai and coworkers extend this strategy for the C-H amination of indole derivatives using tosyl azide as an aminating agent in the presence of airstable Co(III) catalyst (**4.19 a**).[37] Later in 2013 Chang and coworkers extended the directed C-H amination in the presence of iridium catalyst using acyl azides as aminating agent (**4.19 b**). The current transformation works under mild reaction conditions with excellent substrate scope.[38]
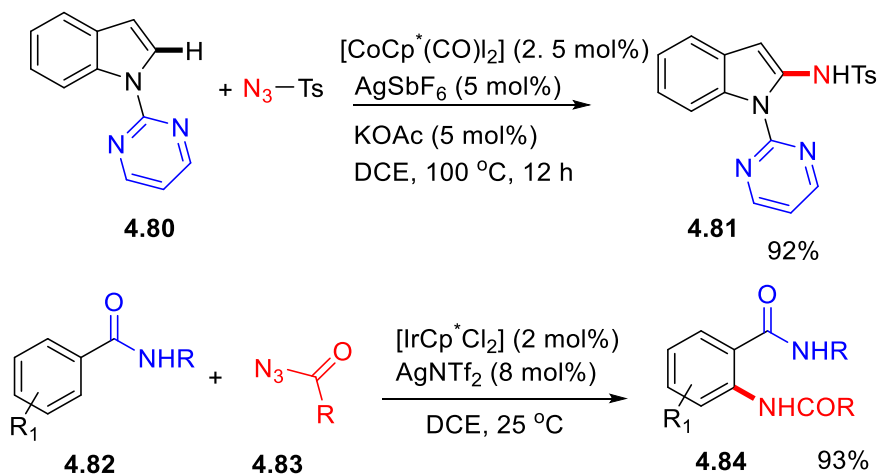
Scheme 4.19. a) Cobalt-catalyzed directed C-H amidation of indole derivatives using organic azides b) Iridium-catalyzed directed C-H of amides using organic azides.

Diaryl amines are widely present in many pharmaceuticals, agrochemicals, and functional materials. Particularly diarylamines bearing *ortho* carbonyl group are vital components of many biologically active compounds. Classical methods for the synthesis of diarylamines produce stoichiometric amounts of waste. Chang et al. disclosed a method for the rhodium-catalyzed C-H amination of benzamides and imines using aryl azides as aminating agents to produces

diarylamines (Scheme 4.20). This protocol works without any external oxidant, and the only byproduct is nitrogen. [39]
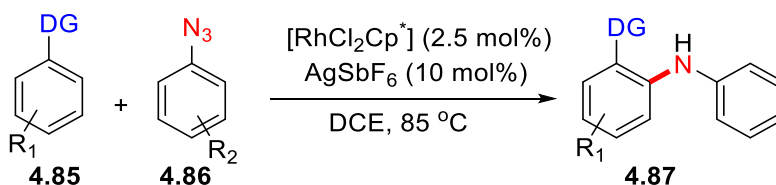
Scheme 4.20. Rhodium-catalyzed diarylamine synthesis using aryl azides as an aminating reagent.

In 2015, Chang's group presented a new aminating agent 1,4,2-Dioxazol-5-one which enabled the C-H amination of arenes at room temperature. This protocol works without oxidant and releases carbon dioxide as a byproduct which makes the current transformation environmentally benign. The newly developed rhodium catalyzed C-H amination is highly efficient and compatible with a broad range of arenes. Authours proposed that the reaction proceed via formation of cyclometallated intermediate followed by coordination of aminating agent leading to the generation of metal-amido intermediate **4.91**. Finally, protonation of rhodium-amido intermediate produces the final product. [40]
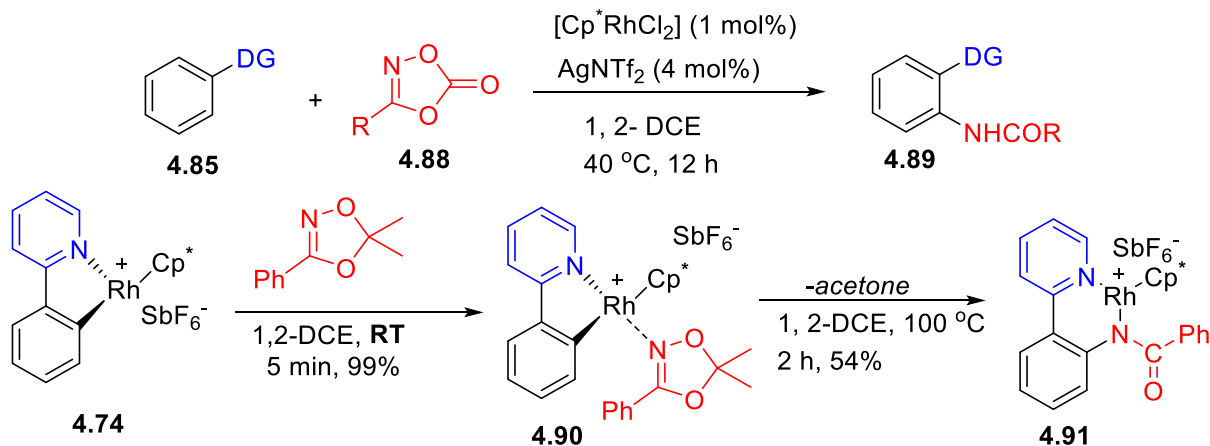
Scheme 4.21. Rhodium-catalyzed direct C−H amidation with dioxazolones.

Later, Ackermann and many other groups used 1,4,2-Dioxazol-5-one as an aminating agent for the C-H amination of various directing groups such as oxazolines, ketones and pyrimidine.[41, 42, 43]

In addition to C-H bond functionalization, directing group also has been employed for the C-C bond cleavage. Suggs and coworkers first demonstrated the C-C bond cleavage of ketones using directing group. In 1995, the group of Jun reported catalytic C-C bond cleavage through the assistance of 2-amino-3-picoline using rhodium(I) catalyst. The mechanism for the C-C bond cleavage is described in the Scheme 4.22. The transformation starts with the formation of ketimine **4.97**, followed by C-C bond cleavage via oxidative addition leading to the formation of **4.98**, which upon β-elimination produces rhodium hydride intermediate (**4.99**). Insertion of incoming alkene into Rh-H bond followed by reductive elimination of **4.100** delivers the final product and regenerates the catalyst through ligand association. [44]
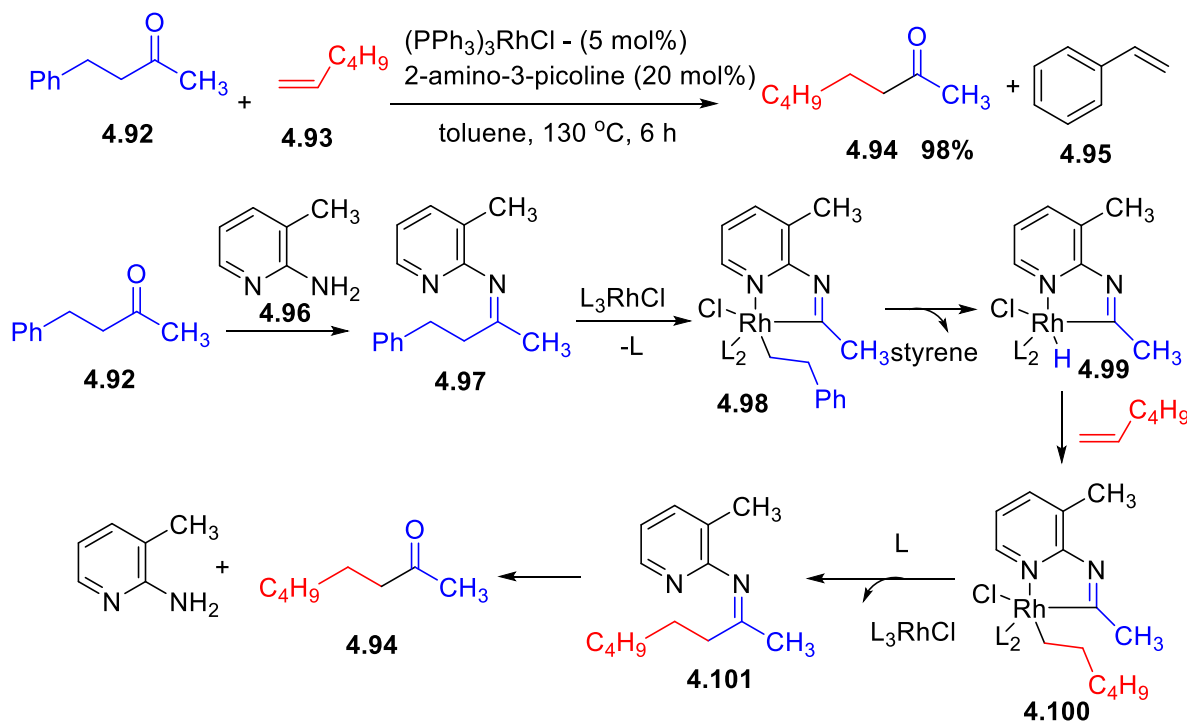
Scheme 4.22. Rh(I) catalyzed C-C bond activation of ketimines.

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This seminal work is the stepping stone for the advancement of C-C bond cleavage through the assistance of directing group. Shi and coworkers reported many methods for C-C bond cleavage using pyridyl directing group. In the initial report, authors reported C-C bond cleavage of diarylmethanols (**4.102**) for the synthesis of alkenyl arenes and biaryl derivatives (Scheme 4.23 a).[45] In 2012, the same group disclosed a new protocol for the rhodium catalyzed decarbonylative biaryl synthesis through directed C-C bond cleavage (Scheme 4.23 b).[46] These reactions proceed via rhodium catalyzed beta carbon elimination through the assistance of pyridyl directing group followed by formation of a five-membered rhodacycle intermediate which undergoes alkenylation and biaryl coupling.
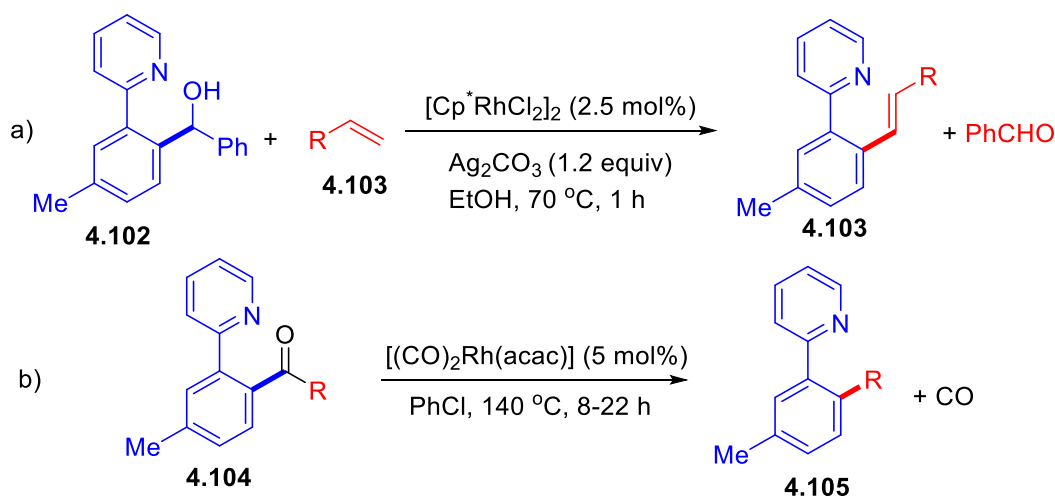
Scheme 4.23. a) Rh-catalyzed alkenylation through directed C-C bond cleavage. b) Rh-catalysed decarbonylative biaryl coupling through directed C-C bond activation.

