Palladium-catalyzed Decarboxylative and Desulfinative Cross-Coupling of Diaryliodonium Triflates

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ABSTRACT

Palladium-catalyzed Decarboxylative and Desulfinative Cross-Coupling of Diaryliodonium salts

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Heteroaromatic compounds have been shown to play a crucial role in several disciplines such as materials chemistry, agrochemical and pharmaceutical industry. Hence, there has been a great emphasis on the development of methodologies for the synthesis of such motifs. Generally, the formation of the new carbon-carbon bond in connecting two aromatic systems can be achieved by the palladium-catalyzed cross-coupling reactions. Although, classic synthetic routes are effective, they may involve the use of harsh reaction conditions and potentially dangerous pre-functionalization of organometallic reagents. More recently, attention has been turned towards the development of more efficient novel methodologies employing more environmental benign and alternative reaction conditions, such as C-H activation, decarboxylative and desulfinative cross-coupling reactions. The advantage of the decarboxylative and desulfinative cross-coupling lies in their ability to be chemo-selective while producing minor amounts of gas as byproduct. Most of the synthetic routes use aryl halides as a coupling partner for the formation of these motifs. Herein, to expand the tool kit, we developed new synthetic routes through the use of diaryliodonium salts to replace aryl halides in accessing heteroaromatics through decarboxylative and desulfinative palladium-catalyzed cross-coupling reactions. Diaryliodonium salts have emerged as a highly versatile reactant applicable in numerous organic reactions. Their structure provides them with the potential to be a more reactive coupling partner in comparison to aryl-halides. In an effort to further improve the decarboxylative cross-coupling reactions, their applicability in the methodology. Furthermore, the reactions of diaryliodonium salts with sulfinate salts in cross-coupling reactions has not been examined to date, creation of a methodology utilizing these compounds could potentially be a big step in these classes of reactions.

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List of abbreviations

Ac	acetyl
acac	acetylacetonate
AcOH	acetic acid
Ar	aryl
Cy	cyclohexyl
Dba	dibenzylideneacetone
DFT	density-functional theory
DMA	dimethylacetamide
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DPEphos	bis(2-diphenylphosphinophenyl)ether
dppf	1,1'-bis(diphenylphosphino)ferrocene
eq.	equivalent
EtOAc	ethyl acetate
FGA	functional group addition
FGI	functional group interconversion
GC	gas chromatography
GC-MS	gas chromatography-mass spectrometry
h	hour
(het)Ar	heteroaromatic
m	meta
M	molar concentration
min	minute
N	nitrogen substituted
NMR	nuclear magnetic resonance
NMP	N-methylpyrrolidone
o	ortho
OTf	triflate
p	para

Chapter 1. Introduction

1.1. Aryl substituted heteroaromatic compounds

Heteroaromatic compounds, compounds that contain a heteroatom as part of cyclic conjugated aromatic system, are shown to play an important role in several different fields of chemistry. Their importance can be highlighted by their common occurrence in natural products[1], pharmaceutical compunds[2] and advanced functional materials[3] amongst other fields. Their importance stems from the core structure that these moieties posses. The conjugated π system renders the molecule rigid while opening the possibility of π- π system interactions at the same time. Furthermore, five-membered heteroaromatic compounds are often employed as benzene substitutes with the added functionality of a heteroatom. Heteroaromatic compounds are frequently encountered in pharmaceuticals, agrochemicals, advanced materials, and natural products (Figure 1).

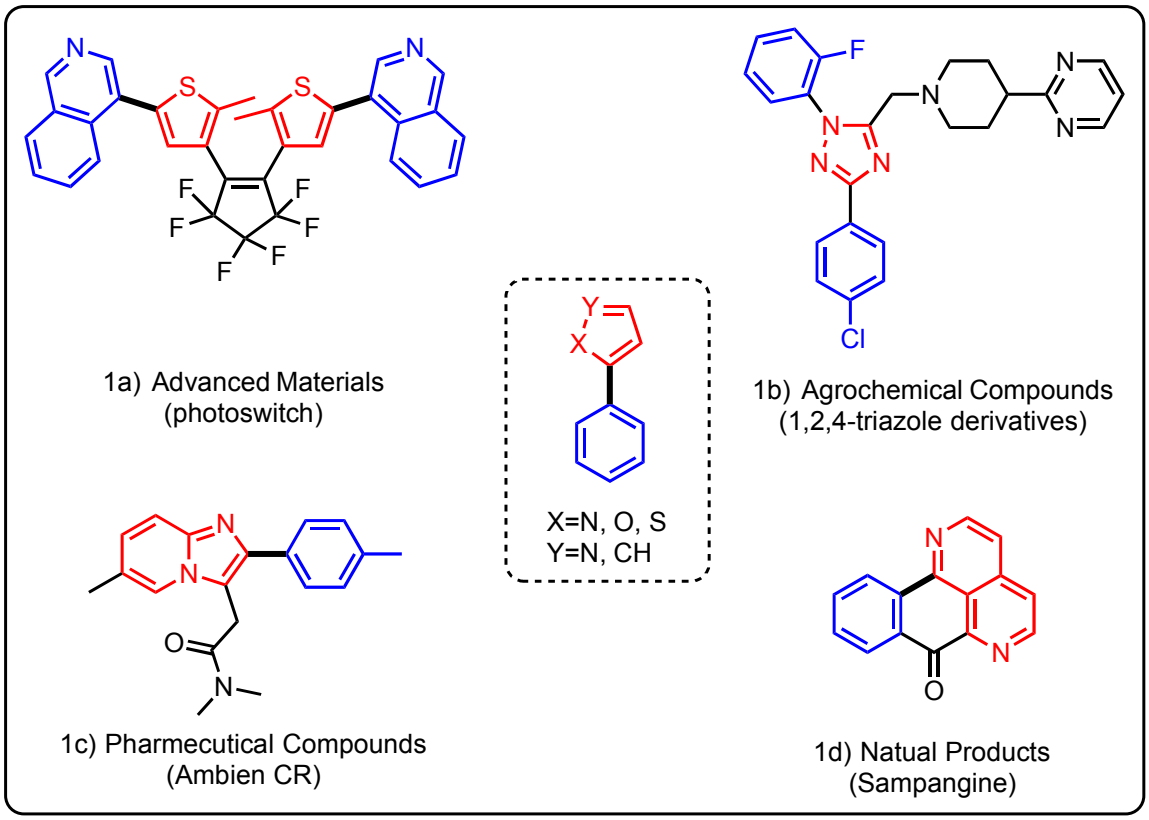


Figure 1. Example of Heteroaromatic motifs

Frequently seen heteroaromatic compounds contain oxygen, nitrogen and sulfur as the heteroatom. Representative heteroaryl compounds from various fields is outlined above (Figure 1). They are applicable in advanced functional materials, one example of which would be the photo-switch **1a** in Figure 1, a large compound containing heteroaryl thiophene and quinoline moieties[4]. In a patent protected work, applicability of heteroaryl compounds has been demonstrated as pesticides as represented by compound **1b**[5] in Figure 1. Ambien CR[6] (Figure 1c) is a drug with over 5.7 million prescriptions that contains a heteroaromatic compound bonded to a benzene ring[2]. As the field of biochemistry grows and isolation and characterizations of natural compounds progress, the presence of heteroaryl compounds become increasingly evident. For example, Sampangine[7], **1d**, is a natural product obtained from plant canaga tree with potential antifungal properties. In all of the above-mentioned examples the hetroaromatic compound is bonded to another heteroaromatic ring or a substituted benzene ring via carbon-carbon bond therefore, showing the importance of this motif and the necessity for synthetic methods for the construction of such bonds.

1.2. Carbon-Carbon bond formation

The formation of larger molecules or complex compounds is possible through the formation of new carbon-carbon bonds. Being key to increasing the carbon skeleton of organic molecules, having different methods for the formation of carbon-carbon bonds is essential in synthetic chemistry. An analysis of different chemical reactions carried out in the pharmaceutical industry has been highlighted by Carey and coworkers (Figure 2).[2]

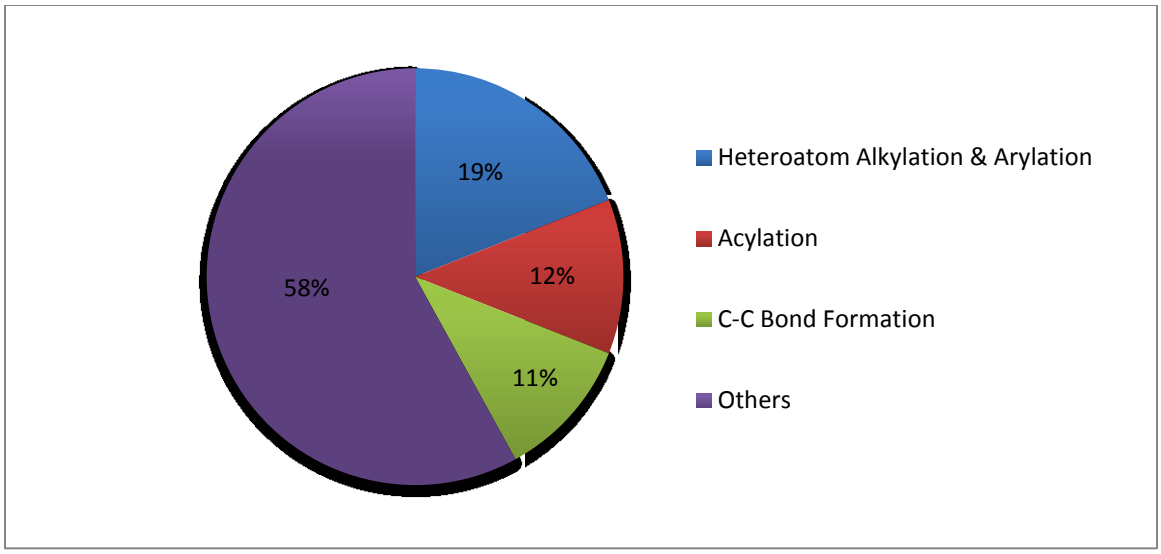


Figure 2. Overview of reactions carried out in pharmaceutical industry

It can be noticed that the majority of reactions carried is heteroatom alkylation and arylation, indicating the importance of heteroatoms. Followed by acylation reactions, carbon-carbon bond formation is the third most carried out reaction. In recent years several researchers dedicated their research towards the development of different C-C bond forming methods in order to provide access to a broad variety compounds. Amongst the various methodologies developed, organometallic reactions are utilized 12% of the time while ester condensation reactions being utilized 14% of the time. Palladium-catalyzed cross-coupling reactions are the most commonly employed, occupying 22% of reactions indicating the effectiveness and usefulness of this class of reactions, as shown below (Figure 3)[2].

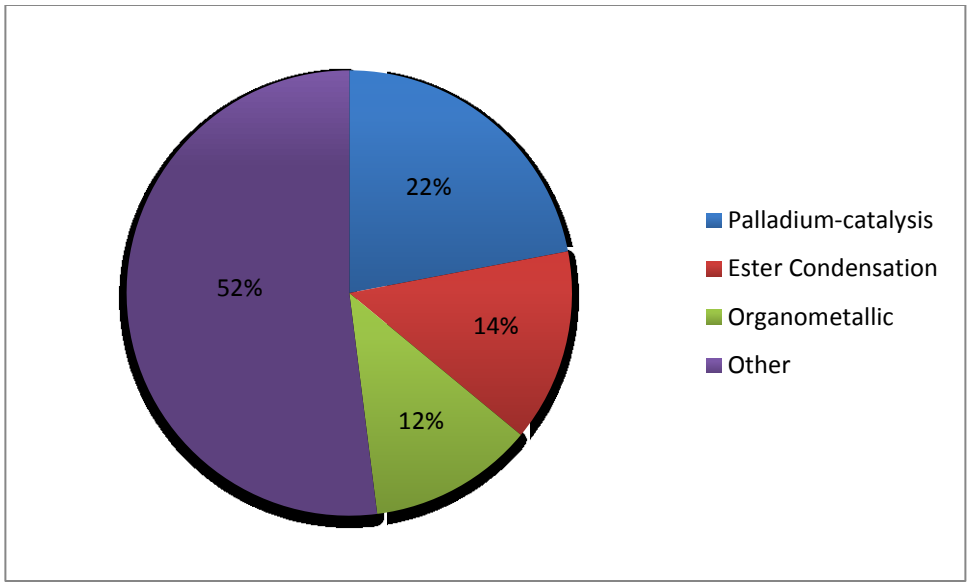


Figure 3. Overview of carbon-carbon bond formation reactions carried out in pharmaceutical industry

1.3. Palladium-catalyzed cross-coupling reactions

Palladium has been proven to be the go-to catalyst for cross-coupling reactions in the process of forming new C-C bonds and enabling construction of larger molecules. While the metal was initially discovered in 1802 and reported in 1805 by Wollaston[8], the importance of palladium was realized only in 1959 by the development of the Wacker process (Figure 4)[9,10], a process that generates acetaldehyde (3) from alkene (2) using palladium and copper catalysts in the presence of water.

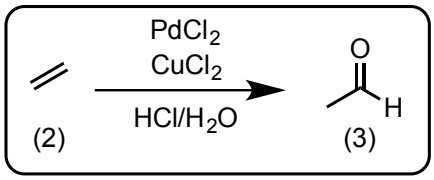


Figure 4. The Wacker Process

The curiosity sparked by the Wacker process attracted significant attention in the scientific community. The true potential of palladium and its diverse applicability in syntheses emerged in the 1970s through its employment in different reactions demonstrated by Heck, Suzuki and Negishi amongst many other researchers.[11] Due to its high applicability, several methodologies have been developed focusing on using different coupling partners for the construction of new C-

C bonds.[2]

1.3.1. Classical methods

In 1970s, palladium-catalyzed reactions was, and is still is, a hot topic in synthetic chemistry. The exploration of coupling partners for palladium-catalyzed reactions has resulted in various methodologies at the disposal of scientific community, enabling them to generate a wide variety of compounds depending on the research of interest.

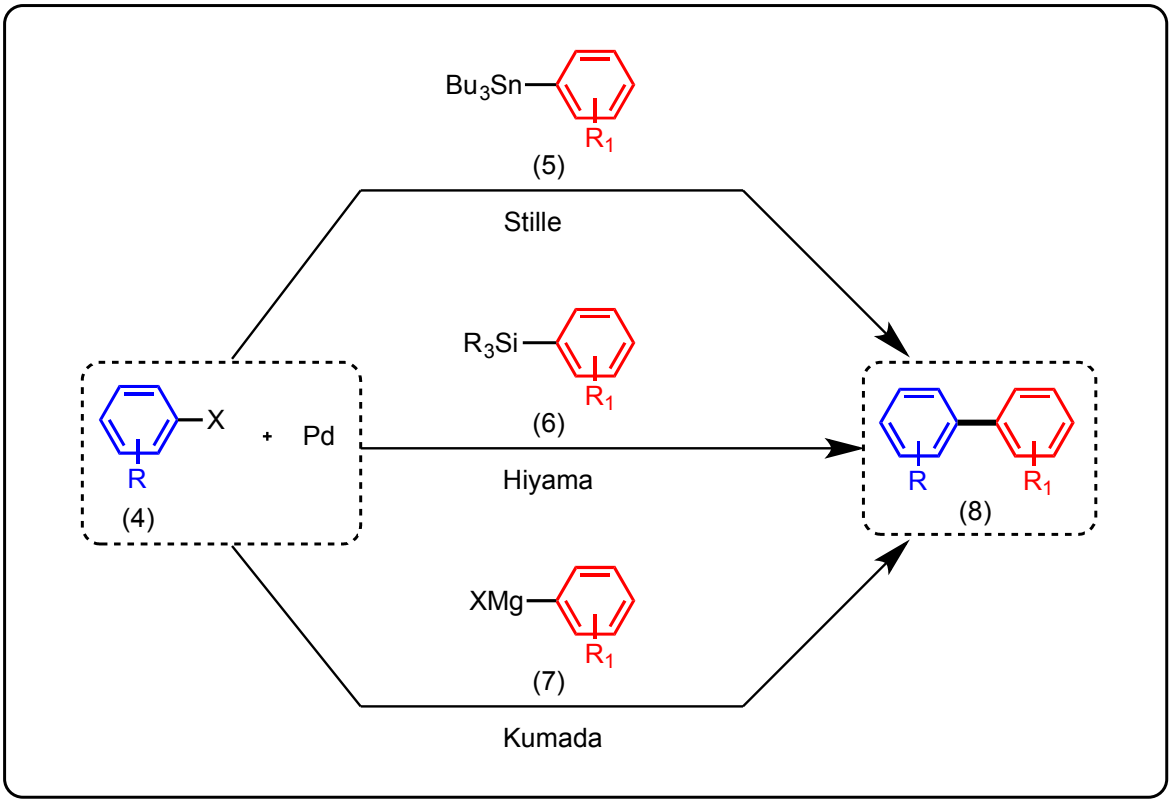


Figure 5. Some of the classic palladium-catalyzed methodologies

Employment of different reactive organometallic species, such as organotin (Figure 5, 5) in the case of the Stille method, organo silanes (Figure 5, 6) in the case of the Hiyama method and Grignard reagent (Figure 5, 7) in the case of the Kumada method with the arylhalide coupling partner (Figure 5, 4) in the presence of palladium has demonstrated the diversity of palladium catalysis for the synthesis of biaryl motifs (Figure 5, 8). However, the effectiveness of these methods are prone to limitations, such as difficulty in the removal of the side product, such as organotin compounds in the Stille couplings, stoichiometric amount of organosilane waste

products in the Hiyama coupling and the sensitivity of the Grignard reagent employed in the Kumada coupling.

Heck, Neighishi and Suzuki have done the pioneering work in the field of palladium-catalyzed reactions (Figure 5). Their methodology is commonly employed in synthetic routes for the formation of potential medicinal drugs. Representative examples for the synthesis of drug molecules using Heck[12], Suzuki[13], and Negishi[14] coupling reactions are shown in Figure 5. These examples clearly demonstrate the applicability of these reactions in the construction of complex large molecules and the wide variety of functional groups that are tolerated. Thus, palladium-catalyzed coupling reactions are useful for late-stage functionalization of organic compounds enabling the synthesis of complex molecules.

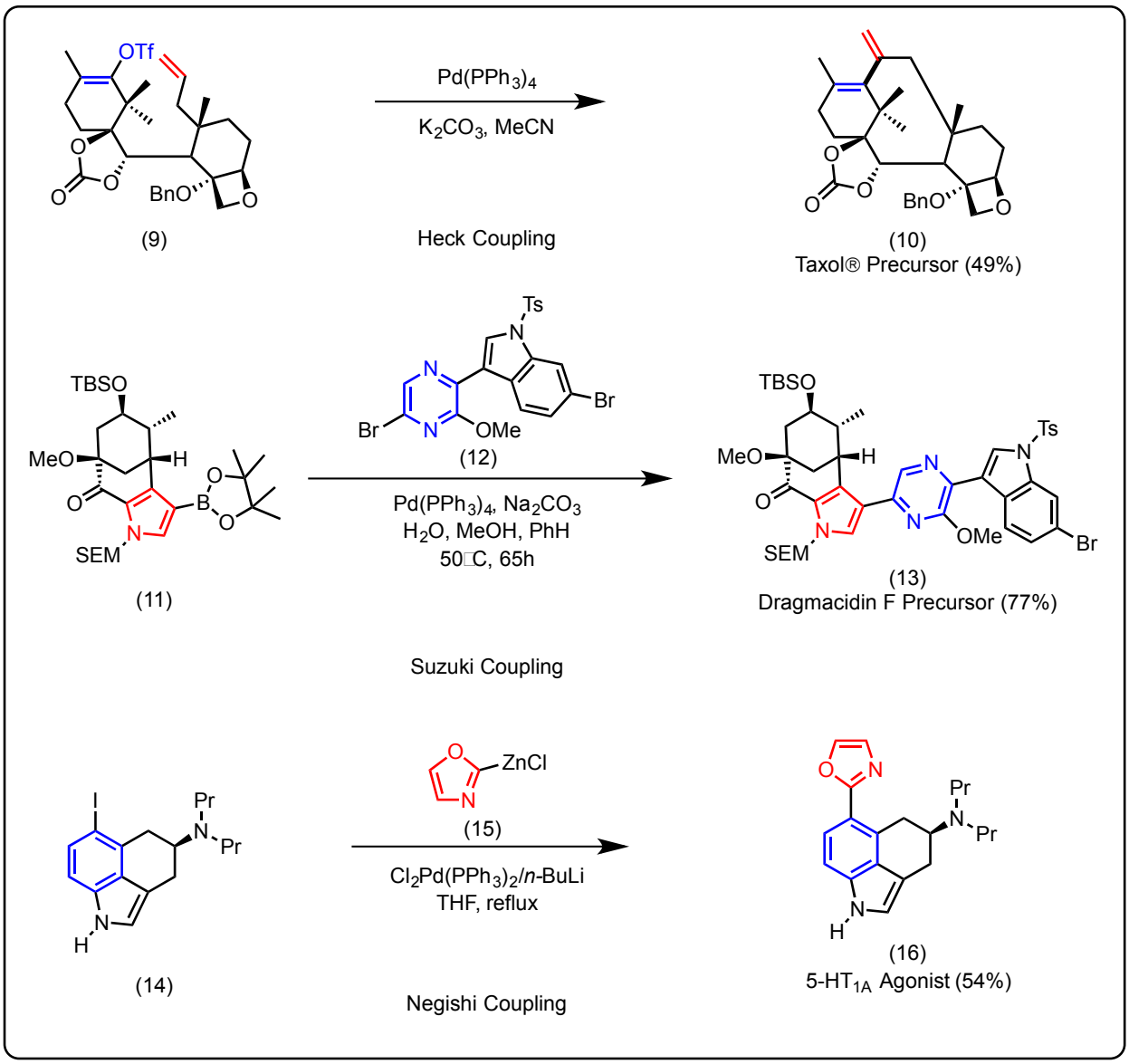


Figure 5. Examples of Heck, Suzuki and Negishi couplings used in pharmaceutical synthesis

Heck, Suzuki, and Negishi were awarded the Nobel price in Chemistry in 2010 for palladium-catalyzed cross-couplings in organic chemistry, highlighting once again the importance of these class of reactions and the use of palladium.[2]

1.3.1.1. Heck method

Richard Heck has developed a methodology using palladium as a catalyst for the alkylation and arylation of olefins.[15,16] The aromatic ethylarylation involves the reaction between an aryl/vinyl halide and an alkene in the presence of palladium chloride. The initial Heck reaction involved the use of non-catalytic amount of palladium along with the use of ally mercuric halides[17–19] (Figure 6).

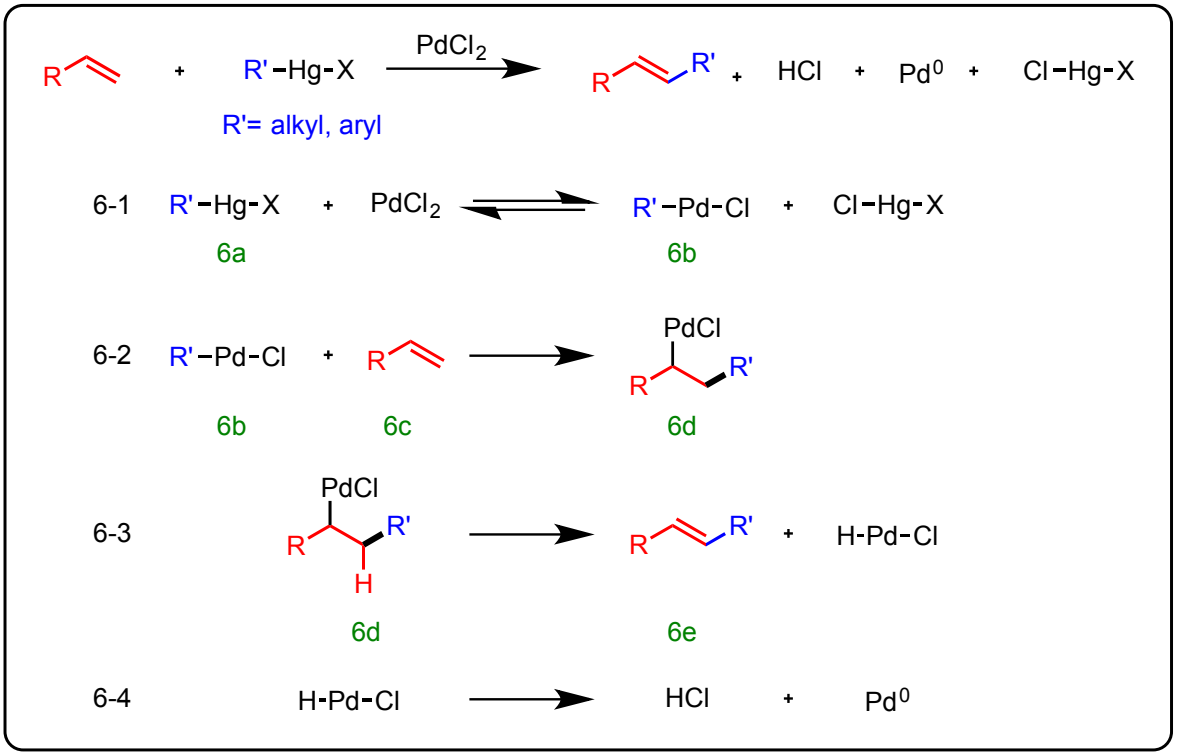


Figure 6. Generic Non-Catalytic Heck Cross-Coupling reaction.

The reaction of mercuric halide with palladium halide through ligand exchange is necessary in order to generate the active palladium species in the system (Figure 6, 6b), which would then insert into the olefin (Figure 6, 6c), thus forming a new carbon-carbon bond. After this point, the palladium species is eliminated through β-hydride elimination pathway. The palladium species then undergoes a reductive elimination and cannot further take part in the reaction. Further developing the methodology through the introduction of cupric halide was the corner stone of palladium-catalyzed reaction. The introduction of cupric halides enables the oxidation of

palladium and allowing it to re-enter the catalytic cycle hence rendering the reaction a catalytic system, however the requirement of stoichiometric amount of mercury still remained as an issue.

