The Pennsylvania State University

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FAST COPPER-CATALYZED ARYL C(sp^2)-H AMINATION WITH *N*-(2-PYRIDYL)SULFONYL DIRECTING GROUP AT AMBIENT TEMPERATURE

A Thesis in

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ABSTRACT

The ubiquity of aryl amines makes them a crucial part in various organic syntheses. An immense effort has been made, therefore, to develop efficient methods to synthesize them. Traditionally, nitration, alkylation and reduction are applied to arenes and derivatives to enable such transformation, which is now often replaced by their counterparts utilizing palladium, nickel and copper catalysis. The rapidly developing field of C-H functionalization has also provided new insights into this topic. This research describes a new method for the synthesis of aryl amines utilizing a cheap copper catalyst copper(II) chloride and an auxiliary agent, magnesium chloride, under the direction of an *N*-(2-pyridyl)sulfonyl group. A thorough and systematic study has been conducted to optimize the reaction yield by changing different aspects of reaction conditions including catalyst, oxidant, solvent, temperature, stoichiometry etc. The optimized conditions allow the reaction to occur at room temperature in 15 min with moderate to good yields. The scope of this reaction as well as a preliminary investigation into the reaction mechanism is also described in this work. While the optimal conditions were determined, the details of mechanism still remain unclear. Possible mechanistic pathways and potential experiments that could help identify the mechanism are proposed in the third chapter.

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Chapter 1

Aryl Amines: Important Building Blocks and Synthesis Methods

This chapter provides a broad overview of traditional protocols and emerging C-H functionalization to synthesize aryl amines. The groundbreaking Buchwald – Hartwig amination utilizing palladium catalysts, its variation of nickel catalysts specialized in using aryl chloride, and the well-known Ullmann condensation are briefly discussed here. In addition, the new C-H amination approach as well as the *N*-(2-pyridyl)sulfonyl directing group is also introduced.

1.1 – Traditional Methods of aryl amine synthesis

Aryl amines are important building blocks of many agrochemicals, pharmaceuticals and conducting polymers. Bentazon, for example, is a widely applied selective herbicide whose structure contains a sulfonamide attached to its benzene moiety to control the spread of weed among crops. Prilocaine is a local anesthetic bearing an aromatic amino amide that is often used in dentistry. Polyaniline (PANI), a semi-flexible conducting polymer, is often used in the development of flexible electronics such as organic field effect transistor (OFET) and organic light emitting diode (OLED) due to its light weight, mechanical flexibility and relatively low cost. Driven by their ubiquity, chemists have striven to develop efficient methods to synthesize aryl amines.

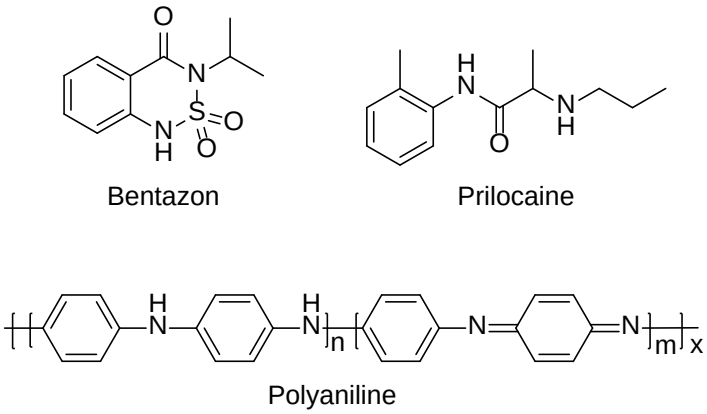


Figure 1-1. Structures of bentazon, prilocaine and polyaniline.

