INVESTIGATIONS IN IRON, COPPER, AND PALLADIUM –CATALYZED C-H BOND FUNCTIONALIZATION

A Dissertation

Presented to

the Faculty of the Department of Chemistry

University of Houston

In Partial Fulfillment

of the Requirement for the Degree

Doctor of Philosophy

By

Ly Dieu Tran

May 2013

INVESTIGATIONS IN IRON, COPPER, AND PALLADIUM –CATALYZED C-H BOND FUNCTIONALIZATION

Ly Dieu Tran

APPROVED

Dr. Olafs Daugulis, Chairman

Dr. Zachary T. Ball

Dr. Arnold Guloy

Dr. Jeremy May

Dr. Randolph P. Thummel

Dean, College of Natural Sciences and Mathematics

ACKNOWLEDGEMENTS

Foremost, I would like to express my sincere appreciation to my advisor, Dr. Olafs Daugulis. As a fantastic mentor, he has given me knowledge, taught me lab skills, and guided me through all the difficulties. I have learned from him a scientific way of thinking and solving problems. I also greatly appreciate his patience toward my complaints about my salary increase.

I would like to thank my committee members: Dr. Zachary T. Ball, Dr. Arnold Guloy, Dr. Jeremy May, and Dr. Randolph P. Thummel. I greatly appreciate Dr. Ball for his insightful comments and questions during the group meetings. I would like to thank Dr. May for the invaluable knowledge that he gave me during the organic synthesis course. I am also thankful to Dr. Guloy and Dr. Thummel for examining my dissertation. I would like to acknowledge Dr. Anderson for his assistance with NMR equipments and Dr. Korp for performing the X-ray analysis.

I also would like to thank all of my former and present labmates. I appreciate Dr. Sabasovs' help with experimental setups during my first year in the lab. I would like to thank Gerson Franco for helping me finish up the most difficult project in my PhD work. I also would like to acknowledge Ilya Popov for the scientific discussions. I am thankful to other group members for their support and help, and also for the good time that we had together.

Lastly, I would like to thank my family, my parents Phuong Nguyen and Huy Tran, also my sister Thu Tran for their support and encouragement. Without their love and care, I would not be able to finish this dissertation.

INVESTIGATIONS IN IRON, COPPER, AND PALLADIUM –CATALYZED C-H BOND FUNCTIONALIZATION

A Dissertation

Presented to

the Faculty of the Department of Chemistry

University of Houston

In Partial Fulfillment

of the Requirement for the Degree

Doctor of Philosophy

By

Ly Dieu Tran

May 2013

ABSTRACT

Transition metal-catalyzed functionalization of C-H bonds has been used as a powerful tool for the construction of C-C and C-heteroatom bonds. Within this dissertation, methods that allow functionalization of C-H bonds via iron and copper catalysis have been developed. Additionally, functionalization of sp^3 C-H bonds in amino acid derivatives using auxiliary-assisted palladium-catalyzed methodology is also demonstrated.

A method for iron-catalyzed alkylation of arenes and heterocycles containing acidic C-H bonds has been developed. Various heterocycles such as pyridine, furan, thiophene, and electron deficient arenes can be coupled with both alkyl bromides and iodides. Magnesium amide base is required for the reaction. Similarly, the deprotonative dimerization of arenes and heterocycles can be effected in the presence of an iron catalyst. Thus, the method allows direct functionalization of arenes and heterocycles. Additionally, the use of an iron catalyst is an advantage compared with existing methods.

Methods for copper-catalyzed direct sulfenylation and amination of sp^2 C-H bonds have been developed. Using 8-aminoquinoline auxiliary and copper catalyst, ortho C-H bonds of benzoic acid amides can be sulfenylated by disulfides. The method provides an alternative, milder way for the preparation of aryl trifluoromethylsulfides. Furthermore, ortho C-H bonds of benzoic acid amides can be aminated by reaction with simple amines using 8-aminoquinoline directing group and a copper catalyst. Sulfenylation and amination of γ-C-H bonds of benzyl amine derivatives using picolinic acid auxiliary were

also demonstrated. Broad substrate scope, high regioselectivity, and good functional group tolerance were observed. The use of a copper catalyst and a removable directing group are significant improvements compared with the existing methods.

Finally, a novel way for synthesis of non-natural amino acids via auxiliary-assisted, palladium-catalyzed C-H functionalization methodology was developed. Under palladium catalysis, 2-methyl thioaniline auxiliary allows the monoarylation of β-C-H bonds of alanine derivatives generating, after directing group removal, substituted phenylalanines. In contrast, using 8-aminoquinoline auxiliary, methylene groups in phenylalanine, leucine, and lysine derivatives can be arylated. Methods for alkylation and acetoxylation were also reported. The directing group can be removed without significant erosion of enantiomeric excess. The method provides a straight-forward way to synthesize non-natural amino acids from the chiral pool.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Ac	acetyl
acac	acetylacetonate
Alk	alkyl
Am	amyl
Ar	aryl
Bn	benzyl
Boc	*t*-butoxycarbonyl
BQ	benzoquinone
Bu	butyl
Bz	benzoyl
cod	cyclooctadiene
coe	cyclooctene
Cy	cyclohexyl
dba	dibenzylideneacetone
DCC	dicyclohexylcarbodiimide
DCE	dichloroethane
DCM	dichloromethane
de	diastereomeric excess
dr	diastereomeric ratio
DG	directing group
DMA	dimethylacetamide
DMF	dimethylformamide
DMSO	Dimethyl sulfoxide

dppa	diphenylphosphoryl azide
dppe	diphenylphosphinoethane
dppb	diphenylphosphinobutane
dppm	diphenylphosphinomethane
EDC	*N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride
ee	enantiomeric excess
Et	ethyl
EWG	electronwithdrawing group
FG	functional group
Hex	hexyl
L	ligand
M	metal
Me	methyl
MS	molecular sieves
NFSI	*N*-fluorobenzenesulfonimide
NMO	*N*-Methylmorpholine *N*-oxide
NMP	*N*-Methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
Ns	nosyl
Ph	phenyl
Piv	pivaloyl
Pr	propyl
TBDPS	*t*-butyldiphenylsilyl
TBS	*t*-butyldimethylsilyl

TEA	triethylamine
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TfO	triflate
THF	tetrahydrofurane
TMEDA	N,N,N’,N’-tetramethylethylenediamine
TMPH	2,2,6,6-tetramethylpiperidine
Tol	tolyl
Ts	tosyl

LIST OF SCHEMES

LIST OF FIGURES

LIST OF TABLES

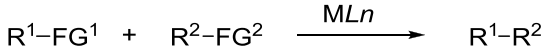
Chapter 1 Iron- and copper-catalyzed carbon-carbon and carbon-heteroatom bond formation from carbon-hydrogen bonds

Carbon-carbon bond formation is perhaps the most important transformation in organic chemistry. Over the past few decades, scientists have witnessed an exponential growth of transition-metal catalysis in organic synthesis. Various methods such as transition-metal-catalyzed cycloaddition, metathesis, cross-coupling, and carbon-hydrogen bond functionalization reactions have become important tools for C-C bond formation.

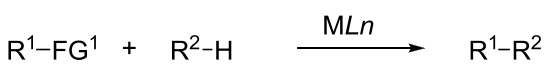
Among those, C-H bond functionalization allows direct conversion of C-H bonds to C-C or C-heteroatom bonds (Scheme 1-1). In the presence of transition-metal catalysts, the C-H bonds can be regioselectively functionalized to generate the desired cross-coupled product.

Scheme 1-1. Conventional cross-coupling reactions and C-H bond functionalization reactions

Conventional cross-coupling reactions



C-H bond functionalization reactions



Various transition metals have been reported as catalysts for C-H bond functionalization. Among those, palladium and ruthenium are the two most commonly used. The concentration of palladium and ruthenium in the Earth's crust is 0.015 g/ton and 0.001 g/ton, respectively.[1] On the other hand, first-row transition metals such as iron and copper are more abundant. Their concentrations in the Earth's crust are 56000 g/ton and 60 g/ton, respectively.[1] Indeed, iron and copper salts are cheap, readily available, and relatively non-toxic. Therefore, use of iron or copper as alternative catalysts for C-H bond functionalization would be advantageous. This chapter will review research achievements in the field of C-H bond functionalization using iron and copper catalysis.

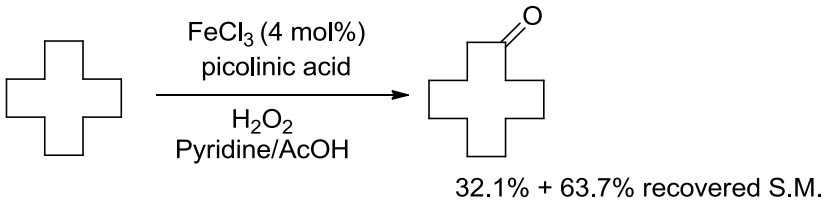
Chapter 1-1 Iron-catalyzed C-H bond functionalization

I. Introduction

Iron is the 4th most abundant element in the Earth crust[1] and is considered as one of the most important metals in nature.[2] Iron is cheap, non-toxic, and environmentally benign. Due to these features, iron catalysis in organic synthesis has recently attracted much attention. In fact, various iron-catalyzed organic transformations have been demonstrated, including cross-coupling reactions, cycloaddition, oxidation, hydrogenation, rearrangement, and polymerization.[3]

The first example of iron complex in stoichiometric C-H bond activation was reported in 1968.[4] However, only recently iron-catalyzed C-H activation has attracted much attention. Within the last two decades, numerous methods have been developed for construction of C-C, C-N, and C-O bonds from C-H bonds. Thus, starting from 1983, Barton and coworkers developed several methods allowing the oxidation of saturated hydrocarbons to ketones under iron catalysis (Scheme 1-2).[5] After Barton's work, significant amount of work has been reported in the field of iron-catalyzed oxidation of C-H bonds. Within this chapter, only C-C bond construction will be reviewed.

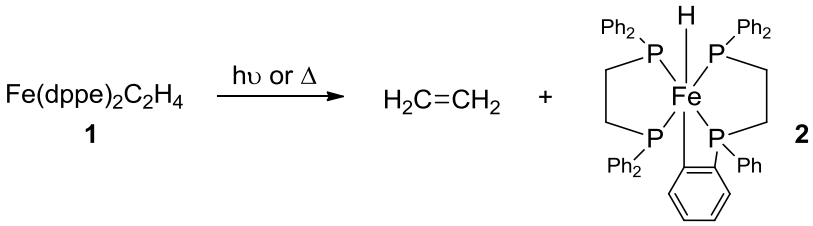
Scheme 1-2. Oxidation of saturated hydrocarbons to ketones using iron catalysis



II. C-H bond activation using iron complexes

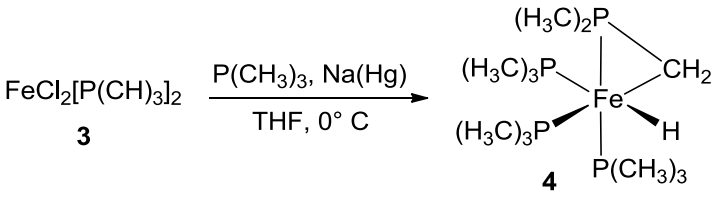
In 1968, Miyake reported the synthesis of complex **1** by treating $Fe(acac)_3$ with ethoxydiethylaluminum in the presence of ethylenebis(diphenylphosphine) (dppe). Interestingly, ultraviolet irradiation or heating of complex **1** afforded complex **2**. Both IR and NMR spectra indicated the presence of Fe-H bond. Structure of **2** was elucidated to contain a bond between metal center and carbon on phenyl ring of the phosphine ligand. Thus, formation of **2** is the first reported example for C-H bond activation by an iron complex.[4]

Scheme 1-3. Activation of aryl C-H bonds by iron complex



The first example for intramolecular C-H addition in a trialkylphosphine iron complex was reported by Muetterties in 1975.[6] Reduction of iron(II) complex **3** with sodium amalgam in THF solvent containing excess of $P(CH_3)_3$ generated complex **4**.

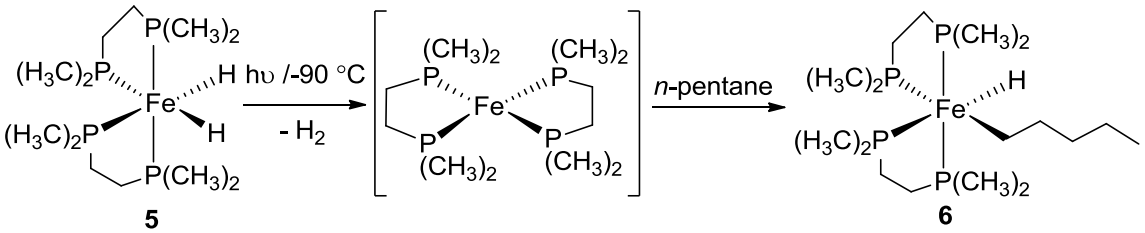
Scheme 1-4. Activation of alkyl C-H bonds by iron complex



Oxidative addition of unactivated sp^3 C-H bonds to transition-metal complexes is an area of intense interest in organometallic chemistry. The intermolecular activation of

unactivated sp^3 C-H bonds by iron complexes was first reported by Field in late 80's. Irradiating dihydride complex **5** at -90 °C in *n*-pentane solution, hydrogen elimination was observed and complex **6** was obtained.[7] It was observed that only the methyl group in pentane reacted with **5**. Secondary C-H bonds were unreactive.

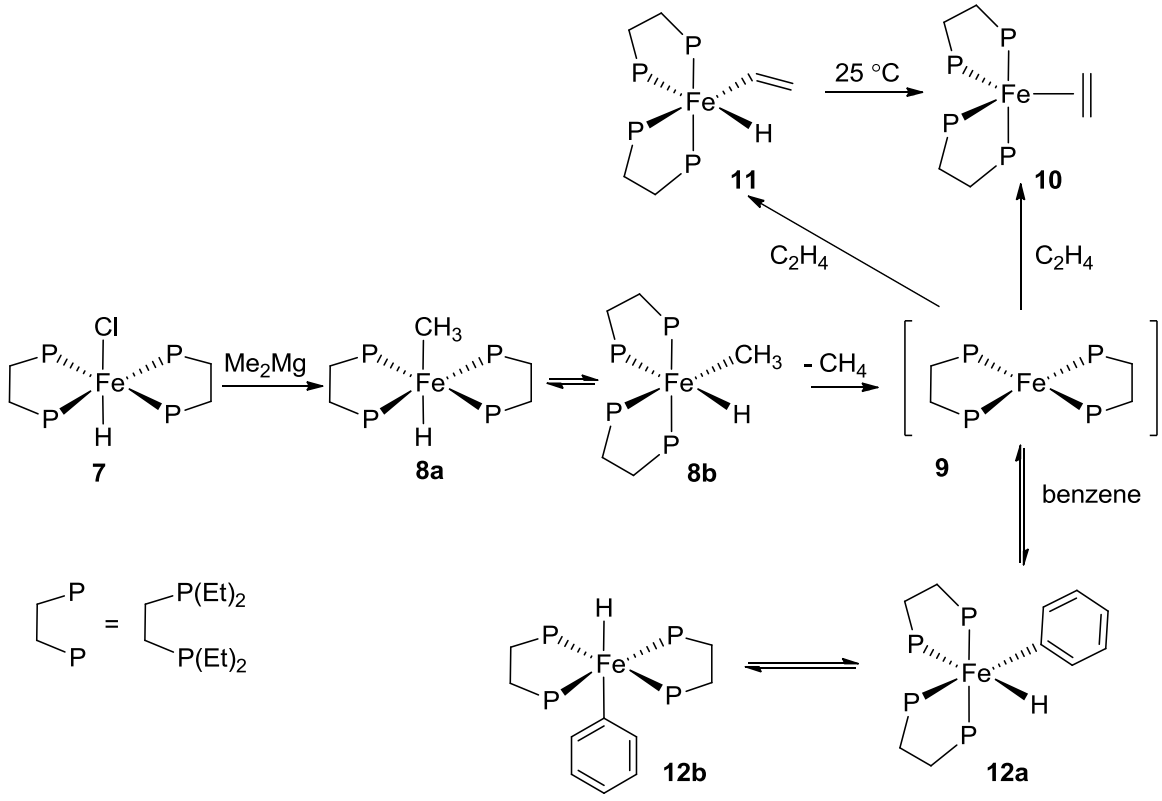
Scheme 1-5. Activation of a primary C-H bond by iron complex



5 **6**

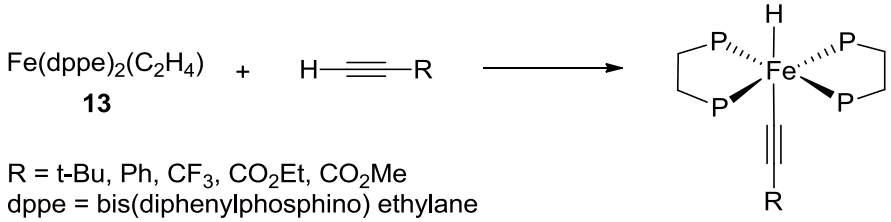
The insertion of iron into alkenyl and aryl C-H bonds was also demonstrated by Field group.[8] The coordinatively unsaturated complex **9** was generated by reductive elimination of methane from the cis-hydrido methyl complex **8b**, which was in turn formed by the reaction of hydrochloride **7** with dimethyl magnesium reagent. Treatment of **9** with ethylene afforded a C-H insertion product **11** and π-coordination product **10**. It was observed that the C-H insertion product **11** was kinetically favored. However, complex **10** is more thermodynamically stable as **11** was converted to **10** on warming. On addition of benzene to **9** at 250 K, the cis-hydrido phenyl complex **12a** was formed which isomerized to a trans-isomer **12b** at higher temperatures.

Scheme 1-6. Activation of C-H bonds by an iron complex



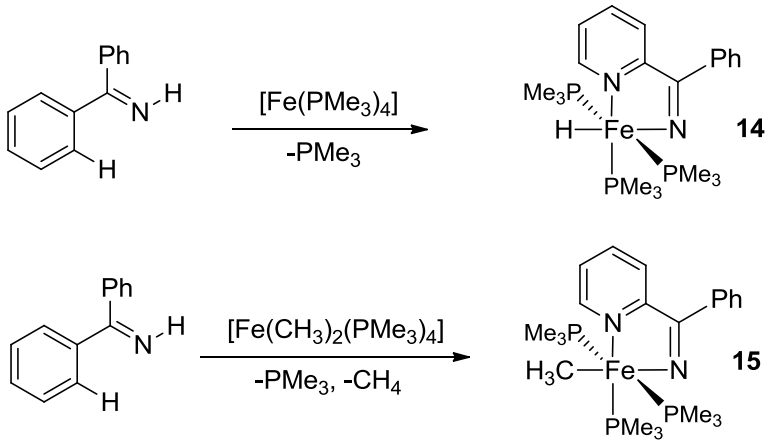
Low valence iron complexes were also reported to cleave the C-H bond of terminal alkynes.[9] Thus, terminal acetylenes react with complex **13** to generate iron hydrido acetylide complexes. The reaction time is significantly dependent on the alkyne substituents with EWGs accelerating the reaction.

Scheme 1-7. Activation of sp C-H bonds by an iron complex



Activation of aromatic C-H bonds by ortho-metallation is a highly desirable transformation as it allows the selective functionalization of ortho C-H bonds. Palladium, ruthenium, and rhodium are widely used for this transformation. Recently, iron complexes were reported to activate and functionalize ortho C-H bonds of imines.[10] Camadanli demonstrated that trimethylphosphine-supported iron complexes such as $Fe(PMe_3)_4$ or $Fe(CH_3)_2(PMe_3)_4$ react with ketimines to generate the corresponding ortho-metalated hydrido-iron **14** and methyl-iron complexes **15**.

Scheme 1-8. Ortho-metallation by iron complexes



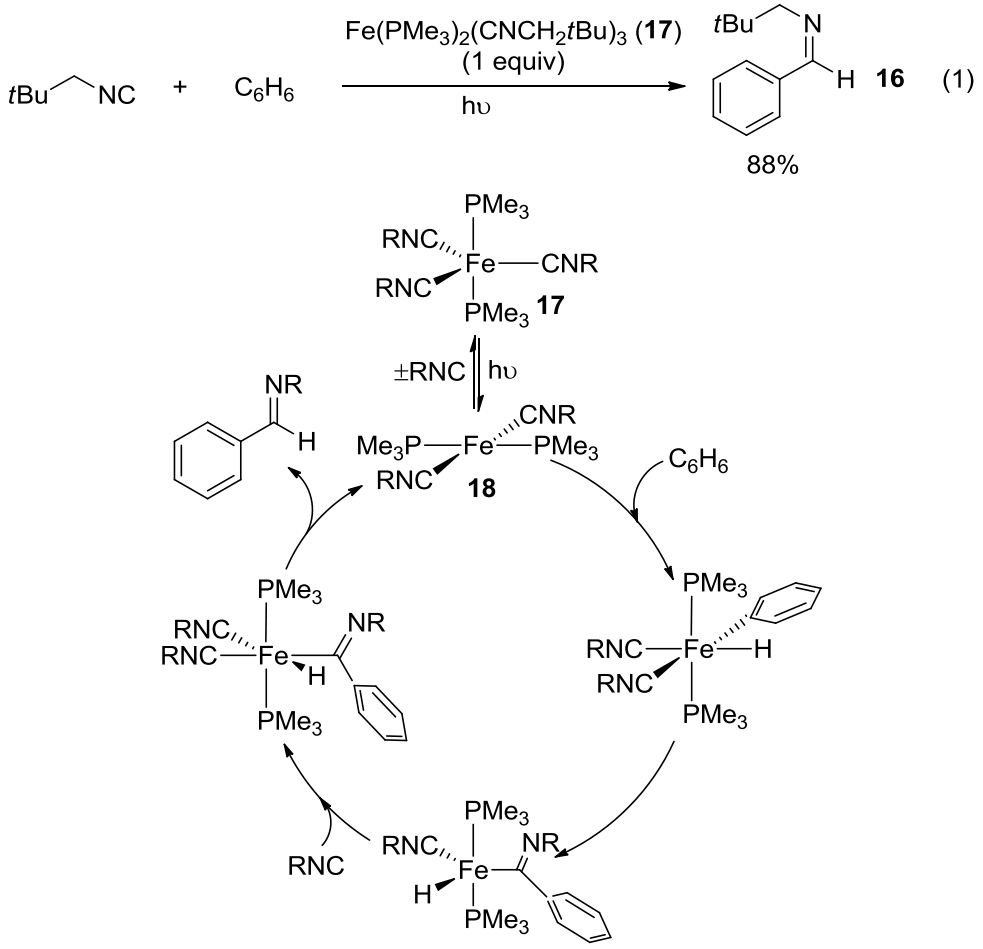
In general, low valence iron complexes have demonstrated the ability to insert into C-H bonds of alkanes, alkenes, alkynes, and arenes. Iron complexes can selectively metalate ortho C-H bonds of arenes in the presence of imines directing group. Thus, these examples show the feasibility of using iron as catalyst for C-H bond functionalization.

III. Carbon-carbon bond formation using iron-catalyzed C-H bond functionalization

3.1 C-H bond arylation

Low valence iron complex **17** was used for the preparation of aldimines from isonitriles and arenes.[11] Thus, aldimine **16** was obtained in 88% yield by irradiating benzene solution of complex **17**. The plausible mechanism for the reaction is shown in Scheme 1.9. Irradiation of complex **17** generated the coordinatively unsaturated complex **18** which inserted into the aryl C-H bond. Migratory insertion of the nitrile followed by reductive elimination generated the desired product. A similar reaction with toluene gave a mixture of *m* and *p*-tolylaldimines in 55% combined yield.

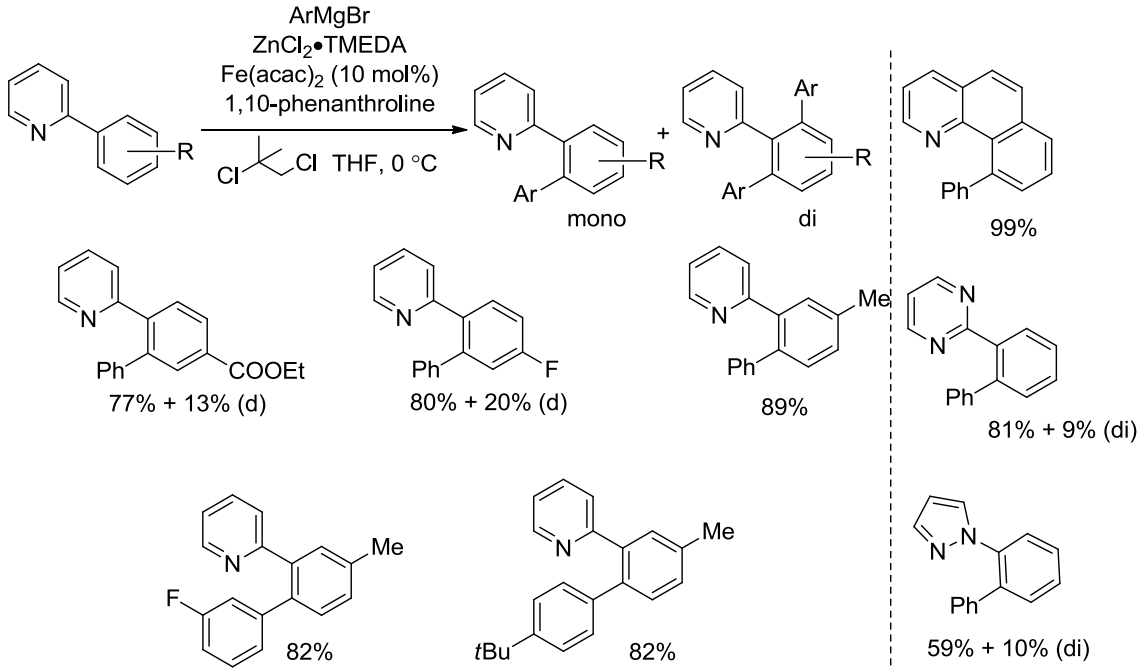
Scheme 1-9. Aryl C-H bond cleavage by iron complex



Iron-catalyzed C-C bond formation by direct C-H bond functionalization has recently been reported by Nakamura and colleagues. They observed the phenylation of 2-phenylpyridine derivatives by using $Fe(acac)_3$ catalyst.[12] The optimized conditions include 1,10-phenanthroline ligand, 1,2-dichloro-2-methylpropane oxidant, and 2 equivalents of Ph_2Zn. Substrates bearing both electron-rich and electron-deficient substituents react smoothly and give the arylated products in excellent yields. Besides 2-phenylpyridine, other nitrogen-containing heterocyles such as α-benzoquinoline, 2-phenylpyrimidine, and 1-phenyl-1H-pyrazole are also reactive. The reaction was carried out at 0 °C which can be

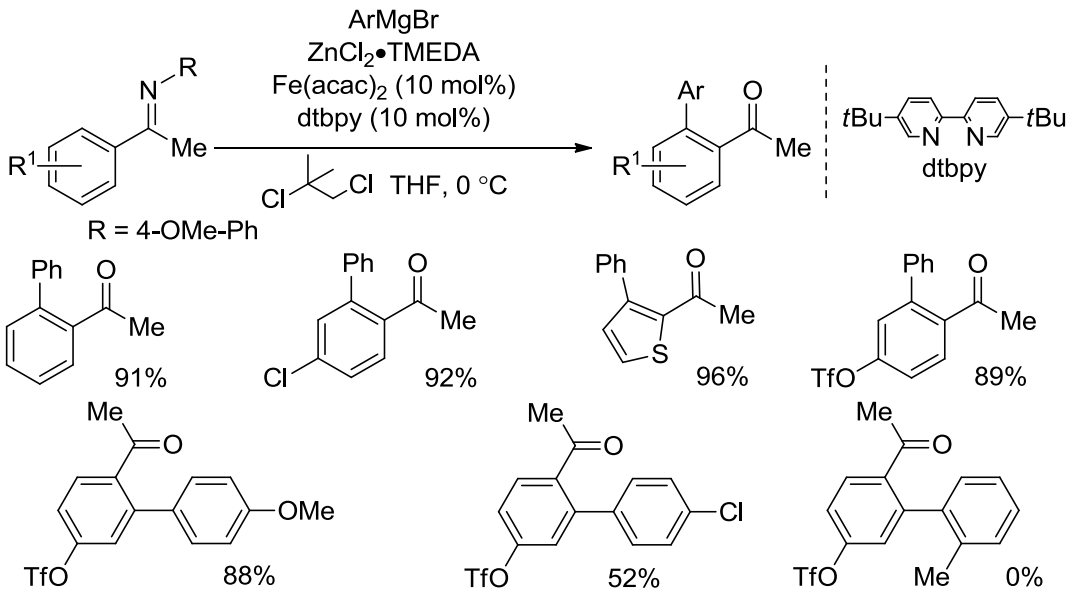
considered as an advantage because most of the reported methods for C-H bond fuctionalization require heating at high temperatures.

Scheme 1-10. Iron-catalyzed arylation of 2-phenylpyridines



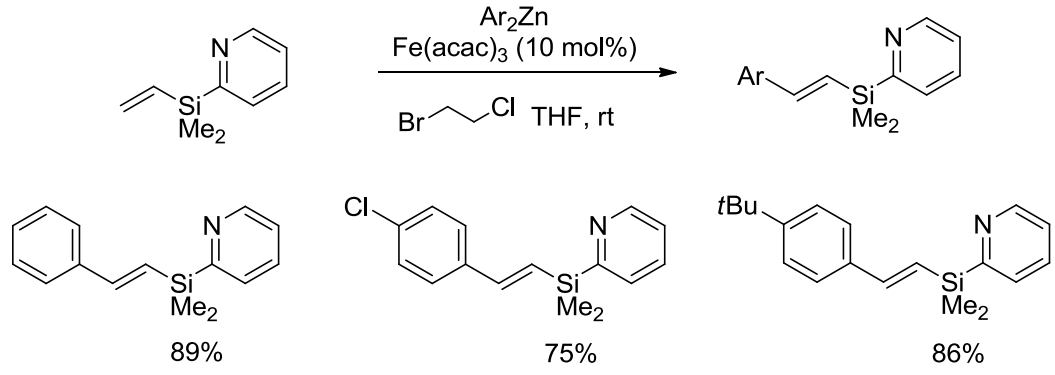
Aryl imines can also serve as directing groups for arylation reactions. In 2009, Nakamura reported the direct ortho-arylation of aryl imine using iron catalysis (Scheme 1-11).[13] Various aryl imines can be arylated in excellent yields affording only mono-arylated products. Steric properties of aryl zinc reagents greatly affect the yields of the reaction. For example, 2-tolylzinc reagent did not provide significant amount of product. This method broadens the scope of the iron-catalyzed direct arylation and provides an alternative way for the synthesis of biaryls.

Scheme 1-11. Iron-catalyzed arylation of aryl imines



A method that allows direct arylation of olefins with aryl zinc reagents using chelation-controlled iron catalysis was developed recently. Thus, using pyridine directing group, a commercially available $Fe(acac)_3$ catalyst, aryl zinc reagents in situ generated from $ZnCl_2$•TMEDA, and corresponding Grignard, the arylated products were obtained in high yield with complete regio and stereo-selectivity. Additional ligands are not required.[14]

Scheme 1-12. Iron-catalyzed arylation of olefins



Noteworthy, Nakamura group has reported the method for C-C bond formation directly from activated sp^3 C-H bonds using iron catalysis. The activation of amine α-C-H bonds is proposed to happen through 1,5-hydrogen transfer from intermediate A to B followed by reductive elimination generating the desired product (Scheme 1-13).[15] Various RMgBr reagents (R = aryl, alkenyl, alkyl) can serve as coupling partners under $Fe(acac)_3$ catalysis and products can be obtained in good yields (Table 1-1). Further mechanistic study observed the lack of intermolecular isotope effect. Consequently, C-H activation is not the rate determining step. Thus, this method is one of rare examples of first row-transition metal catalyzed activation of sp^3 C-H bonds.

Scheme 1-13. Iron-catalyzed arylation of sp^3 C-H bonds

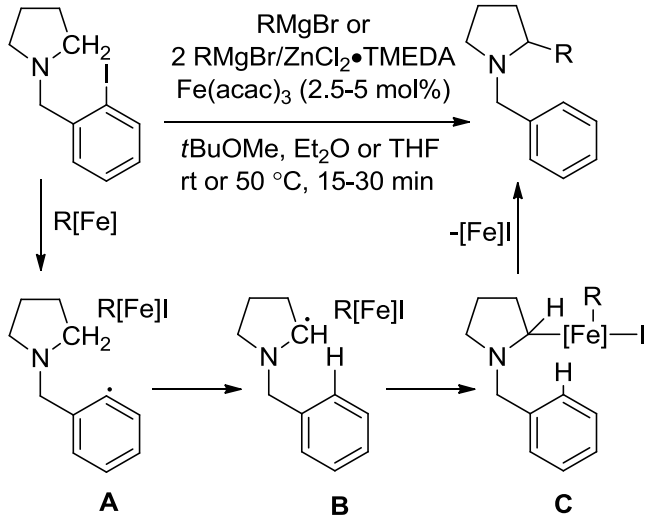
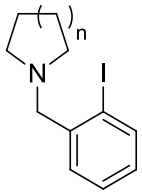
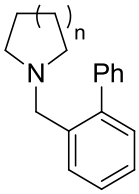
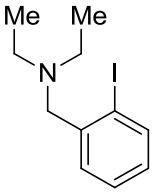
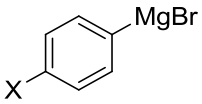
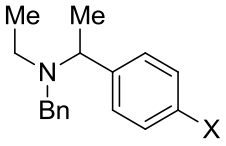
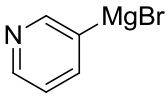
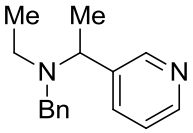
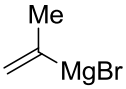
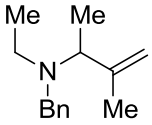


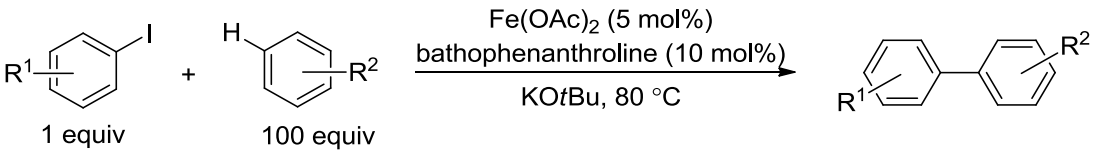
Table 1-1. Iron-catalyzed arylation of activated sp^3 C-H bonds

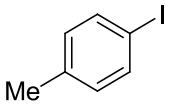
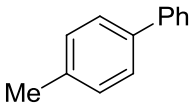
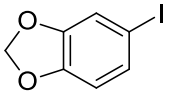
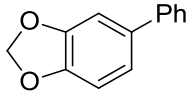
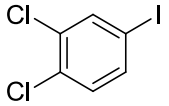
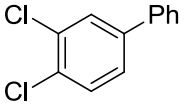
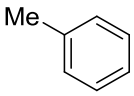
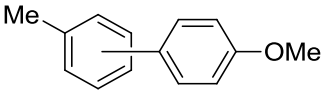
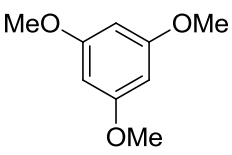
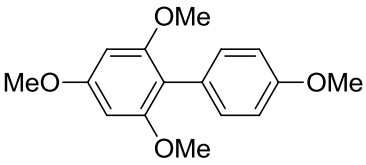
Substrate	Ar-Metal	Product	Yield
	PhMgBr		n = 1 84% n = 2 82% n = 3 82%
			X = F 91% X = Cl 88% X = OMe 90%
			54%
			70%

Despite the fact that methods reported by Nakamura allow the direct arylation of various C-H bonds in good yields, the use of organometal reagents is a disadvantage. Organo-halides, on the other hand, are easier to handle and are readily available. Thus, using organo-halide coupling partners would be beneficial. In fact, the iron-catalyzed direct arylation of sp^2 C-H bonds utilizing aryl iodides, bromides, and chlorides has been reported recently. Under the optimized conditions with $Fe(OAc)_2$ catalyst, bathophenanthroline ligand, and K*t*BuO base, various aryl iodides were shown to react with benzene and produce the biaryl products in good yield.[16] However, when toluene and other mono-substitued benzenes were used as substrate, the isomeric mixture of arylated

products was obtained. Moreover, the reaction requires large excess of arene which can be considered as the biggest limitation of the method.

Table 1-2. Iron-catalyzed arylation of sp^2 C-H bonds by aryliodides



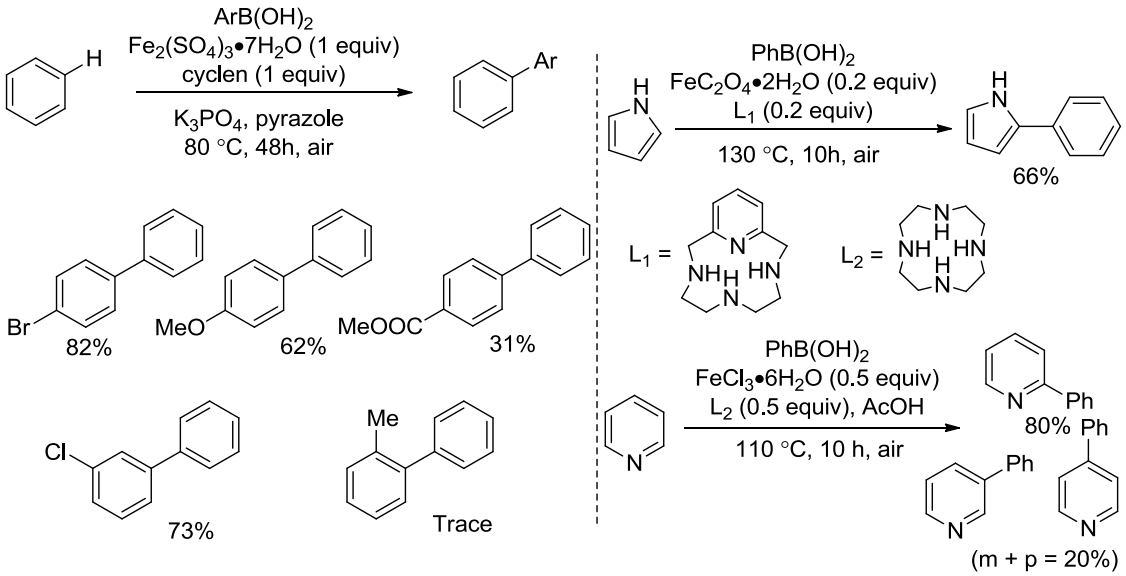
Aryl Halide	Product	Yield
		86%
		72%
		53%
	 o:m:p = 3.1 : 1.9 : 1.0	50%
		41%

Mechanistic studies for the reaction revealed that (1) KIE is 1.04 suggesting that C-H bond breaking is not the rate determining step, (2) radical scavengers such as TEMPO or galvinoxyl completely inhibited the reaction, (3) the metal-free version of the reaction, using AIBN, was possible but resulted in much lower yield. Based on those observations and based on reported mechanism for iron-catalyzed living polymerization reaction, the

plausible mechanism of the reaction was proposed. One-electron transfer from iron catalyst to aryl halide will form aryl radical species which in turn undergoes reaction with arene to afford the cross coupling product.

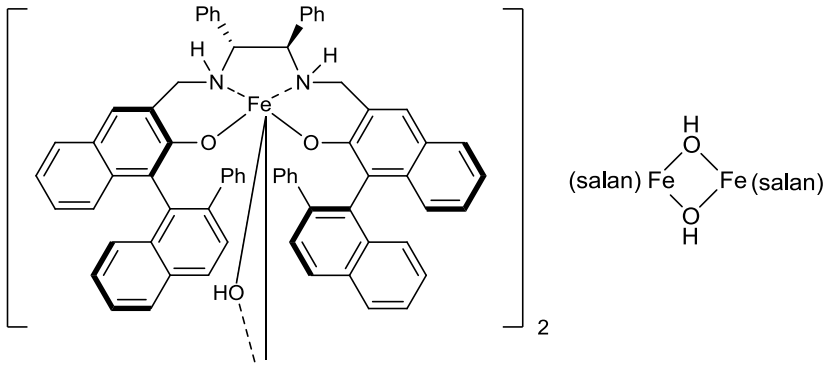
Arylboronic acids have also been employed as reagents for iron-mediated direct arylation reactions. In 2008, Yu group reported the arylation of benzene and its derivatives by various aryl boronic acids in the presence of stoichiometric amount of iron salts, K_3PO_4 base, and cyclone (1,4,7,10-tetraazacyclododecane) ligand.[17] The presence of O_2 is necessary as reaction performed under N_2 resulted in significantly lower yield of the product. Various aryl boronic acids bearing different functional groups are reactive and gave the arylated products in moderate to excellent yields. The reaction is sensitive to steric effects as o-toluyl boronic acid is unreactive. Moreover, when substituted benzenes were used as substrates, mixtures of regionisomers were obtained. Additionally, sp^2 C-H bonds of pyrrole and pyridine can also be directly arylated by aryl boronic acids. The reaction requires high temperature and employment of macrocyclic polyamine ligands.

Scheme 1-14. Iron-mediated arylation of arenes by boronic acids

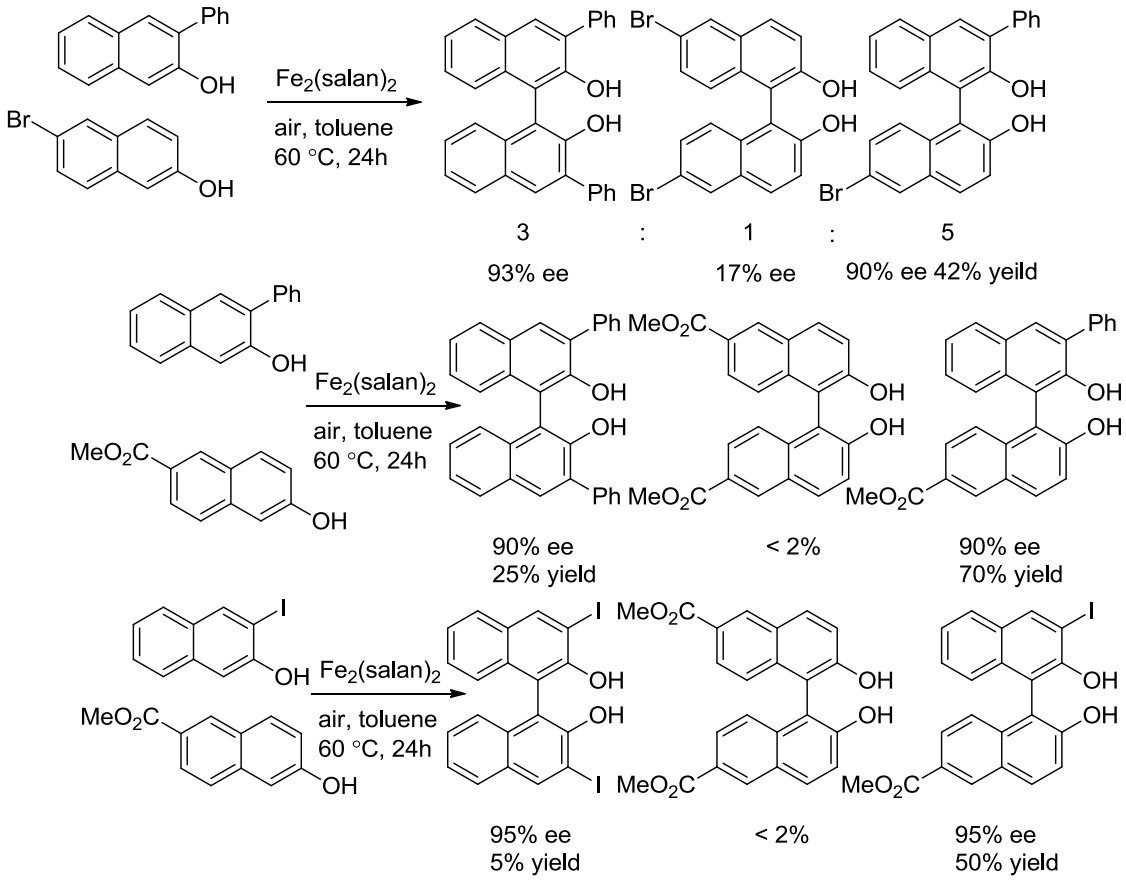


C_2-Symmetric BINOL derivatives have been widely used as chiral ligands or auxiliaries in organic synthesis. Recently, C_1- symmetric BINOLs were introduced as potentially suitable chiral auxiliaries. The most atom-economic and direct way for synthesizing this class of compounds is an asymmetric aerobic oxidative coupling of 2-naphthols. Thus, Katsuki reported a method allowing the cross-coupling of 2-naphthols using enantioenriched iron catalyst.[18] In the presence of Fe(salan) complex (Figure 1-1), a 2-naphthol bearing substituent at C3 and a less electron rich 2-naphthol undergo highly enantioselective cross-coupling. Even though the mixture of homo-coupling and cross-coupling product was obtained, the cross-coupling pathway is more favored and products were formed with excellent enantiomeric excess.

Figure 1-1. Fe(salan) complex



Scheme 1-15. Enantioselective Iron(salan)-catalyzed assymetric oxidative coupling of 2 napthtols



Generally, the iron-catalyzed direct arylation methodology allows the functionalization of both sp^2 and activated sp^3 C-H bonds. Organometalic reagents, aryl halides and aryl

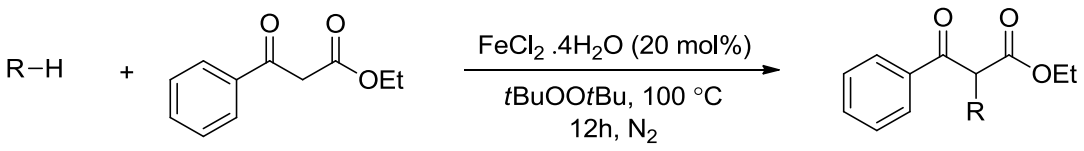
boronic acids can serve as arylating agents. These methods allow the direct and efficient way for the preparation of birayls. Nevertheless, mechanistic studies are required to elucidate the mechanism of the reaction and to further improve the methods.

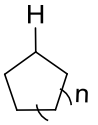
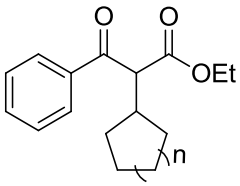
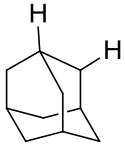
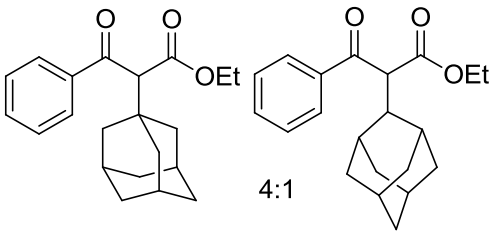
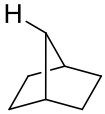
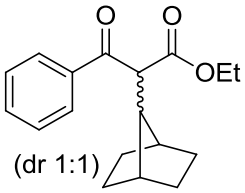
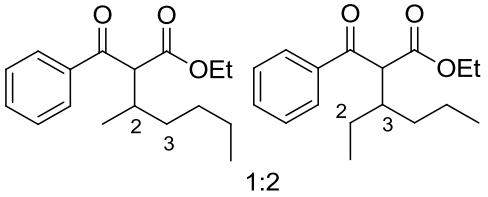
3.2 Carbon-carbon bond formation via cross-dehydrogenative coupling (CDC)

Cross-dehydrogenative coupling is one of the most direct, efficient, and atom-economic methods for the formation of C-C bonds. Recently, chemists have paid significant amount of attention to developing CDC reactions, particularly using iron catalysts.

1,3-Dicarbonyl compounds are the most commonly used substrates for CDC reaction. Thus, various methods allowing the coupling between C-H bond of 1,3-dicarbonyl compounds with simple alkanes,[19] benzylic C-H bonds,[20] or C-H bonds of ethers[21] have been developed. Among those coupling partners, simple alkanes are the most challenging substrates due to the inertness of the C-H bonds. Li group successfully developed the alkylation of 1,3-dicarbonyl compounds using an iron catalyst and simple alkanes.[19] The optimized conditions include $FeCl_2.4H_2O$ catalyst and *t*butyl peroxide oxidant. The scope of substrates with respect to alkanes is shown in Table 1-3. Various cycloalkanes are reactive and gave the coupling products in moderate to excellent yields. In the case of norbornane, 1:1 mixture of two diastereoisomers was obtained. Methyne C-H is more reactive than methylene C-H bond as demonstrated by the reaction of adamantane. The author also observed that β-keto esters are more reactive than 1,3-diketones. The reaction was proposed to occur through radical mechanism.

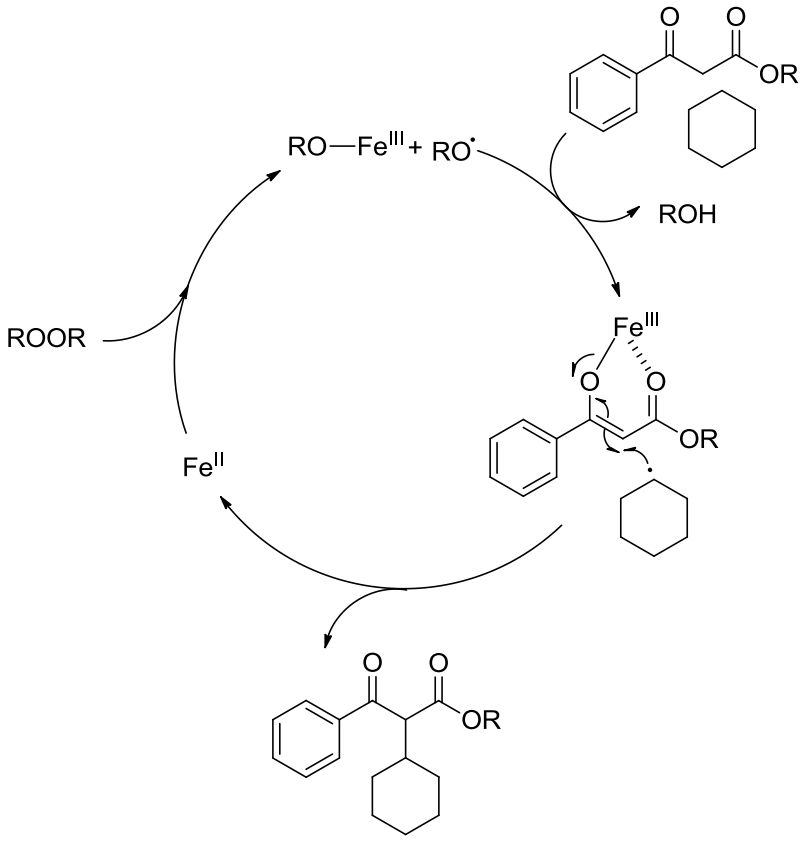
Table 1-3. Iron-catalyzed alkylation of β-ketoesters



Alkane	Product	Alkane	Product
	 n = 1 38% n = 2 88% n = 3 75% n = 4 77%		 4:1 85%
	 82% (dr 1:1)	*n*-hexane	 1:2 46%

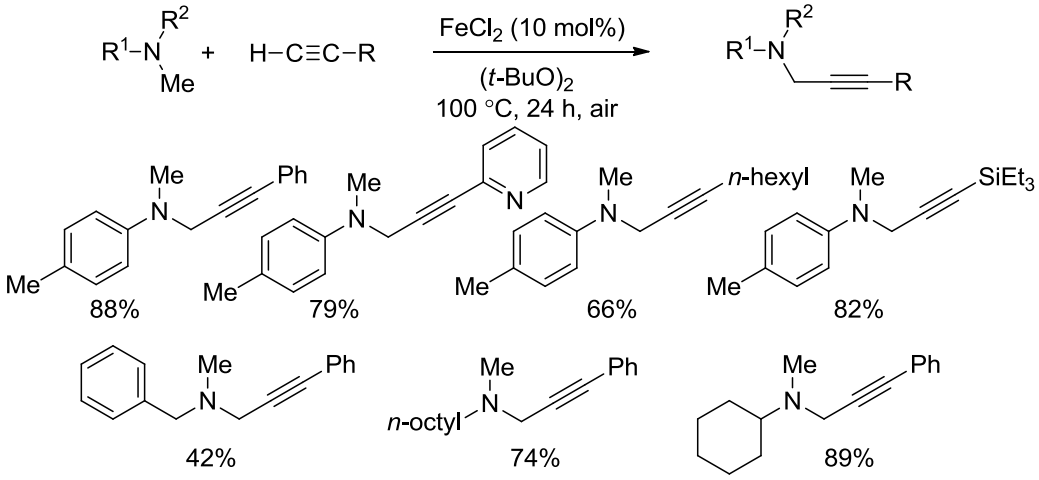
The postulated mechanism for the reaction is shown in Scheme 1-16. Iron(II) catalyzes the homolytic cleavage of the peroxide to generate iron(III) and RO• radical. The alkoxide radical will then abstract H• from cyclohexane producing cyclohexyl radical. Meanwhile, RO-Fe(III) can react with β-keto ester to generate a Fe enolate. Reaction of cyclohexyl radical with this iron enolate will form the product and regenerate the active iron catalyst.

Scheme 1-16. Proposed mechanism



Propargylamines have attracted much attention during the last few years due to their application in drug discovery. In 2009, Vogel reported iron-catalyzed oxidative C-C cross coupling of tertiary amines with terminal alkynes to give propargylamines.[22] The combination of $FeCl_2$ catalyst with *t*BuOO*t*Bu was found to be essential for the reaction. The reaction was run under air as lower yield was obtained under N_2 or O_2 atmosphere. Different substituents on the terminal alkynes such as arene, heterocycle, alkyl, and silyl groups are compatible with reaction conditions. Aniline derivatives and amines containing benzyl or alkyl groups are reactive. High regioselectivity was observed as the methyl group was functionalized even in the presence of benzylic C-H bond.

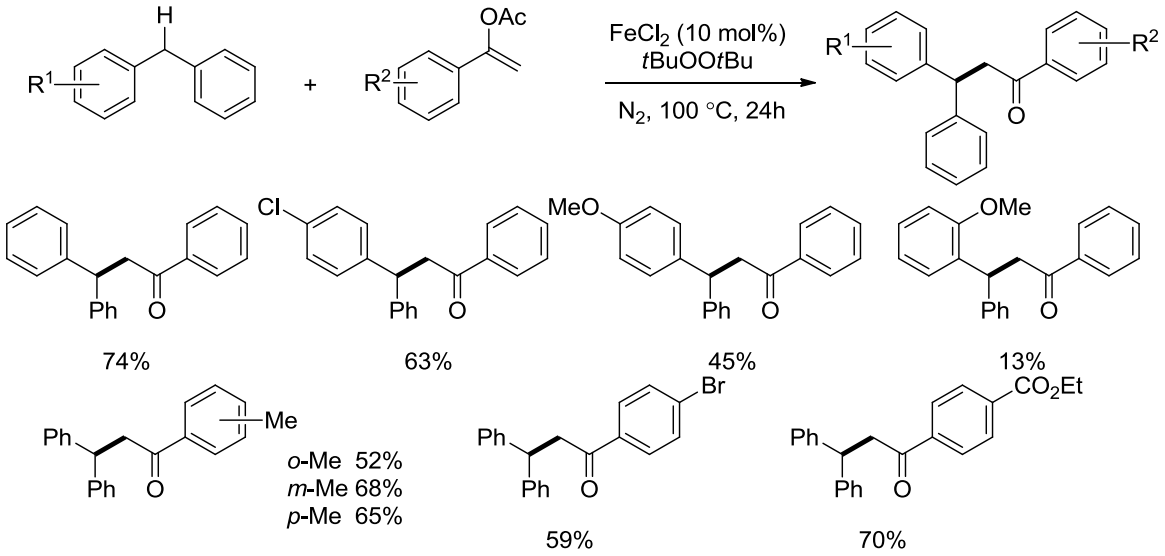
Scheme 1-17. Iron-catalyzed oxidative cross-coupling of tertiary amines with terminal alkynes



3.3 C-C bond formation via reactions with alkenes

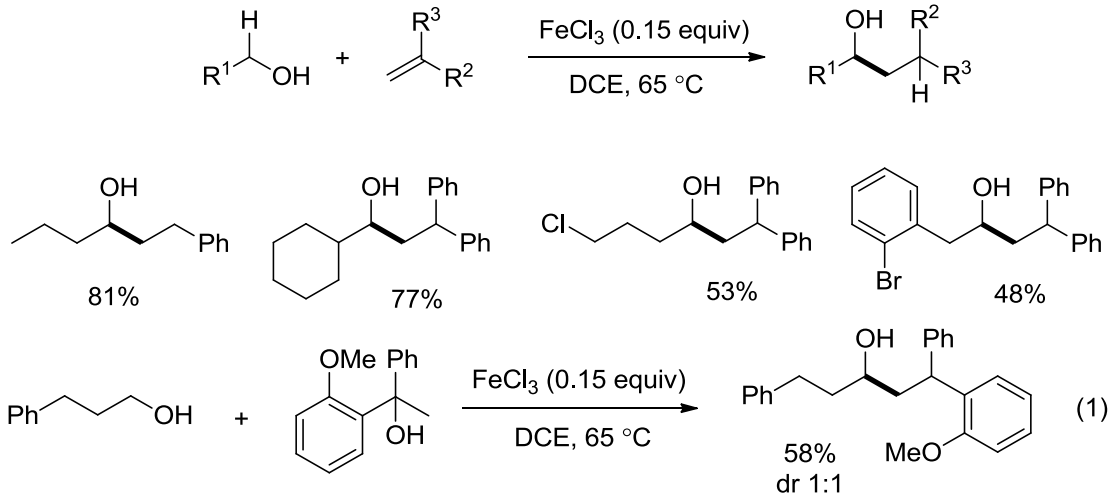
$C(sp^3)$-$C(sp^3)$ bonds can be constructed by iron-catalyzed direct olefination of benzylic C-H bonds. Thus, Shi group reported the insertion of activated olefins into benzylic C-H bonds, using $FeCl_2$ catalyst and di-*t*butyl peroxide oxidant.[23] Electron-withdrawing groups promoted the reaction while electron donating group caused the opposite effect. Steric effects also played important role as ortho substituents on either benzylic substrates or 1-aryl vinyl esters led to drastically lower yields.

Scheme 1-18. Iron-catalyzed direct olefination of benzylic C-H bonds



Iron was also reported to be active catalyst for the direct olefination of α C-H bonds adjacent to hydroxyl groups. Thus, using $FeCl_3$ catalyst and dichloroethane solvent, primary alcohols containing various alkyl groups can be cross-coupled with alkenes (Scheme 1-19). Tertiary alcohols can be employed as olefin precursors (equation 1).[24] Mechanistic studies suggest that the mechanism is different from oxidation/hydroacylation/reduction or transfer hydrogenative coupling.[24]

Scheme 1-19. Iron-catalyzed cross-coupling reactions of alcohols with alkenes



Chapter 1-2 Copper-catalyzed C-H functionalization

I. Introduction

As one of the first-row transition metals, high concentration of copper is present in the Earth's crust.[1] Similar to iron, copper salts are cheap and environmentally friendly. Copper has been widely used in organic synthesis over hundred years. Despite that fact, copper catalysis in C-H bond functionalization is still at an early stage of development.

Copper-catalyzed C-H bond functionalization can be classified into two categories: C-H bond functionalization that (a) is initiated by single electron transfer (SET) or (b) involves organo-copper intermediates.[25] Within the scope of this chapter, both categories will be covered and recent development in aryl-copper(III) complex chemistry will also be mentioned.

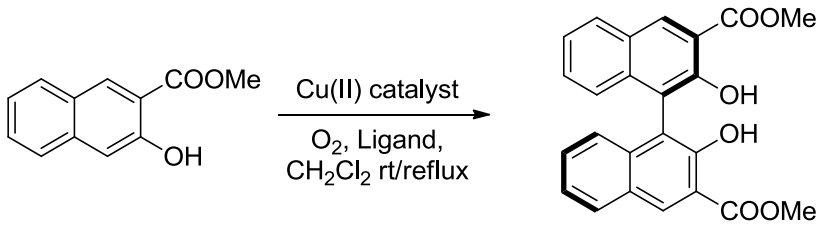
II. C-H functionalization initiated by single electron transfer

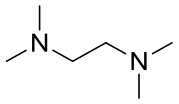
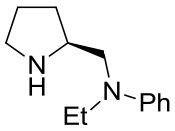
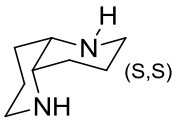
2.1 Oxidative coupling of 2-naphthol derivatives

Homochiral 1,1'-binapthalene derivatives have been widely used as chiral ligands or auxiliaries for asymmetric synthesis. Oxidative coupling of 2-naphthol derivatives to generate binaphthols is a straightforward way for their preparation. Iron, manganese and copper have been reported as active catalysts for the oxidative coupling of 2-napthol derivatives. In 1994, the synthesis of binaphthol derivatives using CuCl(OH) was reported.[26a] TMEDA was employed as a ligand and the couplings of various 2-napthol derivatives were reported in good yields. In 1995, the same group reported an enantioselective version of the reaction. By using CuCl catalyst and diamines derived

from L-proline as chiral ligands, and O_2 oxidant, the binaphthol product was obtained in 70% ee.[26b] Further research revealed that product with 93% ee can be obtained by using 1,5-diaza-cis-decaline ligand.[27]

Scheme 1-20. Copper-catalyzed oxidative homocoupling of 2-naphthol derivatives



	Nakajima and Koga	Nakajima	Kozlowski
	1994	1994	2001
Catalyst	CuCl(OH)	CuCl	CuI
Ligand	 (TMEDA)		
Yield/ee	99%*	78% yield 70% ee	85% yield 90-93% ee

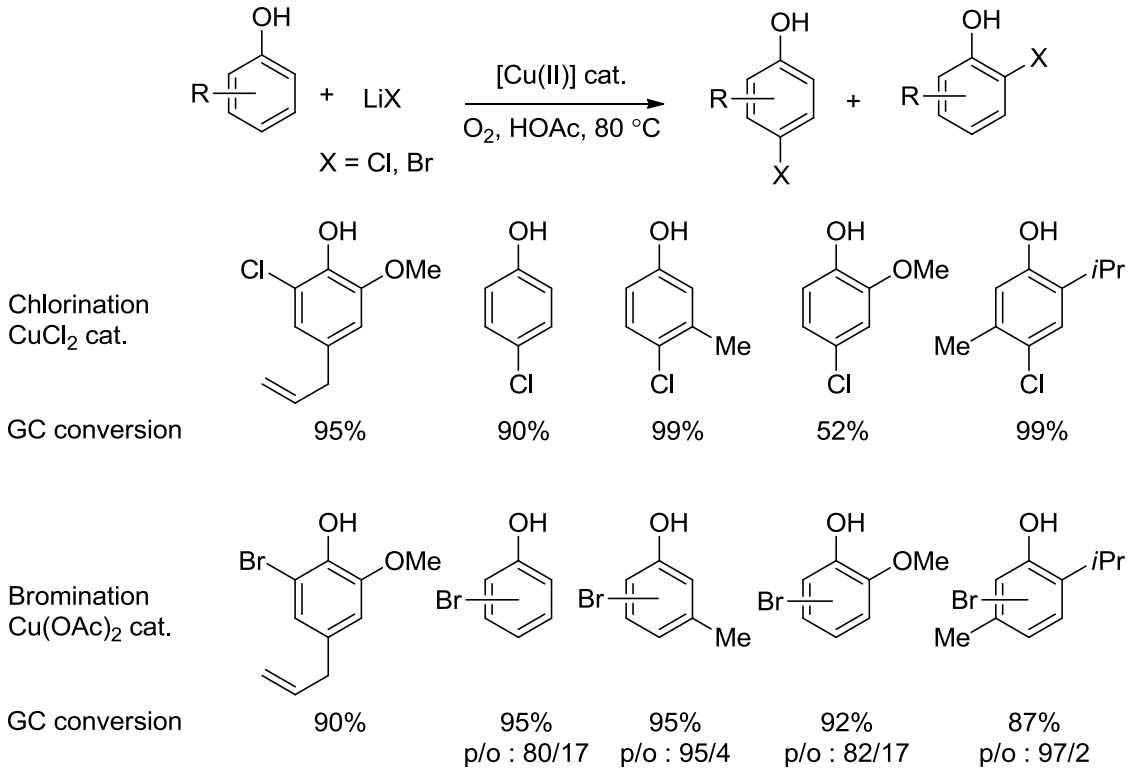
*Reaction was run in MeOH

2.1 Halogenation of electron-rich arenes

Chlorophenols and bromophenols are widely used in pharmaceutical, agrochemical, and dye industries. The conventional ways to synthesize these substrates involves bromination and chlorination of phenolic compounds using electrophilic halogenating reagents such as chlorine or bromine. Chemists have studied alternative methods to prepare chlorophenols and bromophenols by employing nontoxic reagents such as halide salts. Thus, Gusevsaya

demonstrated that employing $CuCl_2$ catalyst, O_2 oxidant, LiCl, and AcOH solvent, phenolic compounds can be chlorinated selectively at para position in excellent conversions.[28] The presence of hydroxyl group is essential for the reaction as non-phenolic compounds such as nitrobenzene or anisole are not reactive. The catalyst systems useful for oxibromination of phenolic compounds were also reported by the same group.[29] Indeed, using $Cu(OAc)_2$ catalyst, O_2 oxidant, LiBr, and AcOH solvent, various bromophenols were obtained in good yields. The reaction showed good chemoselectivity for the mono-bromination and high regioselectivity for para bromination.

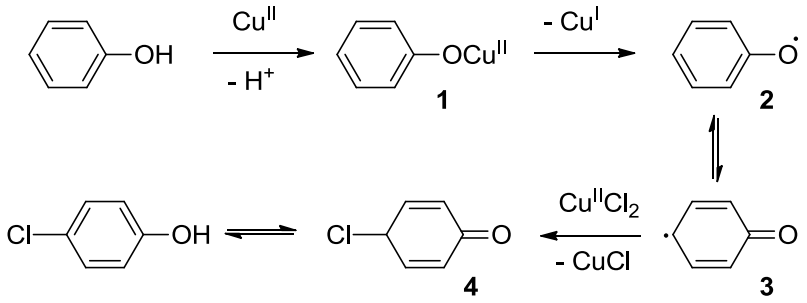
Scheme 1-21. Copper-catalyzed oxychlorination and oxybromination of phenolic compounds



The activation energy of oxychlorination of thymol was measured to be 13 kJ mol^{-1}, suggesting a radical pathway. Kinetic studies for the same substrate revealed that the

reaction is first order in copper catalyst. The plausible reaction pathway is shown in Scheme 1-22. The first step is the oxidation of phenol by Cu(II) to generate phenoxy radical **2**, possibly via the formation of Cu(II)(phenolate) complex **1**. Tautomeric cyclohexadienyl radical **3** abstracts chloride from $CuCl_2$ to generate **4** and CuCl. Tautomerization of **4** form the chlorinated product and O_2 oxidizes Cu(I) to Cu(II) closing the catalytic cycle.

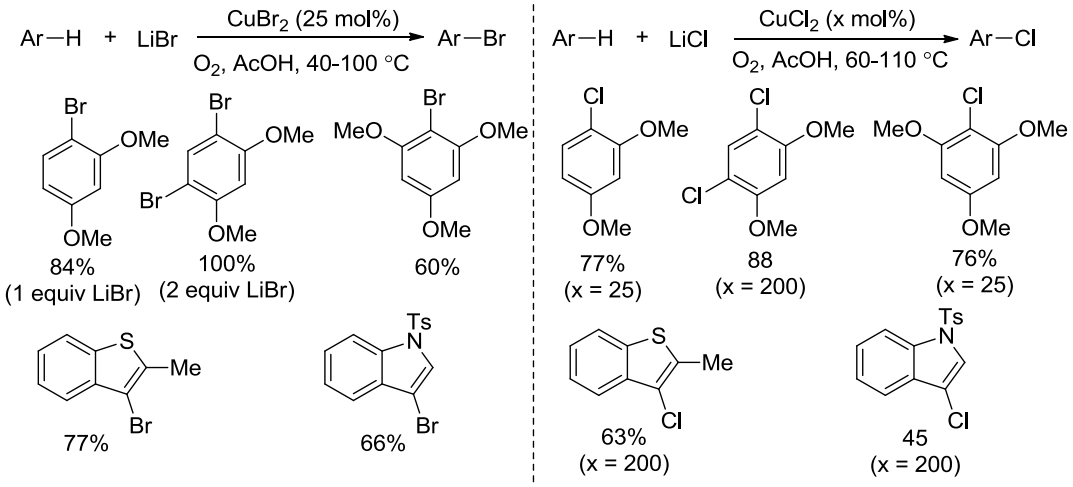
Scheme 1-22. Proposed mechanism for copper-catalyzed oxychlorination of phenolic compounds



In 2009, Stahl group reported the oxychlorination and oxybromination of electron rich arenes. The catalytic system employs $CuBr_2$ catalyst, O_2 oxidant, and LiBr bromide source. It allows the bromination of various electron-rich arenes and heterocycles.[30] By using 1 equivalent of LiBr, mono-brominated products were obtained. Two equivalents of LiBr provided dibrominated products. The authors proposed that oxybromination occurs through electrophilic bromination pathway. Bromine is generated by the decomposition of $CuBr_2$. Oxychlorination of electron-rich arenes and heterocycles requires higher reaction temperatures and higher loading of both $CuCl_2$ and LiCl. Oxychlorination was proposed to occur through radical pathway. It is initiated by electron transfer from electron-rich arene to $CuCl_2$ as shown in Scheme 1-22. An improved method for oxybromination of electron-

rich arenes was reported recently by Li group. In this system, $Cu(NO_3)_2$ was used as a catalyst and HBr solution was employed as bromide source and solvent.[30b]

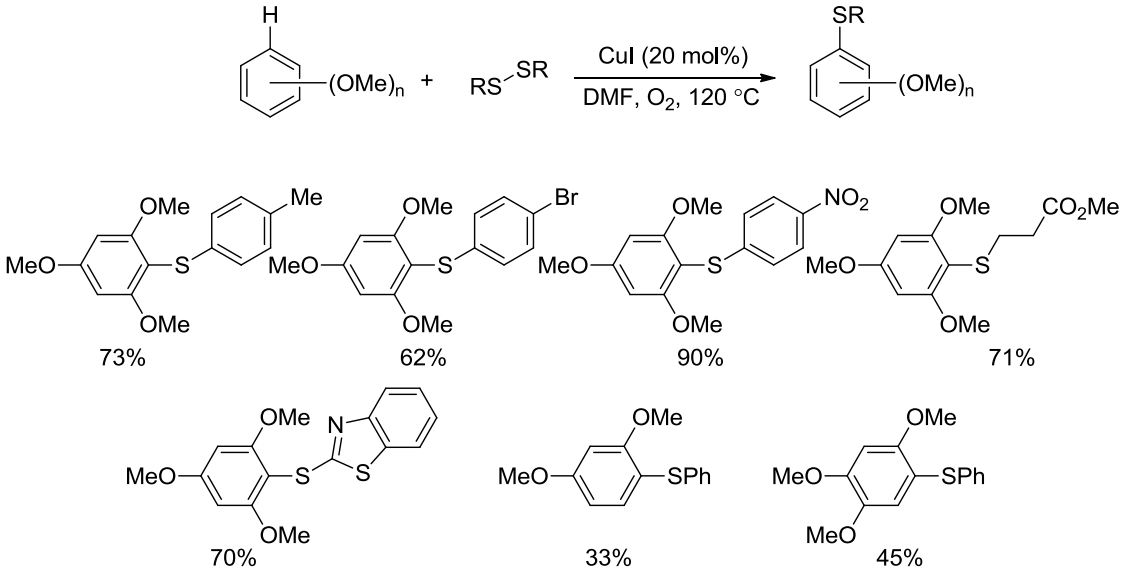
Scheme 1-23. Copper-catalyzed oxybromination and oxychlorination of electron-rich arenes



2.2 Oxidative functionalization of electron-rich arenes

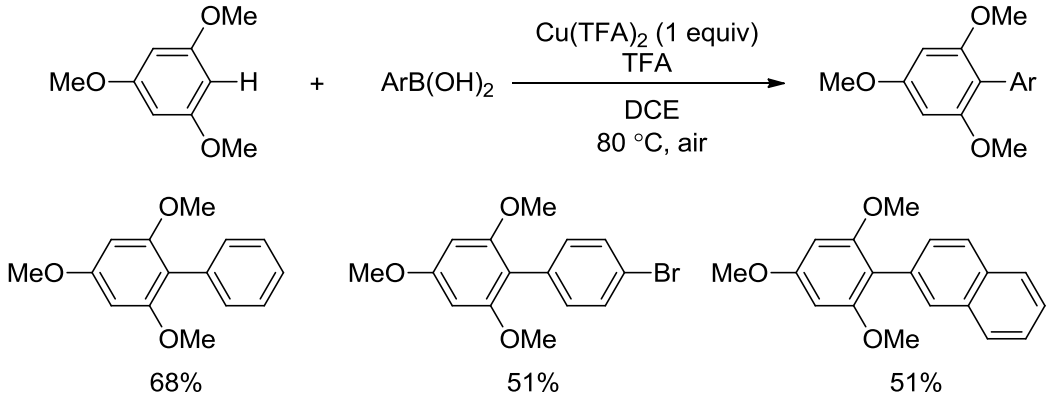
Electron-rich arenes can undergo oxidative functionalization, such as arylation and sulfenylation under copper catalysis. Thus, in the presence of CuI catalyst and O_2 oxidant, trimethoxybenzene was sulfenylated by various diaryl and dialkyl disulfides in moderate to excellent yields.[31] Various functional groups such as bromide, ester and nitro are well tolerated under reaction conditions. However, the scope of substrates is limited since sulfenylation of other electron rich arenes such as dimethoxybenzene and 1,3,4-trimethoxybenzene is much less effective.

Scheme 1-24. Copper-catalyzed sulfenylation of electron-rich arenes



Direct arylation of trimethoxy benzene by arylboronic acids using stiochiometric copper was reported in 2008 by Itami group.[32] The reaction employed stoichiometric amount of $Cu(TFA)_2$ and dichloroethane solvent. Various biaryl compounds bearing different functional groups such as bromide and chloride can be generated in moderate yields. However, the arene substrate scope is limited to 1,3,5-trimethoxy benzene.

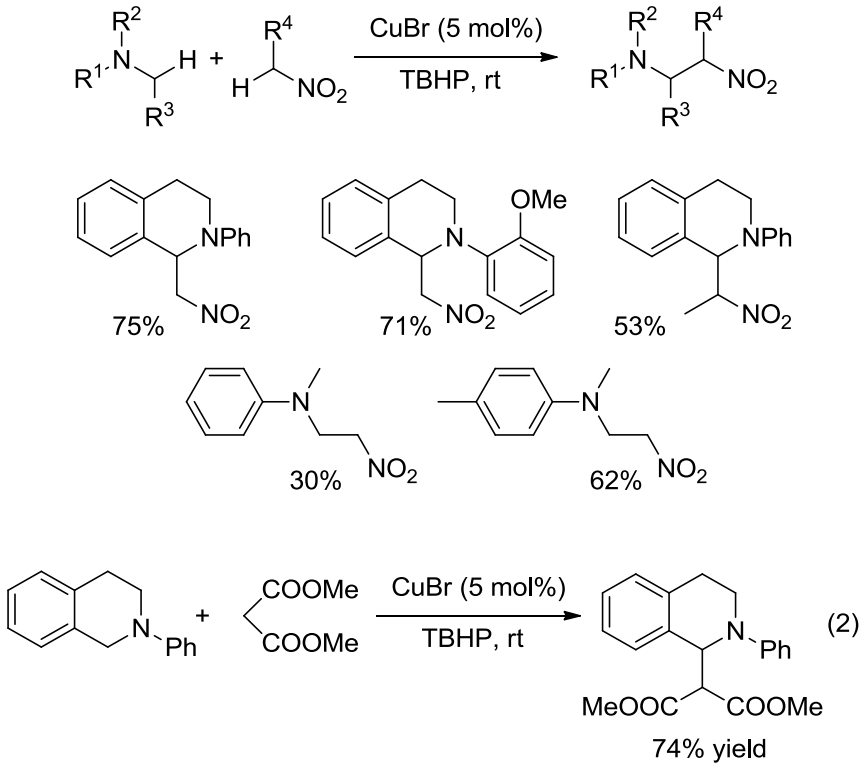
Scheme 1-25. Copper-mediated arylation of trimethoxybenzene by arylboronic acids



2.3 α-Functionalization of tertiary amines

Tertiary amines are electron rich and thus susceptible to one-electron oxidation. The α-C-H bonds adjacent to nitrogen atom can be oxidatively functionalized by ruthenium,[33] iron,[22,34] or copper catalysts. The copper-catalyzed oxidative functionalization of tertiary amines has been extensively studied by Li group. The direct cross coupling of sp^3 C-H bonds with sp^3, sp^2, and sp C-H bonds has been reported.[35] Indeed, *N*,*N*-dimethyl aniline and tetrahydroisoquinoline derivatives can undergo CDC reactions with nitromethane to give β-nitroamine derivatives.[36] The authors used CuBr catalyst and *t*-butyl hydrogen peroxide oxidant (Scheme 1-26).

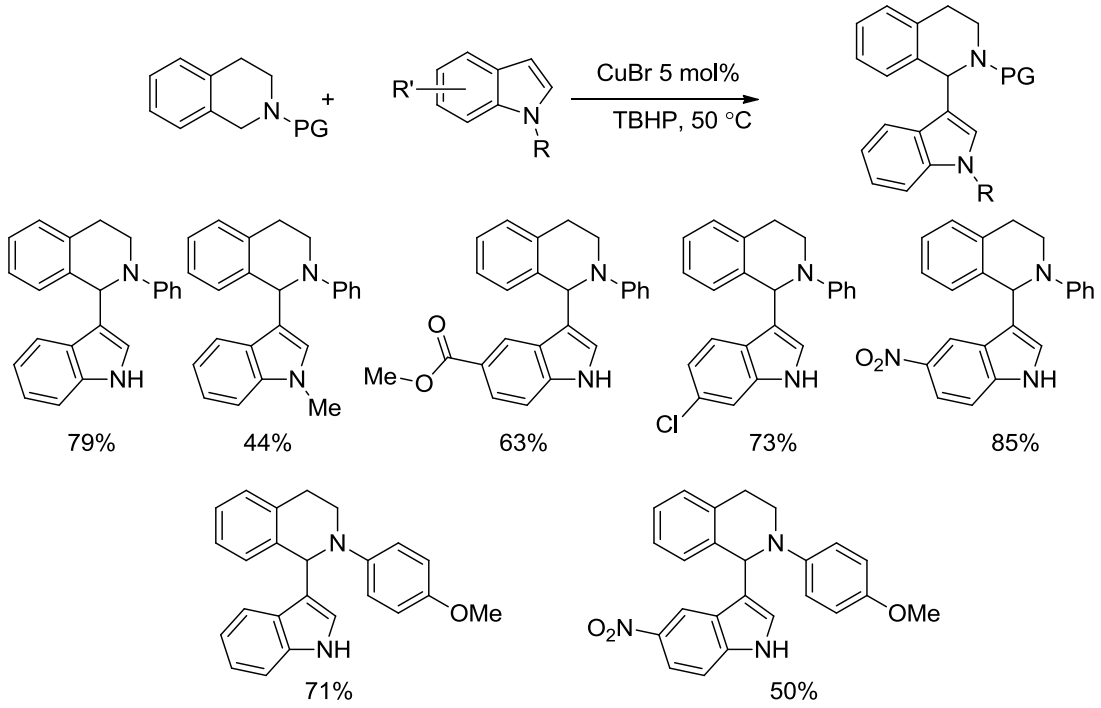
Scheme 1-26. Copper catalyzed CDC between sp^3 C-H bond and sp^3 C-H bond



Activated methylene compounds such as dialkyl malonates are also reactive and can undergo the cross coupling with tetrahydroisoquinoline under the same conditions to generate β-diester amine derivatives (equation 2). The method was improved when O_2 was used as oxidant instead of *t*-butyl hydrogen peroxide and reaction can be run in water.[36c]

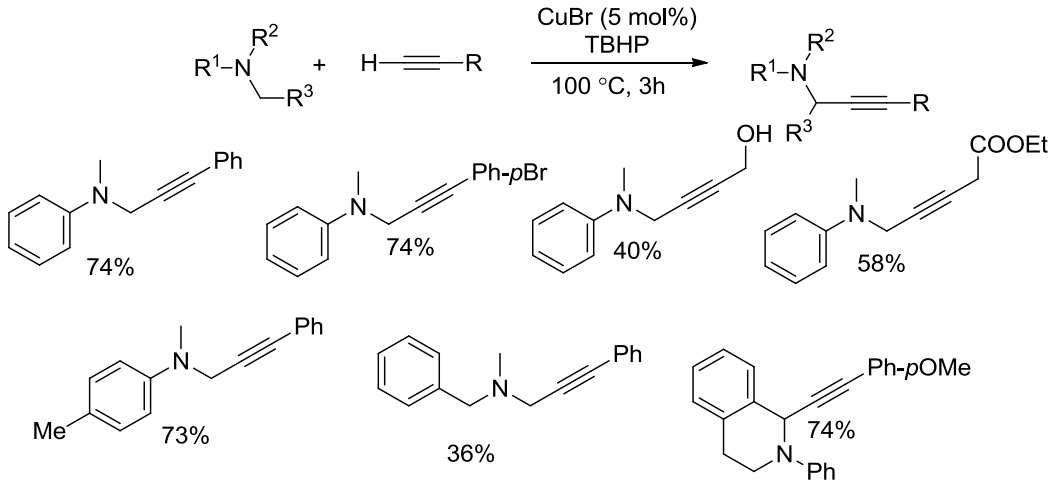
N-Protected tetrahydroisoquinolines can undergo coupling reactions with sp^2 C-H bonds of heterocycles, such as indole to generate indolyl tetrahydroisoquinoline derivatives. The catalytic system included CuBr catalyst and TBHP oxidant.[37] Various indole, bearing different functional groups can react with tertiary amines and generate product in fairy good yields. The reaction selectively affords coupling at C3 position of indoles. When C3 is substituted, C2 position will be reactive. Beside the coupling with indoles, *N*-protected tetrahydroisoquinolines can also undergo arylation with aryl boronic acids under copper catalysis. Other heterocycles, such as indolizine, imidazole, and *N*,*N*-dimethylaniline can cross couple with *N*,*N*-dimethylaniline by employing CuBr catalyst and O_2 oxidant.

