PALLADIUM-CATALYZED SUZUKI-MIYAURA CROSS-COUPLING REACTION OF AROMATIC ESTERS AND AROMATIC DIESTERS WITH ARYLBORONIC ACIDS

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Norah Abdulrahman Almowanas

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The Supervisory Committee certifies that this ***disquisition*** complies with North Dakota State University's regulations and meets the accepted standards for the degree of

MASTER OF SCIENCE

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ABSTRACT

The palladium-catalyzed cross-coupling reactions for the functionalization of the ester bond provides a significant overall improvement in the catalytic system as compared to aryl halides/pseudo-halides electrophilic coupling partners. Several pathways have been developed to construct C-C or C-X (-O,-N,-S,&-P) bonds that avoid pre-functionalization, hard reaction conditions, and waste production. These pathways include decarboxylation, decarbonylative, and non-decarbonylative coupling reactions. The non-decarbonylative coupling reaction of aromatic esters with organoboron compounds has emerged as a novel and valuable solution, providing new methodologies and synthetics in organometallic chemistry. More specifically, this type of reaction has shown promising results for synthesizing biaryl compounds and aryl diketones from aromatic esters. This study found that a series of novel aryl ketone and aryl diketone moieties can be formed via a non-decarbonylative Suzuki-Miyaura coupling reaction using readily available and inexpensive starting materials (e.g., phenyl benzoate, 1,4-diphenyl 1,4-benzenedicarboxylate, and 1,3-diphenyl 1,3-benzenedicarboxylate) with aryl boronic acids in the presence of [Pd(IPr)(***π***-4-$CF_3C_6H_4$-C_3H_5)Cl] precatalysts.

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LIST OF SCHEMES

LIST OF ABBREVIATIONS

CH_3CN.....Acetonitrile

Ar .....Aryl

$CDCl_3$ .....Deuterated chloroform

DCM .....Dichloromethane

DMAP 4-Dimethylaminopyridine

DMSO .....Dimethyl sulfoxide

EDG .....Electron donating group

Equiv .....Equivalent

EtOAc .....Ethyl acetate

EWG .....Electron-withdrawing group

H_2O .....Water

h .....Hours

HCI .....Hydrochloric acid

Hz .....Hertz

KOH .....Potassium Hydroxide

K_3PO_4.....Tri potassium phosphate

K_2CO_3 .....Potassium carbonate

LiOH.....Lithium hydroxide

mL.....Milliliter(s)

NHC .....N-heterocyclic carbene

NMR .....Nuclear magnetic resonance

Ph .....Phenyl

ppm .....Parts per million

rt .....Room temperature

Temp .....Temperature

THF .....Tetrahydrofuran

TLC .....Thin-layer chromatography

UV .....Ultraviolet

CHAPTER 1: GENERAL BACKGROUND OF TRANSITION METAL CATALYSIS REACTIONS

1.1. Introduction

Over the past years, aromatic carboxylic acids have played an essential role in synthesizing various complex molecules. They have become very powerful electrophiles or nucleophiles to create new carbon-carbon and carbon-heteroatom bonds.[1] Recently, the formation of new carbon-carbon and carbon-heteroatom bonds such as biaryl compounds or diaryl ketones from carboxylic acids under catalytic conditions was a highly remarkable transformation. Carboxylic acid derivatives have been widely used structurally in medicine, agriculture, pharmaceuticals, food, and other industries (Figure 1.1).[2] The presence of these privileged structures in many valuable compounds has appealed to synthetic chemists to manipulate their functionalization reactions.

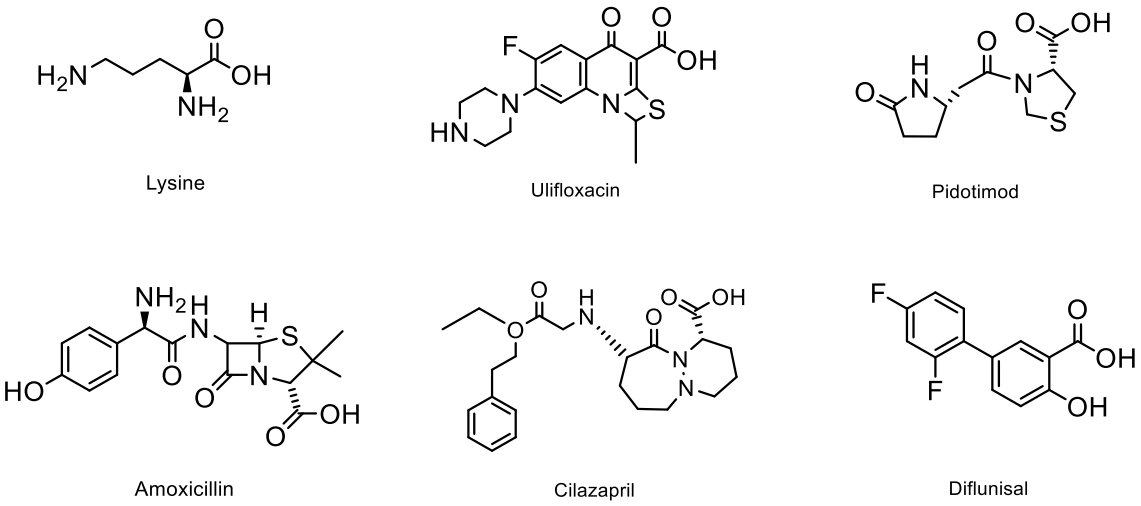
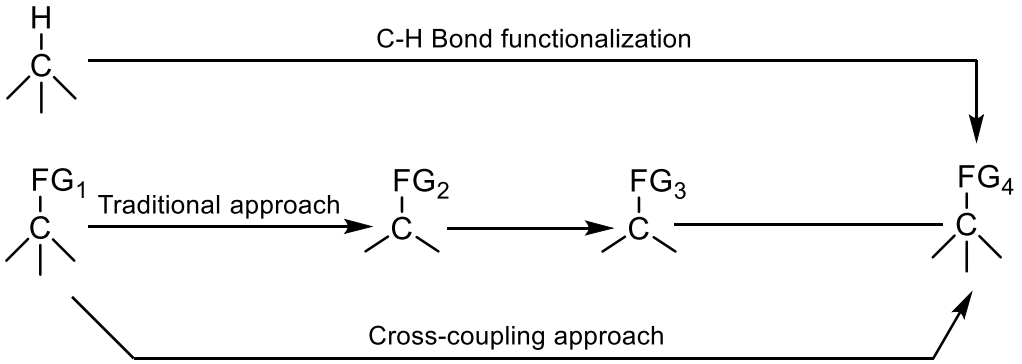


Figure 1.1. Selected biologically and pharmacology active carboxylic acid derivatives.

The main challenge is how to extend the degree of evolving new and more efficient methodologies in almost all areas of synthetic chemistry. Therefore, significantly advanced methods have been discovered and have taken place in organic chemistry to control the reactions' reactivity and the selectivity. There have been three classes of organic compound functionalization

that have been reported to seek different design approaches that were "chemically most attractive, challenging, and satisfying." (Scheme 1.1). [2,3]

1. C-H Bond functionalization.
2. Traditional approach.
3. Cross-coupling approach.



Scheme 1.1. Generic representation of different classes of organic compound functionalization.

Each of these classes is experiencing an intensified interest with individual strengths and weaknesses to obtain the target molecules. The use of these approaches is beneficial not only because they allow for unprecedented control of the molecules' regio- and/or chemoselectivity but because they can provide new synthetic strategies and routes while also help maintain their inherent molecular properties in organic synthesis chemistry.

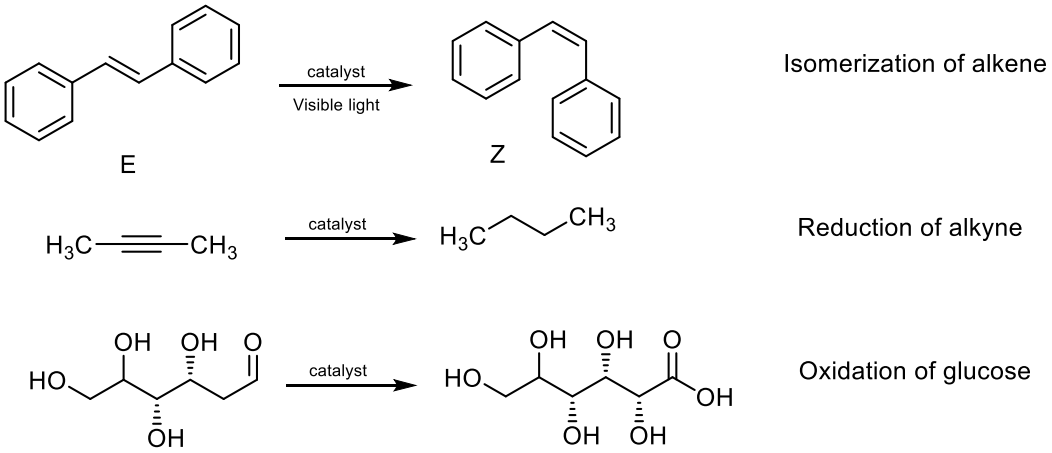
It remains worthwhile to further investigate different approaches to expedite the area of the chemical transformations and to provide novel molecules of interest to pharmaceutical/agro-chemical, polymer, and natural products. Recently, these methodologies have been engaged in designing and synthesizing potent and selective compounds that provide the desired new molecular structures without being time-consuming and while being eco-friendly. This thesis aims to demonstrate the Suzuki–Miyaura cross-coupling reactions of the aromatic carboxylic acid derivatives (e.g., esters and diesters) in the presence of [Pd(IPr)($\boldsymbol{\pi}$-4-$CF_3C_6H_4$-C_3H_5)Cl]

precatalysts to obtain aryl ketones and aryl diketones via a non-decarboxylative coupling reaction. Innumerable reports have evaluated this topic for the functionalization of esters by transition-metal-catalyzed cross-coupling reactions in recent decades.[4,5]

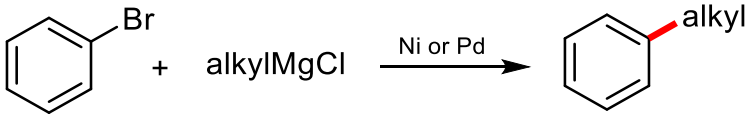
1.2. Modern development of functionalization the inert C-H and C-X bonds by transition-metal catalysis

For many years, a series of transition metal catalysts have shown remarkable results in cross-coupling (Scheme 1.1),[6] C-H activations,[7] isomerizations,[8] reductions,[9] and oxidations reactions[10] because of their ability to create new C–C and C–X (C–O, C–N, C–S, and C–P) bonds (Scheme 1.2). Therefore, the formation of C-C and C-X bonds via transition-metal catalysis has significantly increased. A variety of transition metal salts such as $FeCl_3$, $CoCl_2$, $NiCl_2$, $CuCl_2$, or $CrCl_2$ had been employed as catalysts for the homocoupling of Grignard reagents and (alkyl or aryl halides) as oxidizing agents.[11] For example, in 1972, Tamao and coworkers reported that a new C-C bond could be formed using nickel or palladium metals as catalysts to coupled aryl halides/triflates with Grignard reagents (Scheme 1.3).[12] In 1974, in a seminal work, Kochi described the use of alkenyl halides and Grignard reagents in the presence of ferric chloride ($FeCl_3$) to form olefin product in 1974.[13] In addition, palladium and nickel catalysts have been made a great contribution in cross-coupling reactions because it is not only electronically deactivated the substrates but also the sterically hindered substrates with different Grignard reagents (Scheme1.3).[14-17] This discovery directly inspired more researchers to employ other transition metal catalysis in their reactions. Furthermore, there is always a desire to use metal catalysts that are not air-sensitive and can be easily handled on the benchtop. Therefore, the use of nickel, palladium, copper, rhodium, ruthenium, and indium metals as catalysts has opened new avenues to form C-C and C-X bonds in cross-coupling reactions. Sonogashira coupling,[18]Negishi

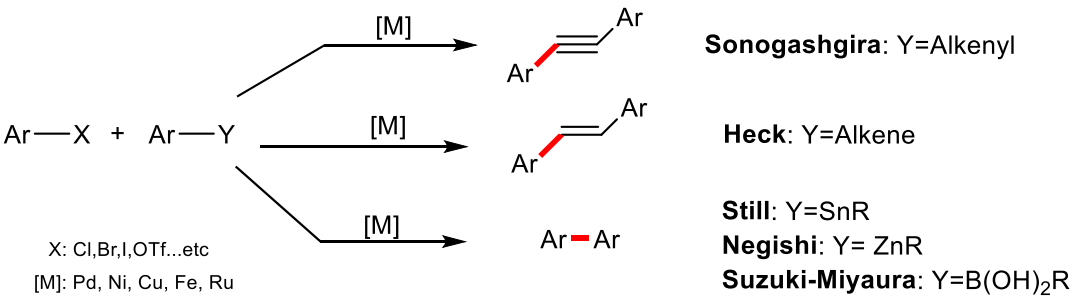
coupling,[19] Stille couplings,[20] Heck coupling,[21] and Suzuki-Miyaura coupling[22] have proved the efficiency and selectivity of using the metal catalyst in cross-coupling reactions (Scheme 1.4). Despite the limitation in coupling chemistry in recent decades, more attention was paid to the synthesis of new organic compounds using the nickel and palladium catalysts rather than other metals.[23] For example, the oxidation states of palladium metal have the potential, and the reactivity toward various organic groups (Pd^0) undergoes oxidative addition to different functional groups, allowing for the initiation of a catalytic cycle. Simultaneously, reductive elimination from (Pd^{II}) intermediate occurs readily to form a new bond between the organic ligands bound to the metal. Palladium is known as the most useful metal for the C-C formation due to its tunability, selectivity, and reactivity.



Scheme 1.2. Examples of using transition metal catalysis in isomerization, reduction, and oxidation reactions.



Scheme 1.3. Generic example of Tamao-Kumada-Corriu cross-coupling reaction.

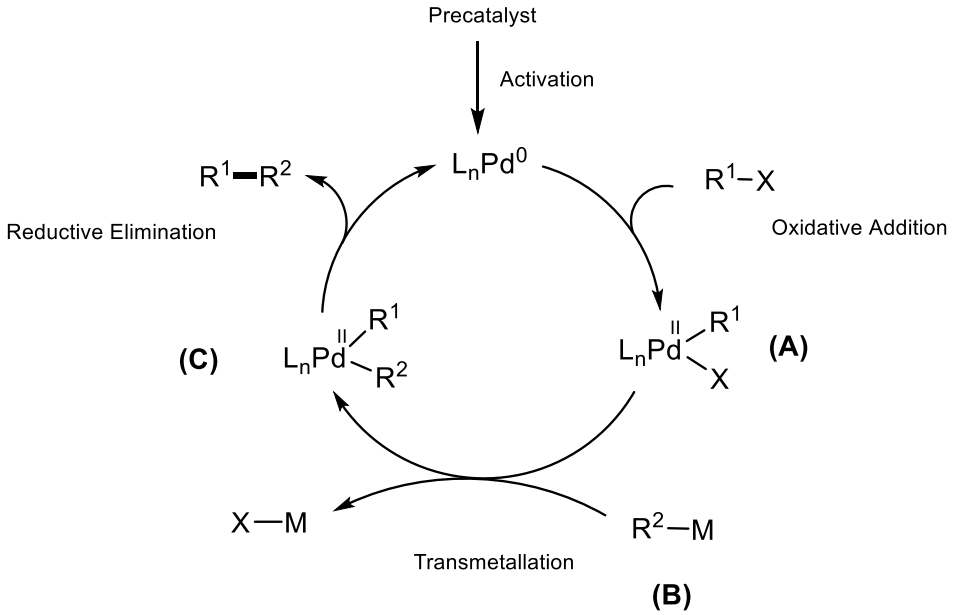


Scheme 1.4. Depiction of generic transition metal-catalyzed cross-coupling reactions.

A broad range of transformations has been developed using nickel and palladium catalysts to form molecules with valuable industrial applications.[24-25] It has been reported that these catalysts were implemented in a highly suitable manner with excellent selectivity and efficiency. Palladium-catalyzed cross-coupling reaction attracted much interest as an efficient method for C-C and C-X bond formations in the 19th century.

Besides, the utilization of Pd metal in this type of reaction would be beneficial because it tends to show more controlled reactivity and better chemoselectivity under mild reaction conditions.[26] The importance and impressive ability of palladium to assemble C-C bonds between appropriately functionalized substrates has allowed synthetic organic chemists to perform transformations that were once impossible to achieve without using multi-step approaches. It is believed that the palladium-catalyzed cross-coupling reaction made way for protocols that exhibit unprecedented complexity, efficiency, and selectivity compared with a traditional organic synthesis, which requires multi-step reactions with the use of several hazardous reagents.[25] In this context, palladium-catalyzed Suzuki-Miyaura coupling represented one of the most common and established methods in industrial and academic applications.[27] A general catalytic cycle of palladium-catalyzed cross-coupling reactions between organo-metallic reagents and organic halides in the presence of a catalytic amount of Pd involves three vital steps: oxidative addition, transmetalation, and reductive elimination (Scheme 1.5).[28] Importantly, the formation of the

catalytic species (**Pd^0**), which generated whether in situ starting from Pd^{II} or directly from (**Pd^0**) derivatives, serves as the foundation to start the catalytic cycle. The oxidative addition step found to be one of the standards and significant steps in cross-coupling reactions where an organic halide (**R^1-X**) is coordinated to the unsaturated (**Pd^0**) catalysts to form the palladium halide (**$L_nPd^{II}R^1X$**) complex. Subsequently, transmetalation is the second step in the catalytic cycle, where (**$L_nPd^{II}R^1X$**) complex reacts with organometallic reagent (**R^2M**) to give (**$L_nPd^{II}R^1R^2$**) complex. The final step in the mechanism is the reductive elimination of complex (**$L_nPd^{II}R^1R^2$**) to afford (**R^1R^2**) coupled product, and the active **Pd^0** is regenerated.



Scheme 1.5. Mechanism of palladium-catalyzed cross-coupling reaction.

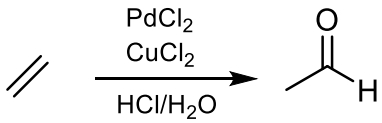
1.3. Development of cross-coupling reactions

1.3.1. Cross-coupling reactions

The construction of new carbon-carbon and carbon-heteroatom bonds via cross-coupling reactions has become a central transformation in organic chemistry.[29] Numerous studies have developed to create molecules with useful industry applications using different nucleophile and

electrophile reagents under new catalytic conditions.[25] Examples of these applications include total synthesis of natural products, pharmaceuticals, chemical biology, materials sciences, supramolecular chemistry, catalysis, and coordination chemistry.[30] The main advantages of the cross-coupling reactions are the use of readily accessible reactants, the toleration of a wide range of functional groups on both coupling partners, the high regio- and stereoselectivity of the reaction, mild reaction conditions, high product yields, and the environmentally friendly process.[31]

In 1959, Wacker Chemie reported the first example of using the metal palladium as a catalyst for the construction of new synthetic building blocks, which is known as the Wacker process.[32-35] The success of the reaction has had a tremendous impact on cross-coupling reactions. It was achievable by utilizing both Pd and Cu metals as an effective catalyst for functionalized aryl halide species for subsequent C–C and C–X bonds. Wacker prepared acetaldehyde by oxidizing ethylene in the presence of the $PdCl_2/CuCl_2$ co-catalysts system in an aqueous HCl solution and an oxidizing agent under homogeneous conditions (Scheme 1.6). In this reaction, the ethylene coordination was attacked by a subsequent nucleophile reagent ($PdCl_2$) to form new bonds. Moreover, the critical feature in the Wacker process was the ability to couple allyl electrophiles with nucleophiles in chemo-, regio-, and stereoselective fashion.



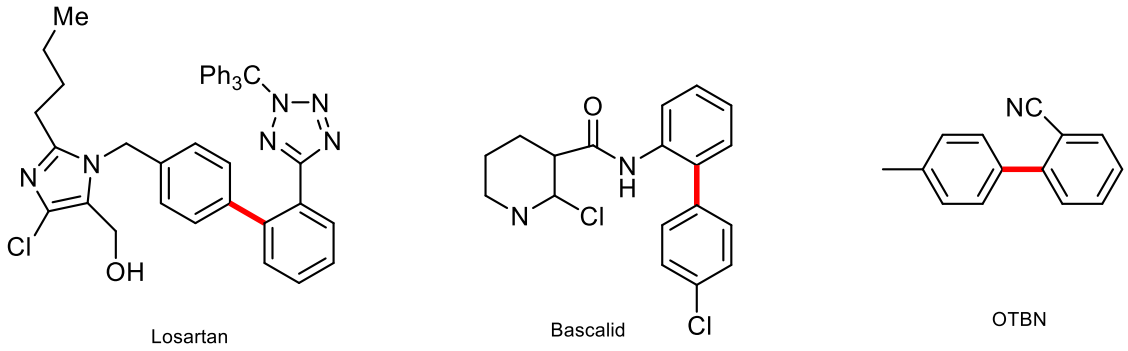
Scheme 1.6. The Wacker processes.

Other researchers were inspired to utilize other transition-metal catalysts and electrophile substrates to form new C-C and C-X bonds. Varieties of cross-coupling reaction (e.g., Tsuji-Trost allylation, Sonogashira coupling, Negishi coupling, Stille coupling, and Suzuki- coupling) have had an incredible impact. They are a useful synthetic toolbox in academic areas due to their

reliability, reproducibility, chemoselectivity, and diversity. In 2010, Richard Heck, Ei-ichi Negishi, and Akira Suzuki were awarded the Nobel Prize in chemistry for successfully developing different approaches to palladium-catalyzed cross-coupling reactions.[36]

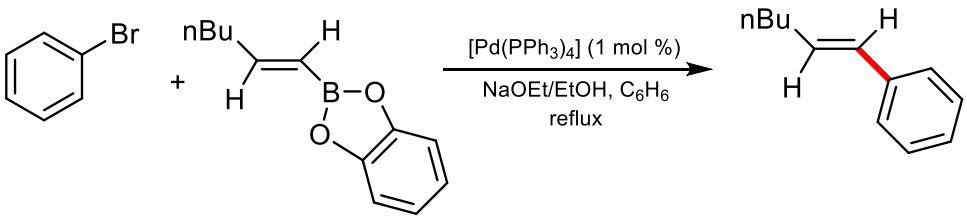
1.3.2. Suzuki-Miyaura cross-coupling reaction

The Suzuki-Miyaura coupling reaction has proven to be a highly valuable transformation in the synthesis of all kinds of biaryl compounds and diaryl ketones.[37] In addition, it has many unique features for large-scale synthesis and the industrial synthesis of pharmaceuticals and fine chemicals (Scheme 1.7).[38-39] In 1974, Heck discovered the coupling of boronic acid with a stereometric amount of palladium.[40] Then, Negishi and coworker has been employed boron to examine the reactivity and the selectively compared to other mild metals in 1982.[41]



Scheme 1.7. Examples of applications that are used the Suzuki-Miyaura coupling reaction.

Generally, organoboron compounds are classified as a highly electrophilic partner. The critical challenge in the Suzuki-Miyaura coupling reaction was transferring the organic group on boron to the metal center.[37] To solve this issue, the negatively charged base was used to activate the organoboronic acids as boronate intermediates, to increase its nucleophilicity, and to facilitate the transfer of the halide on the palladium complex in the transmetalation step. In 1979, Suzuki-Miyaura demonstrated the coupling of organoboronic acids with aryl halides in the presence of a base and palladium as an efficient catalyst to form a new C-C bond (Scheme1.8).[42]



Scheme 1.8. The Suzuki-Miyaura coupling reaction.