Recently Dong et al. used the same strategy for the synthesis of 2-quinolinones (**4.108**) through the coupling of isatins (**4.106**) and alkynes (**4.107**). The transformation proceeds via rhodium catalyzed directed C-C bond cleavage followed by decarbonylation and then insertion of alkynes. This reaction enables the straightforward synthesis of quinolone derivatives, and is compatible with broad range of isatin derivatives and alkynes (Scheme 4.24 a). This concept was also extended for the synthesis of benzimidazolidinones using isocyanates.[47] In 2016, Dong

disclosed a method for the selective cleavage of a C-C bond in cyclopentanone (**4.109**) using 2-aminopyridine as a transient directing group (Scheme 4.24 b).[48]
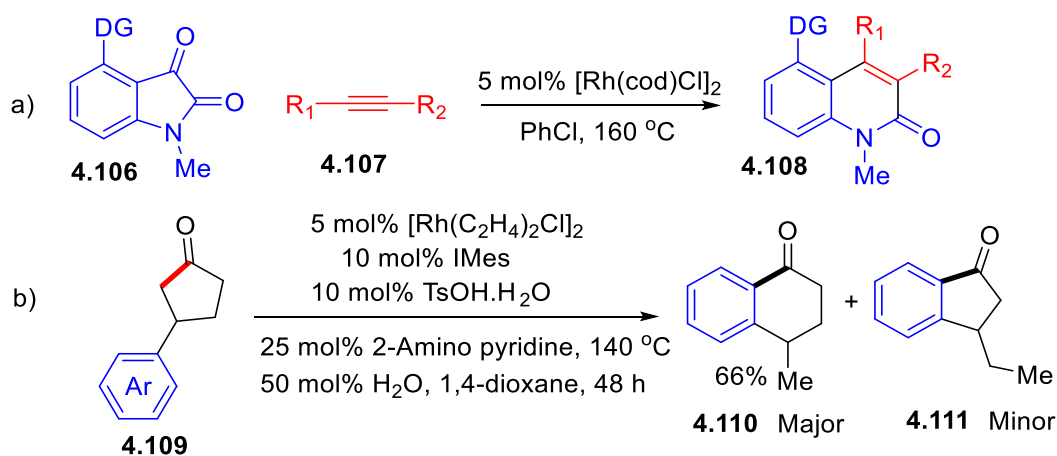
Scheme 4.24. a) Rh-Catalyzed decarbonylative coupling of alkynes and isatins for the synthesis of 2-quinolinones b) Rh-catalysed C-C bond activation of cyclopentanones using transient directing group.

Chatani and co-workers demonstrated the decarbonylative biaryl coupling of ketones using stoichometric amounts of the Ni catalyst which occurs through the C-C bond cleavage.[49] Recently, the group of Wei established a new protocol for Nickel catalyzed directed C-C bond cleavage using pyrimidine directing group (Scheme 4.25). This reaction is an alternative strategy for the synthesis of the 2-aryl indoles (**4.113**) and occurs with broad substrate scope and functional group tolerance.[50]
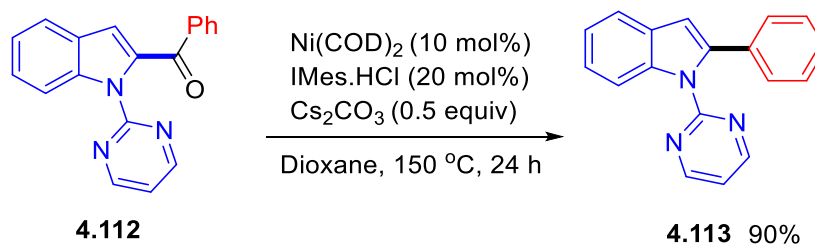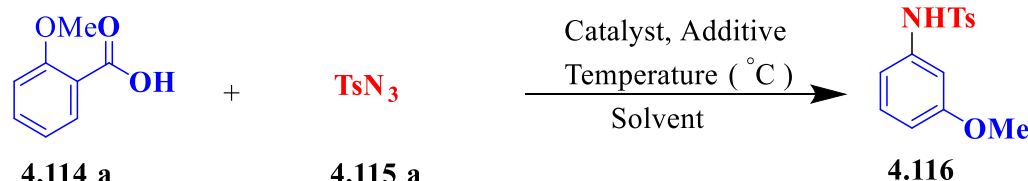
Scheme 4.25. Ni-Catalysed decarbonylative biaryl coupling through directed C-C Bond. Cleavage.

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In this chapter we describe Rh(III)/Ag(I) catalysed chelation assisted decarboxylative amidation of *ortho*-substituted benzoic acids using 3-aryldioxazolones as a coupling partner. The regioselecvity for amidation is regulated by the *ortho* substituent on the benzoic acid.

4.2. Initial Results

We commenced our study by taking *ortho* methoxy benzoic acid (**4.114 a**) and tosyl azide (**4.115 a**) as coupling Partners. After screening various Ruthenium, Iridium, Cobalt and Rhodium catalysts, we were delighted to observe the desired amidation product in 21% yield at 140 °C. In oder to improve efficiency of the reaction, we screened various additives, solvents and the best yield is obtained with 5 mol% $[RhCl_2(Cp^*)]_2$, 20 mol% $AgSbF_6$ and 50 mol% Ag_2CO_3 in DMAC solvent at 140 °C.

Table 4.1. Optimization of rhodium catalyzed decarboxylative amidation (Part I).

Catalyst (mol%)	Additive (X mol%)	Temp(^{O}C)	Solvent	Conversion(%)^a
[RuCl$_2$(*p*-cymene)]$_2$ (5)	NaOAc (20)	120	Dioxane	0
[RuCl$_2$(*p*-cymene)]$_2$ (5)	Pivalic acid (50)	120	Dioxane	0
[Ru(OAc)$_2$(*p*-cymene)] (10)	Pivalic acid (50)	120	Dioxane	0
[Ru(OAc)$_2$(*p*-cymene)] (10)	Ag$_2$CO$_3$ (50)	120	Dioxane	Traces
[Ru(OAc)$_2$(*p*-cymene)] (10)	-	120	Dioxane	Traces
[IrCl$_2$Cp*]$_2$ (5)	AgSbF$_6$ (20)	120	Dioxane	0
[IrCl$_2$Cp*]$_2$ (5)	AgSbF$_6$ (20) + Ag$_2$CO$_3$ (50)	120	Dioxane	0
[IrCl$_2$Cp*]$_2$ (5)	AgSbF$_6$ (20) + Ag$_2$CO$_3$ (50)	140	Dioxane	Traces
[RhCl$_2$Cp*]$_2$ (5)	AgSbF$_6$ (20)	120	Dioxane	0
[RhCl$_2$Cp*]$_2$ (5)	AgSbF$_6$ (20) + Ag$_2$CO$_3$ (50)	120	Dioxane	Traces
[RhCl$_2$Cp*]$_2$ (5)	AgSbF$_6$ (20) + Ag$_2$CO$_3$ (50)	140	DMF	21
[RhCl$_2$Cp*]$_2$ (5)	AgSbF$_6$ (20) + Ag$_2$CO$_3$ (50)	150	DMF	17
[RhCl$_2$Cp*]$_2$ (5)	AgSbF$_6$ (20) + Ag$_2$CO$_3$ (50)	140	DMAC	23
[RhCl$_2$Cp*]$_2$ (5)	AgSbF$_6$ (20) + Ag$_2$CO$_3$ (50)	140	NMP	19
[RhCl$_2$Cp*]$_2$ (5)	AgSbF$_6$ (20) + Ag$_2$CO$_3$ (50)	140	DMSO	13
[RhCl$_2$Cp*]$_2$ (5)	AgSbF$_6$ (20) + Ag$_2$O (50)	140	DMAc	11
[RhCl$_2$Cp*]$_2$ (5)	AgSbF$_6$ (20) + Cu$_2$O (50)	140	DMAc	14
[RhCl$_2$Cp*]$_2$ (5)	AgSbF$_6$ (20) + CuO (50)	140	DMAc	Traces

Reaction conditions: **1** (0.15 mmol, 1 equiv), **2** (0.30 mmol, 2 equiv), Solvent (1 mL);
a: GC yields

4.3. Optimization of Reaction Condition

At this stage we decided to examine various aminating agents (**4.115**) as shown in Table

2. On the basis of initial result we screened the aminating agents using Rh(III)/Ag(I) catalytic

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system. The reaction efficiency is dramatically decreased with **4.15** b-**4.15** e aminating agents.

On the other hand reaction proceeded smoothly with 3-phenldioxazolones (**4.15** f) and the

corresponding product was obtained in 42% yield. Screening of various solvents reavealed

dioxane as optimal solvent. Screening of various bases and other silver or copeer salts did not

improve the reaction efficiency. Pleasigly, switching the equivalents of the reactants significantly

improved the yield and the desired amidation product is obtained in 76% isolated yield.

Table 4.2. Optimization of rhodium catalyzed decarboxylative amidation (Part II).

Catalyst (mol%)	Additive	Aminating agent	Temp ($^\circ$C)	Solvent	Convsn(%)^a
[RhCl$_2$Cp*]$_2$	AgSbF$_6$ + Ag$_2$CO$_3$	**4.115** a	140	DMAC	23
[RhCl$_2$Cp*]$_2$	AgSbF$_6$ + Ag$_2$CO$_3$	**4.115** b	140	DMAC	11
[RhCl$_2$Cp*]$_2$	AgSbF$_6$ + Ag$_2$CO$_3$	**4.115** c	140	DMAC	0
[RhCl$_2$Cp*]$_2$	AgSbF$_6$ + Ag$_2$CO$_3$	**4.115** d	140	DMAC	0
[RhCl$_2$Cp*]$_2$	AgSbF$_6$ + Ag$_2$CO$_3$	**4.115** e	140	DMAC	<10
[RhCl$_2$Cp*]$_2$	AgSbF$_6$ + Ag$_2$CO$_3$	**4.115** f	140	DMAC	42

Reaction conditions: **1** (0.15 mmol, 1 equiv), **2** (0.225 mmol, 1.5 equiv), Solvent (1 mL), Catalyst (5 mol%), AgSbF$_6$ (20 mol%), Ag$_2$CO$_3$ (50 mol%), a: GC yields

Table 4.3. Optimization of rhodium catalyzed decarboxylative amidation (Part III).