Scheme 1-27. Copper-catalyzed indolation of tetrahydroisoquinolines



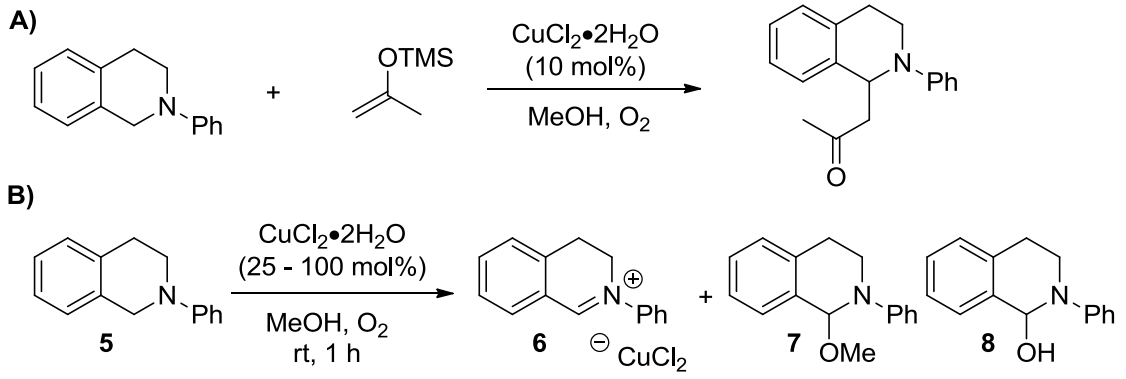
The cross-dehydrogenative coupling between tertiary amines and terminal alkynes using copper catalysis was reported in 2004 by Li group.[38] This method provides the most straightforward way to synthesize propargylamines. Indeed, tertiary amines such as *N*,*N*-dimethylaniline derivatives, benzyldimethylamine, and tetrahydroisoquinoline can be alkynylated in synthetically useful yields.

Scheme 1-28. Copper-catalyzed alkynylation of tertiary amines

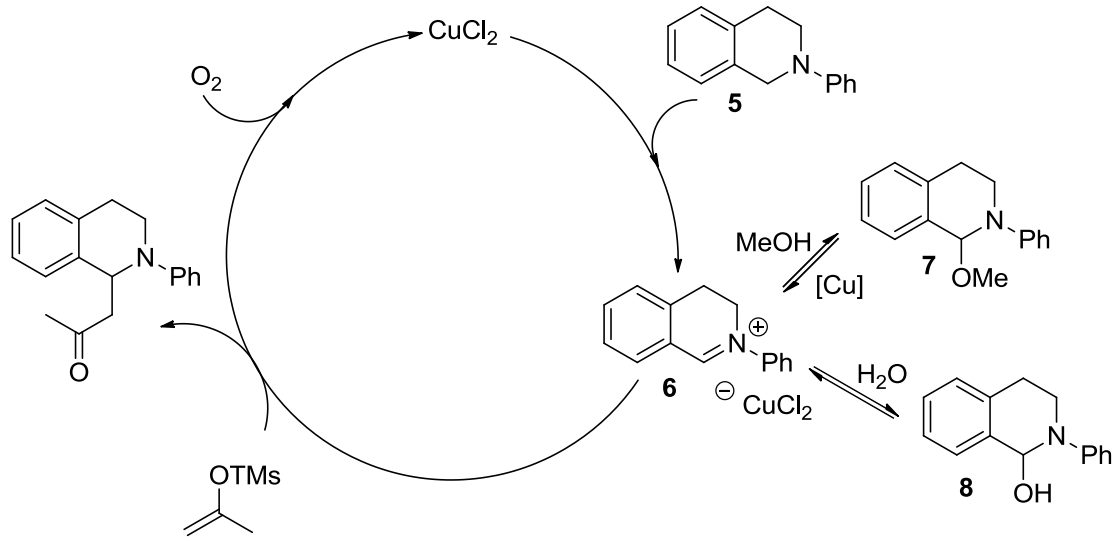


Mechanistic study for the copper-catalyzed oxidative functionalization of tertiary amines was performed based on the reaction between *N*-phenyl tetrahydroisoquinoline and silyl enol ether (Scheme 1-29A). The reaction of amine **5** with stoichiometric $CuCl_2$ in MeOH generated iminium ion **6** and methanol adduct **7** as major products (Scheme 1-29B). The same reaction in acetone generates **6** and hemiaminal **8** as major products. The iminium ion **6** can be isolated and characterization of **6** by X-ray crystallography revealed that counter ion is dichlorocuprate. The author suggested that **6** is a reactive intermediate of the copper-catalyzed oxidative functionalization of tertiary amines. The plausible mechanism was proposed as depicted in Scheme 1-30.[39] Copper will oxidize amine **5** and generate iminium ion **6**, which can undergo an off-cycle reaction with methanol or water to generate compound **7** and **8**, respectively. Reaction of iminium **6** with enol will give the desired product and O_2 reactivates Cu(I) to the active Cu(II).

Scheme 1-29. Experiments for mechanistic study of copper-catalyzed oxidative coupling reaction with *N*-phenyl tetrahydroisoquinoline

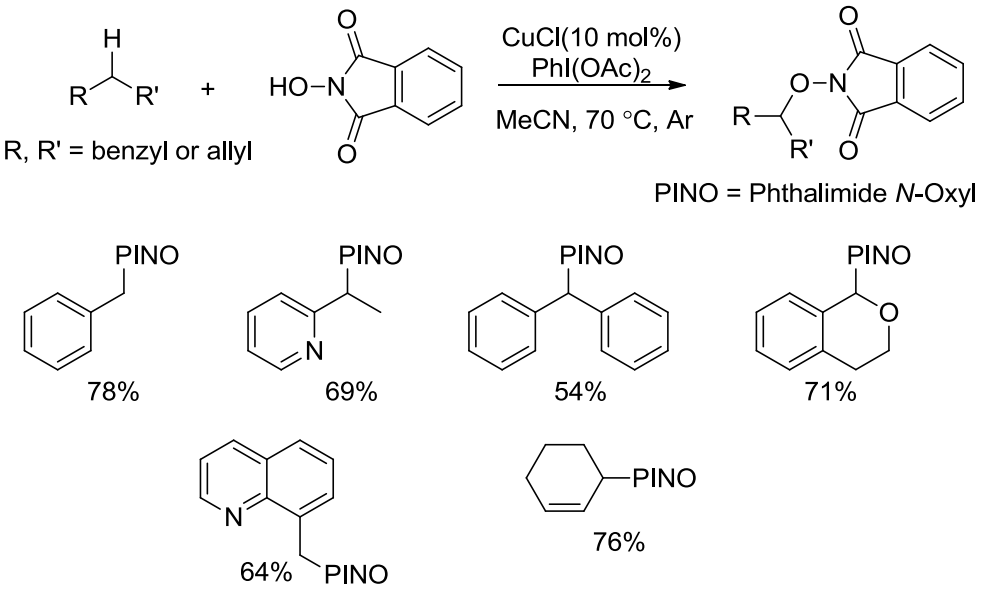


Scheme 1-30. Plausible mechanism



Activated benzylic and allylic sp^3 C-H bonds can also undergo oxidative functionalization under copper catalysis. Thus, by using catalytic amount of CuCl and $PhI(OAc)_2$ oxidant, oxygenated products can be obtained in good yields (Scheme 1-31).[40] The KIE was measured and gave the value of 10.8. This high value suggests that hydrogen abstraction is a rate determining step. The authors also specified that reaction most likely happens through radical pathway.

Scheme 1-31. CuCl-catalyzed oxidative functionalization of benzylic or allylic compounds

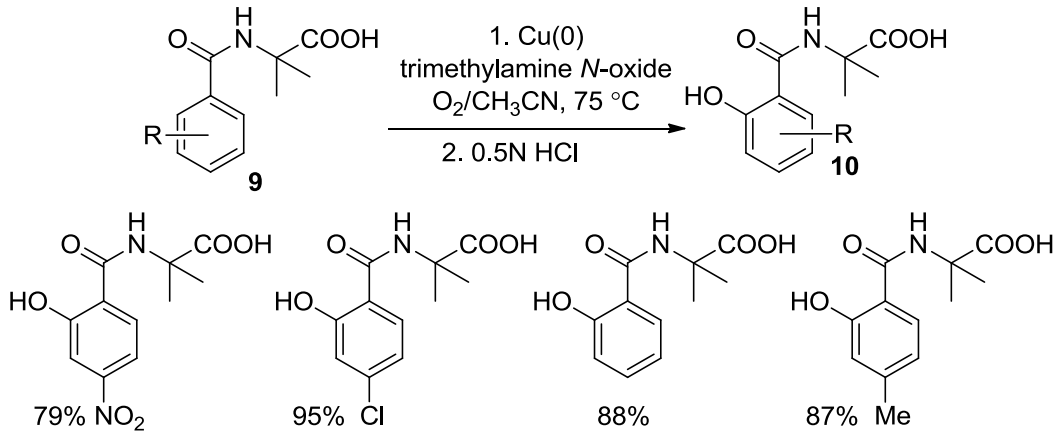


III. C-H bond functionalization involving organo-copper intermediates

3.1 Chelate-directed C-H bond functionalization

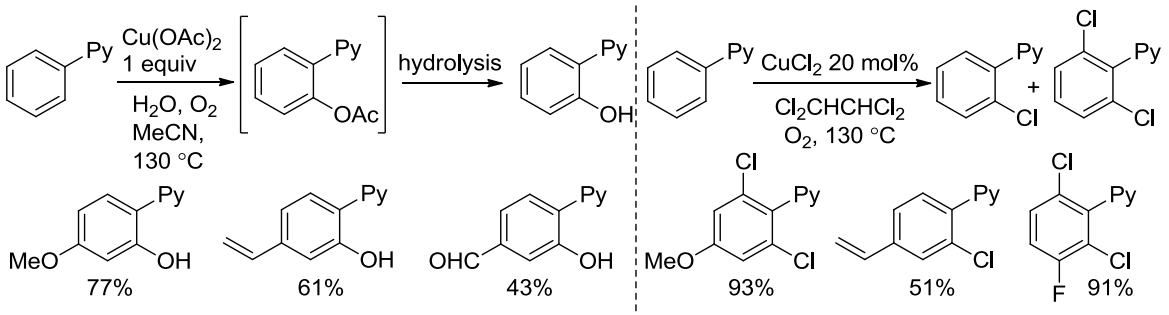
In 1990, in an effort to synthesize salicylic acids from benzoic acids, Reinaud developed a method that allows hydroxylation of sp^2 C-H bonds by chelation-directed copper-mediated oxidation.[41] Thus, subjecting benzoic acid amides **9** to Cu(0), and trimethylamine *N*-oxide oxidant under O_2 atmosphere, the ortho C-H bonds of **9** were hydroxylated. The authors indicated that under O_2 atmosphere, Cu(0) will be oxidized to Cu(II) which then promotes the hydroxylation of ortho C-H bonds with trimethylamine *N*-oxide. Products were obtained in good yields. It was observed that electron-withdrawing groups greatly enhance the reaction rate.

Scheme 1-32. Copper-mediated direct hydroxylation of benzoic acid amides



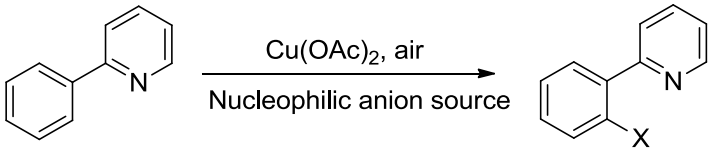
Pyridine has been extensively studied as a directing group for transition metal-catalyzed C-H bond functionalization. In 2006, Yu group reported a method that employs pyridine directing group and Cu(II) for the functionalization of sp^2 C-H bonds.[42] By subjecting 2-phenylpyridine derivatives to stoichiometric amount of $Cu(OAc)_2$ in H_2O and under O_2 atmosphere, the ortho-hydroxylated products were obtained in moderate yields. It is noteworthy that other functional groups such as olefins and aldehydes were compatible with the oxidizing conditions. It was proposed that the acetoxylated products were formed first, followed by fast hydrolysis to generate hydroxylated products. The authors also reported the chlorination of 2-phenylpyridine ortho C-H bonds using $CuCl_2$ catalyst and $Cl_2CHCHCl_2$ as chloride source.

Scheme 1-33. Copper-mediated hydroxylation and copper-catalyzed chlorination of 2-phenyl pyridine derivatives



Interestingly, under copper-mediated conditions, ortho C-H bonds of 2-phenylpyridine can react with various nucleophiles. These conditions, depending on the nucleophiles, allow the bromination, iodination, cyanation, amination, alkoxylation, thiolation, and hydroxylation of 2-phenylpyridine.

Table 1-4. Copper-mediated C-H functionalization



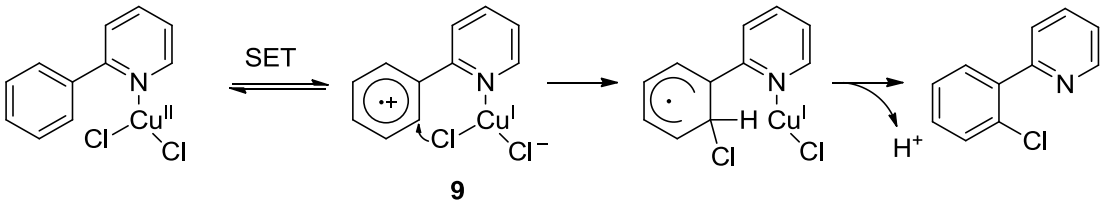
Entry	Anion source	Solvent	Product (X)	Yield
1	–	$Br_2CHCHBr_2$	Br	65%
2	I_2	DCE	I	61%
3	TMSCN	MeCN	CN	42%
4	–	$MeNO_2$	CN	67%

Table 1-4. (*Continued*)

5	$TsNH_2$	MeCN	TsNH	74%
6	*p*-CN-PhOH	MeCN	*p*-CN-PhO	35%
7	PhSH	DMSO	PhS	40%
8	MeSSMe	DMSO	MeS	51%
9	H_2O	DMSO	OH	22% (CuF_2 1 equiv)

Experiments were performed to elucidate the mechanism of the reaction. The following data were obtained: (1) no isotope effect was observed suggesting that mechanism is different from Pd-catalyzed functionalization where a large value of KIE was observed. (2) Chlorination is first order in both catalyst and substrate. (3) Electron-withdrawing groups decrease the reaction rate. The plausible mechanism for the reaction is shown in Scheme 1-34. Single electron transfer (SET) from the aryl ring to coordinated Cu(II) results in the formation of radical-cation intermediate **9** and this step was proposed to be rate determining.

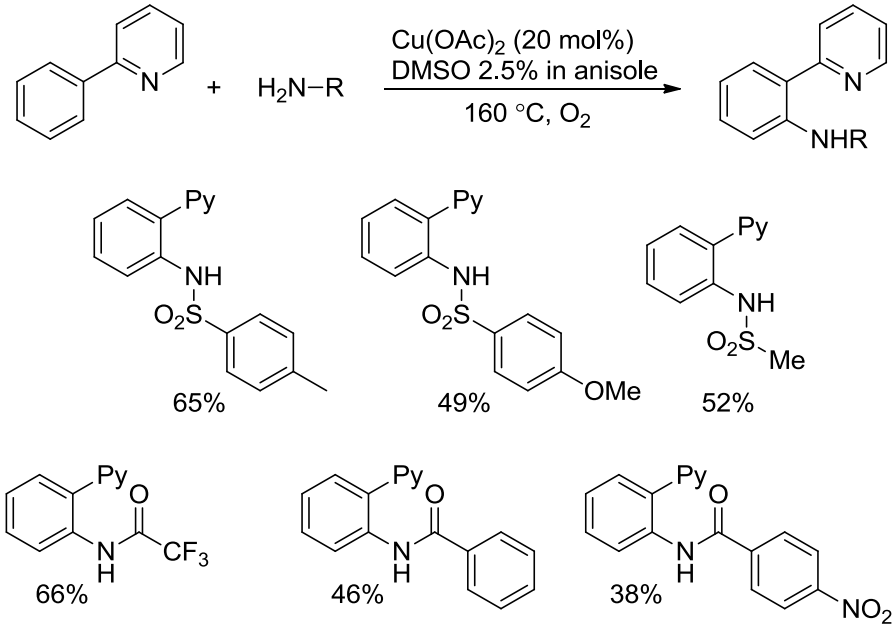
Scheme 1-34. Plausible mechanism



9

The amination of 2-phenylpyridine using catalytic Cu(II) was reported by Nicholas group.[43] Using $Cu(OAc)_2$ and O_2 oxidant in anisole solvent, various amides can aminate C-H bonds of the phenyl ring. The addition of small amount of DMSO is necessary to liberate the products from the copper catalyst. Only moderate yields of products were obtained and this can be explained by the formation of acetoxylated product under the reaction condition.

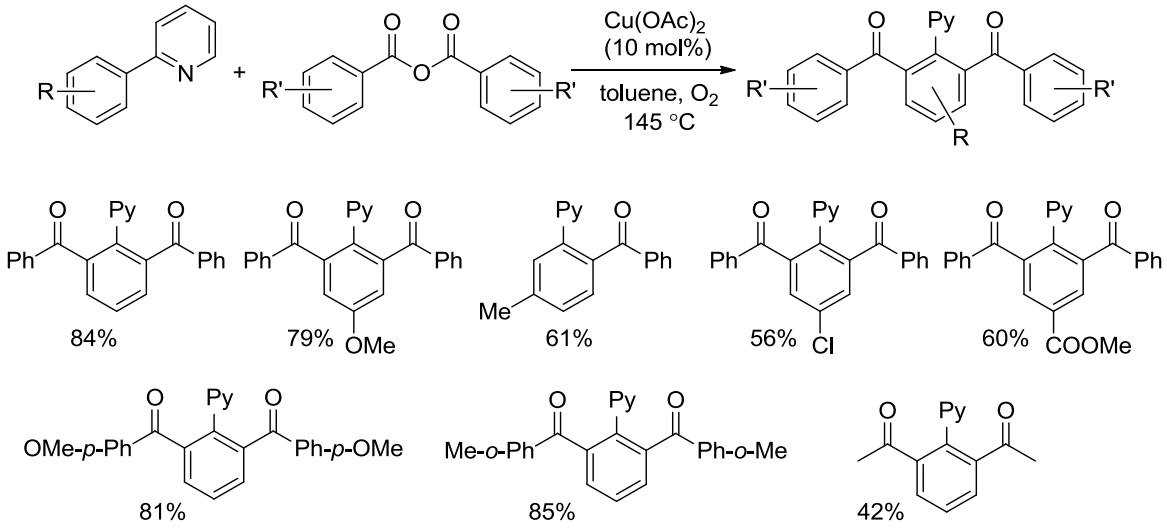
Scheme 1-35. Copper-catalyzed amination of 2-phenylpyridines



The ortho-acyloxylation of 2-phenylpyridine can be performed using a catalytic amount of Cu(II). Thus, employing $Cu(OAc)_2$ catalyst, O_2 oxidant, and carboxylic acid anhydrides,

the mono- or di-acyloxylated products can be generated in moderate to good yields.[44] Depending on the substituent pattern of the aromatic ring, mono- or di-acyloxylated products are formed. Particularly, in the case of meta- or ortho-substituted substrates, mono-substituted products were obtained. Electron-donating groups accelerate the reaction while electron-withdrawing substituents decrease the reaction rate. Good functional group tolerance was demonstrated as groups such as Cl, ester, and Br are tolerated. Besides carboxylic acid anhydrides, acyl chlorides were also reported to be reactive.[45]

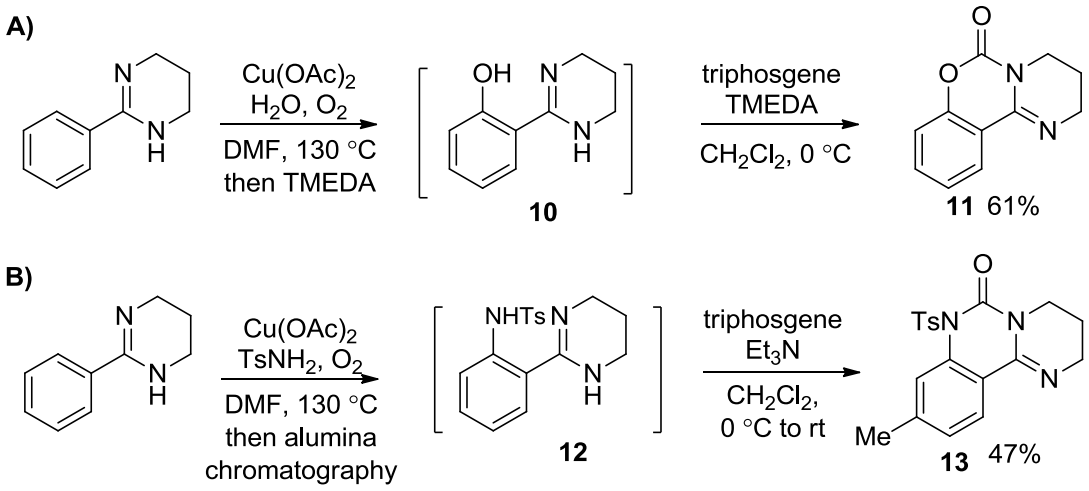
Scheme 1-36. Copper-catalyzed acylation of 2-phenylpyridines



Nitrogen-containing functional groups are known for their ability to chelate transition metals and direct the C-H functionalization. Thus, tetrahydropyrimidinyl group was used as directing group for copper-mediated functionalization of ortho C-H bonds. Fujii and Ohno reported that tetrahydropyrimidinyl benzene can undergoes oxidation of ortho C-H bonds in the presence of stoichiometric amount of $Cu(OAc)_2$, O_2 oxidant, and H_2O.[46] The

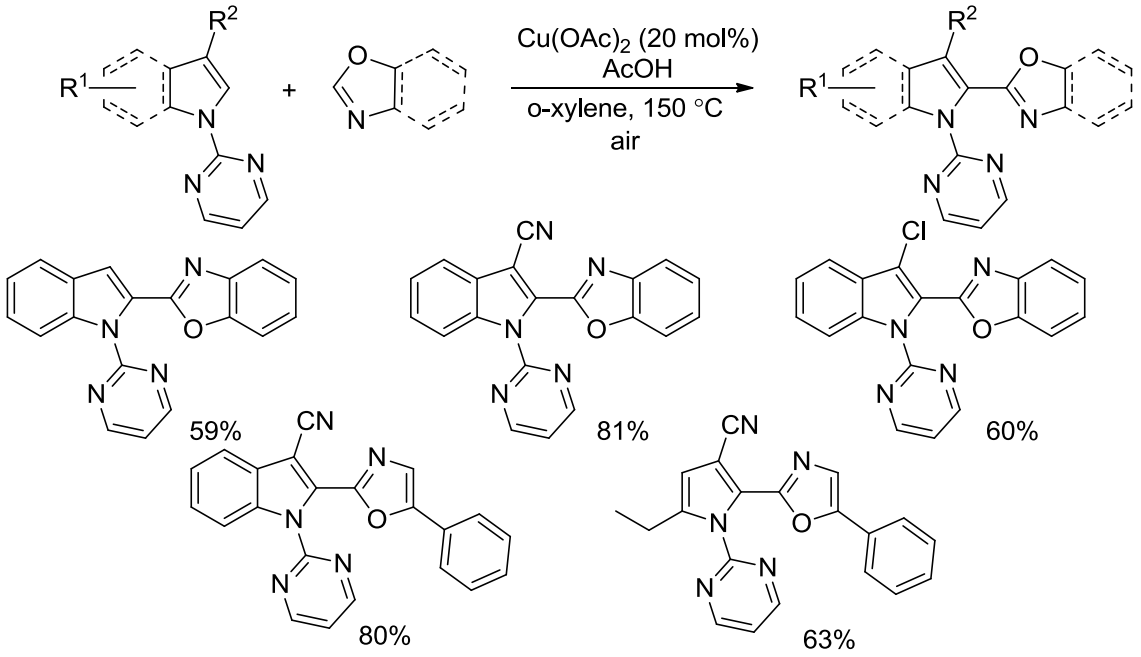
method allowing the introduction of nitrogen to ortho C-H bonds of tetrahydropyrimidinyl benzene was also demonstrated by using similar conditions with tosylamide as an amidating agent. The amidated product **13** was obtained in moderate yield.

Scheme 1-37. Chelation-assisted copper-mediated C-H bond functionalization



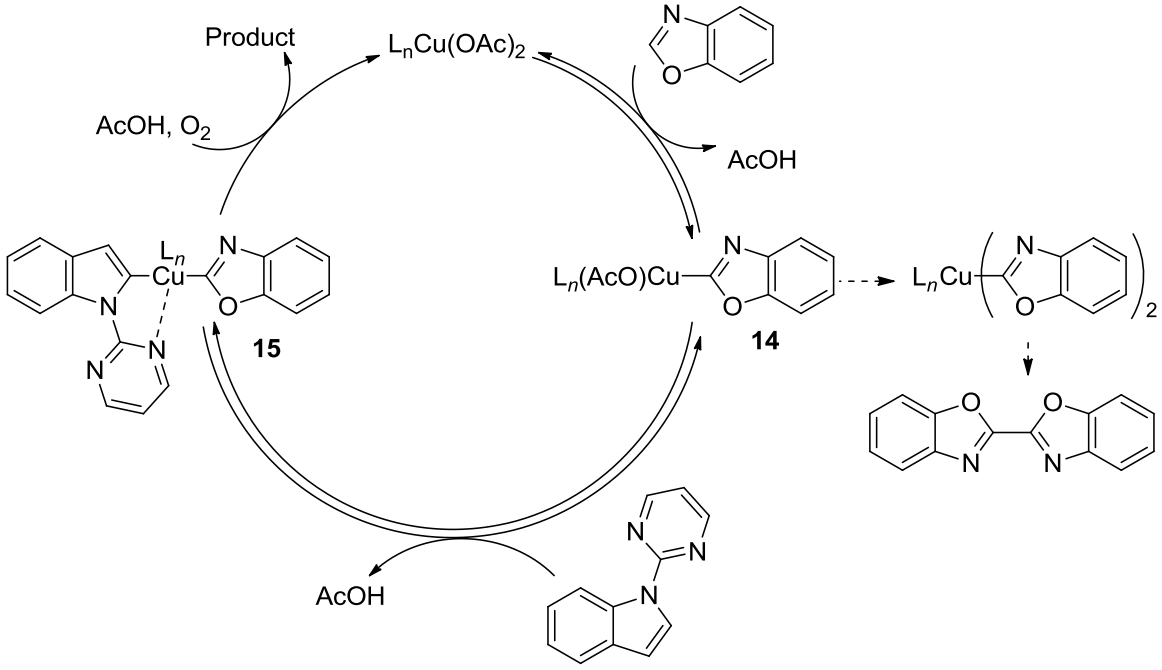
Copper-mediated cross-dehydrogenative coupling between 2-arylpyridines and azoles was reported by the Miura group.[47a] In 2012, an improved method, in which catalytic amount of copper was used together with removable pyrimidine directing group, was demonstrated by the same group.[47b] Thus, indoles and pyrroles can be cross coupled with oxazoles at C_2 positions generating biaryls in good yields. The pyrimidine-directing group can be eventually removed by treating the molecule with NaOMe in DMSO.

Scheme 1-38. Copper-catalyzed cross-coupling of indoles and 1,3-azoles



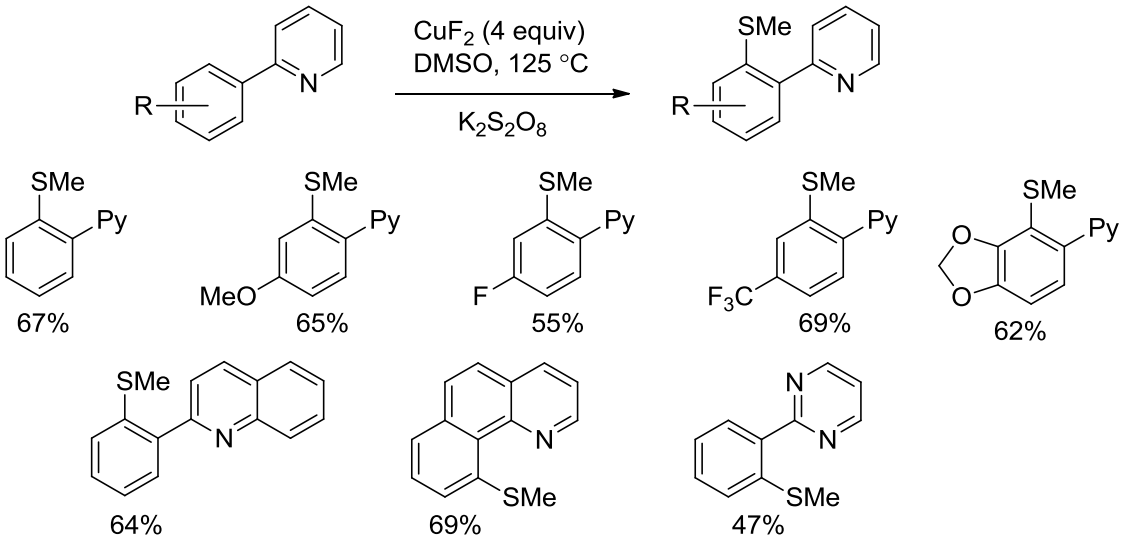
The plausible mechanism is depicted in Scheme 1-39. The first step involves metallation of acidic benzoxazole to generate Cu(II) complex **14**. Subsequent chelation-assisted C-H metallation of indole with **14** results in formation of complex **15**. The authors proposed that highly electron-withdrawing nature of benzoxazole ligand in **14** facilitates the coordination of directing group on indole and thus trigger the second C-H metallation. Reaction of complex **14** with another molecule of benzoxazole leads to the formation of side product, bisbenzoxazole. Reductive elimination from **15** followed by oxidation of copper gives the product and regenerates active catalyst.

Scheme 1-39. Proposed reaction mechanism



Copper-mediated direct thiolation of aryl C-H bonds using *N*-heterocyclic directing group was reported by the Qing group in 2010.[48] The optimized system contains stoichiometric CuF_2, $K_2S_2O_8$, and DMSO as the S source. Both pyridine and pyrimidine can act as directing groups for this reaction.

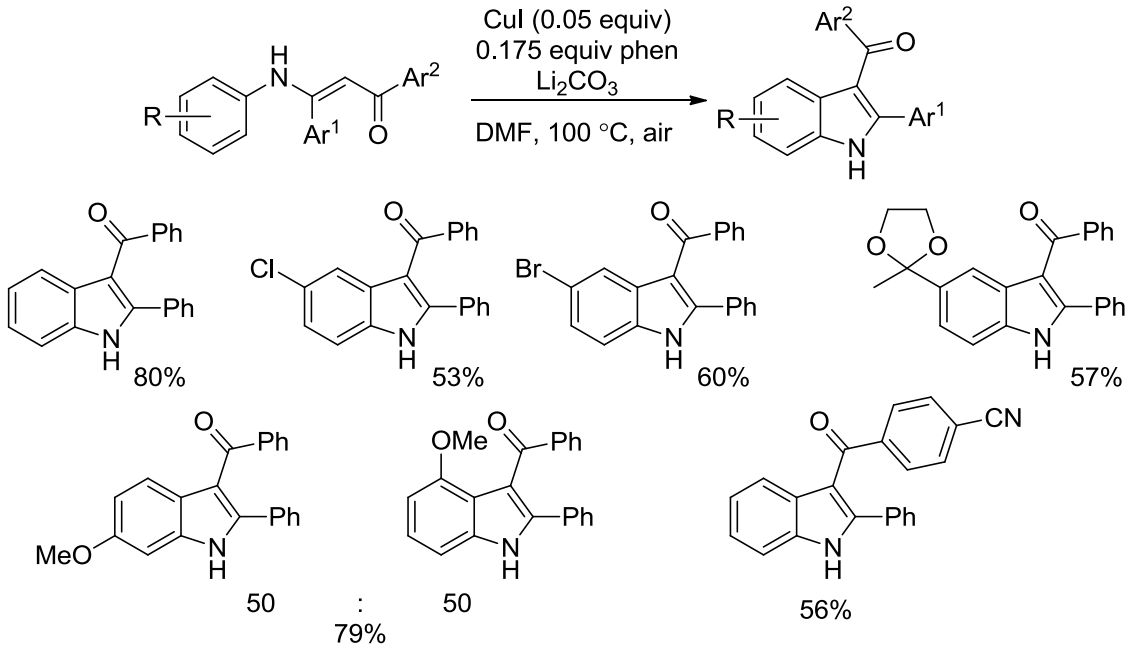
Scheme 1-40. Copper-mediated methylthiolation of 2-arylpyridines by DMSO



3.2 Oxidative annulation reactions

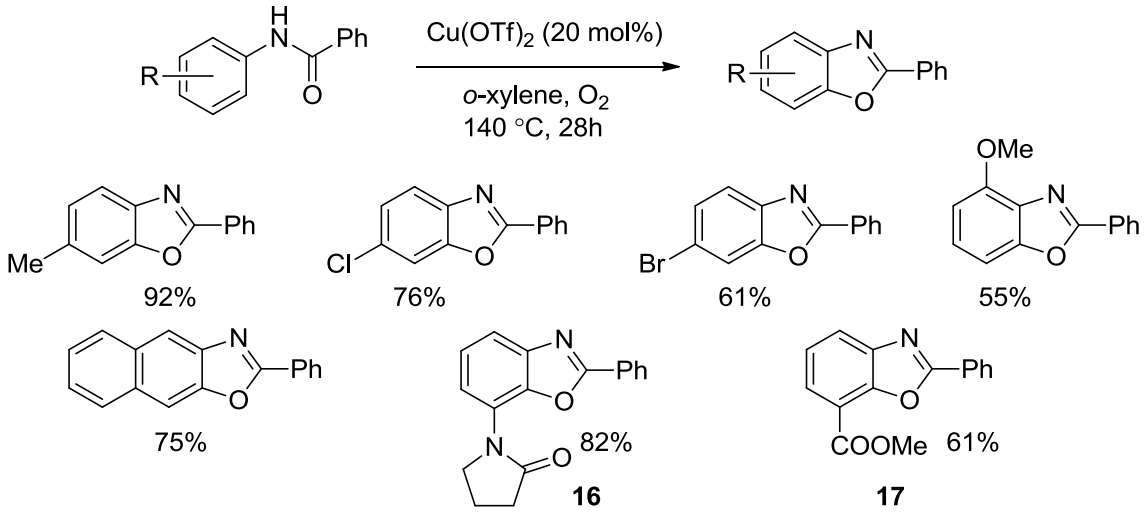
A method for copper-catalyzed intramolecular C-H bond activation/C-C bond formation for the construction of indole derivatives was developed by the Cacchi group.[49] The optimized reaction conditions include CuI catalyst, phenanthroline ligand, and Li_2CO_3 base. Various functional groups such as halide, cyanide, and acetal are compatible with reaction conditions.

Scheme 1-41. Copper-catalyzed intramoleclular C-H bond activation/C-C bond formation



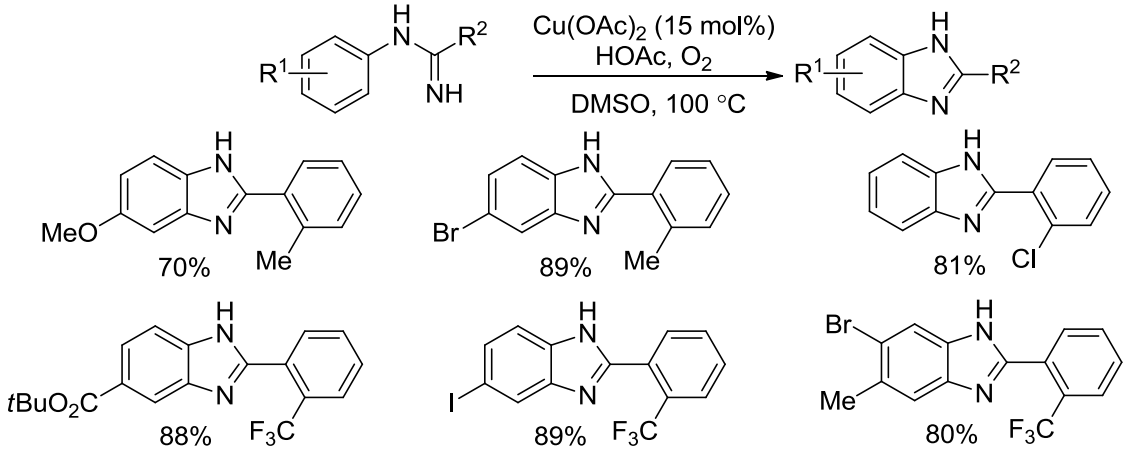
Copper-catalyzed intramolecular C-H bond activation/C-O bond functionalization was reported by the Nagasawa group. The method was used for the synthesis of various 2-arylbenzoxazoles.[50] The optimized reaction conditions involve $Cu(OTf)_2$ catalyst and O_2 oxidant. The ortho-substituted substrates gave slightly lower yield due to steric congestion around the amide. Additional directing groups such as ester or pyrrolidin-2-one at meta position can direct the activation to the more hindered C-H bond as shown for structures **16** and **17** (Scheme 1-42).

Scheme 1-42. Copper-catalyzed intramolecular C-H bond activation/C-O bond formation



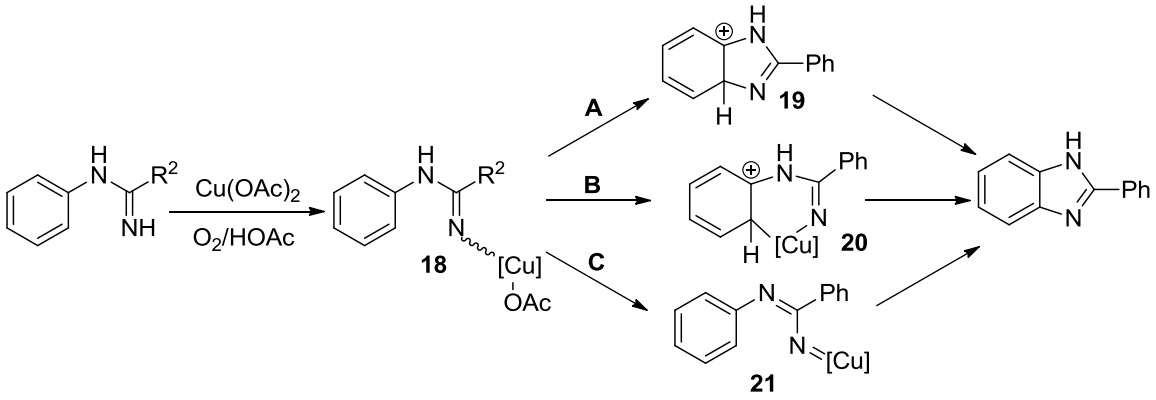
Synthesis of benzimidazoles by C-H bond functionalization/C-N bond formation using copper catalysis was developed by Buchwald.[51] In the presence of $Cu(OAc)_2$ catalyst, amidines undergo intramolecular cyclization with ortho C-H bond to afford benzimidazoles. The reaction requires excess of acetic acid and O_2 oxidant in order to obtain high yields.

Scheme 1-43. Copper-catalyzed intramolecular C-H bond activation/C-N bond formation



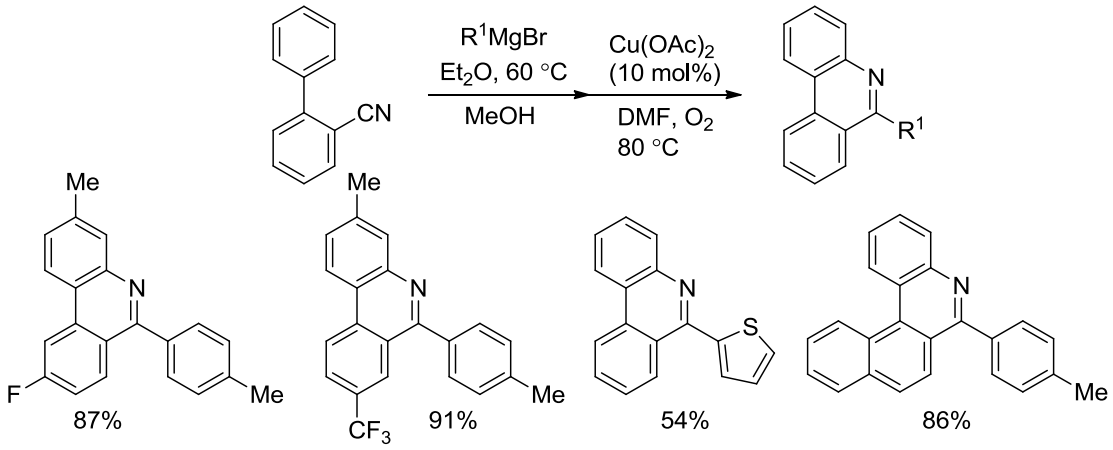
There possible reaction pathways were proposed (Scheme 1-44). Reaction of amidine with $Cu(OAc)_2$ generates Cu-N adduct **18**. Following pathway A, imine will attack the amidine moiety in a manner similar to electrophilic substitution. Rearomatization of **19** will form the product. In pathway B, *N*-phenyl ring will attack Cu to generate intermediate **20**. Reductive elimination and rearomatization leads to the product. In pathway C, nitrene intermediate **21** will insert into C-H bond. Further mechanistic studies are necessary to elucidate the actual mechanism.

Scheme 1-44. Possible reaction pathways



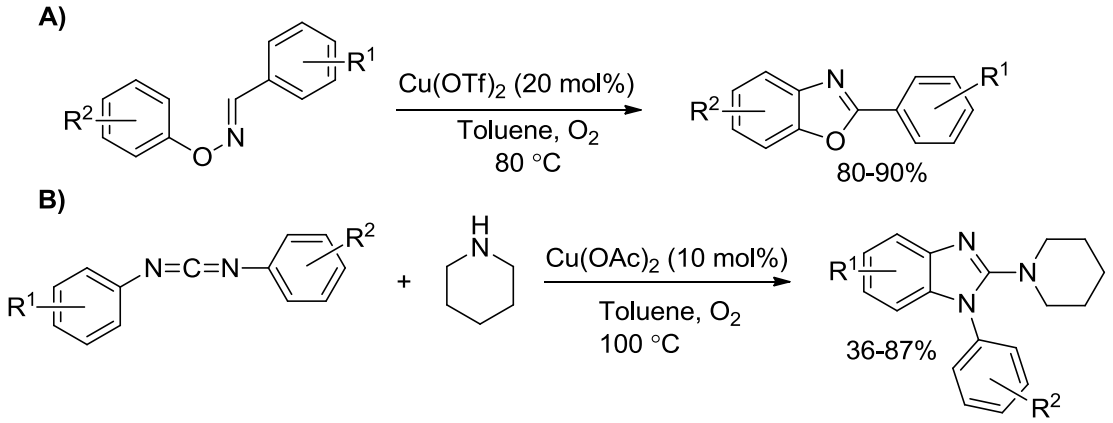
The method that allows a short and direct synthesis of phenanthridine derivatives from biaryl-2-carbonitriles and Grignard reagents using copper catalysis has been reported recently.[52] Using a two-step procedure that involves the nucleophilic addition of Grignard reagent to carbonitrile followed by $Cu(OAc)_2$-catalyzed C-H activation/C-N bond formation, various phenanthridine derivatives and polycyclic azaaromatic compounds were obtained in good yields.

Scheme 1-45. Copper-catalyzed synthesis of phenanthridine derivatives



Benzoxazole derivatives and benzimidazole derivatives can be prepared using copper-catalyzed sp^2 C-H bond activation/C-N or C-O bond formation (Scheme 1-46).[53] In the presence of $Cu(OTf)_2$ catalyst and O_2 oxidants, bisaryloxime ethers can be converted to 2-arylbenzoxazoles in excellent yields. Benzimidazoles can be synthesized from diphenylcarbodiimides with amines using the conditions involving $Cu(OAc)_2$ catalyst and O_2 oxidant.

Scheme 1-46. Copper-catalyzed C-H bond activation/C-heteroatom bond formation

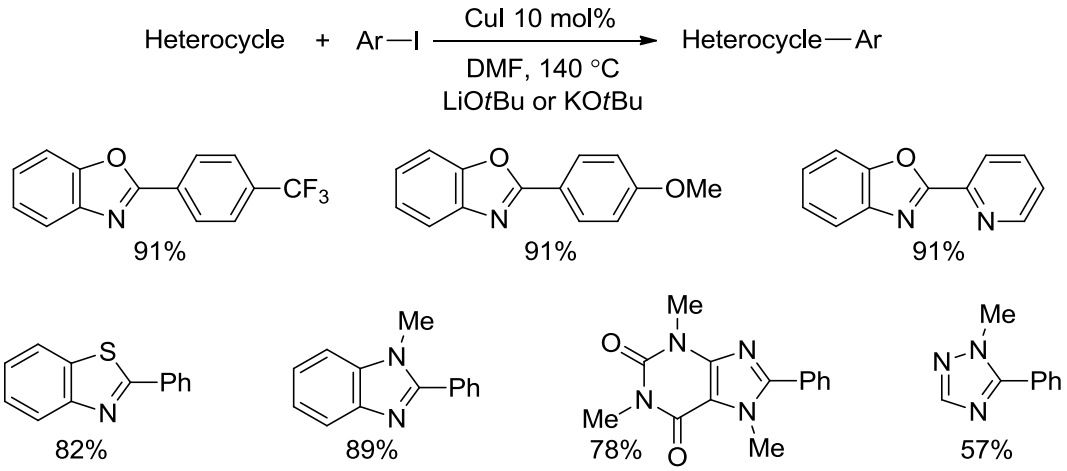


3.3 Functionalization of electron-deficient arenes and heterocycles

3.3.1 C-C bond formation

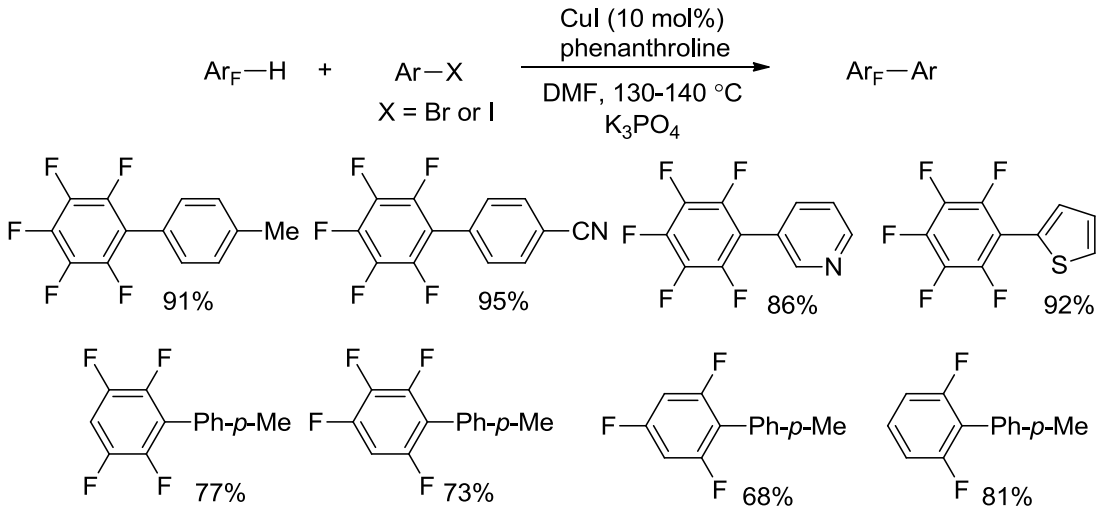
Copper-catalyzed C-H bond functionalization/C-C bond formation has been extensively investigated and is used for the construction of biaryl structures or arylperfluoroalkanes. Biaryl compounds containing heterocycle-aryl linkages are important structures in pharmaceutical, thus making the synthesis of these compounds highly desirable. Hien Do in the Daugulis group has developed methods that allow direct coupling of acidic arenes and heterocycles with aryl halides using copper catalysis. Indeed, these methods provide the shortest and most efficient routes for the synthesis of biaryl compounds. In 2007, the direct arylation of heterocycles by aryl iodides was reported.[54] The optimized reaction conditions involves CuI catalyst and Li*O*tBu base. For less acidic substrates, use of KOtBu base was required. Electron-withdrawing substituents on the aryl iodides accelerate the reaction. Various heterocycles such as oxazoles, thiazoles, imidazoles, caffeine, and pyridine-*N*-oxide were arylated in good yields.

Scheme 1-47. Copper-catalyzed direct arylation of heterocycles



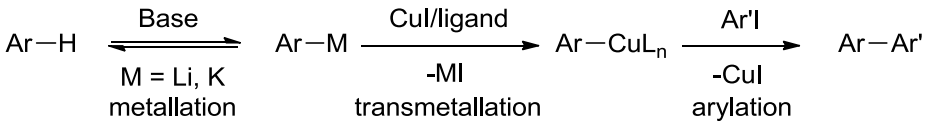
Subsequently, it was reported that the use of phenanthroline ligand allows arylation of broader scope of substrates including polyfluoroarenes.[55] Thus under copper catalysis, tetrafluoro, trifluoro, and difluorobenzenes can be efficiently arylated by both aryl bromides and iodides.

Scheme 1-48. Copper-catalyzed arylation of polyfluoroarenes



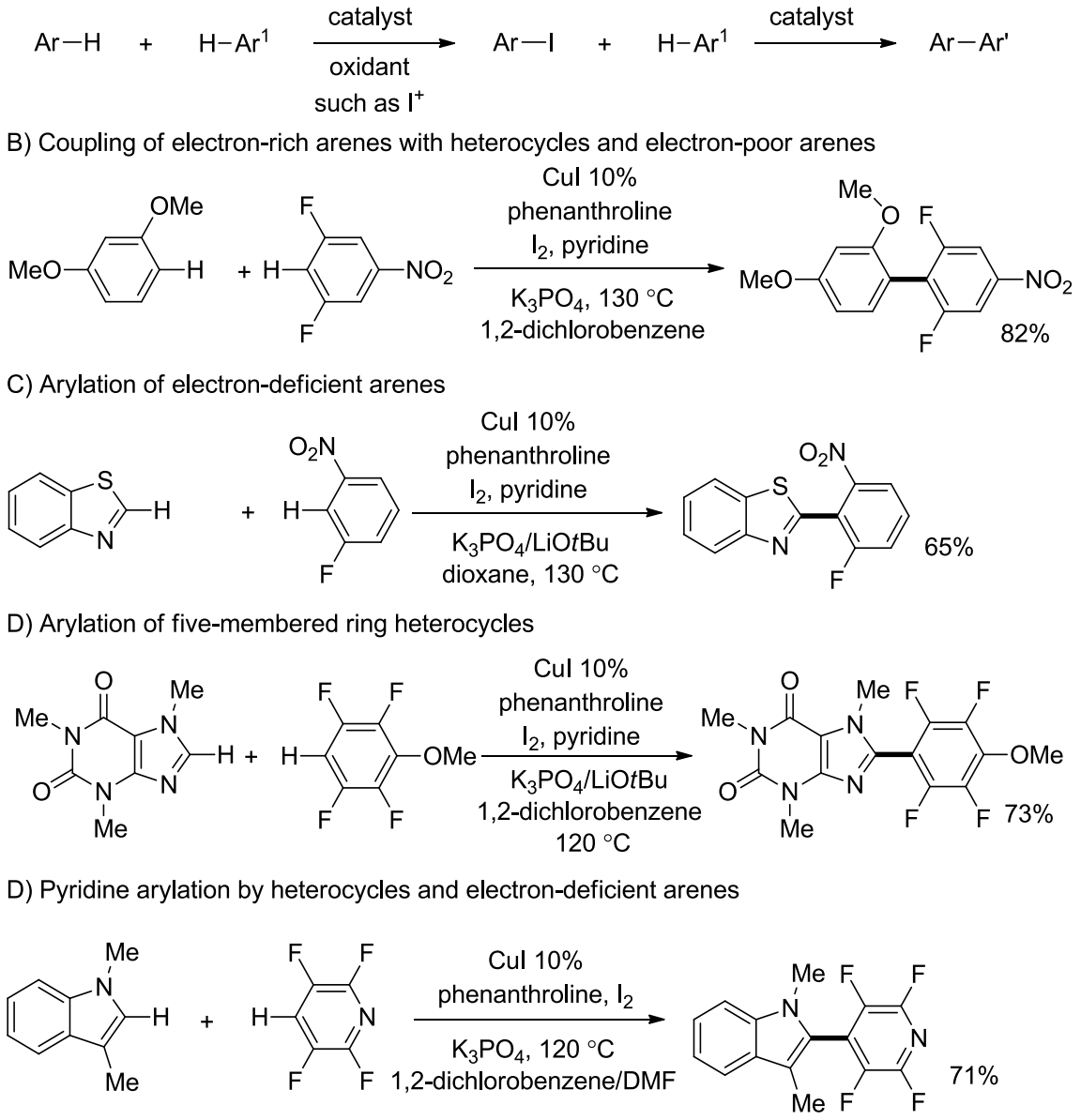
In general, the methods allow the arylation of sp^2 C-H bonds possessing DMSO pKa below 35. Based on the acidity of the C-H bonds, the appropriate base can be used. With comparatively acidic C-H bonds (pKa below 27), K_3PO_4 can be used; the stronger LiO*t*Bu base is necessary for less acidic C-H bonds (pKa 27-35).[56] The mechanism (Scheme 1-49) includes three parts: metallation, transmetallation with copper halide, and reaction of aryl copper with haloarene. For the metallation step, the acidity of substrate determines the position and efficiency of arylation. Arylcopper-phenanthroline complexes were also synthesized and characterized. The reaction of these copper complexes with aryl iodides produced the desired biaryl compounds indicating that arylcopper is a likely intermediate in the reaction.

Scheme 1-49. Proposed reaction pathway



Significant improvement for birayl synthesis was made by the same group as they reported the direct cross-coupling of arenes and heterocycles using copper catalyst and iodine oxidant.[57] The reaction involves iodination of arenes followed by cross coupling with the most acidic C-H bonds of other coupling partners under copper catalysis (Scheme 1-50). The iodination step can happen through electrophilic aromatic substitution by I_2 for electron-rich arenes or, alternatively via deprotonative iodination of electron deficient arenes and heterocyles. Overall, the reaction requires CuI catalyst, phenanthroline ligand, I_2 oxidant, pyridine additive, 1,2-dichlorobenzene solvent, and K_3PO_4 or a mixture of LiO*t*Bu and K_3PO_4.The method allows for coupling of electron-rich arenes with heterocycles and electron-poor arenes; arylation of electron-deficient arenes; arylation of five-membered ring heterocycles; and pyridine arylation by heterocycles and electron-deficient arenes. If the iodination is not efficient, the remaining I_2 can oxidize active Cu(I) to inactive Cu(II) resulting in longer reaction times.

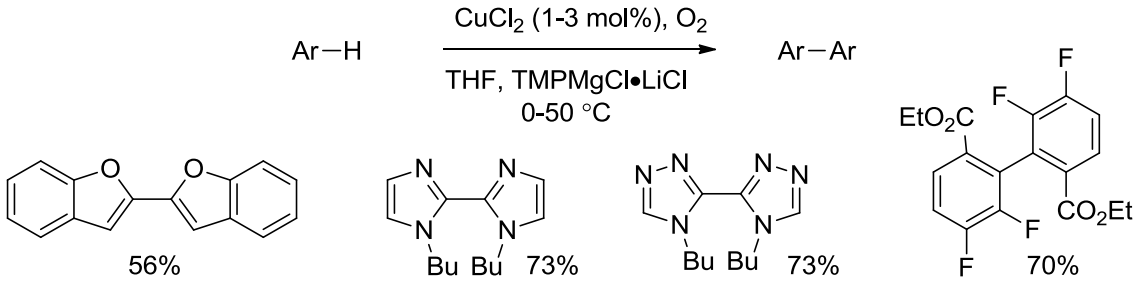
Scheme 1-50. Copper-catalyzed arene cross-dimerization



Copper-catalyzed dimerization of arenes and heterocycles was also demonstrated. The optimized reaction conditions employ $CuCl_2$ catalyst, O_2 oxidant and magnesium or zinc bases.[58] The use of hindered zinc or magnesium amide bases, which were extensively used by Knochel,[59] are essential for the reaction to prevent the formation of phenol byproducts.

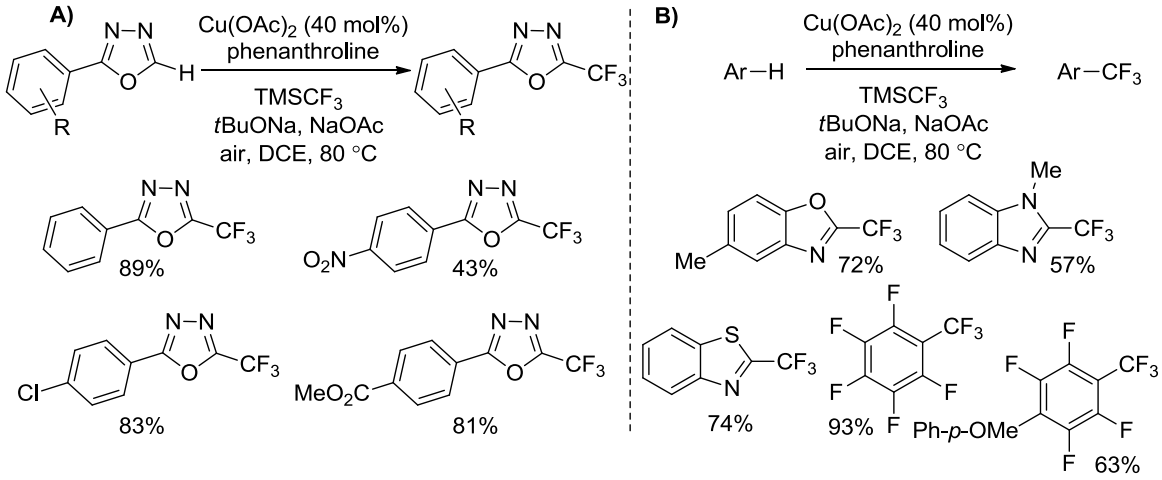
Various electron-rich and electron-deficient hetercycles and polyfluorinated arenes can be dimerized under reaction conditions. Control experiments support the essential role of copper catalyst since only trace amounts of product were obtained when copper was omitted.

Scheme 1-51. Copper-catalyzed deprotonative dimerization of arenes and heterocycles



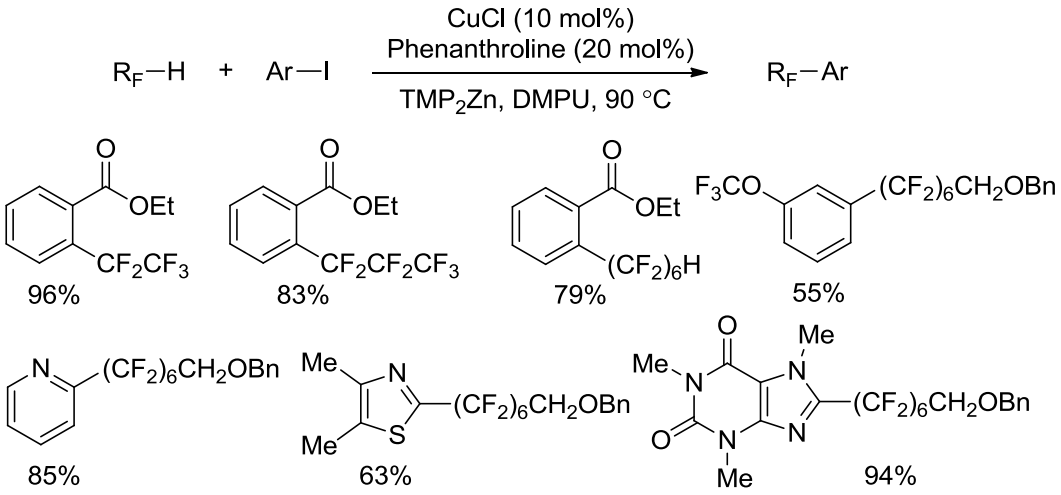
Copper-catalyzed direct trifluoromethylation of arenes and heterocycles is a very challenging yet attractive transformation. Recently, the Qing group reported oxidative trifluoromethylation of acidic C-H bonds in heterocycles and arenes using a cheap $TMSCF_3$ trifluormomethylating agent.[60] The reaction employed $Cu(OAc)_2$ catalyst, phenanthroline ligand, mixture of NaO*t*Bu and NaOAc bases, and different oxidants for different classes of substrates.

Scheme 1-52. Copper-catalyzed direct trifluoromethylation of A) 1,3,4-oxadiazole derivatives B) other heterocyles and polyfluoroarenes



Perfluoroalkyl arenes can be synthesized using copper-catalyzed arylation of 1H-perfluoroalkanes.[61] Acidic C-H bonds in 1H-perfluoroalkanes can be deprotonated by zinc amide base to generate perfluoroalkyl zinc reagents which will cross-couple with aryl iodides under copper catalysis. The optimized conditions include CuCl catalyst, phenanthroline ligand, and TMP_2Zn base. The use of TMP_2Zn base is essential for product formation as it allows the deprotonation of 1H-perfluoroalkanes and the resulting perfluoroalkyl zinc reagents are stable.

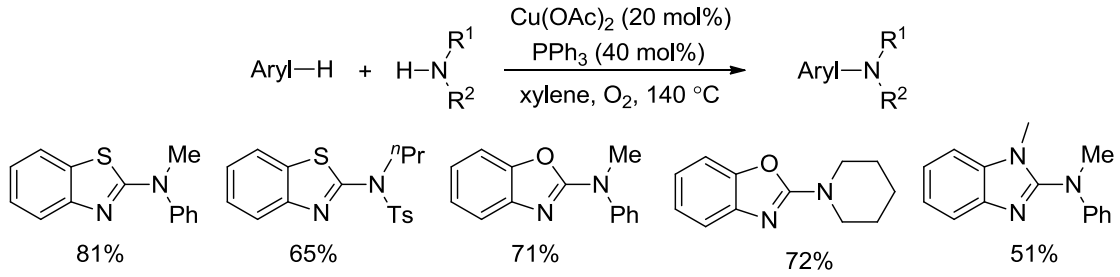
Scheme 1-53. Copper-catalyzed arylation of 1H-perfluoroalkane



3.3.2 C-heteroatom bond formation

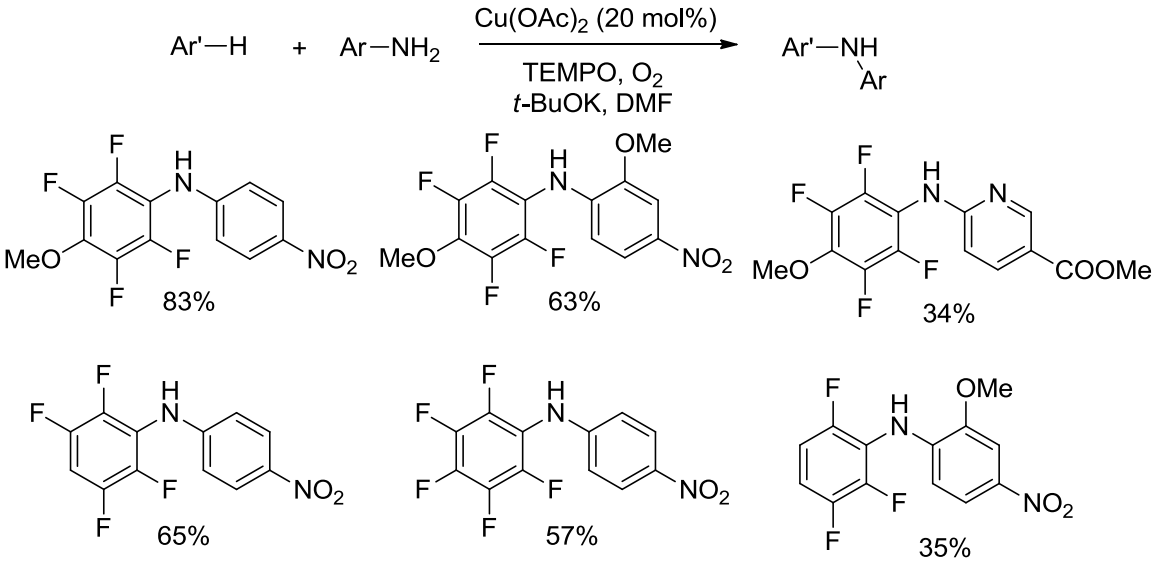
Direct amination of electron-deficient arenes and heterocycles are highly desirable transformations because it provides the most efficient and straightforward way for the synthesis of aromatic amines. Over the last decade, chemists have reported numerous amination methods using amine,[62] amide,[63] sulfoximine[64], or O-acylated hydroxylamine[65] nitrogen sources. In 2009, the amination of azoles using copper catalyzed C-H activation was reported by the Mori group.[62] The optimized conditions include $Cu(OAc)_2$ catalyst, PPh_3 ligand, and O_2 oxidant. Secondary amines can couple with acidic azoles to generate products in good yields. Lately, tertiary amines are also reported to undergo reaction with benzoxazoles under copper catalysis. It is proposed that tertiary amines are oxidized by copper to generate iminium cations which hydrolyze under reaction condition to generate secondary amines that subsequently undergo coupling reaction with heterocycles.[62b]

Scheme 1-54. Copper-catalyzed direct amination of azoles



Direct amination of polyfluoroarenes with primary aromatic amines using copper catalysis has been demonstrated by the Hong group.[66] Using $Cu(OAc)_2$ catalyst, TEMPO oxidant, KO*t*Bu base, and O_2 oxidant, various tri, tetra, and pentafluorinated arenes can be aminated by para-subtituted anilines in good yields. Electron-withdrawing substituents at para position of anilines are essential to obtain high yield.

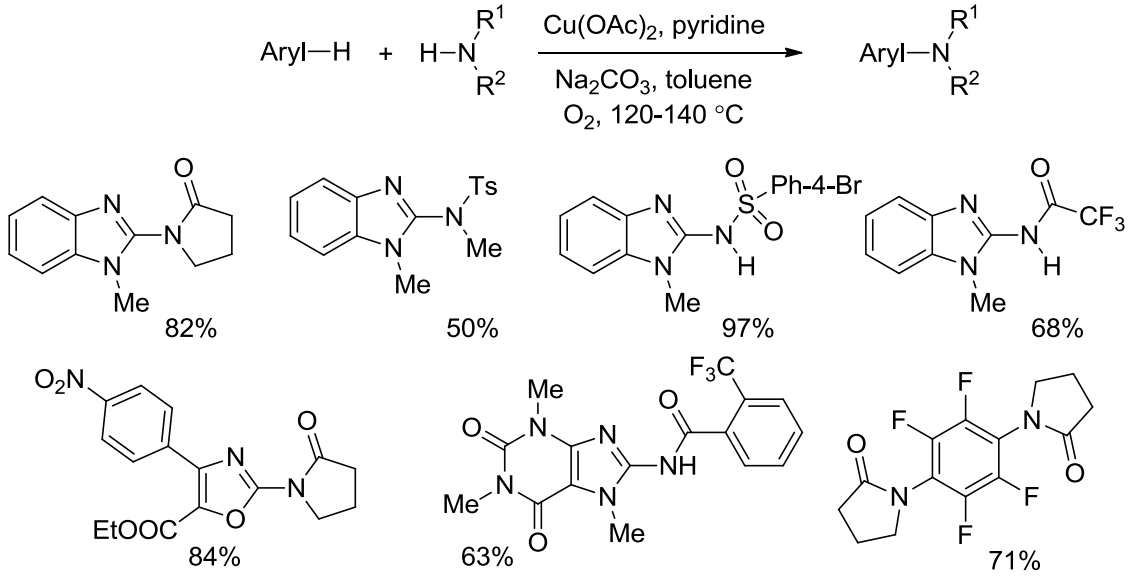
Scheme 1-55. Copper-catalyzed intermolecular amination of acidic aryl C-H bonds with primary aromatic amines



Copper-mediated amidation of heterocyclic and aromatic C-H bonds was developed by the Schreiber group.[54] In the presence of stoichiometric $Cu(OAc)_2$, Na_2CO_3 base, pyridine,

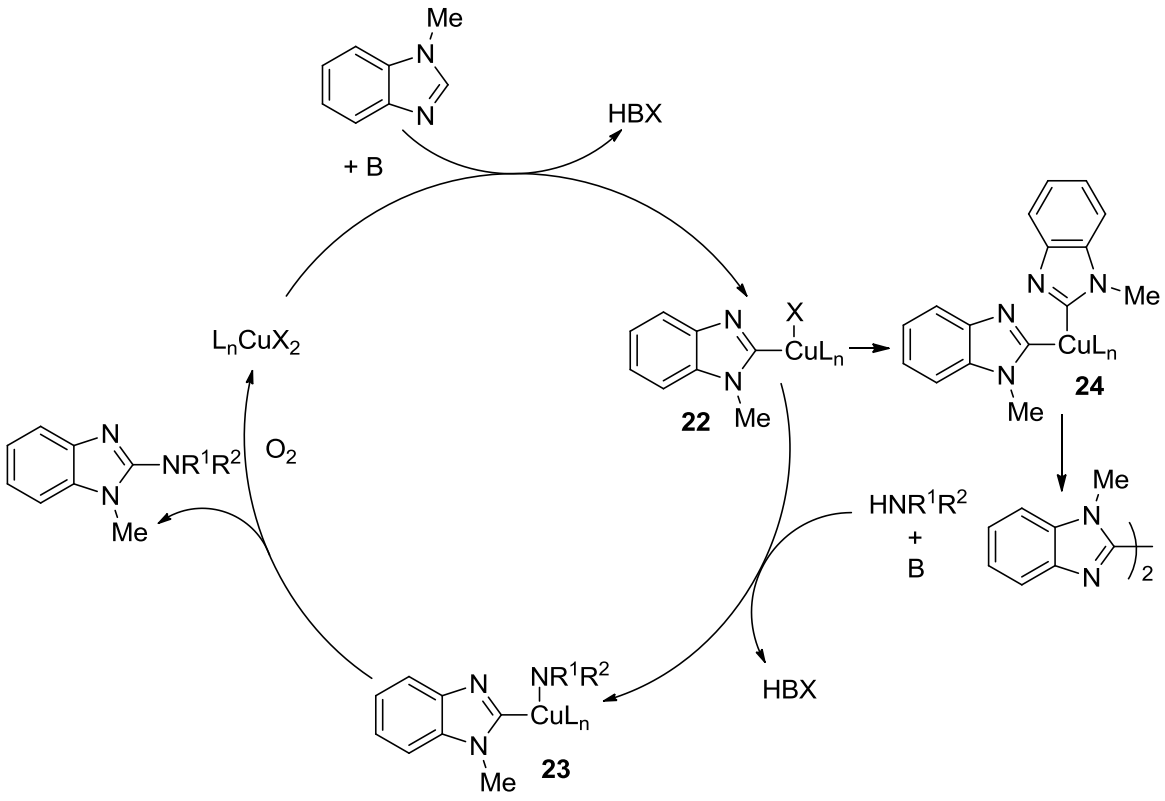
and O_2 oxidant, *N*-methyl benzimidazoles, other azoles and electron-deficient arenes react with amides to generate the amidated products in good yields. The dimerization of heterocycles was also observed.

Scheme 1-56. Copper-catalyzed amidation of hetercycles and polyfluoroarenes



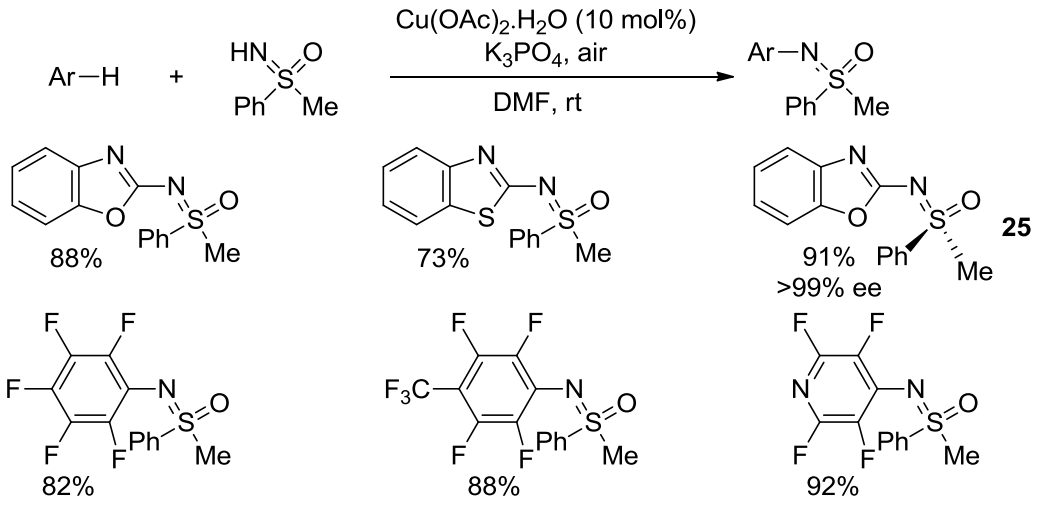
The proposed mechanism is depicted in Scheme 1-57. Base-assisted deprotonation followed by coordination with copper(II) will generate organocopper intermediate **22**. Ligand exchange with amide in the presence of base followed by reductive elimination from the resulting complex **23** will give the amidated product. Complex **22** can also undergo reaction with another benzimidazole to form complex **24**. Reductive elimination form **24** leads to the formation of homocoupling product.

Scheme 1-57. Proposed reaction mechanism for copper-mediated amidation of acidic heterocycles and arenes



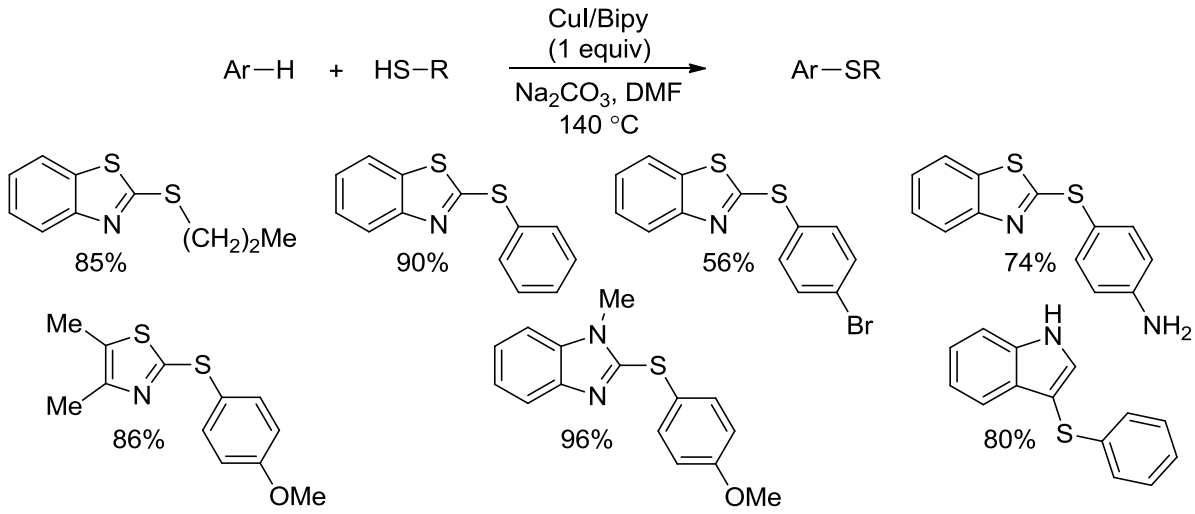
N-(Hetero)arylsulfoximines have attracted significant amount of attention due to the fact that their derivatives show anticancer activity.[64] Direct sulfoximination of heterocycles and arenes is the most effective and convergent approach to these molecules. Thus, copper allows this transformation to proceed in good yield. The reaction conditions include $Cu(OAc)_2.H_2O$ catalyst, and K_3PO_4 base. It was run at room temperature under air. Due to the mild reaction conditions, enantiopure (S)-*S*-methyl-*S*-phenylsulfoximine could be transformed into (S)-*N*-benzoxazolylsulfoximine **25** without affecting the enantiomeric purity.

Scheme 1-58. Copper-catalyzed direct sulfoximination of azoles and polyfluoroarenes

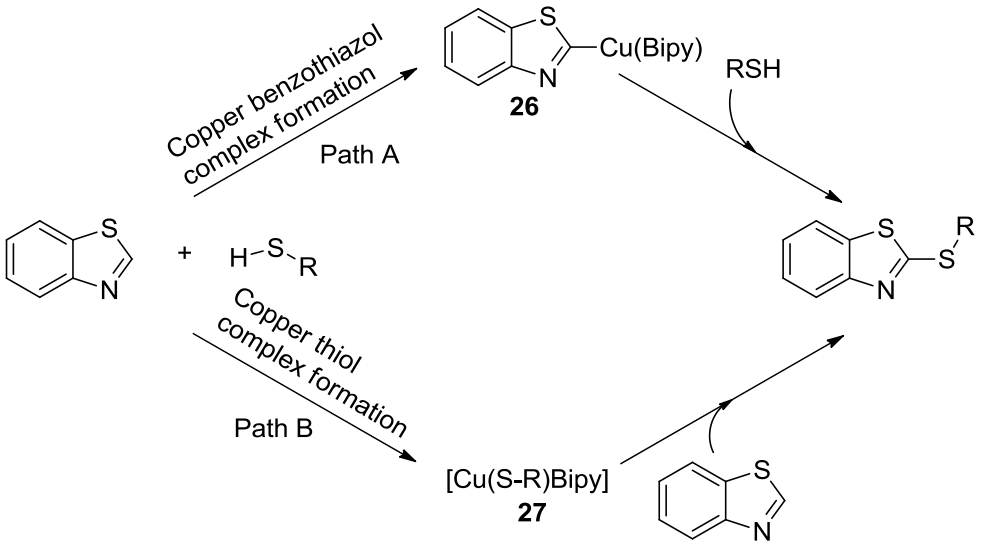


Copper-mediated direct thiolation of heterocycles was reported recently. Thiols,[67] disulfides, or DMSO[68] were employed as S sources. Specifically, in the presence of CuI and 2,2'-bipyridine ligand, benzothiazole and other heterocycles can be thiolated by various alkyl or aryl thiols. The reaction requires stoichiometric amount of Na_2CO_3 base and high temperature. Excellent yields were obtained. Interestingly, when indole was used as substrate, thiolation at C2 position was observed.