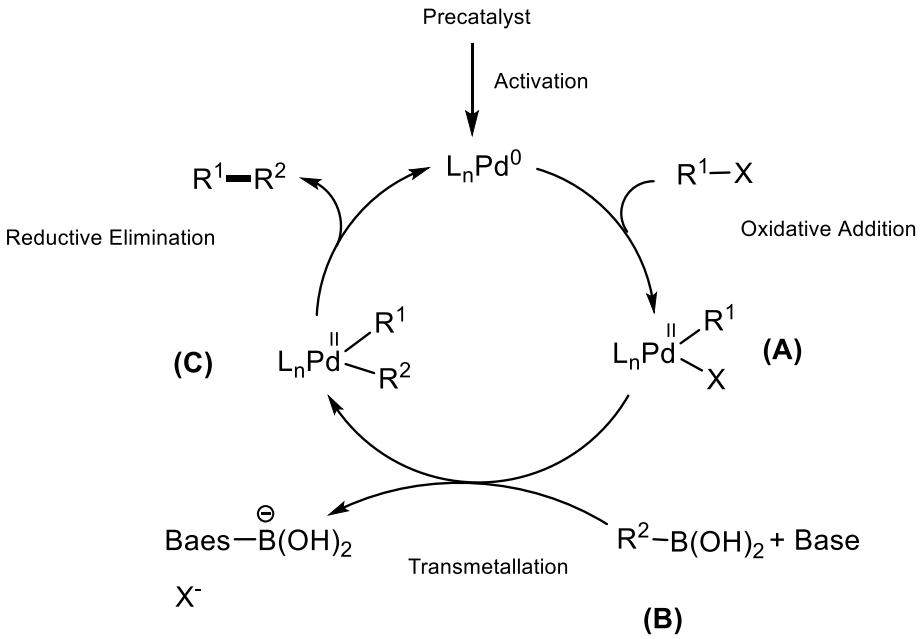
Several studies have reported that organoboron compounds play a significant role in the synthesis of different functional organic materials via palladium-catalyzed cross-coupling reactions. Regarding the advantages of using organoboron as a coupling nucleophile, these include (1) high stability toward water, heat, and air; (2) various functional groups of the organoboron compound which can be synthesized from trialkyl borates with Grignard or organolithium reagents; and (3) low toxicity of the by-product resulted from the reaction.[21]

The properties of using the organoboron compounds and the base led to developing new compounds under mild conditions. Each reaction typically involves two substrates to generate new covalent bonds, often catalyzed as either stoichiometric or catalytic amounts of transition metal and new ligand system in organic synthesis. In recent years, varieties of electrophile and nucleophile substrates have been proven highly useful for the cross-coupling reaction to develop and produce a new organic molecule by establishing a new C-C bond.[43-47]

1.3.2.1. Mechanistic understanding of Suzuki–Miyaura cross-coupling reactions

There has been tremendous progress achieved to obtain the target molecules using Suzuki-Miyaura cross-coupling reactions. The general mechanism of the Suzuki-Miyaura C-C coupling reaction is shown in (Scheme 1.9).[48]An organic halide (**R^1X**), such as alkyl, alkenyl, and aryl halides, which acts as electrophile substrate undergoes oxidative addition with (**Pd^0**) to generate halides complex ((**$L_nPd^{II}R^1X$**). Then, in the transmetalation step, the **R^2** group on the organoboron reagent (**$R^2B(OH)_2$**) acting as a nucleophile coupling partner such as organoborane, organoboronic

acid, organoboroante ester, or potassium trifluoroborate, is transferred to halide complex ($\mathbf{L_nPd^{II}R^1X}$). Thus, both ($\mathbf{R^1}$) and ($\mathbf{R^2}$) take place on the same Pd metal via Pd-C bond ($\mathbf{L_nPdR^1R^2}$). Lastly, the ($\mathbf{R^1}$) and ($\mathbf{R^2}$) groups were coupled to create a new bond, and the Pd^{II} is reduced to Pd^0 to start another catalytic cycle in a process called reductive elimination.

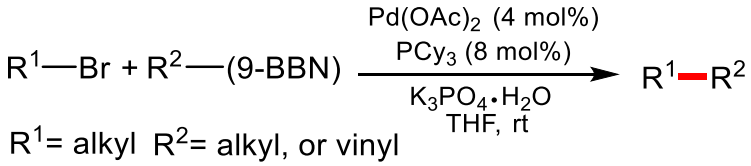


Scheme 1.9. Generic mechanism of Suzuki-Miyaura cross-coupling reaction.

1.3.2.2. Range of electrophile substrates

Significant progress has been made in a range of electrophile substrates other than sp^2-hybridized aryl halides/pseudo halides electrophiles to make the coupling reaction more versatile, sustainable, and atom- efficient. [25] Therefore, much attention has been focused on extending the range of potential electrophile substrates to link with various nucleophile substrates to form new coupled products under suitable conditions. For instance, esters,[49-52] twisted amides,[53-55] ethers,[56-58] carbonates,[59-61] carbamates,[61-63] aziridines,[64-66,] and nitroarenes[67-68] have proven to be useful electrophile substrates in coupling reactions. Although cross-coupling reactions were almost exclusively limited to C(sp^2)-hybridized substrates,[25] C(sp^3) -hybridized substrates have become

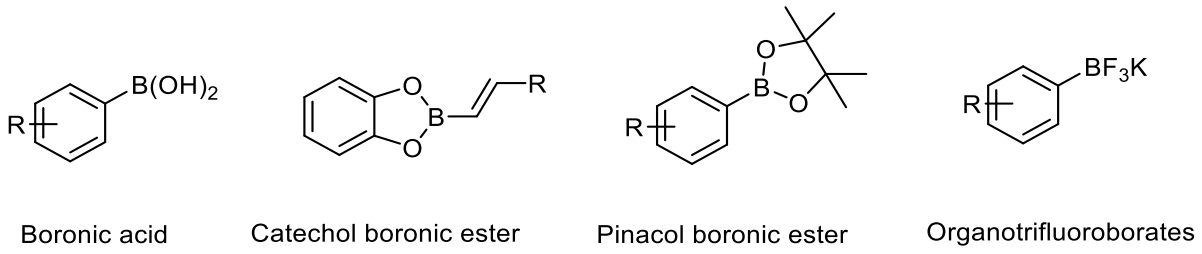
more abundant and have improved the field.[69] In 2001, Fu and his coworkers reported palladium-catalyzed alkyl-alkyl using unactivated alkyl bromides as electrophilic coupling partner at room temperature (Scheme 1.10).[70]



Scheme 1.10. Specific example of using sp^3-hybridized substrates.

1.3.2.3. Range of nucleophile substrates

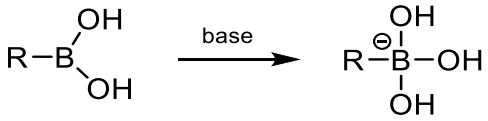
Generally, in cross-coupling reactions, the nucleophile substrates are an essential partner as the electrophilic substrate for constructing a new chemical bond. Among these substrates, anions, hydrocarbons, amines, alcohol, and organometallic reagents have all served as successful nucleophile substrate in the presence of transition metal catalysts under suitable conditions.[71] For example, the Grignard reagents and the organozincates show high reactivity and sensitivity toward air and moisture. In contrast, the organometallic reagents, mainly larger tin and silicon, produce high amounts of metal salts and other by-products.[72] There are significant amounts of current research exploring the development of different nucleophile substrates to couple with electrophile substrates readily under mild conditions. Furthermore, it found that the utilization of organoboron reagents in the Suzuki–Miyaura cross-coupling reaction, which has been far superior to other commonly employed harsh nucleophiles and has heightened interest nowadays due to its unique features (Scheme 1.11).[73]



Scheme 1.11. Common organoboron reagents that are used in transition metal-catalyzed cross-coupling reactions.

1.3.2.4. Range of bases

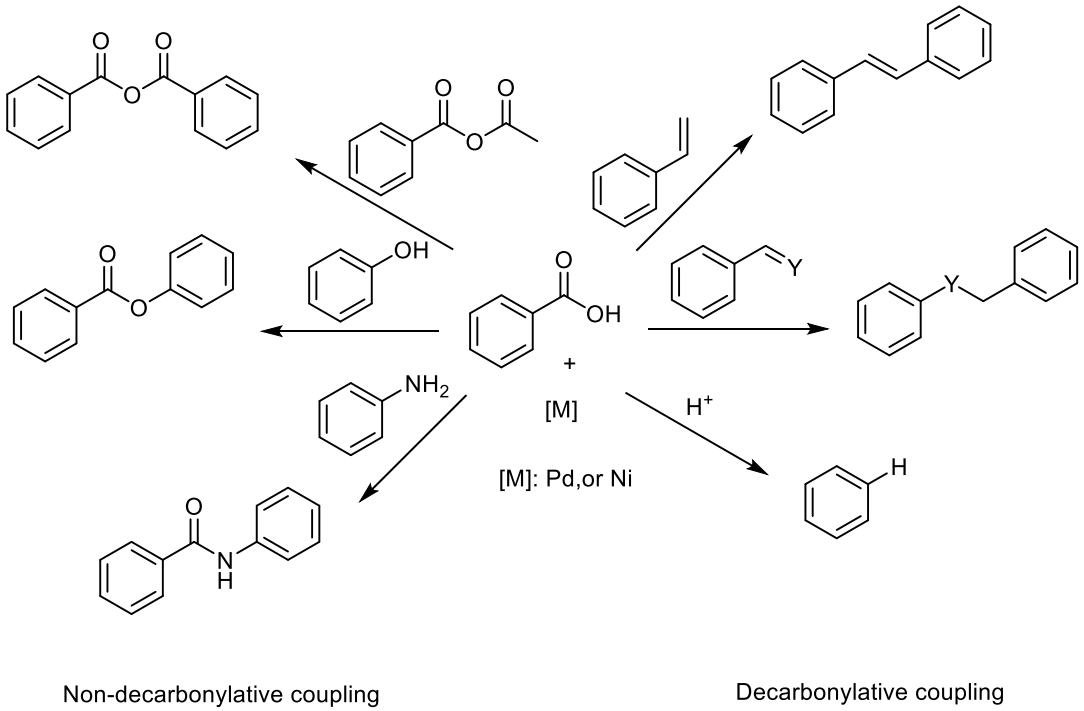
Another important consideration in the Suzuki–Miyaura coupling reaction is the base utilized. Although organoboron compounds have been recognized as strong electrophile substrates, the organic groups on boron are weakly nucleophile and unaffected by water; thus, the utilization of organoboron compounds involved in the ionic reactions. In addition, organoboron compounds have been shown to have low reactivity in the transmetalation step without using the base.[74] Therefore, It was reported that organoboronic acid and boronic ester are smoothly able to transfer their organic groups to the metal center in base-assisted transmetalation reactions due to their high reactivity.[75] Many bases have been employed, such as (NaOH, Na_2CO_3, K_2CO_3, K_3PO_4, CsF, Cs_2CO_3, KOH, TlOH, and KF) under a specific condition in the Suzuki- Miyaura coupling reaction to activate the boron atom and generate the boronate anion (Scheme 1.12).[76] Moreover, it was found that the choice of the base and the solvent depends on the conversion for different boron derivatives.



Scheme 1.12. Example of activated boronic acid using base.

1.4. Practical improvements of electrophile substrates in cross-coupling reaction

Although aryl halides/pseudo halides have become the most conventionally used as coupling electrophiles in catalytic transformations,[77] the use of cheap, air, and moisture-stable, and non-toxic electrophiles has revolutionized the scope of coupling reactions.[78-79] In the last decade, various approaches can be employed and impacted in the area of organic synthesis for the construction of new C-C and C-X bonds. They can be divided into three categories: (1) classical cross-coupling reactions,[80] (2) decarboxylative cross-coupling reactions,[81] and (3) decarbonylative/non-decarbonylative cross-coupling reactions (Scheme 1.13).[82-83]

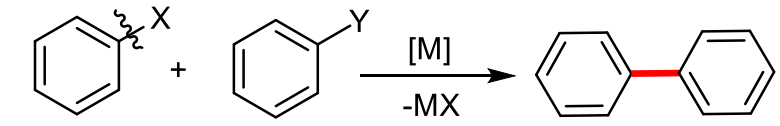


Scheme1.13. Generic representation of decarbonylative and non-decarbonylative cross-coupling reaction.

1.4.1. Classical cross-coupling reactions

Classical cross-coupling reactions have extensively emerged as an approach to construct various chemical bonds in organic chemistry (Scheme 1.14).[81] Several transition metal-catalyzed cross-coupling reactions have found relatively widespread use, especially in an industry dependent

on the type of nucleophile substrates, such as Heck coupling (alkenes), Suzuki coupling (organoboron), Sonogashira coupling (alkyne), Stille coupling (organostannanes), Hiyama coupling (organosilanes), Negishi coupling (organozinc), Kumada coupling (organomagnesium), and Buchwald–Hartwig coupling (primary or secondary amine).



Toxic halides

biaryl coupling

Y: B, Zn, Sn, Mg,Si

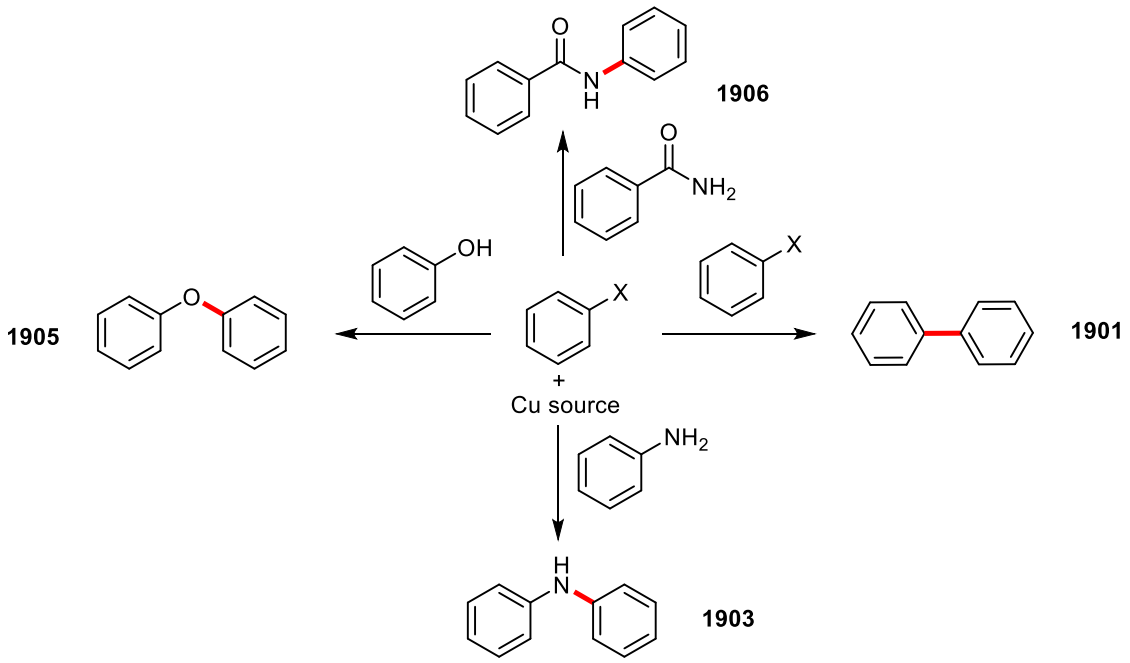
X: Hal (I, Br, Cl, F), OTS, N_2, OR^1, $OCOR^1$, $OCONR^1$

Scheme 1.14. Classical cross-coupling reactions of aryl halides.

Furthermore, the coupling of aryl halides,[84-86] triflates,[87] mesylates/tosylates,[88-89] esters,[90-91] ethers,[92-93] phosphates[94-95], and ammonium salts[96-97] with a nucleophile reagent and the help of metal has been used as an effective electrophile substrate for a vast range of selective C-C bond formations. These electrophiles offer several advantages, such as shortening- steps and promoting chemoselectivity in the synthetic processes. However, the use of aryl (pseudo)halide or sulfur in cross-coupling reactions have various disadvantages. First, they are toxic, expensive, and difficult to handle. Second, they produce corrosive halogen salt and sulfur in the reaction. Finally, they are not always easily available. For example, the synthesis of biaryl compounds of aryl halides often involve pre-functionalization, which can add unnecessary steps to a given synthesis, harsh reaction conditions, and waste production during the reaction.[83]To overcome these issues, new approaches under suitable conditions have been developed using different carbonyl-containing functionalities as the coupling electrophile substrate.

1.4.2. Decarboxylative cross-coupling reactions

Recently the usefulness of decarboxylative cross-coupling has become a central transformation in organic synthesis.[98-100] Using a different type of nucleophiles as a coupling substrate without a metallic group allows for chemo- and regioselective coupling. Additionally, it has shown successful results in decarboxylative aldol reactions,[101] asymmetric carboxylate enolate alkylations,[102] biaryls formations,[103] decarboxylative C-heteroatom cross-couplings,[104] and decarboxylative C-H functionalizations.[105] The decarboxylative reaction of activated carboxylic acid (e.g., ***β***-keto acids, malonic esters) has attracted considerable attention, providing an efficient and modern approach for the construction of the target motifs via the cleaving of the carbonyl group of the carboxylic acid.[106-107] Moreover, they have witnessed increasing interest as a suitable, renewable starting material and potential replacement for unstable, sensitive, and expensive nucleophilic coupling partners. The carboxyl group has been considered as a chemo- and regio-selective leaving group to generate the organometallic intermediates and provided a handle for selective and atom-economic transformations.[108]As one of the pioneering works in this field, Ulmann reported the first example of coupling two aryl halides to form biaryl in the presence of excess metallic copper in 1901.[109] Later, the same process was used between N-aryl amines and ethers to create C–N and C–O bonds in 1903 and 1905, respectively.[110-111]In 1906, another coupling reaction was discovered between aryl amides and aryl halides in the presence of Cu-catalysts by Goldberg (Scheme 1.15).[112]Although aryl halides are effective with copper metal for functionalizing, they suffer from major limitations, including (1) harsh reaction conditions >200 °C,(2) high copper catalyst loading, and (3) poor functional group tolerance with low selectivity.



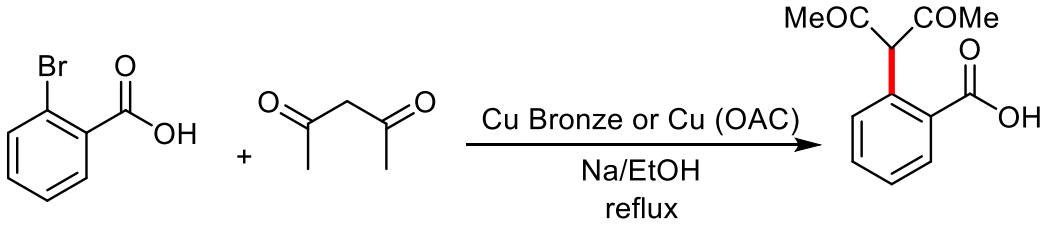
Scheme 1.15. Ullmann reactions: C-C, C–N and C–O bond formations.

In 1929, Hurtley described the first example of copper-catalysis using ubiquitous, inexpensive, and environmentally benign carboxylic acids between β-dicarbonyl and *o*-bromobenzoic acid in the presence of catalytic copper-bronze or copper acetate and sodium, as the base.[113] Similarly, in 1930, Shepard reported that furan-2-carboxylic acids were extended to protodecarboxylation with the aid of copper rather than upon heating alone (Scheme 1.16).[114] The importance of this transformation is to illustrate the great potential benefits of using carboxylic acids and their derivatives as nucleophilic partners to show the highly selective and atom-economicalness of these acids.

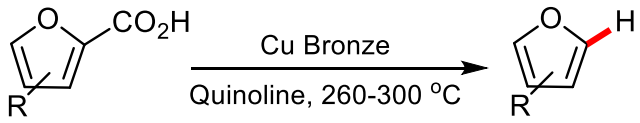
Over the past decades, significant advances have been reported to functionalize the aromatic compounds in the presence of copper metal as a catalyst. However, compared with various transition metals, the Pd-catalyzed reaction has shown great results as effective catalysts to couple the aromatic compounds with aryl halides via a decarboxylative coupling. In 1968, Heck

reported the first example of coupling organomercury compounds with olefins in acetonitrile or methanol at room temperature (Scheme1.17).[115]

Hurtley (1929)

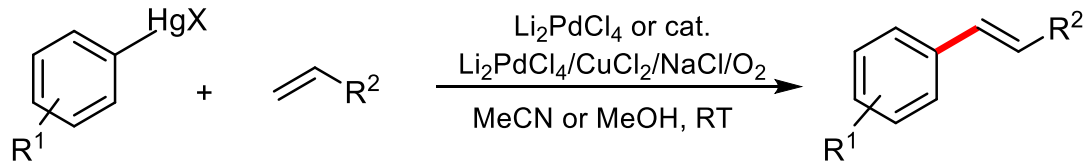


Shepard (1930)



Scheme 1.16. Examples of copper-mediated decarboxylation coupling.

Heck (1968)

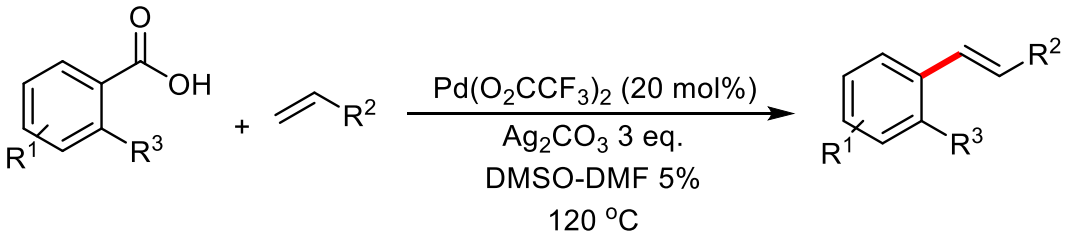


Scheme 1.17. Example of Pd-promoted decarboxylation cross-coupling reaction of organo-mercury and alkene.

The key strength of this transformation lies in the Pd salt's ability to activate the organomercurial compounds. Although several Pd-catalyzed reactions of organomercurial compounds with alkenes were developed in late 1960,[6] makes them a less attractive choice due to the toxicity of certain mercury compounds. This reaction has demonstrated the unique strengths of Pd catalysts in many cross-coupling reactions. Recently, the expansion of the substrate that reacts via this pathway has been particularly important. For example, the synthesis of biaryl from carboxylic acids attracts considerable interest because of their appearance in a wide variety of

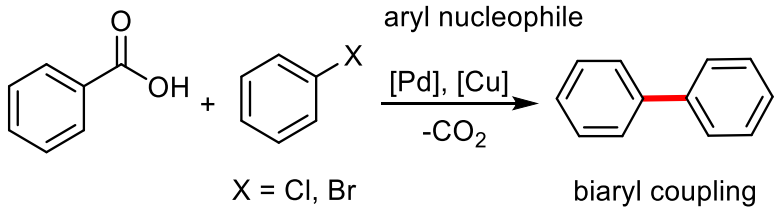
pharmaceuticals, functional materials, and natural products,[116] moreover, the usage of other accessible ready availability of carboxylic acids makes them extremely promising substrates to afford the desired negative synthon in chemical synthesis. In 2002, Myers group disclosed a catalytic decarboxylative cross-coupling reaction of electron-rich aromatic benzoic acid, with alkene applying a stoichiometric amount of palladium ($Pd(O_2CCF_3)_2$ as catalysts and silver carbonate (Ag_2CO_3) as base and oxidant, which lead to the decarboxylative cross-coupling product (Scheme 1.18).[99]

Myers (2002)



Scheme 1.18. Example of Pd-promoted decarboxylation cross-coupling reaction of benzoic acid and alkene.

