学位論文

New C–H Coupling Reactions for Pharmaceutically Relevant Heterobiaryls

創薬関連ヘテロビアリール合成のための
新規 C–H カップリング反応の開発

YAMAGUCHI Kazuya

山口　和也

Preface

The studies described in this thesis have been carried out under the direction of Professor Kenichiro Itami at Department of Chemistry, Faculty of Science, Nagoya University from April, 2011 to March, 2013. The studies are concerned with new C–H coupling reactions for pharmaceutically relevant heterobiaryls.

The author would like to express his deepest gratitude to Professor Kenichiro Itami whose kind guidance, enormous supports and insightful comments were invaluable throughout this work. The author would like to express his great appreciation to Associate Professor Junichiro Yamaguchi whose opinions, information and encouragement have helped him very much throughout the production of this study. The author would like to thank Associate Professor Yasutomo Segawa for his helpful discussion, technical assistance, and the measurement of X-ray crystallography. The author is grateful to Dr. Hideto Ito and Associate Professor Shinya Hagihara for their constant advice and helpful discussion.

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Kazuya Yamaguchi

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General Introduction

Biaryls and heterobiaryls in pharmaceuticals

It has long been recognized that aromatic moieties play a major role in molecular recognition at the interface of chemistry and biology. For example, small-molecule drugs containing aromatic substituents bind to proteins predominantly by interactions with aromatic and hydrophobic residues. In addition, aromatics have been shown to form favorable interactions with polar substituents such as amides or hydroxyl groups, and even with positively charged moieties. Therefore, the biaryl/heterobiaryl moiety has received much attention as a privileged structure by the pharmaceutical industry,[1] and as a result, there are many drugs that contain biaryl/heterobiaryl moieties (Figure 1).[2] These drugs show diverse pharmacological effects for the treatment of hypertension, hyperlipidemia, hyperuricemia, insomnia, obesity, depression, diabetes, myelofibrosis, inflammatory, rheumatism, infection, osteoporosis, and cancer.

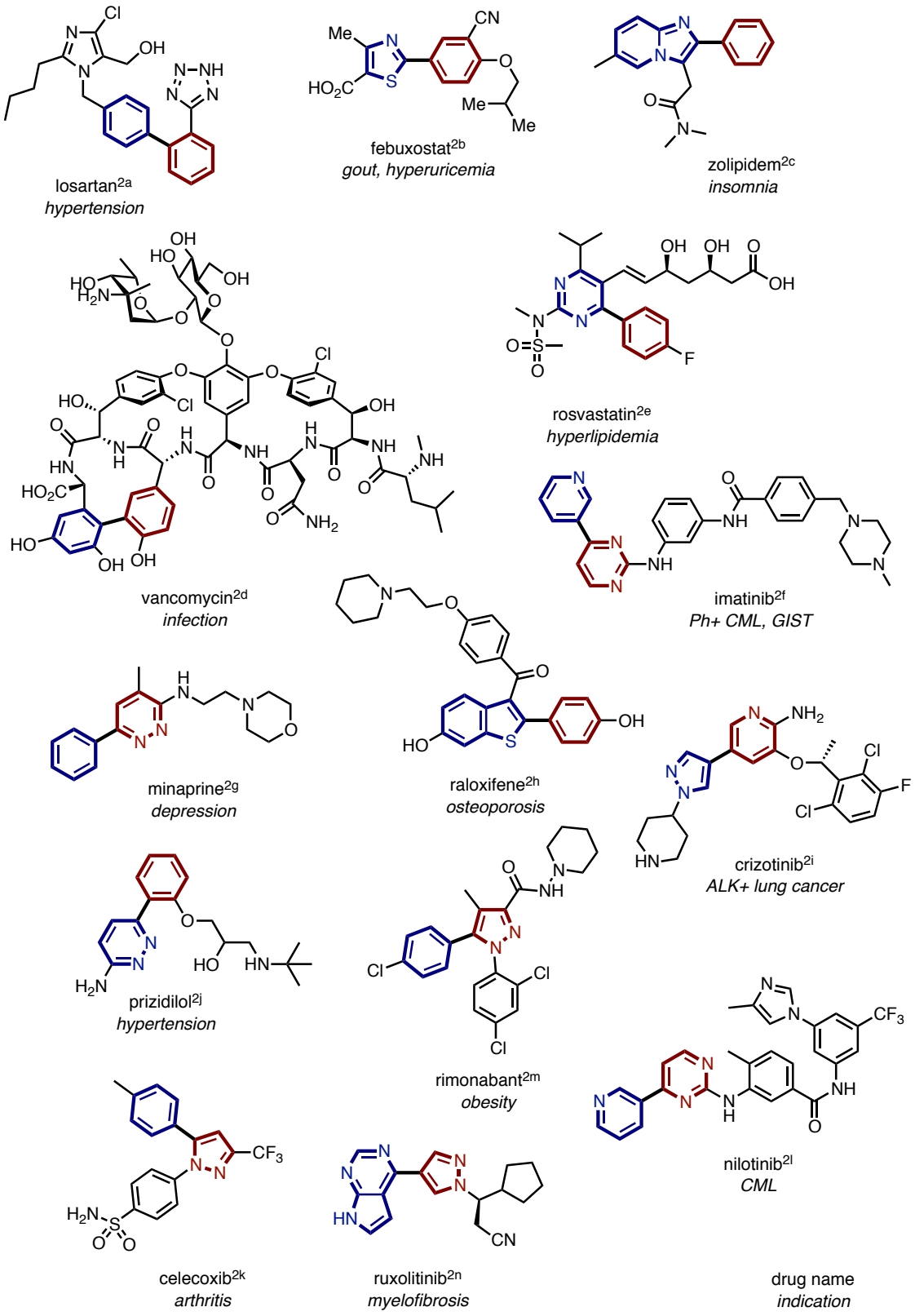


Figure 1. Examples of drugs containing biaryl/heterobiaryl moiety.[2]

The biaryl/heterobiaryl group consists of two aromatic rings whereby the combination of two aromatic rings generates diversity. In some cases, medicinal chemists adjust compound properties by changing the combination of two aromatic rings leading to improved binding affinities for target receptors, selectivity against other targets, superior ADMET (absorption, distribution, metabolism, excretion and toxicity) profiles, better solubility, stability and other drug-like properties, or novel intellectual property.[3] Methods to create a library of related medicinal compounds in a time-efficient manner are always in demand, and therefore countless methods for the functionalization of heteroaromatics have been developed.

The transition-metal catalyzed cross coupling reaction of metalated arenes/heteroarenes and halogenated arenes/heteroarenes is a representative way to construct biaryl and heterobiaryl frameworks.[4] This reliable technology has played a significant role in drug discovery and has supplied important compounds. Although it is an excellent way to construct the biaryl/heterobiaryl scaffold, there are several drawbacks. For example, metalated (hetero)arenes and halogenated (hetero)arenes can only be synthesized from simple (hetero)arenes after several steps. Therefore, the construction of biaryls/heterobiaryls using cross-coupling technology is inevitably lengthy.

Meanwhile, a direct C–H bond functionalization has recently emerged as a streamlined and an ideal method for C–C bond formation. Therefore, the transition metal catalyzed direct C–H arylation of arenes/heteroarenes has become a powerful tool to synthesize biaryls/heterobiaryls. To date, there are many reports on the direct arylation of various heteroarenes.[5] However, the direct arylation of arenes/heteroarenes has not been fully explored in terms of substrate scope.

In medicinal chemistry research, efforts in analog synthesis are always required to elucidate structure-activity relationships (SAR). Therefore, performing direct arylation of heteroarenes using various aryl substrates will allow for the diverse synthesis of analogs and contribute to the advancement of pharmaceutical industry. In this thesis, the author has developed the direct arylation of indazoles and hindered substrates, which are pharmaceutically important scaffolds.

Indazole: An indole bioisostere

Indazoles are present in a variety of heterocyclic drugs, which have shown a wide range of biological activities.[6] For example, pazopanib is a potent and selective multi-targeted tyrosine kinase inhibitor that blocks tumor growth and inhibits angiogenesis.[7] It has been approved for renal cell carcinoma in 2009 and soft tissue sarcoma in 2012 by the Food and Drug Administration (FDA) in the US. Axitinib is a prescription medicine used to treat advanced renal cell carcinoma when one prior drug treatment for this disease has not worked or has stopped working.[8] A serotonin 5-HT_3 receptor antagonist, granisetron has been used clinically to prevent nausea and vomiting following chemotheraphy.[9] YC-1 is a potent inhibitor of HIF-1α expression in hypoxic cancer cells,[10] and has been considered as one of the most attractive drug candidates due to its potent inhibitory activity against HIF-1α. Furthermore, indazole is a privileged structure which has shown diverse pharmacological effects, such as antiplatelet,[6c] neuroprotection,[6d] NOS inhibition[6e] and antitumor activity.[6f]

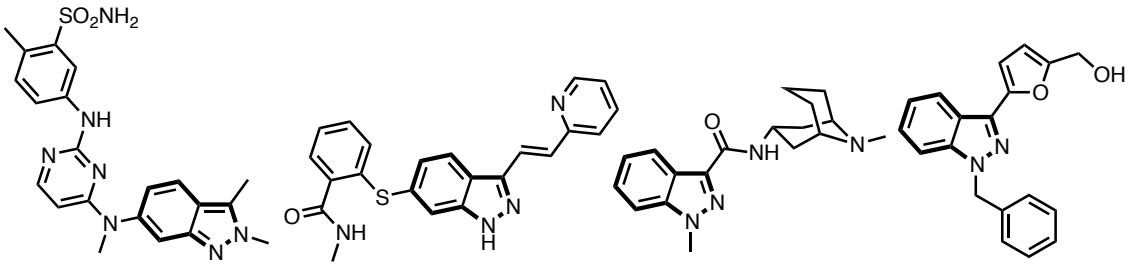
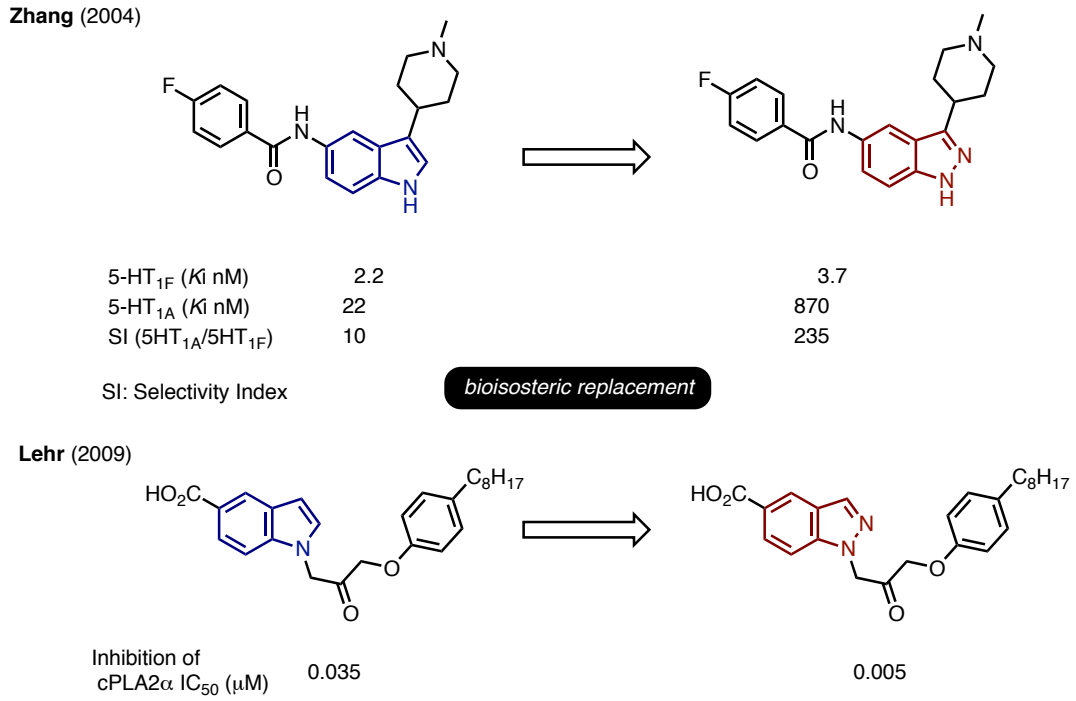


Figure 2. Examples of indazole containing drugs and bioactive compound.

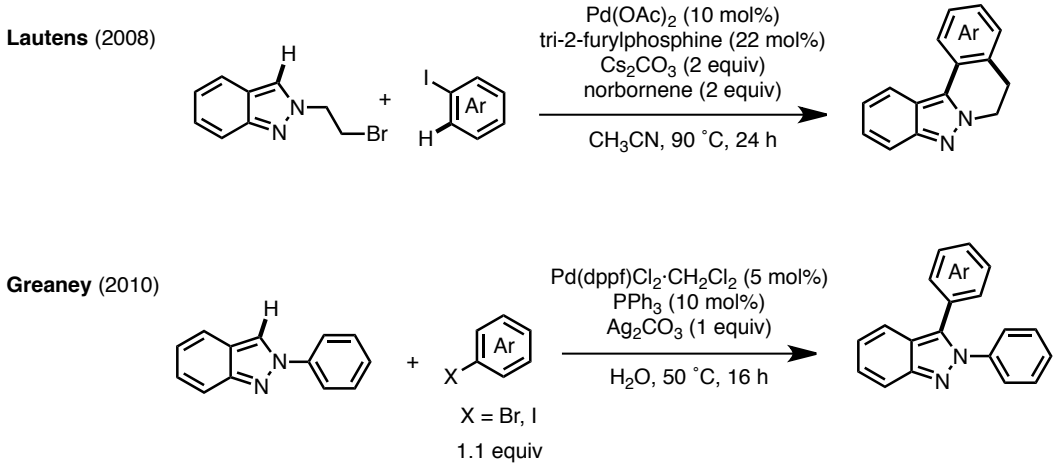
Bioisosteric replacement is a central approach in drug design and optimization that replaces substituents, functional groups, or scaffolds with alternative motifs while retaining similar biological properties.[11] Since indazole is a known as a bioisostere of indole, medicinal chemists have tried to bioisosterically replace indole with indazole with the goal of enhancing the desired biological or physical properties, and/or to decrease undesired properties. For example, Zhang and co-workers reported that a compound could be increased in selectivity without losing affinity to 5-HT_{1F} receptor, by bioisosterically replacing indole with indazole.[12a] Lehr and co-workers reported that a compound containing indazole shows higher activity against human phospholipase

A2α than containing indole (Scheme 1).[12b]



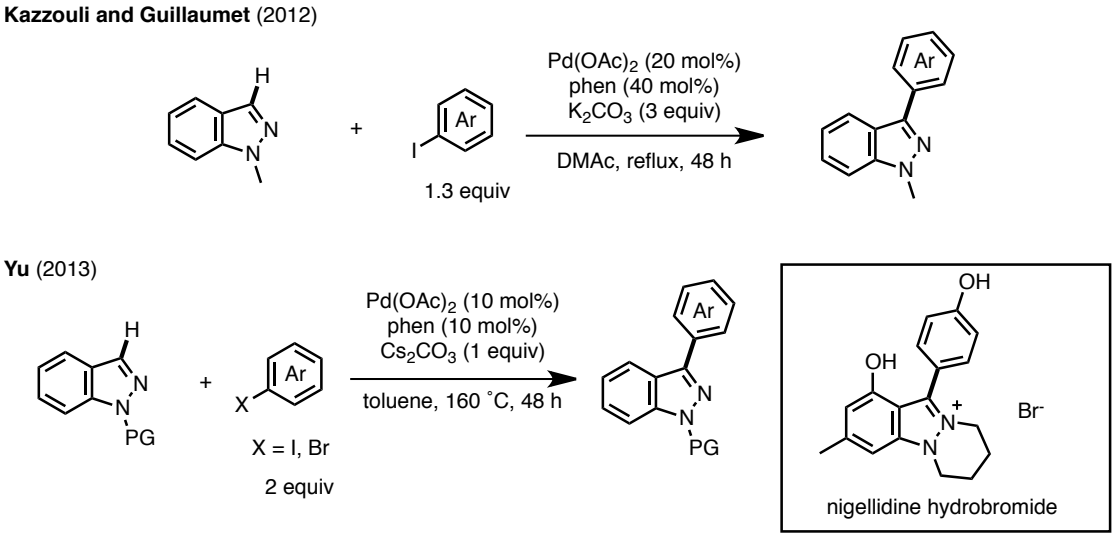
Scheme 1. Bioisosteric replacement from indole to indazole.

There are two indazole isomers, 1*H*-indazole and 2*H*-indazole, which differ by the position of the substituent on the nitrogen atom. Even though indazole is one of the most important structures in the pharmaceutical industry, there are few reports on the direct C–H bond arylation of indazole. In 2008, Lautens and co-workers reported a Pd-catalyzed intramolecular direct arylation of 2*H*-indazole.[13] In 2010, Greaney and co-workers reported a Pd-catalyzed direct arylation of 2*H*-indazole with haloarenes, which is the first time an arylation of indazole has been accomplished in an intermolecular setting.[14] These coupling reactions occur selectively at the C3 position of the indazoles. However, these reports have only focused on 2*H*-indazole and the arylation of 1*H*-indazole has not been reported thus far.



Scheme 2. Direct arylation of 2*H*-indazoles with haloarenes.

While the work described in this thesis was in progress, two reports on the direct arylation of 1*H*-indazole were disclosed: Kazzouli and Guillaumet reported a Pd-catalyzed direct arylation of 1*H*-indazole using haloarenes,[15] and Yu and co-workers reported the Pd-catalyzed direct arylation of 1*H*-indazole and applied it to the synthesis of nigellidine hydrobromide (Scheme 3).[16] These reactions both proceed under a $Pd(OAc)_2$/1,10-phenanthroline (phen) catalyst.



Scheme 3. Direct arylation of 1*H*-indazoles with haloarenes.

Hindered biaryls and heterobiaryls

Recently, medicinal chemists have been searching for ways to "escape from flat land," *i.e.*, planar aromatic compounds with a majority of the atoms in sp^2 hybridization. Researchers have made an effort to reduce aromatic rings, or to disrupt molecular planarity in their drug design. Lovering and co-workers analyzed drug and clinical candidate databases and reported that an increase in the fraction of sp^3 hybridized carbon atoms (Fsp3) is associated with a decrease in melting point.[17] They also showed that marketed drugs tend to have a higher Fsp3 than discovery compounds. More recently, Ritchie and Macdonald have shown a relationship between the number of aromatic rings and several properties such as solubility, CYP inhibition, plasma protein binding, and hERG binding, all of which influence the challenges inherent in developing a compound. They suggested that having fewer aromatic rings in the molecule is preferable for drug developability.[18] Furthermore, Ishikawa and Hashimoto suggested the importance of disruption of molecular planarity. In their review, inclusion of a hindered biaryl motif in a drug is illustrated as an alternative strategy for improving aqueous solubility by means of disruption of planarity.[19] Jorgensen reported that methyl substitution *ortho* to an aryl ring can be particularly effective at improving activity by inducing a propitious conformational change.[20] Thus, reducing the aromatic ring count is not the only means of increasing developability, but disruption of planarity by *ortho*-substitution is also effective. Therefore, *ortho*-substituted biaryls/heterobiaryls, (hindered biaryls/hetrobiaryls) are attractive scaffolds in the "escape from flat land" campaign. For example, vancomycin, a natural product derived from the soil bacterium Actinobacteria species *Amycolatopsis orientalis* has been used as an antibiotic agent. Fasiglifam (TAK-875), a potent GPR40 agonist has undergone phase III clinical trials for the treatment of type II diabetes (Figure 3).[2d,21]

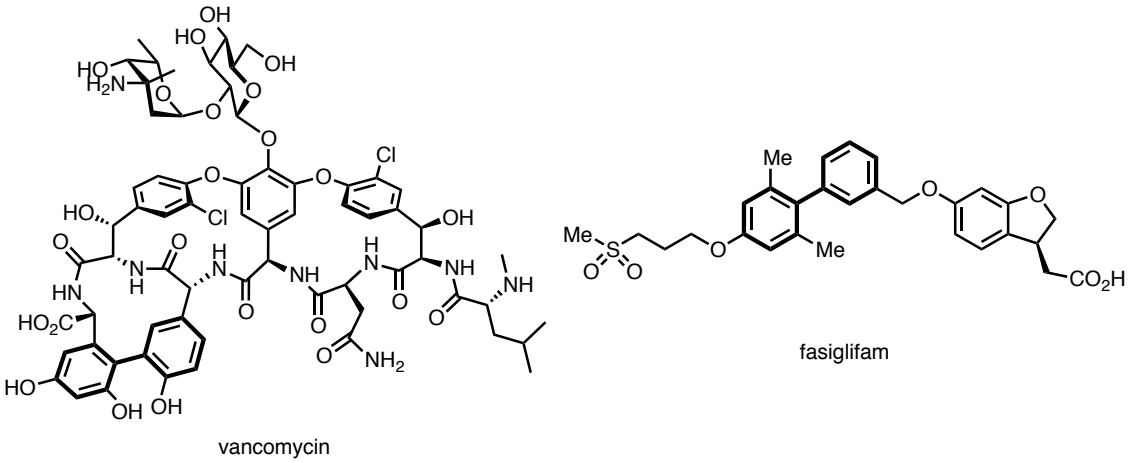
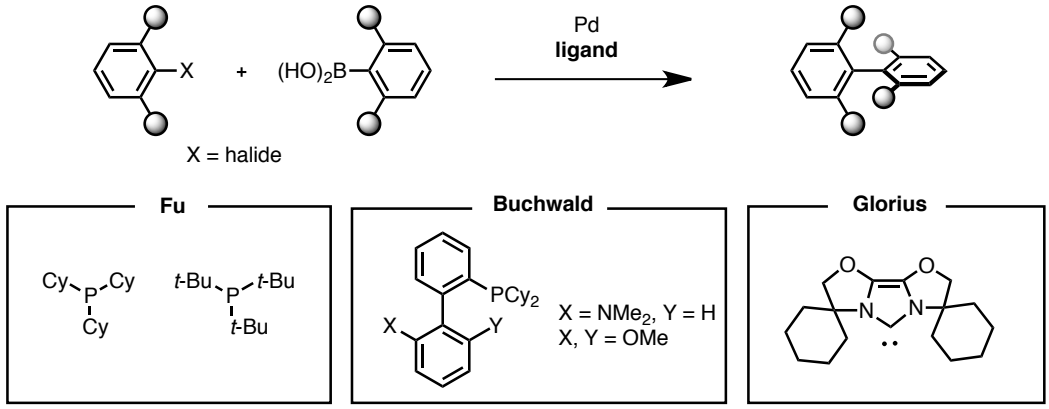


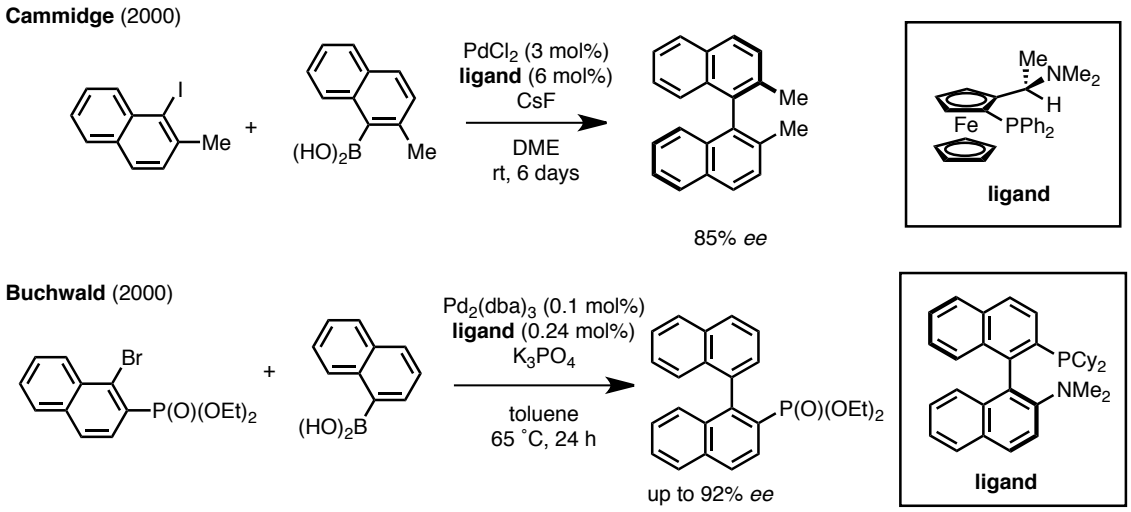
Figure 3. Vancomycin and fasiglifam.

Sterically hindered biaryls are important substructure of biologically active compounds and organic functional materials. However, the construction of hindered biaryl/heterobiaryl motifs is notoriously difficult. To date, the Pd-catalyzed cross coupling of arylboronic acids with aryl halides (Suzuki-Miyaura coupling) is the most reliable method to construct such hindered biaryls. Although numerous types of catalysts have been developed over the last few decades, the cross-coupling of sterically hindered substrates continues to be a significant challenge. To specifically address the low reactivity of hindered coupling partners, innovative families of ligands have been reported. For example, Fu and co-workers have developed Pd/PCy_3 and $Pd/P(t\text{-}Bu)_3$ to access *ortho*-disubstituted and trisubstituted biaryl compounds.[22] The Buchwald group has also introduced numerous dialkyl(biphenyl)phosphine ligands that enhance the activity of palladium catalysts.[23] Glorious and co-workers have developed sterically hindered *N*-heterocyclic carbene ligands, which allow room-temperature cross-coupling reactions using hindered haloarenes.[24]



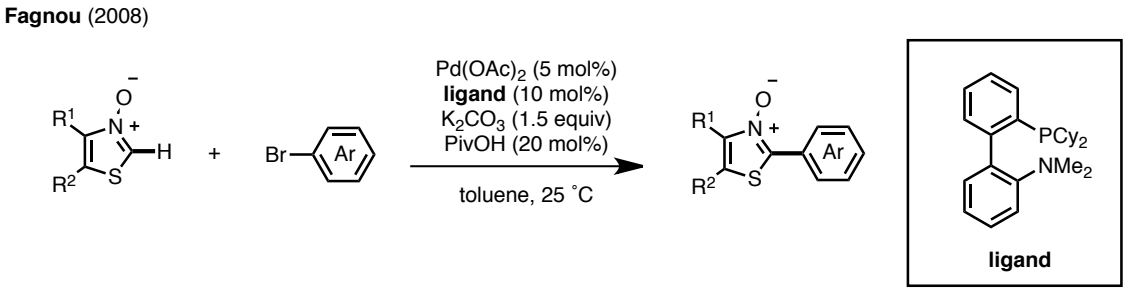
Scheme 4. Suzuki–Miyaura cross-coupling reaction and innovative families of ligands.

More recently, several chiral ligands for asymmetric Suzuki-Miyaura coupling have also been developed. The first asymmetric Suzuki-Miyaura coupling were independently reported by the groups of Cammidge and Buchwald.[25,26] Cammidge *et al*. reported that axially chiral binaphthalenes with up to 85% *ee* were synthesized from 2-methylnaphthylhalide and 2-substituted naphthylboronic acids using a chiral ferrocenylphosphine ligand. Buchwald and co-workers reported the synthesis of various axially chiral biaryls with up to 92% *ee* through asymmetric Suzuki-Miyaura coupling using a chiral binaphthyl-based electron rich phosphine ligand. Although there have been several reports on asymmetric Suzuki-Miyaura coupling[27] following these pioneering works, the development of further efficient catalysts is required.



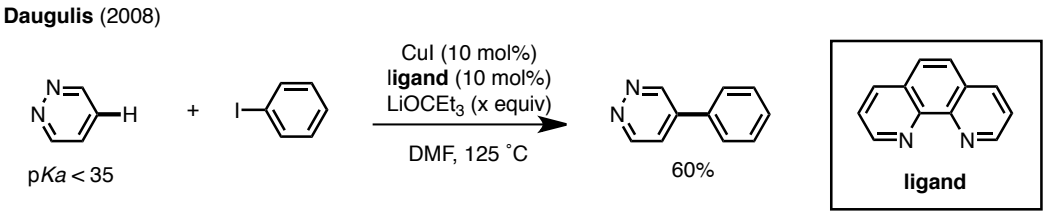
Scheme 5. Asymmetric Suzuki–Miyaura cross-coupling.

Meanwhile, the research area of transition-metal catalyzed direct arylation of aromatic compounds has generated powerful tools to synthesize biaryls/heterobiaryls. The development of catalysts has been essential to overcome limitations such as the need for reactivity or regioselectivity. In order to address such limitations, several groups have embarked on research programs in this area. For example, Fagnou and co-workers reported that the use of phosphine ligands can not only enhance the efficiency of the reaction, but also control the regioselectivity in heteroarenes substrates. When the combination of $Pd(OAc)_2$ and a phosphine ligand was used, C2-selective direct arylation of thiazole *N*-oxides with aryl bromides was achieved (Scheme 6).[28]



Scheme 6. Direct C2 arylation of thiazole *N*-oxides with haloarenes.

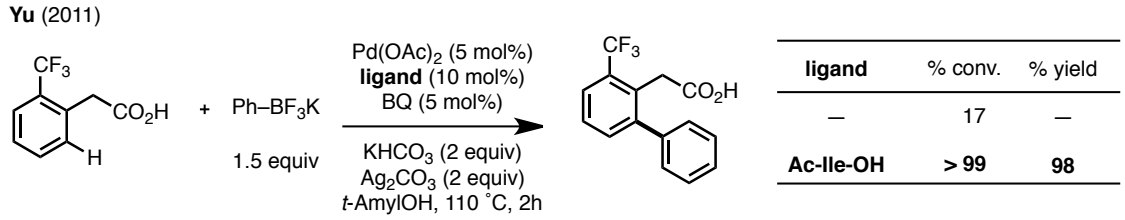
There are a number of other seminal publications in this field, of which the most recent representative examples are described below. Daugulis and co-workers reported a Cu-catalyzed direct arylation of sp^2 C-H bonds possessing pK_a's below 35 (pK_a values in DMSO). A variety of electron-rich and electron-poor heteroarenes can be arylated with iodoarenes using a CuI/phen catalyst and appropriate base (Scheme 7).[29]



Scheme 7. Cu/phen-catalyzed direct arylation of heteroarenes with haloarenes.

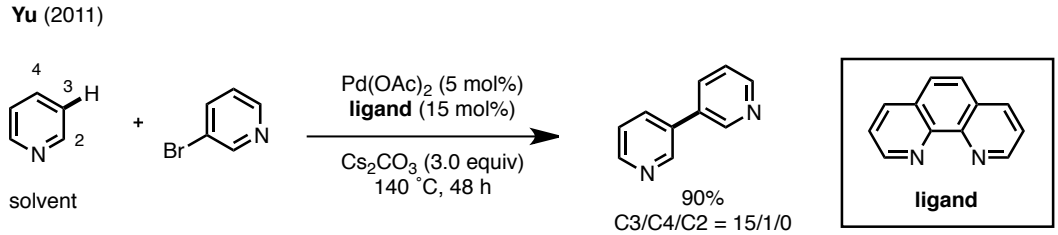
Yu and co-workers reported a "ligand-accelerated" Pd-catalyzed direct arylation of phenylacetic acid substrates with aryltrifluoroborates. Using Ac-Ile-OH as a ligand and

Ag_2CO_3 as an oxidant, a fast, high-yielding, operationally simple, and functional group-tolerant protocol has been developed for the cross-coupling of phenylacetic acid substrates with aryltrifluoroborates (Scheme 8).[30]



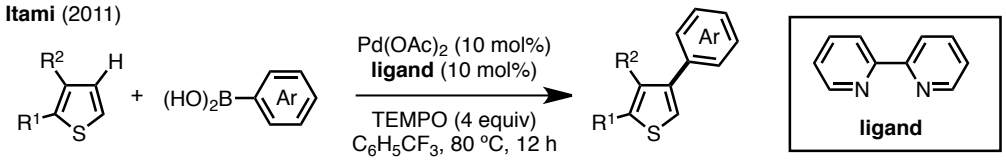
Scheme 8. Ligand-accelerated catalysis.

