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TRANSITION METAL-CATALYZED
OXIDATIVE C-H BOND
FUNCTIONALIZATION REACTIONS

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Ph.D
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2016
The Hong Kong Polytechnic University

Department of Applied Biology and Chemical Technology

Transition Metal-Catalyzed Oxidative C-H Bond Functionalization Reactions

Yuen On Ying

A thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy

August, 2015
Declaration

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it reproduces no material previously published or written, nor material that has been accepted for the award of any other degree or diploma, except where due acknowledgement has been made in the text.

____________________

Yuen On Ying

August, 2015
Abstract

Abstract of thesis entitled “Transition Metal-Catalyzed Oxidative C-H Bond Functionalization Reactions”

Submitted by On-Ying YUEN
for the Degree of Doctor of Philosophy
at The Hong Kong Polytechnic University
in August 2015

Transition metal-catalyzed C-H bond functionalization for the construction of carbon-carbon and carbon-heteroatom bonds that has numerous applications in pharmaceutical, material, and agricultural chemistry has received much attention in the past decade. It is more straightforward and attractive alternative to traditional cross-coupling reactions with organometallic reagents because of better atom economy, environmental friendliness and more streamlined chemical synthesis. Although significant advances to this field have been reported during the past decade, several challenges remain such as difficulty in activation of inert C-H bond and control of site selectivity. This thesis is to explore transition metal-catalyzed cross-coupling reactions through C-H bond functionalization.

In the first half of this dissertation, four studies on palladium-catalyzed functionalization of C-H bonds are explored. Three studies are concerning oxidative reactions between two nucleophiles while another study is regarding traditional protocol utilizing electrophiles and nucleophiles. Firstly, a palladium-catalyzed oxidative Mizoroki-Heck reaction of arylsulfonyl hydrazides with alkenes is developed under atmospheric air as the sole oxidant in an open manner. Using
Pd(OAc)$_2$ (OAc= acetate) and inexpensive, air-stable and moisture-stable phenyl isonicotinate (Chapter 2, L9) as a catalytic system, the efficiency of the reaction can be significantly enhanced. A wide range of arylsulfonyl hydrazides undergo oxidative Mizoroki-Heck reaction with alkenes smoothly. Good to excellent product yields and excellent regio- and steroselectivity are achieved. Functional groups such as halo and ester are well tolerated under this optimized reaction condition. Importantly, this reaction is conducted under atmospheric air in open manner that can reduce heavy metal wastes and lessen the complication of setting reactions’ procedures. Secondly, a direct oxidative C-2-arylation of benzoazoles using arylsulfonyl hydrazides as the aryl sources is described. A simple catalyst system comprising of Pd(OAc)$_2$ and PPh$_3$ allows the reactions to proceed smoothly under oxidative reaction conditions. A broad range of arylsulfonyl hydrazides is coupled successfully. Other heteroarenes such as caffeine and benzothiazole are also applicable substrates. Notably, this catalytic system tolerates halogen substituents that offer complement to current cross-coupling reactions which use aryl halides. Thirdly, a general and simple method of copper-mediated direct and regioselective oxidative C3-cyanation of 2,3-unsubstituted indoles using benzyl cyanide as the cyanide anion source is developed. A wide range of indoles undergo cyanation smoothly by employing an inexpensive reaction system of copper(I) iodide under open-to-air vessels. Lastly, the first general examples of direct coupling of heteroaryl chlorides, especially substituted 2-pyridyl chlorides as electrophile in which they were previously found to be problematic, with electron deficient polyfluoroarenes as nucleophiles are reported. Pd(OAc)$_2$ associated with PCy$_2$-Phendolephos (Chapter 5, L1) serves as the effective catalyst which allows the challenging direct coupling of heteroaryl chlorides and polyfluoroarenes to be succeeded. In addition to heterocycles, a wide range of non-activated and activated aryl chlorides and alkenyl chloride are
also applicable under this catalyst system. A variety of functional groups such as aldehyde, keto, ester, nitile and amide is well tolerated. The catalyst loading down to 1 mol% Pd can be achieved.

In the second half of dissertation, two studies with regard to traditional cross-coupling reactions of aryl chlorides with organometallic reagents are carried out. Firstly, palladium-catalyzed Hiyama cross-coupling reaction of aryl and heteroaryl chlorides with aryl and heteroaryltrialkoxysilanes under solvent-free reaction condition is presented. The catalyst system comprising of Pd(OAc)$_2$ and PCy$_2$-Andolephos (Chapter 6, L2) is a highly effective for this coupling reaction with low catalyst loading (down to 0.05 mol% Pd) and short reaction time (3 h). A broad substrate scope containing electron-rich, -neutral, and -deficient and sterically hindered aryl chlorides is achieved. Notably, the first general examples of Hiyama cross-coupling reaction using heteroaryltrialkoxysilanes are demonstrated. The presence of acetic acid or water suppresses the decomposition of aryl chlorides and promotes the product yields. A large scale experiment without degasification and purification of reactants is also conducted smoothly. Last but not least, a general palladium-catalyzed borylation of aryl chlorides with pinacol borane is reported. A newly modified indolylphosphine ligand (Chapter 7, L18) is prepared via an efficient protocol involving Fischer indolization from readily available phenylhydrazine and 2’-hydroxyacetophenone. The combination of Pd(dba)$_2$ and newly modified indolylphosphine ligand (Chapter 7, L18) are shown to be an effective catalyst for the borylation of non-activated and activated aryl chlorides with pinacol borane. Addition of tetra-$n$-butylammoniumiodide (TBAI) is highly effective for coupling of aryl chlorides bearing function groups such as keto, nitile and ester. 1 mol% Pd catalyst loading can be achieved using this catalytic system.
Publications


13. Yuen, O. Y.; So, C. M.; Kwong, F. Y. Palladium-Catalyzed Direct Arylation of Isophorones with Aryl Chlorides, to be submitted to *Chem. Commun.* *manuscript in
preparation.
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<table>
<thead>
<tr>
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<th>Description</th>
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<tbody>
<tr>
<td>δ</td>
<td>Chemical shift (NMR)</td>
</tr>
<tr>
<td>m/z</td>
<td>Mass-to-charge ratio</td>
</tr>
<tr>
<td>s</td>
<td>Singlet</td>
</tr>
<tr>
<td>d</td>
<td>Doublet</td>
</tr>
<tr>
<td>t</td>
<td>Triplet</td>
</tr>
<tr>
<td>q</td>
<td>Quartet</td>
</tr>
<tr>
<td>m</td>
<td>Multiplet</td>
</tr>
<tr>
<td>GC</td>
<td>Gas chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>High resolution mass spectroscopy</td>
</tr>
<tr>
<td>MS</td>
<td>Mass spectrometry</td>
</tr>
<tr>
<td>IR</td>
<td>Infra-red</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>equiv.</td>
<td>Equivalent</td>
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<td>Hour</td>
</tr>
<tr>
<td>min</td>
<td>minute</td>
</tr>
<tr>
<td>rt</td>
<td>Room temperature</td>
</tr>
<tr>
<td>L</td>
<td>Generalized ligand</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>MeOH</td>
<td>Methanol</td>
</tr>
<tr>
<td>EtOH</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Et₂O</td>
<td>Diethyl ether</td>
</tr>
<tr>
<td>EA</td>
<td>Ethyl acetate</td>
</tr>
<tr>
<td>DMF</td>
<td>N, N-dimethyl formamide</td>
</tr>
<tr>
<td>DCM</td>
<td>Dichloromethane</td>
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</table>
DME 1,2-Dimethoxyethane
$t\text{-BuOH}$ tert-Butanol
$t\text{-AmOH}$ tert-Amyl alcohol
ClPPh$_2$ Chlorodiphenylphosphine
ClPCy$_2$ Chlorodicyclohexylphosphine
dba dibenzylideneacetone
$n\text{-BuLi}$ $n$-Butyllithium
R Generalized alkyl group
Me Methyl
Et Ethyl
$n\text{-Bu}$ $n$-butyl
$i\text{-Pr}$ iso-propyl
$t\text{-Bu}$ tert-butyl
Ar Aryl
Ph Phenyl
Bn Benzyl
Cy Cyclohexyl
Ac Acetyl
Ad Adamantyl
Tol Toluene
OTf Trifluoromethanesulfonate
OTs $p$-Toluenesulfonate
OMs Methanesulfonate
NHC $N$-Heterocyclic Carbene
Chapter 1 Introduction

1.1 Introduction to transition metal-catalyzed C-H functionalization

1.1.1 Background and challenges of C-H functionalization

Functionalizing traditionally inert C-H bonds represents a powerful tool in organic synthesis. C-H bonds embedded in complex molecules are transformed into a wide range of other functional groups such as C-O, C-S, C-X, C-N and C-C bonds which have widespread applications in the synthesis of pharmaceuticals, natural products, polymers and agrochemicals.¹

Although transition metal-catalyzed cross-coupling reactions between organic (pseudo) halides and stoichiometric amounts of organometallic reagents are widely studied for the construction of C-C bonds and C-X bonds, direct C-H bonds functionalization reactions are more attractive. The organometallic reagents are often not readily available or are relatively high cost. They usually prepared from the corresponding arenes through a series of synthetic operations. Undesired byproducts are generated in the course of the preparation of organometallic reagents. Therefore, direct reactions through cleavage of C-H bonds represent an environmentally and economically more attractive protocols which can minimize the formation of side products and allow for streamlining organic synthesis.²

Direct C-H bond functionalization reactions still remain two major challenges: (1) the inert nature of most C-H bonds that have the inherently high bond dissociation energies and (2) the control of site selectivity in complex molecules that contain diverse C-H groups.¹³ The harsh reaction conditions such as very high temperature and the presence of strong oxidants and acidic or basic additives are frequently necessitated for functionalizing C-H bonds. Poor compatibility with most functional groups would be exhibited.⁴
Different approaches have been introduced over the past decade in order to address the main challenges in direct C-H functionalization reactions: (1) substrate-based control over selectivity through the use of directing groups, (2) substrate control through the use of electronically activated substrates and (3) catalyst-based control. For approach 1, functionalizations tend to occur at the C-H bonds ortho to a directing group. For instance, a strongly coordinating nitrogen-containing directing group is typically required to promote facile cyclometallation. For approach 2, the substrates have a significant electronic or steric bias for metalation at a specific site. Electron rich heterocycles are common targets for this approach. For approach 3, metal complexes are specifically applied in direct C-H bond functionalization and they can be tailor-made through the unique ligand design. The site selectivity can be tuned by modifying the structure of the supporting ligands on the metal catalyst.5

In this thesis, our aim was to develop the transition metal-catalyzed mild, regio-, and chemoselective method to functionalize C-H bonds and the corresponding products are essential building blocks in natural products, bioactive molecules, functional materials and pharmaceuticals.

1.2 Oxidative cross-coupling reactions

1.2.1 Palladium-catalyzed oxidative Mizoroki-Heck Reactions

Mizoroki-Heck reaction is one of the powerful protocols to form carbon-carbon bonds. The vinylic C-H bonds in terminal alkenes is directly transformed to synthesize 1,2-disubstituted alkenes in high steroselectivity. Stereodefined alkenes are commonly structural motifs in many biologically relevant molecules, for example, chalcone derivatives have biological activities (antiparasitic, antibacterial, anticancer)
and diketo acids and their amino acid/dipeptidic analogues are for the development of bacterial methionine aminopeptidase inhibitors (Figure 1.1).\(^6\)

![Figure 1.1 Examples of biological molecules containing alkene motifs](image)

Since Mizoroki\(^7\) and Heck\(^8\) discovered the first palladium-catalyzed arylation or vinylation of alkenes with organic halides, numerous modifications of the Mizoroki-Heck reaction have been carried out. For the traditional Mizoroki-Heck reaction, different types of aryl sources including aryl halides,\(^9\) aryl sulfonates,\(^10\) aryl diazonium salts\(^{11}\) and arylsulfonyl chlorides\(^{12}\) are utilized. For oxidative Mizoroki-Heck reaction,\(^{13}\) the scope of aryl sources has been significantly expanded to aromatics,\(^{14}\) arylcarboxylic acids,\(^{15}\) arylboronic acids or esters,\(^{16}\) arylphosphonic acids,\(^{17}\) aryl sulfinic acids or their sodium salts,\(^{18}\) aryl hydrazines,\(^{19}\) arylsulfonyl hydrazides,\(^{20}\) aroyl hydrazides\(^{21}\) and carbazates.\(^{22}\)

1.2.1.1 Development of palladium-catalyzed oxidative Mizoroki-Heck Reactions through cleavage of carbon-nitrogen and/or carbon-sulfur bonds

The cross-coupling reactions through cleavage of the unreactive carbon-nitrogen and/or carbon-sulfur bonds are rarely reported among oxidative Mizoroki-Heck reactions.
In 2011, Deng and coworkers reported palladium-catalyzed desulfitative Heck-type reaction of aryl sulfinic acid sodium salts with alkenes using oxygen as the oxidant (Scheme 1.1). The reaction conditions were milder than those using aryl carboxylic acids as cross-coupling partners. The loss of SO$_2$ occurred at 85 °C which was much lower than the loss of CO$_2$. They found that in the combination of PdCl$_2$ and DPEphos as a catalyst system in anisole, a variety of aryl sulfinic acid sodium salts with alkenes gave the desired products in high yield and selectivity.

Scheme 1.1 Palladium-catalyzed Heck reaction of aryl sulfinic acid sodium salts with alkenes

Later on, Miao and coworkers have developed an efficient protocol for palladium-catalyzed desulfitative Heck-type reaction of aryl sulfinic acids with alkenes (Scheme 1.2). In the presence of the catalytic amount of Pd(OAc)$_2$ and Cu(OAc)$_2$·H$_2$O as oxidant, a wide range of aryl sulfinic acids coupled with alkenes afforded good to excellent product yields.

Scheme 1.2 Palladium-catalyzed Heck reaction of aryl sulfinic acids
After that, Loh and coworkers demonstrated palladium-catalyzed Heck reaction of arylhydrazines with alkenes through the cleavage of carbon-nitrogen bond (Scheme 1.3).\textsuperscript{19} In the presence of Pd(OAc)$_2$ and bipyridine ligand L1, various arylhydrazines reacted with olefins under very mild reaction conditions.

![Scheme 1.3 Palladium-catalyzed Heck reaction of arylhydrazines](image)

It is difficult to occur for the cleavage of unreactive carbon-nitrogen and carbon-sulfur bonds at the same time. In 2012, Tian and coworkers have developed an unprecedented oxidative Heck reaction of arylsulfonyl hydrazides (Scheme 1.4).\textsuperscript{20} In the presence of Pd(OAc)$_2$ and oxygen, a broad range of arylsulfonyl hydrazides underwent oxidative Heck reaction smoothly and afforded desired products in good to excellent yields and with excellent regio- and steroselectivity.

![Scheme 1.4 Palladium-catalyzed Heck reaction of arylsulfonyl hydrazides](image)

In 2013, they reported palladium-catalyzed oxidative alkoxy carbonylation of alkenes with carbazates (Scheme 1.5).\textsuperscript{21} A wide range of alkenes coupled with carbazates smoothly under oxygen atmosphere to generate derivatives of
α,β-unsaturated esters in moderate to good yields with excellent regio- and steroselectivity.

\[ \text{Scheme 1.5 Palladium-catalyzed alkoxy carbonylation of alkenes with carbazates} \]

Afterwards, they have developed palladium and copper-catalyzed oxidative Heck reaction of aroyl hydrazides with alkenes (Scheme 1.6).\(^2\) 1,2-disubstituted alkenes were prepared from aroyl hydrazides open to air in a 1:1 mixture of dimethyl sulfoxide and acetonitrile. They found that oxygen in air and dimethyl sulfoxide were terminal oxidants.

\[ \text{Scheme 1.6 Palladium and copper-catalyzed oxidative Heck reaction of aroyl hydrazides} \]

1.2.2 Palladium-catalyzed oxidative direct arylation of heteroarenes

Aryl and heteroaryl compounds are ubiquitous in natural products, bioactive molecules, functional materials and pharmaceuticals.\(^3\) Due to some intrinsic limitations of organometallic reagents, direct C-H functionalization of heteroarenes is another attractive alternative. This cross-coupling protocol has better atom economy, environmental friendliness and more streamlined chemical synthesis.\(^4,5\) In the past decades, great achievements were achieved in transition metal-catalyzed direct C-H
arylation of heteroarenes with aryl halides for construction of aryl and heteroaryl motifs. Apart from aryl halides,\textsuperscript{26} the scope has been extended to other arylating agents such as arylsulfonates,\textsuperscript{27} aryl silanes,\textsuperscript{28} aryl carboxylic acids,\textsuperscript{29} aryl sodium sulfonates,\textsuperscript{30} and aryl sulfonyl hydrazides.\textsuperscript{31}

1.2.2.1 Development of palladium-catalyzed oxidative direct arylation of heteroarenes through cleavage of carbon-nitrogen and/or carbon-sulfur bonds

In 2011, You and co-workers reported palladium-catalyzed desulfitative C-H arylation of heteroarenes with sodium sulfonates for the first time (Scheme 1.7).\textsuperscript{30a} A wide range of $N$-heteroarenes such as xanthines and azoles was found to be good cross-coupling partners for building aryl-heteroaryl compounds.

\begin{center}
\textbf{Scheme 1.7} Palladium-catalyzed direct C-H arylation of caffeine with aryl sulfinic acid sodium salt
\end{center}

Deng and Wang demonstrated the same reaction using similar reaction conditions individually (Scheme 1.8).\textsuperscript{30b, 30c} A series of aryl-substituted azoles have been synthesized in moderate to good yields.
Later on, You and Wan performed palladium-catalyzed direct C-H arylation of N-heteroarenes with aryl sulfonyl hydrazides individually. You and coworkers carried out the reaction utilizing the combination of Pd(OAc)$_2$ and PPh$_3$ as a catalyst system and Cu(OAc)$_2$ as an oxidant.$^{31a}$ This protocol offers convenient means for constructing aryl-heteroaryl motifs in good to excellent product yields (Scheme 1.9).

Wan and coworkers employed different catalyst system and reaction condition for this reaction (Scheme 1.10.$^{31b}$) A broad range of azoles and arylsulfonyl hydrazides has been coupled to product arylated azoles in high yields.
Scheme 1.10 Palladium-catalyzed direct C-H arylation of azoles with aryl sulfonyl hydrazides

1.2.3 Transition metal-catalyzed cyanation of indole derivatives

Indoles are common structural motifs that are frequently found in natural products, biologically active molecules and pharmaceutical compounds. 32 3-cyanoindoles are important precursors of antiviral, antibacterial and cytotoxic natural products. 33 In addition, the nitrile moiety can further transform to a wide range of function groups such as amines, aldehydes, acids, ketones, amides and heterocycles. 34 Palladium- and copper-catalyzed cyanation of aryl halides and sulfonates are common protocols to produce aryl nitriles. 35 However, there are few reports regarding cyanation of 3-iodoindole and 3-bromoindole and no reports concerning 3-chloroindole and 3-sulfonylindole. The reaction conditions of cyanation of 3-iodoindole and 3-bromoindole were harsh and the product yields were unsatisfied. 36 Organic transformations from modified Madelung reaction 37 and metal-free oxidative synthesis from N-aryl enamines 38 are alternative approaches to afford 3-cyanoindoles (Scheme 1.11A). Direct C-H functionalization of indole derivatives are attractive protocols to produce 3-cyanoindoles. 39 Lewis acid, Fe, Cu and Pd salts are usually employed as the catalyst for accessing 3-cyanoindole using different cyanide sources (Scheme 1.11B).
1.2.3.1 Development of transition metal-catalyzed cyanation of indole derivatives using organic cyanide sources

Metal cyanide sources have several drawbacks: (1) the metal cyanides employed are generally toxic and careful handling is required to prevent the generation of hazardous HCN gas. (2) environmental issue is raised because metal waste is generated in stoichiometric amounts. (3) a careful control of the cyanide concentration is often required to maintain the catalyst activity. Although $K_d[\text{Fe(CN)}_6]$ is exceptionally non-toxic, its low solubility in organic solvent limited its applicability.
As a result, organic cyanide sources for direct C-3 cyanation of indole derivatives are highly recommended.

In 2011, Jiao and co-worker reported palladium-catalyzed cyanation of indoles employing DMF for direct transformation to CN source (Scheme 1.12). Isotopic labeling experiments indicated that both the nitrogen and the carbon incorporated into the cyano group are derivated from DMF. Apart from indoles, the scope could be extended to benzofuran.

Scheme 1.12 Palladium-catalyzed cyanation of indole employing DMF

Later on, Cheng and coworkers demonstrated palladium-catalyzed cyanation of indoles using the combination of NH$_4$HCO$_3$ and DMSO as a CN source (Scheme 1.13). 3-cyanoindole derivatives were obtained in moderate to good yields with excellent regioselectivity.
Scheme 1.13 Palladium-catalyzed cyanation of indole using \( \text{NH}_4\text{HCO}_3 \) and DMSO

Lewis acid-catalyzed cyanation of indoles with \( N\text{-cyano-N-phenyl-p-toluenesulfonamide (NCTS) was reported by Wang and coworkers (Scheme 1.14).}^{39h} \) The reaction was broad in scope with respect to indoles and pyrroles.

Scheme 1.14 \( \text{BF}_3\cdot\text{OEt}_2 \)-catalyzed cyanation of indoles using NCTS

Copper-mediated cyanation of indoles using ammonium iodide and DMF as a combined CN source was developed by Chang and coworkers (Scheme 1.15).\(^{39i} \) The reaction proceeded through two sequential steps: initial iodination followed by cyanation. The substrate scope was broad and functional groups were well tolerated.
Xu and Zhu reported palladium-catalyzed cyanation of indoles using \( t \)-butyl isocyanide as a CN source individually (Scheme 1.16).\textsuperscript{39k, 39l} Zhu and coworkers found that a key electrophilic imidoyl palladium(II) intermediate is followed by the C-N bond breakage to give cyanated product and a tertiary carbon cation-based fragment.

\[ \text{Scheme 1.16 Palladium-catalyzed cyanation of indoles with } \text{\textit{t}} \text{-butyl isocyanide} \]

In 2013, Wang and coworkers demonstrated copper-mediated cyanation of indoles with benzyl cyanide using copper iodide as a metal source (Scheme 1.17).\textsuperscript{39m}
The reaction involved a copper-catalyzed aerobic C-H oxidation, a C-CN bond cleavage and a copper-catalyzed aerobic oxidative C-H functionalization of indoles without directing groups.

Scheme 1.17 Copper-mediated cyanation of indoles using benzyl cyanide

In 2014, Cheng and coworkers demonstrated copper-mediated cyanation of indoles employing $N, N', N'$-tetramethyl-ethane-1,2-diamine and ($NH_4)_2CO_3$ as a combined CN source (Scheme 1.18). $N, N', N'$-tetramethyl-ethane-1,2-diamine generated the iminium ion as the intermediate under oxidative condition. The iminium is sequentially electrophilically attacked by indole and water followed by hydrolyzation to form the aldehyde. The reaction between the aldehyde and ammonium afforded 3-cyanoindoles in good to excellent yield.

Scheme 1.18 Copper-mediated cyanation of indoles using amine and ammonium
Tsuchimoto and coworkers reported zinc-catalyzed cyanation of indoles using nitromethane as a CN source (Scheme 1.19).\textsuperscript{39q} Zn(OTf)$_2$ acted as lewis acid which promoted the reaction efficiently.

\begin{center}
\begin{tikzpicture}
\node at (0,0) [rectangle,draw] {
\textbf{Scheme 1.19} Zinc-catalyzed cyanation of indoles with nitromethane
};
\end{tikzpicture}
\end{center}

1.3 Traditional cross-coupling reactions

1.3.1 Transition metal-catalyzed direct arylation of polyfluoroarenes

Polyfluorobiaryl motifs are commonly found in pharmaceutical and material molecules.\textsuperscript{41} Fluorine introduced into small molecules has historis merits in drug discovery such as increasing their binding affinity and selectivity to the target proteins,\textsuperscript{42} fine tuning lipophilicity\textsuperscript{43} and averting metabolism.\textsuperscript{44} In material chemistry, polyfluorobiaryl compounds have applications as high mobility $n$-type semiconductors, liquid crystals and optoelectronics.\textsuperscript{45} Most importantly, the fluorinated compounds play an important role as active materials in electronic devices, such as organic light-emitting diodes and field-effect transistors. The polyfluorinated aryl group can enhance the photoluminescence efficiency, minimize the self-quenching behavior and lower the HOMO and LUMO energy levels.\textsuperscript{45}

Traditional cross-coupling reactions such as Suzuki,\textsuperscript{46} Hiyama,\textsuperscript{47} Negishi\textsuperscript{48} and Kumada\textsuperscript{49} are successful tools for synthesizing biaryl compounds. However, they suffer from some drawbacks. For example, highly electron-deficient nucleophiles (C$_6$F$_5$B(OH)$_2$) have the difficulty in preparation. The application of electron-poor
nucleophilic cross-coupling partners remains problematic due to the transmetallation step may proceed with difficulty. Therefore, the direct arylation of electron-deficient polyfluoroarenes has emerged. These protocols are attractive when compared with conventional coupling methods due to high atom economy and reduction of the metal wastes.

1.3.1.1 Development of direct arylation of polyfluoroarenes with aryl chlorides

In 2006, Fagnou and coworkers reported the first direct arylation of polyfluoroarenes with aryl halides. In the combination of Pd(OAc)$_2$ and Pr-Bu$_3$Me-HBF$_4$ as a catalytic system, a wide range of aryl bromides coupled with polyfluoroarenes in good to excellent yields. However, only one example of aryl chloride was demonstrated and the corresponding product was obtained in moderate yield. Aryl chlorides are generally more desirable than aryl iodides and bromides because of relatively low cost and broad availability.

Later on, they developed mild and general conditions for direct arylation of polyfluoroarenes with sterically hindered aryl bromides and aryl chlorides (Scheme 1.20). The reaction performed at 80 °C in isopropyl acetate with a catalyst system including Pd(OAc)$_2$ and Sphos. A wide range of aryl and heteroaryl halides were feasible cross-coupling partners under 5 mol% Pd catalyst loading.

Scheme 1.20 Palladium-catalyzed direct arylation of pentafluorobenzene with sterically hindered aryl chloride
In 2008, they demonstrated copper-catalyzed direct arylation of \( \text{sp}^2 \) C-H bonds with pKa value below 35 such as azoles, caffeine, thiophenes, benzofuran, pyridine oxides, pyrazidine, pyrimidine, and polyfluorobenzenes with aryl halides.\(^5^4\) However, there are only two examples of aryl chlorides coupled with pentafluorobenzenes (Scheme 1.21).

![Scheme 1.21](image)

**Scheme 1.21** Copper-catalyzed direct arylation of pentafluorobenzenes with heteroaryl chlorides

Notable findings showed a great achievement in direct arylation of polyfluorobenzenes with aryl iodides, bromides and sulfonates.\(^5^5\) However, using aryl chlorides as electrophiles were still keep silent until 2014. Liu and coworkers reported direct arylation of polyfluoroarenes with aryl bromides and chlorides in the combination of Pd(OAc)\(_2\) and PCy\(_3\) as a catalyst system (Scheme 1.22).\(^5^6\) However, 10 mol\% Pd catalyst loading was necessitated.

![Scheme 1.22](image)

**Scheme 1.22** Palladium-catalyzed direct arylation of polyfluoroarenes with aryl
chlorides

A \( t\)-Bu\(_3\)P-coordinated 2-phenylaniline-based palladacycle complex (Pd1) was found to be effective precatalyst for direct arylation of polyfluoroarenes with aryl bromides and chlorides (Scheme 1.23).\(^{57}\) Good to excellent product yields were obtained, yet high catalyst loading (10 mol\% Pd) was required for aryl chlorides.

![Scheme 1.23 Palladium-catalyzed direct arylation of polyfluoroarenes with aryl chlorides](image)

Cazin and coworkers employed a dual metal system involving [Cu(Cl)(NHC)] and [Pd(Cl)(cin)(NHC)] which was effective for the direct arylation of polyfluoroarenes (Scheme 1.24).\(^{58}\) However, the substrate scope only limited to non-activated aryl chlorides without any functional groups.

![Scheme 1.24 Direct C-H arylation of polyfluorobenzenes using Pd-Cu system](image)
1.3.2 Palladium-catalyzed Hiyama cross-coupling reactions

Palladium-catalyzed cross-coupling reactions constitute an extremely versatile protocol in organic synthesis for the connection of two different fragments via the formation of either carbon-carbon and/or carbon-heteroatom bonds.\(^{59}\) Hiyama,\(^{47}\) Kumada,\(^{49}\) Stille\(^{60}\) and Suzuki\(^{46}\) reactions are common methods for the construction of diversified biaryl motifs, which are important in pharmaceutical, material and agricultural applications.\(^{23}\) Hiyama cross-coupling reaction is one of the potentially most attractive methods because organosilanes are commercially available, low cost, non-toxic, stable and can be easily prepared. However, it constitutes a challenge due to unreactive C-Si bond which has a difficulty in the transmetallation step.

1.3.2.1 Development of palladium-catalyzed Hiyama cross-coupling reaction of aryl chlorides

Although Hiyama cross-coupling reactions are widely studied in the recent years, aryl iodides and bromides as the coupling partners of organosilanes are mainly utilized.\(^{61}\) Aryl chlorides are highly desirable as they are relatively low cost and readily available.

In 1999, DeShong and coworkers reported the first example of Hiyama cross-coupling of aryl chlorides witharyltrimethoxysilanes (Scheme 1.25).\(^{62}\) However, only three examples in moderate product yields were demonstrated even through 10 mol% Pd$_2$dba$_3$ and Cy-Johnphos were used.
Scheme 1.25 The first palladium-catalyzed Hiyama cross-coupling reaction of aryl chlorides

After that, noticeable findings regarding Hiyama cross-coupling reaction of aryl chlorides and aryltrimethoxysilanes were reported. The catalyst systems such as Pd(OAc)$_2$/imidazolium chloride (L2),$^{63}$ palladium-phosphinous acid (POpd1),$^{64}$ Pd(OAc)$_2$/DABCO,$^{65}$ palladium-$\beta$-diimine complex (Pd2),$^{66}$ oxime-derived palladacycles (Pd3 and Pd4),$^{67}$ PdCl$_2$(MeCN)$_2$/P(o-Toly)$_3$,$^{68}$ Pd(acac)$_2$/phosphite (L3),$^{69}$ Pd(dba)$_2$/i-Pr-DPEphos,$^{70}$ Pd(dba)$_2$/H-phosphonate (L4),$^{71}$ PdCl$_2$,$^{72}$ Pd(OAc)$_2$/cyclic thiourea (L5),$^{73}$ palladium on carbon with or without phosphine ligands,$^{74}$ PdCl$_2$/N-methyliminodiacetic acid ligand (L6),$^{75}$ and functionalized SBA-15-supported Pd nanoparticles$^{76}$ were effective for Hiyama cross-coupling reaction of aryl halides (Figure 1.2). However, they suffered from several drawbacks. For example, high catalyst loadings (3-7 mol% Pd) were necessitated. The substrate scopes were narrow. Only activated aryl chlorides were found to be feasible cross-coupling partners. Cross-coupling reaction of aryl chlorides with aryltrimethoxysilanes kept silent until 2011.
In 2011, Verkade and coworkers demonstrated Hiyama cross-coupling reaction of aryl bromides and chlorides employing Pd(OAc)$_2$ and $t$-Bu$_2$P-N=P($t$-BuNCH$_2$CH$_2$)$_2$N (L7) as a catalyst system (Scheme 1.26). Electron-rich, -neutral and -deficient aryl chlorides and heteroaryl chlorides were compatible under their reaction condition. The catalyst loading was ranged from 0.5 mol% to 1 mol% Pd and the reaction was completed within 3 h.
Scheme 1.26 Hiyama cross-coupling reaction of aryl chlorides

Jin and coworkers found that the β-diketiminatophosphane Pd complex was an effective catalyst for Hiyama cross-coupling reaction of a wide range of aryl chlorides and aryltriethoxysilanes in water. Tri-ortho-substituted biary synthesis was achieved successfully (Scheme 1.27). The efficient one-pot double Hiyama cross-coupling reaction of aryl dichlorides was realized for the first time.

Scheme 1.27 Tri-ortho-substituted biaryl synthesis through Hiyama cross-coupling reaction

In 2012, Wang and coworkers reported Hiyama cross-coupling reaction of aryltrialkoxysilanes with aryl chlorides using N-heterocyclic carbene (NHC)-palladium complexes (Scheme 1.28). A wide range of aryl and heteroaryl chlorides was coupled with phenyltrialkoxysilanes successfully under 0.5 mol% Pd catalyst loading.
Scheme 1.28 Hiyama cross-coupling reaction of aryl chlorides using dinuclear NHC-palladium complex

Later on, Lu and coworkers proved that NHC-Pd(II)-Im complex was an efficient catalyst for the Hiyama cross-coupling of a variety of aryl chlorides with aryltrimethoxysilanes (Scheme 1.29). The reaction performed smoothly and gave the corresponding coupling products in moderate to high yield under 1 mol% Pd catalyst loading. However, the reaction of electron-rich aryl chlorides was still a problem.

Scheme 1.29 NHC-Pd(II)-Im complex catalyzed Hiyama cross-coupling reaction
1.3.3 Palladium-catalyzed borylation of aryl halides

Aryl boronic acids, boronate esters and potassium trifluoroborate salts are versatile chemical building blocks and intermediates in organic synthesis. They are important nucleophilic partners in the preparation of diversified biaryl compounds through Suzuki-Miyaura cross-coupling reactions.\(^8^1\) They are usually prepared through the metal-halogen exchange (e.g. Mg or Li) from aryl bromides or iodides and subsequent trapping with trialkylborates. However, this conventional protocol is not compatible with relatively cheaper and commercially available aryl chlorides and aryl halides bearing base-sensitive functional groups (e.g. aldehyde, ketone, nitrile etc.). The additional protection and deprotection steps are required.\(^8^1b\) As a result, transition metal-catalyzed borylation of aryl halides with alkoxyboranes has emerged.

1.3.3.1 Development of palladium-catalyzed borylation of aryl halides with pinacol borane

In 1995, Miyaura and co-workers pioneered a palladium-catalyzed borylation of aryl halides with bis(pinacolato)diboron.\(^8^2\) Since then, considerable attentions have been focused on palladium-catalyzed borylation of aryl bromides and iodosides to construct the corresponding aryl boronate esters.\(^8^3\) Apart from tetraalkoxydiboranes, dialkoxyboranes are more attractive, readily available, and more atom-economical than diboron reagents. In 1997 and 2000, Masuda found that dialkoxyhydroboranes could serve as effective boron sources for coupling with aryl halides and triflates (Scheme 1.30).\(^8^4\) Aryl boronate esters bearing a variety of functional groups such as –COMe, -CN and -NO\(_2\) were readily prepared.
Baudoin and coworkers demonstrated that a catalyst system combining Pd(OAc)$_2$ with Cy-JohnPhos was effective for the borylation of ortho-substituted aryl bromides and iodides (Scheme 1.31). $^{85}$ These findings were extended to unprecedented one-pot-two-steps reaction with ortho-substituted aryl iodides to synthesize sterically hindered 2,2'-biphenyls.

In 2001, Floch and co-workers illustrated borylation of aryl iodides with pinacol borane catalyzed by bis(diphosphaferrocenes)PdCl$_2$ dimers (Scheme 1.32a). $^{86}$ Non-activated aryl and heteroaryl iodides coupled with pinacol borane in excellent product yields. Subsequently, they designed a palladium(II) complex of a S-P-S pincer ligand which was applied in borylation of aryl iodides successfully (Scheme 1.32b). $^{87}$
Scheme 1.32 (a) Borylation of aryl iodides with pinacol borane utilizing bis(diphosphaferrrocene)PdCl$_2$ dimer. (b) Synthesis of arylboronate esters using a palladium(II) complex of a S-P-S pincer ligand.

In 2003, Christophersen and coworkers developed a protocol for the synthesis of 2-substituted 3-thienylboronic acids and esters as well as 3-substituted 2-thienylboronic acids.$^{88}$ A range of 2-substituted 3-bromothiophenes together with 3-substituted 2-bromothiophenes were borylated with pinacol borane by Pd$_2$dba$_3$ and P(t-Bu)$_3$ as a catalyst system under mild reaction condition. Borylation and subsequent Suzuki-Miyaura cross-coupling reaction were demonstrated to afford heteroaryl-aryl compounds without isolation of borate esters (Scheme 1.33).
Zaidlewicz and coworkers described palladium-catalyzed borylation of aryl bromides and iodides with pinacolborane in ionic liquids (Scheme 1.34). Their results showed that the reaction time was shorter compared with that using conventional solvents. The benefits of using ionic liquids include that the products could be directly obtained from the reaction mixtures in good purity by simple extraction and the solution of catalyst in ionic liquid could be recycled. 

In 2004, Colobert and coworkers described palladium-catalyzed borylation of non-activated and sterically hindered aryl bromides with pinacol boranes in the presence of a catalytic amount of Pd(OAc)$_2$ and DPEphos (Scheme 1.35). Compared with the phosphine ligands in the previous reports for synthesizing ortho-substituted aryl boronate esters, the advantage of DPEphos toward dppf is its cheaper availability and its higher air stability compared to Cy-JohnPhos. These findings were extended to one-pot-two-step Suzuki-Miyaura reaction with different
substituted aryl bromides to synthesize unsymmetrical biaryl compounds.

Scheme 1.35 Palladium-catalyzed borylation of aryl bromides using Pd(OAc)$_2$ and DPEphos catalyst system

In 2006, Murate and coworkers developed a general method for the borylation of aryl halides with pinacolborane using Pd(dba)$_2$ and $t$-Bu-DPEPhos as a catalytic system. Electron-rich and deficient aryl bromides were coupled with pinacol borane in good to excellent yields. Extremely sterically hindered aryl bromides also were feasible cross-coupling partners (Scheme 1.36). Particularly, borylation of electron-rich aryl chlorides was reported for the first time although only two examples were demonstrated successfully under 5 mol% Pd catalyst loadings.

Scheme 1.36 Palladium-catalyzed borylation of 2-bromo-1,3,5-triisopropylbenzene

Notably, Buchwald and coworkers found that a PdCl$_2$(CH$_3$CN)$_2$ and Sphos catalyst system was efficient for the borylation of aryl halides with pinacolborane (Scheme 1.37). The reaction of aryl iodides and bromides conducted with relative low Pd catalyst loadings and short reaction times. Moreover, this protocol represented
the first general method for the borylation of aryl and heteroaryl chlorides. However, this method was only applicable to non-activated aryl chlorides under 3 mol% Pd catalyst loadings.

Scheme 1.37 Palladium-catalyzed borylation of aryl halides using PdCl$_2$(CH$_3$CN)$_2$ and Sphos catalyst system

Chai and coworkers demonstrated an unprecedented synthesis of a range of high value homo and heterobiindolyls. The borylation of piancolborane and subsequent Suzuki-Miyaura reaction allowed for the construction of biindolyl compounds (Scheme 1.38).

Scheme 1.38 Synthesis of homo and heterobiindolyls through borylation and subsequent Suzuki-Miyaura reaction
The borylation of aryl chlorides bearing electron-withdrawing groups with pinacolborane is still a challenge. The product yields were low because of the formation of reduced arenes competing with products. In 2010, Murata and coworkers reported the first general palladium-catalyzed borylation of electron-deficient aryl chlorides with pinacolborane using Pd(dba)$_2$ and $t$-Bu-DPEphos as a catalyst system (Scheme 1.39). They found that addition of $n$-Bu$_4$I could improve the product yields of the corresponding electron-deficient aryl chlorides efficiently. The role of iodide ion may be attributed to the halide ligand exchange of the arylpalladium(II) chloride intermediate.

Scheme 1.39 Palladium-catalyzed borylation of electron-deficient aryl chlorides using tetrabutylammonium iodide
1.4 References

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Chapter 2 Palladium-Catalyzed Oxidative Mizoroki-Heck Reaction of Arylsulfonyl Hydrazides with Alkenes under air

2.1 Introduction

The palladium-catalyzed Mizoroki-Heck reaction is one of the most powerful tools for the formation C-C double bond in organic synthesis and plays an important role in both preparative laboratories and industrial applications. In traditional Heck reaction, aryl halides act as electrophiles and couple with alkenes in the presence of palladium catalysts and bases to produce higher substituted alkenes. Other than aryl halides, aryl sulfonates, aryl diazonium salts, arylsulfonyl halides, and arylcarboxylic acid derivatives are also effective aryl sources in the Mizoroki-Heck type reactions.

Oxidative Heck reaction is also an excellent pathway to access the substituted alkene products. The most striking difference between traditional Heck reaction and oxidative Heck reaction is the reaction mechanism. The former is that electrophiles act as self-oxidant carrying out oxidative addition to palladium(0) species to form arylpalladium(II) species. The latter is that extra oxidants such as oxygen or copper(II) salts are required to re-oxidize palladium(0) species to palladium(II) species. Aromatics, arylcarboxylic acids, aryloboronic acid derivatives, arylyphosphonic acids, arylsulfinic acids and its sodium salts, aroylhydrazines, carbazates and aroyl hydrazides are effectively couple with alkenes in the oxidative reactions (Scheme 2.1).

Arylsulfonyl hydrazides are recently a rising electrophile which are readily accessible solids, stable in air and moisture and can be easily prepared in one step from arylsulfonyl chlorides and hydrazine hydrates. Particular noteworthy is that they can serve as arylating agents, which are subjected to denitrogenation and
desulfitation to generate the aryl source for the oxidative palladium-catalyzed coupling reactions.\textsuperscript{19} Oxidative Heck reaction \textsuperscript{19a}, oxidative direct arylation of heteroarenes \textsuperscript{19b-d}, oxidative conjugate addition reaction \textsuperscript{19e}, oxidative homo-coupling reaction \textsuperscript{19f}, oxidative Suzuki reaction \textsuperscript{19g} and oxidative Hiyama reaction \textsuperscript{19h} are reported. However, most of these reactions require excess amount of Cu(OAc)$_2$ or pure oxygen to act as oxidant. The use of Cu(OAc)$_2$ would generate stoichiometric amount of heavy metal waste which is not environmentally benign and reduce the atom economy. Regardless of the use of pure oxygen which may associate with hazardous and dangerous handling (gas tube), the extra gas pressure generates from denitrogenation (N$_2$) and desulfitation (SO$_2$) of arylsulfonyl hydrazides under high temperature and the control of the composition of oxygen atmosphere may limit the utility of the technology for industrial applications. Therefore, if the atmospheric air can act as the re-oxidant allowing the open-air manner, the value of the transformation enhances significantly. However, in general, only inferior yield can be obtained in use of air as reaction atmosphere especially for the heck-type reactions.\textsuperscript{19a,e}

\begin{center}
\textbf{Scheme 2.1} Traditional Heck reaction of aryl halides and oxidative Heck reaction of other aryl sources with alkenes
\end{center}
2.2 Results and discussion

2.2.1 Preliminary evaluation of palladium-catalyzed oxidative Mizoroki-Heck reaction of arylsulfonyl hydrazides with alkenes

In order to test the feasibility of palladium-catalyzed oxidative Mizoroki-Heck reaction of arylsulfonyl hydrazides with alkenes, a series of initial screenings was conducted (Table 2.1). 4-methylbenzenesulfonyl hydrazide and styrene were used as the benchmark substrate. In the survey of common solvents, the solvent DMF gave the best result (Table 2.1, entry 2 and entries 1-11). The initial screening of palladium sources (Table 2.1, entries 12-18) indicated that Pd(OAc)$_2$ was the suitable Pd source for this coupling reaction.

Table 2.1 Initial screening of palladium-catalyzed oxidative Mizoroki-Heck reaction of arylsulfonyl hydrazides$^{[a]}$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Solvent</th>
<th>%Yield$^{[b]}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$ (10)</td>
<td>Dioxane</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$ (10)</td>
<td>DMF</td>
<td>55</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)$_2$ (10)</td>
<td>DMA</td>
<td>47</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)$_2$ (10)</td>
<td>NMP</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)$_2$ (10)</td>
<td>DMSO</td>
<td>14</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)$_2$ (10)</td>
<td>THF</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)$_2$ (10)</td>
<td>t-BuOH</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>Pd(OAc)$_2$ (10)</td>
<td>Toluene</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Reaction condition: 4-methylbenzenesulfonyl hydrazide (0.45 mmol), styrene (0.3 mmol), Pd source (10 mol%), solvent (3.0 mL) were stirred at 90 °C for 16 h under air.</td>
<td></td>
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<tr>
<td>---</td>
<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)$_2$ (10) MeCN 13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Pd(OAc)$_2$ (10) PhCN 26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Pd(OAc)$_2$ (10) AcOH 17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Pd$_2$(dba)$_3$ (10) DMF 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Pd(TFA)$_2$ (10) DMF 41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Pd(acac)$_2$ (10) DMF 23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>PdCl$_2$(CH$_3$CN)$_2$ (10) DMF 51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>PdCl$_2$(PPh$_3$)$_2$ (10) DMF 32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>PdCl$_2$(COD)$_2$ (10) DMF Trace</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>PdCl$_2$ (10) DMF 40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[a] Reaction condition: 4-methylbenzenesulfonyl hydrazide (0.45 mmol), styrene (0.3 mmol), Pd source (10 mol%), solvent (3.0 mL) were stirred at 90 °C for 16 h under air. [b] Calibrated GC yields were reported using dodecane as internal standard.

After the detailed screening of solvents and Pd sources, we still found that the product yield was unsatisfied. Inspired by the poor result of Pd(OAc)$_2$/DMSO system which is one of the well-known catalyst system for the palladium-catalyzed oxidative reactions and also analogy to the aerobic alcohol oxidation reaction and oxidative amination of olefins reaction, we suspect that the inferior yield may result from the slow aerobic oxidation of Pd(0) species to Pd(II) especially under air atmosphere which is low oxygen concentration. Pd(0) species easily aggregate and agglomerate to unreactive palladium black and retard the coupling reaction in the ligand-free heck reactions. Oxidatively stable ligands have been identified to enhance the rate of Pd(0) oxidation particularly with respect to competing Pd(0) aggregation so as to promote catalytic turnover, improve catalyst stability and increases regio- and stereoselectivity.
Uemura’s Pd(OAc)$_2$/pyridine catalyst system were found to be able to promote the oxidation of Pd(0) to Pd(II) in the aerobic alcohol oxidation reaction.$^{[20]}$ Herein, we adopt the Pd(OAc)$_2$/pyridine catalyst system for the oxidative Heck reaction of arylsulfonyl hydrazides with alkenes for the first time.

We found that when pyridine was added, the product yield improved dramatically from 55 % to 77 % (Table 2.2, L1). When the reaction temperature was lowered from 90 °C to 80 °C, the product yield was the same. Investigation of different substituted pyridine ligands L2-L11 indicated that phenyl isonicotinate gave the best yield of product (L9). Although the electronic inference of the pyridine-type ligands in this oxidative heck reaction is still unclear, sterically hindered pyridine type ligands (L10-L11) which hinder the facial coordination to Pd center show minor enhancing effect of the product yield imply the importance of the ligand coordination effect.
Table 2.2 Ligand screening for palladium-catalyzed oxidative Mizoroki-Heck reaction of arylsulfonyl hydrazides\textsuperscript{[a,b]}

\[
\begin{array}{cccc}
\text{SO}_2\text{NNHNH}_2 & \xrightarrow{10 \text{ mol}\% \text{ Pd(OAc)}_2} & \text{Ph} & \xrightarrow{20 \text{ mol}\% \text{ L}} \text{Me-Ph} \\
\text{Me} & \text{DMF} & 80 ^\circ\text{C}, 16 \text{ h} & \text{“under air”} \\
\end{array}
\]

\[
\begin{array}{cccc}
\text{L1 (77\%)} & \text{t-Bu} & \text{OMe} & \text{CF}_3 \\
\text{L2 (73\%)} & \text{OMe} & \text{OMe} & \text{CF}_3 \\
\text{L3 (73\%)} & \text{OMe} & \text{OMe} & \text{CF}_3 \\
\text{L4 (79\%)} & \text{OMe} & \text{OMe} & \text{CF}_3 \\
\text{L5 (69\%)} & \text{CN} & \text{O=OEt} & \text{CN} \\
\text{L6 (77\%)} & \text{CN} & \text{O=OEt} & \text{CN} \\
\text{L7 (76\%)} & \text{CN} & \text{O=OEt} & \text{CN} \\
\text{L8 (76\%)} & \text{CN} & \text{O=OEt} & \text{CN} \\
\text{L9 (87\%)} & \text{OMe} & \text{OMe} & \text{OMe} \\
\text{L10 (58\%)} & \text{OMe} & \text{OMe} & \text{OMe} \\
\text{L11 (58\%)} & \text{OMe} & \text{OMe} & \text{OMe} \\
\end{array}
\]

\text{[a]} \text{ Reaction conditions: 4-methylbenzenesulfonyl hydrazide (0.45 mmol), styrene (0.3 mmol), Pd(OAc)}_2 \text{ (10 mol\%), L (20 mol\%) and DMF(3.0 mL) were stirred at indicated temperature for 16 h under air. [b] Calibrated GC yields were reported using dodecane as internal standard. [c] The reaction was conducted at 90 ^\circ\text{C}.}
2.2.2 Scope of palladium-catalyzed oxidative Mizoroki-Heck reaction of arylsulfonyl hydrazides with alkenes

With the Pd(OAc)$_2$/ L9 system in hand, we next investigated the scope of Mizoroki-Heck reaction of arylsulfonyl hydrazides with alkenes. The results were summarized in Table 2.3. In the presence of 10 mol% Pd(OAc)$_2$, 20 mol% L9, a wide range of arylsulfonylhydrazides carried out oxidative Mizoroki-Heck reaction with styrene smoothly to give 1,2-disubstituted alkenes in moderate to excellent yields under air. Ortho-substituted arylsulfonyl hydrazides were good combinations for this reaction (Table 2.3, compound 3bk and 3gk). Electron rich arylsulfonyl hydrazide afforded moderate yield (Table 2.3, compound 3hk). The highly sterically hindered arylsulfonyl hydrazide could couple with styrene in moderate yield (Table 2.3, compound 3ik). Apart from styrene, a variety of substituted styrenes and acrylates was examined and provided good to excellent product yields. To our delight, the highly sterically hindered arylsulfonyl hydrazide coupled with butyl acrylate in good yield (Table 2.3, compound 3in). Both of electron-deficient and electron-rich substituents on styrenes were feasible cross-coupling partners that provided good to excellent product yields (Table 2.3, compound 3ao, 3ap, 3aq, 3as, 3at and 3au). The highly sterically crowded 2,4,6-trimethylstyrenes was proceeded with 4-chlorobenzenesulfonyl hydrazide smoothly (Table 2.3, compound 3fv). Notably, bromo and chloro groups were compatible under this optimized reaction condition, which are useful components for potential chemical transformations using coupling technology (Table 2.3, compound 3fk, 3aq, 3au and 3fv). A few of arylsulfonyl hydrazides and alkenes were applied in this optimized reaction condition but no desired products could be obtained (Scheme 2.2).
Table 2.3 Palladium-catalyzed oxidative Mizoroki-Heck reaction of arylsulfonylhydrazides and olefins \(^{[a]}\)

\[
\begin{align*}
\text{NH}_2\text{NH}_2 \\
\begin{array}{ccc}
\text{O=S=O} & + & \text{R}^2 \text{CH} \\
\text{R}^1 \text{C}_6 \text{H}_4 \\
\end{array} & \begin{array}{ccc}
1 & \rightarrow & 2 \\
& \text{DMF, 80 °C, 16 h} & \text{"under air"} \\
& 10 \text{ mol% Pd(OAc)}_2 & 20 \text{ mol% L9} \\
\end{array} & \begin{array}{ccc}
\text{O} & \text{O} & \text{Ph} \\
\text{R} & \text{R} & \text{L9} \\
\end{array}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>3ak</td>
<td></td>
<td>87%</td>
</tr>
<tr>
<td>3bk</td>
<td></td>
<td>90%</td>
</tr>
<tr>
<td>3ck</td>
<td></td>
<td>83%</td>
</tr>
<tr>
<td>3dk</td>
<td></td>
<td>84%</td>
</tr>
<tr>
<td>3ek</td>
<td></td>
<td>82%</td>
</tr>
<tr>
<td>3fk</td>
<td></td>
<td>81%</td>
</tr>
<tr>
<td>3gk</td>
<td></td>
<td>75%</td>
</tr>
<tr>
<td>3hk</td>
<td></td>
<td>59%</td>
</tr>
<tr>
<td>3ik</td>
<td></td>
<td>50%(^{[e]})</td>
</tr>
<tr>
<td>3jk</td>
<td></td>
<td>41%(^{[e]})</td>
</tr>
<tr>
<td>3al</td>
<td></td>
<td>64%(^{[e]})</td>
</tr>
<tr>
<td>3am</td>
<td></td>
<td>75%</td>
</tr>
<tr>
<td>3an</td>
<td></td>
<td>84%</td>
</tr>
<tr>
<td>3gn</td>
<td></td>
<td>95%</td>
</tr>
<tr>
<td>3cn</td>
<td></td>
<td>99%</td>
</tr>
<tr>
<td>3in</td>
<td></td>
<td>81%(^{[e]})</td>
</tr>
<tr>
<td>3ao</td>
<td></td>
<td>72%</td>
</tr>
<tr>
<td>3ap</td>
<td></td>
<td>77%</td>
</tr>
<tr>
<td>3aq</td>
<td></td>
<td>79%</td>
</tr>
<tr>
<td>3ar</td>
<td></td>
<td>83%</td>
</tr>
<tr>
<td>3as</td>
<td></td>
<td>68%</td>
</tr>
</tbody>
</table>
[a] Reaction condition: aryl sulfonylhydrazide (0.45 mmol), alkene (0.3 mmol), Pd(OAc)$_2$ (10 mol%), L9 (20 mol%) and DMF (3 mL) were stirred at 80 °C for 16 h under air. [b] Isolated yield. [c] The reaction was conducted at 70 °C. [d] The reaction was conducted at 100 °C. [e] Close system was used. [f] The reaction was conducted for 24 h.

**Scheme 2.2** Unsuccessful examples of arylsulfonyl hydrazides and alkenes in oxidative Mizoroki-Heck reaction (Reaction conditions were same as Table 2.3, compound 3ak)
A proposed catalytic cycle, as adapted from the mechanistic studies performed on the Pd-catalyzed coupling reactions of arylsulfonyl hydrazides and Pd(OAc)$_2$/pyridine oxidation reaction mechanism, is shown in Scheme 2.3. The coordination of the pyridine ligand to Pd(OAc)$_2$ generate complex I which is converted to complex II and HOAc by deprotonation with arylsulfonyl hydrazide. Complex II undergoes β-hydride elimination to give complex III and sulfonyl diazene. Displacement of complex I with sulfonyl diazene gives complex IV. Liberation of N$_2$ with complex IV generates the complex V which is then successive extrusion of SO$_2$ to form complex VI. The coordination of alkene to complex VI which followed by alkene insertion generates complex VII. Complex VII undergoes β-hydride elimination to generate complex III. Reductive elimination of complex III generates complex VIII which is followed by oxidation with oxygen regenerates complex I.

