CARBON–CARBON AND CARBON–HETEROATOM BOND FORMATION THROUGH C–H BOND FUNCTIONALIZATION

A Dissertation Presented to

the Faculty of the Department of Chemistry

University of Houston

In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

By

Thanh V Truong

August 2013

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ABSTRACT

Direct C–H bond functionalization provides an efficient route by allowing the construction of C – C bonds directly from C–H bonds. In this dissertation, methods using first-row transition metals as catalysts for C–H bond functionalization have been developed. Furthermore, protocols for direct arylation via benzyne intermediates have been demonstrated.

A number of first-row transition metal salts such as nickel, cobalt, and manganese chlorides have been shown to catalyze deprotonative dimerization of acidic arenes. Five- or six-membered ring heterocycles as well as electron-poor arenes can be dimerized under oxygen atmosphere when tetramethylpiperidine or dicyclohexylamide bases are employed.

An auxiliary-assisted, copper-catalyzed fluorination of benzoic derivative β-C-H bonds has been developed. The method employs silver(I) fluoride as fluorinating reagent, copper(I) iodide catalyst, and *N*-methylmorpholine oxidant. By optimizing conditions, mono- or di-fluorination can be achieved selectively. The method provides an efficient alternative for preparation of aryl fluorides.

An efficient method for base-promoted direct *C*-arylation of arenes such as heterocycles, alkynes, phenols, and anilines has been demonstrated. Under basic conditions, a variety of arenes can be arylated by aryl halides and aryl triflates. A variety of functional groups, such as alkene, ether, dimethylamino, trifluoromethyl, ester, cyano, halide, hydroxyl, ketone, and silyl are tolerated. The reactions are carried out at mild temperatures and proceed via aryne intermediates. In addition, a general method for

trapping aryl lithium intermediates with various electrophiles has been described. Furthermore, new reaction between phenols and aryl halides forming helicenes has been discovered.

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LIST OF ABBREVIATIONS

Ac	acetyl
acac	acetylacetone
Alk	alkyl
Ar	aryl
Bn	benzyl
Bu	butyl
Bz	benzoyl
Cy	cyclohexyl
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMA	dimethylacetamide
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
Et	ethyl
L	ligand
Me	methyl
M	metal
NMR	nuclear magnetic resonance
OTf	triflate
Ph	phenyl

Phen	phenanthroline
Piv	pivaloyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
BINAPH	1,1′-binaphthyl-2,2′-diamine
BINOL	1,1'-bi-2-naphthol
TBAF	tetra-n-butylammonium fluoride
*m*CPBA	*meta*-chloroperoxybenzoic acid
PET	positron emission tomography
NMO	*N*-methylporpholine oxide
Pr	propyl
THF	tetrahydrofuran
Et_2O	diethyl ether
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
Ts	tosyl
RT	room temperature
N-FTPT	*N*-fluoro-2,4,6-trimethylpyridinium triflate
TMPH	2,2,6,6-tetramethylpiperidine
LDA	lithium diisopropyl amide
Cy_2NLi	lithium dicyclohexyl amide

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LIST OF RELATED PUBLICATIONS

1. Truong, T.; Alvarado, J.; Tran, L. D.; Daugulis, O. "Nickel, Manganese, Cobalt and Iron-Catalyzed Deprotonative Arene Dimerization" *Org. Lett.* **2010**, *12*, 1200.

2. Truong, T.; Daugulis, O. "Base-Mediated Intermolecular sp^2 C−H Bond Arylation via Benzyne Intermediates" *J. Am. Chem. Soc.* **2011**, *133*, 4243

3. Truong, T.; Daugulis, O. ''Transition-Metal-Free Alkynylation of Aryl Chlorides'' *Org. Lett.* **2011**, *13*, 4172

4. Truong, T.; Daugulis, O. ''Directed Functionalization of C-H Bonds: Now also *meta* Selective*''Angew. Chem. Int. Ed.* **2012**, *51*, 2.

5. Truong, T.; Daugulis, O.''Divergent Reaction Pathway for Phenol Arylation by Arynes: Synthesis of Helicenes and 2-Arylphenols''*Chem. Sci.* **2013**, *4*, 531

6. Truong, T.; Daugulis, O. ''Direct Intermolecular Aniline *Ortho*-Arylation via Benzyne Intermediates'' *Org. Lett.* **2012**, *14*, 5964.

7. Truong, T.; Klimovica, K.; Daugulis, O. ''Copper-Catalyzed, Directing Group-Assisted Fluorination of Arene and Heteroarene C-H Bonds'' *J. Am. Chem. Soc.* **2013**, *135*, 9342.

Chapter 1

Biaryl Formation Via Oxidative Homocoupling Reactions

1.1. Transition-metal Catalysis

1.1.1. Introduction

The potential applications of symmetrical bi- or polyaryls in optical materials, molecular devices, or organic conductors are well-recognized.[1] Traditional routes to access these molecules often suffer from disadvantages such as harsh conditions, low yields, and limited reaction scope.[2] Ullmann coupling is an example in which a stoichiometric reductant and high temperature are needed to obtain reasonable yields. Therefore, it is interesting to develop more convenient methods for polyaryl synthesis. Within this chapter, recent developments to construct symmetrical arenes using transition metal catalysts will be reviewed.

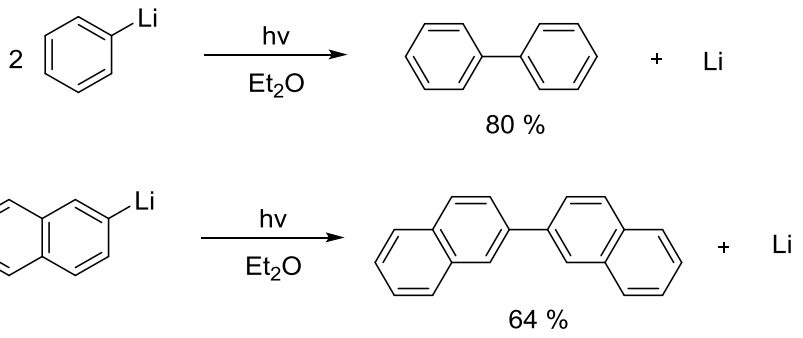
1.1.2. Homocoupling of Arenes

1.1.2.1. Homocoupling of Aryl Metals

Oxidative homocoupling of aryl–metal reagents has been extensively investigated.[3] A wide variety of transition metals such as palladium, copper, and iron have been used as catalysts in combination with various oxidants. Additionally, several other methods have also been disclosed for the formation of symmetrical biaryls from corresponding aryl Grignards.[3,4]

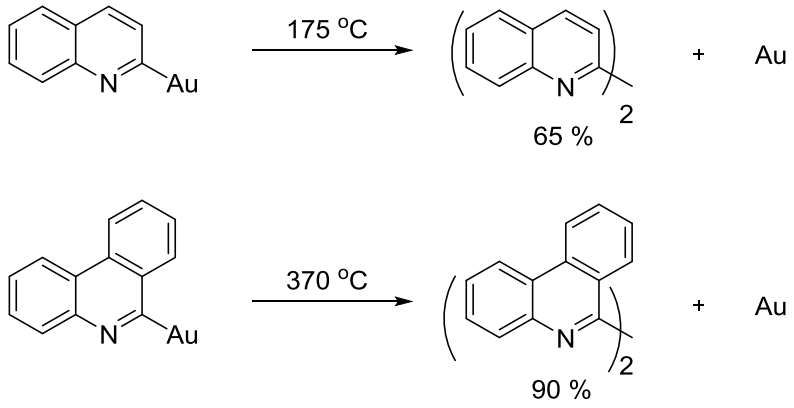
Ellis and co-workers reported the formation of biphenyl by irradiation of aryl lithium.[4] Under a high-pressure mercury arc lamp, 0.04 *M* solutions of phenyllithium in diethyl ether gave over 80% yield of biphenyl and metallic lithium. This coupling is regiospecific. 2-Naphthyllithium afforded exclusively 2,2’-binaphthyl. Only small amounts of products resulting from radical attack on solvent were detected.

Scheme 1.1. Biphenyl formation by irradiation of aryl lithium



Homocoupling of organogold species was also observed by Vaughan.[5] 2-Quinolylgold(I) was subjected to the pyrolysis conditions at high temperatures. Clean formation of 2,2'-biquinolyl was obtained. Similar transformations were reported with other quinolylgold(I) derivatives.

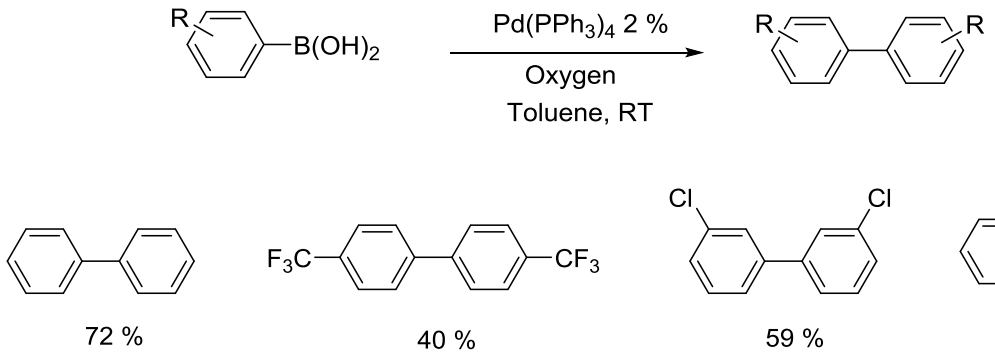
Scheme 1.2. Biaryl formation via organogold species



In 1996, Manas reported a method for symmetric biaryl formation from arylboronic acids under palladium catalysis. Reactions were conducted at room temperature and good yields were obtained with various arylboronic acids when oxygen was used as oxidant.[6] A palladium-catalyzed transformation using arylstannates as starting materials was also described.[7] The method employed a palladium-

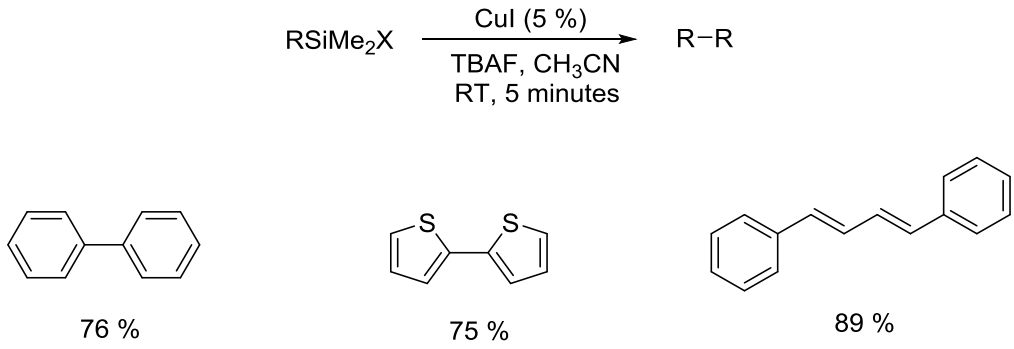
iminophosphine complex as catalyst, air as oxidant and reactions were run at elevated temperatures.

Scheme 1.3. Homocoupling of aryl boronic acids under palladium catalysis



Procedures using non-noble transition metals have been reported. Copper-catalyzed homocoupling of arylsilanes has been disclosed by the Kang group.[8] In the presence of tetrabutylamonium fluoride, a variety of aryl silanes can be efficiently dimerized at room temperature in 5-10 minutes.

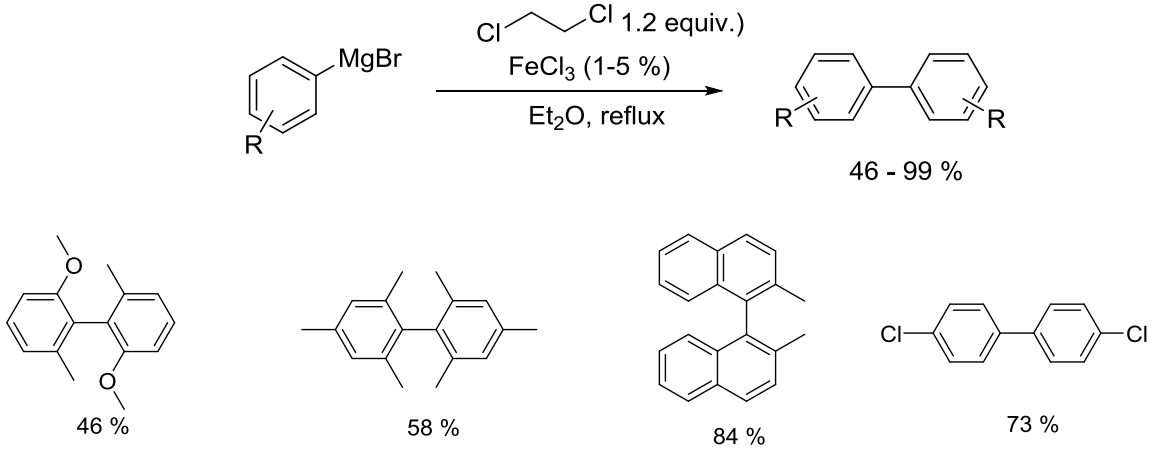
Scheme 1.4. Copper-catalyzed homocoupling of organosilicon compounds



The first catalytic system using iron as a catalyst for homocoupling of aryl grignard reagents was reported by Hayashi.[9] In the presence of 1-5 % $FeCl_3$ and stoichiometric amount of 1,2-dichloroethane oxidant, a variety of arylmagnesium

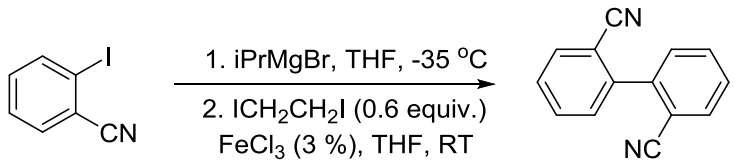
bromides were efficiently converted into the corresponding symmetrical biaryls in good yields.

Scheme 1.5. Iron-catalyzed dimerization of aryl Grignards



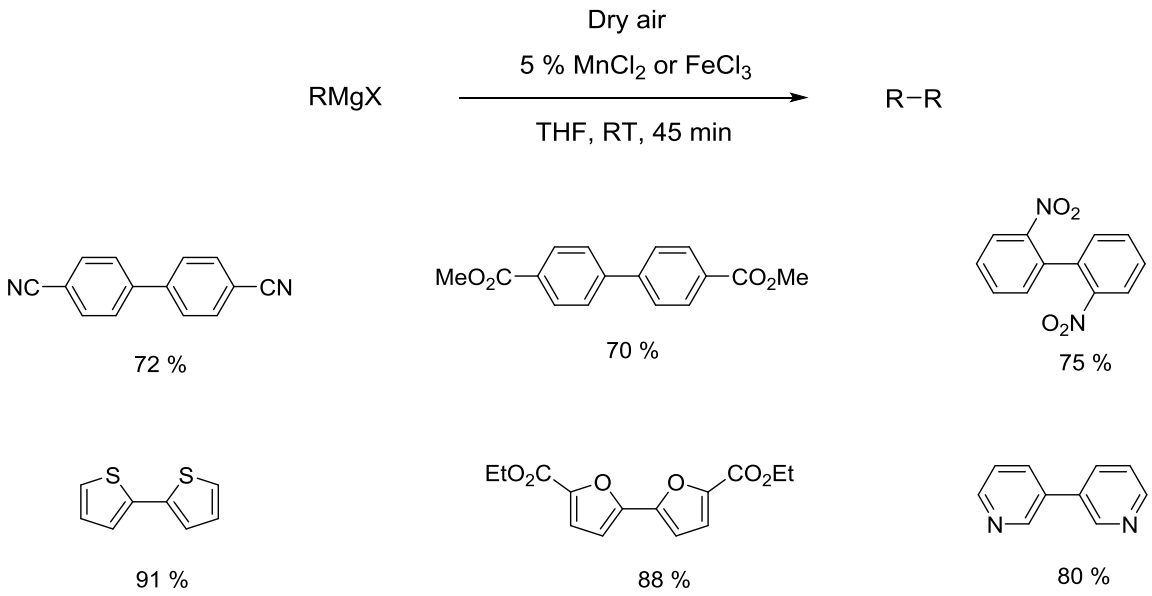
With minor modification in reaction conditions, Cahiez reported a more effient method applicable to wider scope of substates.[10] Aryl Grignards were synthesized *in situ* by treating corresponding aryl iodides with isopropylmagnesium bromide at low temperatures. However, these methods require a stoichiometric amount of organic oxidant.

Scheme 1.6. Iron-catalyzed homocoupling of aryl Grignard



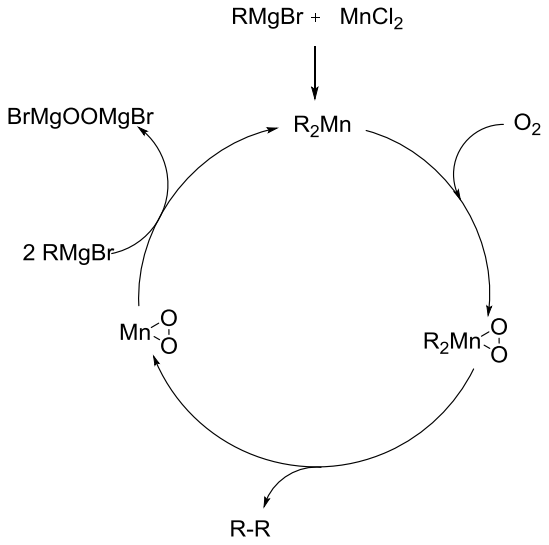
The efficient iron- and manganese-catalyzed procedures to couple aryl Grignard at mild conditions were reported by Cahiez in 2007.[11] For the first time, the method used atmospheric oxygen, an ideal oxidant for practical synthetic applications due to its availability and environmental friendliness.

Scheme 1.7. Homocoupling using atmospheric oxygen as oxidant



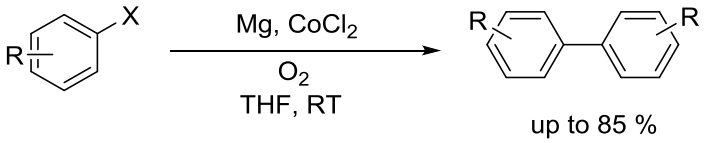
The reaction mechanism under manganese catalysis was proposed. The key step of this catalytic cycle is the conversion of the stable diorganomanganese (II) to a manganese (IV) peroxo complex. Rapid reductive elimination would give the homocoupling product and a manganese (II) peroxo complex which would react with the Grignard reagent to regenerate the diorganomanganese (II) species.

Scheme 1.8. Tentative mechanism for Mn-catalyzed dimerization under oxygen



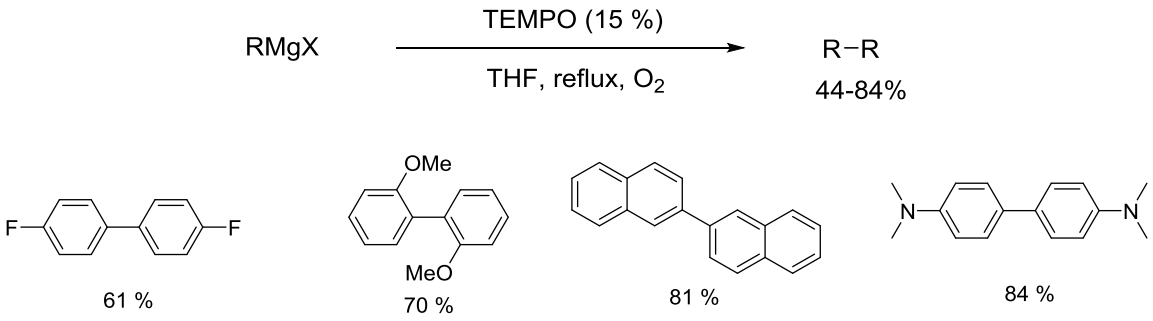
Grignard dimerization under cobalt catalysis is known.[12] In 2009, Yu reported an efficient procedure for cobalt-catalyzed homocoupling of aryl bromides in the presence of metallic magnesium. The method employed $CoCl_2$ as catalyst and oxygen as terminal oxidant.

Scheme 1.9. Homocoupling under cobalt catalysis



Transition-metal-free homocoupling reactions of various organomagnesium compounds in the presence of commercially available TEMPO as an organic oxidant have been developed.[13] The reactions could be conducted with 15 mol% of TEMPO by using dioxygen as the terminal oxidant.

Scheme 1.10. Dimerization of aryl Grignard with TEMPO catalyst under oxygen

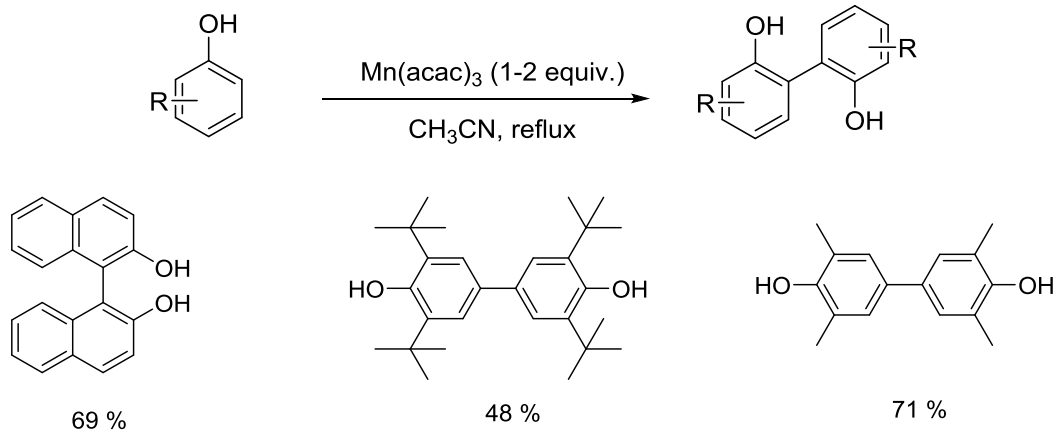


1.1.2.2. **Oxidative Homocoupling of Phenol and Aniline Derivatives**

From economic and environmental perspectives, the direct oxidative coupling of two aromatic rings should be an ideal method for the synthesis of biaryls.[3] The number of synthetic steps in the processes can be significantly reduced, further lowering production cost, and minimizing the amount of hazardous waste. Consequently, an increasing attention has been recently paid to direct oxidative homocoupling methodology.

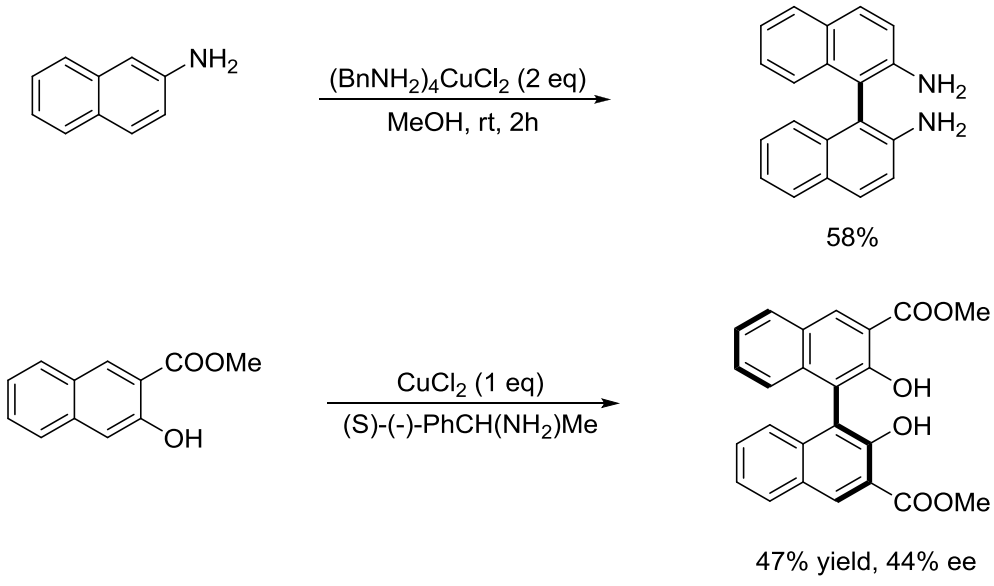
The oxidative coupling of phenols or anilines to dimeric products is a useful procedure which has found extensive applications in chemical synthesis. Nakaya and co-workers reported the first example of manganese-mediated directed dimerization of phenols in late 60s. [14]

Scheme 1.11. Mn-mediated phenol dimerization



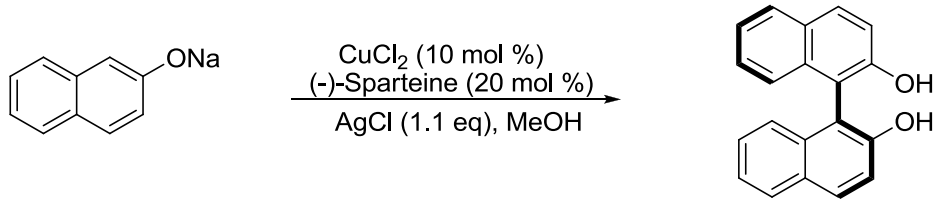
Methods employing other first-row transition metals such as copper have been described.[15] Specifically, Smrcina and co-workers have developed a facile synthesis of BINAPH by oxidation of 2-naphthylamine with $(BnNH_2)_4CuCl_2$ promoter. Reasonable enantioselectivity was obtained when chiral diamine ligands such as (-)-sparteine was used.[16] However, stoichiometric amount of metal was required.

Scheme 1.12. Copper-mediated dimerization of phenols and anilines



The first catalytic phenol homocoupling procedure was reported by Hovorka and co-workers. By using 10 % CuCl catalysts and stoichiometric AgCl oxidant, a variety of BINOLs were obtained in reasonable yields. [17]

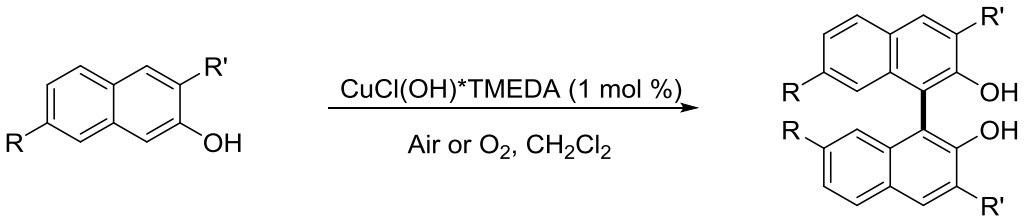
Scheme 1.13. Dimerization of 2-naphtholate under copper catalysis



70% yield, 3% ee

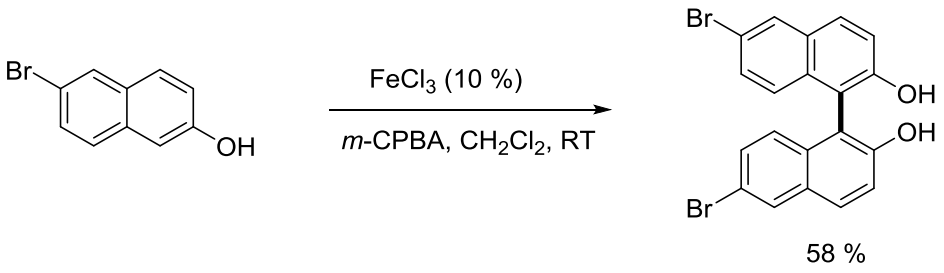
Further modifications of reaction conditions were investigated to avoid the use of silver oxidant. As a result, the first efficient catalytic process for oxidative homocoupling of naphthol derivatives using air as the terminal oxidant under ambient conditions was developed.[18]

Scheme 1.14. Copper-catalyzed dimerization of phenols under oxygen



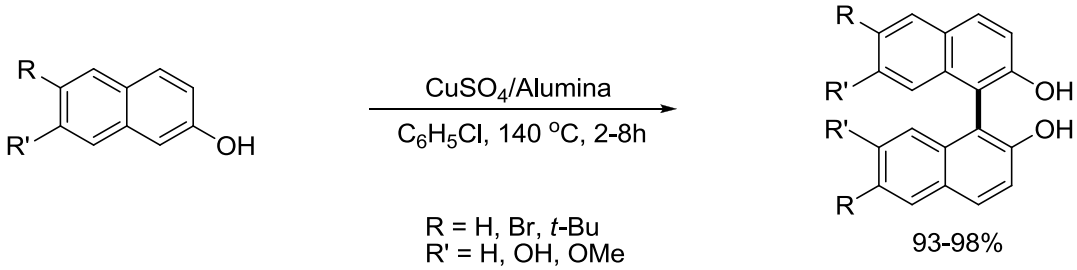
Moverever, Wang and co-workers disclosed the procedure for iron-catalyzed biaryl coupling of 2-naphthols using *meta*-chloroperbenzoic acid (*m*-CPBA) as sole oxidant.[19] Using simple workup procedues and mild conditions, reactions showed the potential for large-scale preparation.

Scheme 1.15. Iron-catalyzed homocoupling of naphthols using *m*-CPBA oxidant



Methods employing heterogeneous catalytic systems were also reported. High-yielding conditions for homocoupling of 2-naphthols using alumina-supported copper(II) sulfate under air were described. Interestingly, the catalysts can be recycled without significant degradation in catalytic activity by appropriate reactivation treatment after oxidation reactions.[20]

Scheme 1.16. Alumina-supported copper-catalyzed dimerization of phenols

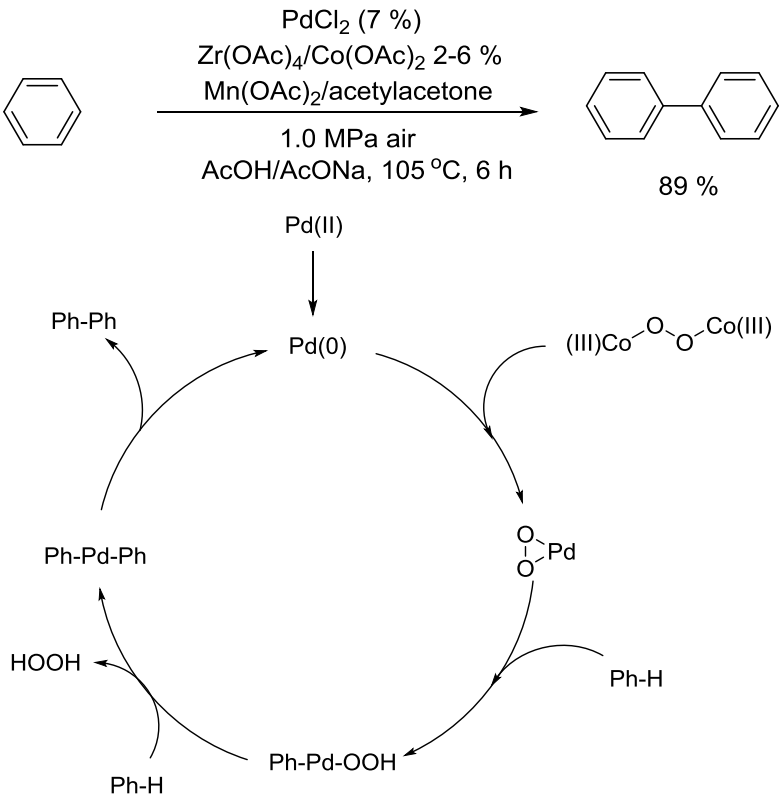


I.2.3 Oxidative Homocoupling of Arenes

In contrast with the dimerization of phenols and anilines, transition-metal-mediated oxidative homocoupling of common arenes is more challenging. Palladium-catalyzed dimerization of benzene has been described by employing high oxygen pressures and temperatures.[3] In particular, protocols for homocoupling of arenes under aerobic oxidation have also been described in the presence of $PdCl_2$ catalyst, $Zr(OAc)_4/Co(OAc)_2$/ $Mn(OAc)_2$/acetylacetone cocatalyst, and AcOH/AcONa.[21] The

authors suggested that a peroxocobalt(III) species, Co(III)-OO-Co(III), could be generated in this system, although the exact role of each metallic salt was unclear. Reaction of Pd(0) with this species could give a Pd(II)-peroxo complex. In this way, it is possible to regenerate the active palladium catalyst with a faster rate than the rate of aggregation of Pd(0) to form inactive palladium black.

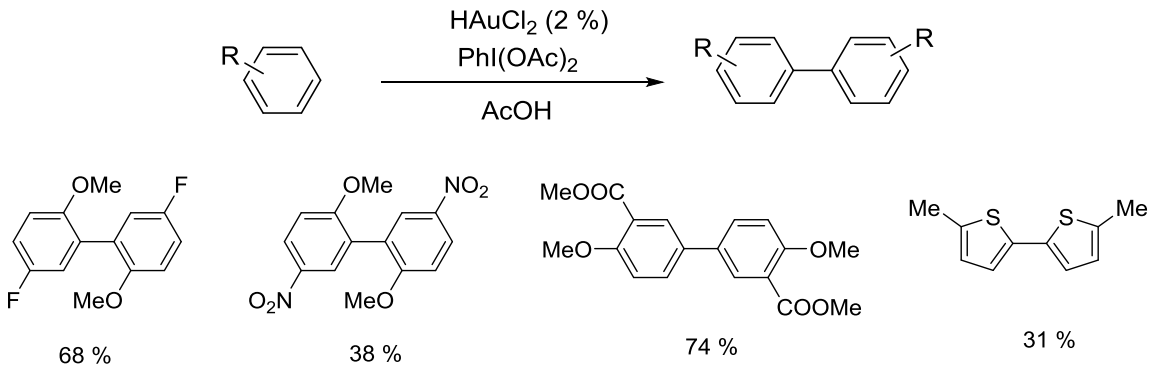
Scheme 1.17. Palladium-catalyzed homocoupling of arenes under aerobic oxidation



Gold could also be an efficient catalyst for the direct oxidative homocoupling of unactivated arenes in the presence of $PhI(OAc)_2$ oxidant.[22] In general, the reaction showed a typical electrophilic aromatic substitution pattern. It is worth mentioning that

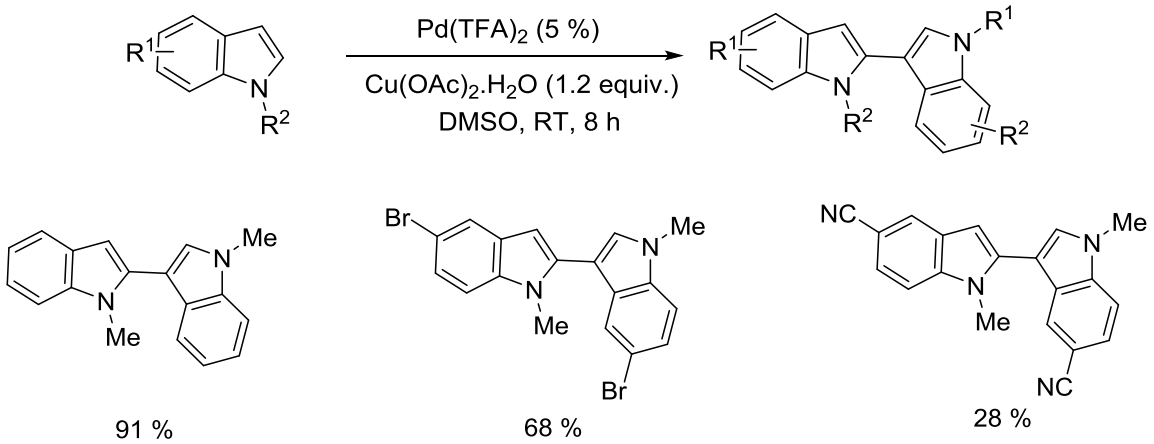
electron-rich heterocycles, such as thiophene, also gave the corresponding products in moderate yields. Remarkable functional group tolerance was observed.

Scheme 1.18. Dimerization of arenes under gold catalysis



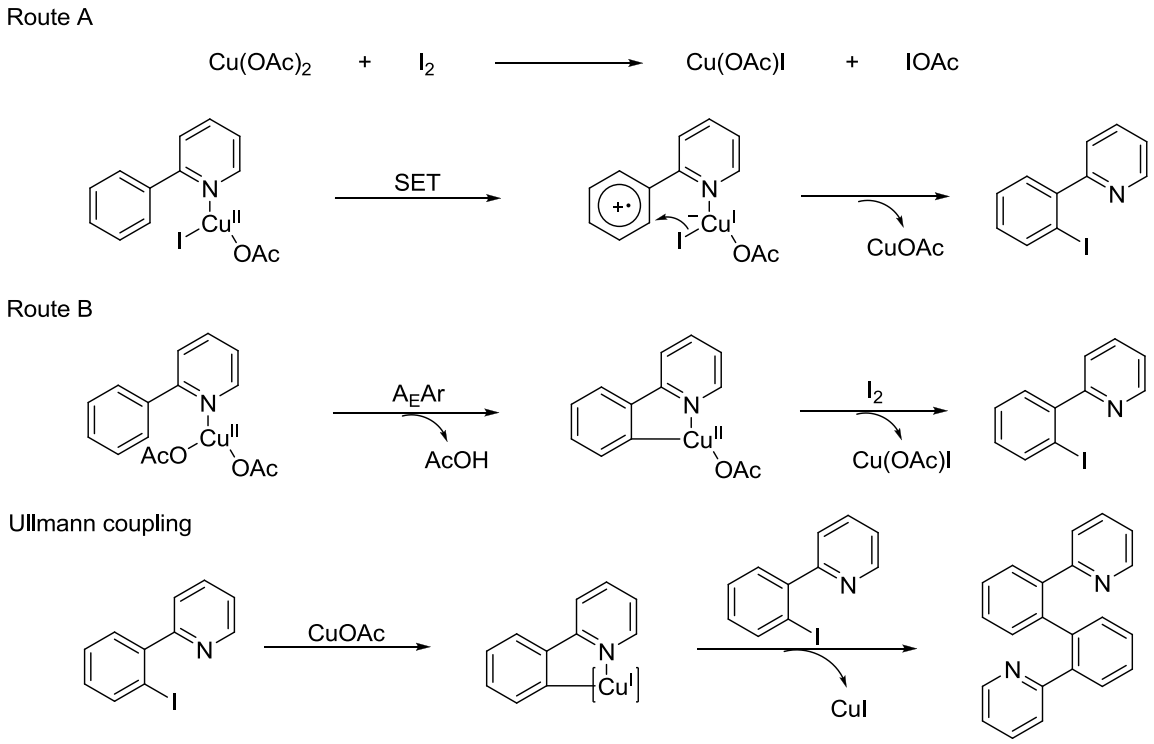
The unsymmetric homocouplings of indoles were performed affording dimers at C2- and C3-positions.[23] $Pd(OAc)_2$ (5 mol %) and 1.5 equiv of monohydrated $Cu(OAc)_2$ were the optimum catalyst and oxidant in DMSO, respectively. Indoles bearing electron-rich to weakly electron-poor substituents were converted to 2,3-biindolyls in moderate to high yields at room temperature.

Scheme 1.19. Unsymmetric homocouplings of indoles using palladium catalyst



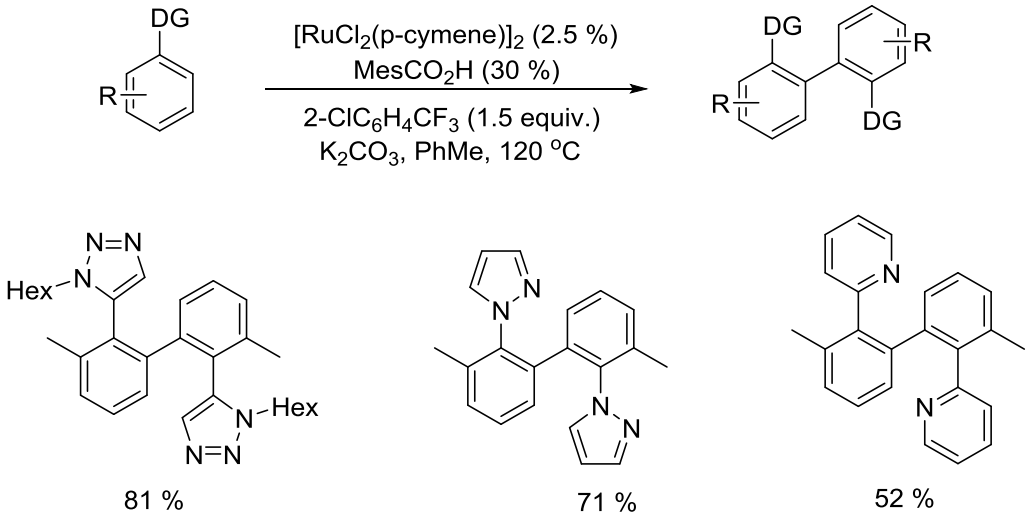
Recently, a method for copper-promoted homocoupling of 2-phenylpyridine was reported by the Yu group.[24] In the presence of iodine, various 2-phenylpyridine derivatives could couple to afford the dimeric products in reasonable yields. The iodinated intermediate is formed either by single electron transfer (route A) or electrophilic metalation/iodination process (route B). This intermediate was suggested to undergo Ullmann coupling to give the desired products.

Scheme 1.20. Proposed mechanisms for oxidative dimerization of 2-phenylpyridine



The same transformations were accomplished by employing ruthenium as the catalyst and $FeCl_3$ as the oxidant.[25] Homocouplings of arenes containing triazole- or pyrazole-directing groups have also been described.[26]

Scheme 1.21. Ruthemium-catalyzed, directing group assisted dimerization of arenes

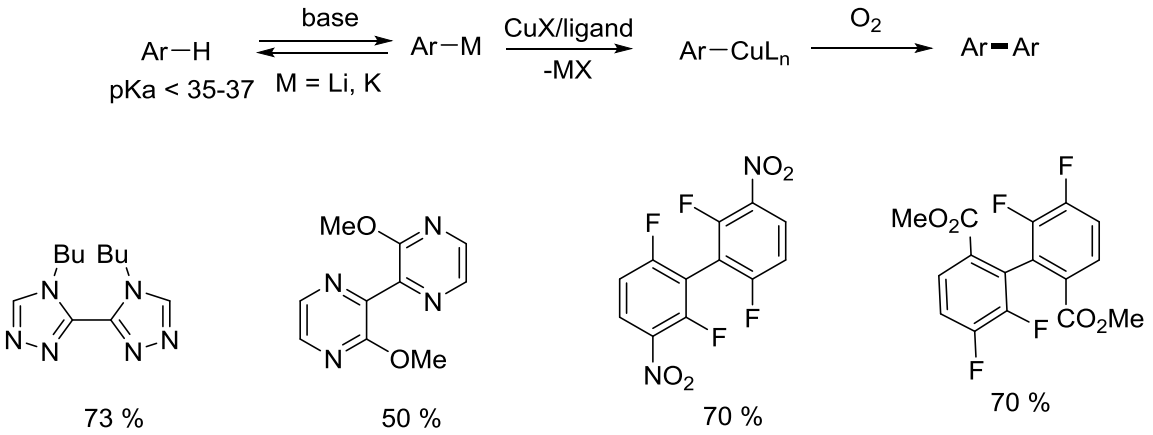


1.2. Nickel, Cobalt, and Manganese-catalyzed Deprotonative Arene Homocoupling

1.2.1. Introduction

Most of the existing biaryl synthesis including Ullmann reaction requires functionalized starting materials. Direct dimerization of non-functionalized aromatic compounds should be beneficial in term of synthetic efficiency. The presence of a stoichiometric oxidant is essential for successful arene dimerization due to unfavorable energetics of dehydrogenative coupling processes. Oxygen is an ideal oxidant for practical synthetic applications due to its availability and environmental friendliness.[27] Palladium-catalyzed arene dimerization by employing oxygen as the terminal oxidant is known.[3] Recently, our group described a method for copper-catalyzed, deprotonative arene dimerization by employing oxygen as the terminal oxidant.[28] By analogy with Glaser-Hay reaction, dimerization products were obtained under oxygen from an organocopper species formed by combination of *in situ* deprotonation and transmetallation.

Scheme 1.22. Copper-catalyzed dimerization of acidic arenes



It is known that dimerization of organometallic species can be catalyzed or promoted by non-noble transition metals such as Mn, Co, or Ni.[11,12,29] As a consequence, one should be able to perform the deprotonation/oxidative dimerization sequences by employing first-row transition metals other than copper, some of which may have advantages.

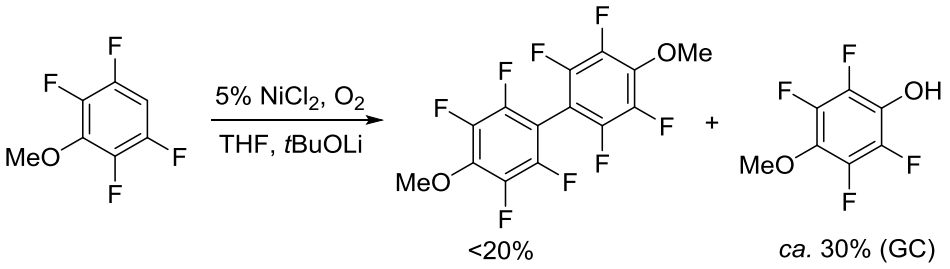
1.2.2. Results and Discussion

1.2.2.1. Nickel Catalysis

Our initial optimization focuses on developing procedure for nickel-catalyzed deprotonative dimerization. Major amounts of phenol byproduct were obtained upon reacting tetrafluoroanisole with lithium or potassium alkoxide bases and catalytic $NiCl_2$ under O_2 atmosphere. As observed in copper catalysis chemistry, phenol byproducts can be formed either by the direct reaction of arylalkali metal intermediate with oxygen or by reaction of a high-valent arylnickel with hydroxide derived from water.[30] Removing hydroxide from the reaction mixture, therefore, should prevent phenol formation. In addition, cations in less polarized carbon-metal bonds can tightly bind to hydroxide as

well as stabilize aryl carbanion resulting in slower reactions of arylmetal towards oxygen and water. As observed for copper-catalyzed dimerization, the best product yields were obtained by employing magnesium or zinc amide bases.

Scheme 1.23. Formation of phenol byproducts in dimerization

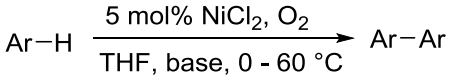


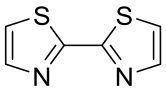
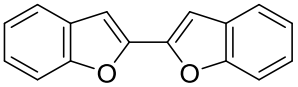
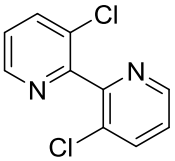
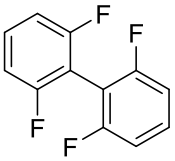
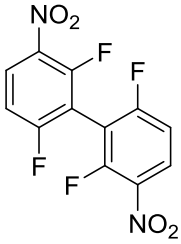
Magnesium tetramethylpiperidides were introducted by Eaton.[31] Numerous tetramethylpiperidide bases have been extensively investigated by Knochel for a variety of deprotonation/functionalization procedures.[32] The rationale for the use of base mixtures is as follows. Even though the basicity of zinc bases is weaker than that of magnesium bases, zinc amide bases afford more stable organometal intermediates avoiding phenol formation. Therefore, for functionalization of highly acidic or sensitive substrates, zinc bases are employed. For less acidic compounds, magnesium amide bases allow for a relatively rapid deprotonation. In most cases, a mixture of magnesium and zinc bases was employed. The optimal composition of the base depends on substrate. Four different bases were synthesized and employed in arene dimerization.

Scheme 1.24. Base sythesis

Base 1	iPrMgCl*LiCl + tetramethylpiperidine (1:1.05)	Base 3	Base 1 + $ZnCl_2$ (1:0.5)
Base 2	iPrMgCl*LiCl + dicyclohexylamine (1:1.05)	Base 4	Base 2 + $ZnCl_2$ (1:0.5)

Table 1.1. Dimerization under nickel catalysis



Entry	Arene, base	Product	Yield (%)
1	Thiazole base 1+base 3 (0.54/1)		83 71[b]
2	Benzofuran, base 1		45
3	3-Chloropyridine, base 1		53
4	1,3-Difluorobenzene, base 1+base 3 (2/1)		75 70[b]
5	2,4-Difluoronitro- benzene, base 3		73

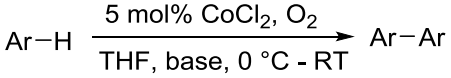
[a]Substrate (1 equiv), base (1.2-1.4 equiv). Yields are isolated yields. [b]Dicyclohexylamide base.

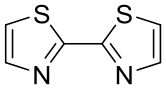
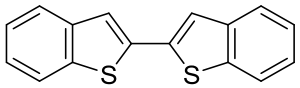
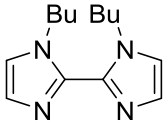
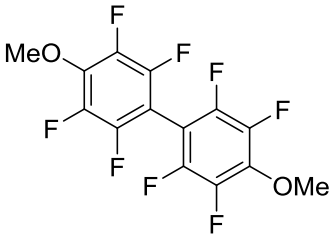
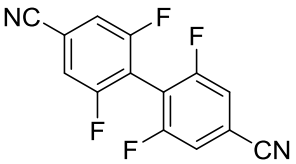
The results of dimerization reactions under nickel catalysis are shown in Table 1.1. The optimal procedure employs 5 mol % of $NiCl_2$ catalyst at 0-60 °C in THF solvent under 1 atm of oxygen. Electron-rich heterocycles such as thiazole (entry 1) and benzofuran (entry 2) can be dimerized in good yields. Six-membered ring heterocycles such as 3-chloropyridine are reactive affording the dimer in 33% yield (entry 3). Reactions are not limited to electron-deficient arenes. 1,3-Difluorobenzene and

difluoronitrobenzene (entries 4 and 5) are functionalized at the most acidic C-H bonds. In entries 1 and 4, cheaper dicyclohexylamide bases afford yields comparable to those using tetramethylpiperidides.

1.2.2.2. Cobalt Catalysis

Table 1.2. Dimerization under cobalt catalysis



Entry	Arene, base	Product	Yield (%)
1	Thiazole base 1+base 3 (0.8/1)		86 70[b]
2	Benzothiophene, base 1		85 78[b]
3	*n*-Butylimidazole, base 1		80
4	Tetrafluoroanisole, base 1+base 3 (7.3/1)		90 87[b]
5	3,5-difluorobenzonitrile, base 1+base 3(1/2)		80

[a]Substrate (1 equiv), base (1.2-1.7 equiv). Yields are isolated yields. [b]Dicyclohexylamide base.

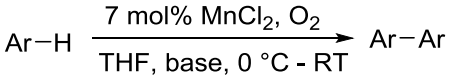
Cobalt salts are known to selectively catalyze dimerization of aryl Grignards.[12] As shown in Table 1.2, under conditions similar to the ones described for nickel**,** cobalt (II) chloride catalyzes arene deprotonative dimerization. The thiazole dimerization is possible affording the dimer in 86% yield (entry 1). Homocoupling of electron-rich

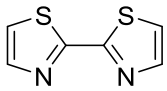
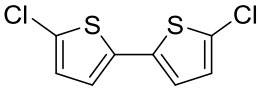
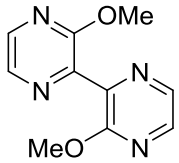
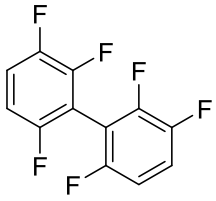
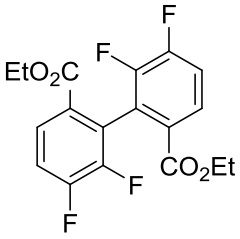
heterocycles such as benzothiophene (entry 2) and *N*-butylimidazole (entry 3) affords products in 85 % and 80 %, respectively. Electron-poor tetrafluoroanisole (entry 4) and difluorobenzonitrile (entry 5) can be dimerized in excellent yields. Entries 1, 2, and 4 were also run with dicyclohexylamide bases.

1.2.2.3. Manganese Catalysis

Dimerization of organomagnesium species can be catalyzed by employing manganese salts.[11] The use of manganese complexes for organic transformations is preferred because of its low toxicity. We show that manganese dichloride catalyzes deprotonative arene dimerization under an atmosphere of oxygen (Table 1.3). Thiazole and 2-chlorothiophene are reactive (entries 1 and 2). Six-membered-ring heterocycle methoxypyrazine is dimerized in an acceptable yield (entry 3). Homocoupling of electron-deficient arenes such as 1,2,4-trifluorobenzene and ethyl 3,4-difluorobenzoate afford products in good yields (entries 4 and 5). As shown in entries 1, 4, and 5, cheaper dicyclohexylamide is almost as efficient as the tetramethylpiperidide base.

Table 1.3. Dimerization under manganese catalysis

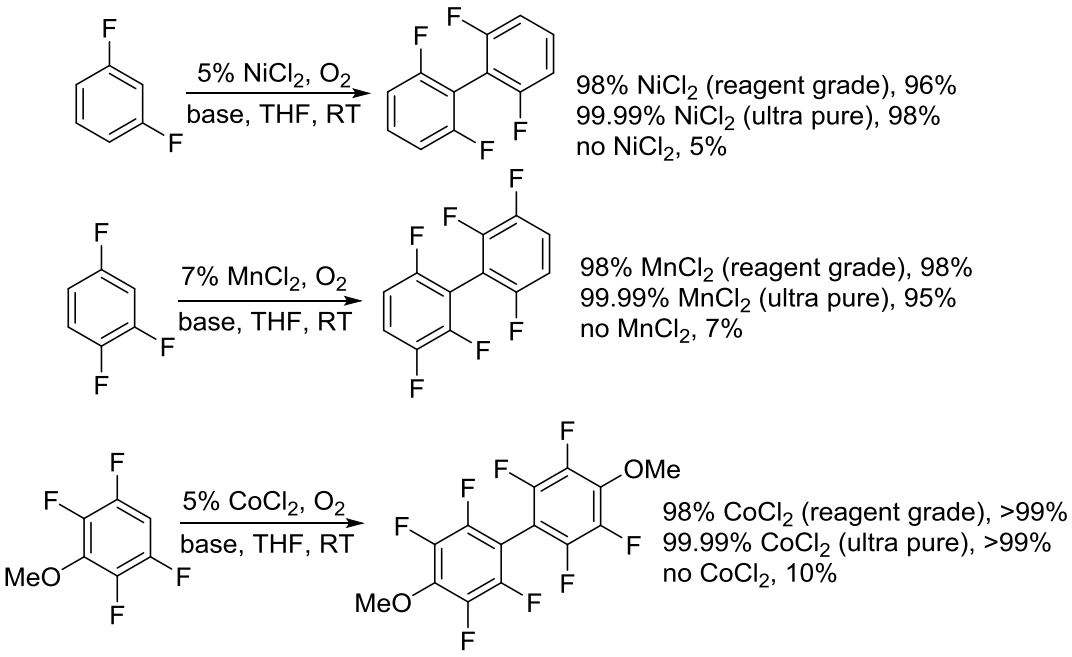


Entry	Arene, base	Product	Yield (%)
1	Thiazole base 1+base 3 (0.54/1)		82 74[b]
2	2-Chlorothiophene, base 1+ base 3 (5/1)		75 70[b]
3	Methoxypyrazine, base 1		42
4	1,2,4-Trifluorobenzene, base 1+base 3 (2/1)		81 71[b]
5	Ethyl-3,4-difluorobenzoate base 1		65

[a]Substrate (1 equiv), base (1.2-1.4 equiv). Yields are isolated yields. [b]Dicyclohexylamide base.

Control experiments were conducted to confirm the essential role of metal catalysts as well as to determine if trace of other transition metal impurities catalyze the dimerization.[33] Reactions run with either reagent grade or ultra-pure metal salts afford similar results indicating that reactivity by contaminants is unlikely. If metal salts were omitted, less than 10 % of desired products were obtained.

Scheme 1.25. Control experiments



1.2.3. Conclusions

We have developed methods for first-row transition-metal-catalyzed, deprotonative dimerization of arenes by employing oxygen as the terminal oxidant. Under nickel, cobalt, and manganese catalysis, 5-membered and 6-membered ring heterocycles as well as electron-deficient arenes react to afford biaryls in good yields. Various functionalities such as nitro, cyano, and ester groups are tolerated.

1.2.4. Experimental Section

General considerations: Reactions were performed in 1-dram vials using screw caps with 13 mm hole and white silicone septum with white teflon face (from SUPELCO). Column chromatography was performed on 60Å silica gel (Sorbent Technologies). Purification by preparative HPLC was performed on a Shimadzu Prominence LC (LC-20AB) equipped with a SPD-20A UV-Vis detector and a Varian Dynamax (250 mm x 21.4 mm) column. GC-MS analyses were performed on a Shimadzu GCMS-QP5000 chromatograph equipped with a Restek column (Rtx-XLB, 30 m x 0.25 mm I.D.). The ^{1}H, ^{19}F and ^{13}C NMR were recorded on a GE QE-300, JEOL EC-400 or JEOL EC-500 spectrometers using residual solvent peak as a reference. α,α,α-Trifluorotoluene (neat, δ = -62.3ppm) was employed as an external standard in ^{19}F NMR spectra. IR spectra were obtained by ThermoNicolet Avatar 370 FT-IR instrument. Analytical thin layer chromatography was performed on silica gel IB-F (Baker-flex) by J. T. Baker.

II.4.2. Materials. The following starting materials were obtained from commercial sources and were used without further purification: nickel(II) chloride (anhydrous), cobalt(II) chloride (anhydrous), manganese(II) chloride (anhydrous), iron(III) chloride (anhydrous), 2-methoxypyrazine, benzothiophene, zinc chloride (anhydrous), and 1,2,4-triazole were purchased from Alfa Aesar. Thiazole, 1,3-difluorobenzene, 2,3,5,6-tetrafluoroanisole, 4,5-dimethylthiazole, 2,3,5,6-tetrafluoropyridine, 2-chlorothiophene, 2,4-difluoronitrobenzene, 2,2,6,6-tetramethylpiperidine, and 3,5-difluorobenzonitrile were bought from Matrix Scientific. Benzofuran was obtained from TCI. 1-Butylimidazole, 3,5-dichloropyridine, *N*-methylbenzimidazole, 3-chloropyridine, 1,2,4-

trifluorobenzene, isopropylmagnesium chloride-lithium chloride complex solution (1.3 M in THF), nickel(II) chloride (99.99%), cobalt(II) chloride (99.99%), manganese(II) chloride (99.999%) were purchased from Aldrich. 1-Butyl-1,2,4-triazole was made from 1,2,4-triazole as previously described.[34]

Preparation of bases

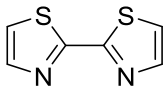
TMPMgCl*LiCl 1.0 M (base 1), **Cy_2NMgCl*LiCl 1.0 M (base 2)**: A reported procedure was followed.[35] Inside the glove box, a dry and argon-flushed 50 mL Schlenk flask, equipped with a magnetic stirring bar and a septum was charged with *i*PrMgCl*LiCl (23 mL, 1.3 M in THF, 30 mmol). The flask was taken out of the glove box and THF (7 mL) was added via syringe to give 30 mL of 1.0 M solution. After that, TMPH (2,2,6,6-tetramethylpiperidine, 4.45 g, 31.5 mmol) or Cy_2NH (dicyclohexylamine, 5.71 g, 31.5 mmol) was added to the Grignard solution. The mixture was stirred at room temperature for 24 hours followed by concentration under reduced pressure to 30 mL. All procedures were performed under Ar atmosphere. The base was titrated before use at 0 ^oC with solution of benzoic acid in THF (0.2 M). (Phenyl)[4-(phenylazo)-phenyl]amine was employed as indicator.[36]

$(TMP)_2Zn*2MgCl_2*2LiCl$ 0.5 M (base 3); **$(Cy_2N)_2Zn*2MgCl_2*2LiCl$ 0.5 M (base 4)**:[37] Inside the glove box, a dry and argon-flushed 25 mL Schlenk flask, equipped with a magnetic stirring bar and a septum, was charged with anhydrous zinc (II) chloride (680 mg, 5 mmol). The flask was taken out the glove box. TMPMgCl*LiCl (1.0 M in THF, 10 mL) or Cy_2NMgCl*LiCl (1.0M, 10 mL) was added dropwise. The mixture was stirred at

room temperature for 8 hours. The fresh base was titrated before use as described above. Note that 1 equivalent of zinc base is able to deprotonate 2 equivalents of C-H.

Nickel catalysis

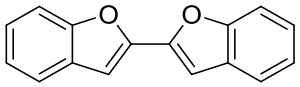
General procedure: A 1 dram vial equipped with a magnetic stir bar was charged with anhydrous nickel (II) chloride (6.5 mg, 0.05 mmol, 5 mol %; use of wet $NiCl_2$ results in lower yields) and substrate (1 mmol). The vial was flushed with argon and capped. To this mixture was added the appropriate base solution (1.2-1.4 equiv) by injecting through the septum via syringe. The vial was flushed with dry oxygen (1 min) and then stirred at room temperature under 1 atmosphere of oxygen for indicated time. The reaction mixture was diluted with ethyl acetate (30 mL) and washed with brine (1 x 10 mL). The aqueous phase was extracted with ethyl acetate (3 x 15 mL). Combined organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in minimum amount of dichloromethane or ethyl acetate and subjected to column chromatography on silica gel (hexane followed by appropriate solvent to elute the products). After concentrating the fractions containing the product, the residue was dried under reduced pressure.



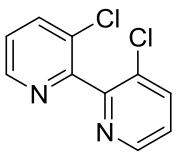
2,2'-Bithiazole (Entry 1, Table 1.1): Nickel(II) chloride (6.5 mg, 0.05 mmol), thiazole (85 mg, 1.0 mmol), $(TMP)_2Zn*2MgCl_2*2LiCl$ (0.5 M, 1.1 mL); or $(Cy_2N)_2Zn*2MgCl_2*2LiCl$ (0.5 M, 0.7 mL). Reaction mixture was cooled to 0 ^oC and TMPMgCl*LiCl (1.0 M, 0.3 mL; cooled to 0 °C before addition) or $Cy_2NMgCl*LiCl$

(1.0 M, 0.7 mL; cooled to 0 °C before addition) was added. Reaction mixture was stirred 5 minutes at 0 ^{o}C and then warmed to room temperature, and stirred for additional 2 hours. After column chromatography (gradient EtOAc/hexane 0/100 – 25/75), 70 mg (83% yield; TMP base) or 60 mg (71% yield; Cy_2N base) of a white solid was obtained. R_f = 0.25 (SiO_2, 3/7 ethyl acetate/hexanes). This compound is known.[38] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J*=3.4 Hz, 2H), 7.90 (d, *J*=3.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 161.7, 144.0, 121.1.

Note: Reaction needs to be run for 5 hours to afford comparable yield if only $(TMP)_2Zn*2MgCl_2*2LiCl$ base (0.5 M, 1.3 mL) is used.

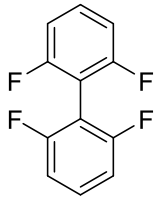


2,2'-Bibenzofuran (Entry 2, Table 1.1): Nickel(II) chloride (6.5 mg, 0.05 mmol), benzofuran (118 mg, 1.0 mmol), TMPMgCl*LiCl (1.0 M, 1.4 mL), 60 ^{o}C, 5 hours. After column chromatography (hexanes, then 5% ethyl acetate in hexanes) and preparative HPLC (2% ethyl acetate in hexanes) 53 mg (45%) of a colorless solid was obtained. R_f = 0.29 (SiO_2, 1% EtOAc in hexanes). This compound is known.[39] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J*=1.0 Hz, 2H), 7.26 (dt, *J*=7.4 Hz, 1.0 Hz, 2H), 7.35 (dt, *J*=7.4 Hz, 1.8 Hz, 2H), 7.55 (d, *J*=7.4 Hz, 2H), 7.60-7.65 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 155.2, 147.8, 128.6, 125.2, 123.5, 121.5, 111.4, 103.8.



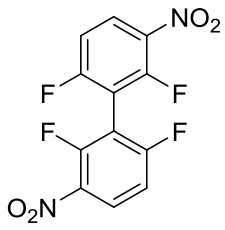
3,3'-Dichloro-2,2'-bipyridine (Entry 3, Table 1.1): Nickel(II) chloride (6.5 mg, 0.05 mmol), 3-chloropyridine (114 mg, 1.0 mmol), TMPMgCl*LiCl (1.0 M, 1.4 mL), room temperature, 2 hours. After column chromatography (gradient EtOAc/hexane 0/100 – 85/15), 37.5 mg (33%) of a white solid was obtained. R_f = 0.38 (SiO_2, 1/4 ethyl acetate/hexanes). This compound is known.[40] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, *J*= 3.4 Hz, 1.8 Hz, 2H), 7.84 (d, *J* = 3.4 Hz, 2H), 8.6 (d, *J*= 1.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 154.4, 147.7, 137.6, 131.2, 124.7.

Note: 20% yield was obtained if $(TMP)_2Zn*2MgCl_2*2LiCl$ base (0.5 M, 1.4 mL) was used.



2,2',6,6'-Tetrafluorobiphenyl (Entry 4, Table 1.1): Nickel(II) chloride (6.5 mg, 0.05 mmol), 1,3-difluorobenzene (114 mg, 1.0 mmol), $(TMP)_2Zn*2MgCl_2*2LiCl$ (0.5 M, 0.6 mL) followed by TMPMgCl*LiCl (1.0 M, 0.6 mL); or $Cy_2NMgCl*LiCl$ (1.0 M, 1.0 mL) followed by $(Cy_2N)_2Zn*2MgCl_2*2LiCl$ (0.5 M, 0.4 mL), room temperature, 1 hour. After column chromatography (gradient Et_2O/pentane 0/100 – 2/98), 85 mg (75%; TMP bases) or 79 mg (70%; Cy_2N bases) of a light tan solid was obtained. R_f = 0.45 (SiO_2, 1/99 diethyl ether/hexanes). This compound is known.[39] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95-7.10 (m, 4H), 7.35-7.45 (m, 2H). ^{19}F (376 MHz, $CDCl_3$) δ -110.5 (s, 4F). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 160.6 (d, J_{C-F} = 256 Hz), 130.8-131 (m), 111.3-111.7 (m), 106.7 (t, J_{C-F}=20.6 Hz).

Note: Substantial amounts of phenol byproduct and fluorine nucleophilic substitution products were obtained when reaction was carried out using only Mg base.



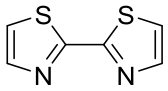
2,2',6,6'-Tetrafluoro-3,3'-dinitrobiphenyl (Entry 5, Table 1.1): Nickel(II) chloride (6.5 mg, 0.05 mmol), 2,4-difluoronitrobenzene (159 mg, 1.0 mmol), cooled $(TMP)_2Zn*2MgCl_2*2LiCl$ (0.5 M, 1.3 mL), 0 ^oC, 1 hour. After column chromatography (gradient EtOAc/hexane 0/100 – 30/70), 116 mg (73%) of a light brown solid was obtained. R_f = 0.30 (SiO_2, 1/4 ethyl acetate/hexanes). This compound is known.[40] ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.30 (m, 2H), 8.30-8.40 (m, 2H). ^{19}F NMR (376MHz, $CDCl_3$) δ -110.8--110.5 (m, 2F), -97.3--97.00 (m, 2F). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.04 (d, J_{C-F} = 262 Hz), 154.3 (d, J_{C-F} = 268 Hz), 134.5 (d, J_{C-F} = 5.5 Hz), 129.3 (t, J_{C-F} =5.5 Hz), 112.4 (d, J_{C-F} =24.5 Hz), 107.6 (t, J_{C-F} =22 Hz).

Note: Only 51% yield was obtained if Mg base was used.

Cobalt catalysis

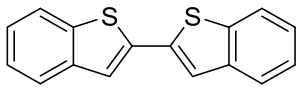
General procedure: Outside the glove box, a 1 dram vial equipped with a magnetic stir bar was charged with anhydrous cobalt (II) chloride (6.5 mg, 0.05 mmol, 5 mol %) and substrate (1 mmol). The vial was flushed with argon and capped. To this mixture was added THF (0.5 – 1.0 mL) by injecting through the septum via syringe. The mixture was stirred until catalyst dissolved. The appropriate base solution (1.1-1.7 equiv) was then

added by injecting through the septum. The vial was flushed by dry oxygen (1 min) followed by stirring at room temperature under oxygen (1 atm) for indicated time. Work-up was performed as described for nickel catalysis.



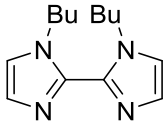
2,2'-Bithiazole (Entry 1, Table 1.3): Cobalt(II) chloride (6.5 mg, 0.05 mmol), THF (0.5 mL), thiazole (85 mg, 1.0 mmol), $(TMP)_2Zn*2MgCl_2*2LiCl$ (0.5 M, 1 mL) followed by TMPMgCl*LiCl (1.0 M, 0.4 mL); or $Cy_2NMgCl*LiCl$ (1.0 M, 0.7 mL) followed by $(Cy_2N)_2Zn*2MgCl_2*2LiCl$ (0.5 M, 0.7 mL), room temperature, 2 hours. After column chromatography (gradient EtOAc/hexane 0/100 – 25/75), 71 mg (86%; TMP bases), or 59 mg (70%; Cy_2N bases) of a white solid was obtained. This compound is known.[38] ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J*=3.4 Hz, 2H), 7.90 (d, *J*=3.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 161.7 , 144.0, 121.1.

Note: Lower yield (75%; TMP bases) was obtained if nickel and manganese catalysts were used under these conditions.

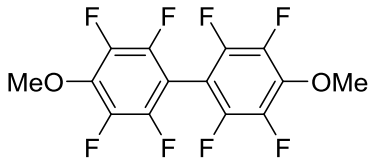


2,2'-Bibenzo[*b*]thiophene (Entry 2, Table 1.3): Cobalt(II) chloride (6.5 mg, 0.05 mmol), benzothiophene (134 mg, 1.0 mmol), THF (1.0 mL), TMPMgCl*LiCl (1.0 M, 1.4 mL); or $Cy_2NMgCl*LiCl$ (1.0 M, 1.7 mL), room temperature, 2 hours. After column chromatography (hexane) 112 mg (85%; TMP base) or 104 mg (78%; Cy_2N base) of a light green solid was obtained. R_f = 0.20 (SiO_2, hexanes). This compound is known.[45] ^1H

NMR (400 MHz, $CDCl_3$) δ 7.31-7.37 (m, 4H), 7.52 (s, 2H), 7.75-7.82 (m, 4H). ^{13}C NMR (125 MHz, DMSO-D6, ppm) δ 140.5, 139.2, 137.1, 125.9, 125.7, 124.5, 123.1, 122.4.



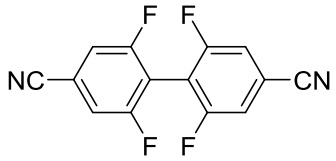
1,1'-Dibutyl-1H,1'H-2,2'-biimidazole (Entry 3, Table 1.3): Cobalt(II) chloride (6.5 mg, 0.05 mmol), 1-butylimidazole (124 mg, 1.0 mmol), THF (0.6 mL), TMPMgCl*LiCl (1.0 M, 1.4 mL), room temperature, 1 hour. After column chromatography (gradient EtOAc/hexane 0/1 – 4/1), 98 mg (80%) of a colorless oil was obtained. R_f = 0.25 (SiO_2, 3/2 ethyl acetate/hexanes). This compound is known.[46] ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J*=7.1 Hz, 6H), 1.23 (sextet, *J*=7.1 Hz, 4H), 1.68 (quintet, *J*=7.1 Hz, 4H), 4.41 (t, *J*=7.1 Hz, 4H), 6.95 (d, *J*=1.2 Hz, 2H), 7.08 (d, *J*=1.2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 138.1, 128.0, 121.1, 47.1, 33.2, 19.7, 13.6.



2,2',3,3',5,5',6,6'-Octafluoro-4,4'-dimethoxybiphenyl (Entry 4, Table 1.3): Cobalt(II) chloride (6.5 mg, 0.05 mmol), 2,3,5,6-tetrafluoroanisole (180 mg, 1.0 mmol), TMPMgCl*LiCl (1.0 M, 1.1 mL); or Cy_2NMgCl*LiCl (1.0 M, 0.8 mL) followed by $(Cy_2N)_2Zn$*2$MgCl_2$*2LiCl (0.5 M, 0.3 mL), room temperature, 1 hour. After column chromatography (hexanes, then 10% ethyl acetate in hexanes) 161 mg (90%; TMP base) or 156 mg (87%; Cy_2N bases) of a white solid was obtained. R_f = 0.25 (SiO_2, 1/10 ethyl acetate/hexanes). This compound is known.[47] ^1H NMR (400 MHz, $CDCl_3$) δ 4.18 (s, 6H).

^{19}F (376 MHz, $CDCl_3$) δ -157.4--157.1 (m, 4F), -139.6--139.5 (m, 4F). ^{13}C NMR (100 MHz, $CDCl_3$, ppm, list of peaks, ^{13}C-^{19}F couplings not assigned) δ146.1-146.0 (m), 143.7-143.5 (m), 142.3-142.1 (m), 139.8-139.6 (m), 100.1-99.9 (m), 62.2. Fluorine nucleophilic substitution products were obtained when reaction was carried out using only Cy_2NMgCl*LiCl, presumably due to lower steric bulk compared with TMP base.

Note: Phenol byproduct was observed if larger excess of magnesium base 1 was used.

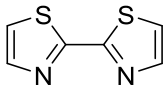


2,2',6,6'-Tetrafluorobiphenyl-4,4'-dicarbonitrile (Entry 5, Table 1.3): Cobalt(II) chloride (6.5 mg, 0.05 mmol), 3,5-difluorobenzonitrile (139 mg, 1.0 mmol), $(TMP)_2Zn$*$2MgCl_2$*2LiCl (0.5 M, 0.7 mL) + TMPMgCl*LiCl (1.0 M, 0.7 mL), room temperature, 4 hours. After column chromatography (gradient EtOAc/hexane 0/1 – 1/4), 110 mg (80%) of a white solid was obtained. R_f = 0.32 (SiO_2, 2/9 ethyl acetate/hexanes). This compound is known.[28] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.45 (m, 4H). ^{19}F (376 MHz, $CDCl_3$) δ-105.1 (s, 4F). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 110.7 (t, *JC-F* = 3.6 Hz;), 115.6-116.3 (m, 4C), 160.2 (dt, *JC-F* = 248 Hz, 3.3 Hz; 4 C).

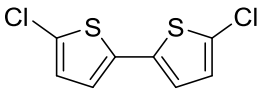
Manganese catalysis

General procedure: Outside the glove box, a 1 dram vial equipped with a magnetic stir bar was charged with the substrate (1 mmol). The vial was flushed with argon, capped and placed into the glove-box. Anhydrous manganese (II) chloride (8.8 mg, 0.07 mmol, 7 mol%) was added and the vial was taken out of the glove box. The appropriate base

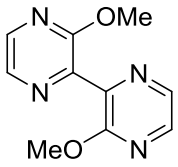
solution (1.2-1.4 eq) was injected through the septum. The vial was flushed with dry oxygen (1 min) followed by stirring at room temperature under oxygen (1 atm) for indicated time. Work-up was performed as described for nickel catalysis.



2,2'-Bithiazole (Entry 1, Table 1.2): Manganese(II) chloride (8.8 mg, 0.07 mmol), thiazole (85 mg, 1.0 mmol), $(TMP)_2Zn*2MgCl_2*2LiCl$ (0.5 M, 1.1 mL) followed by TMPMgCl*LiCl (1.0 M, 0.3 mL); or $Cy_2NMgCl*LiCl$ (1.0 M, 0.7 mL) followed by $(Cy_2N)_2Zn*2MgCl_2*2LiCl$ (0.5 M, 0.7 mL), room temperature, 2 hours. After column chromatography (gradient EtOAc/hexane 0/100 – 25/75), 69 mg (82%; TMP bases) or 62 mg (74%; Cy_2N bases) of a white solid was obtained. This compound is known.[38] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J*=3.4 Hz, 2H), 7.90 (d, *J*=3.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 161.7 , 144.0, 121.1.

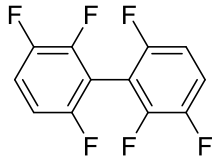


5,5'-Dichloro-2,2'-bithiophene (Entry 2, Table 1.2): Manganese (II) chloride (8.8 mg, 0.07 mmol), 2-chlorothiophene (118.5 mg, 1.0 mmol), $(TMP)_2Zn*2MgCl_2*2LiCl$ (0.5 M, 0.4 mL) followed by TMPMgCl*LiCl (1.0 M, 1 mL); or $Cy_2NMgCl*LiCl$ (1.0 M, 1.3 mL), room temperature, 2 hours. After column chromatography (hexanes, then 5/95 ethyl acetate/hexanes) 87 mg (75%; TMP bases) or 82 mg (70%; Cy_2N base) of a yellow solid was obtained. R_f = 0.62 (SiO_2, 1/99 ethyl acetate/hexanes). This compound is known.[43] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (d, *J*=4.0 Hz, 2H), 6.85 (d, *J*=4.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 135.1, 129.3, 127.0, 123.1.



3,3'-Dimethoxy-2,2'-bipyrazine (Entry 3, Table 1.2): Manganese(II) chloride (8.8 mg, 0.07 mmol), 2-methoxypyrazine (110 mg, 1.0 mmol), TMPMgCl*LiCl (1.0 M, 1.3 mL), room temperature, 2 hours. After column chromatography (gradient EtOAc/hexane 0/100 – 60/40), 45 mg (42%) of a light tan solid was obtained. R_f = 0.23 (SiO_2, 1/1 ethyl acetate/hexanes). This compound is known.[28] ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 6H), 8.18 (d, *J*=2.6 Hz, 2H), 8.25 (d, *J*=2.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ, 158.9, 141.3, 140.5, 136.4, 54.0.

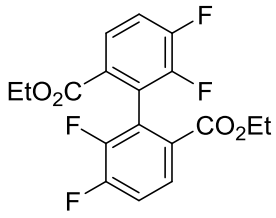
Note: Only 30% conversion was obtained if base 3 was used.



2,2',5,5',6,6'-Hexafluorobiphenyl (Entry 4, Table 1.2): Manganese(II) chloride (8.8 mg, 0.07 mmol), 1,3,4-trifluorobenzene (132 mg, 1.0 mmol), $(TMP)_2Zn*2MgCl_2*2LiCl$ (0.5 M, 0.6 mL) + TMPMgCl*LiCl (1.0 M, 0.6 mL); or $Cy_2NMgCl*LiCl$ (1.0 M, 1.0 mL) + $(Cy_2N)_2Zn*2MgCl_2*2LiCl$ (0.5 M, 0.4 mL), room temperature, 1 hour. After column chromatography (pentane, then 1% diethyl ether in pentane) 105 mg (81%; TMP base) or 93 mg (71%; Cy_2N base) of a white solid was obtained. R_f = 0.40 (SiO_2, hexanes). This compound is known.[44] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.9-7.0 (m, 2H), 7.2-7.3 (m, 2H) .^{19}F (376 MHz, $CDCl_3$) δ -141.6--1.41.5 (m, 2F), -132.6--132.5 (m, 2F), -

115.5--115.4 (m, 2F). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 155.5 (d, J_{C-F} = 246 Hz), 149.4-146.8 (m), 148.4-146.0 (m), 118.5-118.2 (m), 111.3-110.9 (m), 108.0-107.5 (m).

Note: Substantial amounts of phenol byproduct and fluorine nucleophilic substitution products were obtained when reaction was carried out using only Mg bases.



Ethyl-2,2',3,3'-tetrafluorobiphenyl-6,6'-dicarboxylate (Entry 5, Table 1.2): Manganese(II) chloride (8.8 mg, 0.07 mmol), ethyl-3,4-difluorobenzoate (186 mg, 1.0 mmol), TMPMgCl*LiCl (1.0 M, 1.4 mL), 0^{o}C, 1 hour. After column chromatography (gradient EtOAc/hexane 0/100 – 20/80), 120 mg (65%) of a white solid was obtained. R_f = 0.29 (SiO_2, 1/5 ethyl acetate/hexanes). This compound is known.[28] ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (t, *J*= 7.1 Hz, 6H), 4.10 (q, *J*=7.1 Hz, 4H), 7.30 (dd, *J*=17.9 Hz, 9.0 Hz, 2H), 7.95 (ddd, *J*=9.0 Hz, 4.8 Hz, 1.5 Hz, 2H). ^{19}F (376 MHz, $CDCl_3$) δ -136.3--136.1 (m, 2F), -130.4 (m, 2F). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 13.8, 61.3, 116.9 (d, *JC-F* = 17.0 Hz), 125.6 (d, *JC-F* = 14.0 Hz), 126.7 (d, *JC-F* = 2.8Hz), 127.1 (dd, *JC-F* = 7.6 Hz, 3.8 Hz), 147.8 (dd, *JC-F* = 246.0 Hz, 13.3 Hz), 152.9 (dd, *JC-F* =255.0 Hz, 13.3 Hz), 164.6.