In 2011, Yu and co-workers also reported a Pd-catalyzed direct C3-selective arylation of pyridines by employing a catalytic system consisting of $Pd(OAc)_2$ and phen (Scheme 9). [31]



Scheme 9. Pd-cataylzed C3 arylation of pyridines.

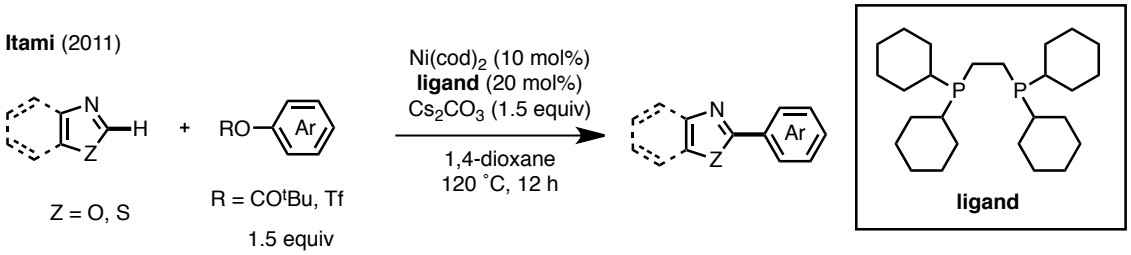
In 2011, our group reported an oxidative biaryl coupling of thiophene with arylboronic acids through $Pd(OAc)_2$/bipy/2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) catalysis. The reactions mostly occur in high yields and excellent regioselectivities (Scheme 10).[32]



Scheme 10. β-Selective arylation of thiophenes with arylboronic acids.

Our group has also reported a nickel-catalyzed C–H bond arylation of azoles with

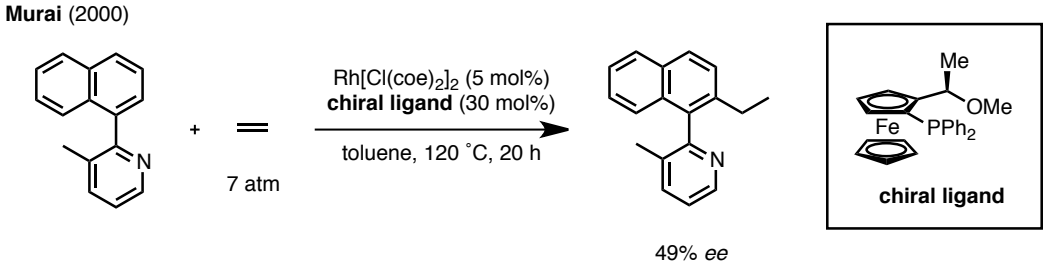
phenol derivatives. A new catalytic system, $Ni(cod)_2$/1,2-bis (dicyclohexylphosphino) ethane (dcype), is active for the coupling of various phenol derivatives such as esters, carbamates, carbonates, sulfamates, triflates, tosylates, and mesylates (Scheme 11).[33]



Scheme 11. Ni-catalyzed direct arylation of azoles with phenol derivatives.

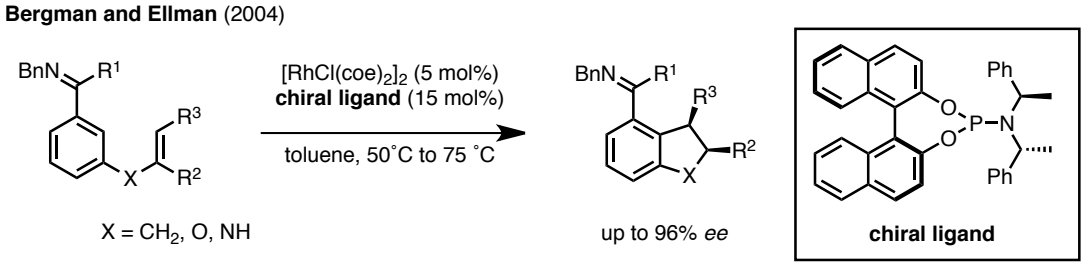
As described above, the transition-metal catalyzed direct arylation of aromatic compounds has received significant attention as a next generation cross-coupling technology, streamlining overall synthetic routes to biaryls/heterobiaryls. However, due to relatively low catalytic activity, there is no example of hindered biaryl formation that proceeds through a C–H coupling manifold, let alone enantioselective biaryl formation. The development of a catalyst that enables hindered biaryl synthesis by C–H coupling manifold is highly required.

Application of a catalytic system to carry out enantioselective C–H functionalization is a significant challenge. Although chiral organometallic intermediates [C–M]* could potentially be functionalized, enantioselective C–H functionalization has remained underdeveloped due to a paucity of appropriate ligands. There are, however, a few notable examples of enantioselective C–H functionalization that have been achieved using chiral catalysts. For example, Murai and co-workers reported the reaction of 2-(1-naphthyl)-3-methylpyridine with olefins in the presence of $[RhCl(coe)_2]_2$ and a chiral ferrocenyl phosphine ligand for the atropselective alkylation of naphthylpyridine derivatives. Ethylene reacted with biaryl substrates to give the corresponding addition products in moderate yields with up to 49% *ee* (Scheme 12).[34]



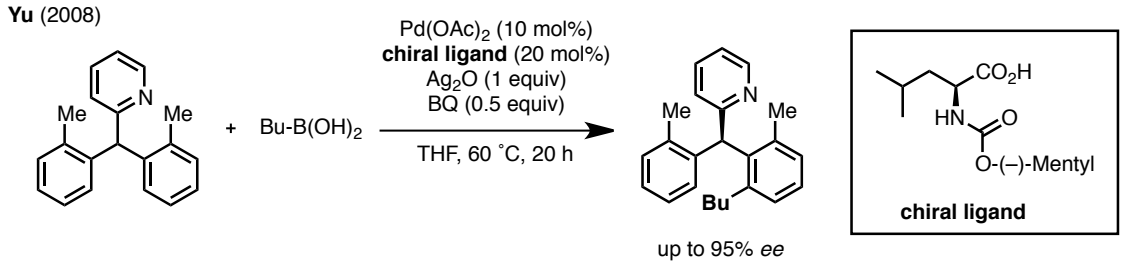
Scheme 12. Enantioselective alkylation of naphthylpyridine derivatives.

Bergman and Ellman have reported enantioselective intramolecular cyclizations. The reaction proceeds under the catalysis of Rh/chiral phosphoramidite ligand to afford cyclic compounds with high enantiomeric excess (Scheme 13).[35]



Scheme 13. Enantioselective intramolecular cyclization.

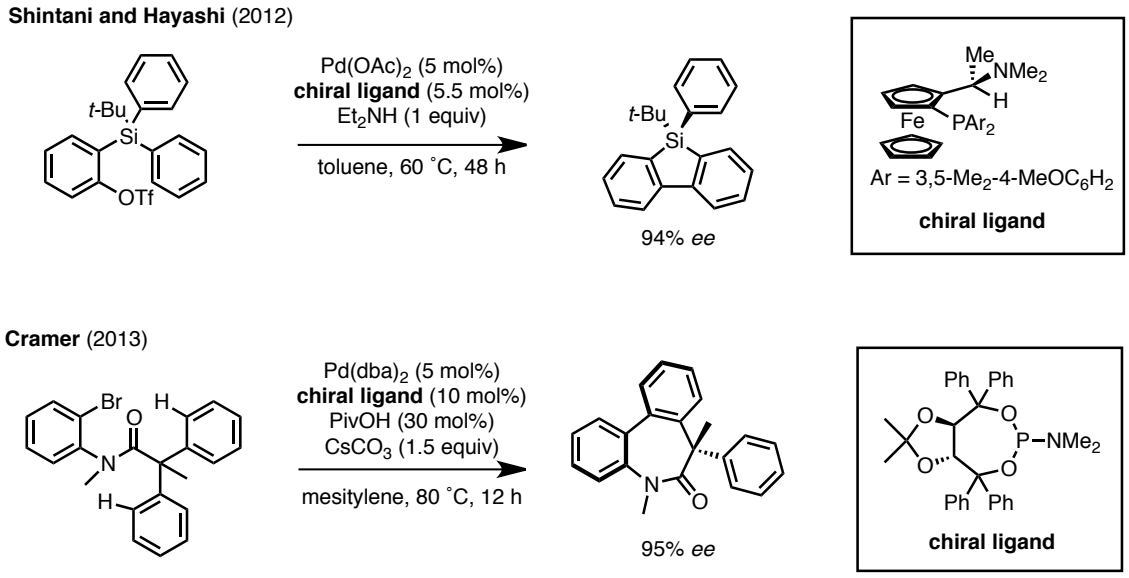
Yu recently reported an example of desymmetrizing aryl functionalization. Pd/amino acid complex capable of catalyzing an asymmetric activation of prochiral C(sp^2)–H and C(sp^3)–H bonds formed chiral products with new C–C bonds in excellent enantioselectivity (Scheme 14).[36]



Scheme 14. Enantioselective desymmetrization by C–H coupling.

Very recently, an enantioselective intramolecular direct arylation of aromatic

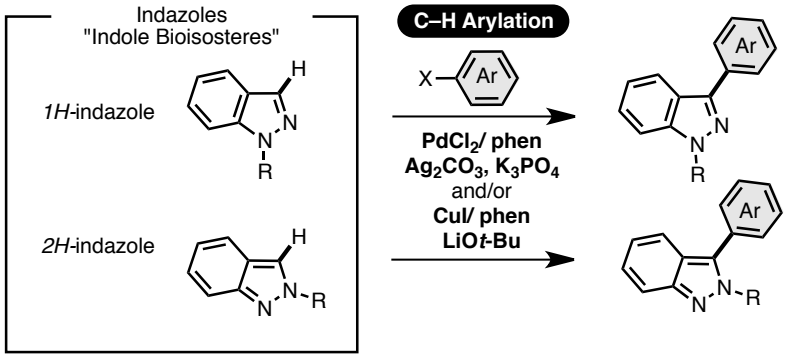
compounds has been disclosed. Shintani and Hayashi reported a Pd-catalyzed asymmetric synthesis of silicon-stereogenic dibenzosiloles via enantioselective C–H bond functionalization. High chemo- and enantioselectivity were achieved by employing a Josiphos-type ligand.[37] Cramer and co-workers reported an enantioselective Pd-catalyzed direct arylation to access highly functionalized dibenzazepinones with excellent selectivity.[38] The reaction proceeds smoothly under Pd/taddol-type phosphoroamidite ligand catalysis (Scheme 15).



Scheme 15. Axially chiral biaryls through intramolecular enantioselective C–H arylation.

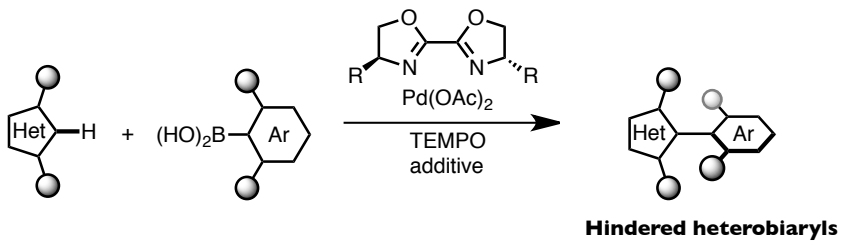
Survey of this thesis

Chapter 1 describes palladium- and copper-catalyzed C–H arylation reactions of 1*H*- and 2*H*-indazoles with haloarenes. The author disclosed that a $PdCl_2$/phen/Ag_2CO_3/K_3PO_4 catalytic system is effective for the C–H arylation of 1*H*- and 2*H*-indazoles with haloarenes, whereas a less expensive CuI/phen/LiO*t*-Bu catalytic system is applicable to the C–H coupling of substituted 2*H*-indazoles and iodoarenes (Scheme 16). The utility of this newly developed catalyst was demonstrated in the rapid synthesis of YC-1 (an antitumor agent) and YD-3 (platelet anti-aggregating agent).



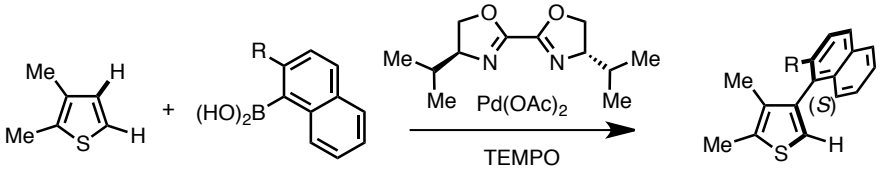
Scheme 16. Direct arylation of 1*H*- and 2*H*- indazoles with haloarenes.

Chapter 2 describes the synthesis of hindered heterobiaryls by C–H coupling and enantioselective C–H coupling. A $Pd(OAc)_2$/bisoxazoline/TEMPO system, which enables the synthesis of sterically hindered heterobiaryls has been identified (Scheme 17).



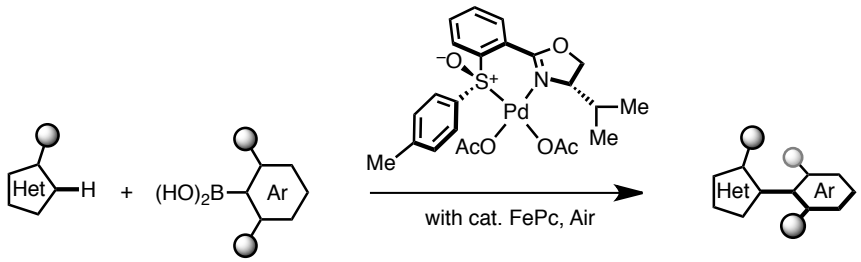
Scheme 17. Pd/bisoxazoline enables hindered biaryl formation by C–H coupling.

The newly established catalytic system not only enables the synthesis of sterically hindered heterobiaryls but also offers an opportunity for enantioselective biaryl coupling through C–H functionalization (Scheme 18).



Scheme 18. Enantioselective C–H coupling.

Chapter 3 describes the development of a second-generation catalyst for aromatic C–H coupling. A new catalytic system that requires neither a stoichiometric transition metal nor a stoichiometric oxidant for the oxidative coupling of arenes/alkenes with arylboronic acids (C–H/C–B coupling) has been established. A Pd(II)/sulfoxide–oxazoline (sox) ligand/iron-phthalocyanine (FePc) catalyst under air enables the synthesis of sterically hindered heterobiaryls and styrene derivatives. Additionally, this chemistry provided a preliminary approach toward an enantioselective biaryl coupling through C–H functionalization (Scheme 19).



Scheme 19. Aromatic C–H coupling with hindered arylboronic acids by Pd/Fe dual catalysts.

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Chapter 1

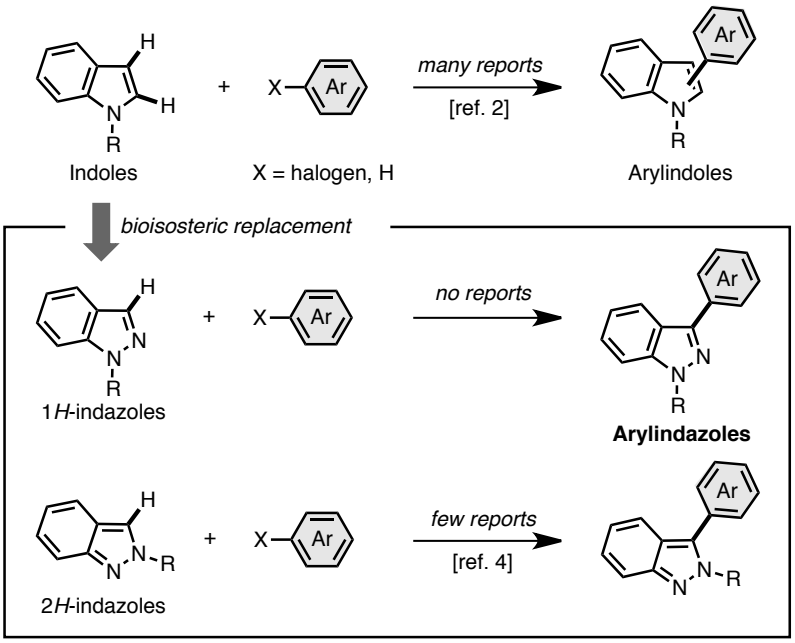
Pd- and Cu-catalyzed Direct C–H Arylation of 1*H*- and 2*H*-Indazoles

Abstract

Palladium- and copper-catalyzed C–H arylation reactions of 1*H*- and 2*H*-indazoles with haloarenes are described. A $PdCl_2$/phen/Ag_2CO_3/K_3PO_4 catalytic system is effective for the C–H arylation of 1*H*- and 2*H*-indazoles with haloarenes, whereas a less expensive CuI/phen/LiO*t*-Bu catalytic system is applicable to the C–H coupling of substituted 2*H*-indazoles and iodoarenes. The utility of the newly developed catalyst was demonstrated in the rapid synthesis of YC-1 (an antitumor agent) and YD-3 (platelet anti-aggregating agent). These new reactions represent important direct functionalization tools of indazoles, which are well-known bioisosteres of pharmaceutically important indole.

1. Introduction

It has been widely recognized that indazoles are not only pharmaceutically important structures, but are also as bioisosteres of indole in the field of medicinal chemistry. Recently, the C–H functionalization of heteroaromatics through transition-metal catalysis has received significant attention as it allows chemists to transform C–H bonds into other functional groups directly, thus saving time and costs of operation. While a number of indole C–H functionalization reactions (particularly C–H arylation) have been developed by various research groups,[1] the C–H functionalization of its bioisosteres, indazoles, is still very rare (Scheme 1). There is a necessity to develop a "chemical toolbox" that enables the rapid functionalization of heteroarene bioisosteres in medicinal chemistry. In an attempt to expand existing knowledge in the chemical manipulation of various heteroarene bioisosteres, we set out to develop the direct C–H arylation of indazoles. There are two indazole isomers, 1*H*-indazole and 2*H*-indazole, depending on the position of the *N*-substituent. Of these two isomers, the C–H arylation of 1*H*-indazoles has not yet been reported.[2,3] As for the C–H arylation of 2*H*-indazoles, there are two available methods reported by Lautens and Greaney using palladium catalysts.[4]



Scheme 1. C–H arylation of 1*H*- and 2*H*-indazoles, which are indole bioisosteres.

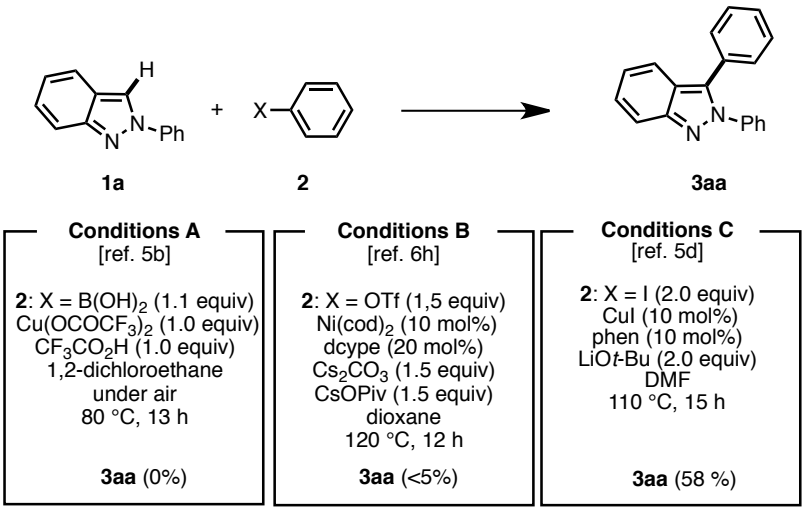
During a study aimed at developing reliable C–H arylation methods for indazoles, the author identified two effective catalytic systems based on palladium and copper. Key findings include (1) the accomplishment of the C–H arylation of 2*H*-indazoles with iodoarenes by a copper-based catalyst; (2) the development of a new palladium-based catalytic system for the C–H arylation of 1*H*- and 2*H*-indazoles with haloarenes; and (3) the application of palladium catalysis to rapid syntheses of biologically active compounds.

2. Results and discussion

2-1. Copper-catalyzed C–H arylation of 2*H*-indazoles

2-1-1. Discovery of copper-catalyzed C–H arylation

The author began this research project by attempting the C–H arylation of 2-substituted 2*H*-indazoles using inexpensive catalysts such as copper and nickel.[5,6] To this end, some representative catalysts and conditions that have previously been used for the C–H arylation of heteroarenes were applied (Scheme 2). The reaction of 2-phenyl-2*H*-indazole (**1a**) and an aryl reagent was used as a model reaction in this screening process. Although a copper-based oxidative C–H arylation protocol (conditions A)[5b] and a nickel-based protocol (conditions B)[6h] were totally ineffective, it was found that Daugulis' copper-based system promoted the reaction (conditions C).[5d] For example, treatment of **1a** (1.0 equiv) with iodobenzene (**2a**; 2.0 equiv) in the presence of CuI (10 mol%), 1,10-phenanthroline (phen; 10 mol%), and LiO*t*-Bu (2.0 equiv) in DMF at 110 °C for 15 h afforded 2,3-diphenyl-2*H*-indazole (**3aa**) in 58% yield.

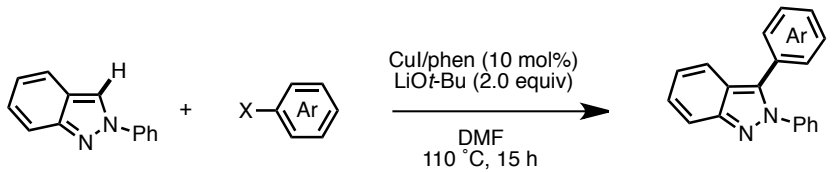


Scheme 2. Discovery of copper-catalyzed C–H arylation of 2*H*-indazoles.

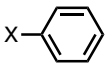
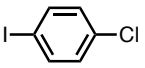
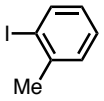
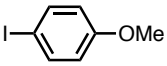
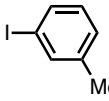
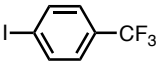
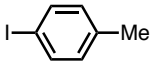
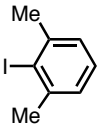
2-1-2. Substrate scope

Next, the scope and limitation of the copper-catalyzed C–H arylation of 2-substituted 2*H*-indazoles with various aryl halides were examined (Table 1). Whereas the use of iodobenzene gave product **3aa** in 58% isolated yield (entry 1), the use of bromobenzene resulted in a lower yield (entry 2). The use of *ortho*-substituted phenyl iodide **2b** furnished the desired coupling product in good yield (entry 3), as did *meta*- and *para*-substituted phenyl iodides (**2c** and **2d**; entries 4 and 5). Aryl iodides bearing electron-withdrawing groups (**2e** and **2g**), as well as those that bear electron-donating groups (**2f**), coupled smoothly with **1a** to provide the corresponding arylindazoles **3** in moderate yields (entries 6–8). Notably, sterically hindered aryl iodide **2h** was also an acceptable coupling partner for the C–H arylation of 2*H*-indazoles (entry 9).

Table 1. Effect of aryl coupling partners in the C–H arylation of 2-phenyl 2*H*-indazoles.

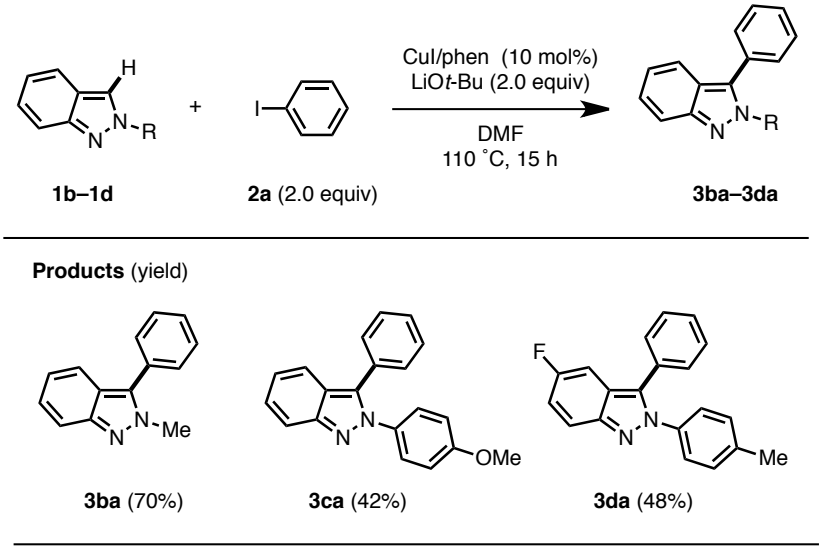


1a **2a–2h** **3aa–3ah**

Entry	2		3 (Yield, %)	Entry	2		3 (Yield, %)
1 2		X = I (**2a**) X = Br	**3aa** (58) **3aa** (4)	6		**2e**	**3ae** (46)
3		**2b**	**3ab** (66)	7		**2f**	**3af** (56)
4		**2c**	**3ac** (37)	8		**2g**	**3ag** (52)
5		**2d**	**3ad** (62)	9		**2h**	**3ah** (40)

This robust CuI/phen/LiO*t*-Bu catalytic system can also be applied to the C–H arylation of a variety of 2*H*-indazoles with iodobenzene (**2a**) (Table 2). Reaction of 2-alkylated 2*H*-indazoles such as **1b** afforded the corresponding coupling product **3ba** in higher yield when compared to the reaction of 2-phenyl-2*H*-indazole (**1a** to **3aa**). Methoxy and fluorine groups on 2-aryl-2*H*-lindazole (**1c** and **1d**) were tolerated to give products **3ca** and **3da** in moderate yields.

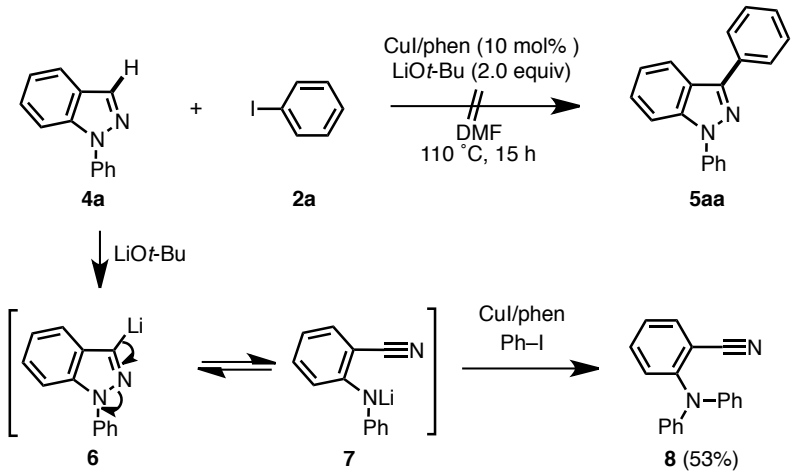
Table 2. Effect of indazole substituents in the C–H arylation of 2*H*-indazoles.



2-2. Palladium-catalyzed C–H arylation of 1*H*-indazoles

2-2-1. Discovery of a new palladium catalyst

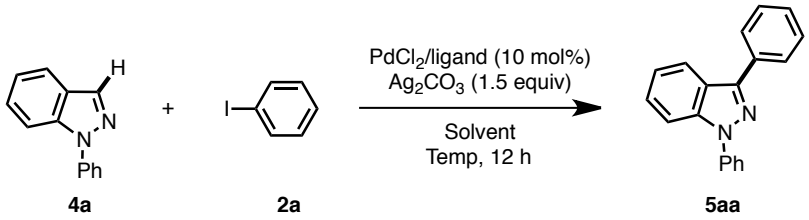
The author was able to demonstrate that Daugulis' copper-based catalytic system is applicable to the C–H arylation of various 2-substituted 2*H*-indazoles with aryl iodides. For the next challenge, the author decided to explore the hitherto unreported C–H arylation of 1*H*-indazoles. Initially, 1-phenyl-1*H*-indazole (**4a**) was treated with iodobenzene (**2a**) under the influence of CuI/phen/LiO*t*-Bu catalytic system (Scheme 3). However, the reaction did not yield the desired product **5aa**. Instead the reaction produced triphenylamine derivative **8** in 53% yield as the main product. This unexpected product **8** might be formed by the sequence consisting of (i) deprotonation of **4a** by strong base LiO*t*-Bu, (ii) ring-opening reaction of lithiated indazole **6** to afford nitrile **7**,[7] and (iii) Cu-catalyzed *N*-arylation reaction of **7** with iodobenzene (**2a**). To prevent this ring-opening reaction manifold, an electrophilic palladium catalytic system without using a strong base was investigated.



Scheme 5. Unexpected reaction of 1-phenyl-1*H*-indazole (**4a**) when using CuI/phen/LiO*t*-Bu.

In 2011, our group previously disclosed that a $PdCl_2$/2,2′-bipyridyl (bipy)/Ag_2CO_3 catalytic system is effective for the C–H arylation of thiophenes and thiazoles with iodoarenes.[8] Thus, the author began by applying these reaction conditions to the C–H arylation of 1-phenyl-1*H*-indazole (**4a**) with iodobenzene (**2a**) (Table 3). However, the standard conditions only gave the coupling product **5aa** in trace amounts (entry 1). By increasing the reaction temperature to 200 °C under microwave irradiation in *N*,*N*-dimethylacetamide (DMAc), the yield of **5aa** improved to 15% GC yield (entry 2). Interestingly, the use of 1,10-phenanthroline (phen) as a ligand resulted in much better yield (45% GC yield; entry 3), and the reaction also proceeded at lower temperature (165 °C) without microwave irradiation (entry 4).

Table 3. Discovery of palladium catalyzed C–H arylation of 1-phenyl-1*H*-indazole (**4a**) with iodobenzene (**2a**).



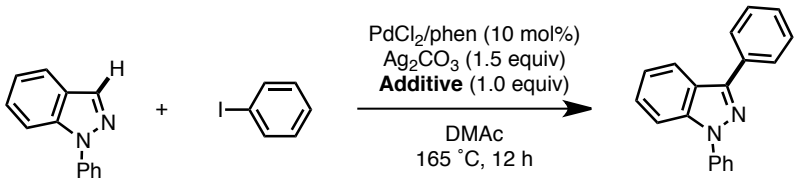
4a **2a** **5aa**

Entry	Ligand	Solvent	Temp (˚C)	Yield (%)[a]
1	bipy	dioxane	120	<1
2	bipy	DMAc	200[b]	15
3	phen	DMAc	200[b]	45
4	phen	DMAc	165	52

[a] Determined by GC analysis. [b] Microwave irradiation for 30 min.

After finding that $PdCl_2$/phen and Ag_2CO_3 are necessary for the reaction to occur, various additives were investigated (Table 4). Acetic acid and cesium pivalate (CsOPiv) were ineffective for the reaction (entries 1 and 2). The extra addition of base such as Cs_2CO_3, K_2CO_3 and K_3PO_4 was effective for the reaction (entries 3–5). Finally, it was found that the yield of **5aa** could be increased to 81% GC yield (60% isolated yield; entry 6) by increasing the amount of iodobenzene (**2a**) and K_3PO_4 to 2.0 equivalents relative to **4a**.

