NANYANG
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# Part I: Desymmetrization of Cyclic Olefins *via* Asymmetric Heck Reaction and Hydroarylation
# Part II: Fast Suzuki Coupling of Aryl Tosylates

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# Part II: Fast Suzuki Coupling of Aryl Tosylates

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A thesis submitted to the Nanyang Technological University in fulfillment of the requirement for the degree of Doctor of Philosophy

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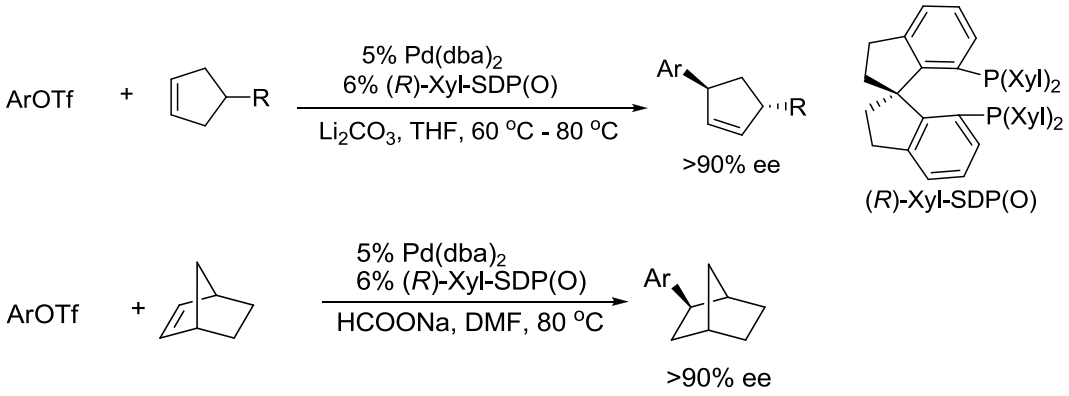
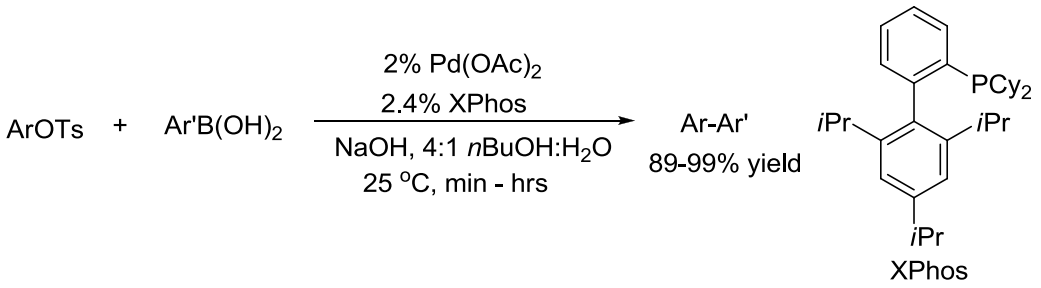
## Summary

Part 1. Asymmetric Heck reaction of substituted cyclopentenes gave one stereoisomer in excellent enantio- and diastereoselectivities. The high selectivity as unprecedented in Heck reaction. (*R*)-Xyl-SDP(O) was uniquely effective as chiral ligand. Various aryl triflates can be used. The same catalyst can be applied to asymmetric hydroarylation of norbornene and other bicyclic derivatives in excellent ee.




Part 2. A general procedure for fast Suzuki coupling of heteroaryl tosylates as developed. Most major families of heteroaryls can couple at room temperature. The method is generally applicable to major families of heterocyclic substrates, and most reactions completed within minutes to hours.



## List of Abbreviations

| | |
|---|---|
| δ | chemical shift (ppm) |
| ℃ | degree centigrade |
| Ac | acetyl |
| acac | acetylacetonyl |
| AIBN | 2,2'-azo *bis*isobutyronitrile |
| Ar | aryl (substituted aromatic ring) |
| Bn | benzyl |
| Boc | *t*-butoxycarbonyl |
| Bu | butyl |
| Br | broad singlet |
| calcd | calculated |
| cat. | catalytic |
| cm-1 | wave number |
| d | doublet |
| dd | doublet of doublets |
| ddd | doublet of doublet of doublets |
| dppm | *bis*(diphenylphosphino)methane |
| dq | doublet of quartets |
| DBU | 1,8-diazabicyclo[5.4.0]undec-7-ene |
| DMAP | 4-dimethylaminopyridine |
| DMF | *N*,*N*-dimethylformamide |
| EDG | electron donating group |
| Ee | enantiomeric excess |
| Equiv | equivalent |
| Et | ethyl |
| EWG | electron withdrawing group |
| Hz | hertz |
| *i*-Pr | *iso*-propyl |

| | |
|---|---|
| IR | infrared spectroscopy |
| *J* | coupling constants |
| LA | Lewis acid |
| M | concentration (mol/L) |
| M+ | parent ion peak (mass spectrum) |
| m | multiplet |
| Me | methyl |
| mg | milligram |
| MHz | megahertz |
| mmol | millimole |
| MOM | methoxymethyl |
| mp | melting point |
| Ms | methanesulfonyl |
| NMR | nuclear magnetic resonance |
| q | quartet |
| rt | room temperature |
| s | singlet |
| t | triplet |
| Tf | trifluoromethanesulfonyl |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TMS | trimethylsilyl |
| Ts | *p*-toluenesulfonyl |

# Part 1. Desymmetrization of Cyclic Olefins *via* Asymmetric Heck Reaction and Hydroarylation

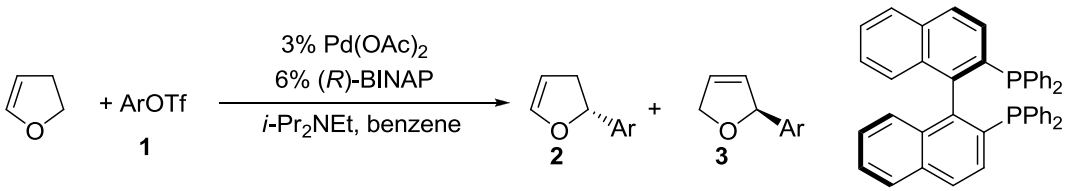
## 1.1 General Introduction

Mizoroki-Heck reaction is Pd-catalyzed arylation of olefins which was first reported independently by Heck and Mizoroki in the early 1970s.[1,2] Today, it is widely applied in the syntheses of pharmaceuticals, agrochemicals and advanced materials.[3,4] The reaction is atom-economic by allowing direct displacement of one vinylic C-H bond with one C-aryl bond and by using commonly available aryl halides or aryl sulfonates as coupling partners.

### 1.1.1 Recent Developments of Intermolecular Asymmetric Heck reaction

The first example of asymmetric Heck reaction between aryl triflates and 2,3-dihydrofuran was reported by Hayashi in 1991.[5] Chiral BINAP was employed as supporting ligand to give up to 93% *ee* (Table 1.1). Notably, the double-bond migration isomers were the major products.

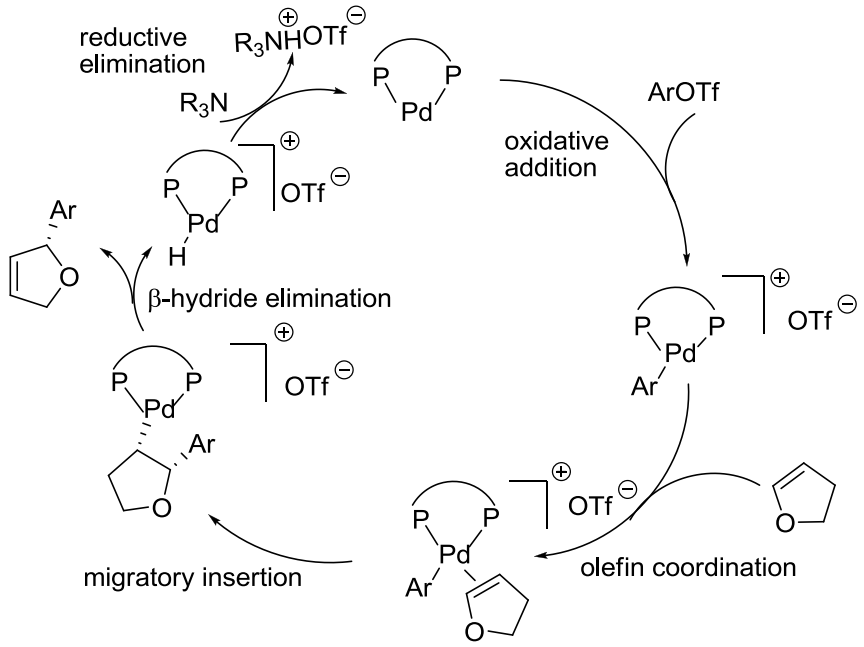
**Table 1.1** First example of intermolecular Heck reaction



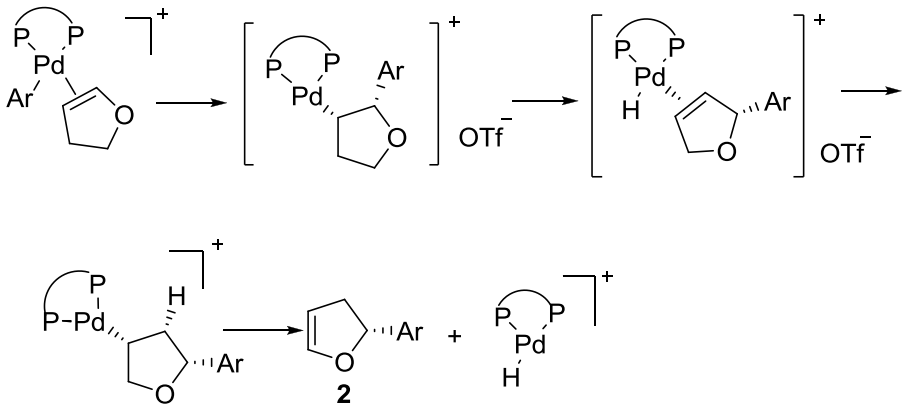

| Entry | ArOTf | Yield (%) of **2** | ee (%) of **2** | **2**/**3** |
|---|---|---|---|---|
| 1 | Ph | 71 | 93 | 89/11 |
| 2 | *p*-$ClC_6H_4$ | 86 | 91 | 83/17 |
| 3 | *p*-$CH_3C_6H_4$ | 76 | 93 | 80/20 |
| 4 | *p*-$NCC_6H_4$ | 79 | 93 | 77/23 |

The catalytic cycle *via* the cationic pathway is shown below (Scheme 1.1). Oxidative addition of ArOTf to Pd(0)(BINAP) provides the cationic phenyl-Pd(II) complex. Olefin insertion then takes place to form an alkyl-Pd species. Subsequent

β-hydride elimination cannot take place using the benzylic hydrogen since it anti to the Pd center. Thus, syn β-hydride elimination happens on the other direction to give the immediate Heck isomers carrying a new stereocenter. Deprotonation of the resulting hydridopalladium complex by a base regenerates the catalytically active species (BINAP)Pd(0). The resulting Pd hydride will have a chance to reinsert into the bound Heck product and cause double-bond migration, if the hydride species is not removed quickly (Scheme 1.2).



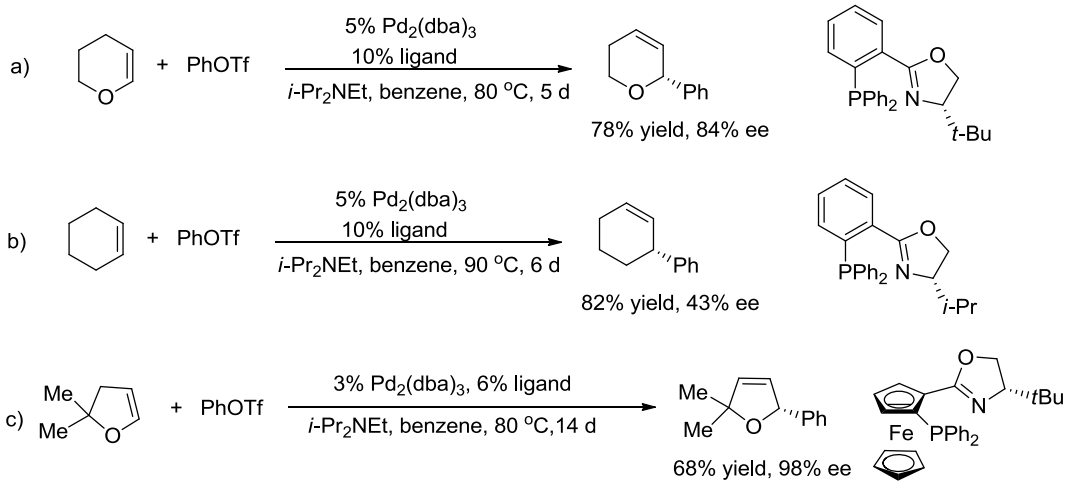

**Scheme 1.1** A catalytic cycle of asymmetric Heck reaction of 2,3-dihydrofuran




**Scheme 1.2** Product isomerization in asymmetric Heck reaction

Since then, a wide range of phosphorus-based chiral ligands have been invented and tested in the asymmetric Heck reaction, with the purpose of finding a more general and stereoselective catalyst. Most of them can be classified into three types: bisphosphines, *P,N*-ligands and bisphosphites.[6]

For example, Pfaltz's PHOX ligand allowed several olefins to couple in high ee without double-bond migration.[7] It can even use difficult six-membered olefins including 2,3-dihydropyran and cyclohexene (Scheme 1.3). However, one significant limitation is that the catalytic turnover was very slow and the reactions usually took a few days to finish. Another example of P,N-ligands was developed by Guiry et al. which were built on a ferrocene backbone. A hindered dialkylated 2,3-dihydrofuran can be coupled in high ee, which was difficult to insert previously due to steric reasons (Scheme 1.3c).[8]

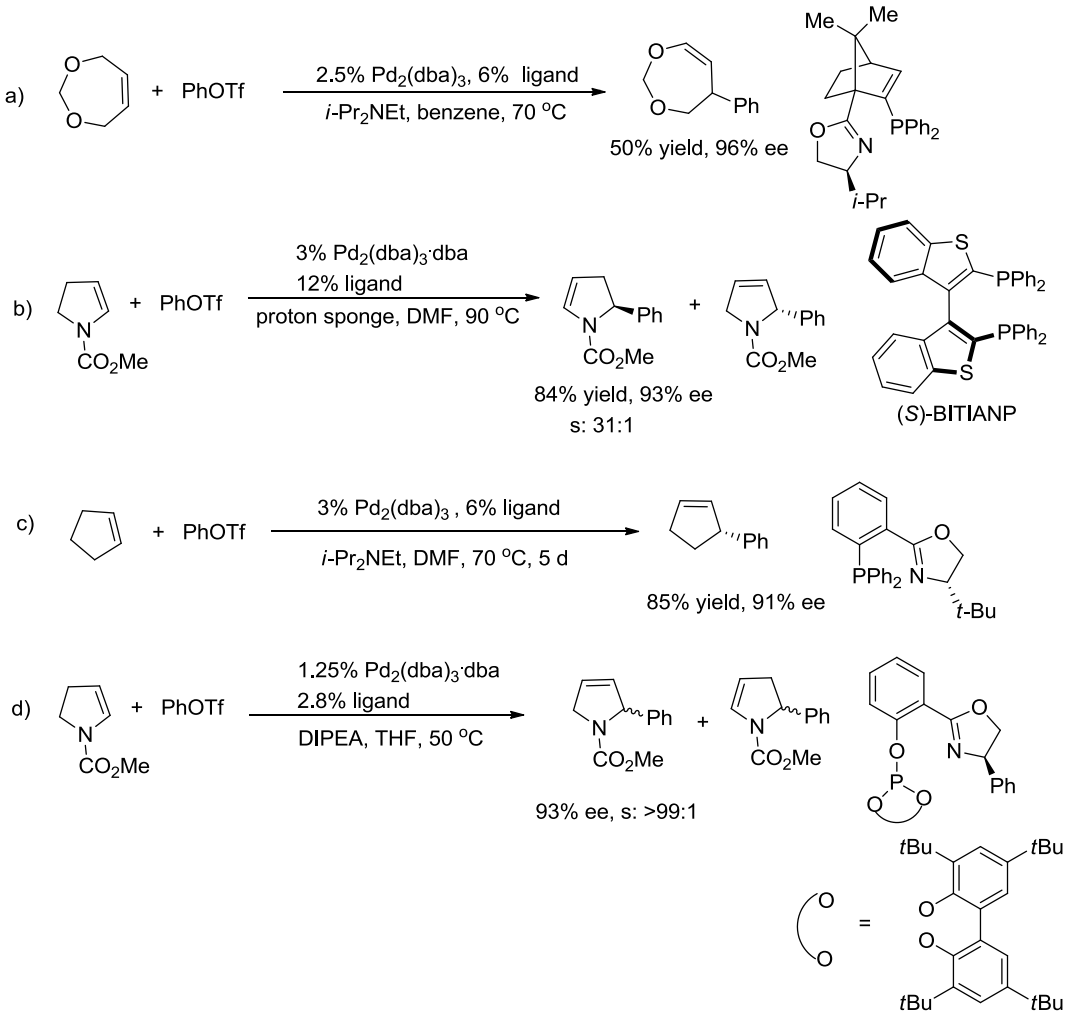



**Scheme 1.3** Asymmetric Heck reaction of challenging olefins

Many other *P,N*-ligands have been examined since then in this asymmetric reaction. For example, Gilbertson *et al.* invented a phosphine-oxazoline based on a norbornyl skeleton. Although for some examples of olefins, high ee was observed, the catalytic activity was limited (Scheme 1.4a).[9]

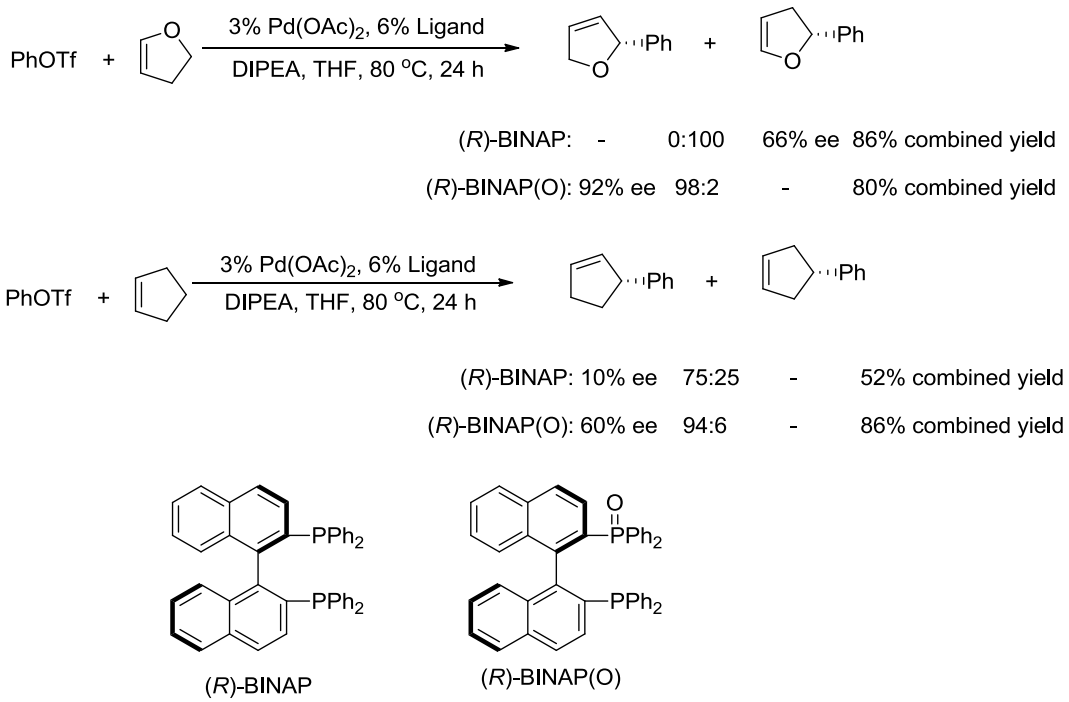
Tietze *et al.* applied (*S*)-BITIANP in asymmetric Heck reactions of 2,3-dihydropyrrole and phenyl triflate.[6g] Excellent *ee* was achieved with 31:1

selectivity favoring the double-bond migration isomers (Scheme 1.4b). The phenylation of cyclopentene also gave good results but with long reaction time (Scheme 1.4c).[7] Phosphite-oxazoline ligands have also been applied in the Pd-catalyzed asymmetric Heck reactions. Several aryl triflates gave arylation products in high selectivities and *ee*s (Scheme 1.4d).[6d]




**Scheme 1.4** Asymmetric Heck reaction of easy cyclic olefins

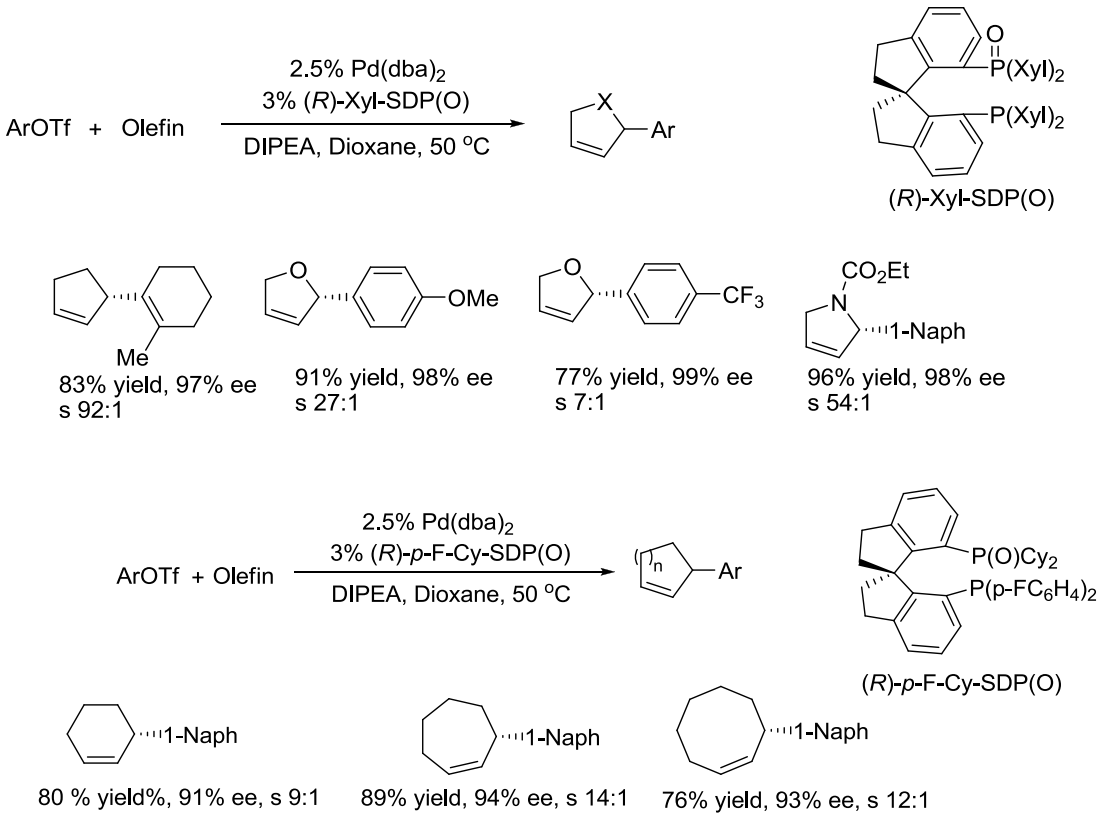
In 2012, Oestreich *et al.* reported that a new type of chiral ligands, bisphosphine oxide BINAP(O). It proved to be more active and stereoselective than BINAP in the Heck reactions.[10] However, for most examples of aryl triflates, the *ee* was below 90% and the scope of olefins was limited (Scheme 1.5).




**Scheme 1.5** The use of Chiral BINAP(O) in asymmetric Heck reaction

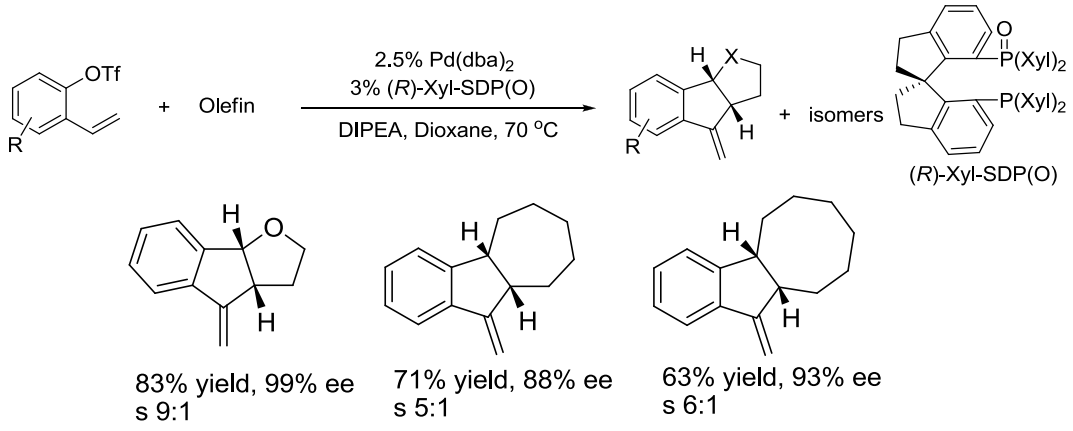
Around the same time, Dr. Jian Hu in our group also discovered that BINAP(O) performed much better than BINAP in the asymmetric Heck reaction of aryl triflate and cyclic olefins (Scheme 1.6).[11] In subsequent research, he found that (*R*)-Xyl-SDP(O), which was built on a spiro backbone, gave much better results. Cyclic olefins of different ring sizes can be applied. Excellent ee and high olefinic selectivity were achieved in many examples.

For the difficult olefin substrate, cyclohexene, (*R*)-Xyl-SDP(O) gave only 83% ee. A modified ligand, (*R*)-*p*-F-Cy-SDP(O) eventually gave >90% ee, but the reaction was limited to 1-napthyl triflate. PhOTf did not react using this new ligand. If the fluorine atom was removed, the corresponding ligand was much less active.



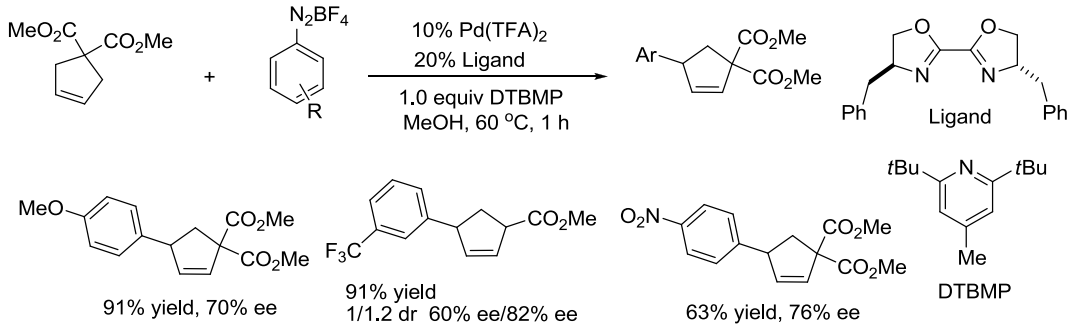

**Scheme 1.6** Asymmetric Heck reaction using SDP oxides as ligands

In 2013, Dr. Jian Hu accomplished domino cyclizations by using *o*-vinylphenyl triflates (Scheme 1.7).[12] Up to 99% *ee* and good olefinic selectivities were achieved. Bicyclic olefins such as norbornene can also be used to give excellent *ee*. The method was applied in asymmetric synthesis of a key intermediate towards (-)-martinellic acid in 99% *ee*.



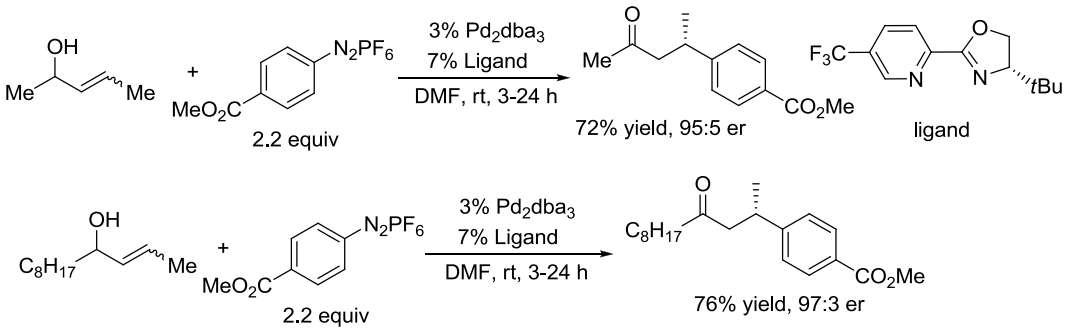

**Scheme 1.7** Asymmetric cascade Heck reactions

The cationic aryl-Pd species generated from aryldiazonium salts usually possess higher reactivity than those obtained from aryl triflates. Thus, they can couple with hindered, substituted cyclic olefins. In 2012, Correia *et al.* reported asymmetric Heck-Matsuda reaction between substituted cyclopentenes and aryldiazonium salts (Scheme 1.8).[13a] A chiral bisoxazoline was employed as the catalyst. Only one example of monosubstituted cyclopentene was tested and it gave poor 1:1.2 *dr* and 82% *ee* from the major isomer. Thus, the stereoselectivity needs significant improvement for the reaction to be synthetically useful.

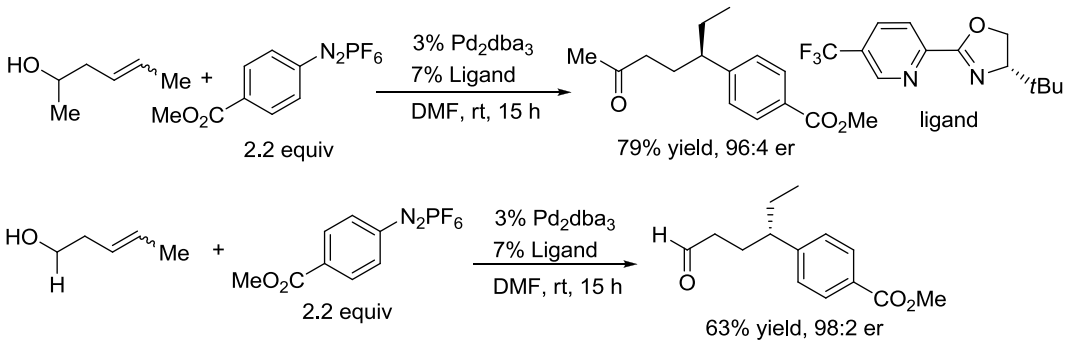



**Scheme 1.8** Asymmetric Heck-Matsuda reaction of substituted cyclopentenes

In 2012, Sigman *et al.* reported enantioselective Heck-Matsuda reaction of acyclic olefins containing distant alcohol groups using aryldiazonium salts. Arylated aldehydes and ketones were obtained carrying distant new stereocenters in high ee (Scheme 1.9).[14] A chiral pyridine-oxazoline ligand was used as auxiliary ligands which were compatible with the Heck-Matsuda process. Phosphine ligands were known to inhibit the catalytic reaction. γ-aryl ketone products can also be obtained with excellent ee (Scheme 1.10). Both (*Z*) and (*E*)-alkenes worked well.




**Scheme 1.9** Asymmetric Heck reaction of allylic alcohols

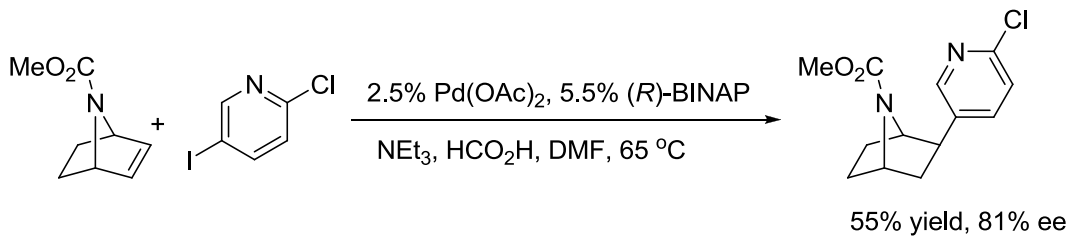



**Scheme 1.10** Selective γ-aryl ketone formation

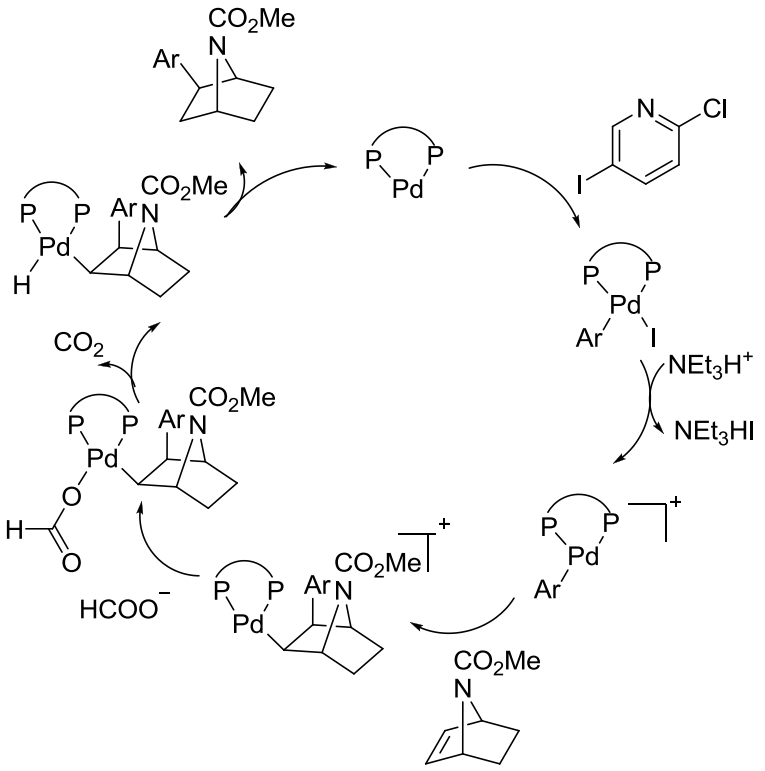
### 1.1.2 Introduction of Asymmetric Hydroarylation

Palladium-catalyzed hydroarylation of olefins occurs in the presence of a hydride donor. Thus, the alkyl-Pd species undergo C-H reductive elimination instead of β-hydride elimination. But no stereoselective catalyst was reported to give satisfactory ee before our study.

The asymmetric hydroarylation method can provide a quick route towards (-)-epibatidine. Epibatidine was an alkaloid isolated from skin of poisonous frog. It showed strong analgesic activity and was 500-times more potent than morphine.[15] In 1999, Kaufmann *et al.* reported an asymmetric synthesis of *N*-protected epibatidine via hydroarylation.[15d] The (*R*)-BINAP ligand gave the epibatidine in 81% *ee* (Scheme 1.11). The revised catalytic cycle by us was shown in Scheme 1.12. We believe that cationic $Et_3NH^+$ species from a combination of $Et_3N$ and HCOOH is important for iodide dissociation from the neutral aryl-Pd species via NH/halide hydrogen bonding.[16]

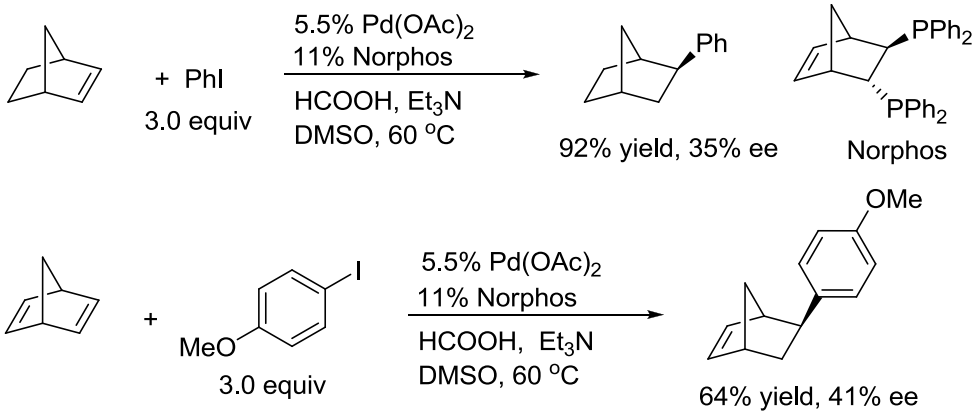



**Scheme 1.11** Synthesis of *N*-protected epibatidine



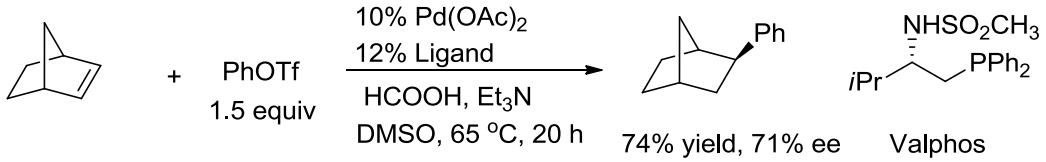

**Scheme 1.12** Catalytic cycle of synthesis of *N*-protected epibatidine

In 1991, Brunner *et al.* reported the first asymmetric hydroarylation of norbornene and norbornadiene (Scheme 1.13).[17] Bisphosphine Norphos gave quite poor ee. Aryl insertion occurred at the less hindered *exo* face of norbornene. The absolute configuration of the major isomer was not determined.




**Scheme 1.13**Asymmetric hydroarylation employing Norphos ligand

Later, Zhou and coworkers reported improved but still moderate *ee* in the asymmetric hydroarylation of norbornene by employing a chiral *P,N*-ligand Valphos derived from valine (Scheme 1.14).[18] The reaction was limited to only one example of phenyl triflate and norbornene. No other example was reported.

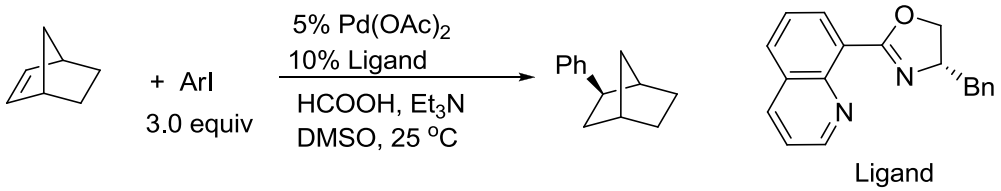



**Scheme 1.14** Asymmetric hydroarylation using Valphos

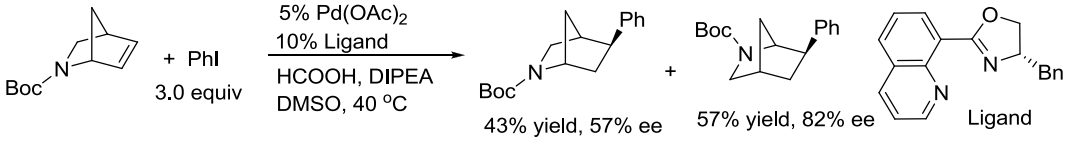
In 2001, Zhou *et al.* attempted asymmetric hydroarylation by employing a quinoline-oxazoline as the supporting ligand (Table 1.2).[19a] Moderate *ee*s and yields were obtained again. The absolute configuration of products was determined to be 2,R after a Ru-catalyzed oxidation of the phenyl ring in the product to carboxylic acid.

Notably, phenyl triflate did not react under the reported conditions. The authors also attempted to use nitrogen-substituted norbornene analogue as the olefin component (Scheme 1.15).[19b] The regioselectivities between two sites of the olefin were very poor.

**Table 1.2** Asymmetric hydroarylation of norbornene using quinoline-oxazoline ligand

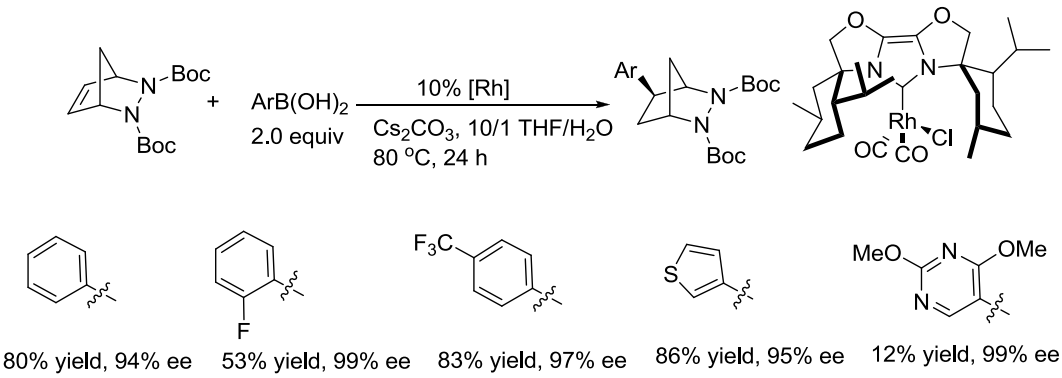



| Entry | ArI | Time | Yield (%) | e.e (%) |
|---|---|---|---|---|
| 1 | PhI | 66 h | 52 | 67 |
| 2 | PhOTf | 7 days | n.d. | n.d. |
| 3 | p-$MeOC_6H_4I$ | 60 h | 59 | 75 |
| 4 | p-$O_2NC_6H_4I$ | 96 h | 29 | 53 |

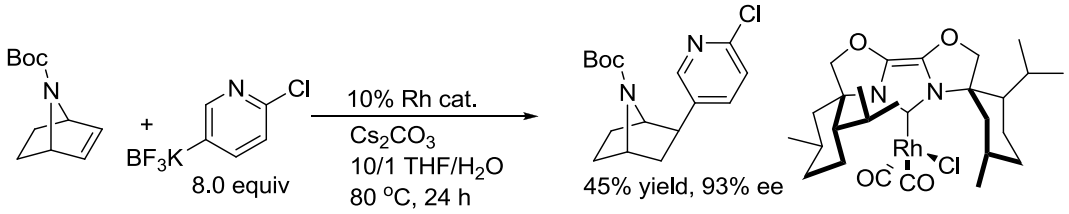



**Scheme 1.15** Asymmetric hydroarylation of heteronorbornene

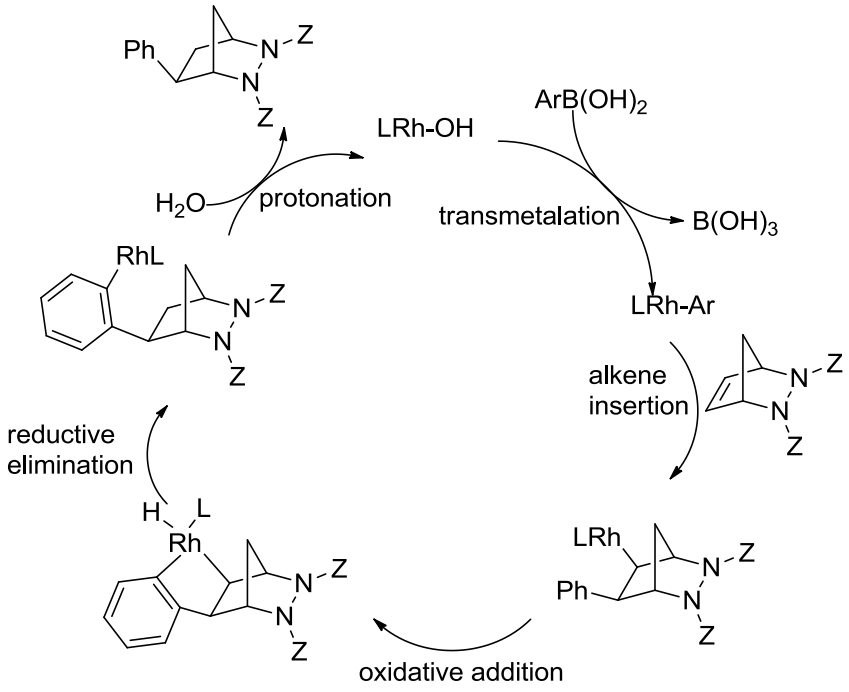
Recently, Lautens *et al.* disclosed rhodium-catalyzed asymmetric hydroarylation of bicyclic olefins using arylboronic acids.[20] Excellent *ee* was achieved by employing a chiral NHC ligand (Scheme 1.16). The reaction of the less-reactive norbornene was not reported. The method was applied to the synthesis of *N*-Boc-epibatidine in >90% ee, but the yield was low even when a large excess of aryltrifluoroborate was used. The pyridylboron reagent was known to show low reactivity in transmetalation (Scheme 1.17). A mechanism for rhodium-catalyzed hydroarylation was proposed as shown below (Scheme 1.18). Interestingly, 1,4-rhodium migration from the norbornylrhodium species was detected by deuterium labeling experiment.