Control reactions:

Reaction conversions were measured by GC using hexadecane as internal standard.

Nickel catalysis:

- Using reagent grade $NiCl_2$ (Alfa Aesar, anhydrous 98%): Nickel (II) chloride (6.5 mg, 0.05 mmol), 1,3-difluorobenzene (114 mg, 1.0 mmol), $(TMP)_2Zn*2MgCl_2*2LiCl$ (0.5 M, 0.6 mL) + TMPMgCl*LiCl (1.0 M, 0.6 mL), room temperature, 1 hour. Conversion: 96%

- Using ultra pure $NiCl_2$ (Aldrich, 99.99%): Nickel (II) chloride (6.5 mg, 0.05 mmol), 1,3-difluorobenzene (114 mg, 1.0 mmol), $(TMP)_2Zn*2MgCl_2*2LiCl$ (0.5 M, 0.6 mL) + TMPMgCl*LiCl (1.0 M, 0.6 mL), 1 hour, rt. Conversion: 98%.

- Without $NiCl_2$ catalyst: 1,3-difluorobenzene (114 mg, 1.0 mmol), $(TMP)_2Zn*2MgCl_2*2LiCl$ (0.5 M, 0.6 mL) + TMPMgCl*LiCl (1.0 M, 0.6 mL), rt, 1 hour. Conversion: 5%.

Manganese catalysis:

- Using reagent grade $MnCl_2$ (Alfa Aesar, anhydrous 98%): Manganese (II) chloride (8.8 mg, 0.07 mmol), 1,3,4-trifluorobenzene (132 mg, 1.0 mmol), $(TMP)_2Zn*2MgCl_2*2LiCl$ (0.5 M, 0.6 mL) + TMPMgCl*LiCl (1.0 M, 0.6 mL), rt, 1 hour. Conversion: 98%.

- Using ultra pure $MnCl_2$ (Aldrich, 99.999%): Manganese (II) chloride (8.8 mg, 0.07 mmol), 1,3,4-trifluorobenzene (132 mg, 1.0 mmol), $(TMP)_2Zn*2MgCl_2*2LiCl$ (0.5 M, 0.6 mL) + TMPMgCl*LiCl (1.0 M, 0.6 mL), rt, 1 hour. Conversion: 95%.

- Without $MnCl_2$ catalyst: 1,3,4-trifluorobenzene (132 mg, 1.0 mmol), $(TMP)_2Zn*2MgCl_2*2LiCl$ (0.5 M, 0.6 mL) + TMPMgCl*LiCl (1.0 M, 0.6 mL), room temperature, 1 hour. Conversion: 7%.

Cobalt catalysis:

- Using reagent grade $CoCl_2$ (Alfa Aesar, anhydrous 98%): Cobalt (II) chloride (6.5 mg, 0.05 mmol), 2,3,5,6-tetrafluoroanisole (180 mg, 1.0 mmol), TMPMgCl*LiCl (1.0 M, 1.1 mL), rt, 1 hour. Conversion: >99%.

- Using ultra pure $CoCl_2$ (Aldrich, 99.99%): Cobalt (II) chloride (6.5 mg, 0.05 mmol), 2,3,5,6-tetrafluoroanisole (180 mg, 1.0 mmol), TMPMgCl*LiCl (1.0 M, 1.1 mL), RT, 1 hour. Conversion: >99%.

- Without $CoCl_2$ catalyst: 2,3,5,6-tetrafluoroanisole (180 mg, 1.0 mmol), TMPMgCl*LiCl (1.0 M, 1.1 mL), rt, 1 hour. Conversion: 10%.

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Chapter 2

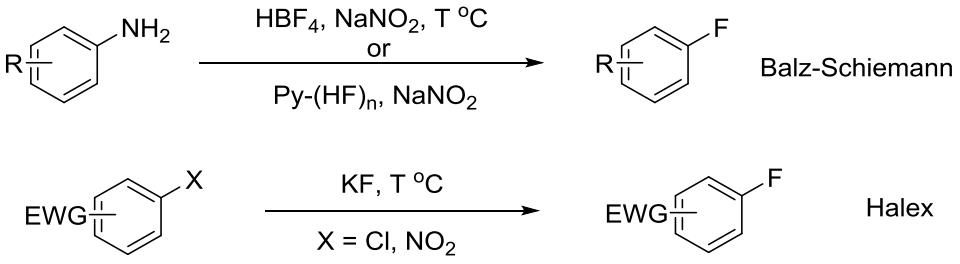
Transition-Metal-Catalyzed Sp^2 C-F Bond Formation

2.1. Sp^2 C-F Bond Formation

2.1.1. Introduction

The presence of fluorine atoms in arenes often affects the reactivity, solubility, and the stability of molecules.[1] A wide range of materials and biologically active compounds contain fluorine substituents. In medicinal chemistry, the high strength of C-F bonds can result in the inhibition of metabolism if fluorine is incorporated at or near a reactive site, improving the efficacy of lead compounds. Furthermore, ^{18}F-labeled organic compounds are widely used as contrast agents for position emission tomography (PET).[2] However, traditional methods to introduce fluorine into an aromatic framework often require harsh conditions. In particular, the conversion of amines via aryldiazonium salt with HBF_4 (Balz-Schiemann reaction) and nucleophilic substitution of electron-deficient chloro- or nitroarenes (Halex reaction) are not compatible with many functional groups (Scheme 2.1).[3]

Scheme 2.1. Traditional routes to aryl fluorides



Additionally, the substrate scope of these reactions is limited and the fluorine source is not readily amenable to the preparation of ^{18} F-labeled compounds. Because of these limitations, fluorine atoms are usually introduced early in the synthetic sequences which greatly increases the difficulty of accessing target molecules. Modern methods

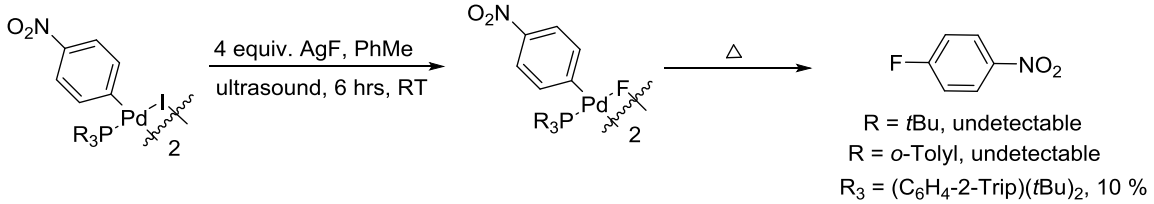
based on transition-metal catalysis, therefore, have been sought as an alternative. Within this chapter, recent developments in constructing fluoroarenes will be discussed.

2.1.2. Aryl Fluoride Formation from Aryl Metals

Because of their remarkable importance in pharmaceuticals, agrochemicals, and biological imaging agents, significant recent efforts have focused on the development of new synthetic procedures for the generation of sp^2 C-F bonds. Transition-metal-promoted fluoroarene formation is of particular interest. Over the past few years, several different methods have been developed to construct sp^2 C-F bonds via cross-coupling with aryl metals.

Studies used to elucidate features of coordination environment of Pd (II) that could enable Ar-F reductive elimination have been reported by Yandulov.[4] Several palladium complexes with bulky ligands were synthesized and characterized (Scheme 2.2). The results indicated that the stability of the fluoride-bridge dimer is a key remaining obstacle to Ar-F reductive elimination (Scheme 2.2). The use of Buchwald's ligand, however, provides the additional steric pressure on the $[PdArL(\mu\text{-}F)]_2$ core, thus enabling formation of Ar-F in quantifiable yield (10 %) via reductive elimination.

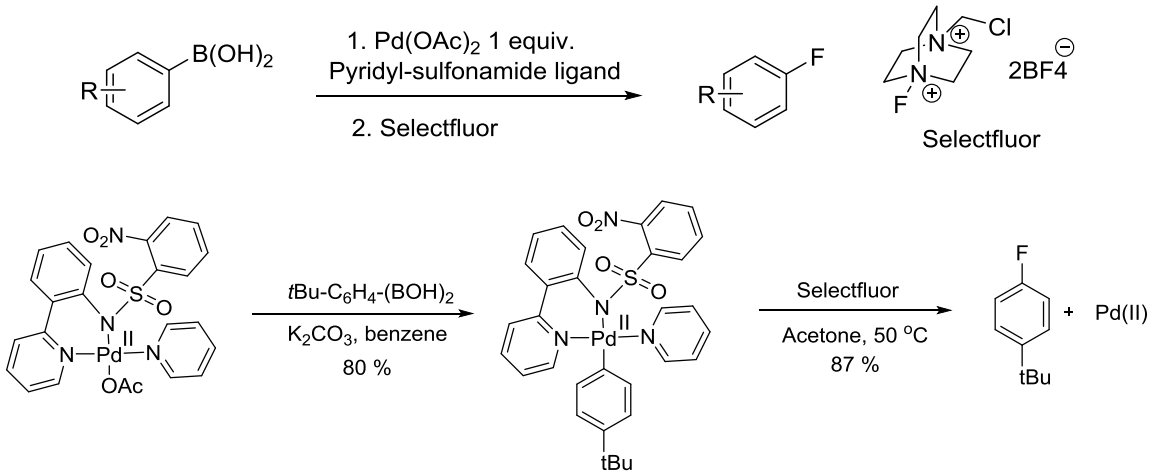
Scheme 2.2. Ar-F reductive elimination from Pd complexes with bulky ligands



The systematic investigation of C-F reductive elimination from Pd(IV) fluoride complexes has also been described.[5] The experimental data suggested that elimination

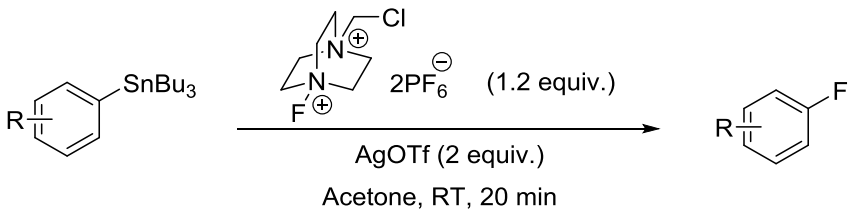
occurs from cationic Pd(IV) fluoride complexes via dissociative mechanism. Specifically, the pyridyl-sulfonamide-supported Pd(IV) has the appropriate geometry and electronic structure to enable reductive elimination (Scheme 2.3). The authors also found that electron-donating ancillary ligand accelerated C-F bond formation. Electron-withdrawing substituents on the carbon ligand accelerate reductive elimination.

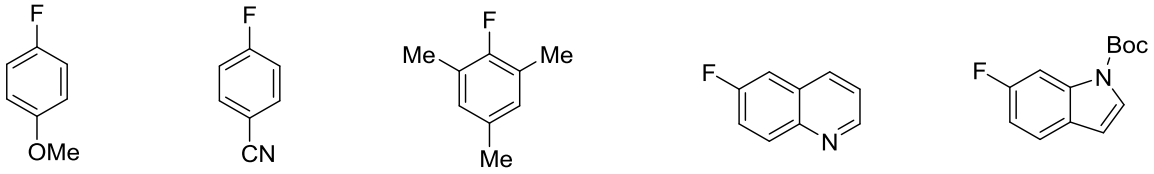
Scheme 2.3. Fluorination of boronic acids via palladium complexes



A procedure for silver-mediated fluorination of functionalized aryl stannanes has been disclosed.[6] Method employs 2 equivalents of silver triflate and uses electrophilic Selectfluor as fluorinating reagent (Scheme 2.4). The applicability to broad substrate scope has been demonstrated. Reactions are regiospecific and wide range of functional groups is tolerated. A bimetallic redox mechanism was proposed.

Scheme 2.4. Silver-mediated electrophilic fluorination of aryl stannanes

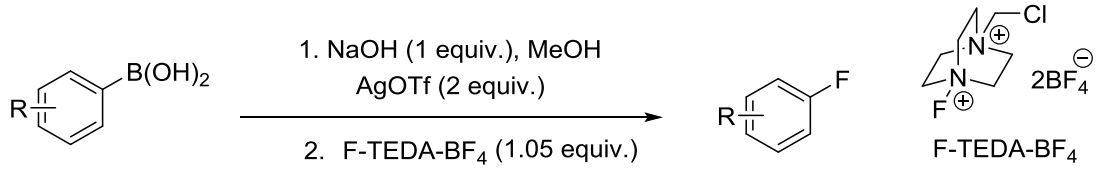


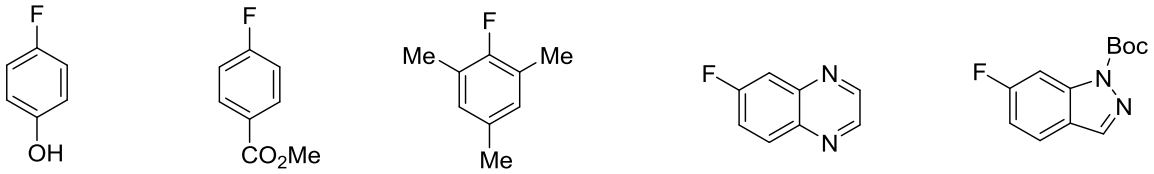


76 % 76 % 73 % 79 % 81 %

Silver-mediated fluorination of aryl boronic acids was also reported by the same group.[7] Electron-rich, electron-poor, and heterocylic boronic acids are active in fluorination (Scheme 2.5). It is worth mentioning that arylboron reagents are valuable alternative sources of aryl groups for the synthesis of aryl fluorides because they are commercially available, non-toxic, and shelf stable. Additionally, conditions are practical and multigram scale synthesis was performed.

Scheme 2.5. Silver-mediated fluorination of aryl boronic acids

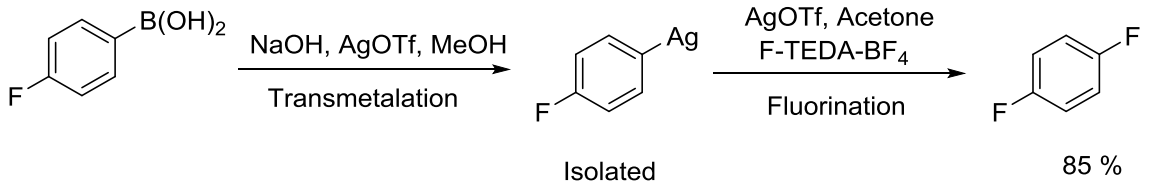




70 % 76 % 73 % 71 % 75 %

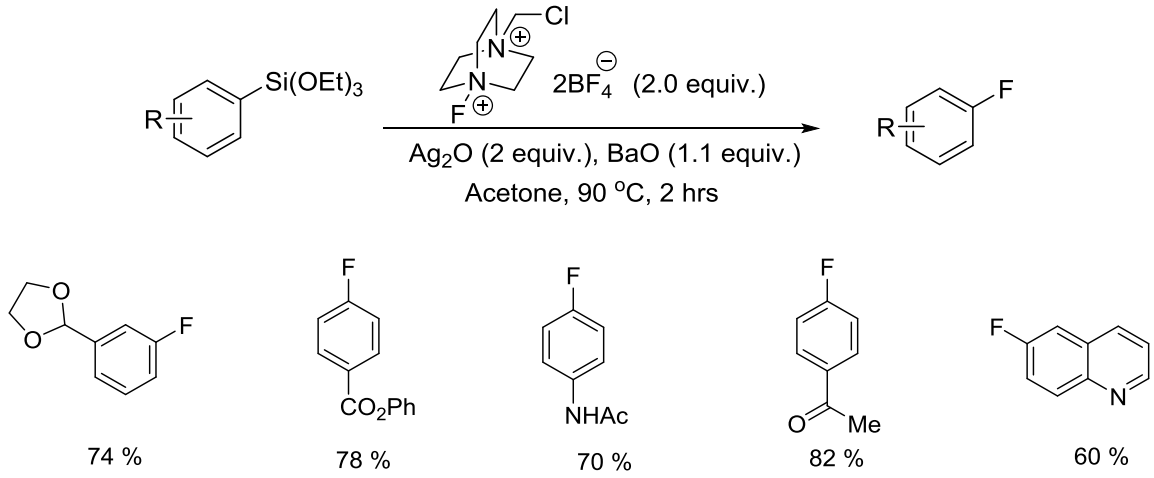
In mechanistic studies, transmetalation from boron to silver was performed and an arylsilver complex was isolated. Subsequent fluorination of this complex with electrophilic F-TEDA-BF_4 in the presence of AgOTf afforded fluoroarene product in 85 % yield (Scheme 2.6).

Scheme 2.6. Transmetalation from boron to silver during reaction



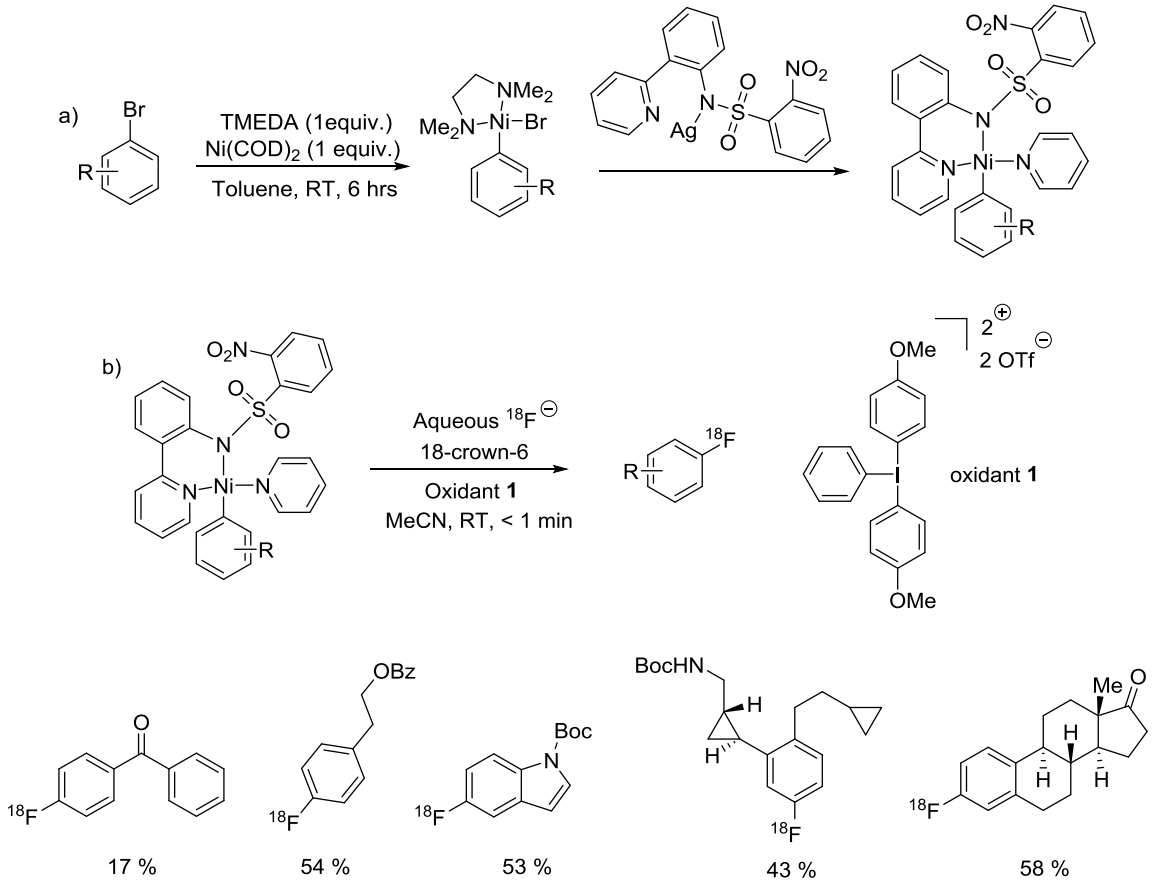
Direct conversion of aryl silanes to aryl fluorides has been achieved.[8] Ritter group reported a functional-group-tolerant, one-step fluorination of aryltriethoxysilanes with F-TEDA-BF_4 mediated by Ag_2O (Scheme 2.7). Although the silver is used in superstoichiometric amounts for optimal results, it can be recycled by appropriate reactivation treatment.

Scheme 2.7. Silver-mediated fluorination of aryl silanes



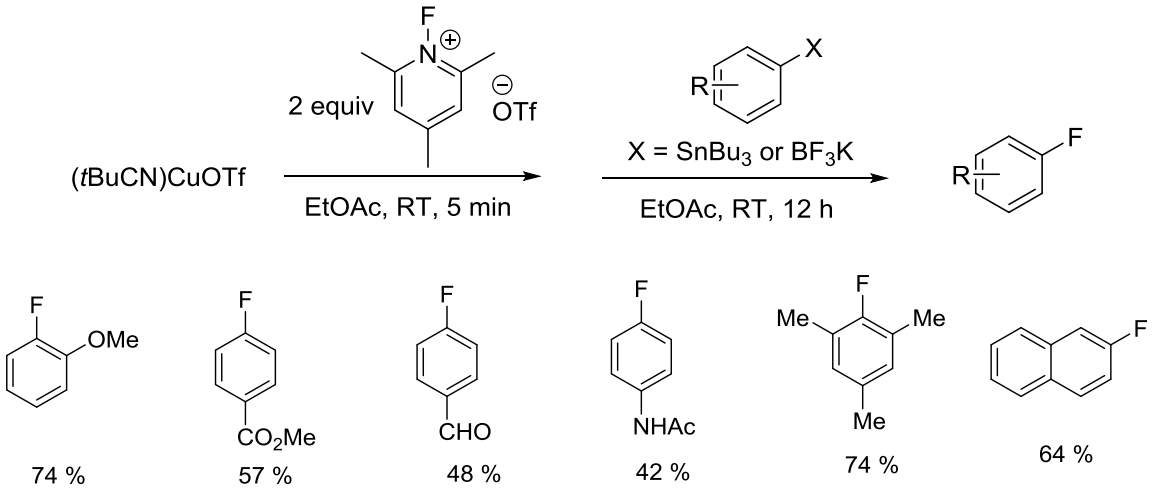
Nickel complexes were also examined in C-F reductive elimination. A one-step oxidative fluorination for C-F bond formation from well-defined nickel complexes with oxidant and aqueous fluoride was presented by the Ritter group.[9] A variety of moisture- and air-stable nickel complexes have been synthesized (Scheme 2.8a). Upon treating with a hypervalent iodine salt oxidant and aqueous fluoride, fluoroarene products were obtained in good yields at room temperature in less than one minute (Scheme 2.8b). The transformation represents the first example of mild fluorination with a first-row transition metal and the first example of a reaction that affords aryl fluoride by ^{18}F-C bond formation via reductive elimination.

Scheme 2.8. Synthesis of Ni(II) aryl complexes and their reactivity toward fluorination



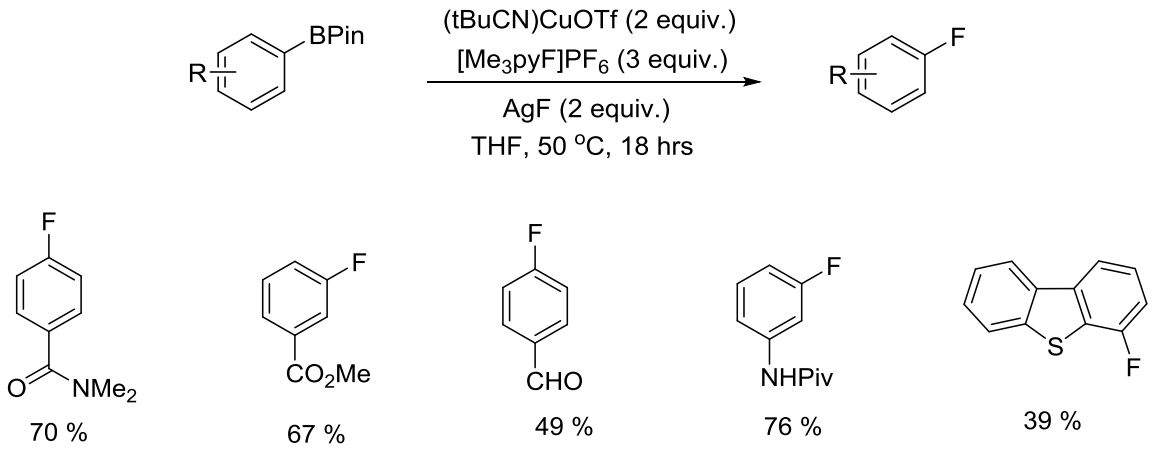
A protocol for copper-mediated fluorination of aryl stannanes and aryl trifluoroborates has been demonstrated.[10] The method employed one equivalent of copper (I) complex and *N*-fluoro-2,4,6-trimethylpyridinium triflate (N-FTPT) fluorinating source at room temperature (Scheme 2.9). The sequential one-pot procedure initially started with oxidation of Cu(I) complex with N-FTPT to form putative Cu(III)-F intermediates followed by addition of stannanes or trifluoroborates. The reaction proceeds at mild temperatures and exhibits a broad substrate scope and functional group tolerance.

Scheme 2.9. Copper-mediated fluorination of aryl stannanes and aryl trifluoborates



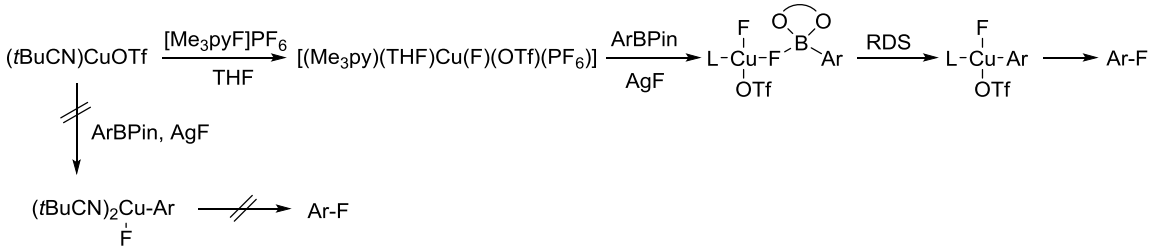
A method for the direct conversion of aryl boronate esters to aryl fluorides using copper salt promoter has also been described by Hartwig.[11] Reaction conditions include stoichiometric amount of Cu(I) complex, electrophilic fluorinating source, and silver (I) fluoride. Electron-rich, electron-deficient, *ortho*-substituted, and diversely functionalized aryl boronate esters undergo fluorination in good yields (Scheme 2.10).

Scheme 2.10. Copper-mediated fluorination of arylboronate esters



Reaction mechanism was also investigated. The authors provided evidence that the fluorination occurs by facile formation of a cationic copper(III) fluoride complex, which reacts with AgF and ArBpin to form neutral fluoroarylboronate complex. Rate-determining transmetalation forms an arylcopper(III) fluoride, which undergoes reductive elimination to form aryl fluoride product (Scheme 2.11). Copper(III) intermediates have been generated independently and identified by NMR and ESI-MS.

Scheme 2.11. Proposed mechanism for the fluorination of ArBPin with (*t*BuCN)$_2$CuOTf

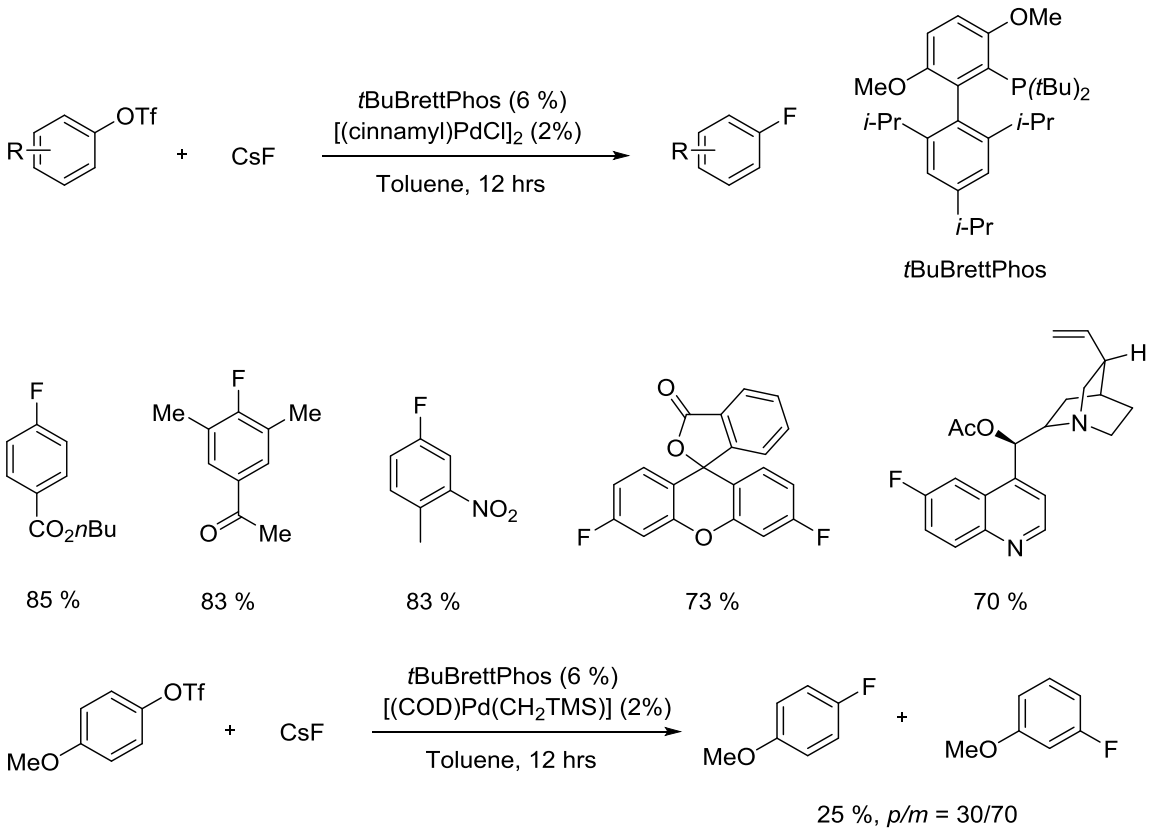


2.1.3 Aryl Fluoride Formation from Aryl Halides and Aryl Triflates

Methods for the conversion of aryl metals such as aryl stannanes, aryl boronic acids, and silanes to aryl fluorides with silver, palladium or copper and an electrophilic fluoride source have been shown. However, aryl nucleophiles in these reactions are often prepared from aryl halides. Therefore, a transition-metal-catalyzed or –mediated formation of fluoroarenes from corresponding aryl halides is a highly desirable transformation.

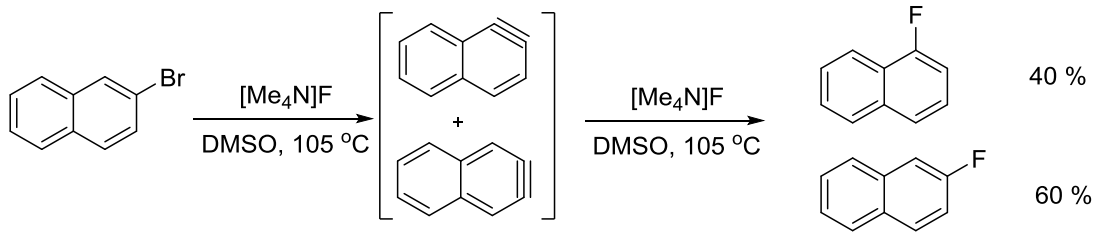
The preparation of a well-characterized Pd(II) complex that undergoes reductive elimination forming an aryl fluoride was reported by Buchwald in 2009.[12] Based on this result, a palladium-catalyzed formation of aryl fluorides from aryl triflates or aryl bromides was developed. The method employs 2-3 % $[(\text{cinnamyl})PdCl_2]_2$ catalyst, 5-7 % *t*BuBrettPhos ligand, and CsF or AgF fluoride sources (Scheme 2.12). Method uses the sterically demanding, electron-rich biaryl monophosphine *t*BuBrettPhos ligand. The authors suggested that this ligand not only facilitates reductive elimination of the Ar-F bond but also prevents the formation of dimeric $[LPdAr(F)]_2$ due to its large size. The transformation exhibits a wide substrate scope and tolerates a number of functional groups. However, in several cases, formation of regioisomeric byproducts was observed.

Scheme 2.12. Pd-catalyzed fluorination of aryl triflates



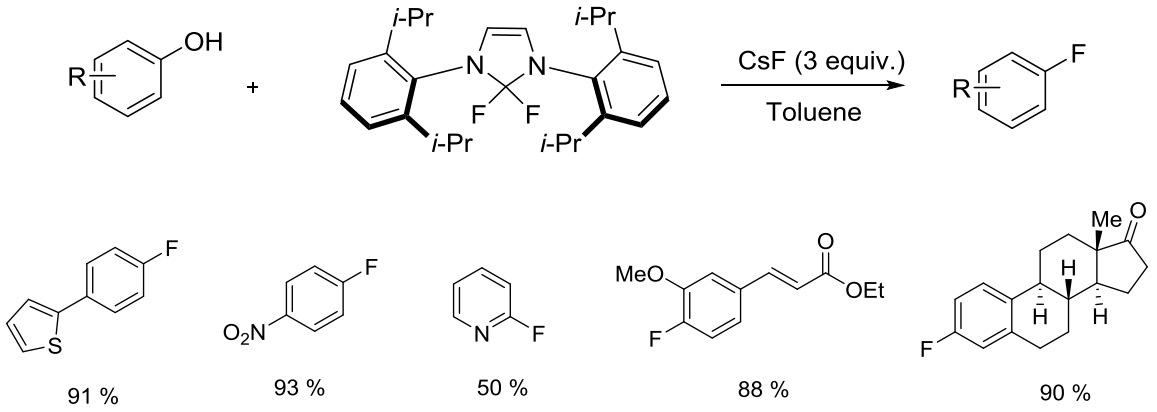
A transition-metal-free approach to aryl fluorides from aryl bromides was also reported.[13] Upon treatment with $[Me_4N]F$ in DMSO at elevated temperatures, bromoarenes are converted to aryl fluorides. Isomeric mixture of products were obtained when unsymmetrical aryl bromides were used indicating aryne intermediacy (Scheme 2.13).

Scheme 2.13. Fluorination of an aryl bromide via benzyne intermediate



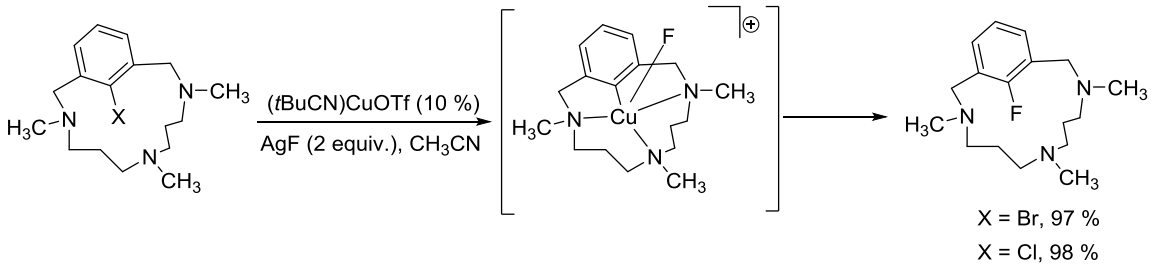
Ritter and co-workers reported a method for fluoroarene formation from phenols.[14] Specifically, a practical deoxyfluorination of phenols was developed using a fluorinating reagent that delivers aryl fluorides from phenols by a one-step *ipso* substitution. From mechanistic viewpoint, hydrogen bonding is crucial for the reaction to proceed. A wide range of common functional groups are tolerated and the method allows the access to complex molecules (Scheme 2.14).

Scheme 2.14. Deoxyfluorination of phenols



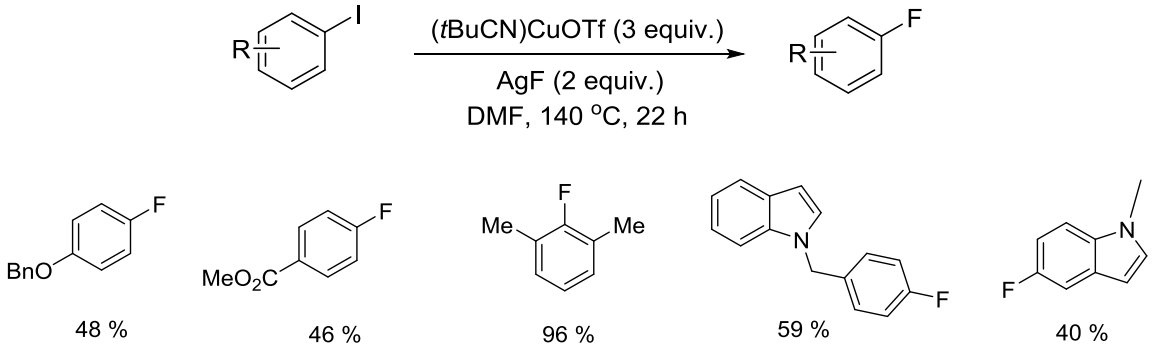
Reductive elimination of Ar-F from well-defined Ar-Cu(III)-F complexes has also been described.[15] Based on these precedents, a method for copper-catalyzed aryl halide fluorination in a macrocyclic polyamine system has been reported (Scheme 2.15). Reactions were proposed to proceed through the intermediacy of Ar-Cu(III)-F species. Furthermore, experimental and computational data support a redox Cu(I)/Cu(III) catalytic cycle involving Ar-X oxidative addition, followed by halide exchange and reductive elimination steps. For the first time, Ar-F reductive elimination from copper centers was shown. Although the work relies on an elaborate model system, these results provide mechanistic understanding for further developments of Cu-based fluorination.

Scheme 2.15. Catalytic fluorination of macrocyclic Ar-X (X = Cl, Br)



A method for copper-mediated direct conversion of aryl iodides to corresponding aryl fluorides has been disclosed.[16] The reactions occur with stoichiometric amounts of (*t*BuCN)CuOTf and silver fluoride in DMF solvent at 140 ^{o}C. Electron-rich, electron-poor, as well as sterically hindered aryl iodides are reactive affording products in good to excellent yields (Scheme 2.16). In addition, various functional groups are tolerated. Preliminary mechanistic results suggest facile reductive elimination from cationic arylcopper(III) fluoride.

Scheme 2.16. Copper-mediated fluorination of aryl iodides

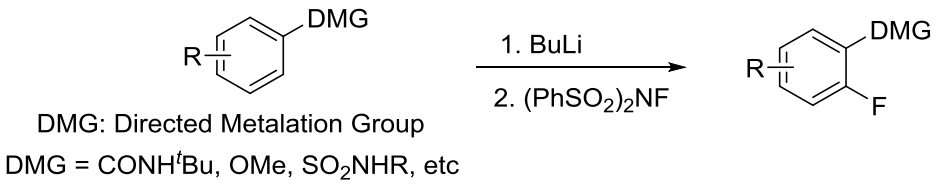


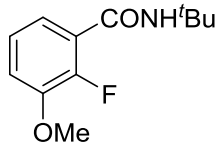
2.1.4. Direct Aryl Fluoride Formation from Arenes

As shown before, several procedures for transition-metal-catalyzed C-F bond formation have been developed and constitute powerful synthetic tools to complement conventional methods. However, the requirement of pre-functionalized starting materials limits their applications in late stage introduction of fluorine into biologically active molecules. Therefore, a method that can directly convert Ar-H bonds into Ar-F bonds would be highly desirable.

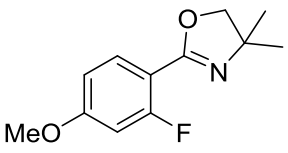
The *ortho*-lithiation/fluorination protocol with F^+ reported by Snieckus and Davis represented an important approach for regioselective fluorination of arenes in early 1990s.[17] In particular, *ortho*-metalated aromatic substrates generated *in situ* by treating arenes with *n*BuLi at low temperatures undergo reactions with *N*-fluorobenzenesulfonimide (NFSi) to provide regiospecifically fluorinated products (Scheme 2.17). However, reaction scope is limited and is not applicable to preparative scale synthesis.

Scheme 2.17. *ortho*-Lithiation/fluorination of arenes

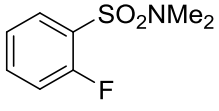




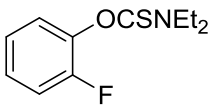
56 %



78 %



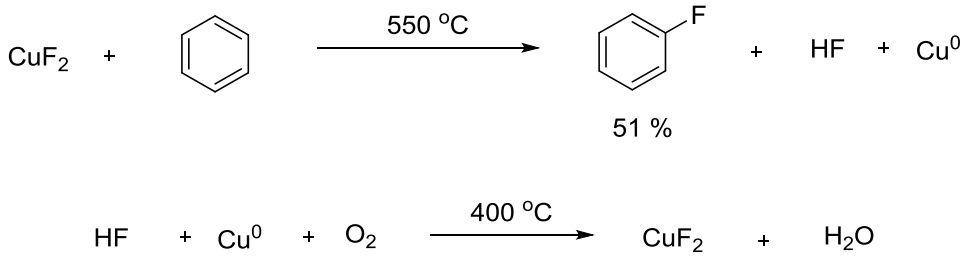
52 %



62 %

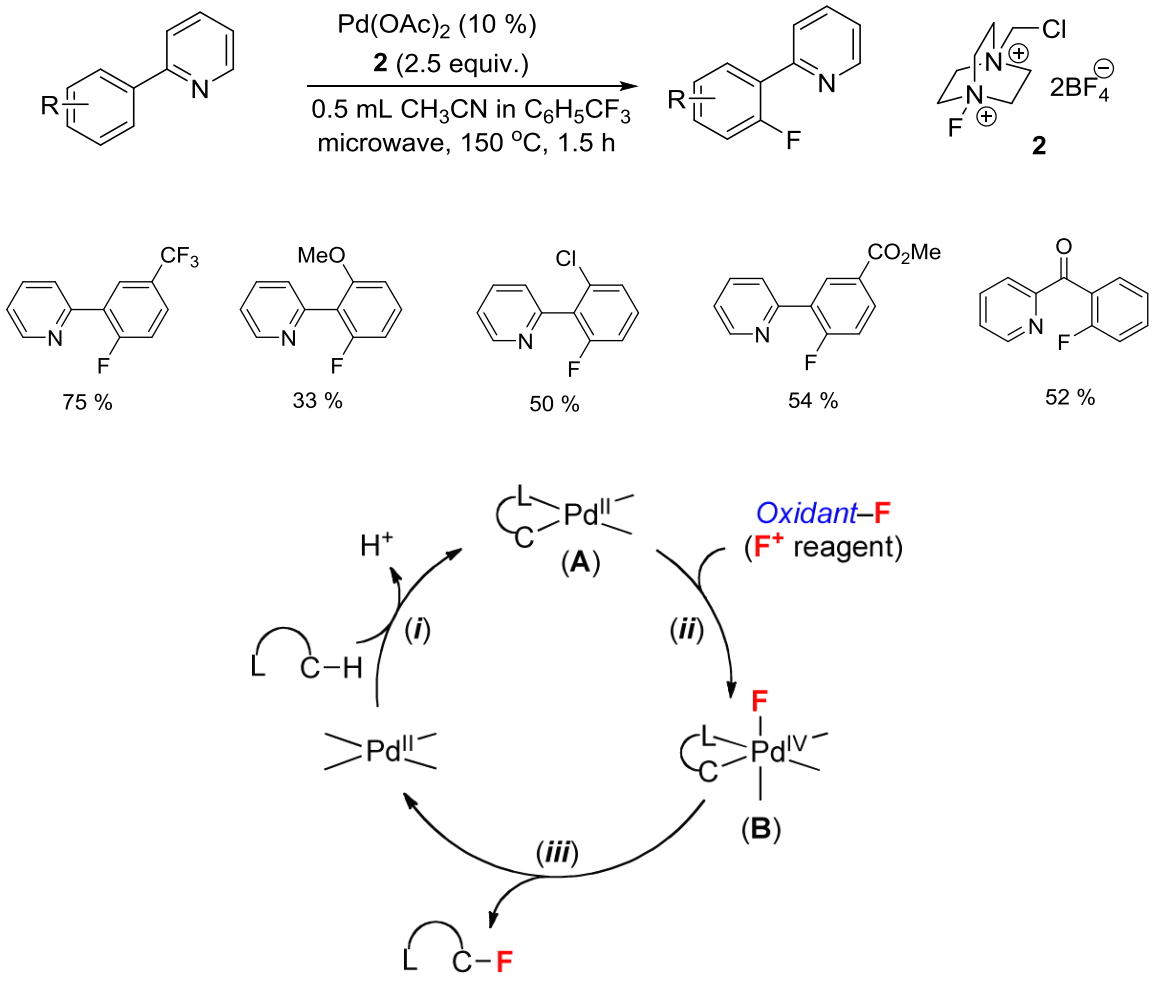
The process for the preparation of fluorobenzene from benzene has been described.[18] The method involves HF, oxygen, and Cu_2O. Acceptable yields were obtained only when high reaction temperature, 500 ^oC, was applied. The process produces H_2O as the only by-product and the reaction cycle is shown in Scheme 2.18.

Scheme 2.18. Fluorobenzene formation via copper (II) fluoride



In a pioneering study, Sanford and co-workers reported the first example of Pd(II)-catalyzed *ortho*-fluorination of C-H bonds in 2-phenylpyridine derivatives.[19] These reactions were achieved under oxidizing conditions using *N*-fluoro-2,4,6-trimethylpyridinium tetrafluorborate as electrophilic fluorinating reagent (Scheme 2.19). In most cases, microware irradiation is required to obtain reasonable yields. Difluoronation is also possible and reactions tolerate ketone, ester, and halide groups. Further mechanistic investigations into the reductive elimination of fluoride from Pd(IV) center provided evidence for the involvement of a Pd(II)/Pd(IV) catalytic cycle.[20]

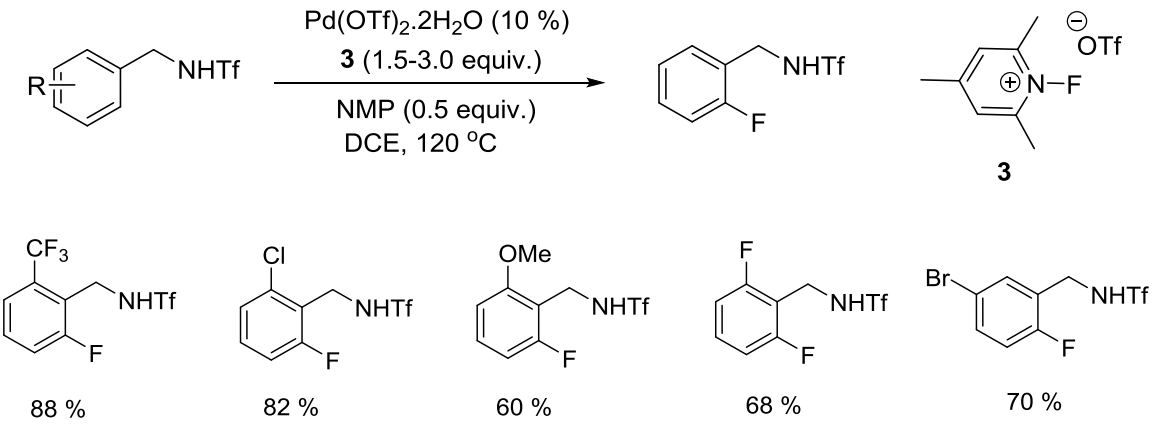
Scheme 2.19. Pd-catalyzed fluorination of 2-phenylpyridine derivatives



A method for palladium-catalyzed *ortho* sp^2 C-H bond fluorination with a removable directing group has also been developed.[21] Yu has demonstrated a protocol for efficient benzylamine triflamide *ortho*-fluorination using $Pd(OTf)_2*2H_2O$ catalyst, *N*-fluoro-2,4,6-trimethylpyridinium triflate F^+ source, and *N*-methylpyrrolidone (NMP) as a crucial promoter (Scheme 2.20). Notably, the aryl fluoride reductive elimination occurs at a satisfactory rate without microware irradiation. In addition, the facile displacement of

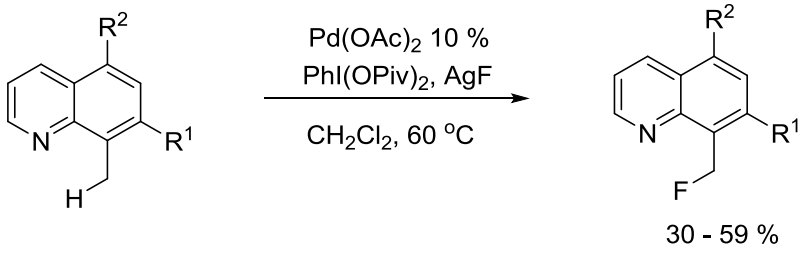
triflamide directing group with a wide range of heteroatom and carbon nucleophiles has been shown.

Scheme 2.20. Pd-catalyzed *ortho*-fluorination of benzylamine derivatives



The palladium-catalyzed C-H fluorination of 8-methylquinoline derivatives with nucleophilic fluoride was reported.[22] The transformation involves the use of silver(I) fluoride in combination with a hypervalent iodine oxidant (Scheme 2.21). Mechanistic studies indicated a key Pd(IV) complex intermediate and two possible pathways for formation of this complex were proposed.

Scheme 2.21. Pd-catalyzed fluorination of 8-methylquinoline derivatives



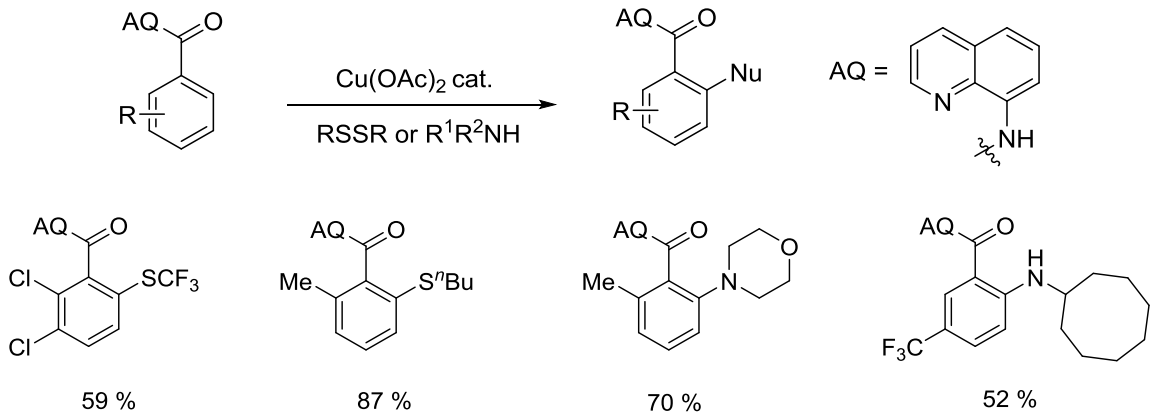
2.2. Copper-catalyzed Direct Fluorination of Sp^2 C-H Bonds

2.2.1. Introduction

Over the last few years, transition-metal catalysis has been exploited in creating aryl-fluorine bonds. Palladium-, silver-, and copper-based protocols have been developed to construct aryl-fluoride bonds via cross-coupling with arylmetals or aryl (pseudo)halides. Despite significant advances, the reaction generally remains limited by requirement of pre-functionalized starting materials. Thus, late stage fluorination in complex molecules is difficult to achieve. Efficient transformations for direct formation of aryl fluorides from arenes have also been described. However, in most cases, expensive palladium catalysts and electrophilic fluorinating reagents are required. A general procedure for non-noble transition-metal-catalyzed direct fluorination of sp^2 C-H bonds has not yet been disclosed.

Recently, our group described methods for copper-catalyzed sulfenylation and amination C-H bonds in 8-aminoquinoline benzamides and benzylamine picolinamides (Scheme 2.22).[23] In addition, C-H activation in macrocylic model substrates using copper salts has been shown.[15] Furthermore, reductive elimination from Ar-Cu(III)-F complexes has been observed.[11,15] Since it is likely that 8-aminoquinoline benzamide could stabilize high-valent copper intermediates, we reasoned that copper-catalyzed aminoquinoline and picolinamide-directed benzoic acid and benzylamine derivative *ortho*-fluorination is possible.

Scheme 2.22. Copper-catalyzed sulfenylation and amination of sp^2 C-H bonds

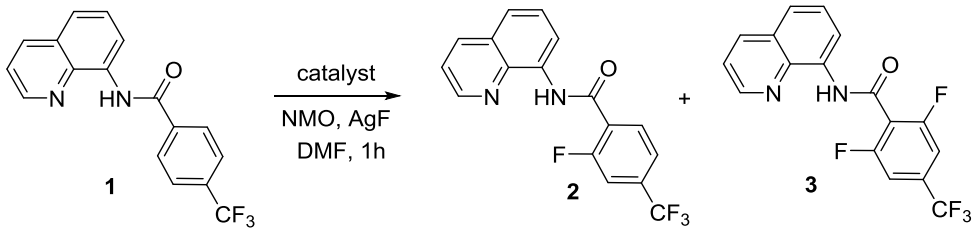


2.2.2. Results and Discussion

2.2.2.1. Monofluorination

Reaction optimization was conducted for monofluorination of *p*-trifluoromethyl-benzamide. Copper catalyst, fluorine source, oxidant, and solvent were investigated (Table 2.1). Oxygen and $Ph(OPiv)_2$ oxidants gave full conversion to product but low yields were obtained due to decomposition (entries 2 and 4). Similar phenomenon was observed when DMSO was used as a solvent (entries 1 and 2). In pyridine, acceptable yields were achieved although longer reaction time was required (entry 9). The optimal conditions for monofluorination involve CuI catalyst, AgF fluorine source, NMO oxidant, and DMF solvent.

Table 2.1. Optimization of Reaction Conditions[a]

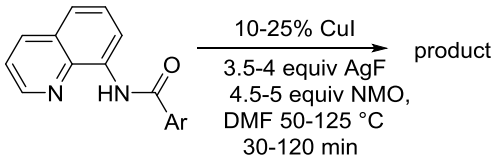


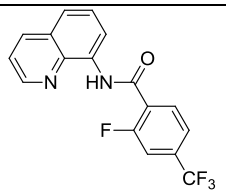
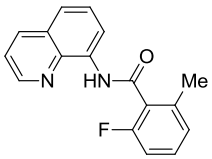
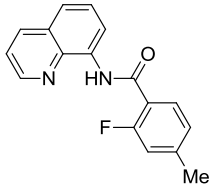
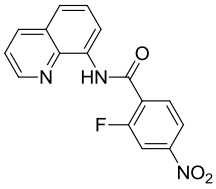
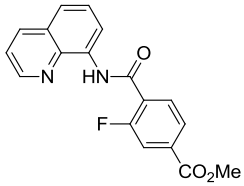
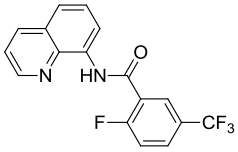
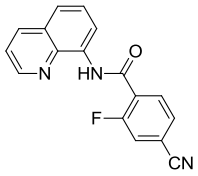
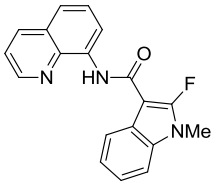
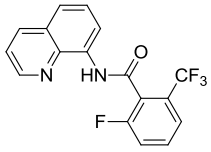
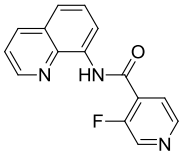
Entry	Catalyst (mol %)	T, °C	**1**, %	**2**, %	**3**, %
1[b]	$Cu(OAc)_2$ (25%)	100	4	17	5
2[b,c]	$Cu(OAc)_2$ (25%)	100	<2	13	4
3	$Cu(OAc)_2$ (25%)	100	20	42	8
4[d]	CuI (25%)	100	4	36	6
5	CuI (25%)	100	11	54	6
6	CuI (25%)	80	20	60	5
7	CuI (15%)	80	18	70	3
8[e]	CuI (15%)	80	4	79	7
9[e,f]	CuI (15%)	80	16	80	3
10[g]	CuI (20%)	80	<2	17	38
11[f,g]	CuI (20%)	80	10	52	33
12[g,h]	CuI (20%)	80	<2	5	78

[a] Amide 0.25 mmol, AgF 3 equiv, NMO 4 equiv, DMF 1 mL. [b] DMSO solvent. [c] $Ph(OPiv)_2$ oxidant instead of NMO. [d] O_2 was used. [e] AgF 4 equiv, NMO 5 equiv. [f] Pyridine solvent. [g] AgF 6 equiv, 8 equiv NMO, 1.5 h. [h] Pyridine additive 2 equiv.

Reaction scope with respect to monofluorination of 8-aminoquinoline benzamides is presented in Table 2.2. Electron-rich (entries 2 and 6) as well as electron-poor (entries 1, 3-5, 7, 8) benzamides are fluorinated in good yields. Reaction of *meta*-substituted benzamide gives monofluorinated product predominantly (entry 8). Heterocyclic 3-indolyl (entry 9) and 4-pyridinyl (entry 10) carboxamides are active. Nitrile, ester, and nitro groups are tolerated under reaction conditions. Pyridine solvent is required to prevent decomposition of strongly electron-deficient substrates such as 4-nitrobenzoyl and pyridyl derivatives (entries 7 and 10). However, longer reaction times are needed to obtain reasonable yields.

Table 2.2. Monofluorination reaction scope



Entry	Ar	Product	Yield, %	Entry	Ar	Product	Yield, %
1	4-$CF_3C_6H_4$		71	6	2-MeC_6H_4		63
2	4-MeC_6H_4		75	7[c]	4-$NO_2C_6H_4$		60
3	4-$MeO_2CC_6H_4$		56	8	3-$CF_3C_6H_4$		71
4	4-NCC_6H_4		62 60[b]	9	3-(*N*-Me-indolyl)		54
5	2-$CF_3C_6H_4$		80	10[c]	4-Pyridyl		62

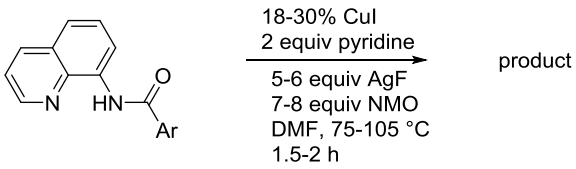
[a] Amide 0.25 mmol, DMF 1 mL. Yields are isolated yields. [b] Reaction scale: 5 mmol. [c] Pyridine solvent.

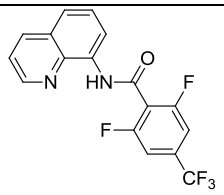
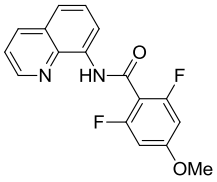
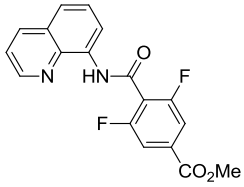
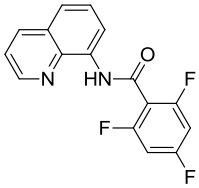
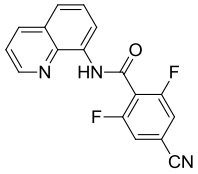
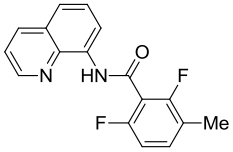
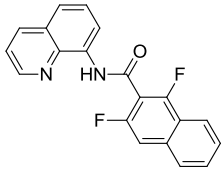
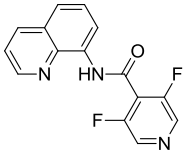
2.2.2.2. Difluorination

Optimization results in Table 2.1 show that fast decomposition and low yields were obtained when CuI and AgF loading, temperature, and reaction time were increased. As observed for monofluorination, the use of pyridine prevents decomposition of aminoquinoline amides. Difluorinated product was formed in good yield when two equivalents of pyridine were added in combination with six equivalents of AgF.

Reaction scope with respect to difluorination is presented in Table 2.3. Similar to monofluorination, difluorination of electron-rich (entries 4, 5, 7), electron-poor (entries 1-3, 6), and heterocyclic (entry 8) amides is possible. Interestingly, difluorination of *m*-substituted amides affords products in good yields (entries 4, 7). Palladium-catalyzed dual C-H functionalization of substrates that possess 3-substituents is not efficient and thus products such as the one generated in entries 4 and 7 typically cannot be accessed under palladium catalysis.

Table 2.3. Difluorination of Carboxylic Acid Derivatives[a]

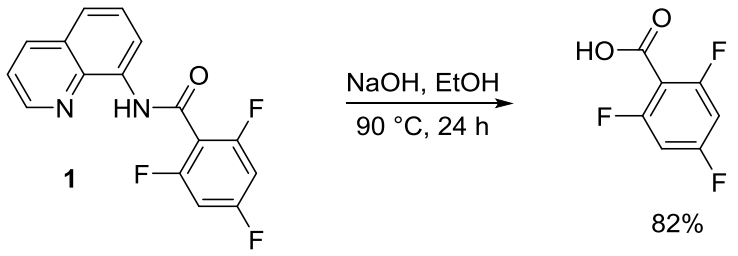


Entry	Ar	Product	Yield, %	Entry	Ar	Product	Yield, %
1	4-$CF_3C_6H_4$		67	5	4-$MeOC_6H_4$		75
2	4-$MeO_2CC_6H_4$		62	6	4-FC_6H_4		61
3	NCC_6H_4		70	7	3-MeC_6H_4		77
4	2-Naphthyl		70	8[b]	4-Pyridyl		61

[a] Amide 0.25 mmol, DMF 1 mL. Yields are isolated yields. [b] Pyridine solvent.

The 8-aminoquinoline group can be efficiently removed by base hydrolysis. Thus, high yield of trifluorobenzoic acid was obtained when amide **1** was treated with NaOH in ethanol (Scheme 2.23).

Scheme 2.23. Removal of directing group



2.2.3. Conclusions

A method for direct, auxiliary-assisted fluorination of β-sp^2 C−H bonds of benzoic acid derivatives has been developed. The reaction employs catalytic CuI (10-30 %), AgF as nucleophilic fluoride source, and DMF or pyridine solvent at moderately elevated temperatures. High generality, excellent selectivity toward *ortho* C−H bonds, as well as good functional group tolerance are observed.

2.2.4. Experimental Section

General Considerations:

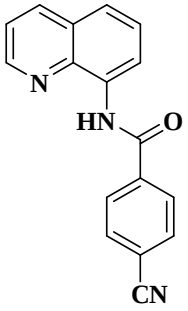
Reactions were run in 1-dram vials using screw caps with PTFE/Liner (from SUPELCO). Column chromatography was performed on 60Å silica gel (Dynamic Adsorbents Inc.). Purification by preparative HPLC was performed on a Shimadzu Prominence LC (LC-20AB) equipped with a SPD-20A UV-Vis detector and a Varian Dynamax (250 mm x 21.4 mm) column. GC-MS analyses were performed on a Shimadzu GCMS-QP5000 chromatograph equipped with a Restek column (Rtx-XLB, 30 m x 0.25 mm I.D.). The ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR were recorded on JEOL EC-400 or JEOL EC-500 spectrometers using residual solvent peak as a reference. Compounds for HRMS were analyzed by positive mode electrospray ionization (ESI) using Agilent QTOF mass spectrometer in the Mass Spectrometry Facility (MSF) of the Department of Chemistry and Biochemistry of University of Texas-Austin. IR-spectra were obtained using a Perkin Elmer Spectrum 100 FT-IR spectrometer. Analytical thin layer chromatography was performed on silica gel IB-F (Baker-flex) by J. T. Baker. All procedures were performed under nitrogen atmosphere unless otherwise noted.

Materials. The following starting materials were obtained from commercial sources and were used without further purification: 8-aminoquinoline, 4-trifluoromethylbenzoyl chloride, 4-methylbenzoyl chloride, 4-cyanobenzoyl chloride, 4-nitrobenzoyl chloride, 3-trifluoromethylbenzoyl chloride, 2-trifluoromethylbenzoyl chloride, 2-naphthoyl chloride, isonicotinic acid, 4-(methoxycarbonyl)benzoic acid, 2-methylbenzoyl chloride, 1-methyl-1H-indole-3-carboxylic acid, 4-fluorobenzoyl chloride, 3-methylbenzoyl

chloride, 4-methoxybenzoyl chloride, silver(I) fluoride, *N*-methylmorphorine oxide (NMO), dimethylformamide, pyridine, thionyl chloride, triethylamine, picolinic acid, *tert*-butyl benzonitrile, 2-phenylpropan-2-amine, dimethylformamide (DMF)

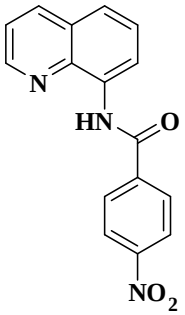
Synthesis of Amides

These amides were synthesized according to literature procedures: *N*-(quinolin-8-yl)-4-(trifluoromethyl)benzamide, *N*-(quinolin-8-yl)-4-methylbenzamide, methyl 4-(quinolin-8-ylcarbamoyl)benzoate, *N*-(quinolin-8-yl)-2-(trifluoromethyl)benzamide, *N*-(quinolin-8-yl)-2-methylbenzamide, *N*-(quinolin-8-yl)-5-(trifluoromethyl)benzamide, *N*-(quinolin-8-yl)-2-naphthamide, *N*-(1-methyl-1-phenylethyl)picolinamide.[23,24,25]



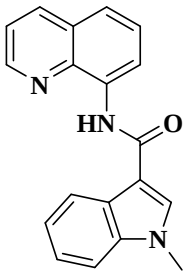
4-Cyano-*N*-(quinolin-8-yl)benzamide: 8-Aminoquinoline (1.44 g, 10 mmol) and triethylamine (1.8 mL, 13 mmol) were dissolved in anhydrous CH_2Cl_2 (20 mL) in a 100 mL round-bottom flask followed by dropwise addition of suspension of 4-cyanobenzoyl chloride (2.15 g, 13 mmol) in 50 mL of CH_2Cl_2 though syringe. The reaction mixture was stirred overnight. After completion, the reaction was diluted with CH_2Cl_2 (50 mL), washed by aqueous HCl (15 mL, 1N), $NaHCO_3$ (saturated aqueous solution, 15 mL), brine (25 mL), and dried over $MgSO_4$. The organic solvent was removed by evaporation. Purification by column chromatography in hexanes/EtOAc (70/30) afforded 2.54 g of

amide (94 %) as an off white solid. R_f = 0.52 (hexane/EtOAc 70/30), mp 150 – 152 ^oC (from diethyl ether). ^1H NMR (400 MHz, $CDCl_3$) δ 10.77 (s, 1H), 8.88 (dd, *J* = 6.7 Hz, 2.4 Hz, 1H), 8.84 (dd, *J* = 4.6 Hz, 1.7 Hz, 1H), 8.20 (dd, *J* = 8.0 Hz, 1.7 Hz, 1H), 8.17 – 8.14 (m, 2H), 7.84 – 7.81 (m, 2H), 7.60 – 7.56 (m, 2H), 7.50 (dd, *J* = 8.0 Hz, 4.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.5, 148.6, 139.0, 138.7, 136.6, 134.0, 132.7, 128.1, 128.0, 127.5, 122.5, 122.0, 118.2, 116.9, 115.4. HRMS (EIS+): Calculated for $C_{17}H_{11}N_3O$ $[M+H]^+$ 274.09749, Found 274.09748.



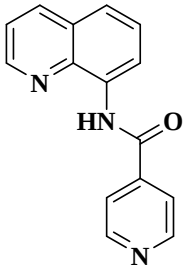
4-Nitro-*N*-(quinolin-8-yl)benzamide: 8-Aminoquinoline (1.44 g, 10 mmol) and triethylamine (1.8 mL, 13 mmol) were dissolved in anhydrous CH_2Cl_2 (20 mL) in a 100 mL round-bottom flask followed by dropwise addition of suspension of 4-nitrobenzoyl chloride (2.4 g, 13 mmol) in 50 mL of CH_2Cl_2 though syringe. The reaction mixture was stirred overnight. After completion, the reaction was diluted with CH_2Cl_2 (50 mL), washed by aqueous HCl (2 x 15 mL, 1N), $NaHCO_3$ (saturated aqueous solution, 15 mL x 2), brine (25 mL), and dried over $MgSO_4$. The organic solvent was removed to afford 2.78 g of amide (96 %) as a yellow solid. R_f = 0.49 (hexane/EtOAc 70/30), mp 158 – 159 ^oC (from diethyl ether). ^1H NMR (400 MHz, $CDCl_3$) δ 10.81 (s, 1H), 8.89 (dd, *J* = 5.9 Hz, 3.2 Hz, 1H), 8.86 (dd, *J* = 4.5 Hz, 1.7 Hz, 1H), 8.40 – 8.36 (m, 2H), 8.24 – 8.20 (m,

3H), 7.63 – 7.56 (m, 2H), 7.51 (dd, *J* = 8.2 Hz, 4.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.3, 149.8, 148.6, 140.7, 138.7, 136.7, 133.9, 128.6, 128.1, 127.5, 124.1, 122.6, 122.1, 116.9. HRMS (EIS+): Calculated for $C_{16}H_{11}N_3O_3$ $[M+H]^+$ 294.08732, Found 294.08705.



1-Methyl-*N*-(quinolin-8-yl)-1H-indole-3-carboxamide: 8-Aminoquinoline (1.44 g, 10 mmol) and triethylamine (3.6 mL, 26 mmol) were dissolved in anhydrous CH_2Cl_2 (20 mL) in a 100 mL round-bottom flask followed by dropwise addition of suspension of 1-methyl-1H-indole-3-carbonyl chloride in 30 mL of CH_2Cl_2 though syringe. The acid chloride was prepared from 1-methyl-1H-indole-3-carboxylic acid (2.3 g, 13 mmol).[23] The reaction mixture was stirred overnight. After completion, the reaction was diluted with CH_2Cl_2 (50 mL), washed by aqueous HCl (15 mL, 1N), $NaHCO_3$ (saturated aqueous solution, 15 mL), brine (25 mL), and dried over $MgSO_4$. The organic solvent was removed by evaporation. Purification by column chromatography in hexane/EtOAc (50/50) afforded 2.31 g of amide (77 %) as a light yellow solid. R_f = 0.38 (hexane/EtOAc 50/50), mp 184 – 186 ^{o}C (from acetonitrile). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.55 (s, 1H), 8.94 (dd, *J* = 7.3 Hz, 1..4 Hz, 1H), 8.88 (dd, *J* = 4.5 Hz, 1.7 Hz, 1H), 8.47 – 8.44 (m, 1H), 8.17 (dd, *J* = 8.0 Hz, 1.4 Hz, 1H), 7.91 (s, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.50 – 7.48 (m, 1H), 7.46 (t, *J* = 4.5 Hz, 1H), 7.40 – 7.32 (m, 3H), 3.87 (s, 3H). ^{13}C NMR (100 MHz,

$CDCl_3$, ppm) δ 163.5, 148.2, 138.7, 137.5, 136.5, 135.3, 133.2, 128.1, 127.7, 125.5, 122.8, 122.0, 121.7, 121.0, 120.8, 116.4, 111.8, 110.2, 33.6. HRMS (EIS+): Calculated for $C_{19}H_{15}N_3O$ $[M+H]^+$ 302.12879, Found 302.12871.



***N*-(Quinolin-8-yl)isonicotinamide:** 8-Aminoquinoline (1.44 g, 10 mmol) and triethyl amine (3.6 mL, 26 mmol) were dissolved in anhydrous CH_2Cl_2 (20 mL) in a 100 mL round-bottom flask followed by dropwise addition of suspension of isonicotinoyl chloride in 30 mL of CH_2Cl_2 though syringe. The acid chloride was prepared from isonicotinic acid (1.6 g, 13 mmol).[24] The reaction mixture was stirred overnight. After completion, the reaction was diluted with CH_2Cl_2 (50 mL), washed by aqueous HCl (15 mL, 1N), $NaHCO_3$ (saturated aqueous solution, 15 mL), brine (25 mL), and dried over $MgSO_4$. The organic solvent was removed by evaporation. Purification by column chromatography in toluene/EtOAc (50/50) afforded 2.2 g of amide (89 %) as an off-white solid. R_f = 0.49 (toluene/EtOAc 50/50), mp 126 – 128 ^oC (from diethyl ether). ^1H NMR (400 MHz, $CDCl_3$) δ 10.80 (s, 1H), 8.88 (dd, *J* = 6.1 Hz, 3.0 Hz, 1H), 8.86 – 8.82 (m, 3H), 8.18 (dd, *J* = 8.2 Hz, 1.7 Hz, 1H), 7.89 (dd, *J* = 4.5 Hz, 1.7 Hz, 2H), 7.60 – 7.55 (m, 2H), 7.48 (dd, *J* = 8.2 Hz, 4.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.4, 151.0, 148.6, 142.1, 138.7, 136.6, 133.9, 128.1, 127.5, 122.6, 122.0, 121.1, 117.0. HRMS (EIS+): Calculated for $C_{15}H_{11}N_3O$ $[M+H]^+$ 250.09749, Found 250.09737.

General procedure for copper-catalyzed monofluorination of quinoline amides in DMF

A 1 dram vial equipped with a magnetic stir bar was charged with amide (0.25 mmol, 1 equiv) and copper iodide (10 – 30 %). The vial was flushed with nitrogen, capped, and placed inside the glovebox. To this mixture was added NMO (3 – 4 equiv.), AgF (3 – 4 equiv.), and anhydrous DMF (1.0 mL). The sealed vial was taken out the glovebox, strongly shaken, and stirred at room temperature for 5 minutes, covered with aluminum foil, and then transferred to preheated oil bath for indicated time. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (2 mL). The suspension was filtered through a pad of Celite® and solid phase was washed with ethyl acetate (4 x 20 mL). The filtrate was concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel in hexane followed by appropriate solvent to elute the products. After concentrating the fractions containing the product, the residue was dried under reduced pressure.

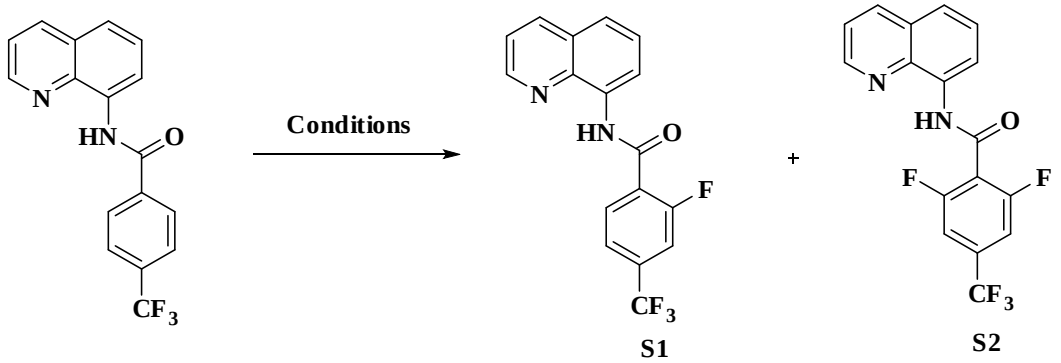
General procedure for copper-catalyzed monofluorination of quinoline amides in pyridine

A 1 dram vial equipped with a magnetic stir bar was charged with amide (0.25 mmol, 1 equiv), copper iodide (10 – 30 %), and pyridine (1 mL). The vial was stirred at room temperature for 3 minutes and then flushed with nitrogen, capped, and placed inside the glovebox. To this mixture was added NMO (3 – 4 equiv) and AgF (3 – 4 equiv). The sealed vial was taken out the glovebox, strongly shaken, stirred at room temperature for 5 minutes, covered with aluminum foil, and then transferred to preheated oil bath for

indicated time. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (2 mL). The suspension was filtered through a pad of Celite® and solid phase was washed with ethyl acetate (4 x 20 mL). The filtrate was concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel in hexane followed by appropriate solvent to elute the products. After concentrating the fractions containing the product, the residue was dried under reduced pressure.

Note: Premixing each and every substance before adding solvent, vigorous stirring (approximately 1500 rpm) at room temperature at least 5 minutes and during reaction time are crucial for reproducible yields.

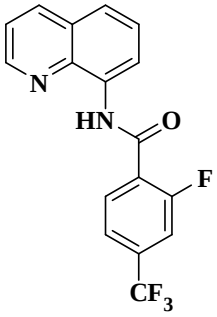
Optimization of monofluorination of quinoline amides: All reactions were carried out following the general procedure using *N*-(4-trifluoromethylbenzoyl)-8-aminoquinoline (80 mg, 0.25 mmol), fluorine source (3 equiv.), oxidant (4 equiv.), solvent (1 mL), 1 hour. 1,3-Dichlorobenzene (5 μL) was added at the end of reaction as external standard. Conversion and GC yields were calculated by GC analysis and presented in Table 2.S1. Mixture with exact molar amounts of pure product and 1.3-dichlorobenzene was used as the standard to determine GC yields. Mixture with exact molar amounts of 1,3-dichlorobenzene and starting material was used as the standard to determine percent of recovered starting material.



Catalysts (%)	Fluoro source	Oxidant	Solvent	T (^{o}C)	% unreacted SM	**S1 (%)**	**S2 (%)**
$Cu(OAc)_2$ (25%)	CsF	NMO	DMSO	100	94		
$Cu(OAc)_2$ (25%)	AgF	NMO	DMSO	100	4	17	5
$Cu(OAc)_2$ (25%)	AgF	O_2 (balloon)	DMSO	100	10	11	3
$Cu(OAc)_2$ (25%)	AgF	Ag_2O	DMSO	100	7	6	12
$Cu(OAc)_2$ (25%)	AgF	$PhI(OPiv)_2$	DMSO	100	< 2	13	4
$Cu(OAc)_2$ (25%)	AgF	NMO	Dioxane	100	55	32	< 2
$Cu(OAc)_2$ (25%)	AgF	NMO	DMF	100	20	42	8
Cu(OTf)(*t*BuCN) (25%)	AgF	NMO	DMF	100	10	55	6
CuI (25%)	AgF	NMO	DMF	100	11	54	6
CuI (25%)	AgF	NMO	DMF	80	20	60	5
CuI (25%)	AgF	NMO	DMF	60	33	55	< 2
CuI(15%)	AgF	NMO	DMF	80	18	70	3
CuI (15%)	AgF (2 equiv.)	NMO	DMF	80	35	44	< 2
CuI (5 %)	AgF	NMO	DMF	80	33	59	5

CuI (15%)	AgF (4 equiv.)	NMO (5 equiv.)	DMF	80	4	79	7
CuI (15 %)	AgF	None	DMF	80	15	4	< 2
CuI(15%)	AgF (4 equiv.)	NMO (5 equiv.)	Pyridine[a]	80	16	80	3
$NiCl_2$ (20 %)	AgF	NMO	DMF	80	> 98		
$CoCl_2$ (20 %)	AgF	NMO	DMF	80	> 98		
$FeCl_3$ (20 %)	AgF	NMO	DMF	80	> 98		
$MnCl_2$ (20 %)	AgF	NMO	DMF	80	> 98		

(a) reaction was run for 2 hours.



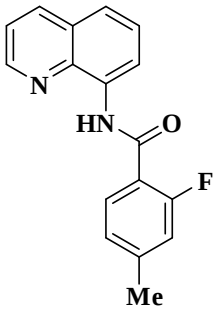
2-Fluoro-*N*-(quinolin-8-yl)-4-(trifluoromethyl)benzamide (Table 2.2, Entry 1)

N-(Quinolin-8-yl)-4-(trifluoromethyl)benzamide (80 mg, 0.25 mmol), CuI (7.1 mg, 0.0375 mmol), AgF (96 mg, 0.75 mmol), NMO (118 mg, 1.0 mmol), DMF (1.0 mL), 80 ^{o}C, 30 minutes. After column chromatography (hexanes, followed by gradient hexanes/EtOAc from 95/5 to 90/10), 50 mg (60 %) of a white solid was obtained.

N-(Quinolin-8-yl)-4-(trifluoromethyl)benzamide (80 mg, 0.25 mmol), CuI (7.1 mg, 0.0375 mmol), AgF (127 mg, 1.0 mmol), NMO (150 mg, 1.25 mmol), DMF (1.0 mL), 80

^{o}C, 30 minutes. After column chromatography (hexanes, followed by gradient hexanes/EtOAc from 95/5 to 90/10), 59 mg (71 %) of a white solid was obtained.