Also, in 2006, Gooßen reported coupling between carboxylic acids and aryl halides in the presence of the Pd/Cu bimetallic catalyst, which is shown to be an attractive alternative nucleophilic coupling partner in the synthesis of biaryls with extruded CO_2 from the reaction mixture. (Scheme 1.19).[117]



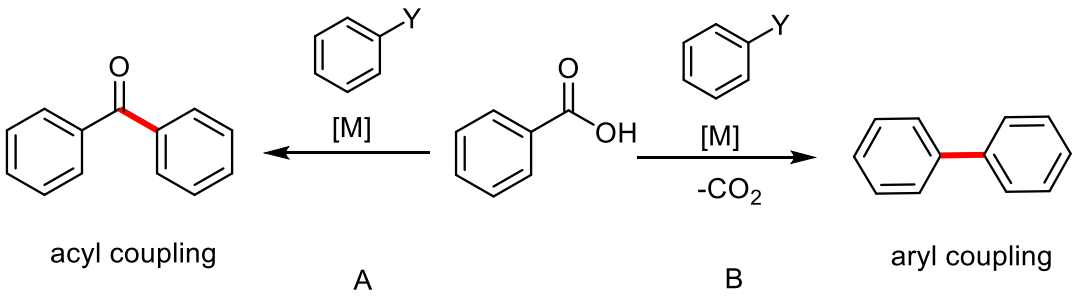
Scheme 1.19. Decarboxylative cross-coupling of carboxylic acid derivatives.

Decarboxylative coupling formed aryl nucleophiles and is performed under oxidative conditions. As an example, couplings of aromatic carboxylic acids for building biaryl products via

decarboxylative coupling are restricted to electron-withdrawing group-containing substrates or a strong oxidant. These reactions often involve another transition metal (catalytic or stoichiometric) such as copper or silver, accelerating the decarboxylation coupling.[118] Even though the decarboxylative coupling represents a mature approach, there is still a significant effort to explore and improve different protocols based on carboxylic acids and derivatives.

1.4.3. Decarbonylative/ Non-decarbonylative cross-coupling reaction

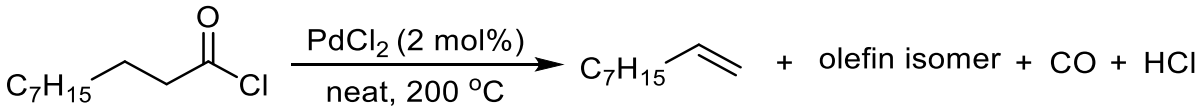
Transition-metal catalyzed cross-coupling reactions of carboxylic acids proceed via decarbonylative or non- decarbonylative pathways to form scaffold molecules or high-value chemicals.[119-121] These two pathways of cross-coupling make a great contribution in organic chemistry. Decarbonylative coupling represents another approach to cleave the carbonyl group in a carboxylic acid with losing carbon dioxide (-CO_2), while a non-decarbonylative coupling is conducted without the loss of the carbonyl group (Scheme 1.20).[122]Decarbonylative coupling forms aryl electrophiles and proceeds under redox- neutral conditions. Activated carboxylic acids that permit selective oxidative addition of a carboxylic acid to a low valent metal center were utilized.



Scheme 1.20. (A) non-decarbonylative pathway, (B) and decarbonylative pathway cross-coupling reactions.

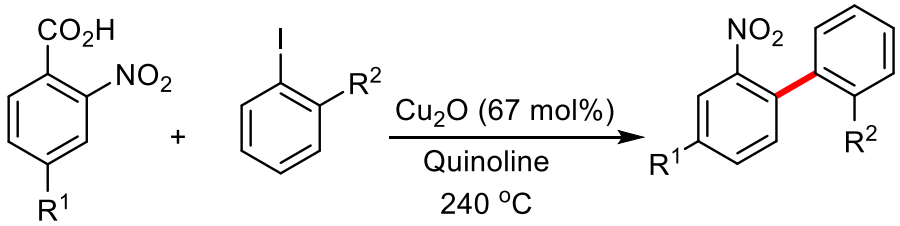
Carboxylic acids have been reported as ideal substrates with transition metal elements, namely copper, nickel, and palladium in decarbonylative and non-decarbonylative coupling

reactions. In 1965, Tsuji and coworkers reported the use of palladium-catalyzed decarbonylative of aliphatic acyl chlorides to form alkenes along with olefin isomer, carbon monoxide, and hydrogen chloride. (Scheme 1.21).[123]



Scheme 1.21. Pd-catalyzed decarbonylative coupling of aliphatic acyl chloride.

After that, in 1966, Nilsson discovered the first example of using aromatic carboxylic acid as an electrophilic coupling partner for the synthesis of 2-nitrobiaryl products via a catalytic decarbonylative coupling. In this reaction, 2-nitrobenzoic acid was successfully coupled with aryl iodides in the presence of Cu_2O as a catalyst in quinoline under harsh conditions to generate both symmetric and unsymmetric biaryls through aryl-Cu intermediates (Scheme 1.22).[124]

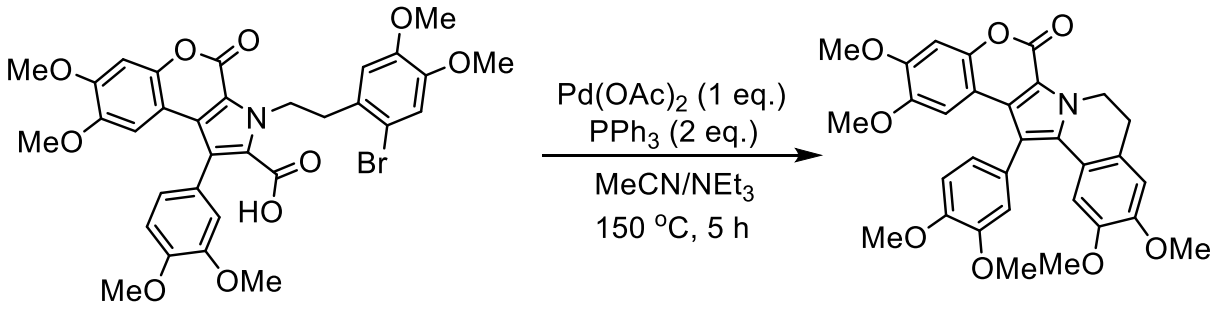


Scheme 1.22. Cu-catalyzed decarbonylative coupling of aryl iodides with 2-nitrobenzoic acid.

These initial findings were remarkable since they showed Cu and Pd are used as a promising catalyst for functionalizing aryl halide species for subsequent C-C and C-X bond formation. However, these reactions suffered from harsh reaction conditions with the heating temperature exceeding 200°C, which resulted in poor chemoselectivity. Furthermore, it is essential to mention that CO extrusions dependent on the nature of the metal catalyst and the ligand employed in the reaction mixture. In 1997, Steglich his coworker, had discovered a Pd-catalyzed intramolecular decarboxylative cross-coupling between a tethered aryl bromide and a

tetrasubstituted pyrrole carboxylic acid in the presence of a stoichiometric amount of palladium to synthesis lamellarin L/G (Scheme 1.23).[125]

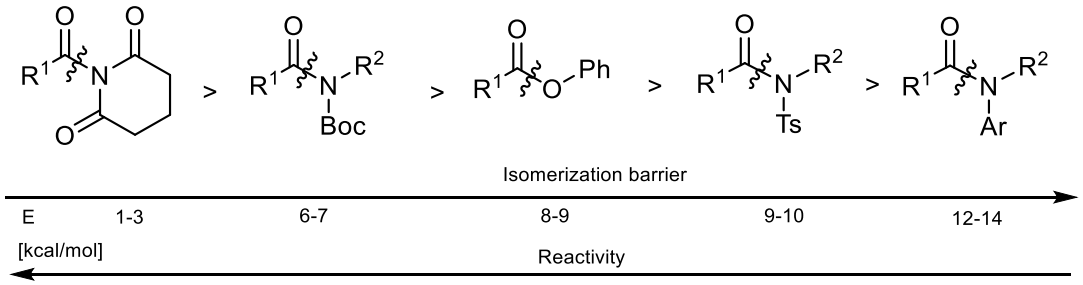
Steglich (1997)



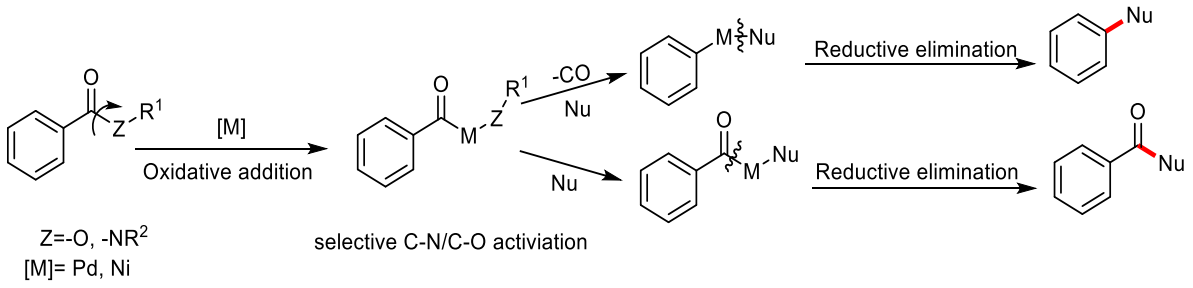
Scheme 1.23. Examples of Pd-promoted decarboxylative cross-coupling reaction of tetra-substituted pyrrole carboxylic acid and tethered aryl bromide.

With the success of decarbonylative coupling of the aromatic carboxylic acid with aryl halides compounds using a monometallic catalytic system, another broad class of carboxylic acids was also employed via this pathway. Acyl chlorides,[126] thioesters,[127] anhydrides,[128,] and aroyl cyanides[129] have been used as electrophile substrates in metal-catalyzed transformations for many years. In addition, amides and esters have also been employed in decarbonylative reactions for the functionalization of inert amide and ester bonds. The resonance stability and the robustness of the amide bonds prevent the insertion of transition metals into an inactive C-N bond to give the coupled products due to amidic resonance (n_N to $\pi^*C{=}O$) conjugation, rotation of ca.15– 20 kcal/ mol in planar amides), which attributes to their low electrophilicity of amides (Scheme 1.24).[130] The development of using transition-metals to activate bench-stable electrophiles has generated major advancements in the field of cross-coupling due to their efficient and selective properties. Moreover, expanding the scope of the reaction to cross-coupling is hard to achieve without activating the inert bond of ester and the amide functional groups. The amide and ester bonds activation can be achieved: (1) electronically or (2) through sterical distortion. Mechanistically,

the activation of the C–O bond proceeds through the ground-state of the destabilization of the amide bond. Then, the insertion of the metal into the C–O bond is followed by the furnishing of acyl–metal intermediate to affording the corresponding coupled products (Scheme 1.24).[131] In this context, aromatic ester electrophiles offer several advantages over aryl halides, phenol, and aniline: (1) they are robust and easy to handle; (2) they can be systematically used as coupling partners in transition metal catalysis under exceedingly mild conditions; (3) they are typically inert to a variety of reaction conditions allowing for ring pre-functionalization, and (4) they can be controlled by their comparatively stable C-O bond toward metal catalysts. With the subsequent improvements, there is a strong impetus to develop transition metal-catalyzed decarbonylative and non-decarbonylative cross-coupling of aromatic esters by C(acyl)-O cleavage due to the prevalence of these precursors in the synthesis of high-value molecules, such as pharmaceuticals, natural products, and fine chemicals.



Scheme 1.24. Reactivity scale of amides and esters in transition metal-catalyzed cross-coupling reaction.

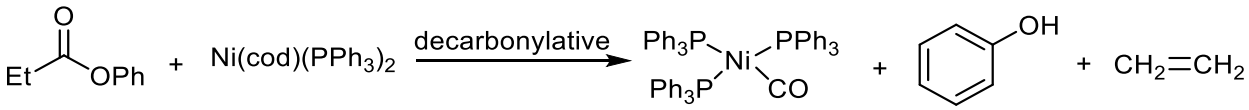


Scheme 1.25. Mechanism for the decarbonylative and non-decarbonylative coupling of aromatic esters or amides.

1.4.3.1. Palladium-catalyzed decarbonylative and non-decarbonylative coupling of unactivated aromatic ester substrates

1.4.3.1.1. Decarbonylative coupling of unactivated aromatic ester substrates

In recent years, there has been a growing interest in the use of aromatic esters in transition-metal-catalyzed decarbonylative cross-coupling reactions because it opens access to a vast number of commercially and synthetically available ester-containing molecules.[132-133] Therefore, Yamamoto has reported that simple ester reacts with a stoichiometric amount of nickel complex $Ni(cod)(PPh_3)_2$, that can be inserted into the C(acyl)-O bond to form complex $Ni(CO)(PPh_3)_3$, phenol, and ethylene (Scheme 1.26).[134] Arising from this groundbreaking discovery, several decarbonylative reactions with unactivated aromatic ester compounds in the presence of Pd catalysts have been reported—for example, Mizoroki-Heck coupling, Suzuki-Miyaura coupling, Sonogashira coupling, and etherification reaction.

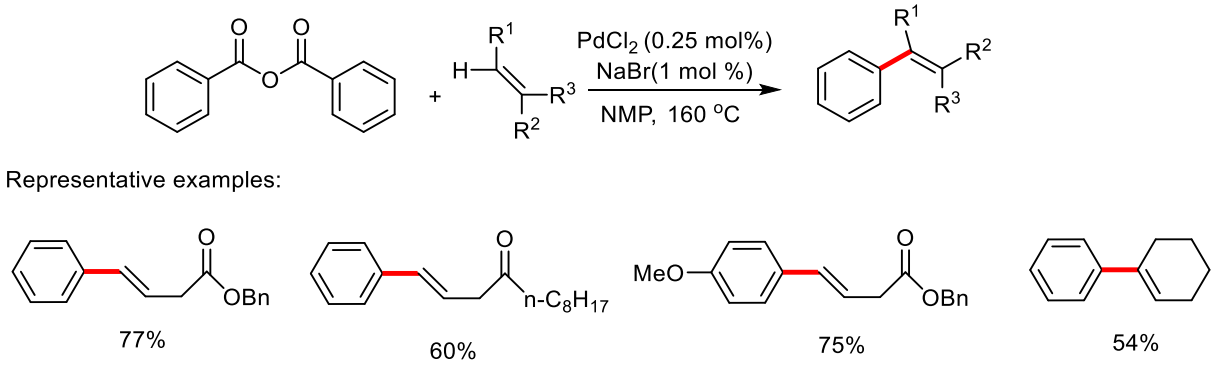


Scheme 1.26. Ni-mediated activation of ester in decarbonylative coupling.

1. Mizoroki-Heck reaction

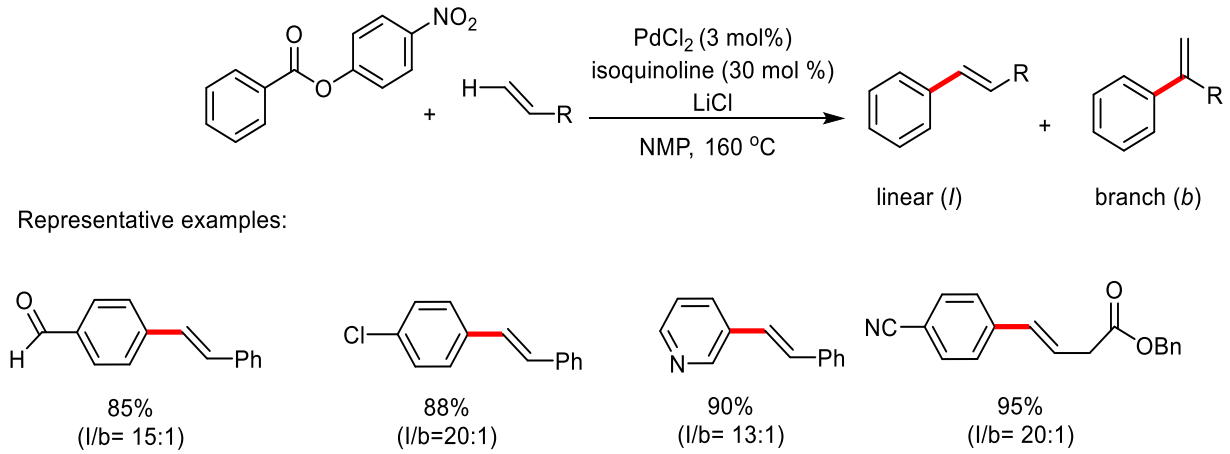
Coupling alkenes with aryl halides has been utilized to generate arylated olefins in academic laboratories and the chemical industry. In late 1998, Stephan and de Vries's group have significantly contributed to this area. Initially, they used aromatic acid anhydrides and n-butyl acrylate in the presence of catalytic $PdCl_2$ and NaBr with NMP as a solvent at 160 °C, but in the absence of a base, vinyl arenes were produced (Scheme 1.27).[135] However, because of the difficulty of dehydrating the benzoic acid, which is formed as a by-product during the reaction into

benzoic anhydride without forming waste, the Mizoroki-Heck coupling could not be achieved with this system.



Scheme 1.27. Pd-catalyzed Mizoroki-Heck decarbonylative coupling of acid anhydride and alkene.

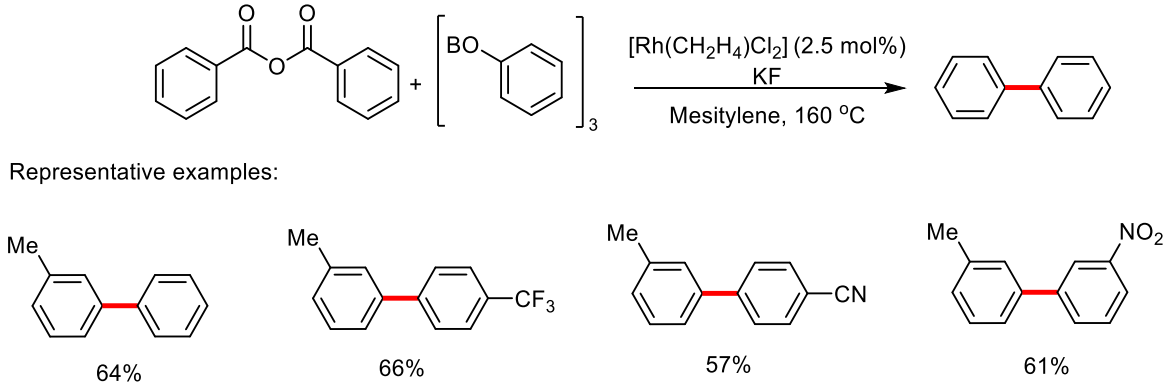
Pd-catalyzed decarbonylative coupling of aromatic esters stems from discoveries made mainly in the 20th century. Various studies on the Pd-catalyzed cross-coupling reactions of the cleavage C-O bonds have been discovered in synthesizing of pharmaceuticals, natural products, and polymers.[136-137] Real waste minimization in this transformation could most likely be achieved using aromatic esters. Since esters are thermodynamically more stable than anhydrides and are directly accessible from carboxylic acids and alcohols, an activated ester such as *p*-nitrophenyl benzoic ester was required for the initial oxidative addition to be achieved. For example, the Gooßen group demonstrated the ability of a Pd-catalysis to activate the C-O bond of an aromatic ester. This reaction proceeded with *p*-nitrophenyl benzoic esters and alkene in the presence of $PdCl_2$ and LiCl at 160 °C to afford linear products as the main product and branched products as a by-product, which represents the first example of using aromatic esters in a decarbonylative coupling (Scheme 1.28).[138] In this reaction, not only was the LiCl needed to promote the product yields, but the isoquinoline also helped stabilize the Pd catalyst and lead to a high yield a coupled product.



Scheme 1.28. Pd-catalyzed Mizoroki-Heck decarbonylative coupling of *p*-nitrophenyl benzoic ester and alkene.

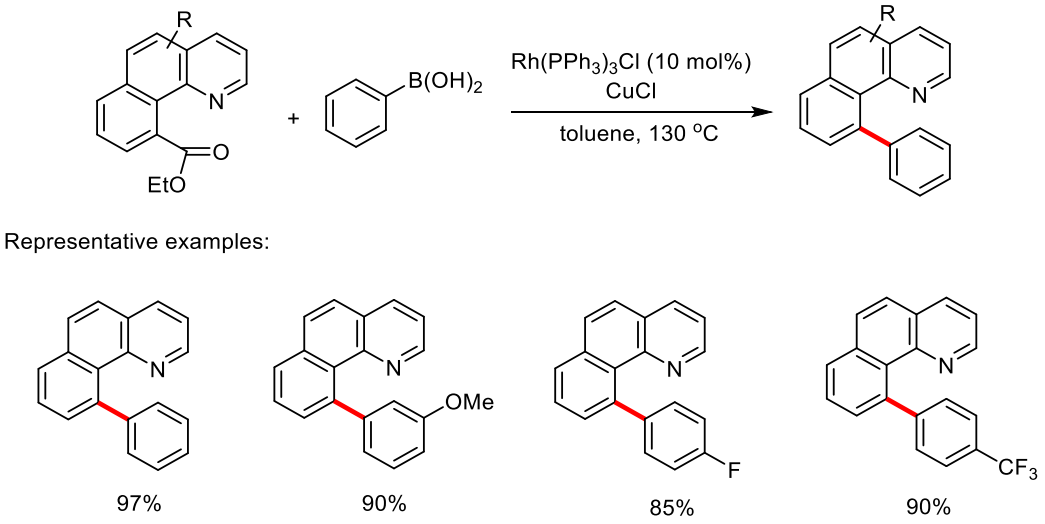
2. Suzuki-Miyaura coupling

Recently, the Suzuki-Miyaura coupling of the unactivated C–O ester electrophile and the organoboron compound has been widely recognized as one of the most critical construction methods for C–C bonds. In 2004, Gooßen and a coworker discovered an Rh-catalyzed Suzuki-Miyaura of 3-methyl benzoic anhydride and aryl boroxines to construct a biaryl compound (Scheme 1.29).[139] Although the fluoride salts, particularly KF, appeared to improve the Rh catalyst's activity, mesitylene also proved to be the optimal solvent for this reaction, as moderate yields of various functional groups were obtained under these conditions.



Scheme 1.29. Rh-catalyzed Suzuki-Miyaura decarbonylative coupling of 3-methyl benzoic anhydride and aryl boroxine.

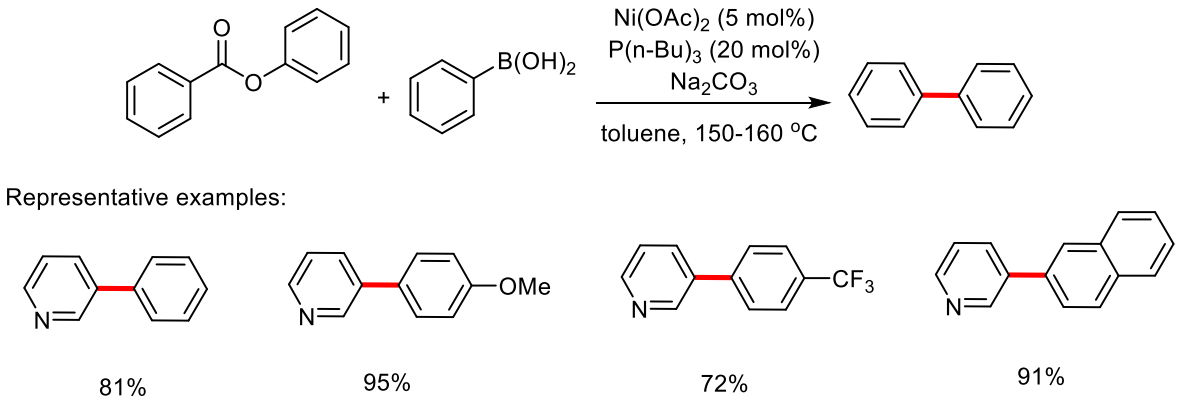
Wang and coworkers subsequently reported similar reactions (Scheme1.30),[140] using ethyl benzo[h]quinoline-10-carboxylates with Rh $(PPh_3)_3Cl$ as a catalyst and aryl boronic acid to obtain the desired product in good to excellent yields with functional group tolerance. The coupling reaction was affected by the $Rh(PPh_3)_3Cl$ catalyst and CuCl via chelation-assisted sp^2 C−COOEt bond activation. The cleavage of the sp^2 C−COOEt is not easily achieved. Therefore, dissociating the strong metal C-O bond requires a significantly high temperature to decrease the bonds strength.