Scheme 1-59. Copper-mediated direct thiolation of heterocycles



Scheme 1-60. Possible reaction pathways



Two possible reaction pathways have been proposed. The pathway A includes the formation of aryl copper complex **26** followed by reaction with thiol to generate the product. In pathway B, Cu-thiolate complex **27** was proposed to undergo reaction with benzoxazole to generate the product. Results from experiments and calculations have

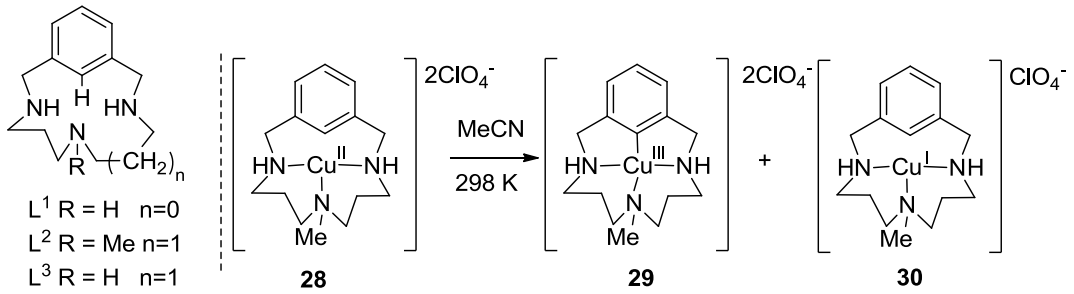
revealed that Cu-thiolate **26** is more likely to be the intermediate of the reaction, thus suggesting that pathway B is more possible.

IV. Organocopper complexes in C-H activation reaction

As reviewed in the previous sections, Cu(II) catalysts have been widely used for oxidative functionalization of C-H bonds. Cu(II) is one-electron oxidant and single electron transfer from aromatic rings to Cu(II) is often proposed as a key step for oxidative coupling reactions. However, this explanation is not compatible with methods that employ electron-deficient or neutral substrates. Further mechanistic studies are necessary for the understanding and improving of these methods. Chemists have recently synthesized organo-Cu(III) complexes and studied the role of these complexes in copper-catalyzed oxidative functionalization of sp^2 C-H bonds.

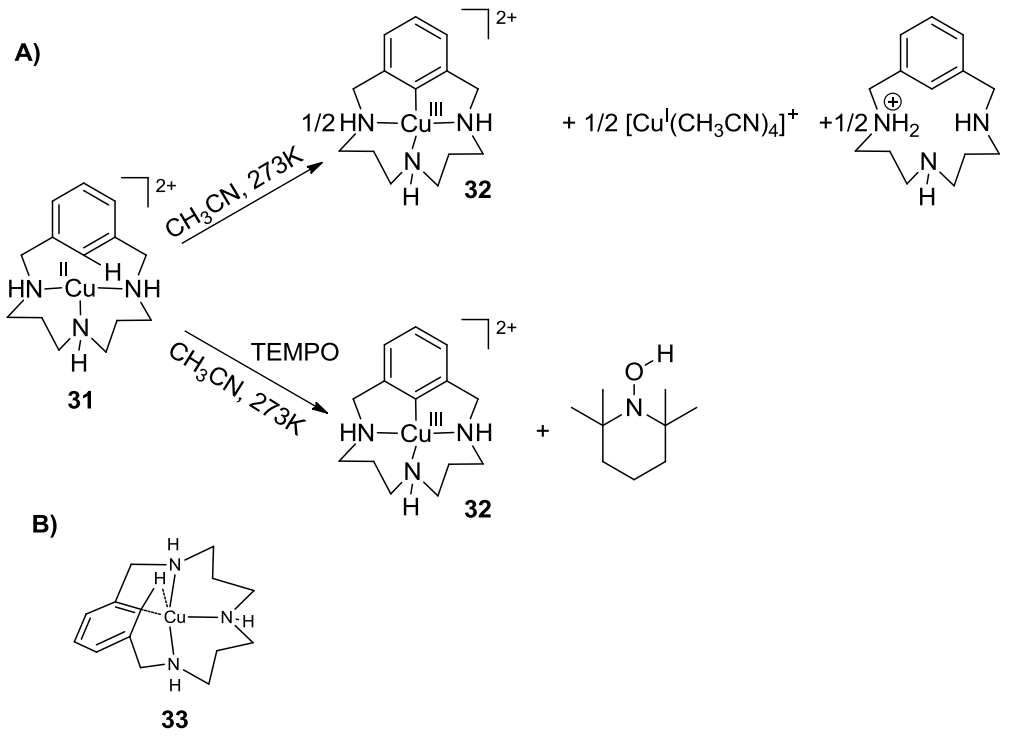
In 2002, aryl-Cu(III) complexes obtained by Cu(II) activation of aryl C-H bonds was reported by Ribas, Llobet, Stack, and coworkers (Scheme 1-61).[69] Reaction of $Cu(ClO_4).6H_2O$ with triazamacrocylic ligand L2 in MeCN at room temperature resulted in the rapid disproportionation of the initially formed complex **28** to Cu(III) complex **29** and Cu(I) complex **30**. Analytical data and crystallographic characterization of **29** indicate the structure depicted in Scheme 1-63. The structure of ligands plays an important role of the reaction. The macrocyclic constraints of L^1-L^3 ligated to Cu(II) through all three nitrogen atoms require the aryl C-H bond to be in close contact with the copper center leading to the enhancement of $\sigma_{C\text{-}H}$-Cu interaction. Such interaction can significantly reduce the pKa of an aryl C-H group. Deprotonation and formation of a $[Cu^{II}L']^+$ complex, where L' is the deprotonated ligand, would lead to the product formation.

Scheme 1-61. Synthesis of aryl-Cu(III) complex through C-H activation by Cu(II)



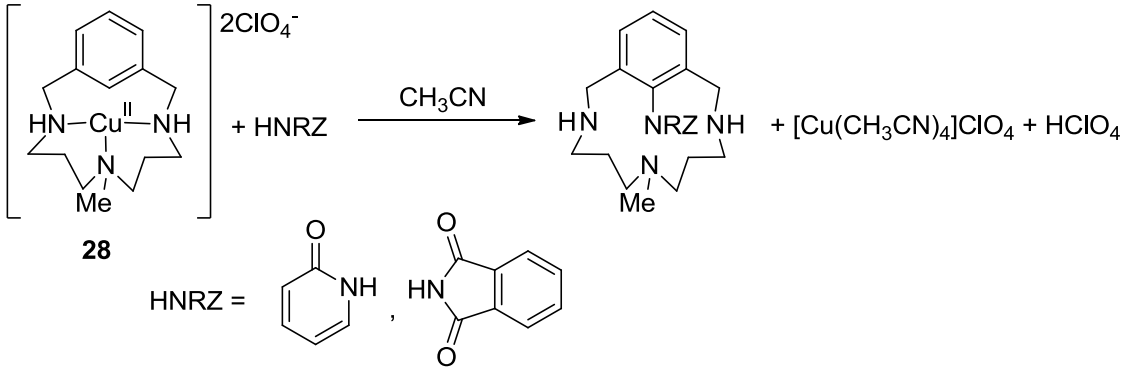
Further mechanistic studies for the C-H activation step were reported by Ribas, Stack, and coworkers in 2010.[70] First, the interaction of an aryl C-H bond and Cu(II) center in complex **31** can be described as a σ-complex with a three-center, three-electron C-H•••Cu^{II} bond (Scheme 1-62B) which was suggested by DFT calculations and EPR. Second, rate determining step was indicated by kinetic data to be a proton-coupled electron-transfer (PCET) between **31** and another copper complex capable of accepting a proton and an electron. Another evidence for this hypothesis is that reaction of **31** with TEMPO, a one-electron oxidant, rapidly results in the formation of Cu(III) complex **32** and TEMPO-H.

Scheme 1-62. A) Copper(II) disproportionation and reaction with TEMPO B) C-H•••Cu^{II} σ interaction



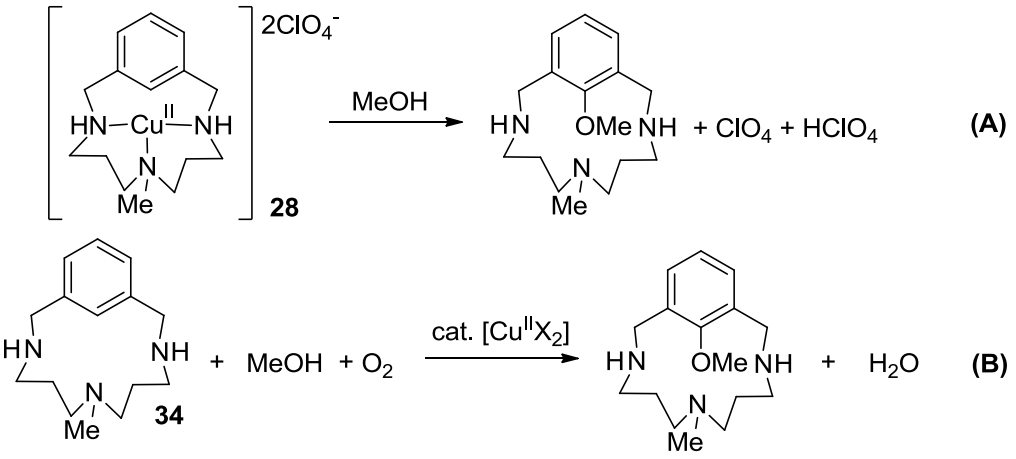
Stahl and Ribas later demonstrated the reaction of aryl-Cu(III) complexes with various nucleophile, thus indicating the role of these complexes as intermediates for copper-catalyzed oxidative functionalization of arene C-H bonds. Mixing complex **28** with phthalimide or pyridone resulted in the formation of C-N coupling products and a Cu^{I} byproduct (Scheme 1-63).[71] Kinetic and electronic effects of the reaction suggested two possible mechanisms for the C-N bond formation step: (a) a three-center C-N reductive elimination from an aryl-Cu(III)(amidate) intermediate, or (b) bimolecular nucleophilic attack of an amidate on the ipso carbon of the aryl ligand.

Scheme 1-63. C-N bond formation involving aryl-copper(III) complexes



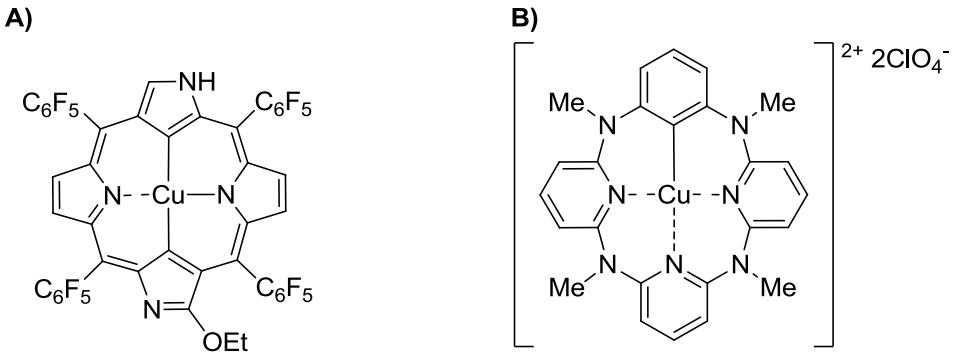
The reaction of aryl-copper(III) complex with oxygen-based nucleophiles was also demonstrated. Lower yield of aryl-copper(III) complex **28** was observed when methanol was used as solvent for the synthesis. Further analysis of the reaction mixture revealed methoxylation of aromatic ring (Scheme 1-64A). The reaction of macrocyclic arene **34** and methanol using $Cu(ClO_4)_2$ or $CuBr_2$ catalysts and O_2 oxidants was studied (Scheme 1-64B).[72] The kinetic studies as well as EPR, UV-Vis spectroscopic analysis suggest that both the Cu(II) and aryl-Cu(III) species are present in the reaction mixture until ful conversion of substrates. These observations suggest that aryl-copper(III) species can be intermediates in copper-catalyzed C-H bond activation/C-O bond formation reaction.

Scheme 1-64. (A) Copper-promoted (B) Copper-catalyzed C-O bond formation



Other amine-containing macrocyles such as *N*-confused porphyrin[73] (Figure 1-1A) and azacalix[1]arene[3]pyridine[74] (Figure 1-2B) also react with Cu(II) to generate aryl-copper(III) species through C-H bond metallation.

Figure 1-2. (A) Cu(III) N-confused porpyrin complex (B) Cu(III) azacalix[1]arene[3]pyridine complex



References

1. Enghag, P. *Encyclopedia of the Elements*; Wiley: Weiheim, **2004.**

2. Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293.

3. (a) Kulkarni, A. A.; Daugulis, O. *Synthesis*, 2009, 24, 4087. (b) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217.

4. Hata, G.; Kondo, H.; Miyake, A. *J. Am. Chem. Soc.* **1968**, *90*, 2278.

5. (a) About-Jaudet, A.; Barton, D. H. R.; Csuhai, E.; Ozbalik, N. *Tetrahedron Lett.* **1990**, *31*, 1657. (b) Barton, D. H. R.; Doller, D. *Acc. Chem. Res.* **1992**, *25*, 504. (c) Barton, D. H. R.; Gastiger, M. J.; Motherwell, W. B. *J. Chem. Soc., Chem. Commun*. **1983**, 41.

6. Rathke, J. W.; Muetterties, E. L. *J. Am. Chem. Soc*. **1975**, *97*, 3272.

7. Baker, M. V.; Field, L. D. *J. Am. Chem. Soc.* **1987**, *109*, 2825.

8. (a) Baker, M. V.; Field, L. D. *J. Am. Chem. Soc.* **1986**, *108*, 7436. (b) Baker, M. V.; Field, L. D. *Organometallic* **1986**, *5*, 821.

9. Ittel, S. D.; Tolman, C. A.; Krusic, P. J.; English, A. D.; Jesson, J. P. *Inorganic Chemistry* **1978**, *17*, 3432.

10. Camadanli, S.; Beck, R.; Florke, U.; Klein, H.-F. *Organometallics* **2009**, *28*, 2300.

11. Jones, W. D.; Foster, G.; Putinas, J. M. *J. Am. Chem. Soc.* **1987**, *109*, 5047.

12. Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 5858.

13. Yoshikai, N.; Matsumoto, A.; Norinder, J.; Nakamura, E. *Angew. Chem. Int. Ed.* **2009**, *48*, 2925.

14. Ilies, L.; Okabe, J.; Yoshikai, N.; Nakamura, E. *Org. Lett.* **2010**, *12*, 2838.

15. Yoshikai, N.; Mieczkowski, A.; Matsumoto, A.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2010**, *132*, 5568.

16. (a) Vallee, F.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 1514. (b) Liu, W.; Cao, H.; Lei. A. *Angew. Chem. Int. Ed.* **2010**, *49*, 2004.

17. (a) Wen, J.; Zhang, J.; Chen, S.; Li, j.; Yu, X.-Q. *Angew. Chem. Int. Ed.* **2008**, *47*, 8897. (b) Wen, J.; Qin, S.; Ma, L.-F.; Dong, L.; Zhang, J.; Liu, S.-S.; Duan, Y.-S.; Chen, S.-Y; Hu, C.-W; Yu, X.-Q. *Org. Lett.* **2010**, *12*, 2694.

18. Egami, H.; Matsumoto, K.; Oguma, T.; Kunisu, T.; Katsuki, T. *J. Am. Chem. Soc.* **2010**, *132*, 13633

19. Zhang, Y.; Li, C.-J. *Eur. J. Org. Chem.* **2007**, 4654.

20. Li, Z.; Cao, L.; Li, C.-J. *Angew. Chem. Int. Ed.* **2007**, *46*, 6505.

21. Li, Z.; Yu, R.; Li, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 7497.

22. Volla, C. M. R.; Vogel, P. *Org. Lett.* **2009**, *11*, 1701.

23. Song, C.-X.; Cai, G.-X.; Farrel, T. R.; Jiang, Z.-P.; Li, H.; Gan, L.-B; Shi. Z.-J. *Chem. Commun.* **2009**, 6002.

24. Zhang, S.–Y.; Tu, Y.-Q.; Fan, C.-A.; Zhang, F.-M.; Shi, L. *Angew. Chem. Int. Ed.* **2009**, *48*, 8761.

25. Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 11062.

26. (a) Noji, M.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1994**, *35*, 7983. (b) Nakajima, M.; Kanayama, K.; Miyoshii, I.; Hashimoto, S. *Tetrahedron Lett.* **1994**, 36, 9519.

27. Li, X.; Yang, J.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 1137.

28. (a) Menini, L.; Gusevskaya, E. V. *Applied Catalysis A: General* **2006**, *309*, 122. (b) Menini, L.; Gusevskaya, E. V. *Chem. Commun.* **2006**, 209.

29. Menini, L.; Parreira, L. A.; Gusevskaya, E. V. *Tetrahedron Lett.* **2007**, *48*, 6401.

30. (a) Yang, L.; Lu, Z.; Stahl, S. S. *Chem Comm* **2009**, 6460. (b) Wang, J.; Wang, W.; Li, J.-H *Green Chem.* **2012**, *12*, 2124.

31. Zhang, S.; Qian, P.; Zhang, M.; Hu, M.; Cheng, J. *J. Org. Chem.* **2010**, *75*, 6732.

32. Ban, I.; Sudo, T.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 3607.

33. (a) Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2008**, *130*, 3208. (b) Murahashi, S.-I.; Komiya, N.; Terai, H.; Nakae, T. *Angew. Chem. Int. Ed.* **2005**, 44, 6931. (c) Murahashi, S.-I.; Naota, T.; Yonemura, K. *J. Am. Chem. Soc.* **1988**, *110*, 8256. (d) Jovel, I.; Prateeptongkum, S.; Jackstell, R.; Vogl, N.; Weckbecker, C.; Beller, M. *Chem. Commun.* **2010**, *46*, 1956. (e) North, M. *Angew. Chem. Int. Ed.* **2004**, 43, 4126.

34. See, for example: Li, H.; He, Z.; Guo, X.; Li, W.; Zhao, X.; Li, Z. *Org. Lett.* **2009**, *11*, 4176.

35. (a) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (b) Li, Z.; Bohle, D. S.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8928.

36. (a) Li, Z.; Li, C-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672; (b) Li, Z.; Li, C.-J. *Eur. J. Org. Chem.* **2005**, 3173.(c) Basle, O.; Li, C.-J. *Green Chem.* **2007**, *9*, 1047.

37. (a) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 6968.(b) Basle, O.; Li, C.-J. *Org. Lett.* **2008**, *10*, 3661.(c) Huang, L.; Niu, T.; Wu, J.; Zhang, Y. *J. Org. Chem.* **2011**, *76*, 1759.

38. Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810.

39. Boess, E.; Sureshkumar, D.; Sud, A.; Wirtz, C.; Fares, C.; Klussmann, M. *J. Am. Chem. Soc.* **2011**, *133*, 8106.

40. Lee, J. M.; Park, E. J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2008**, *130*, 7824.

41. Reinaud, O.; Capdevielle, P.; Maumy, M. *Synthesis* **1990**, 612.

42. (a) Chen, X.; Hao, X.-S.; Goodhue, C.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *126*, 6790. (b) Uemura, T.; Imoto, S.; Chatani, N. *Chem. Lett*. **2006**, *35*, 842.

43. John, A.; Nicholas, K. M. *J. Org. Chem.* **2011**, *76*, 4158.

44. Wang, W.; Luo, F.; Zhang, S.; Cheng, J. *J. Org. Chem.* **2010**, *75*, 2415.

45. Wang, W.; Pan, C.; Cheng, J. *Chem Commun* **2011**, 3978.

46. Mizuhara, T.; Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. *Chem. Commun.* **2009**, 3413.

47. (a) Kitahara, M.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2011**, *133*, 2160. (b) Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Che,. Int. Ed.* **2012**, *51*, 6993.

48. Chu, L.; Yue, X.; Quing, F.-L. *Org. Lett.* **2010**, *12*, 1644.

49. Bernini, R.; Fabrizi, G.; Sferrazza, A.; Cacchi, S. *Angew. Chem. Int. Ed.* **2009**, *48*, 8087.

50. (a) Ueda, S.; Nagasawa, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 6411. (b) Ueada, S.; Nagasawa, H. *J. Org. Chem.* **2009**, *74*, 4272.

51. Brasche, G.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1932.

52. Zhang, L.; Ang, G. Y.; Chiba, S. *Org. Lett.* **2010**, *12*, 3682.

53. Guru, M. M.; Ali, M. A.; Punniyamurthy, T. *Org. Lett.* **2011**, *13*, 1194.

54. Do, H. Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404.

55. Do, H. Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128.

56. Do, H. Q.; Khan, R. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185.

57. Do, H. Q.; Daugulis, O. *J. Am. Chem. Soc.* **2011**, *133*, 13577.

58. Do, H. Q.; Daugulis, O. J. Am. Chem. Soc. **2009**, *131*, 17052.

59. (a) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 2958. (b) Wunderlich, S. H.; Knochel, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 7685.

60. Chu, L.; Quing, F.-L. *J. Am. Chem. Soc.* **2012**, *132*, 1298.

61. Popov, I.; Lindeman, S.; Daugulis, O. *J. Am. Chem. Soc.* **2011**, *133*, 9286.

62. (a) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. *Org. Lett.* **2009**, *11*, 1607. (b) Guo, S.; Qian, B.; Xie, Y.; Xia, C.; Huang, H. *Org. Lett.* **2011**, *13*, 522.

63. (a) Wang, Q.; Schreiber, S. L. Org. Lett. 2009, 11, 5178. (b) Li. Y.; Xie, Y.; Zhang, R.; Jin, K.; Duan, C. *J. Org. Chem.* **2011**, *76*, 5444.

64. Miyasaka, M.; Hirano, K.; Satoh, T.; Kowalczyk, R.; Bolm, C.; Miura, M. *Org. Lett.* **2011**, *13*, 359.

65. Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2011**, *13*, 2860.

66. Zhao, H.; Wang, M.; Su, W.; Hong, M. *Adv. Synth. Cata.* **2010**, *352*, 1301.

67. Ranjit, S.; Lee, R.; Heryasi, D.; Shen, C.; Wu, J.; Zhang, P; Huang, K.-W, Liu, X. *J. Org. Chem.* **2011**, *76*, 8999.

68. (a) Dai, C.; Xu, Z.; Huang, F.; Yu, Z.; Gao, Y.-F. *J. Org. Chem.* **2012**, *77*, 4414. (b) Fukuzawa, S.-I.; Shimizu, E.; Atsuumi, Y.; Haga, M.; Ogata, K. *Tetrahedron Lett.* **2009**, *50*, 2374.

69. Ribas, X.; Jackson, D. A.; Donnadieu, J. M.; Parella, T.; Xifra, R.; Hedman, B.; Hodgson, K. O.; Llobet, A.; Stack, T. D. P. *Angew. Chem. Int. Ed.* **2002**, *41*, 2991.

70. Ribas, X.; Calle, C.; Poater, A.; Casitas, A.; Gomez, L.; Xifra, R.; Parella, T.; Benet-Buchholz, J.; Schweiger, A.; Mitrikas, G.; Sola, M.; Llobet, A.; Stack, T. D. P. *J. Am. Chem. Soc.* **2010**, *132*, 12299.

71. Huffman, L. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 9196.

72. King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 12068.

73. Maeda, H.; Osuka, A.; Furuta, H. *J. Am. Chem. Soc.* **2003**, *125*, 15690.

74. Yao, B.; Wang, D.-X.; Huang, Z.-T.; Wang, M.-X. *Chem. commun.* **2009**, 2899.

Chapter 2 Iron-catalyzed carbon-carbon bond formation through sp^2 carbon-hydrogen bond functionalization

I. Introduction

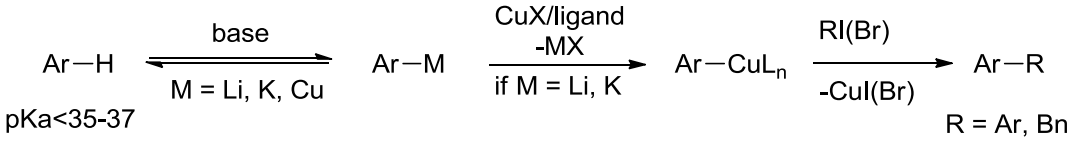
Heterocyles are core structures widely found in bio-active molecules, pharmaceuticals, and organic materials.[1] The functionalization of sp^2 C-H bonds in heterocyles is highly desirable as it provides the most efficient way for the synthesis of their derivatives. Significant achievements have been obtained for direct arylation of heterocyles and directing-group containing arenes.[2] However, transition metal-catalyzed direct alkylation of heterocycles and arenes is still under development.

The most well-known method for direct alkylation of sp^2 C-H bonds is an industrially important Friedel-Crafts alkylation. Nonetheless, this method requires harsh conditions such as strong acid and suffers from side reactions such as carbocation isomerization, polyalkylation, and regioisomer formation that may limit its synthetic applicability.[3] More recently, direct alkylation of directing-group containing arenes and heterocyles by alkenes using ruthernium, rhodium, or cobalt catalysis have been developed.[4] However, the scope of substrates with respect to olefin coupling partner is very limited. Palladium-mediated alkylation of directing-group containing benzenes with alkyl halides was first reported by Tremont and Liebeskind.[5] Since then, palladium-catalyzed alkylation of benzoic acids and heterocyles have been reported in several number of publications.[6] Recently, scientists have paid significant attention towards employing inexpensive, first-row transition metals in C-H bond functionalization. Knochel and coworkers developed a method for the alkylation of arenes by deprotonation with iron amide base followed by cross-coupling

reaction under nickel catalysis.[7] Nickel/copper catalyst system is also demonstrated to effect alkylation of heterocycles.[8] Nonetheless, an example for iron-catalyzed deprotonative alkylation of arenes and heterocycles has not been reported yet.

Deprotonative coupling reactions are commonly used for functionalization of activated C-H bonds. Our group has developed methods for deprotonative arylation of heterocycles and arenes using copper catalysis (Scheme 2-1).[9] An in situ deprotonation/transmetallation step is followed by a cross-coupling with aryl halide to generate a biaryl. Unfortunately, attempts to perform alkylations were unsuccessful. On the other hand, iron-catalyzed alkylation of Grignard reagents or organozinc reagents have been reported by Furstner and Nakamura.[10] We hypothesized that organometal intermediate, particularly organo zinc or magnesium, can be generated in situ by treating the arenes and heterocycles containing acidic C-H bond with a base. Under iron catalysis, this intermediate will undergo cross-coupling reaction with alkyl halides to afford desired products. Thus, a combination of deprotonation and iron-catalyzed alkylation would afford a new method for direct alkylation of arenes and heterocycles.

Scheme 2-1. Arene deprotonative functionalization under copper catalysis



It is known that iron can catalyze or promote dimerization of organometallic species.[11] Cahiez reported dimerization of Grignard reagents in the presence of 5% $FeCl_3$ by employing dry air as an oxidant.[12] On the other hand, copper-catalyzed deprotonative

arene dimerization was recently reported by our group.[13] Since iron is a cheap and nontoxic, iron-catalyzed deprotonative dimerization of arenes could be an improvement over existing methods.

II. Results and discussion

2.1 Deprotonative alkylation of arenes and heterocycles

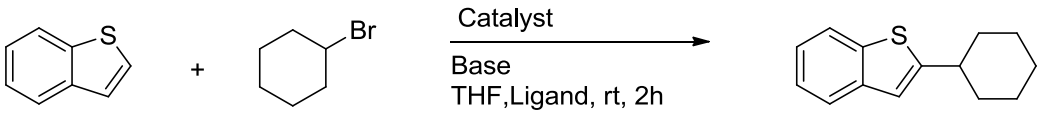
Transition metal-catalyzed C-H bond functionalization has been extensively developed. However, most of the developed methods focused on arylation reactions. Thus, less success has been achieved in alkylation reactions. Our strategy was aimed to develop method that allows the alkylation of sp^2 C-H bonds using an iron catalyst.

2.2.1 Optimization of deprotonative alkylation of benzothiophene

Optimization was performed on the reaction of benzothiophene and cyclohexyl bromide (Table 2-1). The results suggested that base played an important role in the reaction since commercially available bases such as Li*O*t*Bu and K*O*t*Bu did not provide substantial amounts of alkylated product. As suggested in literature, iron-catalyzed alkylation of Grignard reagents and organozinc reagents gave higher yield of the products than the reaction with organolithium reagents.[14] We proposed that a magnesium amide base developed by Knochel[15] will be suitable for the reaction. Indeed, by using TMPMgCl•LiCl, 2-cyclohexyl benzothiophene was obtained in 77% conversion (entry 4). Various iron salts were screened for catalytic activity. It was found that $FeCl_3$ is slightly more efficient than $Fe(acac)_3$ (entry 6). TMEDA or a mixture of TMEDA/HMTA ligands afforded relatively good conversion (entry 9). The best result was obtained by employing *trans-N,N'*-dimethylcyclohexane-1,2-diamine (entry 8). The optimized conditions include

10% mol $FeCl_3$ catalyst, 25 mol % of *trans-N,N'*-dimethylcyclohexane-1,2-diamine ligand, TMPMgCl•LiCl base, and THF solvent at room temperature.

Table 2-1. Optimization for iron-catalyzed deprotonative alkylation



Entry	Base	Catalyst	Ligand	% GC Conversion
1	tBuOLi	$FeCl_3$	*trans-N,N'*-dimethylcyclohexane-1,2-diamine	<2%*
2	tBuOK	$FeCl_3$	*trans-N,N'*-dimethylcyclohexane-1,2-diamine	<2%*
3	Cy_2NLi	$FeCl_3$	*trans-N,N'*-dimethylcyclohexane-1,2-diamine	5%*
4	TMPMgCl•LiCl	$FeCl_3$	*trans-N,N'*-dimethylcyclohexane-1,2-diamine	77%*
5	TMPMgCl•LiCl	$Fe(acac)_3$	*trans-N,N'*-dimethylcyclohexane-1,2-diamine	67%*
6	TMPMgCl•LiCl	$FeCl_3$	*trans-N,N'*-dimethylcyclohexane-1,2-diamine	77%*
7	TMPMgCl•LiCl	$FeCl_3$	*trans-N,N,N',N'*-tetramethylcyclohexane-1,2-diamine	44%
8	TMPMgCl•LiCl	$FeCl_3$	*trans-N,N'*-dimethylcyclohexane-1,2-diamine	99%
9	TMPMgCl•LiCl	$FeCl_3$	TMEDA (20%) HMTA (10%)	74%

(*) % GC conversion using hexadecane as an internal standard

2.2.2 Deprotonative alkylation of arenes and heterocycles

The scope of reaction with respect to the arene coupling partner is shown in Table 2-2. Five-membered-ring heterocycles such as benzofuran (entry 1), 2-methylthiophene (entry

2), and benzothiophene (entry 3) are alkylated in moderate to good yields. Pyridine (entry 4) and its derivatives are functionalized in reasonable yields. Employing 3-methoxypyridine (entry 5) as a substrate, product was obtained in good yield. Pyridines were cyclohexylated at ortho position, in contrast to previous copper-catalyzed arylation methodology where arylation at para-position was observed. Interestingly, 4-methylquinoline (entry 10) was alkylated at the benzylic position, presumably due to the high acidity of benzylic proton. Electron-deficient arenes such as 1-cyano-3-methoxybenzene or ethyl 4-fluorobenzoate are also reactive (entries 8 and 9). In some cases, cheaper $Cy_2NMgCl{\bullet}LiCl$ base can be used (entries 3 and 10). For some substrates, addition of $TMP_2Zn{\bullet}2MgCl_2{\bullet}2LiCl$ helps to increase the yield (entries 4 and 9). Moreover, alkylation cannot proceed for too acidic substrates such as tetrafluoroanisole, 3,5-dichloropyridine, and *N*-butyl-1,2,4-triazole. Consequently, there are both lower and upper limits for acidity that are acceptable for the alkylation.[16]

Table 2-2. Alkylation scope with respect to arene

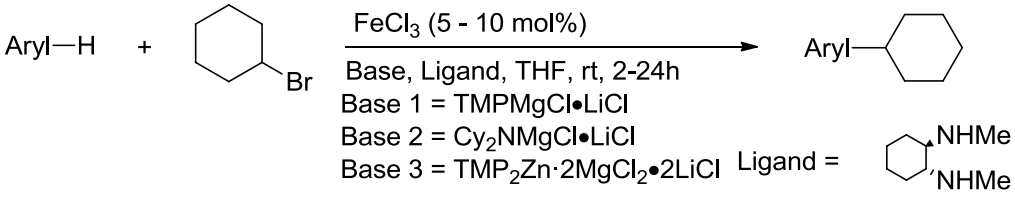
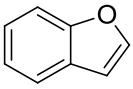
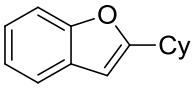
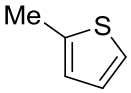
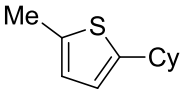
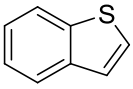
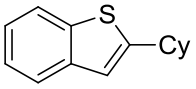
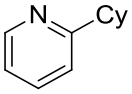
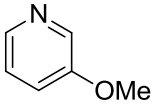
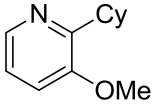
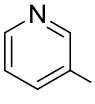
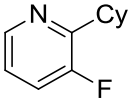
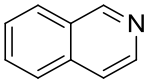
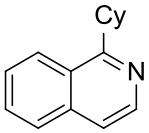
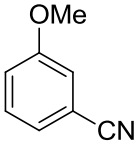
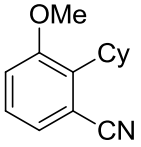
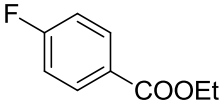
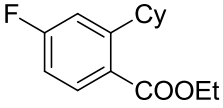
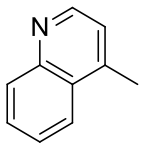
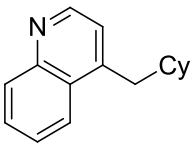


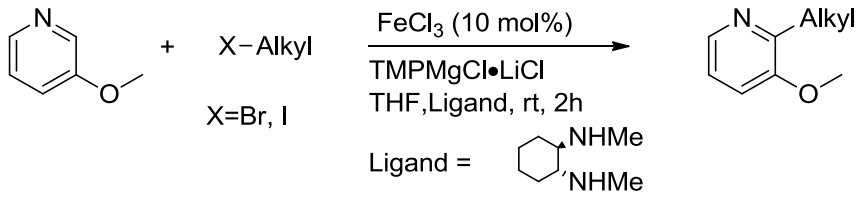
Table 2-2. (*Continued*)

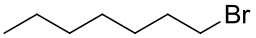
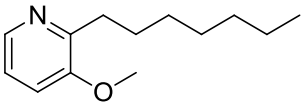
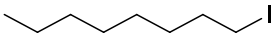
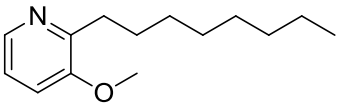
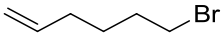
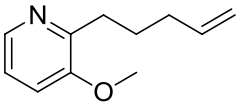
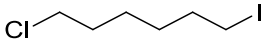
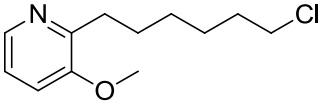
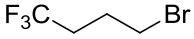
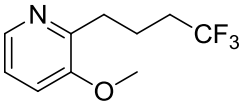
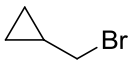
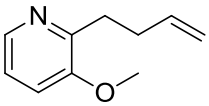
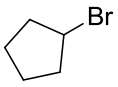
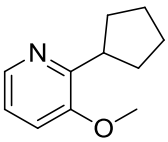
Entry	Aryl-H	Base	Product	Yield
1		Base 1		59%
2		Base 1		44%
3		Base 2		70%
4		Base 1 + 3		51%
5		Base 1		83%
6		Base 1		49%
7		Base 1		45%
8		Base 1		69%
9		Base 1 + 3		78%
10		Base 2		92%

2.2.3 Deprotonative alkylation of 3-methoxy pyridine

The scope of reaction with respect to alkyl halide is presented in Table 2-3.

Table 2-3. Alkylation scope with respect to alkyl halide

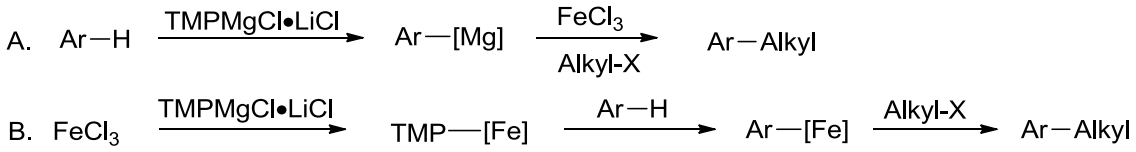


Entry	Alkyl halide	Product	Yield %
1			82
2			78
3			85
4			57
5			68
6			62
7			81

Both alkyl bromides and iodides are reactive. Alkylation can be performed with primary as well as secondary alkyl halides. Some functional groups such as alkene (entry 3), ω-chloride (entry 4), and trifluoromethyl (entry 5) are tolerated. Electron-withdrawing groups on the alkyl chain disfavor the reaction. Interestingly, if cyclopropylmethyl bromide was employed, ring-opening product was obtained, suggesting that the reaction may proceed via radical intermediates.

2.2.4 Mechanistic study for deprotonation step

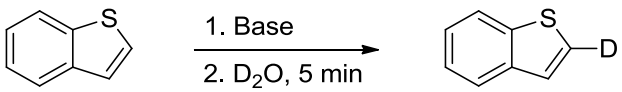
Scheme 2-2. Two possible pathways for iron-catalyzed deprotonative alkylation



Recently, Knochel reported the alkylation of ester and-/or-fluorine-containing arenes by using an iron amide base.[7] Trace of nickel present in the base was the actual catalyst. Taking this into consideration, two reaction pathways can be proposed (Scheme 2-2). The first one is that arenes are deprotonated by TMPMgCl•LiCl to form organomagnesium species followed by iron-catalyzed coupling reaction with alkyl halide. The second possible pathway could be the formation of an iron amide base, followed by arene deprotonation affording an aryliron species. Reaction with alkyl halide would form the product. In order to determine the metalating agent, benzothiophene was subjected to deprotonation by TMPMgCl•LiCl or by TMP_2Fe•2MgCl•4LiCl followed by quench with D_2O and results are shown in Table 2-4. The magnesium base is more efficient deprotonating agent, showing that the pathway in Scheme 2-2A is more likely. At longer

reaction time, the system using $TMP_2Fe{\bullet}2MgCl_2{\bullet}4LiCl$ base caused extensive decomposition of benzothiophene. For catalytic coupling procedure, 64% conversion to 2-cyclohexylbenzothiophene was obtained after 10 minutes.

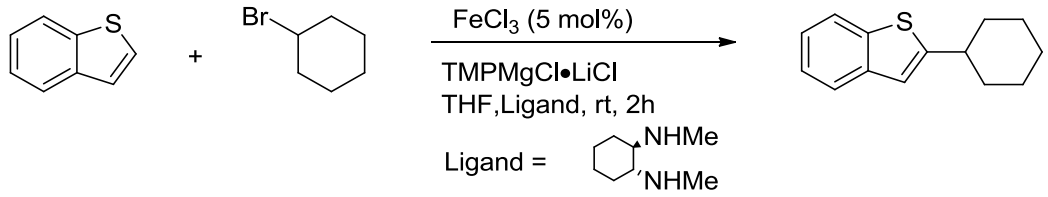
Table 2-4. Experiments to determine metalating agent



Base	% D incorporation
TMPMgCl•LiCl	52%
$TMP_2Fe{\bullet}2MgCl_2{\bullet}4LiCl$	10%

Control experiments were run in order to determine whether a trace of another transition metal catalyzes the reaction (Table 2-5). Identical results were obtained with both reagent-grade and ultra-pure iron catalyst. Without iron catalyst, benzothiophene was not alkylated. These results indicate that catalysis by a contaminant is unlikely.

Table 2-5. Control experiments



Iron Catalyst	%GC Conversion
98% $FeCl_3$	74%
99.99% $FeCl_3$	68%
No $FeCl_3$	<2%

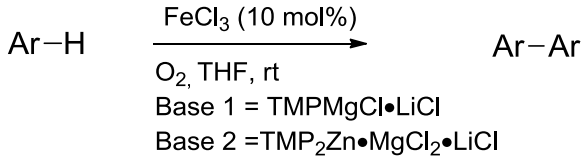
2.4 Deprotonative dimerization of arenes and heterocycles

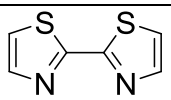
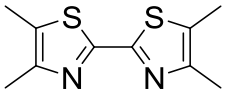
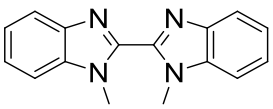
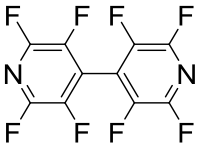
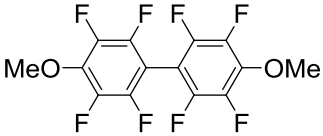
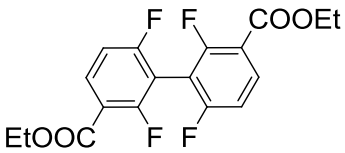
Biaryl linkages are common structures in pharmaceuticals, agrochemicals, and organic materials. Direct cross-coupling or homo-coupling of sp^2 C-H bonds are the most atom-economic ways to synthesize these compounds. Interestingly, large amount of heteroaromatic compounds contain acidic C-H bonds. We hypothesized that this class of compounds can undergo deprotonative dimerization under iron catalysis to generate the homocoupling product, thus providing an alternative method for the preparation of biaryls.

A short optimization was carried out based on the system for copper-catalyzed deprotonative arene dimerization.[13] Magnesium or zinc amide bases were observed to give the best yield. Oxygen was chosen as an oxidant. Iron trichloride is the most efficient iron salt for this reaction. The reaction was run in THF solvent at room temperature. No additional ligand is required for this dimerization.

Variety of heterocycles and arenes were subjected to reaction condition and results are demonstrated in Table 2-6. Five-membered-ring heterocycles such as thiazole (entry 1), 4,5-dimethylthiazole (entry 2), and *N*-methylbenzimidazole (entry 3) are reactive. Tetrafluoropyridine (entry 4), tetrafluoroanisole (entry 5), and ethyl 2,4-difluorobenzoate (entry 6) afford dimerization products in good yield.

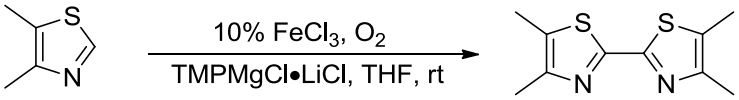
Table 2-6. Iron-catalyzed deprotonative arene dimerization



Entry	Ar-H	Base	Product	Yield %
1	Thiazole	1 + 2		59
2	4,5-Dimethylthiazole	1		68
3	*N*-Methylbenzimidazole	1		77
4	Tetrafluoropyridine	2		54
5	Tetrafluoroanisole	1 + 2		78
6	Ethyl 2,4-difluorobenzoate	1 + 2		70

Since other transition metals such as Ni, Co, Mn, and Cu can also catalyze this reaction,[13,17] control experiments were performed in order to check whether a trace of another metal is a catalyst (Table 2-7). Both reagent-grade iron and ultra-pure iron gave similar results. Omission of iron resulted in no dimerization of 3,4-dimethylthiazole. Thus, catalytic reactivity by another transition metal is unlikely.

Table 2-7. Control experiments



Iron Catalyst	% GC Conversion
98% $FeCl_3$	68%
99.99% $FeCl_3$	70%
No $FeCl_3$	<2%

III. Conclusion

In conclusion, we have developed methods for iron-catalyzed deprotonative alkylation and dimerization of arenes and heterocyles. Various electron-rich heterocyles such as thiophene, furane, imidazole, electron-poor heterocycles such as pyridine and its derivatives, and electron-deficient arenes can be alkylated by primary and secondary alkyl halides. The dimerization conditions allow the homocoupling of various heterocycles and arenes. Reactions can be performed at room temperature, show good functional group tolerance and excellent regioselectivity as only one regioisomer was obtained in all case.

IV. Experimental section

4.1 General consideration

Reactions were performed in 1-dram vials equipped with polypropylene screw caps with a 13 mm hole and white silicone septa with a white Teflon face (SUPELCO). Column chromatography was performed on a 60 Å 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 × 21.4 mm) column. GC-MS analyses were performed on a Shimadzu GCMS-QP5000 chromatograph equipped with a Restek column (Rtx-XLB, 30 m × 0.25 mm I.D.). GC analyses were performed on a Shimadzu GC-2010 chromatograph equipped with a Restek column (Rtx®-5, 15m, 0.25 mm I.D.). 1H, 13C and 19F NMR spectra were recorded on JEOL ECX-400 and JEOL ECX-500 spectrometers using TMS or solvent peak as a standard. Elemental analyses were performed by Atlantic Microlab Inc. of Norcross, GA. IR-spectra were obtained using a ThermoNicolet Avatar 370 FT-IR instrument. Preparative thin layer chromatography was performed on Analtech TLC plates (20 cm × 20 cm, 20 microns).

4.2 Materials

The following starting materials were obtained from commercial sources and were used without further purification: iron(III) chloride (99.99%), magnesium chloride, lithium dicyclohexylamide, trans-N,N'-dimethylcyclohexane-1,2-diamine, 3-methoxy-pyridine, isoquinoline, bromocyclohexane, 1-bromoheptane, 5-bromo-1-pentene, 1-chloro-6-iodohexane, isopropylmagnesium chloride-lithium chloride complex solution (1.3 M in THF), benzofuran, iodocyclohexane, 1-iodooctane, 3-methoxybenzonitrile, 2-

methylthiophene, 1,3-difluorobenzene, 1-bromo-4,4,4-trifluorobutane, iron(III) chloride, zinc(II) chloride, benzothiophene, bromocyclopentane, ethyl 4-fluorobenzoate, 3-fluoropyridine cyclopropylmethyl bromide, lepidine, pyridine, benzyl bromide, thiazole, 4,5-dimethylthiazole, 2,3,5,6-tetrafluoropyridine, 2,3,5,6-tetrafluoroanisole, *N*-methylbenzimidazole, ethyl 2,4-difluorobenzoate. Iron(III) chloride was purchased from Alfa Aesar and was used to prepare a 0.1 M solution in THF. The solution was kept inside the glovebox and used within 1 day. 2,2,6,6-Tetramethylpiperidine was obtained from Matrix Scientific and was distilled before use.

4.3 Deprotonative alkylation of arenes and heterocycles

Base synthesis:

TMPMgCl•LiCl:[15] Inside the glovebox, a dry and argon flushed 50 mL Schlenk flask equipped with a magnetic stir bar and a septum was charged with iPrMgCl•LiCl in THF (20 mL of a 1.3 M solution in THF, 26 mmol). TMPH (tetramethypiperidine) (4.38 g, 31.2 mmol) was added dropwise at room temperature. The capped Schlenk flask was taken out of the glovebox and the mixture was stirred for 36 hours at RT. The resulting solution was evaporated under vacuum to remove the residual propane (total volume loss 2-3 mL). The base was titrated before use at 0 ^{o}C with a solution of benzoic acid in THF (0.2 M) and (phenyl)[4-(phenylazo)-phenyl]amine was employed as an indicator.[18]

Cy_2NMgCl•LiCl: Inside the glove box, a dry and argon flushed 50 ml Schlenk flask equipped with a magnetic stir bar and septum was charged with anhydrous magnesium chloride (2.38 g, 25 mmol) and lithium dicyclohexylamide (4.68 g, 25 mmol). THF (20 mL) was added to the mixture via syringe outside the glove box and the resulting solution

was stirred at room temperature for 24 hours. The base was titrated before use at 0 ^{o}C with solution of benzoic acid in THF (0.2 M) and (phenyl)[4-(phenylazo)-phenyl]amine was employed as an indicator.[18]

$TMP_2Zn•2MgCl_2•2LiCl$:[19] Inside the glovebox, a dry 25 mL Schlenk flask equipped with a magnetic stir bar was charged with anhydrous $ZnCl_2$ (669 mg, 4.92 mmol). The flask was capped with a septum and removed from the glovebox. TMPMgCl•LiCl solution (1.23 M, 8 mL, 9.84 mmol; prepared as described above) was added dropwise at room temperature and the resulting mixture was stirred for 15 hours. The fresh base was titrated before use at 0 ^{o}C with a solution of benzoic acid in THF (0.2 M) and (phenyl)[4-(phenylazo)-phenyl]amine was employed as indicator.[18]

$TMP_2Fe•2MgCl_2•4LiCl$.[7] To 25 mL dry-flame Schlenk flask equipped with a magnetic stir bar was charged with 10 mL TMPMgCl•LiCl solution (1.08 M, 9.26 mL, 10 mmol) and cooled to 0^{o}C. Then, a solution of FeCl•2LiCl (1M in THF, 5 mL, 5 mmol) was added in 2 min. The reaction mixture was stirred at 0^{o}C for 30 min, warmed up to room temperature and continued stirring for 3 hours. The resulting solution was evaporate under vacuum to remove 5 mL of THF and titrated before use at 0 ^{o}C with solution of benzoic acid in THF (0.2 M) and (phenyl)[4-(phenylazo)-phenyl]amine was employed as an indicator.[18]

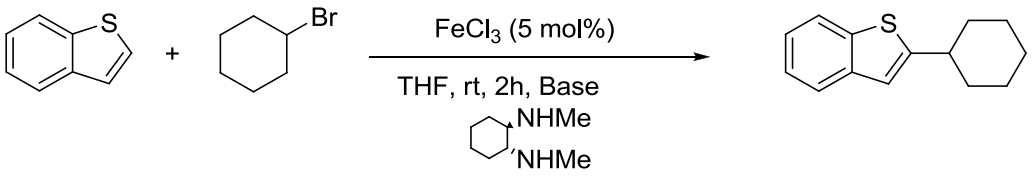
$FeCl_2•2LiCl$.[7] Inside glove box, a 25 mL dry-flame round bottom flask equipped with a magnetic stir bar was charged with anhydrous $FeCl_2$ (1267 mg, 10 mmol) anhydrous LiCl (847.8 mg, 20 mmol). The flask was capped with septum, removed from the glove box

and wrapped with aluminum foil. Then, anhydrous THF (10 mL) was added and the resulting solution was stirred until all the solid dissolved (1 h).

4.3.1 Optimization of deprotonative alkylation of benzothiophene

Base optimization

Table 2-1A. Base optimization



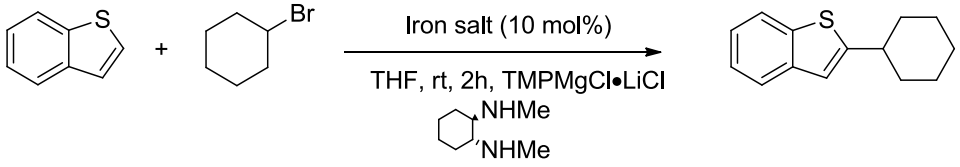
Base	% GC conversion
TMPMgCl•LiCl	77
tBuOLi	< 2
tBuOK	< 2
Cy_2NLi	5

The vial was charged with benzothiophene (1 mmol) and bromocyclohexane (2 mmol). Inside the glove box, a solution of $FeCl_3$ in THF (0.05 mmol), *trans-N,N'*-dimethylcyclohexane-1,2-diamine (0.13 mmol), and THF were added to the vial. Next, base (1.3 mmol) was added to the resulting mixture. In the experiment using TMPMgCl•LiCl as base, TMPMgCl•LiCl (1.37 mL, 0.96M, 1.32 mmol) solution was added dropwise via syringe to the reaction mixture outside the glove box. The reaction mixture was stirred for 2 hours at room temperature. GC conversions based on alkylation product formation were determined by employing hexadecane as an internal standard and are presented in Table 2-1A.

Iron salt optimization

The vial was charged with benzothiophene (0.75 mmol) and bromocyclohexane (0.55 mmol). Inside the glove box, a solution of iron salt in THF (0.1 M, 0.55 mL, 0.055 mmol) and *trans-N,N'*-dimethylcyclohexane-1,2-diamine (0.13 mmol) were added to the vial. Then, outside the glove box, TMPMgCl•LiCl solution (0.82 mmol) was added dropwise via syringe to the resulting solution. The reaction mixture was stirred for 2 hours at room temperature. GC conversions based on alkylation product formation were determined by employing hexadecane as an internal standard and are presented in Table 2-1B.

Table 2-1B. Iron salt optimization studies with benzothiophene



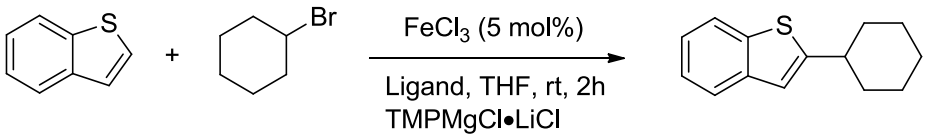
Iron salt	% GC conversion
$Fe(acac)_3$	67
$FeCl_3$	82

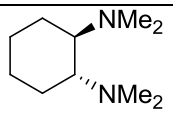
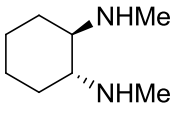
Ligand optimization

General procedure: The vial was charged with benzothiophene (0.65 mmol) and bromocyclohexane (0.5 mmol). Inside the glove box, a solution of $FeCl_3$ in THF (0.25 mL of a 0.1 M solution, 0.025 mmol) was added. Subsequently, THF (0.25 mL) and ligand were added to the vial. Then, outside the glove box, TMPMgCl•LiCl solution was added dropwise via syringe to the reaction mixture followed by stirring for 2 hours at room

temperature. After completion, the reaction mixture was analyzed by GC. GC conversions are presented in Table 2-1C and show the amount of bromocyclohexane consumed (e.g. 98% conversion means that 2% of bromocyclohexane remains and 98% is converted to a product).

Table 2-1C. Ligand optimization



Ligand (% mol)	Base ratio[a] (mol equiv.)	% GC Conversion
 (10%)	1.42	44%
 (13%)	1.69	>99%
TMEDA (10%) HMTA (5%)	1.69	79%

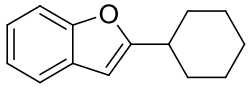
[a] base/bromocyclohexane molar ratio

4.3.2 Deprotonative alkylation of arenes and heterocycles

General procedure. A 1-dram screw-cap vial equipped with a magnetic stir bar was charged with substrates and flushed with argon. The vial was put inside the glovebox and $FeCl_3$ (5–10 mol%) was added as 0.1 M solution in THF, followed by *trans-N,N'*-dimethylcyclohexane-1,2-diamine (13–25 mol%). The vial was removed from glovebox and the base (1.5–3 equiv) was added dropwise via syringe. The resulting solution was

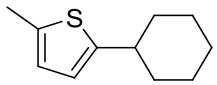
stirred at room temperature for 2-18 hours. The conversion was monitored by GC. After completion, the reaction mixture was quenched with brine (10 mL) and extracted five times with dichloromethane or ethyl acetate (50 ml first extraction followed by 4x20 ml). For reactions that employed $Cy_2MgCl\bullet LiCl$ base, water (20 mL) was added to the aqueous layer after the first extraction. The combined organic layers were dried over Mg_2SO_4 or Na_2SO_4, solvent was evaporated under reduced pressure and the residue was purified by flash chromatography, preparative TLC, and/or HPLC.

2-Cyclohexylbenzofuran (Table 2-2, entry 1)



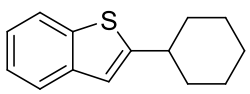
The vial was charged with benzofuran (189 mg, 1.6 mmol) and bromocyclohexane (162 mg, 0.99 mmol). Vial was capped and placed in the glove box. Inside the glove box, a solution of $FeCl_3$ in THF (1.0 mL, 0.1 M, 0.1 mmol) and *trans-N,N'*-dimethylcyclohexane-1,2-diamine (0.04 mL, 0.25 mmol) were added to the vial. Then, outside the glove box, $TMPMgCl\bullet LiCl$ solution (1.07 M, 1.79 mL, 1.92 mmol) was added dropwise via syringe to the resulting solution. The reaction mixture was stirred for 3 hours at room temperature. After completion, the reaction was worked up as described in general procedure. The organic layer was dried over Na_2SO_4. Purification by preparative TLC (hexanes) gave 117 mg (59%) of a yellow liquid. This compound is known.[20] R_f = 0.63 (SiO_2, ethyl acetate/ hexanes 1/5). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.48 (*d*, *J* = 6.6 Hz, 1H) 7.41 (*d*, *J* = 8.0 Hz, 1H) 7.23-7.13 (*m*, 2H) 6.34 (*s*, 1H) 2.79-2.71 (*m*, 1H) 2.15-2.08 (*m*, 2H) 1.88-1.79 (*m*, 2H) 1.78-1.70 (*m*, 1H) 1.52-1.22 (*m*, 5H).

4-Cyclohexyl-2-methylthiophene (Table 2-2, entry 2)



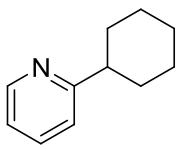
The vial was charged with 2-methylthiophene (167 mg, 1.7 mmol) and bromocyclohexane (163 mg, 1.0 mmol). Vial was capped and placed in the glove box. Inside the glove box, a solution of $FeCl_3$ in THF (0.50 mL of a 0.10 M solution, 0.05 mmol) and *trans-N,N'*-dimethylcyclohexane-1,2-diamine (0.02 mL, 0.13 mmol) were added to the vial. Then, outside the glove box, TMPMgCl•LiCl solution (1.02 M, 1.83 mL, 1.87 mmol) was added dropwise via syringe to the resulting solution. The reaction mixture was stirred for 2 hours at room temperature. After completion, the reaction was worked up as described in general procedure. Organic layer was dried over $MgSO_4$. Purification by flash chromatography in hexanes following by preparative TLC in hexanes gave 79 mg (44%) of a yellow liquid. R_f = 0.73 (SiO_2, 1/5 ethyl acetate/ hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 6.57-6.54 (*m*, 2H) 2.75-2.68 (*m*, 1H) 2.43 (*s*, 3H) 2.06-1.96 (*m*, 2H) 1.86-1.77 (*m*, 2H) 1.74-1.67 (*m*, 1H) 1.45-1.31 (*m*, 4H) 1.28-1.18 (*m*, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 150.2, 136.4, 124.3, 121.3, 39.5, 35.4, 26.5, 26.0, 15.3. FT-IR (neat, cm^{-1}) ν 2924, 2852, 1448. Anal calcd for $C_{11}H_{16}S$ (180.31 g/mol) C: 73.27; H: 8.94; Found C: 73.04; H: 9.09.

2-Cyclohexylbenzothiophene (Table 2-2, entry 3)



The vial was charged with benzothiophene (137 mg, 1.02 mmol) and bromocyclohexane (334 mg, 2.04 mmol). Vial was capped and placed in the glove box. Inside the glove box, a solution of $FeCl_3$ in THF (0.50 mL, 0.10 M, 0.05 mmol) and *trans-N,N'*-dimethyl-cyclohexane-1,2-diamine (0.02 mL, 0.13 mmol) were added to the vial. Then, outside the glove box, $Cy_2NMgCl{\bullet}LiCl$ solution (0.93 M, 1.76 mL, 1.64 mmol) was added dropwise via syringe to the resulting solution. The reaction mixture was stirred for 2 hours at room temperature. After completion, the reaction mixture was quenched by brine and extracted with ethyl acetate as described in general procedure. Water (20 mL) was added to the aqueous layer after the first extraction. The combined organic layer was dried over $MgSO_4$ and concentrated by rotary evaporator for 2 hours to remove solvent and excess bromocyclohexane. Excess bromocyclohexane is difficult to separate from the product by chromatography. Purification by preparative TLC in hexanes/ethyl acetate (10/1) gave 154 mg (70%) of a tan solid. This compound is known.[21] R_f = 0.6 (SiO_2, ethyl acetate/ hexanes 1/5). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.77 (*d*, *J* = 8.0 Hz, 1H) 7.66 (*d*, *J* = 7.8 Hz, 1H) 7.32-7.21 (*m*, 2H) 7.00 (s, 1H) 2.92-2.83 (*m*, 1H) 2.15-2.07 (*m*, 2H) 1.89-1.81 (*m*, 2H) 1.79-1.71 (*m*, 1H) 1.58-1.35 (*m*, 4H) 1.33-1.21 (*m*, 1H).

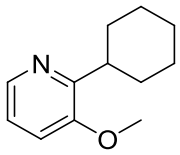
2-Cyclohexylpyridine (Table 2-2, entry 4)



The vial was charged with pyridine (354 mg, 4.5 mmol) and bromocyclohexane (243 mg, 1.49 mmol). Vial was capped and placed in the glove box. Inside the glove box, a solution

of $FeCl_3$ in THF (0.750 mL, 0.100 M, 0.075 mmol) and *trans-N,N'*-dimethylcyclohexane-1,2-diamine (0.03 mL, 0.19 mmol) were added to the vial. Then, outside the glove box, $TMP_2Zn{\bullet}2MgCl_2{\bullet}2LiCl$ solution (0.48 M, 1.53 mL, 0.73 mmol) immediately followed by TMPMgCl•LiCl solution (1.12 M, 3.06 mL, 3.43 mmol) were added dropwise via syringe to the resulting solution. The reaction mixture was stirred for 4 hours at room temperature. After completion, the reaction mixture was quenched with brine (20 mL) followed by extraction with dichloromethane (5 times, 50 ml for the first time and 4x 20 ml). After the first extraction, water (10 mL) was added to the aqueous layer. The combined organic layer was dried over Na_2SO_4. Purification by flash chromatography (hexanes/ethyl acetate 5/1 to 2/1) gave 122 mg (51%) of a yellow liquid. This compound is known.[22] R_f = 0.40 (SiO_2, ethyl acetate/ hexanes 1/5). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.54-8.51 (*m*, 1H) 7.62-7.57 (*m*, 1H) 7.16-7.13 (*m*, 1H) 7.10-7.07 (*m*, 1H) 2.73-2.66 (*m*, 1H) 1.98-1.92 (*m*, 2H) 1.89-1.82 (*m*, 2H) 1.78-1.72 (*m*, 1H) 1.57-1.23 (*m*, 5H).

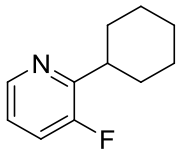
2-Cyclohexyl-3-methoxypyridine (Table 2-2, entry 5)



The vial was charged with 3-methoxypyridine (185 mg, 1.7 mmol) and bromocyclohexane (163 mg, 1.0 mmol). Vial was capped and placed in the glove box. Inside the glove box, a solution of $FeCl_3$ in THF (0.1 M, 1.0 mL, 0.1 mmol) and *trans-N,N'*-dimethylcyclohexane-1,2-diamine (0.04 mL, 0.25 mmol) were added to the vial. Then, outside the glove box, TMPMgCl•LiCl solution (1.09 M, 1.87 mL, 2.03 mmol) was added

dropwise via syringe to the resulting solution. The reaction mixture was stirred for 2 hours at room temperature. After completion, the reaction was worked up as described in the general procedure. The organic layer was dried over Na_2SO_4. Purification by flash chromatography (hexanes/ethyl acetate 1/0 to 5/1) gave 159 mg (83%) of a light yellow liquid. R_f = 0.27 (SiO_2, ethyl acetate/ hexanes 1/5). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.15-8.13 (*m*, 1H) 7.10-7.05 (*m*, 2H) 3.82 (*s*, 3H) 3.13 (*tt*, *J* = 3.5 Hz, *J* = 12.0 Hz, 1H) 1.88-1.77 (*m*, 4H) 1.77-1.70 (*m*, 1H) 1.67-1.57 (*m*, 2H) 1.47-1.25 (*m*, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 156.1, 152.8, 140.5, 121.2, 116.6, 55.2, 38.9, 31.3, 26.8, 26.2. FT–IR (neat, cm^{-1}) ν 2928, 2852, 1585, 1570, 1450, 1431, 1275, 1211, 1099, 1023, 1003. Anal calcd for $C_{12}H_{17}NO$ (191.27 g/mol) C: 75.35; H: 8.96; N: 7.32 Found C: 75.05; H: 9.22; N: 7.06.

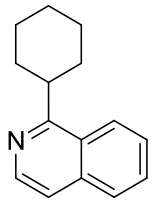
2-Cyclohexyl-3-fluoropyridine (Table 2-2, entry 6)



The vial was charged with 3-fluoropyridine (155 mg, 1.60 mmol) and bromocyclohexane (163 mg, 1.0 mmol). Vial was capped and placed in the glove box. Inside the glove box, a solution of $FeCl_3$ in THF (0.1 M, 1.0 mL, 0.1 mmol) and *trans-N,N'*-dimethylcyclo-hexane-1,2-diamine (0.04 mL, 0.25 mmol) were added to the vial. Then, outside the glove box, TMPMgCl•LiCl solution (1.14 M, 1.53 mL, 1.74 mmol) was added dropwise via syringe to the resulting solution. The reaction mixture was stirred for 2 hours at room temperature. After completion, the reaction was worked up as described in the general

procedure. The organic layer was dried over Na_2SO_4. Purification by flash chromatography (CH_2Cl_2) and preparative TLC (CH_2Cl_2/diethyl ether 3/1) gave 88 mg (49%) of a light yellow liquid. R_f = 0.37 (SiO_2, hexanes/ethyl acetate 5/1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.36-8.33 (*m*, 1H) 7.32-7.27 (*m*, 1H) 7.13-7.08 (*m*, 1H) 3.08-3.00 (*m*, H) 1.89-1.79 (*m*, 4H) 1.77-1.72 (*m*, 1H) 1.71-1.61 (*m*, 2H) 1.47-1.36 (*m*, 2H) 1.35-1.24 (*m*, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 157.3 (*d*, J_{C-F} = 256 Hz) 154.6 (*d*, J_{C-F} = 14.6 Hz) 145 (*d*, J_{C-F} = 5Hz) 122.6 (*d*, J_{C-F} = 19.6 Hz) 122.2 (*d*, J_{C-F} = 3.9 Hz) 39.5, 31.5, 26.7, 26.2. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -126.5 - -126.6 (*m*). FT-IR (neat, cm^{-1}) ν 2930, 2854, 1600, 1449, 1244, 1214, 1161, 1028. Anal calcd for $C_9H_{14}FN$ (179.23 g/mol) C: 73.71; H: 7.87; N: 7.81. Found C: 73.51 ; H: 7.93 ; N: 7.76.

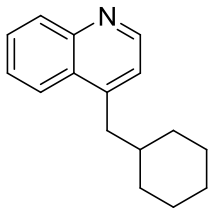
1-Cyclohexylisoquinoline (Table 2-2, entry 7)



The vial was charged with isoquinoline (181 mg, 1.4 mmol) and bromocyclohexane (163 mg, 1.0 mmol). Vial was capped and placed in the glove box. Inside the glove box, a solution of $FeCl_3$ in THF (0.1 M, 1 mL, 0.1 mmol) and *trans-N,N'*-dimethylcyclohexane-1,2-diamine (0.04 mL, 0.25 mmol) were added to the vial. Then, outside the glove box, TMPMgCl•LiCl solution (1.09 M, 1.54 mL, 1.64 mmol) was added dropwise via syringe to the resulting solution. The reaction mixture was stirred for 2 hours at room temperature. After completion, the reaction was worked up as described in the general procedure. The

organic layer was dried over Na_2SO_4. Purification by flash chromatography (hexanes/ethyl acetate 1/0 to 5/1) gave 95 mg (45%) of yellow liquid. This compound is known.[23] R_f = 0.43 (SiO_2, ethyl acetate/ hexanes 1/5). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.48 (*d*, *J* = 5.9 Hz, 1H) 8.23 (*d*, *J* = 8.6 Hz, 1H) 7.81 (*d*, *J* = 8.2 Hz, 1H) 7.68-7.55 (*m*, 2H), 7.48 (*d*, *J* = 5.9 Hz, 1H) 3.56 (*tt*, *J* =3.3 Hz, *J* = 11.6 Hz, 1H) 2.03-1.90 (*m*, 4H) 1.89-1.77 (*m*, 3H) 1.61-1.47 (*m*, 2H) 1.46-1.36 (*m*, 1H).

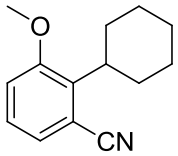
4-(Cyclohexylmethyl)quinoline (Table 2-2, entry 8)



The vial was charged with lepidine (191 mg, 1.3 mmol) and bromocyclohexane (162 mg, 0.99 mmol). Vial was capped and placed in the glove box. Inside the glove box, a solution of $FeCl_3$ in THF (0.1 M, 1 mL, 0.1 mmol) and *trans-N,N'*-dimethylcyclohexane-1,2-diamine (0.04 mL, 0.25 mmol) were added to the vial. Then, outside the glove box, $Cy_2NMgCl\bullet LiCl$ solution (0.76 M, 2.81 mL, 2.14 mmol) was added dropwise via syringe to the resulting solution. The reaction mixture was stirred for 2 hours at room temperature. After completion, the reaction mixture was quenched by brine and extracted with ethyl acetate as described in general procedure. Water (20 mL) was added to the aqueous layer after the first extraction. Combined organic layers were dried over Na_2SO_4. Purification by flash chromatography (CH_2Cl_2/ethyl acetate 1/0 to 5/1) and preparative TLC (CH_2Cl_2/ethyl acetate 5/1) gave 206 mg (92%) of a yellow liquid. R_f = 0.15 (SiO_2, 1/5

ethyl acetate/ hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.79 (*d*, *J* = 4.4 Hz , 1H) 8.11 (*d*, *J* = 8.4 Hz, 1H) 8.03 (*d*, *J* = 8.5 Hz, 1H) 7.72-7.67 (*m*, 1H) 7.58-7.52 (*m*, 1H) 7.18 (*d*, *J* = 4.4 Hz, 1H) 2.93 (*d*, *J* = 6.7 Hz, 2H) 1.77-1.61 (*m*, 5H) 1.22-1.01 (*m*, 5H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 149.9 148.5, 147.3, 130.2, 128.9, 128.0, 126.1, 124.0, 122.0, 40.3, 38.8, 33.6, 26.4, 26.2. FT-IR (neat, cm^{-1}) ν 2924, 2850, 1591, 1568, 1508, 1449. Anal calcd for $C_{16}H_{19}N$ (225.33 g/mol) C: 85.28; H: 8.50; N: 6.22 Found C: 85.06; H: 8.63; N: 6.20.

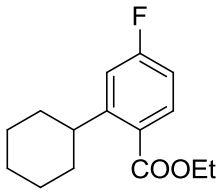
2-Cyclohexyl-3-methoxybenzonitrile (Table 2-2, entry 9)



The vial was charged with 3-methoxybenzonitrile (264 mg, 1.98 mmol) and bromocyclohexane (162 mg, 0.99 mmol). Vial was capped and placed in the glove box. Inside the glove box, a solution of $FeCl_3$ in THF (0.1 M, 1.0 mL, 0.1 mmol) and *trans-N,N'*-dimethylcyclohexane-1,2-diamine (0.04 mL, 0.25 mmol) were added to the vial. Then, outside the glove box, TMPMgCl•LiCl solution (1.09 M, 2.36 mL, 2.57 mmol) was added dropwise via syringe to the resulting solution. The reaction mixture was stirred for 18 hours at room temperature. After completion, the reaction mixture was quenched by brine and extracted with ethyl acetate as described in general procedure. Water (5 mL) was added to the aqueous layer after the first extraction. Combined organic layers were dried over Na_2SO_4. Purification by HPLC (hexanes/ethyl acetate 15/1) gave 129 mg (61%) of a white solid. R_f = 0.5 (SiO_2, hexanes/ethyl acetate 5/1), mp 63.0–64.5 °C. ^{1}H NMR

(500 MHz, $CDCl_3$, ppm) δ 7.24-7.18 (*m*, 1H) 7.02-7.07 (*m*, 1H) 3.84 (*s*, 3H) 3.25-3.14 (*m*, 1H) 2.17-2.04 (m, 2H) 1.87-1.61 (m, 5H) 1.24-1.47 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 158.2, 139.4, 127.5, 125.7, 119.1, 115.6, 112.7, 55.8, 41.6, 30.2, 27.1, 25.9. FT-IR (neat, cm^{-1}) ν 2919, 2847, 2227, 1578, 1469, 1455, 1436, 1297, 1276, 1264, 1238, 1102, 1065, 1001. Anal calcd for $C_{14}H_{17}NO$ (215.29 g/mol) C: 78.10; H: 7.96; N: 6.51. Found C: 77.83; H: 8.05; N: 6.52. NOESY experiment was performed to define a structure of the product. A correlation between protons of a methoxy group (3.84 ppm) and protons of a cyclohexyl ring (2.17-2.04 ppm, 1.87-1.61 ppm) was obtained in the spectra, which indicates that 3-methoxybenzonitrile was alkylated at the ortho position.

Ethyl 3-cyclohexyl-4-fluorobenzoate (Table 2-2, entry 10)

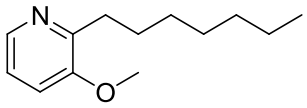


The vial was charged with ethyl 4-fluorobenzoate (336 mg, 2.0 mmol) and bromocyclohexane (163 mg, 1.0 mmol). Vial was capped and placed in the glove box. Inside the glove box, a solution of $FeCl_3$ in THF (0.1 M, 1.0 mL, 0.1 mmol) and *trans-N,N'*-dimethylcyclohexane-1,2-diamine (0.04 mL, 0.25 mmol) were added to the vial. Then, outside the glove box, $TMP_2Zn{\bullet}2MgCl_2{\bullet}2LiCl$ solution (0.52 M, 0.5 mL, 0.26 mmol) immediately followed by TMPMgCl•LiCl solution (1.12 M, 1.86 mL, 2.08 mmol) were added dropwise via syringe to the resulting solution. The reaction mixture was stirred for 18 hours at room temperature. After completion, the reaction mixture was

quenched with brine (20 mL) followed by extraction with ethyl acetate (5 times, 50 ml for the first time followed by 4x20 ml). After the first extraction, 5 mL water was added to the aqueous layer. The combined organic layer was dried over Na_2SO_4. Purification by HPLC (hexanes/ethyl acetate 15/1) gave 194 mg (78%) of a colorless liquid. R_f = 0.6 (SiO_2, hexanes/ethyl acetate 5/1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.83-7.77 (*m*, 1H) 7.08-7.04 (*m*, 1H) 6.92-6.87 (*m*, 1H) 4.35 (*q*, *J* = 7.1 Hz, 2H) 3.45-3.37 (*m*, 1H) 1.91-1.81 (*m*, 4H) 1.81-1.73 (*m*, 1H) 1.49-1.21 (*m*, 8H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 167.7, 165.0 ($J_{C\text{-}F}$ = 251.0 Hz) 152.6 ($J_{C\text{-}F}$ = 7.9 Hz) 132.8 ($J_{C\text{-}F}$ = 9.1 Hz) 126.4 ($J_{C\text{-}F}$ = 3.0 Hz) 114.1 ($J_{C\text{-}F}$ = 22.2 Hz) 112.6 ($J_{C\text{-}F}$ = 22.2 Hz) 61.2, 40.4, 34.5, 27.1, 26.4, 14.5. ^{19}F NMR (376MHz, $CDCl_3$, ppm) -107.7 - -107.8 (*m*, 1F). FT-IR (neat, cm^{-1}) ν 2928, 2854, 1721, 1609, 1584, 1493, 1448, 1366, 1294, 1251, 1237, 1161, 1110, 1073, 1061, 1016. Anal calcd for $C_{15}H_{19}FO_2$ (250.31 g/mol) C: 71.98; H: 7.65. Found C: 72.05; H: 7.61. From DEPT 135 spectra, the quaternary carbon, which has substituted cyclohexyl group can be assigned as 152.6 ($J_{C\text{-}F}$ = 7.9 Hz). Based on the C-F coupling constant, which is a common value for $^3J_{C\text{-}F}$, a suitable structure of product was obtained.

4.3.3 Deprotonative alkylation of 3-methoxy pyridine

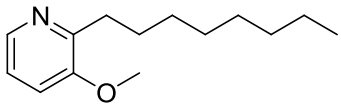
2-n-Heptyl-3-methoxypyridine (Table 2-3, entry 1)



The vial was charged with 3-methoxypyridine (191 mg, 1.75 mmol) and 1-bromoheptane (179 mg, 1.0 mmol). Vial was capped and placed in the glove box. Inside the glove box, a solution of $FeCl_3$ in THF (0.1 M, 1.0 mL, 0.1 mmol) and *trans-N,N'-*

dimethylcyclohexane-1,2-diamine (0.04 mL, 0.25 mmol) were added to the vial. Then, outside the glove box, TMPMgCl•LiCl solution (1.05 M, 1.82 mL, 1.91 mmol) was added dropwise via syringe to the resulting solution. The reaction mixture was stirred for 2 hours at room temperature. After completion, the reaction was worked up as described in the general procedure and the organic layer was dried over Na_2SO_4. Purification by flash chromatography (hexanes/ethyl acetate 1/0 to 5/1) and preparative TLC (hexanes/ethylacetate 3/1) gave 170 mg (82%) of a light yellow liquid. R_f = 0.26 (SiO_2, hexanes/ethyl acetate 5/1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.13-8.09 (*m*, 1H) 7.09-7.07 (*m*, 2H) 3.83 (s, 3H) 2.84-2.77 (*m*, 2H) 1.73-1.63 (*m*, 2H) 1.41-1.22 (*m*, 8H) 0.90-0.84 (*m*, 3H).^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 153.7, 152.9, 140.6, 121.7, 116.7, 55.4, 32.9, 32.0, 29.9, 29.4, 28.6, 22.9, 14.3. FT-IR (neat, cm^{-1}) ν 2957, 2926, 2855, 1588, 1572, 1455, 1431, 1275, 1186, 1132, 1025. Anal calcd for $C_{13}H_{21}NO$ (207.31 g/mol) C: 75.32; H: 10.21; N: 6.76. Found C: 75.45; H: 10.30; N: 6.66.

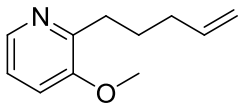
2-n-Octyl-3-methoxypyridine (Table 2-3, entry 2)



The vial was charged with 3-methoxypyridine (176 mg, 1.61 mmol) and 1-iodooctane (240 mg, 1.0 mmol). Vial was capped and placed in the glove box. Inside the glove box, a solution of $FeCl_3$ in THF (0.1 M, 1.0 mL, 0.1 mmol) and *trans-N,N'*-dimethylcyclohexane-1,2-diamine (0.04 mL, 0.25 mmol) were added to the vial. Then, outside the glove box, TMPMgCl•LiCl solution (1.20 M, 1.47 mL, 1.76 mmol) was added

dropwise via syringe to the resulting solution. The reaction mixture was stirred for 2 hours at room temperature. After completion, the reaction was worked up as described in the general procedure and organic layer was dried over Na_2SO_4. Purification by flash chromatography (hexanes/ethyl acetate 1/0 to 3/1) gave 172 mg (78%) of a light yellow liquid. R_f = 0.23 (SiO_2, hexanes/ethyl acetate 5/1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.13-8.09 (*m*, 1H) 7.09-7.07 (*m*, 2H) 3.83 (*s*, 3H) 2.83-2.78 (*m*, 2H) 1.72-1.64 (*m*, 2H) 1.41-1.21 (*m*, 10H) 0.87 (*t*, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 153.7, 152.9, 140.7, 121.7, 116.7, 55.4, 32.9, 32.1, 30.0, 29.7, 29.5, 28.6, 22.9, 14.3. FT-IR (neat, cm^{-1}) ν 2954, 2926, 2854, 1588, 1571, 1455, 1431, 1275, 1185, 1132, 1023. Anal calcd for $C_{14}H_{23}NO$ (221.34 g/mol) C: 75.97; H: 10.47; N: 6.33. Found C: 75.92; H: 10.45; N: 6.33.