Meanwhile, in the scientific community, "oxidative addition of palladium (0) species into aryl-halide bonds generating arylpalladium(II) halides" was demonstrated by Fitton[20,21] in 1968. This finding inspired further advancements to overcome the requirement of stoichiometric mercury. Independent from one another, Mizoroki[22] and Heck[23] demonstrated that the use of aryl-halides would render the system catalytic and eliminate the use of stoichiometric amount of mercury. The methodology developed was then standardized to a generic method and referred to as the Heck reaction (Figure 7).

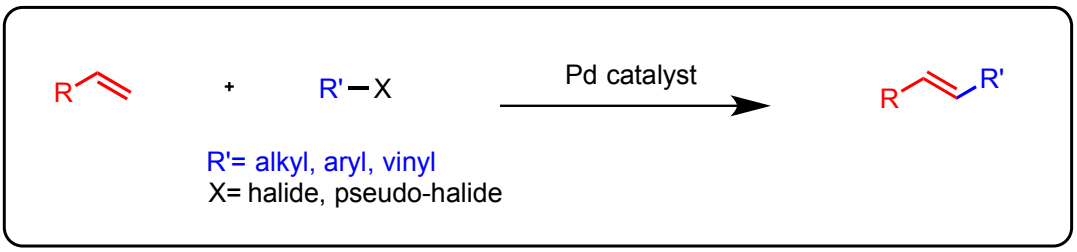


Figure 7. Generic Heck Cross-Coupling

The standardized method involves a similar procedure to generate the carbon-carbon bond however the catalytic cycle for catalyst regeneration is different. The active palladium species can either be generated *in situ* or employed in its active state, Pd(0), and the cycle begins with the oxidative addition (Figure 8, Step A) of the palladium species **17** into the aryl halide **18**. The Pd-R complex, **19** (palladium complex containing the first coupling group, The R group) can then react with the olefin, **20** through *syn*-addition (Figure 8, Step B). This happens through coordination of the palladium to the double bond forming a π-complex, **21**, followed by its insertion (Figure 8, Step C) and hence forming the new carbon-carbon bond, **22**. There are several factors that influence mechanistic pathway and the stereochemistry of the Pd-complexes that are formed, however, for the next step of the catalytic cycle (Figure 8, Step D) the palladium in the complex needs to be *cis* with respect to the hydrogen of the olefin in order for the *syn*-elimination to take place, upon which the desired compound is formed, **23**. The palladium complex, **24**, can then undergo reductive elimination (Figure 8, Step D), forming HX, **25**, by-

product and reintroducing the active palladium complex (Figure 8, 17) to the cycle and enabling more catalytic cycles.

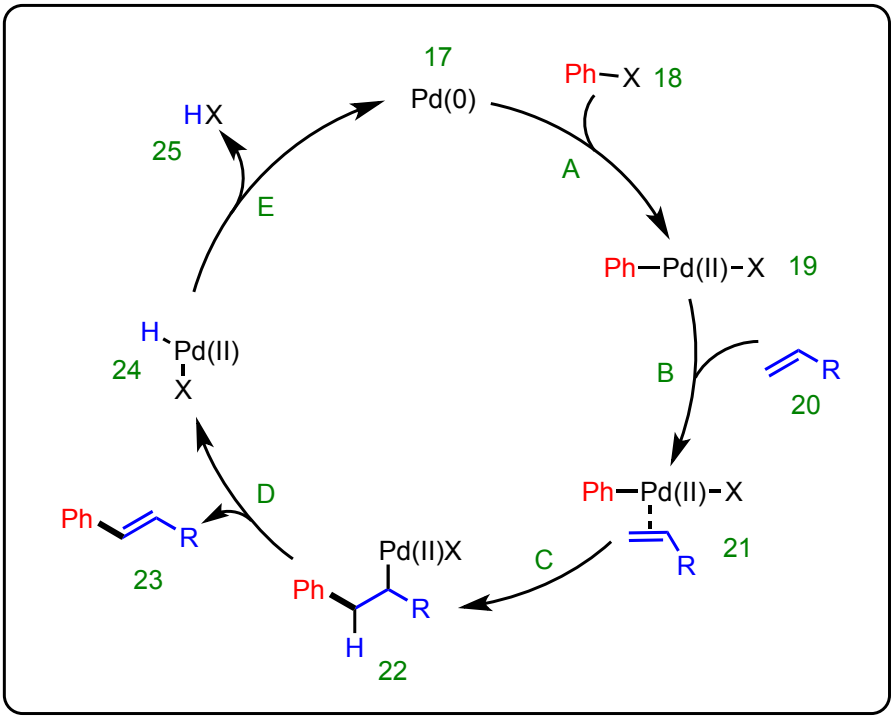


Figure 8. Generic Heck Cross-Coupling Catalytic Cycle

1.3.1.2. Suzuki method

In the late 1970s, Akira Suzuki and coworkers[24–26], developed a methodology employing organoboron compounds in palladium-catalyzed cross-coupling reactions for the formation of biaryl motifs (Figure 9).[2]

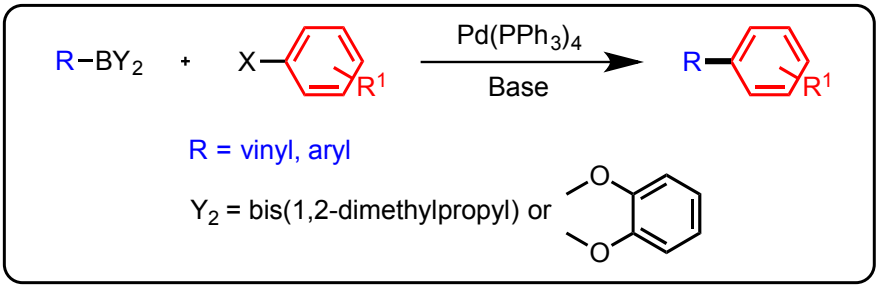


Figure 9. Generic Suzuki Cross-Coupling

This class of nucleophilic coupling partners have been demonstrated to display a wide range of

reactivity with the aryl-halide electrophilic coupling partners. Furthermore, the methodology, due to its expandability, has been further developed to enlarge the substrate scope of compounds that can be employed for the formation of carbon-carbon bonds. The scope encompasses aryl and alkyl chlorides[27,28], a wide variety of ligands[29–31] and the ability to carry out the reaction in aqueous media[29,32], at room temperature[33–35] or even solvent free[36].

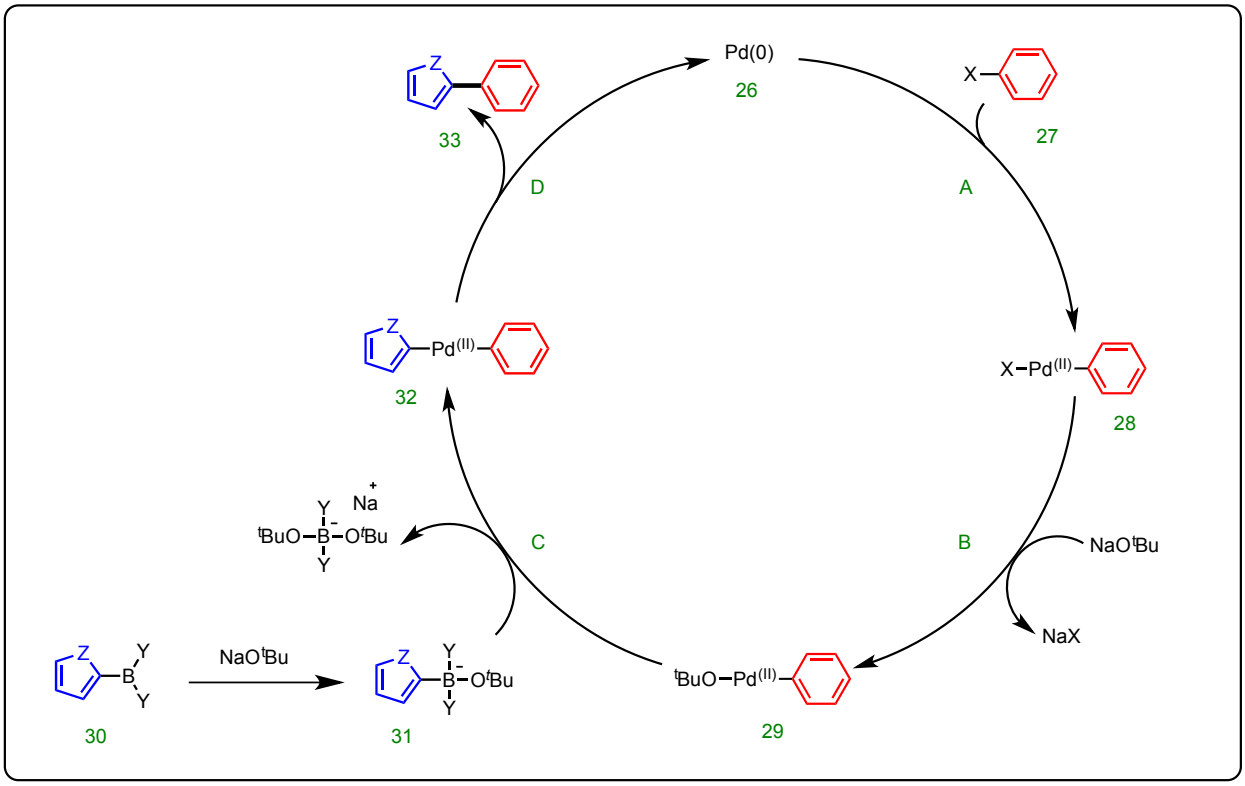


Figure 10. Generic Suzuki Cross-Coupling Catalytic Cycle

The catalytic cycle of the Suzuki methodology (Figure 10) is similar to that of the Heck method. The active palladium species [Pd(0)], **26**, oxidatively adds (Figure 10, Step A) into the aryl halide **27**, forming palladium (II) complex **28**. The presence of the base enables ligand exchange (Figure 10, Step B) (substitution). Similarly, the base also enables the formation of the organoboron complex **31** by reacting with the boronic ester **30**, the key ingredient of Suzuki method, increasing its nucleophilicity and hence its reactivity for its role in the cycle. Transmetalation (Figure 10, Step C) between the organoboron complex and the palladium species **29** results in the formation of a palladium complex **32** that contains the two aryl substrates. Reductive elimination (Figure 10, Step D) results in the formation of the bi-aryl

product **33** containing the new bond along with the reintroduction of the active palladium **26** in to the catalytic cycle.

1.3.1.3. Negishi method

Ei-chi Negishi has developed a method for the formation of bi-aryl motifs through the use of organozinc compounds as a coupling partner with palladium as a catalyst.[2]

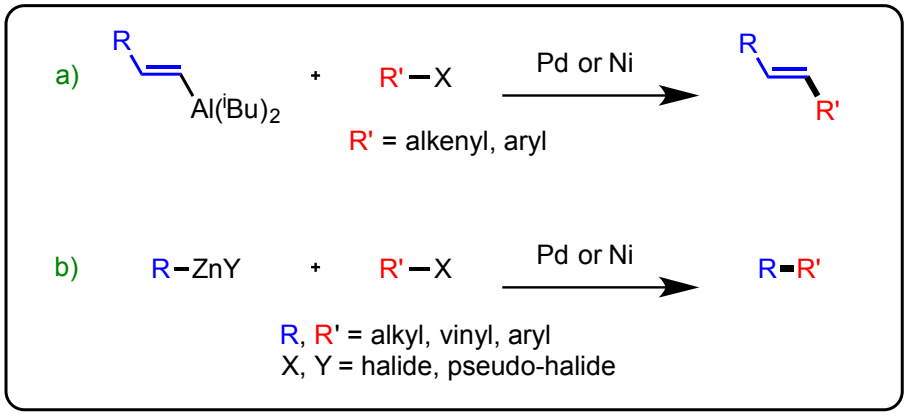


Figure 11. a) Initial, b) Standard Negishi method

First generation protocol developed by Neigishi in 1976 employed nickel as a catalyst (Figure 11, a), further developments of the methodology evolved it to the use of palladium metal as a catalyst (Figure 11, b), which was published a year later by Negishi and Jutand[37]. The contributions provided by Negishi protocol allow these classes of reactions to be carried out in milder conditions that in turn also provide broader substrate scope.

The catalytic cycle for Negishi method (Figure 12) is once again very closely related to the generic palladium-catalyzed cross-coupling cycles, in the sense that the oxidative addition, transmetalation, and reductive elimination (Figure 12, Step A, B, C respectively) are still the key steps in the cycle. The difference however lies in the transmetalation step. Unlike the Suzuki method, the coupling partner, the zinc complex **35** (key ingredient in Negishi method) reacts readily with the palladium species **34** that formed upon oxidative addition, hence reducing the amount of base employed for the reaction.

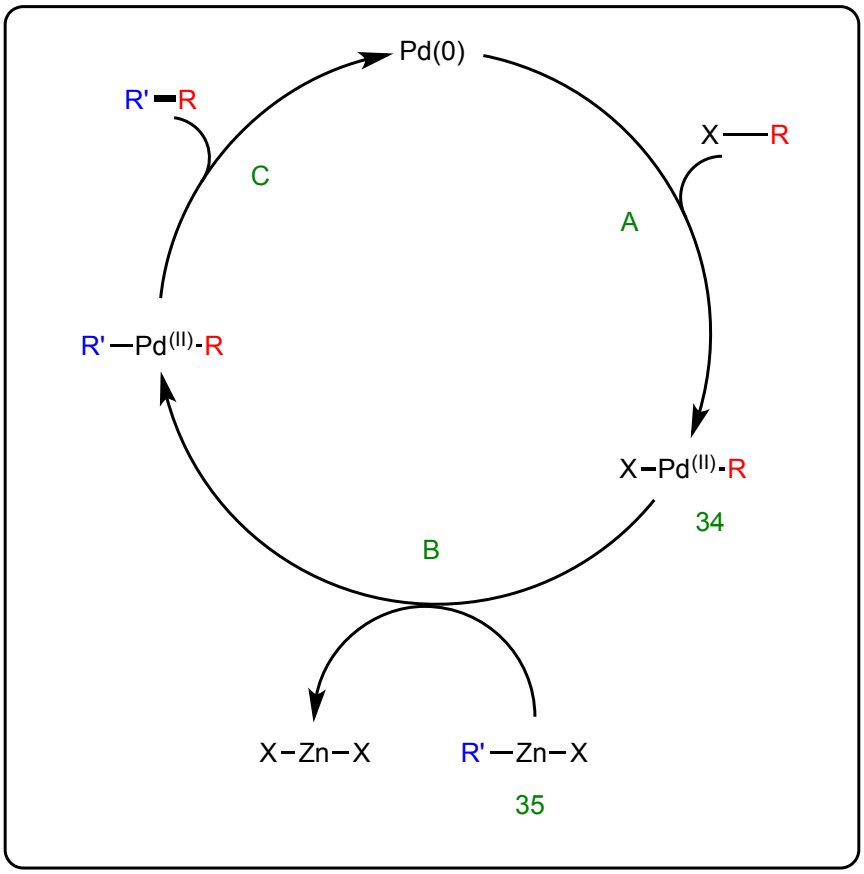


Figure 12. Generic Negishi cross-coupling catalytic cycle

1.3.2. Recent advances on C-C bond formation

Although the classical methods are highly efficient and applicable with a wide variety of reagents, they may have some limitation. Some of the methods require pre-functionalization of reactants being used in the reaction and in these cases the instability of the prepared reagent is one of the limitations. Other potential limitations are the possibility of producing stoichiometric amount of metallic by-products, which may not be easily removed from the reaction mixture. Since these types of reactions are essential in chemistry several different methodologies have been developed that enable the formation of similar motifs overcoming the limitations of classical methods.

1.3.2.1. C-H arylations

To overcome some of the limitations of the classical methods, C-H arylation (Figure 12) has been developed as a very atom economical method of forming these types of motifs. The lack of

organometallic reagent eliminates the requirement of pre-functionalization along with the formation of heavy and stoichiometric amounts of metallic by-products. However, this method often lacks regioselectivity in cases where there are multiple hydrogen atoms in similar chemical environments[38,39]. The benefits introduced by the C-H activation methods influenced several research groups to dedicate their time and efforts in further developing the methodology in order to provide the scientific community with more effective tools for complex syntheses while at the same time advancing novel methods in green chemistry.

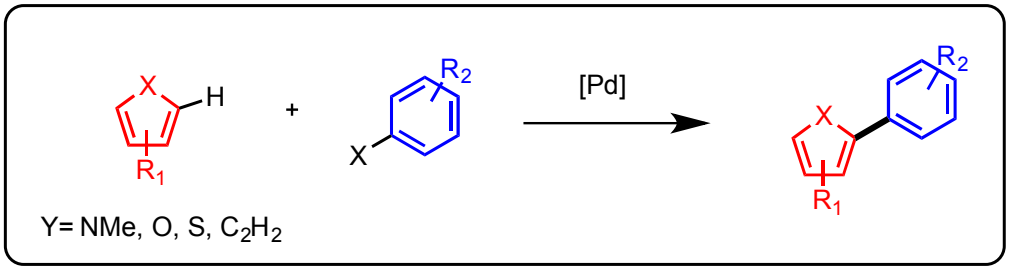


Figure 13. General Scheme for C-H Arylation

Contributions introduced by Fagnou and coworkers (Figure 14)[39,40] broadened the scope of the reaction enormously. The methods developed are applicable to a wide variety of coupling partners with different electronic properties. Furthermore the system is applicable to form aryl-aryl or heteroaryl-aryl motifs, controlled by the selection of different types of ligands, reaction time, and temperature.

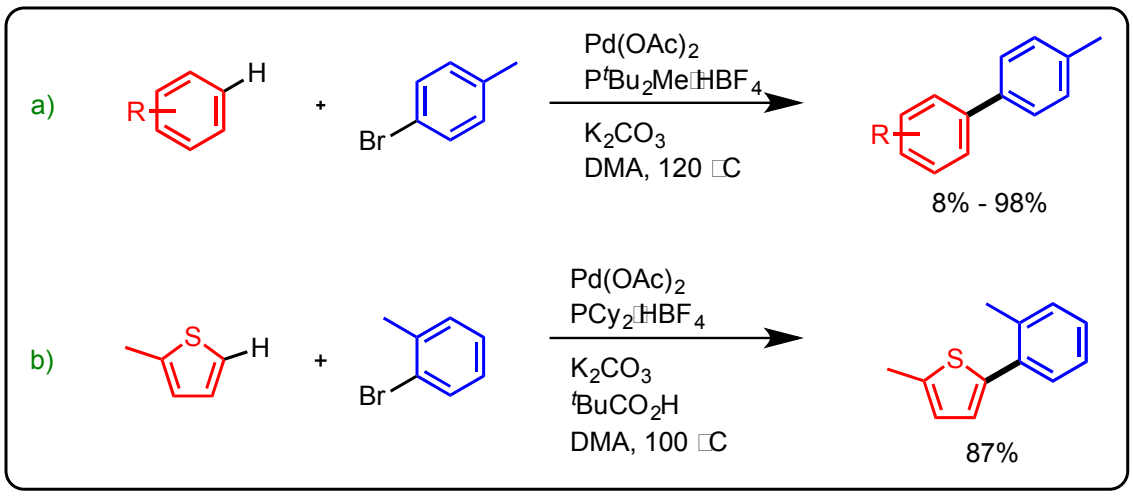


Figure 14. Different Fagnou methodologies

Although highly effective, the initial dilemma of having hydrogen atoms with close reactivity causing undesired by-products still persisted. Illustrated in Figure 15, the presence of similar chemical environments, at positions 2 and 5 of the heteroaromatic ring causes non-regioselective arylation leading to the formation of undesired products. In order to overcome this problem, Sharp and coworkers[41] in 2003 introduced a methodology that employed carboxylic ester moieties as directing groups in order to activate a specific hydrogen bond that could be controlled by the selection of palladium source and solvent (Figure 15). Through the use of Pd/C and NMP regioselectivity was achieved favouring arylation at 2 position (Figure 15) while employment of $Pd(PPh_3)_4$ and Toluene resulted in formation of arylated compound at 5 position selectively.

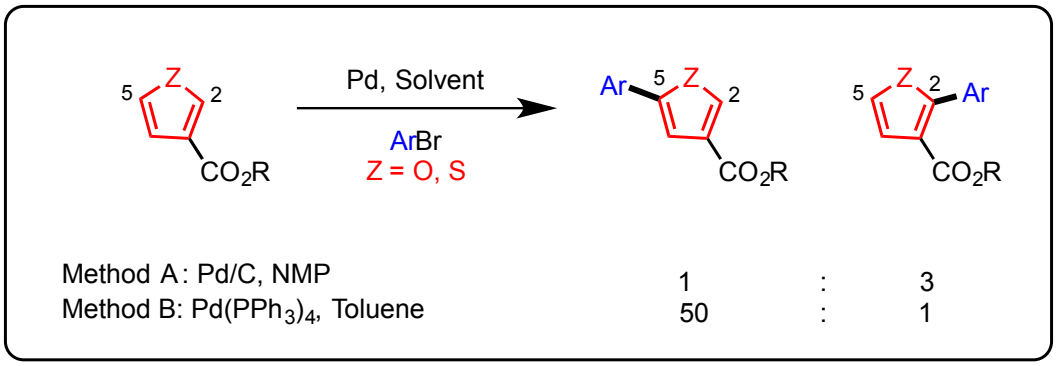


Figure 15. Regioselective Conditions for C-H Arylation

The use of directing groups was effective in controlling regioselectivity to a certain extend by favouring one position over the other, however, gaining full control over the regioselectivity is a persisting challenge. The attachment of the directing group might necessitate its removal after product formation thereby increasing the number of steps in the synthesis.. Furthermore, the lack of regioselectivity is a major concern for the arylation of unsymmetrical five-membered heteroaromatics causing the formation of multiple products.

1.3.2.2. Decarboxylative cross-coupling

Another alternative method to overcome the potential limitations of classical methods and C-H arylation is the decarboxylative cross-coupling reactions (Figure 16). The advantage of this method is the presence of a carboxylic acid moiety as a reactive site, which imparts chemoselectivity to these types of reactions. Furthermore, the by-product is CO_2 gas, which is

relatively more environmentally friendly compared to the metallic waste in the classical methods.[42–45] Similar to C-H arylations, decarboxylative cross-couplings are highly applicable to a wide variety of heteroaromatic or aromatic carboxylic acids. Initial decarboxylative reaction, for the formation of biaryl moieties with the use of carboxylic acids was demonstrated in 1966 by Nilsson and coworkers.[46]

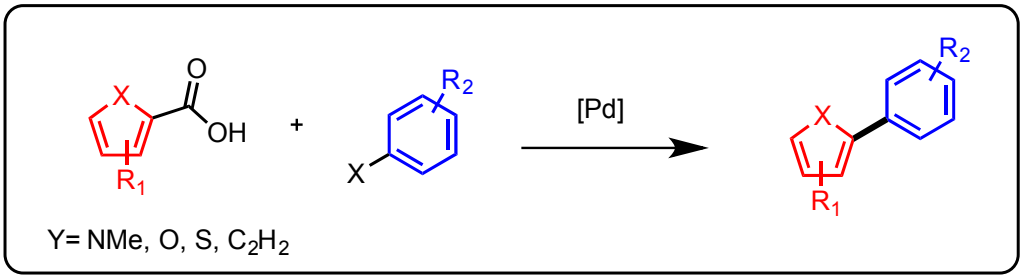


Figure 16. General Scheme for Decarboxylative Cross-Coupling

Decarboxylative cross-coupling reactions can be categorized in several different ways depending on the basis of comparison, such as, categorizing based on reactants or the mechanistic pathway of the reaction or the general reaction conditions itself. A general categorizations of these class of reactions was described by Goossen and coworkers[47].

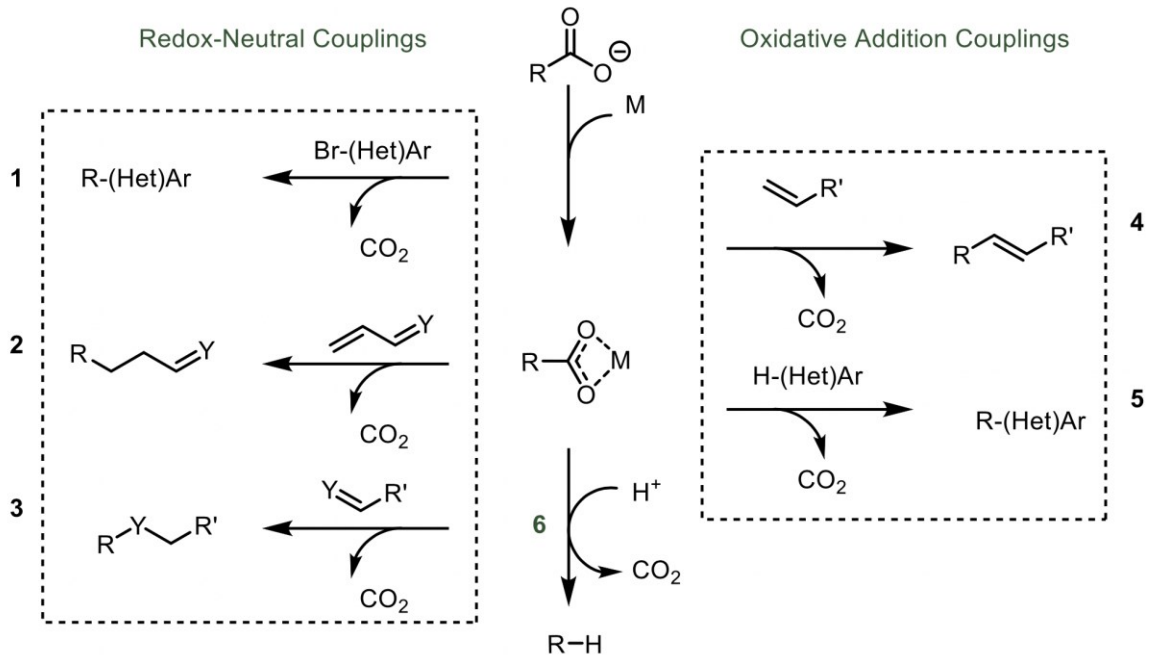


Figure 17. General types of decarboxylative cross-coupling

Based on the coupling partners they can be categorized in five different ways. Aryl, vinyl or allyl electorphiles (Figure 17, 1) participate in conjugate additions (Figure 17, 2), carbon-heteroatom bond forming reactions (Figure 17, 3), Heck-type vinylations (Figure 17, 4), and direct arylations (Figure 17, 5). Proto-decarboxylation (Figure 17, 6) is also a possibility when dealing with carboxylic moieties. Based on mechanistic pathways, the reactions can be categorized into two ways, redox-neutral coupling and oxidative couplings. Furthermore, depending on the mechanistic pathway the carboxylic acid moiety could be participating as an electrophilic or nucleophilic species. Their employment in redox-neutral pathways enables them to behave as nucleophiles and act as substitutes for organometallic reagents as employed in classical coupling reactions. In the case of the oxidative coupling they behave as the electrophilic coupling partner and be substitutes to the halide moieties employed in the classical methods. One key difference between the mechanistic pathways is the active palladium species participating in the reaction. Redox-neutral reactions require palladium(0) complex as the active catalytic species while in the oxidative couplings the active catalytic species is palladium(II) complex. Apart from the mentioned pathways of reactivity, aromatic carboxylic acids are prone to proto-decarboxylation in which case CO_2 is extruded affording the corresponding aromatic compound.