Table 4. Effect of additive in the C–H arylation of 1*H*-indazole.



4a **2a** (x equiv) **5aa**

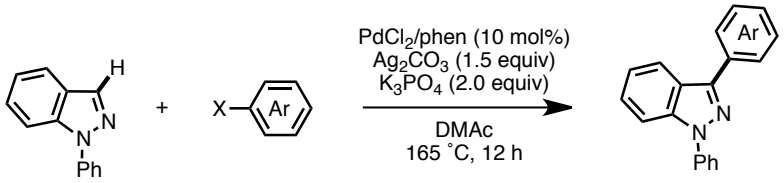
Entry	**2a** (Equiv)	Additive	Yield (%)[a]
1	1.5	AcOH	12
2	1.5	CsOPiv	11
3	1.5	Cs_2CO_3	62
4	1.5	K_2CO_3	44
5	1.5	K_3PO_4	55
6	2.0	K_3PO_4[c]	81 (60)[b]

[a] Determined by GC analysis. [b] Isolated yield. [c] 2.0 equiv of K_3PO_4 was used.

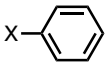
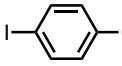
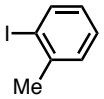
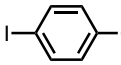
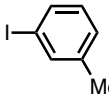
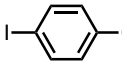
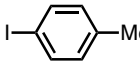
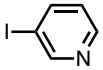
2-2-2. Substrate scope of 1*H*-indazole arylation

The C–H arylation of 1-phenyl-1*H*-indazole (**4a**) with iodobenzene (**2a**) was effectively promoted by $PdCl_2$ (10 mol%), phen (10 mol%), Ag_2CO_3 (1.5 equiv), and K_3PO_4 (2.0 equiv) in DMAc at 165 °C for 12 h to give **5aa** in 60% isolated yield (Table 5, entry 1). With this novel procedure in hand, the scope of applicable haloarenes was next examined (Table 5). When bromobenzene was used instead of iodobenzene as a coupling partner, the yield of **5aa** was decreased (11% yield; entry 2). The use of methyl-substituted iodobenzenes (**2b**–**2d**) successfully gave the resulting coupling products in good yields (entries 3–5). Furthermore, the reactions using iodoarenes bearing chloro (**2e**), methoxy (**2f**), and trifluoromethyl (**2g**) groups as well as 3-iodopyridine (**2i**) proceeded well to afford the corresponding coupling products in moderate yields (entries 6–9).

Table 5. Scope of haloarenes in the C–H arylation of 1-phenyl-1*H*-indazole (**4a**).

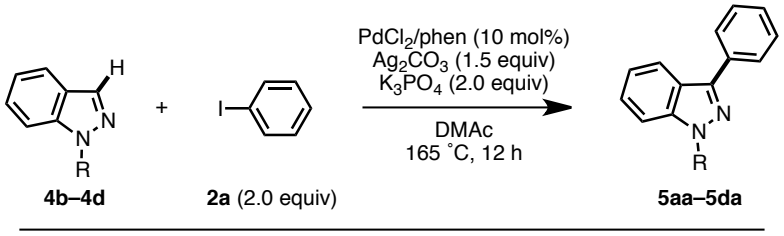


4a **2a–2i** (2.0 equiv) **5aa–5ai**

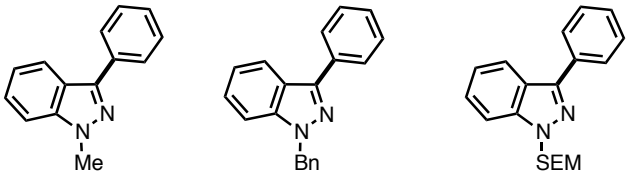
Entry	2		5 (Yield, %)	Entry	2		5 (Yield, %)
1 2		X = I (**2a**) X = Br	**5aa** (60) **5aa** (11)	6		**2e**	**5ae** (51)
3		**2b**	**5ab** (65)	7		**2f**	**5af** (54)
4		**2c**	**5ac** (72)	8		**2g**	**5ag** (71)
5		**2d**	**5ad** (80)	9		**2i**	**5ai** (50)

Substituents other than a phenyl group on 1*H*-indazole were also investigated (Table 6). Gratifyingly, the reactions of methyl-, benzyl-, and [2-(trimethylsilyl)ethoxy]methyl (SEM)-substituted 1*H*-indazoles (**4b**–**4d**) with iodobenzene (**2a**) took place smoothly to deliver the corresponding coupling products in moderate to good yields.

Table 6. Effect of indazole substituents in the C–H arylation of 1*H*-indazoles.



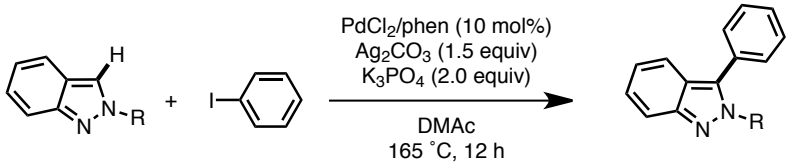
Products (yield)



5ba (62%) **5ca** (88%) **5da** (46%)

2-3. C–H arylation of 2*H*-indazoles under $PdCl_2$/phen/Ag_2CO_3/K_3PO_4 catalytic system

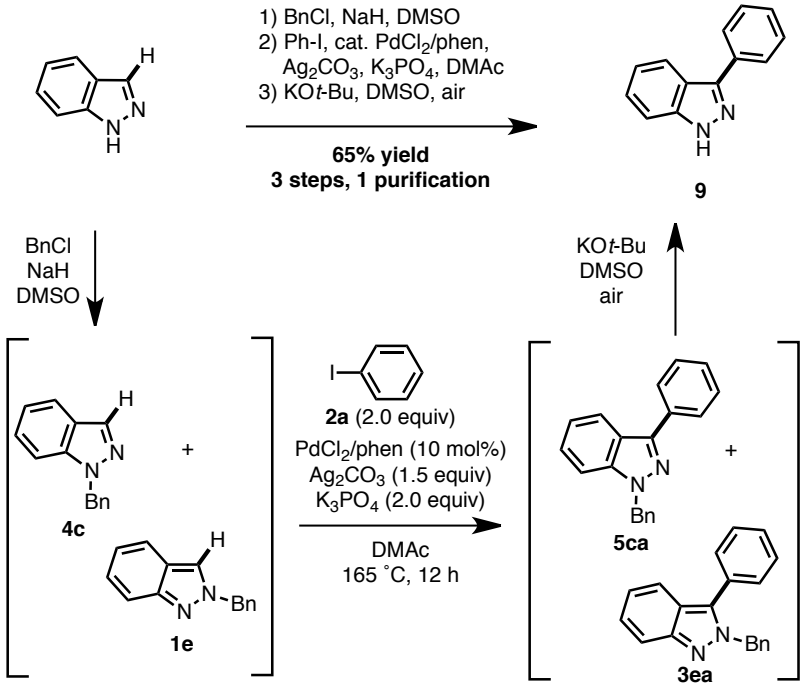
Notably, the newly developed palladium-based catalytic system turned out to be also effective for the C–H arylation of 2*H*-indazoles (Scheme 4). For example, under the influence of $PdCl_2$/phen/Ag_2CO_3/K_3PO_4, 2-phenyl-2*H*-indazole (**1a**) reacted with **2a** to give 2,3-diphenyl-2*H*-indazole (**3aa**) in 87% yield. Similarly, the reaction of 2-benzyl-2*H*-indazole (**1e**) with **2a** afforded 2-benzyl-3-phenyl-2*H*-indazole (**3ea**) in 68% yield. Thus, the $PdCl_2$/phen/Ag_2CO_3/K_3PO_4 system can be considered as a general catalytic protocol for the indazole C–H arylation reaction.



Scheme 4. C–H arylation of 2*H*-indazoles with iodobenzene (**2a**) under palladium catalysis.

Thereafter, the author questioned what would be the outcome of C–H arylation when an indazole bearing a free NH (*i.e.*, unsubstituted indazole; Scheme 5) is used in

the catalytic system. It was discovered that both palladium- and copper-based C–H arylation conditions (optimal conditions for 2-substituted 2*H*-indazoles and 1-substituted 1*H*-indazoles) were not effective. This problem was overcome by developing the following three-step sequence: i) benzylation of NH-free indazole, resulting in a mixture of benzylated 1*H*- and 2*H*-indazoles (**4c**/**1e** = 2:1); ii) palladium-catalyzed C–H arylation of the mixture of **4c** and **1e**, resulting in the C3-arylation of both compounds (**5ca**/**3ea** = 2:1); iii) debenzylation of the mixture of **5ca** and **3ea** with KO*t*-Bu in DMSO under air.[9] Using this method, *N*-unsubstituted 3-aryl-1*H*-indazole (**9**) can be obtained from unsubstituted indazole in 65% yield with only one purification.



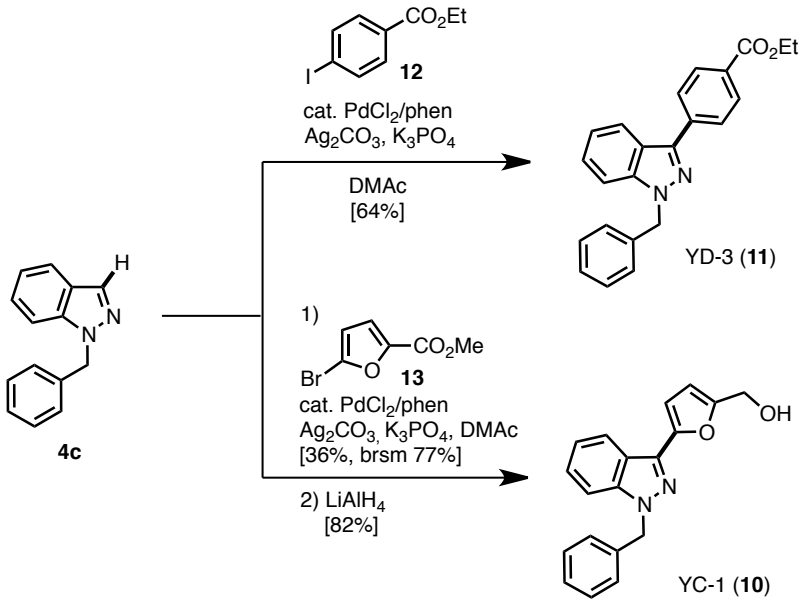
Scheme 5. C–H arylation of unsubstituted indazole.

2-4. Application to the synthesis of biologically active compounds

2-4-1. Syntheses of YC-1 and YD-3 by C–H arylation

To illustrate the utility of the developed arylation methodology of indazoles, the author applied it to the synthesis of biologically active compounds containing arylated indazole scaffold,[10] YC-1 (**10**) and YD-3 (**11**), which are known as a potent anti-tumor agent and platelet anti-aggregation agent, respectively. The syntheses of YD-3 (**11**) and

YC-1 (**10**) commenced with 1-benzyl-2*H*-indazole (**4c**), which was prepared by the benzylation of indazole (Scheme 7). This was then coupled with aryl halides **12** and **13** by the $PdCl_2$/phen/Ag_2CO_3/K_3PO_4 catalyst. The C–H coupling of **4c** and ethyl 4-iodobenzoate (**12**) delivered YD-3 (**11**) in 64% yield. The coupling of **4c** and methyl 5-bromofuran-2-carboxylate (**13**) afforded the resulting coupling product in 36% yield (77% based on recovered starting material). A subsequent reduction of the ester by $LiAlH_4$ yielded YC-1 (**10**) in 82% yield.



Scheme 7. Rapid synthesis of YD-3 (**11**) and YC-1 (**10**).

3. Conclusion

In summary, the palladium- and copper-catalyzed C–H arylation of 1*H*- and 2*H*-indazoles with haloarenes were identified. A $PdCl_2$/phen/Ag_2CO_3/K_3PO_4 catalytic system is effective for the C–H arylation of 1*H*- and 2*H*-indazoles with haloarenes, whereas a less expensive CuI/phen/LiO*t*-Bu catalytic system is applicable to the C–H coupling of substituted 2*H*-indazoles and iodoarenes. The utility of newly developed catalysts was demonstrated in the rapid synthesis of YC-1 (an antitumor agent) and YD-3 (platelet anti-aggregating agent). These new reactions not only represent important direct functionalization tools of indazoles, but also showcase the power of C–H functionalization to rapidly access arylated heteroaromatics. These studies lay the groundwork to continue establishing more methods for the "chemical toolbox" of heteroaromatic bioisostere synthesis.

4. Experimental section

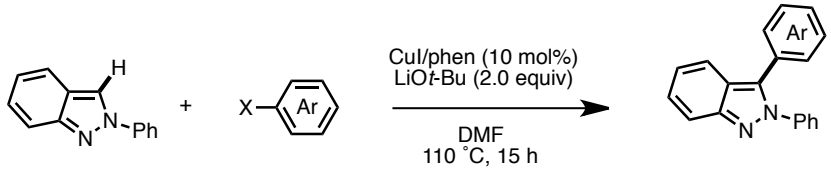
4-1. General

Unless otherwise noted, all materials including dry solvents were obtained from commercial suppliers and used as received. 1-Phenyl-1*H*-indazole,[11] 2-phenyl-2*H*-indazole,[12] 2-methyl-2*H*-indazole,[13] 1-benzyl-1*H*-indazole,[14] 1-SEM-1*H*-indazole,[15] 2-(4-methoxyphenyl)-2*H*-indazole,[12] and 5-fluoro-2-(*p*-tolyl)-2*H*-indazole[16] were synthesized according to procedures reported in the literature. All coupling reactions were performed in 10-mL glass Schlenk tubes equipped with J. Young® O-ring tap and heated in a 8-well reaction block (heater + magnetic stirrer). Other reactions were performed with dry solvents under an atmosphere of argon in flame-dried glassware with standard vacuum-line techniques. 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 F254 precoated plates (0.25 mm). The developed chromatogram was analyzed by UV lamp (254 nm). Flash column chromatography was performed with E. Merck silica gel 60 (230–400 mesh). Preparative thin-layer chromatography (PTLC) was performed using Wakogel B5-F silica coated plates (0.75 mm) prepared in our laboratory. Preparative high performance liquid chromatography (preparative HPLC) was performed with a Biotage Isolera®, one equipped with Biotage SNAP Cartridge KP-C18-HS columns using acetonitrile/water 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). LCMS analysis was conducted on Agilent Technologies 1200 series. High-resolution mass spectra (HRMS) were obtained from a JMS-T100TD instrument (DART). Nuclear magnetic resonance (NMR) spectra were recorded on JEOL JMN-GSX-270 (^{1}H 270 MHz) spectrometer, a JEOL JMN-A-400 (^{1}H 400 MHz) spectrometer and JEOL JMN-ECS400-B (^{1}H 400 MHz) spectrometer. Chemical shifts for ^{1}H NMR are expressed in parts per million (ppm) relative to tetramethylsilane (δ 0.0 ppm) or residual peak of DMSO (δ 2.50 ppm) and CD_2Cl_2 (δ 5.32 ppm). Chemical shifts for ^{13}C NMR are expressed in ppm relative to $CDCl_3$ (δ 77.0 ppm), CD_2Cl_2 (δ 53.8 ppm)

or DMSO (δ 39.5 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplet, t = triplet, q = quartet, m = multiplet, br = broad signal), coupling constant (Hz), and integration.

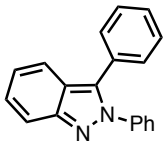
4-2. General procedure of copper-catalyzed C–H arylation of 2-substituted 2*H*-indazoles with iodoarenes.



1a **2a–2h** **3aa–3ah**

A 10-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 tube were added 2-substituted 2*H*-indazole (**1**: 0.40 mmol), CuI (7.6 mg, 0.04 mmol), 1,10-phenanthroline (7.2 mg, 0.04 mmol), LiO*t*-Bu (64 mg, 0.80 mmol), and haloarene (**2**: 0.80 mmol), followed by DMF (0.5 mL) under a stream of argon. The tube was sealed with O-ring tap, and then heated at 110 °C for 15 h in a 8-well reaction block with stirring. After cooling the reaction mixture to room temperature, the mixture was passed through a short pad of Celite® (EtOAc). The filtrate was concentrated and the residue was subjected to preparative HPLC (acetonitrile/water as an eluent) to afford the arylated product **3**.

4-3. Compound data of coupling products 3

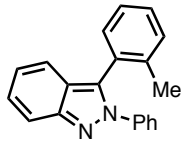


3aa

2,3-Diphenyl-2*H*-indazole (3aa).[17]

3aa (63 mg, 58%) was isolated as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 (d, *J* = 8.8 Hz, 1H), 7.71 (d, *J* = 8.6 Hz, 1H), 7.46–7.31 (m, 11H), 7.15–7.10 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.92, 140.15, 135.32, 129.82, 129.61, 128.92, 128.70, 128.24,

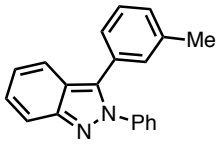
128.19, 126.93, 125.95, 122.45, 121.67, 120.46, 117.69; HRMS calcd for $C_{19}H_{15}N_2$ $[M+H]^+$: 271.1235, found: 271.1235.



3ab

2-Phenyl-3-(*o*-tolyl)-2*H*-indazole (3ab).[4b]

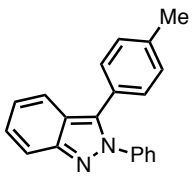
3ab (75 mg, 66%) was isolated as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (d, *J* = 8.6 Hz, 1H), 7.45–7.39 (m, 3H), 7.37–7.21 (m, 8H), 7.10–7.05 (m, 1H), 1.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.75, 140.33, 137.68, 135.14, 131.04, 130.56, 129.53, 129.17, 128.80, 127.79, 126.89, 125.97, 124.67, 122.50, 122.01, 120.62, 117.61, 19.81; HRMS calcd for $C_{20}H_{17}N_2$ $[M+H]^+$: 285.1392, found: 285.1392.



3ac

2-Phenyl-3-(*m*-tolyl)-2*H*-indazole (3ac).

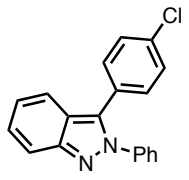
3ac (42 mg, 37%) was isolated as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (d, *J* = 8.8 Hz, 1H), 7.72 (d, *J* = 8.6 Hz, 1H), 7.47–7.32 (m, 6H), 7.27–7.07 (m, 5H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.93, 140.25, 138.44, 135.55, 130.18, 129.76, 129.07, 128.89, 128.58, 128.16, 126.92, 126.83, 125.96, 122.33, 121.68, 120.60, 117.68, 21.40; HRMS calcd for $C_{20}H_{17}N_2$ $[M+H]^+$: 285.1392, found: 285.1393.



3ad

2-Phenyl-3-(*p*-tolyl)-2*H*-indazole (3ad).[4b]

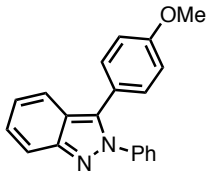
3ad (71 mg, 62%) was isolated as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, *J* = 8.6 Hz, 1H), 7.70 (d, *J* = 9.5 Hz, 1H), 7.46–7.34 (m, 6H), 7.27–7.23 (m, 2H), 7.20–7.18 (m, 2H), 7.14–7.11 (m, 1H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.96, 140.32, 138.27, 135.54, 129.51, 129.47, 128.93, 128.15, 126.91, 126.00, 122.27, 121.64, 120.61, 117.68, 21.31; HRMS calcd for $C_{20}H_{17}N_2$ $[M+H]^+$: 285.1392, found: 285.1388.



3ae

3-(4-Chlorophenyl)-2-phenyl-2*H*-indazole (3ae).[4b]

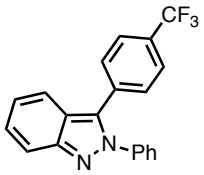
3ae (56 mg, 46%) was isolated as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (d, *J* = 8.8 Hz, 1H), 7.66 (d, *J* = 8.6 Hz, 1H), 7.44–7.33 (m, 8H), 7.30–7.24 (m, 2H), 7.17–7.12 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.93, 139.90, 134.37, 133.99, 130.77, 129.08, 129.05, 128.42, 128.29, 127.03, 125.94, 122.79, 121.64, 120.05, 117.83; HRMS calcd for $C_{19}H_{14}ClN_2$ $[M+H]^+$: 305.0846, found: 305.0849.



3af

3-(4-Methoxyphenyl)-2-phenyl-2*H*-indazole (3af).

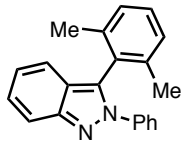
3af (67 mg, 56%) was isolated as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, *J* = 8.7 Hz, 1H), 7.69 (d, *J* = 8.5 Hz, 1H) 7.48-7.25 (m, 8H), 7.14–7.10 (m, 1H), 6.95–6.90 (m, 2H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.54, 148.91, 140.28, 135.34, 130.91, 128.94, 128.11, 126.89, 125.97, 122.16, 122.12, 121.55, 120.57, 117.64, 114.25, 55.24; HRMS calcd for $C_{20}H_{17}N_2O$ $[M+H]^+$: 301.1341, found: 301.1341.



3ag

2-Phenyl-3-(4-(trifluoromethyl)phenyl)-2*H*-indazole (3ag).

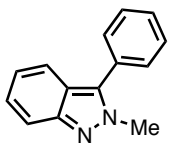
3ag (70 mg, 52%) was isolated as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 (d, *J* = 8.8 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 2H), 7.51–7.36 (m, 8H), 7.22–7.17 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.03, 139.84, 133.60, 133.51, 130.09 (q, *J* = 32.6 Hz), 129.81, 129.25, 128.68, 127.17, 126.02, 125.74 (q, *J* = 3.8 Hz), 123.88 (q, *J* = 274 Hz), 123.27, 121.89, 119.89, 118.03; HRMS calcd for $C_{20}H_{17}F_3N_2$ $[M+H]^+$: 339.1109, found: 339.1108.



3ah

3-(2,6-Dimethylphenyl)-2-phenyl-2*H*-indazole (3ah).

3ah (48 mg, 40%) was isolated as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (d, *J* = 8.8 Hz, 1H), 7.44–7.40 (m, 2H), 7.38–7.24 (m, 6H), 7.14–7.03 (m, 3H), 1.94 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.86, 140.38, 138.38, 134.25, 129.32, 129.20, 128.82, 127.77, 127.68, 126.91, 123.91, 122.15, 121.93, 120.53, 117.83, 20.25; HRMS calcd for $C_{21}H_{19}N_2$ $[M+H]^+$: 299.1548, found: 299.1553.

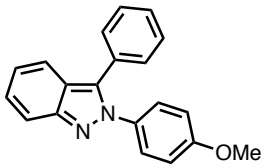


3ba

2-Methyl-3-phenyl-2*H*-indazole (3ba).[4b]

3ba (58 mg, 70%) was isolated as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71

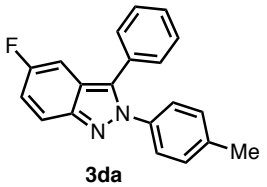
(d, *J* = 8.7 Hz, 1H), 7.58–7.44 (m, 6H), 7.32–7.28 (m, 1H), 7.09–7.04 (m, 1H), 4.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.97, 135.92, 129.62, 129.48, 128.91, 128.61, 126.16, 121.70, 121.09, 120.04, 116.90, 38.44; HRMS calcd for $C_{15}H_{13}N_2$ $[M+H]^+$: 209.1079, found: 209.1076.



3ca

2-(4-Methoxyphenyl)-3-phenyl-2*H*-indazole (3ca).[18]

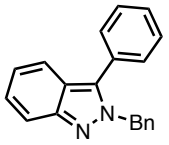
3ca (50 mg, 42%) was isolated as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, *J* = 8.6 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.42–7.32 (m, 8H), 7.16–7.10 (m, 1H), 6.88 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.29, 148.76, 135.21, 133.31, 129.95, 129.63, 128.71, 128.16, 127.12, 126.78, 122.31, 121.54, 120.43, 117.60, 114.09, 55.45; HRMS calcd for $C_{20}H_{17}N_2O$ $[M+H]^+$: 301.1341, found: 301.1341.



3da

5-Fluoro-3-phenyl-2-(*p*-tolyl)-2*H*-indazole (3da).

3da (58 mg, 48%) was isolated as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (dd, *J* = 9.3, 4.8 Hz, 1H), 7.41–7.24 (m, 8H), 7.19–7.11 (m, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.95 (d, *J* = 224 Hz), 146.25, 138.39, 137.64, 135.44 (d, *J* = 8.6 Hz), 129.71, 129.60, 129.46, 128.82, 128.33, 125.60, 121.01 (d, *J* = 11.4 Hz), 119.83 (d, *J* = 9.5 Hz), 118.41 (d, *J* = 29.6 Hz), 102.87 (d, *J* = 25.7 Hz), 21.14; HRMS calcd for $C_{20}H_{16}FN_2$ $[M+H]^+$: 303.1298, found: 303.1303.

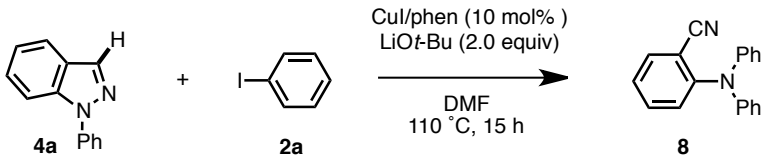


3ea

2-Benzyl-3-phenyl-2*H*-indazole (3ea).

Following the typical procedure (see Section 4-5), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 5:1) to give **3ea** (39 mg, 68%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) □ 7.76 (d, *J* = 8.2 Hz, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.53–7.40 (m, 5H), 7.36–7.21 (m, 4H), 7.12–7.03 (m, 3H), 5.64 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.34, 136.90, 136.47, 129.70, 128.97, 128.87, 128.68, 127.69, 126.88, 126.38, 121.88, 120.34, 117.46, 54.35; HRMS calcd for $C_{20}H_{17}N_2$ $[M+H]^+$: 285.1392, found: 285.1391

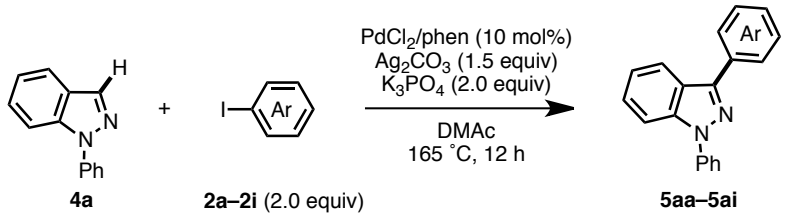
4-4. 2-(Diphenylamino)benzonitrile (8)



4a **2a** **8**

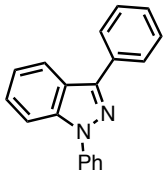
Following the general procedure (see Section 4-2), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 10:1) to give **8** (57 mg, 53%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.57 (d, *J* = 7.7 Hz, 1H), 7.46 (t, *J* = 7.1 Hz, 1H), 7.31–7.24 (m, 4H), 7.20–7.01 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.70, 147.12, 134.73, 133.70, 129.40, 127.37, 123.98, 123.82, 123.71, 117.02, 109.50; HRMS calcd for $C_{19}H_{15}N_2$ $[M+H]^+$: 271.1235, found: 271.1234.

4-5. General procedure of palladium-catalyzed C–H arylation of 1-substituted 1*H*-indazoles with iodoarenes.



To a flame dried 20-mL screw cap vessel containing a magnetic stirring bar were added 1-substituted 1*H*-indazole (**1**: 0.20 mmol), iodoarene (**2**: 0.40 mmol), $PdCl_2$ (3.5 mg, 0.02 mmol), 1,10-phenanthroline (3.6 mg, 0.02 mmol), Ag_2CO_3 (82.7 mg, 0.30 mmol), K_3PO_4 (84.9 mg, 0.40 mmol) and DMAc (0.8 mL). The mixture was stirred at 165 ˚C for 12 h. After cooling the reaction mixture to room temperature, the mixture was passed through a pad of short silica gel (EtOAc) and the filtrate was evaporated under reduced pressure. The residue was purified by preparative thin-layer chromatography to give the arylated product **5**.

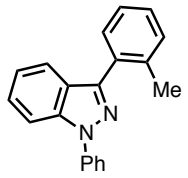
4-6. Compound data of coupling products 5



5aa

1,3-Diphenyl-1*H*-indazole (5aa).[19]

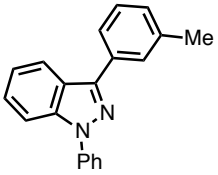
Following the general procedure, the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 10:1) to give **5aa** (33 mg, 60%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (d, *J* = 8.2 Hz, 1H), 8.05 (d, *J* = 7.7 Hz, 2H), 7.83–7.77 (m, 3H), 7.59–7.50 (m, 4H), 7.49–7.35 (m, 3H), 7.32–7.27 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.08, 140.31, 140.11, 133.20, 129.44, 128.82, 128.26, 127.77, 127.10, 126.67, 123.11, 123.00, 121.90, 121.59, 110.67; HRMS calcd for $C_{19}H_{15}N_2$ $[M+H]^+$: 271.1235, found: 271.1236.



5ab

1-Phenyl-3-(*o*-tolyl)-1*H*-indazole (5ab).

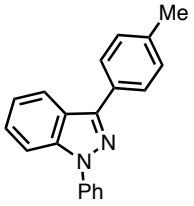
Following the general procedure, the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 10:1) to give **5ab** (37 mg, 65%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86–7.77 (m, 3H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.62–7.51 (m, 3H), 7.49–7.43 (m, 1H), 7.40–7.20 (m, 5H), 2.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.91, 140.24, 139.43, 137.41, 131.84, 130.84, 130.48, 129.39, 128.37, 127.10, 126.40, 125.72, 124.57, 122.64, 121.70, 121.59, 110.51, 20.68; HRMS calcd for $C_{20}H_{17}N_2$ $[M+H]^+$: 285.1392, found: 285.1392.



5ac

1-Phenyl-3-(*m*-tolyl)-1*H*-indazole (5ac).

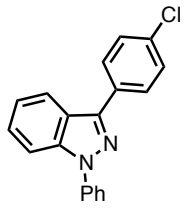
Following the general procedure, the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 10:1) to give **5ac** (41 mg, 72%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08 (d, *J* = 8.2 Hz, 1H), 7.89–7.75 (m, 5H), 7.59–7.52 (m, 2H), 7.49–7.34 (m, 3H), 7.31–7.23 (m, 2H), 2.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.24, 140.28, 140.11, 138.51, 133.05, 129.43, 129.08, 128.69, 128.39, 127.06, 126.64, 124.90, 123.15, 123.01, 121.83, 121.66, 110.62, 21.56; HRMS calcd for $C_{20}H_{17}N_2$ $[M+H]^+$: 285.1392, found: 285.1390.



5ad

1-Phenyl-3-(*p*-tolyl)-1*H*-indazole (5ad).

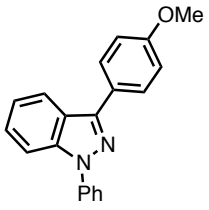
Following the general procedure, the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 10:1) to give **5ad** (45 mg, 80%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 2H), 7.83–7.76 (m, 3H), 7.59–7.52 (m, 2H), 7.48–7.43 (m, 1H), 7.40–7.32 (m, 3H), 7.31–7.25 (m, 1H), 2.45 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.15, 140.27, 140.16, 138.13, 130.32, 129.53, 129.43, 127.63, 127.03, 126.58, 123.15, 122.98, 121.77, 121.66, 110.62, 21.38; HRMS calcd for $C_{20}H_{17}N_2$ $[M+H]^+$: 285.1392, found: 285.1394.