Catalyst (mol%)	Additive (mol%)	Temp (°C)	Solvent	Convsn(%)
[RhCl$_2$Cp*]$_2$	AgSbF$_6$ + Ag$_2$CO$_3$ + K$_2$HPO$_4$	140	DMAC	0
[RhCl$_2$Cp*]$_2$	AgSbF$_6$	140	DMAC	0
-	AgSbF$_6$ + Ag$_2$CO$_3$	140	DMAC	0
[RhCl$_2$Cp*]$_2$	AgSbF$_6$ + Ag$_2$CO$_3$	140	Dioxane	47
[RhCl$_2$Cp*]$_2$	AgSbF$_6$ + Ag$_2$CO$_3$	140	Toluene	13
[RhCl$_2$Cp*]$_2$	AgSbF$_6$ + Ag$_2$CO$_3$	140	Xylene	15
[RhCl$_2$Cp*]$_2$	AgSbF$_6$ + Ag$_2$CO$_3$	140	Acetonitrile	8
[RhCl$_2$Cp*]$_2$	AgSbF$_6$ + Ag$_2$CO$_3$	140	DCE	31
[RhCl$_2$Cp*]$_2$	AgSbF$_6$ + Ag$_2$CO$_3$	140	NMP	41
[RhCl$_2$Cp*]$_2$	AgSbF$_6$ + Ag$_2$CO$_3$	140	DMF	38
[RhCl$_2$Cp*]$_2$	AgSbF$_6$ + Ag$_2$CO$_3$(50)	140	DME	35
[RhCl$_2$Cp*]$_2$	AgSbF$_6$ + Ag$_2$CO$_3$(50)	140	DMSO	26
[RhCl$_2$Cp*]$_2$	AgSbF$_6$ + Ag$_2$CO$_3$(50)	140	Dimethyl carbonate	43
[RhCl$_2$Cp*]$_2$	AgSbF$_6$ + Ag$_2$CO$_3$(50)	140	Diethyl carbonate	36
[RhCl$_2$Cp*]$_2$	AgSbF$_6$ + Ag$_2$CO$_3$(50)	140	Dioxane + DMAC	49
[RhCl$_2$Cp*]$_2$	AgSbF$_6$ + Ag$_2$O(50)	140	Dioxane + DMAC	11
[RhCl$_2$Cp*]$_2$	AgSbF$_6$ + CuO(50)	140	Dioxane + DMAC	22
[RhCl$_2$Cp*]$_2$	AgSbF$_6$ + Cu$_2$O(50)	140	Dioxane + DMAC	9
[RhCl$_2$Cp*]$_2$	AgSbF$_6$ + Cu(OAc)$_2$(50)	140	Dioxane + DMAC	Traces
[RhCl$_2$Cp*]$_2$	AgSbF$_6$ + Ag$_2$CO$_3$(50)	140	Dioxane + DMAC	83[b]
[RhCl$_2$Cp*]$_2$	AgSbF$_6$ + Ag$_2$CO$_3$(50)	140	Dioxane	86[b](**77**)[c]

Reaction conditions: **1** (0.15 mmol, 1 equiv), **2** (0.225 mmol, 1.5 equiv), Solvent (1 mL), Catalyst (5 mol%), AgSbF$_6$ (20 mol%), a: GC yields,
b: **1** (2 equiv) & **2** (1 equiv), C: Isolated yield;

4.4. Substrate Scope

With optimized conditions in hand we evaluated the substrate scope for the decarboxylative amidation of benzoic acids as shown in Figure 4.1. Under established conditions, broad range of *ortho* substituted benzoic acids (**4.114**) reacted smoothly with phenyl dioxazolone (**4.115** f) to afford the corresponding *meta* amidation products.

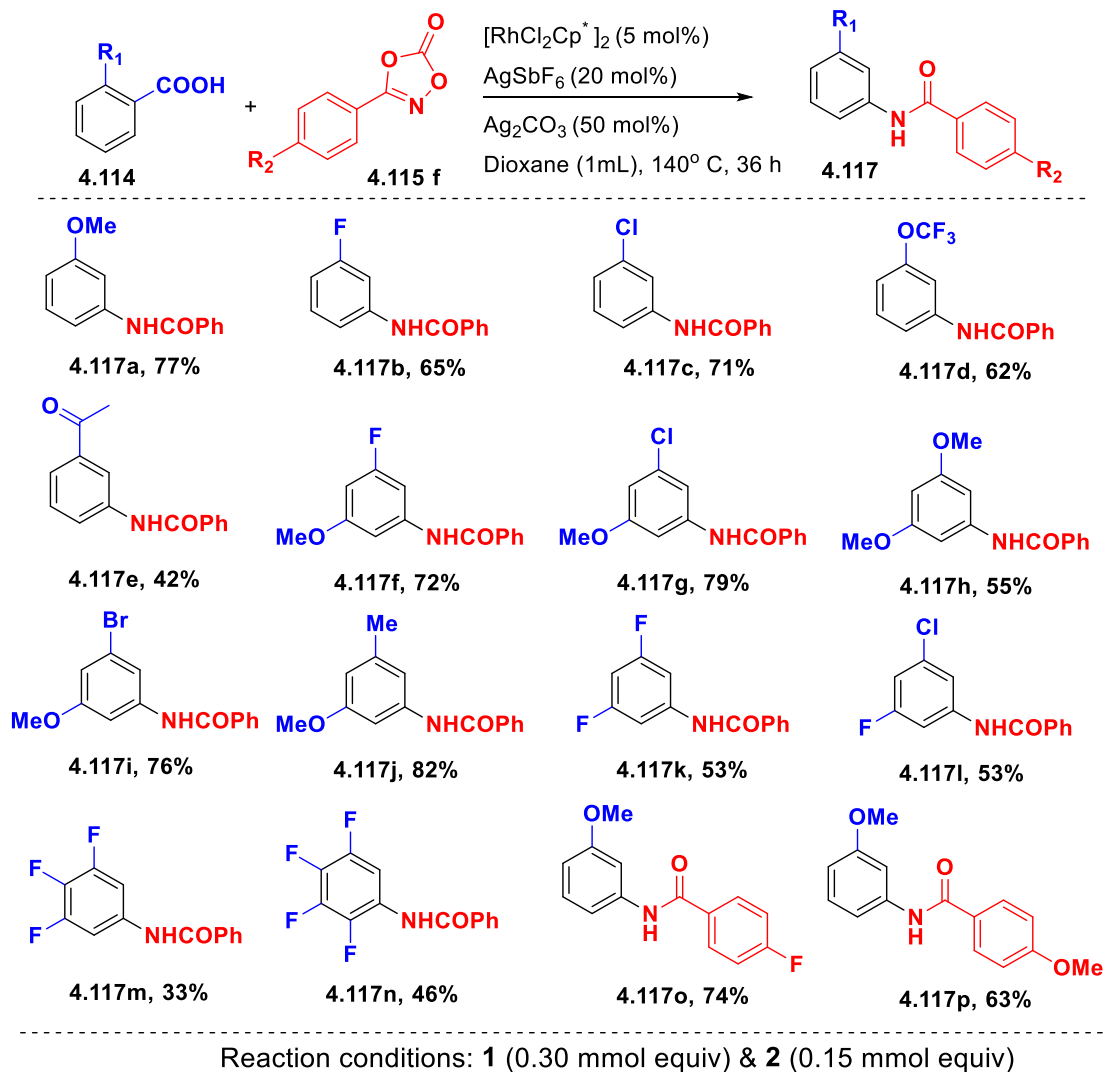Reaction conditions: **1** (0.30 mmol equiv) & **2** (0.15 mmol equiv)

Figure 4.1. Substrate scope for the decarbocxylative C-H amidation through C-H bond activation.

ortho benzoic acids bearing methoxy, fluoro, chloro, trifluoromethoxy and acetyl substrates were smoothely transformed into corresponding amidtion products (**4.117a - 4.117e**)

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with satisfying yields from 77% to 42%. Next, various disubstituted benzoic acids were subjected to decarboxylative amidation and products (**4.117f – 4.117l**) are afforded in good yields. The reactivity of trisubstituted and tetra substituted benzoic acids significatly diminished. The reaction of trifluoro benzoic acid and tetrafluoro benzoic acid with phenyl dioxazolone gave 33% and 45% yields respectively (**4.117m** and **4.117n**). Next we compared the reactivity of dioxazolones by raecting with *ortho* methoxy benzoic acid. 3-(4-Fluoro phenyl)-1,4,2-dioxazolone reacted more efficiently compared to 3-(4-methoxy phenyl)-1,4,2-dioxazolone and the corresponding products are obtained in 74% and 63% yields (**4.117o** & **4.117p**).
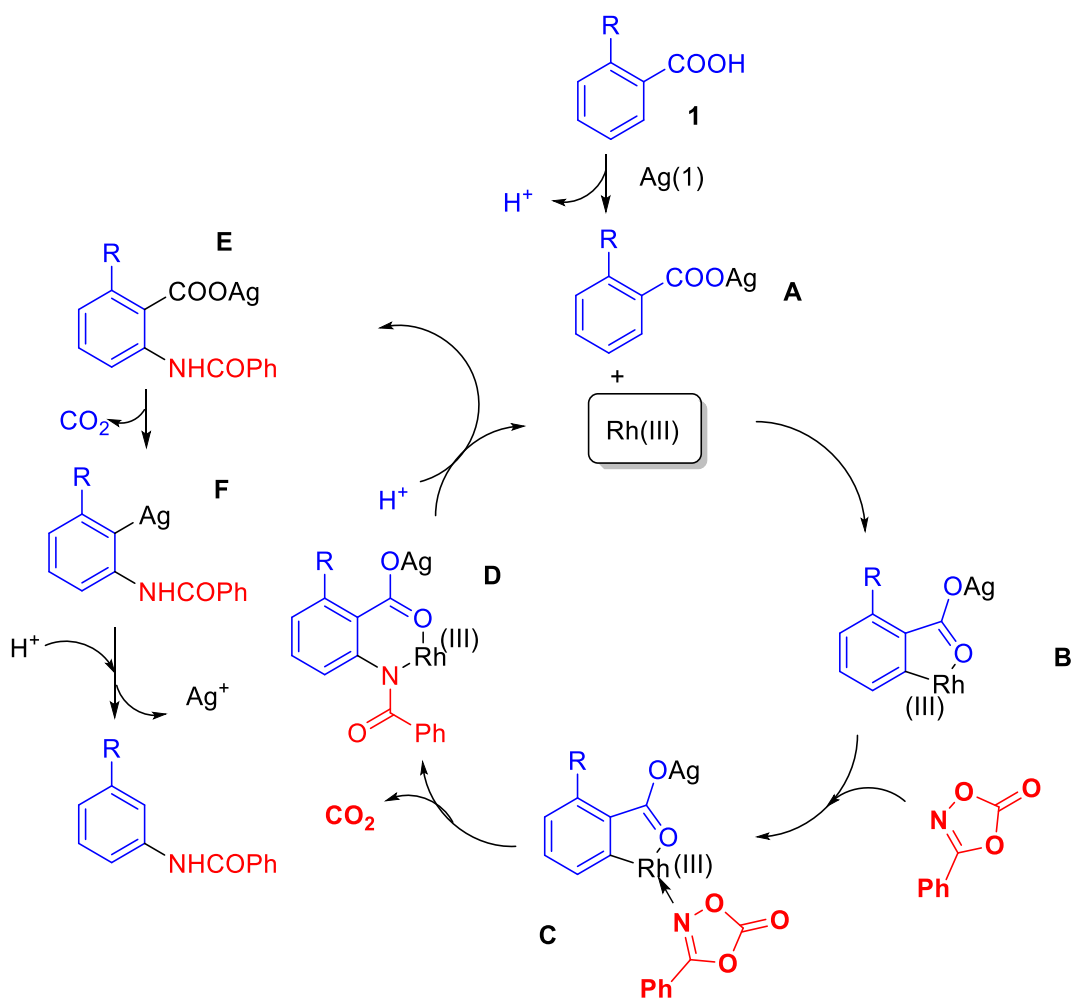
Scheme 4.26. Plausible reaction mechanism for decarboxylative *ortho* amidation of arene carboxylic acids through chelation assisted C-H bond activation.