In 1995, Prof. Buchwald and Prof. Hartwig independently discovered a new protocol which was later named after them. In their seminal publications, Prof. Buchwald and Prof. Hartwig reported the use of an aryl bromide and amine to afford an aryl amine directly in the presence of a base and a phosphane-bearing palladium catalyst.[1] Unlike the preceding research by Migita *et al*. in 1983[2], this breakthrough bypassed the necessity of using poisonous aminostannanes and ameliorated the problem of troublesome workup and inapplicability to primary aliphatic amines. Investigation of ancillary groups has led to impressive progress in expanding the scope of the Buchwald-Hartwig reaction, the use of some sterically hindered, electron-rich ligands, like the commercialized JosiPhos ligand (Figure 1-2) CyPF-*t*Bu, allowed some formerly impossible transformations such as utilizing ammonia as an amine source.[3]

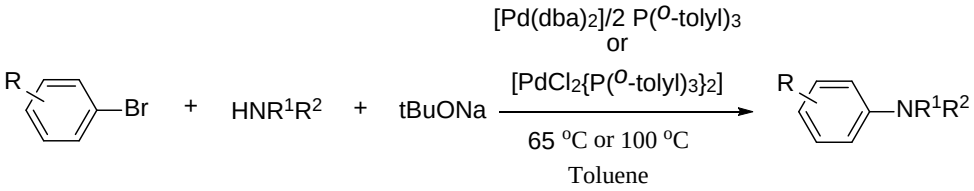


Figure 1-2. Buchwald-Hartwig amination.

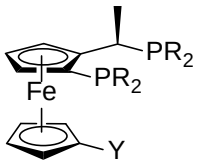


Figure 1-3. Typical structure of JosiPhos ligand.

Notwithstanding the wide scope and well developed protocol of the Buchwald-Hartwig reaction, many problems still remain challenging, one of which is the use of readily available aryl chloride that often requires tailor-made ligands. In regard to the fact that Ni^0 easily inserts into an aryl chloride, a catalytic system with a nickel center becomes a special direction of arene amination. In 1997, the Hartwig group reported the use of a mixture of $Ni(COD)_2$ and 1,1'-bis-(diphenylphosphino)ferrocene (DPPF) in the presence of sodium *tert*-butoxide to promote the coupling of an aryl chloride with amines in moderate to excellent yields.[4] The procedure can tolerate a wide range of functional groups including acetals, nitriles, ethers and non-enolizable ketones and can occur at a temperature as low as 70 °C. In the report by Lipshutz and coworkers, they discovered an industrially interesting catalytic system which adopts a mixture of nickel embedded in a charcoal matrix, *n*BuLi and DPPF.[5] The reaction proceeded under mild heating with electron-rich and electron-poor aryl chlorides and the catalyst can be easily filtered off after completion of reaction.

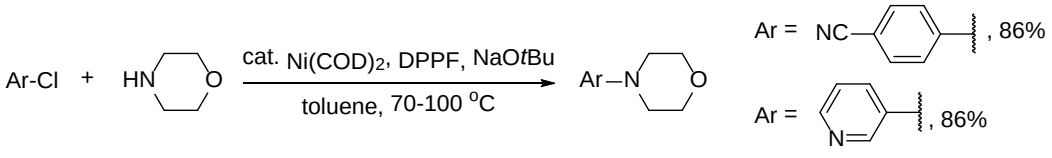


Figure 1-4. Amination of aryl chloride with $Ni(COD)_2$

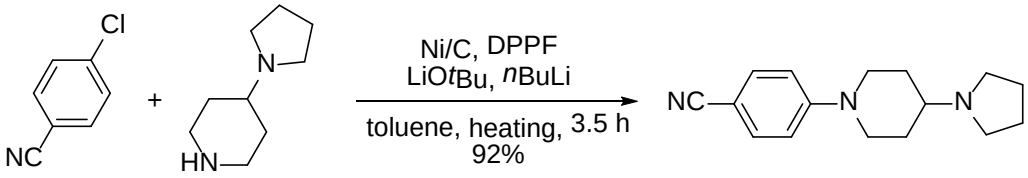


Figure 1-5. Animation of aryl chloride with Ni/C.