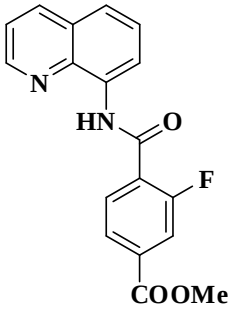
R_f = 0.32 (hexanes/EtOAc 90/10), mp 82 – 84 ^{o}C (from diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.15 (s, 1H), 8.93 (dd, *J* = 6.0 Hz, 3.2 Hz, 1H), 8.86 (dd, *J* = 4.5 Hz, 1.3 Hz, 1H), 8.33 (t, *J* = 7.8 Hz, 1H), 8.17 (dd, *J* = 8.2 Hz, 1.3 Hz, 1H), 7.60 – 7.55 (m, 3H), 7.52 – 7.45 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 160.2 (d, *J* = 2.5 Hz), 160.0 (d, *J* = 252 Hz), 148.7, 138.8, 136.4, 135.3 (dq. *J* = 34 Hz, 8.7 Hz), 134.5, 133.2 (d, *J* = 2.5 Hz), 128.0, 127.4, 125.4 (d, *J* = 11.3 Hz), 122.8 (dq, *J* = 274 Hz, 2.5 Hz), 122.6, 121.9, 121.8 (septet, *J* = 3.6 Hz), 117.5, 114.2 (qq, *J* = 28 Hz, 3.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3$, ppm) -63.0 – - 62.9 (m, 3F), -109.9 – -109.8 (m, 1F). HRMS (EIS+): Calculated for $C_{17}H_{10}F_4N_2O$ $[M+H]^+$ 335.08021, Found 335.08050.



2-Fluoro-*N*-(quinolin-8-yl)-4-methylbenzamide (Table 2.2, Entry 2)

N-(Quinolin-8-yl)-4-methylbenzamide (66 mg, 0.25 mmol), CuI (12.0 mg, 0.0625 mmol), AgF (112 mg, 0.875 mmol), NMO (134 mg, 1.125 mmol), DMF (1.0 mL), 105 ^{o}C, 75 minutes. After column chromatography (hexanes, followed by gradient hexanes/EtOAc from 95/5 to 90/10), 52 mg (75 %) of a white solid was obtained. R_f = 0.31 (hexanes/EtOAc 90/10), mp 112 – 114 ^{o}C (from diethyl ether). ^{1}H NMR (400 MHz,

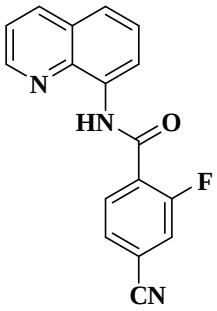
$CDCl_3$, ppm) δ10.15 (s, 1H), 8.97 (dd, *J* = 7.5 Hz, 1.3 Hz, 1H), 8.77 (dd, *J* = 4.3 Hz, 1.7 Hz, 1H), 8.17 (dd, *J* = 8.1 Hz, 1.7 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.45 (dd, *J* = 8.7 Hz, 4.3 Hz, 1H), 7.34 – 7.30 (m, 1H), 7.08 (d, *J* = 8.1 Hz, 1H), 7.02 (t, *J* = 8.7 Hz, 1H), 2.51 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.7, 159.6 (d, *J* = 248 Hz), 148.5, 138.8 (d, *J* = 3.1 Hz), 138.5, 136.5, 134.4, 130.9 (d, *J* = 9.5 Hz), 128.1, 127.5, 126.5 (d, *J* = 3.1 Hz), 125.4 (d, *J* = 17 Hz), 122.2, 121.8, 116.9.113.4 (d, *J* = 22.4), 19.7. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) -115.8 – -115.7 (s, 1F). HRMS (EIS+): Calculated for $C_{17}H_{13}FN_2O$ $[M+H]^+$ 281.10847, Found 281.10851.



Methyl 3-fluoro-4-(quinolin-8-ylcarbamoyl)benzoate (Table 2.2, Entry 3)

Methyl 4-(quinolin-8-ylcarbamoyl)benzoate (77 mg, 0.25 mmol), CuI (4.8 mg, 0.025 mmol), AgF (127 mg, 1.0 mmol), NMO (150 mg, 1.25 mmol), DMF (1.0 mL), 90 ^{o}C, 1 hour. After column chromatography (hexanes, followed by gradient hexanes/EtOAc from 95/5 to 80/20), 45 mg (56 %) of a white solid was obtained. R_f = 0.36 (hexanes/EtOAc 80/20), mp 124 – 125 ^{o}C (from diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 11.18 (s, 1H), 8.95 (dd, *J* = 6.8 Hz, 2.3 Hz, 1H), 8.87 (dd, *J* = 4.5 Hz, 1.7 Hz, 1H), 8.27 (t, *J* = 8.0 Hz, 1H), 8.18 (dd, *J* = 8.0 Hz, 1.7 Hz, 1H), 7.97 (dd, *J* = 8.2 Hz, 1.7 Hz, 1H), 7.89 (dd, *J* = 11.5 Hz, 1.7 Hz, 1H), 7.60 – 7.55 (m, 2H), 7.47 (dd, *J* = 8.2 Hz, 4.5 Hz, 1H),

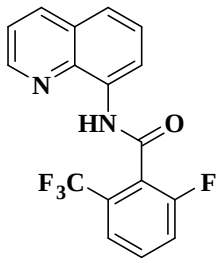
3.96 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 165.3 (d, *J* = 2.4 Hz), 160.7 (d, *J* = 3.5 Hz), 160.2 (d, *J* = 249 Hz), 148.7, 138.8, 136.4, 135.0 (d, *J* = 9.3 Hz), 134.6, 132.4, 128.1, 127.5, 126.0 (d, *J* = 12.3 Hz), 125.8 (*J* = 3.5 Hz), 122.5, 121.9, 117.7 (d, *J* = 26.6 Hz), 117.5, 52.8. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) -111.4 – -111.3 (s, 1F). HRMS (EIS+): Calculated for $C_{18}H_{13}FN_2O_3$ $[M+H]^+$ 325.09830, Found 325.09837.



4-Cyano-2-fluoro-*N*-(quinolin-8-yl)benzamide (Table 2.2, Entry 4)

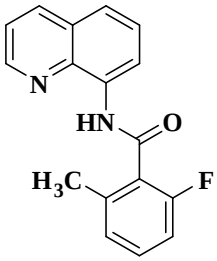
4-Cyano-*N*-(quinolin-8-yl)benzamide (69 mg, 0.25 mmol), CuI (5.7 mg, 0.03 mmol), AgF (112 mg, 0.875 mmol), NMO (134 mg, 1.125 mmol), DMF (1.0 mL), 65 ^{o}C, 75 minutes. After column chromatography (hexanes, followed by gradient hexanes/EtOAc from 95/5 to 80/20), 45 mg (62 %) of a white solid was obtained. R_f = 0.34 (hexanes/EtOAc 80/20), mp 141 – 143 ^{o}C (from diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.16 (s, 1H), 8.92 (t, *J* = 4.5 Hz,, 1H), 8.86 (dd, *J* = 4.5 Hz, 1.7 Hz, 1H), 8.32 (t, *J* = 7.8 Hz, 1H), 8.19 (dd, *J* = 8.2 Hz, 1.4 Hz, 1H), 7.64 – 7.58 (m, 3H), 7.55 (dd, *J* = 10.4 Hz, 1.4 Hz, 1H), 7.49 (dd, *J* = 8.2 Hz, 4.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 159.8 (d, *J* = 252 Hz), 159.7 (d, *J* = 3.6 Hz), 148.8, 138.7, 136.5, 134.3, 133.4 (d, *J* = 2.4 Hz), 128.7 (d, *J* = 3.6 Hz), 128.1, 127.5, 126.6 (d, *J* = 12.4 Hz), 122.9, 122.0 , 120.4 (d, *J* = 28.2 Hz), 117.6, 116.9 (d, *J* = 2.0 Hz), 116.7 (d, *J* = 10.6 Hz). ^{19}F NMR

(376 MHz, $CDCl_3$, ppm) -109.4 – -109.3 (s, 1F). HRMS (EIS+): Calculated for $C_{17}H_{10}F_4N_3O$ $[M+H]^+$ 292.08807, Found 292.08780.



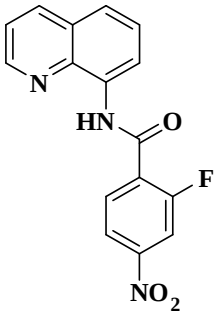
2-Fluoro-*N*-(quinolin-8-yl)-6-(trifluoromethyl)benzamide (Table 2.2, Entry 5)

N-(Quinolin-8-yl)-2-(trifluoromethyl)benzamide (80 mg, 0.25 mmol), CuI (9.6 mg, 0.05 mmol), AgF (127 mg, 1.0 mmol), NMO (150 mg, 1.25 mmol), DMF (1.0 mL), 120 ^oC, 90 minutes. After column chromatography (hexanes, followed by gradient hexanes/EtOAc from 95/5 to 90/10), 66 mg (80 %) of a white solid was obtained. R_f = 0.34 (hexanes/EtOAc 90/10), mp 74 – 76 ^oC (from diethyl ether). ^1H NMR (400 MHz, $CDCl_3$) δ 10.15 (s, 1H), 8.92 (dd, *J* =6.0 Hz, 2.8 Hz, 1H), 8.74 (dd, *J* = 4.3 Hz, 1.7 Hz, 1H), 8.17 (dd, *J* = 8.3 Hz, 1.7 Hz, 1H), 7.61 – 7.57 (m, 4H), 7.45 – 7.38 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 160.7, 159.5 (d, *J* = 252 Hz), 148.5, 138.4, 136.5, 134.1, 131.5 (d, *J* = 8.7 Hz), 129.6 (dq, *J* = 33 Hz, 3.5 Hz), 128.0, 127.5, 124.4 (dd, *J* = 8.7 Hz, 1.8 Hz), 123.2 (dq, *J* = 261 Hz, 1.8 Hz), 122.6, 122.3 (septet, J = 4. 2 Hz), 121.9, 120.1 (d, *J* = 22.4), 117.2. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) -59.0 – -58.7 (s, 3F), -113.0 – -112.9 (m, 1F). HRMS (EIS+): Calculated for $C_{17}H_{10}F_4N_2O$ $[M+H]^+$ 335.08021, Found 335.08056.



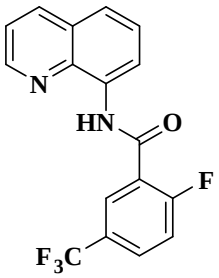
2-Fluoro-*N*-(quinolin-8-yl)-6-methylbenzamide (Table 2.2, Entry 6)

N-(Quinolin-8-yl)-2-methylbenzamide (66 mg, 0.25 mmol), CuI (12.0 mg, 0.0625 mmol), AgF (127 mg, 1.0 mmol), NMO (150 mg, 1.25 mmol), DMF (1.0 mL), 120 ^{o}C, 20 minutes. After column chromatography (hexanes, followed by gradient hexanes/EtOAc from 95/5 to 88/12), 44 mg (63 %) of a white solid was obtained. R_f = 0.32 (hexanes/EtOAc 90/10), mp 88 – 89 ^{o}C (from diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.15 (s, 1H), 8.97 (dd, *J* = 7.5 Hz, 1.4 Hz, 1H), 8.76 (dd, *J* = 4.2 Hz, 1.7 Hz, 1H), 8.17 (dd, *J* = 8.1 Hz, 1.7 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.45 (dd, *J* = 8.1 Hz, 4.2 Hz, 1H), 7.34 – 7.29 (m, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 8.9 Hz,1H), 2.51 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.7, 159.6 (d, *J* = 249 Hz), 148.5, 138.9 (d, *J* = 3.5 Hz), 138.5, 136.5, 134.4, 130.9 (d, *J* = 9.5 Hz), 128.1, 127.5, 126.5 (d, *J* = 2.4 Hz), 125.4 (d, *J* = 17 Hz), 122.3, 121.8, 116.9, 113.4 (d, *J* = 22.1 Hz), 19.7. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) -115.8 – -115.7 (s, 1F). HRMS (EIS+): Calculated for $C_{17}H_{13}FN_2O$ $[M+H]^+$ 281.10847, Found 281.10866.



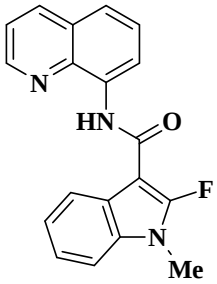
2-Fluoro-4-nitro-*N*-(quinolin-8-yl)benzamide (Table 2.2, Entry 7)

4-Nitro-*N*-(quinolin-8-yl)benzamide (74 mg, 0.25 mmol), CuI (5.7 mg, 0.03 mmol), AgF (127 mg, 1.0 mmol), NMO (150 mg, 1.25 mmol), pyridine (1.0 mL), 60 ^{o}C, 2 hours. After column chromatography (hexanes, followed by gradient hexanes/EtOAc from 95/5 to 80/20), 46 mg (60 %) of a light yellow solid was obtained. R_f = 0.28 (hexanes/EtOAc 80/20), mp 151 – 152 ^{o}C (from diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.20 (d, *J* = 10.8 Hz, 1H), 8.94 – 8.92 (m, 1H), 8.88 (dd, *J* = 4.4 Hz, 1.4 Hz, 1H), 8.41 (t, *J* = 7.8 Hz, 1H), 8.22 – 8.17 (m, 2H), 8.12 (dd, *J* = 10.8 Hz, 1.7 Hz, 1H), 7.62 – 7.60 (m, 2H), 7.51 (dd, *J* = 8.2 Hz, 4.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 159.9 (d, *J* = 254 Hz), 159.4, 159.3, 148.8, 138.8, 136.4, 134.3, 133.4 (d, *J* = 2.4 Hz), 128.1, 128.0 (d, *J* = 12.3 Hz), 127.4, 122.9, 122.0, 119.7 (d, *J* = 3.6 Hz), 117.7, 112.5 (d, *J* = 29.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$, ppm) -107.8 – -107.9 (s, 1F). HRMS (EIS+): Calculated for $C_{16}H_{10}FN_3O_3$ $[M+H]^+$ 312.07790, Found 312.07793.



2-Fluoro-*N*-(quinolin-8-yl)-5-(trifluoromethyl)benzamide (Table 2.2, Entry 8)

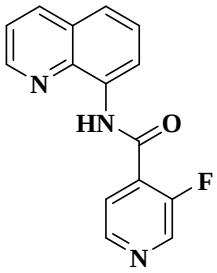
N-(Quinolin-8-yl)-5-(trifluoromethyl)benzamide (80 mg, 0.25 mmol), CuI (5.7 mg, 0.03 mmol), AgF (127 mg, 1.0 mmol), NMO (150 mg, 1.25 mmol), DMF (1.0 mL), 100 ^{o}C, 45 minutes. After column chromatography (hexanes, followed by gradient hexanes/EtOAc from 95/5 to 90/10), 59 mg (71 %) of a white solid was obtained. R_f = 0.34 (hexanes/EtOAc 90/10), mp 83 – 85 ^{o}C (from diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.18 (d, *J* = 12.1 Hz, 1H), 8.93 (dd, *J* = 6.9 Hz, 2.3 Hz, 1H), 8.85 (dd, *J* = 4.1 Hz, 1.7 Hz, 1H), 8.54 (dd, *J* = 6.9 Hz, 2.3 Hz, 1H), 8.18 (dd, *J* = 8.1 Hz, 1.7 Hz, 1H), 7.80 – 7.77 (m, 1H), 7.60 – 7.55 (m, 2H), 7.47 (dd, *J* = 8.3 Hz, 4.1 Hz, 1H), 7.37 – 7.33 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.1 (d, *J* = 254.6 Hz), 160.0 (d, *J* = 3.6 Hz), 148.7, 138.8, 136.4, 134.5, 130.6 (td, *J* = 7.3 Hz, 3.6Hz), 130.1 (t, *J* = 3.6 Hz), 128.0, 127.8 (dq, *J* = 33 Hz, 3.6 Hz), 127.5, 123.4 (q, *J* = 273 Hz), 122.8 (d, *J* = 13 Hz), 122.6, 121.9, 117.5, 117.3. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) -62.5 – -62.9 (s, 3F), -106.9 – -107.0 (m, 1F). HRMS (EIS+): Calculated for $C_{17}H_{10}F_4N_2O$ $[M+H]^+$ 335.08021, Found 335.08051.



2-Fluoro-1-methyl-*N*-(quinolin-8-yl)-1H-indole-3-carboxamide (Table 2.2, Entry 9)

1-Methyl-*N*-(quinolin-8-yl)-1H-indole-3-carboxamide (76 mg, 0.25 mmol), CuI (4.6 mg, 0.025 mmol), AgF (127 mg, 1.0 mmol), NMO (150 mg, 1.25 mmol), DMF (1.0 mL), 50

^{o}C, 1 hour. After column chromatography (hexanes, followed by gradient hexanes/EtOAc from 90/10 to 75/25), 43 mg (54 %) of a light tan solid was obtained. R_f = 0.29 (hexanes/EtOAc 90/10), mp 182 – 184 ^{o}C (from acetonitrile). ^{1}H NMR (400 MHz, DMSO-d_6, ppm) δ 10.45 (d, *J* = 5.7 Hz, 1H), 8.94 (dd, *J* = 4.5 Hz, 1.7 Hz, 1H), 8.81 (dd, *J* = 7.8 Hz, 1.7 Hz, 1H), 8.43 (dd, *J* = 8.6 Hz, 1.7 Hz, 1H), 8.24 (dd, *J* = 5.7 Hz, 2.3 Hz, 1H), 7.66 – 7.54 (m, 4H), 7.31 – 7.26 (m, 2H), 3.78 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6, ppm) δ 160.7 (d, *J* = 4.1 Hz), 153.5, 151.3, 149.6, 138.1, 137.4, 135.2, 129.5 (d, *J* = 283 Hz), 127.8, 123.8 (d, *J* = 3.6 Hz), 123.1, 123.0, 122.9 (d, *J* = 2.3 Hz), 121.7, 121.1 (d, *J* = 5.0 Hz), 115.9, 111.0, 89.2 (d, *J* = 5.9 Hz), 28.9. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) -122.0 (s, 1F). HRMS (EIS+): Calculated for $C_{19}H_{14}F_1N_3O$ $[M+H]^+$ 320.11937, Found 320.11941.



3-Fluoro-*N*-(quinolin-8-yl)isonicotinamide (Table 2.2, Entry 10)

N-(Quinolin-8-yl)isonicotinamide (63 mg, 0.25 mmol), CuI (9.7 mg, 0.05 mmol), AgF (127 mg, 1.0 mmol), NMO (140 mg, 1.25 mmol), pyridine (1 mL), 65 ^{o}C, 2 hours. After column chromatography (hexanes, followed by gradient hexanes/EtOAc from 80/20 to 60/40), and then HPLC (hexanes/EtOAc 65/35), 41.5 mg (62 %) of a white solid was obtained. R_f = 0.47 (hexanes/EtOAc 60/40), mp 122 – 124 ^{o}C (from diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 11.18 (d, *J* = 10.6 Hz, 1H), 8.95 – 8.90 (m, 1H), 8.87

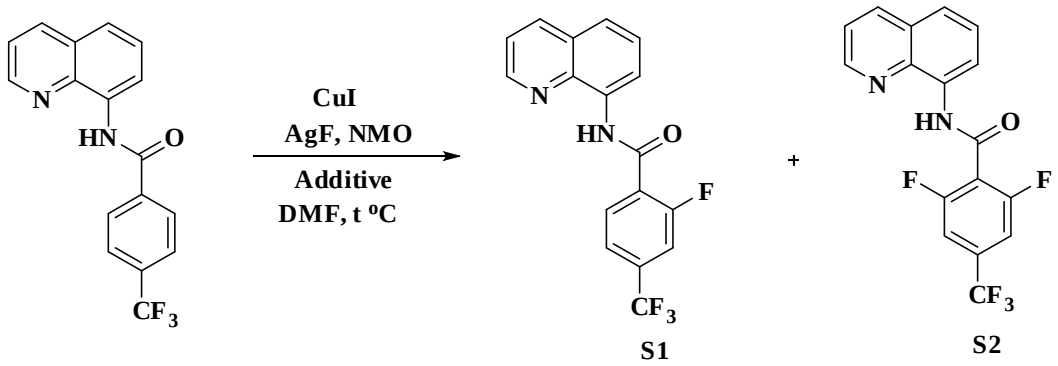
(dd, *J* = 4.2 Hz, 1.8 Hz, 1H), 8.70 (d, *J* = 2.7 Hz, 1H), 8.64 (dd, *J* = 4.2 Hz, 1.4 Hz, 1H), 8.19 (dd, *J* = 8.3 Hz, 1.4 Hz, 1H), 8.06 (dd, *J* = 6.8 Hz, 4.5 Hz, 1H), 7.61 – 7.56 (m, 2H), 7.49 (dd, *J* = 8.3 Hz, 4.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 159.5 (d, *J* = 1.9 Hz), 156.2 (d, *J* = 259.3 Hz), 148.8, 146.9 (d, *J* = 4.9 Hz), 139.8 (d, *J* = 27.4 Hz), 138.7, 136.5, 134.2, 128.7 (d, *J* = 10.6 Hz), 128.1, 127.4, 124.6, 122.9, 122.0, 117.6. ^{19}F NMR (376 MHz, $CDCl_3$, ppm), -127.3 – -127.2 (s, 1F). HRMS (EIS+): Calculated for $C_{15}H_{10}FN_3O$ $[M+H]^+$ 268.08807, Found 268.08824.

General procedure for copper-catalyzed difluorination of quinoline amides

A 1 dram vial equipped with a magnetic stir bar was charged with amide (0.25 mmol, 1 equiv.), copper iodide (10 – 30 %), and additive (pyridine). The vial was flushed with nitrogen, capped, and placed inside the glovebox. To this mixture was added NMO (6 – 8 equiv.), AgF (5 – 6 equiv.), and anhydrous DMF (1.0 mL). The sealed vial was taken out the glovebox, stirred at room temperature for 1 minute, covered with aluminum foil, and then transferred to preheated oil bath for indicated time. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (2 mL). The suspension was filtered through a pad of Celite® and solid phase was washed with ethyl acetate (4 x 20 mL). The filtrate was concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel in hexane followed by appropriate solvent to elute the products. After concentrating the fractions containing the product, the residue was dried under reduced pressure.

Optimization of condition for difluorination of quinoline amides: All reactions were carried out following the general procedure using *N*-(4-trifluoromethylbenzoyl)-8-

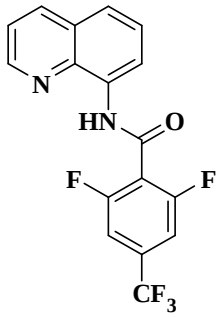
aminoquinoline (80 mg, 0.25 mmol), AgF (x equiv.), NMO [(x + 2) equiv.], solvent (1 mL), 90 minutes. 1,3-Dichlorobenzene (5 μL) was added at the end of reaction as external standard. Conversion and GC yields were calculated by GC analysis and presented in Table 2.S1. Mixture with exact molar amounts of pure product and 1.3-dichlorobenzene was used as the standard to determine GC yields. Mixture with exact molar amounts of 1,3-dichlorobenzene and starting material was used as the standard to determine percent of unreacted starting material.



Amount of CuI (%)	Equiv. of AgF	T (^{o}C)	Additive	% unreacted SM	**S1** (%)	**S2** (%)
10	5	80		6	42	16
20	5	80		3	36	26
40	5	80		< 2	25	23
20	5	100		< 2	31	19
20	6	80		< 2	17	38
20	6	80	K_2CO_3 (1 equiv.)	96	< 2	< 2
20[a]	6	80		10	52	33
20	6	80	Pyridine	< 2	4	70

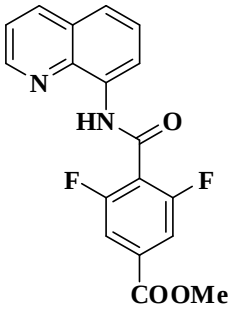
			(1 equiv.)			
20	6	80	Pyridine (2 equiv.)	< 2	5	78

(a) Reaction was carried out in pyridine solvent.



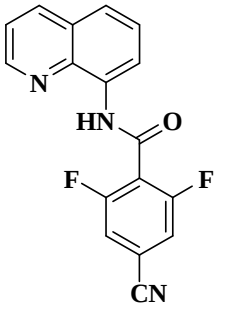
2,6-Difluoro-*N*-(quinolin-8-yl)-4-(trifluoromethyl)benzamide (Table 2.3, Entry 1)

N-(Quinolin-8-yl)-4-(trifluoromethyl)benzamide (80 mg, 0.25 mmol), CuI (9.6 mg, 0.05 mmol), AgF (191 mg, 1.5 mmol), NMO (240 mg, 2.0 mmol), DMF (1.0 mL), pyridine (40 mg, 0.5 mmol), 80 ^{o}C, 90 minutes. After column chromatography (hexanes, followed by gradient hexanes/EtOAc from 95/5 to 90/10), 56 mg (67 %) of a white solid was obtained. R_f = 0.38 (hexanes/EtOAc 90/10), mp 80 – 81 ^{o}C (from diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.38 (s, 1H), 1.89 (septet, *J* = 4.4 Hz, 1H), 8.78 (dd, *J* = 4.4 Hz, 1.7 Hz, 1H), 8.18 (dd, *J* = 8.3 Hz, 1.7 Hz, 1H), 7.59 (d, *J* = 4.4 Hz, 2H), 7.47 (dd, *J* = 8.3 Hz, 4.4 Hz, 1H), 7.30 (d, *J* = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 160.1 (dd, *J* = 256 Hz, 7.5 Hz), 157.1, 148.6, 138.4, 136.6, 134.3 (td, *J* = 34.5 Hz, 10.1 Hz), 133.8, 128.0, 127.4, 122.9, 122.3 (tq, *J* = 273 Hz, 2.8 Hz), 122.0, 118.1 (t, *J* = 19.8 Hz), 117.3, 110.0 (td, *J* = 27 Hz, 2.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -63.0 – -63.6 (m, 3F), -107.7 – -108.0 (s, 2F). HRMS (EIS+): Calculated for $C_{17}H_9F_5N_2O$ $[M+H]^+$ 353.07078, Found 353.07101.



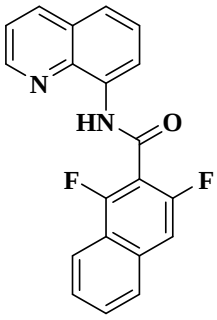
Methyl-3,5-difluoro-4-(quinolin-8-ylcarbamoyl)benzoate (Table 2.3, Entry 2)

Methyl-4-(quinolin-8-ylcarbamoyl)benzoate (77 mg, 0.25 mmol), CuI (9.6 mg, 0.05 mmol), AgF (191 mg, 1.5 mmol), NMO (240 mg, 2.0 mmol), DMF (1.0 mL), pyridine (40 mg, 2.0 mmol), 95 ^{o}C, 90 minutes. After column chromatography (hexanes, followed by gradient hexanes/EtOAc from 95/5 to 90/10), 53 mg (62 %) of a white solid was obtained. R_f = 0.38 (hexanes/EtOAc 80/20), mp 122 – 124 ^{o}C (from diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.36 (s, 1H), 8.90 (dd, *J* = 5.5 Hz, 3.5 Hz, 1H), 8.78 (dd, *J* = 4.4 Hz, 1.7 Hz, 1H), 8.17 (dd, *J* = 8.1 Hz, 1.7 Hz, 1H), 7.68 – 7.64 (m, 2H), 7.60 – 7.56 (m, 2H), 7.45 (dd, *J* = 8.1 Hz, 4.4 Hz, 1H), 3.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 164.3 (t, *J* = 3.0 Hz), 159.9 (dd, *J* = 254.5 Hz, 7.1 Hz), 157.7, 148.6, 138.4, 136.5, 134.0 (t, *J* = 9.5 Hz), 133.9, 128.0, 127.4, 122.8, 122.0, 118.6 (t, *J* = 20.6 Hz), 117.3, 113.5 (d, *J* = 27.4 Hz), 53.1. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -109.9– -110.1 (s, 2F). HRMS (EIS+): Calculated for $C_{18}H_{12}F_2N_2O_3$ $[M+H]^+$ 343.08888, Found 343.08917



4-Cyano-2,6-difluoro-*N*-(quinolin-8-yl)benzamide (Table 2.3, Entry 3)

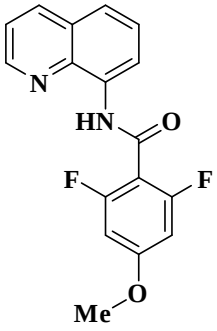
4-Cyano-*N*-(quinolin-8-yl)benzamide (69 mg, 0.25 mmol), CuI (8.6 mg, 0.045 mmol), AgF (165 mg, 1.25 mmol), NMO (210 mg, 1.75 mmol), DMF (1.0 mL), pyridine (40 mg, 0.5 mmol), 75 ^{o}C, 2 hours. After column chromatography (hexanes, followed by gradient hexanes/EtOAc from 95/5 to 80/20), 54 mg (70 %) of a white solid was obtained. R_f = 0.33 (hexanes/EtOAc 80/20), mp 143 – 145 ^{o}C (from diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.37 (s, 1H), 8.87 (dd, *J* = 5.7 Hz, 2.7 Hz, 1H), 8.78 (dd, *J* = 4.3 Hz, 1.7 Hz, 1H), 8.20 (dd, *J* = 8.3 Hz, 1.4 Hz, 1H), 7.63 – 7.57 (m, 2H), 7.48 (dd, *J* = 8.3 Hz, 4.3 Hz, 1H), 7.35 – 7.30 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 160.0 (dd, *J* = 257 Hz, 7.3 Hz), 156.5, 148.7, 138.3, 136.6, 133.7, 128.0, 127.4, 123.1, 122.1, 119.6, (t, *J* = 20.4 Hz), 117.4, 116.5 (dd, *J* = 19.4 Hz, 7.6 Hz), 116.0 (t, *J* = 2.8 Hz), 115.4 (t, *J* = 11.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -107.4 – -117.5 (s, 2F). HRMS (EIS+): Calculated for $C_{17}H_9F_2N_3O$ $[M+H]^+$ 310.07865, Found 310.07878.



1, 3-Difluoro-*N*-(quinolin-8-yl)-2-naphthamide (Table 2.3, Entry 4)

N-(Quinolin-8-yl)-2-naphthamide (75 mg, 0.25 mmol), CuI (11.0 mg, 0.0575 mmol), AgF (191 mg, 1.5 mmol), NMO (240 mg, 2.0 mmol), DMF (1.0 mL), pyridine (40 mg, 2.0 mmol), 100 ^{o}C, 90 minutes. After column chromatography (hexanes, followed by

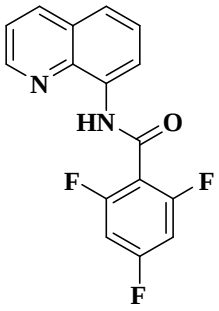
gradient hexanes/EtOAc from 95/5 to 85/15), 58.5 mg (70 %) of a white solid was obtained. R_f = 0.55 (hexanes/EtOAc 80/20), mp 152 – 154 ^oC (from diethyl ether). ^1H NMR (400 MHz, $CDCl_3$) δ 10.46 (s, 1H), 8.99 (dd, *J* = 6.8 Hz, 1.4 Hz, 1H), 8.79 (dd, *J* = 4.2 Hz, 1.4 Hz, 1H), 8.18 (t, *J* = 8.3 Hz, 2H), 7.83 (d, *J* = 8.3 Hz, 1H), 7.66 – 7.54 (m, 4H), 7.48 – 7.40 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 158.9, 156.8 (dd, *J* = 259 Hz, 7.6 Hz), 156.6 (dd, *J* = 253 Hz, 7.2 Hz), 148.5, 138.6, 136.4, 134.5 (t, *J* = 6.6 Hz), 134.4, 129.4, 128.1, 127.5, 127.1 (t, *J* = 4.3 Hz), 126.3, 122.4 , 121.8, 120.7 (d, *J* = 16.4 Hz), 117.2, 112.3 (d, *J* = 18.5 Hz), 112.0 (*J* = 18.5 Hz), 108.1 (dd, *J* = 21.5 Hz, 4.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -116.2 – -116.3 (m, 1F), -118.8 (s, 1F). HRMS (EIS+): Calculated for $C_{17}H_9F_2N_3O$ $[M+H]^+$ 335.09905, Found 335.09926.



2,6-Difluoro-4-methoxy-*N*-(quinolin-8-yl)benzamide (Table 2.3, Entry 5)

4-Methoxy-N-(quinolin-8-yl)benzamide (70 mg, 0.25 mmol), CuI (14.3 mg, 0.075 mmol), AgF (191 mg, 1.5 mmol), NMO (240 mg, 2.0 mmol), DMF (1.0 mL), pyridine (40 mg, 2.0 mmol), 100 ^oC, 90 minutes. After column chromatography (hexanes, followed by gradient hexanes/EtOAc from 95/5 to 85/15), 59 mg (75 %) of a white solid was obtained. R_f = 0.49 (hexanes/EtOAc 80/20), mp 111 – 113 ^oC (from diethyl ether). ^1H NMR (400 MHz, $CDCl_3$) δ 10.37 (s, 1H), 8.91 (d, *J* = 7.0 Hz, 1H), 8.77 (d, *J* = 3.0

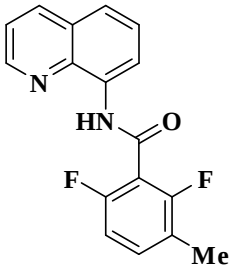
Hz, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 7.57 – 7.50 (m, 2H), 7.41 (dd, *J* = 8.2 Hz, 4.4 Hz, 1H), 6.52 (d, *J* = 10.1 Hz, 2H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.6 (d, *J* = 15.5 Hz), 161.5 (dd, *J* = 252 Hz, 9.5 Hz), 158.8, 148.5, 138.5, 136.4, 134.5, 128.0, 127.4, 122.2, 121.8, 116.9, 107.3 (t, *J* = 18.3 Hz), 98.7 (d, *J* = 28.7 Hz), 56.1. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -109.7– -109.9 (s, 2F). HRMS (EIS+): Calculated for $C_{17}H_{12}F_2N_2O_2$ $[M+H]^+$ 315.09396, Found 315.09422.



2,4,6-Trifluoro-*N*-(quinolin-8-yl)benzamide (Table 2.3, Entry 6)

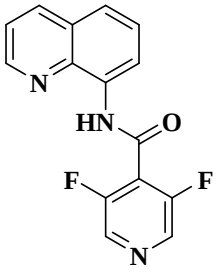
4-Fluoro-*N*-(quinolin-8-yl)benzamide (67 mg, 0.25 mmol), CuI (9.6 mg, 0.05 mmol), AgF (191 mg, 1.5 mmol), NMO (240 mg, 2.0 mmol), DMF (1.0 mL), pyridine (40 mg, 2.0 mmol), 85 ^{o}C, 90 minutes. After column chromatography (hexanes, followed by gradient hexanes/EtOAc from 95/5 to 90/10), 46 mg (61 %) of a white solid was obtained. R_f = 0.42 (hexanes/EtOAc 90/10), mp 72 – 74 ^{o}C (from diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 8.90 (dd, *J* = 6.3 Hz, 2.9 Hz, 1H), 8.79 (dd, *J* = 4.5 Hz, 1.7 Hz, 1H), 8.18 (dd, *J* = 8.3 Hz, 1.7 Hz, 1H), 7.60 – 7.55 (m, 2H), 7.46 (dd, *J* = 8.3 Hz, 4.5 Hz, 1H), 6.82 – 6.77 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.7 (td, *J* = 254.2 Hz, 15.3 Hz), 160.9 (ddd, *J* = 255.2 Hz, 15.3 Hz, 9.1 Hz), 157.8, 148.6, 138.4, 136.5, 134.1, 128.0, 127.5, 122.6, 121.9, 117.2, 111.7 (dt, *J* = 19.1 Hz, 4.7 Hz), 101.3 (dt, *J* = 26.1 Hz, 3.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -103.0– -103.1 (m, 1F), -

107.8– -108.1 (m, 2F). HRMS (EIS+): Calculated for $C_{16}H_9F_3N_2O$ $[M+H]^+$ 303.07398, Found 303.07399.



2,6-Difluoro-3-methyl-*N*-(quinolin-8-yl)benzamide (Table 2.3, Entry 7)

3-Methyl-*N*-(quinolin-8-yl)benzamide (66 mg, 0.25 mmol), CuI (9.6 mg, 0.05 mmol), AgF (191 mg, 1.5 mmol), NMO (240 mg, 2.0 mmol), DMF (1.0 mL), pyridine (40 mg, 2.0 mmol), 105 ^oC, 90 minutes. After column chromatography (hexanes, followed by gradient hexanes/EtOAc from 95/5 to 90/10), 57 mg (77 %) of a white solid was obtained. R_f = 0.37 (hexanes/EtOAc 90/10), mp 102 – 103 ^oC (from diethyl ether). ^1H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.94 (dd, *J* = 6.8 Hz, 1.7 Hz, 1H), 8,79 (dd, *J* = 4.3 Hz, 1.7 Hz, 1H), 8.17 (dd, *J* = 8.3 Hz, 1.7 Hz, 1H), 7.60 – 7.55 (m, 2H), 7.45 (dd, *J* = 8.3 Hz, 4.3 Hz, 1H), 7.28 – 7.24 (m, 1H), 6.92 (dt, *J* = 8.5 Hz, 1.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 159.1, 158.3 (dd, *J* = 250 Hz, 6.6 Hz), 158.0 (dd, *J* = 251 Hz, 7.1 Hz), 148.5, 136.5, 134.3, 133.2 (dd, *J* = 10.5 Hz, 7.1 Hz), 128.0, 127.5, 122.4, 121.8, 121.7 (dd, *J* = 18.1 Hz, 3.6 Hz), 117.2, 114.5 (t, *J* = 20.5 Hz), 111.6 (dd, *J* = 21.7 Hz, 3.5 Hz), 14.4 (d, *J* = 3.5 Hz). Signal for one carbon could not be located. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -114.7– -114.8 (m, 1F), -115.7– -115.9 (m, 1F). HRMS (EIS+): Calculated for $C_{17}H_{12}F_2N_2O$ $[M+H]^+$ 299.09905, Found 299.09936.



3,5-Difluoro-*N*-(quinolin-8-yl)isonicotinamide (Table 2.3, Entry 8)

N-(Quinolin-8-yl)isonicotinamide (63 mg, 0.25 mmol), CuI (11.8 mg, 0.0625 mmol), AgF (191 mg, 1.5 mmol), NMO (240 mg, 2.0 mmol), pyridine (1 mL), 85 ^{o}C, 90 minutes. After column chromatography (hexanes, followed by gradient hexanes/EtOAc from 80/20 to 60/40), and then HPLC (hexanes/EtOAc 65/35), 43.4 mg (61 %) of a white solid was obtained. R_f = 0.47 (hexanes/EtOAc 60/40), mp 118 – 120 ^{o}C (from diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.43 (s, 1H), 8.88 (dd, *J* = 6.7 Hz, 2.3 Hz, 1H), 8.80 (dd, *J* = 4.1 Hz, 1.7 Hz, 1H), 8.52 (s, 2H), 8.20 (dd, *J* = 8.1 Hz, 1.7 Hz, 1H), 7.62 – 7.57 (m, 2H), 7.48 (dd, *J* = 8.1 Hz, 4.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 156.2, 155.6 (d, *J* = 265.3 Hz), 148.7, 138.4, 136.6, 135.5 (dd, *J* = 25.6 Hz, 3.9 Hz), 133.6, 128.0, 127.4, 123.1, 122.1, 120.8 (t, *J* = 16.8 Hz), 117.5. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -126.4 (s, 2F). HRMS (EIS+): Calculated for $C_{15}H_9F_2N_3O$ $[M+H]^+$ 286.07865, Found 286.07802.

Note: Product contains less than 3 % of 3-fluoro-N-(quinolin-8-yl)isonicotinamide.

Control experiments: all reactions were carried out following general procedure for monofluorination.

Attempted fluorination of *N*-isopropylbenzamide under standard conditions afforded no fluorinated product.

Investigating contaminants: Reaction was carried out using new vial and new magnetic stirring bar. N-(Quinolin-8-yl)-4-(trifluoromethyl)benzamide (80 mg, 0.25 mmol), CuI (> 99.99, trace metals basic) (7.1 mg, 0.0375 mmol), AgF (> 99.9 % trace metals basic) (127 mg, 1.0 mmol), NMO (from unopened bottle) (150 mg, 1.25 mmol), anhydrous DMF (from unopened bottle) (1.0 mL), 80 ^{o}C, 30 minutes. After column chromatography (hexanes, followed by gradient hexanes/EtOAc from 95/5 to 90/10), 61 mg (73 %) of a white solid was obtained.

Reaction without copper: N-(Quinolin-8-yl)-4-(trifluoromethyl)benzamide (80 mg, 0.25 mmol), AgF (127 mg, 1.0 mmol), NMO (150 mg, 1.25 mmol), anhydrous DMF (1.0 mL), 80 ^{o}C, 30 minutes. GC analysis showed less than 2 % of desired product.

Large scale synthesis:

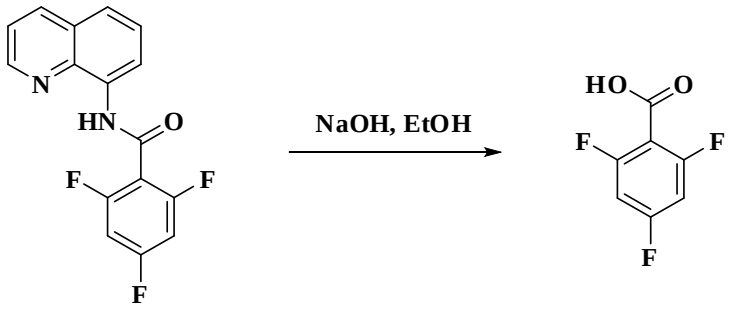
A pressure vessel (50 mL) equipped with a magnetic stir bar (eggshape, 15mm in length x 6mm in diameter) was charged with 4-cyano-*N*-(quinolin-8-yl)benzamide (1.38 g, 5.0 mmol) and CuI (114 mg, 0.6 mmol). The vessel was flushed with nitrogen, capped, and placed inside the glovebox. To this mixture was added AgF (2.24 g, 17.5 mmol), NMO (2.68 g, 22.5 mmol), and DMF (25 mL). The sealed vessel was taken out the glovebox, strongly shaken, stirred at room temperature for 20 minutes, covered with aluminum foil, and then transferred to preheated oil bath at 65 ^{o}C and stirred for 90 minutes. The reaction mixture was cooled to room temperature and diluted with ethyl acetate (20 mL). The suspension was filtered through a pad of Celite® and solid phase was washed with ethyl acetate (6 x 50 mL). The filtrate was concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel in hexane followed by

gradient hexanes/EtOAc from 95/5 to 80/20. White solid (870 mg, 60 %) was obtained. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.16 (s, 1H), 8.92 (t, *J* = 4.5 Hz,, 1H), 8.86 (dd, *J* = 4.5 Hz, 1.8 Hz, 1H), 8.32 (t, *J* = 7.8 Hz, 1H), 8.19 (dd, *J* = 8.2 Hz, 1.4 Hz, 1H), 7.64 – 7.58 (m, 3H), 7.55 (dd, *J* = 10.4 Hz, 1.4 Hz, 1H), 7.49 (dd, *J* = 8.2 Hz, 4.5 Hz, 1H).

Reactions without using glovebox:

A 1 dram vial equipped with a magnetic stir bar was charged with methyl 4-(quinolin-8-ylcarbamoyl)benzoate (77 mg, 0.25 mmol), CuI (4.8 mg, 0.025 mmol), AgF (127 mg, 1.0 mmol), NMO (150 mg, 1.25 mmol), and DMF (1.0 mL). The sealed vial was flushed with nitrogen, capped, strongly shaken, covered with aluminum foil, and stirred at room temperature for 5 minutes. Vial was then transferred to preheated oil bath at 90 ^{o}C for 1 hour. The reaction mixture was worked up following general procedure. After column chromatography (hexanes, followed by gradient hexanes/EtOAc from 95/5 to 80/20), 47 mg (57 %) of a white solid was obtained.

Removal of directing group



A 2 dram vial equipped with a magnetic stir bar was charged 2,4,6-trifluoro-N-(quinolin-8-yl)benzamide (151 mg, 0.5 mmol), NaOH (5 mmol), and EtOH (3 mL). The resulting mixture was stirred at room temperature for 1 minute before being heated to 90 ^{o}C for 24 hours. After completion, reaction was cooled to room temperature and diluted with

dichloromethane (130 mL) followed by addition of aqueous 1N HCl (30 mL). Organic layer was washed with 1N HCl (5 x 20 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure to afford pure product as white solid (82 %, 72 mg). This compound is known.[26] ^1H NMR (400 MHz, $CDCl_3$) δ 11.62 (broad singlet, 1H), 7.68 – 7.73 (m, 2H).

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Chapter 3

Direct Arylation of C-H Bonds via Aryne Intermediates

Introduction

The biaryl structural motif is often found in natural products as well as in many pharmaceutically relevant and biologically active compounds.[1] As a consequence, for over a century new and progressively more efficient aryl-aryl bond-forming methods have been developed. In general, transition metal catalysis is commonly used for the construction of aryl-aryl bonds.[2] Traditional methods for biaryl preparation involve a reaction of aryl halide or pseudohalide with an organometallic reagent. However, the preparation of starting materials adds extra steps to the synthetic sequences. Catalytic direct arylation provides more efficient routes by using simple arenes in the coupling reactions. Since organic molecules usually display many non-equivalent C-H bonds with comparable dissociation energies, modern direct arylation methods that allow reactions to proceed with excellent selectivity and high functional group tolerance are developed.

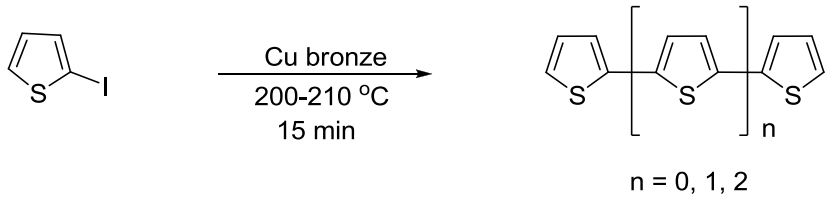
Recently, substantial progresses in transition-metal-catalyzed direct arylation reactions has been achieved. However, transition-metal impurities in the final products represent a major problem regarding purification and applications in pharmaceutical industry.[3] Therefore, there is a need for more efficient routes whereby the same outcome is accomplished without transition-metal involvement. Within this chapter, transition-metal-free direct arylation and alkynylation of sp^2 C-H bonds via aryne intermediates will be discussed. Where appropriate, important previously disclosed reports and transition-metal-free processes will be mentioned.

Chapter 3-1. Direct Arylation of Acidic sp^2 C-H Bonds via Benzyne Intermediates

3.1.1. Transition-metal-catalyzed Arylation of Acidic sp^2 C-H Bonds

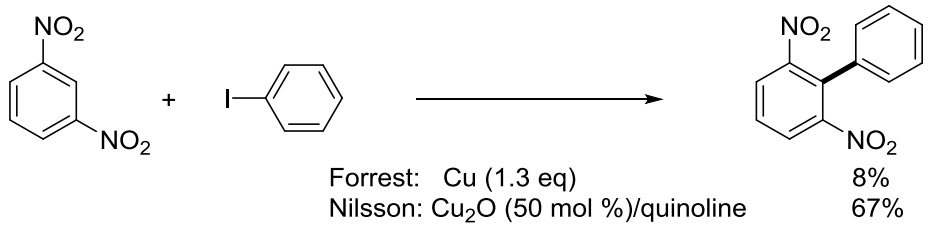
Aryl-aryl bond formation is one of the first reported transition metal-promoted reactions.[4] Copper was the metal most widely employed for aryl-aryl bond formation during the first 70 years of the 20th century. The first example of copper-promoted C-H bond direct arylation was reported in early 1940s.[5] A mixture of dithienyl, trithienyl, and quaterthienyl was obtained when 2-iodothiophene was heated at 200 °C in the presence of copper bronze (Scheme 3.1.1). While dithienyl is the expected as Ullmann product, the formation of higher oligomers (n > 0) indicated the involvement of C-H bond functionalization.

Scheme 3.1.1. Formation of higher oligomers of thiophene



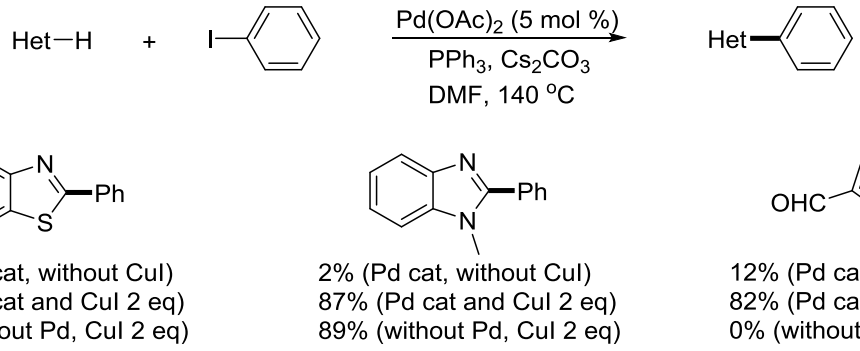
A similar transformation was reported by Forrest in 1960.[6] When *m*-dinitrobenzene was employed as additive in the Ullmann coupling of iodobenzene, a small amount of 2,6-dinitrobiphenyl was observed (Scheme 3.1.2). Björklund and Nilsson subsequently disclosed a method for arylation of 1,3-dinitrobenzene by iodobenzene to afford 2,6-dinitrobiphenyl in good yield (67%) using stoichiometric copper(I) oxide in quinoline at 220 °C.[7]

Scheme 3.1.2. Phenylation of 1,3-dinitrobenzene



In 1985, the palladium-catalyzed direct arylation of indoles was reported by Ohta group.[8] The results indicated the positive effect of CuI additive. A similar influence was also observed later by Miura and co-workers in the arylation of azoles.[9] They found that *N*-methylimidazole is preferentially arylated at 5-position if catalytic Pd is used. However, the arylation occurs at 2-position if stoichiometric amount of CuI is added. Furthermore, CuI itself can mediate the arylation in moderate yield (Scheme 3.1.3).

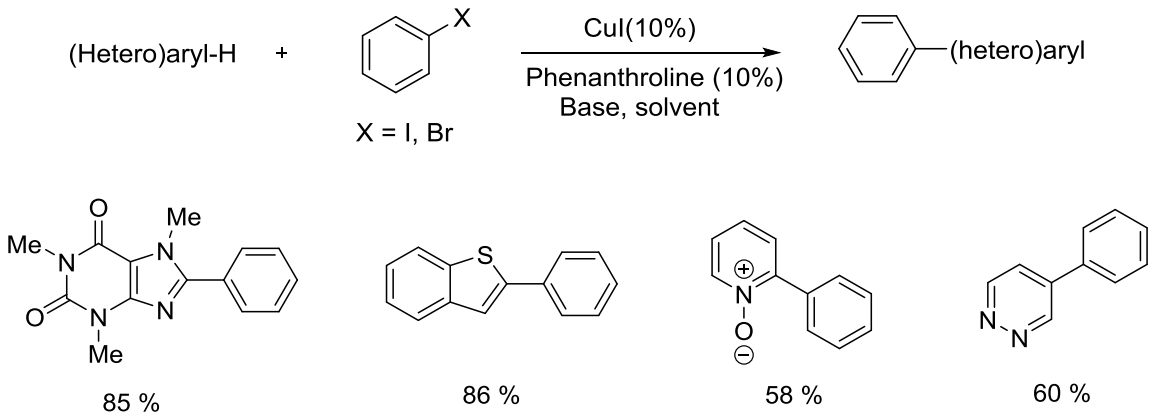
Scheme 3.1.3. Palladium-catalyzed arylation of heterocycles



This effect may arise from the involvement of organocopper intermediates in the reaction. If the presumed intermediate could be generated without a palladium cocatalyst, a cheap and efficient method for the heterocycle arylation would be achieved. By using this hypothesis, our group described a general method for the copper-catalyzed heterocycle arylation by aryl iodides.[10] Strong bases were used to generate organocopper

species by deprotonation/transmetallation sequences. A variety heterocycles as well as electron-poor arenes possessing at least two electron-withdrawing groups on a benzene ring can be arylated in good yields.

Scheme 3.1.4. Copper-catalyzed arylation of acidic arenes

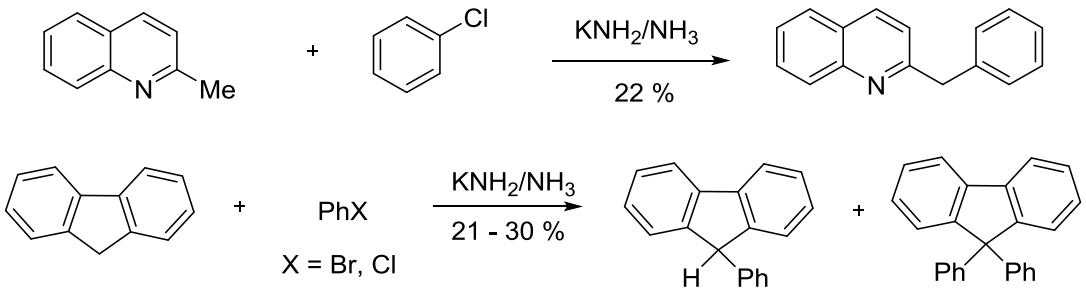


3.1.2. Arylation via Aryne Intermediates

Arynes are highly electrophilic species, and can react with various nucleophiles, forming aryl carbanions. The latter can react further with electrophiles intermolecularly or intramolecularly. A wide variety of anionic and uncharged nucleophiles are known to add readily to arynes.

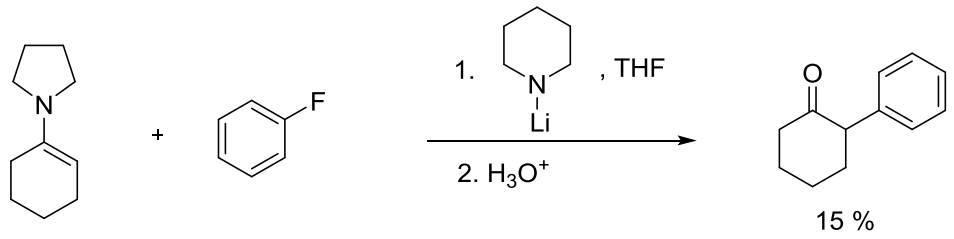
One of the first electrophilic carbon arylation reactions that proceeds via benzyne mechanism was reported in early 1945 by Bergstrom.[11] In the presence of KNH_2 in liquid ammonia, formation of 2-benzylquinoline was observed when chlorobenzene was treated with 2-methylquinoline. Similar results were obtained with pyridine, phenanthridine, and fluorene derivatives.

Scheme 3.1.5. *C*-Arylation of 2-methylquinoline and fluorene



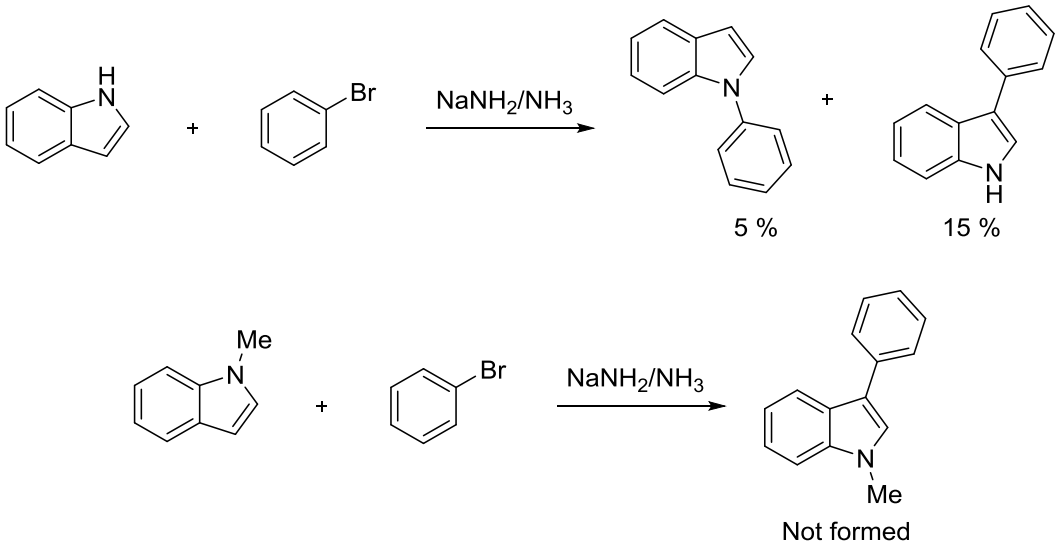
Arylation of enamines via benzyne was also reported.[12] Formation of benzyne from fluorobenzene and piperidyllithium in the presence of 1-pyrrolidiocyclohexene followed by hydrolysis led to the formation of 2-phenylcyclohexanone.

Scheme 3.1.6. Carbon arylation of enamine



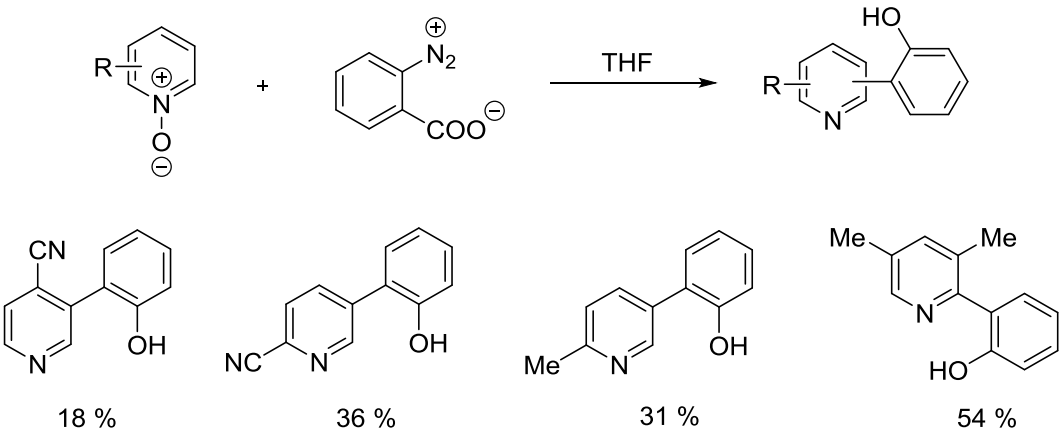
Indoles, like enamines, may be attacked at *N*-1 or *C*-3. Reactions of indoles with benzyne were described by Kuehne group.[13] When benzyne generated from bromobenzene with sodium amide in liquid ammonia was reacted with indole, *N*-phenylindole (5 %) and 3-phenylindole (15 %) were obtained. Under the same conditions, benzyne reaction with *N*-methylindole did not lead to any *N*-methyl-3-phenylindole (Scheme 3.1.7).

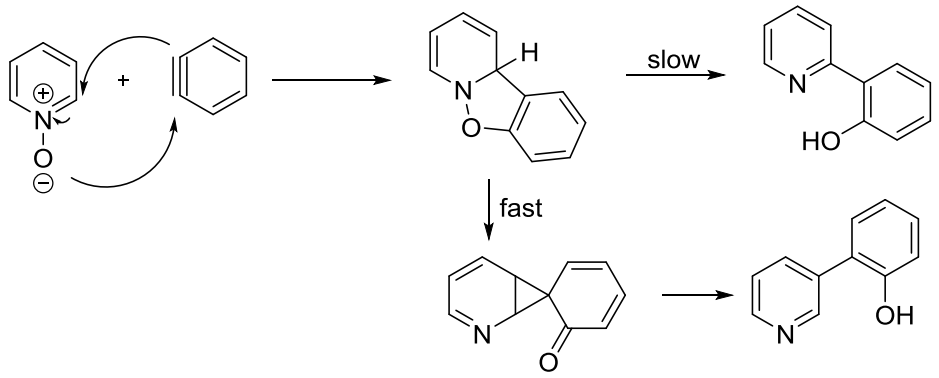
Scheme 3.1.7. Reaction of benzyne and indoles



Formation of (2-hydroxyaryl)pyridine was observed when benzyne was treated with pyridine-*N*-oxide.[14] Benzenediazonium-2-carboxylate was used as benzyne precursor and reactions were proposed to proceed via [2+2+4] rearrangement. Modified conditions were reported by Larock group in 2006.[14b] Arynes were generated from silylaryl triflates and reactions proceed in good yields with high regioselectivity.

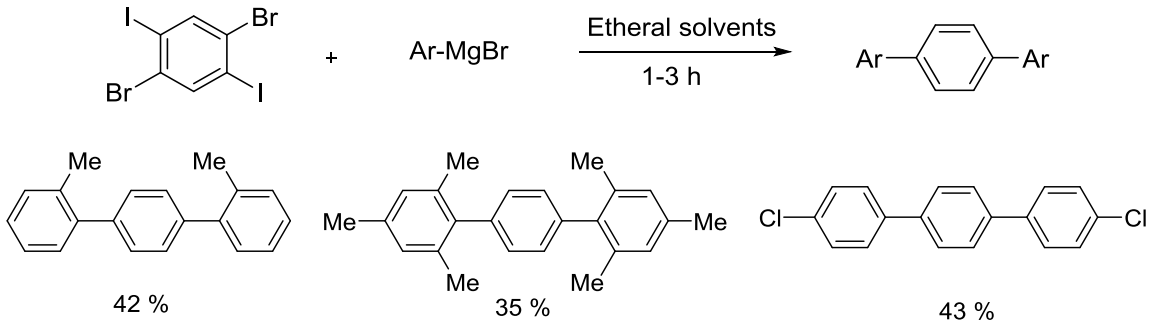
Scheme 3.1.8. Reaction of aryne and pyridine-*N*-oxide





A one-step synthesis of *p*-terphenyl via arynes has been developed.[15] Reaction conditions involve the addition of 1,4-dibromo-2,5-diiodobenzene to excess aryl Grignard reagent. After aqueous quench, *p*-terphenyls were isolated in 30-50 % yields. Interestingly, yields can be improved by adding *t*BuOK or TMPLi to the reaction mixture prior to workup.

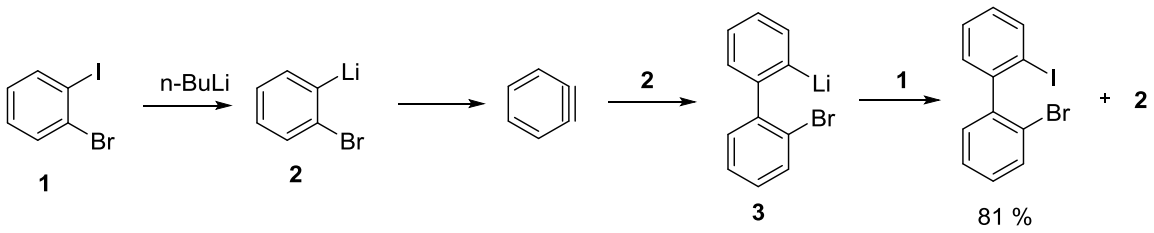
Scheme 3.1.9. Formation of *p*-terphenyl derivatives via benzyne intermediates



Another synthetic protocol to biaryl compounds via an aryne intermediate has been developed by Leroux and Schlosser.[16] When 1-bromo-2-iodobenzene (**1**) was treated with 0.5 equiv of *n* - BuLi, 2-bromo-2′-iodobiphenyl was produced in 81% yield. The reaction presumably starts by an iodine–lithium exchange between **1** and *n* - BuLi, followed by the elimination of LiBr from the organolithium intermediate **2** to generate the transient benzyne species. Subsequent nucleophilic addition of **2** to benzyne generates

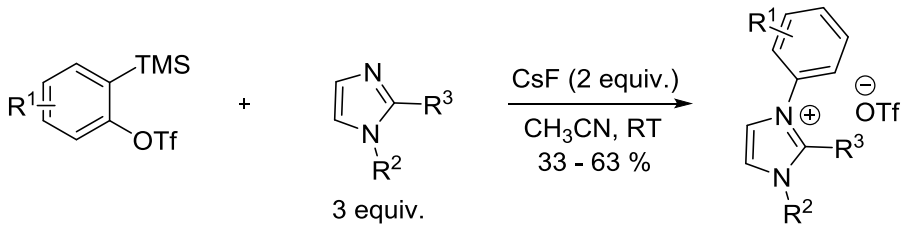
the biphenyl scaffold. The resulting 2-biaryl lithium species **3** then undergoes lithium–iodine exchange with the starting material **1** to afford 2-bromo-2′-iodobiphenyl, together with organolithium species **2.**

Scheme 3.1.10. 2-Bromo-2′-iodobiphenyl formation from 1-bromo-2-iodobenzene



Arynes undergo nucleophilic addition with *N*-alkylimidazoles affording *N*-alkyl-*N*-arylimidazolium salts.[17] In contrast, if *N*-arylimidazoles are employed, desired product is not formed. In the reaction of 3-methoxybenzyne with *N*-methylimidazole, the addition occurs regioselectively at the position *meta* to the methoxy group. Similar regioselectivity has also been observed in other nucleophilic additions to 3-methoxybenzyne.

Scheme 3.1.11. Reactions of arynes with *N*-alkylimidazoles

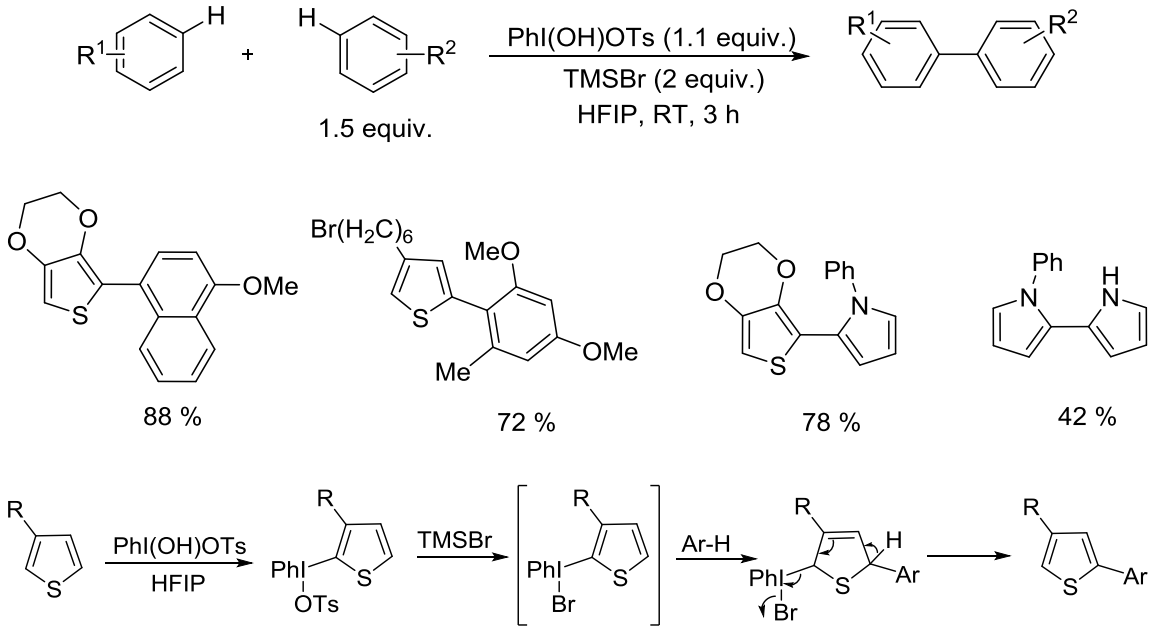


3.1.3. Other Procedures for Transition-metal-free Biaryl Formation

A metal-free selective oxidative cross-coupling method for unfunctionalized electron-rich aromatic compounds has been developed by Kita group.[18] The procedure employs a trivalent organoiodine oxidant. High yields and good regioselectivities were obtained. Initially, reaction of electron-rich aromatic compound with iodine oxidant

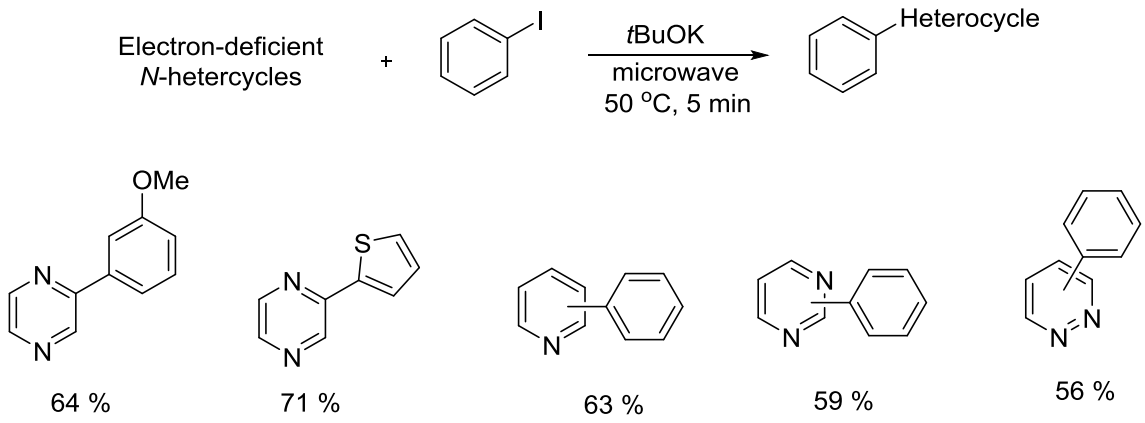
PhI(OH)OTs forms the stable iodonium(III) salts. The added TMSBr induces the reaction of iodonium(III) salts with another arene through the formal hydroarylation and successive elimination of iodobenzene.

Scheme 3.1.12. Oxidative cross-coupling using PhI(OH)OTs oxidant



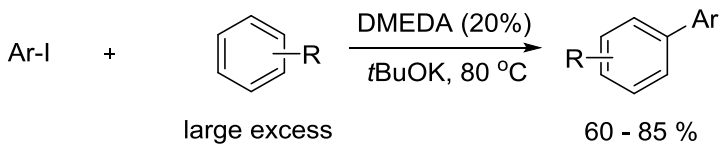
Biaryl coupling of electron-deficient heterocycles containing nitrogen with haloarenes promoted by *t*BuOK has been described by Itami group.[19] Without addition of any exogenous transition metals, electron-deficient heterocycles such as pyridine, pyridazine, pyrimidine, pyrazine, and quinoxaline are arylated with aryl iodides in reasonable yields. However, large excess of heterocycles (40/1) is required and regioisomer mixtures were obtained in some cases. The control experiments indicated that radical processes are involved.

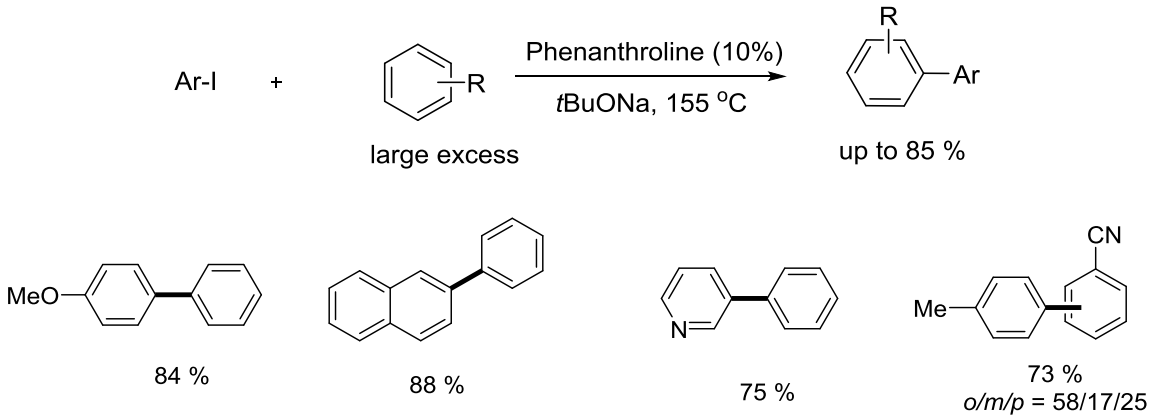
Scheme 3.1.13. *t*BuOK-promoted arylation of *N*-heterocycles



The research groups of Shi, Shirakawa/Hayashi, and Kwong/Lei have recently independently reported in the construction of biaryl compounds from unactivated aromatic rings by direct C-H activation with the aid of organocatalysts.[20] In particular, heating aryl iodides in benzene at 80 °C with one equivalent of potassium *tert*-butoxide and 20 mol% *N,N'*-dimethylethylenediamine (DMEDA) gave biaryls in 60–85% yields. Comparable yields were obtained if 1,10- phenanthroline or a substituted analogue was employed (Scheme 3.1.14). Large excess of arene coupling components is needed and H/D isotope effects are consistent with aryl radicals being involved. The addition of 2,2,6,6-tetramethyl-1-piperidinoxyl (TEMPO) and other inhibitors blocked the reactions. Finally, *ortho* selectivities are observed in the additions of aryl radicals to substitued benzenes.

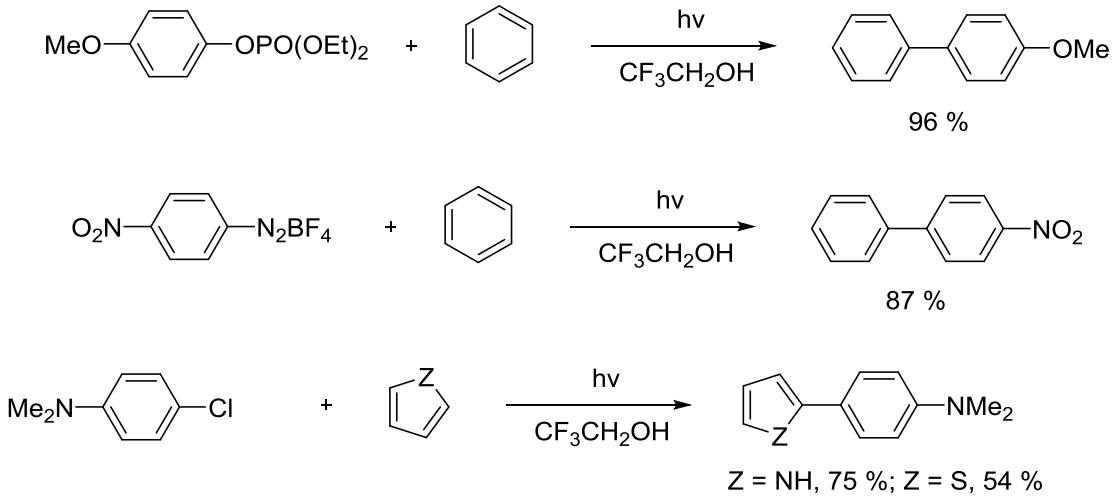
Scheme 3.1.14. Biaryl formation via organocatalysis





Arylation via $S_{RN}1$ pathway has also been disclosed.[21] Photo cleavage of benzenediazonium salts as well as aryl(pseudo) halides containing electron-donating groups leads to the corresponding phenyl cations in the triplet state. These intermediates react selectively with (hetero)arenes via S_N1 pathway giving arylation products in good yields.

Scheme 3.1.15. Photo-induced arylation



3.1.4. Direct Arylation of Acidic sp^2 C-H Bonds via Benzyne Intermediates

3.1.4.1. Introduction

Direct arylation of arene C-H bonds with aryl halides is one of the shortest and most efficient routes to biaryls. However, most of the aforementioned achievements are mediated or catalyzed by transition metals. From a practical point of view, transition-metal-free processes are much preferred, especially in the pharmaceutical industry where the removal of undesired metal contamination can be expensive.[3] Therefore, it is not surprising that numerous transition-metal-free approaches for direct arylation have been developed. Several recent reports describe arene and electron-deficient heterocycle arylation by aryl halides that presumably proceed by radical-type mechanisms without transition-metal involvement.[18-20] However, arylation of simple arenes such as anisole afford isomer mixtures and the arene coupling component is often employed in large excess (up to 100 equivalents) as a solvent. Consequently, methods that are that highly regioselective with respect to arene coupling component and do not require large excess of any coupling components are needed.

3.1.4.2. Results and Discussion

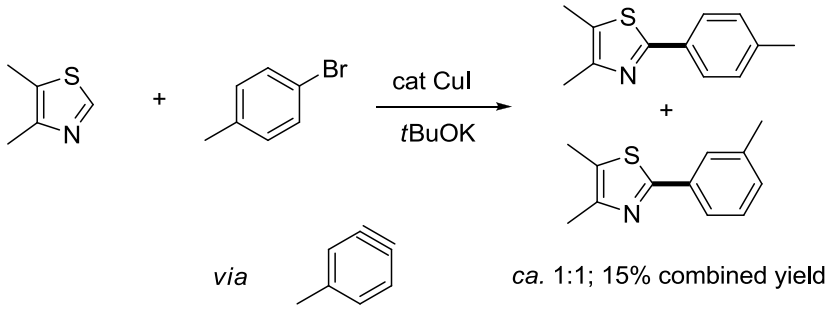
Recent examples of aryne arylations have been described by Hart, Schlosser, Meyers, Aubert, and Mamane.[14-16,22] In all cases, prefunctionalized nucleophilic coupling partners, or transition-metal catalysts are required to obtained reasonable yields. Benzyne can be generated from silyl aryl triflates under mild conditions.[23] However, these starting materials are quite expensive and only a few of them are commercially available.

Consequently, we decided to use readily accessible and cheap aryl chloride as an benzyne sources.

We have recently described a transition-metal-free, base-promoted intramolecular *C*-arylation of phenols with aryl halides.[24] 6H-Benzo[c]chromenes were obtained in high yields when 3-(2-halobenzyloxy)phenols were treated with *t*-BuOK in dioxane at 140 °C. The reaction proceeds by an initial formation of a benzyne intermediate followed by an aromatic sp^2 C-H functionalization to form the carbon-carbon bond. To expand the synthetic utility of the reaction, we decided to investigate intermolecular carbon-carbon bond formation proceeding via benzyne intermediates.

The involvement of benzyne intermediate in intermolecular arylation of acidic arenes by aryl halides was previously observed by our group.[10] In the presence of *t*BuOK, mixture of regioisomeric coupling products were obtained in the reaction between bromotoluene and 4,5-dimethylthiazole. Reaction yield was low due to the nucleophilic attack of base on benzyne.

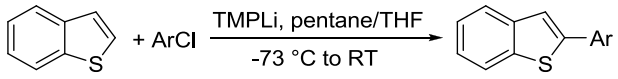
Scheme 3.1.16. Involment of benzyne intermediates in copper-catalyzed arylation

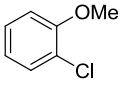
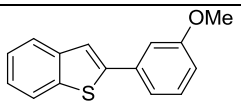
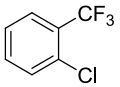
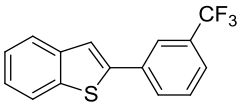
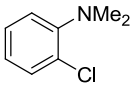
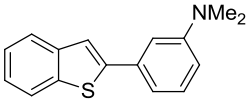
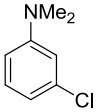
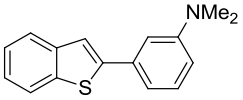
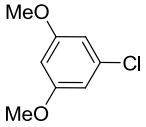
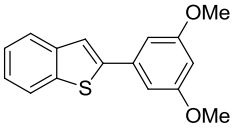
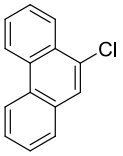
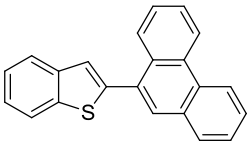
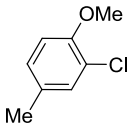
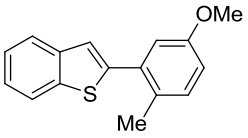


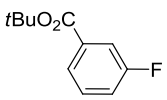
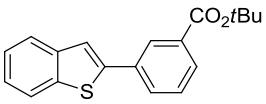
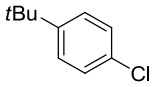
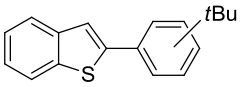
We hypothesized that use of hindered 2,2,6,6-tetramethylpiperidide (TMP) should retard the reaction of benzyne with base.[25] Relative reactivity of the base and aryl anion

with benzyne can be modulated by employing a solvent where amide base is sparingly soluble. A brief optimization of reaction conditions showed that best results are obtained by employing a mixed pentane/THF solvent system. In pentane, the arylations are slow due to low base solubility. Competitive addition of TMPLi to benzyne decreases arylation yields in THF.