**Scheme 2.3 Proposed catalytic cycle**
2.3 Conclusion

In summary, we have reported that the oxidative Mizoroki-Heck reaction of arylsulfonyl hydrazides with alkenes in open-air manner using the stable and inexpensive pyridine ligand \( \text{L9} \). The Pd(OAc)_2/ \( \text{L9} \) catalyst system is effective for the coupling of a wide range of arylsulfonyl hydrazides and alkenes. It is noteworthy that the reaction was conducted under atmospheric air, instead of using Cu(II) salts or pure oxygen. It can reduce heavy metal wastes, risks of explosion and minimized complication of reaction procedures.

2.4 Experimental section

2.4.1 General considerations

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. All oxidative Heck reactions were performed in an open vessel. A vial (approx. 40 mL volume) fitted with an air condenser as cooler was in the presence of Teflon coated magnetic stirrer bar (4 mm x 10 mm). All arylsulfonyl hydrazides except trimethylbenzenesulfonylhydrazide were synthesized according to the literature report. Phenyl isonicotinate was produced by the following procedures. Thin layer chromatography was performed on Merck precoated silica gel 60 F\textsubscript{254} plates. Silica gel (Merck, 70-230 and 230-400 mesh) was used for column chromatography. Melting points were recorded on an uncorrected Büchi Melting Point B-545 instrument. NMR spectra were recorded on a Brüker spectrometer (400 MHz for \(^1\text{H}\), 100 MHz for \(^{13}\text{C}\) and 376 MHz for \(^{19}\text{F}\)). Spectra were referenced internally to the residual proton resonance in CDCl\textsubscript{3} (\(\delta\) 7.26 ppm), or with tetramethylsilane (TMS, \(\delta\) 0.00 ppm) as the internal standard. Chemical shifts (\(\delta\)) were reported as part per million (ppm) in \(\delta\) scale downfield from TMS. \(^{13}\text{C}\) NMR
spectra were referenced to CDCl$_3$ (δ 77.0 ppm, the middle peak). $^{19}$F NMR chemical shifts were determined relative to CFCl$_3$ as the external standard and low field is positive. Coupling constants ($J$) were reported in Hertz (Hz). Mass spectra (EI-MS and ES-MS) were recorded on a HP 5989B Mass Spectrometer. High-resolution mass spectra (HRMS) were obtained on a Brüker APEX 47e FTICR mass spectrometer (ESI-MS). GC-MS analysis was conducted on a HP 5973 GCD system using a HP5MS column (30 m × 0.25 mm). The products described in GC yield were accorded to the authentic samples/dodecane calibration standard from HP 6890 GC-FID system. All yields reported refer to isolated yield of compounds estimated to be greater than 95% purity as determined by capillary gas chromatography (GC) or $^1$H NMR. Compounds described in the literature were characterized by comparison of their $^1$H, $^{13}$C and/or $^{19}$F NMR spectra to the previously reported data. The procedures in this section are representative, and thus the yields may differ from those reported in tables.

2.4.2 General procedure for the preparation of phenyl isonicotinate L9

Phenyl isonicotinate L9$^{22}$

![Phenyl Isonicotinate](image)

Thionyl chloride (5.95 g, 50 mmol) was added dropwise to isonicotinic acid (6.15 g, 50 mmol) and triethylamine (5.05 g, 50 mmol) in chloroform (200 mL). The mixture was refluxed for 2 h and cooled down to room temperature. Phenol (8.78 mL, 100 mmol) was added dropwise to the THF solution containing sodium hydride (4.80 g, 60% in mineral oil, 120 mmol, 2.4 equiv.) suspended in THF (100 mL) under nitrogen and cooled to 0°C in an ice bath and stirred for 1 h to generate a THF
solution of sodium phenoxide. Then a THF solution of sodium phenoxide was added dropwise to the resulting isonicotinyl chloride solution, cooled by salt and ice water. The solution was further refluxed for 2 h, and then water (100 mL) and Ethyl acetate (200 mL) was added. The organic layer was successively washed with 1M sodium hydroxide solution and then washed with saturated brine solution. The organic layer was concentrated under vacuum and pass through a calica pad (5x3 cm) (Eluents = EtOAc: Hexane = 1: 9). The organic layer was concentrated. A white solid was obtained and then further washed with small amount of cool hexane and dry under vacuum. 4.2g (42% yield) product yield of phenyl isonicotinate was obtained. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.21 – 7.23 (m, 2H), 7.26 – 7.32 (m, 1H), 7.42-7.47 (m, 2H), 7.99 - 8.00 (m, 2H), 8.84 - 8.86 (m, 2H) ; $^{13}$C NMR (100 MHz,CDCl$_3$) $\delta$ 121.3, 123.1, 126.3, 129.6, 136.8, 150.4, 150.8, 163.4; MS (EI): $m/z$ (relative intensity) 199.0 (M$^+$, 37), 106.0 (100), 78.0 (50), 65.0 (7), 51.0 (24).

2.4.3 General procedure for the reaction condition screening without pyridine ligand

All reagents were weighted in air and the reactions were performed in an open vessel. Palladium source (0.03 mmol), 4-methylbenzenesulfonyl hydrazide (0.0838 g, 0.45 mmol) and styrene (34.4 μL, 0.3 mmol) were loaded into a 40 mL vial equipped with a Teflon-coated magnetic stir bar. The solvent (3 mL) was added at room temperature. The vial was fitted with an air condenser as cooler and then placed into a preheated oil bath (90 °C) and vigorously stirred for 16 h. After the completion of reaction, the reaction vial was allowed to cool at room temperature. Ethyl acetate(~10 mL) and dodecane (68.4μL, internal standard) were added. The organic layer was subjected to GC analysis. The GC yield obtained was previously calibrated by
2.4.4 General procedure for the reaction condition screening with pyridine ligand

All reagents were weighted in air and the reactions were performed in an open vessel. Pd(OAc)$_2$ (0.0068 g, 0.03 mmol) and pyridine ligand (Pd:L = 1:2) were loaded into a 40 mL vial equipped with a Teflon-coated magnetic stir bar. Precomplexation was applied by adding DMF (1 mL) in to the vial. The palladium complex stock solution was stirred for 10 minutes. 4-methylbenzenesulfonyl hydrazide (0.0838 g, 0.45 mmol) and styrene (34.4 μL, 0.3 mmol) were loaded into the vial. DMF (2 mL) was added with continuous stirring at room temperature. The vial was fitted with an air condenser as cooler and then placed into a preheated oil bath which the temperature was indicated in the table and vigorously stirred for 16 h. After the completion of reaction, the reaction vial was allowed to cool at room temperature. Ethyl acetate (~10 mL) and dodecane (68.4 μL, internal standard) were added. The organic layer was subjected to GC analysis. The GC yield obtained was previously calibrated by authentc sample/dodecane calibration curve.

2.4.5 General procedure for the oxidative heck reaction of arylsulfonyl hydrazides with alkenes

All reagents were weighted in air and the reactions were performed in an open vessel. Pd(OAc)$_2$ (0.0068 g, 0.03 mmol) and L9 (Pd:L = 1:2) were loaded into a 40 mL vial equipped with a Teflon-coated magnetic stir bar. Precomplexation was applied by adding DMF (1 mL) in to the vial. The palladium complex stock solution was stirred for 10 minutes. Arylsulfonyl hydrazide (0.45 mmol) and alkenes (0.3 mmol) were loaded into the vial. DMF (2 mL) was added with continuous stirring at
room temperature. The vial was fitted with an air condenser as cooler and then placed into a preheated oil bath which the temperature was indicated in the table and vigorously stirred for 16 h. After the completion of reaction, the reaction vial was allowed to cool at room temperature. Ethyl acetate (~10 mL) was added. The organic layer was subjected to GC analysis. After analyzing GC spectra, the crude product in the organic layer was extracted and the vial washed with ethyl acetate. The filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (230–400 mesh) to afford the desired product.
### 2.4.6 Characterization data of coupling products

**Benzene, 1-methyl-4-[(1E)-2-phenylethenyl]- (Table 2.3, compound 3ak)\(^{19a}\)**

![Chemical structure](image)

Eluents (Hexane, \(R_f=0.56\)) was used for flash column chromatography. White solid, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.45 (s, 3H), 7.12-7.21 (m, 2H), 7.26 (d, \(J=8.0\) Hz, 2H), 7.31-7.36 (m, 1H), 7.44 (t, \(J=6.8\) Hz, 2H), 7.51 (d, \(J=8.0\) Hz, 2H), 7.59 (d, \(J=7.6\) Hz, 2H); \(^{13}\)C NMR (100 MHz,CDCl\(_3\)) \(\delta\) 21.2, 126.4, 126.7, 128.6, 129.4, 134.5, 137.5; MS (EI): \(m/z\) (relative intensity) 194.1 (M\(^+\), 96), 179.0 (100), 165.0 (12), 152.0 (9), 115.0 (11).

**Benzene, 1-methyl-2-[(1E)-2-phenylethenyl]- (Table 2.3, compound 3bk)\(^{17}\)**

![Chemical structure](image)

Eluents (Hexane, \(R_f=0.56\)) was used for flash column chromatography. White solid, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.52 (s, 3H), 7.07-7.11 (d, \(J=16\) Hz, 1H), 7.26-7.38 (m, 4H), 7.41-7.47 (m, 3H), 7.61 (d, \(J=8.0\) Hz, 2H), 7.69 (d, \(J=6.8\) Hz, 1H); \(^{13}\)C NMR (100 MHz,CDCl\(_3\)) \(\delta\) 19.9, 125.3, 126.2, 126.5, 127.5, 128.6, 130.0, 130.4, 135.8, 136.4, 137.6; MS (EI): \(m/z\) (relative intensity) 194.1 (M\(^+\), 79), 179.0 (100), 165.0 (13), 152.0 (8), 115.0 (22).
Naphthalene, 2-[(1E)-2-phenylethenyl]- (Table 2.3, compound 3ck)\textsuperscript{19a}

Eluents (Hexane, R\textsubscript{f}= .38) was used for flash column chromatography. White solid, \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.25-7.35 (m, 3H), 7.41-7.45 (m, 2H), 7.47-7.56 (m, 2H), 7.60-7.62 (m, 2H), 7.77-7.80 (m, 1H), 7.85-7.89 (m, 4H); \textsuperscript{13}C NMR (100 MHz,CDCl\textsubscript{3}) δ 14.2, 21.0, 29.7, 60.4, 123.5, 125.9, 126.6, 127.7, 128.0, 128.3, 128.7, 129.0, 171.1; MS (EI): m/z (relative intensity) 230.1 (M\textsuperscript{+}, 100), 215.0 (23), 202.0 (11), 114.1 (3), 101.0 (9)

Benzene, 1,1'-(1E)-1,2-ethenediylibis- (Table 2.3, compound 3dk)\textsuperscript{19a}

Eluents (Hexane, R\textsubscript{f}= 0.50) was used for flash column chromatography. White solid, \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.18 (s, 2H), 7.30-7.34 (m, 2H), 7.40-7.44 (m, 4H), 7.57-7.59 (m, 4H); \textsuperscript{13}C NMR (100 MHz,CDCl\textsubscript{3}) δ 126.4, 127.5, 128.6, 137.3; MS (EI): m/z (relative intensity) 180.0 (M\textsuperscript{+}, 100), 165.0 (49), 152.0 (13), 89.0 (27), 76.0 (20), 51.0 (19).

Benzene, 1-fluoro-4-[(1E)-2-phenylethenyl]- (Table 2.3, compound 3ek)\textsuperscript{19a}

Eluents (Hexane, R\textsubscript{f}= 0.44) was used for flash column chromatography. White solid, \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.04-7.14 (m, 4H), 7.28-7.33 (m, 1H), 7.39-7.43 (m,
2H), 7.49-7.55 (m, 4H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 115.5, 115.7, 126.4, 127.4, 127.6, 127.9, 128.4, 133.5, 137.1, 161.1, 163.5; \(^{19}\)F NMR (400 MHz, CDCl\(_3\)) \(\delta\) -114.2; MS (EI): \(m/z\) (relative intensity) 198.0 (M\(^+\), 100), 183.0 (38), 170.0 (8), 120.0 (5), 98.0 (10).

**Benzene, 1-chloro-4-[(1E)-2-phenylethenyl]- (Table 2.3, compound 3fk)**\(^{19a}\)

Eluents (Hexane, \(R_f=0.49\)) was used for flash column chromatography. White solid, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.06-7.15 (m, 2H), 7.28-7.43 (m, 5H), 7.46-7.49 (m, 2H), 7.53-7.55 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 126.5, 127.3, 127.6, 127.8, 128.7, 128.8, 129.3, 133.1, 135.8, 136.9; MS (EI): \(m/z\) (relative intensity) 214.0 (M\(^+\), 78), 178.0 (100), 152.0 (14), 115.0 (2), 76.0 (18).

**Naphthalene, 1-[(1E)-2-phenylethenyl]- (Table 2.3, compound 3gk)**\(^{19a}\)

Eluents (Hexane, \(R_f=0.54\)) was used for flash column chromatography. Yellow solid, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.21 (d, \(J = 16.0\) Hz, 1H), 7.36-7.38 (m, 1H), 7.45-7.48 (m, 2H), 7.53-7.62 (m, 3H), 7.66-7.68 (m, 2H), 7.81 (d, \(J = 7.2\) Hz, 1H), 7.86 (d, \(J = 8.4\) Hz, 1H), 7.92-7.97 (m, 2H), 8.28 (d, \(J = 8.6\) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 123.6, 123.7, 125.7, 125.8, 126.1, 126.7, 127.7, 128.0, 128.6, 128.7, 131.4, 131.7, 133.7, 135.0, 137.6; MS (EI): \(m/z\) (relative intensity) 229.1 (M\(^+\), 100), 215.0 (18), 202.0 (13), 152.0 (21), 128.0 (5).
Benzene, 1-methoxy-4-[(1E)-2-phenylethenyl]- (Table 2.3, compound 3hk)\textsuperscript{19a}

![Chemical Structure Image]

Eluents (EtOAc: Hexane = 1: 20, R\textsubscript{f} = 0.40) was used for flash column chromatography. White solid, \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 3.87 (s, 3H), 6.93-6.97 (m, 2H), 7.01-7.14 (m, 2H), 7.26-7.31 (m, 1H), 7.38-7.41 (m, 2H), 7.49-7.55 (m, 4H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 55.29, 114.13, 126.2, 126.6, 127.2, 127.7, 128.2, 128.6, 130.1, 137.6, 159.3; MS (EI): \(m/z\) (relative intensity) 210.1 (M\textsuperscript{+}, 100), 195.0 (18), 179.0 (15), 165.0 (38), 152.0 (23).

Benzene, 1,3,5-trimethyl-2-[(1E)-2-phenylethenyl]- (Table 2.3, compound 3ik)\textsuperscript{19a}

![Chemical Structure Image]

Eluents (Hexane, R\textsubscript{f} = 0.50) was used for flash column chromatography. White solid, \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 2.36 (s, 3H), 2.41 (s, 6H), 7.66 (d, \(J\) = 16.8 Hz, 1H), 6.97 (s, 2H), 7.17 (d, \(J\) = 16.8 Hz, 1H), 7.33-7.36 (m, 1H), 7.42-7.45 (m, 2H), 7.57 (d, \(J\) = 7.2 Hz, 2H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 20.9, 126.2, 126.8, 127.4, 128.6, 133.6, 133.9, 136.1, 136.2, 137.7; MS (EI): \(m/z\) (relative intensity) 222.1 (M\textsuperscript{+}, 91), 207.1 (100), 192.0 (78), 178.0 (9), 144.0 (9).
Benzene, 1-nitro-4-[(1E)-2-phenylethenyl]- (Table 2.3, compound jk)$^{19a}$

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\text{C} & \quad \text{C} \\
\end{align*}
\]

Eluents (EtOAc: Hexane = 1: 9, R$_f$= 0.70) was used for flash column chromatography. Yellow solid, $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.17 (d, $J$ = 16.4 Hz, 1H), 7.27-7.45 (m, 4H), 7.56-7.59 (m, 2H), 7.64-7.67 (m, 2H), 8.22-8.26 (m, 2H); $^{13}$C NMR (100 MHz,CDCl$_3$) $\delta$ 124.1, 126.3, 126.8, 127.0, 128.9, 133.3, 136.2, 143.8, 146.8; MS (EI): m/z (relative intensity) 225.0 (M$^+$, 83), 207.0 (9), 178.0 (100), 165.0 (13), 152.0 (25).

2-Propenoic acid, 3-(4-methylphenyl)-, methyl ester, (2E)- (Table 2.3, compound 3al)$^{13b}$

\[
\begin{align*}
\text{Me} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\text{O} & \quad \text{Me} \\
\end{align*}
\]

Eluents (EtOAc: Hexane = 1: 9, R$_f$= 0.53) was used for flash column chromatography. White solid, $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.40 (s, 3H), 3.82 (s, 3H), 6.42 (d, $J$ = 16.0 Hz, 1H), 7.21 (d, $J$ = 8.0 Hz, 2H), 7.44 (d, $J$ = 8.0 Hz, 2H), 7.70 (d, $J$ = 16.0 Hz, 1H); $^{13}$C NMR (100 MHz,CDCl$_3$) $\delta$ 21.4, 51.6, 116.7 128.0, 129.6, 131.6, 140.7, 144.8, 167.6; MS (EI): m/z (relative intensity) 176.0 (M$^+$, 63), 161.0 (6), 145.0 (100), 115.0 (50), 91.0 (20).
2-Propenoic acid, 3-(4-methylphenyl)-, ethyl ester, (2E)- (Table 2.3, compound 3am)

Eluents (EtOAc: Hexane = 1: 20, R$_f$ = 0.52) was used for flash column chromatography. Yellow liquid, $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.36 (t, J = 7.2 Hz, 3H), 2.39 (s, 3H), 4.26 – 4.31 (m, 2H), 6.42 (d, J = 16.0 Hz, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 15.6 Hz, 1H); $^{13}$C NMR (100 MHz,CDCl$_3$) $\delta$ 14.3, 21.4, 60.4 117.1, 128.0, 129.6, 131.7, 140.6, 144.5, 167.1; MS (EI): m/z (relative intensity) 190.0 (M$^+$, 48), 175.0 (3), 162.0 (13), 145.0 (100), 115.0 (46).

2-Propenoic acid, 3-(4-methylphenyl)-, butyl ester, (2E)- (Table 2.3, compound 3an)

Eluents (EtOAc: Hexane = 1: 20, R$_f$ = 0.52) was used for flash column chromatography. Colorless liquid, $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.99 (t, J = 7.6 Hz, 3H), 1.44-1.49 (m, 2H), 1.69 – 1.73 (m, 2H), 2.39 (s, 3H), 4.23 (t, J = 6.4 Hz, 2H), 6.42 (d, J = 16.0 Hz, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H), 7.68 (d, J=16.0 Hz, 1H); $^{13}$C NMR (100 MHz,CDCl$_3$) $\delta$ 13.7, 19.1, 21.4 30.7, 64.2, 117.1, 128.0, 129.5, 131.7, 140.5, 144.5, 167.2; MS (EI): m/z (relative intensity) 218.1 (M$^+$, 26), 162.0 (95), 145.0 (100), 115.0 (51), 91.0 (25).
2-Propenoic acid, 3-(1-naphthalenyl)-, butyl ester, (2E) - (Table 2.3, compound 3gn)²³

![Chemical Structure]

Eluents (EtOAc: Hexane = 1: 20, R<sub>f</sub> = 0.64) was used for flash column chromatography. Yellow liquid, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.04 (t, J = 7.2 Hz, 3H), 1.49-1.54 (m, 2H), 1.74-1.79 (m, 2H), 4.31 (t, J = 6.4 Hz, 2H), 6.58 (d, J = 15.6 Hz, 1H), 7.49-7.63 (m, 3H), 7.78 (d, J = 6.8 Hz, 1H), 7.91 (t, J = 7.2 Hz, 2H), 8.23 (d, J = 8.4 Hz, 1H), 8.57 (d, J = 15.6 Hz, 1H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 13.7, 19.2, 30.8, 64.5, 120.9, 123.3, 124.9, 125.4, 126.1, 126.8, 128.7, 130.4, 131.4, 131.8, 133.6, 141.5, 166.9; MS (EI): m/z (relative intensity) 254.1 (M<sup>+</sup>, 27), 198.0 (7), 181.0 (25), 153.0 (100), 76.1 (5).

2-Propenoic acid, 3-(2-naphthalenyl)-, butyl ester, (2E) - (Table 2.3, compound 3cn)³³

![Chemical Structure]

Eluents (EtOAc: Hexane = 1: 20, R<sub>f</sub> = 0.60) was used for flash column chromatography. Colorless liquid, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.02 (t, J = 7.2 Hz, 3H), 1.47-1.53 (m, 2H), 1.71-1.77 (m, 2H), 4.28 (t, J = 6.8 Hz, 2H), 6.59 (d, J = 16.0 Hz, 1H), 7.52-7.54 (m, 2H), 7.68 (d, J = 8.4 Hz, 1H), 7.83-7.94 (m, 5H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 1.0, 13.7, 19.2, 30.8, 64.4, 118.4, 123.4, 126.6, 127.1, 127.7, 128.5, 128.6, 129.8, 131.9, 133.2, 134.1, 144.5, 167.1; MS (EI): m/z (relative intensity) 254.1 (M<sup>+</sup>, 52), 198.0 (100), 181.0 (70), 152.0 (65), 127.0 (11).
2-Propenoic acid, 3-(2,4,6-trimethylphenyl)-, butyl ester, (2E)- (Table 2.3, compound 3in)

Eluents (EtOAc: Hexane = 1: 20, R_f= 0.49) was used for flash column chromatography. White solid, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.01 (t, \(J= 7.6\) Hz, 3H), 1.45-1.51 (m, 2H), 1.70-1.75 (m, 2H), 2.23 (s, 3H), 2.36 (s, 6H), 4.25 (t, \(J= 6.8\) Hz, 2H), 6.09 (d, \(J= 16.4\)Hz, 1H), 6.92 (s, 2H), 7.87 (d, \(J= 16.4\)Hz, 1H); \(^{13}\)C NMR (100 MHz,CDCl\(_3\)) \(\delta\) 13.7, 19.2, 20.9, 21.0, 30.7, 64.3, 123.1, 129.1, 130.9, 136.7, 138.2, 143.1, 167.0; MS (EI): \(m/z\) (relative intensity) 246.1 (M\(^+\), 27), 231.1 (5), 173.0 (100), 144.1 (52), 129.0 (39).

Benzene, 1-fluoro-4-[(1E)-2-(4-methylphenyl)ethenyl]- (Table 2.3, compound 3ao)

Eluents (Hexane, R_f= 0.56) was used for flash column chromatography. White solid, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.41 (s, 3H), 7.05-7.11 (m, 4H), 7.22 (d, \(J= 8.0\) Hz, 2H), 7.45 (d, \(J= 8.0\) Hz, 2H), 7.49-7.52 (m, 2H); \(^{13}\)C NMR (100 MHz,CDCl\(_3\)) \(\delta\) 21.2, 115.4, 115.6, 126.3, 126.4, 127.7, 127.8, 128.4, 129.4, 133.6, 134.3, 137.5, 160.9, 163.4; \(^{19}\)F NMR (400 MHz,CDCl\(_3\)) \(\delta\) -114.6; MS (EI): \(m/z\) (relative intensity) 212.1 (M\(^+\), 100), 197.0 (67), 177.0 (18), 115.0 (8), 91.1 (10).
Benzene, 1-fluoro-3-[2-(4-methylphenyl)ethenyl]-, (E)- (Table 2.3, compound 3ap)\textsuperscript{25}

\begin{align*}
\text{Me} & \quad \text{F} \\
& \quad \text{Me}
\end{align*}

Eluents (Hexane, \(R_f=0.56\)) was used for flash column chromatography. White solid, \(^1\text{H} \text{NMR} \ (400 \text{ MHz}, \text{CDCl}_3) \ \delta \ 2.42 \ (s, \ 3\text{H}), \ 6.96-7.01 \ (m, \ 1\text{H}), \ 7.04-7.15 \ (m, \ 2\text{H}), \ 7.22-7.38 \ (m, \ 5\text{H}), \ 7.46 \ (d, \ J=8.0 \text{ Hz, } 2\text{H}); \(^{13}\text{C} \text{NMR} \ (100 \text{ MHz},\text{CDCl}_3) \ \delta \ 21.3, \ 112.5, \ 112.7, \ 114.0, \ 114.2, \ 122.3, \ 126.5, \ 126.8, \ 129.4, \ 130.0, \ 134.0, \ 138.0, \ 139.9, \ 162.0, \ 164.4; \(^{19}\text{F} \text{NMR} \ (400 \text{ MHz},\text{CDCl}_3) \ \delta \ -113.5; \ MS \ (\text{EI}): \ m/z \ (\text{relative intensity}) \ 212.1 \ (\text{M}^+, \ 100), \ 197.0 \ (88), \ 177.0 \ (24), \ 115.0 \ (8), \ 91.1 \ (10).

Benzene, 1-chloro-4-[(1E)-2-(4-methylphenyl)ethenyl]- (Table 2.3, compound 3aq)\textsuperscript{19a}

\begin{align*}
\text{Me} & \quad \text{Cl} \\
& \quad \text{Me}
\end{align*}

Eluents (Hexane, \(R_f=0.56\)) was used for flash column chromatography. White solid, \(^1\text{H} \text{NMR} \ (400 \text{ MHz, } \text{CDCl}_3) \ \delta \ 2.39 \ (s, \ 3\text{H}), \ 7.00-7.11 \ (m, \ 2\text{H}), \ 7.20 \ (d, \ J=7.6 \text{ Hz, } 2\text{H}), \ 7.33-7.36 \ (m, \ 2\text{H}), \ 7.42-7.47 \ (m, \ 4\text{H}); \(^{13}\text{C} \text{NMR} \ (100 \text{ MHz,CDCl}_3) \ \delta \ 21.3, \ 126.4, \ 126.5, \ 127.5, \ 128.8, \ 129.3, \ 129.4, \ 132.9, \ 134.2, \ 136.1, \ 137.8; \ MS \ (\text{EI}): \ m/z \ (\text{relative intensity}) \ 228.0 \ (\text{M}^+, \ 100), \ 213.0 \ (16), \ 192.0 \ (26), \ 178.0 \ (95), \ 94.7 \ (12).

Benzene, 1,1'-{(1E)-1,2-ethenediylibis[4-methyl}- (Table 2.3, compound 3ar)\textsuperscript{19a}

\begin{align*}
\text{Me} & \quad \text{Me} \\
& \quad \text{Me}
\end{align*}

Eluents (Hexane, \(R_f=0.56\)) was used for flash column chromatography. White solid, \(^1\text{H} \text{NMR} \ (400 \text{ MHz, } \text{CDCl}_3) \ \delta \ 2.42 \ (s, \ 6\text{H}), \ 7.10 \ (s, \ 2\text{H}), \ 7.22 \ (d, \ J=8.0 \text{ Hz, } 4\text{H}), \ 7.46
(d, J = 8.0 Hz, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 21.2, 126.3, 127.6, 129.3, 134.7, 137.2; MS (EI): m/z (relative intensity) 208.1 (M$^+$, 100), 193.0 (57), 178.0 (59), 152.0 (5), 115.0 (13).

**Benzene, 1-methoxy-4-[(1E)-2-(4-methylphenyl)ethenyl]-** (Table 2.3, compound 3as)$^{19a}$

![Structure of Benzene, 1-methoxy-4-[(1E)-2-(4-methylphenyl)ethenyl]-]

Eluents (EtOAc: Hexane = 1: 20, R$_f$ = 0.48) was used for flash column chromatography. White solid, $^1$H NMR (400 MHz, CDCl$_3$) δ 2.40 (s, 3H), 3.86 (s, 3H), 6.92-6.96 (m, 2H), 6.97-7.09 (m, 2H), 7.20 (d, J = 7.6 Hz, 2H), 7.42-7.50 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 21.2, 55.3, 114.1, 126.1, 126.5, 127.2, 127.6, 129.3, 130.3, 134.8, 137.0, 159.1; MS (EI): m/z (relative intensity) 224.1 (M$^+$, 100), 209.0 (25), 194.0 (5), 178.0 (9), 165.0 (33).

**Benzene, 1-[(1E)-2-(4-methylphenyl)ethenyl]-4-(trifluoromethyl)-** (Table 2.3, compound 3at)$^{25}$

![Structure of Benzene, 1-[(1E)-2-(4-methylphenyl)ethenyl]-4-(trifluoromethyl)-]

Eluents (Hexane, R$_f$ = 0.56) was used for flash column chromatography. White solid, $^1$H NMR (400 MHz, CDCl$_3$) δ 2.41 (s, 3H), 7.10 (d, J = 16.4 Hz, 1H), 7.18-7.23 (m, 3H), 7.46 (d, J = 8.4 Hz, 2H), 7.59-7.64 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ, 21.3, 125.6, 126.1, 126.4, 126.7, 128.8, 129.5, 131.1, 133.1, 138.3, 141.0; $^{19}$F NMR (400 MHz, CDCl$_3$) δ -62.4; MS (EI): m/z (relative intensity) 262.1 (M$^+$, 100), 247.0 (41), 227.0 (18), 115.0 (7), 91.0 (8).
Benzene, 1-bromo-2-[(1E)-2-(4-methylphenyl)ethenyl]- (Table 2.3, compound 3au) \(^{26}\)

![Chemical Structure Image]

Eluents (Hexane, \(R_f = 0.56\)) was used for flash column chromatography. Colorless liquid, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.41 (s, 3H), 7.06 (d, \(J = 16.0\) Hz, 1H), 7.12-7.16 (m, 1H), 7.20-7.23 (m, 2H), 7.32-7.36 (m, 1H), 7.44-7.50 (m, 3H), 7.60-7.63 (m, 1H), 7.69-7.71 (m, 1H); \(^{13}\)C NMR (100 MHz,CDCl\(_3\)) \(\delta\) 21.3, 124.0, 126.5, 127.5, 128.5, 128.9, 129.4, 131.4, 132.9, 133.0, 134.2, 137.3, 138.0; MS (EI): \(m/z\) (relative intensity) 272.0 (M\(^+\), 38), 193.0 (23), 178.0 (100), 165.0 (12), 115.0 (7).

Benzene, 1-chloro-4-[(1E)-2-(1,3,5-trimethylphenyl)ethenyl]- (Table 2.3, compound 3av)

![Chemical Structure Image]

Eluents (Hexane, \(R_f = 0.55\)) was used for flash column chromatography. White solid, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.35 (s, 3H), 2.40 (s, 6H), 6.60 (d, \(J = 16.8\) Hz, 1H), 6.97 (s, 2H), 7.13 (d, \(J = 16.4\) Hz, 1H), 7.37-7.40 (m, 2H), 7.45-7.48 (m, 2H); \(^{13}\)C NMR (100 MHz,CDCl\(_3\)) \(\delta\) 21.0, 127.4, 127.6, 132.3, 133.0, 133.6, 136.1, 136.2, 136.5; MS (EI): \(m/z\) (relative intensity) 256.0 (M\(^+\), 63), 241.0 (23), 221.1 (27), 206.0 (100), 191.0 (15); HRMS (ESI) calcd. for \(C_{17}H_{17}Cl\) [M + H\(^+\)]: 256.1019, found 256.1018.
2.5 References


Chapter 3 Palladium-Catalyzed Direct Oxidative C-H Arylation of Benzoxazoles with Arylsulfonyl Hydrazides under air

3.1 Introduction

Cross-coupling protocol has been successful in modern modular organic syntheses for the connection of two different fragments together via the formation of carbon-carbon and/or carbon-heteroatom bonds.\(^1\) To prepare useful biaryl motifs,\(^2\) coupling methods such as Hiyama, Kumada, Negishi, Stille and Suzuki-Miyaura coupling have been found versatile in the past few decades.\(^3\) Even though these reactions are effective, some intrinsic drawbacks are still exist in which the corresponding organometallic nucleophiles are necessary to be prepared in-situ (e.g. \(\text{Ar-MgBr}\), \(\text{Ar-ZnCl}\)) or require isolation, in general, prior to the catalysis (e.g. \(\text{Ar-B(OH)}_2\)). Thus, the assembling and subsequent disposal of stoichiometric organometallic agents are relatively not desirable. In fact, direct C-H functionalization of heteroarenes is actually more straightforward. This protocol serves as an attractive alternative to conventional coupling protocols in terms of better atom economy, environmental friendliness and more streamlined chemical synthesis.\(^3,4\)

In continuing our research focus of applying arylsulfonyl compounds as effective aryl sources,\(^5\) we envisioned that arylsulfonyl hydrazides could be employed as versatile arylation agents. Indeed, arylsulfonyl hydrazides are readily accessible solids, stable in air and moisture and can be simply prepared in one step from commonly available arylsulfonyl chlorides and hydrazine hydrates. In 2012, Tian and co-workers reported the first palladium-catalyzed Mizoroki-Heck reaction of alkenes with arylsulfonyl hydrazides.\(^6\) To the best of our knowledge, the direct C-H arylation of benzoxazoles using arylsulfonyl hydrazides remain sporadically studied.\(^7\)
In fact, with respect to the reaction of olefins, the arylation of heteroarenes is known to be even more challenging because of the undesirable homocoupling outcome and decomposition of heteroarenes are often observed under oxidative conditions. In continuing our research program on C-2 functionalization of benzoxazoles, we herein report our efforts in the palladium-catalyzed direct C-H arylation of benzoxazoles using arylsulfonyl hydrazides under oxidative reaction conditions.

3.2 Results and discussion

3.2.1 Preliminary evaluation of palladium-catalyzed oxidative C-H arylation of benzoxazoles with arylsulfonyl hydrazides

In order to investigate the efficacy of arylsulfonyl hydrazide as the aryl source in the direct C-H arylation of heteroarenes, a series of initial screenings was conducted (Table 3.1). Benzoxazole and 4-tolylsulfonyl hydrazide were used as benchmark substrates. Among commonly used solvents screened, dioxane provided the best results (Table 3.1, entries 1-7). There were little differences in product yield observed in the model reaction when other palladium precursors were investigated (Table 3.1, entries 1 and 8-13). The palladium complex associated with triphenylphosphine gave slightly higher yield (Table 3.1, entry 9 and 13). Common inorganic/organic oxidants were also surveyed (Table 3.1, entries 1 and 14-21). Copper(II) acetate gave the best results while BQ and O₂ provided inferior product yields.
Table 3.1 Initial screening of oxidative arylation of 4-methylbenzenesulfonyl hydrazide and benzoxazole\textsuperscript{[a]}

![Chemical structure diagram]

<table>
<thead>
<tr>
<th>entry</th>
<th>Pd source</th>
<th>solvent</th>
<th>oxidant</th>
<th>yield%\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>Pd(OAc)\textsubscript{2}</td>
<td>dioxane</td>
<td>Cu(OAc)\textsubscript{2}</td>
<td>51</td>
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<tr>
<td>2</td>
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<td>DMF</td>
<td>Cu(OAc)\textsubscript{2}</td>
<td>6</td>
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<td>3</td>
<td>Pd(OAc)\textsubscript{2}</td>
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<td>Cu(OAc)\textsubscript{2}</td>
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<td>Cu(OAc)\textsubscript{2}</td>
<td>10</td>
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<td>Cu(OAc)\textsubscript{2}</td>
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<td>48</td>
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<tr>
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<td>PdCl\textsubscript{2}</td>
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<td>Cu(OAc)\textsubscript{2}</td>
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<tr>
<td>11</td>
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<td>Cu(OAc)\textsubscript{2}</td>
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<tr>
<td>12</td>
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<td>K\textsubscript{2}S\textsubscript{2}O\textsubscript{8}</td>
<td>0</td>
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</table>
[a] Reaction conditions: 4-Tolylsulfonyl hydrazide (0.45 mmol), benzoxazole (0.3 mmol), Pd catalyst (5 mol%), solvent (3 mL) and oxidant (0.6 mmol) were stirred at 120 °C for 18 h under air. [b] Calibrated GC yields were reported using dodecane as internal standard.

In light of the successful initial results achieved, we next examined the effect of phosphine ligands in this reaction (Scheme 3.1). Palladium(II) acetate with triphenylphosphine promoted the reaction and gave the highest product yield. Yet, catalytic system employing our previously developed tunable indolylphosphine ligands (L1-L7) showed moderate efficiency.

Scheme 3.1 A survey of ligand effect in oxidative arylation of benzoxazole (Reaction conditions: 4-methylbenzenesulfonyl hydrazide (0.45 mmol), benzoxazole (0.3 mmol), Pd(OAc)$_2$ (5 mol%), Ligand (10 mol%) , Dioxane (3 mL), Cu(OAc)$_2$ (0.6 mmol) were
stirred at indicated temperature for 18 h under air. Calibrated GC yields were reported using dodecane as internal standard. [a] 100 °C was conducted. [b] 110 °C was conducted. [c] 130 °C was conducted.

3.2.2 Scope of palladium-catalyzed oxidative C-H arylation of benzoxaxoles with arylsulfonyl hydrazides

With our optimized reaction conditions in hand, we next tested the scope of arylsulfonyl hydrazides (Table 3.2). The coupling reaction of sterically hindered 2-tolylsulfonyl hydrazide proceeded smoothly (Table 3.2, entry 3). Halogen substitutents (-F, -Cl, -Br) on arylsulfonyl hydrazide were found to be compatible under these reaction conditions (Table 3.2, entries 4-6). Particularly noteworthy is that the tolerance of chloro and bromo groups can offer an avenue for further versatile functionalization using traditional cross-coupling protocols.¹ A few of arylsulfonyl hydrazides was examined but no desired products could be obtained (Scheme 3.2).
Table 3.2 Palladium-catalyzed oxidative arylation of benzoxazole using arylsulfonyl hydrazides[^a]

![Chemical structures](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>Ar-SO₂-NH NH₂</th>
<th>benzoxazole</th>
<th>product</th>
<th>yield[^b]</th>
</tr>
</thead>
<tbody>
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<td><img src="image" alt="Structure" /></td>
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<td>Me-<img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
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<td>78</td>
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<td>3[^d]</td>
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<td><img src="image" alt="Structure" /></td>
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</tr>
<tr>
<td>4</td>
<td>F-<img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td>66</td>
</tr>
<tr>
<td>5[^c]</td>
<td>Cl-<img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
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<tr>
<td>6[^d]</td>
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<tr>
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<td><img src="image" alt="Structure" /></td>
<td>67</td>
</tr>
<tr>
<td>8</td>
<td>MeO-<img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td><img src="image" alt="Structure" /></td>
<td>52</td>
</tr>
</tbody>
</table>

[^a]: Reaction conditions: Arylsulfonyl hydrazide (0.45 mmol), benzoxazole (0.3 mmol), Pd(OAc)₂ (5 mol%), PPh₃ (10 mol%), dioxane (3 mL), Cu(OAc)₂ (0.6 mmol) were stirred at 120 °C for 18 h under air. [^b]: Isolated yields. [^c]: The reaction was conducted at 110 °C. [^d]: The reaction was conducted at 100 °C.
Scheme 3.2  Unsuccessful arylsulfonyl hydrazides in direct C-2 arylation of benzoxazole (Reaction conditions were same as Table 3.2, entry 2)

3.2.3 Scope of palladium-catalyzed oxidative C-H arylation of substituted benzoxazoles and other heteroarenes with arylsulfonyl hydrazides

In addition to a variety of arylsulfonyl hydrazides examined, the substituted benzoxazoles were found feasible substrates (Table 3.3). Fluoro and chloro groups remained intact during the course of the reaction (Table 3.3, entries 5-6). However, 5-acetylbenzoxazole was incompatible under this optimized reaction condition.
Table 3.3 Palladium-catalyzed oxidative arylation of substituted benzoxazoles with arylsulfonyl hydrazides\textsuperscript{[a]}

\[\text{Ar-SO}_2\text{-NHNH}_2 + \text{benzoxazole} \rightarrow \text{product}\]

<table>
<thead>
<tr>
<th>entry</th>
<th>Ar-SO\textsubscript{2}-NHNH\textsubscript{2}</th>
<th>benzoazole</th>
<th>product</th>
<th>yield\textsuperscript{[b]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me-\text{C}<em>{6}\text{H}</em>{4}-\text{SO}_2-NHNH\textsubscript{2}</td>
<td>Ph-\text{N}\textsubscript{2} \text{O} \text{N} H</td>
<td>Ph-\text{N}\textsubscript{2} \text{O} \text{N} \text{O} \text{H} \text{R}</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>Me-\text{C}<em>{6}\text{H}</em>{4}-\text{SO}_2-NHNH\textsubscript{2}</td>
<td>Me-\text{N}\textsubscript{2} \text{O} \text{N} H</td>
<td>Me-\text{N}\textsubscript{2} \text{O} \text{N} \text{O} \text{H} \text{R}</td>
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</tr>
<tr>
<td>3\textsuperscript{[c]}</td>
<td>Me-\text{C}<em>{6}\text{H}</em>{4}-\text{SO}_2-NHNH\textsubscript{2}</td>
<td>Me-\text{N}\textsubscript{2} \text{O} \text{N} H</td>
<td>Me-\text{N}\textsubscript{2} \text{O} \text{N} \text{O} \text{H} \text{R}</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>Ph-\text{C}<em>{6}\text{H}</em>{4}-\text{SO}_2-NHNH\textsubscript{2}</td>
<td>Me-\text{N}\textsubscript{2} \text{O} \text{N} H</td>
<td>Me-\text{N}\textsubscript{2} \text{O} \text{N} \text{O} \text{H} \text{R}</td>
<td>67</td>
</tr>
<tr>
<td>5</td>
<td>Me-\text{C}<em>{6}\text{H}</em>{4}-\text{SO}_2-NHNH\textsubscript{2}</td>
<td>F-\text{C}<em>{6}\text{H}</em>{4}-\text{N}\textsubscript{2} \text{O} \text{N} H</td>
<td>F-\text{C}<em>{6}\text{H}</em>{4}-\text{N}\textsubscript{2} \text{O} \text{N} \text{O} \text{H} \text{R}</td>
<td>71</td>
</tr>
<tr>
<td>6</td>
<td>Me-\text{C}<em>{6}\text{H}</em>{4}-\text{SO}_2-NHNH\textsubscript{2}</td>
<td>Cl-\text{C}<em>{6}\text{H}</em>{4}-\text{N}\textsubscript{2} \text{O} \text{N} H</td>
<td>Cl-\text{C}<em>{6}\text{H}</em>{4}-\text{N}\textsubscript{2} \text{O} \text{N} \text{O} \text{H} \text{R}</td>
<td>72</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} Reaction conditions: Arylsulfonyl hydrazide (0.45 mmol), substituted benzoxazole (0.3 mmol), Pd(OAc\textsubscript{2}) (5 mol%), PPh\textsubscript{3} (10 mol%), dioxane (3 mL), Cu(OAc\textsubscript{2}) (0.6 mmol) were stirred at 120 °C for 18 h under air. \textsuperscript{[b]} Isolated yields. \textsuperscript{[c]} The reaction was conducted at 100 °C.

Apart from benzoxazole, other heteroarenes were applicable. Caffeine and benzothiazole could be applied in this catalytic system (Scheme 3.3). Moderate-to-good product yields were observed. In particular, the product 1 is a
useful fluorescent molecule for cell imaging. Yet, when benzimidazole and 1-methylbenzimidazole were applied as substrates in this optimized reaction condition, no desired products could be obtained.

**Scheme 3.3** Palladium-catalyzed direct C-H arylation of caffeine and benzothiazole with arylsulfonfyl hydrazides (Reaction conditions: Arylsulfonfyl hydrazide (0.45 mmol), heteroarene (0.3 mmol), Pd(OAc)$_2$ (5 mol%), PPh$_3$ (10 mol%), dioxane (3 mL), Cu(OAc)$_2$ (0.6 mmol) were stirred at 120 °C for 18 h under air and product yields were isolated yields.)

### 3.3 Conclusion

In summary, we have reported an oxidative protocol for C-2 arylation of benzoazoles using readily available and easy-to-handle arylsulfonfyl hydrazides as the aryl sources. Particularly noteworthy is that only a simple catalyst system (Pd(OAc)$_2$ and PPh$_3$) is required for this coupling reaction. This methodology is a useful complement to current cross-coupling protocols as it tolerates halogen substitutents on both arylsulfonfyl hydrazide and heteroarene coupling partners. Detail mechanistic study is currently underway.
3.4 Experimental section

3.4.1 General considerations

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. All oxidative arylations were performed in an open vessel. A vial (approx. 60 mL volume) fitted with an air condenser as cooler was in the presence of Teflon coated magnetic stirrer bar (4 mm x 10 mm). The indolylphosphine ligands (L1-L7) were developed and prepared by our group. All arylsulfonyl hydrazides were synthesized by the following procedure. 5-methylbenzoxazole, 5-phenylbenzoxazole, 5-chlorobenzoxazole and 5-fluorobenzoxazole were synthesized according to the literature method. Thin layer chromatography was performed on Merck precoated silica gel 60 F254 plates. Silica gel (Merck, 70-230 and 230-400 mesh) was used for column chromatography. Melting points were recorded on an uncorrected Büchi Melting Point B-545 instrument. NMR spectra were recorded on a Bruker spectrometer (400 MHz for $^1$H, 100 MHz for $^{13}$C and 376 MHz for $^{19}$F). Spectra were referenced internally to the residual proton resonance in CDCl$_3$ ($\delta$ 7.26 ppm), or with tetramethylsilane (TMS, $\delta$ 0.00 ppm) as the internal standard. Chemical shifts ($\delta$) were reported as part per million (ppm) in $\delta$ scale downfield from TMS. $^{13}$C NMR spectra were referenced to CDCl$_3$ ($\delta$ 77.0 ppm, the middle peak). $^{19}$F NMR chemical shifts were determined relative to CFCl$_3$ as the external standard and low field is positive. Coupling constants ($J$) were reported in Hertz (Hz). Mass spectra (EI-MS and ES-MS) were recorded on a HP 5989B Mass Spectrometer. High-resolution mass spectra (HRMS) were obtained on a Brüker APEX 47e FTICR mass spectrometer (ESI-MS). GC-MS analysis was conducted on a HP 5973 GCD system using a HP5MS column (30 m × 0.25 mm). The products described in GC yield were accorded to the authentic
samples/dodecane calibration standard from HP 6890 GC-FID system. All yields reported refer to isolated yield of compounds estimated to be greater than 95% purity as determined by capillary gas chromatography (GC) or $^1$H NMR. Compounds described in the literature were characterized by comparison of their $^1$H, $^{13}$C and/or $^{19}$F NMR spectra to the previously reported data. The procedures in this section are representative, and thus the yields may differ from those reported in tables.

3.4.2 General procedure for the reaction condition screening without phosphine ligand

All reagents were weighted in air and the reactions were performed in an open vessel. Palladium source (0.015 mmol), 4-methylbenzenesulfonyl hydrazide (0.0838 g, 0.45 mmol), benoxazole (0.0358 g, 0.30 mmol) and oxidant (0.60 mmol) were loaded into a 60 mL vial equipped with a Teflon-coated magnetic stir bar. The solvent (3.0 mL) was added at room temperature. The vial was fitted with an air condenser as cooler and then placed into a preheated oil bath (120 °C) and vigorously stirred for 18 h. After the completion of reaction, the reaction vial was allowed to cool at room temperature. Ethyl acetate (~20 mL), water (~10 mL) and dodecane (68.4 μL, internal standard) were added. The organic layer was subjected to GC analysis. The GC yield obtained was previously calibrated by authentic sample/dodecane calibration curve.

3.4.3 General procedure for the reaction condition screening with phosphine ligand

All reagents were weighted in air and the reactions were performed in an open vessel. Pd(OAc)$_2$ (0.0034 g, 0.015 mmol), phosphine ligand (Pd:L = 1:2), 4-methylbenzenesulfonyl hydrazide (0.0838 g, 0.45 mmol), benoxazole (0.0358 g,
0.30 mmol) and Cu(OAc)$_2$ (0.60 mmol) were loaded into a 60 mL vial equipped with a Teflon-coated magnetic stir bar. Dioxane (3.0 mL) was added at room temperature. The vial was fitted with an air condenser as cooler and then placed into a preheated oil bath which the temperature was indicated in the table and vigorously stirred for 18 h. After the completion of reaction, the reaction vial was allowed to cool at room temperature. Ethyl acetate (~20 mL), water (~10 mL) and dodecane (68.4 μL, internal standard) were added. The organic layer was subjected to GC analysis. The GC yield obtained was previously calibrated by authentic sample/dodecane calibration curve.

### 3.4.3 General procedure for the oxidative arylation of arylsulfonyl hydrazides with heteroarenes

All reagents were weighted in air and the reactions were performed in an open vessel. Pd(OAc)$_2$ (0.0034g, 0.015 mmol), PPh$_3$ (Pd:L = 1:2), arylsulfonyl hydrazides (0.45 mmol), heteroarenes (0.30 mmol) and Cu(OAc)$_2$ (0.60 mmol) were loaded into a 60 mL vial equipped with a Teflon-coated magnetic stir bar. Dioxane (3.0 mL) was added at room temperature. The vial was fitted with an air condenser as cooler and then placed into a preheated oil bath which the temperature was indicated in the table and vigorously stirred for 18 h. After the completion of reaction, the reaction vial was allowed to cool at room temperature. Ethyl acetate (~20 mL), water (~10 mL) was added. The organic layer was subjected to GC analysis. After analyzing GC spectra, the crude product in the organic layer was extracted and the vial washed with ethyl acetate. The filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (230 -400 mesh) to afford the desired product.
3.4.4 Characterization data of coupling products

2-Phenylbenzoxazole (Table 3.2, entry 1)\(^8\)

![2-Phenylbenzoxazole](image)

Eluents (EtOAc: Hexane = 1: 20, \(R_f = 0.62\)) was used for flash column chromatography. 44.5 mg, 76 % yield, white solid, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.36-7.40 (m, 2H), 7.52-7.57 (m, 3H), 7.58-7.63 (m, 1H), 7.79-7.83 (m, 1H), 8.28-8.31 (m, 2H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 110.5, 120.0, 124.5, 125.1, 127.1, 127.6, 128.8, 131.5, 142.0, 150.7, 163.0; MS (EI): \(m/z\) (relative intensity) 195.0 (M\(^+\), 100), 167.0 (18), 139.0 (3), 92.0 (5), 63.0 (14).

2-(4-Methylphenyl)benzoxazole (Table 3.2, entry 2)\(^{14}\)

![2-(4-Methylphenyl)benzoxazole](image)

Eluents (EtOAc: Hexane = 1: 20, \(R_f = 0.61\)) was used for flash column chromatography. 48.9 mg, 78 % yield, white solid, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.45 (s, 3H), 7.34-7.39 (m, 4H), 7.58-7.60 (m, 1H), 7.78-7.80 (m, 1H), 8.17 (d, \(J = 8.5\) Hz, 2H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 21.6, 110.4, 119.8, 124.3, 124.4, 124.8, 127.5, 129.6, 142.0, 142.1, 150.6, 163.2; MS (EI): \(m/z\) (relative intensity) 209.0 (M\(^+\), 100), 180.0 (8), 116.0 (4), 91.0 (9), 77.0 (2).

2-(2-Methylphenyl)benzoxazole (Table 3.2, entry 3)\(^{15}\)

![2-(2-Methylphenyl)benzoxazole](image)

Eluents (EtOAc: Hexane = 1: 20, \(R_f = 0.64\)) was used for flash column chromatography. 45.1 mg, 72 % yield, white solid, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.85 (s, 3H), 7.36-7.46 (m, 5H), 7.60-7.64 (m, 1H), 7.82-7.85 (m, 1H), 8.21 (d, \(J = 7.6\) Hz, 2H).
Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 22.2, 110.5, 120.1, 124.3, 125.0, 126.0, 126.2, 129.9, 130.9, 131.8, 138.8, 142.1, 150.3, 163.4; MS (EI): m/z (relative intensity) 209.0 (M$^+$, 100), 180.0 (30), 116.0 (6), 91.0 (13), 77.0 (5).

2-(4-Fluorophenyl)benzoxazole, (Table 3.2, entry 4)$^{15}$

![structure](image)

Eluents (EtOAc: Hexane = 1: 20, R$_f$ = 0.54) was used for flash column chromatography. 42.2 mg, 66 % yield, white solid, $^1$H NMR (400 MHz, CDCl$_3$) δ 7.19-7.25 (m, 2H), 7.28-7.39 (m, 2H), 7.56-7.60 (m, 1H), 7.77-7.79 (m, 1H), 8.24-8.29 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 110.5, 116.0, 116.2, 119.9, 123.4, 124.6, 125.1, 129.7, 129.8, 142.0, 150.7, 162.1, 163.5, 166.0; $^{19}$F NMR (400 MHz, CDCl$_3$) δ -107.5; MS (EI): m/z (relative intensity) 213.0 (M$^+$, 100), 185.0 (19), 92.2 (6), 75.0 (4), 63.0 (17).

2-(4-Chlorophenyl)benzoxazole (Table 3.2, entry 5)$^{15}$

![structure](image)

Eluents (EtOAc: Hexane = 1: 20, R$_f$ = 0.66) was used for flash column chromatography. 41.3 mg, 60 % yield, white solid, $^1$H NMR (400 MHz, CDCl$_3$) δ 7.36-7.40 (m, 2H), 7.51 (d, J= 8.0 Hz, 2H), 7.55-7.61 (m, 1H), 7.76-7.81 (m, 1H), 8.20 (d, J= 8.8 Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 110.6, 120.0, 124.7, 125.3, 125.6, 128.8, 129.2, 137.7, 142.0, 150.7, 162.0; MS (EI): m/z (relative intensity) 229.0 (M$^+$, 100), 201.0 (11), 166.0 (7), 139.0 (3), 111.0 (3).
2-(4-Bromophenyl)benzoxazole (Table 3.2, entry 6)\(^{15}\)

![2-(4-Bromophenyl)benzoxazole](image)

Eluents (EtOAc: Hexane = 1: 20, \(R_f = 0.63\)) was used for flash column chromatography. 48.3 mg, 59 \% yield, white solid, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\)

7.36-7.41 (m, 2H), 7.55-7.61 (m, 1H), 7.68 (d, \(J = 8.4\) Hz, 2H), 7.77-7.80 (m, 1H), 8.13 (d, \(J = 6.8\) Hz, 2H); \(^1^3\)C NMR (100 MHz,CDCl\(_3\)) \(\delta\)

110.6, 120.1, 124.7, 125.3, 126.1, 126.2, 129.0, 132.2, 142.0, 150.7, 162.1; MS (EI): \(m/z\) (relative intensity)

272.9 (M\(^+\), 100), 246.9 (8), 194.0 (9), 166.0 (7), 140.0 (7).