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The current catalytic system proceeds via Rh(III) catalysed carboxylate-directed C-H amidation followed by Ag(I) catalysed decarboxylation. This protocol is compatible with broad range of arene carboxylic acids with good functional group tolerance. The plausible mechanism for this transformation is depicted in the Scheme **4.26**. The catalytic cycle begins with the formation of silver arylcarboxylate (**A**) through the reaction of arylcarboxylic acid with silvercarbonate. Upon reaction of Rh(III) catalyst with **A** generates the cylometalated intermediate **B** through carboxylate directed C-H bond activation. Next, reaction of dioxazolone with cyclometalated intermediate **B** results in the formation of metal-amido intermediate **D**. Protonation of intermediate **D** regenerates Rh(III) catalyst and produces silver arylcarboxylate intermediate **E**. Decarboxylation of **E** follwed by protonation of **F** delivers the final product.

Surprisingly, when Rhodium/Ag catalytic system is employed to the directing group substituted benzoic acids led to the formation of *ipso*-amidation products. Unlike above-mentioned amidation which occurs through carboxyl directed C-H amidation followed by decarboxylation, this reaction proceeds via DG-assisted decarboxylation and subsequent amidation. Encouraged by this intial result we investigated the best reaction condition for the decarboxylative *ipso* amidation. After having established condition inhand we examined the scope of the reaction as shown in Figure 4.2.
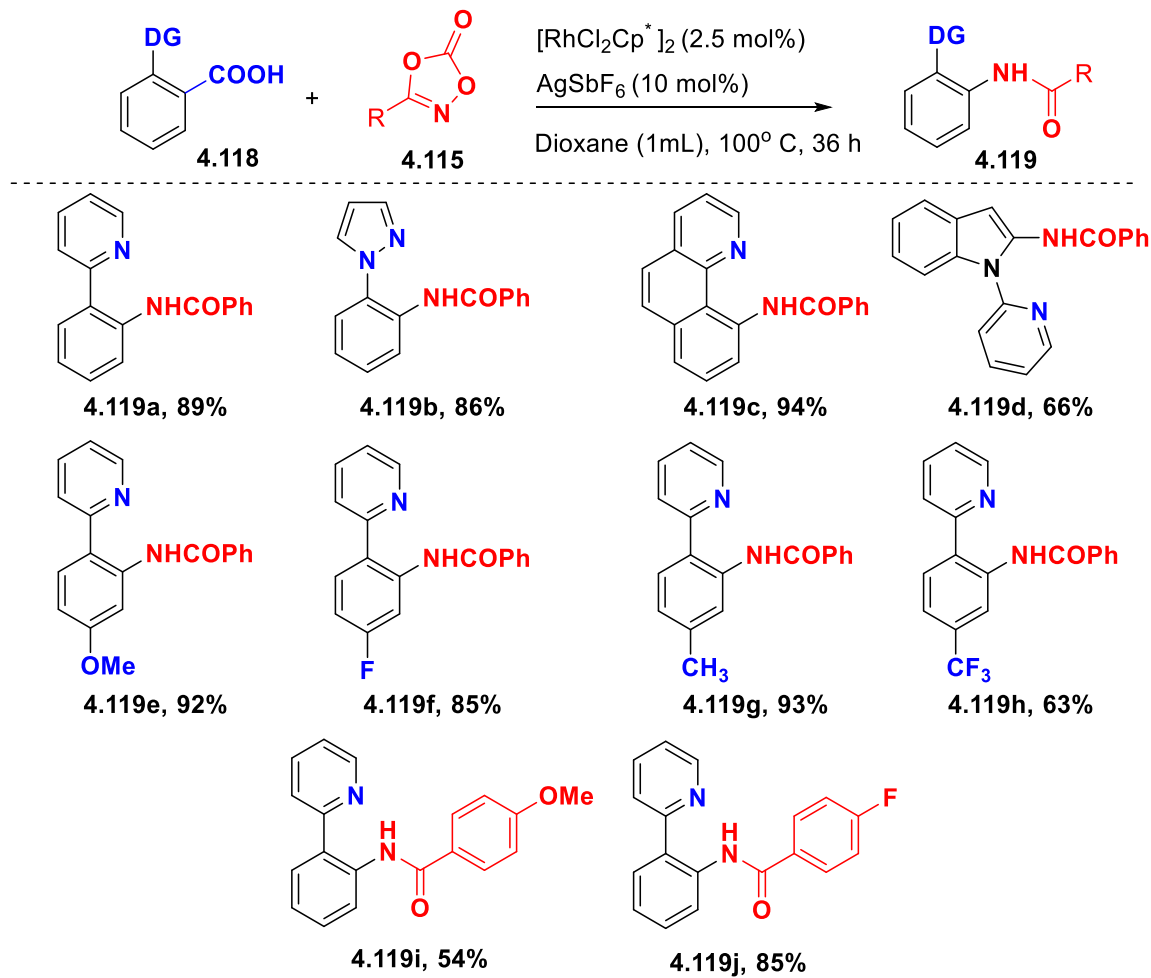
Figure 4.2. Rh(III) catalysed decarboxylative *ipso* amidation of arene carboxylic acids.

As shown above in Figure 4.2, the reaction is suitable for pyridyl, pyrazole and benzo[*h*]quinoline substituted benzoic acids and the corresponding products are obtained in excellent yields (**4.119a** to **4.119c**). The present reaction is also compatible for N-pyridyl indole-2-carboxylic acid for chelation assisted decarboxylative *ipso* amidation with 66% yield. Alteration of electronics on the phenyl ring affected the catalytic activity of the reaction and the substrate bearing electron with-drawing group on the phenyl ring in less reactive compared to the substrates bearing electron rich substituents, and corresponding products are afforded in good

yields (**4.119e** to **4.119f**). Subsequently, variation of electronics on dioxazolone was examined and significant loss of reactivity was observed with 4-methoxyphenyl dioxazolone.

To further gain insight into the mechanism, we performed control experiments as shown in Scheme 4.27 . When the present reaction is performed using cationic Rh(III) catalyst, the reaction proceeded smoothly and afforded the desired product in 91% yield (Scheme 4.27 a). Next, we carried out decarboxylative *ipso* amidation using cyclometalated Rh(III) complex as catalyst, we obtained the corresponding product in 93% yield (Scheme 4.27 b). These experiments revealed that the reaction proceeds via Rh(III) mediated *ipso* decarboxylation followed by amidation.
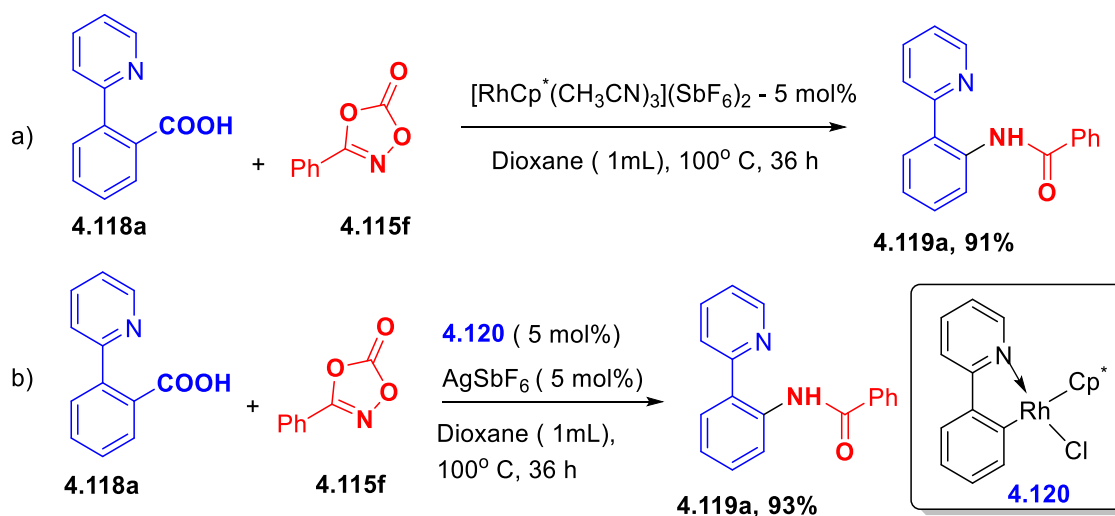
Scheme 4.27. Control experiments for Rh(III) catalysed *ipso* amidation of arenecarboxylic acids through chelation assisted C-C bond activation.

From the above observations, the plausible pathway for *ipso* amidation is proposed in the following Scheme 4.28. Active catalyst generated in the reaction mixture reacts with arene carboxylic acid and generates Rh(III) carboxylate intermediate **A.** Coordination of Dioxazolidinone followed by decarboxylation produces cyclometalated Rh(III) intermediate **C.** Subsequently Rhodium-amido species (**D**) is generated from intermediate **C,** which undergoes protonation with the incoming substrate and delivers the final product.

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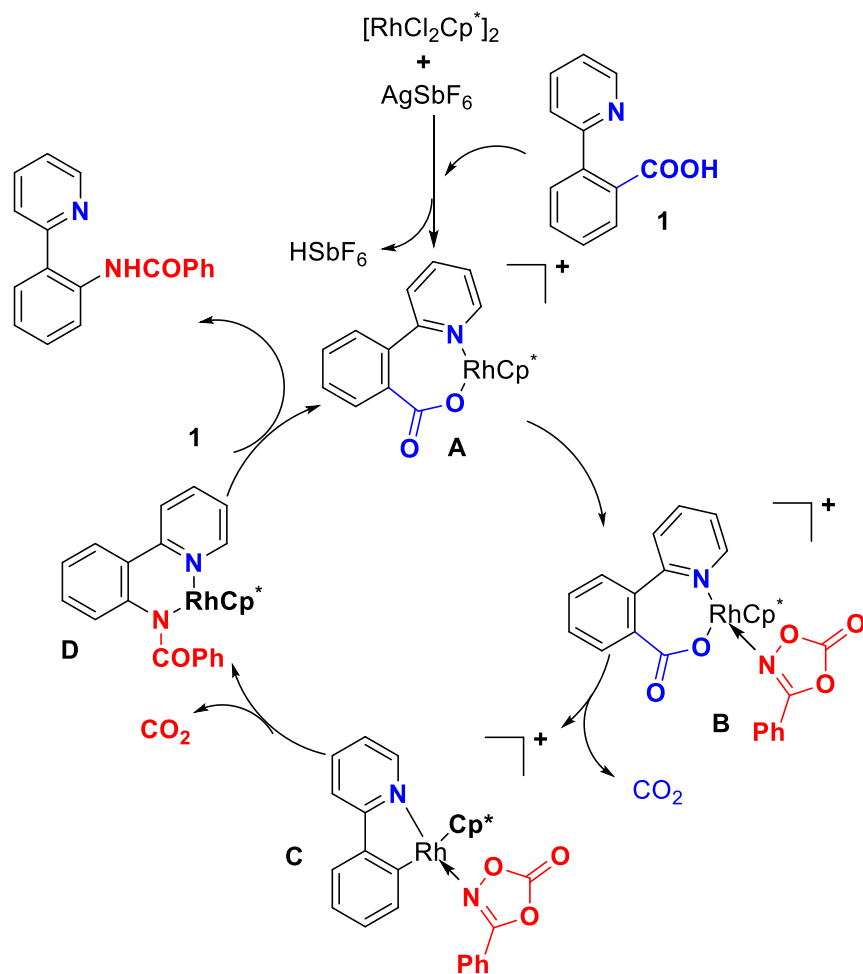
Scheme 4.28. Mechanism for Rh(III) catalysed chelation assisted *ipso* amidation.