Table 3.1.1. Arylation scope with respect to aryl halides[a]



entry	aryl halide	product	yield, %
1			78
2			61
3			77
4			81
5			62
6			75
7			73

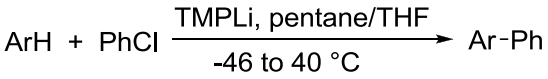
8			60 50[b]
9			85[c]

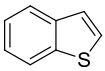
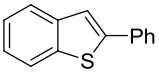
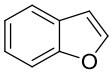
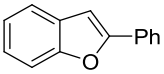
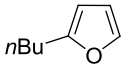
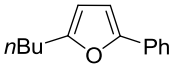
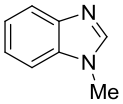
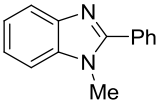
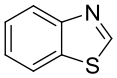
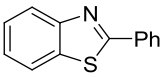
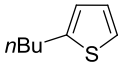
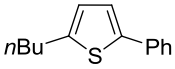
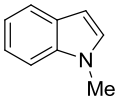
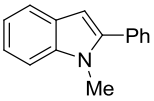
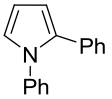
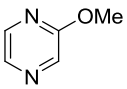
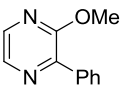
[a] Aryl halide (1.6-2.5 equiv), benzothiophene (1 equiv), 0.5 mmol scale. Yields are isolated yields. [b] *tert*-Butyl-3-bromobenzoate used. [c] Isomer mixture; *m/p* ratio 1/1.2

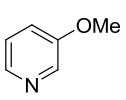
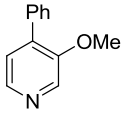
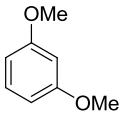
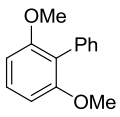
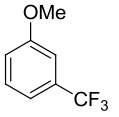
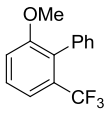
Arylation scope with respect to aryl halides is shown in Table 3.1.1. Benzothiophene is arylated by aryl halides at the most acidic position. *meta*-Substituted products were obtained in good yields when benzothiophene is arylated by 2-chloroanisole and 2-chlorobenzotrifluoride (entries 1 and 2). Arylation by either 2- or 3-chloro-*N*,*N*-dimethylaniline affords the *m*-substitution product (entries 3 and 4). This regioselectivity pattern may be advantageous if *o*-chloroarene is more available than the corresponding *m*-isomer. Substitutions by a benzyne mechanism often produce the same isomer if 2- and 3-haloarene starting materials are used.[26] The regioselective nucleophile addition to benzyne is explained in terms of ground-state polarization of the aryne by electron-withdrawing substituents and the energy that is required to distort the aryne into two possible transition states.[26c] 3,5-Dimethoxychlorobenzene is reactive and arylation product is obtained in good yield (entry 5). Arylation by 2,3,4,5-tetrasubstituted chloroarenes is possible and benzothiophene is arylated by 9-chlorophenanthrene (entry 6). If 3-chloro-4-methoxytoluene is used, the arylation occurs *meta* to the methoxy substituent (entry 7). Fluoroarene starting materials can be employed and the reaction

tolerates an ester group (entry 8). If 4-chloro-*t*-butylbenzene is used, a nearly 1/1 mixture of arylation product isomers is obtained (entry 9).[26]

Table 3.1.2. Arylation scope with respect to heterocycles and arenes[a]



entry	arene	product	yield, %
1			86 72[b] 85[c]
2			81 75[d]
3			80 68[b]
4			91 81[b]
5			72
6			80 74[b]
7			90
8[e]			78
9			55

10			71
11			95
12			81

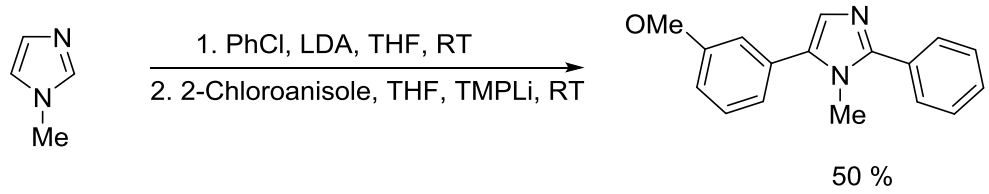
[a] Chlorobenzene (1.3-2 equiv), arene or heterocycle (1 equiv), 0.5 mmol scale. Yields are isolated yields. [b] Lithium dicyclohexylamide base. [c] PhF used instead of PhCl. [d] LiN*i*Pr$_2$ base. [e] Phenylpyrrole (2 equiv), PhCl (1 equiv)

The arylation scope with respect to heterocycles and arenes is presented in Table 3.1.2. In most cases, TMPLi base affords slightly higher yields than either lithium dicyclohexylamide or diisopropylamide (entries 1, 2, 3, 4, 6). Fluorobenzene can be used instead of chlorobenzene and nearly identical yields were obtained in the reactions with benzothiophene (entry 1). Furan derivatives, such as benzofuran and 2-butylfuran, are reactive (entries 2 and 3). *N*-Methylbenzimidazole and benzothiazole are arylated in good yields (entries 4 and 5). Arylation of thiophene, indole, and pyrrole derivatives affords products in excellent yields (entries 6, 7, 8). The reaction is not limited to five-membered ring heterocycles. Arylation of pyridine and pyridazine derivatives is possible and arylated products are obtained in reasonable yields (entries 9 and 10). Arenes such as 1,3-dimethoxybenzene and 3-methoxybenzotrifluoride are reactive (entries 11 and 12).

A sequential, one-pot diarylation of *N*-methylimidazole was performed. The mixture of chlorobenzene with heterocycle was treated with LDA in THF at RT, followed

by quench with MeOH and evaporation. Following addition of 2-chloroanisole and TMPLi in THF, a single isomer of diarylation product was obtained in 50% yield.

Scheme 3.1.17. Sequential diarylation of *N*-methylimidazole



50 %

3.1.4.3. Conclusions

A transition-metal-free method for base-promoted arylation of heterocycles and arenes by aryl chlorides and fluorides has been described. The reactions proceed via aryne intermediates at mild temperatures and allow for highly regioselective arylation of the arene and heterocycle C-H bonds. Functionalization occurs at the most acidic carbon-hydrogen bond.

3.1.4.4. Experimental Section

General considerations: Reactions were performed in 2-dram vials using screw caps with 17 mm hole and white silicone septum with white teflon face (from SUPELCO). Column chromatography was performed on 60Å silica gel (Sorbent Technologies). Purification by preparative HPLC was performed on a Shimadzu Prominence LC (LC-20AB) equipped with a SPD-20A UV-Vis detector and a Varian Dynamax (250 mm x 21.4 mm) column. GC-MS analyses were performed on a Shimadzu GCMS-QP5000 chromatograph equipped with a Restek column (Rtx-XLB, 30 m x 0.25 mm I.D.). The ^{1}H, ^{19}F and ^{13}C NMR were recorded on JEOL EC-400 or JEOL EC-500 spectrometers using residual solvent peak as a reference. α,α,α-Trifluorotoluene (neat, δ = -62.3ppm) was employed as an external standard in ^{19}F NMR spectra. Elemental analyses were performed by Atlantic Microlab Inc. of Norcross, GA. IR spectra were obtained on a ThermoNicolet Avatar 370 FT-IR instrument. Analytical thin layer chromatography was performed on silica gel IB-F (Baker-flex) by J. T. Baker. All procedures were performed under argon atmosphere unless otherwise noted.

Materials. The following starting materials were obtained from commercial sources and were used without further purification: benzothiophene, benzothiazole, 1-methylindole, 1-phenylpyrrole, 3-methoxypyrazine, 3-methoxypyridine, 2-chloroanisole, 2-chlorobenzotrifluoride, 3-fluorobenzoic acid, *N*-methylbenzimidazole, 2-*n*-butylthiophene, 2-*n*-butylfuran, 1,3-dimethoxybenzene, N-methylimidazole, 3-trifluoromethylanisole, 3-chloro-*N*,*N*-dimethylaniline, 2-chloro-*N*,*N*-dimethylaniline, 2,2,6,6-tetramethylpiperidine (TMPH), 9-chlorophenanthrene, 3,5-

dimethoxychlorobenzene, 3-chloro-4-methoxytoluene, 4-*tert*-butylchlorobenzene, 2,3-benzo[b]furan, and *tert*-butyl-3-bromo-benzoate. *tert*-Butyl-3-fluorobenzoate was synthesized from 3-fluorobenzoic acid.[27]

TMPLi, Cy_2NLi, LDA 1M in THF: A 25 mL oven-fried flask equipped with a magnetic stirring bar and a septum was evacuated and backfilled with argon 5 times. TMPH (2,2,6,6-tetramethylpiperidine, 2.32 g, 16.5 mmol) or Cy_2NH (dicyclohexylamine, 2.98 g, 16.5 mmol) or diisopropylamine (1.67 g, 16.5 mmol) was added, followed by anhydrous THF to give 15 mL of solution. The mixture was cooled to -73 ^oC and stirred for 5 minutes. *n*-BuLi (2.5 M in hexanes, 6 mL, 15 mmol) was then added dropwise. The reaction mixture was stirred for 30 minutes at -73 ^oC followed by warming to 0^oC and stirring for additional 30 minutes. After that, the reaction mixture was vacuumed to give 15 mL of solution.

TMPLi 1 M in pentane: A 50 mL oven-fried flask equipped with magnetic stirring bar and a septum was evacuated and backfilled with argon 5 times. TMPH (2,2,6,6-tetramethylpiperidine, 4.64 g, 33.0 mmol) was added, followed by anhydrous pentane to give 30 mL of solution (marked the flask at the desired level). The mixture was cooled to -73 ^oC and stirred for 5 minutes. *n*-BuLi (2.5 M in hexanes, 12 mL, 30 mmol) was added dropwise and reaction mixture was stirred for 30 minutes at -73 ^oC, warmed up to room temperature and stirred overnight. The reaction mixture was vacuumed to give 30 mL (at the marked level) of TMPLi suspension.

The following cooling baths were used to attain the desired temperatures. Temperature control is very important to obtain reproducible yields. Temperature was monitored continuously and typically remained within 2 ^{o}C of the reported value.

Diethylene glycol + CO_2 : -13 ^{o}C

Acetonitrile + CO_2 : -46 ^{o}C

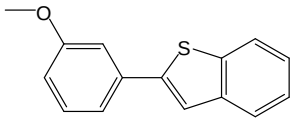
Chloroform + CO_2 : -63 ^{o}C

Acetone + CO_2 : -73 ^{o}C

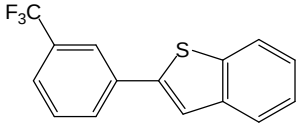
m-Toluidine + CO_2 : -35 ^{o}C

General procedure:

A 2 dram vial equipped with a magnetic stir bar was charged with arene or heterocycle (0.5 mmol) and ArCl (1.3 – 2.5 equiv). The vial was flushed with argon and capped. To this mixture was added the appropriate base solution or suspension (2.5-4.5 equiv) at the specified reaction temperature by injecting through the septum via syringe. If TMPLi in pentane was used, the base suspension was stirred vigorously while being withdrawn by syringe. The vial was flushed with argon (20 seconds) and then stirred at specified temperature for indicated time. Unless otherwise stated, reaction mixture was quenched with anhydrous MeOH (1.0 mL), evacuated to 1.0 mL and subjected to column chromatography on silica gel in hexane followed by appropriate solvent to elute the products. After concentrating the fractions containing the product, the residue was dried under reduced pressure.

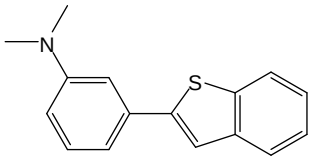


2-(3-Methoxyphenyl)benzothiophene (Entry 1, Table 3.1.1): 2-Chloroanisole (192 mg, 1.35 mmol), benzothiophene (67 mg, 0.5 mmol), TMPLi in THF (1 M, 2.1 mL), rt, 1h. After column chromatography (hexanes/CH_2Cl_2 65/35), 94 mg (78 %) of white solid was obtained. R_f = 0.46 (hexanes/ CH_2Cl_2 60/40). This compound is known.[28] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.84 (m, 1H), 7.80-7.78 (m, 1H), 7.60 (s, 1H), 7.39-7.31 (m, 4H), 7.29-7.27 (m, 1H), 6.91 (td, *J* = 7.0 Hz, 2.3 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 160.1, 144.2, 140.7, 139.6, 135.7, 130.1, 124.7, 124.5, 123.7, 122.4, 119.8, 119.2, 113.9, 112.2, 55.5.



2-(3-Trifluoromethylphenyl)benzothiophene (Entry 2, Table 3.1.1): 2-Chlorobenzotrifluoride (180 mg, 1 mmol), benzothiophene (67 mg, 0.5 mmol), TMPLi in THF (1.8 mL, 1.8 mmol), 0 ^{o}C, 4 hrs. After column chromatography (hexanes/CH_2Cl_2 80/20), 84 mg (61 %) of light yellow solid was obtained. R_f = 0.57 (hexanes/CH_2Cl_2 80/20), mp 108.5-109.5 ^{o}C (from hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.87-7.83 (m, 2H), 7.80 (m, 1H), 7.61-7.51 (m, 3H), 7.37 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 142.4, 140.5, 139.7, 135.2, 131.5 (q, J_{C-F} = 32 Hz), 129.7, 129.6, 125.0, 124.9, 124.8 (q, J_{C-F} = 3.7 Hz), 124.1 (q, J_{C-F} = 272 Hz), 124.0, 123.2 (q, J_{C-F} = 3.7 Hz), 122.5, 120.7. FT-IR (neat, cm^{-1}) υ 1326. 1297, 1179, 800, 754. Anal calcd for $C_{15}H_9F_3S$ (278.04g/mol): C, 64.74; H, 3.26; Found. C, 64.69; H, 3.23.

Note: Less than 5 % of isomeric 2-(2-trifluoromethylphenyl)benzothiophene was observed by GC.



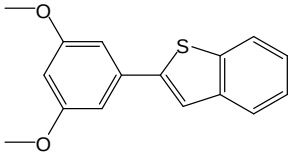
3-Benzothien-2-yl-N,N-dimethylbenzenamine (Entries 3 and 4, Table 3.1.1):

2-Chloro-*N*,*N*-dimethylaniline (195 mg, 1.25 mmol), benzothiophene (67 mg, 0.5 mmol), TMPLi in THF (1 M, 2 mL), rt, 2 hrs. After column chromatography (hexanes/CH_2Cl_2 20/80), 97 mg (77 %) of a light brown solid was obtained.

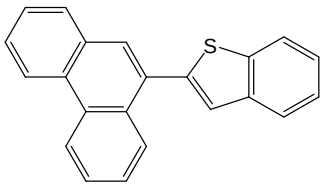
3-Chloro-*N*,*N*-dimethylaniline (195 mg, 1.25 mmol), benzothiophene (67 mg, 0.5 mmol), TMPLi in THF (1 M, 2 mL), rt, 2 hrs. After column chromatography (hexanes/CH_2Cl_2 20/80), 102 mg (81 %) of a light brown solid was obtained.

R_f = 0.58 (hexanes/EtOAc 70/30), mp 77-77.5 ^oC (from hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* =8.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.57 (s, 1H), 7.39-7.31 (m, 3H), 7.12 (d, *J* = 8.1 Hz, 1H), 7.08 (t, *J* = 2.2 Hz, 1H), 6.76 (dd, *J* = 8.1 Hz, 2.2 Hz, 1H), 3.04 (s, 6H) . ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 151.0, 145.5, 140.8, 139.6, 135.1, 129.7, 124.5, 124.2, 123.6, 122.4, 119.4, 115.2, 112.7, 110.6, 40.7. FT-IR (neat, cm^{-1}) υ 1698, 1500, 1439, 823, 760, 754, 725, 680. Anal calcd for $C_{16}H_{15}NS$ (253.09g/mol): C, 75.85; H, 5.97, N, 5.53; Found. C, 75.81; H, 5.90; N, 5.35.

Note: Less than 3% of 2-benzothien-2-yl-N,N-dimethylbenzenamine was detected by GC.

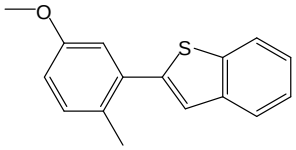


2-(3,5-Dimethoxyphenyl)benzothiophene (Entry 5, Table 3.1.1): 3,5-Dimethoxy-1-chlorobenzene (216 mg, 1.25 mmol), benzothiophene (67 mg, 0.5 mmol), TMPLi in THF (1 M, 2 mL), -73 ^{o}C, 12 hrs. After column chromatography (hexanes/CH_2Cl_2 40/60), 84 mg (62 %) of a light yellow solid was obtained. R_f = 0.39 (hexanes/CH_2Cl_2 50/50). This compound is known.[27] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (dd, *J* = 7.9 Hz, 1.0 Hz, 1H), 7.78 (dd, *J* = 7.9 Hz, 1.0 Hz, 1H), 7.54 (s, 1H), 7.38-7.30 (m, 2H), 6.88 (d, *J* = 2.3 Hz, 2H), 6.48 (t, *J* = 2.3 Hz, 1H), 3.86 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 161.2, 144.2, 140.6, 139.5, 136.2, 124.6, 124.5, 123.7, 122.4, 120.0, 104.9, 100.4, 55.6.

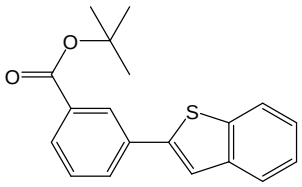


2-(9-Phenanthrenyl)benzothiophene (Entry 6, Table 3.1.1): 9-Chlorophenanthrene (265 mg, 1.25 mmol), benzothiophene (67 mg, 0.5 mmol), TMPLi in THF (1 M, 2 mL), 0 ^{o}C, 3 hrs followed by 1 h at rt. After column chromatography (hexanes/CH_2Cl_2 90/10), 116 mg (75 %) of a light yellow solid was obtained. R_f = 0.25 (hexanes/CH_2Cl_2 90/10), mp 146.5-148 ^{o}C (from hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.8 (d, *J* = 8.3 Hz, 1H), 8.72 (d, *J* = 8.3 Hz, 1H), 8.33 (dd, *J* = 8.2 Hz, 1.0 Hz, 1H), 7.95 (s, 1H), 7.94-7.87 (m, 3H), 7.73-7.60 (m, 4H), 7.51 (s, 1H), 7.46-7.38 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 142.2, 140.4, 140.3, 131.2, 131.1, 130.9, 130.7, 130.4, 129.6, 129.0, 127.4, 127.1, 127.0, 126.9, 126.7, 124.6, 124.5, 124.4, 123.7, 123.1, 122.7, 122.3. FT-IR (neat, cm^{-1}) υ

1705, 1298, 1158. Anal calcd for $C_{22}H_{14}S$ (310.08 g/mol): C, 85.12; H, 4.55; Found. C, 84.98; H, 4.48.



2-(5-Methoxy-2-methylphenyl)benzothiophene (Entry 7, Table 3.1.1): 3-Chloro-4-methoxytoluene (195 mg, 1.25 mmol), benzothiophene (67 mg, 0.5 mmol), TMPLi in THF (1 M, 2 mL), rt, 4 hrs. After column chromatography (hexanes/CH_2Cl_2 70/30), 92 mg (73 %) of a light yellow solid was obtained. R_f = 0.43 (hexanes/CH_2Cl_2 65/35), mp 57.0-58 ^oC (from ether). ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.40-7.32 (m, 2H), 7.27 (s, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 7.04 (d, *J* = 2.8 Hz, 1H), 6.87 (dd, *J* = 8.5 Hz, 2.8 Hz, 1H), 3.83 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 157.6, 143.5, 140.2, 140.1, 135.1, 131.8, 128.5, 124.5, 124.2, 123.6, 123.1, 122.1, 115.9, 114.2, 55.5, 20.3. FT-IR (neat, cm^{-1}) υ 1605, 1500, 1250, 1032. Anal calcd for $C_{16}H_{14}OS$ (254.08g/mol): C, 75.55; H, 5.55; Found. C, 75.04; H, 5.48.



***tert*-Butyl-(3-benzothien-2-yl)benzoate(Entry 8, Table 3.1.1):**

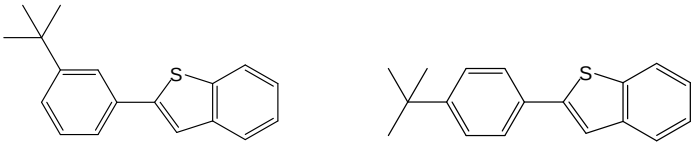
tert-Butyl-3-bromobenzoate (257 mg, 1 mmol), benzothiophene (67 mg, 0.5 mmol), TMPLi in THF (1 M, 2 mL), -73 ^oC while adding and then warm up to -46 ^oC by keeping vial inside the acetone-dry ice bath and not adding dry ice (2 hours); then move to

acetonitrile-dry ice bath, and hold at -46 ^{o}C for 8 hrs; then move to ice bath to warm up to 0 ^{o}C and keep at that temperature for 30 minutes. After column chromatography (hexanes/Et_2O 90/10), 77 mg (50 %) of a yellow solid was obtained.

tert-Butyl-3-fluorobenzoate (192 mg, 1 mmol), benzothiophene (67 mg, 0.5 mmol), TMPLi in THF (1 M, 2 mL), -73 ^{o}C; then slowly warm up to -35 ^{o}C (2 hrs) and keep at that temperature for 8 hrs, then move to ice bath to warm the reaction mixture to 0 ^{o}C and keep at that temperature for 30 minutes. After column chromatography (hexanes/Et_2O 90/10), 93 mg (60 %) of yellow solid was obtained.

R_f = 0.52 (hexanes/Et_2O 90/10), mp 135.8-137.1 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (t, *J* = 1.9 Hz, 1H), 7.96 (td, *J* = 7.8 Hz, 1.4 Hz, 1H), 7.86-7.82 (m, 2H), 7.79 (dd, *J* = 7.8 Hz, 1.9 Hz, 1H), 7.61 (s, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.38-7.31 (m, 2H), 1.64 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.5, 143.3, 140.7, 139.7, 134.5, 132.8, 130.3, 129.1, 129.0, 127.4, 124.8, 124.7, 123.8, 122.4, 120.2, 81.5, 28.3. FT-IR (neat, cm^{-1}) υ 1707, 1300, 1160. Anal calcd for $C_{19}H_{18}O_2S$ (310.10 g/mol): C, 73.52; H, 5.84; Found. C, 73.23; H, 5.72.

Note: The above two reactions were quenched with H_2O (15 mL), followed by addition of Et_2O (15 mL). The organic phase was then washed with brine (15 mL) and the aqueous layers were extracted with Et_2O (2x10 mL). The combined organic phase was then dried over $MgSO_4$, and concentrated under vacuum. The residue was then dissolved in minimum amount of dichloromethane and subjected to the flash chromatography on silica gel. After concentrating the fraction containing the product, the residue was dried over reduced pressure to yield pure product.

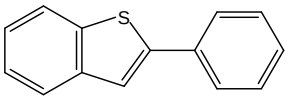


2-(3-t*ert*-Butylphenyl)benzothiophene and 2-(4-*tert*-butylphenyl)benzothiophene (Entry 9, Table 3.1.1): 4-*tert*-butylchlorobenzene (135 mg, 0.8 mmol), benzothiophene (67 mg, 0.5 mmol), TMPLi in pentane (1 M, 1.5 mL) followed by anhydrous THF (0.38 mL), rt, 1.5 hrs. After column chromatography (hexanes/CH_2Cl_2 90/10), 113 mg (85 %) of a white solid was obtained. The isomer ratio was determined to be 1/1.2 *m/p* by GC analysis. The isomers were separated by fractional crystallization from hexanes. *p*-Isomer was crystallized and collected by vacuum filtration at 0 ^oC. Rest of the liquid was cooled down to -20 ^oC. p-Isomer and some m-isomer were collected. Pure m-isomer was isolated from the liquid phase. The following amounts were obtained: *p*-isomer (white solid): 51 mg, *m*-isomer (colorless liquid): 41 mg; additionally, 17 mg of isomer mixture was recovered.

p-Isomer is known.[28] R_f = 0.27 (hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ7.81 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.65 (dt, *J* = 8.2 Hz, 2.0 Hz, 2H), 7.50 (s, 1H), 7.45 (dt, *J* = 8.2 Hz, 2.0 Hz, 2H), 7.36-7.27 (m, 2H), 1.36 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 151.6, 144.4, 140.9, 139.5, 131.6, 126.3, 126.0, 124.5, 124.2, 123.5, 122.3, 119.0, 35.0, 31.3.

m-Isomer: R_f = 0.39 (hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.75-7.73 (m, 1H), 7.56-7.53 (m, 2H), 7.41-7.29 (m, 4H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 152.0, 145.0, 140.8, 139.6, 134.1, 128.8, 125.6, 124.6, 124.3, 123.9, 123.7, 123.6, 122.4, 119.4, 34.9, 31.4. FT-IR (neat, cm^{-1}) υ

1296. Anal calcd for $C_{18}H_{18}S$ (266.11 g/mol): C, 81.15; H, 6.81; Found. C, 80.91; H, 6.71.



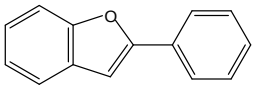
2- Phenylbenzothiophene (Entry 1, Table 3.1.2) :

Benzothiophene (67 mg, 0.5 mmol), PhCl (84 mg, 0.75 mmol), TMPLi in pentane (1 M, 1.4 mL) followed by anhydrous THF (0.35 mL), rt, 30 minutes. After column chromatography (90/10 hexanes/CH_2Cl_2), 90 mg (86 %) of a light yellow solid was obtained.

Benzothiophene (67 mg, 0.5 mmol), PhCl (112.5 mg, 1 mmol), Cy_2NLi in THF (1 M, 2.0 mL), 0 ^oC, 3 hours. After column chromatography (hexanes), 75 mg (72 %) of a light yellow solid was obtained.

Benzothiophene (67 mg, 0.5 mmol), PhF (120 mg, 1.25 mmol), TMPLi in THF (1 M, 2.0 mL), rt, 10 minutes. After column chromatography (90/10 hexanes/DCM), 89 mg (85 %) of a light yellow solid was obtained.

R_f = 0.35 (hexanes/CH_2Cl_2 95/5). This compound is known.[10] ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.8 Hz, 1H), 7.77 (dd, *J* = 7.8 Hz, 1.3 Hz, 1H), 7.73 (dd, *J* = 7.8 Hz, 1.3 Hz, 2H), 7.56 (s, 1H), 7.43 (dt, *J* = 7.8 Hz, 1.3 Hz, 2H), 7.38-7.30 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 144.3, 140.8, 139.6, 134.4, 129.1, 128.4, 126.6, 124.6, 124.4, 123.7, 122.4, 119.6.

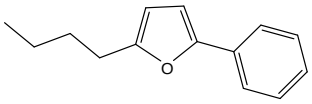


2-Phenylbenzofuran (Entry 2, Table 3.1.2):

Benzofuran (59 mg, 0.5 mmol), PhCl (84 mg, 0.75 mmol), TMPLi in pentane (1 M, 1.4 mL) followed by anhydrous THF (0.07 mL), rt, 2.5 hours. After column chromatography (hexanes/CH_2Cl_2 85/15), 79 mg (81%) of a white solid was obtained.

Benzofuran (59 mg, 0.5 mmol), PhCl (112.5 mg, 1 mmol), LDA in THF (1 M, 1.7 mL), 0 ^oC, 4 hours. After column chromatography (hexanes/ CH_2Cl_2 90/10), 72 mg (75 %) of a white solid was obtained.

R_f = 0.40 (hexanes/CH_2Cl_2 95/5). This compound is known.[10] ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (dt, *J* = 7.3 Hz, 1.3 Hz, 2H), 7.60 (dd, *J* = 7.9 Hz, 1.3 Hz, 1H), 7.55 (dd, *J* = 7.9 Hz, 1.1 Hz, 1H), 7.47 (dt, *J* = 7.9 Hz, 1.8 Hz, 2H), 7.37 (tt, *J* = 7.9 Hz, 1.1 Hz, 1H), 7.23-7.33 (m, 2H), 7.04(s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 156.0, 155.0, 130.6, 129.3, 128.9, 128.7, 125.0, 124.4, 123.0, 121.1, 111.3, 101.4.

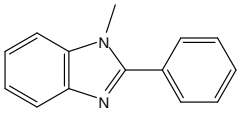


2-*n*-Butyl-5-phenylfuran (Entry 3, Table 3.1.2):

2-*n*-Butylfuran (62 mg, 0.5 mmol), PhCl (84 mg, 0.75 mmol), TMPLi in pentane (1 M, 1.4 mL) followed by anhydrous THF (0.35 mL), rt, 30 minutes. After column chromatography (hexanes/CH_2Cl_2 95/5), 80 mg (80 %) of a colorless oil was obtained.

2-*n*-Butylfuran (62 mg, 0.5 mmol), PhCl (112 mg, 1 mmol), Cy_2NLi in THF (1 M, 1.7 mL), 0 ^oC, 4 hours. After column chromatography (hexanes), 68 mg (68 %) of a colorless oil was obtained.

R_f = 0.53 (hexanes/CH_2Cl_2 95/5). This compound is known.[29] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65-7.62 (m, 2H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.21 (tt, *J* = 7.8 Hz, 1.6 Hz, 1H), 6.55 (d, *J* = 3.3 Hz, 1H), 6.06 (d, *J* = 3.3 Hz, 1H), 2.69 (t, *J* = 7.7 Hz, 2H), 1.68 (pentet, *J* = 7.7 Hz, 2H), 1.42 (s, *J* = 7.7 Hz, 2H), 0.96 (t, *J* = 7.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 156.6, 152.1, 131.3, 128.7, 126.8, 123.4, 106.9, 105.7, 30.3, 28.0, 22.4, 13.9.

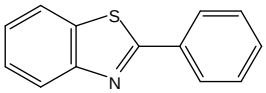


2-Phenyl-1-methylbenzimidazole (Entry 4, Table 3.1.2):

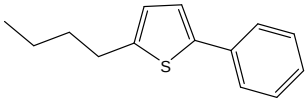
1-Methylbenzimidazole (66 mg, 0.5 mmol), PhCl (84 mg, 0.75 mmol), TMPLi in pentane (1 M, 1.4 mmol) followed by anhydrous THF (0.15 mL), rt, 1 hour. After column chromatography (hexanes/EtOAc 55/45), 95 mg (91%) of a brown solid was obtained.

1-Methylbenzimidazole (66 mg, 0.5 mmol), PhCl (112 mg, 1 mmol), Cy_2NLi in THF (1 M, 2.0 mmol), 0 ^oC, 3 hours. After column chromatography (hexanes/EtOAc 55/45), 84 mg (81 %) of a brown solid was obtained.

R_f = 0.62 (hexanes/EtOAc 50/50). This compound is known.[10] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.81 (m, 1H), 7.77-7.74 (m, 2H), 7.54-7.49 (m, 3H), 7.40-7.37 (m, 1H), 7.34-7.30 (m, 2H), 3.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 153.9, 143.0, 136.7, 130.3, 129.8, 129.6, 128.8, 122.9, 122.5, 119.9, 109.7, 31.8.



2-Phenylbenzothiazole (Entry 5, Table 3.1.2): Benzothiazole (67 mg, 0.5 mmol), PhCl (112.5 mg, 1 mmol), TMPLi in THF (1 M, 1.8 mL), -46 ^{o}C, 12 hours. After column chromatography (hexanes/CH_2Cl_2 55/45), 76 mg (72 %) of a light yellow solid was obtained. R_f = 0.48 (hexanes/EtOAc : 80/20). This compound is known.[30] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11-8.07 (m, 3H), 7.90 (dt, *J* = 7.7 Hz, 0.9 Hz, 1H), 7.51-7.47 (m, 4H), 7.38 (dt, *J* = 7.7 Hz, 0.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 168.2, 154.2, 135.2, 133.7, 131.1, 129.1, 127.7, 126.4, 125.3, 123.3, 121.7.

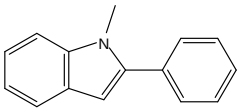


2-*n*-Butyl-5-phenylthiophene (Entry 6, Table 3.1.2):

2-*n*-Butylthiophene (70 mg, 0.5 mmol), PhCl (73 mg, 0.65 mmol), TMPLi in pentane (1 M, 1.4 mL) followed by anhydrous THF (0.15 mL), rt, 1 hour. After column chromatography (hexanes/CH_2Cl_2 95/5), 86 mg (80 %) of a colorless oil was obtained.

2-*n*-Butylthiophene (70 mg, 0.5 mmol), PhCl (112 mg, 1 mmol), Cy_2NLi in THF (1 M, 1.7 mL), 0 ^{o}C, 4 hours. After column chromatography (hexanes), 80 mg (74 %) of a colorless oil was obtained.

R_f = 0.27 (hexanes). This compound is known.[31] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dt, *J* = 8.0 Hz, 1.3 Hz, 2H), 7.34-7.38 (m, 2H), 7.25 (tt, *J* = 8.0 Hz, 1.3 Hz, 1H), 7.14 (d, *J* = 3.5 Hz, 1H), 6.76 (d, *J* = 3.5 Hz, 1H), 2.84 (t, *J* = 7.8 Hz, 2H), 1.71 (pt, *J* = 7.8 Hz, 2H), 1.43 (sextet, *J* = 7.8 Hz, 2H), 0.97 (t, *J* = 7.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 145.8, 141.7, 134.9, 128.9, 127.0, 125.6, 125.1, 122.8, 33.9, 30.1, 22.3, 14.0.

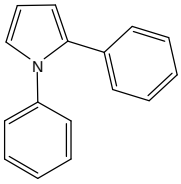


1-Methyl-2-phenylindole (Entry 7, Table 3.1.2):

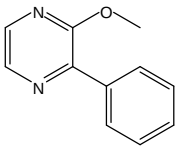
Procedure 1: A 2 dram vial equipped with a magnetic stir bar was charged with 1-methylindole (66 mg, 0.5 mmol). The vial was flushed with argon and capped. To this mixture was added TMPLi as a suspension in pentane (1 M, 1.7 mL), followed by anhydrous THF (0.2 mL) via syringe. The solution was stirred at rt for 30 minutes. PhCl (112 mg, 1 mmol) was dissolved in 9/1 pentane/THF mixture (0.6 mL) and added to the vial via syringe and reaction mixture was stirred for 1.5 hours. After column chromatography (hexanes/CH_2Cl_2 90/10), 93 mg (90 %) of a light brown solid was obtained.

Procedure 2 (following the general procedure): 1-Methylindole (66 mg, 0.5 mmol), PhCl (112 mg, 1 mmol), TMPLi in pentane (1 M, 1.8 mL), 40 ^oC, 24 hours. After column chromatography (hexanes/CH_2Cl_2 90/10), 92 mg (89 %) of a light brown solid was obtained.

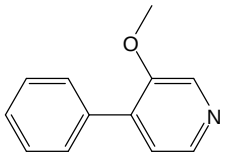
R_f = 0.48 (hexanes/CH_2Cl_2 85/15) . This compound is known.[32] ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (dt, *J* = 7.8 Hz, 0.9 Hz, 1H), 7.56-7.54 (m, 2H), 7.53-7.48 (m, 2H), 7.45-7.39 (m, 2H), 7.29 (dt, *J* = 7.1 Hz, 1.3 Hz, 1H), 7.18 (dt, *J* =7.1 Hz, 1.3 Hz, 1H), 6.6(s, 1H), 3.8 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 141.7, 138.4, 133.0, 129.5, 128.6, 128.0, 127.9, 121.8, 120.6, 120.0, 109.8, 101.8, 31.3.



1,2-Diphenylpyrrole (Entry 8, Table 3.1.2): 1-Phenylpyrrole (143 mg, 1 mmol), PhCl (56 mg, 0.5 mmol), TMPLi in pentane (1 M, 1.4 mL), 40 ^{o}C, 24 hours. After column chromatography (hexanes/CH_2Cl_2 95/5), 85 mg (78%) of a white solid was obtained. R_f = 0.56 (hexanes/CH_2Cl_2 90/10). This compound is known.[33] ^{1}H NMR (400 MHz, $CDCl_3$) δ7.35 (tq, *J* = 7.6 Hz, 1.4 Hz, 2H), 7.31-7.27 (m, 1H), 7.26-7.17 (m, 7H), 6.99 (dd, *J* = 7.6 Hz, 4.5 Hz, 1H), 6.47 (dd, *J* = 7.6 Hz, 4.5 Hz, 1H), 6.41 (t, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 140.6, 133.9, 133.1, 129.1, 128.4, 128.2, 126.7, 125.9, 124.5, 110.8, 109.4.

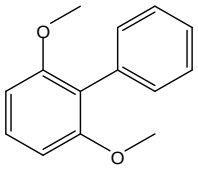


2-Methoxy-3-phenylpyrazine (Entry 9, Table 3.1.2): 2-Methoxypyrazine (55 mg, 0.5 mmol), PhCl (112 mg, 1 mmol), TMPLi in THF (1 M, 1.8 mL), -46 ^{o}C, 12 hours. After column chromatography (hexanes/EtOAc 40/60), 47 mg (55 %) of a yellow solid was obtained. R_f = 0.54 (hexanes/EtOAc 30/70). This compound is known.[34] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 2.8 Hz, 1H), 8.05 (d, *J* = 2.8 Hz, 1H), 8.05-8.02 (m, 2H), 7.49-7.42 (m, 3H), 4.03 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 158.1, 143.5, 139.2, 136.5, 135.9, 129.3, 129.2, 128.3, 53.8.



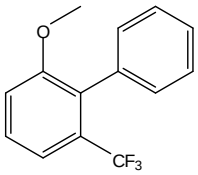
3-Methoxy-4-phenylpyridine (Entry 10, Table 3.1.2):

A 2 dram vial equipped with a magnetic stir bar was charged with 3-methoxypyridine (55 mg, 0.5 mmol), PhCl (112.5 mg, 1 mmol). The vial was flushed with argon, capped and placed into the cooling bath (-13 ^{o}C). To this mixture was slowly added TMPLi in pentane (1 M, 1.7 mL) followed by anhydrous THF (0.13 mL) by injecting through the septum via syringe.. The vial was flushed with argon for 20 seconds and then stirred for 12 hours at -13 °C. After column chromatography (hexanes/EtOAc 20/80), 66 mg (71 %) of a yellow solid was obtained. R_f = 0.32 (hexanes/EtOAc 20/80). This compound is known.[35] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36-8.30 (m, 2H), 7.58-7.55 (m, 2H), 7.45 – 7.37 (m, 3H), 7.24 (d, *J* = 5.3 Hz, 1H). 3.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 152.6, 143.0, 137.7, 135.8, 134.4, 129.3, 128.45, 128.4, 124.6, 56.4.

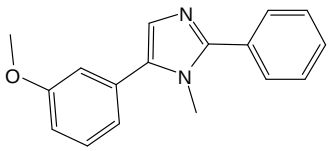


2,6-Dimethoxy-1,1'-biphenyl (Entry 11, Table 3.1.2): 1.3-Dimethoxybenzene (69 mg, 0.5 mmol), PhCl (112 mg, 1 mmol), TMPLi in pentane (1 M, 1.7 mL), 40 ^{o}C, 24 hours. After column chromatography (hexanes/CH_2Cl_2 50/50), 101 mg (95%) of a white solid was obtained. R_f = 0.29 (hexanes/CH_2Cl_2 60/40). This compound is known.[35] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.37 (m, 5H), 7.34 (t, *J* = 8.4 Hz, 1H), 6.71 (d, *J* = 8.4 Hz,

2H), 3.78 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 157.8, 134.3, 131.1, 128.8, 127.8, 126.9, 119.6, 104.3, 56.1.1



2-Methoxy-6-trifluoromethyl-1,1'-biphenyl (Entry 12, Table 3.1.2): 3-Trifluoromethylanisole (88 mg, 0.5 mmol), PhCl (84 mg, 0.75 mmol), TMPLi in pentane (1 M, 1.5 mL), followed by anhydrous THF (0.1 mL), rt, 4h. After column chromatography (hexanes/CH_2Cl_2 80/20), 102 mg (81 %) of a white solid was obtained. R_f = 0.26 (hexanes/DCM 80/20). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.39 (m, 5H), 7.30-7.27 (m, 2H), 7.16 (d, J = 8.3 Hz, 1H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 157.9, 134.9, 130.4, 130.3 (q, J_{C-F} = 29.2 Hz), 130.1, 128.8, 127.7, 127.6, 124.05 (q, J_{C-F} = 280 Hz), 117.85 (q, J_{C-F} = 5.5 Hz), 114.3, 56.2.



2-(3-Methoxyphenyl)-1-methyl-5-phenylimidazole (Scheme 3.1.17)

Two-step method with isolation of intermediate: all reactions follow the general procedure.

Step 1: 1-Methylimidazole (41 mg, 0.5 mmol), PhCl (96 mg, 0.85 mmol), LDA (1 M, 1.6 mL), rt, 3 hours. After column chromatography (hexanes/EtOAc 20/80), 63 mg (80 %) of 1-methyl-2-phenylimidazole (light yellow liquid) was obtained.

Step 2: 1-Methyl-2-phenylimidazole (79 mg, 0.5 mmol), 2-chloroanisole (142.5 mg, 1.0 mmol), TMPLi in THF (1 M, 1.8 mL), rt, 2 hours. After column chromatography (MeOH/EtOAc 10/90), then HPLC (hexanes/EtOAc/MeOH 20/70/10), 94 mg (71 %) of yellowish liquid was obtained.

Reactions without isolation of intermediate: A 2 dram vial equipped with a magnetic stir bar was charged 1-methylimidazole (41 mg, 0.5 mmol), PhCl (96 mg, 0.85 mmol). The vial was flushed with argon and capped. To this mixture was slowly added LDA in THF (1 M, 1.6 mL) by injecting through the septum via syringe. The vial was flushed with argon (20 seconds) and then stirred at room temperature for 3 hours. The reaction mixture was quenched with anhydrous MeOH (0.6 mL) and evacuated to remove all solvent and diisopropylamine. 2-Chloroanisole (142.5 mg, 1.0 mmol) was then added to the vial containing the residue. The vial was flushed with argon and capped. To this mixture was slowly added TMPLi in THF (1 M, 1.8 mL) by injecting through the septum via syringe. The vial was flushed with argon again (20 seconds) and stirred at room temperature for another 2 hours. After column chromatography (MeOH/EtOAc 10/90), and then HPLC (hexanes/EtOAc/MeOH 20/70/10), 66 mg (50 %) of a yellowish liquid was obtained.

R_f = 0.18 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70-7.67 (m, 2H), 7.49-7.34 (m, 4H), 7.20 (s, 1H), 7.03 (d, *J* = 7.8 Hz, 1H), 6.99 – 6.97 (m, 1H), 6.92 (dd, *J* = 7.8 Hz, 2.4 Hz, 1H), 3.85 (s, 3H), 3.67 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 159.9, 149.5, 135.4, 131.6, 130.9, 129.9, 128.9, 128.8, 128.7, 127.7, 121.1, 114.5, 113.3, 55.4, 33.9. FT-IR (neat, cm^{-1}) υ 1605, 1580, 1480. 1467, 1248, 1031. Anal calcd for $C_{17}H_{16}N_2O$ (264.13 g/mol): C, 77.25; H, 6.10; N, 10.60; Found. C, 77.08; H, 6.13; N, 10.88.

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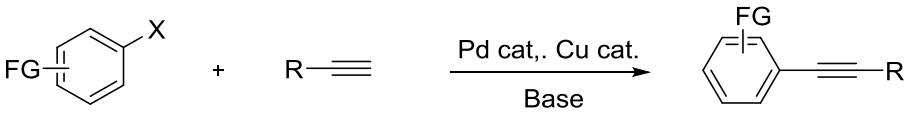
Chapter 3-2. Direct Arylation of Terminal Alkynes via Benzyne Intermediates

3.2.1. Transition-metal-catalyzed Arylation of Terminal Alkynes

The Sonogashira cross-coupling reaction has been increasingly used because of its synthetic utility in the preparation of valuable compounds. Most of this work is still carried out following the procedure based on the combination of $PdCl_2(PPh_3)_2$ and CuI catalysts. The development of more reactive palladium catalysts enables the reaction to proceed in the absence of copper(I) cocatalysis.[1]

Scheme 3.2.1. Sonogashira reactions



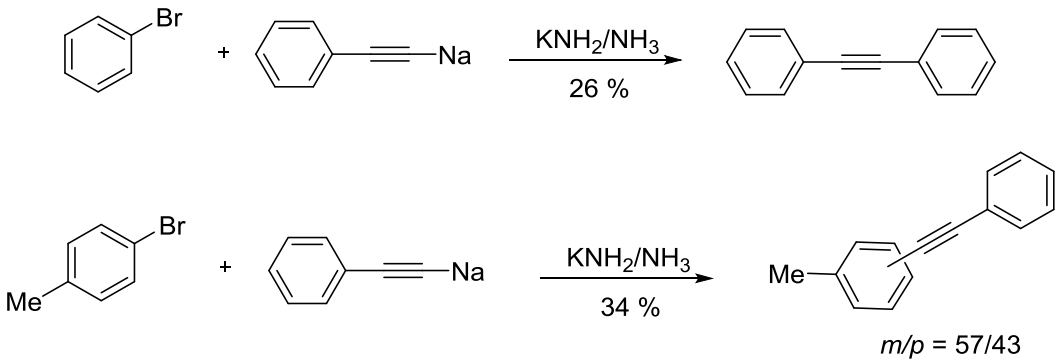
Recently, copper, iron, or nickel species have been reported to act as catalysts for Sonogashira reaction.[2] In particular, the nickel-catalyzed Sonogashira coupling has been carried out for activated aryl iodides and aromatic terminal alkynes using $NiCl_2(PPh_3)_2$ (5 mol %) in the presence of copper(I) iodide (10 mol %). The copper(I) iodide/triphenylphosphine catalytic system allowed the cross-coupling reaction of aryl and vinyl iodides and terminal alkynes. Moreover, iron(III) acetylacetonate (10 mol%) combined with 2,2'-bipyridine (20 mol%) ligand has been found to catalyze cross-coupling of terminal alkynes with aryl iodides. Transition-metal-free Sonogashira couplings have been reported.[3] Different aryl or heteroaryl iodides and bromides were heated and irradiated in water at 170 °C in the presence of phenylacetylene. However, recent studies have shown that palladium contaminants down to 50 ppb found in commercially available sodium carbonate can efficiently catalyze Sonogashira coupling

reactions.[4] Therefore, serious doubts have been raised about the identity of actual catalysts in non-palladium systems.

3.2.2. Alkynylation via Arynes

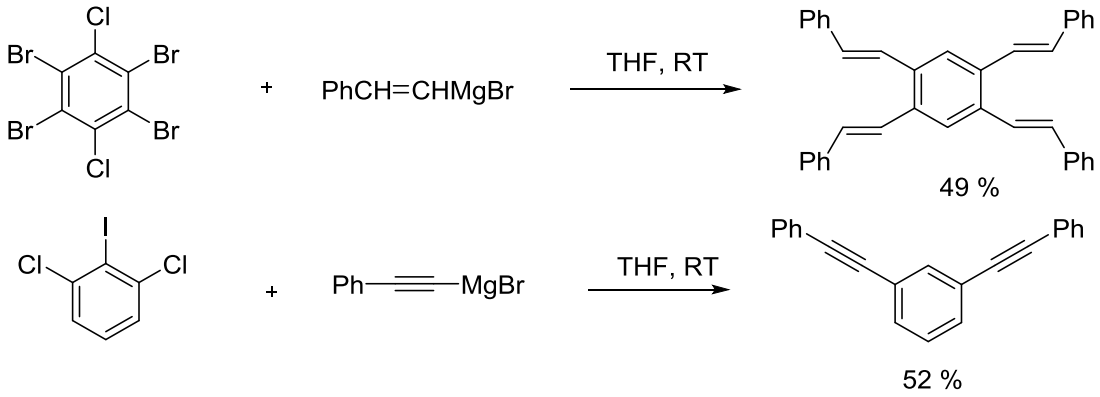
One of the first transition-metal-free aryne alkynylation reactions was described by Roberts.[5] The reactions of non-activated aryl halides with various nucleophiles such as anilide and phenyl acetylide induced by alkali amides in liquid ammonia were carried out. In all cases, isomeric products were obtained if halotoluenes was used indicating the formation of a benzyne intermediate.

Scheme 3.2.2. Aryne alkynylation using aryl bromides in KNH_2/NH_3



A reaction of polyhalobenzenes with alkenyl Grignards has been described.[6] Depending on particular polyhalobenzene used, from one to four new aryl-alkenyl bonds are formed. Three types of reactions are involved: formation of polyhaloaryl Grignards, followed by one or more sequences of aryne formation, and nucleophilic addition to the aryne. Similar reactions can be accomplished with alkynyl Grignards.

Scheme 3.2.3. Polyalkynylation and polyalkenylation via benzyne



Arynes generated from *o*-(trimethylsilyl)aryl triflates undergo cross coupling reactions with terminal alkynes in the presence of a copper catalyst.[7b] Furthermore, other transition-metal-catalyzed reactions of alkynes with arynes have been described.[7]

3.2.3. Direct Arylation of Terminal Alkynes via Benzyne Intermediates

3.2.3.1. Introduction

Transition-metal-catalyzed reactions between aryl halides and terminal alkynes have been employed in a wide variety of areas.[8] During the past decades, remarkable improvements in reaction efficiency have been achieved.[8b] Several examples of transition-metal-free sp^2-sp carbon-carbon bond formation reactions have been described in the literature.[9] In most cases, however, either photochemical activation, preformed Grignard reagents, or activated aryl halides were employed.

Several methods for direct arylation of terminal alkynes via benzyne intermediates have been described. Arynes generated from *o*-(trimethylsilyl)aryl triflates undergo cross coupling reaction with terminal alkynes in the presence of a copper catalyst.[7] As previously mentioned, *o*-(trimethylsilyl)aryl triflates are expensive and their commercial availability is limited. Hart reported a procedure for reaction between polyhaloarenes and alkynyl Grignards proceeding via aryne intermediates.[6] The requirement of preformed alkynylmetals limits the application of this method and only a few examples were disclosed. A general procedure for transition-metal-free direct arylation of alkynes using aryl halides has not been described.

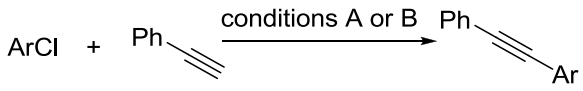
3.2.3.2. Results and Discussion

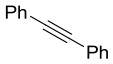
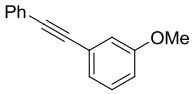
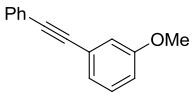
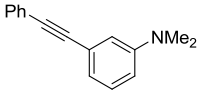
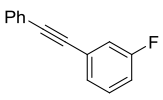
In our previous report, a direct transition-metal-free, base-mediated intermolecular arylation of heterocycles and arenes by aryl halides has been disclosed.[10] The method employed hindered lithium amide bases in pentane/THF mixture. Mechanistically, the reaction proceeds via the simultaneous generation of arynes and aryl

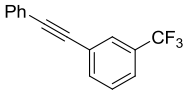
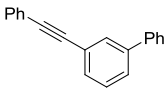
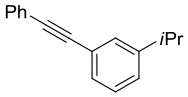
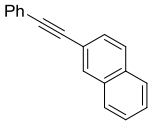
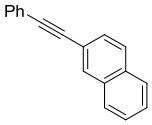
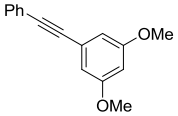
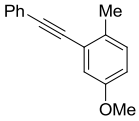
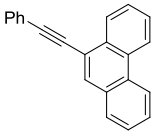
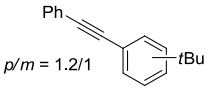
anions from aryl halides and arenes, respectively. Since cross coupling reactions between arynes and alkynyl Grignards are known, we reasoned that direct aryl halide alkynylation under similar conditions is possible.

Hindered LiTMP was used to suppress the reaction of benzyne with base. Relative reactivity of the base and alkynyl anion with benzyne is modulated by employing a solvent where amide base is sparingly soluble. The results indicated that reported conditions for arylation of sp^2 C-H bonds are applicable to the aryl halide alkynylation. Interestingly, comparable yields were obtained when heating reaction mixture in dioxane in the presence of an alkoxide base. The latter set of conditions is based on previously published intramolecular arylation of phenol derivatives.[11]

Table 3.2.1. Alkynylation Scope with Respect to Aryl Chlorides[a]



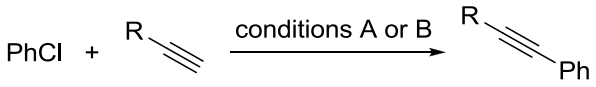
entry	ArCl/conditions	product	yield, %
1	PhCl, A		91
	A		61[b]
	B		77
2	2-ClC_6H_4OMe		
	A		75
3	3-ClC_6H_4OMe		
	B		86
4	3-$ClC_6H_4NMe_2$		
	A		85
5	3-ClC_6H_4F		
	B		82

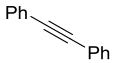
6	3-$ClC_6H_4CF_3$, A B		70 74
7	(a) 2-BrC_6H_4Ph A (b) 2-FC_6H_4Ph, A		78 70
8	2-ClC_6H_4*i*Pr A		85
9	2-naphthyl chloride A		81
10	1-naphthyl chloride A		60
11	3,5-$(MeO)_2C_6H_3Cl$ B		81
12	2-MeO-4-MeC_6H_3Cl A		75
13	9-chlorophen-anthrene A		86
14[c]	4-*t*BuC_6H_4Cl A		90

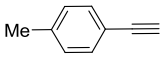
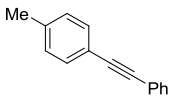
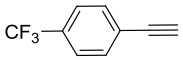
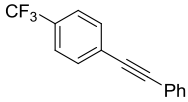
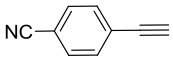
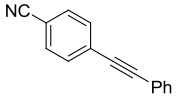
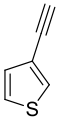
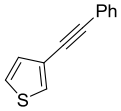
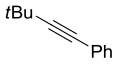
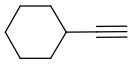
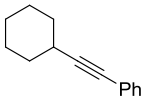
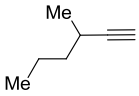
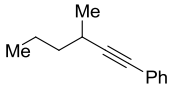
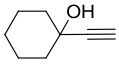
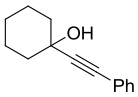
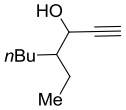
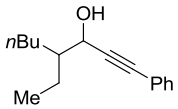
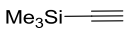
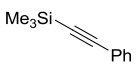
[a] Method A: aryl halide (1.5-2.5 equiv), phenylacetylene (1 equiv), TMPLi (3-4 equiv), pentane/THF, 25 °C. Method B: aryl halide (2.6-3 equiv), phenylacetylene (1 equiv), *t*BuONa or *t*BuOK (7 equiv), dioxane, 106-135 °C. Yields are isolated yields of a pure major isomer unless otherwise noted and reactions were run on 0.5 mmol scale. [b] 1:1 Ratio of PhCl and alkyne. [c] Isomer mixture; *m/p* ratio 1/1.2.

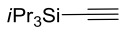
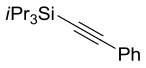
The reactions scope with respect to aryl chlorides is shown in Table 3.2.1. Higher yield was obtained when excess chlorobenzene was used (entry 1). 3-Methoxydiphenylacetylene is obtained when phenylacetylene is arylated by either 2- or 3-chloroanisole (entries 2 and 3).[12] 3-Chlorodimethylaniline and 3-chlorobenzotrifluoride are reactive, and products are obtained in good yields (entries 4 and 6). For the latter substrate, both reaction conditions afford good yields. Interestingly, by employing *t*BuONa base, it is possible to selectively substitute chloride in 3-fluorochlorobenzene (entry 5). In several cases, isomer mixtures are obtained. For 2-chlorocumene (entry 8), a 12/1 isomer mixture was obtained with 3-isomer as a major product. The alkynylation of 1- and 2-chloronaphthalenes affords product as a 5.4/1 and 11.6/1 isomer mixtures, with 2-naphthylphenylacetylene predominating (entries 9 and 10). The reported yields are those of a pure major isomer after purification by HPLC. Arylation by 3,5-dimethoxychlorobenzene, 3-chloro-4-methoxy-toluene, and 9-chlorophenanthrene affords products in good yields (entries 11-13). When 4-chloro-*t*-butylbenzene is used, a nearly 1/1 mixture of alkynylation product isomers is obtained (entry 14).

Table 3.2.2. Alkynylation Scope with Respect to Alkynes[a]



entry	alkyne/conditions	product	yield, %
	Na acetylide (NaCCH)		
1	A[b]		86
	B[c]		78

2	 A B		87 75
3	 A B		90 78
4	 A[d]		50
5	 B		73
6	 A B		93 78
7[e]	 A		67
8[e]	 A		76
9	 A		65
10	 A		62
11	 A		85

12	 A			93

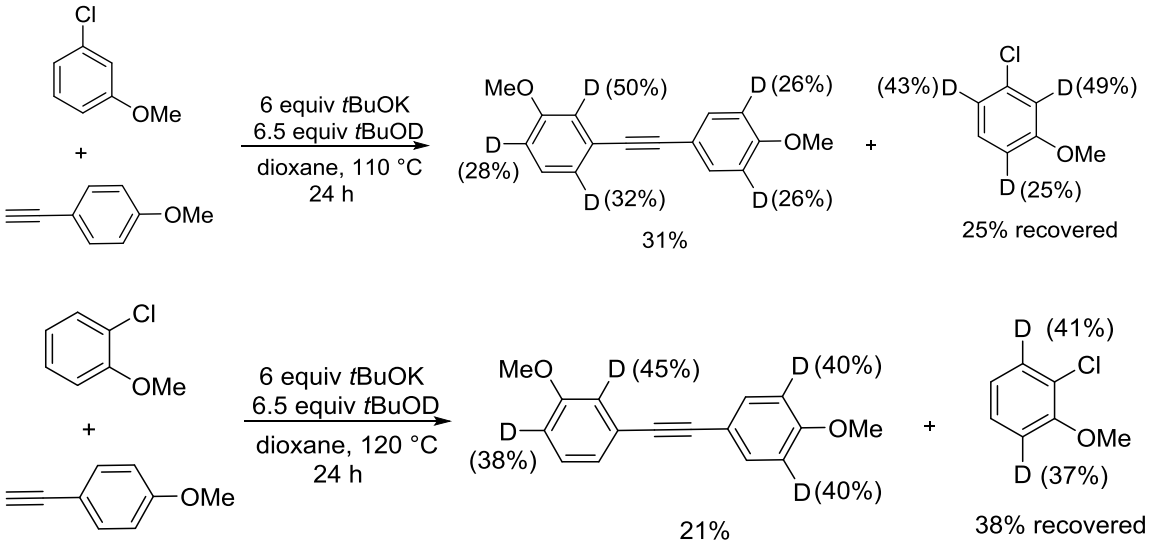
[a] Method A: PhCl (1.8-2 equiv), alkyne (1 equiv), TMPLi (3.2-4.4 equiv), pentane/THF, THF, or diethyl ether solvent, 25 °C. Method B: chlorobenzene (3.0 equiv), alkyne (1.0 equiv), *t*BuOK (7 equiv), dioxane, 106 °C. Yields are isolated yields and reactions were run on 0.5 mmol scale. See Supporting Information for details. [b] PhCl (4 equiv), TMPLi (5.6 equiv). [c] PhCl (5 equiv), *t*BuOK (8 equiv). [d] Reaction at -55 °C. [e] Reaction at -63 °C.

The reaction scope with respect to alkynes is presented in Table 3.2.2. Sodium acetylide can be diarylated in good yield (entry 1). Phenylacetylenes with electron-donating or electron-withdrawing groups are reactive (entries 2-3). Cyano group is tolerated (entry 4). Arylation of 3-ethynylthiophene affords the product in good yield (entry 5). Many aliphatic alkynes can be used as coupling partners. Arylation of *t*-butylacetylene, cyclohexylacetylene, and 3-methyl-1-hexyne is possible and couplings proceed in good yields (entries 6-8). However, for alkynes possessing propargylic hydrogens, careful temperature optimization is required to prevent base-mediated conversion to allene and method B is not applicable due to high reaction temperature. Isomerization to allenes was observed with primary alkylacetylenes and acceptable yields could not be obtained. Substrates containing tertiary and hindered secondary hydroxyl groups can be *C*-arylated selectively (entries 9 and 10). Silyl group-containing alkynes are arylated in good yields and cleavage of the silyl substituent is not observed if TMPLi base is employed (entries 11 and 12).

3.2.3.3. Mechanistic Studies

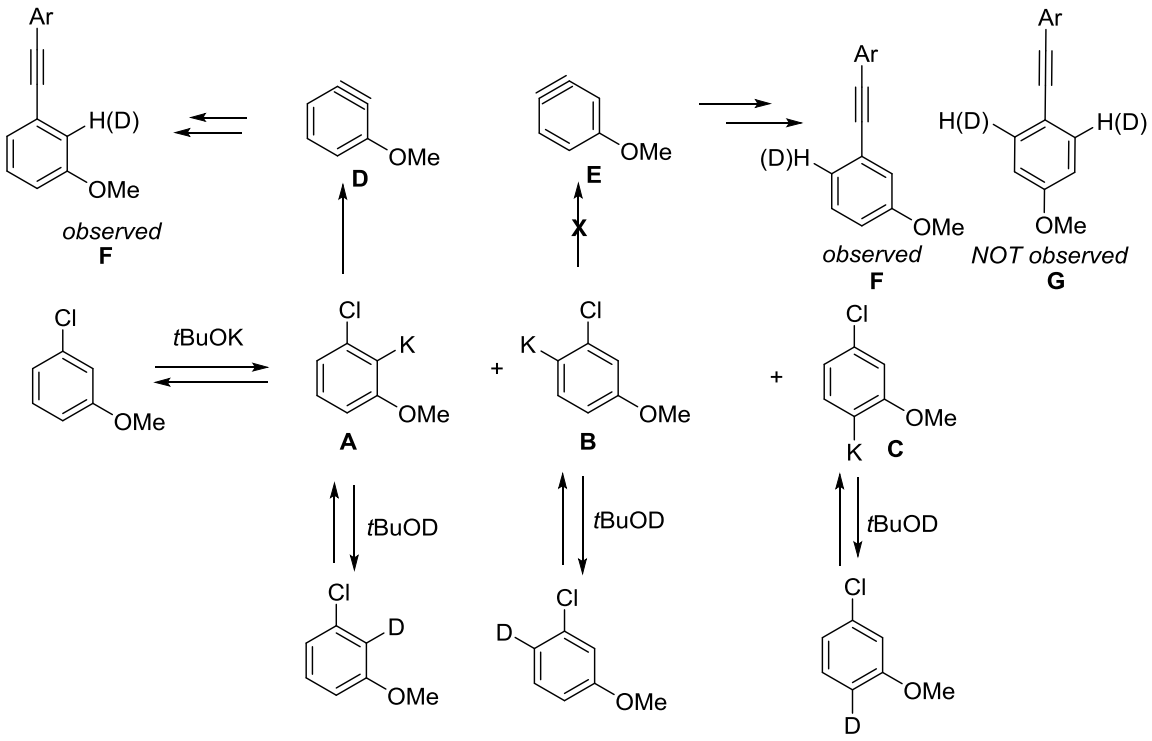
Several experiments with deuterated reagents were conducted to investigate the reaction mechanism. Thus, 6.5 equiv *t*BuOD was added to mixture of 3-chloroanisole, 4-methoxyphenylacetylene, and *t*BuOK in dioxane followed by heating to 110 ° (Scheme 3.2.4). The H/D exchange conditions were chosen to mimic conditions B. After reaction, coupling product was obtained in 31% yield. Unreacted 3-chloroanisole was recovered in 25% yield. Analysis by ^{1}H-NMR showed extensive incorporation of deuterium label adjacent to methoxy and chloro substituents arising from metalation-deuteration sequence in recovered chloroarene and coupling product. Similar results were obtained in the reaction of 2-chloroanisole with 4-methoxyacetylene. Interestingly, *t*-BuOK is able to *ortho*-metalate nonactivated methoxyarenes as evidenced by deuteration of the *p*-methoxyphenyl group.

Scheme 3.2.4. Deuteration Experiments



Deuterium incorporation at 2- and 4-positions of recovered 3-chloroanisole is noteworthy. Deuterium incorporation in recovered 3-chloroanisole can be explained by the intermediacy of three isomers of the arylpotassium species – A, B, and C (Scheme 3.2.5). *ortho*-Aryne can not be formed from C. Compound A can form only 3-methoxybenzyne D that regioselectively reacts with alkyne anion to form the observed product F.[13] On the other hand, arylpotassium B could form 4-methoxybenzyne E that would react to afford two product isomers F and G in nearly equal amounts. Since compound G is not observed, and deuteration experiment suggests that B is present in the reaction mixture, it must be concluded that aryne formation from A is more facile than aryne formation from B.[14] Collum and coworkers have measured the rate constants for benzyne formation from substituted aryllithiums and concluded that haloanisoles are especially reactive toward LiX elimination.

Scheme 3.2.5. Metalation-Benzyne Formation Sequence



3.2.3.4. Conclusions

Two sets of conditions for base-mediated, transition-metal-free alkynylation of aryl chlorides have been developed. The first set of conditions involves the use of hindered TMPLi base in pentane/THF mixture at room temperature. The second set involves use of a metal alkoxide base in dioxane at elevated temperature. Functional groups such as fluoro, trifluoromethyl, silyl, tri-substituted amine, and cyano are tolerated. Tertiary and secondary alcohols are also compatible with the reaction conditions.

3.2.3.5. Experimental Section

General considerations: When TMPLi (lithium 2,2,6,6-tetramethylpiperidide) was used, reactions were performed in 2-dram vials using screw caps with 17 mm hole and white silicone septum with white teflon face (from SUPELCO). If *tert*-butoxide bases were used, reactions were run in 1-dram vials using 13 mm screw caps with PTFE/Liner (from SUPELCO). Column chromatography was performed on 60Å silica gel (Sorbent Technologies). Purification by preparative HPLC was performed on a Shimadzu Prominence LC (LC-20AB) equipped with a SPD-20A UV-Vis detector and a Varian Dynamax (250 mm x 21.4 mm) column. GC-MS analyses were performed on a Shimadzu GCMS-QP5000 chromatograph equipped with a Restek column (Rtx-XLB, 30 m x 0.25 mm I.D.). The ^{1}H, ^{19}F and ^{13}C NMR were recorded on JEOL EC-400 or JEOL EC-500 spectrometers using residual solvent peak as a reference. α,α,α-Trifluorotoluene (neat, δ = -62.3ppm) was employed as an external standard in ^{19}F NMR spectra. Elemental analyses were performed by Atlantic Microlab Inc. of Norcross, GA. IR spectra were obtained on a ThermoNicolet Avatar 370 FT-IR instrument. Analytical thin layer chromatography was performed on silica gel IB-F (Baker-flex) by J. T. Baker. All procedures were performed under argon atmosphere unless otherwise noted.

Materials. The following starting materials were obtained from commercial sources and were used without further purification: sodium *tert*-butoxide, potassium *tert*-butoxide, phenylacetylene, 4-ethynyltoluene, 4-ethynylbenzotrifluoride, triisopropylsilylacetylene, trimethylsilylacetylene, 3-methyl-1-hexyne, cyclohexylacetylene, 3,3-dimethyl-1-butyne, 1-ethynyl-1-cyclohexanol, 4-ethyl-1-octyn-3-ol, 3-ethynylthiophene, 3-chloro-*N*,*N*-

dimethylaniline, 2-chloro-*N*,*N*-dimethylaniline, 2-chloroanisole, 3-chloroanisole, chlorobenzene, 3-chlorobenzotrifluoride, 2-chloroisopropylbenzene, 2-chloronaphthalene, 2-bromobiphenyl, 2-fluorobiphenyl, 1-chloro-3-fluorobenzene, 4-*tert*-butyl-1-chlorobenzene, 2,2,6,6-tetramethylpiperidine (TMPH), 9-chlorophenanthrene, 3,5-dimethoxychlorobenzene, 3-chloro-4-methoxytoluene. Sodium acetylide was purified from mineral oil suspension by repeated washing with pentane followed by drying in vacuum. 1-Chloronaphthalene was synthesized according to literature. [15]

TMPLi 1M in THF: A 25 mL oven-fried flask equipped with a magnetic stirring bar and a septum was evacuated and backfilled with argon 5 times. TMPH (2,2,6,6-tetramethylpiperidine, 2.32 g, 16.5 mmol) was added via syringe, followed by anhydrous THF to give 15 mL of solution. The mixture was cooled to -73 ^{o}C and stirred for 5 minutes. *n*-BuLi (2.5 M in hexanes, 6 mL, 15 mmol) was then added dropwise (in 15 minutes). The reaction mixture was stirred for 45 minutes at -73 ^{o}C followed by warming to 0^{o}C and stirring for additional 15 minutes. After that, the reaction mixture was vacuumed at room temperature to give 15 mL of solution.

TMPLi 1M in Et_2O: A 25 mL oven-fried flask equipped with a magnetic stirring bar and a septum was evacuated and backfilled with argon 5 times. TMPH (2,2,6,6-tetramethylpiperidine, 2.32 g, 16.5 mmol) was added via syringe, followed by anhydrous Et_2O to give 15 mL of solution. The mixture was cooled to -73 ^{o}C and stirred for 5 minutes. *n*-BuLi (2.5 M in hexanes, 6 mL, 15 mmol) was then added dropwise (in 15 minutes). The reaction mixture was stirred for 45 minutes at -73 ^{o}C followed by warming to 0 ^{o}C and stirring for additional 5 minutes. After that, the reaction mixture was

vacuumed at 0 ^{o}C to remove all solvents. Anhydrous Et_2O (15 mL) was added to the precipitate.

TMPLi 1 M in pentane: A 50 mL oven-fried flask equipped with a magnetic stirring bar and a septum was evacuated and backfilled with argon 5 times. TMPH (4.64 g, 33.0 mmol) was added, followed by anhydrous pentane to give 30 mL of solution (marked the flask at the level of solution). The mixture was cooled to -73 °C (dry ice-acetone) and stirred for 5 minutes. *n*-BuLi (2.5 M in hexanes, 12.0 mL, 30 mmol) was added dropwise and reaction mixture was stirred for 30 minutes at -73 °C, warmed up to room temperature and stirred overnight. The reaction mixture was vacuumed to give 30 mL (at the marked level) of TMPLi suspension.

The following cooling baths were used to attain the desired temperatures. Temperature control is very important to obtain reproducible yields. Temperature was monitored continuously and typically remained within 2 °C of the reported value.

Chloroform + CO_2: -63 °C.

Acetone + CO_2: -73 °C.

n-Octane + CO_2: -55 °C.

Room temperature: 25 °C.

General procedures.

Alkynylation using *t*-BuOK and *t*-BuONa bases: Outside the glovebox a 1-dram vial equipped with a magnetic stirring bar was charged with chloroarene (1.5 mmol) and alkyne (0.5 mmol). The vial was flushed with argon, capped and placed inside the glovebox. To this mixture was added dioxane (0.3 mL), *t*-BuONa or *t*-BuOK (3.5 mmol),

and dioxane (0.2 – 0.4 mL). The sealed vial was taken out the glovebox, stirred at room temperature for 5 minutes and then placed in preheated oil bath for indicated time. Reaction vials were occasionally shaken during first few hours to ensure complete mixing. The reaction mixture was cooled to room temperature and quenched with 0.5 mL anhydrous MeOH. The reaction mixture was evacuated to remove all solvent, dissolved in minimal amount of CH_2Cl_2, and subjected to flash chromatography on silica gel in hexanes or pentanes followed by appropriated solvent to elute the products. After concentrating the fractions containing the product, the residue was dried under reduced pressure to yield pure product. If necessary, purification by preparative HPLC was performed.

TMPLi base: A 2 dram vial equipped with a magnetic stir bar was charged with alkyne (0.5 mmol) and ArCl (1.5 – 2.5 equiv). The vial was flushed with argon and capped. To this mixture was added the appropriate base solution or suspension (2.5-4.5 equiv) at the specified reaction temperature by injecting through the septum via 1mL syringe. If TMPLi in pentane was used, the base suspension was stirred vigorously during the time being withdrawn by syringe. The vial was flushed with argon (20 seconds) and then stirred at specified temperature for indicated time. Unless otherwise stated, reaction mixture was quenched with anhydrous MeOH (1.0 mL), evacuated to 1.0 mL and subjected to column chromatography on silica gel in hexane or pentane followed by appropriate solvent to elute the product. After concentrating the fractions containing the product, the residue was dried under reduced pressure.

Phenylethynylbenzene (Table 3.2.1, Entry 1; Table 3.2.2, Entry 1)

Chlorobenzene (85 mg, 0.75 mmol), phenylacetylene (51 mg, 0.5 mmol), TMPLi in pentane (1 M, 1.5 mL), followed by anhydrous THF (0.1 mL), room temperature, 1.5 hours. After column chromatography (hexanes/CH_2Cl_2 90/10), 81 mg (91 %) of a white solid was obtained.

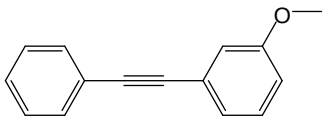
Chlorobenzene (169 mg, 1.5 mmol), phenylacetylene (51 mg, 0.5 mmol), *t*-BuOK (394 mg, 3.5 mmol), dioxane (0.6 mL), 106 °C, 24 hrs. After column chromatography (gradient, hexanes/CH_2Cl_2: 100/0 - 90/10), 68 mg (77 %) of a white solid was obtained.

Chlorobenzene (56.5 mg, 0.5 mmol), phenylacetylene (51 mg, 0.5 mmol), TMPLi in pentane (1 M, 1.1 mL), followed by anhydrous Et_2O (0.1 mL), room temperature, 12 hours. After column chromatography (hexanes/CH_2Cl_2 90/10), 54 mg (61 %) of a white solid was obtained.

Chlorobenzene (284 mg, 2.5 mmol), sodium acetylide (24 mg, 0.5 mmol), *t*-BuOK (448 mg, 4 mmol), dioxane (0.7 mL), 106 °C, 24 hrs. After column chromatography (gradient, hexanes/CH_2Cl_2: 100/0 - 90/10), 69 mg (78 %) of a white solid was obtained.

Chlorobenzene (225 mg, 2.0 mmol), sodium acetylide (24 mg, 0.5 mmol), TMPLi in pentane (1 M, 2.8 mL), followed by anhydrous THF (0.25 mL), room temperature, 3 hours. After column chromatography (hexanes/CH_2Cl_2 90/10), 78 mg (86 %) of a white solid was obtained.

R_f = 0.15 (hexanes). This compound is known.[16] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.54 (m, 4H), 7.38 – 7.34 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 131.7, 128.5, 128.4, 123.4, 89.5.

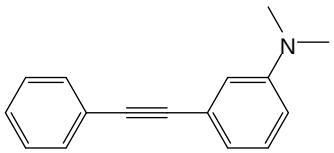


1- Methoxy-3-(2-phenylethynyl)benzene (Table 3.2.1, Entries 2 and 3)

2-Chloroanisole (178 mg, 1.25 mmol), phenylacetylene (51 mg, 0.5 mmol), TMPLi in THF (1M, 2 mL), room temperature, 3 hours. After column chromatography (hexanes/CH_2Cl_2 75/25), 78 mg (75 %) of a yellowish liquid was obtained.

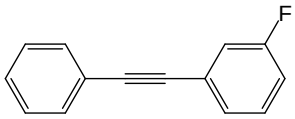
3-Chloroanisole (213.5 mg, 1.5 mmol), phenylacetylene (51 mg, 0.5 mmol), *t*-BuONa (336 mg, 3.5 mmol), dioxane (0.5 mL), 125 °C, 20 hours. After column chromatography (gradient, hexanes/CH_2Cl_2: 100/0 - 75/25), 89 mg (86 %) of a yellowish liquid was obtained.

R_f = 0.18 (hexanes/CH_2Cl_2 80/20). This compound is known.[17] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.55 (m, 2H), 7.39 – 7.34 (m, 3H), 7.26 (d, *J* = 8.0 Hz, 1H), 7.15 (td, *J* = 8.0 Hz, 1.3 Hz, 1H), 7.09 – 7.08 (m, 1H), 6.91 (ddd, *J* = 1.3 Hz, 2.8 Hz, 8.0 Hz, 1H), 3.84 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 159.5, 131.7, 129.5, 128.5, 128.4, 124.4, 124.3, 123.3, 116.4, 115.1, 89.4, 89.3, 55.4.



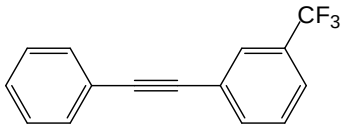
***N*,*N*-Dimethyl-3-(2-phenylethynyl)benzenamine (Table 3.2.1, Entry 4)**

3-Chloro-*N*,*N*-dimethylaniline (155.5 mg, 1.0 mmol), phenylacetylene (51 mg, 0.5 mmol), TMPLi in THF (1M, 1.8 mL), room temperature, 3 hours. After column chromatography (hexanes/CH_2Cl_2 60/40), 95 mg (85 %) of a brownish liquid was obtained. R_f = 0.22 (hexanes/CH_2Cl_2 60/40). This compound is known.[18] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.55 (m, 2H), 7.39 – 7.33 (m, 3H), 7.23 (t, *J* = 8.1 Hz, 1H), 6.94 – 6.92 (m, 2H), 6.74 (dd, *J* = 8.1 Hz, 2.7 Hz, 1H), 2.98 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 150.5, 131.7, 129.2, 128.4, 128.2, 123.7, 123.6, 120.0, 115.4, 113.0, 90.5, 88.4, 40.6.



1- Fluoro-3-(2-phenylethynyl)benzene (Table 3.2.1, Entry 5)

3-Chloro-1-fluorobenzene (195.5 mg, 1.5 mmol), phenylacetylene (51 mg, 0.5 mmol), *t*-BuONa (336 mg, 3.5 mmol), dioxane (0.5 mL), 125 °C, 36 hours. After column chromatography (gradient, hexanes/CH_2Cl_2: 100/0 - 90/10), 80 mg (82 %) of a colorless liquid was obtained. R_f = 0.21 (hexanes/CH_2Cl_2 90/10). This compound is known.[19] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.52 (m, 2H), 7.38 – 7.34 (m, 3H), 7.33 – 7.30 (m, 2H), 7.26 – 7.23 (m, 1H), 7.08 – 7.02 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.5 (d, J_{C-F} = 246.2 Hz), 131.8, 130.0 (d, J_{C-F} = 8.7 Hz), 128.7, 128.5, 127.6 (d, J_{C-F} = 3.0 Hz), 125.2 (d, J_{C-F} = 9.5 Hz), 122.8, 118.5 (d. J_{C-F} = 23.1 Hz), 115.7 (d, J_{C-F} = 21.6 Hz), 90.4, 88.2 (d, J_{C-F} = 3.8 Hz).

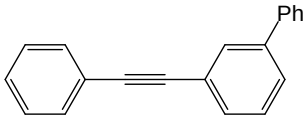


1-(2-Phenylethynyl)-3-(trifluoromethyl)benzene (Table 3.2.1, Entry 6)

3-Chlorobenzotrifluoride (180 mg, 1.0 mmol), phenylacetylene (51 mg, 0.5 mmol), TMPLi in THF (1M, 1.8 mL), followed by anhydrous THF (0.2 mL), room temperature, 2 hours. After column chromatography (hexanes/CH_2Cl_2 90/10), 86 mg (70 %) of a colorless liquid was obtained.

3-Chlorobenzotrifluoride (270 mg, 1.3 mmol), phenylacetylene (51 mg, 0.5 mmol), *t*-BuONa (336 mg, 3.5 mmol), dioxane (0.5 mL), 130 °C, 36 hours. After column chromatography (hexanes/CH_2Cl_2 90/10), 91 mg (74 %) of a colorless liquid was obtained.

R_f = 0.24 (hexanes/CH_2Cl_2 90/10). This compound is known.[16] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.60 – 7.53 (m, 3H), 7.47 (t, J = 7.8 Hz, 1H), 7.40 – 7.35 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 134.7, 131.8, 131.0 (q, J_{C-F} = 32 Hz), 129.0, 128.9, 128.6, 128.5 (q, J_{C-F} = 4.1 Hz), 124.9 (q, J_{C-F} = 4.1 Hz), 124.3, 123.6 (q, J_{C-F} = 272 Hz), 122.7, 91.0, 87.9.



