主論文

Rapid and Programmed Synthesis of Arylated Heteroarenes through Direct C–H Bond Functionalization

炭素–水素結合の直接変換による
アリール化ヘテロ芳香族化合物の迅速・プログラム合成

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Preface

The studies in this thesis have been carried out under the direction of Professor Kenichiro Itami at Nagoya University during April 2005 – March 2011. The studies are concerned with Rapid and Programmed Synthesis of Arylated Heteroarenes through C–H Bond Functionalization.

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Contents

Abbreviations

Ac	Acetyl
acac	acetylacetonato
AIBN	2,2′-azo bisisobutyronitrile
Ar	Aryl
Ar^N	nitrogen heteroarenes
bipy	2,2′-bipyridyl
Bz	benzoyl
cat	catalyst
cod	1,5-cyclooctadiene
CPME	cyclopentyl methyl ether
Cp*	pentamethylcyclopentadienyl
Cy	cyclohexyl
DFT	density functional theory
DMA	*N*,*N*-dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMEDA	*N*,*N*′-dimethylethylenediamine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
dppb	1,4-bis(diphenylphosphino)butane
Elc	electrophile
equiv	equivalent
GC	gas chromatography
h	hour(s)
^{i}Pr	isopropyl
J	coupling constant
KIE	kinetic isotope effect
LHMDS	lithium bis(trimethylsilyl)amide
LUMO	lowest unoccupied molecular orbital
Mes	mesityl
m	meta
μW	microwave
MS	molecular sieves
NMP	*N*-methylpyrrolidone
Nuc	Nucleophile
p	para
Ph	Phenyl
phen	1,10-phenanthroline
py	pyridine
^{t}Bu	*tert*-butyl
rt	room temperature
SEM	2-(trimethylsilyl)ethoxymethyl
Tf	trifluoromethanesulfonyl
THP	2-tetrahydropyranyl
TMEDA	*N*,*N*,*N*′,*N*′-tetramethyl-ethylenediamine

General Introduction

Motivation of This Research

Organic molecules having aryl-aryl bond (arene-assembled molecules) represent important structural motifs frequently found in natural products, or used in pharmaceuticals and functional organic materials (Figure 1).[1] Unique electronic properties and steric environment, provided by biaryl and heterobiaryl moieties, are critical for arene-assembled molecules to display a variety of unique functions such as optoelectronic properties and biological activities. Therefore, the development of efficient methods to access these "privileged" molecular entities in an ideal manner has been extremely important topic in synthetic chemistry.[2]

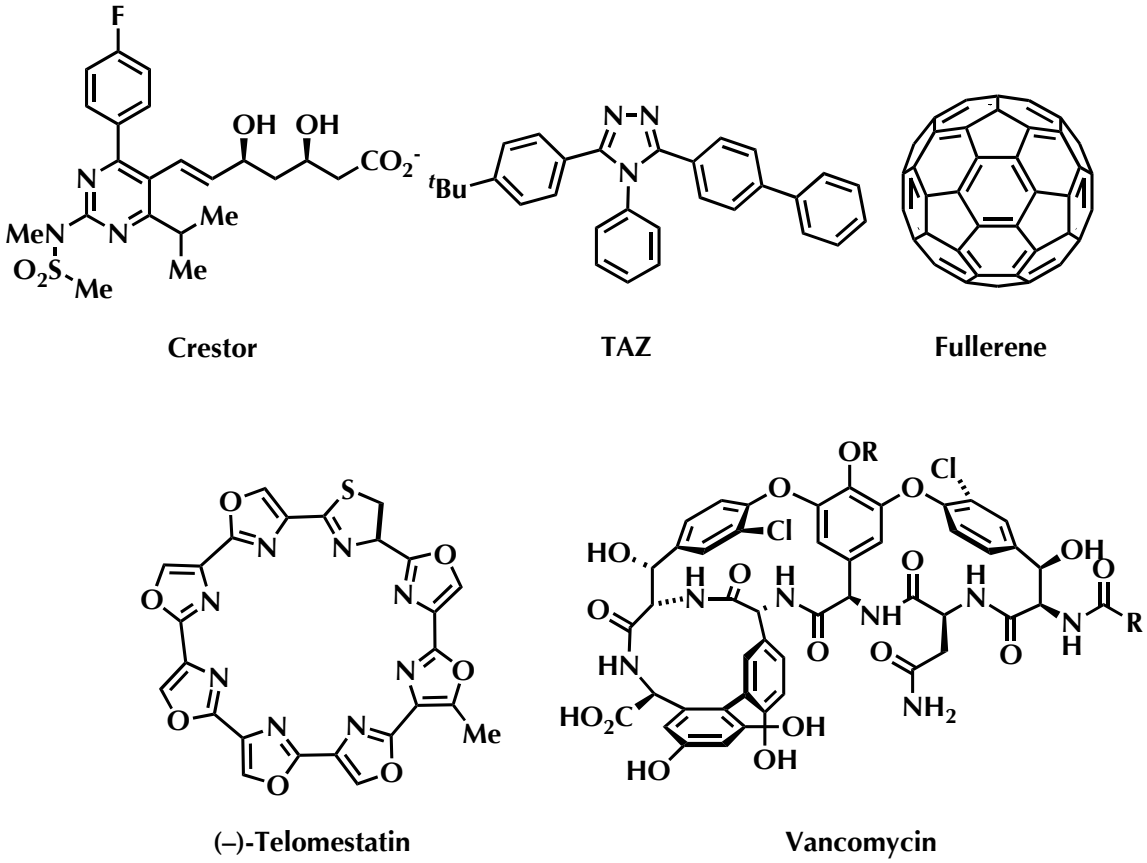


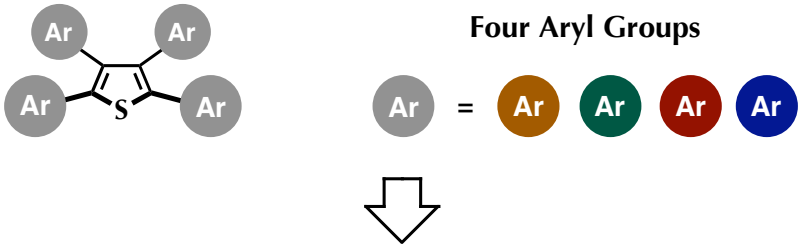
Figure 1. Representative Functional Arene-Assembled Molecules

How to construct these important biaryl structures is one of the highlights in this research. Although the Pd-catalyzed cross-coupling reactions of metalated arene/heteroarene and halogenated arene/heteroarene species are undoubtedly among the most reliable methods for making biaryls and heterobiaryls,[3] the direct C–H bond arylation of arenes and heteroarenes holds significant potential for streamlining overall synthetic routes. Based on this consideration, the author embarked on the development of direct C–H bond arylation of heteroarenes with haloarenes.

Among various arene-assembled molecules, multiply arylated heteroarenes represent privileged structures with many interesting functions and fascinating optoelectronic or biological properties. In order to accelerate the discovery and structure-property relationship studies of new functional molecules of this class, the development of general protocol for the programmable synthesis[4] of multiply arylated heteroarenes is needed. Therefore, rather than developing new C–H bond arylation reactions effective only for simple heteroarene-arene and heteroarene-heteroarene assembly, the author tried to develop an ideal and truly general arene-assembling method en route toward the programmed synthesis of multiply arylated heteroarenes.

However, the establishment of such synthesis is not as straightforward as it had been envisaged. Amazing number of possible compounds within multiply arylated heteroarene motif speaks well for challenges associated with this task. For example, theoretically 136 different tetraarylthiophenes are possible from four aryl groups (Figure 2). Notably, this is a number only from four aryl groups and, in a general formula, the total number of tetraarylthiophenes will be $n^2(n^2 + 1)/2$ from n aryl groups. Given that a number of arylating reagents are now readily available from commercial suppliers (aryl halides, arylboronic acids, etc.), potentially possible compounds run into astronomical numbers. Although this is a formidable task, the author considered that the programmed synthesis of multiply arylated heteroarenes should be viable by developing general catalysts achieving bond-selective and regiodivergent C–H bond arylation of heteroarenes.

In this thesis, the author has developed several new C–H bond arylation reactions of heteroarenes and successfully applied them to the programmed synthesis of tetraarylthiophenes.



Number of possible tetraarylthiophenes from four aryl groups is 136.

General formula: $n^2(n^2 + 1)/2$ compounds from n aryl groups

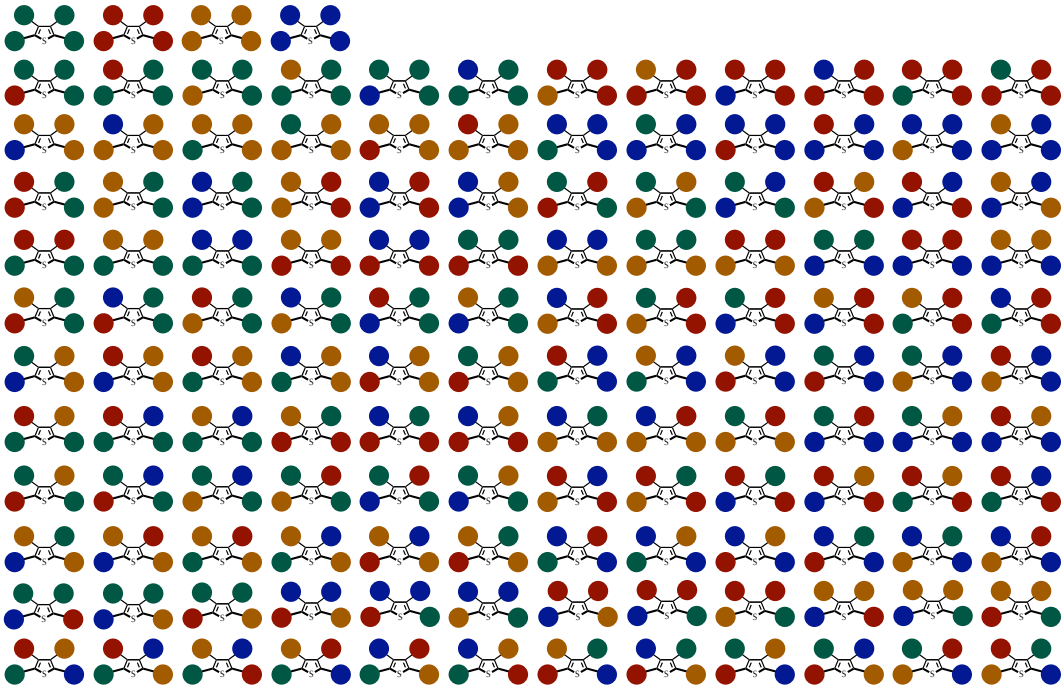
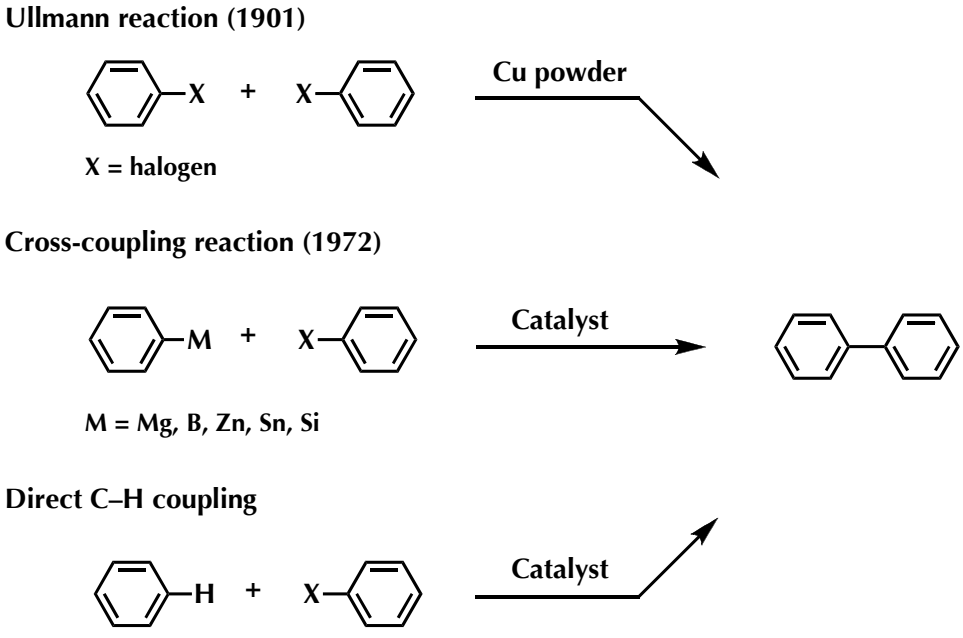


Figure 2. All Possible Tetraarylthiophenes with Four Aryl Groups

Transition Metal-Catalyzed Direct C–H Bond Arylation of Arenes[5]

Driven by the importance of oligoaryl structures in pure and applied chemistry, chemists have devoted significant efforts to the development of efficient method for aryl-aryl bond formation for over one century.[2] Historically, metal-mediated biaryl formation was first uncovered by Firtz Ullmann in 1901.[6] The stoichiometric amounts of copper enabled the reductive coupling of haloarenes, which afforded symmetrical biaryls (Scheme 1). Although this excellent discovery represents the potential of transition metal-mediated biaryl synthesis, few reports about the further development are known during the following decades.

The major technological breakthrough has been provided by Kumada–Tamao and Corriu in 1972. They disclosed that nickel salts or complexes, instead of copper, are able to selectively cross-couple organomagnesium reagents and haloarenes. A number of cross-coupling combinations including biaryl formation were demonstrated.



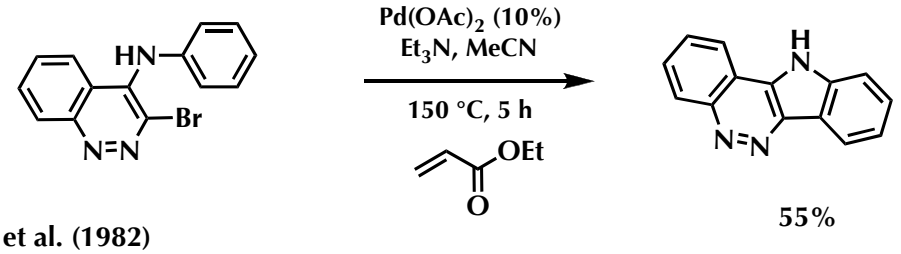
Scheme 1. History of Biaryl Synthesis

Since these epoch-making discoveries, Ni- and Pd-catalyzed biaryl cross-coupling reactions have been investigated extensively in the synthetic community, culminating in a wealth of efficient and practical processes such as Suzuki–Miyaura (Pd/B), Negishi (Pd/Zn), Migita–Kosugi–Stille (Pd/Sn), and Hiyama (Pd/Si) coupling reaction (Scheme 1).

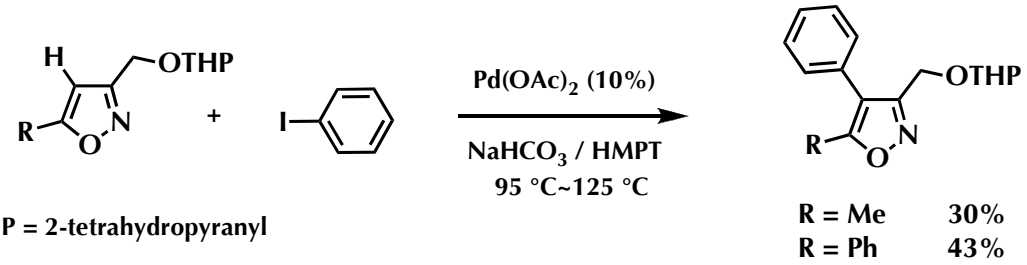
Thus, the Pd-catalyzed cross-coupling reactions of metallated (hetero)arenes and halogenated (hetero)arenes are undoubtedly among the most important and reliable methodologies for making biaryls. The development of improved catalysts and reagents continues to evolve at a rapid pace, and many important organic substances (pharmaceuticals as well as advanced electronic and photonic materials) are now made using this technology.[3] However, there is a common limitation and inefficiency in this cross-coupling technology; not only does it require extra steps to install the metallic and halogen fragments on (hetero)arenes, but it also inevitably produces metal-containing wastes at the end of the reaction. By contrast, the direct C–H bond arylation of arenes with aryl electrophiles is one of the ideal methods to built biaryls and offers the promise of a solution to many of these drawbacks (Scheme 1).[7–15]

One of the pioneering works in transition metal-catalyzed direct C–H bond arylation of (hetero)arenes with aryl halides was disclosed by Ames and co-workers in 1982.[16a] They reported Pd-catalyzed intramolecular direct C–H arylation of aniline derivatives (Scheme 2). During the attempts towards intermolecular arylation of alkene following Heck's protocols, cyclization product was obtained. Following report from the same group suggested that the alkene was not essential for this transformation.[16b] Almost at the same time, Pd-catalyzed intermolecular direct C–H bond arylation of isoxazole derivatives with iodobenzene was reported by Nakamura and co-workers (Scheme 2).[17] Under the influence of catalytic amount of palladium acetate, 3,5-disubstituted isoxazoles could be arylated at C4 position albeit moderate efficiency. Subsequently, Ohta and co-workers reported the direct arylation of indole with chloropyrazine derivatives with excellent regioselectivity in the presence of Pd catalyst (Scheme 2).[18]

Ames et al. (1982)



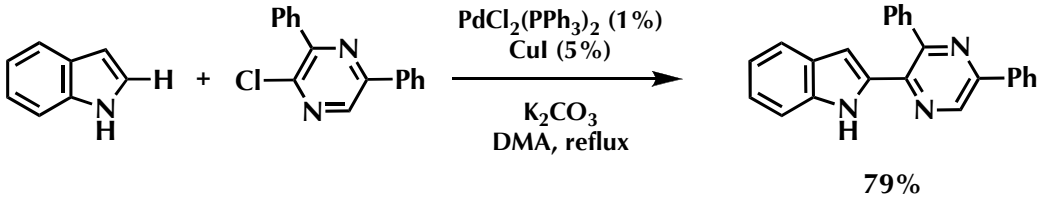
Nakamura et al. (1982)



THP = 2-tetrahydropyranyl

R = Me 30%
R = Ph 43%

Ohta et al. (1985)



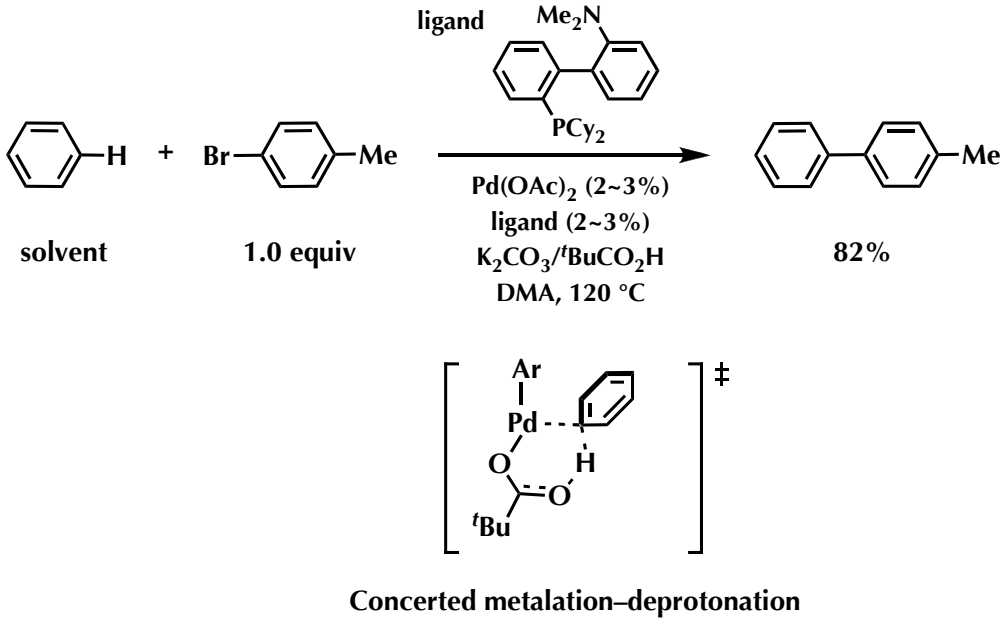
79%

Scheme 2. Pioneering Works in Direct C–H Arylation of (Hetero)arenes

After these pioneering works, the direct C–H bond arylation of various (hetero)arenes catalyzed by transition metals, such as Pd,[9] Rh,[10] Ru,[11] Cu,[12] Ir,[13] Ni,[14] and Fe[15] became one of the emerging topics in synthetic chemistry.[7–15] Though there are a vast number of publications in this research area, the recent representative examples are described below.

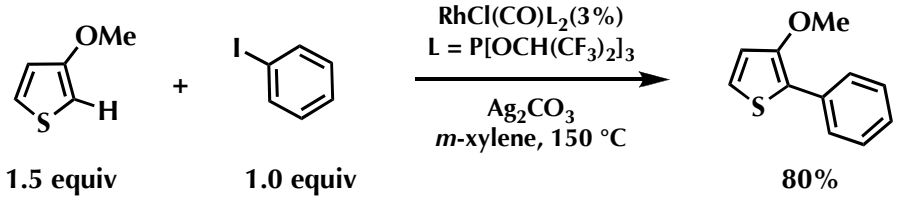
One of the outstanding results in the Pd-catalyzed direct C–H arylation chemistry has been disclosed by Fagnou and co-workers. They have demonstrated the Pd-catalyzed direct arylation of simple benzene, which is one of the challenging substrates in this research area, with haloarenes (Scheme 3).[9f] The addition of $^{t}BuCO_2H$ is essential to realize this reaction. On the basis of experimental and computational

studies, they proposed concerted metalation–deprotonation process for the C–H bond cleavage step.

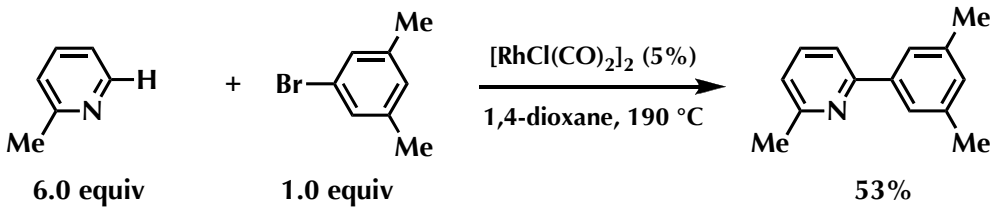


Scheme 3. Pd-Catalyzed Direct Arylation of Simple Benzene (Fagnou, 2006)

Rh-catalyzed direct arylation of a variety of electron-rich (hetero)arenes, such as thiophenes, pyrrole, furan, indole, and alkoxybenzenes, has been developed by Itami and co-workers (Scheme 4).[8b, 8c] The use of strongly π-accepting phosphite ligand and silver carbonate might accelerate the electrophilic rhodation of (hetero)arenes. On the other hand, Ellman and Bergman disclosed the direct arylation of electron-deficient nitrogen heteroarenes with aryl bromides in the presence of Rh catalyst (Scheme 5).[10i]

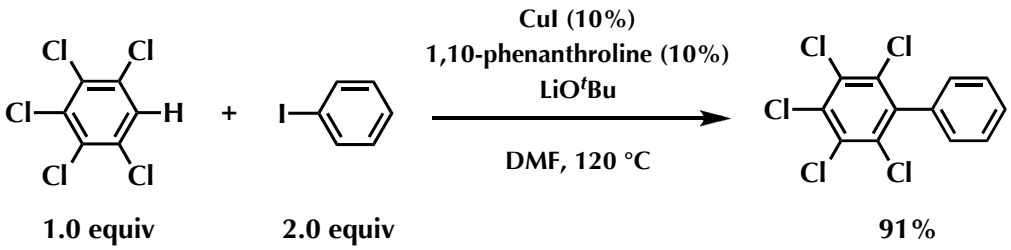


Scheme 4. Rh-Catalyzed Direct Arylation of Electron-Rich (Hetero)arenes (Itami, 2006)



Scheme 5. Rh-Catalyzed Direct Arylation of Electron-Deficient Nitrogen Heteroarenes (Ellman/Bergman, 2008)

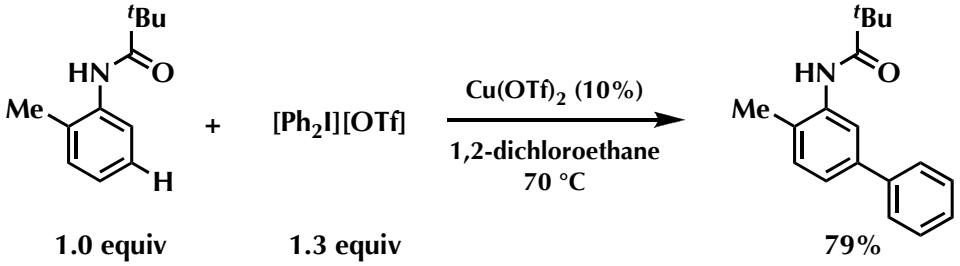
The group of Daugulis found that CuI/phenanthroline system enables the direct arylation of (hetero)arenes with aryl halides (Scheme 6).[12a, 12b] Mechanistic study suggested that the deprotonation of C–H bond of (hetero)arene by strong base such as LiO^tBu, followed by lithium-copper transmetalation affords (hetero)arylcopper species. The reaction of thus-generated copper complex with aryl halide gives the coupling product. The pK_a of C–H bond of (hetero)arenes is critically important in this reaction. In fact, this method is applicable to substrates bearing C–H bonds with pK_a values (DMSO) below 35 such as thiophenes, azoles, pyrimidine, and polyhalogenated benzenes.



Applicable substrates: Substrate bearing C–H bonds with pK_a (DMSO) below 35

Scheme 6. Cu-Catalyzed Direct Arylation of (Hetero)arenes (Daugulis, 2007)

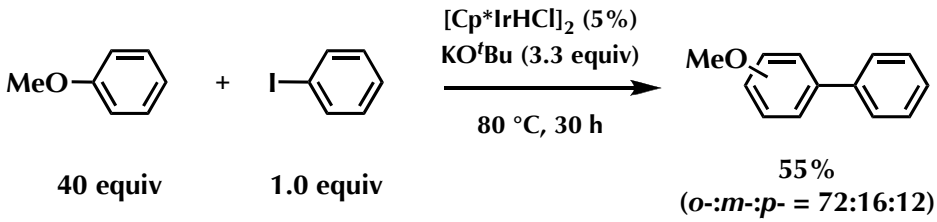
As an important advance in this research area, Cu-catalyzed *meta*-selective direct arylation of anilides with iodonium salt as arylating reagent was established by Gaunt and co-workers (Scheme 7).[12e, 12f] More recently, they demonstrated that almost identical conditions could be applied to the *para*-selective arylation of anilines and phenol derivatives.[12g]



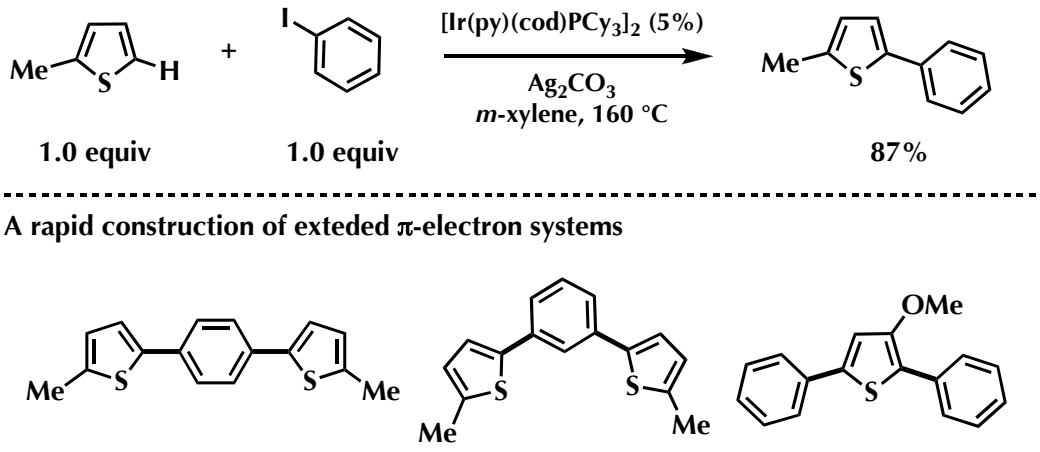
Scheme 7. *meta*-Selective Direct Arylation of Anilides (Gaunt, 2009)

Fujita and Itami uncovered that Ir complexes also possess catalytic activity for direct arylation of (hetero)arenes. Fujita found that [Cp*IrHCl]$_2$ catalyzes the direct arylation of simple arenes with aryl iodides in the presence of KO^{t}Bu.[13] On the basis of regioselectivity in the arylation of anisole with iodobenzene favoring *ortho*-arylation, radical-based mechanism has been proposed (Scheme 8). Subsequently, Itami and

co-workers disclosed the direct arylation of a wide range of electron-rich (hetero)arenes with aryl iodides under the influence of $[Ir(cod)(py)PCy_3]PF_6$ (Crabtree's catalyst) and Ag_2CO_3 (Scheme 9).[8f] This Ir catalysis is applicable to the rapid construction of extended π-electron systems.



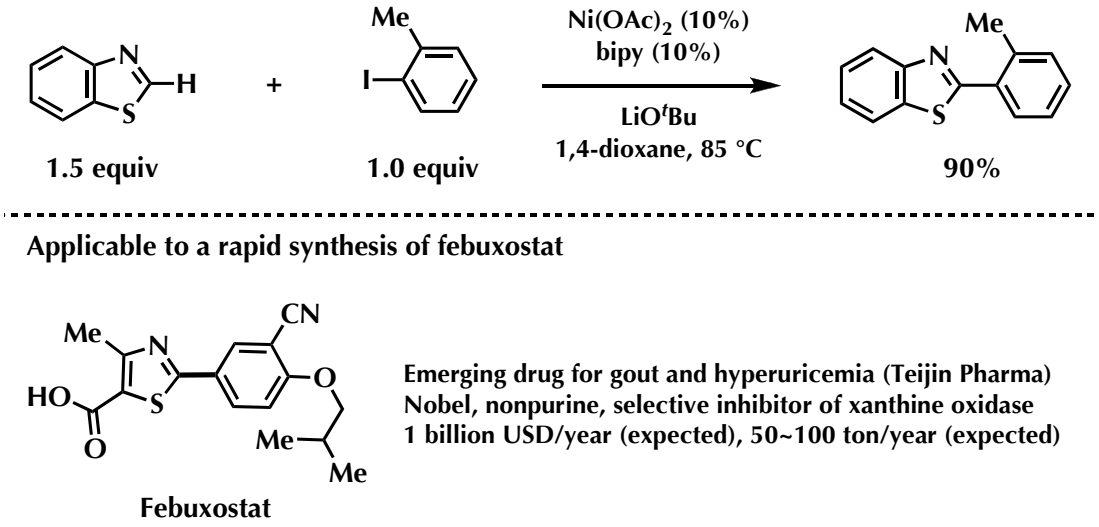
Scheme 8. Ir-Catalyzed Direct Arylation of Benzene Derivatives (Fujita, 2004)



Scheme 9. Ir-Catalyzed Direct Arylation of Electron-Rich (Hetero)arenes and Rapid Construction of Extended π-Electron Systems (Itami, 2009)

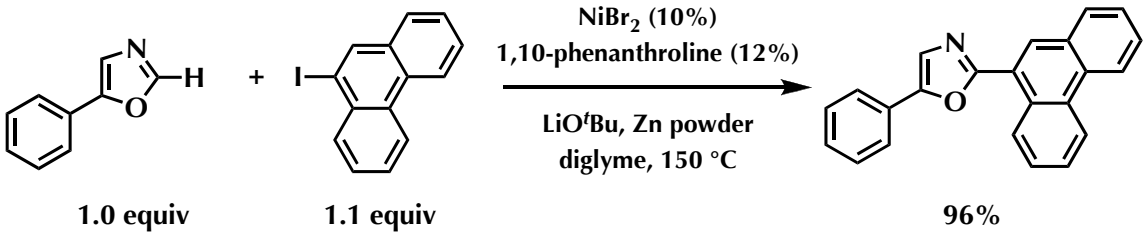
Pioneering studies on the Ni-catalyzed direct C–H arylation of heteroarenes were independently made by the groups of Itami[8g] and Miura.[14a] Itami and co-workers revealed that the nitrogen bidentate ligand and inexpensive $Ni(OAc)_2$ allowed efficient arylation of azoles. More interestingly, they demonstrated this direct arylation method

could be applied to a rapid synthesis of febuxostat (Scheme 10).



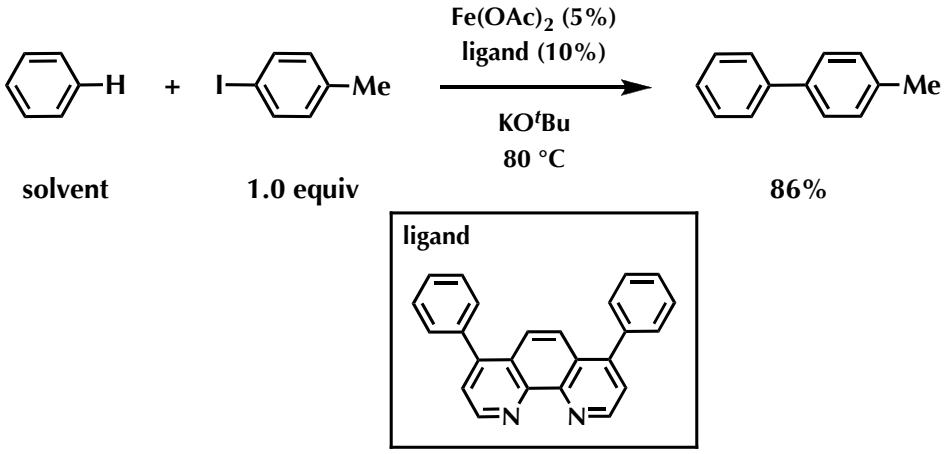
Scheme 10. Ni-Catalyzed Direct Arylation of Azoles and Rapid Synthesis of Febuxostat (Itami, 2009)

At the same time, Miura and co-workers disclosed the same transformation with $NiBr_2$ and 1,10-phenanthroline (Scheme 11). Although detailed information on the mechanism is unclear, they proposed that the catalytic cycle starts with the oxidative addition of aryl halide to Ni(0) species. The generated arylnickel(II) complex undergoes a transmetalation with an in situ generated organolithium reagent. Finally, the reductive elimination provides the desired coupling product.

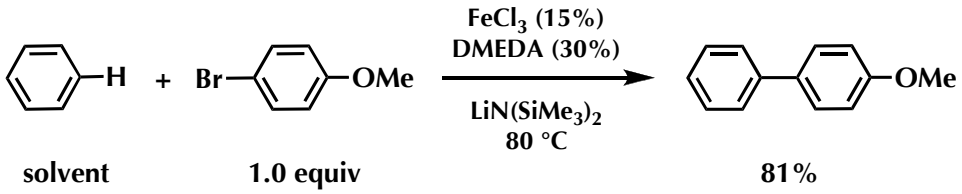


Scheme 11. Ni-Catalyzed Direct Arylation of Azoles (Miura, 2009)

Charette and co-workers demonstrated Fe-catalyzed direct arylation of unactivated benzene with aryl iodides in the presence of 4,7-diphenyl-1,10-phenanthroline ligand and KO^{t}Bu (Scheme 12).[15c] Due to the low product yield in the reaction with radical scavengers, they proposed that the reaction involves the radical pathway. Lei group also disclosed almost identical reaction with aryl bromides under the influence of $FeCl_3$, *N*,*N*′-dimethylethylene diamine (DMEDA), and lithium bis(trimethylsilyl)amide (Scheme 13).[15d] In both cases, the bidentate nitrogen ligand and strong base are essential.



Scheme 12. Fe-Catalyzed Direct Arylation of Unactivated Benzene (Charette, 2010)



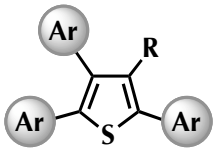
Scheme 13. Fe-Catalyzed Direct Arylation of Unactivated Benzene (Lei, 2010)

Synthesis of Multiply Arylated Heteroarenes through C–H Bond Functionalization

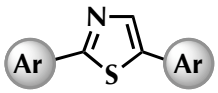
As already discussed above, the establishment of regioselective multiple arylation of heteroarenes is key for the creation of biaryl-based functional molecules. While a number of reports concerning the selective synthesis of mono-arylated heteroarenes have been published to date,[7–15] there are few reports with respect to regioselective multiple arylation of heteroarenes through C–H bond functionalization.[19–30] Representative state-of-the-art achievements in this area are summarized in Figure 3. However, most of molecules that could be synthesized are symmetrical molecules with one aryl group or two different aryl groups.

Considering potential diversity of these molecules (Figure 2), more flexible methods that allow accessing arylated heteroarenes having different aryl groups are required. At this moment, there exist only a handful of methods, including the method established in this work, that allow installing all different aryl groups onto heteroarene core in a programmable format.

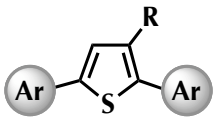
Same Aryl Group



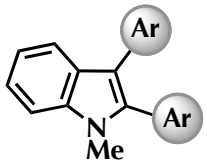
Miura (2002)[19]



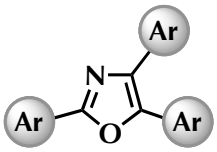
Miura (2003)[20]



Itami (2006, 2009)[8b, 8f]
Daugulis (2008)[12b]

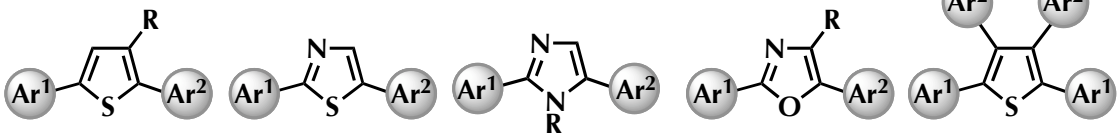


Itami (2008)[8d]
Miura (2009)[21]



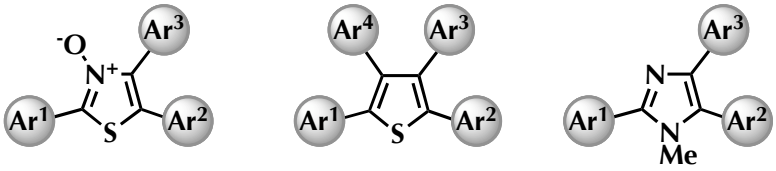
Shibahara, Murai (2010)[22]

Two Different Aryl Goups



Lemeire (2007)[23] **Mori (2004)[24]** **Bellina, Rossi (2008)[25]** **Hoarau (2008)[26]** **Miura (2008)[27]**

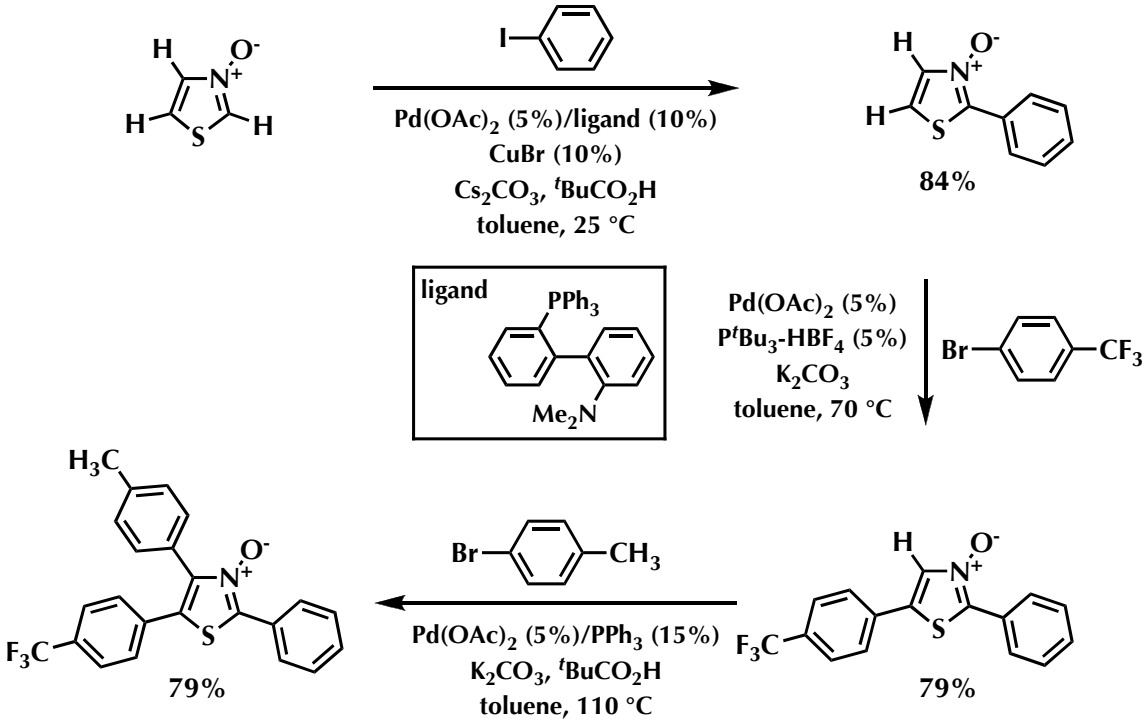
All Different Aryl Groups



Fagnou (2008)[28] **Itami (2009)[8h]** **Sames (2010)[29]**

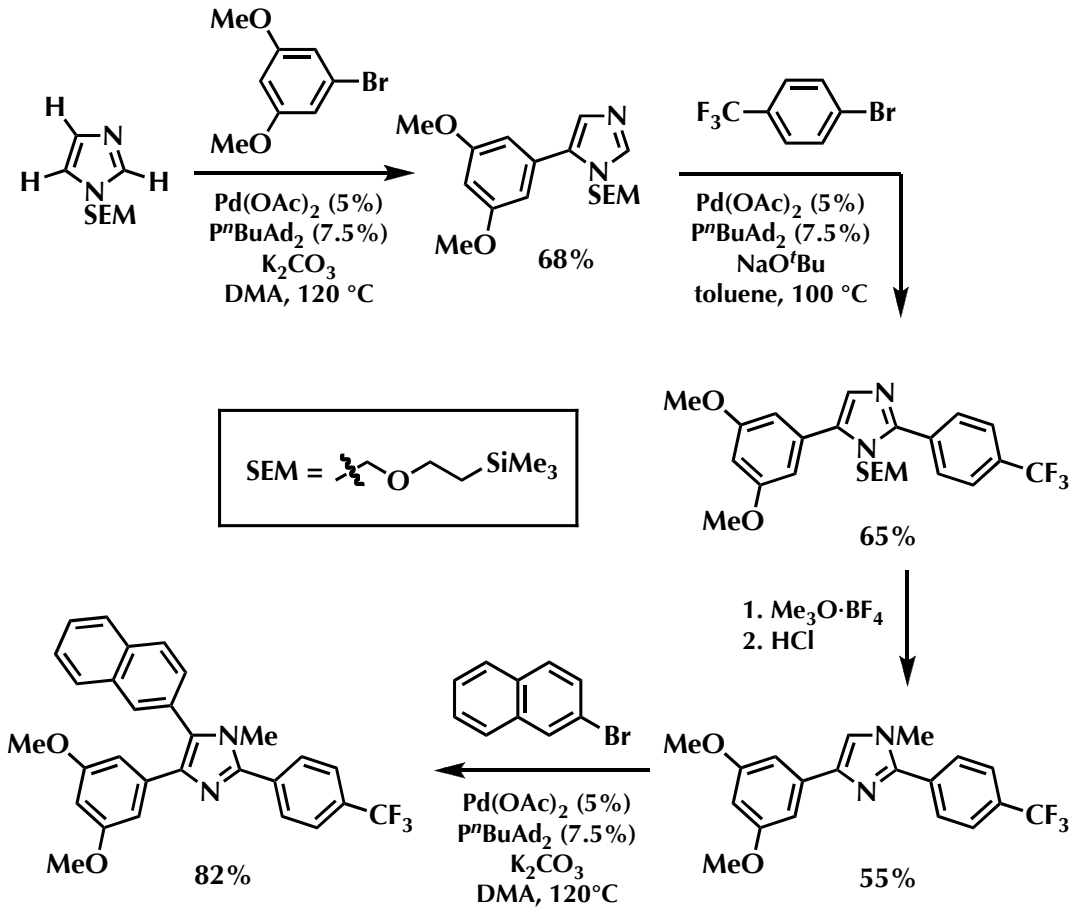
Figure 3. Representative States-of-the-Art Achievements in Multiple C–H Arylation of Heteroarenes

During this study, the regioselective multiple arylation of thiazole *N*-oxide was disclosed by Fagnou and co-workers (Scheme 14).[28] The use of *N*-oxide derivatives is key for discriminating C2 and C5 positions of thiazole ring in arylation reactions, which enables installing all different aryl groups onto thiazole core. This method is applicable to the regioselective sequential arylation of imidazole *N*-oxide as well.[28]



Scheme 14. Regioselective Sequential Arylation of Thiazole *N*-Oxide (Fagnou, 2008)

Sames and co-workers reported the regioselective sequential arylation of SEM-protected imidazole by using ingenious protecting group exchange strategy (Scheme 15).[29a] The same strategy is applicable to the triarylpyrazole synthesis in a programmed manner.[29b]

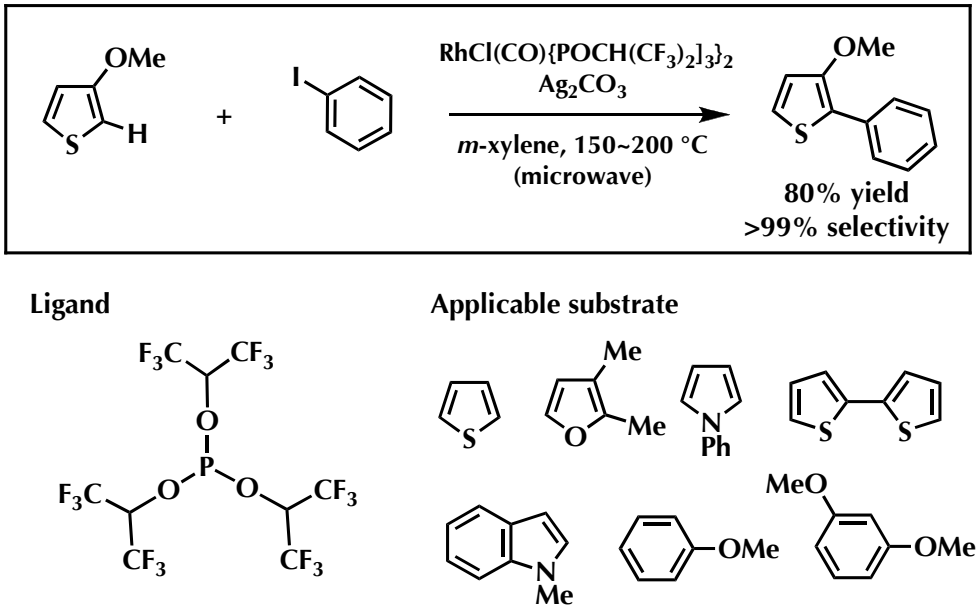


Scheme 15. Regioselective Sequential Arylation of SEM-Protected Imidazole (Sames, 2010)

As indicated by the limited number of successful examples, the programmed synthesis of multiply arylated heteroarenes having all different aryl groups is the challenging topic in the field. One reason for this limitation is the lack of proper catalyst that possesses perfect regioselectivity with sufficient reactivity for heteroarene C–H bond arylation. Accordingly, the development of catalyst that enables the bond-selective and regiodivergent C–H arylation of heteroarenes is highly desired.

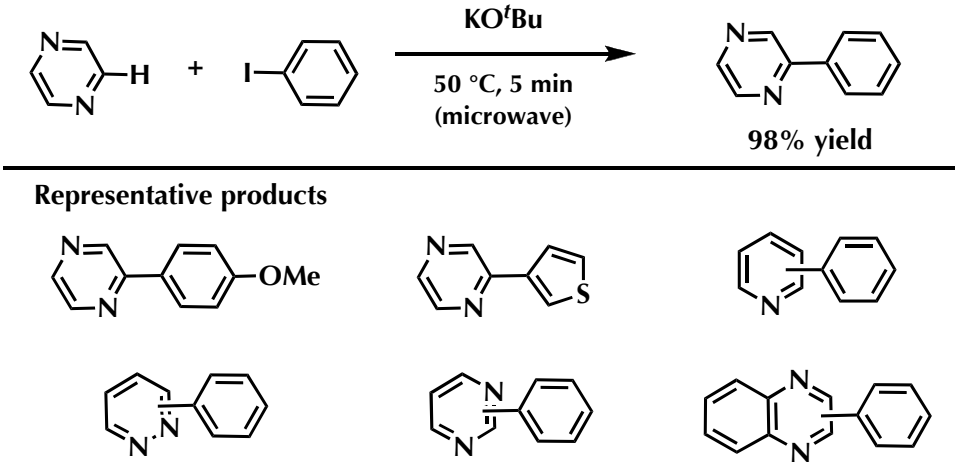
Survey of This Thesis

In Chapter 1, a new rhodium-based catalytic system for the direct C–H coupling of arenes and iodoarenes that shows high activity with reasonably broad scope was developed. Under the catalytic influence of $RhCl(CO)\{P[OCH(CF_3)_2]_3\}_2$ and Ag_2CO_3, the direct C–H arylation of heteroarenes and arenes took place with iodoarenes to afford a range of biaryls in good to excellent yields with high regioselectivity. Thiophenes, furans, pyrroles, indoles, and alkoxybenzenes are applicable to this arylation protocol.