Ullmann condensation, especially its aryl amide variation which is named as the Goldberg reaction, is a natural alternative of the palladium catalyzed reactions. Great effort has been made to tune the conditions to be less demanding than the original. The use of bidentate ligands such as amino acids[6], aliphatic diamines[7] and diethylsalicylamide[8] has allowed milder reaction conditions. The use of *N*-methyl glycine reported by Zhang's group in 2003, for example, has successfully lowered the temperature of reaction between the aryl iodide and benzyl amine to 40 °C.[6] In 2006, the Buchwald's group introduced a catalytic system formed *in situ* by combining CuI and β-diketone to enable the reaction between aryl iodide and amines at the unprecedented room temperature.[9]

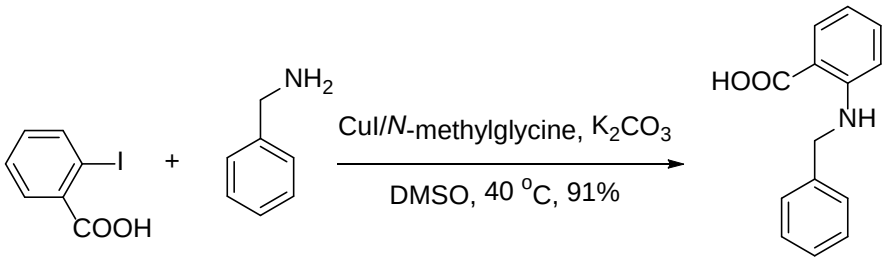


Figure 1-6. Cu-catalyzed aryl amination in the presence of an amino acid.

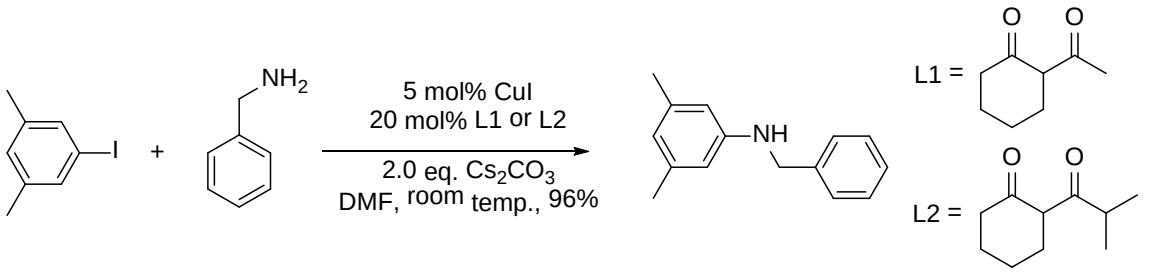


Figure 1-7. Room temperature Cu-catalyzed amination with *β*-diketone as ligand.

1.2 – C-H Functionalization as a New Approach for Aryl Amination

The burgeoning field of C-H activation in recent years has shed light on aryl amination. The possibility of directly replacing a hydrogen atom with an amino group offers unique opportunities in synthesis compared with the aforementioned methodologies. Despite of the fact that pioneering research led by the groups of Sloan, Kahn and Turner dated back to late 1960s[10], it was not until the publication by R. Breslow and Gellman on the use of iron porphyrin or rhodium acetate to facilitate intramolecular C-H amination[11] and the intermolecular counterpart reported by Mansuy *et al.*[12] that the way for further investigation was paved. The rapid development of this chemistry, especially in the intramolecular field, has granted chemists new accesses to C-N bond formation. With the help of carefully designed directing group, such transformation occurring intermolecularly can be achieved more selectively at milder conditions.