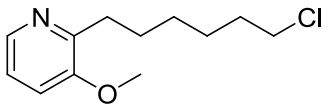
2-(4'-Pentenyl)-3-methoxypyridine (Table 2-3, entry 3)



The vial was charged with 3-methoxypyridine (174 mg, 1.59 mmol) and 5-bromopentene (150 mg, 1.01 mmol). Vial was capped and placed in the glove box. Inside the glove box, a solution of $FeCl_3$ in THF (0.1 M, 1.0 mL, 0.1 mmol) and *trans-N,N'*-dimethylcyclohexane-1,2-diamine (0.04 mL, 0.25 mmol) were added to the vial. Then, outside the glove box, TMPMgCl•LiCl solution (1.05 M, 1.66 mL, 1.74 mmol) was added dropwise via syringe to the resulting solution. The reaction mixture was stirred for 2 hours at room temperature. After completion, the reaction was worked up as described in the general procedure and organic layer was dried over Na_2SO_4. Purification by flash chromatography (hexanes/ethyl acetate 1/0 to 3/1) gave 153 mg (85%) of a light yellow

liquid. R_f = 0.20 (SiO_2, hexanes/ethyl acetate 5/1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.13-8.10 (*m*, 1H) 7.10-7.08 (*m*, 2H) 5.86 (*ddt*, *J* = 16.8 Hz , *J* = 10.1 Hz, *J* = 6.6 Hz , 1H) 5.03 (*ddt*, *J* = 17.0 Hz, *J* = 1.9 Hz, *J* = 1.9 Hz, 1H) 4.96 (*ddt*, *J* = 10.3 Hz, *J* = 2.1 Hz, *J* = 1.1 Hz, 1H) 3.83 (*s*, 3H) 2.86-2.81 (*m*, 2H) 2.17-2.11 (*m*, 2H) 1.83-1.76 (*m*, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 153.8, 152.5, 140.7, 139.0, 121.8, 116.7, 114.7, 55.4, 33.9, 32.3, 27.7. FT-IR (neat, cm^{-1}) ν 2934, 1640, 1587, 1572, 1456, 1431, 1275, 1187, 1132, 1024. Anal calcd for $C_{11}H_{15}NO$ (177.24 g/mol) C: 74.54; H: 8.53; N: 7.90. Found C: 74.36; H: 8.68; N: 7.74.

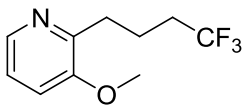
2-(6'-Chlorohexyl)-3-methoxypyridine (Table 2-3, entry 4)



The vial was charged with 3-methoxypyridine (154 mg, 1.41 mmol) and 1-chloro-6-iodo hexane (248 mg, 1.0 mmol). Vial was capped and placed in the glove box. A solution of $FeCl_3$ in THF (0.1 M, 1.0 mL, 0.1 mmol) and *trans-N,N'*-dimethylcyclohexane-1,2-diamine (0.04 mL, 0.25 mmol) were then added to the vial. TMPMgCl•LiCl solution (1.14 M, 1.49 mL, 1.70 mmol) was added dropwise to the resulting solution. The reaction mixture was stirred for 2 hours at room temperature. After completion, the reaction was worked up as described in the general procedure and organic layer was dried over Na_2SO_4. Purification by flash chromatography (hexanes/ethyl acetate 1/0 to 2/1) gave 130 mg (57%) of a light yellow liquid. R_f = 0.13 (SiO_2, hexanes/ethyl acetate 5/1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.13-8.09 (*m*, 1H) 7.11-7.08 (*m*, 2H) 3.83 (*s*, 3H) 3.53 (*t*, *J* = 6.8 Hz,

2H) 2.85-2.79 (*m*, 2H) 1.82-1.67 (*m*, 4H) 1.52-1.36 (*m*, 4H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 153.8, 152.6, 140.7, 121.8, 116.8, 55.4, 45.4, 32.8, 32.6, 29.0, 28.2, 27..FT-IR (neat, cm^{-1}) ν 2934, 2858, 1587, 1571, 1455, 1431, 1275, 1185, 1115, 1021. Anal calcd for $C_{12}H_{18}ClNO$ (227.13 g/mol) C: 63.29; H: 7.97; N: 6.15. Found C: 63.22; H: 7.95; N: 5.98.

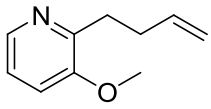
2-(4',4',4'-Trifluorobutyl)-3-methoxypyridine (Table 2-3, entry 5)



The vial was charged with 3-methoxypyridine (154 mg, 1.41 mmol) and 1-bromo-4,4,4-trifluorobutane (191 mg, 1.0 mmol). Vial was capped and placed in the glove box. Inside the glove box, a solution of $FeCl_3$ in THF (0.1 M, 1.0 mL, 0.1 mmol) and *trans-N,N'*-dimethylcyclohexane-1,2-diamine (0.04 mL, 0.25 mmol) were added to the vial. Then, outside the glove box, TMPMgCl•LiCl solution (1.08 M, 1.43 mL, 1.54 mmol) was added dropwise via syringe to the resulting solution. The reaction mixture was stirred for 2 hours at room temperature. After completion, the reaction was worked up as described in the general procedure and organic layer was dried over Na_2SO_4. Purification by flash chromatography (CH_2Cl_2/diethyl ether 1/0 to 15/1) gave 149 mg (68%) of a light yellow liquid. R_f = 0.17 (SiO_2, hexanes/ethyl acetate 5/1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.14-8.10 (*m*, 1H) 7.16-7.09 (*m*, 2H) 3.84 (*s*, 3H) 2.93-2.86 (*m*, 2H) 2.23-2.09 (*m*, 2H) 2.04-1.94 (*m*, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 153.8, 150.7, 140.7, 127.5 (*q*, J_{C-F} = 276.3 Hz), 122.3, 116.9, 55.4, 33.6 (*q*, J_{C-F} = 28.2 Hz), 31.4, 20.54 (*m*). ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -66.0 - -66.2 (*m*). FT-IR (neat, cm^{-1})

ν 1589, 1573, 1458, 1433, 1276, 1254, 1175, 1135, 1024, 1004. Anal calcd for $C_{10}H_{12}F_3NO_3$ (219.20 g/mol) C: 54.79; H: 5.52; N: 6.39. Found C: 55.03; H: 5.68; N: 6.31.

2-(3'-Butenyl)-3-methoxypyridine (Table 2-3, entry 6)



The vial was charged with 3-methoxypyridine (153 mg, 1.40 mmol) and cyclopropyl methyl bromide (135 mg, 1.0 mmol). Vial was capped and placed in the glove box. Inside the glove box, a solution of $FeCl_3$ in THF (0.1 M, 1.0 mL, 0.1 mmol) and *trans-N,N'*-dimethylcyclohexane-1,2-diamine (0.04 mL, 0.25 mmol) were added to the vial. Then, outside the glove box, TMPMgCl•LiCl solution (1.08 M, 1.41 mL, 1.52 mmol) was added dropwise via syringe to the resulting solution. The reaction mixture was stirred for 2 hours at room temperature. After completion, the reaction was worked up as described in the general procedure and organic layer was dried over Na_2SO_4. Purification by flash chromatography (hexanes/ethyl acetate 1/0 to 3/1) gave 101 mg (62%) of a light yellow liquid. R_f = 0.23 (SiO_2, hexanes/ethyl acetate 5/1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.14-8.09 (*m*, 1H), 7.13-7.07 (*m*, 2H) 5.92 (*ddt*, *J* = 16.9 Hz, *J* = 10.3 Hz, *J* = 6.6 Hz) 5.08-5.06 (*m*, 1H) 4.98-4.93 (*m*, 1H) 3.83 (*s*, 3H) 2.95-2.89 (*m*, 2H) 2.50-2.42 (*m*, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 153.8, 151.8, 140.6, 138.6, 121.9, 116.8, 114.7, 55.4, 32.5, 32.1. FT-IR (neat, cm^{-1})

ν 1640, 1588, 1572, 1455, 1431, 1276, 1187, 1132, 1023. Anal calcd for $C_{10}H_{13}NO$ (163.22 g/mol) C: 73.59; H: 8.03; N: 8.58. Found C: 73.40; H: 8.17; N: 8.38.

2-Cyclopentyl-3-methoxypyridine (Table 2-3, entry 7)

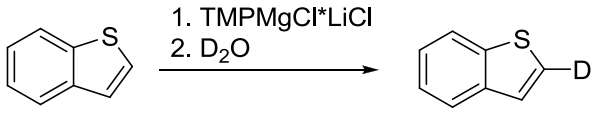
The vial was charged with 3-methoxypyridine (164 mg, 1.5 mmol) and bromocyclopentane (149 mg, 1.0 mmol). Vial was capped and placed in the glove box. Inside the glove box, a solution of $FeCl_3$ in THF (0.1 M, 1.0 mL, 0.1 mmol) and *trans-N,N'*-dimethylcyclohexane-1,2-diamine (0.04 mL, 0.25 mmol) were added to the vial. Then, outside the glove box, TMPMgCl•LiCl solution (1.20 M, 1.63 mL, 1.96 mmol) was added dropwise via syringe to the resulting solution. The reaction mixture was stirred for 2 hours at room temperature. After completion, the reaction was worked up as described in the general procedure and organic layer was dried over Na_2SO_4. Purification by flash chromatography (hexanes/ethyl acetate 1/0 to 3/1) and preparative TLC (hexanes/ethyl acetate 3/1) gave 144 mg (81%) of a light yellow liquid. R_f = 0.31 (SiO_2, hexanes/ethyl acetate 5/1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.16-8.12 (*m*, 1H) 7.10-7.04 (*m*, 2H) 3.82 (*s*, 3H) 3.55 (*quintet*, J_{C-H} = 8 Hz, 1H) 2.03-1.91 (*m*, 2H) 1.89-1.77 (*m*, 4H) 1.73-1.61 (*m*, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 155.4, 153.6, 140.7, 121.4, 116.7, 55.4, 40.8, 32.0, 26.1. FT-IR (neat, cm^{-1}) ν 2952, 2866, 1586, 1570, 1451, 1430, 1275, 1215, 1111, 1022. Anal calcd for $C_{11}H_{15}NO$ (177.24 g/mol) C: 74.54; H: 8.53; N: 7.90. Found C: 74.28; H: 8.59; N: 7.63.

4.3.4 Mechanistic study for deprotonation step

Deprotonation of benzothiophene by TMPMgCl•LiCl followed by deuteration

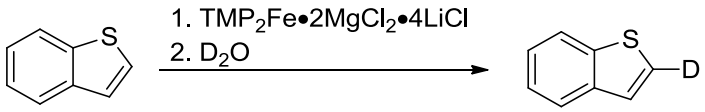
The vial was charged with benzothiophene (1 mmol) and purged with argon. Then, TMPMgCl•LiCl solution (0.98 M, 1.33 mL, 1.3 mmol) was added dropwise via syringe. The resulting mixture was stirred at room temperature. Samples of the reaction mixture (0.1 mL each) were taken at 5 min, 30 min, 1h, and 2h, followed by quenching by D_2O (0.05 mL). Deuterium incorporation at C-2 was determined by ^1H NMR and is shown in Table 2-4.

Table 2-4. Deprotonation of benzothiophene by TMPMgCl•LiCl



Time	% Deuterium incorporation
5 min	52%
30 min	52%
1 h	51%
2 h	46%

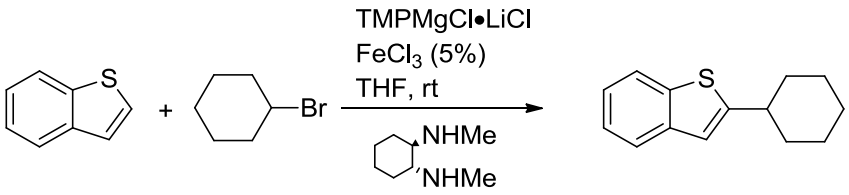
Deprotonation of benzothiophene by $TMP_2Fe•2MgCl_2•4LiCl$ followed by deuteration



The vial was charged with benzothiophene (1 mmol) and purged with argon. Then $TMP_2Fe•2MgCl_2•4LiCl$ solution (0.88 M, 1.48 mL, 1.3 mmol) was added dropwise through syringe. The resulting mixture was stirred at room temperature. Samples of the reaction mixture (0.1 mL each) were taken at 5 min, 30 min, 1h, and 2h followed by quenching by D_2O (0.05 mL). Deuterium incorporation at C-2 was determined by ^{1}H-NMR. The spectrum indicates 10% deuterium incorporation after 5 min. After that, extensive decomposition of benzothiophene was observed and determination of deuterium incorporation was impossible.

Rate of coupling reaction

The vial was charged with benzothiophene (140 mg, 1.04 mmol) and bromocyclohexane (326 mg, 2.0 mmol). Inside the glove box, a solution of $FeCl_3$ in THF (0.1M, 0.5 mL, 0.05 mmol), *trans-N,N'*-dimethylcyclohexane-1,2-diamine (0.02 mL, 0.13 mmol), and THF (0.5 mL) were added to the vial. Then, outside glove box, TMPMgCl•LiCl solution (1.45 mL, 0.93M, 1.35 mmol) was added dropwise via syringe to the reaction mixture. The reaction mixture was stirred at room temperature and samples were taken at 10min, 1h, and 2h. GC conversions based on alkylation product formation were determined by employing hexadecane as an internal standard and are presented below.



Time	GC conversion
10 min	64
1 h	74
2 h	71

Control Experiments. The following reactions were run in parallel.

Alkylation of benzothiophene using reagent grade $FeCl_3$ (98%) catalyst: The vial was charged with benzothiophene (67 mg, 0.5 mmol) and bromocyclohexane (163 mg, 1.0 mmol). Vial was capped and placed in the glove box. A solution of $FeCl_3$ in THF (0.1 M, 0.25 mL, 0.025 mmol), *trans-N,N'*-dimethylcyclohexane-1,2-diamine (0.01 mL, 0.063 mmol), and THF (0.25 mL) were then added to the vial. TMPMgCl•LiCl solution (1.0 M, 0.65 mL, 0.65 mmol) was added dropwise via syringe to the resulting solution outside the glove box. The reaction mixture was stirred for 6 hours at room temperature. Checking by GC with hexadecane as internal standard showed 74% conversion to 2-cyclohexylbenzothiophene.

Alkylation of benzothiophene using ultra-pure $FeCl_3$ (99.99%) catalyst: The vial was charged with benzothiophene (67 mg, 0.5 mmol) and bromocyclohexane (163 mg, 1.0 mmol). Vial was capped and placed in the glove box. $FeCl_3$ (99.99% pure; 4 mg, 0.025

mmol), THF (0.50 mL), and *trans*-*N,N'*-dimethylcyclohexane-1,2-diamine (0.01 mL, 0.063 mmol) were then added to the vial. TMPMgCl•LiCl solution (1.0 M, 0.65 mL, 0.65 mmol) was added dropwise via syringe to the resulting solution outside the glove box. The reaction mixture was stirred for 6 hours at room temperature. Checking by GC with hexadecane as internal standard showed 68% conversion to 2-cyclohexylbenzothiophene.

Alkylation of benzothiophene without iron catalyst: The vial was charged with benzothiophene (67 mg, 0.5 mmol) and bromocyclohexane (163 mg, 1.0 mmol). Vial was capped and placed in the glove box. THF (0.50 mL) and *trans*-*N,N'*-dimethylcyclo-hexane-1,2-diamine (0.01 mL, 0.063 mmol) were then added to the vial. TMPMgCl•LiCl solution (1.0 M, 0.65 mL, 0.65 mmol) was added dropwise via syringe to the resulting solution outside the glove box. The reaction mixture was stirred for 6 hours at room temperature. Checking by GC with hexadecane as internal standard showed <1% conversion to 2-cyclohexylbenzothiophene.

Unsuccessful reactions

Alkylation of thiazole, *n*-butyl-1,2,4-triazole, nicotinic acid ethyl ester, 1,2,3,4-tetrafluorobenzene, *n*-butylimidazole, 3,5-difluoropyridine, pyrimidine, pyridazine, *N,N*-dimethylaminopyridine, and mesitylene did not afford substantial amounts of the desired product. Reactions with the following alkyl halide substrates were not successful: chlorocyclohexane, 1-iodo-3,3,3-trifluoropropane, 10-bromodecanoic acid ethyl ester, 5-phthalimido-1-bromopentane, allyl bromide, and tert-butyl 2-bromoisobutyrate.

4.4 Deprotonative dimerization of arenes and heterocycles

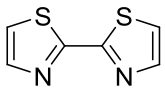
TMPMgCl•LiCl:[15] Inside the glovebox, a dry and argon flushed 50 mL Schlenk flask, equipped with a magnetic stir bar and septum was charged with iPrMgCl.LiCl 1.3M solution in THF (20 mL, 26 mmol). TMPH (tetramethypiperidine) (4.38 g, 31.2 mmol) was added dropwise at room temperature and stirred for 36 hours outside the glovebox. The resulting solution was concentrated under vacuum to 20 mL. The base was titrated before use at 0 ^{o}C with solution of benzoic acid in THF (0.2M) and (phenyl)[4-(phenylazo)-phenyl]amine was employed as indicator.[18]

TMP_2Zn•$2MgCl_2$•2LiCl:[19] Inside the glovebox, a dry 25 mL Schlenk flask equipped with a magnetic stir bar was charged with anhydrous $ZnCl_2$ (669.12 mg, 4.92 mmol). Then, the flask was capped with septum and taken out of the glovebox. TMPMgCl•LiCl solution (1.23M, 8 mL, 9.84 mmol) was added dropwise at room temperature and stirred for 15 hours. The fresh base was titrated before use at 0 ^{o}C with solution of benzoic acid in THF (0.2M) and (phenyl)[4-(phenylazo)-phenyl]amine was employed as indicator.[18]

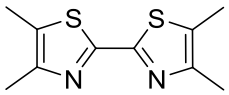
General procedure

A 1-dram screw-cap vial equipped with a magnetic stir bar was charged with substrate and flushed with argon. The vial was placed inside the glovebox and $FeCl_3$ was added as 0.1M solution in THF. Then, outside the glovebox, base (1-1.3 equiv) was added dropwise via syringe through the septum. The resulting solution was flushed with oxygen for 20 seconds and stirred at room temperature under the continuous flow of oxygen for 5-48 hours. The conversion was monitored by GC. After completion, the reaction mixture was quenched with mixture of brine and water and extracted five times with dichloromethane

or ethyl acetate (50 mL, followed by 4×20 mL). For bis-thiazole, bis-4,5-dimethylthiazole and bis-*N*-methylbenzimidazole, TMEDA (*N,N,N',N'*-tetramethylethylene-1,2-diamine) was added to both the aqueous and organic layers after the first extraction. The combined organic layers were dried over Na_2SO_4 (for the cases of bis-*N*-methylbenzimidazole, bis-thiazole and bis-4,5-dimethylthiazole) or $MgSO_4$ (for bis-2,3,5,6-tetrafluoroanisole, bis-2,3,5,6-tetrafluoropyridine, Diethyl 2,2',6,6'-tetrafluorobiphenyl-3,3'-dicarboxylate)**,** evaporated under reduced pressure and the residue was purified by flash chromatography.

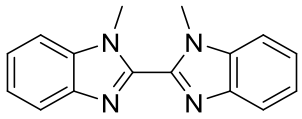


Bis-thiazole (Table 2-6, entry 1): The vial was charged with thiazole (128 mg, 1.50 mmol). 0.1M solution of $FeCl_3$ in THF (1.50 mL, 0.15 mmol) was then added to the vial. $TMP_2Zn{\bullet}2MgCl_2{\bullet}2LiCl$ solution (0.47M, 0.62 mL, 0.29 mmol) and later TMPMgCl•LiCl solution (1.18M, 1.16 mL, 1.37 mmol) were added dropwise to the resulting solution. The reaction mixture was stirred under oxygen for 4 hours. Extraction with dichloromethane and purification by flash chromatography (hexanes/ethyl acetate 10/1 to 10/3) gave 73 mg (59%) of light yellow product. This compound is known.[24] ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.90 (*d*, *J* = 2.9 Hz, 2H) 7.45 (*d*, *J* = 2.9 Hz, 2H).

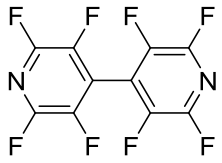


Bis-4,5-dimethylthiazole (Table 2-6, entry 2): The vial was charged with 4,5-dimethylthiazole (171.4 mg, 1.51 mmol). 0.1M solution of $FeCl_3$ in THF (1.51 mL, 0.15 mmol) was added to the vial. TMPMgCl•LiCl solution (1.18M, 1.4 mL, 1.65 mmol) was

added dropwise to the resulting solution. The reaction mixture was stirred under oxygen for 5 hours. Extraction with ethyl acetate and purification by flash chromatography (hexanes/ethyl acetate 10/1 to 5/1) gave 117 mg (68%) of a yellow solid product. This compound is known.[25] ^{1}H NMR (400, $CDCl_3$, ppm) δ 2.39 (*s*, 6H) 2.62 (*s*, 6H).

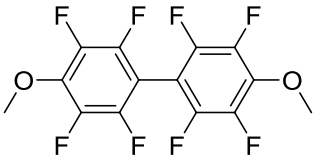


Bis-*N*-methylbenzimidazole (Table 2-6, entry 3): The vial was charged with *N*-methylbenzimidazole (133 mg, 1.01 mmol). 0.1M solution of $FeCl_3$ (1.01 mL, 0.1 mmol) was added to the vial. TMPMgCl•LiCl solution (1.15M, 0.95 mL, 1.09 mmol) was added dropwise to the resulting solution. The reaction mixture was stirred under oxygen for 5 hours. Extraction with dichloromethane and purification by flash chromatography (dichloromethane/ethyl acetate 15/1 to 10/1) gave 102 mg (77%) of a product as a white solid. This compound is known.[26] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.88 (d, J = 7.3 Hz, 2H) 7.49 (d, J = 7.8 Hz, 2H) 7.34-7.43 (m, 4H) 4.33 (s, 6H).

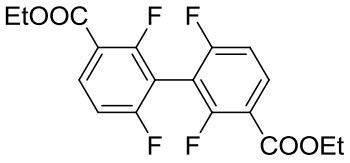


Bis-2,3,5,6-tetrafluoropyridine (Table 2-6, entry 4): The vial was charged with 2,3,5,6-tetrafluoropyridine (152 mg, 1.01 mmol). 0.1M solution of $FeCl_3$ in THF (1.01 mL, 0.1 mmol) was then added to the vial. $TMP_2Zn•2MgCl_2•2LiCl$ solution (0.46M, 1.19 mL, 0.55 mmol) was added dropwise to the resulting solution. The reaction mixture was stirred

under oxygen for 48 hours. Extraction with dichloromethane and purification by flash chromatography (pentane/dichloromethane 1/0 to 10/1) gave 82 mg (54%) of a product as a colorless solid. This compound is known.[27] ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -86.97- -86.89 (m, 4F) -137.83- -137.78 (m, 4F).



Bis-2,3,5,6-tetrafluoroanisole (Table 2-6, entry 5): The vial was charged with 2,3,5,6-tetrafluoroanisole (181.3 mg, 1.01 mmol). 0.1M solution of $FeCl_3$ in THF (1.01 mL, 0.1 mmol) was then added to the vial. $TMP_2Zn{\bullet}2MgCl_2{\bullet}2LiCl$ solution (0.45M, 1.02 mL, 0.46 mmol) and later TMPMgCl•LiCl solution (1.2M, 0.33 mL, 0.4 mmol) were added dropwise to the resulting solution. The reaction mixture was stirred under oxygen for 24 hours. Extraction with ethyl acetate and purification by flash chromatography (hexanes/ethyl acetate 1/0 to 20/1) gave 142 mg (78%) of a product as a white solid. This compound is known.[28] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 4.21-4.14 (m, 6H).



Diethyl 2,2',6,6'-tetrafluorobiphenyl-3,3'-dicarboxylate (Table 2-6, entry 6): The vial was charged with ethyl 2,4-difluorobenzoate (186.9 mg, 1 mmol). 0.1M solution of $FeCl_3$ in THF (1 mL, 0.1 mmol) was then added to the vial. $TMP_2Zn{\bullet}2MgCl_2{\bullet}$LiCl solution (0.45M, 0.44 mL, 0.2 mmol) and later TMPMgCl•LiCl solution (1.25M, 0.73 mL, 0.91

mmol) were added dropwise to the resulting solution. The reaction mixture was stirred under oxygen for 30 hours. Extraction with dichloromethane and purification by flash chromatography (hexanes/dichloromethane/ethyl acetate 90%/5%/5% to 80%/5%/15%) gave 131 mg (70%) of a product as a white solid. R_f = 0.23 (SiO_2, 1/10 ethyl acetate/ hexanes), mp 76.2–78.2°C . ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.07-8.13 (m, 2H) 7.07-7.11 (m, 2H) 4.39 (q, J = 7.3 Hz, 4H) 1.4 (t, J = 7.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 161.8-164.4 (doublet of multiplets, J_{C-F} = 258.8 Hz), 163.6 (s) 159.0-161.6 (doublet of multiplets, J_{C-F} = 264.5 Hz), 134.6 (dd, J_{C-F} = 5.7 Hz, J = 5.4 Hz), 116.0 (d, J_{C-F} = 9.6 Hz), 111.8 (d, J_{C-F} = 22.2 Hz), 107.0-107.7 (m), 61.9, 14.4. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) -102.1- -101.9 (m, 2F) -104.4- -104.2(m, 2F). FT-IR (neat, cm^{-1}) ν 1712, 1614, 1444, 1368, 1319, 1286, 1267, 1275, 1206, 1131, 1020. Anal calcd for $C_{18}H_{14}F_4O_4$ (370.29 g/mol): C, 58.38; H, 3.81; Found. C, 58.49; H, 3.82.

Homocoupling of 4,5-dimethylthiazole using normal $FeCl_3$ as catalyst: The vial was charged with 4,5-dimethylthiazole (171.4 mg, 1.51 mmol). 0.1M solution of $FeCl_3$ in THF (1.51 mL, 0.15 mmol) was added to the vial. TMPMgCl•LiCl solution (1.18M, 1.4 mL, 1.65 mmol) was added dropwise to the resulting solution. The reaction mixture was stirred under oxygen for 5 hours. Extraction with ethyl acetate and purification by flash chromatography (hexanes/ethyl acetate 10/1 to 5/1) gave 117 mg (68%) of dimer product.

Homocoupling of 4,5-dimethylthiazole using $FeCl_3$ 99.99% pure as catalyst: The vial was charged with 4,5-dimethylthiazole (124 mg, 1.1 mmol). $FeCl_3$ (99.99% pure) (18 mg, 0.11 mmol) was added to the vial. TMPMgCl•LiCl solution (1.04M, 1.15 mL, 1.2 mmol) was added dropwise to the resulting solution. The reaction mixture was stirred under

oxygen for 5 hours. Checking by GC with hexadecane as internal standard gave the result of 70% conversion.

Homocoupling of 4,5-dimethylthiazole without iron catalyst: The vial was charged with 4,5-dimethylthiazole (121.6 mg, 1.07 mmol). TMPMgCl•LiCl solution (1M, 1.17 mL, 1.17 mmol) was added dropwise to the vial. The reaction mixture was stirred under oxygen for 5 hours. Checking by GC with hexadecane as internal standard gave only trace amount of product.

V. References

1. (a) T. Eicher, S. Hauptmann, *The Chemistry of Heterocycles*, Wiley-VCH, Weinheim, **2003**. (b) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol.Chem.* **2006**, *4*, 2337. (c) Kraft, A.; Grimsdale, A. C.; Holmes, A. B. *Angew. Chem. Int. Ed.* **1998**, *37*, 402.

2. Selected reviews: (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (b) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (d) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (e) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (f) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (g) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174.

3. Roberts, R. M.; Khalaf, A. A. Friedel-Crafts *Alkylation Chemistry: A Century of Discovery*; Marcel Dekker: New York, **1984**.

4. (a) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529. (b) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1999**, *121*, 6616. (c) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 5332. (d) Lail, M.; Arrowood, B. N.; Gunnoe, T. B. *J. Am. Chem. Soc.* **2003**, *125*, 7506.

5. (a) Tremont, S. J.; Rahman, H. U. *J. Am. Chem. Soc.* **1984**, *106*, 5759. (b) McCallum, J. S.; Gasdaska, J. R.; Liebeskind, L. S.; Tremont, S. J. *Tetrahedron Lett.* **1989**, *30*, 4085.

6. (a) Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, 11, 4160. (b) Zhang, Y.-H.; Shi, B.-F.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 6097. (c) Ackermann, L.; Nova´k, P.; Vicente, R.; Hofmann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6045. (d) Mukai, T.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 1360. (e) Yue, W.; Li, Y.; Jiang, W.; Zhen, Y.; Wang, Z. *Org. Lett.* **2009**, *11*, 5430. Other alkylation methods: (f) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. (g) Catellani, M.; Motti, E.; Della Ca', N. *Acc. Chem. Res.* **2008**, *41*, 1512. (h) Rudolph, A.; Rackelmann, N.; Lautens, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1485. (i) Chen, X.; Li, J.-J.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 78. (j) Sc catalysis: Deng, G.; Li, C.-J. *Org. Lett.* **2009**, *11*, 1171.

7. Wunderlich, S. H.; Knochel, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 9717.

8. Vechorkin, O.; Proust, V.; Hu, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 3061.

9. (a) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404. (b) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 1128. (c) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185. (d) Yotphan, S.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2009**, *11*, 1511. Fe catalysis: (e) Norinder, J.; Matsumoto, A.; Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 5858.

10. (a) Furstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 8773. (b) Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297. Review: (c) Sherry, B. D.; Furstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500. (d) Martin, R.; Furstner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3955. (d) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 3686. (e) Czaplik, W. M.; Mayer, M.; Jacobi von Wangelin, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 607. (f) Tamura, M.; Kochi, J.

K. *J. Am. Chem. Soc.* **1971**, *93*, 1487. (g) Cahiez, G.; Habiak, V.; Duplais, C.; Moyeux, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 4364.

11. (a) Bennett, G. M.; Tunner, E. E. *J. Chem. Soc.* **1914**, 1057. (b) Gilman, H.; Lichtenwalter, M. *J. Am. Chem. Soc.* **1939**, *61*, 957.

12. Cahiez, G.; Moyeux, A.; Buendia, J.; Duplais, C. *J. Am. Chem. Soc.* **2007**, *129*, 13788.

13. Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2009**, *131*, 17052.

14. Furstner, A.; Leitner, A.; Mendez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856

15. Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 2958.

16. (a) Shen, K.; Fu, Y.; Li, J.-N.; Liu, L.; Guo, Q.-X. *Tetrahedron* **2007**, *63*, 1568. (b) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.

17. Truong, T.; Alvarado, J.; Tran, L. D.; Daugulis, O. *Org. Lett.* **2010**, *12*, 1200.

18. Rohbogner, C. J.; Wunderlich, S. H.; Clososki, G. C.; Knochel, P. *Eur. J. Org. Chem*. **2009**, 1781.

19. Wunderlich, S. H.; Knochel, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 7685.

20. Karakhanov, E. A.; Ermolaeva, S. K.; Nikolaeva, V. M.; Viktorova, E. A. *Vestnik Moskovskogo Universiteta, Seriya 2: Khimiya* **1974**, *15*, 225.

21. Descamps, M.; Gubin, J. Patent No. FR 2279395, 1976.

22. Czaplik, W. M.; Mayer, M.; Wangelin, A. J. v. *Angew. Chem. Int. Ed.* **2009**, *48*, 607.

23. Minisci, F.; Vismara, E.; Fontana, F. *J. Org. Chem.* **1989**, *54*, 5224.

24. Kurata, H.; Takakuwa, H.; Matsumoto, K.; Kawase, T.' Oda, M. *Synlett*. **2008**, 2882.

25. Mostaghim, R.; Beni, Y. A. *Indian Journal of Chemistry* **2001**, *40B(6*), 498.

26. Park, S. B.; Alper, H. *Org. Lett*. **2003**, *5*, 3209.

27. Green, M.; Taunton-Rigby, A.; Stone, F. G. A. *J. Chem. Soc. A* **1968**, 2762.

28. Deacon, G. B.; Phillips, R. J. *Aust. J. Chem*. **1978**, *31*, 1709.

Chapter 3 Copper-catalyzed carbon-heteroatom bond formation through sp^2 carbon-hydrogen bond activation

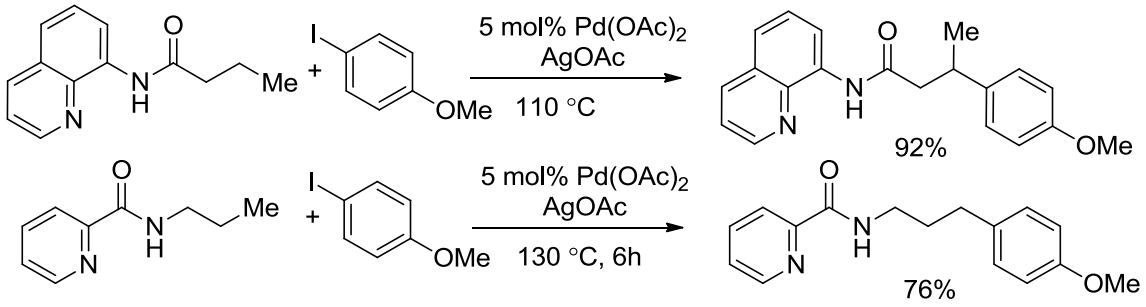
I. Introduction

The use of first-row transition metals, such as copper, as alternative catalysts for C-H bond functionalization has attracted much attention due to their low cost.[1-5] Indeed, Yu has showed that ortho C–H bond of 2-phenyl pyridine can be converted to various functional groups by copper-catalyzed or mediated reactions.[2] Daugulis and coworkers demonstrated the deprotonative arylation and perfluoroalkylation of arenes and heterocycles using copper catalysis.[3] Several groups have presented the synthesis of heterocyles by utilizing copper-catalyzed intramolecular C–H bond functionalization/C–N, and C-O bond formation.[4] However, the scope of substrates is still limited to either 2-phenylpyridine or arenes and heterocycles containing acidic C-H bonds.[5] Indeed, a method that allows direct heterocoupling of sp^2 C-H bond using removable directing groups and copper catalysis has not been reported yet.

Our group has demonstrated that using 8-aminoquinoline or picolinic acid as removable directing groups, β-C-H bonds of carboxylic acid and γ-C-H bonds of amine derivatives can be arylated or alkylated in good yields under palladium catalysis (Scheme 3-1).[6] Copper-catalyzed functionalization of nonacidic C-H bonds by using a pyridine directing group has been described in literature.[2] We proposed that in the presence of 8-aminoquinoline directing group, ortho C-H bond of benzoic acid derivatives can be activated under copper catalysis. Subsequent coupling reactions with sulfenylating or aminating reagents would afford C-heteroatom bonds. This would allow direct amination

and sulfenylation of sp^2 C-H bond using inexpensive copper catalyst and a removable directing group. Furthermore, this methodology would have higher synthetic utility and practicality compared with existing methods.

Scheme 3-1. Palladium-catalyzed C-H bond arylation



II. Results and discussions

2.1 Copper-promoted sulfenylation of sp^2 C-H bonds

Aryl trifluoromethyl sulfides are important compounds in pharmaceutical and agrochemical industries. The introduction of SCF_3 group to arenes leads to the increase of lipophilicity thus enhancing bioavailability.[7,8] Moreover, Ar-SCF_3 are important intermediates for the synthesis of trifluoromethyl sulfones and sulfoxides.[9] Conventional methods to introduce SCF_3 moiety require harsh reaction conditions, high temperature, and/or stoichiometric amount of metal-SCF_3 salts.[7,10] Recently, more efficient methods utilizing milder protocols have been developed. Buchwald demonstrated trifluoromethylthiolation of aryl bromides using a Pd catalyst and $AgSCF_3$ reagent.[11] Aryl bromides and iodides can also be converted to $ArSCF_3$ by a Ni-catalyzed method developed by Vicic.[12] More recently, the Qing group reported the preparation of $ArSCF_3$ from aryl boronic acids by copper-catalyzed method.[13] However, despite the

improvements, these methods require pre-functionalized starting materials. Hence, direct trifluoromethylthiolation of aromatic C-H bonds would be advantageous.

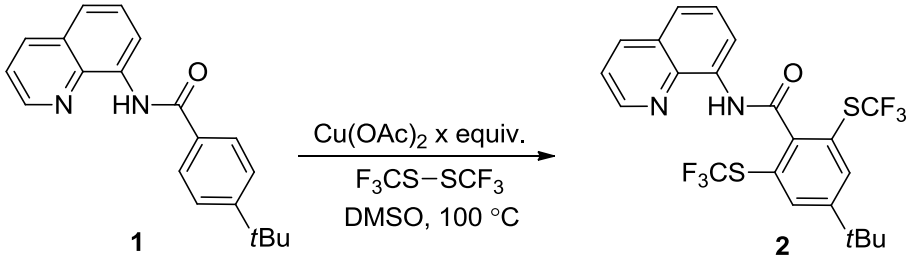
As discussed before, we hypothesized that 8-aminoquinoline and picolinic acid auxiliaries would facilitate the ortho-trifluoromethylsulfenylation of benzoic acid and benzylamine derivatives. Among the two auxiliaries, 8-aminoquinoline is more efficient since it allows the arylation and alkylation of carboxylic acid derivatives in good yields. Thus, 8-aminoquinoline was chosen as the auxiliary for the reaction. Trifluoromethyl sulfide salts are the most common reagents used in recently developed methods for the introduction of trifluoromeylsulfide group. However, most of these salts are thermally unstable, and/or require several step syntheses.[14] Bis(trifluoromethyl) disulfide, on the other hand, is commercially available, thermally stable, and easy to handle. Moreover, bis(trifluoromethyl) disulfide can act both as sulfenylating reagent and oxidant. Therefore it is the most suitable coupling partner for the reaction. Lastly, dimethyl sulfoxide (DMSO) is selected as a solvent due to its ability to oxidize thiols to disulfides.[15] Trifluoromethyl thiol (CF_3SH) might be formed as one of the possible products and can be reconverted to disulfide by DMSO.

2.1.1 Optimization for trifluoromethylsulfenylation of benzoic acid amides

Optimization of the reaction conditions were studied based on reaction between 8-aminoquinoline 4-*t*-butylbenzoic acid amide **1** and bis(trifluoromethyl) disulfide using different amounts of $Cu(OAc)_2$ in DMSO solvent (Table 3-1). To our delight, stoichiometric copper afforded good conversion to the desired product (entry 1). Decreasing the amount of $Cu(OAc)_2$ improved the yield of the product (entry 2, 3).

However, when $Cu(OAc)_2$ loading was decreased to 0.2 equivalents, only 44% of the desired product was formed (entry 4). As a consequence, 0.5 equivalents of $Cu(OAc)_2$ were used for further studies.

Table 3-1. Optimization of C-H bond trifluoromethylsulfenylation



Entry	x	% yield
1	1	61
2	0.8	70
3	0.5	74
4	0.2	44

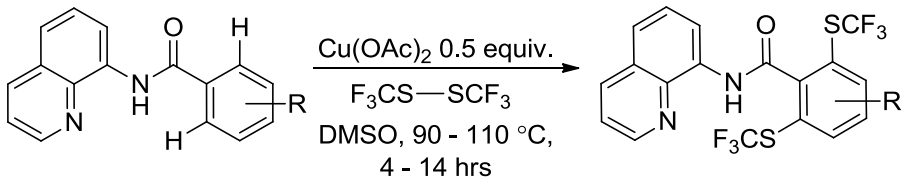
*Yield was determined by NMR

2.1.2 Trifluoromethylsulfenylation of benzoic acid amides

After the optimization, the scope of reaction with respect to carboxylic acid derivatives was studied (Table 3-2). Various amides bearing electron-donating and electron-withdrawing groups are suitable substrates providing products in moderate to good yields. The reaction does not show any profound electronic preference as both electron-rich (entries 1, 2, 5) and electron-poor benzamides (entries 3, 4, 6) afford products in good yields. Steric properties of the carboxylic acid residues, on the other hand, have a significant effect on the yield of the products. Para-substituted benzamides gave better

conversion toward the desired products than ortho-substituted amides (entry 1 versus 5 and 6). The reaction affords difunctionalization products even with meta-substituted amides (entry 7) in contrast with our previous palladium catalyzed arylation methodology where only monoarylated products were obtained in such cases.[6a,b] Moreover, the reaction demonstrated excellent functional group tolerance. Bromide (entry 4) and chloride functionalities (entry 6) are tolerated.

Table 3-2. Copper-catalyzed trifluoromethylsulfenylation of carboxylic acid derivatives



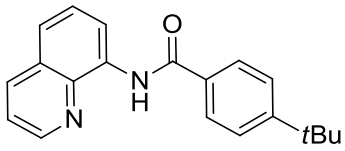
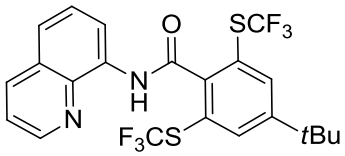
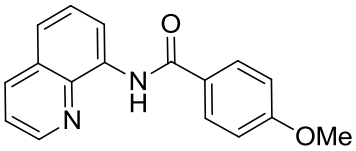
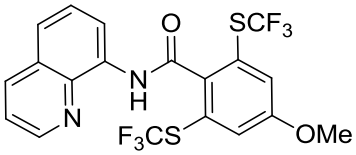
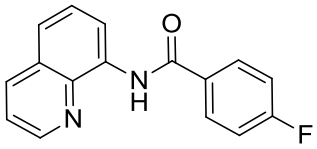
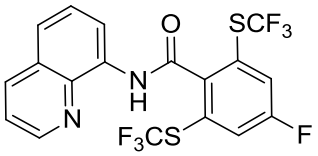
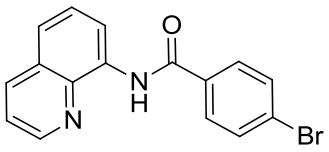
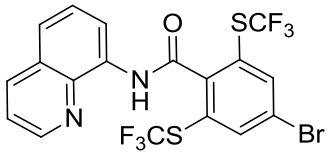
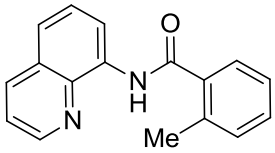
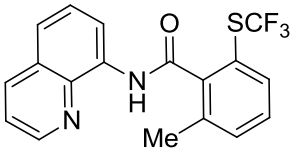
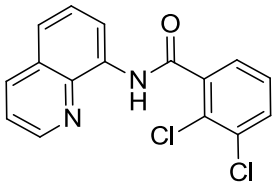
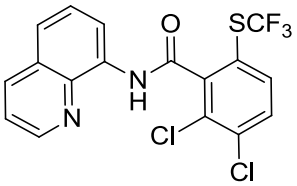
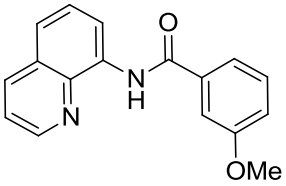
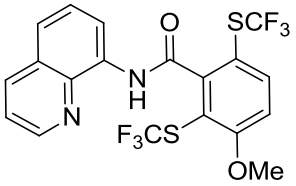
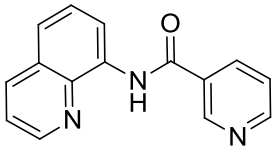
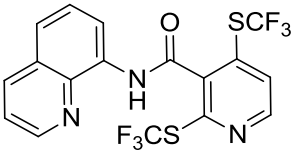
Entry	Starting amide	Product	yield
1			76%
2			67%
3			73%

Table 3-2. (*Continued*)

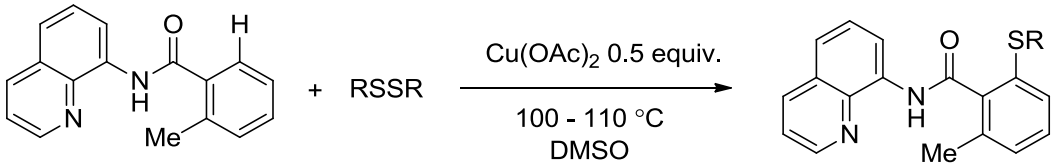
4			79%
5			63%
6			59%
7			70%
8			43%

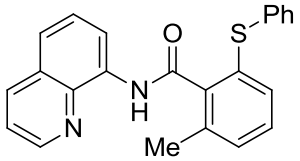
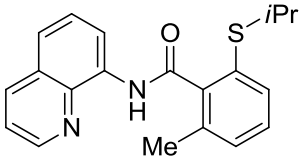
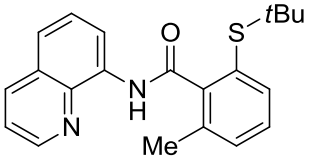
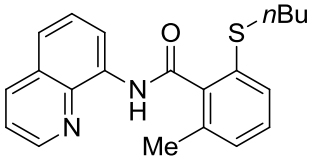
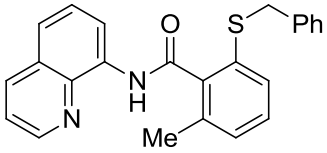
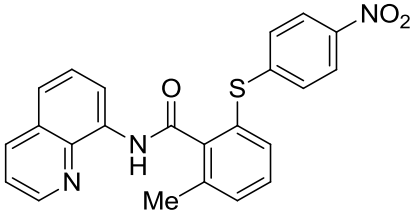
Heterocyclic substrates are also reactive as nicotinamide (entry 8) was converted to disubstituted product in synthetically useful yield. Selectively mono-trifluoromethylsulfenylation could not be archieved

2.1.3 Sulfenylation of *o*-toluic acid amide

Besides bis(trifluoromethyl) disulfide, other aryl and alkyl disulfides are also active sulfenylating reagents. Reactions of *o*-toluic acid amide with different disulfides are shown in Table 3-3.

Table 3-3. Disulfide scope in C-H bond sulfenylation



Entry	RSSR	Product	Yield
1	PhSSPh		86%
2	*i*PrS*S*i*Pr*		90%
3	*t*BuS*S*t*Bu*		69%
4	*n*BuS*S*n*Bu*		87%
5	BnSSBn		85%
6	*p*-NO_2PhSSPh-*p*-NO_2		81%

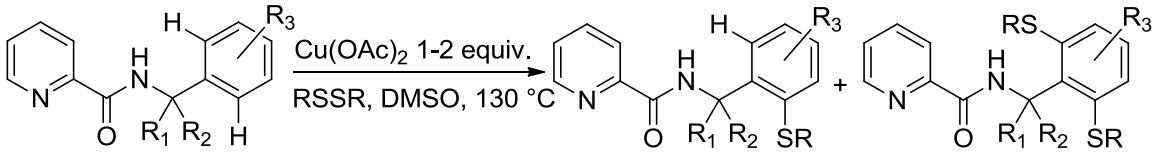
A short optimization revealed that the reaction using diphenyl disulfide reagent requires K_2CO_3 base in order to reach high conversion (entry 1). Various dialkyl (entries 2–5) and diaryl disulfides (entries 1, 6) are reactive and provide products in excellent yields. However, di-*t*-butyl disulfide gave slightly lower yield (entry 3), possibly due to the steric

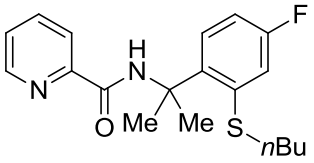
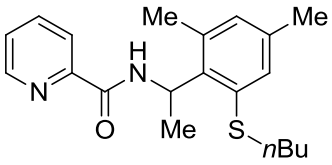
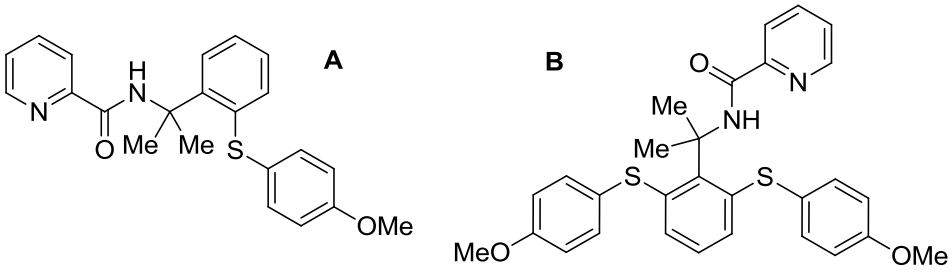
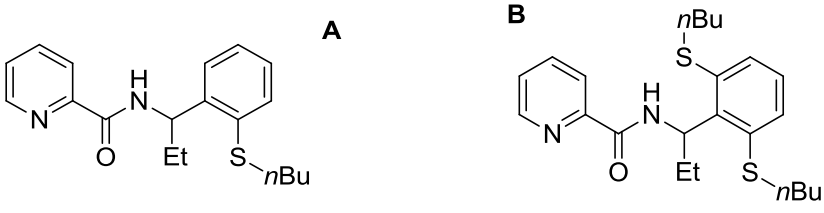
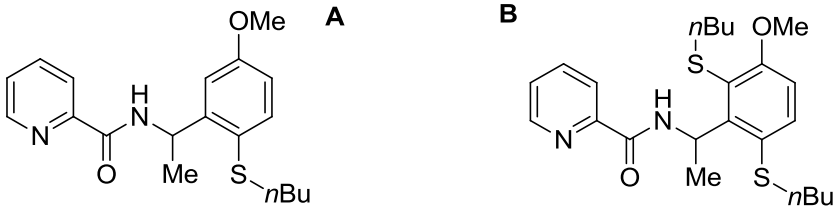
bulk. Noteworthy, the nitro group is tolerated under the reaction conditions (entry 6) which further demonstrates the excellent functional group tolerance of the method.

2.1.4 Sulfenylation of benzylamine derivatives

Benzylamine derivatives can also be sulfenylated by using $Cu(OAc)_2$, disulfide reagents, and picolinic acid directing group. Compared to 8-aminoquinoline, picolinic acid auxiliary requires stoichiometric amount of copper and higher reaction temperature. Using the optimized conditions, various benzylamine derivatives were sulfenylated at γ C–H positions in moderate to good yields (Table 3-4).The reaction works well for α-mono and α,α-disubstituted benzylamine derivatives. In fact, α-substituent is essential for the product formation as the reaction with *N*-benzylpicolylamide gave trace amount of desired product. These observations can possibly be explained by the Thorpe-Ingold effect.[16] *p*-Fluoro-α,α-dimethylbenzylamine and 2,4-dimethyl-α-methylbenzylamine amides were mono-*n*-butylsulfenylated in good yields (entries 1 and 2). *p*-Methoxyphenylthiolation of α,α-dimethylbenzylamine picolinamide affords monosubstitution product in 62% yield accompanied by disubstitution product in 16% yield (entries 3A-B). α-Ethylbenzylamine and α–methyl-3-methoxybenzylamine amides gave a mixture of approximately equal amounts of mono- and disubstitution products (entries 4A-B and 5A-B).

Table 3-4. Copper-mediated sulfenylation of amine derivatives

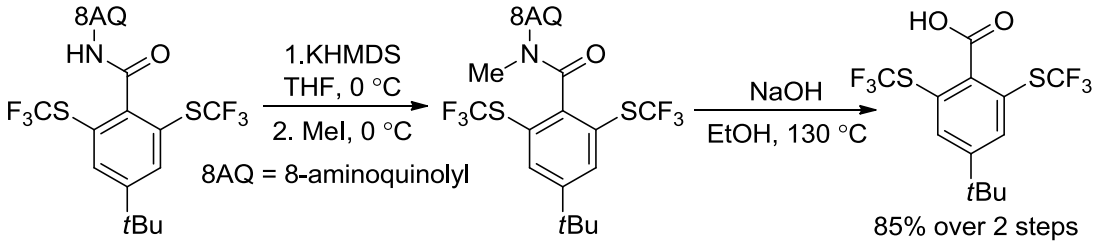


Entry	Product	Yield
1		70%
2		63%
3		62% (A) 16% (B)
4		25% (A) 36% (B)
5		42% (A) 26% (B)

2.1.5 Removal of directing group

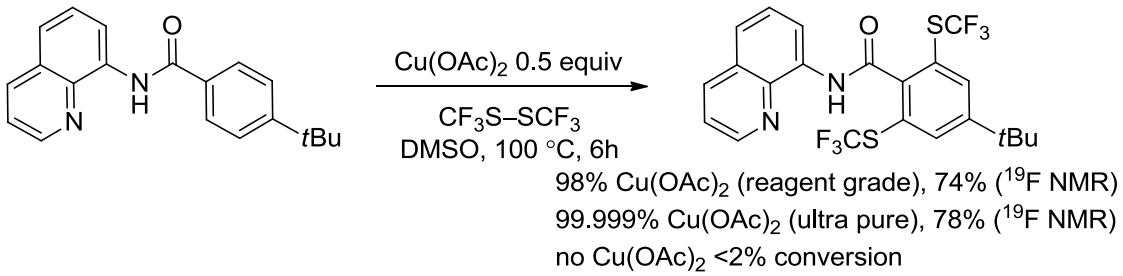
The 8-aminoquinoline group can be efficiently removed in a two-step procedure by amide *N*-methylation followed by base hydrolysis. The trifluoromethylthiolated acid was obtained in high yield (Scheme 3-2).

Scheme 3-2. Removal of 8-aminoquinoline auxiliary



In order to confirm the role of the copper as the active catalyst, control experiments were performed. With reagent grade and ultra-pure $Cu(OAc)_2$ nearly identical results were obtained, showing that reactivity by contaminants is unlikely. If copper salt was omitted, no product was obtained (Scheme 3-3).

Scheme 3-3. Control experiments for copper-promoted sulfenylation of sp^2 C-H bonds



2.2 Copper-catalyzed amination of non-acidic sp^2 C-H bonds

Aryl and heteroarylamines are prevalent in pharmaceuticals and organic materials. As a consequence, direct amination of sp^2 C-H bonds is a highly desirable transformation as

evidenced by a significant amount of publications.[17-20] Intramolecular C-H bond activation/C-N bond formation has been demonstrated.[17] In contrast, intermolecular reaction is more challenging. Nitrenoid intermediates are commonly used for intermolecular amination of C-H bonds.[18] However, these methods require harsh reaction conditions which are incompatible with sensitive functional groups. Palladium-catalyzed direct amination are also reported in literature.[17,19] Nonetheless, substitution of palladium by copper catalyst would be beneficial due to the low cost of copper salts.

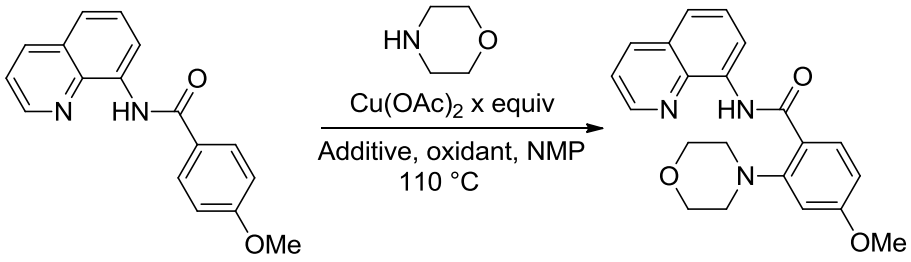
Heterocycles containing acidic protons can undergo deprotonative amination by employing stoichiometric or catalytic copper.[1j,20] Substrate scope is limited to most acidic heterocycles such as thiazoles or oxazoles. Direct amination or amidation of 2-arylpyridines was reported recently.[1h-i,2a] In this case, use of pyridine, which is a nonremovable directing group, significantly restricts synthetic applications of the methods. Our stratergy is aimed to develop methods that allow direct amination of aryl C-H bonds using copper catalysis and removable directing group.

Our previous work has indicated that 8-aminoquinoline and picolinic acid auxiliaries can direct the sulfenylation of ortho-C-H bonds in benzoic acid and benzylamine derivatives in the presence of a copper catalyst. Additionally, copper can serve as the promoter for ortho-amination of 2-phenylpyridine derivatives. Based on these facts, we hypothesized that 8-aminoquinoline and picolinic acid auxilaries would effect ortho-C-H amination of sp^2 C-H bonds.

2.1.1 Optimization of conditions for direct amination of benzoic acid amides

The reaction conditions between 8-aminoquinoline *p*-methoxybenzamide and morpholine was investigated with respect to oxidants, additives, and amount of $Cu(OAc)_2$ (Table 3-5). To our delight, reaction with stoichiometric $Cu(OAc)_2$ gave 39% yield of the desired product. Lower catalyst loading together with employing oxidants such as O_2 or NMO slightly increased yield of the reaction. Noteworthy, when Ag_2CO_3 was used as a co-oxidant, 74% of the aminated product was obtained (entry 4). Subsequently, decreasing the loading of $Cu(OAc)_2$ and Ag_2CO_3 gave the best yield (entry 5). Control experiment showed that $Cu(OAc)_2$ is essential for the amination reaction (entry 7).

Table 3-5. Optimization of reaction conditions



Entry	x equiv	Oxidant	Additive	Yield %
1	1	None	None	39[a]
2	0.5	O_2	None	51[a]
3	0.25	NMO	K_2CO_3	44[a]
4	0.25	NMO	Ag_2CO_3 0.25 equiv	74[b]

Table 3-5. (*Continued*)

5	0.1	NMO	Ag_2CO_3 0.13 equiv	87[b]
6	0.05	NMO	Ag_2CO_3 0.075 equiv	80[a]
7	0	NMO	Ag_2CO_3 0.125 equiv	<2

[a] NMR yield, [b] isolated yield

2.1.2 Amination of benzoic acid amides

After finding the optimized reaction conditions, the scope of reaction with respect to carboxylic acid derivatives was studied (Table 3-6). The amination is successful for both electron-rich (entries 1, 3, 5, 7, 8) and electron-poor amides (entries 2, 4, 6). In contrast with copper-promoted sulfenylation, the amination is selective for monofunctionalization. The amination occurs at the less sterically demanding position (entries 5, 6, 8). Only traces of diamination products were observed in crude reaction mixtures.

Table 3-6. Copper-catalyzed reaction of morpholine with carboxylic acid derivatives

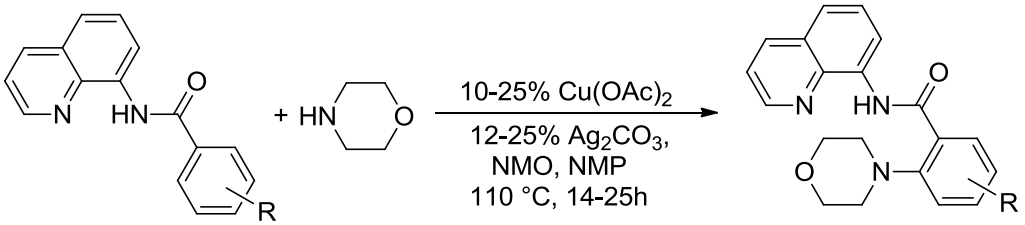
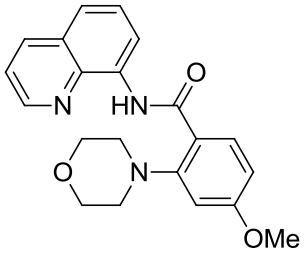
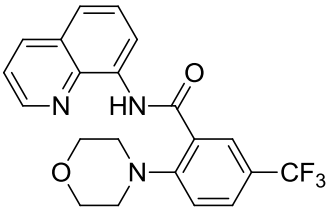
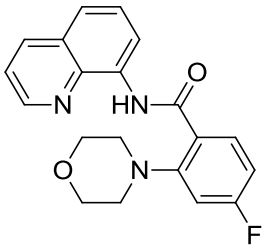
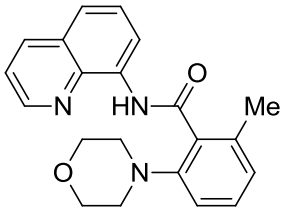
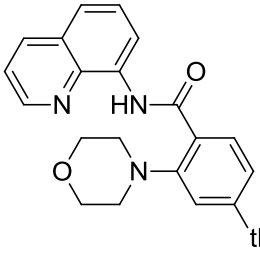
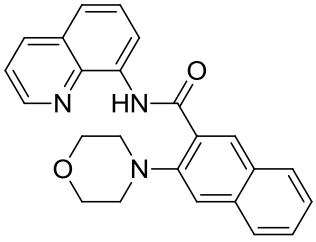
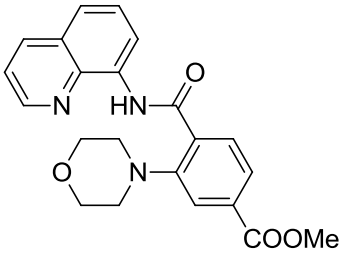
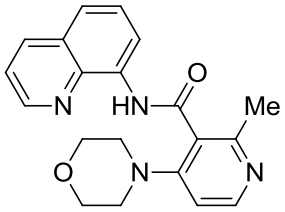
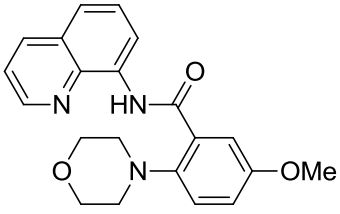
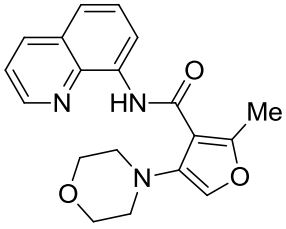


Table 3-6. (*Continued*)

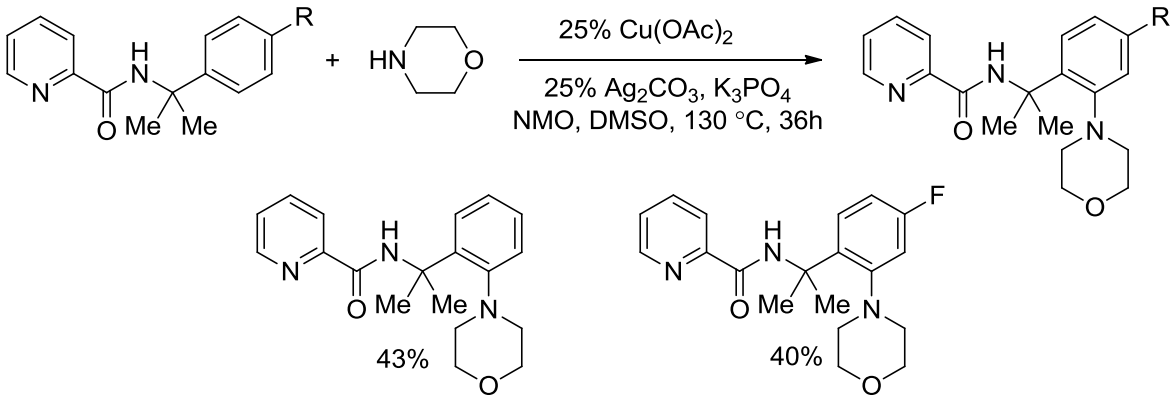
Entry	Product	Yield, %	Entry	Product	yield
1		87	6		67
2		70	7		70
3		81 80 (5 mmol scale)	8		66
4		68	9		56
5		82	10		57

The reaction shows good functional group tolerance. Ethers (entries 1 and 5), fluoride (entry 2), and ester (entry 4) are tolerated. Moreover, the reaction is successful for five- and six-membered ring heterocycles. Pyridine (entry 9) and furan (entry 10) derivatives are aminated in good yields. Substrates possessing electron-withdrawing groups require higher catalyst loading. Reactions can be scaled up at least tenfold with no significant loss of yield (entry 3).

2.1.3 Amination of benzylamine derivatives

Using picolinic acid directing group, benzylamine derivatives can be aminated in moderate yields (Scheme 3-4). Thus, α,α-dimethylbenzylamine and its *p*-fluoroderivative were reacted with morpholine under copper catalysis and the amination products were isolated in moderate yields. The reactions require higher temperatures and longer times compared with aminoquinoline benzamide aminations. In addition, K_3PO_4 base is required.

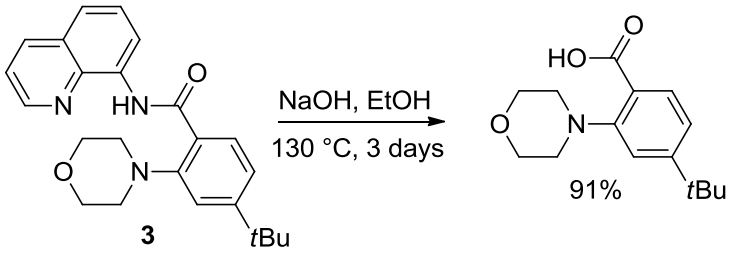
Scheme 3-4. Benzylamine picolinamide amination



2.1.5 Removal of directing group

The 8-aminoquinoline directing group can be effectively removed by base hydrolysis. Thus, heating the aminated product **3** with NaOH in EtOH afforded 4-*t*-butyl-2-morpholinobenzoic acid in high yield (Scheme 3-5).

Scheme 3-5. Removal of 8-aminoquinoline auxiliary



The mechanism of the reactions is unclear at this point. Aryl C-H bond activation by Cu(II) to generate aryl-Cu(III) complex in a highly geometrically constrained system has been reported by Ribas and coworkers.[21] Stahl has demonstrated that aryl-Cu(III) complexes can react with nucleophiles to form C-heteroatom bonds.[22] Thus, Cu(III) intermediates may be involved in the reaction. Nonetheless, mechanistic studies are necessary to understand the mechanism and to further improve the reaction.

III. Conclusion and future work

In conclusion, we have developed methods that allow the direct sulfenylation and amination of β-sp^2 C-H bonds of benzoic acid derivatives and γ-sp^2 C-H bonds of benzylamine derivatives. We also demonstrated that sulfenylation reaction can be used for the direct trifluoromethylsulfenylation of sp^2 C-H bonds. The reactions show high generality and excellent chemoselectivity and functional group tolerance. The utilization of inexpensive copper acetate and removable directing group are significant advantages

that allow broader synthetic utility compared with the existing methods. Additionally, the use of simple amines as nitrogen sources demonstrated the simplicity and efficiency of the method.

IV. Experimental section

4.1 General considerations

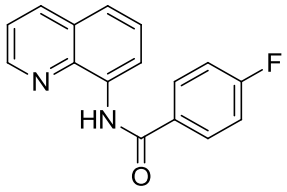
Reactions were performed without special precautions to exclude air or moisture in 2-dram or 1-dram screw-cap vials equipped with Teflon® liners and a stir bar or using a 10 ml Kontes flask. Column chromatography was performed on 60 Å silica gel (Dynamic Adsorbents Inc). Purification by preparative HPLC was performed on a Shimadzu Prominence LC (LC-20AB) equipped with a SPD-20A UV-Vis detector and a Varian Dynamax (250 mm × 21.4 mm) column. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on JEOL ECX-400 and JEOL ECX-500 spectrometers using TMS or residual solvent peak as a standard. Compounds for HRMS were analyzed by positive mode electrospray ionization (ESI) using Agilent 6530 QTOF mass spectrometer in the Mass Spectrometry Facility (MSF) of the Department of Chemistry & Biochemistry of the University of Texas at Austin. IR-spectra were obtained using a ThermoNicolet Avatar 370 FT-IR instrument. Preparative thin layer chromatography was performed on Analtech TLC plates (20 cm × 20 cm, 20 microns).

4.2 Materials

The following starting materials were obtained from commercial sources and were used without further purification: 8-aminoquinoline, 4-fluorobenzoyl chloride, 4-methoxybenzoyl chloride, 4-*t*-butylbenzoyl chloride, 4-bromobenzoyl chloride,

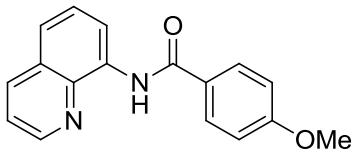
monomethyl terephthalate, 3-methoxybenzoic acid, 2-methylbenzoyl chloride, 2-trifluoromethylbenzoyl chloride, 2-naphthalenecarboxylic acid, 2-methylnicotinic acid, 2-methyl-3-furancarboxylic acid, nicotinic acid, picolinic acid, ethyl chloroformate, cumylamine, 1-(3-methoxyphenyl)ethylamine, 1-amino-1-phenylpropylamine, diphenyl disulfide, di-*t*-butyl disulfide, di-*n*-butyl disulfide, diisopropyl disulfide, dibenzyl disulfide, bis(4-nitrophenyl) disulfide, bis (4-methoxyphenyl) disulfide, potassium bis(trimethylsilyl)amide, methyl iodide, 1-(2,4-dimethylphenyl)ethanamine, 1-(4-fluorophenyl)-1-methylethylamine, morpholine. Bis(trifluoromethyl) disulfide was purchased from Synquest Laboratories. It was transferred to a 50 mL round-bottom flask precooled at 0 °C under air and stored at −20 °C in the refrigerator.

Synthesis of starting amides



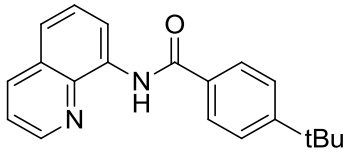
***N*-(4-Fluorobenzoyl)-8-aminoquinoline**: 8-Aminoquinoline (1.44 g, 10 mmol) and triethylamine (1.8 mL, 13 mmol) were dissolved in anhydrous CH_2Cl_2 (30 mL) in a 50 ml round-bottom flask followed by dropwise addition of 4-fluorobenzoyl chloride (2.06 g, 13.2 mmol) through syringe. The reaction mixture was stirred overnight. After completion, the reaction was diluted with CH_2Cl_2 (25 mL), washed by aqueous HCl (15 mL, 1N), $NaHCO_3$ (15 mL of saturated aqueous solution), brine (25 mL), and dried over Na_2SO_4. The organic solvent was removed by evaporation. Purification by column chromatography in toluene/ethyl acetate (20:1) afforded 2.56 g of pure amide (96%) as a

light yellow solid. R_f =0.58 (SiO_2, hexanes/EtOAc, 3:1), mp 117-119 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 10.86 (*s*, 1H) 8.87 (*d*, *J* = 8.0 Hz, 1H) 8.86 – 8.81 (*m*, 1H) 8.20–8.14 (*m*, 1H) 8.12–8.05 (*m*, 2H) 7.61–7.55 (*m*, 1H) 7.55–7.50 (*m*, 1H) 7.49–7.43 (*m*, 1H) 7.24–7.18 (*m*, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) 165.3 (*d*, J^1_{C-F} = 252.8 Hz) 164.6, 148.6, 139.0, 136.7, 134.7, 131.6, 130.0 (*d*, J^3_{C-F} = 8.8 Hz), 128.3, 127.7, 122.1, 122.0, 116.8, 116.1 (*d*, J^2_{C-F} = 21.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -107.4 – -107.6 (*m*). FT-IR (neat, cm^{-1}) υ 3355, 1667, 1541, 1508, 1490, 1227, 1169. HRMS (ESI+): Calculated for $C_{16}H_{12}FN_2O$ $[M+H]^+$ 267.09282, Found 267.09267.

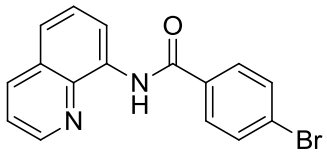


***N*-(4-Methoxybenzoyl)-8-aminoquinoline**: 8-Aminoquinoline (2.17 g, 15 mmol) and triethylamine (2.8 mL, 20 mmol) were dissolved in anhydrous CH_2Cl_2 (40 mL) in a 100 ml round-bottom flask followed by dropwise addition of 4-methoxybenzoyl chloride (3.41 g, 20 mmol) through syringe. The reaction mixture was stirred overnight. After completion, the reaction was diluted with CH_2Cl_2 (50 mL), washed by aqueous HCl (15 mL, 1N), $NaHCO_3$ (15 mL of saturated aqueous solution), brine (25 mL), and dried over Na_2SO_4. The organic solvent was removed by evaporation. Purification by column chromatography in toluene/ethyl acetate (30:1) afforded 3.86 g of pure amide (92%) as a white solid. This compound is known.[23] ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 10.69 (*s*, 1H) 8.93 (*dd*, *J* = 7.4 Hz, *J* = 1.1 Hz, 1H) 8.85 (*dd*, *J* = 4.0 Hz, *J* = 1.7 Hz, 1H) 8.18 (*dd*, *J* =

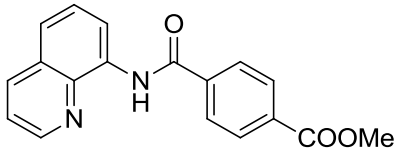
8.6 Hz, *J* = 1.7 Hz, 1H) 8.09–8.04 (*m*, 2H) 7.59 (*t*, *J* = 8.0, 1H) 7.55–7.51 (*m*, 1H) 7.47 (*dd*, *J* = 4.6 Hz, *J* = 8.6 Hz, 1H) 7.07–7.01 (*m*, 2H) 3.89 (*s*, 3H).



***N*-(4-*t*-Butylbenzoyl)-8-aminoquinoline (1)**: 8-Aminoquinoline (1.44 g, 10 mmol) and triethylamine (1.8 mL, 13 mmol) were dissolved in anhydrous CH_2Cl_2 (30 mL) in a 50 ml round-bottom flask followed by dropwise addition of 4-*t*-butylbenzoyl chloride (2.56 g, 13 mmol) through syringe. The reaction mixture was stirred overnight. After completion, the reaction was diluted with CH_2Cl_2 (25 mL), washed by aqueous HCl (15 mL, 1N), $NaHCO_3$ (15 mL of saturated aqueous solution), brine (25 mL), and dried over Na_2SO_4. The organic solvent was removed by evaporation. Purification by column chromatography in toluene/ethyl acetate (50:1 to 40:1) afforded 3.01 g of pure amide (99%) as a white solid. R_f = 0.65 (SiO_2, hexanes/ EtOAc 3:1), mp 71-73 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 10.73 (*s*, 1H) 8.94 (*dd*, *J* = 7.8 Hz, *J* = 1.4 Hz, 1H) 8.85–8.81 (*m*, 1H) 8.19–8.13 (*m*, 1H) 8.06–8.00 (*m*, 2H) 7.61–7.49 (*m*, 4H) 7.48–7.43 (*m*, 1H) 1.38 (*s*, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.8, 155.7, 148.5, 139.1, 136.7, 135.0, 132.7, 128.3, 127.8, 127.5, 126.1, 122.0, 121.8, 116.7, 35.3, 31.5. FT-IR (neat, cm^{-1}) υ 3355, 2949, 1666, 1542, 1513, 1489, 1331, 1269. HRMS (ESI+): Calculated for $C_{20}H_{21}N_2O$ $[M+H]^+$ 305.16484, Found 305.16463.

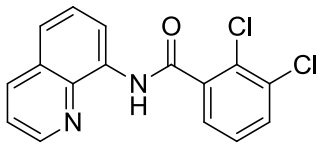


***N*-(4-Bromobenzoyl)-8-aminoquinoline**: This compound was synthesized following the reported procedure.[6b] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 10.72 (*s*, 1H) 8.90 (*dd*, *J* = 7.3 Hz, *J* = 1.4 Hz, 1H) 8.85 (*dd*, *J* = 1.8 Hz, *J* = 4.1 Hz, 1H) 8.19 (*dd*, *J* = 1.8 Hz, *J* = 8.2 Hz, 1H) 7.97–7.92 (*m*, 2H) 7.71–7.65 (*m*, 2H) 7.62–7.53 (*m*, 2H) 7.49 (*dd*, *J* = 8.2 Hz, *J* = 4.1 Hz, 1H).

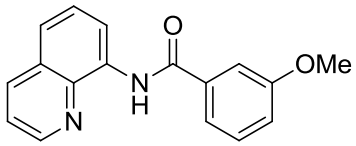


Methyl 4-(quinolin-8-ylcarbamoyl)benzoate: 8-Aminoquinoline (1.44 g, 10 mmol) and triethylamine (1.8 mL, 13 mmol) were dissolved in anhydrous CH_2Cl_2 (30 mL) in a 50 ml round-bottom flask followed by dropwise addition of the acid chloride solution in CH_2Cl_2 (10 mL) through cannula. The acid chloride was prepared from monomethyl terephthalate (2.34 g, 13 mmol).[24] The reaction mixture was stirred overnight. After completion, the reaction was diluted with CH_2Cl_2 (25 mL), washed by aqueous HCl (15 mL, 1N), $NaHCO_3$ (15 mL of saturated aqueous solution), brine (25 mL), and dried over Na_2SO_4. The organic solvent was removed by evaporation. Purification by column chromatography in toluene/ethyl acetate (30:1) afforded 2.56 g of pure amide (84%) as a light yellow solid. This compound is known.[23] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 10.78 (*s*, 1H) 8.92 (*dd*, *J*

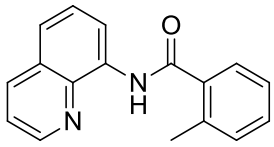
= 6.9 Hz, *J* = 1.4 Hz, 1H) 8.85 (*dd*, *J* = 4.0 Hz, *J* = 1.8 Hz, 1H) 8.24–8.10 (*m*, 5H) 7.64–7.53 (*m*, 2H) 7.48 (*dd*, *J* = 4.1 Hz, *J* = 8.3 Hz, 1H) 3.97 (*s*, 3H).



***N*-(2,3-Dichlorobenzoyl)-8-aminoquinoline**. 8-Aminoquinoline (1.38 g, 9.5 mmol) and triethylamine (3 mL, 21 mmol) were dissolved in anhydrous CH_2Cl_2 (25 mL) in a 50 ml round-bottom flask followed by dropwise addition of 2,3-dichlorobenzoyl chloride (3.0 g, 14 mmol) solution in CH_2Cl_2 (20 mL) through cannula. The reaction mixture was stirred overnight. After completion, the reaction was diluted with CH_2Cl_2 (25 mL), washed by aqueous HCl (15 mL, 1N), $NaHCO_3$ (15 mL of saturated aqueous solution), brine (25 mL), and dried over Na_2SO_4. The organic solvent was removed by evaporation. Purification by column chromatography in hexanes/ethyl acetate (7:1) afforded 2.89 g of pure amide (95%) as a brown solid. R_f = 0.53 (SiO_2, hexanes/EtOAc 3:1), mp 148-149 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 10.36 (*s*, 1H) 8.92 (*dd*, *J* = 6.9 Hz, *J* = 2.3 Hz, 1H) 8.77 (*dd*, *J* = 1.4 Hz, *J* = 4.1 Hz, 1H) 8.17 (*dd*, *J* = 8.2 Hz, *J* = 1.8 Hz, 1H) 7.66–7.54 (*m*, 4H) 7.45 (*dd*, *J* = 8.2 Hz, *J* = 4.1 Hz, 1H) 7.32 (*t*, *J* = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 164.6, 148.7, 138.8, 138.5, 136.7, 134.4, 132.4, 129.9, 128.2, 128.1, 127.9, 127.6, 122.7, 122.1, 117.2. Signal for one carbon could not be located. FT-IR (neat, cm^{-1}) υ 3325, 1673, 1539, 1491, 1410. HRMS (ESI+): Calculated for $C_{16}H_{11}Cl_2N_2O$ $[M+H]^+$ 317.02429, Found 317.02432.

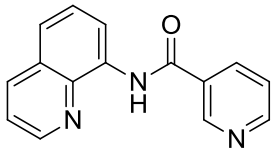


***N*-(3-Methoxybenzoyl)-8-aminoquinoline**: 8-Aminoquinoline (2.17 g, 15 mmol) and triethyl amine (2.8 mL, 20 mmol) were dissolved in anhydrous CH_2Cl_2 (30 mL) in a 100 ml round-bottom flask followed by dropwise addition of 3-methoxybezoyl chloride solution in CH_2Cl_2 (10 mL) through cannula. The acid chloride was prepared from 3-methoxybenzoic acid (3.04 g, 20 mmol).[3] The reaction mixture was stirred overnight. After completion, the reaction was diluted with CH_2Cl_2 (25 mL), washed by aqueous HCl (15 mL, 1N), $NaHCO_3$ (15 mL of saturated aqueous solution), brine (25 mL), and dried over Na_2SO_4. The organic solvent was removed by evaporation. Purification by column chromatography in toluene/ethyl acetate (30:1) afforded 3.86 g of pure amide (92%) as a white solid. This compound is known.[23] ^{1}H NMR (MHz, $CDCl_3$, ppm) δ 10.74 (*s*, 1H) 8.93 (*dd*, *J* = 7.5 Hz, *J* = 1.2 Hz, 1H) 8.85 (*dd*, *J* = 4.0 Hz, *J* = 1.7 Hz, 1H) 8.19 (*dd*, *J* = 1.7 Hz, *J* = 8.0 Hz, 1H) 7.68–7.52 (*m*, 4H) 7.51–7.42 (*m*, 2H) 7.15-7.10 (*m*, 1H) 3.92 (*s*, 3H).