**Scheme 1.16** Rhodium-catalyzed asymmetric hydroarylation

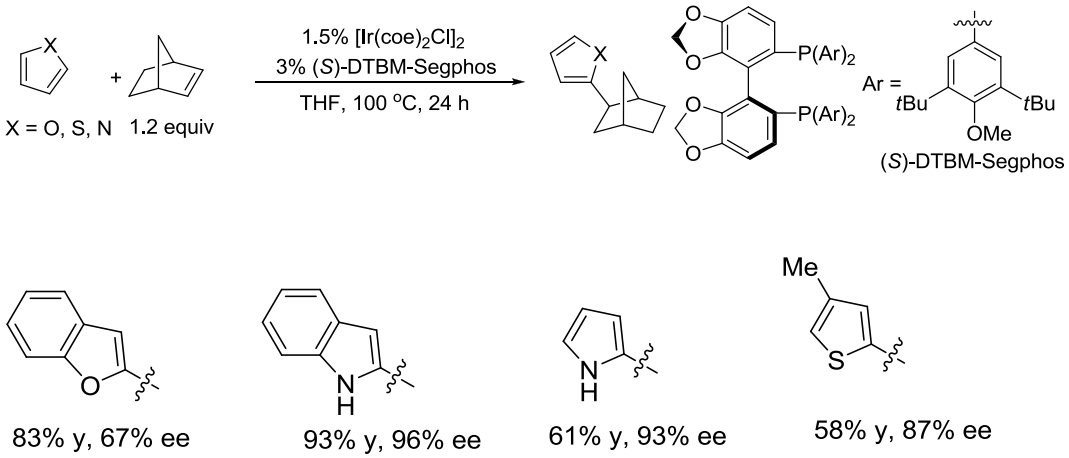



**Scheme 1.17** Synthesis of *N*-protected epibatidine

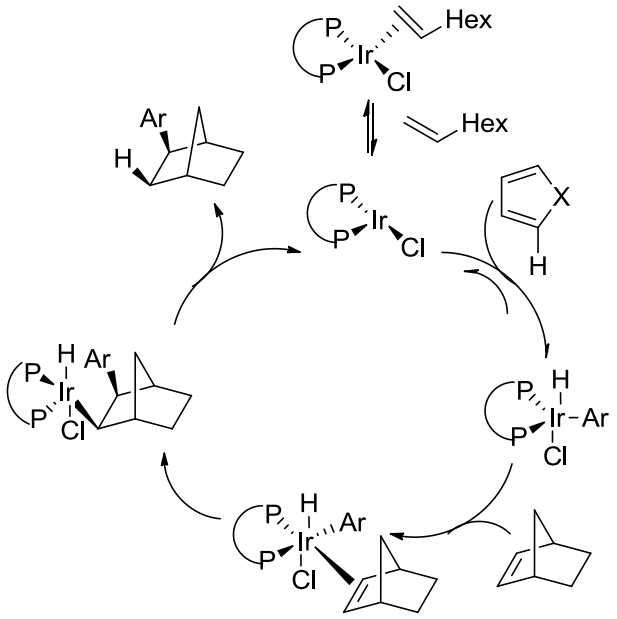



**Scheme 1.18** A mechanism for Rh-catalyzed hydroarylation

Very recently, Hartwig *et al.* reported an asymmetric addition of heteroarenes to norbornene and norbornadiene *via* selective C-H activation next to heteroatoms (Scheme 1.19).[21] (*S*)-DTBM-Segphos was used to provide excellent *ee* in most cases. The proposed catalytic cycle was shown as follows (Scheme 1.20).




**Scheme 1.19** Iridium-catalyzed asymmetric hydroarylation

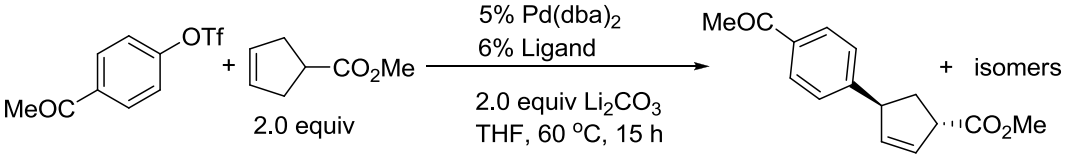


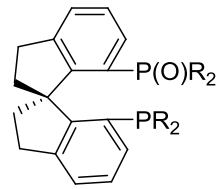

**Scheme 1.20** A catalytic cycle for iridium-catalyzed asymmetric hydroarylation

## 1.2 Results and discussion

### 1.2.1 Condition optimization

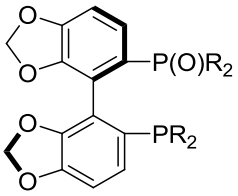
**Table 1.3** Effect of chiral ligands



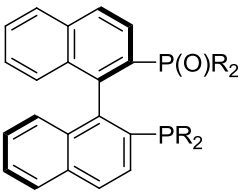

R = *m*-Xyl (*R*)-Xyl-SDP(O)

R = Ph (*R*)-Ph-SDP(O)



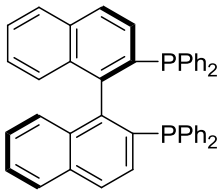

R = Ph (*R*)-SEGPhos(O)

R = *m*-Xyl (*R*)-Xyl-SEGPhos(O)

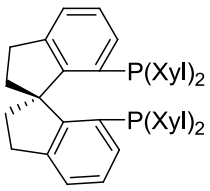



R = Ph (*R*)-BINAP(O)

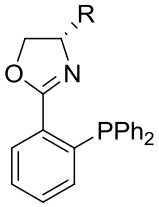
R = *m*-Xyl (*R*)-BINAP(O)




(*R*)-BINAP




(*R*)-Xyl-SDP




R = Ph (*R*)-Ph-PHOX

R = *i*Pr (*R*)-*i*Pr-PHOX

R = *t*Bu (*R*)-*t*Bu-PHOX

| Entry | Ligand | Conv (%) | Yield (%) | Selectivity | Ee (%) |
|---|---|---|---|---|---|
| 1 | (*R*)-Xyl-SDP(O) | 100 | 97 | 27:1 | 97 |
| 2 | (*R*)-Ph-SDP(O) | 62 | 40 | 26:1 | 90 |
| 3 | (*R*)-Segphos(O) | 53 | 31 | 9:1 | -84 |
| 4 | (*R*)-Xyl-Segphos(O) | 59 | 49 | 9:1 | -86 |
| 5 | (*R*)-BINAP(O) | 94 | 70 | 4:1 | 84 |
| 6 | (*R*)-Xyl-BINAP(O) | 100 | 94 | 7:1 | -99 |
| 7 | (*R*)-BINAP | 86 | 54 | 1:3.6 | -36 |
| 8 | (*R*)-Xyl-SDP | 61 | 44 | 1:3.5 | -10 |
| 9 | (*R*)-Ph-PHOX | 36 | <5 | - | - |
| 10 | (*R*)-*i*Pr-PHOX | 34 | <5 | - | - |
| 11 | (*R*)-*t*Bu-PHOX | 57 | 39 | 1.2:1 | -92 |

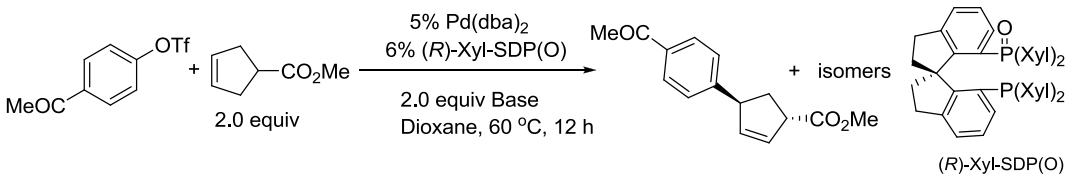
We chose a model reaction of an ArOTf and an ester-substituted cyclopentene to search for a suitable chiral ligand. The family of bisphosphine oxides which we developed for simple asymmetric Heck reaction gave very promising results. For example, (*R*)-BINAP oxide gave predominantly the *trans*-isomer in 84% *ee*. Its ratio to the sum of two minor isomers, or selectivity was determined by GC to be 4:1. The *trans* configuration of the major isomer was established by comparison with reported NMR data.[22] The structures of minor isomers were not assigned. The 1,1'-spirobiindane-7,7'-bisphosphine oxide or SDP(O) produced 90% *ee* and much higher selectivity (26:1).

In both ligand series, if phenyl groups on both phosphorus atoms were replaced by *m*-xylyl, the *ee* was improved further. In particular, (*R*)-Xyl-SDP(O) afforded the trans-isomer almost exclusively (97% ee and 27:1 *s* ratio). Notably, (*R*)-BINAP(O) and (*R*)-SDP(O) gave minor images of the major isomers. The two ligands are technically "pseudoenantiomers" because of the difference in nomenclature.

In comparison, the two bisphosphines, (*R*)-BINAP and (*R*)-Xyl-SDP led to the formation of 6 isomers in total and the *trans*-isomer was formed as a minor component in poor ee. Additionally, Pfaltz's *t*BuPhOX provided five isomers among which the *trans* isomer was the major (*s* 1.2:1). The other two PHOX ligands showed very poor catalytic activity.

The asymmetric Heck reaction can be sensitive to the choice of base. We tested both organic and inorganic bases in dioxane solvent (Table 1.4). Most of the bases can give Heck products in good yields and excellent *ee*s including DIPEA, $Li_2CO_3$ and LiOAc. Urotropine and proton sponge, however, proved to be unsatisfactory.

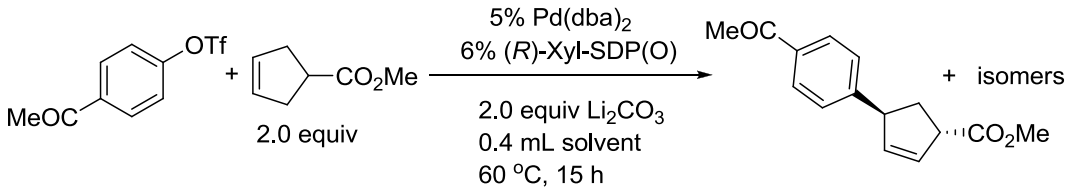
**Table 1.4** Effect of bases




| Entry | Base | Conv (%) | GC yield (%) | Selectivity | Ee (%) |
|---|---|---|---|---|---|
| 1 | DIPEA | 100 | 90 | 26:1 | 97 |
| 2 | 2,6-lutidine | 93 | 83 | 20:1 | 97 |
| 3 | $Et_3N$ | 87 | 71 | 16:1 | 97 |
| 4 | Urotropine | 32 | Trace | - | - |
| 5 | Proton sponge | 86 | 78 | 10:1 | 97 |
| 6 | $Li_2CO_3$ | 100 | 95 | 29:1 | 97 |
| 7 | LiOAc | 100 | 93 | 29:1 | 97 |

Ethereal solvents were found to be better than alcohols (Table1.5). Among them, THF gave similar results as dioxane. Toluene and $PhCF_3$ can also give the Heck product but in lower yields. We chose THF in the subsequent studies.

**Table 1.5** Effect of solvents

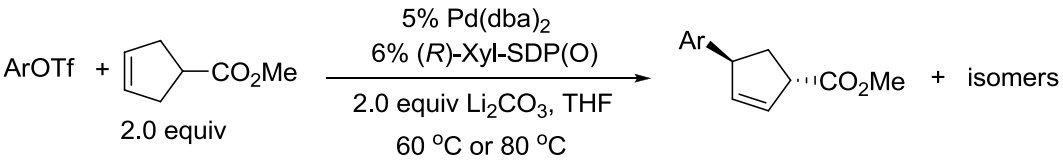


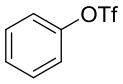
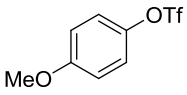
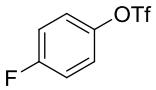
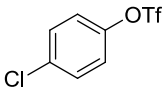
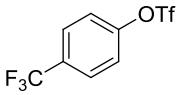
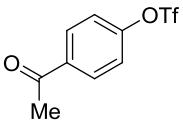
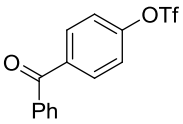
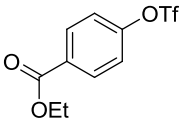
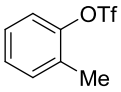
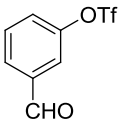
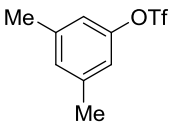

| Entry | Solvent | Conv (%) | GC yield (%) | Selectivity | Ee (%) |
|---|---|---|---|---|---|
| 1 | Toluene | 100 | 83 | 26:1 | 98 |
| 2 | TBME | 100 | 83 | 14:1 | 98 |
| 3 | Dioxane | 100 | 95 | 28:1 | 97 |
| 4 | THF | 100 | 97 | 30:1 | 97 |
| 5 | $PhCF_3$ | 100 | 78 | 12:1 | 98 |
| 6 | *n*BuOH | 74 | 66 | 10:1 | 98 |

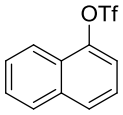
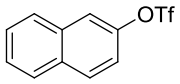
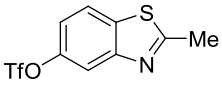
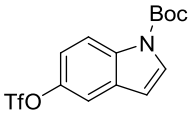
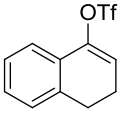
### 1.2.2 Scope of Substrates

With the optimized catalytic conditions in hand, we tested different kinds of aryl triflates using one model cyclopentene (Table 1.6). All the substrates can give Heck products in excellent yields and enantioselectivities. Aryl triflates carrying electron-withdrawing groups reacted faster than electron-rich groups because of faster oxidative addition. Electron-rich *p*-anisyl triflate also coupled well. The condition also worked well with aryl rings carrying *ortho* groups. Heteroaryl triflates derived from indole and benzothiozole also gave the Heck products in excellent yields and *ee*s. One vinyl triflate can be coupled in 99% enantioselectivity and 10:1 regioselectivity (entry 16).

**Table 1.6** Examples of aryl triflates

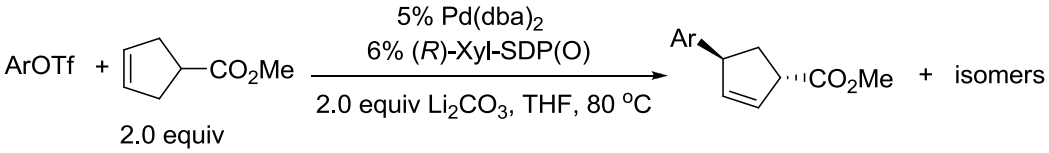


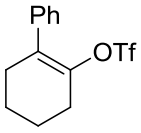
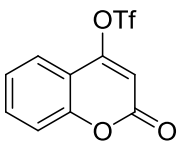

| entry | ArOTf | Temp (°C) | Time (hr) | Yield (%) | ee (%) | selectivity |
|---|---|---|---|---|---|---|
| 1 |  | 60 | 12 | 90 | 96 | 29:1 |
| 2 |  | 80 | 20 | 93 | 97 | 30:1 |
| 3 |  | 80 | 12 | 92 | 98 | 25:1 |
| 4 |  | 80 | 12 | 92 | 96 | 17:1 |
| 5 |  | 80 | 6 | 86 | 92 | 21:1 |
| 6 |  | 60 | 12 | 94 | 97 | 20:1 |
| 7 |  | 60 | 12 | 95 | 98 | 15:1 |
| 8 |  | 60 | 12 | 88 | 97 | 15:1 |
| 9 |  | 80 | 12 | 89 | 93 | >100:1 |
| 10 |  | 80 | 17 | 83 | 96 | >50:1 |
| 11 |  | 80 | 12 | 90 | 84 | 10:1 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 12 |  | 80 | 17 | 82 | 96 | 40:1 |
| 13 |  | 80 | 16 | 92 | 96 | 15:1 |
| 14 |  | 80 | 16 | 84 | 93 | 12:1 |
| 15 |  | 80 | 16 | 89 | 95 | 20:1 |
| 16 |  | 80 | 13 | 92 | 99 | 10:1 |

We also studied other vinyl triflates under optimized conditions (Table 1.7). Very poor *ee* was obtained in entry 1, because of steric hindrance of the vinyl substrate. Acetophenone-derived vinyl triflate gave only about 1:1 olefinic selectivity. Entry 3 did not give any Heck products under the catalytic condition.

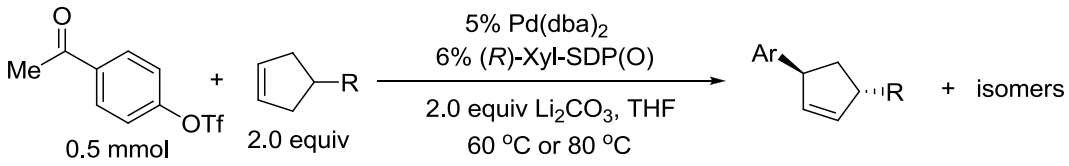
**Table 1.7** Unsuccessful aryl triflates




| entry | ArOTf | conversion (%) | selectivity | ee (%) |
|---|---|---|---|---|
| 1 |  | 100 | 15:1 | 75 |
| 2 |  | 100 | 1:1 | not determined |
| 3 |  | no reaction | | |

Several substituted cyclopentenes have been tested (Table 1.8). Most of them can give the Heck products in high yields and excellent enantioselectivities. Similar results were obtained for cyclopentenes carrying esters, silyl ethers, free alcohols and nitriles.

**Table 1.8** Scope of olefins



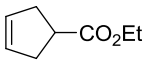
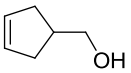
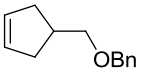
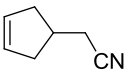
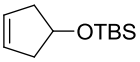
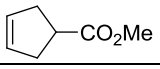
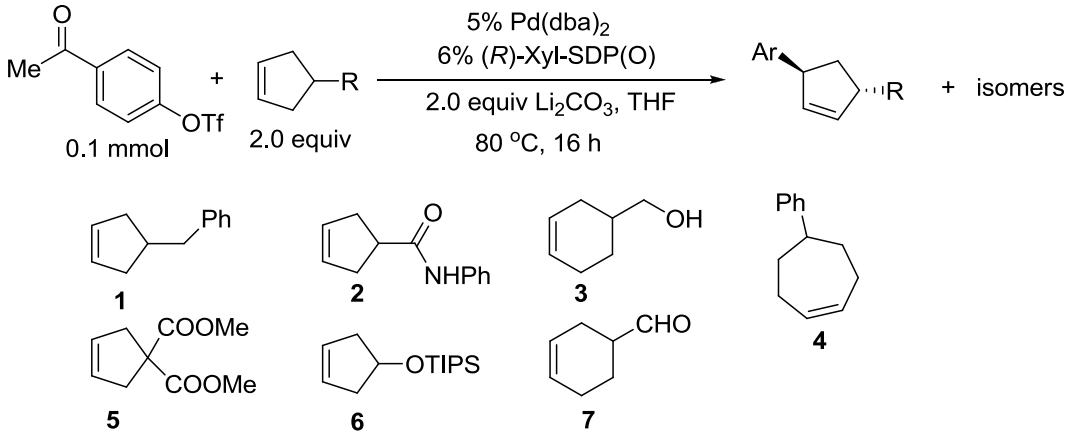

| entry | Olefin | Temp (°C) | Time (hr) | Yield (%) | ee (%) | selectivity |
|---|---|---|---|---|---|---|
| 1 |  | 60 | 17 | 85 | 98 | 20:1 |
| 2 |  | 60 | 13 | 79 | 92 | 13:1 |
| 3 |  | 60 | 17 | 92 | 97 | 20:1 |
| 4 |  | 80 | 18 | 92 | 90 | 20:1 |
| 5 |  | 80 | 15 | 94 | 92 | 28:1 |
| 6 |  | 60 | 12 | 94 | 97 | 20:1 |

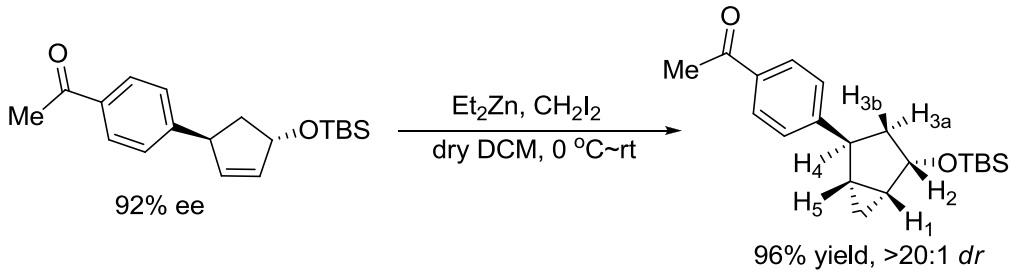
**Table 1.9** Examples of unsuccessful olefins



We also tried other olefins with different substituents and ring sizes (Table 1.9). Benzyl substituted cyclopentene **1** failed to give any Heck product. Diester-substituted cyclopentene substrate **5** did not couple. Phenyl substituted cyclohenptene **4** also failed to couple. We also tried cyclohexenes **3** and **7**, neither of them gave Heck product. The amide group on the cyclopentene **2** probably bind tightly to the vacant site of cationic aryl-Pd species and inhibited the catalysis.

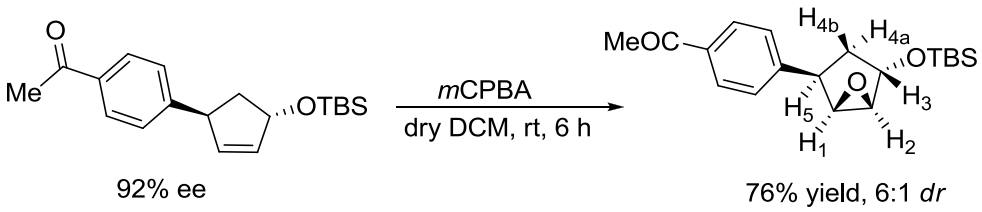
### 1.2.3 Product derivatizations

The olefin in the Heck products can be readily converted to other functional groups with facial selectivity. We tried the Simmons-Smith reaction with the Heck product (Scheme 1.21). The reaction was set up using $Et_2Zn$ and diiodomethane according to Nishimura's procedure.[23] $^1H$ NMR spectroscopy of the crude product showed >20:1 *dr*. Cyclopropanation occurred *syn* to the OTBS group based on $^1H$-$^1H$ NOESY analysis according to the signal between $H_1$ and $H_2$.



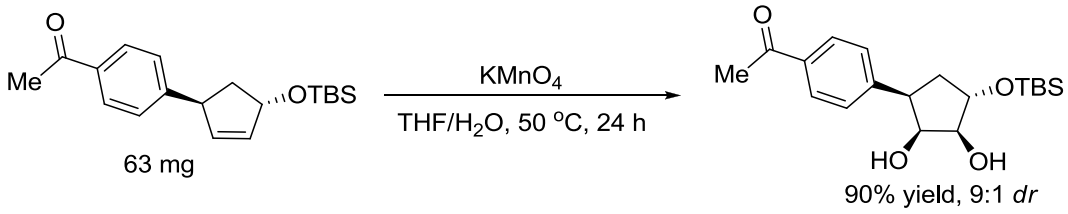

**Scheme 1.21** Cyclopropanation of asymmetric Heck product

Epoxidation reaction was also successfully applied on the Heck product (Scheme 1.22). 6:1 *dr* was obtained at room temperature (determined by GC). The major isomer was *cis* to aryl group based on $^1H$-$^1H$ NOESY analysis. The relative configuration was established by the cross signal between $H_1$ and $H_5$.




**Scheme 1.22** Epoxidation of asymmetric Heck product

Dihydroxylation reaction of the Heck product was also examined according to a reported procedure (Scheme 1.23).[24] 5 equiv of $KMnO_4$ was needed to give the desired product in 9:1 selectivity. The selectivity was determined by $^1H$ NMR spectroscopy of the crude mixture. The relative configuration of the major isomer was determined by X-Ray diffrational analysis (Figure 1).




**Scheme 1.23** Dihydroxylation of asymmetric Heck product

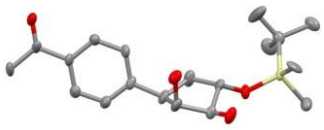
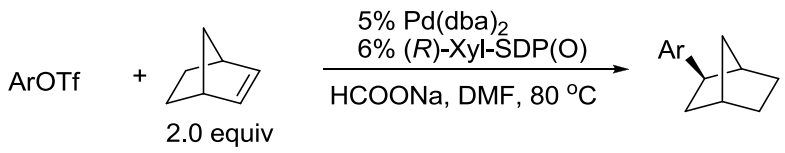
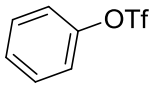
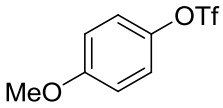
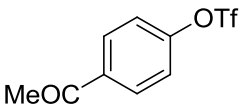


**Figure 1.** ORTEP of the diol derivative (50% thermal ellipsoid and hydrogen atoms omitted for clarity)

### 1.2.4 Asymmetric hydroarylation of bicyclic olefins

**Table 1.10 Examples of aryl triflates in the reaction with norbornene**

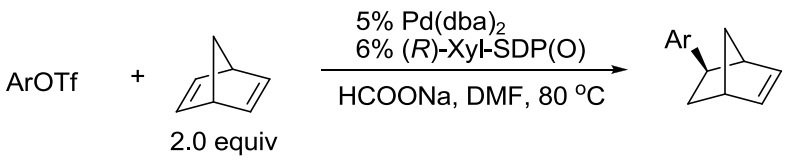


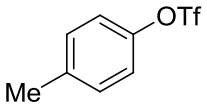
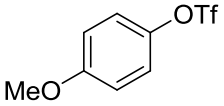
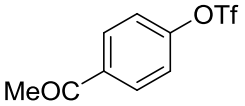

| entry | ArOTf | Time (hr) | Yield (%) | ee (%) |
|---|---|---|---|---|
| 1 |  | 12 | 83 | 96 |
| 2 |  | 16 | 95 | 93 |
| 3 |  | 20 | 93 | 95 |

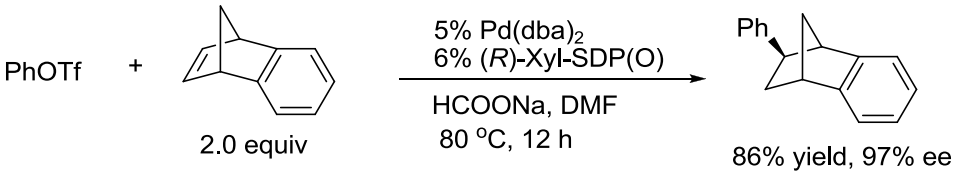
We tried the Heck type asymmetric hydroarylation of norbornene using (*R*)-Xyl-SDP(O) as ligand and sodium formate as hydride donor. Electronically diverse aryl triflates worked well. The absolute configuration of one product was determined to be 2*R*, by comparison with a reported optical rotation.[18]

Norbornadiene can also be used as the olefinic substrate. The reaction worked well with various aryl triflates in excellent *ee* and yield. Benzonorbornadiene also coupled in high *ee* in this kind of reactions (Scheme 1.24).

**Table 1.11 Examples of aryl triflates in the reaction with norbornadiene**




| entry | ArOTf | Time (hr) | Yield (%) | ee (%) |
|---|---|---|---|---|
| 1 |  | 12 | 83 | 94 |
| 2 |  | 16 | 85 | 95 |
| 3 |  | 12 | 80 | 96 |




**Scheme 1.24** Asymmetric hydroarylation of benzonorbornadiene

## 1.3 Conclusion

In this asymmetric Heck reaction, an efficient catalytic system was developed. (*R*)-Xyl-SDP(O) ligand was an effective ligand to give the products in high yields, and enantioselectivities. Highly enantioselective Heck type hydroarylation of bicyclic olefins has also been studied with this catalytic system. Norbornene, norbornadiene and benzonorbornene worked well to give the hydroarylation products in high *ee*.

## 1.4 Experimental section

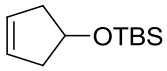
### General information

$^{1}$H NMR spectra were acquired at 400 MHz or 300 MHz and chemical shifts were recorded relative to $SiMe_4$ (δ 0.00) or residual protiated solvents ($CDCl_3$: δ 7.26; $C_6D_6$: δ 7.16; $CD_2Cl_2$: 5.30). Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The number of protons (n) for a given resonance was indicated by *n*H. Coupling constants were reported as a *J* value in Hz. $^{13}$C NMR spectra were obtained at 100 MHz on 400 MHz or 75 MHz on 300 MHz instruments and chemical shifts were recorded relative to solvent resonance ($CDCl_3$: δ 77.25). Proof of purity of new compounds was demonstrated with copies of NMR spectra.

Dry diethyl ether, toluene, hexane and dichloromethane were collected from a solvent purification system containing a column of activated alumina (1 m x 2) under argon. DMSO, DMF and 1,4-dioxane (Aldrich) were used without further purification and were stored in the glove box. Dry THF was freshly distilled from sodium/benzophenone under argon before use. All of anhydrous solvents were stored over activated 4Å molecular sieve beads in Schlenk tubes in an argon-filled glove box. Unless noted otherwise, commercially available chemicals were used without further purification. The GC internal standard, *n*-dodecane was degassed and dried over activated 4 Å molecular sieve beads before use.

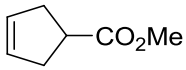
Glassware was dried at 120 $^{o}$C for at least 3 hours before use. Flash chromatography was preformed using Merck 40-63D 60 Å silica gel. GC and GC/MS analysis were conducted with Agilent J&W GC column DB-5MS-UI. Chiral HPLC analysis was performed on a Shimadzu LC-20AD instrument using Daicel Chiracel columns at 25 ℃. Optical rotation was measured using a JASCO P-1030 Polarimeter equipped with a sodium vapor lamp at 589 nm and the concentration of samples was denoted as *c*. X-ray crystallography analysis of single crystals was performed on a Bruker X8 APEX X-Ray diffractometer.

### 1.4.1 Substrate synthesis



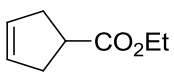

***4-(t*-Butyldimethylsiloxy)cyclopent-1-ene [68845-72-7].**[25] Under argon, to a dry 25-mL Schlenk tube was added cyclopent-3-enol (200 mg, 2.40 mmol), TBSCl (431 mg, 2.80 mmol), imidazole (194 mg, 2.80 mmol) and 5.0 mL dry DMF. After stirring at room temperature for 18 hours, diethyl ether (20 mL) was added. After extraction, the combined organic layers were dried over $MgSO_4$ and then evaporated to dryness under vacuum. The titled compound was obtained after flash chromatography (1:20 EA/hexanes) on silica gel as colorless oil (404 mg, 85% yield).

$^1$H NMR (300 MHz, $CDCl_3$): δ 5.67 (s, 2H), 4.56-4.51 (m, 1H), 2.59-2.55 (m, 2H), 2.30- 2.25 (m, 2H), 0.90 (s, 9H), 0.08 (s, 6H).




**Methyl cyclopent-2-ene-1-carboxylate [58101-60-3].** Under argon, to a 100-mL Schlenk tube was added cyclopent-3-ene-1-carboxylic acid (3.36 g, 30 mmol), methyl iodide (8.50 g, 60 mmol), $K_2CO_3$ (10.0 g, 75 mmol) and dry DMF (25 mL). The resulting solution was stirred at room temperature for 16 hours until TLC indicated full conversion of carboxylic acid. Extractive workup with diethyl ether and water gave a pure product as light yellow oil (3.29 g, 87% yield). Some product may have been lost during concentration under reduced pressure.

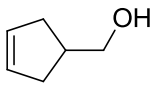
$^1$H NMR (300 MHz, $CDCl_3$): δ 5.67 (s, 2H), 3.71 (s, 3H), 3.20-3.09 (m, 1H), 2.66 (ψd, $J$ = 8.8 Hz, 4H).




**Ethyl cyclopent-3-ene-1-carboxylate [21622-01-5].**[26] Under argon, to a 25-mL Schlenk tube containing dry EtOH (5.0 mL) maintained in a -10 $^o$C salt-ice bath, $SOCl_2$ (714 mg, 6.0 mmol) was added, followed by addition of cyclopent-3-ene-1-

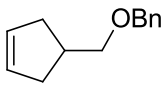
carboxylic acid (560 mg, 5.0 mmol) in one portion. The reaction mixture was stirred at room temperature for 3 hours and then refluxed for 1 hour until TLC showed full consumption of starting material. The titled compound was obtained after flash chromatography (1:20 EA/hexanes) as colorless oil (560 mg, 80% yield). Some product may be lost during concentration under reduced pressure.

$^1$H NMR (300 MHz, $CDCl_3$): δ 5.66 (s, 2H), 4.05-3.99 (m, 2H), 3.15-3.05 (m, 1H), 2.64 (ψd, *J* = 8.2 Hz, 4H), 1.26 (t, *J* = 7.1 Hz, 3H).



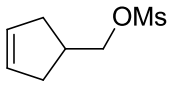

**4-Hydroxymethylcyclopent-1-ene [25125-21-7].**[27] Under argon, to dry THF (30 mL) in a dry 100-mL round bottom flask was added powder $LiAlH_4$ (3.14 g, 80 mmol). After the suspension was cooled to 0 $^o$C in an ice bath, a solution of cyclopent-3-ene-1-carboxylic acid (2.24 g, 20 mmol) in THF (5.0 mL) was added over 10 min and an exothermic reaction was observed during addition. Then the reaction mixture was refluxed for 16 hours until TLC indicated full consumption of starting material. The reaction mixture was chilled to 0 $^o$C and then was carefully quenched with 20 mL of saturated aq. $NH_4Cl$. After stirring for 30 minutes, the suspension was then passed through a pad of silica gel to remove aluminum salt with diethyl ether washing. The combined organic layers were dried over $MgSO_4$ and then evaporated to give the pure alcohol as colorless oil (1.69 g, 86% yield).

$^1$H NMR (400 MHz, $CDCl_3$): δ 5.68 (s, 2H), 3.57 (d, *J* = 5.9 Hz, 2H), 2.55-2.46 (m, 3H), 2.18-2.09 (m, 2H), 1.52 (br s, OH).



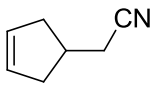

**4-(Benzyolxymethyl)cyclopent-1-ene [260443-67-2].**[28] 60% wt/wt NaH suspension in oil was washed with dry hexanes in the glove box and then dried under vacuum before use. Under argon, to a 25-mL Schlenk tube was added 4-hydroxymethylcyclopent-1-ene (490 mg, 5.0 mmol), NaH (240 mg, 10.0 mmol) and dry THF (5.0 mL). The suspension was stirred at room temperature for 1 hour

and then benzyl bromide (1.28 g, 7.5 mmol) was added dropwise over 5 minutes. The reaction mixture was stirred at room temperature for 3 hours more until TLC show no more starting material remained. The reaction was quenched with 10 mL of saturated aq. $NH_4Cl$. After extraction from water, titled compound was obtained after flash chromatography (1:10 EA/hexanes) as colorless oil (714 mg, 76% yield). $^1$H NMR (400 MHz, $CDCl_3$): δ 7.34-7.33 (m, 5H), 5.66-5.64 (m, 2H), 4.52 (s, 2H), 3.37 (d, *J* = 7.2 Hz, 2H), 2.67-2.56 (m, 1H), 2.51-2.46 (m, 2H), 2.14-2.09 (m, 2H).




**3-Cyclopentenylmethyl methanesulfonate [321386-75-8].**[27] Under argon, to a 100-mL Schlenk flask was added hydroxymethylcyclopent-1-ene (490 mg, 5.0 mmol) and 25 mL of dry DCM. After the mixture was cooled to 0 $^o$C in an ice bath, $Et_3N$ (606 mg, 6.0 mmol) and MsCl (629 mg, 5.5 mmol) were added. The reaction mixture was stirred at 0 $^o$C for 30 min, warmed to room temperature and kept stirred for 10 hours until TLC indicated full conversion of starting material. After the reaction was complete, the crude product was extracted with DCM from water. The organic layers were dried over $Na_2SO_4$ and then concentrated under reduced pressure. The titled compound was obtained after flash chromatography (1:5 EA/hexanes) as colorless oil (740 mg, 84% yield).

$^1$H NMR (400 MHz, $CDCl_3$): δ 5.67 (s, 2H), 4.13 (d, *J* = 7.3 Hz, 2H), 3.01 (s, 3H), 2.74-2.70 (m, 1H), 2.57-2.53 (m, 2H), 2.17 - 2.14 (m, 2H).




**3-Cyclopentenylacetonitrile [21860-24-2].** Under argon, to a 100-mL Schlenk flask was added 3-cyclopentenylmethyl methanesulfonate (740 mg, 4.2 mmol), KCN (1.28 g, 19.70 mmol) and dry DMSO (30 mL). The reaction mixture was sealed and heated in a 50 $^o$C oil bath for 3 days. After extraction using diethyl ether (100 mL x 2) from water, organic layers were dried over $MgSO_4$ and concentrated to give the pure product as colorless oil (337 mg, 75% yield).

$^1$H NMR (400 MHz, $CDCl_3$): δ 5.70 (s, 2H), 2.66-2.64 (m, 3H), 2.40 (m, 2H), 2.20-2.16 (m, 2H).

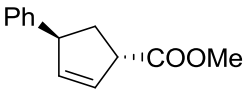
### 1.4.2 Procedure for condition optimization of asymmetric Heck reaction

*Typical procedure for condition optimization:* in an argon-filled glove box, a dry 10-mL reaction tube was charged with $Pd(dba)_2$ (2.9 mg, 0.005 mmol), (*R*)-xyl-SDP(O) (4.3 mg, 0.006 mmol) and 0.4 mL of dry THF. After stirring at 25 $^oC$ for 15 minutes, the mixture was treated with $Li_2CO_3$ (14.8 mg, 0.20 mmol), 4-acetyl phenyl triflate (27 mg, 0.1 mmol) methyl cyclopent-3-enecarboxylate (25 mg, 0.20 mmol) and GC standard, *n*-dodecane (10 μL). The tube was capped tightly and stirred at 60 $^oC$ until the aryl triflate was fully consumed. At intervals, an aliquot of the reaction mixture was taken in the glove box and quickly passed through a short plug of silica gel with diethyl ether washing to remove the Pd catalyst and inorganic salts. The filtrate was directly used in GC analysis to determine the conversion of 4-acetyl phenyl triflate and GC yield of the coupling product. For determination of enantioselectivity of the coupling product in the reaction mixture, the solvent of the filtrate was removed by and the residue was dissolved in 1:10 *i*-PrOH and *n*-hexane for chiral HPLC analysis (Daicel CHIRALCEL OD-H; 2% *i*-PrOH in hexanes).

### 1.4.3 Procedure for asymmetric Heck reaction

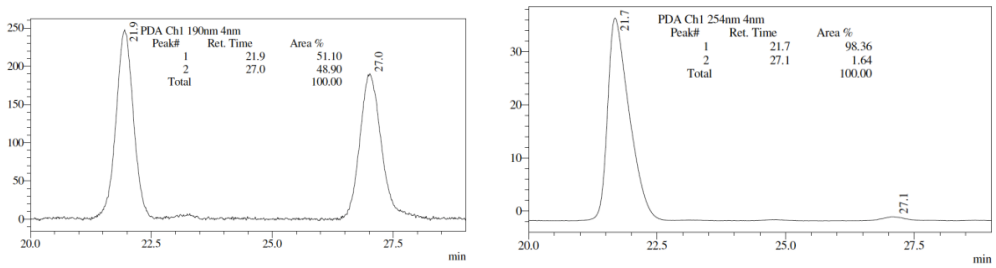
In an argon-filled glove box, to a dry 25-mL sealed tube was added $Pd(dba)_2$ (5 mol%, 14.4 mg, 0.025 mmol), ligand (*R*)-Xyl-SDP(O) (6 mol%, 21.5 mg, 0.03 mmol) and 1.0 mL of dry THF. After prestirring at room temperature for 15 minutes, the mixture was treated with $Li_2CO_3$ (74 mg, 1.0 mmol), Aryl triflate (0.5 mmol), methyl cyclopent-3-enecarboxylate (126 mg, 0.20 mmol) and GC standard *n*-dodecane (20 μL). The tube was capped tightly and stirred at indicated time until aryl triflate was fully consumed (monitored by GC). The reaction mixture was directly filtered through a pad of silica gel with diethyl ether washings (~20 mL) to remove Pd catalyst and inorganic salts. The filtrate was concentrated on a rotary evaporator and the residue was directly subjected to flash chromatography. The enantioselectivity of the purified product was determined by chiral HPLC analysis of purified samples.

To facilitate chiral HPLC analysis of asymmetric coupling products, the corresponding racemic compounds were prepared using the same procedure, except that racemic Xyl-SDP(O) was used as ligand.