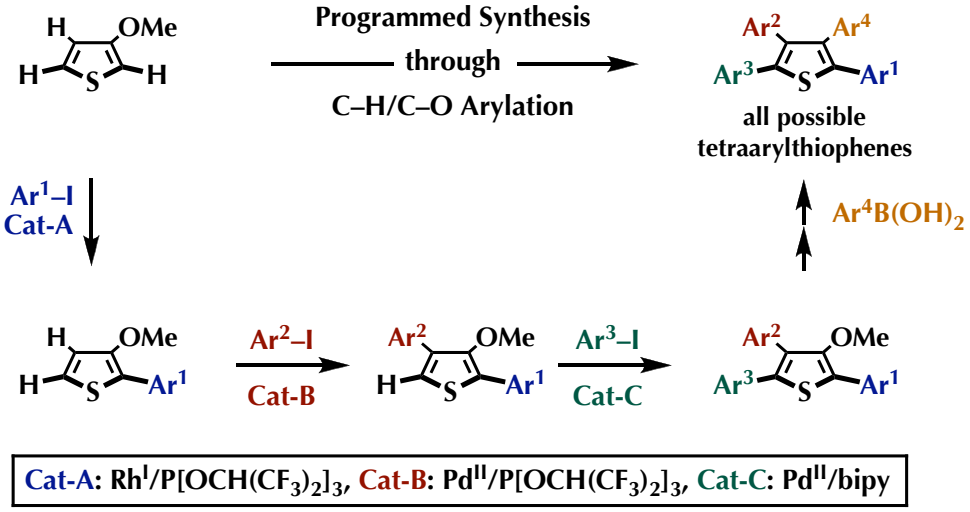
Scheme 16. Rh-Catalyzed Direct C–H Arylation of (Hetero)arenes with Iodoarenes

In Chapter 2, the biaryl coupling of electron-deficient nitrogen heteroarenes and haloarenes can be promoted by potassium *t*-butoxide alone, without the addition of any exogenous transition metal species. Electron-deficient nitrogen heteroarenes such as pyridine, pyridazine, pyrimidine, pyrazine, and quinoxaline are arylated with haloarenes. Control experiments support a radical-based mechanism.



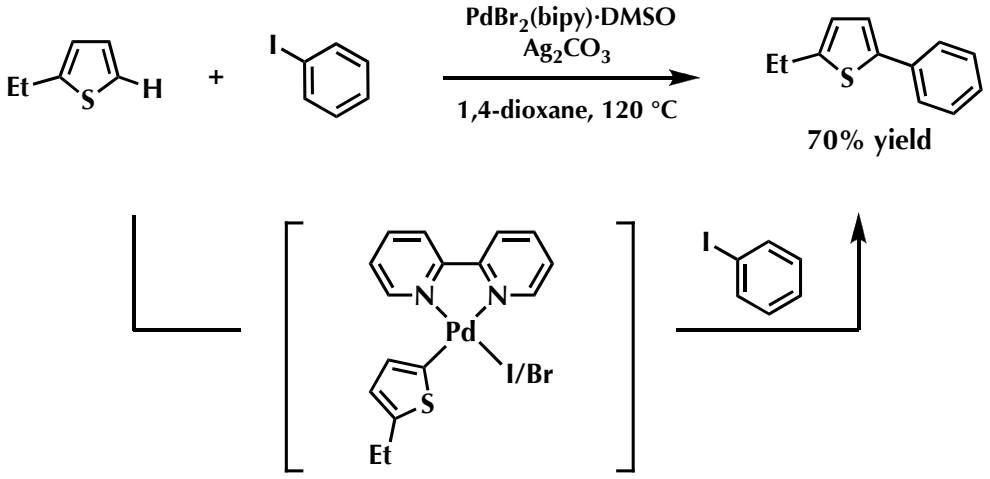
Scheme 17. KO^{t}Bu-Mediated Direct C–H Arylation of Nitrogen Heteroarenes

In Chapter 3, a general protocol for the programmed synthesis of tetraarylthiophenes has been established. The utilization of three catalysts, $RhCl(CO)\{P[OCH(CF_3)_2]_3\}_2$, $PdCl_2/P[OCH(CF_3)_2]_3$, and $PdCl_2$/2,2′-bipyridyl, enables the regioselective sequential arylations at the three C–H bonds of 3-methoxythiophene with iodoarenes. Interesting metal- and ligand-controlled regiodivergent C–H arylations have been uncovered during this study. The installation of fourth aryl groups to the thus-generated 2,4,5-triaryl-3-methoxythiophenes has been accomplished through a sequence of demethylation, triflation, and Suzuki–Miyaura coupling.



Scheme 18. Programmed Synthesis of Tetraarylthiophenes

In Chapter 4, development, scope, and mechanism of Pd/bipy-based catalytic system for the C–H bond arylation of heteroarenes with haloarenes are described. The complex $PdBr_2$(bipy)·DMSO, whose structure was unambiguously determined by X-ray crystallography, turned out to be a general catalyst precursor for the process. The reaction is applicable to a range of electron-rich five-membered heteroarenes such as thiophenes, thiazoles, benzofurans, and indoles. Mechanistic study implicated that the reaction occurs not through a conventional Pd^0/Pd^{II} redox catalysis but rather through a Pd^{II} non-redox or Pd^{II}/Pd^{IV} redox catalysis.



Thiophenes (not haloarenes) are the first-reacting reagents for Pd species.

Scheme 19. Pd/bipy-Catalyzed C–H Arylation of Heteroarenes with Haloarenes

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Chapter 1

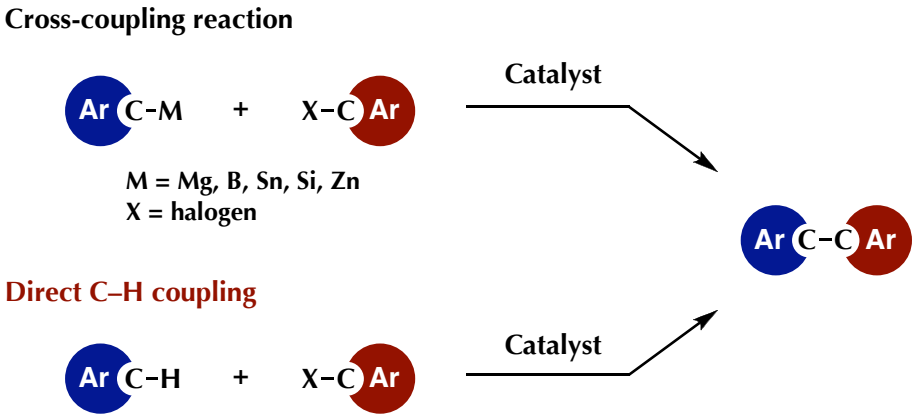
Rhodium-Catalyzed C–H Bond Arylation of (Hetero)arenes with Iodoarenes

Abstract: A new rhodium-based catalytic system for the direct C–H coupling of arenes and iodoarenes that shows high activity with reasonably broad scope was developed. Under the catalytic influence of $RhCl(CO)\{P[OCH(CF_3)_2]_3\}_2$ and Ag_2CO_3, the direct C–H arylation of heteroarenes and arenes took place with iodoarenes to afford a range of biaryls in good to excellent yields with high regioselectivity. Thiophenes, furans, pyrroles, indoles, and alkoxybenzenes are applicable to this arylation protocol.

1. Introduction

Organic molecules having (hetero)aryl–(hetero)aryl bonds represent privileged structural motifs frequently found in natural products or used in pharmaceuticals and functional organic materials. Therefore, the development of efficient methods for biaryl formation has been a topic of great importance in all aspects of pure and applied chemistry.[1]

Although the Pd-catalyzed cross-coupling reactions of metalated arene/heteroarene and halogenated arene/heteroarene species are undoubtedly among the most reliable methods for making biaryls and heterobiaryls,[1,2] the C–H bond arylation of arenes and heteroarenes holds significant potential for streamlining overall synthetic routes (Scheme 1).[3,4] Indeed, recent worldwide research has resulted in impressive progress for the direct C–H coupling methodology in making biaryls (mainly palladium-based systems).[3–11] However, there still exists considerable room for further development. For example, a universal catalyst that can directly arylate a variety of heteroarenes as well as simple arenes are much limited.



Scheme 1. Cross-Coupling and Direct C–H Coupling for Biaryl Formation.

In this Chapter, the development of a rhodium complex bearing a strongly π-accepting ligand $P[OCH(CF_3)_2]_3$ as an efficient catalyst precursor for direct C–H bond arylation of electron-rich arenes is described (Figure 1).

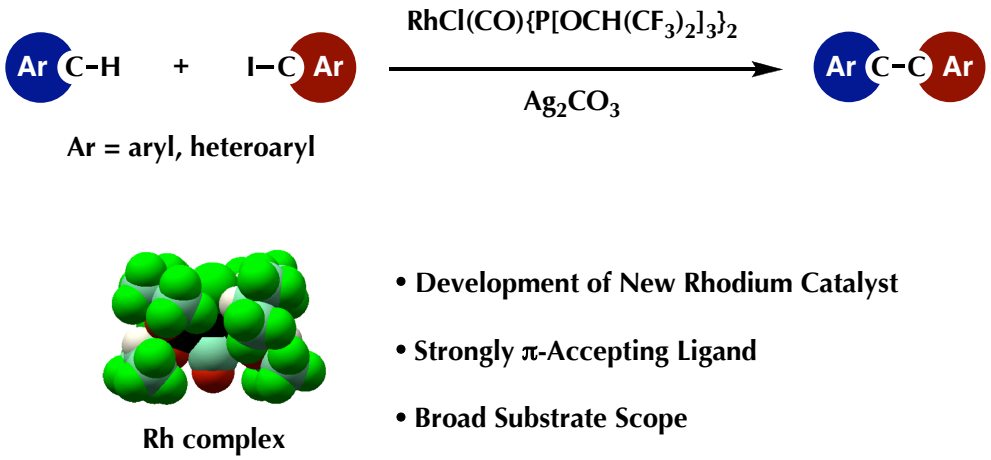
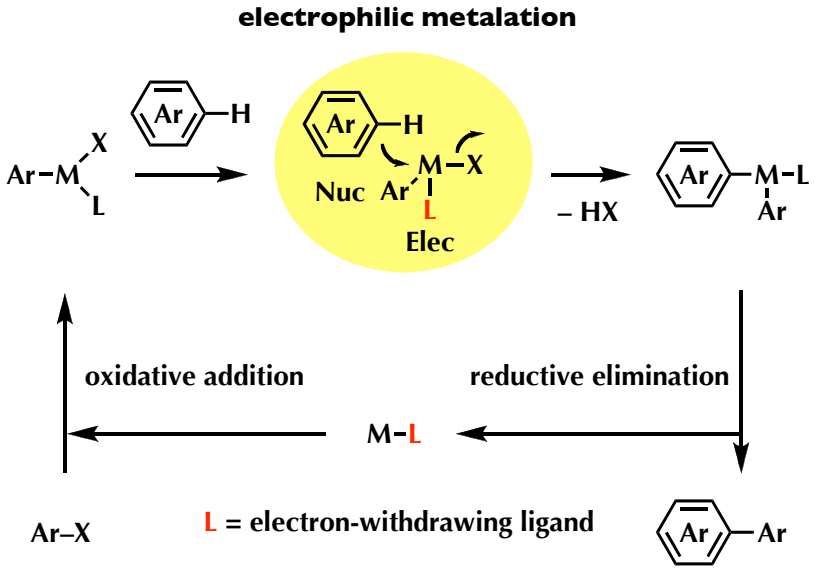


Figure 1. Direct Coupling of Arenes and Iodoarenes Catalyzed by Rhodium Complex

2. Results and Discussion

2-1. Strategy and Discovery of Rhodium Catalysis

Initial scenario for realizing an efficient transition metal-catalyzed biaryl coupling of arenes with haloarenes (C–H/C–X biaryl coupling) has been the redox-catalysis shown in Scheme 2. This involves (i) oxidative addition of haloarene (Ar–X) to transition metal complex (M), (ii) electrophilic metalation of arene (Ar–H) with thus-formed Ar–M–X giving diarylmetal species, and (iii) reductive elimination of biaryl product (Ar–Ar) with the regeneration of catalyst M. The author envisaged that the use of electron-withdrawing neutral ligand (L) would lead to a distinct nucleophile-electrophile interaction between an arene (Ar–H) and Ar–M–X species, thereby promoting electrophilic arene metalation. Moreover, such a ligand was expected to facilitate the product-forming reductive elimination step as well. This mechanistic blueprint means that designed C–H/C–X biaryl coupling should best be described as a 'Friedel–Crafts' aromatic arylation reaction.

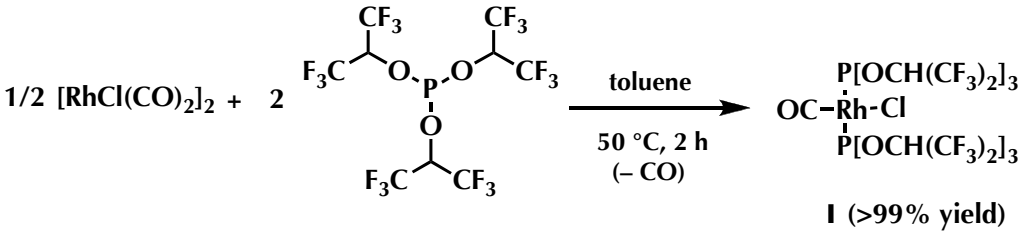


Scheme 2. Initial Scenario for Direct C–H Arylation of Arenes

In order to find an as-yet unexplored catalyst of this kind, the author took a very distinct and unconventional approach. Rather than screening various ligands for a transition metal, the investigation of transition metals by fixing the ligand as $P[OCH(CF_3)_2]_3$ which is known to be one of the most electron-withdrawing neutral ligands was carried out.[12] After extensive screening, Rh^8 was found to be the best metal center which is able to realize our concept.

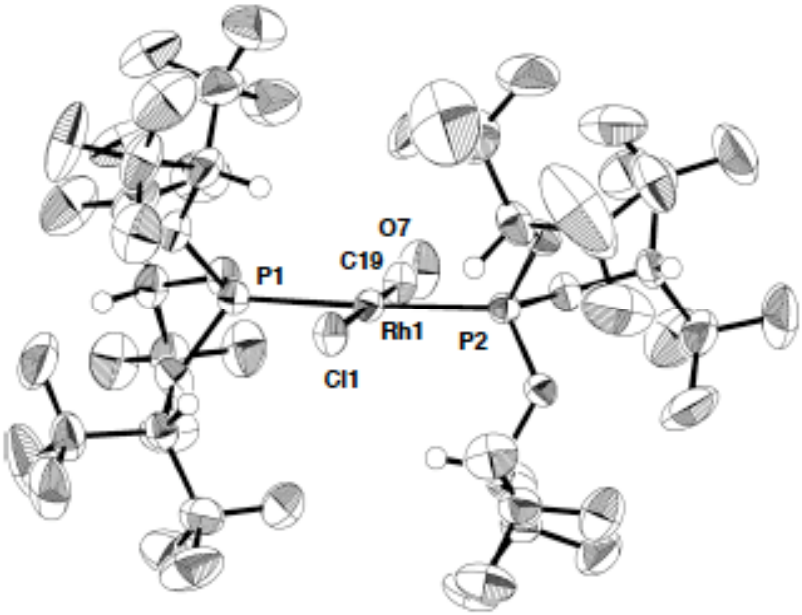
2-2. Synthesis and Structure of Rhodium Complex 1

The synthesis of $RhCl(CO)\{P[OCH(CF_3)_2]_3\}_2$ (**1**) is straightforward and easy to conduct (Scheme 3). Thus, a solution of $[RhCl(CO)_2]_2$ and $P[OCH(CF_3)_2]_3$ in dry toluene was stirred at 50 °C for 2 h under argon. After cooling the reaction mixture to room temperature, solvent was removed under reduced pressure. Reprecipitation from THF/toluene followed by filtration and vacuum drying afforded **1** as yellow solid (>99% yield). This complex is very stable against air and moisture in the solid state. Virtually no decomposition of **1** has been detected after extended (>10 months) exposure to air.



Scheme 3. Synthesis of Rhodium Complex

The X-ray crystal structure of **1** indicates that the high stability of **1** may be due to the effective shielding of the rhodium atom by two bulky phosphite ligands (Figure 2). In addition, a "push" electronic effect of Cl, rendering the rhodium center less unsaturated than a formal 16-electron species through a π-donation from Cl to Rh, might also contribute to its high stability.[13,14]



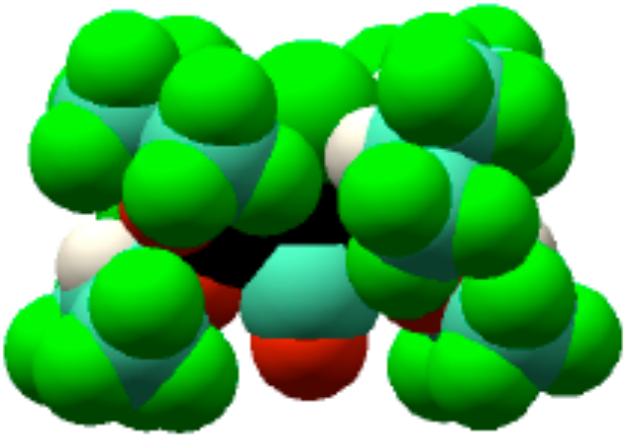
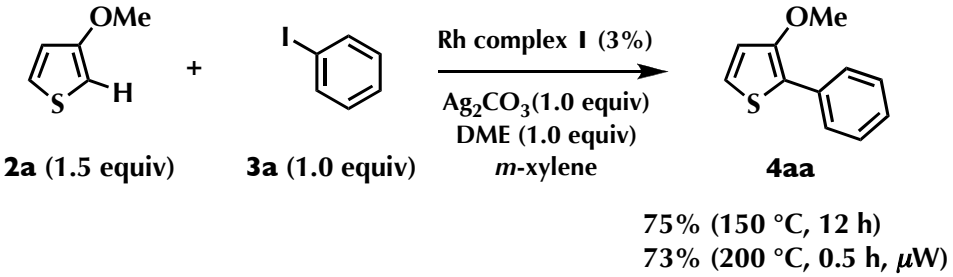


Figure 2. The X-ray Structure of **1** (above: ORTEP drawing, bottom: space-filling model). Thermal ellipsoids are drawn at the 50% probability level.

2-3. Direct Coupling of Heteroarenes and Iodoarenes

The author discovered that the rhodium complex **1** functions as an efficient catalyst precursor, with the assistance of silver carbonate, for the direct coupling of electron-rich heteroarenes and iodoarenes. For example, when a mixture of 3-methoxythiophene (**2a**) (1.5 equiv) and iodobenzene (**3a**) (1.0 equiv) in *m*-xylene was stirred at 150 °C for 12 h in the presence of **1** (3%), Ag_2CO_3 (1.0 equiv) and 1,2-dimethoxyethane (DME) (1.0 equiv), a direct C–H coupling took place at the 2-position of **2a** to afford **4aa** in 75% yield with virtually complete regioselectivity (Scheme 4).[15] When the reaction was conducted at 200 °C under microwave irradiation, the reaction was complete within 0.5 h to furnish **4aa** in 73% yield.

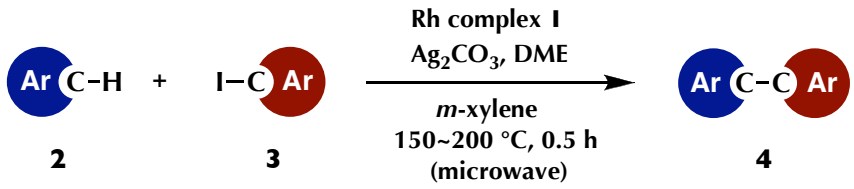


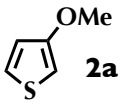
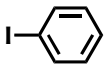
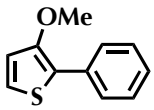
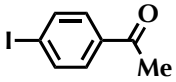
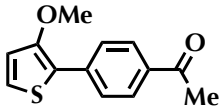
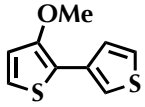
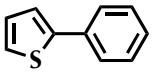
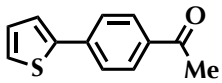
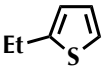
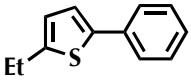
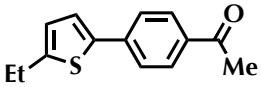
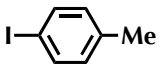
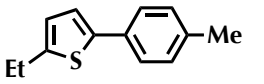
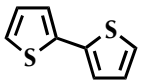
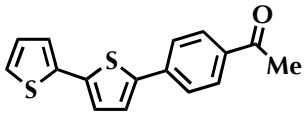
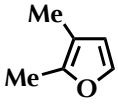
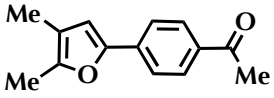
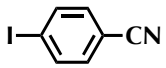
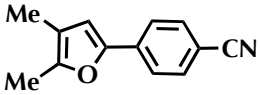
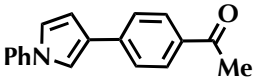
Scheme 4. Representative Examples of Direct Coupling of Arenes with Iodoarenes

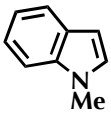
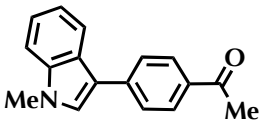
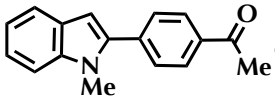
With a new rhodium-based system catalyzing the direct C–H coupling in hand, the author surveyed heteroarenes and haloarenes that could be applied to our system (Table 1). It was found that the direct coupling proceeded efficiently with electron-neutral and -deficient iodoarenes by using **2a** as a model substrate (entries 1–3). Iodoheteroarenes and electron-rich iodoarenes were also found to be applicable, but they tend to possess somewhat lower reactivity (entries 3 and 8). Unfortunately, the corresponding bromides, chlorides, and triflates were found to be poor substrates with this first generation catalytic system.

As for heteroarenes, it was found that a range of electron-rich five-membered heteroarenes such as thiophenes, furans, pyrroles, and indoles were applicable to the present catalysis (Table 1). Not only 3-methoxythiophene (**2a**), but also thiophene (**2b**), 2-ethylthiophene (**2c**), and bithiophene (**2d**) were found to cross-couple with iodoarenes affording the corresponding biaryls in good yields (entries 1–9). Furans such as 2,3-dimethylfuran (**2e**) were also arylated well (entries 10 and 11). For all thiophenes and furans examined, the direct coupling proceeded selectively at carbon adjacent to sulfurs or oxygens. When 1-phenylpyrrole (**2f**) was used as a substrate, the direct coupling with **3b** took place selectively at 3-position of the pyrrole ring (entry 12). The direct coupling of 1-methylindole (**2g**) and **3b** also took place efficiently, but resulted in a 71:29 mixture of regioisomers favoring the C3-arylation product (entry 13). Unfortunately, the C–H coupling did not proceed with electron-deficient six-membered heteroarenes such as pyridine using our first generation catalyst.

Table 1. Rhodium-Catalyzed Direct Coupling of Heteroarenes and Iodoarenes[a]



entry	2	3	product 4	% yield[b]
1	 **2a**	 **3a**	 **4aa**	73 (80)
2	**2a**	 **3b**	 **4ab**	94 (99)
3	**2a**	 **3c**	 **4ac**	52 (58)
4	 **2b**	**3a**	 **4ba**	53 (80)[c]
5	**2b**	**3b**	 **4bb**	83[c]
6	 **2c**	**3a**	 **4ca**	76 (99)
7	**2c**	**3b**	 **4cb**	79 (87)
8	**2c**	 **3d**	 **4cd**	50 (64)
9	 **2d**	**3b**	 **4db**	64
10	 **2e**	**3b**	 **4eb**	64
11	**2e**	 **3e**	 **4ee**	66
12	 **2f**	**3b**	 **4fb**	58 (86)

entry	**2**	**3**	product **4**	% yield[b]
13	 **2g**	**3b**	 **4gb** (C-3)	57
			 **4gb'** (C-2)	23

[a] Conditions: **I** (3%), **2** (1.5 equiv), **3** (1.0 equiv), Ag_2CO_3 (1.0 equiv), DME (1.0 equiv), *m*-xylene, 150~200 °C, 0.5 h (microwave). [b] Isolated yield. The yield in parentheses is determined by NMR. [c] Conditions: **I** (10%), **2** (15 equiv), **3** (1.0 equiv), Ag_2CO_3 (1.0 equiv), 150 °C. Reactions were conducted under conventional heating (150 °C, 14~15 h).

2-4. Mechanistic Considerations

Although the precise mechanism remains unknown, our current approximation is shown in Figure 3. The author surmises that ligand dissociation (most likely the phosphite) from **1** is an initial step generating a coordinatively unsaturated rhodium(I) species **A**, which thereafter initiates a Rh^{I}/Rh^{III} redox cycle. This includes (i) oxidative addition of iodoarene **3** (Ar^1–I) to **A**, (ii) generation of cationic arylrhodium(III) species **B** with the assistance of silver carbonate, (iii) electrophilic metalation (rhodation) of arene **2** (Ar^2–H) with **B** giving diarylrhodium(III) species **C**, and (iv) reductive elimination of biaryl product (**4**) with the regeneration of **A**.[16]

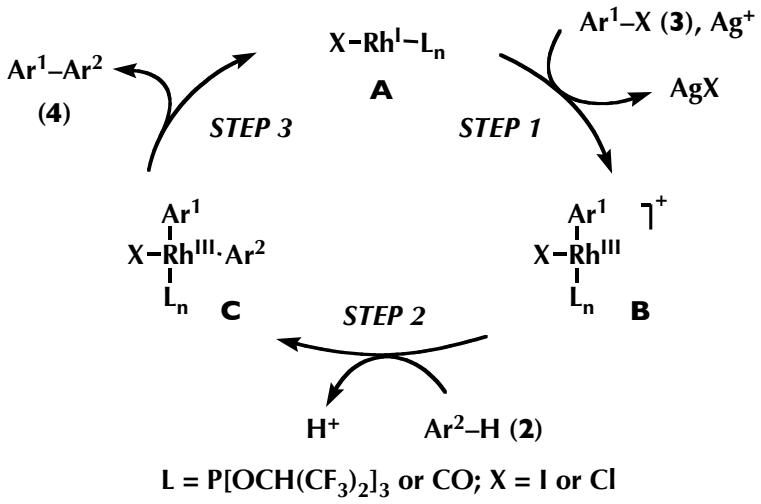
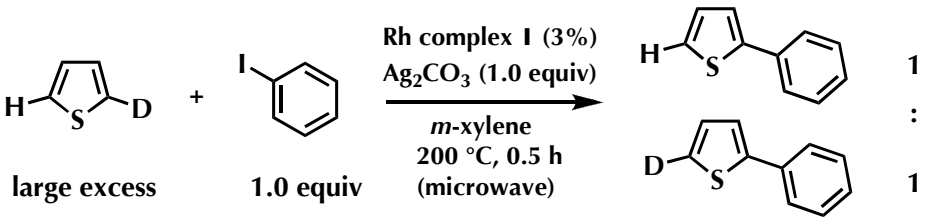


Figure 3. A Possible Mechanism of Rhodium Catalysis

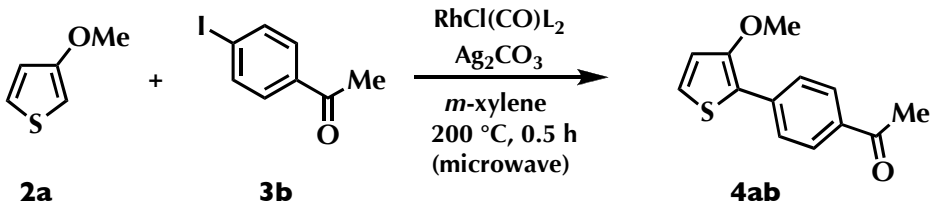
The beneficial effect of strongly π-accepting $P[OCH(CF_3)_2]_3$ might be to render the rhodium center electron-deficient, thereby facilitating electrophilic metalation as well as reductive elimination step. A preliminary experimental study using deuterium-labeled substrates is in line with such an assumption. For example, when large excess of deuterium-labeled thiophene was subjected to the coupling with iodobenzene under the influence of **1** and Ag_2CO_3, both C–H and C–D bonds adjacent to sulfur were phenylated to a degree virtually equal, indicating a negligible kinetic isotope effect (Scheme 5). This result indicates that the C–H bond-cleaving step (possibly electrophilic rhodation; **B** → **C** in Figure 3) is not a turnover-limiting step in this rhodium catalysis.



Scheme 5. Intramolecular Competitive Reaction using Deuterium-labeled Thiophene

In line with initial mechanistic assumption that the use of strongly π-accepting $P[OCH(CF_3)_2]_3$ as a ligand has a strong impact on the energetic profile in the catalytic cycle, a strong ligand effect in the present catalysis was observed (Table 2). For example, when a less π-accepting ligand such as $P(C_6H_5)[OCH(CF_3)_2]_2$, $P(OC_6H_5)_3$, $P[OCH(CH_3)_2]_3$, or $P(C_6H_5)_3$ was used in place of $P[OCH(CF_3)_2]_3$ for the reaction of **2a** and **3b**, the yield of the arylation product **4ab** decreased from 94% to 31%, 6%, 9%, and 0%, respectively (Table 2). There is a clear correlation between the arylation efficiency and the π-accepting ability of the ligand, as judged by electronic parameters[17] based on the carbonyl stretching frequency (υ_{CO}) in *trans*-$RhCl(CO)L_2$ complexes. In particular, the dramatic difference between $P[OCH(CF_3)_2]_3$ and $P[OCH(CH_3)_2]_3$, which are almost identical in size, is a clear indication that the π-accepting nature of the ancillary ligand has the greatest benefit in our catalysis.

Table 2. Effect of Ligand in Rh-Catalyzed Direct Coupling[a]



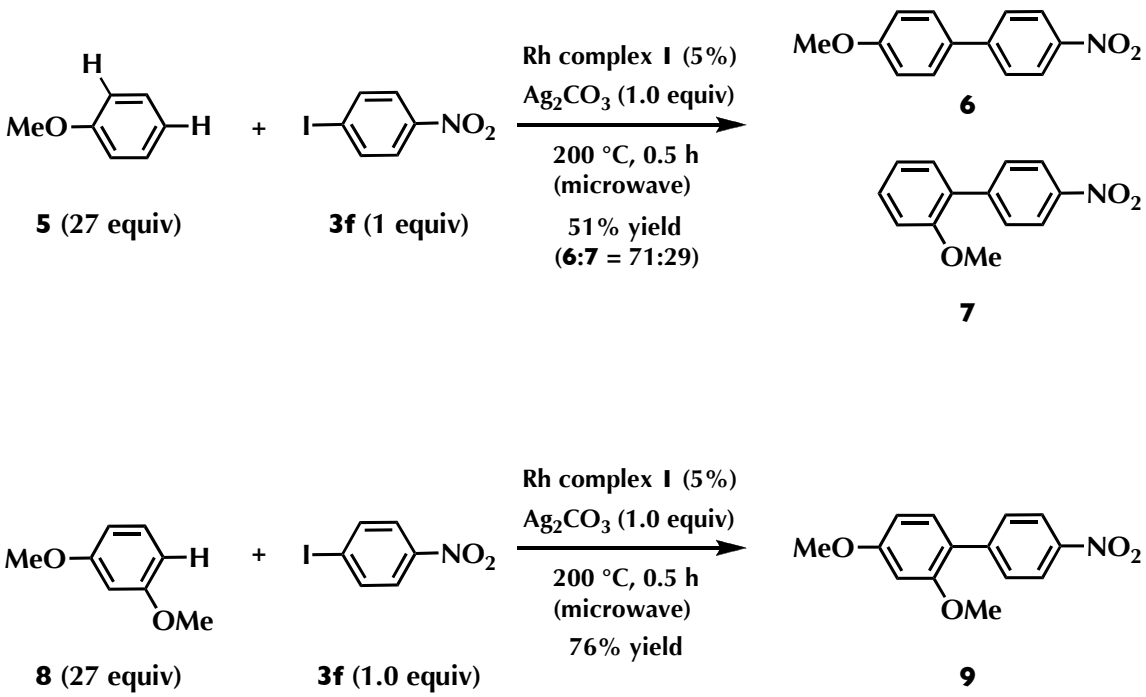
2a **3b** **4ab**

ligand (L)	yield of **4ab** (%)	ν_{CO} in $RhCl(CO)L_2$ (cm^{-1})
$P[OCH(CF_3)_2]_3$	94	2070
$P(C_6H_5)[OCH(CF_3)_2]_2$	31	2038
$P(OC_6H_5)_3$	6	2018
$P[OCH(CH_3)_2]_3$	9	2002
$P(C_6H_5)_3$	0	1983

[a] Conditions: **2a** (1.5 equiv), **3b** (1.0 equiv), $[RhCl(CO)_2]_2$ (1.5%), ligand (6%), Ag_2CO_3 (1.0 equiv), *m*-xylene, 150 °C.

2-5. Direct Coupling of Benzene Derivatives and Iodoarenes

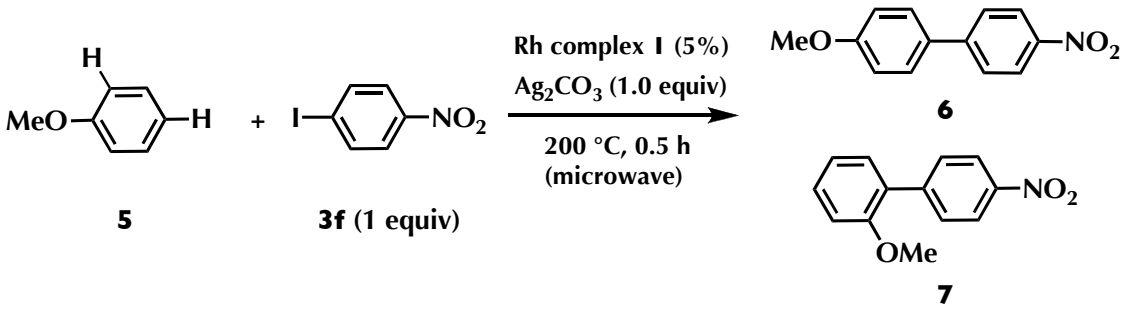
The aforementioned substrate survey (Table 1) revealed that this rhodium catalyst has a reasonably broad scope of substrates but is not yet truly universal, which encourages us to develop it further. The author found that this rhodium catalyst can effect the direct C–H coupling of benzene derivatives, which have proven to be the most challenging substrate class in this field (Scheme 6).[3,4] For example, when anisole (**5**) (27 equiv) was treated with *p*-nitrophenyl iodide (**3f**) (1.0 equiv) under the influence of **1** (5%) and Ag_2CO_3 (1.0 equiv), arylated anisoles (**6** and **7**) were obtained as a mixture of regioisomers (51% yield; *o*:*m*:*p* = 29:0:71). When 1,3-dimethoxybenzene (**8**) was used as a substrate, arylation occurred exclusively at the 4-position giving the corresponding biaryl **9** in 76% yield.



Scheme 6. Arylation of Benzene Derivatives

The investigation on the reactivity of anisole (**5**) in this reaction was further conducted. The yield of arylation products (**6** and **7**) gradually decreased as the amount of anisole (**5**) is decreased (Table 3). For example, the yield of arylated anisoles (**6** and **7**) was slightly decreased when 10 or 5 equivalent of anisole was used (entries 2 and 3). It was found that small excess of anisole (**5**) (2.0 equiv) is enough to promote the reaction by using *n*-octane as a co-solvent.

Table 3. Reactivity of Anisole (**5**) under Rh Catalysis[a]



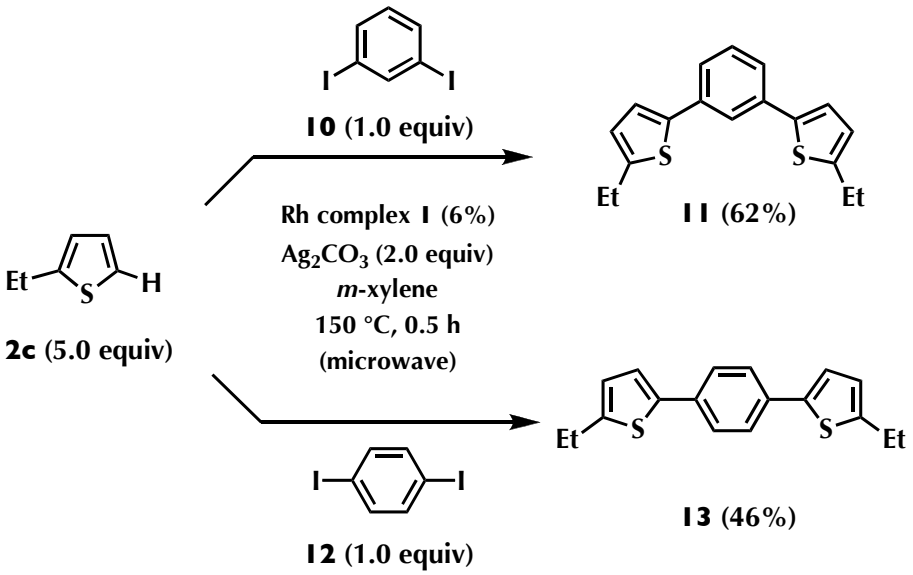
entry	anisole (**5**)	yield (**6** + **7**) (%)
1	27 equiv	51
2	10 equiv	48
3[a]	5.0 equiv	42
4[a]	2.0 equiv	25

[a] 6 equiv of *n*-octane was used as a co-solvent.

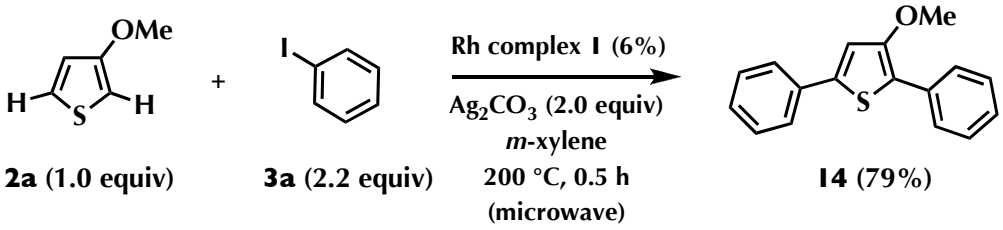
These reactions not only serve as successful examples of functionalization of relatively simple benzene derivatives but also shed some light on the mechanism. The manifestation of clear *ortho-para* selectivity in the arylation of alkoxybenzenes is consistent with the C–H bond cleavage based on electrophilic metalation (Figure 3) but not with those through directed *ortho*-metalation and/or C–H oxidative addition as have been proposed in some other C–H bond functionalization reaction.[4] Although the reactivity of C–H arylation of alkoxybenzenes is still low under the present conditions, the successful arylation of benzene derivatives without catalyst-directing groups is noteworthy.[4]

2-6. Synthesis of Extended π-Systems through One-pot Multiple Arylation

The author envisages that the rhodium-catalyzed direct C–H coupling technology has broad potential for further applications. For example, a range of extended π-electron systems can be easily constructed through multiple C–H coupling (Scheme 7 and 8). When 1,3-diiodobenzene (**10**) was treated with an excess amount of 2-ethylthiophene (**2c**, 5.0 equiv to **10**), a double C–H arylation took place giving an interesting benzene-core π-system **11** in 62% yield (Scheme 7). When 1,4-diiodobenzene (**12**) was used as a core substrate, fully conjugated π-system **13** was obtained in 46% yield (Scheme 7). Double C–H bond arylations of the same heteroarene core was also achieved (Scheme 8). For example, when 3-methoxythiophene (**2a**) was treated with an excess amount of **3a** (2.2 equiv to **2a**), a double C–H arylation of the thiophene core took place at C2 and C5 positions, furnishing the benzene-thiophene-benzene triad **14** in 79% yield.



Scheme 7. Synthesis of Benzene-core π-Systems by Twofold C–H Arylation



Scheme 8. Double C–H Bond Arylation

3. Conclusion

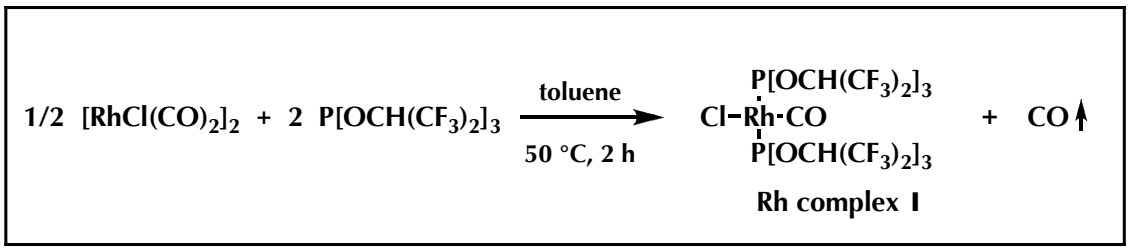
In summary, a new rhodium-based catalytic system for the direct C–H coupling of electron-rich arenes, such as thiophene, pyrrole, furan, indole, and alkoxybenzene with iodoarenes that show high activity with reasonably broad scope was developed. In many aspects, the present reaction can be best described as a Friedel–Crafts-type arylation of arenes.

4. Experimental

4-1. General

Unless otherwise noted, all materials including dry solvents (toluene, THF and *m*-xylene) were obtained from commercial suppliers and used without further purification. The ligand $P[OCH(CF_3)_2]_3$ was prepared according to procedures reported in the literature.[12a] Unless otherwise noted, all reactions were performed with dry solvents under an atmosphere of argon in flame-dried glassware with standard vacuum-line techniques. All coupling reactions using conventional heating were carried out in glass vessels equipped with J. Young® O-ring tap, heated in a 8-well reaction block (heater + magnetic stirrer). All microwave reactions were performed in a regularly calibrated CEM Focused Microwave™ Synthesis System (Discover) with IR temperature monitor and non-invasive pressure transducer using 10 mL vials with septa. All work-up and purification procedures were carried out with reagent-grade solvents in air. Preparative recycling gel permeation chromatography (GPC) was performed with a JAI LC-9204 instrument equipped with JAIGEL-1H/JAIGEL-2H columns using chloroform as an eluent. High resolution mass spectra (HRMS) were obtained from a Waters Micromass LCT Premier (electrospray ionization time-of-flight mass spectrometry, ESI-TOFMS) or JEOL JMS-700 (fast atom bombardment mass spectrometry, FABMS). Infrared spectra were recorded on a JASCO FTIR-6100 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-ECA-600 (^{1}H 600 MHz, ^{13}C 150 MHz, ^{31}P 243 MHz), spectrometer. Chemical shifts for ^{1}H NMR are expressed in parts per million (ppm) relative to tetramethylsilane (δ 0.0 ppm). Chemical shifts for ^{13}C NMR are expressed in ppm relative to $CDCl_3$ (δ 77.0 ppm). Chemical shifts for $^{31}P\{^1H\}$ NMR are reported downfield in ppm relative to external 85% H_3PO_4 (δ 0.0 ppm). Data are reported as follow: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet, br = broad signal), coupling constant (Hz), and integration. The structure of arylation products were determined based on 2D NMR experiments.

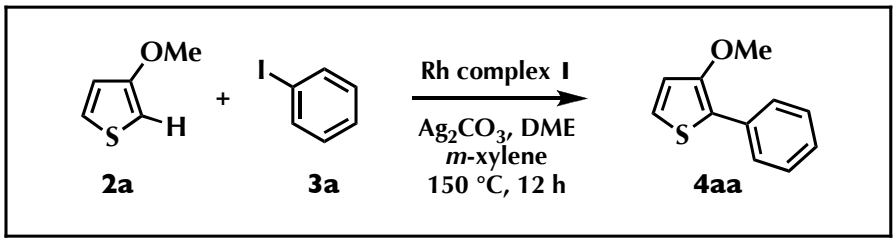
4-2. Synthesis and Crystal Structure Analysis of Rhodium Complex 1.



A solution of $[RhCl(CO)_2]_2$ (200.4 mg, 0.51 mmol) and $P[OCH(CF_3)_2]_3$ (1.09 g, 2.06 mmol) in dry toluene (2.0 ml) was stirred at 50 °C for 2 h under argon. After cooling the reaction mixture to room temperature, solvent was removed under reduced pressure. Reprecipitation from THF/toluene followed by filtration and vacuum drying afforded *trans*-$RhCl(CO)\{P[OCH(CF_3)_2]_3\}_2$ (**1**: 1.25 g, quant) as yellow solid.

^1H NMR (600 MHz, $CDCl_3$) δ 5.64 (br, 6H). $^{31}P\{^1H\}$ NMR (243 MHz, THF-d_8) δ 123.3 (d, $J_{Rh\text{-}P}$ = 224 Hz). IR (KBr) 2070, 1371, 1302, 1250, 1207, 1113, 1088 cm^{-1}. Single crystals suitable for X-ray analysis were obtained by slow diffusion of toluene into an acetonitrile solution of **1**. Intensity data were collected at 173K on a Rigaku Single Crystal CCD X-ray Diffractometer (Saturn 70 with MicroMax-007) with graphite-monochromated Mo-Kα radiation. A total 30758 reflections were corrected, of which 8832 were independent reflections (R_{int} = 0.0312). The structure was solved by direct methods (SHELEX-97[18]) and refined by the full-matrix least squares on F^2 (SHELEX-97[18]). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. The crystal data are as follows: $C_{19}H_6ClF_{36}O_7P_2Rh$, *FW* = 1230.54, crystal size 0.20 × 0.20 × 0.20 mm^3, monoclinic, space group *C*2/*c* (No.15). *a* = 33.050(5) Å, *b* = 17.903(2) Å, *c* = 13.525(2) Å, α = 90°, β = 105.3324(7) °, γ = 90°, *V* = 7717.8(19) $Å^3$, *Z* = 4, D_c = 1.059 g/cm^3. The refinement converged to R_1 = 0.0419, wR_2 = 0.1010 (I > 2s(*I*)), GOF = 1.105. Selected bond lengths (Å): Rh(1)–Cl(1) = 2.3561(8), Rh(1)–P(1) = 2.2597(8), Rh(1)–P(2) = 2.2550(7), Rh(1)–C(19) = 1.853(3), C(19)–O(7) = 1.127(4). Selected angles (deg): P(1)–Rh(1)–Cl(1) = 90.90(3), Cl(1)–Rh(1)–P(2) = 89.87(3), P(2)–Rh(1)–C(19) = 89.74(9), C(19)–Rh(1)–P(1) = 89.50(9), P(1)–Rh(1)–P(2) = 177.93(3), Cl(1)–Rh(1)–C(19) = 179.93(3), Cl(1)–Rh(1)–C(19) = 179.58(10), Rh(1)–C(19)–O(7) = 179.5(3).