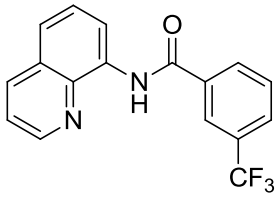
***N*-(2-Methylbenzoyl)-8-aminoquinoline**: 8-Aminoquinoline (1.44 g, 10 mmol) and triethyl amine (1.8 mL, 13 mmol) were dissolved in anhydrous CH_2Cl_2 (30 mL) in a 50 ml round-bottom flask followed by dropwise addition of 2-methylbenzoyl chloride (2.04 g, 13.2 mmol) through syringe. The reaction mixture was stirred overnight. After

completion, the reaction was diluted with CH_2Cl_2 (25 mL), washed by aqueous HCl (15 mL, 1N), $NaHCO_3$ (15 mL of saturated aqueous solution), brine (25 mL), and dried over Na_2SO_4. The organic solvent was removed by evaporation. Purification by column chromatography in toluene/ethyl acetate (40:1) afforded 2.78 g of pure amide (87%) as a white solid. This compound is known.[23] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 10.21 (*s*, 1H) 8.99–8.91 (*m*, 1H) 8.78 (*dd*, *J* = 4.1 Hz, *J* = 1.8 Hz, 1H) 8.19 (*dd*, *J* = 8.2 Hz, *J* = 1.4 Hz, 1H) 7.66–7.72 (*m*, 1H) 7.53–7.64 (*m*, 2H) 7.46 (*dd*, *J* = 8.2 Hz, *J* = 4.1 Hz, 1H) 7.44–7.37 (*m*, 1H) 7.36–7.29 (*m*, 2H) 2.61 (*s*, 3H).

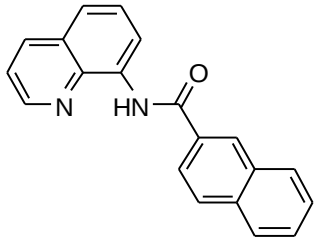


***N*-(Nicotinoyl)-8-aminoquinoline**: 8-Aminoquinoline (1.44 g, 10 mmol) and triethylamine (3.6 mL, 26 mmol) were dissolved in anhydrous CH_2Cl_2 (30 mL) in a 50 ml round-bottom flask followed by dropwise addition of nicotinoyl chloride solution in CH_2Cl_2 (10 mL) through pipette. The acid chloride was prepared from nicotinic acid (1.60 g, 13 mmol).[3] The reaction mixture was stirred overnight. After completion, the reaction was diluted with CH_2Cl_2 (25 mL), washed by aqueous HCl (15 mL, 1N), $NaHCO_3$ (15 mL of saturated aqueous solution), brine (25 mL), and dried over Na_2SO_4. The organic solvent was removed by evaporation. Purification by column chromatography in toluene/ethyl acetate (1:1) afforded 1.28 g of pure amide (52%) as a tan solid. This compound is known.[25] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 10.80 (*s*, 1H) 9.35 (*d*, *J* = 2.3 Hz, 1H) 8.91 (*dd*, *J* = 6.9 Hz, *J* = 2.3 Hz, 1H) 8.86 (*dd*, *J* = 4.1 Hz, *J* = 1.4 Hz, 1H) 8.83 (*dd*, *J* = 4.6 Hz,

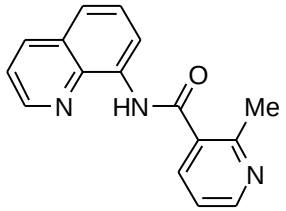
J = 1.4 Hz, 1H) 8.38 (*td*, J_t = 7.8 Hz, J_d = 2.3 Hz, 1H) 8.21 (*dd*, *J* = 8.2 Hz, *J* = 1.4 Hz, 1H) 7.65–7.56 (*m*, 2H) 7.54–7.47 (*m*, 2H).



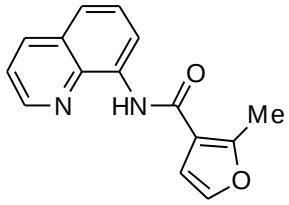
***N*-(3-Trifluoromethylbenzoyl)-8-aminoquinoline**: 8-Aminoquinoline (1.44 g, 10 mmol) and triethyl amine (1.8 mL, 13 mmol) were dissolved in anhydrous CH_2Cl_2 (30 mL) in a 50 ml round-bottom flask followed by dropwise addition of 2-trifluoromethylbenzoyl chloride (2.68 g, 12.8 mmol) through syringe. The reaction mixture was stirred overnight. After completion, the reaction was diluted with CH_2Cl_2 (25 mL), washed by aqueous HCl (15 mL, 1N), $NaHCO_3$ (15 mL of saturated aqueous solution), brine (25 mL), and dried over Na_2SO_4. The organic solvent was removed by evaporation. Purification by column chromatography in toluene/ethyl acetate (20:1) afforded 3.05 g of pure amide (96%) as a white solid. This compound is known.[23] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 10.83 (*s*, 1H) 8.95–8.87 (*m*, 2H) 8.37 (*s*, 1H) 8.33–8.25 (*m*, 2H) 7.87–7.81 (*m*, 1H) 7.73–7.67 (*m*, 1H) 7.67–7.60 (*m*, 2H) 7.56 (*dd*, *J* = 8.1 Hz, *J* = 4.1 Hz, 1H).



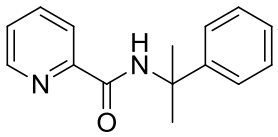
***N*-(2-Naphthalenecarbonyl)-8-aminoquinoline**: 8-Aminoquinoline (1.44 g, 10 mmol) and triethylamine (1.8 mL, 13 mmol) were dissolved in anhydrous CH_2Cl_2 (30 mL) in a 50 ml round-bottom flask followed by dropwise addition of the acid chloride solution in CH_2Cl_2 (10 mL) through cannula. The acid chloride was prepared from 2-naphthalenecarboxylic acid (2.24 g, 13 mmol).[24] The reaction mixture was stirred overnight. After completion, the reaction was diluted with CH_2Cl_2 (25 mL), washed by aqueous HCl (15 mL, 1N), $NaHCO_3$ (15 mL of saturated aqueous solution), brine (25 mL), and dried over Na_2SO_4. The organic solvent was removed by evaporation. Purification by column chromatography in toluene/ethyl acetate (30:1) afforded 2.14 g of pure amide (72%) as a light yellow solid. This compound is known.[23] ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ10.95–10.85 (*s*, 1H) 9.00 (*dd*, *J* = 7.4 Hz, *J* = 1.2 Hz, 1H) 8.89 (*dd*, *J* = 4.0 Hz, *J* = 1.7 Hz, 1H) 8.61 (*s*, 1H), 8.21 (*dd*, *J* = 8.0 Hz, *J* = 1.7 Hz, 1H) 8.14 (*dd*, *J* = 8.6 Hz, *J* = 1.7 Hz, 1H) 8.07–8.04 (*m*, 1H) 8.00 (*d*, *J* = 8.6 Hz, 1H) 7.95–7.91 (*m*, 1H) 7.65–7.55 (*m*, 4H) 7.50 (*dd*, *J* = 4.0 Hz, *J* = 8.0 Hz, 1H).



***N*-(2-methylnicotinoyl)-8-aminoquinoline**: 8-Aminoquinoline (1.44 g, 10 mmol), 2-methylnicotinic acid (2.74 g, 20 mmol), EDC (2.10 g, 11 mmol), and DMAP (2.44 g, 20 mmol) were placed in a 100 mL round-bottom flask. Anhydrous CH_2Cl_2 (30 mL) was added at room temperature. Reaction mixture was allowed to stir for 48 hours. Reaction mixture was dry-sorbed on the silica gel and purified using column chromatography using hexanes/ethyl acetate (1:1 to 1:5) affording product as a tan solid (656 mg, 25%). R_f = 0.54 (SiO_2, toluene/EtOAc, 1:3), mp 138–140 °C (from hexanes/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 10.31–10.199 (*s*, 1H) 8.95–8.90 (*m*, 1H) 8.79 (*dd*, *J* = 4.0 Hz, *J* = 1.7 Hz, 1H) 8.65 (*dd*, *J* = 4.6 Hz, *J* = 1.7 Hz, 1H) 8.21 (*dd*, *J* = 8.6 Hz, *J* = 1.7 Hz, 1H) 7.98 (*dd*, *J* = 7.6 Hz, *J* = 1.7 Hz, 1H) 7.64–7.57 (*m*, 2H) 7.48 (*dd*, *J* = 8.6 Hz, *J* = 4.6 Hz, 1H) 7.29 (*dd*, *J* = 7.5 Hz, *J* = 4.6 Hz, 1H) 2.85 (*s*, 3H) . ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 166.9, 157.0, 150.9, 148.7, 138.8, 136.8, 135.5, 134.6, 132.3, 128.3, 127.7, 122.5, 122.1, 121.3, 117.0, 23.8. FT-IR (neat, cm^{-1}) υ 3352, 1678, 1533, 1490, 1430. HRMS (ESI+): Calculated for $C_{16}H_{13}N_3O$ $[M]^+$ 263.1059 Found 263.1061.

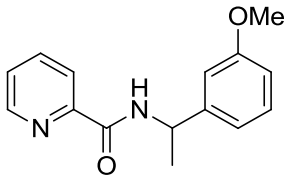


***N*-(2-Methyl-3-furanoyl)-8-aminoquinoline**: 8-Aminoquinoline (1.44 g, 10 mmol), 2-methyl-3-furancarboxylic acid (2.52 g, 20 mmol), EDC (2.10 g, 11 mmol), and DMAP (2.44 g, 20 mmol) were placed in a 100 mL round-bottom flask. Anhydrous CH_2Cl_2 (30 mL) was added at room temperature. Reaction mixture was allowed to stir for 48 hours. Reaction mixture was dry-sorbed on the silica gel and purified using column chromatography using toluene/ethyl acetate (30:1) affording product as a white solid (1.46 g, 58%). R_f = 0.54 (SiO_2, hexanes/EtOAc, 3:1), mp 92–94 °C (from hexanes/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 10.36–10.21 (*s*, 1H) 8.86 (*dd*, *J* = 7.4 Hz, *J* = 1.1 Hz, 1H) 8.82 (*dd*, *J* = 4.0 Hz, *J* = 1.7 Hz, 1H) 8.16 (*dd*, *J* = 8.6 Hz, *J* = 1.7 Hz, 1H) 7.59–7.53 (*m*, 1H) 7.53–7.48 (*m*, 1H) 7.45 (*dd*, *J* = 8.0 Hz, *J* = 4.0 Hz, 1H) 7.35 (*d*, *J* = 2.3 Hz, 1H) 6.82 (*d*, *J* = 2.3 Hz, 1H) 2.74 (*s*, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 162.4, 157.9, 148.5, 140.8, 138.9, 136.7, 135.0, 128.3, 127.8, 122.0, 121.7, 117.0, 116.5, 109.2, 14.1. FT-IR (neat, cm^{-1}) υ 3352, 1661, 1534, 1520, 1492. HRMS (ESI+): Calculated for $C_{15}H_{12}N_2O_2$ $[M]^+$ 252.0899, Found 252.0901.



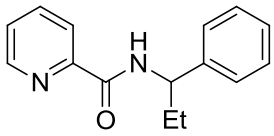
***N*-(1-Methyl-1-phenylethyl)picolinamide**: Picolinic acid (2.15 g, 17.5 mmol) and triethylamine (5 mL, 35 mmol) were dissolved in CH_2Cl_2 (40 mL) in a 100 mL round-

bottom flask. The resulting mixture was cooled to 0 °C followed by dropwise addition of ethyl chloroformate (1.7 mL, 17.5 mmol). The solution was stirred for 30 minutes followed by dropwise addition of cumylamine (1.36 g, 10 mmol) via syringe. The suspension was stirred for 1 hour. The reaction was warmed up to room temperature and stirred for another 24 hours. After completion, water (50 ml) was added to the reaction mixture and the layers were separated. The aqueous layer was extracted by CH_2Cl_2 (2 x 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to remove the solvent. Purification by column choromatography in hexanes/ethyl acetate (2:1) gave 2.11 g of the desired amide (88%) as a colorless oil. R_f = 0.38 (SiO_2, hexanes/EtOAc 3:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.58–8.53(*m*, 1H) 8.42–8.53 (*m*, 1H) 8.14 (*d*, *J* = 7.8 Hz, 1H) 7.83 (*td*, J_t = 7.8 Hz, J_d = 1.8 Hz, 1H) 7.50–7.45 (*m*, 2H) 7.44–7.39 (*m*, 1H) 7.37–7.30 (*m*, 2H) 7.27–7.21 (*m*, 1H) 1.85 (*s*, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.5, 150.8, 148.1, 147.1, 137.7, 128.7, 127.0, 126.3, 125.1, 122.2, 55.9, 29.5. FT-IR (neat, cm^{-1}) υ 3374, 1681, 1515, 1463, 1447, 1433. HRMS (ESI+): Calculated for $C_{15}H_{16}N_2NaO$ $[M+Na]^+$ 263.11548, Found 263.11577.



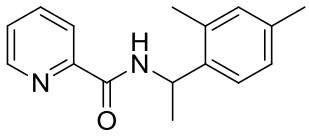
***N*-(1-(3-Methoxyphenyl)ethyl)picolinamide**: Picolinic acid (2.15 g, 17.5 mmol) and triethylamine (5 mL, 35 mmol) were dissolved in CH_2Cl_2 (40 mL) in a 100 mL round-bottom flask. The resulting mixture was cooled to 0 °C followed by dropwise addition of ethyl chloroformate (1.7 mL, 17.5 mmol). The solution was stirred for 30 minutes

followed by dropwise addition of 1-(3-methoxyphenyl)ethylamine (1.55 g, 10.2 mmol) via syringe. The suspension was stirred for 1 hour. The reaction was warmed up to room temperature and stirred for another 24 hours. After completion, water (50 ml) was added to the reaction mixture and the layers were separated. The aqueous layer was extracted by CH_2Cl_2 (2 x 25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to remove the solvent. Purification by column choromatography in hexanes/ethyl acetate (2:1) gave 2.34 g of the desired amide (89%) as a colorless oil. R_f = 0.25 (SiO_2, hexanes/EtOAc 3:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.55–8.50 (*m*, 1H) 8.40–8.30 (*m*, 1H) 8.19 (*dt*, J_d = 7.8 Hz, J_t = 0.9 Hz, 1H) 7.82 (*td*, J_t = 7.8 Hz, J_d = 1.4 Hz, 1H) 7.43–7.37 (*m*, 1H) 7.27 (*t*, *J* = 7.8 Hz, 1H) 7.03–6.98 (*m*, 1H) 6,95 (*t*, *J* = 2.3 Hz, 1H) 6.82–6.78 (*m*, 1H) 5.30 (*quintet*, *J* = 6.9 Hz, 1H) 3.79 (*s*, 3H) 1.61 (*d*, *J* = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.6, 160.0, 150.1, 148.3, 145.2, 137.6, 130.0, 126.4, 122.5, 118.7, 112.7, 112.5, 55.4, 49.1, 22.4. FT-IR (neat, cm^{-1}) υ 3392, 1671, 1514, 1489, 1465, 1434, 1257, 1043. HRMS (ESI+): Calculated for $C_{15}H_{17}N_2O_2$ $[M+H]^+$ 257.12845, Found 257.12838.



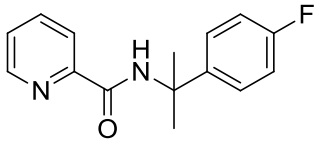
***N*-(1-Phenylpropyl)picolinamide:** Ethyl picolinate (1.10 g, 7.3 mmol) and 1-phenylpropylamine (1.01 g, 7.3 mmol) were placed in the 2-dram vial equipped with a magnetic stir bar. Reaction mixture was purged with nitrogen, capped and placed in the oil bath preheated to 130°C. After 20 h, mixture was allowed to cool to RT and filtered through the plug of silica gel using hexanes/ CH_2Cl_2 (1:1) as the eluent. After removal of

the solvent 1.16 g (66%) of the product was obtained as a white solid. This compound is known.[26] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.55 – 8.51 (*m*, 1H), 8.36 (*br d*, *J* = 7.8Hz, 1H), 8.20 – 8.15 (*m*, 1H), 7.84 – 7.77 (*m*, 1H), 7.42 – 7.30 (*m*, 5H), 7.27 – 7.21 (*m*, 1H), 5.12 – 5.03 (*m*, 1H), 2.04 – 1.89 (*m*, 2H), 1.00-0.92 (*m*, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.8, 150.2, 148.2, 142.5, 137.6, 128.9, 127.5, 126.9, 126.4, 122.5, 55.2, 29.7, 11.1.



***N*-(1-(2,4-Dimethylphenyl)ethyl)picolinamide:** Picolinic acid (0.615 g, 5.0 mmol) and triethylamine (1 mL, 7.1 mmol) were placed in the 25 mL flask, followed by addition of dry CH_2Cl_2 (5 mL). The resulting mixture was cooled to 0 °C followed by dropwise addition of ethyl chloroformate (0.54 g, 5.0 mmol). The solution was stirred for 30 minutes at 0 °C, followed by addition of 1-(2,4-dimethylphenyl)ethanamine (0.500 g, 3.35 mmol) in one portion via syringe. The suspension was allowed to warm up to the room temperature and stirred overnight. Reaction mixture was dry-absorbed on the silica gel and subjected to the column chromatography eluting with mixture CH_2Cl_2/hexanes (gradient 50% to 80% of CH_2Cl_2) affording 0.82 g (96%) of the product as a colorless thick oil. R_f = 0.38 (SiO_2, hexanes/EtOAc 3:1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.52 – 8.49 (*m*, 1H), 8.29 (*br d*, *J* = 8.0 Hz, 1H), 8.21 – 8.17 (*m*, 1H), 7.80 (*dt*, J_d = 1.7 Hz, J_t = 8.0 Hz, 1H),7.40 – 7.35 (*m*, 1H), 7.32 (*d*, *J* = 8.0 Hz, 1H), 7.06 – 6.99 (m, 2H), 5.52 (*quartet*, *J* = 6.9 Hz, 1H), 2.41 (*s*, 3H) 2.30 (*s*, 3H), 1.60 (*d*, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz,

$CDCl_3$, ppm) δ 163.2, 149.9, 148.0, 138.3, 137.4, 136.8, 135.6, 131.5, 127.0, 126.2, 125.0, 122.2, 45.3, 21.4, 21.0, 19.2. FT-IR (neat, cm^{-1}) υ 3383, 1617, 1512, 1464, 1433. HRMS (ESI+): Calculated for $C_{16}H_{19}N_2O$ $[M+H]^+$ 255.14919, Found 255.14902.



***N*-(1-Methyl-1-(4-fluorophenyl)ethyl)picolinamide:** Picolinic acid (1.23 g, 10 mmol) and triethylamine (3 mL, 20 mmol) were placed in a 50 mL flask, followed addition of dry CH_2Cl_2 (30 mL). The resulting mixture was cooled to 0 °C followed by dropwise addition of ethyl chloroformate (1.14 g, 10 mmol). The solution was stirred for 30 minutes at 0 °C. After that, 1-(4-fluorophenyl)-1-methylethylamine (1.0 g, 6.5 mmol) was added in one portion via syringe and the suspension was allowed to warm up to the room temperature and stirred overnight. Reaction mixture was dry-absorbed on the silica gel and subjected to the column chromatography first eluting with pure CH_2Cl_2 and then with mixture of hexanes/EtOAc (9:1) affording 1.66 g (98%) of the product as a yellowish thick oil. R_f = 0.38 (SiO_2, hexanes/EtOAc 3:1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.57 – 8.52 (*m*, 1H), 8.46 (*br s*, 1H), 8.12 (*d*, *J* = 8.0 Hz, 1H), 8.85 – 7.78 (*m*, 1H), 7.46 – 7.36 (*m*, 3H), 7.03 – 6.96 (*m*, 2H), 1.82 (*s*, 6H).^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 163.4, 161.7 (*d*, J_{C-F} = 244.7 Hz), 150.6, 148.1, 142.8, 137.6, 126.8 (*d*, J_{C-F} = 8.4 Hz), 126.4, 122.2, 115.3 (*d*, J_{C-F} = 21.6 Hz), 55.3, 29.6. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -117.9 – -118.0 (m, 1F). FT-IR (neat, cm^{-1}) υ 3380, 1681, 1512, 1463, 1433, 1230, 1164. HRMS (ESI+): Calculated for $C_{15}H_{15}FN_2NaO$ $[M+Na]^+$ 281.10606, Found 281.10609.

4.3 Copper-promoted sulfenylation of sp^2 C-H bonds

4.3.1 Optimization for trifluoromethylsulfenylation of benzoic acid amides

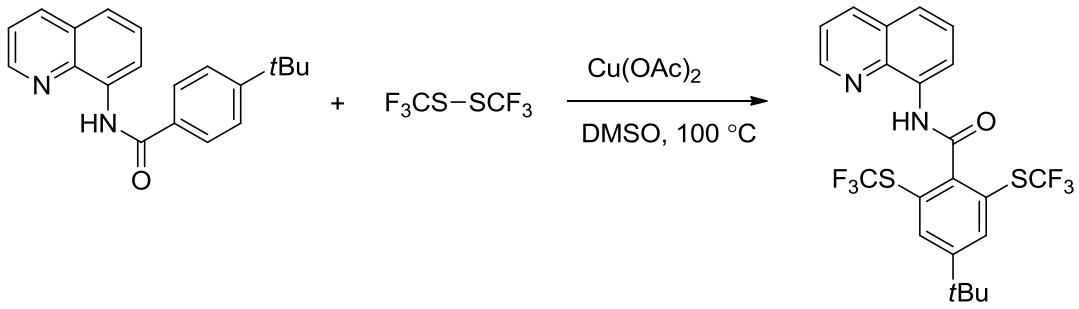
Optimization of the amount of copper catalyst in trifluoromethylsulfenylation reactions

General Procedure: A 10 mL Kontes flask equipped with a stir bar was charged with *N*-(4-*t*-butylbenzoyl)-8-aminoquinoline (0.25 mmol, 1 equiv) and $Cu(OAc)_2$. Subsequently, cold bis(trifluoromethyl) disulfide (0.06 mL, 0.45 mmol, 1.8 equiv.) and DMSO (1 mL) were added via syringe. The resulting mixture was stirred at 100 °C for 7 h 40 minutes. After completion, the mixture was cooled to room temperature and diluted with ethyl acetate (5 mL). The solution was filtered through a pad of silicagel, and washed with ethyl acetate (2 × 25 mL). The filtrate was concentrated under reduced pressure and yield of reaction was determined by ^{19}F NMR using trifluoromethylbenzene as an internal standard.

Trifluoromethylsulfenylation reaction under argon atmosphere (entry 5, Table 3-1): A 10 mL Kontes flask equipped with a stir bar was charged with *N*-(4-*t*-butylbenzoyl)-8-aminoquinoline (76 mg, 0.25 mmol, 1 equiv) and $Cu(OAc)_2$ (23 mg, 0.13 mmol, 0.5 equiv.). The flask was evacuated and filled with argon. Subsequently, cold bis(trifluoromethyl) disulfide (0.07 mL, 0.52 mmol, 2.1 equiv.) and DMSO (1 mL) were added via syringe under argon atmosphere. The resulting mixture was stirred at 100 °C for 8h. After completion, the mixture was cooled to room temperature and diluted with ethyl acetate (5 mL). The solution was filtered through a pad of silicagel, and washed with ethyl

acetate (2 × 25 mL). The yield of reaction was determined by ^{19}F NMR using trifluoromethoxybenzene as an internal standard.

Table 3-1. Optimization for amount of copper catalyst in trifluoromethylsulfenylation reactions



Entry	$Cu(OAc)_2$ (equiv.)	% yield
1	1 equiv.	61
2	0.8 equiv.	70
3	0.5 equiv.	74
4	0.2 equiv.	44
5[a]	0.5 equiv.	67

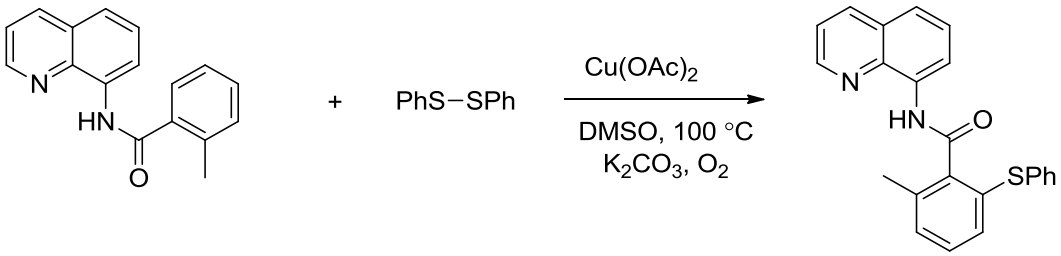
[a] Reaction was run under Ar

Optimization of phenylsulfenylation reactions

General Procedure: To a 2-dram vial equipped with a stir bar was added *N*-(2-methylbenzoyl)-8-aminoquinoline (0.25 mmol, 1 equiv.), $Cu(OAc)_2$, diphenyl disulfide (2 equiv), and DMSO (1 mL). For entry 6 and 7, Table 3-7, K_2CO_3 was added to the reaction mixture before the addition of diphenyl disulfide. For entry 7, Table 3-7, the vial was filled with O_2 before heating. The resulting mixture was stirred at 100 °C for 8 hours.

After completion, the mixture was cooled to room temperature and diluted by ethyl acetate (5 mL). The solution was filtered through a pad of silica gel and washed with ethyl acetate (2 × 25 mL). The filtrate was concentrated under reduced pressure and percent yield was determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

Table 3-7. Optimization of reaction conditions for phenylsulfenylation reactions

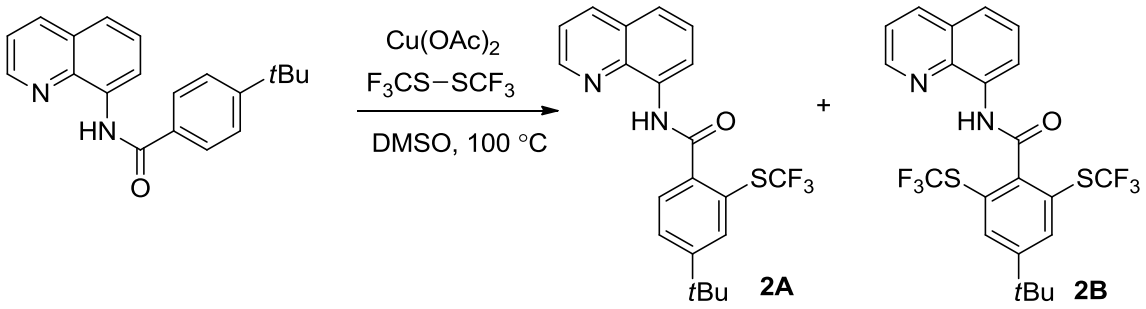


$Cu(OAc)_2$ (equiv.)	K_2CO_3 (equiv.)	Oxidant	% yield
1.2	_	_	96
1.0	_	_	71
0.8	_	_	60
0.5	_	_	77
0.2	_	_	< 5
0.5	1	_	98
0.5	1	O_2	60

Selectivity between mono-trifluoromethylsulfenylated and di-trifluoromethylsulfenylated products Table 3-8): A 10 mL Kontes flask equipped with a stir bar was charged with *N*-(4-*t*-butylbenzoyl)-8-aminoquinoline (0.25 mmol, 1 equiv) and $Cu(OAc)_2$. Subsequently, cold bis(trifluoromethyl) disulfide (0.03 mL, 0.22 mmol, 0.9

equiv.) and DMSO (1 mL) were added via syringe. The resulting mixture was stirred at 100 °C for 5 h. After completion, the mixture was cooled to room temperature and diluted with ethyl acetate (5 mL). The solution was filtered through a pad of silica gel, and washed with ethyl acetate (2 × 25 mL). The yield of reactions was determined by ^{19}F NMR using trifluoromethoxybenzene as an internal standard.

Table 3-8. Selectivity between mono-trifluoromethylsulfenylated and di-trifluoromethylsulfenylated products.



$Cu(OAc)_2$ equiv.	% yield*	2A:2B
0.3	46	1:1.1
0.2	27	2:1
0.1	22	2.6:1

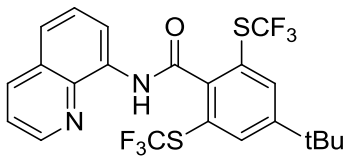
*Yield is the combined yield of products 2A and 2B.

Trifluoromethylsulfenylation of *N*-(1-methyl-1(4-fluorophenyl)ethyl)picolinamide: To a 10 mL Kontes flask equipped with a stir bar was added *N*-(1-methyl-1(4-fluorophenyl)ethyl)picolinamide (66 mg, 0.26 mmol), $Cu(OAc)_2$ (23 mg, 0.13 mmol) followed by DMSO (0.5 mL). Subsequently, cold bis(trifluoromethyl) disulfide (0.13 mL, 0.98 mmol) and DMSO (0.5 mL) were added visa syringe. The resulting mixture was stirred at 120 °C for 8 hours. After completion, the mixture was cooled to room

temperature and diluted with ethyl acetate (5 mL). The solution was filtered through a pad of silica gel and solid phase was washed with ethyl acetate (2 × 25 mL). Measuring the yield of reaction by ^{19}F NMR with trifluoromethoxybenzene as an internal standard gave 5% yield of the product.

4.3.2 Trifluoromethylsulfenylation of benzoic acid amides

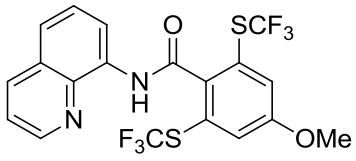
General procedure: To a 10 mL Kontes flask equipped with a stir bar was added amide (1 equiv), $Cu(OAc)_2$ (0.5 equiv), followed by bis(trifluoromethyl) disulfide (2-2.5 equiv) and DMSO via syringe. The resulting mixture was stirred at 90 °C – 110 °C for the indicated time. After completion, the mixture was cooled down to room temperature and diluted with ethyl acetate (5 mL). The solution was filtered through a pad of cellite®, and solid phase was washed with ethyl acetate (2 × 25 mL). The filtrate was concentrated under reduced pressure. Purification by column chromatography provided the desired product.



***N*-(2,6-Di(trifluoromethylthio)-4-*t*-butylbenzoyl)-8-aminoquinoline (Table 3-2, entry 1)**: To a 10 mL Kontes flask equipped with a stir bar was added *N*-(4-*t*-butylbenzoyl)-8-aminoquinoline (76 mg, 0.25 mmol), $Cu(OAc)_2$ (23 mg, 0.13 mmol), followed by bis(trifluoromethyl)disulfide (66 μL, 0.50 mmol) and DMSO (1 mL) via syringe. The resulting mixture was stirred at 100 °C for 5 hours. After work up following the general procedure, purification by column chromatography using CH_2Cl_2/hexanes (gradient 20%

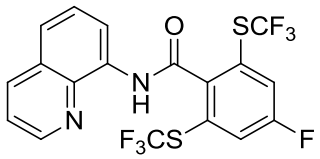
to 70% CH_2Cl_2) as an eluent afforded 96 mg of the desired product (76% yield). R_f =0.69 (SiO_2, hexanes/EtOAc, 3:1), mp 115-116 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 10.1 (*s*, 1H) 8.94 (*dd*, *J* = 6.3 Hz, *J* = 2.3 Hz, 1H) 8.73 (*dd*, *J* = 4.0 Hz, *J* = 1.7 Hz, 1H) 8.19 (*dd*, *J* = 8.6 Hz, *J* = 1.7 Hz, 1H) 7.94 (*s*, 2H) 7.59–7.66 (*m*, 2H) 7.45 (*dd*, *J* = 8.0 Hz, *J* = 4.0 Hz, 1H) 1.41 (*s*, 9H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) 164.1, 154.9, 148.7, 147.4, 138.8, 137.9, 136.6, 134.2, 129.4 (*quartet*, $J_{C\text{-}F}$ = 309.4 Hz) 128.3, 127.6, 123.5, 122.9, 122.1, 117.4, 35.5, 31.2. ^{19}F NMR (470 MHz, $CDCl_3$, ppm) δ -41.6 (*s*). FT-IR (neat, cm^{-1}) υ 3346,1682, 1529, 1488, 1106. HRMS (ESI+): Calculated for $C_{22}H_{19}F_6N_2OS_2$ $[M+H]^+$ 505.08375, Found 505.08378.

A large scale (5 mmol) synthesis: Reaction was performed in a 120 ml pressure flask according to the general procedure by increasing the amount of the reagents and solvent by a factor of 20. Column chromatography on silica gel afforded 1.54 g (61%) of the product.



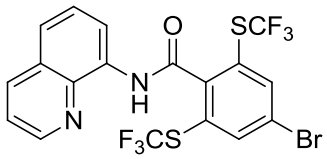
***N*-(2,6-Di(trifluoromethylthio)4-methoxybenzoyl)-8-aminoquinoline (Table 3-2, entry 2)**: To a 10 mL Kontes flask equipped with a stir bar was added *N*-(4-methoxybenzoyl)-8-aminoquinoline (70 mg, 0.25 mmol), $Cu(OAc)_2$ (23 mg, 0.13 mmol), followed by bis(trifluoromethyl) disulfide (0.06 mL, 0.45 mmol) and DMSO (1 mL) via syringe. The resulting mixture was stirred at 100 °C for 5 hours 45 minutes. After work up following the general procedure, purification by column chromatography in toluene/ethyl acetate

(gradient toluene to T/E 50:1) gave 81 mg of the product as a white solid (67%). R_f = 0.51 (SiO_2, hexanes/EtOAc, 3:1), mp 114-115 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 10.09 (*s*, 1H) 8.93 (*dd*, *J* = 5.9 Hz, *J* = 2.3 Hz, 1H) 8.73 (*dd*, *J* = 1.4 Hz, *J* = 4.1 Hz, 1H) 8.19 (*dd*, *J* = 1.4 Hz, *J* = 8.2 Hz, 1H) 7.66–7.58 (*m*, 2H) 7.49–7.42 (*m*, 3H) 3.93 (*s*, 3H) . ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.9, 160.2, 148.7, 142.3, 138.8, 136.6, 134.2, 129.3 (*quartet*, $J_{C\text{-}F}$ = 309.6 Hz) 128.3, 127.6, 125.3, 125.0, 122.8, 122.1, 117.3, 56.4. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -41.3 (*s*). FT-IR (neat, cm^{-1}) υ 3319, 1667, 1534, 1290, 1247, 1142, 1101. HRMS (ESI+): Calculated for $C_{19}H_{13}F_6N_2O_2S_2$ $[M+H]^+$ 479.03171, Found 479.03234.



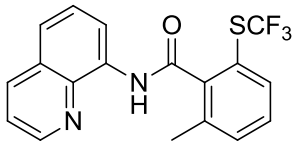
***N*-(2,6-Di(trifluoromethylthio)-4-fluorobenzoyl)-8-aminoquinoline (Table 3-2, entry 3)**: To a 10 mL Kontes flask equipped with a stir bar was added *N*-(4-fluorobenzoyl)-8-aminoquinoline (67 mg, 0.25 mmol), $Cu(OAc)_2$ (23 mg, 0.13 mmol), followed by bis(trifluoromethyl) disulfide (0.06 mL, 0.45 mmol) and DMSO (1 mL) via syringe. The resulting mixture was stirred at 100 °C for 5 hours. After work up following the general procedure, purification by column chromatography in toluene/ethyl acetate (gradient toluene to T/E 50:1) gave 86 mg of a white solid product (73%). R_f = 0.63 (SiO_2, hexanes/EtOAc, 3:1), mp 123-124 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 10.13 (*s*, 1H) 8.94–8.87 (*m*, 1H) 8.74 (*dd*, *J* = 4.1 Hz, *J* = 1.8 Hz, 1H) 8.20 (*dd*, *J* = 8.2 Hz, *J* = 1.4 Hz, 1H) 7.69 (*d*, *J* = 7.8 Hz, 2H) 7.63 (*d*, *J* = 4.6 Hz, 2H) 7.47 (*dd*, *J* = 8.2 Hz, *J* = 4.6 Hz,

1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 163.0, 161.8 (*d*, J^1_{C-F} = 258.3 Hz) 148.8, 145.9, 138.8, 136.6, 134.0, 129.0 (*quartet*, $J_{C\text{-}F}$ = 310 Hz) 128.3, 127.6, 126.8 (*d*, J^2_{C-F} = 22.8 Hz) 126.2 (*d*, J^3_{C-F} = 8.2 Hz) 123.2, 122.2, 117.5. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -41.1 (*s*), -106.6 – -106.7 (*m*). FT-IR (neat, cm^{-1}) υ 3322, 3304, 1671, 1580, 1535, 1130, 1100. HRMS (ESI+): Calculated for $C_{18}H_{10}F_7N_2OS_2$ $[M+H]^+$ 467.01173, Found 467.01210.

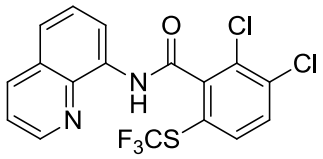


***N*-(2,6-Di(trifluoromethylthio)-4-bromobenzoyl)-8-aminoquinoline (Table 3-2, entry 4)**: To a 10 mL Kontes flask equipped with a stir bar was added *N*-(4-bromobenzoyl)-8-aminoquinoline (82 mg, 0.25 mmol), $Cu(OAc)_2$ (23 mg, 0.13 mmol), followed by bis(trifluoromethyl) disulfide (0.06 mL, 0.45 mmol) and DMSO (1 mL) via syringe. The resulting mixture was stirred at 100 °C for 5 hours. After work up following the general procedure, purification by column chromatography in toluene/ethyl acetate (gradient toluene to T/E 50:1) gave 92 mg of a white solid product (70%). R_f = 0.63 (SiO_2, hexanes/EtOAc, 3:1), mp 154-156 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ10.13 (*s*, 1H) 8.86–8.93 (*m*, 1H) 8.73 (*dd*, *J* = 4.1 Hz, *J* = 1.4 Hz, 1H) 8.20 (*dd*, *J* = 8.2 Hz, *J* = 1.8 Hz, 1H) 8.10 (*s*, 2H) 7.66–7.60 (*m*, 2H) 7.47 (*dd*, *J* = 8.2 Hz, *J* = 4.1 Hz, 1H) . ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 163.0, 148.8, 148.5, 142.4, 138.8, 136.7, 133.9, 129.0 (*quartet*, $J_{C\text{-}F}$ = 309.8 Hz) 128.3, 127.6, 125.7, 124.1, 123.2, 122.2, 117.5. ^{19}F NMR (376 MHz, $CDCl_3$,

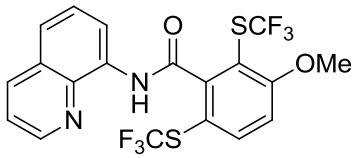
ppm) δ -41.1 (*s*). FT-IR (neat, cm^{-1}) υ 3304, 1669, 1534, 1488, 1157, 1124, 1101. HRMS (ESI+): Calculated for $C_{18}H_{10}BrF_6N_2OS_2$ $[M+H]^+$ 526.93166, Found 526.93224.



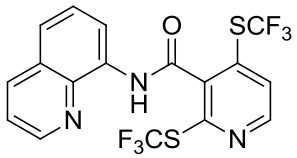
***N*-(6-Methyl-2-trifluoromethylthiobenzoyl)-8-aminoquinoline (Table 3-2, entry 5)**: To a 10 mL Kontes flask equipped with a stir bar was added *N*-(2-methylbenzoyl)-8-aminoquinoline (66 mg, 0.25 mmol) and $Cu(OAc)_2$ (23 mg, 0.13 mmol), followed by bis(trifluoromethyl) disulfide (0.08 mL, 0.59 mmol) and DMSO (1 mL) via syringe. The resulting mixture was stirred at 100 °C for 9 hours. After work up following the general procedure, purification by column chromatography in hexanes/ethyl acetate (10:1 to 5:1) followed by HPLC in hexanes/ethyl acetate (5:1) for the contaminated fractions gave 57 mg of a light yellow solid product (63%). R_f = 0.51 (SiO_2, hexanes/EtOAc, 3:1), mp 114-116 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 10.01 (*s*, 1H) 8.98 (*dd*, *J* = 7.3 Hz, *J* = 2.3 Hz, 1H) 8.74 (*dd*, *J* = 4.2 Hz, *J* = 1.8 Hz, 1H) 8.19 (*dd*, *J* = 8.2 Hz, *J* = 1.4 Hz, 1H) 7.68–7.56 (*m*, 3H) 7.48–7.38 (*m*, 3H) 2.49 (*s*, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) 166.4, 148.7, 144.3, 138.8, 137.1, 136.7, 135.2, 134.4, 133.5, 130.2, 129.4 (*quartet*, *J* = 308.9 Hz) 128.3, 127.7, 122.7, 122.1, 121.7, 117.3, 20.0. ^{19}F NMR (470 MHz, $CDCl_3$, ppm) δ -41.83 (*s*). FT-IR (neat, cm^{-1}) υ 3349, 1677, 1524, 1486, 1157, 1127, 1109. HRMS (ESI+): Calculated for $C_{18}H_{14}F_3N_2OS$ $[M+H]^+$ 363.07734, Found 363.07717.



***N*-(5,6-Dichloro-2-(trifluoromethylthio)benzoyl)-8-aminoquinoline (Table 3-2, entry 6)**: To a 10 mL Kontes flask equipped with a stir bar was added *N*-(2,3-dichlorobenzoyl)-8-aminoquinoline (79 mg, 0.25 mmol) and $Cu(OAc)_2$ (23 mg, 0.13 mmol), followed by bis(trifluoromethyl) disulfide (0.06 mL, 0.45 mmol) and DMSO (1 mL) via syringe. The resulting mixture was stirred at 110 °C for 5 hours. After work up following the general procedure, purification by column chromatography in toluene/ethyl acetate (gradient toluene to T/E 50:1) gave 61 mg of a white solid product (59%). R_f = 0.57 (SiO_2, hexanes/EtOAc, 3:1), mp 157-159 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 10.10 (*s*, 1H) 8.96–8.90 (*m*, 1H) 8.76 (*dd*, *J* = 4.1 Hz, *J* = 1.4 Hz, 1H) 8.21 (*dd*, *J* = 8.7 Hz, *J* = 1.8 Hz, 1H) 7.72–7.60 (*m*, 4H) 7.47 (*dd*, *J* = 8.2 Hz, *J* = 4.1 Hz, 1H). ^{13}C NMR (MHz, $CDCl_3$, ppm) 162.7, 148.8, 144.8, 138.8, 137.5, 136.7, 136.6, 134.0, 131.8, 131.6, 129.1 (*quartet*, $J_{C\text{-}F}$ = 305.11 Hz) 128.3, 127.7, 123.1, 122.3, 122.2, 117.6. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -41.5 (*s*). FT-IR (neat, cm^{-1}) υ 3340, 3316, 1681, 1525, 1487, 1175, 1161, 1141, 1112, 1092. HRMS (ESI+): Calculated for $C_{17}H_{10}Cl_2F_3N_2OS$ $[M+H]^+$ 416.98375, Found 416.98391.



***N*-(2,6-Di(trifluoromethylthio)3-methoxybenzoyl)-8-aminoquinoline (Table 3-2, entry 7)**: To a 10 mL Kontes flask equipped with a stir bar was added *N*-(3-methoxybenzoyl)-8-aminoquinoline (71 mg, 0.25 mmol) and $Cu(OAc)_2$ (23 mg, 0.13 mmol), followed by bis(trifluoromethyl) disulfide (0.06 mL, 0.45 mmol) and DMSO (1 mL) via syringe. The resulting mixture was stirred at 100 °C for 4 hours. After work up following the general procedure, purification by column chromatography in toluene/ethyl acetate (50:1 to 30:1) gave 86 mg of a light yellow solid product (70%). R_f = 0.37 (SiO_2, hexanes/EtOAc, 3:1), mp 135-137 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 10.09 (*s*, 1H) 8.94 (*dd*, *J* = 6.9 Hz, *J* = 2.3 Hz, 1H) 8.72 (*dd*, *J* = 8.0 Hz, *J* = 4.6 Hz, 1H) 8.18 (*dd* , *J* = 1.7 Hz, *J* = 8.0 Hz, 1H) 7.93 (*d*, *J* = 9.2 Hz, 1H) 7.57–7.65 (*m*, 2H) 7.44 (*dd*, *J* = 8.6 Hz, *J* = 4.6 Hz, 1H) 7.13 (*d*, *J* = 8.6 Hz, 1H) 4.01 (*s*, 3H) . ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 163.8, 163.7, 153.3, 148.7, 143.6, 138.8, 136.6, 134.2, 129.3 (*quartet*, $J_{C\text{-}F}$ = 309.7 Hz) 129.11 (*quartet*, $J_{C\text{-}F}$ = 311.5 Hz) 128.3, 127.6, 122.8, 122.1, 117.3, 113.6, 113.3, 111.9, 57.1. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -40.8 (*s*), -42.6 (*s*). FT-IR (neat, cm^{-1}) υ 3334, 1672, 1530, 1487, 1427, 1289, 1131, 1113. HRMS (ESI+): Calculated for $C_{19}H_{13}F_6N_2O_2S_2$ $[M+H]^+$ 479.03171, Found 479.03197.

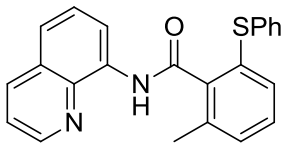


***N*-(2,4-di(Trifluoromethylthio)nicotinoyl)-8-aminoquinoline (Table 3-2, entry 8)**: To a 10 mL Kontes flask equipped with a stir bar was added *N*-(nicotinoyl)-8-aminoquinoline (62 mg, 0.25 mmol) and $Cu(OAc)_2$ (23 mg, 0.13 mmol), followed by bis(trifluoromethyl) disulfide (0.06 mL, 0.45 mmol) and DMSO (1 mL) via syringe. The resulting mixture was stirred at 90 °C for 13 hours and 15 minutes. After work up following the general procedure, purification by column chromatography in toluene/ethyl acetate (50:1) gave 48 mg of a light yellow solid product (43%). R_f =0.51 (SiO_2, hexanes/EtOAc, 3:1), mp 138-140 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 10.29 (*s*, 1H) 8.88(*dd*, *J* = 6.9 Hz, *J* = 2.3 Hz, 1H) 8.79 (*dd*, *J* = 4.1 Hz, *J* = 1.4 Hz, 1H) 8.74 (*d*, *J* = 5.0 Hz, 1H) 8.22 (*dd*, *J* = 8.2 Hz, *J* = 1.4 Hz, 1H) 7.7–7.6 (*m*, 3H) 7.50 (*dd*, *J* = 8.2 Hz, *J* = 4.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 161.9, 151.1, 149.9, 149.0, 138.8, 137.8, 136.8, 136.6, 133.6, 128.8 (quartet, J_{C-F} = 310 Hz, 2C) 128.3, 127.6, 127.1, 123.6, 122.4, 117.7. ^{19}F NMR (376 MHz, $CDCl_3$, ppm) δ -39.03 (*s*) -39.53 (*s*). FT-IR (neat, cm^{-1}) υ 3313, 1663, 1532, 1487, 1139, 1094. HRMS (ESI+): Calculated for $C_{17}H_{10}F_6N_3OS_2$ $[M+H]^+$ 450.01640, Found 450.01628.

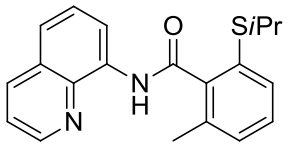
4.3.3 Sulfenylation of *o*-toluic acid amide

General procedure: To a 2-dram vial equipped with a stir bar was added *N*-(2-methylbenzoyl)-8-aminoquinoline (1 equiv), $Cu(OAc)_2$ (0.5 equiv), K_2CO_3 (1 equiv for diphenyl disulfide), disulfide (2-2.5 equiv), and DMSO. The resulting mixture was stirred at 100 °C – 110 °C for the indicated time. After completion, the mixture was cooled to

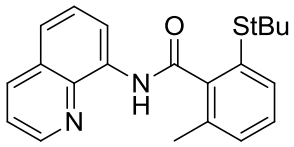
room temperature and diluted by ethyl acetate (5 mL). The solution was filtered through a pad of celite®, and solid phase was washed with ethyl acetate (2 × 25 mL). The filtrate was concentrated under reduced pressure. Purification by column chromatography gave the desired product.



***N*-(6-Methyl-2-phenylthiobenzoyl)-8-aminoquinoline (Table 3-3, entry 1)**: To a 2-dram vial equipped with a stir bar was added *N*-(2-methylbenzoyl)-8-aminoquinoline (66 mg, 0.25 mmol), $Cu(OAc)_2$ (23 mg, 0.13 mmol), K_2CO_3 (35 mg, 0.25), diphenyl disulfide (137 mg, 0.63 mmol), and DMSO (1 mL). The resulting mixture was stirred at 100 °C for 8 hours and 30 minutes. After work up following the general procedure, purification by column chromatography in toluene/ethyl acetate (40:1 to 30:1) gave 80 mg of a tan solid product (86%). R_f =0.49 (SiO_2, hexanes/EtOAc, 3:1), mp 146-148 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.94 (*s*, 1H) 8.97 (*dd*, *J* = 7.3 Hz, *J* = 1.4 Hz, 1H) 8.68 (*dd*, *J* = 4.1 Hz, *J* = 1.8 Hz, 1H) 8.16 (*dd*, *J* = 8.2 Hz, *J* = 1.8 Hz, 1H) 7.62–7.52 (*m*, 2H) 7.42 (*dd*, *J* = 8.2 Hz, *J* = 4.1 Hz, 1H) 7.37–7.30 (*m*, 2H) 7.29–7.23 (*m*, 1H) 7.23–7.12 (*m*, 5H) 2.47 (*s*, 3H) . ^{13}C NMR (100 MHz, $CDCl_3$, ppm) 167.3, 148.5, 140.4, 138.8, 136.6, 136.5, 136.0, 134.6, 133.3, 131.7, 130.7, 130.0, 129.9, 129.4, 128.2, 127.7, 127.4, 122.3, 121.9, 117.2, 19.9. FT-IR (neat, cm^{-1}) υ 3328, 1675, 1524, 1481, 1327. HRMS (ESI+): Calculated for $C_{23}H_{19}N_2OS$ $[M+H]^+$ 371.12126, Found 371.12100.

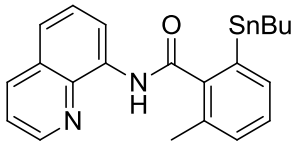


***N*-(6-Methyl-2-isopropylthiobenzoyl)-8-aminoquinoline (Table 3-3, entry 2)**: To a 2-dram vial equipped with a stir bar was added *N*-(2-methylbenzoyl)-8-aminoquinoline (66 mg, 0.25 mmol), $Cu(OAc)_2$ (23 mg, 0.13 mmol), diisopropyl disulfide (75 mg, 0.5 mmol), and DMSO (1 mL). The resulting mixture was stirred at 110 °C for 14 hours. After work up following the general procedure, purification by column chromatography in toluene/ethyl acetate (40:1) gave 76 mg of an oil (90%). R_f = 0.65 (SiO_2, hexanes/EtOAc, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.91 (*s*, 1H) 9.00 (*dd*, *J* = 7.3 Hz, *J* = 1.4 Hz, 1H) 8.73 (*dd*, *J* = 4.1 Hz, *J* = 1.9 Hz, 1H) 8.18 (*dd*, *J* = 8.2 Hz, *J* = 1.8 Hz, 1H) 7.65–7.54 (*m*, 2H) 7.44 (*dd*, *J* = 8.2 Hz, *J* = 4.1 Hz, 1H) 7.39 (*d*, *J* = 7.3, 1H) 7.33–7.27 (*m*, 1H) 7.18 (*d*, *J* = 7.3 Hz, 1H) 3.44 (septet, *J* = 6.9 Hz, 1H) 2.44 (*s*, 3H) 1.24 (*d*, *J* = 6.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) 167.8, 148.5. 141.8, 138.9, 136.6, 135.1, 134.8, 132.8, 131.2, 129.6, 129.5, 128.3, 127.8, 122.2, 121.9, 117.1, 39.9, 23.4, 19.9. FT-IR (neat, cm^{-1}) υ 3343. 1677, 1521, 1483, 1450, 1424, 1385, 1326. HRMS (ESI+): Calculated for $C_{20}H_{21}N_2OS$ $[M+H]^+$ 337.13691, Found 337.13659.



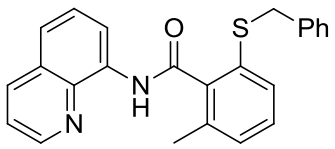
***N*-(6-Methyl-2-*t*-butylthiobenzoyl)-8-aminoquinoline (Table 3-3, entry 3)**: To a 2-dram vial equipped with a stir bar was added *N*-(2-methylbenzoyl)-8-aminoquinoline (66 mg, 0.25 mmol), $Cu(OAc)_2$ (23 mg, 0.13 mmol), di-*t*-butyl disulfide (115 mg, 0.64 mmol),

and DMSO (1 mL). The resulting mixture was stirred at 110 °C for 24 hours. After work up following the general procedure, purification by column chromatography in hexanes/ethyl acetate (10:1 to 5:1) gave 61 mg of a tan solid product (69%). R_f = 0.57 (SiO_2, heaxanes/EtOAc, 3:1), mp 96-99 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.85 (*s*, 1H) 8.99 (*dd*, *J* = 7.3 Hz, *J* = 1.4 Hz, 1H) 8.72 (*dd*, *J* = 4.6 Hz, *J* = 1.8 Hz, 1H) 8.17 (*dd*, *J* = 8.2 Hz, *J* = 1.8 Hz, 1H) 7.48–7.64 (*m*, 3H) 7.43 (*dd*, *J* = 4.1 Hz, *J* = 8.2 Hz, 1H) 7.34–7.26 (*m*, 2H) 2.45 (*s*, 3H) 1.31 (*s*, 9H) . ^{13}C NMR (100 MHz, $CDCl_3$, ppm) 167.9, 148.5, 144.7, 138.9, 136.6, 136.2, 135.9, 134.9, 131.1, 130.2, 129.0, 128.4, 127.8, 122.1, 121.9, 117.1, 47.6, 31.8, 20.1. FT-IR (neat, cm^{-1}) υ 3362, 3331, 1678, 1521, 1484, 1424, 1386, 1327. HRMS (ESI+): Calculated for $C_{21}H_{23}N_2OS$ $[M+H]^+$ 351.15256, Found 351.15242.

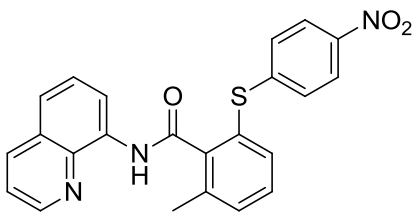


***N*-(6-Methyl-2-*n*-butylthiobenzoyl)-8-aminoquinoline (Table 3-3, entry 4)**: To a 2-dram vial equipped with a stir bar was added *N*-(2-methylbenzoyl)-8-aminoquinoline (66 mg, 0.25 mmol), $Cu(OAc)_2$ (23 mg, 0.13 mmol), di-*n*-butyl disulfide (89 mg, 0.5 mmol), and DMSO (1 mL). The resulting mixture was stirred at 110 °C for 4 hours. After work up following the general procedure, purification by column chromatography in toluene/ethyl acetate (40:1 to 30:1) gave 76 mg of a light yellow oil (87%). R_f =0.57 (SiO_2, hexanes/EtOAc, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.95 (*s*, 1H) 9.01 (*dd*, *J* = 7.5 Hz, *J* = 1.1 Hz, 1H) 8.74 (*dd*, *J* = 8.6 Hz, *J* = 1.7 Hz, 1H) 8.17 (*dd*, *J* = 8.6 Hz, *J* = 1.7 Hz, 1H) 7.64–7.54 (*m*, 2H) 7.44 (*dd*, *J* = 4.0 Hz, *J* = 8.0 Hz, 1H) 7.35–7.26 (*m*, 2H) 7.14 (*d*, *J*

= 7.5 Hz, 1H) 2.91 (*t*, *J* = 7.4 Hz, 2H) 2.43 (*s*, 3H) 1.57 (*quintet*, *J* = 7.4 Hz, 2H) 1.37 (*sextet*, *J* = 7.4 Hz, 2H) 0.83 (*t*, *J* = 7.4, 3H) . ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 167.7, 148.6, 140.2, 138.9, 136.6, 136.1, 134.8, 134.1, 129.6, 128.8, 128.5, 128.4, 127.8, 122.3, 121.9, 117.2, 35.1, 31.6, 22.2, 19.9, 13.9. FT-IR (neat, cm^{-1}) υ 3355, 1677, 1521, 1483, 1458, 1424, 1385, 1326. HRMS (ESI+): Calculated for $C_{21}H_{23}N_2OS$ $[M+H]^+$ 351.15256, Found 351.15231.



***N*-(2-Benzylthio-6-methylbenzoyl)-8-aminoquinoline (Table 3-3, entry 5)**: To a 2-dram vial equipped with a stir bar was added *N*-(2-methylbenzoyl)-8-aminoquinoline (66 mg, 0.25 mmol), $Cu(OAc)_2$ (23 mg, 0.13 mmol), dibenzyl disulfide (154 mg, 0.63 mmol), and DMSO (1 mL). The resulting mixture was stirred at 110 °C for 14 hours. After work up following the general procedure, purification by column chromatography in toluene/ethyl acetate (40:1) gave 82 mg of a yellow solid product (85%). R_f =0.53 (SiO_2, hexanes/EtOAc, 3:1), mp 148-150 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 9.92 (*s*, 1H) 9.07 (*dd*, *J* = 7.3 Hz, *J* = 1.4 Hz, 1H) 8.75 (*dd*, *J* = 4.0 Hz, *J* = 1.3 Hz, 1H) 8.18 (*dd*, *J* = 8.2 Hz, *J* = 1.8 Hz, 1H) 7.65–7.55 (*m*, 2H) 7.45 (*dd*, *J* = 8.2 Hz, *J* = 4.1 Hz, 1H) 7.25–7.13 (*m*, 8H) 4.12 (*s*, 2H) 2.44 (*s*, 3H) . ^{13}C NMR (100 MHz, $CDCl_3$, ppm) 167.7, 148.6, 140.9, 138.9, 137.6, 136.7, 136.1, 134.9, 133.0, 130.1, 129.6, 129.6, 129.4, 128.7, 128.4, 127.8, 127.4, 122.3, 122.0, 117.3, 40.7, 19.9. FT-IR (neat, cm^{-1}) υ 3337, 1660, 1519, 1483, 1325. HRMS (ESI+): Calculated for $C_{24}H_{21}N_2OS$ $[M+H]^+$ 385.13691, Found 385.13697.

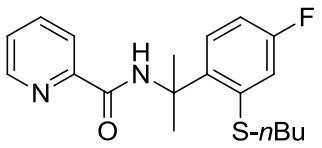


***N*-(6-Methyl-2-(4-nitrophenylthio)benzoyl)-8-aminoquinoline (Table 3-3, entry 6)**: To a 2-dram vial equipped with a stir bar was added *N*-(2-methylbenzoyl)-8-aminoquinoline (66 mg, 0.25 mmol), $Cu(OAc)_2$ (23 mg, 0.13 mmol), di(4-nitrophenyl) disulfide (155 mg, 0.50 mmol) and DMSO (1 mL). The resulting mixture was stirred at 110 °C for 14 hours. After work up following the general procedure, purification by column chromatography in toluene/ethyl acetate (40:1) gave 85 mg of a yellow solid product (81%). R_f = 0.40 (SiO_2, hexanes/EtOAc, 3:1), mp 131-133°C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.73 (*s*, 1H) 8.86 (*dd*, *J* = 7.5 Hz, *J* = 2.3 Hz, 1H) 8.54 (*dd*, *J* = 4.1 Hz, *J* = 1.7 Hz, 1H) 8.13 (*dd*, *J* = 8.0 Hz, *J* = 1.2 Hz, 1H) 7.95–7.91 (*m*, 2H) 7.58–7.50 (*m*, 3H) 7.48–7.43 (*m*, 2H) 7.38 (*dd*, *J* = 4.6 Hz, *J* = 8.6 Hz, 1H) 7.17–7.13 (*m*, 2H) 2.51 (*s*, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 166.6, 148.4, 148.3, 145.7, 143.4, 138.5, 137.6, 136.7, 134.4, 134.2, 132.7, 130.7, 128.2, 127.7, 127.7, 127.5, 124.3, 122.5, 122.0, 117.1, 20.0. FT-IR (neat, cm^{-1}) υ 3334, 1679, 1518, 1484, 1338, 1328. HRMS (ESI+): Calculated for $C_{23}H_{18}N_3O_3S$ $[M+H]^+$ 416.10634, Found 416.10623.

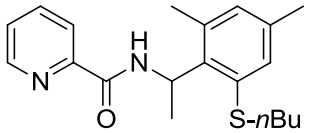
4.3.4 Sulfenylation of benzylamine derivatives

General procedure: To a 2-dram vial equipped with a stir bar was added amide (1 equiv), $Cu(OAc)_2$ (1-2 equiv), K_2CO_3 (1 equiv for bis(4-methoxyphenyl) disulfide), disulfide (2-2.5 equiv), and DMSO. The resulting mixture was stirred at 130 °C for the indicated time. After completion, the mixture was cooled to room temperature and diluted with ethyl

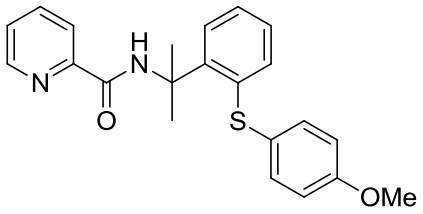
acetate (5 mL). The solution was filtered through a pad of celite®, and washed with ethyl acetate (2 × 25 mL each). The filtrate was concentrated under reduced pressure. Purification by column chromatography gave the desired product.



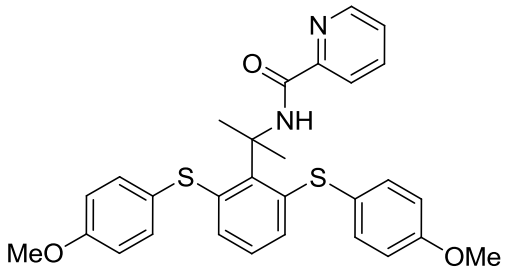
***N*-(1-Methyl-1-(4-fluoro-2-(*n*-butylthio)phenyl)ethyl)picolinamide (Table 3-4, entry 1):** To a 2-dram vial equipped with a stir bar was added *N*-(1-methyl-1(4-fluorophenyl)ethyl)picolinamide (65 mg, 0.25 mmol), $Cu(OAc)_2$ (45 mg, 0.25 mmol), di-*n*-butyl disulfide (89 mg, 0.50 mmol), and DMSO (1 mL). The resulting mixture was stirred at 130 °C for 24 hours. After work up following the general procedure, purification by column chromatography in hexanes/ethyl acetate (5:1 to 2:1) followed by HPLC for contaminated fractions in hexanes/ethyl acetate (2:1) gave 61 mg of a yellow oil (70%). R_f =0.43 (SiO_2, hexanes/EtOAc, 3:1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.61–8.51 (*m*, 2H) 8.11–8.06 (*m*, 1H) 7.80 (*td*, J_t = 8.0 Hz, J_d = 1.7 Hz, 1H) 7.48 (*dd*, *J* = 8.6 Hz, *J* = 6.3 Hz, 1H) 7.43–7.38 (*m*, 1H) 6.96 (*dd*, *J* = 2.9 Hz, *J* = 10.3 Hz, 1H) 6.87–6.81 (*m*, 1H) 2.78 (*t*, *J* = 7.5 Hz, 2H) 1.93 (*s*, 6H) 1.51 (*quintet*, *J* = 7.5 Hz, 2H) 1.28 (*sextet*, *J* = 7.5 Hz, 2H) 0.81 (*t*, *J* = 7.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm). 161.8 (*d*, J^1_{C-F} = 246.3 Hz) 162.7, 150.6, 148.2, 139.8 (*d*, J^4_{C-F} = 2.9 Hz) 137.9 (*d*, J^3_{C-F} = 7.3 Hz) 137.6, 128.3 (*d*, J^3_{C-F} = 8.8 Hz) 126.2, 122.2, 115.3 (*d*, J^2_{C-F} = 24.12 Hz) 117.9 (*d*, J^2_{C-F} = 20.46 Hz) 55.7, 34.1, 30.7, 28.5, 22.4, 13.9. FT-IR (neat, cm^{-1}) 3389, 1679, 1513, 1476, 1464, 1433, 1247, 1234. HRMS (ESI+): Calculated for $C_{19}H_{24}FN_2OS_2$ $[M+H]^+$ 347.15879, Found 347.15914.



***N*-(1-(2,4-Dimethyl-6-(*n*-butylthio)phenyl)ethyl)picolinamide (Table 3-4, entry 2):** To a 2-dram vial equipped with a stir bar was added *N*-(1-(2,4-dimethylphenyl)ethyl)picolinamide (64 mg, 0.25 mmol), $Cu(OAc)_2$ (91 mg, 0.50 mmol), di-*n*-butyl disulfide (90 mg, 0.50 mmol), and DMSO (1 mL). The resulting mixture was stirred at 130 °C for 24 hours. After work up following the general procedure, purification by column chromatography in hexanes/ethyl acetate (10:1 to 5:1) gave 54 mg of a yellow oil (63%). R_f =0.50 (SiO_2, hexanes/EtOAc, 3:1). ^{1}H NMR (MHz, $CDCl_3$, ppm) δ 9.80–9.30 (*s*, 1H) 8.57–8.53 (*m*, 1H) 8.15 (*d*, *J* = 8.02 Hz, 1H) 7.79 (*dd*, *J* = 7.5 Hz, *J* = 1.7 Hz, 1H) 7.40–7.35 (*m*, 1H) 7.10 (*s*, 1H) 6.85 (*s*, 1H) 5.95–5.81 (*m*, 1H) 2.93 (*t*, *J* = 8.0 Hz, 2H) 2.54 (*s*, 3H) 2.24 (*s*, 3H) 1.72–1.63 (*m*, 5H) 1.46–1.36 (*m*, 2H) 0.86 (*t*, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 163.4, 130.6, 148.3, 139.2, 137.4, 137.0, 136.7, 134.9, 131.6, 130.8, 126.1, 122.5, 45.4, 36.4, 31.5, 22.4, 21.3, 21.2, 21.0, 14.0. FT-IR (neat, cm^{-1}) υ 3391, 1672, 1510, 1463, 1432. HRMS (ESI+): Calculated for $C_{20}H_{27}N_2OS$ $[M+H]^+$ 343.18386, Found 343.18318.



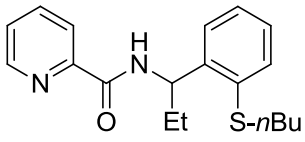
***N*-(1-Methyl-1-(2-(4-methoxyphenylthio)phenyl)ethyl)picolinamide (Table 3-4, entry 3A)**



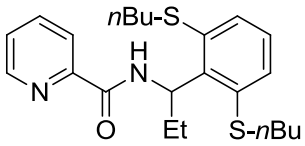
***N*-(1-Methyl-1-(2,6-di(4-methoxyphenylthio)phenyl)ethyl)picolinamide (Table 3-4, entry 3B)**

To a 2-dram vial equipped with a stir bar was added *N*-(1-methyl-1-phenylethyl)picolinamide (61 mg, 0.25 mmol), $Cu(OAc)_2$ (46 mg, 0.25 mmol), bis(4-methoxyphenyl) disulfide (139 mg, 0.50 mmol), K_2CO_3(35 mg, 0.25 mmol) and DMSO (1 mL). The resulting mixture was stirred at 130 °C for 24 hours. After work up following the general procedure, purification by column chromatography in hexanes/ethyl acetate (3:1 to 2:1) followed by another column chromatography in toluene/ethyl acetate (15:1) gave 60 mg of white solid **product A** (62%) and 22 mg of **product B** as a brown oil (16%). **Product A:** R_f =0.2 (SiO_2, hexanes/EtOAc 3:1), mp 174-177 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.67 (*s*, 1H) 8.55–8.51 (*m*, 1H) 8.06 (*d*, *J* = 7.4 Hz, 1H) 7.77 (*td*, J_t = 7.5 Hz, J_d = 1.7 Hz, 1H) 7.57 (*dd*, *J* = 8.0 Hz, *J* = 1.2 Hz, 1H) 7.39–7.34 (*m*, 1H) 7.22–7.17 (*m*, 1H) 7.17–7.12 (*m*, 2H) 7.06 (*dd*, *J* = 8.0 Hz, *J* = 1.2 Hz, 1H) 6.98 (*dd*, *J* = 7.5 Hz, *J* = 1.2 Hz, 1H) 6.76–6.71 (*m*, 2H) 3.75 (*s*, 3H) 2.02 (*s*, 6H) . ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 162.7, 159.5, 150.7, 148.1, 144.6, 137.4, 135.8, 134.6, 132.6, 127.7, 126.9, 126.8, 126.5, 126.1, 122.2, 115.0, 56.0, 55.6, 28.6. FT-IR (neat, cm^{-1}) υ 3379, 1682, 1589, 509, 1491, 1467, 1289, 1246. HRMS (ESI+): Calculated for $C_{22}H_{23}N_2O_2S$ $[M+H]^+$ 379.14748, Found 379.14741. **Product B:** R_f = 0.17 (SiO_2, hexanes/EtOAc, 3/1). ^{1}H NMR (400 MHz,

$CDCl_3$, ppm) δ 8.79 (*s*, 1H) 8.60–8.56 (*m*, 1H) 8.16 (*d*, *J* = 7.8 Hz, 1H) 7.82 (*td*, J_t = 7.8 Hz, J_d = 1.8 Hz, 1H) 7.44–7.37 (*m*, 1H) 7.25–7.21 (*m*, 4H) 6.91–6.73 (*m*, 7H) 3.78 (*s*, 6H) 2.27 (*s*, 6H). ^{13}C NMR (MHz, $CDCl_3$, ppm) 162.2, 159.5, 150.8, 148.2, 145.2, 137.6, 137.5, 134.7, 131.8, 128.4, 126.9, 126.1, 122.3, 115.2, 59.0, 55.6, 29.8. FT-IR (neat, cm^{-1}) υ 3370, 1677, 1591, 1508, 1493, 1462, 1287, 1246, 1029. HRMS (ESI+): Calculated for $C_{29}H_{28}N_2NaO_3S_2$ $[M+Na]^+$ 539.14336, Found 539.14381.



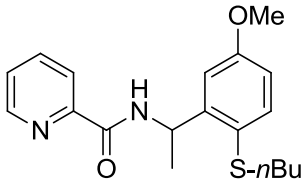
***N*-(1-(2-(*n*-Butylthio)phenylpropyl)picolinamide (Table 3-4, entry 4A)**



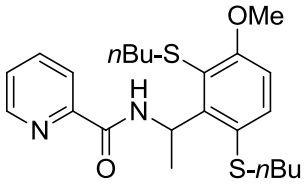
***N*-(1-(2,6-di(*n*-Butylthio)phenylpropyl) picolinamide (Table 3-4, entry 4B)**

To a 2-dram vial equipped with a stir bar was added *N*-(1-phenylpropyl)picolinamide (119 mg, 0.50 mmol), $Cu(OAc)_2$ (182 mg, 1 mmol), di-*n*-butyl disulfide (178 mg, 1 mmol), and DMSO (2 mL). The resulting mixture was stirred at 130 °C for 24 hours. After work up following the general procedure, purification by column chromatography in hexanes/ethyl acetate (5:1 to 3:1) gave 40 mg of **product A** as a yellow oil (25%) and 74 mg of **product B** as a yellow oil (36%). **Product A:** R_f = 0.43 (SiO_2, hexanes/EtOAc, 3:1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.67–8.54 (*m*, 2H) 8.18 (*d*, *J* = 7.3 Hz, 1H) 7.83 (*dd*, *J* = 7.5 Hz, *J* = 1.7 Hz, 1H) 7.44–7.38 (*m*, 2H) 7.36–7.32 (*m*, 1H) 7.22–7.17 (*m*, 2H) 5.54 (*q*, *J* = 7.6 Hz, 1H) 2.96 (*t*, *J* = 7.4 Hz, 2H) 1.96 (*sextet*, *J* = 7.5 Hz, 2H) 1.66 (*quintet*, *J* = 7.5 Hz, 2H) 1.49–1.50 (*m*, 2H) 1.00 (*t*, *J* = 7.4 Hz, 3H) 0.90 (*t*, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 163.9, 150.4, 148.3, 143.0, 137.6, 135.6, 131.2, 127.8, 127.0, 126.8,

126.4, 122.6, 53.5, 35.0, 31.5, 29.8, 22.4, 14.0, 11.3. FT-IR (neat, cm^{-1}) υ 3395, 1675, 1512, 1464, 1433. HRMS (ESI+): Calculated for $C_{19}H_{25}N_2OS$ $[M+H]^+$ 329.16821, Found 329.16801. **Product B:** R_f =0.57 (SiO_2, hexanes/EtOAc, 3:1). ^1H NMR (500 MHz, $CDCl_3$, ppm) δ 9.68–9.59 (*m*, 1H) 8.56 (*d*, *J* = 4.0 Hz, 1H) 8.19 (*d*, *J* = 8.0 Hz, 1H) 7.80 (*td*, J_t = 7.5 Hz, J_d = 1.7 Hz, 1H) 7.41–7.37 (*m*, 1H) 7.28–7.24 (*m*, 2H) 7.12 (*t*, *J* = 7.5 Hz, 1H) 6.25–6.18 (*m*, 1H) 3.04–2.89 (*m*, 4H) 2.25–2.13 (*m*, 1H) 2.07–1.97 (*m*, 1H) 1.68 (*quintet*, *J* = 1.4 Hz, 4H) 1.56–1.35 (*m*, 4H) 1.00 (*t*, *J* = 7.4 Hz, 3H) 0.96–0.81 (*m*, 6H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 163.8, 150.8, 148.3, 142.6, 137.5, 131.0, 129.1, 127.7, 126.1, 122.8, 52.5, 31.4, 28.9, 22.5, 14.0, 11.7. Signal for one carbon could not be located. FT-IR (neat, cm^{-1}) υ 3358, 1675, 1507, 1563, 1433. HRMS (ESI+): Calculated for $C_{23}H_{33}N_2OS_2$ $[M+H]^+$ 417.20288, Found 417.20247.



***N*-(1-(3-Methoxy-6-(*n*-butylthio)phenyl)-1-methylethyl)picolinamide (Table 3-4, entry 5A)**

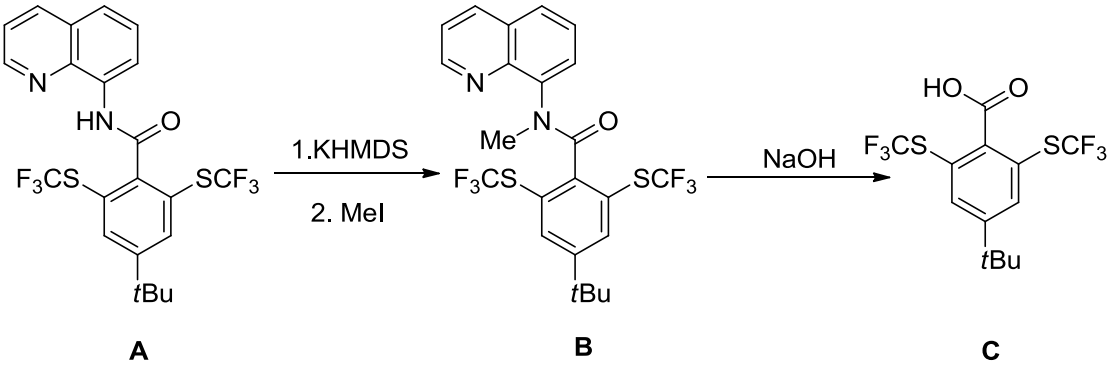


***N*-(1-(3-Methoxy-2,6-di(*n*-butylthio)phenyl)-1-methylethyl)picolinamide (Table 3-4, entry 5B)**

To a 2-dram vial equipped with a stir bar was added *N*-(1-(3-methoxyphenyl)-1-methylethyl)picolinamide (128 mg, 0.50 mmol), $Cu(OAc)_2$ (183 mg, 1 mmol), di-*n*-butyl disulfide (195 mg, 1.09 mmol), and DMSO (2 mL). The resulting mixture was stirred at 130 °C for 24 hours. After work up following the general procedure, purification by column chromatography in hexanes/ethyl acetate (5:1 to 3:1) gave 72 mg of **product A** (42%) as a yellow oil and 56 mg of **product B** (26%) as a dark yellow oil. **Product A:** R_f

=0.29 (SiO_2,hexanes/EtOAc, 3:1).^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.58–8.51 (*m*, 2H) 8.18 (*d*, *J* = 7.5 Hz, 1H) 7.83 (*dd*, *J* = 8.0 Hz, *J* = 1.7 Hz, 1H) 7.45–7.39 (*m*, 2H) 6.96 (*d*, *J* = 2.9 Hz, 1H) 6.76 (*dd*, *J* = 8.6 Hz, *J* = 2.9 Hz, 1H) 5.75 (quintet, *J* = 7.1 Hz, 1H) 3.78 (*s*, 3H) 2.93–2.81 (*m*, 2H) 1.56–1.64 (*m*, 5H) 1.44–1.38 (*m*, 2H) 0.87 (*t*, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 163.6, 159.8, 150.3, 148.3, 147.5, 137.6, 136.0, 126.4, 125.3, 122.6, 112.9, 112.8, 55.6, 48.2, 36.8, 31.8, 22.8, 22.3, 14.0. FT-IR (neat, cm^{-1}) υ 3395, 1675, 1596, 1512, 1468, 1433, 1289, 1232. HRMS (ESI+): Calculated for $C_{19}H_{25}N_2O_2S$ $[M+H]^+$ 345.16313, Found 345.16306. **Product B:** R_f = 0.49 (SiO_2, hexanes/EtOAc, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 10.00–9.50 (*m*, 1H) 8.56 (*d*, *J* = 4.1 Hz, 1H) 8.18 (*d*, *J* = 7.8 Hz, 1H) 7.80 (*td*, J_t = 7.7 Hz, J_d = 1.8 Hz, 1H) 7.55–7.36 (*m*, 2H) 6.76 (*d*, *J* = 8.7 Hz, 1H) 6.72–6.49 (*m*, 1H) 3.88 (*s*, 3H) 3.04–2.66 (*m*, 4H) 1.77–1.57 (*m*, 8H) 1.55–1.21 (*m*, 3H) 0.98–0.78 (*m*, 6H). ^{13}C NMR (MHz, $CDCl_3$, ppm) 163.2, 160.8, 150.8, 149.6, 148.2, 137.4, 136.4, 127.2, 126.1, 123.2, 122.7, 110.3, 56.3, 47.9, 37.9, 36.7, 35.2, 31.6, 30.0, 22.6, 22.3, 14.0. Signal for one carbon could not be located. FT-IR (neat, cm^{-1}) υ 3377, 1674, 1505, 1458, 1431, 1273, 1085, 1023. HRMS (ESI+): Calculated for $C_{23}H_{33}N_2O_2S_2$ $[M+H]^+$ 433.19780, Found 433.19757.

4.3.5 Removal of directing group



A **B** **C**

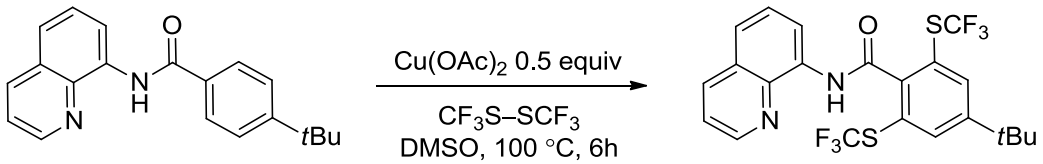
4-*t*-Butyl-2,6-di(trifluoromethylthio)benzoic acid (C): *N*-(2,6-Di(trifluoromethylthio)-4-*t*-butylbenzoyl)-8-aminoquinoline (506 mg, 1 mmol) was dissolved in anhydrous THF (5 mL) and the resulting solution was cooled to 0°C. To this solution KHMDS (1. 5 mL of a 1 M solution in THF, 1.5 mmol) was added via syringe in 5 minutes. Resulting dark red solution was allowed to stir for 30 min. MeI (710 mg, 5 mmol) was added at once, and reaction mixture was stirred for additional 2 hours at 0 °C. After that, silica gel (5 mL) was added to the reaction mixture and solvent was removed under vacuum. Filtration through a plug of silica gel using CH_2Cl_2 as eluent and evaporation of the solvent afforded intermediate B as a foam (458 mg). Intermediate B (260 mg, 0.5 mmol) and NaOH (307 mg, 7.5 mmol) were dissolved in EtOH (3 ml). The resulting mixture was stirred at 130 °C for 64 hours. After that, reaction mixture was diluted with EtOAc (100 mL) and 1N HCl (30 mL) was added. Organic layer was washed with 1N HCl (5 x 20 mL), dried over $MgSO_4$, filtered and the solvent was evaporated under vacuum affording pure product as a tan solid (85%). R_f =0.34 (SiO_2, toluene/EtOAc, 5:1 with 5% of acetic acid), mp 170-173 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.91 (*s*, 2H) 1.38 (*s*, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 170.0, 155.5, 143.7, 137.7, 129.2 (*quartet*, J_{C-F} = 309.4 Hz) 123.0, 35.6, 31.2. ^{19}F NMR (470 MHz, $CDCl_3$, ppm) δ -41.8. FT-IR (neat, cm^{-1}) υ 1714, 1586, 1468, 1391, 1290, 1137, 1103. HRMS (ESI+): Calculated for $C_{13}H_{12}F_6NaO_2S_2$ $[M+Na]^+$ 401.00746, Found 401.00746.