**(1*S*,4*S*)-Methyl 4-phenylcyclopent-2-enecarboxylate.** The reaction was set up using phenyl triflate (0.50 mmol, 113 mg) and methyl cyclopent-3-enecarboxylate (126 mg, 1.0 mmol). The reaction finished after 19 hours at 80 $^{o}$C.The titled compound was obtained after flash chromatography (1:30 EA/hexane) as light yellow oil (91 mg, 90% yield). The ratio of the desired regioisomer versus all other isomers in the crude product was determined to be 29:1 by GC.

Ee of the purified products was determined to be 96% by chiral HPLC analysis (Daicel CHIRALCEL OJ-H; Hexanes: *i*-PrOH = 98:2; detection wavelengths = 190 nm; flow rate = 0.5 mL/min). $T_R$ = 27.1 min (minor) and 21.7 min (major).

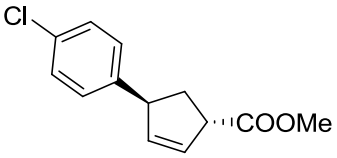



$[\alpha]^{22}_{D}$ = -1.1$^{o}$ (*c* = 1.2, $CHCl_3$) for a sample of 96% ee.

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.32-7.28 (m, 2H), 7.23-7.17 (m, 3H), 5.97-5.92 (m, 2H), 4.14-4.09 (m, 1H), 3.78-3.74 (m, 1H), 3.72 (s, 3H), 2.77-2.70 (m, 1H), 2.05-1.99 (m, 1H).

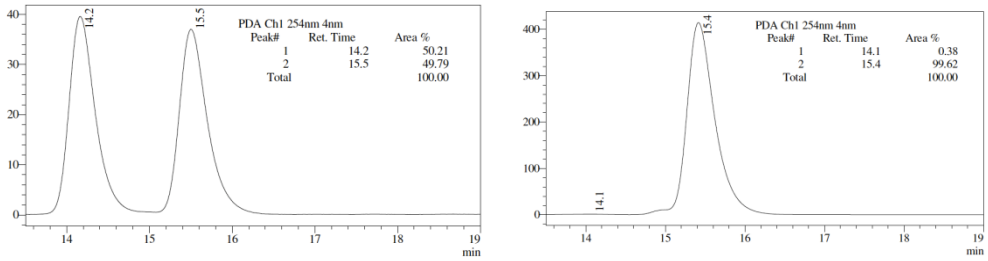
$^{13}$C NMR (100 MHz, $CDCl_3$): δ 175.1, 145.3, 137.7, 129.8, 128.8, 127.4, 126.6, 52.2, 51.1, 50.8, 37.3.

GCMS (EI): calcd for $C_{13}H_{14}O_2$ M: 202.10. Found: 202.04.



**(1*S*,4*S*)-Methyl 4-(4-chlorophenyl)cyclopent-2-enecarboxylate**. The reaction was set up using 4-chlorophenyl triflate (0.50 mmol, 130 mg) and methyl cyclopent-3-enecarboxylate (126 mg, 1.0 mmol). The reaction finished after 20 hours at 80 $^{o}$C.The titled compound was obtained after flash chromatography (1:30 EA/hexane) as light yellow oil (109 mg, 92% yield). The ratio of the desired regioisomer versus all other isomers in the crude product was determined to be 17:1 by GC.

Ee of the purified products was determined to be 96% by chiral HPLC analysis (Daicel CHIRALCEL AS-H; Hexanes: *i*-PrOH = 98:2; detection wavelengths = 254 nm; flow rate = 0.5 mL/min). $T_R$ = 14.1 min (minor) and 15.4 min (major).

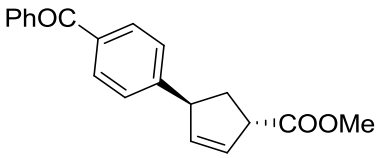



$[\alpha]^{22}_{D}$ = -0.18$^{o}$ (*c* = 2.5, $CHCl_3$) for a sample of 96% ee.

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 6.4 Hz, 2H), 7.11-7.08 (m, 2H), 5.95-5.89 (m, 2H), 4.10-4.06 (m, 1H), 3.77-3.73 (m, 1H), 3.72 (s, 3H), 2.76-2.69 (m, 1H), 1.99-1.92 (m, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 174.9, 143.7, 137.2, 132.3, 130.3, 128.9, 128.7, 52.6, 50.7, 50.4, 37.2.

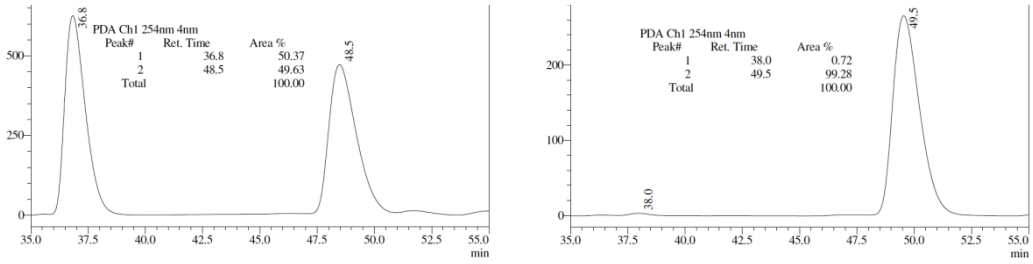
GCMS (EI): calcd for $C_{13}H_{13}ClO_2$ M: 236.06. Found: 236.04.




**(1*S*,4*S*)-Methyl 4-(*p*-benzoylphenyl)cyclopent-2-enecarboxylate**. The reaction was set up using 4-benzoylphenyl triflate (0.50 mmol, 165 mg) and methyl cyclopent-3-enecarboxylate (126 mg, 1.0 mmol). The reaction finished after 15 hours at 60 $^{o}$C. The titled compound was obtained after flash chromatography (1:20 EA/hexane) as light yellow oil (145 mg, 95% yield). The ratio of the desired

regioisomer versus all other isomers in the crude product was determined to be 15:1 by GC.

Ee of the purified products was determined to be 98% by chiral HPLC analysis (Daicel CHIRALCEL OD-H; Hexanes: *i*-PrOH = 98:2; detection wavelengths = 254 nm; flow rate = 0.5 mL/min). $T_R$ = 38.0 min (minor) and 49.5 min (major).

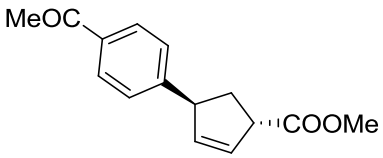



$[\alpha]^{22}_D$ = -0.7° (*c* = 3.0, $CHCl_3$) for a sample of 98% ee.

$^1$H NMR (300 MHz, $CDCl_3$): δ 7.81-7.74 (m, 4H), 7.61-7.55 (m, 1H), 7.50-7.45 (m, 2H), 7.29-7.27 (m, 2H), 6.00-5.96 (m, 2H), 4.20 (dd, *J* = 6.6 Hz, 1H), 3.80-3.75 (m, 1H), 3.73 (s, 3H), 2.83-2.74 (m, 1H), 2.08-1.99 (m, 1H).

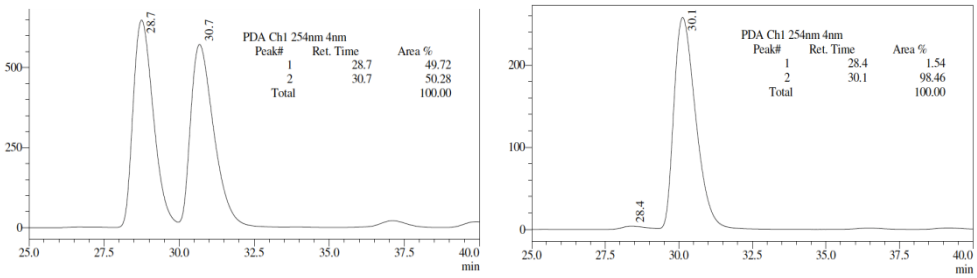
$^{13}$C NMR (100 MHz, $CDCl_3$): δ 196.2, 174.5, 150.0, 137.8, 136.6, 135.8, 132.3, 130.6, 130.5, 130.0, 128.3, 127.2, 52.0, 50.8, 50.5, 36.8.

GCMS (EI): calcd for $C_{20}H_{18}O_3$ M: 306.13. Found: 306.10.




**(1*S*,4*S*)-Methyl 4-(*p*-acetylphenyl)cyclopent-2-enecarboxylate**. The reaction was set up using 4-acetylphenyl triflate (0.50 mmol, 134 mg) and methyl cyclopent-3-enecarboxylate (126 mg, 1.0 mmol). The reaction finished after 15 hours at 60 °C. The titled compound was obtained after flash chromatography (1:20 EA/hexane) as colorless oil (115 mg, 94% yield). The ratio of the desired regioisomer versus all other isomers in the crude product was determined to be 20:1 by GC.

Ee of the purified products was determined to be 97% by chiral HPLC analysis (Daicel CHIRALCEL OD-H; Hexanes: *i*-PrOH = 98:2; detection wavelengths = 254 nm; flow rate = 0.5 mL/min). $T_R$ = 28.4 min (minor) and 30.1 min (major).

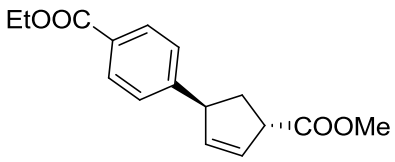



$[\alpha]^{22}_{D}$ = -0.6° (*c* = 4.5, $CHCl_3$) for a sample of 97% ee.

$^1$H NMR (300 MHz, $CDCl_3$): δ 7.90 (dd, *J* = 6.6, 1.8 Hz, 2H), 7.26 (dd, *J* = 6.4, 1.8 Hz, 2H), 5.99-5.92 (m, 2H), 4.20-4.15 (m, 1H), 3.79-3.74 (m, 1H), 3.73 (s, 3H), 2.82-2.73 (m, 1H), 2.59 (s, 3H), 2.05-1.95 (m, 1H).

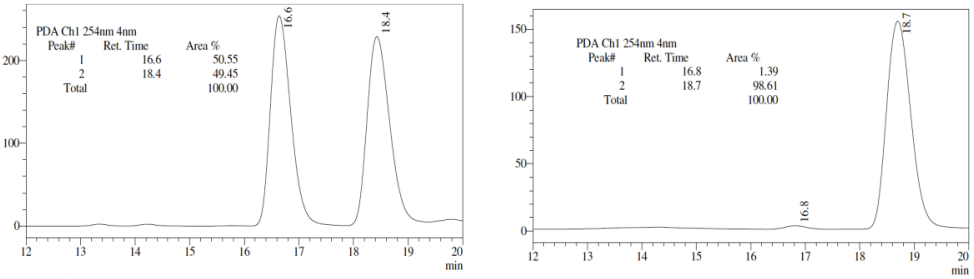
$^{13}$C NMR (75 MHz, $CDCl_3$): δ 197.6, 174.5, 150.7, 136.6, 135.6, 130.5, 128.8, 127.4, 52.0, 50.8, 50.5, 36.8, 26.6.

GCMS (EI): calcd for $C_{15}H_{16}O_3$ M: 244.11. Found: 244.09.




**(1*S*,4*S*)-Ethyl 4-(4-(methoxycarbonyl)cyclopent-2-en-1-yl)benzoate**. The reaction was set up using ethyl (*p*-trifluoromethanesulfonyloxy)benzoate (0.50 mmol, 149 mg) and methyl cyclopent-3-enecarboxylate (126 mg, 1.0 mmol). The reaction finished after 15 hours at 80 °C. The titled compound was obtained after flash chromatography (1:30 EA/hexane) as light yellow oil (120 mg, 88% yield). The ratio of the desired regioisomer versus all other isomers in the crude product was determined to be 15:1 by GC.

Ee of the purified products was determined to be 97% by chiral HPLC analysis (Daicel CHIRALCEL OD-H; Hexanes: *i*-PrOH = 98:2; detection wavelengths = 254 nm; flow rate = 0.5 mL/min). $T_R$ = 16.8 min (minor) and 18.7 min (major).

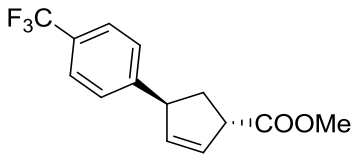



$[\alpha]^{22}_{D}$ = -0.3° (*c* = 2.6, $CHCl_3$) for a sample of 97% ee.

$^{1}$H NMR (300 MHz, $CDCl_3$): δ 7.97 (dd, *J* = 6.6, 1.8 Hz, 2H), 7.26 (dd, *J* = 6.4, 1.8 Hz, 2H), 5.99-5.92 (m, 2H), 4.37 (q, *J* = 7.2 Hz, 2H), 4.19-4.13 (m, 1H), 3.78-3.74 (m, 1H), 3.73 (s, 3H), 2.80-2.72 (m, 1H), 2.04-1.95 (m, 1H), 1.39 (t, *J* = 7.2 Hz, 3H).

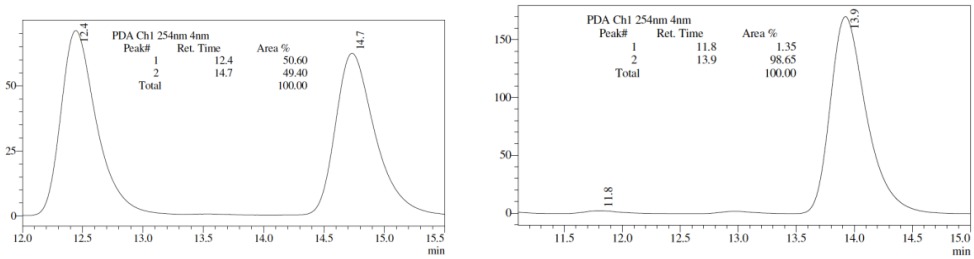
$^{13}$C NMR (75 MHz, $CDCl_3$): δ 174.8, 166.7, 150.5, 136.8, 130.5, 130.1, 127.3, 61.0, 52.2, 51.0, 50.7, 37.0, 14.5.

GCMS (EI): calcd for $C_{16}H_{18}O_4$ M: 274.12. Found: 274.07.




**(1*S*,4*S*)-Methyl 4-(4-(trifluoromethyl)phenyl)cyclopent-2-enecarboxylate**. The reaction was set up using 4-(trifluoromethyl) phenyl triflate (0.50 mmol, 147 mg) and methyl cyclopent-3-enecarboxylate (126 mg, 1.0 mmol). The reaction finished after 6 hours at 80 $^{o}$C. The titled compound was obtained after flash chromatography (1:30 EA/hexane) as colorless oil (116 mg, 86% yield). The ratio of the desired regioisomer versus all other isomers in the crude product was determined to be 21:1 by GC.

Ee of the purified products was determined to be 97% by chiral HPLC analysis (Daicel CHIRALCEL AS-H; Hexanes: *i*-PrOH = 98:2; detection wavelengths = 254 nm; flow rate = 0.5 mL/min). $T_R$ = 11.8 min (minor) and 13.9 min (major).



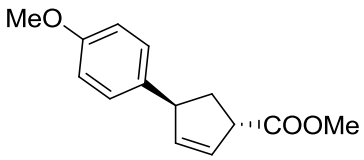

$[\alpha]^{22}_{D}$ = -1.2$^{o}$ (*c* = 2.3, $CHCl_3$) for a sample of 97% ee.

$^{1}$H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 6.00-5.92 (m, 2H), 4.20-4.13 (m, 1H), 3.78-3.74 (m, 1H), 3.73 (s, 3H), 2.82-2.73 (m, 1H), 2.04-1.94 (m, 1H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ 174.8, 149.3, 136.8, 130.8, 129.0 (q, *J* = 32.4 Hz), 127.7, 125.7 (q, *J* = 3.8 Hz), 124.5 (q, *J* = 274.5 Hz), 52.3, 50.9, 50.7, 37.1.

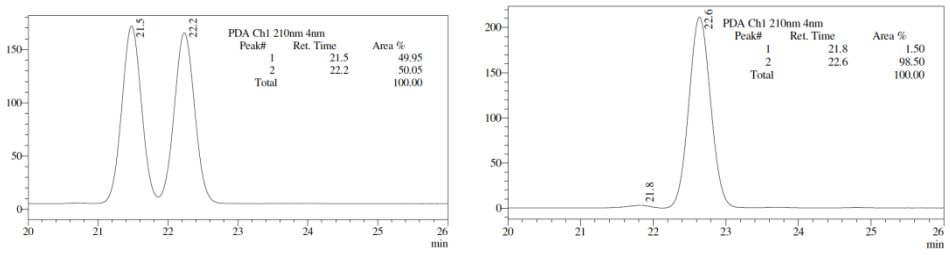
$^{19}$F NMR (282 MHz, $CDCl_3$): δ -62.4.

GCMS (EI): calcd for $C_{14}H_{13}F_3O_2$ M: 270.09. Found: 270.02.




**(1*S*,4*S*)-Methyl 4-(4-methoxyphenyl)cyclopent-2-enecarboxylate.** The reaction was set up using 4-methoxyphenyl triflate (0.50 mmol, 128 mg) and methyl cyclopent-3-enecarboxylate (126 mg, 1.0 mmol). The reaction finished after 20h hours at 80 $^{o}$C. The titled compound was obtained after flash chromatography (1:30 EA/hexane) as colorless oil (108 mg, 93% yield). The ratio of the desired regioisomer versus all other isomers in the crude product was determined to be 30:1 by GC.

Ee of the purified products was determined to be 97% by chiral HPLC analysis (Daicel CHIRALCEL IC-H; Hexanes: *i*-PrOH = 98:2; detection wavelengths = 210 nm; flow rate = 0.5 mL/min). $T_R$ = 21.8 min (minor) and 22.6 min (major).

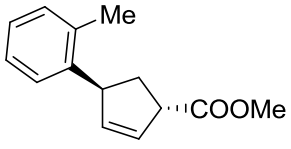



$[\alpha]^{22}_D$ = -2.7$^{o}$ (*c* = 2.7, $CHCl_3$) for a sample of 97% ee.

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.11-7.07 (m, 2H), 6.86-6.83 (m, 2H), 5.94-5.89 (m, 2H), 4.09-4.05 (m, 1H), 3.79 (s, 3H), 3.77-3.73 (m, 1H), 3.72 (s, 3H), 2.73-2.67 (m, 1H), 2.01-1.95(m, 1H).

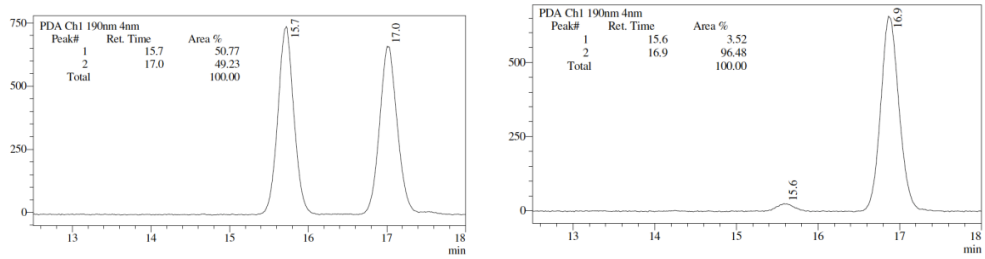
$^{13}$C NMR (100 MHz, $CDCl_3$): δ 175.2, 158.4, 138.0, 137.3, 129.4, 128.3, 114.2, 55.5, 52.1, 50.7, 50.2, 37.4.

GCMS (EI): calcd for $C_{14}H_{16}O_3$ M: 232.11. Found: 232.04.



**(1*S*,4*S*)-Methyl 4-o-tolylcyclopent-2-enecarboxylate.** The reaction was set up using *o*-tolyl triflate (0.50 mmol, 120 mg) and methyl cyclopent-3-enecarboxylate (126 mg, 1.0 mmol). The reaction finished after 20h hours at 80 $^{o}$C. The titled compound was obtained after flash chromatography (1:30 EA/hexane) as colorless oil (96 mg, 89% yield). The ratio of the desired regioisomer versus all other isomers in the crude product was determined to be 100:1 by GC.

Ee of the purified products was determined to be 93% by chiral HPLC analysis (Daicel CHIRALCEL IC-H; Hexanes: *i*-PrOH = 99:1; detection wavelengths = 190 nm; flow rate = 0.5 mL/min). $T_R$ = 15.6 min (minor) and 16.9 min (major).

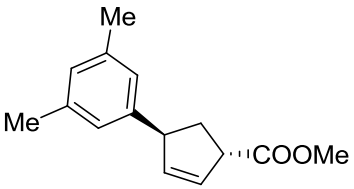



$[\alpha]^{22}_{D}$ = -0.48$^{o}$ (*c* = 1.0, $CHCl_3$) for a sample of 93% ee.

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.17-7.07 (m, 4H), 5.98-5.92 (m, 2H), 4.33-4.22 (m, 1H), 3.78-3.72 (m, 1H), 3.71 (s, 3H), 2.80-2.73 (m, 1H), 2.37 (s, 3H), 1.94-1.87 (m, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 175.2, 143.4, 137.3, 135.9, 130.5, 130.0, 126.5, 126.4, 126.1, 52.2, 50.6, 47.2, 35.9, 19.9.

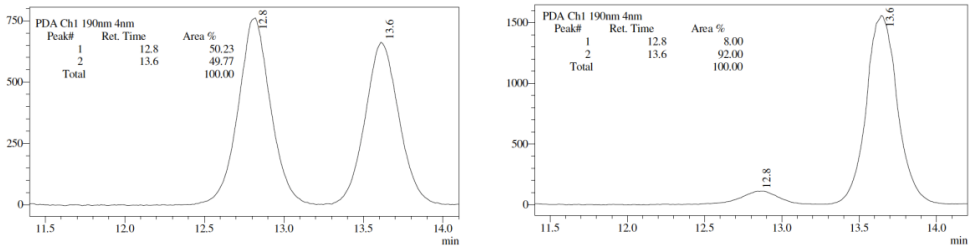
GCMS (EI): calcd for $C_{14}H_{16}O_2$ M: 216.12. Found: 215.99.




**(1*S*,4*S*)-Methyl 4-(3,5-dimethylphenyl)cyclopent-2-enecarboxylate.** The reaction was set up using 3,5-dimethylphenyl triflate (0.50 mmol, 127 mg) and methyl cyclopent-3-enecarboxylate (126 mg, 1.0 mmol). The reaction finished after 20 hours at 80 $^{o}$C. The titled compound was obtained after flash chromatography (1:30 EA/hexane) as colorless oil (104 mg, 90% yield). The ratio

of the desired regioisomer versus all other isomers in the crude product was determined to be 10:1 by GC.

Ee of the purified products was determined to be 84% by chiral HPLC analysis (Daicel CHIRALCEL OJ-H; Hexanes: *i*-PrOH = 98:2; detection wavelengths = 190 nm; flow rate = 0.5 mL/min). $T_R$ = 12.8 min (minor) and 13.6 min (major).

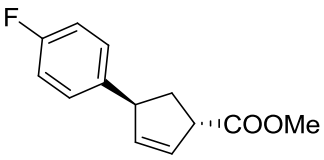



$[\alpha]^{22}_D$ = -0.75° (*c* = 2.0, $CHCl_3$) for a sample of 84% ee.

$^1$H NMR (400 MHz, $CDCl_3$): δ 6.86 (s, 1H), 6.77 (s, 2H), 5.95-5.89 (m, 2H), 4.06-4.01 (m, 1H), 3.77-3.73 (m, 1H), 3.72 (s, 3H), 2.73-2.66 (m, 1H), 2.29 (s, 6H), 2.04-1.97 (m, 1H).

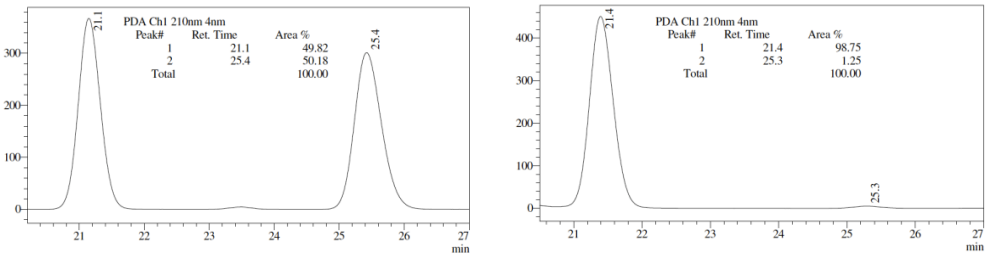
$^{13}$C NMR (100 MHz, $CDCl_3$): δ 175.2, 145.2, 138.3, 138.0, 129.5, 128.3, 125.2, 52.2, 50.9, 50.8, 37.2, 21.5.

GCMS (EI): calcd for $C_{15}H_{18}O_2$ M: 230.13. Found: 230.10.




**(1*S*,4*S*)-Methyl 4-(4-fluorophenyl)cyclopent-2-enecarboxylate.** The reaction was set up using 4-fluorophenyl triflate (0.50 mmol, 122 mg) and methyl cyclopent-3-enecarboxylate (126 mg, 1.0 mmol). The reaction finished after 12 hours at 80 °C. The titled compound was obtained after flash chromatography (1:30 EA/hexane) as colorless oil (101 mg, 92% yield). The ratio of the desired regioisomer versus all other isomers in the crude product was determined to be 25:1 by GC.

Ee of the purified products was determined to be 98% by chiral HPLC analysis (Daicel CHIRALCEL OJ-H; Hexanes: *i*-PrOH = 98:2; detection wavelengths = 210 nm; flow rate = 0.5 mL/min). $T_R$ = 25.3 min (minor) and 21.4 min (major).



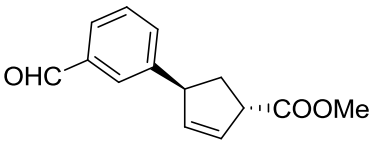

$[\alpha]^{22}_{D}$ = -0.10° (*c* = 2.0, $CHCl_3$) for a sample of 98% ee.

$^{1}$H NMR (300 MHz, $CDCl_3$): δ 7.13-7.09 (m, 2H), 6.99-6.95 (m, 2H), 5.92 (ψt, *J* = 2.8 Hz, 2H), 4.11-4.07 (m, 1H), 3.76-3.73 (m, 1H), 3.71 (s, 3H), 2.75-2.67 (m, 1H), 1.98-1.91 (m, 1H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ 175.0, 161.8 (d, *J* = 244.3 Hz), 140.9 (d, *J* = 3.3 Hz), 137.5, 128.8 (d, *J* = 7.8 Hz), 115.5 (d, *J* = 21.2 Hz), 52.2, 50.7, 50.3, 37.4.

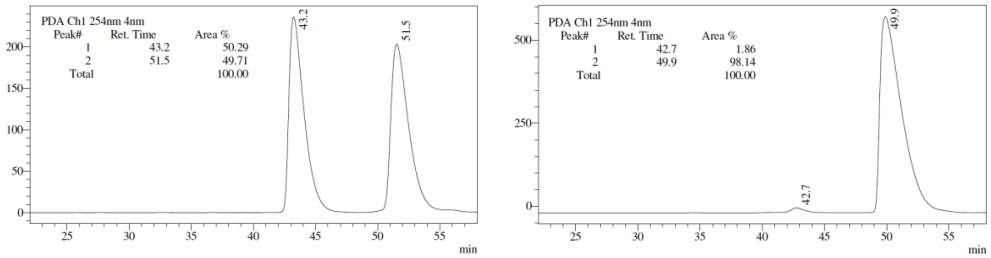
$^{19}$F NMR (376 MHz, $CDCl_3$): δ -116.9.

GCMS (EI): calcd for $C_{13}H_{13}FO_2$ M: 220.09. Found: 219.96.




**(1*S*,4*S*)-Methyl 4-(3-formylphenyl)cyclopent-2-enecarboxylate**. The reaction was set up using 3-formylphenyl triflate (0.50 mmol, 127 mg) and methyl cyclopent-3-enecarboxylate (126 mg, 1.0 mmol). The reaction finished after 17 hours at 80 °C. The titled compound was obtained after flash chromatography (1:20 EA/hexane) as colorless oil (95 mg, 83% yield). The ratio of the desired regioisomer versus all other isomers in the crude product was determined to be >50:1 by GC.

Ee of the purified products was determined to be 96% by chiral HPLC analysis (Daicel CHIRALCEL AS-H; Hexanes: *i*-PrOH = 98:2; detection wavelengths = 254 nm; flow rate = 0.5 mL/min). $T_R$ = 42.7 min (minor) and 49.9 min (major).

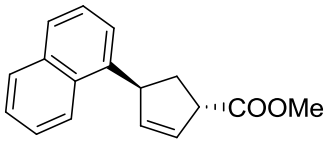



$[\alpha]^{22}_{D}$ = -2.4° (*c* = 4.0, $CHCl_3$) for a sample of 96% ee.

$^{1}$H NMR (300 MHz, $CDCl_3$): δ 9.96 (s, 1H), 7.71-7.67 (m, 2H), 7.47-7.41 (m, 2H), 5.98-5.90 (m, 2H), 4.20-4.14 (m, 1H), 3.77-3.72 (m, 1H), 3.69 (s, 3H), 2.80-2.71 (m, 1H), 2.02-1.92 (m, 1H).

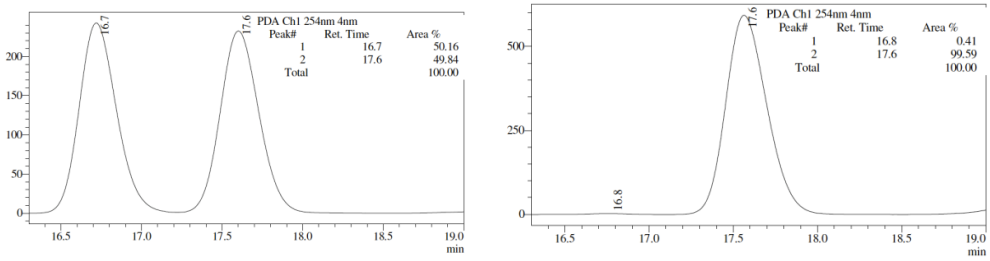
$^{13}$C NMR (75MHz, $CDCl_3$): δ 192.5, 174.7, 146.4, 136.9, 136.7, 133.6, 130.7, 129.4, 128.4, 128.1, 52.2, 50.64, 50.62, 37.0.

GCMS (EI): calcd for $C_{14}H_{14}O_3$ M: 230.09. Found: 230.02.




**(1*S*,4*S*)-Methyl 4-(naphthalen-1-yl)cyclopent-2-enecarboxylate**. The reaction was set up using naphthalen-1-yl triflate (0.50 mmol, 138 mg) and methyl cyclopent-3-enecarboxylate (126 mg, 1.0 mmol). The reaction finished after 17 hours at 80 $^{o}$C. The titled compound was obtained after flash chromatography (1:25 EA/hexane) as colorless oil (103 mg, 82% yield). The ratio of the desired regioisomer versus all other isomers in the crude product was determined to be 40:1 by GC.

Ee of the purified products was determined to be 99% by chiral HPLC analysis (Daicel CHIRALCEL IC-H; Hexanes: *i*-PrOH = 98:2; detection wavelengths = 254 nm; flow rate = 0.5 mL/min). $T_R$ = 16.8 min (minor) and 17.6 min (major).

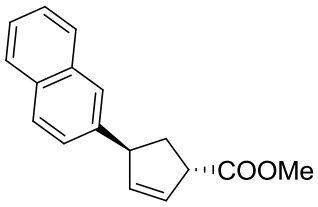



$[\alpha]^{22}_{D}$ = -0.4$^{o}$ (*c* = 2.0, $CHCl_3$) for a sample of 99% ee.

$^{1}$H NMR (300 MHz, $CDCl_3$): δ 8.11 (d, *J* = 8.1 Hz, 1H), 7.84 (dd, *J* = 9.0, 7.5 Hz, 1H), 7.70 (d, J = 8.1 Hz, 1H), 7.54-7.45 (m, 2H), 7.37 (ψt, *J* = 7.5 Hz, 1H), 7.25 (d, J = 6.9 Hz, 1H), 6.12-6.03 (m, 2H), 4.85-4.84 (m, 1H), 3.72 (s, 3H), 2.98-2.89 (m, 1H), 2.09-2.00 (m, 1H).

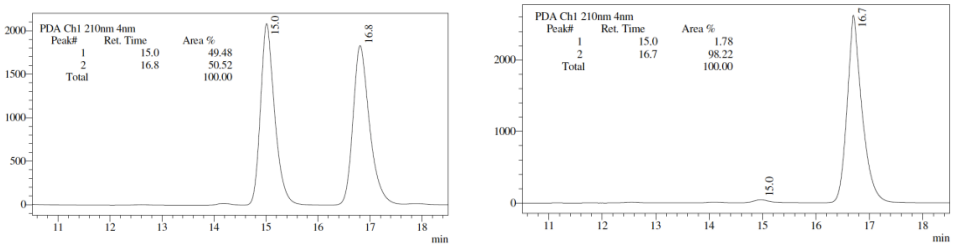
$^{13}$C NMR (75MHz, $CDCl_3$): δ 175.1, 141.1, 136.8, 134.2, 131.9, 130.5, 128.9, 127.2, 126.2, 125.8, 125.7, 123.9, 123.0, 52.2, 50.6, 46.7, 36.4.

GCMS (EI): calcd for $C_{17}H_{16}O_2$ M: 252.12. Found: 252.06.




**(1*S*,4*S*)-Methyl 4-(naphthalen-2-yl)cyclopent-2-enecarboxylate**. The reaction was set up according to the general procedure by using naphthalen-2-yl triflate (0.50 mmol, 138 mg) and methyl cyclopent-3-enecarboxylate (126 mg, 1.0 mmol). The reaction finished after 20 hours at 80 $^{o}$C. The titled compound was obtained after flash chromatography (1:30 EA/hexane) as colorless oil (116 mg, 92% yield). The ratio of the desired regioisomer versus all other isomers in the crude product was determined to be 15:1 by GC.

Ee of the purified products was determined to be 96% by chiral HPLC analysis (Daicel CHIRALCEL OD-H; Hexanes: *i*-PrOH = 98:2; detection wavelengths = 210 nm; flow rate = 0.5 mL/min). $T_R$ = 15.0 min (minor) and 16.7 min (major).

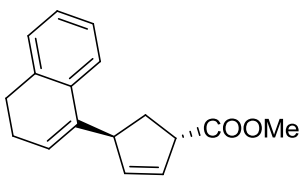



$[\alpha]^{22}_{D}$ =-2.5$^{o}$ (*c* = 1.9, $CHCl_3$) for a sample of 96% ee.

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.81-7.76 (m, 3H), 7.61 (s, 1H), 7.48-7.41 (m, 2H), 7.31 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.05-5.98 (m, 1H), 4.29-4.27 (m, 1H), 3.82-3.76 (m, 1H), 3.74 (s, 3H), 2.83-2.77 (m, 1H), 2.14-2.11 (m, 1H).

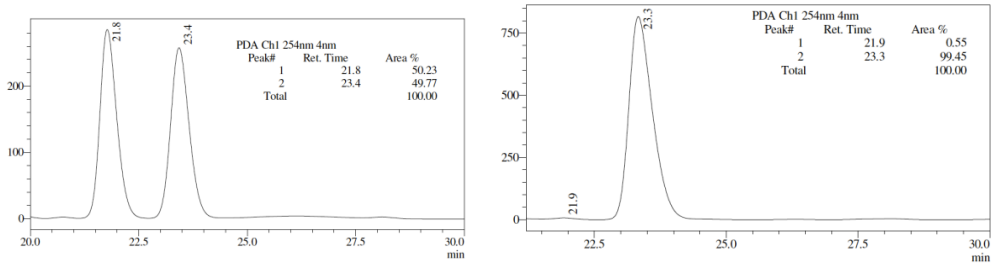
$^{13}$C NMR (100 MHz, $CDCl_3$): δ 175.1, 141.6, 137.6, 133.8, 132.6, 130.1, 128.5, 127.84, 127.81, 126.3, 126.1, 125.6, 125.5, 52.2, 51.2, 50.8, 37.1.

GCMS (EI): calcd for $C_{17}H_{16}O_2$ M: 252.12. Found: 252.08.



**(1*S*,4*S*)-Methyl 4-(3,4-dihydronaphthalen-1-yl)cyclopent-2-enecarboxylate**. The reaction was set up according to the general procedure by using 3,4-dihydronaphthalen-1-yl triflate (0.50 mmol, 139 mg) and methyl cyclopent-3-enecarboxylate (126 mg, 1.0 mmol). The reaction finished after 13 hours at 60 $^{o}$C. The titled compound was obtained after flash chromatography (1:40 EA/hexane) as colorless oil (117 mg, 92% yield). The ratio of the desired regioisomer versus all other isomers in the crude product was determined to be 10:1 by GC.

Ee of the purified products was determined to be 99% by chiral HPLC analysis (Daicel CHIRALCEL ID-H; Hexanes: *i*-PrOH = 98:2; detection wavelengths = 254 nm; flow rate = 0.5 mL/min). $T_R$ = 21.9 min (minor) and 23.3 min (major).

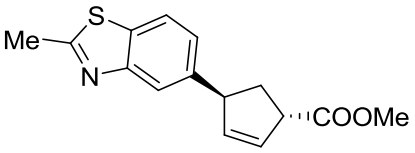



$[\alpha]^{22}_{D}$ = -1.0 $^{o}$ (*c* = 3.0, $CHCl_3$) for a sample of 99% ee.

$^{1}$H NMR (300 MHz, $CDCl_3$): δ 7.34-7.15 (m, 4H), 5.99-5.93 (m, 2H), 5.82 (ψt, *J* = 4.2 Hz, 1H), 4.10-4.04 (m, 1H), 3.79 (s, 3H), 3.73-3.66 (m, 1H), 2.77-2.64 (m, 3H), 2.95-2.45 (m, 2H), 2.02-1.93 (m, 1H).

$^{13}$C NMR (75MHz, $CDCl_3$): δ 175.2, 139.4, 137.0, 136.6, 135.0, 129.8, 127.8, 126.9, 126.6, 123.3, 123.1, 52.1, 50.3, 46.5, 34.9, 28.5, 23.3.

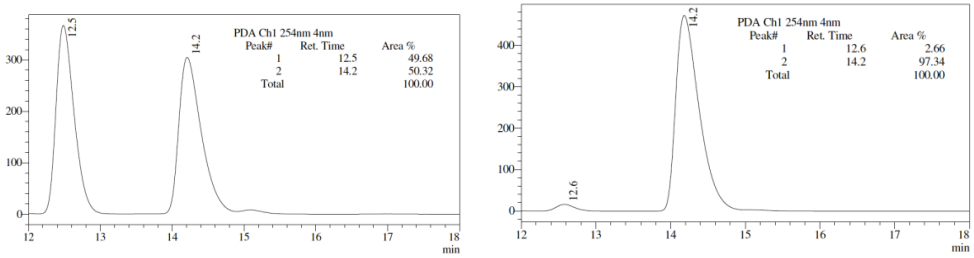
GCMS (EI): calcd for $C_{17}H_{18}O_2$ M: 254.1. Found: 254.0.




**(1*S*,4*S*)-Methyl 4-(2-methylbenzo[*d*]thiazol-5-yl)cyclopent-2-enecarboxylate.** The reaction was set up according to the general procedure by using 2-methylbenzo[*d*]thiazol-5-yl triflate (0.50 mmol, 148 mg) and methyl cyclopent-3-enecarboxylate (126 mg, 1.0 mmol). The reaction finished after 20 hours at 80 $^{o}$C. The titled compound was obtained after flash chromatography (1:10 EA/hexane) as

colorless oil (115 mg, 84% yield). The ratio of the desired regioisomer versus all other isomers in the crude product was determined to be 12:1 by GC.

Ee of the purified products was determined to be 93% by chiral HPLC analysis (Daicel CHIRALCEL ID-H; Hexanes: *i*-PrOH = 80:20; detection wavelengths = 254 nm; flow rate = 1.0 mL/min). $T_R$ = 12.6 min (minor) and 14.2 min (major).

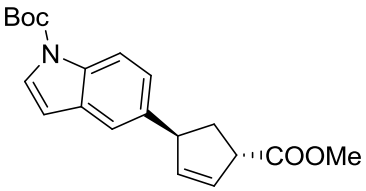



$[\alpha]^{22}_D$ = -1.9$^o$ (*c* = 1.0, $CHCl_3$) for a sample of 93% ee.

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.75-7.72 (m, 2H), 7.17 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.00-5.95 (m, 2H), 4.26-4.22 (m, 1H), 3.78-3.72 (m, 1H), 3.72 (s, 3H), 2.82 (s, 3H), 2.80-2.75 (m, 1H), 2.09-2.02 (m, 1H).

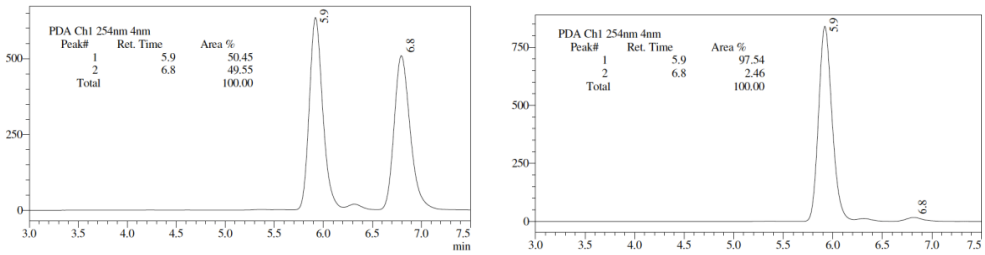
$^{13}$C NMR (100 MHz, $CDCl_3$): δ 175.0, 167.6, 154.1, 143.6, 137.5, 133.9, 130.2, 124.5, 121.6, 120.8, 52.2, 50.9, 50.7, 37.5, 20.4.

GCMS (EI): calcd for $C_{15}H_{15}NO_2S$ M: 273.08. Found: 273.01.




**(1*S*,4*S*)-*Tert*-butyl 5-(4-(methoxycarbonyl)cyclopent-2-en-1-yl)-1*H*-indole-1-carboxylate.** The reaction was set up according to the general procedure by using *tert*-butyl 5-(((trifluoromethyl)sulfonyl)oxy)-1*H*-indole-1-carboxylate (0.50 mmol, 183 mg) and methyl cyclopent-3-enecarboxylate (126 mg, 1.0 mmol). The reaction finished after 20 hours at 80 $^o$C. The titled compound was obtained after flash chromatography (1:40 EA/hexane) as colorless oil (152 mg, 89% yield). The ratio of the desired regioisomer versus all other isomers in the crude product was determined to be 20:1 by GC.

Ee of the purified products was determined to be 95% by chiral HPLC analysis (Daicel CHIRALCEL ID-H; Hexanes: *i*-PrOH = 90:10; detection wavelengths = 254 nm; flow rate = 1.0 mL/min). $T_R$ = 6.8 min (minor) and 5.9 min (major).