Scheme 1.30. Rh-catalyzed Suzuki-Miyaura decarbonylative coupling of ethyl benzo[h] quinoline-10-carboxylates and aryl boronic acid.

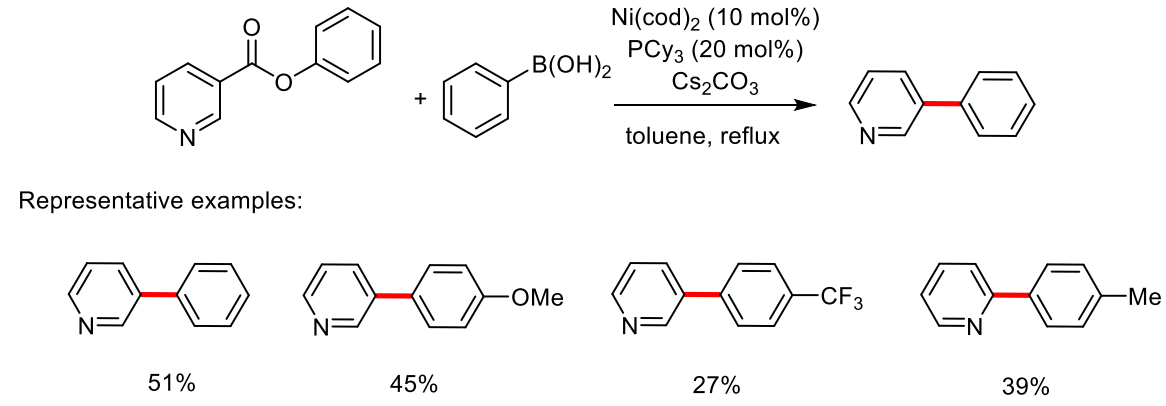
Recently, more attention has been drawn to the use of inexpensive nickel catalysts along with phenyl esters of aromatic, heteroaromatic, and aliphatic carboxylic acids reacting with boronic acids via a decarbonylative pathway. In 2015, among the numerous improvements for the biaryl compound preparation, phenyl esters were treated with aryl boronic acids in toluene using an inexpensive $Ni(OAc)_2/P(n\text{-}Bu)_3$ as a catalyst to furnish coupling products bearing versatile, functional groups in moderate to good yields by Itami, Yamaguchi, and Musaev (Scheme 1.31).[141] $Ni(OAc)_2/P(n\text{-}Bu)_3$ catalyst showed a high molecular recognition ability and chemoselectivity.

Furthermore, during their investigation of Ni catalyzed decarbonylative coupling, they found that Na_2CO_3 was assisted in accelerating the reaction.



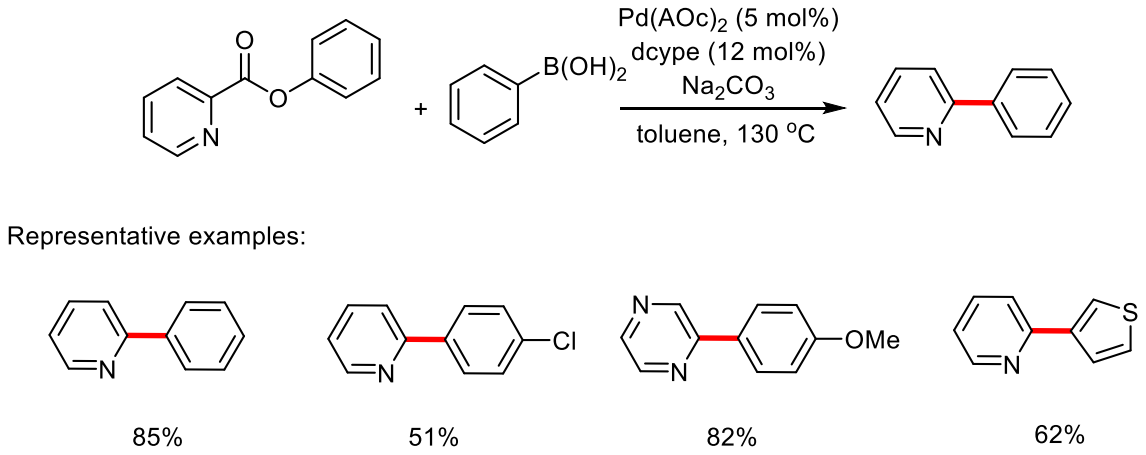
Scheme 1.31. Decarbonylative organoboron cross-coupling of phenyl ester catalyzed by $Ni(OAc)_2/P(n\text{-}Bu)_3$.

In the same year, Love reported that phenyl esters and aryl boronic acids in the presence of a low-toxic catalyst system composed of $Ni(cod)_2$ and PCy_3 to obtain a biaryl compound with a high functional group tolerance low to moderate yields (Scheme 1.32).[142] They found Cs_2CO_3 to be essential for this transformation. Although this reaction provided a new route to afford the desired products, the CO poisoning of the Ni catalyst system might be the cause of the low turnover.



Scheme 1.32: Decarbonylative organoboron cross-coupling of phenyl ester catalyzed by $Ni(cod)_2/PCy_3$.

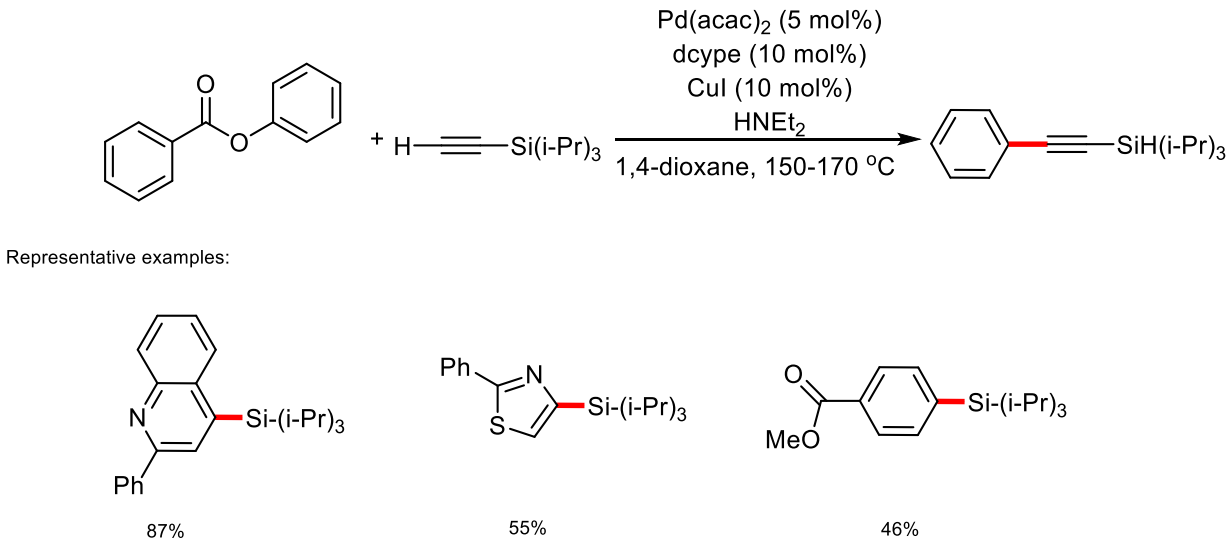
Considerable progress has been achieved in palladium-catalyzed decarbonylative cross-coupling reactions using readily available and versatile C-O electrophiles. In this context, unitizing $Pd(OAc)_2$/dcype catalysts was found to be useful for this transformation via a decarbonylative pathway to generate 2-azinecarboxylates with good functional group compatibility by Yamaguchi and Itami groups in 2016 (Scheme 1.33).[143]



Scheme 1.33. Decarbonylative organoboron cross-coupling of phenyl esters by $Pd(AOc)_2$/dcype.

3. Sonogashira coupling

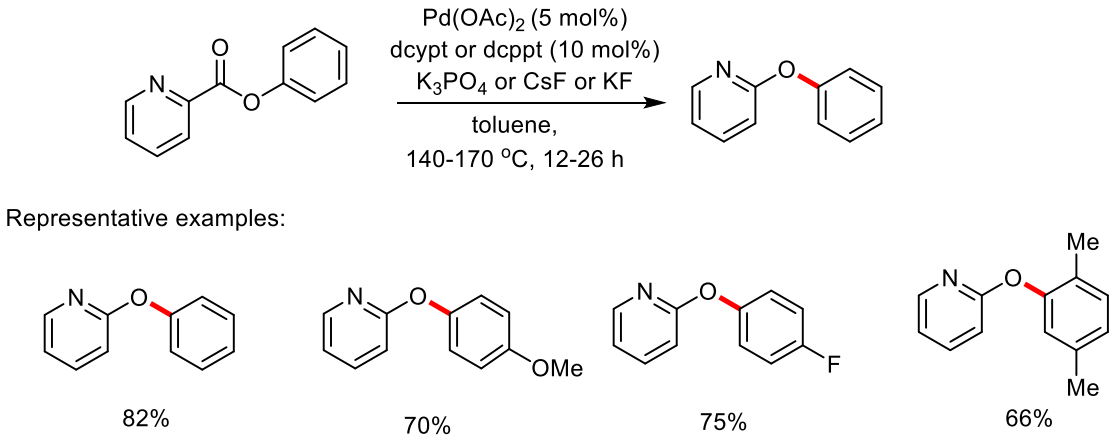
Conventionally, the Sonogashira coupling uses aryl halides as the electrophilic component with alkynes to generate frameworks of organic materials. In 2017, Yamaguchi and Itami reported that phenyl esters could be cross-coupled with TIPS acetylene in the presence of a Pd/Cu co-catalytic to form the corresponding various alkylated arenes in moderate to good yields (Scheme1.34).[144] The reaction represented the first example of Csp^2-Csp bond formation via a decarbonylative pathway. In addition, oxidative C–H arylation with arylsilane in the presence of a Pd/ Cu bimetallic system was achievable compared with other transition-metal catalysts.



Scheme 1.34. Decarbonylative coupling of phenyl ester and alkynes by Pd/Cu catalysts.

4. Etherification reaction

Etherification is well-known as the process of converting alcohol or phenol into an ether. Starting from copper-mediated Ullmann coupling of ether synthesis, the formation of a diaryl ether compound is now considered a "conventional" route. In 2017, Yamaguchi and Itami discovered that aryl esters and phenol with Pd $(OAc)_2$ in the presence of diphosphine ligand form a variety of 2- or 4-arenoxyazine derivatives. The reaction has proceeded smoothly, whether using dccpt [3,4-bis(dicyclopentylphosphino)thiophene] or dcypt [3,4-bis(dicyclohexylphosphino)thiopheneas] ligands to give the products with good functional group tolerance in good to excellent yields. It can be regarded as an important finding because it functions in an intramolecular setting and allows for a cross-etherification using other phenols (Scheme 1.35).[145]



Scheme 1.35. Diaryl ether synthesis from aryl ester by Pd catalysts.

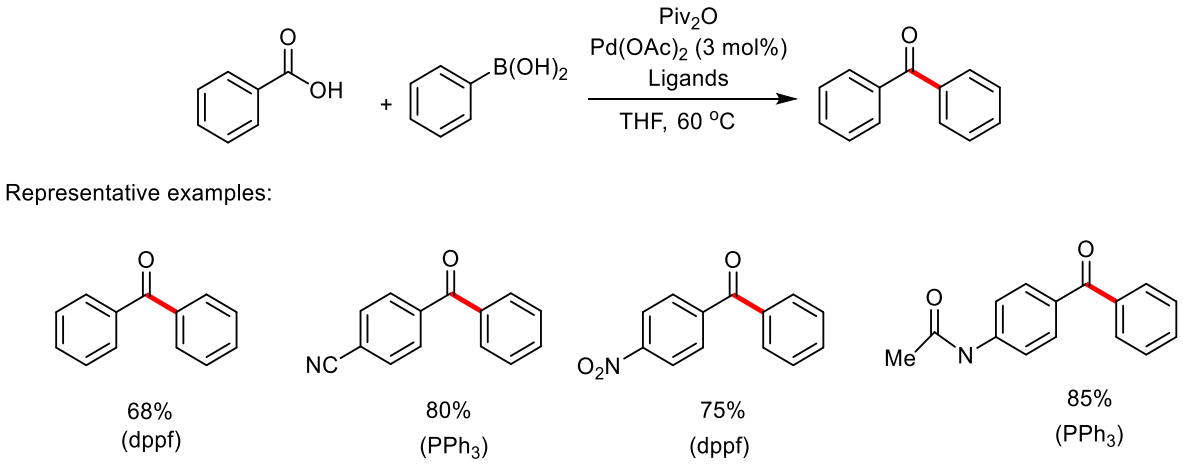
1.4.3.1.2. Non-decarbonylative coupling of unactivated aromatic ester substrates

It was found that non-decarbonylative coupling reactions of aromatic esters have been a dominant approach in synthetic chemistry. In this type of coupling, aromatic ester proved to be a capable electrophile partner despite its high stabilization in the ground state. Therefore, further studies have shown that the Suzuki-Miyaura coupling reaction and amidation reaction using transition metal catalysts are the most common reactions via the non-decarbonylative pathway.

1. Suzuki-Miyaura coupling

Extensive studies have demonstrated that a non-decarbonylative coupling provides a significant improvement in the Suzuki-Miyaura coupling through the use of a bench-stable aromatic ester. In general, the synthesis of ketones from carboxylic acid derivatives goes through a Weinreb amide or acid chlorides but faces issues of chemoselectivity and functional group tolerance limit application.[79] As a result of this limitation, in 2001, Gooßen and a coworker explored the first example of using acid anhydrides as activating agents and aryl boronic acids with the aid of Pd catalyst to give diaryl ketones in a convenient one-pot procedure. This finding was of central importance in terms of reaction conditions, functional group tolerance; thermal, air, and moisture stability; and commercially available organoboron reagents as a nucleophilic partner

(Scheme 1.36).[146] This reaction showed a general route in creating ketones from carboxylic acids using alternative activating reagents to the synthesis from acyl halides.

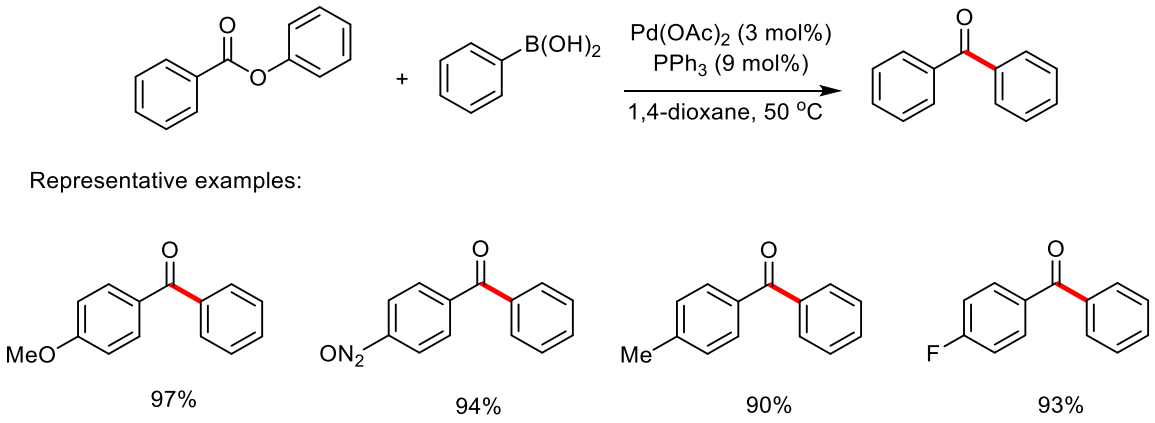


Scheme 1.36. Pd-catalyzed coupling reaction of activated acid anhydride and aryl boronic acids for ketone synthesis.

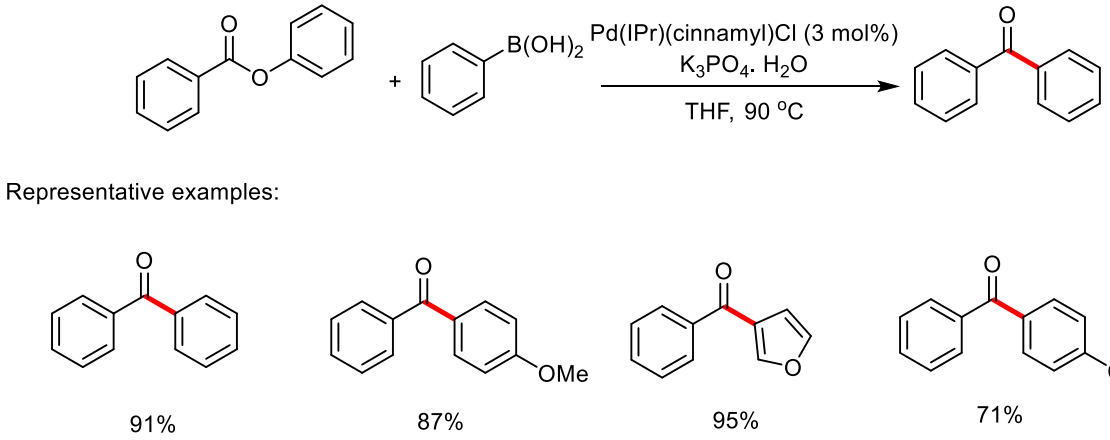
In 2004, Chatani and coworker developed another approach for diaryl ketone synthesis via the non-decarbonylative pathway of 2-pyridyl esters with aryl boronic acids in the presence of a $Pd(OAc)_2$ PPh_3 catalyst. During the investigation, they found that 2-pyridyl esters were smoothly converted to obtain the desired products under mild conditions because of their high reactivity. They also reported that the coordination of the nitrogen with the Pd catalyst is important for increasing the reaction efficiency (Scheme 1.37).[147]

Furthermore, it was reported that a variety of well-defined air-and moisture-stable Pd(II)-NHC precatalysts had been employed in these reactions because of their high effectivity and high structural stability. In a seminal work, Newman and Houk developed the first decarbonylative coupling between phenyl esters and aryl boronic acids using an NHC-based Pd catalyst to form diaryl ketones without the generation of decarbonylative products (Scheme 1.38).[148] The success of their reaction was realized by utilizing a commercially available, bench stable, and operationally-convenient Pd(IPr)(cinnamyl)Cl precatalyst, which allows the synthesis of various

ketone-containing products at elevated temperatures with various functional groups, providing excellent yields. The ability to develop valuable diaryl ketones from ubiquitous esters using Pd precatalysts under mild conditions has gained immense attention in organometallic chemistry.



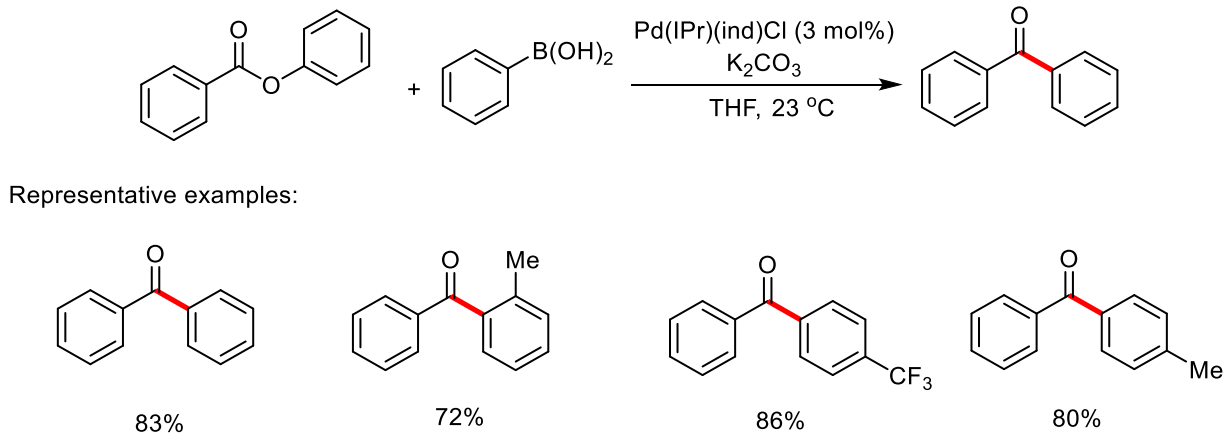
Scheme 1.37. Non-decarbonylative coupling reactions of 2-pyridyl ester and aryl boronic acids by $Pd(OAc)_2PPh_3$ catalyst.



Scheme 1.38. Non-decarbonylative coupling reactions of phenyl ester and aryl boronic acids by Pd (IPr)(cinnamyl)Cl precatalysts.

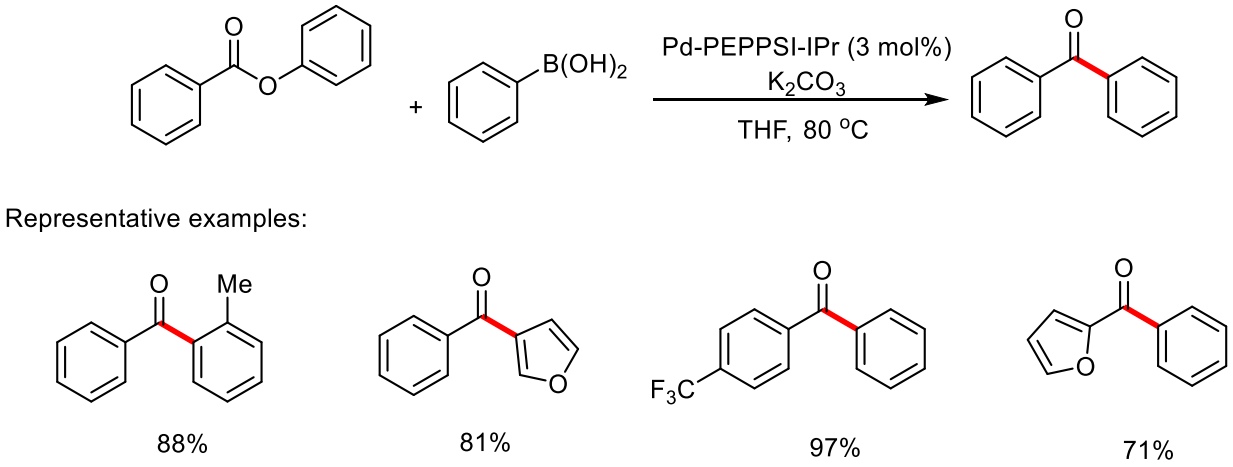
In 2017, the Szostak group demonstrated that the Pd(IPr)(ind)Cl precatalyst is another effective catalyst for the coupling of phenyl ester and aryl boronic acid to generate diaryl ketones with high functional group compatibility at mild room temperature and a with mild carbonate base

(Scheme 1.39).[149] This single catalyst system was found to have a crucial effect in enabling Suzuki-Miyaura coupling of esters by selective C-O cleavage.



Scheme 1.39. Non-decarbonylative coupling reactions of phenyl ester and aryl boronic acids by Pd(IPr)(ind)Cl precatalysts.