The *N*-(2-pyridyl)sulfonyl group was first applied as a directing group to introduce alkenylation of indoles and pyrroles by the Carretero group in 2009.[13] Though previously often used in asymmetric C-C bond forming as a protecting group or stereocontroller[14], the *N*-(2-pyridyl)sulfonyl group turned out to show good directing capabilities in C-H functionalization. In the aforementioned work on indoles and pyrroles, regioselective alkenylation was achieved with moderate to good yields. Later in 2013, the Carretero group reported remote C(sp^3)-H arylation of

dipeptide[15] and ortho-halogenation[16], both utilizing the *N*-(2-pyridyl)sulfonyl group as a removable directing group. Prompted by our interest in the activity of *N*-(2-pyridyl)sulfonyl group on other possible C-H functionalizations, we focused our study on the amination of arenes.

In this research, we studied *N*-(2-pyridyl)sulfonyl-directed C(sp^2)-H amination under Cu(II) catalysts. In the presence of a hypervalent iodide oxidant $PhI(OAc)_2$, the reaction can occur at ambient temperature in 1 min. A condition at ambient temperature with 15 min results in moderate to good yields. We believe that such a reaction could be industrially attractive due to its mild conditions and fast nature if applied using a continuous flow synthesis, which may benefit large-scale production and quality control. However, further investigation is needed to better explore the mechanism and broaden the substrate scope.

Chapter 2

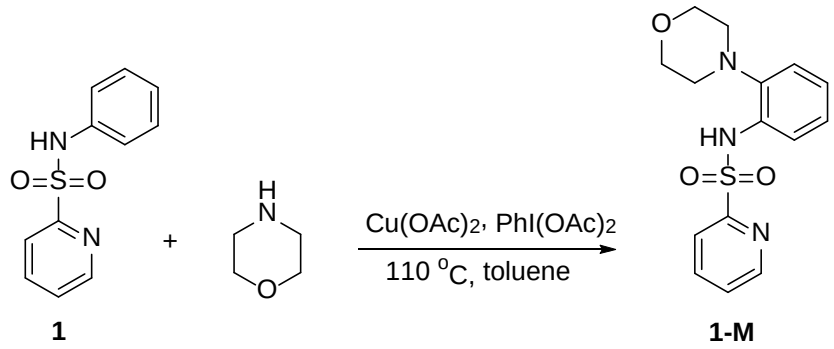
Amination of *N*-(2-pyridyl)sulfonyl Directed Arene

This chapter will deal with the details of reaction condition screening. The optimal conditions and underlying logic are discussed with the emphasis placed on an explanation of experimental phenomena and reasoning of optimization. The scope of this reaction is also discussed at the end of this chapter.

2.1 – Screening of Conditions

Potential active amines

Inspired by the early success using hypervalent iodine(III) reagent like $PhI(OAc)_2$ in palladium-catalyzed C-H oxygenation[17], a combination of the aforementioned $PhI(OAc)_2$ and $Cu(OAc)_2$ was selected to start the pilot run at 110 °C for 24 h with toluene as the solvent. As Table 2-1 illustrates, aliphatic amines generally showed no reactivity while alicyclic amines like morpholine and piperidine gave promising feedback.



1 **1-M**

Figure 2-1. Initial reaction condition using **1** as substrate and morpholine as amine source. 110 °C, toluene, $PhI(OAc)_2$ (2 equiv.), amine (2 equiv.), $Cu(OAc)_2$ (20 mol %), 24 h.

Table 2-1. Screening of active amines.