1.3.2.2.1 Aryl-aryl cross-coupling

Methodology developed by Goossen and coworkers have demonstrated the applicability of decarboxylative cross-coupling reactions for the formation of biaryl motifs (Figure 18). Through the employment of bimetallic system the method is capable of coupling aryl carboxylic acids containing an electron-withdrawing group (EWG) with aryl halides. Although the initial metho utilized stoichiometric amounts of copper halide[48], further optimizations enabled the use of catalytic amounts of copper halide[49].

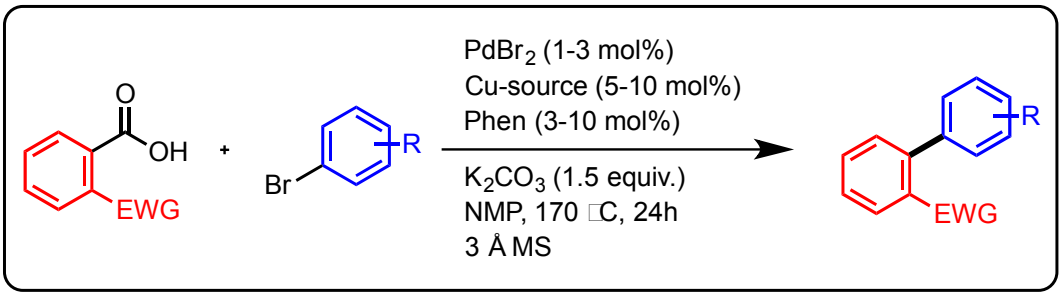


Figure 18. Goossen protocol

The mechanistic pathway proposed by Goossen involves two catalytic cycles, one for each metal that share overlapping transmetalation steps (Figure 19, Step C).

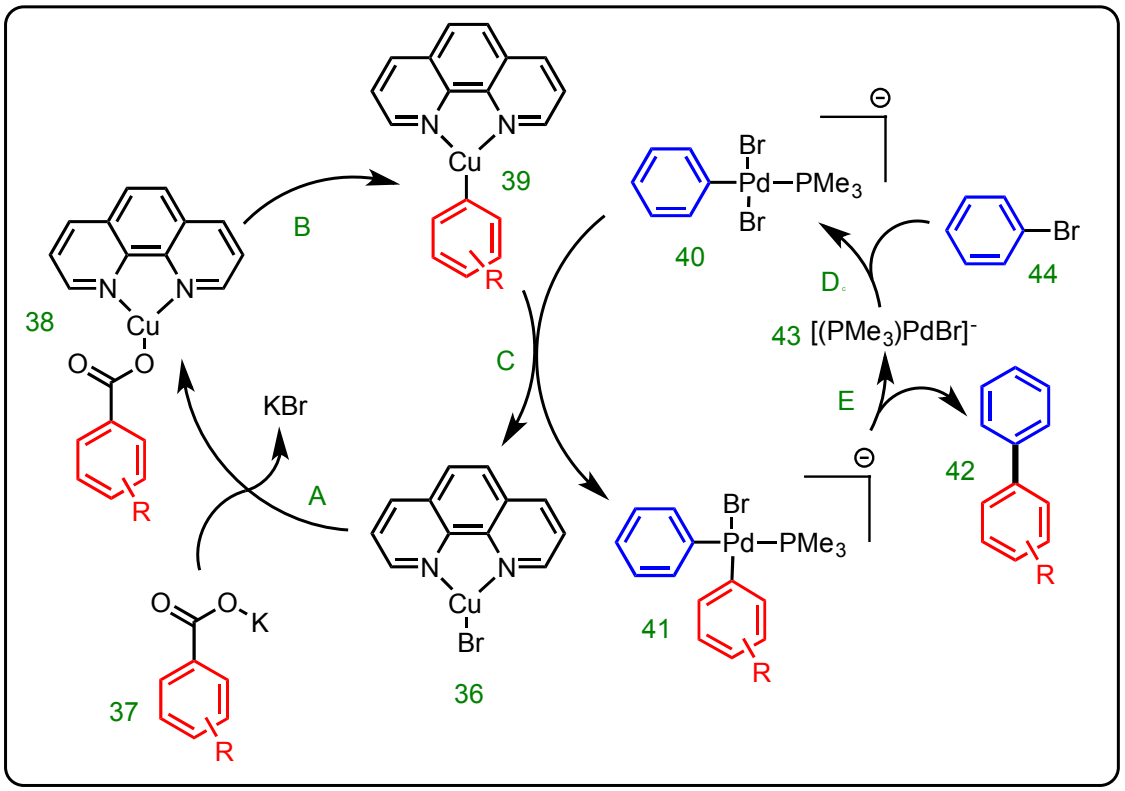


Figure 19. Mechanistic pathway of Goossen protocol

The reaction begins via initiation of the copper cycle through anion exchange (Figure 19, Step A) of the copper source **36** with the carboxylate **37**. Following this step is the decarboxylation (Figure 19, Step A), which forms a bond between the copper source and the aryl moiety **37** resulting in the organocuprate compound **38**, which then undergoes decarboxylation (Figure 19,

B) forming copper complex **39**. Meanwhile in the palladium cycle, the oxidative addition (Figure 19, Step D) of palladium **43** into the aryl halide **44** forms the palladium species **40** that can then undergo transmetalation (Figure 19, Step C) with the copper complex. Upon transmetalation, the copper species is reintroduced to the copper catalytic cycle while the palladium complex **41** undergoes reductive elimination (Figure 19, Step E) forming the desired compound **42** and reintroducing the palladium catalyst back into the cycle. The scope of this methodology encompasses electron-rich and electron-poor aryl halides, however, it required the presence of *o*-nitrobenzoic acids. This limitation was overcome by the creation of a new catalytic system (Figure 20), which enabled it to work with arylcarboxylic acids containing an electron-withdrawing substituent as a directing group.

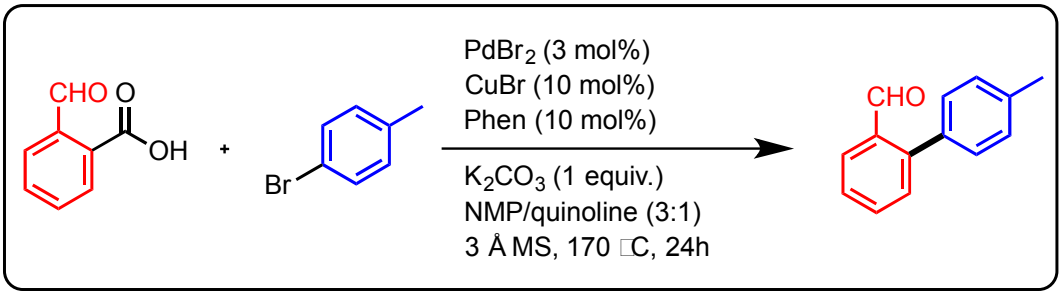


Figure 20. Goossen protocol with new catalytic system

However, the requirement now was the presence of the electron-withdrawing directing group. This was essential in the method developed due to the nature of the aryl halides employed. Their ability to coordinate strongly to the copper prevented ligand exchange from taking place at thermodynamically favourable conditions. Further advancement to the methodology was the employment of aryl triflates as opposed to aryl halides. The product of transmetalation now being unable to coordinate to copper does not prevent the catalytic activity[50].

Around the same time as Goossen's early findings, Becht and coworkers also developed a similar methodology (Figure 21), cross-coupling of electron-rich benzoic acids with aryl iododes[51,52]. By using excess silver carbonate in the presence of $AsPh_3$ ligand, this method enabled the formation of electron-rich biaryl moieties.

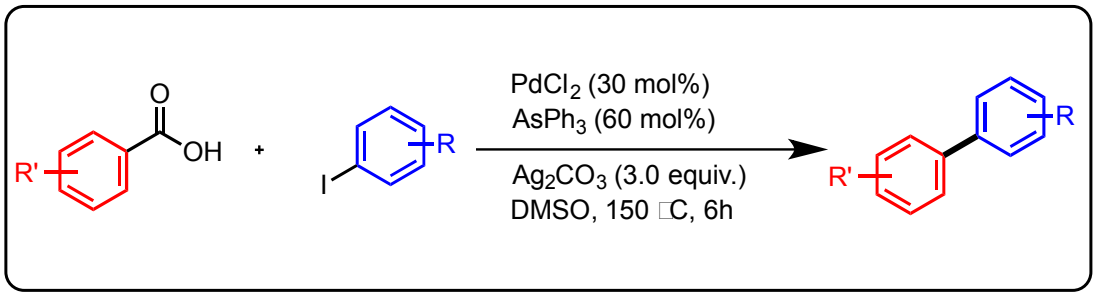


Figure 21. Becht's protocol

1.3.2.2.2 Heteroaryl-aryl cross-coupling

Around the same time of Goossen and Becht findings, the applicability of decarboxylative cross-coupling reaction for heteroaromatic carboxylic acids were demonstrated by Forgione and coworkers (Figure 22)[45]. In an attempt to perform C-H activation an unexpected reaction took place that was a decarboxylative cross-coupling. Extension of the general decarboxylative cross-coupling scope and by demonstrating the ability of heteroaromatic carboxylic acids to participate in these types of reactions further enlightened the scientific community and inspired further research for heteroaromatic decarboxylative cross-couplings.

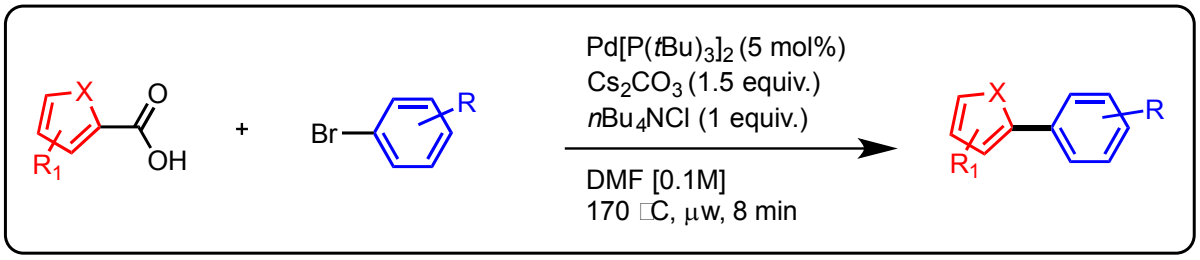


Figure 22. Unexpected decarboxylative cross-coupling of heteroaromatic acids

This finding was especially interesting for the fact that it did not require a co-catalyst, the extrusion of carbon dioxide is possible to proceed with the palladium species itself.

The initial mechanism proposed by Forgione consisted of 3 possible pathways leading to the desired compound and is shown in Figure 23.

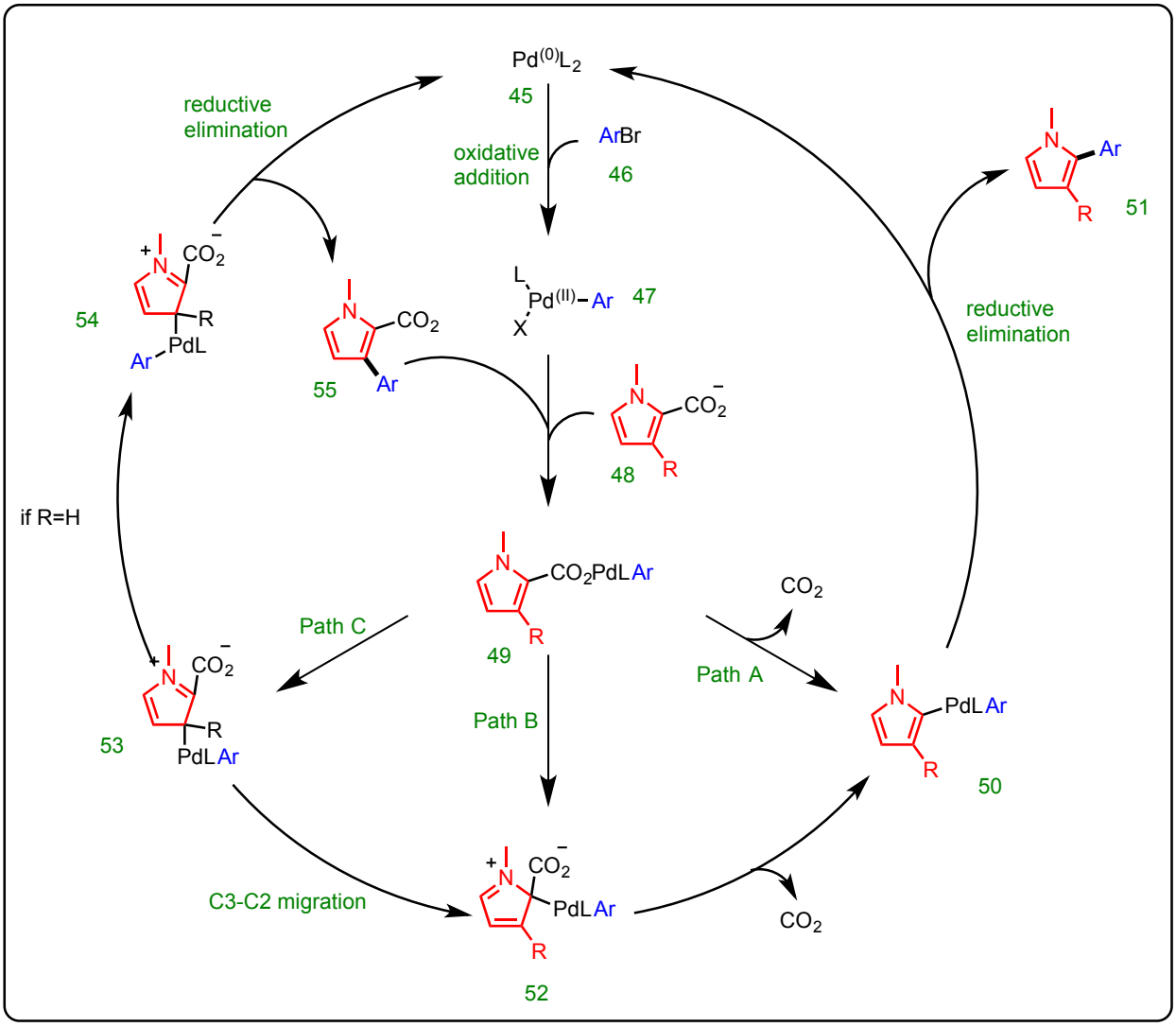


Figure 23. Proposed mechanistic pathway for Forgione-Bilodeau Methodology

The cycle starts like typical palladium cycle, that is the oxidative addition of the palladium catalyst, in this case the palladium(0) **45**, into the aryl halide moiety **46**. The aryl carboxylate **48** can then displace the halide in the palladium complex **47** generating **49**. From this point onwards there were 3 proposed mechanistic pathways. Path A being direct extrusion of carbon dioxide gas to produce **50** which would then undergo reductive elimination and result in the formation of the heteroaryl-aryl compound **51**. Path B and C involves electrophilic palladation, attributed to the electron richness of the heterocycle. Out of the three proposed pathways, path A was dismissed due to the inapplicability of the method to benzoic acids and heteroaryls (Figure 24)

having the carboxylic acid group at C3 position as opposed to the C2 position, which indicated the necessity of the heteroaromatic partner with the applied reaction conditions.

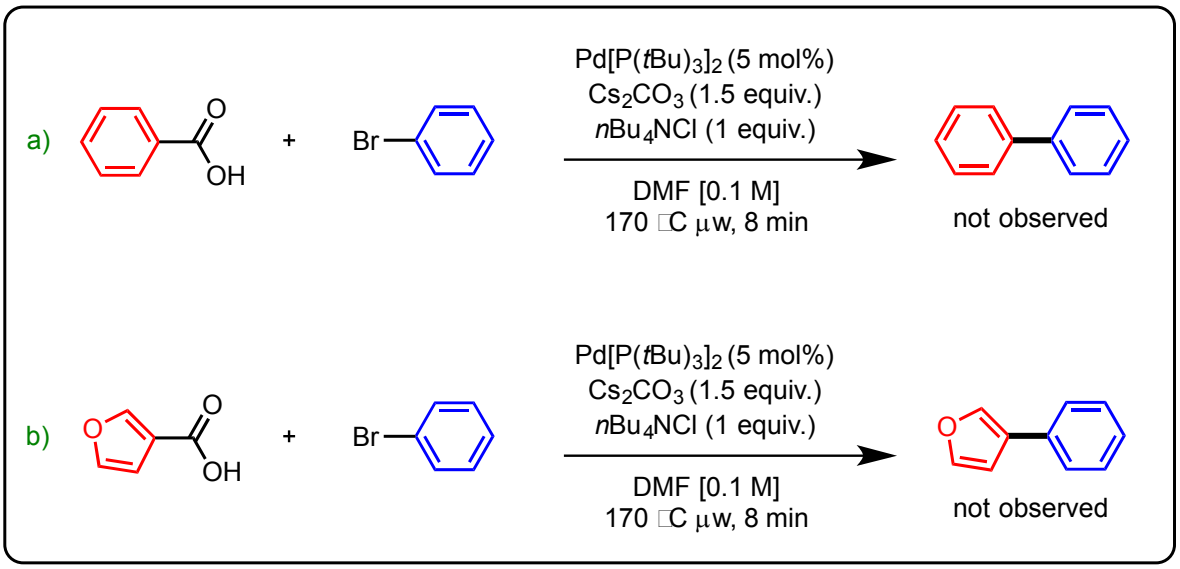


Figure 24. Application of Forgione-Bilodeau Methodology to a)benzoic acids, b)hetero-3-carboxylic acids

Eliminating the possibility of direct decarboxylation, path B was hypothesized to be the main pathway for the catalytic cycle, upon electrophilic palladation to yield intermediate **52** it can undergo decarboxylation followed by reductive elimination to produce the desired compound **51**. Path C was proposed in order to justify the side product obtained which contained two aryl groups attached to the heterocycle. Upon formation of **53**, depending on the substituent attached to the carbon with a bond to the palladium, it could either undergo migration from C3 position to C2 position resulting in the formation of **52** and following the rest of the cycle to generate the heterocyclic compounds with one aryl group attached or in the cases where the substituent attached is hydrogen, it could undergo re-aromatization **54** which would then undergo reductive elimination to reintroduce palladium into the catalytic cycle along with the arylated heterocyclic compound which still contains the carboxylate moiety **55** which could then re-enter the catalytic cycle and produce the diarylated heterocyclic compound.

1.3.2.3. Desulfinative cross-coupling

Similar to the decarboxylation reactions, cross-coupling reactions can also be carried out employing sulfinate salts. The similarity between sulfinate group and carboxylate renders similar chemoselectivity to these reactions. Furthermore, the by-product SO_2 gas is easier to extrude from the reaction mixture.[53–56]

These sulfinate salts are highly versatile reagents capable of participating in cross-coupling reactions either as a nucleophilic or electrophilic coupling partners depending on the reagents applied and the reactants present. The application of desulfinative cross-coupling reactions can be dated back to 1970, displayed by Garves and coworkers[57] (Figure 25). Utilization of the sulfinate salts **56** for homocopling reactions to form biaryl motifs **57** along with their ability to participate in Heck-like reactions with **58** have been demonstrated (Figure 25, c)[57].

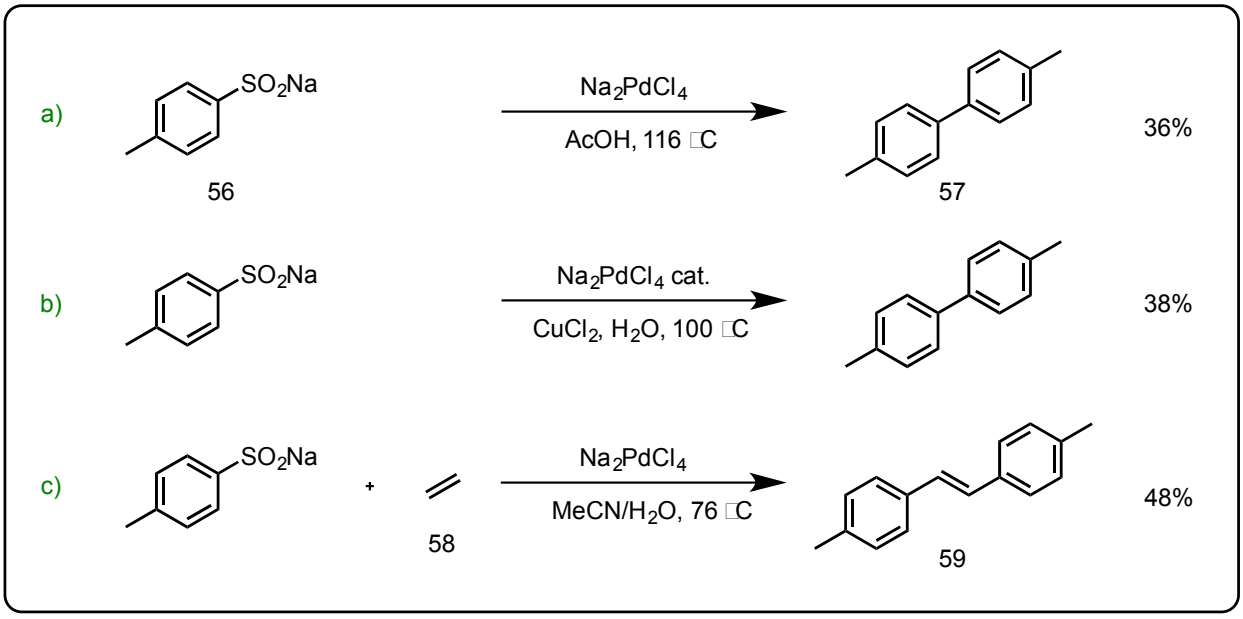


Figure 25. Garves 1970: Early examples of desulfinative cross-coupling

Sulfinate salts hold the potential to be employed as electrophilic coupling partners in cross-coupling reactions. Their applicability in oxidative heck reactions and direct arylation *via* C-H activation has been demonstrated by Deng and coworkers[55,58] (Figure 26).

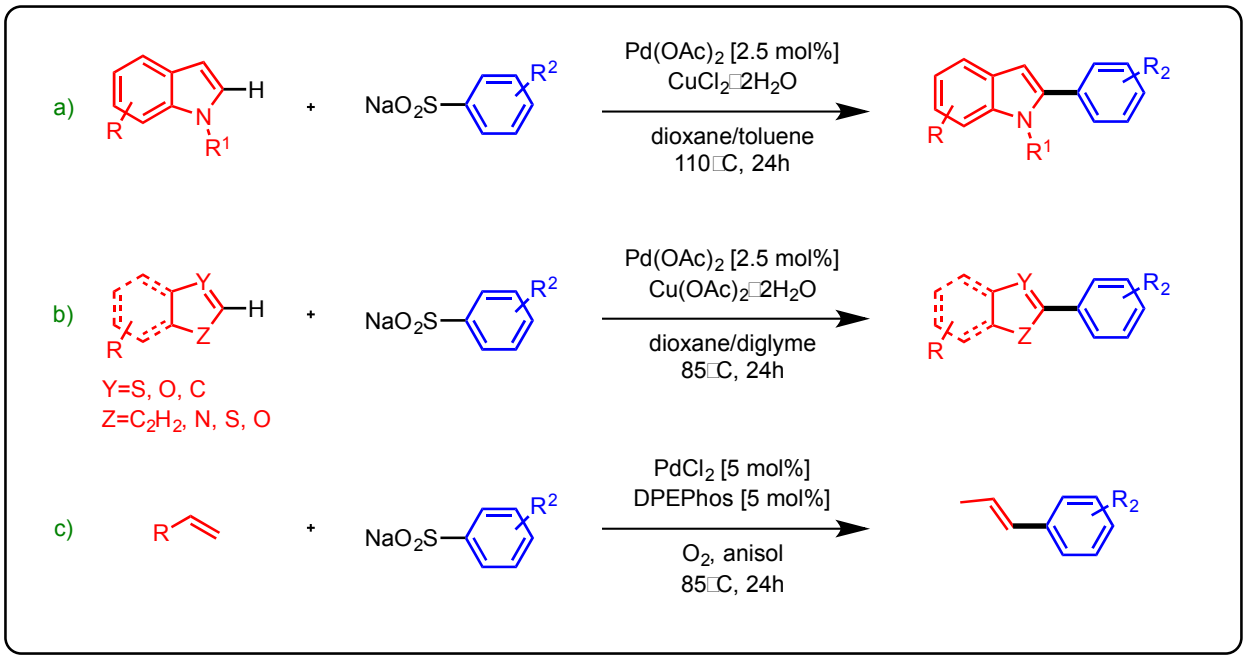


Figure 26. Deng methodology for desulfinative cross-coupling

Although effective electrophilic coupling partners, sulfinate salts also posses the ability to participate in a reaction as a nucleophilic species. Early demonstration of their use as nucleophilic coupling partners was done by Sato and Okoshi[59] (Figure 27). In their patent sulfinate salts were utilized as coupling partners in reactions with aryl bromides, establishing their ability to part take in cross-coupling reactions as nucleophilic coupling partners.