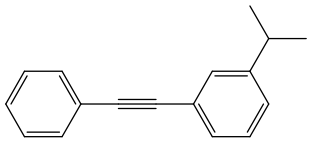
3-(Phenylethynyl)-1,1'-biphenyl (Table 3.2.1, Entry 7)

2-Bromobiphenyl (209.7 mg, 0.9 mmol), phenylacetylene (51 mg, 0.5 mmol), TMPLi in pentane (1 M, 1.6 mL), followed by anhydrous THF (0.12 mL), room temperature, 5

hours. After column chromatography (hexanes/CH_2Cl_2 90/10), 99 mg (78 %) of a light yellow liquid was obtained.

2-Fluorobiphenyl (172 mg, 1.0 mmol), phenylacetylene (51 mg, 0.5 mmol), TMPLi in pentane (1 M, 1.7 mL), followed by anhydrous THF (0.08 mL), room temperature, 3 hours. After column chromatography (hexanes/CH_2Cl_2 90/10), 89 mg (70 %) of a light yellow liquid was obtained.

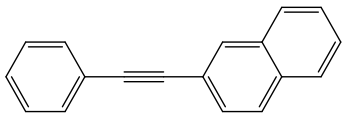
R_f = 0.15 (hexanes/CH_2Cl_2 90/10). This compound is known.[20] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (m, 1H), 7.65 – 7.62 (m, 2H), 7.60 – 7.57 (m, 4H), 7.51 – 7.44 (m, 3H), 7.42 – 7.36 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 141.5, 140.5, 131.8, 130.5, 129.0, 128.5, 128.4, 128.3, 127.7, 127.3, 127.2, 123.8, 123.3, 89.6, 89.5. Signal for one carbon could not be located.



1- Isopropyl-3-(2-phenylethynyl)benzene (Table 3.2.1, Entry 8)

2-Chloroisopropylbenzene (139 mg, 0.9 mmol), phenylacetylene (51 mg, 0.5 mmol), TMPLi in pentane (1M, 1.6 mL), followed by anhydrous THF (0.15 mL), room temperature, 2 hours. GC Analysis showed that two isomers are formed in 12.2/1 ratio. After column chromatography (hexanes/CH_2Cl_2 95/5), 106 mg (96 %) of a colorless liquid containing 2 isomers in 12.1/1 ratio was obtained. The mixture was subjected to HPLC in hexanes to give 93.5 mg (85 %) of single major isomer as a colorless liquid. R_f = 0.18 (hexanes/CH_2Cl_2 95/5). This compound is known.[21] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.52 (m, 2H), 7.41 (t, *J* = 1.8 Hz, 1H), 7.36 – 7.31 (m, 4H), 7.27 (t, *J* = 7.8 Hz,

1H), 7.20 (td, *J* = 7.8 Hz, 1.8 Hz, 1H), 2.9 (septet, *J* = 7.0 Hz, 1H), 1.26 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 149.1, 131.7, 129.6, 129.2, 128.4, 128.3, 126.8, 123.4, 123.1, 89.6, 89.0, 34.1, 24.0. Signal for one carbon could not be located.

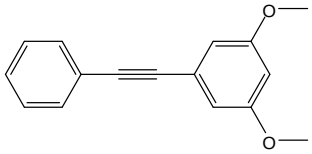


2-(2-Phenylethynyl)naphthalene (Table 3.2.1, Entries 9 and 10)

2-Chloronaphthalene (162.5 mg, 1.0 mmol), phenylacetylene (51 mg, 0.5 mmol), TMPLi in pentane (1M, 1.8 mL), followed by anhydrous THF (0.2 mL), room temperature, 2 hours. GC Analysis showed that two isomers are obtained in 11.5/1 ratio. After column chromatography (hexanes/CH_2Cl_2 90/10), 110 mg (94 %) of a white solid containing 2 isomers in 11.6/1 ratio was obtained. The mixture was subjected to HPLC (hexanes/CH_2Cl_2 95/5), and 92 mg (81 %) of a single isomer as a white solid was isolated.

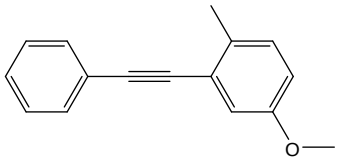
1-Chloronaphthalene (162.5 mg, 1.0 mmol), phenylacetylene (51 mg, 0.5 mmol), TMPLi in pentane (1M, 1.8 mL), followed by anhydrous THF (0.2 mL), room temperature, 2 hours. GC Analysis showed that two isomers are obtained in 5.4/1 ratio. After column chromatography (hexanes/CH_2Cl_2 90/10), 103 mg (90 %) of white solid containing 2 isomers in 5.4/1 ratio was obtained. The mixture was then subjected to HPLC (hexanes/CH_2Cl_2 95/5) and 68 mg (60 %) of a single isomer as a white solid was isolated. R_f = 0.28 (hexanes/CH_2Cl_2 85/15). This compound is known.[16] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.84 – 7.81 (m, 3H), 7.60 – 7.58 (m, 3H), 7.52 – 7.48 (m, 2H), 7.40 – 7.35 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 133.1, 132.9, 131.8, 131.6,

128.6, 128.5, 128.4, 128.1, 127.9, 126.8, 126.7, 123.4, 120.7, 89.9, 89.8. Signal for one carbon could not be located.



1,3-Dimethoxy-5-(2-phenylethynyl)benzene (Table 3.2.1, Entry 11)

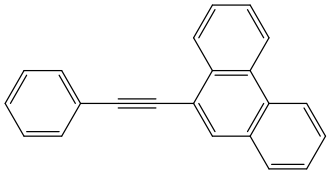
5-Chloro-1,3-dimethoxybenzene (258.5 mg, 1.5 mmol), phenylacetylene (51 mg, 0.5 mmol), *t*-BuONa (336 mg, 3.5 mmol), dioxane (0.5 mL), 125 °C, 18 hours. After column chromatography (gradient, hexanes/CH_2Cl_2: 100/0 - 30/70), 96 mg (81 %) of a yellowish liquid was obtained. R_f = 0.28 (hexanes/CH_2Cl_2 85/15). This compound is known.[22] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.52 (m, 2H), 7.37 – 7.33 (m, 3H), 6.70 (d, *J* = 2.3 Hz, 2H), 6.47 (t, *J* = 2.3 Hz, 1H), 3.81 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 160.6, 131.8, 131.7, 128.5, 124.6, 123.2, 109.4, 101.9, 89.5, 89.0, 55.5.



4-Methoxy-2-(2-phenylethynyl)toluene (Table 3.2.1, Entry 12)

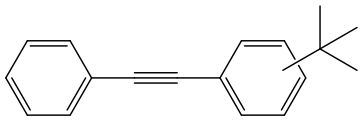
3-Chloro-4-methoxytoluene (195.5 mg, 1.25 mmol), phenylacetylene (51 mg, 0.5 mmol), TMPLi in THF (1M, 2 mL), room temperature, 4 hours. After column chromatography (hexanes/CH_2Cl_2 70/30), 84 mg (75 %) of a pale yellow liquid was obtained. R_f = 0.21 (hexanes/CH_2Cl_2 70/30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.52 (m, 2H), 7.38 – 7.31 (m, 3H), 7.12 (d, *J* = 8.3 Hz, 1H), 7.04 (d, *J* = 2.8 Hz, 1H), 6.81 (dd, *J* = 8.3 Hz, 2.8 Hz, 1H), 3.80 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 157.4, 132.5, 131.6,

130.5, 128.5, 128.4, 123.7, 123.5, 116.2, 115.2, 93.2, 88.5, 55.5, 19.9. FT-IR (neat, cm^{-1}) υ 1604, 1501, 1229, 1102, 1037. Anal calcd for $C_{16}H_{14}O$ (222.28 g/mol): C, 86.45; H, 6.35; Found. C, 86.44; H, 6.40.



9-(2-Phenylethynyl)phenanthrene (Table 3.2.1, Entry 13)

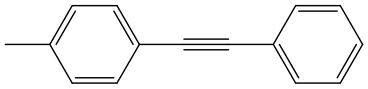
9-Chlorophenanthrene (212.5 mg, 1.0 mmol), phenylacetylene (51 mg, 0.5 mmol), TMPLi in pentane (1M, 1.8 mL), followed by anhydrous THF (0.2 mL), room temperature, 4 hours. After column chromatography (hexanes/CH_2Cl_2 80/20), 119 mg (86 %) of a yellow solid was obtained. R_f = 0.30 (hexanes/CH_2Cl_2 80/20). This compound is known.[23] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 – 8.66 (m, 2H), 8.59 – 8.55 (m, 1H), 8.10 (s, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.74 – 7.59 (m, 6H), 7.45 – 7.38 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 131.9, 131.8, 131.4, 131.2, 130.4, 130.3, 130.2, 128.7, 128.6, 127.6, 127.2, 127.1, 123.5, 122.9, 122.7, 119.8, 119.7, 94.0, 87.8. Signal for one carbon could not be located.



A mixture of 1-(1,1-dimethylethyl)-4-(2-phenylethynyl)benzene [1] and 1-(1,1-dimethylethyl)-3-(2-phenylethynyl)benzene [2] (Table 3.2.1, Entry 14)

1-*tert*-Butyl-1-chlorobenzene (168.5 mg, 1.0 mmol), phenylacetylene (51 mg, 0.5 mmol), TMPLi in pentane (1M, 1.8 mL), followed by anhydrous THF (0.15 mL), room

temperature, 4 hours. Analysis by GC showed that two isomers are obtained in 1.2/1 ([1]/[2]) ratio. After column chromatography (hexanes/CH_2Cl_2 90/10), 105 mg (90 %) of a colorless liquid containing 2 isomers in the same ratio was obtained. These compounds are known.[24] ^{1}H NMR of mixture of isolated two isomers (400 MHz, $CDCl_3$) δ 7.60 – 7.28 (m, 9H), 1.35 – 1.34 (overlapping singlets, 9H).

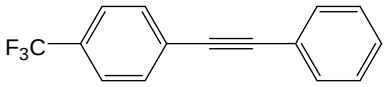


4-(2-Phenylethynyl)toluene (Table 3.2.2, Entry 2)

4-Ethynyltoluene (58 mg, 0.5 mmol), PhCl (102 mg, 0.9 mmol), TMPLi in pentane (1M, 1.6 mL), followed by anhydrous THF (0.15 mL), room temperature, 2 hours. After column chromatography (hexanes/CH_2Cl_2 90/10), 84 mg (87 %) of a white solid was obtained.

4-Ethynyltoluene (58 mg, 0.5 mmol), PhCl (169 mg, 1.5 mmol), *t*-BuOK (393 mg, 3.5 mmol), dioxane (0.5 mL), 106 °C, 24 hours. After column chromatography (gradient, hexanes/CH_2Cl_2: 100/0 - 90/10), 72 mg (75 %) of a white solid was obtained.

R_f = 0.19 (hexanes/CH_2Cl_2 90/10). This compound is known.[16] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.52 (m, 2H), 7.46 – 7.44 (m, 2H), 7.40 – 7.32 (m, 3H), 7.18 – 7.15 (m, 2H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 138.5, 131.7, 131.6, 129.2, 128.4, 128.2, 123.6, 120.3, 89.7, 88.8, 21.7.

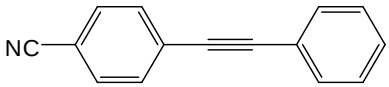


1-(2-Phenylethynyl)-4-(trifluoromethyl)benzene (Table 3.2.2, Entry 3)

4-Ethynylbenzotrifluoride (85 mg, 0.5 mmol), PhCl (102 mg, 0.9 mmol), TMPLi in pentane (1M, 1.6 mL), followed by anhydrous THF (0.15 mL), room temperature, 2 hours. After column chromatography (hexanes/CH_2Cl_2 90/10), 110 mg (90 %) of a white solid was obtained.

4-Ethynylbenzotrifluoride (85 mg, 0.5 mmol), PhCl (169 mg, 1.5 mmol), *t*-BuOK (393 mg, 3.5 mmol), dioxane (0.5 mL), 106 °C, 24 hours. After column chromatography (gradient, hexanes/CH_2Cl_2: 100/0 - 90/10), 96 mg (78 %) of a white solid was obtained.

R_f = 0.19 (hexanes/CH_2Cl_2 90/10). This compound is known.[16] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.59 (m, 4H), 7.58 – 7.54 (m, 2H), 7.39 – 7.34 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 131.9, 131.8, 130.0 (q, J_{C-F} = 32 Hz), 128.9, 128.6, 127.2, 125.4 (q, J_{C-F} = 3.7 Hz), 124.0 (q, J_{C-F} = 262 Hz), 122.6, 91.8, 88.1.

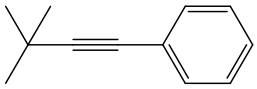


4-(2-Phenylethynyl)benzonitrile (Table 3.2.2, Entry 4)

4-Ethynylbenzonitrile (63.5 mg, 0.5 mmol), PhCl (112.5 mg, 1.0 mmol), TMPLi in Et_2O (1M, 1.7 mL), -55 °C, 14 hours. After column chromatography (hexanes/Et_2O 93/7), 51 mg (50 %) of a white solid was obtained. R_f = 0.26 (hexanes/Et_2O 90/10). This compound is known.[25] ^{1}H NMR (400 MHz, $CDCl_3$) δ7.62 – 7.51 (m, 6H), 7.39 – 7.34 (m, 3H) .^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 132.2, 131.9, 129.3, 128.6, 128.3, 122.3, 118.7, 111.5, 93.9, 87.9.

3-(Phenylethynyl)thiophene (Table 3.2.2, Entry 5)

3-Ethynylthiophene (54 mg, 0.5 mmol), PhCl (169 mg, 1.5 mmol), *t*-BuOK (393 mg, 3.5 mmol), dioxane (0.5 mL), 106 °C, 24 hours. After column chromatography (hexanes/CH_2Cl_2 85/15), 67 mg (73 %) of a yellowish liquid was obtained. R_f = 0.23 (hexanes/CH_2Cl_2 85/15). This compound is known.[24a] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.50 (m, 3H), 7.36 – 7.32 (m, 3H), 7.31 – 7.29 (m, 1H), 7.20 (dd, *J* = 5.0 Hz, 1.2 Hz, 1H) .^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 131.6, 130.0, 128.7, 128.5, 128.3, 125.5, 123.3, 122.4, 89.0, 84.6.

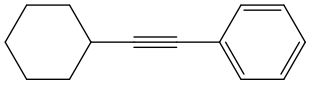


(3,3-Dimethyl-1-butynyl)benzene (Table 3.2.2, Entry 6)

3,3-Dimethyl-1-butyne (41 mg, 0.5 mmol), PhCl (102 mg, 0.9 mmol), TMPLi in pentane (1M, 1.6 mL), followed by anhydrous THF (0.15 mL), room temperature, 2 hours. After column chromatography (pentane/CH_2Cl_2 95/5), 74 mg (93 %) of a colorless liquid was obtained.

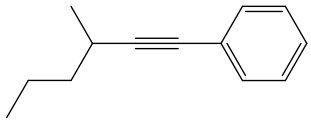
3,3-Dimethyl-1-butyne (41 mg, 0.5 mmol), PhCl (169 mg, 1.5 mmol), *t*-BuOK (393 mg, 3.5 mmol), dioxane (0.5 mL), 106 °C, 24 hours. After column chromatography (pentane/CH_2Cl_2 95/5), 62 mg (78 %) of a colorless liquid was obtained.

R_f = 0.35 (pentane/CH_2Cl_2 95/5). This compound is known.[26] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 - 7.36 (m, 2H), 7.29 – 7.23 (m, 3H), 1.31 (s, 9H) .^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 131.6, 128.2, 127.5, 124.1, 98.6, 79.1, 31.1, 28.0.



(2-Cyclohexylethynyl)benzene (Table 3.2.2, Entry 7)

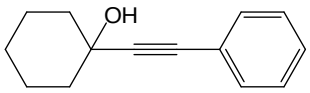
Cyclohexylacetylene (54 mg, 0.5 mmol), PhCl (112.5 mmol. 1.0 mmol), TMPLi in THF (1M, 1.8 mL), -63 °C, 16 hours. After column chromatography (pentanes), 62 mg (67 %) of a colorless liquid was obtained. R_f = 0.29 (hexanes/CH_2Cl_2 95/5). This compound is known.[16] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.38 (m, 2H), 7.30 – 7.25 (m, 3H), 2.6 (septet, *J* = 4.0 Hz, 1H), 1.90 – 1.87 (m, 2H), 1.78 – 1.73 (m, 2H), 1.59 – 1.51 (m, 3H), 1.41 – 1.31 (m, 3H) .^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 131.7, 128.2, 127.5, 124.2, 94.6, 80.6, 32.8, 29.8, 26.0, 25.0.



(3-Methyl-1-hexyn-1-yl)benzene (Table 3.2.2, Entry 8)

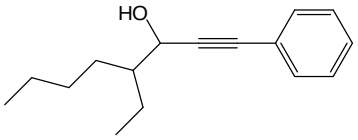
3-Methyl-1-hexyne (48 mg, 0.5 mmol), PhCl (112.5 mg, 1.0 mmol), TMPLi in THF (1M, 1.8 mL), -63 °C, 14 hours. After column chromatography (pentanes), 66 mg (76 %) of a colorless liquid was obtained. R_f = 0.35 (pentane/CH_2Cl_2 95/5). This compound is known.[27] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.40 (m, 2H), 7.31 – 7.25 (m, 3H), 2.67 (sextet, *J* = 7.0 Hz, 1H), 1.61 – 1.45 (m, 4H), 1.27 (d, *J* = 7.0 Hz, 3H), 0.97 (t, *J* = 7.0 Hz, 3H) .^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 131.7, 128.2, 127.5, 124.2, 94.9, 80.8, 39.3, 26.4, 21.2, 20.7, 14.1.

Note: Product contains 13% of another isomer derived from isomeric impurity present in starting material.



1-(2-Phenylethynyl)cyclohexanol (Table 3.2.2, Entry 9)

1-Ethynyl-1-cyclohexanol (62 mg, 0.5 mmol), PhCl (112.5 mg, 1.0 mmol), TMPLi in THF (1M, 2.2 mL), room temperature, 3 hours. Reaction mixture was quenched with H_2O (1 mL), followed by addition of Et_2O (30 mL). The organic phase was then washed with brine (15 mL) and the aqueous layers were extracted with Et_2O (3x15 mL). The combined organic phase was then dried over $MgSO_4$ and concentrated under vacuum. The residue was dissolved in minimal amount of dichloromethane and subjected to flash chromatography on silica gel in a slow hexanes/ Et_2O gradient (100/0 - 75/25). After concentrating the fractions containing the product, the residue was dried under reduced pressure to yield 65 mg (65 %) of a white solid. R_f = 0.19 (hexanes/Et_2O 80/20). This compound is known.[16] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.40 (m, 2H), 7.31 – 7.28 (m, 3H), 2.11 (s, 1H), 2.02 – 1.96 (m, 2H), 1.76 – 1.56 (m, 7H), 1.31 – 1.20 (m, 1H).^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 131.8, 128.4, 128.3, 123.0, 92.8, 88.4, 69.2, 40.1, 25.3, 23.5.

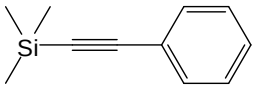


4-Ethyl-1-phenyl-1-octyn-3-ol (Table 3.2.2, Entry 10)

A 2 dram vial equipped with a magnetic stir bar was charged with 3-ethyl-1-octyn-3-ol (78 mg, 0.5 mmol; mixture of two diastereomers) and PhCl (112.5 mg, 1.0 mmol). The vial was flushed with argon and capped. To this mixture was added TMPLi in pentane

(1M, 2.0 mL) at room temperature by injecting through the septum via syringe. The viscous reaction mixture was shaken vigorously followed by addition of anhydrous THF (0.13 mL). The vial was shaken again until all solids dissolved, then flushed with argon (20 seconds) and stirred at room temperature for 3 hours. Reaction mixture was quenched with H_2O (1 mL), followed by addition of Et_2O (30 mL). The organic phase was washed with brine (15 mL) and the aqueous layer was extracted with Et_2O (3x15 mL). The combined organic phase was dried over $MgSO_4$ and concentrated under vacuum. The residue was dissolved in minimal amount of dichloromethane and subjected to flash chromatography on silica gel in hexanes/Et_2O: 70/30. The fractions containing the product were concentrated and subjected to additional purification by HPLC (hexanes/Et_2O: 80/20). Pure product (72 mg, 62 %) was obtained as a yellowish oil. R_f = 0.30 (hexanes/Et_2O 80/20). This compound is known.[28] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.40 (m, 2H), 7.32 – 7.28 (m, 3H), 4.64 – 4.62 (m, 1H), 1.85 (s, 1H), 1.68 – 1.29 (m, 9H), 1.00 – 0.87 (m, 6H).

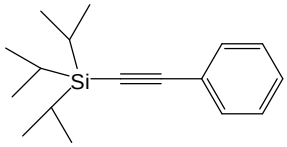
Note: Product is obtained as a mixture of diastereomers corresponding to two diastereomers in starting material.



Trimethyl(phenylethynyl)silane (Table 3.2.2, Entry 11)

Trimethylsilylacetylene (49 mg, 0.5 mmol), PhCl (102 mg, 0.9 mmol), TMPLi in pentane (1M, 1.6 mL), followed by anhydrous THF (0.15 mL), room temperature, 2 hours. After column chromatography (pentanes), 74 mg (85 %) of a colorless liquid was obtained. R_f = 0.25 (pentane). This compound is known.[29] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.45

(m, 2H), 7.31 – 7.27 (m, 3H), 0.24 (s, 9H) .^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 132.1, 128.6, 128.3, 123.2, 105.2, 94.2, 0.07.

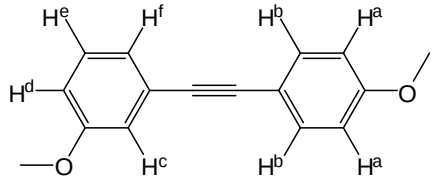


[2-[Tris(1-methylethyl)silyl]ethynyl]benzene (Table 3.2.2, Entry 12)

Triisopropylsilylacetylene (91 mg, 0.5 mmol), PhCl (102 mg, 0.9 mmol), TMPLi in pentane (1M, 1.6 mL), followed by anhydrous THF (0.15 mL), room temperature, 2 hours. After column chromatography (pentane/CH_2Cl_2 95/5), 120 mg (93 %) of a colorless liquid was obtained. R_f = 0.35 (pentane). This compound is known.[16] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.48 (m, 2H), 7.32 – 7.29 (m, 3H), 1.15 (s, 21H) .^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 132.1, 128.4, 128.3, 123.7, 107.2, 90.5, 18.8, 11.4.

Mechanistic studies

Reaction between 3-chloroanisole and 4-ethynylanisole:

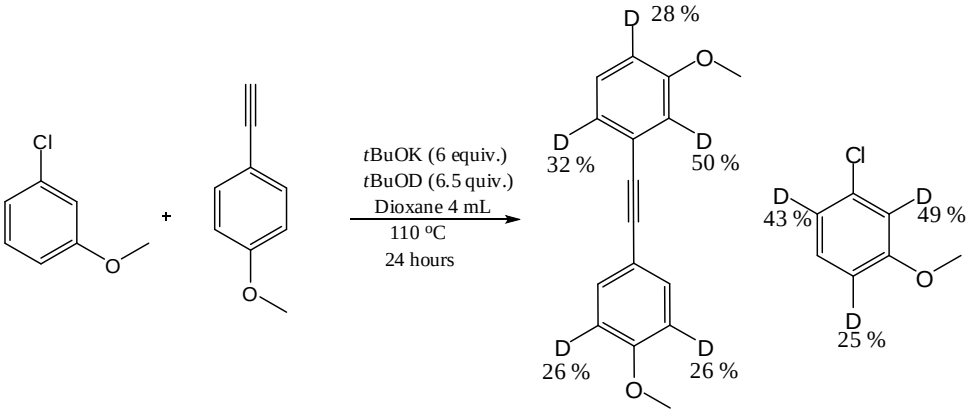


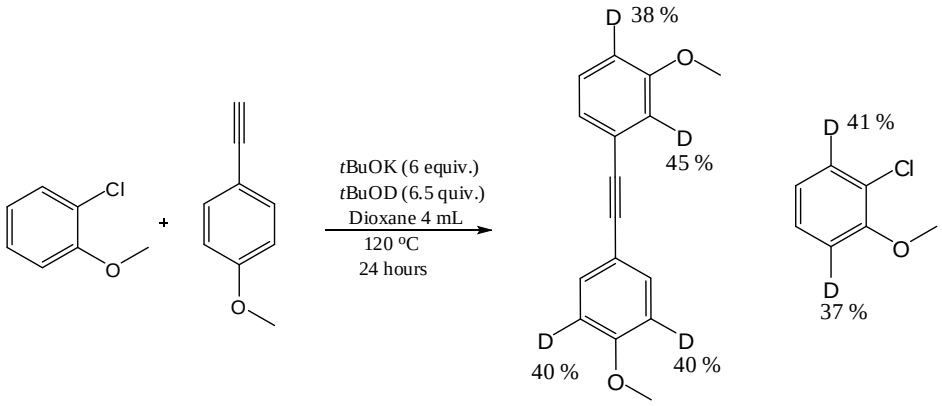
3-Chloroanisole (214 mg, 1.5 mmol), 4-ethynylanisole (66 mg, 0.5 mmol), tBuONa (336 mg, 3.5 mmol), dioxane (0.5 mL), 125 ^{o}C, 18 hours. After column chromatography (hexanes/CH_2Cl_2 72/25), 101 mg (85%) of a light yellow liquid was obtained. This compound is known.[30] ^{1}H (400 MHz, C_6D_6) δ 7.42 – 7.45 (m, 2H, H^b), 7.21 (dt, *J* = 7.8 Hz, 1.1 Hz, 1H, H^f), 7.16 – 7.18 (m, 1H, H^c), 6.92 (t, *J* = 7.8 Hz, 1H, H^e), 6.67 (ddd, *J* = 7.8 Hz, 2.76 Hz, 1.1 Hz, 1H, H^d), 6.60 – 6.63 (m, 2H, H^a), 3.14 (s, 3H), 3.10 (s, 3H) . ^{13}C

NMR (125 MHz, C_6D_6, ppm) δ 159.7, 159.4, 133.2, 129.5, 124.7, 124.1, 116.2, 115.4, 114.7, 114.1, 89.3. 88.1, 55.4.

Alkynylation of 3-chloroanisole or 2-chloroanisole with added t-BuOD [Scheme 3.2.5]: A 4-dram vial equipped with a magnetic stirring bar was charged with 3-chloroanisole (427.5 mg, 3 mmol) or 2-chloroanisole (427.5 mg, 3 mmol), 4-ethynylanisole (264 mg, 2.0 mmol), *t*-BuOD (1.0 g, 6.5 equiv.). The vial was flushed with argon and placed inside the glovebox. After addition of *t*-BuOK (1.24 g, 12 mmol) and dioxane (4 mL) the vial was sealed and taken out of the glovebox. The reaction mixture was stirred at room temperature for 5 minutes followed by heating at 110 °C (3-chloroanisole) or 120 °C (2-chloroanisole) for 24 hours. The reaction was then cooled to room temperature and diluted with ethyl acetate (30 mL). The resulting solution was washed with brine (3 x 15 mL), dried over $MgSO_4$, and concentrated under vacuum. The residue was dissolved in minimal amount of dichloromethane and subjected to flash chromatography on silica gel (CH_2Cl_2/hexanes 25/75). The fractions containing product and unreacted starting material were collected and solvent was removed. In the alkynylation of 3-chloroanisole, 147 mg (31%) of product was obtained and 71 mg (25%) of 3-chloroanisole was recovered. In the alkynylation of 2-chloroanisole, 100 mg (21 %) of product was obtained and 108 mg (38%) of unreacted 2-chloroanisole was recovered. In both cases, 3,4'-dimethoxydiphenylacetylene was the only product isolated.

Hydrogen signals were assigned by using COSY spectrum. Deuterium incorporation was determined by integration of ^1H signals and relaxation delay of 20 seconds was used. Methoxy group was used as standard in calculation.


Cl
O
O
tBuOK (6 equiv.)
tBuOD (6.5 quiv.)
Dioxane 4 mL
110 ºC
24 hours
D 28 %
O
D
32 %
D
50 %
D
26 %
O
D
26 %
Cl
D
43 %
D
49 %
O
D
25 %


Cl
O
O
tBuOK (6 equiv.)
tBuOD (6.5 quiv.)
Dioxane 4 mL
120 ºC
24 hours
D 38 %
O
D
45 %
D
40 %
O
D
40 %
D 41 %
Cl
O
D
37 %

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Chapter 3-3. Arylation of Acidic sp^2 C-H Bonds Followed by Trapping of Aryllithium Intermediates

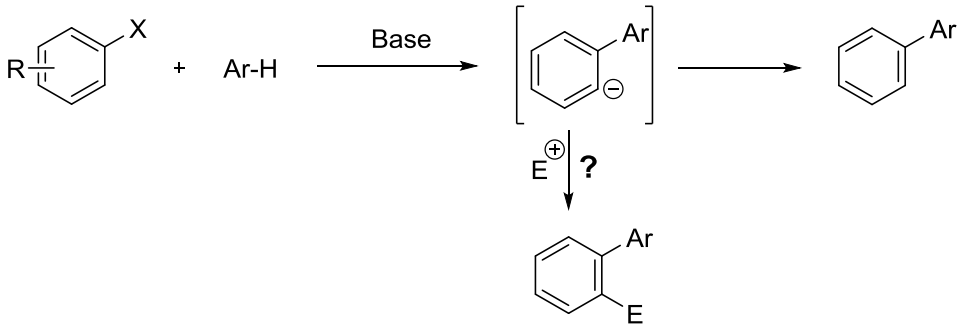
3.3.1. Introduction

The biaryl structure is a central building block in a large number of natural products, organic materials, and biologically active compounds.[1] Direct arylation through C-H cleavage represents an attractive and efficient alternative to classical methods for poly-aryl preparation.[2] Second-row transition metals such as palladium, ruthenium, rhodium, and iridium have emerged as catalysts in many direct arylation reactions. Excellent regioselectivity with respect to arene C-H bonds has been achieved for arylation of heterocycles and directing-group containing arenes. In contrast, functionalization of electrically neutral arenes often suffers from unsatisfactory selectivity. More recently, efforts toward the use of inexpensive first-row-metal catalysts have attracted substantial interest. These non-noble transition metals, including copper, nickel, and iron, have demonstrated reactivity and selectivity in direct arylation of sp^2 C-H bonds.[2d] However, purification of products contaminated with transition metals is often problematic.[3]

We have recently described direct base-promoted intermolecular arylation of heterocycle and arene C-H bonds. Reactions were carried at mild temperature, only 1.5 - 2.5 equiv of a C-H bond coupling partner was used, and functionalization occurs at the most acidic carbon-hydrogen bond. Mechanistically, in the presence of hindered amide bases, the (hetero)arene is deprotonated while the aryl halide undergoes aryne formation. Addition of aryl anion to the aryne affords the *o*-anionic biaryl intermediate which is

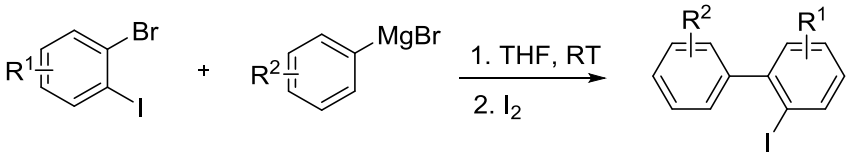
protonated to form product (Scheme 3.3.1). It is well known that aryl lithium protonation by hindered amide bases such as TMPH at low temperature is slow.[4] As a consequence, if benzyne can be generated at low temperature, intermediate aryl lithium could be trapped with different electrophiles. This would provide an efficient method to a wide range of substituted biaryl derivatives.

Scheme 3.3.1. Mechanism of base-promoted arylation of heterocycle and arene C-H bonds



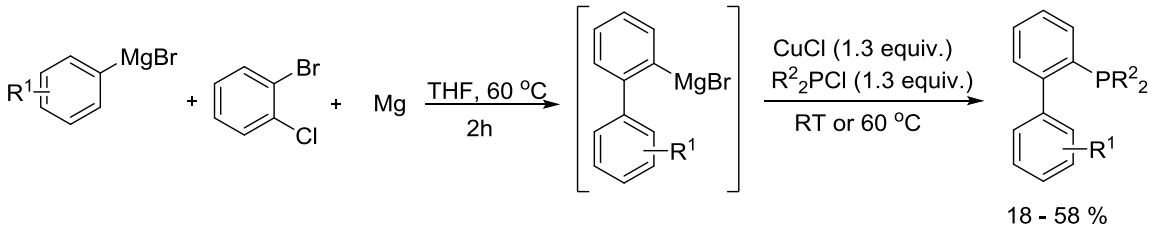
Reactions of arynes with nucleophiles followed by trapping of aryl Grignard intermediates with electrophiles have been shown.[5-8] 2-Iodobiaryls were obtained when iodine was used to quench reactions between *o*-bromoiodoarenes with arylmagnesium bromide (Scheme 3.3.2).[4]

Scheme 3.3.2. Reactions of *o*-bromoiodoarenes with arylmagnesium bromide followed by iodine quenching



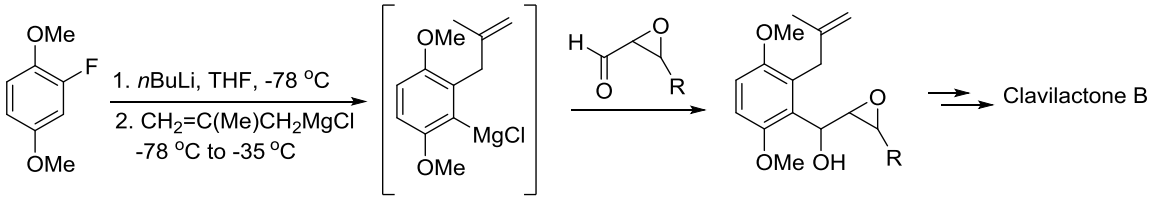
Buchwald and co-workers have reported a useful synthetic route to functionalized (dialkylphosphino)biphenyl ligands by the addition of arylmagnesium halides to benzyne, followed by further reaction with dialkylchlorophosphines.[6] This economical one-pot process has been subsequently applied to the synthesis of a number of structurally related biphenyl phosphine ligands.

Scheme 3.3.3. (Dialkylphosphino)biphenyl ligand synthesis via benzynes



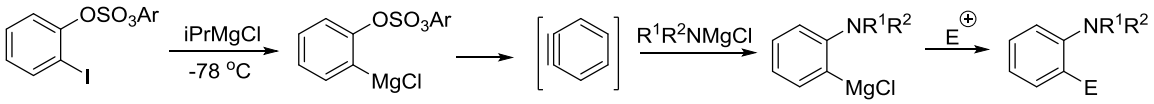
A method for trapping arynes by nucleophilic addition and iodination was recently described.[7a] Barrett and co-workers employed this strategy to synthesize a key intermediate in the synthesis of clavilactone B.[7b]

Scheme 3.3.4. Aryne in total synthesis of clavilactone B



Arynes prepared from the aryl iodides via 2-magnesiated aryl sulfonates have been reported to undergo reaction with magnesium amides (Scheme 3.3.5).[8] Intermediate *ortho*-aminoaryl magnesium species can be trapped *in situ* by various electrophiles.

Scheme 3.3.5. Addition of magnesium amide to aryne and trapping of intermediates



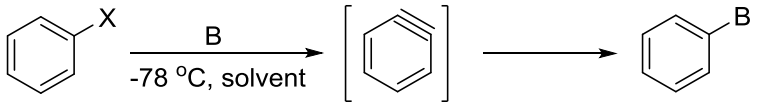
In most cases, however, disubstituted arenes and preformed nucleophiles are required and reaction scope is limited. A general procedure employing an accessible aryl halide aryne precursor, C-H bond nucleophiles and diverse trapping reagents has not been demonstrated. We report here a highly regioselective method for arylation of sp^2 C-H bonds via benzyne intermediates. Electron-rich and electron-poor heterocycles as well as a variety of arenes can be used. Trapping of intermediate aryl anions with a variety of electrophiles is performed.

3.3.2.Results and Discussion

We have previously used commercially available aryl halides as benzyne sources in direct arylation reactions.[10] Formation of benzyne from halobenzene is achieved by deprotonation affording 2-haloarylanion followed by elimination of halide ion. Thus, better leaving group than halide would accelerate formation of benzyne allowing generation of benzyne at low temperatures, which is necessary for electrophilic trapping of intermediate aryl metals to avoid competitive protonation by TMPH. Aryl triflates react with LDA in THF at - 78 °C to form diisopropylanilines via benzyne intermediates (Table 3.3.1, entry 1).[9] Treating chlorobenzene under the same conditions gave only a trace amount of corresponding product (entry 2). In diethyl ether, similar result was obtained when phenyl triflate was treated with LDA at- 78 °C (entry 3). Gratifyingly, in the presence of TMPLi, about 70 % of phenyl triflate was converted to benzyne (entry 4).

In addition, adding 2 % of THF to diethyl ether solvent shortened reaction time and higher conversion was obtained (entry 5). Consequently, the use of aryl triflates to generate benzyne at low temperature could allow us to arylate wide range of arenes and heterocycles and trap the aryl lithium intermediates with electrophiles.

Table 3.3.1. Optimization of benzyne formation



entry	X	base (B)	solvent	conversion (%)
1	OTf	LDA	THF	95
2	Cl	LDA	THF	trace
3	OTf	LDA	Et_2O	trace
4	OTf	TMPLi	Et_2O	70
5	OTf	TMPLi	Et_2O/THF (50/1)	89

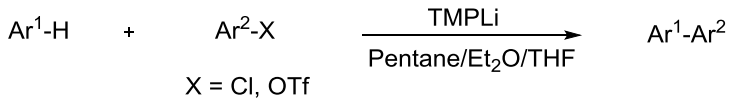
[a] Total volume of solvent 1.5 mL, 0.25 mmol scale, PhX/Base 1/2; 10 h; 6 h for entry 5.

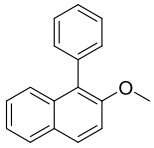
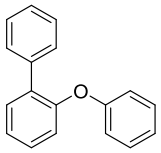
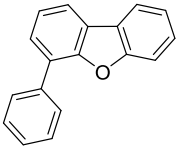
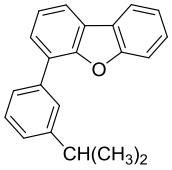
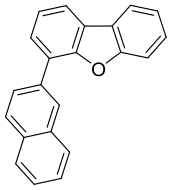
3.3.2.1. Expansion of Reaction Scope for Arylation of Arenes

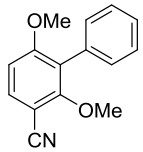
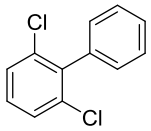
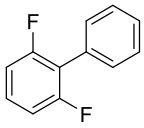
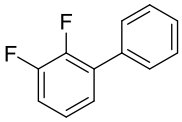
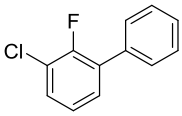
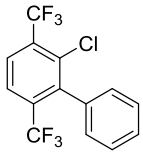
We have reported a method for base-mediated arylation of (hetero)arenes by aryl halides.[10] Best results in arene arylation were obtained by employing LiTMP and pentane/THF mixture. Tetrahydrofuran was added to accelerate benzyne formation. Under our previous reported conditions, some limitations were observed. Mono-substituted methoxyarene arylation failed to give acceptable yields due to the nucleophilic attack of base on benzyne. In addition, arylation of arenes containing halides was not successful. Competition generation of arynes from these haloarenes was observed. As described by Mulvey and Stuart, *o*-metalation of simple benzene derivatives such as methoxyarenes by LiTMP is slow.[11] We reasoned that using pentane as sole

solvent or conducting reactions at low temperature should allow for an efficient mono-substituted arene arylation by slowing benzyne formation. Furthermore, as described in Table 3.3.1, an introduction of halide functionality is possible by the use of aryl triflate benzyne precursors. We were pleased to discover that modified conditions enable the arylation of arenes that were not reactive under our previous conditions (Table 3.3.2).

Table 3.3.2. Arylation Scope with Respect to Arenes



entry	arene	ArX	product	yield,%
1	2-Methoxynaphthalene	PhCl		52
2	Diphenyl ether	PhCl		71
3	Dibenzofuran	PhCl		78
4	Dibenzofuran	2-Bromo cumene		66
5	Dibenzofuran	2-Chloro naphthalene		70

6	2,4-Dimethoxybenzonitrile	PhCl		51
7	1,3-Dichlorobenzene	PhOTf		82
8	1,3-Difluorobenzene	PhOTf		79
9	1,2-Difluorobenzene	PhOTf		59
10	2-chloro-1-fluorobenzene	PhOTf		62
11	2-Chloro-1,4-bis(trifluoromethyl)benzene	PhOTf		65

Conditions: ArX (1.7 – 3.0 equiv.), arene (1 equiv.), 0.25 mmol scale. Yields are isolated yields. See Experimental section for details.

Reaction of 2-methoxynapthalene with chlorobenzene affords *o*-phenylated product in reasonable yield (entry 1). Diphenyl ether is also reactive (entry 2). Dibenzofuran can be arylated by different aryl chlorides in good yields (entries 3-5). Polysubstituted arenes such as 2,4-dimethoxybenzonitrile can be used and arylated product was obtained in reasonable yield (entry 6). For electron-deficient arenes possessing halide groups, aryl triflates are required for optimal results. 1,3-Dichlorobenzene, 1,2-difluorobenzene, and 1,3-difluorobenzene are efficiently arylated

by phenyl triflate (entries 7-9). Reaction of 1,4-bis(trifluoromethyl)-2-chlorobenzene with phenyl triflate affords product in good yield (entry 11). Interestingly, arylation of 1-chloro-2-fluorobenzene gave only biaryl product in which phenyl substituent is adjacent to fluoride group (entry 10). Functionalization of arenes occurs at most acidic carbon-hydrogen bond.

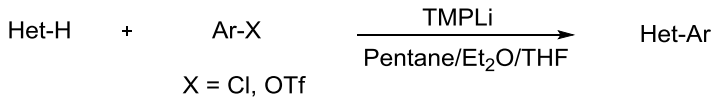
3.3.2.2. Arylation of Heteroarenes

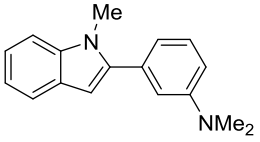
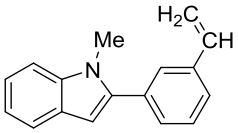
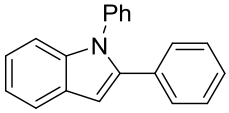
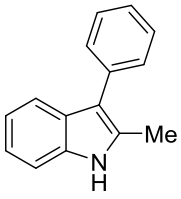
Furans, imidazoles, indoles, pyrroles, pyrazine, and pyridines can be arylated by aryl halides using hindered amide bases. However, some heterocyles are not compatible with strong bases. Attempts to arylate several heterocyles such as triazole and halopyridines failed under our previous conditions. To expand the synthetic utility of the transformation, broader reactions scope with respect to heterocycles was investigated by using low reaction temperatures and aryl triflate benzyne precursors.

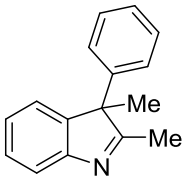
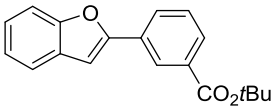
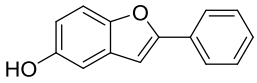
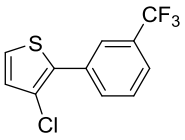
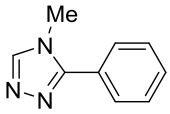
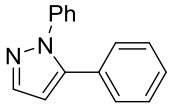
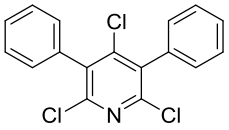
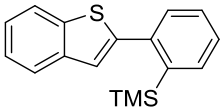
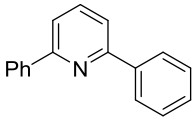
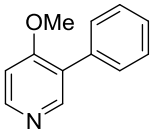
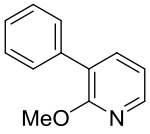
The examples of heterocycle arylation are presented in Table 3.3.3. Arylation of 1-methylindole by 2-chlorostyrene and 2-choro-*N*,*N*-dimethylaniline affords C2-arylation products in good yields (entries 1,2). 1-Phenylindole is reactive (entry 3). Noteworthy, under modified conditions, reactions of unprotected indoles afford C3-arylation products with only minor amounts of *N*-arylation (entries 4, 5). Ester and hydroxy groups are tolerated (entries 6, 7). By using LDA base, 3-chlorothiophene can be monoarylated selectively at most acidic position (entry 8). Additionally, the use of aryl triflates allows for the arylation of heterocycles that was not possible when aryl halides were employed. In particular, reactions of 1-methyl-1,3,4-triazole and 1-phenylpyrazole with phenyl triflate afforded products in reasonable yields (entries 9, 10). Electron-poor six-member

ring heterocycles are reactive. 2,4,6-Trichloropyridine can be diarylated (entry 11). Interestingly, arylation by 2-trimethylsilyl phenyltriflate, common benzyne precursor, affords the *ortho*-substituted product in good yield with silyl group intact (entry 12). The regioselectivity can be explained by inductive electron donating effect of silicon.[12] Furthermore, substituents on pyridine derivatives can determine the arylation regioselectivity. Arylation of 2-phenylpyridine occurs at C6 position (entry 13) while 2-methoxypyridine was arylated at C3 (entry 14). It is likely that methoxy group orients the deprotonation. As expected, when 4-methoxypyridine was used, functionalization occurs at C3 (entry 15).

Table 3.3.3. Arylation Scope with Respect to Heterocycles[a]



entry	heterocycle	Ar-X	product	yield,%
1	1-Methylindole	Dimethylaniline		70
2	1-Methylindole	2-Bromostyrene		68
3	1-Phenylindole	PhCl		78
4[b]	2-Methylindole	PhCl		80

5[b]	2,3-Dimethylindole	PhCl		77
6	Benzofuran	*tert*-Butyl -3-bromobenzoate		50
7	5-Hydroxybenzofuran	PhCl		53
8[c]	3-Chlorothiophene	2-Chloro benzotrifluoride		62
9[c]	1-Methyl-1,2,4-triazole	PhOTf		71
10	1-Phenylpyrazole	PhOTf		58
11	2,4,6-Trichloropyridine	PhOTf		60
12	Benzothiophene	*o*-TMS-PhOTf		68
13	2-Phenylpyridine	PhCl		70
14	4-Methoxypyridine	PhCl		72
15	2-Methoxypyridine	PhCl		63

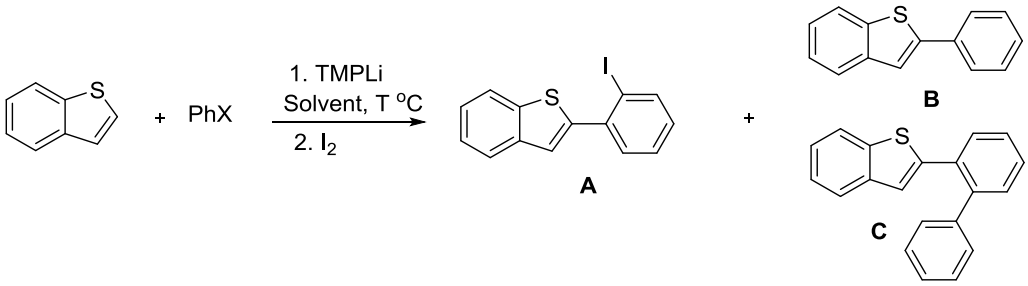
Conditions: ArX (1.8 – 3.0 equiv.), heterocycle (1 equiv.), 0.25 mmol scale. Yields are isolated yields. [b] PhCl/Indole 1/3 was used. [c] LDA was used as base. See Experimental section for details

3.3.2.3. (Hetero)Arene Arylation with Subsequent Aryl Lithium Intermediate Trapping

Considerations

The synthesis of highly functionalized biaryls has been extensively investigated due to their widespread applications.[13] Transition-metal-catalyzed multiple transformations or tandem reactions have been used to prepare these valuable compounds.[14] The incorporation of benzyne into such multi-component coupling processes avoids the use of transition metals. In our reported conditions, arylated products were obtained by the protonation of *o*-anionic biaryl intermediates. Reaction of phenyllithium with TMPH at low temperature (- 78 °C) is slow.[4] Thus, trapping aryl lithium intermediates with electrophiles other than proton should be feasible.

Table 3.3.4. Trapping of intermediate reaction optimization



entry	PhX	solvent	T (°C)	conversion	A/(B+C)
1	PhCl	THF	-65	78	1/2
2	PhCl	Et_2O	-65	5	15/1
3	PhCl	Et_2O	-20	74	1/22

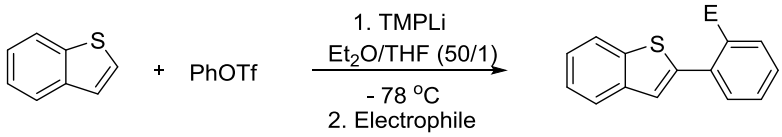
4	PhCl	Et_2O	-45	10	16/1
5	PhCl	Et_2O/THF (9/1)	-45	87	10/1
6	PhOTf	Et_2O/THF (50/1)	-78	91	12/1

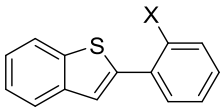
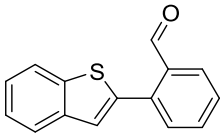
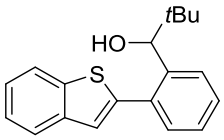
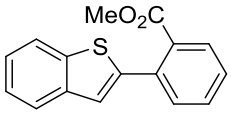
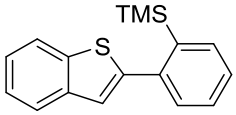
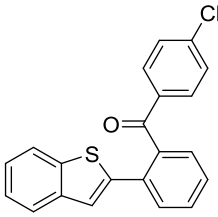
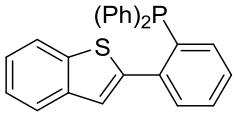
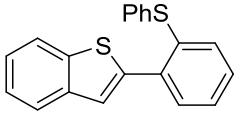
[a] PhX/benzothiophene 1.8/1; 24 hours, 0.25 mmol scale. 10 hours

Optimization of trapping conditions is shown in Table 3.3.4. Slow generation of benzyne from chlorobenzene was observed in THF at -63 °C when TMPLi was used.[11] Attempts to trap *o*-anionic biaryl intermediates with I_2 at this temperature failed to give reasonable yields of A (entry 1). Changing solvent from THF to ether or hydrocarbon solvents gave 15/1 ratio of A/(B +C) but only 5 % conversion (entry 2). At - 20 °C, 75 % conversion was observed in diethyl ether and undesired B, C were formed predominantly (entry 3). Reactions at - 45 °C resulted in slow benzyne formation and 85 % of 2-iodobenzothiophene was observed (entry 4). We reasoned that adding THF should facilitate benzyne formation. Gratifyingly, A was obtained in 80 % yield when reaction was run at - 45 °C in Et_2O with 10 % THF as co-solvent (entry 5). Additionally, under modified condition using aryl triflates at -78 ^oC, shorter reaction time and higher conversion was obtained without significant change in A/B ratio (entry 6). Two sets of conditions, in summary, can be applied for arylation with subsequent trapping of aryl lithium intermediates. The first set of conditions involves the use of aryl chlorides in Et_2O/THF (9/1) mixture at about -45 ^oC. The second set involve the use of aryl triflates in Et_2O/THF (50/1) mixture at -78 ^oC. The later set of condition is beneficial for substrates that are thermally unstable or react with TMPLi.

Reaction Scope

Table 3.3.5. Use of Various Electrophiles

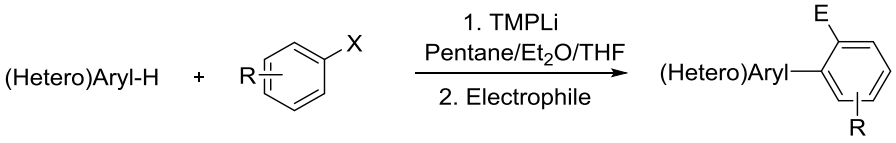


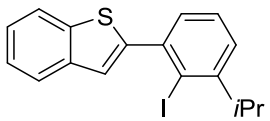
entry	electrophile	product	Yield, %
1	I_2 CBr_4 CCl_4		X = I, 73 X = Br, 81 X = Cl, 86
2	DMF		78
3	Pivaldehyde		74
4	Methylchloroformate or CO_2, MeI		76 62
5	TMSCl		68
6	4-Chlorobenzoyl chloride		62
7	$P(Ph)_2Cl$		61
8	PhSSPh		80

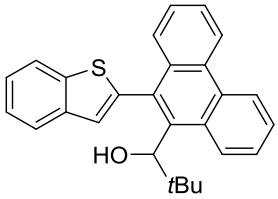
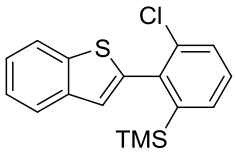
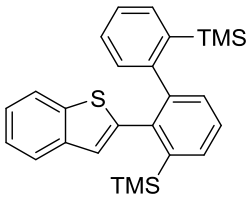
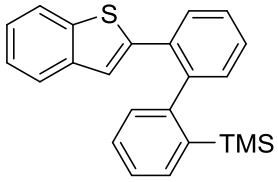
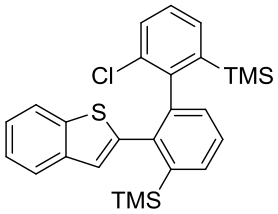
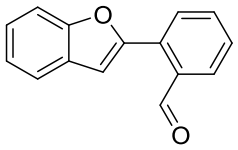
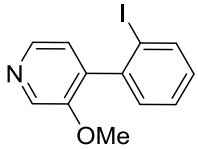
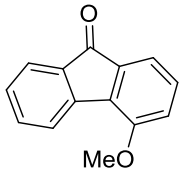
Conditions: PhOTf/benzothiophene 1.8/1, 0.25 mmol scale. Yields are isolated yields.

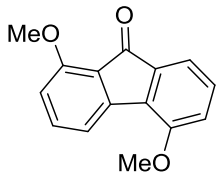
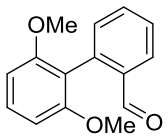
The scope of arylation followed by aryllithium trapping is presented in Table 3.3.5. Various electrophiles can be used in arylation of benzothiophene with phenyl triflate. Trapping by I_2, CBr_4, and CCl_4 affords corresponding 2-(2-halophenyl)benzothiophene products in good to excellent yields (entry 1). These products can be further functionalized by cross-coupling reactions. When DMF was used as electrophile, aldehyde was obtained in good yield (entry 2). As expected, biaryl lithium was quenched with pivaldehyde to form secondary alcohol (entry 3). Trapping of reaction mixture with methyl chloroformate or CO_2 followed by MeI/NaH affords methyl 2-(benzothiophen-2-yl)benzoate in good yield (entry 4). 4-Chlorobenzoyl chloride is reactive and diaryl ketone was obtained in a reasonable yield (entry 6). Other electrophiles such as PhSSPh and TMSCl can be used (entries 5, 8). Interestingly, treating reaction mixture with chlorodiphenylphosphine generates corresponding triarylphosphine in good yield. The reaction could be beneficial for efficient preparation of arylphosphine ligands.

Table 3.3.6. Arylation of (Hetero)Arenes and Trapping of Aryllithium Intermediates



entry	(hetero)arene	ArX/Electrophile	Product	Yield,%
1	Benzothiophene	2-Bromocumene/I_2		70

2	Benzothiophene	9-Bromophenanthrene /pivaldehyde		65
3	Benzothiophene	*o*-TMS-PhOTf/CCl4		71
4	Benzothiophene	*o*-TMS-PhOTf		76
5	Benzothiophene	PhOTf/TMSCl		70
6	Benzothiophene	*o*-TMS-PhOTf/CCl4		79
7	Benzofuran	PhOTf/DMF		71
8	3-Methoxy pyridine	PhCl/I_2		64
9	3-Methoxy benzonitrile	PhCl/none		78

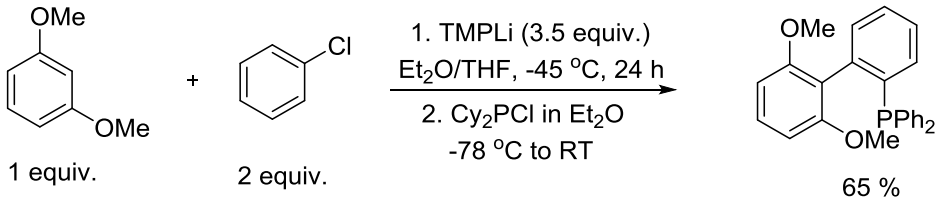
10	3-Methoxy benzonitrile	2-Chloroanisole/none		72
11	1,3-Dimethoxy benzene	PhCl/DMF		74

ArX(1.7 – 2.0 equiv.), Hetero(arene) (1 equiv.), 0.25 mmol. Yields are isolated yield.

Arylation of various (hetero)arenes by different aryl halides with subsequent trapping of aryl lithium intermediates is presented in Table 3.3.6. Arylation by 2-bromocumene followed by quenching with I_2 reagent afforded *o*-iodinated product in good yield (entry 1). When 9-bromophenanthrene was used and reaction mixture was quenched with pivaldehyde, 1-aryl-2,2-dimethylpropanol was obtained in reasonable yield (entry 2). Arylation by *o*-TMS-PhOTf followed by adding CCl_4 afforded chlorobiaryl product in excellent yield (entry 3). Trapping reaction mixture with another benzyne molecule is also possible (entry 4). Interestingly, biaryl anion intermediate reacts with another equivalent of benzyne before being quenched with electrophile (entries 5, 6). Arylation of benzofuran followed by trapping with DMF gives 2-(benzofuran-2-yl)benzaldehyde in comparable yield to benzothiophene (entry 7). Six-memebered ring heterocycles are reactive. 3-Methoxypyridine was treated with chlorobenzene followed by trapping with iodine, and 4-(2-iodophenyl)-3-methoxypyridine was obtained in good yield (entry 8). Simple arenes can also be used and intramolecular trapping products are successfully obtained. When 3-methoxybenzonitrile was employed in reaction with chlorobenzene, aryllithium intermediate was trapped with cyano group forming 4-methoxy-9-fluorenone (entry 9) after hydrolysis. This method could be beneficial for

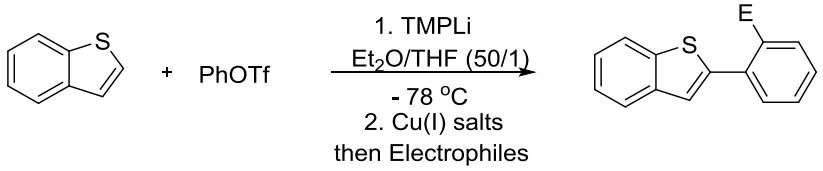
making 9-fluorenone derivatives (entries 9, 10). Notably, when DMF quench was used for reaction of 1,3-dimethoxybenzene with chlorobenzene, 2',6'-dimethoxybiphenyl-2-carbaldehyde was prepared in good yield (entry 11). By taking advantage of this reaction, we were able to synthesize Buchwald's Sphos ligand in one-pot reaction with reasonable yield (Scheme 3.3.6).

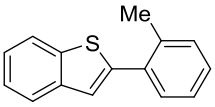
Scheme 3.3.6. Buchwald's Sphos ligand synthesis via one-pot reaction

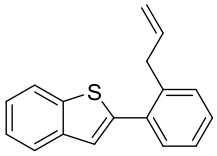
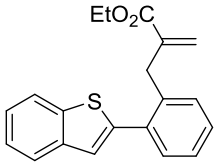
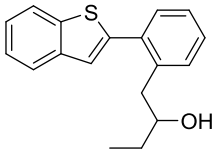
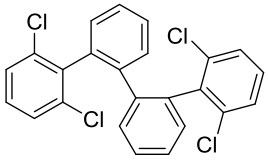
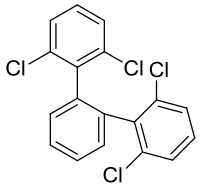
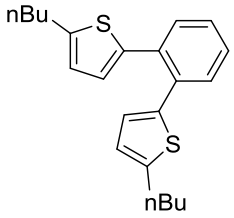


An important use of organolithium reagents is in the preparation of other organometallic compounds, usually by transmetallation. Among those, organocopper reagents are important in synthetic organic chemistry. Thus, transmetalation of biaryl lithium intermediates to aryl copper reagents was investigated (Table 3.3.7).

Table 3.3.7. Intermediate trapping with copper salts and further transformations



Entry	(Hetero)arene	Reagent	Product	Yield,%
1	Benzothiophene	MeI		85

2	Benzothiophene	Allyl bromide		74
3	Benzothiophene	Ethyl-2-(bromomethyl) acrylate		68
4	Benzothiophene	2-Ethyloxirane		75
5	1,3-Dichlorobenzene	O_2		54
6[b]	1,3-Dichlorobenzene	O_2		48
7[c]	*n*-Butylthiophene	O_2		39

Conditions: PhOTf/(hetero)arene = 1.8/1, 0.25 mmol scale. Yields are isolated yields. [b] 1,3-$C_6H_4Cl_2$/PhOTf = 4. [c] *n*-Butylthiophene/PhOTf = 1/1. See Experimental section for details.

Biaryl lithium was generated by reaction of benzothiophene, phenyltriflate, and TMPLi. Transmetalation of reaction mixture with CuCN.LiCl followed by adding MeI afforded 2-o-tolylbenzothiophene in excellent yield (entry 1). Allyl bromide is reactive (entry 2). Alkylating reagent possessing ester group can be used and product was obtained in good yield (entry 3). Epoxide opening is possible and substitution takes place

at the less hindered position (entry 4). Reactions without added CuCN.LiCl gave substantially lower yields of products.

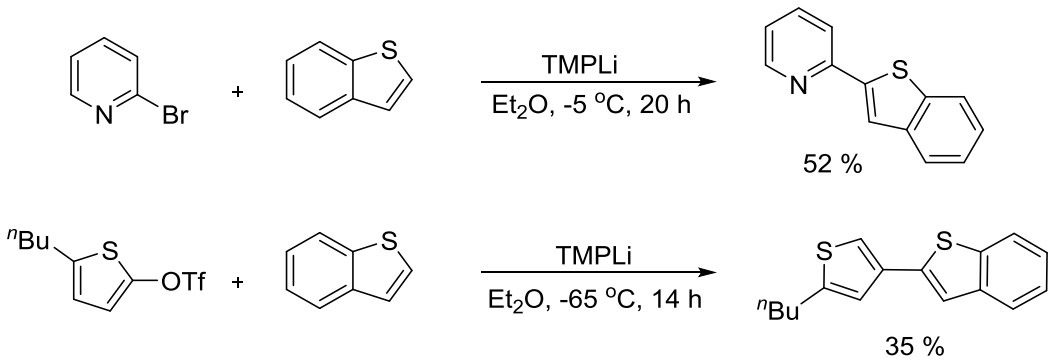
A method for first-row transition-metal-catalyzed deprotonative arene dimerization has been described.[15] When oxygen was used as oxidant, a variety of arene and heterocycles can be efficiently dimerized. By employing this methodology, we were able to dimerize aryl copper reagents in good yield (entry 5). Interestingly, when heteroarenes are used in excess, cross-dimerization between biaryl copper and starting heteroaryl copper occurs predominately (entries 6, 7). These reactions produce diverse arenes in a one-pot fashion from readily available starting materials.

3.3.2.4. Heterocyclic Arynes

Benzyne and its derivatives have been well-explored.[16] In contrast, relatively few heterocyclic arynes have been investigated. Pyridynes and indolynes have been employed in the synthesis of complex natural products.[17] To examine potential utility of heterocyclic arynes under our conditions, several attempts were made to investigate their formation, reactivity, and reaction regioselectivity. Treating benzothiophene with 2-bromopyridine in the presence of TMPLi, 52 % of coupling product was obtained and nucleophilic attack occurred at C2 of pyridine (Scheme 3.3.7). The site of attack is in agreement with literature report.[18] For challenging thiophyne generation, thiophenyl triflates are required. Interestingly, reaction of 2-butyl thiophenyl triflate with benzothiophene affords a single product in 35 % yield (Scheme 3.3.7). Analysis of product indicates that nucleophilic attack occurs at C3 position. These reactions show

potential in synthesis of structures which are challenging to access using traditional approaches.

Scheme 3.3.7. Reactions of heterocyclic arynes



3.3.3. Summary

A transition-metal-free method for base-promoted arylation of arenes and heterocycles by aryl halides and aryl triflates has been developed. The generation of arynes from corresponding aryl triflates at low temperature allows access to wide range of coupling products. A variety of functional groups are tolerated with alkene, ether, dimethylamino, trifluoromethyl, ester, cyano, halide, hydroxyl, and silyl functionalities compatible with reaction conditions. Moreover, *NH*-containing indole arylation at 3-position by aryl chlorides was achieved. Additionally, a general method for trapping aryl lithium intermediates with various electrophiles is described. The method provides easy access to wide range of highly functionalized biaryls from readily available starting materials. Furthermore, synthesis of functionalized heterocyles using heterocylic aryne intermediates is also described.

3.3.4. Experimental Section

General considerations:

Reactions were performed in 2-dram vials using screw caps with 17 mm hole and white silicone septum with white teflon face (from SUPELCO). Column chromatography was performed on 60Å silica gel (Sorbent Technologies). Purification by preparative HPLC was performed on a Shimadzu Prominence LC (LC-20AB) equipped with a SPD-20A UV-Vis detector and a Varian Dynamax (250 mm x 21.4 mm) column. GC-MS analyses were performed on a Shimadzu GCMS-QP5000 chromatograph equipped with a Restek column (Rtx-XLB, 30 m x 0.25 mm I.D.). The ^{1}H and ^{13}C NMR were recorded on JEOL EC-400 or JEOL EC-500 spectrometers using residual solvent peak as a reference. Elemental analyses were performed by Atlantic Microlab Inc. of Norcross, GA. IR spectra were obtained on a ThermoNicolet Avatar 370 FT-IR instrument. Analytical thin layer chromatography was performed on silica gel IB-F (Baker-flex) by J. T. Baker. All procedures were performed under nitrogen atmosphere unless otherwise noted.

Room temperature: 23 ^{o}C.

Materials. The following starting materials were obtained from commercial sources and were used without further purification: dibenzofuran, 1,3-dichlorobenzene, 1,3-difluorobenzene, 1,2-difluorobenzene, 3-methoxybenzonitrile, 2,4-dimethoxybenzonitrile, 1,4-bis(trifluoromethyl)-2-chlorobenzene, 1-chloro-2-fluorobenzene, 2-methoxynapthalene, 2-bromocumene, 2-chloronapthalene, 3-chloroanisole, 2-chloroanisole, 2-chloro-N,N-dimethylaniline, 2-chlorostyrene, 2-chlorobenzotrifluoride, 1-methylindole, 1-methyl-1,3,4-triazole, 1-phenylpyrazole, 2-

phenylpyridine, 2-methoxypyridine, 3-methoxypyridine, 4-methoxypyridine, 2,4,6-trichloropyridine, 3-chlorothiophene, *tert*-butyl-3-bromobenzoate, benzothiophene, benzoxazole, iodine, anhydrous dimethylformamide, pivaldehyde, chloro methylformate, chlorotrimethylsilane, benzoyl chloride, chlorodiphenylphosphine, diphenylsulfide, 9-brormophenathrene, 1,3-dimethoxybenzene, chlorodicyclohexyl phosphine, methyl idodide, allyl bromide, ethyl-2-methylbromide arylate, copper cyanide lithium chloride in THF, 2-bromopyridine, 2-methoxypyridine, *o*-trimethylsilylphenyl triflate, 2-butylthiophene.

TMPLi: A 250 mL oven-dried flask equipped with a magnetic stirring bar and a septum was evacuated and backfilled with nitrogen 5 times. TMPH (15.5 g, 18.5 mL, 110 mmol) was added via syringe, followed by anhydrous pentane to give approximately 100 mL of solution. The mixture was cooled to -73 °C (dry ice-acetone bath) and stirred for 10 minutes. *n*-BuLi (2.5 M in hexanes, 40.0 mL, 100 mmol) was added dropwise and reaction mixture was stirred for 30 minutes at -73 °C, then warmed up to room temperature (25 °C) and stirred overnight. The reaction mixture was vacuumed to remove all solvent and dried under vacuum for at least 5 hours. A light yellow powder of solid TMPLi was obtained.

TMPLi 1 M in pentane/hexanes: A 50 mL oven-dried flask equipped with a magnetic stirring bar and a septum was evacuated and backfilled with argon 5 times. TMPH (4.64 g, 33.0 mmol) was added, followed by anhydrous pentane to give 30 mL of solution (marked the flask at the level of solution). The mixture was cooled to -73 °C (dry ice-acetone) and stirred for 5 minutes. *n*-BuLi (2.5 M in hexanes, 12.0 mL, 30 mmol) was

added dropwise and reaction mixture was stirred for 30 minutes at -73 °C, then warmed up to room temperature and stirred overnight. The reaction mixture was vacuumed to give 30 mL (at the marked level) of TMPLi suspension.

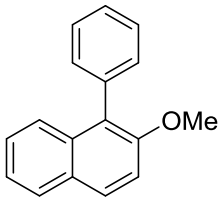
General procedure for reactions without quenching intermediates:

Outside the glovebox a 2-dram vial was equipped with a magnetic stirring bar. The vial was placed inside the glovebox. To the vial was added solid TMPLi (0.8 – 1.5 mmol). The sealed vial was taken out of the glovebox and placed into oil bath/ cooling bath at reaction temperature. Half of solvent or solvent mixture (0.8 - 1.0 mL) was added via syringe to reaction vial. Following that, heterocycle or arene (0.25 mmol) and chloroarene (0.5 – 1.0 mmol) or aryl triflate (0.5 – 1.0 mmol) were dissolved in another half of reaction solvents (0.8 – 1.0 mL) and added via syringe at reaction temperature. Reactions were run for indicated time. Reactions were quenched with methanol (0.5 mL, unless otherwise stated), diluted with ethyl acetate (30 mL) or dichloromethane (30 mL). Mixture were filtered through pad of short silicagel, washed with same solvent and evacuated. Residue was dissolved in eluent (1.5 mL) and subjected to flash chromatography in hexanes followed by appropriated solvent to elute the products. After concentrating the fractions containing the product, the residue was dried under reduced pressure to yield pure product. If necessary, purification by preparative HPLC was performed. Note: strong stirring (higher than 1000 rpm) is necessary to get reproducible yields.

General procedure for reactions with quenching intermediates with electrophiles:

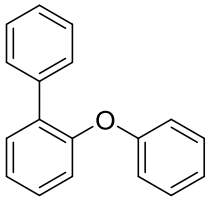
Outside the glovebox a 2-dram vial was equipped with a magnetic stirring bar. The vial was placed inside the glovebox. To the vial was added solid TMPLi (0.8 – 1.5 mmol). The sealed vial was taken out of the glovebox and placed into oil bath/ cooling bath at reaction temperature. Solvent mixture (1.0 mL) was added via syringe to reaction vial. Following that, heterocycle or arene (0.25 mmol) and chloroarene (0.5 – 1.0 mmol) or aryl triflate (0.5 – 1.0 mmol) were dissolved in reaction solvent (1.0 mL) and added via syringe at reaction temperature. Reactions were run for indicated time. Reactions were cooled to -75 °C. Electrophiles were added at -75 °C, followed by stirring at -75 °C for 1 hour. Subsequently, reactions were warmed up to room temperature (approximately 3 hours). Reaction mixture was diluted with ethyl acetate (30 mL) or dichloromethane (30 mL) and filtered through pad of Celite. Celite pad was washed with diethyl ether and solvent was evaporated. Residue was dissolved in eluent (1.5 mL) and subjected to flash chromatography in hexanes followed by appropriate solvent to elute the products. After concentrating the fractions containing the product, the residue was dried under reduced pressure to yield pure product. If necessary, purification by preparative HPLC was performed. Note: strong stirring (higher than 1000 rpm) is necessary to get reproducible yields.

A**rylation of Arenes**



1-Phenyl-2-methoxynaphthalene (Table 3.3.2, Entry 1)

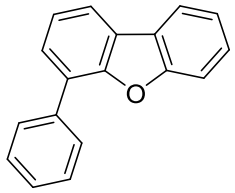
2-Methoxynapthalene (0.25 mmol), chlorobenzene (112.5 mg, 1.0 mmol), TMPLi (215 mg, 1.5 mmol), pentane, 40 °C, 48 hours. After column chromatography (hexanes followed by hexanes/dichloromethane: 85/15), 30 mg (%) of a colorless oil was obtained. This compound is known.[19] R_f = 0.43 (hexanes/dichloromethane 80/20). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.76 (m, 3H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.47 – 7.43 (m, 3H), 7.39 – 7.34 (m, 2H), 7.23 (d, *J* = 8.2 Hz, 1H), 3.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 155.3, 138.4, 134.1, 132.5, 130.1, 129.9, 128.9, 128.1, 127.8, 127.3, 126.4, 124.0, 105.7, 55.7. Signal for one carbon could not be located.



2-Phenoxy-1,1'-biphenyl (Table 3.3.2, Entry 2)

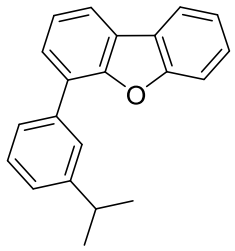
Diphenyl ether (42.5 mg, 0.25 mmol), chlorobenzene (70 mg, 0.625 mmol), TMPLi (180 mg, 1.25 mmol), diethyl ether (1.5 mL), tetrahydrofuran (THF) (0.2 mL), - 45 °C, 36 hours. After column chromatography (hexanes followed by hexanes/dichloromethane: 85/15), 43 mg (71 %) of a colorless oil was obtained. This compound is known.[20] R_f = 0.37 (hexanes/dichloromethane 85/15). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 – 7.59 (m,

2H), 7.54 – 7.49 (m, 1H), 7.45 – 7.24 (m, 7H), 7.10 – 7.04 (m, 2H), 7.02 – 6.95 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 157.9, 153.7, 137.9, 133.8, 131.5, 129.8, 129.4, 128.8, 128.3, 127.4, 124.2, 122.8, 120.3, 118.3.



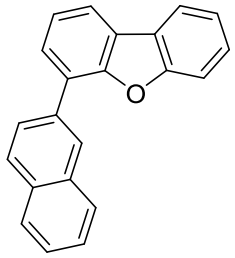
4-Phenyldibenzofuran (Table 3.3.2, Entry 3)

Dibenzofuran (42 mg, 0.25 mmol), chlorobenzene (113 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), diether ether (1.5 mL), tetrahydrofuran (THF) (0.2 mL), -50 °C, 24 hours. After column chromatography (hexanes followed by hexanes/dichloromethane: 80/20), 47 mg (78 %) of a white solid was obtained. This compound is known.[21] R_f = 0.31 (hexanes/dichloromethane 80/20). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.8 Hz, 1H), 7.98 – 7.95 (m, 3H), 7.65 – 7.63 (m, 2H), 7.61 – 7.56 (m, 2H), 7.52 – 7.44 (m, 3H), 7.39 (dt, *J* = 7.8 Hz, 0.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 156.3, 153.3, 136.6, 129.0, 128.8, 127.9, 127.4, 127.0, 126.0, 125.0, 124.4, 123.3, 122.9, 120.8, 119.8, 112.0.



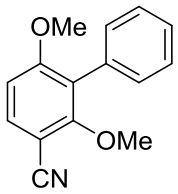
4-[3-(1-Methylethyl)phenyl]dibenzofuran (Table 3.3.2, Entry 4)

Dibenzofuran (42 mg, 0.25 mmol), 2-bromocumene (100 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), diether ether (1.5 mL), tetrahydrofuran (THF) (0.2 mL), -45 °C, 36 hours. After column chromatography (hexanes followed by hexanes/dichloromethane: 90/10), 47 mg (66 %) of a colorless oil was obtained. R_f = 0.30 (hexanes/dichloromethane 90/10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.5 Hz, 1H), 7.96 (d, *J* = 7.5 Hz, 1H), 7.81 – 7.78 (m, 2H), 7.64 (t, *J* = 7.2 Hz, 2H), 7.53 – 7.43 (m, 3H), 7.40 – 7.33 (m, 2H), 3.08 (heptet, *J* = 6.8 Hz, 1H), 1.40 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 156.3, 153.5, 149.4, 136.5, 128.7, 127.3, 127.2, 127.1, 126.6, 126.4, 126.1, 125.0, 124.4, 123.3, 122.9, 120.8, 119.7, 112.0, 34.4, 24.2.



4-(2-Naphthyl)dibenzofuran (Table 3.3.2, Entry 5)

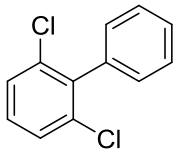
Dibenzofuran (42 mg, 0.25 mmol), 2-chloronaphthalene (82 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), diether ether (1.5 mL), tetrahydrofuran (THF) (0.2 mL), -45 °C, 24 hours. After column chromatography (hexanes followed by hexanes/dichloromethane: 85/15), 51 mg (70 %) of a white solid was obtained. R_f = 0.32 (hexanes/dichloromethane 80/20). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.08 – 7.92 (m, 5H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.57 – 7.46 (m, 4H), 7.39 (t, *J* = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 156.3, 153.7, 134.0, 133.7, 133.0, 128.5, 128.3, 128.0, 127.8, 127.4, 127.3, 126.9, 126.4, 126.3, 126.0, 125.1, 124.3, 123.4, 122.9, 120.8, 119.9, 112.0.



2,6-Dimethoxy-3-carbonitrile-1,1'-biphenyl (Table 3.3.2, Entry 6)

2,4-Dimethoxybenzonitrile (41 mg, 0.25 mmol), chlorobenzene (85 mg, 0.75 mmol), TMPLi (180 mg, 1.25 mmol), tetrahydrofuran (THF) (1.5 mL), - 65 °C, 30 hours. After column chromatography (hexanes followed by hexanes/EtOAc: 85/15), 31 mg (%) of a colorless oil was obtained. R_f = 0.38 (hexanes/EtOAc 80/20. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.7 Hz, 1H), 7.45 – 7.32 (m, 5H), 6.78 (d, *J* = 8.7 Hz, 1H), 3.79 (s, 3H), 3.55 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 161.6, 161.1, 133.8, 132.1, 130.4,128.2, 127.8, 125.0, 117.2, 107.1, 99.1, 61.7, 56.3.

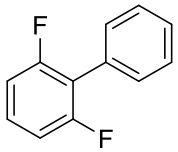
Note: Product contains less than 7 % of 2,4-dimethoxybenzonitrile starting material.



2,6-Dichloro-1,1'-biphenyl (Table 3.3.2, Entry 7)

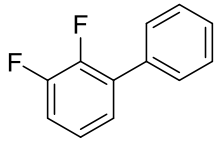
1,3-Dichlorobenzene (0.25 mmol), phenyl triflate (113 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), diether ether (1.5 mL), tetrahydrofuran (THF) (0.05 mL), -75 °C, 12 hours. After column chromatography (hexanes followed by hexanes/dichloromethane: 90/10), 45 mg (82 %) of a colorless oil was obtained. This compound is known.[22] R_f = 0.40 (hexanes/dichloromethane 90/10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.43 (m, 3H),

7.41 (d, *J* = 7.9 Hz, 2H), 7.29 – 7.26 (m, 2H), 7.24 (dd, *J* = 8.6 Hz, 1.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 139.6, 137.1, 135.1, 129.6, 129.1, 128.3, 128.2, 128.1.



2,6-Difluoro-1,1'-biphenyl (Table 3.3.2, Entry 8)

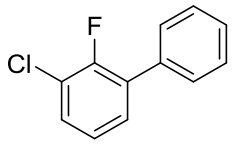
1,3-Difluorobenzene (29 mg, 0.25 mmol), phenyl triflate (113 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), diether ether (1.5 mL), tetrahydrofuran (THF) (0.05 mL), -75 °C, 12 hours. After column chromatography (hexanes followed by hexanes/dichloromethane: 90/10), 37 mg (79 %) of a colorless oil was obtained. This compound is known.[23] R_f = 0.42 (hexanes/dichloromethane 90/10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 5.0 Hz, 4H), 7.44 – 7.37 (m, 1H), 7.30 – 7.24 (m, 1H), 6.98 (dt, *J* = 7.4 Hz, 1.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 160.1 (dd, *J* = 248 Hz, 7.0 Hz), 130.4, 129.2, 128.9 (t, *J* = 10 Hz), 128.4, 128.3, 118.6 (t, *J* = 18.0 Hz), 111.8 (dd, *J* = 18.0 Hz, 7.0 Hz).