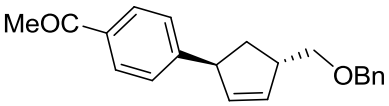



$[\alpha]^{22}_D = -2.2^o$ ($c$ = 2.0, $CHCl_3$) for a sample of 95% ee.

$^1H$ NMR (400 MHz, $CDCl_3$): δ 8.06 (d, $J$ = 8.0 Hz, 1H), 7.58 (d, $J$ = 3.6 Hz, 1H), 7.35 (d, $J$ = 1.6 Hz, 1H), 7.13 (dd, $J$ = 8.4, 1.6 Hz, 1H), 6.51 (d, $J$ = 3.6 Hz, 1H), 6.01-5.93 (m, 2H), 4.22-4.19 (m, 1H), 3.80-3.77 (m, 1H), 3.72 (s, 3H), 2.80-2.73 (m, 1H), 2.08-2.04 (m, 1H), 1.67 (s, 9H).

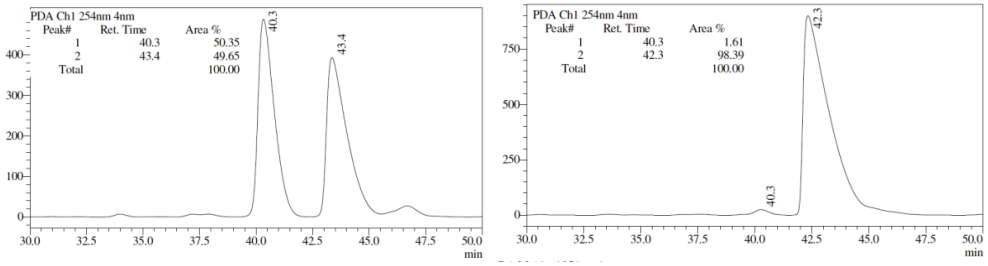
$^{13}C$ NMR (100 MHz, $CDCl_3$): δ 175.2, 150.0, 139.7, 138.1, 134.2, 131.1, 129.5, 126.4, 123.8, 119.3, 115.4, 107.4, 83.8, 52.1, 51.0, 50.8, 37.7, 28.4.

GCMS (EI): calcd for $C_{20}H_{23}NO_4$ M: 341.16. Found: 241.08 (-Boc).




**(1*S*,4*S*)-1-(4-(4-((Benzyloxy)methyl)cyclopent-2-en-1-yl)phenyl)ethanone**. The reaction was set up using 4-acetyphenyl triflate (0.50 mmol, 134 mg) and ((cyclopent-3-en-1-ylmethoxy)methyl)benzene (188 mg, 1.0 mmol). The reaction finished after 17 hours at 80 $^oC$. The titled compound was obtained after flash chromatography (1:30 EA/hexane) as light yellow oil (141 mg, 92% yield). The ratio of the desired regioisomer versus all other isomers in the crude product was determined to be 20:1 by GC.

Ee of the purified products was determined to be 97% by chiral HPLC analysis (Daicel CHIRALCEL ID-H; Hexanes: *i*-PrOH = 98:2; detection wavelengths = 254 nm; flow rate = 0.5 mL/min). $T_R$ = 40.3 min (minor) and 42.3 min (major).

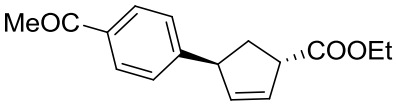



$[\alpha]^{22}_D = -0.3^o$ ($c$ = 2.0, $CHCl_3$) for a sample of 97% ee.

$^{1}$H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.7 Hz, 2H), 7.35-7.24 (m, 7H), 5.98-5.94 (m, 1H), 5.84-5.81 (m, 1H), 4.54 (s, 2H), 4.03-3.98 (m, 1H), 3.45-3.42 (m, 2H), 3.24-3.13 (m, 1H), 2.55 (s, 3H), 2.26-2.16 (m, 1H), 1.95-1.89 (m, 1H).

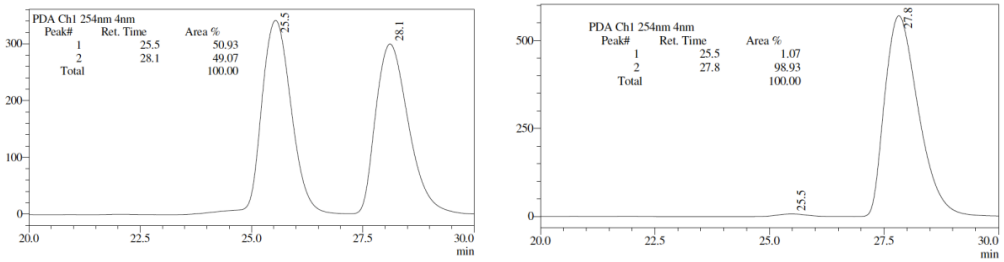
$^{13}$C NMR (75MHz, $CDCl_3$): δ 197.9, 151.9, 138.6, 135.5, 134.8, 134.2, 128.8, 128.5, 127.8, 127.7, 127.6, 127.5, 50.7, 46.3, 37.2, 26.7.

GCMS (EI): calcd for $C_{21}H_{22}O_2$ M: 306.16. Found: 251.1(-Bn).




**(1*S*,4*S*)-Ethyl 4-(4-acetylphenyl)cyclopent-2-enecarboxylate**. The reaction was set up using 4-acetyphenyl triflate (0.50 mmol, 134 mg) and ethyl cyclopent-3-enecarboxylate (140 mg, 1.0 mmol). The reaction finished after 17 hours at 80 $^{o}$C. The titled compound was obtained after flash chromatography (1:20 EA/hexane) as light yellow oil (110 mg, 85% yield). The ratio of the desired regioisomer versus all other isomers in the crude product was determined to be 20:1 by GC.

Ee of the purified products was determined to be 98% by chiral HPLC analysis (Daicel CHIRALCEL OD-H; Hexanes: *i*-PrOH = 98:2; detection wavelengths = 254 nm; flow rate = 0.5 mL/min). $T_R$ = 25.5 min (minor) and 27.8 min (major).

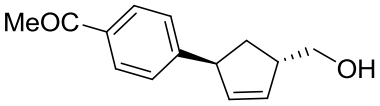



$[\alpha]^{22}_{D}$ = -0.6$^{o}$ (*c* = 3.0, $CHCl_3$) for a sample of 98% ee.

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 5.97-5.88 (m, 2H), 5.84-5.81 (m, 1H), 4.14 (q, *J* = 10.4 Hz, 3H), 3.73-3.69 (m, 1H), 2.77-2.56 (m, 1H), 2.55 (s, 3H), 1.97-1.93 (m, 1H), 1.26 (t, *J* = 7.2 Hz, 3H).

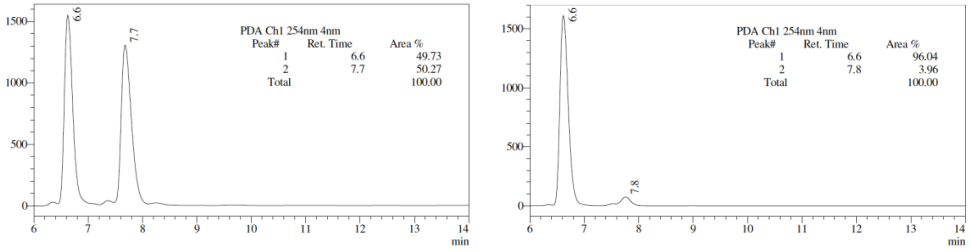
$^{13}$C NMR (100 MHz, $CDCl_3$): δ 197.8, 174.2, 150.9, 136.6, 135.7, 130.8, 128.9, 127.5, 60.9, 50.9, 50.8, 36.9, 26.7, 14.4.

GCMS (EI): calcd for $C_{16}H_{18}O_3$ M: 258.13. Found: 258.10.




**(1*S*,4*S*)-1-(4-(4-(Hydroxymethyl)cyclopent-2-en-1-yl)phenyl)ethanone**. The reaction was set up using 4-acetyphenyl triflate (0.50 mmol, 134 mg) and ethyl cyclopent-3-en-1-ylmethanol (98 mg, 1.0 mmol). The reaction finished after 13 hours at 80 $^{o}$C. The titled compound was obtained after flash chromatography (1:20 $Et_2O$/DCM) as light yellow oil (85 mg, 79% yield). The ratio of the desired regioisomer versus all other isomers in the crude product was determined to be 13:1 by GC.

Ee of the purified products was determined to be 92% by chiral HPLC analysis (Daicel CHIRALCEL ID-H; Hexanes: *i*-PrOH = 70:30; detection wavelengths = 254 nm; flow rate = 1.0 mL/min). $T_R$ = 6.6 min (major) and 7.8 min (minor).

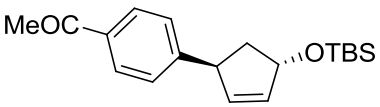



$[\alpha]^{22}_{D}$ = -1.0$^{o}$ (*c* = 2.9, $CHCl_3$) for a sample of 92% ee.

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 5.94-5.83 (m, 2H), 4.04-3.99 (m, 2H), 3.61 (d, *J* = 6.0 Hz, 2H), 3.10-3.07 (m, 1H), 2.55 (s, 3H), 2.29 (s, 1H), 2.27-2.21 (m, 1H), 1.91-1.87 (m, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 198.2, 152.0, 135.6, 135.4, 133.6, 128.8, 127.5, 66.1, 50.9, 48.6, 36.8, 26.7.

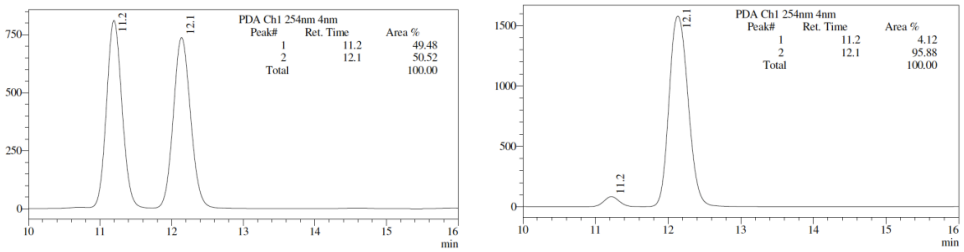
GCMS (EI): calcd for $C_{16}H_{18}O_3$ M: 216.12. Found: 216.10.




**(1*S*,4*S*)-1-(4-(4-((*Tert*-butyldimethylsilyl)oxy)cyclopent-2-en-1-yl)phenyl)ethanone.** The reaction was set up using 4-acetyphenyl triflate (0.50 mmol, 134 mg) and *tert*-butyl(cyclopent-3-en-1-yloxy)dimethylsilane (198 mg, 1.0 mmol). The reaction finished after 15 hours at 80 $^{o}$C. The titled compound was

obtained after flash chromatography (1:40 EA/Hexane) as colorless oil (149 mg, 94% yield). The ratio of the desired regioisomer versus all other isomers in the crude product was determined to be 28:1 by GC.

Ee of the purified products was determined to be 92% by chiral HPLC analysis (Daicel CHIRALCEL OJ-H; Hexanes: *i*-PrOH = 98:2; detection wavelengths = 254 nm; flow rate = 0.5 mL/min). $T_R$ = 12.1 min (major) and 11.2 min (minor).

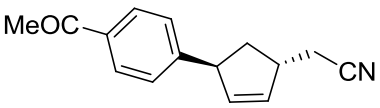



$[\alpha]^{22}_D$ = -1.6° (*c* = 1.1, $CHCl_3$) for a sample of 92% ee.

$^1$H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, *J* = 6.0 Hz, 2H), 7.21 (d, *J* = 6.0 Hz, 2H), 5.95 (ψt, *J* = 5.4 Hz, 2H), 5.08-5.07 (m, 1H), 4.19-4.16 (m, 1H), 2.56 (s, 3H), 2.29-2.23 (m, 1H), 2.07-2.01 (m, 1H), 0.91 (s, 9H), 0.09 (s, 6H).

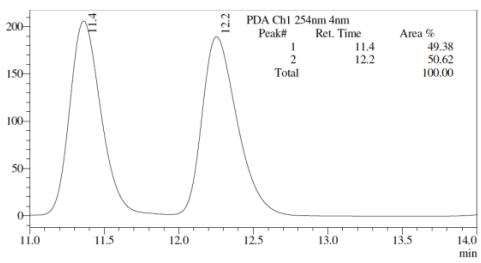
$^{13}$C NMR (75 MHz, $CDCl_3$): δ 197.8, 151.3, 136.7, 135.6, 128.9, 127.5, 77.8, 50.3, 44.1, 26.7, 26.2, 18.5, -4.3, -4.4.

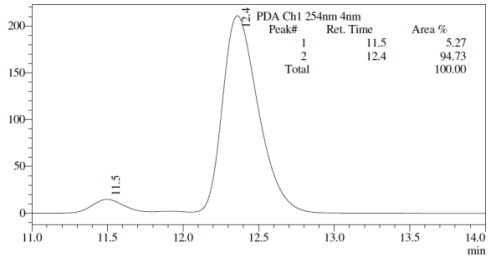
GCMS (ESI): calcd for $C_{19}H_{29}O_2Si$ (M+1): 317.19. Found: 317.11.




**(1*S*,4*S*)-1-(4-(4-(cyanomethyl)cyclopent-2-en-1-yl)phenyl)ethanone**. The reaction was set up according to the general procedure. The reaction finished after 18 hours at 80 °C.The titled compound was obtained after flash chromatography (1:5 EA/Hexane) as colorless oil (103 mg, 92% yield). The ratio of the desired regioisomer versus all other isomers in the crude product was determined to be 20:1 by GC.

Ee of the purified products was determined to be 90% by chiral HPLC analysis (Daicel CHIRALCEL ID-H; Hexanes: *i*-PrOH = 70:30; detection wavelengths = 254 nm; flow rate = 0.5 mL/min). $T_R$ = 11.5 min (minor) and 12.4 min (major).



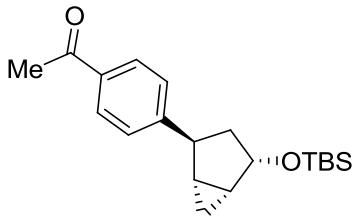

$[\alpha]^{22}_{D}$ = -0.02$^{o}$ (*c* = 1.0, $CHCl_3$) for a sample of 90% ee.

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.90 (dd, *J* = 4.0, 2.0 Hz, 2H), 7.2 (d, *J* = 1.6 Hz, 2H), 5.95 (ψt, *J* = 2.0 Hz, 2H), 4.18-4.14 (m, 1H), 3.29-3.22 (m, 1H), 2.59 (s, 3H), 2.47 (d, *J* = 6.4 Hz, 2H), 2.65-2.17 (m, 1H), 2.13-2.06 (m, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 197.9, 150.6, 136.5, 135.8, 133.6, 129.0, 127.5, 118.9, 50.7, 42.3, 39.4, 26.8, 23.3.

GCMS (EI): calcd for $C_{15}H_{15}NO$ M: 225.12. Found: 225.04.

### 1.4.3 Procedure for product derivatizations



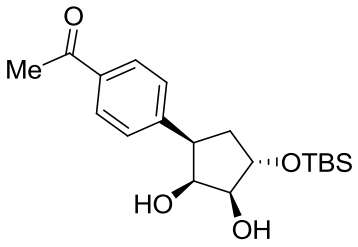

**1-(4-((1*R*,2*S*,4*S*,5*R*)-4-(*tert*-butyldimethylsilyloxy)bicyclo[3.1.0]hexan-2-yl)phenyl)ethanone.** Under argon, to a dry 10mL Schlenk tube was added 1-(4-(4-((*Tert*-butyldimethylsilyl)oxy)cyclopent-2-en-1-yl)phenyl)ethanone (63 mg, 0.2 mmol) and dry DCM 0.5mL, followed by $Et_2Zn$ (490 mg, 10% wt in hexane, 0.4 mmol). After the reaction mixture was cooled to 0 $^{o}$C in an ice bath, $CH_2I_2$ (107 mg, 0.4 mmol) was added dropwise in a period of 15 min, the reaction was allowed to warm to room temperature slowly and keep on stirring for 18 h at room temperature. The reaction mixture was then passed through a silica-gel pad and washed with DCM (50 mL), evaporated, crude GC and HNMR show only single isomer was obtained. A flash chromatography (1:40 EA/Hexane) was needed to get pure compound 63 mg in 96% yield as colorless oil.

$[\alpha]^{22}_{D}$ = -0.03$^{o}$ (*c* = 1.3, $CHCl_3$)

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.90 (dd, *J* = 6.4, 1.6 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 4.77-4.72 (m, 1H), 3.31 (d, *J* = 8.0 Hz, 1H), 2.59 (s, 3H), 1.79-1.74 (m, 1H), 1.70-1.62 (m, 2H), 1.42-1.37 (m, 1H), 0.89 (s, 9H), 0.78-0.73 (m, 1H), 0.62-0.56 (m, 1H), 0.08 (s, 3H), 0.05 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 198.0, 153.6, 135.4, 128.9, 127.4, 73.7, 44.9, 38.0, 26.8, 26.2, 23.7, 22.7, 18.5, 5.8, -4.2, -4.4.

GCMS (EI): calcd for $C_{20}H_{30}O_2Si$ M: 330.20. Found: 273.12 (-*t*Bu).



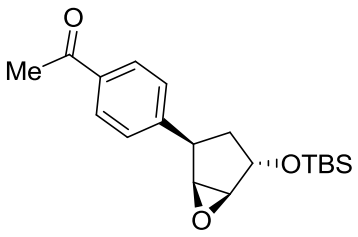

**1-(4-((1*R*,2*S*,3*S*,4*S*)-4-(*tert*-butyldimethylsilyloxy)-2,3-dihydroxycyclopentyl)phenyl)ethanone.** Under air, to a 10mL schlenk tube was added 1-(4-(4-((*Tert*-butyldimethylsilyl)oxy)cyclopent-2-en-1-yl)phenyl)ethanone (63 mg, 0.2 mmol) and AR-grade acetone 1.0 mL, $KMnO_4$ (158 mg, 1.0 mmol) in 0.5 mL DI-water. The tube was capped well and heated to 50$^{o}$C for 24 h. After the reaction was finished. HNMR of crude reaction mixture was obtained to determine the regioselectivity of 9:1. The reaction mixture was loaded onto silica-gel flash chromatography directly and washed with 1:2 EA/Hexane to give product as white solid 63 mg in 90% yield. The relative structure was confirmed by single X-ray analysis.

$[\alpha]^{22}_{D}$ = -0.22$^{o}$ (*c* = 1.8, $CHCl_3$)

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.93 (dd, *J* = 6.8, 2.0 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 4.31-4.28 (m, 2H), 4.15-4.08 (m, 1H), 3.58-3.52 (m, 1H), 2.59 (s, 3H), 2.49-2.43 (m, 2H), 1.96-1.87 (m, 2H), 0.92 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 198.2, 145.7, 136.1, 129.4, 128.8, 82.1, 78.3, 75.1, 46.1, 37.5, 26.9, 26.1, 18.4, 0.28, -4.3.

GCMS (ESI): calcd for $C_{19}H_{30}O_4SiNa$ (M+Na): 373.18. Found:373.10.




**1-(4-((1*S*,2*R*,4*S*,5*S*)-4-(*tert*-butyldimethylsilyloxy)-6-oxabicyclo[3.1.0]hexan-2-yl)phenyl)ethanone.** Under air, to a 10mL schlenk tube was added 1-(4-(4-((*Tert*-butyldimethylsilyl)oxy)cyclopent-2-en-1-yl)phenyl)ethanone (63 mg, 0.2 mmol) and AR-grade DCM 1.0 mL, followed by a portionwise addition of *m*CPBA ( 69 mg, 0.4 mmol). The reaction was stirred at room temperature for 6 h to reach completion. The regioselectivity was determined by GC of 6:1. The titled compound was obtained by silica-gel flash chromatography by using EA/Hexane 1:20 to give product as colorless oil 50 mg in 76% yield.

$[\alpha]^{22}_{D} = -0.62^{o}$ (*c* = 1.0, $CHCl_3$)

$^{1}$H NMR (300 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.1 Hz, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 4.45 (d, *J* = 4.8 Hz, 1H), 3.67 (d, *J* = 1.8 Hz, 1H), 3.55-3.41 (m, 2H), 2.59 (s, 3H), 1.95-1.88 (m, 1H), 1.72-1.55 (m, 1H), 0.93 (s, 9H), 0.12 (d, *J* = 1.8 Hz, 6H).

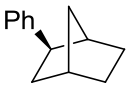
$^{13}$C NMR (75 MHz, $CDCl_3$): δ 198.1, 147.5, 136.0, 128.9, 128.3, 72.7, 59.8, 58.2, 53.7, 39.1, 26.8, 26.1, 18.4, -4.4, -4.5.

MS (ESI): calcd for $C_{19}H_{29}O_3Si$ (M+H): 333.19. Found: 333.18.

### 1.4.4 Procedure for asymmetric hydroarylation of bicyclic olefins

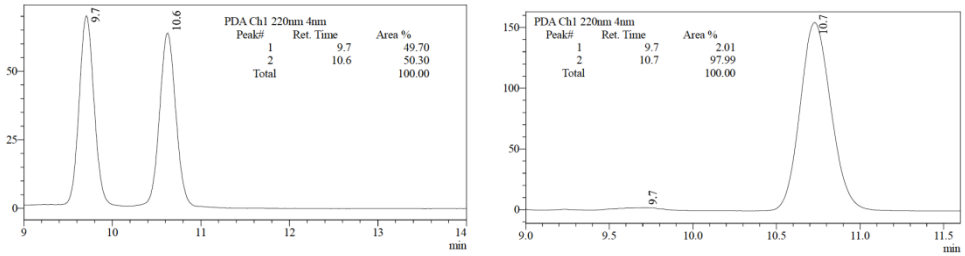
In an argon-filled glove box, a dry 25-mL Schlenk tube was charged with $Pd(dba)_2$ (5 mol%, 14.4 mg, 0.025 mmol), (*R*)-Xyl-SDP(O) (6 mol%, 21.5 mg, 0.030 mmol) and 1.0 mL of dry DMF. After stirring at room temperature for 15 minutes, the mixture was treated with HCOONa (68 mg, 1.0 mmol), aryl triflate (0.50 mmol), bicyclic olefin (1.0 mmol) and GC standard n-dodecane (20 μL). The tube was capped tightly and stirred at an 80 $^{o}$C oil bath until aryl triflate was fully consumed (monitored by GC). At the end of the reaction, the reaction mixture was directly filtered through a pad of silica gel with diethyl ether washings (20 mL) to remove Pd catalyst and inorganic salts. The filtrate was concentrated on a rotary evaporator and the residue was directly subjected to flash chromatography. The enantioselectivity of the purified product was determined by chiral HPLC analysis

of purified samples. To facilitate chiral HPLC analysis of Heck products, the racemic samples were prepared using racemic BINAP ligand. Similar results were obtained by using standard Schlenk technique involving a vacuum manifold.



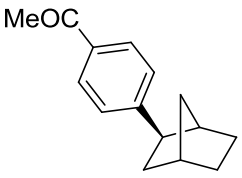

**(2*R*)-(-)-exo-2-Phenylnorbornane [139152-86-6].** The reaction was set up according to the general procedure by using phenyl triflate (0.50 mmol, 113 mg) and norbornene (94 mg, 1.0 mmol). The reaction finished after 12 hours at 80 $^{o}$C. The titled compound was obtained after flash chromatography (hexanes) as colorless oil (71 mg, 83% yield).

The ee of the purified products was determined to be 96% by chiral HPLC analysis (Daicel CHIRALCEL OJ-H; Hexanes: *i*-PrOH = 98:2; detection wavelengths = 220 nm; flow rate = 0.5 mL/min). TR = 9.7 min (minor) and 10.7 min (major).




$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.28-7.25 (m, 2H), 7.21-7.20 (m, 2H), 7.16-7.12 (m, 1H), 2.74 (dd, *J* = 8.8, 5.8 Hz, 1H), 2.37-2.34 (m, 2H), 1.79-1.74 (m, 1H), 1.69-1.63 (m, 1H), 1.61-1.51 (m, 3H), 1.38-1.31 (m, 1H), 1.29-1.24 (m, 1H), 1.19-1.16 (m, 1H).

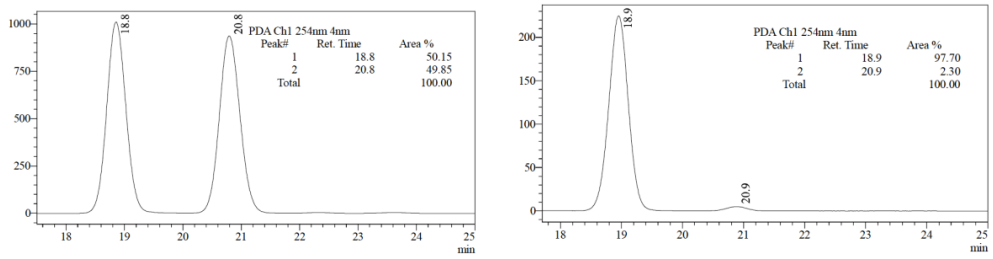
GCMS (EI): calcd for $C_{13}H_{16}$ M: 172.13. Found: 172.10.




**(2*R*)-(-)-exo-2-(*p*-Acetylphenyl)norbornane [54762-82-2].** The reaction was set up according to the general procedure by using *p*-acetyl phenyl triflate (0.50 mmol,

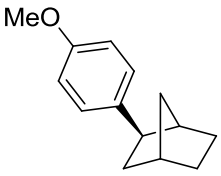
134 mg) and norbornene (94 mg, 1.0 mmol). The reaction finished after 20 hours at 80 $^{o}$C. The titled compound was obtained after flash chromatography (1:40 EA/Hexanes) as colorless oil (100 mg, 93% yield).

The ee of the purified products was determined to be 95% by chiral HPLC analysis (Daicel CHIRALCEL OJ-H; Hexanes: *i*-PrOH = 98:2; detection wavelengths = 254 nm; flow rate = 0.5 mL/min). TR = 20.9 min (minor) and 18.9 min (major).



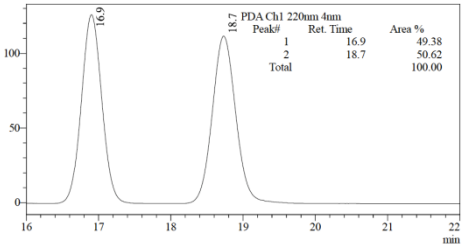

$^{1}$H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 2.82-2.77 (m, 1H), 2.58 (s, 3H), 2.39 (s, 2H), 1.85-1.77 (m, 1H), 1.69-1.57 (m, 3H), 1.54-1.49 (m, 1H), 1.42-1.20 (m, 3H).

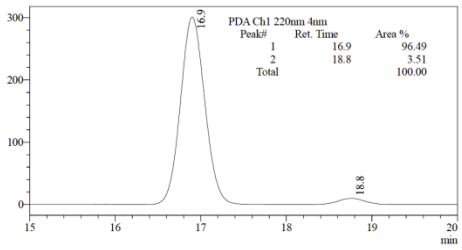
GCMS (EI): calcd for $C_{15}H_{18}O$ M: 214.14. Found: 214.04.




**(2*R*)-(-)-exo-2-(*p*-Methoxylphenyl)norbornane [406946-53-0].** The reaction was set up according to the general procedure by using *p*-methoxyl phenyl triflate (0.50 mmol, 128 mg) and norbornene (94 mg, 1.0 mmol). The reaction finished after 16 hours at 80 $^{o}$C. The titled compound was obtained after flash chromatography (1:40 EA/Hexane) as colorless oil (96 mg, 95% yield).

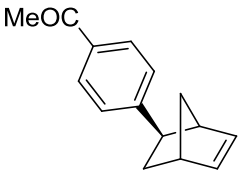
The ee of the purified products was determined to be 93% by chiral HPLC analysis (Daicel CHIRALCEL OJ-H; Hexanes: *i*-PrOH = 98:2; detection wavelengths = 220 nm; flow rate = 0.5 mL/min). TR = 18.8 min (minor) and 16.9 min (major).



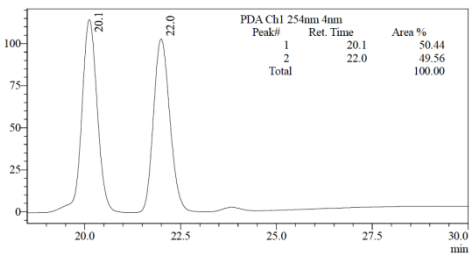

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.15 (d, *J* = 8.4 Hz, 2H), 6.74 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H), 2.72-2.69 (m, 1H), 2.35-2.33 (m, 2H), 1.79-1.73 (m, 1H), 1.68-1.52 (m, 4H), 1.39-1.25 (m, 2H), 1.20-1.16 (m, 1H).

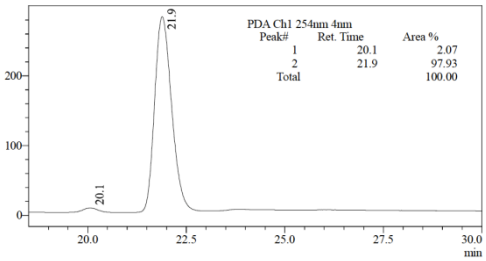
GCMS (EI): calcd for $C_{15}H_{18}O$ M: 202.14. Found: 202.09.




**(2*R*)-(-)-exo-2-(*p*-Acetylphenyl)norbornadiene [1092115-36-0].** The reaction was set up according to the general procedure by using *p*-actyl phenyl triflate (0.50 mmol, 134 mg) and norbornadiene (92 mg, 1.0 mmol). The reaction finished after 12 hours at 80 $^o$C. The titled compound was obtained after flash chromatography (1:50 ethyl acetate/hexanes) as colorless oil (85 mg, 80% yield).

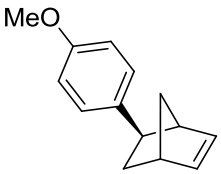
The ee of the purified products was determined to be 96% by chiral HPLC analysis (Daicel CHIRALCEL ID-H; Hexanes: *i*-PrOH = 98:2; detection wavelengths = 254 nm; flow rate = 0.5 mL/min). TR = 20.1 min (minor) and 21.9 min (major).



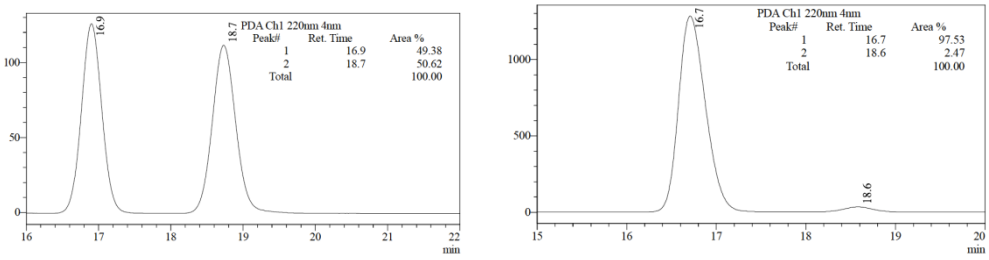

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 6.27-6.18 (m, 2H), 2.99 (s, 1H), 2.94 (s, 1H), 2.78-2.74 (m, 1H), 2.59 (s, 3H), 1.75-1.68 (m, 2H), 1.58-1.54 (m, 2H), 1.48-1.46 (m, 1H).

GCMS (EI): calcd for $C_{15}H_{16}O$ M: 212.12. Found: 212.09.



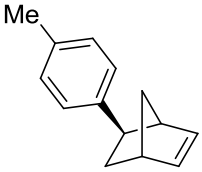

**(2*R*)-(-)-exo-2-(*p*-Methoxylphenyl)norbornadiene [139153-93-5].** The reaction was set up according to the general procedure by using *p*-methoxyl phenyl triflate (0.50 mmol, 128 mg) and norbornadiene (92 mg, 1.0 mmol). The reaction finished after 12 hours at 80 $^{o}$C. The titled compound was obtained after flash chromatography (1:50 ethyl acetate/hexanes) as colorless oil (85 mg, 85% yield).

The ee of the purified products was determined after hydrogenation. The hydrogenation was carried out by using 10 mg of product and 5% Pd/C (0.5 mg) in 0.2 mL MeOH. The reaction finished after 7 hours at 100 psi of $H_2$. Ee after hydrogenation was determined to be 95% by chiral HPLC analysis (Daicel CHIRALCEL OJ-H; Hexanes: *i*-PrOH = 98:2; detection wavelengths = 220 nm; flow rate = 0.5 mL/min). TR = 18.6 min (minor) and 16.7 min (major).




$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.25-6.14 (m, 2H), 3.80 (s, 3H), 2.95 (s, 1H), 2.85-2.84 (m, 1H), 2.68-2.65 (m, 1H), 1.73-1.68 (m, 1H), 1.64-1.57 (m, 2H), 1.55-1.41 (m, 1H).

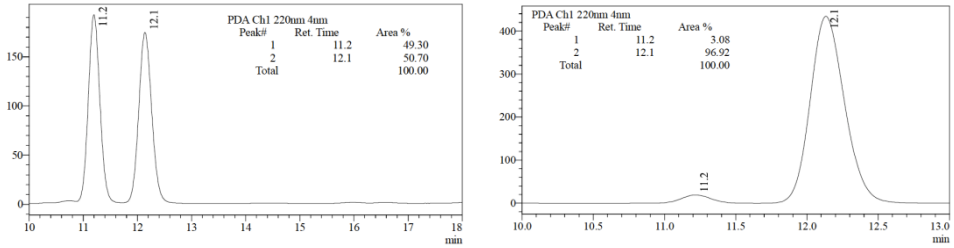
GCMS (EI): calcd for $C_{14}H_{16}O$ M: 200.12. Found: 200.09.




**(2*R*)-(-)-exo-2-(*p*-Methylphenyl)norbornadiene [51690-57-4].** The reaction was set up according to the general procedure by using *p*-methyl phenyl triflate (0.50 mmol, 112 mg) and norbornadiene (92 mg, 1.0 mmol). The reaction finished after

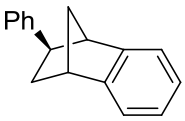
12 hours at 80 $^{o}$C. The titled compound was obtained after flash chromatography (1:50 ethyl acetate/hexanes) as colorless oil (76 mg, 83% yield).

The ee of the purified products was determined to be 94% by chiral HPLC analysis (Daicel CHIRALCEL OJ-H; Hexanes: *i*-PrOH = 98:2; detection wavelengths = 254 nm; flow rate = 0.5 mL/min). TR = 11.2 min (minor) and 12.1 min (major).



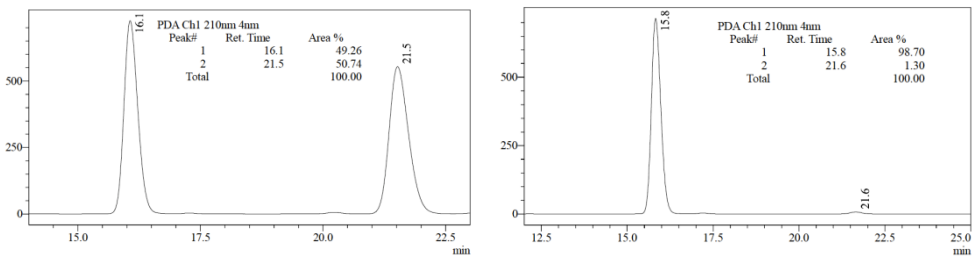

$^{1}$H NMR (300 MHz, $CDCl_3$): δ 7.17 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 6.26-6.14 (m, 2H), 2.95 (s, 1H), 2.87 (s, 1H), 2.70-2.66 (m, 1H), 2.32 (s, 3H), 1.76-1.69 (m, 1H), 1.65-1.56 (m, 2H), 1.43-1.40 (m, 1H).

GCMS (EI): calcd for $C_{14}H_{16}$ M: 184.13. Found: 184.02.




**(2*R*)-2-Phenyl-1,2,3,4-tetrahydro-1,4-methanonaphthalene[58653-72-8].** The reaction was set up according to the general procedure by using phenyl triflate (0.50 mmol, 113 mg) and benzonorbornene (142 mg, 1.0 mmol). The reaction finished after 12 hours at 80 $^{o}$C. The titled compound was obtained after flash chromatography (hexanes) as colorless oil (95 mg, 86% yield).

The ee of the purified products was determined to be 97% by chiral HPLC analysis (Daicel CHIRALCEL OJ-H; Hexanes: *i*-PrOH = 98:2; detection wavelengths = 210 nm; flow rate = 0.5 mL/min). TR = 21.6 min (minor) and 15.8 min (major).



$^{1}$H NMR (300 MHz, $CDCl_3$): δ 7.34-7.33 (m, 4H), 7.26-7.20 (m, 3H), 7.13-7.10 (m, 2H), 3.46 (s, 2H), 2.89-2.84 (m, 1H), 2.08-1.98 (m, 2H), 1.97-1.82 (m, 2H).

GCMS (EI): calcd for $C_{17}H_{16}$ M: 220.13. Found: 220.00.

# Part 2. Fast Suzuki Coupling of Heteroaryl Tosylates

## 2.1 Introduction

### 2.1.1 Introduction of Suzuki Coupling

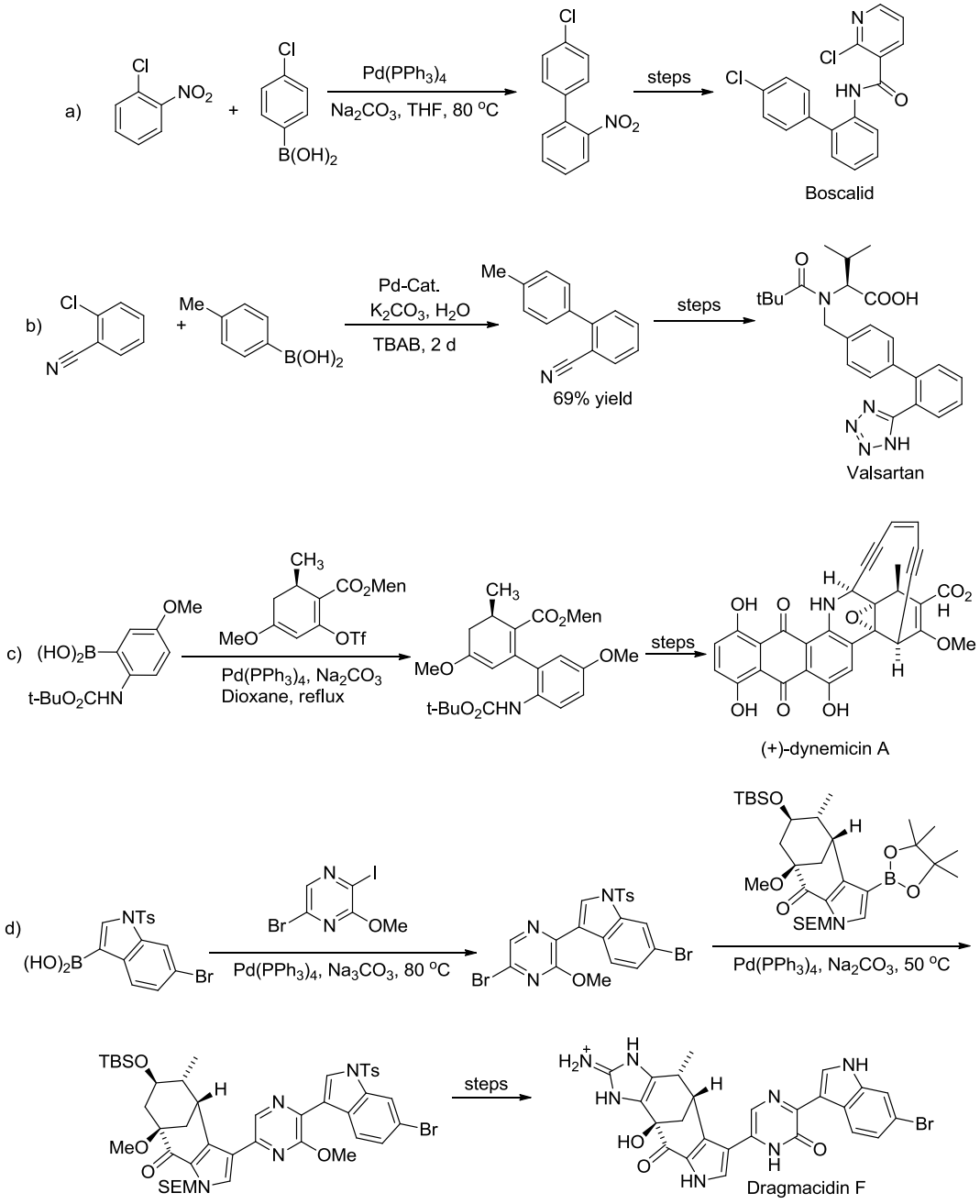
The first general Pd-catalyzed cross-coupling of organoboron reagents was reported by Suzuki *et al.* in 1979.[29] Since then, Suzuki coupling has been extensively studied and its substrate scope was tremendously expended by the advent of highly active Pd or Ni catalysts.[30-43] It is now frequently used to prepare biaryl motifs that are present in medicines, agrochemicals, conjugate polymers and other functional materials.[30,34,42,43] Compared to other cross-coupling reactions, Suzuki reaction usually shows very broad substrate scope and excellent tolerance of polar functional groups; the coupling reagents, organoboronic acids and esters are of low toxicity or almost nontoxic; they are stable towards air, water and heating around 100 $^{o}$C; the boron byproducts could be easily separated after reaction. In addition, most organoboronic esters and acids are now commercially available and many functionalized heteroaryl and arylboronic acids can also be readily prepared via metal-catalyzed borylation of arene C-H[36-38] and C-X[39-41] bonds.

In industry, Suzuki coupling is employed in synthesis of the Sartan family of antihypertensive drugs and Boscalid. Suzuki coupling is employed in synthesis of the Valsartan **5** for the treatment of hypertension (Scheme 2.1a). It had global sales of US$ 4.2 billion in 2006. Boscalid is a fungicide developed by BASF in 1997 (Scheme 2.1b).