CONTROL EXPERIMENTS

General procedure: A 10 mL Kontes flask equipped with a stir bar was charged with *N*-(4-*t*-butylbenzoyl)-8-aminoquinoline (76 mg, 0.25 mmol, 1 equiv), $Cu(OAc)_2$ (23 mg,

0.13 mmol, 0.5 equiv.) and no $Cu(OAc)_2$ was added for entry 3 Table 3-9. Subsequently, cold bis(trifluoromethyl) disulfide (0.06 mL, 0.45 mmol, 1.8 equiv.) and DMSO (1 mL) were added via syringe. The resulting mixture was stirred at 100 °C for 6 h. After completion, the mixture was cooled to room temperature and diluted with ethyl acetate (5 mL). The solution was filtered through a pad of silicagel, and washed with ethyl acetate (2 × 25 mL). The filtrate was concentrated under reduced pressure and yield of reaction was determined by ^{19}F NMR using trifluoromethylbenzene as an internal standard.

Table 3-9. Control experiments



$Cu(OAc)_2$ sources	% yield
98% (reagent grade)	74%
99.999% (ultra-pure)	78%
No $Cu(OAc)_2$	< 2%

4.4 Copper-catalyzed amination of non-acidic sp^2 C-H bonds

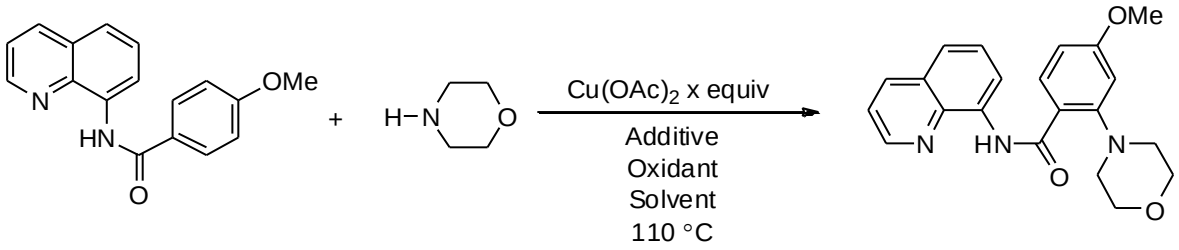
4.4.1 Optimization for direct amination of benzoic acid amides

General procedure for reactions without additives (entries 1,2 Table 3-5): A 1-dram vial equipped with a stir bar was charged with *N*-(4-methoxybenzoyl)-8-aminoquinoline (70 mg, 0.25 mmol, 1 equiv), $Cu(OAc)_2$, NMP (1 mL) and morpholine (0.05 mL, 0.57 mmol, 2.3 equiv). For entry 2, the vial was filled with O_2. The resulting mixture was heated with stirring at 110 °C for 12h. After completion, the reaction mixture was cooled

down to room temperature and diluted with ethyl acetate (5 mL). The solution was filtered through a pad of silicagel and washed with ethyl acetate (2 × 25 mL). The yield of reaction was determined by ^{1}H NMR using trimethoxybenzene as an internal standard.

General procedure for reactions using NMO oxidant (entries 3-6, table 3-5): A 1 dram vial equipped with a stir bar was charged with *N*-(4-methoxybenzoyl)-8-aminoquinoline (70 mg, 0.25 mmol, 1 equiv), Cu(OAc), and K_2CO_3 (34 mg, 0.25 mmol, 1equiv, for entry 3) or Ag_2CO_3 (for entries 4-6). Inside the glove box, NMO (*N*-methylmorpholine *N*-oxide) (59 mg, 0.5 mmol, 2 equiv) was added to the vial. Outside the glove box, NMP (1 mL) and morpholine (0.05 mL, 0.57 mmol, 2 equiv) were added to the resulting mixture. The vial was wrapped with aluminum foil (entries 4-6) and stirred at 110 °C for 14h 30 min (entries 4, 5) or 12h (entries 3, 6). For entries 4, 5: after completion, the reaction mixture was dry absorbed on the silica gel followed by purification by column chromatography in hexanes/ethyl acetate (3:1 to 2:1). For entries 3, 6: after completion, the reaction mixture was cooled down to room temperature, diluted by ethyl acetate (5 mL). The solution was filtered through a pad of silicagel, and washed with ethyl acetate (2 × 25 mL). The yield of reaction was determined by ^{1}H NMR using trimethoxybenzene as an internal standard.

Table 3-5. Optimization of reaction conditions

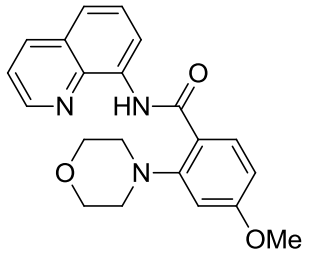


Entry	x equiv.	Oxidant	Additive	Solvent	% yield
1	1	-		NMP	39%*
2	0.5	O_2		NMP	51%*
3	0.25	NMO	K_2CO_3	NMP	44%*
4	0.25	NMO	Ag_2CO_3 (0.25 equiv)	NMP	74%
5	0.1	NMO	Ag_2CO_3 (0.13 equiv)	NMP	87%
6	0.05	NMO	Ag_2CO_3 (0.075 equiv)	NMP	80%*

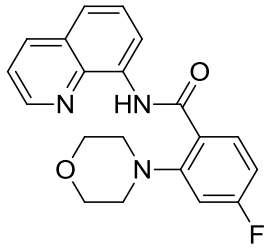
*^{1}H NMR yield

4.4.2 Amination of benzoic acid amides

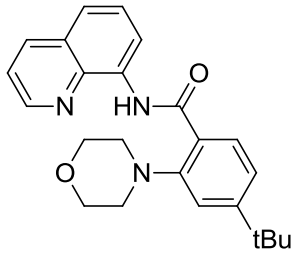
General procedure: To a 1-dram vial equipped with a stir bar was added amide (0.5 mmol, 1 equiv), $Cu(OAc)_2$ (0.1–0.25 equiv) and Ag_2CO_3 (0.125–0.25 equiv). Inside the glove box, NMO (2 equiv) was added to the vial. Outside the glove box NMP (2 mL) and morpholine (2 equiv) were added to the resulting mixture. The vial was wrapped with aluminum foil and stirred at 110 °C for indicated time. After completion, the reaction mixture was cooled down to room temperature and dry absorbed on silica gel. Purification by column chromatography provided the desired product.



***N*-(2-Morpholino-4-methoxybenzoyl)-8-aminoquinoline (Table 3-6, entry 1)**: To a 1-dram vial equipped with stir bar was added *N*-4-methoxybenzoyl-8-aminoquinoline (139 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 0.05 mmol), and Ag_2CO_3 (17 mg, 0.06 mmol). Inside the glove box, NMO (118 mg, 1.0 mmol) was added to the vial. Outside the glove box NMP (*N*-methylpyrrolidone, 2 mL) and morpholine (0.09 mL, 1.03 mmol) were added to the resulting mixture. The vial was wrapped by aluminum foil and stirred at 110 °C for 13 h 30 min. After completion, the reaction mixture was cooled down to room temperature and dry absorbed on silica gel. Purification by column chromatography in hexanes/ethyl acetate (3:1 to 2:1) gave 158 mg (87%) of product as a white solid. R_f = 0.16 (SiO_2, hexanes/EtOAc, 3:1), mp 175-176 °C (from hexanes/CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 12.68–12.58 (*s*, 1H) 9.12 (*dd*, *J* = 7.3 Hz, *J* = 1.4 Hz, 1H) 8.88 (*dd*, *J* = 4.6 Hz, *J* = 1.8 Hz, 1H) 8.21–8.16 (*m*, 2H) 7.63–7.56 (*m*, 1H) 7.56–7.51 (*m*, 1H) 7.48 (*dd*, *J* = 8.2 Hz, *J* = 4.1 Hz,1H) 6.80–6.75 (*m*, 2H) 4.03–3.95 (*m*, 4H) 3.89 (*s*, 3H) 3.18–3.11 (*m*, 4H) . ^{13}C NMR (100 MHz, $CDCl_3$, ppm) 165.7, 163.1, 153.3, 148.4, 139.1, 136.7, 136.1, 134.4, 128.6, 127.9, 122.0, 121.8, 121.8, 117.9, 108.6, 106.4, 66.4, 55.8, 54.2 δ. FT-IR (neat, cm^{-1}) υ 2973, 2934, 2846, 1652, 1518, 1485, 1109, 1033. HRMS (ESI+): Calculated for $C_{21}H_{21}N_3O_3$ $[M+H]^+$ 364.1661, Found 364.1661.

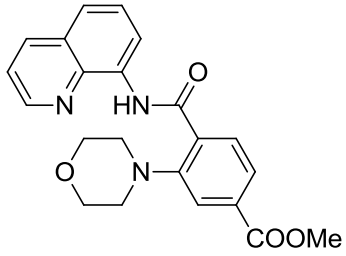


***N*-(2-Morpholino-4-fluorobenzoyl)-8-aminoquinoline (Table 3-6, entry 2)**: To a 1-dram vial equipped with stir bar was added *N*-4-fluorobenzoyl-8-aminoquinoline (133 mg, 0.5 mmol), $Cu(OAc)_2$ (18 mg, 0.10 mmol), and Ag_2CO_3 (28 mg, 0.10 mmol). Inside the glove box, NMO (117 mg, 1.0 mmol) was added to the vial. Outside the glove box NMP (2 mL) and morpholine (0.09 mL, 1.03 mmol) were added to the resulting mixture. The vial was wrapped by aluminum foil and stirred at 110 °C for 14 h. After completion, the reaction mixture was cooled down to room temperature and dry absorbed on silica gel. Purification by column chromatography in hexanes/ethyl acetate (4:1) gave 123 mg (70%) of product. R_f = 0.32 (SiO_2, hexanes/EtOAc, 3:1), mp 178-180 °C (from hexanes/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 12.51–21.44 (*s*, 1H) 9.10 (*dd*, *J* = 7.4 Hz, *J* = 1.7 Hz, 1H) 8.88 (*dd*, *J* = 4.0 Hz, *J* = 1.7 Hz, 1H) 8.23–8.15 (*m*, 2H) 7.63–7.53 (*m*, 2H) 7.50 (*dd*, *J* = 8.0 Hz, *J* = 4.0 Hz, 1H) 6.97–6.91 (*m*, 2H) 3.99–3.93 (*m*, 4H) 3.17–3.11 (*m*, 4H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 165.4 (*d*, J_{C-F} = 252.8 Hz), 165.1, 153.6 (*d*, J_{C-F} = 8.2 Hz), 148.5, 139.0, 136.8, 135.7, 134.7 (*d*, J_{C-F} = 10.0 Hz), 128.7, 127.9, 125.3 (*d*, J_{C-F} = 2.7 Hz), 122.1, 122.0, 118.0, 111.3 (*d*, J_{C-F} = 21.0 Hz) 107.0 (*d*, J_{C-F} = 22.8 Hz), 66.3, 54.1. ^{19}F NMR (470 MHz, $CDCl_3$, ppm) δ -106.3 – -106.4 (m, 1F). FT-IR (neat, cm^{-1}) υ 1646, 1520, 1484, 1110. HRMS (ESI+): Calculated for $C_{20}H_{18}FN_3O_2$ $[M+H]^+$ 352.1461, Found 352.1460.



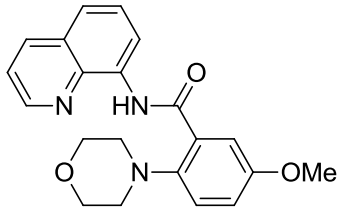
***N*-(2-Morpholino-4-*t*-butylbenzoyl)-8-aminoquinoline (Table 3-6, entry 3)**: To a 1-dram vial equipped with stir bar was added *N*-4-*t*-butylbenzoyl-8-aminoquinoline (152 mg, 0.5 mmol), $Cu(OAc)_2$ (11 mg, 0.06 mmol), and Ag_2CO_3 (17 mg, 0.06 mmol). Inside the glove box, NMO (117 mg, 1.0 mmol) was added to the vial. Outside the glove box NMP (2 mL) and morpholine (0.09 mL, 1.03 mmol) were added to the resulting mixture. The vial was wrapped with aluminum foil and stirred at 110 °C for 11 h 15 min. After completion, the reaction mixture was cooled down to room temperature and dry absorbed on silica gel. Purification by column chromatography in hexanes/ethyl acetate (4:1) gave 158 mg (81%) of product as a tan solid. R_f = 0.40 (SiO_2, hexanes/EtOAc, 3:1), mp 142-144 °C (from hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 12.75–12.67 (*s*, 1H) 9.13 (*dd*, *J* = 7.8 Hz, *J* = 1.4 Hz, 1H) 8.87 (*dd*, *J* = 4.1 Hz, *J* = 1.8 Hz, 1H) 8.19 (*dd*, *J* = 8.2 Hz, *J* = 1.4 Hz, 1H) 8.13 (*d*, *J* = 8.2 Hz, 1H) 7.63–7.51 (*m*, 2H) 7.48 (*dd*, *J* = 8.2 Hz, *J* = 4.1 Hz, 1H) 7.31–7.26 (*m*, 2H) 4.03–3.93 (*m*, 4H) 3.21–3.15 (*m*, 4H) 1.37 (*s*, 9H) . ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.0, 156.3, 151.2, 148.4, 139.2, 136.7, 136.1, 132.3, 128.7, 127.9, 126.3, 121.9, 121.8, 118.0, 116.4, 66.5, 54.3, 35.6, 31.3. Signal for one carbon could not be located. FT-IR (neat, cm^{-1}) υ 2961, 1660, 1526, 1486, 1112. HRMS (ESI+): Calculated for $C_{24}H_{27}N_3O_2$ $[M+H]^+$ 390.2182, Found 390.2184.

Large scale synthesis: To a 6-dram vial equipped with stir bar was added *N*-4-*t*-butylbenzoyl-8-aminoquinoline (1.52 g, 5.0 mmol), $Cu(OAc)_2$ (181 mg, 1.0 mmol), and Ag_2CO_3 (275 mg, 1.0 mmol). Inside the glove box, NMO (11.7 g, 10 mmol) was added to the vial. Outside the glove box NMP (10 mL) and morpholine (0.87 mL, 10 mmol) were added to the resulting mixture. The vial was wrapped with aluminum foil and stirred at 110 °C for 39 h. After completion, the reaction mixture was cooled down to room temperature and dry absorbed on silica gel. Purification by column chromatography in hexanes/ethyl acetate (4:1) gave 1.55 g (80%) of product.



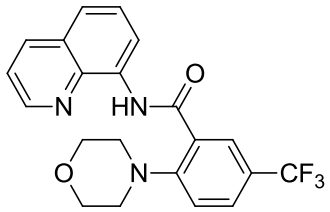
Methyl 3-morpholino-4-(quinolin-8-ylcarbamoyl)benzoate (Table 3-6, entry 4): To a 1-dram vial equipped with stir bar was added methyl 4-(quinolin-8-ylcarbamoyl)benzoate (153 mg, 0.5 mmol), $Cu(OAc)_2$ (18 mg, 0.10 mmol), and Ag_2CO_3 (28 mg, 0.10 mmol). Inside the glove box NMO (120 mg, 1.0 mmol) was added to the vial. Outside the glove box NMP (2 mL) and morpholine (0.09 mL, 1.03 mmol) were added to the resulting mixture. The vial was wrapped with aluminum foil and stirred at 110 °C for 14 h 30 min. After completion, the reaction mixture was cooled down to room temperature and dry absorbed on silica gel. Purification by column chromatography in hexanes/ethyl acetate (2:1) gave 133 mg (68%) of product as a yellow solid. R_f = 0.16 (SiO_2, hexanes/EtOAc, 3:1), mp 183-184 °C (from hexanes/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 12.63–

12.56 (*s*, 1H) 9.11 (*dd*, *J* = 7.4 Hz, *J* = 1.7 Hz, 1H) 8.88 (*dd*, *J* = 4.6 Hz, *J* = 1.7 Hz, 1H) 8.24–8.19 (*m*, 2H) 7.93–7.87 (*m*, 2H) 7.64–7.55 (*m*, 2H) 7.50 (*dd*, *J* = 8.6 Hz, *J* = 4.6 Hz, 1H) 4.00–3.93 (*m*, 7H) 3.22–3.16 (*m*, 4H) . ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.7, 165.2, 151.3, 148.6, 139.1, 136.8, 135.5, 133.7, 133.1, 132.6, 128.6, 127.9, 125.4, 122.5, 122.1, 120.7, 118.1, 66.4, 54.1, 52.8. FT-IR (neat, cm^{-1}) υ 2824, 1722, 1653, 1523, 1491, 1430, 1279, 1112. HRMS (ESI+): Calculated for $C_{22}H_{21}N_3O_4$ $[M+H]^+$ 392.1610, Found 392.1612.



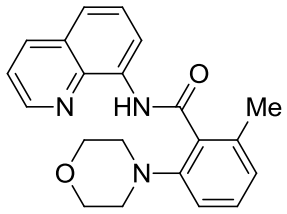
***N*-(2-Morpholino-5-methoxybenzoyl)-8-aminoquinoline (Table 3-6, entry 5)**: To a 1-dram vial equipped with stir bar was added *N*-(3-methoxybenzoyl)-8-aminoquinoline (139 mg, 0.50 mmol), $Cu(OAc)_2$ (11 mg, 0.06 mmol), and Ag_2CO_3 (18 mg, 0.06 mmol). Inside the glove box NMO (117 mg, 1.0 mmol) was added to the vial. Outside the glove box NMP (2 mL) and morpholine (0.09 mL, 1.03 mmol) were added to the resulting mixture. The vial was wrapped by aluminum foil and stirred at 110 °C for 14 h 30 min. After completion, the reaction mixture was cooled down to room temperature and dry absorbed on silica gel. Purification by column chromatography in hexanes/ethyl acetate (2:1) gave 149 mg (82%) of product as a tan solid. R_f = 0.19 (SiO_2, hexanes/EtOAc, 3:1), mp 148-151 °C (from hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 13.16–13.07 (*s*, 1H) 9.14 (*dd*, *J* = 7.3 Hz, *J* = 1.4 Hz, 1H) 8.90 (*dd*, *J* = 4.1 Hz, *J* = 1.4 Hz, 1H) 8.20 (*dd*, *J* = 8.2 Hz, *J* = 1.4 Hz, 1H) 7.83 (*d*, *J* = 3.2 Hz, 1H) 7.64–7.53 (*m*, 2H) 7.50 (*dd*, *J* = 8.2 Hz, *J*

= 4.6 Hz, 1H) 7.29–7.25 (*m*, 1H) 7.07 (*dd*, *J* = 8.7 Hz, *J* = 3.2 Hz, 1H) 4.06–3.99 (*m*, 4H), 3.88 (*s*, 3H) 3.14–3.08 (*m*, 4H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 165.5, 156.9, 148.4, 145.0, 139.3, 136.8, 136.1, 130.2, 128.7, 127.9, 122.2, 122.0, 121.7, 119.4, 118.5, 115.9, 66.6, 56.0, 54.6. FT-IR (neat, cm^{-1}) υ 2843, 1651, 1528, 1488, 1282, 1262, 1114. HRMS (ESI+): Calculated for $C_{21}H_{21}N_3O_3$ $[M+H]^+$ 364.1661, Found 364.1663.



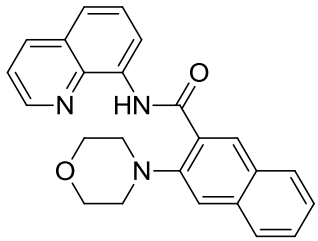
***N*-(2-Morpholino 5-trifluoromethylbenzoyl)-8-aminoquinoline (Table 3-6, entry 6)**: To a 1-dram vial equipped with stir bar was added *N*-(3-trifluoromethylbenzoyl)-8-aminoquinoline (159 mg, 0.50 mmol), $Cu(OAc)_2$ (18 mg, 0.10 mmol), and Ag_2CO_3 (28 mg, 0.10 mmol). Inside the glove box, NMO (117 mg, 1.0 mmol) was added to the vial. Outside the glove box NMP (2 mL) and morpholine (0.09 mL, 1.03 mmol) were added to the resulting mixture. The vial was wrapped by aluminum foil and stirred at 110 °C for 24 h. After completion, the reaction mixture was cooled down to room temperature and dry absorbed on silica gel. Purification by column chromatography in hexanes/ethyl acetate (3:1 to 2:1) gave 135 mg (67%) of an oil. R_f = 0.19 (SiO_2, hexanes/EtOAc, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 12.41–12.31 (*s*, 1H) 9.12–9.07 (*m*, 1H) 8.90–8.84 (*m*, 1H) 8.41 (*s*, 1H) 8.24–8.18 (*m*, 1H) 8.24–7.70 (*m*, 1H) 7.65–7.55 (*m*, 2H) 7.51 (*dd*, *J* = 8.2 Hz, *J* = 4.1 Hz, 1H) 7.31 (*d*, *J* = 8.70 Hz, 1H) 3.98–3.92 (*m*, 4H) 3.24–3.17 (*m*, 4H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 164.8, 153.9, 148.6, 138.9, 136.9, 135.3, 129.9, 129.5, 129.3,

128.6, 127.9, 126.3 (*q*, $J_{C\text{-}F}$ = 33.6 Hz), 124.2 (*q*, $J_{C\text{-}F}$ = 271.0 Hz), 122.5, 122.1, 119.5, 118.0, 66.3, 53.9. ^{19}F NMR (470 MHz, $CDCl_3$, ppm) δ -62.1 (s, 1F). FT-IR (neat, cm^{-1}) υ 3243, 2973, 1669, 1529, 1330, 1256, 1272, 1114, 1106, 1081. HRMS (ESI+): Calculated for $C_{21}H_{18}F_3N_3O_2$ $[M+H]^+$ 402.1429, Found 402.1431.



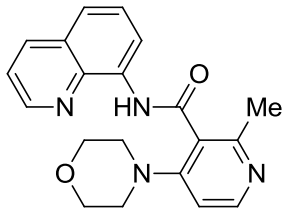
***N*-(2-Morpholino-6-methylbenzoyl)-8-aminoquinoline (Table 3-6, entry 7)**: To a 1-dram vial equipped with stir bar was added *N*-(2-methylbenzoyl)-8-aminoquinoline (131 mg, 0.50 mmol), $Cu(OAc)_2$ (18 mg, 0.1 mmol), and Ag_2CO_3 (28 mg, 0.10 mmol). Inside the glove box NMO (117 mg, 1.0 mmol) was added to the vial. Outside the glove box NMP (2 mL) and morpholine (0.09 mL, 1.03 mmol) were added to the resulting mixture. The vial was wrapped by aluminum foil and stirred at 110 °C for 14 h. After completion, the reaction mixture was cooled down to room temperature and dry absorbed on silica gel. Purification by column chromatography in hexanes/ethyl acetate (3:1) gave 122 mg (70%) of brown oil. R_f = 0.33 (SiO_2, hexanes/EtOAc, 3:1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) *δ*.10.68–10.58 (*s*, 1H) 9.00 (*dd*, *J* = 7.4 Hz, *J* = 1.1 Hz, 1H) 8.77 (*dd*, *J* = 4.0 Hz, *J* = 1.7 Hz, 1H) 8.19 (*dd*, *J* = 8.0 Hz, *J* = 1.7 Hz, 1H) 7.64–7.53 (*m*, 2H) 7.45 (*dd*, *J* = 8.0 Hz, *J* = 4.0 Hz, 1H) 7.31 (*t*, *J* = 8.0 Hz, 1H) 7.03–6.95 (*m*, 2H) 3.59–3.53 (*m*, 4H) 3.11–3.06 (*m*, 4H) 2.50 (*s*, 3H) .^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 168.2, 150.3, 148.5, 138.8, 138.6, 136.7, 135.3, 132.1, 130.4, 128.5, 127.8, 126.2, 122.0, 122.0, 116.8, 116.7, 67.2, 53.3,

20.7. FT-IR (neat, cm^{-1}) υ 3349, 2858, 2836, 1661, 1522, 1484, 1325, 1113. HRMS (ESI+): Calculated for $C_{21}H_{21}N_3O_2$ $[M+H]^+$ 348.1712, Found 348.1713.



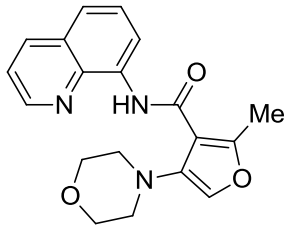
***N*-(1-Morpholino-2-napthalenecarbonyl)-8-aminoquinoline (Table 3-6, entry 8)**: To a 1-dram vial equipped with stir bar was added *N*-(2-naphthalenecarbonyl)-8-aminoquinoline (149 mg, 0.5 mmol), $Cu(OAc)_2$ (18 mg, 0.1 mmol), and Ag_2CO_3 (28 mg, 0.1 mmol). Inside the glove box NMO (117 mg, 1.0 mmol) was added to the vial. Outside the glove box NMP (2 mL) and morpholine (0.09 mL, 1.03 mmol) were added to the resulting mixture. The vial was wrapped by aluminum foil and stirred at 110 °C for 24 h. After completion, the reaction mixture was cooled down to room temperature and dry absorbed on silica gel. Purification by column chromatography in toluene/ethyl acetate (20:1) gave 126 mg (66%) of product as a light brown solid. R_f = 0.22 (SiO_2, hexanes/EtOAc, 3:1), mp 214-216 °C (from hexanes/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 12.74–12.64 (*s*, 1H), 9.18 (*dd*, *J* = 8.0 Hz, *J* = 1.1 Hz, 1H) 8.89 (*dd*, *J* = 4.0 Hz, *J* = 1.1 Hz, 1H) 8.71 (*s*, 1H) 8.21 (*dd*, *J* = 8.6 Hz, *J* = 1.7 Hz, 1H) 7.93 (*d*, *J* = 8.0 Hz, 1H) 7.82 (*d*, *J* = 8.0 Hz, 1H) 7.63 (*t*, *J* = 7.7 Hz, 1H) 7.59–7.52 (*m*, 3H) 7.52–7.44 (*m*, 2H) 4.03–3.96 (*m*, 4H) 3.31–31.21 (*m*, 4H) .^{13}C NMR (100 MHz, $CDCl_3$, ppm) δ 166.0, 148.5, 148.2, 139.1, 136.7, 135.9, 135.6, 134.0, 130.2, 129.3, 128.8, 128.7, 128.4, 127.9, 127.1, 125.8, 122.2, 122.0, 118.1, 116.3, 66.5, 54.4. FT-IR (neat, cm^{-1}) υ 2927, 2858, 1667, 1523,

1485, 1326, 1114. HRMS (ESI+): Calculated for $C_{24}H_{21}N_3O_2$ $[M+H]^+$ 384.1712, Found 384.1714.



***N*-(2-Methyl-6-morpholinonicotinoyl)-8-aminoquinoline (Table 3-6, entry 9)**: To a 1-dram vial equipped with stir bar was added *N*-(2-methylnicotinoyl)-8-aminoquinoline (132 mg, 0.50 mmol), $Cu(OAc)_2$ (22 mg, 0.12 mmol), and Ag_2CO_3 (34 mg, 0.12 mmol). Inside the glove box NMO (117 mg, 1.0 mmol) was added to the vial. Outside the glove box NMP (2 mL) and morpholine (0.09 mL, 1.03 mmol) were added to the resulting mixture. The vial was wrapped by aluminum foil and stirred at 110 °C for 25 h. After completion, the reaction mixture was cooled down to room temperature, diluted with ethyl acetate (30 mL), extracted with H_2O (3 × 10 ml), and dried over Mg_2SO_4. The organic solvent was removed by evaporation. Purification by column chromatography in the eluent system of toluene/ethyl acetate (1:3) with triethyl amine (1.6%) followed by drying under high vacuum to remove trace amounts of NMP gave 98 mg (56%) of a yellow oil. R_f = 0.20 (SiO_2, toluene/EtOAc, 3:1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 10.58–10.47 (*s*, 1H), 8.96 (*dd*, *J* = 6.9 Hz, *J* = 1.7 Hz, 1H) 8.80 (*dd*, *J* = 4.0 Hz, *J* = 1.7 Hz, 1H) 8.41 (*d*, *J* = 5.7 Hz, 1H) 8.22 (*dd*, *J* = 8.0 Hz, *J* = 1.7 Hz, 1H) 7.67–7.56 (*m*, 2H) 7.49 (*dd*, *J* = 8.0 Hz, *J* = 4.0 Hz, 1H) 6.78 (*d*, *J* = 5.7 Hz, 1H) 3.61–3.55 (*m*, 4H) 3.24–3.19 (*m*, 4H) 2.69 (*s*, 3H).^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 167.1, 158.4, 156.1, 150.9, 148.7, 138.6, 136.8, 134.7,

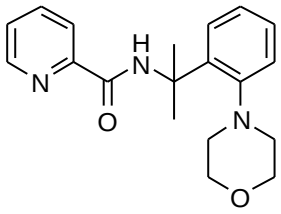
128.5, 127.8, 124.2, 122.5, 122.2, 117.0, 110.5, 66.6, 51.5, 23.7. FT-IR (neat, cm^{-1}) υ 1670, 1574, 1523, 1484, 1452, 1327, 1116. HRMS (ESI+): Calculated for $C_{20}H_{20}N_4O_2$ $[M+H]^+$ 349.1665, Found 349.1667.



***N*-(2-Methyl-4-morpholino-3-furanoyl)-8-aminoquinoline (Table 3-6, entry 10)**: To a 1-dram vial equipped with stir bar was added *N*-(2-methyl-3-furanoyl)-8-aminoquinoline (126 mg, 0.5 mmol), $Cu(OAc)_2$ (18 mg, 0.10 mmol), and Ag_2CO_3 (28 mg, 0.10 mmol). Inside the glove box NMO (117 mg, 1.0 mmol) was added to the vial. Outside the glove box NMP (2 mL) and morpholine (0.09 mL, 1.03 mmol) were added to the resulting mixture. The vial was stirred at 110 °C for 22 h. After completion, the reaction mixture was cooled down to room temperature and dry absorbed on silica gel. Purification by column chromatography in toluene/ethyl acetate (30:1 to 20:1) gave 96 mg (57%) of product as a tan solid. R_f = 0.30 (SiO_2, hexanes/EtOAc, 3:1), mp 184–185 °C (from hexanes/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 11.87–11.77 (*s*, 1H) 9.04 (*dd*, *J* = 7.4 Hz, *J* = 1.1 Hz, 1H) 8.91 (*dd*, *J* = 4.6 Hz, *J* = 1.7 Hz, 1H) 8.18 (*dd*, *J* = 8.0 Hz, *J* = 1.1 Hz, 1H) 7.60–7.51 (*m*, 2H) 7.49 (*dd*, *J* = 8.6 Hz, *J* = 4.6 Hz, 1H) 7.17 (*s*, 1H) 4.02–3.94 (*m*, 4H) 3.07–3.00 (*m*, 4H) 2.66 (*s*, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 162.7, 159.5, 148.4, 139.3, 139.3, 136.7, 136.1, 130.0, 128.5, 127.8, 121.9, 121.8, 117.7, 112.4,

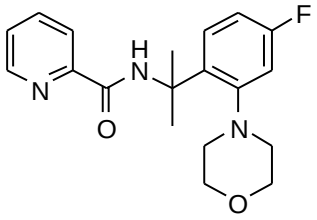
66.8, 54.6, 14.7. FT-IR (neat, cm^{-1}) υ 3137, 2922, 1667, 1602, 1526, 1323, 1263, 1113. HRMS (ESI+): Calculated for $C_{19}H_{19}N_3O_3$ $[M+H]^+$ 338.1505, Found 338.1507.

4.4.3 Amination of benzylamine derivatives



***N*-(1-Methyl-1(-2-morpholinophenyl)ethyl)picolinamide** (**Scheme 3-4**) To a 10 mL pressure vessel equipped with stir bar was added *N*-(1-methyl-1-phenylethyl)picolinamide (120 mg, 0.5 mmol), $Cu(OAc)_2$ (23 mg, 0.12 mmol), and Ag_2CO_3 (34 mg, 0.12 mmol). Inside the glove box, K_3PO_4 (212 mg, 1.0 mmol) and NMO (117 mg, 1.0 mmol) were added to the vial. Outside the glove box DMSO (dimethyl sulfoxide, 2 mL) and morpholine (0.09 mL, 1.03 mmol) were added to the resulting mixture. The vial was stirred at 130 °C for 36 h 30min. After completion, the reaction mixture was cooled down to room temperature and dry absorbed on silica gel. Purification by column chromatography in toluene/ethyl acetate (10:1 to 5:1) gave 70 mg (43%) of a yellow oil. R_f = 0.17 (SiO_2, hexanes/EtOAc, 3:1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.92–8.85 (*s*, 1H) 8.57–8.53 (*m*, 1H) 8.08 (*d*, *J* = 7.4 Hz, 1H) 7.79 (*td*, J_t = 7.4 Hz, J_d = 1.7 Hz, 1H) 7.58 (*dd*, *J* = 8.0 Hz, *J* = 1.7 Hz, 1H) 7.39 (*ddd*, *J* = 7.4 Hz, *J* = 4.6 Hz, *J* = 1.1 Hz, 1H) 7.33 (*dd*, *J* = 8.0 Hz, *J* = 1.1 Hz, 1H) 7.31–7.26 (*m*, 1H) 7.25–7.19 (*m*, 1H) 3.86–3.76 (*m*, 2H) 3.76–3.68 (*m*, 2H) 2.94 (*td*, J_t = 11.5 Hz, J_d = 2.9 Hz, 2H) 2.53 (*d*, *J* = 12.0 Hz, 2H) 1.99 (*s*, 6H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 162.8, 151.7, 151.0, 148.0, 143.1, 137.7, 128.5, 127.7, 126.5, 126.2, 125.8, 122.2, 67.7, 53.4, 54.5, 29.2. FT-IR (neat, cm^{-1}) υ 2955,

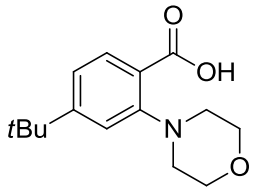
2934, 2858, 1676, 1510, 1454, 1431, 1112. HRMS (ESI+): Calculated for $C_{19}H_{23}N_3O_2$ $[M+H]^+$ 326.1869, Found 326.1866.



***N*-(1-Methyl-1-(4-fluoro-2-morpholinophenyl)ethyl)picolinamide (Scheme 3-4)**: To a 10 mL pressure vessel equipped with stir bar was added *N*-(1-methyl-1-(4-fluorophenyl)ethyl)picolinamide (127 mg, 0.49 mmol), $Cu(OAc)_2$ (23 mg, 0.12 mmol), and Ag_2CO_3 (34 mg, 0.12 mmol). Inside the glove box, K_3PO_4 (212 mg, 1.0 mmol) and NMO (117 mg, 1.0 mmol) were added to the vial. Outside the glove box DMSO (2 mL) and morpholine (0.09 mL, 1.03 mmol) were added to the resulting mixture. The vial was stirred at 130 °C for 38 h 40min. After completion, the reaction mixture was cooled down to room temperature and dry absorbed on silica gel. Purification by column chromatography in hexanes/ethyl acetate (2:1) gave 67 mg (40%) of a yellow oil. R_f = 0.14 (SiO_2, hexanes/EtOAc, 3:1). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.85–8.78 (*s*, 1H) 8.57–8.53 (*m*, 1H) 8.10 (*d*, *J* = 8.0 Hz, 1H) 7.79 (*td*, J_t = 7.4 Hz, J_d = 1.1 Hz, 1H) 7.55 (*dd*, *J* = 8.6 Hz, *J* = 6.9 Hz, 1H) 7.40 (*dd*, *J* = 6.9 Hz, *J* = 5.1 Hz, 1H) 7.03 (*dd*, *J* = 2.9 Hz, *J* = 10.3 Hz, 1H) 6.94–6.87 (*m*, 1H) 3.84–3.75 (*m*, 2H) 3.75–3.68 (*m*, 2H) 2.90–2.78 (*m*, 2H) 2.58–2.46 (*m*, 2H) 1.96 (*s*, 6H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 162.6 (*d*, J_{C-F} = 248.2 Hz), 162.8, 153.4 (*d*, J_{C-F} = 6.4 Hz), 150.8, 148.0, 139.1 (*d*, J_{C-F} = 3.6 Hz), 137.7, 129.1 (*d*, J_{C-F} = 9.1 Hz), 126.3, 122.2, 113.3 (*d*, J_{C-F} = 21.0 Hz), 112.9 (*d*, J_{C-F} = 19.2 Hz),

67.5, 54.9, 54.5, 29.2. FT-IR (neat, cm^{-1}) υ 3374, 2964, 2928, 2852, 2822, 1673, 1587, 1612, 1498, 1261, 1157, 1113. HRMS (ESI+): Calculated for $C_{19}H_{22}FN_3O_2$ $[M+H]^+$ 344.1774, Found 344.1769

4.4.4 Removal of directing group



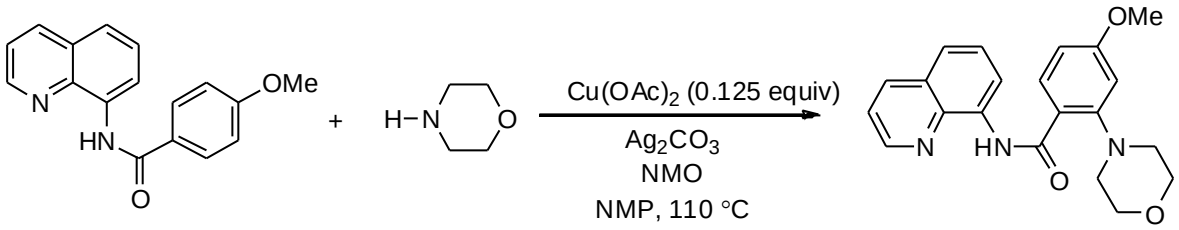
2-Morpholino-4-*t*-butylbenzoic acid: A 10 mL Kontes flask equipped with a stir bar was charged with *N*-(2-morpholino-4-*t*-butylbenzoyl)-8-aminoquinoline (97 mg, 0.25 mmol), NaOH (150 mg, 3.75 mmol) and EtOH (1 mL). The resulting mixture was stirred at 130 °C for 3 days. After completion, the reaction mixture was cooled down to room temperature, diluted by 50 mL ethyl acetate and washed by HCl (4 × 20 mL of 0.5N aqueous solution). The aqueous layers were combined and extracted with ethyl acetate (3 × 15 mL).Combined organic layers were dried over $MgSO_4$. Evaporation to remove organic solvent gave 60 mg (91%) of pure acid as a light brown solid. This compound is known.[19b] ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.22 (*d*, *J* = 8.0 Hz, 1H) 7.45 (*d*, *J* = 8.6 Hz, 1H) 7.43 (*s*, 1H) 3.97 (*brs*, 4H) 3.10 (*brs*, 4H) 1.35 (*s*, 9H).

CONTROL EXPERIMENTS

General procedure: To a 1-dram vial equipped with stir bar was added *N*-4-methoxybenzoyl-8-aminoquinoline (70 mg, 0.5 mmol), $Cu(OAc)_2$ (6 mg, 0.03 mmol), and Ag_2CO_3 (9 mg, 0.03 mmol). Inside the glove box, NMO (59 mg, 0.50 mmol) was added to

the vial. Outside the glove box NMP (1 mL) and morpholine (0.05 mL, 0.57 mmol) were added to the resulting mixture. The vial was wrapped by aluminum foil and stirred at 110 °C for 15 h. After completion, the reaction mixture was cooled to room temperature and diluted with ethyl acetate (5 mL). The solution was filtered through a pad of silicagel and washed with ethyl acetate (2 × 25 mL). The yield of reaction was determined by ^{1}H NMR using trimethoxybenzene as an internal standard.

Table 3-10. Control experiments



$Cu(OAc)_2$ (purity)	% yield
98% (reagent grade)	78%
99.999% (ultra-pure)	85%
No $Cu(OAc)_2$	< 2%

V. References

1. (a) Wendlandt, A. E.; Suess, A. M.; Stahl, S. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 11062. (b) Kitahara, M.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2011**, *133*, 2160. (c) Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 6993,(d) Li, Z.; Bohle, D. S.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8928. (e) Ban, I.; Sudo, T.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 3607. (f) Wang, W.; Luo, F.; Zhang, S.; Cheng, J. *J. Org. Chem.* **2010**, *75*, 2415. (g) Wang, W.; Pan, C.; Chen, F.; Cheng, J. *Chem. Commun.* **2011**, *47*, 3978. (h) Uemura, T.; Imoto, S.; Chatani, N. *Chem. Lett.* **2006**, *35*, 842. (i) John, A.; Nicholas, K. M. *J. Org. Chem.* **2011**, *76*, 4158. (j) Wang, Q.; Schreiber, S. L. *Org. Lett.* **2009**, *11*, 5178. (l) King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. *J. Am. Chem. Soc*, **2010**, *132*, 12068. (m) Usui, S.; Hashimoto, Y.; Morey, J. V.; Wheatley. A. E. H.; Uchiyama, M. *J. Am. Chem. Soc.* **2007**, *129*, 15102. (p) Holland, P. L.; Rodgers, K. R.; Tolman, W. B. *Angew. Chem. Int. Ed.* **1999**, *38*, 1139.

2. (a) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790. (b) Chen, X.; Dobereiner, G.; Hao, X. –S.; Giri, R.; Maugel, N.; Yu, J.-Q. *Tetrahedron* **2009**, *65*, 3085.

3. (a) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404. (b) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185. (c) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2009**, *131*, 17052. (d) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2011**, *133*, 13577. (e) Popov, I.; Lindeman, S.; Daugulis, O. *J. Am. Chem. Soc.* **2011**, *133*, 9286.

4. (a) Brasche, G.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2008**, 47, 1932. (b) Bernini, R.; Fabrizi, G.; Sferrazza, A.; Cacchi, S. *Angew. Chem. Int. Ed.* **2009**, *48,* 8087. (c) Ueda, S.; Nagasawa, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 6411. (d) Ueda, S., Nagasawa, H. *J. Org. Chem.* **2009**, *74*, 4272. (e) Guru, M. M.; Ali, M. A.; Punniyamurthy, T. *Org. Lett.* **2011**, *13*, 1194–1197. Wang, H.; Wang, Y.; Peng, C.; Zhang, J.; Zhu, Q. *J. Am. Chem. Soc.* **2010**, *132*, 13217.

5. (a) Zhang, S.; Qian, P.; Zhang, M.; Hu, M.; Cheng, J. *J. Org. Chem.* **2010**, *75*, 6732. (b) Chu, L.; Yue, X; Qing, F.-L.; *Org. Lett.* **2010**, *12*, 1644. (c) Ranjit, S.; Lee, R.; Heryadi, D.; Shen, C.; Wu, J.; Zhang, P.; Huang, K.-W; Liu, X. *J. Org. Chem.* **2011**, *76*, 8999. (d) Dai, C.; Xu, Z.; Huang, F.; Yu, Z.; Gao, Y.-F. *J. Org. Chem.* **2012**, *77*, 4414.

6. (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. (c) Nadres, E. T.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 7. (d) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3.

7. (a) Leroux, F.; Jeschke, P.; Schlosser, M. *Chem. Rev.* **2005**, *105*, 827 (b) Boiko, V. N. *Beilstein J. Org. Chem.* **2010**, *6*, 880.

8. (a) Jeschke, P. *Pest. Manag. Sci.* **2010**, *66*, 10. (b) Yagupol'skii, L. M.; Il'chenko, A. Ya.; Kondratenko, N. V. *Russ. Chem. Rev.* **1974**, *43*, 64. (c) Hansch, C.; Leo, A.; Unger, S. H.; Kim, K. H.; Nikaitani, D.; Lien, E. J. *J. Med. Chem.* **1973**, *16*, 1207.

9. (a) Xu, L.; Cheng, J.; Trudell, M. L. *J. Org. Chem.* **2003**, *68,* 5388. (b) Tang, R.-Y.; Zhong, P.; Lin, Q.-L., *J. Fluorine Chem.* **2007**, *128*, 636. (c) Marom, H.; Antonov, S.; Popowski, Y.; Gozin, M. *J. Org. Chem.* **2011**, *76*, 5240. (d) Kirsch, P.; Lenges, M.; Kühne, D.; Wanczek, K.-P. *Eur. J. Org. Chem.* **2005**, 797.

10. (a) Manteau, B.; Pazenok, S.; Vors, J.-P.; Leroux, F. R. *J. Fluorine Chem.* **2010**, *131*, 140. Electrophilic trifluoromethylsulfenylation: (b) Baert, F.; Colomb, J.; Billard, T. *Angew. Chem. Int. Ed.* **2012**, *51*, 10382.

11. Teverovskiy, G.; Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 7312.

12. (a) Zhang, C.-P.; Vicic, D. A. *J. Am. Chem. Soc.* **2012**, *134*, 183. (b) Zhang, C.-P.; Vicic, D. A. *Chem. Asian. J.* **2012**, *7*, 1756.

13. Chen, C., Xie, Y., Chu, L., Wang, R.-W., Zhang, X., Qing, F.-L. *Angew. Chem. Int. Ed.* **2012**, *51*, 2492.

14. (a) Tyrra, W.; Naumann, D.; Hoge, B.; Yagupolskii, Y. L. *J. Fluorine Chem.* **2003**, *119*, 101. (b) Tavener, S.; Adams, D. J.; Clark, J. H. *J. Fluorine Chem.* **1999**, *95*, 171. (c) Adams, D. J.; Clark, J. H.; Heath, P. A.; Hansen, L. B.; Sanders, V. C.; Tavener, S. J. *J. Fluorine Chem.* **2000**, *101*, 187. (d) Clark, J. H.; Smith. H. *J. Fluorine Chem.* **1993**, *61*, 223. (e) Dmowski, W.; Hass, A. *J. Chem. Soc. Perkin Trans. I* **1987**, 2119. (f) Emeléus, H. J.; MacDuffie, D. E. *J. Chem. Soc.* **1961**, 2597.

15. Wallace, T. J. *J. Am. Chem. Soc.* **1964**, *86*, 2018.

16. Beesley, R. M.; Ingold, K.; Thorpe, J. F. *J. Chem. Soc. Perkin Trans. I* **1915**, 1080.

17. (a) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (b) Inamoto, K.; Saito, T.; Katsuno, M.; Sakamoto, T.; Hiroya, K. *Org. Lett.* **2007**, *9*, 2931. (c) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058. (d) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184. (e) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806. (f) Tan, Y.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 3676. (g) Nadres, E. T.; Daugulis, O.

J. Am. Chem. Soc. **2012**, *134*, 7. (h) He, G.; Lu, C.; Zhao, Y.; Nack, W. A.; Chen, G. *Org. Lett.* **2012**, *14*, 2944. (i) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3.

18. (a) Ng, K. –H.; Chan, A. S. C.; Yu, W.-Y. *J. Am. Chem. Soc.* **2010**, *132*, 12862. (b) Zalatan, D. N.; Du Bois, J. *In Topics in Current Chemistry*; Yu, J.-Q., Shi, Z., Eds.; Springer-Verlag; Berlin, Germany, **2010**; Vol. *292*, pp 347. (c) Hamilton, C. W.; Laitar, D. S.; Sadighi, J. P. *Chem. Commun.* **2004**, 1628. (d) Badiei, Y. M.; Dinescu, A.; Dai, X.; Palomino, R. M.; Heinemann, F. W.; Cundari, T. R.; Warren, T. H. *Angew. Chem. Int. Ed.* **2008**, *47*, 9961. (e) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048. (f) Lu, H.; Subbarayan, V.; Tao, J.; Zhang, X. P. *Organometallics* **2010**, *29*, 389. (g) Ichinose, M.; Suematsu, H.; Yasutomi, Y.; Nishioka, Y.; Uchida, T.; Katsuki, T. *Angew. Chem. Int. Ed.* **2011**, *50*, 9884. (h) Vedernikov, A. N.; Caul-ton, K. G. *Chem. Commun.* **2004**, 162.

19. (a) Sun, K.; Li, Y.; Xiong, T.; Zhang, J.; Zhang, Q. *J. Am. Chem. Soc.* **2011**, *133*, 1694. (b) Yoo, E. J.; Ma, S.; Mei, T.-S.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7652. (c) Xiao, B.; Gong, T.-J.; Xu, J.; Liu, Z.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 1466. (d) Yin, G.; Wu, Y.; Liu, G. *J. Am. Chem. Soc.* **2010**, *132*, 11978. (e) Rice, G. T.; White, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 11707. (f) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 8590. (g) Pan, J.; Su, M.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 8647.

20. Zhao, H.; Wang, M.; Su, W.; Hong, M. *Adv. Synth. Cata.* **2010**, *352*, 1301. (b) Li. Y.; Xie, Y.; Zhang, R.; Jin, K.; Duan, C. *J. Org. Chem.* **2011**, *76*, 5444.

21. Ribas, X.; Jackson, D. A.; Donnadieu, J. M.; Parella, T.; Xifra, R.; Hedman, B.; Hodgson, K. O.; Llobet, A.; Stack, T. D. P. *Angew. Chem. Int. Ed.* **2002**, *41*, 2991.

22. Huffman, L. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 9196. (b) King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2010**, *132*, 12068.

23. Ano, Y.; Tobisu, M.; Chatani, N. *Org. Lett.* **2012**, *14*, 354.

24. Tran, L. D.; Daugulis, O. *Angew. Chem. Int. Ed.* **2012**, *51*, 5188.

25. Goldfarb, D. S. US 20090163545 A1, **2009**.

26. Zhang, S.-Y.; He, G.; Zhao, Y.; Wright, K.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 7313.

Chapter 4 Auxiliary-assisted, palladium-catalyzed functionalization of amino acid C-H bonds

Chapter 4-1 Transition metal-catalyzed functionalization of sp^3 C-H bonds

I. Introduction

Transition-metal catalyzed C-H bond functionalization has been used as a powerful tool for the construction of C-C and C-heteroatom bonds. Nonetheless, most of the developed methods focus on the functionalization of sp^2 C-H bonds. In fact, the activation of sp^3 C-H bonds is more challenging because of several factors such as lack of precoordination to transition metals, susceptibility to β-hydride elimination reaction. Additionally, the resulting alkyl-metal bond is typically weaker than aryl-metal bond obtained in sp^2 C-H bond activation.[1]

Overall, current achievements in activation of sp^3 C-H bonds have allowed the direct formation of C-C and C-heteroatom bonds. However, most of the methods are applicable to functionalization of primary C-H bonds. The functionalization of secondary C-H bonds is more difficult because of their higher steric hindrance. Despite that fact, several auxiliaries have been shown to effectively overcome this problem and allow the functionalization of secondary C-H bonds. Within the scope of this chapter, only the functionalization of unactivated sp^3 C-H bonds resulting in the formation of C-C bonds will be covered.

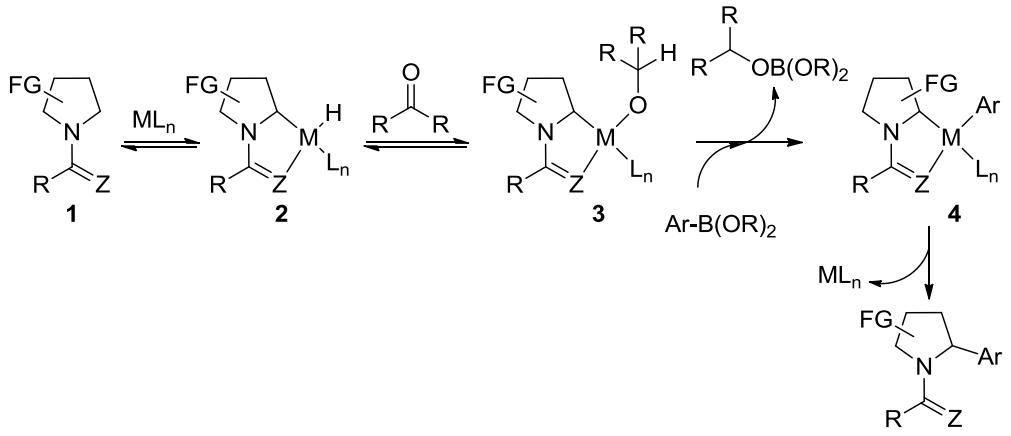
II. Direct arylation and alkylation of sp^3 C-H bonds

2.1 Heteroatom-directed functionalization of sp^3 C-H bonds

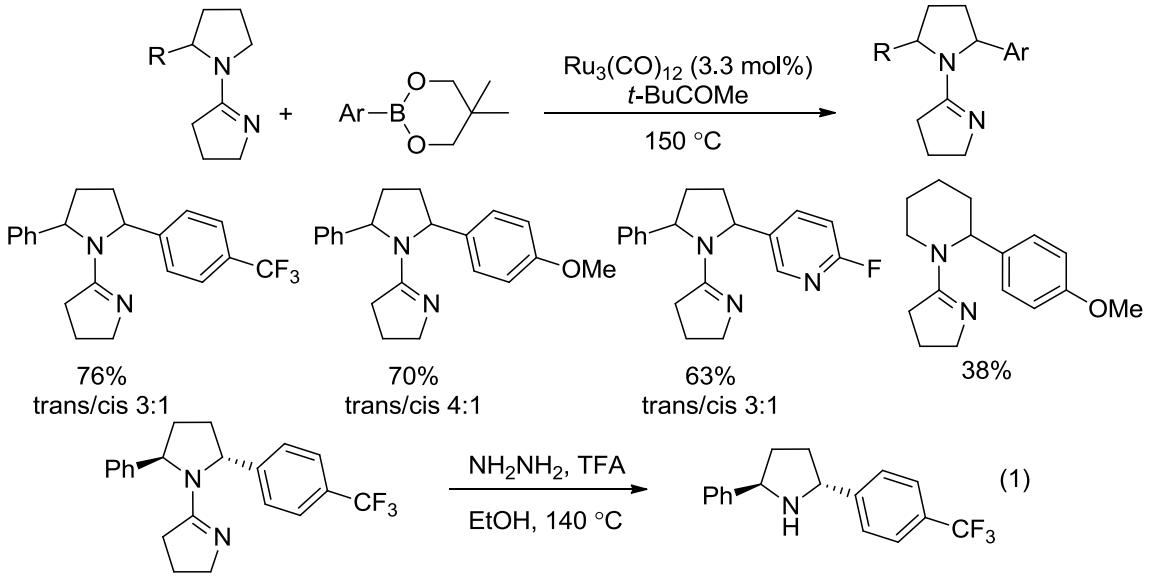
Chelation-controlled, transition metal-catalyzed cleavage of C-H bonds is the most commonly used strategy for the functionalization of sp^3 C-H bonds. In this strategy, the presence of a heteroatom-containing directing group, usually nitrogen or oxygen bearing functional group, is necessary for the selective activation of sp^3 C-H bonds. Between various reported catalysts, palladium is the most commonly used catalyst for functionalization of sp^3 C-H bonds.

In 2006, Sames and coworkers reported the α-arylation of pyrrolidines using imine directing group and a low valent Ru catalyst. [2] The authors proposed that the first step involves insertion of low-valent transition metal into the desired sp^3 C-H bond followed by transmetallation with aryl boronate esters to generate complex **4**. This step occurs through metal alkoxide intermediate **3** obtained via the reaction of ketone with metal-hydride complex **2** (Scheme 4-1). Reductive elimination from complex **4** will generate the arylated product and active catalyst. The optimized conditions involve amidine directing group, $Ru_3(CO)_{12}$ catalyst, *t*-butyl methylketone, and arylboronate ester as coupling partners. The reaction works for both aryl and heteroaryl boronate esters. Besides amidine, other nitrogen-containing directing groups such as pyridine or pyrimidine are also active. However, these directing groups require higher catalyst loading. Finally, the directing group can be removed by treating 2,5-disubstituted amidines with NH_2NH_2 in acetic acid to afford arylated pyrrolidines (equation 1).

Scheme 4-1. Mechanistic guide for sp^3 C-H bond arylation



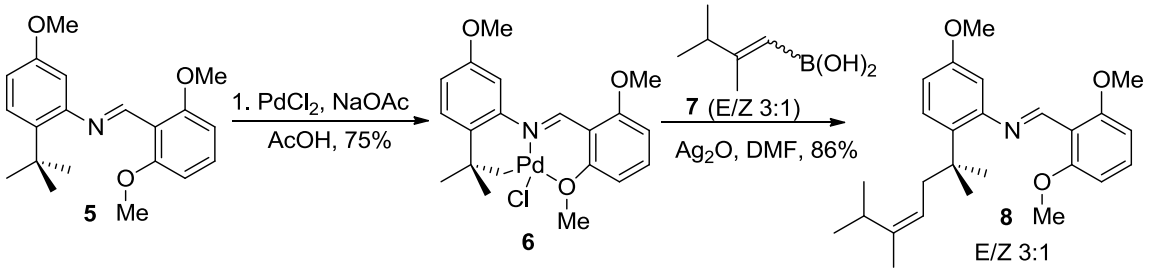
Scheme 4-2. Ruthenium-catalyzed α-arylation of pyrollidines and piperidines



Compared with pyrolidines, six-membered piperidine ring is less reactive due to its chair conformation. Lower yields are obtained under the same reaction conditions. Modified conditions that allow α-arylation of piperidine via a $Ru_3(CO)_{12}$ catalyst have been developed.[3] Pyridine was used as directing group and pinacolboranes were found to be more reactive arylation agents.

In an effort to synthesize teleocidin B-4 core, Sames developed palladium-promoted activation of sp^3 C-H bonds. [4] Palladacycle **6** was formed by treating Schiff base **5** with $PdCl_2$ in the presence of NaOAc and AcOH. The transmetallation of **6** with vinyl boronic acid **7** followed by reductive elimination affords **8** in good yield. Thus, this work demonstrated the ability of palladium to cleave unactivated sp^3 C-H bonds.

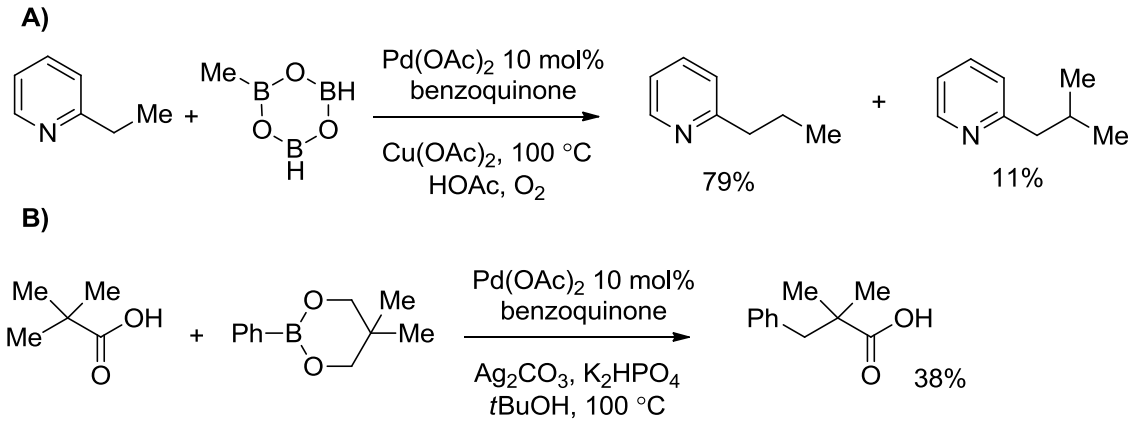
Scheme 4-3. sp^3 C-H bond activation using stoichiometric palladium



Use of boronic acids and boronate esters in palladium-catalyzed sp^3 C-H bond activation/C-C bond formation was extensively developed by the Yu group. In 2006, the methylation of sp^3 C-H bonds by methylboroxine was reported. [5] The catalytic system employs pyridine directing group, $Pd(OAc)_2$ catalyst, benzoquinone, and $Cu(OAc)_2$ oxidant. The reaction was run in acetic acid under O_2 atmosphere (Scheme 4-4A). However, the use of pyridine directing group significantly limits the synthetic applicability of the method. In fact, use of carboxylic acid directing group is more desirable due to broad utility of this functional group in organic synthesis. Additionally, it can potentially shorten the synthetic pathways as the installation and removal of directing groups is not required. Yu group has demonstrated that this strategy can be obtained by using $Pd(OAc)_2$ catalyst, benzoquinone and Ag_2CO_3 oxidant (Scheme 4-4B).[5] K_2HPO_4 base is essential to generate potassium carboxylate salts in situ. Nonetheless, β-arylated

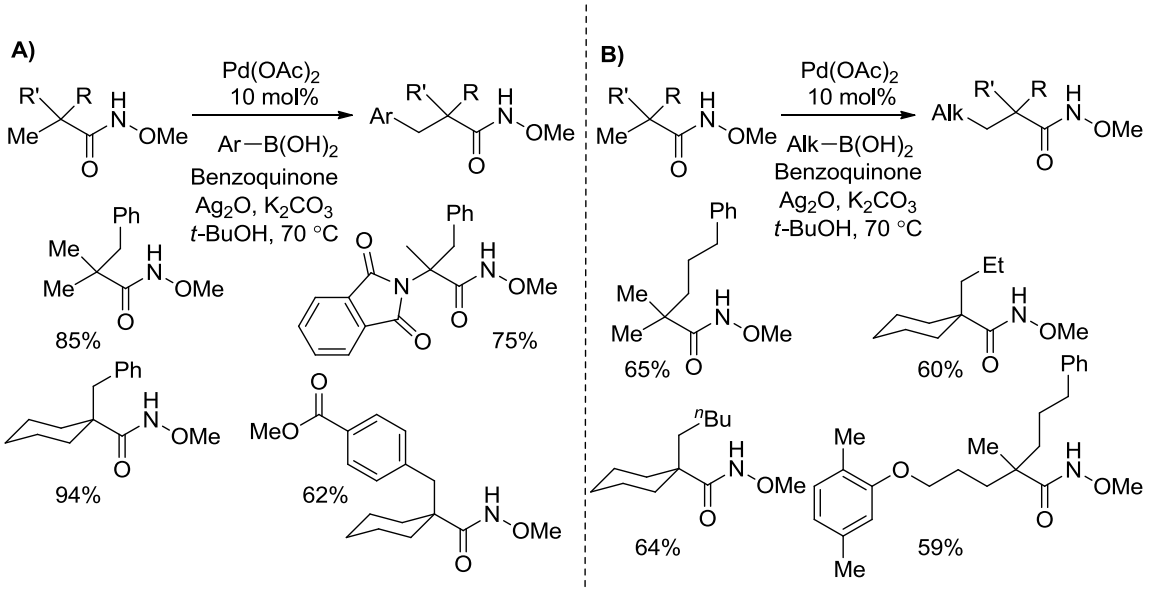
products were obtained in low yields, thus requiring development of more efficient methods.

Scheme 4-4. Palladium-catalyzed methylation and arylation of sp^3 C-H bond



Carboxylic acid derivatives, particularly *O*-methyl hydroxamic acids containing CO-NH-OMe group, can be arylated or alkylated by boronic acids under palladium catalysis. [6] Optimized conditions for arylation reaction involve $Pd(OAc)_2$ catalyst, Ag_2O and benzoquinone oxidants, and K_2CO_3 base (Scheme 4-5A). The alkylation using phenylethyl or butyl boronic acids are more challenging due to β-hydride elimination and homocoupling reactions. These obstacles can be overcome by using 2,2,5,5-tetramethyltetrahydrofuran solvent as it can potentially serve as a bulky ligand on palladium, thus preventing side reactions. Under the optimized conditions, *O*-methyl hydroxamic acids can be alkylated by various alkyl boronic acids in good yields (Scheme 4-5B). Conditions employing air instead of the expensive Ag_2O oxidant were also demonstrated. The CONHOMe directing group can be readily converted to esters and amides or reduced to alkanes.

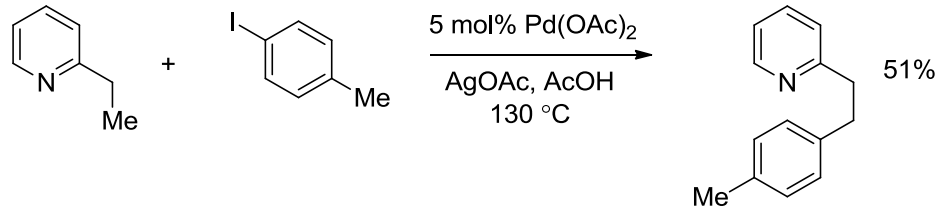
Scheme 4-5. Arylation and alkylation of *O*-methyl hydroxamic acids by palladium catalysis



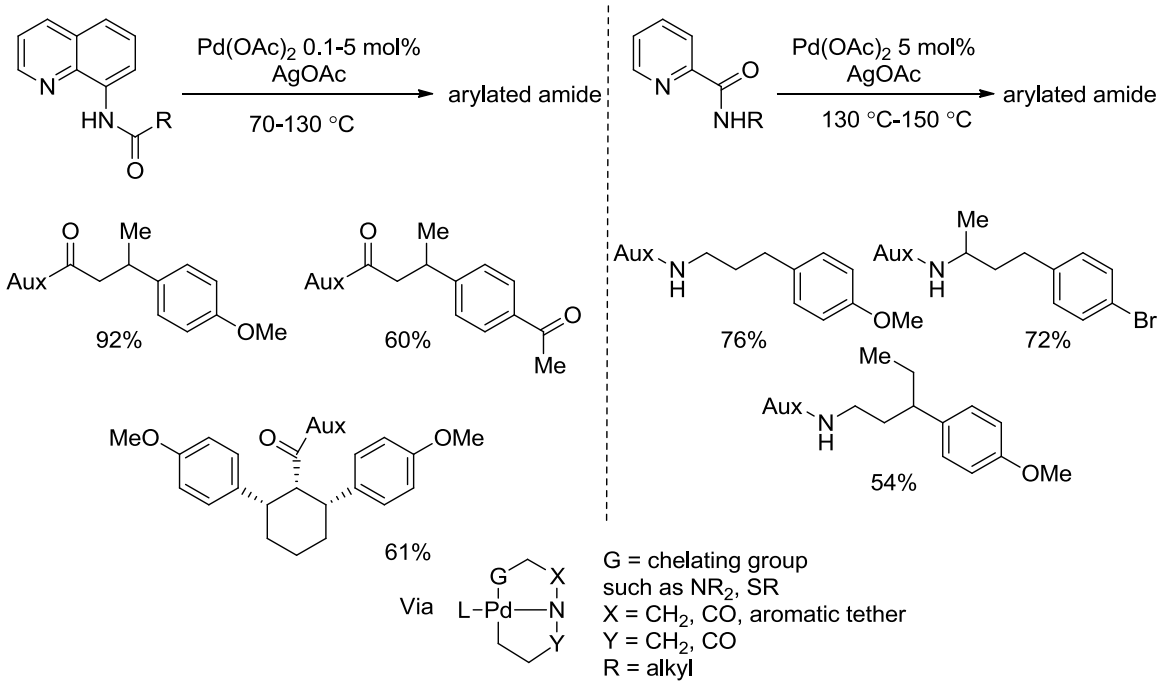
Arylation of sp^3 C-H bonds using aryl iodide coupling partners is more beneficial because of their availability. In an effort to perform direct arylation of pyridines and pyrazoles using palladium catalysis and aryl iodides coupling partners, Daugulis and coworker observed the arylation of methyl group in 2-ethyl pyridine (Scheme 4-6). [7] After this work, improved methods that allow direct arylation and alkylation of unactivated sp^3 C-H bonds have been developed by the same group. [8a] By using 8-aminoquinoline and pycolinic acid auxiliaries, unactivated C-H bonds of carboxylic acids and amine derivatives can be arylated in good yields. The method employs $Pd(OAc)_2$ catalyst, AgOAc base, and does not require solvent. Excellent regioselectivity was observed. With 8-aminoquinoline auxiliary, β-C-H bonds of carboxylic acids can be arylated. When picolinic acic was used, amine derivatives could be selectively arylated at γ position. These results can be explained by the formation of favored five-member ring palladacycle (Scheme 4-7).

Significantly, the method allows the functionalization of aryl, methyl, and more challenging methylene C-H bonds.

Scheme 4-6. Palladium-catalyzed arylation of 2-ethyl pyridine



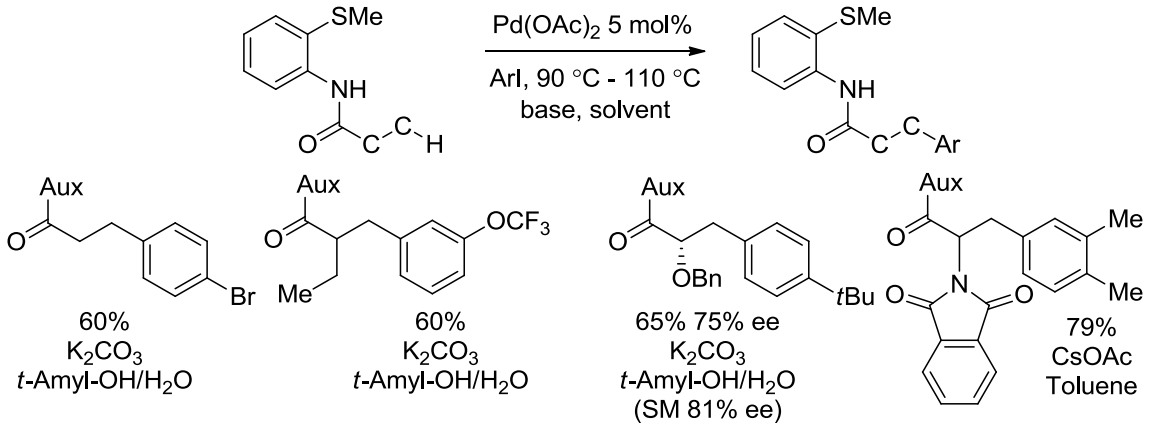
Scheme 4-7. Auxliary-assisted palladium-catalyzed arylation of unactivated sp^3 C-H bonds



Although 8-aminoquinoline is very efficient in functionalization of secondary C-H bonds, this auxiliary does not allow the mono-arylation of primary C-H bonds. Auxiliary optimization studies revealed that a successful auxiliary requires a nitrogen or sulfur coordinating group and a comparatively acidic NH bond.[8b] In fact, methyl thioaniline has been found to efficiently mono-arylate primary C-H bonds in carboxylic acid derivatives.

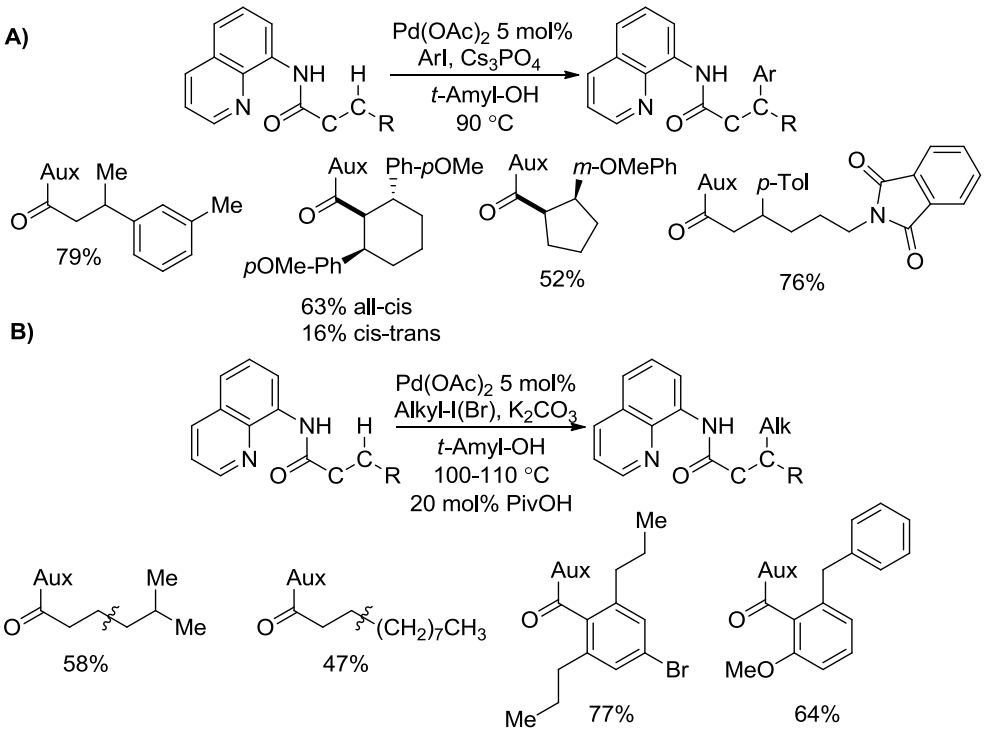
The reaction conditions involve $Pd(OAc)_2$ catalyst, inorganic base such as K_2CO_3 or CsOAc, and *t*-amyl-OH or toluene solvent.

Scheme 4-8. Palladium-catalyzed arylation of primary C-H bonds using methyl thioaniline auxiliary



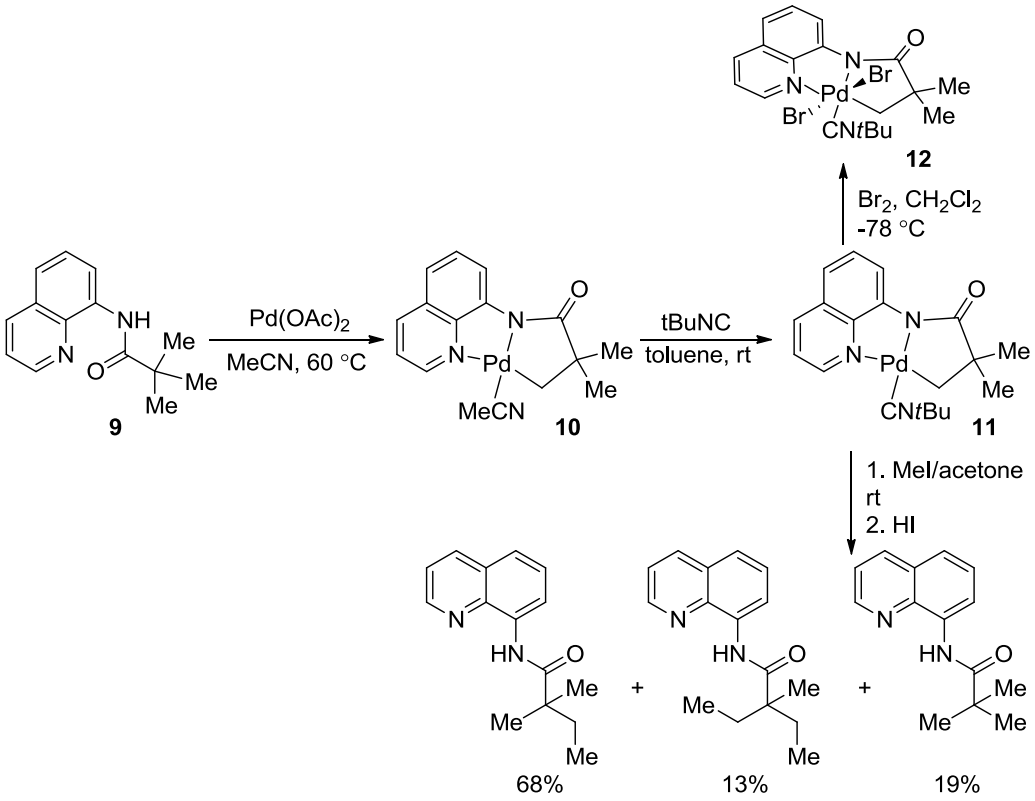
Method for arylation of secondary C-H bonds employing Cs_3PO_4 base instead of AgOAc was also reported. Conditions for alkylation of β-C-H bonds of carboxylic acid derivatives were also developed. The alkylation requires $Pd(OAc)_2$ catalyst, K_2CO_3 base, and pivalic acid additive. Lastly, methyl thioaniline or 8-aminoquinoline auxiliaries can be removed by base or acid hydrolysis.

Scheme 4-9. Palladium-catalyzed (A) arylation and (B) alkylation of β-C-H bonds of carboxylic acid derivatives



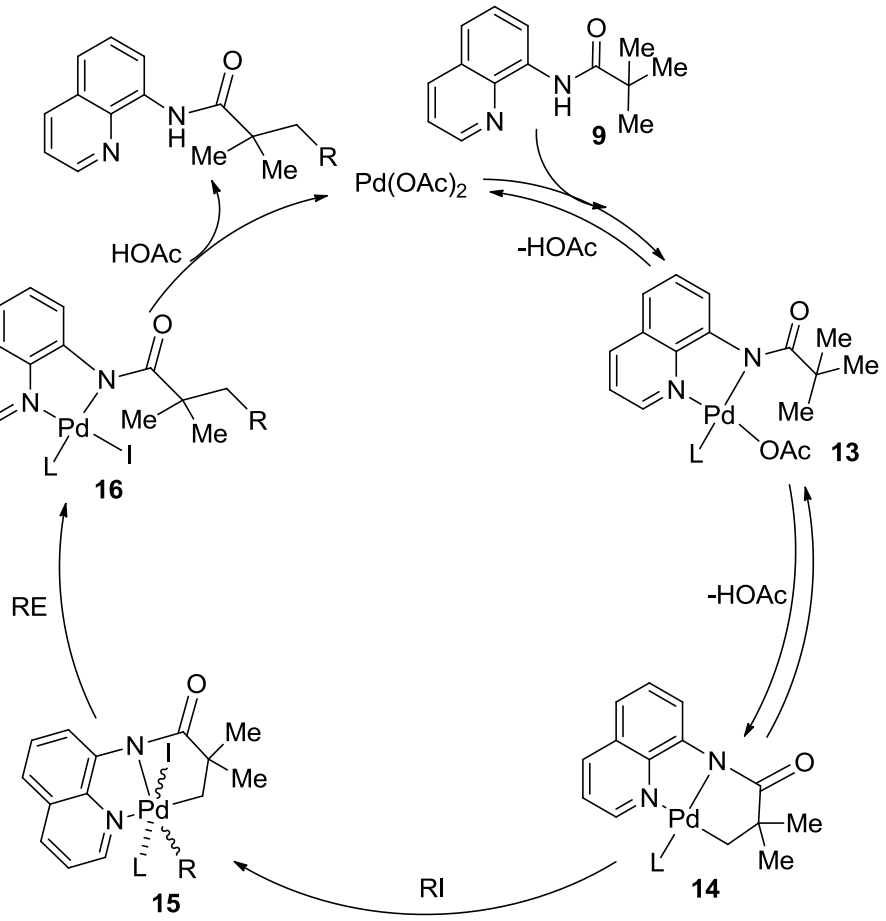
Mechanistic studies were performed to elucidate the mechanism and several interesting results were obtained. (1) The bicyclic palladacycles **10** and **11** were prepared in reaction of amide **9** and stoichiometric $Pd(OAc)_2$ and characterized by X-ray crystallography. (2) Treating **11** with bromine at -78 °C afforded Pd(IV) alkyl dibromide complex **12**. (3) The reaction of **11** with methyl iodide in acetone resulted in quantitative formation of a mixture of mono and dimethylated products which indicates that monomeric palladated complexes can be competent intermediates of the catalytic cycle.

Scheme 4-10. Mechanistic studies



The catalytic cycle for auxiliary-assisted, palladium-catalyzed functionalization of β-C-H bonds of carboxylic acid derivatives is postulated in Scheme 4-11. Palladium acetate reacts with amide **9** to generate complex **13**. The presence of NH bond in the auxiliary is essential for the formation of bidentate complex **13**. In the next step, a fast cyclometallation of *t*-butyl group will occur, resulting in the formation of palladacyle **14**. Oxidative addition of aryl or alkyl iodides to complex **14** affords a Pd(IV) complex **15**. Reductive elimination from complex **15** followed by ligand exchange releases the product and regenerates Pd(II) catalyst.