2-(2-Naphthalenyl)benzoxazole (Table 3.2, entry 7)\(^8\)

![2-(2-Naphthalenyl)benzoxazole](image)

Eluents (EtOAc: Hexane = 1: 20, \(R_f = 0.50\)) was used for flash column chromatography. 49.2 mg, 67 \% yield, white solid, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\)

7.37-7.40 (m, 2H), 7.55-7.64 (m, 3H), 7.99 (t, \(J = 7.8\) Hz, 2H), 8.33 (d, \(J = 8.8\) Hz, 1H), 8.78 (s, 1H); \(^1^3\)C NMR (100 MHz,CDCl\(_3\)) \(\delta\)

110.6, 120.0, 123.9, 124.4, 124.6, 125.1, 126.1, 127.7, 127.9, 128.1, 128.7, 128.9, 132.9, 134.7, 142.2, 150.8, 163.2; MS (EI):

\(m/z\) (relative intensity) 245.0 (M\(^+\), 100), 216.0 (6), 153.0 (9), 127.0 (12), 92.0 (3).

2-(4-Methoxyphenyl)benzoxazole (Table 3.2, entry 8)\(^8\)

![2-(4-Methoxyphenyl)benzoxazole](image)

Eluents (EtOAc: Hexane = 1: 20, \(R_f = 0.39\)) was used for flash column chromatography. 35.1 mg, 52 \% yield, white solid, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\)

3.90 (s, 3H), 7.04 (d, \(J = 8.8\) Hz, 2H), 7.31-7.37 (m, 2H), 7.57 (d, \(J = 6.2\) Hz, 1H), 7.76 (d, \(J = 6.0\) Hz, 1H), 8.22 (d, \(J = 8.8\) Hz, 2H); \(^1^3\)C NMR (100 MHz,CDCl\(_3\)) \(\delta\)

55.4, 110.3,
114.3, 119.6, 119.7, 124.4, 124.6, 129.3, 142.2, 150.6, 162.3, 163.1; MS (EI): m/z (relative intensity) 225.0 (M⁺, 100), 206 (34), 182.0 (36), 127.0 (9), 90.0 (1).

2-(4-Methylphenyl)-5-phenylbenzoxazole (Table 3.3, entry 1)₁⁶

Eluents (EtOAc: Hexane = 1: 20, Rf = 0.47) was used for flash column chromatography. 59.9 mg, 70 % yield, white solid, ¹H NMR (400 MHz, CDCl₃) δ 2.47 (s, 3H), 7.35-7.68 (m, 9H), 7.99 (s, 1H), 8.19 (d, J = 7.6 Hz, 2H); ¹³C NMR (100 MHz,CDCl₃) δ 21.6, 110.4, 118.2, 124.3, 124.4, 127.1, 127.4, 127.6, 128.8, 129.6, 138.3, 141.1, 142.1, 142.8, 150.2, 163.8; MS (EI): m/z (relative intensity) 285.1 (M⁺, 100), 207.0 (6), 139.0 (30), 114.0 (2), 89.0 (3).

5-Methyl-2-(4-methylphenyl)benzoxazole (Table 3.3, entry 2)₁⁴

Eluents (EtOAc: Hexane = 1: 20, Rf = 0.50) was used for flash column chromatography. 50.2 mg, 75 % yield, white solid, ¹H NMR (400 MHz, CDCl₃) δ 2.45 (s, 3H), 2.50 (s, 3H), 7.15 (d, J= 8.2 Hz, 1H), 7.33 (d, J= 8.0 Hz, 2H), 7.45 (d, J= 8.0 Hz, 1H), 7.56 (s, 1H), 8.15 (d, J= 8.0 Hz, 2H); ¹³C NMR (100 MHz,CDCl₃) δ 21.5, 21.6, 109.8, 119.7, 124.5, 125.9, 127.5, 129.6, 134.2, 141.8, 142.4, 148.9, 163.4; MS (EI): m/z (relative intensity) 223.0 (M⁺, 100), 194.0 (5), 111.5 (4), 78.0 (16), 51.0 (8).
5-Methyl-2-(2-methylphenyl)benzoxazole (Table 3.3, entry 3)

Eluents (EtOAc: Hexane = 1: 20, Rf = 0.66) was used for flash column chromatography. 48.2 mg, 72 % yield, white solid, m.p. 92-95 °C, 1H NMR (400 MHz, CDCl₃) δ 2.52 (s, 3H), 2.84 (s, 3H), 7.19 (d, J= 8.2 Hz, 1H), 7.35-7.49 (m, 4H), 7.63 (s, 1H), 8.19 (d, J= 6.4 Hz, 1H); 13C NMR (100 MHz,CDCl₃) δ 21.4, 22.1, 109.7, 120.0, 125.9, 126.0, 126.3, 129.8, 130.7, 131.7, 134.1, 138.7, 142.3, 148.5 163.5; MS (EI): m/z (relative intensity) 223.1 (M⁺, 100), 194.0 (14), 180.0 (9), 91.0 (5), 77.0 (12); HRMS (ESI) calcd. for C₁₅H₁₄NO [M + H⁺]: 224.1075, found 224.1072.

5-Methyl-2-(2-naphthalenyl)benzoxazole (Table 3.3, entry 4)

Eluents (EtOAc: Hexane = 1: 20, Rf = 0.49) was used for flash column chromatography. 52.1 mg, 67 % yield, white solid, 1H NMR (400 MHz, CDCl₃) δ 2.52 (s, 3H), 7.19 (d, J= 8.0 Hz, 1H), 7.50 (d, J= 8.4 Hz, 1H), 7.55-7.61 (m, 3H), 7.90 (d, J= 7.6 Hz, 1H), 7.99 (t, J= 8.0 Hz, 2H), 8.32 (d, J= 8.6 Hz, 1H), 8.77 (s, 1H); 13C NMR (100 MHz,CDCl₃) δ 21.5, 109.9, 119.9, 123.9, 124.5, 126.2, 126.8, 127.7, 127.8, 127.9, 128.7, 128.9, 132.9, 134.4, 134.6, 142.4, 149.1, 163.2; MS (EI): m/z (relative intensity) 259.0 (M⁺, 100), 230.0 (5), 153.0 (16), 127.0 (9), 77.0 (11).
5-Fluoro-2-(4-methylphenyl)benzoxazole (Table 3.3, entry 5)\textsuperscript{18}

![Structure of 5-Fluoro-2-(4-methylphenyl)benzoxazole]

Eluents (EtOAc: Hexane = 1: 20, R\textsubscript{f}= 0.51) was used for flash column chromatography. 48.4 mg, 71 % yield, white solid, \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 2.45 (s, 3H), 7.04-7.09 (m, 1H), 7.33 (d, \(J= 8.0\) Hz, 2H), 7.43-7.50 (m, 2H), 8.12 (d, \(J= 8.4\) Hz, 2H); \textsuperscript{13}C NMR (100 MHz,CDCl\textsubscript{3}) \(\delta\) 21.6, 106.1, 106.4, 110.6, 110.7, 112.2, 112.5, 124.1, 127.6, 129.7, 142.4, 142.9, 143.1, 147.0, 158.9, 161.3, 165.0; \textsuperscript{19}F NMR (400 MHz,CDCl\textsubscript{3}) \(\delta\) -117.9; MS (EI): \textit{m/z} (relative intensity) 227.0 (M\textsuperscript{+}, 100), 198.0 (5), 116.0 (4), 91.0 (15), 63.0 (7).

5-Chloro-2-(4-methylphenyl)benzoxazole (Table 3.3, entry 6)\textsuperscript{14}

![Structure of 5-Chloro-2-(4-methylphenyl)benzoxazole]

Eluents (EtOAc: Hexane = 1: 20, R\textsubscript{f}= 0.53) was used for flash column chromatography. 52.6 mg, 72 % yield, white solid, \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 2.45 (s, 3H), 7.29-7.34 (m, 3H), 7.47 (d, \(J= 8.4\) Hz, 1H), 7.73 (s, 1H), 8.12 (d, \(J= 8.0\) Hz, 2H); \textsuperscript{13}C NMR (100 MHz,CDCl\textsubscript{3}) \(\delta\) 21.7, 111.1, 119.8, 123.9, 125.1, 127.7, 129.7, 129.9, 142.5, 143.3, 149.2, 164.6; \textsuperscript{19}F NMR (400 MHz,CDCl\textsubscript{3}) \(\delta\) -117.9; MS (EI): \textit{m/z} (relative intensity) 243.0 (M\textsuperscript{+}, 100), 215.0 (3), 116.0 (4), 91.0 (17), 63.0 (23).
1,3,7-Trimethyl-8-(4-tolyl)-xanthine (Scheme 3.3, compound 1)\textsuperscript{14}

Eluents (EtOAc: Hexane = 1: 20, \( R_f = 0.44 \)) was used for flash column chromatography. 53.7 mg, 63 \% yield, white solid, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 2.44 (s, 3H), 3.43 (s, 3H), 3.62 (s, 3H), 4.05 (s, 3H), 7.33 (d, \( J = 7.6 \text{ Hz}, 2\text{H} \)), 7.58 (d, \( J = 8.4 \text{ Hz}, 2\text{H} \)); \(^{13}\)C NMR (100 MHz,CDCl\(_3\)) \( \delta \) 21.4, 27.8, 29.7, 33.8, 108.3, 125.4, 128.9, 129.5, 140.6, 148.2, 151.6, 152.2, 155.4; MS (EI): \( m/z \) (relative intensity) 284.1 (\( M^+ \), 100), 255.0 (4), 226.0 (5), 184.0 (5), 82.0 (30).

2-Phenylbenzothiazole (Scheme 3.3, compound 2)\textsuperscript{14}

Eluents (EtOAc: Hexane = 1: 20, \( R_f = 0.64 \)) was used for flash column chromatography. 42.4 mg, 67 \% yield, white solid, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.41 (t, \( J = 7.0 \text{ Hz}, 1\text{H} \)), 7.50-7.55 (m, 4H), 7.93 (d, \( J = 8.0 \text{ Hz}, 1\text{H} \)), 8.11-8.15 (m, 3H); \(^{13}\)C NMR (100 MHz,CDCl\(_3\)) \( \delta \) 121.6, 123.2, 125.2, 126.3, 127.5, 129.0, 130.9, 133.6, 135.0, 154.1, 168.0; MS (EI): \( m/z \) (relative intensity) 211.0 (\( M^+ \), 100), 184.0 (4), 167.0 (5), 108.0 (20), 69.0 (13).

2-(4-Methylphenyl)benzothiazole (Scheme 3.3, compound 3)\textsuperscript{14}

Eluents (EtOAc: Hexane = 1: 20, \( R_f = 0.59 \)) was used for flash column chromatography. 46.6 mg, 69 \% yield, white solid, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 2.45 (s, 3H), 3.72 (d, \( J = 8.0 \text{ Hz}, 2\text{H} \)), 7.39 (t, \( J = 7.0 \text{ Hz}, 1\text{H} \)), 7.51 (t, \( J = 7.2 \text{ Hz}, 1\text{H} \)), 7.91 (d, \( J = 7.8 \text{ Hz}, 1\text{H} \)), 8.01 (d, \( J = 8.0 \text{ Hz}, 2\text{H} \)), 8.10 (d, \( J = 8.0 \text{ Hz}, 1\text{H} \)); \(^{13}\)C NMR
(100 MHz, CDCl₃) δ 21.5, 121.6, 123.1, 125.0, 126.2, 127.5, 129.7, 131.0, 135.0, 141.4, 154.2, 168.2; MS (EI): m/z (relative intensity) 225.0 (M⁺, 100), 108.0 (7), 91.0 (4), 68.9 (8), 51.0 (2).

3.5 References


Chapter 4 Copper-Mediated C-3 Cyanation of Indole Derivatives
using Benzyl Cyanide as cyanating agent

4.1 Introduction

Indole scaffold is exemplified as an important subunit not only in pharmaceutical and agrochemical products, but also basic constituents of dyes and herbicides. In particular, 3-cyanoindole is a key building block in pharmaceutical syntheses that can be applied in medicinal chemistry and drug discovery. With the nitrile moiety, further transformations of this group into a broad range of functional groups, such as amines, aldehydes, acids, amides, ketones and heterocycles, can be made. In fact, 3-cyanoindole scaffold containing structures have been well-known for their uses as therapeutic estrogen receptor ligand, acetyl-CoA carboxylase inhibitors for type 2 diabetes, xanthine-oxidase inhibitors, antiviral hepatitis C virus inhibitors, aldosterone synthase modulator for cardiovascular diseases, anticancer agents, and antithrombotics factor Xa inhibitors (Figure 4.1).
Aryl nitriles are generally prepared from classical organic transformations, such as Sandmeyer and Rosenmund-von Braun reaction, in which pre-functionalized starting materials are often required. Palladium- and copper-catalyzed cyanation of aryl halides and sulfonates are also well documented methods. Yet, there has been no example reported for the conversion of 3-bromoindole to 3-cyanoindole. In fact, organic transformations from modified Madelung reaction, metal-free oxidative synthesis from N-aryl enamines, palladium-catalyzed N-heterocyclization and propylphosphonic anhydride-promoted conversion of aldehydes are alternative approaches to afford 3-cyanoindoles. Indeed, emerging methods for facile synthesis of 3-cyanoindoles using direct C-H functionalization protocol are highly desirable. Lewis acid, Fe, Cu and Pd salts are usually employed as the catalyst for accessing 3-cyanoindole using various metal cyanides and other cyanide anion (CN⁻) surrogates.

Nevertheless, most commonly available metal cyanides are extremely toxic. Although K₄[Fe(CN)₆] is exceptionally non-toxic, its low solubility in organic solvent limited its applicability. Despite these limited CN⁻ sources, an exploration of other user-friendly organic CN⁻ source for direct cyanation of indole would be highly favorable. In the recent years, Wang and co-workers firstly reported palladium-catalyzed cyanation of aryl halides, Copper-mediated cyanation of arenes, aryl halides, indole derivatives and arylboronic acids using benzyl cyanide as a CN⁻ surrogate. This notable reagent is commercially available, hazardless, inexpensive and highly soluble in common organic solvents. In view of the beneficial features associating with this CN⁻ source as well as our current interest in cyanation reactions, herein we disclose our efforts on copper-mediated direct
cyanation of indole using benzyl cyanide in a highly regioselective manner.

4.2 Results and discussion

4.2.1 Preliminary evaluation of copper-mediated direct C3-cyanation of indole derivatives

In order to achieve the C-3 indole functionalization for cyanation, a series of reaction parameter optimization were deployed (Table 4.1). N-Methylindole was chosen as the benchmark substrate. Commercially available copper salts were investigated (Table 4.1, entries 2-8). CuI showed successful cyanation of indole while other Cu complexes did not. A screening of solvent revealed that DMF was the solvent of choice (Table 4.1, entries 6, 9-12). When the reaction temperature was increased from 110 °C to 130 °C and the reaction time was extended to 24 h, the product yield was improved (Table 4.1, entries 1 and 2, 2 and 6).

Table 4.1 Initial optimization of direct C3-cyanation of N-methylindole\[a\]

<table>
<thead>
<tr>
<th>entry</th>
<th>[Cu] (equiv.)</th>
<th>solvent</th>
<th>time (h)</th>
<th>% yield[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1[^{[c]}]</td>
<td>CuI (1)</td>
<td>DMF</td>
<td>20</td>
<td>Trace</td>
</tr>
<tr>
<td>2</td>
<td>CuI (1)</td>
<td>DMF</td>
<td>20</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>Cu(_2)O (1)</td>
<td>DMF</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OAc) (1)</td>
<td>DMF</td>
<td>20</td>
<td>Trace</td>
</tr>
<tr>
<td></td>
<td>Copper Source</td>
<td>Solvent</td>
<td>Temp (°C)</td>
<td>Yield</td>
</tr>
<tr>
<td>----</td>
<td>--------------</td>
<td>---------</td>
<td>-----------</td>
<td>-------</td>
</tr>
<tr>
<td>5</td>
<td>Cu(OAc)_2 (1)</td>
<td>DMF</td>
<td>20</td>
<td>Trace</td>
</tr>
<tr>
<td>6</td>
<td>CuI (1)</td>
<td>DMF</td>
<td>24</td>
<td>89</td>
</tr>
<tr>
<td>7</td>
<td>CuBr (1)</td>
<td>DMF</td>
<td>24</td>
<td>Trace</td>
</tr>
<tr>
<td>8</td>
<td>CuCl (1)</td>
<td>DMF</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>CuI (1)</td>
<td>CH_3CN</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>CuI (1)</td>
<td>DMSO</td>
<td>24</td>
<td>Trace</td>
</tr>
<tr>
<td>11</td>
<td>CuI (1)</td>
<td>toluene</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>CuI (1)</td>
<td>DMSO</td>
<td>24</td>
<td>Trace</td>
</tr>
<tr>
<td>13</td>
<td>CuI (1)</td>
<td>DMF</td>
<td>24</td>
<td>79</td>
</tr>
<tr>
<td>14</td>
<td>CuI (1.5)</td>
<td>DMF</td>
<td>24</td>
<td>91</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: copper source (0.5 mmol, 1 equiv), N-methylindole (0.5 mmol), PhCH_2CN (0.75 mmol) and solvent (2.0 mL) were stirred under air at 130 °C for indicated period of time. [b] Calibrated GC yields were reported using pentadecane as the internal standard. [c] 110 °C was used. [d] 140 °C was used.

### 4.2.2 Scope of copper-mediated direct C3-cyanation of indole derivatives

Having the optimized reaction conditions in hand, we next examined the substrate scope of this cyanation reaction (Table 4.2). N-Alkylated indoles proceeded smoothly to give the corresponding products in good yields (Table 4.2, entries 1-2). Allyl group remained intact during the course of the reaction (Table 4.2, entry 3). Disappointingly, unprotected NH indole showed poor conversion under these reaction conditions (Table 4.2, entry 4). It is possibly due to the decomposition of unprotected indole. N-Arylindoles were also tested (Table 4.2, entries 5-7). Moderate yields were generally obtained.
Table 4.2 Copper-mediated direct C3-cyanation of indoles\textsuperscript{[a]}

<table>
<thead>
<tr>
<th>entry</th>
<th>indole</th>
<th>product</th>
<th>time (h)</th>
<th>% yield\textsuperscript{[b]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Indole 1" /></td>
<td><img src="image2" alt="Product 1" /></td>
<td>24 h</td>
<td>86</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Indole 2" /></td>
<td><img src="image4" alt="Product 2" /></td>
<td>24 h</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Indole 3" /></td>
<td><img src="image6" alt="Product 3" /></td>
<td>24 h</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Indole 4" /></td>
<td><img src="image8" alt="Product 4" /></td>
<td>24 h</td>
<td>17</td>
</tr>
<tr>
<td>5\textsuperscript{[c]}</td>
<td><img src="image9" alt="Indole 5" /></td>
<td><img src="image10" alt="Product 5" /></td>
<td>48 h</td>
<td>60</td>
</tr>
<tr>
<td>6\textsuperscript{[c]}</td>
<td><img src="image11" alt="Indole 6" /></td>
<td><img src="image12" alt="Product 6" /></td>
<td>46 h</td>
<td>66</td>
</tr>
<tr>
<td>7\textsuperscript{[c]}</td>
<td><img src="image13" alt="Indole 7" /></td>
<td><img src="image14" alt="Product 7" /></td>
<td>48 h</td>
<td>57</td>
</tr>
</tbody>
</table>
[a] Reaction conditions: CuI (0.5 mmol), N-substituted indole (0.5 mmol), PhCH$_2$CN (0.75 mmol) and DMF (2.0 mL) were stirred under air at 130 °C for indicated time. 

[b] Isolated yield. [c] 1.5 equiv. of CuI was used.

To further test the generality of the reaction system, a series of substituted N-benzylindoles was probed in this cyanation system (Table 4.3). Functional groups such as fluoro, chloro, and methoxy were compatible under these reaction conditions (Table 4.3, entries 2-4). The intact chloro group is beneficial for later functionalization using other coupling protocols.$^{24}$ In fact, these nitrile containing products can undergo further organic transformations to afford a variety of potential xanthine oxidase inhibitors, HCV inhibitors and therapeutic estrogen receptor ligands.$^{3,5,6}$ N-Benzylindoles with 5- and 7-substituents furnished the desired product smoothly with extended reaction times (Table 4.3, entries 5-7). Azaindole and sterically hindered 2-methyl-N-benzylindole were found to be feasible substrates for the cyanation (Table 4.3, entries 8 and 9).
Table 4.3 Copper-mediated direct C3-cyanation of benzylindoles\[^{[a]}\]

<table>
<thead>
<tr>
<th>entry</th>
<th>indole</th>
<th>product</th>
<th>time</th>
<th>% yield[^{[b]}]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Indole 1" /></td>
<td><img src="image2" alt="Product 1" /></td>
<td>24 h</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Indole 2" /></td>
<td><img src="image4" alt="Product 2" /></td>
<td>24 h</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Indole 3" /></td>
<td><img src="image6" alt="Product 3" /></td>
<td>28 h</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Indole 4" /></td>
<td><img src="image8" alt="Product 4" /></td>
<td>28 h</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Indole 5" /></td>
<td><img src="image10" alt="Product 5" /></td>
<td>49 h</td>
<td>77</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11" alt="Indole 6" /></td>
<td><img src="image12" alt="Product 6" /></td>
<td>46 h</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td><img src="image13" alt="Indole 7" /></td>
<td><img src="image14" alt="Product 7" /></td>
<td>46 h</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td><img src="image15" alt="Indole 8" /></td>
<td><img src="image16" alt="Product 8" /></td>
<td>6 h</td>
<td>65</td>
</tr>
<tr>
<td>g[^{[c]}]</td>
<td><img src="image17" alt="Indole g" /></td>
<td><img src="image18" alt="Product g" /></td>
<td>48 h</td>
<td>56</td>
</tr>
</tbody>
</table>

\[^{[a]}\] Reaction conditions: CuI (0.5 mmol), substituted benzylindole (0.5 mmol),
PhCH$_2$CN (0.75 mmol) and DMF (2.0 mL) were stirred under air at 130 °C for indicated time. [b] Isolated yield. [c] 1.5 equiv. of CuI was used.

Highly sterically congested 2-aryl-\(N\)-methylinondoles were applicable substrates for direct cyanation (Scheme 4.1). 2-(1-Naphthyl)-\(N\)-methylindoled afforded the desired product in lower yield presumably due to the large steric hindrance of the \textit{ortho}-naphthyl moiety.

![Scheme 4.1](image)

**Scheme 4.1** Copper-mediated direct C3-cyanation of \(N\)-methyl indoles (reaction conditions were the same as in Table 4.2, entry 5). [a] 1.0 mmol PhCH$_2$CN was used.

Other heteroarenes were used as substrates in this optimized reaction condition (Scheme 4.2). However, no desired products could be obtained.

![Scheme 4.2](image)

**Scheme 4.2** Unsuccessful examples of copper-mediated direct cyanation of heteroarenes (Reaction conditions were same as Table 4.2, entry 1)

4.3 Conclusion

In summary, we have developed a simple protocol for facile preparation of 3-cyanotindoles. Inexpensive reaction system, copper(I) iodide and benzyl cyanide, is found effective to promote regioselective cyanation of indoles in open-to-air vessel.
This protocol potentially provides a more direct and complementary access of pharmaceutically useful intermediates.

4.4 Experimental section

4.4.1 General considerations

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. All cyanations were performed in an open vessel, a vial (approx. 60 mL volume), fitted with an air condenser and equipped with Teflon coated magnetic stir bar (4 mm x 10 mm). All indole derivatives except indole, N-methylinole and N-methyl-2-phenylindole, were synthesized according to the literature methods. Thin layer chromatography was performed on Merck precoated silica gel 60 F plates. Silica gel (Merck, 70-230 and 230-400 mesh) was used for column chromatography. Melting points were recorded on an uncorrected Büchi Melting Point B-545 instrument. NMR spectra were recorded on a Bruker spectrometer (400 MHz for $^1$H, 100 MHz for $^{13}$C and 376 MHz for $^{19}$F). Spectra were referenced internally to the residual proton resonance in CDCl$_3$ ($\delta$ 7.26 ppm), or with tetramethylsilane (TMS, $\delta$ 0.00 ppm) as the internal standard. Chemical shifts ($\delta$) were reported as part per million (ppm) in $\delta$ scale downfield from TMS. $^{13}$C NMR spectra were referenced to CDCl$_3$ ($\delta$ 77.0 ppm, the middle peak). $^{19}$F NMR chemical shifts were determined relative to CFCl$_3$ as the external standard and low field is positive. Coupling constants ($J$) were reported in Hertz (Hz). Mass spectra (EI-MS and ES-MS) were recorded on a HP 5989B Mass Spectrometer. High-resolution mass spectra (HRMS) were obtained on a Bruker APEX 47e FTICR mass spectrometer (ESI-MS). GC-MS analysis was conducted on a HP 5973 GCD system using a HP5MS column (30 m $\times$ 0.25 mm). The products described in GC...
yield were accorded to the authentic samples/dodecane calibration standard from HP 6890 GC-FID system. All yields reported refer to isolated yield of compounds estimated to be greater than 95% purity as determined by capillary gas chromatography (GC) or $^1$H NMR. Compounds described in the literature were characterized by comparison of their $^1$H, $^{13}$C and/or $^{19}$F NMR spectra to the previously reported data. The procedures in this section are representative, and thus the yields may differ from those reported in tables.

4.4.2 General procedure for reaction condition screenings

All reagents were weighted in air and the reactions were performed in an open-to-air vessel. Copper salt (0.25-0.75 mmol), $N$-methylindole (0.5 mmol) and PhCH$_2$CN (0.75 mmol) were loaded into a 60 mL vial equipped with a Teflon-coated magnetic stir bar. The solvent (2 mL) was added at room temperature. The vial was fitted with an air condenser and then placed into a preheated oil bath with vigorous stirring for the indicated time. After the completion of reaction, the vial was allowed to cool at room temperature. Ethyl acetate (~20 mL) and pentadecane (internal standard) were added. The organic layer was subjected to GC analysis.

4.4.3 General procedure for cyanation of indoles with benzyl cyanide

Copper(I) iodide (0.5-0.75 mmol), PhCH$_2$CN (0.75-1.0 mmol), indole derivatives (0.5 mmol) and DMF (2.0 mL) were loaded into a 60 mL vial equipped with an air condenser and Teflon-coated magnetic stir bar under air. The vial was then placed into a preheated oil bath which the temperature was indicated in the table and vigorously stirred in an open system for the indicated time. After the
completion of reaction, the reaction vial was allowed to cool at room temperature. Ethyl acetate (~20 mL) was added for dilution. The organic layer was subjected to GC analysis. After analyzing GC spectra, the crude product was further extracted with ethyl acetate (2 x 10 mL). The filtrate was concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel to afford the desired product.

4.4.4 Characterization data of substituted cyanoidole products

1-Methyl-1H-indole-3-carbonitrile (Table 4.2, entry 1)

![Methyl-1H-indole-3-carbonitrile](image)

Eluents (DCM: Hexane = 1: 1, R_f = 0.5) was used for flash column chromatography. 67.1 mg, 86 % yield, brown liquid, ^1^H NMR (400 MHz, CDCl_3) δ 3.85 (s, 3H), 7.29-7.42 (m, 3H), 7.55 (s, 1H), 7.76 (d, J = 7.6 Hz, 1H); ^13^C NMR (100 MHz, CDCl_3) δ 33.6, 85.3, 110.3, 115.9, 122.1, 123.8, 127.7, 135.5, 136.0.

1-Isopropyl-1H-indole-3-carbonitrile (Table 4.2, entry 2)

![1-Isopropyl-1H-indole-3-carbonitrile](image)

Eluents (DCM: Hexane = 1: 1, R_f = 0.35) was used for flash column chromatography. 64.4 mg, 70 % yield, brown liquid, ^1^H NMR (400 MHz, CDCl_3) δ 1.59 (d, J = 6.8 Hz, 6H), 4.70-4.77 (m, 1H), 7.29-7.38 (m, 2H), 7.48 (d, J = 8.0 Hz, 1H), 7.74 (s, 1H), 7.78
(d, J= 7.6 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 22.6, 48.4, 85.6, 110.7, 116.2, 119.9, 122.1, 123.6, 128.0, 131.2, 135.0; HRMS (ESI) calcd. for C$_{12}$H$_{13}$N$_2$[M + H$^+$]: 185.1079, found 185.1083.

1-Allyl-1H-indole-3-carbonitrile (Table 4.2, entry 3)$^{17i}$

![1-Allyl-1H-indole-3-carbonitrile](image)

Eluents (DCM: Hexane = 1: 1, R$_f$= 0.35) was used for flash column chromatography. 64.4 mg, 73 % yield, brown liquid, $^1$H NMR (400 MHz, CDCl$_3$) δ 4.79 (d, J= 5.6 Hz, 2H), 5.18 (d, J= 17.2 Hz, 1H), 5.33 (d, J= 10.4 Hz, 1H), 5.96-6.06 (m, 1H), 7.30-7.39 (m, 2H), 7.42 (d, J= 7.4 Hz, 1H), 7.63 (s, 1H), 7.79 (d, J= 7.6 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 49.4, 86.0, 110.7, 115.8, 119.0, 119.9, 122.2, 123.8, 127.9, 131.6, 134.6, 135.4.

$^{17i}$

1H-Indole-3-carbonitrile (Table 4.2, entry 4)$^{17i}$

![1H-Indole-3-carbonitrile](image)

Eluents (DCM: Hexane = 6: 1, R$_f$= 0.20) was used for flash column chromatography. 12.1 mg, 17 % yield, yellow solid, $^1$H NMR (400 MHz, CDCl$_3$) δ 7.31-7.42 (m, 2H), 7.51 (d, J= 8.4 Hz, 1H), 7.76 (s, 1H), 7.81 (d, J= 6.4 Hz, 1H), 8.86 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 87.5, 112.0, 115.7, 119.6, 122.3, 124.3, 126.9, 131.7, 134.8.
1-Phenyl-1H-indole-3-carbonitrile (Table 4.2, entry 5)\textsuperscript{17i}

![1Phenyl-1H-indole-3-carbonitrile](image)

Eluents (DCM: Hexane = 1: 1, R\textsubscript{f}= 0.5) was used for flash column chromatography. 65.4 mg, 60 % yield, light orange solid, \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.35-7.39 (m, 2H), 7.49-7.56 (m, 4H), 7.59-7.63 (m, 2H), 7.82 (s, 1H), 7.84-7.86 (m, 1H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 88.0, 111.5, 115.4, 119.9, 122.7, 124.5, 124.8, 127.9, 128.3, 130.0, 134.6, 135.5, 137.2.

1-(4-Methoxyphenyl)-1H-indole-3-carbonitrile (Table 4.2, entry 6)\textsuperscript{17i}

![1-(4-Methoxyphenyl)-1H-indole-3-carbonitrile](image)

Eluents (DCM: Hexane = 1: 1, R\textsubscript{f}= 0.25) was used for flash column chromatography. 81.8 mg, 66 % yield, white solid, \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 3.92 (s, 3H), 7.09 (d, \(J= 8.8\) Hz, 2H), 7.34-7.36 (m, 2H), 7.40 (d, \(J= 8.8\) Hz, 2H), 7.43-7.46 (m, 1H), 7.76 (s, 1H), 7.82-7.84 (m, 1H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 55.6, 87.4, 111.4, 115.0, 115.6, 119.8, 122.5, 124.3, 126.3, 127.7, 130.5, 134.9, 136.0, 159.4.
1-(3,5-Dimethylphenyl)-5-methoxy-1H-indole-3-carbonitrile (Table 4.2, entry 7)

![Chemical Structure](image)

Eluents (DCM: Hexane = 1: 1, R_f = 0.25) was used for flash column chromatography. 78.7 mg, 57 % yield, light orange solid, m.p. 140.7 – 141.8 °C, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.43 (s, 6H), 3.91 (s, 3H), 6.97 (d, \(J = 8.8\) Hz, 1H), 7.08 (s, 2H), 7.11 (s, 1H), 7.23 (s, 1H), 7.41 (d, \(J = 8.8\) Hz, 1H), 7.72 (s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 21.3, 55.8, 87.2, 100.8, 112.7, 115.1, 122.3, 128.9, 129.9, 130.5, 134.5, 137.8, 139.9, 156.3; HRMS (ESI) calcd. for C\(_{18}\)H\(_{17}\)N\(_2\)O [M + H\(^+\)]: 277.1341, found 277.1332.

1-Benzyl-1H-indole-3-carbonitrile (Table 4.3, entry 1)\(^{17i}\)

![Chemical Structure](image)

Eluents (DCM: Hexane = 1: 1, R_f = 0.5) was used for flash column chromatography. 95.1 mg, 82 % yield, brown liquid, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.36 (s, 2H), 7.16-7.19 (m, 2H), 7.32-7.41 (m, 6H), 7.62 (s, 1H), 7.80-7.82 (m, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 50.8, 86.1, 110.7, 119.9, 122.2, 123.9, 127.0, 127.9, 128.3, 129.0, 134.9, 135.1, 135.5.
1-Benzyl-5-methoxy-1H-indole-3-carbonitrile (Table 4.3, entry 2)\textsuperscript{26}

\[
\text{MeO} \quad \overset{\text{CN}}{\text{\textsuperscript{N}Bn}}
\]

Eluents (DCM: Hexane = 1: 1, R\textsubscript{f} = 0.2) was used for flash column chromatography.

102.2 mg, 78 % yield, white solid, \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 3.88 (s, 3H), 5.30 (m, 2H), 6.95 (dd, \(J\) = 2.4, 9.2 Hz, 1H), 7.14-7.17 (m, 2H), 7.19 (s, 1H), 7.24 (d, \(J\) = 9.2 Hz, 1H), 7.34-7.37 (m, 3H), 7.56 (s, 1H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 50.9, 55.6, 85.5, 100.8, 111.7, 114.6, 126.9, 128.3, 128.8, 129.0, 130.4, 134.8, 135.2, 156.0.

1-Benzyl-5-fluoro-1H-indole-3-carbonitrile (Table 4.3, entry 3)

\[
\text{F} \quad \overset{\text{CN}}{\text{\textsuperscript{N}Bn}}
\]

Eluents (DCM: Hexane = 1: 1, R\textsubscript{f} = 0.25) was used for flash column chromatography.

77.5 mg, 62 % yield, orange solid, m.p. 93.4-95.2 \textdegree C, \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 5.35 (s, 2H), 7.05 (td, \(J\) = 2.4, 8.8 Hz, 1H), 7.17 (d, \(J\) = 6.8 Hz, 2H), 7.29-7.34 (m, 1H), 7.36-7.42 (m, 4H), 7.65 (s, 1H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 51.1, 86.1, 104.9, 105.2, 111.9, 112.5, 112.8, 115.2, 127.0, 128.5, 129.1, 132.0, 134.8, 136.1, 157.9, 160.3; \textsuperscript{19}F NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) -120.3; HRMS (ESI) calcd. for C\textsubscript{16}H\textsubscript{11}N\textsubscript{2}F [M + Na\textsuperscript{+}]: 273.0804, found 273.0810.
1-Benzyl-5-chloro-1H-indole-3-carbonitrile (Table 4.3, entry 4)

![Chemical Structure Image]

Eluents (DCM: Hexane = 1: 1, R_f = 0.4) was used for flash column chromatography. 97.3 mg, 73 % yield, orange solid, m.p. 117.9-120.0 °C, ¹H NMR (400 MHz, CDCl₃) δ 5.35 (s, 2H), 7.15 (d, J= 6.0 Hz, 2H), 7.25-7.31 (m, 2H), 7.36-7.41 (m, 3H), 7.63 (s, 1H), 7.75 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 51.0, 85.7, 112.0, 115.0, 119.2, 124.4, 127.0, 128.2, 128.5, 128.8, 129.1, 133.8, 134.7, 135.9; HRMS (ESI) calcd. for C₁₆H₁₂N₂Cl [M + H⁺]: 267.0689, found 267.0684.

1-Benzyl-5-methyl-1H-indole-3-carbonitrile (Table 4.3, entry 5)¹³d

![Chemical Structure Image]

Eluents (DCM: Hexane = 1: 1, R_f = 0.45) was used for flash column chromatography. 94.5 mg, 77 % yield, light orange solid, ¹H NMR (400 MHz, CDCl₃) δ 2.50 (s, 3H), 5.33 (s, 2H), 7.14-7.17 (m, 3H), 7.26 (d, J= 8.4 Hz, 1H), 7.34-7.39 (m, 3H), 7.58 (d, J= 7.2 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 21.4, 50.9, 85.6, 110.5, 116.0, 119.6, 125.7, 127.1, 128.3, 128.4, 129.1, 132.1, 134.0, 134.9, 135.4.
1-Benzyl-7-methoxy-1H-indole-3-carbonitrile (Table 4.3, entry 6)

Eluents (DCM: Hexane = 1: 1, Rf= 0.2) was used for flash column chromatography. 90.4 mg, 69 % yield, light orange solid, m.p. 142.8-146.9 °C, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.89 (s, 3H), 5.66 (s, 2H), 6.75 (d, \(J=\) 8.0 Hz, 1H), 7.15 (d, \(J=\) 7.2 Hz, 2H), 7.21 (t, \(J=\) 8.0 Hz, 1H), 7.31-7.38 (m, 4H), 7.50 (s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 53.4, 55.4, 86.4, 104.7, 112.3, 115.8, 122.9, 125.4, 126.9, 127.9, 128.8, 130.2, 135.4, 137.2, 147.9; HRMS (ESI) calcd. for C\(_{17}\)H\(_{15}\)N\(_2\)O [M + H\(^+\)]: 263.1184, found 263.1191.

1-Benzyl-7-methyl-1H-indole-3-carbonitrile (Table 4.3, entry 7)

Eluents (DCM: Hexane = 1: 1, Rf= 0.45) was used for flash column chromatography. 71.3 mg, 58 % yield, yellow solid, m.p. 153.7-154.5 °C, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.57 (s, 3H), 5.63 (s, 2H), 6.97 (d, \(J=\) 7.2 Hz, 2H), 7.04 (d, \(J=\) 7.2 Hz, 1H), 7.20 (t, \(J=\) 7.6 Hz, 1H), 7.32-7.38 (m, 3H), 7.56 (s, 1H), 7.67 (d, \(J=\) 8.0 Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 19.2, 52.9, 86.4, 115.6, 117.9, 122.1, 122.4, 125.5, 126.8, 128.0, 128.9, 129.1, 130.7, 134.4, 136.4, 137.1; HRMS (ESI) calcd. for C\(_{17}\)H\(_{15}\)N\(_2\) [M + H\(^+\)]: 247.1235, found 247.1226.
1-Benzyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (Table 4.3, entry 8)

Eluents (DCM: Hexane = 1: 1, R_f= 0.2) was used for flash column chromatography. 
75.7 mg, 65 % yield, yellow solid, m.p. 90.3-91.6 °C, ^1^H NMR (400 MHz, CDCl$_3$) δ 
5.56 (s, 2H), 7.28-7.38 (m, 6H), 7.71 (s, 1H), 8.12 (dd, J= 1.6, 6.4 Hz, 1H), 8.51 (dd, 
J= 1.6, 4.8 Hz, 1H); ^13^C NMR (100 MHz, CDCl$_3$) δ 48.7, 85.0, 118.3, 120.1, 127.9, 
128.4, 128.5, 129.0, 134.9, 135.6, 145.2, 146.4; HRMS (ESI) calcd. for C$_{15}$H$_{12}$N$_3$ [M 
+ H$^+$]: 234.1031, found 234.1041.

1-Benzyl-2-methyl-1H-indole-3-carbonitrile (Table 4.3, entry 9)$^{17d}$

Eluents (DCM: Hexane = 1: 1, R_f= 0.45) was used for flash column chromatography. 
68.9 mg, 56 % yield, yellow liquid, ^1^H NMR (400 MHz, CDCl$_3$) δ 2.55 (s, 3H), 5.35 
(s, 2H), 7.00 (d, J= 6.4 Hz, 2H), 7.26-7.33(m, 6H), 7.73 (d, J= 7.2 Hz, 1H); ^13^C NMR 
(100 MHz, CDCl$_3$) δ 12.1, 47.3, 85.7, 110.3, 116.5, 119.1, 122.2, 123.4, 126.0, 127.2, 
128.0, 129.1, 135.7, 136.2, 145.8.
1-Methyl-2-phenyl-1H-indole-3-carbonitrile (Scheme 4.1, compound 1) \(^{17h}\)

![Chemical Structure](image)

Eluents (DCM: Hexane = 1: 1, \(R_f = 0.4\)) was used for flash column chromatography. 88.2 mg, 76 % yield, yellow liquid, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.76 (s, 3H), 7.37-7.44 (m, 3H), 7.58 (s, 5H), 7.80 (s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 31.6, 85.2, 110.5, 119.2, 122.2, 123.7, 127.4, 128.5, 128.8, 129.7, 136.7, 147.9.

1-Methyl-2-(o-tolyl)-1H-indole-3-carbonitrile (Scheme 4.1, compound 2)

![Chemical Structure](image)

Eluents (DCM: Hexane = 1: 1, \(R_f = 0.6\)) was used for flash column chromatography. 73.8 mg, 60 % yield, yellow solid, m.p. 113.9-114.9 °C, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.26 (s, 3H), 3.60 (s, 3H), 7.34-7.44 (m, 5H), 7.46-7.50 (m, 2H), 7.83 (d, \(J = 8.4\) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 19.7, 31.0, 86.2, 110.6, 116.3, 119.5, 122.4, 123.7, 126.2, 127.5, 128.4, 130.3, 130.6, 130.7, 136.4, 138.0, 148.1; HRMS (ESI) calcd. for C\(_{17}\)H\(_{15}\)N\(_2\) [M + H\(^+\)]: 247.1235, found 247.1229.
1-Methyl-2-(naphthalen-1-yl)-1H-indole-3-carbonitrile (Scheme 4.1, compound 3)\textsuperscript{17k}

Eluents (DCM: Hexane = 1: 1, R\textsubscript{f} = 0.45) was used for flash column chromatography. 70.8 mg, 50 % yield, orange liquid, \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 3.55 (s, 3H), 7.39-7.44 (m, 1H), 7.46-7.55 (m, 4H), 7.59 (t, \( J = 7.6 \) Hz, 1H), 7.65-7.67 (m, 2H), 7.89 (d, \( J = 7.8 \) Hz, 1H), 8.00 (d, \( J = 8.0 \) Hz, 1H), 8.08 (m, 1H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \( \delta \) 31.5, 110.5, 119.7, 122.5, 123.9, 124.9, 125.4, 126.6, 127.5, 128.8, 129.6, 130.8, 133.6.

4.5 References


(4) Barnes, D. W.; Bebernitx, G. R.; Clairmont, K.; Cohen, S. L.; Damon, Robert


Chapter 5 Palladium-Catalyzed Direct Arylation of Polyfluoroarenes with Heteroaryl and Aryl Chlorides

5.1 Introduction

Heterobiaryl motifs are commonly found in biologically active compounds, natural products, pharmaceutically effective molecules and functional materials. Particularly, 2-substituted nitrogen-containing compounds constitute high relevance in pharmaceutical chemistry and material sciences.\(^1\) For examples, polymer and hybrid electron accepting materials based on semiconducting perfluorophenylquinoline (P5FQ),\(^2\) the sensitization of TiO\(_2\) nanoparticles and electrodes with perfluoroaryl motif in organic semiconducting dye for photochemical applications (Ph5FQ-TiO\(_2\))\(^3\), and betaine dyes for determination of solvent polarity (eicosanfluoro (F\(_{20}\))-substituted betaine dye) (Figure 5.1)

![Figure 5.1 Examples of useful heteroaryl-perfluoroaryl-containing molecules](image)

Transition metal-catalyzed cross-coupling constitutes as useful method for connecting two aromatic building blocks together. However, integrating an electron-deficient aromatic fragment to the target molecule has encountered difficulty.
For instance, the general use of highly electron-deficient nucleophilic partners (e.g. C₆F₅B(OH)₂) are still problematic. Those challenges may arise from: (1) the preparation of highly electron-deficient nucleophiles is not straightforward;⁴ (2) electron-deficient heteroaryl and polyfluoroaryl nucleophiles often undergo transmetallation process at a relatively slower rate; and (3) electron-deficient aryloboronic acids are moderately stable and usually decompose via rapid protodeboronation during the course of coupling reactions. Indeed, these problematic issues must be tackled in order to afford target product in a better yield.⁴,⁵ One of the usual solutions is to circumvent the selection of relatively electron-deficient arene as the nucleophilic partner between two coupling components (Scheme 5.1). Nevertheless, this strategy would become a challenge, if both of the coupling partners are electron-deficient aromatics (Scheme 5.1). Hence, effort in seeking efficient protocol for obtaining electron-deficient biaryls is indeed demanded.

Scheme 5.1 Advantages and limitations of interchanging nucleophile strategy
Direct C-H arylation of polyfluoroarenes is an excellent alternative to conventional cross-coupling reactions when heteroaryl and polyfluoroaryl components are used. This synthetic route allows a better atom economy and more streamlined chemical synthesis. For instance, the direct usage of polyfluoroaryl could avoid the multi-step synthesis of unstable heteroarylboronic acid or polyfluoroarylboronic acid and thus eventually improves the step-economy.

Despite the advantages of using direct arylation method, there have been only a few reports regarding the successful direct C-H arylation of polyfluoroarenes with heteroaryl halides and sulfonates, in particular 2-substituted-pyridyl halides and sulfonates (Scheme 5.2). In 2008, Daugulis initially reported a copper-catalyzed arylation of polyfluorobenzenes with aryl and heteroaryl iodides and bromides. One example concerning the coupling of 2-bromopyridine was demonstrated. Later, they employed the same catalyst system and similar reaction conditions for 2-pyridyl chloride coupling. Nevertheless, even under the harsh reaction conditions (120-150 °C), the yield of the corresponding coupling product from 2-chloropyridine and pentafluorobenzene was moderate. In 2011, Zhang reported a palladium-catalyzed direct arylation of polyfluoroarenes with heteroaryl tosylates. Indeed, aryl sulfonates are the most versatile complementary substrates to aryl halides for various coupling reactions. Yet, the cost of substituted hydroxypyridines (as the precursors for the corresponding tosylates) is exceptionally higher when compared to the direct usage of substituted pyridyl chlorides. Moreover, additional tosylation step of hydroxypyridines is required too. Therefore, the development of a new catalytic system for direct usage of inexpensive and versatile heteroaryl chlorides is still highly desirable.
Scheme 5.2 Transition metal-catalyzed direct arylation of polyfluoroarenes with substituted 2-pyridyl halides and sulfonates

In view of current drawbacks and our persisting interests in palladium-catalyzed direct C-H arylation reaction\textsuperscript{13} and phosphine ligand synthesis and applications,\textsuperscript{14} we aim to develop an efficient protocol for coupling of electron-deficient polyfluoroarenes with heteroaryl chlorides, and especially substituted 2-pyridyl chlorides.
5.2 Results and discussion

5.2.1 Preliminary evaluation of palladium-catalyzed direct arylation of polyfluoroarenes with heteroaryl chlorides

We initially chose the 3-(dicyclohexylphosphino)-2-phenylindole (PCy$_2$Phendole-Phos) L1 to test the feasibility of direct arylation of polyfluoroarenes with heteroaryl chlorides. This ligand features of commercially available and inexpensive starting materials and can be easily prepared in large scale in 2 steps (Scheme 5.3).

![Scheme 5.3 Two-step synthesis of indolyl phosphine L1 from commercially available materials](image)

To evaluate the effectiveness of L1 for direct arylation of polyfluorobenzenes with heteroaryl chlorides, 2-chloroquinoline and pentafluorobenzene were used as benchmark substrates (Table 5.1). Catalyst loading of 2.0 mol% Pd was initially applied in probing the ligand efficacy. Pd(OAc)$_2$ was found to be superior among Pd$_2$(dba)$_3$, PdCl$_2$(CH$_3$CN)$_2$, Pd(TFA)$_2$ and Pd(OAc)$_2$ screened (Table 5.1, entries 1-4). Addition of 10 mol% PivOH improved the desired product yield from 43% to 84% (Table 5.1, entries 1 and 5). Na$_3$PO$_4$, KOAc and Na$_2$CO$_3$ provided comparable product yields among the common inorganic bases examined (Table 5.1, entries 6-10). DMA was found to be the best choice of solvent (Table 5.1, entries 1 and 11-13).
Table 5.1 Initial screening of palladium-catalyzed direct arylation of polyfluoroarenes with heteroaryl chlorides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd source (mol %)</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield %[^b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$ (2)</td>
<td>Na$_3$PO$_4$</td>
<td>DMA</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>Pd(TFA)$_2$ (2)</td>
<td>Na$_3$PO$_4$</td>
<td>DMA</td>
<td>Trace</td>
</tr>
<tr>
<td>3</td>
<td>PdCl$_2$(CH$_3$CN)$_2$ (2)</td>
<td>Na$_3$PO$_4$</td>
<td>DMA</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>Pd$_2$(dba)$_3$ (2)</td>
<td>Na$_3$PO$_4$</td>
<td>DMA</td>
<td>Trace</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)$_2$ (2)</td>
<td>Na$_3$PO$_4$</td>
<td>DMA</td>
<td>84[^c]</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)$_2$ (0.5)</td>
<td>Na$_3$PO$_4$</td>
<td>DMA</td>
<td>82[^c]</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)$_2$ (0.5)</td>
<td>NaOAc</td>
<td>DMA</td>
<td>56[^c]</td>
</tr>
<tr>
<td>8</td>
<td>Pd(OAc)$_2$ (0.5)</td>
<td>KOAc</td>
<td>DMA</td>
<td>82[^c]</td>
</tr>
<tr>
<td>9</td>
<td>Pd(OAc)$_2$ (0.5)</td>
<td>Na$_2$CO$_3$</td>
<td>DMA</td>
<td>79[^c]</td>
</tr>
<tr>
<td>10</td>
<td>Pd(OAc)$_2$ (0.5)</td>
<td>K$_2$CO$_3$</td>
<td>DMA</td>
<td>21[^c]</td>
</tr>
<tr>
<td>11</td>
<td>Pd(OAc)$_2$ (2)</td>
<td>Na$_3$PO$_4$</td>
<td>Toluene</td>
<td>32</td>
</tr>
<tr>
<td>12</td>
<td>Pd(OAc)$_2$ (2)</td>
<td>Na$_3$PO$_4$</td>
<td>DMF</td>
<td>41</td>
</tr>
<tr>
<td>13</td>
<td>Pd(OAc)$_2$ (0.5)</td>
<td>Na$_3$PO$_4$</td>
<td>i-PrOAc</td>
<td>34[^c]</td>
</tr>
</tbody>
</table>

[^a] Reaction conditions: 2-Chloroquinoline (0.5 mmol), pentafluorobenzene (1.0 mmol), Pd source (2 mol%), L1 (8 mol%), base (0.75 mmol) and solvent (1.0 mL) were stirred at 100 °C for 18 h under N$_2$.  
[^b] Calibrated GC yields were reported using dodecane as internal standard.  
[^c] 10 mol% PivOH was added.
With these encouraging results in hand, we next investigated the effect of phosphine ligands in this reaction (Scheme 5.4). Previously reported indolylphosphine ligands where the phosphino group is attached to different positions of the indole ring were examined (L1-L4). Ligand L1 was found to be the best ligand for this reaction. A list of commercially available and well-recognized effective phosphine ligands were further evaluated (L5-L12), such as PCy₃, PPh₃, CataCXium®, CataCXium®PCy, cataCXium®PInCy, SPhos, XPhos and Cy-JohnPhos. Surprisingly, other than XPhos (L6) could give a better yield among the ligands examined, poor substrate conversions and product yields were observed from L5 and L7-L12. Therefore, catalyst system comprising Pd(OAc)₂ and L1 was employed to test the scope of this reaction.
Scheme 5.4 Investigation of phosphine ligands in Pd-catalyzed direct arylation of perfluorobenzene with 2-quinolyl chlorides. Reaction conditions: 2-chloroquinoline (0.50 mmol), pentafluorobenzene (1.0 mmol), Pd(OAc)$_2$ (2 mol%), $L$ (8 mol%), Na$_3$PO$_4$ (0.75 mmol) and DMA (1.0 mL) were stirred at 100 °C for 18 h under nitrogen. Calibrated GC yields were reported using dodecane as internal standard.
5.2.2 Scope of palladium-catalyzed direct arylation of polyfluoroarenes with heteroaryl chlorides

A wide range of heteroaryl chlorides were probed in order to test the efficacy of the new catalytic system (Table 5.2). 2-Chloropyridine, in which it is the most challenging cross-coupling partner \(^{10}\) showed excellent product yield under these reaction conditions (Table 5.2, 3au). 6-Substituted-2-chloropyridines were efficiently coupled smoothly with pentafluorobenzene in good yields (Table 5.2, 3cu-3gu). Diphenylation could be done when 2,6-dichloropyridine was used (Table 5.2, 3hu). Other polyfluoroarenes were also applicable coupling partners (Table 5.2, 3cv-3cz). It should be noted that 10 new compounds were synthesized among the 13 entries which may implies the lack of current effective methods for accessing pyridyl/polyfluoro biaryl compounds, in spite of the usefulness of polyfluoroarene compounds.
Table 5.2 Palladium-catalyzed direct arylation of polyfluoroarenes with heteroaryl chlorides\(^{(a,b)}\)

<table>
<thead>
<tr>
<th>Reaction conditions: Heteroaryl chlorides (0.5 mmol), polyfluorobenzenes (1.0 mmol), Pd(OAc)(_2) (1.0 mmol), L1 (2 mol%), PivOH (1.0 equiv), Na(_2)PO(_4) (1.0 equiv), DMA, 100 °C, 24 h</th>
<th>Products</th>
<th>Yields</th>
</tr>
</thead>
<tbody>
<tr>
<td>R=Cl, Me, MeO, Me</td>
<td>3au</td>
<td>90% (5 mol% Pd)(^{(c)})</td>
</tr>
<tr>
<td>R=Cl, Me, MeO, Me</td>
<td>3bu</td>
<td>81% (2 mol% Pd)(^{(d)})</td>
</tr>
<tr>
<td>R=Cl, Me, MeO, Me</td>
<td>3cu</td>
<td>85% (1 mol% Pd)</td>
</tr>
<tr>
<td>R=Cl, Me, MeO, Me</td>
<td>3du</td>
<td>80% (1 mol% Pd)</td>
</tr>
<tr>
<td>R=Cl, Me, MeO, Me</td>
<td>3eu</td>
<td>82% (1 mol% Pd)</td>
</tr>
<tr>
<td>R=Cl, Me, MeO, Me</td>
<td>3fu</td>
<td>85% (1 mol% Pd)</td>
</tr>
<tr>
<td>R=Cl, Me, MeO, Me</td>
<td>3gu</td>
<td>81% (2 mol% Pd)(^{(e)})</td>
</tr>
<tr>
<td>R=Cl, Me, MeO, Me</td>
<td>3hv</td>
<td>95% (1 mol% Pd)(^{(f)})</td>
</tr>
<tr>
<td>R=Cl, Me, MeO, Me</td>
<td>3cv</td>
<td>70% (1 mol% Pd)</td>
</tr>
<tr>
<td>R=Cl, Me, MeO, Me</td>
<td>3cw</td>
<td>96% (1 mol% Pd)(^{(g)})</td>
</tr>
<tr>
<td>R=Cl, Me, MeO, Me</td>
<td>3cx</td>
<td>65% (1 mol% Pd)</td>
</tr>
<tr>
<td>R=Cl, Me, MeO, Me</td>
<td>3cy</td>
<td>65% (1 mol% Pd)(^{(g)})</td>
</tr>
<tr>
<td>R=Cl, Me, MeO, Me</td>
<td>3cz</td>
<td>73% (1 mol% Pd)(^{(h)})</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: Heteroaryl chlorides (0.5 mmol), polyfluorobenzenes (1.0 mmol), Pd(OAc)\(_2\) (1.0 mmol), L1 (2 mol%), PivOH (1.0 equiv), Na\(_2\)PO\(_4\) (1.0 equiv), DMA, 100 °C, 24 h
mmol), Pd(OAc)\textsubscript{2} : L\textsubscript{1} (1 : 4), Na\textsubscript{3}PO\textsubscript{4} (0.75 mmol), PivOH (10 mol\%) and DMA (1.0 mL) were stirred at 100 °C for 24 h under nitrogen. [b] Isolated yields. [c] Dioxane (1.0 mL) was used and stirred at 110 °C. [d] Dioxane : DMA (1 : 1, total 1.0 mL) was used and stirred at 110 °C. [e] Dioxane : DMA (4 : 1, total 1.0 mL) was used and stirred at 110 °C. [f] polyfluorobenzenes (2.0 mmol), Pd(OAc)\textsubscript{2} : L\textsubscript{1} (1 : 4), Na\textsubscript{3}PO\textsubscript{4} (1.50 mmol), PivOH (20 mol\%) and dioxane : DMA (4 : 1, total 2.0 mL) were stirred at 110 °C. [g] 4 equiv. polyfluorobenzene was used. [h] 3 equiv. polyfluorobenzene was used. [i] 5 equiv. polyfluorobenzene was used.