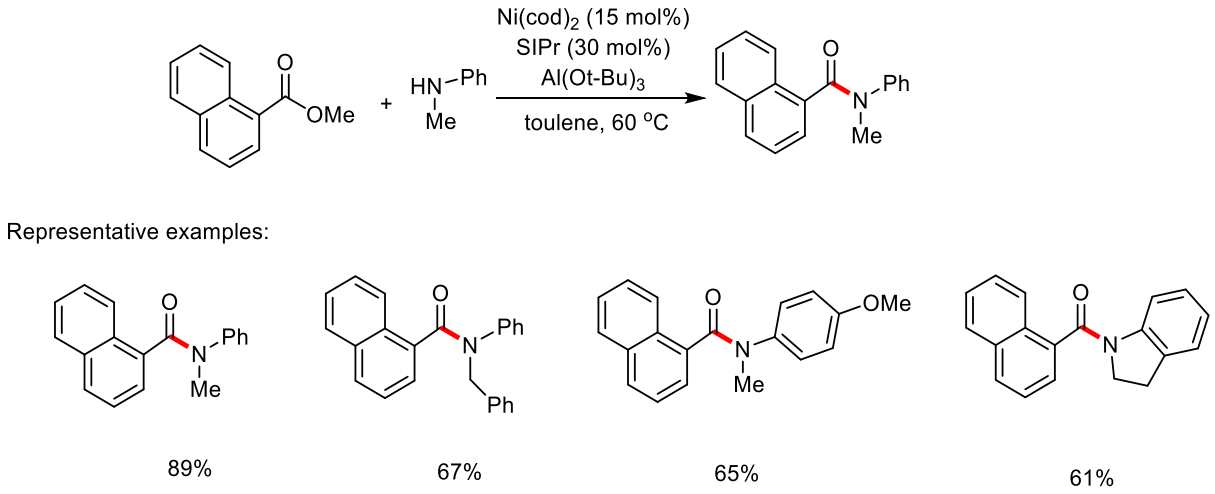
Since then, there has been tremendous progress to employ new general catalyst systems that operate under operationally simple conditions. Therefore, they established that the Suzuki-Miyaura cross-coupling of phenyl esters and aryl boronic acids catalyzed by well-defined Pd-PEPPSI type precatalysts bearing pyridine "throw-away" ligands are capable of cleaving inert C-O bonds to afford diaryl ketones (Scheme 1.40).[150] Furthermore, they found that Pd-PEPPSI type precatalysts serve as highly reactive catalysts for the direct Suzuki-Miyaura cross-coupling of esters.



Scheme 1.40. Non-decarbonylative coupling reactions of phenyl ester and aryl boronic acids by Pd-PEPPSI-IPr precatalysts.

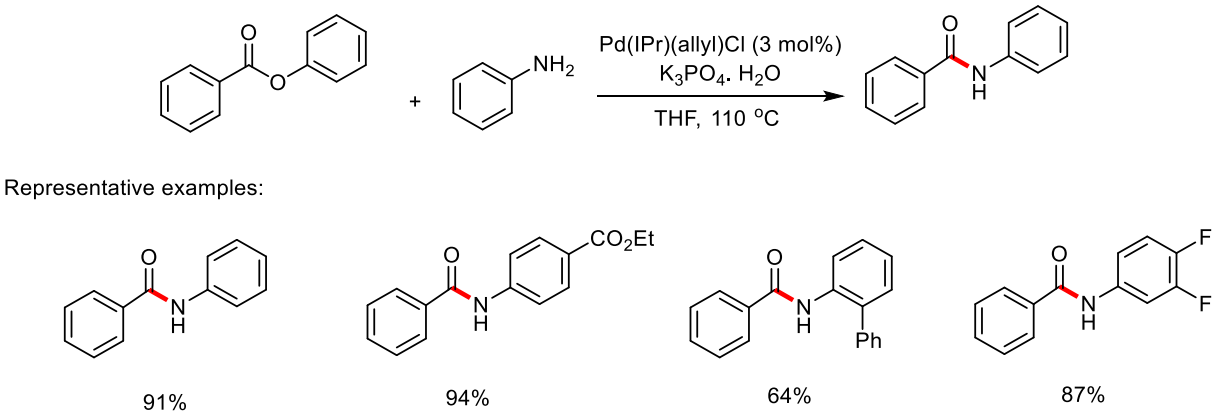
2. Amidation reaction

Direct amidation of esters is an attractive method of converting esters into amides in organic synthesis due to the presence of the amides in biomolecules, fine chemical, and drug candidates. Garg and Houk reported the first example of using nickel catalysts to activate the C–O bonds of methyl esters through an oxidative addition process (Scheme 1.41).[151] This reaction allowed for the use of methyl 1-naphthoate as an alternative to methyl benzoate due to the higher reactivity at the same time; they found that Al(Ot-Bu) had a significant effect in this transformation. DFT calculations showed that the kinetics barrier decreased considerably between the oxidative addition and ligand exchanges process (OMe to NR^1 R^2), which was concluded by the aluminum tert-butoxide Al $(Ot\text{-}Bu)_3$ stoichiometric coordination. Furthermore, the bulkiness of Lewis acid significantly enhances the reactivity of methyl 1-naphthoate.



Scheme 1.41. Ni-catalyzed of amide from methyl ester via a non-decarbonylative coupling.

Intending to further expand the manifold of more direct, efficient amidation reactions, Newman and his coworkers reported non-decarbonylative transformations of aromatic esters in the presence of a Pd (IPr)(allyl)Cl precatalyst. Phenyl esters were converted to corresponding amides in good to excellent yields (Scheme 1.42).[152] This study provides a new approach to the synthesis of valuable amide bonds from relatively non-nucleophilic nitrogen species that do not react in the absence of a catalyst.



Scheme 1.42. Pd-catalyzed of amide from phenyl ester via a non-decarbonylative coupling.

1.5. Conclusion

The Pd-catalyzed cross-coupling reaction of aromatic esters has been attracted considerable attention in organic chemistry for the formation of C–C and C–X (–O, –N, –S, and –P) bonds. Aromatic esters have been recognized as alternative electrophilic partners due to their ready availability, stability, and low activity compared to aryl halides in cross-coupling reactions. Several pathways of cross-coupling have been developed to form new chemical bonds and to avoid pre-functionalization, hard reaction conditions, and waste production. These pathways include decarboxylation, decarbonylative, and non-decarbonylative coupling reactions. The non-decarbonylative coupling reaction of aromatic esters with organoboron compounds has played a vital role in evolving new methodologies and synthetics in organometallic chemistry. The cross-coupling reaction of aromatic esters has stood out as an important reaction for the synthesis of biaryl compounds and diaryl ketones compound from aromatic esters in the presence of varieties of well-defined palladium (II)-NHC precatalysts.

1.6. References

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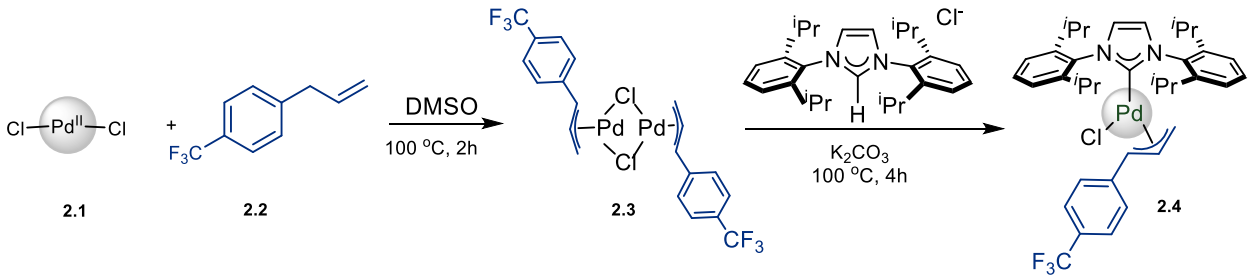
CHAPTER 2: PALLADIUM-CATALYZED SUZUKI-MIYAURA CROSS-COUPLING REACTION OF AROMATIC ESTER AND AROMATIC DIESTER

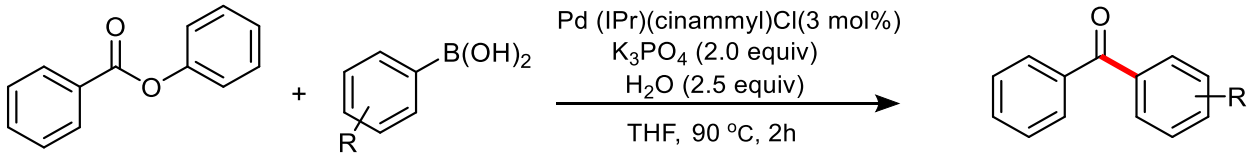
2.1. Introduction

Aromatic esters and diesters are used as an abundant, inexpensive chemical feedstock in organic synthesis and can be derived into various aromatic compounds. The continuously growing interest in aromatic esters and diesters is observed among researchers working in medicinal chemistry and chemistry of metal complexes. Their accessibility, stability, and unique properties make them promising substrates for numerous natural products, pharmaceuticals, photosensitizers, and advanced organic materials.[1-4] New routes for the synthesis and functionalization of aromatic esters under catalytic conditions continue to be developed. For example, well-defined $Pd^{(II)}$-NHC precatalysts for use in the Suzuki-Miyaura cross-coupling of unreactive aromatic esters with aryl boronic acid has received more attention in recent years. The functional group of C-O bond activation of aromatic esters and diesters remains an elusive goal in organic synthesis due to their robustness and high resonance stability toward metal catalysts.[5] In the study of synthesizing a new methodology of electron-deficient [Pd(IPr)($\boldsymbol{\pi}$-4-$CF_3C_6H_4$-C_3H_5)Cl] precatalysts (Scheme 2.1**)**.[6] demonstrated in our lab, palladium chloride ($PdCl_2$) (**2.1)** with olefin (**2.2)** were heated in DMSO to form the allylpalladium chloride dimer *in situ* **(2.3)**. Upon heating, with IPr-chloride and potassium carbonates, the electron-deficient [Pd(IPr)($\boldsymbol{\pi}$-4-$CF_3C_6H_4$-C_3H_5)Cl] precatalysts (**2.4)** was generated in 78% yield. This result demonstrated that the electron-deficient allyl ligands have the ability to affect on the rate reduction of unactive $Pd^{(II)}$ to active $Pd^{(0)}$ catalyst and to avoid the formation of inactive bimetallic $Pd^{(I)}$-$Pd^{(I)}$ dimer. The key success the of method laid on their simple and efficient synthesized of $Pd^{(II)}$-NHC precatalysts compared to other challenging synthetic methods that are utilized allyl palladium acetate to generate $Pd^{(II)}$ -NHC precatalysts.



Scheme 2.1. Synthesis of [Pd(IPr)(***π***-4-$CF_3C_6H_4$-C_3H_5)Cl] precatalysts.

In a pioneering example, in 2017, Newman demonstrated the first example of Suzuki cross-coupling of an aromatic ester with aryl boronic acid using Pd-NHC precatalysts to generate aryl ketone (Scheme 2.2).[7] In recent times, cross-coupling reactions have been extended to include a wide range of electrophile substrates. For example, esters,[49-52] twisted amides,[53-55] ethers,[56-58] carbonates,[59-61] carbamates,[61-63] aziridines,[64-66] and nitroarenes.[67-68]



Scheme 2.2. First example of using phenyl benzoate as an electrophile in Suzuki-Miyaura coupling reaction.

Despite the significant advancements made in Suzuki-Miyaura coupling, utilizing rousted, non-traditional electrophile as aromatic esters with aryl boronic acid has proven more challenging to obtain the coupled product. Therefore, the functionalization of complicated aromatic diester coupling partners with boronic acid has been regarded as a new electrophilic substrate (Figure 2.1).

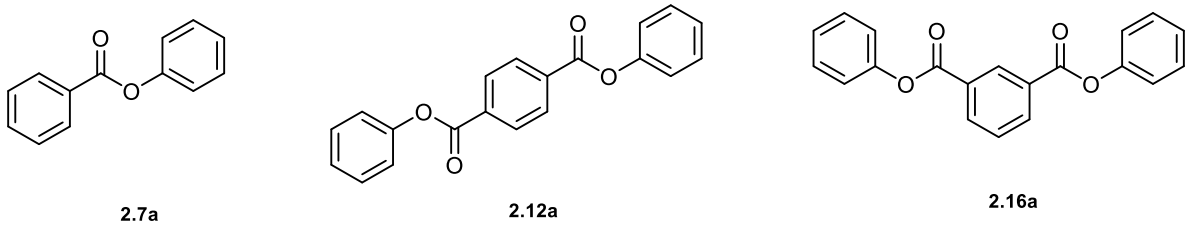
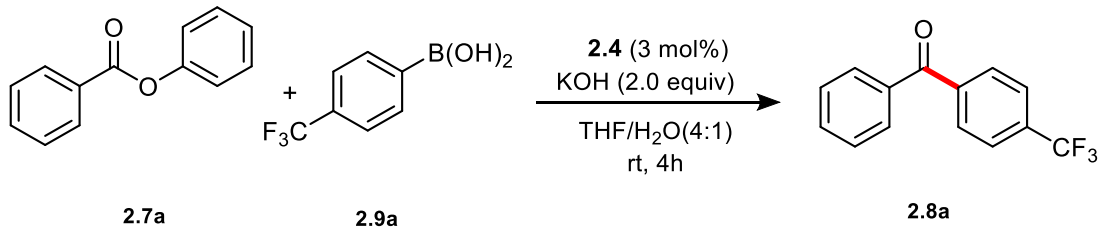


Figure 2.1. Selected substrates of aromatic ester **2.7a** /aromatic diesters **2.12a**/**2.16a** that are used as an electrophile substrate.

2.2. Non-decarbonylative Suzuki cross-coupling reaction of phenyl benzoate

Phenyl benzoates are of continued interest due to their presence in many natural products, pharmaceuticals, agrochemicals, and organic functional materials. Palladium-catalyzed Suzuki-Miyaura cross-coupling reaction has revolutionized the modification of aromatic esters, with the C-C bond-forming process. Various new synthetic methodologies have been extensively succeeded in producing aryl ketones in laboratory synthesis and industrial processes. Therefore, Sandeep has been developed a new protocol of Suzuki-Miyaura coupling of aromatic esters as an electrophile substrate with 4-trifluoromethylphenylboronic acid as nucleophile substrate in the presence of [Pd(IPr)(***π***-4-$CF_3C_6H_4$-C_3H_5)Cl] precatalysts (**2.4)** to generate 4-(trifluoromethyl) benzophenone **2.6a**. The [Pd(IPr)(***π***-4-$CF_3C_6H_4$-C_3H_5)Cl] precatalysts (**2.4)** reveals its high catalytic activity to active the C-O bond with stationary yields of the cross-coupling product under mild conditions (Scheme 2.3).[6]

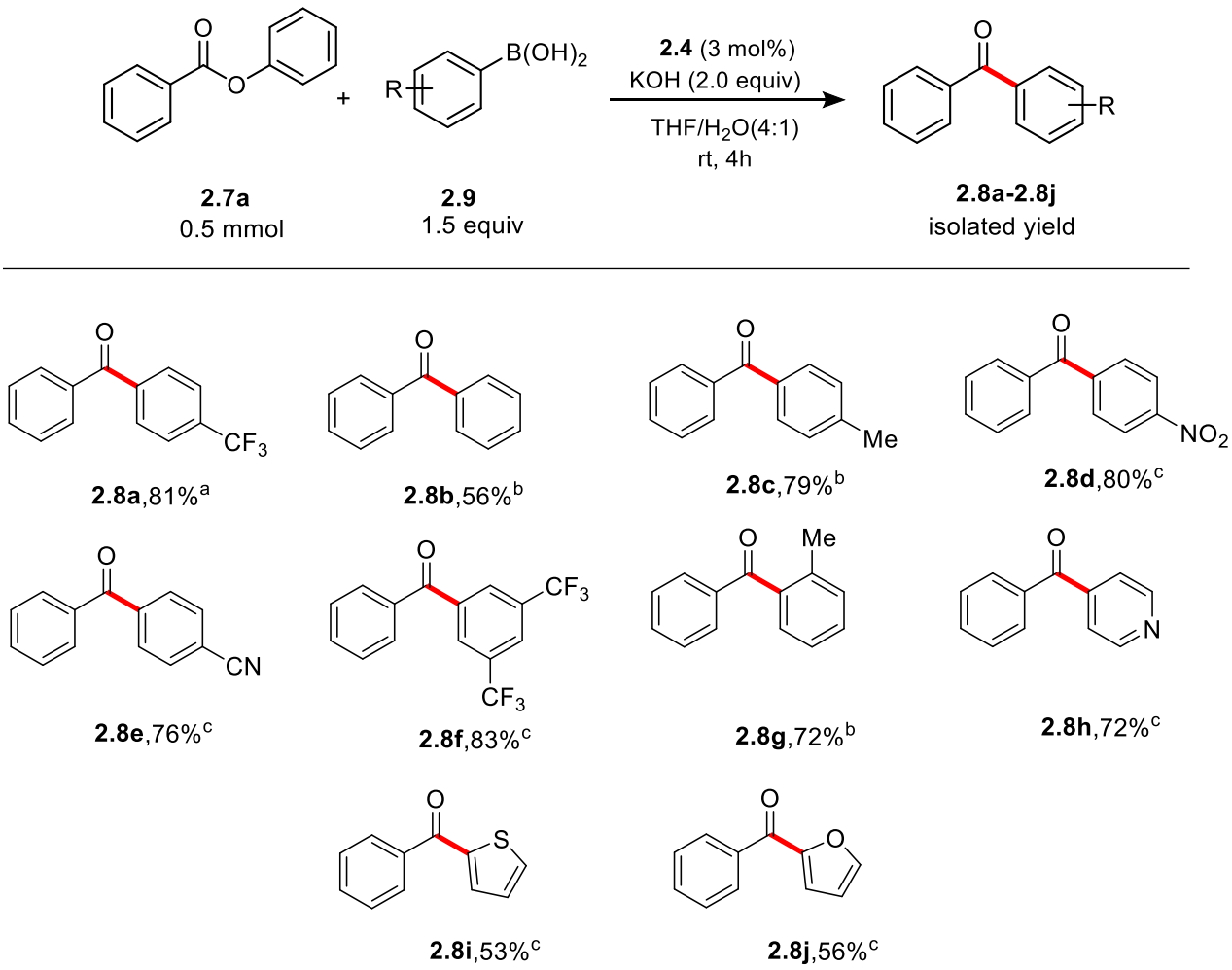


Scheme 2.3. Suzuki-Miyaura coupling reaction of aromatic ester with aryl boronic acid.

2.2.1. Results and discussion

The observation of the great potential catalytic activity of (**2.4)** in coupling phenyl benzoates (**2.7a)** with 4-trifluoromethylphenylboronic acid (**2.9a)** encouraged us to investigate the catalytic performance with series of electron-neutral (**2.9b)**, electron-donating (4-methyl, **2.9c**), electron-withdrawing (4-nitro, **2.9d**, 4-Cayno, **2.9e**, and 3,5-bis-(trifluoromethyl), **2.9f**), sterically hindered (2-methyl, **2.6g**), and heterocyclic (pyridyl, **2.9h**, thienyl **2.9i**, and furyl, **2.9j**) boronic acids to show their effects and the versatility of this protocol (Scheme 2.4). Although this reaction was required a shorter reaction time (4h), phenylboronic acid (**2.9b)** gave **2.8b**,56% coupled product. Phenyl benzoate (**2.7a**) with an electron-withdrawing group of boronic acids (**2.9d**, **2.9e**, and **2.9f**), providing high yields similar to the electron-donating group (**2.9c**). The reaction of phenyl benzoate worked smoothly with boronic acid having an electron-withdrawing group on the phenyl ring of the boronic acid to afford desired products (**2.8d**, **2.8e**, and **2.8f**) with yields ranging from 76% to 83% yields, while the aryl boronic species electron-donating group (**2.9c**) provided (**2.8c**) with 79% yield. Sterically hindered aryl boronic acids (**2.9g**) also underwent cross-coupling reactions successfully and gave the coupled product **(2.8g**) in 72% yield. Heterocyclic boronic acid groups, such as 4-pyridinylboronic acid (**2.9h**). 2-thienylboronic acid (**2.9i**) and 2-furanylboronic acid (**2.9j**) with phenyl benzoate (**2.7a**) were successfully transformed into the desired product in good yields of 60%, 53%, and 56%, respectively. These results indicated that this catalytic system was efficient for the Suzuki-Miyaura cross-coupling reactions of phenyl benzoate with boronic acid species despite the high stability and the orthogonal of the inert C-O bond. We were able to break the C-O and generate aryl ketone compounds from simple starting materials with high selectivity under mild conditions.

Scheme 2.4. Pd-catalyzed cross-coupling phenyl benzoate **2.7a** with aryl boronic acid derivatives **2.9**.

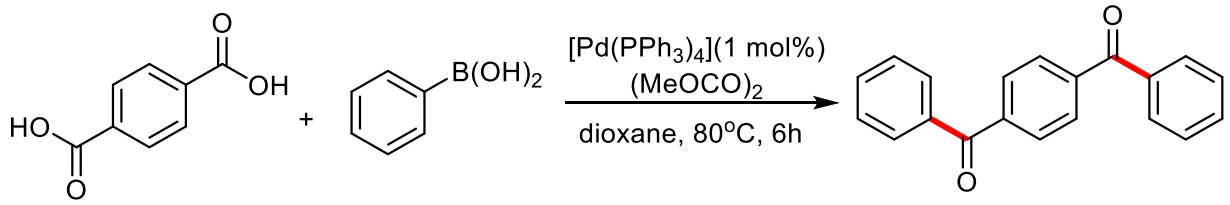


Reaction conditions: 2.7a (0.5 mmol) and **2.9** (0.5 mmol) in the presence of **2.4** (3 mol%) were subjected to under different times in THF/H_2O (2.5 mL) at 25 °C. All reactions were run three times. [a]See references 6. [b]See references 131. [c]See references 11.

2.3. Non-decarbonylative Suzuki-Miyaura cross-coupling reaction of terephthalic acids

Difunctionalized dicarboxylic acids under catalytic conditions have gained attention in the last few years as an alternative to aromatic esters as electrophilic substrate. Palladium-catalyzed Suzuki-Miyaura cross-coupling reaction of the organoboron nucleophile with carbon-heteroatom bonds is considered one of the most widely used coupling reactions due to its reliability,

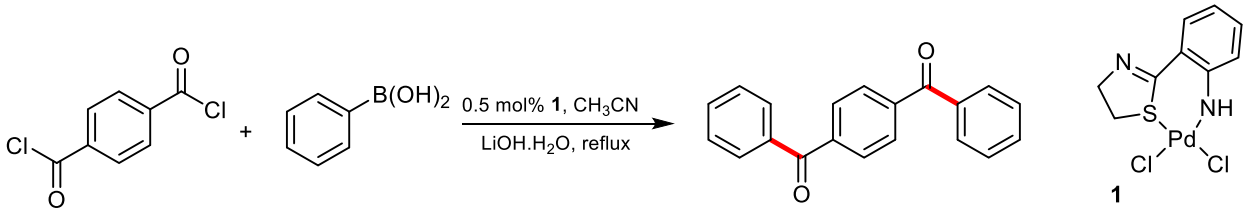
chemoselectivity, and diversity for carbon-carbon bond formation. In 2002, Yamamoto demonstrated that the terephthalic acid is catalytically converted into corresponding aryl diketones. This reaction has proved that the [$Pd(PPh_3)_4$] catalysts have the ability to cleavage the acyl C-O bond for the construction of the C-C bond (Scheme 2.5**)**.[8]



Scheme 2.5. Suzuki-coupling reaction of the carboxylic acid with aryl boronic acid.