(+)-*Dynemicin A* is an enediyne natural product found to process potent cytotoxicity against a variety of human tumor cell lines. An efficient total synthesis of (+)-*Dynemicin A* was reported by Jutand employing Suzuki coupling (Scheme 2.1c).[44]

Dragmacidin F was isolated from Mediterranean sponge Halicortex. It displayed potent antiviral activity against herpes simplex virus and human immunodeficiency

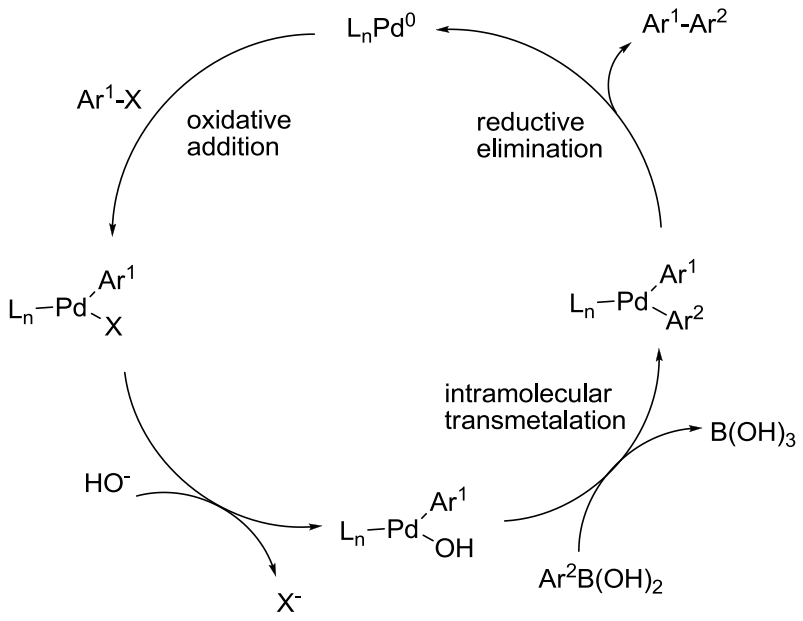
virus. In the total synthesis reported by Stoltz *et al.*, two halogen-selective Suzuki couplings were used (Scheme 2.1d).[45]




**Scheme 2.1** Applications of Suzuki coupling

The catalytic cycle of the palladium-catalyzed Suzuki coupling follows a three-step sequence: oxidative addition of an aryl halide to a Pd(0) complex forms an aryl palladium(II) halide intermediate. Relative reactivity of oxidative addition is

as follows: Ar-I > Ar-OTf > Ar-Br >> Ar-Cl > ArOTs. The second step is transmetalation of arylboronic acid with the assistance of base. Finally, reductive elimination from the diary palladium complex provides the biaryl product and regenerates the Pd(0) complex (Scheme 2.2).[33]

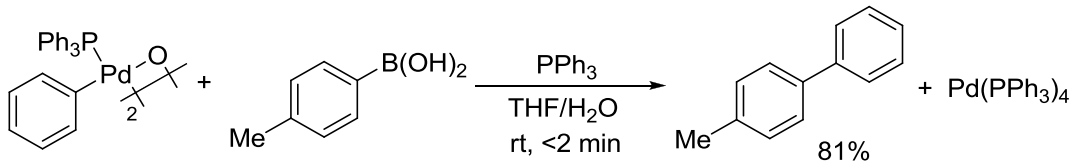



**Scheme 2.2** Catalytic cycle for Suzuki coupling

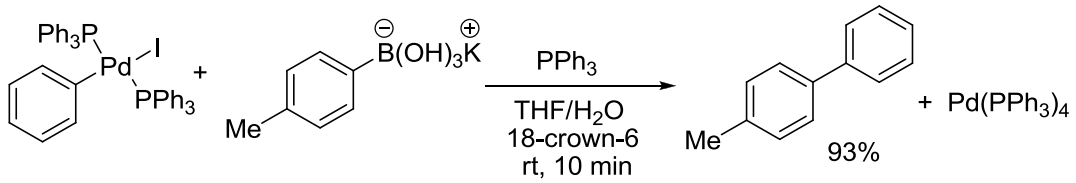
Bases which are crucial in these reactions facilitate the transmetalation of the boronic acids by forming a more reactive boronate species or by replacing the halide in the coordination sphere of the palladium complex and facilitate an intramolecular transmetalation. In 2011, John F. Hartwig group reported that replacement of the halide is preferred if a weak base is employed based on a quantitative assessment.[46] They studied the stoichiometric scale reactions of isolated aryl palladium hydroxo complex and boronic acid in one case together with aryl palladium halide complex and trihydroxyborate in other case. The reaction of aryl palladium hydroxo complex with *p*-tolylboronic acids (eq 1) proceeded faster than the reaction of aryl palladium halide complex with *p*-tolyltrihydroxyborate (eq 2). While the reaction of phenyl iodide with *p*-tolylboronic acid (eq 3) needed 3 hours at 80 $^{o}$C to reach completion. So the

transmetalation step makes the coupling reactions having different reaction rates.

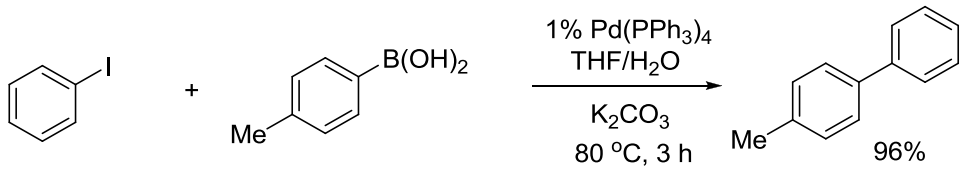
Eq 1




Eq 2




Eq 3



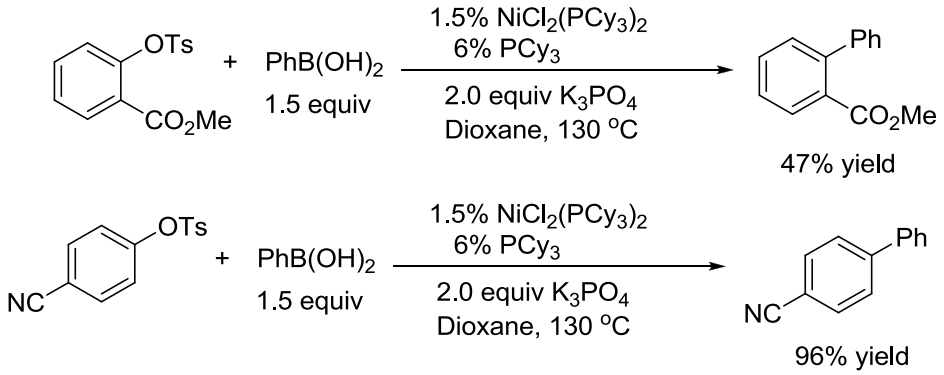

The role of hydroxide bases in Suzuki coupling has been investigated also by Jutand *et al.*[47] Transmetalation of $ArB(OH)_2$ to LPd(Ar)(OH) was proved to be more preferred than that of $ArB(OH)_3^-$ to LPd(Ar)(OH). Roles of the hydroxide anion were examined: (a) promotion of transmetalation via the formation of hydroxo complexes *trans*-[LPd(Ar)(OH)]; (b) inhibition of transmetalation by the formation of unreactive $ArB(OH)_3^-$; and (c) acceleration of reductive elimination. Thus, a reasonably higher ratio of $[OH^-]/[ArB(OH)_2]$ can give faster coupling reactions.

### 2.1.2 Suzuki Couplings of Aryl Tosylates

In the past few years, considerable efforts have been devoted to develop Suzuki coupling reactions of heteroaryl halides and boronic acids.[48-53] However, a general method for Suzuki coupling of heteroaryl tosylates at room temperature is still lacking. Aryl sulfonates which are attractive to make a large family of materials since they can be easily prepared from phenols and cheap arenesufonyl chlorides.

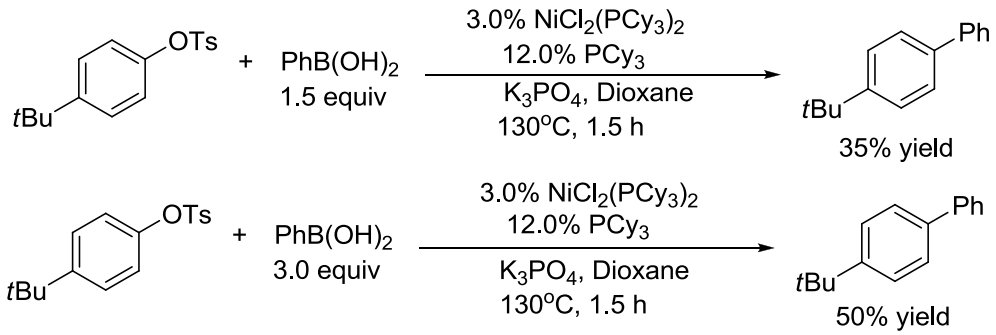
Compared to triflates, aryl tosylates are more stable, less susceptible to hydrolysis, crystalline, cheaper to make, but less reactive. To date, only a few reported works have been published including much fewer examples of hetero aryltosylates. The reported systems usually required high reaction temperature or mild reaction temperature with limited substrates scope.

In 2001, Monteiro *et al.* reported a nickel-catalyzed Suzuki coupling of aryl tosylates for the first time.[54] The employing of $NiCl_2(PCy_3)_2$ catalyst allowed the coupling of different aryl tosylates and arylboronic acids realized. A wide scope of substrates and excellent yields were achieved at 130 $^oC$ in dioxane (Scheme 2.3).



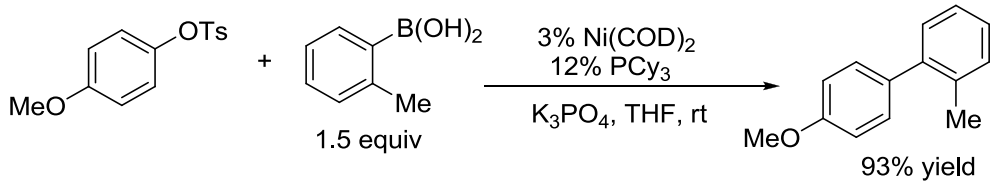

**Scheme 2.3** $NiCl_2(PCy_3)_2$ catalyzed Suzuki coupling of aryl tosylates

In this work, the author also reported that the transmetalation step is the rate-determining step. The evidence is that the reaction of 4-*t*$BuC_6H_4OTs$ with $PhB(OH)_2$ proceeded more faster once the amount of Phenylboronic acid was increased. A 35% yield in product was obtained after 1.5 h with 1.5 equiv of $PhB(OH)_2$ versus 50% yield was obtained when 3.0 equiv of $PhB(OH)_2$ was employed (Scheme 2.4).




**Scheme 2.4** Evidence on rate-determining step

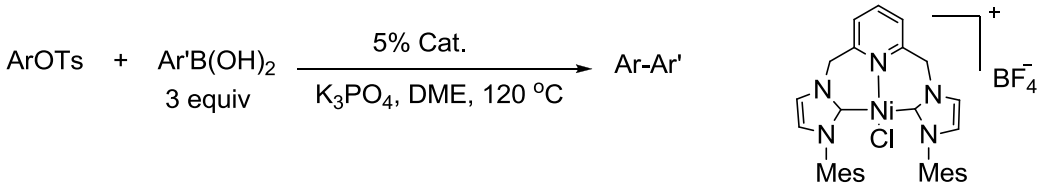
Later, a room temperature Suzuki coupling of aryl tosylates was achieved by Hu *et al.* for the first time.[55] A catalyst system derived from $Ni(COD)_2$ and $PCy_3$ allowed the coupling of activated aryl tosylates with arylboronic acids realized at room temperature (Scheme 2.5). There was no example of heteroaryl tosylates and the scope of arylboronic acids was limited to only a few electron-rich ones.

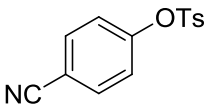
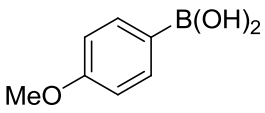
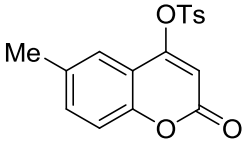
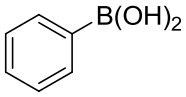
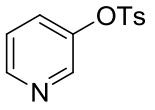
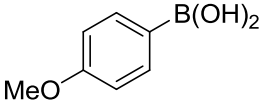



**Scheme 2.5** First room temperature Suzuki coupling of aryl tosylates

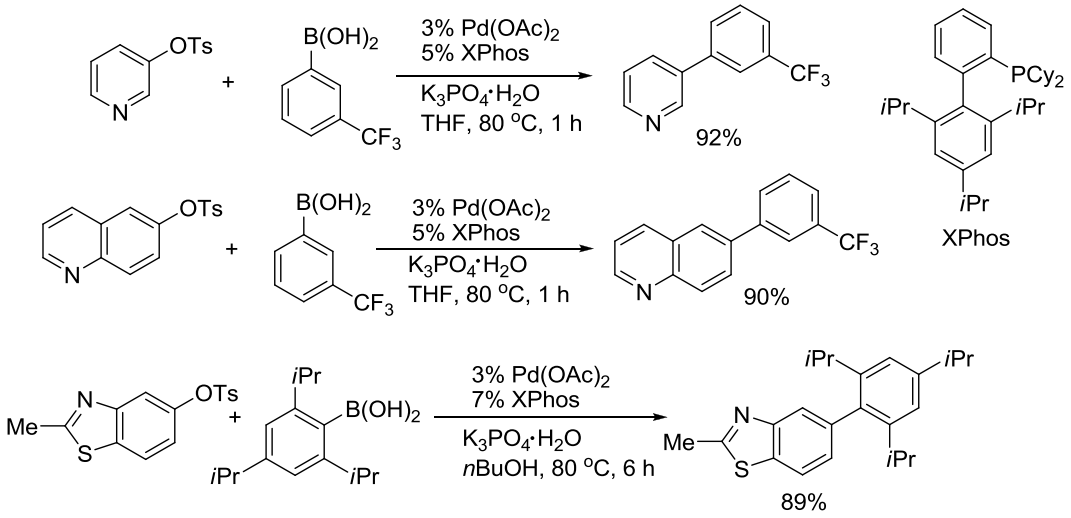
A N-Heterocyclic Carbene based catalyst was then reported by Doi *et al.* in 2009. It was effective for many electron-poor aryl and alkenyl tosylates.[56] One example of heteroaryl tosylate (3-pyridinyl tosylate) was included in the paper requiring prolonged reaction time (48 h) (Table 2.1).

**Table 2.1** NHC-derived Ni(II)-catalyzed Suzuki couplings of aryl tosylates



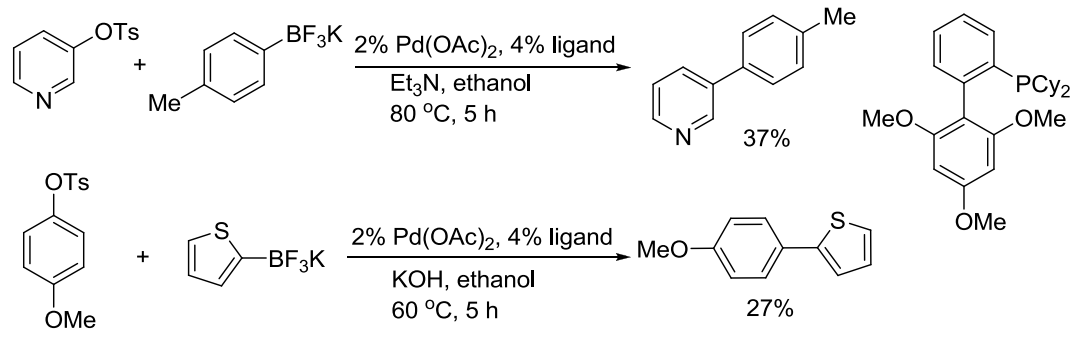

| ArOTs/VinylOTs | Ar'B(OH)$_2$ | Time | Yield (%) |
|---|---|---|---|
|  |  | 24 h | 55 |
|  |  | 3 h | 62 |
|  |  | 48 h | 69 |

In 2003, Buchwald *et al.* reported the first palladium-catalyzed Suzuki coupling of aryl and heteroaryl tosylates.[57] In this work, XPhos was used as ligand. The catalytic system worked well with a wide range of aryl, alkenyl and heteroaryl tosylates (Scheme 2.6). But no examples of electron-rich aryl tosylates or heteroarylboronic acids were included.



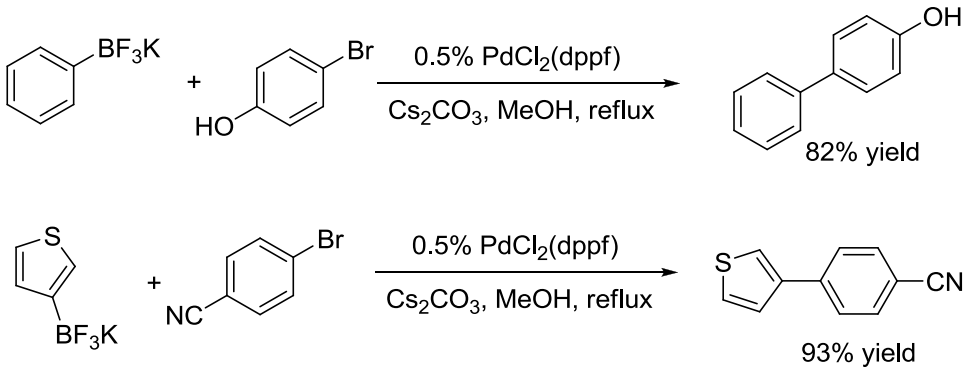

**Scheme 2.6** First Pd catalyzed Suzuki coupling of aryl tosylates

Suzuki coupling of aryl tosylates was also tried with potassium aryl trifluoroborates by Wu *et al.* in 2007.[58] The author disclosed an efficient method for the Suzuki coupling in excellent yields. Heteroaryl tosylates and heteroaryl potassium trifluoroborates were also applied, but the yields were quite low (Scheme 2.7).




**Scheme 2.7** Suzuki coupling of heteroaryl tosylates and heteroaryl potassium trifluoroborates

In 2003, Molander *et al*. demonstrated the Suzuki coupling of organotrifluoroborates.[59] A wide array of electron-deficient and electron-rich groups in both coupling partners was tolerated.

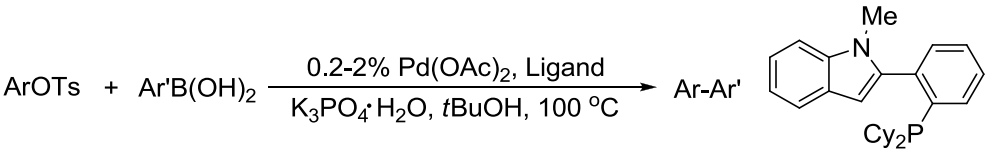


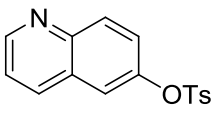
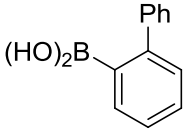
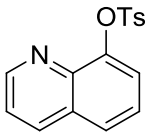
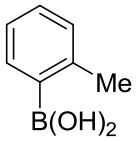
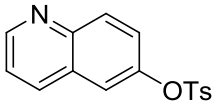
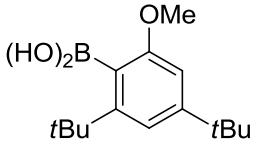
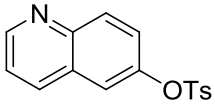
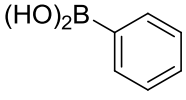

**Scheme 2.8** Suzuki coupling of aryl potassium trifluoroborates

The first example for room temperature palladium-catalyzed Suzuki coupling

reaction of aryl tosylate was successfully realized by employing an Indolyl type phosphine ligand.[60] Different aryl and heteroaryl tosylates were applied in this system, whereas only 6-quinolinyl tosylate was coupled with phenylboronic acid at room temperature in excellent yield after 78 h (Table 2.2). This system showed a good functional group tolerance and generally required less than 2 mol % Pd. However, no examples using electron-deficient, heteroaryl, or alkenyl boronic acids were included.

**Table 2.2** Coupling of heteroaryl tosylates catalyzed by indolyl phosphine

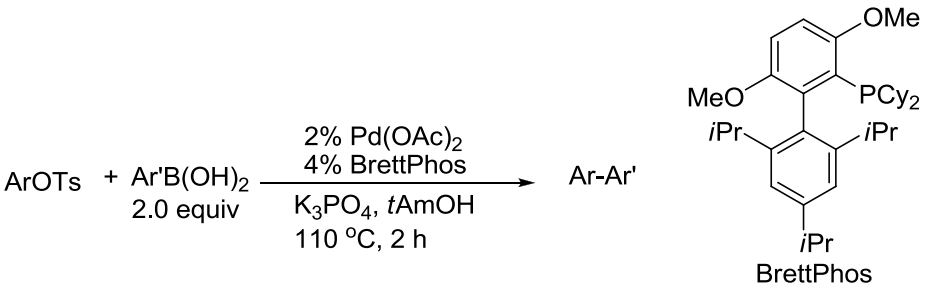


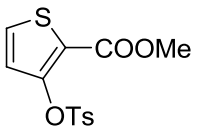
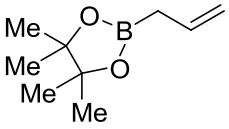
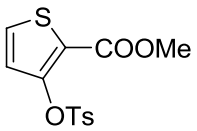
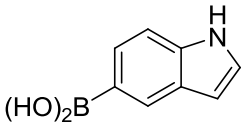
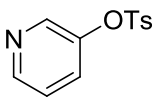
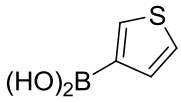
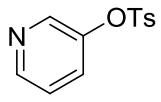
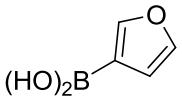

| ArOTs | Ar'B(OH)$_2$ | Product Yield (%) |
|---|---|---|
|  |  | 99% |
|  |  | 99% |
|  |  | 91% |
|  |  | rt, 78 h, 94% |

In 2009, Buchwald *et al.* developed a versatile catalytic system based on BrettPhos for the Suzuki coupling reactions. Aryl and heteroaryl tosylates were successfully coupled with heteroarylboronic acids for the first time (Table 2.3).[61]

This system provided an efficient method for the coupling between different aryl tosylates and arylboronic acids in terms of both electronic properties and steric properties at elevated reaction temperatures.

**Table 2.3** Suzuki coupling of tosylates with heteroarylboronic acids




| ArOTs | $Ar'B(OH)_2$ | Product Yield (%) |
|---|---|---|
|  |  | 72% |
|  |  | 85% |
|  |  | 87% |
|  |  | 72% |

In summary, many works have been done to develop an efficient catalyst system for Suzuki coupling reactions. Until now, no catalytic system was general enough for an efficient Suzuki coupling reaction between difficult heteroaryl tosylates and heteroarylboronic acids at mild conditions. Biheterocycles are useful building blocks in medicinal chemistry. So it's important to develop an efficient catalyst system for Suzuki coupling reactions between heterocycles. In this following

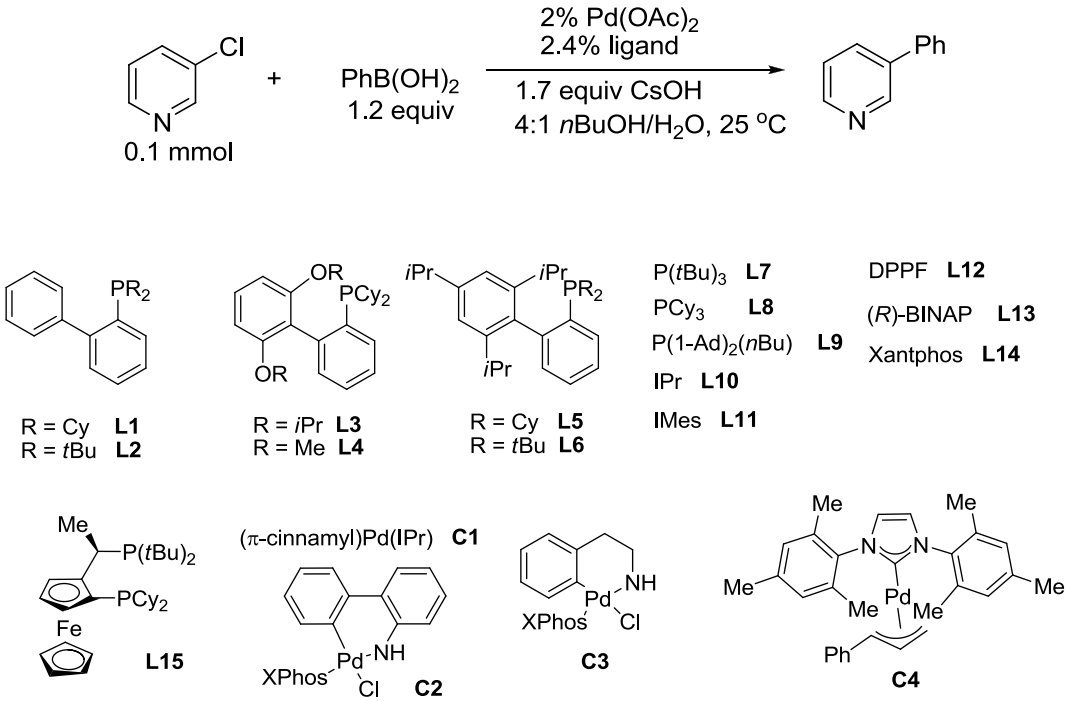
chapter, an efficient coupling of heteroaryl tosylates with both aryl and heteroaryl boronic acids at room temperature within minutes to hours will be described. The mild condition is compatible with many sensitive functional groups and allowed heteroaryl tosylates and heteroarylboronic acids with different electronic substituents coupled at room temperature in excellent yields.

## 2.2 Results and Discussion

### 2.2.1 Condition Optimization

Based on the ligands screening results of aryl chlorides in our group (Table 2.4), we still chose XPhos as the ligand of choice. XPhos gave a delicate balance between electronic effects and steric effects in the catalyst system, by which the reaction could finish within minutes to hours.

**Table 2.4** Screening of ligands

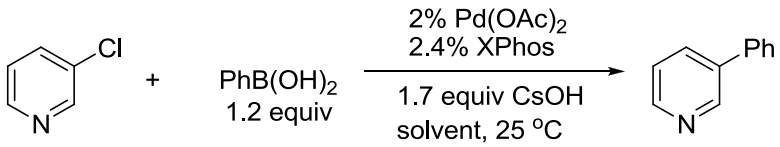


| Entry | Ligand | 5 min | | 15 min | | 1 h | |
|---|---|---|---|---|---|---|---|
| | | conv (%) | Yield (%) | conv (%) | Yield (%) | conv (%) | Yield (%) |
| 1 | **L1** | 28 | 28 | 44 | 43 | 56 | 54 |
| 2 | **L2** | 54 | 49 | 83 | 83 | 100 | 100 |
| 3 | **L3** | 92 | 92 | 100 | 100 | 100 | 100 |
| 4 | **L4** | 92 | 92 | 99 | 99 | 100 | 100 |
| 5 | **L5 (XPhos)** | 100 | 98 | 100 | 98 | 100 | 98 |
| 6 | **L6** | 27 | 26 | 48 | 48 | 67 | 67 |
| 7 | **L7** | 40 | 39 | 43 | 41 | 45 | 42 |
| 8 | **L8** | 57 | 57 | 82 | 82 | 89 | 89 |
| 9 | **L9** | 79 | 79 | 86 | 86 | 87 | 87 |
| 10 | **L10** | 0 | 0 | 0 | 0 | 0 | 0 |
| 11 | **L11** | 2 | 2 | 9 | 6 | 13 | 10 |
| 12 | **L12** | 0 | 0 | 0 | 0 | 0 | 0 |
| 13 | **L13** | 0 | 0 | 0 | 0 | 0 | 0 |
| 14 | **L14** | 0 | 0 | 0 | 0 | 0 | 0 |
| 15 | **L15** | 9 | 3 | 15 | 4 | 18 | 6 |
| 16 | **C1**[a] | 2 | 0 | 2 | 0 | 4 | 4 |
| 17 | **C2**[a] | 71 | 70 | 100 | 97 | 100 | 97 |
| 18 | **C3**[a] | 3 | 0 | 5 | 2 | 22 | 21 |
| 19 | **C4**[a] | 0 | 0 | 0 | 0 | 0 | 0 |

[a] No $Pd(OAc)_2$ was added.

Based on the solvent screening of aryl chloride in Suzuki coupling reaction in our group (Table 2.5), *n*BuOH:$H_2O$ 4:1 (ratio of volume) is the solvent of choice. Alcohol solvents are usually better than other kinds of solvents. Water is also necessary in the reaction to improve the solubility of base. That will facilitate transmetalation of bronic acids and also will give a more homogenous reaction mixture.

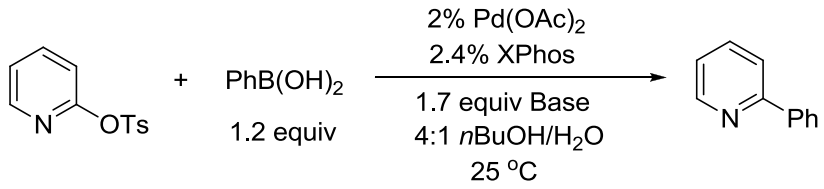
**Table 2.5** Screening of solvents




| Entry | Solvent | 5 min | | 15 min | | 1 h | |
|---|---|---|---|---|---|---|---|
| | | conv (%) | Yield (%) | conv (%) | Yield (%) | conv (%) | Yield (%) |
| 1 | 4:1 *n*BuOH/ $H_2O$ | 100 | 98 | 100 | 98 | 100 | 98 |
| 2 | dry *n*BuOH | 95 | 93 | 100 | 98 | 100 | 98 |
| 3 | 4:1 EtOH/ $H_2O$ | 60 | 51 | 95 | 85 | 100 | 94 |
| 4 | dry EtOH | 92 | 92 | 100 | 97 | 100 | 97 |
| 5 | 4:1 dioxane/ $H_2O$ | 16 | 14 | 45 | 42 | 70 | 70 |
| 6 | dry dioxane | 0 | 0 | 0 | 0 | 0 | 0 |
| 7 | 4:1 THF/ $H_2O$ | 26 | 22 | 63 | 60 | 93 | 93 |
| 8 | dry THF | 0 | 0 | 0 | 0 | 8 | 8 |
| 9 | 4:1 toluene/ $H_2O$ | 0 | 0 | 0 | 0 | 0 | 0 |
| 10 | dry toluene | 0 | 0 | 0 | 0 | 0 | 0 |
| 11 | $H_2O$ | 0 | 0 | 0 | 0 | 0 | 0 |

We took 2-pyridine tosylate and phenylboronic acid as model substrates to investigate different bases' effects in Suzuki coupling reactions (Table 2.6). Most bases could give very fast coupling reactions which needed 15 minutes to 1 hour to reach completions. NaOH was superior which could facilitate the reaction to completion after 15 minutes with a 95% conversion after 5 minutes. Metal hydroxide bases are more helpful than metal carbonates in the reactions.

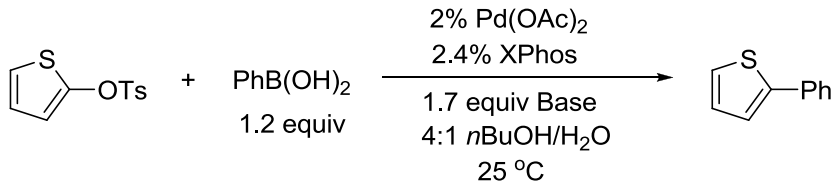
**Table 2.6** Screening of bases




| Entry | Base | 5 min | | 15 min | | 1 h | |
|---|---|---|---|---|---|---|---|
| | | conv (%) | Yield (%) | conv (%) | Yield (%) | conv (%) | Yield (%) |
| 1 | LiOH | 38 | 38 | 100 | 99 | 100 | 99 |
| 2 | NaOH | 95 | 95 | 100 | 99 | 100 | 99 |
| 3 | KOH | 94 | 89 | 100 | 99 | 100 | 99 |
| 4 | CsOH | 91 | 89 | 100 | 94 | 100 | 94 |
| 5 | $K_2CO_3$ | 31 | 31 | 52 | 46 | 80 | 73 |
| 6 | $Cs_2CO_3$ | 36 | 33 | 56 | 49 | 83 | 82 |
| 7 | $K_3PO_4$ | 91 | 91 | 100 | 99 | 100 | 99 |

When we chose NaOH as the base of choice to look at different aryl tosylates, 2-thiophene tosylate gave the coupling product in a low yield companied with partial starting tosylate hydrolyzed byproduct. NaOH was probably too strong for this sensitive substrates. Then we looked at some weaker bases for 2-thiophene tosylate and found that $K_3PO_4$ gave a reasonable yield and fast reaction rate (Table 2.7). So $K_3PO_4$ was the base of choice for 2-thiophene tosylate.

**Table 2.7** Screening of bases for 2-thiophene tosylate



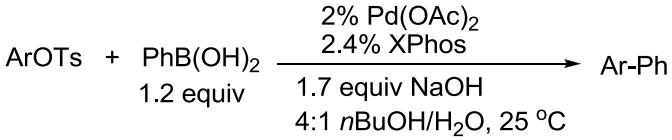

| Entry | Base | 5 min | | 15 min | |
|---|---|---|---|---|---|
| | | conv (%) | Yield (%) | conv (%) | Yield (%) |
| 1 | NaOH | 100 | 81 | 100 | 81 |
| 2 | CsOH | 100 | 97 | 100 | 97 |
| 3 | $Na_2CO_3$ | 70 | 37 | 90 | 72 |
| 4 | $K_2CO_3$ | 82 | 67 | 100 | 80 |
| 5 | $K_3PO_4$ | 100 | 96 | 100 | 96 |

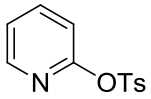
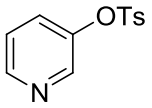
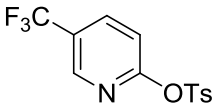
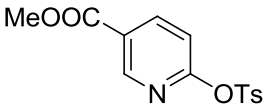
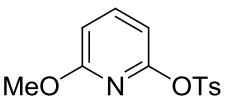
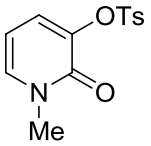
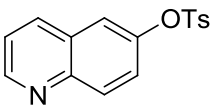
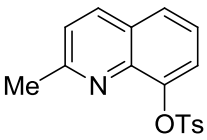
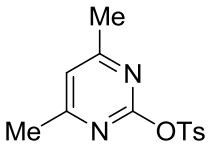
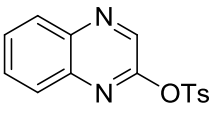
### 2.2.2 Scope of Heteroaryl Tosylates

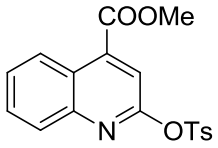
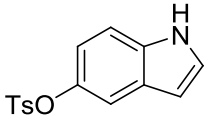
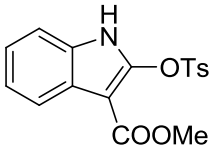
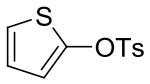
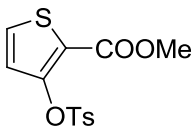
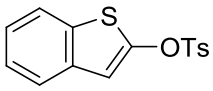
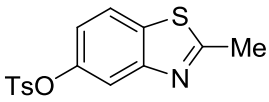
With the optimized conditions in hand, we explored different heteroaryl tosylates. We found that many families of heteroaryl tosylates gave coupling products with phenyl boronic acid in high yields at room temperature after minutes or hours. The results are summarized in Table 2.8. These heteroaryl tosylates including pyridines, quinolines (entry 7, 8 and 11), indoles, thiophenes and derived ones worked well in the catalytic system. We found that the electron-withdrawing ester (entry 4) and trifluoromethyl (entry 3) groups accelerated the coupling reactions, probably due to their effects on the oxidative addition step. Also the electron-rich indole substrates (entry 12) required longer reaction time comparing with the pyridine substrates (entry 1), this may due to the slow oxidative addition. For the 2-Thiophene (entry 14) and 2-Benzothiophene tosylates (entry 16), $K_3PO_4$ was the suitable base since these two substrates are prone to undergo hydrolysis

under strong basic conditions.

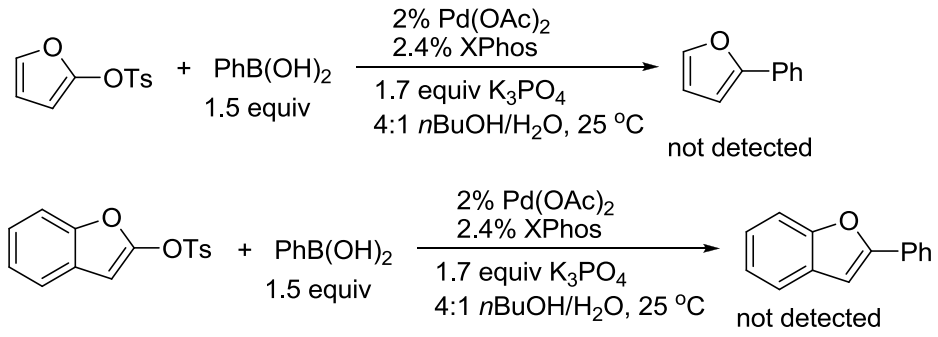
**Table 2.8** Coupling of various heteroaryl tosylates with phenyl boronic acids




| entry | ArOTs | Yield (%) | Time | Comment |
|---|---|---|---|---|
| 1 |  | 95 | 15 min | |
| 2 |  | 95 | 20 h | |
| 3 |  | 95 | 5 min | |
| 4 |  | 90 | 5 min | 1.5 equiv $PhB(OH)_2$ |
| 5 |  | 92 | 15 min | |
| 6 |  | 95 | 1 h | |
| 7 |  | 95 | 5 h | |
| 8 |  | 94 | 3 h | |
| 9 |  | 96 | 1 h | |
| 10 |  | 93 | 5 min | |

| | | | | |
|---|---|---|---|---|
| 11 |  | 89 | 2 h | |
| 12 |  | 89 | 20 h | |
| 13 |  | 90 | 4 h | |
| 14 |  | 93 | 5 min | $K_3PO_4$ as base |
| 15 |  | 94 | 5 min | |
| 16 |  | 99 | 5 min | $K_3PO_4$ as base |
| 17 |  | 96 | 5 h | |

In addition, hydrolysis of both 2-furan and 2-benzofuran tosylates was too fast and they could not be applied in these coupling conditions. We also tried the Suzuki coupling reactions of freshly prepared 2-furyl tosylate and 2-benzofuryl tosylate with phenylboronic acid individually. After 5 min, all starting tosylates materials were disappeared unproductively with NaOH or $K_3PO_4$ as bases. Due to the fast hydrolysis of the unstable 2-furyl tosylate or 2-benzofuryl tosylate, we failed to apply them in Suzuki coupling reaction in our catalyst system (Scheme 2.10).

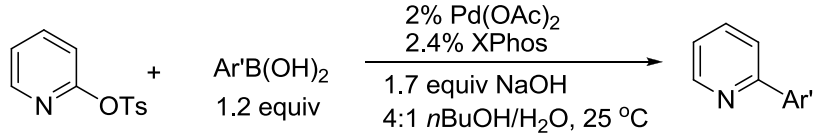


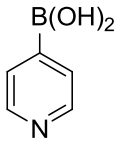
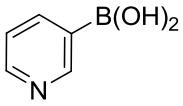
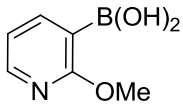
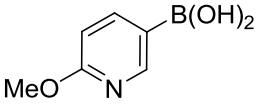
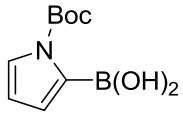
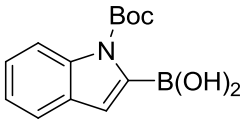
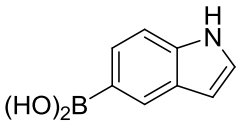
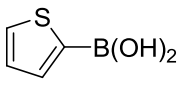
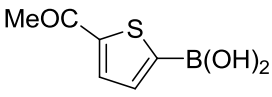
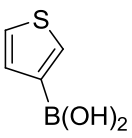

**Scheme 2.10** Unsuccessful coupling of 2-furyl tosylate and 2-benzofuryl tosylate

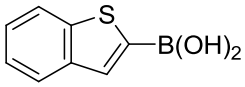
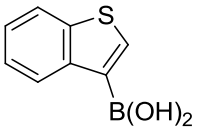
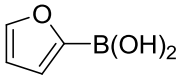
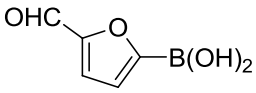
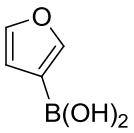
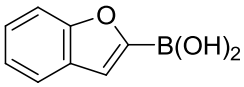
### 2.2.3 Coupling Reactions of Heteroarylboronic acids

We took a typical electron-poor electrophile 2-pyridine tosylate to study the electronic effects on the coupling rates and the scope of arylbronic acids. Results were summarized in Table 2.9. Most heteroarylboronic acids were examined including pyridines (entry 1, 2, 3 and 4), pyrroles (entry 5), thiophenes (8, 9 and 10), benzothiophenes (entry 11 and 12), indoles (entry 6 and 7), furans (entry 13, 14 and 15) and related benzofused heteroarylboronic acids (entry 16). In most cases, completions were reached in excellent yields within minutes to 1 h. At room temperature, 3- and 4-pyridineboronic acids (entry 1 and entry 2) did not give any coupling products with either 2-pyridine tosylate or 2-thiophene tosylate. By increasing the reaction temperature to 80 $^{o}$C, the reactions then proceeded well in high yields. In order to minimize the hydrolysis of both 3- and 4-pyridineboronic acids, $K_3PO_4$ was the base for these two substrates. Electron rich indole substrates and pyrrole substrate can give the coupling products within 5 min in high yields. Since 2- and 3-furan boronic acids (entry 13 and entry 15) are prone to undergo hydrolysis under the catalytic conditions, an excess amount (1.5 equiv) of boronic acids were needed to solve the problems. In the coupling reaction of 2-pyridine tosylate and 5-formylfuranboronic acid (entry 14), longer time was needed to reach a full conversion. Electron-rich thiophene substrates can also give the products in high yields after 5 min to 1 hour.