5.2.3 Scope of palladium-catalyzed direct arylation of polyfluoroarenes with aryl and alkenyl chlorides

In order to probe the generality of the Pd-L\textsubscript{1} catalyst system, a series of the electron neutral, electron rich and functionalized aryl chlorides were further examined (Table 5.3). Electron rich aryl chlorides were coupled with pentafluorobenzene in excellent yields (Table 5.3, 5eu-5hu). Functional groups, such as –CHO, –COMe, –COOMe, –COPh, –CN, were compatible under these reaction conditions (Table 5.3, 5iu-5ou). Particularly, the free amino groups remained intact during the course of the reaction (Table 3, 5qu and 5ru). Alkenyl chloride could also serve as an effective substrate for direct arylation of pentafluorobenzene (Table 3, 5su). To the best of our knowledge, it is the lowest palladium catalyst loading reported to date for this reaction.
Table 5.3 Palladium-catalyzed direct arylation of polyfluoroarenes with aryl chlorides

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Reaction Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 + 2 → 5</td>
<td>5au</td>
<td>91% (1 mol% Pd)</td>
<td>Pd(OAc)$_2$, L1, PivOH, Na$_2$PO$_4$, DMA, 100 °C, 24 h</td>
</tr>
<tr>
<td></td>
<td>5bu</td>
<td>82% (1 mol% Pd)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5cu</td>
<td>86% (1 mol% Pd)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5du</td>
<td>80% (1 mol% Pd)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5eu</td>
<td>87% (2 mol% Pd)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5fu</td>
<td>87% (1 mol% Pd)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5gu</td>
<td>90% (1 mol% Pd)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5hu</td>
<td>80% (2 mol% Pd)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5iu</td>
<td>70% (1 mol% Pd)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5ju</td>
<td>75% (1 mol% Pd)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5ku</td>
<td>84% (1 mol% Pd)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5lu</td>
<td>73% (1 mol% Pd)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5mu</td>
<td>85% (1 mol% Pd)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5nu</td>
<td>80% (2 mol% Pd)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5ou</td>
<td>80% (2 mol% Pd)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5pu</td>
<td>84% (1 mol% Pd)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5qu</td>
<td>91% (1 mol% Pd)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5ru</td>
<td>93% (1 mol% Pd)</td>
<td></td>
</tr>
</tbody>
</table>
[a] Reaction conditions: Aryl chlorides (0.5 mmol), polyfluorobenzenes (1.0 mmol), Pd(OAc)$_2$ : L1 (1 : 4), Na$_3$PO$_4$(0.75 mmol), PivOH (10 mol%) and DMA (1.0 mL) were stirred at 100 °C for 24 h. [b] Isolated yields. [c] without 10 mol% PivOH.

5.3 Conclusion

In conclusion, we reported the first general palladium-catalyzed direct arylation of polyfluorobenzenes with heteroaryl chlorides especially substituted 2-pyridyl chlorides using the combination of Pd(OAc)$_2$ and indolylphosphine ligand L1 as catalyst system. Particularly noteworthy is that the reaction conditions were mild and the catalyst loading down to 1 mol% Pd could be achieved. Moreover, the substrate scope can be extended to non-activated and activated aryl chlorides and alkenyl chloride without difficulty. General functional groups such as –CHO, –C(O)Me, –COOMe, –C(O)Ph, –NHC(O)Me, –CN, –NH$_2$ were compatible under these reaction conditions. We believe that this direct heteroarylation protocol provides a useful and facile access to polyfluoro/hetero biaryl compounds that are important in pharmaceutical chemistry and material sciences.
5.4 Experimental section

5.4.1 General considerations

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. All arylation reactions were performed in Rotaflo® (England) resealable screw cap Schlenk flask (approx. 20 mL volume) in the presence of Teflon coated magnetic stirrer bar (4 mm × 10 mm). Toluene and dioxane were distilled from sodium and sodium benzophenone ketyl under nitrogen, respectively. Anhydrous N, N-dimethylformamide (DMF) and anhydrous N, N-dimethylacetamide (DMA) in Sure/Seal bottles were purchased from Aldrich and used directly. NaN₃, Na₂CO₃, K₂CO₃, NaOAc and KOAc were purchased from chemical supplier and used without grinding. Commercial aryl chlorides (liquid form only) were purified by passed through a short plug (0.5 cm wide × 4 cm high) of neutral alumina or distillation. Indolylphosphine ligands (L₁-L₄) were prepared according to the reported procedure. Ligands (L₅-L₁₂) were purchased from commercial suppliers. Thin layer chromatography was performed on Merck precoated silica gel 60 F₂₅₄ plates. Silica gel (Merck, 70-230 and 230-400 mesh) was used for column chromatography. Melting points were recorded on an uncorrected Büchi Melting Point B-545 instrument. NMR spectra were recorded on a Brüker spectrometer (400 MHz for ¹H, 100 MHz for ¹³C, 376 MHz for ¹⁹F and 162 MHz for ³¹P). Spectra were referenced internally to the residual proton resonance in CDCl₃ (δ 7.26 ppm), or with tetramethylsilane (TMS, δ 0.00 ppm) as the internal standard. Chemical shifts (δ) were reported as part per million (ppm) in δ scale downfield from TMS. ¹³C NMR spectra were referenced to CDCl₃ (δ 77.0 ppm, the middle peak). ¹⁹F NMR chemical shifts were determined relative to CFCl₃ as the external standard and low field is positive. ³¹P NMR spectra were referenced to 85% H₃PO₄ externally. Coupling
constants \((J)\) were reported in Hertz (Hz). Mass spectra (EI-MS and ES-MS) were recorded on a HP 5989B Mass Spectrometer. High-resolution mass spectra (HRMS) were obtained on a Brüker APEX 47e FTICR mass spectrometer (ESI-MS). GC-MS analysis was conducted on a HP 5973 GCD system using a HP5MS column (30 m × 0.25 mm). The products described in GC yield were accorded to the authentic samples/dodecane calibration standard from HP 6890 GC-FID system. All yields reported refer to isolated yield of compounds estimated to be greater than 95% purity as determined by capillary gas chromatography (GC) or \(^1\)H NMR. Compounds described in the literature were characterized by comparison of their \(^1\)H, \(^{13}\)C, \(^{19}\)F and/or \(^{31}\)P NMR spectra to the previously reported data. The procedures in this section are representative, and thus the yields may differ from those reported in tables.

5.4.2 Preparation of indolylphosphine ligand L1 in large scale

3-Bromo-1-methyl-2-phenyl-1H-indole\(^{14d}\)

The synthesis of 3-bromo-1-methyl-2-phenyl-1H-indole was modified from the literature method.\(^{14d}\) To a solution of \(N\)-methyl-2-phenyl-1H-indole (10.4 g, 50.0 mmol) in chloroform (100 mL), a solution of \(N\)-bromosuccinimide (8.90 g, 50.0 mmol) in chloroform (200 mL) was added at room temperature. After stirring for 30 min, the reaction mixture was poured onto water (150 mL). The organic layer was washed with water twice, dried with \(\text{Na}_2\text{SO}_4\) and was then concentrated. The concentrated solution was filtered over a pad of silica (3 × 2 inch) and eluted with DCM/hexane (1:9). The solution was evaporated to give white solid product. The final product 3-bromo-1-methyl-2-phenyl-1H-indole was dried under vacuum (13.8 g, 97%) to give
white solid as the desired compound. $^1$H NMR (400MHz, CDCl$_3$) δ 3.62 (s, 3H), 7.18–7.27 (m, 1H), 7.28–7.33 (m, 2H), 7.43–7.50 (m, 5H), 7.61 (d, $J= 7.8$ Hz, 1H); $^{13}$C NMR (100MHz, CDCl$_3$) δ 31.6, 90.1, 109.7, 119.3, 120.5, 122.8, 127.2, 128.4, 128.6, 130.4, 130.7, 136.8, 138.0; MS (EI): m/z (relative intensity) 285.1 (M$^+$, 100), 204.1 (51), 191.1 (16), 178.1 (15).

3-(Dicyclohexylphosphino)-1-methyl-2-phenyl-1$H$-indole (L1)$^{14d}$

![Structure](image)

3-Bromo-1-methyl-2-phenyl-1$H$-indole (10.3 g, 36.0 mmol) was dissolved in freshly distilled THF (120 mL) at room temperature under nitrogen atmosphere. The solution was cooled to -78 °C in dry ice/acetone bath. Titrated n-BuLi (39.6 mmol) was added dropwise by syringe. After the reaction mixture was stirred for 30 min at -78°C, chlorodicyclosphosphine (9.54 ml, 43.2 mmol) was added dropwise by syringe. The reaction was allowed to warm to room temperature and stirred overnight. Solvent was removed under reduced pressure. After the solvent was removed under vacuum, the product was successively washing with cold MeOH. The product was then dried under vacuum. 3-(Dicyclohexylphosphino)-1-methyl-2-phenyl-1$H$-indole was obtained as a white solid (10.4 g, 72%). $^1$H NMR (400MHz, CD$_2$Cl$_2$) δ 1.03–1.35 (m, 10H), 1.55–1.90 (m, 10H), 2.30–2.35 (m, 2H), 3.53 (s, 3H), 7.17 (t, $J= 7.4$ Hz, 1H), 7.25–7.29 (m, 1H), 7.37–7.49 (m, 6H), 7.88 (d, $J= 8.0$ Hz, 1H); $^{13}$C NMR (100MHz, CD$_2$Cl$_2$) δ 27.1, 27.21, 27.24, 27.3, 30.6, 30.7, 31.0, 32.2, 32.4, 34.3, 34.4, 104.2, 104.4, 109.8, 119.8, 121.6, 121.7, 127.7, 128.0, 128.2, 130.5, 130.6, 131.67, 131.69, 132.95, 132.98, 138.2, 149.7, 150.1 (unresolved complex C-P splittings were observed); $^{31}$P NMR (162MHz, CD$_2$Cl$_2$) δ -18.26; MS (EI): m/z (relative intensity)
403.3 (M⁺, 17), 348.3 (4), 321.2 (31), 238.1 (100), 207.1 (12).

5.4.3 General procedures for initial ligand and reaction conditions screening

General Procedure for reaction condition screenings (Pd catalysts loading equal to 2.0 mol%): Pd source (0.010 mmol) and ligand (Pd : L = 1 : 4) were loaded into a Schlenk tube equipped with a Teflon-coated magnetic stir bar. The tubes were evacuated and backfilled with nitrogen (3 cycles). Precomplexation was applied by adding freshly distilled dichloromethane (1.0 mL) and Et₃N (0.10 mL) into the tube. The palladium complex stock solution was stirred and warmed using a hair drier for 1 to 2 minutes until the solvent started boiling. The solvent was then evaporated under high vacuum. 2-Chloroquinoline (0.50 mmol, 0.082 g) and base (0.75 mmol) were loaded into the tube, and the system was further evacuated and flushed with nitrogen for three times. Pentafluorobenzene (1.0 mmol, 111 µL) and solvent (1.0 mL) were added into the tube via syringe and the mixture was stirred at room temperature for several minutes. The tube was then placed into a preheated oil bath (100 °C) and stirred for 18 h. After the completion of the reaction, the reaction tube was allowed to reach room temperature. Ethyl acetate (~10 mL), dodecane (114 µL, internal standard) and water (~3 mL) were added. The organic layer was subjected to GC analysis. The GC yield was previously calibrated by authentic sample/dodecane calibration curve.

General procedure for screening (Pd catalysts loading lower than 1.0 mol%): A stock solution of Pd(OAc)₂ (11.5 mg, 0.050 mmol) with L1 (Pd : L = 1 : 4) in freshly distilled 10 mL DCM (1.0 mol% Pd per 1 mL stock solution) was initially prepared with continuously stirring at room temperature. An array of Schlenk tubes equipped
with a Teflon-coated magnetic stir bar were evacuated and backfilled with nitrogen (3 cycles). The corresponding volume of stock solution and Et$_3$N (0.10 mL) were transferred to an array of Schlenk tubes via syringes. The solution was stirred and warmed using hair drier for about 1 to 2 minutes until the solvent started boiling. The solvent was then evaporated under high vacuum. 2-Chloroquinoline (0.50 mmol, 82 mg) and base (0.75 mmol) were loaded into the tube, and the system was further evacuated and flushed with nitrogen for three times. Pentafluorobenzene (1.0 mmol, 111 µL), pivalic acid (5.1 mg, 0.050 mmol, if necessary) and solvent (1.0 mL) were added into the tube via syringe and the mixture was stirred at room temperature for several minutes. The tube was then placed into a preheated oil bath (100 °C) and stirred for the time as indicated. After the completion of the reaction, the reaction tube was allowed to reach room temperature. Ethyl acetate (~10 mL), dodecane (114 µL, internal standard) and water (~3 mL) were added. The organic layer was subjected to GC analysis. The GC yield was previously calibrated by authentic sample/dodecane calibration curve.

5.4.4 General procedures for direct arylation of polyfluoroarenes with aryl chlorides

General Procedure for direct arylation of polyfluoroarenes with aryl chlorides (Pd catalysts loading equal to or larger than 2.0 mol%): Pd(OAc)$_2$ (Pd loading indicated in the entry table) and L1 (Pd : L = 1 : 4) were loaded into a Schlenk tube equipped with a Teflon-coated magnetic stir bar. The tubes were evacuated and backfilled with nitrogen (3 cycles). Precomplexation was applied by adding freshly distilled dichloromethane (1.0 mL) and Et$_3$N (0.10 mL) into the tube. The palladium complex stock solution was stirred and warmed using a hair drier for 1 to 2 minutes.
until the solvent started boiling. The solvent was then evaporated under high vacuum. Na$_3$PO$_4$ (0.164 g, 0.75 mmol) and solid aryl chlorides (0.50 mmol) were loaded into the tube, and the system was further evacuated and flushed with nitrogen for three times. Polyfluoroarenes (1.0 mmol), liquid aryl chlorides (0.5 mmol), pivalic acid (5.1 mg, 0.050 mmol) and DMA (1.0 mL) were added into the tube via syringe and the mixture was stirred at room temperature for several minutes. The tube was then placed into a preheated oil bath (100 °C) and stirred for 24 h. After the completion of the reaction, the reaction tube was allowed to reach room temperature. Ethyl acetate (~10 mL) and water (~3 mL) were added. The organic layer was subjected to GC analysis. The filtrate was concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel (230-400 mesh) to afford the desired product.

**General procedures for direct arylation of polyfluoroarenes with aryl chlorides** (*Pd catalysts loading equal to 1.0 mol%*): A stock solution of Pd(OAc)$_2$ (11.5 mg, 0.050 mmol) with L1 (Pd : L = 1 : 4) in freshly distilled 10 mL DCM (1.0 mol% Pd per 1 mL stock solution) was initially prepared with continuously stirring at room temperature. An array of Schlenk tubes equipped with a Teflon-coated magnetic stir bar were evacuated and backfilled with nitrogen (3 cycles). The corresponding volume of stock solution and Et$_3$N (0.10 mL) were transferred to an array of Schlenk tubes via syringes. The solution was stirred and warmed using hair drier for about 1 to 2 minutes until the solvent started boiling. The solvent was then evaporated under high vacuum. Na$_3$PO$_4$ (0.164 g, 0.75 mmol) and solid aryl chlorides (0.50 mmol) were loaded into the tube, and the system was further evacuated and flushed with nitrogen for three times. Polyfluoroarenes (1.0 mmol), liquid aryl chlorides (0.5 mmol), pivalic acid (5.1 mg, 0.050 mmol) and DMA (1.0 mL) were added into the
tube via syringe and the mixture was stirred at room temperature for several minutes. The tube was then placed into a preheated oil bath (100 °C) and stirred for 24 h. After the completion of the reaction, the reaction tube was allowed to reach room temperature. Ethyl acetate (~10 mL) and water (~3 mL) were added. The organic layer was subjected to GC analysis. The filtrate was concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel (230–400 mesh) to afford the desired product.

5.4.5 Characterization data for cross-coupling products

2-(Perfluorophenyl)pyridine (Table 5.2, compound 3au)\(^{16}\)

![Chemical Structure]

Eluents (Ethyl acetate: Hexane= 1: 9, R\(_f\)= 0.30) was used for flash column chromatography. \(^1\)H NMR (400MHz, CDCl\(_3\)) \(\delta\) 7.35–7.38 (m, 1H), 7.46 (d, \(J= 7.6\) Hz, 1H), 7.82 (t, \(J= 8.0\) Hz, 1H), 8.75 (d, \(J= 4.4\) Hz, 1H); \(^{13}\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 115.2–115.5 (m), 123.8, 125.9, 136.3–136.6 (m), 136.7, 138.7–139.2 (m), 139.7–140.1 (m), 142.2–142.7 (m), 143.1–143.5 (m), 145.6–146.0 (m), 146.8, 150.1; \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) -162.0 (m, 2F), -154.0 (t, \(J= 18.8\) Hz, 1F), -143.3 (dd, \(J= 22.5\) Hz, 7.5 Hz, 2F); MS (EI): \(m/z\) (relative intensity) 245.0 (M\(^{+}\), 100), 226.0 (47), 191.9 (19), 116.9 (9), 93.0 (6).
3-(Perfluorophenyl)pyridine (Table 5.2, compound 3bu)\(^\text{17}\)

![3-(Perfluorophenyl)pyridine](image)

Eluents (Ethyl acetate: Hexane= 1: 4, \(R_f= 0.45\)) was used for flash column chromatography. \(^1\)H NMR (400MHz, CDCl\(_3\)) \(\delta\) 7.44 (dd, \(J= 7.6\) Hz, \(J= 4.8\) Hz, 1H), 7.77 (d, \(J= 8.0\) Hz, 1H), 8.68–8.69 (m, 2H); \(^{13}\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 112.2–112.8 (m), 123.0, 123.6, 136.4–136.9 (m), 137.5, 138.9–139.4 (m), 139.5–139.9 (m), 142.0–142.5 (m), 142.7–143.2 (m), 145.2–145.7 (m), 150.3, 150.4; \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) -161.2 (m, 2F), -153.5 (t, \(J= 22.5\) Hz, 1F), -143.0 (dd, \(J= 22.5\) Hz, 7.5 Hz, 2F); MS (EI): \(m/z\) (relative intensity) 245.0 (M\(^+\), 100), 226.0 (20), 192.0 (34), 122.9 (6), 99.0 (3).

2-Methyl-6-(perfluorophenyl)pyridine (Table 5.2, compound 3cu)

Eluents (Ethyl acetate: Hexane= 1: 9, \(R_f= 0.60\)) was used for flash column chromatography. Colorless liquid; \(^1\)H NMR (400MHz, CD\(_2\)Cl\(_2\)) \(\delta\) 2.61 (s, 3H), 7.27–7.30 (m, 2H), 7.75 (t, \(J= 7.8\) Hz, 1H); \(^{13}\)C NMR (100MHz, CD\(_2\)Cl\(_2\)) \(\delta\) 24.0, 115.6–116.3 (m), 122.8, 123.4, 136.2–136.7 (m), 136.8, 138.7–139.2 (m), 139.5–140.1 (m), 142.0–142.5 (m), 143.1–143.6 (m), 145.8, 159.3; \(^{19}\)F NMR (376 MHz, CD\(_2\)Cl\(_2\)) \(\delta\) -163.1 (m, 2F), -155.6 (t, \(J= 22.5\) Hz, 1F), -143.9 (dd, \(J= 22.5\) Hz, 7.5 Hz, 2F); MS (EI): \(m/z\) (relative intensity) 259.0 (M\(^+\), 100), 192.9 (18), 167.9 (6), 90.9 (16), 65.0 (9); HRMS: calcd. for C\(_{12}\)H\(_7\)F\(_5\)N\(^+\): 260.0493, found 260.0496.
2-Methoxy-6-(perfluorophenyl)pyridine (Table 5.2, compound 3du)

![Chemical Structure]

Eluents (Ethyl acetate: Hexane= 1: 9, $R_f= 0.40$) was used for flash column chromatography. Colorless liquid; $^1$H NMR (400MHz, CDCl$_3$) $\delta$ 3.94 (s, 3H), 6.81 (d, $J= 8.4$ Hz, 1H), 7.05 (d, $J= 7.2$ Hz, 1H), 7.68 (t, $J= 7.8$ Hz, 1H); $^{13}$C NMR (100MHz, CDCl$_3$) $\delta$ 53.6, 111.4, 115.4, 115.0–115.7 (m), 118.8, 136.2–136.9 (m), 138.8, 139.5–140.1 (m), 142.1–142.6 (m), 142.2–143.7 (m), 143.8, 145.7–146.3, 164.0; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -162.5 (m, 2F), -154.8 (t, $J= 22.5$ Hz, 1F), -142.8 (dd, $J= 22.5$ Hz, 7.5 Hz, 2F); MS (EI): m/z (relative intensity) 273.9 (M$^+$, 100), 244.9 (34), 226.1 (44), 191.9 (35), 93.0 (14); HRMS: calcd. for C$_{12}$H$_7$F$_5$NO$^+$: 276.0442, found 276.0443.

2-(Perfluorophenyl)quinoline (Table 5.2, compound 3eu)$^{11}$

![Chemical Structure]

Eluents (Ethyl acetate: Hexane= 1: 4, $R_f= 0.45$) was used for flash column chromatography. $^1$H NMR (400MHz, CDCl$_3$) $\delta$ 7.53 (d, $J= 8.4$ Hz, 1H), 7.63 (t, $J= 7.4$ Hz, 1H), 7.78 (t, $J= 8.4$ Hz, 1H), 7.89 (d, $J= 8.0$ Hz, 1H), 8.16 (d, $J= 8.4$ Hz, 1H), 8.29 (d, $J= 8.4$ Hz, 1H); $^{13}$C NMR (100MHz, CDCl$_3$) $\delta$ 115.6–115.9 (m), 122.7, 127.4, 127.6, 127.7, 129.7, 130.2, 136.4–136.8 (m), 136.9, 138.9–139.4 (m), 140.0–140.4 (m), 142.5–142.9 (m), 143.3–143.8 (m), 145.8–146.2 (m), 147.0, 148.2; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -161.6 (m, 2F), -153.5 (t, $J= 22.5$ Hz, 1F), -142.8 (dd, $J= 22.5$ Hz, 7.5 Hz, 2F); MS (EI): m/z (relative intensity) 295.0 (M$^+$, 100), 276.0 (31), 192.9
2-Methyl-7-(perfluorophenyl)quinoline (Table 5.2, compound 3fu)

![Chemical structure](image)

Eluents (Ethyl acetate: Hexane = 1: 4, R_f = 0.45) was used for flash column chromatography. White solid; m.p. 148.7 – 150.9 °C; ^1H NMR (400MHz, CDCl₃) δ 2.75 (s, 3H), 7.33 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 8.05–8.10 (m, 2H); ^13C NMR (100MHz, CDCl₃) δ 25.3, 115.2–115.7 (m), 123.0, 126.5, 126.9, 127.3, 127.9, 130.8, 135.8, 136.4–136.9 (m), 138.9–139.2 (m), 139.2–139.5 (m), 141.6–142.2 (m), 142.7–143.2 (m), 145.2–145.6 (m), 147.5, 160.1; ^19F NMR (376 MHz, CDCl₃) δ -161.9 (m, 2F), -154.8 (t, J = 22.5 Hz, 1F), -142.9 (dd, J = 22.5 Hz, 7.5 Hz, 2F); MS (EI): m/z (relative intensity) 309.0 (M⁺, 100), 290.0 (5), 191.9 (6), 154.5 (9), 63 (5); HRMS: calcd. for C₁₆H₉F₅N⁺: 310.0650, found 310.0646.

3-Methoxy-6-(perfluorophenyl)pyridazine (Table 5.2, compound 3gu)

![Chemical structure](image)

Eluents (Ethyl acetate: Hexane = 1: 4, R_f = 0.40) was used for flash column chromatography. White solid; m.p. 88.4 – 90.8 °C; ^1H NMR (400MHz, CDCl₃) δ 4.19 (s, 3H), 7.10 (d, J = 9.2 Hz, 1H), 7.51 (d, J = 9.2 Hz, 1H); ^13C NMR (100MHz, CDCl₃) δ 55.1, 112.2–112.7 (m), 117.3, 130.9, 136.3–136.7 (m), 138.8–139.2 (m), 140.1–140.5 (m), 142.7–143.1 (m), 143.2–143.6 (m), 145.8–146.0 (m), 146.1, 164.6; ^19F NMR (376 MHz, CDCl₃) δ -161.4 (m, 2F), -152.6 (t, J = 22.5 Hz, 1F), -142.6 (dd, J =
22.5 Hz, 7.5 Hz, 2F); MS (EI): \textit{m/z} (relative intensity) 276.0 (M$^+$, 36), 205.0 (100), 192.0 (11), 179.0 (11), 117.0 (8); HRMS: calcd. for C$_{11}$H$_6$F$_5$N$_2$O$^+$: 277.0395, found 277.0392.

2,6-Bis(perfluorophenyl)pyridine (Table 5.2, compound 3hu)

![Structure of 2,6-Bis(perfluorophenyl)pyridine]

Eluents (Ethyl Acetate: Hexane= 1: 9, R$_f$ = 0.60) was used for flash column chromatography. White solid; m.p. 76.9 – 80.5 °C; $^1$H NMR (400MHz, CDCl$_3$) $\delta$ 7.57 (d, $J$ = 7.6 Hz, 2H), 8.00 (t, $J$ = 8.0 Hz, 1H); $^{13}$C NMR (100MHz, CDCl$_3$) $\delta$ 114.5–114.8 (m), 125.9, 136.4–136.8 (m), 137.5, 138.9–139.3 (m), 140.1–140.5 (m), 142.6–143.0 (m), 143.2-143.6 (m), 145.7–146.1 (m), 147.4; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -161.7 (m, 2F), -153.3 (t, $J$ = 22.5 Hz, 1F), -143.0 (dd, $J$ = 22.5 Hz, 7.5 Hz, 2F); MS (EI): \textit{m/z} (relative intensity) 411.1 (M$^+$, 100), 392.1 (37), 244.0 (10), 192.0 (35), 93.0 (4); HRMS: calcd. for C$_{17}$H$_4$F$_{10}$N$^+$: 412.0179, found 412.0178.

2-Methyl-6-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)pyridine (Table 5.2, compound 3cv)

![Structure of 2-Methyl-6-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)pyridine]

Eluents (Ethyl acetate: Hexane= 1: 4, R$_f$ = 0.50) was used for flash column chromatography. White solid; m.p. 54.7 – 57.5 °C; $^1$H NMR (400MHz, CDCl$_3$) $\delta$ 2.62 (s, 3H), 7.26–7.30 (m, 2H), 7.73 (t, $J$ = 7.8 Hz, 1H); $^{13}$C NMR (100MHz, CDCl$_3$) $\delta$
24.4, 108.9–110.1 (m), 119.5, 122.2, 122.7, 124.0, 124.1–124.5 (m), 136.9, 142.8–143.5 (m), 145.6, 145.6–145.9 (m), 159.5; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -141.1 (m, 2F), -140.6 (m, 2F), -56.5 (m, 3F); MS (EI): $m/z$ (relative intensity) 309.0 (M$^+$, 100), 289.9 (16), 192.9 (10), 90.9 (5), 68.9 (26); HRMS: calcd. for C$_{13}$H$_7$F$_7$N$: 310.0461, found 310.0465.

2-Methyl-6-(2,3,5,6-tetrafluoro-4-methylphenyl)pyridine (Table 5.2, compound 3cw)

Eluents (Ethyl acetate: Hexane= 1: 4, R$_f$= 0.50) was used for flash column chromatography. White solid; m.p. 72.3 – 75.3 °C; $^1$H NMR (400MHz, CDCl$_3$) $\delta$ 2.29 (s, 3H), 2.60 (s, 3H), 7.18 (d, $J$= 7.6 Hz, 1H), 7.24 (d, $J$= 7.6 Hz, 1H), 7.66 (t, $J$= 7.8 Hz, 1H); $^{13}$C NMR (100MHz, CDCl$_3$) $\delta$ 7.5, 24.4, 115.8–116.2 (m), 117.4–117.8 (m), 122.7, 123.0, 136.6, 142.4–142.8 (m), 143.7–144.1 (m), 144.9–145.2 (m), 146.1–146.5 (m), 147.1, 158.9; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -145.4 (dd, $J$= 22.5 Hz, 11.3 Hz, 2F), -143.9 (dd, $J$= 22.5 Hz, 11.3 Hz, 2F); MS (EI): $m/z$ (relative intensity) 255.1 (M$^+$, 100), 234.0 (11), 213.0 (5), 187.0 (15), 91.0 (32); HRMS: calcd. for C$_{13}$H$_{10}$F$_4$N$: 256.0744, found 256.0742.

2-Methyl-6-(2,3,5,6-tetrafluorophenyl)pyridine (Table 5.2, compound 3cx)

Eluents (Ethyl acetate: Hexane= 1: 9, R$_f$= 0.50) was used for flash column
chromatography. Colorless liquid; $^1$H NMR (400MHz, CDCl$_3$) $\delta$ 2.61 (s, 3H), 7.04 – 7.13 (m, 1H), 7.21 (d, $J$= 7.6 Hz, 1H), 7.26 (d, $J$= 7.6 Hz, 1H), 7.69 (t, $J$= 7.8 Hz, 1H); $^{13}$C NMR (100MHz, CDCl$_3$) $\delta$ 24.4, 105.4–105.9 (m), 120.9–121.2 (m), 122.7, 123.3, 136.7, 142.6–143.0 (m), 144.6–145.0 (m), 145.1–145.5 (m), 146.8, 147.1–147.5 (m), 159.0; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -143.6 (dd, $J$= 22.5 Hz, 15.0 Hz, 2F), -138.9 (dd, $J$= 22.5 Hz, 11.3 Hz, 2F); MS (EI): $m/z$ (relative intensity) 241.0 (M$^+$, 100), 221.0 (5), 174.0 (15), 91.0 (32), 66.0 (11); HRMS: calcd. for C$_{12}$H$_8$F$_4$N+: 242.0587, found 242.0585.

2-Methyl-6-(2,3,4,6-tetrafluorophenyl)pyridine (Table 5.2, compound 3cy)

Eluents (Ethyl acetate: Hexane= 1: 4, $R_f$= 0.70) was used for flash column chromatography. Colorless liquid; $^1$H NMR (400MHz, CDCl$_3$) $\delta$ 2.61 (s, 3H), 6.81–6.88 (m, 1H), 7.19 (d, $J$= 8.0 Hz, 1H), 7.22 (d, $J$=7.6 Hz, 1H), 7.67 (t, $J$= 7.8 Hz, 1H); $^{13}$C NMR (100MHz, CDCl$_3$) $\delta$ 24.5, 100.8–101.3 (m), 115.7-116.1 (m), 122.8, 123.1, 136.0–136.3 (m), 136.7, 138.4–138.8 (m), 147.0, 147.9–148.3 (m), 149.0–149.4 (m), 150.4–150.8 (m), 151.5–151.9 (m), 153.2–153.5 (m), 155.6–156.0 (m), 158.9; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -164.9 (m, 1F), 135.2 (dd, $J$= 22.5 Hz, 7.5 Hz, 1F), 132.0 (m, 1F), -117.9 (d, $J$= 11.3 Hz, 1F); MS (EI): $m/z$ (relative intensity) 241.0 (M$^+$, 100), 221.0 (5), 174.0 (15), 91.0 (32), 66.0 (11); HRMS: calcd. for C$_{12}$H$_8$F$_4$N+: 242.0587, found 242.0587.
2-Methyl-6-(2,4,6-trifluorophenyl)pyridine (Table 5.2, compound 3cz)

![Chemical Structure]

Eluents (Ethyl acetate: Hexane= 1: 4, R_f = 0.70) was used for flash column chromatography. Colorless liquid; \(^1^H\) NMR (400MHz, CDCl\(_3\)) \(\delta\) 2.62 (s, 3H), 6.73–6.78 (m, 2H), 7.18 (d, \(J = 7.8\) Hz, 1H), 7.23 (d, \(J = 7.6\) Hz, 1H), 7.67 (t, \(J = 7.8\) Hz, 1H); \(^{13}\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 24.4, 100.2–100.7 (m), 114.7–115.2 (m), 122.6, 122.7, 136.5, 147.8, 158.6, 159.2–159.6 (m), 160.9–161.3 (m), 161.7–162.0 (m), 163.4–163.7 (m); \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) -111.2 (d, \(J = 7.5\) Hz, 2F), -107.6 (t, \(J = 7.5\) Hz, 1F); MS (EI): \(m/z\) (relative intensity) 223.0 (M\(^+\), 100), 155.9 (10), 90.9 (13), 66.0 (3), 51.0 (2); HRMS: calcd. for C\(_{12}\)H\(_9\)F\(_3\)N\(^+\): 224.0682, found 224.0678.

2,3,4,5,6-Pentafluoro-4'-methyl-1,1'-biphenyl (Table 5.3, compound 5au)

![Chemical Structure]

Eluents (Hexane, \(R_f = 0.5\)) was used for flash column chromatography. \(^1^H\) NMR (400MHz, CDCl\(_3\)) \(\delta\) 2.44 (s, 3H), 7.31–7.33 (m, 4H); \(^{13}\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 21.3, 115.7–116.2 (m), 123.4, 129.4, 130.0, 136.4–136.7 (m), 138.8–139.3 (m), 139.4, 141.3–141.6 (m), 142.7–143.1 (m), 145.2–145.6 (m); \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) -162.5 (m, 2F), -156.2 (t, \(J = 22.5\) Hz, 1F), -143.4 (dd, \(J = 22.5\) Hz, \(J = 7.5\) Hz, 2F); MS (EI): \(m/z\) (relative intensity) 258.0 (M\(^+\), 100), 237.0 (54), 219 (24), 187.9 (14), 91.0 (9).
2,3,4,5,6-Pentafluoro-3'-methyl-1,1'-biphenyl (Table 5.3, compound 5bu)\(^e\)

![Structure of 2,3,4,5,6-Pentafluoro-3'-methyl-1,1'-biphenyl](image)

Eluents (Hexane, \(R_f = 0.5\)) was used for flash column chromatography. \(^1\)H NMR (400MHz, CDCl\(_3\)) \(\delta\) 2.45 (s, 3H), 7.23–7.26 (m, 2H), 7.30 (d, \(J = 7.6\) Hz, 1H), 7.41 (t, \(J = 7.6\) Hz , 1H); \(^13\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 21.3, 115.8–116.4 (m), 126.3, 127.2, 128.6, 130.1, 130.7, 136.4–136.8 (m), 138.5, 138.7–139.3 (m), 141.2–141.8 (m), 142.8–143.2 (m), 145.2–145.6 (m); \(^19\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) -162.5 (m, 2F), -156.0 (t, \(J = 22.5\) Hz, 1F), 143.2 (dd, \(J = 22.5\) Hz, \(J = 7.5\) Hz, 2F) ; MS (EI): \(m/z\) (relative intensity) 258.0 (M\(^+\), 100), 237.0 (62), 218.9 (33), 188.0 (20), 90.9 (12).

2-(Perfluorophenyl)naphthalene (Table 5.3, compound 5cu)\(^1^8\)

![Structure of 2-(Perfluorophenyl)naphthalene](image)

Eluents (Ethyl acetate: Hexane= 1: 9, \(R_f = 0.70\)) was used for flash column chromatography. \(^1\)H NMR (400MHz, CDCl\(_3\)) \(\delta\) 7.48–7.52 (m, 1H), 7.54–7.60 (m, 2H), 7.89–7.92 (m, 2H), 7.94–7.97 (m, 2H); \(^13\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 115.7–116.2 (m), 123.7, 126.7, 127.0, 127.8, 128.3, 128.4, 130.1, 133.0, 133.3, 136.4–136.8 (m), 138.9–139.4 (m), 141.5–141.9 (m), 143.0–143.3 (m), 145.3–145.7 (m); \(^19\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) -162.1 (m, 2F), -155.4 (t, \(J = 22.5\) Hz, 1F), -143.0 (dd, \(J = 22.5\) Hz, \(J = 7.5\) Hz, 2F) ; MS (EI): \(m/z\) (relative intensity) 294.0 (M\(^+\), 100), 274.0 (30), 243.0 (10), 225.0 (11), 92.9 (3).
2,3,4,5,6-Pentafluoro-4'-vinyl-1,1'-biphenyl (Table 5.3, compound 5du)\(^{18}\)

\[
\begin{align*}
\text{Eluents (Hexane, } R_f &= 0.50) & \text{was used for flash column chromatography. } ^1H \text{ NMR} \\
& (400MHz, CDCl}_3) \delta 5.37 (d, J = 10.8 Hz, 1H), 5.86 (d, J = 17.6 Hz, 1H), 6.78 (dd, J = 10.8 Hz, J = 17.6 Hz, 1H), 7.41 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H); ^{13}C \text{ NMR} \\
& (100MHz, CDCl}_3) \delta 115.3, 115.4–115.9 (m), 125.6, 126.4, 130.3, 136.0, 136.4–136.9 (m), 138.6, 138.9–139.3 (m), 141.6–141.9 (m), 142.7–143.1 (m), 145.2–145.6 (m); \\
^{19}F \text{ NMR} & (376 MHz, CDCl}_3) \delta -162.3 (m, 2F), -155.7 (t, J = 22.5 Hz, 1F), -143.2 (dd, J = 22.5 Hz, J = 7.5 Hz, 2F); MS (EI): m/z \text{ (relative intensity) 270.1 (M}^+ , 100), 250.0 (53), 219.0 (67), 201 (41), 135 (14).
\end{align*}
\]

2,3,4,5,6-Pentafluoro-4'-methoxy-1,1'-biphenyl (Table 5.3, compound 5eu)\(^{6g}\)

\[
\begin{align*}
\text{Eluents (Ethyl acetate: Hexane= 1: 50, } R_f &= 0.45) & \text{was used for flash column chromatography. } ^1H \text{ NMR} \\
& (400MHz, CDCl}_3) \delta 3.87 (s, 3H), 7.02 (d, J = 8.8 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H); ^{13}C \text{ NMR} (100MHz, CDCl}_3) \delta 55.3, 114.2, 115.2–116.2 (m), 118.4, 131.4, 136.1–137.0, 138.4–139.5 (m), 140.9–141.6 (m), 142.6–143.4 (m), 145.0–145.7 (m), 160.3; ^{19}F \text{ NMR} & (376 MHz, CDCl}_3) \delta -162.7 (m, 2F), -156.6 (t, J = 22.5 Hz, 1F), -143.7 (dd, J = 22.5 Hz, J = 7.5 Hz, 2F); MS (EI): m/z \text{ (relative intensity) 274.0 (M}^+ , 100), 230.9 (83), 205.0 (34), 180.9 (18), 92.9 (7).
\end{align*}
\]
2,3,4,5,6-Pentafluoro-3'-methoxy-1,1'-biphenyl (Table 5.3, compound 5fu)

Eluents (Ethyl acetate: Hexane = 1: 50, Rf = 0.45) was used for flash column chromatography. $^1$H NMR (400MHz, CDCl$_3$) δ 3.85 (s, 3H), 6.96 (s, 1H), 7.00–7.03 (m, 2H), 7.41 (t, J = 8.0 Hz, 1H); $^{13}$C NMR (100MHz, CDCl$_3$) δ 55.3, 114.8, 115.8, 122.4, 127.5, 129.7, 136.3–136.8 (m), 138.8–139.4 (m), 141.5–142.0, 142.6–143.1 (m), 145.1–145.7 (m), 159.7; $^{19}$F NMR (376 MHz, CDCl$_3$) δ -162.4 (m, 2F), -155.7 (t, J = 22.5 Hz, 1F), -142.9 (dd, J = 22.5 Hz, J = 11.3 Hz, 2F); MS (EI): m/z (relative intensity) 274.0 (M$^+$, 100), 243.9 (33), 230.9 (55), 204.9 (31), 191.9 (12).

3'-Ethoxy-2,3,4,5,6-pentafluoro-1,1'-biphenyl (Table 5.3, compound 5gu)

Eluents (Ethyl acetate: Hexane = 1: 50, Rf = 0.50) was used for flash column chromatography. Colorless liquid; $^1$H NMR (400MHz, CDCl$_3$) δ 1.45 (t, J = 6.8 Hz, 3H), 4.08 (q, J = 6.8 Hz, 2H), 6.95 (s, 1H), 6.98–7.02 (m, 2H), 7.40 (t, J = 8.0 Hz, 1H); $^{13}$C NMR (100MHz, CDCl$_3$) δ 14.7, 63.6, 115.4, 115.6–116.2 (m), 116.3, 122.3, 127.4, 129.7, 136.3–136.7 (m), 138.8–139.3 (m), 141.4–141.9 (m), 142.7–143.0 (m), 145.2–145.7 (m), 159.1; $^{19}$F NMR (376 MHz, CDCl$_3$) δ -162.4 (m, 2F), -155.8 (t, J = 22.5 Hz, 1F), -142.9 (dd, J = 22.5 Hz, J = 7.5 Hz, 2F); MS (EI): m/z (relative intensity) 288.0 (M$^+$, 42), 260.0 (100), 231.0 (26), 204.9 (16), 193.0 (13); HRMS: calcd. for C$_{14}$H$_9$OF$_5$+: 288.0574, found 288.0584.
5-(Perfluorophenyl)benzo[d][1,3]dioxole (Table 5.3, compound 5hu)\textsuperscript{17}

\begin{center}
\includegraphics[width=0.2\textwidth]{figure1}
\end{center}

Eluents (Ethyl acetate: Hexane= 1: 20, R\textsubscript{f} = 0.40) was used for flash column chromatography. \textsuperscript{1}H NMR (400MHz, CDCl\textsubscript{3}) \( \delta \) 6.03 (s, 2H), 6.88–6.93 (m, 3H); \textsuperscript{13}C NMR (100MHz, CDCl\textsubscript{3}) \( \delta \) 101.5, 108.6, 110.3, 115.4–115.9 (m), 119.4, 124.2, 136.2–136.9 (m), 138.7–139.4 (m), 141.2–141.8 (m), 142.6–143.1 (m), 145.2–145.6 (m), 148.0, 148.5; \textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3}) \( \delta \) -162.5 (m, 2F), -156.2 (t, \( J \text{= 22.5 Hz, 1F} \)), 143.3 (dd, \( J \text{= 22.5 Hz, } J \text{= 7.5 Hz, 2F} \)); MS (EI): \( m/z \) (relative intensity) 288.0 (M\textsuperscript{+}, 100), 229.0 (22), 211.0 (48), 180.0 (14), 143.6 (18).

\textit{2',3',4',5',6'-Pentafluoro-[1,1'-biphenyl]-4-carbaldehyde} (Table 5.3, compound 5iu)\textsuperscript{13c}

\begin{center}
\includegraphics[width=0.2\textwidth]{figure2}
\end{center}

Eluents (Ethyl acetate: Hexane= 1: 20, R\textsubscript{f} = 0.50) was used for flash column chromatography. \textsuperscript{1}H NMR (400MHz, CDCl\textsubscript{3}) \( \delta \) 7.62 (d, \( J \text{= 8.4 Hz, 2H} \)), 8.02 d, \( J \text{=} 6.4 \text{ Hz, 2H} \), 10.08 (s, 1H); \textsuperscript{13}C NMR (100MHz, CDCl\textsubscript{3}) \( \delta \) 114.3–115.2 (m), 129.8, 130.9, 132.4, 136.6, 138.7–139.5 (m), 139.5–140.0 (m), 142.0–142.5(m), 142.5–143.1 (m), 145.0–145.6 (m), 191.4; \textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3}) \( \delta \) -161.4 (m, 2F), -153.6 (t, \( J \text{=} 22.5 \text{ Hz, 1F} \)), -142.7 (dd, \( J \text{=} 22.5 \text{ Hz, } J \text{=} 7.5 \text{ Hz, 2F} \)); MS (EI): \( m/z \) (relative intensity) 271.9 (M\textsuperscript{+}, 100), 241.9 (45), 223.9 (59), 192.9 (26), 73.9 (11).
1-(2',3',4',5',6'-Pentafluoro-[1,1'-biphenyl]-4-yl)ethanone (Table 5.3, compound 5ju)\textsuperscript{18}

![Chemical structure]

Eluents (Ethyl acetate: Hexane= 1: 20, R$_f$ = 0.50) was used for flash column chromatography. $^1$H NMR (400MHz, CDCl$_3$) $\delta$ 2.64 (s, 3H), 7.53 (d, $J$= 8.0 Hz, 2H), 8.06 (d, $J$= 8.4 Hz , 2H); $^{13}$C NMR (100MHz, CDCl$_3$) $\delta$ 26.5, 114.6–115.1 (m), 128.5, 130.4, 131.0, 136.4–136.9 (m), 137.4, 138.9–139.3 (m), 139.3–139.7 (m), 141.7–142.3 (m), 142.6–143.0 (m), 145.0–145.5 (m), 197.2; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -161.7 (m, 2F), -154.1 (t, $J$= 22.5 Hz, 1F), -142.9 (dd, $J$= 22.5 Hz, $J$= 7.5 Hz, 2F); MS (EI): m/z (relative intensity) 286.0 (M$^+$, 26), 271.0 (100), 242.0 (34), 224.0 (30), 193.0 (24).

(2',3',4',5',6'-Pentafluoro-[1,1'-biphenyl]-4-yl)(phenyl)methanone (Table 5.3, compound 5ku)\textsuperscript{13c}

![Chemical structure]

Eluents (Ethyl acetate: Hexane= 1: 20, R$_f$ = 0.20) was used for flash column chromatography. $^1$H NMR (400MHz, CDCl$_3$) $\delta$ 7.49–7.63 (m, 5H), 7.84 (d, $J$= 7.2 Hz , 2H), 7.92 (d, $J$= 8.0 Hz, 2H); $^{13}$C NMR (100MHz, CDCl$_3$) $\delta$ 114.5–115.3 (m), 128.3, 129.9, 130.1, 130.3, 132.7, 136.4–136.9 (m), 137.1, 138.1, 138.7–139.2 (m), 139.2–139.9 (m), 141.8–142.2 (m), 142.8–143.1 (m), 145.1–145.5 (m), 195.7; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ -161.6 (m, 2F), -154.2 (t, $J$= 18.8 Hz, 1F), -142.8 (dd, $J$= 22.5 Hz, $J$= 7.5 Hz, 2F); MS (EI): m/z (relative intensity) 348.0 (M$^+$, 100), 270.9 (74), 242.0 (34), 224.0 (30), 193.0 (24).
Methyl 2',3',4',5',6'-pentafluoro-[1,1'-biphenyl]-4-carboxylate (Table 5.3, compound 5lu)\textsuperscript{17}

\[
\begin{align*}
\text{MeO} & \quad \text{F} \\
\text{F} & \quad \text{F} \\
\text{F} & \quad \text{F}
\end{align*}
\]

Eluents (Ethyl acetate: Hexane= 1: 10, R\textsubscript{f} = 0.40) was used for flash column chromatography. \textsuperscript{1}H NMR (400MHz, CDCl\textsubscript{3}) \(\delta\) 3.95 (s, 3H), 7.50 (d, \(J = 8.0\) Hz, 2H), 8.14 (d, \(J = 8.0\) Hz , 2H); \textsuperscript{13}C NMR (100MHz, CDCl\textsubscript{3}) \(\delta\) 52.3, 114.7–115.1 (m), 129.8, 130.2, 130.9, 136.4–136.9 (m), 138.9–139.3 (m), 139.3–139.7 (m), 141.8–142.3 (m), 142.6–143.0 (m), 145.1–145.6 (m), 166.3; \textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3}) \(\delta\) -161.7 (m, 2F), -153.3 (t, \(J = 22.5\) Hz, 1F), -142.9 (dd, \(J = 22.5\) Hz, \(J = 7.5\) Hz, 2F); MS (EI): \(m/z\) (relative intensity) 302.0 (M\textsuperscript{+}, 43), 270.9 (100), 241.9 (34), 224.0 (29), 193.0 (20).

Methyl 2',3',4',5',6'-pentafluoro-[1,1'-biphenyl]-3-carboxylate (Table 5.3, compound 5mu)\textsuperscript{17}

\[
\begin{align*}
\text{MeO} & \quad \text{F} \\
\text{F} & \quad \text{F} \\
\text{F} & \quad \text{F}
\end{align*}
\]

Eluents (Ethyl acetate: Hexane= 1: 20, R\textsubscript{f} = 0.20) was used for flash column chromatography. \textsuperscript{1}H NMR (400MHz, CDCl\textsubscript{3}) \(\delta\) 3.93 (s, 3H), 7.55–7.61 (m, 2H), 8.11–8.13 (m, 2H); \textsuperscript{13}C NMR (100MHz, CDCl\textsubscript{3}) \(\delta\) 52.3, 114.6–115.1 (m), 126.7, 128.8, 130.3, 130.9, 131.3, 134.4, 136.4–136.8 (m), 138.9–139.2 (m), 139.2–139.6 (m), 141.6–142.1 (m), 142.7–143.1 (m), 145.1–145.5 (m), 166.2; \textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3}) \(\delta\) -161.9 (m, 2F), -154.8 (t, \(J = 22.5\) Hz, 1F), -143.2 (dd, \(J = 22.5\) Hz, \(J = 7.5\) Hz,
2F); MS (EI): m/z (relative intensity) 302.0 (M⁺, 54), 270.9 (100), 241.9 (37), 223.9 (30), 192.9 (16).

2',3',4',5',6'-Pentafluoro-[1,1'-biphenyl]-4-carbonitrile (Table 5.3, compound 5ou)\textsuperscript{13c}

![Chemical structure of 2',3',4',5',6'-Pentafluoro-[1,1'-biphenyl]-4-carbonitrile](image)

Eluents (Ethyl acetate: Hexane = 1: 9, Rᶠ = 0.50) was used for flash column chromatography. \(^1\)H NMR (400MHz, CDCl\(_3\)) \(\delta\) 7.56 (d, \(J = 8.0\) Hz, 2H), 7.80 (d, \(J = 8.0\) Hz, 2H); \(^13\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 113.3, 113.7–114.5 (m), 118.0, 130.9, 131.1, 132.4, 136.5–137.0 (m), 139.0–139.5 (m), 139.6–140.1 (m), 142.2–142.6 (m), 142.6–143.0 (m), 145.0–145.5 (m); \(^19\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) -160.9 (m, 2F), -152.9 (t, \(J = 22.5\) Hz, 1F), -142.7 (dd, \(J = 22.5\) Hz, \(J = 7.5\) Hz, 2F); MS (EI): m/z (relative intensity) 268.9 (M⁺, 100), 248.9 (12), 217.8 (10), 199.9 (9), 92.9 (8).

2',3',4',5',6'-Pentafluoro-[1,1'-biphenyl]-3-carbonitrile (Table 5.3, compound 5ou)\textsuperscript{19}

![Chemical structure of 2',3',4',5',6'-Pentafluoro-[1,1'-biphenyl]-3-carbonitrile](image)

Eluents (Ethyl acetate: Hexane = 1: 9, Rᶠ = 0.50) was used for flash column chromatography. \(^1\)H NMR (400MHz, CDCl\(_3\)) \(\delta\) 7.62–7.69 (m, 2H), 7.74–7.78 (m, 2H); \(^13\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 113.4, 113.4–113.8 (m), 117.9, 127.8, 129.7, 132.8, 133.6, 134.5, 136.4–137.0 (m), 139.0–139.5 (m), 139.6–140.1 (m), 142.1–142.6 (m), 142.6–143.0 (m), 145.1–145.6 (m); \(^19\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) -160.9 (m, 2F),
-153.0 (t, J= 22.5 Hz, 1F), -143.0 (dd, J= 22.5 Hz, J= 7.5 Hz, 2F); MS (EI): m/z (relative intensity) 268.9 (M⁺, 100), 248.9 (13), 217.9 (6), 192.0 (10), 92.9 (5).

1-(2′,3′,4′,5′,6′-Pentafluoro-[1,1′-biphenyl]-3-yl)-1H-pyrrole (Table 5.3, compound 5pu)

Eluents (Ethyl acetate: Hexane= 1: 4, Rf= 0.70) was used for flash column chromatography. Orange solid; m.p. 98.3 – 99.3 °C; ¹H NMR (400MHz, CDCl3) δ 6.41–6.42 (m, 2H), 7.14–7.15 (m, 2H), 7.33 (d, J= 7.2 Hz, 1H), 7.49 – 7.53 (m, 2H), 7.56–7.58 (m, 1H); ¹³C NMR (100MHz, CDCl3) δ 110.9, 114.9–115.4 (m), 119.2, 121.2, 122.1, 127.2, 127.7, 129.9, 136.3–136.9 (m), 138.8–139.7 (m), 141.1, 141.7–142.1 (m), 142.7–143.2 (m), 145.1–145.6 (m); ¹⁹F NMR (376 MHz, CDCl3) δ -161.8 (m, 2F), -154.7 (t, J= 22.5 Hz, 1F), -142.8 (dd, J= 22.5 Hz, J= 7.5 Hz, 2F); MS (EI): m/z (relative intensity) 309.1 (M⁺, 100), 281.0 (16), 261.0 (9), 242.0 (9), 154.5 (8); HRMS: calcd. for C₁₆H₈NF₅⁺: 309.0577, found 309.0579

2′,3′,4′,5′,6′-Pentafluoro-[1,1′-biphenyl]-3-amine (Table 5.3, compound 5qu)¹³c

Eluents (Ethyl acetate: Hexane= 1: 1, Rf= 0.70) was used for flash column chromatography. ¹H NMR (400MHz, CDCl3) δ 3.73 (s, 2H), 6.71 (s, 1H), 6.76–6.80 (m, 2H), 7.27 (t, J= 7.8 Hz, 1H); ¹³C NMR (100MHz, CDCl3) δ 115.9, 116.0–116.2 (m), 116.4, 120.2, 127.2, 129.5, 136.2–136.8 (m), 138.6–139.2 (m), 141.2-141.7 (m),
142.6–143.1 (m), 145.1–145.6 (m), 146.6; $^{19}$F NMR (376 MHz, CDCl$_3$) δ -162.5 (m, 2F), -156.1 (t, $J$ = 22.5 Hz, 1F), -142.8 (dd, $J$ = 22.5 Hz, $J$ = 7.5 Hz, 2F); MS (EI): $m$/z (relative intensity) 258.8 (M$^+$, 74), 191.9 (60), 160.8 (29), 116.9 (62), 93.0 (45).