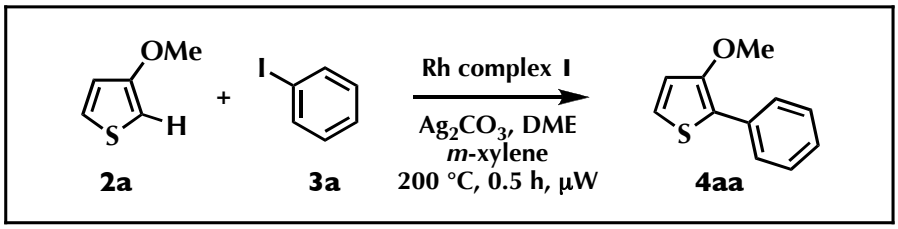
4-3. Typical Procedure for Coupling of Heteroarenes and Iodoarenes (conventional heating protocol)



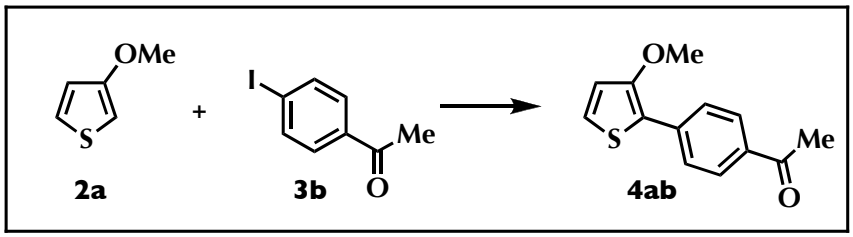
3-Methoxy-2-phenylthiophene (4aa): A 20-mL glass vessel equipped with J. Young® O-ring tap, containing a magnetic stirring bar, was flame-dried under vacuum and filled with argon after cooling to room temperature. To this vessel were added Rh complex **1** (14.9 mg, 12 μmol), Ag_2CO_3 (111.9 mg, 0.41 mmol), 1,2-dimethoxyethane (36.0 mg, 0.40 mmol), 3-methoxythiophene (**2a**: 68.5 mg, 0.60 mmol), iodobenzene (**3a**: 81.6 mg, 0.40 mmol), and dry *m*-xylene (2.0 mL) under a stream of argon. The vessel was sealed with O-ring tap, and then heated at 150 °C for 12 h in a 8-well reaction block with stirring. After cooling the reaction mixture to room temperature, the mmixture was passed through a short silica gel pad (EtOAc/$CHCl_3$). The filtrate was evaporated and the residue was subjected to gel permeation chromatography ($CHCl_3$) to afford 3-methoxy-2-phenylthiophene (**4aa**: 57.1 mg, 75%) as pale yellow oil.

^{1}H NMR (600 MHz, 1H), 7.14 (d, J = 5.5 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.35 (t, J = 7.6 Hz, 2H), 7.73 (d, J = 7.6 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 58.7, 117.5, 120.2, 122.1, 126.4, 126.9, 128.5, 133.4, 153.7. HRMS (ESI-TOF) m/z calcd. for $C_{11}H_{11}OS$ $[MH]^+$: 191.0531, found 191.0540.

4-4. Typical Procedure for Coupling of Heteroarenes and Iodoarenes (microwave heating protocol)

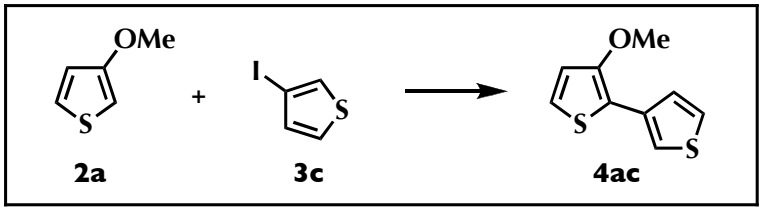


A 10-mL flame-dried microwave vial containing a magnetic stirring bar was fitted with a septum and cooled under stream of argon. To this vial were added Rh complex **1** (18.8 mg, 15 μmol), Ag_2CO_3 (138.7 mg, 0.50 mmol), 1,2-dimethoxyethane (45.1 mg, 0.50 mmol), 3-methoxythiophene (**2a**: 86.6 mg, 0.75 mmol), iodobenzene (**3a**: 102.0 mg, 0.50 mmol), and dry *m*-xylene (2.5 mL). The vial was sealed and heated with stirring at 200 °C for 30 min in CEM Discover microwave apparatus. After the reaction vial was cooled down to room temperature, the mixture was passed through a short silica gel pad (EtOAc / $CHCl_3$). The filtrate was evaporated and the residue was subjected to gel permeation chromatography ($CHCl_3$) to afford **4aa** (69.7 mg, 73%) as pale yellow oil.

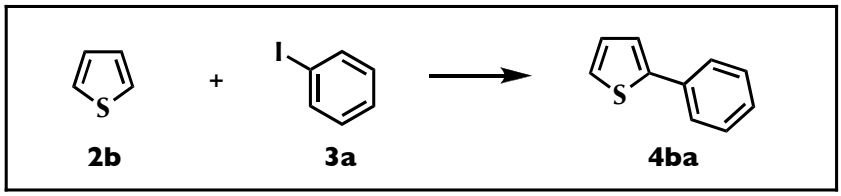


4-4-1. 2-(*p*-Acetylphenyl)-3-methoxythiophene (4ab): 94% isolated yield (99% NMR yield) from 3-methoxythiophene (**2a**) and 4-iodobenzene (**3b**) (microwave heating, 200 °C, 30 min).

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.59 (s, 3H), 3.95 (s, 3H), 6.94 (d, J = 5.5 Hz, 1H), 7.24 (d, J = 5.5 Hz, 1H), 7.83 (d, J = 8.9 Hz, 2H), 7.94 (d, J = 8.9 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.5, 58.7, 117.3, 118.7, 124.0, 126.2, 128.7, 134.4, 138.3, 155.3, 197.4. HRMS (ESI-TOF) m/z calcd. for $C_{13}H_{13}O_2S$ $[MH]^+$: 233.0636, found 233.0635.

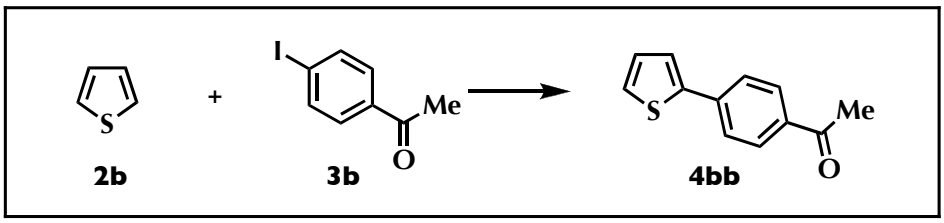


4-4-2. 3-Methoxy-2,3′-bithiophene (4ac): 52% isolated yield (58% NMR yield) from 3-methoxythiophene (**2a**) and 3-iodothiophene (**3c**) (microwave heating, 200 °C, 30 min). ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.92 (s, 3H), 6.88 (d, *J* = 5.5 Hz, 1H), 7.06 (d, *J* = 5.5 Hz, 1H), 7.29 (dd, *J* = 4.8, 2.8 Hz, 1H), 7.38 (dd, *J* = 4.8, 1.4 Hz, 1H), 7.57 (dd, *J* = 2.8, 1.4 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 58.6, 116.0, 116.9, 119.5, 121.1, 125.2, 126.5, 133.3, 153.4. HRMS (ESI-TOF) *m*/*z* calcd. for $C_9H_9OS_2$ $[MH]^+$: 197.0095, found 197.0094.



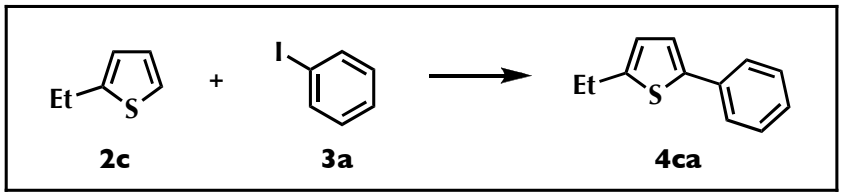
4-4-3. 2-Phenylthiophene (4ba):[19] 53% isolated yield (80% NMR yield) from thiophene (**2b**) and iodobenzene (**3a**) (conventional heating, 150 °C, 15 h). Molar ratio: **1**:**2b**:**3a**:Ag_2CO_3:DME = 0.1:15:1.0:1.0:0.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.08 (dd, *J* = 5.5, 3.4 Hz, 1H), 7.26–7.29 (m, 2H), 7.31 (d, *J* = 3.4 Hz, 1H), 7.38 (t, *J* = 8.2 Hz, 2H), 7.62 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 123.1, 124.8, 126.0, 127.4, 128.0, 128.9, 134.4, 144.4.

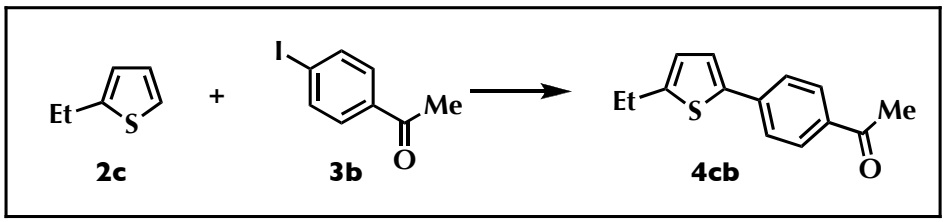


4-4-4. 2-(*p*-Acetylphenyl)thiophene (4bb):[20] 83% isolated yield from thiophene (**2b**) and 4-iodoacetophenone (**3b**) (conventional heating, 150 °C, 14 h). Molar ratio: **1**:**2b**:**3a**:Ag_2CO_3:DME = 0.1:15:1.0:1.0:0.

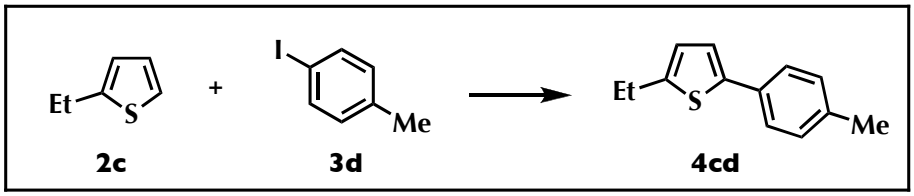
^{1}H NMR (600 MHz, $CDCl_3$) δ 2.61 (s, 3H) 7.12 (dd, *J* = 4.8, 3.4 Hz, 1H), 7.37 (dm, *J* = 4.8 Hz, 1H), 7.43 (d, *J* = 3.4 Hz, 1H), 7.69 (d, *J* = 7.6 Hz, 2H), 7.96 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.5, 124.6, 125.6, 126.4, 128.3, 129.1, 135.8, 138.8, 142.9, 197.2.



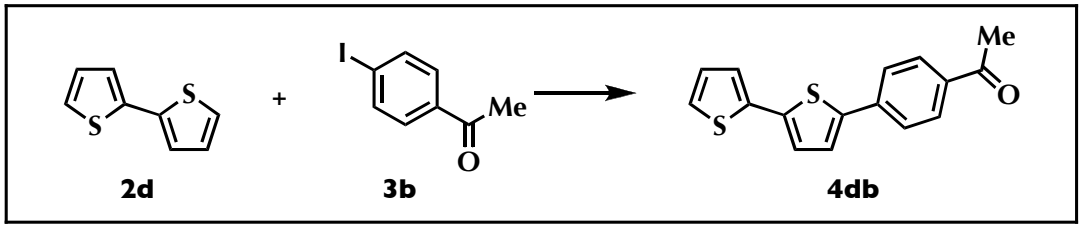
4-4-5. 2-Ethyl-5-phenyl-thiophene (4ca): 76% isolated yield (99% NMR yield) from 2-ethylthiophene (**2c**) and iodobenzene (**3a**) (microwave heating, 200 °C, 30 min).
^{1}H NMR (600 MHz, $CDCl_3$) δ 1.34 (t, *J* = 7.6 Hz, 3H), 2.86 (q, *J* = 7.6 Hz, 2H), 6.75 (d, *J* = 3.4 Hz, 1H), 7.12 (d, *J* = 3.4 Hz, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.56 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.9, 23.6, 122.7, 124.3, 125.5, 127.0, 128.8, 134.8, 141.6, 147.2. HRMS (FAB) *m*/*z* calcd. for $C_{12}H_{12}S$ $[M]^+$: 188.0660, found 188.0661.



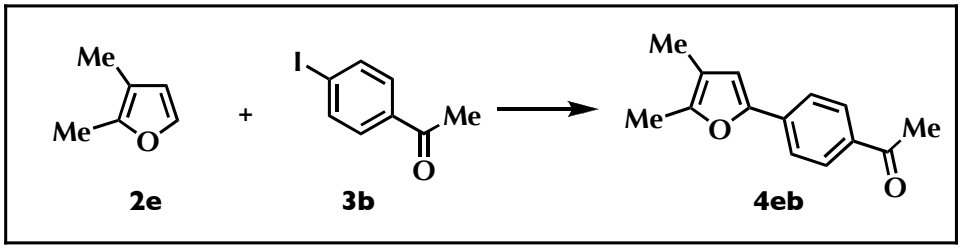
4-4-6. 2-(*p*-Acetylphenyl)-5-ethylthiophene (4cb): 79% isolated yield (87% NMR yield) from 2-ethylthiophene (**2c**) and 4-iodoacetophenone (**3b**) (microwave heating, 200 °C, 30 min).
^{1}H NMR (600 MHz, $CDCl_3$) δ 1.34 (t, *J* = 7.6 Hz, 3H), 2.58 (s, 3H), 2.87 (q, *J* = 7.6 Hz, 2H), 6.78 (d, *J* = 3.4 Hz, 1H), 7.23 (d, *J* = 3.4 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.92 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.7, 23.6, 26.5, 124.4, 124.8, 125.0, 129.0, 135.2, 139.1, 140.0, 149.2, 197.2. HRMS (ESI-TOF) *m*/*z* calcd. for $C_{14}H_{15}OS$ $[M]^+$: 231.0844, found 231.0843.



4-4-7. 2-Ethyl-5-*p*-tolylthiophene (4cd): 50% isolated yield (64% NMR yield) from 2-ethylthiophene (**2c**) and 4-iodotoluene (**3d**) (microwave heating, 180 °C, 30 min). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.33 (t, *J* = 7.6 Hz, 3H), 2.34 (s, 3H), 2.85 (q, *J* = 7.6 Hz, 2H), 6.73 (d, *J* = 3.4 Hz, 1H), 7.07 (d, *J* = 3.4 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 2H), 7.44 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.9, 21.1, 23.6, 122.1, 124.2, 125.4, 129.4, 132.0, 136.8, 141.7, 146.6. HRMS (FAB) *m*/*z* calcd. for $C_{13}H_{14}S$ $[M]^+$: 202.0816, found 202.0819.

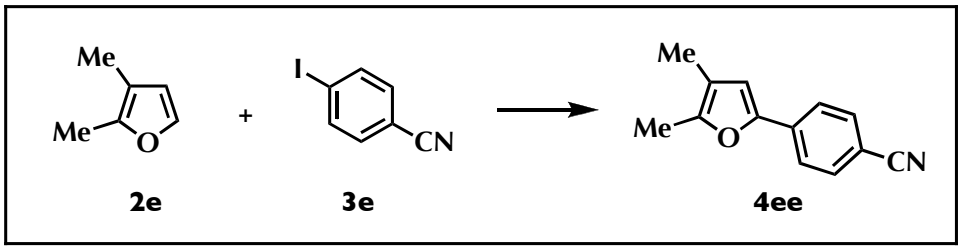


4-4-8. 5-(*p*-Acetylphenyl)-2,2′-bithiophene (4db): 64% isolated yield from 2,2′-bithiophene (**2d**) and 4-iodoacetophenone (**3b**) (microwave heating, 200 °C, 30 min). ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.61 (s, 3H), 7.04 (dd, *J* = 5.5, 4.1 Hz, 1H), 7.17 (d, *J* = 3.4 Hz, 1H), 7.25 (d, *J* = 5.5 Hz, 1H), 7.34 (d, *J* = 4.1 Hz, 1H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.96 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.5, 124.1, 124.8, 124.9, 125.27, 125.33, 128.0, 129.1, 135.7, 137.0, 138.4, 138.5, 141.4, 197.2. HRMS (ESI-TOF) *m*/*z* calcd. for $C_{16}H_{13}OS_2$ $[M]^+$: 285.0408, found 285.0416.



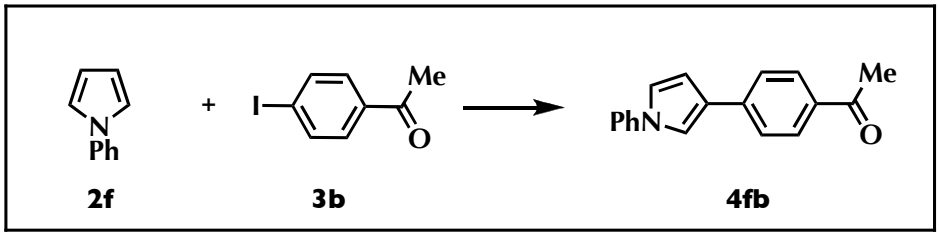
4-4-9. 2-(*p*-Acetylphenyl)-4,5-dimethylfuran (4eb): 64% isolated yield from 2,3-dimethylfuran (**2e**) and 4-iodoacetophenone (**3b**) (microwave heating, 200 °C, 30 min).

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.99 (s, 3H), 2.29 (s, 3H), 2.58 (s, 3H), 6.59 (s, 1H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.93 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 9.9, 11.6, 26.4, 111.1, 116.8, 122.7, 128.9, 134.8, 135.2, 149.1, 149.7, 197.3. HRMS (ESI-TOF) *m*/*z* calcd. for $C_{14}H_{15}O_2$ $[M]^+$: 215.1072, found 215.1073.



4-4-10. 2-(*p*-Cyanophenyl)-4,5-dimethylfuran (4ee): 66% isolated yield from 2,3-dimethylfuran (**2e**) and 4-iodobenzonitrile (**3b**) (microwave heating, 150 °C, 30 min).

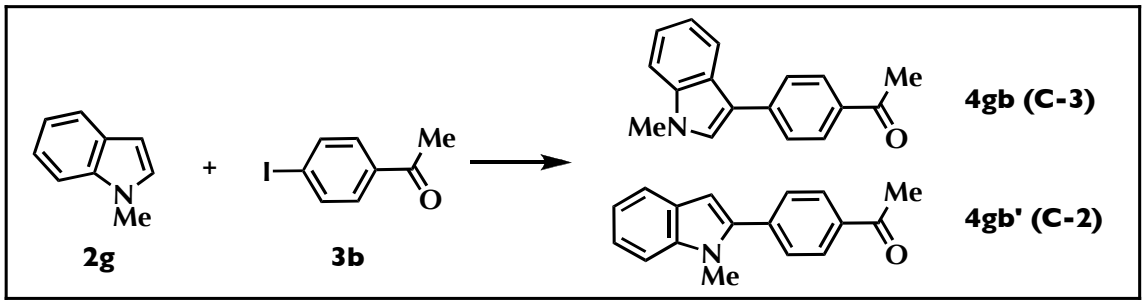
^{1}H NMR (600 MHz, $CDCl_3$) δ 1.99 (s, 3H), 2.29 (s, 3H), 6.59 (s, 1H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.63 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 9.8, 11.6, 111.7, 117.0, 119.2, 123.1, 132.4, 134.9, 148.9, 149.5. HRMS (ESI-TOF) *m*/*z* calcd. for $C_{13}H_{12}NO$ $[MH]^+$: 198.0919, found 198.0918.



4-4-11. 3-(*p*-Acetylphenyl)-1-phenylpyrrole (4fb): 58% isolated yield (86% NMR yield) from 1-phenylpyrrole (**2f**) and 4-iodoacetophenone (**3b**) (microwave heating, 200 °C, 30 min).

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.56 (s, 3H), 6.66–6.67 (m, 1H), 7.09–7.11 (m, 1H), 7.24–7.27 (m, 1H) 7.40–7.44 (m, 5H), 7.60 (d, *J* = 8.3 Hz, 2H), 7.92 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.4, 108.8, 117.0, 120.5, 120.9, 124.7, 125.6, 126.1, 129.0, 129.7, 134.4,

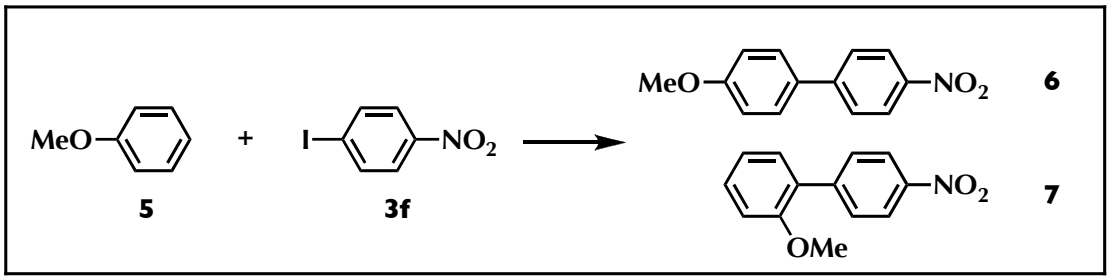
140.19, 140.22, 197.5. HRMS (FAB) *m*/*z* calcd. for $C_{18}H_{15}NO$ $[M]^+$: 261.1154, found 261.1153.



4-4-12. (*p*-Acetylphenyl)-1-methylindole 4gb (C-3): 57% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.62 (s, 3H), 3.84 (s, 3H), 7.23 (dd, *J* = 8.3, 6.8 Hz, 1H), 7.31 (dd, *J* = 8.3, 6.8 Hz, 1H), 7.34 (s, 1H) 7.38 (d, J = 8.3 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.97 (d, *J* = 8.3 Hz, 2H), 8.02 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.5, 33.0, 109.8, 115.5, 119.8, 120.5, 122.3, 125.8, 126.6, 127.6, 129.0, 134.2, 137.7, 140.8, 197.6. HRMS (ESI-TOF) *m*/*z* calcd. for $C_{17}H_{16}NO$ $[MH]^+$: 250.1232, found 250.1234.

4gb′ (C-2): 23% isolated yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.66 (s, 3H), 3.79 (s, 3H), 6.66 (s, 1H), 7.16 (dd, *J* = 8.2, 6.8 Hz, 1H), 7.29 (dd, *J* = 8.2, 6.8 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.63 (d, *J* = 8.3 Hz, 2H), 7.65 (d, *J* = 8.2 Hz, 2H), 8.06 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.7, 31.4, 103.0, 109.8, 120.2, 120.8, 122.4, 127.9, 128.6, 129.2, 136.1, 137.4, 138.9, 140.2, 197.6. HRMS (ESI-TOF) *m*/*z* calcd. for $C_{17}H_{16}NO$ $[MH]^+$: 250.1232, found 250.1224.

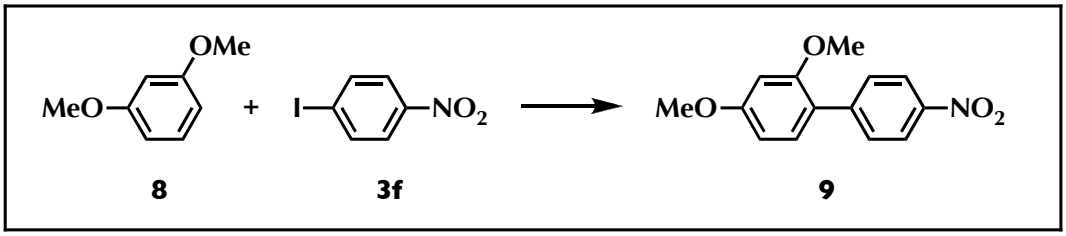
4-5. Coupling of Benzene Derivatives and Iodoarenes



4-5-1. 4-Methoxy-4′-nitrobiphenyl (6): A 10-mL flame-dried microwave vial containing a magnetic stirring bar was fitted with a septum and cooled under a stream of argon. To this vial were added Rh complex **1** (32.3 mg, 26 μmol), Ag_2CO_3 (139.9 mg, 0.51 mmol), anisole (**5**: 1.49 g, 13.8 mmol), and 1-iodo-4-nitrobenzene (**3f**: 128.5 mg, 0.52 mmol). The vial was sealed and heated with stirring at 200 °C for 30 min in a CEM Discover microwave apparatus. After the reaction vial was cooled down to room temperature, the mixture was passed through a short silica gel pad (EtOAc). The filtrate was evaporated and the residue was subjected to gel permeation chromatography ($CHCl_3$) to afford biaryls (58.1 mg, 51%) as a mixture of *para*-isomer **6** and *ortho*-isomer **7**. The ratio of **6**/**7** was determined to be 71/29 by ^{1}H NMR analysis. These isomers could be separated by HPLC (silica gel).

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.87 (s, 3H), 7.01 (d, *J* = 8.9 Hz, 2H), 7.57 (d, *J* = 8.9 Hz, 2H), 7.67 (d, *J* = 8.9 Hz, 2H), 8.25 (d, *J* = 8.9 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 55.4, 114.6, 124.1, 127.0, 128.5, 131.0, 146.5, 147.1, 160.4. HRMS (ESI-TOF) *m*/*z* calcd. for $C_{13}H_{11}NO_3$ $[M]^+$: 229.0739, found 229.0739.

4′-Methoxy-2-nitrobiphenyl (7): ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.80 (s, 3H), 6.98 (d, *J* = 8.3 Hz, 1H), 7.03 (t, *J* = 7.6 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.36 (dd, *J* = 8.3, 7.6 Hz, 1H), 7.65 (d, *J* = 8.9 Hz, 2H), 8.21 (d, *J* = 8.9 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 55.6, 111.4, 121.1, 123.2, 128.2, 130.1, 130.3, 145.4, 146.6, 156.4. HRMS (FAB) *m*/*z* calcd. for $C_{13}H_{11}NO_3$ $[M]^+$: 229.0739, found 229.0739

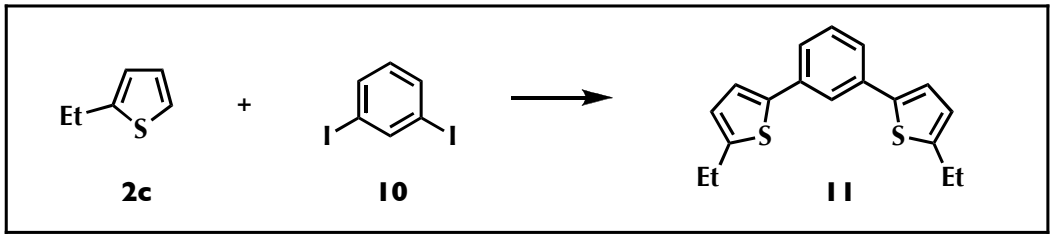


4-5-2. 2,4-Dimethoxy-4′-nitrobiphenyl (9): A 10-mL flame-dried microwave vial containing a magnetic stirring bar was fitted with a septum and cooled under a steam of argon. To this vial were added Rh complex **1** (31.5 mg, 26 μmol), Ag_2CO_3 (139.7 mg, 0.51 mmol), 1,3-dimethoxybenzene (**8**: 1.90 g, 13.7 mmol), and 1-iodo-4-nitrobenzene (**3f**: 127.5 mg, 0.50 mmol). The vial was sealed and heated with stirring at 200 °C for 30 min in a CEM Discover microwave apparatus. After the reaction vial was cooled down to

room temperature, the mixture was passed through a short silica gel pad (EtOAc). The filtrate was evaporated and the residue was subjected to gel permeation chromatography ($CHCl_3$) to afford **9** (98.5 mg, 76%) as pale yellow solid.

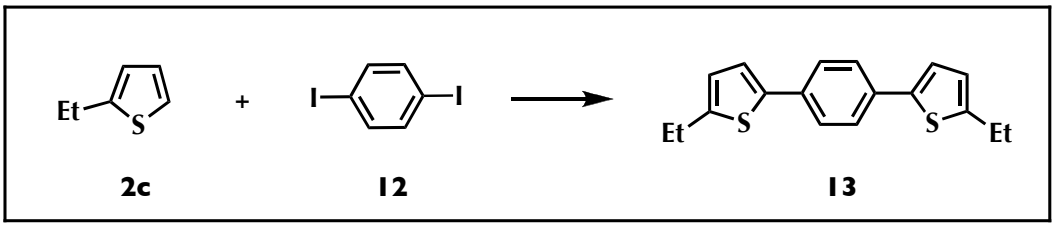
^{1}H NMR (600 MHz, $CDCl_3$) δ 3.82 (s, 3H), 3.86 (s, 3H), 6.58 (d, *J* = 2.1 Hz, 1H), 6.59 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 8.9 Hz, 2H), 8.21 (d, *J* = 8.9 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 55.4, 55.5, 99.0, 105.1, 121.0, 123.2, 129.9, 131.3, 145.3, 146.1, 157.5, 161.5. HRMS (FAB) *m*/*z* calcd. for $C_{14}H_{13}NO_4$ $[M]^+$: 259.0845, found 259.0847.

4-6. Synthesis of Extended π-systems through Multiple C–H Couplings



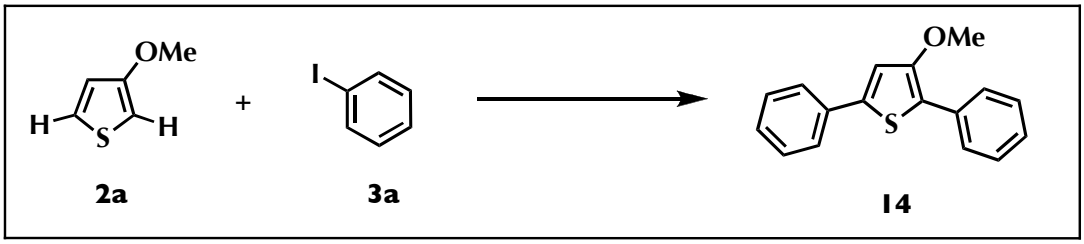
4-6-1. 5,5′-(1,3-Phenylene)bis(2-ethylthiophene) (11): A 10-mL flame-dried microwave vial containing a magnetic stirring bar was fitted with septum and cooled under a stream of argon. To this vial were added Rh complex **1** (30.3 mg, 25 μmol), Ag_2CO_3 (220.1 mg, 0.80 mmol), 2-ethylthiophene (**2c**: 224.7 mg, 2.0 mmol), 1,3-diiodobenzene (**10**: 133.3 mg, 0.4 mmol), and dry *m*-xylene (2.5 mL). The vial was sealed and heated with stirring at 150 °C for 30 min in a CEM Discover microwave apparatus. After the reaction vial was cooled down to room temperature, the mixture was passed through a pad of Celite® copious washing with $CHCl_3$. The filtrate was evaporated and the residue was subjected to gel permeation chromatography ($CHCl_3$) to afford **11** (74.5 mg, 62%) as pale yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.33 (t, *J* = 7.6 Hz, 6H), 2.85 (q, *J* = 7.6 Hz, 4H), 6.75 (d, *J* = 3.8 Hz, 2H), 7.15 (d, *J* = 3.8 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.42 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.73 (t, *J* = 2.0 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.9, 23.6, 122.6, 123.0, 124.2, 124.3, 129.2, 135.3, 141.2, 147.4. HRMS (ESI-TOF) *m*/*z* calcd. for $C_{18}H_{19}S_2$ $[MH]^+$: 299.0928, found 299.0927.



4-6-2. 5,5′-(1,4-Phenylene)bis(2-ethylthiophene) (13): A 10-mL flame-dried microwave vial containing a magnetic stirring bar was fitted with septum and cooled under a stream of argon. To this vial were added Rh complex **1** (30.4 mg, 25 μmol), Ag_2CO_3 (225.7 mg, 0.82 mmol), 2-ethylthiophene (**2c**: 224.7 mg, 2.0 mmol), 1,4-diiodobenzene (**12**: 132.8 mg, 0.40 mmol), and dry *m*-xylene (2.5 mL). The vial was sealed and heated with stirring at 150 °C for 30 min in a CEM Discover microwave apparatus. After the reaction vial was cooled down to room temperature, the mixture was passed through a pad of Celite® copious washing with $CHCl_3$. The filtrate was evaporated and the residue was subjected to gel permeation chromatography ($CHCl_3$) to afford **13** (56.0 mg, 46%) as pale yellow oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.34 (t, J = 7.6 Hz, 6H), 2.87 (q, J = 7.6 Hz, 4H), 6.76 (d, J = 3.4 Hz, 2H), 7.13 (d, J = 3.4 Hz, 2H), 7.53 (s, 4H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.9, 23.6, 122.6, 124.4, 125.7, 133.4, 141.2, 147.4. HRMS (ESI-TOF) m/z calcd. for $C_{18}H_{19}S_2$ $[MH]^+$: 299.0928, found 299.0927.



4-6-3. 3-Methoxy-2,5-diphenylthiophene (14): A 10-mL flame-dried microwave vial containing a magnetic stirring bar was fitted with a septum and cooled under a steam of argon. To this vial were added Rh complex **1** (29.5 mg, 24 μmol), Ag_2CO_3 (220.6 mg, 0.80 mmol), 3-methoxythiophene (**2a**: 45.7 mg, 0.40 mmol), iodobenzene (**3a**: 179.5 mg, 0.88 mmol), and dry *m*-xylene (2.0 mL). The vial was sealed and heated with stirring at 200 °C for 30 min in a CEM Discover microwave apparatus. After the reaction vial was

cooled down to room temperature, the mixture was passed through a short silica gel pad (EtOAc/$CHCl_3$). The filtrate was evaporated and the residue was subjected to gel permeation chromatography ($CHCl_3$) to afford 3-methoxy-2,5-diphenylthiophene (**14**: 84.1 mg, 79%) as pale yellow solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.93 (s, 3H), 7.13 (s, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.58 (d, *J* = 7.6 Hz, 2H), 7.74 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 58.8, 113.4, 120.0, 125.1, 126.4, 126.7, 127.7, 128.5, 128.9, 133.4, 134.2, 139.8, 154.0. HRMS (ESI-TOF) *m*/*z* calcd for $C_{17}H_{15}OS$ $[MH]^+$: 267.0844, found 267.0834.

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Chapter 2

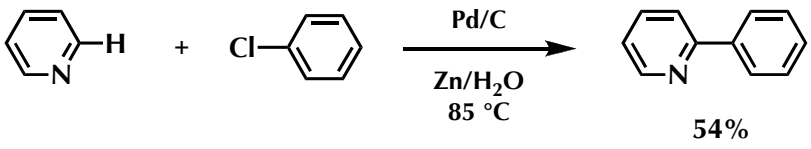
Potassium *t*-Butoxide-Mediated C–H Bond Arylation of Electron-Deficient Nitrogen Heteroarenes with Haloarenes

Abstract: The biaryl coupling of electron-deficient nitrogen heteroarenes and haloarenes can be promoted by potassium *t*-butoxide alone, without the addition of any exogenous transition metal species. Electron-deficient nitrogen heteroarenes such as pyridine, pyridazine, pyrimidine, pyrazine, and quinoxaline are arylated with haloarenes. Control experiments support a radical-based mechanism.

1. Introduction

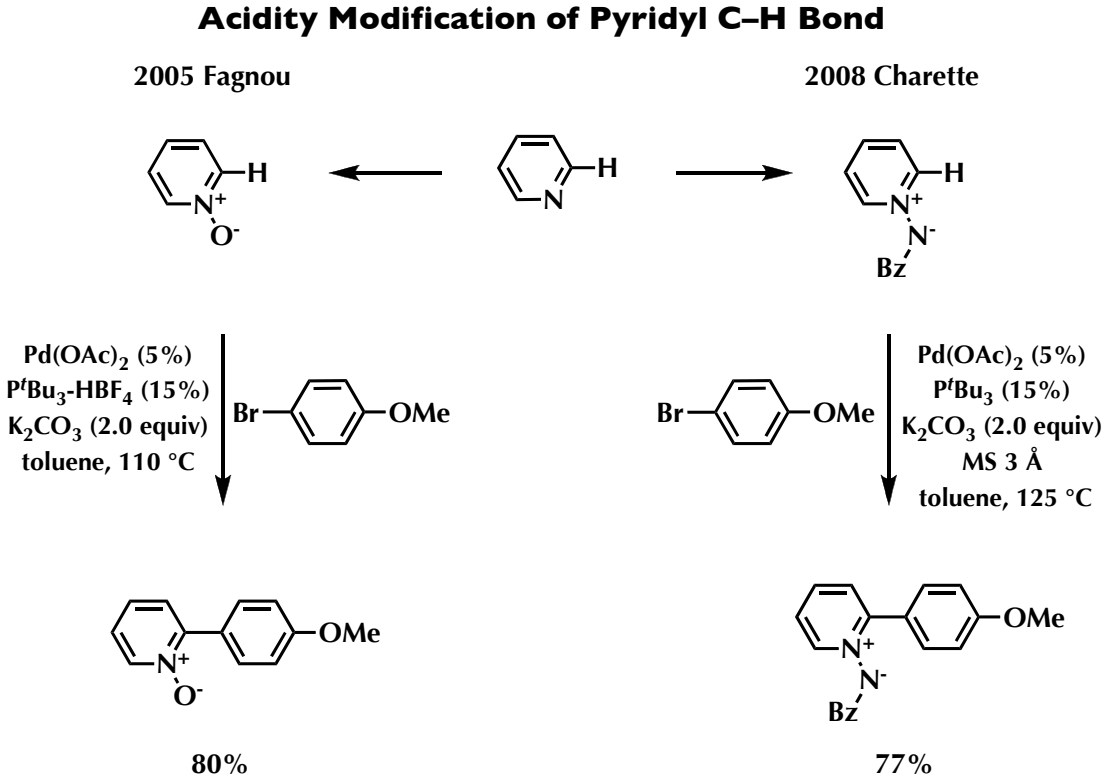
The transition metal-catalyzed arylation of nucleophilic organic compounds with haloarenes are commonplace in modern organic synthesis.[1] Representative examples include the palladium-catalyzed arylation of organometallic reagents, amines, alcohols, and carbonyl compounds with haloarenes.[2,3] More recently, the C–H bond arylation of arenes with haloarenes has become a rapidly growing area of extensive research in these days.[4] As a part of program aimed at establishing a new catalytic biaryl coupling through C–H bond functionalization, the author found that $RhCl(CO)\{P[OCH(CF_3)_2]_3\}_2$ can catalyze the C–H bond arylation of arenes with iodoarenes as described in Chapter 1.[5] Since the rhodium catalysis was best with electron-rich arenes, the development of a protocol applicable for electron-deficient arenes such as pyridine has been next goal. [6, 7]

One of the early works on the direct C–H bond arylation of nitrogen heteroarenes with aryl halides has been disclosed by Sasson and co-workers in 2000.[6a] The phenylation of pyridine at 2-position takes place with palladium/charcoal in the presence of zinc and water at 85 °C, which afforded 2-phenylpyridine in 54% yield (Scheme 1). They proposed that this reaction occurs via the formation of phenyl radical.



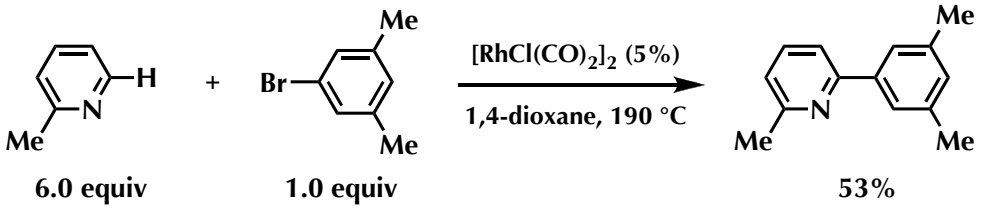
Scheme 1. Pd/C-Catalyzed Arylation of Pyridine

Subsequently, the Fagnou group reported the palladium-catalyzed arylation of pyridine *N*-oxide and its derivatives (Scheme 2).[6b, 6c] The use of pyridine *N*-oxide is speculated to decrease the pK_a of C–H bond on pyridine ring for the facile C–H bond palladation with palladium catalyst. With the same strategy, Charette and co-workers demonstrated that *N*-iminopyridinium ylide could be arylated with aryl bromides under the influence of palladium catalyst (Scheme 2).[6d]



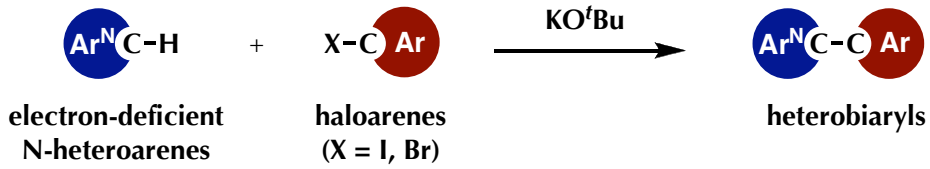
Scheme 2. Pd-Catalyzed C–H Bond Arylation of Pyridine Derivatives

Ellman and Bergman reported rhodium-catalyzed arylation of alkylated pyridines or quinolines with aryl bromides without any additive and ligand (Scheme 3).[6e] The prefunctionalization of pyridine is not necessary for this reaction.



Scheme 3. Rh-Catalyzed C–H Bond Arylation of Substituted Pyridines

In this Chapter, the author describes a surprising result, which demonstrates that the biaryl coupling of electron-deficient nitrogen heteroarenes and haloarenes can be promoted *by potassium t-butoxide alone, without the addition of any exogenous transition metal species* (Scheme 4).



- **Biaryl formation without the addition of any exogenous transition metal species**
- **Quantitative elemental analysis using ICP-AES (KO^tBu) All Transition Metals (<0.5 ppm)**

Scheme 4. KO^tBu-Mediated Biaryl Coupling of Electron-Deficient Nitrogen Heteroarenes

Although the reaction is still in its infancy from a practical point of view, the discovered new reactivity of *t*-butoxides should raise concerns to the synthetic community. Considering the occasional employment of *t*-butoxide bases and haloarenes in arylation reactions,[1-4] gauging the ability of these reagents to promote reactions in the absence of presumed metal catalysts is obviously critical.

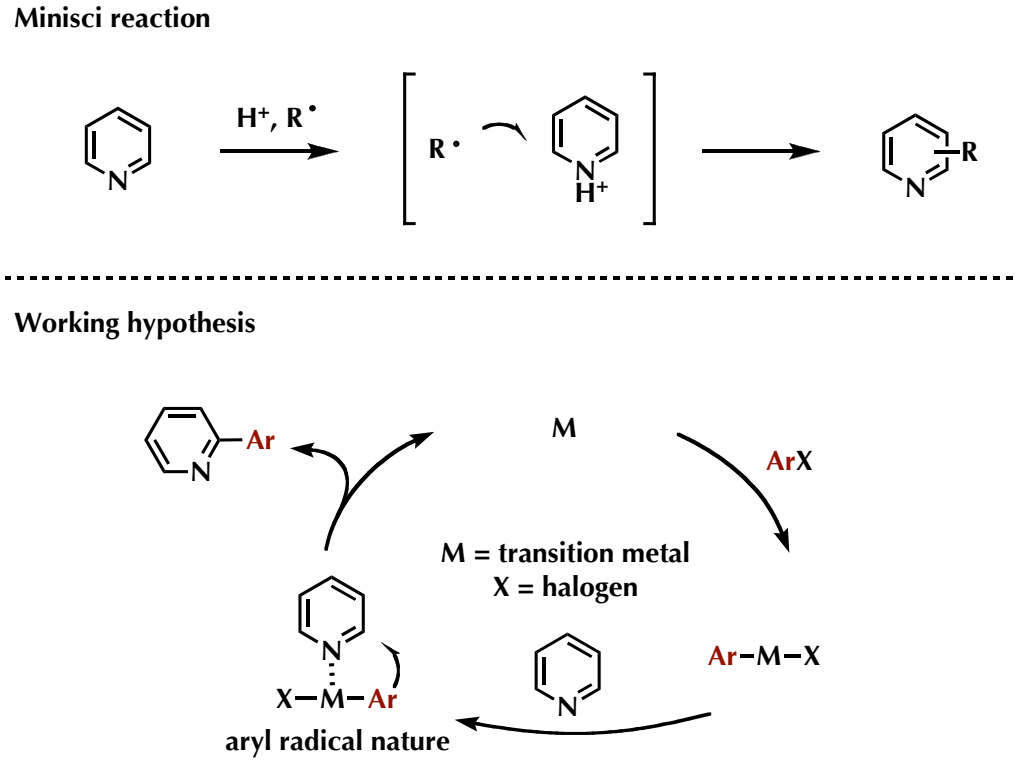
2. Results and Discussion

2-1. Strategy

The Minisci reaction, which is generally conducted with alkyl radical source (alkyl halide, alkyl carboxylic acid etc.) and radical initiator under acidic conditions, has been known for the functionalization of electron-deficient arenes (Scheme 5). It has been proposed that protonated nitrogen heteroarenes are reacted with nucleophilic alkyl

radical generated in situ.[8] Taking this reaction into consideration, the author envisaged that radical species might be key for achieving the direct arylation of electron-deficient nitrogen heteroarenes.

Since certain aryl transition metal species are known to have radical nature to some extent, the author hypothesized that the arylation of electron-deficient arenes could be achieved by taking advantage of this nature and the coordination of pyridine nitrogen atom to transition metal.

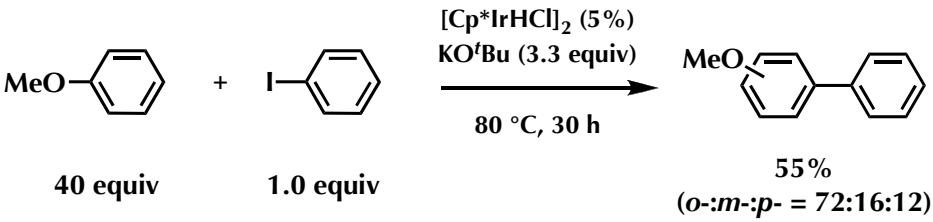


Scheme 5. Typical Minisci Reaction and Working Hypothesis

2-2. Discovery of KO^{t}Bu-Promoted Arylation of Electron-Deficient Nitrogen Heteroarenes with Haloarenes

In 2004, Ir-catalyzed direct arylation of benzene derivatives with iodoarenes in the presence of KO^{t}Bu was disclosed by Fujita and co-workers.[9] For example, when the mixture of solvent amount of anisole and iodobenzene were stirred with KO^{t}Bu under

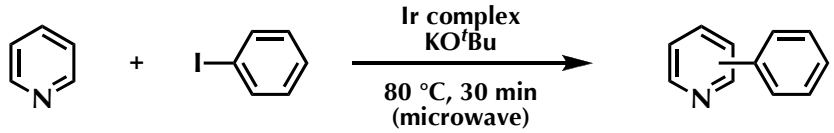
the influence of iridium catalyst $[Cp^*IrHCl]_2$ at 80 °C, phenylated anisoles were obtained as a mixture of regioisomers in 55% yield (Scheme 6). Based on this regioselectivity, Fujita and co-workers assumed that radical intermediate would be involved in this reaction.



Scheme 6. Ir-Catalyzed Direct C–H Arylation by Fujita Group

With the hypothesis that a "radical-type" transition metal-mediated reaction might be optimal to achieve direct C–H arylation of electron-deficient nitrogen heteroarenes,[10] the author examined Fujita's Ir-based protocol for the coupling of pyridine and iodobenzene. In fact, the C–H bond phenylation of pyridine (40 equiv) with iodobenzene (1.0 equiv) can be affected in the presence of $[Cp^*IrHCl]_2$ (5%) and KO^tBu (1.5 equiv) at 80 °C for 30 min under microwave irradiation to give phenylpyridine in 30% yield as a mixture of regioisomers (Table 1, entry 1). As shown in Table 1, a variety of Ir sources were apparently able to catalyze this reaction in moderate yield. Struck by the similarity of reactions employing dramatically distinct Ir sources (entries 1–7), the author carried out the coupling reaction in the absence of Ir and remarkably found that the coupling reaction proceeded to the same extent with KO^tBu as the sole reagent (entry 8).

Table 1. Discovery of KO^{t}Bu-Promoted Biaryl Coupling[a]



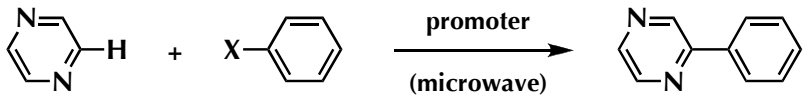
entry	Ir complex	yield (%)[b]
1	$[Cp^*IrHCl]_2$	30
2	$[Cp^*IrCl_2]_2$	32
3	$[IrCl(cod)]_2$	17
4	Ir(acac)(cod)	18
5	$IrH(CO)(PPh_3)_3$	29
6	$IrCl(CO)(PPh_3)_2$	41
7	$(NH_4)_3IrCl_6$	26
8	none	39

[a] Conditions: pyridine (40 equiv), iodobenzene (1.0 equiv), Ir complex (5%), KO^{t}Bu (3.3 equiv), 80 °C, 30 min, under microwave irradiation. [b] As a mixture of regioisomers.

With these unexpected results in hand, the author further examined the reaction conditions (Table 2). For simplicity, pyrazine was chosen as a substrate for this study. When a mixture of pyrazine (40 equiv), iodobenzene (1.0 equiv), and KO^{t}Bu (1.5 equiv) was stirred in the dark at 50 °C for 5 min under microwave irradiation, C–H bond phenylation took place to afford 2-phenylpyrazine in 98% yield (Table 2, entry 1).[11] The reaction also occurred under conventional heating but required higher temperatures and longer reaction times to achieve full conversion (79% at 120 °C, 13 h, entry 2). *N*,*N*-Dimethylacetamide (DMA) could also be used as a solvent for this reaction (54% at 80 °C, 0.5 h, entry 3). Interestingly, the use of DMA as a solvent allowed the reaction to proceed at lower substrate loading (entry 4) or at room temperature (entry 5), albeit less efficiently. The reaction also took place with bromobenzene at 80 °C (54%, entry 6), but chlorobenzene and fluorobenzene were virtually unreactive under these conditions (entries 7 and 8). Other potential promoters related to KO^{t}Bu were also examined

(entries 9–12). The use of NaO^{t}Bu or LiO^{t}Bu instead of KO^{t}Bu did not give the product under these conditions (50 °C, 5 min). However, it should be noted that, at temperatures above 80 °C, NaO^{t}Bu also promoted the biaryl coupling. In addition to the nature of the metal cation (K), the *t*-butoxide moiety is also crucial, as KOMe and KOH exhibited nearly no reactivity (entries 11 and 12).