Entry	Amine	Solv.	Temp./°C	Time/h	GC Yield/%
1	Propylamine	Toluene	110	24	--
2	Butylamine	Toluene	110	24	--
3	Hexylamine	Toluene	110	24	--
4	Dodecylamine	Toluene	110	24	--
5	**Morpholine**	**Toluene**	**110**	**24**	**42**
6	**Piperidine**	**Toluene**	**110**	**24**	**21**

Solvent effect

Solvent was screened first to determine the best environment for this reaction. It was found that dichloroethane (DCE) (Table 2-2, entry 5) and tetrahydrofuran (THF) (Table 2-2, entry 7) showed higher yields and produced fewer side products. Toluene and *p*-xylene (Table 2-2, entry 1-2) led to significantly more side products as illustrated by similar yields but higher conversions. The better yields with THF, toluene and *p*-xylene may be attributed to their ability to serve as effective coordinating ligands, while the harsh conditions, i.e. high temperature and presence of oxidant, could lead to oxidation of the solvent. Better solubility of the reactants and

intermediates could account for the better performance of DCE. In ambient temperature reactions (*vide infra*), toluene and *p*-xylene were re-screened and both showed comparable yields with greatly reduced formation of side product.

Table 2-2. Investigation of effective solvent.

Entry	Solv.	Temp./°C	Time/h	Conversion/%	GC Yield/%
1	Toluene	110	24	75	42
2	*p*-Xylene	110	24	81	43
3	Benzene	110	24	49	31
4	PhCl	110	24	55	27
5	**DCE**	**110**	**24**	**44**	**44**
6	*p*-Dioxane	110	24	36	20
7	**THF**	**110**	**24**	**47**	**42**
8	*t*-BuOH	110	24	54	26
9	*t*-Amyl-OH	110	24	55	36
10	DMF	110	24	28	22
11	DMSO	110	24	20	14
12	CH_3CN	110	24	26	20
13	CH_3NO_2	110	24	20	11

Efficient oxidants

Encouraged by the success of (diacetoxyiodo)benzene ($PhI(OAc)_2$), we began to investigate potential efficient oxidants in DCE and THF. Eleven oxidants were chosen based on their performance in research of C-H functionalization as depicted in Table 2-3. Surprisingly, our first choice of $PhI(OAc)_2$ (Table 2-3, entry 1) gave the best result among all 12 oxidants. Other oxidants like $Ce(SO_4)_2$ (Table 2-3, entry 5), MnO_2 (Table 2-3, entry 7) or $NaIO_4$ (Table 2-3, entry 21) are far less effective. In addition, we noted that even oxygen (Table 2-3, entry 8) showed positive feedback. This became very interesting since all experiments were conducted under

argon protection. Formation of the desired product under aerobic environment implied that this reaction could occur without inert gas protection, which was proved true.

Table 2-3. Screening of Oxidants.

Entry	Oxidant	Cat.	Solv.	Temp./°C	Time/h	GC Yield/%
1	**$PhI(OAc)_2$**	**$Cu(OAc)_2$**	**DCE**	**110**	**24**	**44**
2	Ag_2CO_3	$Cu(OAc)_2$	DCE	110	24	6
3	AgOAc	$Cu(OAc)_2$	DCE	110	24	3
4	Oxone	$Cu(OAc)_2$	DCE	110	24	--
5	$Ce(SO_4)_2$	$Cu(OAc)_2$	DCE	110	24	10
6	$KMnO_4$	$Cu(OAc)_2$	DCE	110	24	7
7	MnO_2	$Cu(OAc)_2$	DCE	110	24	16
8	O_2	$Cu(OAc)_2$	DCE	110	24	2
9	$NaIO_4$	$Cu(OAc)_2$	DCE	110	24	4
10	$Na_2S_2O_8$	$Cu(OAc)_2$	DCE	110	24	5
11	$K_2S_2O_8$	$Cu(OAc)_2$	DCE	110	24	3
12	NMO	$Cu(OAc)_2$	DCE	110	24	0.7
13	**$PhI(OAc)_2$**	**$Cu(OAc)_2$**	**THF**	**110**	**24**	**42**
14	Ag_2CO_3	$Cu(OAc)_2$	THF	110	24	9
15	AgOAc	$Cu(OAc)_2$	THF	110	24	--
16	Oxone	$Cu(OAc)_2$	THF	110	24	--
17	$Ce(SO_4)_2$	$Cu(OAc)_2$	THF	110	24	5
18	$KMnO_4$	$Cu(OAc)_2$	THF	110	24	--
19	MnO_2	$Cu(OAc)_2$	THF	110	24	7
20	O_2	$Cu(OAc)_2$	THF	110	24	3
21	$NaIO_4$	$Cu(OAc)_2$	THF	110	24	10
22	$Na_2S_2O_8$	$Cu(OAc)_2$	THF	110	24	3
23	$K_2S_2O_8$	$Cu(OAc)_2$	THF	110	24	1
24	NMO	$Cu(OAc)_2$	THF	110	24	--