2,3-Difluoro-1,1'-biphenyl (Table 3.3.2, Entry 9)

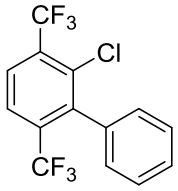
1,2-Difluorobenzene (29 mg, 0.25 mmol), phenyl triflate (113 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), diether ether (1.5 mL), tetrahydrofuran (THF) (0.05 mL), -75 °C, 12 hours. After column chromatography (hexanes followed by hexanes/dichloromethane: 90/10), 28 mg (59 %) of a colorless oil was obtained. This compound is known.[24] R_f = 0.43 (hexanes/dichloromethane 90/10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.52 (m,

2H), 7.45 (tt, *J* = 7.3 Hz, 1.4 Hz, 2H), 7.41 – 7.37 (m, 1H), 7.21 – 7.11 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 151.3 (dd, *J* = 248.0 Hz, 13.6 Hz), 148.0 (dd, *J* = 248.0 Hz, 13.6 Hz). 134.8 (d, *J* = 2.4 Hz), 131.4 (d, *J* = 10.5 Hz), 129.0 (d, *J* = 2.4 Hz), 128.7, 128.3, 125.4 (t, *J* = 2.4 Hz), 124.2 (dd, *J* = 7.8 Hz, 4.9 Hz), 116.1 (d, *J* = 17.2 Hz).



3-Chloro-2-fluoro-1,1'-biphenyl (Table 3.3.2, Entry 10)

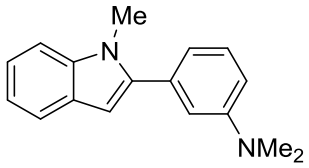
1-Chloro-2-fluorobenzene (0.25 mmol), phenyl triflate (113 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), diether ether (1.5 mL), tetrahydrofuran (THF) (0.05 mL), -75 °C, 12 hours. After column chromatography (hexanes followed by hexanes/dichloromethane: 90/10), 32 mg (62 %) of a colorless oil was obtained. R_f = 0.37 (hexanes/dichloromethane 90/10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.51 (m, 2H), 7.47 – 7.44 (m ,2H), 7.41 – 7.37 (m, 2H), 7.32 (dt, *J* = 7.5 Hz, 1.8 Hz, 1H), 7.14 (dt, *J* = 8.1 Hz, 1.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 155.3 (d, *J* = 250 Hz), 135.0, 130.8 (d, *J* = 13.3 Hz), 129.6, 129.2 (d, *J* = 2.5 Hz), 129.1 (d, *J* = 2.5 Hz), 128.6, 128.2, 124.7 (d, *J* = 5.0 Hz), 121.9 (d, *J* = 18.0 Hz).



3,6-Bis(trifluoromethyl)-2-chloro-1,1'-biphenyl (Table 3.3.2, Entry 11)

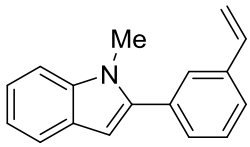
1,4-Bis(trifluoromethyl)-2-chlorobenzene (62 mg, 0.25 mmol), phenyl triflate (113 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), diether ether (1.5 mL), tetrahydrofuran (THF)

(0.05 mL), - 75 °C, 12 hours. After column chromatography (hexanes followed by hexanes/dichloromethane: 85/15), 53 mg (65 %) of a colorless oil was obtained. This compound is known.[25] R_f = 0.33 (hexanes/dichloromethane 85/15). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 1.7 Hz, 1H), 7.77 (d, *J* = 1.7 Hz, 1H), 7.49 – 7.46 (m, 3H), 7.40 – 7.38 (m, 2H).



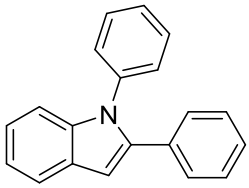
***N*,*N*-Dimethyl-4-(1-methyl-2-indolyl)benzenamine (Table 3.3.3, Entry 1)**

1-Methylindole (33 mg, 0.25 mmol), 2-chloro-*N*,*N*-dimethylaniline (97 mg, 0.625 mmol), TMPLi (180 mg, 1.25 mmol), pentane (2.0 mL), THF (0.1 mL), rt, 36 hours. After column chromatography (hexanes followed by hexanes/dichloromethane: 80/20), 43 mg (70 %) of a colorless oil was obtained. This compound is known.[26] R_f = 0.28 (hexanes/dichloromethane 80/20). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.8 Hz, 1H), 7.41 – 7.35 (m, 2H), 7.30 – 7.25 (m, 1H), 7.18 (t, *J* = 7.8 Hz, 1H), 6.90 – 6.88 (m, 2H), 6.82 (dd, *J* = 8.2 Hz, 1.4 Hz, 1H), 6.61 (s, 1H), 3.79 (s, 3H), 3.02 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 150.7, 142.7, 138.3, 133.7, 129.2, 128.1, 121.6, 120.5, 119.9, 117.8, 113.8, 112.2, 109.7, 101.4, 40.7, 31.3.



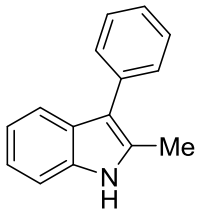
2-(3-Ethenyl-1-phenyl)-1-methylindole (Table 3.3.3, Entry 2)

1-Methylindole (33 mg, 0.25 mmol), 2-chlorostyrene (87 mg, 0.625 mmol), TMPLi (180 mg, 1.5 mmol), pentane (2.0 mL), THF (0.05mL), rt, 36 hours. After column chromatography (hexanes followed by hexanes/dichloromethane: 90/10), 39 mg (68 %) of a colorless oil was obtained. R_f = 0.25 (hexanes/dichloromethane 90/10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.8 Hz, 1H), 7.57 (s, 1H), 7.48 – 7.38 (m, 4H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.17 (t, *J* = 7.8 Hz, 1H), 6.80 (dd, *J* = 17.6 Hz, 10.7 Hz, 1H), 6.60 (s, 1H), 5.84 (d, *J* = 17.6 Hz, 1H), 5.34 (d, *J* = 10.7 Hz, 1H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 141.5, 138.4, 138.0, 136.6, 133.2, 128.9, 128.8, 128.0, 127.4, 125.8, 121.8, 120.6, 120.0, 114.8, 109.8, 101.8, 31.3.



1,2-Diphenylindole (Table 3.3.3, Entry 3)

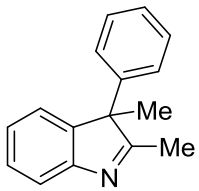
1-Phenylindole (49 mg, 0.25 mmol), chlorobenzene (57 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), pentane (2.0 mL), THF (0.1 mL), rt, 36 hours. After column chromatography (hexanes followed by hexanes/dichloromethane: 90/10), 52 mg (78 %) of a colorless oil was obtained. This compound is known.[27] R_f = 0.30 (hexanes/dichloromethane 90/10) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.73 (m, 1H), 7.47 – 7.45 (m, 2H), 7.43 – 7.22 (m, 11H), 6.87 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 140.9, 139.1, 138.6, 132.7, 129.4, 129.1, 128.4, 128.3, 128.2, 127.5, 127.4, 122.5, 120.9, 120.7, 110.8, 103.9.



2-Methyl-3-phenyl-1*H*-indole (Table 3.3.3, Entry 4)

2-Methylindole (131 mg, 1.0 mmol), chlorobenzene (57 mg, 0.5 mmol), TMPLi (270 mg, 1.8 mmol), anhydrous cyclohexane (0.7 mL), anhydrous Et_2O (0.7 mL), room temperature, 24 hours. After column chromatography (hexanes followed by hexanes/EtOAc 90/10), 83 mg (80 %) of a light yellowish oil was obtained. Less than 5 % of *N*-arylation product was observed in crude reaction mixture by GC analysis.

R_f = 0.33 (hexanes/EtOAc 90/10). This compound is known.[28] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.56 – 7.54 (m, 2H), 7.52 – 7.48 (m, 2H), 7.36 – 7.31 (m, 2H), 7.20 (dt, *J* = 7.2 Hz, 1.3 Hz, 1H), 7.15 (dt, *J* = 7.2 Hz, 1.3 Hz, 1H), 2.5 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 135.6, 135.3, 131.6, 129.5, 128.6, 127.9, 125.9, 121.6, 120.1, 118.9, 114.6, 110.5, 12.7.

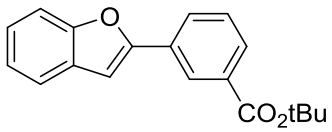


2,3-Dimethyl-3-phenyl-1*H*-indole (Table 3.3.3, Entry 5)

2,3-Dimethylindole (145 mg, 1.0 mmol), chlorobenzene (57 mg, 0.5 mmol), TMPLi (270 mg, 1.8 mmol), anhydrous cyclohexane (0.7 mL), anhydrous Et_2O (0.7 mL), room temperature, 24 hours. After column chromatography (hexanes followed by

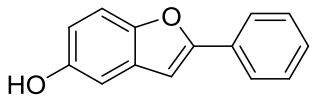
hexanes/EtOAc 70/30), 85 mg (77 %) of a light yellowish oil was obtained. Less than 5 % of *N*-arylation product was observed in crude reaction mixture by GC analysis.

R_f = 0.22 (hexanes/EtOAc: 70/30). This compound is known.[29] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.9 Hz, 1H), 7.32 (dt, J = 7.5 Hz, 1.1 Hz, 1H), 7.28 – 7.21 (m, 3H), 7.14 (dt, *J* = 7.5 Hz, 1.1 Hz, 1H), 7.08 (d, *J* = 7.2 Hz, 1H), 7.03 – 7.01 (m, 2H), 2.11 (s, 3H), 1.68 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 187.3, 154.6, 147.2, 139.5, 128.9, 127.9, 127.3, 126.2, 125.8, 122.5, 120.2, 61.9, 20.4, 16.0.



3-(2-Benzofuranyl)-1,1-dimethylethylbenzoate (Table 3.3.3, Entry 6)

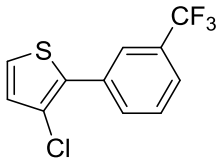
tert-Butyl-3-fluorobenzoate (96 mg, 0.5 mmol), benzofuran (34 mg, 0.25 mmol), TMPLi (1.0 mmol), THF (2 mL), -73 °C; then slowly warm up to -35 °C (2 hrs) and keep at that temperature for 8 hrs, then move to ice bath to warm the reaction mixture to 0 °C and keep at that temperature for 30 minutes. After column chromatography (hexanes/Et_2O 90/10), 37 mg (50 %) of light yellow solid was obtained. R_f = 0.52 (hexanes/Et_2O 90/10), mp 123-125 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (t, *J* = 1.8 Hz, 1H), 7.95 (td, *J* = 7.8 Hz, 1.4 Hz, 1H), 7.85-7.82 (m, 2H), 7.78 (dd, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.61 (s, 1H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.38-7.31 (m, 2H), 1.62 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.4, 143.3, 140.5, 139.7, 134.4, 132.8, 130.3, 129.0, 128.9, 127.4, 124.8, 124.7, 123.8, 122.3, 120.2, 81.3, 28.2.



2-Phenyl-5-benzofuranol (Table 3.3.3, Entry 7)

5-Hydroxybenzofuran (34 mg, 0.25 mmol), chlorobenzene (43 mg, 0.375 mmol), TMPLi (150 mg, 1.0 mmol), diethyl ether (1.6 mL). THF (0.4 mL), -50 °C, 14 hours. After column chromatography (hexanes followed by hexanes/EtOAc = 90/10), 27 mg (53 %) of a white solid was obtained. This compound is known.[30] R_f = 0.34 (hexanes/Et_2O 80/20), ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.8 Hz, 2H), 7.47 – 7.41 (m, 2H), 7.38 – 7.32 (m, 2H), 6.99 (d, *J* = 2.4 Hz, 1H), 6.93 (s, 1H), 6.79 (dd, *J* = 8.6 Hz, 2.4 Hz, 1H), 4.66 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 157.0, 151.7, 150.1, 130.5, 130.2, 128.8, 128.7, 125.0, 112.9, 111.7, 105.9, 101.3.

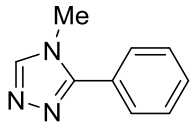
Note: The above two reactions (Table 3.3.3, entries 6, 7) were quenched with H_2O (15 mL), followed by addition of Et_2O (15 mL). The organic phase was then washed with brine (15 mL) and the aqueous layers were extracted with Et_2O (2x10 mL). The combined organic phase was then dried over $MgSO_4$, and concentrated under vacuum. The residue was then dissolved in minimum amount of dichloromethane and subjected to the flash chromatography on silica gel. After concentrating the fraction containing the product, the residue was dried over reduced pressure to yield pure product.



3-Chloro-2-[3-(trifluoromethyl)-1-phenyl]thiophene (Table 3.3.3, Entry 8)

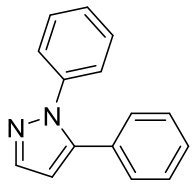
3-Chlorothiophene (30 mg, 0.25 mmol), 2-chlorobenzotrifluoride (135 mg, 0.75 mmol), LDA (1.25 mmol), THF, 0 °C, 4 hours. After column chromatography (hexanes followed

by hexanes/dichloromethane: 85/15), 40 mg (62 %) of a colorless oil was obtained. R_f = 0.42 (hexanes/dichloromethane 80/20). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.32 (d, *J* = 5.5 Hz, 1H), 7.03 (d, *J* = 5.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 134.5, 133.1, 132.0, 131.2 (q, *J* = 33.5 Hz), 129.6, 129.2, 125.5 (q, *J* = 3.8 Hz), 124.7, 124.8, 123.4 (q, *J* = 271 Hz), 122.4.



1-Methyl-2-phenyl-1,3,4-triazole (Table 3.3.3, Entry 9)

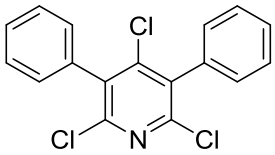
1-Methyl-1,3,4-triazole (21 mg, 0.25 mmol), phenyl triflate (170 mg, 0.75 mmol), LDA (1.25 mmol), THF, -75 °C, 10 hours. After column chromatography (hexanes followed by hexanes/EtOAc: 40/60), 28 mg (71 %) of a colorless oil was obtained. This compound is known[31]. R_f = 0.25 (hexanes/EtOAc 40/60). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.66 – 7.64 (m, 2H), 7.50 – 7.46 (m, 3H), 3.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 154.7, 150.8, 130.2, 128.9, 128.7, 127.9, 37.1.



1,5-Diphenylpyrazole (Table 3.3.3, Entry 10)

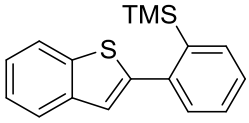
1-Phenylpyrazole (37 mg, 0.25 mmol), phenyl triflate (170 mg, 0.75 mmol), TMPLi (184 mg, 1.25 mmol), diethyl ether (2.0 mL). THF (0.05 mL), -75 °C, 12 hours. After column chromatography (hexanes followed by hexanes/EtOAc: 60/40), 31 mg (58 %) of a colorless oil was obtained. This compound is known.[31] R_f = 0.35 (hexanes/EtOAc 50/50).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 1.8 Hz, 1H), 7.35 – 7.27 (m, 8H), 7.25 – 7.21 (m, 2H), 6.51 (d, *J* = 1.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 143.1, 140.4, 140.2, 130.7, 129.0, 128.9, 128.6, 128.3, 127.5, 125.3, 107.9.



2,4,6-Trichloro-3,5-diphenylpyridine (Table 3.3.3, Entry 11)

2,4,6-Trichloropyridine (46 mg, 0.25 mmol), phenyl triflate (228 mg, 1.0 mmol), TMPLi (215 mg, 1.5 mmol), diethyl ether (2.0 mL). THF (0.05 mL), -75 °C, 12 hours. After column chromatography (hexanes followed by hexanes/dichloromethane: 60/40), 50 mg (60 %) of a white solid was obtained. R_f = 0.34 (hexanes/dichloromethane 50/50). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.45 (m, 6H), 7.32 – 7.28 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 149.1, 146.8, 135.3, 134.8, 129.4, 129.0, 128.8.



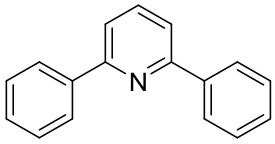
2-[2-(Trimethylsilyl)-1-phenyl]benzothiophene (Table 3.3.3, Entry 12 and Table 3.3.5, Entry 5)

o-Trimethylsilylphenyl triflate (57 mg, 0.25 mmol), benzothiophene (67 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), diethyl ether (2.0 mL), THF (0.05 mL), -75 °C, 36 hours. After column chromatography (hexanes/dichloromethane 90/10), 48 mg (68 %) of colorless oil was obtained. TMPLi (150 mg, 1.0 mmol), pentane (2.0 mL), THF (0.15

mL), -15 °C, 24 hours. After column chromatography (hexanes/Et_2O 60/40), 29 mg (63 %) of yellowish oil was obtained.

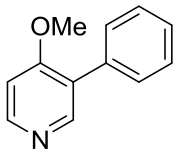
Benzothiophene (34 mg, 0.25 mmol), phenyl triflate (112 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), Et_2O (1.5 mL), THF (0.05 mL), -75 °C, 12 hours. TMSCl (1.25 mmol) in Et_2O was slowly added via syringe. After column chromatography (hexanes), 48 mg (68 %) of colorless oil was obtained.

R_f = 0.29 (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 4.7 Hz, 1H), 7.61 (d, *J* = 7.3 Hz, 1H), 7.57 – 7.53 (m, 2H), 7.44 – 7.40 (m, 2H), 7.37 – 7.32 (m, 1H), 6.99 – 6.95 (dd, *J* = 7.3 Hz, 4.7 Hz, 1H), 3.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 161.0, 145.8, 138.7, 136.9, 129.3, 128.3, 127.6, 124.8, 117.2, 53.6.



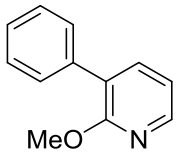
2,6-Diphenylpyridine (Table 3.3.3, Entry 13)

2-Phenylpyridine (39 mg, 0.25 mmol), chlorobenzene (57 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), diethyl ether (1.5 mL), THF (0.15 mL), - 40 °C, 36 hours. After column chromatography (hexanes followed by hexanes/EtOAc: 90/10), 40 mg (70 %) of a colorless oil was obtained. This compound is known.[32] R_f = 0.34 (hexanes/EtOAc 90/10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.16 (m, 4H), 7.83 – 7.80 (m, 1H), 7.71 – 7.69 (m, 2H), 7.53 – 7.49 (m, 4H), 7.46 – 7.42 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 156.9, 139.6, 137.6, 129.1, 128.8, 127.1, 118.7.



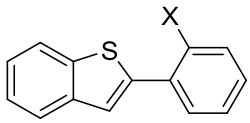
4-Methoxy-3-phenylpyridine (Table 3.3.3, Entry 14)

4-Methoxypyridine (28 mg, 0.25 mmol), chlorobenzene (57 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), pentane (2.0 mL), THF (0.15 mL), -15 °C, 24 hours. After column chromatography (hexanes/EtOAc 40/60), 33 mg (72 %) of yellowish oil was obtained. This compound is known.[33] R_f = 0.28 (hexanes/EtOAc 40/60). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 5.7 Hz, 1H), 8.44 (s, 1H), 7.52 – 7.49 (m, 2H), 7.45 – 7.41 (m, 2H), 7.37 (tt, *J* = 7.4 Hz, 2.3 Hz, 1H), 6.89 (d, *J* = 5.7 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.6, 150.9, 150.6, 134.9, 129.6, 128.4, 127.8, 126.6, 106.5, 55.5.



2-Methoxy-3-phenylpyridine (Table 3.3.3, Entry 15)

2-Methoxypyridine (28 mg, 0.25 mmol), chlorobenzene (57 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), pentane (2.0 mL), THF (0.15 mL), -15 °C, 24 hours. After column chromatography (hexanes/Et_2O 60/40), 29 mg (63 %) of yellowish oil was obtained. This compound is known.[34] R_f = 0.38 (hexanes/EtOAc 70/30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 4.7 Hz, 1H), 7.61 (d, *J* = 7.3 Hz, 1H), 7.57 – 7.53 (m, 2H), 7.44 – 7.40 (m, 2H), 7.37 – 7.32 (m, 1H), 6.99 – 6.95 (dd, *J* = 7.3 Hz, 4.7 Hz, 1H), 3.97 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 161.0, 145.8, 138.7, 136.9, 129.3, 128.3, 127.6, 124.8, 117.2, 53.6.



(X : halogen)

2-(2-Iodophenyl)benzothiophene (Table 3.3.5, Entry 1)

Benzothiophene (34 mg, 0.25 mmol), phenyl triflate (122 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), Et_2O (1.5 mL), THF (0.05 mL), - 75 °C, 12 hours. I_2 (320 mg, 1.25 mmol) in Et_2O/THF (80/20; 0.8 mL) was slowly added via syringe at - 75 °C. Reaction was poured into aqueous saturated solution of NaI and $Na_2S_2O_3$ (20 mL), diluted with Et_2O (30 mL) and strongly stirred for 30 minutes. Aqueous layers were extracted with Et_2O (2x20 mL). The combined organic phase was then dried over $MgSO_4$, and concentrated under vacuum. Residue was dissolved hexane/dichloromethane (90/10; 1.5 mL) and subjected to flash chromatography in hexanes to elute the products. After concentrating the fractions containing the product, the residue was dried under reduced pressure to yield 61 mg of colorless oil. R_f = 0.26 (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.0 (dd, *J* = 8.2 Hz, 1.1 Hz, 1H), 7.87 – 7.82 (m, 2H), 7.50 (dd, *J* = 7.6 Hz, 1.6 Hz, 1H), 7.42 – 7.36 (m, 4H), 7.07 (dt, *J* = 7.6 Hz, 1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 145.2, 140.3, 140.1, 139.7, 139.5, 131.6, 129.9, 128.2, 124.6, 124.4, 124.0, 122.3, 99.2.Signal for one carbon could not be located.

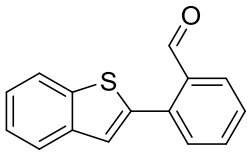
2-(2-Bromophenyl)benzothiophene (Table 3.3.5, Entry 1)

Benzothiophene (34 mg, 0.25 mmol), phenyl triflate (112 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), Et_2O (1.5 mL), THF (0.05 mL), -75 °C, 12 hours. CBr_4 (415 mg, 1.25 mmol) in Et_2O/THF (80/20; 0.8 mL) was slowly added via syringe at - 75 °C. After

column chromatography (hexanes), 58 mg (81 %) of white solid was obtained. This compound is known.[35] R_f = 0.26 (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.82 (m, 2H), 7.71 (dd, *J* = 8.2 Hz, 1.1 Hz, 1H), 7.56 (dd, *J* = 7.8 Hz, 1.7 Hz, 1H), 7.51 (s, 1H), 7.41 – 7.35 (m, 3H), 7.23 (dt, *J* = 7.8 Hz, 1.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 142.0, 140.3, 139.8, 135.4, 133.8, 132.4, 129.7, 127.6, 124.7, 124.6, 124.5, 124.0, 123.1, 122.2.

2-(2-Chlorophenyl)benzothiophene (Table 3.3.5, Entry 1)

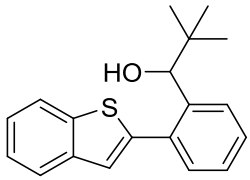
Benzothiophene (34 mg, 0.25 mmol), phenyl triflate (112 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), Et_2O (1.5 mL), THF (0.05 mL), -75 °C, 12 hours. CCl_4 (193 mg, 1.25 mmol) in Et_2O/THF (80/20; 0.8 mL) was slowly added via syringe. After column chromatography (hexanes), 50 mg (82 %) of white solid was obtained. This compound is known.[35] R_f = 0.25 (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.87 – 7.82 (m, 2H), 7.61 (dd, *J* = 7.3 Hz, 2.2 Hz, 1H), 7.59 (s, 1H), 7.51 (dd, *J* = 7.3 Hz, 1.8 Hz, 1H), 7.41 – 7.28 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 140.4, 140.3, 140.0, 133.3, 132.9, 132.0, 130.7, 129.4, 127.1, 124.7, 124.6, 124.5, 124.0, 122.2.



2-Benzothien-2-yl-benzaldehyde (Table 3.3.5, Entry 2)

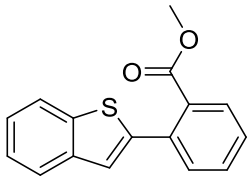
Benzothiophene (34 mg, 0.25 mmol), phenyl triflate (112 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), Et_2O (1.5 mL), THF (0.05 mL), -75 °C, 12 hours. DMF (1.5 mmol) in

Et_2O (0.5 mL) was slowly added via syringe. After column chromatography (hexanes/Et_2O 90/10), 46 mg (78 %) of white solid was obtained. This compound is known.[36] R_f = 0.29 (hexanes/Et_2O 90/10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (s, 1H), 8.04 (d, *J* = 7.7 Hz, 1H), 7.87 (dd, *J* = 7.0 Hz, 1.7 Hz, 1H), 7.82 (dd, *J* = 7.0 Hz, 1.7 Hz, 1H), 7.68 – 7.61 (m, 2H), 7.53 (dt, *J* = 7.0 Hz, 1.5 Hz, 1H), 7.45 – 7.37 (m, 2H), 7.28 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 192.0, 140.7, 140.0, 138.9, 138.1, 134.6, 133.7, 131.5, 128.9, 128.0, 126.5, 125.1, 125.0, 124.0, 122.2.



1-[(2-Benzothien-2-yl)phenyl]-2,2-dimethylpropanol (Table 3.3.5, Entry 3)

Benzothiophene (34 mg, 0.25 mmol), phenyl triflate (112 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), Et_2O (1.5 mL), THF (0.05 mL), -75 °C, 12 hours. Pivaldehyde (1.5 mmol) in Et_2O (0.5 mL) was slowly added via syringe. After column chromatography (hexanes/Et_2O 95/5), 54 mg (74 %) of colorless oil was obtained. R_f = 0.42 (hexanes/Et_2O 90/10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.7 Hz, 1H), 7.79 (dd, *J* = 7.7 Hz, 1.1 Hz, 1H), 7.69 (dd, *J* = 7.7 Hz, 1.1 Hz, 1H), 7.45 – 7.30 (m, 5H), 7.21 (s, 1H), 5.15 (s, 1H), 1.92 (broad singlet, 1H), 0.83 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 143.7, 141.1, 140.4, 140.1, 134.3, 131.3, 128.3, 128.2, 127.3, 124.5, 124.3, 123.8, 123.6, 122.2, 77.0, 36.7, 26.2.

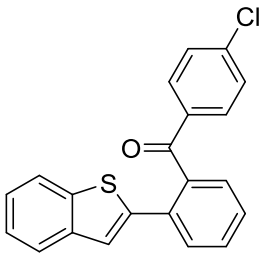


2-(Benzothien-2-yl)methylbenzoate (Table 3.3.5, Entry 4)

Benzothiophene (34 mg, 0.25 mmol), phenyl triflate (112 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), Et_2O (1.5 mL), THF (0.05 mL), -75 °C, 12 hours. Methyl chloroformate (1.5 mmol) in Et_2O (0.5 mL) was slowly added via syringe. After column chromatography (hexanes/Et_2O 90/10), 50 mg (76 %) of colorless oil was obtained.

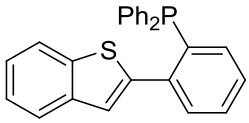
Benzothiophene (34 mg, 0.25 mmol), phenyl triflate (112 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), Et_2O (1.5 mL), THF (0.05 mL), -75 °C, 12 hours. Gaseous CO_2 was then then introduced into reaction mixture via syringe needle. Reaction was stirred at -75 °C for 6 hours before warming up to RT. Solution of MeI (1.25 mol) in THF (0.7 mL) was added, followed by addition of THF suspension of NaH (1.5 mmol, 1.0 mL). Reaction was stirred overnight. General work-up procedure was followed. After column chromatography (hexanes/Et_2O 90/10), 41 mg (62 %) of colorless oil was obtained.

This compound is known.[37] R_f = 0.31 (hexanes/Et_2O 90/10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.7 Hz, 1H), 7.79 (td, *J* = 7.7 Hz, 2.0 Hz, 2H), 7.58 – 7.51 (m, 2H), 7.45 (dt, *J* = 7.4 Hz, 1.3 Hz, 1H), 7.35 (doublet of quintet, *J* = 7.7 Hz, 1.3 Hz, 2H), 7.26 (s, 1H), 3.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 169.0, 142.5, 140.5, 140.2, 134.4, 131.9, 131.5, 131.3, 129.7, 128.4, 124.5, 124.4, 123.8, 122.9, 122.2, 52.2.



(2-Benzothien-2-ylphenyl)(4-chlorophenyl)methanone (Table 3.3.5, Entry 6)

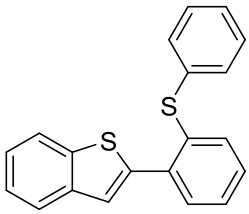
Benzothiophene (34 mg, 0.25 mmol), phenyl triflate (112 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), Et_2O (1.5 mL), THF (0.05 mL), -75 °C, 12 hours. 4-Chlorobenzoyl chloride (1.5 mmol) in Et_2O (0.5 mL) was slowly added via syringe. After column chromatography (hexanes/Et_2O 80/20), 54mg (62 %) of white solid was obtained. R_f = 0.27 (hexanes/Et_2O 80/20). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.69 (m, 1H), 7.67 – 7.55 (m, 5H), 7.51 – 7.44 (m, 2H), 7.29 – 7.22 (m, 4H), 7.12 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 197.3, 141.3, 140.2, 140.1, 139.8, 139.0, 135.4, 133.0, 131.1, 130.5, 128.8, 128.5, 128.4, 124.7, 124.6, 124.5, 123.9, 122.1. Signal for one carbon could not be located.



(2-Benzothien-2-ylphenyl)diphenylphosphine (Table 3.3.5, Entry 7)

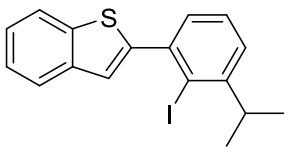
Benzothiophene (34 mg, 0.25 mmol), phenyl triflate (112 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), Et_2O (1.5 mL), THF (0.05 mL), -75 °C, 12 hours. Chlorodiphenylphosphine (1.5 mmol) in Et_2O (0.5 mL) was slowly added via syringe. After column chromatography (hexanes/dichloromethane 85/15), 60 mg (61 %) of light yellow solid was obtained. This compound is known.[38] R_f = 0.33

(hexanes/dichloromethane 80/20). ^{1}H NMR (400 MHz, $CDCl_3$) δ7.80 – 7.78 (m, 1H), 7.64 – 7.61 (m, 1H), 7.59 – 7.56 (m, 1H), 7.41 (dt, *J* = 7.8 Hz, 1.3 Hz, 1H), 7.35 – 7.25 (m, 13H), 7.08 (ddd, *J* = 7.8 Hz, 3.7 Hz, 1.0 Hz, 1H), 7.00 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 142.8 (d, *J* = 6.6 Hz), 140.5, 140.4 (d, *J* = 27 Hz), 139.9, 137.7 (d, *J* = 12 Hz), 137.3 (d, *J* = 16 Hz), 134.6, 134.1, 133.9, 131.4 (d, *J* = 4.3 Hz), 128.8, 128.7, 128.6 (d, *J* = 35 Hz), 128.5, 125.2 (d, *J* = 5.8 Hz), 124.3 (d, *J* = 4.8 Hz), 123.8, 122.1.



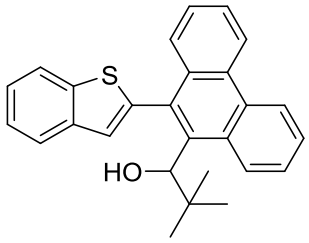
2-[2-(Phenylthio)phenyl]benzothiophene (Table 3.3.5, Entry 8)

Benzothiophene (34 mg, 0.25 mmol), phenyl triflate (112 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), Et_2O (1.5 mL), THF (0.05 mL), -75 °C, 12 hours. Diphenylsulfide (1.5 mmol) in Et_2O/THF (4/1; 0.7 mL) was slowly added via syringe. After column chromatography (hexanes/dichloromethane 90/10), 63 mg (80 %) of yellow solid was obtained. R_f = 0.36 (hexanes/dichloromethane 85/15). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.85 (m, 1H), 7.83 – 7.81 (m, 1H), 7.59 (dd, *J* = 7.2 Hz, 1.8 Hz, 1H), 7.51 (s, 1H), 7.41 – 7.25 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 141.7, 140.5, 140.0, 136.4, 135.1, 135.0, 132.4, 131.5, 131.4, 129.5, 129.0, 127.7, 126.8, 124.6, 124.5, 124.4, 123.9, 122.2.



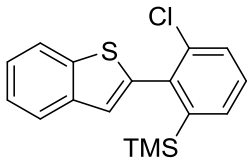
2-[2-Iodo-3-(1-methylethyl)phenyl]benzothiophene (Table 3.3.6, Entry 1)

Benzothiophene (34 mg, 0.25 mmol), 2-bromocumene (100 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), Et_2O (2.0 mL), THF (0.2 mL), - 45 °C, 36 hours. I_2 (1.5 mmol) in Et_2O/THF (4/1; 0.7 mL) was slowly added via syringe. After column chromatography (hexanes), 66 mg (70 %) of light brown oil was obtained. R_f = 0.30 (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.80 (m, 2H), 7.41 – 7.25 (m, 6H), 3.42 (heptet, *J* = 6.9 Hz, 1H), 1.29 (d, *J* = 6. 9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 151.9, 147.5, 140.8, 140.3, 139.7, 129.2, 128.0, 126.0, 124.5, 124.4, 124.3, 123.9, 122.2, 107.2, 39.4, 23.4.



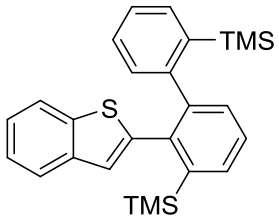
1-[9-(10-Benzothio-2-yl)phenathrenyl]-2,2-dimethylpropanol (Table 3.3.6, Entry 2)

Benzothiophene (0.25 mmol), 9-bromophenathrene (256 mg, 1.0 mmol), TMPLi (250 mg, 1.75 mmol), Et_2O (2.0 mL), THF (0.2 mL), - 35 °C, 24 hours. Pivaldehyde (1.5 mmol) in Et_2O (0.5 mL) was slowly added via syringe. After column chromatography (hexanes/dichloromethane 60/40), 64 mg (65 %) of yellow solid was obtained. R_f = 0.36 (hexanes/dichloromethane 50/50). ^{1}H NMR (400 MHz, $CDCl_3$, 50 ^{o}C) δ 9.20 (d, *J* = 6.8 Hz, 1H), 8.73 (t, *J* = 7.8 Hz, 2H), 8.0 – 7.8 (m, 2H), 7.70 – 7.55 (m, 4H), 7.48 – 7.38 (m, 4H), 5.4 (s, 1H), 2.3 (s, 1H), 0.99 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm, 50 ^{o}C) δ 141.8, 140.6, 140.1, 136.8, 131.7, 131.5, 131.0, 130.9, 130.7, 130.3, 128.2, 127.9, 127.4, 127.0, 126.9, 125.4, 124.7, 124.6, 123.7, 122.5, 122.4, 122.2, 81.9, 37.8, 29.0.



2-[2-Chloro-6-(trimethylsilyl)phenyl]benzothiophene (Table 3.3.6, Entry 3)

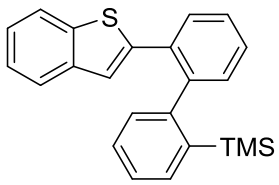
o-Trimethylsilylphenyl triflate (89 mg, 0.3 mmol), benzothiophene (34 mg, 0.25 mmol), TMPLi (150 mg, 1.0 mmol), diethyl ether (2.0 mL), THF (0.05 mL), -75 °C, 24 hours. CCl_4 (193 mg, 1.25 mmol) in Et_2O/THF (4/1; 0.7 mL) was slowly added via syringe. After column chromatography (hexanes/dichloromethane 97/3), 56 mg (71 %) of colorless oil was obtained. R_f = 0.34 (hexanes/dichloromethane 95/5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.5 Hz, 1H), 7.82 (d, *J* = 7.5 Hz, 1H), 7.56 (dd, *J* = 8.0 Hz, 1.8 Hz, 1H), 7.50 – 7.48 (m, 2H), 7.40 – 7.29 (m, 3H), 0.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 141.2, 140.7, 140.4, 140.0, 139.6, 135.7, 133.6, 133.3, 126.3, 124.6, 124.5, 124.4, 123.9, 122.2, -0.4.



2-{2-(Trimethylsilyl)-6-[(2-(trimethylsilyl)phenyl]phenyl}benzothiophene (Table 3.3.6, Entry 4)

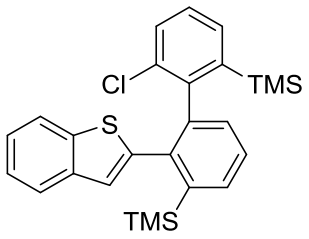
o-Trimethylsilylphenyl triflate (180 mg, 0.6 mmol), benzothiophene (34 mg, 0.25 mmol), TMPLi (150 mg, 1.0 mmol), diethyl ether (2.0 mL), THF (0.05 mL), -75 °C, 12 hours. After column chromatography (hexanes), 91 mg (85 %) of white solid was obtained. R_f = 0.36 (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.67 (m, 3H), 7.56 (d, J = Hz, 1H),

7.48 – 7.43 (m, 3H), 7.27 – 7.17 (m, 4H), 6.78 (s, 1H), 0.21 (s, 9H), 0.02 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 147.8, 144.1, 140.9, 140.5, 140.4, 139.9, 139.4, 136.1, 134.7, 134.0, 132.3, 131.3, 131.1, 127.1, 126.9, 124.0, 123.8, 123.7, 123.4, 121.9, 0.7, -1.1.



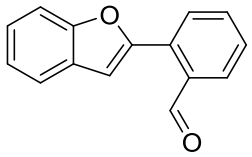
2-{2-[2-(Trimethylsilyl)phenyl]phenyl}benzothiophene (Table 3.3.6, Entry 5)

Benzothiophene (34 mg, 0.25 mmol), phenyl triflate (172 mg, 0.75 mmol), TMPLi (185 mg, 1.25 mmol), Et_2O (1.5 mL), THF (0.05 mL), -75 °C, 12 hours. TMSCl (1.25 mmol) in Et_2O (0.5 mL) was slowly added via syringe. After column chromatography (hexanes), 62 mg (70 %) of colorless oil was obtained. R_f = 0.34 (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.8 Hz, 1H), 7.68 – 7.63 (m, 2H), 7.58 – 7.55 (m, 1H), 7.44 (dt, *J* = 7.5 Hz, 1.4 Hz, 1H), 7.36 (tt, *J* = 7.5 Hz, 1.4 Hz, 2H), 7.29 (dd, *J* = 7.5 Hz, 1.4 Hz, 2H), 7.27 – 7.18 (m, 2H), 7.14 – 7.12 (m, 1H), 6.86 (s, 1H), 0.01 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 147.3, 143.7, 142.4, 140.2, 139.9, 139.4, 135.0, 133.4, 131.7, 130.4, 129.7, 128.6, 128.0, 127.3, 126.8, 124.1, 124.0, 123.6, 123.3, 121.9, 0.3.



2-{2-[2-(Trimethylsilyl)phenyl]-6-[2-chloro-6-(trimethylsilyl)phenyl]phenyl} benzothiophene (Table 3.3.6, Entry 6)

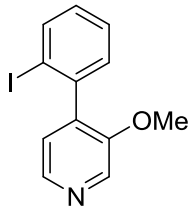
o-Trimethylsilylphenyl triflate (180 mg, 0.6 mmol), benzothiophene (34 mg, 0.25 mmol), TMPLi (150 mg, 1.0 mmol), diethyl ether (2.0 mL), THF (0.05 mL), -75 °C, 12 hours. CCl_4 (193 mg, 1.25 mmol) in Et_2O/THF (4/1; 0.7 mL) was slowly added via syringe. After column chromatography (hexanes), 87 mg (76 %) of white solid was obtained. R_f = 0.33 (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.65 (m, 3H), 7.56 (dd, *J* = 7.0 Hz, 1.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.41 (dd, *J* = 7.0 Hz, 2.0 Hz, 1H), 7.27 – 7.18 (m, 4H), 6.89 (s, 1H), 0.31 (s, 9H), 0.01 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 144.7, 143.3, 141.9, 140.3, 140.4, 140.2, 139.9, 139.2, 135.3, 134.8, 133.9, 133.5, 131.3, 127.3, 125.6, 124.0, 123.8, 123.4, 123.1, 121.8, 0.3, -0.7.



2-(2-Benzofuranyl)benzaldehyde (Table 3.3.6, Entry 7)

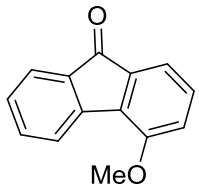
Benzoxazole (30 mg, 0.25 mmol), phenyl triflate (112 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), Et_2O (1.5 mL), THF (0.05 mL), -75 °C, 12 hours. DMF (1.5 mmol) in Et_2O (0.5 mL) was slowly added via syringe. After column chromatography (hexanes/Et_2O 90/10), 39 mg (71 %) of colorless oil was obtained. This compound is known.[39] R_f = 0.38 (hexanes/EtOAc 95/5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.48 (s, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.70 – 7.64 (m, 2H), 7.57 – 7.51 (m, 2H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.29 (t, *J* = 7.3 Hz, 1H), 6.98 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ

192.2, 155.6, 153.0, 134.0, 133.7, 133.2, 129.3, 129.1, 128.7, 128.3, 125.3, 123.5, 121.5, 111.6, 108.0.



3-Methoxy-4-(2-iodophenyl)pyridine (Table 3.3.6, Entry 8)

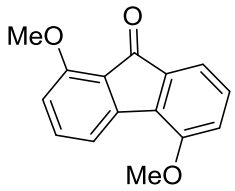
3-Methoxypyridine (28 mg, 0.25 mmol), chlorobenzene (57 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), Et_2O (2.0 mL), THF (0.2 mL), - 45 °C, 24 hours. I_2 (1.5 mmol) in Et_2O/THF (4/1; 0.7 mL) was slowly added via syringe. After column chromatography (hexanes/Et_2O 60/40), 49 mg (64 %) of light brown liquid was obtained. R_f = 0.36 (hexanes/EtOAc 70/30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 – 8.33 (m, 2H), 7.93 (dd, *J* = 7.8 Hz, 1.0 Hz, 1H), 7.41 (dt, *J* = 7.8 Hz, 1.0 Hz, 1H), 7.20 (dd, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.10 – 7.05 (m, 2H), 3.88 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 152.5, 142.7, 141.5, 140.3, 139.2, 134.3, 130.0, 129.6, 128.2, 125.0, 98.6, 56.3.



4-Methoxy-9-fluorenone (Table 3.3.6, Entry 9)

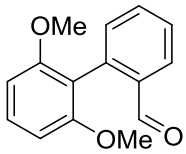
3-Methoxybenzonitrile (34 mg, 0.25 mmol), chlorobenzene (57 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), Et_2O (1.0 mL), THF (1.0 mL), - 50 °C, 36 hours. After column chromatography (hexanes/EtOAc 80/20), 40 mg (78 %) of white solid was obtained. This compound is known.[40] R_f = 0.41 (hexanes/EtOAc 70/30). ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.79 (d, *J* = 7.8 Hz, 1H), 7.61 (dd, *J* = 7.4 Hz, 1.0 Hz, 1H), 7.43 (dt, *J* = 7.8 Hz, 1.3 Hz, 1H), 7.28 – 7.18 (m, 2H), 7.02 (dd, *J* = 7.8 Hz, 1.3 Hz, 1H), 3.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 194.4, 155.5, 143.9, 135.8, 134.9, 133.6, 131.3, 130.5, 128.1, 124.4, 124.0, 117.9, 116.6, 55.7.



1,5-Dimethoxy-9-fluorenone (Table 3.3.6, Entry 10)

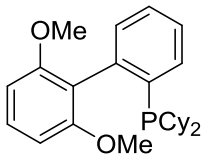
3-Methoxybenzonitrile (34 mg, 0.25 mmol), 2-chloroanisole (107 mg, 0.75 mmol), TMPLi (185 mg, 1.25 mmol), THF (1.8 mL), -50 °C, 24 hours. After column chromatography (hexanes/EtOAc 70/30), 43 mg (72 %) of white solid was obtained. This compound is known.[41] R_f = 0.35 (hexanes/EtOAc 70/30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.38 (m, 2H), 7.28 – 7.21 (m, 2H), 7.00 (d, *J* = 7.7 Hz, 1H), 6.77 (d, *J* = 8.3 Hz, 1H), 3.97 – 3.95 (two overlapped singlets, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 192.3, 158.1, 155.4, 145.9, 137.0, 136.3, 130.6, 129.9, 119.4, 117.3, 117.1, 116.3, 112.3, 55.9, 55.7.



2',6'-Dimethoxy-1,1'-Biphenyl-2-carboxaldehyde (Table 3.3.6, Entry 11)

1,3-Dimethoxybenzene (35 mg, 0.25 mmol), chlorobenzene (57 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), Et_2O (1.5 mL), THF (0.2 mL), - 45 °C, 24 hours. DMF (1.5 mmol)

in Et_2O (0.5 mL) was slowly added via syringe. After column chromatography (hexanes/Et_2O 70/30), 44 mg (74 %) of colorless oil was obtained. This compound is known.[42] R_f = 0.34 (hexanes/EtOAc 80/20). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 8.01 (d, *J* = 7.8 Hz, 1H), 7.63 (dt, *J* = 7.5 Hz, 1.4 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.38 – 7.34 (m, 2H), 6.67 (d, *J* = 8.3 Hz, 2H), 3.71 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 193.1, 157.8, 138.2, 134.4, 133.5, 132.5, 130.1, 127.7, 126.6, 114.6, 104.0, 55.9.



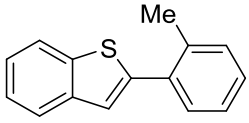
Dicyclohexyl[2',6'-dimethoxy(1,1'-biphenyl)-2-yl]phosphine (Scheme 3.3.6)

A 50 mL oven-dried flask equipped with a magnetic stirring bar was placed inside the glovebox. To the flask was added solid TMPLi (2.7 g, 18 mmol). The sealed vial was taken out of the glovebox and placed into cooling bath at - 45 °C. Anhydrous Et_2O (30 mL) was added via syringe and mixture was stirred for 15 minutes. 1,3-Dimethoxybenzene (690 mg, 5.0 mmol) was added via syringe followed by chlorobenzene (1.13 g, 10.0 mmol). To this mixture, THF (3.0 mL) was added and reaction was stirred for 24 hours at - 45 °C. Cooling bath was used to cool reaction mixture to - 75 °C. Chlorodicyclohexylphosphine (2.35 g, 10 mmol) from a feshly opened bottle was added dropwise via syringe in 10 minutes. Reaction was stirred for another 3 hours before slowly warming up to room temperature over a period of 3 hours and stirring for additional 1 hour at room temperature. The reaction mixture was filtered through the degassed plug of Celite® under Ar, eluting with EtOAc (100 mL). The

resulting mixture was evaporated under reduced pressure. The residue was recrystallized under nitrogen from acetone to give 1.3 g of pure product (65 %) as white solid. This compound is known.[43] ^{1}H NMR (400 MHz, C_6D_6) δ 7.57 (d, *J* = 7.3 Hz, 1H), 7.43 – 7.39 (m, 1H), 7.24 – 7.13 (m, 3H), 6.41 (d, *J* = 8.5 Hz, 2H), 3.32 (s, 6H), 1.91 – 1.60 (m, 12H), 1.38 – 1.00 (m, 10 H). ^{31}P NMR (161 MHz, C_6D_6) δ: 8.7.

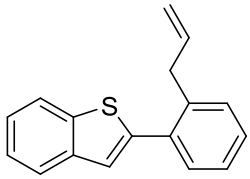
Transmetallation and cross coupling reactions

General procedure: Outside the glovebox a 2-dram vial was equipped with a magnetic stirring bar. The vial was placed inside the glovebox. To the vial was added solid TMPLi (0.8 – 1.5 mmol). The sealed vial was taken out of the glovebox and placed into oil bath/ cooling bath at reaction temperature. Reaction solvent (1.0 mL) was added via syringe to reaction vial. Following that, heterocycle or arene (0.25 mmol) and chloroarene (0.5 – 1.0 mmol) or aryl triflate (0.5 – 1.0 mmol) were dissolved in reaction solvent (1.0 mL) and added via syringe at reaction temperature. Reactions were run for indicated time. CuCN.2LiCl solution in THF (0.95 – 1.10 M, 0.3 mL) was slowly added to vial. Reactions were stirred for additional 30 minutes at -75 °C followed by slow addition of electrophiles or injection of oxygen at -75 °C. THF (1 mL) was added in some cases. Subsequently, reaction was allowed to warm up to room temperature over the period of 3 hours.



2-(2-Methylphenyl)benzothiophene (Table 3.3.7, Entry 1)

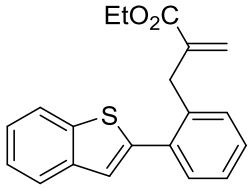
Benzothiophene (34 mg, 0.25 mmol), phenyl triflate (114 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), Et_2O (1.5 mL), THF (0.05 mL), -75 °C, 12 hours. CuCN.2LiCl (0.95 – 1.10 M, 0.3 mL) was added. Reactions were stirred for additional 30 minutes at -75 °C. MeI (1.5 mmol) was dissolved in Et_2O (0.5 mL) and added to reaction mixture via syringe. After column chromatography (hexanes), 47 mg (85 %) of white solid was obtained. This compound is known.[44] R_f = 0.31 (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 7.5 Hz, 1H), 7.52 (d, *J* = 7.0 Hz, 1H), 7.42 – 7.28 (m, 6H), 2.51 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 143.6, 140.3, 140.2, 136.6, 134.3, 130.9, 130.8, 128.5, 126.1, 124.5, 124.2, 123.6, 123.2, 122.2, 21.2.



2-[(2-propen-1-yl)phenyl]benzothiophene (Table 3.3.7, Entry 2)

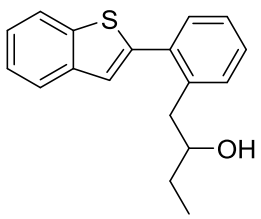
Benzothiophene (34 mg, 0.25 mmol), phenyl triflate (114 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), Et_2O (1.5 mL), THF (0.05 mL), -75 °C, 12 hours. CuCN.2LiCl (0.95 – 1.10 M, 0.3 mL) was added. Reactions were stirred for additional 30 minutes at -75 °C. Allyl bromide (1.25 mmol) was dissolved in Et_2O (0.5 mL) and added to reaction mixture via syringe. After column chromatography (hexanes/dichloromethane 97/3), 46 mg (74 %) of colorless oil was obtained. R_f = 0.20 (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.9 Hz, 1H), 7.80 (d, *J* = 7.9 Hz, 1H), 7.49 (dd, *J* = 7.7 Hz, 1.0 Hz, 1H), 7.41 – 7.28 (m, 5H), 7.27 (s, 1H), 6.05 – 5.96 (m, 1H), 5.10 (qd, *J* = 9.7 Hz, 1.7 Hz, 1H), 5.00

(qd, *J* = 16.7 Hz, 1.7 Hz, 1H), 3.57 (td, *J* = 6.3 Hz, 1.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 143.0, 140.3, 140.2, 138.5, 137.7, 134.2, 131.2, 130.3, 128.7, 126.4, 124.5, 124.2, 123.6, 123.3, 122.1, 116.3, 37.8.



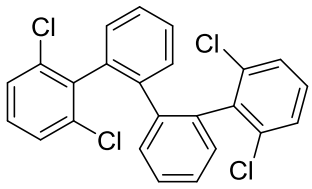
2-(2-Benzothionyl)-α-methylene ethylbenzenepropanoate (Table 3.3.7, Entry 3)

Benzothiophene (34 mg, 0.25 mmol), phenyl triflate (114 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), Et_2O (1.5 mL), THF (0.05 mL), -75 °C, 12 hours. CuCN.2LiCl (0.95 – 1.10 M, 0.3 mL) was added. Reactions were stirred for additional 30 minutes at -75 °C. Ethyl-2-(methylenbromide) acrylate (1.25 mmol) was dissolved in Et_2O (0.5 mL) and added to reaction mixture via syringe. After column chromatography (hexanes/dichloromehane 70/30), 54 mg (68 %) of colorless oil was obtained. R_f = 0.25 (hexanes/dichloromethane 70/30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.5 Hz, 1H), 7.78 (d, *J* = 7.0 Hz, 1H), 7.50 (dd, *J* = 7.5 Hz, 1.4 Hz, 1H), 7.39 – 7.27 (m, 5H), 7.23 (s, 1H), 6.28 (d, *J* = 1.5 Hz, 1H), 6.26 (d, *J* = 1.5 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 2H), 1.23 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 167.0, 142.8, 140.5, 140.3, 140.2, 137.2, 134.7, 131.4, 130.6, 128.7, 126.8, 126.7, 124.5, 124.2, 123.7, 123.2, 122.1, 60.9, 35.7, 14.3.



2-(2-Benzothionyl)-α-ethyl benzeneethanol (Table 3.3.7, Entry 4)

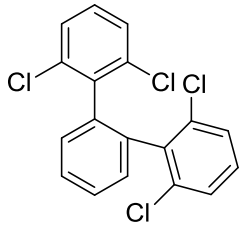
Benzothiophene (34 mg, 0.25 mmol), phenyl triflate (114 mg, 0.5 mmol), TMPLi (150 mg, 1.0 mmol), Et_2O (1.5 mL), THF (0.05 mL), -75 °C, 12 hours. CuCN.2LiCl (0.95 – 1.10 M, 0.3 mL) was added. Reactions were stirred for additional 30 minutes at -75 °C. 2-Ethyloxirane (1.25 mmol) was dissolved in Et_2O (0.5 mL) and added to reaction mixture via syringe. After column chromatography (hexanes/EtOAc 90/10), 52 mg (75 %) of white solid was obtained. R_f = 0.32 (hexanes/EtOAc 90/10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 7.4 Hz, 1H), 7.41 – 7.28 (m, 5H), 7.27 (s, 1H), 3.72 (heptet, *J* = 4.3 Hz, 1H), 3.06 (dd, *J* = 14.2 Hz, 4.3 Hz, 1H), 2.86 (dd, *J* = 14.2 Hz, 8.8 Hz, 1H), 1.60 – 1.41 (m, 3H), 0.87 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 143.1, 140.4, 140.1, 137.7, 134.8, 131.6, 130.7, 128.7, 126.6, 124.5, 124.3, 123.7, 122.1, 73.8, 41.0, 29.9, 10.1. Signal for one carbon could not be located.



2, 2''',6,6'''-Tetrachloro- 1,1':2',1'':2'',1'''-quaterphenyl (Table 3.3.7, Entry 5)

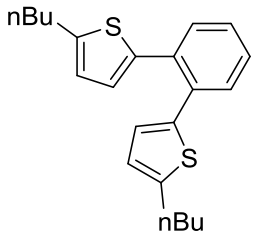
1,3-Dichlorobenzene (0.25 mmol), phenyl triflate (0.5 mmol), TMPLi (150 mg, 1.0 mmol), Et_2O (1.5 mL), THF (0.05 mL), - 75 °C, 12 hours. CuCN.LiCl (0.95 – 1.10 M, 0.3 mL) was added followed by addition of THF (0.75 mL) at -75 °C. Reaction was stirred at -75 °C for 2 hours before O_2 was introduced via syringe and needle. Mixture was warmed up to room temperature over the period of 5 hours and stirred overnight.

After column chromatography (hexanes/dichloromethane 90/10), 59 mg (54 %) of white solid was obtained. R_f = 0.33 (hexanes/dichloromethane 90/10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, *J* = 7.8 Hz, 1.4 Hz, 2H), 7.43 (dt, *J* = 7.8 Hz, 1.4 Hz, 2H), 7.34 (dd, *J* = 7.4 Hz, 1.4 Hz, 2H), 7.16 – 7.13 (m, 4H), 7.09 – 7.07 (m, 2H), 7.01 (dd, *J* = 7.8 Hz, 1.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 141.0, 138.5, 135.8, 135.3, 134.2, 131.1, 129.4, 128.3, 127.8, 127.0.



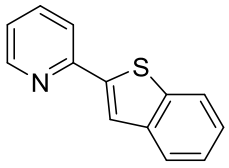
2,2'',6,6''-Tetrachloro- 1,1':2',1''-terphenyl (Table 3.3.7, Entry 6)

1,3-Dichlorobenzene (147 mg, 1.0 mmol), phenyl triflate (0.25 mmol), TMPLi (215 mg, 1.5 mmol), Et_2O (1.5 mL), THF (0.05 mL), -75 °C, 24 hours. CuCN.LiCl (0.95 – 1.10 M, 0.3 mL) was added followed by addition of THF (0.75 mL) at -75 °C. Reaction was stirred at -75 °C for 1 hour before O_2 was introduced via syringe and needle. Mixture was warmed up to RT over the period of 5 hours and stirred overnight. After column chromatography (hexanes/dichloromethane 90/10), 43 mg (48 %) of white solid was obtained. R_f = 0.27 (hexanes/dichloromethane 90/10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.51 (m, 2H), 7.44 – 7.41 (m, 2H), 7.26 – 7.21 (m, 4H), 7.10 (d, *J* = 7.3 Hz, 1H), 7.08 (d, *J* = 7.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 137.6, 136.1, 136.0, 132.2, 129.0, 128.2, 128.1.



2,2'-(1,2-Phenylene) bis(5,5-butylthiophene) (Table 3.3.7, Entry 7)

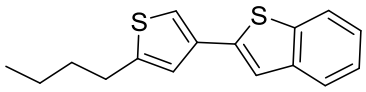
2-Butylthiophene (0.5 mmol), chlorobenzene (0.5 mmol), TMPLi (150 mg, 1.0 mmol), Et_2O (1.5 mL), THF (0.2 mL), - 45 °C, 24 hours. Reaction was cooled down to -75 °C. CuCN.LiCl (0.95 – 1.10 M, 0.3 mL) was added followed by addition of THF (0.75 mL) at -75 °C. Reaction was stirred at -75 °C for 1 hour before O_2 was introduced via syringe and needle. Mixture was warmed up to RT over the period of 5 hours and stirred overnight. After column chromatography (hexanes), 34 mg (39 %) of white solid was obtained. R_f = 0.28 (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.45 (m, 2H), 7.31 – 7.29 (m, 2H), 6.71 (d, *J* = 3.5 Hz, 2H), 6.63 (d, *J* = Hz, 2H), 2.77 (t, *J* = 7.5 Hz, 4H), 1.63 (quintet, *J* = 7.6 Hz, 4H), 1.38 (quintet, *J* = 7.6 Hz, 4H), 0.91 (t, *J* = 7.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 146.7, 140.3, 134.1, 130.9, 127.6, 126.7, 123.9, 33.9, 29.9, 22.2, 13.9.



2-Benzothien-2-ylpyridine (Scheme 3.3.7)

Benzothiophene (34 mg, 0.25 mmol), 2-bromopyridine (158 mg, 1.0 mmol), TMPLi (215 mg, 1.5 mmol), Et_2O (1.5 mL), - 5 °C, 24 hours. After column chromatography (hexanes/Et_2O 60/40), 27 mg (52 %) of light brown oil was obtained. This compound is

known.[45] R_f = 0.24 (hexanes/EtOAc 80/20). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 – 8.62 (m, 1H), 7.88 – 7.79 (m, 4H), 7.73 (dt, *J* = 7.8 Hz, 1.8 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.23 – 7.19 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 152.6, 149.8, 144.9, 140.7, 140.5, 136.7, 125.2, 124.6, 124.2, 122.7, 122.6, 121.2, 119.7.



2-(5-Butyl-3-thienyl)benzothiophene (Scheme 3.3.7)

Benzothiophene (34 mg, 0.25 mmol), 2-butylthiophenyl triflate (288 mg, 1.0 mmol), TMPLi (215 mg, 1.5 mmol), Et_2O (1.5 mL), - 65 °C, 24 hours. After column chromatography (hexanes), 23 mg (35 %) of colorless oil was obtained. R_f = 0.31 (hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 7.1 Hz, 1H), 7.37 (s, 1H), 7.36 – 7.26 (m, 3H), 7.11 – 7.09 (m, 1H), 2.85 (t, *J* = 7.5 Hz, 2H), 1.70 (quintet, *J* = 7.5 Hz, 2H), 1.44 (sextet, *J* = 7.5 Hz, 2H), 0.97 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 147.2, 140.6, 139.5, 139.0, 135.2, 124.6, 124.2, 123.4, 123.2, 122.3, 119.1, 119.0, 33.8, 29.9, 22.3, 14.0.

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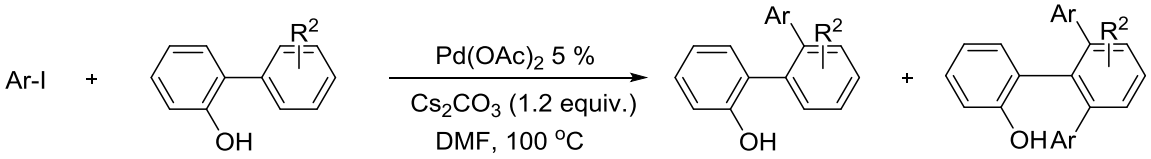
Chapter 3-4. *ortho*-Arylation of Phenols and Anilines via Benzyne Intermediates

3.4.1. Transition-metal-catalyzed *C*-Arylation of Phenols and Anilines

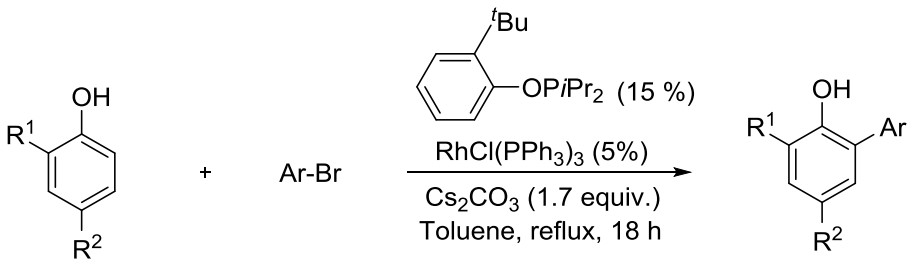
The first transition-metal-catalyzed *ortho*-arylation of phenol derivatives was reported by Miura.[1] Under palladium catalysis, 2-phenylphenols and naphthols were mono- and diarylated regioselectively with aryl halides in good yields. In mechanistic studies, coordination of the phenolic oxygen to the palladium center was considered to be the key for the regioselective C-H bond activation.

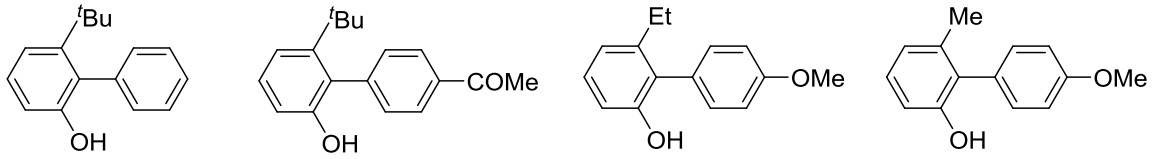
Scheme 3.4.1. Miura's *ortho*-arylation of phenol derivatives



A method for rhodium-catalyzed arylation of 2-substituted phenols has been described by Bedford group.[2] The authors employed 5 % $RhCl(PPh_3)_3$, Cs_2CO_3 base, and 15 % of a bulky phosphinite cocatalyst. The reduction in catalytic activity with decreasing steric bulk at phenol 2- position implies that the rate-determining step is likely the *ortho*-metalation of the phosphinite ligand. No activity was observed with unsubstituted phenol.

Scheme 3.4.2. *ortho*-Arylation of 2-substituted phenols

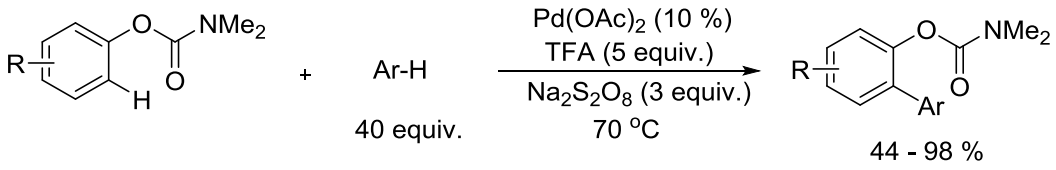




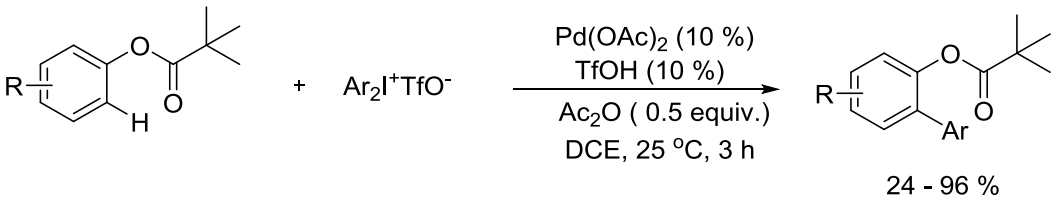
Recently, Dong has shown that phenols possessing ester and carbamate directing groups can be arylated under palladium catalysis by simple arenes.[3] Reactions were run under acidic conditions with large excess of arenes and inexpensive sodium persulfate was used as an oxidant. Excellent reaction efficiencies and regioselectivities were observed with a range of electron-rich, electron-neutral, and electron-deficient arenes. Cyclopalladation, electrophilic metalation, and Pd(0/II) catalytic cycle were proposed to account for the reaction mechanism. A similar transformation using high valent arylidonium salts as arylating reagents was reported by Liu.[4]

Scheme 3.4.3. *C*-Arylation of phenol esters and carbamates

Dong



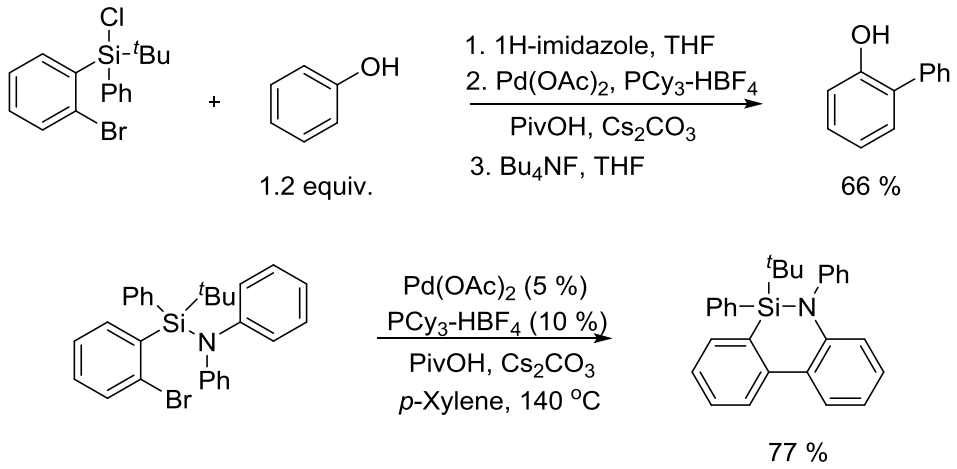
Liu



Gevorgyan has shown that selective phenol and aniline derivative *ortho*-arylation is possible by employing a silicon-based tether that can be subsequently removed.[5] In

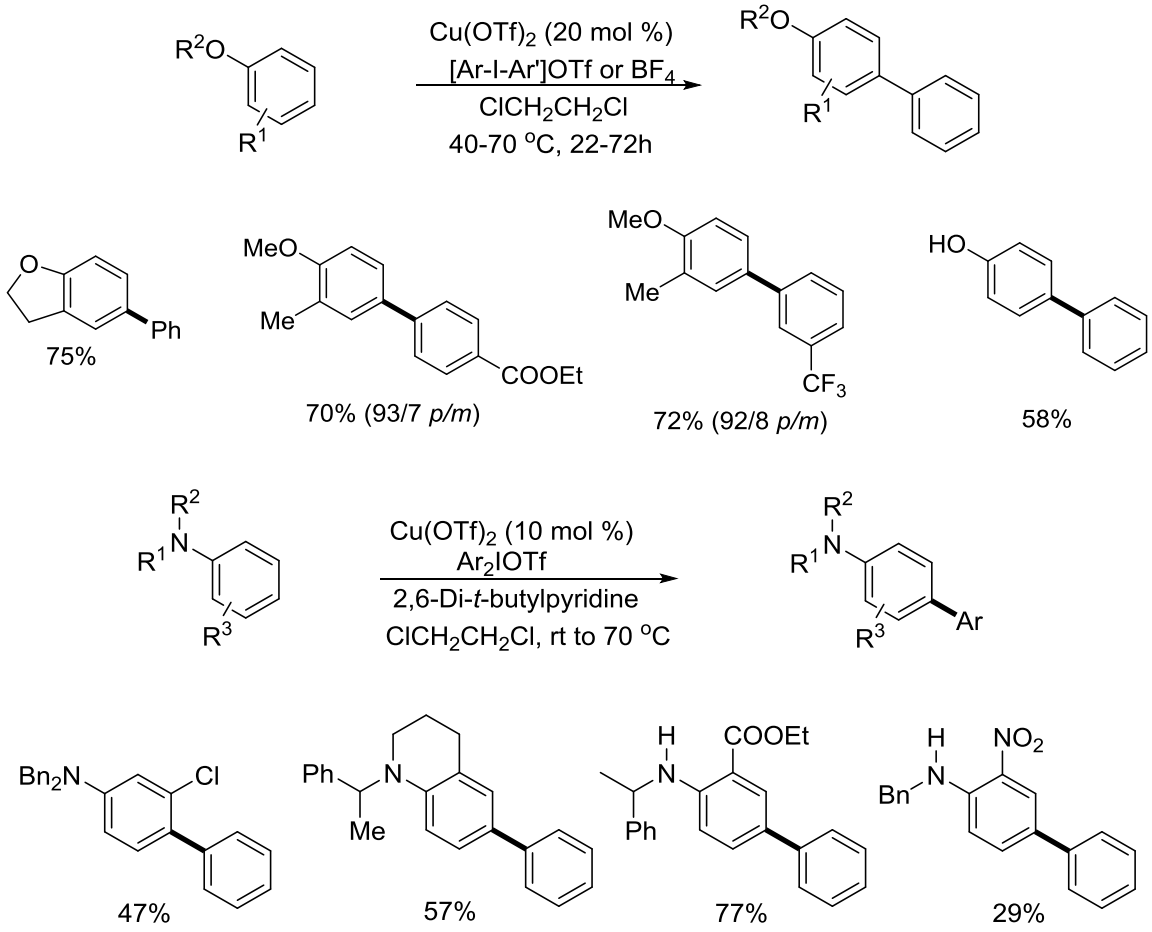
particular, the TBDPS protecting group serves as a convenient aryl group donor for *o*-bromophenols via an intramolecular arylation/deprotection sequence. Furthermore, employment of the newly designed Br-TBDPS protecting group in the same sequence allows for the facile introduction of a phenyl group at the *ortho* position of phenols and anilines.

Scheme 3.4.4. Phenol and aniline *ortho*-arylation with silicon-base tether directing groups



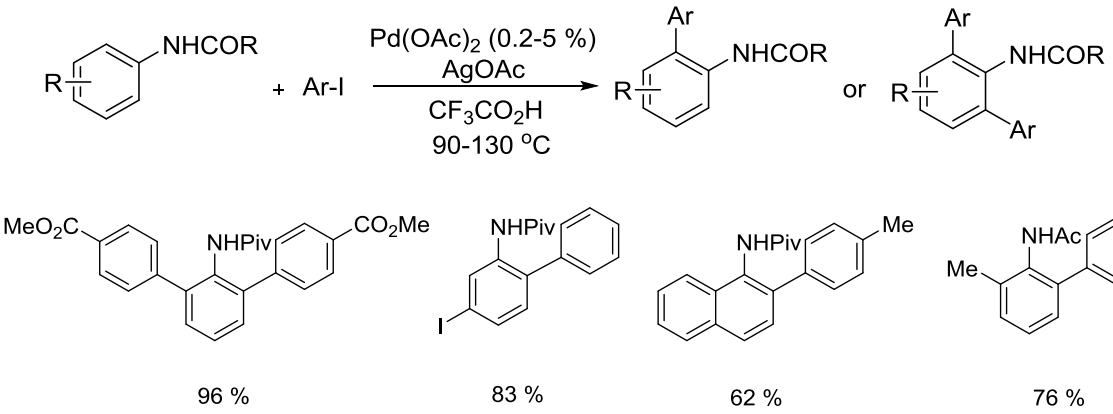
The Gaunt group has recently reported a direct arylation of phenol derivatives with exclusive *para*-selectivity.[6] Blocking the *para* position results in *ortho*-arylation. Interestingly, phenol is a suitable substrate offering a direct access to arylated phenols. To increase the generality of this protocol, authors turned their attention to aniline derivatives. In the presence of 2,6-di-*t*-butylpyridine various mono- and dialkyl-protected anilines could be arylated in good yields. Although the mechanism is still not clearly elucidated, the authors suggested that Friedel-Crafts-type arylation could be operative in their arylation process.

Scheme 3.4.5. Copper-catalyzed *para*-arylation of phenols and anilines



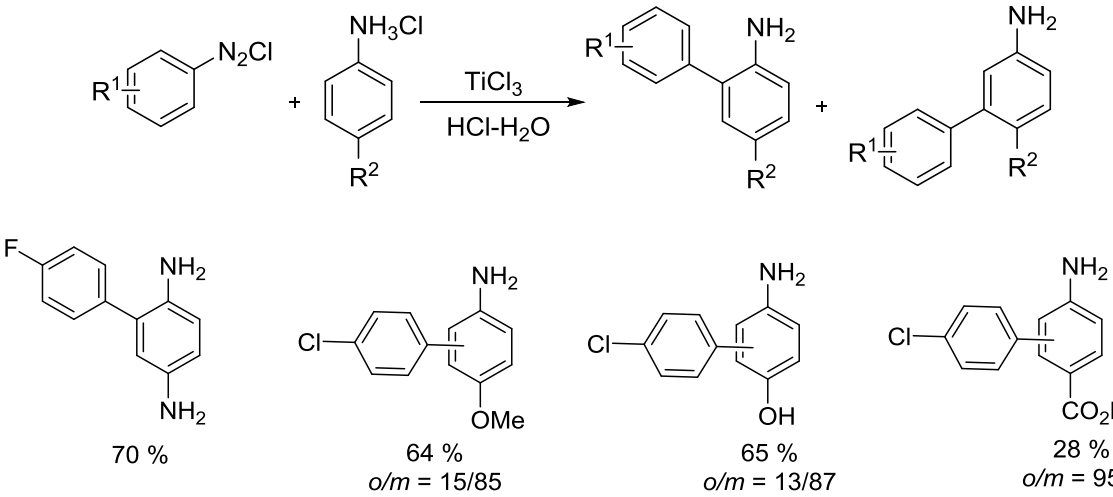
Our group has developed a method for *ortho*-arylation of anilides.[7] The procedure involves the combination of silver acetate, aryl iodides, and palladium catalyst under acidic conditions. Generally, the pivaloyl derivatives gave the cleanest reactions; however, acetamides are also compatible with the reaction conditions. The reaction is highly tolerant with respect to substituents on the anilide and aryl iodides.

Scheme 3.4.6. Palladium-catalyzed *ortho*-arylation of anilides



Direct arylation of anilines possessing no protecting or directing groups has also been disclosed. The synthesis of aminobiaryls by radical chain reaction of arenediazonium salts with anilines was reported by Heinrich group.[8] The method employed $TiCl_3$ as promoter in aqueous HCl solution and electron-rich anilines were shown to be best suited precursors. However, isomer mixtures were obtained in many cases.

Scheme 3.4.7. Ti-catalyzed C-arylation of unprotected anilines



3.4.2. Transition-metal-free *ortho*-Arylation of Anilines

3.4.2.1. Introduction

Functionalized aminoarenes are an important class of molecules because of their broad applications in new medicines, materials, and catalysis.[9] The last few years have witnessed spectacular progress in developing aniline derivative C-H bond functionalization.[10] Transition-metal-catalyzed arylation of aniline derivatives is of particular interest. The Buchwald-Hartwig amination is known to be applicable for *N*-arylation of anilines.[11a] Formation of *N*-arylated anilines has been described under copper catalysis.[11b] An immediate obstacle to aniline C-H bond arylation is related to competition between *N*- and *C*-arylation. Thus, protected anilines have been frequently used in their C-H functionalization. Palladium-catalyzed *ortho*-arylation of anilides offers a short pathway to 2-aminobiphenyls or terphenyls.[7] A method for intramolecular palladium-catalyzed arylation of anilines by employing a temporary silyl tether has been recently developed.[5] However, several extra steps to install and remove directing groups are added into the synthetic sequences. In addition, selective transition-metal-free *para*-arylation of *N*-substituted anilines by employing diaryliodonium salt electrophiles has been recently reported.[6] Moreover, a method for Ti-catalyzed arylation of free anilines affording aminobiphenyls by diazonium salts has been demonstrated.[8] However, isomer mixtures were obtained in many cases.

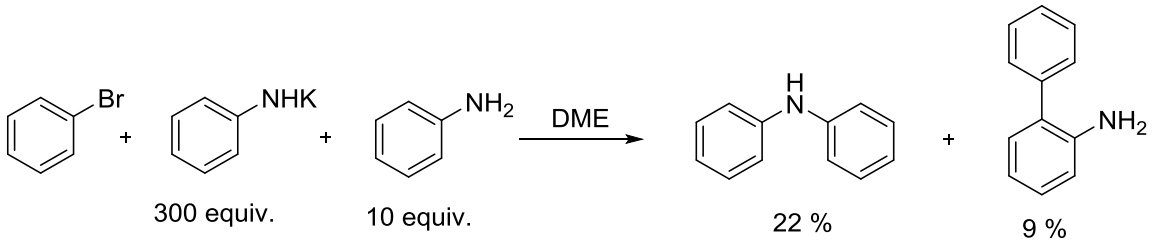
Arynes are well known to react with anilines forming *N*-arylation products.[9] By introducing a bulky trityl group substituent on the nitrogen atom, a direct *ortho*-arylation of anilines via benzyne has been described.[12] An ene mechanism was suggested.

However, acceptable yields could not be achieved for *N*- and *o*-substituted anilines. Therefore, a method for selective, direct *o*-arylation of unprotected anilines has not been yet disclosed.

3.4.2.2. Results and Discussion

Haberfield observed that *o*-phenylaniline side product was formed when benzyne was generated in the presence of anilide.[13] Interestingly, *C/N* arylation ratio increased when an excess of aniline was present in the reaction mixture and 2-aminobiphenyl could be obtained in up to 9 % yield.

Scheme 3.4.8. Formation of *o*-phenylaniline

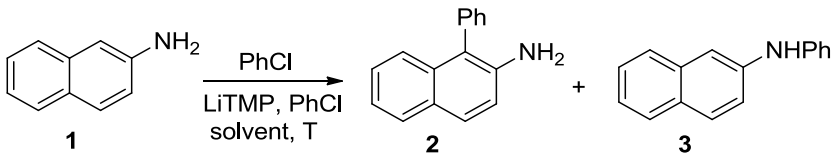


We have recently reported direct *C*-arylation of heterocycles, arenes, and alkynes proceeding via benzyne intermediates.[14] The amount of *C*-arylation and the ratio of *C*- *vs.* *N*-arylation were observed to be dependent on the solvent. To expand the utility of this methodology, we decided to investigate aniline *o*-arylation. To increase the applicability of the arylation, readily accessible and cheap aryl chlorides were used as as aryne sources.

The optimization of reaction conditions was carried out for 2-naphthylamine **1** arylation by chlorobenzene using lithium 2,2,6,6-tetramethylpiperidide (LiTMP) base (Table 3.4.1). Solvent, base, and **1**/base ratio were found to have impact on the ratio of *C*-

arylation vs. *N*-arylation. In THF, *N*-arylation product was formed predominantly and only minor amounts of *C*-arylation product was observed (entries 1-2). Arylation in Et_2O afforded *N*-substitution (entry 3). If LDA was used instead of LiTMP, clean formation of *N*-phenyl-2-naphtylamine was observed (entry 4). Good *C*-arylation selectivity in diethyl ether was obtained when the reaction was run at -20 °C (entry 5). Reactions in pentane at 40 °C gave substantial amount of *C*-arylation (entries 6-7). However, competitive formation of PhTMP was observed. Use of pentane/Et_2O mixtures increased the *C*/*N*-arylation ratio (entries 8-10). The optimal results were obtained in cyclohexane/diethyl ether mixed solvent at 25-50 °C (entries 11, 13, and 14) by using excess **1**. Sensitive substrates can be arylated at low temperatures in diethyl ether.