In conclusion we disclosed a new protocol for Rh(III)/Ag catalysed amidation of arene carboxylic acids using aryl dioxazolones. The reaction proceeds in two different pathways depending on the *ortho* substituents of arene carboxylic acids. With nondirecting substituents the reaction proceeds via Rhodium catalysed chelation assisted C-H amidation followed by silver catalysed decarboxylation. On the otherhand with directing group substituents the reaction occurs via Rhodium catalysed chelation assisted decarboxylation followed by amidation. The current reaction proceeds with good yields and high functional group tolerance.

4.5. Experimental Procedures

4.5.1. General Experimental Procedures and Reagent Availability

Unless otherwise noted, all manipulations were carried out under a nitrogen atmosphere using standard Schlenk-line or glove box techniques. All glasswares were oven-dried for at least 1 h prior to use. Toluene and hexane solvents were degassed by purging with nitrogen for 45 min and dried with a solvent purification system (MBraun MB-SPS). THF and dichloromethane were dried over activated 3Å molecular sieves and degassed by purging with nitrogen. Other reagents and starting materials for substrate synthesis were purchased from commercial vendors and used as received. TLC plates were visualized by exposure to ultraviolet light.

Organic solutions were concentrated by rotary evaporation at ~10 torr. Flash column chromatography was performed with 40–63 microns silica gel. ^{1}H NMR and ^{13}C NMR spectra were obtained on a 400 MHz spectrometer, and chemical shifts were recorded relative to residual protiated solvent. Both ^{1}H and ^{13}C NMR chemical shifts were reported in parts per million downfield from tetramethylsilane ($\delta = 0$ ppm). ^{19}F NMR spectra were obtained at 282.4 MHz, and all chemical shifts were reported in parts per million upfield of CF_3COOH ($\delta = -78.5$ ppm). High resolution mass spectra were obtained at a Waters HRMS spectrometer.

**4.5.2. Synthesis of Reagents for C-H Amidation**

4.5.2.1. *Preparation of TsN₃[51]*
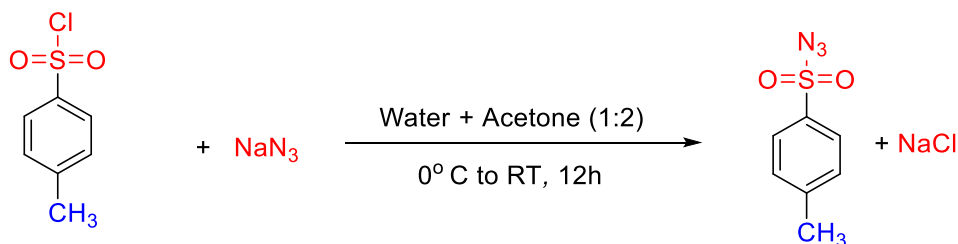
Scheme 4.29. Synthesis of tosyl azide.

Into a 100 mL round-bottom flask equipped with a magnetic stir-bar was added solution of sodium azide (30 mmol) in water (20 mL). To the above solution, *p*-toluene sulfonyl chloride (20 mmol) in acetone (40 mL) was added dropwise at 0 ºC. The reaction mixture was heated to room temperature and stirred for overnight. After removing the acetone under reduced pressure, the mixture was extracted with ethylacetate (40 mL). The combined organic layers were washed with 5% Na_2CO_3 (2×50 mL), water (2×50 mL) and then dried over $MgSO_4$. The solvent was removed under reduced pressure to afford tosyl azide (14 mmol) as a colorless oil.

4.5.2.2. *Preparation of 5,5-dimethyl-3-phenyl-1,4,2-dioxazole*[52]
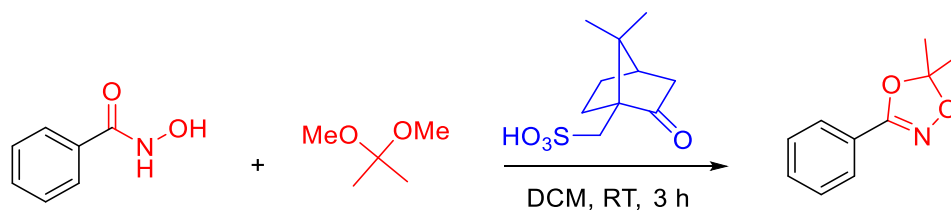
Scheme 4.30. Synthesis of 5,5-dimethyl-3-phenyl-1,4,2-dioxazole.

Procedure: Into a 250mL round bottom flask equipped with magnetic stir-bar was added a solution of benzohydroxamic acid (1.4 g, 10 mmol) and 2,2-dimethylpropane (3.1g, 30 mmol) in 150 mL of dichloromethane. To the above solution camphorsulfonic acid (2.3 g, 10 mmol) was added and stirred at room temperature for 3 h. After three hours, the reaction mixture was quenched with sodium bicarbonate (20 mL) and the aqueous layer was extracted with diethyl ether (100 mL x 3). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The crude mixture was purified by column chromatography (hexane/EtOAc) to obtain the desired product.

4.5.2.3. *Preparation of 5-phenyl-1,3,2,4-dioxathiazole 2-oxide[53]*
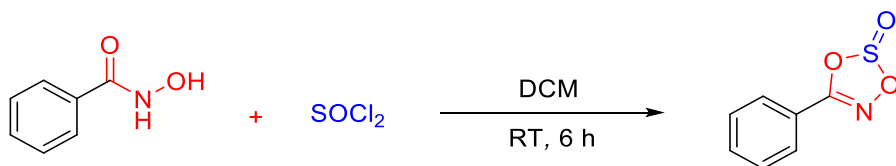
Scheme 4.31. Synthesis of 5-phenyl-1,3,2,4-dioxathiazole 2-oxide.

Into a 250 mL round bottom flask was added a solution of thionyl chloride (40.0 mmol) in dichloromethane (40 mL). To the above solution benzohydroxamic acid (1.4 g, 10 mmol) was added at room temperature and stirred for 6 h. After six hours excessive thionyl chloride and solvent were removed under reduced pressure to give 5-phenyl-1,3,2,4-dioxathiazole 2-oxide (81%) as light yellow liquid.

4.5.2.4. *Preparation of 3-substituted-1,4,2-dioxazol-5-one[54]*
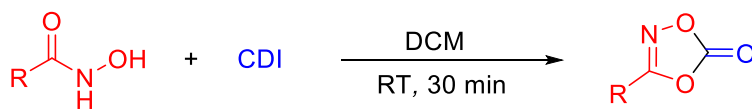
CDI = Carbonyl diimidazole

Scheme 4.32. Synthesis of 3-substituted-1,4,2-dioxazol-5-one.

Into a 250mL round bottom flask was added a solution of hydoxamic acid (10.0 mmol) in dichloromethane (150 mL). To the above solution 1,1′-carbonyldiimidazole (1.62 g,10.0 mmol) was added in one portion at room temperature. After stirring the solution for 30 min, the reaction mixture was quenched with 1 N HCl (100 mL) and extracted with dichloromethane three times (100 mL x 3) and dried over magnesium sulfate. The solvent was removed under reduced pressure and product was recrystallized with acetone/hexane, to afford 3-substituted 1,4,2-dioxazol-5-ones.

4.5.2.5. *Preparation of tert-Butyloxycarbonylazide* [55]
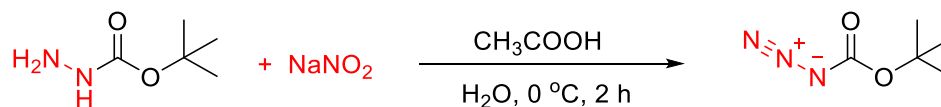
Scheme 4.33. Synthesis of *tert*-Butyloxycarbonylazide.

Procedure: Into a 25mL round bottom flask was added a solution of tert-Butylcarbazate (3.00 g, 22.7 mmol, 1.0 eq.) in a mixture of water (7.0 mL) and acetic acid (5.0 mL). To the above solution NaNO$_2$ (1.72 g, 25.0 mmol, 1.1 eq.) was added at 0 $^{\circ}$C over 5 minutes and the resulting mixture was stirred for two hours. After two hours, the reaction mixture was brought to room temperature and then 20 mL Water was added and the mixture was extracted with Et$_2$O (3 × 70 mL). The organic layer was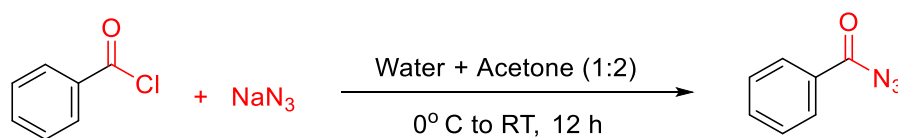 washed with half saturated NaHCO$_3$(2 × 50 mL), brine (30 mL) and then dried over Na$_2$SO$_4$ and filtered. The solvent was removed in vacuum at room temperature. The BocN$_3$ (3.25 g, 22.7 mmol, quant.) was obtained as a yellow liquid and was pure enough for further applications.

4.5.2.6. *Preparation of Benzoyl azide*[56]

Scheme 4.34. Synthesis of benzoyl azide.

Procedure: Into a 100mL round bottom flask was added a solution of sodium azide (1.99 g, 30 mmol) in water (10 mL). The solution was cooled to 0 $^{\circ}$C and then acyl chloride (20 mmol) in acetone (20 mL) was added dropwise. The resulting mixture mixture was warmed up to room temperature and stirred for overnight. Acetone was removed under reduced pressure and the reaction mixture was extracted with EtOAc (50 mL x 3). The combined organic layers were

dried over MgSO$_4$and solvent was removed under reduced pressure. The crude mixture was purified using silica gel column chromatography (n-Hexane/EtOAc).

4.5.3. General Procedure for Decarboxylative *ortho* Amidation of Arenecarboxylic Acids through Chelation Assisted C-H Bond Activation

Into a 4 mL scintillation vial equipped with a magnetic stir bar was placed [RhCl$_2$Cp*]$_2$ (5 mol%), AgSbF$_6$ (20 mol%), Ag$_2$CO$_3$ (50 mol%), phenyl-1,4,2-dioxazolone (0.15 mmol). arenecarboxylicacid (0.30 mmol) and Dioxane (1.0 mL). The reaction mixture was stirred at room temperature for 5 minutes and the vial was sealed with a silicone-lined screw-cap and electrical tape before being transferred out of the glovebox and stirred at 140 °C for 36 hours. The reaction mixture was cooled to room temperature and volatiles were removed under reduced pressure. The crude product was purified by flash-column chromatography on silica.