5ae

3-(4-Chlorophenyl)-1-phenyl-1*H*-indazole (5ae).

Following the general procedure, the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 10:1) to give **5ae** (31 mg, 51%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (d, *J* = 8.2 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 2H), 7.79 (d, *J* = 7.7 Hz, 3H), 7.61–7.23 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.88, 140.38, 139.97, 134.15, 131.75, 129.50, 129.05, 128.90, 127.23, 126.87, 123.06, 122.89, 122.15, 121.29, 110.81; HRMS calcd for $C_{19}H_{14}ClN_2$ $[M+H]^+$: 305.0846, found: 305.0848.

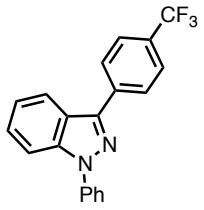


5af

3-(4-Methoxyphenyl)-1-phenyl-1H-indazole (5af).[20]

Following the general procedure, the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 10:1) to give **5af** (33 mg, 54%) as a white

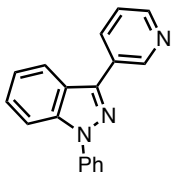
solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05 (d, *J* = 8.6 Hz, 1H), 8.01–7.95 (m, 2H), 7.82-7.95 (m, 3H), 7.58–7.51 (m, 2H), 7.47–7.42 (m, 1H), 7.39–7.33 (m, 1H), 7.30–7.24 (m, 1H), 7.10–7.04 (m, 2H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.75, 145.92, 140.23, 140.16, 129.41, 128.97, 127.02, 126.50, 125.80, 123.07, 122.90, 121.70, 121.61, 114.27, 110.60, 55.35; HRMS calcd for $C_{20}H_{17}N_2O$ $[M+H]^+$: 301.1341, found: 301.1344.



5ag

1-Phenyl-3-(4-(trifluoromethyl)phenyl)-1*H*-indazole (5ag).

Following the general procedure, the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 10:1) to give **5ag** (48 mg, 71%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.18 (d, *J* = 8.2 Hz, 2H), 8.07 (d, *J* = 8.2 Hz, 1H), 7.82–7.76 (m, 5H), 7.57 (t, *J* = 7.8 Hz, 2H), 7.43–7.38 (m, 1H), 7.41 (t, *J* = 10.6 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.45, 140.44, 139.83, 136.79, 136.79, 128.99 (q, *J* = 32.4 Hz), 129.53, 127.78, 127.33, 127.06, 125.74 (q, *J* = 3.8 Hz), 124.23 (q, *J* = 271.8 Hz), 123.12, 122.90, 122.43, 121.14, 110.92; HRMS calcd for $C_{20}H_{14}F_3N_2$ $[M+H]^+$: 339.1109, found: 339.1109.

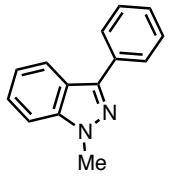


5ai

1-Phenyl-3-(pyridin-3-yl)-1*H*-indazole (5ai).

Following the general procedure, the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 1:1) to give **5ai** (27 mg, 50%) as a white solid. ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 9.29 (d, *J* = 2.3 Hz, 1H), 8.66 (dd, *J* = 4.5, 1.4 Hz, 1H), 8.37–8.31 (m, 1H), 8.09 (d, *J* = 8.2 Hz, 1H), 7.86–7.77 (m, 3H), 7.64–7.55 (m, 2H), 7.54–7.39 (m, 3H), 7.38–7.30 (m, 1H); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 149.67, 148.96,

143.34, 140.71, 140.36, 134.91, 129.90, 129.71, 127.75, 127.31, 124.09, 123.31, 123.27, 122.77, 121.45, 111.28; HRMS calcd for $C_{18}H_{14}N_3$ $[M+H]^+$: 272.1188, found: 272.1187.



5ba

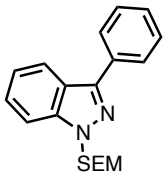
1-Methyl-3-phenyl-1*H*-indazole (5ba).

Following the general procedure, the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 10:1) to give **5ba** (26 mg, 62%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03 (d, *J* = 8.6 Hz), 7.96 (d, *J* = 7.3 Hz, 2H), 7.54-–7.47 (m, 2H), 7.46–7.37 (m, 3H), 7.25–7.18 (m, 1H), 4.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.69, 141.40, 133.66, 128.77, 127.78, 127.34, 126.23, 121.58, 121.32, 120.88, 109.17, 35.52; HRMS calcd for $C_{14}H_{13}N_2$ $[M+H]^+$: 209.1079, found: 209.1076.

5ca

1-Benzyl-3-phenyl-1*H*-indazole (5ca).[21]

Following the general procedure, the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 8:1) to give **5ca** (50 mg, 88%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03 (d, *J* = 8.2 Hz, 1H), 8.01–7.93 (m, 2H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.43–7.13 (m, 9H), 5.66 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.16, 141.04, 136.87, 133.64, 128.78, 128.69, 127.87, 127.68, 127.52, 127.12, 126.36, 122.09, 121.41, 121.09, 109.63, 53.06; HRMS calcd for $C_{20}H_{17}N_2$ $[M+H]^+$: 285.1392, found: 285.1394.

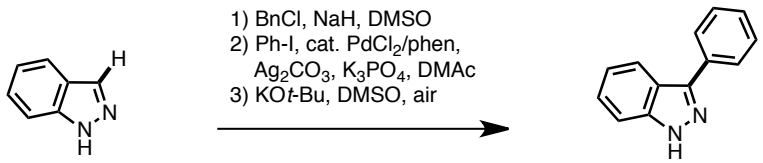


5da

3-Phenyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-indazole (5da).

Following the general procedure, the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 10:1) to give **5da** (30 mg, 46%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.02 (d, *J* = 8.2 Hz, 1H), 7.99–7.94 (m, 2H), 7.62 (d, *J* = 8.6 Hz, 1H), 7.55–7.39 (m, 4H), 7.30–7.24 (m, 1H), 5.80 (s, 2H), 3.67–3.60 (m, 2H), 0.95–0.88 (m, 2H), –0.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.85, 141.26, 133.37, 128.79, 128.10, 127.61, 126.72, 122.58, 121.66, 121.34, 109.95, 77.75, 66.42, 17.75, –1.47; HRMS calcd for $C_{19}H_{25}N_2OSi$ $[M+H]^+$: 325.1736, found: 325.1734.

4-7. Synthesis of 3-phenyl-1*H*-indazole (9).

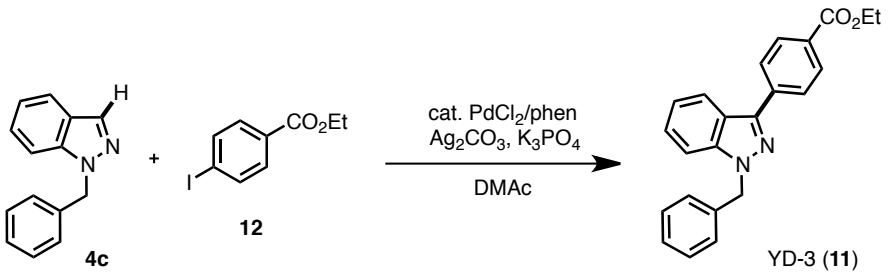


9

To a solution of 1*H*-indazole (24 mg, 0.20 mmol) in DMSO (2 mL) was added NaH (60% in oil, 9 mg, 0.21 mmol). After the mixture was stirred at room temperature for 20 min, benzyl chloride (24 mL, 0.21 mmol) was added, and the resultant mixture was stirred at room temperature for 2 h. The mixture was poured into water and extracted with EtOAc. The organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give the benzylated product as a mixture of **4c** and **1e**. The crude mixture was subjected to the C–H arylation with iodobenzene under $PdCl_2$/phen/Ag_2CO_3/K_3PO_4 catalyst (see Section 4-5). The reaction mixture was passed through a pad of short silica gel (EtOAc) and the filtrate was washed with water, brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give the mixture of **5ca** and **3ea**. Then to a solution of the crude in DMSO (2 mL) was added KO*t*-Bu (157 mg, 1.40 mmol) and stirred at room

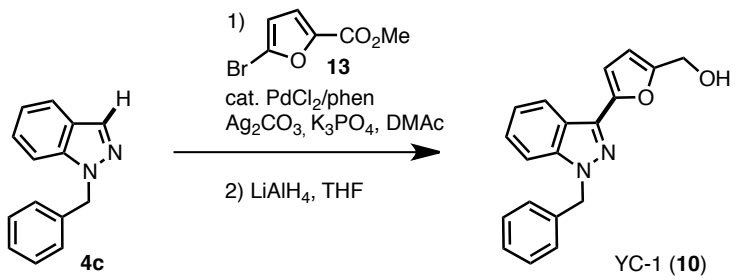
temperature for 3 h under air. The mixture was poured into water, and then extracted with EtOAc. The organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by preparative thin-layer chromatography (hexane/EtOAc = 2:1) to give **9** (25 mg, 65% from 1*H*-indazole) as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.75 (br s, 1H), 8.08–7.95 (m, 3H), 7.57–7.35 (m, 5H), 7.26–7.19 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.83, 141.66, 133.54, 128.88, 128.15, 127.63, 126.81, 121.40, 121.17, 121.01, 110.06; HRMS calcd for $C_{13}H_{21}N_2$ $[M+H]^+$: 195.0922, found: 195.0923.

4-8. Synthesis of YD-3 (11).[22]



Following the general procedure (see Section 4-5), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 10:1) to give YD-3 (**11**: 46 mg, 64%) as a white solid. ^{1}HNMR (DMSO-d_6, 400 MHz) δ 8.21–8.14 (m, 3H), 8.11 (d, J = 8.2 Hz, 1H), 7.82 (d, J = 8.2 Hz, 1H), 7.52–7.44 (m, 1H), 7.38–7.22 (m, 6H), 5.78 (s, 2H), 4.36 (q, J = 7.3 Hz, 2H), 1.36 (q, J = 7.3 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 165.51, 141.44, 140.98, 137.65, 137.20, 129.81, 128.77, 128.62, 127.61, 127.37, 126.73, 126.66, 121.94, 121.00, 120.92, 110.59, 60.76, 52.05, 14.20; HRMS calcd for $C_{23}H_{21}N_2O_2$ $[M+H]^+$: 357.1603, found: 357.1604.

4-9. Synthesis of YC-1 (10).[21]



To a flame dried microwave vessel in K_3PO_4 (85 mg, 0.40 mmol) were added **4c** (42 mg, 0.20 mmol), **13** (41 mg, 0.40 mmol), $PdCl_2$ (3.5 mg, 0.02 mmol), 1,10-phenanthroline (3.6 mg, 0.02 mmol), Ag_2CO_3 (28 mg, 0.1 mmol), and DMAc (0.8 mL). The mixture was heated at 200 ˚C for 5 min under microwave irradiation. To the reaction mixture were added **13** (41 mg, 0.40 mmol) and Ag_2CO_3 (28 mg, 0.1 mmol), then heated at 200˚C for 5 min. Then **13** (41 mg, 0.40 mmol) and Ag_2CO_3 (28 mg, 0.1 mmol) were added and heated at 200 ˚C for 5 min again. After cooling the mixture to room temperature, the mixture was passed through a pad of short silica gel (EtOAc) and the filtrate was evaporated under reduced pressure. The residue was semipurified by preparative thin-layer chromatography (hexane/EtOAc = 3:1) to give the corresponding coupling product (24 mg, 36%; 77% brsm) as a white solid and recovered starting material **4c** (21 mg, 49%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.26 (d, *J* = 8.5 Hz, 1H), 7.41–7.19 (m, 9H), 7.01 (d, *J* = 3.6 Hz, 1H), 5.65 (s, 2H), 3.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.18, 152.93, 143.56, 140.50, 136.28, 135.29, 128.75, 127.87, 127.08, 127.04, 122.10, 121.97, 121.72, 119.79, 109.62, 108.07, 53.39, 51.86; HRMS calcd for $C_{20}H_{17}N_2O_3$ $[M+H]^+$: 333.1239, found: 333.1239.

To a solution of the resulting coupling product (24 mg, 0.07 mmol) in THF (5 mL) was added $LiAlH_4$ (5.4 mg, 0.15 mmol) and stirred at room temperature for 2 h. Then $Na_2SO_4{\cdot}10H_2O$ (55 mg) was added and stirred at room temperature for 30 min. The mixture was passed through a pad of Celite® and the filtrate was concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography (hexane/EtOAc = 1:1) to give YC-1 (**10**: 18 mg, 82%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (d, *J* = 8.2 Hz, 1H), 7.45–7.17 (m, 8H), 6.88 (d, *J* = 3.2 Hz, 1H), 6.48 (d, *J* = 3.2 Hz, 1H), 5.66 (s, 2H), 4.75 (d, *J* = 5.0 Hz, 2H), 2.05-1.90 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.85, 148.65, 140.51, 136.57, 136.16, 128.71, 127.77, 127.04, 126.86, 121.51, 121.42, 121.33, 109.70, 109.63, 107.90, 57.64, 53.20; HRMS calcd for $C_{19}H_{17}N_2O_2$ $[M+H]^+$: 305.1290, found: 305.1291.

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Chapter 2

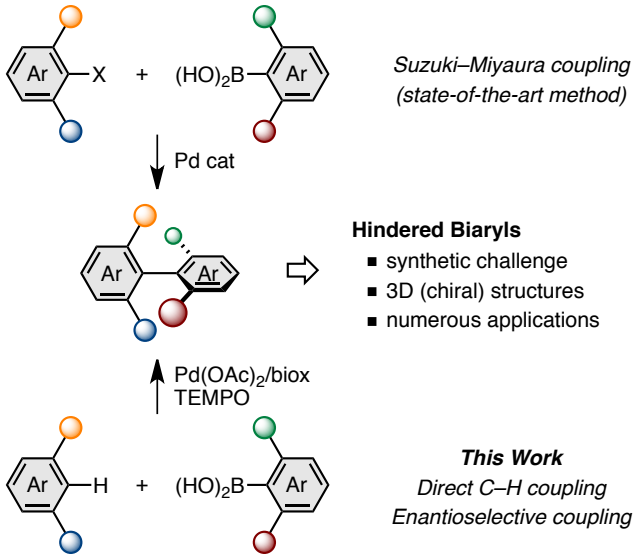
Hindered Biaryls by C–H Coupling: Bisoxazoline-Pd Catalysis Leading to Enantioselective C–H Coupling

Abstract

A new Pd-catalyzed C–H/C–B coupling of sterically hindered heteroarenes and arylboronic acids has been identified. The newly established $Pd(OAc)_2$/bisoxazoline/TEMPO system not only enables the synthesis of sterically hindered heterobiaryls but also offers an opportunity for enantioselective biaryl coupling through C–H functionalization.

1. Introduction

Sterically hindered biaryls and heterobiaryls with multiple *ortho*-substituents have numerous applications.[1] To date, the Pd-catalyzed coupling of arylboronic acids with aryl halides (Suzuki–Miyaura coupling) is the most reliable method to construct biaryls.[2] Although numerous types of catalysts have been developed over the last few decades, the cross-coupling of sterically hindered substrates continues to be a significant challenge (Scheme 1). To specifically address the low reactivity of hindered coupling partners, innovative families of ligands have been reported.[3] On the other hand, despite recent progress of the transition-metal-catalyzed direct C–H arylation of aromatic compounds, due to the relatively low catalytic activity, there is virtually no example of hindered biaryl formation that proceeds through a C–H coupling manifold. Inspired by the recent success of Yu demonstrating that amino acid ligands accelerate some Pd-catalyzed C–H functionalization reactions,[8,9] the author envisioned that the discovery of an enabling ligand is crucial to realize C–H arylations leading to hindered biaryls. In this chapter, the author describes the first efficient catalyst that enables the synthesis of hindered heterobiaryls by direct C–H coupling (Scheme 1). The discovery of bisoxazoline-Pd catalysis led to the demonstration of the first enantioselective biaryl coupling through C–H functionalization.[5]



Scheme 1. Sterically hindered biaryls by direct C–H coupling.

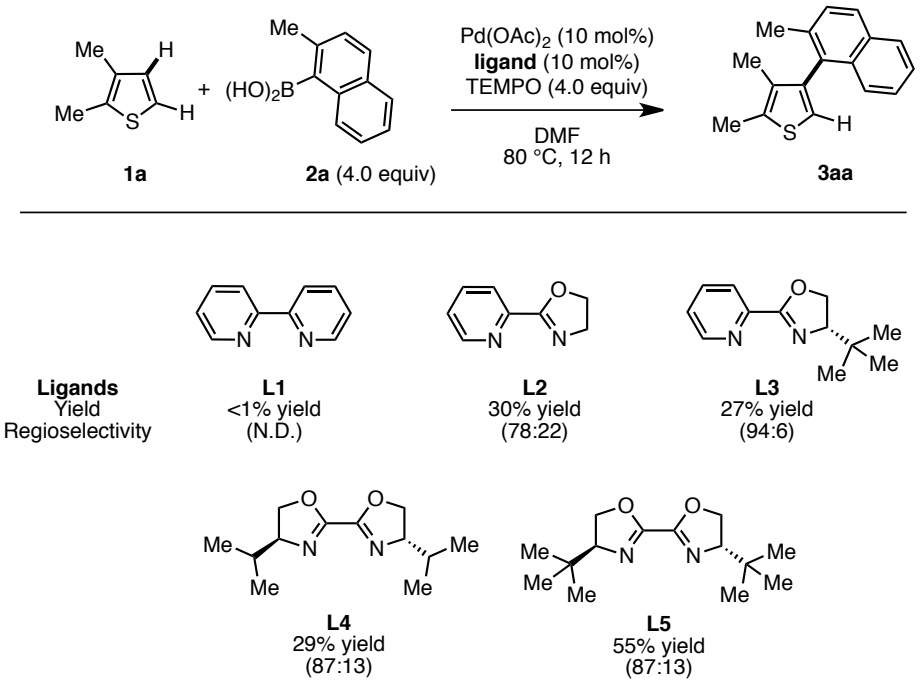
2. Results and discussion

2-1. Hindered biaryls by C–H coupling

2-1-1. Discovery of bisoxazoline ligand

The author decided to revisit one of the aromatic C–H arylation reactions developed in our group[7] to identify ligands capable of forming hindered biaryls (Table 1). In 2011, our group developed the β-selective C–H arylation of thiophenes with arylboronic acids.[7f] The reaction is typically promoted by $Pd(OAc)_2$ (10 mol%), 2,2′-bipyridyl (bipy, **L1**: 10 mol%), and 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO: 4 equiv) in DMF or $C_6H_5CF_3$ at 80 °C.[10] Although the reaction proceeds well and with high β regioselectivity for unhindered substrates, the above-mentioned conditions cannot be applied toward making hindered biaryls. For example, when 2,3-dimethylthiophene (**1a**) and 2-methylnaphthalen-1-ylboronic acid (**2a**) were reacted, the corresponding coupling product (**3aa**) was not formed (Table 1). Thus, the author rescreened ligands using **1a** and **2a** as model hindered substrates. Gratifyingly, when 2-(2′-pyridyl)oxazoline (pyox: **L2**) was used as the ligand, the desired coupling product **3aa** was obtained in 30% yield. Furthermore, 2,2′-bis(2-oxazoline) ligands (biox: **L4** and **L5**) were found to increase the yield of the product **3aa** to 29% and 55%, respectively.

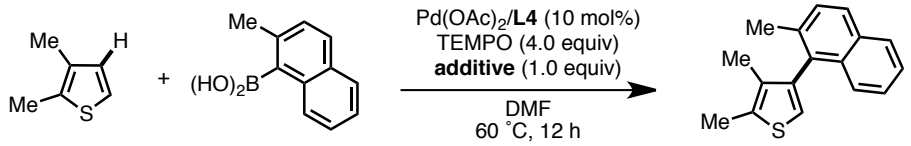
Table 1. Discovery of bisoxazoline-Pd catalysis for the C–H arylation of thiophenes with arylboronic acids.



2-1-2. Reaction optimization

With effective bisoxazoline ligands (**L4** and **L5**) in hand, the author further examined screening of reaction conditions. The effect of reaction parameters (additives, equivalents of CF_3CO_2H, catalytic amount of $Pd(OAc)_2$, ligand, equivalents of TEMPO, and reaction atmosphere) was investigated. The arylation of 2,3-dimethylthiophene (**1a**) with 2-methylnaphthalen-1-ylboronic acid (**2a**) was used as the model reaction, for which the author investigated the effect of additives (Table 2). The reaction was conducted under the conditions of **1a** and **2a** (4 equiv) with $Pd(OAc)_2$/**L4** catalyst, TEMPO (4 equiv) and additive (1 equiv) in DMF at 60 ˚C for 12 h. Added alcohols such as MeOH and *i*-PrOH hardly changed the reaction outcome (entries 1 and 2). When acetic acid or pivalic acid was added, the yields of **3aa** were increased to 55% and 59%, respectively (entries 3 and 4). Finally, it was found that when trifluoroacetic acid was added, **3aa** was obtained in 74% yield with excellent C4 regioselectivity (entry 5).

Table 2. Effect of additive.



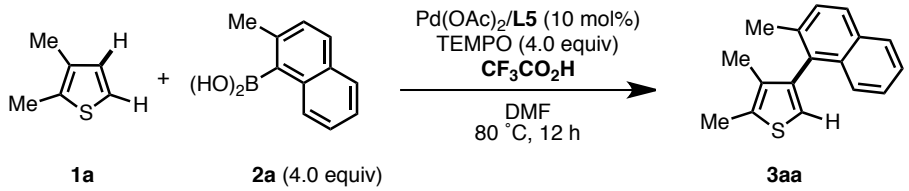
1a **2a** (4.0 equiv) **3aa**

Entry	Additive	Yield (%)[a]	C4/C5[b]
1	MeOH	38	90:10
2	*i*-PrOH	42	91:9
3	AcOH	55	96:4
4	PivOH	59	97:3
5	CF_3CO_2H	74	99:1
6	—	41	88:12

[a] Isolated yield. [b] Determined by ^{1}H NMR.

Next, the effect of amount of trifluoroacetic acid as additive was investigated using **L5** ligand at 80 ˚C (Table 3). The yield of **3aa** was gradually increased when increasing amounts of trifluoroacetic acid was employed. Finally, it was found that the addition of more than 2.0 equiv of trifluoroacetic acid as additive to the **L5**-promoted reaction raised the yield to over 81% with 99% C4 regioselectivity.

Table 3. Effect of CF_3CO_2H.



1a **2a** (4.0 equiv) **3aa**

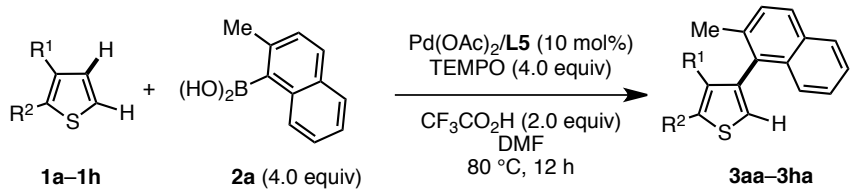
Entry	CF_3CO_2H/equiv	Yield (%)[a]	C4/C5[b]
1	0	55	87:13
2	0.5	56	94:6
3	1.0	74	98:2
4	2.0	84	99:1
5	3.0	88	99:1
6	4.0	81	99:1

[a] Isolated yield. [b] Determined by ^{1}H NMR.

2-1-3. Substrate scope

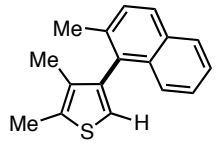
Having discovered the dramatic effect of biox ligand (**L5**) and acid (CF_3CO_2H) in the C–H arylation of thiophenes, the substrate scope with respect to the thiophene coupling partner was examined (Table 4). The newly developed catalytic system allowed the efficient reaction of various mono- and disubstituted thiophenes (**1a**–**1h**) with **2a** to afford the corresponding hindered heterobiaryls (**3aa**–**3ha**) in good yields with excellent C4 regioselectivities. 3-Alkylthiophenes and 2-alkylthiophenes as well as 2,3-disubstituted thiophenes and benzothiophene can be used as heteroaromatic C–H coupling partners. More impressively, the coupling reaction proceeded with 2,3,5-trimethylthiophene (**1h**) to afford tetra-*ortho*-substituted heterobiaryl **3ha** in good yield. It should be noted that all of these coupling reactions are sluggish under the conditions using bipy (**L1**) as a ligand (<1% yield).

Table 4. Substrate scope of thiophene coupling partners.

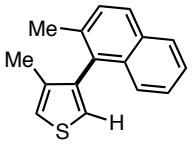


1a–1h **2a** (4.0 equiv) **3aa–3ha**

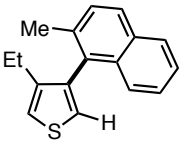
Products (yield, regioselectivity)



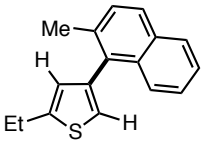
3aa
84%, 99:1
(<1% with bipy)



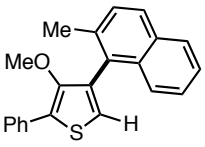
3ba
68%, 95:5
(<1% with bipy)



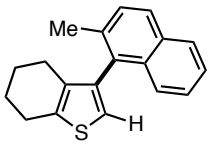
3ca
64%, 97:3
(<1% with bipy)



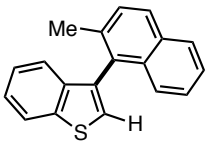
3da
66%, 92:8
(<1% with bipy)



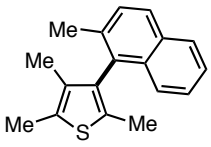
3ea
68%, 94:6
(<1% with bipy)



3fa
61%, >99:1
(<1% with bipy)



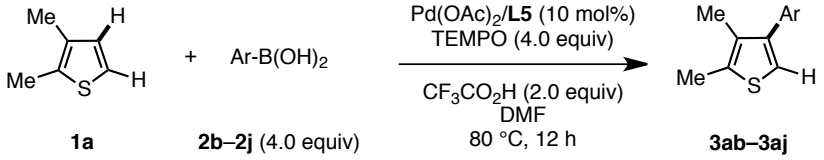
3ga
73%, >99:1
(<1% with bipy)



3ha
70%
(<1% with bipy)

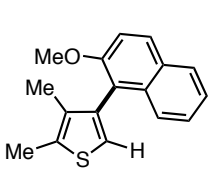
The author next assessed the scope of various sterically encumbered arylboronic acids (Table 5). *ortho*-Substituted 1-naphthylboronic acids such as 2-methoxy-, 2,4-dimethyl-, 2-ethyl, and 2-isopropyl-1-naphthylboronic acids (**2b**–**2e**) were found to cross-couple with 2,3-dimethylthiophene (**1a**) in good yields with very high C4 regioselectivities. Reactions using 2,6-disubstituted phenylboronic acids (**2f**–**2h**) also proceeded to furnish the corresponding tri-*ortho*-substituted heterobiaryls (**3af**–**3ah**). Electron-deficient and pyridine-based arylboronic acids also reacted well (**3ai** and **3aj**).

Table 5. Substrate scope of arylboron coupling partners.

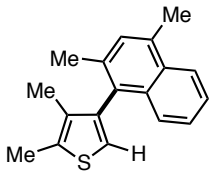


1a **2b–2j** (4.0 equiv) **3ab–3aj**

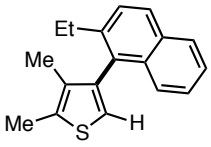
Products (yield, regioselectivity)



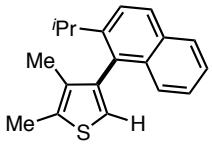
3ab
76%, >99:1
(<1% with bipy)



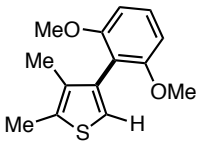
3ac
73%, >99:1
(<1% with bipy)



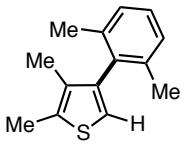
3ad
69%, 98:2
(<1% with bipy)



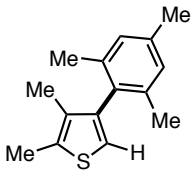
3ae
62%, 98:2
(<1% with bipy)



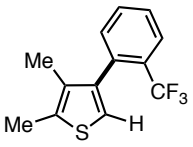
3af
76%, >99:1
(<1% with bipy)



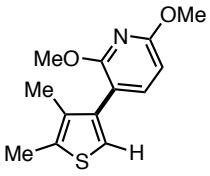
3ag
67%, >99:1
(<1% with bipy)



3ah
72%, >99:1
(<1% with bipy)



3ai
75%, 91:9
(<1% with bipy)



3aj
50%, >99:1
(6% with bipy)

The successful synthesis of tetra-*ortho*-substituted heterobiaryl **3ha** with reasonable efficiency highlights the power of new $Pd(OAc)_2$/biox catalysis. As shown in Figure 1, the optimized conditions can be applied to the synthesis of various hindered heterobiaryls. It should be noted that the $Pd(OAc)_2$/biox catalyst is not limited to the arylation of thiophenes; benzofurans and indoles can also be cross-coupled with hindered arylboronic acids.

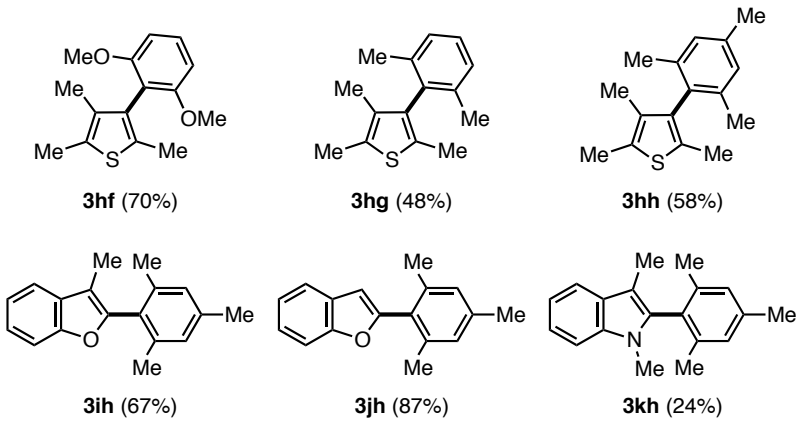


Figure 1. Synthesis of other hindered hetrobiaryls

2-2. Enantioselective C–H coupling

2-2-1. Axial chirality

The present finding of a new catalytic system for C–H coupling offers additional applications. Since the best performing ligands (biox **L4** and **L5**) are chiral, asymmetric induction leading to heterobiaryl products should be possible if the ligands are bound to the palladium center in the stereo-determining step(s) of the catalytic cycle. Prior to experimentation, it was necessary to establish that the axial chirality (atropisomerism) of substituted arylthiophenes is conformationally stable to racemization. Thus, the rotational barrier of 3-methyl-4-(2-methylnaphthalen-1-yl)thiophene (**3ba**) was evaluated by the DFT calculations at B3LYP/6-31G(d) level of theory (Figure 2). It was found that the activation energies for the two modes of rotation (racemization) are comparable (33.5 kcal·mol^{-1} for **TS1** and 33.2 kcal·mol^{-1} for **TS2**) and high enough for the two enantiomers to exist as stable atropisomers at room temperature.