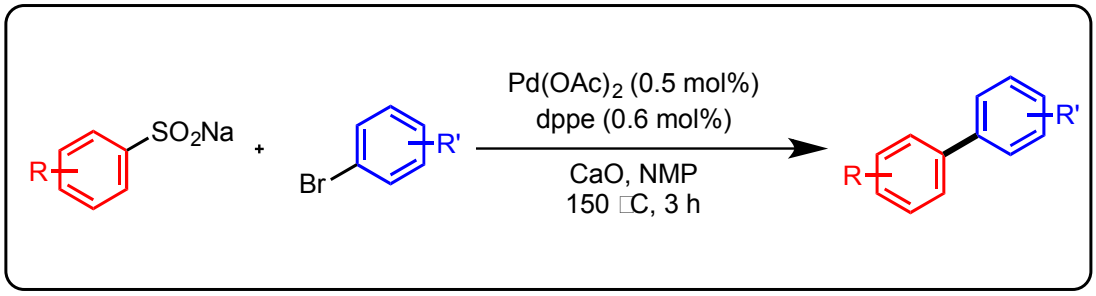


Figure 27. Sato and Okoshi desulfinative reaction

Growing interests in these salts have escalated over the recent years. In 2012, Duan and coworkers[60] have demonstrated a method that utilizes these salts in cross-coupling reactions with aryl triflates. Although a proof of concept was demonstrated (Figure 28), the methodology

required electron-rich sulfinate salts and electron-deficient aryl triflates in order to maintain high yields.

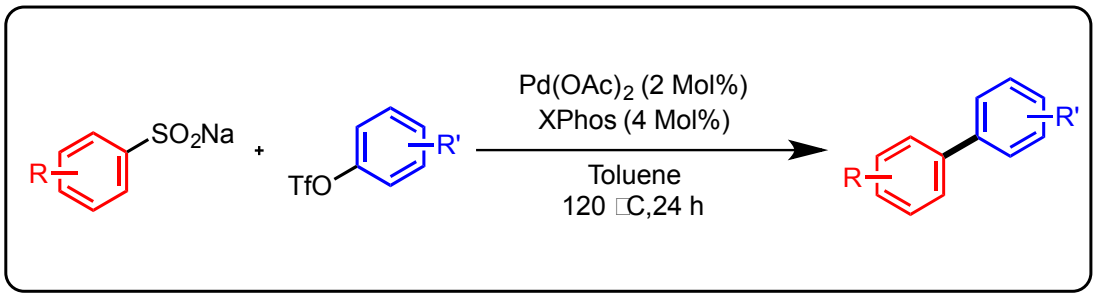


Figure 28. Duan methodology

The scope of sulfinate salts as nucleophilic coupling partners was further broadened by Forgione and coworkers[61]. Developing a method for the coupling of sulfinate salts with aryl bromides for the formation of biaryl compounds (Figure 29). Although the method was applicable to a wide variety of sulfinate salts and aryl bromides, higher yields were obtained when electron deficient aryl halides and electron rich sulfinate salts were employed.

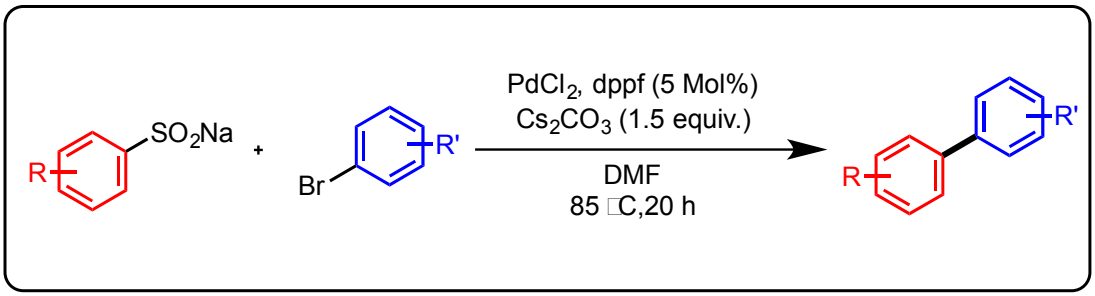


Figure 29. Forgione methodology

Further developments by Forgione and coworkers has demonstrated the possibility of using sulfinate salts as nucleophilic partners in cross-coupling reactions with heterocycles (Figure 30)[56].

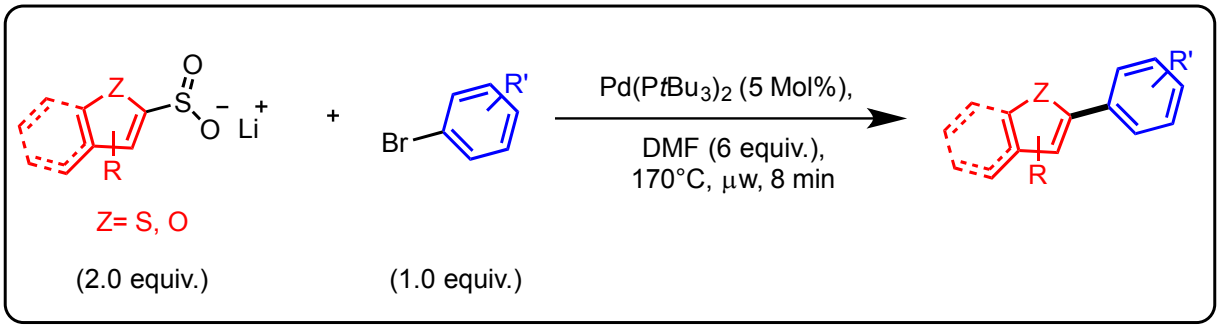


Figure 30. Forgione methodology for heteroaromatic sulfinate salts cross-coupling

Parallel to the decarboxylative work, Forgione and coworkers have demonstrated multiple ways for the synthesis of aryl-aryl or heteroaryl-aryl moieties. The catalytic cycle proposed for the cross-coupling of sulfinate salts is highly similar to that of the decarboxylative cross-coupling (Figure 31).[56] Like a typical palladium cycle, the first step is the oxidative addition (Figure 31, Step A) of the palladium (0) to aryl bromide followed by the ligand exchange (Figure 30, Step B) between the palladium complex formed and sulfinate salt. Upon this point onwards two pathways were proposed to generate intermediate **I**. Path A being the direct extrusion (Figure 31, Step C) of SO_2 while path B involves the electrophilic aromatic substitution (Figure 31, Step D) at the carbon attached to the sulfur generating intermediate **II** (Figure 31, II) which can then undergo SO_2 extrusion (Figure 31, Step E). When compared to the removal of CO_2, the extrusion of SO_2 is easier hence providing an advantage to the desulfinative cross-coupling reactions when compared to the decarboxylative cross-coupling reactions. Regardless of the path taken the cycle is completed with the reductive elimination (Figure 31, Step F) forming the desired product and reintroducing the active palladium species into the cycle.

Compared to decarboxylative cross-couplings, desulfinative cross-coupling reactions are as selective and effective. Furthermore, the ability of the desulfinative cross-coupling to tolerate aqueous media and the absence of co-catalyst, base or additive renders this methodology more environmentally friendly.

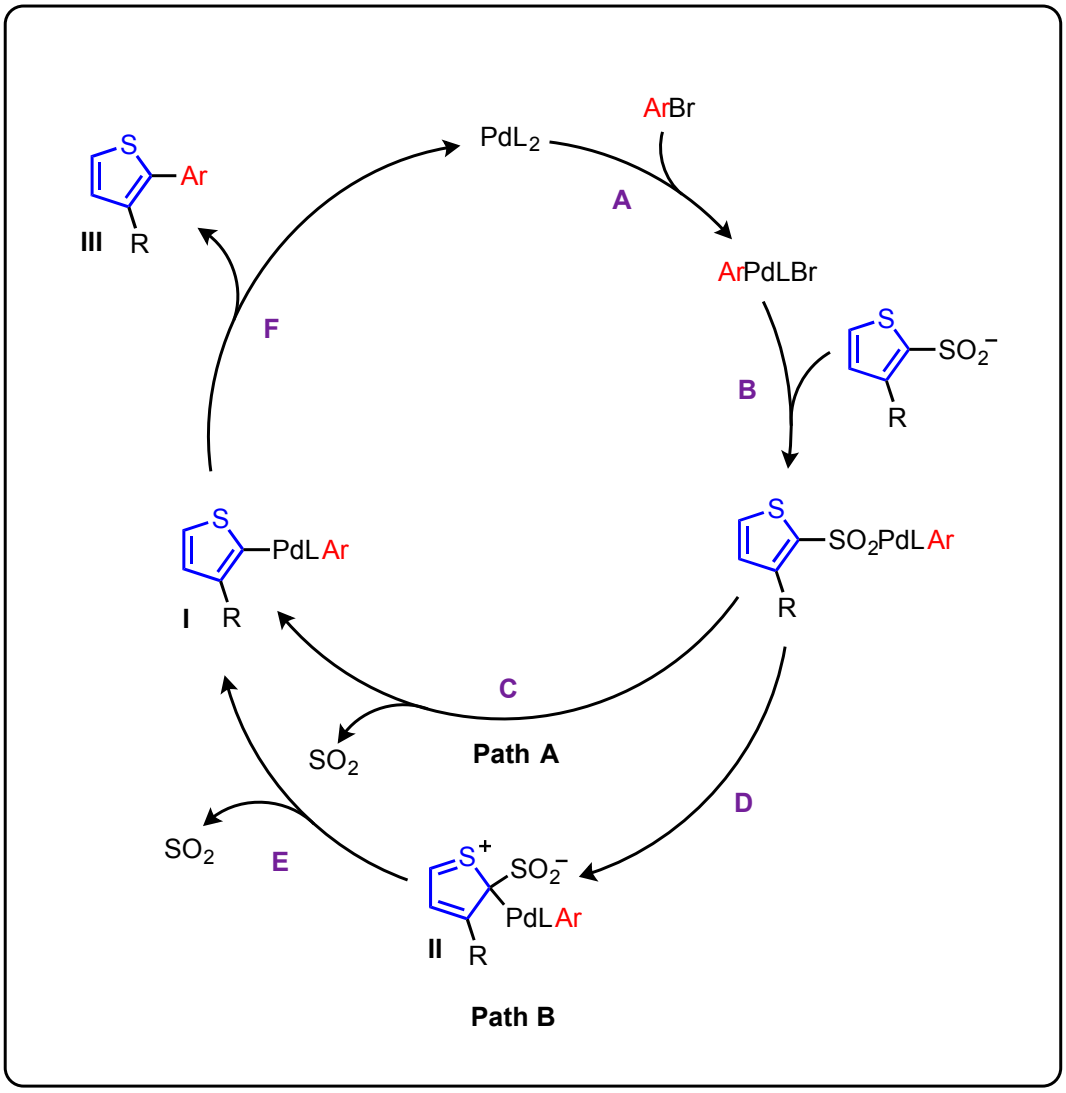


Figure 31. Forgione methodology desulfinative cross-coupling proposed mechanism

1.4. Diaryliodonium salts

The story of organic hypervalent iodine compounds start at 1886, with the discovery of (dichloroiodo)benzene by German chemist Willgerodt obtaining yellow needles of this compound that began a new field of research[62]. Soon after, the discovery of various other organic hypervalent iodonine compounds by Willgerodt[63] and Victor Meyer[64], such as, *iodosyl-, iodyl-iodoxy*-benzene and diphenyliodonium salts, enlarged the scope of this class of compounds. A comprehensive list of organic hypervalent compounds synthesized in the early 19th century was published by Willgerodt[65], however, the first spark in the field of organic hypervalent iodoine compounds unfortunately did not last long and around the era of First World War research in the

field was minimal. Generally iodonium salts (Figure 32) consist of iodine(III) attached to two aryl groups and a counter ion. Depending on the aryl substituents the salts can be referred to as symmetric or unsymmetric. Symmetric when both aryl groups are the same and unsymmetric when the aryl groups are different.

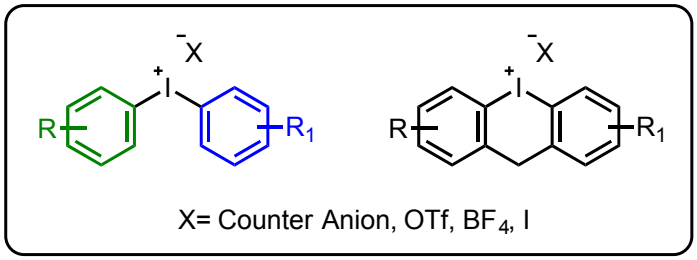


Figure 32. General structure of diaryliodonium salts

Frederick Marshall reignited the flame post World War II during 1950s. Development of different synthetic routes to access these compounds along with their early applications in organic chemistry was demonstrated.[66] First synthesized by Victor Meyer[64,67] and later optimized to one-pot synthesis by Beringer (Figure 33, a) in the 1950s laid the foundation for the synthesis of these class of compounds.

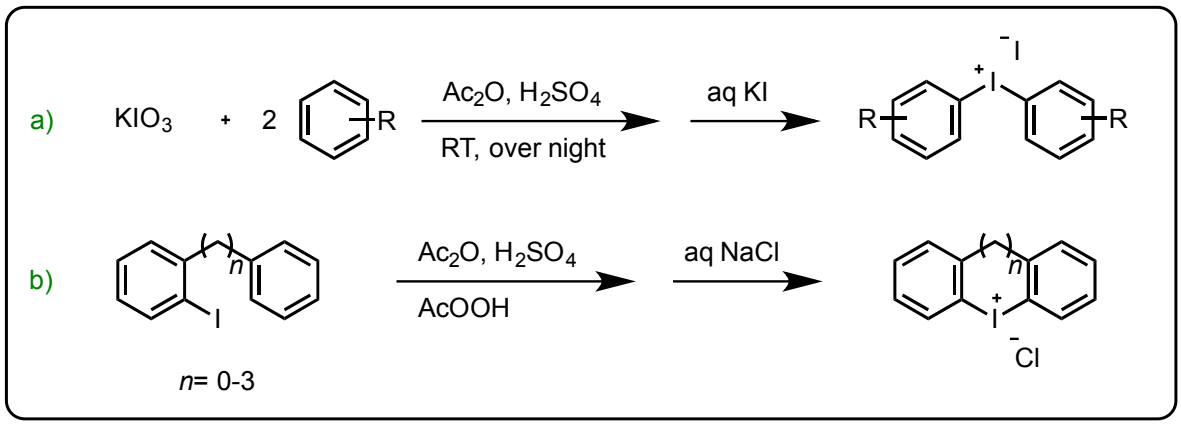


Figure 33. One-pot syntheses of diaryliodonium salts from aryl iodides

Following Beringer, in 1956 Sandin and coworkers reported the synthesis of cyclical iodonium salts. Through exposure of 2-iodobiphenyl and similar compounds to peracetic acid followed by sulfuric acid, ring closure was achieved (Figure 33, b)[68]. This discovery was an excellent addition to the scope of organic hypervalent iodine compounds. Further developments for the

synthetic pathways to achieve diaryliodonium salts have been demonstrated by various research groups[65]. Unfortunately this was not enough to impress a large population of the scientific community. This all changed when in 1980s Dess-Martin periodinane (DMP) was discovered by Dess and Martin[69]. This discovery enabled organic hypervalent iodine compounds to commonly be used in organic reactions, thus obtaining a place in the scientific community.

Over the recent years, as the utility of diaryliodonium salts were revealed, several other methodologies were developed in order to synthesize a wide variety of these compounds to be utilized in multiple fields. Amongst many research groups, Olofsson and coworkers demonstrated the various synthetic methods for these salts.[65,70–74] A simple one-pot method applicable to the synthesis of a plethora of symmetric and unsymmetric diaryliodonium salts, mainly containing triflate anions. The general methodology employs *m*CPBA as the oxidant and triflic acid for the activation of the oxidant and introduction of the anion (Figure 34, a). The methodology was then extended and utilized for the formation of diaryliodonium salts from iodine and arenes (Figure 34, b). Although only applicable to symmetric salts along with higher amounts of reagents required, this method was still highly interesting as it is applicable to sterically hindered aryl groups.

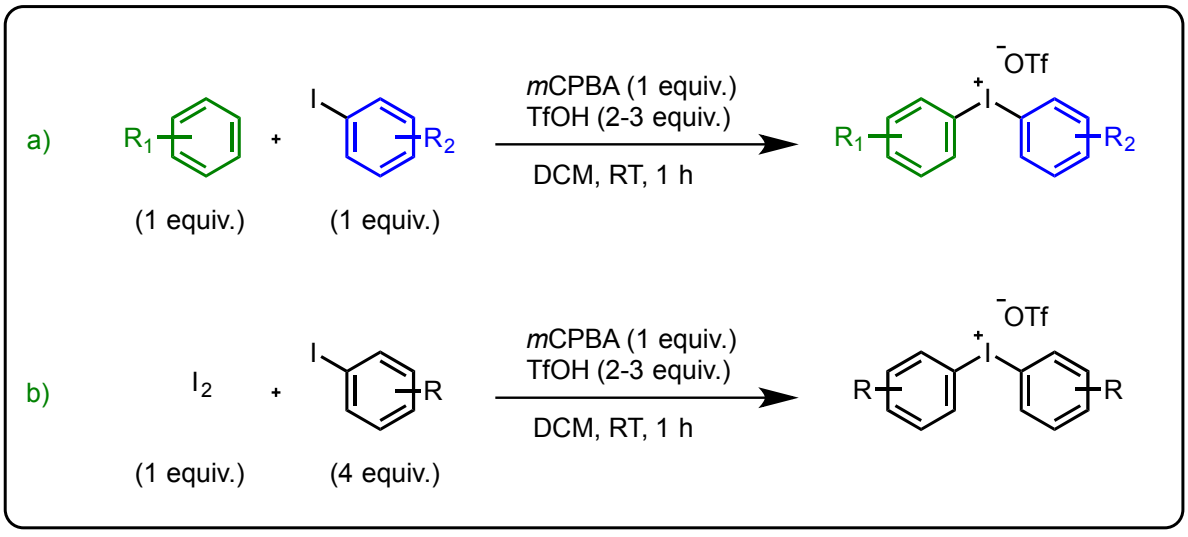


Figure 34. Olofsson methodology for the synthesis of diaryliodonium triflates

Over the past decades, diaryliodonium salts have attracted significant attention as a general reactant in organic reactions mostly as supplementary coupling partner to overcome certain limitations encountered by aryl halides. An interesting feature of the unsymmetric salts is the fact that one of them is designed to be a leaving group, also referred to as a dummy group. Through controlling the electron richness of the aryl groups it is possible to selectively transfer one aryl group. In cases where aryl halides are used as coupling partners, the halide is the leaving group. In the case of diaryliodonium salts the leaving group is iodo-aryl which is a better leaving group in comparison to the halide itself hence potentially providing energetic advantage in the reactions they are employed.[75] Furthermore the presence of the counter ion enables the tuning of the solubility and reactivity of these compounds.

Even though research in the field of organic hypervalent iodine compounds has been like ocean tides with certain highs and lows based on the amounts of work being published, since their discovery they have demonstrated to be useful building blocks and highly applicable in organic synthesis. Their reactivity includes α-arylation of carbonyl compounds, arenes, alkynes, and alkenes[75]. Although these are metal catalyzed reactions, diaryliodonium salts also undergo metal free cross-coupling reactions such as the arylation of heteroatom nucleophiles[76].

Several research groups have demonstrated the use of diaryliodonium salts in several different types of metal-catalyzed organic reactions. They are highly effective in arylation of malonates (Figure 35, A)[77]. They can also be employed in Heck-type cross-coupling reactions requiring significantly reduced reaction time (Figure 35, B)[78] and carbonylative Stille-type cross-coupling reactions (Figure 35, C)[79]. Furthermore, they can be used to over come the limitation of aryl iododies in Sonagashira-type cross-coupling reactions (Figure 35, D)[80].

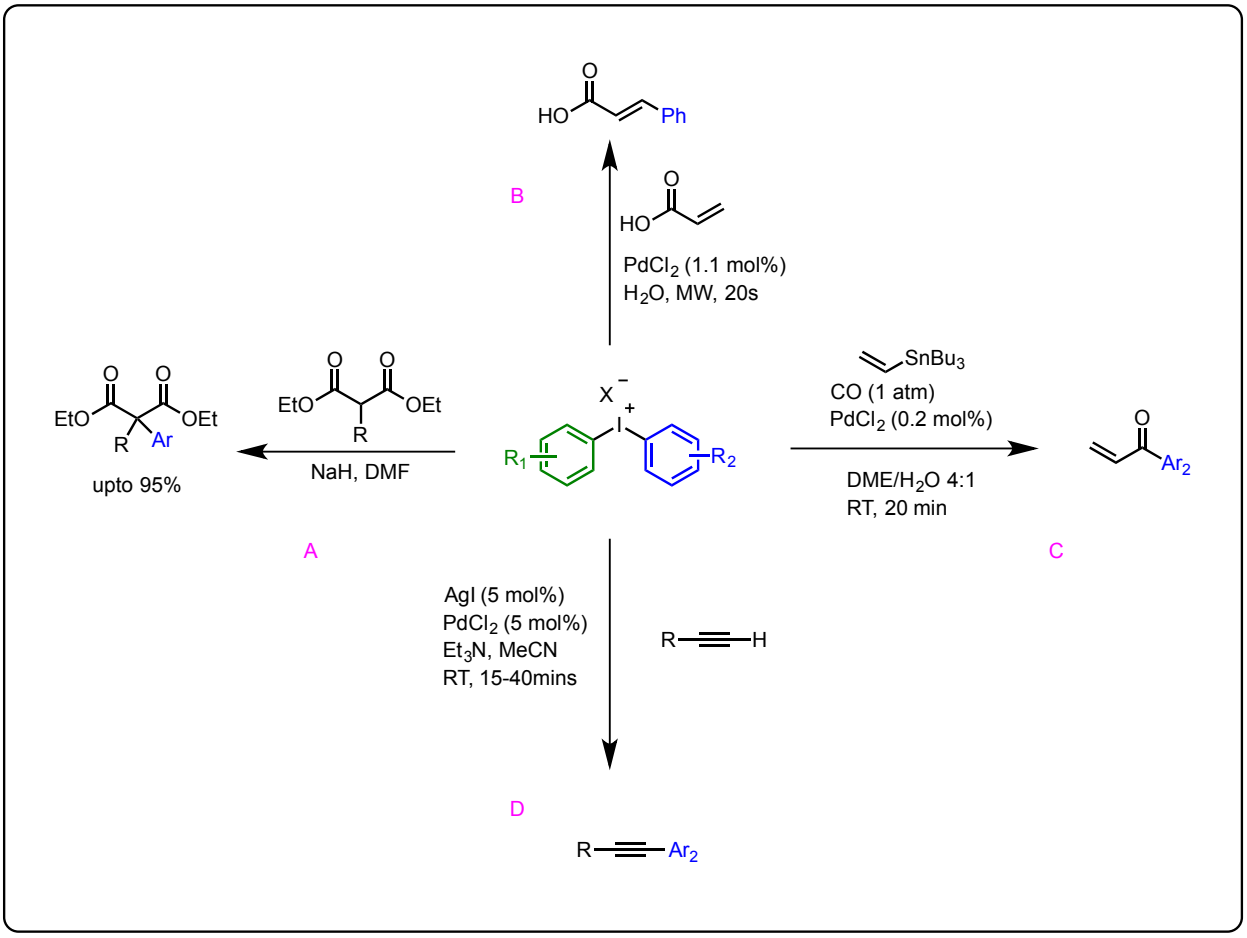


Figure 35. Reactions of diaryliodonium salts

Zhu and coworkers[78] have demonstrated the applicability of diaryliodonium salts to Heck-type coupling reactions (Figure 35, B). The method employs very low amount of catalyst loading, requires extremely short amount of reaction time, and can be carried out in water.

These salts are also able to participate in cross-coupling reactions with arylboronic acids, thus going under Suzuki-type reactions. Demonstrated by Ho and coworkers (Figure 36, a) diaryliodonium salt, **61**, can be employed in cross-coupling reactions with boronic ester, **60**, to yield biaryl motif **62** in excellent yields.[81] Furthermore, the possibility of forming aryl-heteroaryl motifs, **64**, through the use of iodonium salt **63** is also possible through this methodology (Figure 36, b).