Stoichiometry

The effect of stoichiometry was tabulated in Table 2-4. It was found that the yield increased as the amount of oxidant or morpholine increased and it would reach a maximum when both were two equivalents to the substrate (Table 2-4, entry 3). Beyond two equivalents, the yield dropped as the amount of oxidant or morpholine further increased.

Table 2-4. Investigations on Stoichiometry.

Entry	Morpholine /eq.	Oxidant/eq.	Cat./eq.	Solv.	Temp./°C	Time/h	GC Yield/%
1	2	1 $PhI(OAc)_2$	0.2 $Cu(OAc)_2$	DCE	110	24	19
2	2	1.5 $PhI(OAc)_2$	0.2 $Cu(OAc)_2$	DCE	110	24	24
3	**2**	**2 $PhI(OAc)_2$**	**0.2 $Cu(OAc)_2$**	**DCE**	**110**	**24**	**44**
4	2	2.5 $PhI(OAc)_2$	0.2 $Cu(OAc)_2$	DCE	110	24	26
5	2	3 $PhI(OAc)_2$	0.2 $Cu(OAc)_2$	DCE	110	24	21
6	2	3.5 $PhI(OAc)_2$	0.2 $Cu(OAc)_2$	DCE	110	24	6
7	1.5	2 $PhI(OAc)_2$	0.2 $Cu(OAc)_2$	DCE	110	24	18
8	2.5	2 $PhI(OAc)_2$	0.2 $Cu(OAc)_2$	DCE	110	24	40
9	3	2 $PhI(OAc)_2$	0.2 $Cu(OAc)_2$	DCE	110	24	25
10	3.5	2 $PhI(OAc)_2$	0.2 $Cu(OAc)_2$	DCE	110	24	27
11	4	2 $PhI(OAc)_2$	0.2 $Cu(OAc)_2$	DCE	110	24	18

Catalyst, copper(I) and copper(II) salts

To further improve the protocol, common copper catalysts were screened using THF as the solvent. It was found that the chloride-containing catalysts CuCl and $CuCl_2$ gave better yields (42% and 52% respectively). With the exception of CuBr, all other copper(I) and copper(II) catalysts showed catalytic ability and Cu(II) catalysts generally worked better than Cu(I) catalysts.

Table 2-5. Screening of common copper catalyst.

Entry	Oxidant	Cat.	Solv.	Temp./°C	Time/h	GC Yield/%
1	$PhI(OAc)_2$	$CuSO_4$	THF	110	24h	12
2	$PhI(OAc)_2$	$CuBr_2$	THF	110	24h	27
3	**$PhI(OAc)_2$**	**$CuCl_2$**	**THF**	**110**	**24h**	**52**
4	$PhI(OAc)_2$	$Cu(OTf)_2$	THF	110	24h	6
5	$PhI(OAc)_2$	CuOAc	THF	110	24h	18
6	$PhI(OAc)_2$	CuCl	THF	110	24h	42
7	$PhI(OAc)_2$	CuBr	THF	110	24h	--
8	$PhI(OAc)_2$	CuI	THF	110	24h	30
9	$PhI(OAc)_2$	anh. $Cu(OAc)_2$	THF	110	24h	18
10	$PhI(OAc)_2$	Cu(OTf) benzene cplx.	THF	110	24h	9