Table 3.4.1. Optimization of Reaction Conditions[a]



Entry	**1**/PhCl/base	Temp, °C	solvent	**2**/**3**
1	1/2/3.6	25 °C	THF	1/8 (10)
2	2/1/3.6	25 °C	THF	1/3 (12)
3	1/2/3.6	25 °C	Et_2O	1/5 (16)
4[b]	1/2/3.6	25 °C	Et_2O	1/50(<2)
5	2/1/3.6	-20 °C	Et_2O	11/1(27)
6	1/2/3.6	40 °C	C_5H_{12}	1/2(29)
7	2/1/3.6	40 °C	C_5H_{12}	2/1(35)
8	1/2/3.6	25 °C	C_5H_{12}/Et_2O 20:1	1.3/1(43)
9	2/1/3.6	25 °C	C_5H_{12}/Et_2O 20:1	12/1(27)
10	2/1/3.6	25 °C	C_5H_{12}/Et_2O 1:1	9/1(64)
11	2/1/3.6	25 °C	C_6H_{12}/Et_2O 1:1	18/1(74)

12	1/2/3.6	25 °C	C_5H_{12}/Et_2O 1:1	1/2.2(25)
13	3/1/4.8	50 °C	C_5H_{12}/Et_2O 14:1	50/1(78)
14	3/1/4.8	50 °C	C_5H_{12}/Et_2O 1:1	5/1(50)

[a] Total volume of solvent 0.9 mL, 0.25 mmol scale, 24 h; 12 h for entry 5. [b] LDA base.

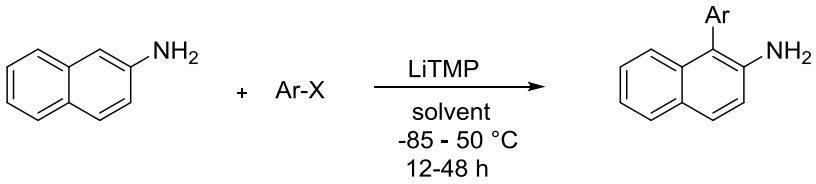
The reaction scope with respect to aryl halides is presented in Table 3.4.2. Fluoro-, chloro-, and bromobenzene can be used in the arylation of 2-naphthylamine (entries 1-3). Interestingly, the arylation of 2-naphthylamine occurs selectively at 1-position. Arylation by 2-chlorostyrene affords the product in a good yield (entry 4). As expected, substitution occurs mainly at 3-position of the phenyl group, with less than 3% of 1-(2-vinylphenyl)-2-naphthylamine formed. 2-Naphthylamine is *ortho*-arylated by 2-chloroanisole, 2-chlorobenzotrifluoride, and 2-bromobiphenyl and the corresponding arylation products were obtained in good yields (entries 5, 6, and 7). Polycyclic aromatic chlorides are active (entries 8 and 9). Arylation product was obtained in moderate yield when 2-chlorodimethylaniline was employed (entry 10). At low temperature, arylation by 3-chlorophenyl triflate is feasible and chloride group is tolerated (entry 11). Arylation by 3-bromobenzoate ester results in substitution at 2-position of aryne, presumably by initial formation of 2-naphthylamide of 3-bromobenzoic acid (entry 12). As anticipated, 4-chlorotoluene gave nearly equal mixture of isomeric products (entry 13).

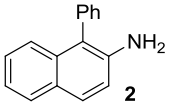
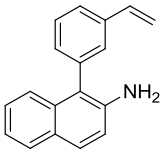
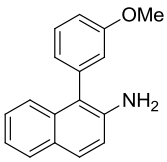
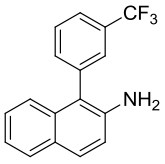
The 2-naphthylamine arylation occurs selectively at the 1-position. In that context, observations by Pierini and Rossi may be informative.[15] They have reported the photostimulated reaction of unactivated aryl bromides and iodides with 2-naphthylamide. Substitution occurred at *N*- and 1-positions of 2-naphthylamine. The authors explain the

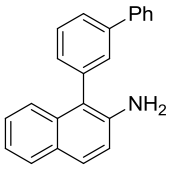
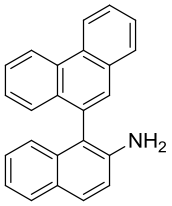
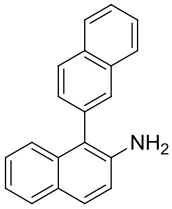
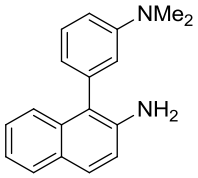
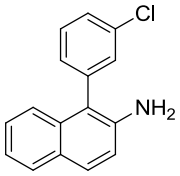
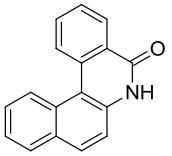
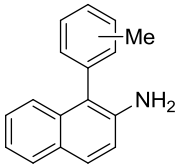
arylation selectivity by the relative basicities of sites in an ambident naphthylamide anion.

Lower *C*-/*N*-arylation product ratios were obtained with substrates containing groups that can coordinate lithium. In order to obtain better yields and arylation selectivities, low temperatures are required. For example, presence of the dimethylamino substituent reduces C/N arylation selectivity from >50/1 (entry 2, Table 3.4.2) to about 11/1 (entry 10, Table 3.4.2) even if temperature is lowered to -30 °C.

Table 3.4.2. Arylation of 2-Naphthylamine[a]



Entry	ArX	Product	Yield, %
1[b]	PhF	 **2**	68
2[b]	PhCl	**2**	72
3[b]	PhBr	**2**	70
4[c]	2-chlorostyrene		70
5[c]	2-chloroanisole		67
6[c]	2-chlorobenzo-trifluoride		65

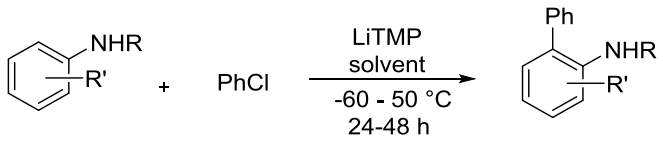
7[d]	2-bromobiphenyl		70
8[d]	9-chloro-phenanthrene		71
9[e]	2-chloro-naphthalene		82
10[f]	2-chloro-*N*,*N*-di-methylaniline		61
11[g]	3-chlorophenyl triflate		50
12[h]	*t*-butyl-3-bromo-benzoate		70
13[d]	4-chlorotoluene		78

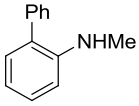
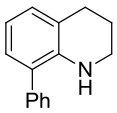
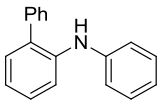
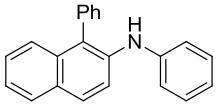
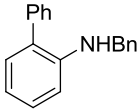
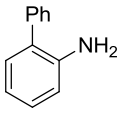
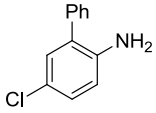
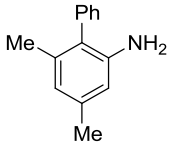
[a] 2-Naphthylamine (1-2 mmol), ArX (0.5 mmol), LiTMP (1.8-3.4 mmol), solvent (1.4-3 mL), -85 to 50 °C, 12-48 h. Yields are isolated yields. [b] Cyclohexane/Et_2O (14/1), 25 °C, <5% *N*-arylation product observed in crude reaction mixture. [c] Et_2O, -25 °C, *ca.* 10% *N*-arylation. [d] Cyclohexane/Et_2O (14/1), 50 °C, <10 % *N*-arylation. [e] Cyclohexane/Et_2O (1/1), 25 °C, <5% *N*-

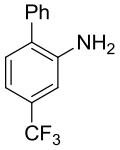
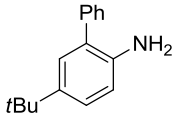
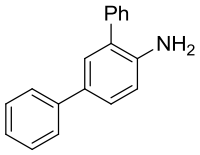
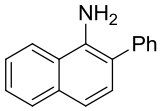
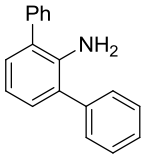
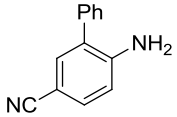
arylation. [f] Et_2O, -30 °C, 8 % *N*-arylation. [g] THF,-85 °C, 7% *N*-arylation. [h] Cyclohexane/Et_2O (1/1), -35 °C, LDA base.

The reaction scope with respect to anilines is presented in Table 3.4.3. Arylations of *N*-alkyl- and- arylanilines are possible (entries 1-5). Specifically, anilines possessing *N*-methyl-, phenyl, and benzyl substituents all give products in good to excellent yields (entries 1, 3, 5). Arylation of 1,2,3,4-tetrahydroisoquinoline occurs at 7-position and product was obtained in good yield (entry 2). Selective and efficient monoarylation of unsubstituted anilines (entries 6-14) can be achieved. Thus, aniline can be *ortho*-phenylated in a moderate yield (entry 6). 3-Aminobenzotrifluoride is arylated giving about 3/1 mixture of isomers. 2-Phenyl-5-trifluoromethylaniline was isolated in 50% yield (entry 9). 3,5-Dimethylaniline is arylated in *ortho*-position in a good yield (entry 8). Anilides that possess 3- substituents are not efficiently *ortho*-arylated under palladium catalysis and thus product in entry 8 typically cannot be accessed by using transition-metal catalysis. 4-Substituted anilines are arylated in good yields (entries 7, 10 and 11). Arylation of 1-naphthylamine occurs at 2-position (entry 12). 2-Aminobiphenyl can be arylated at 6-position affording 2,6-diphenylaniline (entry 13). 2,6-Diarylanilines are used in the synthesis of ligands for Brookhart-type transition-metal catalyzed olefin polymerization.[16] The reaction tolerates chloro- and cyano substituents (entries 7 and 14). Arylation of enantiopure binaphthyldiamine afforded the monoarylation product in 47% yield and >99% ee (Scheme 3.4.9).

Table 3.4.3. Arylamine Phenylation[a]

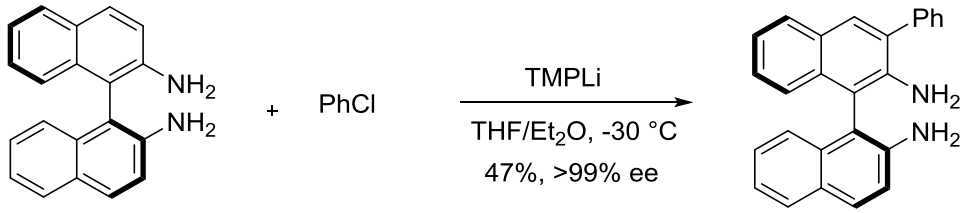


Entry	Amine	Product	Yield, %
1[b]	PhNHMe		62
2[b]	1,2,3,4-tetra-hydroquinoline		70
3[b]	diphenylamine		78
4[b]	*N*-phenyl-2-naphthylamine		80
5[c]	*N*-benzylamine		70
6[d]	aniline		55
7[e]	*p*-chloroaniline		60
8[d]	3,5-dimethylaniline		70

9[d,f]	3-aminobenzotri-fluoride		50
10[d]	4-*t*-butylaniline		60
11[d]	4-aminobiphenyl		67
12[b]	1-naphthylamine		85
13[d]	2-aminobiphenyl		70
14[g]	4-cyanoaniline		65

[a] Amine (1-2 mmol), PhCl (0.5 mmol), LiTMP (1.8-3.4 mmol), solvent (1.4-3 mL), -60-50 °C, 24-48 h. Yields are isolated yields. Please see Experimetal Section for *C/N* ratios. [b] Cyclohexane/Et_2O (1/1), 25 °C. [c] Pentane/THF (36/1), 25 °C. [d] Cyclohexane/Et_2O (14/1), 50 °C. [e] Pentane/Et_2O (1/1), -50 °C, PhOTf. [f] Isomeric 2-phenyl-3-trifluoromethylaniline also isolated (17%). [g] THF/Et_2O (1:1), -60 °C.

Scheme 3.4.9. *o*-Phenylation of enantiopure binaphthyldiamine



The reaction is selective (>50/1) for *ortho*-arylation as opposed to *para*-arylation. For entries 1, 6, and 13, Table 3.4.3, the crude reaction mixtures were analyzed by GC for the presence of *p*-phenyl derivatives (comparison with authentic commercial samples). No products arising from *p*-arylation were observed.

The amount of *N*- vs. *C*-arylation is dependent on solvent coordination ability, aniline/LiTMP base ratio, and reaction temperature. These features point to different reactivities of intermediate lithium anilide/LiTMP aggregates as the reason for switch in arylation regioselectivity. Due to complexity of lithium anilide solution state structures and insolubility of LiCl additive in reaction mixture further mechanistic speculations are premature at this point.[17]

3.4.2.3. Conclusions

A method for direct, transition-metal-free *ortho*-arylation of anilines by aryl chlorides, bromides, and fluorides has been developed. This methodology provides the most direct approach to 2-arylanilines since no protecting or directing groups on nitrogen are required. Easily available aryl chlorides can be used as the coupling partners. The arylation is functional-group tolerant, with alkene, ether, trifluoromethyl, dimethylamino, carbonyl, chloro, and cyano functionalities tolerated.

3.4.3. Reactions of Arynes with Phenols: Formation of 2-Arylphenols and Helicenes

3.4.3.1. Introduction

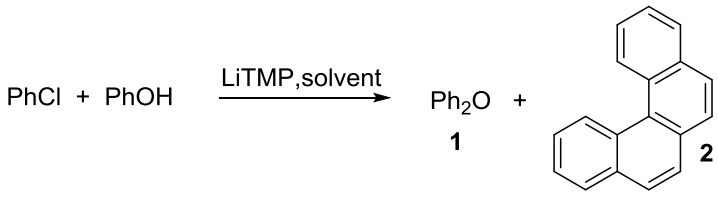
2-Arylphenols are substructures of organocatalysts, phosphite ligands, and biologically active substances.[18] The traditional methods for synthesis of these structures involve cross-coupling of an organometallic reagent with an aryl halide or pseudohalide.[19] However, the requirement of protection of phenols adds extra steps to the synthetic sequences. Recent developments using C-H bond functionalization methodology provide shorter synthetic routes to 2-arylphenols.[1-6] Miura reported a method for palladium-catalyzed *ortho*-arylations of 2-phenylphenol.[1] However, in many cases, formation of a mixture of mono- and di-arylation products was obtained. Subsequently, a method for rhodium-catalyzed arylation of 2-substituted phenols was developed by Bedford group.[2] Additionally, phenols possessing ester and carbamate directing groups can be arylated under palladium catalysis by aryl halides or simple arenes.[3,4] A procedure for selective phenol derivative *ortho*-arylation has been recently demonstrated by employing a silicon-based tether.[5] Direct arylation of phenol derivatives with exclusive *para*-selectivity is possible by using diaryliodonium salts.[6] Direct *ortho*-arylation of unprotected phenols by aryl chlorides has not yet been disclosed.

3.4.3.2. Results and Disscussion

It is well known that *O*-arylation is preferentially observed in the reaction of benzynes with phenol.[20] Minor amounts of *C*-arylation products may accompany diaryl ethers.[21] We have recently reported direct *C*-arylation of heterocycles, arenes, and anilines proceeding via benzyne intermediates.[14] The amount of *C*-arylation and the ratio

of *C- vs.* heteroatom arylation were observed to be dependent on the solvent and base. Thus, we decided to investigate phenol *o*-arylation. Arynes can be generated from silyl aryl triflates under nearly neutral conditions at room temperature.[22] These starting materials are expensive and only a few of them are commercially available. Consequently, we used readily accessible and cheap aryl chlorides as aryne sources. Two different reaction conditions were examined for phenol arylation. The first set of conditions employs lithium 2,2,6,6-tetramethylpiperidide (LiTMP) base. The second set of conditions involves an alkalimetal alkoxide base in dioxane. These conditions are based on our earlier reports for heterocycle arylation and intramolecular phenol arylation, respectively.[23]

Table 3.4.4. Optimization of Reaction Conditions[a]



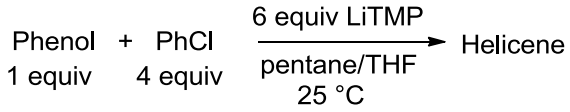
entry	PhOH/PhCl/LiTMP	solvent	**1/2**/conv.
1	1/2/3.6	THF	4/1/32%
2	1/2/3.6	Et_2O	3/1/21%
3[b]	1/2/3.6	C_5H_{12}	1/7/35%
4	1/2/3.6	C_5H_{12}/THF 20:1	1/40/52%
5	1/2/3.6	C_5H_{12}/THF 50:1	1/50/65%
6	1/4/6	C_5H_{12}/THF 50:1	1/50/80%

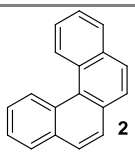
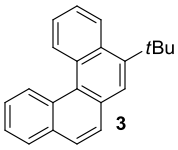
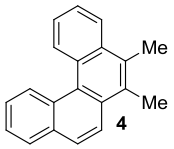
[a] Volume of solvent 1 mL, 0.25 mmol scale, 24 h, 25 °C. Conversion by GC analysis. [b] At 40 °C.

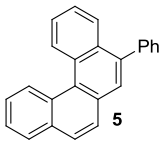
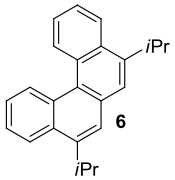
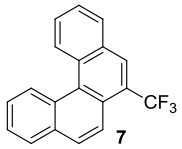
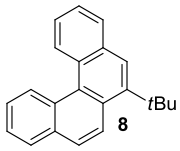
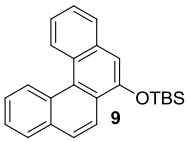
Diphenyl ether together with a hydrocarbon in 4/1 ratio were obtained when phenol was reacted with chlorobenzene in presence of TMPLi solution in THF (Table

3.4.1, entry 1). The hydrocarbon product was shown to be benzo[c]phenanthrene (tetrahelicene). Helicenes have been used in asymmetric catalysis, as molecular machines for molecular recognition, and in materials science.[24] Their syntheses require several steps.[25] Therefore, formation of helicenes from simple, commercially available starting materials via one-step reaction would make these interesting structures more available. For example, 1,12-disubstituted helicene has been prepared in seven steps by employing Friedel-Crafts acylation.[24] Consequently, we decided to optimize the helicene formation and investigate the reaction mechanism. As shown in Table 3.4.4, increase of phenol/chlorobenzene ratio to 1/4 and use of mixed pentane/THF solvent resulted in 80% conversion to tetrahelicene (entry 6).

Table 3.4.5. Helicene Synthesis[a]



entry	phenol	helicene	yield, %
1	PhOH	 **2**	67
2	2-*t*Bu-phenol	 *t*Bu **3**	48
3	2,3-di-Me-phenol	 Me Me **4**	58

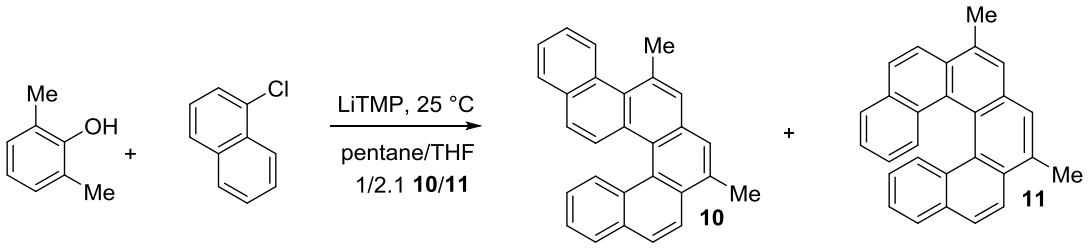
4	2-Ph-phenol		65
5	2,6-di-*i*Pr-phenol		40
6	3-CF_3-phenol		40
7	3-*t*Bu-phenol		51
8	3-TBSO-phenol		52

[a] Scale: 0.5 mmol. Yields are isolated yields

Examples of helicene synthesis are presented in Table 3.4.5. Reaction of phenol with chlorobenzene affords a 67% isolated yield of tetrahelicene (entry 1). 5-*t*-Butyltetrahelicene is obtained in 48% yield from 2-*t*-butylphenol and chlorobenzene (entry 2). If 2,3-dimethylphenol is used as starting material, 5,6-dimethyltetrahelicene is produced in 58% yield (entry 3). Reaction of 2-phenylphenol affords 5-phenyltetrahelicene in 65% yield (entry 4). Helicene synthesis from hindered 2,6-diisopropylphenol is possible and 5,8-diisopropyltetrahelicene was formed in 40% yield (entry 5). 6-Trifluoromethyltetrahelicene can be obtained in 40% yield (entry 6). 3-*t*-Butylphenol can be converted to 6-*t*-butyltetrahelicene in 51% yield (entry 7). A TBS-

protected resorcinol afforded the product in a good yield (entry 8). Formation of two isomeric hydrocarbons in 2.1/1 ratio and 60% yield was obtained when 2,6-dimethylphenol reacted with 1-chloronaphthalene. The major product was hexahelicene **11** that could be isolated in 26% yield by fractional crystallization of the isomer mixture (Scheme 3.4.10).

Scheme 3.4.10. Hexahelicene synthesis

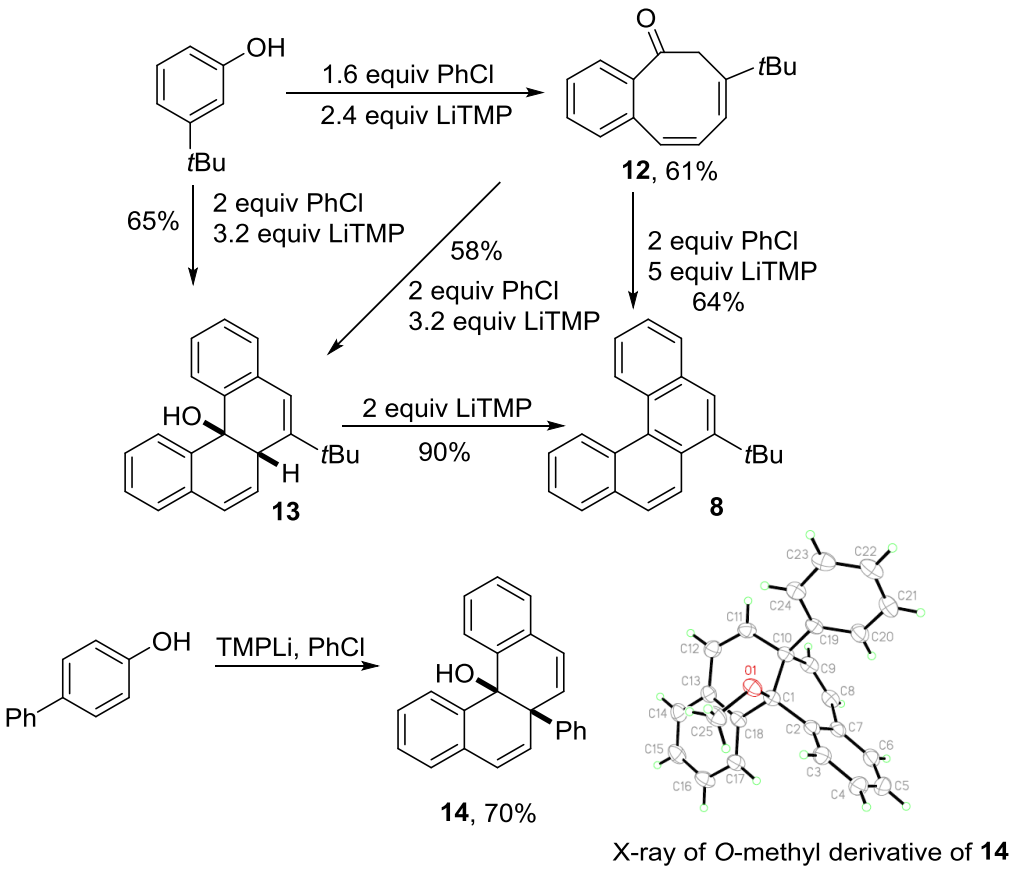


60% combined; 26% pure **11**

Analysis of the reaction products shows that two molecules of aryl chloride with one molecule of phenol are required for helicene formation. Reaction of 3-*t*-butylphenol with chlorobenzene was carried out by changing reactant ratios (Scheme 3.4.11). Benzocyclooctadienone **12** was obtained in 61% yield if 1.6 equiv. of chlorobenzene was employed. Increasing amount chlorobenzene (3 equiv.) and LiTMP (4.2 equiv) led to the formation of compound **13** in 64% yield. Interestingly, compound **12** could be converted to **13** by reacting with 2 equiv of PhCl in the presence of 3.2 equiv LiTMP. *t*-Butyltetrahelicene **8** can be obtained from either **12** or **13** (Scheme 3.4.11). Direct reaction of 4 equiv chlorobenzene with 3-*t*-butylphenol in the presence of 6 equiv LiTMP affords **8** (entry 7, Table 3.4.5). In addition, the reaction of 4-hydroxybiphenyl with chlorobenzene afforded **14** which cannot easily aromatize by water elimination. These experiments show that **12** and **13** are competent intermediates *en route* to **8**. X-Ray

crystallographic analysis of *O*-methyl derivative of **14** showed that hydroxyl and phenyl groups are in cis arrangement.

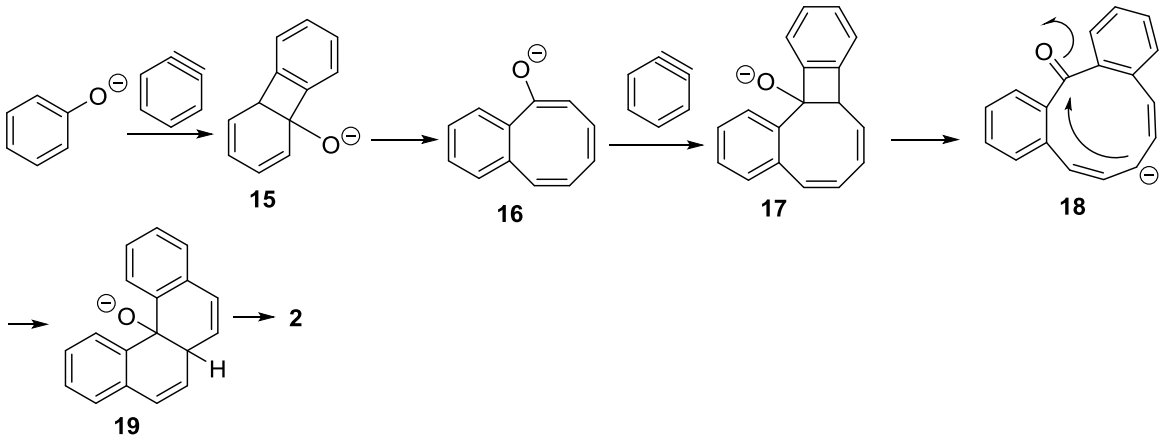
Scheme 3.4.11. Reaction intermediates



The following reaction mechanism is proposed (Scheme 3.4.12). Reaction of phenol with benzyne generated from chlorobenzene forms a benzocyclobutene **15**. Product of ring-opening **16** undergoes another reaction with benzyne to form **17**. Ten-membered ring ketone **18** is formed via subsequent opening of the strained four-membered ring in **17**. Intramolecular nucleophilic attack followed by dehydration affords tetrahelicene **2**. Intermediates related to **16** and **19** have been isolated and characterized

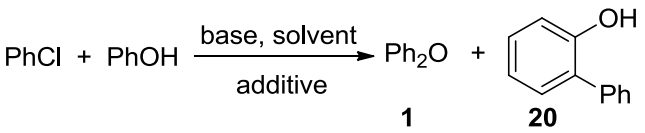
(**12** and **14**, Scheme 3.4.1). Benzene cycloaddition with benzyne producing a benzocyclobutane derivative that subsequently ring-opens to give benzocyclooctatetraene in low yield has been reported showing the viability of intermediates such as **15** and **17**.[26a]

Scheme 3.4.12. Reaction mechanism



As described above, *C*-arylated phenols could not be obtained if TMPLi was used. Minor amount of *C*-arylation product was obtained in dioxane by employing *t*BuONa base (Table 3.4.6). In enolate chemistry, the *C*- vs. *O*-functionalization ratios can be tuned by changing metal counterion.[26b] Brookhart reported a procedure where *C*-functionalization of hexafluoroacetylacetone can be achieved via its Ag salt.[26a] Thus, 0.5-1 equiv AgOAc was added to reaction mixture and good selectivity for *C*-arylation was observed. The optimized conditions include AgOAc additive, 155 °C, dioxane solvent, and NaO*t*Bu base.

Table 3.4.6. Optimization of Phenol Arylation[a]

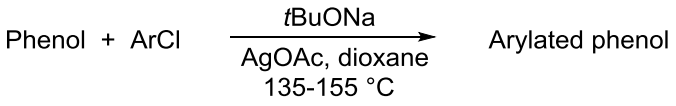


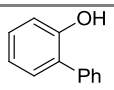
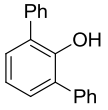
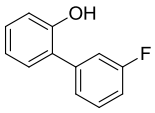
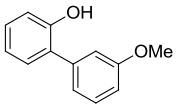
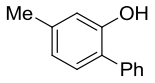
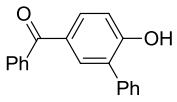
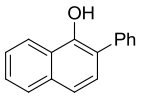
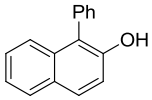
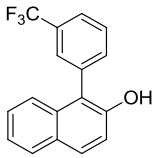
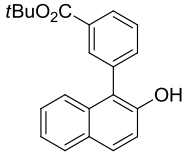
entry	PhCl/PhOH/base	solvent, T	**1**/**20**/conv
1	2/1/3.9/LiTMP	Et_2O, 25 °C	50/<1/32%
2	2/1/3.9/*t*BuOK	dioxane, 110 °C	9/1/91%
3	2/1/3.9/*t*BuONa	dioxane, 155 °C	7/1/87%
4[b]	2/1/3.9/*t*BuONa	dioxane, 155 °C	1/30/87%
5[c]	2/1/3.9/*t*BuONa	dioxane, 155 °C	1/15/65%

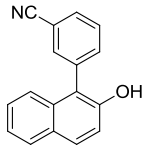
[a] Solvent (1 mL), 0.25 mmol scale, 24 h. Conversion by GC analysis.[b] Additive: 1 equiv AgOAc. [c] Additive: 0.1 equiv AgOAc.

The arylation scope is presented in Table 3.4.7. Mono- or diarylation can be selectively achieved by changing phenol/chlorobenzene ratio (entries 1 and 2). Introduction of 3-fluorophenyl substituent is possible (entry 3). 3-Methoxyphenylated derivative is generated in good yield by reaction of phenol with 2-chloroanisole (entry 4). Arylations of substituted phenols, such as 3-methylphenol (entry 5), 4-hydroxybenzophenone (entry 6), 1-naphthol (entry 7), and 2-naphthol (entry 8) afford products in good to excellent yields. The reaction is surprisingly functional group tolerant despite the use of strong *t*-butoxide base. Thus, fluoride (entry 3), ether (entry 4), ketone (entry 6), trifluoromethyl (entry 9), ester (entry 10), and cyano groups (entry 11) are tolerated. It is worth mentioning that arylation of 2-naphthol (entries 8-11) is possible in the absence of AgOAc.

Table 3.4.7. Phenol arylation[a]



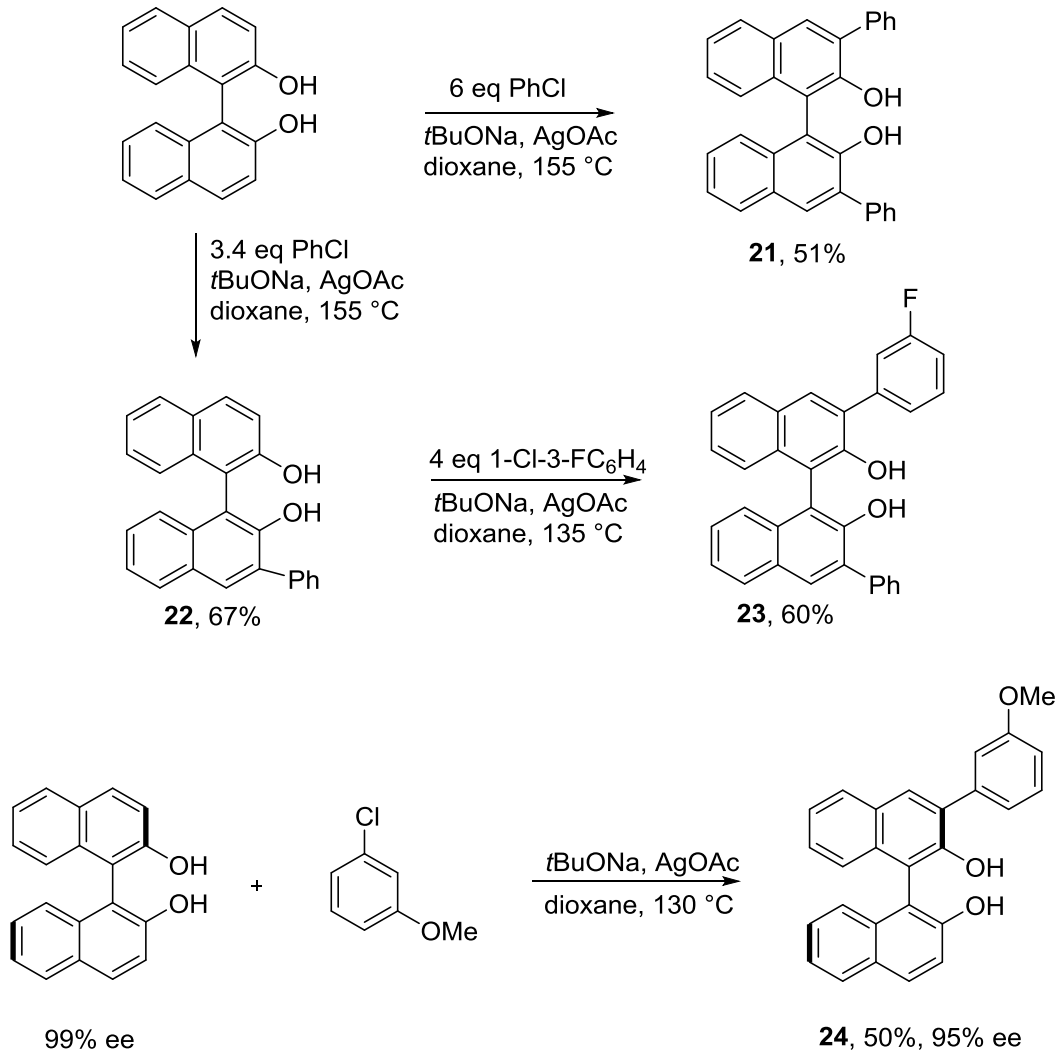
entry	phenol	ArCl	product	yield, %
1	phenol	PhCl		78
2	phenol	PhCl		60
3	phenol	1-Cl-3-FC_6H_4		72
4[b]	phenol	2-Cl-1-$MeOC_6H_4$		64
5	3-Me-phenol	PhCl		80
6	4-hydroxy-benzophenone	PhCl		58
7	1-naphthol	PhCl		82
8[c]	2-naphthol	PhCl		80
9[c]	2-naphthol	3-Cl-1-$CF_3C_6H_4$		74
10[c]	2-naphthol	3-Br-1-*t*$BuO_2CC_6H_4$		66

11[c]	2-naphthol	3-Cl-1-CNC_6H_4		65

[a] Scale: 0.5 mmol, 48-96 h, 0.5-2 equiv AgOAc, 1.6-5/1/3.6-8 ratio of ArCl/phenol/base. Yields are isolated yields. [b] Crude: 9/1 isomer mixture. Yield of pure major isomer. [c] No AgOAc additive.

Arylated binol functionality is found in organocatalysts.[18] The most common methods for synthesis of these structures require several steps from relatively expensive starting materials.[18] Direct *C*-arylation of binol is the shortest possible route to such compounds. In addition, the introduction of two different aryl groups into binol moiety is also feasible, thus allowing access to structurally diverse organocatalysts. Diarylation of binol can be performed if excess chlorobenzene is used and product **21** was formed in 51% yield (Scheme 3.4.13). A two-step synthesis of an unsymmetrical diarylbinol was also developed. Thus, binol was phenylated to afford 3-phenylbinol **22** in 67% yield. Subsequently, **22** was arylated by 1-chloro-3-fluorobenzene to afford 3,3'-diarylbinol **22** in 60% yield. Additionally, enantiopure (*R*)- binol was arylated with 3-chloroanisole affording product **24** in 50% yield and 95 % ee. This reaction shows the applicability of the method to the synthesis of enantioenriched organocatalysts.

Scheme 3.4.13. Direct *C*-arylation of binols



3.4.3.3. Conclusions

Two reactions of phenols with arynes were described. Helicene synthesis can be obtained by reaction of aryl chlorides with phenols in TMPLi base. If *t*BuONa base is used in dioxane at elevated temperature in the presence of AgOAc, selective *o*-arylation of phenols can be achieved. Direct *C*-arylation of binol, the shortest route to *o,o*'-

diarylbinols, is demonstrated. Enantiopure binol arylation is also performed without significant loss in enantiomeric excess.

3.4.4. Experimental Section

3.4.4.1. Transition-metal-free *ortho*-Arylation of Anilines

General considerations: All reactions were performed in 2-dram vials using screw caps with 17 mm holes and white silicone septum with white teflon face (from SUPELCO). Column chromatography was performed on 60Å silica gel (Sorbent Technologies). Purification by preparative HPLC was performed on a Shimadzu Prominence LC (LC-20AB) equipped with a SPD-20A UV-Vis detector and a Varian Dynamax (250 mm x 21.4 mm) column. GC-MS analyses were performed on a Shimadzu GCMS-QP5000 chromatograph equipped with a Restek column (Rtx-XLB, 30 m x 0.25 mm I.D.). The ^{1}H and ^{13}C NMR were recorded on JEOL EC-400 or JEOL EC-500 spectrometers using residual solvent peak as a reference. Elemental analyses were performed by Atlantic Microlab Inc. of Norcross, GA. IR spectra were obtained on a ThermoNicolet Avatar 370 FT-IR instrument. Analytical thin layer chromatography was performed on silica gel IB-F (Baker-flex) by J. T. Baker. Low temperature reactions were performed using Immersion Cooler FC100 with Flexi Probe from SP Scientific. All procedures were performed under nitrogen atmosphere unless otherwise noted.

Materials. The following starting materials were obtained from commercial sources and were used without further purification: 2-chloro-*N*,*N*-dimethylaniline, chlorobenzene, bromobenzene, fluorobenzene, 2-chlorobenzotrifluoride, 2-chloronaphthalene, 2-bromonaphthalene, 2-bromobiphenyl, 2-fluorobiphenyl, 4-chlorotoluene, 2,2,6,6-tetramethylpiperidine (TMPH), 9-chlorophenanthrene, 2-chlorostyrene, N-methylaniline, 1,2,3,4-tetrahydroquinoline, diphenylamine, N-phenyl-2-naphthylamine, N-benzylaniline,

aniline, 3,5-dimethylaniline, 4-*tert*-butylaniline, 4-aminobiphenyl, 2-aminobiphenyl, 1-naphthylamine, anhydrous cyclohexane, 2-chloroanisol, *tert*-butyl-3-bromobenzoate, 3-aminobenzotrifluoride, 3-chlorophenol, 4-chloroaniline, 4-aminobenzonitrile, 1,1'-bis(2-napthylamine) and 2-naphthylamine (**CAUTION: environmental carcinogen; induces bladder cancer**). All aryl triflates were synthesized according to literature.[27]

Attempted arylation of 2,6-dimethylaniline resulted in *N*-arylation product and no *C*-arylation product was observed by GC.

TMPLi: A 250 mL oven-dried flask equipped with a magnetic stirring bar and a septum was evacuated and backfilled with nitrogen 5 times. TMPH (15.5 g, 18.5 mL, 110 mmol) was added via syringe, followed by anhydrous pentane to give approximately 100 mL of solution. The mixture was cooled to -73 °C (dry ice-acetone bath) and stirred for 10 minutes. *n*-BuLi (2.5 M in hexanes, 40.0 mL, 100 mmol) was added dropwise and reaction mixture was stirred for 30 minutes at -73 °C, warmed up to room temperature (25 °C) and stirred overnight. The reaction mixture was vacuumed to remove all solvent and dried under vacuum for at least 5 hours. A light yellow powder of solid TMPLi was obtained.

TMPLi 1 M in pentane/hexanes: A 50 mL oven-dried flask equipped with a magnetic stirring bar and a septum was evacuated and backfilled with argon 5 times. TMPH (4.64 g, 33.0 mmol) was added, followed by anhydrous pentane to give 30 mL of solution (marked the flask at the level of solution). The mixture was cooled to -73 °C (dry ice-acetone) and stirred for 5 minutes. *n*-BuLi (2.5 M in hexanes, 12.0 mL, 30 mmol) was added dropwise and reaction mixture was stirred for 30 minutes at -73 °C, then warmed

up to room temperature and stirred overnight. The reaction mixture was vacuumed to give 30 mL (at the marked level) of TMPLi suspension.

General Procedures.

Reactions at room temperature (25 °C): Outside the glovebox a 2-dram vial was equipped with a magnetic stirring bar. The vial was placed inside the glovebox. To the vial was added solid TMPLi (1.8 – 3.5 mmol). The sealed vial was taken out of the glovebox, cyclohexane and diethyl ether were added via syringe and the reaction mixture became homogeneous. Following that, amine (1.0 – 2.0 mmol) and chloroarene (0.5 mmol) were added via syringe. Reactions were run at room temperature for 24 hours.

Reactions at 50 °C: Outside the glovebox a 2-dram vial was equipped with a magnetic stirring bar. The vial was placed inside the glovebox. To the vial was added solid TMPLi (1.8 – 3.5 mmol). The sealed vial was taken out the glovebox, cyclohexane and diethyl ether were added via syringe and the reaction mixture became homogeneous. If hydrocarbon solvents were used (Table 3.4.S1, entries 6-8), the reaction mixture became viscous. Following that, amine (1.0 – 2.0 mmol) and chloroarene (0.5 mmol) were added via syringe. Vial was then placed in preheated oil bath for indicated time.

Work-up procedure for reactions at room temperature and 50 °C:

The reaction mixture was cooled to room temperature (if necessary) and quenched by slow addition of anhydrous methanol (0.5 mL). The reaction mixture was evacuated to remove all solvent, residue was dissolved in minimal amount of ethyl acetate or dichloromethane and subjected to flash chromatography on silica gel in hexanes followed by appropriated solvent to elute the products. After concentrating the fractions containing

the product, the residue was dried under reduced pressure to yield pure product. If necessary, purification by preparative HPLC was performed.

Reactions at low temperature (from – 85 to 0 ^{o}C): Outside the glovebox a 2-dram vial was equipped with a magnetic stirring bar. The vial was placed inside the glovebox. To the vial was added solid TMPLi (1.8 – 3.5 mmol). The sealed vial was taken out of the glovebox and placed into cooling bath. Mixed solvents were cooled to reaction temperature and added via syringe to reaction vial. Following that, amine (0.5 – 2.0 mmol) and chloroarene (0.5 – 1.5 mmol) or aryl triflate (1.0 – 2.0 mmol) were added via syringe. Reactions were run at specified temperature for indicated time. Reactions were quenched with H_2O (2 mL) at low temperature, diluted with EtOAc (20 mL), washed with brine (30 mL). Aqueous layer was washed again with EtOAc (2 x 15 mL). Combined organic layer was dried over $MgSO_4$ and evacuated to 1 mL. Residue was subjected to flash chromatography in hexanes followed by appropriated solvent to elute the products. After concentrating the fractions containing the product, the residue was dried under reduced pressure to yield pure product. If necessary, purification by preparative HPLC was performed.

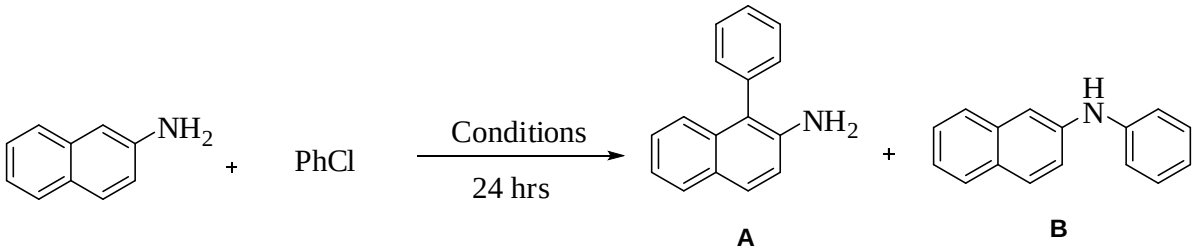
Note:

- In all procedures, the vial was charged with aniline and chloroarene outside the glovebox if these reagents are solid at room temperature unless otherwise stated.
- Strong stirring (higher than 1200 rpm) is necessary to get reproducible yields

Optimization of Conditions

Procedure: All reactions were carried out following the general procedure, but on 0.25 mmol scale. 2-Naphthylamine (x mmol), chlorobenzene (y mmol), TMPLi [1.2(x + y) mmol], solvents (0.9 mL total), 24 hours. Conversions and A/B ratio were calculated by GC analysis. Conversions are presented in Table 3.4.S1 and show the amount of product A and B formed (e.g. 70 % means that 70 % of starting limiting reagent is converted to A and B). Mixture with exact molar amounts of pure A and pure B was used as the standard to determine the ratio A/B.

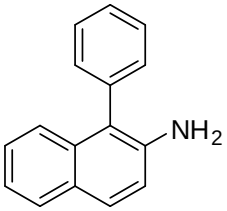
Table 3.4.S1. Optimization of Conditions



Entry	Amine/PhCl /TMPLi	Base/temperature	Solvents	Conversion (%)	Ratio A/B
1	1/2/3.6	TMPLi/ 25 ^{o}C	THF	97	1/8
2	2/1/3.6	TMPLi/ 25 ^{o}C	THF	43	1/3
3	1/2/3.6	TMPLi/ 25 ^{o}C	Ether	94	1/5
4	1/2/3.6	TMPLi/ - 46 ^{o}C	Ether (12 hours)	29	8/1
5	1/2/3.6	LDA/ 25 ^{o}C	Ether	83	1/50
6	1/2/3.6	TMPLi/ 40 ^{o}C	Pentane	70	1/2
7	1/4/6	TMPLi/ 40 ^{o}C	Pentane	55	1/5

8	2/1/3.6	TMPLi/ 40 ^{o}C	Pentane	62	2/1
9	1/2/3.6	TMPLi/ 25 ^{o}C	Pentane/THF (20/1)	95	1.5/1
10	1/2/3.6	TMPLi/ 25 ^{o}C	Pentane/ether (20/1)	92	1.3/1
11	2/1/3.6	TMPLi/ 25 ^{o}C	Pentane/ether (20/1)	35	12/1
12	2/1/3.6	TMPLi/ 25 ^{o}C	Pentane/ether (1/1)	85	9/1
13	**2/1/3.6**	**TMPLi/ 25 ^{o}C**	**Cyclohexane/ether (1/1)**	**94**	**18/1**
14	1/2/3.6	TMPLi/ 25 ^{o}C	Cyclohexane/ether (1/1)	96	1/2.2
15	2/1/7.2	TMPLi/ 25 ^{o}C	Cyclohexane/ether (1/1)	70	5/1
16	2/4/3.6	TMPLi/ 25 ^{o}C	Cyclohexane/ether (1/1)	50	20/1
17[a]	2/1/3.6	TMPLi/ 25 ^{o}C	Cyclohexane/ether (1/1)	97	15.5/ 1
18	**4/1/6**	**TMPLi/ 25 ^{o}C**	**Cyclohexane/ether (1/1)**	**99**	**40/1**
19	**3/1/4.8**	**TMPLi/ 50 ^{o}C**	**Cyclohexane/ether (14/1)**	**95**	**50/1**
20	3/1/4.8	TMPLi/ 50 ^{o}C	Cyclohexane/ether (1/1)	72	5/1
21	4/1/6	TMPLi/ 50 ^{o}C	Cyclohexane/ether (14/1)	96	>50/1

Reactions were run at 0.25 mmol scale. [a] Solvent 1.8 mL - compare to 0.9 mL in entry 13. Changing the concentration of 2-napthylamine in reaction mixture does not make significant difference in reaction conversion and A/B ratio. Less than 7 % of *C, N*-diarylation product was observed by GC under all conditions in Table 3.4.4.



1-Phenyl-2-naphthylamine (Table 3.4.2, Entries 1, 2, and 3):

2-Naphthylamine (143 mg, 1.0 mmol), chlorobenzene (57 mg, 0.5 mmol), TMPLi (265 mg, 1.8 mmol), anhydrous cyclohexane (1.5 mL), anhydrous Et_2O (0.1 mL), 50 °C, 48 hours. After column chromatography (hexanes followed by hexanes/EtOAc: 90/10), 78 mg (72%) of a tan solid was obtained. Less than 5% of *N*-arylation product was observed in crude reaction mixture by GC analysis.

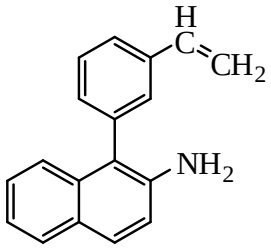
2-Naphthylamine (215 mg, 1.5 mmol), chlorobenzene (57 mg, 0.5 mmol), TMPLi (340 mg, 2.3 mmol), anhydrous cyclohexane (0.7 mL), anhydrous Et_2O (0.7 mL), room temperature, 24 hours. After column chromatography (hexanes followed by hexanes/EtOAc: 90/10), 91 mg (84 %) of a tan solid was obtained. Less than 5% of *N*-arylation product was observed in crude reaction mixture by GC analysis.

2-Naphthylamine (143 mg, 1.0 mmol), bromobenzene (79 mg, 0.5 mmol), TMPLi (265 mg, 1.8 mmol), anhydrous cyclohexane (1.5 mL), anhydrous Et_2O (0.1 mL), 50 °C, 48 hours. After column chromatography (hexanes followed by hexanes/EtOAc: 90/10), 76 mg (70%) of a tan solid was obtained. Less than 5% of *N*-arylation product was observed in crude reaction mixture by GC analysis.

2-Naphthylamine (143 mg, 1.0 mmol), fluorobenzene (49 mg, 0.5 mmol), TMPLi (265 mg, 1.8 mmol), anhydrous cyclohexane (1.5 mL), anhydrous Et_2O (0.1 mL), 50 °C, 48 hours. After column chromatography (hexanes followed by hexanes/EtOAc: 90/10), 74

mg (68%) of a tan solid was obtained. Less than 5% of *N*-arylation product was observed in crude reaction mixture by GC analysis.

R_f = 0.27 (hexanes/EtOAc: 90/10). This compound is known.[28] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.71 (m, 2H), 7.60 – 7.54 (m, 2H), 7.49 – 7.45 (m, 1H), 7.41 – 7.39 (m, 2H), 7.34 – 7.22 (m, 3H), 7.05 (d, *J* = 8.7 Hz, 1H), 3.71 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 141.2, 137.2, 133.9, 131.0, 129.4, 128.8, 128.1, 128.0, 127.7, 126.4, 124.3, 122.3, 120.0, 118.2.



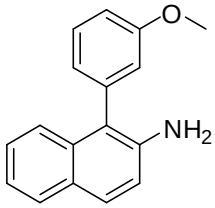
1-(3-Vinylphenyl)-2-naphthylamine (Table 3.4.2, Entry 4):

2-Naphthylamine (286 mg, 2.0 mmol), 2-chlorostyrene (70 mg, 0.5 mmol), TMPLi (500 mg, 3.4 mmol), anhydrous cyclohexane (2.8 mL), anhydrous Et_2O (0.2 mL), 50 ^oC, 48 hours. After column chromatography (hexanes followed by hexanes/EtOAc: 90/10), 76 mg (62 %) of a yellowish oil was obtained. About 20% of *N*-arylation product was observed in crude reaction mixture by GC analysis.

2-Naphthylamine (77 mg, 0.5 mmol), 2-chlorostyrene (210 mg, 1.5 mmol), TMPLi (370 mg, 2.5 mmol), anhydrous Et_2O (1.5 mL), - 25 ^oC, 48 hours. After column chromatography (hexanes followed by hexanes/EtOAc: 90/10), 85 mg (70 %) of a yellowish oil was obtained. About 10 % of *N*-arylation product was observed in crude reaction mixture by GC analysis.

R_f = 0.21 (hexanes/EtOAc: 90/10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.70 (m, 2H), 7.54 – 7.50 (m, 2H), 7.44 (s, 1H), 7.31 – 7.24 (m, 4H), 7.05 (d, *J* = 8.7 Hz, 1H), 6.79 (dd, *J* = 17.7 Hz, 11.0 Hz, 1H), 5.81 (d, *J* = 17.7 Hz, 1H), 5.30 (d, *J* = 11.0 Hz, 1H), 3.71 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 141.2, 138.6, 137.5, 136.7, 133.8, 130.5, 129.6, 128.9, 128.8, 128.0, 126.5, 125.5, 124.3, 122.3, 119.7, 118.2, 114.5. Signal for one carbon could not be located. FT-IR (neat, cm^{-1}) υ 2979, 1620, 1517. Anal calcd for $C_{18}H_{14}N$ (245.12 g/mol): C, 88.13; H, 6.16; N, 5.71; Found. C, 88.55; H, 5.72; N, 5.38.

Note: Product contains less than 4 % of another isomer, presumably 1-(2-vinylphenyl)-2-naphthylamine.

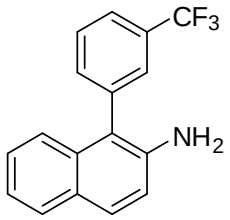


1-(3-Methoxy)-2-naphthylamine (Table 3.4.2, Entry 5):

2-Naphthylamine (77 mg, 0.5 mmol), 2-chloroanisole (215 mg, 1.5 mmol), TMPLi (440 mg, 3.0 mmol), anhydrous Et_2O (1.5 mL), - 25 ^oC, 48 hours. After column chromatography (hexanes followed by hexanes/EtOAc: 80/20), 84 mg (67%) of light tan solid was obtained. About 10 % of *N*-arylation product was observed in crude reaction mixture by GC analysis.

R_f = 0.28 (hexanes/EtOAc: 80/20). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.2 Hz, 1.1 Hz, 1H), 7.70 (d, *J* = 8.7 Hz, 1H), 7.46 (t, *J* = 8.2 Hz, 1H), 7.34 – 7.21 (m, 3H), 7.04 (d, *J* = 8.7 Hz, 1H), 7.00 – 6.91 (m, 3H), 3.84 (s, 3H), 3.74 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 160.4, 141.1, 138.6, 133.7, 130.4, 128.8, 128.0, 126.4, 124.4, 123.2,

122.3, 119.8, 118.2, 116.0, 113.5, 55.4.. FT-IR (neat, cm^{-1}) υ 3364, 2968, 1622, 1597. Anal calcd for $C_{17}H_{15}O$ (g/mol): C, 81.90 ; H, 6.06; N 5.62. Found. C, 81.45; H, 5.94; N, 5.78.



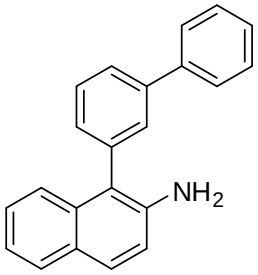
1-(3-Trifluoromethylphenyl)-2-naphthylamine (Table 3.4.2, Entry 6):

2-Naphthylamine (215 mg, 2.0 mmol), 2-chlorobenzotrifluoride (91 mg, 0.5 mmol), TMPLi (500 mg, 3.4 mmol), anhydrous cyclohexane (0.7 mL), anhydrous Et_2O (0.7 mL), room temperature, 24 hours. After column chromatography (hexanes followed by hexanes/EtOAc: 90/10), 86 mg (60%) of light tan oil was obtained. About 15% of *N*-arylation product was observed in crude reaction mixture by GC analysis.

2-Naphthylamine (77 mg, 0.5 mmol), 2-chlorobenzotrifluoride (270 mg, 1.5 mmol), TMPLi (370 mg, 2.5 mmol), anhydrous Et_2O (1.5 mL), - 25 ^oC, 48 hours. After column chromatography (hexanes followed by hexanes/EtOAc: 90/10), 93 mg (65%) of light tan oil was obtained. About 8 % of *N*-arylation product was observed in crude reaction mixture by GC analysis.

R_f = 0.30 (hexanes/EtOAc: 90/10). ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.67 (m 5H), 7.61 – 7.60 (m, 1H), 7.33 – 7.25 (m, 2H), 7.21 – 7. 19 (m, 1H), 7.05 (d, *J* = 8.7 Hz, 1H), 3.68 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 141.3, 138.2, 134.7, 133.6, 131.8 (q, *J* = 32.1 Hz), 130.0, 129.5, 128.2, 128.0, 127.9 (q, *J* = 4.8 Hz), 126.8, 124.6 (q, *J* = 4.8 Hz), 124.3 (q, *J* = 272.2 Hz), 123.7, 122.5, 118.2, 118.1. FT-IR (neat, cm^{-1}) υ 2921, 1626,

1326, 1120. Anal calcd for $C_{17}H_{12}F_3N$ (287.09 g/mol): C, 77.01; H, 4.21; N, 4.88. Found. C, 77.32; H, 4.32; N, 4.89.



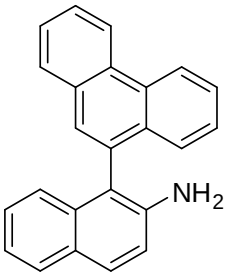
1-(1,1'-Biphenyl)-3-yl-2-naphthylamine (Table 3.4.2, Entry 7):

2-Naphthylamine (286 mg, 2.0 mmol), 2-bromobiphenyl (117 mg, 0.5 mmol), TMPLi (500 mg, 3.4 mmol), anhydrous cyclohexane (2.8 mL), anhydrous Et_2O (0.2 mL), 50 ^oC, 48 hours. After column chromatography (hexanes followed by hexanes/EtOAc: 90/10), 103 mg (70%) of a tan solid was obtained. Less than 10% of *N*-arylation product was observed in crude reaction mixture by GC analysis.

2-Naphthylamine (286 mg, 2.0 mmol), 2-fluorobiphenyl (87 mg, 0.5 mmol), TMPLi (500 mg, 3.4 mmol), anhydrous cyclohexane (2.8 mL), anhydrous Et_2O (0.2 mL), 50 ^oC, 48 hours. After column chromatography (hexanes followed by hexanes/EtOAc: 90/10),95 mg (65%) of a tan solid was obtained. Less than 10% of *N*-arylation product was observed in crude reaction mixture by GC analysis.

R_f = 0.24 (hexanes/EtOAc: 90/10), mp 114 – 115 ^oC (from hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.65 (m, 7H), 7.51 – 7.40 (m, 5H), 7.39 – 7.27 (m, 2H), 7.08 (d, *J* = 8.7 Hz, 1H), 3.80 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 142.2, 141.2, 140.9, 137.8, 130.0, 129.9, 129.8, 129.0, 128.2, 128.1, 127.7, 127.3, 126.6, 126.4, 124.4, 122.4, 119.9, 118.3. Signals for two carbons could not be located. FT-IR (neat, cm^{-1}) υ 2998,

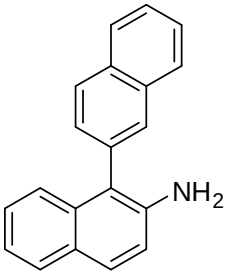
1626, 1510, 1392. Anal calcd for $C_{22}H_{17}N$ (295.14 g/mol): C, 89.46; H, 5.80; N, 4.74; Found. C, 89.03; H, 5.69; N, 4.60.



1-(9-Phenanthrenyl)-2-naphthylamine (Table 3.4.2, Entry 8):

2-Naphthylamine (215 mg, 1.5 mmol), 9-chlorophenanthrene (107 mg, 0.5 mmol), TMPLi (380 mg, 2.6 mmol), anhydrous cyclohexane (2.8 mL), anhydrous Et_2O (0.2 mL), 50 ^oC, 48 hours. After column chromatography (hexanes followed by hexanes/EtOAc: 85/15), 113 mg (71%) of a light yellow solid was obtained.

R_f = 0.22 (hexanes/EtOAc: 85/15), mp 189 – 190 ^oC (from hexanes). ^1H NMR (400 MHz, $CDCl_3$) δ 8.84 (t, *J* = 8.1 Hz, 2H),7.92 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.86 – 7.82 (m, 3H), 7.76 (dt, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.71 – 7.65 (m, 2H), 7.54 – 7.52 (m, 1H), 7.46 – 7.43 (m, 1H), 7.29 – 7.25 (m, 1H), 7.22 – 7.16 (m, 2H), 7.14 (d, *J* = 8.7 Hz, 1H), 3.66 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 142.1, 134.6, 133.5, 132.2, 131.4, 131.2, 130.6, 130.0, 129.3, 128.9, 128.2, 128.1, 127.2, 127.1, 127.0, 126.7, 126.6, 124.7, 123.1, 122.8, 122.4, 118.3, 117.4. Signal for one carbon could not be located. FT-IR (neat, cm^{-1}) υ 3005, 1623, 1513. Anal calcd for $C_{24}H_{17}N$ (319.14 g/mol): C, 90.25; H, 5.36; N, 4.39; Found. C, 88.73; H, 5.30; N, 4.32.



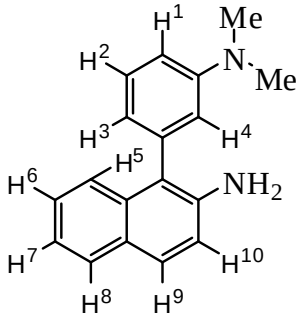
1-(2-Naphthalenyl)-2-naphthylamine (Table 3.4.2, Entry 9):

2-Naphthylamine (215 mg, 1.5 mmol), 2-chloronaphthalene (82 mg, 0.5 mmol), TMPLi (380 mg, 2.6 mmol), anhydrous cyclohexane (0.7 mL), anhydrous Et_2O (0.7 mL), room temperature, 24 hours. After column chromatography (hexanes followed by hexanes/EtOAc: 90/10), 110 mg (82%) of light brown oil was obtained. Less than 5% of *N*-arylation product was observed in crude reaction mixture by GC analysis.

2-Naphthylamine (215 mg, 1.5 mmol), 2-bromonaphthalene (107 mg, 0.5 mmol), TMPLi (380 mg, 2.6 mmol), anhydrous cyclohexane (0.7 mL), anhydrous Et_2O (0.7 mL), room temperature, 24 hours. After column chromatography (hexanes followed by hexanes/EtOAc: 90/10), 107 mg (80%) of light brown oil was obtained. Less than 5% of *N*-arylation product was observed in crude reaction mixture by GC analysis.

R_f = 0.31 (hexanes/EtOAc: 90/10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, *J* = 8.6 Hz, 1H), 7.99 – 7.97 (m, 1H), 7.92 – 7.89 (m, 2H), 7.81 – 7.76 (m, 2H), 7.61 – 7.50 (m, 3H), 7.39 – 7.36 (m, 1H), 7.31 – 7.25 (m, 2H), 7.08 (d, *J* = 8.6 Hz, 1H), 3.75 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 141.5, 134.8, 134.1, 134.0, 132.9, 130.0, 129.2, 129.1, 129.0, 128.1, 128.0, 126.6, 126.4, 126.3, 124.4, 122.4, 119.7, 118.3. Signals for two carbons could not be located. FT-IR (neat, cm^{-1}) υ 3057, 1620, 1513. Anal calcd for $C_{20}H_{15}N$ (269.12 g/mol): C, 89.19; H, 5.61; N, 5.20; Found. C, 89.14; H, 5.50; N, 5.03.

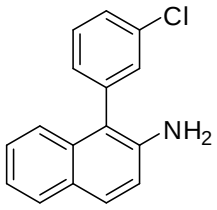
Note: Product contains less than 3 % of another isomer, presumably 1-(1-naphthalenyl)-2-naphthylamine**.**



1-[3-(Dimethylamino)phenyl]-2-naphthylamine (Table 3.4.2, Entry 10).

2-Naphthylamine (77 mg, 0.5 mmol), 2-chloro-*N*,*N*-dimethylaniline (230 mg, 1.5 mmol), TMPLi (440 mg, 3.0 mmol), anhydrous Et_2O (1.5 mL), - 30 ^oC, 48 hours. After column chromatography (hexanes followed by hexanes/EtOAc: 70/30), 79 mg (61 %) of a brown solid was obtained. About 8 % of *N*-arylation product was observed in crude reaction mixture by GC analysis.

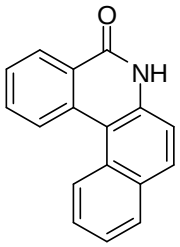
R_f = 0.23 (hexanes/EtOAc: 70/30), mp 108 – 110 °C (from hexanes). ^1H NMR (400 MHz, C_6D_6) δ 7.75 (d, *J* = 7.5 Hz, H^5), 7.61 (d, *J* = 7.5 Hz, H^8), 7.51 (d, *J* = 8.8 Hz, H^9), 7.27 (dd, *J* = 8.8 Hz, 7.5 Hz, H^2), 7.15 (dt, *J* = 7.5 Hz, 1.4 Hz, H^6), 7.08 (dt, *J* = 7.5 Hz, 1.4 Hz, H^7), 6.77 (d, *J* = 7.5 Hz, H^3), 6.67 (s, H^4), 6.62 (d, *J* = 8.8 Hz, H^{10}), 6.58 (dd, *J* = 8.8 Hz, 2.5 Hz, H^1), 3.23 (s, 2H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 151.4, 141.1, 138.0, 133.9 130.0, 128.5, 128.0, 127.9, 126.3, 124.7, 122.2, 121.0, 118.9, 118.2, 114.8, 111.7, 40.7. FT-IR (neat, cm^{-1}) υ 2976, 1600, 1357. Anal calcd for $C_{18}H_{18}N_2$ (262.15 g/mol): C, 82.41; H, 6.92; N, 10.68 Found. C, 82.73; H, 6.91; N, 10.54.



1-(3-Chlorophenyl)naphthalen-2-amine (Table 3.4.2, Entry 11)

2-Naphthylamine (0.71 mg, 0.5 mmol), 3-chlorophenyl trifluoromethanesulfonate (400 mg, 1.5 mmol), lithium diisopropylamide (LDA) (140 mg, 2.3 mmol), anhydrous THF (1.5 mL), - 85 ^{o}C, 12 hours. After column chromatography (hexanes followed by hexanes/EtOAc: 90/10), 64 mg (50%) of a tan solid was obtained. About 7 % of *N*-arylation product was observed in crude reaction mixture by GC analysis.

R_f = 0.30 (hexanes/EtOAc: 90/10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.69 (m, 2H), 7.50 – 7.41 (m, 2H), 7.39 (t, *J* = 1.8 Hz, 1H), 7.36 – 7.21 (m, 4H), 7.03 (d, *J* = 8.7 Hz, 1H), 3.70 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 141.1, 139.2, 135.2, 133.6, 131.1, 130.7, 129.4, 129.3, 128.1, 128.0, 127.9, 126.7, 123.9, 122.4, 118.3, 118.2. FT-IR (neat, cm^{-1}) υ 3376, 2232, 1513, 1273. Anal calcd for $C_{16}H_{12}ClN$ (253.07 g/mol): C, 75.74; H, 4.77; N, 5.52. Found. C, 76.02; H, 4.56; N, 5.12.

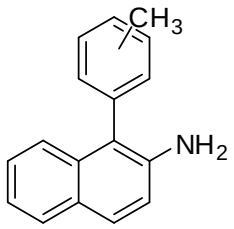


Benzo[a]phenanthridin-5(6H)-one (Table 3.4.2, Entry 12)

2-Naphthylamine (71 mg, 0.5 mmol), *tert*-butyl-3-bromobenzoate (257 mg, 1.0 mmol), TMPLi (267 mg, 1.8 mmol), anhydrous Et_2O (0.7 mL), anhydrous cyclohexane (0.7 mL),

- 35 ^{o}C, 12 hours and then 0 ^{o}C, 1 hour. After column chromatography (hexanes followed by hexanes/EtOAc: 50/50), 86 mg (70%) of light yellow solid was obtained. *N*-arylation product was not observed in crude reaction mixture by GC analysis.

R_f = 0.20 (hexanes/EtOAc: 40/60). This compound is known.[29] ^{1}H NMR (400 MHz, DMSO-d6) δ 10.53 (s, 1H), 8.42 (t, *J* = 2.5 Hz, 1H), 8.17 (t, *J* = 1.8 Hz, 1H), 7.98 – 7.96 (m, 1H), 7.87 – 7.77 (m, 4H), 7.51 – 7.38 (m, 3H). ^{13}C NMR (100 MHz, DMSO-d6, ppm) δ 164.7, 137.6, 137.0, 136.9, 134.9, 133.8, 131.3, 130.8, 130.6, 128.8, 128.0, 127.5, 127.9, 125.4, 122.3, 121.4, 117.2.

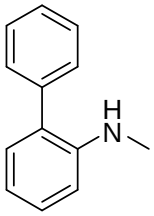


1-(4-Methylphenyl)-2-naphthylamine and **1-(3-Methylphenyl)-2-naphthylamine (Table 3.4.2, Entry 13).** 2-Naphthylamine (215 mg, 1.5 mmol), 4-chlorotoluene (64 mg, 0.5 mmol), TMPLi (385 mg, 2.6 mmol), anhydrous cyclohexane (2.8 mL), anhydrous Et_2O (0.2 mL), 50 ^{o}C, 48 hours. After column chromatography (hexanes followed by hexanes/EtOAc: 90/10), 91 mg (78%) of a light tan solid was obtained.

2-Naphthylamine (144 mg, 1.0 mmol), 4-chlorotoluene (64 mg, 0.5 mmol), TMPLi (270 mg,1.8 mmol), anhydrous cyclohexane (0.7 mL), anhydrous Et_2O (0.7 mL), room temperature, 24 hours. After column chromatography (hexanes followed by hexanes/EtOAc: 90/10), 85 mg (73%) of a light tan solid was obtained.

Ratio of *p/m* determined by integration of methyl ^{1}H signals is 1.3/1. Analysis by GC showed that two isomers are obtained in 1.3/1 ratio. In both conditions, less than 5% of *N*-arylation product was observed in crude reaction mixture by GC analysis.

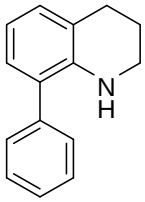
R_f = 0.31 (hexanes/EtOAc: 90/10). ^{1}H NMR of mixture of isolated two isomers (400 MHz, $CDCl_3$) δ 7.83 – 7.68 (overlapping multiplets, 2H), 7.47 – 7.19 (overlapping multiplets of 2 isomers, 7H), 7.05 (overlapping doublets, *J* = 8.7 Hz, 1H), 3.71 (overlapping singlets, 2H), 2.48 (singlet of *m*-isomer, 1.3H), 2.45 (singlet of *p*-isomer, 1.7H).



***N*-Methyl-(1,1'-biphenyl)-2-amine (Table 3.4.3, Entry 1).**

N-Methylaniline (162 mg, 1.5 mmol), chlorobenzene (57 mg, 0.5 mmol), TMPLi (340 mg, 2.3 mmol), anhydrous cyclohexane (0.7 mL), anhydrous Et_2O (0.7 mL), room temperature, 25 hours. After column chromatography (hexanes followed by hexanes/CH_2Cl_2 40/60), 56 mg (62%) of a light brown oil was obtained. About 20% of *N*-arylation product was observed in crude reaction mixture by GC analysis.

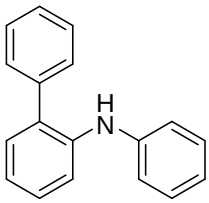
R_f = 0.32 (hexanes/CH_2Cl_2: 40/60). This compound is known.[30] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.43 (m, 4H), 7.38 – 7.35 (m, 1H), 7.32 – 7.26 (m, 1H), 7.13 – 7.10 (m, 1H), 6.80 (dt, *J* = 8.0 Hz, 1.1 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 3.98 (s, 1H), 2.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 146.3, 139.6, 130.1, 129.5, 129.0, 128.9, 127.7, 127.3, 116.9, 109.9, 30.9.



1,2,3,4-Tetrahydro-8-phenylquinoline (Table 3.4.3, Entry 2).

1,2,3,4-Terahydroquinoline (200 mg, 1.5 mmol), chlorobenzene (57 mg, 0.5 mmol), TMPLi (340 mg, 2.3 mmol), anhydrous cyclohexane (0.7 mL), anhydrous Et_2O (0.7 mL), room temperature, 24 hours. After column chromatography (hexanes followed by hexanes/CH_2Cl_2 60/40), 73 mg (70%) of a colorless oil was obtained. About 15% of *N*-arylation product was observed in crude reaction mixture by GC analysis.

R_f = 0.25 (hexanes/CH_2Cl_2: 50/50).This compound is known.[31] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.43 (m, 4H), 7.38 – 7.33 (m, 1H), 6.99 (dd, *J* = 7.3 Hz, 1.3 Hz, 1H), 6.94 (dd, *J* = 7.3 Hz, 1.3 Hz, 1H), 6.68 (t, *J* = 7.3 Hz, 1H), 4.10 (s, 1H), 3.26 (t, *J* = 5.4 Hz, 2H), 2.86 (t, *J* = 6.4 Hz, 2H), 1.99 – 1.93 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 141.8, 139.7, 129.5, 129.0, 128.9, 128.1, 127.1, 126.7, 121.4, 116.4, 42.1, 27.6, 22.1.



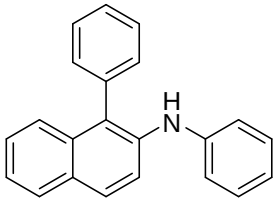
***N*-Phenyl-(1,1'-biphenyl)-2-amine (Table 3.4.3, Entry 3).**

Biphenylamine (170 mg, 1.0 mmol), chlorobenzene (57 mg, 0.5 mmol), TMPLi (270 mg, 1.8 mmol), anhydrous cyclohexane (0.7 mL), anhydrous Et_2O (0.7 mL), room temperature, 24 hours. After column chromatography (hexanes followed by

hexanes/CH_2Cl_2 80/20), 95 mg (78%) of a white solid was obtained. Less than 5% of *N*-arylation product was observed in crude reaction mixture by GC analysis.

Biphenylamine (255 mg, 1.5 mmol), chlorobenzene (57 mg, 0.5 mmol), TMPLi (340 mg, 2.3 mmol), anhydrous cyclohexane (0.7 mL), anhydrous Et_2O (0.7 mL), room temperature, 24 hours. After column chromatography (hexanes followed by hexanes/CH_2Cl_2 80/20), 105 mg (87%) of a white solid was obtained. Less than 5% of *N*-arylation product was observed in crude reaction mixture by GC analysis.

R_f = 0.34 (hexanes/CH_2Cl_2: 80/20).This compound is known.[32] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.38 (m, 6H), 7.32 – 7.28 (m, 4H), 7.09 – 7.04 (m, 3H), 6.97 (tt, *J* = 7.6 Hz, 1.1 Hz, 1H), 5.66 (s, 1H). ^{13}C NMR (125 MHz, C_6D_6, ppm) δ 143.7, 140.3, 139.4, 132.0, 131.0, 129.4, 129.3, 128.9, 128.4, 127.4, 121.5, 120.9, 118.4, 117.8.

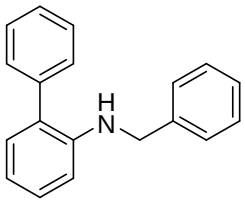


1,*N*-Diphenyl-2-naphthylamine (Table 3.4.3, Entry 4).

N-Phenyl-2-naphthylamine (219 mg, 1.0 mmol), chlorobenzene (57 mg, 0.5 mmol), TMPLi (270 mg, 1.8 mmol), anhydrous cyclohexane (0.7 mL), anhydrous Et_2O (0.7 mL), room temperature, 24 hours. After column chromatography (hexanes followed by hexanes/CH_2Cl_2 80/20), followed by HPLC (hexanes/CH_2Cl_2: 93/7), 118 mg (80%) of a light brown solid was obtained. Less than 5% of *N*-arylation product was observed in crude reaction mixture by GC analysis.

R_f = 0.32 (hexanes/CH_2Cl_2: 85/15), mp 100 – 101 ^oC (from hexanes).^1H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.78 (m, 2H), 7.61 (d, *J* = 8.9 Hz, 1H), 7.57 – 7.53 (m, 2H), 7.49 – 7.47 (m, 1H), 7.41 – 7.34 (m, 3H), 7.33 – 7.30 (m, 2H), 7.28 – 7.23 (m, 2H), 7.03 (d, *J* = 7.8 Hz, 1H), 6.95 (t, *J* = 7.8 Hz, 1H), 5.55 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 143.6, 138.1, 136.7, 133.9, 131.1, 129.4, 129.3, 128.4, 128.0, 127.9, 126.4, 125.3, 125.0, 123.4, 121.5, 118.9, 118.7. Signal for one carbon could not be located. FT-IR (neat, cm^{-1}) υ 1595, 1503, 1315. Anal calcd for $C_{22}H_{17}N$ (295.14 g/mol): C, 89.46; H, 5.80; N, 4.74 Found. C, 89.65; H, 5.52; N, 4.46.

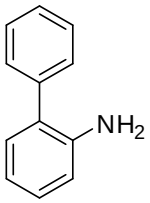
In order to confirm the arylation regioselectivity, 1,*N*-diphenyl-2-naphthylamine was prepared as follows: A 2 dram vial equipped with magnetic stirring bar was charged with 1-phenyl-2-naphthylamine (110 mg, 0.5 mmol), PhI (204 mg, 1.0 mmol), CuI (20 mg, 0.1 mmol), phenanthroline (36 mg, 0.2 mmol), K_3PO_4 (318 mg, 1.5 mmol), and DMF (1 mL). Vial was then flushed with nitrogen and placed in the preheated oil bath (100 ^oC) for 24 hours. The reaction mixture was cooled to room temperature. The reaction mixture was subjected to flash chromatography on silica gel in hexanes followed by hexane/CH_2Cl_2 (85/15) to elute the product. After concentrating the fractions containing the product, the residue was dried under reduced pressure to yield 88 mg (60 %) of a light brown solid. ^1H NMR (400 MHz, $CDCl_3$) is identical with the product above (Table 3.4.3, Entry 4). The experiment shows that the arylation for Table 3.4.3, entry 4 occurs on naphthyl and not phenyl group.



***N*-(Phenylmethyl)-(1,1'-biphenyl)-2-amine (Table 3.4.3, Entry 5):**

N-Benzylaniline (92 mg, 0.5 mmol), chlorobenzene (90mg, 0.8 mmol), TMPLi (265 mg, 1.8 mmol), anhydrous pentane (1.8 mL), anhydrous THF (0.05 mL), room temperature, 24 hours. After column chromatography (hexanes followed by hexanes/CH_2Cl_2 75/25), 90 mg (70%) of a white solid was obtained. Less than 10% of *N*-arylation product was observed in crude reaction mixture by GC analysis.

R_f = 0.33 (hexanes/CH_2Cl_2: 75/25). This compound is known.[33] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.45 (m, 4H), 7.40 – 7.32 (m, 5H), 7.30 – 7.19 (m, 2H), 7.15 (dd, *J* = 7.4 Hz, 1.1 Hz, 1H), 6.81 (dt, *J* = 7.4 Hz, 1.1 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 4.44 (s, 1H), 4.36 (d, *J* = 4.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 145.0, 139.6, 130.4, 129.5, 129.1, 128.8, 128.7, 127.7, 127.4, 127.2, 117.3, 110.8, 48.2. Signals for two carbons could not be located.



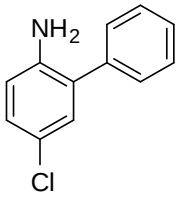
2-Aminobiphenyl (Table 3.4.3, Entry 6).

Aniline (186 mg, 2.0 mmol), chlorobenzene (57 mg, 0.5 mmol), TMPLi (500 mg, 3.4 mmol), anhydrous cyclohexane (2.8 mL), anhydrous Et_2O (0.2 mL), 50 ^oC, 48 hours. After column chromatography (hexanes followed by hexanes/EtOAc: 90/10), 46 mg (55

%) of a light brown solid was obtained. About 25% of *N*-arylation product was observed in crude reaction mixture by GC analysis.