**N-(2',3',4',5',6'-Pentafluoro-[1,1'-biphenyl]-3-yl)acetamide (Table 5.3, compound 5ru)**

![Chemical Structure](image)

Eluents (Ethyl acetate: Hexane= 1: 1, R$_f$ = 0.70) was used for flash column chromatography. White solid; m.p. 184.1 – 185.4 °C; $^1$H NMR (400MHz, (CD$_3$)$_2$CO) δ 2.12 (s, 3H), 7.19 (d, $J$ = 7.6 Hz, 1H), 7.48 (t, $J$ = 8.0 Hz, 1H), 7.72 (d, $J$ = 8.0 Hz, 1H), 7.92 (s, 1H), 9.37 (s, 1H); $^{13}$C NMR (100MHz, CDCl$_3$) δ 25.3, 115.9–116.5 (m), 121.3, 122.0, 126.7, 127.8, 130.0, 137.0–137.5(m), 139.0, 139.4–140.2 (m), 142.0–142.7 (m) 143.3–143.9 (m), 145.7–146.3 (m), 169.1; $^{19}$F NMR (376 MHz, (CD$_3$)$_2$CO) δ -164.8 (m, 2F), -158.4 (t, $J$ = 22.5 Hz, 1F), -144.7 (dd, $J$ = 22.5 Hz, $J$ = 7.5 Hz, 2F); MS (EI): $m$/z (relative intensity) 301.0 (M$^+$, 23), 259.0 (100), 231.0 (11), 205.0 (6), 181.0 (4); HRMS: calcd. for C$_{14}$H$_9$NOF$_5$$^+$: 302.0599, found 302.0601.

**1-(Cyclopent-1-en-1-yl)-2,3,4,5,6-pentafluorobenzene (Table 5.3, compound 5su)**

![Chemical Structure](image)

Eluents (Hexane, R$_f$ = 0.50) was used for flash column chromatography. Colorless liquid; $^1$H NMR (400MHz, CDCl$_3$) δ 1.97–2.05 (m, 2H), 2.52–2.57 (m, 2H), 2.57–2.76 (m, 2H), 6.22 (bs, 1H); $^{13}$C NMR (100MHz, CDCl$_3$) δ 23.3, 33.3, 35.4, 112.6–
113.1 (m), 129.2, 136.1–136.6 (m), 136.7, 138.0–138.6 (m), 138.6–139.2 (m), 140.5–140.9 (m), 143.0–143.5 (m), 145.4–145.9 (m); $^{19}$F NMR (376 MHz, CDCl$_3$) δ -163.5 (m, 2F), -157.7 (t, $J$ = 22.5 Hz, 1F), -140.5 (dd, $J$ = 22.5 Hz, $J$ = 7.5 Hz, 2F); MS (EI): $m$/z (relative intensity) 234.0 (M$^+$, 81), 218.9 (87), 180.9 (38), 87.0 (100), 69 (23); HRMS: calcd. for C$_{11}$H$_7$F$_5^+$: 234.0468, found 234.0456.

2,3,5,6-Tetrafluoro-4'-methyl-4-(trifluoromethyl)-1,1'-biphenyl (Table 5.3, compound 5av)$^{20}$

Eluents (Hexane, R$_f$ = 0.50) was used for flash column chromatography. $^1$H NMR (400MHz, CDCl$_3$) δ 2.46 (s, 3H), 7.34–7.40 (m, 4H); $^{13}$C NMR (100MHz, CDCl$_3$) δ 21.3, 108.0, 116.9, 119.6, 122.3, 123.1, 124.8–125.1 (m), 129.6, 129.8, 140.3, 142.7–143.3 (m), 145.1–146.0 (m); $^{19}$F NMR (376 MHz, CDCl$_3$) δ -141.7 (m, 2F), -141.1 (m, 2F), -56.3 (t, $J$ = 22.5 Hz, 3F); MS (EI): $m$/z (relative intensity) 308.0 (M$^+$, 100), 289.0 (25), 219.0 (64), 91.1 (13), 69.0 (42).

5.5 References


(7) The cost of 2-Pyridineboronic acid is USD 86.2/100mg for Aldrich in 2014-2015.


(12) For selected example of raw materials of heteroaryl tosylates and heteroaryl chlorides: The cost of 2(1H)-pyridinone and 2-chloropyridine are USD 92.7/10 mg and USD 27.5/10 g, respectively, from Aldrich catalogue 2014-2015.


(16) Shabalin, A. Y.; Adonin, N. Y.; Bardin, V. V.; Parmon, V. N. Tetrahedron, 2014, 3720.


Chapter 6 Palladium-Catalyzed Hiyama Cross-Coupling Reaction of Aryl and Heteroaryl Chlorides under Solvent-Free Reaction Condition

6.1 Introduction

Palladium-catalyzed cross-coupling reactions have become versatile protocols in organic synthesis for construction of carbon-carbon or carbon-heteroatom bonds.\textsuperscript{1} Suzuki,\textsuperscript{2} Negishi,\textsuperscript{3} Kumada,\textsuperscript{4} and Stille\textsuperscript{5} reactions are common methods for the preparation of biaryls which have numerous applications in pharmaceutical, material, and agricultural chemistry.\textsuperscript{6} Hiyama\textsuperscript{7} cross-coupling reaction is one of the most attractive methodology to access biaryl compounds because of low cost, low toxicity, commercial availability, easy preparation and handling and high stability to a variety of reaction conditions of organosilicon reagents. However, organosilicons are less reactive electrophiles owing to their less polarized carbon and silicon bonds.

Aryl(alkoxy)silane is one of the most extensively studied organosilicons\textsuperscript{8} in Hiyama coupling since the initial report by Shibata and coworkers.\textsuperscript{9} Reactive aryl iodides and bromides have been predominantly used as electrophiles in the Hiyama coupling reactions instead of the relatively cheaper and more commercially available aryl chlorides.\textsuperscript{10} Since the initial attempt of the use of 10mol% Pd\textsubscript{2}dba\textsubscript{3}/John-phos system for the Hiyama coupling of PhSi(OMe)\textsubscript{3} with 4-chloroacetophenone to give 47% product yield\textsuperscript{11}, the effectiveness of the Hiyama coupling of aryl chlorides has not been improved significantly comparing with other cross-coupling methodologies. Palladium catalytic systems such as Pd/(o-tol)\textsubscript{3}P\textsuperscript{12}, Pd/i-Pr-DPE phos\textsuperscript{13}, Pd/(4-FC\textsubscript{6}H\textsubscript{4})\textsubscript{3}P\textsuperscript{14}, Pd/phosphite\textsuperscript{15}, Pd/phosphonate\textsuperscript{16}, Pd/carbene ligand\textsuperscript{17}, Pd/diamine ligand\textsuperscript{18}, Pd/diimine ligand\textsuperscript{19}, Pd/thiourea ligand\textsuperscript{20}, Pd/MIDA ligand\textsuperscript{21}, ligand free Pd/C systems\textsuperscript{22} and SBA-15-supported Pd nanoparticles\textsuperscript{23} for the Hiyama coupling of aryl(alkoxy)silane with aryl chlorides have been reported. However, in
general, these reports are commonly suffered from 1) narrow substrate scope (unreactive/poor results for the electron rich aryl chlorides and/or functionalized aryl chlorides); 2) limited examples (only few aryl chlorides are demonstrated in some reports); 3) high catalyst loading (3-5 mol% Pd catalysts are commonly used), 4) long reaction time (10-24 h for conventional heating). Moreover, in some cases, rising the reaction temperature is not the effective mean to improve the yield. [16, 18]

![Hiyama Coupling](image)

**Previous work:**

- **Conventional heating**
  1. Medium to high catalyst loading (0.5-5 mol%Pd)
  2. Long reaction time (12-24 h)
  3. Require solvents (e.g. Toluene, Dioxane)
  4. Limited examples for solvent-free conditions of aryl chlorides

- **Microwave heating**
  1. Medium to low catalyst loading (0.5-1 mol%Pd)
  2. Short reaction time (0.5 h)
  3. Require solvents (e.g. H2O)
  4. High instrumental cost

- **Common limitations**
  1. Lack of the use of heteroaryl silanes for heteroaryl-heteroaryl synthesis
  2. Limited examples for sterically hindered biaryl synthesis

**This work:**

- **Conventional heating**
  1. Low catalyst loading (down to 0.05 mol%Pd)
  2. Short reaction time (3 h)
  3. Solvent-free conditions for most of substrates
  4. Wide substrate scope (32 examples)
  5. Solventless large-scaled synthesis (100 mmol scale)
  6. Success in sterically hindered di-ortho substituted biaryl synthesis
  7. First report of heteroaryl-heteroaryl synthesis
  8. Demonstrate acid or water protocol to minimize side products

**Figure 6.1** General limitations of Hiyama-coupling of aryl chlorides by conventional heating.
Recently, breakthrough such as lowering the catalyst loading to 0.5 mol% Pd, shorter reaction time, wider substrate scope (steric hindered aryl chlorides) have been made by Verkade and coworker’s Pd/\textit{t}Bu\textsubscript{3}P-N=P(\textit{t}BuNCH\textsubscript{2}CH\textsubscript{2})\textsubscript{3}N catalyst\textsuperscript{24}, Jin and coworker’s β-diketiminatophosphate Pd complex\textsuperscript{19b} and wang and coworker’s dinuclear NHC/Pd complex\textsuperscript{17c}. Yet, catalyst loading remains high and the heteroaryl-heteraryl Hiyama coupling keep silent. Microwave irradiation is found to be an alternative to improve the catalytic activity of the Hiyama coupling of aryl chlorides.\textsuperscript{25,26} Despite of the high cost, the availability of the microwave instrument and technical concerns such as solvent and heat control especially for large scale synthesis\textsuperscript{27}, aryl bromides are still predominantly used in current microwave irradiated Hiyama coupling reaction. Therefore, development of highly effective catalyst for the Hiyama coupling reactions by all means is highly desired.

In view of the current limitations and our persisting interests in the palladium-catalyzed coupling reactions, we would like to develop a highly active catalytic system and environmental friendly solvent-free condition with conventional heating to achieve multi-target of Hiyama coupling reaction such as lowering the catalyst loading\textsuperscript{28}, expending the substrate scope, and applying the catalysis to pilot scale (50-200 mmol\textsuperscript{28}). Indole-scaffolded phosphine ligands, which are developed by our group, showed excellent activities towards a board range of palladium-catalyzed coupling reactions.\textsuperscript{29} Among them, the 3-(dicyclohexylphosphino)-2-phenylindole \textbf{L1} is effective ligand in various coupling reactions with aryl chlorides.\textsuperscript{30} We believed that the indolyl scaffold may provide effective steric and electronic influence\textsuperscript{31} towards palladium center and increase the catalytic activity of the catalytic system. Herein, we report the highly efficient indolyl phosphine ligand \textbf{L2} to the solvent-free Hiyama coupling reaction of aryl/heteroaryl chlorides with aryl/heteroaryl tri(alkoxy)silanes.
6.2 Results and discussion

6.2.1 Preliminary evaluation of palladium-catalyzed Hiyama cross-coupling reaction of aryl chlorides

In order to investigate the feasibility of palladium-catalyzed Hiyama cross-coupling reaction of aryl chlorides, sterically hindered 2-chlorotoluene and phenyltrimethoxysilane were chosen as the benchmark substrates. The results are promising, under 0.2 mol% Pd, indolyl phosphine ligands that the phosphino group attached to the 3-position of indole ring (Table 6.1, entries 1-3) are highly active towards the Hiyama coupling reaction. The results (Table 6.1, entries 1-5) also shows that the Hiyama coupling reaction is sensitive to the steric (product yield increase along with increasing the ortho steric hindrance of the indole bottom ring, (L1-L3)) and electronic factors (product yield significantly decrease, if attaching the phosphino group to the nitrogen position, (L1 and L4)) of the phosphine ligands and the 2-arylindole provided an excellent scaffold (L1 and L5) to affect the Hiyama coupling reaction. Commercially available and well recognized ligands such as phosphine ligands L6 (CataCXiumA), L7 (dppf), dinitrogen ligand L8 (DABCO), and NHC carbine ligands L9 (IMes•HCl), L10 (IPr•HCl) were examined. However, they were found to be inactive ligands towards the Pd-catalyzed Hiyama coupling reaction. Commonly used fluoride bases were screened (Table 6.1, entries 1, 11 and 12). TBAF•3H2O was found to be the best base while KF and CsF hardly promoted the Hiyama reaction. Upon surveying the Pd sources (Table 6.1, entries 1, 11 and 12), Pd(OAc)2 afforded the best product yield. It is worthy to note that Pd/L2 system gives the best result among L1-L10 under solvent-free condition and also achieved the lowest catalyst loading so far for this entry in Hiyama coupling reaction (Table 6.1, entry 2).
Table 6.1 Initial screenings of palladium-catalyzed Hiyama cross-coupling reaction of 2-chlorotoluene with phenyltrimethoxysilane\textsuperscript{[a]}

<table>
<thead>
<tr>
<th>entry</th>
<th>Pd source</th>
<th>promotor/base</th>
<th>ligand</th>
<th>% yield\textsuperscript{[b]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)\textsubscript{2}</td>
<td>TBAF’3H\textsubscript{2}O</td>
<td>L1</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)\textsubscript{2}</td>
<td>TBAF’3H\textsubscript{2}O</td>
<td>L2</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)\textsubscript{2}</td>
<td>TBAF’3H\textsubscript{2}O</td>
<td>L3</td>
<td>77</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)\textsubscript{2}</td>
<td>TBAF’3H\textsubscript{2}O</td>
<td>L4</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)\textsubscript{2}</td>
<td>TBAF’3H\textsubscript{2}O</td>
<td>L5</td>
<td>33</td>
</tr>
<tr>
<td>6</td>
<td>Pd(OAc)\textsubscript{2}</td>
<td>TBAF’3H\textsubscript{2}O</td>
<td>L6</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>Pd(OAc)\textsubscript{2}</td>
<td>TBAF’3H\textsubscript{2}O</td>
<td>L7</td>
<td>0\textsuperscript{[c]}</td>
</tr>
<tr>
<td>8</td>
<td>Pd(OAc)\textsubscript{2}</td>
<td>TBAF’3H\textsubscript{2}O</td>
<td>L8</td>
<td>0</td>
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<td>Pd(OAc)\textsubscript{2}</td>
<td>TBAF’3H\textsubscript{2}O</td>
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<td>TBAF’3H\textsubscript{2}O</td>
<td>L10</td>
<td>0</td>
</tr>
</tbody>
</table>
6.2.2 Scope of palladium-catalyzed Hiyama cross-coupling reaction of aryl chlorides

With the preliminary optimized reaction conditions in hand, a wide range of electron rich, electron neutral and functionalized aryl chlorides were used to test the efficiency of the Pd/L2 system. Sterically hindered, electron neutral and electron rich aryl chlorides were coupled with phenyl(trimethoxy)silane to give excellent yields (Table 6.2, entries 1-8). Apart from aryl chlorides, electron-deficient and -rich trialkoxysilanes were also able to couple and gave products in good yields (Table 6.2, entries 9-11). An array of common function groups such as -CF3, -F, -COMe, -CO2Me, -COPh and -CN were compatible and afforded excellent product yields (Table 6.2, entries 12-22). A free -NH2 group in 3-chloroaniline was remained intact under this optimized reaction condition (Table 6.2, entry 23). During the study of the Hiyama reaction, we observed lower yield for the ArCl baring an ester functional group (Table 6.2, entries 15 and 19) and corresponding benzoic acid. The addition of acetic acid to the reaction mixture was found to able to neutralize the methoxide anion32, and thus to reduce the possibility of alkaline hydrolysis of ester group and improve the product.
yield (Table 6.2, entries 15-20). The catalyst loading could be down to 0.2-0.05 mol% Pd. To our best knowledge, this is the lowest catalyst loading reported for the Hiyama coupling of aryl chlorides with aryl(trialkoxy)silanes.33

**Table 6.2** Palladium-catalyzed Hiyama cross-coupling reaction of aryl chlorides$^\text{[a]}$

<table>
<thead>
<tr>
<th>entry</th>
<th>ArCl</th>
<th>Ar’Si(OR)$_3$</th>
<th>product</th>
<th>mol% Pd</th>
<th>% yield$^\text{[b]}$</th>
</tr>
</thead>
</table>
| 1     | \(\text{Me}^+\text{Me}^-\text{Cl}^-\) | (MeO)$_3$Si   | \(\text{Me}^+\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^-\text{Me}^{
[a] Reaction condition: ArCl (0.5 mmol), Ar’Si(OR)₃ (1.0 mmol), Pd(OAc)₂/ L₁ = 1:4 and TBAF·3H₂O (1.0 mmol) were stirred for 3 h at 110 °C under nitrogen. [b] Isolated yields. [c] 0.35 equiv. AcOH was added. [d] 0.25 equiv. AcOH was added. [e] 0.25 equiv. AcOH and toluene (0.5 mL) were added. [f] 0.50 equiv. AcOH was added. [g] Toluene (0.5 mL) was added.
6.2.3 Investigation of proton source of reduced product of sterically hindered aryl chloride and scope of palladium-catalyzed Hiyama cross-coupling reaction of sterically hindered aryl chlorides

Sterically hindered di-ortho-substituted aryl chlorides were found to be extremely difficult substrates in Hiyama coupling with aryl(alkoxy)silanes, which only has single report up to date.\textsuperscript{19b} With the excellent results, we attempted to apply the highly active Pd/L\textsubscript{2} system to the Hiyama coupling of extremely sterically hindered 1-chloro-2,4,6-triisopropylbenzene. However, without the desired coupling product, we obtain reduced 1,3,5-triisopropylbenzene as sole product (Scheme 6.1). We think the methoxide anion which generated from the phenyl(trimethoxy)silane may compete with the transmetalation step of the corresponding silane to undergo the ligand substitution of chloride anion and following the -hydride elimination and reductive elimination to give the reduced arene (Scheme 6.2). We synthesized the SiPh(OCD\textsubscript{3})\textsubscript{3} to perform the deuterium experiment and the reduced 1,3,5-triisopropylbenzene has 99\%D at the reduction position which support our hypothesis (Scheme 6.1).

![Scheme 6.1](image)

**Scheme 6.1** Deuterium experiment of Hiyama coupling reaction of 1-chloro-2,4,6-triisopropylbenzene.
Addition of 0.25-0.50 equivalent of acetic acid to neutralize the methoxide anion was successfully suppressed the generation of 1,3-dimethylbenzene and increased the yield of desired coupling product (Table 6.3, entries 2-4). Since certain amount of 1,3-dimethylbenzene still observed (Table 6.3, entries 2-4) and excess acetic acid reduced the rate of reaction (Table 6.3, entries 4 and 5), we attempted to use water as a mild proton source to protonate the methoxide anion meanwhile the reaction rate is able to remain intact (Table 6.3, entries 6-9). The addition of 10 equiv of water is highly sufficient to suppress the formation of 1,3-dimethylbenzene so as to greatly improve the desired yield (Table 6.3, entries 1 and 8). The highly sterically congested di-ortho-substituted aryl chlorides were found to be feasible coupling partners in the Hiyama coupling reaction with this new reaction protocol (Table 6.4, entries 1-5). Fair yield could also be obtained in the tri-ortho-substituted Hiyama coupling reaction (Table 6.4, entry 6).
Table 6.3 Investigation of water and acid effect on Hiyama cross-coupling reaction of sterically hindered aryl chlorides\(^{[a]}\)

<table>
<thead>
<tr>
<th>entry</th>
<th>AcOH (equiv.)</th>
<th>H(_2)O (equiv.)</th>
<th>% yield(^{[b]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>56(^{[c]})</td>
</tr>
<tr>
<td>2</td>
<td>0.25</td>
<td>-</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>0.35</td>
<td>-</td>
<td>74(^{[d]})</td>
</tr>
<tr>
<td>4</td>
<td>0.50</td>
<td>-</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>1.0</td>
<td>-</td>
<td>22</td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>2.5</td>
<td>69</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>5.0</td>
<td>81</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>10</td>
<td>97</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>20</td>
<td>49</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Reaction condition: 1,3-dimethyl-2-chlorobenzene (0.5 mmol), phenyltrimethoxysilane (1.0 mmol), Pd(OAc)\(_2\)/L1 =1:4, TBAF·3H\(_2\)O and acetic acid or water additive were stirred at 110 °C for 3 h. \(^{[b]}\) FID yield calibrated using dodecane as internal standard. \(^{[c]}\) 0.5 mol%Pd(OAc)\(_2\). \(^{[d]}\) Isolated yield.
Table 6.4 Palladium-catalyzed Hiyama cross-coupling reaction of steric hindered aryl chlorides\(^{[a]}\)

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>ArCl</th>
<th>Ar‘Si(OR)(_3)</th>
<th>product</th>
<th>mol% Pd</th>
<th>% yield(^{[b]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>0.2</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>0.2</td>
<td>74(^{[c]})</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td>0.5</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td>0.5</td>
<td>70(^{[c]})</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td>1.0</td>
<td>66(^{[d]})</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td>1.0</td>
<td>36(^{[c,d]})</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Reaction condition: ArCl (0.5 mmol), Ar‘Si(OR)\(_3\) (1.0 mmol), Pd(OAc)\(_2\)/L1 =1:4, TBAF\(3\)H\(_2\)O (1.0 mmol), and 10 equivalent of H\(_2\)O were stirred for 3 h at 110 °C under nitrogen. \(^{[b]}\) Isolated yields. \(^{[c]}\) 0.35 equivalent of AcOH was used instead of H\(_2\)O. \(^{[d]}\) NMR yield.
6.2.4 Scope of palladium-catalyzed Hiyama cross-coupling reaction of heteroaryl chlorides and alkenyl chloride

Apart from electron rich and steric hindered aryl chlorides, heteroaryl chlorides are another difficult class of substrates in Hiyama coupling reaction. In general, even assisting with the microwave irradiation, 0.5-1.0 mol%Pd is still necessary to affect the Hiyama coupling reaction of heteroaryl chlorides to obtain good to excellent product yield. However, using Pd/L2 system, a range of heteroaryl chlorides can be smoothly coupled with aryltrialkyl oxysilanes to give good to excellent yields of the corresponding produces under solvent-free condition and the catalyst loading can be down to 0.05mol%Pd (Table 6.5, entries 1-5). Alkenyl chloride is also a feasible coupling partner for the Hiyama coupling reaction (Table 6.5, entry 6).
Table 6.5 Palladium-catalyzed Hiyama cross-coupling reaction of heteroaryl chlorides and alkenyl chloride with aryltrialkoxyxilanes\[^{[a]}\]

\[
\text{Cl} \quad \text{N} \quad \text{R'} + \text{Si(OR)}_3 \quad \text{Pd(OAc)}_2/\text{L2} \quad \text{TBAF} \cdot 3\text{H}_2\text{O} \quad \text{"Solventless"} \\
\text{110 }^\circ\text{C, 3 h}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>Het-ArCl</th>
<th>Ar'Si(OR)_3</th>
<th>product</th>
<th>mol% Pd</th>
<th>% yield[^{[b]}]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeO</td>
<td>(MeO)_3Si</td>
<td>MeO</td>
<td>0.05</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>(MeO)_3Si</td>
<td>Me</td>
<td>0.1</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>(MeO)_3Si</td>
<td>N</td>
<td>0.2</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>(MeO)_3Si</td>
<td>N</td>
<td>0.2</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>(MeO)_3Si</td>
<td>N</td>
<td>0.1</td>
<td>81</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>(EtO)_3Si</td>
<td>OMe</td>
<td>0.2</td>
<td>63</td>
</tr>
</tbody>
</table>

[^{[a]}]: Reaction condition: ArCl (0.5 mmol), Ar'Si(OR)_3 (1.0 mmol), Pd(OAc)_2/ L1 =1:4 and TBAF·3H_2O (1.0 mmol) were stirred for 3 h at 110 °C under nitrogen. [^{[b]}]: Isolated yields.

6.2.5 Scope of palladium-catalyzed Hiyama cross-coupling reaction of heteroaryl trialkoxyxilanes

Heteroaryl-heteroaryl cross-coupling reaction is found to be one of the most difficult coupling reactions. Since both of the coupling partners are electron-deficient
aromatic compounds which the electron-deficient nucleophiles are usually unstable and often undergo a transmetallation process at a relatively slower rate. With 1mol% Pd catalyst of Pd/L2 system and toluene as solvent\textsuperscript{34}, electron-deficient and heteroaryl chlorides were coupled with heteroaryl (ethoxy)silanes for the first time in Hiyama coupling reaction (Table 6.6, entries 1-5).

Table 6.6 Palladium-catalyzed Hiyama cross-coupling reaction of aryl- or hetero-aryl chlorides with heteroaryl trialkyoxysilanes\textsuperscript{[a]}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Het-ArCl</th>
<th>Het-Ar’Si(OR)\textsubscript{3}</th>
<th>Product</th>
<th>mol% Pd</th>
<th>% yield\textsuperscript{[b]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F\textsubscript{3}C-C-Cl</td>
<td>(EtO)\textsubscript{3}Si-Cl</td>
<td>![Product Image]</td>
<td>1</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>N/Me-Cl</td>
<td>(EtO)\textsubscript{3}Si-Cl</td>
<td>![Product Image]</td>
<td>1</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>N/OMe-Cl</td>
<td>(EtO)\textsubscript{3}Si-Cl</td>
<td>![Product Image]</td>
<td>1</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>N/Me-Cl</td>
<td>(EtO)\textsubscript{3}Si-Cl</td>
<td>![Product Image]</td>
<td>1</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>OMe/N/Cl</td>
<td>(EtO)\textsubscript{3}Si-Cl</td>
<td>![Product Image]</td>
<td>1</td>
<td>54</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} Reaction condition: ArCl (0.5 mmol), Ar’Si(OR)\textsubscript{3} (1.0 mmol), Pd(OAc)\textsubscript{2}/ L1 =1:4,
TBAF·3H₂O (1.0 mmol), and 1mL toluene were stirred for 3 h at 110 °C under nitrogen. [b] Isolated yields.

6.2.6 Application in large-scaled biaryl synthesis

To test the feasibility of scaling up the current reaction condition and to magnify the advantages of conventional heating for the routine application, a large scale Hiyama cross-coupling reaction was conducted (Scheme 6.3). Notably, without degasification and purification of the reactants, 3-chlorotoluene and phenyltrimethoxysilane was directly scaled up 200 times as Table 6.2 conditions to give the coupling product without any diminishing of the yield (Table 6.2, entry 4 and scheme 6.3).

![Scheme 6.3 Large scale solvent-free Hiyama cross-coupling reaction of 3-chlorotoluene and phenyltrimethoxysilane.](image)

6.3 Conclusion

In conclusion, the Pd/L2 system is highly efficient towards Hiyama cross-coupling reaction. Aryl and heteroaryl chlorides are smoothly coupled with aryltrialkoxysilanes under solvent-free condition to give excellent yields within 3h. A wide range of aryl chlorides bearing common functional groups such as cyano, ketone, ester, and amine were compatible in the mild reaction conditions and the catalyst loading can be down to 0.05mol%Pd for the first time. The deuterium experiment reveals the possible pathway of the formation of reduced arenes and implies an
addition of acid or water protocol which improves the yield of Hiyama coupling of the sterically hindered aryl chlorides dramatically. Particularly noteworthy is that the Hiyama coupling of heteroaryl chlorides with heteroaryltrialkoxytirisilanes are reported for the first time. Under the conventional heating, the reaction can be easily scale up 200 times (100mmol) without degasification and purification of reactants. We are anticipating this highly efficient protocol to be widely adapted in routine synthesis.

6.4 Experimental section

6.4.1 General considerations

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. All Hiyama cross-coupling reactions were performed in resealable screw cap Schlenk tube (approx. 15 mL volume) in the presence of Teflon-coated magnetic stirrer bar (4 mm × 10 mm). A blast shield was applied to all close-capped reactions. Toluene and tetrahydrofuran (THF) were distillated from sodium and sodium benzophenone ketyl under nitrogen, respectively. Indolylphosphine ligand L1, L3 and L4 were prepared according to the reported procedures. Indolylphosphine ligand L1, L3 and L4 were prepared according to the reported procedures. Ligands L5 – L10 were purchased from commercial suppliers. Tetrabutylammonium fluoride trihydrate (TBAF·3H2O) was purchased from Fluka. KF and CsF were purchased from Aldrich. Aryl silanes except for 1H-indole, 1-methyl-5-(triethoxysilyl) and silane, tri(methoxy-d5)phenyl- (9CI) were purchased from commercial suppliers and used directly. 1H-indole, 1-methyl-5-(triethoxysilyl) and silane, tri(methoxy-d5)phenyl- (9CI) were synthesized according to the reported procedures. New bottle of n-butyllithium was used (Note: since the concentration of n-BuLi may vary, we recommend performing a titration prior to use). Thin layer chromatography was performed on pre-coated silica gel 60 F254 plates. Silica gel
(Merck, 70-230 and 230-400 mesh) was used for column chromatography. Melting points were recorded on an uncorrected Büchi Melting Point B-545 instrument. NMR spectra were recorded on a Bruker spectrometer (400 MHz for $^1$H, 100 MHz for $^{13}$C, 376 MHz for $^{19}$F and 162 MHz for $^{31}$P). Spectra were referenced internally to the residual proton resonance in CDCl$_3$ ($\delta$ 7.26 ppm) as the internal standard. Chemical shifts ($\delta$) were reported as part per million (ppm) in $\delta$ scale downfield from TMS. $^{13}$C NMR spectra were referenced to CDCl$_3$ ($\delta$ 77.0 ppm, the middle peak). $^{19}$F NMR chemical shifts were determined relative to CFCl$_3$ as the external standard and low field is positive. $^{31}$P NMR spectra were referenced to 85% H$_3$PO$_4$ externally. Coupling constants ($J$) were reported in Hertz (Hz). Mass spectra (EI-MS and ES-MS) were recorded on a HP 5989B Mass Spectrometer. High-resolution mass spectra (HRMS) were obtained on a Bruker APEX 47e FTICR mass spectrometer (ESI-MS). GC-MS analysis was conducted on a HP 5973 GCD system using a HP5MS column (30 m × 0.25 mm). The products described in GC yield were accorded to the authentic samples/dodecane calibration standard from HP 6890 GC-FID system. All yields reported refer to isolated yield of compounds estimated to be greater than 95% purity as determined by capillary gas chromatography (GC) or $^1$H NMR. Compounds described in the literature were characterized by comparison of their $^1$H, $^{13}$C and/or $^{19}$F NMR spectra to the previously reported data. The procedures in this section are representative, and thus the yields may differ from those reported in tables.
6.4.2 Preparation of indolylphosphine ligand L2

Indolylphosphine ligand L2 was prepared according to the reported procedures without modification.36b

3-(Dicyclohexylphosphino)-2-(2-methoxyphenyl)-1-methyl-1H-indole (L2)

3-Bromo-2-(2-methoxyphenyl)-1-methyl-1H-indole (10 mmol), n-BuLi (11 mmol) and chlorodicyclohexylphosphine (12 mmol) in THF (25 ml) were given white solid product (3.1 g, 71%). 1H NMR (400 MHz, C₆D₆) δ 1.02-1.39 (m, 10H), 1.50-2.01 (m, 10H), 2.31-2.37 (m, 1H), 2.47-2.54 (m, 1H), 3.09 (s, 3H), 3.23 (s, 3H), 7.09-7.13 (m, 1H), 7.14-7.16 (m, 1H), 7.22-7.26 (m, 2H), 7.44 (d, J = 7.4 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H); 13C NMR (100 MHz, C₆D₆) δ 27.2, 27.3, 29.9, 30.2, 30.3, 30.8, 30.9, 31.8, 32.0, 32.2, 32.4, 33.9, 34.0, 34.5, 34.7, 54.5, 104.5, 104.7, 109.7, 110.4, 119.7, 119.9, 121.3, 121.5, 122.1, 129.8, 130.9, 131.0, 134.01, 134.04, 138.3, 146.5, 146.9, 158.2; 31P NMR (162 MHz, C₆D₆) δ -17.87; MS (EI): m/z (relative intensity) 433.3 (M⁺, 5), 402.3 (100), 320 (10), 268.1 (30).

6.4.3 General procedure for initial ligand and reaction conditions screening

An array of stock solutions of Pd metal sources (0.010 mmol) with ligand (Pd:L =1:4) in freshly distilled THF (4.0 mL) were initially prepared with continuously stirring at room temperature for 1 min. An array of Schlenk tubes were charged with
magnetic stirrer bar (4 mm x 10 mm) and were evacuated and backfilled with nitrogen (3 cycles). The stock solutions (0.40 mL, 0.20 mol% Pd) were added by syringe to the array of Schlenk tubes respectively. The solvent in Schlenk tubes were removed under reduced pressure. The Schlenk tubes were charged with bases and were again evacuated and backfilled with nitrogen (3 cycles). The Schlenk tubes were then added with trimethoxyphenylsilane (0.19 mL, 1.0 mmol) via autopipette. The reaction mixtures were allowed stir for 1 min and 2-chlorotoluene (59 L, 0.50 mmol) was added to each Schlenk tubes via autopipette. This batch of Schlenk tube was resealed and magnetically stirred in a preheated 110 °C oil bath for 3 h. The reactions were allowed to reach room temperature. Ethyl acetate (~8 mL), dodecane (113 μL, internal standard) and water (~2 mL) were added. The organic layer was subjected to GC analysis. The GC yield was previously calibrated by authentic sample/dodecane calibration curve.

6.4.4 General procedure for palladium-catalyzed Hiyama coupling of aryl chlorides

Pd(OAc)$_2$ (2.3 mg, 0.010 mmol) with ligand L$_2$ (17.3 mg, 0.040 mmol) in freshly distilled 10 mL THF (0.2 mol% Pd per 1 mL stock solution) were initially prepared with continuously stirring at room temperature for 1 min. Schlenk tube was charged with magnetic stirrer bar (4 mm x 10 mm) and was evacuated and backfilled with nitrogen (3 cycles). The corresponding volume of stock solution was added by syringe to the tube. The solvent was removed under reduced pressure. TBAF•3H$_2$O (0.32 g, 1.0 mmol) and solid aryl chlorides (0.50 mmol) was added to the tube which was again evacuated and backfilled with nitrogen (3 cycles). trimethoxyphenylsilane (0.19 mL, 1.0 mmol) was then added to the tube via
autopipette and the reaction mixture was allowed stir for 1 min. Liquid aryl chlorides (0.50 mmol) was added to the tube via autopipette. Acetic acid and/or toluene (0.50 mL) were then added via autopipette and syringe respectively (if needed, as indicated in Table 2 and 3). The tube was resealed and magnetically stirred in a preheated 110 °C oil bath for 3 h. The reaction was allowed to reach room temperature. Ethyl acetate (~8 mL), water (~2 mL) were added. The organic layers were combined and concentrated. The crude products were purified by column chromatography on silica gel (230-400 mesh).

6.4.5 General procedure for large-scale Hiyama coupling of aryl chlorides

Pd(OAc)$_2$ (23 mg, 0.10 mmol) and ligand L2 (0.173 g, 0.40 mmol) were loaded to a 250 mL Schlenk flask (with a glass stopcock and 24/29 joint with hooks) which equipped with a magnetic stirrer bar (30 mm x 6 mm) and fitted with septum. The flask was carefully evacuated and backfilled with nitrogen for three cycles. Precomplexation was accomplished by adding 10 mL freshly distilled THF in to the flask and the solution was allowed to stir at room temperature for 1 min. The solvent was removed under reduced pressure. TBAF•3H$_2$O (63 g, 0.20 mol) was quickly charged to the flask which was evacuated and backfilled with nitrogen for other three cycles. Trimethoxyphenylsilane (38 mL, 0.20 mol) was then added to the tube by syringe and the reaction mixture was allowed to stir for 10 min. 3-chlorotoluene (11.8 mL, 0.10 mol) was added to the flask by syringe and allowed to stir for another 5 min. The septum was replaced with a 24/29 stopper with hooks which was then fixed with wire to the flask. The stopcock was closed and the flask was placed in a preheated 110 °C oil bath for 3 h. The reaction was allowed to reach room temperature. Ethyl acetate and water were added to the flask and the mixture was transferred to
separating funnel and subjected to extraction. The organic layers were combined and concentrated. The crude product was filtered through a pad of silica gel (10 cm x 20 cm, 230-400 mesh) and eluted with hexane to yield the pure 3-methylbiphenyl (16.6 g, 99%).

6.4.6 Characterization data for cross-coupling products

2-Methyl-1,1'-biphenyl (Table 6.2, entry 1)\textsuperscript{36a}

\[
\begin{align*}
\text{Me} & \\
\textbf{Me} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

Eluents (Hexane, \(R_f = 0.55\)) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.36 (s, 3H), 7.32–7.36 (m, 4H), 7.40–7.43 (m, 3H), 7.47–7.51 (m, 2H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 20.4, 125.7, 126.7, 127.2, 128.0, 129.2, 129.8, 130.3, 135.3, 141.9, 142.0; MS (EI): \(m/z\) (relative intensity) 168.1 (M\(^+\), 100), 153.0 (40), 139.0 (8), 115.0 (14), 77.0 (4).

2,3-Dimethyl-1,1'-biphenyl (Table 6.2, entry 2)\textsuperscript{38}

\[
\begin{align*}
\text{Me} & \\
\text{Me} & \\
\textbf{Me} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

Eluents (Hexane, \(R_f = 0.50\)) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.55 (s, 3H), 2.44 (s, 3H), 7.18-7.27 (m, 3H), 7.39–7.44 (m, 3H), 7.49 (t, \(J = 7.2\) Hz, 2H); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 16.9, 20.7, 125.2, 126.6, 127.6, 128.8, 129.4, 134.0, 137.1, 142.2, 142.6; MS (EI): \(m/z\) (relative intensity) 182.1 (M\(^+\), 95), 167.1 (100), 152.0 (26), 128.0 (8), 76.0 (8).
4-Methyl-1,1’-biphenyl (Table 6.2, entry 3)\textsuperscript{36a}

Eluents (Hexane, \(R_f = 0.50\)) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.48 (s, 3H), 7.33 (d, \(J = 7.6\) Hz, 2H), 7.40 (t, \(J = 7.6\) Hz, 1H), 7.50 (t, \(J = 7.6\) Hz, 2H), 7.58 (d, \(J = 8.0\) Hz, 2H), 7.66 (d, \(J = 7.2\) Hz, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 21.1, 126.9, 127.0, 128.7, 129.4, 137.0, 138.3, 141.1; MS (EI): \(m/z\) (relative intensity) 168.0 (M\(^+\), 100), 139.0 (8), 115.0 (15), 91.0 (6), 62.9 (9).

3-Methyl-1,1’-biphenyl (Table 6.2, entry 4)\textsuperscript{39}

Eluents (Hexane, \(R_f = 0.50\)) was used for flash column chromatography. \(^1\)H NMR (400MHz, CDCl\(_3\)) \(\delta\) 2.48 (s, 3H), 7.29 (d, \(J = 7.6\) Hz, 1H), 7.46 (t, \(J = 7.6\) Hz, 2H), 7.52–7.57 (m, 4H), 7.72 (d, \(J = 7.8\) Hz, 2H); \(^{13}\)C NMR (100MHz, CDCl\(_3\)) \(\delta\) 21.5, 124.2, 127.1, 127.2, 127.9, 128.0, 128.6, 128.7, 138.3, 141.2, 141.3; MS (EI): \(m/z\) (relative intensity) 168.1 (M\(^+\), 100), 152.0 (23), 139.0 (5), 115.0 (8), 89.0 (4).

2-Phenynaphthalene (Table 6.2, entry 5)\textsuperscript{32}

Eluents (Hexane, \(R_f = 0.50\)) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.48 (s, 3H), 7.47–7.51 (m, 1H), 7.57–7.63 (m, 4H), 7.82–7.87 (m, 3H), 7.96–8.02 (m, 3H), 8.16 (s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 125.5, 125.7, 125.9, 126.2, 127.3, 127.4, 127.6, 128.2, 128.4, 128.8, 132.6, 133.6, 138.5, 141.1; MS (EI): \(m/z\) (relative intensity) 204.1 (M\(^+\), 100), 176.0 (3), 152.1 (3), 126.0 (3), 101.0
3-Methoxy-1,1'-biphenyl (Table 6.2, entry 6)$^{40}$

Eluents (Ethyl acetate: Hexane= 1: 50, $R_f$= 0.40) was used for flash column chromatography. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.96 (s, 3H), 7.03 (d, $J$= 8.2 Hz, 1H), 7.29 (s, 1H), 7.33 (d, $J$= 8.0 Hz, 1H), 7.46–7.50 (m, 2H), 7.56 (t, $J$= 7.6 Hz, 2H), 7.73 (d, $J$= 7.2 Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 55.1, 112.6, 112.8, 119.6, 127.1, 127.3, 128.7, 129.7, 141.0, 142.7, 159.9; MS (EI): $m/z$ (relative intensity) 184.0 (M$^+$, 100), 154.1 (28), 141.0 (51), 115.0 (92), 76.1 (17).

4-Methoxy-1,1'-biphenyl (Table 6.2, entry 7)$^{36a}$

Eluents (Ethyl acetate: Hexane= 1: 20, $R_f$= 0.50) was used for flash column chromatography. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.90 (s, 3H), 7.05 (d, $J$= 8.8 Hz, 2H), 7.38 (t, $J$= 7.6 Hz, 1H), 7.49 (t, $J$= 7.6 Hz, 1H), 7.59–7.65 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 55.2, 114.2, 126.6, 126.7, 128.1, 128.7, 133.7, 140.8, 159.1; MS (EI): $m/z$ (relative intensity) 184.0 (M$^+$, 100), 169.0 (47), 141.0 (57), 115.0 (52), 89.1 (7).

5-Phenylbenzo[d][1,3]dioxole (Table 6.2, entry 8)$^{32}$

Eluents (Ethyl acetate: Hexane= 1: 9, $R_f$= 0.40) was used for flash column chromatography. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.03 (s, 3H), 6.94 (d, $J$= 8.0 Hz, 1H),
7.11-7.15 (m, 2H), 7.37 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.58 (d, J = 7.2 Hz, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 101.0, 107.6, 108.5, 120.5, 126.8, 126.9, 128.7, 135.5, 140.8, 147.0, 148.0; MS (EI): \(m/z\) (relative intensity) 198.0 (M\(^+\), 100), 139.0 (44), 115.0 (4), 98.8 (4), 77.0 (2).

3-Methyl-4'-(trifluoromethyl)-1,1'-biphenyl (Table 6.2, entry 9)\(^{41}\)

![3-Methyl-4'-(trifluoromethyl)-1,1'-biphenyl](image)

Eluents (Hexane, \(R_f = 0.50\)) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.48 (s, 3H), 7.26 (d, J = 7.4 Hz, 1H), 7.38-7.45 (m, 3H), 7.72 (s, 4H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 21.5, 124.36 (q, J = 270 Hz), 124.37, 125.6 (q, J = 4.0 Hz), 127.4, 128.0, 128.88, 128.92, 129.2 (q, J = 32 Hz), 138.6, 139.8, 144.9; \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) -62.3; MS (EI): \(m/z\) (relative intensity) 236.0 (M\(^+\), 100), 217.1 (13), 165.0 (45), 152.0 (16), 91.1 (6).

4'-Methoxy-3-methyl-1,1'-biphenyl (Table 6.2, entry 10)\(^{42}\)

![4'-Methoxy-3-methyl-1,1'-biphenyl](image)

Eluents (Ethyl acetate: Hexane= 1: 50, \(R_f = 0.50\)) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.47 (s, 3H), 3.89 (s, 3H), 7.03 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 7.6 Hz, 1H), 7.37 (t, J = 7.4 Hz, 1H), 7.41–7.44 (m, 2H), 7.59 (d, J = 8.8 Hz, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 21.5, 55.2, 114.1, 123.8, 127.4, 127.5, 128.1, 128.6, 133.8, 138.2, 140.8, 159.0; MS (EI): \(m/z\) (relative intensity) 198.1 (M\(^+\), 100), 183.0 (51), 155.0 (40), 128.0 (16), 89.0 (4).
4-Methoxy-4'-methyl-1,1'-biphenyl (Table 6.2, entry 11)\(^\text{40}\)

![Structure of 4-Methoxy-4'-methyl-1,1'-biphenyl]

Eluents (Ethyl acetate: Hexane= 1: 9, \(R_f= 0.40\)) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 2.46\) (s, 3H), \(3.90\) (s, 3H), \(7.04\) (d, \(J= 8.4\) Hz, 2H), \(7.30\) (d, \(J= 7.6\) Hz, 2H), \(7.53\) (d, \(J= 6.4\) Hz, 2H), \(7.59\) (d, \(J= 7.8\) Hz, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 21.0\), 55.3, 114.2, 126.6, 127.9, 129.4, 133.7, 136.3, 138.0, 158.9; MS (EI): m/z (relative intensity) 198.1 (M\(^+\), 100), 183.1 (61), 155.0 (45), 128.0 (19), 77.1 (6).

4-(Trifluoromethyl)-1,1'-biphenyl (Table 6.2, entry 12)\(^\text{43}\)

![Structure of 4-(Trifluoromethyl)-1,1'-biphenyl]

Eluents (Hexane, \(R_f= 0.60\)) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.46\) (d, \(J= 7.2\) Hz, 1H), \(7.52\) (t, \(J= 7.6\) Hz, 2H), \(7.64\) (d, \(J= 7.6\) Hz, 2H), \(7.71\)-7.75 (m, 4H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 124.3\) (q, \(J= 270.0\) Hz), 125.7 (q, \(J= 4.0\) Hz), 127.3, 127.4, 128.1, 129.0, 129.3 (q, \(J= 33.0\) Hz), 139.7, 144.7; \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta -62.3\); MS (EI): m/z (relative intensity) 222.1 (M\(^+\), 100), 201.0 (12), 172.0 (4), 152.0 (24), 75.0 (3).

4-Fluoro-1,1'-biphenyl (Table 2, entry 13)\(^\text{43}\)

![Structure of 4-Fluoro-1,1'-biphenyl]

Eluents (Hexane, \(R_f= 0.50\)) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.14\) (t, \(J= 8.6\) Hz, 2H), \(7.36\) (t, \(J= 7.4\) Hz, 1H), \(7.45\) (t, \(J= 7.4\) Hz, 2H), \(7.55\)-7.57 (m, 4H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 115.6\) (d, \(J= 22.0\) Hz), 126.9, 127.2, 128.6 (d, \(J= 8.0\) Hz), 128.8, 137.3 (d, \(J= 3.0\) Hz), 140.2, 162.4 (d, \(J= 244.0\) Hz); \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta -115.7\); MS (EI): m/z (relative intensity) 172.0 (M\(^+\), 100), 151.9 (61).
100), 146.0 (6), 120.0 (3), 74.0 (4), 51.0 (3).

1-([1,1'-Biphenyl]-4-yl)ethanone (Table 6.2, entry 14)\textsuperscript{44}

![Chemical structure of 1-([1,1'-Biphenyl]-4-yl)ethanone]

Eluents (Ethyl acetate: Hexane= 1: 9, R\textsubscript{f} = 0.40) was used for flash column chromatography. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 2.63 (s, 3H), 7.41 (t, \(J = 7.4\) Hz, 1H), 7.47 (t, \(J = 7.4\) Hz, 2H), 7.63 (d, \(J = 7.2\) Hz, 2H), 7.68 (d, \(J = 8.4\) Hz, 2H), 8.03 (d, \(J = 8.4\) Hz, 2H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 26.5, 127.0, 127.1, 128.1, 128.8, 128.9, 135.7, 139.7, 145.6, 197.6; MS (EI): \textit{m/z} (relative intensity) 196.0 (M\textsuperscript{+}, 43), 181.0 (100), 152.0 (65), 126.9 (6), 76.0 (10).

Methyl [1,1'-biphenyl]-3-carboxylate (Table 6.2, entry 15-18)\textsuperscript{45}

![Chemical structure of Methyl [1,1'-biphenyl]-3-carboxylate]

Eluents (Ethyl acetate: Hexane= 1: 9, R\textsubscript{f} = 0.50) was used for flash column chromatography. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 3.96 (s, 3H), 7.39 (t, \(J = 7.2\) Hz, 1H), 7.46-7.54 (m, 3H), 7.64 (d, \(J = 7.2\) Hz, 2H), 7.80 (d, \(J = 7.6\) Hz, 1H), 8.04 (d, \(J = 7.6\) Hz, 1H), 8.31 (s, 1H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 52.1, 127.1, 127.7, 128.2, 128.3, 128.8, 128.9, 130.6, 131.5, 140.0, 141.4, 167.0; MS (EI): \textit{m/z} (relative intensity) 212.0 (M\textsuperscript{+}, 87), 196.0 (8), 181.0 (100), 152.0 (92), 76.0 (19).
Methyl [1,1'-biphenyl]-4-carboxylate (Table 6.2, entry 19-20)\(^{40}\)

![Methyl [1,1'-biphenyl]-4-carboxylate](image)

Eluents (Ethyl acetate: Hexane= 1: 9, \(R_f= 0.40\)) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.95 (s, 3H), 7.40 (t, \(J= 7.2\) Hz, 1H), 7.47 (t, \(J= 7.4\) Hz, 2H), 7.62-7.67 (m, 4H), 8.13 (d, \(J= 8.4\) Hz, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 51.9, 126.9, 127.1, 128.0, 128.7, 128.8, 130.0, 139.8, 145.4, 166.8; MS (EI): \(m/z\) (relative intensity) 212.1 (M\(^+\), 72), 181.0 (100), 152.0 (56), 126.0 (5), 76.0 (9).

[1,1'-Biphenyl]-4-yl(phenyl)methanone (Table 6.2, entry 21)\(^{40}\)

![[1,1'-Biphenyl]-4-yl(phenyl)methanone](image)

Eluents (Ethyl acetate: Hexane= 1: 4, \(R_f= 0.50\)) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.41-7.45 (m, 1H), 7.49 (t, \(J= 7.4\) Hz, 1H), 7.58-7.63 (m, 1H), 7.67 (d, \(J= 8.0\) Hz, 2H), 7.72 (d, \(J= 8.4\) Hz, 2H), 7.82-7.86 (m, 2H), 7.92 (d, \(J= 8.4\) Hz, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 126.8, 127.1, 128.1, 128.2, 128.8, 129.9, 130.6, 132.2, 136.1, 137.6, 139.8, 145.0, 196.2; MS (EI): \(m/z\) (relative intensity) 258.1 (M\(^+\), 75), 181.0 (100), 152.0 (64), 105.0 (24), 77.0 (40).

[1,1'-Biphenyl]-4-carbonitrile (Table 6.2, entry 22)\(^{46}\)

![[1,1'-Biphenyl]-4-carbonitrile](image)

Eluents (Ethyl acetate: Hexane= 1: 4, \(R_f= 0.50\)) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.41-7.45 (m, 1H), 7.49 (t, \(J= 7.4\) Hz,
2H), 7.59-7.61 (m, 2H), 7.67-7.73 (m, 4H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 110.8, 118.8, 127.1, 127.6, 128.6, 129.0, 132.5, 139.0, 145.5; MS (EI): m/z (relative intensity) 179.1 (M$^+$, 100), 151.0 (14), 126.0 (3), 100.0 (2), 76.0 (6).

[1,1'-Biphenyl]-3-amine (Table 6.2, entry 23)$^{47}$

![Biphenyl-3-amine](image)

Eluents (Ethyl acetate: Hexane= 1: 2, R$_f$= 0.60) was used for flash column chromatography. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.62 (s, 2H), 6.71 (d, $J$= 7.2 Hz, 1H), 6.94 (s, 1H), 7.04 (d, $J$= 7.6 Hz, 1H), 7.27 (t, $J$= 7.6 Hz, 2H), 7.37 (t, $J$= 7.2 Hz, 1H), 7.46 (t, $J$= 7.6 Hz, 2H), 7.61 (d, $J$= 7.2 Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 113.8, 114.0, 117.6, 127.0, 127.1, 128.6, 129.6, 141.3, 142.4, 146.6; MS (EI): m/z (relative intensity) 169.0 (M$^+$, 100), 141.0 (11), 115.0 (11), 89.0 (4), 71.6 (3).

Benzene-$d$, 2,4,6-tris(1-methylethyl)- (Scheme 6.1)

![Benzene-$d$, 2,4,6-tris(1-methylethyl)](image)

Eluents (Hexane, R$_f$= 0.50) was used for flash column chromatography. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.36 (d, $J$= 6.8 Hz, 18H), 2.93-3.03 (m, 3H), 7.02 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 24.1, 34.2, 34.3, 122.1, 148.6, 148.7; MS (EI): m/z (relative intensity) 205.2 (M$^+$, 27), 190.1 (100), 162.1 (51), 106.0 (20), 92.0 (11); HRMS: calcd. for C$_{15}$H$_{24}$D$^+$: 206.2019, found 206.2016.
2,6-Dimethyl-1,1'-biphenyl (Table 6.4, entry 1-2)\textsuperscript{36a}

![2,6-Dimethyl-1,1'-biphenyl](image)

Eluents (Hexane, \(R_f=0.55\)) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.11 (s, 6H), 7.17-7.26 (m, 5H), 7.40 (t, \(J=7.4\) Hz, 1H), 7.49 (t, \(J=7.4\) Hz, 2H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 20.8, 126.6, 127.0, 127.2, 128.4, 129.0, 136.0, 141.0, 141.8; MS (EI): \(m/z\) (relative intensity) 182.0 (M\(^+\), 72), 167.0 (100), 152.0 (30), 115.0 (21), 77.0 (15).

2,4,6-Trimethyl-1,1'-biphenyl (Table 6.4, entry 3-4)\textsuperscript{38}

![2,4,6-Trimethyl-1,1'-biphenyl](image)

Eluents (Hexane, \(R_f=0.55\)) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.07 (s, 6H), 2.40 (s, 3H), 7.01 (s, 2H), 7.20 (d, \(J=7.8\) Hz, 2H), 7.38 (t, \(J=7.4\) Hz, 1H), 7.47 (t, \(J=7.2\) Hz, 2H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 20.7, 21.0, 126.5, 128.0, 128.3, 129.3, 135.9, 136.5, 139.0, 141.1; MS (EI): \(m/z\) (relative intensity) 196.1 (M\(^+\), 100), 165.0 (66), 141.0 (7), 115.0 (15), 89.0 (13).