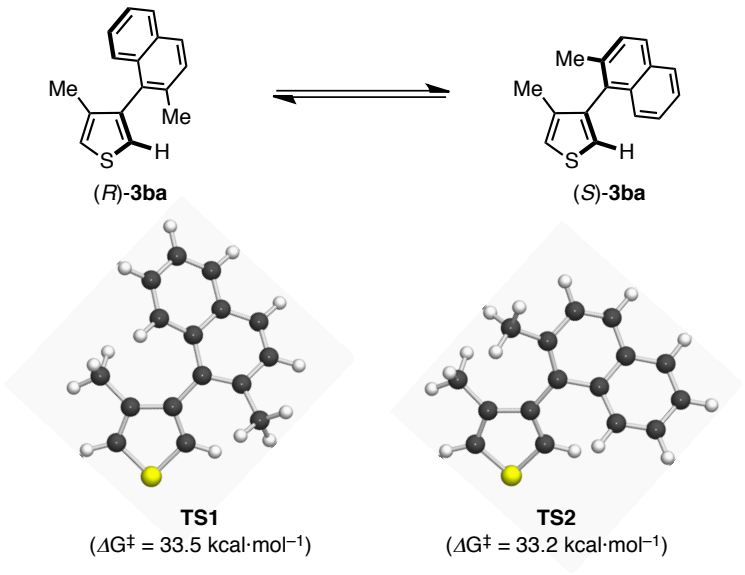
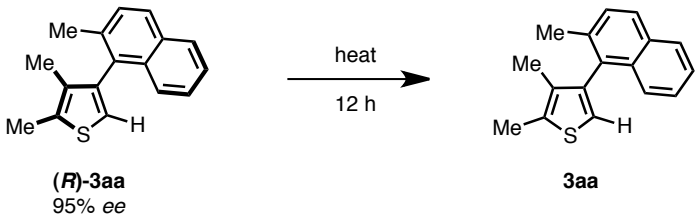


Figure 2. Rotation energies of **3ba** calculated at the B3LYP/6-31G(d) level of theory.

Moreover, to confirm that the axial chirality of substituted arylthiophenes is conformationally stable to racemization, a preliminary racemization study was examined using enantiomerically enriched (*R*)-**3aa**, which was obtained by chiral HPLC separation. When (*R*)-**3aa** was heated to 80 ˚C, no racemization was observed. However, when (*R*)-**3aa** was heated to 120 ˚C, obvious erosion of *ee* was observed.



Conditions	Result
80 ˚C (hexane)	95% *ee*
120˚ C (DMF)	13% *ee*

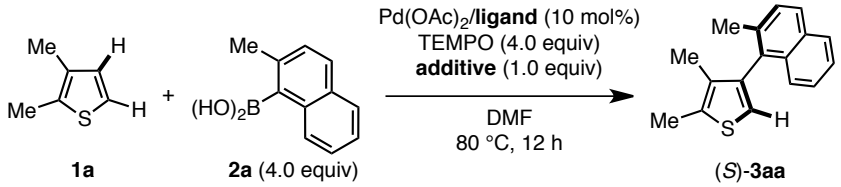
Scheme 2. Racemization study using enantiomerically enriched **3aa**.

2-2-2. Enantioselective C–H coupling

The author then revisited the reaction screening and identified that asymmetric induction does indeed occur (Table 6). The use of chiral ligands **L4** and **L5** gave

enantiomerically enriched **3aa** with 14% *ee* and 20% *ee*, respectively (entries 1 and 2). Additives such as CF_3CO_2H was not effective in asymmetric induction (entry 3).

Table 6. Discovery of asymmetric induction by C–H coupling.



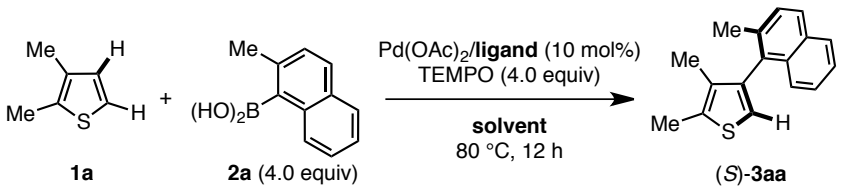
1a **2a** (4.0 equiv) (*S*)-**3aa**

Entry	Ligand	Additive	Yield (%)[a]	Ee (% *ee*)[b]
1	**L4**	—	29	14
2	**L5**	—	55	20
3	**L5**	CF_3CO_2H	74	0

[a] Isolated yield. [b] Determined by chiral HPLC (OD-H).

Next, the effect of solvent was examined (Table 7). In the case of **L5**, DMF was superior to *i*-PrOH (entries 1 and 2). On the other hand, with **L4**, DMF was less effective than *i*-PrOH (entries 3 and 4). When *i*-PrOH was used, the *ee* was increased up to 34% *ee* (entry 4). After solvent screening, it was found that *n*-PrOH gives the highest *ee* (38% *ee*, entry 5).

Table 7. Solvent effect.



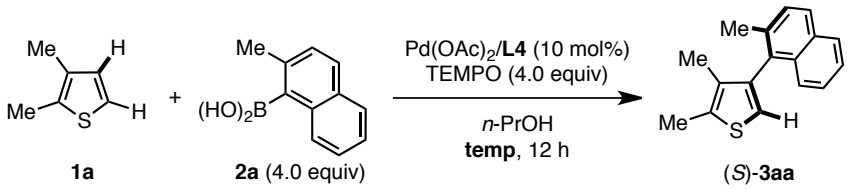
1a **2a** (4.0 equiv) (*S*)-**3aa**

Entry	Ligand	Solvent	Yield (%)[a]	Ee (% *ee*)[b]
1	**L5**	DMF	55	20
2	**L5**	*i*-PrOH	33	4
3	**L4**	DMF	29	14
4	**L4**	*i*-PrOH	26	34
5	**L4**	*n*-PrOH	49	38

[a] Isolated yield. [b] Determined by chiral HPLC (OD-H).

The effect of temperature was also examined while using the condition of 10 mol% of $Pd(OAc)_2$ and 10 mol% of **L4** and 4 equiv of TEMPO in *n*-PrOH (Table 8). It was found that the reaction at 70˚C showed the best result for the present system (41% *ee*, entry 2).

Table 8. Effect of temperature.

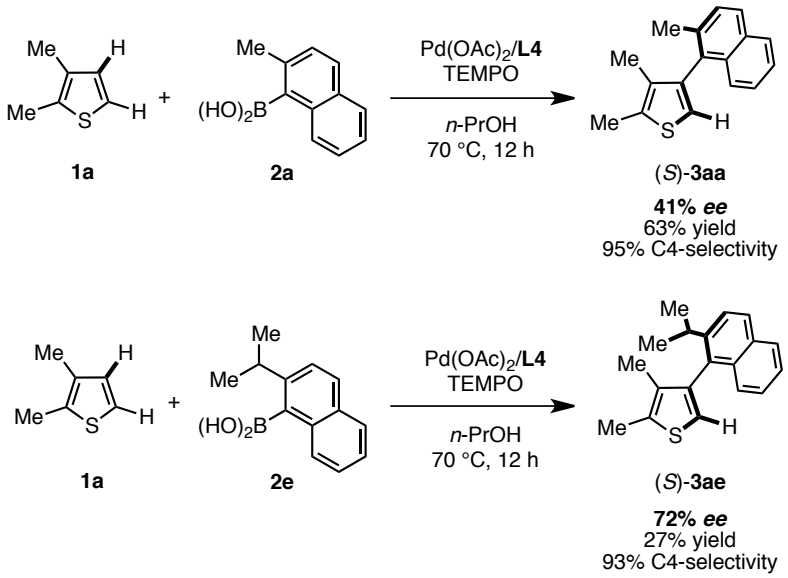


1a **2a** (4.0 equiv) (*S*)-**3aa**

Entry	Temp (˚C)	Yield (%)[a]	Ee (% *ee*)[b]
1	80	49	38
2	70	63	41
3	60	52	34

[a] Isolated yield. [b] Determined by chiral HPLC (OD-H).

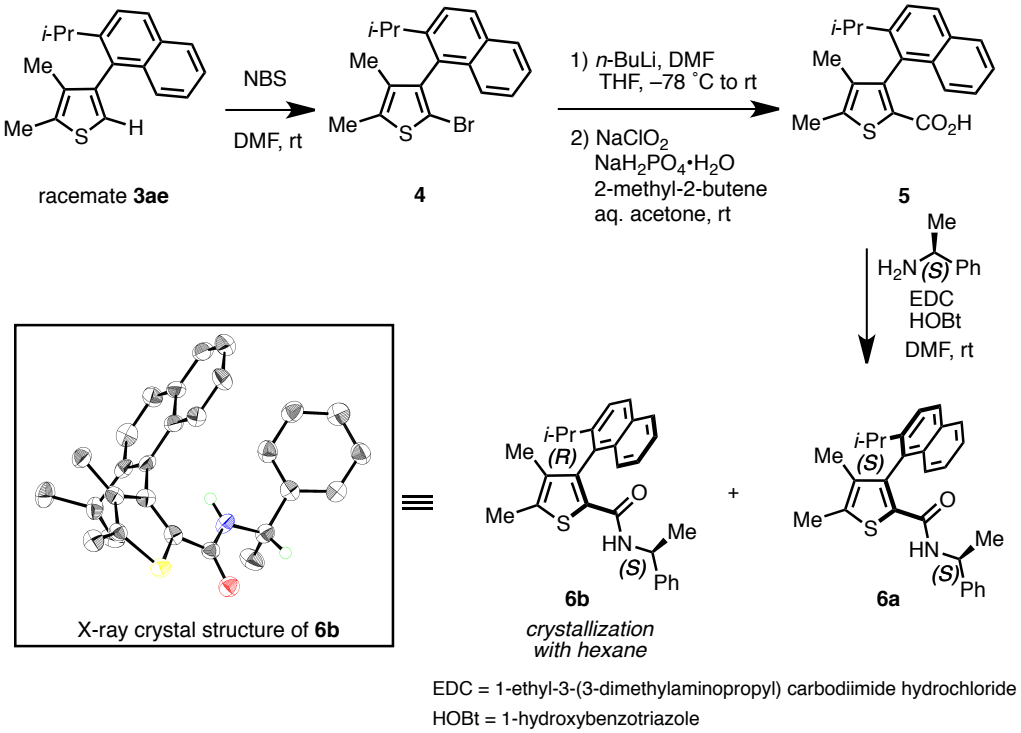
Under the optimized conditions, when a *n*-PrOH solution of **1a** and **2a** was treated with $Pd(OAc)_2$/**L4** catalyst and TEMPO at 70 °C for 12 h under air, (*S*)-**3aa** was obtained in 41% *ee* (63% yield, 95% C4-selectivity; Scheme 3). When a more hindered arylboronic acid **2e** was used, the enantiomeric excess of product was increased to 72% *ee* at the expense of lower yield. Despite the fact that there is a clear reactivity-selectivity dilemma, this is the first demonstration of enantioselective biaryl coupling through catalytic C–H bond functionalization.[4,5,11]



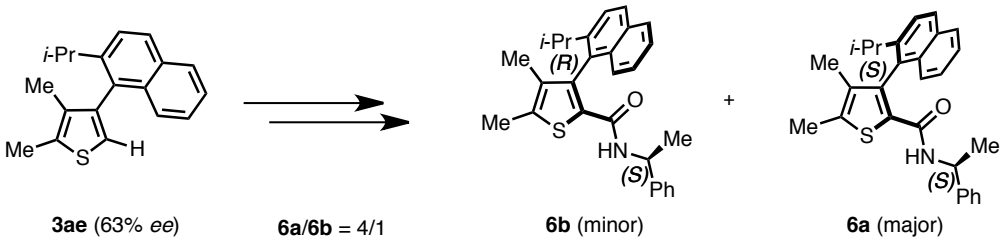
Scheme 3. Enantioselective C–H coupling of thiophene with arylboronic acid.

2-2-3. Determination of absolute stereochemistry

The absolute stereochemistry of coupling product **3ae** was established by X-ray crystallography after derivatization of both racemic (Scheme 4) and enantiomerically enriched **3ae** (Scheme 5). Racemic coupling product (±)-**3ae** was converted into carboxylic acid (±)-**5** in 3 steps (Scheme 4). Condensation of (±)-**5** and (*S*)-1-phenethylamine gave a mixture of diastereomers **6a** and **6b** (ratio of **6a**/**6b** = 1:1 by ^{1}H NMR analysis). Finally, **6b** was separated from the mixture of **6a** and **6b** by crystallization, and the absolute stereochemistry of **6b** was determined as the *R* configuration at the biaryl junction by X-ray analysis. Therefore, compound **6a** was determined as having the *S* configuration at the biaryl junction. Following the above procedure, enantiomerically enriched **3ae** (63% *ee*) also delivered a mixture of **6a** and **6b** (ratio of **6a**/**6b** = 4:1 by ^{1}H NMR analysis) as shown in Scheme 5. According to these results, the enantioselective C–H arylation of thiophene **1a** with arylboronic acid **2e** using ligand **L4** was found to selectively afford the *S* configuration in heterobiaryl **3ae**.



Scheme 4. Transformation from racemic **3ae**.



Scheme 5. Transformation from enantiomerically enriched **3ae**.

3. Conclusion

In summary, a Pd-catalyzed C–H arylation of heteroarenes with arylboronic acids capable of accessing hindered heterobiaryls has been achieved. The use of the $Pd(OAc)_2$/biox catalyst is crucial for the success of this challenging transformation, and trifluoroacetic acid is an essential additive for enhancing the yield and regioselectivity. Upon further investigation, the first enantioselective biaryl coupling through catalytic C–H bond functionalization has been demonstrated.

4. Experimental section

4-1. General

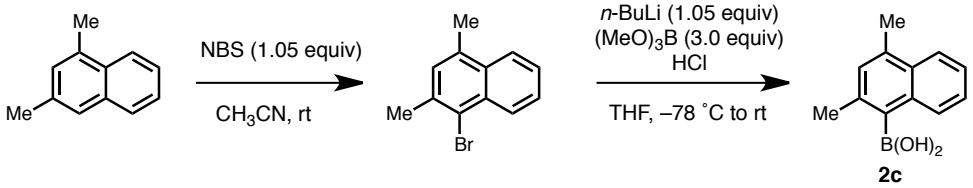
Unless otherwise noted, all materials including dry solvents were obtained from commercial suppliers and used as received. 4,5,6,7-Tetrahydrobenzo[*b*]thiophene (**1f**),[12] 2-methylnaphthalen-1-ylboronic acid (**2a**),[13] 2-methoxynaphthalen-1-ylboronic acid (**2b**),[14] and **L2–L5**[15,16] were synthesized 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 C–H bond arylation reactions were performed in screw cap 20 mL glass vessel tubes and heated in an 8-well reaction block (heater + magnetic stirrer) unless otherwise noted. 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). Flash column chromatography was performed with E. Merck silica gel 60 (230–400 mesh). Preparative thin-layer chromatography (PTLC) was performed using Wakogel 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). 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 JEOL JMS-T100GCV (EI), JMS-T100TD (DART) or JMS-700 (FAB) instruments. Chiral HPLC analysis was conducted on a Shimazu prominance 2000 instrument equipped with DAISO Chiralcel OD-H (4.6 mm x 250 mm). Optical rotations were measured using a JASCO P-1010-GT digital polarimeter with $CHCl_3$ as the solvent.

Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL ECS-400 (^{1}H 400 MHz, ^{13}C 100 MHz) spectrometer. Chemical shifts for ^{1}H NMR are expressed in parts per million (ppm) relative to tetramethylsilane (δ 0.00 ppm) or residual peak of DMSO (δ 2.50 ppm) and CD_2Cl_2 (δ 5.32 ppm). Chemical shifts for ^{13}C NMR are expressed in ppm relative to $CDCl_3$ (δ 77.0 ppm), CD_2Cl_2 (δ 53.8 ppm) or DMSO (δ 39.5 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet,

dd = doublet of doublets, t = triplet, q = quartet, sep = septet, m = multiplet, br = broad signal), coupling constant (Hz), and integration.

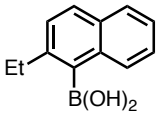
4-2. Preparation of arylboronic acid



2c

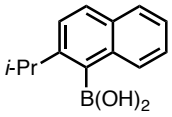
General procedure

(2,4-Dimethylnaphthalen-1-yl)boronic acid (2c): To a solution of 1,3-dimethylnaphthalene (2.11 g, 13.5 mmol) in CH_3CN (20 mL) was added *N*-bromosuccinimide (2.53 g, 14.2 mmol). The mixture was stirred at room temperature for 2 h and evaporated under reduced pressure. The resulting precipitate was filtered off and the filtrate was evaporated under reduced pressure. The residue was purified by short silica-gel column chromatography (hexane/EtOAc = 9:1) to give 1-bromo-2,4-dimethylnaphthalene as a colorless oil which was used for the next step without further purification. To a solution of 1-bromo-2,4-dimethylnaphthalene (3.16 g, 12.5 mmol) in THF (25 mL) was slowly added *n*-BuLi (1.6 M in hexane, 8.19 mL, 13.1 mmol) at –78 ˚C under argon atmosphere. After stirring at –78 ˚C for 1 h, trimethyl borate (4.18 mL, 37.5 mmol) was added, stirred at –78 ˚C for 30 min, then room temperature for 30 min. To the mixture was added 10% HCl (60 mL) and stirred for 1 h. The mixture was extracted with EtOAc and the organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. To the residue was added hexane and stirred, the resulting precipitate was collected to give **2c** (2.01 g, 74%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98–7.91 (m, 1H), 7.84–7.77 (m, 1H), 7.49–7.40 (m, 2H), 7.12 (s, 1H), 5.01 (s, 2H), 2.63 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.81, 135.20, 130.54, 129.09, 127.94, 125.96, 124.81, 124.30, 22.40, 19.36; HRMS (EI) *m*/*z* calcd for $C_{12}H_{13}BO_2$ $[M]^+$ 200.1009, found 200.1013.



2d

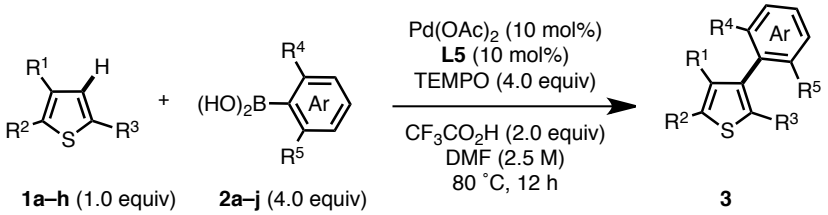
(2-Ethylnaphthalen-1-yl)boronic acid (2d): Following the general procedure, **2d** (5.32 g, 42%) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90–7.77 (m, 3H), 7.51–7.39 (m, 2H), 7.36 (d, J = 8.5 Hz, 1H), 4.83 (s, 2H), 2.85 (q, J = 7.6 Hz, 2H), 1.32 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.69, 135.00, 131.43, 129.17, 128.28, 127.48, 126.82, 126.22, 125.04, 30.16, 16.87; HRMS (EI) m/z calcd for $C_{12}H_{13}BO_2$ [M]$^+$: 200.1009, found: 200.1014.



2e

(2-Isopropylnaphthalen-1-yl)boronic acid (2e): Following the general procedure, **2e** (4.09 g, 57%) was obtained as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.74 (m, 3H), 7.50–7.36 (m, 3H), 4.89 (s, 2H), 3.21–3.06 (m, 1H), 1.34 (d, J = 6.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.55, 134.81, 131.68, 129.31, 128.23, 127.60, 126.20, 125.11, 123.29, 35.34, 24.42; HRMS (EI) m/z calcd for $C_{13}H_{15}BO_2$ [M]$^+$: 214.1165, found: 214.1166.

4-3. General procedure for hindered heterobiaryls by C–H coupling

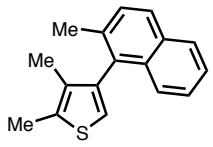


1a–h (1.0 equiv) **2a–j** (4.0 equiv) **3**

To a 20-mL screw cap glass vessel containing a magnetic stirring bar were added $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), **L5** (6.3 mg, 0.025 mmol) and DMF (0.1 mL), following by CF_3CO_2H (37 μL, 0.5 mmol). The mixture was stirred at 80 °C for 10 min and cooled to room temperature. To this mixture were added thiophene **1** (0.25 mmol), arylboronic

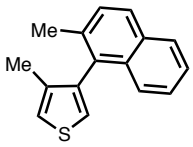
acid **2** (1.0 mmol) and TEMPO (156 mg, 1.0 mmol), and the mixture was stirred at 80 ˚C for 12 h under air. After cooling the reaction mixture to room temperature, the mixture was passed through a short pad of silica gel (EtOAc) and the filtrate was evaporated under reduced pressure. The residue was purified by preparative thin-layer chromatography to give the arylated product **3**. The C4/C5 regioselectivity of the reaction was determined by ^{1}H NMR.

4-4. Compound data of coupling products



3aa

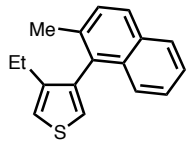
2,3-Dimethyl-4-(2-methylnaphthalen-1-yl)thiophene (3aa): Following the general procedure with 2,3-dimethylthiophene (**1a**: 28 mg) and 2-methylnaphthalen-1-ylboronic acid (**2a**: 186 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3aa** (53 mg, 84%, C4/C5 = 99:1) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 8.3 Hz, 1H), 7.43–7.27 (m, 4H), 6.84 (s, 1H), 2.46 (s, 3H), 2.22 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.57, 134.45, 133.85, 133.42, 133.21, 132.93, 131.87, 128.44, 127.70, 127.26, 125.91, 125.86, 124.74, 118.83, 20.43, 13.74, 12.19; HRMS (DART) *m*/*z* calcd for $C_{17}H_{17}S$ $[M+H]^+$: 253.1051, found: 253.1049.



3ba

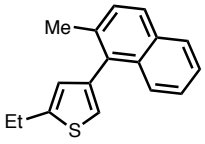
3-Methyl-4-(2-methylnaphthalen-1-yl)thiophene (3ba): Following the general procedure with 3-methylthiophene (**1b**: 25 mg) and 2-methylnaphthalen-1-ylboronic acid (**2a**: 186 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3ba** (40 mg, 68%, C4/C5 = 95:5) as a colorless oil. ^{1}H

NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.1 Hz, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.43–7.31 (m, 4H), 7.15–7.11 (m, 1H), 7.09 (d, *J* = 3.1 Hz, 1H), 2.22 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.32, 137.77, 134.55, 133.41, 132.89, 131.91, 128.45, 127.77, 127.43, 125.97, 125.77, 124.81, 123.32, 121.15, 20.40, 14.48; HRMS (DART) *m*/*z* calcd for $C_{16}H_{15}S$ $[M+H]^+$: 239.0894, found: 239.0890.



3ca

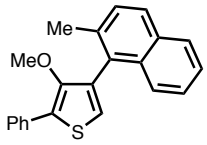
3-Ethyl-4-(2-methylnaphthalen-1-yl)thiophene (3ca): Following the general procedure with 3-ethylthiophene (**1c**: 28 mg) and 2-methylnaphthalen-1-ylboronic acid (**2a**: 186 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3ca** (40 mg, 64%, C4/C5 = 97:3) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.1 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.45–7.30 (m, 4H), 7.18–7.14 (m, 1H), 7.08 (d, *J* = 3.1 Hz, 1H), 2.22 (s, 3H), 2.18 (q, *J* = 7.6 Hz, 2H), 1.01 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.36, 139.79, 134.60, 133.49, 132.95, 131.88, 128.45, 127.74, 127.42, 125.92, 125.85, 124.79, 123.36, 119.86, 22.21, 20.49, 13.85; HRMS (DART) *m*/*z* calcd for $C_{17}H_{17}S$ $[M+H]^+$: 253.1051, found: 253.1054.



3da

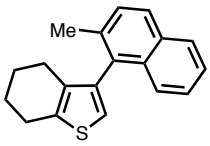
2-Ethyl-4-(2-methylnaphthalen-1-yl)thiophene (3da): Following the general procedure with 2-ethylthiophene (**1d**: 28 mg) and 2-methylnaphthalen-1-ylboronic acid (**2a**: 186 mg), the crude was purified by preparative thin-layer chromatography (hexane) to give **3da** (42 mg, 66%, C4/C5 = 92:8) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.78 (m, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.60 (d, *J* = 8.2 Hz, 1H), 7.43–7.31 (m, 3H), 6.94 (d, *J* = 1.0 Hz, 1H), 6.74 (d, *J* = 1.4 Hz, 1H), 2.94 (q, *J* = 7.7 Hz, 2H), 2.32 (s, 3H), 1.38 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.19, 139.00, 134.02, 133.72, 133.33,

131.88, 128.52, 127.67, 127.19, 126.15, 126.09, 125.81, 124.74, 120.94, 23.46, 20.82, 15.93; HRMS (DART) *m*/*z* calcd for $C_{17}H_{17}S$ $[M+H]^+$: 253.1051, found: 253.1048.



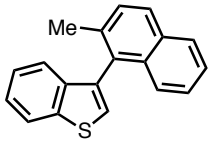
3ea

3-Methoxy-4-(2-methylnaphthalen-1-yl)-2-phenylthiophene (3ea): Following the general procedure with 3-methoxy-2-phenylthiophene (**1e**: 48 mg) and 2-methylnaphthalen-1-ylboronic acid (**2a**: 186 mg), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 49:1) to give **3ea** (56 mg, 68%, C4/C5 = 94:6) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.75 (m, 4H), 7.74–7.66 (m, 1H), 7.49–7.34 (m, 5H), 7.31–7.21 (m, 1H), 7.00 (s, 1H), 3.26 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.74, 134.97, 134.83, 133.30, 133.23, 131.95, 131.27, 128.66, 128.51, 127.84, 127.83, 127.10, 127.04, 126.74, 126.17, 125.81, 124.90, 121.12, 60.33, 20.70; HRMS (DART) *m*/*z* calcd for $C_{22}H_{19}OS$ $[M+H]^+$: 331.1157, found: 331.1163.



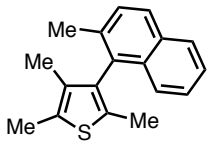
3fa

3-(2-Methylnaphthalen-1-yl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene (3fa): Following the general procedure with 4,5,6,7-tetrahydrobenzo[*b*]thiophene (**1f**: 35 mg) and 2-methylnaphthalen-1-ylboronic acid (**2a**: 186 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3fa** (43 mg, 61%, C4/C5 = >99:1) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.9 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.47–7.28 (m, 4H), 6.87 (s, 1H), 2.95–2.82 (m, 2H), 2.23 (s, 3H), 2.12–1.97 (m, 2H), 1.91–1.80 (m, 2H), 1.73–1.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.01, 135.86, 135.47, 134.38, 133.38, 133.16, 131.87, 128.44, 127.74, 127.24, 125.90, 125.85, 124.73, 119.37, 25.42, 24.60, 23.53, 22.67, 20.48ß; HRMS (DART) *m*/*z* calcd for $C_{19}H_{19}S$ $[M+H]^+$: 279.1207, found: 279.1204.



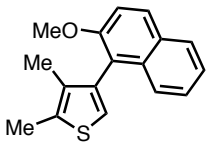
3ga

3-(2-Methylnaphthalen-1-yl)benzo[*b*]thiophene (3ga): Following the general procedure with benzo[*b*]thiophene (**3g**: 34 mg) with 2-methylnaphthalen-1-ylboronic acid (**2a**: 186 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3ga** (50 mg, 73%, C4/C5 = >99:1) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.1 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.42–7.32 (m, 4H), 7.30–7.19 (m, 2H), 7.15 (d, *J* = 8.1 Hz, 1H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.99, 139.49, 135.26, 135.11, 133.53, 132.02, 131.31, 128.60, 127.93, 127.81, 126.06, 125.90, 124.94, 124.74, 124.41, 124.21, 123.17, 122.68, 20.55; HRMS (DART) *m*/*z* calcd for $C_{19}H_{15}S$ $[M+H]^+$: 275.0894, found: 275.0892.



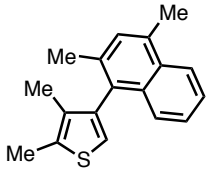
3ha

2,3,5-Trimethyl-4-(2-methylnaphthalen-1-yl)thiophene (3ha): Following the general procedure with 2,3,5-trimethylthiophene (**1h**: 32 mg) and 2-methylnaphthalen-1-ylboronic acid (**2a**: 186 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3ha** (47 mg, 70%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.6 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.44–7.30 (m, 4H), 2.39 (s, 3H), 2.18 (s, 3H), 1.98 (s, 3H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.20, 134.73, 133.28, 133.11, 132.94, 132.03, 130.55, 128.87, 128.49, 127.83, 127.21, 125.95, 125.62, 124.74, 20.05, 13.42, 13.32, 12.68; HRMS (DART) *m*/*z* calcd for $C_{18}H_{19}S$ $[M+H]^+$: 267.1208, found: 267.1206.



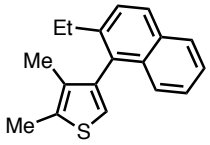
3ab

4-(2-Methoxynaphthalen-1-yl)-2,3-dimethylthiophene (3ab): Following the general procedure with 2,3-dimethylthiophene (**1a**: 28 mg) and 2-methoxynaphthalen-1-ylboronic acid (**2b**: 202 mg), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 49:1) to give **3ab** (51 mg, 76%, C4/C5 = >99:1) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 9.0 Hz, 1H), 7.83–7.77 (m, 1H), 7.49–7.43 (m, 1H), 7.37–7.29 (m, 3H), 6.93 (s, 1H), 3.85 (s, 3H), 2.46 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.51, 137.19, 134.26, 133.88, 132.43, 129.13, 128.95, 127.75, 126.32, 125.27, 123.49, 120.82, 119.81, 113.59, 56.62, 13.80, 12.36; HRMS (DART) *m*/*z* calcd for $C_{17}H_{17}OS$ $[M+H]^+$: 269.1000, found: 269.1007.



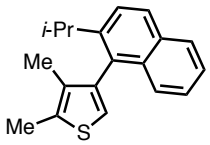
3ac

4-(2,4-dimethylnaphthalen-1-yl)-2,3-dimethylthiophene (3ac): Following the general procedure with 2,3-dimethylthiophene (**1a**: 28 mg) and 2,4-dimethylnaphthalen-1-ylboronic acid (**2c**: 200 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3ac** (49 mg, 73%, C4/C5 = >99:1) as a white solid. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.98 (d, *J* = 8.1 Hz, 1H), 7.46–7.40 (m, 1H), 7.39–7.30 (m, 2H), 7.28 (s, 1H), 6.82 (s, 1H), 2.70 (s, 3H), 2.46 (s, 3H), 2.17 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.80, 134.04, 133.56, 133.40, 133.36, 132.78, 132.11, 131.01, 129.32, 126.49, 125.56, 124.58, 123.91, 118.92, 20.31, 19.33, 13.75, 12.22; HRMS (DART) *m*/*z* calcd for $C_{18}H_{19}S$ $[M+H]^+$: 267.1207, found: 267.1208.