Using TMPLi solution: Vial equipped with magnetic stirring bar was charged with aniline (186 mg, 2.0 mmol) and chlorobenzene (57 mg, 0.5 mmol). Vial was flushed with nitrogen and capped. TMPLi 1M suspension in pentane (3.2 mL, 3.2 mmol) was added, followed by anhydrous Et_2O (0.2 mL) via syringe. Reaction was run at 50 ^oC for 48 hours. General work up procedure was followed. After column chromatography (hexanes followed by hexanes/EtOAc: 90/10), 44 mg (53 %) of a light brown solid was obtained. About 25 % of *N*-arylation product was observed in crude reaction mixture by GC analysis.

R_f = 0.26 (hexanes/EtOAc: 90/10). This compound is known.[34] ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.43 (m, 4H), 7.37 – 7.33 (m, 1H), 7.18 – 7.13 (m, 2H), 6.84 (dt, *J* = 7.6 Hz, 1.3 Hz, 1H), 6.75 (d, *J* = 7.6 Hz, 1H), 3.76 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 143.6, 139.6, 130.5, 129.2, 128.9, 128.6, 127.7, 127.3, 118.7, 115.7.

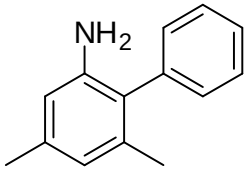


5-Chlorobiphenyl-2-amine (Table 3.4.3, Entry 7)

4-Chloroaniline (64 mg, 0.5 mmol), phenyltrifluoromethanesulfonate (340 mg, 1.5 mmol), TMPLi (338 mg, 2.3 mmol), anhydrous Et_2O (0.7 mL), anhydrous pentane (0.7 mL), - 50 ^oC, 24 hours. After column chromatography (hexanes followed by

hexanes/EtOAc: 90/10), 61 mg (60%) of a tan solid was obtained. About 5 % of *N*-arylation product was observed in crude reaction mixture by GC analysis.

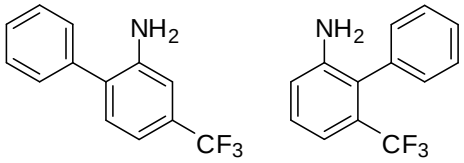
R_f = 0.30 (hexanes/EtOAc: 90/10). This compound is known.[12] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.40 (m, 4H), 7.36 (tt, *J* = 6.8 Hz, 1.7 Hz, 1H), 7.11- 7.08 (m, 2H), 6.68 (d, *J* = 8.8 Hz, 1H), 3.75 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 142.0, 138.3, 130.1, 129.2, 129.1, 129.0, 128.3, 127.8, 123.4, 116.9.



4,6-Dimethyl-(1,1'-biphenyl)-2-amine (Table 3.4.3, Entry 8):

3,5-Dimethylaniline (242 mg, 2.0 mmol), chlorobenzene (57 mg, 0.5 mmol), TMPLi (500 mg, 3.4 mmol), anhydrous cyclohexane (2.8 mL), anhydrous Et_2O (0.2 mL), 50 ^{o}C, 48 hours. After column chromatography (hexanes followed by hexanes/EtOAc: 90/10), 68 mg (70 %) of a light brown oil was obtained. About 10% of *N*-arylation product was observed in crude reaction mixture by GC analysis.

R_f = 0.29 (hexanes/EtOAc: 90/10). This compound is known.[35] ^{1}H NMR (400 MHz, $CDCl_3$) δ 748 – 7.44 (m, 2H), 7.38 – 7.33 (m, 1H), 7.24 – 7.27 (m, 2H), 6.57 (s, 1H), 6.50 (s, 1H), 3.42c (s, 2H), 2.29 (s, 3H), 2.00 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 144.1, 138.4, 137.9, 136.9, 130.2, 129.1, 127.2, 125.3, 121.1, 113.5, 21.3, 20.6.

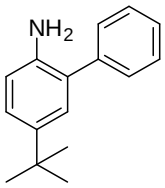


6-(Trifluoromethyl)biphenyl-2-amine and 4-(trifluoromethyl)biphenyl-2-amine (Table 3.4.3, Entry 9)

3-Aminobenzotrifluoride (322 mg, 2.0 mmol), chlorobenzene (57 mg, 0.5 mmol), TMPLi (485 mg, 3.2 mmol), anhydrous cyclohexane (2.8 mL), anhydrous Et_2O (0.2 mL), 50 ^oC, 48 hours. After column chromatography (hexanes followed by hexanes/EtOAc: 90/10), 20 mg (17 %) of a light brown oil [4-(trifluoromethyl)biphenyl-2-amine] and 59 mg (50 %) of a tan oil [6-(trifluoromethyl)biphenyl-2-amine] were obtained. About 15 % of *N*-arylation product was observed in crude reaction mixture by GC analysis.These compounds are known.[36]

4-(Trifluoromethyl)biphenyl-2-amine: R_f = 0.32 (hexane/EtOAc = 95/5). ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.42 (m, 4H), 7.39 (tt, *J* = 7.5 Hz, 1.7 Hz, 1H), 7.20 (d, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 6.98 (s, 1H), 3.92 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 143.7, 138.2, 131.0, 130.9, 130.8 (q, *J* = 24.2 Hz), 129.1, 128.9, 128.0, 124.2 (q, *J* = 273 Hz), 115.2 (q, *J* = 3.2 Hz), 112.1 (q, *J* = 3.6 Hz).

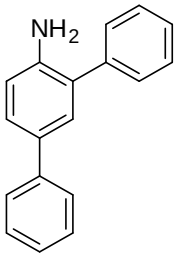
6-(Trifluoromethyl)biphenyl-2-amine: R_f = 0.27 (hexane/EtOAc = 90/10). ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.44 (m, 2H), 7.40 (tt, *J* = 7.5 Hz, 1.2 Hz, 1H), 7.27 – 7.22 (m, 3H), 7.14 (d, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 3.56 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 145.6, 135.3, 130.1, 129.7 (q, *J* = 29.3 Hz), 128.8, 128.3, 128.1, 125.6, 124.2 (q, *J* = 273 Hz), 118.3 (q, J = 2.4 Hz), 115.5 (q, J = 5.8 Hz).



5-(1,1-Dimethylethyl)-(1,1'-biphenyl)-2-amine (Table 3.4.3, Entry 10):

4-*tert*-Butylaniline (298 mg, 2.0 mmol), chlorobenzene (57 mg, 0.5 mmol), TMPLi (500 mg, 3.4 mmol), anhydrous cyclohexane (2.8 mL), anhydrous Et_2O (0.2 mL), 50 ^oC, 48 hours. After column chromatography (hexanes followed by hexanes/EtOAc 90/10), 67 mg (60 %) of a brown solid was obtained. About 15 % of *N*-arylation product was observed in crude reaction mixture by GC analysis.

R_f = 0.34 (hexanes/EtOAc: 90/10). This compound is known.[37] ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.45 (m, 4H), 7.38 – 7.34 (m, 1H), 7.22 (dd, *J* = 8.4 Hz, 2.3 Hz, 1H), 7.17 (d, *J* = 2.3 Hz, 1H), 6.74 (d, *J* = 8.4 Hz, 1H), 3.68 (s, 2H), 1.32 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 141.6, 141.1, 140.2, 129.3, 128.9, 127.5, 127.3, 127.2, 125.5, 115.6, 34.1, 31.7.

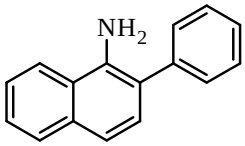


(1,1':3',1''-Terphenyl)-4'-amine (Table 3.4.3, Entry 11).

4-Aminobiphenyl (338 mg, 2.0 mmol), chlorobenzene (57 mg, 0.5 mmol), TMPLi (500 mg, 3.4 mmol), anhydrous cyclohexane (2.8 mL), anhydrous Et_2O (0.2 mL), 50 ^oC, 48 hours. After column chromatography (hexanes followed by hexanes/EtOAc 85/15), 81

mg (67 %) of a light brown solid was obtained. About 20% of *N*-arylation product was observed in crude reaction mixture by GC analysis.

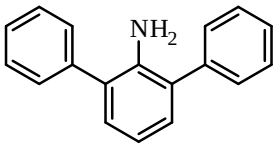
R_f = 0.27 (hexanes/EtOAc = 80/20). This compound is known.[38] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 – 7.59 (m, 2H), 7.55 – 7.53 (m, 2H), 7.52 – 7.46 (m, 3H), 7.45 – 7.38 (m, 4H), 7.30 (t, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 3.85 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 143.1, 141.1, 139.5, 131.8, 129.3, 129.2, 129.0, 128.8, 128.0, 127.5, 127.2, 126.6, 126.5, 116.1.



2-Phenyl-1-naphthylamine (Table 3.4.3, Entry 12):

1-Naphthylamine (143 mg, 1.0 mmol), chlorobenzene (57 mg, 0.5 mmol), TMPLi (340 mg, 2.3 mmol), anhydrous cyclohexane (0.7 mL), anhydrous Et_2O (0.7 mL), room temperature, 24 hours. After column chromatography (hexanes followed by hexanes/EtOAc: 90/10), 92 mg (85 %) of a tan solid was obtained. Less than 5% of *N*-arylation product was observed in crude reaction mixture by GC analysis.

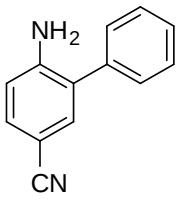
R_f = 0.23 (hexanes/EtOAc 90/10). This compound is known.[39] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.86 (m, 2H), 7.60 – 7.51 (m, 6H), 7.46 – 7.42 (m, 2H), 7.37 (d, *J* = 8.5 Hz, 1H), 4.34 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 140.3, 138.7, 133.9, 129.8, 129.1, 128.8, 128.7, 127.3, 126.0, 125.5, 123.8, 122.2, 121.3, 118.7.



(1,1':3',1''-Terphenyl)-2'-amine (Table 3.4.3, Entry 13):

2-Aminobiphenyl (338 mg, 1.5 mmol), chlorobenzene (57 mg, 0.5 mmol), TMPLi (500 mg, 3.4 mmol), anhydrous cyclohexane (2.8 mL), anhydrous Et_2O (0.2 mL), 50 ^oC, 48 hours. After column chromatography (hexanes followed by hexanes/EtOAc: 90/10), 85 mg (70 %) of a light brown solid was obtained. About 15 % of *N*-arylation product was observed in crude reaction mixture by GC analysis.

R_f = 0.22 (hexanes/EtOAc: 90/10). This compound is known.[40] ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.55 (m, 4H), 7.51 – 7.48 (m, 4H), 7.42 – 7.38 (m, 2H), 7.18 (d, *J* = 7.6 Hz, 2H), 6.93 (t, *J* = 7.6 Hz, 1H), 3.88 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 140.9, 139.9, 129.9, 129.5, 129.0, 128.0, 127.4, 118.3.

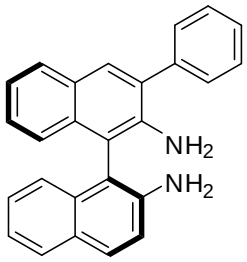


6-Aminobiphenyl-3-carbonitrile (Table 3.4.3, Entry 14)

Outside the glovebox a 2-dram vial was equipped with a magnetic stirring bar. The vial was placed inside the glovebox. To the vial was added solid TMPLi (300 mg, 2.0 mmol). The sealed vial was taken out of the glovebox and placed into cooling bath at -60 ^oC. Anhydrous Et_2O (0.7 mL) was added via syringe to reaction vial. 4-Aminobenzonitrile (60 mg, 0.5 mmol) solution in anhydrous THF (0.7 mL) was cooled to -60 ^oC and added slowly to reaction mixture. Following that, chlorobenzene (113 mg, 1.0 mmol) was added

to vial. Reaction was run at -60 ^{o}C for 24 hours. Work-up procedure for reactions at low temperature was applied. After column chromatography (hexanes followed by hexanes/EtOAc: 75/25), 63 mg (65 %) of a brown oil was obtained. About 15 % of *N*-arylation product was observed in crude reaction mixture by GC analysis.

R_f = 0.23 (hexanes/EtOAc 70/30). This compound is known.[41] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 7.6 Hz, 0.9 Hz, 1H), 7.58 (dt, *J* = 7.6 Hz, 1.4 Hz, 1H), 7.46 (d (*J* = 8.0 Hz, 1H), 7.39 – 7.23 (m, 3H), 6.77 (d, *J* = 8.7 Hz, 2H), 3.82 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 147.2, 145.7, 133.9, 132.8, 130.0, 129.8, 128.2, 126.7, 119.4, 115.1, 110.8.



3-Phenyl-1,1'-binaphthyl-2,2'-diamine (Scheme 3.4.9)

Outside the glovebox a 2-dram vial was equipped with a magnetic stirring bar. The vial was placed inside the glovebox. To the vial was added solid TMPLi (265 mg, 1.8 mmol). The sealed vial was taken out of the glovebox and placed into cooling bath at -30 ^{o}C. Anhydrous Et_2O (1.4 mL) was added via syringe to reaction vial. (S)-(-)1,1'-Bis(2-naphthylamine) (36 mg, 0.25 mmol) solution in anhydrous THF (0.7 mL) was added slowly to reaction mixture. Following that, chlorobenzene (113 mg, 1.0 mmol) was added to vial. Reaction was stirred at -30 ^{o}C for 48 hours. Work-up procedure for reactions at

low temperature was applied. Reaction residue was chromatographed with hexanes followed by hexanes/EtOAc (85/15) to obtain 26 mg (47 %) of a white solid.

Determination of % ee by HPLC on chiral stationary phase: CHIRALCEL OD-H, hexanes/isopropanol 95:5, 0.75 mL/min, > 99 % ee. Retention time: major, (S) = 14.2 min, (R) = 12.1 min.

R_f = 0.28 (hexanes/EtOAc: 80/20). This compound is known.[42] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.78 (m, 3H), 7.76 (s, 1H), 7.62 (dd, *J* = 7.8 Hz, 1.4 Hz, 2H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.40 (tt, *J* = 7.4 Hz, 2.5 Hz, 1H), 7.23 – 7.23 (m, 4H), 7.16 (d, *J* = 8.2 Hz, 2H), 7.06 (d, *J* = 8.2 Hz, 1H), 3.78 (broad overlapping singlet, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 142.8, 140.8, 139.3, 133.7, 133.2, 130.8, 129.9, 129.6, 129.5, 129.4, 129.0, 128.9, 128.5, 128.3, 127.8, 127.0, 126.9, 124.1, 123.9, 122.7, 122.6, 118.5, 113.0, 112.7.

3.4.4.2. Reactions Between Arynes and Phenols: 2-Arylphenols and Helicenes Synthesis

General considerations:

For helicene synthesis, reactions were performed in 2-dram vials using screw caps with 17 mm hole and white silicone septum with white teflon face (from SUPELCO). For phenol arylation, reactions were run in 2-dram vials using 17 mm screw caps with PTFE/Liner (from SUPELCO). Column chromatography was performed on 60Å silica gel (Sorbent Technologies). Purification by preparative HPLC was performed on a Shimadzu Prominence LC (LC-20AB) equipped with a SPD-20A UV-Vis detector and a Varian Dynamax (250 mm x 21.4 mm) column. GC-MS analyses were performed on a Shimadzu GCMS-QP5000 chromatograph equipped with a Restek column (Rtx-XLB, 30 m x 0.25 mm I.D.). The ^{1}H and ^{13}C NMR were recorded on JEOL EC-400 or JEOL EC-500 spectrometers using residual solvent peak as a reference. Elemental analyses were performed by Atlantic Microlab Inc. of Norcross, GA. IR spectra were obtained on a ThermoNicolet Avatar 370 FT-IR instrument. Analytical thin layer chromatography was performed on silica gel IB-F (Baker-flex) by J. T. Baker. All procedures were performed under nitrogen atmosphere unless otherwise noted.

Room temperature: 25 ^{o}C.

Materials. The following starting materials were obtained from commercial sources and were used without further purification: phenol, 2-*tert*-butylphenol, 3-*tert*-butylphenol, 2,3-dimethylphenol, 2,6-diisopropylphenol, 2-hydroxybenzotrifluoride, 4-hydroxybiphenyl, 1-naphthol, 2-naphthol, 7-methoxy-2-naphthol, 4-

hydroxybenzophenone, chlorobenzene, 2-chloroanisole, 3-chloro-1-fluorobenzene, 3-chlorobenzonitrile 1-chloronaphthalene, 3-chlorobenzotrifluoride, 1,1'-binaphthyl-2,2'-diol (racemic), silver acetate, *tert*-butyl-3-bromobenzoate, 2,2,6,6-tetramethylpiperidine (TMPH), iodomethane, *m*-cresol, (R)-(+)-1,1'-bi(2-naphthol). 3-(*tert*-Butyldimethylsilyloxy) phenol was synthesized according to literature.[43]

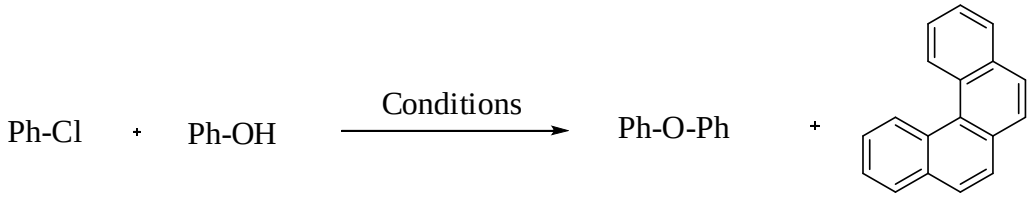
TMPLi: A 250 mL oven-dried flask equipped with a magnetic stirring bar and a septum was evacuated and backfilled with nitrogen 5 times. TMPH (15.5 g, 18.5 mL, 110 mmol) was added via syringe, followed by anhydrous pentane to give approximately 100 mL of solution. The mixture was cooled to -73 °C (dry ice-acetone bath) and stirred for 10 minutes. *n*-BuLi (2.5 M in hexanes, 40.0 mL, 100 mmol) was added dropwise and reaction mixture was stirred for 30 minutes at -73 °C, then warmed up to room temperature (25 °C) and stirred overnight. The reaction mixture was vacuumed to remove all solvent and dried under vacuum for at least 5 hours. A light yellow powder of solid TMPLi was obtained.

TMPLi 1 M in pentane/hexanes: A 50 mL oven-dried flask equipped with a magnetic stirring bar and a septum was evacuated and backfilled with argon 5 times. TMPH (4.64 g, 33.0 mmol) was added, followed by anhydrous pentane to give 30 mL of solution (marked the flask at the level of solution). The mixture was cooled to -73 °C (dry ice-acetone) and stirred for 5 minutes. *n*-BuLi (2.5 M in hexanes, 12.0 mL, 30 mmol) was added dropwise and reaction mixture was stirred for 30 minutes at -73 °C, then warmed up to room temperature and stirred overnight. The reaction mixture was vacuumed to give 30 mL (at the marked level) of TMPLi suspension.

General procedure for synthesis of helicenes: A 2 dram vial equipped with a magnetic stir bar was charged with appropriate phenol (0.5 mmol) and ArCl (3 – 4 equiv). The vial was flushed with nitrogen and capped. To this mixture was added the appropriate base solution or suspension (3.7 – 4.7 equiv) at the specified reaction temperature by injecting through the septum by 1 mL syringe. The base suspension was stirred vigorously during the time being withdrawn by syringe. Tetrahydrofuran (THF) or diethyl ether was then promptly added. The vial was flushed with nitrogen (20 seconds) and then stirred at specified temperature for indicated time. Unless otherwise stated, reaction mixture was quenched with anhydrous MeOH (0.5 mL), evacuated to volume of 1 mL and subjected to column chromatography on silica gel in hexanes or pentane followed by appropriate solvent to elute the product. After concentrating the fractions containing the product, the residue was dried under reduced pressure.

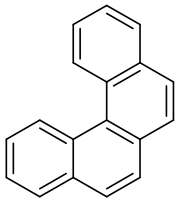
Optimization of conditions of helicene synthesis: All reactions were carried out following the general procedure. Phenol (x mmol), chlorobenzene (y mmol), TMPLi [1M suspention in pentane/hexanes, 1.2*(x + y) mmol], 24 hours. Conversions and **1/2** ratio were calculated by GC analysis. Conversions are presented in Table 3.4.S1 and show the amount of product **1** and **2** formed (e.g. 70 % means that 70 % of starting limiting reagent is converted to **1** and **2**). Mixture with exact molar amounts of pure **1** and pure **2** was used as the standard to determine the ratio **2/1**.

Table 3.4.14. Reaction optimization in details



1 **2**

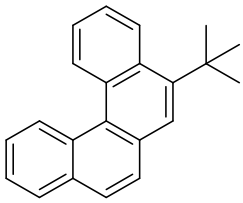
Entry	PhOH /PhCl	Base/T (^{o}C)	Solvent	Conversion	**2/1**
1	1/2	TMPLi/ 25 ^{o}C	THF	32	1/4
2	1/2	TMPLi/ 25 ^{o}C	Et_2O	21	1/3
3	1/2	LDA/ 25 ^{o}C	Et_2O	27	< 1/50
3	1/2	TMPLi/ 40 ^{o}C	Pentane	35	7/1
4	2/1	TMPLi/ 40 ^{o}C	Pentane	17	1/2
5	1/2	TMPLi/ 25 ^{o}C	Pentane/THF (10/1)	40	8/1
6	1/2	TMPLi/ 25 ^{o}C	Pentane/THF (8/1)	34	7/1
7	1/2	TMPLi/ 25 ^{o}C	Pentane/THF (20/1)	52	40/1
8	1/2	TMPLi/ 25 ^{o}C	Pentane/THF (36/1)	61	> 50/1
9	1/2	TMPLi/ 25 ^{o}C	Pentane/THF (50/1)	65	> 50/1
10	1/4	TMPLi/ 25 ^{o}C	Pentane/THF (50/1)	80	> 50/1



Benzophenanthrene (2) (Table 3.4.5, Entry 1)

Chlorobenzene (225 mg, 2.0 mmol), phenol (48 mg, 0.5 mmol), TMPLi in pentane/hexanes (1M, 2.7 mL), followed by THF (0.05 mL), rt, 24 hours. After column chromatography (hexanes, followed by hexanes/CH_2Cl_2 90/10), 76 mg (67 %) of a light yellow solid was obtained.

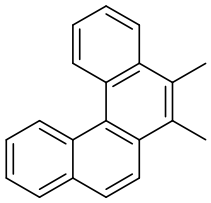
Chlorobenzene (112.5 mg, 1.0 mmol), benzocyclooctenone-5(6H) (85 mg, 0.5 mmol), TMPLi in pentane (1M, 1.8 mL), followed by THF (0.05 mL), rt, 24 hours. After column chromatography (hexanes, followed by hexanes/CH_2Cl_2 90/10), 102 mg (90 %) of a light yellow solid was obtained. R_f = 0.24 (hexanes/CH_2Cl_2 90/10). This compound is known.[44] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (d, *J* = 8.4 Hz, 2H), 8.03 (dd, *J* = 8.0 Hz, 1.3 Hz, 2H), 7.93 – 7.90 (m, 2H), 7.85 – 7.82 (m, 2H), 7.71 – 7.61 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 133.6, 131.1, 130.4, 128.6, 128.0, 127.6, 127.4, 127.0, 126.2, 126.0.



5-*tert*-Butylbenzophenanthrene (3) (Table 3.4.5, Entry 2)

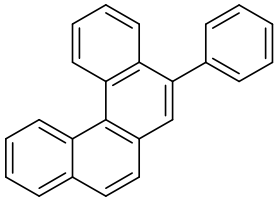
Chlorobenzene (225 mg, 2.0 mmol), 2-*tert*-butylphenol (75 mg, 0.5 mmol), TMPLi in pentane/hexanes (1M, 2.7 mL), followed by THF (0.05 mL), rt, 24 hours. After column

chromatography (hexanes, followed by hexanes/CH_2Cl_2 90/10), 68 mg (48 %) of a colorless oil was obtained. R_f = 0.35 (hexanes/CH_2Cl_2 90/10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 – 9.14 (m, 1H), 9.04 (d, *J* = 8.5 Hz, 1H), 8.69 – 8.66 (m, 1H), 8.01 (dd, *J* = 7.8 Hz, 1.3 Hz, 1H), 7.91 – 7.80 (m, 3H), 7.69 – 7.59 (m, 5H), 1.76 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 144.6, 133.6, 132.0, 131.9, 130.4, 129.9, 129.3, 128.6, 128.2, 127.6, 127.1, 127.0, 126.7, 126.2, 125.6, 124.8, 124.7, 124.3, 36.0, 32.1. FT-IR (neat, cm^{-1}) 2965, 1599, 1368, 887. Anal calcd for $C_{22}H_{20}$ (284.16 g/mol): C, 92.91; H, 7.09; Found. C, 92.51; H, 7.15.



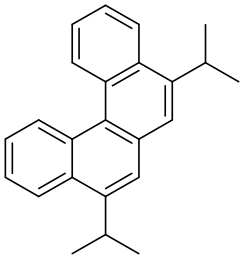
5,6-Dimethylbenzophenanthrene (4) (Table 3.4.5, Entry 3)

Chlorobenzene (225 mg, 2.0 mmol), 2,3-dimethylphenol (61 mg, 0.5 mmol), TMPLi in pentane/hexanes (1M, 2.7 mL), followed by THF (0.05 mL), rt, 24 hours. After column chromatography (hexanes, followed by hexanes/CH_2Cl_2 90/10), 74 mg (58 %) of a white solid was obtained. R_f = 0.27 (hexanes/CH_2Cl_2 90/10). This compound is known.[45] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 – 9.01 (m, 2H), 8.24 (dd, *J* = 8.2 Hz, 1.5 Hz, 1H), 8.12 (d, *J* = 9.1 Hz, 1H), 8.02 (dd, *J* = 7.8 Hz, 1.5 Hz, 1H), 7.93 (d, *J* = 9.1 Hz, 1H), 7.68 – 7.59 (m, 4H), 2.81 (s, 3H), 2.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 133.2, 132.7, 130.7, 130.2, 130.0, 129.6, 129.1, 128.8, 128.7, 128.2, 127.2, 126.8, 126.0, 125.9, 125.6, 124.7, 124.1, 122.8, 16.4, 16.2.



5-Phenylbenzophenanthrene (5) (Table 3.4.5, Entry 4)

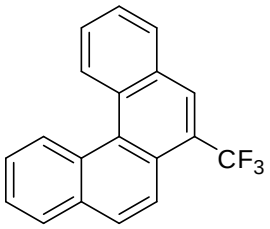
Chlorobenzene (225 mg, 2.0 mmol), 2-phenylphenol (85 mg, 0.5 mmol), TMPLi in pentane/hexanes (1M, 2.7 mL), followed by THF (0.05 mL), rt, 24 hours. After column chromatography (hexanes, followed by hexanes/CH_2Cl_2 90/10), 98 mg (65 %) of a light yellow solid was obtained. R_f = 0.19 (hexanes/CH_2Cl_2 90/10). This compound is known.[46] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (d, *J* = 8.6 Hz, 1H), 9.21 (d, *J* = 8.6 Hz, 1H), 8.14 (dd, *J* = 8.0 Hz, 1.1 Hz, 1H), 8.08 (dd, *J* = 8.0 Hz, 1.1 Hz, 1H), 7.95 (d, *J* = 8.6 Hz, 1H), 7.86 (d, *J* = 8.6 Hz, 1H), 7.84 (s, 1H), 7.77 – 7.72 (m, 2H), 7.69 – 7.66 (m, 3H), 7.61 – 7.57 (m, 3H), 7.55 – 7.52 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 140.7, 139.2, 133.7, 132.4, 130.9, 130.5, 130.3, 128.8, 128.6, 128.4, 128.1, 128.0, 127.6, 127.1, 127.0, 126.9, 126.4, 126.2, 126.1, 126.0. Signals for two carbons could not be located.



5,8-Diisopropylbenzophenanthrene (6) (Table 3.4.5, Entry 5)

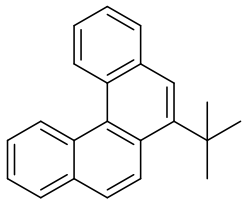
Chlorobenzene (225 mg, 2.0 mmol), 2.6-diisopropylphenol (89 mg, 0.5 mmol), TMPLi in pentane/hexanes (1M, 2.7 mL), followed by THF (0.05 mL), rt, 24 hours. After column chromatography (hexanes, followed by hexanes/CH_2Cl_2 90/10), 62 mg (40 %) of a white

solid was obtained. R_f = 0.34 (hexanes/CH_2Cl_2 90/10), mp 91 – 93 ^oC (from hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 9.07 – 9.04 (m, 2H), 8.31 – 8.29 (m, 2H), 7.73 (s, 2H), 7.67 – 7.62 (m, 4H), 3.84 (heptet, *J* = 6.5 Hz, 2H), 1.52 (d, *J* = 6.5 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 143.2, 131.7, 130.6, 130.5, 128.9, 125.5, 125.4, 125.1, 123.7, 122.5, 28.6, 23.5. FT-IR (neat, cm^{-1}) 2963, 1603, 1521, 893. Anal calcd for $C_{24}H_{24}$ (312.19 g/mol): C, 92.26; H, 7.74; Found. C, 92.55; H, 7.32.



6-(Trifluoromethyl)benzophenanthrene (7) (Table 3.4.5, Entry 6)

Chlorobenzene (225 mg, 2.0 mmol), 3-hydroxybenzotrifluoride (81 mg, 0.5 mmol), TMPLi in pentane/hexanes (1M, 2.7 mL), followed by THF (0.05 mL), rt, 24 hours. After column chromatography (hexanes, followed by hexanes/CH_2Cl_2 90/10), 59 mg (40 %) of a white solid was obtained. R_f = 0.31 (hexanes/CH_2Cl_2 90/10), mp 78 – 80 ^oC (from hexane). ^1H NMR (400 MHz, $CDCl_3$) δ 9.06 – 9.01 (m, 2H), 8.31 (s, 1H), 8.18 – 8.15 (m, 1H), 8.08 – 8.02 (m, 2H), 7.98 (d, *J* = 9.1 Hz, 1H), 7.78 – 7.74 (m, 1H), 7.70 – 7.65 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 133.2, 131.6, 131.0, 130.0, 129.6, 129.5, 129.1, 128.4, 128.3, 128.2, 127.0 (q, *J* = 6.7 Hz), 126.9, 126.8, 126.5, 126.0, 124.9 (q, *J* = 273 Hz), 124.5, (q, *J* = 30.8 Hz), 122.2 (q, *J* = 2.7 Hz). Signal for one carbon could not be located. FT-IR (neat, cm^{-1}) 3680, 2967, 1328, 1110, 1054, 1032. Anal calcd for $C_{19}H_{11}F_3$ (296.08 g/mol): C, 77.02; H, 3.74; Found. C, 77.41; H, 3.72.



6-*tert*-Butylbenzophenanthrene (8) (Table 3.4.5, Entry 7)

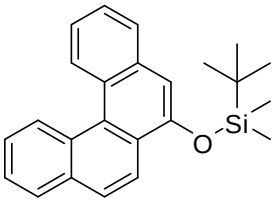
Chlorobenzene (225 mg, 2.0 mmol), 3-*tert*-butylphenol (75 mg, 0.5 mmol), TMPLi in pentane/hexanes (1M, 3.0 mL), followed by THF (0.05 mL), rt, 24 hours. After column chromatography (hexanes, followed by hexanes/CH_2Cl_2 90/10), 72 mg (51 %) of a light yellowish oil was obtained.

6-*tert*-Butyl-6a,12b-dihydrobenzophenanthren-12b-ol (**12**) (151 mg, 0.5 mmol), TMPLi in pentane/hexanes (1M, 1.0 mL), followed by THF (0.03 mL), rt, 24 hours. After column chromatography (hexanes, followed by hexanes/CH_2Cl_2 90/10), 127 mg (90 %) of a light yellowish oil was obtained.

Chlorobenzene (112.5 mg, 1.0 mmol), (7E,9Z)-7-tert-butylbenzo[8]annulen-5(6H)-one **(11)** (113 mg, 0.5 mmol), TMPLi in pentane/hexanes (1M, 2.5 mL), followed by THF (0.05 mL), rt, 24 hours. After column chromatography (hexanes, followed by hexanes/CH_2Cl_2 90/10), 82 mg (58 %) of a light yellow oil was obtained.

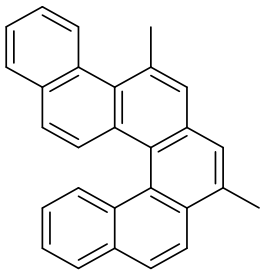
R_f = 0.34 (hexanes/CH_2Cl_2 90/10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 – 8.99 (m, 1H), 8.94 – 8.92 (m, 1H), 8.51 (d, *J* = 9.1 Hz, 1H), 8.00 – 7.95 (m, 2H), 7.90 (s, 1H), 7.87 (d, *J* = 9.1 Hz, 1H), 7.62 – 7.56 (m, 4H), 1.72 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 143.9, 132.9, 132.3, 130.7, 129.8, 129.6, 129.2, 129.1, 128.4, 128.2, 127.7, 126.0, 125.6, 125.5, 125.3, 125.2, 124.5, 36.1, 32.3. Signal for one carbon could not be located. FT-IR

(neat, cm^{-1}) 2960, 1487, 1367, 889. Anal calcd for $C_{22}H_{20}$ (284.16 g/mol): C, 92.91; H, 7.09; Found. C, 92.76; H, 6.88.

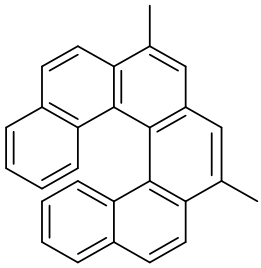


(Benzo[c]phenanthren-6-yloxy)(tert-butyl)dimethylsilane (9) (Table 3.4.5, Entry 8)

Chlorobenzene (225 mg, 2.0 mmol), 3-(*tert*-butyldimethylsilyloxy) phenol (112 mg, 0.5 mmol), TMPLi in pentane/hexanes (1M, 3.0 mL), followed by THF (0.05 mL), rt, 24 hours. After column chromatography (hexanes, followed by hexanes/CH_2Cl_2 90/10), 93 mg (52 %) of a light yellow oil was obtained. R_f = 0.23 (hexanes/CH_2Cl_2 90/10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (d, *J* = 8.1 Hz, 1H), 9.08 (d, *J* = 8.1 Hz, 1H), 8.38 (d, *J* = 8.7 Hz, 1H), 8.06 (dd, *J* = 7.9 Hz, 1.4 Hz, 1H), 7.97 (d, *J* = 8.7 Hz, 1H), 7.91 (dd, *J* = 7.9 Hz, 1.4 Hz, 1H), 7.72 – 7.64 (m, 2H), 7.62 – 7.56 (m, 2H), 7.30 (s, 1H), 1.21 (s, 9H), 0.42 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 149.8, 134.2, 133.7, 130.3, 129.3, 128.6, 128.3, 128.1, 127.4, 127.3, 127.2, 126.7, 126.3, 126.2, 126.1, 124.0, 121.0, 112.0, 26.1, 18.7, -4.0.



7,10-Dimethylnaphtho[2,1-c]chrysene (10)



3,6-Dimethylphenanthro[3,4-c]phenanthrene (11)

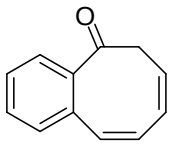
(Scheme 3.4.10)

1-Chloronaphthalene (335 mg, 2.0 mmol), 2,6-dimethylphenol (62 mg, 0.5 mmol), TMPLi in pentane/hexanes (1M, 2.7 mL), followed by THF (0.05 mL), rt, 24 hours. After column chromatography (hexanes, followed by hexanes/CH_2Cl_2 90/10), 106 mg (60 %) of a light brown solid (mixture of isomers) was obtained. The isomer ratio was determined to be 2/1 **10/9** by ^{1}HNMR. The isomers were separated by fractional crystallization from hexanes. Compound **10** crystallized out and was collected by vacuum filtration at - 20 ^{o}C. Residue from crystallization contains a mixture of two isomers. White crystalline **10** was obtained (45 mg, 26% yield) and 61 mg of isomer mixture was recovered. Mixture: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (d, *J* = 8.5 Hz), 8.16 – 8.11 (m), 8.05 – 8.03 (m), 7.99 – 7.89 (m), 7.83 – 7.81 (m), 7.75 – 7.72 (m), 7.68 – 7.62 (m), 7.53 – 7.47 (m), 7.43 (d, *J* = 8.8 Hz), 7.21 – 7.17 (m), 6.65 – 6.61 (m), 3.17 (s), 2.90 (s), 2.86 (s).

3,6-Dimethylphenanthro[3,4-c]phenanthrene (11) (Scheme 3.4.10)

R_f = 0.19 (hexanes/CH_2Cl_2 90/10), mp 240 – 242 ^{o}C (from hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 9.1 Hz, 2H), 7.93 (d, *J* = 9.1 Hz, 2H), 7.80 (dd, *J* = 8.3 Hz, 0.9 Hz, 2H), 7.76 (s, 2H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.19 = 7.15 (m, 2H), 7.65 – 7.60 (m, 2H),

2.90 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 133.2, 132.6, 131.4, 130.2, 130.1, 128.6, 128.2, 127.3, 127.2, 126.8, 125.4, 124.5, 122.2, 122.1, 20.1. FT-IR (neat, cm^{-1}) 2380, 2343, 2334. Anal calcd for $C_{28}H_{20}$ (356.16 g/mol): C, 94.34; H, 5.66; Found. C, 93.96; H, 5.64.

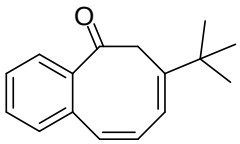


5(6H)-Benzocyclooctenone (16) (Scheme 3.4.12)

Chlorobenzene (90 mg, 0.8 mmol), phenol (48 mg, 0.5 mmol), TMPLi in pentane/hexanes (1M, 1.5 mL), followed by THF (0.04 mL), rt, 24 hours. After column chromatography (hexanes, followed by hexanes/EtOAc 70/30), 46 mg (55 %) of a colorless oil was obtained.

Chlorobenzene (56 mg, 0.5 mmol), phenol (94 mg, 1.0 mmol), solid TMPLi (265 mg, 1.8 mmol), benzene (1 mL), 45 ^{o}C, 24 hours. After column chromatography (hexanes, followed by hexanes/EtOAc 70/30), 53 mg (63 %) of a colorless oil was obtained.

R_f = 0.32 (hexanes/EtOAc 70/30). This compound is known.[47] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (dd, *J* = 8.0 Hz, 1.1 Hz, 1H), 7.54 (dt, *J* = 7.5 Hz, 1.6 Hz, 1H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.37 (dt, *J* = 7.5 Hz, 1.1 Hz, 1H), 6.87 (d, *J* = 12.9 Hz, 1H), 6.41 (dd, *J* = 12.9 Hz, 4.5 Hz, 1H), 6.30 (dd, *J* = 10.1 Hz, 4.5 Hz, 1H), 5.86 (q, *J* = 10.1 Hz, 1H), 3.42 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 193.7, 137.3, 136.7, 134.4, 132.4, 132.1, 131.0, 130.2, 128.8, 128.0, 127.1, 43.8.

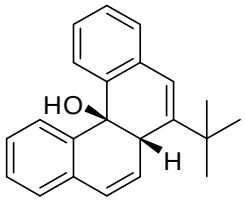


(7E,9Z)-7-*tert*-Butylbenzo[8]annulen-5(6H)-one (12) (Scheme 3.4.11)

Chlorobenzene (90 mg, 0.8 mmol), 3-*tert*-butylphenol (75 mg, 0.5 mmol), TMPLi in pentane/hexanes (1M, 1.4 mL), followed by THF (0.03 mL), rt, 24 hours. After column chromatography (hexanes, followed by hexanes/EtOAc 95/5), 69 mg (61 %) of a colorless oil was obtained.

Chlorobenzene (56 mg, 0.5 mmol), 3-*tert*-butylphenol (225 mg, 1.5 mmol), TMPLi in pentane/hexanes (1M, 1.4 mL), followed by Et_2O (0.03 mL), rt, 24 hours. After column chromatography (hexanes, followed by hexanes/EtOAc 95/5), 73 mg (65 %) of a colorless oil was obtained.

R_f = 0.29 (hexanes/EtOAc 95/5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 8.1 Hz, 1.3 Hz, 1H), 7.48 (dt, *J* = 7.4 Hz, 1.3 Hz, 1H), 7.33 – 7.27 (m, 1H), 6.78 (d, *J* = 12.3 Hz, 1H), 6.41 (dd, *J* = 12.3 Hz, 4.5 Hz, 1H), 6.03 (d, *J* = 4.5 Hz, 1H), 3.55 (s, 2H), 1.12 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 199.9, 149.0, 137.5, 137.0, 132.1, 131.9, 131.1, 130.7, 130.6, 127.0, 122.2, 45.9, 37.6, 29.3. . FT-IR (neat, cm^{-1}) 2963, 1669, 1595, 1289. Anal calcd for $C_{16}H_{18}O$ (226.14 g/mol): C, 84.91; H, 8.02; Found. C, 84.68; H, 7.85.

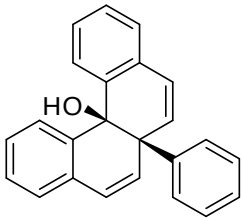


6-*tert*-Butyl-6a,12b-dihydrobenzophenanthren-12b-ol (13) (Scheme 3.4.11)

Chlorobenzene (168 mg, 1.5 mmol), 3-*tert*-butylphenol (75 mg, 0.5 mmol), TMPLi in pentane/hexanes (1M, 2.1 mL), followed by THF (0.04 mL), rt, 24 hours. After column chromatography (hexanes, followed by hexanes/EtOAc 95/15), 98 mg (65 %) of a yellowish oil was obtained.

Chlorobenzene (112.5 mg, 1.0 mmol), (7E,9Z)-7-tert-butylbenzo[8]annulen-5(6H)-one **(11)** (113 mg, 0.5 mmol), TMPLi in pentane/hexanes (1M, 1.6 mL), followed by THF (0.03 mL), rt, 24 hours. After column chromatography (hexanes, followed by hexanes/EtOAc 95/15), 96 mg (64 %) of a light yellow oil was obtained.

R_f = 0.34 (hexanes/EtOAc 95/5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (dd. *J* = 7.8 Hz, 0.8 Hz, 1H), 7.42 (dt, *J* = 7.8 Hz, 1.3 Hz, 1H), 7.34 (dt, *J* = 7.8 Hz, 1.3 Hz, 1H), 7.21 (dt, *J* = 7.5 Hz, 1.3 Hz, 1H), 7.14 – 7.08 (m, 2H), 6.98 (dt, *J* = 7.5 Hz, 1.3 Hz, 1H), 6.55 – 6.52 (m, 2H), 6.42 (dd, *J* = 9.5 Hz, 3.2 Hz, 1H), 5.58 (dd, *J* = 9.5 Hz, 2.2 Hz, 1H), 3.73 (t, *J* = 2.8 Hz, 1H), 2.45 (s, 1H), 1.26 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 147.5, 138.0, 136.9, 133.9, 133.2, 129.5, 129.3, 128.6, 127.9, 127.8, 127.3, 126.9, 126.4, 126.2, 126.0, 119.5, 74.9, 43.9, 36.2, 28.6. FT-IR (neat, cm^{-1}) 2950, 1537, 1321. Anal calcd for $C_{22}H_{22}O$ (302.17 g/mol): C, 87.38; H, 7.33; Found. C, 86.98; H, 7.45.

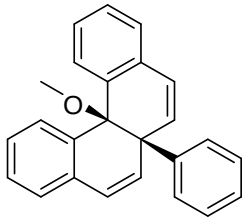


6a-Phenyl-6a,12b-dihydrobenzophenanthren-12b-ol (14) (Scheme 3.4.11)

Chlorobenzene (225 mg, 2.0 mmol), 4-hydroxybiphenyl (85 mg, 0.5 mmol), TMPLi in pentane/hexanes (1M, 2.7 mL), followed by THF (0.05 mL), rt, 24 hours. After column

chromatography (hexanes, followed by hexanes/EtOAc 95/5), 122 mg (70 %) of a white solid was obtained.

R_f = 0.31 (hexanes/EtOAc 90/10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.40 (m, 3H), 7.30 – 7.22 (m, 6H), 7.17 – 7.14 (m, 4H), 6.77 (d, *J* = 9.0 Hz, 2H), 5.97 (broad singlet, 2H), 1.89 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 137.9, 136.9, 132.8 (broad), 131.7 (broad), 129.4, 128.4, 128.3, 128.1, 127.7, 127.0, 126.5, 51.8. Signals for two carbons could not be located. FT-IR (neat, cm^{-1}) 2955, 1544, 1334, 1235. Anal calcd for $C_{24}H_{18}O$ (322.14 g/mol): C, 89.41; H, 5.63; Found. C, 88.97; H, 5.55.



6a-Phenyl-6a-hydro-12b-methoxybenzophenanthrene (Scheme 3.4.11)

A 2 dram vial equipped with magnetic stirring bar was charged with 6a-phenyl-6a,12b-dihydrobenzophenanthren-12b-ol **(13)** (175 mg, 0.5 mmol), MeI (284 mg, 2.0 mmol). Vial was flushed with nitrogen and taken into glovebox. To this mixture, THF (1 mL) was added, followed by NaH (24 mg, 1.0 mmol). Vial was shaken to release all generated hydrogen. Vial was capped, taken out glovebox and placed in oil bath at 50 ^{o}C for 4 hours. After completion, vial was allowed to cool down to room temperature and reaction mixture was quenched with H_2O (10 mL). The reaction mixture was diluted with ethyl acetate (30 mL) and washed with brine (1 x 30 mL). The aqueous phase was extracted with ethyl acetate (3 x 15 mL). Combined organic phase was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved EtOAc (1

mL) and subjected to column chromatography on silica gel (hexane followed 95/5 hexane/EtOAc). After concentration of fractions containing product, 173 mg (91 %) of a light yellow solid was obtained.

Recrystallization procedure: Vial equipped with magnetic stirring bar was charged with 50 mg of product. Hexane (1.5 mL) was then added. Vial was placed into oil bath at 60 ^{o}C for an hour. CH_2Cl_2 was added to vial dropwise at 40 ^{o}C until all solid dissolved. Vial was capped and taken out oil bath and allowed to cool down to room temperature to obtain crystals suiTable 3.4.for X-ray analysis.

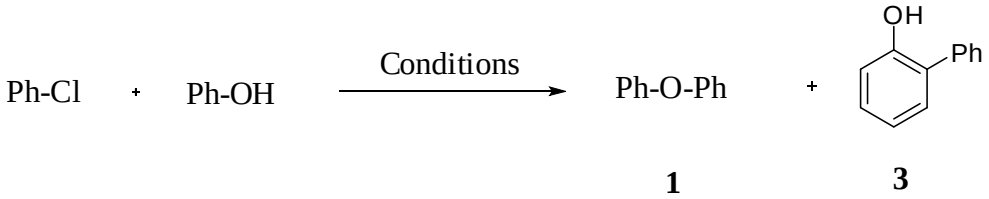
R_f = 0.33 (hexanes/EtOAc 95/5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.32 (m, 3H), 7.28 – 7.24 (m, 3H), 7.22 – 7.17 (m, 4H), 7.17 – 7.10 (m, 4H), 6.66 (d, *J* = 9.6 Hz, 2H), 5.98 (broad singlet, 2H), 3.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 138.63, 134.0 (broad), 133.5 (broad), 129.3, 128.5, 128.2, 127.9, 127.7, 127.0, 126.0, 81.2, 53.6, 51.5. Signals for two carbons could not be located.

General procedure for arylation of phenols: Outside the glovebox a 2-dram vial equipped with a magnetic stirring bar was charged with chloroarene (0.8 – 2.0 mmol), phenol (0.5 mmol), and AgOAc (0 – 1.0 mmol). The vial was flushed with nitrogen, capped and placed inside the glovebox. To this mixture was added dioxane (0.8 – 1.3 mL), *t*-BuONa (1.5 – 3.0 mmol). The sealed vial was taken out the glovebox, stirred at room temperature for 5 minutes, placed in ultrasonic bath for 1 minute, covered with aluminum foil, and then transferred to preheated oil bath for indicated time. Reaction vials were occasionally shaken during first few hours to ensure complete mixing which is important to ensure reproducible yields. The reaction mixture was cooled to room

temperature and quenched with 10 % aqueous citric acid (10 mL). The reaction mixture was diluted with ethyl acetate (30 mL) and washed with brine (1 x 30 mL). The aqueous phase was extracted with ethyl acetate (3 x 15 mL). Combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in minimal amount of ethyl acetate and subjected to column chromatography on silica gel in hexane followed by appropriate solvent to elute the products. After concentrating the fractions containing the product, the residue was dried under reduced pressure.

Optimization of conditions for phenol arylation: All reactions were carried out following the general procedure. Phenol (x mmol), chlorobenzene (y mmol), base [1.3*(x + y) mmol], solvent (1 mL), 24 hours. Conversions and **3/1** ratio were calculated by GC analysis. Conversions are presented in Table 3.4.S1 and show the amount of product **1** and **3** formed (e.g. 70 % means that 70 % of starting limiting reagent is converted to **1** and **3**). Mixture with exact molar amounts of pure **1** and pure **3** was used as the standard to determine the ratio **3/1**.

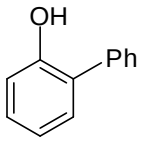
Table 3.4.15. Optimization of phenol *o*-arylation



1 **3**

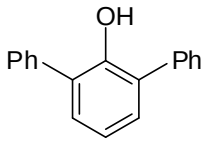
Entry	PhOH/ PhCl	Base/T (^oC)	Solvent	Additive /equiv.	Conversion	**3/1**
1	1/2	TMPLi/25	Etheral	None	32	< 1/50

2	1/2	TMPLi/25	Pentane/Ether	None	15	< 1/50
3	1/2	NaHMDS/50	THF	None	95	< 1/50
4	1/2	*t*-BuOK/110	Dioxane	None	91	1/9
5	1/2	*t*-BuONa/155	Dioxane	None	87	1/7
6	2/1	*t*-BuONa/155	Dioxane	None	68	1/11
7	1/2	*t*-BuONa/155	Toluene	None	45	1/10
8	1/2	*t*-BuONa/155	Dioxane	AgOAc/1.0	87	30/1
9	1/2	*t*-BuONa/155	Dioxane	AgOAc/0.5	79	24/1
10	1/2	*t*-BuONa/155	Dioxane	AgOAc/0.1	65	15/1
11	1/2	*t*-BuONa/155	Dioxane	$MnCl_2$/1.0	32	7/1
12	1/2	*t*-BuONa/155	Dioxane	$NiCl_2$/1.0	< 5	ND
14	1/2	*t*-BuONa/155	Dioxane	$FeCl_3$/1.0	13	3/1



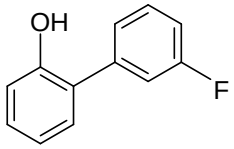
2-Phenylphenol (Table 3.4.7, Entry 1)

Chlorobenzene (101 mg, 0.9 mmol), phenol (47 mg, 0.5 mmol), AgOAc (42 mg, 0.25 mmol), *t*-BuONa (192 mg, 2.0 mmol), dioxane (0.8 mL), 155 ^{o}C, 48 hours. After column chromatography (hexanes, followed by hexanes/EtOAc 90/10), 66 mg (78 %) of a light yellow solid was obtained. R_f = 0.32 (hexanes/EtOAc 90/10). This compound is known.[48] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.49 (m, 4H), 7.45 – 7.40 (m, 1H), 7.32 – 7.27 (m, 2H), 7.06 – 7.00 (m, 2H), 5.30 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 152.5, 137.2, 130.4, 129.5, 129.3, 129.2, 128.3, 128.0, 121.0, 116.0.



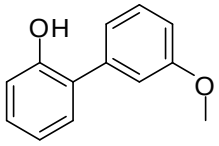
2,6-Diphenylphenol (Table 3.4.7, Entry 2)

Chlorobenzene (282 mg, 2.5 mmol), phenol (47 mg, 0.5 mmol), AgOAc (125 mg, 0.75 mmol), *t*-BuONa (336 mg, 3.5 mmol), dioxane (1.2 mL), 155 ^{o}C, 96 hours. After column chromatography (hexanes, followed by hexanes/EtOAc 95/5), 73 mg (60 %) of a white solid was obtained. R_f = 0.27 (hexanes/EtOAc 95/5). This compound is known.[49] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 – 7.58 (m, 4H), 7.53 – 7.49 (m, 4H), 7.44 – 7.40 (m, 2H), 7.31 (d, *J* = 7.5 Hz, 2H), 7.09 (t, *J* = 7.5 Hz, 1H), 5.44 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 149.4, 137.7, 130.1, 129.5, 129.0, 128.9, 127.8, 120.8.



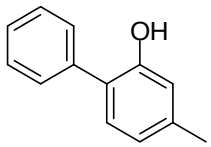
3'-Fluorobiphenyl-2-ol (Table 3.4.7, Entry 3)

1-Fluoro-3-chlorobenzene (105 mg, 0.8 mmol), phenol (47 mg, 0.5 mmol), AgOAc (58 mg, 0.35 mmol), *t*-BuONa (173 mg, 1.8 mmol), dioxane (1.0 mL), 135 ^{o}C, 48 hours. After column chromatography (hexanes, followed by hexanes/EtOAc 90/10), 67 mg (72 %) of a light yellowish oil was obtained. R_f = 0.29 (hexanes/EtOAc 90/10). This compound is known.[50] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.41 (m, 1H), 7.30 – 7.19 (m, 4H), 7.11 – 7.06 (m, 1H), 7.02 – 6.96 (m, 2H), 5.17 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.3 (d, J_{C-F} = 247.7 Hz), 152.4, 139.5 (d, J_{C-F} = 7.8 Hz), 130.7 (d, J_{C-F} = 8.7 Hz), 130.3, 129.7, 127.0, 124.8 (d, J_{C-F} = 2.5 Hz), 121.2, 116.3 (d, J_{C-F} = 21.9 Hz), 116.2, 114.8 (d, J_{C-F} = 21.9 Hz).



3'-Methoxybiphenyl-2-ol (Table 3.4.7, Entry 4)

2-Chloroanisole (215 mg, 1.5 mmol), phenol (47 mg, 0.5 mmol), *t*-BuONa (240 mg, 2.5 mmol), AgOAc (67 mg, 0.4 mmol), dioxane (1.0 mL), 155 ^{o}C, 48 hours. After column chromatography (hexanes, followed by hexanes/EtOAc 85/15), 64 mg (64 %) of a white solid was obtained. R_f = 0.25 (hexanes/EtOAc 85/15). This compound is known.[51] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (t, *J* = 7.8 Hz, 1H), 7.30 – 7.25 (m, 2H), 7.07 – 7.04 (m, 1H), 7.02 – 6.99 (m, 3H), 6.95 (dd, *J* = 8,2 Hz, 2.7 Hz, 1H), 5.39 (s, 1H), 3.85 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 160.4, 152.5, 138.5, 130.5, 130.2, 129.4, 128.0, 121.3, 120.9, 115.9, 114.6, 113.7, 55.4.

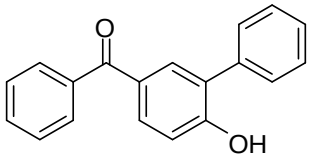


4-Methylbiphenyl-2-ol (Table 3.4.7, Entry 5)

Chlorobenzene (170 mg, 1.5 mmol), *m*-cresol (54 mg, 0.5 mmol), AgOAc (144 mg, 0.85 mmol), sodium *tert*-pentoxide (336 mg, 3.0 mmol), dioxane (1.0 mL), 155 ^{o}C, 48 hours. After column chromatography (hexanes, followed by hexanes/EtOAc 93/7), 73 mg (80 %) of a colorless oil was obtained. Isomer ratio in crude product was determined to be 9/1 (4-methylbiphenyl-2-ol)/(6-methylbiphenyl-2-ol) by GC analysis.

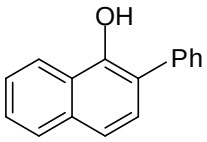
R_f = 0.28 (hexanes/EtOAc 93/7). This compound is known.[52] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.44 (m, 4H), 7.39 – 7.36 (m, 1H), 7.13 (d, J = Hz, 1H), 6.82 – 6.81 (m,

2H), 5.15 (s, 1H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 152.3, 139.5, 137.2, 130.1, 129.4, 129.2, 127.8, 125.3, 121.8, 116.5, 21.3.



(6-Hydroxybiphenyl-3-yl)(phenyl)methanone (Table 3.4.7, Entry 6)

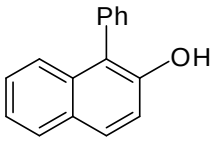
Chlorobenzene (225 mg, 2.0 mmol), 4-hydroxybenzophenone (99 mg, 0.5 mmol), *t*-BuONa (338 mg, 3.5 mmol), AgOAc (167 mg, 1.0 mmol), dioxane (1.0 mL), 155 ^{o}C, 96 hours. After column chromatography (hexanes, followed by hexanes/EtOAc 50/50), 79 mg (58 %) of a white solid was obtained. R_f = 0.31 (hexanes/EtOAc 40/60). This compound is known.[53] ^{1}H NMR (400 MHz, DMSO-d6) δ 10.64 (s, 1H), 7.69 – 7.67 (m, 2H), 7.63 – 7.58 (m, 3H), 7.52 – 7.49 (m, 4H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.29 (tt, *J* = 7.6 Hz, 2.2 Hz, 1H), 7.06 (d, *J* = 8.7 Hz, 1H).^{13}C NMR (100 MHz, DMSO-d6, ppm) δ 194.8, 159.5, 138.5, 138.0, 133.5, 132.5, 131.9, 129.8, 129.6, 129.0, 128.8, 128.7, 128.3, 127.6, 116.5.



1-Phenyl-1-naphthol (Table 3.4.7, Entry 7)

Chlorobenzene (225 mg, 2.0 mmol), 1-naphthol (72 mg, 0.5 mmol), AgOAc (167 mg, 1.0 mmol), *t*-BuONa (384 mg, 4.0 mmol), dioxane (1.0 mL), 155 ^{o}C, 48 hours. After column chromatography (hexanes, followed by hexanes/EtOAc 93/7), 90 mg (82 %) of a white solid was obtained. R_f = 0.28 (hexanes/EtOAc 90/10). This compound is known.[54] ^{1}H

NMR (400 MHz, $CDCl_3$) δ 8.31 – 8.29 (m, 1H), 7.84 – 7.81 (m, 1H), 7.58 – 7.54 (m, 4H), 7.53 – 7.48 (m, 3H), 7.47 – 7.42 (m, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 5.84 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 147.8, 137.5, 134.3, 129.7, 129.5, 128.0, 127.7, 127.6, 126.6, 125.7, 124.4, 122.5, 121.3, 120.3.



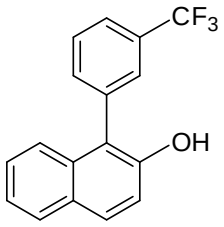
1-Phenyl-2-naphthol (Table 3.4.7, Entry 8)

Chlorobenzene (225 mg, 2.0 mmol), 2-naphthol (72 mg, 0.5 mmol), *t*-BuONa (384 mg, 4.0 mmol), dioxane (1.0 mL), 155 ^oC, 72 hours. After column chromatography (hexanes, followed by hexanes/EtOAc 93/7), 87 mg (80 %) of a light brown solid was obtained.

Large scale synthesis: A 50 mL pressure vessel equipped with a stir bar was charged with 2-naphthol (1.44 g, 10.0 mmol) and chlorobenzene (4.5 g, 40.0 mmol). The vessel was flushed with nitrogen, capped and placed inside the glovebox. To this mixture was added dioxane (20 mL) and *t*-BuONa (7.6 g, 80 mmol). The sealed vessel was taken out the glovebox, reaction mixture was stirred at room temperature for 5 minutes, then placed in preheated oil bath at 155 ^oC for 72 hours. The reaction mixture was cooled to room temperature and quenched with 10 % aqueous citric acid (50 mL). The reaction mixture was diluted with ethyl acetate (100 mL) and washed with brine (1 x 50 mL). The aqueous phase was extracted with ethyl acetate (3 x 30 mL). Combined organic phases were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in minimal amount of ethyl acetate and subjected to column chromatography on silica gel in hexane followed by hexanes/EtOAc 93/7 to elute the product. After

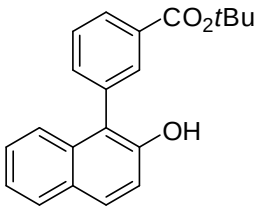
concentrating the fractions containing the product, 1.69 g (77 %) of a light brown solid was obtained.

R_f = 0.27 (hexanes/EtOAc 90/10). This compound is known.[55] ^{1}H NMR (400 MHz, $CDCl_3$) δ7.85 – 7.81 (m, 2H), 7.61 – 7.58 (m, 2H), 7.54 – 7.50 (m, 1H), 7.45 – 7.41 (m, 3H), 7.37 – 7.33 (m, 2H), 7.28 (d, *J* = 8.6 Hz, 1H), 5.18 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 150.3, 134.3, 133.3, 131.3, 129.8, 129.6, 129.0, 128.6, 128.2, 126.6, 124.7, 123.4, 121.1, 117.5.



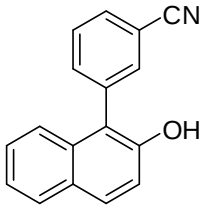
1-(3-(Trifluoromethyl)phenyl)-2-naphthol (Table 3.4.7, Entry 9)

3-Chlorobenzotrifluoride (360 mg, 2.0 mmol), 2-naphthol (72 mg, 0.5 mmol), *t*-BuONa (384 mg, 4.0 mmol), dioxane (1.0 mL), 135 ^{o}C, 48 hours. After column chromatography (hexanes, followed by hexanes/EtOAc 90/10), 106 mg (74 %) of a light brown oil was obtained. R_f = 0.29 (hexanes/EtOAc 90/10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.82 (m, 2H), 7.80 – 7.78 (m, 1H), 7.75 – 7.70 (m, 2H), 7.65 – 7.63 (m, 1H), 7.41 – 7.31 (m, 3H), 7.27 (d, *J* = 8.8 Hz, 1H), 5.1 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 150.3, 135.6, 134.8, 133.2, 132.0 (q, J_{C-F} = 32 Hz), 130.3, 130.1, 129.1, 128.3, 128.2 (q, J_{C-F} = 3.7 Hz), 127.0, 125.3 (q, J_{C-F} = 3.7 Hz), 124.3, 124.0 (q, J_{C-F} = 272 Hz), 123.7, 119.7, 117.7. FT-IR (neat, cm^{-1}) 1331, 1166, 1123. Anal calcd for $C_{17}H_{11}F_3O$ (288.08 g/mol): C, 70.83; H, 3.85; Found. C, 71.12; H, 3.52.



tert-Butyl 3-(2-hydroxynaphthalen-1-yl)benzoate (Table 3.4.7, Entry 10)

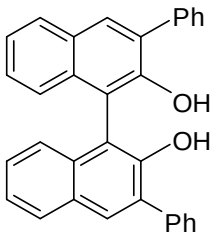
tert-Butyl-3-bromobenzoate (385 mg, 1.5 mmol), 2-naphthol (72 mg, 0.5 mmol), *t*-BuONa (384 mg, 4.0 mmol), dioxane (1.0 mL), 150 ^{o}C, 24 hours. After column chromatography (hexanes, followed by hexanes/EtOAc 90/10), 112 mg of a light yellowish oil containing a mixture of product and 2-naphthol was obtained. NMR analysis showed that the mixture contains 104 mg (66 %) of product. Attempts to completely separate product from starting material by preparative TLC and HPLC failed. R_f = 0.27 (hexanes/EtOAc 90/10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (td, *J* = 7.8 Hz, 1.4 Hz, 1H), 8.04 (t, *J* = 1.4 Hz, 1H), 7.84 – 7.81 (m, 2H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.58 (td, *J* = 7.8 Hz, 1.4 Hz, 1H), 7.36 – 7.30 (m, 3H), 7.25 (s, 1H), 5.00 (s, 1H), 1.59 (s, 9H) . ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.4, 150.3, 135.4, 134.5, 133.5, 133.3, 132.1, 129.9, 129.7, 129.6, 129.0, 128.2, 126.8, 124.5, 123.6, 120.3, 117.5, 81.6, 28.3. FT-IR (neat, cm^{-1}) 2965, 1662, 1597, 1289. Anal calcd for $C_{21}H_{20}O_3$ (320.14 g/mol): C, 78.73; H, 6.29; Found. C, 78.24; H, 6.03.



3-(2-Hydroxynaphthalen-1-yl)benzonitrile (Table 3.4.7, Entry 11)

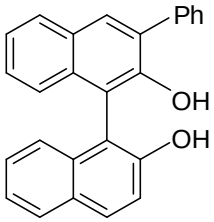
3-Chlorobenzonitrile (205.5 mg, 1.5 mmol), 2-naphthol (72 mg, 0.5 mmol), *t*-BuONa (288 mg, 3.0 mmol), dioxane (1.0 mL), 140 ^{o}C, 72 hours. After column chromatography (hexanes, followed by hexanes/EtOAc 75/25), 79 mg (65 %) of a brown oil was obtained. R_f = 0.22 (hexanes/EtOAc 75/25). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.81 (m, 2H), 7.79 – 7.74 (m, 2H), 7.69 – 7.67 (m, 2H), 7.39 – 7.35 (m, 2H), 7.30 – 7.26 (m, 1H), 7.25 (d, *J* = 8.7 Hz, 1H), 5.48 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 150.3, 136.6, 136.1, 135.0, 133.1, 131.9, 130.5, 130.3, 129.0, 128.4, 127.2, 124.0, 123.8, 119.1, 118.6, 117.8, 113.5. FT-IR (neat, cm^{-1}) 3394, 2232, 1513, 1273. Anal calcd for $C_{17}H_{11}NO$ (245.08 g/mol): C, 83.25; H, 4.52; Found. C, 83.41; H, 4.04.

Note: product contains less than 3 % of another isomer.



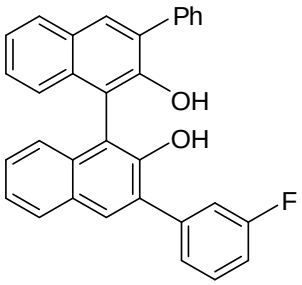
3,3'-Diphenyl-1,1'-binaphthyl-2,2'-diol (21) (Scheme 3.4.13)

Chlorobenzene (337 mg, 3.0 mmol), 1,1'-binaphthyl-2,2'-diol (143 mg, 0.5 mmol), *t*-BuONa (432 mg, 4.5 mmol), AgOAc (168 mg, 1.0 mmol), dioxane (1.3 mL), 155 ^{o}C, 96 hours. After column chromatography (hexanes, followed by hexanes/EtOAc 90/10), 111 mg (51 %) of a light yellow solid was obtained. R_f = 0.36 (hexanes/EtOAc 90/10). This compound is known.[56] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 2H), 7.92 (d, *J* = 8.3 Hz, 2H), 7.75 – 7.71 (m, 4H), 7.51 – 7.47 (m, 4H), 7.42 – 7.37 (m, 4H), 7.34 – 7.30 (m, 2H), 7.24 (t, *J* = 8.7 Hz, 2H), 5.35 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 150.2, 137.5, 133.0, 131.5, 130.7, 129.7, 129.5, 128.6, 128.5, 127.9, 127.5, 124.4, 124.3, 112.4.



3-Phenyl-1,1'-binaphthyl-2,2'-diol (22) (Scheme 3.4.13)

Chlorobenzene (192 mg, 1.7 mmol), 1,1'-binaphthyl-2,2'-diol (143 mg, 0.5 mmol), *t*-BuONa (288 mg, 3.0 mmol), AgOAc (144 mg, 0.85 mmol), dioxane (1.0 mL), 155 ^{o}C, 48 hours. After column chromatography (hexanes, followed by hexanes/EtOAc 87/13), 120 mg (67 %) of a light yellow solid was obtained. R_f = 0.26 (hexanes/EtOAc 85/15). This compound is known.[57] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.97 (d, *J* = 9.1 Hz, 1H), 7.94 – 7.89 (m, 2H), 7.76 – 7.73 (m, 2H), 7.53 – 7.49 (m, 2H), 7.45 – 7.31 (m, 6H), 7.27 – 7.25 (m, 1H), 7.17 (d, *J* = 8.5 Hz, 1H), 5.33 (s, 1H), 5.13 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 152.8, 150.4, 137.5, 133.5, 133.1, 131.6, 131.5, 130.8, 129.7, 129.6, 128.7, 128.6, 128.5, 127.9, 127.6, 124.5, 124.4, 124.3, 124.1, 117.9, 111.9, 111.6. Signals for two carbons could not be located.

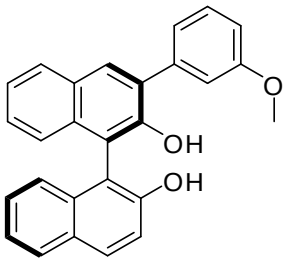


3-(3-Fluorophenyl)-3'-phenyl-1,1'-binaphthyl-2,2'-diol (23) (Scheme 3.4.13)

1-Chloro-3-fluorobenzene (260 mg, 2.0 mmol), 3-phenyl-1,1'-binaphthyl-2,2'-diol (180 mg, 0.5 mmol), *t*-BuONa (338 mg, 3.5 mmol), AgOAc (168 mg, 1.0 mmol), dioxane (1.0

mL), 135 ^{o}C, 96 hours. After column chromatography (hexanes, followed by hexanes/EtOAc 93/7), 136 mg (60 %) of a light yellow solid was obtained. R_f = 0.31 (hexanes/EtOAc 90/10), mp 118 – 120 ^{o}C (from hexanes). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 2.7 Hz, 2H), 7.95 (d, *J* = 7.8 Hz, 2H), 7.77 – 7.74 (m, 2H), 7.55 – 7.50 (m, 4H), 7.46 – 7.40 (m, 4H), 7.37 – 7.33 (m, 2H), 7.27 – 7.24 (m, 2H), 7.12 (ddt, *J* = 8.4 Hz, 2.7 Hz, 0.9 Hz, 1H), 5.39 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 162.8 (d, J_{C-F} = 244.6 Hz), 150.4, 150.0, 139.8 (d, J_{C-F} = 7.9 Hz), 137.4, 133.2, 133.0, 131.7 (d, J_{C-F} = 10.4 Hz), 130.8, 129.9, 129.8, 129.7, 129.6, 129.5, 128.8, 128.7, 128.6, 128.0, 127.8, 127.6, 125.4 (d, J_{C-F} = 2.8 Hz), 124.6, 124.4, 124.3, 116.8 (d, J_{C-F} = 22.2 Hz), 114.6 (d, J_{C-F} = 22.2 Hz).112.8, 112.0. Signals for two carbons could not be located. FT-IR (neat, cm^{-1}) 2956, 1434, 1263, 1121. Anal calcd for $C_{32}H_{21}FO_2$ (456.15 g/mol): C, 84.19; H, 4.64; Found. C, 84.01; H, 4.65.

Note: product contains less than 4 % of another isomer.



3-(3-Methoxyphenyl)-(R)-(+)-1,1'-binaphthyl-2,2'-diol (24) (Scheme 3.4.13)

3-Chloroanisole (285 mg, 2.0 mmol), (R)-(+)-1,1'-bi(2-naphthol) (143 mg, 0.5 mmol), *t*-BuONa (336 mg, 3.5 mmol), AgOAc (153 mg, 0.9 mmol), dioxane (1.0 mL), 130 ^{o}C, 36 hours. After column chromatography (hexanes, followed by hexanes/EtOAc 85/15), and then HPLC (hexanes/EtOAc 87/13), 97 mg (50 %) of a light yellow solid was obtained.

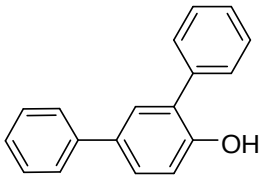
Determination of % ee by HPLC on chiral stationary phase: CHIRALPAK ID, hexanes/isopropanol 95:5, 0.75 mL/min, 95 % ee. Retention time: major, (R) = 31.3 min, (S) = 34.6 min.

R_f = 0.22 (hexanes/EtOAc 85/15). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.97 (d, *J* = 8.9 Hz, 1H), 7.90 (t, *J* = 8.5 Hz, 2H), 7.42 – 7.35 (m, 4H), 7.33 – 7.21 (m, 5H), 7.15 (d, *J* = 8.5 Hz, 1H), 6.96 (ddd, *J* = 8.2 Hz, 2.7 Hz, 0.9 Hz, 1H), 5.16 (broad singlet, 2H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 159.8, 152.8, 152.7, 150.3, 138.8, 133.5, 131.6, 131.5, 131.4, 129.7, 129.6, 128.6, 128.5, 127.6, 127.5, 124.5, 124.4, 124.3, 124.1, 122.0, 117.8, 115.3, 113.6, 111.9, 111.7, 110.9, 55.5. FT-IR (neat, cm^{-1}) 2946, 1344, 1363. Anal calcd for $C_{27}H_{20}O_3$ (492.14 g/mol): C, 82.63; H, 5.14; Found. C, 82.11; H, 4.85.

Note: Product contains less than 3 % of 1,1'-bi(2-naphthol).

Control experiment: Diphenyl ether (78 mg, 0.5 mmol), PhCl (113 mg, 1.0 mmol), AgOAc (170 mg, 1.0 mmol), dioxane (1 mL), 155 ^{o}C, 48 hours. No detectable amount of 2-phenylphenol was observed by GC and diphenyl ether was recovered.

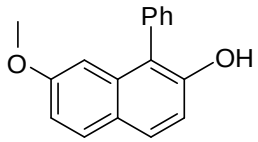
Additional examples



2,4-Diphenylphenol

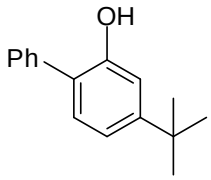
Chlorobenzene (136 mg, 1.2 mmol), 4-phenylphenol (85 mg, 0.5 mmol), AgOAc (42 mg, 0.25 mmol), *t*-BuONa (192 mg, 2.0 mmol), dioxane (1.0 mL), 155 ^{o}C, 72 hours. After

column chromatography (hexanes, followed by hexanes/EtOAc 90/10), 94 mg (77 %) of a white solid was obtained. R_f = 0.25 (hexanes/EtOAc 90/10). This compound is known.[58] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.6 – 7.56 (m ,2H), 7.54 – 7.49 (m, 6H), 7.44 – 7.40 (m, 3H), 7.33 – 7.29 (m, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 5.29 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 152.1, 140.7, 137.1, 134.1, 129.5, 129.3, 129.1, 128.9, 128.5, 128.1, 127.9, 127.0, 126.9, 116.4.



7-Methoxy-1-phenyl-2-naphthol

Chlorobenzene (225 mg, 2.0 mmol), 7-methoxy-2-naphthol (87 mg, 0.5 mmol), *t*-BuONa (384 mg, 4.0 mmol), dioxane (1.0 mL), 155 ^{o}C, 48 hours. After column chromatography (hexanes, followed by hexanes/EtOAc 85/15), 108 mg (87 %) of a white solid was obtained. R_f = 0.21 (hexanes/EtOAc 85/15). This compound is known.[59] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.71 (m, 2H), 7.61 – 7.57 (m, 2H), 7.52 – 7.48 (m, 1H), 7.46 – 7.43 (m, 2H), 7.13 (d, *J* = 8.7 Hz, 1H), 7.01 (dd, *J* = 8.7 Hz, 2.4 Hz, 1H), 6.72 (d, *J* = 2.4 Hz, 1H), 5.18 (s, 1H), 3.70 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 158.4, 150.9, 134.7, 134.5, 131.3, 129.8, 129.7, 129.4, 128.6, 124.4, 120.4, 115.4, 115.0, 103.9, 55.2.



4-*tert*-Butylbiphenyl-2-ol

Chlorobenzene (136 mg, 1.2 mmol), 3-*tert*-butylphenol (75 mg, 0.5 mmol), AgOAc (42 mg, 0.25 mmol), *t*-BuONa (192 mg, 2.0 mmol), dioxane (1.0 mL), 155 ^{o}C, 48 hours. After column chromatography (hexanes, followed by hexanes/EtOAc 95/5), 81 mg (72 %) of a white solid was obtained. R_f = 0.33 (hexanes/EtOAc 95/5). This compound is known.[60] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.45 (m, 4H), 7.40 – 7.36 (m, 1H), 7.20 – 7.17 (m, 1H), 7.05 – 7.01 (m, 2H), 5.18 (s, 1H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 153.0, 152.1, 137.2, 129.8, 129.4, 129.1, 127.7, 125.2, 118.1, 113.1, 34.7, 31.4.

X-RAY DATA

All measurements were made with a Siemens SMART platform diffractometer equipped with a 4K CCD APEX II detector. A hemisphere of data (1271 frames at 6 cm detector distance) was collected using a narrow-frame algorithm with scan widths of 0.30\% in omega and an exposure time of 45s/frame. The data were integrated using the Bruker-Nonius SAINT program, with the intensities corrected for Lorentz factor, polarization, air absorption, and absorption due to variation in the path length through the detector faceplate. A psi scan absorption correction was applied based on the entire data set. Redundant reflections were averaged. Final cell constants were refined using 3030 reflections having I>10\s(I), and these, along with other information pertinent to data collection and refinement, are listed in Table 3.4.S1. The Laue symmetry was determined to be 2/m, and from the systematic absences noted the space group was shown unambiguously to be P2(1)/c.

Crystal Data and Structure Refinement for *O*-methylated 14

Empirical formular	$C_{25}H_{20}O$
Formular weight	336.41
Temperature	223 (2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P-2
Unit cell dimensions	a = 11.7510 (9) Å alpha = 90.00
	b = 7.5332 (6) Å beta = 95.651 (1)
	c = 19.9382 (15) Å gamma = 90.00
Volume	1756.4 (2) Å^3
Z, calculated density	4, 1.272 Mg/m^3
Absorption coefficient	0.076 mm^-1
F(000)	712
Crystal color and shape	colorless plate
Crystal size	0.35 x 0.30 x 0.06 mm
Theta range for data collection	1.74 to 25.02 deg.
Limiting indices	-13<=h<=13, 0<=k<=8, 0<=l<=23
Reflections collected/unique	8948/3346 [R(int) = 0.0277]
Completeness to theta 25.02	96.2 %
Absorption correction	Empirical
Max. and min. transmission	0.9877 and 0.8927
Refinement method	Full-matrix least squares on F^2

Data/restrains/parameter	3090/0/237
Goodness-of-fit on F^2	0.973
Final R indices [I>4sigma(I)]	R_1 = 0.0299 and wR_2 = 0.0772
R indices (all data)	R_1 = 0.0525 and wR_2 = 0.0916

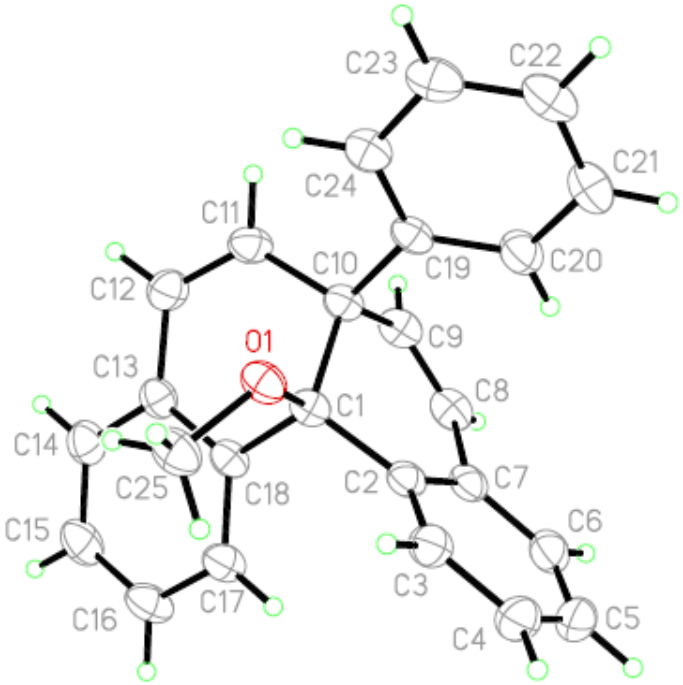


Figure 3.4.1. ORTEP view of 6a-phenyl-6a-hydro-12b-methoxybenzophenanthrene

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