**Table 2.9** Coupling of various heteroarylboronic acids with 2-pyridine tosylate

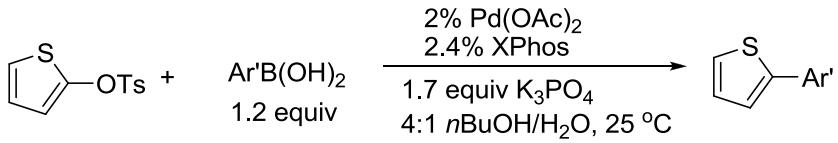


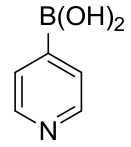
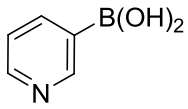
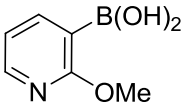
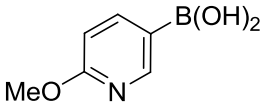
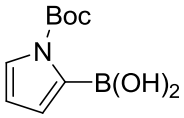
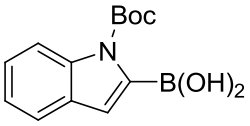
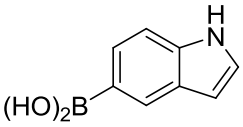
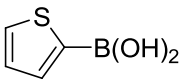
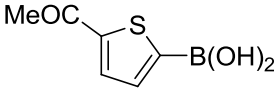
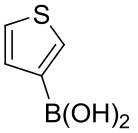

| entry | $Ar'B(OH)_2$ | Yield (%) | Time | Comment |
|---|---|---|---|---|
| 1 |  | 97 | 2 h | $K_3PO_4$ as base<br>80 °C |
| 2 |  | 95 | 15 min | $K_3PO_4$ as base<br>80 °C |
| 3 |  | 92 | 15 min | |
| 4 |  | 94 | 2 h | |
| 5 |  | 93 | 5 min | |
| 6 |  | 92 | 5 min | |
| 7 |  | 91 | 5 min | |
| 8 |  | 95 | 15 min | |
| 9 |  | 95 | 1 h | |
| 10 |  | 91 | 15 min | |

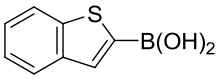
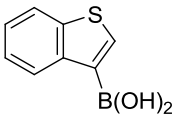
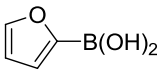
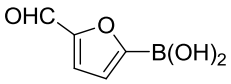
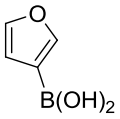
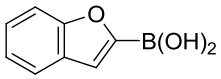
| | | | | |
|---|---|---|---|---|
| 11 |  | 97 | 15 min | |
| 12 |  | 97 | 5 min | |
| 13 |  | 92 | 15 min | 1.5 equiv $ArB(OH)_2$ |
| 14 |  | 90 | 8 h | |
| 15 |  | 90 | 15 min | 1.5 equiv $ArB(OH)_2$ |
| 16 |  | 90 | 1 h | |

We also took 2-thiophene tosylate as a typical electron-rich electrophile to study the scope of different heteroarylboronic acids. Results were summarized in Table 2.10. Different families of heteroaryl bronic acids have been successfully coupled with 2-thiophene tosylate under the catalytic condition. The reactions of 2-thiophene tosylate gave a similar trend of coupling rate with the reactions of 2-pyridine tosylate in terms of electronic effects of different heteroarylboronic acids. Usually, electron donating substituents on heteroarylboronic acids made the molecule more electron-rich resulting in an accelerated coupling reaction rate. In the case of 5-formyl furanboronic acid (entry 14), prolonged reaction time was also required to reach a full conversion of tosylate.

**Table 2.10** Coupling of various heteroarylboronic acids with 2-thiophene tosylate




| entry | $Ar'B(OH)_2$ | Yield (%) | Time | Comment |
|---|---|---|---|---|
| 1 |  | 95 | 18 h | 80 °C |
| 2 |  | 99 | 5 h | 80 °C |
| 3 |  | 93 | 5 min | |
| 4 |  | 95 | 5 h | |
| 5 |  | 93 | 5 min | |
| 6 |  | 99 | 5 min | |
| 7 |  | 93 | 1 h | |
| 8 |  | 90 | 15 min | |
| 9 |  | 90 | 15 min | |
| 10 |  | 92 | 15 min | |

| | | | | |
|---|---|---|---|---|
| 11 |  | 96 | 15 min | |
| 12 |  | 98 | 15 min | |
| 13 |  | 90 | 15 min | 1.5 equiv $ArB(OH)_2$ |
| 14 |  | 98 | 8 h | |
| 15 |  | 92 | 15 min | 1.5 equiv $ArB(OH)_2$ |
| 16 |  | 90 | 15 min | |

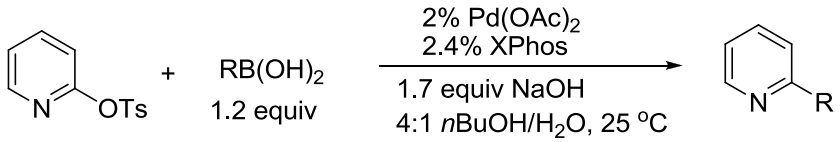
### 2.2.4 Coupling of aryl and alkenyl organoboronic acids

We have compared the relative reactivities of different aryl boronic acids in coupling reactions of 2-pyridine tosylate. Results are summarized in Table 2.11. Most aryl boronic acids reacted smoothly at room temperature with an exception of 2,6-disubstituted phenyl boronic aicds. The hindered arylboronic acids (entry 17 and 18) underwent efficient coupling at elevated reaction temperature (80 $^{o}$C) and most cases reached full conversion within minutes. In coupling reactions of 2-pyridine tosylate with monosubstituted phenyl boronic acids, a clear trend of electronic effect of substitution on the rates was observed. In *para*-substituted phenyl boronic acids, substrates with electron-donating groups (entry 2, 3 and 4) reacted faster in the reactions, all of which finished within minutes. And substrates with electron-withdrawing groups on *para*-position (entry 5, 6, 7, 8 and 9) gave slower couplings, probably due to a slower transmetalation or a slower reductive elimination. A similar trend was observed with arylboronic acids carrying ortho-substituents. Inductive effects from substituents on the *meta* position of phenyl

boronic acid (entry 13, 14 and 15) were rather weak and no obvious influences on the rates of coupling were detected.

We have also examined two alkenyl bornic acids. (*E*)-cinnamyl boronic acid (entry 20) was much less reactive than (*E*)-1-octenyl boronic acid (entry 19). Although the slow coupling of (*E*)-cinnamyl boronic acids can reach full conversion after 20 or 30 hours at room temperature. The reaction proceeded more efficiently at elevated temperature which can finish within minutes at 80 $^{o}$C.

**Table 2.11** Coupling of various arylboronic acids with 2-pyridine tosylate

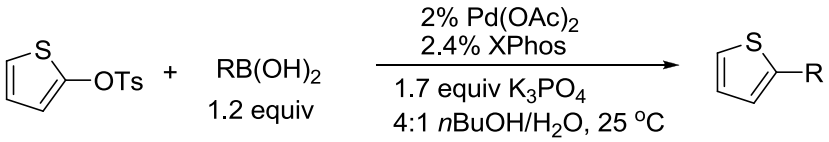



| entry | R | Yield (%) | Time | Comment |
|---|---|---|---|---|
| 1 | Ph | 95 | 15 min | |
| 2 | 4-Me$C_6H_4$ | 98 | 5 min | |
| 3 | 4-MeO$C_6H_4$ | 93 | 5 min | |
| 4 | 4-$NMe_2C_6H_4$ | 90 | 5 min | |
| 5 | 4-$CF_3C_6H_4$ | 95 | 1 h | |
| 6 | 4-COMe$C_6H_4$ | 95 | 4 h | |
| 7 | 4-CHO$C_6H_4$ | 93 | 4 h | |
| 8 | 4-CN$C_6H_4$ | 90 | 4 h | |
| 9 | 4-COOMe$C_6H_4$ | 98 | 5 h | |
| 10 | 2-Me$C_6H_4$ | 96 | 5 min | |
| 11 | 2-MeO$C_6H_4$ | 95 | 5 min | |
| 12 | 2-COMe$C_6H_4$ | 95 | 2 h | 1.5 equiv $ArB(OH)_2$ |

| | | | | |
|---|---|---|---|---|
| 13 | 3,5-DiMeC$_6$H$_3$ | 92 | 15 min | |
| 14 | 3,5-DiMeOC$_6$H$_3$ | 96 | 15 min | |
| 15 | 3,5-DiCF$_3$C$_6$H$_3$ | 90 | 15 min | |
| 16 | 1-Naphthyl | 96 | 5 min | |
| 17 | 2,4,6-TriMeC$_6$H$_2$ | 96 | 5 min | 80 °C |
| 18 | 2,6-DiMeOC$_6$H$_3$ | 98 | 15 min | 1.5 equiv ArB(OH)$_2$<br>80 °C |
| 19 | *(E)*-1-Octenyl | 91 | 1 h | |
| 20 | *(E)-cinnamyl* | 94 | 20 h | 5 min at 80 °C, 93% yield |

We have also compared the relative reactivities of different arylboronic acids in the coupling reactions of 2-thiophene tosylate. A similar trend of coupling rates due to different electronic properties of arylboronic acids was also observed, but not so clear-cut as in the coupling reactions of 2-pyridine tosylate.

**Table 2.12** Coupling of various arylboronic acids with 2-thiophene tosylate




| entry | R | Yield (%) | Time | Comment |
|---|---|---|---|---|
| 1 | Ph | 93 | 5 min | |
| 2 | 4-MeC$_6$H$_4$ | 90 | 5 min | |
| 3 | 4-MeOC$_6$H$_4$ | 90 | 5 min | |
| 4 | 4-NMe$_2$C$_6$H$_4$ | 92 | 15 min | |
| 5 | 4-CF$_3$C$_6$H$_4$ | 99 | 5 min | |
| 6 | 4-COMeC$_6$H$_4$ | 94 | 15 min | |
| 7 | 4-CHOC$_6$H$_4$ | 99 | 5 h | |

| | | | | |
|---|---|---|---|---|
| 8 | 4-$CNC_6H_4$ | 98 | 1 h | |
| 9 | 4-$COOMeC_6H_4$ | 94 | 15 min | |
| 10 | 2-$MeC_6H_4$ | 93 | 15 min | |
| 11 | 2-$MeOC_6H_4$ | 91 | 5 min | |
| 12 | 2-$COMeC_6H_4$ | 95 | 15 min | |
| 13 | 2-$CHOC_6H_4$ | 99 | 5 h | |
| 14 | 3,5-$DiMeC_6H_3$ | 95 | 15 min | |
| 15 | 3,5-$DiMeOC_6H_3$ | 95 | 5 min | |
| 16 | 3,5-$DiCF_3C_6H_3$ | 93 | 5 min | |
| 17 | 1-Naphthyl | 93 | 5 min | |
| 18 | 2,4,6-$TriMeC_6H_2$ | 93 | 15 min | 80 $^oC$ |
| 19 | 2,6-$DiMeOC_6H_3$ | 99 | 8 h | 1.5 equiv $ArB(OH)_2$<br>80 $^oC$ |
| 20 | *(E)*-1-Octenyl | 93 | 5 h | |
| 21 | *(E)-cinnamyl* | 97 | 30 h | 15 min at 80 $^oC$, 97% yield |

## 2.3 Conclusion

A general method for Suzuki coupling of heteroaryl tosylates and aryl or hetero arylbronic acids at room temperature has been developed. The method is generally applicable to major families of heterocyclic substrates, and most reactions can complete within minutes to hours. The condition is compatible with sensitive functional groups such as esters, ketones and aldehydes, and it is also readily adaptable for gram–scale synthesis using Schlenk technique.

## 2.4 Experimental Section

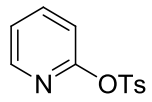
### General information

$^{1}$H NMR spectra were acquired at 400 MHz or 300 MHz and chemical shifts were recorded relative to $SiMe_4$ (δ 0.00) or residual protiated solvents ($CDCl_3$: δ 7.26; $C_6D_6$: δ 7.16; $CD_2Cl_2$: 5.30). Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The number of protons (n) for a given resonance was indicated by *n*H. Coupling constants were reported as a *J* value in Hz. $^{13}$C NMR spectra were obtained at 100 MHz on 400 MHz or 75 MHz on 300 MHz instruments and chemical shifts were recorded relative to solvent resonance ($CDCl_3$: δ 77.25). Proof of purity of new compounds was demonstrated with copies of NMR spectra.

Dry diethyl ether, toluene, hexane and dichloromethane were collected from a solvent purification system containing a column of activated alumina (1 m x 2) under argon. DMSO, DMF and 1,4-dioxane (Aldrich) were used without further purification and were stored in the glove box. Dry THF was freshly distilled from sodium/benzophenone under argon before use. All of anhydrous solvents were stored over activated 4Å molecular sieve beads in Schlenk tubes in an argon-filled glove box. Unless noted otherwise, commercially available chemicals were used without further purification. The GC internal standard, *n*-dodecane was degassed and dried over activated 4 Å molecular sieve beads before use.

Glassware was dried at 120 $^{o}$C for at least 3 hours before use. Flash chromatography was preformed using Merck 40-63D 60 Å silica gel. GC and GC/MS analysis were conducted with Agilent J&W GC column DB-5MS-UI. Chiral HPLC analysis was performed on a Shimadzu LC-20AD instrument using Daicel Chiracel columns at 25℃. Optical rotation was measured using a JASCO P-1030 Polarimeter equipped with a sodium vapor lamp at 589 nm and the concentration of samples was denoted as *c*. X-ray crystallography analysis of single crystals was performed on a Bruker X8 APEX X-Ray diffractometer.

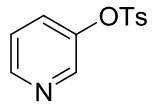
### 2.4.1 Procedure for Preparing Substrates




**2-Pyridinyl *p*-toluenesulfonate [57785-86-1].**[62] In air, 2-hydroxypyridine (5.00 g, 52.0 mmol), *p*-toluenesulfonyl chloride (12.00 g, 63.2 mmol), triethylamine (14.5 mL, 104.0 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (190 mg, 1.56 mmol) were added into a 250 mL round-bottom flask containing 150 mL of analytical-grade $CH_2Cl_2$. After stirring at 25 $^oC$ for 18 h, the reaction mixture was diluted with water (100 mL) and extracted with $Et_2O$ (100 mL x 2). The organic extracts were dried over $MgSO_4$ and then concentrated on a rotary evaporator. The resulting residue was purified by silica gel flash chromatography (ethyl acetate/hexane 1:5 to 1:3) to afford the titled compound (12.56 g, 97%) as white solid.

$^1H$ NMR (400 MHz, $CDCl_3$): δ 8.26 (dd, *J* = 4.8, 1.8 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 2H), 7.79-7.45 (m, 1H), 7.34 (d, *J* = 8.2 Hz, 2H), 7.22 (dd *J* = 7.2, 4.8 Hz, 1H), 7.12 (d, *J* = 8.2 Hz, 1H), 2.45 (s, 3H).

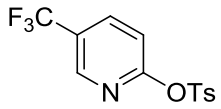
ESI-MS: Calcd for $C_{12}H_{12}NO_3S$ $(M+H)^+$: 250.1. Found: 250.0.




**3-Pyridinyl *p*-toluenesulfonate [67284-17-7].**[63] In air, 3-hydroxypyridine (5.70 g, 60.0 mmol), *p*-toluenesulfonyl chloride (13.67 g, 72.0 mmol), triethylamine (16.7 mL, 120.0 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (220 mg, 1.80 mmol) were added into a 250 mL round-bottom flask containing 150 mL of analytical-grade $CH_2Cl_2$. After stirring at 25 $^oC$ for 18 h, the reaction mixture was diluted with water (100 mL) and extracted with $Et_2O$ (100 mL x 2). The organic extracts were dried over $MgSO_4$ and then concentrated on a rotary evaporator. The resulting residue was purified by silica gel flash chromatography (ethyl acetate/hexane 1:5 to 1:3) to afford the titled compound (14.40 g, 95%) as white solid.

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.50 (dd, *J* = 4.8, 1.3 Hz, 1H), 8.15 (d, *J* = 2.8 Hz, 1H), 7.71 (d, *J* = 8.7 Hz, 2H), 7.48 (ddd, *J* = 8.4, 2.8, 1.3 Hz, 1H), 7.34 (d, *J* = 8.7 Hz, 2H), 7.31-7.28 (m, 1H), 2.46 (s, 3H).

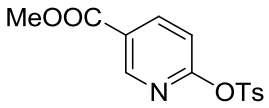
ESI-MS: Calcd for $C_{12}H_{12}NO_3S$ $(M+H)^+$: 250.1. Found: 250.1.




**5-(Trifluoromethyl)-2-pyridyl *p*-toluenesulfonate [321970-36-9].**[62] The compound was prepared according to a reported procedure.(1) In air, 2-hydroxy-5-(trifluoromethyl)pyridine (1.63 g, 10.0 mmol), *p*-toluenesulfonyl chloride (2.28 g, 12.0 mmol), triethylamine (2.5 mL, 18.0 mmol) were added to a 100 mL round-bottom flask containing 50 mL of analytic-grade $CH_2Cl_2$. After stirring at 25 $^oC$ for 1 h, $Et_2O$ (analytical grade, 50 mL) was added and the organic phase was washed with water (75 mL x 2) and brine (75 mL), and then was dried over $MgSO_4$. After concentration on a rotary evaporator, the resulting residue was purified by silica gel flash chromatography (ethyl acetate/hexane 1:5 to 1:3) to afford the titled compound (2.47 g, 78%) as white solid.

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.54 (d, *J* = 2.4 Hz, 1H), 8.0 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 1H), 2.47 (s, 3H).

ESI-MS: Calcd for $C_{13}H_{11}F_3NO_3S$ $(M+H)^+$: 318.0. Found: 317.8.



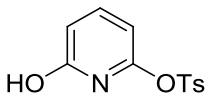

**Methyl 6-(*p*-toluenesulfoxy)nicotinate [325489-33-6].**[62] In air, 6-hydroxynicotinic acid (3.89 g, 28.0 mmol) was added to a 100 mL round-bottom flask containing 20 mL of analytic-grade MeOH, followed by concentrated sulfuric acid (3.6 ml). The mixture was refluxed for 20 hours. At the end of the reaction, the mixture was quenched with water (50 mL) and extracted with ethyl acetate (75 mL × 3). The combined organic extracts were washed with water (75 mL x 3) and

then dried over $Na_2SO_4$. Concentration on a rotary evaporator gave crude methyl 6-hydroxynicotinate as white solid.

In air, crude methyl 6-hydroxynicotinate (4.30 g), *p*-toluenesulfonyl chloride (63.8 g, 33.6 mmol), triethylamine (7.8 ml, 56.0 mmol) and 4-*N*,*N* dimethylamino-pyridine (68 mg, 0.56 mmol) were added to a 250 ml round-bottom flask containing 75 mL of analytic-grade $CH_2Cl_2$. The reaction mixture was refluxed for 18 h. At the end of the reaction, $Et_2O$ (analytical grade, 100 mL) was added and the organic phase was washed with water (100 mL x 3) and brine (100 mL), and then it was dried over $MgSO_4$. After concentration on a rotary evaporator, the resulting residue was purified by silica gel flash chromatography (ethyl acetate/hexane 1:5 to 1:3) to afford the titled compound (6.20 g, 72% over 2 steps) as colorless crystal.

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.87 (d, *J* = 2.4 Hz, 1H), 8.35 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 8.5 Hz, 1H), 3.94 (s, 3H), 2.46 (s, 3H).

ESI-MS: Calcd for $C_{14}H_{14}NO_5S$ $(M+H)^+$: 308.1. Found: 307.9.

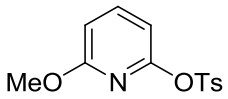



**6-Hydroxy-2-pyridyl *p*-tolylsulfonate.** In air, 2,6-dihydroxypyridine hydrochloride (971 mg, 6.6 mmol), *p*-toluenesulfonyl chloride (1.38 g, 7.2 mmol) and potassium carbonate (1.91 g, 13.8 mmol) were added to a 50 mL round-bottom flask containing 20 mL of analytical-grade acetone. The reaction mixture was stirred at 25 $^o$C for 18 h. At the end of the reaction, the crude mixture was diluted with ethyl acetate (75 mL x 3) and then washed with water (75 mL x 3). The organic layer was dried over $Na_2SO_4$ and concentrated on a rotary evaporator. Crystallization from $CH_2Cl_2$/hexane afforded the product as white solid (1.19 g, 68%).

$^1$H NMR (400 MHz, DMSO-$d_6$): δ 11.31 (s, 1H), 7.85 (d, *J* = 8.3 Hz, 2H), 7.66 (dd, *J* = 8.0, 7.7 Hz, 1H), 7.48 (d, *J* = 8.3 Hz, 2H), 6.61 (d, *J* = 8.0 Hz, 1H), 6.51 (d, *J* = 7.7 Hz, 1H), 2.42 (s, 3H).

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 163.0, 154.1, 145.5, 142.9, 132.8, 130.1, 128.2, 108.5, 105.7, 21.1.

ESI-MS: Calcd for $C_{12}H_{12}NO_4S$ $(M+H)^+$: 266.0. Found: 266.0.

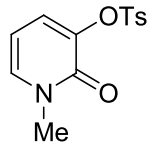



**6-Methoxy-2-pyridyl *p*-toluenesulfonate.** In air, 6-hydroxy-2-pyridyl *p*-tolylsulfonate (1.75 g, 6.60 mmol) and $K_2CO_3$ (1.82 g, 13.2 mmol) were added to a 50 ml sealed tube containing 15 mL of analytical-grade acetone. The reaction mixture was stirred 25 $^o$C for 1 h and then was treated with MeI (4.1 mL, 66.0 mmol). The mixture was refluxed for 24 h. At the end of the reaction (monitored by TLC), $K_2CO_3$ was filtered and the filtrate was concentrated on a rotary evaporator. The resulting residue was purified on silica gel flash chromatography (ethyl acetate/hexane 1:7) to afford the titled compound (1.71 g, 93%) as white solid.

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.4 Hz, 2H), 7.60 (pseudotriplet, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 6.67 (d, *J* = 7.9 Hz, 1H), 6.62 (d, *J* = 7.9 Hz, 1H), 3.62 (s, 3H), 2.45 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 163.2, 155.1, 145.2, 141.8, 134.2, 129.6, 128.6, 109.4, 107.0, 53.8, 21.7.

ESI-MS: Calcd for $C_{13}H_{14}NO_4S$ $(M+H)^+$: 280.1. Found: 280.1.




**1-Methyl-2-oxo-1,2-dihydropyridin-3-yl *p*-toluenesulfonate.** In air, 2,3-dihydroxy -pyridine (1.11 g, 10.0 mmol), *p*-toluenesulfonyl chloride (2.27 g, 12.0 mmol), triethylamine (2.78 ml, 20.0 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (37 mg, 0.30 mmol) were added to a 100 ml round-bottom flask containing 25 mL of analytical -grade $CH_2Cl_2$. The reaction mixture was stirred at 25 $^o$C for 24 h.

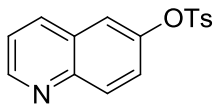
The crude mixture was obtained in 60% crude yield and submitted to the next step without further purification.

In air, crude 1-methyl-2-oxo-1,2-dihydropyridin-3-yl *p*-toluenesulfonate (10.0 mmol), $K_2CO_3$ (2.76 g, 20.0 mmol) were added to a 100 mL sealed tube containing 20 mL of analytical-grade acetone. The mixture was stirred at 25 $^oC$ for 1 h and then MeI (6.0 mL, 100 mmol) was added, followed by reflux for 24 h. At the end of the reaction (monitored by TLC), $K_2CO_3$ was filtered and the filtrate was concentrated on a rotary evaporator. The resulting residue was purified on silica gel flash chromatography (ethyl acetate/hexane 1:2 to 2:3) to afford the titled compound (1.17 g, 40% over 2 steps) as white solid.

$^1H$ NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.0 Hz, 2H), 7.39 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.22 (dd, *J* = 7.2, 2.0 Hz, 1H), 6.12 (pseudotriplet, *J* = 7.2 Hz, 1H), 3.52 (s, 3H), 2.45 (s, 3H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ 157.7, 145.5, 139.1, 137.4, 133.0, 131.3, 130.0, 128.5, 103.7, 37.8, 21.7.

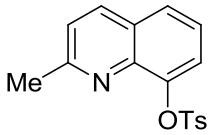
ESI-MS: Calcd for $C_{13}H_{14}NO_4S$ $(M+H)^+$: 280.1. Found: 280.1.




**6-Quinolinyl *p*-toluenesulfonate [426265-40-9].** In air, 6-quinolinol (2.00 g, 13.7 mmol) and *p*-toluenesulfonyl chloride (3.14 g, 16.5 mmol) were added to a 100 mL round-bottom flask containing pyridine (analytical grade, 20 mL) at 25 $^oC$. The reaction mixture was then allowed to stir in a 45 ℃ oil bath for 24 h. At the end of the reaction, it was cooled to room temperature, diluted with $CH_2Cl_2$ (analytical grade, 50 mL), and washed with 100 mL of 1N HCl. The organic layer was dried over anhydrous $MgSO_4$. After concentration on a rotary evaporator, the resulting residue was purified by silica gel flash chromatography (ethyl acetate /hexane 1:10 to 1:5) to afford the titled compound (3.20 g, 78%) as white solid.

$^1H$ NMR (400 MHz, $CDCl_3$): δ 8.93 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.10 (d, *J* = 8.2, 1.8 Hz, 1H), 8.01 (d, *J* = 9.2 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 2.2 Hz, 1H), 7.43 (dd, *J* = 8.2, 4.1 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.27-7.24 (m, 2H), 2.45 (s, 3H).

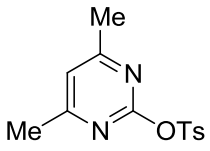
ESI-MS: Calcd for $C_{16}H_{14}NO_3S$ $(M+H)^+$: 300.1. Found: 300.1.




**2-Methyl-8-quinolinyl *p*-toluenesulfonate [93316-56-4].** In air, 2-methyl -8-quinolinol (1.59 g, 10.0 mmol), *p*-toluenesulfonyl chloride (2.28 g, 12.0 mmol), triethylamine (2.8 mL, 20.0 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (36.6 mg, 0.3 mmol) were added into a 250 mL round-bottom flask containing 50 mL of analytical-grade $CH_2Cl_2$. After stirring at 25 $^oC$ for 20 h, the reaction mixture was diluted with water (100 mL) and extracted with $Et_2O$ (50 mL x 2). The organic extracts were dried over $MgSO_4$ and concentrated on a rotary evaporator. The resulting residue was purified by silica gel flash chromatography (ethyl acetate /hexane 1:3 to 1:1) to afford the titled compound (2.59 g, 83%) as white solid.

$^1H$ NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.68 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.64 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.44 (dd, *J* = 8.2, 7.7 Hz, 1H), 7.22 (m, 3H), 2.54 (s, 3H), 2.40 (s, 3H).

ESI-MS: Calcd for $C_{17}H_{16}NO_3S$ $(M+H)^+$: 314.1. Found: 314.0.

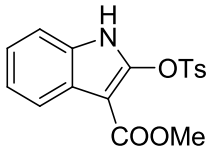



**2,6-Dimethyl-4-pyrimidinyl *p*-toluenesulfonate [40227-86-9].**[62] In air, 2,6-dimethyl-4-pyrimidinol (4.96 g, 40.0 mmol), *p*-toluenesulfonyl chloride (9.12 g, 48.0 mmol), triethylamine (11.1 mL, 80.0 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (74 mg, 0.60 mmol) were added to a 100 mL round-bottom flask containing 50 mL of analytical-grade $CH_2Cl_2$. After stirring at 25 $^oC$ for 3 h, $Et_2O$ (analytical grade, 50 mL) was added and the organic phase was washed with water (75 mL x 2) and brine (75 mL), and then was dried over $MgSO_4$. After concentration on a rotary evaporator, the resulting residue was

purified by silica gel flash chromatography (ethyl acetate /hexane 1:5 to 1:3) to afford the titled compound (9.89 g, 89%) as colorless crystal.

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.4 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 6.77 (s, 1H), 2.57 (s, 3H), 2.49 (s, 3H), 2.47 (s, 3H).

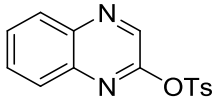
ESI-MS: Calcd for $C_{13}H_{15}N_2O_3S$ $(M+H)^+$: 279.1. Found: 278.9.




**3-Methoxycarbonyl-2-(*p*-toluenesulfoxy)indole [95-751-37-8].**[64] Under argon, dimethyl carbonate (540 mg, 6.0 mmol) was added to a stirring suspension of 60% suspension of NaH in mineral oil (80 mg, 2.0 mmol) in dry DMA (2 mL) at room temperature. Then, a solution of oxindole (266 mg, 2.0 mol) in DMA (2 mL) was added dropwise at 0 ℃ using an ice bath. After stirring for 1 h at room temperature, the reaction mixture was warmed to 70 ℃ and further stirred for 5 h at the same temperature. The reaction mixture was cooled to 50 ℃, and TsCl (416 mg, 2.2 mmol) was added portionwisely at the same temperature, stirred at room temperature. After reaction completed (mornitored by TLC), 10 mL water was added at 0 $^o$C, and do extractive workup with diethyl ether (10 mL x 3). The organic layer was dried over $Mg_2SO_4$. After concentration on a rotary evaporator, the resulting residue was purified by silica gel flash chromatography (ethyl acetate /hexane 1:6 to 1:4) to afford the product (523 mg, 76% yield) as white solid.

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.95 (br s, 1H), 8.06 (d, *J* = 7.6 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.38-7.36 (m, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.27-7.23 (m, 2H), 3.63 (s, 3H), 2.42 (s, 3H).

ESI-MS: Calcd for $C_{15}H_{16}NO_5S$ $(M^+)$: 346.0. Found: 345.9.

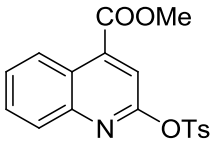



**2-Quinoxalinyl *p*-toluenesulfonate [418764-67-7].**[61] In air, 2-quinoxalinol (2.00 g, 13.7 mmol) and *p*-toluenesulfonyl chloride (3.12 g, 16.4 mmol) were added to a

100 mL round-bottom flask containing 10 mL of analytic-grade pyridine at 25 ℃. The reaction mixture was then stirred in a 45 ℃ oil bath for 24 h. At the end of the reaction, it was cooled to room temperature, diluted with 50 mL of $CH_2Cl_2$, and washed with 100 mL of 1.0 N HCl. The organic layer was separated and dried over $Na_2SO_4$. After concentration on a rotary evaporator, the resulting residue was purified by silica gel flash chromatography (ethyl acetate/hexane 1:5 to 1:3) to afford the titled compound (1.85 g, 45 %) as white solid.

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.66 (s, 1H), 8.12-8.10 (m, 1H), 8.03 (d, *J* = 8.4 Hz, 2H), 7.93-7.90 (m, 1H), 7.79-7.74 (m, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 2.47 (s, 3H).

ESI-MS: Calcd for $C_{15}H_{13}N_2O_3S$ $(M+H)^+$: 301.1. Found: 300.9.

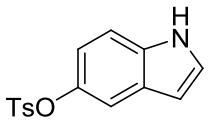



**Methyl 2-(tosyloxy)quinoline-4-carboxylate [1174281-19-6].**[62] In air, 2-hydroxyquinoline- 4-carboxylic acid (2.00 g, 10.6 mmol) was added to a 100 mL round-bottom flask containing 20 mL of analytic-grade MeOH, followed by concentrated sulfuric acid (1.5 mL). The mixture was refluxed for 20 hours. At the end of the reaction, the reaction mixture was extracted with ethyl acetate (40 mL x 3). The combined organic extracts were washed with water (40 mL x 3) and then dried over $Na_2SO_4$. After concentration on a rotary evaporator, the crude product, methyl 3-hydroxy-1- naphthoate was obtained as colorless solid in 85% crude yield (2.15 g), which was directly used in the next step without further purification.

In air, crude methyl 2-hydroxyquinoline-4-carboxylate (2.15 g) and potassium carbonate (4.39 g, 31.8 mmol) were added to a 100 mL round-bottom flask containing 100 mL of analytical-grade acetone. *p*-Toluenesulfonyl chloride (2.00 g, 10.6 mmol) was then added and the mixture was stirred at 25 $^o$C overnight. After concentration on a rotary evaporator, the resulting residue was purified by silica gel flash chromatography using $CH_2Cl_2$ as eluent to afford the titled compound (3.11 g, 82% over 2 steps) as white solid.

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.74 (d, *J* = 8.5 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 2H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.77-7.72 (m, 2H), 7.65-7.61 (m, 1H), 7.37 (d, *J* = 8.4 Hz, 2H), 4.04 (s, 3H), 2.46 (s, 3H).

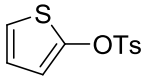
ESI-MS: Calcd for $C_{18}H_{16}NO_5S$ $(M+H)^+$: 358.1. Found: 357.9.




**5-Indolyl *p*-toluenesulfonate [144150-77-6].** In air, 5-hydroxyindole (500 mg, 3.76 mmol) and *p*-toluenesulfonyl chloride (857 mg, 4.51 mmol) was added to a 100 mL round-bottom flask containing 10 mL of analytic-grade pyridine at 25 $^oC$. The reaction mixture was then stirred in a 45 ℃ oil bath for 24 h. At the end of the reaction, it was cooled to room temperature, diluted with 50 mL of $CH_2Cl_2$. The organic layer was washed with 40 mL of 1N HCl and then dried over $Na_2SO_4$. After concentration on a rotary evaporator, the resulting residue was purified by silica gel flash chromatography (ethyl acetate/hexane 1:5 to 1:3) to afford the titled compound (700 mg, 65%) as white solid.

$^1H$ NMR (400 MHz, $CDCl_3$): δ 8.19 (br s, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.25-7.23 (m, 3H), 6.81 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.50-6.48 (m, 1H), 2.44 (s, 3H).

ESI-MS: Calcd for $C_{15}H_{14}NO_3S$ $(M+H)^+$: 288.1. Found: 287.9.



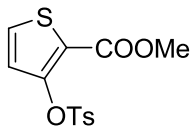

**2-Thienyl *p*-toluenesulfonate.**[65] Under argon, 5*H*-thiophen-2-one (1.56 g, 15.6 mmol) was added to a 25 mL dried Schlenk tube containing 5 mL of dry $CH_2Cl_2$ in an ice/water bath. To the stirred solution was added triethylamine (3.4 mL, 23.4 mmol) dropwise over 15 min. Then 4-*N*,*N*-dimethylamino- pyridine (57 mg, 0.47 mmol) was added to the stirred mixture, followed by *p*-toluenesulfonic anhydride (2.20 g, 11.5 mmol) in about 12 portions over 30 min. The ice bath was removed and the reaction mixture was allowed to warm up to 25 $^oC$ and was stirred at for 2 h. At the end of the reaction, 50 mL of water and 50 mL of diethyl ether were added, and the organic phase was separated and then dried over $Mg_2SO_4$. After concentration on a rotary evaporator, the resulting residue was purified by silica

gel flash chromatography (ethyl acetate /hexane 1:10) to afford the titled compound (3.58 g, 91%) as white solid.

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 6.87 (dd, *J* = 5.8, 1.5 Hz, 1H), 6.73 (dd, *J* = 5.8, 3.8 Hz, 1H), 6.54 (dd, *J* = 3.8, 1.5 Hz, 1H), 2.49 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 150.6, 146.1, 130.5, 129.8, 128.6, 124.2, 120.1, 117.7, 21.5.

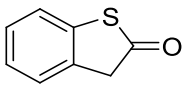
ESI-MS: Calcd for $C_{22}H_{20}O_6S_4$ ($2M^+$): 508.0. Found: 507.5.




**2-Methoxycarbonyl-3-(*p*-toluenesulfonoxy)thiophene [181226-89-1].**[61] In air, methyl 3-hydroxy- thiophene-2-carboxylate (1.58 g, 10.0 mmol) and *p*-toluenesulfonyl chloride (2.28 g, 12.0 mmol) were added to a 250 mL round-bottom flask containing 50 mL of analytical-grade $CH_2Cl_2$ in an ice/water bath. To the stirred solution was added triethylamine (2.1 mL, 15.0 mmol) dropwise over 15 min. The ice bath was then removed and the reaction mixture was allowed to warm up to 25 $^o$C and then was stirred for 20 h. At the end of the reaction, 50 mL of water and 50 mL of $CH_2Cl_2$ were added, and the organic phase was separated and then dried over $Na_2SO_4$. After concentration on a rotary evaporator, the crude product was purified by silica gel flash chromatography (ethyl acetate /hexane 1:5 to 1:3) to afford the titled compound (2.40 g, 77%) as light yellow solid.

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 5.5 Hz, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 5.5 Hz, 1H), 3.71 (s, 3H), 2.45 (s, 3H).

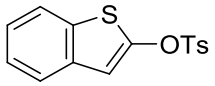
ESI-MS: Calcd for $C_{13}H_{13}O_5S_2$ $(M+H)^+$: 313.0. Found: 312.7.




**Benzothiophen-2(3*H*)-one [496-31-1].**[66] Under argon, benzothiophene (3.35 g, 25.0 mmol) was added to 250 mL round-bottom flask containing 25 mL of dry diethyl ether in an ice/water bath. Then a solution of 2 M *n*-butyllithium in cyclohexane (14 mL, 27.5 mmol) was added over 5 min. The resulting yellow

solution was stirred at room temperature for 1 h and trimethylborate (1.90 mL, 17.0 mmol) in 10 mL of dry diethyl ether was added dropwise at 0 $^{o}$C over 10 min. After the reaction mixture was stirred for another hour, 3N HCl solution was added until pH value reached to 5~6. After stirring for another hour, aqueous NaOH solution was added to adjust pH value to 8. Then a 30% hydrogen peroxide solution (10 mL) was added at 0 $^{o}$C, the resulting reaction mixture was stirred at 25 $^{o}$C overnight. After extraction using diethyl ether (75 mL x 3), the crude product was purified by silica gel flash chromatography (ethyl acetate /hexane 1:5) to afford the titled compound (2.81 g, 75% yield) as yellow solid.

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.36-7.21 (m, 4H), 3.97 (s, 2H).

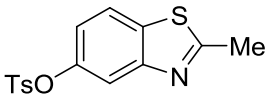



**2-Benzothienyl *p*-toluenesulfonate.** Under argon, benzothiophen-2(3*H*)-one (750 mg, 5.0 mmol) was added to a 50 mL dried round bottom flask containing 10 mL of dry $CH_2Cl_2$ at 0 ℃ . To the vigorously stirred solution was added dry triethylamine (1.1 mL, 7.5 mmol) dropwise over a period of 5 min. Then 4-*N*,*N*-dimethylamino- pyridine (18.3 mg, 0.15 mmol) was added to the stirred mixture, followed by *p*-toluenesulfonic anhydride (1.96 g, 6.0 mmol) in 3 portions over 30 minutes. The ice bath was then removed and the reaction mixture was allowed to warm up to room temperature and kept stirring for 2 h. At the end of the reaction, 50 mL of water and 50 mL of diethyl ether were added to the reaction, and the organic phase was separated and then dried over $Mg_2SO_4$. After concentration on a rotary evaporator, the resulting residue was purified by silica gel flash chromatography (ethyl acetate /hexane 1:15) to afford the titled compound (1.44 g, 95% yield) as white solid.

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, $J$ = 8.4 Hz, 2H), 7.63-7.61 (m, 2H), 7.34-7.28 (m, 4H), 6.85 (s, 1H), 2.45 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 150.5, 146.4, 136.1, 135.1, 131.0, 130.0, 128.8, 125.0, 124.9, 124.0, 122.2, 114.1, 21.8.

ESI-MS: Calcd for $C_{15}H_{13}O_3S_2$ $(M+H)^+$: 305.0. Found: 304.7.




**2-Methyl-5-benzothiazolyl *p*-toluenesulfonate [611235-48-4]**.[47] In air, 5-hydroxy-2-methyl- benzothiazole (1.00 g, 6.06 mmol) and *p*-toluenesulfonyl chloride (1.38 g, 7.27 mmol) were added to a 100 mL round-bottom flask containing 10 mL of analytical-grade pyridine at 25 $^{o}$C. The reaction mixture was then stirred in a 45 ℃ oil bath for 24 h. At the end of the reaction, it was cooled to room temperature and then diluted with 50 mL of $CH_2Cl_2$. The organic layer was washed with 30 mL of 1N HCl and then dried over $Na_2SO_4$. After concentration on a rotary evaporator, the resulting residue was purified by silica gel flash chromatography (ethyl acetate /hexane 1:5 to 1:3) to afford the titled compound (1.84 g, 95%) as white solid.

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.75-7.71 (m, 3H), 7.44 (d, *J* = 2.3 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.13 (dd, *J* = 8.8, 2.3 Hz, 1H), 2.81 (s, 3H), 2.44 (s, 3H).

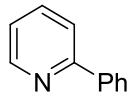
ESI-MS: Calcd for $C_{15}H_{14}NO_3S_2$ $(M+H)^+$: 320.0. Found: 320.0

### 2.4.2 Procedure for Room Temperature Suzuki Coupling Reactions

General Procedure for Suzuki Coupling of Heteroaryl Tosylate with Phenylboronic Acids

In an argon-filled glove box, to a 25 mL Schlenk tube was added sequentially $Pd(OAc)_2$ (0.010 mmol, 2.4 mg), XPhos (0.012 mmol, 5.7 mg), heteroaryl tosylate (0.50 mmol), phenyl boronic acid (0.60 mmol, 73 mg), 40 μL of *n*-dodecane (GC internal standard) and *n*-butanol (2.8 mL). After stirring at 25 $^{o}$C for 15 minutes, a solution of NaOH (0.85 mmol, 34 mg) in 0.68 mL of degassed $H_2O$ was added to initiate Suzuki reaction. The Schlenk tube was capped tightly and the reaction mixture was stirred vigorously at 25 $^{o}$C until all the heteroaryl *p*-tosylate was consumed (monitored by GC or $^1$H NMR spectropscopy). At the end of the reaction, the reaction mixture was passed through a short plug of silica gel (~3 cm long) with ethyl acetate washings (5 mL) and the filtrate was then concentrated on a rotary evaporator. The resulting residue was purified by silica gel flash chromatography using a mixed solvent of hexane and acetyl acetate as eluent to

provide the coupling product. All the Suzuki reactions were conducted according to the general procedure unless noted otherwise. The 15 min prestirring helped to improve reproducibility of the reaction kinetics. Without the prestirring, the coupling was still very fast.

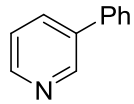



**2-Phenylpyridine [1008-89-5].** The titled compound was prepared according to the general procedure with 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) and phenyl boronic acid (73 mg, 0.60 mmol) at 25 $^{o}$C for 15 min. The conversion of heteroaryl tosylate was determined by GC: 5 min, 85%; 15 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:15 to 1:10) as eluent, the titled compound was isolated as colorless oil (74 mg, 95% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.70 (d, *J* = 4.0 Hz, 1H), 8.00-7.98 (m, 2H), 7.75-7.71 (m, 2H), 7.50-7.47 (m, 2H), 7.44-7.40 (m, 1H), 7.25-7.21 (m, 1H).

ESI-MS: Calcd for $C_{11}H_{10}N$ $(M+H)^{+}$: 156.1. Found: 156.4.

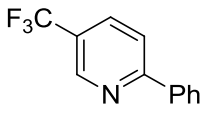



**3-Phenylpyridine [1008-88-4].** The titled compound was prepared according to the general procedure with 3-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) and phenyl boronic acid (73 mg, 0.60 mmol) at 25 $^{o}$C for 20 h. The conversion of heteroaryl tosylate was determined by GC: 5 min, 31%; 15 min, 48%; 1 h, 56%; 5 h, 70%; 20 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:20 to 1:10) as eluent, the titled compound was isolated as colorless oil (74 mg, 95% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.86 (d, *J* = 2.0 Hz, 1H), 8.60 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.89 (ddd, *J* = 8.0, 2.0, 1.5 Hz, 1H), 7.60-7.57 (m, 2H), 7.51-7.47 (m, 2H), 7.43-7.35 (m, 2H).