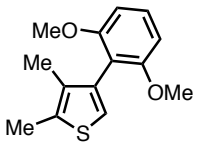
3ad

4-(2-Ethylnaphthalen-1-yl)-2,3-dimethylthiophene (3ad): Following the general procedure with 2,3-dimethylthiophene (**1a**: 28 mg) and 2-ethylnaphthalen-1-ylboronic acid (**2d**: 200 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3ad** (46 mg, 69%, C4/C5 = 98:2) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.6 Hz, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.44 (d, *J* = 8.5 Hz, 1H), 7.42–7.29 (m, 3H), 6.86 (s, 1H), 2.64–2.41 (m, 5H), 1.70 (s, 3H), 1.13 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.63, 140.22, 133.46, 133.10, 132.67, 131.88, 127.69, 127.65, 127.02, 126.10, 125.85, 124.82, 119.07, 26.93, 15.73, 13.75, 12.31; HRMS (DART) *m*/*z* calcd for $C_{18}H_{19}S$ $[M+H]^+$: 267.1207, found: 267.1203.



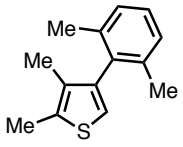
3ae

4-(2-Isopropylnaphthalen-1-yl)-2,3-dimethylthiophene (3ae): Following the general procedure with 2,3-dimethylthiophene (**1a**: 28 mg) and 2-isopropylnaphthalen-1-ylboronic acid (**2e**: 214 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3ae** (44 mg, 62%, C4/C5 = 98:2) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.6 Hz, 1H), 7.81 (d, *J* = 8.6 Hz, 1H), 7.52 (d, *J* = 8.6 Hz, 1H), 7.42–7.37 (m, 1H), 7.36–7.29 (m, 2H), 6.85 (s, 1H), 2.92 (sep, *J* = 6.8 Hz, 1H), 2.47 (s, 3H), 1.72 (s, 3H), 1.20 (d, *J* = 6.8 Hz, 3H), 1.18 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.89, 140.33, 133.58, 133.40, 132.66, 132.26, 131.85, 127.95, 127.64, 126.38, 125.84, 124.89, 123.65, 118.98, 30.52, 24.54, 23.20, 13.77, 12.35; HRMS (DART) *m*/*z* calcd for $C_{19}H_{21}S$ $[M+H]^+$: 281.1364, found: 281.1369.



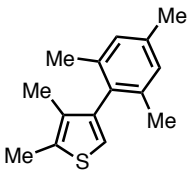
3af

4-(2,6-Dimethoxyphenyl)-2,3-dimethylthiophene (3af): Following the general procedure with 2,3-dimethylthiophene (**1a**: 28 mg) and 2,6-dimethoxyphenylboronic acid (**2f**: 182 mg), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 49:1) to give **3ae** (47 mg, 76%, C4/C5 = >99:1) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (t, *J* = 8.4 Hz, 1H), 6.88 (s, 1H), 6.62 (d, *J* = 8.5 Hz, 2H), 3.73 (s, 6H), 2.39 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.35, 134.64, 133.64, 131.60, 128.67, 119.70, 115.09, 103.93, 55.84, 13.80, 12.44; HRMS (DART) *m*/*z* calcd for $C_{14}H_{17}O_2S$ $[M+H]^+$: 249.0953, found: 239.0949.



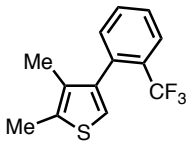
3ag

4-(2,6-Dimethylphenyl)-2,3-dimethylthiophene (3ag): Following the general procedure with 2,3-dimethylthiophene (**1a**: 28 mg) and 2,6-dimethylphenylboronic acid (**2g**: 150 mg), the ctude product was purified by preparative thin-layer chromatography (hexane) to give **3ag** (36 mg, 67%, C4/C5 = >99:1) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18–7.11 (m, 1H), 7.07 (d, *J* = 7.9 Hz, 2H), 6.69 (s, 1H), 2.41 (s, 3H), 2.01 (s, 6H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.95, 137.50, 137.28, 132.91, 132.08, 127.08, 126.99, 117.18, 20.36, 13.69, 12.04; HRMS (DART) *m*/*z* calcd for $C_{14}H_{17}S$ $[M+H]^+$: 217.0501, found: 217.0503.



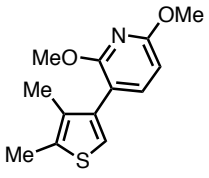
3ah

4-Mesityl-2,3-dimethylthiophene (3ah): Following the general procedure with 2,3-dimethylthiophene (**1a**: 28 mg) and 2,4,6-trimethylphenylboronic acid (**2h**: 164 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3ah** (41 mg, 72%, C4/C5 = >99:1) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 2H), 6.68 (s, 1H), 2.40 (s, 3H), 2.31 (s, 3H), 1.97 (s, 6H), 1.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.95, 137.14, 136.60, 134.53, 132.75, 132.26, 127.81, 117.34, 21.05, 20.26, 13.72, 12.09; HRMS (DART) *m*/*z* calcd for $C_{15}H_{19}S$ $[M+H]^+$: 231.1207, found: 231.1209.



3ai

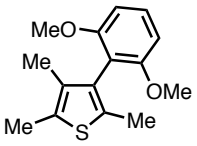
2,3-Dimethyl-4-(2-(trifluoromethyl)phenyl)thiophene (3ai): Following the general procedure with 2,3-dimethylthiophene (**1a**: 28 mg) and 2-(trifluoromethyl)phenylboronic acid (**2i**: 190 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3ai** (48 mg, 75%, C4/C5 = 91:9) as a colorless oil. ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.75 (d, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 6.89 (s, 1H), 2.40 (s, 3H), 1.84 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 140.16, 137.48, 133.12, 132.77, 132.73, 131.72, 129.69 (q, *J* = 29.1 Hz), 127.92, 126.30 (q, *J* = 4.7 Hz), 124.60 (q, *J* = 274.4 Hz), 119.93, 13.70, 12.62; HRMS (DART) *m*/*z* calcd for $C_{13}H_{12}F_3S$ $[M+H]^+$: 257.0612, found: 257.0615.



3aj

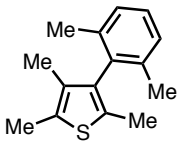
3-(4,5-Dimethylthiophen-3-yl)-2,6-dimethoxypyridine (3aj): Following the general procedure with 2,3-dimethylthiophene (**1a**: 28 mg) and (2,6-dimethoxypyridin-3-yl)boronic acid (**2j**: 183 mg), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 6:1) to give **3aj** (31 mg,

50%, C4/C5 = >99:1) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.1 Hz, 1H), 6.89 (s, 1H), 6.34 (d, *J* = 7.9 Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 2.39 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.35, 159.75, 142.29, 138.40, 133.05, 132.73, 119.11, 111.95, 100.35, 53.55, 53.34, 13,.6, 12.67; HRMS (DART) *m*/*z* calcd for $C_{13}H_{16}NO_2S$ $[M+H]^+$: 250.0902, found: 250.0907.



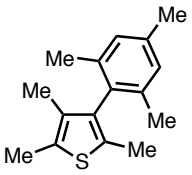
3hf

3-(2,6-Dimethoxyphenyl)-2,4,5-trimethylthiophene (3hf): Following the general procedure with 2,3,5-dimethylthiophene (**1h**: 32 mg) and (2,6-dimethoxyphenyl)boronic acid (**2f**: 182 mg), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 10:1) to give **3hf** (46 mg, 70%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.24 (m, 1H), 6.63 (d, *J* = 8.5 Hz, 2H), 3.74 (s, 6H), 2.33 (s, 3H), 2.12 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.36, 133.45, 131.51, 128.72, 127.74, 114.23, 103.85, 55.76, 13.80, 13.40, 12.79; HRMS (DART) *m*/*z* calcd for $C_{15}H_{19}O_2S$ $[M+H]^+$: 263.1106, found: 263.1104.



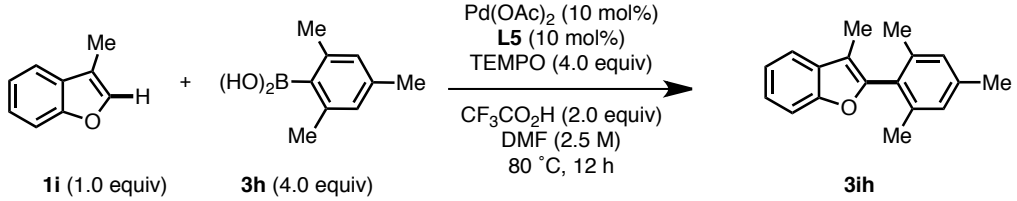
3hg

3-(2,6-Dimethylphenyl)-2,4,5-trimethylthiophene (3hg): Following the general procedure with 2,3,5-dimethylthiophene (**1h**: 32 mg) and (2,6-dimethyphenyl)boronic acid (**2g**: 150 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3hg** (28 mg, 48%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17–7.06 (m, 3H), 2.34 (s, 3H), 2.02 (s, 3H), 1.97 (s, 6H), 1.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.71, 137.34, 136.74, 131.77, 128.88, 128.81, 127.01, 19.99, 13.28, 13.21, 12.56; HRMS (DART) *m*/*z* calcd for $C_{15}H_{19}S$ $[M+H]^+$: 231.1208, found: 231.1207.



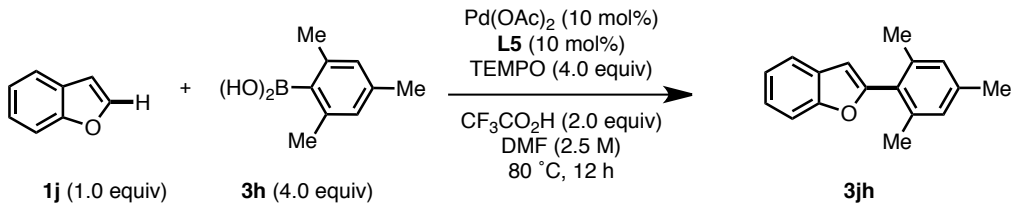
3hh

3-Mesityl-2,4,5-trimethylthiophene (3hh): Following the general procedure with 2,3,5-dimethylthiophene (**1h**: 32 mg) and mesitylboronic acid (**2h**: 164 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3hh** (35 mg, 58%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 2H), 2.34 (s, 3H), 2.32 (s, 3H), 2.02 (s, 3H), 1.93 (s, 6H), 1.69 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.71, 137.16, 136.42, 133.72, 131.98, 128.90, 128.65, 127.84, 21.11, 19.91, 13.30, 13.25, 12.62. HRMS (DART) *m*/*z* calcd for $C_{16}H_{21}S$ $[M+H]^+$: 245.1364, found: 245.1363.

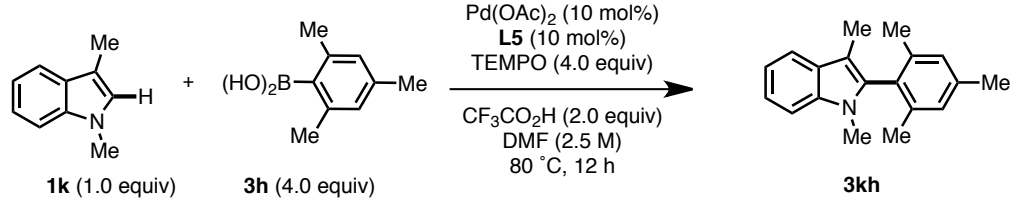


1i (1.0 equiv) **3h** (4.0 equiv) **3ih**

2-Mesityl-3-methylbenzofuran (3ih): Following the general procedure with 3-methylbenzofuran (**1i**: 33 mg) and mesitylboronic acid (**2h**: 164 mg), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 99:1) to give **3ih** (42 mg, 67%) as a colorless oil.^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.61–7.55 (m, 1H), 7.50–7.43 (m, 1H), 7.33–7.25 (m, 2H), 7.00 (s, 2H), 2.36 (s, 3H), 2.13 (s, 6H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 154.88, 151.62, 139.54, 139.26, 130.51, 128.41, 127.25, 123.96, 122.44, 119.52, 113.13, 111.21, 21.33, 19.97, 8.39; HRMS (DART) *m*/*z* calcd for $C_{18}H_{19}O$ $[M+H]^+$: 251.1436, found: 251.1434.

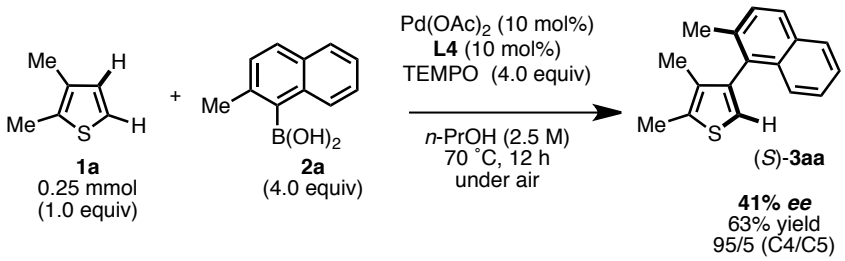


2-Mesitylbenzofuran (3jh): Following the general procedure with benzofuran (**1j**: 30 mg) and mesitylboronic acid (**2h**: 164 mg), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 99:1) to give **3jh** (52 mg, 87%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.58 (m, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.32–7.22 (m, 2H), 6.96 (s, 2H), 6.64 (s, 1H), 2.33 (s, 3H), 2.22 (s, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.02, 154.71, 139.01, 138.38, 128.83, 128.35, 127.69, 123.64, 122.55, 120.67, 111.14, 106.04, 21.18, 20.49. HRMS (DART) *m*/*z* calcd for $C_{17}H_{17}O$ $[M+H]^+$: 237.1279, found: 237.1279.

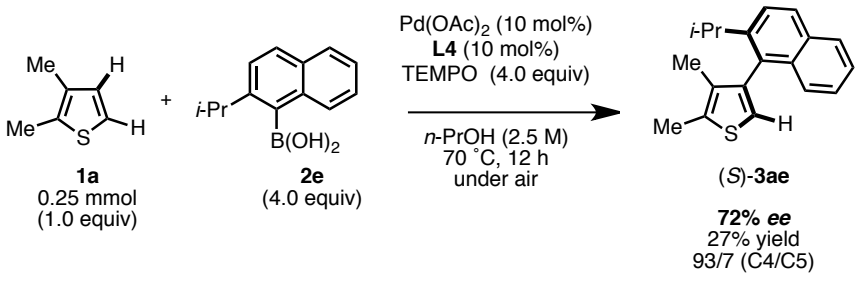


2-Mesityl-1,3-dimethyl-1*H*-indole (3kh): Following the general procedure with 1,3-dimethyl-1*H*-indole (**1k**: 36 mg) and mesitylboronic acid (**2h**: 164 mg), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 20:1) to give **3jh** (16 mg, 24%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.58 (m, 1H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.25–7.20 (m, 1H), 7.17–7.12 (m, 1H), 6.98 (s, 2H), 3.39 (s, 3H), 2.36 (s, 3H), 2.06 (s, 3H), 1.97 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.84, 138.17, 136.78, 136.15, 128.49, 128.30, 127.94, 120.74, 118.53, 118.51, 108.96, 107.61, 29.65, 21.21, 19.99, 8.86; HRMS (DART) *m*/*z* calcd for $C_{19}H_{22}N$ $[M+H]^+$: 264.1752, found: 264.1752.

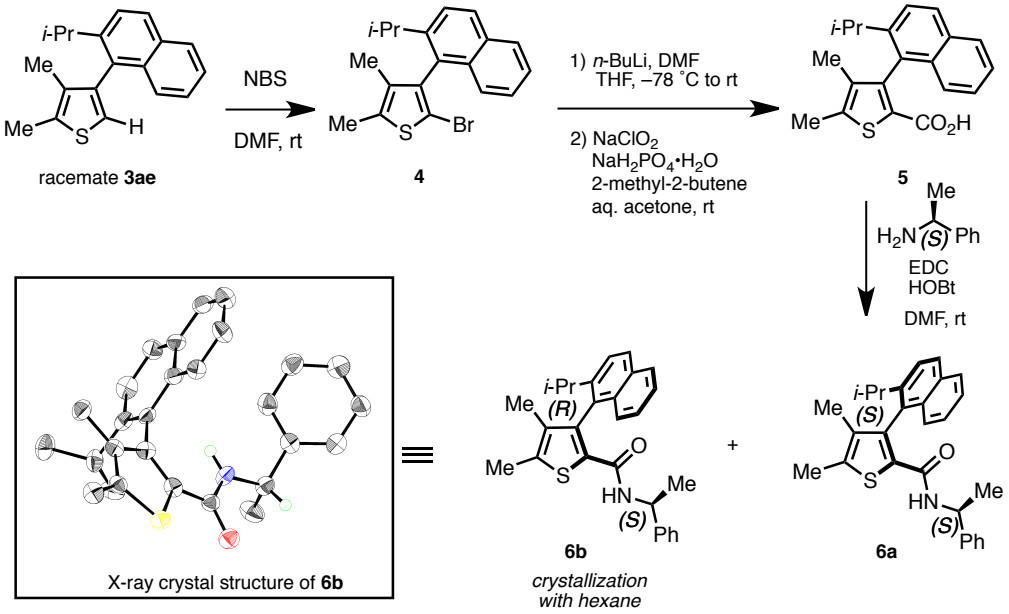
4-5. Enantioselective C–H coupling



To a 20-mL screw cap glass vessel containing a magnetic stirring bar were added $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), **L4** (5.6 mg, 0.025 mmol) and *n*-PrOH (0.1 mL). The mixture was stirred at 70 ˚C for 10 min and cooled to room temperature. To the mixture were added 2,3-dimethylthiophene (**1a**: 28 mg, 0.25 mmol), 2-methylnaphthalen-1-ylboronic acid (**2a**: 186 mg, 1.00 mmol) and TEMPO (156 mg, 1.00 mmol), and the mixture was stirred at 70 ˚C for 12 h under air. After cooling the reaction mixture to room temperature, the mixture was passed through a short pad of silica gel (EtOAc) and the filtrate was evaporated under reduced pressure. The residue was purified by preparative thin-layer chromatography (hexane) to give (*S*)-**3aa** (40 mg, 63% yield, C4/C5 = 95:5, 41% *ee*) as a colorless oil. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column, UV detected at 254 nm, flow rate 1.0 mL/min (hexane). Retention times (tr): major enantiomer tr =11.0 min, minor enantiomer tr = 9.5 min.



(*S*)-**3ae** (19 mg, 27% yield, C4/C5 = 93:7, 72% *ee*) was obtained with 2-isopropylnaphthalen-1-ylboronic acid (**2e**: 214 mg) as a colorless oil. Analytically pure compound was obtained by using GPC system. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column, UV detected at 254 nm, flow rate 1.0 mL/min (hexane). Retention times (tr); major enantiomer tr = 8.5 min, minor enantiomer tr = 7.6 min. $[\alpha]_D^{21}$ +35.5 (*c* 1.00, $CHCl_3$)



2-Bromo-3-(2-isopropylnaphthalen-1-yl)-4,5-dimethylthiophene (4): To a solution of **3ae** (194 mg, 0.69 mmol) in DMF (3.0 mL) was added *N*-bromosuccinimide (185 mg, 1.04 mmol). After stirring the mixture for 24 h at room temperature, the residue was purified by preparative thin-layer chromatography (hexane) to give brominated compound **4** (196 mg, 79%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.5 Hz, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.45–7.31 (m, 2H), 7.28–7.20 (m, 1H), 2.83 (sep, J = 6.7 Hz, 1H), 2.41 (s, 3H), 1.69 (s, 3H), 1.27 (d, J = 6.7 Hz, 3H), 1.19 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.24, 140.83, 133.98, 133.32, 132.38, 131.99, 130.32, 128.65, 127.89, 126.25, 125.57, 125.09, 123.71, 106.58, 30.96, 23.94, 23.64, 13.69, 13.24; HRMS (DART) m/z calcd for $C_{19}H_{20}BrS$ $[M+H]^+$: 359.0469, found: 359.0478.

3-(2-Isopropylnaphthalen-1-yl)-4,5-dimethylthiophene-2-carboxylic acid (5): To a solution of **4** (234 mg, 0.65 mmol) in THF (5.0 mL) was slowly added *n*-BuLi (1.6 M in hexane, 447 μL, 0.72 mmol) at –78 °C. After stirring at –78 °C for 30 min, the solution of DMF (76 μL, 0.98 mmol) in THF (1.0 mL) was added and stirred at –78 °C for 1 h and room temperature for 1 h. The mixture was poured into saturated aqueous NH_4Cl, and then extracted with EtOAc. The organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by preparative thin-layer chromatography (hexane/EtOAc = 5:1) to give a formyletad product (105 mg, 52%) as a yellow oil. To the resulting compound (49 mg,

0.16 mmol) in aqueous acetone (2.0 mL) was added $NaClO_2$ (29 mg, 0.32 mmol), $NaH_2PO_4 \cdot H_2O$ (38 mg, 0.32 mmol) and 2-methyl-2-butene (39 mg, 0.56 mmol) and the mixture was stirred at room temperature for 2 days. The mixture was diluted with EtOAc and water, and then extracted with EtOAc. The organic layer was washed with brine, water, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by preparative thin-layer chromatography (hexane/EtOAc = 1:1) to give the carboxylic acid **5** (49 mg, 96%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.3 (br s, 1H), 7.97–7.83 (m, 2H), 7.58 (d, J = 8.5 Hz, 1H), 7.48–7.29 (m, 2H), 7.05 (d, J = 8.5 Hz, 1H), 2.72–2.60 (m, 1H), 2.47 (s, 3H), 1.56 (s, 3H), 1.15 (d, J = 6.7 Hz, 3H), 1.11 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.46, 145.47, 142.95, 139.67, 135.29, 131.65, 131.50, 131.26, 127.84, 127.77, 126.27, 126.08, 124.88, 123.62, 30.70, 23.31, 23.08, 13.76, 12.19; HRMS (FAB) m/z calcd for $C_{20}H_{20}O_2S$ $[M]^+$: 325.1184, found: 324.1175.

(*R*)-3-(2-Isopropylnaphthalen-1-yl)-4,5-dimethyl-*N*-((*S*)-1-phenylethyl)thiophene-2-carboxamide (6b): To a solution of carboxylic acid **5** (36 mg, 0.11 mmol) and (*S*)-1-phenethylamine (17 μL, 0.13 mmol) in DMF (1.0 mL) were added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (25 mg, 0.13 mmol) and 1-hydroxybenzotriazole (15 mg, 0.11 mmol). After stirring the mixture at room temperature for 12 h, the mixture was poured into saturated aqueous $NaHCO_3$, and then extracted with EtOAc. The organic layer was washed with water, brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was purified by preparative thin-layer chromatography (hexane/EtOAc = 5:1) to give a mixture of **6a** and **6b** (39 mg, 83%) as a pale yellow oil. To the residue was added hexane (1.0 mL) and the resulting precipitate was collected by filtration to give the single isomer product **6b** (11 mg) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.5 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.52–7.43 (m, 1H), 7.39–7.31 (m, 1H), 7.29–7.20 (m, 1H), 7.03–6.95 (m, 1H), 6.94–6.84 (m, 2H), 6.20 (d, J = 7.6 Hz, 2H), 5.36 (d, J = 7.6 Hz, 1H), 4.85–4.75 (m, 1H), 2.87 (sep, J = 6.7 Hz, 1H), 2.48 (s, 3H), 1.71 (s, 3H), 1.24 (d, J = 6.7 Hz, 3H), 1.23 (d, J = 6.7 Hz, 3H), 0.90 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.76, 145.47, 143.01, 139.56, 138.78, 134.87, 132.36, 132.33, 132.08, 129.93, 129.52, 128.12, 128.02, 127.19, 126.45, 125.97, 125.62, 124.99, 123.98, 48.41, 30.91, 23.81, 23.49, 22.61, 14.09, 12.58; HRMS (DART) m/z calcd for $C_{28}H_{30}NOS$

$[M+H]^+$: 428.2048, found: 428.2052.

4-6. X-ray crystal structure analysis of 6b

A suitable crystal was mounted with mineral oil on a glass fiber and transferred to the goniometer of a Rigaku Saturn CCD diffractometer. Graphite-monochromated Mo Kα radiation (λ = 0.71070 Å) was used. The structures were solved by direct methods with (SIR-97)[20] and refined by full-matrix least-squares techniques against F^2 (SHELXL-97).[21] The intensities were corrected for Lorentz and polarization effects. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed using AFIX instructions. Details of the crystal data and a summary of the intensity data collection parameters for **6b** are listed in Table 9.

Table 9. Crystallographic data and structure refinement details for **6b**.

	6b
formula	$C_{28}H_{29}NOS$
fw	427.58
T (K)	103(2)
λ (Å)	0.71070
cryst syst	Orthorhombic
space group	$P2_12_12_1$
a, (Å)	9.357(7)
b, (Å)	13.439(9)
c, (Å)	18.660(13)
α, (deg)	90
β, (deg)	90
γ, (deg)	90
V, (Å^3)	2346(3)
Z	4
D_{calc}, (g / cm^3)	1.210
μ (mm^{-1})	0.158
F(000)	912
cryst size (mm)	0.20 × 0.10 × 0.01
2θ range, (deg)	3.03–25.00
reflns collected	23359
indep reflns/R_{int}	4115/0.1799
params	285
GOF on F^2	1.047
R_1, wR_2 [I>2s(I)]	0.1054, 0.2507
R_1, wR_2 (all data)	0.1360, 0.2823
abs struct param	-0.1(2)

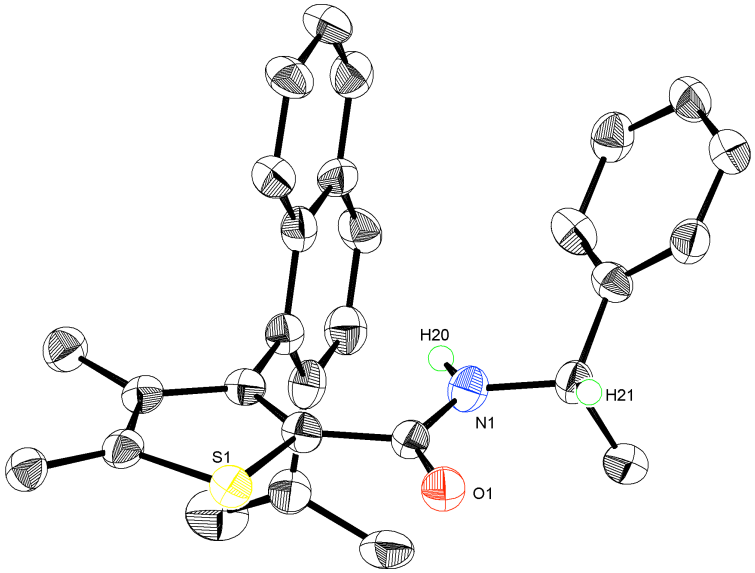


Figure 3. ORTEP drawing of **6b** with 50% thermal ellipsoid. All hydrogen atoms except N–H and C*–H are omitted for clarity.

4-7. Computational study

The Gaussian 03 program running on a SGI Altix4700 system was used for optimization (B3LYP/6-31G(d)). All structures were optimized without any symmetry assumptions. Zero-point energy, enthalpy, and Gibbs free energy at 298.15 K and 1 atm were estimated from the gas-phase studies unless otherwise noted. Harmonic vibration frequency calculations at the same level were performed to verify all stationary points as local minima (with no imaginary frequency) or transition states (with one imaginary frequency). IRC calculations were also performed to check transition states. Visualization of the results was performed by use of POV-Ray for Windows v3.5 software.

Table 10. Uncorrected and thermal-corrected (298K) energies of stationary points (Hartree).[a]

compound	E	E + ZPE	H	G
3ba	-1016.33524198	-1016.084792	-1016.068980	-1016.128094
TS-1	-1016.28869529	-1016.036565	-1016.022705	-1016.075221
TS-2	-1016.28803339	-1016.035947	-1016.021987	-1016.074743

a) E: electronic energy; ZPE: zero-point energy; H (=E+ZPE+E_{vib}+E_{rot}+E_{trans}+RT): sum of electronic and themal enthalpies; G (=H–TS): sum of electronic and thermal free energies.

Table 11. Cartesian coordinates of optimized species.

3ba

C	2.212267	-2.532229	-0.174894	H	4.379132	-2.667551	-0.129516	C	-1.957507	-0.373548	1.030164
C	1.115994	-1.698319	-0.178430	C	1.674301	2.493653	-0.052925	S	-3.551973	-0.762561	-0.973596
C	1.268170	-0.283755	-0.132536	C	0.347315	1.986760	-0.089352	H	-1.682948	0.128674	-2.307534
C	2.597188	0.251831	-0.091653	H	3.772153	2.068960	-0.020464	C	-3.210915	-0.831569	0.727069
C	3.706507	-0.635817	-0.091021	H	1.818615	3.571006	-0.020242	H	-3.958560	-1.208340	1.412940
C	3.522598	-1.998793	-0.130167	C	-0.809295	2.962404	-0.094855	C	-1.385011	-0.314417	2.421078
H	2.071449	-3.609339	-0.210371	H	-0.483651	3.954460	0.234221	H	-0.471951	-0.916300	2.501590
H	0.115338	-2.115996	-0.222252	H	-1.236869	3.072433	-1.099633	H	-1.113795	0.711449	2.698976
C	0.146192	0.610612	-0.130442	H	-1.624461	2.634911	0.557996	H	-2.102470	-0.685723	3.159099
C	2.765148	1.659355	-0.053022	C	-1.239197	0.053427	-0.151762				
H	4.708862	-0.214505	-0.059893	C	-1.980302	-0.103454	-1.293481				

TS-1

C	2.673918	-2.165214	0.524335	H	4.699537	-2.167096	-0.261331	C	-1.783699	-1.415186	0.025640
C	1.492425	-1.461296	0.641253	C	1.454756	2.597813	-0.153673	S	-3.882195	0.067382	-0.378030
C	1.326720	-0.158002	0.108115	C	0.242555	1.997030	0.286181	H	-2.328678	1.892661	-0.312461
C	2.516189	0.466808	-0.399858	H	3.410760	2.352879	-0.998604	C	-3.135762	-1.471963	-0.188835
C	3.701186	-0.295691	-0.574658	H	1.505665	3.684473	-0.154303	H	-3.727885	-2.373314	-0.271080
C	3.779995	-1.600269	-0.144339	C	-0.748879	2.987949	0.875109	C	-1.091363	-2.763859	0.058553
H	2.756933	-3.151367	0.973836	H	-0.185539	3.731435	1.451071	H	-0.209856	-2.802727	-0.584380
H	0.696788	-1.877873	1.235773	H	-1.313479	3.552156	0.119398	H	-0.786460	-3.073652	1.064524
C	0.082545	0.596727	0.203784	H	-1.465607	2.516178	1.550292	H	-1.792756	-3.522908	-0.301679
C	2.522781	1.868596	-0.600531	C	-1.292592	-0.019740	0.092131				
H	4.568806	0.197017	-1.007577	C	-2.359627	0.830303	-0.162371				

TS-2

C	-2.640521	-2.225340	0.704723	H	-4.673288	-2.314220	-0.056375	C	2.613850	0.376644	0.003442
C	-1.467794	-1.498393	0.762763	C	-1.513053	2.501084	-0.335149	S	2.823512	-2.191808	-0.321314
C	-1.332317	-0.221972	0.143238	C	-0.294404	1.962896	0.169585	H	0.420094	-2.164857	-0.282127
C	-2.535779	0.338811	-0.400447	H	-3.458025	2.151411	-1.167289	C	3.528378	-0.627896	-0.168552
C	-3.709281	-0.452765	-0.507512	H	-1.584164	3.583801	-0.417103	H	4.598987	-0.504173	-0.261534
C	-3.762883	-1.725335	0.012889	C	0.612850	2.996970	0.804864	C	3.171012	1.781409	-0.069686
H	-2.701609	-3.180861	1.218963	H	-0.023228	3.681069	1.379348	H	2.629594	2.393909	-0.794960
H	-0.652641	-1.884145	1.362295	H	1.312566	2.552068	1.509748	H	3.175092	2.313508	0.884682
C	-0.097074	0.570124	0.167904	H	1.170270	3.614114	0.092938	H	4.209702	1.729234	-0.409653
C	-2.564173	1.719118	-0.725062	C	1.230518	-0.137107	0.085095				
H	-4.587661	-0.006856	-0.968604	C	1.258690	-1.507428	-0.139648				

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Chapter 3

Aromatic C–H Coupling with Hindered Arylboronic Acids by Pd/Fe Dual Catalysts

Abstract

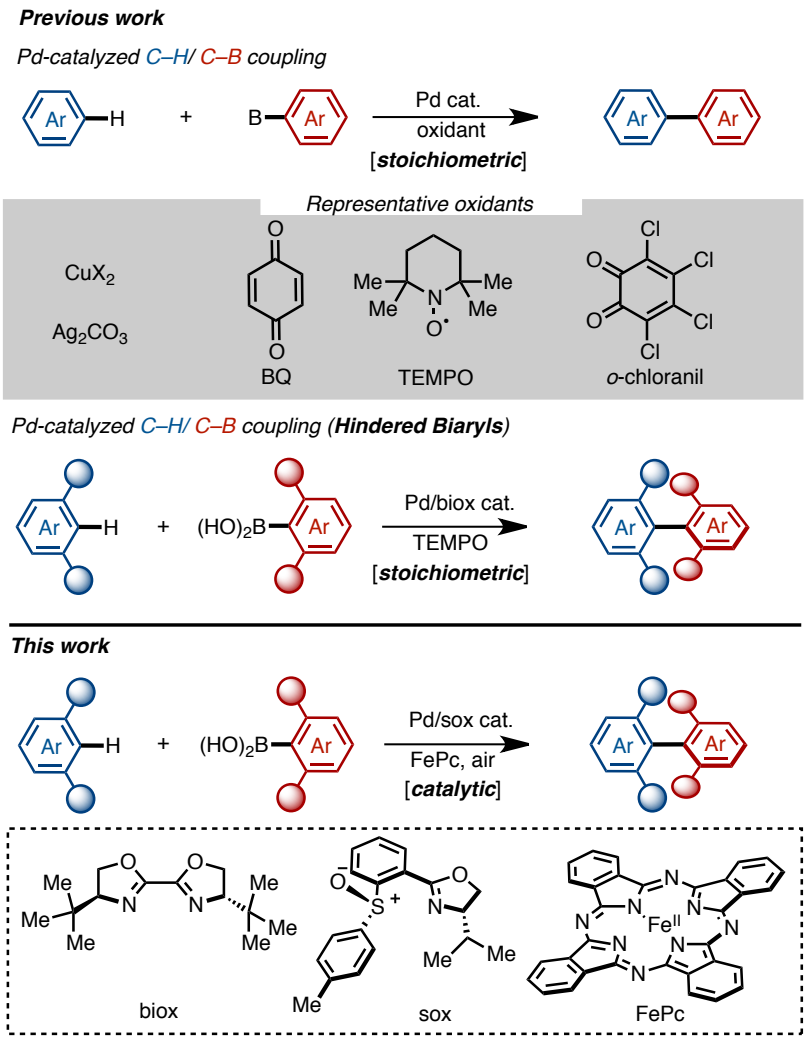
An aerobic oxidative coupling of arenes/alkenes with arylboronic acids (C–H/C–B coupling) using catalytic Pd(II)–sulfoxide–oxazoline (sox) ligand and iron–phthalocyanine (FePc) has been developed.