Reaction time, temperature and solvent re-selection at room temperature

Reaction time was investigated next to see if it can be shortened. In order to be consistent, experiments regarding time were conducted in a one-pot manner rather than in parallel, and the amount of samples withdrawn for GC analyses was controlled to be less than 1% to impose as little impact as possible. To our delight, we found that this reaction can finish within 15 min, as opposed to the original 24 h as shown in Table 2-6. The fast nature of this reaction inspired us to conduct a trial at ambient temperature, which proved successful and became the biggest breakthrough of this project thus far. A series of follow-up investigations (Table 2-7) at ambient temperature showed that the reaction can finish even in 1 min. The lower yield at room temperature led us to a re-screening of solvents. We found that toluene (Table 2-8, entry 1) showed higher yield with less side product formed and DCE (Table 2-8, entry 3) gave comparable yield to experiment at elevated temperature.

Table 2-6. Investigation on reaction time at 110 °C.

Entry	Oxidant	**Cat.**	**Solv.**	**Temp./°C**	**Time/h**	**GC Yield/%**
1	$PhI(OAc)_2$	$CuCl_2$	THF	110	24	52
2	$PhI(OAc)_2$	$CuCl_2$	THF	110	18	54
3	$PhI(OAc)_2$	$CuCl_2$	THF	110	12	49
4	$PhI(OAc)_2$	$CuCl_2$	THF	110	8	55
5	$PhI(OAc)_2$	$CuCl_2$	THF	110	4	59
6	$PhI(OAc)_2$	$CuCl_2$	THF	110	2	41
7	$PhI(OAc)_2$	$CuCl_2$	THF	110	1	44
8	$PhI(OAc)_2$	$CuCl_2$	THF	110	0.5	48
9	**$PhI(OAc)_2$**	**$CuCl_2$**	**THF**	**110**	**0.25**	**53**

Table 2-7. Investigation on reaction time at room temperature

Entry	Oxidant	**Cat.**	**Solv.**	**Temp./°C**	**Time**	**GC Yield/%**
1	$PhI(OAc)_2$	$CuCl_2$	THF	r.t.	24 h	24
2	$PhI(OAc)_2$	$CuCl_2$	THF	r.t.	12 h	24
3	$PhI(OAc)_2$	$CuCl_2$	THF	r.t.	8 h	21
4	$PhI(OAc)_2$	$CuCl_2$	THF	r.t.	4 h	27
5	$PhI(OAc)_2$	$CuCl_2$	THF	r.t.	2 h	22
6	$PhI(OAc)_2$	$CuCl_2$	THF	r.t.	1 h	22
7	$PhI(OAc)_2$	$CuCl_2$	THF	r.t.	30 min	21
8	$PhI(OAc)_2$	$CuCl_2$	THF	r.t.	15 min	23
9	$PhI(OAc)_2$	$CuCl_2$	THF	r.t.	5 min	22
10	**$PhI(OAc)_2$**	**$CuCl_2$**	**THF**	**r.t.**	**1 min**	**21**

Table 2-8. Re-screening of solvent at ambient temperature.

Entry	Oxidant	**Cat.**	**Solv.**	**Temp./°C**	**Time/h**	**GC Yield/%**
1	$PhI(OAc)_2$	$CuCl_2$	Toluene	r.t.	0.25	49
2	$PhI(OAc)_2$	$CuCl_2$	*p*-Xylene	r.t.	0.25	43
3	**$PhI(OAc)_2$**	**$CuCl_2$**	**DCE**	**r.t.**	**0.25**	**54**

Catalyst loading

We also conducted experiments to investigate the effect of catalyst loading. As Table 2-9 illustrates, the yield decreases significantly if the amount of catalyst is lowered to 10 mol %. Yield reaches a maximum when catalyst is 45 mol % and will start to drop beyond this point.

Table 2-9. Effect of catalyst loading.