Table 2. Phenylation of Pyrazine with Halobenzene[a]



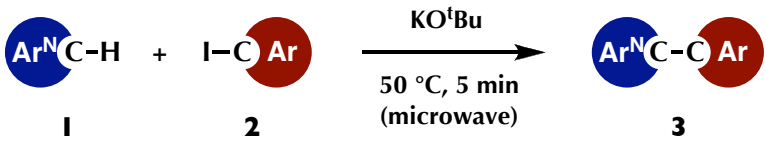
entry	X	promoter	conditions	yield (%)[b]
1	I	KO^{t}Bu	50 °C, 5 min	98[f]
2[c]	I	KO^{t}Bu	120 °C, 13 h	79[f]
3[d]	I	KO^{t}Bu	80 °C, 0.5 h (in DMA)	54
4[d,e]	I	KO^{t}Bu	80 °C, 0.5 h (in DMA)	35
5[c,d]	I	KO^{t}Bu	23 °C, 72 h (in DMA)	26
6	Br	KO^{t}Bu	80 °C, 0.5 h	54
7	Cl	KO^{t}Bu	80 °C, 0.5 h	<1
8	F	KO^{t}Bu	80 °C, 0.5 h	<1
9	I	NaO^{t}Bu	50 °C, 5 min	<1
10	I	LiO^{t}Bu	50 °C, 5 min	<1
11	I	KOMe	50 °C, 5 min	<1
12	I	KOH	50 °C, 5 min	<1

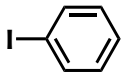
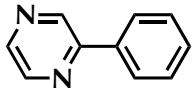
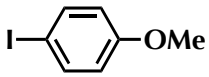
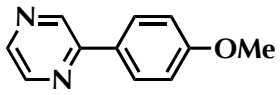
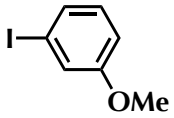
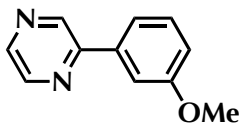
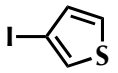
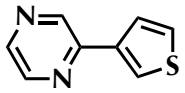
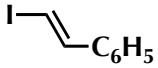
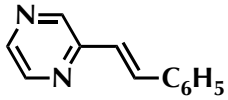
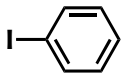
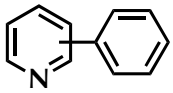
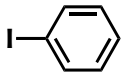
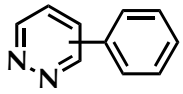
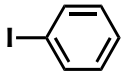
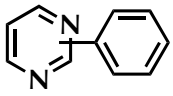
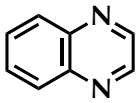
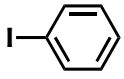
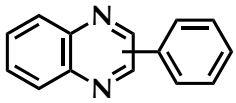
[a] Conditions: pyrazine (40 equiv), halobenzene (1.0 equiv), promoter (1.5 equiv), under microwave irradiation. [b] GC yield. [c] Reaction was conducted without microwave irradiation. [d] 0.5 mL of *N,N*-dimethylacetamide (DMA) was used as a solvent. [e] 10 equiv of pyrazine was employed. [f] Isolated yield.

2-3. Substrate Scope

Next the scope of the reaction with respect to the iodoarene and nitrogen heteroarene was examined. Representative results are summarized in Table 3.

Table 3. Substrate Scope of KO^{t}Bu-Promoted Biaryl Coupling[a]



entry	1	2	3 (yield, %)[b]
1			 98
2[c]			 83
3[c]			 64
4[c]			 71
5[c]			 33
6			 63[d]
7			 56[e]
8[c]			 59[f]
9			 75[g]

[a] Conditions: **1** (40 equiv), **2** (1.0 equiv), KO^{t}Bu (1.5 equiv), 50 °C, 5 min, under microwave irradiation. [b] Isolated yield. [c] Conditions: **1** (40 equiv), **2** (1.0 equiv), KO^{t}Bu (2.0 equiv), 80 °C, 30 min, under microwave irradiation. [d] Isomer ratio: 2-/3-/4- = 36:21:43. [e] Isomer ratio: 3-/4- = 24:76. [f] Isomer ratio: 2-/4-/5- = 23:52:25. [g] Isomer ratio: 2-/5- = 64:36.

Various iodoarenes reacted with pyrazine to give the corresponding nitrogen-containing biaryls in good yields (entries 1–4). These reactions took place exclusively at the C–I bond of iodoarenes and regioisomers with respect to the iodoarene were not detected.[12] Other than iodoarenes, iodoalkene such as *β*-iodostyrene also reacted with pyrazine (entry 5). A range of electron-deficient nitrogen heteroarenes other than pyrazine underwent arylation with iodoarenes. For example, pyridine, pyridazine, pyrimidine, and quinoxaline reacted with iodobenzene to afford the coupling products in good yields, albeit with poor regioselectivity with respect to the heteroarene (entries 6–9).

2-4. ICP-AES Analysis

Considering that trace transition metals present in sodium carbonate have been shown to catalyze coupling reactions such as the Suzuki–Miyaura reaction when performed under forcing conditions,[13] all reagents were purified extensively before use, including sublimation for KO^{t}Bu.[14] All reaction glassware and equipment were thoroughly cleaned prior to use. Finally, the quantitative elemental analysis of KO^{t}Bu and other potential promoters examined in Table 2 was conducted by ICP-AES (inductively coupled plasma-atomic emission spectrometry). The results are summarized in Table 4. Though very low in concentration, the most abundant exogenous elements found to be present in the KO^{t}Bu used in this study were Si (0.92 ppm), Al (0.38 ppm), and Ca (0.048 ppm). These elements are unlikely to be promoters for the present coupling reaction since there is no correlation between the yield of coupling product and the concentration of these elements in the promoters. More importantly, the concentration of all transition metals in the KO^{t}Bu employed in this study was less than 0.50 ppm. In particular, Pd, Rh, and Ru, which one might suspect as potential catalysts for such biaryl couplings,[4] were not found in concentrations above the detection limits (Pd: <0.06 ppm, Rh: <0.20 ppm, Ru: <0.30 ppm). Although the possibility of transition metal mediation in this reaction cannot be completely excluded, such a catalyst, if any, must be effective at low parts per billion concentrations.[13]

Table 4. ICP-AES Analysis of Promoter[a]

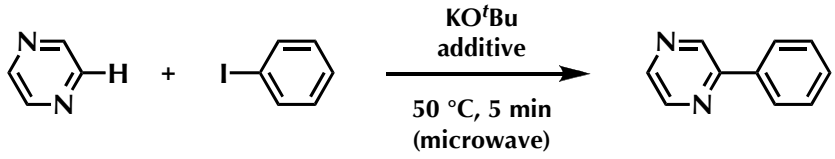
element	KO^{t}Bu	NaO^{t}Bu	LiO^{t}Bu	KOMe	KOH
Si	0.92	1.0	16	0.33	0.83
Al	0.38	<0.50	16	0.18	<0.50
Ca	0.048	34	9.2	0.69	1.0
Mg	0.0022	0.19	1.3	0.022	0.020
Fe	<0.50	1.1	0.36	0.36	0.25
Sr	<0.50	0.36	0.68	0.11	0.075
Ba	<0.50	0.030	0.049	0.050	0.015
Zn	<0.50	<0.50	<0.50	0.18	<0.50
Other metals	<0.50	<0.50	<0.50	<0.50	<0.50

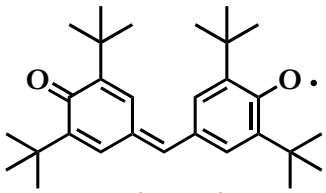
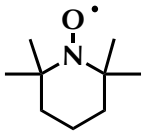
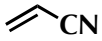
[a] See the Experimetal for detailed conditions. All values are expressed in ppm.

2-5. Mechanistic Considerations

Although the precise mechanism of this reaction remains to be determined, current hypotheses favor either homolytic aromatic substitution[15] or $S_{RN}1$ reaction,[16] both of which involve the generation of an aryl radical from iodoarene as a key step. While other possibilities such as S_NAr and aryl cation[17] mechanisms cannot be rigorously excluded at this stage, the radical nature of the present reaction was supported by control experiments performed in the presence of radical scavengers (Table 5). For example, the addition of galvinoxyl (entry 2), TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) (entry 3), or acrylonitrile (entry 4) to the reaction of pyrazine, iodobenzene, and KO^{t}Bu completely shut down the otherwise efficient biaryl coupling.

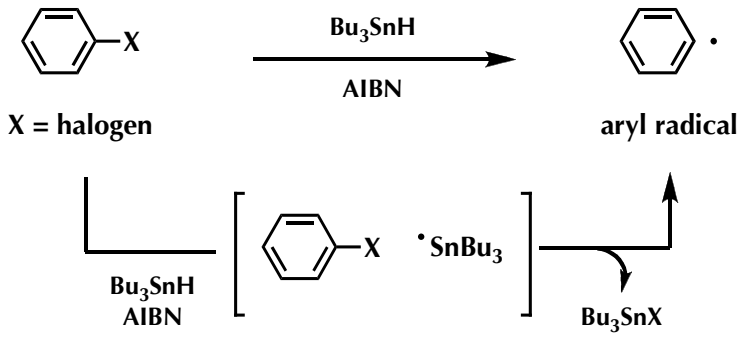
Table 5. Effect of Radical Scavenger[a]



entry	additive	yield (%)
1	none	98
2	 galvinoxyl	<1
3	 TEMPO	<1
4		<1

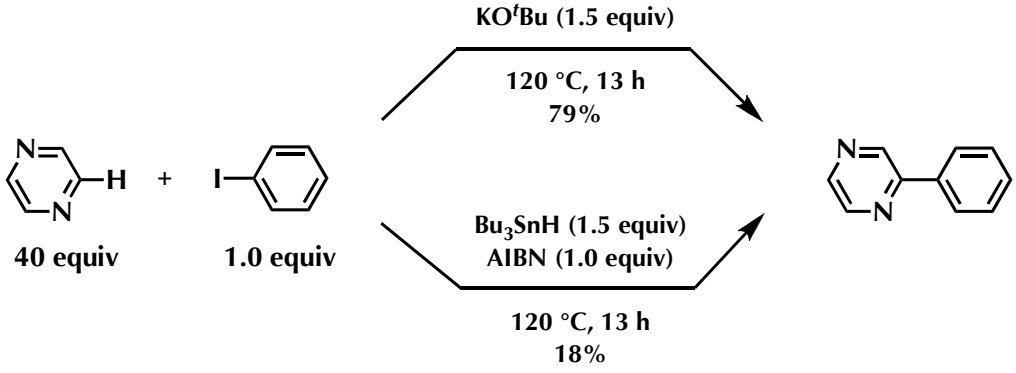
[a] Conditions: pyrazine (40 equiv), iodobenzene (1.0 equiv), KO^{t}Bu (1.5 equiv), additive (1.0 equiv), 50 °C, 5 min, under microwave irradiation.

To gain further insight into the aryl radical intermediate, aryl radicals were generated with other methods and then reacted with electron-deficient nitrogen heteroarenes. In this study, the author followed the literature method, generating phenyl radical from iodobenzene, tributyltin hydride, and AIBN (Scheme 7).[18]



Scheme 7. Bu_3SnH/AIBN-Mediated Aryl Radical Generation

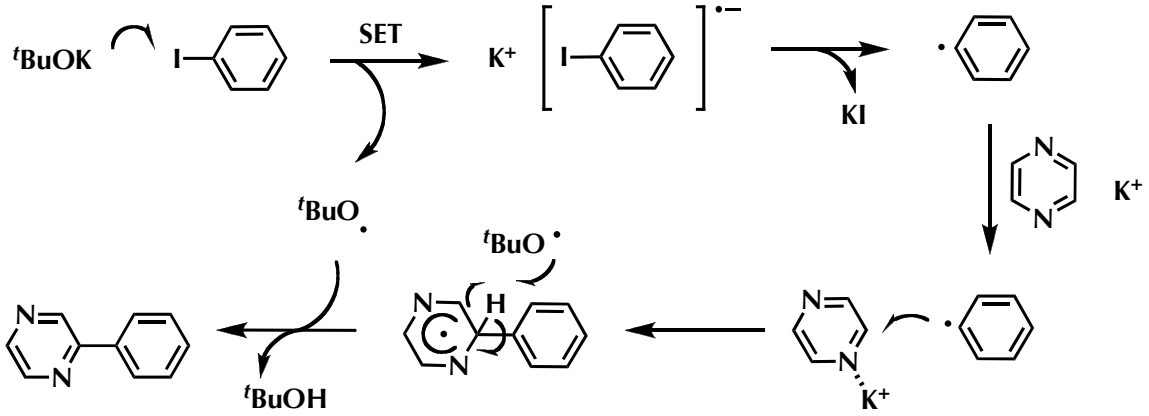
When a mixture of pyrazine (40 equiv) and iodobenzene (1.0 equiv) was stirred at 120 °C for 13 h in the presence of tributyltin hydride (1.5 equiv) and AIBN (1.0 equiv), 2-phenylpyrazine was obtained in 18% yield (Scheme 8). Although the yield was low compared with the reaction using KO^{t}Bu under otherwise identical conditions (79% yield), this result supports the involvement of aryl radical in the KO^{t}Bu-mediated reaction.



Scheme 8. Controlled Experiments for Supporting Aryl Radical Mechanism

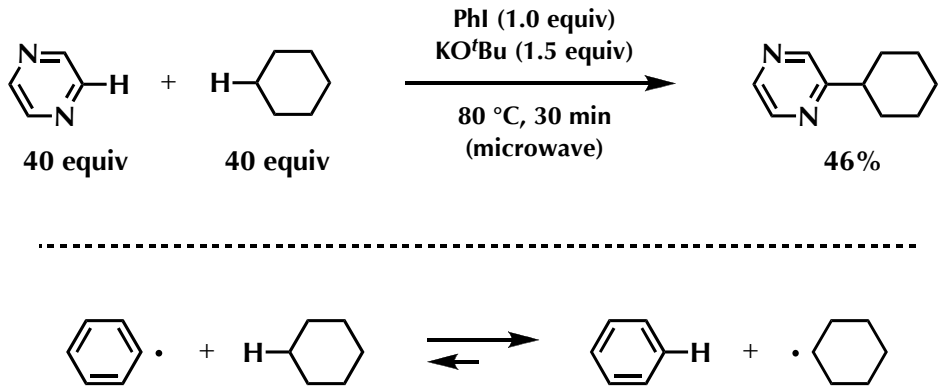
A radical nature of the present reaction is obvious from these results. Shown in Scheme 9 is a possible homolytic aromatic substitution mechanism. Single electron

transfer (SET) from KO^{t}Bu to iodobenzene is an initial step generating radical anion species. With the formation of KI, highly reactive phenyl radical is generated, which is followed by nucleophilic radical addition to pyrazine ring. ^{t}BuO radical abstracts hydrogen radical from thus-generated phenylated pyrazyl radical forming 2-phenylpyradine and ^{t}BuOH. Judging from the investigation of promoter examined in Table 2, the potassium-nitrogen interaction seems to be also important.



Scheme 9. A Possible Reaction Mechanism

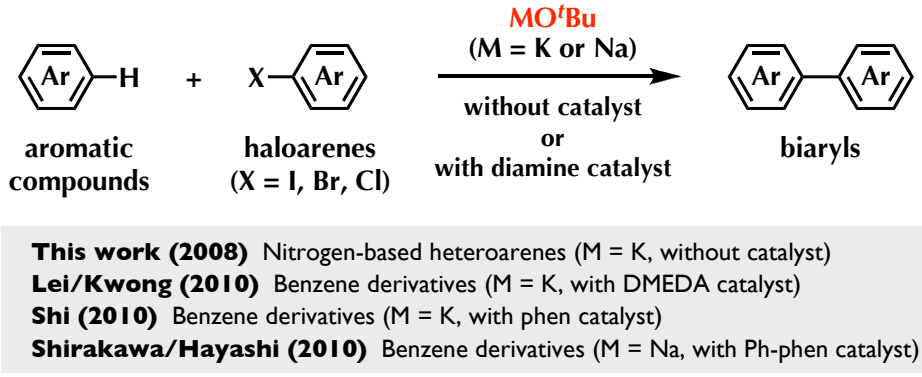
As a more convincing evidence for the involvement of aryl radicals in the KO^{t}Bu-mediated biaryl coupling, the author observed the formation of 2-cyclohexylpyrazine (46% yield) when the KO^{t}Bu-mediated reaction of pyrazine and iodobenzene was conducted in the presence of cyclohexane (Scheme 10). This reaction most likely proceeds through cyclohexyl radical, generated by the radical exchange reaction of phenyl radical and cyclohexane. The successful coupling of nitrogen heteroarenes and alkanes not only supports the radical nature of the KO^{t}Bu-promoted biaryl coupling, but also serves as a starting point toward the development of new transition-metal-free cross-coupling at two different C–H bonds.[19]



Scheme 10. Reaction in the Presence of Cyclohexane

2-6. Comparison with Other Reports[20]

After our report,[21] the research groups led by Lei/Kwong,[22a] Shi,[22b] and Shirakawa/Hayashi[22c] have also reported that the C–H bond arylation of aromatic compounds with haloarenes can be promoted by potassium or sodium *t*-butoxide, without the addition of any exogenous transition metal species (Scheme 11). In 2008, the author uncovered the *t*-butoxide-mediated biaryl coupling of electron-deficient nitrogen heteroarenes and haloarenes. In 2010, the other three groups substantially broadened the scope of reaction to a level applicable to unactivated aromatic substrates, such as benzene, through the discovery of catalysis by certain diamines. In all cases, various control experiments support a radical-based mechanism.



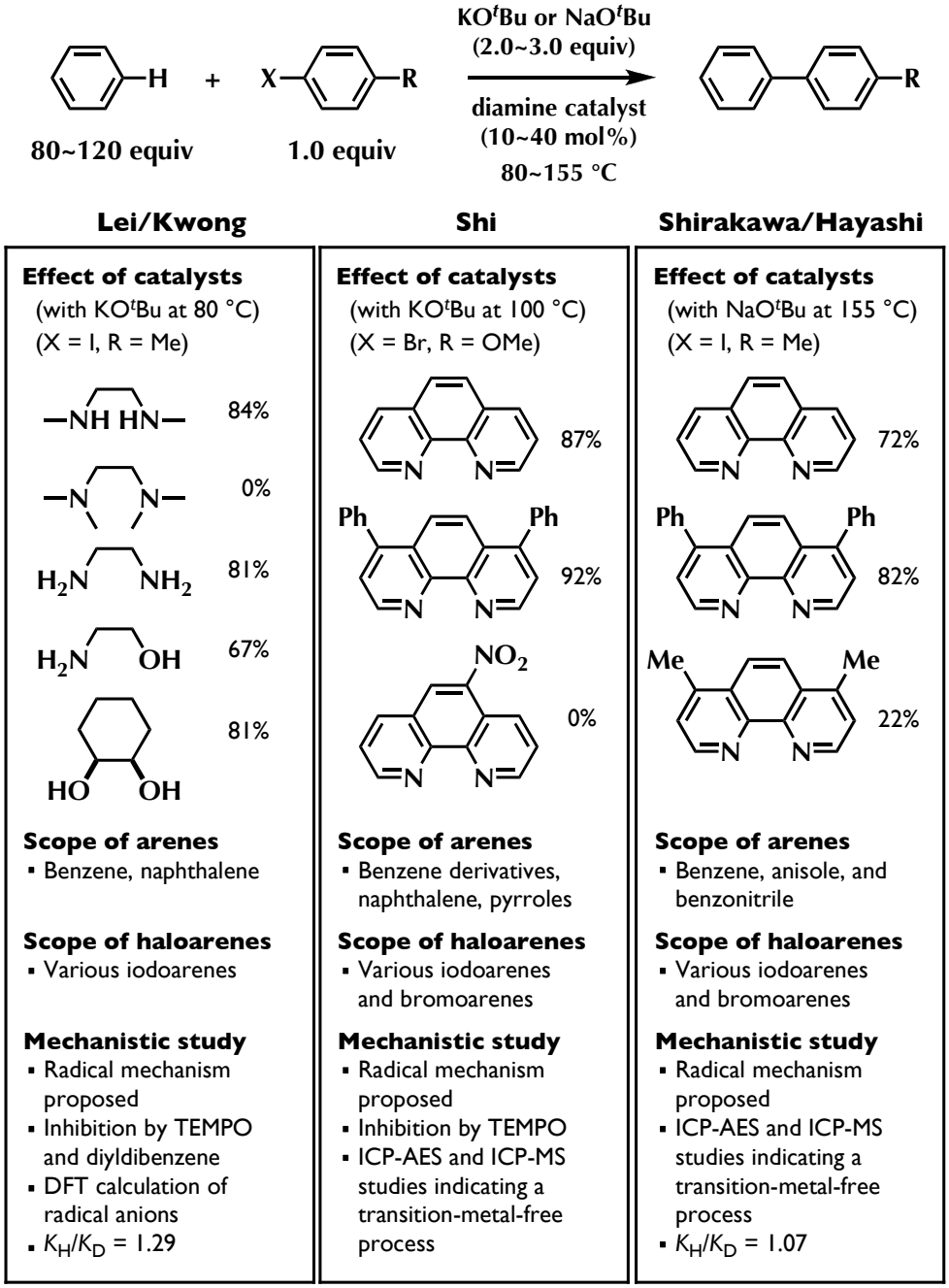
Scheme 11. *t*-Butoxide-Mediated C–H Bond Arylation of Aromatic Compounds

During the course of their studies on the iron-catalyzed C–H bond arylation of benzene with haloarenes,[23] Lei and co-workers discovered that such biaryl coupling can occur in the presence of a catalytic amount of *N,N'*-dimethylethane-1,2-diamine (DMEDA) and a stoichiometric amount of KO^{t}Bu (Scheme 12).[22a] Free NH and/or OH moieties seem to be the key for catalytic activity. Interestingly, the present biaryl coupling is also best with KO^{t}Bu; NaO^{t}Bu, LiO^{t}Bu, KOH, KOAc, NaH, and Na_2CO_3 are all ineffective at 80 °C. Although the full scope with respect to arene coupling partners is not clear at present, the scope of iodoarenes is broad. These reactions occur at the C–I bond of iodoarenes, and the regioisomers with respect to the iodoarenes are not detected. These results imply that the reaction does not proceed through aryne intermediates. They also conducted a range of control experiments and DFT studies, which are in accordance with a radical-based biaryl coupling mechanism.

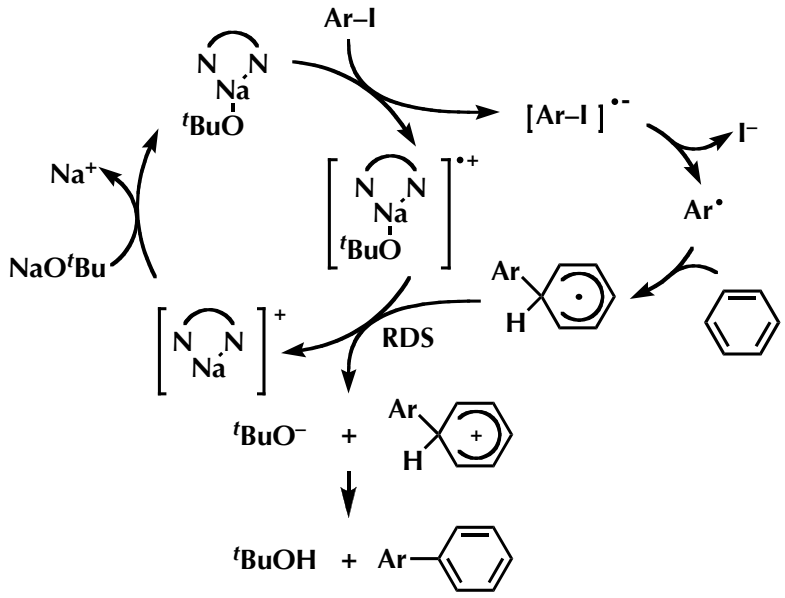
Quite independently and in almost same time, the group led by Shi reported that 1,10-phenanthroline (phen) serves as a catalyst for the same KO^{t}Bu-mediated coupling of benzene and haloarenes. 4,7-Diphenyl-1,10-phenanthroline (Ph-phen) is a even better catalyst (Scheme 12).[22b] The reaction manifests broad substrate scope. Like the other groups they also conducted a variety of control experiments including ICP-AES and ICP-MS experiments, which are in support of transition-metal-free, radical-based mechanism. For example, the addition of 10–1000 times amounts of various transition metal salts to the reaction system does not obviously enhance the reaction rate. In the kinetic studies with transition metal salts, exponential decay of starting material and formation of product is observed, indicating the zero-order dependence on transition metals.

In the same year, Shirakawa, Hayashi and coworkers also reported the *t*-butoxide-mediated, phenanthroline-catalyzed biaryl coupling of benzene and haloarenes, which is more or less identical to Shi's reaction (Scheme 12).[22c] In the Shirakawa/Hayashi system, NaO^{t}Bu is employed and the reactions are typically conducted at higher temperature (155 °C). They also propose a homolytic aromatic substitution mechanism with a number of convincing experimental supports (Scheme 13). They assume that, due to a low-lying LUMO, phenanthrolines act as SET mediators receiving an electron to form radical anions and pass the electron to aryl halides. Several competition reactions and control experiments indicate that neither the generation of aryl radical, the radical addition to benzene, and the C–H bond cleaving step are a

rate-determining step. They conclude that the single electron oxidation from cyclohexadienyl radical to the corresponding cation seems to be the rate-determining step of the reaction.



Scheme 12. Diamine Catalysts Enable the *t*-Butoxide-Mediated C–H Bond Arylation of Unactivated Benzene Derivatives



Scheme 13. A Mechanism Proposed by Shirakawa and Hayashi

The discovered new reactivity of *t*-butoxides and catalytic activity of diamines are noteworthy from fundamental reactivity point of view. However, it is also obvious that further studies are needed for these reactions to reach its full synthetic potential. Other than the practical advantages and disadvantages, people's attention inevitably goes to whether these processes are a "transition-metal-free" or not.[20b] Of course all groups including our own took great care in the analysis and interpretation of these reactions, being perhaps influenced by the past records that trace transition metals have been shown in some cases to catalyze coupling reactions such as the Suzuki–Miyaura reaction.[13] Although a number of accumulated data are in accordance with a "transition-metal-free" radical-based biaryl coupling process, it is impossible to completely exclude the possibility of transition metal mediation. A scenario that there *exists* transition metal mediation (catalysis)[23b] but *not essential* for the reaction to occur[22b] might be possible. Proving/disproving experiments are important, but even more productive may be to develop useful, practical, and otherwise-difficult transformations hinted from the new reactivities learned during these endeavors.

3. Conclusion

In summary, the direct arylation of electron-deficient nitrogen heteroarenes with iodoarenes promoted by potassium *t*-butoxide has been described. Although further mechanistic studies and a systematic optimization of the reaction conditions are warranted for this reaction to reach its full synthetic potential, the discovered new reactivity of *t*-butoxides should raise concerns to the synthetic community. Given the occasional use of *t*-butoxide bases and haloarenes in transition metal-catalyzed arylation reactions (e.g. C–H bond functionalization and amination),[24, 25] the ability of these bases to promote coupling reactions is of significant importance. Taking these findings into account, radical processes may be partially involved in the reported transition metal-catalyzed arylation reactions employing these *t*-butoxide bases and haloarenes under elevated temperatures or under microwave irradiation. Thus, great care is urged in the analysis and interpretation of such reactions.

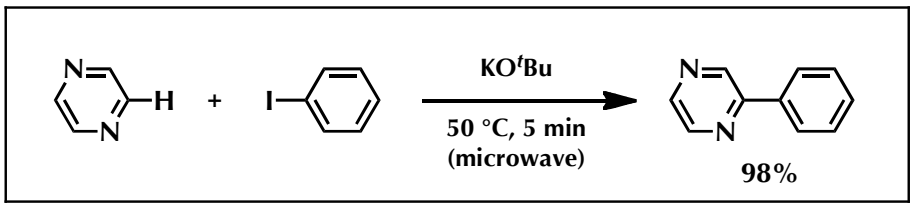
4. Experimental

4-1. General

Potassium *t*-butoxide was obtained from commercial supplier and purified by sublimation under reduced pressure (0.7 mmHg; bath temp 175~180 °C). Nitrogen heterocycles and haloarenes were obtained from commercial suppliers and purified by distillation or recrystallization prior to use. β-Iodostyrene was prepared from β-bromostyrene following the procedure developed by Buchwald.[26] $[Cp^*IrHCl]_2$ was prepared by the literature procedure.[27] Other iridium complexes were obtained from commercial supplier and used as received. Dry solvents were obtained from commercial suppliers and were degassed prior to use. Unless otherwise noted, all reactions were performed in the dark under an atmosphere of argon in flame-dried glassware with standard vacuum-line techniques. All microwave reactions were performed in a regularly calibrated CEM Focused Microwave™ Synthesis System (Discover) with IR temperature monitor and non-invasive pressure transducer using 10 mL vials with septa. All reactions using conventional heating were carried out in glass vessels equipped with J. Young® O-ring tap, heated in a 8-well reaction block (heater + magnetic stirrer). All work-up and purification procedures were carried out with reagent-grade solvents. Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F_{254} precoated plates (0.25 mm). The developed chromatogram was analyzed by UV lamp (254 nm) and ethanolic phosphomolybdic acid. Flash column chromatography was performed with E. Merck silica gel 60 (230–400 mesh). Preparative HPLC was performed with a Yamazen YFLC equipped with Ultra Pack S1-40B column using ethyl acetate and hexane as eluents. Preparative recycling gel permeation chromatography (GPC) was performed with a Japan Analytical Industry LC-9204 instrument equipped with JAIGEL-1H/JAIGEL-2H columns using chloroform as an eluent. Gas chromatography (GC) analysis was conducted on a Shimadzu GC-2010 instrument equipped with a HP-5 column (30 m × 0.25 mm, Hewlett-Packard). GCMS analysis was conducted on a Shimadzu GCMS-QP2010 instrument equipped with a HP-5 column (30 m × 0.25 mm, Hewlett-Packard). High-resolution mass spectra (HRMS) were obtained from a JEOL JMS-700 instrument (EI). Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-ECA-600 (^{1}H 600 MHz, ^{13}C 150 MHz) spectrometer. Chemical shifts for ^{1}H NMR are expressed in parts per million

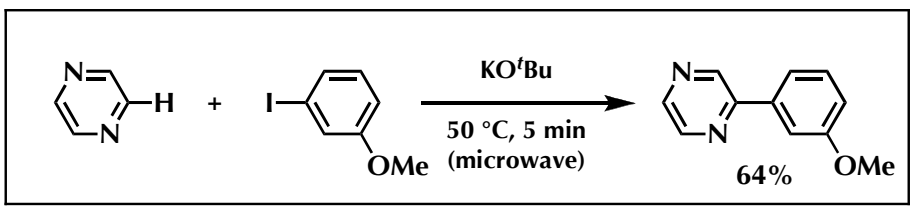
(ppm) relative to tetramethylsilane (δ 0.0 ppm). Chemical shifts for ^{13}C NMR are expressed in ppm relative to $CDCl_3$ (δ 77.0 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet, br = broad signal), coupling constant (Hz), and integration. Inductively coupled plasma-atomic emission spectroscopy (ICP-AES) was performed with a Shimadzu ICPE-9000 instrument. An analytical sample was prepared by treating a sample (1.00 g) with nitric acid (1 mL) and pure water (total volume: 20 mL). Analytical conditions are as follows, Instrument: ICPE-9000; Radio frequency: 27 MHz; Power: 1.20 kW; Plasma gas (Ar): 1.20 L/min; Cooling gas (Ar): 18.0 L/min; Carrier gas (Ar): 0.70 L/min; Sample introduction: coaxial nebulizer; Misting chamber: cyclone chamber; Attached instruments: mini torch; View direction: axial/radial.

4-2. Typical Procedure for KO^{t}Bu Promoted Biaryl Coupling (Microwave Heating Protocol)

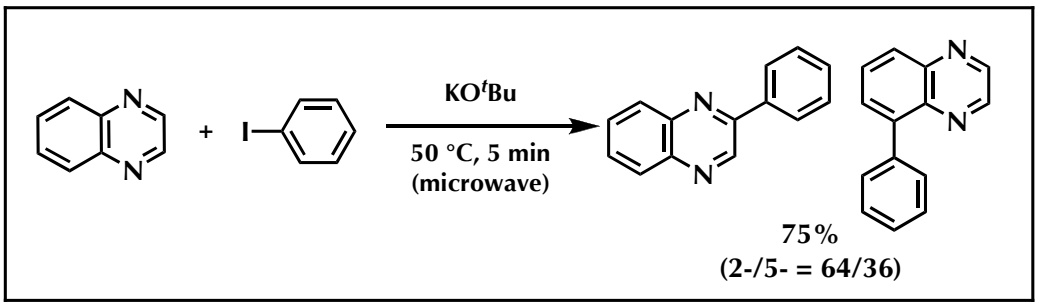


A 10-mL flame-dried microwave vial containing a magnetic stirring bar was fitted with a septum and cooled under a stream of argon. To this vial were added KO^{t}Bu (84.1 mg, 0.75 mmol), pyrazine (1.60 g, 20 mmol), and iodobenzene (102.5 mg, 0.50 mmol). The vial was sealed and heated with stirring at 50 °C for 5 min in a CEM Discover microwave apparatus. After the reaction vial was cooled down to room temperature, the mixture was passed through a short silica gel pad (EtOAc). The filtrate was evaporated and the residue was subjected to preparative HPLC (EtOAc/hexane) to afford 2-phenylpyrazine (76.5 mg, 98%) as colorless solid. The product was identified by ^{1}H NMR, ^{13}C NMR, and GCMS and these data were consistent with literature values.[28]

All reactions described in Table 3 were performed by basically following the procedure described above. Unless otherwise noted, those products were isolated and identified by ^{1}H NMR, ^{13}C NMR, and GCMS. Data were consistent with literature value: 2-(2-methoxyphenyl)pyrazine (entry 2)[29], 2-(3-thienyl)pyrazine (entry 4),[30] (*E*)-2-styrylpyrazine (entry 5),[31] 2-phenylpyridine (entry 6),[32] 3-phenylpyridine (entry 6),[33] 4-phenylpyridine (entry 6),[34] 3-phenylpyridazine (entry 7),[35] 4-phenylpyridazine (entry 7),[36] 2-phenylpyrimidine (entry 8),[37] 4-phenylpyrimidine (entry 8),[38] 5-phenylpyrimidine (entry 8),[39] 2-phenylquinoxaline (entry 9).[28]

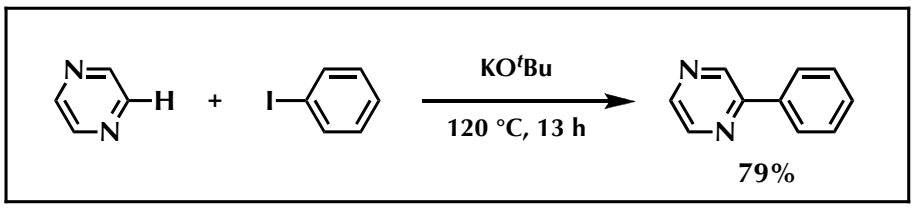


2-(3-Methoxyphenyl)pyrazine (entry 3): ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.89 (s, 3H), 7.02 (d, *J* = 7.2 Hz, 1H), 7.42 (dd, *J* = 7.6, 7.2 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.60 (s, 1H), 8.50 (s, 1H), 8.62 (s, 1H), 9.02 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 55.3, 112.0, 115.9, 119.1, 130.0, 137.7, 142.3, 143.0, 144.0, 152.5, 160.2. HRMS (EI) *m*/*z* calcd for $C_{11}H_{10}N_2O$: 186.0793, found 186.0799.



5-Phenylquinoxaline (entry 9): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.0 Hz, 2H), 7.67 (d, *J* = 7.6 Hz, 2H), 7.81–7.86 (m, 2H), 8.13 (d, *J* = 8.3 Hz, 1H), 8.86 (d, *J* = 1.4 Hz, 1H), 8.88 (d, *J* = 1.4 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 127.8, 128.1, 129.0, 129.8, 130.5, 130.6, 138.2, 141.0, 141.2, 143.3, 144.6, 144.7. HRMS (EI) *m*/*z* calcd for $C_{14}H_{10}N_2$: 206.0844, found 206.0838.

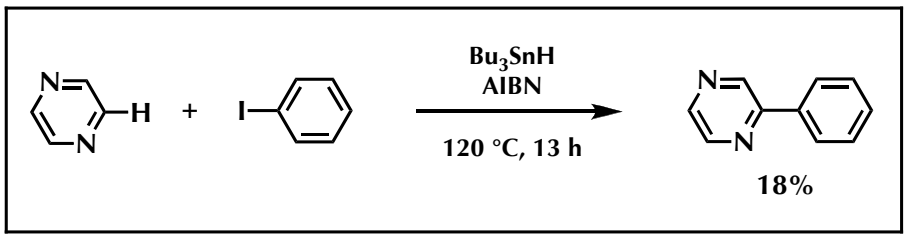
4-3. Typical Procedure for KO^{t}Bu Promoted Biaryl Coupling (Conventional Heating Protocol)



A 20-mL glass vessel equipped with J. Young® O-ring tap, containing a magnetic stirring bar, was flame-dried under vacuum and filled with argon after cooling to room temperature. To this vial were added KO^{t}Bu (86.0 mg, 0.77 mmol), pyrazine (1.60 g, 20 mmol), and iodobenzene (107.9 mg, 0.53 mmol) under a stream of argon. The vessel was sealed with O-ring tap, and then heated at 120 °C for 13 h in a 8-well reaction block with stirring. After the reaction vessel was cooled down to room temperature, the mixture

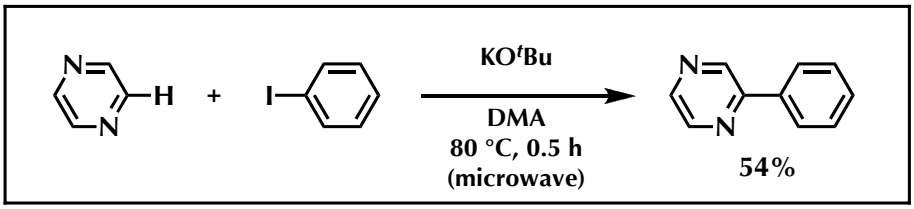
was passed through a short silica gel pad (EtOAc). The filtrate was evaporated and the residue was subjected to silica gel chromatography (EtOAc/hexane) to afford 2-phenylpyrazine (65.6 mg, 79%) as colorless solid.

4-4. Procedure for Bu_3SnH and AIBN Promoted Biaryl Coupling



A 20-mL glass vessel equipped with J. Young® O-ring tap, containing a magnetic stirring bar, was flame-dried under vacuum and filled with argon after cooling to room temperature. To this vial were added Bu_3SnH (218.3 mg, 0.75 mmol), AIBN (84.8 mg, 0.52 mmol), pyrazine (1.60 g, 20 mmol), and iodobenzene (127.3 mg, 0.62 mmol) under a stream of argon. The vessel was sealed with O-ring tap, and then heated at 120 °C for 13 h in a 8-well reaction block with stirring. After the reaction vessel was cooled down to room temperature, the mixture was passed through a short silica gel pad (EtOAc). The filtrate was evaporated and and undecane (internal standard for GC analysis) were added to the mixture. The yield of 2-phenylpyrazine was estimated to be 18% by GC analysis.

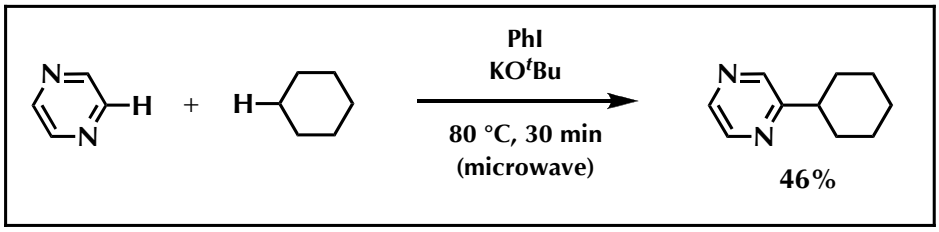
4-5. Procedure for KO^{t}Bu Promoted Biaryl Coupling (DMA Solvent Protocol)



A 10-mL flame-dried microwave vial containing a magnetic stirring bar was fitted with a septum and cooled under a stream of argon. To this vial were added KO^{t}Bu (112.3 mg, 1.0 mmol), pyrazine (1.60 g, 20 mmol), iodobenzene (102.0 mg, 0.50 mmol),

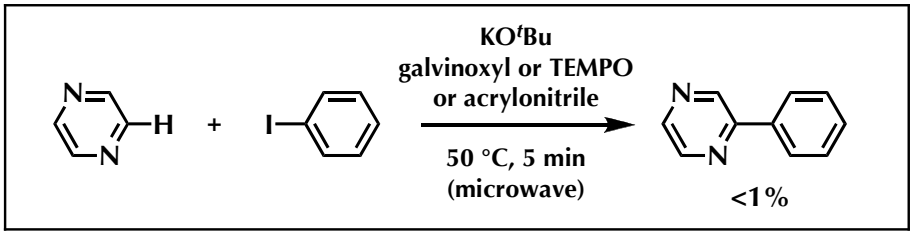
and DMA (0.5 mL). The vial was sealed and heated with stirring at 80 °C for 30 min in a CEM Discover microwave apparatus. After the reaction vial was cooled down to room temperature, methanol, chloroform, and undecane (internal standard for GC analysis) were added to the mixture. The yield of 2-phenylpyrazine was estimated to be 54% by GC analysis.

4-6. Procedure for KO^{t}Bu Promoted Reaction of Pyrazine and Iodobenzene in the Presence of Cyclohexane



A 10-mL flame-dried microwave vial containing a magnetic stirring bar was fitted with a septum and cooled under a stream of argon. To this vial were added KO^{t}Bu (84.3 mg, 0.75 mmol), pyrazine (1.60 g, 20 mmol), iodobenzene (102.5 mg, 0.50 mmol), and cyclohexane (1.69 g, 20 mmol) . The vial was sealed and heated with stirring at 50 °C for 5 min in a CEM Discover microwave apparatus. After the reaction vial was cooled down to room temperature, the mixture was passed through a short silica gel pad (EtOAc). The filtrate was evaporated and the residue was subjected to preparative HPLC (EtOAc/hexane) to afford 2-cyclohexylpyrazine (37.6 mg, 46%) as yellow oil. The product was identified by ^{1}H NMR, ^{13}C NMR, and GCMS and these data were consistent with literature values.[40]

4-7. Typical Procedure for KO^{t}Bu Promoted Biaryl Coupling with Radical Scavenger



A 10-mL flame-dried microwave vial containing a magnetic stirring bar was fitted with a septum and cooled under a stream of argon. To this vial were added KO^{t}Bu (84.2 mg, 0.75 mmol), pyrazine (1.60 g, 20 mmol), iodobenzene (103.2 mg, 0.50 mmol), and galvinoxyl (208.9 mg, 0.50 mmol). The vial was sealed and heated with stirring at 50 °C for 5 min in a CEM Discover microwave apparatus. After the reaction vial was cooled down to room temperature, methanol, chloroform, and undecane (internal standard for GC analysis) were added to the mixture. The yield of 2-phenylpyrazine was estimated to be <1% by GC analysis.

Similarly, the reactions using 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) or acrylonitrile did not gave 2-phenylpyrazine as well.

Refereneces and Notes

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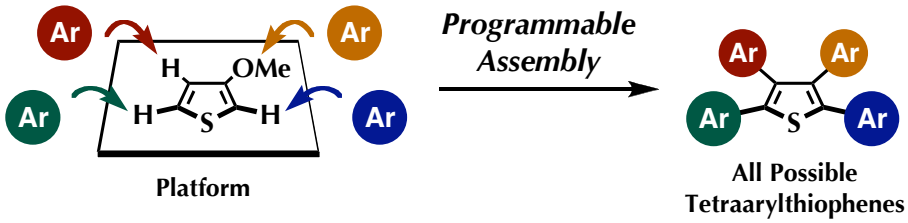
Chapter 3

Programmed Synthesis of Tetraarylthiophenes through C–H Bond Functionalization

Abstract: A general protocol for the programmed synthesis of tetraarylthiophenes has been established. The utilization of three catalysts, $RhCl(CO)\{P[OCH(CF_3)_2]_3\}_2$, $PdCl_2/P[OCH(CF_3)_2]_3$, and $PdCl_2$/2,2′-bipyridyl, enables the regioselective sequential arylations at the three C–H bonds of 3-methoxythiophene with iodoarenes. Interesting metal- and ligand-controlled regiodivergent C–H arylations have been uncovered during this study. The installation of fourth aryl groups to the thus-generated 2,4,5-triaryl-3-methoxythiophenes has been accomplished through a sequence of demethylation, triflation, and Suzuki–Miyaura coupling.

1. Introduction

Multiply arylated thiophenes are privileged structures with many interesting functions including optoelectronic[1] and biological[2] properties. In order to accelerate the discovery and structure-property relationship studies of new functional molecules of this class, a flexible method accessing all possible molecules in a programmable format is highly called for. In this chapter, a general protocol for the programmed synthesis of tetraarylthiophenes[3,4] through the sequential C–H/C–O arylation of 3-methoxythiophene (**1**) is described (Figure 1). The development of regioselective C–H bond arylation catalysts has been a key in realizing this concept.



- **Sequential direct C–H arylation**
- **Development of regioselective C–H arylation catalysts**
- **Access to all possible tetraarylthiophenes**

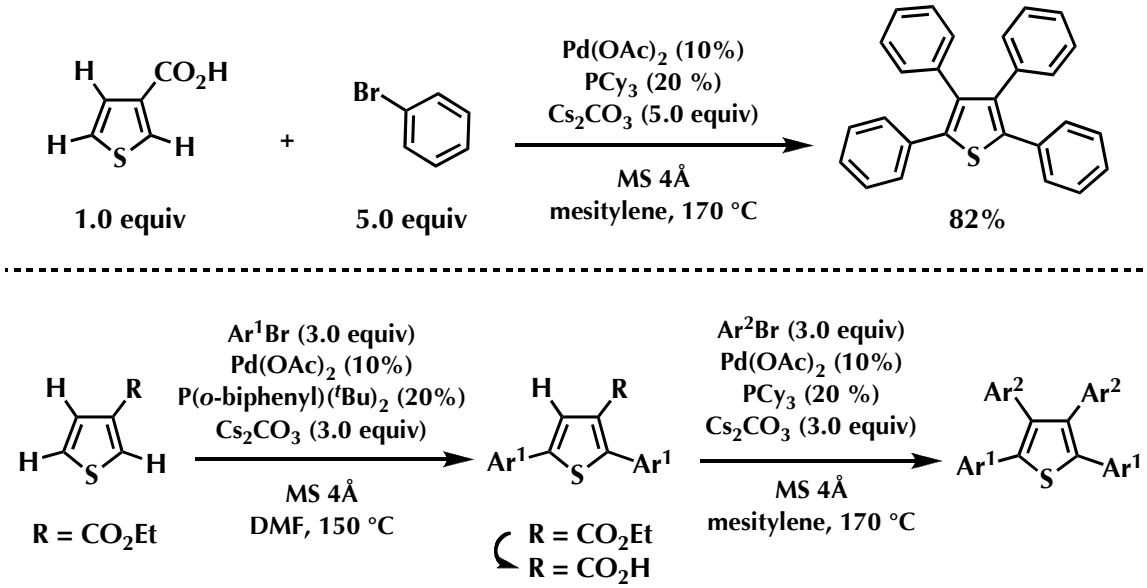
Figure 1. Programmed Synthesis of Tetraarylthiophenes

To realize a programmed synthesis of tetraarylthiophenes, a general method allowing regioselective arylations onto a thiophene core must be developed. As a means for installing aryl groups onto the core, the author selected the metal-catalyzed C–H bond arylation of thiophenes in view of synthetic expediency.[5,6] Though conceptually attractive, obstacles to overcome include insufficient reactivity and the control of regioselectivity of thienyl C–H bonds toward catalytic C–H arylation reactions.[5]

For example, several groups including our own have demonstrated that certain Pd,[5,7] Cu,[8] Rh,[9] and Ir[10] catalysts can promote the C2/C5 diarylation of thiophenes, but the

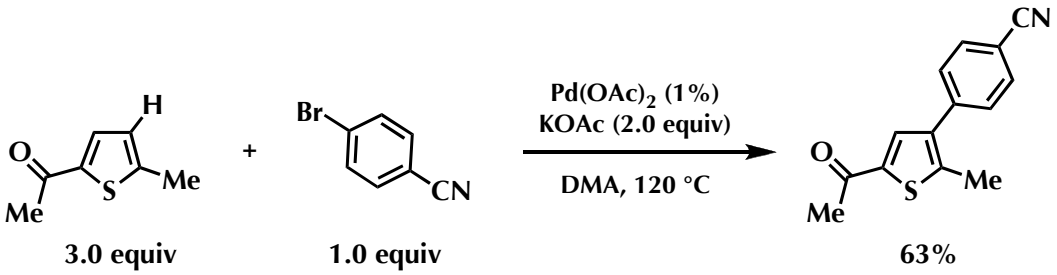
arylation at the C3/C4 position is very difficult.[11,12] As an early example of C3/C4-arylation of thiophenes, Lemaire and co-workers have reported that the direct C–H arylation of 3-formylthiophene and 3-cyanothiophene with iodoarenes resulted in a mixture of 2-arylthiophenes and 2,4-diarylthiophenes.[13]

In 2002, Miura and co-workers have reported the Pd-catalyzed multiple arylation of thiophene derivatives. When 2-thiophenecarboxamide is used as a thiophene substrate, triarylation takes place efficiently accompanied by decarbamoylation.[14a] Very recently, they demonstrated that 3-thiophenecarboxylic acid undergoes Pd-catalyzed tetraarylation with bromoarenes, by cleavage of three C–H bonds and decarboxylation (Scheme 1).[14b] Moreover, the preparation of tetraarylthiophenes having two different aryl groups at C2/C5 and C3/C4 positions is also possible. Starting from ethyl 3-thiophenecarboxylate, C2 and C5 diarylations take place, which is followed by hydrolysis of ester group. Subsequently, diarylation of thus-obtained carboxylic acid takes place at C3 and C4 positions (Scheme 1). The arylation at C3 and/or C4 position occurs likely with the aid of carbamoyl and carbonyl groups as palladium-directing groups.