1. Introduction

The concept of C–H arylation has received much attention from the organic chemistry community because of its green and ideal way to introduce aryl groups to organic molecules without pre-functionalization. Many protocols have been established thus far for various aryl nucleophiles and electrophiles. One representative C–H arylation reaction involves the Pd-catalyzed C–H/C–B coupling between unfunctionalized arenes and arylboronic acids.[1–3] Although oxygen (air) is the ideal terminal oxidant to allow for a greener process, this C–H/C–B coupling reaction generally requires the use of stoichiometric co-oxidants such as Cu(II) halides, Ag(I) salts (Ag_2O, Ag_2CO_3) and 1,4-benzoquinone (BQ), 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), and *o*-chloranil.[4]

To exacerbate the problem, these catalysts display low reactivity, and occasionally reactions do not proceed when using sterically hindered substrates in either the (hetero)arene or the arylboronic acid coupling partner. In order to address this problem, the author and co-workers have developed a ligand-enabled C–H coupling for the synthesis of hindered heterobiaryls using a Pd/bisoxazoline (biox)/TEMPO catalytic system as described in the previous chapter.[5] However, the catalytic system used therein is not completely catalytic, since it requires TEMPO as a stoichiometric co-oxidant.

In this chapter, the author describes the discovery of a catalytic system that does not use any stoichiometric co-oxidant for the coupling of heteroarenes with hindered arylboronic acids (C–H/C–B coupling; Scheme 1). This is achieved by using a Pd(II)/ sulfoxide–oxazoline (sox) / iron-phthalocyanine (FePc) dual catalyst. The author first describes the experimental background that led to an aerobic catalytic system, followed by a discussion of the substrate scope. Furthermore, an approach toward an enantioselective biaryl coupling through C–H functionalization is also detailed.



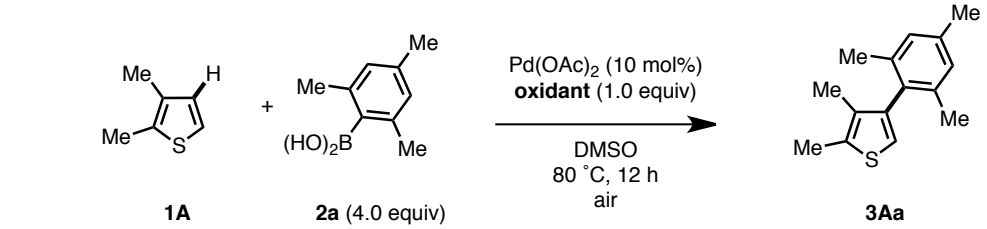
Scheme 1. Pd-catalyzed (hetero)biaryl formation by C–H/C–B coupling.

2. Results and discussion

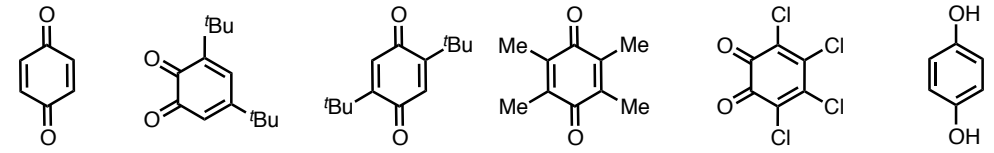
2-1. Discovery of a Pd/FePc catalytic system

The author began this study by searching a non-TEMPO co-oxidant for the aerobic C–H/C–B coupling of heteroarenes and hindered arylboronic acids. Gratifyingly, the author initially found that BQ could function as co-oxidant when the reactions were conducted in DMSO as a solvent (Scheme 2). For example, C–H/C–B coupling of 2,3-dimethylthiophene (**1A**: 1.0 equiv) and (2,4,6-trimethylphenyl)boronic acid (**2a**: 4.0 equiv) took place in the presence of $Pd(OAc)_2$ (10 mol%) and BQ (1.0 equiv) in DMSO at 80 °C for 12 h under air to furnish the corresponding coupling product **3Aa** in 83%

yield. Following this discovery, the author further investigated other quinone derivatives. 3,5-Di-*tert*-butyl-1,2-benzoquinone (*o*-DBQ) showed similar results, however, other quinone derivatives did not work very well. Other oxidants such as copper salts (*e.g.*, $Cu(OAc)_2$,) and peroxide (*e.g.*, ^{t}BuOOBz) were ineffective.



1A **2a** (4.0 equiv) **3Aa**



BQ	*o*-DBQ[a]	*p*-DBQ[b]	TMBQ[c]	*o*-chloranil	HQ[d]
3Aa: 83%	83%	32%	15%	ND	10%

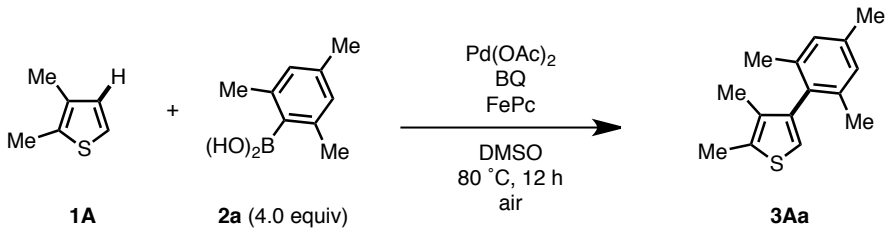
[a] 3,5-Di-*tert*-butyl-1,2-benzoquinone. [b] 2,5-Di-*tert*-butyl-1,4-benzoquinone. [c] 2,3,5,6-tetra-1,4-benzoquinone. [d] 1,4-hydroquinone.

***Scheme* 2.** Screening of non-TEMPO oxidant.

In order to render the coupling reaction catalytic in BQ, the author then applied Bäckvall's "triple" catalytic system using a metal-macrocycle (such as FePc and Co(salophen)) as a co-catalyst to re-oxidize hydroquinone to BQ by applying air (oxygen) as the terminal oxidant (Table 1).[6] Indeed, when the reaction was conducted in the presence of a catalytic amount of FePc (5 mol%), efficient coupling occurred even with a catalytic amount of BQ (entry 1). When hydroquinone (HQ) was used instead of BQ, the coupling product was obtained in equally good yield (entry 2). The yield of **3Aa** was decreased to 46% when the loading amount of FePc was lowered to 1 mol% (entry 3) and the reaction did not work at all without it (entry 4), demonstrating its indispensability. Curiously however, the loading amount of BQ did not influence the yield of **3Aa** (entry 5) and the yield was maintained without any BQ at all (entry 6). This reveals that the FePc catalyst does not function by oxidizing hydroquinone. Obviously, the reaction did not proceed without $Pd(OAc)_2$ (entry 7) and was very

sluggish under nitrogen atmosphere (entry 8). In all these reactions, the C4/C5 regioselectivity was always found to be greater than 95% selective at C4.

Table 1. Discovery of a Pd/Fe dual catalyst for the C–H arylation of thiophenes with arylboronic acids.



1A **2a** (4.0 equiv) **3Aa**

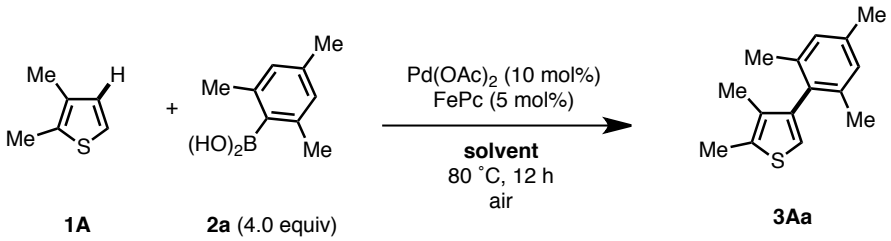
Entry	$Pd(OAc)_2$ (mol%)	BQ (mol%)	FePc (mol%)	Yield (%)
1	10	10	5	81
2[a]	10	10	5	80
3	10	10	1	46
4	10	10	—	trace
5	10	5	5	84
6	10	—	5	83
7	—	—	5	ND
8[b]	10	10	5	10

[a] HQ was used instead of BQ. [b] The reaction was conducted under nitrogen atmosphere.

2-2. Effect of DMSO

Having discovered the dramatic effect of the Pd/FePc catalytic system, the author next investigated solvent effects (Table 2). When the solvent was changed from DMSO to DMF, the yield of product **3Aa** decreased to 32% (entry 2), and other solvents were also ineffective.

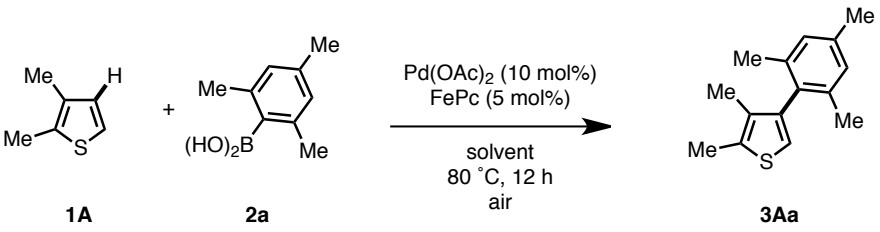
Table 2. Effect of solvent.



1A **2a** (4.0 equiv) **3Aa**

Entry	Solvent	Yield (%)
1	DMSO	83
2	DMF	32
3	DMAc	7
4	*i*-PrOH	ND
5	CH_3CN	trace
6	toluene	trace
7	NMP	12

Upon investigation of solvent effects, an intriguing phenomenon was observed (Scheme 3). When only 100 mol% DMSO was added (*i.e.*, no longer as solvent), the yield was maintained, and the same effect was observed for 20 mol% DMSO. It was assumed that the DMSO functions as a ligand, and therefore the author examined the effect of the ligand for the C–H/C–B coupling reaction.



1A **2a** **3Aa**

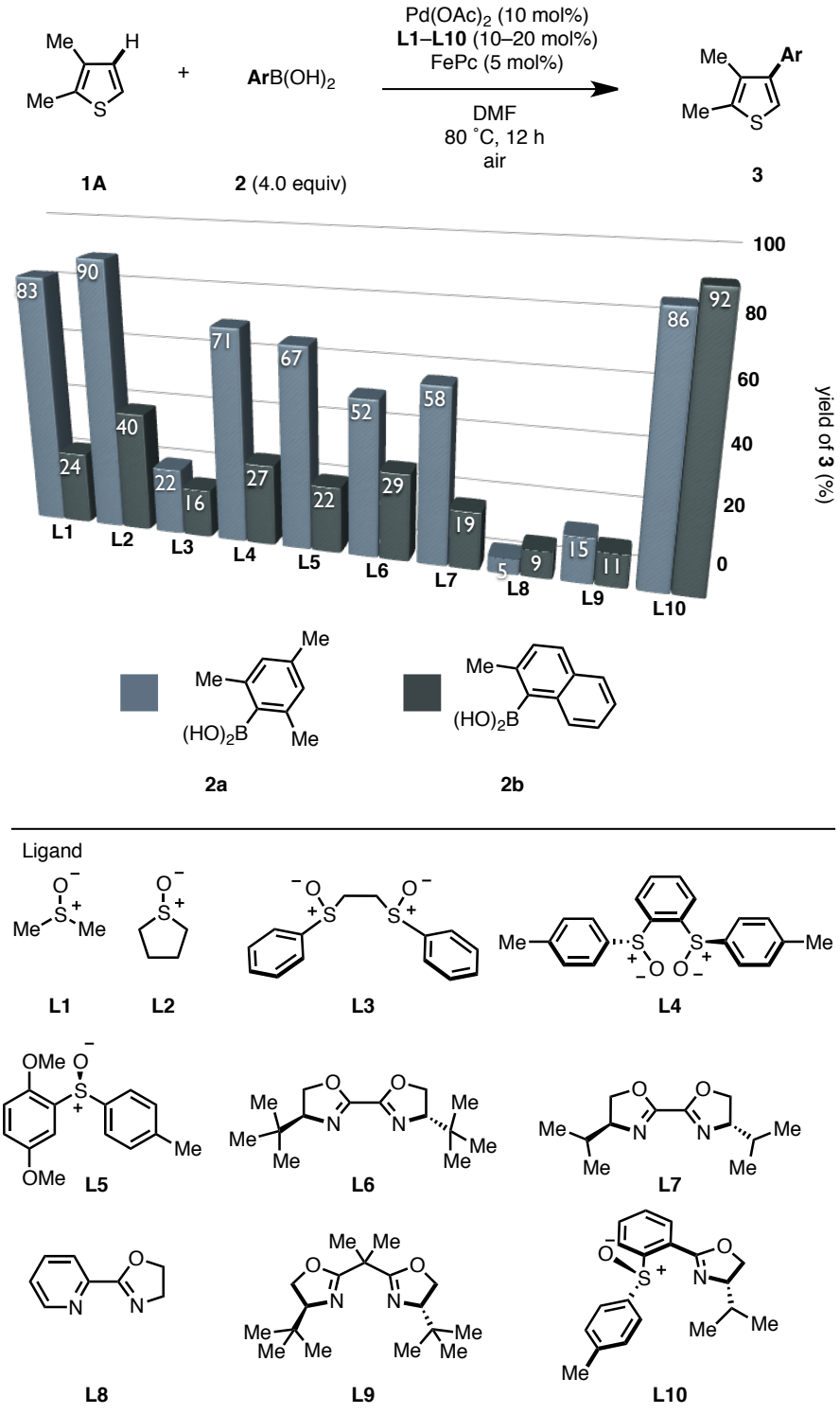
DMSO	83%
DMF	32%
DMF (100 mol% DMSO)	83%
DMF (20 mol%)	86%

Scheme 3. Effect of DMSO.

2-3. Discovery of sox ligand

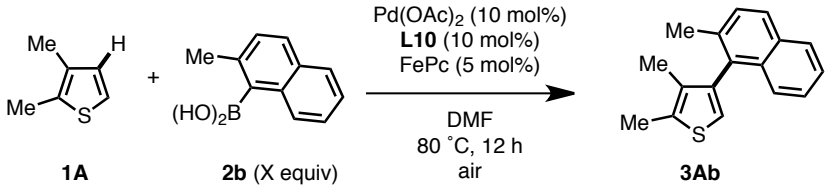
The author studied the effect of the ligand for the reaction between dimethylthiophene (**1A**) and arylboronic acids (**2a** and **2b**) in the presence of 10 mol% $Pd(OAc)_2$, 10–20 mol% ligand (**L1**–**L10**), and 5 mol% FePc in DMF at 80 °C under air for 12 h (Table 3). When DMSO was used as the ligand, the yield of **3Aa** was 83% whereas the yield of **3Ab** was 24% (**L1**). Tetramethylene sulfoxide (TMSO) and White's ligand,[7] which are effective for palladium-catalyzed C–H oxidation reactions, were ineffective for this reaction (**L2** and **L3**). Other bis-sulfoxide and mono-sulfoxide ligands (**L4** and **L5**)[8] were only effective when **2a** was used. Bis-oxazoline ligands **L6** and **L7**, which had accelerated a hindered C–H/C–B coupling reaction in our previous report,[5] slightly increased the yields of **3Aa** and **3Ab**. Other bidentate ligands such as **L8** and **L9** were not effective at all. After screening further ligands, the author noticed that sulfoxide and oxazoline ligands are effective, and the author therefore hypothesized that a hybrid ligand should be much more effective for this reaction. To this end, sox ligand (**L10**)[9] was applied to the reaction, smoothly reacting with both arylboronic acid substrates to give **3Aa** and **3Ab** in 86% and 92% yields, respectively.

Table 3. Discovery of a suitable "hybrid" ligand for oxidative C–H coupling.



The author next attempted to reduce the amount of arylboronic acid (Table 4). Gratifyingly, it was found that the reaction equally took place when the amount of arylboronic acid was reduced from 4.0 equiv to 2.0 equiv (entries 1 and 2), and the yield of **3Ab** was 61% with equimolar amounts of the reaction partners (**1A**/**2b** = 1) (entry 4).

Table 4. Effect of the amount of arylboronic acid.



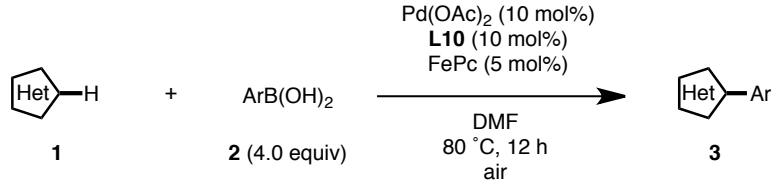
1A **2b** (X equiv) **3Ab**

Entry	**2b** (equiv)	Yield (%)
1	4.0	92
2	2.0	89
3	1.5	77
4	1.0	61

2-4. Substrate scope

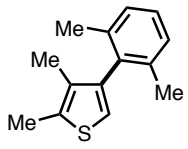
With optimal conditions in hand, the author explored the substrate scope of the C–H/C–B coupling of various heteroaromatics and arylboronic acids for the synthesis of hindered heterobiaryls (Table 5). (2,6-Dimethylphenyl)boronic acid (**2c**) and sterically more hindered (2-isopropylnaphthalen-1-yl)boronic acid (**2d**) gave the corresponding coupling products **3Ac** and **3Ad** in good yields. Thiophene derivatives **1B–1E** afforded the coupling products **3Ba**, **3Cb**, **3Db**, **3Ea**, and **3Eb** in moderate to good yields. The coupling of indole derivatives **1F–1H** with hindered arylboronic acids gave heterobiaryls **3Fa**, **3Ga**, **3Ha**, and **3Hb** in slightly lower yields compared with the thiophene series, but was regioselective, favoring the C3 position of indole (87 to >95% C3-selectivity). Pyrroles **1I** and **1J** as well as a furan derivative **1K** can be used as heteroarenes to afford the corresponding products in good yield with virtually complete C2-selectivity at the 5-membered heteroarene **3Ia**, **3Ib**, **3Jb**, **3Jd**, and **3Ka**.[10,11]

Table 5. Scope of heteroaromatics and arylboronic acids.

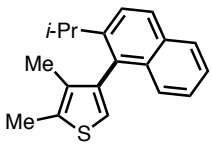


1 **2** (4.0 equiv) **3**

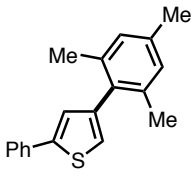
Product (yield)



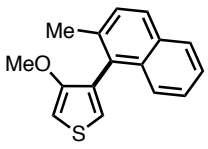
3Ac (69%)



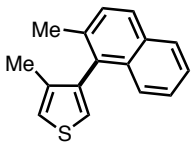
3Ad (70%)[a]



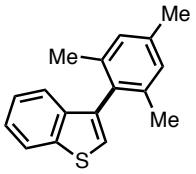
3Ba (53%)



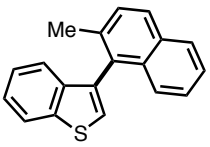
3Cb (63%)



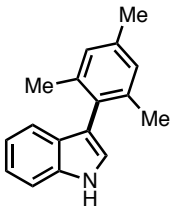
3Db (67%)



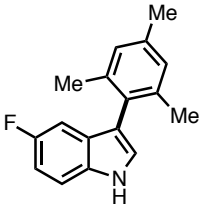
3Ea (73%)



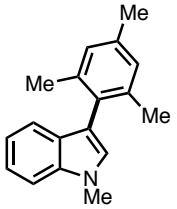
3Eb (80%)



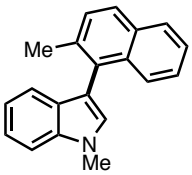
3Fa (57%)[b]



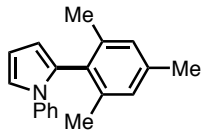
3Ga (47%)[c]



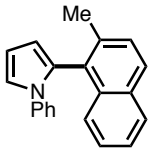
3Ha (49%)



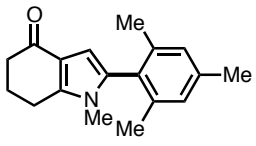
3Hb (86%)[c]



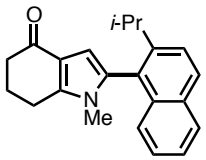
3Ia (41%)



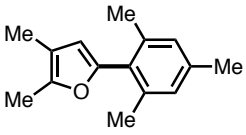
3Ib (49%)



3Jb (89%)



3Jd (55%)

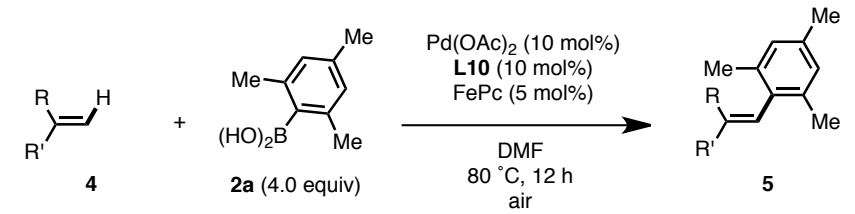


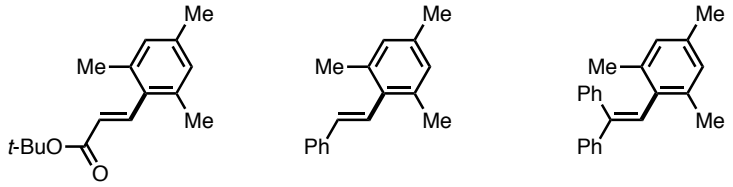
3Ka (80%)[d,e]

[a] The regioselectivity of C4/C5 = 90:10. [b] The regioselectivity of C3/C2 = 88:12. [c] The regioselectivity of C3/C2 = 87:13.
[d] DMSO was used as a solvent. [e] Without **L10**.

When alkenes were used instead of heteroarenes, the reaction also proceeded smoothly to give the corresponding coupling products (**5La**, **5Ma**, and **5Na**) in good to excellent yields (Table 6).[12]

Table 6. Oxidative coupling of alkenes with hindered arylboronic acid.



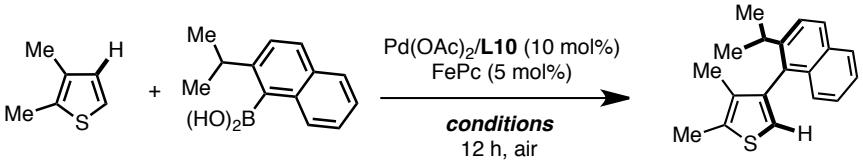


[a] DMSO was used as a solvent. [b] Without **L10**.

2-5. Application to enantioselective C–H coupling.

Finally, this catalytic C–H coupling was applied to an enantioselective C–H coupling reaction. The author studied the reaction between dimethylthiophene (**1A**) and arylboronic acids **2d** in the presence of 10 mol% $Pd(OAc)_2$, 10 mol% **L10**, and 5 mol% FePc in DMF or DMAc under air (Table 7). It was found that this reaction in DMF furnishes (*S*)-**3Ad** with 45% *ee* (entry 1).[5] When the solvent was changed to DMAc, the *ee* was increased to 55% *ee* (entry 2). Next, when the solvent concentration was diluted, the *ee* was slightly increased (entry 3). Finally, the author investigated reaction *ee* changes due to temperature (entries 3–5). The optimal reaction temperature was 70° C (61% *ee*).

Table 7. Reaction optimization for an enantioselective C–H coupling reaction.

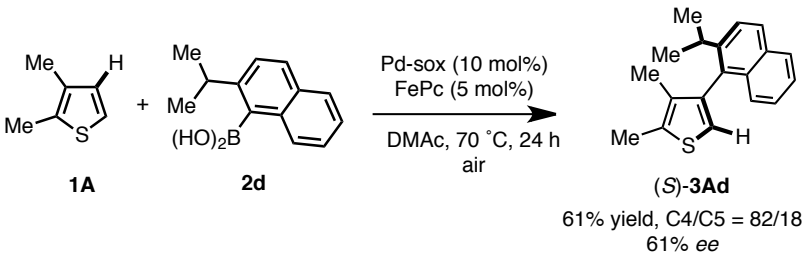


1A **2d** (4.0 equiv) (*S*)-**3Ad**

Entry	Solvent	Conc (M)	Temp (˚C)	Yield (%)	C4/C5[a]	Ee (%)[b]
1	DMF	1.25	80	70	90:10	45
2	DMAc	1.25	80	57	86:14	55
3[c]	DMAc	0.5	80	54	85:15	58
4[c]	DMAc	0.5	70	61	82:18	61
5[c]	DMAc	0.5	60	52	87:13	54

[a] Determined by ^{1}H NMR. [b] Determined by chiral HPLC (OD-H).[c] Reaction time was 24 h.

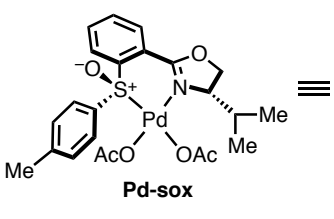
During the optimization, the isolation of $Pd(OAc)_2$-sox (**L10**) complex was successful and it was used for the enantioselective C–H coupling reaction (Scheme 4). The coupling reaction of 2,3-dimethylthiophene (**1A**) and (2-isopropylnaphthalen-1-yl)boronic acid (**2d**) was conducted in the presence of 10 mol% Pd-sox catalyst and 5 mol% FePc in DMAc at 70 °C under air. As a result, the enantioselectivity of the corresponding coupling product (*S*)-**3Ad** was 61% *ee*. Although the enantioselectivity did not increase compared to the previous report described in Chapter 2,[5] the reaction yield was greater.



1A **2d** (*S*)-**3Ad**

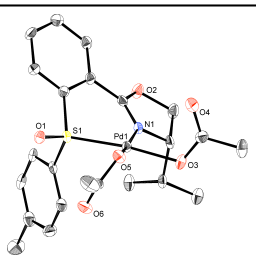
61% yield, C4/C5 = 82/18

61% *ee*



Pd-sox

≡



Scheme 4. Enantioselective C–H coupling reaction.

3. Conclusion

In summary, an efficient catalytic system (Pd/sox/FePc) that operates with air as a terminal oxidant for the coupling of arenes/alkenes with arylboronic acids (C–H/C–B coupling) has been discovered. This catalytic system enabled the synthesis of hindered heterobiaryls in good yields, and provided an approach toward an enantioselective C–H coupling reaction.

4. Experimental section

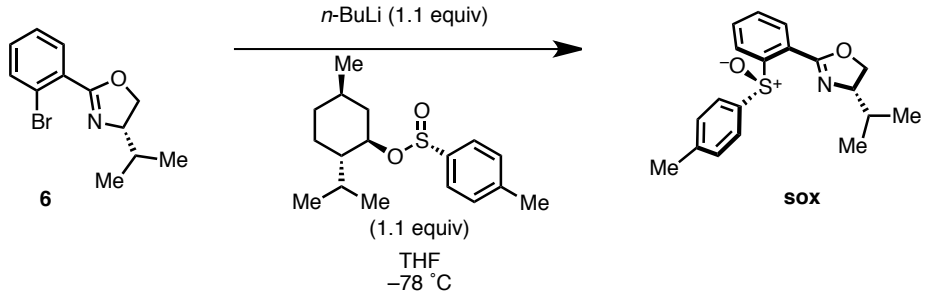
4-1. General

Unless otherwise noted, all materials including dry solvents were obtained from commercial suppliers and used as received. 1-Methyl-6,7-dihydro-1*H*-indol-4(5*H*)-one (**1J**),[13] 2-methylnaphthalen-1-ylboronic acid (**2b**),[14] 2-isopropylnaphthalen-1-ylboronic acid (**2d**),[5] and **L4,**[8] **L5,**[15] **L10 (sox)**[9] were synthesized 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 C–H bond arylation reactions were performed in screw cap 20 mL glass vessel tubes and heated in an 8-well reaction block (heater + magnetic stirrer) unless otherwise noted. 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). Flash column chromatography was performed with E. Merck silica gel 60 (230–400 mesh). Preparative thin-layer chromatography (PTLC) was performed using Wakogel B5-F silica coated plates (0.75 mm) prepared in our laboratory. Preparative high performance liquid chromatography (preparative HPLC) was performed with a Biotage Isolera®, one equipped with Biotage SNAP Cartridge KP-C18-HS columns using acetonitrile/water 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 JMS-T100TD (DART) or JMS-700 (FAB) instruments. Chiral HPLC analysis was conducted on a Shimadzu Prominence 2000 instrument equipped with DAICEL Chiracel OD-H (4.6 mm x 250 mm). Nuclear magnetic resonance (NMR) spectra were recorded on JEOL ECS-400 (^{1}H 400 MHz, ^{13}C 100 MHz) or JEOL ECA-600 (^{1}H 600 MHz, ^{13}C 150 MHz) spectrometers. Chemical shifts for ^{1}H NMR are expressed in parts per million (ppm) relative to tetramethylsilane (δ 0.00 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,

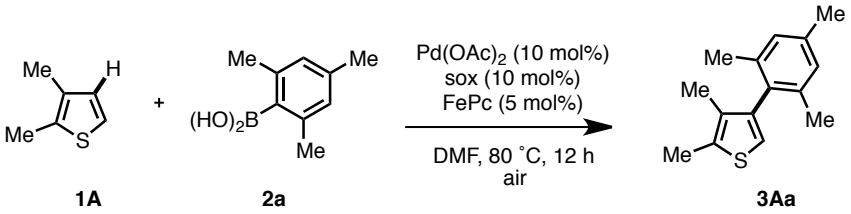
q = quartet, sep = septet, m = multiplet, br = broad signal), coupling constant (Hz), and integration.