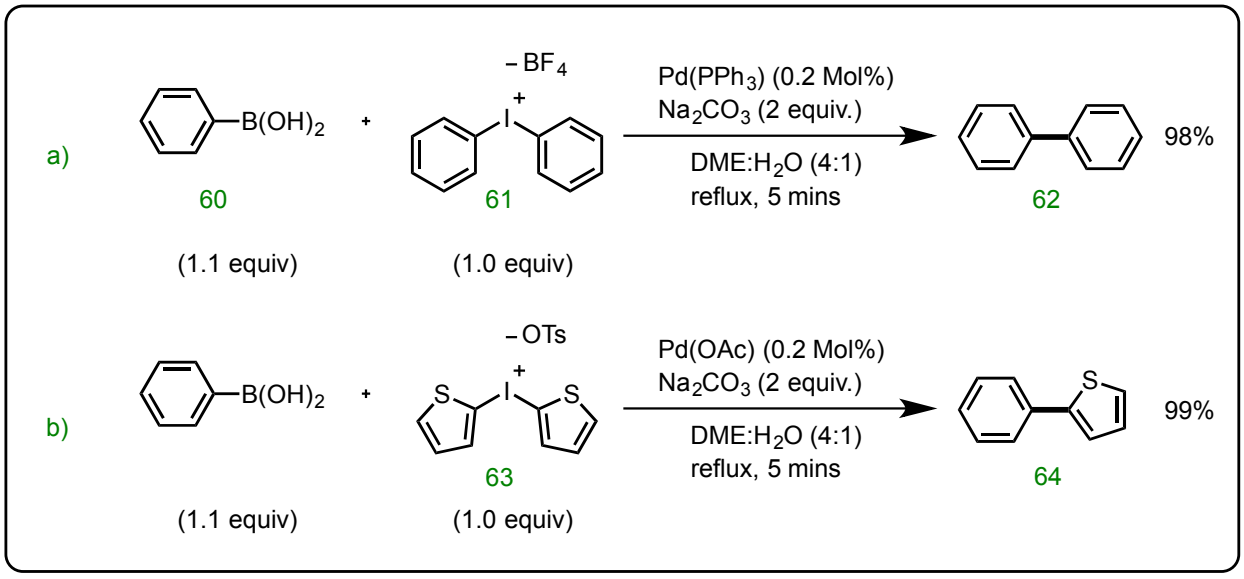


Figure 36. Suzuki coupling of diaryliodonium salts

1.4.1. Decarboxylative reactions of diaryliodonium salts

Diaryliodonium salts have been shown to be a compatible reactant for decarboxylative cross-coupling reactions. Soon after developing the methodology for the cross-coupling of benzoic acid derivatives for aryl iodides, Becht and coworkers extended their methodology by utilizing diaryliodonium salts as the electrophilic coupling partner as opposed to the aryl iodides (Figure 37, a)[43,82]. The advantage of the iodonium salts in comparison to the aryl iodide is in the difference between the leaving groups. In the case of aryl iodides the leaving group in the course of the reaction is the halide species while in the case of the iodonium salts it is an aryl iodide.

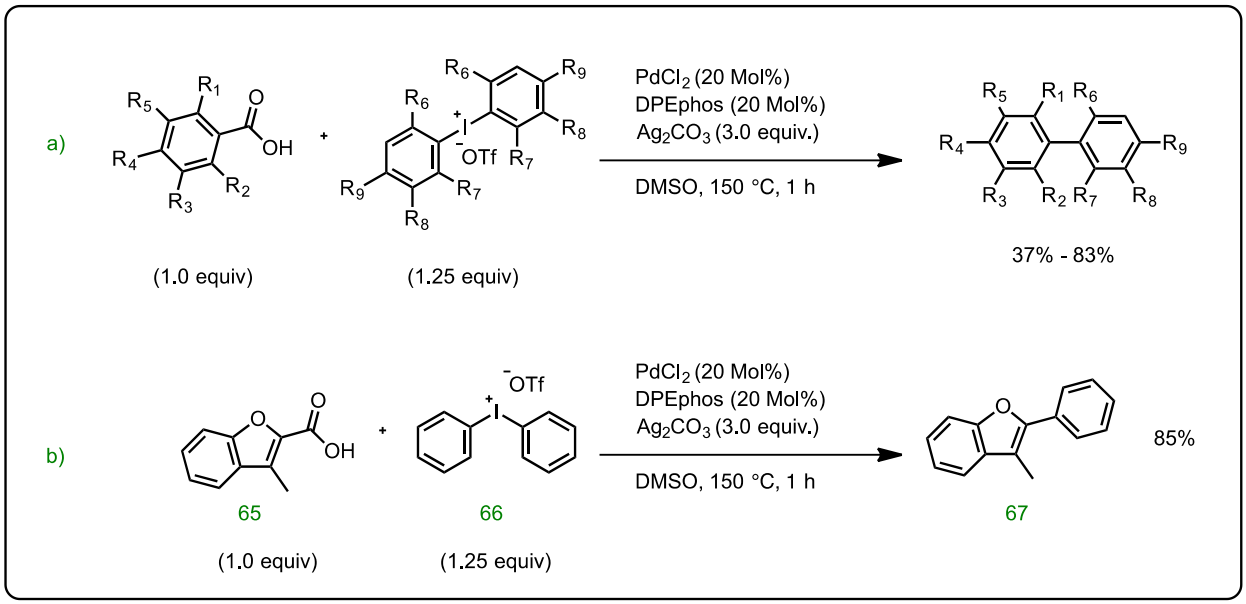


Figure 37. Becht protocol for decarboxylative cross-coupling reactions of diaryliodonium triflates

Although the methodology requires a large amount of catalyst loading, it has been a good addition to the repertoire of decarboxylative cross-coupling reactions for the formation of aryl-aryl motifs. Becht and coworkers have subjected the diaryliodonium salts to their developed methodology to assess the tolerance of the method to a variety of substrates. They have establishied a proof of concept for the application of diaryliodonium salts in decarboxylative cross-coupling reactions with heteroaromatic systems, by demonstrating the reaction of **65** with **66** resulting in the formation of **67** with 85% yield. However, they have not examined the incorporation of the heteroaromatic acids to the methodology or have a wide enough scope to evaluate the diversity of the methodology. The importance of heteroaromatic compounds can not be expressed enough, hence, having methodologies for their preparation is of interest. Given the improvements in the field of cross-coupling reactions and the trend in decarboxylative cross-couplings the development of such methodology for the cross-coupling reactions of 5-membered heteroaromatic acids with diaryliodonium salts would be beneficial to the scientific community and will help to further diversify the tool box of reactions at the disposal of researchers.

1.4.2. Desulfinative reactions of diaryliodonium salts

Although there is a plethora of reactions displaying the versatile applicability of diaryliodonium salts in organic reactions, their cross-coupling with sulfinate salts has not been investigated to date. Desulfinative cross-coupling reactions have been proven to be versatile methods accommodating a large variety of reactants and effectively prepare desired compounds in a greener manner. In order to exploit the applications of these salts, a methodology utilizing both could prove to be a modern and efficient method for the preparation of heteroaryl moieties.

1.5. Research objectives

The developed methodologies for the cross-coupling reactions thus far have been dominated by the use of aryl-halides as a coupling partner. Even though they are highly applicable with a variety of reactions they too suffer from certain limitations such as lack of reactivity depending on the substituent attached at the aryl ring. To overcome these limitations and expand the tool kit of applicable coupling partners in cross-coupling reactions, diaryliodonium salts will be investigated as electrophilic cross-coupling partners in the reactions involving five membered heteroaromatic carboxylic acids and sulfinate salts.

Chapter 2. Decarboxylative cross-coupling reactions of diaryliodonium triflates with heteroaromatic carboxylic acids

2.1. Abstract

Biaryl compounds bearing heteroaromatic ring have been shown to play a crucial role in several disciplines. Although effective, classical synthetic routes for the formation of these motifs involve the use of potentially dangerous organometallic compounds. More recently, attention has been turned towards the development of more efficient novel methodologies employing milder reaction conditions and environmentally safe compounds. Herein, we discuss new synthetic routes to form aryl-heteroaryl motifs in a simple yet efficient manner through the use of diaryliodonium salts and heteroaryl carboxylic acids as coupling partners.

2.2. Decarboxylative cross-coupling reactions of diaryliodonium triflates

The emergence of decarboxylative cross-coupling reactions for the synthesis of aryl-aryl or aryl-heteroaryl compounds has been a step towards greener methodologies in cross-coupling reactions. Due to their advancements, it is in the interest of the scientific community to explore these types of reactions to accommodate a broad scope of compounds that can part take in decarboxylative cross-coupling.

Formation of heteroaryl compounds through decarboxylative cross-coupling of 5-membered heteroaromatic acids with aryl halides has been established by Forgione and coworkers (Figure 38).[45] The method is applicable to a wide variety of coupling partners forming desired compounds with moderate to excellent yields. In effort to further improve the existing methodology, diaryliodonium salts as a replacement of aryl halides has been examined. Initiation of screening for cross-coupling of diaryliodonium salts with 5-membered heteroaromatic acids was achieved through the employment of existing reaction conditions (Figure 37). Each reaction component was then optimized for the incorporation of diaryliodonium salts or aryl halide replacements in decarboxylative cross-coupling reactions.

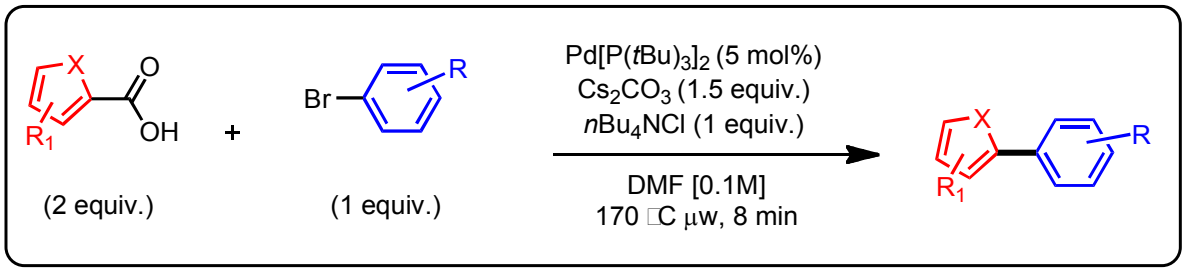
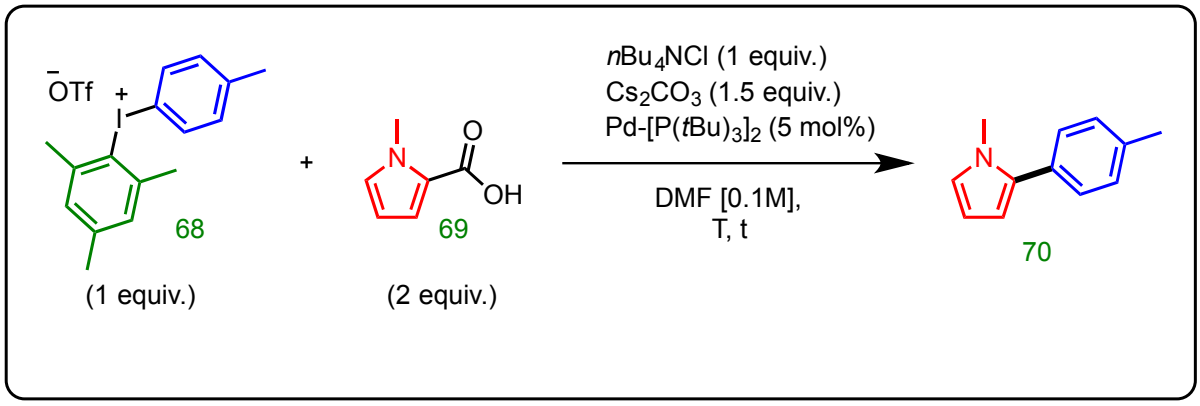


Figure 38. Forgione-Bilodeau methodology

2.2.1. Time and temperature screening

Optimization of reaction conditions was performed on the coupling of *N*-methylpyrrole-2-carboxylic acid, **68** and (4-methylphenyl)(2,4,6-trimethylphenyl)iodonium triflate, **69**. Utilizing the already reported methodology[45], optimization of reactions conditions was initiated by the adjustment of time (t) and temperature (T) (Scheme 1).



Scheme 1.Optimization of time and temperature

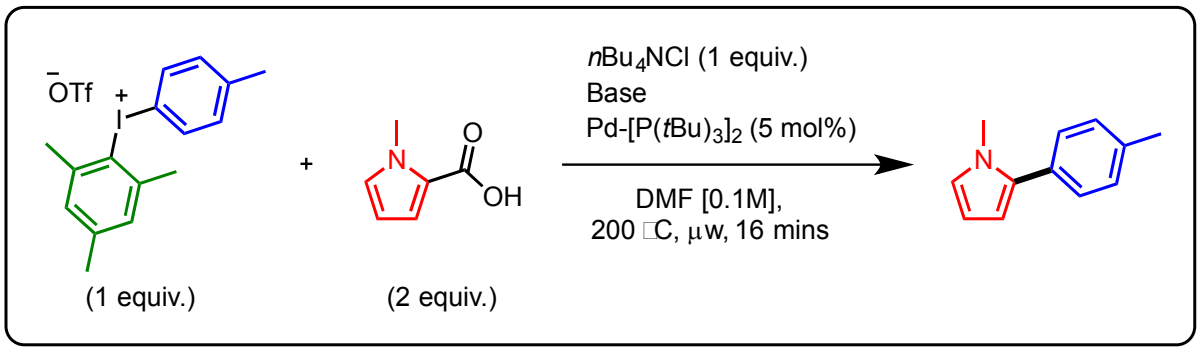
Starting from 170 °C, with the aim of making the reactions greener, the temperature was lowered. Not observing an increase in yield, the temperature was then increased, as shown in table 1 below. Higher temperatures seemed to be better in terms of the yields obtained. Next the time was increased and optimal time and temperature was determined to be 200 °C and 16 minutes.

Table 1. Time and Temperature Screening

Entry	Heating Method	T (°C)	Time (t)	Yield
1	μw	170	8 mins	55%
2	μw	180	8 mins	55%
3	μw	190	8 mins	64%
4	μw	200	8 mins	65%
5	μw	200	16 mins	75%
6	μw	200	32 mins	60%
8	Δ	200	24 h	36%

2.2.2. Base screening

Following the optimization of time and temperature, optimization of base employed was examined next (Scheme 2). The existing methodology employed Cs_2CO_3, during reaction optimization this base resulted in a 75% yield (Table 2, entry 1).



Scheme 2.Screening of different base

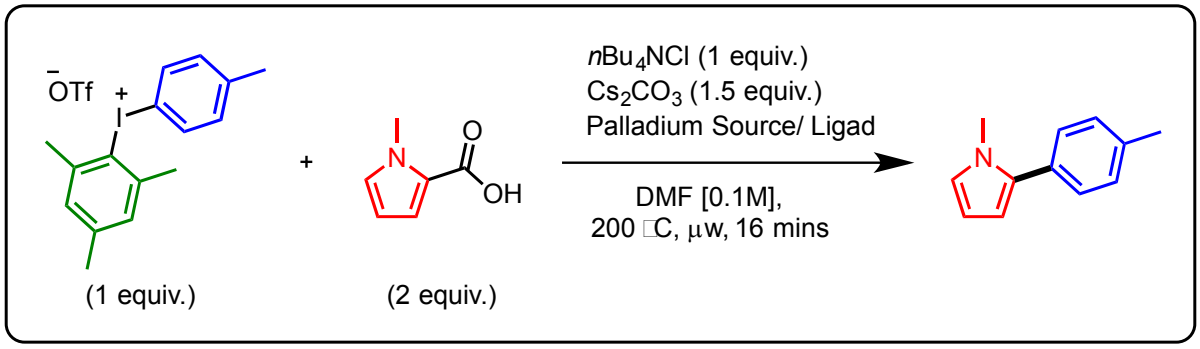
Deprotonation of the carboxylic acid aids the decarboxylative step and the extrusion of CO_2 from the reaction mixture therefore, a base was added to the reaction.[45,83] Since the existing method employed carbonate base, the screening for base optimization was initiated with a set of carbonate bases. Although Ag_2CO_3 resulted in a drastic decrease in yield, 30 % (Table 2, entry 2), Na_2CO_3 caused a decrease in yield as well (Table 2, entry 3). Having no increase in yield with carbonate bases, next a set of non-carbonate bases were screened. However, KOAc (Table 2, entry 4), *t*BuOK (Table 2, entry 5), NaOEt (Table 2, entry 6) and NEt_3 (Table 2, entry 7) did not result in an increase in yield.

Table 2. Results for base screening

Entry	Base	Yield
1	Cs_2CO_3	75%
2	Ag_2CO_3	30%
3	Na_2CO_3	62%
4	KOAc	46%
5	*t*BuOK	53%
6	NaOEt	33%
7	Et_3N	49%

2.2.3. Catalyst screening

Having screened time, temperature and base, next was to study the effects of different catalyst on the yield of the reaction (Scheme 3). The existing method employed $Pd[P(tBu)_3]_2$, a preformed catalyst. Using this catalyst resulted in 75% yield. (Table 2, entry 4).



Scheme 3.Screening of different catalysts

The instability of the catalytic source would be a potential drawback of the method; hence attention was given to a catalytic system that consisted of the palladium source and a ligand in order to form the active catalytic species *in situ*. A series of monodentate and bidentate ligands with various electronic and steric properties were screened for the generation of the catalyst. The screening was initiated with carrying out the reaction with $PdCl_2$ (Table 3, entry 1) and using no ligand. The use of 200 °C in microwave could potentially produce the active palladium species (Pd(0)) by reduction of $PdCl_2$. This indeed seems to work, since the reaction yielded 70%, which is similar to the previous yield of 75%. Using a ligand for the reduction of the palladium however is more effective, the best combination being $PdCl_2$ and dppf (Table 3, entry 2) producing a 77% yield. It was of interest to find a catalytic system that utilized $PdCl_2$ as it is one of the cheaper sources of palladium, hence a wide library of phosphine-based ligands were tested to determine the optimum metal-ligand combination that would result in higher yields. Ligand screening with $PdCl_2$ as the metal source is summarized in Table 3 (entries 3-18). Unfortunately none of the combinations resulted in an increase in yield. Therefore, the screening was continued by varying the palladium source. The next catalyst tested was $Pd(acac)_2$ alone (Table 3, entry 19) that provided an interesting yield of 77%.

Table 3. Results for catalytic system screening

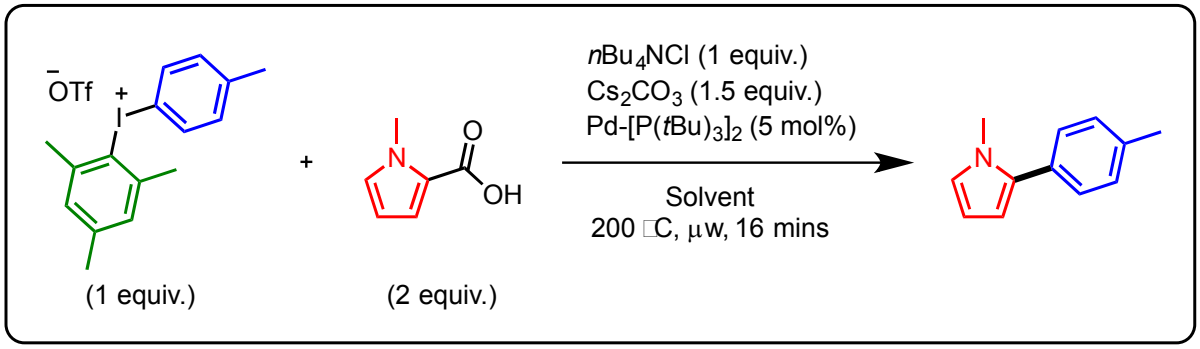
Entry	Catalyst + Ligand	Yield	Entry	Catalyst + Ligand	Yield
1	$PdCl_2$	70%	19	$Pd(acac)_2$	77%
2	$PdCl_2$ + dppf	74%	20	$Pd(acac)_2$ + dppf	70%
3	$PdCl_2$ + Johnphos	53%	21	$Pd(acac)_2$ + Johnphos	50%
4	$PdCl_2$ + *t*-Bu-Mephos	63%	22	$Pd(acac)_2$ + *t*-Bu-Mephos	64%
5	$PdCl_2$ + *t*-Bu-Xphos	42%	23	$Pd(OAc)_2$ + dppf	72%
6	$PdCl_2$ + PPh_3	53%	24	$Pd(OAc)_2$ + Johnphos	40%
7	$PdCl_2$ + $HP(tBu_3)_3BF_4$	42%	25	$Pd(OAc)_2$ + *t*-Bu-Mephos	50%
8	$PdCl_2$ + $HPCy_3BF_4$	21%	26	$Pd(OAc)_2$ + PPh_3	65%
9	$PdCl_2$ + CyJohnPhos	37%	27	$Pd(OAc)_2$ + Mor-DalPhos	75%
10	$PdCl_2$ + Xphos	26%	28	$Pd(dba)_2$	51%
11	$PdCl_2$ + MePhos	42%	29	$Pd(dba)_2$ + dppf	49%
12	$PdCl_2$ + Mor-DalPhos	60%	30	$Pd(dba)_2$ + Johnphos	67%
13	$PdCl_2$ + SPhos	*	31	$Pd(dba)_2$ + *t*-Bu-Mephos	67%
14	$PdCl_2$ + Davephos	*	32	$Pd(TFA)_2$ + JohnPhos	48%
15	$PdCl_2$ + P(o-tolyl)$_3$	*	33	$Pd(TFA)_2$ + *t*-Bu-Mephos	61%
16	$PdCl_2$ + Ph-DavePhos	*	34	PdI_2 + JohnPhos	48%
17	$PdCl_2$ + DPEPhos	*	35	PdI_2 + *t*-Bu-Mephos	54%
18	$PdCl_2$ + RuPhos	*	36	$Pd(PPh_3)_4$	45%

***Trace amounts of product observed**

Further trials with $Pd(acac)_2$, $Pd(OAc)_2$, $Pd(dba)_2$, $Pd(TFA)_2$, PdI_2, and the preformed $Pd(PPh_3)_4$ were investigated resulting in an extensive library of catalytic systems. Unfortunately no other combination of catalytic system could increase the yield significantly when compared to $Pd[P(tBu)_3]_2$. Hence, further reaction were performed using $Pd[P(tBu)_3]_2$ as the catalyst.

2.2.4. Solvent screening

Next the effect of different solvents was examined. The solvent contributes to the medium polarity and the solubility of compounds in the reaction mixture, hence a screening was performed in order to examine these effects in an attempt to increase the overall yield of the reactions.



Scheme 4.Screening of different solvents

The initial reaction conditions from literature employed DMF as the solvent.[45] When diaryliodonium triflates were subjected to the reaction in DMF, the yield obtained was between 75% - 77%. In an effort to increase the yield, solvents with various polarities were tested. Changing the solvent to the highly polar and coordinating DMSO (Table 4, entry 2) resulted in 12% yield. Since the increase in polarity of the solvent did not cause an increase in the yield, screening of the reaction conditions were continued by gradually lowering solvent polarity. Using un-dried DMF that contains water in approximately 3:1 ratio (DMF:H_2O) lowered the yield greatly. This result could be ascribed to the degradation of the iodonium salts in water to give phenols and unidentified side products. *N*-methylpyrrolidone (NMP) and dimethylacetamide (DMA) provided similar yields of 50% and 68%, respectively. Attempting the reaction in the strongly coordinating acetonitrile greatly reduced the yield to 20% while the slightly less polar and less coordinating THF did not improve the yield beyond 38%.

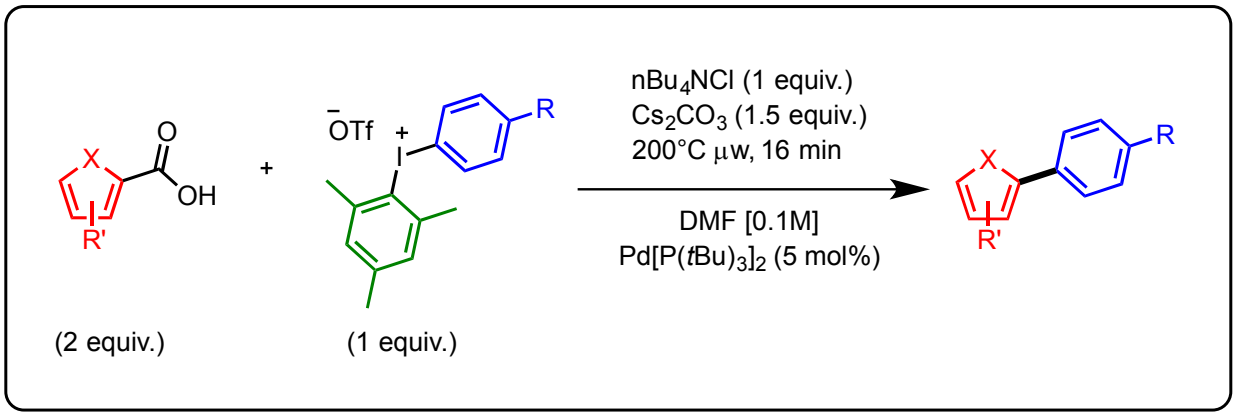
Surprisingly, xylenes, the least polar solvent in the series, provided the product in 60% yield. In conclusion, DMF provided the highest yield and was chosen as the solvent for the subsequent coupling reactions.

Table 4. Results for solvent screening

Entry	Solvent	Yield	Entry	Solvent	Yield
1	DMF	75%	5	DMA	68%
2	DMSO	12%	6	Acetonitrile	20%
3	DMF:H_2O (3:1)	10%	7	THF	34%
4	NMP	50%	8	Xylenes	60%

2.2.5. Substrate scope

Following the screening of the reactions conditions, it was concluded that the optimal reactions conditions that result in high and reproducible yields were very similar to the existing reported method (Scheme 5)[45].



Scheme 5.Optimized reaction conditions

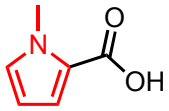
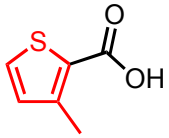
The methodology developed by optimizing the cross-coupling reaction of *N*-methylpyrolle-2-carboxylic acid and the iodonium salt containing a mesitylene dummy group and toluene coupling-partner. Having established the optimized conditions substrate scope was performed next.

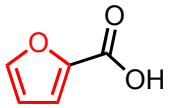
A variety of diaryliodonium salts containing mesitylene as a dummy group and another aryl moiety containing substituents with varying electronic properties were selected for the screening (Scheme 5 and Table 5). The purpose of the dummy group is to facilitate the oxidative addition of Pd(0) species by being a favourable leaving group in comparison to a halide when aryl-halides are employed, in this way enabling a facile attachment of the other aryl moiety of the diaryliodonium salt, commonly referred to as attaching group.