2.4. Non-decarbonylative Suzuki-Miyaura cross-coupling reaction of terephthalic acid dichloride

The extension of using the complicated electrophilic substrates has become a highly desirable and ongoing goal in synthetic organic reactions. Although palladium-catalyzed Suzuki-Miyaura coupling of carboxylic acid derivatives with very weak C(acyl)–X bonds is known for many years, acyl dichloride has been shown as a promising substrate regardless of the development of carbon-carbon bonds. For example, acyl dichloride has been reported as an attractive electrophile and can be converted into a corresponding aryl diketone coupled product with good yield. In 2018, Suresh reported a pioneering study in the transition-metal-catalyzed cross- coupling reaction of terephthalic dichloride with phenylboronic acids in the presence of Pd as a catalyst (Scheme 2.6).[9]



Scheme 2.6. Suzuki-coupling reaction of terephthalic acid dichloride with aryl boronic acid.

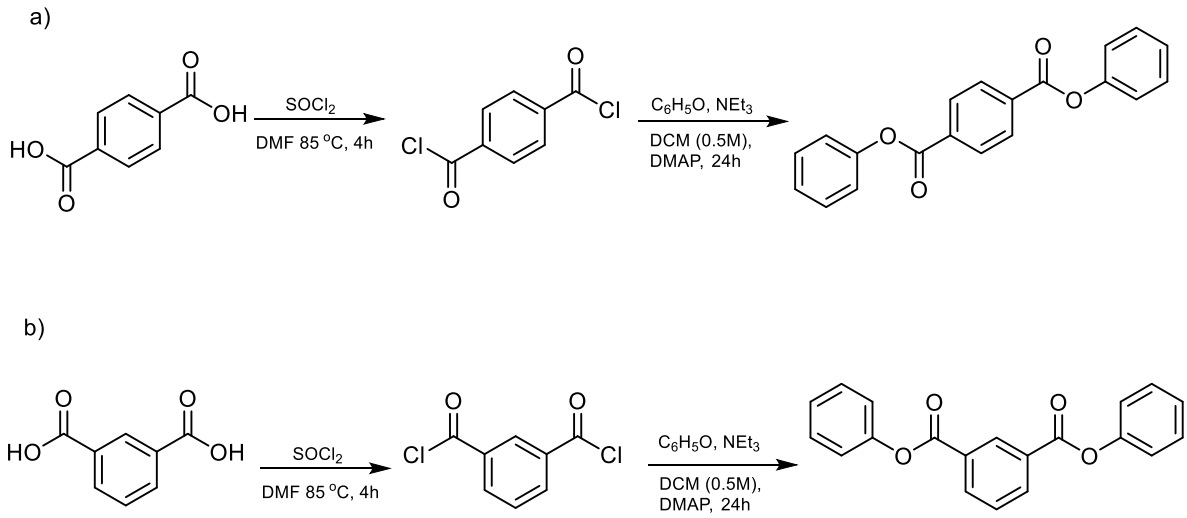
Palladium complex containing the thiazloine/imidazoline hemi-labile ligands $PdCl_2\{\kappa2-N, N'-(4,5\text{-dihydro-1H-imidazol-2-yl})\text{aniline}\}$ have emerged as effective catalysts for cross-coupling reactions of terephthalic dichloride with phenylboronic to produce 1,4-Dibenzoylbenzene coupled product. Although the high reactivity of acyl dichloride as a leaving group, the toxicity makes it less attractive substrates in cross-coupling reactions. Therefore, finding more ubiquitous, readily available, and inexpensive molecular scaffolds electrophilic substrates is needed for reducing the toxicity and produce coupled product with high selectivity and avoidance of the maximum amount of halogen waste as a by-product in the reaction mixture. The recent growth in the use of diesters in the Suzuki-Miyaura coupling reaction has been shown as one of the most productive methods in the coupling reaction field due to its high stability, easy to handle, and low toxicity (Figure 2.1).

2.5. Non-decarbonylative Suzuki-Miyaura cross-coupling reaction of 1,4-Diphenyl 1,4-benzene dicarboxylate and 1,3-Diphenyl 1,3-benzene dicarboxylate

2.5.1. Results and discussion

Once it was realized that the palladium-catalyzed cross-coupling of dicarboxylic acid derivatives with the organoboron compound was proved to be a useful electrophilic substrate, more attention was turned towards the investigation of a new route for the difunctionalization of aromatic diesters substrates **2.12a** and **2.16a** under new developing Pd-precatalysts to generate the desired ketone-containing products. First, 1,4-diphenyl 1,4-benzene dicarboxylate (**2.12a)** and 1,3-

diphenyl 1,3-benzene dicarboxylate (**2.16a)** were synthesized from terephthalic acid (**2.10)** and isophthalic acid (**2.14)**, respectively. The (**2.10)** and (**2.14)** were converted into (**2.11)** and (**2.15)** by reacted with $SOCl_2$ in DMF. Then, terephthalic acid dichloride (**2.11)** and isophthalic acid dichloride (**2.15)** with phenol were reacted to afforded desired 1,4-Diphenyl 1,4-benzene dicarboxylate (**2.12a)** and 1,3-diphenyl 1,3-benzene dicarboxylate (**2.16a)** in high yields (Scheme 2.7).



Scheme 2.7. Synthesis of a) 1,4-diphenyl 1,4-benzenedicarboxylate **2.12a** and b) 1,3-diphenyl 1,3-benzenedicarboxylate **2.16a**.

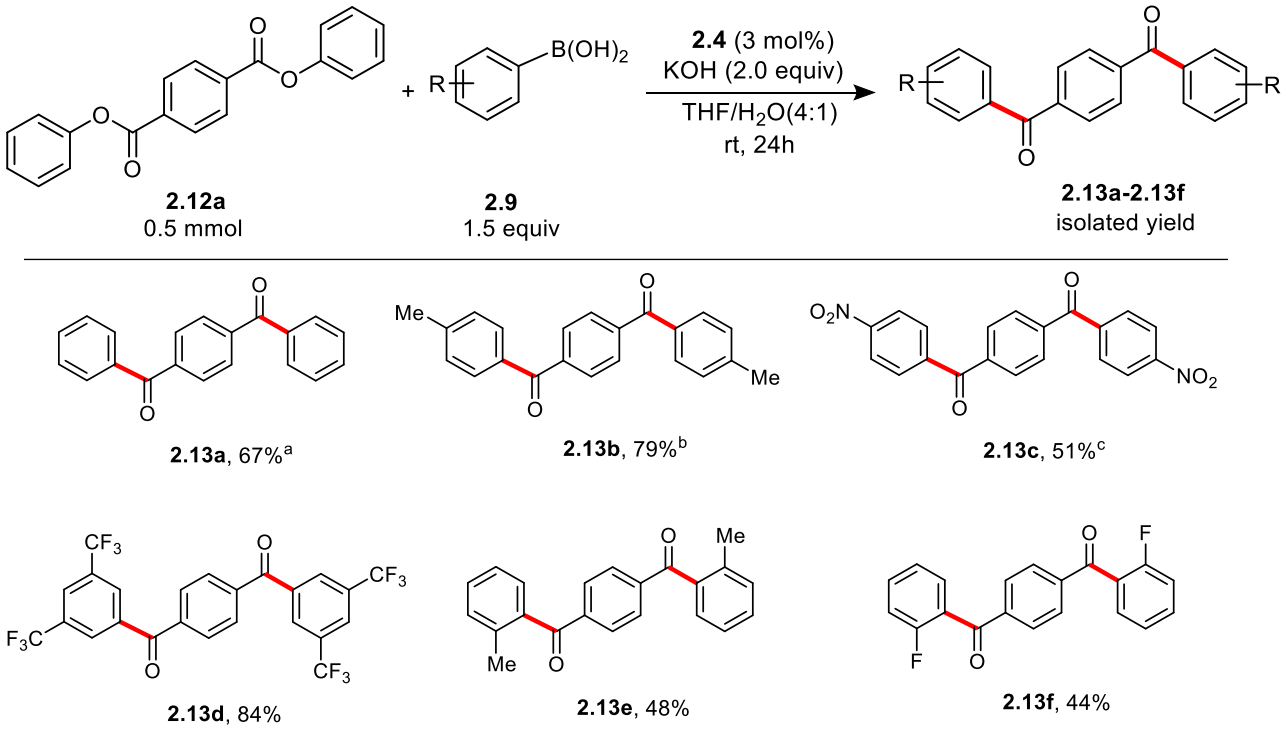
Our starting point was examining the catalytic activity of [Pd(IPr)(***π***-4-$CF_3C_6H_4$-C_3H_5)Cl] (**2.4)** on Suzuki-Miyaura coupling reaction to cleavage the unactivated C-O bond utilize established protocol reported by Sandeep for the reaction of phenyl benzoate (**2.7a)** with 4-(trifluoromethyl) phenylboronic acid (**2.9a)** (Scheme 2.3). In this standard reaction, 1,4-diphenyl 1,4-benzene dicarboxylate was used as electrophile substrate (**2.12a),** and phenylboronic acid as a nucleophile substrate (**2.9b)** with 3 mol% of Pd precatalysts (**2.4)** ligated with NHC ligand under strong KOH base in THF/H_2O as a co-solvent at room temperature. Under these conditions, 1,4-

diphenyl 1,4-benzene dicarboxylate (**2.12a)** did not produce any coupled product. This result implied that defunctionalizing 1,4-diphenyl 1,4-benzene dicarboxylate (**2.12a)** under same conditions that we had found to be optimal for coupling phenyl benzoate (**2.7a**) with aryl boronic acid derivatives were unsuccessful; therefore, that was leading us to modifying the conditions of the reaction in order to optimize conversion. A suitable condition was successfully achieved for coupling 1,4-diphenyl 1,4-benzene dicarboxylate **(2.12a)** with phenylboronic acid **(2.9b)** to produce the difunctionalized 1,4-dibenzoylbenzene after (24 h) **(2.17a)** with 61% yield.

Despite the high stability and the difficulty to activate of C-O bond, we observed that the utilization of aromatic diesters **(2.12a)** and **(2.16a)** with **(2.4)** enable the formation of C-C cross-coupling product under exceedingly mild conditions. We found that extending the time, which plays a crucial role in this reaction, led to active the inert C-O bond in the oxidation addition step and produce complex. The KOH has a great assist in increasing the nucleophilicity of the phenylboronic acid **(2.9b)** in the reaction. In addition, using THF/H_2O as a co-solvent was proved to have a beneficial effect on the solubility of the base and phenylboronic acid **(2.9b)** and increase the rate activation of Pd precatalysts. Under these conditions, aryl diketones derived from electron-natural (**2.9b)**, electron-donating (4-methyl, **2.9c**), electron-withdrawing (4-nitro,**2.9d**, and 3,5-Bis-(trifluoromethyl) phenylboronic acid, **(2.9f)**, and sterically hindered (2-methyl, **2.9g,** and 2-fluoro, **2.9k**) boronic acids could also be prepared. Beyond the synthesis of the parent 1,4-dibenzoylbenzene **(2.13a)** in (67%) yield, varieties of coupled products arising from the coupling of the electron-donating boronic acid were prepared **(2.13b)** in 79% yield, whereas electron-withdrawing **(2.9d, and 2.9f)** boronic acids provided (**2.13c**, and **2.13d)** in 51%, and 84% respectively. Coupled products derived from sterically hindered **(2.9g**, and **2.9k)** boronic acids were provided lower yields (**2.13e**, and **2.13f),** (48%, and 44%), though still >30% (Scheme 2.8).

Surprisingly, no evidence of mono-coupled products or homocoupling products were observed in the reaction. We believe that the presence of either electron-withdrawing, electron-donating, or sterically hindered groups on the boronic acids can affect on its reactivity and in the transmetalation step in this coupling reaction.

Scheme 2.8. Pd-catalyzed cross-coupling of 1,4-diphenyl 1,4-benzene dicarboxylate **2.12a** with aryl boronic acid derivatives **2.9**.

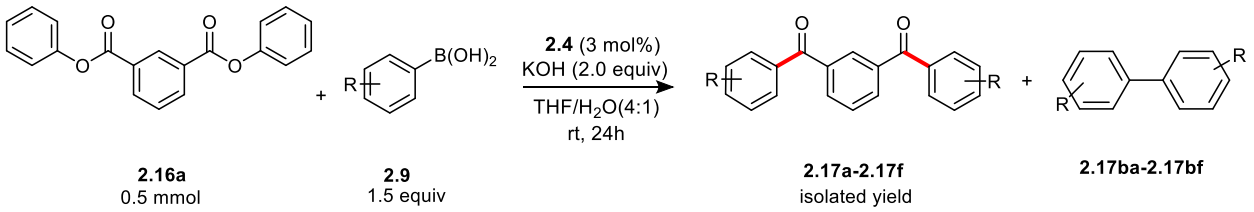


Reaction conditions: 2.12a (0.5 mmol) and **2.9** (0.5 mmol) in the presence of **2.4** (3 mol%) were subjected to under different times in THF/H_2O (2.5 mL) at 25 °C. All reactions were run three times. [a]See references 8. [b]See references 13. [c]See references 14.

Having found that the 1,4-diphenyl 1,4-benzene dicarboxylate **(2.12a)** was catalytically converted into aryl diketones on treatment with aryl boronic acid in the presence of Pd- catalyzed, we further expand the scope of the carbon-carbon bond coupling methodology by introducing another alternative electrophile substrate **(2.16a)** to establish their reactivity and feasibility as promising coupling partner in Suzuki-Miyaura cross-coupling reactions under same previous

conditions. As shown in (Scheme 2.9), The cross-coupling reaction of 1,3-diphenyl 1,3-benzene dicarboxylate (**2.16a)** with aryl boronic acids having electron-natural **(2.9b)**, electron-donating (4-methyl, **2.9c**), electron-withdrawing (4-nitro,**2.9d**, and 3,5-bis-(trifluoromethyl) phenylboronic acid, **2.9f**), and sterically hindered (2-methyl, **2.9g,** and 2-fluoro, **2.9k**) substituents worked well and delivered expected coupled products aryl diketones with symmetrical biaryls as a side product in synthetically useful yields. The reaction of 1,3-diphenyl 1,3-benzene dicarboxylate **(2.16a)** with phenylboronic acid **(2.9b)** proceed smoothly to afford **(2.17a)** in 68%, along with homocoupling product **(2.17ab),** < 5% observed via NMR (Table 2.2, entry 4). It is worth noting that the electron-donating **(2.9c)** also reacted smoothly to give the coupled product **(2.17b)**, in 78% yield, while the electron-withdrawing on the phenyl ring gave the target products with low to good yields arising from the NO_2, and CF_3-containing boronic acids (**2.17c**, 36%, and **2.17d**, 85%).Both electron-withdrawing and electron-donating efficiently underwent this transformation. In addition, sterically hindered boronic acid **(2.9g**, and **2.9**k) provided the product in (**2.17e**, 38%, and **2.17f**, 54%) yield. There is a significant difference in both reaction rates when using electron-donating groups compared to electron-withdrawing groups. Moreover, the rate-determining step may be affected by the steric hindrance groups.

Scheme 2.9. Pd-catalyzed cross-coupling of 1,3-diphenyl 1,3-benzene dicarboxylate **2.16a** with aryl boronic acid derivatives **2.9**.

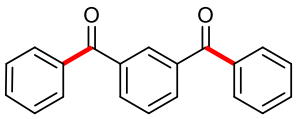


2.16a
0.5 mmol

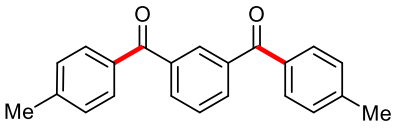
2.9
1.5 equiv

2.17a-2.17f
isolated yield

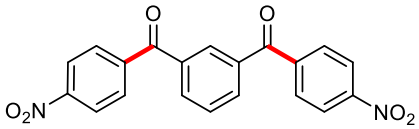
2.17ba-2.17bf



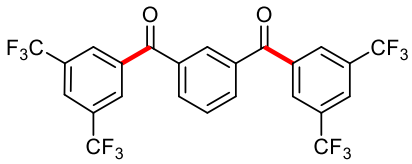
2.17a:2.17ba
68%[a]:1%



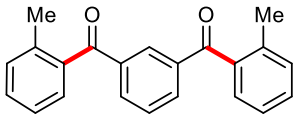
2.17b:2.17bb
78%[b]:0.8%



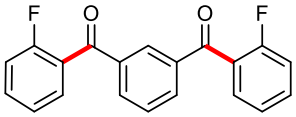
2.17c:2.17bc
36%[b]:2%



2.17d:2.17bd
85%:0.5%



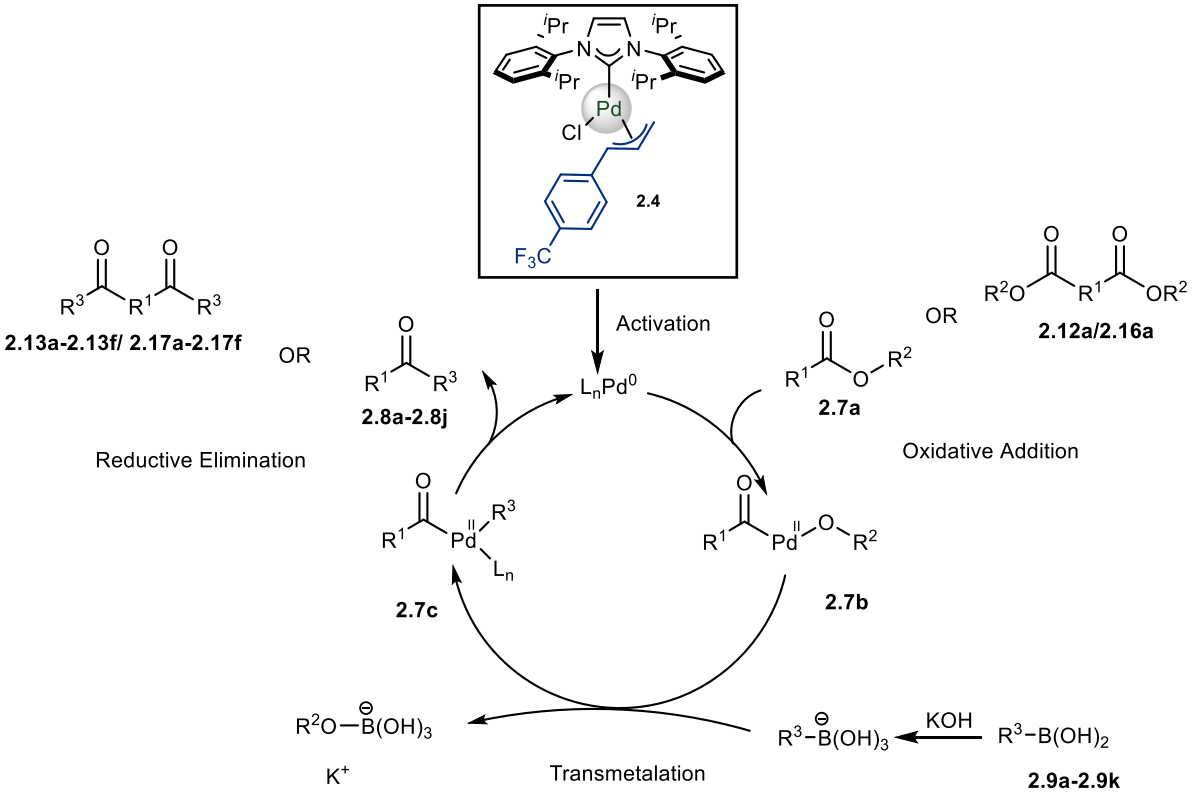
2.17e:2.17be
38%:2%



2.17f:2.17bf
54%:1%

Reaction conditions: 2.16a (0.5 mmol) and **2.9** (0.5 mmol) in the presence of **2.4** (3 mol%) were subjected to under different times in THF/H_2O (2.5 mL) at 25 °C. All reactions were run single. [a]See references 1. [b]See references 16.

2.6. Proposed mechanism of non-decarbonylative Suzuki- Miyaura cross-coupling reaction



Scheme 2.10. Mechanism of Pd-catalyzed cross-coupling Suzuki-Miyaura cross-coupling reaction between phenyl benzoate **2.7a**/ 1,4-diphenyl 1,4-benzene dicarboxylate **2.12a**/ 1,3-diphenyl 1,3-benzene dicarboxylate **2.16a** with aryl boronic acids **2.9**.

The mechanism of Pd-catalyzed cross-coupling of aromatic ester **2.7a** and aromatic diesters **2.12a/2.16a** with aryl boronic acids **2.9a-2.9k** was proposed via three fundamental steps: oxidative addition, transmetalation, and reductive elimination. First, the catalytic cycle starts with oxidative addition of the **2.7a,** and **2.12a/2.16a** to Pd0 center to generate **2.7b,** and **2.12b/2.16b** complex**,** then the following of Oxidative addition results **2.7b,** and **2.12b/2.16b,** which reacts with aryl boronic acids **2.9a-2.9k** in the transmetalation step to afford **2.7c,** and **2.12c/1.16c** complex. Finally, in the reductive elimination, the coupled product **2.8a-2.8j** and **2.13a-2.13f/2.17a-2.17** formed and regenerated the Pd^0 active catalyst (Scheme 2.10).

2.7. Conclusion

Our observation applies new precatalysts in Suzuki-Miyaura cross-coupling reaction of the bench- stable, aromatic esters moieties (phenyl benzoate, 1,4-diphenyl 1,4-benzene dicarboxylate, and 1,3-diphenyl 1,3-benzene dicarboxylate), were reacted with aryl boronic acids containing electron-natural, electron-withdrawing, electron-donating, sterically hindered, and heterocyclic group for generating C-C bond under mild conditions. Although the rate-determining step of the reaction may change depending on the choice of aromatic ester/ diester substrates with boronic acid substrates, the [Pd(IPr)($\boldsymbol{\pi}$-4-$CF_3C_6H_4$-C_3H_5)Cl] precatalysts were found able to active the C-O bond selectivity in the oxidation addition step. The successful coupling of aromatic ester and aromatic diester with aryl boronic acids constitutes a new development for this transformation. Further investigation can be exploited in the synthesis valuable moieties derived from heteroatomic or aliphatic diesters/diamides under catalytic conditions for drug discovery and for materials chemistry applications. One-pot methodologies could also be investigated.

2.8. Experimental procedures

2.8.1. General experimental details

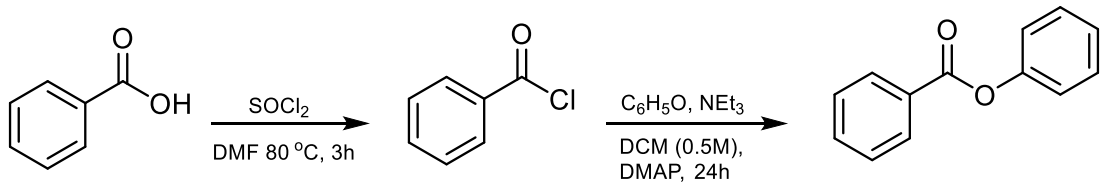
All reactions were carried out under N_2 atmosphere using glovebox techniques. All glassware was oven-dried for at least 1h. Solvents were degassed by purging with nitrogen for 45 min and dried prior to use. Most of the commercially obtained organic compounds were purchased from Alfa Aesar®, Sigma-Aldrich®, Acros®, TCI America®, Mallinckrodt®, and Oakwood® Products chemical companies, and used as received without further purification.

2.8.2. Chromatography and instrumentation

Thin-layer chromatography (TLC) was performed on the silica gel from Sorbtech glass plates, and the component was visualized by exposure to (UV) ultraviolet light. Flash column chromatography was performed with 32–63 microns silica gel. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer, and chemical shifts were recorded relative to the residual protiated solvent. ^{13}C NMR spectra were recorded at 101 MHz, and chemical shifts were recorded to the solvent resonance. Both ^{1}H and ^{13}C NMR chemical shifts were reported in relative to TMS, and coupling constants in Hz. ^{19} F NMR spectra were obtained at 376 MHz, and all chemical shifts were reported in parts per million up field of CF_3COOH (δ = -78.5 ppm). Coupling constants (J) are reported in hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: s (singlet), br (broad), d (doublet), t (triplet), q (quartet), and m (multiplet). Data for ^{13}C NMR spectra are reported in terms of chemical shifts (δ ppm). ^{1}H NMR and ^{13}C NMR data are given for all new compounds. All products have been previously reported, unless stated otherwise.