2-Methoxy-6-phenylpyridine (Table 6.5, entry 1)\textsuperscript{40}

![2-Methoxy-6-phenylpyridine](image)

Eluents (Ethyl acetate: Hexane= 3: 7, \(R_f=0.50\)) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.09 (s, 3H), 6.74 (d, \(J=8.0\) Hz, 1H), 7.37 (d, \(J=7.6\) Hz, 1H), 7.44 (t, \(J=7.2\) Hz, 1H), 7.51 (t, \(J=7.4\) Hz, 2H), 7.64 (t,
$J = 7.8 \text{ Hz, } 1\text{H}), 8.11 \text{ (d, } J = 7.2 \text{ Hz, } 2\text{H); }^{13}\text{C NMR (100 MHz, CDCl}_3\text{) } \delta 53.1, 109.2, 112.7, 126.6, 128.5, 128.8, 139.0, 139.1, 154.6, 163.7; \text{ MS (EI): } m/z \text{ (relative intensity) 184.0 (M}^+\text{, 100), 154.0 (60), 127.0 (10), 102.0 (6), 77.0 (8).}$

2-Methyl-6-phenylpyridine (Table 6.5, entry 2)$^{40}$

![Structure of 2-Methyl-6-phenylpyridine](image)

Eluents (Ethyl acetate: Hexane= 1: 4, $R_f= 0.50$) was used for flash column chromatography. $^1\text{H NMR (400 MHz, CDCl}_3\text{) } \delta 2.65 \text{ (s, } 3\text{H), 7.08 \text{ (d, } J = 7.6 \text{ Hz, } 1\text{H), 7.42 \text{ (t, } J = 7.2 \text{ Hz, } 1\text{H), 7.47-7.52 \text{ (m, } 3\text{H), 7.61 \text{ (t, } J = 7.6 \text{ Hz, } 1\text{H), 8.02 \text{ (d, } J = 7.6 \text{ Hz, } 2\text{H); }^{13}\text{C NMR (100 MHz, CDCl}_3\text{) } \delta 24.6, 117.5, 121.4, 126.9, 128.5, 128.6, 136.7, 139.6, 156.8, 158.2; \text{ MS (EI): } m/z \text{ (relative intensity) 169.1 (M}^+\text{, 100), 154.0 (8), 127.0 (6), 115.0 (5), 77.0 (6).}$

3-Phenylpyridine (Table 6.5, entry 3)$^{40}$

![Structure of 3-Phenylpyridine](image)

Eluents (Ethyl acetate: Hexane= 1: 2, $R_f= 0.40$) was used for flash column chromatography. $^1\text{H NMR (400 MHz, CDCl}_3\text{) } \delta 7.32-7.35 \text{ (m, } 1\text{H), 7.37-7.41 \text{ (m, } 1\text{H), 7.46 \text{ (t, } J = 7.4 \text{ Hz, } 2\text{H), 7.56 \text{ (d, } J = 7.2 \text{ Hz, } 2\text{H), 7.85 \text{ (d, } J = 7.6 \text{ Hz, } 1\text{H), 8.58 \text{ (d, } J = 3.6 \text{ Hz, } 1\text{H), 8.85 \text{ (s, } 1\text{H); }^{13}\text{C NMR (100 MHz, CDCl}_3\text{) } \delta 123.4, 127.0, 128.0, 129.0, 134.2, 136.5, 137.7, 148.2, 148.3; \text{ MS (EI): } m/z \text{ (relative intensity) 155.1 (M}^+, 100), 127.0 (16), 102.0 (14), 76.0 (7), 51.0 (9).$
6-Phenylquinoline (Table 6.5, entry 4)\textsuperscript{50}

\[
\begin{array}{c}
\text{N} \\
\text{C} \\
\text{C} \\
\text{C} \\
\text{C} \\
\text{C} \\
\text{C} \\
\text{C} \\
\text{C} \\
\end{array}
\]

Eluents (Ethyl acetate: Hexane= 1: 4, \( R_f = 0.25 \)) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 7.35-7.41 (m, 2H), 7.48 (t, \( J = 7.6 \) Hz, 2H), 7.69 (d, \( J = 7.6 \) Hz, 2H), 7.95-7.97 (m, 2H), 8.13-8.19 (m, 2H), 8.89-8.91 (m, 1H); \(^1^3\)C NMR (100 MHz, CDCl\textsubscript{3}) \( \delta \) 121.3, 125.3, 127.3, 127.6, 128.3, 128.8, 129.0, 129.7, 136.1, 139.1, 140.1, 147.5, 150.2; MS (EI): \textit{m/z} (relative intensity) 205.1 (M\textsuperscript{+}, 100), 176.0 (12), 151.0 (6), 102.1 (8), 76.0 (5).

2-Phenylquinoline (Table 6.5, entry 5)\textsuperscript{51}

\[
\begin{array}{c}
\text{N} \\
\text{C} \\
\text{C} \\
\text{C} \\
\text{C} \\
\text{C} \\
\text{C} \\
\text{C} \\
\text{C} \\
\end{array}
\]

Eluents (Ethyl acetate: Hexane= 1: 2, \( R_f = 0.30 \)) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 7.47-7.57 (m, 4H), 7.81 (d, \( J = 8.0 \) Hz, 1H), 7.85 (d, \( J = 8.8 \) Hz, 1H), 7.17-8.24 (m, 4H); \(^1^3\)C NMR (100 MHz, CDCl\textsubscript{3}) \( \delta \) 118.9, 126.2, 127.1, 127.4, 127.5, 128.7, 129.2, 129.5, 129.6, 136.7, 139.5, 148.2, 157.2; MS (EI): \textit{m/z} (relative intensity) 205.1 (M\textsuperscript{+}, 100), 176.0 (6), 151.0 (3), 102.1 (6), 75.0 (4).

1-Cyclopentenyl-4-methoxybenzene (Table 6.5, entry 6)\textsuperscript{36b}

\[
\begin{array}{c}
\text{O} \\
\text{Me} \\
\text{C} \\
\end{array}
\]

Eluents (Hexane, \( R_f = 0.30 \)) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 1.99-2.07 (m, 2H), 2.51-2.56 (m, 2H), 2.67-2.72 (m, 2H), 3.82 (s, 3H), 6.06-6.08 (m, 1H), 6.87 (d, \( J = 8.8 \) Hz, 2H), 7.40 (d, \( J = 8.8 \) Hz, 2H); \(^1^3\)C NMR
(100 MHz, CDCl₃) δ 23.4, 33.2, 33.3, 55.2, 113.6, 123.9, 126.7, 129.7, 141.8, 158.6 ; MS (EI): m/z (relative intensity) 174.1 (M⁺, 100), 159.0 (37), 143.1 (54), 128.0 (35), 91.0 (20).

3-(4-(Trifluoromethyl)phenyl)furan (Table 6.6, entry 1)^52

Eluents (Ethyl acetate: Hexane= 1: 20, Rf= 0.80) was used for flash column chromatography. ¹H NMR (400 MHz, CDCl₃) δ 6.73 (d, J= 0.8 Hz, 1H), 7.52 (dd, J=1.6 Hz, 1.6 Hz, 1H), 7.58 (d, J= 8.0 Hz, 2H), 7.63 (d, J= 8.4 Hz, 2H), 7.80 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ ; ¹⁹F NMR (376 MHz, CDCl₃) δ -62.5; MS (EI): m/z (relative intensity) 212.0 (M⁺, 100), 183.0 (40), 164.0 (15), 133.0 (29), 115.0 (76).

2-(Furan-3-yl)-6-methylpyridine (Table 6.6, entry 2)

Eluents (Ethyl acetate: Hexane= 1: 9, Rf= 0.35) was used for flash column chromatography. ¹H NMR (400 MHz, CDCl₃) δ 2.56 (s, 3H), 6.88 (d, J= 1.2 Hz, 1H), 6.99 (d, J= 7.6 Hz, 1H), 7.24 (d, J= 7.6 Hz, 1H), 7.47 (dd, J= 1.8 Hz, 1.6 Hz, 1H), 7.54 (t, J= 7.6 Hz, 1H), 8.02 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 24.5, 108.7, 117.1, 121.2, 127.2, 136.7, 141.1, 143.6, 151.1, 158.4 ; MS (EI): m/z (relative intensity) 159.0 (M⁺, 100), 130.0 (100), 118.0 (4), 103.0 (13), 77.0 (17); HRMS: calcd. for C₁₀H₁₀NO⁺: 160.0757, found 160.0757.
2-(Furan-3-yl)-6-methoxypyridine (Table 6.6, entry 3)\textsuperscript{53}

\begin{center}
\includegraphics[width=0.2\textwidth]{2-(Furan-3-yl)-6-methoxypyridine.png}
\end{center}

Eluents (Ethyl acetate: Hexane= 1: 9, $R_f= 0.50$) was used for flash column chromatography. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) $\delta$ 3.98 (s, 3H), 6.61 (d, $J= 8.4$ Hz, 1H), 6.87 (d, $J= 0.8$ Hz, 1H), 7.03 (d, $J= 7.2$ Hz, 1H), 7.48 (dd, $J= 1.6$ Hz, 1.6 Hz, 1H), 7.54 (t, $J= 8.0$ Hz, 1H), 8.03 (s, 1H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) $\delta$ 53.1, 108.5, 108.6, 112.4, 127.0, 138.9, 141.2, 143.6, 149.2, 163.7; MS (EI): $m/z$ (relative intensity) 175.0 (M+, 100), 146.0 (32), 117.0 (49), 90.0 (26), 77.0 (10).

1-Methyl-5-(6-methylpyridin-2-yl)-1H-indole (Table 6.6, entry 4)

\begin{center}
\includegraphics[width=0.2\textwidth]{1-Methyl-5-(6-methylpyridin-2-yl)-1H-indole.png}
\end{center}

Eluents (Ethyl acetate: Hexane= 1: 9, $R_f= 0.45$) was used for flash column chromatography. Yellow solid; m.p.= 129.9-132.2; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) $\delta$ 2.65 (s, 3H), 3.82 (s, 3H), 6.57 (d, $J= 2.8$ Hz, 1H), 7.03-7.08 (m, 2H), 7.39 (d, $J= 8.8$ Hz, 1H), 7.56-7.63 (m, 2H), 7.91 (d, $J= 8.8$ Hz, 1H), 8.27 (s, 1H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) $\delta$ 24.8, 32.9, 101.8, 109.3, 117.4, 119.7, 120.5, 121.0, 128.8, 129.4, 131.4, 136.7, 137.2, 158.0, 158.3; MS (EI): $m/z$ (relative intensity) 222.1 (M+, 100), 206.1 (6), 180.1 (5), 155.0 (5), 111.0 (3); HRMS: calcd. for C\textsubscript{15}H\textsubscript{15}N\textsubscript{2}+: 223.1230, found 223.1231.
5-(6-Methoxypyridin-2-yl)-1-methyl-1H-indole (Table 6.6, entry 5)

![Molecule Structure]

Eluents (Ethyl acetate: Hexane= 1: 9, Rf = 0.30) was used for flash column chromatography. Yellow solid; m.p.= 117.3-120.8; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.83 (s, 3H), 4.09 (s, 3H), 6.58 (d, $J$ = 2.8 Hz, 1H), 6.64 (d, $J$ = 8.0 Hz, 1H), 7.08 (d, $J$ = 2.8 Hz, 1H), 7.37-7.41 (m, 2H), 7.62 (t, $J$ = 8.0 Hz, 1H), 7.98 (d, $J$ = 8.8 Hz, 1H); 8.35 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 32.9, 53.2, 101.8, 107.7, 109.2, 112.4, 119.5, 120.8, 128.8, 129.5, 130.7, 139.0, 163.6; MS (EI): m/z (relative intensity) 238.1 (M$^+$, 100), 207.1 (31), 192.0 (11), 155.0 (8), 103.1 (6); HRMS: calcd. for C$_{15}$H$_{15}$N$_2$O$^+$: 239.1179, found 239.1181.

3-Methyl-1,1'-biphenyl (Scheme 6.3)$^{39}$

![Biphenyl Structure]

Eluents (Hexane, Rf = 0.50) was used for flash column chromatography. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.68 (s, 3H), 7.43 (d, $J$ = 7.6 Hz, 1H), 7.59 (t, $J$ = 7.6 Hz, 2H), 7.67–7.70 (m, 4H), 7.87 (d, $J$ = 7.6 Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 21.4, 124.2, 127.1, 127.8, 127.9, 128.4, 128.60, 128.62, 138.2, 141.2, 141.3; MS (EI): m/z (relative intensity) 168.1 (M$^+$, 100), 152.0 (26), 115.0 (10), 82.8 (5), 63.0 (5).
6.5 References


(25) The catalyst loading for limited examples such as 4-chloroanisole, 4-chloroacetophenone, 4-chlorobenzaldehyde, 4-chloronitrobenzene and 4-chlorobenzotrifluoride could be down to 0.1 mol% Pd with moderate to excellent yields under 90-130 °C. However, 1.0-1.5 mol% Pd was still essential for heterocyclic and other aryl chlorides to obtain good yield.


(31) The C-3 position is estimated to be 1013 more reactive than benzene to electrophilic attack, see: Laws, A. P.; Taylor, R. J. Chem. Soc. Perkin Trans. 2 1987, 591.


(33) The only exceptional example is table 2, entry 7. 0.1 mol% Pd was achieved by microwave heating at 120 °C, see: ref. 23b.

(34) Using toluene as solvent can minimize the rapid decomposition of heteraryl(alkoxy)silanes during the Hiyama coupling reaction.


(43) Tang, R.-J.; He, Q.; Yang, L. Chem. Commun. 2015, 51, 5925.


Ed. 2009, 48, 2383.
Chapter 7 Palladium-Catalyzed Borylation of Aryl Chlorides with Pinacol Borane

7.1 Introduction

Arylboronic acids, boronate esters, and potassium trifluoroborate salts are commonly used organoboron intermediates in metal-catalyzed cross-coupling reactions. Suzuki-Miyaura cross-coupling reaction is one of the most significant methodologies utilizing organoboron nucleophiles for the synthesis of biaryl compounds which are important structural motifs in biological active molecules and pharmaceutical compounds. ¹ Although arylboronic acids, boronate esters and potassium trifluoroborate salts are highly stable and non-toxic, their syntheses sometimes are challenging. The traditional method for preparing arylboronic acids and boronate esters is via the halogen-metal exchange (e.g. Mg or Li) of aryl bromides or iodides and subsequent trapping with trialkylborates. However, this synthetic route is incompatible with base-sensitive functional groups (e.g. aldehyde, ketone, nitrile, etc.)³ Therefore, additional protection and deprotection steps are usually required for this synthetic method. Moreover, this protocol is incompatible with relatively inexpensive and broadly available aryl chlorides. Hence, to solve the limitations of the conventional method for preparing arylboronic reagents, transition metal-catalyzed borylation of aryl halides and sulfonates with alkoxyboranes has been developed.² Another approach for constructing C-(sp²)-B bonds involves Re, Ru, Rh and especially Ir-catalyzed direct C-H borylation of arenes.³ However, it is difficult to control the regioselectivity. In 1995, Miyaura pioneered a palladium-catalyzed borylation of aryl halides with bis(pinacolato)diborane.⁴ Since then, a number of palladium-catalyzed borylation has emerged for converting aryl halides and sulfonates to corresponding arylboronate esters. Nickel-catalyzed borylations being other
protocols for generating arylboronic sources have been reported by Perce and co-workers. Although recent notable findings showed great achievements in palladium-catalyzed borylation of aryl halides and sulfonates with tetraalkoxydiboranes, limited palladium catalyst system are effective for borylation of relatively inexpensive and commercially available aryl chlorides with dialkoxyboranes. Dialkoxyboranes such as pinacolborane are more attractive because of relatively low cost, commercial availability and high atom economy.

In 1997, Masuda and coworkers reported palladium-catalyzed borylation of aryl iodides and bromides with dialkoxyhydroborane. Since then, there are great advancements in developing palladium catalyst system for converting aryl iodides, bromides and triflates to corresponding arylboronate esters. Until to 2006, Masuda and coworkers demonstrated that the combination of Pd(dba)$_2$ and $t$-Bu-DPEphos was efficient for coupling of pinacolborane with aryl bromides and chlorides. However, 5 mol% Pd catalyst loading was required and only two examples of aryl chlorides were demonstrated successfully. In 2008, Buchwald and coworkers developed the first general catalyst system consisting of PdCl$_2$(CH$_3$CN)$_2$ and Sphos that converting aryl and heteroaryl chlorides with pinacolborane to corresponding boronate esters successfully. Nevertheless, 3 mol% Pd catalyst loading was required and the substrate scope was limited. Aryl chlorides bearing electron-withdrawing groups were incompatible in that reaction condition. To solve the issue of substrate scope, Masuda and coworkers reported the borylation of electron-deficient aryl chlorides with pinacolborane in the presence of NBu$_4$I as an additive using Pd(dba)$_2$ and $t$-Bu-DPEphos as a catalyst system. Although the aryl chlorides bearing electron-deficient groups were effective substrates under that reaction condition, 5 mol% Pd catalyst loading was required and only activated aryl chlorides were feasible cross-coupling partners. In 2011, Watanabe and coworkers reported the
palladium-catalyzed borylation of arylsulphonates with pinacolborane utilizing Pd(dba)$_2$ and d-t-bpf as a catalyst system.$^{11}$ Aryl sulphonates are the most versatile complementary substrates to aryl halides for various coupling reactions. However, additional protection step of substituted phenols is required. The atom economy is lower compared with that of aryl chlorides. Besides, 5 mol% Pd catalyst loading was required and only activated aryl sulphonates were converted to corresponding arylboronate esters successfully.

To the best of our knowledge, a general protocol for borylation of both non-activated and activated aryl chlorides with pinacolborane under low catalyst loading has been sporadically reported to date. As a result, developing an effective catalyst system for converting a broad range of aryl chlorides to corresponding arylboronate esters using pinacolborane is worthwhile.

Our group has developed two series of C-P type indolylphosphine ligands previously. One is the phosphine group attached to the bottom ring (CM-phos). Another one is the phosphine group incorporated into C-3 position of the indole ring. They are good matching partners with palladium precursors that compose effective catalyst systems for serval cross-coupling reactions (Scheme 7.1, L1, L11, L16 and L2).$^{12}$ They are prepared by simple and straightforward Fischer indolization, bromination (for the indolylphosphine ligands in which the phosphine group attached to C-3 position of the indole ring) and phosphination. Apart from simple and straightforward ligand preparation, the starting materials are inexpensive and readily available. The indolylphosphine ligands are purified easily by single crystallization after phosphination. This type of ligands exhibits high air and moisture stability in both solid and solution states. Particular noteworthy is that the ligand diversity is easily accessed by changing different substituents in different positions of indolyl scaffold for providing a high level of steric and electronic fine-tuning (Figure 7.1 and
7.2). With our previous experiences in dealing with indolylphosphine ligands, we plan to apply well developed Fischer Indolization as our protocol for a new ligand synthesis. With respect to the indolyl scaffold in which the phosphine group attached to the bottom ring, different substituents of the bottom ring are changed, the alkyl groups at the N-position of indolyl scaffold are altered and a variety of substituents attached to the indolyl ring are adjusted for providing additional steric and electronic effects (Scheme 7.1, L2-L9). In regard to the indolyl scaffold in which the phosphine group attached to C-3 position of the indole ring, the bottom ring of indolyl scaffold is fine-tuned by using different substituted acetophenones and the alkyl groups at the N-position of indolyl scaffold are expanded for offering potential of steric and electronic properties fine tuning (Scheme 7.1, L10, L12-L15, L17-L20 and L22-L24).

In continuing our research interests in development of indolylphosphine ligands and palladium-catalyzed borylation of aryl sulfonates and chlorides with bis(pinacolato)boron, herein, we report our effort in developing general catalyst system for coupling aryl chlorides with pinacolborane at 1.0 mol% Pd catalyst loading.
**Figure 7.1** Proposed ligand design with high potential of tunability for indolylphosphine ligands in which the phosphine group attached to the bottom ring.

- **Offers potential of steric and electronic properties fine tuning**
  - e.g. R= Ph, Cy etc.

  - **Offers extra ligand tunability**
    - Providing ortho-steric hindrance by indolyl scaffold
    - Attaching different substituents to provide extra steric hindered and electron tunability
    - e.g. R"= 2-Me, 2-Et etc.

- **Offers high potential of ligand tunability**
  - Incorporating different substituted aryl rings for providing steric and electronic effects
  - e.g. R'= 5-OMe, 5-NMe₂, 5-Me etc.

  - **Offers easy fine tuning**
    - Attaching different substituents on nitrogen atom to afford steric hindered and electronic effect
    - e.g. R"= Me, i-Pr etc.

---

**Figure 7.2** Proposed ligand design with high potential of tunability for indolylphosphine ligands in which the phosphine group attached to C-3 position of the indole ring.

- **Offers potential of steric and electronic properties fine tuning**
  - e.g. R= Ph, Cy etc.

  - **Offers extra ligand tunability**
    - Providing ortho-steric hindrance by indolyl scaffold
    - Attaching different substituents to provide extra steric hindered and electron tunability
    - e.g. R"= 2-Me, 2-Et etc.

- **Offers high potential of ligand tunability**
  - Incorporating different substituted aryl rings for providing steric and electronic effects
  - e.g. R'= 2-Me, 2-OMe, 2-OCH₂Ph, 2-Oi-Pr etc.

  - **Offers easy fine tuning**
    - Attaching different substituents on nitrogen atom to afford steric hindered and electronic effect
    - e.g. R"= Me, i-Pr etc.
**Scheme 7.1** Exploration of two series of indolylphosphine ligands in which the phosphine group attached to the bottom ring and at C-3 position of the indole ring.
7.2 Results and discussion

7.2.1 Preliminary evaluation of palladium-catalyzed borylation of aryl chlorides with pinacol borane

In order to investigate the feasibility of palladium-catalyzed borylation of aryl chlorides with pinacol borane, a series of screening experiments was carried out. 4-chlorotoluene and pinacolborane were used as benchmark substrates. Commercially available and well recognized ligands and our group developed indolylphosphine ligands were examined (Table 7.1). $N$-phosphine substituted ligand L1 showed no product conversion. A variety of the indolylphosphine ligands based on CM-phos ligand scaffold was investigated and afforded poor to moderate product yields (Table 7.1, L2-L10). C3-phosphine-substituted indolylphosphine ligands were then examined (Table 7.1, L11-L27). L18 was the best choice of the indolylphosphine ligands. Changing the substituents of the bottom ring and the $N$-position of C3-indolyl scaffold simultaneously enhanced the catalytic efficiency of the reaction. Disappointingly, ligand L19-L26 with a diphenylphosphine moiety exhibited no product conversion. Buchwald-type ligands L28-L30 and Beller-type ligands L31-L33 showed poor to good catalytic performance. As a result, the catalyst system comprising of Pd$_2$dba$_3$ and L18 was chosen for further optimization of the reaction conditions.
Table 7.1 Investigation of ligand effect on palladium-catalyzed borylation of 4-chlorotoluene with pinacol borane$^{[a,b]}$

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Yield (%)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>L1</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>L2</td>
<td>62% (1 mol% Pd)$^{[c]}$</td>
<td></td>
</tr>
<tr>
<td>L3</td>
<td>7% (1 mol% Pd)$^{[c]}$</td>
<td></td>
</tr>
<tr>
<td>L4</td>
<td>29% (1 mol% Pd)$^{[c]}$</td>
<td></td>
</tr>
<tr>
<td>L5</td>
<td>56% (1 mol% Pd)$^{[c]}$</td>
<td></td>
</tr>
<tr>
<td>L6</td>
<td>45% (1 mol% Pd)$^{[c]}$</td>
<td></td>
</tr>
<tr>
<td>L7</td>
<td>53% (1 mol% Pd)$^{[c]}$</td>
<td></td>
</tr>
<tr>
<td>L8</td>
<td>44% (1 mol% Pd)$^{[c]}$</td>
<td></td>
</tr>
<tr>
<td>L9</td>
<td>34% (1 mol% Pd)$^{[c]}$</td>
<td></td>
</tr>
<tr>
<td>L10</td>
<td>51% (1 mol% Pd)$^{[c]}$</td>
<td></td>
</tr>
<tr>
<td>L11</td>
<td>trace (1 mol% Pd)$^{[c]}$</td>
<td></td>
</tr>
<tr>
<td>L12</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>L13</td>
<td>trace (1 mol% Pd)$^{[c]}$</td>
<td></td>
</tr>
<tr>
<td>L14</td>
<td>24% (1 mol% Pd)$^{[c]}$</td>
<td></td>
</tr>
<tr>
<td>L15</td>
<td>31%</td>
<td></td>
</tr>
<tr>
<td>L16</td>
<td>34%</td>
<td></td>
</tr>
</tbody>
</table>
\[
\begin{align*}
\text{L17} & \quad 33\% \\
\text{L18} & \quad 62\% \\
\text{L19} & \quad 0\% \\
\text{L20} & \quad 0\% (1\text{ mol}\%\text{ Pd})^\text{[c]} \\
\text{L21} & \quad 0\% \\
\text{L22} & \quad 0\% \\
\text{L23} & \quad 0\% \\
\text{L24} & \quad 0\% (1\text{ mol}\%\text{ Pd})^\text{[c]} \\
\text{L25} & \quad \text{trace} (1\text{ mol}\%\text{ Pd})^\text{[c]} \\
\text{L26} & \quad 0\% \\
\text{L27} & \quad 0\% (1\text{ mol}\%\text{ Pd})^\text{[c]} \\
\text{L28} & \quad 44\% \\
\text{L29} & \quad 62\% \\
\text{L30} & \quad 60\% \\
\text{L31} & \quad 3\% \\
\text{L32} & \quad 23\% \\
\text{L33} & \quad 32\% \\
\end{align*}
\]
[a] Reaction condition: 4-chlorotoluene (1.0 mmol), HBpin (1.5 mmol), Pd$_2$(dba)$_3$ (0.25 mol%), L (2.0 mol%), NEt$_3$ (3.0 mmol) and dioxane (3.0 mL) were stirred at 110 °C for 24 h. [b] FID-Calibrated yield using dodecane as internal standard [c] Reaction condition: 4-chlorotoluene (0.5 mmol), HBpin (0.75 mmol), Pd$_2$(dba)$_3$ (0.5 mol%), L (4.0 mol%), NEt$_3$ (1.5 mmol) and dioxane (1.5 mL) were stirred at 110 °C for 24 h.

A variety of palladium sources, bases and solvents were examined and the results were summarized in Table 7.2. Upon surveying the palladium sources (Table 7.2, entries 1, 3-6 and 8), Pd(dba)$_2$ (Table 7.2, entry 3) gave the best result with the product yield of 88% while Pd$_2$(dba)$_3$, PdCl$_2$(CH$_3$CN)$_2$ and Pd(TFA)$_2$ (Table 7.2, entries 1, 6 and 8) also provided compatible yields. Commonly used solvents were examined (Table 7.2, entries 1 and 9-15). Dioxane was the best choice of solvents (Table 7.2, entry 1). An inferior result was obtained when NEt$_3$ was chosen as solvent (Table 7.2, entry 15). Other organic and inorganic bases were investigated (Table 7.2, entries 1 and 16-19). NEt$_3$ was found to be a superior base (Table 7.1, entry 1). NEt$_i$-Pr$_2$ afforded poorer result due to the steric bulkiness causing the difficulty in coordination of Pd precursor when compared with NEt$_3$ (Table 7.1, entry 19). Reaction temperatures (90-120 °C) have been studied (Table 7.2, entry1 and 20-23). The product yields increased from 35% to 84% when the temperature was raised from 90 °C to 110 °C. The slightly decreased yield was obtained when the reaction temperature was further increased to 120 °C (Table 7.2, entry 23). The temperature of 110°C gave the best yield and thus was chosen as a reaction temperature for further investigation (Table 7.2, entry 1).
Table 7.2 Investigation of reaction parameters on palladium-catalyzed borylation of 4-chlorotoluene with pinacol borane

![Chemical structure image]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pd source</th>
<th>Temp. (°C)</th>
<th>Base</th>
<th>Solvent</th>
<th>Pd Loading (mol%), Time (h)</th>
<th>Yield (%)[^b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd$_2$(dba)$_3$</td>
<td>110</td>
<td>NEt$_3$</td>
<td>Dioxane</td>
<td>1 (24)</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>Pd$_2$(dba)$_3$</td>
<td>110</td>
<td>NEt$_3$</td>
<td>Dioxane</td>
<td>0.5 (24)</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>Pd(dba)$_2$</td>
<td>110</td>
<td>NEt$_3$</td>
<td>Dioxane</td>
<td>1 (24)</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)$_2$</td>
<td>110</td>
<td>NEt$_3$</td>
<td>Dioxane</td>
<td>1 (24)</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>PdCl$_2$</td>
<td>110</td>
<td>NEt$_3$</td>
<td>Dioxane</td>
<td>1 (24)</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>PdCl$_2$(CH$_3$CN)$_2$</td>
<td>110</td>
<td>NEt$_3$</td>
<td>Dioxane</td>
<td>1 (24)</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>PdCl$_2$(CH$_3$CN)$_2$</td>
<td>110</td>
<td>NEt$_3$, NEt$_3$</td>
<td>1 (24)</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Pd(TFA)$_2$</td>
<td>110</td>
<td>NEt$_3$</td>
<td>Dioxane</td>
<td>1 (24)</td>
<td>82</td>
</tr>
<tr>
<td>9</td>
<td>Pd$_2$(dba)$_3$</td>
<td>110</td>
<td>NEt$_3$</td>
<td>CH$_3$CN</td>
<td>1 (24)</td>
<td>30</td>
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<td>10</td>
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<td>Toluene</td>
<td>1 (24)</td>
<td>80</td>
</tr>
<tr>
<td>11</td>
<td>Pd$_2$(dba)$_3$</td>
<td>110</td>
<td>NEt$_3$</td>
<td>DMF</td>
<td>1 (24)</td>
<td>trace</td>
</tr>
<tr>
<td>12</td>
<td>Pd$_2$(dba)$_3$</td>
<td>110</td>
<td>NEt$_3$</td>
<td>t-BuOH</td>
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<td>0</td>
</tr>
<tr>
<td>13</td>
<td>Pd$_2$(dba)$_3$</td>
<td>110</td>
<td>NEt$_3$</td>
<td>H$_2$O</td>
<td>1 (24)</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>Pd$_2$(dba)$_3$</td>
<td>110</td>
<td>NEt$_3$</td>
<td>THF</td>
<td>1 (24)</td>
<td>42</td>
</tr>
<tr>
<td>15</td>
<td>Pd$_2$(dba)$_3$</td>
<td>110</td>
<td>NEt$_3$, NEt$_3$</td>
<td>1 (24)</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Pd$_2$(dba)$_3$</td>
<td>110</td>
<td>DMAP</td>
<td>Dioxane</td>
<td>1 (24)</td>
<td>0</td>
</tr>
</tbody>
</table>

[^a]: Reaction conditions: 2 equiv. of 4-chlorotoluene, 2.5 equiv. of pinacol borane L18, 2.5 equiv. of the base, 1 mol% catalyst. 
[^b]: Yields are determined by GC analysis.
<table>
<thead>
<tr>
<th></th>
<th>Pd$_2$(dba)$_3$</th>
<th>Temperature</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>110</td>
<td>DBU</td>
<td>Dioxane</td>
<td>1 (24)</td>
<td>0</td>
</tr>
<tr>
<td>18</td>
<td>110</td>
<td>KOAc</td>
<td>Dioxane</td>
<td>1 (24)</td>
<td>0</td>
</tr>
<tr>
<td>19</td>
<td>110</td>
<td>NEt$_i$-Pr$_2$</td>
<td>Dioxane</td>
<td>1 (24)</td>
<td>73</td>
</tr>
<tr>
<td>20</td>
<td>90</td>
<td>NEt$_3$</td>
<td>Dioxane</td>
<td>1 (24)</td>
<td>35</td>
</tr>
<tr>
<td>21</td>
<td>90</td>
<td>NEt$_3$</td>
<td>Dioxane</td>
<td>2 (24)</td>
<td>50</td>
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<td>100</td>
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<td>1 (24)</td>
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<td>23</td>
<td>120</td>
<td>NEt$_3$</td>
<td>Dioxane</td>
<td>1(24)</td>
<td>78</td>
</tr>
</tbody>
</table>

[a] Reaction condition: 4-chlorotoluene (0.5 mmol), HBpin (0.75 mmol), Pd source (1.0 mol%), L18 (4.0 mol%), base (1.5 mmol) and solvent (1.5 mL) stirred at indicated temperature for 24 h. [b] FID-Calibrated yield using dodecane as internal standard.

7.2.2 Scope of palladium-catalyzed borylation of aryl chlorides with pinacol borane

With the optimized reaction conditions in hand, we next examined the scope of this reaction. A wide range of non-activated aryl chlorides was investigated under this optimized reaction condition and the results are listed in Table 7.3. The aryl chloride containing ortho-methyl group was found to be feasible cross-coupling partner and furnished good product yield (Table 7.3, entry 3). Electron-rich 4-chloroanisole was coupled with pinacolborane to corresponding product in excellent yield. The alkenyl groups attached on aryl chlorides were remained intact in this optimized reaction condition and afforded moderate to good product yields (Table 7.3, entry 10 and 11).
Table 7.3 Palladium-catalyzed borylation of non-activated aryl chlorides with pinacol borane\textsuperscript{[a]}

![Diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArCl</th>
<th>Product</th>
<th>Pd (mol%)</th>
<th>Time (h)</th>
<th>Yield (%)\textsuperscript{[b]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me-Cl</td>
<td>Me-Cl</td>
<td>1</td>
<td>24</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>Me-Cl</td>
<td>Me-Cl</td>
<td>1</td>
<td>24</td>
<td>81</td>
</tr>
<tr>
<td>3</td>
<td>Me-Cl</td>
<td>Me-Cl</td>
<td>1</td>
<td>24</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>Me-Cl</td>
<td>Me-Cl</td>
<td>1</td>
<td>24</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>MeO-Cl</td>
<td>MeO-Cl</td>
<td>1</td>
<td>24</td>
<td>71</td>
</tr>
<tr>
<td>6</td>
<td>MeO-Cl</td>
<td>MeO-Cl</td>
<td>1</td>
<td>24</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>MeS-Cl</td>
<td>MeS-Cl</td>
<td>1</td>
<td>24</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>MeO-Cl</td>
<td>MeO-Cl</td>
<td>1</td>
<td>24</td>
<td>70</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} Reaction conditions: 1 mol\% Pd(dba\textsubscript{2}), 4 mol\% L18, \(1\) equiv. pinacolborane, 110 °C, 18-24 h in Dioxane.

\textsuperscript{[b]} Reaction yield.
Apart from non-activated aryl chlorides, activated aryl chlorides also were applicable substrates in this Pd(dba)$_2$ and L18 catalytic system (Table 7.4). Addition of tetrabutylammonium iodide (TBAI) was found to be afforded better product yields for borylation of activated aryl chlorides with pinacol borane (Table 7.4, entry 1 and 2). Common functional groups such as -CN, -COOMe and -COMe were compatible under this mild reaction condition (Table 7.4, entries 4-11). Good to excellent product yields were obtained.
Table 7.4 Palladium-catalyzed borylation of activated aryl chlorides with pinacol borane\textsuperscript{[a]}

<table>
<thead>
<tr>
<th>Entry</th>
<th>ArCl</th>
<th>Product</th>
<th>Pd (mol%)</th>
<th>Time (h)</th>
<th>Yield (%)\textsuperscript{[b]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F\textsubscript{3}C-Ph-Cl</td>
<td>F\textsubscript{3}C-Ph-B &amp; Me &amp; Me &amp; Me &amp; Me &amp; 1 &amp; 24 &amp; trace</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>F\textsubscript{2}C-Ph-Cl</td>
<td>F\textsubscript{2}C-Ph-B &amp; Me &amp; Me &amp; Me &amp; Me &amp; 1 &amp; 18 &amp; 60\textsuperscript{[c]}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>F-Ph-Cl</td>
<td>F-Ph-B &amp; Me &amp; Me &amp; Me &amp; Me &amp; 1 &amp; 18 &amp; 50\textsuperscript{[c]}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>NC-Ph-Cl</td>
<td>NC-Ph-B &amp; Me &amp; Me &amp; Me &amp; Me &amp; 1 &amp; 24 &amp; trace</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>NC-Ph-Cl</td>
<td>NC-Ph-B &amp; Me &amp; Me &amp; Me &amp; Me &amp; 1 &amp; 18 &amp; 70\textsuperscript{[c]}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>NC-Ph-Cl</td>
<td>NC-Ph-B &amp; Me &amp; Me &amp; Me &amp; Me &amp; 1 &amp; 18 &amp; 80\textsuperscript{[c]}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>MeO-Ph-Cl</td>
<td>MeO-Ph-B &amp; Me &amp; Me &amp; Me &amp; Me &amp; 1 &amp; 18 &amp; 74\textsuperscript{[c]}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>OCONH-Cl</td>
<td>OCONH-B &amp; Me &amp; Me &amp; Me &amp; Me &amp; 1 &amp; 19 &amp; 80\textsuperscript{[c]}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>OCONH-Cl</td>
<td>OCONH-B &amp; Me &amp; Me &amp; Me &amp; Me &amp; 1 &amp; 24 &amp; trace</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>OCONH-Cl</td>
<td>OCONH-B &amp; Me &amp; Me &amp; Me &amp; Me &amp; 1 &amp; 18 &amp; 66\textsuperscript{[c]}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>OCONH-Cl</td>
<td>OCONH-B &amp; Me &amp; Me &amp; Me &amp; Me &amp; 1 &amp; 18 &amp; 77\textsuperscript{[c]}</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} Reaction conditions: 1 mol\% Pd(db)\textsubscript{2}, 4 mol\% L\textsubscript{18}, NE\textsubscript{3}, Dioxane, 110°C, 18-24 h.

\textsuperscript{[b]} Isolated yields, determined by NMR spectroscopy.

\textsuperscript{[c]} Reaction carried out at 120°C.
[a] Reaction condition: ArCl (0.5 mmol), HBpin (0.75 mmol), Pd(dba)$_2$ (1.0 mol%), L18 (4 mol%), NEt$_3$ (1.5 mmol) and dioxane (1.5 mL) stirred at 110 °C for 18-24 h. [b] Isolated yields. [c] TBAI (0.75 mmol) was added.

7.3 Conclusion

In conclusion, new ligand design based on our group previously developed C3-indolyl scaffold (L18) was synthesized. The palladium catalyst system comprising of Pd(dba)$_2$ and novel indolylphosphine ligand (L18) was found to be effective for borylation of aryl chlorides with cheaper and more atom economical pinacol borane. A wide range of non-activated and activated aryl chlorides can be converted to corresponding arylboronate esters under this optimized reaction condition. Notably, it is the first general report of borylation of both electron-rich and –deficient aryl chlorides using pinacol borane as the boron source. The catalyst loading can be down to 1 mol% Pd that is the lowest compared with the previous reports.

7.4 Experimental section

7.4.1 General considerations

Unless otherwise noted, all reagents were purchased from commercial suppliers and used without purification. All borylation reactions were performed in Rotaflo® (England) resealable screw cap Schlenk flask (approx. 20 mL volume) in the presence of Teflon coated magnetic stirrer bar (4 mm × 10 mm). Toluene, tetrahydrofuran (THF) and dioxane were distilled from sodium and sodium benzophenone ketyl under nitrogen, respectively. tert-Butanol was distilled from sodium under nitrogen and stored with calcium hydride. Triethylamine and acetonitrile were distillated from
ca\textit{cium hydride under nitrogen. Water was distillated under nitrogen. Anhydrous \textit{N, N}-dimethylformamide (DMF) in Sure/Seal bottles were purchased from Aldrich and used directly. The indolylphosphine ligands \textbf{L1-L2, L12, L15-L19, L21-L23} and \textbf{L26} were synthesized by the reported procedures.}^{12h, 12i, 13a, 13b, 16} \text{Ligands \textbf{L28-L33} were purchased from commercial suppliers. Commercially available aryl chlorides (liquid form only) were purified by passed through a short plug (0.5 cm width \times 4 cm height) of neutral alumina or distillation. New bottle of \textit{n}-butyllithium was used (Note: since the concentration of \textit{n}-BuLi from old bottle may vary, we recommend performing a titration prior to use). Thin layer chromatography was performed on Merck precoated silica gel 60 F\textsubscript{254} plates. Silica gel (Merck, 70-230 and 230-400 mesh) was used for column chromatography. NMR spectra were recorded on a Br\text{"u}ker spectrometer (400 MHz for \textit{1H}, 100 MHz for \textit{13C}, 376 MHz for \textit{19F} and 162 MHz for \textit{31P}). Spectra were referenced internally to the residual proton resonance in CDCl\textsubscript{3} (\(\delta\) 7.26 ppm), or with tetramethysiliane (TMS, \(\delta\) 0.00 ppm) as the internal standard. Chemical shifts (\(\delta\)) were reported as part per million (ppm) in \(\delta\) scale downfield from TMS. \textit{13C} NMR spectra were referenced to CDCl\textsubscript{3} (\(\delta\) 77.0 ppm, the middle peak). \textit{19F} NMR chemical shifts were determined relative to CFCl\textsubscript{3} as the external standard and low field is positive. \textit{31P} NMR spectra were referenced to 85\% H\textsubscript{3}PO\textsubscript{4} externally. Coupling constants (\(J\)) were reported in Hertz (Hz). Mass spectra (EI-MS and ES-MS) were recorded on a HP 5989B Mass Spectrometer. GC-MS analysis was conducted on a HP 5973 GCD system using a HP5MS column (30 m \times 0.25 mm). The products described in GC yield were accorded to the authentic samples/dodecane calibration standard from HP 6890 GC-FID system. All yields reported refer to isolated yield of compounds estimated to be greater than 95\% purity as determined by capillary gas chromatography (GC) or \textit{1H} NMR. Compounds described in the literature were characterized by comparison of their \textit{1H}, \textit{13C}, \textit{19F} and/or \textit{31P} NMR spectra to the
previously reported data. The procedures in this section are representative, and thus the yields may differ from those reported in tables.

7.4.2 Preparation of indolylphosphine ligands L3-L11, L13-L14, L20, L24-L25 and L27

7.4.2.1 Preparation of indolylphosphine ligand L3

![Reaction Scheme]

2-(2-Bromophenyl)-1H-indole

A general procedure for Fischer-indole synthesis of 2-(2-bromophenyl)-1H-indole was used according to the previous report.\textsuperscript{13b} 2’-Bromoacetophenone (20 mmol), phenylhydrazine (24 mmol), H\textsubscript{3}PO\textsubscript{4} (10 mL) and PPA (60 g) were given the desired product as an off-white powder (3.3 g, 61%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 6.86 (s, 1H), 7.17-7.23 (m, 1H), 7.25-7.30 (m, 2H), 7.40-7.47 (m, 2H), 7.63-7.66 (m, 1H), 7.70-7.74 (m, 2H), 8.66 (s, 1H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3})
MHz, CDCl$_3$) $\delta$ 103.6, 110.9, 120.1, 120.8, 121.3, 122.6, 127.7, 128.1, 129.2, 131.4, 133.4, 133.9, 136.2; MS (EI): $m/z$ (relative intensity) 271 (M$^+$, 100), 191 (19), 165 (49), 95 (13).

2-(2-Bromophenyl)-1-(methoxymethyl)-1H-indole

2-(2-bromophenyl)-1H-indole (5.0 mmol) was dissolved in 15 mL anhydrous DMF in dropping funnel and added dropwise to the 10 mL anhydrous DMF solution contained NaH (15 mmol, 60% in mineral oil) at room temperature under nitrogen atmosphere. NaH was washed with hexane (10 mL x3) under N$_2$. The mixture was stirred for 30 min at room temperature. BrCH$_2$OMe (6.0 mmol) was then added to the mixture dropwise. After the mixture was stirred at room temperature for overnight, EtOAc and water was added to the mixture and the organic phase was separated. The organic phase was washed with large amount of water and was then concentrated. The concentrated mixture was purified by column chromatography on silica gel (25 x 3 cm) and eluted with EtOAc/hexane (1:9). The solution was evaporated in vacuum to give the desired product as a pale yellow liquid (0.79 g, 50%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.10 (s, 3H), 5.36 (s, 2H), 6.59 (s, 1H), 7.23 (t, $J$= 8.0 Hz, 1H), 7.28-7.37 (m, 2H), 7.44 (t, $J$= 8.0 Hz, 1H), 7.51 (d, $J$= 8.0 Hz, 1H), 7.59 (d, $J$= 8.0 Hz, 1H), 7.70 (d, $J$= 8.0 Hz, 1H), 7.74 (d, $J$= 8.0 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 55.7, 74.9, 104.3, 110.5, 120.6, 120.8, 122.4, 125.1, 127.2, 128.1, 130.2, 132.9, 133.1, 133.7, 136.9, 139.2; MS (EI): $m/z$ (relative intensity) 315 (M$^+$, 100), 286 (41), 205 (69), 190 (32); HRMS: calcd. for C$_{16}$H$_{14}$NOBrH$: 316.0332, found 316.0330.
2-(2-(Dicyclohexylphosphino)phenyl)-1-(methoxymethyl)-1H-indole L3

2-(2-Bromophenyl)-1-(methoxymethyl)-1H-indole (2.93 mmol) was dissolved in freshly distilled THF (20 mL) at room temperature under nitrogen atmosphere. The solution was cooled to -78 °C in dry ice/acetone bath. Titrated n-BuLi (3.3 mmol) was added dropwise by syringe. After the reaction mixture was stirred for 30 min at 78 °C, chlorodicyclohexylphosphine (3.3 mmol) in THF (5 mL) was added. The reaction was allowed to warm to room temperature and stirred overnight. Solvent was removed under reduced pressure. After the solvent was removed under vacuum, the product was successively washing with cold MeOH. The product was then dried under vacuum. 2-(2-(Dicyclohexylphosphino)phenyl)-1-(methoxymethyl)-1H-indole was obtained as an off-white solid (0.58 g, 50%). $^1$H NMR (400 MHz, C$_6$D$_6$) δ 0.95-1.25 (m, 10H), 1.56-1.73 (m, 12H), 2.81 (s, 3H), 5.35 (bs, 1H), 6.62 (s, 1H), 7.10-7.14 (m, 1H), 7.17-7.29 (m, 3H), 7.43-7.46 (m, 2H), 7.60 (d, J= 8.0 Hz, 1H), 7.70 (d, J= 8.0 Hz, 1H); $^{13}$C NMR (100 MHz, C$_6$D$_6$) δ 26.4, 27.2, 30.3, 55.0, 75.2, 75.3, 105.5, 110.8, 120.46, 120.55, 122.1, 127.8, 128.1, 128.5, 132.28, 132.31, 132.59, 132.65, 137.0, 137.6, 140.6, 140.88, 140.94; $^{31}$P NMR (162 MHz, C$_6$D$_6$) δ -10.37; MS (EI): m/z (relative intensity) 433 (M$^+$, 55), 418 (24), 368 (100), 350 (85), 236 (67); HRMS: calcd. for C$_{28}$H$_{36}$NOPH$^+$: 434.2613, found 434.2633.
7.4.2.2 Preparation of indolylphosphine ligand L4-L5

4-Bromo-3-(1H-indol-2-yl)-N,N-dimethylaniline

A general procedure for Fischer-indole synthesis of 4-bromo-3-(1H-indol-2-yl)-N,N-dimethylaniline was used according to the previous report with a slight modification.\textsuperscript{13b} 1-(2-Bromo-5-(dimethylamino)phenyl)ethanone (5.7 mmol), phenylhydrazine (6.84 mmol), H\textsubscript{3}PO\textsubscript{4} (2.0 mL) and PPA (20 g) were given the reaction mixture. The mixture was poured into crashed ice cube and then neutralized with 2 M NaOH and extracted with CH\textsubscript{2}Cl\textsubscript{2}. The combined organic extracts were dried over anhydrous Na\textsubscript{2}SO\textsubscript{4} and then concentrated under reduced pressure. The crude product was purified according to the previous report\textsuperscript{13b} to give the desired product as a light yellow powder (1.04 g, 58%). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 3.03 (s, 6H), 6.67 (d, J= 8.0 Hz, 1H). 6.90 (s, 1H), 6.98 (s, 1H), 7.24-7.35
(m, 2H), 7.48 (d, J= 8.0 Hz, 1H), 7.56 (d, J= 8.0 Hz, 1H), 7.78 (d, J= 8.0 Hz, 1H), 8.68 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 40.4, 102.9, 107.4, 110.9, 113.6, 114.9, 119.9, 120.5, 122.2, 128.1, 133.4, 133.9, 135.9, 137.2, 149.6; MS (EI): m/z (relative intensity) 314 (M$^+$, 100), 235 (36), 220 (32), 207 (28), 191 (28); HRMS: calcd. for C$_{16}$H$_{15}$N$_2$BrH$: 315.0497$, found 315.0495.

4-Bromo-$N,N$-dimethyl-3-(1-methyl-1H-indol-2-yl)aniline

4-Bromo-3-(1H-indol-2-yl)-$N,N$-dimethylaniline (3.2 mmol) was dissolved in 10 mL freshly distilled THF in dropping funnel and added dropwise to the 5 mL freshly distilled THF solution contained NaH (4.8 mmol, 60% in mineral oil) at room temperature. NaH was washed with hexane (10 mL x3) under N$_2$. The mixture was stirred for 15 min at room temperature. Me$_2$SO$_4$ (3.36 mmol) was then added to the mixture dropwise. After the mixture was stirred at room temperature for overnight, solvent was removed by vacuum. EtOAc and water was added to the mixture and the organic phase was separated. The combined organic phase was washed with brine several times and concentrated. The concentrated mixture was purified by column chromatography on silica gel (10 × 3 cm) and eluted with EtOAc/hexane (1:9). The solution was evaporated in vacuum to give the desired product as a white powder (0.84 g, 80%). $^1$H NMR (400 MHz, CDCl$_3$) δ 2.99 (s, 6H), 3.62 (s, 3H), 6.53 (s, 1H), 6.72 (d, J= 8.7 Hz, 1H), 6.79 (s, 1H), 7.17 (t, J= 8.0 Hz, 1H), 7.28 (t, J= 8.0 Hz, 1H), 7.39 (d, J= 8.0 Hz, 1H), 7.52 (d, J= 8.0 Hz, 1H), 7.68 (d, J= 8.0 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 30.6, 40.7, 101.6, 109.5, 114.4, 116.9, 119.7, 120.6, 121.6, 127.7, 132.0, 132.9, 134.4, 137.2, 140.7, 143.4; MS (EI): m/z (relative intensity) 328
(M⁺, 100), 249 (44), 233 (30), 204 (50); HRMS: calcd. for C₁₇H₁₇N₂BrH⁺: 329.0653, found 329.0650.

4-(Dicyclohexylphosphino)-N,N-dimethyl-3-(1-methyl-1H-indol-2-yl)aniline L₄

The general procedure for the synthesis of 2-(2-(Dicyclohexylphosphino)phenyl)-1-(methoxymethyl)-1H-indole L₃ was followed. 4-Bromo-N,N-dimethyl-3-(1-methyl-1H-indol-2-yl)aniline (1.42 mmol) in 10 mL THF, n-BuLi (1.56 mmol) and PCy₂Cl (1.56 mmol) in 3 mL THF were given the desired product as a white solid (0.44 g, 69%). ¹H NMR (400 MHz, C₆D₆) δ 1.13-1.30 (m, 11H), 1.69-1.80 (m, 11 H), 2.48 (s, 6H), 3.40 (s, 3H), 6.64 (d, J = 10.0 Hz, 1H), 6.74 (s, 1H), 6.78 (t, J = 4.0 Hz, 1H), 7.23-7.30 (m, 3H), 7.48 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H); ¹³C NMR (100 MHz, C₆D₆) δ 26.4, 27.3, 30.4, 30.5, 39.2, 102.9, 109.4, 111.9, 115.47, 115.5, 119.4, 120.2, 120.9, 121.5, 121.6, 127.4, 128.2, 133.26, 133.3, 136.9, 142.0, 142.3, 142.46, 142.5, 149.9; ³¹P NMR (162 MHz, C₆D₆) δ -13.30; MS (EI): m/z (relative intensity) 446 (M⁺, 37), 431 (6), 363 (100), 281 (88), 265 (25); HRMS: calcd. for C₂₉H₃₉N₂PH⁺: 447.2929, found 447.2913.

2-(2-Bromo-5-fluorophenyl)-1H-indole

A general procedure for Fischer-indole synthesis of 2-(2-bromo-5-fluorophenyl)-1H-indole was used according to the previous report.¹³b
1-(2-bromo-5-fluorophenyl)ethanone (10 mmol), phenylhydrazine (15 mmol), H$_3$PO$_4$ (4.0 mL) and PPA (30 g) were given the desired product as a white solid (1.68 g, 58%). $^1$H NMR (400 MHz, CDCl$_3$) δ 6.89 (s, 1H), 6.95-7.00 (m, 1H), 7.18 (d, $J$ = 6.0 Hz, 1H), 7.28 (t, $J$ = 8.0 Hz, 2H), 7.35-7.39 (m, 1H), 7.46 (d, $J$ = 8.0 Hz, 1H), 7.65-7.71 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 104.3, 111.1, 114.1, 116.2, 116.4, 117.9, 118.2, 120.4, 120.9, 123.0, 128.0, 134.9, 135.4; $^{19}$F NMR (376 MHz, CDCl$_3$) δ -144.28; MS (EI): $m/z$ (relative intensity) 289 (M$^+$, 100), 208 (21), 183 (67); HRMS: calcd. for C$_{14}$H$_9$NFBrH$: 289.9981$, found $289.9987$.