4-2. Preparation of ligand (sox)



To a solution of (*S*)-2-(2-bromophenyl)-4-isopropyl-4,5-dihydrooxazole[16] (**6**: 678 mg, 3.0 mmol) in THF (15 mL) was slowly added *n*-BuLi (1.6 M in hexane, 2.1 mL, 3.3 mmol) at –78 ˚C under nitrogen atmosphere. After stirring at –78 ˚C for 1 h, a solution of (1*R*,2*S*,5*R*)-(-)-menthyl (*S*)-*p*-toluenesulfinate (971 mg, 3.3 mmol) in THF (15 m L) was added dropwise, stirred at –78 ˚C for 30 min, then room temperature for 30 min. To the mixture was added saturated aqueous NH_4Cl and the mixture was extracted with EtOAc. The organic layer was washed with water, brine, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica-gel column chromatography (hexane/EtOAc = 3:1) to give the desired product (**sox**) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.91 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.75–7.68 (m, 1H), 7.58–7.48 (m, 3H), 7.16 (d, *J* = 8.2 Hz, 2H), 4.34 (dd, *J* = 9.2, 7.3 Hz, 1H), 4.15–4.01 (m, 2H), 2.32 (s, 3H), 1.82–1.70 (m, 1H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.72 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.65, 146.19, 143.62, 140.85, 131.79, 130.19, 129.68, 129.47, 126.45, 125.56, 125.28, 73.29, 69.84, 32.44, 21.28, 18.93, 17.85; HRMS (DART) *m*/*z* calcd for $C_{19}H_{22}NO_2S$ $[M+H]^+$: 328.1371, found: 328.1373.

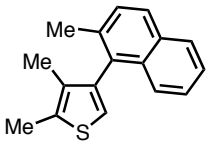
4-3-1. General procedure for C–H coupling with hindered arylboronic acid



To a screw cap 20 mL glass vessel containing a magnetic stirring bar were added 2,3-dimethylthiophene (**1A**: 28 mg, 0.25 mmol), mesitylboronic acid (**2a**: 164 mg, 1.0 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), sox (8.2 mg, 0.025 mmol), FePc (7.1 mg, 0.0125 mmol) and DMF (0.2 mL). The mixture was stirred at 80 ˚C for 12 h under air, cooled to room temperature, passed through a short pad of silica gel (EtOAc) and the filtrate was evaporated under reduced pressure. The residue was purified by preparative thin-layer chromatography (hexane) to give **3Aa** (50 mg, 86%, C4/C5 = 99:1) as a colorless oil. The yield was as isolated yield, and C4/C5 ratio was determined by ^{1}H NMR.

2,3-Dimethyl-4-(2-methylnaphthalen-1-yl)thiophene[5] **(3Aa):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 2H), 6.68 (s, 1H), 2.40 (s, 3H), 2.32 (s, 3H), 1.97 (s, 6H), 1.76 (s, 3H).

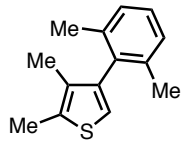
4-3-2. Compound data of coupling product.



3Ab

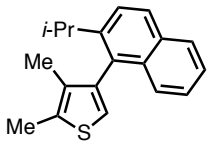
2,3-Dimethyl-4-(2-methylnaphthalen-1-yl)thiophene[5] **(3Ab):** Following the general procedure with 2,3-dimethylthiophene (**1A**: 28 mg) and (2-methylnaphthalene-1-yl)boronic acid (**2b**: 186 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3Ab** (58 mg, 92%, C4/C5 = 98:2) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86–7.73 (m, 2H), 7.44–7.31 (m,

4H), 6.84 (s, 1H), 2.47 (s, 3H), 2.22 (s, 3H), 1.71 (s, 3H).



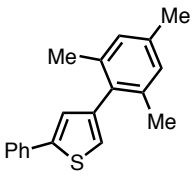
3Ac

4-(2,6-dimethylphenyl)-2,3-dimethylthiophene[5] **(3Ac):** Following the general procedure with 2,3-dimethylthiophene (**1A**: 28 mg) and (2,6-dimethylphenyl)boronic acid (**2c**: 150 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give the coupling product **3Ac** (37 mg, 69%, C4/C5 = 97:3) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.18–7.12 (m, 1H), 7.08 (d, *J* = 7.8 Hz, 2H), 6.69 (s, 1H), 2.41 (s, 3H), 2.01 (s, 6H), 1.76 (s, 3H).



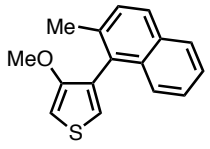
3Ad

4-(2-Isopropylnaphthalen-1-yl)-2,3-dimethylthiophene[5] **(3Ad):** Following the general procedure with 2,3-dimethylthiophene (**1A**: 28 mg) and (2-isopropylnaphthalene-1-yl)boronic acid (**2d**: 214 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give the coupling product **3Ad** (49 mg, 70%, C4/C5 = 90:10) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.7 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.52 (d, *J* = 8.7 Hz, 1H), 7.43–7.29 (m, 3H), 6.85 (s, 1H), 2.97–2.85 (m, 1H), 2.47 (s, 3H), 1.71 (s, 3H), 1.20 (d, *J* = 7.3 Hz, 3H), 1.17 (d, *J* = 6.9 Hz, 3H).



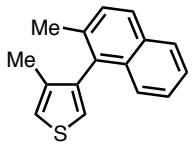
3Ba

4-Mesityl-2-phenylthiophene (3Ba): Following the general procedure with 2-phenylthiophene (**1B**: 40 mg) and mesitylboronic acid (**2a**: 164 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3Ba** (37 mg, 53%, C4/C5 = 99:1) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.62 (m, 2H), 7.38 (t, *J* = 8.0 Hz, 2H), 7.32–7.25 (m, 1H), 7.15 (d, *J* = 1.2 Hz, 1H), 6.96–6.94 (m, 3H), 2.33 (s, 3H), 2.12 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.97, 141.69, 136.96, 136.91, 134.41, 133.90, 128.89, 128.05, 127.44, 125.67, 125.05, 121.89, 21.03, 20.71; HRMS (DART) *m*/*z* calcd for $C_{19}H_{19}S$ $[M+H]^+$: 279.1207, found: 279.1209.



3Cb

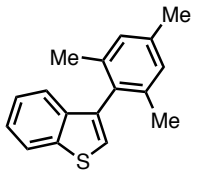
3-Methoxy-4-(2-methylnaphthalen-1-yl)thiophene (3Cb): Following the general procedure with 3-methoxylthiophene (**1C**: 29 mg) and (2-methylnaphthalene-1-yl)boronic acid (**2b**: 186 mg), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 50:1) to give **3Cb** (40 mg, 63%, C4/C5 = >99:1) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.76 (m, 2H), 7.52 (d, *J* = 9.1 Hz, 1H), 7.41–7.33 (m, 3H), 7.08 (d, *J* = 3.4 Hz, 1H), 6.43 (d, *J* = 3.4 Hz, 1H), 3.74 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.96, 135.07, 133.37, 131.93, 130.97, 130.59, 128.45, 127.78, 127.72, 125.88, 125.77, 124.72, 123.39, 96.59, 57.48, 20.51; HRMS (DART) *m*/*z* calcd for $C_{16}H_{15}OS$ $[M+H]^+$: 255.0844, found: 255.0845.



3Db

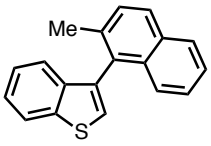
3-Methyl-4-(2-methylnaphthalen-1-yl)thiophene[5] **(3Db):** Following the general procedure with 3-methylthiophene (**3D**: 25 mg) and 2-methylnaphthalene-1-lyboronic acid (**2b**: 186 mg), the crude product was purified by preparative thin-layer

chromatography (hexane) to give **3Db** (40 mg, 67%, C4/C5 = >99:1) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.76 (m, 2H), 7.42–7.34 (m, 4H), 7.13–7.12 (m, 1H), 7.08 (d, *J* = 3.2 Hz, 1H), 2.22 (s, 3H), 1.86 (s, 3H).



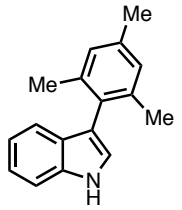
3Ea

3-Mesitylbenzo[*b*]thiophene (3Ea): Following the general procedure with benzo[*b*]thiophene (**1E**: 34 mg) and mesitylboronic acid (**2a**: 164 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3Ea** (46 mg, 73%, C4/C5 = >99:1) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.39–7.33 (m, 1H), 7.32–7.25 (m, 2H), 7.18 (s, 1H), 6.99 (s, 2H), 2.37 (s, 3H), 1.98 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.00, 138.89, 137.71, 137.30, 136.40, 131.91, 128.12, 124.23, 124.08, 123.30, 122.74, 122.67, 21.11, 20.24; HRMS (DART) *m*/*z* calcd for $C_{17}H_{17}S$ $[M+H]^+$: 253.1051, found: 253.1051.



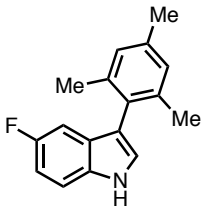
3Eb

3-(2-Methylnaphthalen-1-yl)benzo[*b*]thiophene[5] **(3Eb):** Following the general procedure with benzo[*b*]thiophene (**1E**: 34 mg) and (2-methylnaphthalene-1-yl)boronic acid (**2b**: 186 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **3Eb** (55 mg, 80%, C4/C5 = >99:1) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.1 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.46 (d, *J* = 8.5 Hz, 1H), 7.42–7.32 (m, 4H), 7.30–7.19 (m, 2H), 7.15 (d, *J* = 8.1 Hz, 1H), 2.21 (s, 3H).



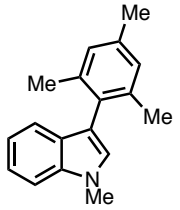
3Fa

3-Mesityl-1*H*-indole (3Fa): Following the general procedure with indole (**1F**: 29 mg) and mesitylboronic acid (**2a**: 164 mg), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 5:1) to give **3Fa** (34 mg, 57%, C3/C2 = 88:12) as an orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (brs, 1H), 7.45–7.41 (m, 1H), 7.26–7.18 (m, 2H), 7.10–7.01 (m, 2H), 6.99 (s, 2H), 2.36 (s, 3H), 2.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.41, 136.52, 135.97, 130.86, 127.96, 127.37, 122.40, 121.93, 119.89, 119.55, 115.82, 111.02, 21.06, 20.77; HRMS (DART) *m*/*z* calcd for $C_{17}H_{18}N$ $[M+H]^+$: 236.1439, found: 236.1439.



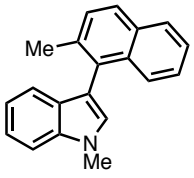
3Ga

5-Fluoro-3-mesityl-1*H*-indole (3Ga): Following the general procedure with 5-fluoro-1*H*-indole (**1G**: 34 mg) and mesitylboronic acid (**2a**: 164 mg), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 5:1) to give **3Ga** (29 mg, 47%, C3/C2 = 87:13) as a purple solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.36–7.32 (m, 1H), 7.08 (d, J = 2.0 Hz, 1H), 6.98–6.93 (m, 3H), 6.90–6.78 (m, 1H), 2.35 (s, 3H), 2.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.56 (d, J_{FC} = 236 Hz), 138.31, 136.78, 132.47, 130.28, 128.04, 127.88 (d, J_{FC} = 15 Hz), 124.19, 116.07 (d, J_{FC} = 4.8 Hz), 111.61 (d, J_{FC} = 9.6 Hz), 110.39 (d, J_{FC} = 27 Hz), 104.58 (J_{FC} = 23 Hz), 21.06, 20.71; HRMS (DART) *m*/*z* calcd for $C_{17}H_{17}FN$ $[M+H]^+$: 254.1345, found: 254.1345.



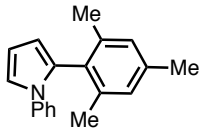
3Ha

3-Mesityl-1-methyl-1*H*-indole (3Ha): Following the general procedure with *N*-methylindole (**1H:** 33 mg) and mesitylboronic acid (**2a**: 164 mg), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 5:1) to give **3Ha** (31mg, 49%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.35 (m, 1H), 7.27–7.22 (m, 2H), 7.09–7.04 (m, 1H), 6.98 (s, 2H), 6.87 (s, 1H), 3.85 (s, 3H), 2.35 (s, 3H), 2.06 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.39, 136.83, 136.35, 130.99, 127.95, 127.85, 127.09, 121.43, 120.04, 118.98, 114.27, 109.10, 32.77, 21.06, 20.87; HRMS (DART) *m*/*z* calcd for $C_{18}H_{20}N$ $[M+H]^+$: 250.1596, found: 250.1596.



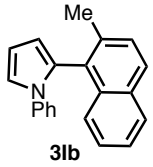
3Hb

1-Methyl-3-(2-methylnaphthalen-1-yl)-1*H*-indole (3Hb): Following the general procedure with *N*-methylindole (**1H**: 33 mg) and (2-methylnaphthalene-1-yl)boronic acid (**2b**: 186 mg), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 7:1) to give **3Hb** (53mg, 86%, C3/C2= 87:13) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.46 (t, *J* = 9.2 Hz, 2H), 7.41–7.37 (m, 1H), 7.31–7.25 (m, 2H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.08–7.04 (m, 2H), 3.93 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.82, 135.46, 134.24, 132.08, 130.62, 128.67, 128.53, 128.26, 127.68, 127.04, 126.61, 125.53, 124.60, 121.64, 120.35, 119.24, 112.84, 109.22, 32.88, 21.15; HRMS (DART) *m*/*z* calcd for $C_{20}H_{18}N$ $[M+H]^+$: 272.1439, found: 272.1439.



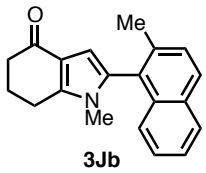
3Ia

2-Mesityl-1-phenyl-1*H*-pyrrole (3Ia): Following the general procedure with 1-phenyl-1*H*-pyrrole (**1I**: 36 mg) and mesitylboronic acid (**2a**: 164 mg), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 20:1) and reverse phase HPLC using Isolera® to give **3Ia** (27 mg, 41%) as a purple solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.18 (m, 2H), 7.15–7.13 (m, 1H), 7.04–6.99 (m, 3H), 6.81 (s, 2H), 6.38 (t, *J* = 3.2 Hz, 1H), 6.14–6.11 (m, 1H), 2.26 (s, 3H), 1.98 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.60, 138.57, 137.48, 131.18, 130.23, 128.70, 127.94, 125.76, 123.75, 121.03, 110.72, 108.87, 21.08, 20.54; HRMS (DART) *m*/*z* calcd for $C_{19}H_{20}N$ $[M+H]^+$: 262.1596, found: 262.1597.



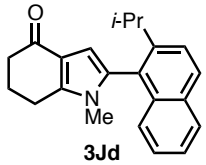
3Ib

2-(2-Methylnaphthalen-1-yl)-1-phenyl-1*H*-pyrrole (3Ib): Following the general procedure with 1-phenyl-1*H*-pyrrole (**1I**: 36 mg) and (2-methylnaphthalene-1-yl)boronic acid (**2b**: 186 mg), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 20:1) and reverse phase HPLC using Isolera® to give **3Ib** (35 mg, 49%) as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.75 (m, 2H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.43–7.37 (m, 2H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.13–7.01 (m, 4H), 6.98–6.93 (m, 2H), 6.50 (t, *J* = 4.0 Hz, 1H), 6.33–6.29 (m, 1H), 2.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.34, 136.57, 134.45, 131.82, 129.46, 128.61, 128.24, 128.07, 127.72, 126.16, 125.93, 124.81, 123.91, 121.69, 112.05, 109.05, 20.56; HRMS (DART) *m*/*z* calcd for $C_{21}H_{18}N$ $[M+H]^+$: 284.1439, found: 284.1437.



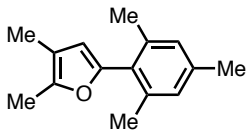
3Jb

1-Methyl-2-(2-methylnaphthalen-1-yl)-6,7-dihydro-1*H*-indol-4(5*H*)-one (3Jb): Following the general procedure with 1-methyl-6,7-dihydro-1*H*-indol-4(5*H*)-one (**1J**: 37 mg) and (2-methylnaphthalene-1-yl)boronic acid (**2b**: 186 mg), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 1:1) to give **3Jb** (60 mg, 89%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 8.7, 2.8 Hz, 2H), 7.47–7.33 (m, 4H), 6.55 (s, 1H), 3.11 (s, 3H), 2.91–2.84 (m, 2H), 2.62–2.53 (m, 2H), 2.33–2.21 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.25, 143.86, 137.02, 134.06, 131.84, 131.79, 128.80, 128.31, 127.87, 127.82, 126.54, 125.47, 125.15, 120.36, 106.22, 37.84, 30.80, 23.64, 22.16, 20.56; HRMS (DART) *m*/*z* calcd for $C_{20}H_{20}NO$ $[M+H]^+$: 290.1545, found: 290.1547.



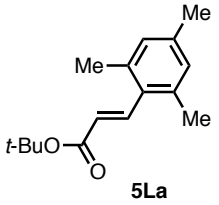
3Jd

2-(2-Isopropylnaphthalen-1-yl)-1-methyl-6,7-dihydro-1*H*-indol-4(5*H*)-one (3Jd): Following the general procedure with 1-methyl-6,7-dihydro-1*H*-indol-4(5*H*)-one (**1J**: 37 mg) and (2-isopropylnaphthalene-1-yl)boronic acid (**2d**: 214 mg), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 1:1) to give **3Jd** (43 mg, 55%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.7 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.45–7.38 (m, 2H), 7.31–7.24 (m, 1H), 6.57 (s, 1H), 3.10 (s, 3H), 3.03–2.92 (m, 1H), 2.90–2.81 (m, 2H), 2.62–2.51 (m, 2H), 2.31–2.21 (m, 2H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.19 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.22, 147.40, 143.77, 134.00, 131.78, 131.37, 129.48, 127.80, 126.51, 126.16, 125.78, 125.25, 123.59, 120.28, 106.51, 37.81, 30.89, 30.83, 24.51, 23.60, 23.11, 22.14; HRMS (DART) *m*/*z* calcd for $C_{22}H_{23}NO$ $[M+H]^+$: 318.1858, found: 318.1857.



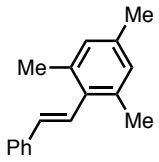
3Ka

5-Mesityl-2,3-dimethylfuran (3Ka): To a screw cap 20 mL glass vessel containing a magnetic stirring bar were added 2,3-dimethylfuran (**1K**: 24 mg, 0.25 mmol), mesitylboronic acid (**2a**: 164 mg, 1.0 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), FePc (7.1 mg, 0.0125 mmol) and DMSO (0.2 mL). The mixture was stirred at 80 ˚C for 12 h under air, cooled to room temperature, passed through a short pad of silica gel (EtOAc) and the filtrate was evaporated under reduced pressure. The residue was purified by preparative thin-layer chromatography (hexane) to give the product as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (s, 2H), 6.00 (s, 1H), 2.29 (s, 3H), 2.23 (s, 3H), 2.19 (s, 6H), 2.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.00, 146.16, 138.05, 137.78, 128.63, 128.24, 114.46, 112.34, 21.06, 20.64, 11.33, 10.01; HRMS (DART) *m*/*z* calcd for $C_{15}H_{19}O$ $[M+H]^+$: 215.1436, found: 215.1438.



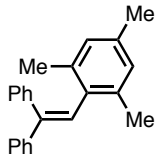
5La

(*E*)-*tert*-Butyl 3-mesitylacrylate (5La): Following the general procedure with *tert*-butyl acrylate (**4L**: 32 mg) and mesitylboronic acid (**2a**: 164 mg), the crude product was purified by preparative thin-layer chromatography (hexane/EtOAc = 20:1) to give **5La** (55 mg, 89%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 16.5 Hz, 1H), 6.88 (s, 2H), 5.97 (d, *J* = 16.5 Hz, 1H), 2.33 (s, 6H), 2.28 (s, 3H), 1.56 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.41, 142.01, 138.02, 136.80, 131.07, 129.06, 124.85, 80.42, 28.23, 21.13, 21.01; HRMS (DART) *m*/*z* calcd for $C_{16}H_{23}O_2$ $[M+H]^+$: 247.1698, found: 247.1698.



5Ma

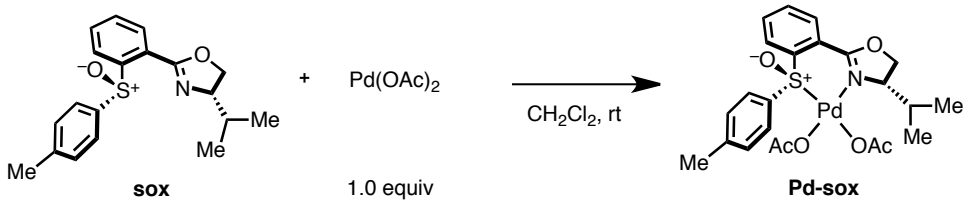
(*E*)-1,3,5-Trimethyl-2-styrylbenzene (5Ma): To a screw cap 20 mL glass vessel containing a magnetic stirring bar were added styrene (**4M**: 26 mg, 0.25 mmol), mesitylboronic acid (**2a**: 164 mg, 1.0 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), FePc (7.1 mg, 0.0125 mmol) and DMSO (0.2 mL). The mixture was stirred at 80 ˚C for 12 h under air, cooled to room temperature, passed through a short pad of silica gel (EtOAc) and the filtrate was evaporated under reduced pressure. The residue was purified by preparative thin-layer chromatography (hexane) to give **5Ma** (54 mg, 98%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.8 Hz, 2H), 7.37 (t, *J* = 7.8 Hz, 2H), 7.30–7.25 (m, 1H), 7.10 (d, *J* = 16.4 Hz, 1H), 6.91 (s, 2H), 6.59 (d, *J* = 16.4 Hz, 1H), 2.34 (s, 6H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.71, 136.30, 136.15, 133.96, 133.62, 128.69, 128.63, 127.43, 126.88, 126.20, 21.00, 20.96; HRMS (DART) *m*/*z* calcd for $C_{17}H_{19}$ $[M+H]^+$: 223.1487, found: 223.1482.



5Na

(2-Mesitylethene-1,1-diyl)dibenzene (5Na): Following the general procedure with ethene-1,1-diyldibenzene (**4N**: 45 mg) and mesitylboronic acid (**2a**: 164 mg), the crude product was purified by preparative thin-layer chromatography (hexane) to give **5Na** (49 mg, 65%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.28 (m, 5H), 7.17–7.08 (m, 3H), 7.00–6.93 (m, 2H), 6.80 (s, 1H), 6.75 (s, 2H), 2.23 (s, 3H), 2.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.17, 143.56, 140.38, 136.14, 135.94, 133.91, 129.80, 128.40, 128.09, 128.03, 127.66, 127.52, 127.40, 127.05, 20.98, 20.45; HRMS (DART) *m*/*z* calcd for $C_{23}H_{23}$ $[M+H]^+$: 299.1800, found: 299.1801.

4-5. Preparation of Pd-sox complex



Crystals of $Pd(OAc)_2$/sox (**Pd-sox**) were obtained by vapor diffusion of pentane into a $CHCl_3$ solution of $Pd(OAc)_2$ and **sox** (1.0 equiv) at room temperature. $Pd(OAc)_2$ (11.2 mg, 0.050 mmol) and **sox** (16.4 mg, 0.050 mmol) were dissolved with dichloromethane (1.0 mL). The solution was evaporated under reduced pressure. The residue was dissolved with $CHCl_3$ and then transferred into a vial containing pentane. The vial was sealed with a Teflon cap and maintained at room temperature. Yellow crystalline plate formed. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 8.2 Hz, 1H), 8.18 (d, J = 8.7 Hz, 2H), 8.08–7.97 (m, 2H), 7.88–7.81 (m, 1H), 7.30 (d, J = 8.7 Hz, 2H), 4.46 (t, J = 9.6 Hz, 1H), 4.36–4.24 (m, 2H), 2.54–2.41 (m, 1H), 2.39 (s, 3H), 2.07 (s, 3H), 2.03 (s, 3H), 0.85 (d, J = 6.9 Hz, 3H), 0.09 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.02, 160.54, 145.39, 140.46, 136.93, 134,66, 133.60, 132.38, 130.50, 130.32, 128.31, 127.18, 120.90, 69.97, 69.61, 29.95, 22.19, 21.56, 19.35, 13.78; HRMS (FAB) m/z calcd for $C_{21}H_{24}NO_4PdS$ $[M–OAc]^+$: 492.0461, found: 492.0457.

4-6. X-ray crystal structure analysis of Pd-sox

A suitable crystal was mounted with mineral oil on a glass fiber and transferred to the goniometer of a Rigaku Saturn CCD diffractometer. Graphite-monochromated Mo Kα radiation (λ = 0.71070 Å) was used. The structures were solved by direct methods with (SIR-97)[17] and refined by full-matrix least-squares techniques against F^2 (SHELXL-97).[18] The intensities were corrected for Lorentz and polarization effects. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed using AFIX instructions. Details of the crystal data and a summary of the intensity data collection parameters for **Pd-sox** are listed in Table 8.

Table 8. Crystallographic data and structure refinement details for **Pd-sox**.

	Pd-sox
Formula	$C_{24}H_{28}Cl_3NO_6PdS$
Fw	671.28
T (K)	103(2)
λ (Å)	0.71070
cryst syst	Monoclinic
space group	$P2_1$
a, (Å)	9.3736(10)
b, (Å)	15.1780(11)
c, (Å)	10.1053(9)
α, (deg)	90
β, (deg)	107.302(4)
γ, (deg)	90
V, (Å^3)	1372.7(2)
Z	2
D_{calc}, (g / cm^3)	1.642
μ (mm^{-1})	1.083
F(000)	680
cryst size (mm)	0.15 × 0.15 × 0.15
2θ range, (deg)	3.54–25.00
reflns collected	8294
indep reflns / R_{int}	4743 / 0.0287
params	330
GOF on F^2	1.024
R_1, wR_2 [I>2s(I)]	0.0261, 0.0686
R_1, wR_2 (all data)	0.0289, 0.0696
abs struct param	-0.02(2)

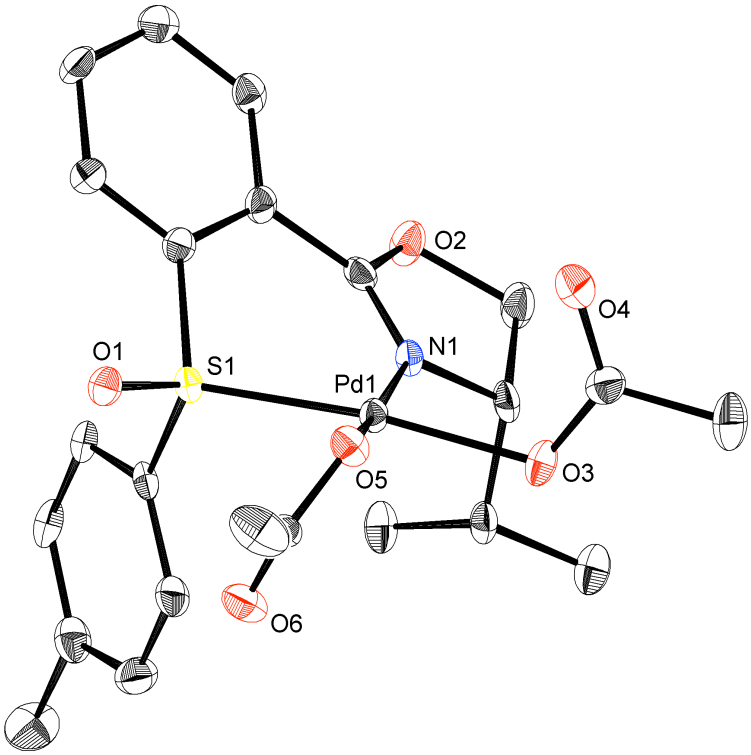
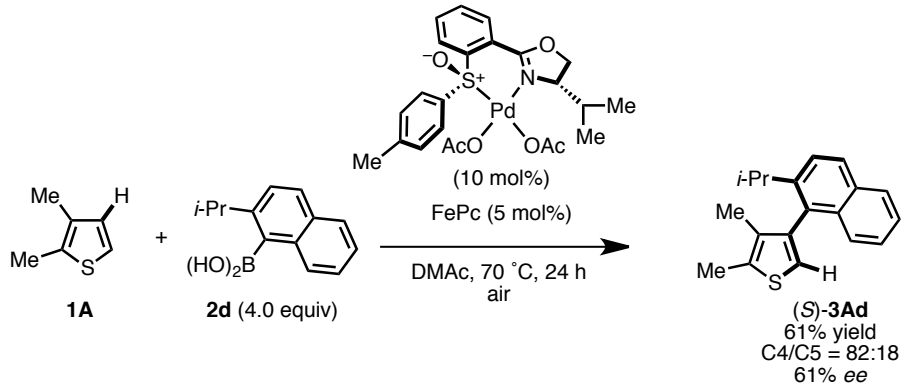


Figure 1. ORTEP drawing of **Pd-sox** with 50% thermal ellipsoid. All hydrogen atoms and solvent molecule are omitted for clarity.

4-7-1. Enantioselective C–H coupling



To a screw cap 20 mL glass vessel containing a magnetic stirring bar were added 2,3-dimethylthiophene (**1A**: 28 mg, 0.25 mmol), (2-isopropylnaphtalene-1-yl)boronic acid (**2d**: 214 mg, 1.0 mmol), **Pd-sox** (13.8 mg, 0.025 mmol), FePc (7.1 mg, 0.0125 mmol) and DMAc (0.5 mL). The mixture was stirred at 70 ˚C for 24 h under air, cooled to room temperature, passed through a short pad of silica gel (EtOAc) and the filtrate was evaporated under reduced pressure. The residue was purified by preparative thin-layer chromatography (hexane) to give (*S*)-**3Ad** (43 mg, 61%, C4/C5 = 82:18, 61% *ee*) as a colorless oil. The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column, UV detected at 254 nm, flow rate 1.0 mL/min (hexane). Retention times (tr); major enantiomer tr = 9.6 min, minor enantiomer tr = 7.8 min. According to the literature value,[5] the absolute configuration was determined as *S*-configuration.

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