2.8.3. General procedure for aromatic ester and aromatic diester synthesis

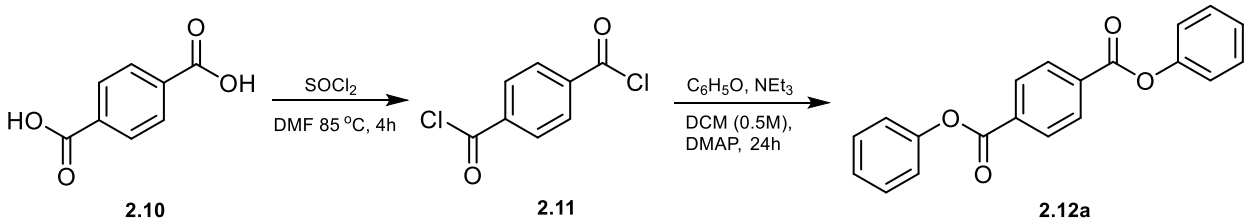
1. **Synthesis of phenyl benzoate 2.7a**[10]



2.5 **2.6** **2.7a**

To a round bottom flask, carboxylic acid **2.5** (17.84 mmol, 1 equiv.) was added to (2.5 mL) of thionyl chloride $SOCl_2$ and two drops of DMF. The reaction mixture was stirred under N_2 atmosphere at 80 °C for 3 h. Then, it was concentrated under reduced pressure to remove the excess of $SOCl_2$. Phenol (4.02 g, 2.4 equiv), triethylamine (10 mL, 4 equiv) and N,N-dimethyl-4-aminopyridine (0.01 g, 1 mol%) in DCM (0.5 M), were added slowly to benzoyl chloride **2.6**.The reaction mixture was warmed to room temperature and stirred overnight. Completion of the reaction was monitored by TLC. The reaction was quenched with saturated $NaHCO_3$(aq). The mixture was washed three times with H_2O, then brine. The combined organic layers were dried over Na_2SO_4, filtered, evaporated, and concentrated under reduced pressure to give a crude product. Purification was done by flash chromatography (90:10-hexanes/ethyl acetate) to afford the desired **2.7a** as a white solid (90% yield).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.25 – 8.18 (m, 2H), 7.64 (ddd, J = 8.8, 4.7, 2.0 Hz, 1H), 7.56 – 7.48 (m, 2H), 7.47 – 7.40 (m, 2H), 7.29 (dt, J = 7.9, 1.4 Hz, 1H), 7.22 (ddd, J = 2.9, 2.2, 1.1 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.2, 150.9, 133.5, 130.2, 129.6, 129.5, 128.5, 125.9, 121.7.

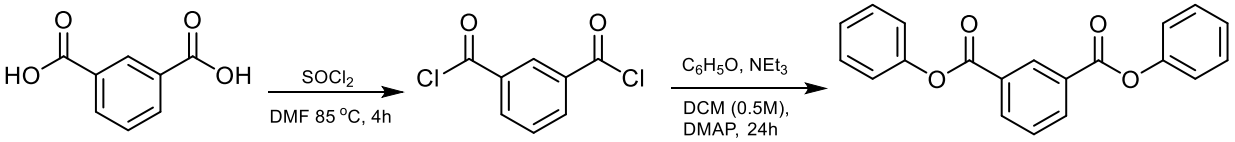
2. Synthesis of 1,4-diphenyl 1,4-benzenedicarboxylate 2.12a[10]



2.10 **2.11** **2.12a**

To a round bottom flask, terephthalic acid **2.10** (17.84 mmol, 1 equiv.) was added to (2.5 mL) of thionyl chloride $SOCl_2$ and two drops of DMF. The reaction mixture was stirred under N_2 atmosphere at 85 ^oC for 4 h. Then, it was concentrated under reduced pressure to remove the excess of $SOCl_2$. Phenol (4.02 g, 2.4 equiv), triethylamine (10 mL, 4 equiv), and N,N-dimethyl-4-aminopyridine (0.01 g, 1 mol%) in DCM (0.5 M), were added slowly to terephthalic acid dichloride **2.11.** The reaction mixture was warmed to room temperature and stirred overnight. Completion of the reaction was monitored by TLC. The reaction was quenched with saturated $NaHCO_3$(aq). The mixture was washed three times with H_2O, then brine. The combined organic layers were dried over Na_2SO_4, filtered, evaporated, and concentrated under reduced pressure to give a crude product. Purification was done by flash chromatography (85:15-hexanes/ethyl acetate) to afford the desired **2.12a** as a white solid (92% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.34 (s, 4H), 7.51 – 7.41 (m, 4H), 7.33 – 7.28 (m, 2H), 7.28 – 7.26 (m, 2H), 7.25 (dd, J = 2.8 Hz, 2H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.3, 150.7, 133.9, 130.3, 129.6, 126.2, 121.5.

3. Synthesis of 1,3-diphenyl 1,3-benzenedicarboxylate 2.16a[12]

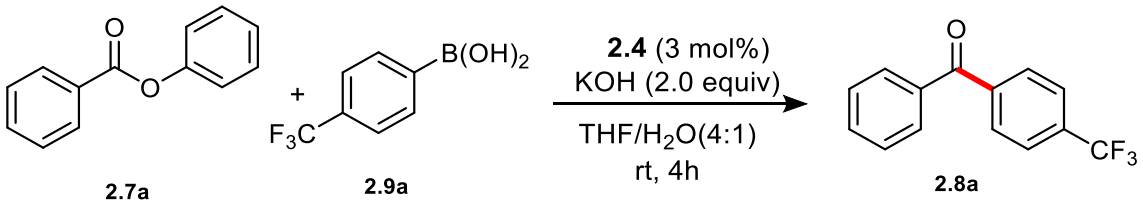


2.14 **2.15** **2.16a**

To a round bottom flask, isophthalic acid **2.14** (17.84 mmol, 1 equiv.) was added to (2.5 mL) of thionyl chloride $SOCl_2$ and two drops of DMF. The reaction mixture was stirred under N_2 atmosphere at 85 °C for 4 h. Then, it was concentrated under reduced pressure to remove the excess of $SOCl_2$. Phenol (4.02 g, 2.4 equi.), triethylamine (10 mL, 4 equiv) and N,N-dimethyl-4-aminopyridine (0.01 g, 1 mol%) in DCM (0.5 M), were added slowly to isophthalic acid dichloride **2.15**. The reaction mixture was warmed to room temperature and stirred overnight. Completion of the reaction was monitored by TLC. The reaction was quenched with saturated $NaHCO_3$(aq). The mixture was washed three times with H_2O, then brine. The combined organic layers were dried over Na_2SO_4, filtered, evaporated, and concentrated under reduced pressure to give a crude product. Purification was done by flash chromatography (85:15-hexane/ethyl acetate) to afford the desired **2.16a** as a white solid **(**89% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.03 (q, J = 1.3 Hz, 1H), 8.47 (dd, J = 7.8, 1.8 Hz, 2H), 7.69 (td, J = 7.9, 0.4 Hz, 1H), 7.49 – 7.42 (m, 5H), 7.33 – 7.28 (m, 3H), 7.25 – 7.22 (m, 2H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.2, 150.7, 134.9, 131.7, 130.3, 129.6, 129.1, 126.1, 121.6.

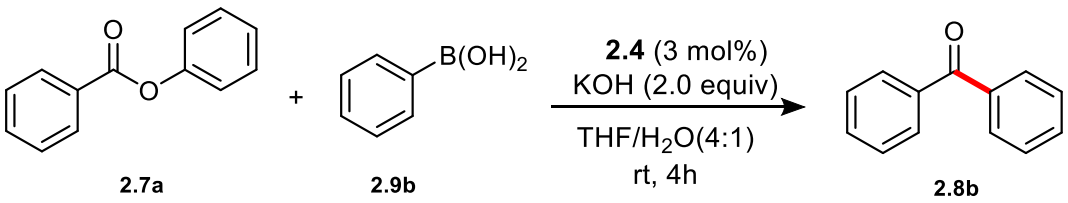
2.8.4. Experimental procedure for the synthesis of aryl ketones 2.8a-2.8j

Experimental procedure for the synthesis (4-(Trifluoromethyl)benzophenone) 2.8a [6]



In a glove box, a 1-dram vial was charged with phenyl benzoate **2.7a** (99.11 mg, 0.5 mmol), potassium hydroxide (56.1 mg, 2.0 equiv),4-trifluormethylphenylboronic acid **2.9a** (142.44 mg, 1.5 equiv), Pd-complex **2.4** (10.8 mg, 3 mol%), in 4:1 mixture of THF/H_2O (2.5 mL) and then stirred at rt for 4 h. The reaction mixture was diluted with DCM then filtered. The residue was purified on a SiO_2 column to afford the desired **2.8a** as a white solid (101.7 mg, 81% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.1 Hz, 2H), 7.81 (d, J = 7.4 Hz, 2H), 7.76 (d, J = 7.6 Hz, 2H), 7.63 (t, J = 7.3 Hz, 1H), 7.51 (t, J = 7.2 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ195.5, 140.7, 136.7, 133.6 (J = 32.54 Hz), 133.0, 130.1 (J = 4.2 Hz), 128.5, 125.3 (J = 3.7 Hz), 124.7 (J = 258.1 Hz). **^{19}F NMR** (376 MHz, $CDCl_3$) δ -63.02 (s).

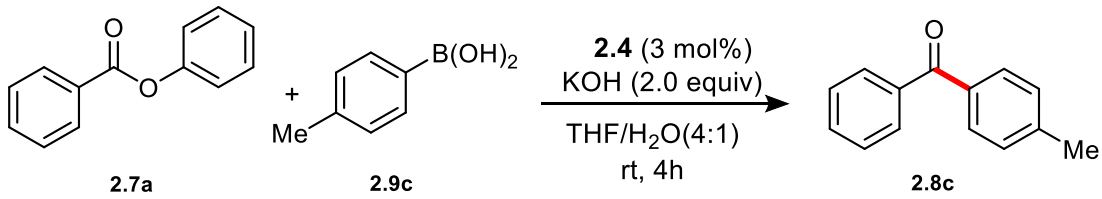
Experimental procedure for the synthesis (Benzophenone) 2.8b [131]



In a glove box, a 1-dram vial was charged with phenyl benzoate **2.7a** (99.11 mg, 0.5 mmol), potassium hydroxide (56.1 mg, 2.0 equiv), phenylboronic acid **2.9b** (91.44 mg, 1.5 equiv), Pd-complex **2.4** (10.8 mg, 3 mol%), in 4:1 mixture of THF/H_2O (2.5 mL) and then stirred at rt for 4 h. The reaction mixture was diluted with DCM then filtered. The residue was purified on a SiO_2 column to afford the desired **2.8b** as a white solid (51.2 mg, 56% yield). **^{1}H NMR** (400 MHz,

$CDCl_3$) δ 7.84 (d, J = 8.2 Hz, 4 H), 7.63 (t, J = 6.4 Hz, 2 H), 7.53 (t, J = 7.6 Hz, 4 H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 196.7, 137.6, 132.4, 130.0, 128.2.

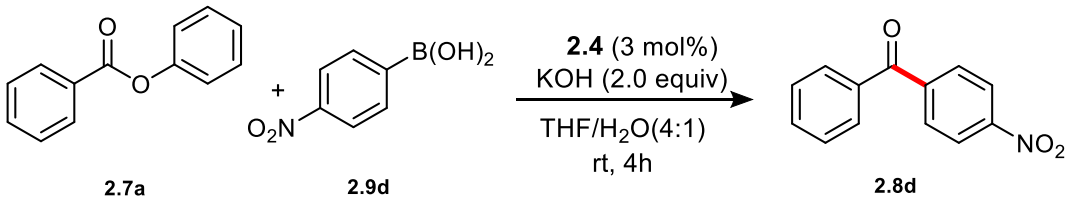
Experimental procedure for the synthesis (4-Methylbenzophenone) 2.8c [131]



2.7a **2.9c** **2.8c**

In a glove box, a 1-dram vial was charged with phenyl benzoate **2.7a** (99.11 mg, 0.5 mmol), potassium hydroxide (56.1 mg, 2.0 equiv), 4-Methylboronic acid **2.9c** (101.97 mg, 1.5 equiv), Pd-complex **2.4** (10.8 mg, 3 mol%), in 4:1 mixture of THF/H_2O (2.5 mL) and then stirred at rt for 4 h. The reaction mixture was diluted with DCM then filtered. The residue was purified on a SiO_2 column to afford the desired **2.8c** as a white solid (71.21 mg, 79% yield).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.0 Hz, 2H), 7.76 (d, J = 8.0 Hz, 2H), 7.62 (t, J = 7.5 Hz, 1H), 7.51 (t, J = 7.6 Hz, 2H), 7.32 (d, J = 7.9 Hz, 2H), 2.47 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ195.5, 143.2, 137.9, 134.9, 132.1, 130.3, 129.9, 128.9, 128.2, 21.6.

Experimental procedure for the synthesis (4-Nitrobenzophenone) 2.8d [11]

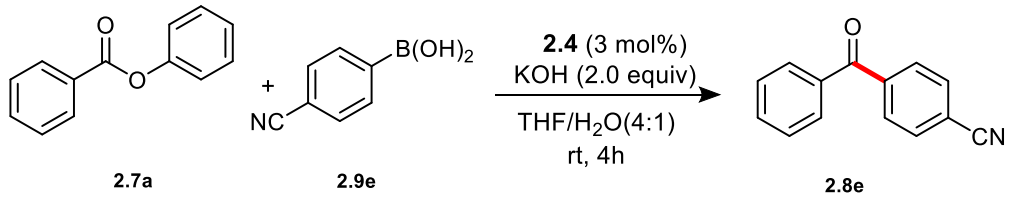


2.7a **2.9d** **2.8d**

In a glove box, a 1-dram vial was charged with phenyl benzoate **2.7a** (99.11 mg, 0.5 mmol), potassium hydroxide (56.1 mg, 2.0 equiv), 4-Nitroboronic acid **2.9d** (125.19 mg, 1.5 equiv), Pd-complex **2.4** (10.8 mg, 3 mol%), in 4:1 mixture of THF/H_2O (2.5 mL) and then stirred at rt for 4 h. The reaction mixture was diluted with DCM then filtered. The residue was purified on a SiO_2 column to afford the desired **2.8d** as a pale yellow solid (91.1 mg, 80% yield). **^{1}H NMR**

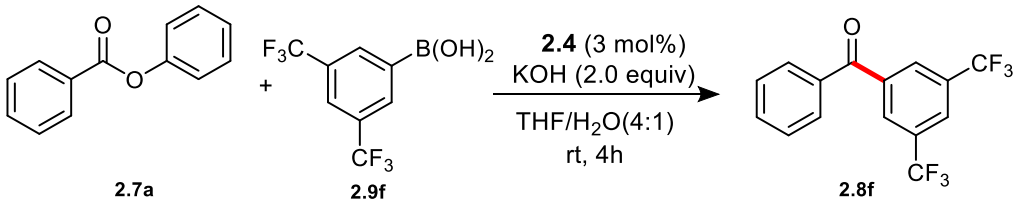
(400 MHz, $CDCl_3$) δ 8.27 – 8.22 (m, 2H), 7.71 – 7.62 (m, 1H), 7.58 – 7.50 (m, 2H), 7.49 – 7.42 (m, 2H), 7.32 – 7.28 (m, 1H), 7.25 – 7.23 (m, 1H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.8, 151.0, 143.0, 133.6, 130.2, 129.6, 129.5, 128.6, 121.7.

Experimental procedure for the synthesis (4-Cyanobenzophenone) 2.8e [11]



In a glove box, a 1-dram vial was charged with phenyl benzoate **2.7a** (99.11 mg, 0.5 mmol), potassium hydroxide (56.1 mg, 2.0 equiv), 4-Cyanoboronic acid **2.9e** (110.20 mg, 1.5 equiv), Pd-complex **2.4** (10.8 mg, 3 mol%), in 4:1 mixture of THF/H_2O (2.5 mL) and then stirred at rt for 4 h. The reaction mixture was diluted with DCM then filtered. The residue was purified on a SiO_2 column to afford the desired **2.8e a**s a pale yellow solid (79.3 mg, 76% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (d, J = 7.8 Hz, 2H), 7.82−7.74 (m, 4H), 7.64 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.5 Hz, 2H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 195.0, 141.2, 136.4, 133.3, 132.3, 130.1, 130.2, 128.2, 118.2, 115.6.

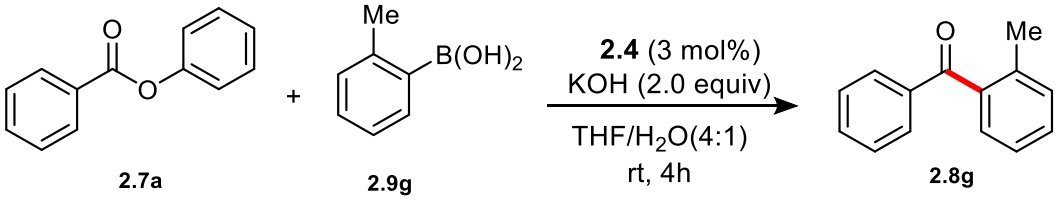
Experimental procedure for the synthesis (3,5-Bis(trifluoromethyl)benzophenone) 2.8f [11]



In a glove box, a 1-dram vial was charged with phenyl benzoate **2.7a** (99.11 mg, 0.5 mmol), potassium hydroxide (56.1 mg, 2.0 equiv), 3,5-Bis(trifluoromethyl) phenylboronic acid **2.9f** (193.44 mg, 1.5 equiv), Pd-complex **2.4** (10.8 mg, 3 mol%), in 4:1 mixture of THF/H_2O (2.5 mL) and then stirred at rt for 4 h. The reaction mixture was diluted with DCM then filtered. The

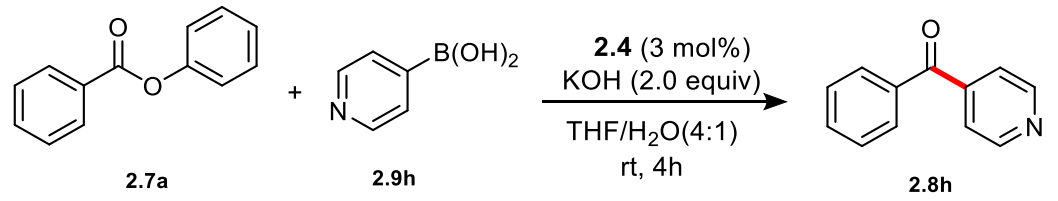
residue was purified on a SiO_2 column to afford the desired **2.8f** as a white solid (101.7 mg, 83% yield).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.30 – 8.10 (m, 2H), 7.64 (t, J = 7.4 Hz, 1H), 7.52 (t, J = 7.8 Hz, 2H), 7.48–7.40 (m, 2H), 7.31– 7.27 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 193.7, 139.5, 135.9, 133.5, 130.3, 130.1, 129.5, 128.5, 125.9, 121.7. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.43 (s).

Experimental procedure for the synthesis (2-Methylbenzophenone) 2.8g [131]



In a glove box, a 1-dram vial was charged with phenyl benzoate **2.7a** (99.11 mg, 0.5 mmol), potassium hydroxide (56.1 mg, 2.0 equiv), 2-Methylphenylboronic acid **2.9g** (101.97 mg, 1.5 equiv), Pd-complex **2.4** (10.8 mg, 3 mol%), in 4:1 mixture of THF/H_2O (2.5 mL) and then stirred at rt for 4 h. The reaction mixture was diluted with DCM then filtered. The residue was purified on a SiO_2 column to afford the desired **2.8g** as a white solid (77.7 mg, 72% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 – 7.79 (m, 2H), 7.61 – 7.56 (m, 1H), 7.48 – 7.43 (m, 2H), 7.42 – 7.37 (m, 1H), 7.33 – 7.27 (m, 2H), 7.25 – 7.22 (m, 1H), 2.34 (s, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 198.6, 138.6, 137.7, 136.7, 133.1, 131.0, 130.2, 130.1, 128.5, 128.4, 125.2, 19.9.

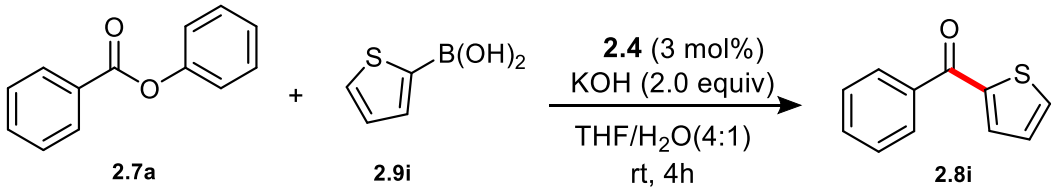
Experimental procedure for the synthesis (4-Benzoylpyridine) 2.8h [11]



In a glove box, a 1-dram vial was charged with phenyl benzoate **2.7a** (99.11 mg, 0.5 mmol), potassium hydroxide (56.1 mg, 2.0 equiv), 4-Pyridinylboronic acid **2.9h** (92.19 mg, 1.5 equiv), Pd-complex **2.4** (10.8 mg, 3 mol%), in 4:1 mixture of THF/H_2O (2.5 mL) and then stirred

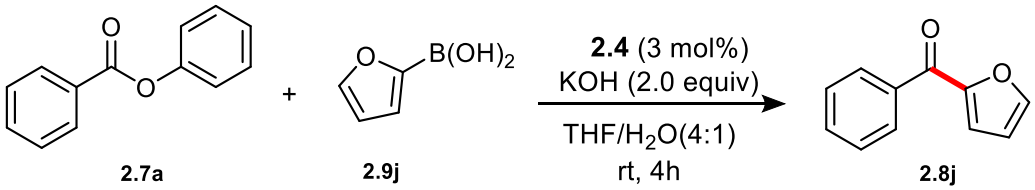
at rt for 4 h. The reaction mixture was diluted with DCM then filtered. The residue was purified on a SiO_2 column to afford the desired **2.8h** as a white solid (55.1 mg, 60% yield).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.27 – 8.22 (m, 2H), 7.70 – 7.64 (m, 1H), 7.58 – 7.52 (m, 2H), 7.46 (tt, J = 4.0, 2.3 Hz, 2H), 7.33 – 7.28 (m, 1H), 7.25 – 7.21 (m, 1H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ195.0, 150.7, 144.5, 136.1, 133.9, 130.3, 128.3, 121.5.

Experimental procedure for the synthesis (2-Benzoylthiophene) 2.8i [11]



In a glove box, a 1-dram vial was charged with phenyl benzoate **2.7a** (99.11 mg, 0.5 mmol), potassium hydroxide (56.1 mg, 2.0 equiv), 2-Thiopheneboronic acid **2.9i** (95.97 mg, 1.5 equi.), Pd-complex **2.4** (10.8 mg, 3 mol%), in 4:1 mixture of THF/H_2O (2.5 mL) and then stirred at rt for 4 h. The reaction mixture was diluted with DCM then filtered. The residue was purified on a SiO_2 column to afford the desired **2.8i** as a white solid (49.7 mg, 53% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.2 Hz, 2H), 7.76 (d, J = 4.9 Hz, 1H), 7.68 (d, J = 3.7 Hz, 1H), 7.64 (t, J = 7.5 Hz, 1H), 7.54 (t, J = 7.7 Hz, 2H), 7.20 (t, J = 4.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 188.2, 143.6, 138.1, 134.8, 134.2, 132.2, 129.1, 128.4, 127.9.