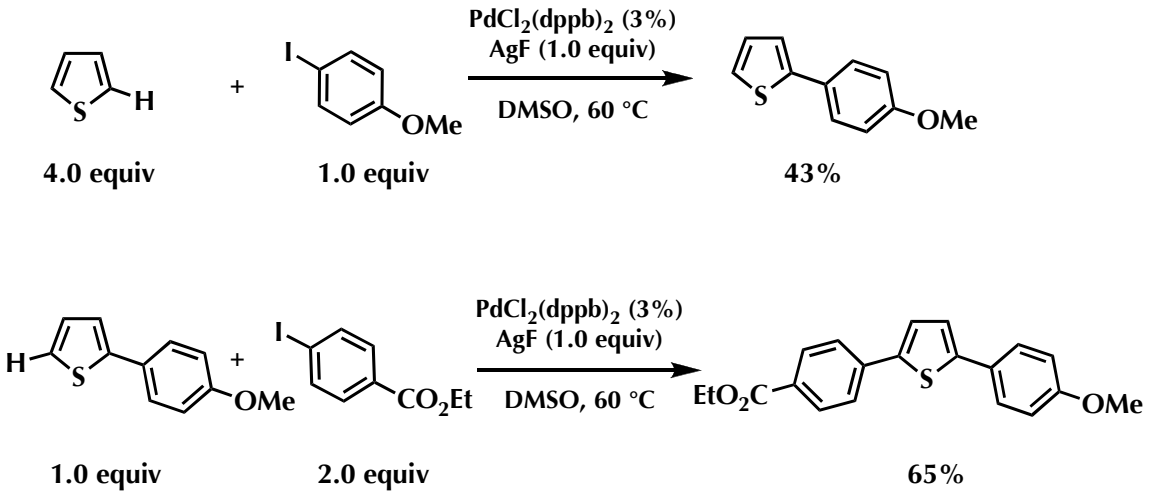
Scheme 1. Miura's Synthesis of Tetraarylthiophenes

Doucet and co-workers have demonstrated Pd-catalyzed C3 or C4 position arylation of 2,5-disubstituted thiophene with aryl bromides. For example, 2-acetyl-5-methylthiophene is arylated at C4 position with 4-bromobenzonitrile in the presence of palladium acetate and potassium acetate (Scheme 2).[11b]



Scheme 2. C4-Arylation of 2,5-Disubstitued Thiophenes

As for the regioselective multiple arylation to a thiophene ring, sequential diarylation of thiophene with two different aryl groups has been disclosed by Mori and co-workers (Scheme 3).[15] First arylation of thiophene with 4-iodoanisole takes place at C2 position under the influence of Pd catalyst with the aid of silver fluoride. Subsequently, the second arylation undergoes with ethyl 4-iodobenzoate at C5 position under otherwise identical conditions to afford 2,5-diarylthiophene having two different aryl groups in 65% yield. Rostaing and co-workers also reported same type of sequential diarylation of substituted thiophene under Pd catalysis.[2b] However, the regioselective installation of four different aryl groups onto thiophene ring through C–H bond functionalization has not been realized.[3]

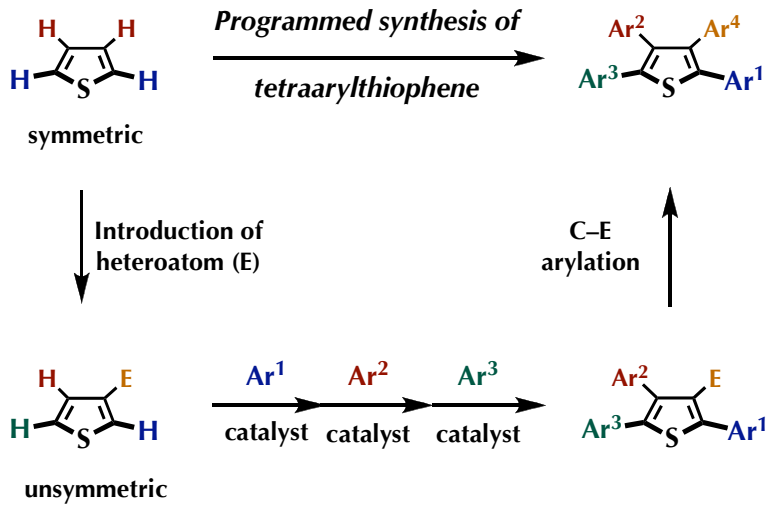


Scheme 3. Sequential Diarylation at C2/C5 Positions of Thiophene

2. Results and Discussion

2-1. Strategy

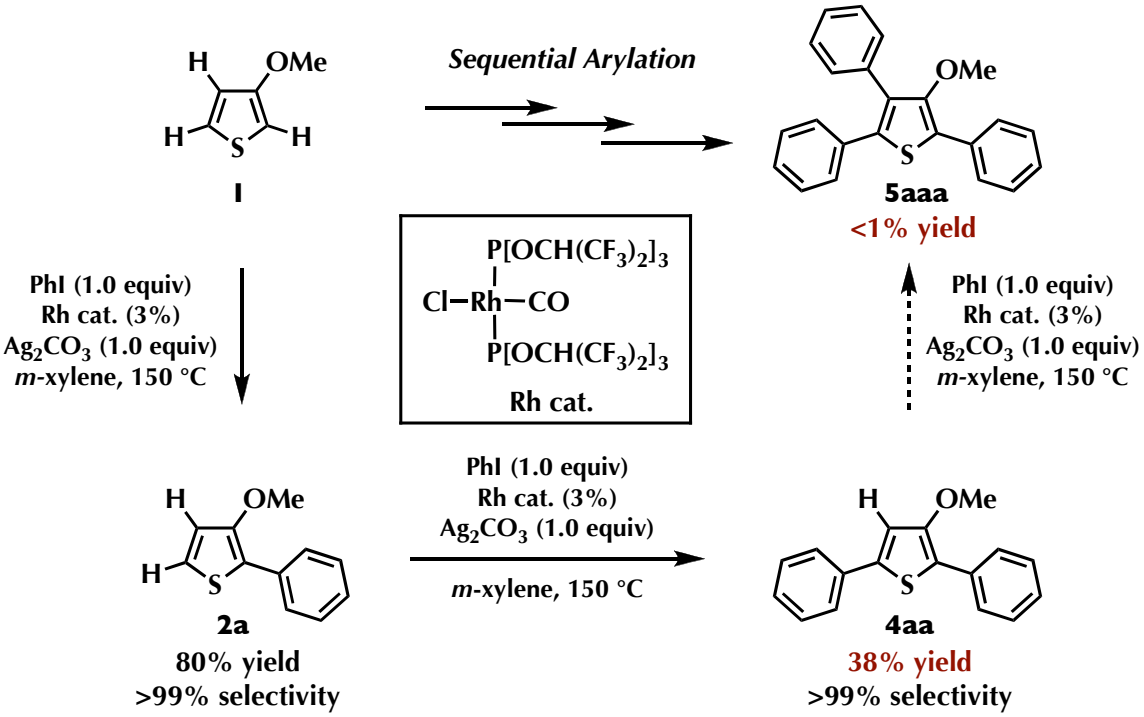
The author first designed a basic structure of starting material (thiophene derivatives) suitable for the programmed synthesis of tetraarylthiophenes. Although thiophene itself is the most straightforward starting material, achieving complete regioselectivity in C–H bond arylations might be difficult due to its symmetrical structure (existence of two sets of chemically equivalent C–H bonds). Thus, the author decided to replace one of the hydrogen atom on thiophene with a heteroatom (E) that can be transformed to an aryl group afterwards. Such desymmetrization of the thiophene ring (reactivity differentiation of thienyl C–H bonds) would in principle allow regioselective sequential arylations of the thiophene core, realizing a programmed synthesis of tetraarylthiophenes (Scheme 4).



Scheme 4. Strategy for the Programmed Synthesis of Tetraarylthiophenes

2-2. Limitation of Rhodium Catalyst System

The author selected 3-methoxythiophene (**1**) as our first-generation platform[16] for the programmed synthesis of tetraarylthiophenes due to its high reactivity and selectivity in the catalytic C–H bond arylation with iodoarenes.[9] For example, **1** reacts with iodobenzene in the presence of $RhCl(CO)\{P[OCH(CF_3)_2]_3\}_2$ catalyst (**Cat-A**) and Ag_2CO_3 to afford 3-methoxy-2-phenylthiophene (**2a**) in 80% yield with virtually complete regioselectivity. This C2-selective arylation occurs with various iodoarenes.[9] Thus, the focal point of this study was to establish a C4 and/or C5-selective catalyst for the arylation of 2-aryl-3-methoxythiophene. However, the author identified that **Cat-A** was problematic for further arylations. For example, the reaction of **2a** (1.5 equiv) and iodobenzene (1.0 equiv) in the presence of **Cat-A** (3%) and Ag_2CO_3 (1.0 equiv) in *m*-xylene at 150 °C furnished the C5 phenylation product (**4aa**) in only 38% yield (Scheme 5). Even more critically, further arylation (C4 arylation) of **4aa** did not take place with **Cat-A** (Scheme 5). Thus, the need for a new catalytic system was obvious at this point. In particlular, the development of a catalyst promoting the hard-to-achieve arylation at the β-position of thiophene ring was crucial.



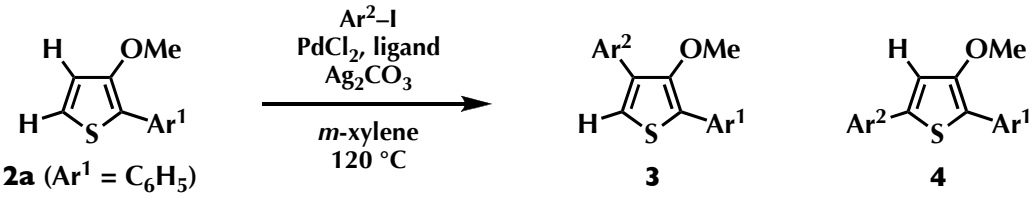
Scheme 5. Problems in Rh Catalyst

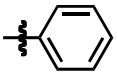
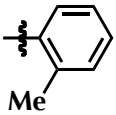
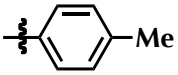
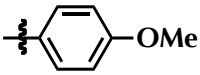
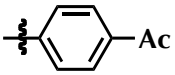
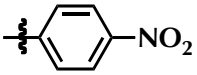
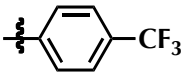
2-3. Discovery of Ligand-Controlled Regiodivergent C–H Arylation

After extensive screening, two catalysts (**Cat-B** and **Cat-C**) have been developed for the second/third arylation of **1**. The author first found that the otherwise difficult C4-selective aryaltion of **2a** with iodoarenes can be promoted by $PdCl_2/P[OCH(CF_3)_2]_3$ catalyst (**Cat-B**) and Ag_2CO_3 in *m*-xylene at 120 °C, furnishing **3** with high regioselectivity (93~98% C4) (Table 1). Given the C5-selectivity of **Cat-A** for the arylation of **2a** (*vide supra*), an interesting metal-controlled regiodivergency[17] (C5 for Rh^{I}, C4 for Pd^{II}) has been identified in $P[OCH(CF_3)_2]_3$-bound metal catalysts. More interestingly, it was found that the C4-selectivity of **Cat-B** can be switched to C5-selectivity (98~>99%) by changing the supporting neutral ligand to 2,2′-bipyridyl[18] (**Cat-C**). This ligand-controlled regiodivergent C–H arylation (C4 for $P[OCH(CF_3)_2]_3$, C5 for 2,2′-bipyridyl) turned out to be general for $PdCl_2/Ag_2CO_3$ catalysis (Table 1).

The C4-selective arylation of **2a** could be applicable to a number of aryl halides having electron-donating, electron-withdrawing, and sterically hindered substituents. The C5-selective arylation of **2a** was also successfully applicable to a variety of aryl halides.

Table 1. Ligand-Controlled Regiodivergent Arylation of **2a**[a]

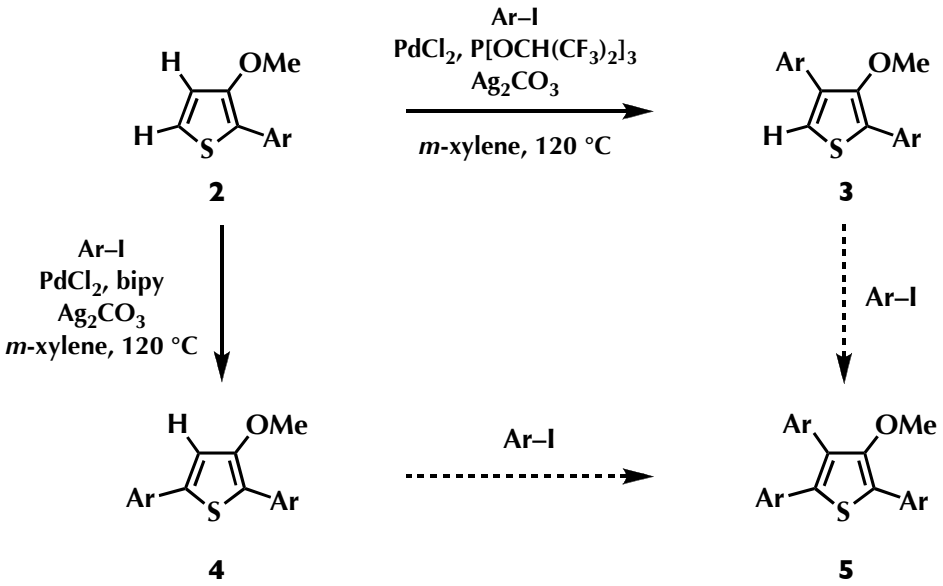


entry	Ar^2		ligand	major product	yield % (**3**/**4**)[b]
1		**a**	$P[OCH(CF_3)_2]_3$	**3aa**	80 (97:3)
2			2,2'-bipyridyl	**4aa**	89 (1:99)
3		**b**	$P[OCH(CF_3)_2]_3$	**3ab**	88 (98:2)
4			2,2'-bipyridyl	**4ab**	98 (2:98)
5[c]		**c**	$P[OCH(CF_3)_2]_3$	**3ac**	83 (96:4)
6			2,2'-bipyridyl	**4ac**	91 (1:99)
7[c]		**d**	$P[OCH(CF_3)_2]_3$	**3ad**	75 (98:2)
8			2,2'-bipyridyl	**4ad**	83 (1:>99)
9		**e**	$P[OCH(CF_3)_2]_3$	**3ae**	71 (95:5)
10			2,2'-bipyridyl	**4ae**	80 (1:>99)
11		**f**	$P[OCH(CF_3)_2]_3$	**3af**	69 (93:7)
12			2,2'-bipyridyl	**4af**	69 (2:98)
13		**g**	$P[OCH(CF_3)_2]_3$	**3ag**	77 (95:5)
14			2,2'-bipyridyl	**4ag**	77 (1:>99)

[a] Conditions: **2a** (1.5 equiv), Ar^2I (1.0 equiv), $PdCl_2$ (5%), ligand (10%), Ag_2CO_3 (1.0 equiv), *m*-xylene, 120 °C. [b] Isolated yield. Isomer ratio was determined by ^1H-NMR and GC analyses. [c] $PdCl_2$ (10%) and $P[OCH(CF_3)_2]_3$ (20%) were employed.

2-4. The Third Arylation

With two regiodivergent C–H arylation catalysts in hand, the third C–H arylation to synthesize 2,4,5-triaryl-3-methoxythiophenes **5** was next examined through two possible routes either via **3** or **4** (Scheme 6).



Scheme 6. Possible Routes to **5**

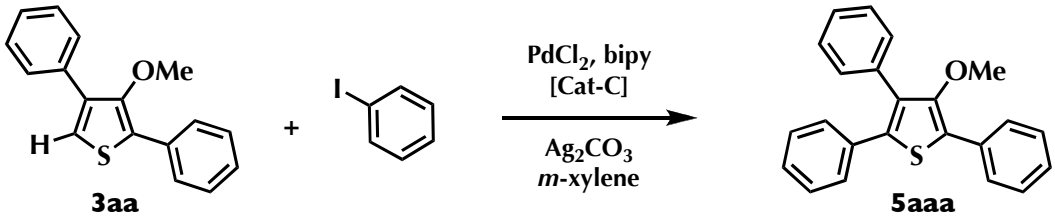
By applying three catalysts (**Cat-A**, **Cat-B**, and **Cat-C**), the proper route toward 2,4,5-triaryl-3-methoxythiophenes **5** was investigated using **3aa** or **4aa** as a model substrate. The reaction did not take place from **4aa** in the presence of any of these catalysts, even under forcing conditions; excess amount of iodobenzene, high catalyst loading, and high temperature (up to 150 °C).

Gratifyingly, the **Cat-C** system was found to promote the C5-arylation of 3-methoxy-2,4-diphenylthiophene (**3aa**) with iodobenzene giving **5aa** in 39% yield under the identical conditions to the second arylation (Table 2, entry 1). On the other hand, both **Cat-A** and **Cat-B** systems were unable to promote the arylation of **3aa** efficiently.

Encouraged by these results, further optimization was carried out with **Cat-C**. The

amount of catalyst and higher temperature did not give dramatic effect on the reactivity of the third arylation (entries 2 and 3). Significant difference in reactivity was observed by changing the amount of silver carbonate (entries 4–6). That is, the desired 3-methoxy-2,4,5-triphenylthiophene (**5aaa**) was obtained in 87% isolated yield in the case of using 2.0 equivalent of silver carbonate (entry 6). The reactions employing lower amount of silver carbonate (1.2–1.5 equiv relative to **3aa**) gave poor results (entries 4 and 5).

Table 2. Optimization of Third Arylation[a]

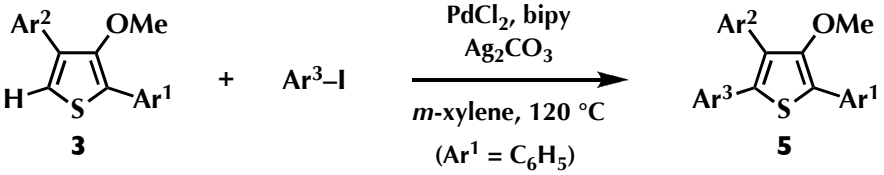


entry	catalyst	Ag_2CO_3	temp (°C)	yield (%)[b]
1	5%	1.0 equiv	120	39
2	10%	1.0 equiv	120	50
3	5%	1.0 equiv	170	49
4	5%	1.2 equiv	120	56
5	5%	1.5 equiv	120	58
6	5%	2.0 equiv	120	87[c]

[a] Conditions: **3aa** (1.0 equiv), PhI (3.0 equiv), **Cat-C** ($PdCl_2$/bipy = 1:2), Ag_2CO_3, *m*-xylene. [b] Yields are determined by ^1H NMR. [c] Isolated yield.

To our delight, a variety of 2,4,5-triaryl-3-methoxythiophenes **5** could be synthesized in good to high yields under present conditions (Table 3).

Table 3. Arylation of **3** Catalyzed by Pd/bipy/Ag_2CO_3[a]

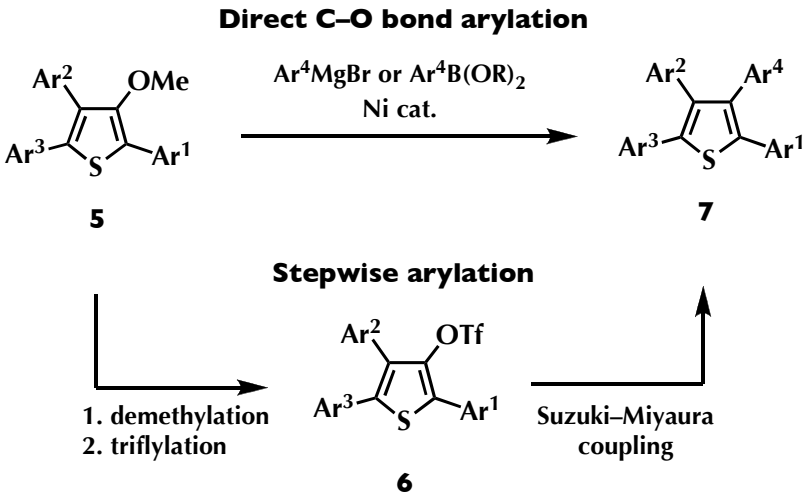


entry	Ar^2		Ar^3		**5** (yield, %)[b]
1		**a**		**a**	**5aaa** (87)
2	Me	**c**	NO_2	**f**	**5acf** (61)
3[c]	Me	**c**	CF_3	**g**	**5acg** (70)
4[c]	Ac	**e**	Me	**c**	**5aec** (65)
5	Ac	**e**	NO_2	**f**	**5aef** (73)
6[c]	CF_3	**g**	Me	**c**	**5agc** (70)

[a] Conditions: **3** (1.0 equiv), Ar^3I (3.0 equiv), $PdCl_2$ (5%), 2,2'-bipyridyl (10%), Ag_2CO_3 (2.0 equiv), *m*-xylene, 120 °C. [b] Isolated yield. [c] 1.0 equiv of Ag_2CO_3 was employed.

2-5. The Fourth Arylation

Finally, the fourth arylation furnishing the targeted tetraarylthiophenes **7** was investigated. There are several possibilities to synthesize tetraarylthiophenes **7** from 2,4,5-triaryl-3-methoxythiophenes **5** (Scheme 7). As an initial attempt, the author envisaged that the use of nickel-catalyzed C–O bond arylation of **5** with arylmetal reagents (boronic esters or Grignard reagents) could be applied for the fourth arylation to give **7** directly.[19] Unfortunately, this direct C–O bond arylation procedure was not applicable to **5**.

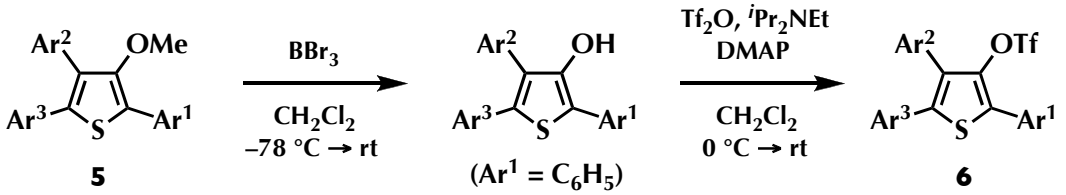


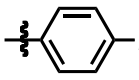
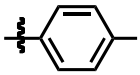
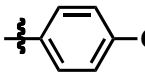
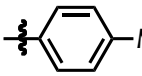
Scheme 7. Possible Methods for Fourth Arylation

Subsequently, the fourth arylation was investigated by demethylation and trifluoromethanesulfonylation of 2,4,5-triaryl-3-methoxythiophenes **5**, which was followed by Suzuki–Miyaura coupling of thus-generated triflates **6** with arylboronic acids (Scheme 7).[20] Gratifyingly, the BBr_3-promoted demethylation of **5** took place in almost quantitative yield, which was followed by treatment of thus-obtained crude alcohols with $Tf_2O/{}^{i}Pr_2NEt$/DMAP to produce the corresponding triflates **6** in high yields (Table 4).

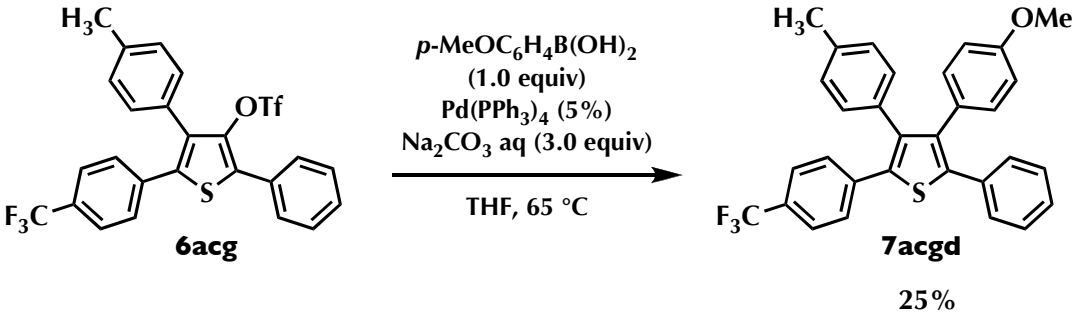
Although thus-obtained triflate **6acg** was treated with standard Suzuki–Miyaura coupling conditions, such as $Pd(PPh_3)_4/Na_2CO_3$ aq, the reaction did not take place efficiently (Scheme 8). Then, the author started the optimization of fourth arylation by using the reaction of **6acg** with *p*-anisylboronic acid as a model reaction. Since the starting material **6acg** seems to be sterically hindered, $Ba(OH)_2$, which is known as an effective base for the Suzuki–Miyaura coupling of bulky substrates, was selected for the fourth arylation.[21]

Table 4. Triflylation of **5**[a]



entry	Ar^2		Ar^3		**6** (yield, %)
1		**c**		**g**	**6acg** (71)
2		**g**		**c**	**6agc** (75)

[a] Conditions: **5** (1.0 equiv), BBr_3 (1.3 equiv), CH_2Cl_2, –78 °C to rt, then Tf_2O (5.0 equiv), $^iPr_2NEt$ (2.0 equiv), DMAP (0.1 equiv), CH_2Cl_2, 0 °C to rt.

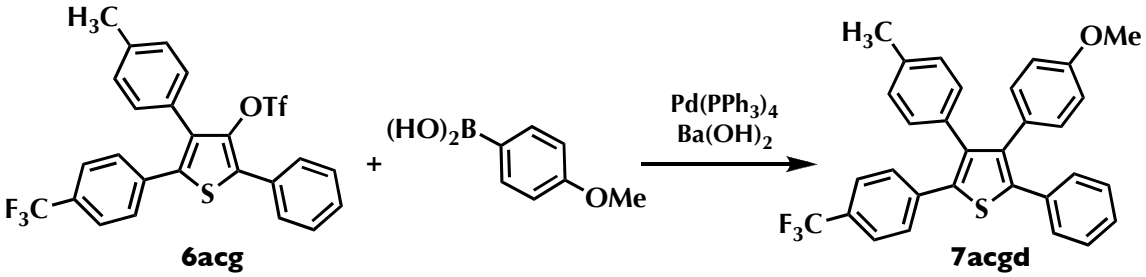


Scheme 8. Fourth Arylation under Standard Suzuki–Miyaura Coupling

The fourth arylation was promoted by using $Ba(OH)_2$ as a base in DME/H_2O solvent to afford tetraarylthiophene **7acgd** in 50% yield accompanied with hydrolysis of starting material (Table 5, entry 1). The use of toluene instead of DME completely shut down the reaction (entry 2). On the other hand, 1-butanol/H_2O solvent system gave the desired coupling product in good yield (entries 3 and 4). As the solubility of H_2O in homogeneous solution was suspected to be important to suppress hydrolysis product,

the ratio of H_2O with 1-butanol was next investigated (entries 4–6). The 1-butanol/H_2O ratio of 5:4 (v/v) turned out to be best in this reaction. For example, when the mixture of **6acg** (1.0 equiv), *p*-anisylboronic acid (3.0 equiv), $Pd(PPh_3)_4$ (5%), and $Ba(OH)_2$ (2.0 equiv) in 1-butanol/H_2O (5:4) was stirred at 65 °C, tetraarylthiophene **7acgd** was isolated in 75% yield (entry 5). Better results were not obtained under forcing conditions; higher temperature (100 °C) and higher loading of catalyst and base (entries 7–9).

Table 5. Optimization of Forth Arylation[a]

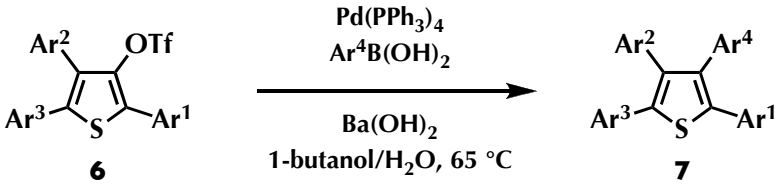


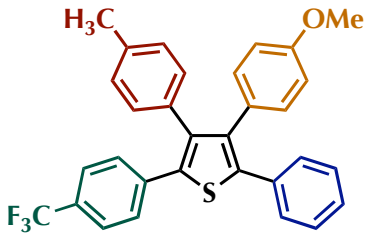
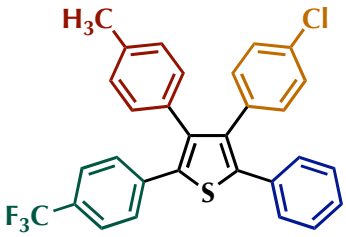
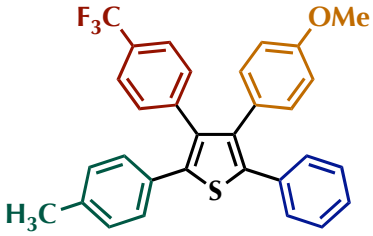
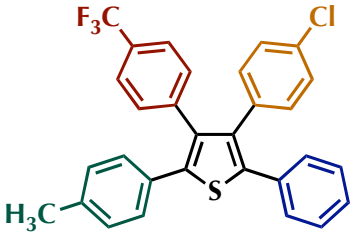
entry	boronic acid	solvent	temp (°C)	yield (%)[b]
1	1.5 equiv	DME/H_2O (2:1)	80	50
2	1.5 equiv	toluene/H_2O (2:1)	80	0
3	3.0 equiv	1-butanol/H_2O (2:1)	80	70
4	3.0 equiv	1-butanol/H_2O (2:1)	65	68
5	3.0 equiv	1-butanol/H_2O (5:4)	65	75[e]
6	3.0 equiv	1-butanol/H_2O (1:1)	65	57
7	3.0 equiv	1-butanol/H_2O (2:1)	100	56
8[c]	3.0 equiv	1-butanol/H_2O (2:1)	65	59
9[d]	3.0 equiv	1-butanol/H_2O (2:1)	65	57

[a] Conditions: **6acg** (1.0 equiv), *p*-$MeOC_6H_4B(OH)_2$, $Pd(PPh_3)_4$ (5%), $Ba(OH)_2$ (2.0 equiv), solvent. [b] Yields are determined by ^1H NMR. [c] $Pd(PPh_3)_4$ (10%). [d] $Ba(OH)_2$ (3.0 equiv). [e] Isolated yield.

A variety of tetraarylthiophenes **7** were synthesized under the optimized conditions (Table 6). All of these compounds were obtained with virtually complete isomeric purities.

Table 6. Forth Arylation of **6**[a]



Final product **7** (yield of cross-coupling)	
 **7acgd** (75%)	 **7acgh** (82%)
 **7agcd** (74%)	 **7agch** (77%)

[a] Conditions: **6** (1.0 equiv), $Ar^4B(OH)_2$ (3.0 equiv), $Pd(PPh_3)_4$ (5%), $Ba(OH)_2$ (2.0 equiv), 1-butanol/H_2O (5:4), 65 °C.

3. Conclusion

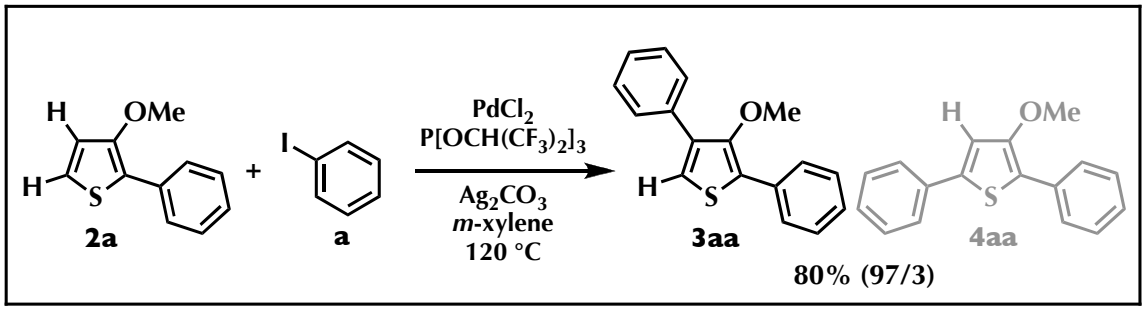
In summary, the author has established a general protocol for the programmed synthesis of tetraarylthiophenes. The utilization of three catalysts, $RhCl(CO)\{P[OCH(CF_3)_2]_3\}_2$, $PdCl_2/P[OCH(CF_3)_2]_3$, and $PdCl_2$/bipy, enables the regioselective sequential arylations at the three C–H bonds of 3-methoxythiophene with iodoarenes. Interesting metal- and ligand-controlled regiodivergent C–H arylations have been uncovered during this study. Noteworthy features of the present method are that (i) all aryl groups assembled on thiophene core stem from readily available aryl iodides or boronic acids, (ii) the installation of aryl groups at the desired position can be achieved, and (iii) simple alteration of application order of aryl reagents in the sequence results in the production of all possible tetraarylthiophenes. Although in this study the author focused on the synthesis of tetraarylthiophenes, this strategy is also applicable to the regioselective synthesis of di- or triarylated thiophenes by skipping one or two C–H arylation step(s) prior to the final C–O bond arylation. The present strategy should find many uses for combinatorial lead-structure identification and optimization in the development of functional organic materials where the structure-property relationships are often not easily predictable.

4. Experimental

4-1. General

Unless otherwise noted, all materials including dry solvents were obtained from commercial suppliers and used without further purification. The ligand $P[OCH(CF_3)_2]_3$[22], rhodium complex $RhCl(CO)\{P[OCH(CF_3)_2]_3\}_2$, and 3-methoxy-2-phenylthiophene (**2a**)[9] were prepared according to procedures reported in the literature. Unless otherwise noted, all reactions were performed with dry solvents under an atmosphere of argon in flame-dried glassware, using standard vacuum-line techniques. All arylation reactions using conventional heating were carried out in glass vessels equipped with J. Young® O-ring tap, heated in a 8-well reaction block (heater + magnetic stirrer). All work-up and purification procedures were carried out with reagent-grade solvents in air. Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F_{254} precoated plates (0.25 mm). The developed chromatogram was analyzed by UV lamp (254 nm) and ethanolic phosphomolybdic acid/sulfuric acid. Flash column chromatography was performed with E. Merck silica gel 60 (230–400 mesh). Preparative recycling gel permeation chromatography (GPC) was performed with a JAI LC-9204 instrument equipped with JAIGEL-1H/JAIGEL-2H columns using chloroform as an eluent. Preparative thin-layer chromatography (PTLC) was performed using Wako-gel® B5-F silica coated plates (0.75 mm) prepared in our laboratory. Gas chromatography (GC) analysis was conducted on a Shimazu GC-2010 instrument equipped with a HP-5 column (30 m × 0.25 mm, Hewlett-Packard). GC/MS analysis was conducted on a Shimazu GCMS-QP2010 instrument equipped with a HP-5 column (30 m × 0.25 mm, Hewlett-Packard). High-resolution mass spectra (HRMS) were obtained from a JEOL JMS-700 instrument (EI). Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-ECA-600 (^{1}H 600 MHz, ^{13}C 150 MHz) spectrometer. Chemical shifts for ^{1}H NMR are expressed in parts per million (ppm) relative to tetramethylsilane (δ 0.0 ppm). Chemical shifts for ^{13}C NMR are expressed in ppm relative to $CDCl_3$ (δ 77.0 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet, br = broad signal), coupling constant (Hz), and integration.

4-2. Typical Procedure for C4-Arylation of 2a

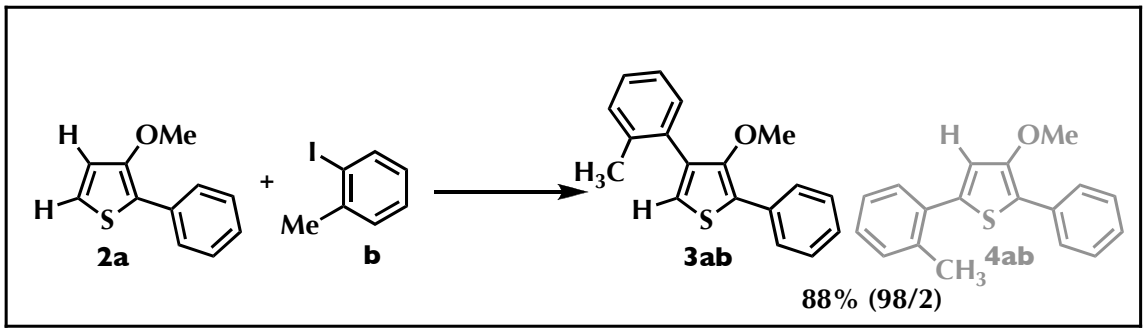


A 20-mL glass vessel equipped with J. Young® O-ring tap, containing a magnetic stirring bar, was flame-dried under vacuum and filled with argon after cooling to room temperature. To this vessel were added $PdCl_2$ (4.8 mg, 27 μmol), $P[OCH(CF_3)_2]_3$ (26.6 mg, 50 μmol), Ag_2CO_3 (137.5 mg, 0.50 mmol) and dry *m*-xylene (0.5 mL) under a stream of argon. The vessel was heated at 60 °C for 0.5 h. To this vessel were added 3-methoxy-2-phenylthiophene (**2a**: 142.7 mg, 0.75 mmol), iodobenzene (**a**: 92.4 mg, 0.45 mmol), and dry *m*-xylene (2.0 mL) under a stream of argon. The vessel was sealed with O-ring tap, and then heated at 120 °C for 22 h in a 8-well reaction block with stirring. After cooling the reaction mixture to room temperature, the mixture was passed through a short silica gel pad (EtOAc). The filtrate was evaporated and the residue was subjected to gel permeation chromatography (GPC) to afford arylated products (95.6 mg, 80%) as mixture of 3-methoxy-2,4-diphenylthiophene (**3aa**) and 3-methoxy-2,5-diphenylthiophene (**4aa**). The ratio of **3aa**/**4aa** was determined to be 97/3 by ^{1}H NMR analysis. These isomers could be separated by PTLC (Hexane/ EtOAc = 10/1). **3aa** was obtained as yellow solid.

3-Methoxy-2,4-diphenylthiophene (3aa): ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.49 (s, 3H), 7.17 (s, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.41 (d, *J* = 7.6 Hz, 2H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 60.7, 119.5, 127.19, 127.28, 127.3, 127.5, 128.5, 128.7, 133.1, 136.8, 151.6. HRMS (EI) *m*/*z* calcd. for $C_{17}H_{14}OS$: 266.0765, found 266.0760.

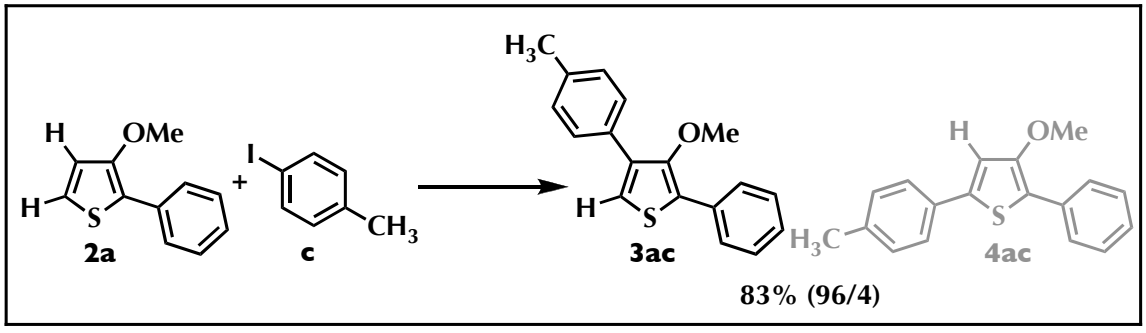
4-3. Compound Data for Other C4-Arylation Products of 2a

All arylated compounds **3** described in this section were prepared following the typical procedure given in Section 4-2. Compounds were purified by preparative thin-layer chromatography (PTLC) and/or gel permeation chromatography (GPC).



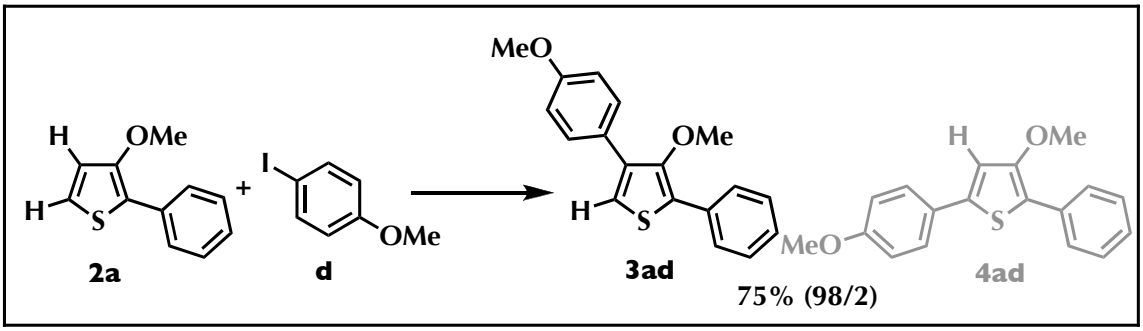
3-Methoxy-2-phenyl-4-(*o*-tolyl)thiophene (3ab): 88% isolated yield as mixture of regioisomers from 3-methoxy-2-phenylthiophene (**2a**: 144.9 mg, 0.76 mmol), *o*-iodotoluene (**b**: 109.1 mg, 0.5 mmol), $PdCl_2$ (4.6 mg, 25 μmol), $P[OCH(CF_3)_2]_3$ (26.6 mg, 0.05 mmol), Ag_2CO_3 (138.0 mg, 0.50 mmol), and dry *m*-xylene (2.5 mL). The ratio of **3ab**/**4ab** was determined to be 98/2 by ^1H NMR and GC analyses. These isomers could be separated by PTLC (Hexane/EtOAc = 10/1). **3ab** was obtained as colorless oil.

^1H NMR (600 MHz, $CDCl_3$) δ 2.32 (s, 3H), 3.38 (s, 3H), 6.96 (s, 1H), 7.18–7.26 (m, 4H), 7.31 (d, J = 7.6 Hz, 1H), 7.37 (t, J = 7.6 Hz, 2H), 7.76 (d, J = 6.9 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.2, 60.5, 120.2, 125.5, 126.6, 127.0, 127.2, 127.7, 128.6, 129.96, 130.02, 133.2, 135.1, 136.9, 137.3, 152.0. HRMS (EI) m/z calcd. for $C_{18}H_{16}OS$: 280.0922, found 280.0909.



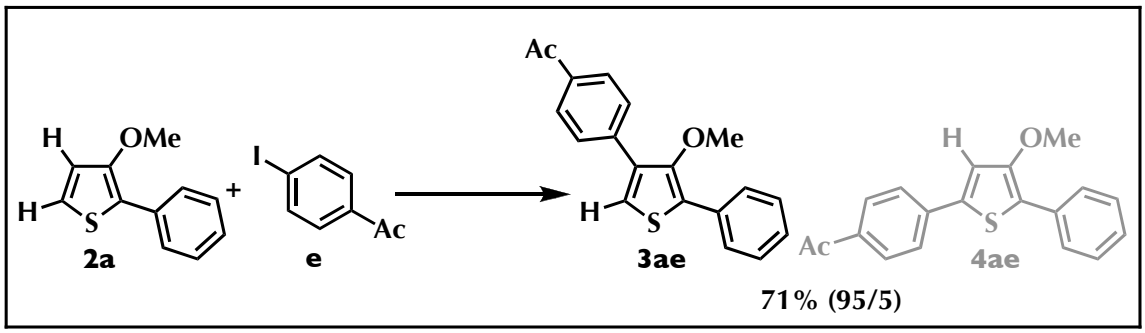
3-Methoxy-2-phenyl-4-(*p*-tolyl)thiophene (3ac): 83% isolated yield as mixture of regioisomers from 3-methoxy-2-phenylthiophene (**2a**: 142.5 mg, 0.75 mmol), *p*-iodotoluene (**c**: 108.8 mg, 0.5 mmol), $PdCl_2$ (8.9 mg, 50 μmol), $P[OCH(CF_3)_2]_3$ (53.2 mg, 0.10 mmol), Ag_2CO_3 (138.5 mg, 0.50 mmol), and dry *m*-xylene (2.5 mL). The ratio of **3ac**/**4ac** was determined to be 96/4 by ^{1}H NMR analysis. These isomers could be separated by PTLC (Hexane/ EtOAc = 10/1). **3ac** was obtained as white solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.49 (s, 3H), 7.14 (s, 1H), 7.22 (d, *J* = 7.6 Hz, 2H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.56 (d, *J* = 7.6 Hz, 2H), 7.76 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.2, 60.6, 119.1, 127.2, 127.3, 127.4, 128.0, 128.7, 129.2, 132.2, 133.2, 136.8, 137.1, 151.7. HRMS (EI) *m*/*z* calcd. for $C_{18}H_{16}OS$: 280.0922, found 280.0924.

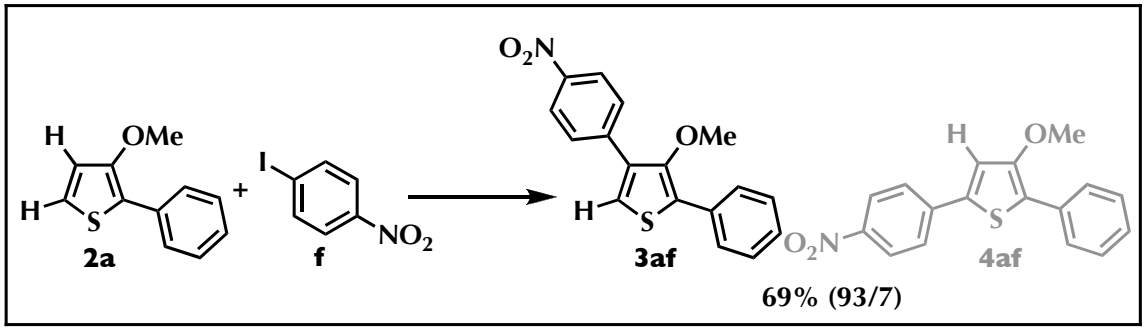


3-Methoxy-4-(*p*-methoxyphenyl)-2-phenylthiophene (3ad): 75% isolated yield as mixture of regioisomers from 3-methoxy-2-phenylthiophene (**2a**: 142.5 mg, 0.75 mmol), *p*-iodoanisole (**d:** 116.9 mg, 0.50 mmol), $PdCl_2$ (9.0 mg, 50 μmol), $P[OCH(CF_3)_2]_3$ (53.2 mg, 0.10 mmol), Ag_2CO_3 (138.5 mg, 0.50 mmol), and dry *m*-xylene (2.5 mL). The ratio of **3ad**/**4ad** was determined to be 98/2 by ^{1}H NMR analysis. These isomers could be separated by PTLC (Hexane/ EtOAc = 10/1). **3ad** was obtained as yellow solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.50 (s, 3H), 3.85 (s, 3H), 6.96 (d, *J* = 8.9 Hz, 2H), 7.11 (s, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.59 (d, *J* = 8.9 Hz, 2H), 7.76 (d, *J* = 8.9 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 55.3, 60.5, 114.0, 118.5, 127.1, 127.3, 127.7, 128.0, 128.66, 128.69, 133.2, 136.5, 151.6, 159.0. HRMS (EI) *m*/*z* calcd. for $C_{18}H_{16}O_2S$: 296.0871, found 296.0881.