When subjecting *N*-methylpyrolle-2-carboxylic acid to diaryliodonium triflate derivatives with varying functional groups (Table 5, entry 1-5) higher yields were obtained for substrates with electron-rich substituent such as CH_3 (Table 5, entry 4) and OMe (Table 5, entry 5), a representative of electron neutral substituent is a benzene ring (Table 5, entry 3) which resulted in lower yield. Moving to electron withdrawing substituents, the yields were lower with CF_3 (Table 5, entry 2) and CN (Table 5, entry 1). Changing the heteroaromatic acid to 3-methylthiophene-2-carboxylic acid resulted in moderate yields for a variety of substituents (Table 5, entry 7-10) with the lowest yield obtained for the nitrile-substituted substrate (Table 5, entry 6). Next Furan-2-carboxylic acid was subjected to the same set of diaryliodonium triflates. Once again substrates containing electron rich functional groups resulted in higher yields.

Based on the results summarized in Table 5, the coupling of 5-membered heteroaromatic carboxylic acids is applicable to pyrolles, thiophenes, and furans with variable iodonium salts containing electron-donating, -neutral, and -withdrawing groups. However, electron-withdrawing substituents on the diaryliodonium triflate provided lower yields of the coupled product.

Table 5. Substrate scope with Mesitylene dummy group

Entry	Heteroaromatic Acid	Diaryliodonium Salt	Yields
1		R: CN	50% [22%]
2		R: CF_3	51% [-]
3		R: H	55% [44%]
4		R: CH_3	82% [74%]
5		R: OMe	63% [-]
6		R: CN	30% [28%]
7		R: CF_3	60% [-]
8		R: H	64% [-]

9		R: CH_3	- [40%]
10		R: OMe	62% [-]
11		R: CN	28% [-]
12		R: CF_3	20% [-]
13		R: H	76% [-]
14		R: CH_3	62% [-]
15		R: OMe	- [54%]

[1]H NMR yield [Isolated yield]

2.3. Conclusion

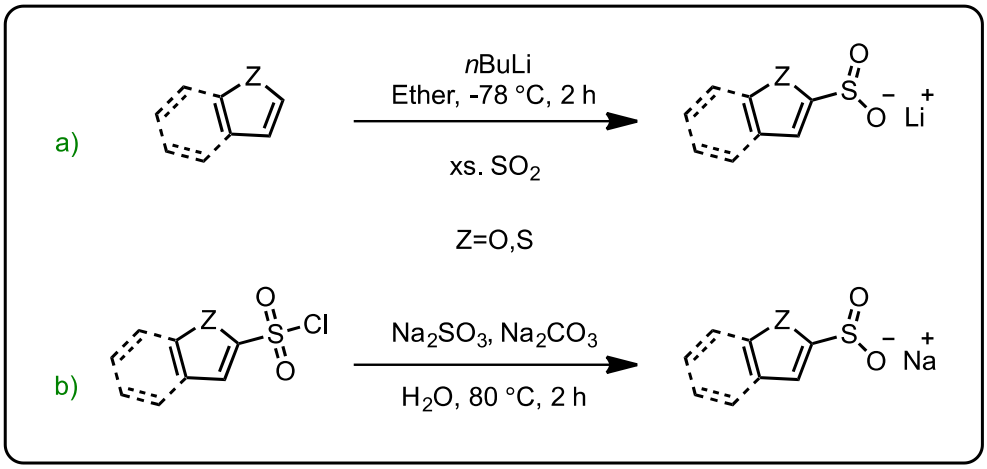
In conclusion a method for the coupling of 5-membered heteroaromatic carboxylic acids with iodonium triflate salts was established. This method employs similar reagents and conditions as the reported decarboxylative cross-coupling reactions and provides moderate to good yields of the coupling products for electron-neutral and electron-rich iodonium slats. For electron-poor iodonium slats however, a different more bulky dummy aryl group had to be employed. It is notable that the cross-coupling of the dummy group to carboxylic acids is a very minor product of this reaction. Hence, this method delivers a chemoselective cross-coupling strategy all the while providing an inert handle, i.e. dummy aryl group, for tuning the electronic and steric properties of the iodonium salts; a feature that is not available with aryl halides. Future work will be directed towards studying the effect of different dummy groups on the reaction yield and establishing a structural relationship to increase the scope and utility of this method.

Chapter 3. Desulfinative cross-coupling reactions of diaryliodonium triflates with heteroaromatic sulfinate salts

3.1. Sulfinate salts

Palladium-catalyzed cross-couplings have been proven to be a very versatile and effective technique for the formation of variety of compounds. Due to its versatility it can be carried out with a wide array of coupling partners depending on the desired product. Sulfinate salts are a class of compounds that can be accommodated into palladium catalyzed cross-coupling reactions, either as an electrophilic or nucleophilic coupling partner.

The salts can be either commercially obtained or synthesized (Scheme 6). Deprotonation of aromatic C-H bonds with strong base to form the organolithium intermediate followed by quenching with SO_2 gas provides sulfinate salts for a variety of aromatic compounds with Li ion. Alternatively, the organolithium intermediate can be obtained via halogen-metal exchange on aryl halides. Formation of sulfinate salts containing Na ion can be achieved through reduction of their counter sulfonyl chlorides



Scheme 6. Generalized scheme for the synthesis of sulfinate salts

The carboxylate and sulfinate moieties resemble each other, hence, these class of compounds can undergo similar reactions, however, the possibility of stronger coordination between the sulfinate group and the metal complex as opposed to the carboxylate group is one of the reasons why sulfinate salts could have more versatility and wider range of applications.

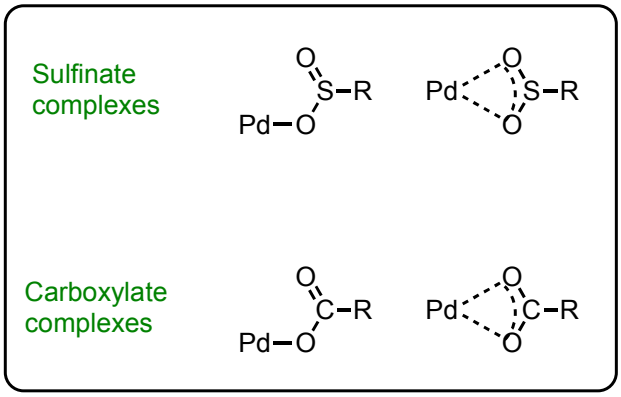


Figure 39. Sulfinate and Carboxylate complexes

Depending on the compounds present in the reaction mixture, sulfinate salts can act as a nucleophile or an electrophile. In order for it to act as an electrophilic coupling partner the catalytic species required is Pd(II), this is because oxidative addition into the arylhalide is not required. In the catalytic cycle for these class of reactions, shuttling between the catalytically active Pd(II) and its reduced form Pd(0) is achieved by the presence of an oxidant in the reactions mixture. Deng and coworkers have displayed the ability of sulfinate salts to act as electrophilic coupling partners in Mizoroki-Heck type of reactions (Figure 40, a)[55,58].

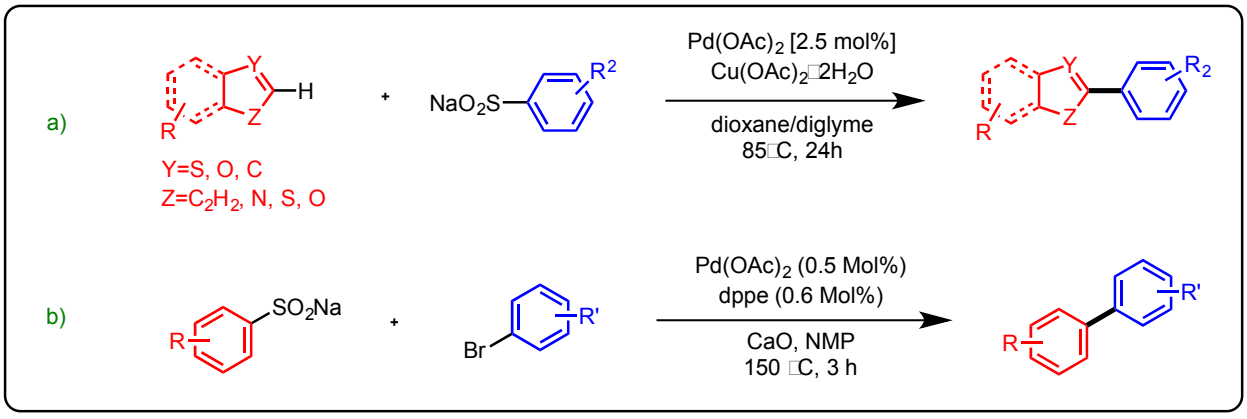


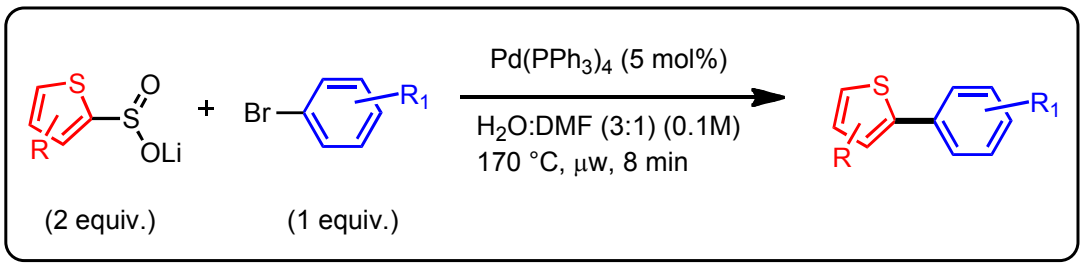
Figure 40. Sulfinate salts behaving as a) electrophilic coupling partner, b) nucleophilic coupling partner

Although it is a versatile electrophilic coupling partner, given the right conditions, sulfinate salts can also behave as a nucleophilic coupling partner (Figure 40, b)[59]. In 1992, the ability of sulfinate salts to part take in palladium-catalyzed cross-coupling reactions was demonstrated by Sato and Okoshi[59]. Gone unnoticed for decades, the scope of sulfinate salts ability to act as nucleophilic coupling partners was expanded, in 2012 by Duan and co-workers[60] and in 2013 by Forgione and co-workers[61]. The application of sulfinate salts in the synthesis of aryl-heteroaryl compounds has also been explored and a wide scope has been demonstrated by Forgione and co-workers[56,84].

3.2. Desulfinative cross-coupling reactions of diaryliodonium triflates

Although sulfinate salts has been more or less well explored for their reactivity in cross-coupling reactions, the methodologies developed utilize an arylhalide partner in the cross-coupling reactions. The emergence of diaryliodonium salts as a cross-coupling partner has been demonstrated by several researchers displaying their wide applicability in organic reactions, however, the reactions of diaryliodonium triflates with sulfinate salts remains yet to be explored.

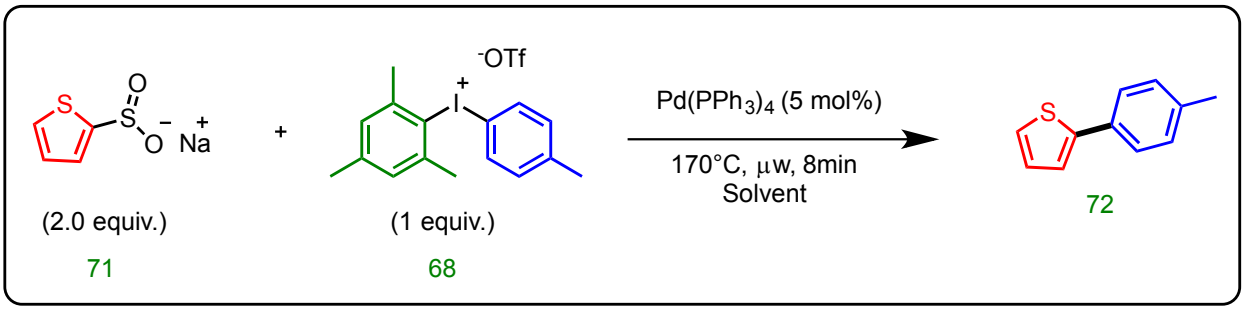
Inspired by previous research on desulfinative cross-coupling reactions in our research group, the ability of diaryliodonium salts as a coupling partner in these types of reactions were examined and different reaction conditions were screened in order to optimize the method and render it applicable with a variety of reactants.



Scheme 7. Methodolody developed by the Forgione group.

3.2.1. Solvent screening

Screening of reaction conditions for cross-coupling of sodium thiophene-2-sulfinate **71** with (4-methylphenyl)(2,4,6-trimethylphenyl)iodonium triflate **68** for the formation of 2-(4-methylphenyl)thiophene **72** were initiated by varying the solvent. This is important due to the fact that existing method employs a mixture of H_2O and DMF. Use of aqueous solvents is always of interest in order to steer the reaction into environmentally friendly direction. Although the sulfinate salts can be employed in aqueous medium, diaryliodonium triflates however are sensitive to water. The ability of water to act as a nucleophile in the reaction medium causes the dissociation of the diaryliodonium triflates into the aryliodides and phenols, hence, inspired by the optimization of decarboxylative cross-coupling, a select set of solvents were screened.



Scheme 8.Screening of solvents

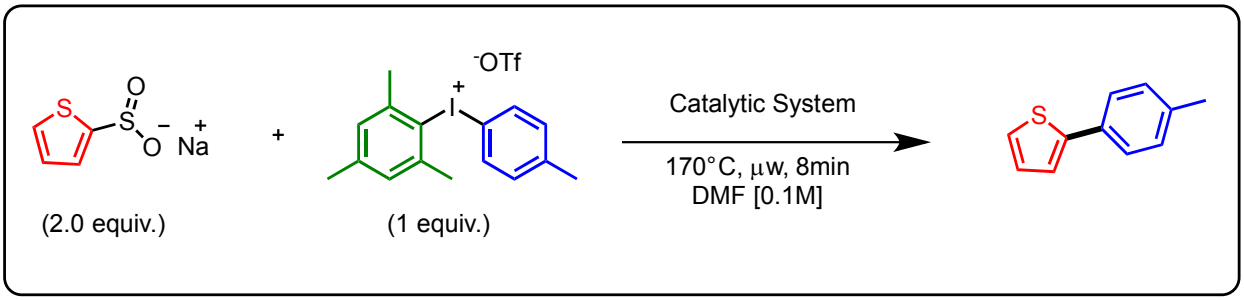
Employing DMF (Table 6, entry 1) resulted in 49% yield while DMA (Table 6, entry 2) resulted in 47% yield and NMP (Table 6, entry 3) resulted in 46% yield. Keeping DMF as the reaction solvent, which resulted in the highest yield, optimization of reaction conditions was continued.

Table 6. Screening of solvents

Entry	Solvent	^{1}H NMR yield
1	DMF	49%
2	DMA	47%
3	NMP	46%
4	EtOH	40%

3.2.2. Catalyst screening

As the catalyst source and the supporting ligand influences the outcome of coupling reactions, screening of catalyst was performed next. The initial reaction conditions employed a preformed palladium(0) catalyst, $Pd(PPh_3)_4$. To assess the ligand effect on the catalytic reaction other palladium(0) sources with various phosphine-based ligands were screened.



Scheme 9.Screening of catalysts

Utilizing $Pd(PPh)_4$ (Table 7, entry 1) the yield was at 49%, analysis of different preformed catalytic systems (Pd(0)), $Pd[P(tBu)_3]_2$ (Table 7, entry 2) and $Pd(dba)_2$ (Table 7, entry 3) resulted in 47% and 46% yield, respectively, which was not a significant change. Next, different palladium sources and ligand combinations were tested to analyze the performance of *in-situ* generated catalysts in order to increase the yield. For this purpose $Pd(dba)_2$ was used as the source of Pd(0). Combination of $Pd(dba)_2$ and PPh_3 (Table 7, entry 4) resulted in 54% yield, while $Pd(dba)_2$ and *t*BuMePhos (Table 7, entry 5) yielded 29%. Next, different combinations of $Pd(acac)_2$ – as Pd(II) source – were examined. A combination of $Pd(acac)_2$ and low cone angle ligand, PPh_3 (Table 7, entry 6) yielded 59%, while $Pd(acac)_2$ and *t*BuMePhos (Table 7, entry 7) 44%, trying the combination of $Pd(acac)_2$ with the bulky JohnPhos and large cone angle (Table 7, entry 8) yielded 26%. Therefore, with Pd(0) source non-bulky ligand gives higher yields. Changing the palladium source to $Pd(OAc)_2$ - another Pd(II) source - and ligands with varying cone angles were tested. Combination of $Pd(OAc)_2$ and PPh_3 (Table 7, entry 9) yielded 52%, while combination of $Pd(OAc)_2$ with 2 (Table 7, entry 10) or 4 (Table 7, entry 11) equivalents of JohnPhos resulted in no considerable product formation. Moving on, various combinations of $PdCl_2$ and ligands with different equivalents were screened. Combination of $PdCl_2$ and 4 equivalents of PPh_3 (Table 7, entry 12) yielded 57% while 5 equivalence of PPh_3 (Table 7, entry 13) yielded 42% of the coupled product. Several ligands with varying cone angles were combined, such, $PdCl_2$ +$[HP(Cy)_3]BF_4$ (1:4), $PdCl_2$ + $[HP(tBu)_3]BF_4$ (1:4), $PdCl_2$ + JohnPhos (1:2), $PdCl_2$ + *t*BuMePhos (1:2), $PdCl_2$ + *t*BuMePhos (1:4), $PdCl_2$ + dppf (1:2), however, no increase in yield was achieved. Employment of bidentate ligand, dppf, resulted in 53% yield (Table 8, entry 19). Absence of catalyst resulted in no formation of the desired product, but rather formed a sulfone moiety. In conclusion, based on the screening result, $PdCl_2$ and PPh_3 in 1 to 4 ratio was used as the catalyst and the supportive ligand.

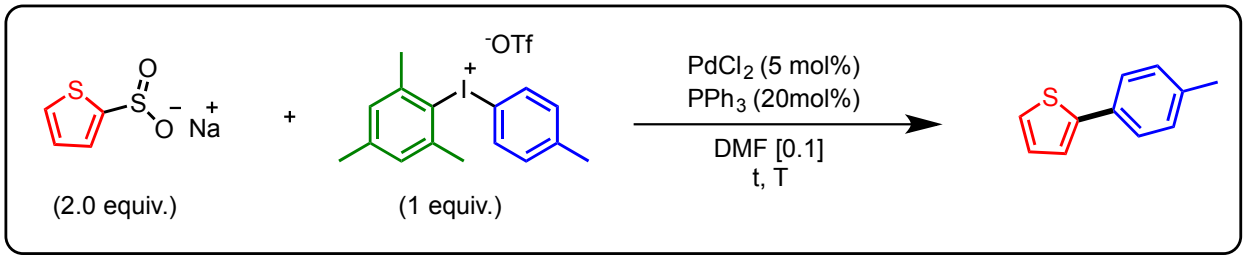
Table 7. Screening of the catalytic system

Entry	Catalyst + Ligand	Yield	Entry	Catalyst + Ligand	Yield
1	$Pd(PPh_3)_4$	49%	11	$Pd(OAc)_2$ + JohnPhos (1:4)	-%
2	$Pd[P(tBu)_3]_2$	47%	12	$PdCl_2$ + PPh_3 (1:4)	57%
3	$Pd(dba)_2$	46%	13	$PdCl_2$ + PPh_3 (1:5)	42%
4	$Pd(dba)_2$ + PPh_3 (1:4)	54%	14	$PdCl_2$ +$[HP(Cy)_3]BF_4$ (1:4)	20%
5	$Pd(dba)_2$ + *t*BuMePhos (1:4)	29%	15	$PdCl_2$ + $[HP(tBu)_3]BF_4$ (1:4)	35%
6	$Pd(acac)_2$ + PPh_3 (1:4)	59%	16	$PdCl_2$ + JohnPhos (1:2)	30%
7	Pd(acac)2 + tBuMePhos (1:4)	44%	17	$PdCl_2$ + *t*BuMePhos (1:2)	25%
8	$Pd(acac)_2$ + JohnPhos (1:4)	26%	18	$PdCl_2$ + *t*BuMePhos (1:4)	20%
9	$Pd(OAc)_2$ + PPh_3 (1:4)	51%	19	$PdCl_2$ + dppf (1:2)	53%
10	$Pd(OAc)_2$ + JohnPhos (1:2)	-%	20	No Catalyst	0%*

* Biarylsulfone was obtained

3.2.3. Time and temperature screening

Having performed the screening of different catalytic systems, the highest yielding combination, $PdCl_2$ and PPh_3 (4 equivalence) was used to carry on with the screening of reaction conditions. Different temperatures and reaction time combinations were screened in an attempt to increase the yield .



Scheme 10.Screening of time and temperature

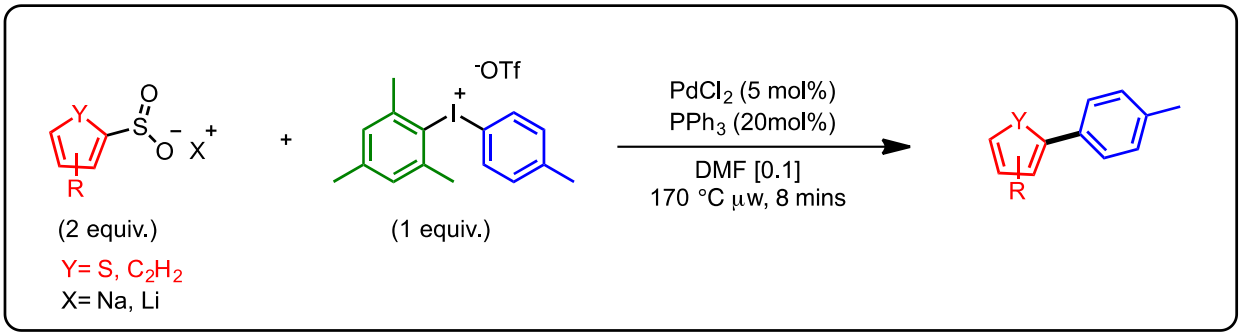
In an attempt to render the reaction greener, screening of reaction conditions were initiated by decreasing the temperature to 160 °C (Table 8, entry 2), this however resulted in significant decrease in yield. Next the effect of increasing the temperature was analyzed by raising the temperature to 180 °C (Table 8, entry 3) and 190 °C (Table 8, entry 4) decreased the yield to 47%. Since temperature change did not increase the yield, the time of the reaction was increased to 16 mins (Table 8, entry 5). Unfortunately this did not cause an increase in yield either. The decrease in yield can be attributed to disproportionation of the sulfinate salt. With higher temperatures this process is more favourable, hence reducing the amount of sulfinate salt available that can undergo cross-coupling reaction. Hence, for further reactions microwave heating for 8 minutes at 170 °C was employed.

Table 8. Screening of time and temperature

Entry	Time	Temperature	^{1}H-NMR Yield
1	8 min	160 °C	34%
2	8 min	170 °C	57%
3	8 min	180 °C	47%
4	8 min	190 °C	47%
5	16 min	170 °C	37%

3.2.4. Substrate scope

Having performed a refined screening of reaction conditions, the scope of the methodology was tested in order to explore the type of reactants that can be subjected to the new reaction conditions and also to exploit the compounds that could be synthesized through coupling of sulfinate salts and diaryliodonium triflates.

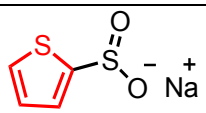
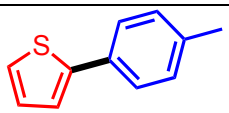
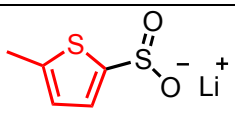
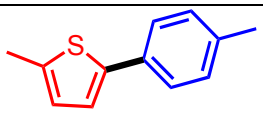
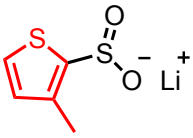
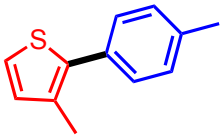
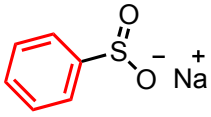
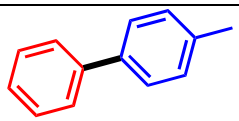
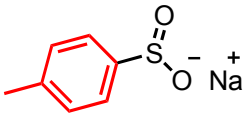
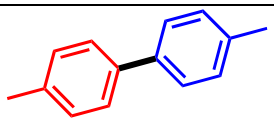


Scheme 11.Optimized reaction conditions employed for substrate scope

A variety of sulfinate salts were subjected to the optimized reaction conditions (Scheme 9). The method is suitable for the cross-coupling of heteroaryl sulfinate salts with methyl substituents

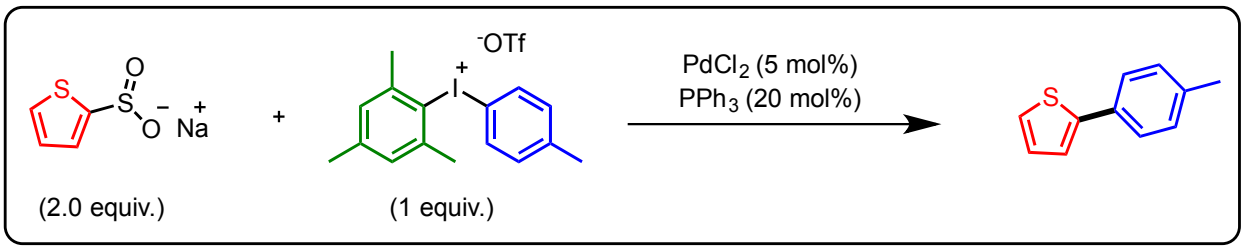
attached at various positions. Although not resulting in high yields, the capability of diaryliodonium triflates in desulfinative cross-coupling reactions has been demonstrated. Furthermore, the reaction is not limited to 5-membered heteroaromatic sulfinate salts. Aryl sodium sulfinates such as sodium benzenesulfinate (Table 9, entry 4) and sodium 4-methylbenzenesulfinate (Table 9, entry 5) resulted in the formation of biaryl moieties.