ESI-MS: Calcd for $C_{11}H_{10}N$ $(M+H)^+$: 156.1. Found: 156.4.

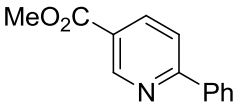



**2-Phenyl-5-(trifluoromethyl)pyridine [188527-56-2]**. The titled compound was prepared according to the general procedure with 5-trifluoromethyl-2-pyridyl *p*-toluenesulfonate (159 mg, 0.50 mmol) and phenyl boronic acid (73 mg, 0.60 mmol) at 25 $^oC$ for 5 min. The conversion of heteroaryl tosylate was determined by GC: 5 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:20 to 1:10) as eluent, the titled compound was isolated as white solid (106 mg, 95% yield).

$^1H$ NMR (400 MHz, $CDCl_3$): δ 8.95 (br s, 1H), 8.05-8.02 (m, 2H), 7.99 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.54-7.48 (m, 3H).

ESI-MS: Calcd for $C_{12}H_9F_3N$ $(M+H)^+$: 224.1. Found: 224.4.

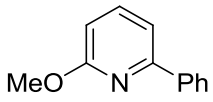



**Methyl 6-phenylnicotinate [4634-13-3].** The titled compound was prepared according to the general procedure with methyl 6-(*p*-toluensulfoxy)nicotinate (154 mg, 0.50 mmol) and phenyl boronic acid (92 mg, 0.75 mmol) at 25 $^oC$ for 5 min. The conversion of heteroaryl tosylate was determined by GC: 5 min, 97%.

After purification by flash chromatography using ethyl acetate/hexane (1:15 to 1:10) as eluent, the titled compound was isolated as white solid (96 mg, 90% yield).

$^1H$ NMR (400 MHz, $CDCl_3$): δ 9.28 (d, *J* = 2.2 Hz, 1H), 8.35 (dd, *J* = 8.3, 2.2 Hz, 1H), 8.08-8.05 (m, 2H), 7.82 (d, *J* = 8.3 Hz, 1H), 7.53-7.47 (m, 3H), 3.97 (s, 3H).

ESI-MS: Calcd for $C_{13}H_{12}NO_2$ $(M+H)^+$: 214.1. Found: 214.4.

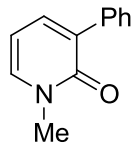



**2-Methoxy-6-phenylpyridine [35070-08-7].** The titled compound was prepared according to the general procedure with 6-methoxy-2-pyridyl *p*-toluenesulfonate (140 mg, 0.50 mmol) and phenyl boronic acid (73 mg, 0.60 mmol) at 25 $^{o}$C for 15 min. The conversion of heteroaryl tosylate was determined by GC: 5 min, 90%; 15 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:30 to 1:20) as eluent, the titled compound was isolated as colorless oil (85 mg, 92% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.06-8.04 (m, 2H), 7.62 (pseudotriplet, *J* = 8.2 Hz, 1H), 7.47-7.43 (m, 2H), 7.41-7.38 (m, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 6.69 (d, *J* = 8.2 Hz, 1H), 4.04 (s, 3H).

ESI-MS: Calcd for $C_{12}H_{12}NO$ $(M+H)^{+}$: 186.1. Found: 186.2.

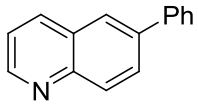



**1-Methyl-3-phenylpyridin-2(1*H*)-one [13180-21-7].** The titled compound was prepared according to the general procedure with 1-methyl-2-oxo-1,2-dihydropyridin-3-yl *p*-toluenesulfonate (140 mg, 0.50 mmol) and phenylboronic acid (73 mg, 0.60 mmol) at 25 $^{o}$C for 1 h. 1,2,3,4,5,6,7,8,9,10,11,12-dodecahydrotriphenylene (30 mg, 0.125 mmol) was used as $^{1}$H NMR internal standard and $K_3PO_4$ (180 mg, 0.85 mmol) was used as base instead of NaOH. The conversion of heteroaryl tosylate was determined by $^{1}$H NMR spectroscopy: 5 min, 47%; 15 min, 49%; 1 h, 100%.

After purification by flash chromatography using dicholoromethane/ethyl acetate/hexane (0:1:2 to 1:1:2) as eluent, the titled compound was isolated as yellow solid (88 mg, 95% yield).

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.70-7.68 (m, 2H), 7.49 (dd, *J* = 7.0, 3.0 Hz, 1H), 7.42-7.37 (m, 2H), 7.34-7.30 (m, 2H), 6.25 (pseudotriplet, *J* = 7.0 Hz, 1H), 3.62 (s, 3H).

ESI-MS: Calcd for $C_{12}H_{12}NO$ $(M+H)^+$: 186.1. Found: 186.2.

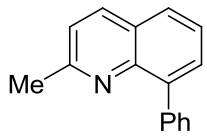



**6-Phenylquinoline [612-95-3].** The titled compound was prepared according to the general procedure with 6-quinolinyl *p*-toluenesulfonate (150 mg, 0.50 mmol) and phenyl boronic acid (73 mg, 0.60 mmol) at 25 $^o$C for 5 h. The conversion of heteroaryl tosylate was determined by GC: 1 h, 11%; 5 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:10 to 1:5) as eluent, the titled compound was isolated as white solid (97 mg, 95% yield).

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.92 (d, *J* = 3.2 Hz, 1H), 8.23-8.17 (m, 2H), 8.01-7.98 (m, 2H), 7.73 (d, *J* = 7.8 Hz, 2H), 7.50 (pseudotriplet, *J* = 7.5 Hz, 2H), 7.42-7.38 (m, 2H).

ESI-MS: Calcd for $C_{15}H_{12}N$ $(M+H)^+$: 206.1. Found: 206.4.



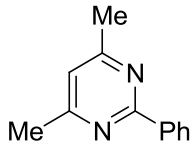

**2-Methyl-8-phenylquinoline.** The titled compound was prepared according to the general procedure with 2-methyl-8-quinolinyl *p*-toluenesulfonate (157 mg, 0.50 mmol) and phenyl boronic acid (73 mg, 0.60 mmol) at 25 $^o$C for 3 h. The conversion of heteroaryl tosylate was determined by GC: 5 min, 14%; 15 min, 49%; 1 h, 69%; 2 h, 92%; 3 h 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:15 to 1:10) as eluent, the titled compound was isolated as pale yellow oil (103 mg, 94% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.4 Hz, 1H), 7.80-7.71 (m, 4H), 7.54-7.46 (m, 3H), 7.41-7.38 (m, 1H), 7.29 (d, *J* = 8.4 Hz, 1H), 2.69 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 158.9, 145.6, 140.1, 139.8, 136.4, 131.2, 130.5, 127.9, 127.4, 127.3, 127.1, 125.6, 122.0, 25.9.

ESI-MS: Calcd for $C_{16}H_{14}N$ $(M+H)^+$: 220.1. Found: 220.4.

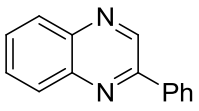



**2,4-Dimethyl-6-phenylpyrimidine [64571-30-8].** The titled compound was prepared according to the general procedure with 2,6-dimethyl-4-pyrimidinyl *p*-toluenesulfonate (139 mg, 0.50 mmol) and phenyl boronic acid (73 mg, 0.60 mmol) at 25 $^{o}$C for 1 h. The conversion of heteroaryl tosylate was determined by GC: 5 min, 23%; 15 min, 76%; 1 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:30 to 1:25) as eluent, the titled compound was isolated as colorless oil (88 mg, 96% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.06-8.04 (m, 2H), 7.50-7.48 (m, 3H), 7.38 (s, 1H), 2.77 (s, 3H), 2.56 (s, 3H).

ESI-MS: Calcd for $C_{12}H_{13}N_2$ $(M+H)^+$: 185.1. Found: 185.3.

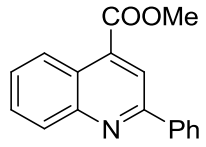



**2-Phenylquinoxaline [5021-43-2]**. The titled compound was prepared according to the general procedure with 2-quinoxalinyl *p*-toluenesulfonate (150 mg, 0.50 mmol) and phenyl boronic acid (73 mg, 0.60 mmol) at 25 $^{o}$C for 5 min. The conversion of heteroaryl tosylate was determined by GC: 5 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:10 to 1:3) as eluent, the titled compound was isolated as white solid (96 mg, 93% yield).

$^1$H NMR (400 MHz, $CDCl_3$): δ 9.27 (s, 1H), 8.15-8.04 (m, 4H), 7.75-7.67 (m, 2H), 7.54-7.44 (m, 3H).

ESI-MS: Calcd for $C_{14}H_{11}N_2$ $(M+H)^+$: 207.1. Found: 207.3.

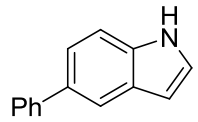



**Methyl 2-phenylquinoline-4-carboxylate [4546-48-9].** The titled compound was prepared according to the general procedure with methyl 2-(*p*-toluenesulfoxy)-quinoline-4-carboxylate (179 mg, 0.50 mmol) and phenyl boronic acid (73 mg, 0.60 mmol) at 25 $^o$C for 1 h. The conversion of heteroaryl tosylate was determined by GC: 5 min, 45%; 15 min, 77%; 1 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:30) as eluent, the titled compound was isolated as colorless oil (117 mg, 89% yield).

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.75 (d, $J$ = 8.8 Hz, 1H), 8.42 (s, 1H), 8.24-8.20 (m, 3H), 7.80-7.76 (m, 1H), 7.66-7.61 (m, 1H), 7.57-7.49 (m, 3H), 4.08 (s, 3H).

ESI-MS: Calcd for $C_{17}H_{14}NO_2$ $(M+H)^+$: 264.1. Found: 264.3.

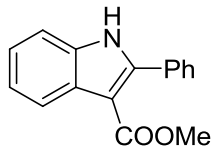



**5-Phenylindole [66616-72-6].** The titled compound was prepared according to the general procedure with 5-indolyl *p*-toluenesulfonate (144 mg, 0.50 mmol) and phenylboronic acid (73 mg, 0.60 mmol) at 25 $^o$C for 20 h. 1,2,3,4,5,6,7,8,9,10,11,12 -dodecahydrotriphenylene (30 mg, 0.125 mmol) was used as $^1$H NMR internal standard. The conversion of heteroaryl tosylate was determined by $^1$H NMR spectroscopy: 1 h, 25%; 6 h, 76%; 20 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:20 to 1:10) as eluent, the titled compound was isolated as yellow oil (86 mg, 89% yield).

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.16 (br s, 1H), 7.86 (s, 1H), 7.67-7.64 (m, 2H), 7.45-7.41 (m, 4H), 7.32-7.29 (m, 1H), 7.24-7.23 (m, 1H), 6.60 (pseudotriplet, $J$ = 2.7 Hz, 1H).

ESI-MS: Calcd for $C_{14}H_{12}N$ $(M+H)^+$: 194.1. Found: 194.3.

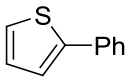



**3-Methoxycarbonyl-2-phenylindole [36779-17-6].** The titled compound was prepared according to the general procedure with methyl 3-methoxycarbonyl -2-(*p*-toluenesulfoxy)indole (173 mg, 0.50 mmol) and phenyl boronic acid (73 mg, 0.60 mmol) at 25 $^o$C for 4 h. 1,2,3,4,5,6,7,8,9,10,11,12-dodecahydrotriphenylene (30 mg, 0.125 mmol) was used as $^1$H NMR internal standard. The conversion of heteroaryl tosylate was determined by $^1$H NMR spectroscopy: 2 h, 80%; 4 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:15 to 1:10) as eluent, the titled compound was isolated as yellow solid (113 mg, 90% yield).

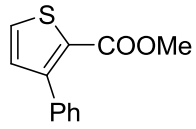
$^1$H NMR (400 MHz, $CDCl_3$): δ 8.62 (br s, 1H), 8.22-8.19 (m, 1H), 7.66-7.62 (m, 2H), 7.47-7.42 (m, 3H), 7.39-7.35 (m, 1H), 7.30-7.24 (m, 2H), 3.82 (s, 3H).

ESI-MS: Calcd for $C_{16}H_{14}NO_2$ $(M+H)^+$: 252.1. Found: 252.1.




**2-Phenylthiophene [825-55-8].** The titled compound was prepared according to the general procedure 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol), phenyl boronic acid (73 mg, 0.60 mmol) at 25 $^o$C for 5 min. 1,2,3,4,5,6,7,8,9,10,11,12 -dodecahydrotriphenylene (30 mg, 0.125 mmol) was used as $^1$H NMR internal standard and $K_3PO_4$ (180 mg, 0.85 mmol) was used as base instead of NaOH. The conversion of heteroaryl tosylate was determined by $^1$H NMR spectroscopy: 5 min, 97%.

After purification by flash chromatography using hexane as eluent, the titled compound was isolated as white solid (74 mg, 93% yield).

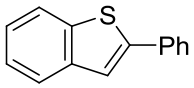



**Methyl 3-phenylthiophene-2-carboxylate [188527-56-2]**. The titled compound was prepared according to the general procedure with 2-methoxycarbonyl-3- (*p*-toluenesulfoxy)thiophene (156 mg, 0.50 mmol) and phenyl boronic acid (73 mg, 0.60 mmol) at 25 $^{o}$C for 5 min. The conversion of heteroaryl tosylate was determined by GC: 5 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:15 to 1:10) as eluent, the titled compound was isolated as colorless crystal (102 mg, 94% yield).

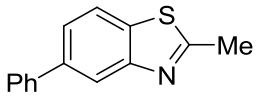
$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 5.0 Hz, 1H), 7.47-7.44 (m, 2H), 7.43-7.37 (m, 3H), 7.09 (d, *J* = 5.0 Hz, 1H), 3.78 (s, 3H).

EI-MS: Calcd for $C_{12}H_{10}O_2S$ ($M^+$): 218.0. Found: 218.1.




**2-Phenylbenzothiophene [1207-95-0].** The titled compound was prepared according to the general procedure with 2-benzothienyl *p*-toluenesulfonate (152 mg, 0.50 mmol) and phenyl boronic acid (73 mg, 0.60 mmol) at 25 $^{o}$C for 5 min. 1,2,3,4,5,6,7,8,9,10,11,12-dodecahydrotriphenylene (30 mg, 0.125 mmol) was used as $^{1}$H NMR internal standard and $K_3PO_4$ (180 mg, 0.85 mmol) was used as base instead of NaOH. The conversion of heteroaryl tosylate was determined by $^{1}$H NMR spectroscopy: 5 min, 100%.

After purification by flash chromatography using hexane as eluent, the titled compound was isolated as yellow solid (95 mg, 99% yield).




**2-Methyl-5-phenylbenzothiazole [71215-89-9]**. The titled compound was prepared according to the general procedure with 2-methyl-5-benzothiazolyl *p*-toluenesulfonate (160 mg, 0.50 mmol) and phenyl boronic acid (73 mg, 0.60 mmol) at 25 $^{o}$C for 5 h. The conversion of heteroaryl tosylate was determined by GC: 5 min, 27%: 15 min, 41%; 1 h, 71%; 5 h, 100%.

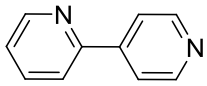
After purification by flash chromatography using ethyl acetate/hexane (1:10 to 1:6) as eluent, the titled compound was isolated as colorless oil (108 mg, 96% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, *J* = 1.4 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.68-7.66 (m, 2H), 7.60 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.50-7.46 (m, 2H), 7.40-7.36 (m, 1H), 2.86 (s, 1H).

ESI-MS: Calcd for $C_{14}H_{12}NS$ $(M+H)^{+}$: 226.1. Found: 226.3.

General Procedure A for Suzuki Coupling of 2-Pyridine Tosylate with Various Heteroarylboronic Acids

In an argon-filled glove box, to a 25 mL Schlenk tube was added sequentially $Pd(OAc)_2$ (0.010 mmol, 2.4 mg), XPhos (0.012 mmol, 5.7 mg), 2-pyridyl tosylate (125 mg, 0.50 mmol), heteroaryl boronic acid (0.60 mmol), 40 μL of *n*-dodecane (GC internal standard), and *n*-butanol (2.8 mL). After stirring at 25 $^{o}$C for 15 minutes, a solution of NaOH (0.85 mmol, 34 mg) in 0.68 mL of degassed $H_2O$ was added to initiate the Suzuki reaction. The Schlenk tube was capped tightly and the reaction mixture was stirred vigorously at 25 $^{o}$C until all the heteroaryl *p*-tosylate was consumed (monitored by TLC and GC). At the end of the reaction, the reaction mixture was passed through a short plug of silica gel with ethyl acetate washings (5 mL) and the filtrate was concentrated on a rotary evaporator. The resulting residue was purified by silica gel flash chromatography using a mixed solvent of hexane and acetyl acetate as eluent to provide the coupling product. The general procedure for all isolation was used unless stated otherwise. The 15 min prestirring helped to improve reproducibility of the reaction kinetics. Without the prestirring, the coupling was still very fast.

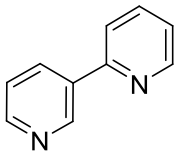


**2,4'-Bipyridine [581-47-5].** The titled compound was prepared according to the general procedure with 4-pyridyl boronic acid (87 mg, 0.60 mmol; containing 15%wt water) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 100 $^{o}$C for 2 h. $K_3PO_4$ (180 mg, 0.85 mmol) was used as base instead of NaOH. The conversion of heteroaryl tosylate was determined by GC: 15 min, 20%; 1 h, 85%; 2 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (3:1 to 1:1) as eluent, the titled compound was isolated as white solid (76 mg, 97% yield).

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.76-8.72 (m, 3H), 7.90-7.84 (m, 2H), 8.84-7.79 (m, 2H), 7.36-7.32 (m, 1H).

ESI-MS: Calcd for $C_{10}H_8N_2$ $(M+H)^+$: 157.1. Found: 157.3.

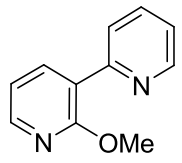


**2,3'-Bipyridine [581-50-0].** The titled compound was prepared according to the general procedure with 3-pyridyl boronic acid (73 mg, 0.60 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 100 $^{o}$C for 15 min. $K_3PO_4$ (180 mg, 0.85 mmol) was used as base instead of NaOH. The conversion of heteroaryl tosylate was determined by GC: 5 min, 48%; 15 min, 97%.

After purification by flash chromatography using ethyl acetate/hexane (1:1) as eluent, the titled compound was isolated as colorless oil (74 mg, 95% yield).

$^1$H NMR (400 MHz, $CDCl_3$): δ 9.20 (d, $J$ = 1.8 Hz, 1H), 8.73 (d, $J$ = 4.4 Hz, 1H), 8.66 (dd, $J$ = 4.4, 1.4 Hz, 1H), 8.33 (ddd, $J$ = 8.0, 1.8, 1.4 Hz, 1H), 7.83-7.75 (m, 2H), 7.42 (d, $J$ = 8.0, 4.4 Hz, 1H), 7.32-7.26 (m, 1H).

ESI-MS: Calcd for $C_{10}H_8N_2$ $(M+H)^+$: 157.1. Found: 157.3.



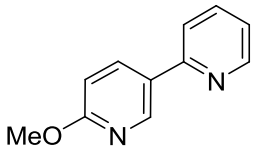

**2'-Methoxy-2,3'-bipyridine.** The titled compound was prepared according to the general procedure with 2-methoxy-3-pyridyl boronic acid (92 mg, 0.60 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^{o}$C for 15 min. The conversion of heteroaryl tosylate was determined by GC: 5 min, 36%; 15 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:15 to 1:10) as eluent, the titled compound was isolated as colorless oil (86 mg, 92% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.71-8.69 (m, 1H), 8.24-8.21 (m, 2H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.76-7.71 (m, 1H), 7.24 (ddd, *J* = 5.9, 4.9, 1.0 Hz, 1H), 7.04 (dd, *J* = 7.1, 5.3 Hz, 1H), 4.04 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 161.3, 154.4, 150.0, 147.2, 139.6, 139.2, 124.8, 123.2, 122.4, 117.6, 53.8.

ESI-MS: Calcd for $C_{11}H_{11}N_2O$ $(M+H)^+$: 187.1. Found: 187.3.

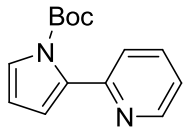



**6'-Methoxy-2,3'-bipyridine [381725-49-1].** The titled compound was prepared according to the general procedure with 6-methoxy-3-pyridyl boronic acid (92 mg, 0.60 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^{o}$C for 2 h. The conversion of heteroaryl tosylate was determined by GC: 1 h, 37%; 2 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:10 to 1:5) as eluent, the titled compound was isolated as colorless oil (87 mg, 94% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.74 (d, *J* = 2.3 Hz, 1H), 8.66 (d, *J* = 4.8 Hz, 1H), 8.24 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.74-7.70 (m, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.22-7.19 (m, 1H), 6.84 (dd, *J* = 8.7, 0.4 Hz, 1H), 4.00 (s, 3H).

ESI-MS: Calcd for $C_{11}H_{11}N_2O$ $(M+H)^+$: 187.1. Found: 187.3.

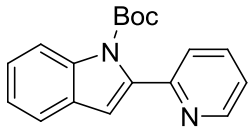



***N*-(*tert*-Butoxycarbonyl)-2-(2-pyridyl)pyrrole [856702-64-2].** The titled compound was prepared according to the general procedure with *N*-(*tert*-butoxy-carbonyl)-2-pyrrolyl boronic acid (127 mg, 0.60 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^oC$ for 5 min. The conversion of heteroaryl tosylate was determined by GC: 5 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:20 to 1:10) as eluent, the titled compound was isolated as colorless oil (114 mg, 93% yield).

$^1H$ NMR (400 MHz, $CDCl_3$): δ 8.61 (d, *J* = 4.8 Hz, 1H), 7.70-7.66 (m, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.36 (dd, *J* = 3.3, 1.7 Hz, 1H), 7.20 (ddd, *J* = 5.6, 4.8, 0.8 Hz, 1H), 6.41 (dd, *J* = 3.3, 1.7 Hz, 1H), 6.24 (pseudotriplet, *J* = 3.3 Hz, 1H), 1.36 (s, 9H).

ESI-MS: Calcd for $C_{14}H_{17}N_2O_2$ $(M+H)^+$: 245.21, Found: 244.83.

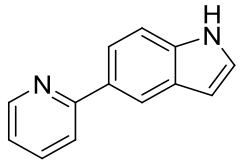



***N*-(*tert*-Butoxycarbonyl)-2-(2-pyridyl)indole [205310-34-5].** The titled compound was prepared according to the general procedure with *N*-(*tert*-butoxycarbonyl)-2-indolyl boronic acid (157 mg, 0.60 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^oC$ for 5 min. The conversion of heteroaryl tosylate was determined by GC: 5 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane 1:30 as eluent, the titled compound was isolated as yellow oil (135 mg, 92% yield).

$^1H$ NMR (400 MHz, $CDCl_3$): δ 8.70 (d, *J* = 4.2 Hz, 1H), 8.21 (d, *J* = 8.2 Hz, 1H), 7.78-7.75 (m, 1H), 7.61 (d, *J* = 7.7 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.37-7.36 (m, 1H), 7.30-7.26 (m, 2H), 6.80 (s, 1H), 1.36 (s, 9H).

ESI-MS: Calcd for $C_{18}H_{19}N_2O_2$ ($M^+$): 294.1. Found: 294.8.

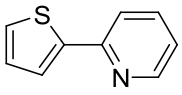


**5-(2-Pyridyl)indole [117908-10-8].** The titled compound was prepared according to the general procedure with 5-indolyl boronic acid (97 mg, 0.60 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^oC$ for 1 h. The conversion of heteroaryl tosylate was mornitored by GC: 5 min, 20%; 15 min, 61%; 1 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:10 to 1:3) as eluent, the titled compound was isolated as white solid (88 mg, 91% yield).

$^1H$ NMR (400 MHz, $CDCl_3$): δ 8.72 (d, *J* = 4.7 Hz, 1H), 8.31 (d, *J* = 1.7 Hz, 1H), 8.28 (br s, 1H), 7.92 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.78-7.74 (m, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.28-7.26 (m, 1H), 7.22-7.19 (m, 1H), 6.66 (pseudotriplet, *J* = 2.1 Hz, 1H).

ESI-MS: Calcd for $C_{13}H_{11}N_2$ $(M+H)^+$: 195.1. Found: 195.4.

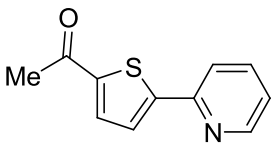


**2-(2-Thienyl)pyridine [3319-99-1]**. The titled compound was prepared according to the general procedure with 2-thienyl boronic acid (77 mg, 0.60 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^oC$ for 5 min. The conversion of heteroaryl tosylate was determined by GC: 5 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:15 to 1:10) as eluent, the titled compound was isolated as white solid (76 mg, 95% yield).

$^1H$ NMR (400 MHz, $CDCl_3$): δ 8.57 (d, *J* = 4.8 Hz, 1H), 7.71-7.65 (m, 2H), 7.59 (dd, *J* = 3.7, 1.0 Hz, 1H), 7.40 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.16-7.12 (m, 2H).

ESI-MS: Calcd for $C_9H_8NS$ $(M+H)^+$: 162.0. Found: 162.3.

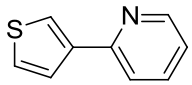



**2-Acetyl-5-(2-pyridyl)thiophene [123784-11-2].** The titled compound was prepared according to the general procedure with 5-acetyl-2-thienyl boronic acid (102 mg, 0.60 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^{o}$C for 5 min. The conversion of heteroaryl tosylate was determined by GC: 5 min, 97%.

After purification by flash chromatography using ethyl acetate/hexane (1:15 to 1:10) as eluent, the titled compound was isolated as pale yellow solid (99 mg, 98% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, *J* = 4.9 Hz, 1H), 7.75-7.70 (m, 3H), 7.60 (d, *J* = 4.0 Hz, 1H), 7.25-7.23 (m, 1H), 2.59 (s, 3H).

ESI-MS: Calcd for $C_{11}H_{10}NOS$ $(M+H)^{+}$: 204.1. Found: 204.1.

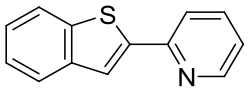



**2-(3-Thienyl)pyridine [21298-55-5]**. The titled compound was prepared according to the general procedure with 3-thienyl boronic acid (77 mg, 0.60 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^{o}$C for 15 min. The conversion of heteroaryl tosylate was determined by GC: 5 min, 96%; 15 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:15 to 1:10) as eluent, the titled compound was isolated as colorless oil (73 mg, 91% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, *J* = 4.8 Hz, 1H), 7.90 (dd, *J* = 3.2, 1.2 Hz, 1H), 7.71-7.65 (m, 2H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.39 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.18-7.15 (m, 1H).

ESI-MS: Calcd for $C_9H_8NS$ $(M+H)^{+}$: 162.0. Found: 162.3.

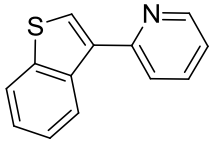



**2-(2-Benzothienyl)pyridine [38210-35-4].** The titled compound was prepared according to the general procedure with 2-benzothienyl boronic acid (107 mg, 0.60 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^{o}$C for 5 min. The conversion of heteroaryl tosylate was determined by GC: 5 min, 100%. After purification by flash chromatography using ethyl acetate/hexane (1:15 to 1:10) as eluent, the titled compound was isolated as white solid (103 mg, 97% yield).

*Gram-scale procedure*: Under argon, a 100-mL round bottom flask containing a magnetic stir bar was charged sequentially with $Pd(OAc)_2$ (29.3 mg, 0.12 mmol), XPhos (66.6 mg, 0.14 mmol), 2-pyridyl *p*-toluenesulfonate (1.49 g, 6.0 mmol), 2-benzothienyl boronic acid (1.28 g, 7.2 mmol), *n*-dodecane (200 μL as GC internal standard), and 33 mL of degassed *n*-butanol. The mixture was prestirred at 25 $^{o}$C for 15 min, and then a solution of NaOH (408 mg, 10.2 mmol) in 8.1 mL of degassed $H_2O$ was added to initiate the Suzuki reaction. The flask was capped tightly and the reaction mixture was stirred vigorously at 25 $^{o}$C for 5 min until all the 2-pyridyl *p*-toluenesulfonate was consumed (monitored by GC: 5 min). After routine workup and purification by flash chromatography (1:30 to 1:10 ethyl acetate/hexane as eluent), the titled compound was isolated as yellow solid (1.221 g, 96% yield).

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.63 (d, *J* = 4.9 Hz, 1H), 7.88-7.77 (m, 4H), 7.70 (ddd, *J* = 9.2, 7.4, 1.8 Hz, 1H), 7.38-7.32 (m, 2H), 7.19 (ddd, *J* = 6.0, 4.9, 1.2 Hz, 1H).

ESI-MS: Calcd for $C_{13}H_{10}NS$ $(M+H)^+$: 212.1. Found: 212.4.




**2-(3-Benzothienyl)pyridine.** The titled compound was prepared according to the general procedure with 3-benzothioenyl boronic acid (107 mg, 0.60 mmol) and 2-

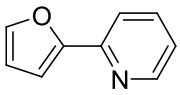
pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^{o}$C for 5 min. The conversion of heteroaryl tosylate was mornitored by GC: 5 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:15 to 1:10) as eluent, the titled compound was isolated as colorless oil (102 mg, 97% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.73 (d, *J* = 5.4 Hz, 1H), 8.46 (d, *J* = 7.8 Hz, 1H), 7.89 (d, *J* = 7.9 Hz, 1H), 7.77 (s, 1H), 7.75-7.71 (m, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.45-7.35 (m, 2H), 7.24-7.21 (m, 1H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 154.7, 149.7, 141.0, 137.4, 136.8, 136.7, 126.5, 124.8, 124.7, 124.3, 122.8, 122.7, 122.1.

ESI-MS: Calcd for $C_{13}H_{10}NS$ $(M+H)^+$: 212.1. Found: 212.4.

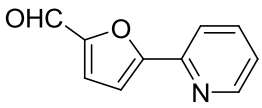



**2-(2-Furyl)pyridine [55484-03-2]**. The titled compound was prepared according to the general procedure with 2-furyl boronic acid (84 mg, 0.75 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^{o}$C for 15 min. The conversion of heteroaryl tosylate was determined by GC: 5 min, 90%; 15 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:15 to 1:10) as eluent, the titled compound was isolated as colorless oil (67 mg, 92% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, *J* = 4.8 Hz, 1H), 7.73-7.68 (m, 2H), 7.53 (d, *J* = 1.0 Hz, 1H), 7.17-7.13 (m, 1H), 7.06 (d, *J* = 3.3 Hz, 1H), 6.53 (dd, *J* = 3.3, 1.0 Hz, 1H).

ESI-MS: Calcd for $C_9H_8NO$ $(M+H)^+$: 146.1. Found: 146.3.

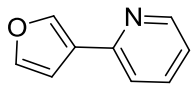


**2-Formyl-5-(2-pyridyl)furan [55484-36-1]**. The titled compound was prepared according to the general procedure with 5-formyl-2-furyl boronic acid (84 mg, 0.60 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^{o}$C for 8 h. The conversion of heteroaryl tosylate was determined by GC: 1 h, 44%; 5 h, 96%; 8 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:20) as eluent, the titled compound was isolated as pale yellow solid (78 mg, 90% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 9.65 (s, 1H), 8.59 (d, *J* = 4.7 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.73 (ddd, *J* = 7.8, 7.5, 1.7 Hz, 1H), 7.29 (d, *J* = 3.7 Hz, 1H), 7.22 (dd, *J* = 7.5, 4.8 Hz, 1H), 7.19 (d, *J* = 3.7 Hz, 1H).

ESI-MS: Calcd for $C_{10}H_8NO_2$ $(M+H)^+$: 174.1. Found: 174.3.

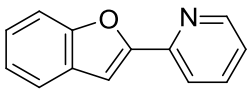



**2-(3-Furyl)pyridine [55484-05-4]**. The titled compound was prepared according to the general procedure with 3-furyl boronic acid (84 mg, 0.75 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^{o}$C for 15 min. The conversion of heteroaryl tosylate was determined by GC: 5 min, 87%; 15 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:30 to 1:20) as eluent, the titled compound was isolated as colorless oil (65 mg, 90% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.59 (d, *J* = 4.3 Hz, 1H), 8.02 (s, 1H), 7.70-7.65 (m, 1H), 7.50-7.49 (m, 1H), 7.46 (d, *J* = 8.0 Hz, 1H), 7.16-7.13 (m, 1H), 6.90 (d, *J* = 1.1 Hz, 1H).

ESI-MS: Calcd for $C_9H_8NO$ $(M+H)^+$: 146.1. Found: 146.3.



**2-(2-Benzofuryl)pyridine [7035-05-4]**. The titled compound was prepared according to the general procedure with 2-benzofuryl boronic acid (97 mg, 0.60 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^{o}$C for 1 h. The conversion of heteroaryl tosylate was determined by GC: 5 min, 9%; 15 min, 72%; 1 h, 100%.

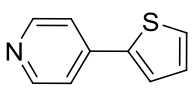
After purification by flash chromatography using ethyl acetate/hexane (1:15 to 1:10) as eluent, the titled compound was isolated as pale yellow solid (88 mg, 90% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.69 (d, *J* = 4.4 Hz, 1H), 7.90 (d, *J* = 7.9 Hz, 1H), 7.80-7.76 (m, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.43 (s, 1H), 7.36-7.32 (m, 1H), 7.28-7.23 (m, 2H).

ESI-MS: Calcd for $C_{13}H_{10}NO$ $(M+H)^{+}$: 196.1. Found: 196.3.

General Procedure B for Suzuki Coupling of 2-Thiophene Tosylate with Various Heteroarylboronic Acids

In an argon-filled glove box, to a 25 mL Schlenk tube was added sequentially $Pd(OAc)_2$ (0.010 mmol, 2.4 mg), XPhos (0.012 mmol, 5.7 mg), 2-thienyl tosylate (127 mg, 0.50 mmol), and heteroaryl boronic acid (0.60 mmol), followed by the NMR internal standard, 1,2,3,4,5,6,7,8,9,10,11,12 –dodecahydro- triphenylene (30 mg, 0.125 mmol), and *n*-butanol (2.8 mL). After the mixture was stirred at 25 $^{o}$C for 15 min, a solution of $K_3PO_4$ (0.85 mmol, 180 mg) in 0.68 mL of degassed $H_2O$ was added to initiate the Suzuki coupling. The Schlenk tube was capped tightly and the reaction mixture was stirred vigorously at 25 $^{o}$C until all the 2-thienyl tosylate was consumed (monitored by $^{1}$H NMR). At the end of the reaction, the mixture was passed through a short plug of silica gel plug with ethyl acetate washings (5 mL) and the filtrate was concentrated on a rotary evaporator. The resulting residue was purified by silica gel flash chromatography using a mixed solvent of hexane and ethyl acetate as eluent to provide the coupling product. The general procedure was used for all isolation, unless stated otherwise.



**4-(2-Thienyl)pyridine [21298-54-4].** The titled compound was prepared according to the general procedure with 4-pyridyl boronic acid (87 mg, 0.60 mmol containing 15%wt water) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 80 $^{o}$C for 18 h. The conversion of heteroaryl tosylate was determined by $^{1}$H NMR spectroscopy: 5 h, 21%; 8 h, 30%; 18 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:10 to 1:5) as eluent, the titled compound was isolated as yellow solid (76 mg, 95% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.60-8.58 (m, 2H), 7.52-7.47 (m, 3H), 7.41 (dd, *J* = 5.2, 1.0 Hz, 1H), 7.13 (dd, *J* = 5.0, 3.7 Hz, 1H).

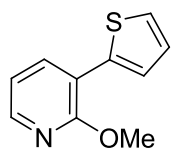
ESI-MS: Calcd for $C_9H_7NS$ $(M+H)^+$: 162.03, Found: 162.29.


**3-(2-Thienyl)pyridine [21298-53-3].** The titled compound was prepared according to the general procedure with 3-pyridyl boronic acid (92 mg, 0.75 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 80 $^{o}$C for 5 h. The conversion of heteroaryl tosylate was determined by $^{1}$H NMR spectroscopy: 1 h, 86%; 5 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:10 to 1:5) as eluent, the titled compound was isolated as light yellow oil (80 mg, 99% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.88 (d, *J* = 1.9 Hz, 1H), 8.51 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.86 (ddd, *J* = 7.9, 1.9, 1.5 Hz, 1H), 7.37-7.36 (m, 2H), 7.30 (dd, *J* = 7.9, 4.8 Hz, 1H), 7.13 (dd, *J* = 4.8, 3.9 Hz, 1H).

ESI-MS: Calcd for $C_9H_7NS$ $(M+H)^+$: 162.03, Found: 162.29.



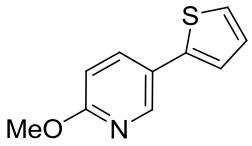
**2-Methoxy-3-(2-thienyl)pyridine.** The titled compound was prepared according to the general procedure with 2-methoxy-3-pyridyl boronic acid (92 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^{o}$C for 5 min. The conversion of heteroaryl tosylate was determined by $^{1}$H NMR spectroscopy: 5 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane 1:20 as eluent, the titled compound was isolated as light yellow oil (89 mg, 93% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.10 (dd, *J* = 4.9, 1.8 Hz, 1H), 7.89 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.58 (dd, *J* = 3.7, 1.0 Hz, 1H), 7.36 (dd, *J* = 5.1, 1.0 Hz, 1H), 7.10 (dd, *J* = 5.1, 3.7 Hz, 1H), 6.95 (dd, *J* = 7.5, 4.9 Hz, 1H), 4.08 (s, 3H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 159.7, 145.4, 138.0, 136.1, 127.4, 126.2, 126.1, 118.1, 117.2, 53.7.

ESI-MS: Calcd for $C_{10}H_{10}NOS$ $(M+H)^{+}$: 192.04. Found: 192.12.

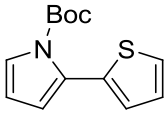



**2-Methoxy-5-(2-thienyl)pyridine [475275-84-4].** The titled compound was prepared according to the general procedure with 6-methoxy-3-pyridyl boronic acid (92 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^{o}$C for 5 h. The conversion of heteroaryl tosylate was determined by $^{1}$H NMR spectroscopy: 1 h, 76%; 5 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane 1:40 as eluent, the titled compound was isolated as light yellow oil (91 mg, 95% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.42 (d, *J* = 2.4 Hz, 1H), 7.77 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.27 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.21 (dd, *J* = 3.6, 1.1 Hz, 1H), 7.08 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.77 (d, *J* = 8.6 Hz, 1H), 3.97 (s, 3H).

ESI-MS: Calcd for $C_{10}H_{10}NOS$ $(M+H)^{+}$: 192.04. Found: 192.15.

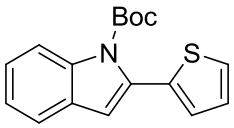


***N*-(*tert*-Butoxycarbonyl)-2-(2-thienyl)pyrrole [215187-33-0].** The titled compound was prepared according to the general procedure with *N*-(*tert*-butoxycarbonyl)-2-pyrrolyl boronic acid (127 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^{o}$C for 5 min. The conversion of heteroaryl tosylate was determined by $^{1}$H NMR spectroscopy: 5 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane 1:30 as eluent, the titled compound was isolated as colorless oil (116 mg, 93% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.37 (dd, *J* = 3.3, 1.8 Hz, 1H), 7.31 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.06-7.05 (m, 1H), 7.01 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.31 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.21 (pseudotriplet, *J* = 3.3 Hz 1H), 1.43 (s, 9H).

ESI-MS: Calcd for $C_{13}H_{16}NO_2S$ $(M+H)^+$: 250.08. Found: 249.87.

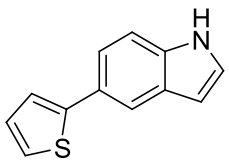



***N*-(*tert*-Butoxycarbonyl)-2-(2-thienyl)indole [929284-23-1]**. The titled compound was prepared according to the general procedure with *N*-(*tert*-butoxycarbonyl)-2-indolyl boronic acid (157 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^{o}$C for 5 min. The conversion of heteroaryl tosylate was determined by $^{1}$H NMR spectroscopy: 5 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:20) as eluent, the titled compound was isolated as yellow oil (148 mg, 99% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.38-7.31 (m, 2H), 7.27-7.24 (m, 1H), 7.10 (dd, *J* = 3.5, 1.2 Hz, 1H), 7.06 (dd, *J* = 5.1, 3.5 Hz 1H), 6.67 (s, 1H), 1.41 (s, 9H),

ESI-MS: Calcd for $C_{17}H_{18}NO_2S$ $(M+H)^+$: 300.10. Found: 299.83.

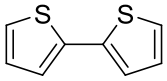


**5-(2-Thienyl)indole [144104-54-1].** The titled compound was prepared according to the general procedure with 2-indolyl boronic acid (97 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^{o}$C for 1 h. The conversion of heteroaryl tosylate was determined by $^{1}$H NMR spectroscopy: 5 min, 78%; 15 min, 93%; 1 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:20 to 1:10) as eluent, the titled compound was isolated as yellow oil (90 mg, 93% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.18 (br s, 1H), 7.93-7.92 (m, 1H), 7.52 (d, *J* = 8.4, 1.7 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.31 (dd, *J* = 3.6, 1.1 Hz, 1H), 7.26-7.24 (m, 2H), 7.10 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.62-6.60 (m, 1H).

EI-MS: Calcd for $C_{12}H_8NS$ $M^+$: 199.1. Found: 199.0.

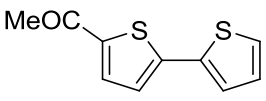



**2,2'-Bithiophene [492-97-7].** The titled compound was prepared according to the general procedure with 2-thienyl boronic acid (77 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^{o}$C for 15 min. The conversion of heteroaryl tosylate was determined by $^{1}$H NMR spectroscopy: 5 min, 91%; 15 min, 96%.

After purification by flash chromatography using hexane as eluent, the titled compound was isolated as yellow oil (75 mg, 90% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.24-7.20 (m, 4H), 7.05-7.02 (m, 2H).

EI-MS: Calcd for $C_8H_6S_2$ $M^+$: 166.0. Found: 165.7.