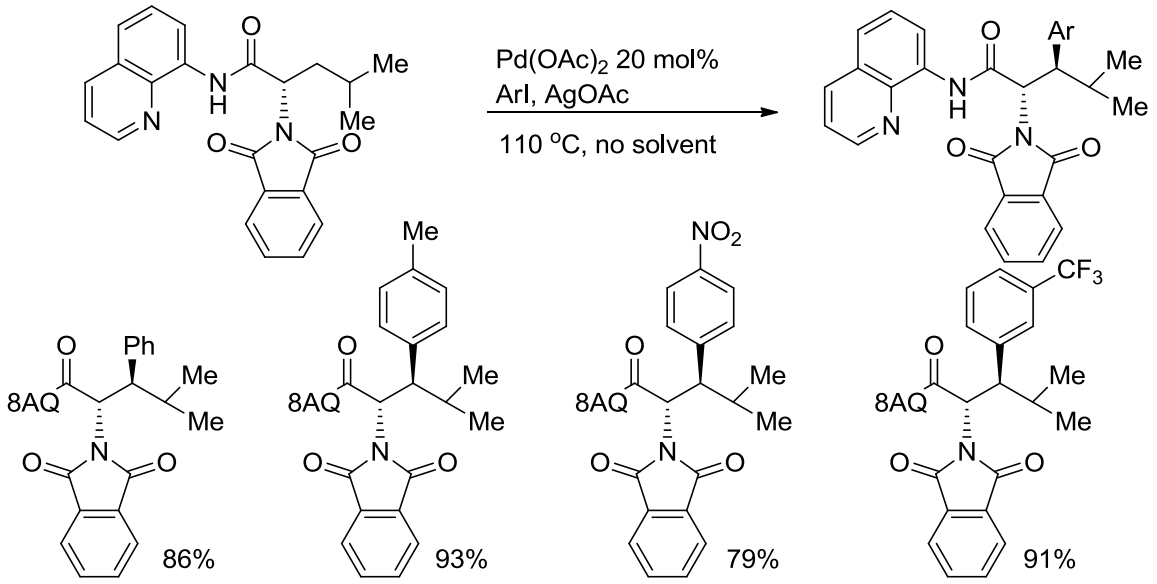
Scheme 4-11. Reaction mechanism



The method has high practicality as several groups have used this strategy for the construction of important core structures in total synthesis. The Chen group applied the method in the total synthesis of Celogentin C[9] and developed the intramolecular version of the reaction allowing annulation of benzo-rings.[10] The alkylation of γ C-H bond of amine derivatives via picolinic acid-directed palladium-catalyzed methodology was also reported recently.[11] Corey and coworkers reported the arylation and acetoxylation of amino acid C-H bonds using auxiliary-assisted palladium-catalyzed methodology.[12] Using 8-aminoquinoline auxiliary, $Pd(OAc)_2$ catalyst and AgOAc base, β-C-H bonds of various

amino acid amides were arylated in good yields. Nonetheless, mono arylation of protected alanine was not achieved using 8-aminoquinoline auxiliary.

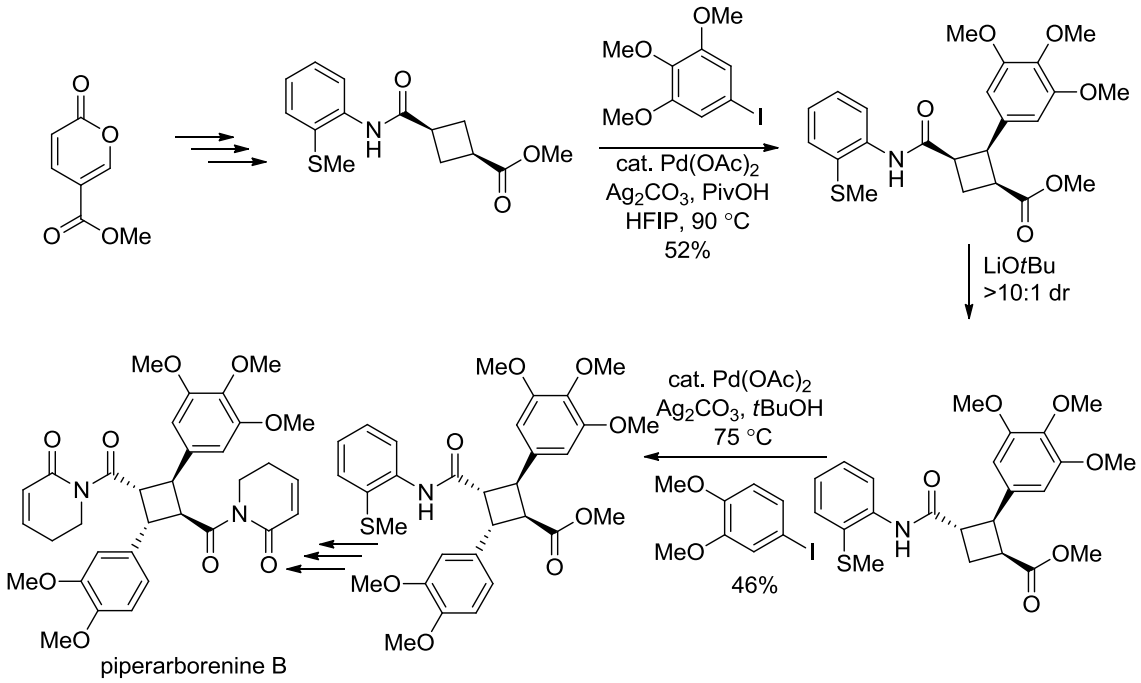
Scheme 4-12. Palladium-catalyzed functionalization of amino acid C-H bonds



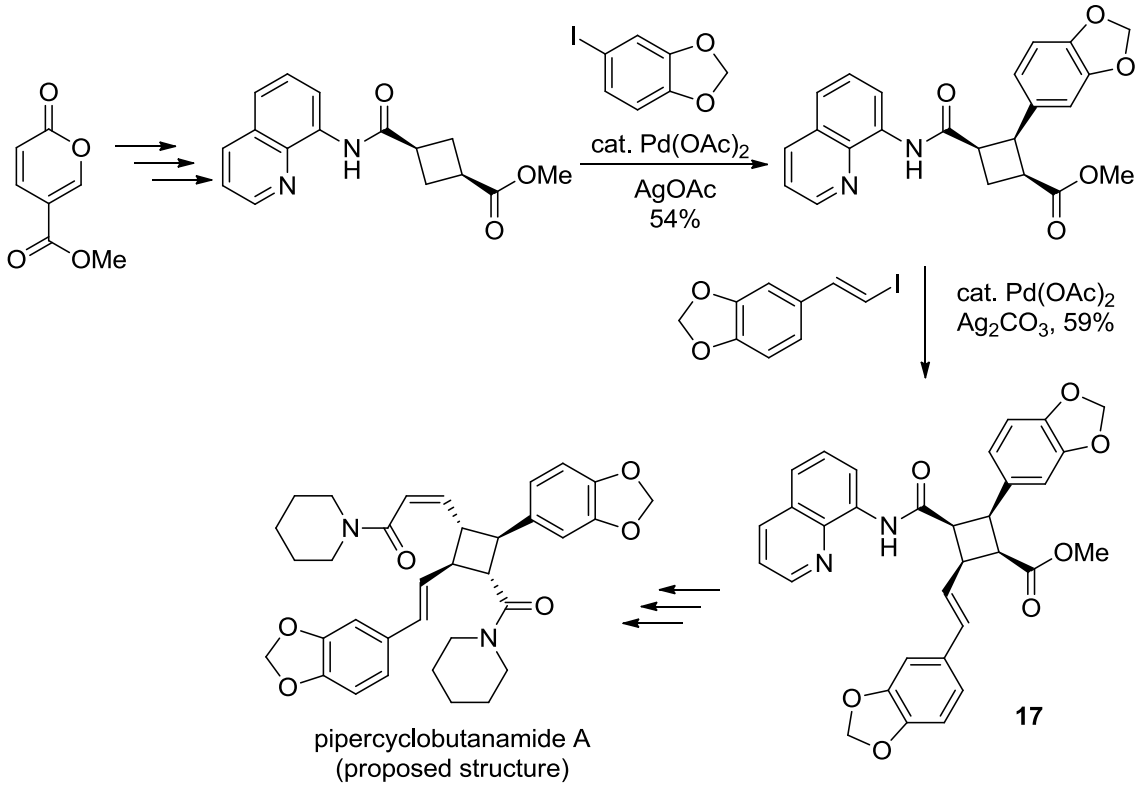
Baran and coworkers reported the total synthesis of piperarborenines (Scheme 4-13) and pipercyclobutanamide A (Scheme 4-14) via sequential cyclobutane sp^3 C-H bond arylation and olefination. Even though a direct [2+2] photocycloaddition of two similar yet distinct olefins is an appealing route for the synthesis of these natural products, this strategy has several limitations including homodimerization, orientation (head-to-head vesus head-to-tail), and E/Z isomerization resulting in variety of possible structures outcome. Alternatively, functionalization of cyclobutane C-H bonds via auxiliary-assisted palladium-catalyzed methodology would be an attractive strategy. Thus, the pre-existing carboxylic acid groups were used to guide the sequential C-H arylation and olefination of cyclobutane moiety. Using 2-methylthioaniline auxiliary, two different aryl iodides were consecutively introduced in good yields. Further removal of the auxiliary and installation

of new amides completed the synthesis of piperarborenine B.[13] With 8-aminoquinoline auxiliary, arylation and olefination can be achieved from amide **17** allowing the synthesis of pipercyclobutanamide A in 7 steps.[14]

Scheme 4-13. Total synthesis of piperarborenine B

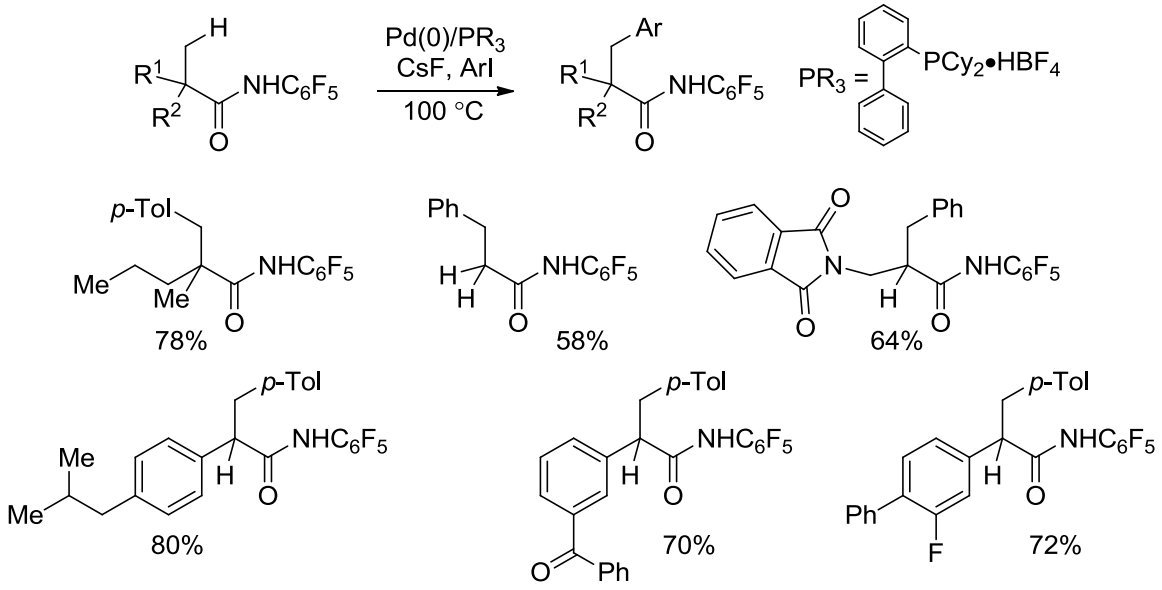


Scheme 4-14. Total synthesis of pipercyclobutanamide A



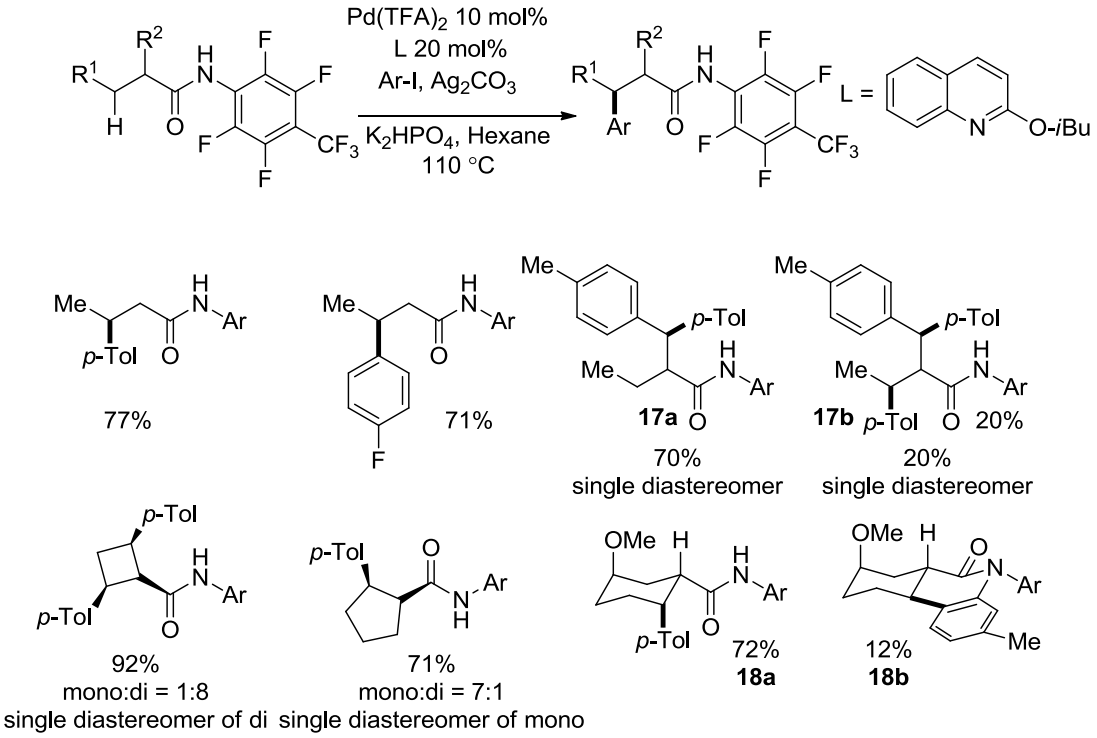
In 2009, the Yu group reported another method for β-arylation of carboxylic acid derivatives.[15] The method employs Pd(0)/Pd(II) catalytic cycle with $Pd(OAc)_2$ catalyst and Buchwald's Cyclohexyl JohnPhos ligand together with CsF base. The use of CO-NH-C_6F_5 directing group is essential for the product formation because pentafluorobenzoyl group decreases the nucleophilicity of amide, minimizing the side reaction of C-N bond formation. Using optimized conditions, various α-methyl carboxylic acid amides were arylated in good yields. However, the method works only for primary C-H bonds.

Scheme 4-15. Pd(0)/PR_3-catalyzed intermolecular arylation of sp^3 C-H bonds



As discussed earlier, the activation of methylene group is more challenging. Based on the reported system for arylation of primary C-H bonds, Yu and coworkers developed functionalization of methylene C-H bonds. The catalytic system employs $Pd(OAc)_2$ catalyst, Ag_2CO_3 oxidant, K_2HPO_4 base, and hexane solvent. Pyridine-based ligand is necessary for the reaction. The authors indicated that both the steric bulk and electron-donating ability of the ligand are crucial for achieving the desired selectivity.[16] Optimization has shown that 2-isobutoxyquinoline is the best ligand. It was observed that, benzylic C-H bonds are more reactive than alkyl C-H bonds. Interestingly, product **18b** (Scheme 4-16) was obtained through arylation of β-C-H bond followed by Pd-mediated *o*-C-H amidation of the trans-arylated product.

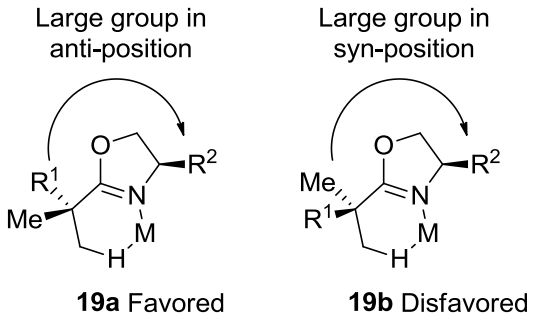
Scheme 4-16. Palladium-catalyzed arylation of methylene C-H bonds



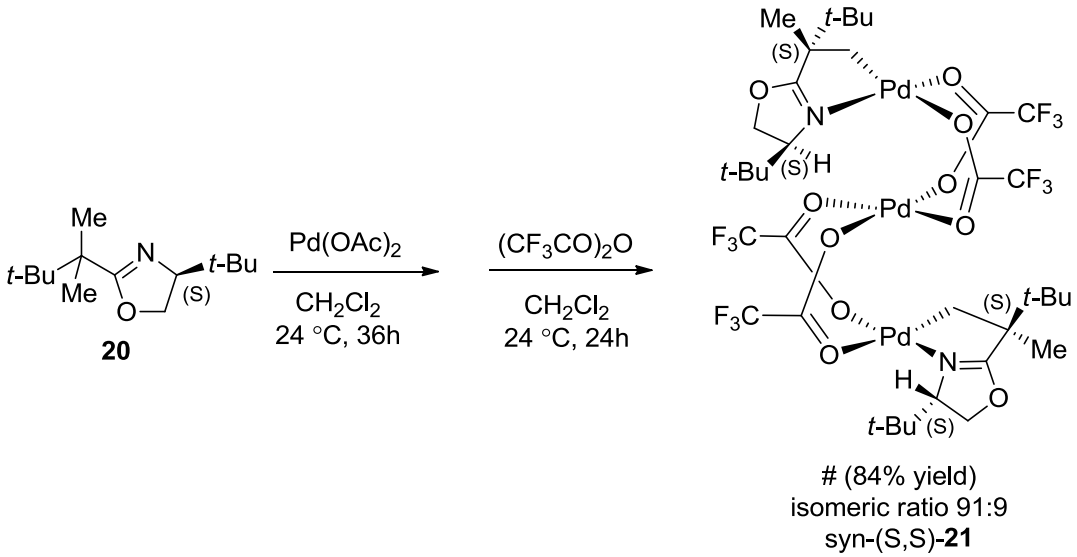
The reactivity and stereoselectivity of the oxazoline-directed palladium-catalyzed sp^3 C-H bond activation was studied by the Yu group.[17] Two bicyclic transition states **19a** and **19b** were proposed. In **19a**, the bulky R^1 and R^2 groups are in anti-position, thus making **19a** more favored than **19b**. As a consequence, predominant C-H activation pathway will occur through **19a**. This hypothesis was supported by experimental data and calculations. The trinuclear Pd(II) complex **21** was prepared from reaction of oxazoline **20** with $Pd(OAc)_2$ followed by ligand exchange with trifluoroacetic acid. Characterization of **21** by X-ray crystallography reveals syn-(S,S) configuration (Scheme 4-17). As predicted by model **19a**, the *t*-butyl groups on carboxylic acid and oxazoline moiety in complex **21** are oriented in anti-positions. *t*-Butyl substituent at R^2 is essential to achieve high selectivity.

Replacing *t*-butyl group by a smaller group such as *i*-Pr resulted in lower diastereoselectivity.

Figure 4-1. Model for diastereoselective C-H cleavage



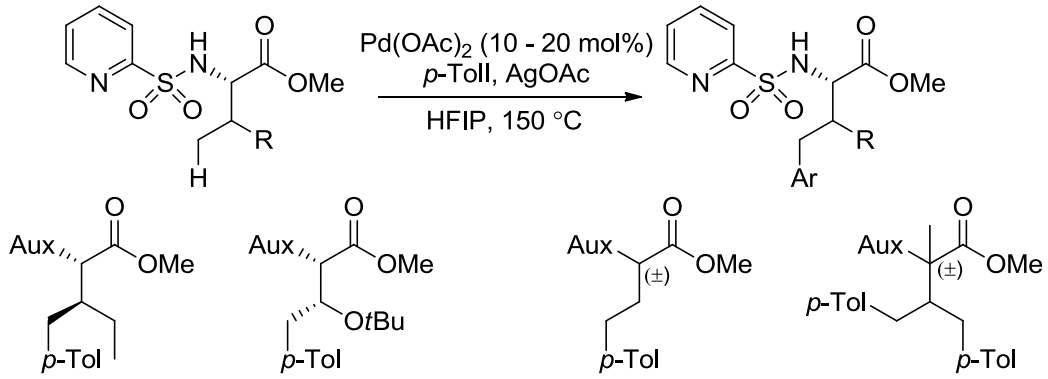
Scheme 4-17. Trinuclear Pd(II) complex



Recently, *N*-(2-pyridyl)sulfonyl group has been used as an auxiliary for the arylation of sp^3 γ C-H bonds of amino acid derivatives via palladium catalysis.[18] The optimized conditions involve $Pd(OAc)_2$ catalyst, AgOAc base, and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) solvent. Various amino acids such as valine, isoleucine, and threonine can be arylated in good yields. High diastereoselectivity was observed. Additionally, β-

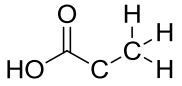
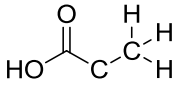
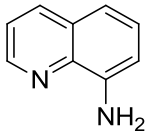
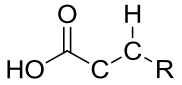
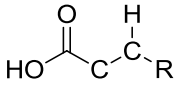
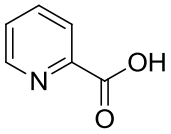
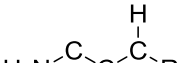
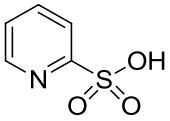
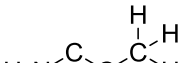
amino acids can also be arylated using this method. Lastly, reductive removal of the auxiliary afforded non-natural amino acids.

Scheme 4-18. Palladium-catalyzed arylation of γ-C-H bonds of amino acids



In general, significant research achievements have been accomplished in the field of auxiliary-assisted palladium-catalyzed functionalization of unactivated sp^3 C-H bonds. Auxiliaries and their corresponding active substrates are summarized in Table 4-1. Using 2-methylthioaniline (entry 1) or NH-C_6F_5 (entry 4) directing groups, primary C-H bonds of carboxylic acids can be arylated. In contrast, 8-aminoquinoline (entry 2) or NH-C_6F_4-CF_3 (entry 5) auxiliaries allow diarylation of methyl or monoarylation of methylene C-H bonds. Amine derivatives can be functionalized at γ-C-H bonds using either picolinic acid (entry 3) or *N*-(2-pyridyl)sulfonyl (entry 6) auxiliaries. Accordingly, these methods allow quick access to various carboxylic acid and amine derivatives.

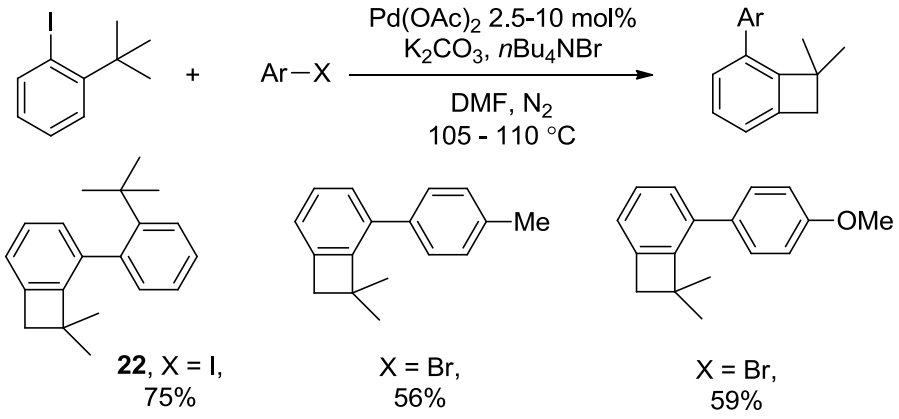
Table 4-1. Auxiliaries for palladium-catalyzed activation of sp^3 C-H bonds

Entry	Auxiliary	Reactive C-H bonds	Entry	Auxiliary	Reactive C-H bonds
1			4	HN-C_6F_5	
2			5	HN-C_6F_4-CF_3	
3			6		

2.2 Oxidative addition/metalation-induced functionalization of sp^3 C-H bonds

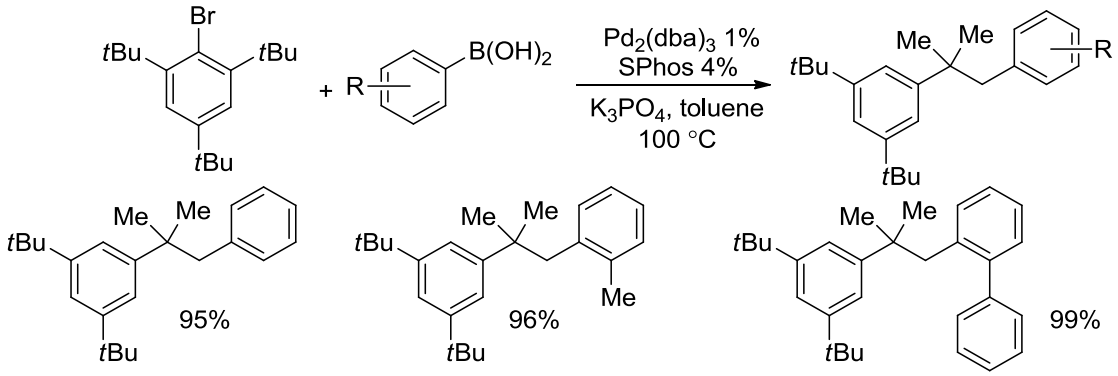
Oxidative addition-induced functionalization of sp^3 C-H bonds is another strategy widely used for the activation of sp^3 C-H bonds. In 1994, Dyker reported the homocoupling of 1-*t*butyl-2-iodobenzene under palladium catalysis to form the strained 1,2-dihydrocyclobutabenzene derivative **22** (Scheme 4-19).[19] This work is one of the first examples of oxidative addition-induced activation of sp^3 C-H bonds. Additionally, other aryl bromides were also reactive and afforded products in moderate yields.

Scheme 4-19. Palladium-catalyzed C-H activation of *t*Butyl groups



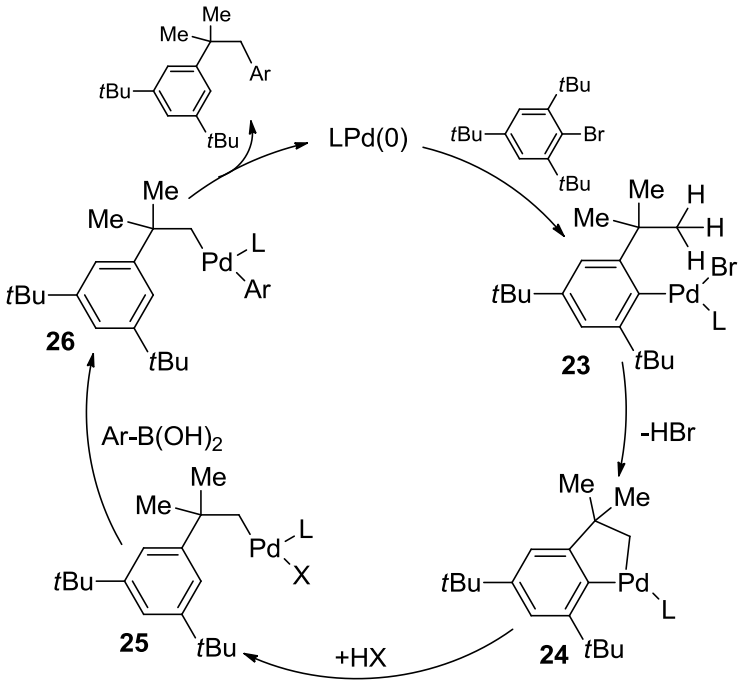
In 2005, while studying the effect of ligand structure on Suzuki-Miyaura coupling reaction, Buchwald and coworkers observed interesting C-H bond functionalization/cross-coupling sequence for hindered aryl bromides.[20] When 2,4,6-tri-*t*butylbromobenzene was subjected to reaction with phenylboronic acid under $Pd_2(dba)_3$ catalysis, the α,α-dimethyl-β-phenyl hydrostyrene derivative was obtained instead of biaryl product.

Scheme 4-20. Palladium-catalyzed C-H activation followed by coupling with arylboronic acids



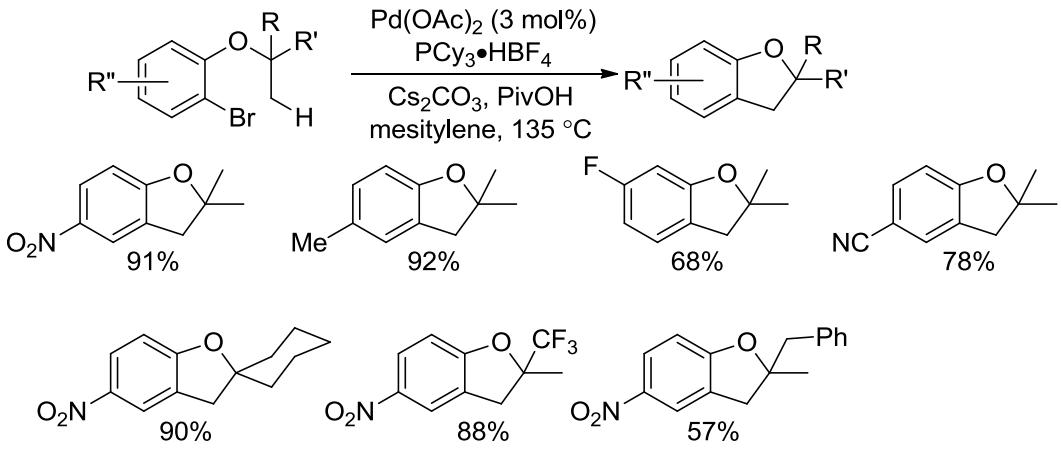
The mechanism of the reaction is shown in Scheme 4-21. In the first step, oxidative addition of aryl bromide to Pd(0) affords complex **23**. Cyclometalation with *t*-butyl group occurs to form the palladacycle **24**. Protonation and transmetalation with aryl boronic acid gives complex **26** which undergoes reductive elimination to generate the arylated product.

Scheme 4-21. Possible mechanism



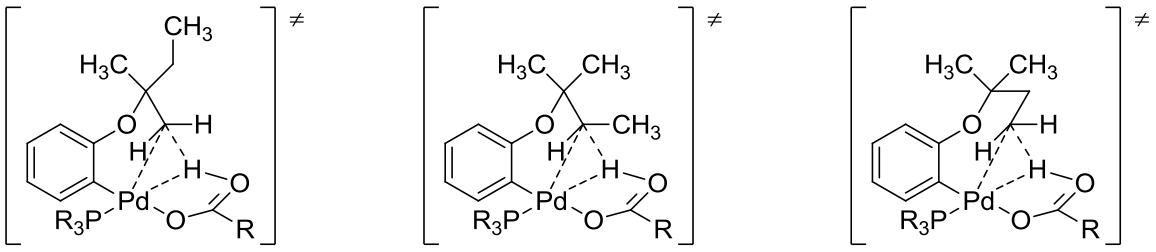
The palladium-catalyzed intramolecular arylation of alkanes was reported by Fagnou in 2007.[21] The method allows direct synthesis of 2,2-dialkyldihydrobenzofuranes from the corresponding aryl bromides. The optimized reaction conditions involve $Pd(OAc)_2$ catalyst, $PCy_3 \bullet HBF_4$ ligand, and pivalic acid additive. Sensitive functional groups such as nitro and cyanide are well tolerated under reaction conditions. High selectivity for primary C-H bonds over secondary C-H bonds was observed.

Scheme 4-22. Palldium-catalyzed alkane arylation



Mechanistic studies using DFT calculations suggested the involvement of agostic transition state in the palladation-deprotonation step. Reaction barriers for methyl C-H bonds (**TS-27**), methylene C-H bonds (**TS-28**), and the most remote methyl C-H bonds (**TS-29**) were calculated to be 27 kcal/mol, 32.5 kcal/mol, and 33.1 kcal/mol respectively. This data explained the site selectivity of the reaction.

Figure 4-2. Mechanistic rationale for site selectivity



TS-27
$\Delta G^{\neq}$ = 27.0 kcal/mol

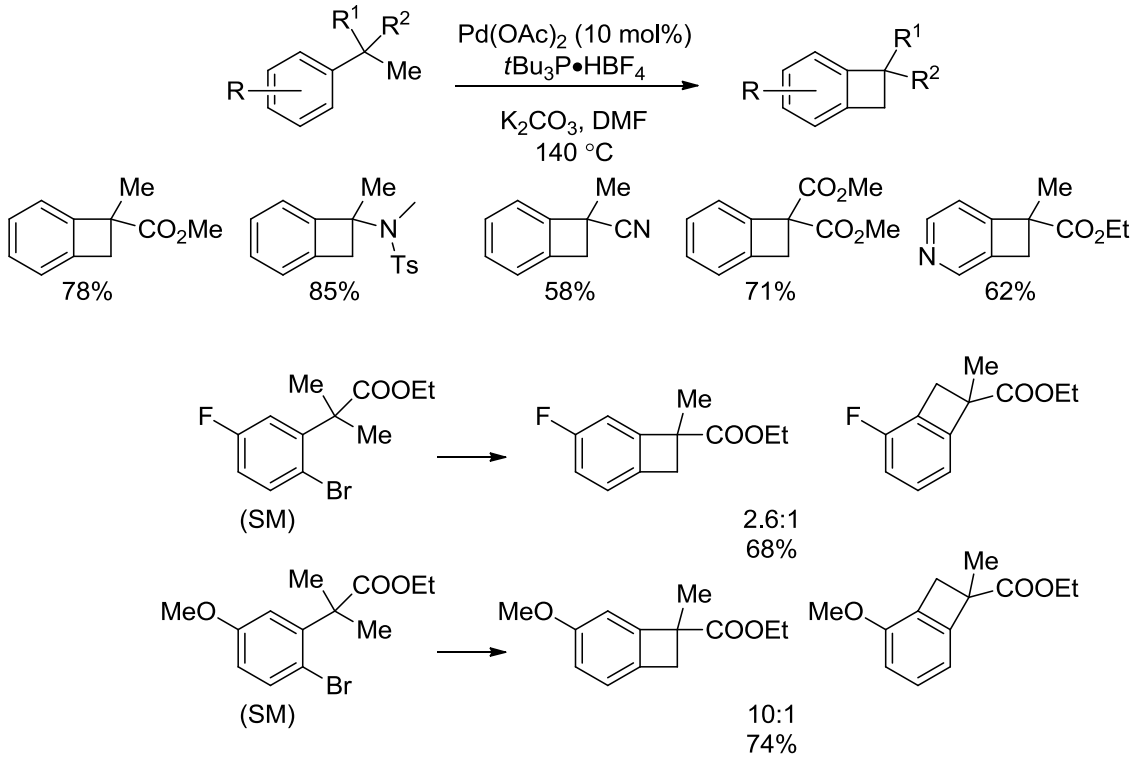
TS-28
$\Delta G^{\neq}$ = 32.5 kcal/mol

TS-29
$\Delta G^{\neq}$ = 33.1 kcal/mol

Benzocyclobutanes are important structures in pharmaceuticals and valuable intermediates for organic synthesis. General method that allows direct preparation of functionalized benzocyclobutanes via palladium-catalyzed sp^3 C-H bond activation was developed by

Baudoin group (Scheme 4-23).[22] The optimized conditions involve $Pd(OAc)_2$ catalyst, tBu$_3$P•HBF$_4$ ligand, and K_2CO_3 base. The scope of substrates was limited to aryl bromides containing quaternary benzylic substituents. Interestingly, with substrates bearing small substituents at para position to bromide, unexpected regioisomers arose from 1,4-migration of palladium.

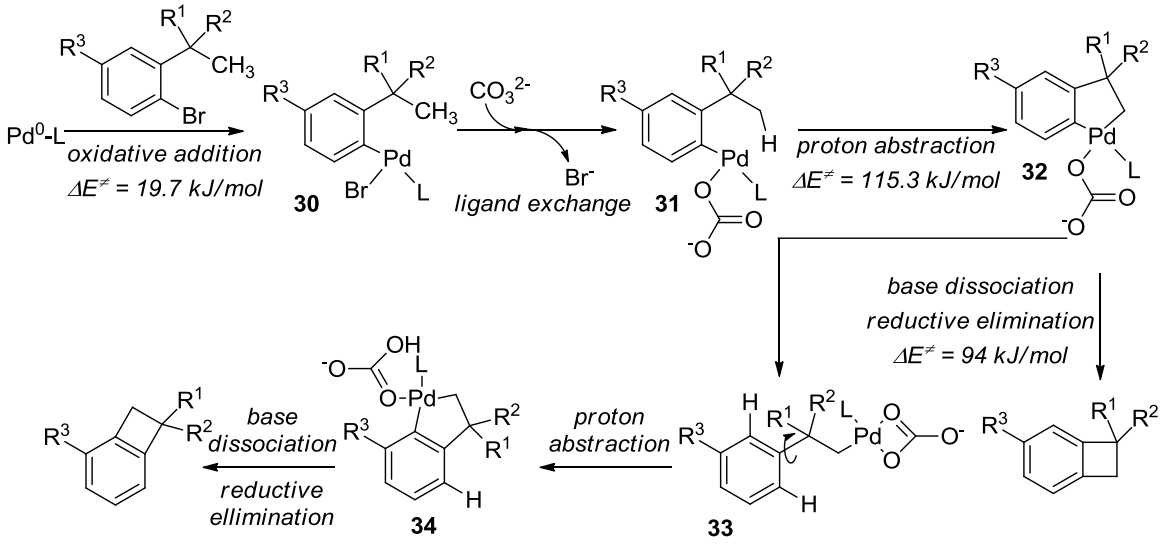
Scheme 4-23. Synthesis of benzocyclobutanes by palladium-catalyzed sp^3 C-H bond functionalization



The mechanism according to DFT calculations is postulated in Scheme 4-24. There are several important features that can be extrapolated from calculation data such as (i) the bulk of phosphine ligand is necessary to create monoligated Pd(0) complex **30** active species and to allow κ^1 coordination of the base cis to metallated aromatic ring (complex **31**) to accelerate activation of sp^3 C-H bonds; (ii) dissociation of protonated base from

complex **32** is essential for the reductive elimination/formation of cyclobutane ring. The formation of unexpected regioisomers via 1,4-palladium migration was explained through protonation of the metallated aromatic ring in complex **32** followed by cyclopalladation at the other position. Reductive elimination will then afford the 1,4-migration products.

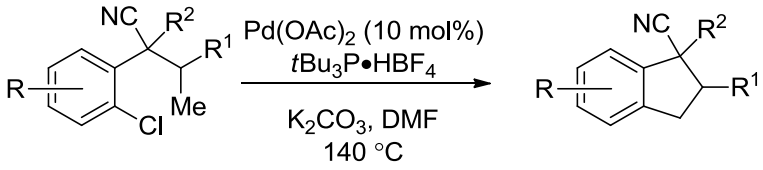
Scheme 4-24. Overall mechanism

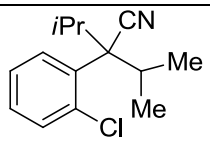
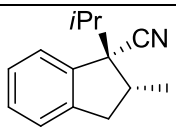
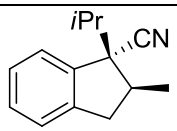
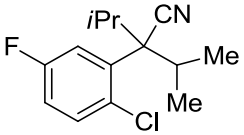
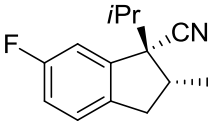
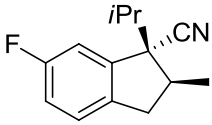
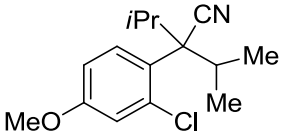
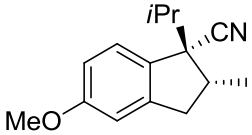
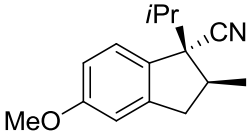
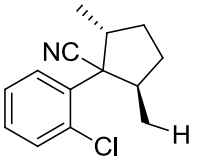
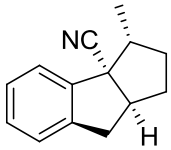
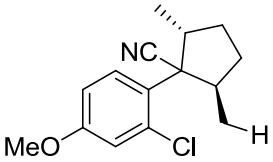
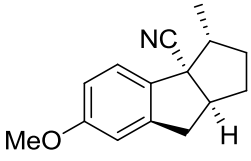


Using aryl chloride coupling partners for C-H bond arylation is highly attractive due to the low cost and greater avalibility of these compounds. It is also challenging because of strong aryl-Cl bonds. Fagnou and Baudoin have developed improved methods allowing intramolecular arylation sp^3 C-H bond using aryl chlorides.[23] In the presence of $Pd(OAc)_2$ catalyst and trialkylphosphine ligands, various aryl and heteroaryl chlorides are converted to benzocyclobutanes, indanes, dihydrobenzofuranes, or indolines. Particularly, the conditions for synthesis of indanes includes $Pd(OAc)_2$ catalyst, $(Cyp_3PH)BF_4$ ligand, and K_2CO_3 base. The activation at methyl C-H bonds is favored compared with methine C-H bonds, resulting in the formation of five-membered ring rather than four-membered ring

products (Table 4-2). The following observations were made (1) reaction occurs selectively at primary C-H bonds; (2) the formation of five-membered ring palladacyclic intermediates are favored over six- and seven-membered rings; (3) DFT calculations demonstrated that C-H activation is the rate-determining step; and (4) the Pd•••H-C agostic interaction increases the acidity of the geminal C-H bond, which is a critical factor for the regiochemistry control.

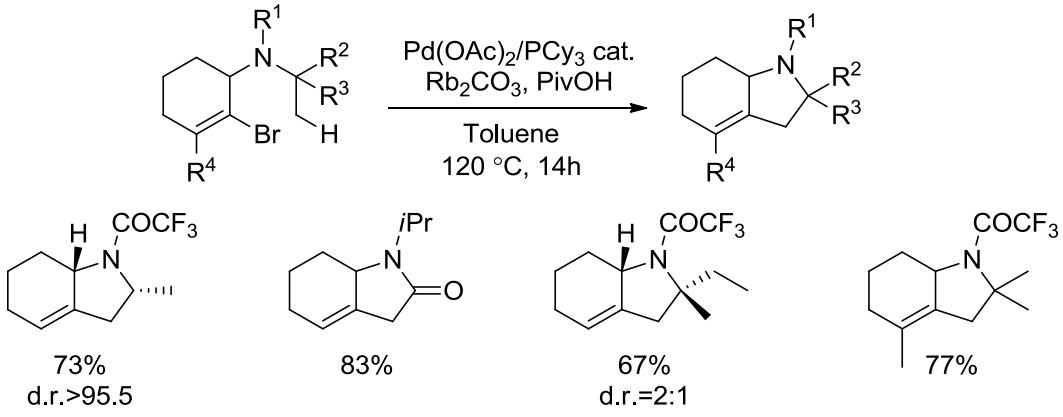
Table 4-2. Indanes synthesized by intramolecular C(sp^3)-H arylation



Aryl/heteroaryl chloride	Product		Yield%
			4:1 92
			3.3:1 84
			4:1 88
			79
			94

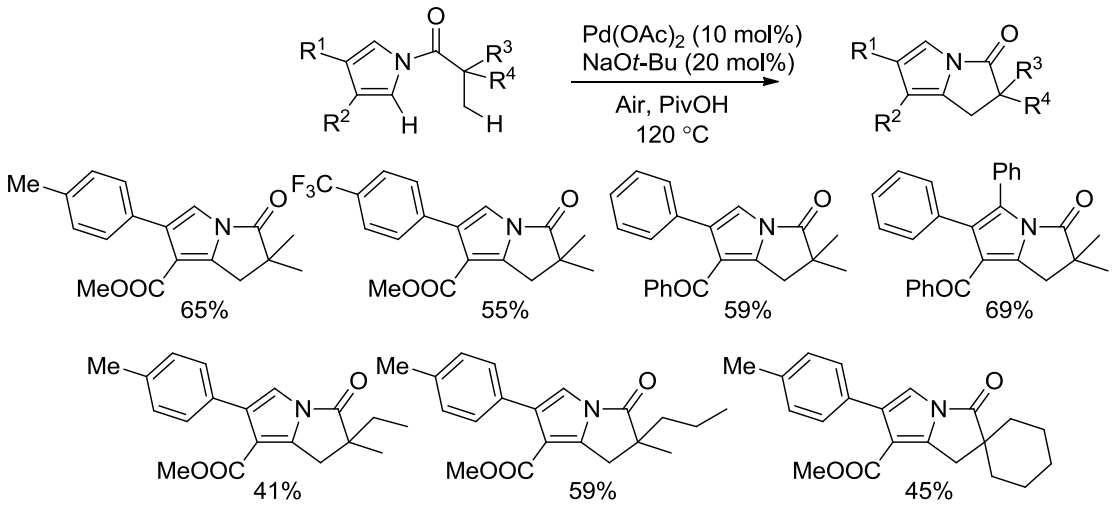
Beside aryl halides, alkenyl bromides are also active coupling partners for palladium-catalyzed intermolecular alkyl C-H bond functionalization.[24] In fact, using $Pd(OAc)_2$ catalyst, PCy_3 ligand, Rb_2CO_3 base, and pivalic acid additive, hexahydoindoles bearing various substituents can be synthesized in good yields. The catalyst selectively activates primary C-H bonds over secondary and tertiary C-H bonds.

Scheme 4-25. Palladium-catalyzed intramolecular alkenylation of sp^3 C-H bonds



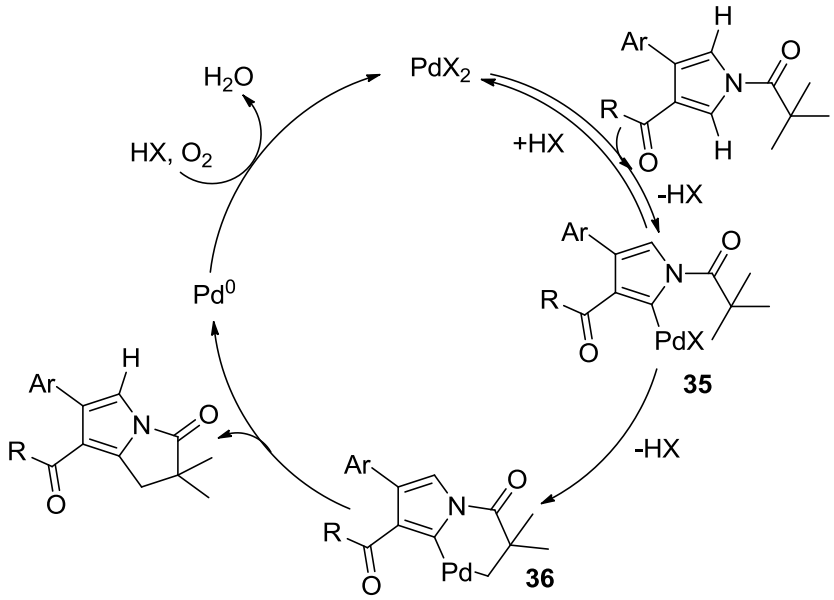
The direct cross coupling between (hetero)aryl C-H bonds and alkane C-H bonds would be beneficial in term of atom economy. Thus, the strategy of using metallation of aryl acidic C-H bonds for activation of sp^3 C-H bonds was developed by the Fagnou group. [25] This method provides a straight-forward way for the synthesis of bicyclic compounds. The optimized conditions involve $Pd(OAc)_2$ catalyst, NaO*t*Bu base, pivalic acid additive, and air oxidant.

Scheme 4-26. Palladium-catalyzed intramolecular coupling of arenes and unactivated alkanes



The mechanism of the reaction is shown in Scheme 4-27. First, a reversible palladation of acidic pyrrole C-H bond will occur, followed by the irreversible cleavage of sp^3 C-H bonds to form the palladacycle complex **36**. Reductive elimination from this complex will afford the desired product.

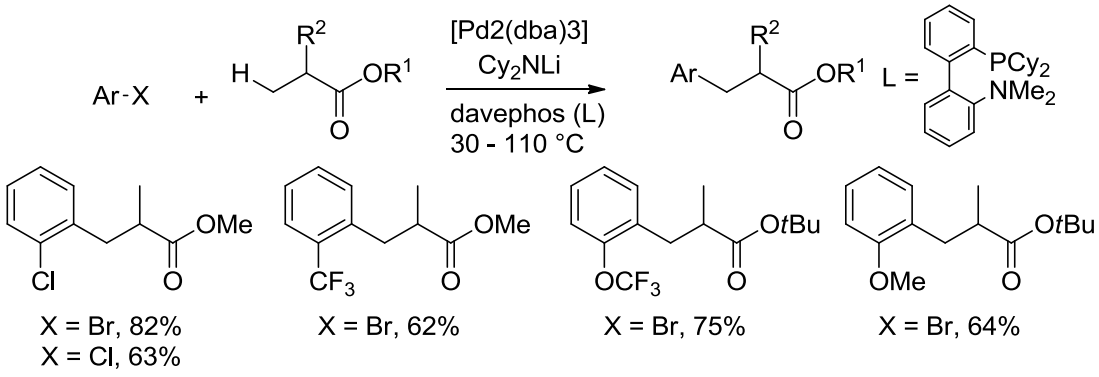
Scheme 4-27. Plausible mechanism



2.3 Non-directed intermolecular functionalization of sp^3 C-H bonds

Palladium-catalyzed β arylation of carboxylic esters was developed recently by the Baudoin group.[26] The optimized conditions involve $Pd_2(dba)_3$ complex, Cy_2NLi base, and Davephos ligand. Both aryl bromides and aryl chlorides can be used. It is observed that an electronegative group at ortho position of aryl bromide favors the arylation. An asymmetric reaction was also developed using chiral version of Davephos ligand. However, only moderate enantiomeric ratio was obtained. The same strategy was applied for the β- and γ-arylation of protected amino acid esters.[27]

Scheme 4-28. Palladium-catalyzed β-arylation of carboxylic esters



X = Br, 82%
X = Cl, 63%

X = Br, 62%

X = Br, 75%

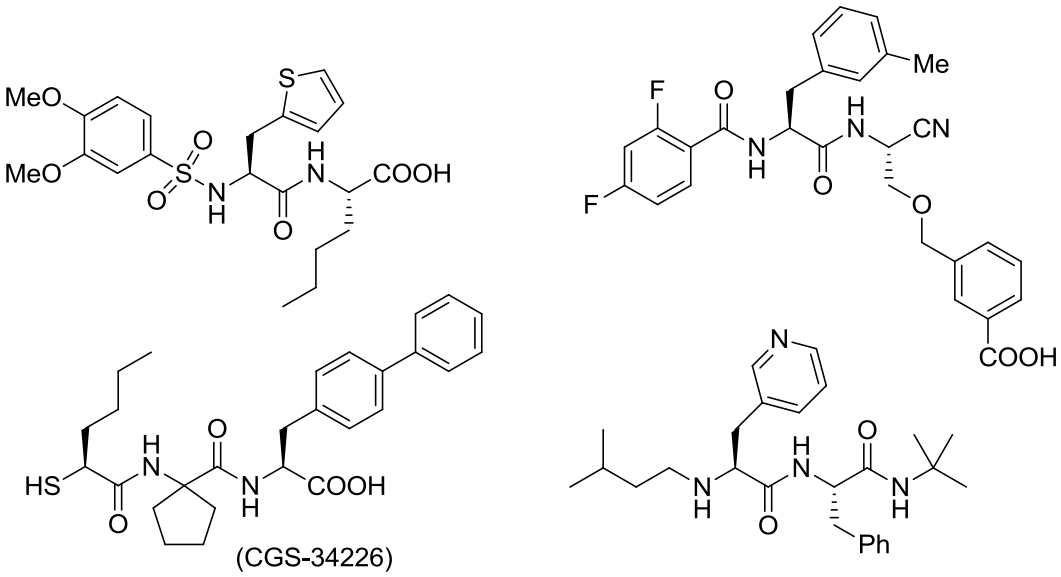
X = Br, 64%

Chapter 4-2 Auxiliary-assisted palladium catalyzed functionalization of amino acid C-H bonds

I. Introduction

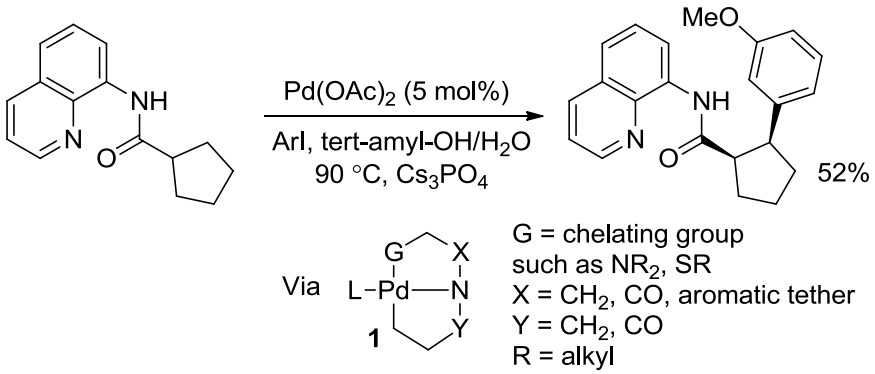
Non-natural amino acids have been widely used in drug discovery, protein engineering, peptidomimetics, glycopeptide synthesis, and click chemistry in biologically relevant systems.[28] Some examples of bioactive molecules containing (hetero)arylalanine units, which have been developed recently by pharmaceutical companies, are shown in Figure 4-3.[27] Conventional methods for the preparation of chiral, non-natural amino acids have several limitations, including requirement for the use of chiral ligands or auxiliaries, resolution, or asymmetric hydrogenation.[29] Therefore, alternative methods for the synthesis of these compounds are highly desirable. The synthesis of non-natural amino acids from chiral pool-natural amino acids would be beneficial due to the low cost and wide availability of the substrates. Our strategy was to develop a method that allow direct functionalization of amino acid C-H bonds by using auxiliary-assisted, palladium-catalyzed C-H bond functionalization methodology.

Figure 4-3. Bioactive molecules containing (hetero)arylalanine units



In 2005, we reported the β-arylation of carboxylic acids and γ-arylation of amine derivatives using a palladium catalyst and 8-aminoquinoline or picolinic acid auxiliaries.[8a] Further studies for auxiliary optimization have revealed that 2-methylthioaniline directing group allows selective monoarylation of primary C-H bonds.[8b] In contrast, 8-aminoquinoline allows diarylation of primary C-H bonds or monoarylation of secondary C-H bonds. The double five-membered chelate **1** is formed during the reaction and accounts for the observed regioselectivity. Several other groups have used this method for the total synthesis of natural products.[9,12-14] The Corey group reported the arylation and acetoxylation of β-C-H bonds of amino acid derivatives using 8-aminoquinoline auxiliary.[12] However, mono functionalization of alanine as well as the removal of directing group was not reported. Additionally, the effect of reaction conditions toward stereochemical integrity of the products was also unexplored.

Scheme 4-29. Auxiliaries for C-H bond arylation



II. Results and discussions

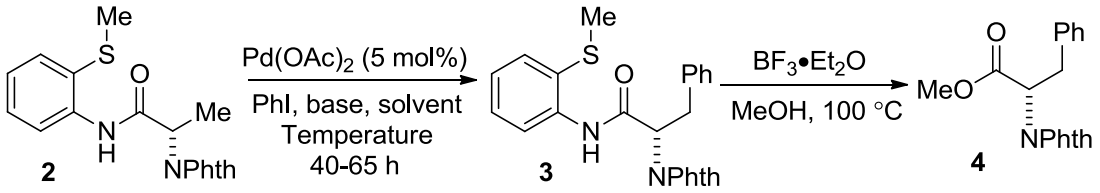
Most of the reports for transition-metal catalyzed C-H bond activation/C-C bond formations have been concentrated on method development or mechanistic investigations. Their applications in the synthesis of natural products are rare.[4,30] This can be explained by the fact that many of the methods employ harsh reaction conditions that are not compatible with sensitive functional groups. Moreover, there are relatively few methods allowing the activation of sp^3 C-H bonds.[1-27,31] Additionally, the use of non-removable directing groups in some of the methods significantly limits the practicality of the reactions. Within this work, we demonstrate the application of auxiliary-assisted palladium-catalyzed methodology developed by our group to the functionalization of amino acid sp^3 C-H bonds.

2.1 Optimization for arylation reaction with 2-methylthioaniline auxiliary

The functionalization of amino acid C-H bonds requires protection of amino group and installation of a directing group. A phthaloyl group was chosen to protect amino functionality.[32] Both 2-methylthioaniline and 8-aminoquinoline can be employed as

directing groups. The auxiliary was installed by treating phthaloylamino acid chlorides with the corresponding amines.[33]

Table 4-3. Reaction optimization



Entry	Base	T [°C]	Solvent	3 conv [%]	4 ee%	Note
1	CsOAc	110	Toluene	68*	77	
2	CsOAc	90	Toluene	61*	55	PivOH additive
3	CsOAc	60	Toluene	51	92	
4	AgOAc	70	-	90	88	
5	AgOAc	60	-	78*	92	
6	$AgOCOCF_3$	70	-	78	91	
7	$AgOCOCF_3$	60	-	77	92	
8	$AgOCOCF_3$	70	-	59	93	$Pd(OCOCF_3)_2$ catalyst

*isolated yield

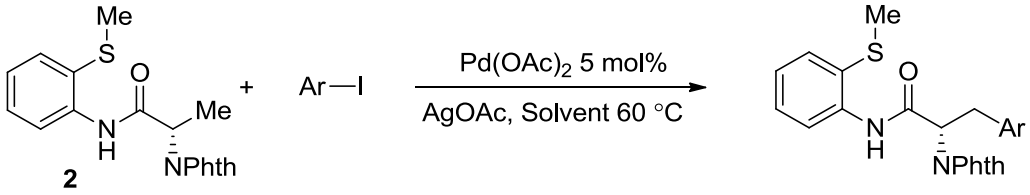
The optimization sequence was performed starting with arylation reaction of *N*-phthaloylalanine derivatives **2** with aryl iodide in the presence of $Pd(OAc)_2$ catalyst, using various bases. In the next step, auxiliary was removed by treating the arylated product **3** with $BF_3•Et_2O$ in methanol at 100 °C.[34] Nearly identical enantiomeric excess of **4** was observed by employing AgOAc, $AgOCOCF_3$, or CsOAc bases at 60-70 °C (entries 3-8). Higher reaction temperatures or addition of pivalic acid led to substantial erosion of

product enantiomeric excess (entries 1, 2, 4). To our delight, using $Pd(OAc)_2$ catalyst together with AgOAc base at 60 °C gave the optimal combination of yield and enantiomeric excess. These conditions were chosen for all further reactions.

2.2 Synthesis of modified phenylalanine derivatives

Using the optimized reaction conditions, alanine derivative **2** can be mono-arylated in good yield, thus allowing the direct synthesis of modified phenylalanines. Arylation of **2** with phenyl iodide and *p*-iodoanisole generate **3** and **4** in 78% and 68% yield, respectively. Other aryl and heteroaryl iodides such as 2-iodonaphthalene, 2-iodobenzothiophene, and 3-iodoindole are also active coupling partners, affording products **6**, **7**, and **8** in good yields. β-(2-Naphthyl)alanine-containing peptides are highly specific and potent Pin1 (peptidyl prolyl cis/trans isomerase) inhibitors.[35] Interestingly, the azide functionality is tolerated under reaction condition and 3-azidophenylalanine derivative **9** was obtained in 81% yield. Thus, this method allows the direct preparation of various phenylalanine derivatives from alanine derivatives.

Table 4-4. Monoarylation of alanine derivatives



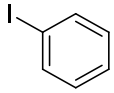
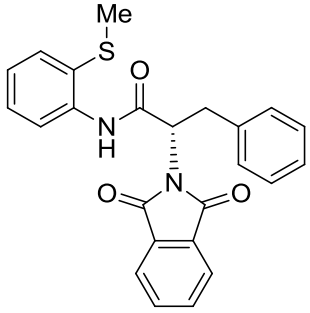
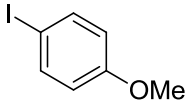
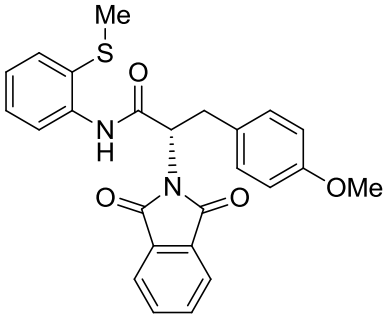
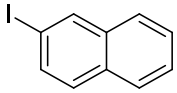
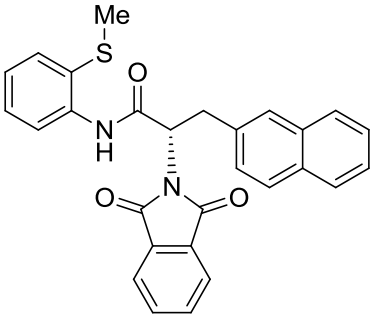
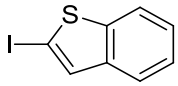
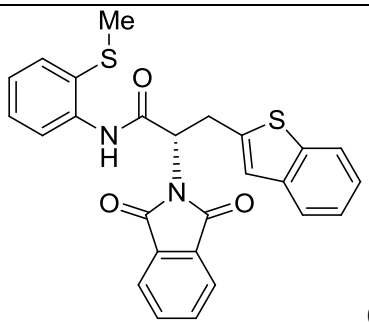
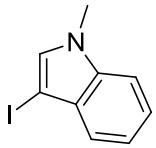
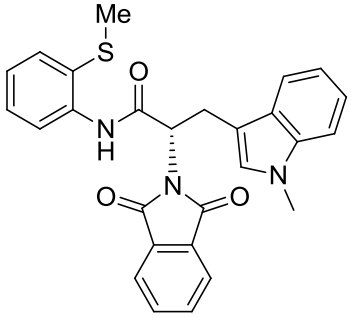
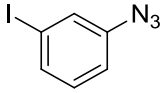
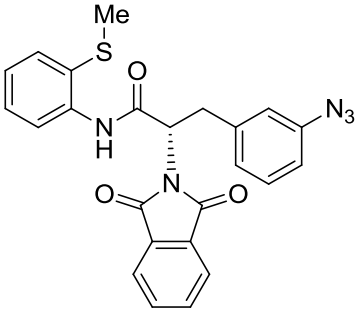
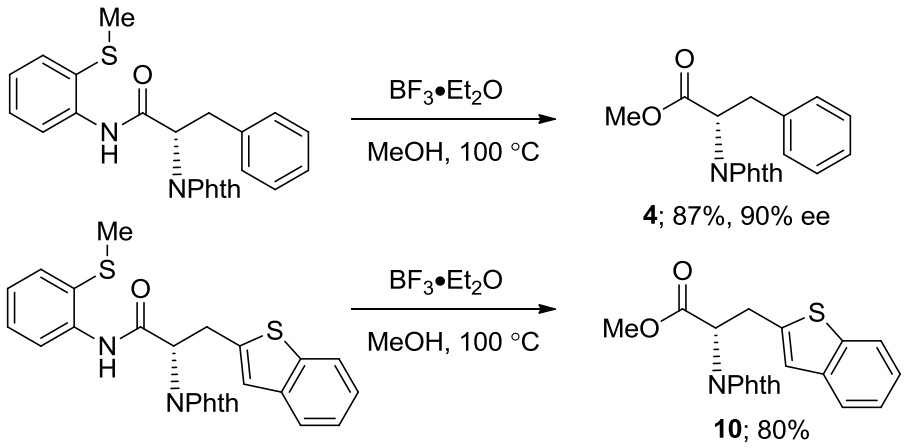
Entry	Ar-I	Products	Yield %
1		 **3**	78
2		 **4**	68
3		 **5**	60

Table 4-4. (*Continued*)

4		 **6**	74
5		 **7**	61
6		 **8**	81

2-Methylthioaniline auxiliary can be effectively removed by reaction with $BF_3 \bullet Et_2O$ in methanol, affording methyl ester **4** in 87% yield and 90% ee. Benzothiophene derivatives **10** was obtained in 80% yield.

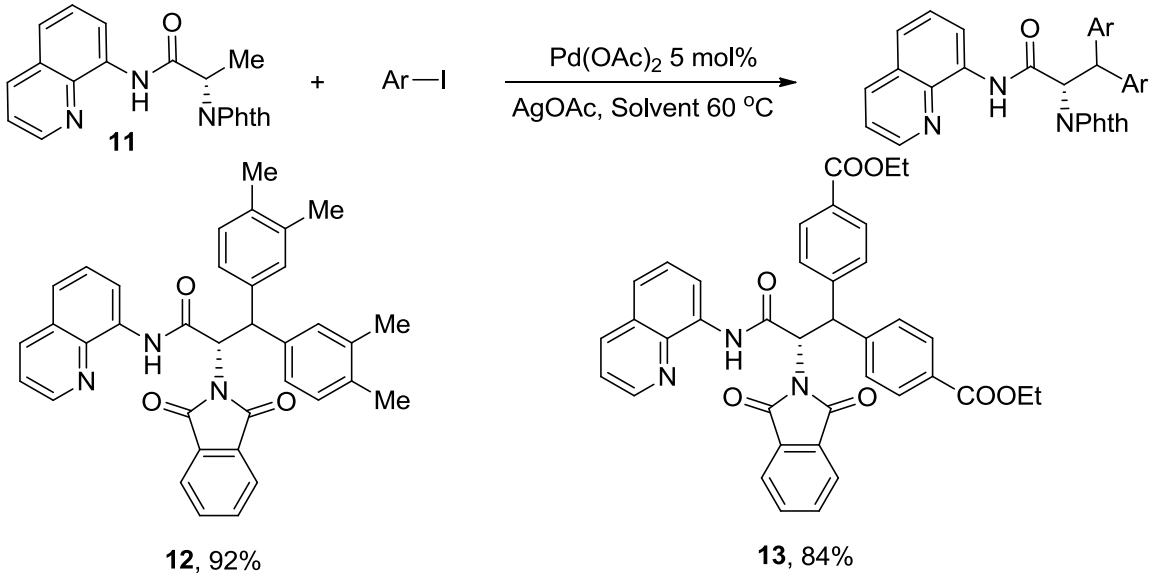
Scheme 4-30. Removal of auxiliary



2.3 8-Aminoquinoline for functionalization of amino acid C-H bonds

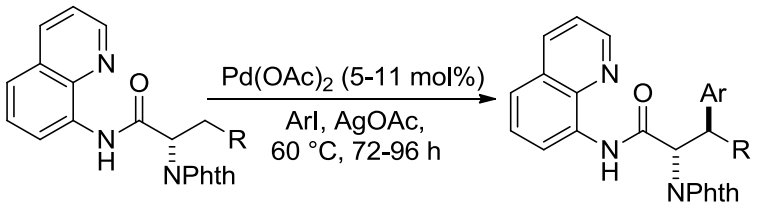
Using 8-aminoquinoline directing group, diarylation of methyl group and monoarylation of methylene group can be observed. In fact, compounds **12** and **13** were obtained in excellent yields from the reaction of alanine derivative **11** with 3,4-dimethyl-1-iodobenzene and ethyl-4-iodobenzoate, respectively.

Scheme 4-31. Diraylation of alanine derivative



Phenylalanine derivative **14** can be β-arylated to form products **15** and **16** in excellent yields and with high diastereoselectivity. The reaction of lysine derivative **17** with *p*-iodoanisole and 2-iodothiophene affords the arylated products **17** and **18** in 85% and 80% yields respectively. Product **21** was obtained in 77% yield with very high diastereomeric ratio in the arylation of leucine derivative **20**. Similarly, **22** was formed in 80% yield and 24:1 diastereomeric ratio. In general, the arylation is successful with both aryl and heteroayl iodides and affords products in good yields with high diastereoselectivities. The reaction can be scaled up to 5.55 mmol scale for leucine derivative and 67% yield of product **21** was obtained.

Table 4-5. Arylation of methylene C-H bonds in amino acid derivatives



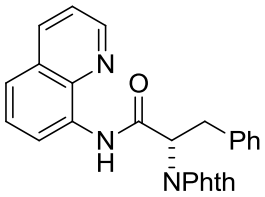
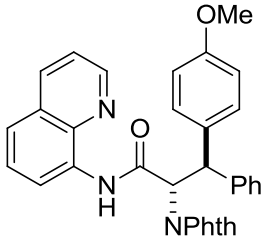
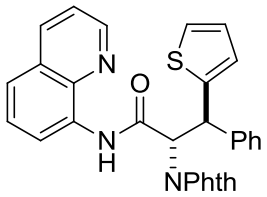
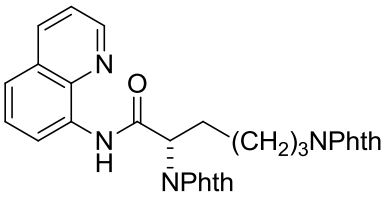
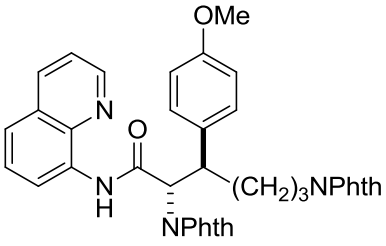
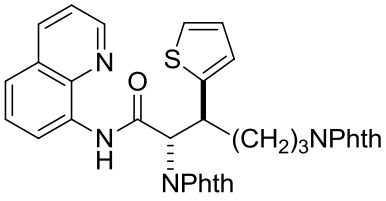
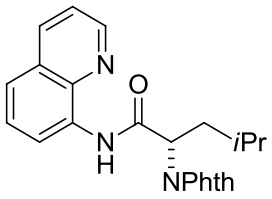
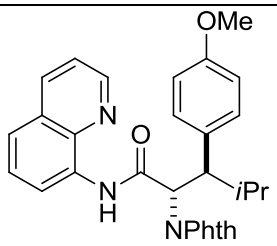
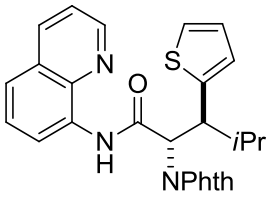
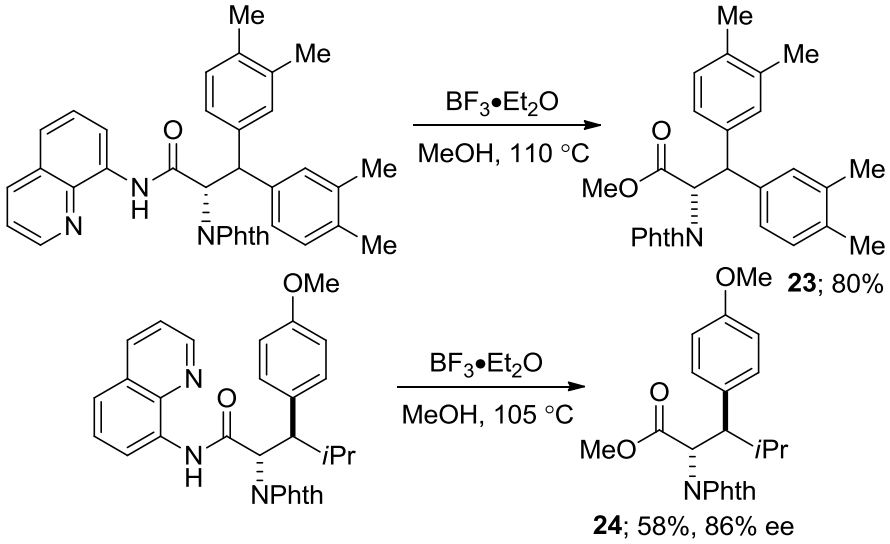
Substrate	Product	Yield, crude d.r.
 **14**	 **15**	91% 24:1
	 **16**	95% >50:1
 **17**	 **18**	85% 16:1
	 **19**	80% 13:1

Table 4-5. (*Continued*)

 **20**	 **21**	77% >50:1
	 **22**	80% 24:1

8-Aminoquinoline auxiliary was removed to form methyl esters **23** and **24**. Compound **23** was obtained with 86% ee which can be increased to 95% ee after one recrystallization. Additionally, relative stereochemistry of **24**, which is a derivative of highly constrained β-isopropyltyrosine,[36] was verified by X-ray crystallography.

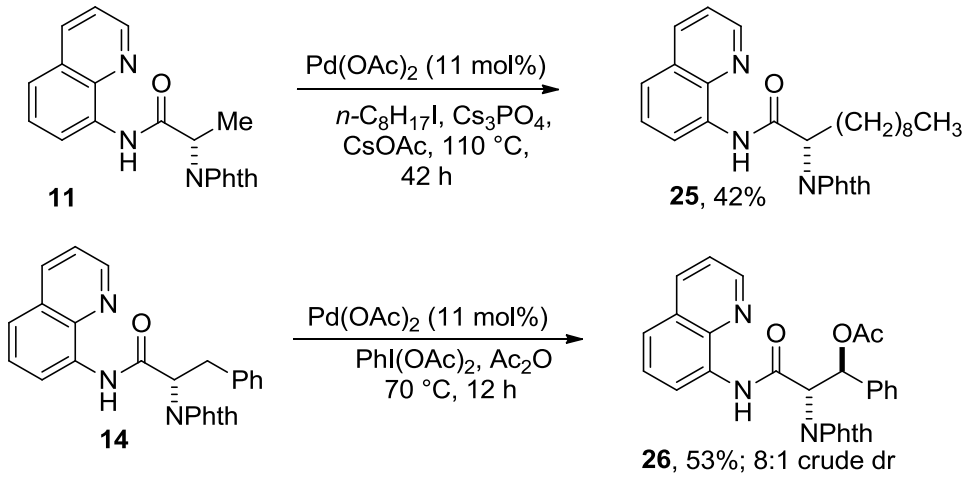
Scheme 4-32. Removal of 8-aminoquinoline auxiliary



2.4 Alkylation and acetoxylation of amino acid derivatives

Preliminary results in alkylation and acetoxylation of amino acid C-H bonds are reported in Scheme 4-32. Thus, in the presence of $Pd(OAc)_2$ catalyst, Cs_3PO_4, and CsOPiv bases, alanine derivative **11** was alkylated by 1-iodooctane affording **25** in 42% yield. Compound **25** is a derivative of a lipidic amino acid which has shown tumor cell growth inhibitor activity.[37] Acetoxylation of **14** gave **26** in 53% yield by using $PhI(OAc)_2$ oxidant.

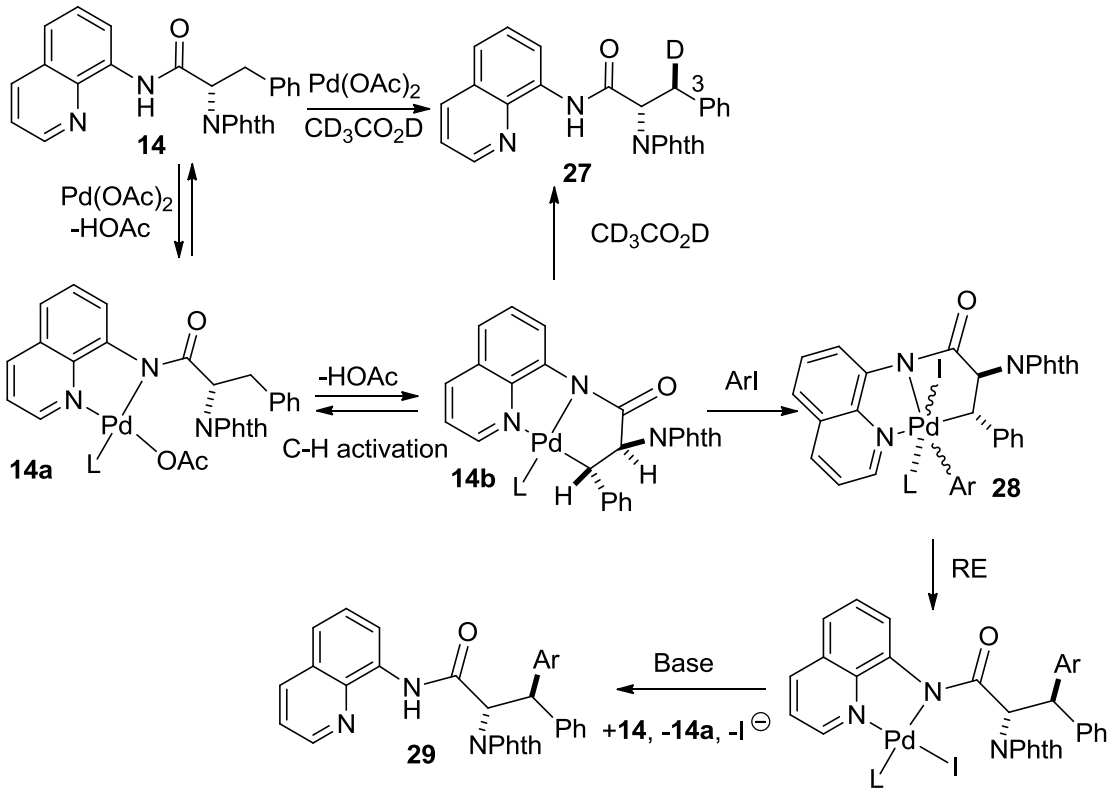
Scheme 4-33. Alkylation and acetoxylation of amino acid derivatives



2.4 Mechanistic considerations

Mechanistic study was performed to explain the high diastereoselectivity of the reaction. Overall, two steps in the catalytic cycle that can affect diastereoselectivity are the C-H activation and reductive elimination steps.[38] The H/D exchange in **14** was examined by heating the substrate with catalytic $Pd(OAc)_2$ in CD_3CO_2D-toluene-d8 mixture (Scheme 4-34). After 5 hours at 100 °C, 64% of deuterium incorporation was observed at 3S position with minimal (<10%) incorporation at 3R position. A generalized reaction mechanism can be proposed. Formation of a palladium amide **14a** is followed by the C-H activation that affords **14b**. The complex **14b** then can be protonated or deuterated leading to **27**. Since protonation likely occurs with retention of configuration,[39] it can be assumed that **14b** has a trans arrangement of phthaloyl and phenyl groups and that the diastereoselectivity of the arylation is set at the stage of palladation. Oxidative addition to give a high-valent[40] Pd intermediate **28** is followed by reductive elimination that proceeds with retention of configuration. The oxidative addition of aryl iodide to Pd(II) might be accelerated by silver salts.[41] Ligand exchange affords **29** and regenerates **14a**.

Scheme 4-34. Mechanistic considerations



III. Conclusions

In conclusion, we have developed an alternative method for the synthesis of non-natural amino acids from natural amino acids via auxiliary-assisted, palladium-catalyzed methodology. A variety of substituted phenylalanines can be prepared in a highly convergent way by using 2-methylthioaniline auxiliary. With 8-aminoquinoline auxiliary, diarylation of methyl groups and diastereoselective monoarylation of methylene groups in amino acids can be achieved. In the final step, the auxiliary was efficiently removed with minimal erosion of enantiomeric excess.

IV. Experimental section

4.1 General considerations

Reactions were performed without special precautions in 1-dram screw-cap vials equipped with a stir bar. Column chromatography was performed on 60 Å 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 × 21.4 mm) column. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on JEOL ECX-400 and JEOL ECX-500 spectrometers using TMS or solvent peak as a standard. Elemental analyses were performed by Atlantic Microlab Inc. of Norcross, GA. IR-spectra were obtained using a ThermoNicolet Avatar 370 FT-IR instrument. Preparative thin layer chromatography was performed on Analtech TLC plates (20 cm × 20 cm, 20 microns).

The racemic mixtures of the following compounds: methyl 3-(benzothiophene-2-yl)-2-phthalimidopropionate, methyl 3,3-di(3,4-dimethylphenyl)-2-phthalimidopropionate, methyl 3-(4-methoxyphenyl)-4-methyl-2-phthalimidopentanoate were sent to Chiral Technologies, Inc. and Regis Technologies, Inc. for screening on chiral stationary phases. Unfortunately, only methyl 3-(4-methoxyphenyl)-4-methyl-2-phthalimidopentanoate was separated on Chiralpack IA and methyl 2-phthalimido-3-phenylpropionate was separable on Chiralcel OJ-H.