Table 9. Substrate scope

Entry	Sulfinate Salt	Product	^{1}H NMR Yield
1			57%
2			35%
3			42%
4			22%
5			20%

3.2.5. Solid state reactions

Due to the fact that both reactants in the methodology developed are in solid state, i.e. salts, it was of interest to explore their solid-state reactivity in an attempt to reduce the amount of organic solvent used. A brief screening of solid-state reactions (Scheme 12) were performed as a proof of concept to determine whether the solid-state reactions would be applicable.



Scheme 12.General solid state reaction

The solid state reactions were initiated by placing the reactants in a mortar and grinding for 8 mins, this reaction produced trace amounts of the product as was determined by ^{1}H-NMR. The reaction was then carried out in a ball mill for 8 mins and the yield was significantly increased to 60%. Given the similar yields in both cases, the mechanochemical method is promising and can lead to a new, efficient, and clean method for the formation of aryl-heteroaryl motifs from heteroarylsulfinates and aryliodonium salts.

Table 10. Reaction conditions for solid state reactions

Entry	Reaction Conditions	^{1}H NMR yield
1	Grinding for 8 mins	Trace
2	Ball milling for 8 mins	60%

3.3. Conclusion

In summary a new method for the coupling of sulfinate salts with diaryliodonium salts using palladium catalyst was developed. Even though substrate scope is limited at the moment, and is a currently undergoing work, the results are promising. As with the decarboxylative cross-coupling reactions it is expected that modifications of the dummy group will affect the scope of the reaction. Preliminary results indicate that the reaction can be carried out mechanochemically without solvent thus simplifying reaction setup and reducing amount of material used. Future work will be directed towards exploring the full potential of this reaction by expanding the substrate scope and translating the process into solid-state reaction.

Chapter 4. Conclusions

Through an exhaustive screening process, we have demonstrated the applicability of diaryliodonium salts as a complimentary electrophilic cross-coupling partner in palladium catalyzed cross-coupling reactions with five membered heteroaromatics.

4.1. Decarboxylative cross-coupling reactions of diaryliodonoum triflates

The existing methodology for the cross-coupling reactions employing heteroaromatic acids and arylhalides is highly versatile. With slight modifications this method is amenable to the coupling of diaryliodonium triflates with 5-membered heteroaromatic carboxylic acid. It is of the essence to have multiple routes for the synthesis of compounds in order to expand the scope of substrates and through the incorporation of diaryliodonium triflates, the synthetic tool-box for the scientific community has been further diversified.

4.2. Desulfinative cross-coupling reactions of diaryliodonoum triflates

The application of sulfinate salts in cross-coupling reactions has been established, however, the full potential of these salts are yet to be discovered. Development of synthetic routes employing sulfinate salts are essential in order to diversify the synthetic methodologies and also to further discover the potential of sulfinate salts. Furthermore, diaryliodonium triflates, although known for a while are considered relatively new set of compounds due to the fact that they have not been utilized or researched in enough details. Method development utilizing these two relatively new reactants would be beneficial not only for the diversification of synthetic routes but also to inspire new research with these set of compounds.

Chapter 5. Future work

Through the extensive research carried out and presented in this thesis, the use of diaryliodonium triflates in decarboxylative cross-coupling with heteroaromatic carboxylic acids and desulfinative cross-coupling reactions with aryl/heteroaryl sulfinate salts has been demonstrated. Although the general applicability of diaryliodonium triflates in cross-coupling reactions with five membered heteroaromatic systems has been demonstrated, the number of diaryliodonium triflates that were synthesized limits the substrate scope of the developed methodology. The synthesis of these salts through more efficient methods are possible, such as synthesis in flow system as opposed to one-pot batch synthesis, therefore it is of interest to develop a flow reactor suitable to carry out reactions for the formation of these salts. Once a wide variety of iodonium salts is made available, the structural effect of the dummy group on reaction yield and scope will be explored and this in turn will provide insight into the reaction mechanism. Finally, preliminary results for the mechanochemical desulfinative cross-coupling reactions is an exciting new avenue for the optimization of the methodology places the reaction in accordance with the principles of green chemistry.

Chapter 6. Experimental

6.1. General Procedures

6.1.1. Synthesis of diaryliodonium salts

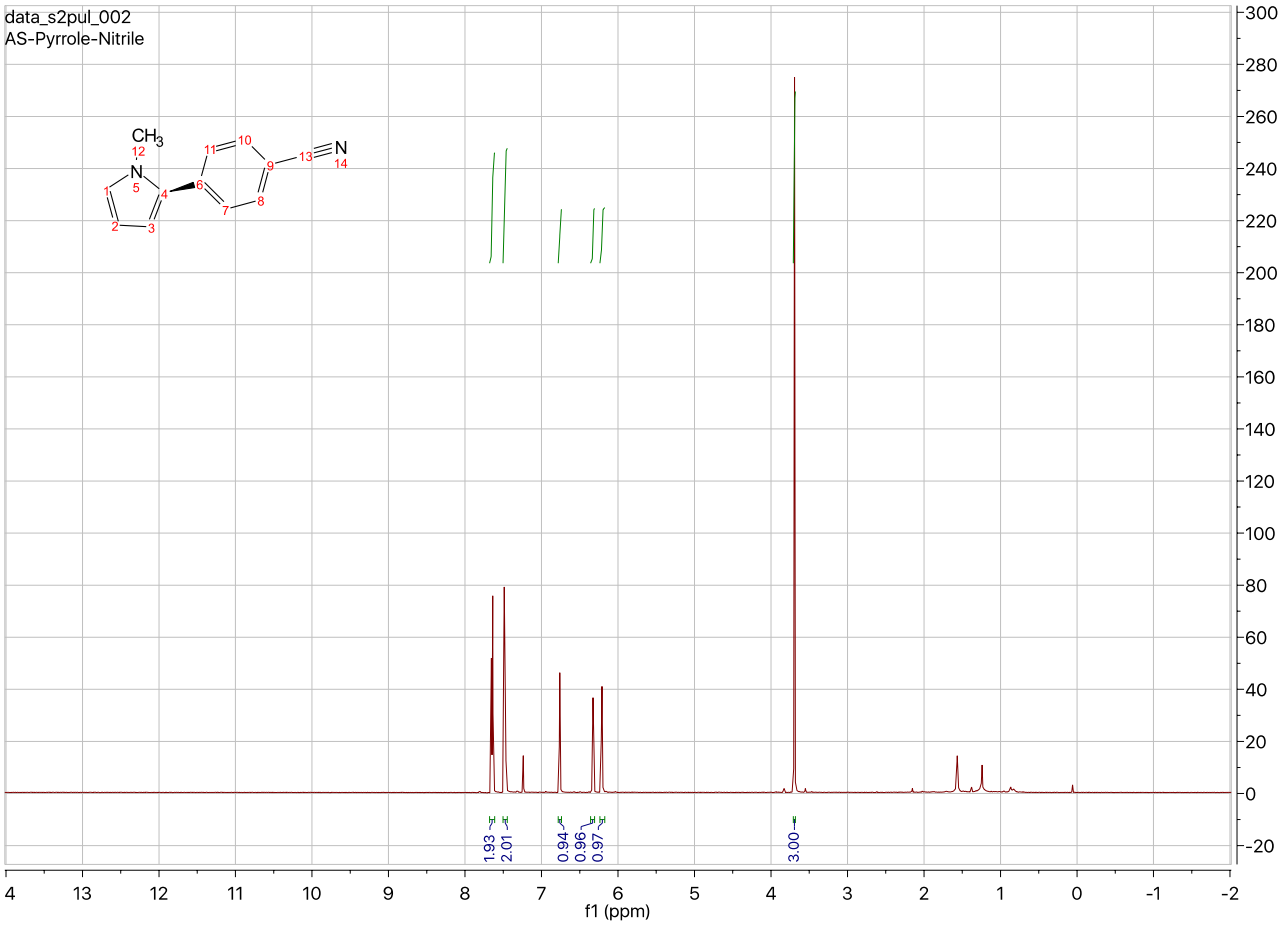
Diaryliodonium triflates were prepared as per the procedure from published literature,[73] purity was determined by matching the ^{1}H NMR of the compounds produced to the reported literature data. To an oven-dried round-bottom flask was added *m*-CPBA (1.10 equiv) and CH_2Cl_2 (0.20 M), followed by the appropriate iodoarene (1.00 equiv) and mesitylene (1.10 equiv). The mixture was cooled to 0 ºC and trifluoromethanesulfonic acid (1.70 equiv) was added slowly with stirring. The reaction was allowed to warm to room temperature and stir for 2h. The solvent was removed *in vacuo* and Et_2O was added. The heterogeneous mixture was cooled to –20 ºC for at least 30 minutes. The diaryliodonium trifluoromethansulfonate was collected via filtration, washed with Et_2O, and dried under vacuum.

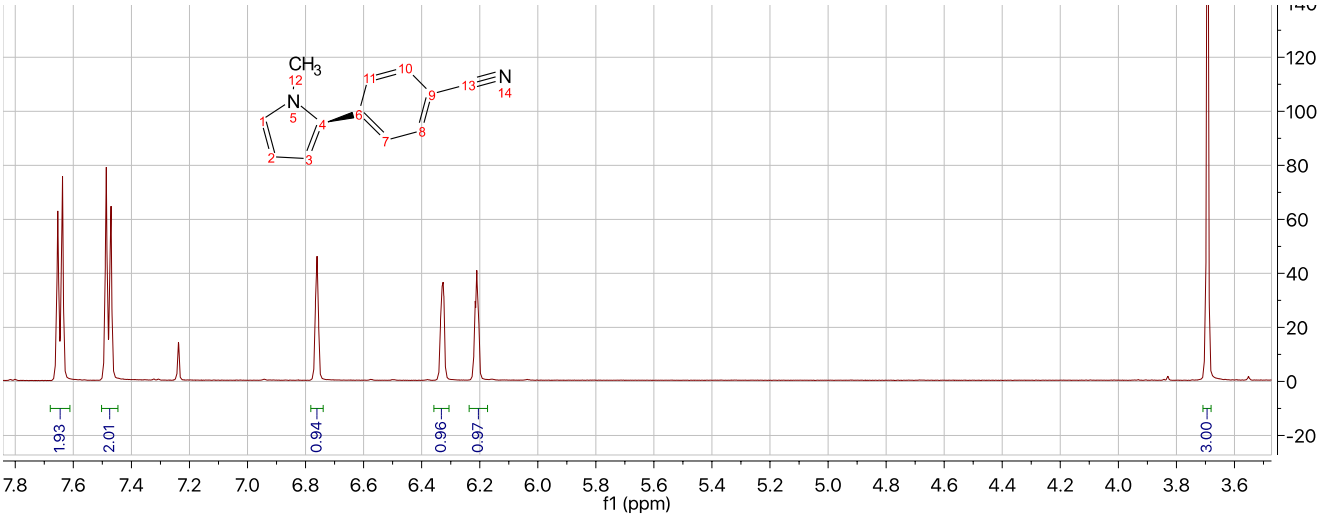
6.1.2. Microwave reactions

To a 5 mL conical microwave vial equipped with a spin-vein was added heteroaromatic sulfinate or carboxylic acid, diaryliodonium salt, Pd and ligand. 2 mL of solvent was added and the vial was pre-stirred for 30 sec at 23 ºC followed by appropriate heating. The crude solution was diluted with EtOAc (5 mL). The organic layer was washed with a saturated NaCl aqueous solution (2x5 mL), saturated $NaHCO_3$ aqueous solution (2x5 mL), distilled H_2O (1x5 mL), and saturated NaCl aqueous solution (1x5 mL). The combined aqueous phases were further extracted with EtOAc (3x5 mL). The combined organic phases were then dried over Na_2SO_4 and after filtration the solvent evaporated under reduced pressure and the oily residue was purified by flash column chromatography.

6.1.3. Characterization

4-(1-methyl-1*H*-pyrrol-2-yl)benzonitrile(Table 5, Entry 1): Compound synthesized as per general procedure (B). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (m, 2H), δ 7.50 (m, 2H), δ 6.78 (dd, *J*= 2.7, 1.8 Hz, 1H), δ 6.23 (dd, *J*= 3.7, 2.7 Hz, 1H), δ 3.71 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ, 137.71, 132.58, 132.18, 128.23, 125.80, 119.01, 108.60, 35.06, 29.89.

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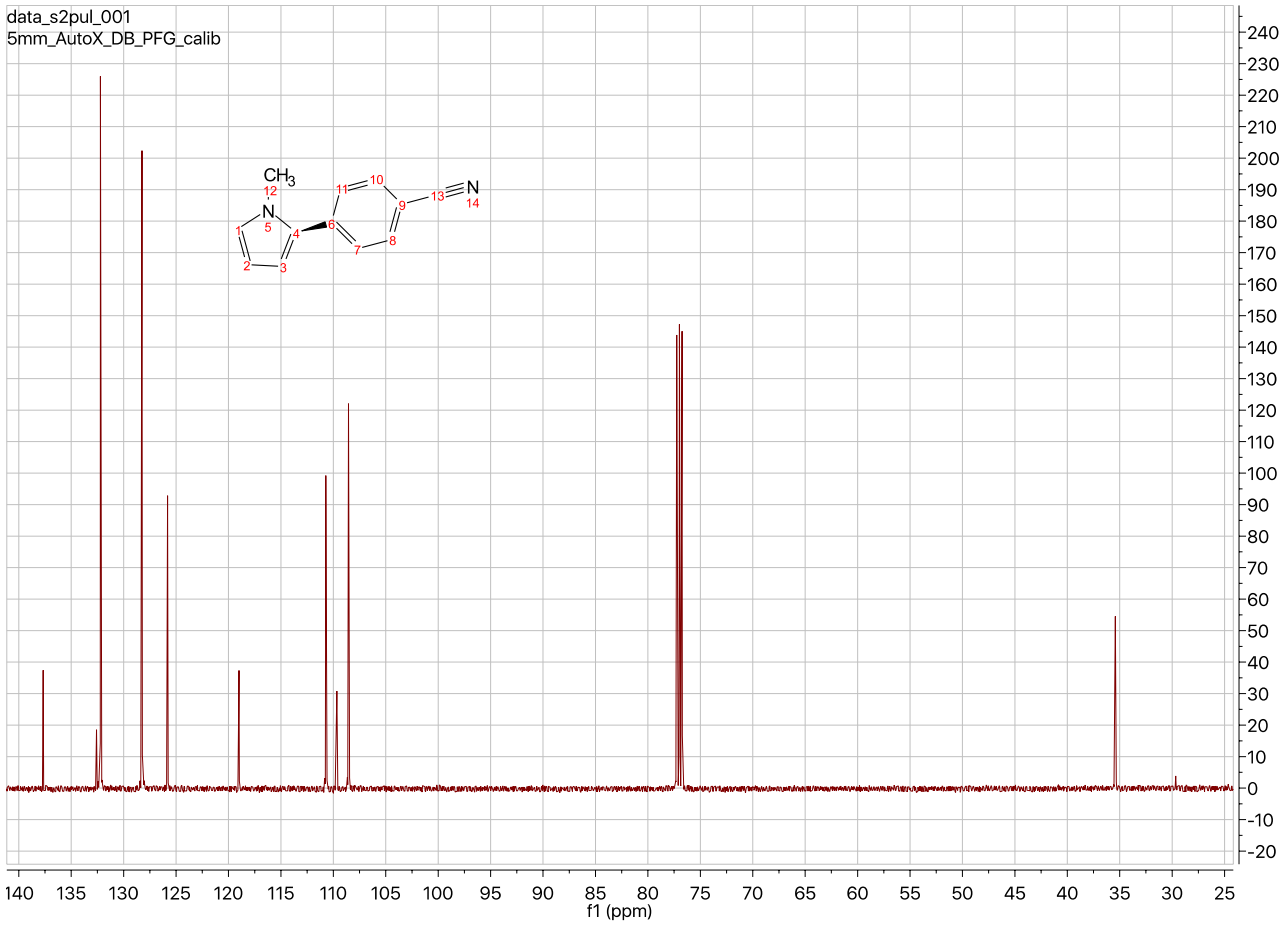
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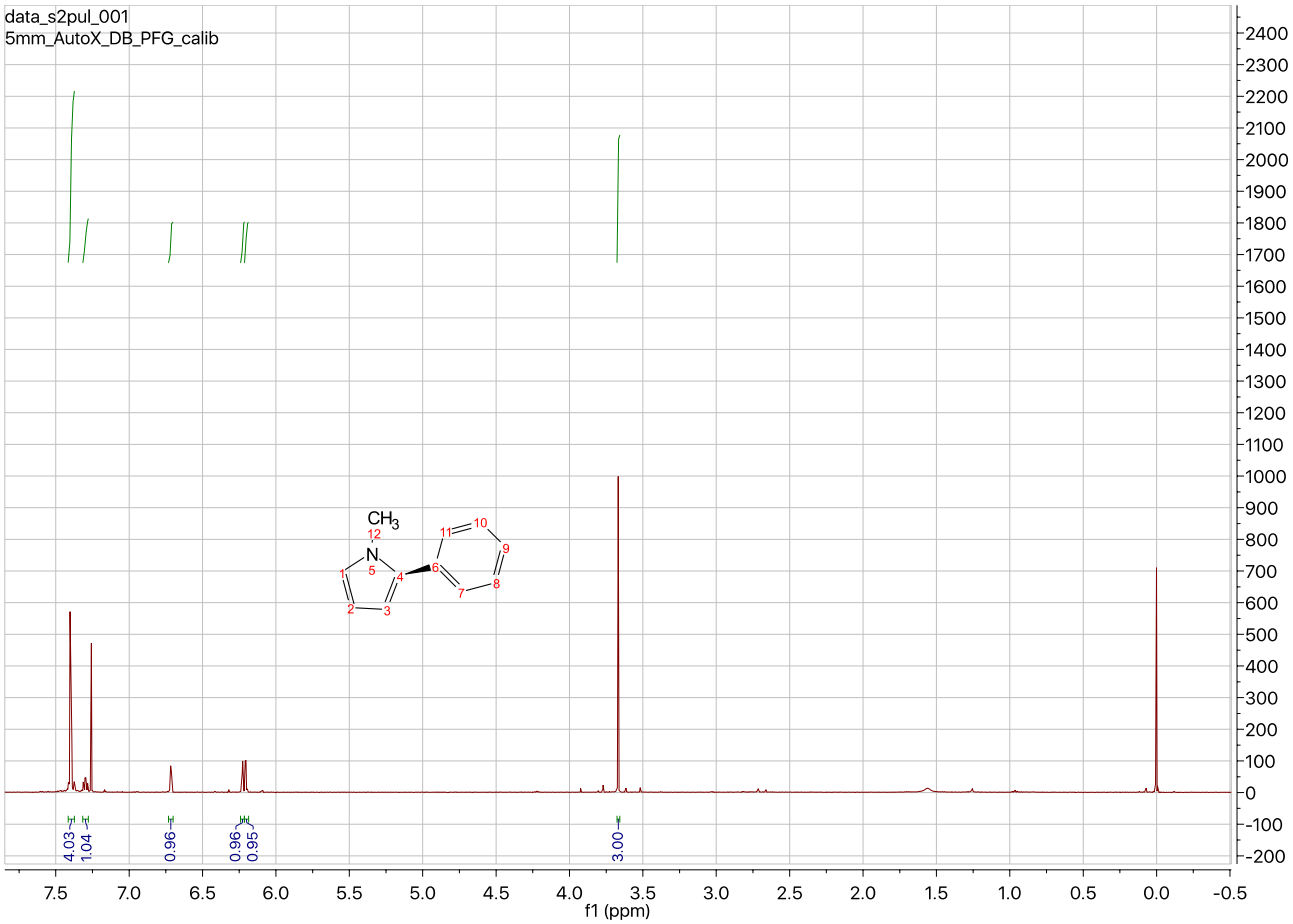
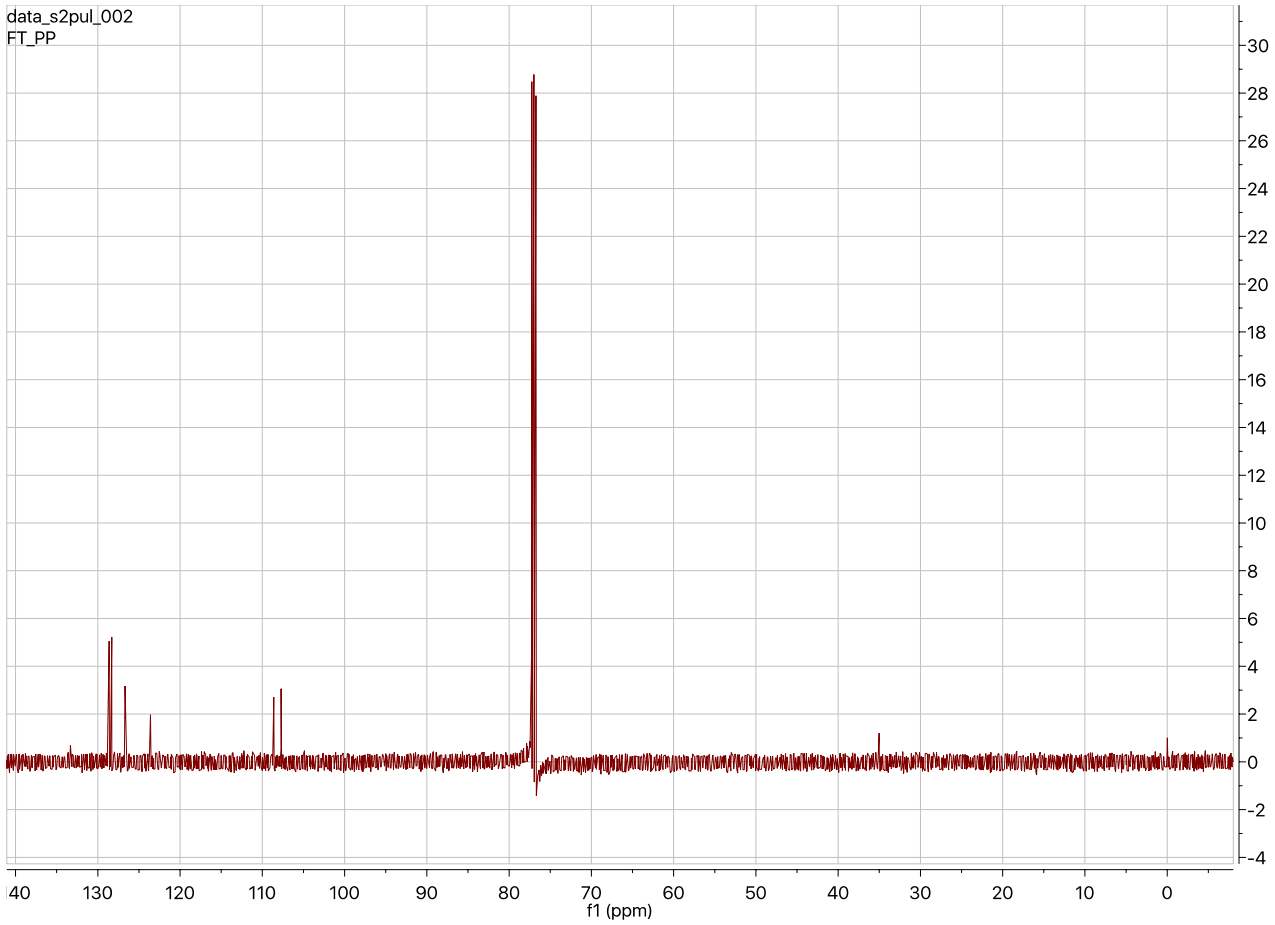
f1 (ppm)

1-methyl-2-(4-(trifluoromethyl)phenyl)pyrrole (Table 5, Entry 2): Compound synthesized as per general procedure (B). Yield was determined by ^{1}H NMR.