4.5.4. General Procedure for Decarboxylative *ipso* Amidation of Arenecarboxylic Acids through Chelation Assisted C-C Bond Activation

Into a 4 mL scintillation vial equipped with a magnetic stir bar was placed [RhCl$_2$Cp*]$_2$ (2.5 mol%) and AgSbF$_6$ (10 mol%). Phenyl-1,4,2-dioxazolone (0.15 mmol), arenecarboxylicacid (0.30 mmol) and Dioxane (1.0 mL) were subsequently added. The reaction mixture was stirred at room temperature for 5 minutes and the vial was sealed with a silicone-lined screw-cap, and electrical tape before being transferred into the preheated oil bath. After stirring the reaction mixture at 140 °C for 36 hours, it was cooled to room temperature and volatiles were removed under reduced pressure to afford crude product. The crude product was purified by flash-column chromatography on silica.
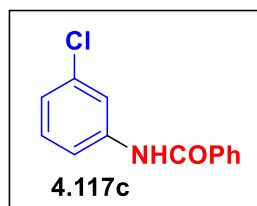
4.6. Spectral Data
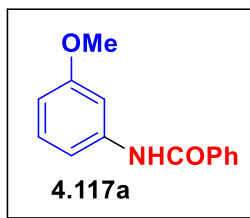
4.117a

N-(3-methoxyphenyl)benzamide (4.117a): The compound **4.117a** was synthesized according to the general procedure described above and purified by flash column chromatography (0 to 7% ethyl acetate in hexanes) in 77% yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.01 – 7.82 (m, 3H), 7.52 (dt, J = 31.6, 7.8 Hz, 4H), 7.31 – 7.23 (m, 1H), 7.13 (d, J = 8.0 Hz, 1H), 6.73 (ddd, J = 8.2, 2.4, 0.9 Hz, 1H), 3.84 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 165.8, 160.2, 139.1, 134.9, 131.8, 129.7, 128.7, 127.0, 112.3, 110.5, 105.8, 77.3, 77.0, 76.7, 55.3. HRMS: m/z calcd for C$_{14}$H$_{13}$NO$_2$: 228.1024; found: 228.1037.
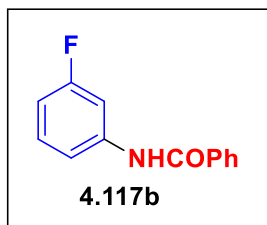
4.117b

N-(3-fluorophenyl)benzamide (4.117b): The compound **4.117b** was synthesized according to the general procedure described above and purified by flash column chromatography (0 to 4 % ethyl acetate in hexanes) in 65% yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.17 – 7.97 (m, 1H), 7.94 – 7.77 (m, 2H), 7.69 – 7.42 (m, 4H), 7.36 – 7.23 (m, 2H), 6.87 (ddt, J = 7.9, 6.7, 2.5 Hz, 1H). ^{13}C NMR (101 MHz CDCl$_3$) δ 165.9, 163.0 (d, J = 244.8 Hz), 139.4 (d, J = 10.9 Hz), 134.6, 132.0, 130.1 (d, J = 9.4 Hz), 128.8, 127.0, 115.4 (d, J = 3.0 Hz), 111.2 (d, J = 21.3 Hz), 107.7 (d, J = 26.4 Hz), 77.3, 77.0, 76.7. ^{19}F NMR (376 MHz, CDCl$_3$) δ -111.31. HRMS: m/z calcd for C$_{13}$H$_{10}$FNO: 216.0825; found: 216.0819.
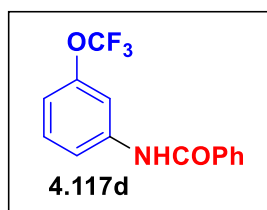
4.117c

N-(3-chlorophenyl)benzamide(4.117c): The compound **4.117c** was synthesized

according to the general procedure described above and purified by flash column

chromatography (0 to 4 % ethyl acetate in hexanes) in 71 % yield as a white solid. ^{1}H NMR (400

MHz, CDCl$_3$) δ 8.22 (s, 1H), 7.89 – 7.74 (m, 3H), 7.59 – 7.39 (m, 4H), 7.26 (t, J = 8.1 Hz, 1H),

7.12 (ddd, J = 8.0, 1.9, 0.9 Hz, 1H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 166.1, 139.1, 134.6, 134.4,

132.0, 130.0, 128.7, 127.1, 124.6, 120.5, 118.4, 77.3, 77.0, 76.7. HRMS: m/z calcd for

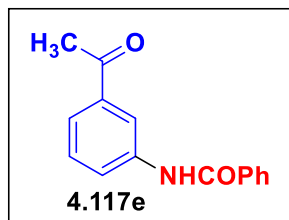C$_{13}$H$_{10}$NOCl:232.0529; found: 232.0536.

4.117d

N-(3-(trifluoromethoxy)phenyl)benzamide (4.117d): The compound **4.117d** was

synthesized according to the general procedure described above and purified by flash column

chromatography (0 to 4% ethyl acetate in hexanes) in 52% yield as a white solid. ^{1}H NMR (400

MHz, CDCl$_3$) δ 8.23 (s, 1H), 7.95 – 7.79 (m, 2H), 7.78 – 7.64 (m, 1H), 7.61 – 7.23 (m, 5H), 7.02

(dd, J = 8.1, 2.3 Hz, 1H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 166.0, 149.6 (q, J = , 2.0 Hz), 139.3,

134.4, 132.1, 130.0, 128.8, 127.0, 121.7, 119.1, 118.3, 116.6, 113.1, 77.3, 77.0, 76.7. ^{19}F NMR

(376 MHz, CDCl$_3$) δ -57.7. HRMS: m/z calcd for C$_{14}$H$_{10}$NO$_2$F$_3$:282.0742; found: 282.0755.

4.117e

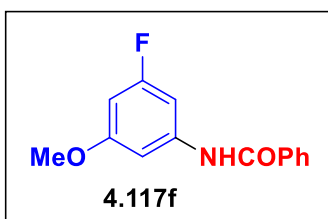**N-(2-acetylphenyl)benzamide (4.117e):** The compound **4.117e** was synthesized according to the general procedure described above and purified by flash column chromatography (0 to 10 % ethyl acetate in hexanes) in 42% yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.69 (s, 1H), 8.22 (t, J = 1.9 Hz, 1H), 8.12 (ddd, J = 8.2, 2.2, 1.0 Hz, 1H), 7.98 – 7.86 (m, 2H), 7.70 (ddd, J = 7.8, 1.7, 1.0 Hz, 1H), 7.60 – 7.50 (m, 1H), 7.45 (td, J = 7.9, 6.5 Hz, 3H), 2.57 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 198.3, 166.2, 138.7, 137.6, 134.5, 132.0, 129.3, 128.7, 127.2, 125.1, 124.3, 119.8, 77.3, 77.0, 76.7, 26.6. HRMS: m/z calcd for C$_{15}$H$_{13}$NO$_2$: 240.1024; found: 240.1037.

4.117f

N-(3-fluoro-5-methoxyphenyl)benzamide (4.117f): The compound **4.117f** was synthesized according to the general procedure described above and purified by flash column chromatography (0 to 8% ethyl acetate in hexanes) in 72% yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.37 (s, 1H), 7.88 – 7.75 (m, 2H), 7.56 – 7.46 (m, 1H), 7.46 – 7.35 (m, 2H), 7.16 – 7.03 (m, 2H), 6.41 (dt, J = 10.5, 2.3 Hz, 1H), 3.75 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 166.2, 163.6 (d, J = 242.9 Hz), 161.1 (d, J = 13.0 Hz), 139.9 (d, J = 13.7 Hz), 134.5, 132.0, 128.7, 127.1, 101.7 (d, J = 2.9 Hz), 100.1 (d, J = 26.6 Hz), 98.0 (d, J = 25.2 Hz), 77.4 , 77.0 ,

76.7 , 55.5. ^{19}F NMR (376 MHz, CDCl$_3$) δ -110.6. HRMS: m/z calcd for C$_{14}$H$_{12}$NO$_2$F: 246.0930; found: 246.0938.
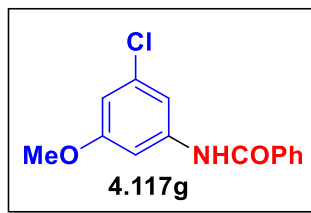

4.117g

N-(3-chloro-5-methoxyphenyl)benzamide (4.117g): The compound **4.117g** was synthesized according to the general procedure described above and purified by flash column chromatography (0 to 8% ethyl acetate in hexanes) in 79% yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.18 (s, 1H), 7.91 – 7.74 (m, 2H), 7.62 – 7.36 (m, 3H), 7.26 (dt, J = 10.6, 1.9 Hz, 2H), 6.69 (t, J = 2.1 Hz, 1H), 3.78 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 166.0, 160.6, 139.7, 135.0, 134.4, 132.0, 128.7, 127.0, 112.7, 110.7, 104.5, 77.3, 77.0, 76.7, 55.5. HRMS: m/z calcd for C$_{14}$H$_{12}$NO$_2$Cl: 262.0635; found: 262.0645;
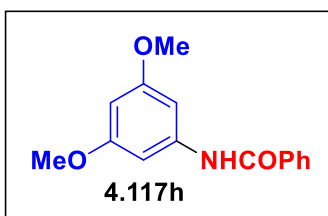

4.117h

N-(3,5-dimethoxyphenyl)benzamide (4.117h): The compound **4.117h** was synthesized according to the general procedure described above and purified by flash column chromatography (0 to 12 % ethyl acetate in hexanes) in 55% yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.24 (s, 1H), 7.92 – 7.77 (m, 2H), 7.57 – 7.35 (m, 3H), 6.95 (d, J = 2.2 Hz, 2H), 6.28 (t, J = 2.2 Hz, 1H), 3.76 (s, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 166.0, 161.0, 139.8, 134.8, 131.8, 128.6, 127.0, 98.5, 97.1, 77.4, 77.1, 76.8, 55.3. HRMS: m/z calcd for C$_{15}$H$_{15}$NO$_3$: 258.1130; found: 258.1133.
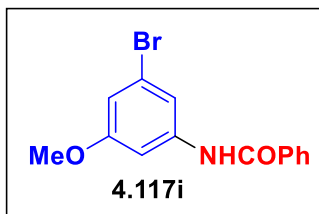
N-(3-bromo-5-methoxyphenyl)benzamide (**4.117i**): The compound **4.117i** was synthesized according to the general procedure described above and purified by flash column chromatography (0 to 5% ethyl acetate in hexanes) in 76 % yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.41 (s, 1H), 7.82 (d, J = 7.8 Hz, 2H), 7.59 – 7.19 (m, 5H), 6.82 (s, 1H), 3.74 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 166.2, 160.6, 140.0, 134.4, 132.0, 128.7, 127.1, 122.7, 115.7, 113.6, 105.2, 77.4, 77.1, 76.8, 55.5. HRMS: m/z calcd for C14H12NO2Br: 306.0130; found: 306.0139.
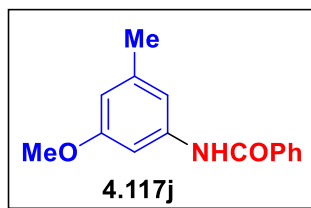

N-(3-methoxy-5-methylphenyl)benzamide(4.117j): The compound **4.117j** was synthesized according to the general procedure described above and purified by flash column chromatography (0 to 8% ethyl acetate in hexanes) in 82% yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.05 (s, 1H), 7.92 – 7.80 (m, 2H), 7.58 – 7.39 (m, 3H), 7.27 – 7.20 (m, 1H), 7.01 (q, J = 1.4, 0.9 Hz, 1H), 6.54 (ddd, J = 2.2, 1.4, 0.7 Hz, 1H), 3.79 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 165.8, 160.1, 139.9, 138.9, 135.0, 131.7, 128.7, 127.0, 113.2, 111.4, 103.0, 77.4, 77.0, 76.7, 55.2, 21.6. HRMS: m/z calcd for C$_{15}$H$_{15}$NO$_2$: 242.1181; found: 242.1188.
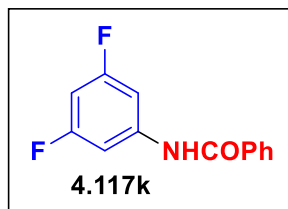
4.117k