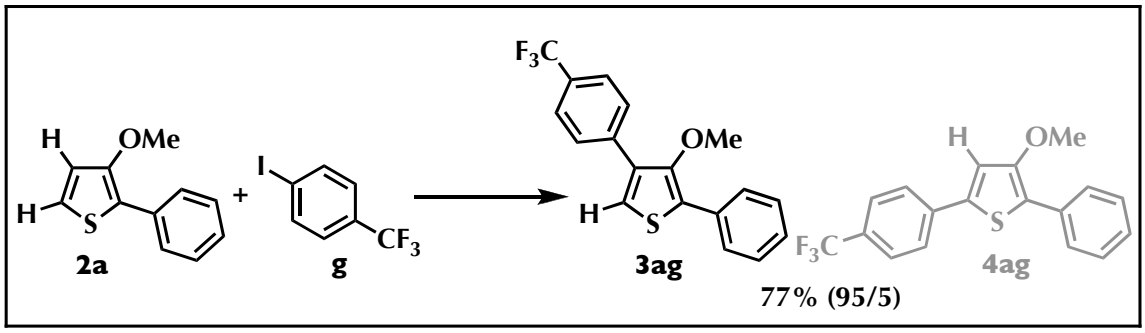
4-(*p*-Acetylphenyl)-3-methoxy-2-phenylthiophene (3ae): 72% isolated yield as mixture of regioisomers from 3-methoxy-2-phenylthiophene (**2a**: 142.5 mg, 0.75 mmol), *p*-iodoacetophenone (**e**: 123.5 mg, 0.50 mmol), $PdCl_2$ (4.7 mg, 25 μmol), $P[OCH(CF_3)_2]_3$ (26.6 mg, 50 μmol), Ag_2CO_3 (138.2 mg, 0.50 mmol), and dry *m*-xylene (2.5 mL). The ratio of **3ae**/**4ae** was determined to be 95/5 by ^{1}H NMR analysis. These isomers could be separated by PTLC (Hexane/ EtOAc = 10/1). **3ae** was obtained as yellow solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 2.64 (s, 3H), 3.50 (s, 3H), 7.29 (s, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.79 (d, *J* = 8.2 Hz, 2H), 8.02 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.6, 60.8, 120.7, 127.4, 127.5, 127.5, 128.69, 128.74, 128.74, 132.8, 135.5, 135.8, 139.6, 151.5, 197.7. HRMS (EI) *m*/*z* calcd. for $C_{19}H_{16}O_2S$: 308.0871, found 308.0861.



3-Methoxy-4-(*p*-nitrophenyl)-2-phenylthiophene (3af): 69% isolated yield as mixture of regioisomers from 3-methoxy-2-phenylthiophene (**2a**: 142.5 mg, 0.75 mmol), *p*-iodonitrobenzene (**f**: 124.7 mg, 0.50 mmol), $PdCl_2$ (4.4 mg, 25 μmol), $P[OCH(CF_3)_2]_3$ (26.6 mg, 50 μmol), Ag_2CO_3 (138.1 mg, 0.50 mmol), and dry *m*-xylene (2.5 mL). The ratio of **3af**/**4af** was determined to be 93/7 by ^{1}H NMR analysis. These isomers could be

separated by PTLC (Hexane/ EtOAc = 10/1). **3af** was obtained as yellow solid.

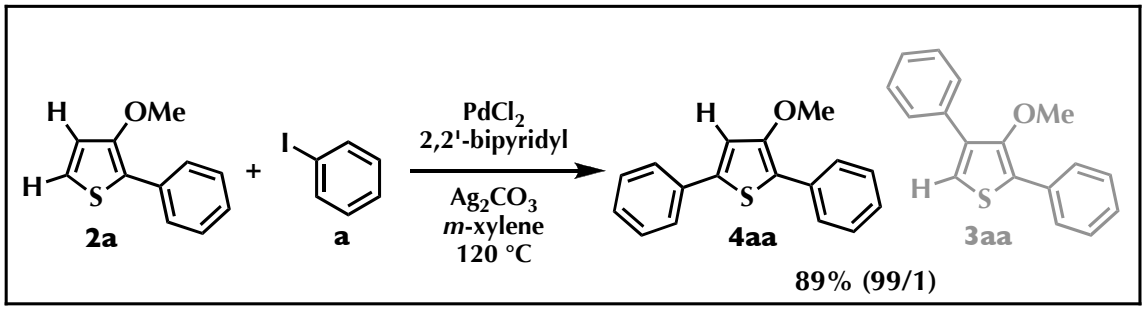
^{1}H NMR (600 MHz, $CDCl_3$) δ 3.51 (s, 3H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.36 (s, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.75 (d, *J* = 6.9 Hz, 2H), 7.86 (d, *J* = 8.9 Hz, 2H), 8.29 (d, *J* = 8.9 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 60.9, 121.6, 123.9, 127.4, 127.7, 128.0, 128.8, 129.2, 132.5, 134.4, 141.3, 146.8, 151.3. HRMS (EI) *m*/*z* calcd. for $C_{17}H_{13}NO_3S$: 311.0616, found 311.0605.



3-Methoxy-2-phenyl-4-(*p*-trifluoromethylphenyl)thiophene (3ag): 77% isolated yield as mixture of regioisomers 3-methoxy-2-phenylthiophene (**2a**: 142.5 mg, 0.75 mmol), *p*-iodobenzotrifluoride (**g:** 136 mg, 0.50 mmol), $PdCl_2$ (4.4 mg, 25 μmol), $P[OCH(CF_3)_2]_3$ (26.6 mg, 50 μmol), Ag_2CO_3 (137.1 mg, 0.50 mmol), and dry *m*-xylene (2.5 mL). The ratio of **3ag**/**4ag** was determined to be 95/5 by ^{1}H NMR analysis. These isomers could be separated by PTLC (Hexane/ EtOAc = 10/1). **3ag** was obtained as white solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.49 (s, 3H), 7.26 (s, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.76 (d, *J* = 7.6 Hz, 2H), 7.79 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 60.8, 120.6, 124.3 (q, $^1J_{CF}$ = 275 Hz), 125.5 (d, $^3J_{CF}$ = 4.3 Hz), 127.4, 127.5, 127.7, 128.8, 129.3 (q, $^2J_{CF}$ = 32 Hz), 132.8, 135.3, 138.4, 151.4. HRMS (EI) *m*/*z* calcd. for $C_{18}H_{13}F_3OS$: 334.0639, found 334.0630.

4-4. Typical Procedure for C5-Arylation of 2a

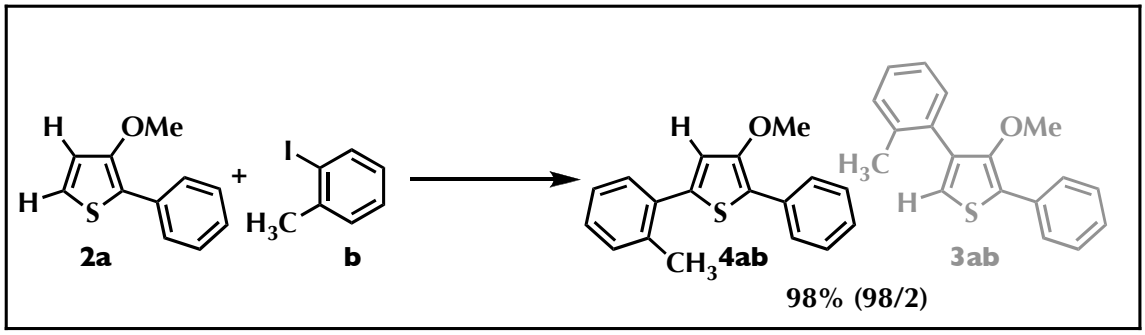


A 20-mL glass vessel equipped with J. Young® O-ring tap, containing a magnetic stirring bar, was flame-dried under vacuum and filled with argon after cooling to room temperature. To this vessel were added $PdCl_2$ (4.6 mg, 26 μmol), 2,2′-bipyridyl (7.8 mg, 50 μmol), Ag_2CO_3 (138.0 mg, 0.50 mmol) and dry *m*-xylene (0.5 mL) under a stream of argon. The vessel was heated at 60 °C for 0.5 h. To this vessel were added 3-methoxy-2-phenylthiophene (**2a**: 142.7 mg, 0.75 mmol), iodobenzene (**a**: 91.6 mg, 0.45 mmol), and dry *m*-xylene (2.0 mL) under a stream of argon. The vessel was sealed with O-ring tap, and then heated at 120 °C for 22 h in a 8-well reaction block with stirring. After cooling the reaction mixture to room temperature, the mixture was passed through a short silica gel pad (EtOAc). The filtrate was evaporated and the residue was subjected to gel permeation chromatography (GPC) to afford arylated products (96 mg, 80%) as mixture of 3-methoxy-2,5-diphenylthiophene (**4aa**) and 3-methoxy-2,4-diphenylthiophene (**3aa**). The ratio of **4aa**/**3aa** was determined to be 99/1 by ^{1}H NMR analysis. These isomers could be separated by PTLC (Hexane/ EtOAc = 10/1). **4aa** was obtained as pale yellow solid.

3-Methoxy-2,5-diphenylthiophene (4aa): Data were consistent with literature values.[9]

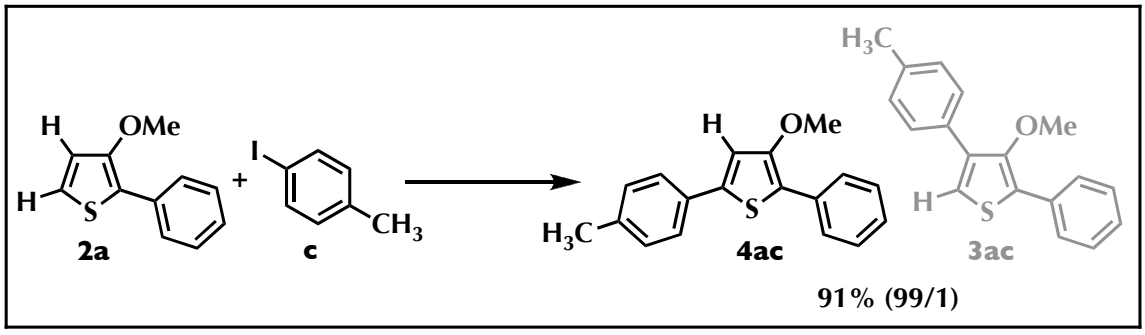
4-5. Compound Data for Other C5-Arylation Products of 2a

All arylated compounds (**4**) described in this section were prepared following the typical procedure given in Section 4-4. Compounds were purified by preparative thin-layer chromatography (PTLC) and/or gel permeation chromatography (GPC).



3-Methoxy-2-phenyl-5-(*o*-tolyl)thiophene (4ab): 98% isolated yield as mixture of regioisomers from 3-methoxy-2-phenylthiophene (**2a**) and *o*-iodotoluene (**b**). The ratio of **4ab**/**3ab** was determined to be 98/2 by ^{1}H NMR and GC analyses. These isomers could be separated by PTLC (Hexane/EtOAc = 10/1). **4ab** was obtained as yellow oil.

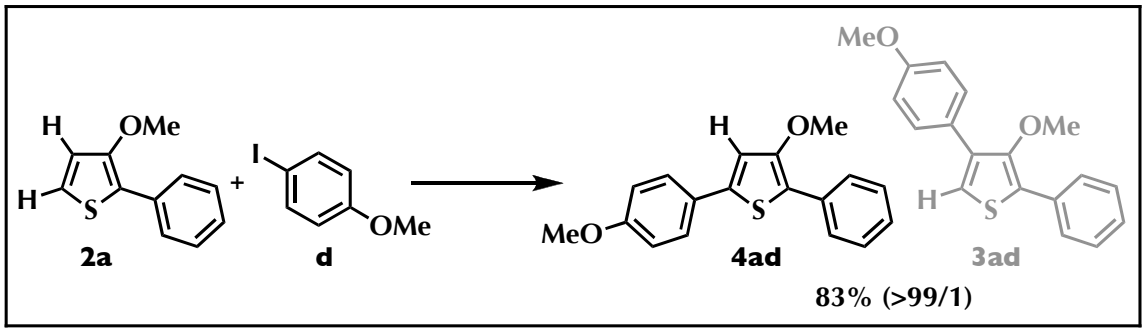
^{1}H NMR (600 MHz, $CDCl_3$) δ 2.47 (s, 3H), 3.88 (s, 3H), 6.89 (s, 1H), 7.18–7.23 (m, 4H), 7.34 (t, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.1, 58.7, 117.0, 120.2, 126.0, 126.2, 126.7, 127.9, 128.5, 129.8, 130.8, 133.3, 134.1, 135.8, 139.2, 153.1. HRMS (EI) *m*/*z* calcd. for $C_{18}H_{16}OS$: 280.0922, found 280.0909.



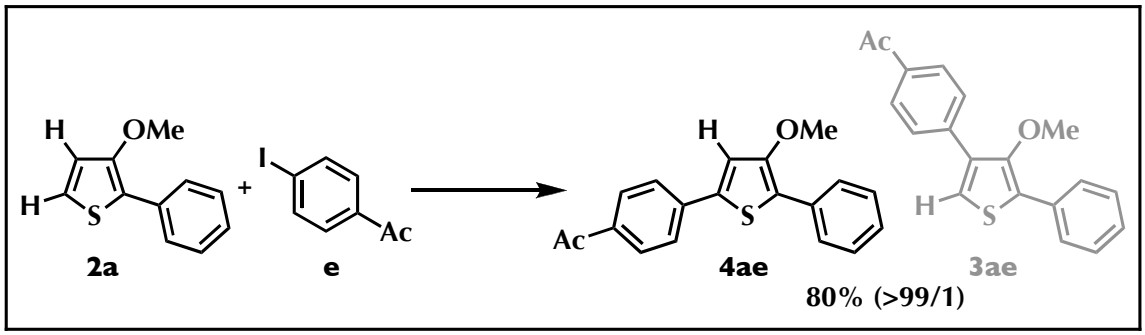
3-Methoxy-2-phenyl-5-(*p*-tolyl)thiophene (4ac): 91% isolated yield as mixture of regioisomers from 3-methoxy-2-phenylthiophene (**2a**) and *p*-iodotoluene (**c**). The ratio of **4ac**/**3ac** was determined to be 99/1 by ^{1}H NMR analysis. These isomers could be separated by PTLC (Hexane/ EtOAc = 10/1). **4ac** was obtained as white solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.35 (s, 3H), 3.92 (s, 3H), 7.09 (s, 1H), 7.17 (d, *J* = 8.2 Hz, 2H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.48 (d, *J* = 7.6 Hz, 2H), 7.75 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.2, 58.7, 112.9, 119.3, 125.0, 126.2, 126.6, 128.5, 129.5, 131.4, 133.4, 137.6, 140.0, 153.9. HRMS (EI) *m*/*z* calcd. for $C_{18}H_{16}OS$: 280.0922, found

280.0919.



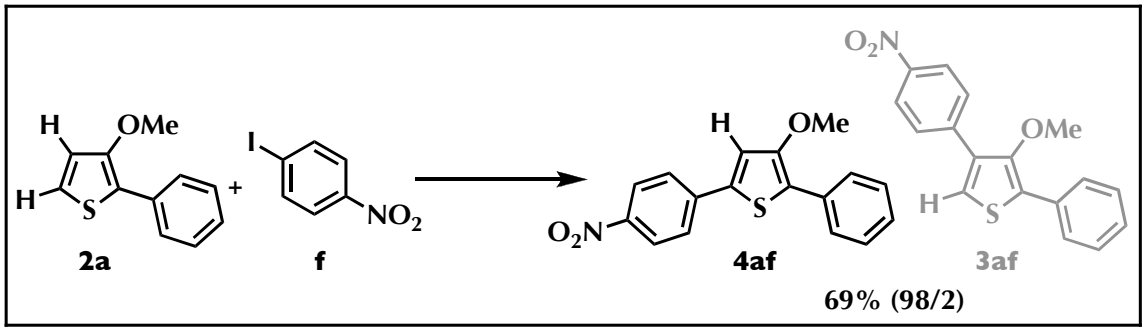
3-Methoxy-4-(*p*-methoxyphenyl)-2-phenylthiophene (4ad): 83% isolated yield as mixture of regioisomers from 3-methoxy-2-phenylthiophene (**2a**) and *p*-iodoanisole (**d**). The ratio of **4ad**/**3ad** was determined to be >99 /1 by ^{1}H NMR analysis. These isomers could be separated by PTLC (Hexane/ EtOAc = 10/1). **4ad** was obtained as yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.91 (s, 3H), 6.89 (d, *J* = 8.9 Hz, 2H), 7.02 (s, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.50 (d, *J* = 8.9 Hz, 2H), 7.74 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 55.3, 58.9, 112.5, 114.3, 118.8, 126.1, 126.4, 126.6, 127.1, 128.5, 133.5, 139.8, 153.9, 159.4. HRMS (EI) *m*/*z* calcd. for $C_{18}H_{16}O_2S$: 296.0871, found 296.0873.



4-(*p*-Acetylphenyl)-3-methoxy-2-phenylthiophene (4ae): 83% isolated yield as mixture of regioisomers from 3-methoxy-2-phenylthiophene (**2a**) and *p*-iodoacetophenone (**e**). The ratio of **4ae**/**3ae** was determined to be >99/1 by ^{1}H NMR analysis. These isomers could be separated by PTLC (Hexane/ EtOAc = 10/1). **4ae** was obtained as yellow solid.

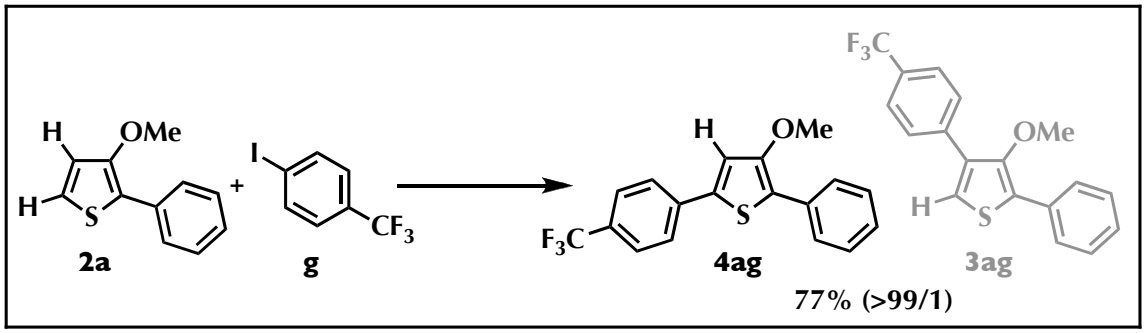
^{1}H NMR (600 MHz, $CDCl_3$) δ 2.61 (s, 3H), 3.98 (s, 3H), 7.23–7.26 (m, 2H), 7.38 (t, *J* = 8.3

Hz, 2H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.97 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.5, 58.8, 114.7, 122.0, 124.8, 126.8, 126.9, 128.6, 129.1, 133.0, 135.8, 138.0, 138.5, 154.3, 197.1. HRMS (EI) *m*/*z* calcd. for $C_{19}H_{16}O_2S$: 308.0871, found 308.0868.



3-Methoxy-4-(*p*-nitrophenyl)-2-phenylthiophene (4af): 69% isolated yield as mixture of regioisomers from 3-methoxy-2-phenylthiophene (**2a**) and *p*-iodonitrobenzene (**f**). The ratio of **4af**/**3af** was determined to be 98/2 by ^{1}H NMR analysis. These isomers could be separated by PTLC (Hexane/ EtOAc = 10/1). **4af** was obtained as orange solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.98 (s, 3H), 7.25 (s, 1H), 7.27 (t, *J* = 8.9 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.72 (d, *J* = 8.9 Hz, 2H), 7.77 (d, *J* = 8.9 Hz, 2H), 8.23 (d, *J* = 8.9 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 58.9, 115.6, 123.5, 124.4, 125.1, 127.0, 127.2, 128.7, 132.6, 136.5, 140.3, 146.6, 154.5. HRMS (EI) *m*/*z* calcd. for $C_{17}H_{13}NO_3S$: 311.0616, found 311.0612.

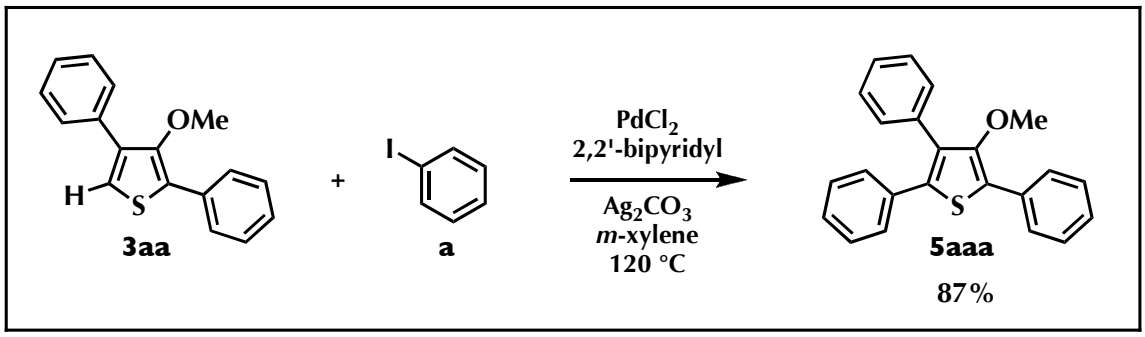


3-Methoxy-2-phenyl-4-(*p*-trifluoromethylphenyl)thiophene (4ag): 77% isolated yield as mixture of regioisomers from 3-methoxy-2-phenylthiophene (**2a**) and *p*-iodobenzotrifluoride (**g**). The ratio of **4ag**/**3ag** was determined to be >99 /1 by ^{1}H

NMR analysis. These isomers could be separated by PTLC (Hexane/ EtOAc = 10/1). **4ag** was obtained as white solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.93 (s, 3H), 7.19 (s, 1H), 7.23 (t, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.75 (d, *J* = 7.6 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 58.8, 114.6, 121.7, 124.0 (q, $^1J_{CF}$ = 232 Hz), 125.0, 125.9 (d, $^3J_{CF}$ = 3.4 Hz), 126.78, 126.84, 128.6, 129.3 (q, $^2J_{CF}$ = 33 Hz), 133.0, 137.5, 137.7, 154.2. HRMS (EI) *m*/*z* calcd. for $C_{18}H_{13}F_3OS$: 334.0639, found 334.0642.

4-6. Typical Procedure for C5-Arylation of 3



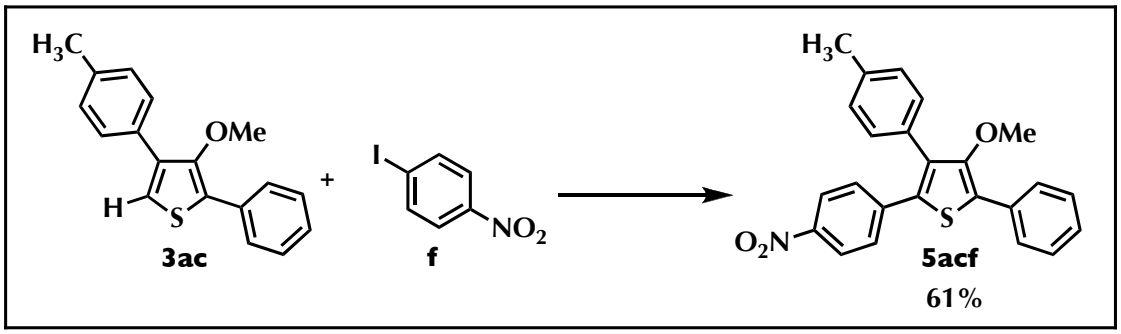
A 20-mL glass vessel equipped with J. Young® O-ring tap, containing a magnetic stirring bar, was flame-dried under vacuum and filled with argon after cooling to room temperature. To this vessel were added $PdCl_2$ (3.8 mg, 21 μmol), 2,2′-bipyridyl (5.6 mg, 36 μmol), Ag_2CO_3 (199.0 mg, 0.72 mmol) and dry *m*-xylene (1.0 mL) under a stream of argon. The vessel was heated at 60 °C for 0.5 h. To this vessel were added 3-methoxy-2,4-diphenylthiophene (**3aa**: 97 mg, 0.36 mmol), iodobenzene (**a**: 222 mg, 1.09 mmol), and dry *m*-xylene (1.0 mL) under a stream of argon. The vessel was sealed with O-ring tap, and then heated at 120 °C for 12 h in a 8-well reaction block with stirring. After cooling the reaction mixture to room temperature, the mixture was passed through a short silica gel pad (EtOAc). The filtrate was evaporated and the residue was subjected to gel permeation chromatography (GPC) to afford 3-methoxy-2,4,5-triphenylthiophene (**5aaa**) (107.4 mg, 87%) as white solid.

3-Methoxy-2,4,5-triphenylthiophene (5aaa): ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.37 (s, 3H), 7.20–7.36 (m, 11H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.80 (t, *J* = 7.6 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 60.6, 126.6, 127.1, 127.2, 127.2, 127.4, 128.3, 128.4, 128.7, 128.8, 130.1, 132.9,

133.5, 134.4, 134.5, 136.2, 152.2. HRMS (EI) *m*/*z* calcd. for $C_{23}H_{18}OS$: 342.1078, found 342.1081.

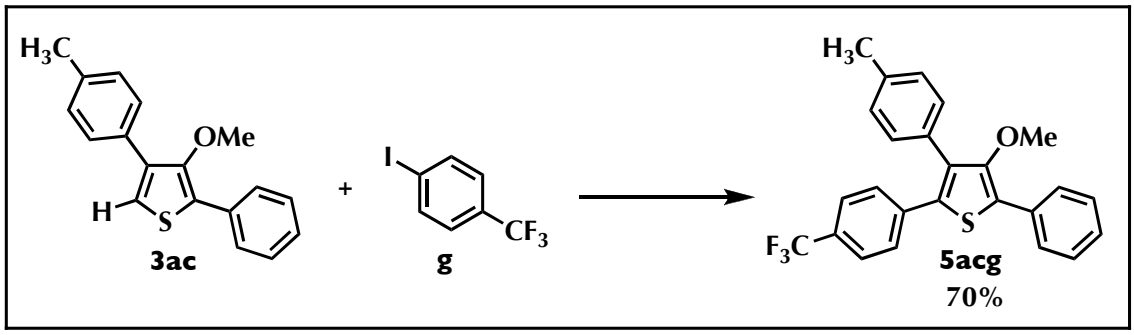
4-7. Compound Data for Other C5-Arylation Products of 3

All arylated compounds (**5**) described in this section were prepared following the typical procedure given in Section 4-6. Compounds were purified by gel permeation chromatography (GPC).



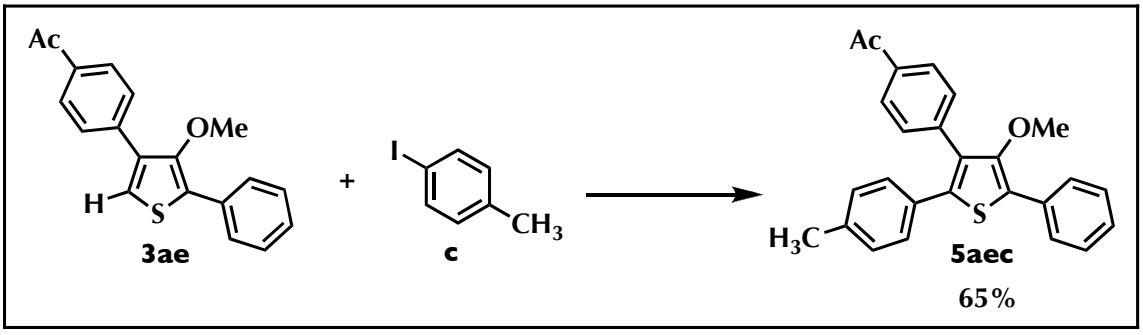
3-Methoxy-5-(*p*-nitrophenyl)-2-phenyl-4-(*p*-tolyl)thiophene (5acf): 61% isolated yield from 3-methoxy-2-phenyl-4-(*p*-tolyl)thiophene (**3ac**: 149.8 mg, 0.53 mmol), *p*-iodonitrobenzene (**f**: 395.1 mg, 1.6 mmol), $PdCl_2$ (5.0 mg, 27 μmol), 2,2′-bipyridyl (8 mg, 53 μmol), Ag_2CO_3 (294.5 mg, 1.1 mmol), and dry *m*-xylene (2.5 mL). **5acf** was obtained as orange solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.38 (s, 3H), 7.19 (d, *J* = 7.6 Hz, 2H), 7.22 (d, *J* = 8.3 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 8.9 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.80 (d, *J* = 7.6 Hz, 2H), 8.06 (d, *J* = 8.9 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.3, 60.7, 123.7, 127.3, 127.7, 128.8, 128.9, 129.0, 129.5, 129.7, 130.7, 132.3, 132.7, 136.0, 137.8, 141.2, 146.4, 152.7. HRMS (EI) *m*/*z* calcd. for $C_{24}H_{19}NO_3S$: 401.1086, found 401.1078.



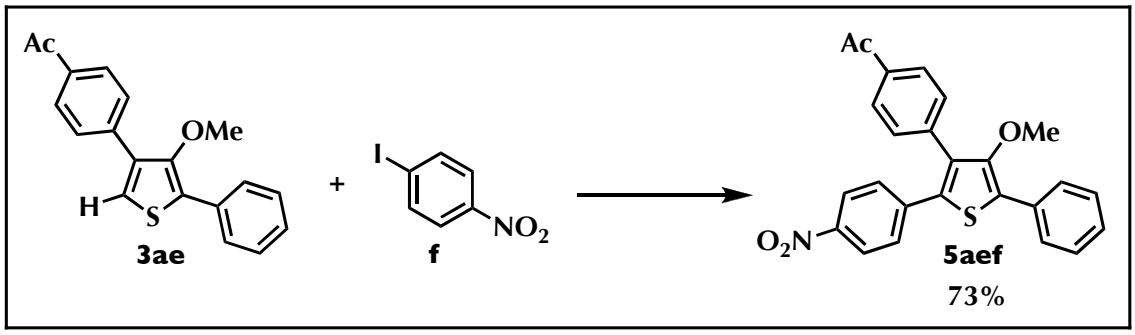
3-Methoxy-2-phenyl-4-(*p*-tolyl)-5-(*p*-trifluoromethylphenyl)thiophene (5acg): 70% isolated yield from 3-methoxy-2-phenyl-4-(*p*-tolyl)thiophene (**3ac**: 77.5 mg, 0.28 mmol), *p*-iodobenzotrifluoride (**g**: 225.5 mg, 0.83 mmol), $PdCl_2$ (3.0 mg, 17 μmol), 2,2′-bipyridyl (4.5 mg, 29 μmol), Ag_2CO_3 (77.5 mg, 0.28 mmol), and dry *m*-xylene (1.5 mL). **5acg** was obtained as white solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.38 (s, 3H), 3.38 (s, 3H), 7.17 (d, J = 8.2 Hz, 2H), 7.22 (d, J = 8.2 Hz, 2H), 7.30 (t, J = 7.6 Hz, 1H), 7.34 (d, J = 8.2 Hz, 2H), 7.41 (t, J = 7.6 Hz, 2H), 7.47 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 8.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.3, 60.6, 124.1 (q, $^1J_{CF}$ = 271 Hz), 125.3 (d, $^3J_{CF}$ = 4.3 Hz), 127.3, 127.4, 127.7, 128.74, 128.79, 129.2 (q, $^2J_{CF}$ = 32 Hz), 129.3, 129.8, 131.0, 132.6, 133.8, 134.8, 137.4, 138.1, 152.5. HRMS (EI) *m*/*z* calcd. for $C_{25}H_{19}F_3OS$: 424.1109, found 424.1111.



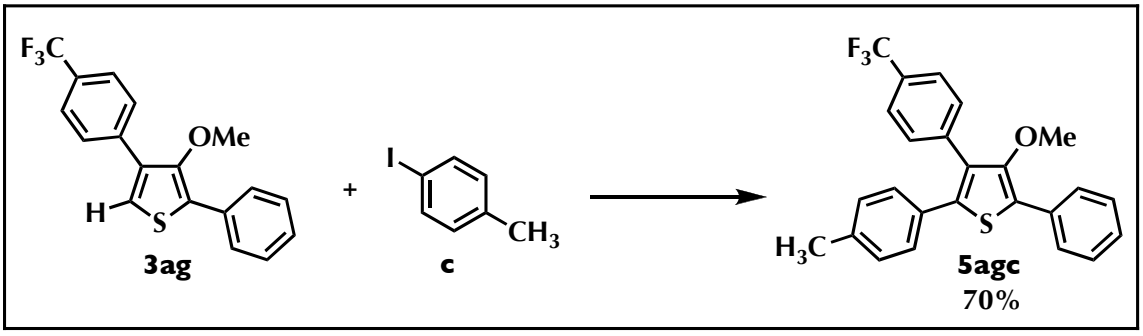
4-(*p*-Acetylphenyl)-3-methoxy-2-phenyl-5-(*p*-tolyl)thiophene (5aec): 65% isolated yield from 3-methoxy-2-phenyl-4-(*p*-tolyl)thiophene (**3ae**: 165.6 mg, 0.54 mmol), *p*-iodotoluene (**c**: 350.8 mg, 1.6 mmol), $PdCl_2$ (4.9 mg, 26 μmol), 2,2′-bipyridyl (8.7 mg, 53 μmol), Ag_2CO_3 (148.3 mg, 0.54 mmol), and dry *m*-xylene (2.5 mL). **5aec** was obtained as yellow solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.30 (s, 3H), 2.60 (s, 3H), 3.36 (s, 3H), 7.04 (d, *J* = 8.2 Hz, 2H), 7.11 (d, *J* = 8.2 Hz, 2H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.46 (t, *J* = 8.3 Hz, 2H), 7.78 (d, *J* = 8.3 Hz, 2H), 7.92 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.1, 26.5, 60.6, 126.6, 127.15, 127.22, 128.3, 128.6, 128.7, 129.3, 130.2, 131.0, 131.7, 132.6, 135.6, 137.4, 137.7, 139.6, 151.8, 197.8. HRMS (EI) *m*/*z* calcd. for $C_{26}H_{22}O_2S$: 398.1341, found 398.1339.



4-(*p*-Acetylphenyl)-3-methoxy-2-phenyl-5-(*p*-tolyl)thiophene (5aef): 73% isolated yield from 3-methoxy-2-phenyl-4-(*p*-tolyl)thiophene (**3ae**: 116.1 mg, 0.38 mmol), *p*-iodonitorobenzene (**f**: 282.3 mg, 1.1 mmol), $PdCl_2$ (3.9 mg, 22 μmol), 2,2′-bipyridyl (6.2 mg, 40 μmol), Ag_2CO_3 (210 mg, 0.76 mmol), and dry *m*-xylene (2.0 mL). **5aef** was obtained as orange solid.

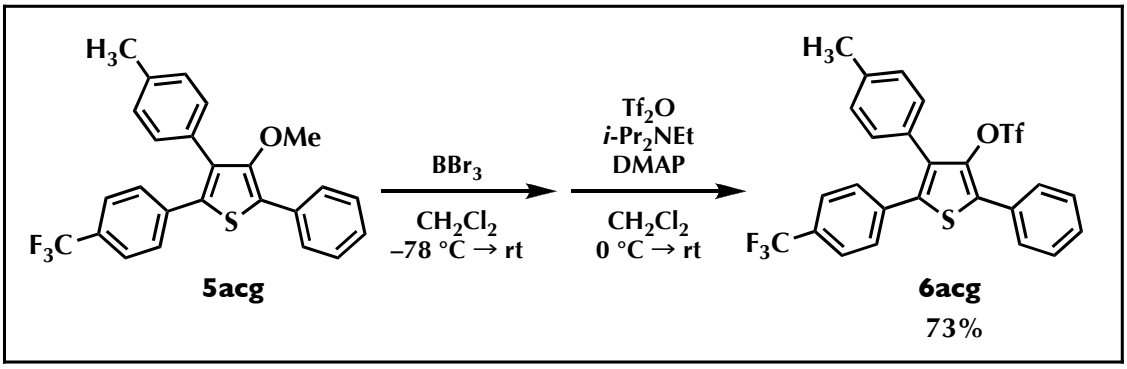
^{1}H NMR (600 MHz, $CDCl_3$) δ 2.64 (s, 3H), 3.38 (s, 3H), 7.35 (t, *J* = 8.9 Hz, 1H), 7.43–7.46 (m, 4H), 7.80 (d, *J* = 6.9 Hz, 2H), 7.98 (d, *J* = 8.3 Hz, 2H), 8.09 (d, *J* = 6.9 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 26.6, 60.8, 123.9, 127.3, 127.9, 128.6, 128.9, 129.0, 129.5, 130.1, 131.9, 133.8, 134.4, 136.2, 138.6, 140.5, 146.6, 152.2, 197.6. HRMS (EI) *m*/*z* calcd. for $C_{25}H_{19}NO_4S$: 429.1035, found 429.1031.



3-Methoxy-2-phenyl-5-(*p*-tolyl)-4-(*p*-trifluoromethylphenyl)thiophene (5agc): 70% isolated yield from 3-methoxy-2-phenyl-4-(*p*-tolyl)thiophene (**3ag**: 102.0 mg, 0.31 mmol), *p*-iodotoluene (**c**: 200 mg, 0.92 mmol), $PdCl_2$ (3.1 mg, 17 μmol), 2,2′-bipyridyl (8 mg, 29 μmol), Ag_2CO_3 (85.7 mg, 0.31 mmol), and dry *m*-xylene (2.0 mL). **5agc** was obtained as pale yellow solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.31 (s, 3H), 3.36 (s, 3H), 7.06 (d, J = 8.2 Hz, 2H), 7.10 (d, J = 8.2 Hz, 2H), 7.29 (t, J = 7.6 Hz, 1H), 7.41 (t, J = 7.6 Hz, 2H), 7.48 (d, J = 8.2 Hz, 2H), 7.58 (d, J = 8.2 Hz, 2H), 7.78 (d, J = 7.6 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.2, 60.7, 125.2 (d, $^3J_{CF}$ = 4.3 Hz), 126.7, 127.2, 127.3, 128.7, 128.8, 129.4, 130.4, 131.0, 131.5, 132.7, 137.5, 137.8, 138.3, 151.8. CF_3 and the carbon next to CF_3 are not seen. HRMS (EI) *m*/*z* calcd. for $C_{25}H_{19}F_3OS$: 424.1109, found 424.1113.

4-8. Typical Procedure for Triflation



A 20-mL glass Schlenk, containing a magnetic stirring bar, was flame-dried under vacuum and filled with argon after cooling to room temperature. To this vessel were added 3-methoxy-2-phenyl-4-(*p*-tolyl)-5-(*p*-trifluoromethylphenyl)thiophene (**5acg**) (42.6 mg, 0.10 mmol) and dry dichloromethane (1.5 mL) under a stream of argon. The contents were cooled at –78 °C, and to this vessel was added boron tribromide (0.13 mL, 1M in CH_2Cl_2, 0.13 mmol). The resultant mixture was stirred at –78 °C for 0.5 h. After warming the reaction mixture to room temperature and stirring for 2 h, the mixture was passed through a short silica gel pad (Hexane/EtOAc = 1/1). The filtrate was evaporated, and directly used for the next step without further purification.

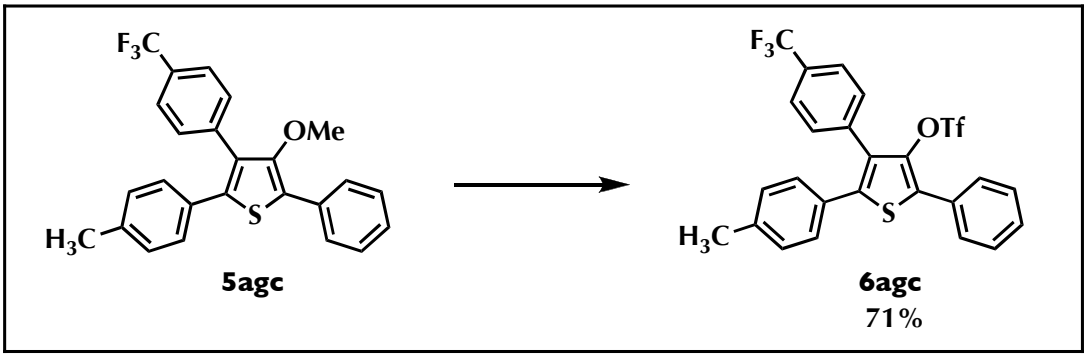
A 20-mL glass Schlenk, containing a magnetic stirring bar, was flame-dried under vacuum and filled with argon after cooling to room temperature. To this vessel was

added resultant mixture obtained above and dry dichloromethane (1.5 mL) under a stream of argon. The contents were cooled at 0 °C, and to this vessel were added *N*,*N*-diisopropylethylamine (25.9 mg, 0.2 mmol), *N*,*N*-dimethylaminopyridine (1.1 mg, 10 μmol), and trifluoromethanesulfonic anhydride (141.1 mg, 0.5 mmol). The resultant mixture was stirred at 0 °C for 0.5 h. After warming the reaction mixture to room temperature and stirring for 12 h, the mixture was passed through a short silica gel pad (Hexane/EtOAc = 1/1). The filtrate was evaporated, and the residue was purified by PTLC (Hexane/EtOAc = 10/1) to afford 2-phenyl-4-(*p*-tolyl)-5-(*p*-trifluoromethylphenyl)thiophen-3-yl trifluoromethanesulfonate (**6acg**) (39.8 mg, 73%) as white solid.

2-Phenyl-4-(*p*-tolyl)-5-(*p*-trifluoromethylphenyl)thiophen-3-yl trifluoromethanesulfonate (**6acg**): ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.39 (s, 3H), 7.17–7.20 (m, 4H), 7.30–7.35 (m, 2H), 7.43 (t, J = 7.6 Hz, 2H), 7.48 (d, J = 7.6 Hz, 2H), 7.51 (d, J = 8.2 Hz, 2H), 7.64 (d, J = 7.6 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.4, 117.9 (q, $^1J_{CF}$ = 319 Hz), 124.0 (q, $^1J_{CF}$ = 267 Hz), 124.8, 125.6 (d, $^3J_{CF}$ = 4.3 Hz), 128.7, 128.9, 129.1, 129.2, 129.6, 130.0 (q, $^2J_{CF}$ = 32 Hz), 130.1, 130.2, 133.5, 133.8, 135.5, 137.0, 137.6, 138.5. HRMS (EI) *m*/*z* calcd. for $C_{25}H_{16}F_6O_3S_2$: 542.0445, found 542.0442.

4-9. Compound Data for Other Triflation Product

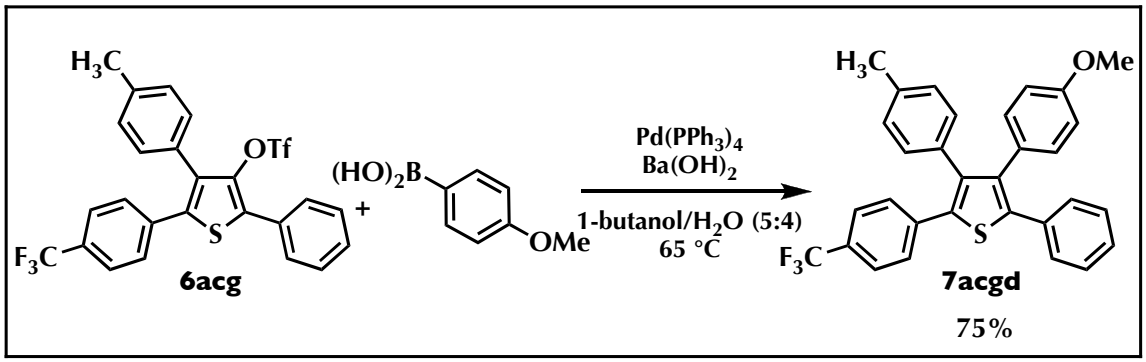
All triflation compound (**6**) described in this section were prepared following the typical procedure given in Section 4-8. Compounds were purified by preparative thin-layer chromatography (PTLC).



2-Phenyl-5-(*p*-tolyl)-4-(*p*-trifluoromethylphenyl)thiophen-3-yl trifluoromehanesulfonate (6agc): 71% isolated yield from 3-methoxy-2-phenyl-5-(*p*-tolyl)-4-(*p*-trifluoromethylphenyl)thiophene (**5agc**). **6agc** was obtained as white solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.33 (s, 3H), 7.09–7.10 (m, 4H), 7.39–7.44 (m, 3H), 7.48 (t, J = 7.6 Hz, 2H), 7.60–7.63 (m, 4H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.2, 117.8 (q, $^1J_{CF}$ = 319 Hz), 124.0 (q, $^1J_{CF}$ = 267 Hz), 124.6, 125.5, 128.7, 129.1, 129.6, 129.7, 130.1, 130.4, 130.8, 130.9, 132.8, 136.2, 136.7, 138.7, 139.0. The carbon next to CF_3 is not seen. HRMS (EI) m/z calcd. for $C_{25}H_{16}F_6O_3S_2$: 542.0445, found 542.0448.

4-10. Typical Procedure for Suzuki-Miyaura Coupling of 6

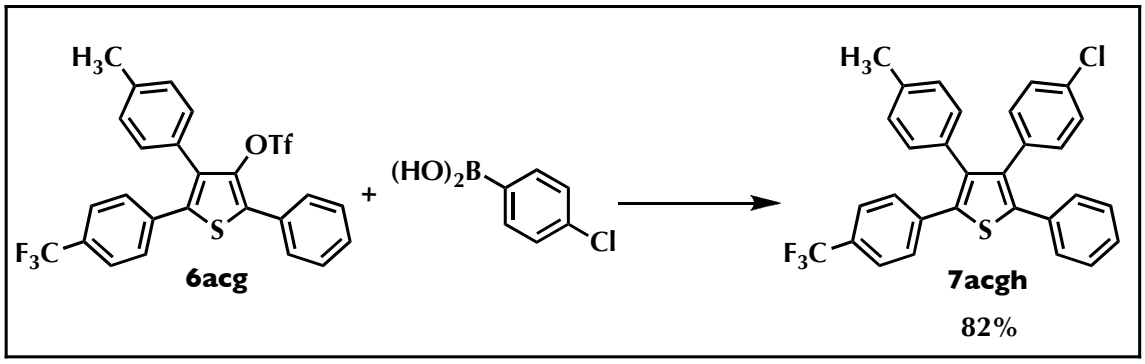


A 20-mL glass Schlenk, containing a magnetic stirring bar, was flame-dried under vacuum and filled with argon after cooling to room temperature. To this vessel were added $Pd(PPh_3)_4$ (2.8 mg, 2.4 μmol), $Ba(OH)_2$ (15.4 mg, 90 μmol), *p*-methoxyphenylboronic acid (20.0 mg, 0.135 mmol), 2-phenyl-4-(*p*-tolyl)-5-(*p*-trifluoromethylphenyl)thiophen-3-yl trifluoromethanesulfonate (**6acg**: 24.4 mg, 45 μmol), dry 1-butanol (1.8 mL) and H_2O (1.5 mL) under a stream of argon. The vessel was heated at 65 °C for 15 h. After cooling the reaction mixture to room temperature, the mixture was passed through a short silica gel pad (EtOAc). The filtrate was evaporated and the residue was purified by PTLC (Hexane/EtOAc = 10/1) to afford 3-(*p*-methoxyphenyl)-2-phenyl-4-(*p*-tolyl)-5-(*p*-trifluoromethylphenyl)thiophene (**7acgd**) (16.8 mg, 75%) as white solid.