1-methyl-2-phenylpyrrole(Table 5, Entry 3): Compounds synthesized as per general procedure (B). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (m, 4H), δ 7.30 (m, 1H), δ 6.72 (dd, *J*= 2.7, 1.9 Hz, 2H), δ 6.21 (m, 2H), δ 3.67 (s, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ, 133.36, 128.67, 128.30, 126.67, 123.60, 108.6, 107.73, 35.02

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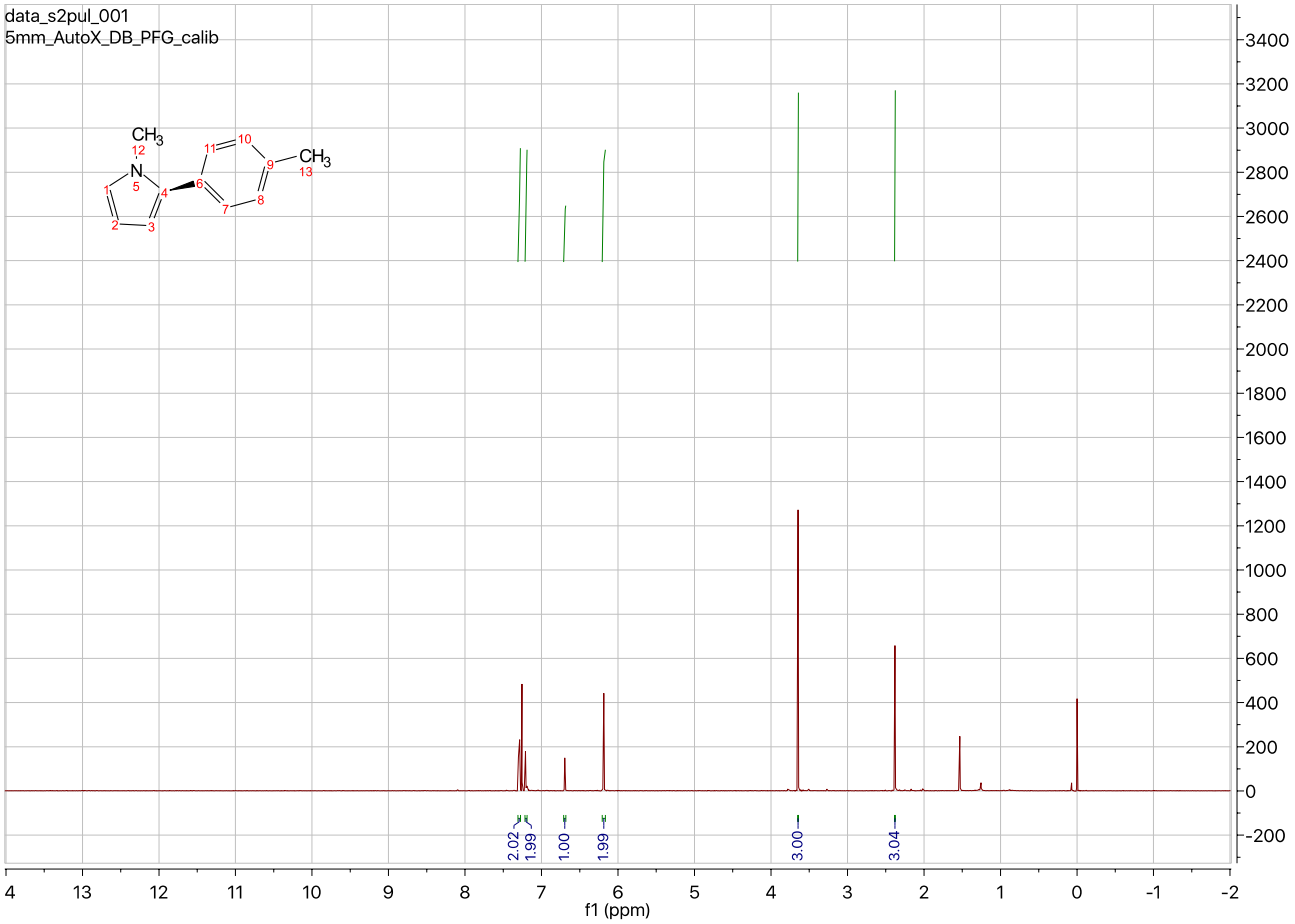
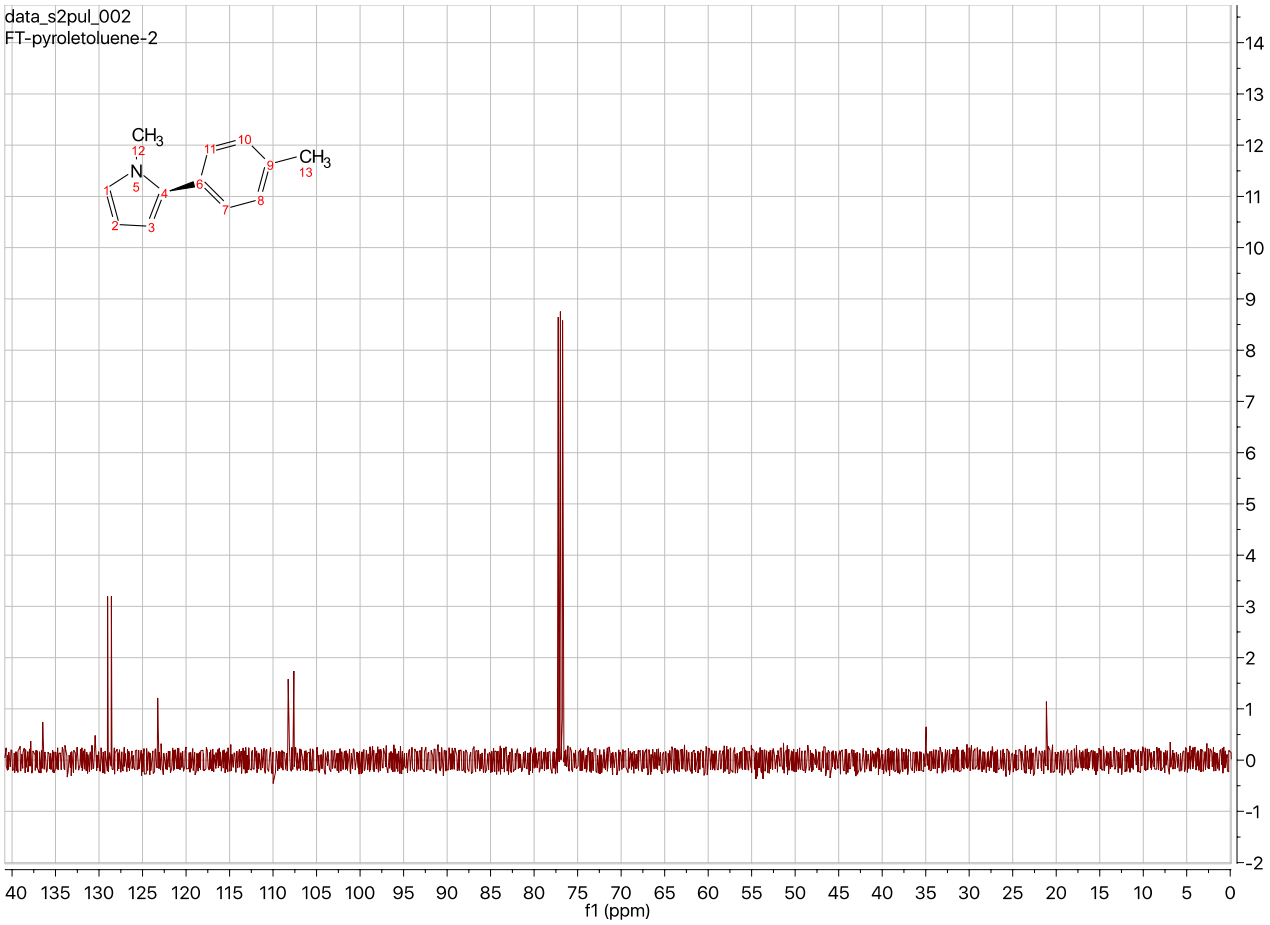
f1 (ppm)

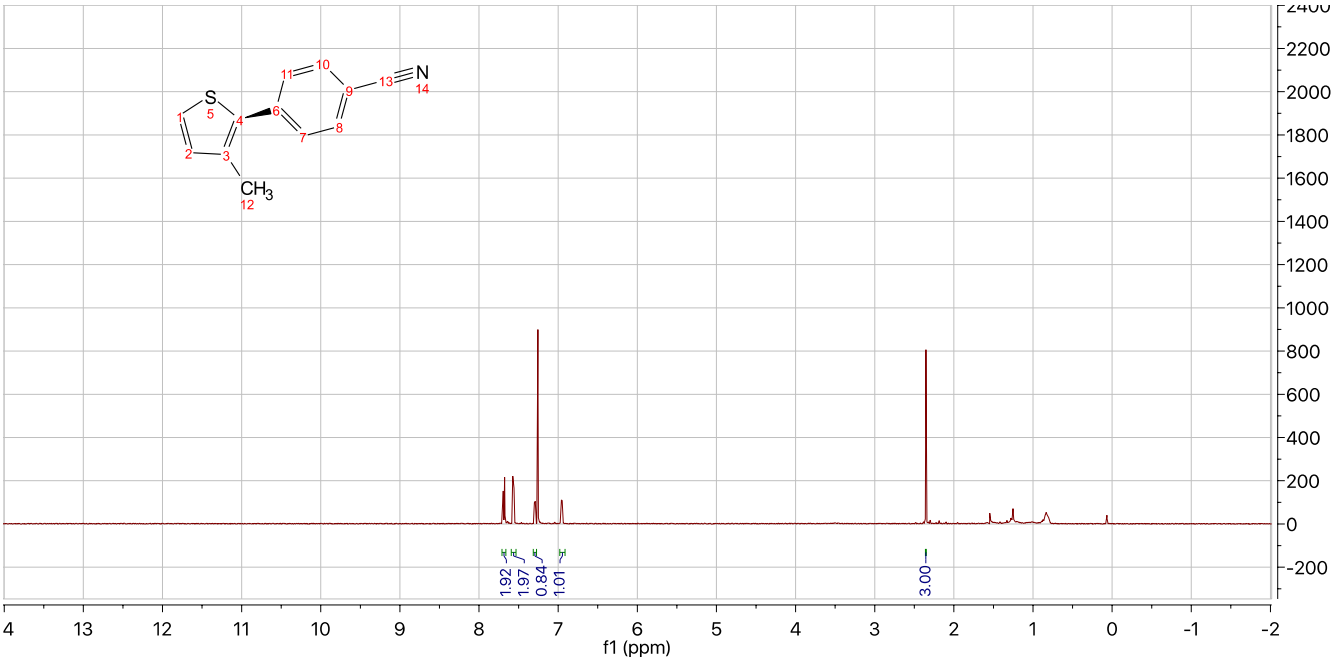
1-methyl-2-(*p*-tolyl)pyrrole (Table 5, Entry 4): Compounds synthesized as per general procedure (B). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (m, 2H), δ 7.20 (m, 2H), δ 6.70 (t, *J*= 2.3 Hz, 1H), δ 6.19 (d, *J*= 2.3 Hz, 2H), δ 3.65 (s, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ, 136.62, 130.41, 129.00, 128.57, 123.16, 108.26, 107.61, 35.06, 21.27.

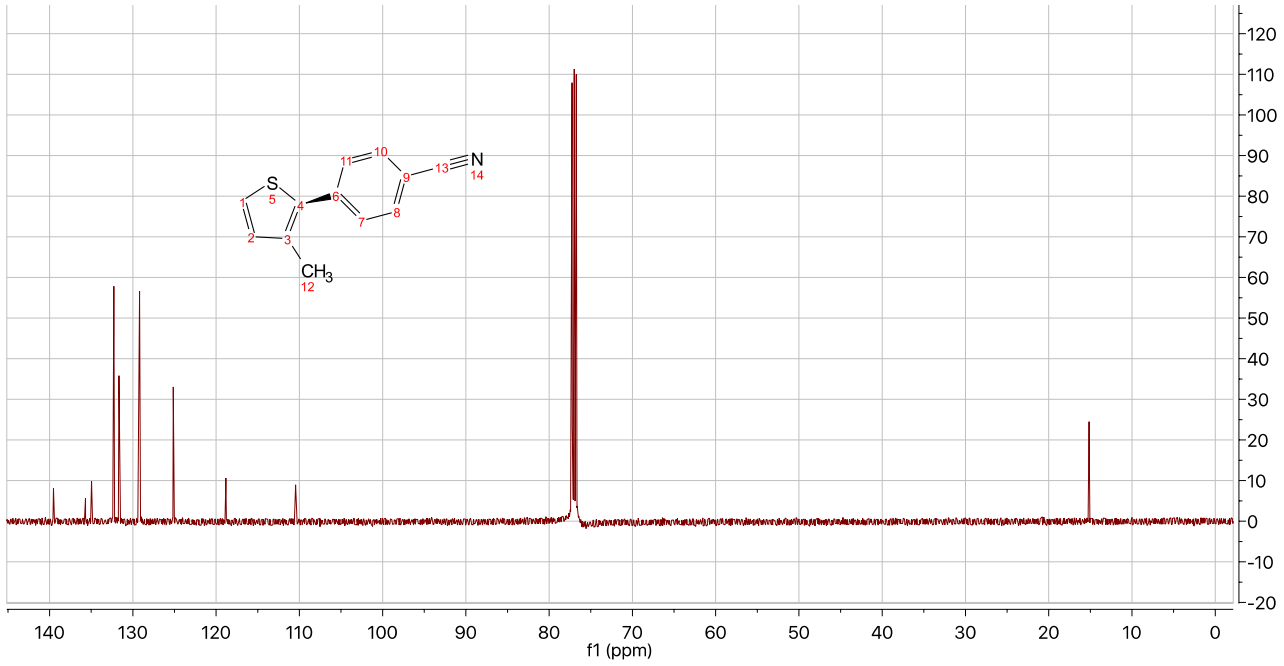




1-methyl-2-(*p*-methoxy)pyrrole (Table 5, Entry 5) : ^{1}H NMR yield reported using literature values of expected product as reference.

4-(3-methylthiophen-2-yl)benzonitrile (Table 5, Entry 6): Compound synthesized as per general procedure (B), 19a with 70% yield (0.055 in 0.4mmol scale). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (m, 2H), δ 7.57 (m, 2H), δ 7.30 (d, *J*= 5.1 Hz, 1H), δ 6.96 (m, 1H), δ 2.36 (s, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ, 139.71, 135.69, 134.93, 132.26, 131.70, 129.20, 125.13, 118.81, 110.45, 15.32.

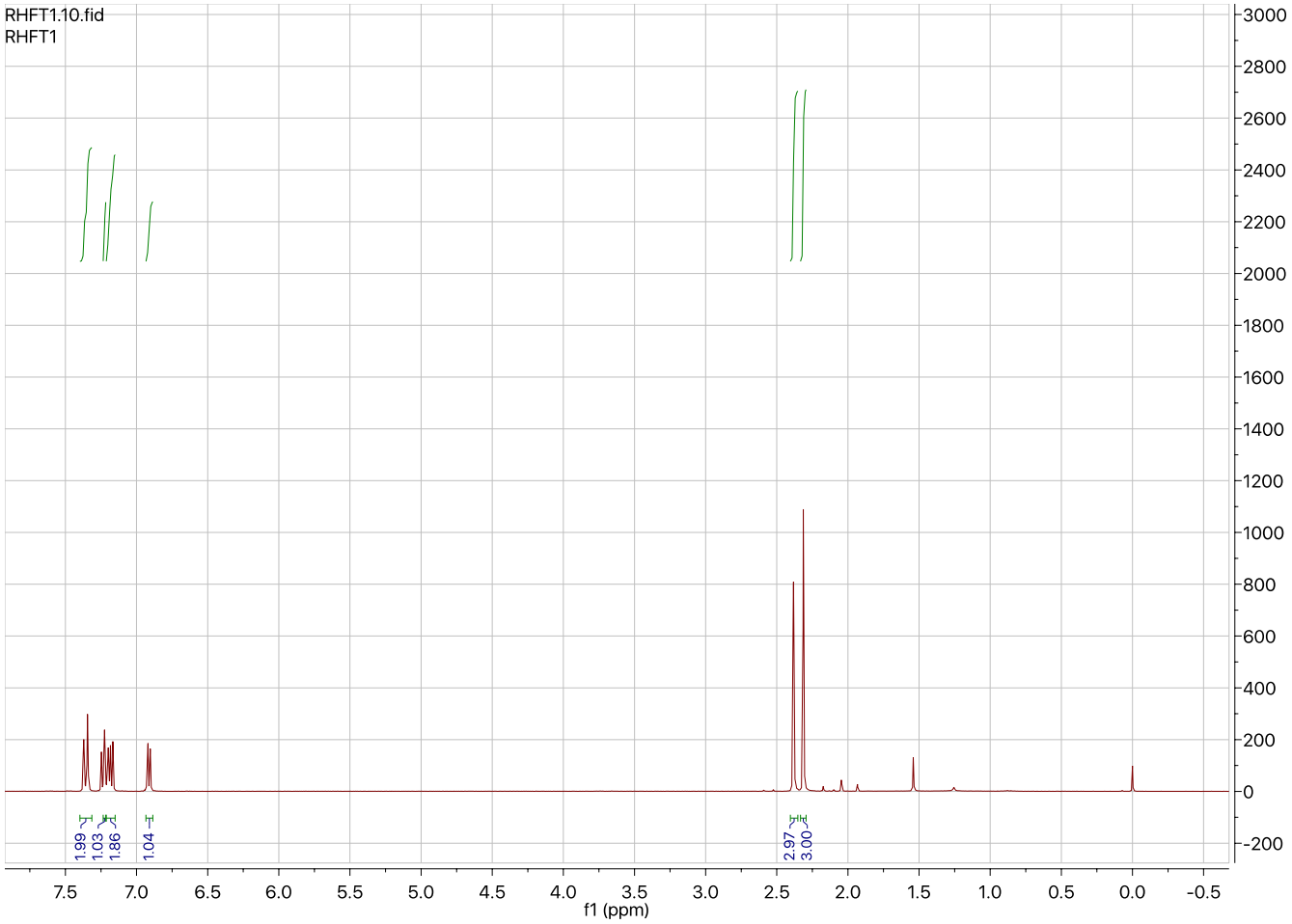




3-methyl-2-(4-(trifluoromethyl)phenyl)thiophene (Table 5, Entry 7): ^{1}H NMR yield reported using literature values of expected product as reference.

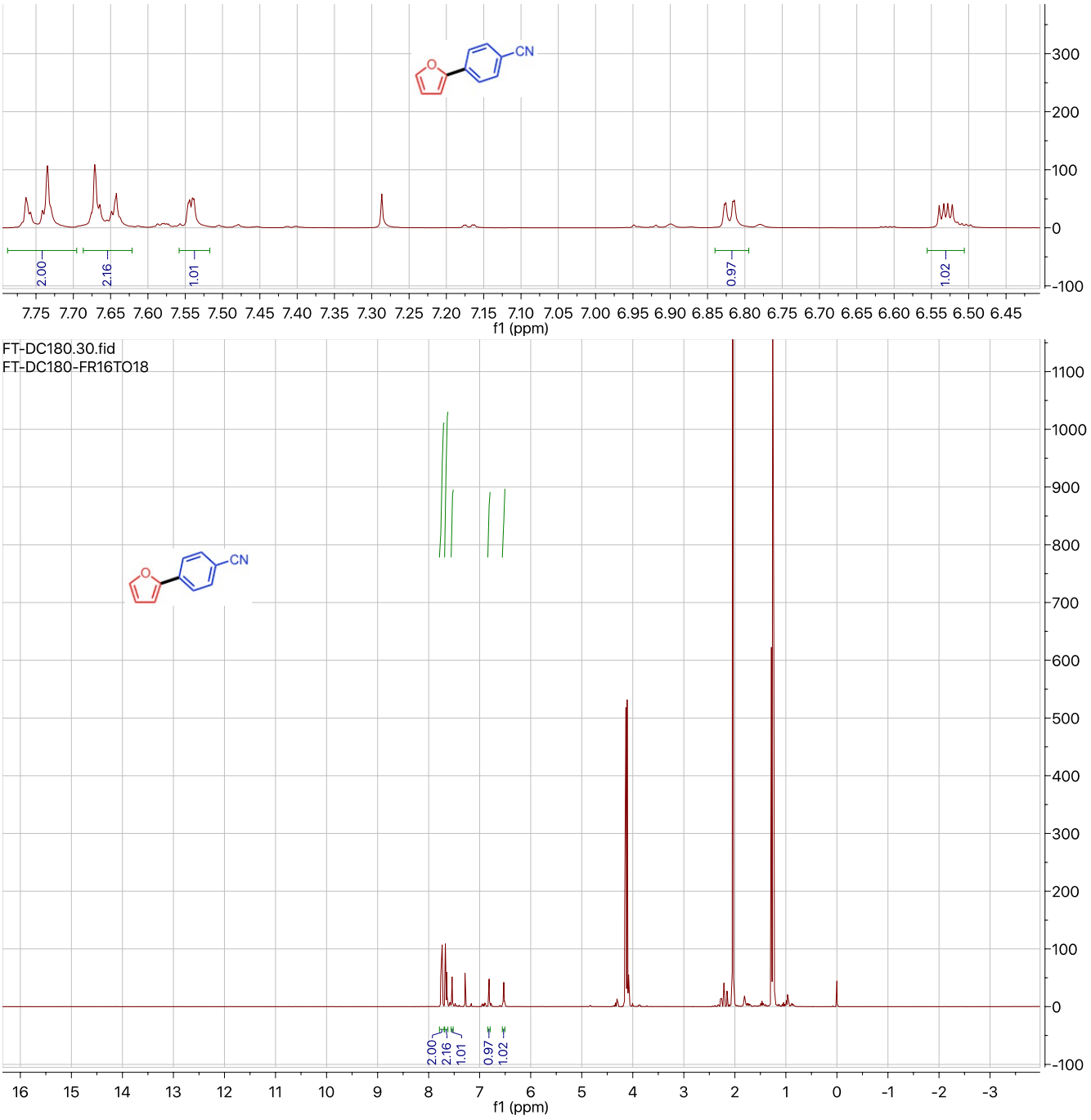
3-methyl-2-phenylthiophene (Table 5, Entry 8): ^{1}H NMR yield reported using literature values of expected product as reference.

3-methyl-2-(*p*-tolyl)thiophene (Table 5, Entry 9): Compound synthesized as per general procedure (B), 19a with 40% yield (0.4mmol scale). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, 2H), δ 7.22 (s, 1H), δ 7.18 (t, 2H), δ 6.91 (d, 1H), δ 2.38 (s, 3H) , δ 2.31 (s, 3H);



2-(4-methoxyphenyl)-3-methylthiophene (Table 5, Entry 10): ^{1}H NMR yield reported using literature values of expected product as reference.

4-(furan-2-yl)benzonitrile (Table 5, Entry 11) : Compound synthesized as per general procedure (B), 1a with 30% yield (0.0406g in 0.8mmol scale). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (m, 2H), δ 7.66 (m, 2H), δ 7.55 (dd, *J*= 1.8, 0.7 Hz, 1H), δ 6.82 (dd, *J*= 3.4. 0.7 Hz, 1H), δ 6.53 (dt, *J*= 3.9, 1.9, 1H).

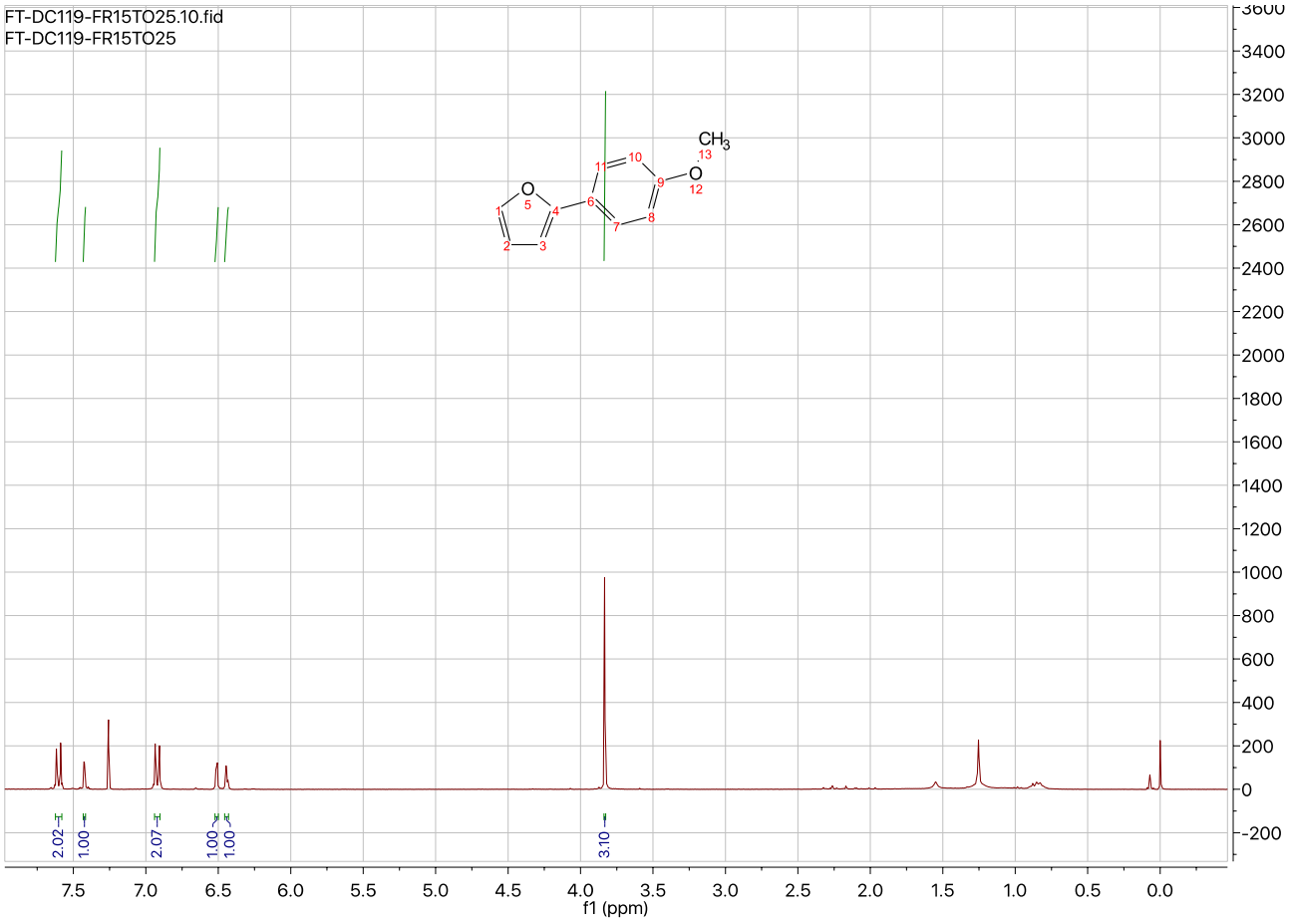


2-(4-(trifluoromethyl)phenyl)furan (Table 5, Entry 12): ^{1}H NMR yield reported using literature values of expected product as reference.

2-phenylfuran (Table 5, Entry 13): The compound decomposes in column; ^{1}H NMR yield reported using literature values of expected product as reference.

2-(*p*-tolyl)furan (Table 5, Entry 14): ^{1}H NMR yield reported using literature values of expected product as reference.

2-(4-methoxyphenyl)furan (Table 5, Entry 15): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (m, 2H), δ 7.41 (s, 1H), δ 6.92 (d, 2H), δ 6.51 (dd, 1H), δ 6.44 (m, 1H), δ 6.92 (s, 3H)



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