N-(3,5-difluorophenyl)benzamide (4.117k): The compound **4.117k** was synthesized according to the general procedure described above and purified by flash column chromatography (0 to 4% ethyl acetate in hexanes) in 53% yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.10 (s, 1H), 7.92 – 7.77 (m, 2H), 7.62 – 7.54 (m, 1H), 7.48 (tt, J = 6.7, 1.5 Hz, 2H), 7.34 – 7.24 (m, 2H), 6.61 (tt, J = 8.9, 2.3 Hz, 1H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 165.9, 164.4 (d, J = 14.7 Hz), 162.0 (d, J = 14.6 Hz), 140.0 (t, J = 13.3 Hz), 134.2, 132.3, 128.9, 127.0, 103.4 – 102.8 (m), 99.8 (t, J = 25.6 Hz), 77.3, 77.0, 76.7. ^{19}F NMR (376 MHz, CDCl$_3$) δ -108.7. HRMS: m/z calcd for C$_{13}$H$_9$NOF$_2$: 234.0730; found: 234.0731.
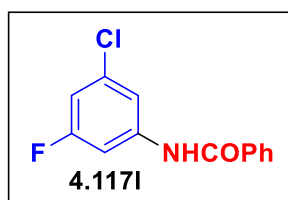

4.117l

N-(3-chloro-5-fluorophenyl)benzamide (4.117l): The compound **4.117l** was synthesized according to the general procedure described above and purified by flash column chromatography (0 to 4% ethyl acetate in hexanes) in 53% yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.26 (s, 1H), 7.89 – 7.75 (m, 2H), 7.61 – 7.37 (m, 5H), 6.87 (dt, J = 8.3, 2.1 Hz, 1H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 166.1, 162.8 (d, J = 247.8 Hz), 140.0 (d, J = 12.2 Hz), 135.2 (d, J = 12.4 Hz), 134.1, 132.3, 128.8, 127.1 , 115.9 (d, J = 3.2 Hz), 112.1 (d, J = 25.0 Hz), 106.0 (d, J = 26.4 Hz), 77.3 , 77.0 , 76.7. ^{19}F NMR (376 MHz, CDCl$_3$) δ -109.5. HRMS: m/z calcd for C$_{13}$H$_9$ClFNO: 250.0435; found: 250.0440.
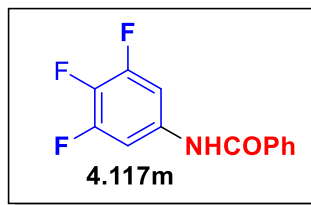
4.117m

N-(3,4,5-trifluorophenyl)benzamide (4.117m): The compound **4.117m** was synthesized according to the general procedure described above and purified by flash column chromatography (0 to 6 % ethyl acetate in hexanes) in 33 % yield as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.55 (s, 1H), 7.97 – 7.89 (m, 2H), 7.74 (ddd, J = 10.5, 6.6, 2.0 Hz, 2H), 7.65 – 7.48 (m, 3H). ^{13}C NMR (101 MHz, DMSO) δ ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.4, 166.3, 151.6 (dd, J = 9.9, 5.3 Hz), 149.1 (dd, J = 10.0, 5.3 Hz), 136.1 (d, J = 3.7 Hz), 136.0 (d, J = 3.6 Hz), 135.9 (d, J = 2.7 Hz), 134.5 (d, J = 5.8 Hz), 132.5, 128.9, 128.1, 104.7 (dd, J = 25.0, 7.9 Hz). ^{19}F NMR (376 MHz, DMSO) δ -135.0, -135.0, -135.0, -135.0, -167.7, -167.8, -167.8. HRMS: m/z calcd for $C_{13}H_8F_3NO$: 252.0636; found: 252.0642.
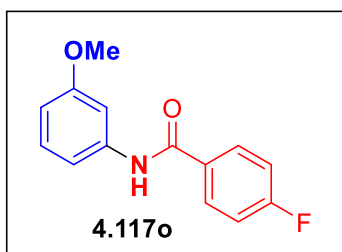

4.117o

4-fluoro-N-(3-methoxyphenyl)benzamide (4.117o): The compound **4.117o** was synthesized according to the general procedure described above and purified by flash column chromatography (0 to 8 % ethyl acetate in hexanes) in 74% yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.00 (s, 1H), 7.93 – 7.80 (m, 2H), 7.41 (t, J = 2.2 Hz, 1H), 7.31 – 7.20 (m, 1H), 7.19 – 7.06 (m, 3H), 6.72 (dd, J = 8.2, 2.0 Hz, 1H), 3.82 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) ^{13}C NMR (101 MHz, CDCl$_3$) δ 165.5 (d, J = 131.0 Hz), 163.6 , 160.2 , 139.0 , 131.1 (d, J = 3.1 Hz), 129.7, 129.4 (d, J = 9.0 Hz), 115.8 (d, J = 22.0 Hz), 112.5, 110.6, 106.0, 77.3, 77.0, 76.7,

55.32. ^{19}F NMR (376 MHz, CDCl$_3$) δ -107.41. HRMS: m/z calcd for C$_{14}$H$_{13}$FNO:246.0930; found: 246.0936.

4-methoxy-N-(3-methoxyphenyl)benzamide (4.117p): The compound **4.117p** was synthesized according to the general procedure described above and purified by flash column chromatography (0 to 15% ethyl acetate in hexanes) in 63% yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.85 (d, J = 8.8 Hz, 3H), 7.46 (t, J = 2.2 Hz, 1H), 7.32 – 7.19 (m, 1H), 7.16 – 7.06 (m, 1H), 6.97 (dd, J = 8.8, 1.6 Hz, 2H), 6.71 (ddd, J = 8.3, 2.5, 0.9 Hz, 1H), 3.86 (d, J = 18.2 Hz, 6H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 165.2, 162.4, 160.2, 139.4, 129.6, 128.8, 127.1, 113.9, 112.2, 110.3, 105.7, 77.3, 77.0, 76.7, 55.4, 55.3. HRMS: m/z calcd for C$_{15}$H$_{15}$NO$_3$: 258.1130; found: 258.1140.
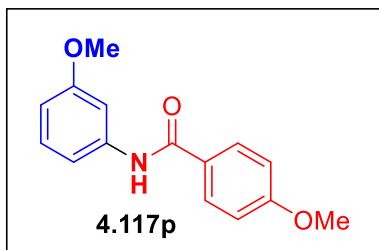

N-(2-(pyridin-2-yl)-phenyl)benzamide (4.119a): The compound **4.119a** was synthesized according to the general procedure described above and purified by flash column chromatography (0 to 6% ethyl acetate in hexanes) in 89% yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 13.30 (s, 1H), 8.99 – 8.47 (m, 2H), 8.07 (dd, J = 8.0, 1.8 Hz, 2H), 7.96 – 7.67 (m, 3H), 7.63 – 7.41 (m, 4H), 7.39 – 7.09 (m, 2H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 165.5, 158.1,

147.1, 138.1, 138.0, 135.6, 131.5, 130.3, 128.8, 128.6, 127.3, 125.6, 123.6, 123.0, 122.0, 77.4, 77.1, 76.8. HRMS: m/z calcd for $C_{18}H_{14}N_2O$: 275.1184; found: 275.1194.

4.119b

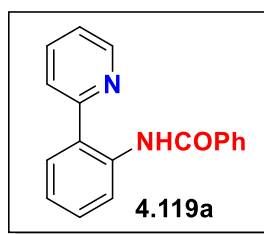**N-(2-(1H-pyrazol-1-yl)phenyl)benzamide (4.119b)**: The compound **4.119b** was synthesized according to the general procedure described above and purified by flash column chromatography (0 to 6% ethyl acetate in hexanes) in 86% yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 11.34 (s, 1H), 8.74 (dd, J = 8.3, 1.4 Hz, 1H), 8.06 − 7.82 (m, 4H), 7.61 − 7.35 (m, 5H), 7.23 (td, J = 7.7, 1.4 Hz, 1H), 6.55 (t, J = 2.1 Hz, 1H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 165.3, 141.1, 134.8, 131.8, 131.8, 130.2, 129.1, 128.6, 128.1, 127.3, 124.0, 122.9, 122.2, 107.3, 77.3, 77.0, 76.7. HRMS: m/z calcd for $C_{16}H_{13}N_3O$: 264.1137; found: 264.1149.
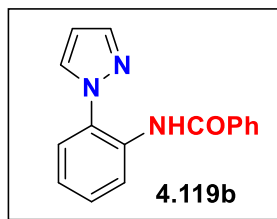

4.119c

N-(benzo[h]quinolin-10-yl)benzamide (4.119c): The compound **4.119c** was synthesized according to the general procedure described above and purified by flash column chromatography (0 to 5% ethyl acetate in hexanes) in 94% yield as a light yellow solid.
^{1}H NMR (400 MHz, CDCl3) δ 15.65 (s, 1H), 9.35 (dt, J = 8.3, 1.5 Hz, 1H), 8.82 (ddd, J = 6.6, 4.4, 2.2 Hz, 1H), 8.36 − 8.09 (m, 3H), 7.74 (dtd, J = 7.7, 4.9, 2.3 Hz, 2H), 7.66 − 7.44 (m, 6H).
^{13}C NMR (101 MHz, CDCl$_3$) δ 166.3, 147.6, 145.4, 139.6, 136.6, 136.5, 135.0, 131.4, 129.4,

129.0, 128.6, 127.6, 127.5, 125.0, 123.1, 120.7, 118.3, 117.8, 77.3, 77.0, 76.7. HRMS: m/z calcd

for $C_{20}H_{14}N_2O$: 299.1184; found: 299.1190.

4.119d

N-(1-(pyridin-2-yl)-1H-indol-2-yl)benzamide (**4.119d**): The compound **4.119d** was

synthesized according to the general procedure described above and purified by flash column

chromatography (0 to 10% ethyl acetate in hexanes) in 66% yield as a white solid.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 11.95 (s, 1H), 8.55 (dd, *J* = 5.2, 1.9 Hz, 1H), 8.00 − 7.90

(m, 2H), 7.83 (td, *J* = 7.8, 2.0 Hz, 1H), 7.70 − 7.61 (m, 2H), 7.59 − 7.45 (m, 4H), 7.37 (s, 1H),

7.26 − 7.13 (m, 3H). ^{13}C NMR (101 MHz, CDCl₃) δ 163.6, 151.8, 148.1, 139.5, 134.9, 134.1,

132.0, 131.9, 129.6, 128.8, 127.0, 122.1, 121.8, 120.8, 120.6, 117.7, 110.6, 93.7, 77.6, 77.3, 77.0.

HRMS: m/z calcd for $C_{20}H_{15}N_3O$: 314.1293; found: 314.1300.
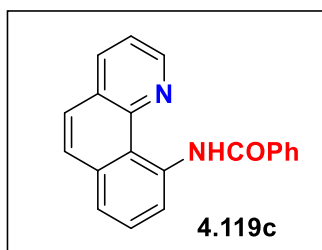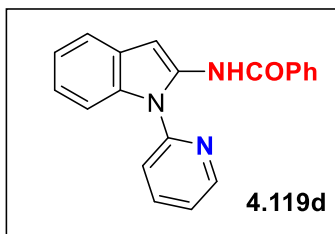

4.119e

N-(5-methoxy-2-(pyridin-2-yl)phenyl)benzamide (4.119e): The compound **4.119e** was

synthesized according to the general procedure described above and purified by flash column

chromatography (0 to 8% ethyl acetate in hexanes) in 92% yield as a white solid. ^{1}H NMR (400

MHz, CDCl₃) δ 13.84 (s, 1H), 8.66 − 8.59 (m, 2H), 8.13 − 8.05 (m, 2H), 7.85 − 7.66 (m, 3H),

7.60 − 7.49 (m, 3H), 7.23 (ddd, *J* = 7.3, 4.9, 1.3 Hz, 1H), 6.77 (dd, *J* = 8.8, 2.7 Hz, 1H), 3.95 (s,

3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 165.8, 161.0, 158.1, 146.9, 140.0, 137.7, 135.8, 131.5, 129.5, 128.6, 127.4, 121.9, 121.1, 117.6, 110.6, 105.5, 77.3, 77.0, 76.7, 55.4. HRMS: m/z calcd for C$_{19}$H$_{16}$N$_2$O$_2$:305.1290; found: 305.1299.