2-(2-Bromo-5-fluorophenyl)-1-methyl-1H-indole

The general procedure for the synthesis of 4-bromo-$N,N$-dimethyl-3-(1-methyl-1H-indol-2-yl)aniline was followed. 2-(2-Bromo-5-fluorophenyl)-1H-indole (5.5 mmol) in 15 mL THF, NaH (8.3 mmol) in 5 mL THF and Me$_2$SO$_4$ (5.8 mmol) were given the desired product as a white solid (1.33 g, 80%). $^1$H NMR (400 MHz, CDCl$_3$) δ 3.62 (s, 3H), 6.56 (s, 1H), 7.06-7.11 (m, 1H), 7.17-7.22 (m, 2H), 7.32 (t, $J$ = 8.0 Hz, 1H), 7.41 (d, $J$ = 8.0 Hz, 1H), 7.67-7.71 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 30.7, 102.5, 109.6, 117.3 (d, $J$ = 22.0 Hz), 119.5, 119.8 (d, $J$ = 22.0 Hz), 119.9, 120.9, 122.1, 127.5, 134.0 (d, $J$ = 8.0 Hz), 136.0 (d, $J$ = 8.0 Hz), 137.3, 138.4, 161.4 (d, $J$ = 247.0 Hz); $^{19}$F NMR (376 MHz, CDCl$_3$) δ -114.70; MS (EI): $m/z$ (relative intensity) 305 (M$^+$, 100), 222 (100), 208 (22), 196 (39), 111 (44); HRMS: calcd. for C$_{15}$H$_{11}$NFBrH$: 304.0151$, found $304.0137$. 
The general procedure for the synthesis of 2-(2-(dicyclohexylphosphino)phenyl)-1-(methoxymethyl)-1H-indole L3 was followed. 2-(2-bromo-5-fluorophenyl)-1-methyl-1H-indole (4.30 mmol) in 15 mL THF, n-BuLi (4.73 mmol) and Pi-Pr₂Cl (4.73 mmol) in 5 mL THF were given the desired product as a white solid (0.73 g, 50%). ¹H NMR (400 MHz, C₆D₆) δ 0.77-0.82 (m, 6H), 0.84-0.89 (m, 6H), 1.65-1.80 (m, 2H), 3.15 (s, 3H), 6.47 (s, 1H), 6.82-6.87 (m, 1H), 6.97-7.00 (m, 1H), 7.09-7.13 (m, 1H), 7.22-7.30 (m, 2H), 7.72 (d, J= 8.0 Hz, 1H); ¹³C NMR (100 MHz, C₆D₆) δ 18.8, 19.5, 19.7, 23.6, 30.2, 30.3, 103.77, 103.79, 109.4, 114.7, 114.9, 118.65, 118.71, 118.85, 118.91, 119.6, 120.4, 121.4, 132.9, 133.1, 133.83, 133.86, 133.91, 133.94, 136.9, 139.33, 139.36, 142.91, 142.99, 143.2, 143.3, 161.2, 163.7; ³¹P NMR (162 MHz, C₆D₆) δ -3.28; ¹⁹F NMR (376 MHz, CDCl₃) δ -112.67; MS (EI): m/z (relative intensity) 341 (M⁺, 19), 298 (100), 254 (46), 240 (31); HRMS: calcd. for C₂₁H₂₅NFPH⁺: 342.1787, found 342.1798.
7.4.2.3 Preparation of indolylphosphine ligand L6-L10

2-(2-Bromophenyl)-7-methyl-1H-indole

A general procedure for Fischer-indole synthesis of 2-(2-bromophenyl)-7-methyl-1H-indole was used according to the previous reports with a slight modification.\textsuperscript{13a, 13b} 2'-Bromoacetophenone (10 mmol), 2-methylphenylhydrazine hydrochloride (12 mmol), ethanol (5 mL), glacial acetic acid (a few drops) were stirred at 80 °C for 3 h. Solvent was evaporated to yield the phenylhydrazone intermediate. PPA (30 g) was added to the phenylhydrazone intermediate. The mixture was heated slowly to 120 °C and kept at this temperature for 1 h. The mixture was poured into ice water and then extracted with Et\(_2\)O. The organic phases were combined, dried over Na\(_2\)SO\(_4\) and concentrated under reduced
pressure. The crude product was purified by column chromatography on silica gel (20 × 4 cm) and eluted with EtOAc/hexane (1:9). The solution was evaporated in vacuum to give the desired product as a yellow liquid (1.52 g, 54%). \( ^1 \text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 2.62 (s, 3H), 6.92 (s, 1H), 7.11-7.19 (m, 2H), 7.27 (t, \( J = 8.0 \) Hz, 1H), 7.45 (t, \( J = 8.0 \) Hz, 1H), 7.62 (d, \( J = 8.0 \) Hz, 1H), 7.70 (d, \( J = 8.0 \) Hz, 1H), 7.77 (d, \( J = 8.0 \) Hz, 1H), 8.65 (s, 1H); \(^{13} \text{C} \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 16.5, 104.0, 118.4, 120.1, 120.3, 121.2, 123.0, 127.58, 127.6, 129.0, 131.3, 133.4, 133.9, 135.79, 135.83; MS (EI): \( m/z \) (relative intensity) 285 (M\(^+\), 100), 204 (28), 190 (6), 179 (14); HRMS: calcd. for C\(_{15}\)H\(_{12}\)NBrH\(^+\): 286.0231, found 286.0226.

2-(2-Bromophenyl)-1,7-dimethyl-1\( H \)-indole

The general procedure for the synthesis of 4-bromo-\( \text{N}, \text{N} \)-dimethyl-3-(1-methyl-1\( H \)-indol-2-yl)aniline was followed.

2-(2-Bromophenyl)-7-methyl-1\( H \)-indole (5.34 mmol) in 10 mL THF, NaH (10.67 mmol) in 5 mL THF and Me\(_2\)SO\(_4\) (5.6 mmol) were given the desired product as a light yellow solid (1.33 g, 90%). \(^1 \text{H} \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 2.86 (s, 3H), 3.84 (s, 3H), 6.50 (s, 1H), 6.98-7.06 (m, 2H), 7.32-7.36 (m, 1H), 7.41-7.45 (m, 1H), 7.52 (d, \( J = 8.0 \) Hz, 1H), 7.74 (d, \( J = 8.0 \) Hz, 1H); \(^{13} \text{C} \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 20.1, 33.9, 102.6, 118.9, 119.9, 121.3, 124.7, 125.4, 127.2, 128.5, 130.0, 132.7, 132.9, 134.6, 136.2, 140.4; MS (EI): \( m/z \) (relative intensity) 299 (M\(^+\), 100), 284 (95), 217 (14), 204 (40), 191 (19); HRMS: calcd. for C\(_{16}\)H\(_{14}\)NBrH\(^+\): 300.0388, found 300.0390.
2-(2-(Dicyclohexylphosphino)phenyl)-1,7-dimethyl-1H-indole L6

The general procedure for the synthesis of 2-(2-(dicyclohexylphosphino)phenyl)-1-(methoxymethyl)-1H-indole L3 was followed. 2-(2-Bromo-5-fluorophenyl)-1-methyl-1H-indole (4.0 mmol) in 15 mL THF, n-BuLi (4.4 mmol) and PCy2Cl (4.4 mmol) in 5 mL THF were given the desired product as a white solid (0.98 g, 59%). $^1$H NMR (400 MHz, C$_6$D$_6$) δ 0.94-1.36 (m, 10H), 1.46-1.82 (m, 12H), 2.48 (s, 3H), 3.53 (s, 3H), 6.62 (s, 1H), 6.95 (d, J = 8.0 Hz, 1H), 7.11-7.22 (m, 3H), 7.37-7.40 (m, 1H), 7.47-7.50 (m, 1H), 7.63 (d, J = 8.0 Hz, 1H); $^{13}$C NMR (100 MHz, C$_6$D$_6$) δ 19.7, 26.1, 26.4, 26.8, 27.3, 28.4, 29.9, 30.4, 32.5, 33.80, 33.87, 35.4, 104.1, 118.6, 119.6, 120.9, 124.3, 127.3, 127.5, 127.8, 128.1, 128.9, 132.05, 132.11, 132.21, 132.24, 135.9, 137.5, 137.7, 141.46, 141.50, 141.6, 141.8; $^{31}$P NMR (162 MHz, C$_6$D$_6$) δ -10.04; MS (EI): m/z (relative intensity) 417 (M$^+$, 14), 402 (7), 334 (100), 252 (43), 236 (36); HRMS: calcd. for C$_{28}$H$_{36}$NPH$^+$: 418.2664, found 418.2656.

2-(2-Bromophenyl)-7-ethyl-1H-indole

The general procedure for the synthesis of 2-(2-bromophenyl)-7-methyl-1H-indole was followed. 2’-Bromoacetophenone (10 mmol), 2-ethylphenylhydrazine hydrochloride (12 mmol), ethanol (10 mL), glacial acetic acid (a few drops) and PPA (30 g) were given the desired product as a yellow
liquid (1.54 g, 52%). $^1$H NMR (400 MHz, CDCl$_3$) δ 1.48 (t, $J= 6.0$ Hz, 3H), 2.95-3.01 (m, 2H), 6.89 (s, 1H), 7.12-7.19 (m, 2H), 7.26 (t, $J= 8.0$ Hz, 1H), 7.44 (t, $J= 8.0$ Hz, 1H), 7.60 (d, $J= 4.0$ Hz, 1H), 7.68-7.76 (m, 2H), 8.71 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 13.9, 24.2, 104.0, 118.6, 120.5, 121.1, 126.4, 127.7, 127.9, 129.1, 131.5, 133.6, 134.0, 135.2, 135.8; MS (EI): $m/z$ (relative intensity) 299 (M$^+$, 100), 284 (75), 218 (18), 204 (55), 191 (20); HRMS: calcd. for C$_{16}$H$_{13}$NBrH$: 300.0388, found 300.0387.

2-(2-Bromophenyl)-7-ethyl-1-methyl-1H-indole

The general procedure for the synthesis of 4-bromo-$N,N$-dimethyl-3-(1-methyl-1H-indol-2-yl)aniline was followed. 2-(2-Bromophenyl)-7-ethyl-1H-indole (5.2 mmol) in 10 mL THF, NaH (10.4 mmol) in 5 mL THF and Me$_2$SO$_4$ (5.5 mmol) were given the desired product as a light yellow solid (1.38 g, 85%). $^1$H NMR (400 MHz, CDCl$_3$) δ 1.42 (t, $J= 8.0$ Hz, 3H), 3.18-3.23 (m, 2H), 3.80 (s, 3H), 6.53 (s, 1H), 7.08-7.12 (m, 2H), 7.34 (t, $J= 8.0$ Hz, 1H), 7.43-7.47 (m, 2H), 7.53 (d, $J= 8.0$ Hz, 1H), 7.74 (t, $J= 8.0$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 16.8, 25.7, 33.7, 102.8, 118.8, 120.0, 123.0, 125.4, 127.2, 128.0, 128.8, 130.0, 132.7, 132.9, 134.6, 140.6; MS (EI): $m/z$ (relative intensity) 313 (M$^+$, 100), 298 (21), 219 (91), 204 (39); HRMS: calcd. for C$_{17}$H$_{15}$NBrH$: 314.0544, found 314.0544.
2-(2-(Dicyclohexylphosphino)phenyl)-7-ethyl-1-methyl-1H-indole L7

The general procedure for the synthesis of 2-(2-(dicyclohexylphosphino)phenyl)-1-(methoxymethyl)-1H-indole L3 was followed. 2-(2-Bromophenyl)-7-ethyl-1-methyl-1H-indole (3.0 mmol) in 10 mL THF, n-BuLi (3.3 mmol) and PCy₂Cl (3.3 mmol) in 5 mL THF were given the desired product as a white solid (0.82 g, 63%). ¹H NMR (400 MHz, CD₆D₆) δ 0.81-1.31 (m, 13H), 1.37-1.81 (m, 12H), 2.88-2.93 (m, 2H), 3.55 (s, 3H), 6.64 (s, 1H), 7.04 (d, J = 8.0 Hz, 1H), 7.17-7.22 (m, 3H), 7.38-7.41 (m, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H); ¹³C NMR (100 MHz, CD₆D₆) δ 26.4, 26.8, 27.3, 28.3, 29.8, 30.0, 30.2, 32.4, 32.5, 33.7, 33.8, 35.4, 35.6, 104.3, 118.6, 119.7, 122.6, 128.1, 129.3, 131.9, 132.0, 132.25, 132.27, 135.1, 137.5, 137.7, 141.5, 141.7, 141.8; ³¹P NMR (162 MHz, CD₆D₆) δ -9.86; MS (EI): m/z (relative intensity) 431 (M⁺, 17), 416 (8), 348 (100), 266 (33), 236 (33); HRMS: calcd. for C₂₉H₂₈NPH⁺: 432.2820, found 432.2813.

2-(2-Bromophenyl)-4,7-dimethyl-1H-indole

The general procedure for the synthesis of 2-(2-bromophenyl)-7-methyl-1H-indole was followed. 2’-Bromoacetophenone (5.0 mmol), 2,5-dimethylphenylhydrazine hydrochloride (6.0 mmol), ethanol (10 mL), glacial acetic acid (a few drops) were stirred at 80 °C for 1 h. PPA (15 g) was added and given the desired product as a yellow liquid (0.68 g, 48%). ¹H NMR (400 MHz,
CDCl$_3$) $\delta$ 2.78 (s, 3H), 2.94 (s, 3H) 7.19-7.24 (m, 2H), 7.28 (d, $J$= 8.0 Hz, 1H), 7.40 (t, $J$= 8.0 Hz, 1H), 7.59 (t, $J$= 8.0 Hz, 1H), 7.89 (d, $J$= 8.0 Hz, 1H), 8.91 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 16.2, 18.5, 102.5, 117.4, 120.2, 121.0, 123.0, 127.4, 127.5, 127.6, 128.7, 131.1, 133.4, 133.7, 135.1, 135.4; MS (EI): $m/z$ (relative intensity) 301 (M$^+$, 100), 284 (29), 218 (16), 204 (20); HRMS: calcd. for C$_{16}$H$_{14}$NBrH$^+$: 300.0388, found 300.0381.

2-(2-Bromophenyl)-1,4,7-trimethyl-1H-indole

The general procedure for the synthesis of 4-bromo-$N,N$-dimethyl-3-(1-methyl-1H-indol-2-yl)aniline was followed. 2-(2-Bromophenyl)-4,7-dimethyl-1H-indole (4.9 mmol) in 20 mL THF, NaH (9.7 mmol) in 5 mL THF and Me$_2$SO$_4$ (5.2 mmol) were given the desired product as a light yellow solid (1.23 g, 80%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.56 (s, 3H), 2.83 (s, 3H), 3.84 (s, 3H), 6.51 (s, 1H), 6.85 (d, $J$= 8.0 Hz, 1H), 6.91 (d, $J$= 8.0 Hz, 1H), 7.32-7.36 (m, 1H), 7.42-7.47 (m, 2H), 7.74 (d, $J$= 8.0 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 18.4, 19.8, 33.8, 99.9, 101.1, 118.9, 119.9, 124.7, 125.4, 127.2, 128.0, 129.9, 132.7, 133.0, 134.8, 135.8, 139.9; MS (EI): $m/z$ (relative intensity) 315 (M$^+$, 100), 300 (29), 232 (29), 218 (37), 204 (15); HRMS: calcd. for C$_{17}$H$_{15}$NBrH$^+$: 314.0544, found 314.0540.
2-(2-(Dicyclohexylphosphino)phenyl)-1,4,7-trimethyl-1H-indole L8

The general procedure for the synthesis of 2-(2-(dicyclohexylphosphino)phenyl)-1-(methoxymethyl)-1H-indole L3 was followed. 2-(2-Bromophenyl)-7-ethyl-1-methyl-1H-indole (2.6 mmol) in 10 mL THF, n-BuLi (2.9 mmol) and PCy₂Cl (2.9 mmol) in 5 mL THF were given the desired product as a white solid (0.46 g, 41%). ¹H NMR (400 MHz, CD₆D₆) δ 0.97-1.34 (m, 10H), 1.46-1.81 (m, 12H), 2.50 (s, 3H), 2.57 (s, 3H), 3.55 (s, 3H), 6.61 (s, 1H), 6.91-6.97 (m, 2H), 7.18-7.23 (m, 2H), 7.40-7.50 (m, 1H); ¹³C NMR (100 MHz, CD₆D₆) δ 18.4, 19.7, 26.5, 27.0, 27.5, 28.8, 30.1, 32.5, 33.9, 34.0, 35.7, 102.8, 104.5, 118.6, 120.0, 124.5, 127.2, 127.9, 128.1, 128.8, 132.2, 132.29, 132.32, 135.6, 137.8, 138.1, 140.9, 141.0, 141.7, 142.0, 145.3; ³¹P NMR (162 MHz, CD₆D₆) δ -9.94; MS (EI): m/z (relative intensity) 431 (M⁺, 20), 348 (100), 266 (47), 250 (27), 236 (20); HRMS: calcd. for C₂₉H₃₈NPH⁺: 432.2820, found 432.2839.

2-(2-Bromophenyl)-6-fluoro-1H-indole

The general procedure for the synthesis of 2-(2-bromophenyl)-7-methyl-1H-indole was followed. 2’-Bromoacetophenone (10.0 mmol), 3-fluorophenylhydrazine hydrochloride (12.0 mmol), ethanol (15 mL), glacial acetic acid (a few drops) and PPA (30 g) was added and given the desired product as a white solid (1.56 g, 54%). ¹H NMR (400 MHz, CDCl₃) δ 6.82 (s, 1H), 6.94 (d, J= 8.0
Hz, 1H), 7.14 (d, \( J = 8.0 \) Hz, 1H), 7.25 (t, \( J = 8.0 \) Hz, 1H), 7.42 (t, \( J = 6.0 \) Hz, 1H), 7.58-7.62 (m, 2H), 7.72 (d, \( J = 8.0 \) Hz, 1H), 8.68 (s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 97.3 (d, \( J = 26.0 \) Hz), 103.5, 109.0 (d, \( J = 24.0 \) Hz), 121.2, 121.6 (d, \( J = 10.0 \) Hz), 124.7, 127.7, 129.3, 131.2, 133.1, 134.0, 136.1 (d, \( J = 4.0 \) Hz), 136.7 (d, \( J = 21.0 \) Hz), 160.1 (d, \( J = 237.0 \) Hz); \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \( \delta \) -119.92; MS (EI): \( m/z \) (relative intensity) 288 (M\(^+\), 100), 209 (21), 183 (59), 104 (10); HRMS: calcd. for C\(_{14}\)H\(_9\)NFBr\(^+\): 289.9981, found 289.9972.

**2-(2-Bromophenyl)-6-fluoro-1-methyl-1H-indole**

![Chemical Structure](image)

The general procedure for the synthesis of 4-bromo-\( N,N \)-dimethyl-3-(1-methyl-1H-indol-2-yl)aniline was followed.

2-(2-Bromophenyl)-4,7-dimethyl-1H-indole (3.4 mmol) in 10 mL THF, NaH (5.1 mmol) in 5 mL THF and Me\(_2\)SO\(_4\) (3.6 mmol) were given the desired product as a light yellow solid (1.01 g, 98%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 3.55 (s, 3H), 6.51 (s, 1H), 6.95 (t, \( J = 8.0 \) Hz, 1H), 7.07 (d, \( J = 8.0 \) Hz, 1H), 7.33-7.37 (m, 1H), 7.44 (d, \( J = 4.0 \) Hz, 2H), 7.57-7.61 (m, 1H), 7.74 (d, \( J = 8.0 \) Hz, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 30.8, 95.9 (d, \( J = 26.0 \) Hz), 100.0, 102.1, 108.4 (d, \( J = 24.0 \) Hz), 121.4 (d, \( J = 10.0 \) Hz), 124.0, 125.2, 127.2, 130.2, 132.8, 133.9, 137.3 (d, \( J = 11.0 \) Hz), 140.1, 159.8 (d, \( J = 236.0 \) Hz); \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \( \delta \) -120.51; MS (EI): \( m/z \) (relative intensity) 303 (M\(^+\), 100), 222 (79), 208 (14), 194 (11), 111 (20); HRMS: calcd. for C\(_{15}\)H\(_{11}\)NBrFH\(^+\): 304.0137, found 304.0125.
2-(2-(Dicyclohexylphosphino)phenyl)-6-fluoro-1-methyl-1\textit{H}-indole L9

\[
\begin{align*}
\text{F} & \quad \text{Cy}_2\text{P} \\
\text{N} & \quad \text{Me} \\
\end{align*}
\]

The general procedure for the synthesis of 2-(2-(dicyclohexylphosphino)phenyl)-1-(methoxymethyl)-1\textit{H}-indole L3 was followed. 2-(2-Bromophenyl)-6-fluoro-1-methyl-1\textit{H}-indole (3.28 mmol) in 10 mL THF, \textit{n}-BuLi (3.6 mmol) and PCy\textsubscript{2}Cl (3.9 mmol) in 5 mL THF were given the desired product as a white solid (1.11 g, 81\%). \textsuperscript{1}H NMR (400 MHz, C\textsubscript{6}D\textsubscript{6}) \(\delta\) 0.91-1.25 (m, 11H), 1.48-1.78 (m, 11H), 3.06 (s, 3H), 6.52 (s, 1H), 6.89 (d, \(J = 10.0\) Hz, 1H), 6.97 (t, \(J = 10.0\) Hz, 1H), 7.11 (t, \(J = 8.0\) Hz, 1H), 7.19 (t, \(J = 8.0\) Hz, 1H), 7.26-7.29 (m, 1H), 7.42-7.46 (m, 2H); \textsuperscript{13}C NMR (100 MHz, C\textsubscript{6}D\textsubscript{6}) \(\delta\) 26.4, 27.2, 30.47, 30.55, 95.9, 96.2, 103.5, 107.9, 108.2, 121.0, 121.1, 124.5, 137.0, 137.2, 137.5, 137.8, 140.8, 141.1, 141.7, 158.8, 161.1; \textsuperscript{31}P NMR (162 MHz, C\textsubscript{6}D\textsubscript{6}) \(\delta\) -9.96; \textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3}) \(\delta\) -121.38; MS (EI): \textit{m}/\textit{z} (relative intensity) 421 (M\textsuperscript{+}, 30), 338 (100), 256 (70), 240 (40); HRMS: calcd. for C\textsubscript{27}H\textsubscript{33}NFP\textsuperscript{+}: 422.2413, found 422.2408.

2-(2-Bromophenyl)-5,6-dimethyl-1\textit{H}-indole

\[
\begin{align*}
\text{Me} & \quad \text{Br} \\
\text{Me} & \quad \text{N} \\
\end{align*}
\]

The general procedure for the synthesis of 2-(2-bromophenyl)-7-methyl-1\textit{H}-indole was followed. 2'-Bromoacetophenone (10.0 mmol), 3,4-dimethylphenylhydrazine hydrochloride (12.0 mmol), ethanol (15 mL), glacial acetic acid (a few drops) and PPA (30 g) was added and given the product. The product was washing with small amount of hexane for further purification. The
desired product was given as a light yellow solid (1.49 g, 50%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.40 (s, 3H), 2.42 (s, 3H), 6.74 (s, 1H), 7.19-7.24 (m, 2H), 7.39 (t, $J$= 8.0 Hz, 1H), 7.45 (s, 1H), 7.63 (d, $J$= 8.0 Hz, 1H), 7.70 (d, $J$= 8.0 Hz, 1H), 8.50 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 20.0, 20.5, 102.9, 111.3, 120.7, 121.1, 126.5, 127.5, 128.8, 131.2, 131.7, 133.7, 133.9, 135.25, 135.33; MS (EI): $m$/z (relative intensity) 299 (M$^+$, 100), 286 (35), 218 (13), 204 (20); HRMS: calcd. for C$_{16}$H$_{14}$NBrH$: 300.0388, found 300.0376.

2-(2-Bromophenyl)-1,5,6-trimethyl-1H-indole

![Structure of 2-(2-Bromophenyl)-1,5,6-trimethyl-1H-indole]

The general procedure for the synthesis of 4-bromo-N,N-dimethyl-3-(1-methyl-1H-indol-2-yl)aniline was followed. 2-(2-Bromophenyl)-4,7-dimethyl-1H-indole (2.54 mmol) in 10 mL THF, NaH (3.8 mmol) in 5 mL THF and Me$_2$SO$_4$ (2.67 mmol) were given the desired product as a light yellow solid (0.66 g, 83%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.41 (s, 3H), 2.46 (s, 3H), 3.55 (s, 3H), 6.42 (s, 1H), 7.18 (s, 1H), 7.30-7.34 (m, 1H), 7.39-7.45 (m, 3H), 7.72 (d, $J$= 8.0 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 20.0, 20.7, 30.6, 101.3, 109.9, 120.7, 125.3, 125.9, 127.1, 128.4, 129.9, 130.8, 132.7, 132.8, 134.5, 136.3, 138.9; MS (EI): $m$/z (relative intensity) 313 (M$^+$, 100), 300 (24), 232 (18), 218 (24), 204 (11); HRMS: calcd. for C$_{17}$H$_{18}$NBrH$: 314.0544, found 314.0551.
2-(2-(Dicyclohexylphosphino)phenyl)-1,5,6-trimethyl-1H-indole L10

The general procedure for the synthesis of 2-(2-(dicyclohexylphosphino)phenyl)-1-(methoxymethyl)-1H-indole L3 was followed. 2-(2-Bromophenyl)-1,5,6-trimethyl-1H-indole (1.79 mmol) in 8 mL THF, n-BuLi (2.0 mmol) and PCy₂Cl (2.0 mmol) in 5 mL THF were given the desired product as a white solid (0.45 g, 60%). ¹H NMR (400 MHz, C₆D₆) δ 0.95-1.25 (m, 10H), 1.52-1.85 (m, 12H), 2.34 (s, 3H), 2.37 (s, 3H), 2.28 (s, 3H), 7.58 (s, 1H), 7.04 (s, 1H), 7.11-7.21 (m, 2H), 7.35-7.38 (m, 1H), 7.47-7.50 (m, 2H); ¹³C NMR (100 MHz, C₆D₆) δ 20.0, 20.6, 26.5, 27.3, 29.4, 30.2, 30.4, 30.5, 30.6, 103.01, 103.03, 110.1, 120.8, 126.7, 127.5, 1281.1, 129.2, 129.6, 132.1, 132.2, 132.29, 132.31, 136.4, 137.6, 137.8, 140.2, 140.3, 141.5, 141.8; ³¹P NMR (162 MHz, C₆D₆) δ -9.78; MS (EI): m/z (relative intensity) 431 (M⁺, 11), 348 (100), 266 (32), 250 (23), 236 (14); HRMS: calcd. for C₂₉H₃₈NPH⁺: 432.2820, found 432.2837.
7.4.2.4 Preparation of indolylphosphine ligand \textbf{L11}

![Chemical structure]

1,2-Dimethyl-1H-indole\textsuperscript{17}

The general procedure for the synthesis of 4-bromo-\(N,N\)-dimethyl-3-(1-methyl-1H-indol-2-yl)aniline was followed. 2-Methyl-1H-indole (10 mmol) in 15 mL THF, NaH (15.0 mmol) in 5 mL THF and Me\(_2\)SO\(_4\) (10.5 mmol) were given the desired product as a white solid (1.30 g, 90%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.50 (s, 3H), 3.72 (s, 3H), 5.83 (s, 1H), 7.16 (t, \(J= 8.0\text{ Hz}, 1\text{H}\)), 7.24 (t, \(J= 8.0\text{ Hz}, 1\text{H}\)), 7.33 (d, \(J= 8.0\text{ Hz}, 1\text{H}\)), 7.61 (d, \(J= 8.0\text{ Hz}, 1\text{H}\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 12.7, 99.4, 108.6, 119.1, 119.5, 120.3, 127.9, 136.7, 137.2; MS (EI): \(m/z\) (relative intensity) 144 (M\(^+\), 100), 127 (9), 114 (22), 102 (22), 77 (18).

3-Bromo-1,2-dimethyl-1H-indole\textsuperscript{18}

To a solution of 1,2-dimethyl-1H-indole (7.5 mmol) in anhydrous DMF (15 mL), a solution of \(N\)-bromosuccinimide (7.88 mmol) in anhydrous DMF (10 mL) was added dropwise at room temperature under nitrogen atmosphere. After stirring for 2 h,
the reaction mixture was poured onto crushed ice and CH₂Cl₂ was added to the flask followed by water. The organic phase was washed with large amount of water and then concentrated. The concentrated solution was filtered over a pad of silica (15 x 3 cm) and washed with EtOAc/hexane (1:20). The solution was evaporated to give the desired product as a white solid (0.84 g, 50%). ¹H NMR (400 MHz, CDCl₃) δ 2.46 (s, 3H), 3.72 (s, 3H), 7.16-7.29 (m, 3H), 7.52 (d, J= 7.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 11.0, 30.2, 89.0, 108.8, 118.3, 119.9, 121.6, 126.8, 134.0, 136.1; MS (EI): m/z (relative intensity) 224 (M⁺, 100), 144 (82), 128 (47), 102 (34), 76 (24).

3-(Dicyclohexylphosphino)-1,2-dimethyl-1H-indole L11

The general procedure for the synthesis of 2-(2-(dicyclohexylphosphino)phenyl)-1-(methoxymethyl)-1H-indole L3 was followed. 3-Bromo-1,2-dimethyl-1H-indole (3.0 mmol) in 6 mL THF, n-BuLi (3.3 mmol) and PCy₂Cl (3.3 mmol) in 3 mL THF were given the desired product as a white solid (0.72 g, 70%). ¹H NMR (400 MHz, C₆D₆) δ 1.02-1.44 (m, 10H), 1.51-1.61 (m, 4H), 1.72-1.88 (m, 4H), 2.04-2.17 (m, 2H), 2.41 (s, 3H); 2.43-2.52 (m, 2H), 2.81 (s, 3H); 7.03 (d, J= 6.0 Hz, 1H), 7.20-7.26 (m, 2H), 7.97 (d, J= 4.0 Hz, 1H); ¹³C NMR (100 MHz, C₆D₆) δ 26.5, 27.08, 27.12, 27.2, 28.8, 30.3, 30.4, 32.0, 32.2, 33.7, 33.8, 101.5, 101.6, 109.0, 119.8, 120.8, 120.9, 131.2, 138.0; ³¹P NMR (162 MHz, C₆D₆) δ -18.04; MS (EI): m/z (relative intensity) 341 (M⁺, 15), 259 (23), 176 (100); HRMS: calcd. for C₂₂H₃₂NPH⁺: 342.2351, found 342.2361.
7.4.2.5 Preparation of substituted acetophenone and indolylphosphine ligand L13, L14 and L20

A general procedure for synthesis of 1-(4-methoxy-3,5-dimethylphenyl)ethanone was used according to the previous reports with a slight modification. 1-(4-Hydroxy-3,5-dimethylphenyl)ethanone (20 mmol) dissolved in 50 mL acetone. KOH (60 mmol) and Me2SO4 (21 mmol) were added and then stirred at room temperature for 4 h. After the completion of the reaction, extraction and purification
according to the previous report, the desired product as a colorless oil was given (3.58 g, 99%). $^1$H NMR (400 MHz, CDCl$_3$) δ 2.31 (s, 6H), 2.53 (s, 3H), 3.74 (s, 3H), 7.62 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 16.0, 26.3, 59.5, 129.2, 130.9, 132.7, 161.1, 197.4; MS (EI): m/z (relative intensity) 178 (M+, 65), 163 (100), 105 (52), 91 (55), 77 (23).

2-(Pyridin-2-yl)-1H-indole

![Structure of 2-(Pyridin-2-yl)-1H-indole]

The general procedure for the synthesis of 2-(2-bromophenyl)-7-methyl-1H-indole was followed. 1-(Pyridin-2-yl)ethanone (20 mmol), phenylhydrazine (24 mmol), ethanol (10 mL) and glacial acetic acid (a few drops) were stirred at 80 °C for 1 h. Solvent was evaporated under reduced pressure. PPA (20 g) was added to yield the reaction mixture. After the reaction, extraction and purification by column chromatography according to the previous procedure, the solution was evaporated in vacuum to give the desired product. The product was recrystallized by small amount of CH$_2$Cl$_2$ and cold hexane for further purification. The product was then dried under vacuum to afford a yellow solid (3.10 g, 80%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.08 (s, 1H), 7.16-7.25 (m, 3H), 7.38 (d, $J$= 8.0 Hz, 1H), 7.71-7.77 (m, 2H), 7.85 (d, $J$= 8.0 Hz, 1H), 8.63 (d, $J$= 8.0 Hz, 1H), 10.23 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 100.6, 111.4, 119.9, 120.0, 121.1, 121.9, 123.1, 129.0, 136.65, 136.68, 136.73, 149.0, 150.4; MS (EI): m/z (relative intensity) 194 (M+, 100), 167 (100), 139 (48), 114 (20), 89 (88).
2-(4-Methoxy-3,5-dimethylphenyl)-1H-indole

The general procedure for the synthesis of 2-(2-bromophenyl)-7-methyl-1H-indole was followed. 1-(4-Methoxy-3,5-dimethylphenyl)ethanone (15 mmol), phenylhydrazine (18 mmol), ethanol (10 mL) and glacial acetic acid (a few drops) were stirred at 80 °C for 2 h. Solvent was evaporated under reduced pressure. PPA (30 g) was added to yield the reaction mixture. After the reaction, extraction and purification by column chromatography according to the previous procedure, the solution was evaporated in vacuum to give the desired product and small amount of cold hexane was used to further wash the product. The product was then dried under vacuum to afford a light yellow solid (3.27 g, 87%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.39 (s, 6H), 3.81 (s, 3H), 6.78 (s, 1H), 7.14-7.24 (m, 2H), 7.36-7.42 (m, 3H), 7.66 (d, \(J=8.0\) Hz, 1H), 8.34 (s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 16.2, 40.3, 59.7, 99.2, 110.7, 120.1, 120.4, 121.9, 125.6, 127.9, 129.3, 131.5, 136.6, 137.9, 156.8; MS (EI): \(m/z\) (relative intensity) 251 (M\(^+\), 87), 236 (100), 220 (5), 193 (15); HRMS: calcd. for C\(_{17}\)H\(_{17}\)NOH\(^+\): 252.1388, found 252.1379.

1-Methyl-2-(pyridin-2-yl)-1H-indole\(^{21}\)

The general procedure for the synthesis of 4-bromo-N,N-dimethyl-3-(1-methyl-1H-indol-2-yl)aniline was followed. 2-(Pyridin-2-yl)-1H-indole (8.5 mmol) in 20 mL THF, NaH (12.8 mmol) in 5 mL THF
and Me$_2$SO$_4$ (9 mmol) were given the desired product as a light yellow solid (1.74 g, 99%). $^1$H NMR (400 MHz, CDCl$_3$) δ 4.1 (s, 3H), 6.92 (s, 3H), 7.17 (t, $J$ = 8.0 Hz, 1H), 7.26-7.33 (m, 2H), 7.44 (d, $J$ = 8.0 Hz, 1H), 7.69 (d, $J$ = 8.0 Hz, 1H), 7.14-7.83 (m, 2H), 8.74 (d, $J$ = 8.0 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 31.9, 103.4, 109.8, 119.9, 120.9, 121.7, 122.5, 123.5, 127.4, 136.5, 139.0, 139.3, 149.0, 152.5; MS (EI): m/z (relative intensity) 207 (M$^+$, 100), 192 (4), 180 (13), 130 (17), 78 (19).

2-(4-Methoxy-3,5-dimethylphenyl)-1-methyl-1H-indole

![Structural diagram]

The general procedure for the synthesis of 4-bromo-$N,N$-dimethyl-3-(1-methyl-1H-indol-2-yl)aniline was followed. 2-(4-Methoxy-3,5-dimethylphenyl)-1H-indole (12 mmol) in 20 mL THF, NaH (24 mmol) in 5 mL THF and Me$_2$SO$_4$ (12.6 mmol) were given the desired product as a light yellow solid (2.99 g, 94%). $^1$H NMR (400 MHz, CDCl$_3$) δ 2.40 (s, 6H), 3.78 (s, 3H), 3.83 (s, 3H), 6.53 (s, 1H), 7.15-7.20 (m, 3H), 7.27 (t, $J$ = 8.0 Hz, 1H), 7.39 (d, $J$ = 8.0 Hz, 1H), 7.66 (d, $J$ = 8.0 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 16.2, 31.1, 59.7, 101.1, 109.5, 119.7, 120.3, 121.3, 127.9, 128.3, 129.8, 131.0, 138.1, 141.5, 156.9; MS (EI): m/z (relative intensity) 265 (M$^+$, 100), 250 (100), 234 (4), 207 (11); HRMS: calcd. for C$_{18}$H$_{19}$NOH$^+$: 266.1545, found 266.1542.
3-Bromo-1-methyl-2-(pyridin-2-yl)-1H-indole

The general procedure for the synthesis of 3-bromo-1,2-dimethyl-1H-indole was followed. 1-Methyl-2-(pyridin-2-yl)-1H-indole (8 mmol) in 15 mL DMF and N-bromosuccinimide (8.4 mmol) in 15 mL DMF were given the desired product as a light yellow solid (2.19 g, 96%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.91 (s, 3H), 7.27 (t, $J= 6.0$ Hz, 1H), 7.34-7.38 (m, 2H), 7.42 (d, $J= 8.0$ Hz, 1H), 7.67 (d, $J= 8.0$ Hz, 1H), 7.85-7.91 (m, 2H), 8.82 (d, $J= 4.0$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 32.0, 91.4, 110.0, 119.8, 120.6, 122.7, 123.7, 126.7, 127.1, 135.7, 136.4, 137.4, 149.5, 150.0; MS (EI): $m/z$ (relative intensity) 286 (M$^+$, 63), 207 (100), 180 (29), 152 (25), 78 (46); HRMS: calcd. for C$_{14}$H$_{11}$N$_2$BrH$: 287.0184$, found 287.0195.

3-Bromo-2-(4-methoxy-3,5-dimethylphenyl)-1-methyl-1H-indole

The general procedure for the synthesis of 3-bromo-1,2-dimethyl-1H-indole was followed. 2-(4-Methoxy-3,5-dimethylphenyl)-1-methyl-1H-indole (9.5 mmol) in 18 mL DMF and N-bromosuccinimide (10 mmol) in 15 mL DMF were given the desired product as a white solid (3.25 g, 99%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.41 (s, 6H), 3.69 (s, 3H), 3.85 (s, 3H), 7.17 (s, 2H), 7.24-7.38 (m, 3H), 7.63 (d, $J= 8.0$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 16.2, 31.6, 59.7, 89.7, 109.6, 119.2, 120.4, 122.6, 125.7, 127.2, 131.0, 131.1, 136.7, 138.0, 157.3; MS (EI): $m/z$ (relative intensity) 345 (M$^+$, 5), 331 (5), 300 (100), 285 (11); HRMS: calcd. for C$_{18}$H$_{18}$NOBrH$: 344.0650$, found 344.0651.
found 344.0656.

3-(Dicyclohexylphosphino)-1-methyl-2-(pyridin-2-yl)-1H-indole L13

The procedure of preparation of 2-(2-(dicyclohexylphosphino)phenyl)-1-(methoxymethyl)-1H-indole L3 was followed. 3-Bromo-1-methyl-2-(pyridin-2-yl)-1H-indole (3.5 mmol) in 10 mL THF, n-BuLi (3.9 mmol) and PCy₂Cl (3.9 mmol) in 5 mL THF were given the desired product as a white solid (0.56 g, 40%). \(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)) \(\delta\) 0.98-1.43 (m, 10H), 1.44-2.00 (m, 10H), 2.42-2.53 (m, 2H), 3.37 (s, 3H), 6.66-6.69 (m, 1H), 7.10-7.14 (m, 1H), 7.21-7.30 (m, 3H), 7.80 (d, \(J= 8.0\) Hz, 1H), 8.07-8.09 (m, 1H), 8.58 (d, \(J= 4.0\) Hz, 1H); \(^13\)C NMR (100 MHz, C\(_6\)D\(_6\)) \(\delta\) 26.3, 26.85, 26.97, 26.98, 27.0, 30.5, 30.6, 30.7, 32.1, 32.3, 34.5, 34.6, 105.1, 105.3, 110.1, 114.2, 120.1, 121.81, 121.83, 122.2, 128.4, 128.5, 130.4, 130.5, 134.5, 138.6, 147.8, 148.2, 148.7, 152.1; \(^{31}\)P NMR (162 MHz, C\(_6\)D\(_6\)) \(\delta\) -17.72; MS (EI): \(m/z\) (relative intensity) 404 (M\(^+\), 6), 321 (100), 239 (73), 223 (33); HRMS: calcd. for C\(_{26}\)H\(_{33}\)N\(_2\)PH\(^+\): 405.2459, found 405.2446.

3-(Diphenylphosphino)-1-methyl-2-(pyridin-2-yl)-1H-indole L20

The procedure of preparation of 2-(2-(dicyclohexylphosphino)phenyl)-1-(methoxymethyl)-1H-indole L3 was followed. 3-Bromo-1-methyl-2-(pyridin-2-yl)-1H-indole (3.5 mmol) in 10 mL THF, n-BuLi (3.9
mmol) and PPh₂Cl (3.9 mmol) in 5 mL THF were given the desired product as a white solid (1.01 g, 76%). ¹H NMR (400 MHz, C₆D₆) δ 3.48 (s, 3H), 6.61-6.65 (m, 1H), 6.92-7.17 (m, 10H), 7.36 (d, J= 8.0 Hz, 1H), 7.54 (d, J= 8.0 Hz, 1H), 7.58-7.62 (m, 4H), 8.54 (d, J= 8.0 Hz, 1H); ¹³C NMR (100 MHz, C₆D₆) δ 31.0, 105.2, 110.2, 120.5, 122.3, 122.6, 122.7, 129.79, 129.8, 132.5, 132.7, 135.0, 138.3, 138.4, 139.2, 147.4, 147.9, 149.0, 151.2; ³¹P NMR (162 MHz, C₆D₆) δ -27.22; MS (EI): m/z (relative intensity) 392 (M⁺, 33), 315 (100), 238 (13), 223 (25); HRMS: calcd. for C₂₆H₂₁N₂PH⁺: 393.1521, found 393.1519.

3-(Dicyclohexylphosphino)-2-(4-methoxy-3,5-dimethylphenyl)-1-methyl-1H-indole L14

The procedure of preparation of 2-(2-(dicyclohexylphosphino)phenyl)-1-(methoxymethyl)-1H-indole L3 was followed. 3-Bromo-2-(4-methoxy-3,5-dimethylphenyl)-1-methyl-1H-indole (9.3 mmol) in 20 mL THF, n-BuLi (10.3 mmol) and PCy₂Cl (10.3 mmol) in 5 mL THF were given the desired product as a white solid (3.06 g, 75%). ¹H NMR (400 MHz, CDCl₃) δ 0.99-1.38 (m, 9H), 1.52-1.92 (m, 11H), 2.21-2.37 (m, 2H), 2.36 (s, 6H), 3.52 (s, 3H), 3.82 (s, 3H), 6.97 (s, 2H), 7.18 (t, J= 8.0 Hz, 1H), 7.28 (t, J= 8.0 Hz, 1H), 7.37 (d, J= 8.0 Hz, 1H), 7.88 (d, J= 8.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 26.4, 27.2, 27.27, 27.32, 27.4, 30.5, 30.6, 31.0, 31.9, 32.1, 34.2, 34.3, 59.7, 109.5, 119.6, 121.4, 121.7, 127.6, 130.2, 130.7, 131.9, 138.1, 157.0; ³¹P NMR (162 MHz, CDCl₃) δ -17.83; MS (EI): m/z (relative intensity) 461 (M⁺, 23), 379 (31), 296 (100), 265 (23), 250 (19); HRMS: calcd. for C₃₀H₄₀NOPH⁺: 462.2926, found 462.2921.
7.4.2.6 Preparation of indolylphosphine ligand $L_{24}$

\[
\begin{align*}
\text{Me} & \text{CO} \\
\text{OH} & \\
\text{Ph} & \text{NHNH}_2 \\
\begin{array}{c}
\text{NaH} \\
\text{Me}_2\text{SO}_4 \\
\text{THF}
\end{array} & \rightarrow \text{PhH}_2\text{CO} \\
\text{Me} & \text{N} \\
\text{Ph} & \text{OCH}_2\text{Ph} \\
\begin{array}{c}
\text{NBS} \\
\text{DMF}
\end{array} & \rightarrow \text{Br} \\
\text{Me} & \text{N} \\
\text{Ph} & \text{OCH}_2\text{Ph} \\
\begin{array}{c}
n-\text{BuLi} \\
\text{THF}
\end{array} & \rightarrow \text{PPh}_2 \\
\text{Me} & \text{N} \\
\text{Ph} & \text{OCH}_2\text{Ph} \\
\begin{array}{c}
\text{K}_2\text{CO}_3 \\
\text{PhCH}_2\text{Br}
\end{array} & \rightarrow \text{PhH}_2\text{CO} \\
\end{align*}
\]

$2-(1H-\text{Indol-2-yl})\text{phenol}$

A general procedure for Fischer-indole synthesis of $2-(1H-\text{Indol-2-yl})\text{phenol}$ was used according to the previous reports.\(^{22}\) 1-(2-Hydroxyphenyl)ethanone (100 mmol), phenylhydrazine (110 mmol), ethanol (50 mL), glacial acetic acid (a few drops) and PPA (100 g) were given the desired product as light brown solid (15.0 g, 72%). $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 6.83 (t, $J = 7.5$ Hz, 1H), 6.89-6.93 (m, 2H), 6.96-7.01 (m, 2H), 7.06 (t, $J = 7.8$ Hz, 1H), 7.43 (t, $J = 8.5$ Hz, 2H), 7.66 (d, $J = 7.8$ Hz, 1H), 11.01 (s, 1H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 101.2, 112.0, 117.1, 119.4, 119.8, 120.3, 120.4, 121.8, 128.1, 128.8, 129.0, 136.1, 136.8, 154.7; MS (EI) cannot detect the products.
2-(2-(Benzyloxy)phenyl)-1H-indole

![Structural formula of 2-(2-(Benzyloxy)phenyl)-1H-indole]

After 2-(1H-indol-2-yl)phenol (10 mmol) was dissolved in 20 ml DMF, K$_2$CO$_3$ (30 mmol) was then added and stirred at room temperature for 30 min. Benzyl bromide (15 mmol) was added dropwise and stirred at room temperature for overnight. After stirring for overnight, the reaction mixture was poured onto crushed ice and CH$_2$Cl$_2$ was added to the flask followed by water. The organic phase was washed with large amount of water and then concentrated. The concentrated solution was isolated by flash column chromatography on silica gel (25 x 4 cm) and eluted with CH$_2$Cl$_2$/hexane (3:7). The solution was evaporated to give the desired product as a light brown solid (2.39 g, 80%). $^1$H NMR (400 MHz, CDCl$_3$) δ 5.27 (s, 2H), 6.98 (s, 1H), 7.12-7.25 (m, 5H), 7.28-7.35 (m, 1H), 7.46-7.56 (m, 5H), 7.69 (d, $J$ = 7.9 Hz, 1H), 7.94 (d, $J$ = 7.6 Hz, 1H), 9.78 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 71.2, 99.7, 110.8, 113.5, 119.7, 120.2, 120.9, 121.7, 121.9, 127.7, 127.9, 128.2, 128.4, 128.5, 128.9, 135.8, 136.0, 136.3, 154.9; MS (EI): m/z (relative intensity) 299 (M$^+$, 38), 222 (19), 208 (100), 180 (38), 152 (25).

2-(2-(Benzyloxy)phenyl)-1-methyl-1H-indole

The general procedure for the synthesis of 4-bromo-$N,N$-dimethyl-3-(1-methyl-1H-indol-2-yl)aniline was followed. 2-(2-(benzyloxy)phenyl)-1H-indole (8 mmol) 20 mL THF, NaH (12 mmol) in 5 mL
THF and Me$_2$SO$_4$ (8.4 mmol) were given the desired product as a white solid (2.59 g, 90%). $^1$H NMR (400 MHz, CDCl$_3$) δ 3.66 (s, 3H), 5.14 (s, 3H), 6.61 (s, 1H), 7.11-7.16 (m, 2H), 7.21 (t, $J$= 8.0 Hz, 1H), 7.28-7.33 (m, 6H), 7.40-7.48 (m, 3H), 7.73 (d, $J$= 8.0 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 31.0, 70.5, 101.9, 109.3, 113.3, 119.3, 120.3, 121.2, 122.8, 126.8, 127.7, 128.0, 128.4, 129.9, 132.7, 136.8, 137.7, 138.6, 156.6; MS (EI): m/z (relative intensity) 313 (M$^+$, 2), 251 (64), 209 (100), 180 (47).

2-(2-(Benzyloxy)phenyl)-3-bromo-1-methyl-1H-indole

The general procedure for the synthesis of 3-bromo-1,2-dimethyl-1H-indole was followed. 2-(2-(Benzyloxy)phenyl)-1-methyl-1H-indole (6.5 mmol) in 15 mL DMF and N-bromosuccinimide (6.9 mmol) in 10 mL DMF were given the desired product as a white solid (2.4 g, 95%). $^1$H NMR (400 MHz, CDCl$_3$) δ 3.06 (s, H), 5.1 (s, 2H), 7.10-7.17 (m, 2H), 7.22-7.30 (m, 6H), 7.31-7.37 (m, 2H), 7.42-7.48 (m, 2H), 7.66 (d, $J$= 8.0 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 31.5, 70.7, 109.5, 113.8, 119.2, 120.1, 120.4, 121.2, 122.4, 126.9, 127.8, 128.5, 130.8, 133.5, 136.8; MS (EI): m/z (relative intensity) 391 (M$^+$, 8), 312 (34), 221 (10), 91 (61); HRMS: calcd. for C$_{22}$H$_{18}$NOBrH$: 392.0650, found 392.0668.

2-(2-(Benzyloxy)phenyl)-3-(diphenylphosphino)-1-methyl-1H-indole L24

![Image of 2-(2-(Benzyloxy)phenyl)-3-(diphenylphosphino)-1-methyl-1H-indole L24](image-url)
The procedure of preparation of 2-(2-(dicyclohexylphosphino)phenyl)-1-(methoxymethyl)-1H-indole L3 was followed. 2-(2-(Benzyloxy)phenyl)-3-bromo-1-methyl-1H-indole (2.31 mmol) in 5 mL THF, n-BuLi (2.55 mmol) and PPh₂Cl (2.55 mmol) in 3 mL THF were given the desired product as a white solid (0.77 g, 68%). ¹H NMR (400 MHz, CDCl₃) δ 3.68 (s, 3H), 5.04-5.15 (m, 2H), 6.99 (t, J= 8.0 Hz, 1H), 7.06-7.13 (m, 3H), 7.16-7.31 (m, 9H), 7.32-7.50 (m, 8H), 7.56-7.65 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 30.9, 70.2, 103.8, 109.6, 113.1, 119.8, 120.7, 121.5, 121.6, 121.8, 126.6, 127.1, 127.5, 127.6, 127.8, 127.9, 128.07, 128.13, 128.13, 128.4, 129.6, 130.6, 131.9, 132.1, 132.6, 132.8, 133.6, 136.8, 138.2, 138.5, 146.8, 147.3, 157.0; ³¹P NMR (162 MHz, CDCl₃) δ -28.01; MS (EI): m/z (relative intensity) 497 (M⁺, 7), 406 (20), 390 (100), 252 (20); HRMS: calcd. for C₃₄H₂₈NOPH⁺: 498.1987, found 498.2003.

7.4.2.7 Preparation of indolylphosphine ligand L25

![Chemical diagram]

1-(1H-Indol-2-yl)naphthalen-2-ol was prepared according to the previous report.²⁵
2-(2-Methoxynaphthalen-1-yl)-1-methyl-1H-indole

The general procedure for the synthesis of 4-bromo-N,N-dimethyl-3-(1-methyl-1H-indol-2-yl)aniline was followed. 1-(1H-indol-2-yl)naphthalen-2-ol (10 mmol) in 15 mL THF, NaH (24.0 mmol) in 10 mL THF and Me$_2$SO$_4$ (21.0 mmol) were given the desired product as a white solid (2.78 g, 97%). $^1$H NMR (400 MHz, CDCl$_3$) δ 3.50 (s, 3H), 3.90 (s, 3H), 6.61 (s, 1H), 7.20 (t, $J$= 8.0 Hz, 1H), 7.31 (d, $J$= 8.0 Hz, 1H), 7.36-7.45 (m, 4H), 7.63 (t, $J$= 4.0 Hz, 1H), 7.73 (d, $J$= 8.0 Hz, 1H), 7.88 (t, $J$= 8.0 Hz, 1H), 8.01 (d, $J$= 8.0 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 30.1, 56.5, 103.1, 109.4, 113.1, 119.3, 120.5, 121.0, 123.8, 125.3, 126.9, 127.8, 130.7; MS (El): $m/z$ (relative intensity) 287 (M$^+$, 100), 270 (15), 254 (18), 228 (15).

3-Bromo-2-(2-methoxynaphthalen-1-yl)-1-methyl-1H-indole

The general procedure for the synthesis of 3-bromo-1,2-dimethyl-1H-indole was followed. 2-(2-Methoxynaphthalen-1-yl)-1-methyl-1H-indole (9.0 mmol) in 25 mL DMF and N-bromosuccinimide (9.5 mmol) in 20 mL DMF were given the desired product as a white solid (3.1 g, 96%). $^1$H NMR (400 MHz, CDCl$_3$) δ 3.54 (s, 3H), 3.93 (s, 3H), 7.31-7.48 (m, 7H), 7.63 (d, $J$= 7.7 Hz, 1H), 7.93-7.95 (m, 1H), 8.05 (d, $J$= 9.1 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 30.9, 56.6, 92.0, 109.6, 113.1, 113.2, 113.4, 120.1, 122.3, 124.0, 124.9, 127.2, 127.3, 128.1, 128.8, 131.6, 133.4, 133.8,
136.7, 156.4; MS (EI): m/z (relative intensity) 365 (M+, 86), 296 (100), 271 (84), 255 (28), 241 (37), 143 (23); HRMS: calcd. for C$_{20}$H$_{16}$NBrOH$^+$: 366.0488, found 366.0491.