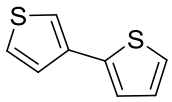

**5-Acetyl-2,2'-bithiophene [3515-18-2].** The titled compound was prepared according to the general procedure with 2-(5-acetyl)thienyl boronic acid (102 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^{o}$C for 15

min. The conversion of heteroaryl tosylate was determined by $^1$H NMR spectroscopy: 5 min, 88%; 15 min, 96%.

After purification by flash chromatography using ethyl acetate/hexane (1:30 to 1:20) as eluent, the titled compound was isolated as white solid (94 mg, 90% yield).

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, *J* = 4.0 Hz, 1H), 7.33-7.31 (m, 2H), 7.18 (d, *J* = 4.0 Hz, 1H), 7.06 (dd, *J* = 5.0, 3.8 Hz, 1H), 2.55 (s, 3H).

EI-MS: Calcd for $C_{10}H_9OS_2$ $M^+$: 208.0. Found: 207.9.

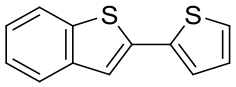



**2,3'-Bithiophene [2404-89-9].** The titled compound was prepared according to the general procedure with 3-thienyl boronic acid (77 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^o$C for 15 min. The conversion of heteroaryl tosylate was determined by $^1$H NMR spectroscopy: 5 min, 89%; 15 min, 96%.

After purification by flash chromatography using hexane as eluent, the titled compound was isolated as white solid (76 mg, 92% yield).

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.40-7.32 (m, 3H), 7.23-7.21 (m, 2H), 7.05 (dd, *J* = 4.8, 3.6 Hz, 1H).

EI-MS: Calcd for $C_8H_6S_2$ $M^+$: 166.0. Found: 165.9.

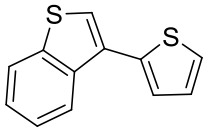



**2-(2-Thienyl)benzothiophene [55164-48-2].** The titled compound was prepared according to the general procedure with 2-benzothienyl boronic acid (107 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^o$C for 15 min. The conversion of heteroaryl tosylate was determined by $^1$H NMR spectroscopy: 5 min, 91%; 15 min, 96%.

After purification by flash chromatography using hexane as eluent, the titled compound was isolated as white solid (104 mg, 96% yield).

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.81-7.73 (m, 2H), 7.41 (s, 1H), 7.36-7.31 (m, 4H), 7.09-7.07 (m, 1H).

EI-MS: Calcd for $C_{12}H_9S_2$ $M^+$: 216.0. Found: 216.2.

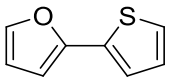


**3-(2-Thienyl)benzothiophene [105789-79-5].** The titled compound was prepared according to the general procedure with 3-benzothienyl boronic acid (107 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^o$C for 15 min. The conversion of heteroaryl tosylate was determined by $^1$H NMR spectroscopy: 5 min, 85%; 15 min, 100%.

After purification by flash chromatography using hexane as eluent, the titled compound was isolated as light yellow oil (106 mg, 98% yield).

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.7 Hz, 1H), 7.91 (d, *J* = 7.3 Hz, 1H), 7.51(s, 1H), 7.47-7.34 (m, 4H), 7.17(dd, *J* = 4.8, 3.6 Hz, 1H)

EI-MS: Calcd for $C_{12}H_9S_2$ $M^+$: 216.0. Found: 215.9.

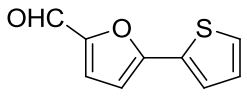


**2-(2-Thienyl)furan [27521-80-8].** The titled compound was prepared according to the general procedure with 2-furyl boronic acid (84 mg, 0.75 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^o$C for 15 min. The conversion of heteroaryl tosylate was determined by $^1$H NMR spectroscopy: 5 min, 89%; 15 min, 97%.

After purification by flash chromatography using hexane as eluent, the titled compound was isolated as light yellow oil (67 mg, 90% yield).

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 1.8 Hz, 1H), 7.25-7.21 (m, 2H), 7.04 (dd, *J* = 5.0, 3.6 Hz, 1H), 6.50 (d, *J* = 3.3 Hz, 1H), 6.44 (dd, *J* = 3.3, 1.8 Hz, 1H).

EI-MS: Calcd for $C_8H_6OS$ $M^+$: 150.0. Found: 149.9.

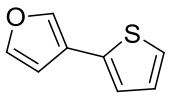



**2-Formyl-5-(2-thienyl)furan [32364-30-0].** The titled compound was prepared according to the general procedure with 5-formyl-2-furyl boronic acid (84 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^{o}$C for 8 h. The conversion of heteroaryl tosylate was determined by $^{1}$H NMR spectroscopy: 5 min, 12%; 15 min, 32%; 1 h, 58%; 5 h, 89%; 8 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:20 to 1:10) as eluent, the titled compound was isolated as light yellow oil (87 mg, 98% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 9.62 (s, 1H), 7.53 (dd, *J* = 3.7, 1.0 Hz, 1H), 7.41 (dd, *J* = 5.2, 1.0 Hz, 1H), 7.29 (d, *J* = 3.7 Hz, 1H), 7.11 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.68 (d, *J* = 3.7 Hz, 1H).

ESI-MS: Calcd for $C_9H_7O_2S$ $(M+H)^+$: 179.01. Found: 179.16.

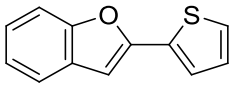



**3-(2-Thienyl)furan [27521-81-9].** The titled compound was prepared according to the general procedure with 3-furyl boronic acid (84 mg, 0.75 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^{o}$C for 15 min. The conversion of heteroaryl tosylate was determined by $^{1}$H NMR spectroscopy: 5 min, 73%; 15 min, 95%.

After purification by flash chromatography using hexane as eluent, the titled compound was isolated as light yellow oil (69 mg, 92% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.67 (br s, 1H), 7.44 (pseudotriplet, *J* = 1.7 Hz, 1H), 7.20 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.10 (dd, *J* = 3.5, 1.1 Hz, 1H), 7.03 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.62 (dd, *J* = 1.7, 0.8 Hz, 1H).

EI-MS: Calcd for $C_8H_6OS$ $M^+$: 150.0. Found: 149.7.



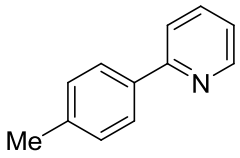

**2-(2-Thienyl)benzofuran [65246-50-6].** The titled compound was prepared according to the general procedure with 2-benzofuryl boronic acid (97 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^{o}$C for 15 min. The conversion of heteroaryl tosylate was determined by $^{1}$H NMR spectroscopy: 5 min, 85%; 15 min, 98%.

After purification by flash chromatography using hexane as eluent, the titled compound was isolated as light yellow solid (90 mg, 90% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.56-7.54 (m, 1H), δ 7.51-7.49 (m, 2H), 7.35 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.30-7.22 (m, 2H), 7.11 (dd, *J* = 5.0, 3.6 Hz, 1H), 6.87 (s, 1H).

EI-MS: Calcd for $C_{12}H_9OS$ $M^+$: 200.0. Found: 200.0.

Suzuki Coupling of 2-Pyridine Tosylate with Various Arylboronic Acids and Alkenylboronic Acids

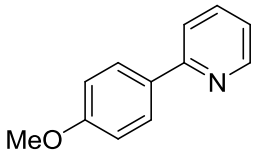



**2-(*p*-Tolyl)pyridine [4467-06-5].** The titled compound was prepared according to the general procedure A with *p*-tolyl boronic acid (82 mg, 0.60 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^{o}$C for 5 min. The conversion of heteroaryl tosylate was determined by GC: 5 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:25) as eluent, the titled compound was isolated as colorless oil (83 mg, 98% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.68 (d, *J* = 4.7 Hz, 1H), 7.89 (d, *J* = 8.2 Hz, 2H), 7.73-7.71 (m, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.21-7.17 (m, 1H), 2.41 (s, 3H).

ESI-MS: Calcd for $C_{12}H_{12}N$ $(M+H)^+$: 170.1. Found: 170.4.

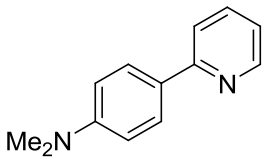



**2-(*p*-Anisyl)pyridine [5957-90-4].** The titled compound was prepared according to the general procedure A with *p*-anisyl boronic acid (91 mg, 0.60 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^{o}$C for 5 min. The conversion of heteroaryl tosylate was determined by GC: 5 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:30 to 1:20) as eluent, the titled compound was isolated as light yellow solid (86 mg, 93% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.66 (d, *J* = 4.8 Hz, 1H), 7.97-7.94 (m, 2H), 7.74-7.66 (m, 2H), 7.18-7.15 (m, 1H), 7.02-6.98 (m, 2H), 3.84 (s, 3H).

ESI-MS: Calcd for $C_{12}H_{12}NO$ $(M+H)^{+}$: 186.1. Found: 186.2.

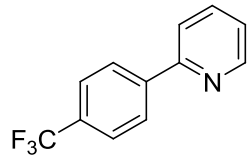



***N*,*N*-Dimethyl-4-(2-pyridyl)aniline [100381-45-1].** The titled compound was prepared according to the general procedure A with 4-(*N*,*N*-dimethylamino)phenyl boronic acid (99.0 mg, 0.60 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^{o}$C for 5 min. The conversion of heteroaryl tosylate was determined by GC: 5 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:20) as eluent, the titled compound was isolated as white solid (89 mg, 90% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, *J* = 4.7 Hz, 1H), 7.93-7.91 (m, 2H), 7.67-7.65 (m, 2H), 7.11-7.08 (m, 1H), 6.81-6.79 (m, 2H), 3.00 (s, 3H).

ESI-MS: Calcd for $C_{13}H_{15}N_2$ $(M+H)^{+}$: 199.1. Found: 199.3.

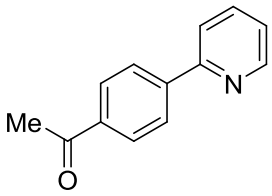



**2-(4-(Trifluoromethyl)phenyl)pyridine [203065-88-7].** The titled compound was prepared according to the general procedure A with 4-(trifluoromethyl)phenyl boronic acid (114 mg, 0.60 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^{o}$C for 1 h. The conversion of heteroaryl tosylate was determined by GC: 15 min, 44%; 1 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:30) as eluent, the titled compound was isolated as yellow solid (106 mg, 95% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.71 (d, *J* = 4.7 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 2H), 7.78-7.01 (m, 4H), 7.28-7.25 (m, 1H).

ESI-MS: Calcd for $C_{12}H_8F_3N$ $(M+H)^+$: 224.1. Found: 224.4.

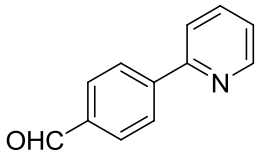



**4-(2-Pyridyl)acetophenone [173681-56-6].** The titled compound was prepared according to the general procedure A with 4-acetylphenyl boronic acid (98 mg, 0.60 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^{o}$C for 4 h. The conversion of heteroaryl tosylate was determined by GC: 1 h, 33%; 4 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:15) as eluent, the titled compound was isolated as white solid (94 mg, 95% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.73 (d, *J* = 4.8 Hz, 1H), 8.11-8.04 (m, 4H), 7.79-7.77 (m, 2H), 7.30-7.26 (m, 1H), 2.65 (s, 3H).

ESI-MS: Calcd for $C_{13}H_{12}NO$ $(M+H)^+$: 198.1. Found: 198.2.

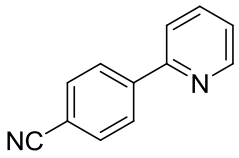


**4-(2-Pyridyl)benzaldehyde [127406-56-8].** The titled compound was prepared according to the general procedure A with 4-formylphenyl boronic acid (90 mg, 0.60 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^{o}$C for 4 h. The conversion of heteroaryl tosylate was determined by GC: 5 min, 5%; 15 min, 16%; 1 h, 57%; 4 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:15) as eluent, the titled compound was isolated as white solid (85 mg, 93% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1H), 8.68 (d, *J* = 4.7 Hz, 1H), 8.11 (d, *J* = 8.2 Hz, 2H), 7.93 (d, *J* = 8.2 Hz, 2H), 7.75-7.74 (m, 2H), 7.26-7.19 (m, 1H).

ESI-MS: Calcd for $C_{12}H_{10}NO$ $(M+H)^{+}$: 184.1. Found: 184.2.

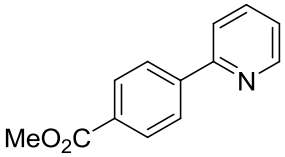



**4-(2-Pyridyl)benzonitrile [32111-34-5].** The titled compound was prepared according to the general procedure A with 4-cyanophenyl boronic acid (88 mg, 0.60 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^{o}$C for 4 h. The conversion of heteroaryl tosylate was determined by GC: 1 h, 28%; 4 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:15) as eluent, the titled compound was isolated as white solid (81 mg, 90% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.74 (d, *J* = 4.4 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 2H), 7.84-7.76 (m, 4H), 7.34-7.30 (m, 1H).

ESI-MS: Calcd for $C_{12}H_8N_2$ $(M+H)^{+}$: 181.1. Found: 181.3.



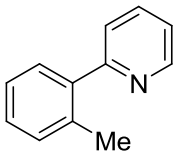

**Methyl 4-(2-pyridyl)benzoate [98061-21-3].** The titled compound was prepared according to the general procedure A with 4-(methoxycarbonyl)phenyl boronic acid (108 mg, 0.60 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol)

at 25 $^{o}$C for 5 h. The conversion of heteroaryl tosylate was determined by GC: 5 min, 7%; 15 min, 32%; 1 h, 83%; 5 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:15 to 1:10) as eluent, the titled compound was isolated as white solid (104 mg, 98% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.73 (d, *J* = 4.8 Hz, 1H), 8.15 (d, *J* = 8.5 Hz, 2H), 8.08 (d, *J* = 8.5 Hz, 2H), 7.80-7.78 (m, 2H), 7.30-7.26 (m, 1H), 3.95 (s, 3H).

ESI-MS: Calcd for $C_{13}H_{12}NO_2$ $(M+H)^+$: 214.1. Found: 214.3.

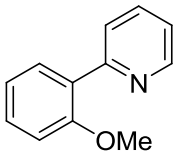



**2-(*o*-Tolyl)pyridine [10273-89-9].** The titled compound was prepared according to the general procedure A with *o*-tolyl boronic acid (82 mg, 0.60 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^{o}$C for 5 min. The conversion of heteroaryl tosylate was determined by GC: 5 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:30) as eluent, the titled compound was isolated as colorless oil (81 mg, 96% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.70 (d, *J* = 4.0 Hz, 1H), 7.77-7.72 (m, 1H), 7.41-7.39 (m, 2H), 7.30-7.22 (m, 4H), 2.37 (s, 3H).

ESI-MS: Calcd for $C_{12}H_{12}N$ $(M+H)^+$: 170.1. Found: 170.4.

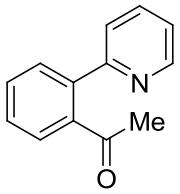



**2-(*o*-Anisyl)pyridine [5957-89-1].** The titled compound was prepared according to the general procedure A with *o*-anisyl boronic acid (91 mg, 0.60 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^{o}$C for 5 min. The conversion of heteroaryl tosylate was determined by GC: 5 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:25) as eluent, the titled compound was isolated as light yellow solid (88 mg, 95% yield).

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.70 (d, *J* = 4.8 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.76 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.73-7.69 (m, 1H), 7.38-7.35 (m, 1H), 7.21-7.18 (m, 1H), 7.10-7.06 (m, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 3.86 (s, 3H).

ESI-MS: Calcd for $C_{12}H_{12}NO$ $(M+H)^+$: 186.1. Found: 186.2.

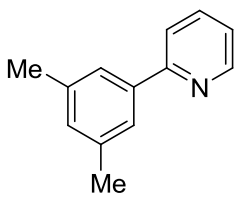



**2-(2-pyridyl)acetophenone [137103-78-7].** The titled compound was prepared according to the general procedure A with 2-acetylphenyl boronic acid (123 mg, 0.75 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^o$C for 2 h. The conversion of heteroaryl tosylate was determined by GC: 5 min, 5%; 15 min, 32%; 1 h, 81%; 2 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:10 to 1:3) as eluent, the titled compound was isolated as white solid (94 mg, 95% yield).

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, *J* = 4.5 Hz, 1H), 7.80-7.76 (m, 1H), 7.63-7.45 (m, 5H), 7.28-7.26 (m, 1H), 2.23 (s, 3H).

ESI-MS: Calcd for $C_{13}H_{11}NO$ $(M+H)^+$: 198.1. Found: 198.2.



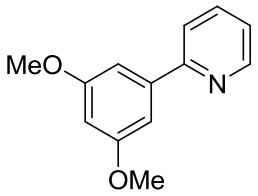

**1,3-Dimethyl-5-(2-pyridyl)benzene [1101187-10-3].** The titled compound was prepared according to the general procedure A with 3,5-dimethylphenyl boronic

acid (90 mg, 0.60 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^{o}$C for 15 min. The conversion of heteroaryl tosylate was determined by GC: 5 min, 84%; 15 min, 95%.

After purification by flash chromatography using ethyl acetate/hexane (1:30) as eluent, the titled compound was isolated as yellow oil (87 mg, 95% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.68 (d, *J* = 4.8 Hz, 1H), 7.73-7.69 (m, 2H), 7.60 (s, 2H), 7.22-7.19 (m, 1H), 7.06 (s, 1H), 2.40 (s, 6H).

ESI-MS: Calcd for $C_{13}H_{14}N$ $(M+H)^{+}$: 184.1. Found: 184.3.

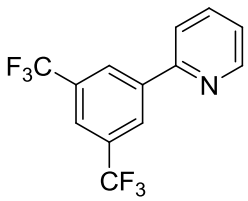



**1,3-Dimethoxy-5-(2-pyridyl)benzene [1189375-65-2].** The titled compound was prepared according to the general procedure A with 3,5-dimethoxyphenyl boronic acid (109 mg, 0.60 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^{o}$C for 15 min. The conversion of heteroaryl tosylate was determined by GC: 5 min, 85%; 15 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:30 to 1:20) as eluent, the titled compound was isolated as colorless oil (104 mg, 96% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.69 (d, *J* = 4.0, Hz, 1H), 7.74-7.69 (m, 2H), 7.25-7.23 (m, 1H), 7.16 (d, *J* = 2.4 Hz, 2H), 6.54 (t, *J* = 2.0, 2.0 Hz, 1H), 3.88 (s, 6H).

ESI-MS: Calcd for $C_{13}H_{14}NO_2$ $(M+H)^{+}$: 216.1. Found: 216.2.

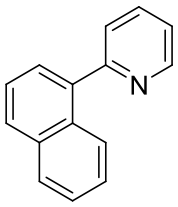


**1-(2-Pyridyl)-3,5-bis(trifluoromethyl)benzene [664989-77-9].** The titled compound was prepared according to the general procedure A with 3,5-bis(trifluoro -methyl)phenyl boronic acid (155 mg, 0.60 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^{o}$C for 15 min. The conversion of heteroaryl tosylate was determined by GC: 5 min, 29%; 15 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:30) as eluent, the titled compound was isolated as white solid (131 mg, 90% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.76-8.74 (m, 1H), 8.49 (s, 2H), 7.92 (s, 1H), 7.87-7.80 (m, 2H), 7.37-7.34 (m, 1H).

ESI-MS: Calcd for $C_{13}H_8F_6N$ $(M+H)^+$: 292.1. Found: 292.3.

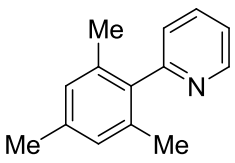



**2-(1-Naphthyl)pyridine [76759-26-7].** The titled compound was prepared according to the general procedure A with 1-naphthyl boronic acid (103 mg, 0.60 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^{o}$C for 5 min. The conversion of heteroaryl tosylate was determined by GC: 5 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:30 to 1:25) as eluent, the titled compound was isolated as light yellow oil (99 mg, 96% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.79 (d, $J$ = 4.8 Hz, 1H), 8.08 (d, $J$ = 7.6 Hz, 1H), 7.91 (d, $J$ = 8.3 Hz, 2H), 7.84-7.80 (m, 1H), 7.61-7.45 (m, 5H), 7.35-7.31 (m, 1H).

ESI-MS: Calcd for $C_{15}H_{11}N$ $(M+H)^+$: 206.1. Found: 206.4.

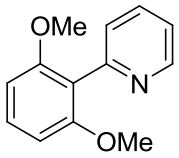


**2-Mesitylpyridine [75722-64-4].** The titled compound was prepared according to the general procedure A with 2-mesityl boronic acid (98 mg, 0.60 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 80 $^{o}$C for 5 min. The conversion of heteroaryl tosylate was determined by GC: 5 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:15) as eluent, the titled compound was isolated as colorless oil (95 mg, 96% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.71-8.70 (m, 1H), 7.75-7.71 (m, 1H), 7.26-7.21 (m, 2H), 6.92 (s, 2H), 2.32 (s, 3H), 2.01 (s, 6H).

ESI-MS: Calcd for $C_{14}H_{16}N$ $(M+H)^{+}$: 198.1. Found: 198.2.

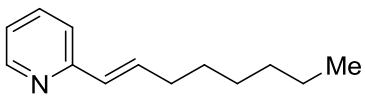



**1,3-Dimethoxy-2-(2-pyridyl)benzene [98061-25-7].** The titled compound was prepared according to the general procedure A with 2,6-dimethoxyphenyl boronic acid (137 mg, 0.75 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 80 $^{o}$C for 15 min. The conversion of heteroaryl tosylate was determined by GC: 5 min, 94%; 15 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:5 to 1:1) as eluent, the titled compound was isolated as yellow oil (105 mg, 98% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.73 (d, *J* = 4.9 Hz, 1H), 7.73-7.70 (m, 1H), 7.34-7.29 (m, 2H), 7.24-7.21 (m, 1H), 6.65 (d, *J* = 8.4 Hz, 2H), 3.73 (s, 6H).

ESI-MS: Calcd for $C_{13}H_{14}NO_2$ $(M+H)^{+}$: 216.1. Found: 216.2.

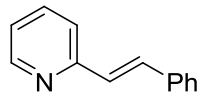



**(*E*)-2-(1-Octenyl)pyridine [102312-86-7].** The titled compound was prepared according to the general procedure A with (*E*)-1-octenyl boronic acid (94 mg, 0.60 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 25 $^{o}$C for 1 h. The conversion of heteroaryl tosylate was determined by GC: 5 min, 73%; 15 min, 89%; 1 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:25) as eluent, the titled compound was isolated as colorless oil (86 mg, 91% yield).

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.52 (d, *J* = 4.8 Hz, 1H), 7.60-7.56 (m, 1H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.07 (dd, *J* = 7.2, 4.8 Hz, 1H), 6.78-6.70 (doublet of triplet, *J* = 15.7, 7.0 Hz 1H), 6.50-6.46 (d, *J* = 15.7 Hz, 1H), 2.22-2.16 (pseudoquartet, *J* = 7.0 Hz, 2H), 1.47-1.39 (pseudoquintet, *J* = 7.0 Hz, 2H), 1.32-1.21 (m, 6H), 0.83-0.80 (t, *J* = 7.0 Hz, 3H).

ESI-MS: Calcd for $C_{13}H_{19}N$ $(M+H)^+$: 190.2. Found: 190.2.



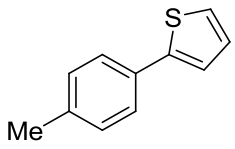

**2-(*E*)-Styrylpyridine [538-49-8].** The titled compound was prepared according to the general procedure A with (*E*)-styryl boronic acid (111 mg, 0.75 mmol) and 2-pyridyl *p*-toluenesulfonate (125 mg, 0.50 mmol) at 80 $^o$C for 5 min. The conversion of heteroaryl tosylate was determined by GC: 5 min, 93% (conversion at 25 $^o$C: 20 h, 94%).

After purification by flash chromatography using ethyl acetate/hexane (1:20) as eluent, the titled compound was isolated as white solid (84 mg, 93% yield).

$^1$H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, *J* = 4.1 Hz, 1H), 7.69-7.58 (m, 4H), 7.40-7.36 (m, 3H), 7.32-7.28 (m, 1H), 7.20-7.13 (m, 2H).

ESI-MS: Calcd for $C_{13}H_{11}N$ $(M+H)^+$: 182.1. Found: 182.4.

Suzuki Coupling of 2-Thiophene Tosylate with Various Arylboronic Acids and Alkenylboronic Acids



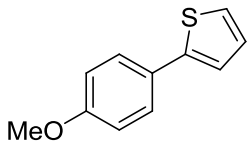

**2-(*p*-Tolyl)thiophene [16939-04-1].** The titled compound was prepared according to the general procedure with *p*-tolyl boronic acid (82 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^o$C for 5 min. The

conversion of heteroaryl tosylate was determined by $^1$H NMR spectroscopy: 5 min, 100%.

After purification by flash chromatography using hexane as eluent, the titled compound was isolated as white solid (78 mg, 90% yield).

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.1 Hz, 2H), 7.27-7.24 (m, 2H), 7.19 (d, *J* = 8.1, 2H), 7.07 (dd, *J* = 5.1, 3.6 Hz, 1H), 2.36 (s, 3H).

EI-MS: Calcd for $C_{11}H_{10}S$ $M^+$: 174.1. Found: 174.0.

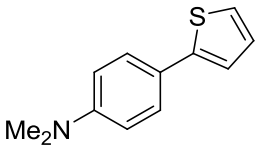



**2-(p-Anisyl)thiophene [42545-43-7].** The titled compound was prepared according to the general procedure with *p*-anisyl boronic acid (91 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^o$C for 5 min. The conversion of heteroaryl tosylate was determined by $^1$H NMR spectroscopy: 5 min, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:50) as eluent, the titled compound was isolated as white solid (86 mg, 90% yield).

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.55-7.53 (m, 2H), 7.22-7.19 (m, 2H), 7.06 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.93-6.91 (m, 2H), 3.84 (s, 3H).

EI-MS: Calcd for $C_{11}H_{10}OS$ $(M+H)^+$: 190.05. Found: 190.20.

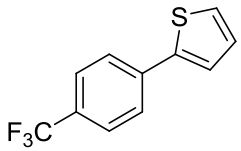



***N,N*-Dimethyl-4-(2-thienyl)aniline [88613-62-1].** The titled compound was prepared according to the general procedure with 4-(dimethylamino)phenyl boronic acid (99 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^o$C for 15 min. The conversion of heteroaryl tosylate was determined by $^1$H NMR spectroscopy: 5 min, 87%; 15 min, 96%.

After purification by flash chromatography using hexane as eluent, the titled compound was isolated as white solid (94 mg, 92% yield).

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.50-7.48 (m, 2H), 7.16-7.15 (m, 2H), 7.04-7.02 (m, 1H), 6.74-6.72 (m, 2H), 2.98 (s, 6H).

ESI-MS: Calcd for $C_{12}H_{14}NS$ $(M+H)^+$: 204.08. Found: 204.13.

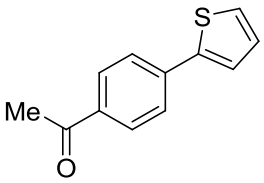



**1-(2-Thienyl)-4-(trifluoromethyl)benzene [115933-15-8].** The titled compound was prepared according to the general procedure with 4-(trifluoromethyl)phenyl boronic acid (114 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^o$C for 5 min. The conversion of heteroaryl tosylate was determined by $^1$H NMR spectroscopy: 5 min, 94%.

After purification by flash chromatography using ethyl acetate/hexane (1:30) as eluent, the titled compound was isolated as white solid (113 mg, 99% yield).

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.0 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.40 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.36 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.12 (dd, *J* = 5.2, 3.6 Hz, 1H).

EI-MS: Calcd for $C_{11}H_9F_3S$ $M^+$: 228.0. Found: 227.9.

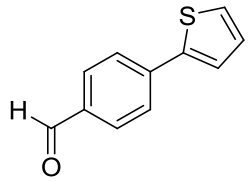



**4-(2-Thienyl)acetophenone [35294-37-2].** The titled compound was prepared according to the general procedure with 4-acetylphenyl boronic acid (98 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^o$C for 15 min. The conversion of heteroaryl tosylate was determined by $^1$H NMR spectroscopy: 5 min, 83%; 15 min, 94%.

After purification by flash chromatography using ethyl acetate/hexane (1:20 to 1:10) as eluent, the titled compound was isolated as white solid (95 mg, 94% yield).

$^1$H NMR (400 MHz, $CDCl_3$): δ 7.98-7.96 (m, 2H), 7.71-7.69 (m, 2H), 7.43 (dd, *J* = 3.6, 1.1 Hz, 1H), 7.37 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.12 (dd, *J* = 5.1, 3.6 Hz, 1H), 2.62 (s, 3H).

ESI-MS: Calcd for $C_{12}H_{11}OS$ $(M+H)^+$: 203.05. Found: 203.11.

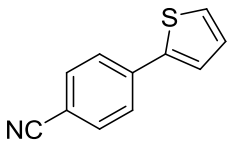



**4-(2-Thienyl)benzaldehyde [107834-03-7].** The titled compound was prepared according to the general procedure with 4-formylphenyl boronic acid (90 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^o$C for 5 h. The conversion of heteroaryl tosylate was determined by $^1$H NMR spectroscopy: 5 min, 19%; 15 min, 34%; 1 h, 64%; 5 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:20) as eluent, the titled compound was isolated as white solid (94 mg, 99% yield).

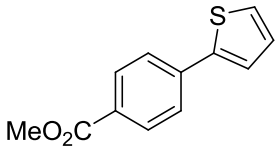
$^1$H NMR (400 MHz, $CDCl_3$): δ 10.01 (s, 1H), 7.90-7.88 (m, 2H), 7.78-7.76 (m, 2H), 7.47 (dd, *J* = 4.0, 1.2 Hz, 1H), 7.40 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.14 (dd, *J* = 5.2, 4.0 Hz, 1H).

EI-MS: Calcd for $C_{11}H_9OS$ $M^+$: 188.0. Found: 188.0.




**4-(2-Thienyl)benzonitrile[15961-46-3].** The titled compound was prepared according to the general procedure with 4-cyanophenyl boronic acid (88 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^o$C for 1 h. The conversion of heteroaryl tosylate was determined by $^1$H NMR spectroscopy: 5 min, 76%; 15 min, 94%; 1 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:20) as eluent, the titled compound was isolated as white solid (90 mg, 98% yield).

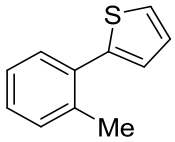



**Methyl 4-(2-thienyl)benzoate[17595-86-7].** The titled compound was prepared according to the general procedure with 4-(methoxycarbonyl)phenyl boronic acid (108 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^{o}$C for 15 min. The conversion of heteroaryl tosylate was determined by $^{1}$H NMR spectroscopy: 5 min, 91%; 15 min, 98%.

After purification by flash chromatography using ethyl acetate/hexane (1:20) as eluent, the titled compound was isolated as white solid (103 mg, 94% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.05-8.03 (m, 2H), 7.69-7.67 (m, 2H), 7.42 (dd, *J* = 3.6, 1.0 Hz, 1H), 7.37 (dd, *J* = 5.1, 1.0 Hz, 1H), 7.12 (dd, *J* = 5.1, 3.6 Hz, 1H), 3.93 (s, 3H).

EI-MS: Calcd for $C_{12}H_{10}O_2S$ $M^+$: 218.0. Found: 217.9.

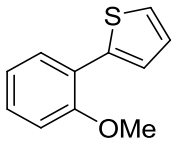



**2-(*o*-Tolyl)thiophene [99846-56-7].** The titled compound was prepared according to the general procedure with o-tolyl boronic acid (82 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^{o}$C for 15 min. The conversion of heteroaryl tosylate was determined by $^{1}$H NMR spectroscopy: 5 min, 91%; 15 min, 98%.

After purification by flash chromatography using hexane as eluent, the titled compound was isolated as colorless oil (81 mg, 93% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.41-7.39 (m, 1H), 7.33-7.32 (m, 1H), 7.25-7.21 (m, 3H), 7.09-7.05 (m, 2H), 2.42 (s, 3H).

EI-MS: Calcd for $C_{11}H_{10}S$ $M^+$: 174.1. Found: 174.0.

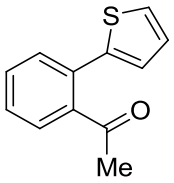



**2-(*o*-Anisyl)thiophene [17595-92-5].** The titled compound was prepared according to the general procedure with *o*-anisyl boronic acid (91 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^{o}$C for 5 min. The conversion of heteroaryl tosylate was determined by $^{1}$H NMR spectroscopy: 5 min, 96%.

After purification by flash chromatography using ethyl acetate/hexane (1:30) as eluent, the titled compound was isolated as light yellow oil (86 mg, 91% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.65 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.50 (d, *J* = 3.7 Hz, 1H), 7.33 (d, *J* = 5.1 Hz, 1H), 7.27 (doublet of pseudotriplet, *J* = 7.5, 1.6 Hz, 1H), 7.09 (dd, *J* = 5.1, 3.7 Hz, 1H), 7.02-6.98 (m, 2H), 3.94 (s, 3H).

ESI-MS: Calcd for $C_{11}H_{11}OS$ $(M+H)^{+}$: 191.05. Found: 191.20.




**2-(2-Thienyl)acetophenone [893739-40-7].** The titled compound was prepared according to the general procedure with 2-acetylphenyl boronic acid (98 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^{o}$C for 1 h. The conversion of heteroaryl tosylate was determined by $^{1}$H NMR spectroscopy: 5 min, 73%; 15 min, 81%; 1 h, 96%.

After purification by flash chromatography using ethyl acetate/hexane (1:20) as eluent, the titled compound was isolated as white solid (100 mg, 99% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.48-7.46 (m, 3H), 7.42-7.39 (m, 2H), 7.08 (dd, *J* = 4.8, 3.2 Hz, 1H), 7.00 (dd, *J* = 3.6, 0.8 Hz, 1H), 2.14 (s, 3H).

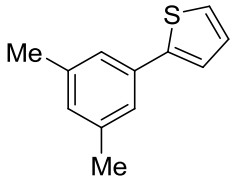
EI-MS: Calcd for $C_{12}H_{11}OS$ $M^{+}$: 202.0. Found: 201.4.


**2-(2-Thienyl)benzaldehyde [99902-07-5].** The titled compound was prepared according to the general procedure with 2-formylphenyl boronic acid (90 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^{o}$C for 5 h. The conversion of heteroaryl tosylate was determined by $^{1}$H NMR spectroscopy: 5 min, 30%; 15 min, 51%; 1 h, 72%; 5 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:20) as eluent, the titled compound was isolated as yellow oil (95 mg, 99% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 10.19 (s, 1H), 8.02 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.62 (doublet of pseudotriplet, *J* = 7.7, 1.3 Hz, 1H), 7.55 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.50(d, *J* = 7.7 Hz, 1H), 7.47 (dd, *J* = 5.1, 1.1 Hz, 1H) 7.16 (dd, *J* = 5.1, 3.6 Hz, 1H), 7.08 (dd, *J* = 3.6, 1.1 Hz, 1H).

ESI-MS: Calcd for $C_{11}H_8OS$ $(M+H)^+$: 189.03. Found: 189.10.

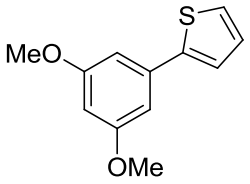



**1,3-Dimethylphenyl-5-(2-thienyl)benzene [1070403-62-1].** The titled compound was prepared according to the general procedure with 3,5-dimethylphenyl boronic acid (90 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^{o}$C for 1 h. The conversion of heteroaryl tosylate was determined by $^{1}$H NMR spectroscopy: 5 min, 83%; 15 min, 95%; 1 h, 100%.

After purification by flash chromatography using hexane as eluent, the titled compound was isolated as colorless oil (89 mg, 95% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.28-7.24 (m, 4H), 7.07-7.05 (m, 1H), 6.93 (s, 1H), 2.35 (s, 6H).

EI-MS: Calcd for $C_{12}H_{12}S$ $M^+$: 188.1. Found: 188.0.



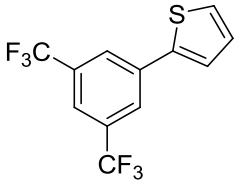

**1,3-Dimethoxy-5-(2-thienyl)benzene [1335213-07-4].** The titled compound was prepared according to the general procedure with 3,5-dimethoxy -phenyl boronic acid (109 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^{o}$C for 1 h. The conversion of heteroaryl tosylate was determined by $^{1}$H NMR spectroscopy: 5 min, 90%; 15 min, 92%; 1 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:20) as eluent, the titled compound was isolated as colorless oil (105 mg, 95% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.30 (dd, *J* = 3.6, 1.1 Hz, 1H), 7.28 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.07 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.77 (d, *J* = 2.2 Hz, 2H), 6.42 (t, *J* = 2.2 Hz, 1H), 3.84 (s, 6H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ 161.1, 144.3, 136.3, 127.9, 124.9, 123.5, 104.4, 99.6, 55.4.

ESI-MS: Calcd for $C_{12}H_{12}SO_2$ $(M+H)^+$: 221.06. Found: 221.17.

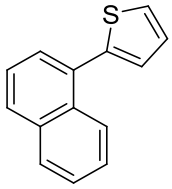



**1-(2-Thienyl)-3,5-bis(trifluoromethyl)benzene [460743-68-4].** The titled compound was prepared according to the general procedure with 3,5-bis(trifluoro -methyl)phenyl boronic acid (155 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^{o}$C for 5 min. The conversion of heteroaryl tosylate was determined by $^{1}$H NMR spectroscopy: 5 min, 100%.

After purification by flash chromatography using hexane as eluent, the titled compound was isolated as yellow solid (136 mg, 93% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.99 (s, 2H), 7.76 (s, 1H), 7.44 (dd, *J* = 3.6, 1.1 Hz, 1H), 7.42 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.15 (dd, *J* = 5.1, 3.6 Hz, 1H).

EI-MS: Calcd for $C_{12}H_7F_6S$ $M^+$: 296.0. Found: 296.0.

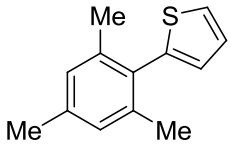



**2-(1-Naphthyl)thiophene [4632-51-3].** The titled compound was prepared according to the general procedure with 1-naphthyl boronic acid (103 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^{o}$C for 5 min. The conversion of heteroaryl tosylate was determined by $^{1}$H NMR spectroscopy: 5 min, 100%.

After purification by flash chromatography using hexane as eluent, the titled compound was isolated as colorless oil (98 mg, 93% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.24-8.22 (m, 1H), 7.92-7.86 (m, 2H), 7.59-7.43 (m, 5H), 7.27-7.25 (m, 1H), 7.19 (dd, *J* = 5.2, 3.6 Hz, 1H).

EI-MS: Calcd for $C_{14}H_{10}S$ $M^{+}$: 210.0. Found: 210.2.

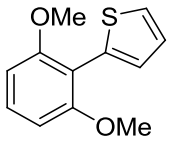



**2-Mesitylthiophene [920449-57-6].** The titled compound was prepared according to the general procedure with 2-mesityl boronic acid (98 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 80 $^{o}$C for 15 min. The conversion of heteroaryl tosylate was determined by $^{1}$H NMR spectroscopy: 5 min, 81%; 15 min, 100%.

After purification by flash chromatography using hexane as eluent, the titled compound was isolated as colorless oil (94 mg, 93% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.36 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.09 (dd, *J* = 5.2, 3.6 Hz, 1H), 6.93 (s, 2H), 6.80 (dd, *J* = 3.6, 1.2 Hz, 1H), 2.32 (s, 3H), 2.11 (s, 6 H).

EI-MS: Calcd for $C_{13}H_{14}S$ $M^{+}$: 202.1, Found: 202.0.

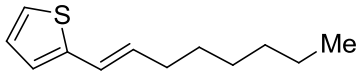



**1,3-Dimethoxy-2-(2-thienyl)benzene [30143-75-0].** The titled compound was prepared according to the general procedure with 2,6-dimethoxyphenyl boronic acid (137 mg, 0.75 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 80 $^{o}$C for 10 h. The conversion of heteroaryl tosylate was determined by $^{1}$H NMR spectroscopy: 5 min, 54%; 1 h, 72%; 5 h, 90%; 10 h, 100%.

After purification by flash chromatography using ethyl acetate/hexane (1:50) as eluent, the titled compound was isolated as white solid (109 mg, 99% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.40-7.36 (m, 2H), 7.25 (t, *J* = 8.3 Hz, 1H), 7.10 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.65 (d, *J* = 8.3 Hz, 2H), 3.83 (s, 6H).

ESI-MS: Calcd for $C_{12}H_{13}O_2S$ $(M+H)^+$: 221.06. Found: 221.15.

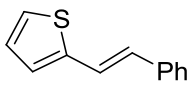



**(*E*)-2-(1-Octenyl)thiophene [109786-59-6].** The titled compound was prepared according to the general procedure with (*E*)-1-octenyl boronic acid (94 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 25 $^{o}$C for 5 h. The conversion of heteroaryl tosylate was determined by $^{1}$H NMR spectroscopy: 1 h, 86%; 5 h, 100%.

After purification by flash chromatography using hexane as eluent, the titled compound was isolated as colorless oil (90 mg, 93% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.07 (d, *J* = 4.8 Hz, 1H), 6.93 (dd, *J* = 5.2, 3.6 Hz, 1H), 6.86 (d, *J* = 3.2 Hz, 1H), 6.49 (d, *J* = 15.6 Hz, 1H), 6.07 (dt, *J* = 15.6, 7.1 Hz, 1H), 2.17 (pseudoquartet, *J* = 7.1 Hz, 2H), 1.43 (pseudoquintet, *J* = 7.6 Hz, 2H), 1.35-1.30 (m, 6H), 0.90 (t, *J* = 6.7 Hz, 3H).

EI-MS: Calcd for $C_{12}H_{18}S$ $M^+$: 194.1. Found: 194.0.



**(*E*)-2-Styrylthiophene [26708-50-9].** The titled compound was prepared according to the general procedure with (*E*)-styryl boronic acid (89 mg, 0.60 mmol) and 2-thienyl *p*-toluenesulfonate (127 mg, 0.50 mmol) at 80 $^{o}$C for 15 min. The conversion of heteroaryl tosylate was determined by $^{1}$H NMR spectroscopy: 5 min, 83%; 15 min, 100%.

After purification by flash chromatography using hexane as eluent, the titled compound was isolated as white solid (91 mg, 97% yield).

$^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 7.6 Hz, 2H), 7.35 (pseudotriplet, *J* = 7.6 Hz, 2H), 7.27-7.19 (m, 3H), 7.08 (d, *J* = 4.8 Hz, 1H), 7.02-7.00 (m, 1H), 6.94 (d, *J* = 16.0 Hz, 1H).

EI-MS: Calcd for $C_{12}H_{10}S$ $M^{+}$: 186.0. Found: 186.3.

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