4.119f

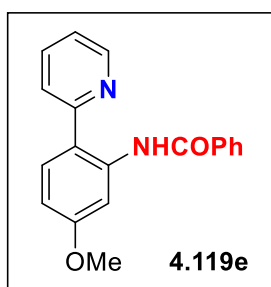**N-(5-fluoro-2-(pyridin-2-yl)phenyl)benzamide (4.119f):** The compound **4.119f** was synthesized according to the general procedure described above and purified by flash column chromatography (0 to 5 % ethyl acetate in hexanes) in 85% yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 13.70 (s, 1H), 8.81 − 8.53 (m, 2H), 8.13 − 7.96 (m, 2H), 7.90 − 7.65 (m, 3H), 7.54 (qd, J = 8.7, 7.8, 3.5 Hz, 3H), 7.29 (dd, J = 7.4, 4.9 Hz, 1H), 6.88 (ddd, J = 8.9, 7.6, 2.8 Hz, 1H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 165.74 , 163.50 (d, J = 247.7 Hz), 157.46 , 147.14 , 140.11 (d, J = 11.9 Hz), 137.98 , 135.40 , 131.77 , 130.04 (d, J = 9.9 Hz), 128.68 , 127.39 , 122.57 , 121.97 , 121.12 (d, J = 3.2 Hz), 110.32 (d, J = 22.2 Hz), 108.67 (d, J = 27.6 Hz), 77.42 , 77.10 , 76.79 . ^{19}F NMR (376 MHz, CDCl$_3$) δ -108.8. HRMS: m/z calcd for C$_{18}$H$_{13}$FN$_2$O: 293.1090; found: 293.1100.
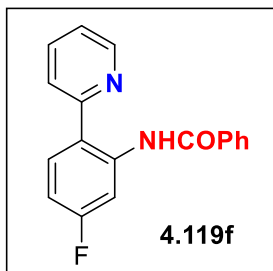

4.119g

N-(5-methyl-2-(pyridin-2-yl)phenyl)benzamide (4.119g): The compound **4.119g** was synthesized according to the general procedure described above and purified by flash column

chromatography (0 to 6% ethyl acetate in hexanes) in 93% yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 13.47 (s, 1H), 8.80 – 8.54 (m, 2H), 8.18 – 7.96 (m, 2H), 7.88 – 7.73 (m, 2H), 7.64 (d, J = 8.0 Hz, 1H), 7.60 – 7.45 (m, 3H), 7.26 (ddd, J = 6.7, 5.6, 3.1 Hz, 1H), 7.03 (dd, J = 8.1, 1.9 Hz, 1H), 2.47 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 165.5, 158.3, 147.1, 140.6, 138.1, 137.7, 135.8, 131.4, 128.6, 128.5, 127.3, 124.4, 122.7, 122.5, 122.2, 121.6, 77.4, 77.1, 76.7, 21.7. HRMS: m/z calcd for C$_{19}$H$_{16}$N$_2$O: 289.1341; found: 289.1348.

N-(2-(pyridin-2-yl)-5-(trifluoromethyl)phenyl)benzamide (4.119h): The compound **4.119h** was synthesized according to the general procedure described above and purified by flash column chromatography (0 to 5% ethyl acetate in hexanes) in 63% yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 13.47 (s, 1H), 9.21 (d, J = 1.8 Hz, 1H), 8.73 (dd, J = 4.6, 2.0 Hz, 1H), 8.05 (dd, J = 7.9, 1.6 Hz, 2H), 7.98 – 7.78 (m, 3H), 7.63 – 7.49 (m, 3H), 7.49 – 7.34 (m, 2H). ^{13}C NMR (101 MHz, Chloroform-d) δ 165.7, 157.0, 147.5, 138.7, 138.2, 135.2, 131.9 (q, J = 32.6 Hz), 131.8, 129.0, 128.7, 127.9, 127.4, 123.9 (q, J = 272.5 Hz) , 123.3, 122.9 , 119.8 (q, J = 3.9, 3.5 Hz), 118.8.0 (q, J = 4.2 Hz), 77. 4, 77.1, 76.7. ^{19}F NMR (376 MHz, CDCl$_3$) δ -62.8, -62.8. HRMS: m/z calcd for C$_{19}$H$_{13}$N$_2$OF$_3$:343.1058; found: 343.1068.
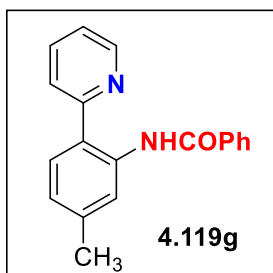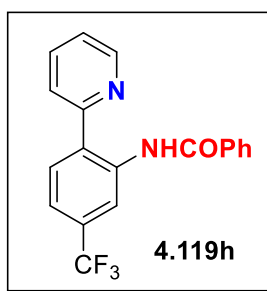
4-methoxy-N-(2-(pyridin-2-yl)phenyl)benzamide (4.119i): The compound **4.119i** was synthesized according to the general procedure described above and purified by flash column chromatography (0 to 8% ethyl acetate in hexanes) in 54% yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 13.24 (s, 1H), 8.82 (dd, J = 8.4, 1.2 Hz, 1H), 8.68 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H), 8.11 – 7.96 (m, 2H), 7.89 – 7.66 (m, 3H), 7.47 (ddd, J = 8.5, 7.3, 1.6 Hz, 1H), 7.34 – 7.11 (m, 2H), 7.08 – 6.91 (m, 2H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) δ 165.1, 162.2, 158.3, 147.2, 138.3, 137.8, 130.2, 129.2, 128.7, 128.0, 125.4, 123.3, 122.9, 121.9, 121.8, 113.8, 77.4, 77.1, 76.8, 55.4. HRMS: m/z calcd for C$_{19}$H$_{16}$N$_2$O$_2$:305.1290; found: 305.1295.
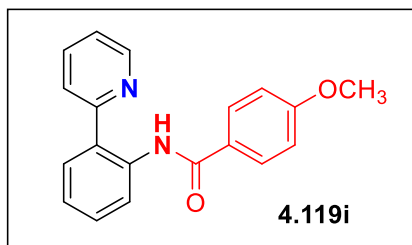

4.119j

4-fluoro-N-(2-(pyridin-2-yl)phenyl)benzamide (4.119j): The compound **4.119j** was synthesized according to the general procedure descri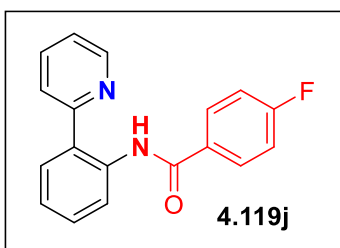bed above and purified by flash column chromatography (0 to 5% ethyl acetate in hexanes) in 85% yield as a white solid. ^{1}H NMR (400 MHz, CDCl$_3$) δ 13.36 (s, 1H), 8.88 – 8.58 (m, 2H), 8.13 – 8.02 (m, 2H), 7.93 – 7.79 (m, 2H), 7.76 (dd, J = 7.9, 1.6 Hz, 1H), 7.49 (ddd, J = 8.6, 7.3, 1.6 Hz, 1H), 7.37 – 7.27 (m, 1H), 7.26 – 7.14 (m, 3H). ^{13}C NMR (101 MHz, CDCl$_3$) ^{13}C NMR (101 MHz, CDCl$_3$) δ 164.8 (d, J = 251.9 Hz), 164.4, 158.3, 147.2, 138.1, 137.9, 131.9 (d, J = 3.2 Hz), 130.3, 129.7 (d, J = 8.9 Hz), 128.7, 125.4, 121.95 (d, J = 21.4 Hz), 115.7, 115.5, 77.4, 77.0, 76.7. ^{19}F NMR (376 MHz, CDCl$_3$) δ -108.3. HRMS: m/z calcd for C$_{18}$H$_{13}$FN$_2$O: 293.1090; found: 293.1102.

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5. CONCLUSION

In summary, we have developed three new catalytic methods through directing group-assisted transition metal catalysed C-H bond functionalisation. One of the main challenges in directed C-H bond activation is installation and removole of directing groups which hurts the step and atom economy of direct C-H bond functionalisation. To overcome the aforementioned challenge in directed C-H bond functionalisation we aimed at heteroatom-based directing groups (DGs) that are multi-tasking, transformable, and/or readily removable.

We demonstrated a ruthenium/NHC based catalytic system with intramolecular alkene hydroarylation of N-aryl acrylamides to form oxindoles, which are important synthetic targets due to their biological activities. The transformation proceeds via tandem sequence of amide-directed aromatic C–H bond activation and intramolecular alkene arylmetalation. This Ru-catalyzed cyclization process does not require additional DG assistance and the directing group is incrporated into the product backnone. With the redox-neutral nature and high atom-efficiency of alkene hydroarylation, the reaction is compatible with broad range of aromatic and vinyl substituents.

Next, we explored carboxylic acids as a traceless or removable directing group for chelation assited C-H bond functionaisation. we disclosed a protocol for the alkenylation of various heteroarenes through decarboxylative hydroheteroarylation of alkynes. The reaction occrs via carboxylate-directed C-H activation, alkyne insertion, and subsequent decarboxylation. This method enbles the alkenylation of heteroarens such as Indole, Benzofuran, Benzothiophene, Thiophene and Pyrrole at both C-2 and C-3 positions by overcoming their inherent reactivity. In addition, we have extended the scope of this decarboxylative C-H functionalization by coupling hateroarene carboxylicacids and acrylates under modified catalytic conditions.

Metal-catalyzed decarboxylation enables the use of arenecarboxylic acids as readily available aromatic building blocks. Long-standing challenges in this area include harnessing the effects of aromatic substituents on decarboxylation activity and achieving broader scopes and controlled regiochemistry for subsequent arene functionalization. Towards these goals, we have developed a Rh/Ag-bimetallic catalyst for decarboxylative amidation of *ortho*-substituted benzoic acids with 3-aryldioxazolones. Regioselectivity of this reaction is determined by nature of *ortho*-substituents through two forms of proposed chelation assistance: (1) A wide range of non-directing *ortho*-substituents led to *ortho*-amidation products via carboxylate-directed C-H amidation and subsequent decarboxylation. (2) 2-Pyridyl and analogous DGs led to *ipso*-amidation products via DG-assisted decarboxylation and subsequent amidation. Although this protocol works well for the *ortho* substituted arene carboxylic acids but it's not suitable for other arenen carboxylic acids such as *para* and *meta* substituted arene carboxylic acids. Future plans will be focused on developemnt of new catalytic system for decarboxylative C-H bond functionalisation which is suitable for broad range of arenes carboxylic acids.

Although significant advancements have been made in the field of transition metal catalysed chelation assisted C-H bond functionalisation, there is still room for the improvement. Notably, it is highly desirable to develop methods for C-H bond functionalisation with low catalytic loading and low temperature. It is necessary to explore less explore less expensive metals such as Cobalt, Nickel and Copper for the C-H bond functionalisation.