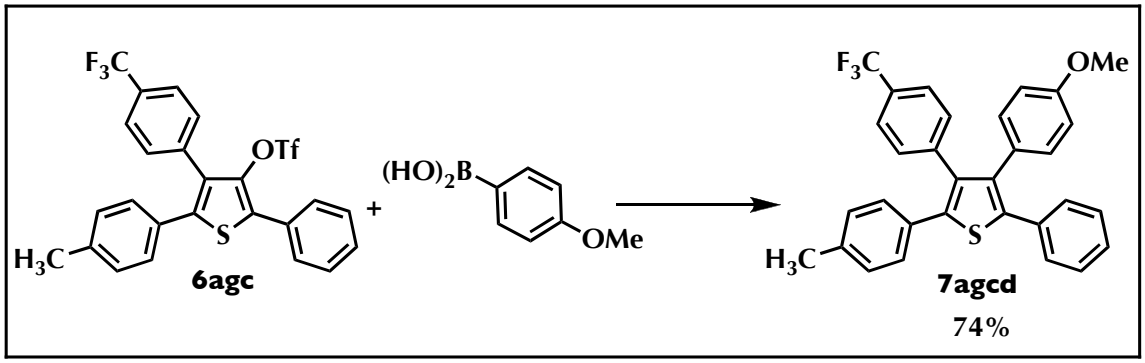
3-(*p*-Methoxyphenyl)-2-phenyl-4-(*p*-tolyl)-5-(*p*-trifluoromethylphenyl)thiophene (**7acgd**): ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.28 (s, 3H), 3.74 (s, 3H), 6.66 (d, *J* = 8.9 Hz, 2H), 6.84 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.9 Hz, 2H), 6.95 (d, *J* = 7.6 Hz, 2H), 7.21–7.25 (m, 5H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.46 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.2, 55.1, 113.9, 125.2, 127.3, 128.4, 128.5, 128.9, 129.1, 129.2, 130.5, 131.9, 133.0, 134.2, 136.2, 136.5, 138.2, 139.2, 139.5, 140.8, 158.3. CF_3 and the carbon next to CF_3 are not seen. HRMS (EI) *m*/*z* calcd. for $C_{31}H_{23}F_3OS$: 500.1422, found 500.1416.

4-11. Compound Data for Other Tetraarylthiophene

All compounds (**7**) described in this section were prepared following the typical procedure given in Section 4-10. Compounds were purified by preparative thin-layer chromatography (PTLC).

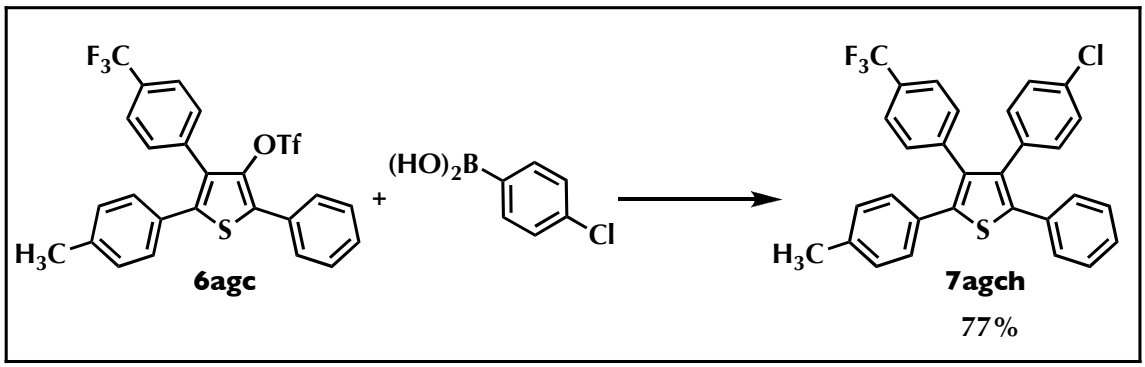


3-(*p*-Chlorophenyl)-2-phenyl-4-(*p*-tolyl)-5-(*p*-trifluoromethylphenyl)thiophene (**7acgh**): 82% isolated yield from 2-phenyl-4-(*p*-tolyl)-5-(*p*-trifluoromethylphenyl)thiophen-3-yl trifluoromethanesulfonate (**6acg**) and *p*-chlorophenylboronic acid. **7acgh** was obtained as white solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 2.29 (s, 3H), 6.82 (d, *J* = 8.3 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 2H), 6.96 (d, *J* = 7.6 Hz, 2H), 7.09 (d, *J* = 8.9 Hz, 2H), 7.21–7.25 (m, 5H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.2, 125.3, 127.7, 128.2, 128.5, 129.0, 129.16, 129.23, 130.5, 132.1, 132.6, 132.7, 133.7, 134.7, 136.7, 136.9, 137.9, 138.4, 140.0, 140.4. CF_3 and the carbon next to CF_3 are not seen. HRMS (EI) *m*/*z* calcd. for $C_{30}H_{20}ClF_3S$: 504.0926, found 504.0917.



3-(*p*-Methoxyphenyl)-2-phenyl-5-(*p*-tolyl)-4-(*p*-trifluoromethylphenyl)thiophene (**7agcd**): 74% isolated yield from 2-phenyl-5-(*p*-tolyl)-4-(*p*-trifluoromethylphenyl)thiophen-3-yl trifluoromehanesulfonate (**6agc**) and *p*-chlorophenylboronic acid. **7agcd** was obtained as white solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.31 (s, 3H), 3.74 (s, 3H), 6.67 (d, *J* = 8.3 Hz, 2H), 6.84 (d, *J* = 8.3 Hz, 2H), 7.04 (d, *J* = 8.2 Hz, 2H), 7.06–7.09 (m, 4H), 7.20–7.23 (m, 5H), 7.37 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.2, 55.1, 113.5, 124.7, 124.7, 126.1 (q, $^{1}J_{CF}$ = 273 Hz), 127.2, 128.3, 128.6, 129.1 (d, $^{3}J_{CF}$ = 4.3 Hz), 129.2, 130.9, 131.2, 131.8, 134.2, 137.4, 137.6, 138.4, 138.7, 139.6, 140.6, 158.4. HRMS (EI) *m*/*z* calcd. for $C_{31}H_{23}F_3OS$: 500.1422, found 500.1416.



3-(*p*-Chlorophenyl)-2-phenyl-5-(*p*-tolyl)-4-(*p*-trifluoromethylphenyl)thiophene (**7agch**): 77% isolated yield from 2-phenyl-5-(*p*-tolyl)-4-(*p*-trifluoromethylphenyl)thiophen-3-yl trifluoromehanesulfonate (**6agc**) and *p*-chlorophenylboronic acid. **7agch** was obtained as white solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.32 (s, 3H), 6.86 (d, *J* = 8.3 Hz, 2H), 7.04–7.08 (m, 6H), 7.10 (d, *J* = 8.9 Hz, 2H), 7.20–7.25 (m, 5H), 7.39 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.2, 124.9, 127.7, 128.4, 128.5, 129.1, 129.2, 129.3, 130.6, 131.1, 132.1, 132.9, 133.7, 134.5, 137.2, 137.6, 137.7, 139.2, 140.06, 140.13. CF_3 and the carbon next to CF_3 are not seen. HRMS (EI) *m*/*z* calcd. for $C_{30}H_{20}ClF_3S$: 504.0926, found 504.0933.

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Chapter 4

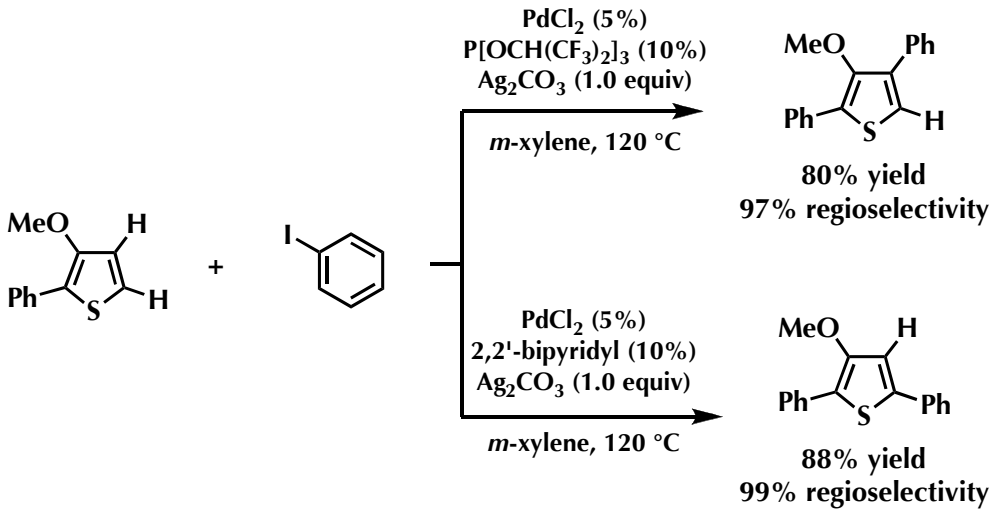
Palladium/2,2′-Bipyridyl/Ag_2CO_3 Catalyst for C–H Bond Arylation of Heteroarenes with Haloarenes

Abstract: Development, scope, and mechanism of Pd/bipy-based catalytic system for the C–H bond arylation of heteroarenes with haloarenes are described. The complex $PdBr_2$(bipy)·DMSO, whose structure was unambiguously determined by X-ray crystallography, turned out to be a general catalyst precursor for the process. The reaction is applicable to a range of electron-rich five-membered heteroarenes such as thiophenes, thiazoles, benzofurans, and indoles. Mechanistic study implicated that the reaction occurs not through a conventional Pd^0/Pd^{II} redox catalysis but rather through a Pd^{II} non-redox or Pd^{II}/Pd^{IV} redox catalysis.

1. Introduction

Heterobiaryls are one of the most important molecules that are frequently found in functional materials, pharmaceuticals, and natural products.[1] Consequently, the development of efficient methods to connect heteroarene and arene has been a topic of immense importance in chemical synthesis.[2] Although transition metal-catalyzed cross-coupling reactions have been a reliable and excellent method for constructing the biaryl structures,[3] there are common drawbacks such as inevitable production of stoichiometric amount of metallic waste and necessity for preparing organometallic reagents from arenes prior to cross-coupling. Recently, transition metal-catalyzed direct C–H bond arylation of heteroarenes has received much attention as an alternative method for heterobiaryl synthesis by a number of research groups (Pd, Rh, Cu, Ni, Ir, Ru, and Fe).[4–9] The author has also developed several unique catalysts for this transformation as described in Chapter 1,[5] 2,[6] and 3.[7]

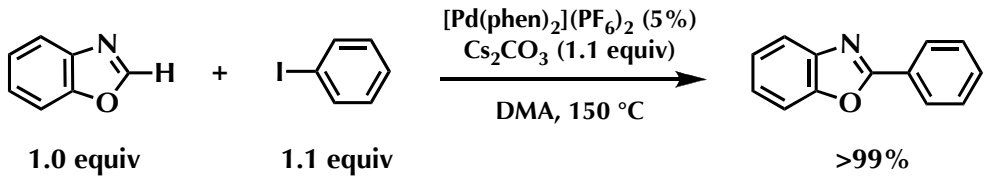
During the study of programmed synthesis of tetraarylthiophenes described in Chapter 3, the author has discovered ligand-controlled regiodivergent C–H bond arylations of 3-methoxy-2-phenylthiophene (Scheme 1).[7] For example, the reaction of 3-methoxy-2-phenylthiophene and iodobenzene in the presence of $PdCl_2$, $P[OCH(CF_3)_2]_3$, and Ag_2CO_3 in *m*-xylene at 120 °C furnished C4-phenylated product in 80% yield with 97% regioselectivity. Interestingly, the C4 regioselectivity could be switched to C5 regioselectivity by simply changing the neutral ligand from $P[OCH(CF_3)_2]_3$ to 2,2′-bipyridyl (bipy), with which 2,5-diphenyl-3-methoxythiophene (C5-phenylated product) was obtained in 88% yield with 99% regioselectivity (Scheme 1). To our delight, it was found that this unique C4-selective C–H arylation is applicable not only to 3-methoxy-2-phenylthiophene but also to a wide range of thiophene derivatives in general.[8] The author envisaged that the Pd/bipy/Ag_2CO_3 catalyst system might also have excellent potential for the C–H bond arylation of other heteroarenes.



Scheme 1. Discovery of Ligand-Controlled Regiodivergent C–H Bond Arylation

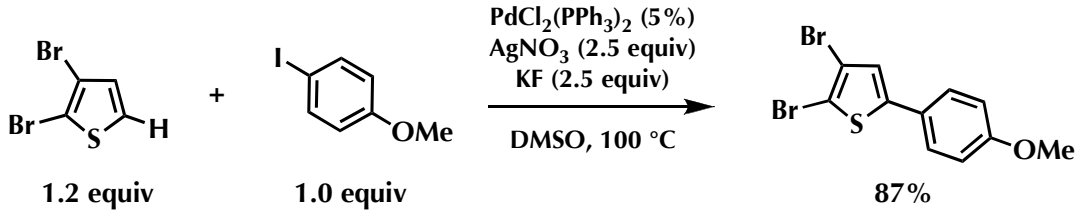
To date, a number of Pd-catalyzed direct C–H arylation reactions have been developed. However, most of the reported systems utilize phosphine-based supporting ligands and the example using nitrogen-based bidentate ligands such as 2,2′-bipyridyl is very rare.[4] Though the mechanistic study on the direct C–H arylation of heteroarenes is rather limited, it is important not only for understanding reaction but also for developing new generation catalysts.

Other than our catalytic system (Pd/bipy/Ag_2CO_3), there is only one example for the direct C–H bond arylation of heteroarenes catalyzed by a Pd complex having nitrogen-based bidentate ligand. Very recently, Shibahara and Murai demonstrated that the cationic palladium complex bearing 1,10-phenanthroline (phen) ligand, $[Pd(phen)_2](PF_6)_2$, promotes the direct C–H bond arylation of various five-membered heteroarenes with haloarenes (Scheme 2).[10] Cesium carbonate was used as a basic additive for the coupling. However, the mechanism of this intriguing process remains undetermined.



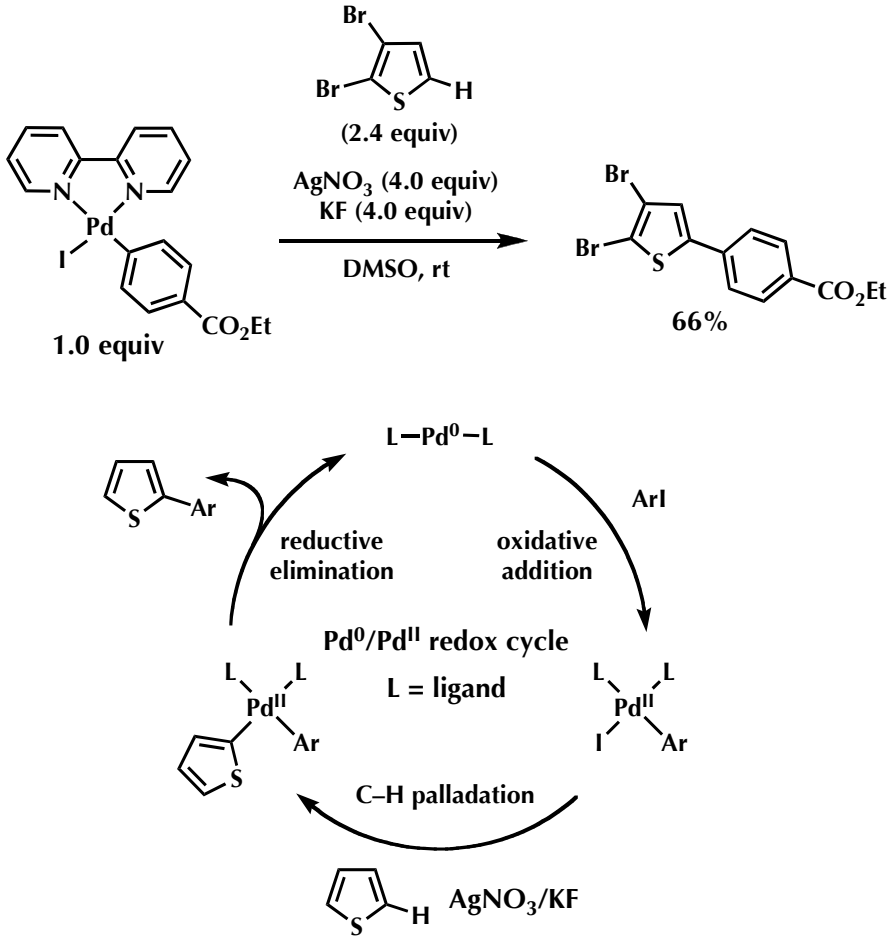
Scheme 2. Pd/Phen-Catalyzed C–H Arylation of Heteroarenes (Shibahara/Murai, 2010)

In 2005, Mori and co-workers have reported that the C–H bond arylation of thiophenes with iodoarenes could occur under the influence of $PdCl_2(PPh_3)_2$ catalyst, $AgNO_3$, and KF in DMSO at 100 °C (Scheme 3).[11] For the purpose of elucidating the mechanism, they investigated several stoichiometric reactions of organopalladium complexes ligated by 2,2′-bipyridyl.[12]



Scheme 3. Pd-Catalyzed Direct Arylation of Thiophenes by Mori

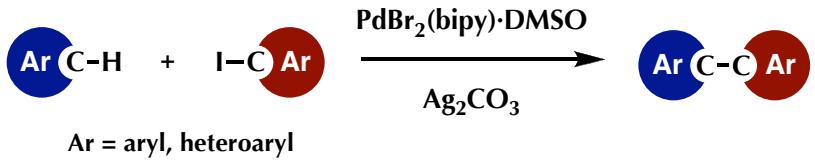
When bipy-bound arylpalladium(II) iodide was treated with 2,3-dibromothiophene in the presence of $AgNO_3$ and KF, the corresponding arylated thiophene was obtained in 66% yield (Scheme 4). On the basis of this result, Mori proposed the following mechanism.



Scheme 4. Stoichiometric Reaction and Pd^0/Pd^{II} Redox Cycle Proposed by Mori

Initially, iodoarenes oxidatively add to Pd(0) to afford $ArPd^{II}I$ complex. With the aid of $AgNO_3$ and KF, thiophenes then undergo C–H palladation with $ArPd^{II}I$ complex to give $ArPd^{II}Th$ complex (Th = thienyl). Finally, the reductive elimination takes place from the complex to furnish the product with regenerating Pd(0) species. It should be noted that this represents a typical Pd^0/Pd^{II} redox mechanism proposed for the Pd-catalyzed C–H bond arylation of heteroarenes with haloarenes.[4]

Considering these backgrounds, the author decided to investigate Pd/bipy catalyst system described in Chapter 3 in detail. The focal points of this study has been (i) to identify catalyst components necessary for the coupling, (ii) to develop user-friendly and air-stable precatalyst, (iii) to identify the scope of heteroarene/haloarene coupling partners, and (iv) to gain better grasp toward the reaction mechanism (Scheme 5).



Ar = aryl, heteroaryl

- **Pd/bipy catalyst for direct C–H arylation of heteroarenes**
- **Development of user-friendly and air-stable precatalyst**
- **Mechanistic investigation**

Scheme 5. Pd/bipy-Catalyzed Direct C–H Arylation of Heteroarenes with Haloarenes

2. Results and Discussion

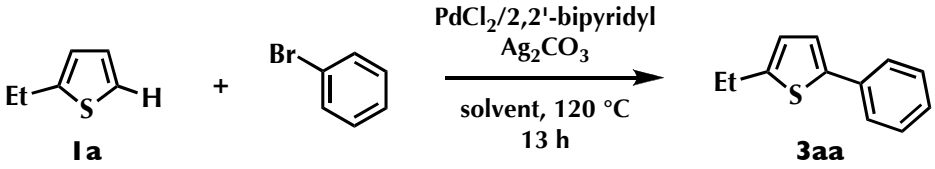
2-1. Effect of Catalyst Components

Following the finding of Pd/bipy/Ag_2CO_3 catalysis, the effect of catalyst components was investigated in detail.

2-1-1.Effect of Solvent

The author began by examining the solvent effect in the coupling reaction between 2-ethylthiophene (**1a**) and bromobenzene. When bromobenzene was used as a substrate instead of iodobenzene (suitable phenylating agent established in Chapter 3), in the presence of $PdCl_2$ (5%), 2,2′-bipyridyl (5%), and Ag_2CO_3 (1.0 equiv) in *m*-xylene at 120 °C, 2-ethyl-5-phenylthiophene (**3aa**) was obtained only in 2% yield (Table 1, entry 1). To our surprise, DMA and DMF, which are usually used in C–H bond arylation of (hetero)arenes, showed poor results (entries 2 and 3). As a result, it was found that 1,4-dioxane is the best solvent for the present system, which afforded the desired coupling product **3aa** in 32% yield (entry 4). On the other hand, DMSO, cyclopentyl methyl ether (CPME), ethanol, 1,2-dichloroethane, and *n*-octane were ineffective solvents (entries 5–9).

Table 1. Effect of Solvent[a]



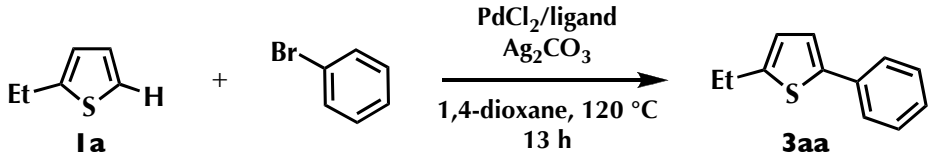
entry	solvent	yield (%)[b]
1	*m*-xylene	2
2	DMA	14
3	DMF	7
4	1,4-dioxane	32
5	DMSO	3
6	CPME	3
7	ethanol	<2
8	1,2-dichloroethane	<2
9	*n*-octane	<2

[a] Conditions: **1a** (1.0 equiv), bromobenzene (1.0 equiv), $PdCl_2$ (5%), 2,2'-bipyridyl (5%), Ag_2CO_3 (1.0 equiv), solvent, 120 °C, 13 h. [b] GC yield.

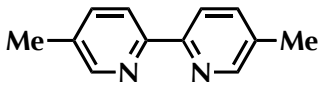
2-1-2. Effect of Ligand

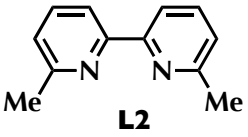
Subsequently, the ligand effect was examined focusing on nitrogen-based ligands (Table 2). First of all, the coupling reaction conducted without any ligand gave only trace amount of product (entry 1). The sp^3 nitrogen ligand such as TMEDA was ineffective for this reaction (entry 2). Since 2,2′-bipyridyl gave relatively good result (entry 3), a variety of bipyridyl-based ligands were investigated (entries 4–8). It was found that the reactivity is influenced by the steric environment around bipyridyl core. While C5-substituted 2,2′-bipyridyl ligand **L1** brought relatively good result (entry 4), ligands bearing substituents at C4 or C6 position (**L2**–**L5**) were ineffective (entries 5–8). Moreover, the use of 1,10-phenanthroline was found to be ineffective (entry 9). Monodentate pyridine-based ligands (pyridine and **L6**–**L8**) did not promote the reaction efficiently (entries 10–13).

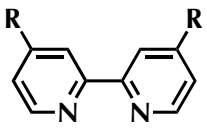
Table 2. Effect of Ligand[a]



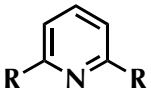
ligands:







R = OMe (L3)
R = ^{t}Bu (L4)
R = CF_3 (L5)



R = Me (L6)
R = ^{t}Bu (L7)
R = F (L8)

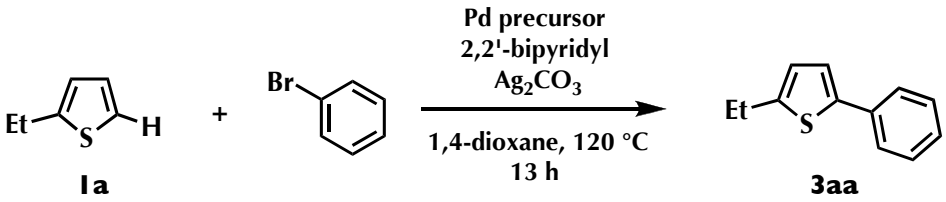
entry	ligand	yield (%)[b]
1	none	<2
2	TMEDA	5
3	2,2'-bipyridyl	32
4	**L1**	21
5[c]	**L2**	2
6	**L3**	3
7	**L4**	6
8[c]	**L5**	8
9	1,10-phenanthroline	12
10[d]	pyridine	8
11[d]	**L6**	<2
12[d]	**L7**	<2
13[d]	**L8**	<2

[a] Conditions: **1a** (1.0 equiv), bromobenzene (1.0 equiv), $PdCl_2$ (5%), ligand (5%), Ag_2CO_3 (1.0 equiv), 1,4-dioxane, 120 °C, 13 h. [b] GC yield. [c] $PdBr_2$ was used instead of $PdCl_2$. [d] 10% ligand was used.

2-1-3. Effect of Pd Precursor

The effect of Pd precursor was also investigated and the results are summarized in Table 3. Pd(II) salts with two halogen ligands, such as $PdCl_2$, $PdBr_2$, and PdI_2, worked well (entries 1–3). On the other hand, $Pd(OAc)_2$ and $Pd(OCOCF_3)_2$ were not effective for this transformation (entries 4 and 5). The cationic palladium complex, $[Pd(CH_3CN)_4](BF_4)_2$, displayed almost no catalytic activity with 2,2′-bipyridyl ligand (entry 6). Based on the inefficiency with 1,10-phenanthroline ligand and the fact that cationic palladium complex possesses poor reactivity, the present Pd system is likely to be different from the Pd catalysis developed by Shibahara and Murai (Scheme 2).[10] When $Pd_2(dba)_3{\cdot}CHCl_3$ was used as a precursor, the desired biaryl **3aa** was obtained only in 3% yield (entry 7). This result implies that Pd(0) species might not be included in the catalytic cycle under the present conditions.

Table 3. Effect of Palladium Precursor[a]



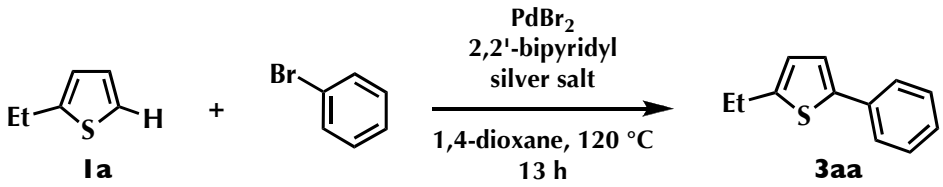
entry	Pd precursor	yield (%)[b]
1	$PdCl_2$	32
2	$PdBr_2$	59
3	PdI_2	39
4	$Pd(OAc)_2$	12
5	$Pd(OCOCF_3)_2$	3
6	$[Pd(MeCN)_4](BF_4)_2$	<2
7[c]	$Pd_2(dba)_3{\cdot}CHCl_3$	3

[a] Conditions: **1a** (1.0 equiv), bromobenzene (1.0 equiv), Pd precursor (5%), 2,2'-bipyridyl (5%), Ag_2CO_3 (1.0 equiv), 1,4-dioxane, 120 °C, 13 h. [b] GC yield. [c] 2.5% of $Pd_2(dba)_3{\cdot}CHCl_3$ was employed.

2-1-4. Effect of Silver Salt

The investigation of silver salt was also conducted with $PdBr_2$/bipy system in 1,4-dioxane. The results are shown in Table 4. The reaction in the absence of silver salt under the standard catalytic conditions did not give the arylated product **3aa** efficiently (entry 1). Silver salts that are generally used for the generation of cationic transition metal species, such as $AgBF_4$, $AgPF_6$, $AgSbF_6$ and AgOTf did not work well (entries 2–5). Silver acetate and silver fluoride also did not promote the reaction efficiently (entries 6 and 7). Though AgO promoted the reaction, the efficiency was low (21% yield, entry 8). Finally, Ag_2CO_3 was found to be the best silver-based additive giving rise to **3aa** in 59% yield (entry 9). It is clear from these results that the counter anion of silver salt plays key role in this catalysis.

Table 4. Effect of Silver Salt[a]

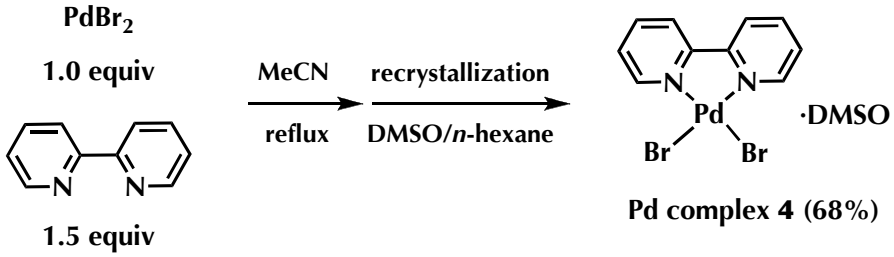


entry	silver salt	yield (%)[b]
1	none	<2
2	$AgBF_4$	<2
3	$AgPF_6$	<2
4	$AgSbF_6$	<2
5	AgOTf	<2
6	AgOAc	2
7	AgF	<2
8	AgO	21
9	Ag_2CO_3	59

[a] Conditions: **1a** (1.0 equiv), bromobenzene (1.0 equiv), $PdBr_2$ (5%), 2,2'-bipyridyl (5%), silver salt (1.0 equiv), 1,4-dioxane, 120 °C, 13 h. [b] GC yield.

2-2. Synthesis, Structure, and Catalytic Activity of $PdBr_2$(bipy) Complex

Considering the results obtained during the optimization of catalyst components, $PdBr_2$/bipy seems to be the best combination for the coupling. To simplify the reaction system, the author prepared the $PdBr_2$(bipy) complex. Although the preparation and crystal structure of $PdBr_2$(bipy) was already reported,[13] the author developed a new simple synthetic route to $PdBr_2$(bipy). Treatment of $PdBr_2$ (1.0 equiv) with 2,2′-bipyridyl (1.5 equiv) in refluxing MeCN followed by recrystallization from DMSO/*n*-hexane gave $PdBr_2$(bipy)·DMSO (**4**) in 68% yield as orange crystal (Scheme 6). The molecular structure of **4** was confirmed by X-ray crystal structure analysis (Figure 1).[14] The crystal packing of **4** was found to be different from that of the previously reported $PdBr_2$(bipy) complex.[13]



Scheme 6. The Synthesis of Palladium Complex **4**

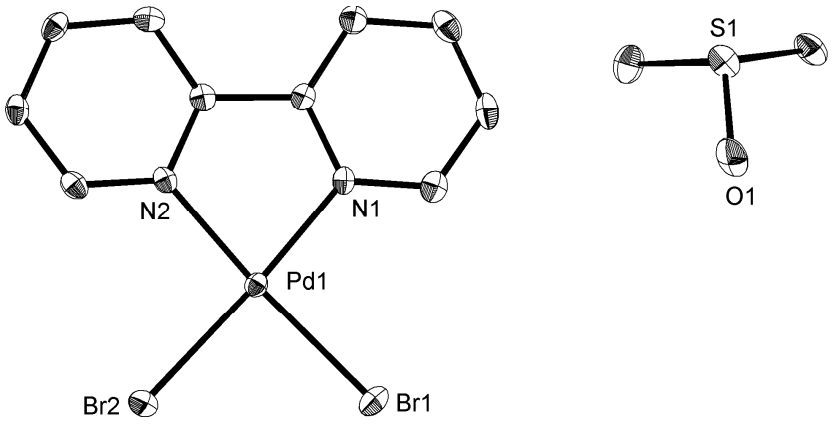
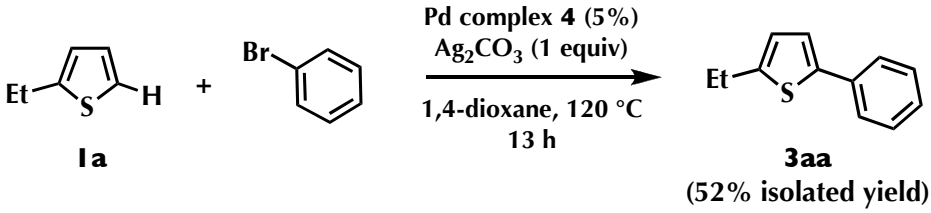


Figure 1. X-ray Crystal Structure of **4** (50% thermal ellipsolids). All hydrogen atoms are omitted for clarity.

Subsequently, the reaction of 2-ethylthiophene (**1a**: 1.0 equiv) and bromobenzene (1.0 equiv) was carried out in the presence of $PdBr_2$(bipy)·DMSO (**4**) (5%) and Ag_2CO_3 (1.0 equiv) in 1,4-dioxane at 120 °C for 13 h, and the C–H arylation product **3aa** was obtained in 52% isolated yield (Scheme 7). Based on these results, the author decided to use the complex $PdBr_2$(bipy)·DMSO (**4**) as a catalyst precursor for further investigations.

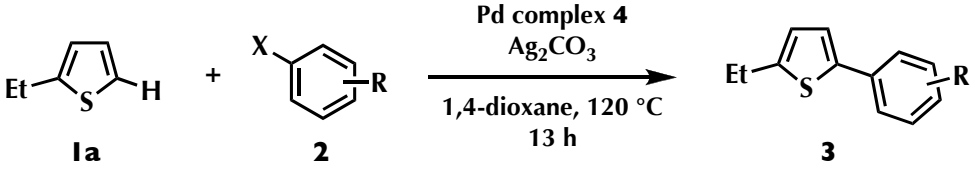


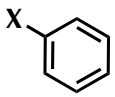
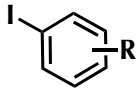
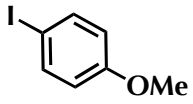
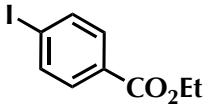
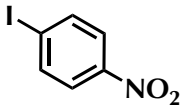
Scheme 7. Coupling Reaction Catalyzed by Palladium Complex **4**

2-3. Substrate Scope in C–H Bond Arylation of Heteroarenes with Haloarenes Catalyzed by $PdBr_2$(bipy)·DMSO (4)

With the optimized conditions and air-stable pre-catalyst **4** in hand, the author investigated the substrate scope with respect to haloarenes **2** (Table 5). Although the present system was not applicable to chlorobenzene and phenyl triflate, the coupling reactions using bromo- and iodobenzene (**2a**) took place efficiently (entries 1–4). To our delight, various electronically and structurally diverse haloarenes **2** were applicable to this coupling (entries 5–10). Noteworthy, the utilization of sterically hindered 2-iodotoluene (**2b**) also afforded the desired coupling product **3ab** in excellent yield (entry 5). Moreover, a range of functional groups, such as methoxy, ester, and nitro groups were tolerated in this coupling (entries 8–10). Heteroarenes possessing electron-donating groups tend to show higher reactivity compared with those with electron-withdrawing groups.

Table 5. Scope of Haloarenes[a]

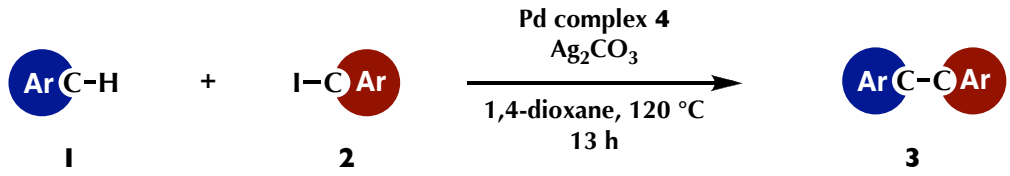


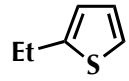
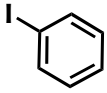
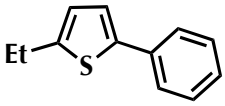
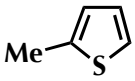
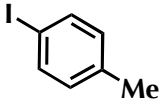
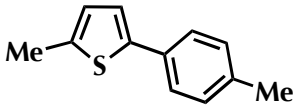
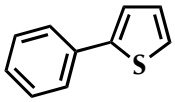
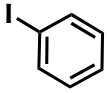
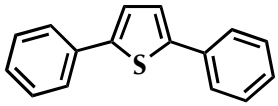
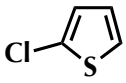
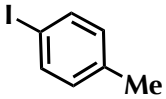
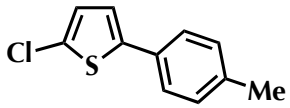
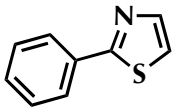
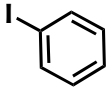
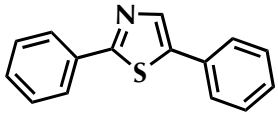
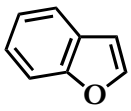
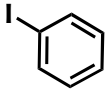
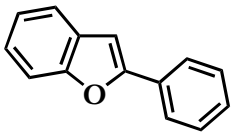
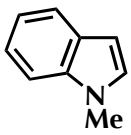
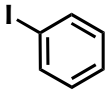
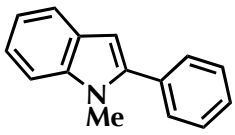
entry	2			3 (yield, %)[b]
1		X = I	**2a**	**3aa** (70)
2		= Br		**3aa** (52)
3		= OTf		**3aa** (2)
4[c]		= Cl		**3aa** (<2)
5		R = 2-Me	**2b**	**3ab** (80)
6		= 3-Me	**2c**	**3ac** (82)
7		= 4-Me	**2d**	**3ad** (78)
8			**2e**	**3ae** (77)
9			**2f**	**3af** (52)
10			**2g**	**3ag** (43)

[a] Conditions: **1a** (1.0 equiv), **2** (1.0 equiv), **4** (5%), Ag_2CO_3 (1.0 equiv), 1,4-dioxane, 120 °C, 13 h. [b] Isolated yield. [c] $PdCl_2$/2,2'-bipyridyl was used instead of **4**.

By using the optimized conditions, the author also surveyed heteroarenes that could be applied to this system. It was found that a variety of electron-rich five-membered heteroarenes, such as thiophenes, thiazoles, benzofurans, and indoles, were arylated with iodoarenes (Table 6). For example, 2-methylthiophene (**1b**), 2-phenylthiophene (**1c**), and 2-chlorothiophene (**1d**) were arylated in good to high yields (entries 2–4). 2-Phenylthiazole (**1e**), which could be potentially arylated at the phenyl ring through thiazole-directed arylation,[15] was selectively arylated at the C5 position on thiazole ring with iodobenzene (**2a**) in 63% yield (entry 5).

Table 6. Substrate Scope of Heteroarenes[a]



entry	1		2		3 (yield, %)[b]
1		**1a**		**2a**	 **3aa** (70)
2		**1b**		**2d**	 **3bd** (80)
3		**1c**		**2a**	 **3ca** (59)
4		**1d**		**2d**	 **3dd** (41)
5[c]		**1e**		**2a**	 **3ea** (63)
6[d]		**1f**		**2a**	 **3fa** (48)[e]
7[d]		**1g**		**2a**	 **3ga** (60)[f]

[a] Conditions: **1** (1.0 equiv), **2** (1.0 equiv), **4** (5%), Ag_2CO_3 (1.0 equiv), 1,4-dioxane, 120 °C, 13 h. [b] Isolated yield. [c] 1.5 equiv of **1e** was employed. [d] Conditions: **1** (1.5 equiv), **2** (1.0 equiv), **4** (10%), Ag_2CO_3 (1.0 equiv), 1,4-dioxane, 150 °C, 13 h. [e] C3 Isomer was also obtained. Isomer ratio: 2-/3- = 90/10. [f] C3 Isomer was also obtained. Isomer ratio: 2-/3- = 93/7.

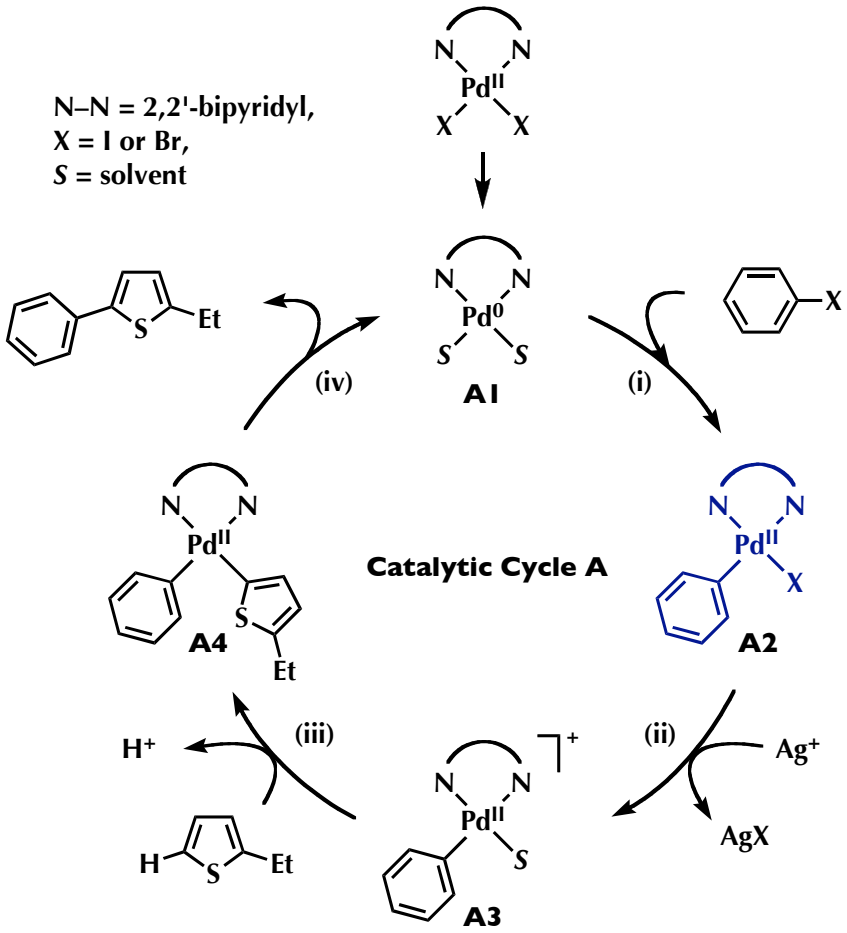
The arylation of benzofuran (**1f**) and *N*-methylindole (**1g**) took place, albeit as a mixture of regioisomers (entries 6 and 7). Unfortunately the electron-deficient aromatics such as pyridine and pyrazine could not be arylated with haloarenes under the present system.

2-4. Mechanistic Considerations

Although the precise mechanism of the present Pd-catalyzed reaction remains unknown, the author investigated to gain better grasp toward the reaction mechanism. In this study, two distinct catalytic cycles were considered and examined.

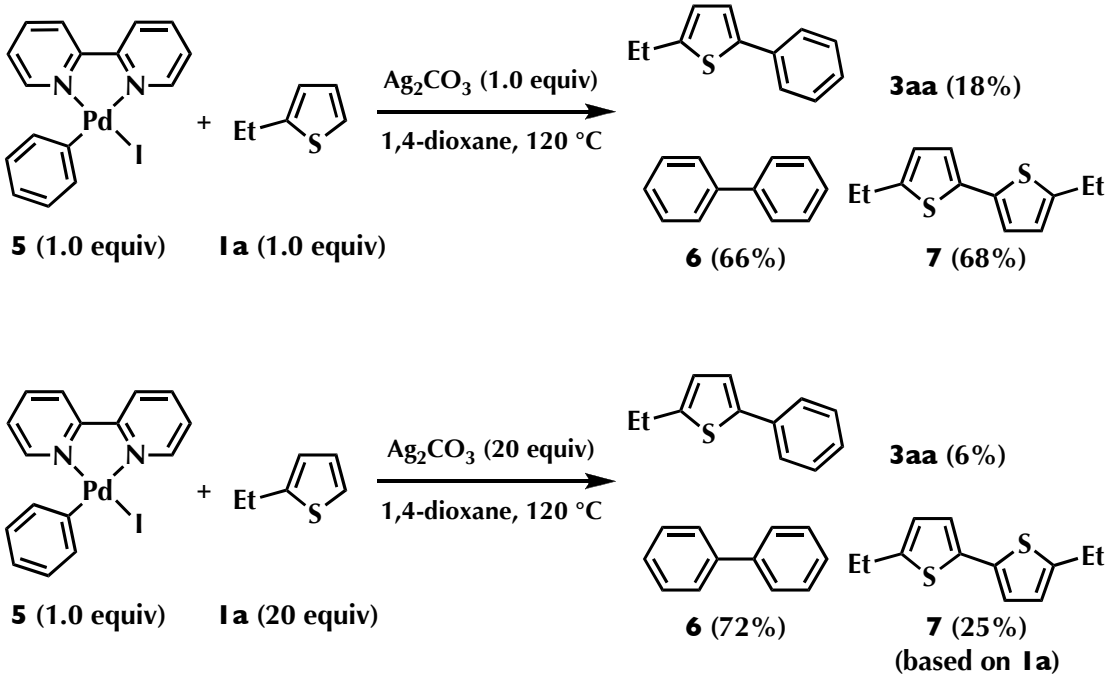
2-4-1. Possibility of Pd^0/Pd^{II} Redox Catalysis

As already mentioned, many Pd-catalyzed heteroarene C–H bond arylation reactions with haloarenes are considered to occur through Pd^0/Pd^{II} redox cycle initiated by the oxidative addition of a haloarene to Pd(0) species. Mori's reaction described in Scheme 4 is such a reaction. Thus, the author began by investigating such a mechanism with Pd/bipy/Ag_2CO_3 system (catalytic cycle A, Scheme 8).



Scheme 8. Catalytic Cycle A. (i) oxidative addition of haloarene, (ii) generation of cationic Pd species, (iii) palladation of thiophene C–H bond, (iv) reductive elimination of product

In the catalytic cycle A, halobenzene is the first-reacting reagent to Pd species. To this catalytic cycle to work, Pd(0) species **A1** must be generated from Pd(II) precursor such as **4**. Thereafter, halobenzene oxidatively adds to Pd(0) to afford the $PhPd^{II}X$ complex **A2**. After removing a halogen atom from Pd by Ag_2CO_3 to form **A3**, 2-ethylthiophene (**1a**) comes into the coordination sphere of Pd and then undergoes C–H palladation to give $PhPd^{II}Th$ complex **A4**. Finally, the reductive elimination takes place from **A4** to furnish the product **3aa** with regenerating Pd(0) species **A1** to close the catalytic cycle.

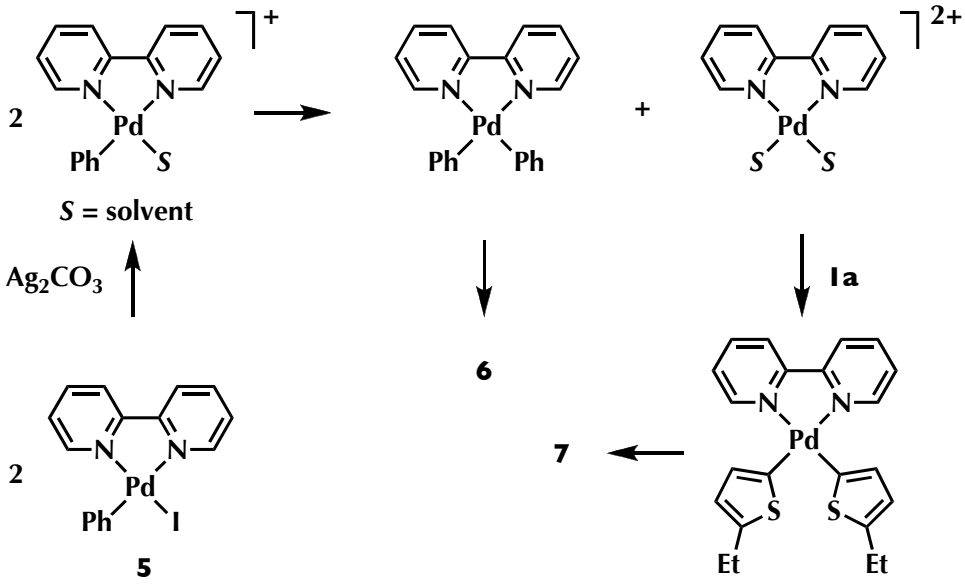


Scheme 9. Stoichiometric Reactions of Pd Complex **5**

To gain further insight into the mechanism A, the organopalladium complex **5**[16] (complex **A2**, X = I; Scheme 8) was prepared and subjected to the stoichiometric reaction with 2-ethylthiophene (**1a**: 1.0 equiv) and Ag_2CO_3 (1.0 equiv) in 1,4-dioxane at 120 °C (Scheme 9). Quite surprisingly, the desired **3aa** was produced only in 18% yield. Moreover, the fate of phenyl group on Pd complex **5** was found to be mainly biphenyl (**6**,

66%). Under these conditions, **1a** was converted to the corresponding homo-coupling product **7** in 68% yield. Notably, both of these homo-coupling products (**6** and **7**) are not significantly observed in the catalytic reactions (<10%). The reaction using excess amounts of **1a** and Ag_2CO_3 (20 equiv each) was also conducted to mimic the conditions in a real catalytic reaction. However, the yield of **3aa** decreased to 6% and the yield of **7** increased to 72% (Scheme 9).