Experimental procedure for the synthesis (2-Benzoylfuran) 2.8j [11]

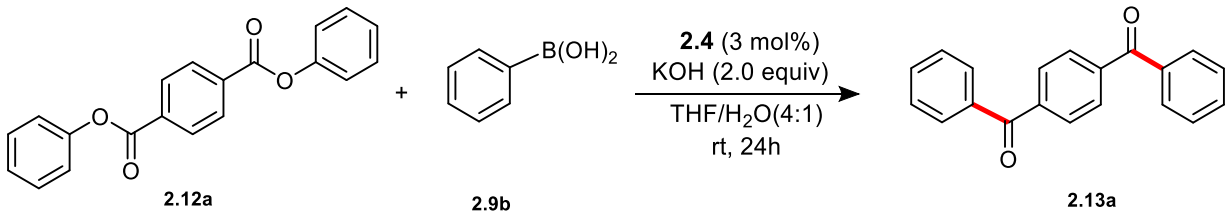


In a glove box, a 1-dram vial was charged with phenyl benzoate **2.7a** (99.11 mg, 0.5 mmol), potassium hydroxide (56.1 mg, 2.0 equiv), 2-Furanphenylboronic acid **2.9j** (83.91 mg, 1.5

equiv), Pd-complex **2.4** (10.8 mg, 3 mol%), in 4:1 mixture of THF/H_2O (2.5 mL) and then stirred at rt for 4 h. The reaction mixture was diluted with DCM then filtered. The residue was purified on a SiO_2 column to afford the desired **2.8j** as a white solid (48.1 mg, 56% yield).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.42 – 8.03 (m, 2H), 7.69 – 7.62 (m, 1H), 7.57–7.51 (m, 1H), 7.46 (td, J = 7.6, 2 Hz, 2H), 7.33 – 7.28 (m, 1H), 7.25 – 7.23 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.9, 151.0, 146.9, 137.0, 133.6, 129.5, 128.5, 121.7, 112.5.

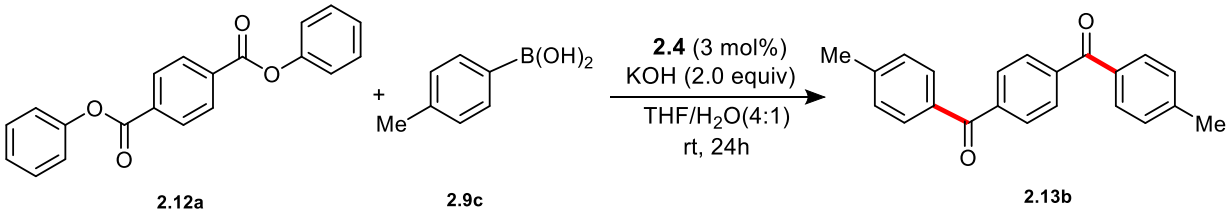
2.8.5. Experimental procedure for the synthesis of aryl diketones 2.13a-2.13f/2.17a-2.17f

Experimental procedure for the synthesis (1,4-Dibenzoylbenzene) 2.13a [8]



In a glove box, a 1-dram vial was charged with 1,4-diphenyl 1,4-benzenedicarboxylate **2.12a** (159.16 mg, 0.5 mmol), potassium hydroxide (56.1 mg, 2.0 equiv), phenylboronic acid **2.9b** (91.44 mg, 1.5 equiv), Pd-complex **2.4** (10.8 mg, 3 mol%), in 4:1 mixture of THF/H_2O (2.5 mL) and then stirred at rt for 24 h. The reaction mixture was diluted with DCM then filtered. The residue was purified on a SiO_2 column to afford the desired **2.13a** as a white solid (70.4 mg, 67% yield).**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89 (s, 4H), 7.84 (dd, J = 8.3, 1.3 Hz, 4H), 7.65 – 7.60 (m, 2H), 7.54 – 7.49 (m, 4H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 196.1, 140.7, 136.9, 132.9, 130.1, 129.7, 128.5.

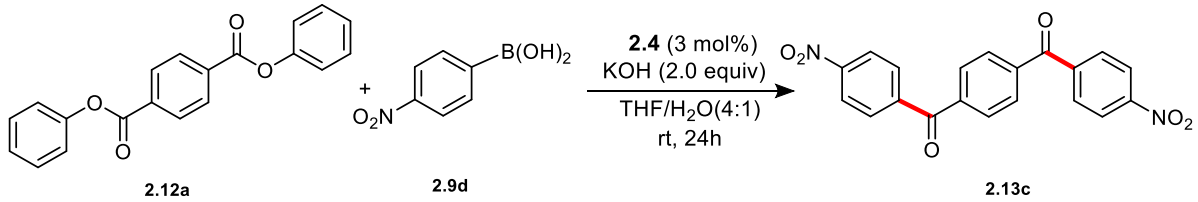
Experimental procedure for the synthesis (1,4-Bis(4-methylbenzoyl) benzene) 2.13b [13]



In a glove box, a 1-dram vial was charged with 1,4-diphenyl 1,4-benzenedicarboxylate **2.12a** (159.16 mg, 0.5 mmol), potassium hydroxide (56.1 mg, 2.0 equiv), 4-Methylphenylboronic acid **2.9c** (101.97 mg, 1.5 equiv), Pd-complex (10.8 mg, 3 mol%), in 4:1 mixture of THF/H_2O (2.5 mL) and then stirred at rt for 24 h. The reaction mixture was diluted with DCM then filtered. The residue was purified on a SiO_2 column to afford the desired **2.13b** as a white solid. (100.5 mg, 79% yield**). ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.86 (s, 4H), 7.78 – 7.74 (m, 4H), 7.31 (d, J = 7.9 Hz,

4H), 2.46 (s, 6H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 195.8, 143.9, 140.8, 134.3, 133.0, 130.3, 129.5, 129.1, 21.7.

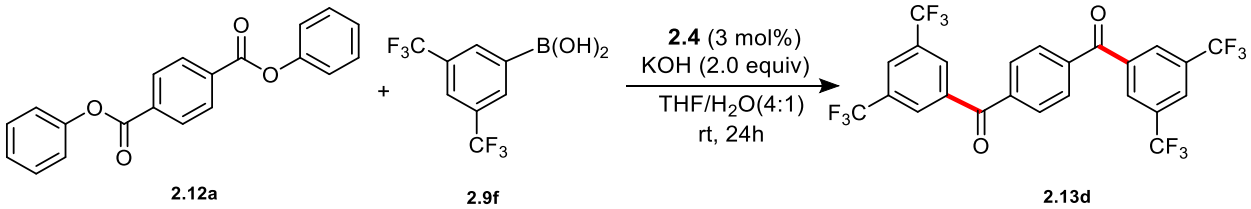
Experimental procedure for the synthesis (1,4-Bis(4-nitrobenzoyl) benzene) 2.13c [14]



2.12a 2.9d 2.13c

In a glove box, a 1-dram vial was charged with 1,4-diphenyl 1,4-benzenedicarboxylate **2.12a** (159.16 mg, 0.5 mmol), potassium hydroxide (56.1 mg, 2.0 equiv), 4-Nitrophenylboronic acid **2.9d** (125.19 mg, 1.5 equiv), Pd-complex **2.4** (10.8 mg, 3 mol%), in 4:1 mixture of THF/H_2O (2.5 mL) and then stirred at rt for 24 h. The reaction mixture was diluted with DCM then filtered. The residue was purified on a SiO_2 column to afford the desired **2.13c** as a light yellow solid (73.9 mg, 51% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.36 (s, 4H), 7.48 (dd, J = 6.9, 1.1 Hz, 4H), 7.36 – 7.27 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.4, 150.7, 133.9, 130.3, 129.6, 128.3, 126.2.

Experimental procedure for the synthesis (1,4-Bis(3,5-Bis(trifluoromethylbenzoyl)benzene) 2.13d

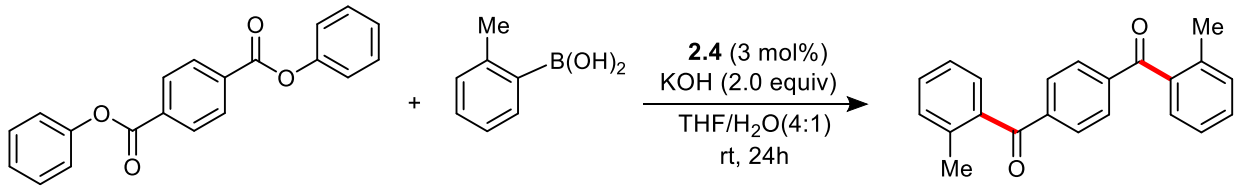


2.12a 2.9f 2.13d

In a glove box, a 1-dram vial was charged with 1,4-diphenyl 1,4-benzenedicarboxylate **2.12a** (159.16 mg, 0.5 mmol), potassium hydroxide (56.1 mg, 2.0 equiv), 3,5-Bis(trifluoromethyl)phenylboronic acid **2.9f** (193.44 mg, 1.5 equiv), Pd-complex **2.4** (10.8 mg, 3 mol%), in 4:1 mixture of THF/H_2O (2.5 mL) and then stirred at rt for 24 h. The reaction mixture

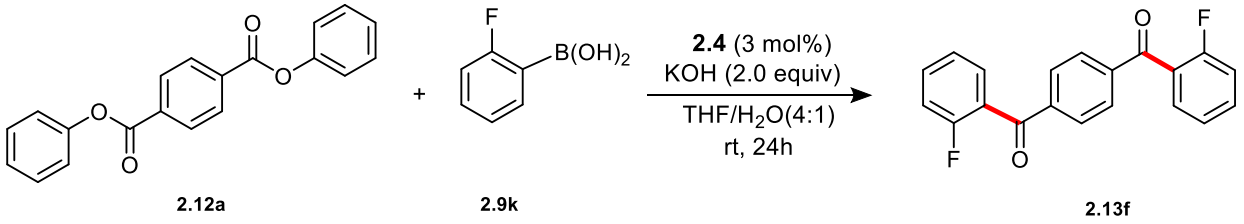
was diluted with DCM then filtered. The residue was purified on a SiO_2 column to afford the desired **2.13d** as a white solid (175.7 mg, 84% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.34 (s, 4H), 7.49 – 7.43 (m, 4H), 7.33 – 7.28 (m, 2H) **^{13}C NMR** (101 MHz, $CDCl_3$) δ 197.7, 136.5, 132.0, 130.3, 129.6, 126.2, 121.5, 117.0. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.85 (s).

Experimental procedure for the synthesis (2-methylbenzoyl benzene) 2.13e



In a glove box, a 1-dram vial was charged with 1,4-diphenyl 1,4-benzenedicarboxylate **2.12a** (159.16 mg, 0.5 mmol), potassium hydroxide (56.1 mg, 2.0 equiv), 2-Methylphenylboronic acid **2.9g** (101.97 mg, 1.5 equiv), Pd-complex **2.4** (10.8 mg, 3 mol%), in 4:1 mixture of THF/H_2O (2.5 mL) and then stirred at rt for 24 h. The reaction mixture was diluted with DCM then filtered. The residue was purified on a SiO_2 column to afford the desired **2.13e** as a white solid (60.4 mg, 48% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (s, 4H), 7.47 – 7.41 (m, 2H), 7.37 – 7.32 (m, 4H), 2.39 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 198.2, 141.1, 137.7, 137.2, 131.3, 130.9, 130.0, 129.6, 128.9, 20.2.

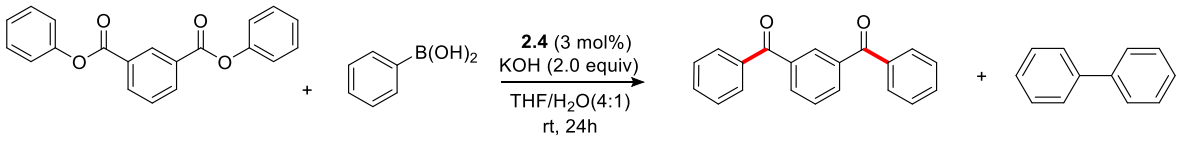
Experimental procedure for the synthesis (1,4-Bis(2-fluorobenzoyl) benzene) 2.13f



2.12a 2.9k 2.13f

In a glove box, a 1-dram vial was charged with 1,4-diphenyl 1,4-benzenedicarboxylate **2.12a** (159.16 mg, 0.5 mmol), potassium hydroxide (56.1 mg, 2.0 equiv), 2-Fluorophenylboronic acid **2.9k** (104.94 mg, 1.5 equiv), Pd-complex **2.4** (10.8 mg, 3 mol%), in 4:1 mixture of THF/H_2O (2.5 mL) and then stirred at rt for 24 h. The reaction mixture was diluted with DCM then filtered. The residue was purified on a SiO_2 column to afford the desired **2.13f** as a pale yellow solid (53.6 mg, 44% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.35 (s, 4H), 7.62 – 7.52 (m, 2H), 7.46 (t, *J* = 7.9 Hz, 4H), 7.30 (dd, *J* = 11.8, 4.3 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 196.1, 150.8, 134.0, 133.9, 130.3, 129.6, 128.9, 126.2, 118.6. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -110.25 (s).

Experimental procedure for the synthesis (1,3-Dibenzoylbenzene) 2.17a [15]

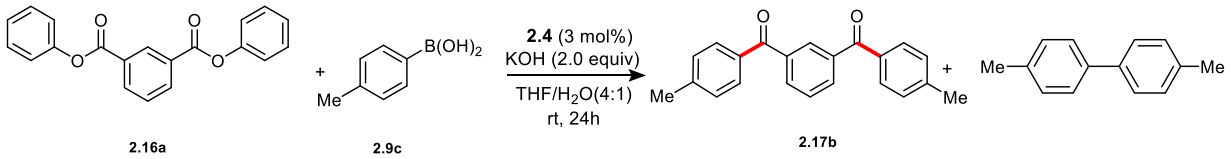


2.16a 2.9b 2.17a

In a glove box, a 1-dram vial was charged with 1,3-diphenyl 1,3-benzenedicarboxylate **2.16**a (159.16 mg, 0.5 mmol), potassium hydroxide (56.1 mg, 2.0 equiv), phenylboronic acid **2.9b** (91.44 mg, 1.5 equiv), Pd-complex **2.4** (10.8 mg, 3 mol%), in 4:1 mixture of THF/H_2O (2.5 mL) and then stirred at rt for 24 h. The reaction mixture was diluted with DCM then filtered. The residue was purified on a SiO_2 column to afford the desired **2.17a** as a white solid (72.9 mg, 68% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.19 (t, *J* = 1.5 Hz, 1H), 8.03 (dd, *J* = 7.7, 1.7 Hz, 2H), 7.83 (dd, *J*

= 8.3, 1.3 Hz, 4H), 7.67 – 7.58 (m, 3H), 7.53 – 7.47 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 195.8, 137.8, 136.9, 133.5, 132.9, 131.2, 130.1, 129.6, 128.5, 128.5.

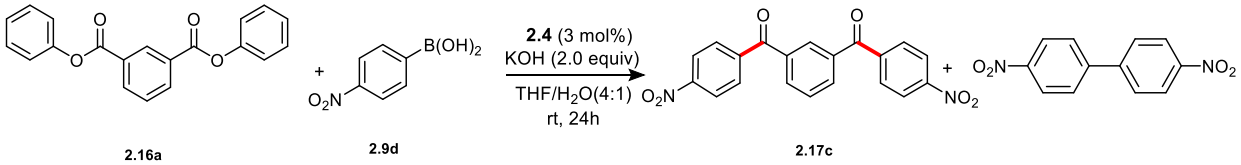
Experimental procedure for the synthesis (1,3-Bis(4-methylbenzoyl) benzene) 2.17b [16]



2.16a 2.9c 2.17b

In a glove box, a 1-dram vial was charged with 1,3-diphenyl 1,3-benzenedicarboxylate **2.16a** (159.16 mg, 0.5 mmol), potassium hydroxide (56.1 mg, 2.0 equiv), 4-Methylphenylboronic acid **2.9c** (101.97 mg, 1.5 equiv), Pd-complex **2.4** (10.8 mg, 3 mol%), in 4:1 mixture of THF/H_2O (2.5 mL) and then stirred at rt for 24 h. The reaction mixture was diluted with DCM then filtered. The residue was purified on a SiO_2 column to afford the desired **2.17b** as a white solid (98.9 mg, 78% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 (t, J = 1.5 Hz, 1H), 7.99 (dd, J = 7.7, 1.7 Hz, 2H), 7.76 – 7.71 (m, 4H), 7.61 (t, J = 7.5 Hz, 1H), 7.32 – 7.27 (m, 4H), 2.44 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 195.6, 143.7, 138.1, 134.3, 133.1, 130.9, 130.3, 129.1, 128.4, 21.7.

Experimental procedure for the synthesis (1,3-Bis(4-nitrobenzoyl) benzene) 2.17c [16]

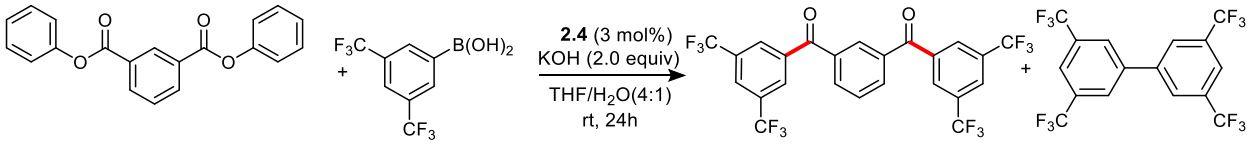


2.16a 2.9d 2.17c

In a glove box, a 1-dram vial was charged with 1,3-diphenyl 1,3-benzenedicarboxylate **2.16a** (159.16 mg, 0.5 mmol), potassium hydroxide (56.1 mg, 2.0 equiv), 4-Nitrophenylboronic acid **2.9d** (125.19 mg, 1.5 equiv), Pd-complex **2.4** (10.8 mg, 3 mol%), in 4:1 mixture of THF/H_2O (2.5 mL) and then stirred at rt for 24 h. The reaction mixture was diluted with DCM then filtered. The residue was purified on a SiO_2 column to afford the desired **2.17c** as a light yellow solid. (51.8

mg, 36% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.03 (t, J = 1.5 Hz, 1H), 8.47 (dd, J = 7.8, 1.8 Hz, 2H), 7.69 (t, J = 7.8 Hz, 1H), 7.49 – 7.42 (m, 4H), 7.33 (ddd, J = 8.6, 2.2, 1.1 Hz, 2H), 7.24 (t, J = 2.3 Hz, 2H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ195.0, 150.7, 134.9, 131.7, 130.3, 129.6, 129.1, 126.1, 121.6.

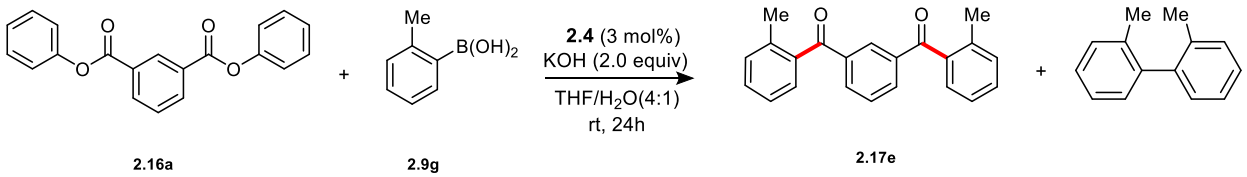
Experimental procedure for the synthesis (1,3-Bis(3,5-Bis(trifluoromethylbenzoyl)benzene) 2.17d



2.16a **2.9f** **2.17d**

In a glove box, a 1-dram vial was charged with 1,3-diphenyl 1,3-benzenedicarboxylate **2.16a** (159.16 mg, 0.5 mmol), potassium hydroxide (56.1 mg, 2.0 equiv), 3,5-Bis(trifluoromethyl)phenylboronic acid **2.9f** (193.44 mg, 1.5 equiv), Pd-complex **2.4** (10.8 mg, 3 mol%), in 4:1 mixture of THF/H_2O (2.5 mL) and then stirred at rt for 24 h. The reaction mixture was diluted with DCM then filtered. The residue was purified on a SiO_2 column to afford the desired **2.17d** as a white solid (177.9 mg, 85% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.03 (t, J = 1.5 Hz, 1H), 8.47 (dd, J = 7.8, 1.8 Hz, 2H), 7.69 (td, J = 7.9, 0.4 Hz, 1H), 7.52 – 7.39 (m, 4H), 7.49 – 7.43 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.1, 164.2, 150.7, 134.9, 131.7, 130.3, 129.6, 129.1, 126.1, 121.6. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -62.96 (s).

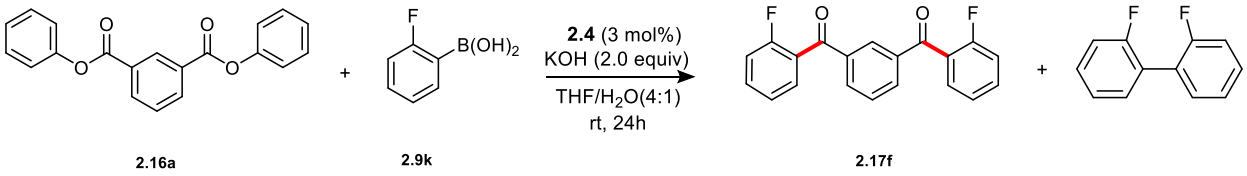
Experimental procedure for the synthesis (1,3-Bis(2-methylbenzoyl benzene) 2.17e



2.16a 2.9g 2.17e

In a glove box, a 1-dram vial was charged with 1,3-diphenyl 1,3-benzenedicarboxylate **2.16a** (159.16 mg, 0.5 mmol), potassium hydroxide (56.1 mg, 2.0 equiv), 2-Methylphenylboronic acid **2.9g** (101.97 mg, 1.5 equiv), Pd-complex **2.4** (10.8 mg, 3 mol%), in 4:1 mixture of THF/H_2O (2.5 mL) and then stirred at rt for 24 h. The reaction mixture was diluted with DCM then filtered. The residue was purified on a SiO_2 column to afford the desired **2.17e** as a white solid (48.1 mg, 38% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.22 (t, J = 1.5 Hz, 1H), 7.99 (dd, J = 7.7, 1.7 Hz, 2H), 7.56 (t, J = 7.7 Hz, 1H), 7.41 (td, J = 7.5, 1.5 Hz, 2H), 7.34 – 7.26 (m, 4H), 7.24 (d, J = 7.6 Hz, 2H), 2.37 (d, J = 9.3 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 197.6, 137.7, 137.1, 134.2, 131.3, 128.8, 128.7, 125.3, 20.1.

Experimental procedure for the synthesis (1,3-Bis(2-fluorobenzoyl)benzene) 2.17f



2.16a 2.9k 2.17f

In a glove box, a 1-dram vial was charged with 1,3-diphenyl 1,3-benzenedicarboxylate **2.16a** (159.16 mg, 0.5 mmol), potassium hydroxide (56.1 mg, 2.0 equiv), 2-Fluorophenylboronic acid **2.9k** (104.94 mg, 1.5 equiv), Pd-complex **2.4** (10.8 mg, 3 mol%), in 4:1 mixture of THF/H_2O (2.5 mL) and then stirred at rt for 24 h. The reaction mixture was diluted with DCM then filtered. The residue was purified on a SiO_2 column to afford the desired **2.17f** as a pale yellow solid (65.2 mg, 54% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.25 (t, J = 1.3 Hz, 1H), 8.10 – 8.03 (m, 2H), 7.65

– 7.51 (m, 5H), 7.28 (td, J = 7.6, 1.0 Hz, 2H), 7.20 – 7.14 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.5, 161.4, 137.7, 137.7, 134.0, 133.6, 131.0, 130.8, 128.8, 126.2, 124.4, 116.5, 116.3. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -110.25 (s).

2.9. References

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