4.2 Materials

The following starting materials were obtained from commercial sources and were used without further purification: phthalic anhydride, L-alanine, L-leucine, L-phenylalanine, L-

lysine, thionyl chloride, $Pd(OAc)_2$, iodobenzene, CsOAc, AgOAc, dry methanol, BF_3Et_2O, 4-iodoanisole, benzothiophene, *n*butyllitium 2.5M solution in hexane, I_2, *N*-methylindole, 1-azido-3-iodobenzene 0.5M solution in methyl *t*-butyl ether, 4-iodo-*o*-xylene, ethyl 4-iodobenzoate, 2-iodothiophene, Cs_3PO_4, CsOPiv, 1-iodooctane, $PhI(OAc)_2$, acetic anhydride, acetic acid-D4, and toluene-D8. 2-Iodonapthalene was synthesized by a known procedure. [42] *N*-(2-phthalimidopropionyl)-2-methylthioaniline was prepared following the reported procedure starting from L-alanine.[8] Chiralpack IA and Chiralcel OJ-H columns were purchased from Chiral Technologies, Inc.

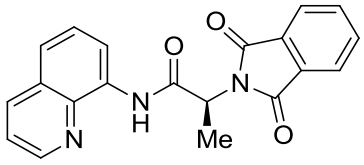
SYNTHESIS OF STARTING AMIDES

General procedure for protecting amine group of amino acids: Phthalimido-protected amino acids were prepared by following a reported procedure.[32] The appropriate amino acid and finely ground phthalic anhydride were heated at 160 °C in a 250 mL round-bottom flask equipped with a condenser and stir bar for 2 hours. After cooling to room temperature, the solid mixture was dissolved in minimum amount of boiling methanol. The filtrate was diluted with cold water and white solid appeared slowly. The crystals were collected and washed with cold water followed by drying under high vacuum.

General procedure for synthesizing amino acid chlorides: Acyl chlorides of phthalimido-protected amino acids were prepared by following a reported procedure.[33] Phthalimido-protected amino acid, thionyl chloride and few drops of DMF were reacted in toluene at 80 °C in a 100 ml round-bottom flask equipped with a condenser and a stir bar for 2-3 h. After the reaction, toluene and the excess of thionyl chloride were removed by

vacuum distillation. The crude residual acyl chloride was dissolved in anhydrous CH_2Cl_2 for the next reaction.

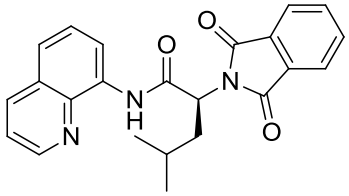
General procedure for amide synthesis: 8-Aminoquinoline and 2,6-lutidine were dissolved in anhydrous CH_2Cl_2 in a 100 ml round-bottom flask followed by dropwise addition of acyl chloride solution in CH_2Cl_2 through cannula. The reaction mixture was stirred overnight. The reaction was diluted with CH_2Cl_2 (25 mL), washed by aqueous HCl (15 mL, 1N), $NaHCO_3$ (15 mL of saturated aqueous solution), brine (25 mL), and dried over Na_2SO_4. The organic solvent was removed by evaporation. Purification by column chromatography afforded pure amides.



(S)-*N*-(2-Phthalimidopropionyl)-8-aminoquinoline (11) L-Alanine (8.9 g, 100 mmol) and phthalic anhydride (15.3 g, 103 mmol) were heated at 160 °C for 2 h. After cooling to room temperature, the solid mixture was dissolved in minimum amount of boiling methanol. The filtrate was diluted with cold water (70 mL) and white solid appeared slowly. Collecting and washing the precipitate with cold water gave (S)-2-phthalimidopropionic acid (16 g, 73%).

(S)-2-Phthalimidopropionic acid (4.4 g, 20 mmol), thionyl chloride (9 mL, 120 mmol), and 4 drops of dimethylformamide were heated in toluene (40 mL) at 80 °C for 2 h. After the reaction, toluene and excess of thionyl chloride were removed by vacuum distillation. The acid chloride was dissolved in CH_2Cl_2 (10 mL) and used for next reaction.

8-Aminoquinoline (2.2 g, 15 mmol) and 2,6-lutidine (2.2 g, 20 mmol) were dissolved in CH_2Cl_2 (30 mL) followed by dropwise addition of (S)-2-phthalimidopropionyl chloride (20 mmol) in CH_2Cl_2 (10 mL) via cannula. The reaction mixture was stirred overnight at rt. Column chromatography in toluene/ethyl acetate 5:1 gave 4.45 g (87%) of amide as a white solid. This compound is known.[12] ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 10.41-10.26 (*s*, 1H) 8.75-8.66 (*m*, 2H) 8.14 (*dd*, 1H, *J*= 1.83, 8.2 Hz) 7.90 (*dd*, 2H, *J*= 3.2, 5.4 Hz) 7.75 (*dd*, 2H, *J*= 2.7, 5.5 Hz) 7.54-7.48 (*m*, 2H) 7.41 (*dd*, 1H, *J*=4.1, 8.2 Hz) 5.27 (*q*, 1H, *J*= 7.3 Hz) 1.98 (*d*, 3H, *J*= 7.3 Hz).

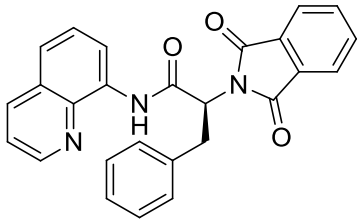


(S)-*N*-(2-Phthalimido-4-methylpentanoyl)-8-aminoquinoline (20) L-Leucine (13.1 g, 100 mmol) and phthalic anhydride (14.8 g, 100 mmol) were heated at 160 °C for 2 h. After cooling to room temperature, the solid mixture was dissolved in minimum amount of boiling methanol. The filtrate was diluted with cold water (400 mL) and white solid appeared slowly. Collecting and washing the precipitate with cold water gave 23.0 g of (S)-2-phthalimido-4-methylpentanoic acid (88% yield).

(S)-2-Phthalimido-4-methylpentanoic acid (5.2 g, 20 mmol), thionyl chloride (4.5 mL, 60 mmol), and 4 drops of dimethylformamide were heated in toluene (40 mL) at 80 °C for 2 h. After the reaction, toluene and excess of thionyl chloride were removed by vacuum

distillation. The acid chloride residue was dissolved in CH_2Cl_2 (10 mL) and used for next reaction.

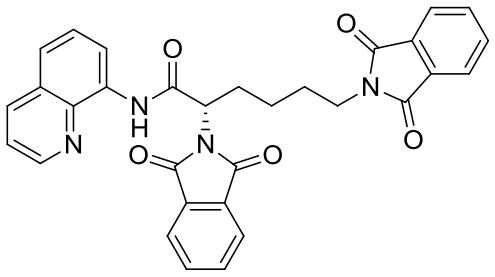
8-Aminoquinoline (2.2 g, 15 mmol) and 2,6-lutidine (2.1 g, 20 mmol) were dissolved in CH_2Cl_2 (30 mL) followed by dropwise addition of (S)-2-phthalimido-4-methylpentanyl chloride (20 mmol) solution in CH_2Cl_2 (10 mL) via cannula. The reaction mixture was stirred overnight at rt. Column chromatography in toluene/ethyl acetate 15:1 gave 5.7 g (99%) of the amide as a white solid. This compound is known.[12] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 10.33 (*s*, 1H) 8.75-8.69 (*m*, 2H) 8.14 (*dd*, 1H, *J*= 1.4, 8.2 Hz) 7.91 (*dd*, 2H, *J*= 3.24, 5.5 Hz) 7.76 (*dd*, 2H, *J*= 3.2, 5.5 Hz) 7.54-7.48 (m, 2H) 7.42 *(dd,* 1H, *J*= 4.1, 8.2 Hz) 5.23 *(dd,* 1H, *J*= 5.0, 11.4 Hz) 2.66 (ddd, 1H, *J*= 4.6, 11.4, 14.2 Hz) 2.11 (ddd, 1H, *J*= 5.0, 10.1, 14.2 Hz) 1.70-1.57 (m, 1H) 1.09-1.01 (m, 6H).



(S)-*N*-(3-Phenyl-2-phthalimidopropionyl)-8-aminoquinoline (14) L-Phenylalanine (4.1 g, 25 mmol) and phthalic anhydride (3.7 g, 25 mmol) were heated at 160 °C for 2 h. After cooling to room temperature, the solid mixture was dissolved in minimum amount of boiling methanol. The filtrate was diluted with cold water (400 mL) and white solid appeared slowly. Collecting and washing the precipitate with cold water gave (S)-2-phthalimido-3-phenylpropionic acid (5.3 g, 72%).

(S)-2-Phthalimido-3-phenylpropionic acid (2.95 g, 10 mmol), thionyl chloride (2.2 mL, 30 mmol), and 4 drops of dimethylformamide were heated in toluene (30 mL) at 80 °C for 2 h. After the reaction, toluene and excess of thionyl chloride were removed by vacuum distillation. The acid chloride obtained was dissolved in CH_2Cl_2 (10 mL) and used for next reaction.

8-Aminoquinoline (1.01 g, 7 mmol) and 2,6-lutidine (1.07 g, 10 mmol) were dissolved in CH_2Cl_2 (20 mL) followed by the dropwise addition of (S)-2-phthalimido-3-phenylpropionyl chloride (10 mmol) solution in CH_2Cl_2 (10 mL) via cannula. The reaction mixture was stirred overnight at rt. Column chromatography in toluene/ethyl acetate 20:1 gave 2.67 g (91%) of the amide as a tan solid. This compound is known.[12] ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 10.33 (s, 1H) 8.74 (*dd*, 2H, *J*= 2.3, 6.5 Hz) 8.61 (*dd*, 1H, *J*= 1.7, 4.2 Hz) 8.13 (*dd*, 1H, *J*= 1.7, 8.6 Hz) 7.71 (*dd*, 2H, *J*= 2.9, 5.1 Hz) 7.83 (*dd*, 2H, *J*= 2.9, 5.1 Hz) 7.55-7.49 (*m*, 2H) 7.39 (*dd*, 1H, *J*= 4.0, 8.0 Hz) 7.31-7.27 (*m*, 2H) 7.25-7.20 (*m*, 2H) 7.19-7.14 (*m*, 1H) 5.45 (*dd*, 1H, *J*= 6.9, 9.7 Hz) 3.86-3.75 (*m*, 2H).



(S)-*N*-(2,6-Diphthalimidohexanoyl)-8-aminoquinoline (17) L-Lysine (3.66 g, 25 mmol) and phthalic anhydride (7.4 g, 50 mmol) were heated at 160 °C for 2 h. After cooling to

room temperature, the solid mixture was recrystallized from ethanol giving 8.47 g of (S)-2,6-diphthalimidohexanoic acid (83%).

(S)-2,6-Diphthalimidohexanoic acid (4.06 g, 10 mmol), thionyl chloride (2.2 mL, 30 mmol), and 4 drops of dimethylformamide were heated in toluene (30 mL) at 80 °C for 2 h. After the reaction, toluene and the excess of thionyl chloride were removed by vacuum distillation. The acid chloride residue was dissolved in CH_2Cl_2 (10 mL) and used for next reaction.

8-Aminoquinoline (1.01 g, 7 mmol) and 2,6-lutidine (1.07 g, 10 mmol) were dissolved in CH_2Cl_2 (20 mL) followed by the dropwise addition of (S)-2,6-diphthalimidohexanyl chloride (10 mmol) solution in CH_2Cl_2 (10 mL) through cannula. The reaction mixture was stirred overnight at rt. Column chromatography in toluene/ethyl acetate (10:1 to 7:1) gave 3.06 g (82%) of the amide as a pale yellow solid. R_f = 0.41 (SiO_2, 1/5 ethyl acetate/ toluene), mp 144.5-145.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 10.32 (*s*, 1H) 8.73-8.66 (*m*, 2H) 8.13 (*dd*, 1H, *J*= 1.8, 8.2 Hz) 7.88 (*dd*, 2H, *J*= 3.2, 5.5 Hz) 7.90 (*dd*, 2H, *J*= 3.2, 5.5 Hz) 7.69 (*dd*, 2H, *J*= 3.2, 5.5 Hz) 7.53-7.48 (*m*, 2H) 7.41 (*dd*, 1H, *J*= 4.1, 8.2 Hz) 5.11 (*dd*, 1H, *J*= 5.0, 10.5 Hz) 3.69 (*t*, 2H, *J*= 7.3 Hz) 2.70-2.56 (*m*, 1H) 2.52-2.38 (*m*, 1H) 1.94-1.71 (*m*, 2H) 1.58-1.43 (*m*, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 168.4, 168.2, 166.8, 148.5, 138.6, 136.4, 134.3, 134.0, 132.2, 131.9, 127.9, 127.4, 123.8, 123.3, 122.0, 121.7, 116.8, 55.1, 37.7, 28.4, 28.2, 24.1 Signal for one carbon could not be located. FT-IR (neat, cm^{-1}) 3328, 1770.14, 1708.59, 1543.63, 1372.73, 1032.97. Calcd for $C_{31}H_{24}N_4O_5$ (532.55 g/mol) C: 69.92; H: 4.54; N: 10.52; Found C: 69.83; H: 4.51; N: 10.37.

4.3 Optimization for arylation reaction with 2-methylthioaniline auxiliary

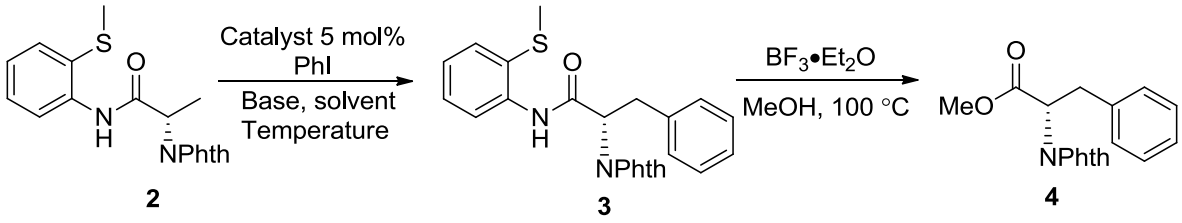
General arylation procedure for Table 4-3: To a 1-dram vial was added (S)-*N*-(2-phthalimidopropionyl)-2-methylthioaniline (1 equiv, 0.5 mmol; 1 mmol for entry 1), catalyst (5 mol %, 0.027 mmol; 0.054 mmol for entry 1), iodobenzene (4 equiv, 2 mmol; 4 mmol for entry 1), base (2.5 equiv), pivalic acid (1 mmol, 2 equiv, only for entry 2), and toluene (0.5 mL in case of CsOAc base, 0.4 mL in case of silver base, and 2 ml for entry 1). The mixture was stirred at given temperature for 40 – 65 h. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and extracted with brine (15 mL). For the entries that used $AgOCOCF_3$, the reaction was quenched by saturated aqueous $NaHCO_3$ solution (1 mL) before extraction. The aqueous layer was extracted with CH_2Cl_2 (2x15 mL). Combined organic layers were dried over $MgSO_4$. Evaporation to remove the organic solvents followed by purification by flash chromatography in toluene/ethyl acetate (100% toluene to 30:1) gave the product as a light yellow solid.

General procedure for cleavage step: A methyl ester **4** was produced from an amide **3** follow the reported procedure.[31] To a 10 mL Kontes flask equipped with a stir bar was added (S)-*N*-(2-phthalimido-3-phenylpropionyl)-2-methylthioaniline (0.1–0.25 mmol, 1 equiv.). Inside the glove box, dry methanol (1.75–3.75 mL, to obtain a 0.07 M solution) was added to the flask. Outside the glove box, BF_3*Et_2O (0.09–0.2 mL, 6 equiv) was added dropwise to the stirred solution. The resulting mixture was stirred at 100 °C for 24 h. After cooling to rt, Et_3N (0.16–3.75 mL, 10 equiv) was added dropwise to the reaction mixture with stirring. Evaporation to remove the organic solvents followed by purification

by flash chromatography in hexanes/ethyl acetate (100% hexane to 5:1) gave the product as colorless oil.

The % ee was determined using Chiracel OJ-H column, eluent hexanes/ethanol 80:20, 0.9 mL/min. The racemic mixture was used as a standard. Retention times: (S) enantiomer (major) 15.8 min., (R) enantiomer (minor) 20.1 min.

Table 4-3. Optimization for enantiomeric excess



2 **3** **4**

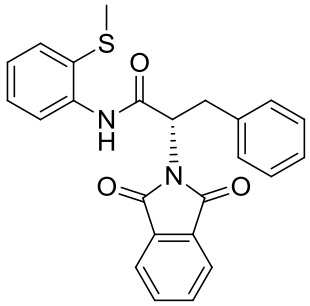
Entry	Catalyst	Base	Solvent	Temp	Time	%Conv.	% ee	Note
1	$Pd(OAc)_2$	CsOAc	Toluene	110 °C	48 h	68%[a]	77	
2	$Pd(OAc)_2$	CsOAc	Toluene	90 °C	40 h	61%[a]	55	Pivalic acid additive
3	$Pd(OAc)_2$	CsOAc	Toluene	60 °C	63 h	51%	92	
4	$Pd(OAc)_2$	AgOAc	No solvent	70 °C	40 h	90%	88	
5	$Pd(OAc)_2$	AgOAc	No solvent	60 °C	60 h	78%[a]	92	

Table 4-3. (*Continued*)

6	$Pd(OAc)_2$	$AgOCOCF_3$	No solvent	60 °C	65 h	77%	92
7	$Pd(OCOCF_3)_2$	$AgOCOCF_3$	No solvent	70 °C	38 h	59%	93
8	$Pd(OAc)_2$	$AgOCOCF_3$	No solvent	70 °C	49 h	78%	91

[a] isolated yield. Conversion was measured by ^{1}H NMR of crude reaction mixture.

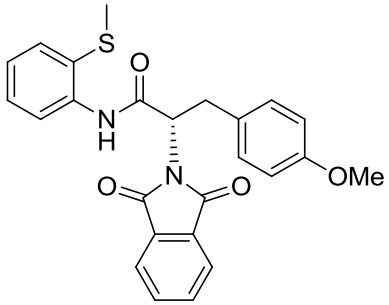
4.4 Synthesis of modified phenylalanine derivatives



(S)-*N*-(2-Phthalimido-3-phenylpropionyl)-2-methylthioaniline (3)

To a 1-dram vial was added (S)-*N*-(2-phthalimidopropionyl)-2-methylthioaniline (171 mg, 0.5 mmol), $Pd(OAc)_2$ (6 mg, 0.027 mmol), iodobenzene (411 mg, 2.0 mmol), and AgOAc (209 mg, 1.25 mmol). The mixture was stirred at 60 °C for 60 h. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and extracted by brine (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2x15 mL). Combined organic layers were dried over $MgSO_4$. Evaporation to remove the organic solvents followed by purification by flash chromatography in toluene/ethyl acetate (100% toluene to 30:1) gave 164 mg of a light yellow solid (78%). R_f = 0.44 (SiO_2, 1/10 ethyl acetate/ toluene), mp 99-103 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.94 (*s*, 1H) 8.37-8.32 (*m*, 1H) 7.81 (*dd*, 2H,

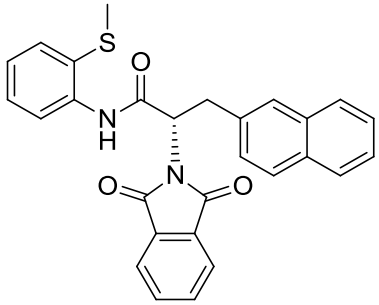
J= 2.9, 5.73= Hz) 7.71 (*dd*, 2H, *J*= 2.9, 5.7 Hz) 7.47-7.42 (*m*, 1H) 7.43-7.28 (*m*, 1H) 7.24-7.17 (*m*, 4H) 7.16-7.11 (*m*, 1H) 7.09-7.04 (*m*, 1H) 5.32 (*dd*, 1H, *J*= 5.7, 10.9 Hz) 3.75 (*dd*, 1H, *J*= 5.7, 14.3 Hz) 3.69 (*dd*, 1H, *J*= 10.9, 14.3 Hz) 2.20 (*s*, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 167.9, 166.5, 138.1, 136.7, 134.5, 133.6, 131.5, 129.4, 129.0, 128.8, 127.1, 125.5, 124.9, 123.7, 120.7, 56.4, 34.4, 19.2. FT-IR (neat, cm^{-1}) 2366, 1714, 1673, 1512, 1380, 1102. Calcd for $C_{24}H_{20}N_2O_3S$ (416.49 g/mol) C: 69.21; H: 4.84; N: 6.73; Found C: 69.28; H: 5.03; N: 6.51.



(S)-*N*-(3-(4-Methoxyphenyl)-2-phthalimidopropionyl)-2-methylthioaniline (5)

To a 1-dram vial was added (S)-*N*-(2-phthalimidopropionyl)-2-methylthioaniline (170 mg, 0.5 mmol), $Pd(OAc)_2$ (6 mg, 0.027 mmol), 4-iodoanisole (702 mg, 3.0 mmol), AgOAc (209 mg, 1.25 mmol), and toluene (0.4 mL). The mixture was stirred at 60 °C for 72 h. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and extracted with brine (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2x15 mL). Combined organic layers were dried over $MgSO_4$. Evaporation to remove organic solvents followed by purification by flash chromatography in hexanes/ethyl acetate (10:1 to 2:1) gave 152 mg of a colorless oil (68%). R_f = 0.40 (SiO_2, 1/2 ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.96 (*s*, 1H) 8.36-8.29 (*m*, 1H) 7.82 (*dd*, 2H, *J*= 2.9,

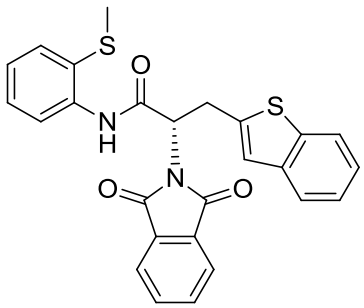
5.15= Hz) 7.72 (*dd*, 2H, *J*= 2.9, 5.2 Hz) 7.47-7.42 (*m*, 1H) 7.32-7.27 (*m*, 1H) 7.16-7.11 (*m*, 2H) 7.09-7.03 (*m*, 1H) 6.76-6.70 (*m*, 2H) 5.27 (*dd*, 1H, *J*= 5.73, 10.31 Hz) 3.74-3.69 (*m*, 5H) 2.20 (*s*, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 167.9, 166.6, 158.6, 138.1, 134.5, 133.5, 131.5, 130.5, 130.0, 129.3, 128.6, 125.6, 124.9, 123.7, 120.7, 114.2, 56.6, 55.3, 33.6. FT-IR (neat, cm^{-1}) 2337, 1715, 1512, 1381, 1249. Calcd for $C_{25}H_{22}N_2O_4S$ (446.52 g/mol) C: 67.25; H: 4.97; N: 6.27; Found C: 67.44; H: 5.04; N: 6.14.



(S)-*N*-(3-(2-Naphthyl)-2-phthalimidopropionyl)-2-methylthioaniline (6)

To a 1-dram vial was added (S)-*N*-(2-phthalimidopropionyl)-2-methylthioaniline (170 mg, 0.5 mmol), $Pd(OAc)_2$ (6 mg, 0.027 mmol), 2-iodonaphthalane (762 mg, 3.0 mmol), AgOAc (209 mg, 1.25 mmol), and toluene (0.4 mL). The mixture was stirred at 60 °C for 62 h. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and extracted with brine (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2x15 mL). Combined organic layers were dried over $MgSO_4$. Evaporation to remove the organic solvents followed by purification by flash chromatography in toluene/ethyl acetate (100% toluene to 30:1) and preparative HPLC in hexanes/ethyl acetate 4:1 gave 140 mg of a colorless oil (60% yield). R_f = 0.44 (SiO_2, 1/10 ethyl acetate/toluene). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.98 (*s*, 1H) 8.39-8.32 (*m*, 1H) 7.80-7.76 (*m*, 2H) 7.71-

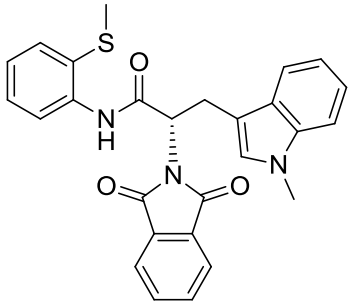
7.75 (*m*, 2H) 7.69-7.65 (*m*, 4H) 7.46-7.36 (*m*, 4H) 7.33-7.28 (*m*, 1H) 7.09-7.04 (*m*, 1H) 5.46 (*dd*, 1H, *J*= 6.3, 10.1 Hz) 3.95-3.84 (*m*, 2H) 2.15 (*s*, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 167.9, 166.5, 138.1, 134.5, 134.4, 133.6 (2C), 132.5, 131.5, 129.3, 128.6, 128.0, 127.7, 127.7, 126.8, 126.2, 125.8, 125.6, 124.9, 123.7, 120.7, 56.2, 34.7, 19.2. FT-IR (neat, cm^{-1}) 2369, 1713, 1517, 1381. Calcd for $C_{28}H_{22}N_2O_3S$ (466.55 g/mol) C: 72.08 ; H: 4.75; N: 6.00; Found C: 72.04;H: 4.85; N: 5.99.



(S)-*N*-(3-(Benzothiophene-2-yl)-2-phthalimidopropionyl)-2-methylthioaniline (7)

2-Iodobenzothiophene. To a 200 mL flame-dried Schlenk flask was added benzothiophene (4.03 g, 30 mmol) and THF (60 mL). *n*-Butyllithium (13.2 mL, 33 mmol as a 2.5 M solution in hexanes) was added dropwise to the resulting mixture at -78 °C. The reaction was stirred for 30 minutes and the solution of I_2 (8.34 g, 33 mmol) in THF (90 mL) was added dropwise via cannula. The mixture was stirred for another 30 minutes followed by warming to rt. The reaction was quenched with saturated aqueous NH_4Cl (40 mL) and extracted with ethyl acetate (50 mL). The organic layer was washed with saturated aqueous $Na_2S_2O_3$ (40 mL), brine (40 mL), and dried over Na_2SO_4. Evaporation to remove organic solvents followed by purification by flash chromatography in hexanes gave 6.96 g of yellow solid (89% yield). The compound was used for the next reaction.

To a 1-dram vial was added (S)-*N*-(2-phthalimidopropionyl)-2-methylthioaniline (170 mg, 0.5 mmol), $Pd(OAc)_2$ (6 mg, 0.027 mmol), 2-iodobenzothiophene (785 mg, 3.0 mmol), AgOAc (209 mg, 1.25 mmol), and toluene (0.4 mL). The mixture was stirred at 60 °C for 64 h. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and extracted with brine (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2x15 mL). Combined organic layers were dried over $MgSO_4$. Evaporation to remove the organic solvents followed by purification by flash chromatography in hexanes/ethyl acetate (100% hexanes to 3:1) and preparative HPLC in hexanes/ethyl acetate 4:1 for contaminated fractions gave 175 mg of colorless oil (74%). R_f = 0.45 (SiO_2, 1/2 ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.95 (*s*, 1H) 8.37-8.31 (*m*, 1H) 7.87-7.82 (*m*, 2H) 7.75-7.67 (*m*, 3H) 7.62-7.58 (*m*, 1H) 7.45-7.41 (*m*, 1H) 7.33-7.20 (*m*, 4H) 7.80-7.04 (*m*, 1H) 5.40 (*dd*, 1H, *J*= 5.7, 10.3 Hz) 4.03 (*dd*, 1H, *J*= 5.1, 14.9 Hz) 4.11 (*dd*, 1H, *J*= 10.9, 15.5 Hz) 2.13 (*s*, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 167.8, 165.8, 140.1, 139.9, 138.0, 134.7, 133.6, 131.5, 129.4, 125.5, 125.0, 124.3, 124.1, 123.9, 123.4, 123.3, 122.3, 120.6, 55.9, 29.7, 19.2 Signal for one carbon could not be located. FT-IR (neat, cm^{-1}) 1715, 1513, 1436, 1380. Calcd for $C_{26}H_{20}N_2O_3S_2$ (472.58 g/mol) C: 66.08; H: 4.27; N: 5.93; Found C: 65.82; H: 4.45; N: 5.72.

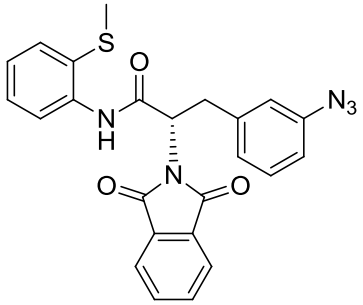


(S)-*N*-(3-(*N*-Methylindole-3-yl-2-phthalimidopropionyl)-2-methylthioaniline (8)

***N*-Methyl-3-iodoindole.** To a 50 mL Kontes flask equipped with a stirrer was added I_2 (3.66 g, 14 mmol), pyridine (483 mg, 6.11 mmol), and dioxane/DMF 9:1 (12 mL), followed by *N*-methylindole (1.58 g, 12 mmol). Inside the glove box, K_3PO_4 (5.09 g, 24 mmol) was added to the reaction. The resulting mixture was stirred at 110 °C for 1 h. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (50 mL) and extracted with brine (20 mL) and water (10 mL). The aqueous layer was extracted with ethyl acetate (2x50 mL). Combined organic layers were dried over Na_2SO_4. Evaporation to remove the organic solvents followed by purification by flash chromatography in hexanes/ethyl acetate (100% hexanes to 40:1) gave 2.47 g (80%) of an orange oil. The product was transferred to the glove box and used for the next reaction within a day.

To a 1-dram vial was added (S)-*N*-(2-phthalimidopropionyl)-2-methylthioaniline (171 mg, 0.5 mmol), $Pd(OAc)_2$ (7 mg, 0.031 mmol), AgOAc (209 mg, 1.25 mmol), and toluene (0.4 mL). Inside the glove box, 3-iodo-*N*-methylindole (771.2 mg, 3.0 mmol) was added. The mixture was stirred at 60 °C for 62 h and was protected from light by aluminum foil during that time. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and extracted with brine (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2x15 mL). Combined organic layers were dried over $MgSO_4$. Evaporation to remove the organic solvents followed by purification by flash chromatography in hexanes/ethyl acetate (10:1 to 2.5:1) and preparative HPLC in hexanes/ethyl acetate 2.5:1 gave 145 mg of a yellow oil (61%). R_f = 0.33 (SiO_2, 1/2 ethyl acetate/hexanes). ^{1}H NMR

(500 MHz, $CDCl_3$, ppm) δ 8.91 (*s*, 1H) 8.36-8.30 (*m*, 1H) 7.85-7.79 (*m*, 2H) 7.74-7.65 (*m*, 3H) 7.43-7.38 (*m*, 1H) 7.30-7.16 (*m*, 3H) 7.12-7.06 (*m*, 1H) 7.05-7.00 (*m*, 1H) 6.99 (*s*, 1H) 5.48 (*dd*, 1H, *J*= 7.4, 8.2 Hz) 3.98 (*dd*, 1H, *J*= 7.3, 15.1 Hz) 3.76 (*dd*, 1H, *J*= 8.7, 15.1 Hz) 3.68 (*s*, 3H) 2.04 (*s*, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) 168.1, 166.9, 138.3, 137.2, 134.3, 133.5, 131.8, 129.3, 127.9, 127.6, 125.5, 124.7, 123.6, 122.0, 120.8, 119.4, 118.9, 109.4, 109.3, 55.2, 32.8, 25.4, 19.0. FT-IR (neat, cm^{-1}) 2353, 1713, 1516, 1382. Calcd for $C_{27}H_{23}N_3O_3S$ (469.55 g/mol) C: 69.06; H: 4.94; N: 8.95; Found C: 68.76; H: 4.87; N: 8.68.

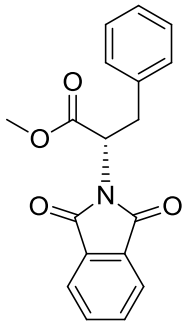


(S)-*N*-(3-(3-Azidophenyl)-2-phthalimidopropionyl)-2-methylthioaniline (9)

To a 25 mL Schlenk flask equipped with a stir bar was added 1-azido-3-iodobenzene solution in methyl *t*-butyl ether (6.2 mL, 0.5M, 3.1 mmol). The solvent was then removed under vacuum. (S)-*N*-(2-Phthalimidopropionyl)-2-methylthioaniline (170 mg, 0.5 mmol), $Pd(OAc)_2$ (6 mg, 0.027 mmol), AgOAc (209 mg, 1.25 mmol), and toluene (0.4 mL) were then added to the flask. The mixture was stirred at 60 °C for 70 h. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and extracted with brine (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2x15 mL). Combined organic layers were dried over Na_2SO_4. Evaporation to remove the organic solvents

followed by purification by flash chromatography in toluene/ethyl acetate (100% toluene to 50:1) gave 186 mg of a yellow oil (81%). R_f = 0.43 (SiO_2, 1/10 ethyl acetate/toluene). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.94 (*s*, 1H) 8.35-8.30 (*m*, 1H) 7.84 (*dd*, 2H, *J*= 2.9, 5.7 Hz) 7.74 (*dd*, 2H, *J*= 2.9, 5.7 Hz) 7.46-7.42 (*m*, 1H) 7.33-7.28 (*m*, 1H) 7.21-7.15 (*m*, 1H) 7.09-7.04 (*m*, 1H) 7.02-6.98 (*m*, 1H) 6.86 (*s*, 1H) 6.83-6.79 (*m*, 1H) 5.29 (*dd*, 1H, *J*= 5.7, 10.9 Hz) 3.73 (*dd*, 1H, *J*= 5.7, 14.3 Hz) 3.67 (*dd*, 1H, *J*= 11.5, 14.3 Hz) 2.19 (*s*, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 167.8, 166.2, 140.5, 138.9, 137.9, 134.7, 133.6, 131.4, 130.2, 129.4, 125.6, 125.0, 123.8, 120.7, 119.6, 117.8, 56.1, 34.2, 19.2. Signal for one carbon could not be located. FT-IR (neat, cm^{-1}) 2361, 2324, 2113, 1773, 1714, 1679, 1582, 1518, 1438, 1378, 1348, 1298. Calcd for C24H19N5O3S (457.50 g/mol) C: 63.01; H: 4.19; N: 15.31; Found C: 63.22; H: 4.20; N: 14.64.

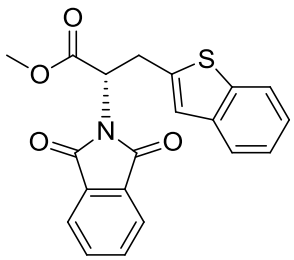
MONOARYLATION PRODUCT AUXILIARY CLEAVAGE



Methyl (S)-2-phthalimido-3-phenylpropionate (4)

To a 10 mL Kontes flask equipped with a stir bar was added (S)-*N*-(2-phthalimido-3-phenylpropionyl)-2-methylthioaniline (72 mg, 0.17 mmol). Inside the glove box, dry methanol (2.6 mL) was added to the flask. Outside the glove box, BF_3•Et_2O (0.14 mL,

1.13 mmol) was added dropwise to the stirred solution. The resulting mixture was stirred at 100 °C for 20 h. After cooling to rt, Et_3N (0.24 mL, 1.72 mmol) was added dropwise to the reaction mixture with stirring. Evaporation to remove the organic solvents followed by purification by flash chromatography in hexanes/ethyl acetate (100% hexanes to 5:1) gave 46 mg of a colorless oil (87%). Determination of % ee by HPLC on chiral stationary phase: Chiralcel OJ-H, hexanes/ethanol 80:20, 0.9 mL/min, 90% ee. Retention times: major, (S) = 15.8 min, (R) = 20.1 min. This compound is known. [43] ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.78 (*dd*, 2H, *J*= 3.2, 5.5 Hz) 7.69 (*dd*, 2H, *J*= 3.2, 5.5 Hz) 7.21-7.12 (*m*, 5H) 5.16 (*dd*, 1H, *J*= 5.0, 11.0 Hz) 3.78 (*s*, 3H) 3.61 (*dd*, 1H, *J*= 5.5, 14.2 Hz) 3.53 (*dd*, 1H, *J*= 11.0, 14.2 Hz).

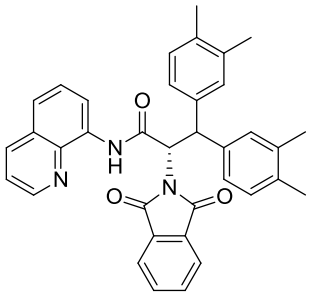


Methyl (S)-3-(benzothiophene-2-yl)-2-phthalimidopropionate (10)

To a 10 mL Kontes flask equipped with a stir bar was added (S)-*N*-(3-(benzothiophene-2-yl)-2-phthalimido)-2-methylthioaniline (157 mg, 0.33 mmol). Inside the glove box, dry methanol (5 mL) was added to the flask. Outside the glove box, BF_3•Et_2O (0.27 mL, 2.19 mmol) was added dropwise to the stirred solution. The resulting mixture was stirred at 100 °C for 24 h. After cooling to rt, Et_3N (0.47 mL, 3.37 mmol) was added dropwise to the stirred reaction mixture. Evaporation to remove the organic solvents followed by

purification by flash chromatography in hexanes/ethyl acetate (100% hexanes to 4:1) and preparative HPLC in hexanes/ethyl acetate 4:1 for the contaminated fractions gave 97 mg of a crystalline solid (80 %). R_f = 0.50 (SiO_2, 1/2 ethyl acetate/hexanes), mp 104.5-108.5 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.81 (*dd*, 2H, *J*= 2.9, 4.9 Hz) 7.72-7.66 (*m*, 3H) 7.61-7.57 (*m*, 1H) 7.27-7.19 (*m*, 2H) 7.05 (*s*, 1H) 5.26 (*dd*, 1H, *J*= 4.6, 11.5 Hz) 3.99 (*dd*, 1H, *J*= 12.0, 15.5 Hz) 3.86 (*dd*, 1H, *J*= 4.6, 15.5 Hz) 3.70 (*s*, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 168.9, 167.6, 140.0, 139.9, 139.8, 134.4, 131.8, 124.3, 124.0, 123.8, 123.2, 123.1, 122.3, 53.2, 53.0, 30.0. FT-IR (neat, cm^{-1}) 2336, 1747, 1716, 1391, 1278. Calcd for $C_{20}H_{15}NO_4S$ (365.40 g/mol) C: 65.74; H: 4.14; N: 3.83; Found C: 65.65; H: 4.15; N: 3.88.

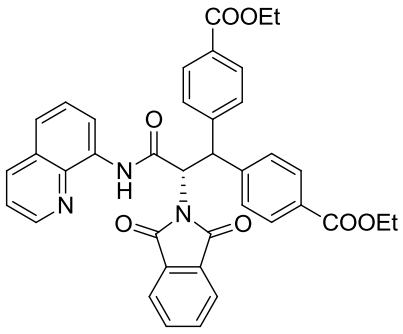
4.5 8-Aminoquinoline for functionalization of amino acid C-H bonds



(S)-*N*-(3,3-Di(3,4-dimethylphenyl)-2-phthalimidopropionyl)-8-aminoquinoline (12)

To a 1-dram vial was added (S)-*N*-(2-phthalimidopropionyl)-8-aminoquinoline (173 mg, 0.5 mmol), $Pd(OAc)_2$ (6 mg, 0.027 mmol), 4-iodo-*o*-xylene (580 mg, 2.5 mmol), AgOAc (209 mg, 1.25 mmol), and toluene (0.4 mL). The mixture was stirred at 60 °C for 62 h. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and extracted with brine (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2x15 mL). Combined organic layers were dried over $MgSO_4$. Evaporation to remove the

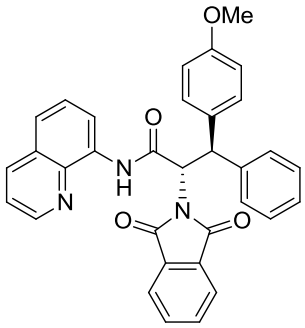
organic solvents followed by purification by flash chromatography in toluene/ethyl acetate 30:1 gave 254 mg of a white powder (92%). R_f = 0.48 (SiO_2, 1/10 ethyl acetate/ toluene), mp 225-227 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 10.08 (*s*, 1H) 8.68-8.61 (*m*, 2H) 8.07 (*dd*, 1H, *J*= 1.7, 8.6 Hz) 7.76 (*dd*, 2H, *J*= 2.9, 5.7 Hz) 7.63 (*dd*, 2H, *J*= 2.9, 5.7 Hz) 7.45-7.36 (*m*, 3H) 7.35-7.30 (*m*, 2H) 7.12-7.07 (*m*, 2H) 7.01 (*d*, 1H, *J*= 7.5 Hz) 6.90 (*d*, 1H, *J*= 8.0 Hz) 5.93 (*d*, 1H, *J*= 12.0 Hz) 5.48 (*d*, 1H, *J*= 12.0 Hz) 2.11 (*s*, 3H) 2.08 (*s*, 3H) 2.07 (*s*, 3H) 2.04 (*s*, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 168.1, 166.2, 148.0, 138.6, 138.5, 138.4, 137.4, 136.8, 136.1, 135.5, 135.0, 134.3, 134.0, 131.8, 130.5, 129.9, 129.5, 129.3, 127.8, 127.3, 125.3, 124.7, 123.5, 121.9, 121.5, 117.0, 59.0, 20.0, 19.9, 19.5, 19.4. Signal for one carbon could not be located. FT-IR (neat, cm^{-1}) 2362, 1716, 1533, 1386. Calcd for $C_{36}H_{31}N_3O_3$ (553.65 g/mol) C: 78.10; H: 5.64; N: 7.59; Found C: 78.04; H: 5.67; N: 7.39.



(S)-*N*-(3,3-Di(ethyl benzoate-4-yl)-2-phthalimidopropionyl)-8-aminoquinoline (13)

To a 1-dram vial was added (S)-*N*-(2-phthalimidopropionyl)-8-aminoquinoline (173 mg, 0.5 mmol), $Pd(OAc)_2$ (7 mg, 0.031 mmol), ethyl-4-iodobenzoate (897 mg, 3.25 mmol), and AgOAc (209 mg, 1.25 mmol). The mixture was stirred at 60 °C for 70 h. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and extracted with brine (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2x15 mL).

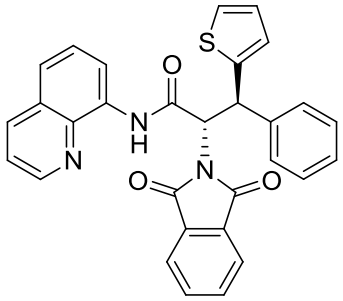
Combined organic layers were dried over $MgSO_4$. Evaporation to remove the organic solvents followed by purification by flash chromatography in toluene/ethyl acetate (50:1 to 10:1) gave 268 mg of a white powder (84%). R_f = 0.51 (SiO_2, 1/5 ethyl acetate/ toluene), mp 94-95 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 10.08 (*s*, 1H) 8.63 (*dd*, 1H, *J*= 1.8, 4.6 Hz) 8.59 (*dd*, *J*= 1.8, 7.3 Hz) 8.08 (*dd*, 1H, *J*= 1.8, 8.2 Hz) 7.98 (*d*, 2H, *J*= 8.2 Hz) 7.87 (*d*, 2H, *J*= 8.2 Hz) 7.77 (*dd*, 2H, *J*= 3.2, 5.5 Hz) 7.71-7.63 (*m*, 4H) 7.49-7.34 (*m*, 5H) 6.02 (*d*, 1H, *J*= 12.4 Hz) 5.81 (*d*, 1H, *J*= 12.4 Hz) 4.35-4.23 (*m*, 4H) 1.36-1.27 (*m*, 6H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 167.9, 166.3, 166.2, 165.0, 148.3, 145.2, 145.1, 138.4, 136.2, 134.4, 133.8, 131.3, 130.7, 130.3, 129.9, 129.5, 128.3, 128.0, 127.8, 127.2, 123.8, 122.3, 121.7, 117.0, 61.1, 61.0, 58.1, 50.2, 14.3, 14.4. FT-IR (neat, cm^{-1}) 2365, 1719, 1534, 1277. Calcd for $C_{38}H_{31}N_3O_7$ (641.67 g/mol) C: 71.13; H: 4.87; N: 6.55; Found C: 70.62; H: 4.98; N: 6.45.



2S,3R-*N*-(3-(4-Methoxyphenyl)-3-phenyl-2-phthalimidopropionyl)-8-aminoquinoline (15)

To a 1-dram vial was added (S)-*N*-(3-phenyl-2-phthalimidopropionyl)-8-aminoquinoline (211 mg, 0.5 mmol), $Pd(OAc)_2$ (6 mg, 0.027 mmol), 4-iodoanisole (585 mg, 2.5 mmol), AgOAc (209 mg, 1.25 mmol), and toluene (0.4 mL). The mixture was stirred at 60 °C for

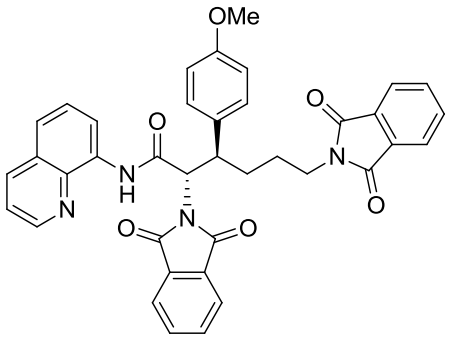
77 h. Analysis of crude reaction mixture by ^{1}H NMR showed 24:1 diastereomer ratio. After completion, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and extracted with brine (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2x15 mL). Combined organic layers were dried over $MgSO_4$. Evaporation to remove the organic solvents followed by purification by flash chromatography in toluene/ethyl acetate (100% toluene to 15:1) gave 240 mg of white solid (91%). This compound is known.[12] ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 10.15 (*s*, 1H) 8.68-8.62 (*m*, 2H) 8.08 (*dd*, 1H, *J*= 1.7, 8.6 Hz) 7.75 (*dd*, 2H, *J*= 3.4, 5.7 Hz) 7.62 (*dd*, 2H, *J*= 3.4, 5.7 Hz) 7.56-7.52 (*m*, 2H) 7.46-7.33 (*m*, 5H) 7.19-7.13 (*m*, 2H) 7.05-7.0 (*m*, 1H) 6.86-6.81 (*m*, 2H) 5.93 (*d*, 1H, *J*= 12.6 Hz) 5.57 (*d*, 1H, *J*= 12.6 Hz) 3.68 (*s*, 3H).



2S,3S-*N*-(2-Phthalimido-3-phenyl-3-(thiophene-2-yl)propionyl)-8-aminoquinoline (16)

To a 1-dram vial was added (S)-*N*-(3-phenyl-2-phthalimidopropionyl)-8-aminoquinoline (211 mg, 0.5 mmol), $Pd(OAc)_2$ (6 mg, 0.027 mmol), 2-iodothiophene (528 mg, 2.51 mmol), AgOAc (209 mg, 1.25 mmol), and toluene (0.4 mL). The mixture was stirred at 60 °C for 77 h. Analysis of crude reaction mixture by ^{1}H NMR showed presence of only one diastereomer. After completion, the reaction mixture was diluted with CH_2Cl_2 (25 mL)

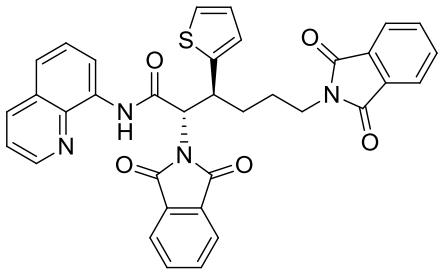
and extracted with brine (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2x15 mL). Combined organic layers were dried over $MgSO_4$. Evaporation to remove the organic solvents followed by purification by flash chromatography in toluene/ethyl acetate (100% toluene to 30:1) gave 240 mg of a light green powder (95%). R_f = 0.40 (SiO_2, 1/10 ethyl acetate/toluene), mp 270-272 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 10.34 (*s*, 1H) 8.74 (*dd*, 1H, *J*= 1.7, 4.0 Hz) 8.70 (*dd*, 1H, *J*= 2.9, 6.9 Hz) 8.09 (*dd*, 1H, *J*= 1.7, 8.0 Hz) 7.73 (*dd*, 2H, *J*= 2.9, 5.1 Hz) 7.61 (*dd*, 2H, *J*= 2.9, 5.1 Hz) 7.49-7.38 (*m*, 5H) 7.27-7.23 (*m*, 1H) 7.21-7.15 (*m*, 3H) 7.09-7.04 (*m*, 1H) 6.90 (*dd*, 1H, *J*= 4.0, 5.1 Hz) 5.93-5.83 (*m*, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 167.8, 165.4, 148.3, 144.2, 140.4, 138.6, 136.2, 134.2, 134.2, 131.4, 128.9, 128.0, 127.9, 127.4, 127.3, 127.3, 125.8, 125.3, 123.6, 122.1, 121.7, 117.1, 59.8, 45.7. FT-IR (neat, cm^{-1}) 1713, 1680, 1534, 1388. Calcd for $C_{30}H_{21}N_3O_3S$ (503.57 g/mol) C: 71.55 ; H: 4.20; N: 8.34; Found C: 71.68; H: 4.16; N: 8.16.



2S,3R-*N*-(2,6-Diphthalimido-3-(4-methoxyphenyl)hexanoyl)-8-aminoquinoline (18)

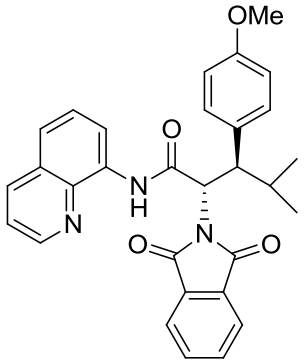
To a 1-dram vial was added (S)-*N*-(2,6-diphthalimidohexanoyl)-8-aminoquinoline (266 mg, 0.5 mmol), $Pd(OAc)_2$ (13 mg, 0.058 mmol), 4-iodoanisole (585 mg, 2.5 mmol), AgOAc (209 mg, 1.25 mmol), and toluene (0.4 mL). The mixture was stirred at 60 °C for

77 h. Analysis of crude reaction mixture by ^{1}H NMR showed 16:1 diastereomer ratio. After completion, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and extracted with brine (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2x15 mL). Combined organic layers were dried over $MgSO_4$. Evaporation to remove the organic solvents followed by purification by flash chromatography in hexanes/ethyl acetate (20:1 to 1:1) gave 270 mg of a white solid (85%). R_f = 0.38 (SiO_2, 1/5 ethyl acetate/toluene), mp 211-214 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 9.91 (*s*, 1H) 8,67 (*dd*, 1H, *J*= 1.7, 4.1 Hz) 8.54 (*dd*, 1H, *J*= 1.7, 7.4 Hz) 8.05 (*dd*, 1H, *J*= 1.1, 8.0 Hz) 7.90-7.85 (*m*, 2H) 7.77-7.70 (*m*, 4H) 7.67-7.63 (*m*, 2H) 7.43-7.34 (*m*, 5H) 6.82 (*d*, 2H, *J*= 8.6 Hz) 5.28 (*d*, 1H, *J*= 12.0 Hz) 4.16 (*dt*, 1H, *J*= 11.5, 4.0 Hz) 3.68 (*s*, 3H) 3.61-3.46 (*m*, 2H) 1.77-1.61 (*m*, 2H) 1.55-1.37 (*m*, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 168.4, 168.2, 166.0, 159.0, 148.1, 138.5, 136.0, 134.3, 134.1, 133.9, 132.1, 131.8, 131.6, 129.7, 127.8, 127.2, 123.8, 123.2, 121.8, 121.6, 116.9, 114.8, 61.2, 55.2, 43.1, 37.8, 30.8, 25.9. FT-IR (neat, cm^{-1}) 2353, 2319, 1710, 1703, 1530. Calcd for $C_{38}H_{30}N_4O_6$ (638.67 g/mol) C: 71.46; H: 4.73; N: 8.77; Found C: 70.71; H: 4.70; N: 8.62.



2S,3S-*N*-(2,6-Diphthalimido-3-(thiophene-2-yl)hexanoyl)-8-aminoquinoline (19)

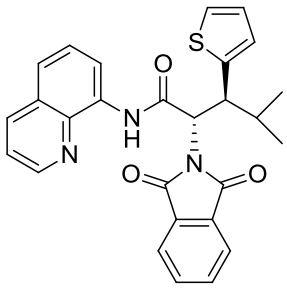
To a 1-dram vial was added (S)-*N*-(2,6-diphthalimidohexanoyl)-8-aminoquinoline (266 mg, 0.5 mmol), $Pd(OAc)_2$ (13 mg, 0.058 mmol), 2-iodothiophene (527 mg, 2.51 mmol), AgOAc (209 mg, 1.25 mmol), and toluene (0.4 mL). The mixture was stirred at 60 °C for 77 h. Analysis of crude reaction mixture by ^{1}H NMR showed 13:1 diastereomer ratio. After completion, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and extracted with brine (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2x15 mL). Combined organic layers were dried over $MgSO_4$. Evaporation to remove the organic solvents followed by purification by flash chromatography in toluene/ethyl acetate (30:1 to 5:1) and preparative TLC in toluene/ethyl acetate (5:1) gave 247 mg of light green solid (80%). R_f = 0.46 (SiO_2, 1/5 ethyl acetate/toluene), mp 157-159.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 10.06 (*s*, 1H) 8.71 (*dd*, 1H, *J*= 1.8, 4.6 Hz) 8.58 (*dd*, 1H, *J*= 1.8, 6.9 Hz) 8.07 (*dd*, 1H, *J*= 1.8, 8.2 Hz) 7.91-7.85 (*m*, 2H) 7.91-7.85 (*m*, 2H) 7.77-7.72 (*m*, 4H) 7.67-7.64 (*m*, 2H) 7.45-7.36 (*m*, 3H) 7.19-7.12 (*m*, 2H) 6.87 (*dd*, 1H, *J*= 3.7, 5.0 Hz) 5.25 (*d*, 1H, *J*= 11 Hz) 4.62 (*dt*, 1H, *J*= 3.2, 10.5) 3.66-3.50 (*m*, 2H) 1.88-1.78 (*m*, 1H) 1.73-1.55 (*m*, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) 168.3, 168.2, 165.6, 148.2, 143.0, 138.6, 136.1, 134.4, 134.1, 133.9, 132.1, 131.8, 127.8, 127.3, 127.2, 127.2, 125.0, 123.9, 123.2, 122.0, 121.6, 116.9, 61.6, 39.6, 37.7, 31.9, 25.8. FT-IR (neat, cm^{-1}) 2360, 1704, 1529, 1380. Calcd for $C_{35}H_{26}N_4O_5S$ (614.67 g/mol) C: 68.39; H: 4.26; N: 9.11; Found C: 68.48; H: 4.40; N: 9.06.



2S,3R-*N*-(3-(4-Methoxyphenyl)-4-methyl-2-phthalimidopentanoyl)-8-aminoquinoline (21)

To a 1-dram vial was added (S)-*N*-(4-methyl-2-phthalimidopentanoyl)-8-aminoquinoline (194 mg, 0.5 mmol), $Pd(OAc)_2$ (12 mg, 0.051 mmol), 4-iodoanisole (722 mg, 3.1 mmol), AgOAc (209 mg, 1.25 mmol), and toluene (0.4 mL). The mixture was stirred at 60 °C for 72 h. Analysis of crude reaction mixture by ^{1}H NMR showed presence of only one diastereomer. After completion, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and extracted with brine (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2x15 mL). Combined organic layers were dried over $MgSO_4$. Evaporation to remove the organic solvents followed by purification by flash chromatography in hexanes/ethyl acetate (10:1 to 2:1) gave 190 mg of a white solid (77%). This compound is known.[12] ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 10.06 (*s*, 1H) 8.67 (*dd*, 1H, *J*= 1.7, 4.6 Hz) 8.55 (*dd*, 1H, *J*= 1.7, 8.6 Hz) 7.92 (*dd*, 2H, *J*= 2.9, 5.1 Hz) 7.75 (*dd*, 2H, *J*= 2.9, 5.1 Hz) 7.43-7.34 (*m*, 5H) 6.92 (*d*, 2H, *J*= 9.2 Hz) 5.62 (*d*, 1H, *J*= 12.6 Hz) 4.20 (*dd*, 2H, *J*= 3.4, 12.6 Hz) 3.78 (*s*, 3H) 2.02-1.94 (*m*, 1H) 0.83 (*d*, 3H, *J*= 6.9 Hz) 0.77 (*d*, 3H, *J*= 6.9 Hz).

Large scale synthesis: a 25 mL-Schlenk flask equipped with a stir bar was charged with *N*-(4-methyl-2-phthalimidopentanyl)-8-aminoquinoline (2.15 g, 5.55 mmol), $Pd(OAc)_2$ (125 mg, 0.56 mmol), 4-iodoanisole (8.06 g, 3.1 mmol), AgOAc (2.32 g, 13.89 mmol), and toluene (4.5 mL). The mixture was stirred at 60 °C for 5 days. After completion, the reaction mixture was diluted with CH_2Cl_2 (50 mL) and extracted with brine (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2x35 mL). Combined organic layers were dried over $MgSO_4$. Evaporation to remove the organic solvents followed by purification by flash chromatography in hexanes/ethyl acetate (5:1 to 2:1) and preparative HPLC in hexanes/ethyl acetate 3:1 for the contaminated fractions gave 1.83 g of a white solid (67% yield).

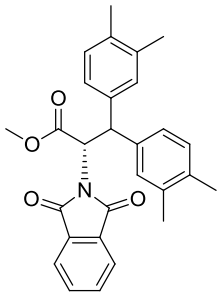


2S,3S-*N*-(3-(Thiophene-2-yl)-4-methyl-2-phthalimidopentanoyl)-8-aminoquinoline (22)

To a 1-dram vial was added (S)-*N*-(4-methyl-2-phthalimidopentanoyl)-8-aminoquinoline (194 mg, 0.5 mmol), $Pd(OAc)_2$ (12 mg, 0.051 mmol), 2-iodothiophene (651 mg, 3.1 mmol), and AgOAc (209 mg, 1.25 mmol). The mixture was stirred at 60 °C for 96 h. Analysis of crude reaction mixture by ^1H NMR showed 24:1 diastereomer ratio. After completion, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and extracted with

brine (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2x15 mL). Combined organic layers were dried over $MgSO_4$. Evaporation to remove the organic solvents followed by purification by flash chromatography in toluene/ethyl acetate (100% toluene to 30:1) gave 188 mg of a light green solid (80% yield). R_f = 0.40 (SiO_2, 1/10 ethyl acetate/toluene), mp 167-170 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 10.12 (*s*, 1H) 8.75 (*dd*, 1H, J= 1.4, 4.1 Hz) 8.58 (*dd*, 1H, J= 1.8, 7.3 Hz) 8.09-8.04 (*m*, 1H) 7.92 (*dd*, 2H, J= 2.7, 5.0 Hz) 7.75 (*dd*, 2H, J= 2.7, 5.0 Hz) 7.44-7.36 (*m*, 2H) 7.22-7.15 (*m*, 2H) 7.01-6.97 (*m*, 1H) 5.47 (*d*, 1H, J= 11.9 Hz) 4.64 (*dd*, 1H, J= 3.2, 11.9 Hz) 2.09-1.98 (*m*, 1H) 0.94 (*d*, 3H, J= 6.9 Hz) 0.86 (*d*, 3H, J= 6.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, ppm) 68.5, 166.1, 148.2, 139.2, 138.6, 136.1, 134.4, 134.3, 131.9, 127.8, 127.7, 127.2, 127.0, 124.8, 123.9, 121.9, 121.6, 117.0, 59.3, 44.2, 28.9, 21.6, 16.3. FT-IR (neat, cm^{-1}) 2357, 1717, 1531, 1488, 1381, 1326. Calcd for $C_{27}H_{23}N_3O_3S$ (469.55 g/mol) C: 69.06; H: 4.94; N: 8.95; Found C: 68.87; H: 5.02; N: 8.88.

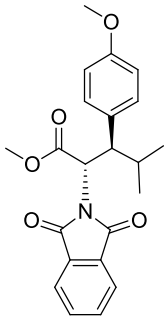
REMOVAL OF AUXILIARY



Methyl (S)-3,3-di(3,4-dimethylphenyl)-2-phthalimidopropionate (23)

To a 10 mL Kontes flask equipped with a stir bar was added (S)-*N*-(3,3-di(3,4-dimethylphenyl)-2-phthalimidopropionyl)-8-aminoquinoline (92 mg, 0.17 mmol). Inside

the glove box, dry methanol (2.6 mL) was added to the flask. Outside the glove box, BF_3*Et_2O (0.14 mL, 1.13 mmol) was added dropwise to the stirred solution. The resulting mixture was stirred at 110 °C for 37 h. After cooling to rt, Et_3N (0.24 mL, 1.72 mmol) was added dropwise to the reaction mixture with stirring. Evaporation to remove the organic solvents followed by purification by flash chromatography in toluene/ethyl acetate (100% toluene to 20:1) gave 59 mg of tan solid (80%). R_f = 0.55 (SiO_2, 1/10 ethyl acetate/toluene), mp 171-174 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.74 (*dd*, 2H, *J*= 2.9, 5.1 Hz) 7.63 (*dd*, 2H, *J*= 2.9, 5.7 Hz) 7.23-7.19 (*m*, 2H) 7.09-7.05 (*m*, 1H) 6.98-6.94 (*m*, 2H) 6.84-6.81 (*m*, 1H) 5.70 (*d*, 1H, *J*= 12.0 Hz) 5.12 (*d*, 1H, *J*= 12.0 Hz) 3.57 (*s*, 3H) 2.23 (*s*, 3H) 2.18 (*s*, 3H) 2.02 (*s*, 3H) 1.99 (*s*, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 169.0, 167.5, 139.4, 138.2, 136.9, 136.6, 135.0, 134.9, 134.1, 131.6, 120.0, 129.8, 129.4, 129.1, 125.0, 125.7, 123.5, 55.0, 52.7, 49.8, 20.1, 19.8, 19.5, 19.3. FT-IR (neat, cm^{-1}) 2338, 1751, 1737, 1713, 1388, 1268. Calcd for $C_{28}H_{27}NO_4$ (441.52 g/mol) C: 76.17; H: 6.16; N: 3.17; Found C: 75.89; H: 6.15; N: 3.21.



Methyl 2-(S)-3-(R)-3-(4-methoxyphenyl)-4-methyl-2-phthalimidopentanoate (24)

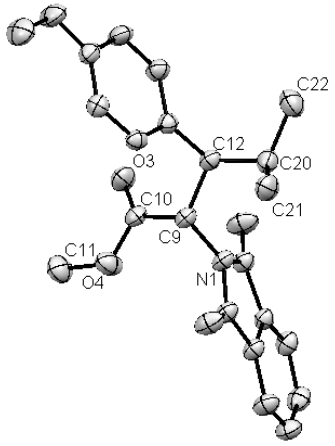
To a 10 mL Kontes flask equipped with a stir bar was added 2S,3S-*N*-(3-(4-methoxyphenyl)-4-methyl-2-phthalimidopentanoyl)-8-aminoquinoline (117 mg, 0.24

mmol). Inside the glove box, dry methanol (2.3 mL) was added to the flask. Outside the glove box, BF_3*Et_2O (0.12 mL, 0.97 mmol) was added dropwise to the stirred solution. The resulting mixture was stirred at 105 °C for 4 days. After cooling to rt, Et_3N (0.21 mL, 1.51 mmol) was added dropwise to the reaction mixture with stirring. Evaporation to remove the organic solvents followed by purification by flash chromatography in toluene/ethyl acetate (100% toluene to 20:1) gave 52 mg of a white solid (58%). Analysis of % ee by HPLC on chiral stationary phase: Chiralpack IA, eluent hexane/isopropanol/triethyl amine 70:30:0.1, 1 mL/min, 86% ee. Retention times: S,R (major enantiomer) = 7.0 min., R,S (minor enantiomer) 9.21 min. R_f = 0.51 (SiO_2, 1/2 ethyl acetate/hexanes), mp 141-144 °C. ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.91 (*dd*, 2H, *J*= 2.9, 5.1 Hz) 7.77 (*dd*, 2H, *J*= 2.9, 5.1 Hz) 7.24-7.19 (m, 2H) 6.89-6.85 (*m*, 2H) 5.35 (*d*, 1H, *J*= 11.5 Hz) 3.84 (*dd*, 1H, *J*= 4.0, 11.5 Hz) 3.81 (*s*, 3H) 1.90-1.80 (*m*, 1H) 0.77-0.72 (*m*, 6H). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 169.2, 167.9, 158.4, 134.4, 131.8, 130.6, 129.9, 123.8, 113.3, 55.2, 54.6, 52.5, 48.4, 28.6, 21.6, 17.1. FT-IR (neat, cm^{-1}) 2315, 1750, 1717, 1511, 1386, 1248, 1171. Calcd for $C_{22}H_{23}NO_5$ (381.42 g/mol) C: 69.28; H: 6.08; N: 3.67; Found C: 69.28; H: 6.08; N: 3.67.

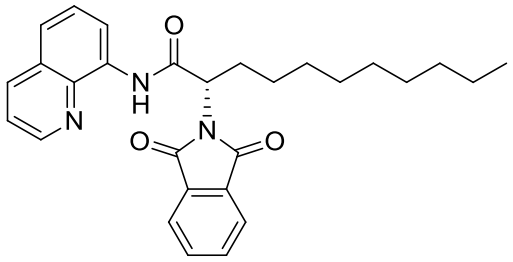
A large scale synthesis: a 100 mL Kontes flask equipped with a stir bar was charged with *N*-(3-(4-methoxyphenyl)-4-methyl-2-phthalimidopentanoyl)-8-aminoquinoline (1.62 g, 3.28 mmol). Inside the glove box, dry methanol (30 mL) was added to the flask. Outside the glove box, BF_3*Et_2O (1.62 mL, 13.13 mmol) was added dropwise to the stirred solution. The resulting mixture was stirred at 105 °C for 5 days. After cooling to rt, Et_3N (2.84 mL, 20.36 mmol) was added dropwise to the reaction mixture with stirring.

Evaporation to remove the organic solvents was followed by purification by flash chromatography in toluene/ethyl acetate (100 % toluene to 20:1) and preparative TLC in toluene/ethyl acetate 10:1. The contaminated fractions were further purified by preparative HPLC in hexanes/ethyl acetate 3:1. The product was obtained as a white solid (671 mg, 54%). Analysis of % ee by HPLC on chiral stationary phase as described above showed that product has 85% ee. Recrystallization of 192 mg product gave 162 mg (85%) recovery with 95% ee. Single crystals suitable for X-ray diffraction studies were obtained by layering the concentrated solution of CH_2Cl_2 with a mixture of hexanes/ethyl acetate (5:1) and storing the resulting mixture at -20 °C overnight.

Scheme 4-35. ORTEP representation of the molecular structure of methyl 2-(S)-3-(R)-3-(4-methoxyphenyl)-4-methyl-2-phthalimidopentanoate (24) obtained from single crystal X-ray diffraction.



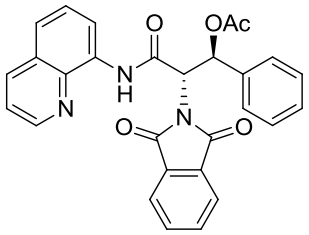
4.6 Alkylation and acetoxylation of amino acid derivatives



(S)-*N*-(2-Phthalimidoundecanoyl)-8-aminoquinoline (25)

To a 25 mL round-bottom flask equipped with a stir bar was added (S)-*N*-(2-phthalimidopropionyl)-8-aminoquinoline (173 mg, 0.5 mmol), $Pd(OAc)_2$ (12 mg, 0.053 mmol), and 1-iodooctane (961 mg, 4 mmol). Inside the glove box, Cs_3PO_4 (987 mg, 2 mmol) and cesium pivalate (117 mg, 0.5 mmol) were added to the flask. Outside the glove box, *o*-dichlorobenzne (1 mL) was added to the resulting mixture. The reaction was stirred at 110 °C for 42 h. After completion, the reaction mixture was diluted with CH_2Cl_2 (25 mL) and extracted with brine (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2x15 mL). Combined organic layers were dried over $MgSO_4$. Evaporation to remove the organic solvents followed by purification by flash chromatography in hexanes/ethyl acetate 5:1 gave 97 mg of a yellow liquid (42%). R_f = 0.54 (SiO_2, 1/2 ethyl acetate/hexanes). ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 10.34 (*s*, 1H) 8.74-8.68 (*m*, 2H) 8.14 (*dd*, 1H, *J*= 1.7, 8.0 Hz) 7.91 (*dd*, 2H, *J*= 2.9, 5.7 Hz) 7.76 (*dd*, 2H, *J*= 2.9, 5.7 Hz) 7.53-7.49 (*m*, 2H) 7.42 (*dd*, 1H, *J*= 4.0, 8.0 Hz) 5.13 (*dd*, 1H, *J*= 5.7, 10.9 Hz) 2.64-2.54 (*m*, 1H) 2.43-2.35 (*m*, 1H) 1.50-1.34 (*m*, 4H) 1.32-1.18 (*m*, 10H) 0.87 (*t*, 3H, *J*= 6.9 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, ppm) 168.3, 167.2, 148.4, 138.6, 136.4, 134.3, 134.1, 131.9,

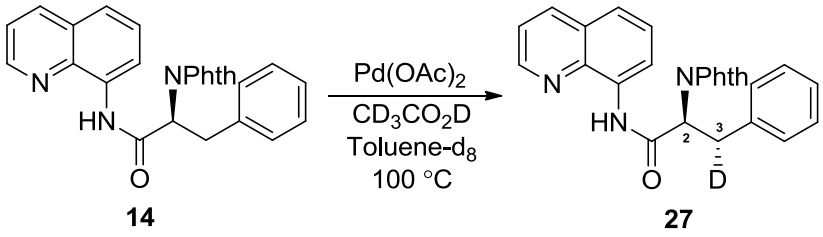
127.9, 127.4, 123.7, 122.0, 121.7, 116.8, 55.4, 31.9, 29.6, 29.5, 29.3, 29.1, 28.8, 26.8, 22.8, 14.2. FT-IR (neat, cm^{-1}) 2358, 2328, 1716, 1531, 1386. Calcd for $C_{28}H_{31}N_3O_3$ (457.56 g/mol) C: 73.50; H: 6.83; N: 9.18; Found C: 73.22; H: 6.80; N: 8.91.



2S,3S-*N*-(3-Acetyl-2-phthalimido-3-phenylpropionyl)-8-aminoquinoline (26)

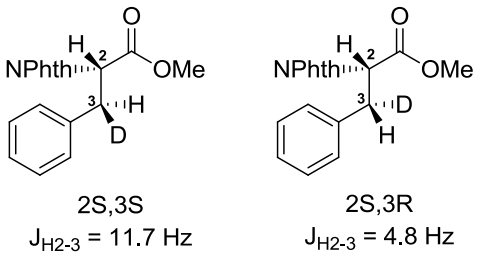
To a 2-dram vial equipped with a stirrer was added (S)-*N*-(2-phthalimido-3-phenylpropionyl)-8-aminoquinoline (211 mg, 0.5 mmol), $Pd(OAc)_2$ (13 mg, 0.058 mmol), iodobenzene diacetate (242 mg, 0.75 mmol), acetic anhydride (131 mg, 1.28 mmol), and *o*-dichlorobenzene (1.4 mL). The mixture was stirred at 70 °C for 12 h. After completion, the reaction mixture was concentrated under vacuum. Analysis of crude reaction mixture by ^{1}H NMR showed 8:1 diastereomer ratio. Purification of the residue by flash chromatography in toluene/ethyl acetate (toluene 100% to 30:1) gave 127 mg of a white solid (53%). This compound is known.[12] ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 10.75 (*s*, 1H) 8.80 (*dd*, 1H, *J*= 1.8, 4.1 Hz) 8.77 (*dd*, 1H, *J*= 1.8, 6.9 Hz) 8.19 (*dd*, 1H, *J*= 1.3, 8.2 Hz) 7.75 (*dd*, 2H, *J*= 3.2, 5.9 Hz) 7.65 (*dd*, 2H, *J*= 3.2, 5.5 Hz) 7.58-7.45 (*m*, 5H) 7.26-7.15 (*m*, 3H) 6.88 (*d*, 1H, *J*= 10.5 Hz) 5.65 (*d*, 1H, *J*= 10.5 Hz) 2.32 (*s*, 3H).

4.7 Mechanistic considerations



To a 1-dram vial was added (S)-*N*-(3-phenyl-2-phthalimidopropionyl)-8-aminoquinoline (105 mg, 0.25 mmol), CD_3COOD (430 µL, 7.51 mmol), $Pd(OAc)_2$ (6 mg, 0.031 mmol), and toluene-d8 (0.5 mL). The reaction mixture was stirred at 100 °C for 5 h and sample was taken for ^1H NMR analysis. ^1H NMR spectrum in toluene-d8 showed 64% deuterium incorporation and $J_{H2\text{-}H3}$= 11.5 Hz. This value of coupling constant suggests the configuration 2S, 3S due to similarity with reported coupling constant in a similar structure ($J_{H2\text{-}H3}$= 11.7 Hz, Scheme 4-35). [44]

Scheme 4-36.



V. References

1. Jones, W. D. *Inorg. Chem.* **2005**, *44*, 4475.

2. Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220.

3. Prokopcova, H.; Bergman, S. D.; Aelvoet, K.; Smout, V.; Herrebout, W.; Veken, B. V. D.; Meerpoel, L.; Maes, B. U. W. *Chem. Eur. J.* **2010**, *16*, 13063.

4. Dangel, B. D.; Godula, K.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 11856.

5. (a) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634. (b) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, E. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510.

6. Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190.

7. Shabashov, D.; Daugulis, O. *Org. Lett.* **2005**, *7*, 3657.

8. (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965.

9. Feng, Y.; Chen, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 958.

10. Feng, Y.; Wang, Y.; Landgraf, B.; Liu, S.; Chen, G. *Org. Lett.* **2010**, *12*, 3414.

11. Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chem. Soc.* dx.doi.org/10.1021/ja312277g

12. Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391.

13. Gutekunst, W. R.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 19076.

14. Gutekunst, W. R.; Gianatassio, R.; Baran, P. S. *Angew. Chem. Int. Ed.* **2012**, *51*, 7507.

15. Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 9886.

16. Wasa, M.; Chan, K. S. L.; Zhang, X.-G.; He, J.; Miura, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 18570.

17. Giri, R.; Lan, Y.; Liu, P.; Houk. K. N.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 14118.

18. Rodriguez, N.; Romero-Revilla, J. A.; Fernandez-Ibanez, M. A.; Carretero, J. C. *Chem. Sci*. **2013**, *4*, 175.

19. Dyker, G. *Angew. Chem. Int. Ed.* **1994**, *33*, 103.

20. Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685.

21. Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570.

22. (a) Chaumontet, M.; Piccardi, R.; Audic, N.; Hitce, J.; Peglion, J.-L.; Clot, E.; Baudoin, O. *J. Am. Chem. Soc.* **2008**, *130*, 15157. (b) Hitce, J.; Retailleau, P.; Baudoin, O. *Chem. Eur. J.* **2007**, *13*, 792

23. Rousseaux, S.; Davi, M.; Sofack-Kreutzer, J.; Pierre, C.; Kefalidis, C. E.; Clot, E.; Fagnou, K.; Baudoin, O. *J. Am. Chem. Soc.* **2010**, *132*, 10706.

24. Sofack-Kreutzer, J.; Martin, N.; Renaudat, A.; Jazzar, R.; Baudoin, O. *Angew. Chem. Int. Ed.* **2012**, *51*, 10399.

25. Liegault, B.; Fagnou, K. *Organometallics* **2008**, *27*, 4841.

26. Renaudat, A.; Jean-Gerard, L.; Jazzar, R.; Kefalidis, C. E.; Clot, E.; Baudoin, O. *Angew. Chem. Int. Ed.* **2010**, *49*, 7261.

27. Aspin, S.; Goutierre, A.-S.; Larini, P.; Jazzar, R.; Baudoin, O. *Angew. Chem. Int. Ed.* **2012**, *51*, 10808.

28. (a) Kast, P. *Chem. Bio. Chem.* **2011**, *12*, 2395. (b) Young, T. S.; Schultz, P. G. *J. Biol. Chem.* **2010**, *285*, 11039. (c) Nestor, J. J. Jr. *Curr. Med. Chem.* **2009**, *16*, 4399. (d) Sommer, S.; Weikart, N. D.; Brockmeyer, A.; Janning, P.; Mootz, H. D. *Angew. Chem. Int. Ed.* **2011**, *50*, 9888.

29. Reviews: (a) Ager, D. J. Unnatural Amino Acids, in: *Process Chemistry in the Pharmaceutical Industry*, Vol. 2 (Eds: K. Gadamasetti, T. Braish) CRC Press, **2008**, pp. 157. (b) Au-Yeung, T. T.-L.; Chan, S.-S.; Chan, A. S. C. in: *Transition Metals for Organic Synthesis*, Vol. 2 (Eds: M. Beller, C. Bolm), Wiley-VCH, **2004**, pp. 14-28. (c) Perdih, A. ; Dolenc, M. S. *Curr. Org. Chem*. **2011**, *15*, 3750.

30. (a) O'Malley, S. J.; Tan, K. L.; Watzke, A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13496. (b) Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 5767. (c) Mandal, D.; Yamaguchi, A. D.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2011**, *133*, 19660. (d) Marcé, P.; Díaz, Y.; Matheu, I.; Castillón, S. *Org. Lett.* **2008**, *10*, 4735. (e) Larivée, A.; Mousseau, J. J.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 52. (f) Chaumontet, M.; Piccardi, R.; Baudoin, O. *Angew. Chem., Int. Ed.* **2009**, *48*, 179. (g) Ahrendt, K. A.; Bergman, R. G.; Ellman, J. A. *Org. Lett.* **2003**, *5*, 1301. (h) Bowie, A. L. Jr.; Hughes, C. C.; Trauner, D. *Org. Lett.* **2005**, *7*, 5207. (i) Leblanc, M.; Fagnou, K. *Org. Lett.* **2005**, *7*, 2849.

31. (a) Yoo, E. J.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 17378. (b) Wasa, M.; Yu, J.-Q. *Tetrahedron* **2010**, *66*, 4811. (c) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am Chem. Soc.* **2010**, *132*, 3680. (d) Watanabe, T.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2008**, *10*, 1759. (e) Stowers, K. J.; Fortner, K. C.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 6541. (f) Deng, G.; Zhao, L.; Li, C.-J. *Angew. Chem. Int. Ed.* **2008**, *47*, 6278. (g)

Hasegawa, N.; Charra, V.; Inoue, S.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 8070.

32. Wen, S. –J.; Yao, Z. –J. *Org. Lett.* **2004**, *6*, 2721.

33. Ma, T.; Gao, Q.; Chen, Z.; Wang, L.; Liu, G. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1079.

34. Miltsov, S.; Rivera, L.; Encinas, C.; Alonso, J. *Tetrahedron Letters*, **2003**, *44*, 2301.

35. Wildemann, D.; Erdmann, F.; Alvarez, B. H.; Stoller, G.; Zhou, X. Z.; Fanghänel, J.; Schutkowski, M.; Lu, K. P.; Fischer, G. *J. Med. Chem.* **2006**, *49*, 2147.

36. Lin, J.; Liao, S.; Han, Y.; Qiu, W.; Hruby, V. J. *Tetrahedron: Asymmetry* **1997**, *8*, 3213.

37. (a) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc*. **2004**, *126*, 9542. (b) Giri, R.; Liang, J.; Lei, J.-G.; Li, J- J.; Wang, D.-H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420.

38. (a) Stille, J. K. In: *The Chemistry of the Metal-Carbon Bond*, Hartley, F. R.; S. Patai, S., Eds.; Wiley, New York, 1985, Vol. 2, chap. 9. (b) Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3910.

39. (a) Fryzuk, M.D.;Bosnich, B. *J. Am. Chem. Soc*. **1979**, *101*, 3043. (b) Labinger, J. A.; Hart, D. W.; Seibert III, W. E.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 3851.

40. Intermediate **28** is drawn as a Pd(IV) complex. However, intermediacy of Pd(III) complexes cannot be excluded. (a) Powers, D. C.; Geibel, M. A. L.; Klein, J. E. M. N.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 17050. (b) Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234. (c) Canty, A. J. *Acc. Chem. Res.* **1992**, *25*, 83. (d) Sobanov,

A. A.; Vedernikov, A. N.; Dyker, G.; Solomonov, B. N. *Mendeleev Commun*. **2002**, *1*, 14. (e) Amatore, C.; Catellani, M.; Deledda, S.; Jutand, A.; Motti, E. *Organometallics* **2008**, *27*, 4549.

41. Powell, J.; Horvath, M.; Lough, A. *J. Chem. Soc. Chem. Commun.* **1993**, 733.

42. Jean, M; Renault, J.; Uriac, P.; Capet, M.; Weghe, P. V. D. *Org. Lett.* **2007**, *9*, 3623.

43. Navarre, L.; Martinez, R.; Genet, R.-P.; Darses, S. *J. Am. Chem. Soc.* **2008**, *130*, 6159.

44. Easton, C. J.; Hutton, C. A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3545.