3-(Diphenylphosphino)-2-(2-methoxynaphthalen-1-yl)-1-methyl-1H-indole L25

![Image of L25](image)

The general procedure for the synthesis of 2-(2-(dicyclohexylphosphino)phenyl)-1-(methoxymethyl)-1H-indole L3 was followed. 3-Bromo-2-(2-methoxynaphthalen-1-yl)-1-methyl-1H-indole (8.5 mmol) in 20 mL THF, n-BuLi (9.4 mmol) and PPh$_2$Cl (10.2 mmol) in 5 mL THF were given the desired product as a white solid (2.8 g, 70%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.55 (s, 3H), 3.69 (s, 3H), 7.07 (t, J= 8.0 Hz, 1H), 7.23 (d, J= 8.0 Hz, 1H), 7.29-7.56 (m, 16H), 7.93 (d, J= 8.0 Hz, 1H), 8.07 (d, J= 8.0 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 30.6, 55.9, 105.0, 109.7, 112.9, 114.3, 119.9, 121.5, 121.7, 123.7, 124.7, 127.1, 127.28, 127.33, 127.78, 127.82, 127.84, 127.88, 128.0, 128.5, 129.7, 129.8, 131.3, 132.3, 132.4, 132.5, 132.6, 134.4, 137.85, 137.92, 138.1, 138.81, 138.84, 144.1, 144.6, 158.2; $^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ -27.54; MS (EI): m/z (relative intensity) 471 (M$^+$, 36), 440 (100), 348 (7), 286 (14), 235 (18); HRMS: calcd. for C$_{32}$H$_{26}$NOPH$^+$: 472.1825, found 472.1838.
7.4.2.8 Preparation of indolylphosphine ligand $\mathbf{L_{27}}$

$$\begin{align*}
\text{Me} & \text{O} \\
\begin{array}{c}
\text{Br} \\
\text{NMeNH}_2
\end{array} \\
\text{Br} & \text{N} & \text{Me} & \text{Br} & \text{N} & \text{Me} & \text{Br} & \text{Br}
\end{align*}$$

$2$-(2-Bromophenyl)-1-methyl-$1H$-indole was prepared according to the previous report.$^{13b}$

$3$-Bromo-$2$-(2-bromophenyl)-1-methyl-$1H$-indole

The general procedure for the synthesis of 3-bromo-$1,2$-dimethyl-$1H$-indole was followed. $2$-(2-Bromophenyl)-1-methyl-$1H$-indole (15 mmol) in 20 mL DMF and $N$-bromosuccinimide (16 mmol) in 15 mL DMF were given the desired product as a light yellow solid (2.8 g, 77%). $^1H$ NMR (400 MHz, CDCl$_3$) $\delta$ 3.61 (s, 3H), 7.28-7.31 (m, 1H), 7.35-7.52 (m, 5H), 7.67-7.69 (m, 1H), 7.78-7.81 (m, 1H); $^{13}C$ NMR (100 MHz, CDCl$_3$) $\delta$ 31.22, 90.68, 109.69, 119.39, 120.43, 122.90, 125.45, 127.73, 127.39, 130.87, 132.11, 132.89, 133.23, 136.23, 137.06; MS (EI): $m/z$ (relative intensity) 365 ($M^+$, 100), 283 (10), 204 (95); HRMS: calcd. for $\text{C}_{15}\text{H}_{11}\text{NBr}_2$: 363.9349, found 363.9337.
3-(Diisopropylphosphino)-2-(2-(diisopropylphosphino)phenyl)-1-methyl-1H-indole L27

The general procedure for the synthesis of 2-(2-(dicyclohexylphosphino)phenyl)-1-(methoxymethyl)-1H-indole L3 was followed. 3-Bromo-2-(2-bromophenyl)-1-methyl-1H-indole (5.0 mmol) in 15 mL THF, n-BuLi (11.0 mmol) and Pi-Pr₂Cl (12.0 mmol) in 5 mL THF were given the desired product as a white solid (1.51 g, 70%). ¹H NMR (400 MHz, C₆D₆) δ 0.86-1.28 (m, 27H), 1.85-2.05 (m, 2H), 2.22-2.34 (m, 1H), 2.77-2.88 (m, 1H), 3.12 (s, 3H), 7.17-7.20 (m, 3H), 7.25-7.29 (m, 3H), 7.40 (d, J = 8.0 Hz, 1H), 7.97 (s, J = 4.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 18.1, 18.2, 20.2, 20.4, 20.9, 21.1, 21.5, 21.6, 21.7, 21.9, 22.3, 22.4, 22.5, 22.7, 22.9, 23.1, 23.8, 23.9, 25.8, 25.9, 26.7, 26.8, 31.5, 31.6, 84.3, 105.9, 109.9, 119.5, 121.4, 121.8, 127.8, 128.2, 130.3, 131.9, 132.0, 133.6, 137.9, 139.4, 139.5, 139.7, 157.8; ³¹P NMR (162 MHz, C₆D₆) δ -7.82, -2.47; MS (EI): m/z (relative intensity) 438 (M⁺, 0), 396 (100), 236 (74); HRMS: calcd. for C₂₇H₃₉NP₂H⁺: 440.2636, found 440.2622.

7.4.3 General procedures for initial ligands and reaction conditions screening

General procedure for initial ligands screening (Pd catalysts loading equal to 0.5 mol%): Ligand (Pd : L = 1 : 4) was loaded into the Schlenk tube with a Teflon-coated magnetic stir bar. A stock solution of Pd₂dba₃ (0.025 mmol) in freshly distilled 10 mL dioxane (0.5 mol% Pd per 1 mL stock solution) was initially prepared with continuously stirring at room temperature. An array of Schlenk tubes
containing ligands equipped with a Teflon-coated magnetic stir bar were evacuated and backfilled with nitrogen for three times. The corresponding volume of stock solution was transferred to an array of Schlenk tubes via syringes. The palladium complex stock solution was stirred for 10 minutes. 4-chlorotoluene (1.0 mmol), pinacol borane (0.22 mL, 1.5 mmol) and NEt₃ (0.42 mL, 3.0 mmol) were loaded into the tube subsequently. Dioxane (2.0 mL) was added into the reaction system with continuous stirring. The Schlenk tube was resealed and placed into a pre-heated oil bath (110 °C) for 24 h. After completion of the reaction, the tube was allowed to cool down at room temperature. Ethyl acetate (~8.0 mL), dodecane (113 μL, internal standard) and water (~2.0 mL) were added. The organic layer was subjected to GC analysis. The GC yield was previously calibrated by authentic sample/dodecane calibration curve.

*General Procedure for reaction conditions screening (Pd catalysts loading equal to 1.0 mol%):* Pd source (0.005 mmol) and ligand (Pd : L = 1 : 4) were loaded subsequently into the Schlenk tube with a Teflon-coated magnetic stir bar. The Schlenk tube was evacuated and backfilled with nitrogen for three times. Precomplexation was applied by adding freshly distilled solvent (0.5 mL) into the tube. The palladium complex stock solution was stirred for 10 minutes. 4-chlorotoluene (0.5 mmol), pinacol borane (0.11 mL, 0.75 mmol) and base (1.5 mmol) were loaded into the tube subsequently. The solvent (1.0 mL) was added into the reaction system with continuous stirring. The Schlenk tube was resealed and placed into a pre-heated oil bath (reaction temperature as noted in Table 3) for 24 h. After completion of the reaction, the tube was allowed to cool down at room temperature. Ethyl acetate (~8.0 mL), dodecane (113 μL, internal standard) and water (~2.0 mL) were added. The organic layer was subjected to GC analysis. The GC yield
7.4.3 General procedures for borylation of aryl chlorides

Indollyphosphine ligand L18 (0.0098 g, 0.02 mmol) and Pd(dba)$_2$ (0.0029 g, 0.005 mmol) were loaded subsequently into the Schlenk tube with a Teflon-coated magnetic stir bar. The Schlenk tube was evacuated and flushed with nitrogen for three times. Precomplexation was applied by adding dioxane (0.5 mL) into the tube. The palladium complex stock solution was stirred for 10 minutes. Tetrabutylammonium iodide (0.2770 g, 0.75 mmol) was added if necessary. Aryl chlorides (0.5 mmol), pinacol borane (0.11 mL, 0.75 mmol) and triethylamine (0.21 mL, 1.5 mmol) were loaded into the tube subsequently. Dioxane (1.0 mL) was added into the reaction system. After continue stirring for another 5 minutes, the tube was put into a pre-heated oil bath (110 °C) for 18-24 h. After completion of the reaction, the tube was allowed to cool down to room temperature. Ethyl acetate (~8.0 mL), water (~2.0 mL) were added. The organic layers were combined and concentrated. The crude products were purified by column chromatography on silica gel (230-400 mesh).
7.4.4 Characterization data for coupling products

4,4,5,5-Tetramethyl-2-(p-tolyl)-1,3,2-dioxaborolane (Table 7.3, Entry 1)\(^{12}\)

![Chemical Structure](image)

Eluents (Ethyl acetate: Hexane = 1: 50, \(R_f= 0.40\)) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.37 (s, 12H), 2.39 (s, 3H), 7.22 (d, \(J= 7.6\) Hz, 2H), 7.75 (d, \(J= 7.8\) Hz, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 21.7, 24.8, 83.5, 128.5, 134.8, 141.3; MS (EI): \(m/z\) (relative intensity) 218.1 (M\(^+\), 21), 203.1 (31), 132.1 (59), 119.0 (100), 91.0 (13), 65.0 (5), 41.1 (21).

4,4,5,5-Tetramethyl-2-(m-tolyl)-1,3,2-dioxaborolane (Table 7.3, Entry 2)\(^{12}\)

![Chemical Structure](image)

Eluents (Ethyl acetate: Hexane = 1: 50, \(R_f= 0.40\)) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.38 (s, 12H), 2.58 (s, 3H), 7.18-7.21

4,4,5,5-Tetramethyl-2-(o-tolyl)-1,3,2-dioxaborolane (Table 7.3, Entry 3)\(^{12}\)

![Chemical Structure](image)

Eluents (Ethyl acetate: Hexane = 1: 50, \(R_f= 0.40\)) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.38 (s, 12H), 2.58 (s, 3H), 7.18-7.21
(m, 2H), 7.35 (t, J= 7.6 Hz, 1H), 7.81 (d, J= 7.6 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 22.2, 24.9, 83.3, 124.7, 129.71, 130.7, 135.8, 144.8; MS (EI): m/z (relative intensity) 218.1 (M$^+$, 15), 203.1 (26), 161.1(79), 132.1 (13), 119.1 (100), 91.1 (16), 41.1 (7).

**2-(2,6-Dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 7.3, Entry 4)**$^{12}$

![Structure](image)

Eluents (Ethyl acetate: Hexane= 1: 50, R$_f$= 0.40) was used for flash column chromatography. $^1$H NMR (400 MHz, CDCl$_3$) δ 1.39 (s, 12H), 2.40 (s, 6H), 6.94 (d, J= 7.6 Hz, 2H), 7.13 (t, J= 7.5 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 22.2, 25.0, 83.6, 126.4, 141.7; MS (EI): m/z (relative intensity) 232.1 (M$^+$, 22), 175.1 (100), 132.0 (74), 117.0 (13), 105.0 (16), 91.0 (20), 43.0 (20), 28.1 (82).

**2-(3-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 7.3, Entry 5)**$^{26}$

![Structure](image)

Eluents (Ethyl acetate: Hexane= 1: 20, R$_f$= 0.40) was used for flash column chromatography. $^1$H NMR (400 MHz, CDCl$_3$) δ 1.36 (s, 12H), 3.84 (s, 3H), 7.02 (d, J= 8.2 Hz, 1H), 7.31 (t, J= 7.4 Hz, 1H), 7.35 (s, 1H), 7.43 (d, J= 7.2 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 24.8, 55.2, 83.8, 117.8, 118.7, 127.1, 128.9, 159.0; MS (EI): m/z (relative intensity) 234.1 (M$^+$, 66), 219.1 (28), 148.1 (87), 134.0 (100), 104.0 (12), 91.0 (11), 77.0 (9), 41.1 (9).
2-(4-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 7.3, Entry 6)\textsuperscript{26}

![Structure of 2-(4-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane]

Eluents (Ethyl acetate: Hexane = 1: 20, R\textsubscript{f} = 0.40) was used for flash column chromatography. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 1.35 (s, 12H), 3.82 (s, 3H), 6.91 (d, \(J = 8.7\) Hz, 2H), 7.78 (d, \(J = 8.7\) Hz, 2H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 25.8, 55.0, 83.5, 113.2, 136.5, 162.1; MS (EI): m/z (relative intensity) 234.1 (M\textsuperscript{+}, 53), 219.1 (33), 148.1 (45), 134.0 (100), 104.0 (9), 91.0 (7), 77.0 (7), 41.1 (6).

4,4,5,5-Tetramethyl-2-(4-(methylthio)phenyl)-1,3,2-dioxaborolane (Table 7.3, Entry 7)\textsuperscript{27}

![Structure of 4,4,5,5-Tetramethyl-2-(4-(methylthio)phenyl)-1,3,2-dioxaborolane]

Eluents (Ethyl acetate: Hexane = 1: 20, R\textsubscript{f} = 0.40) was used for flash column chromatography. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 1.34 (s, 12H), 2.49 (s, 3H), 7.23 (d, \(J = 8.4\) Hz, 2H), 7.72 (d, \(J = 8.3\) Hz, 2H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 15.0, 24.8, 83.7, 124.9, 135.0, 142.5; MS (EI): m/z (relative intensity) 250.1 (M\textsuperscript{+}, 71), 235.1 (18), 164.0 (27), 150.0 (100), 136.0 (10), 117.0 (10), 43.1 (9), 28.1 (9).
2-(Benzo[d][1,3]dioxol-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 7.3, Entry 8)\(^{27}\)

![Chemical Structure](image)

Eluents (Ethyl acetate: Hexane = 1: 20, \(R_f = 0.50\)) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.33 (s, 12H), 5.94 (s, 2H), 6.83 (d, \(J = 7.7\) Hz, 1H), 7.25 (s, 1H), 7.37 (d, \(J = 7.7\) Hz, 1H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 24.8, 83.6, 100.7, 108.2, 113.9, 129.7, 147.1, 150.1; MS (EI): \(m/z\) (relative intensity) 248.1 (M\(^+\), 87), 233.1 (29), 162.1 (70), 148.1 (100), 116.8 (8), 91.0 (11), 41.1 (11).

4,4,5,5-Tetramethyl-2-(naphthalen-2-yl)-1,3,2-dioxaborolane (Table 7.3, Entry 9)\(^{12}\)

![Chemical Structure](image)

Eluents (Ethyl acetate: Hexane = 1: 50, \(R_f = 0.50\)) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.42 (s, 12H), 7.48-7.56 (m, 2H), 7.85-7.93 (m, 4H), 8.43 (s, 1H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 24.9, 83.9, 125.8, 127.0, 127.0, 127.7, 128.6, 130.4, 132.8, 135.0, 136.2; MS (EI): \(m/z\) (relative intensity) 254.1 (M\(^+\), 36), 239.1 (9), 168.1 (66), 154.1 (100), 127.0 (7), 41.1 (5).
4,4,5,5-Tetramethyl-2-(4-(prop-1-en-2-yl)phenyl)-1,3,2-dioxaborolane (Table 7.3, Entry 10)\textsuperscript{28}

\[
\begin{align*}
\text{Me} & \quad \text{B} & \quad \text{O} \\
\text{Me} & & \text{Me} \\
\end{align*}
\]

Eluents (Ethyl acetate: Hexane= 1: 50, \(R_f=0.40\)) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.36 (s, 12H), 2.17 (s, 3H), 5.13 (s, 2H), 7.48 (d, \(J=8.3\) Hz, 2H), 7.80 (d, \(J=8.3\) Hz, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 21.7, 24.8, 83.7, 1132, 124.8, 134.8, 143.2, 144.0; MS (EI): \(m/z\) (relative intensity) 244.1 (M\(^+\), 59), 229.1 (34), 158.1 (90), 145.1 (100), 129.0 (10), 115.0 (19), 85.1 (10), 77.0 (15), 41.1 (14), 28.1 (13).

4,4,5,5-Tetramethyl-2-(4-vinylphenyl)-1,3,2-dioxaborolane (Table 7.3, Entry 11)\textsuperscript{27}

\[
\begin{align*}
\text{Me} & \quad \text{B} & \quad \text{O} \\
\text{Me} & & \text{Me} \\
\end{align*}
\]

Eluents (Ethyl acetate: Hexane= 1: 50, \(R_f=0.40\)) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.36 (s, 12H), 5.30 (d, \(J=10.9\) Hz, 1H), 5.82 (d, \(J=17.6\) Hz, 1H), 6.70-6.77 (m, 1H), 7.42 (d, \(J=8.0\) Hz, 2H), 7.78 (d, \(J=8.1\) Hz, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 24.8, 83.7, 114.8, 125.5, 135.0, 136.8, 140.2; MS (EI): \(m/z\) (relative intensity) 230.1 (M\(^+\), 41), 215.1 (33), 144.1 (77), 130.0 (100), 103.0 (9), 85.1 (10), 77.0 (15), 43.1 (15), 28.1 (19).
4,4,5,5-Tetramethyl-2-(4-(trifluoromethyl)phenyl)-1,3,2-dioxaborolane (Table 7.4, Entry 1 and 2)\textsuperscript{12j}

Eluents (Ethyl acetate: Hexane = 1: 50, \( R_f = 0.50 \)) was used for flash column chromatography. \( ^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.36 (s, 12H), 7.62 (d, \( J= 7.7 \) Hz, 2H), 7.92 (d, \( J= 7.7 \) Hz, 2H); \( ^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 24.8, 84.3, 124.1 (q, \( J= 270 \) Hz), 124.3 (q, \( J= 3.0 \) Hz), 132.8 (q, \( J= 32.0 \) Hz), 135.0; \( ^{19}\)F NMR (376 MHz, CDCl\(_3\)) \( \delta \) -63.0 (s, 3F); MS (EI): \textit{m/z} (relative intensity) 272.1 (M\(^+\), 6), 257.1 (95), 229.1 (9), 186.1 (94), 173.0 (100), 154.0 (9), 142.2 (9), 85.1 (19), 58.1 (25), 43.1 (42), 28.1 (23).

2-(3,4-Difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 7.4, Entry 3)\textsuperscript{29}

Eluents (Ethyl acetate: Hexane = 1: 50, \( R_f = 0.40 \)) was used for flash column chromatography. \( ^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.34 (s, 12H), 7.11-7.17 (m, 1H), 7.51-7.61 (m, 2H); \( ^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 24.8, 84.2, 116.9 (d, \( J= 16.0 \) Hz), 123.3 (d, \( J= 15.0 \) Hz), 128.4 (d, \( J= 12.0 \) Hz), 131.4 (dd, \( J= 6.0 \) Hz, 4.0 Hz), 152.6 (dd, \( J= 251 \) Hz, 12 Hz); \( ^{19}\)F NMR (376 MHz, CDCl\(_3\)) \( \delta \) -139.5 (d, \( J= 18.8 \) Hz, 1F), -133.9 (d, \( J= 18.8 \) Hz, 1F); MS (EI): \textit{m/z} (relative intensity) 240.2 (M\(^+\), 22), 225.2 (100), 197.1 (9), 154.1 (66), 141.1 (87), 85.1 (13), 75.1 (5), 58.1 (13), 43.1 (17).
4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (Table 7.4, Entry 4 and 5)\textsuperscript{12)

\[
\begin{array}{c}
\text{NC} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{B} \\
\text{O} \\
\end{array}
\]

Eluents (Ethyl acetate: Hexane = 1: 20, \( R_f \) = 0.30) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.34 (s, 12H), 7.62 (d, \( J \) = 8.3 Hz, 2H), 7.87 (d, \( J \) = 8.2 Hz, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 24.8, 84.4, 114.5, 118.8, 131.0, 135.0; MS (EI): \( m/z \) (relative intensity) 229.1 (M\(^+\), 8), 214.1 (100), 186.1 (13), 172.0 (6), 143.1 (100), 130.0 (69), 103.0 (13), 85.1 (16), 58.1 (27), 43.1 (41), 28.1 (26).

3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (Table 7.4, Entry 6)\textsuperscript{12)

\[
\begin{array}{c}
\text{NC} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{Me} \\
\text{B} \\
\text{O} \\
\end{array}
\]

Eluents (Ethyl acetate: Hexane = 1: 20, \( R_f \) = 0.30) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.34 (s, 12H), 7.45 (t, \( J \) = 7.6 Hz, 1H), 7.70 (d, \( J \) = 7.8 Hz, 1H), 8.00 (d, \( J \) = 7.5 Hz, 1H), 8.08 (s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 24.8, 84.4, 128.3, 134.3, 138.3, 138.7; MS (EI): \( m/z \) (relative intensity) 229.1 (M\(^+\), 19), 214.1 (94), 143.1 (100), 130.1 (61).
Methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (Table 7.4, Entry 7)\textsuperscript{12j}

![Chemical Structure]

Eluents (Ethyl acetate: Hexane= 1: 20, \( R_f = 0.30 \)) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.34 (s, 12H), 3.90 (s, 3H), 7.86 (d, \( J = 8.2 \) Hz, 2H), 8.01 (d, \( J = 8.3 \) Hz, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 24.8, 52.0, 84.1, 128.5, 132.2, 134.6, 167.0; MS (EI): \( m/z \) (relative intensity) 262.1 (M\(^+\), 16), 247.2 (69), 231.2 (16), 177.1 (89), 163.1 (100), 131.1 (17), 103.1 (17), 85.1 (11), 59.1 (8), 43.1 (10).

Methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (Table 7.4, Entry 8)\textsuperscript{12j}

![Chemical Structure]

Eluents (Ethyl acetate: Hexane= 1: 20, \( R_f = 0.30 \)) was used for flash column chromatography. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.35 (s, 12H), 3.92 (s, 3H), 7.45 (t, \( J = 7.6 \) Hz, 1H), 7.98 (d, \( J = 6.8 \) Hz, 1H), 8.13 (d, \( J = 7.9 \) Hz, 1H), 8.47 (s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 24.9, 52.0, 84.1, 127.8, 129.6, 132.2, 35.8, 139.1, 167.1; MS (EI): \( m/z \) (relative intensity) 262.1 (M\(^+\), 10), 247.1 (27), 231.1 (14), 219.1 (100), 163.1 (79), 131.0 (29), 103.1 (29).
1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethan-1-one (Table 7.4, Entry 9 and 10)\textsuperscript{12j}

![Chemical structure](image)

Eluents (Ethyl acetate: Hexane= 1: 20, R\textsubscript{f}= 0.40) was used for flash column chromatography. $^1$H NMR (400 MHz, CDCl\textsubscript{3}) δ 1.38 (s, 12H), 2.63 (s, 3H), 7.90-7.96 (m, 4H); $^{13}$C NMR (100 MHz, CDCl\textsubscript{3}) δ 24.7, 26.6, 84.1, 127.1, 134.8, 138.9; MS (EI): m/z (relative intensity) 246.1 (M\textsuperscript{+}, 21), 231.2 (100), 203.1 (8), 189.1 (12), 160.1 (41), 147.1 (98), 131.0 (24), 103.0 (16), 85.1 (12), 59.1 (7), 43.1 (22).

1-((3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethan-1-one (Table 7.4, Entry 11)\textsuperscript{28}

![Chemical structure](image)

Eluents (Ethyl acetate: Hexane= 1: 20, R\textsubscript{f}= 0.40) was used for flash column chromatography. $^1$H NMR (400 MHz, CDCl\textsubscript{3}) δ 1.36 (s, 12H), 2.63 (s, 3H), 7.47 (t, J= 7.4 Hz, 1H), 8.00 (d, J= 7.3 Hz, 1H), 8.06 (d, J= 7.8 Hz, 1H), 8.37 (s, 1H); $^{13}$C NMR (100 MHz, CDCl\textsubscript{3}) δ 24.8, 84.1, 128.0, 130.7, 134.8, 136.4, 139.4; MS (EI): m/z (relative intensity) 246.1 (M\textsuperscript{+}, 9), 231.1 (94), 203.0 (49), 185.0 (14), 160.0 (16), 147.0 (100), 131.0 (32), 103.0 (23), 85.0 (18), 59.0 (12), 43.0 (61), 28.0 (21).
7.5 References


2015, 10, 857.


(23) Alsabeh, P. G.; Lundgren, R. J.; Longobardi, L. E.; Stradiotto, M. Chem.
Commun. 2011, 47, 6936.


Appendix

Phenyl isonicotinate (Table 2.2, L9)
Benzene, 1-methyl-4-[(1E)-2-phenylethenyl]- (Table 2.3, compound 3ak)
Benzene, 1-methyl-2-[(1E)-2-phenylethenyl]- (Table 2.3, compound 3bk)
Naphthalene, 2-[(1E)-2-phenylethenyl]- (Table 2.3, compound 3ck)
Benzene, 1,1'-(1E)-1,2-ethenediylbis- (Table 2.3, compound 3dk)
Benzene, 1-fluoro-4-[(1E)-2-phenylethenyl]- (Table 2.3, compound 3ek)
Benzene, 1-fluoro-4-[(1E)-2-phenylethenyl] - (Table 2.3, compound 3ek)
Benzene, 1-chloro-4-[(1E)-2-phenylethenyl]- (Table 2.3, compound 3fk)
Naphthalene, 1-[(1E)-2-phenylethenyl]- (Table 2.3, compound 3gk)
Benzene, 1-methoxy-4-[(1E)-2-phenylethenyl]- (Table 2.3, compound 3hk)
Benzene, 1,3,5-trimethyl-2-[(1E)-2-phenylethenyl]- (Table 2.3, compound 3ik)
Benzene, 1-nitro-4-[(1\textit{E})-2-phenylethenyl]- (Table 2.3, compound jk)
2-Propenoic acid, 3-(4-methylphenyl)-, methyl ester, (2E)- (Table 2.3, compound 3al)
2-Propenoic acid, 3-(4-methylphenyl)-, ethyl ester, (2E)- (Table 2.3, compound 3am)
2-Propenoic acid, 3-(4-methylphenyl)-, butyl ester, (2E)- (Table 2.3, compound 3an)
2-Propenoic acid, 3-(1-naphthalenyl)-, butyl ester, (2E)- (Table 2.3, compound 3gn)
2-Propenoic acid, 3-(2-naphthalenyl)-, butyl ester, (2E)- (Table 2.3, compound 3cn)
2-Propenoic acid, 3-(2,4,6-trimethylphenyl)-, butyl ester, (2E)- (Table 2.3, compound 3in)
Benzene, 1-fluoro-4-[(1E)-2-(4-methylphenyl)ethenyl]- (Table 2.3, compound 3ao)
Benzene, 1-fluoro-4-[(1E)-2-(4-methylphenyl)ethenyl] (Table 2.3, compound 3ao)
Benzene, 1-fluoro-3-[2-(4-methylphenyl)ethenyl]-, (E)-  

(Table 2.3, compound 3ap)
Benzene, 1-fluoro-3-[2-(4-methylphenyl)ethenyl]-, (E)- 

(Table 2.3, compound 3ap)
Benzene, 1-chloro-4-[(1E)-2-(4-methylphenyl)ethenyl]- (Table 2.3, compound 3aq)
Benzene, 1,1'-(1E)-1,2-ethenediyibis[4-methyl- (Table 2.3, compound 3ar)
Benzene, 1-methoxy-4-[(1E)-2-(4-methylphenyl)ethenyl]- (Table 2.3, compound 3as)
Benzene, 1-[(1E)-2-(4-methylphenyl)ethenyl]-4-(trifluoromethyl) - (Table 2.3, compound 3a)
Benzene, 1-[(1E)-2-(4-methylphenyl)ethenyl]-4-(trifluoromethyl)- (Table 2.3, compound 3at)
Benzene, 1-bromo-2-[(1E)-2-(4-methylphenyl)ethenyl]- (Table 2.3, compound 3au)
Benzene, 1-chloro-4-[(1E)-2-(1,3,5-trimethylphenyl)ethenyl]- (Table 2.3, compound 3fv)
Benzene, 1-chloro-4-[(1E)-2-(1,3,5-trimethylphenyl)ethenyl]- (Table 2.3, compound 3fv)
2-Phenylbenzoxazole (Table 3.2, entry 1)
2-(4-Methylphenyl)benzoxazole (Table 3.2, entry 2)
2-(2-Methylphenyl)benzoxazole (Table 3.2, entry 3)
2-(4-Fluorophenyl)benzoxazole, (Table 3.2, entry 4)
2-(4-Fluorophenyl)benzoxazole, (Table 3.2, entry 4)
2-(4-Chlorophenyl)benzoxazole (Table 3.2, entry 5)
2-(4-Bromophenyl)benzoxazole (Table 2, entry 6, compound 3fa)
2-(4-Methoxyphenyl)benzoxazole (Table 3.2, entry 8)
2-(4-Methylphenyl)-5-phenylbenzoxazole (Table 3.3, entry 1)
5-Methyl-2-(4-methylphenyl)benzoxazole (Table 3.3, entry 2)
5-Methyl-2-(2-methylphenyl)benzoxazole (Table 3.3, entry 3)
5-Methyl-2-(2-methylphenyl)benzoxazole (Table 3.3, entry 3)

HS
5-Methyl-2-(2-naphthalenyl)benzoxazole (Table 3.3, entry 4)
5-Fluoro-2-(4-methylphenyl)benzoxazole (Table 3.3, entry 5)
5-Fluoro-2-(4-methylphenyl)benzoxazole (Table 3.3, entry 5)
5-Chloro-2-(4-methylphenyl)benzoxazole (Table 3.3, entry 6)
1,3,7-Trimethyl-8-(4-tolyl)-xanthine (Scheme 3.3, compound 1)
2-Phenylbenzothiazole (Scheme 3.3, compound 2)
2-(4-Methylphenyl)benzothiazole (Scheme 3.3, compound 3)
1-Methyl-1H-indole-3-carbonitrile (Table 4.2, entry 1)
1-Isopropyl-1H-indole-3-carbonitrile (Table 4.2, entry 2)
1-Isopropyl-1\textit{H}-indole-3-carbonitrile (Table 4.2, entry 2)

HS

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$1H$-Indole-3-carbonitrile (Table 4.2, entry 4)
1-Phenyl-1H-indole-3-carbonitrile (Table 4.2, entry 5)
1-(4-Methoxyphenyl)-1H-indole-3-carbonitrile (Table 4.2, entry 6)
1-(3,5-Dimethylphenyl)-5-methoxy-1H-indole-3-carbonitrile (Table 4.2, entry 7)
1-(3,5-Dimethylphenyl)-5-methoxy-1H-indole-3-carbonitrile (Table 4.2, entry 7)
1-Benzyl-1H-indole-3-carbonitrile (Table 4.3, entry 1)
1-Benzyl-5-methoxy-1H-indole-3-carbonitrile (Table 4.3, entry 2)
1-Benzyl-5-fluoro-1H-indole-3-carbonitrile (Table 4.3, entry 3)

**F1104a**

![NMR spectrum](image)

**F1104b**

![NMR spectrum](image)
1-Benzyl-5-fluoro-1H-indole-3-carbonitrile (Table 4.3, entry 3)

HS

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Kin-Dept-12122012-s7 39 (0.731) TOF MS ES+
1-Benzyl-5-chloro-1H-indole-3-carbonitrile (Table 4.3, entry 4)
1-Benzyl-5-chloro-1\textit{H}-indole-3-carbonitrile (Table 4.3, entry 4)

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1-Benzyl-5-methyl-1H-indole-3-carbonitrile (Table 4.3, entry 5)
1-Benzyl-7-methoxy-1H-indole-3-carbonitrile (Table 4.3, entry 6)
1-Benzyl-7-methoxy-1H-indole-3-carbonitrile (Table 4.3, entry 6)

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1-Benzyl-7-methyl-1H-indole-3-carbonitrile (Table 4.3, entry 7)
1-Benzyl-7-methyl-1H-indole-3-carbonitrile (Table 4.3, entry 7)
1-Benzyl-1H-pyrrolo[2,3-b]pyridine-3-carbonitrile (Table 4.3, entry 8)
1-Benzyl-1\textit{H}-pyrrolo[2,3-\textit{b}]pyridine-3-carbonitrile (Table 4.3, entry 8)
1-Benzyl-2-methyl-1H-indole-3-carbonitrile (Table 4.3, entry 9)
1-Methyl-2-phenyl-1H-indole-3-carbonitrile (Scheme 4.1, compound 1)
1-Methyl-2-(o-tolyl)-1H-indole-3-carbonitrile (Scheme 4.1, compound 2)
1-Methyl-2-(o-tolyl)-1H-indole-3-carbonitrile (Scheme 4.1, compound 2)

Mass  Calc. Mass  mDa  PPM  DBE  i-FIT  Formula
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1-Methyl-2-(naphthalen-1-yl)-1H-indole-3-carbonitrile (Scheme 4.1, compound 3)
3-Bromo-1-methyl-2-phenyl-1H-indole (Scheme 5.4, L1 precursor)
3-(Dicyclohexylphosphino)-1-methyl-2-phenyl-1H-indole (Scheme 5.4, L1)
3-(Dicyclohexylphosphino)-1-methyl-2-phenyl-1H-indole (Scheme 5.4, L1)
2-(Perfluorophenyl)pyridine (Table 5.2, compound 3au)
2-(Perfluorophenyl)pyridine (Table 5.2, compound 3au)
3-(Perfluorophenyl)pyridine (Table 5.2, compound 3bu)
3-(Perfluorophenyl)pyridine (Table 5.2, compound 3bu)
2-Methyl-6-(perfluorophenyl)pyridine (Table 5.2, compound 3cu)
2-Methyl-6-(perfluorophenyl)pyridine (Table 5.2, compound 3cu)
2-Methoxy-6-(perfluorophenyl)pyridine (Table 5.2, compound 3du)
2-Methoxy-6-(perfluorophenyl)pyridine (Table 5.2, compound 3du)
2-(Perfluorophenyl)quinoline (Table 5.2, compound 3eu)
2-(Perfluorophenyl)quinoline (Table 5.2, compound 3eu)
2-Methyl-7-(perfluorophenyl)quinoline (Table 5.2, compound 3fu)
2-Methyl-7-(perfluorophenyl)quinoline (Table 5.2, compound 3fu)
3-Methoxy-6-(perfluorophenyl)pyridazine (Table 5.2, compound 3gu)
3-Methoxy-6-(perfluorophenyl)pyridazine (Table 5.2, compound 3gu)

[Chemical structure image]

[Mass spectrum image]

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2,6-Bis(perfluorophenyl)pyridine (Table 5.2, compound 3hu)
2,6-Bis(perfluorophenyl)pyridine (Table 5.2, compound 3hu)
2-Methyl-6-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)pyridine (Table 5.2, compound 3cv)
2-Methyl-6-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)pyridine (Table 5.2, compound 3cv)
2-Methyl-6-(2,3,5,6-tetrafluoro-4-methylphenyl)pyridine (Table 5.2, compound 3cw)
2-Methyl-6-(2,3,5,6-tetrafluoro-4-methylphenyl)pyridine (Table 5.2, compound 3cw)
2-Methyl-6-(2,3,5,6-tetrafluorophenyl)pyridine (Table 5.2, compound 3cx)
2-Methyl-6-(2,3,5,6-tetrafluorophenyl)pyridine (Table 5.2, compound 3cx)
2-Methyl-6-(2,3,4,6-tetrafluorophenyl)pyridine (Table 5.2, compound 3cy)
2-Methyl-6-(2,3,4,6-tetrafluorophenyl)pyridine (Table 5.2, compound 3cy)
2-Methyl-6-(2,4,6-trifluorophenyl)pyridine (Table 5.2, compound 3cz)
2-Methyl-6-(2,4,6-trifluorophenyl)pyridine (Table 5.2, compound 3cz)
2,3,4,5,6-Pentafluoro-4'-methyl-1,1'-biphenyl (Table 5.3, compound 5au)
2,3,4,5,6-Pentafluoro-4'-methyl-1,1'-biphenyl (Table 5.3, compound 5au)
2,3,4,5,6-Pentafluoro-3'-methyl-1,1'-biphenyl (Table 5.3, compound 5bu)
2,3,4,5,6-Pentafluoro-3'-methyl-1,1'-biphenyl (Table 5.3, compound 5bu)
2-(Perfluorophenyl)naphthalene (Table 5.3, compound 5cu)
2-(Perfluorophenyl)naphthalene (Table 5.3, compound 5cu)
2,3,4,5,6-Pentafluoro-4'-vinyl-1,1'-biphenyl (Table 5.3, compound 5du)
2,3,4,5,6-Pentafluoro-4'-vinyl-1,1'-biphenyl (Table 5.3, compound 5du)
2,3,4,5,6-Pentafluoro-4'-methoxy-1,1'-biphenyl (Table 5.3, compound 5eu)
2,3,4,5,6-Pentafluoro-4'-methoxy-1,1'-biphenyl (Table 5.3, compound 5eu)
2,3,4,5,6-Pentafluoro-3'-methoxy-1,1'-biphenyl (Table 5.3, compound 5fu)
2,3,4,5,6-Pentafluoro-3'-methoxy-1,1'-biphenyl (Table 5.3, compound 5fu)
3'-Ethoxy-2,3,4,5,6-pentafluoro-1,1'-biphenyl (Table 5.3, compound 5gu)
3'-Ethoxy-2,3,4,5,6-pentafluoro-1,1'-biphenyl (Table 5.3, compound 5gi)
5-(Perfluorophenyl)benzo[d][1,3]dioxole (Table 5.3, compound 5hu)
5-(Perfluorophenyl)benzo[d][1,3]dioxole (Table 5.3, compound 5hu)
2',3',4',5',6'-Pentafluoro-[1,1'-biphenyl]-4-carbaldehyde (Table 5.3, compound 5iu)
2',3',4',5',6'-Pentafluoro-[1,1'-biphenyl]-4-carbaldehyde (Table 5.3, compound 5iu)
1-(2',3',4',5',6'-Pentafluoro-[1,1'-biphenyl]-4-yl)ethanone (Table 5.3, compound 5ju)
1-(2',3',4',5',6'-Pentafluoro-[1,1'-biphenyl]-4-yl)ethanone (Table 5.3, compound 5ju)
(2',3',4',5',6'-Pentafluoro-[1,1'-biphenyl]-4-yl)(phenyl)methanone (Table 5.3, compound 5ku)
(2',3',4',5',6'-Pentafluoro-[1,1'-biphenyl]-4-yl)(phenyl)methanone (Table 5.3, compound 5ku)
Methyl 2',3',4',5',6'-pentafluoro-[1,1'-biphenyl]-4-carboxylate (Table 5.3, compound 5lu)
Methyl 2',3',4',5',6'-pentafluoro-[1,1'-biphenyl]-4-carboxylate (Table 5.3, compound 5lu)
Methyl 2',3',4',5',6'-pentafluoro-[1,1'-biphenyl]-3-carboxylate (Table 5.3, compound 5mu)
Methyl 2',3',4',5',6'-pentafluoro-[1,1'-biphenyl]-3-carboxylate (Table 5.3, compound 5mu)
2',3',4',5',6’-Pentafluoro-[1,1'-biphenyl]-4-carbonitrile (Table 5.3, compound 5ou)
2',3',4',5',6'-Pentafluoro-[1,1'-biphenyl]-4-carbonitrile (Table 5.3, compound 5ou)
2',3',4',5',6'-Pentafluoro-[1,1'-biphenyl]-3-carbonitrile (Table 5.3, compound 5ou)
$2',3',4',5',6'$-Pentafluoro-$[1,1'$-biphenyl$]$-3$-carbonitrile (Table 5.3, compound 5ou)
1-(2',3',4',5',6'-Pentafluoro-[1,1'-biphenyl]-3-yl)-1H-pyrrole (Table 5.3, compound 5pu)
1-(2',3',4',5',6'-Pentafluoro-[1,1'-biphenyl]-3-yl)-1H-pyrrole (Table 5.3, compound 5pu)
2',3',4',5',6'-Pentafluoro-[1,1'-biphenyl]-3-amine (Table 5.3, compound 5qu)
2',3',4',5',6'-Pentafluoro-[1,1'-biphenyl]-3-amine (Table 5.3, compound 5qu)
"N-(2',3',4',5',6'-Pentafluoro-[1,1'-biphenyl]-3-yl)acetamide (Table 5.3, compound 5ru)"
$N$-(2',3',4',5',6'-Pentafluoro-[1,1'-biphenyl]-3-yl)acetamide (Table 5.3, compound 5ru)
1-(Cyclopent-1-en-1-yl)-2,3,4,5,6-pentafluorobenzene (Table 5.3, compound 5su)
1-(Cyclopent-1-en-yl)-2,3,4,5,6-pentafluorobenzene (Table 5.3, compound 5su)
2,3,5,6-Tetrafluoro-4'-methyl-4-(trifluoromethyl)-1,1'-biphenyl (Table 5.3, compound 5av)
2,3,5,6-Tetrafluoro-4'-methyl-4-(trifluoromethyl)-1,1'-biphenyl (Table 5.3, compound 5av)
3-(Dicyclohexylphosphino)-2-(2-methoxyphenyl)-1-methyl-1-H-indole (Table 6.1, L2)
3-(Dicyclohexylphosphino)-2-(2-methoxyphenyl)-1-methyl-1-H-indole (Table 6.1, L2)
2-Methyl-1,1'-biphenyl (Table 6.2, entry 1)
2,3-Dimethyl-1,1'-biphenyl (Table 6.2, entry 2)
4-Methyl-1,1'-biphenyl (Table 6.2, entry 3)
3-Methyl-1,1'-biphenyl (Table 6.2, entry 4)
2-Phenylnaphthalene (Table 6.2, entry 5)
3-Methoxy-1,1'-biphenyl (Table 6.2, entry 6)
4-Methoxy-1,1'-biphenyl (Table 6.2, entry 7)
5-Phenylbenzo[d][1,3]dioxole (Table 6.2, entry 8)
3-Methyl-4'-{(trifluoromethyl)}-1,1'-biphenyl (Table 6.2, entry 9)
3-Methyl-4’-(trifluoromethyl)-1,1’-biphenyl (Table 6.2, entry 9)
4'-Methoxy-3-methyl-1,1'-biphenyl (Table 6.2, entry 10)
4-Methoxy-4'-methyl-1,1'-biphenyl (Table 6.2, entry 11)
4-(Trifluoromethyl)-1,1'-biphenyl (Table 6.2, entry 12)
4-(Trifluoromethyl)-1,1'-biphenyl (Table 6.2, entry 12)
4-Fluoro-1,1’-biphenyl (Table 2, entry 13)
4-Fluoro-1,1'-biphenyl (Table 2, entry 13)
1-([1,1'-Biphenyl]-4-yl)ethanone (Table 6.2, entry 14)
Methyl [1,1'-biphenyl]-3-carboxylate (Table 6.2, entry 15-18)
Methyl [1,1'-biphenyl]-4-carboxylate (Table 6.2, entry 19-20)
[1,1'-Biphenyl]-4-yl(phenyl)methanone (Table 6.2, entry 21)
[1,1'-Biphenyl]-4-carbonitrile (Table 6.2, entry 22)
[1,1'-Biphenyl]-3-amine (Table 6.2, entry 23)
Benzene-$d$, 2,4,6-tris(1-methylethyl)- (Scheme 6.1)
Benzene-\textit{d}, 2,4,6-tris(1-methylethyl)- (Scheme 6.1)
2,6-Dimethyl-1,1'-biphenyl (Table 6.4, entry 1-2)
2,4,6-Trimethyl-1,1'-biphenyl (Table 6.4, entry 3-4)
2-Methoxy-6-phenylpyridine (Table 6.5, entry 1)
2-Methyl-6-phenylpyridine (Table 6.5, entry 2)
3-Phenylpyridine (Table 6.5, entry 3)
6-Phenylquinoline (Table 6.5, entry 4)
2-Phenylquinoline (Table 6.5, entry 5)
1-Cyclopentenyl-4-methoxybenzene (Table 6.5, entry 6)
3-(4-(Trifluoromethyl)phenyl)furan (Table 6.6, entry 1)
3-(4-(Trifluoromethyl)phenyl)furan (Table 6.6, entry 1)
2-(Furan-3-yl)-6-methylpyridine (Table 6.6, entry 2)
2-(Furan-3-yl)-6-methylpyridine (Table 6.6, entry 2)
2-(Furan-3-yl)-6-methoxypyridine (Table 6.6, entry 3)
1-Methyl-5-(6-methylpyridin-2-yl)-1H-indole (Table 6.6, entry 4)
1-Methyl-5-(6-methylpyridin-2-yl)-1H-indole (Table 6.6, entry 4)
5-(6-Methoxypyridin-2-yl)-1-methyl-1H-indole (Table 6.6, entry 5)
5-(6-Methoxypyridin-2-yl)-1-methyl-1H-indole (Table 6.6, entry 5)
3-Methyl-1,1'-biphenyl (Scheme 6.3)
2-(2-Bromophenyl)-1H-indole (Table 7.1, L3 precursor)
2-(2-Bromophenyl)-1-(methoxymethyl)-1H-indole (Table 7.1, L3 precursor)
2-(2-Bromophenyl)-1-(methoxymethyl)-1H-indole (Table 7.1, L3 precursor)
2-(2-(Dicyclocexylphosphino)phenyl)-1-(methoxymethyl)-1H-indole (Table 7.1, L3)
2-(2-(Dicyclohexylphosphino)phenyl)-1-(methoxymethyl)-1H-indole (Table 7.1, L3)
4-Bromo-3-(1H-indol-2-yl)-N,N-dimethylaniline (Table 7.1, L4 precursor)
4-Bromo-3-(1H-indol-2-yl)-N,N-dimethylaniline (Table 7.1, L4 precursor)
4-Bromo-N,N-dimethyl-3-(1-methyl-1H-indol-2-yl)aniline (Table 7.1, L4 precursor)
4-Bromo-N,N-dimethyl-3-(1-methyl-1H-indol-2-yl)aniline (Table 7.1, L4 precursor)
4-(Dicyclohexylphosphino)-N,N-dimethyl-3-(1-methyl-1H-indol-2-yl)aniline
(Table 7.1, L4)
4-(Dicyclohexylphosphino)-N,N-dimethyl-3-(1-methyl-1H-indol-2-yl)aniline
(Table 7.1, L4)
2-(2-Bromo-5-fluorophenyl)-1H-indole (Table 7.1, L5 precursor)
2-(2-Bromo-5-fluorophenyl)-1H-indole (Table 7.1, L5 precursor)
2-(2-Bromo-5-fluorophenyl)-1-methyl-1H-indole (Table 7.1, L5 precursor)
2-(2-Bromo-5-fluorophenyl)-1-methyl-1H-indole (Table 7.1, L5 precursor)

Formula: [C15H12BrFN]
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PPM: 4.6
2-(2-(Diisopropylphosphino)-5-fluorophenyl)-1-methyl-1H-indole (Table 7.1, L5)
2-(2-(Diisopropylphosphino)-5-fluorophenyl)-1-methyl-1H-indole (Table 7.1, L5)
2-(2-(Diisopropylphosphino)-5-fluorophenyl)-1-methyl-1H-indole (Table 7.1, L5)
2-(2-Bromophenyl)-7-methyl-1H-indole (Table 7.1, L6 precursor)
2-(2-Bromophenyl)-7-methyl-1H-indole (Table 7.1, L6 precursor)
2-(2-Bromophenyl)-1,7-dimethyl-1H-indole (Table 7.1, L6 precursor)
2-(2-Bromophenyl)-1,7-dimethyl-1H-indole (Table 7.1, L6 precursor)

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2-(2-(Dicyclohexylphosphino)phenyl)-1,7-dimethyl-1H-indole (Table 7.1, L6)
2-(2-(Dicyclohexylphosphino)phenyl)-1,7-dimethyl-1H-indole (Table 7.1, L6)
2-(2-Bromophenyl)-7-ethyl-1H-indole (Table 7.1, L7 precursor)
2-(2-Bromophenyl)-7-ethyl-1H-indole (Table 7.1, L7 precursor)

HS

KIN DEPT 18072013 S9 HS 76 (1.430) Cn (Cen,5, 80.00, Ar); Sm (S)

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303.0383

305.1365

m/z
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2-(2-Bromophenyl)-7-ethyl-1-methyl-1H-indole (Table 7.1, L7 precursor)
2-(2-(Dicyclohexylphosphino)phenyl)-7-ethyl-1-methyl-1H-indole (Table 7.1, L7)
2-(2-(Dicyclohexylphosphino)phenyl)-7-ethyl-1-methyl-1H-indole (Table 7.1, L7)
2-(2-Bromophenyl)-4,7-dimethyl-1H-indole (Table 7.1, L8 precursor)
2-(2-Bromophenyl)-4,7-dimethyl-1\textit{H}-indole (Table 7.1, L8 precursor)

![Chemical structure of 2-(2-Bromophenyl)-4,7-dimethyl-1\textit{H}-indole]

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2-(2-Bromophenyl)-1,4,7-trimethyl-1H-indole (Table 7.1, L8 precursor)
2-(2-Bromophenyl)-1,4,7-trimethyl-1H-indole (Table 7.1, L8 precursor)
2-(2-(Dicyclohexylphosphino)phenyl)-1,4,7-trimethyl-1H-indole (Table 7.1, L8)
2-(2-(Dicyclohexylphosphino)phenyl)-1,4,7-trimethyl-1H-indole (Table 7.1, L8)
2-(2-Bromophenyl)-6-fluoro-1H-indole (Table 7.1, L9 precursor)
2-(2-Bromophenyl)-6-fluoro-1H-indole (Table 7.1, L9 precursor)

HS

Kin-Dept 24102013 HR S15 34 (0.638) CH (Cen, 4, 80.00, Ar; Sm (SIG, 2x0.00); Sb (10.40.00); Cm (34.50) TOF MS ES+ 4.05e3
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2-(2-Bromophenyl)-6-fluoro-1-methyl-1H-indole (Table 7.1, L9 precursor)
2-(2-(Dicyclohexylphosphino)phenyl)-6-fluoro-1-methyl-1H-indole (Table 7.1, L9)
2-(2-(Dicyclohexylphosphino)phenyl)-6-fluoro-1-methyl-1H-indole (Table 7.1, L9)
2-(2-(Dicyclohexylphosphino)phenyl)-6-fluoro-1-methyl-1H-indole (Table 7.1, L9)
2-(2-Bromophenyl)-5,6-dimethyl-1H-indole (Table 7.1, L10 precursor)
2-(2-Bromophenyl)-5,6-dimethyl-1H-indole (Table 7.1, L10 precursor)

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2-(2-Bromophenyl)-1,5,6-trimethyl-1H-indole (Table 7.1, L10 precursor)
2-(2-(Dicyclohexylphosphino)phenyl)-1,5,6-trimethyl-1H-indole (Table 7.1, L10)
2-(2-(Dicyclohexylphosphino)phenyl)-1,5,6-trimethyl-1H-indole (Table 7.1, L10)
1,2-Dimethyl-1H-indole (Table 7.1, L11 precursor)
3-Bromo-1,2-dimethyl-1H-indole (Table 7.1, L11 precursor)
3-(Dicyclohexylphosphino)-1,2-dimethyl-1\textit{H}-indole (Table 7.1, L11)
3-(Dicyclohexylphosphino)-1,2-dimethyl-1H-indole (Table 7.1, L11)
2-(Pyridin-2-yl)-1H-indole (Table 7.1, L13 and L20 precursor)
1-Methyl-2-(pyridin-2-yl)-1H-indole (Table 7.1, L13 and L20 precursor)
3-Bromo-1-methyl-2-(pyridin-2-yl)-1H-indole (Table 7.1, L13 and L20 precursor)
3-Bromo-1-methyl-2-(pyridin-2-yl)-1H-indole (Table 7.1, L13 and L20 precursor)
3-(Dicyclohexylphosphino)-1-methyl-2-(pyridin-2-yl)-1H-indole (Table 7.1, L13)
3-(Dicyclohexylphosphino)-1-methyl-2-(pyridin-2-yl)-1H-indole (Table 7.1, L13)

Formula: C_{26}H_{34}N_{2}P
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3-(Diphenylphosphino)-1-methyl-2-(pyridin-2-yl)-1H-indole (Table 7.1, L20)
3-(Diphenylphosphino)-1-methyl-2-(pyridin-2-yl)-1H-indole (Table 7.1, L20)
1-(4-Methoxy-3,5-dimethylphenyl)ethanone (Table 7.1, L14 precursor)
2-(4-Methoxy-3,5-dimethylphenyl)-1H-indole  (Table 7.1, L14 precursor)
2-(4-Methoxy-3,5-dimethylphenyl)-1H-indole  (Table 7.1, L14 precursor)
2-(4-Methoxy-3,5-dimethylphenyl)-1-methyl-1H-indole (Table 7.1, L14 precursor)
2-(4-Methoxy-3,5-dimethylphenyl)-1-methyl-1H-indole (Table 7.1, L14 precursor)
3-Bromo-2-(4-methoxy-3,5-dimethylphenyl)-1-methyl-1H-indole (Table 7.1, L14 precursor)
3-Bromo-2-(4-methoxy-3,5-dimethylphenyl)-1-methyl-1H-indole (Table 7.1, L14 precursor)
3-(Dicyclohexylphosphino)-2-(4-methoxy-3,5-dimethylphenyl)-1-methyl-1H-indole (Table 7.1, L14)
3-(Dicyclohexylphosphino)-2-(4-methoxy-3,5-dimethylphenyl)-1-methyl-1H-indole (Table 7.1, L14)
2-(1H-Indol-2-yl)phenol (Table 7.1, L24 precursor)
2-(2-(Benzyloxy)phenyl)-1H-indole (Table 7.1, L24 precursor)
2-(2-(Benzyloxy)phenyl)-1-methyl-1H-indole (Table 7.1, L24 precursor)
2-(2-(Benzyloxy)phenyl)-3-bromo-1-methyl-1H-indole (Table 7.1, L24 precursor)
2-(2-(Benzyloxy)phenyl)-3-bromo-1-methyl-1H-indole (Table 7.1, L24 precursor)
2-(2-(Benzyloxy)phenyl)-3-(diphenylphosphino)-1-methyl-1H-indole (Table 7.1, L.24)
2-(2-(Benzyloxy)phenyl)-3-(diphenylphosphino)-1-methyl-1H-indole (Table 7.1, L24)
2-(2-Methoxynaphthalen-1-yl)-1-methyl-1H-indole (Table 7.1, L25 precursor)
3-Bromo-2-(2-methoxynaphthalen-1-yl)-1-methyl-1H-indole (Table 7.1, L25 precursor)
3-Bromo-2-(2-methoxynaphthalen-1-yl)-1-methyl-1H-indole (Table 7.1, L25 precursor)

HS

![Chemical structure](image)

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<td>C20 H17 Br N O</td>
</tr>
</tbody>
</table>
3-(Diphenylphosphino)-2-(2-methoxynaphthalen-1-yl)-1-methyl-1H-indole (Table 7.1, L25)
3-(Diphenylphosphino)-2-(2-methoxynaphthalen-1-yl)-1-methyl-1H-indole (Table 7.1, L25)
3-Bromo-2-(2-bromophenyl)-1-methyl-1H-indole (Table 7.1, L27 precursor)
3-Bromo-2-(2-bromophenyl)-1-methyl-1H-indole (Table 7.1, L27 precursor)
3-(Diisopropylphosphino)-2-(2-(diisopropylphosphino)phenyl)-1-methyl-1H-indole (Table 7.1, L27)
3-(Diisopropylphosphino)-2-(2-(diisopropylphosphino)phenyl)-1-methyl-1H-indole (Table 7.1, L27)
4,4,5,5-Tetramethyl-2-(p-tolyl)-1,3,2-dioxaborolane (Table 7.3, Entry 1)
4,4,5,5-Tetramethyl-2-(m-tolyl)-1,3,2-dioxaborolane (Table 7.3, Entry 2)
4,4,5,5-Tetramethyl-2-(o-tolyl)-1,3,2-dioxaborolane (Table 7.3, Entry 3)
2-(2,6-Dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 7.3, Entry 4)
2-(3-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 7.3, Entry 5)
2-(4-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 7.3, Entry 6)
4,4,5,5-Tetramethyl-2-(4-(methylthio)phenyl)-1,3,2-dioxaborolane (Table 7.3, Entry 7)
2-(Benzo[d][1,3]dioxol-5-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 7.3, Entry 8)
4,4,5,5-Tetramethyl-2-(naphthalen-2-yl)-1,3,2-dioxaborolane (Table 7.3, Entry 9)
4,4,5,5-Tetramethyl-2-(4-(prop-1-en-2-yl)phenyl)-1,3,2-dioxaborolane (Table 7.3, Entry 10)
4,4,5,5-Tetramethyl-2-(4-vinylphenyl)-1,3,2-dioxaborolane (Table 7.3, Entry 11)
4,4,5,5-Tetramethyl-2-(4-(trifluoromethyl)phenyl)-1,3,2-dioxaborolane (Table 7.4, Entry 1 and 2)
4,4,5,5-Tetramethyl-2-(4-(trifluoromethyl)phenyl)-1,3,2-dioxaborolane (Table 7.4, Entry 1 and 2)
2-(3,4-Difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 7.4, Entry 3)
2-(3,4-Difluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (Table 7.4, Entry 3)
4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (Table 7.4, Entry 4 and 5)
3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (Table 7.4, Entry 6)
Methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (Table 7.4, Entry 7)
Methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (Table 7.4, Entry 8)
1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethan-1-one (Table 7.4, Entry 9 and 10)
1-(3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethan-1-one (Table 7.4, Entry 11)