The formation of biphenyl (**6**) can be rationalized by the biaryl formation from arylpalladium(bipy) species in the presence of silver salt, a somewhat known process in the literature (Scheme 10).[17] Another homo-coupling product **7** might be produced by the twofold C–H palladation of **1a** with the cationic Pd complex generated in the above-mentioned reaction, followed by reductive elimination (Scheme 10).



Scheme 10. Possible Pathways for the Production of **6** and **7** from **5**, **1a**, and Ag_2CO_3

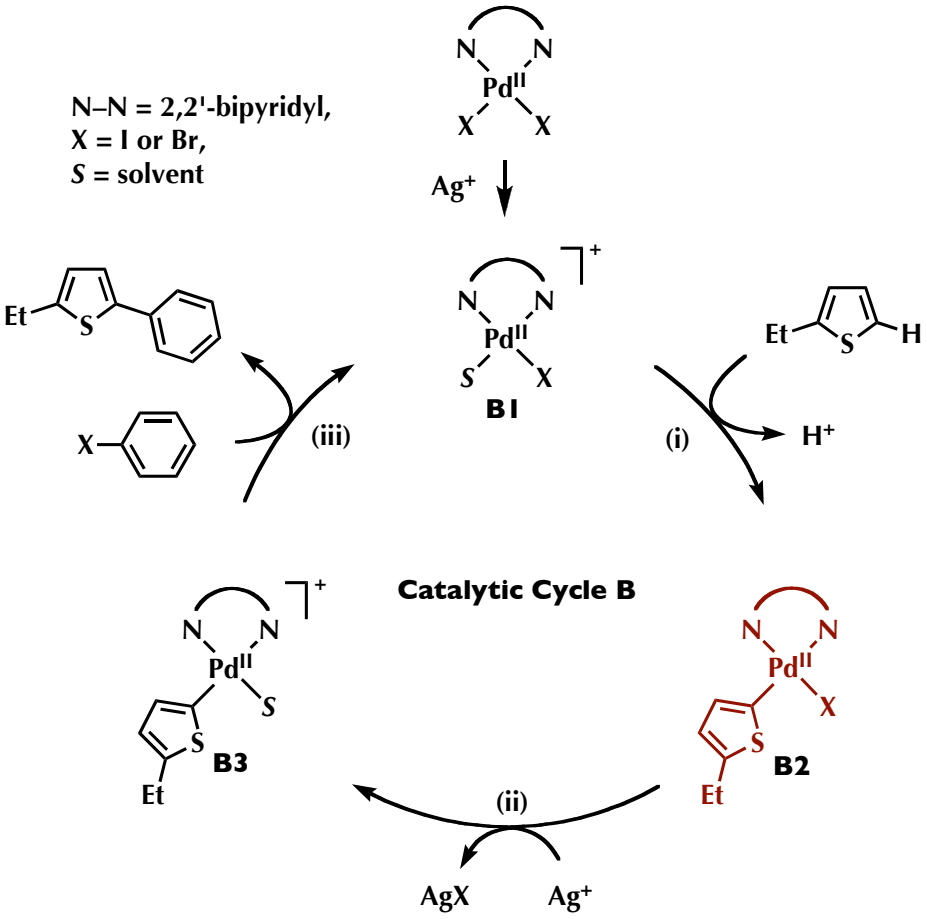
These results are in a sharp contrast to the results obtained by Mori (Scheme 4). Nevertheless, based on the stoichiometric reactions described in Scheme 9 as well as the previous finding that Pd(0) precursor is sluggish in catalytic reaction (Table 3, entry 7),

the author assumes that Pd^0/Pd^{II} redox catalysis (catalytic cycle A) is most likely not operative in the present Pd/bipy/Ag_2CO_3 system.

2-4-2. Possibility of Pd^{II}-Based Catalysis

Based on the above-mentioned investigation, which led to the assumption that Pd^0/Pd^{II} redox catalysis is not the mechanism, other unconventional mechanism must be considered for Pd/bipy/Ag_2CO_3 catalysis. An important implication obtained from these studies is that haloarenes are not first-reacting reagents to Pd species. Therefore, the author considered alternative Pd^{II}-based mechanism where thiophenes (heteroarenes) are first-reacting reagents to Pd species (catalytic cycle B, Scheme 11).

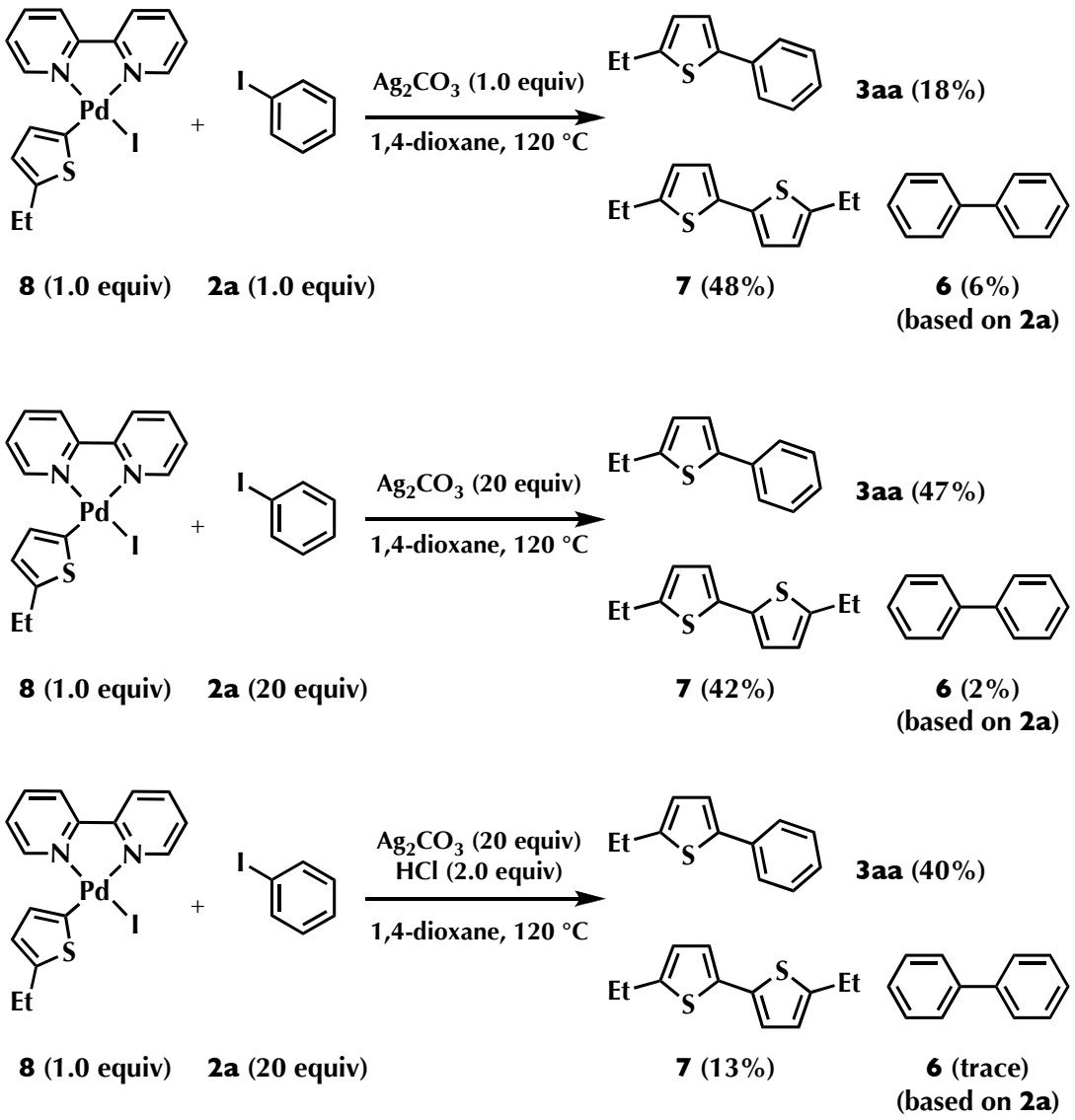
The catalytic cycle B starts with the reaction of neutral Pd(II) complex (**4** in catalytic reaction) with Ag_2CO_3 to generate the cationic Pd species **B1**. With the coordination site opened, 2-ethylthiophene (**1a**) coordinates to Pd and thereafter undergoes C–H palladation to afford ThPd^{II}X complex **B2**. This complex reacts with halobenzene with the aid of Ag_2CO_3 to give the biaryl product **3aa**, likely through the cationic thienylpalladium species **B3**, and regenerates the cationic Pd species **B1**. Possible mechanisms for the reaction of **B3** and halobenzene producing the biaryl product **3aa** will be discussed later.



Scheme 11. Catalytic Cycle B. (i) palladation of thiophene C–H bond, (ii) generation of cationic Pd species, (iii) product-generating unknown process

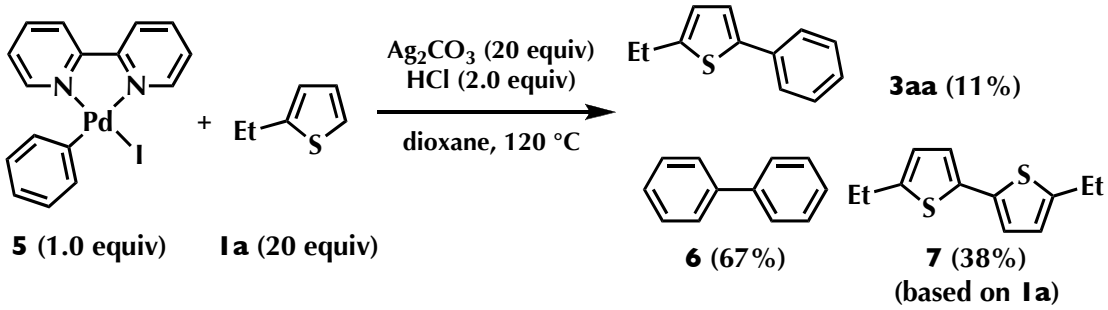
With a new mechanistic scenario, the assumed thienylpalladium complex **8** (**B2**, X = I; Scheme 11) was prepared and subjected to the stoichiometric reactions with iodobenzene (**2a**) and Ag_2CO_3 (Scheme 12). When **8** was reacted with **2a** (1.0 equiv) and Ag_2CO_3 (1.0 equiv) in 1,4-dioxane at 120 °C, the desired coupling product **3aa** was obtained in 18% yield, together with bithiophene **7** (48%) and **6** (6%). When the reaction was conducted with excess amounts of **2a** and Ag_2CO_3 (20 equiv each), the yield of **3aa** increased to 47% without significantly changing the yields of **7** (42%) and **6** (2%). Overall, these results based on the catalytic cycle B are consistent with the results of catalytic reactions. However, the formation of considerable amount of **7** (42%) is still inconsistent with the catalytic system. The author envisaged that this might be

attributed to the lack of key species formed in situ in the real catalytic conditions. Thus HCl (2.0 equiv) was added as proton, which should be generated in the thiophene palladation step, to the stoichiometric reaction of **8** (Scheme 12). Gratifyingly, the formation of **7** and **6** was suppressed while producing the desired **3aa** in reasonable yield (40%).



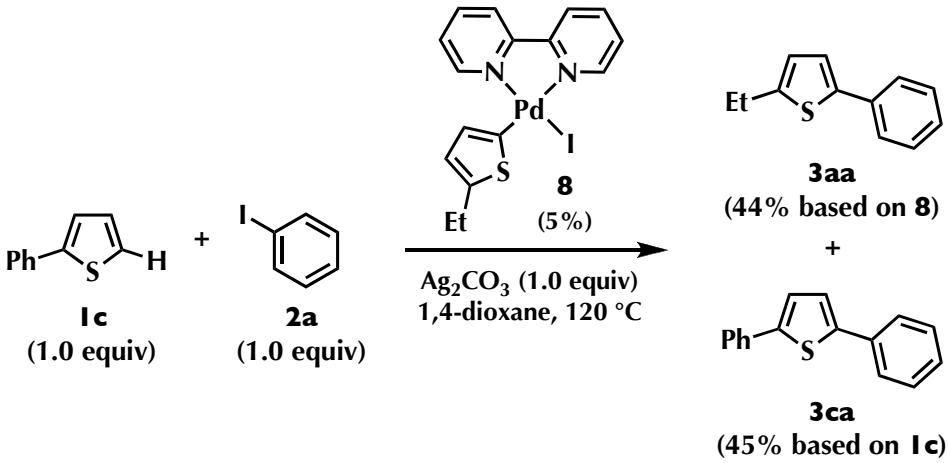
Scheme 12. Stoichiometric Reactions of Pd Complex **8**

Following the finding of acid effect in the reaction of **8**, the author investigated the effect of acid in the stoichiometric reaction of complex **5**. However, the author could not observe a noticeable acid effect. For example, when adding HCl (2.0 equiv relative to **5**) to the reaction described in Scheme 9 (bottom reaction), significant biphenyl (**6**) was still obtained (67%) along with small amount of **3aa** (11%) and **7** (38%) (Scheme 13).



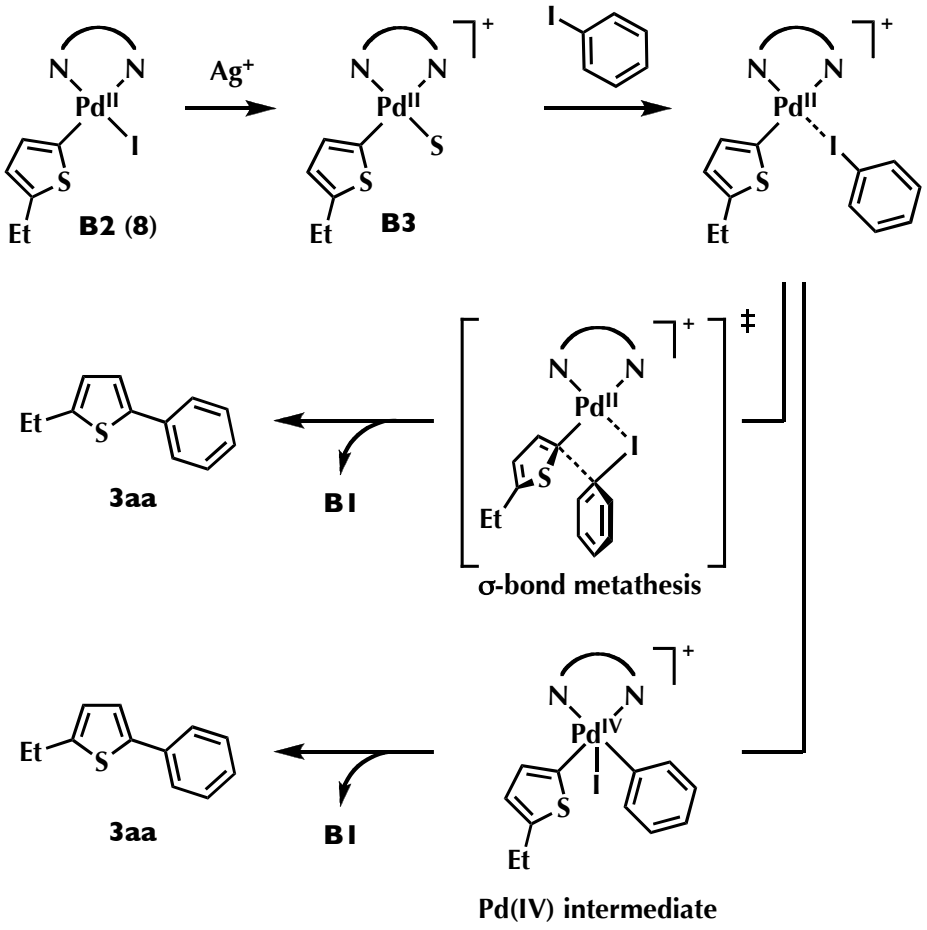
Scheme 13. Stoichiometric Reaction of Pd Complex **5** with Acid

Having observed the existence of pathway generating biaryl product **3aa** from thienylpalladium(II) complex **8** and iodobenzene (**2a**), the author next investigated whether also the complex **8** catalyzes the coupling. When the mixture of 2-phenylthiophene (**1c**: 1.0 equiv), **2a** (1.0 equiv), and Ag_2CO_3 (1.0 equiv) in 1,4-dioxane was heated at 120 °C in the presence of a catalytic amount of **8** (5%), 2-ethyl-5-phenylthiophene (**3aa**: 44% yield based on **8**) and 2,5-diphenylthiophene (**3ca**: 45% yield based on **1c**) were obtained (Scheme 14). Through the initial reaction with **2a** producing **3aa** (in a catalytic amount), the complex **8** was most likely transformed to the Pd(II) complex **B1**, which should eventually catalyze the coupling of **1c** and **2a** to afford **3ca**. These results are all in agreement with the mechanistic scenario shown in Scheme 11 (catalytic cycle B). Although other possibilities cannot be excluded, the obtained results at least suggest that the first-reacting reagents to Pd species should be thiophene substrates (heteroarenes) in the present Pd/bipy/Ag_2CO_3 catalytic system.



Scheme 14. Catalytic Reaction Promoted by Pd Complex **8**

Within the assumed catalytic cycle B, the mechanism forming **3aa** from complex **B2** (**8**) and iodobenzene is still unclear. Two distinct mechanisms can be speculated for this unprecedented transformation (Scheme 15). Common reactions for both mechanisms might be the generation of cationic thienylpalladium(II) complex **B3** assisted by Ag_2CO_3, followed by the coordination of iodobenzene. From this complex, it might be possible to undergo σ-bond metathesis reaction[18] at thienyl–Pd and Ph–I bonds, forming the product **3aa** directly and regenerating Pd complex **B1**. The second possible mechanism involves oxidative addition of iodobenzene to thienylpalladium(II) complex forming the corresponding Pd(IV) complex.[19] Subsequent reductive elimination affords the desired coupling product with regeneration of cationic Pd(II) species **B1**. However, no experimental evidence has been obtained at present to support these speculations.



Scheme 15. Possible Mechanisms for Final Product-Forming Step

3. Conclusion

In this Chapter, the author described the effect of catalyst components, and the scope of Pd/bipy/Ag_2CO_3 catalyzed C–H bond arylation of heteroarenes with haloarenes. The complex $PdBr_2$(bipy)·DMSO, whose structure was unambiguously determined by X-ray crystallography, turned out to be a general catalyst precursor for the process. The reaction is applicable to a range of electron-rich five-membered heteroarenes such as thiophenes, thiazoles, benzofurans, and indoles. Mechanistic study of Pd/bipy/Ag_2CO_3 catalysis based on a number of stoichiometric reactions implicates that the reaction likely occurs not through a conventional Pd^0/Pd^{II} redox catalysis but through a Pd^{II} non-redox or Pd^{II}/Pd^{IV} redox catalysis. Since the mechanisms proposed herein are

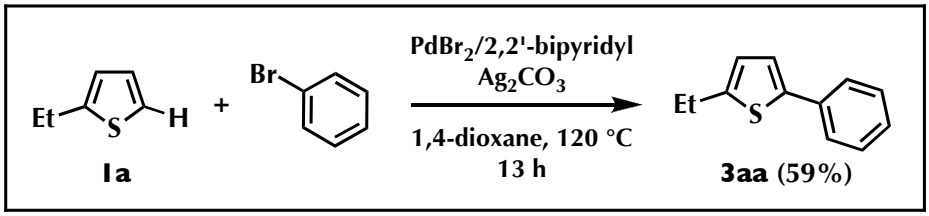
uncommon, the author believes that the present study should shed light on the development of new generation catalysts for the direct C–H bond functionalization of heteroarenes.

4. Experimental

4-1. General

Unless otherwise noted, all materials including dry solvents were obtained from commercial suppliers and used without further purification. The ligand **L5**[20] used in Table 2 and Pd complex **5**[16] were prepared according to procedures reported in the literature. Unless otherwise noted, all reactions were performed with dry solvents under an atmosphere of argon in flame-dried glassware, using standard vacuum-line techniques. All arylation reactions using conventional heating were carried out in glass vessels equipped with J. Young® O-ring tap, heated in oil bath (heater + magnetic stirrer). All work-up and purification procedures were carried out with reagent-grade solvents in air. Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F_{254} precoated plates (0.25 mm). The developed chromatogram was analyzed by UV lamp (254 nm) and ethanolic phosphomolybdic acid/sulfuric acid. Flash column chromatography was performed with E. Merck silica gel 60 (230–400 mesh). Preparative recycling gel permeation chromatography (GPC) was performed with a JAI LC-9204 instrument equipped with JAIGEL-1H/JAIGEL-2H columns using chloroform as an eluent. Preparative thin-layer chromatography (PTLC) was performed using Wako-gel® B5-F silica coated plates (0.75 mm) prepared in our laboratory. Gas chromatography (GC) analysis was conducted on a Shimadzu GC-2010 instrument equipped with a HP-5 column (30 m × 0.25 mm, Hewlett-Packard). GC/MS analysis was conducted on a Shimadzu GCMS-QP2010 instrument equipped with a HP-5 column (30 m × 0.25 mm, Hewlett-Packard). High-resolution mass spectra (HRMS) were obtained from a JMS-T100TD (direct analysis in real time mass spectrometry, DARTMS) or a JEOL JMS-700 (fast atom bombardment mass spectrometry, FABMS) instrument. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-ECA-600 (^{1}H 600 MHz, ^{13}C 150 MHz) spectrometer. Chemical shifts for ^{1}H NMR are expressed in parts per million (ppm) relative to tetramethylsilane (δ 0.0 ppm). Chemical shifts for ^{13}C NMR are expressed in ppm relative to $CDCl_3$ (δ 77.0 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet, br = broad signal), coupling constant (Hz), and integration.

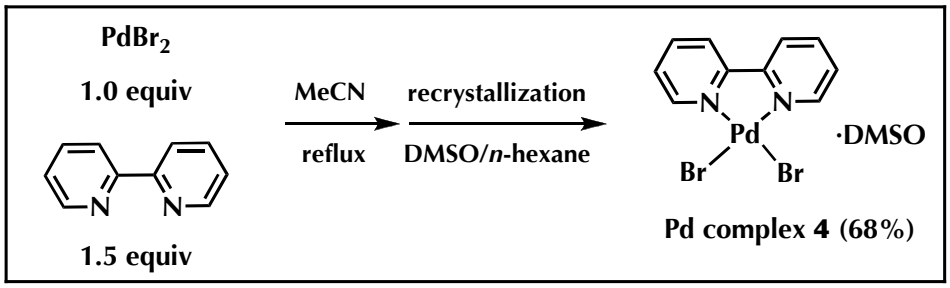
4-2. Typical Procedure for Coupling of Heteroarenes and Bromobenzene using $PdBr_2$/2,2′-bipyridyl



2-Ethyl-5-phenylthiophene (3aa): A 20-mL glass vessel equipped with J. Young® O-ring tap, containing a magnetic stirring bar, was flame-dried under vacuum and filled with argon after cooling to room temperature. To this vessel were added $PdBr_2$ (4.0 mg, 15 μmol), 2,2′-bipyridyl (2.3 mg, 15 μmol), Ag_2CO_3 (82.6 mg, 0.30 mmol), and dry 1,4-dioxane (0.75 mL) under a stream of argon. The vessel was heated at 60 °C for 0.5 h. To this vessel were added 2-ethylthiophene (**1a**: 33.7 mg, 0.30 mmol), bromobenzene (33.3 mg, 0.30 mmol), and dry 1,4-dioxane (0.75 mL) under a stream of argon. The vessel was sealed with O-ring tap, and then heated at 120 °C for 13 h in oil bath with stirring. After cooling the reaction mixture to room temperature, the mixture was passed through a short silica gel pad (EtOAc). The filtrate was evaporated and *n*-undecane (internal standard for GC analysis) was added to the residue. The yield of 2-ethyl-5-phenylthiophene (**3aa**) was estimated to be 59% by GC analysis. The product was purified by gel permeation chromatography (GPC) and identified by ^{1}H NMR, ^{13}C NMR, and GCMS and these data were consistent with literature values.[5]

All reactions described in Table 1–4 were performed by basically following the procedure described above.

4-3. Syntheisis and X-ray Crystal Structure Analysis of Pd Complex 4



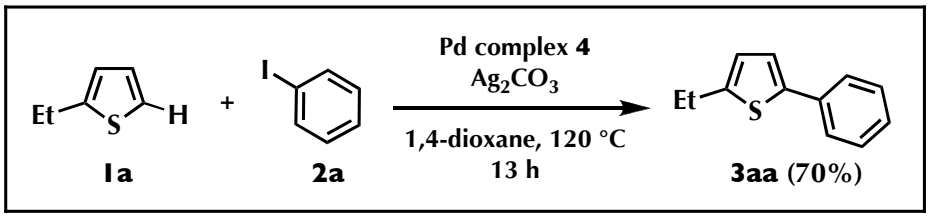
A solution of $PdBr_2$ (79.9 mg, 0.3 mmol) in dry acetonitrile (1.5 mL) was refluxed for 0.5 h under argon. After cooling the reaction mixture to room temperature, 2,2′-bipyridyl (70.3 mg, 0.45 mmol) was added to this vessel and stirred at room temperature for 1 h. Recrystallized from DMSO/*n*-hexane followed by filtration and washing with MeOH and ether afforded $PdBr_2$(2,2′-bipyridyl)·DMSO (**4**: 102 mg, 68%) as orange crystal.

^{1}H NMR (600 MHz, DMSO-d_6) δ 7.79–7.81 (m, 2H), 8.36 (dd, J = 7.9 Hz, 7.6 Hz, 2H), 8.59 (d, J = 7.6 Hz, 2H), 9.39 (d, J = 5.5 Hz, 2H).

Intensity data were collected at 123 K on a Rigaku Single Crystal CCD X-ray Diffractometer (Saturn 70 with MicroMax-007) with graphite-monochromated Mo-Kα radiation (λ = 0.7107 Å). A total 9953 reflections were corrected, of which 2704 were independent reflections (R_{int} = 0.0290). The structure was solved by direct methods (SIR-97[21]) and refined by the full-matrix least-squares techniques against F^2 (SHELEX-97[22]). All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed using AFIX instructions. The crystal data are as follows: $C_{12}H_{14}Br_2N_2OPdS$, FW = 500.53, crystal size 0.10 × 0.10 × 0.05 mm^3, monoclinic, space group $C2/c$ (No.15). a = 29.710(8) Å, b = 7.9377(14) Å, c = 22.102(6) Å, α = 90°, β = 143.908(7)°, γ = 90°, V = 3070.4(12) Å^3, Z = 8, D_{calc} = 2.166 g/cm^3. The refinement converged to R_1 = 0.0232, wR_2 = 0.0469 (I > 2σ(I)), R_1 = 0.0270, wR_2 = 0.0484 (for all data), GOF = 1.047. Selected bond lengths (Å): Pd(1)–N(1) = 2.035(2), Pd(1)–N(2) = 2.040(2), Pd(1)–Br(1) = 2.4118(6), Pd(1)–Br(2) = 2.4179(7). Selected angles (deg): N(1)–Pd(1)–N(2) = 80.66(10), N(2)–Pd(1)–Br(2) = 95.49(7), Br(2)–Pd(1)–Br(1) = 88.96(3), Br(1)–Pd(1)–N(1) = 94.93(7), N(1)–Pd(1)–Br(2) = 175.15(6), N(2)–Pd(1)–Br(1) = 175.48(7).

4-4. Typical Procedure for C–H Bond Arylation of Heteroarenes 1 and Haloarenes 2 Catalyzed by 4

All the arylated compounds in this section were purified by preparative thin-layer chromatography (PTLC) and/or gel permeation chromatography (GPC).

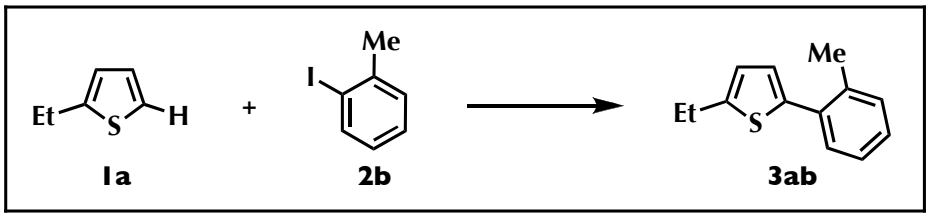


2-Ethyl-5-phenylthiophene (3aa): A 20-mL glass vessel equipped with J. Young® O-ring tap, containing a magnetic stirring bar, was flame-dried under vacuum and filled with argon after cooling to room temperature. To this vessel were added Pd complex **4** (8.1 mg, 16 μmol), Ag_2CO_3 (82.4 mg, 0.3 mmol), and dry 1,4-dioxane (0.75 mL) under a stream of argon. The vessel was heated at 60 °C for 0.5 h. To this vessel were added 2-ethylthiophene (**1a**: 33.7 mg, 0.30 mmol), iodobenzene (57 mg, 0.28 mmol), and dry 1,4-dioxane (0.75 mL) under a stream of argon. The vessel was sealed with O-ring tap, and then heated at 120 °C for 13 h in oil bath with stirring. After cooling the reaction mixture to room temperature, the mixture was passed through a short silica gel pad (EtOAc). The filtrate was evaporated and the residue was subjected to gel permeation chromatography ($CHCl_3$) to afford 2-ethyl-5-phenylthiophene (**3aa**: 36.9 mg, 70%) as colorless oil.

All reactions described in Scheme 7, Table 5, and 6 were performed by basically following the procedure described above. Unless otherwise noted, those products were isolated and identified by ^{1}H NMR, ^{13}C NMR, and GCMS. The isomer ratio of **3fa** and **3ga** was determined by ^{1}H NMR. Data were consistent with literature value: 2-ethyl-5-(4-methylphenyl)thiophene[5] (**3ad**) (Table 5, entry 2), 2-methyl-5-(4-methylphenyl)thiophene[9e] (**3bd**) (Table 6, entry 2), 2,5-diphenylthiophene[23] (**3ca**) (Table 6, entry 3), 2-chloro-5-(4-methylphenyl)thiophene[24] (**3dd**) (Table 6, entry 4), 2,5-diphenylthiazole[25] (**3ea**) (Table 6, entry 5),

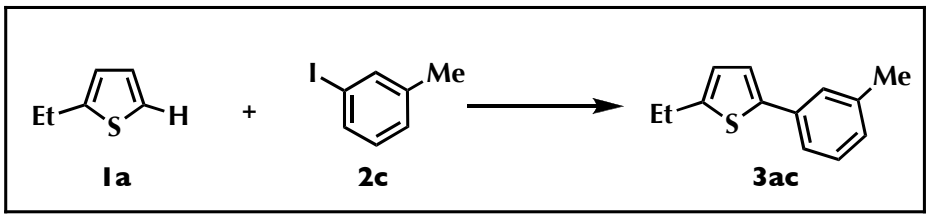
2-phenylbenzofuran[26] (**3fa**) and 3-phenylbenzofuran[27] (^{1}H NMR and GCMS analysis) (Table 6, entry 6), 1-methyl-2-phenylindole[28] (**3ga**) and 1-methyl-3-phenylindole[9e] (Table 6, entry 7).

4-5. Compound Data for Other Arylation Products 3



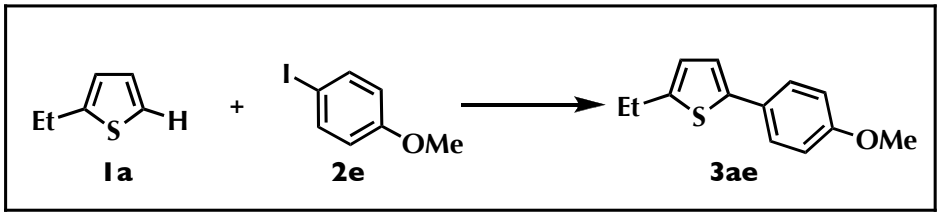
4-5-1. 2-Ethyl-5-(2-methylphenyl)thiophene (3ab): 80% isolated yield from 2-ethylthiophene (**1a**) and 2-iodotoluene (**2b**).

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.34 (t, *J* = 7.6 Hz, 3H), 2.43 (s, 3H), 2.87 (q, *J* = 7.6 Hz, 2H), 6.75 (d, *J* = 3.4 Hz, 1H), 6.86 (d, *J* = 3.4 Hz, 1H), 7.18–7.24 (m, 3H), 7.38 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.8, 21.2, 23.4, 123.3, 125.8, 126.0, 127.4, 130.2, 130.7, 134.6, 135.9, 140.4, 147.3. HRMS (DART) *m*/*z* calcd. for $C_{13}H_{15}S$ $[MH]^+$: 203.0895, found 203.0892.



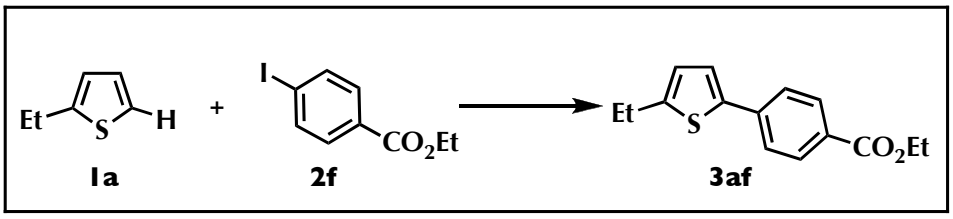
4-5-2. 2-Ethyl-5-(3-methylphenyl)thiophene (3ac): 82% isolated yield from 2-ethylthiophene (**1a**) and 3-iodotoluene (**2c**).

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.32 (t, *J* = 7.6 Hz, 3H), 2.36 (s, 3H), 2.84 (q, *J* = 7.6 Hz, 2H), 6.73 (d, *J* = 3.4 Hz, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 3.4 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.35–7.37 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.9, 21.4, 23.6, 122.5, 122.6, 124.2, 126.2, 127.8, 128.6, 134.6, 138.3, 141.7, 147.0. HRMS (DART) *m*/*z* calcd. for $C_{13}H_{15}S$ $[MH]^+$: 203.0895, found 203.0899.



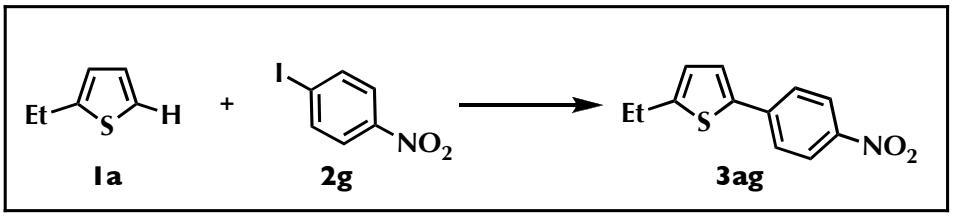
4-5-3. 2-Ethyl-5-(4-methoxylphenyl)thiophene (3ae): 77% isolated yield from 2-ethylthiophene (**1a**) and 4-iodoanisole (**2e**).

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.32 (t, *J* = 7.6 Hz, 3H), 2.84 (q, *J* = 7.6 Hz, 2H), 3.80 (s, 3H), 6.71 (d, *J* = 3.4 Hz, 1H), 6.88 (d, *J* = 8.9 Hz, 2H), 6.99 (d, *J*= 3.4 Hz, 1H), 7.47 (d, *J* = 8.9 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.9, 23.5, 55.3, 114.2, 121.6, 124.1, 126.7, 127.7, 141.5, 146.2, 158.8. HRMS (DART) *m*/*z* calcd. for $C_{13}H_{15}OS$ $[MH]^+$: 219.0844, found 219.0847.



4-5-4. Ethyl 4-(5-ethylthiophen-2-yl)benzoate (3af): 52% isolated yield from 2-ethylthiophene (**1a**) and ethyl 4-iodobenzoate (**2f**).

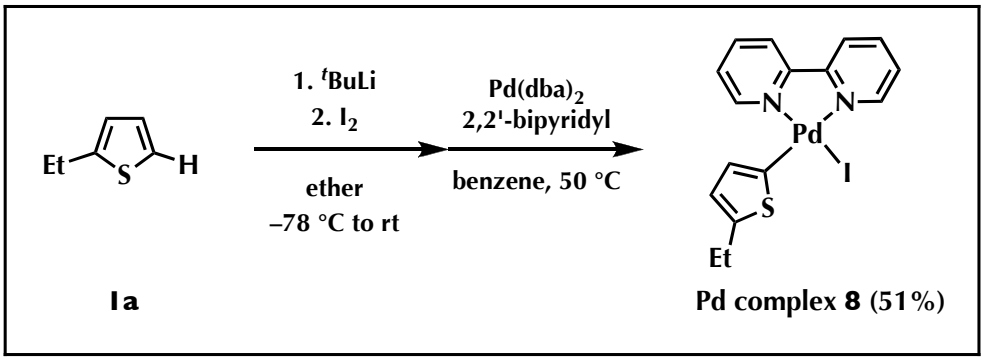
^{1}H NMR (600 MHz, $CDCl_3$) δ 1.34 (t, *J* = 7.6 Hz, 3H), 1.40 (t, *J* = 7.6 Hz, 3H), 2.87 (q, *J* = 7.6 Hz, 2H), 4.38 (q, *J* = 7.6 Hz, 2H), 6.78 (d, *J* = 3.5 Hz, 1H), 7.23 (d, *J* = 3.5 Hz, 1H), 7.60 (d, *J*= 8.9 Hz, 2H), 8.01 (d, *J* = 8.9 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3, 15.8, 23.6, 60.9, 124.2, 124.7, 124.9, 128.5, 130.1, 138.9, 140.2, 148.9, 166.3. HRMS (DART) *m*/*z* calcd. for $C_{15}H_{16}O_2S$ $[MH]^+$: 261.0949, found 261.0957.



4-5-5. 2-Ethyl-5-(4-nitrophenyl)thiophene (3ag): 43% isolated yield from 2-ethylthiophene (**1a**) and 4-iodonitrobenzene (**2g**).

^{1}H NMR (600 MHz, $CDCl_3$) δ 1.35 (t, *J* = 7.6 Hz, 3H), 2.89 (q, *J* = 7.6 Hz, 2H), 6.83 (d, *J* = 3.5 Hz, 1H), 7.30 (d, *J* = 3.5 Hz, 1H), 7.66 (d, *J*= 8.9 Hz, 2H), 8.20 (d, *J* = 8.9 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.8, 23.7, 124.3, 125.2, 125.3, 125.6, 138.7, 140.9, 146.1, 150.7. HRMS (DART) *m*/*z* calcd. for $C_{12}H_{12}NO_2S$ $[MH]^+$: 234.0589, found 234.0587.

4-6. Synthesis of Pd Complex 8



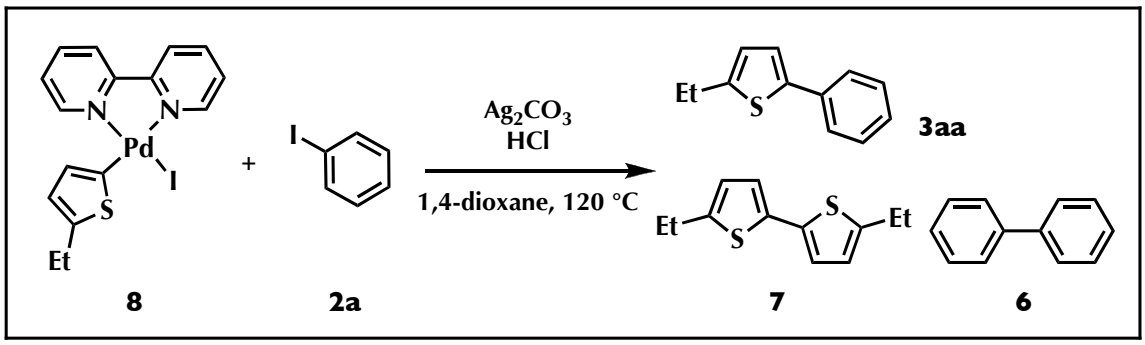
A 20-mL Schlenk flask, containing a magnetic stirring bar, was flame-dried under vacuum and filled with argon after cooling to room temperature. To this flask were added 2-ethylthiophene (**1a**: 415 mg, 3.7 mmol) and dry diethyl ether (1.5 mL) under a stream of argon. The contents were cooled at –78 °C, and to this flask was added *tert*-buthyl lithium (2.6 mL, 1.49 M in pentane, 3.9 mmol). The resultant mixture was stirred at –78 °C for 1 h. To this flask was added dropwise 2 mL solution of iodine in diethyl ether (495.3 mg, 3.9 mmol) at –78 °C. After warming the reaction mixture to room temperature and stirring for 5 h, the mixture was extracted with diethyl ether/sat. $Na_2S_2O_3$ aq. The organic phase was evaporated and directly used for the next step without further purification.

A 20-mL Schlenk flask, containing a magnetic stirring bar, was flame-dried under vacuum and filled with argon after cooling to room temperature. To this flask was added 5-ethyl-2-iodothiophene (all contents obtained above), $Pd(dba)_2$ (2.1 g, 3.7 mmol), 2,2′-bipyridyl (577.8 mg, 3.7 mmol), and dry benzene (15 mL) under a stream of argon. The contents were heated at 50 °C and stirring for 5 min. After cooling the reaction mixture to room temperature, the obtained mixture was filtrated over a pad of Celite®

and washed with benzene to remove the dba. Finally washing with dichloromethane provided the product Pd complex **8** (942.5 mg, 51%) as yellow solid.

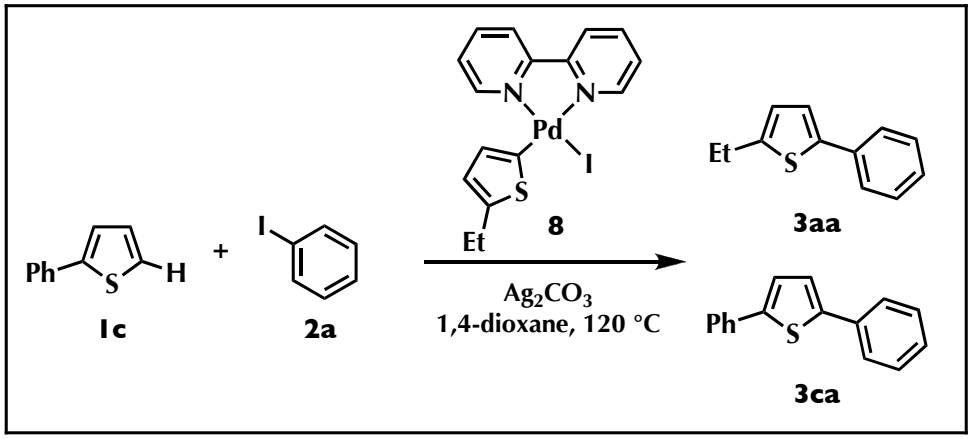
^{1}H NMR (600 MHz, $CDCl_3$) δ 1.30 (t, *J* = 7.6 Hz, 3H), 2.87 (q, *J* = 7.6 Hz, 2 H), 6.58 (d, *J* = 3.4 Hz, 1H), 6.74 (d, *J* = 3.4 Hz, 1H), 7.37–7.40 (m, 2H), 7.79 (d, *J* = 4.8 Hz, 1H), 8.01–8.06 (m, 2H), 8.13 (d, *J* = 7.6 Hz, 1H), 8.16 (d, *J* = 8.2 Hz, 1H), 9.52 (d, *J* = 4.1 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 15.8, 23.7, 122.2, 122.3, 123.9, 126.4, 126.8, 129.2, 129.3, 139.0, 139.1, 150.2, 150.3, 153.2, 154.0, 155.6. HRMS (FAB) *m*/*z* calcd. for $C_{16}H_{15}IN_2PdS$: 499.9035, found 499.9037.

4-7. Representative Stoichiometric Reaction of Pd Complex 8 and 2a



A 20-mL glass vessel equipped with J. Young® O-ring tap, containing a magnetic stirring bar, was flame-dried under vacuum and filled with argon after cooling to room temperature. To this vessel were added Pd complex **8** (25 mg, 50 μmol), iodobenzene (**2a**: 179.5 mg, 0.88 mmol), Ag_2CO_3 (270.9 mg, 0.98 mmol), HCl (25 μL, 4.0 M solution in 1,4-dioxane, 0.1 mmol), and dry 1,4-dioxane (2.5 mL) under a stream of argon. The vessel was sealed with O-ring tap, and then heated at 120 °C for 13 h with stirring. After cooling the reaction mixture to room temperature, the mixture was passed through a short silica gel pad (EtOAc). The filtrate was evaporated and *n*-undecane (internal standard for GC analysis) was added to the residue. The yields of 2-ethyl-5-phenylthiophene (**3aa**: 20 μmol), 5,5′-diethyl-2,2′-bithiophene (**7**: 3.3 μmol), and biphenyl (**6**: trace) were estimated by GC analysis.

4-8. C–H Bond Arylation of 1c with 2a Catalyzed by Pd complex 8



A 20-mL glass vessel equipped with J. Young® O-ring tap, containing a magnetic stirring bar, was flame-dried under vacuum and filled with argon after cooling to room temperature. To this vessel were added Pd complex **8** (25 mg, 50 μmol), 2-phenylthiophene (**1c**: 152.2 mg, 0.95 mmol), iodobenzene (**2a**: 199.0 mg, 0.98 mmol), Ag_2CO_3 (277.0 mg, 1.0 mmol), and dry 1,4-dioxane (5 mL) under a stream of argon. The vessel was sealed with O-ring tap, and then heated at 120 °C for 13 h with stirring. After cooling the reaction mixture to room temperature, the mixture was passed through a short silica gel pad (EtOAc). The filtrate was evaporated and *n*-undecane (internal standard for GC analysis) was added to the residue. The yields of 2-ethyl-5-phenylthiophene (**3aa**: 22 μmol, 44% yield based on **8**), 5,5′-diethyl-2,2′-bithiophene (**7**: 9.2 μmol), and biphenyl (**6**: trace) were estimated by GC analysis. The residue was then subjected to gel permeation chromatography ($CHCl_3$) to afford 2,5-diphenylthiophene (**3ca**: 101.7 mg, 0.43 mmol, 45% yield based on **1c**) as colorless solid.

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List of Publications

(副論文)

1. Direct C–H Arylation of (Hetero)arenes with Aryl Iodides via Rhodium Catalysis
   Shuichi Yanagisawa, Tomoko Sudo, Ryoji Noyori, Kenichiro Itami
   J. Am. Chem. Soc. **2006**, *128*, 11748–11749.

2. Direct Coupling of Arenes and Iodoarenes Catalyzed by a Rhodium Complex with a Strongly π-Accepting Phosphite Ligand
   Shuichi Yanagisawa, Tomoko Sudo, Ryoji Noyori, Kenichiro Itami
   Tetrahedron **2008**, *64*, 6073–6081.

3. Potassium *t*-Butoxide Alone Can Promote the Biaryl Coupling of Electron-Deficient Nitrogen Heterocycles and Haloarenes
   Shuichi Yanagisawa, Kirika Ueda, Tadashi Taniguchi, Kenichiro Itami
   Org. Lett. **2008**, *10*, 4673–4676.

4. Programmed Synthesis of Tetraarylthiophenes through Sequential C–H Arylation
   Shuichi Yanagisawa, Kirika Ueda, Hiromi Sekizawa, Kenichiro Itami
   J. Am. Chem. Soc. **2009**, *131*, 14622–14623.

5. Palladium/2,2′-bipyridyl/Ag_2CO_3 Catalyst for C–H Bond Arylation of Heteroarenes with Haloarenes: Development, Scope, and Mechanism
   Shuichi Yanagisawa, Kenichiro Itami
   Submitted.

（参考論文）

1. Coupling of Nitrogen Heteroaromatics and Alkanes without Transition Metals: A New Oxidative Cross-Coupling at C–H/C–H Bonds
Guojun Deng, Kirika Ueda, Shuichi Yanagisawa, Kenichiro Itami, Chao-Jun Li
Chem. Eur. J. **2009**, *15*, 333–337.

2. A General Catalyst for the β-Selective C–H Bond Arylation of Thiophenes with Iodoarenes
Kirika Ueda, Shuichi Yanagisawa, Junichiro Yamaguchi, Kenichiro Itami
Angew. Chem. Int. Ed. **2010**, *49*, 8946–8949.

3. *tert*-Butoxide-Mediated C–H Bond Arylation of Aromatic Compounds with Haloarenes
Shuichi Yanagisawa, Kenichiro Itami
ChemCatChem **2011**, *in press*.

4. Palladium/2,2′-bipyridyl/Ag_2CO_3 Catalyst for Oxidative Homo-Coupling of Heteroarenes
Satoshi Tani, Shuichi Yanagisawa, Kenichiro Itami
To be submitted.