Entry	Oxidant	Cat./eq.	Solv.	Temp./°C	Time/h	GC Yield/%
1	$PhI(OAc)_2$	0.1 $CuCl_2$	DCE	r.t.	0.25	36
2	$PhI(OAc)_2$	0.2 $CuCl_2$	DCE	r.t.	0.25	54
3	$PhI(OAc)_2$	0.3 $CuCl_2$	DCE	r.t.	0.25	62
4	$PhI(OAc)_2$	0.4 $CuCl_2$	DCE	r.t.	0.25	57
5	**$PhI(OAc)_2$**	**0.45 $CuCl_2$**	**DCE**	**r.t.**	**0.25**	**70**
6	$PhI(OAc)_2$	0.5 $CuCl_2$	DCE	r.t.	0.25	60

Auxiliary agent

To control the catalyst loading while maintaining the yield, we tried to add auxiliary agents into the system to help with the catalysis. Interestingly, we discovered that an addition of $MgCl_2$ can help maintain the yield with only 20 mol % of catalyst. (Table 2-10, entry 4) Nevertheless, lower catalyst loading with addition of $MgCl_2$ still resulted in greatly reduced yield. (Table 2-10, entry 2) To eliminate the possibility that $MgCl_2$ can catalyze this reaction, a blank control experiment (Table 2-10, entry 1) in which no copper catalyst was added was conducted. No desired product was formed in the control, showing that $MgCl_2$ only works as an auxiliary agent. Reducing or increasing the loading of $MgCl_2$ (Table 2-10, entry 3 & 5) does not further improve the yield. Another Mg^{2+} salt, $Mg(OAc)_2$, was also tested but showed no such activity. (Table 2-10, entry 6) Another control experiment which contained the same amount of chloride

and inactive sodium counter ion also gave no desired product. (Table 2-10, entry 7) Other chloride containing Group II(A) salts were tested (Table 2-10, entry 7-9), however none of them showed similar effect as $MgCl_2$ did. It was postulated that Mg^{2+} might participate in binding with two substrate molecules, thus increasing the availability of the catalyst by freeing one Cu^{2+} per two substrate molecules.

Table 2-10. Effect of $MgCl_2$ auxiliary and other Group(II) A salts.

Entry	Oxidant	Cat./eq.	Additive/eq.	Solv.	Temp./°C	Time/h	GC Yield/%
1	$PhI(OAc)_2$	None	0.2 $MgCl_2$	DCE	r.t.	0.25	--
2	$PhI(OAc)_2$	0.1 $CuCl_2$	0.2 $MgCl_2$	DCE	r.t.	0.25	38
3	$PhI(OAc)_2$	0.2 $CuCl_2$	0.1 $MgCl_2$	DCE	r.t.	0.25	53
4	**$PhI(OAc)_2$**	**0.2 $CuCl_2$**	**0.2 $MgCl_2$**	**DCE**	**r.t.**	**0.25**	**65**
5	$PhI(OAc)_2$	0.2 $CuCl_2$	0.4 $MgCl_2$	DCE	r.t.	0.25	46
6	$PhI(OAc)_2$	0.2 $CuCl_2$	0.2 $Mg(OAc)_2$	DCE	r.t.	0.25	52
7	$PhI(OAc)_2$	0.2 $CuCl_2$	0.4 NaCl	DCE	r.t.	0.25	46
8	$PhI(OAc)_2$	0.2 $CuCl_2$	0.2 $CaCl_2$	DCE	r.t.	0.25	45
9	$PhI(OAc)_2$	0.2 $CuCl_2$	0.2 $SrCl_2$	DCE	r.t.	0.25	52
10	$PhI(OAc)_2$	0.2 $CuCl_2$	0.2 $BaCl_2$	DCE	r.t.	0.25	54

Protocol improvement trials

The difference in appearance of reaction mixture at elevated temperature and room temperature led us to consider possible ways to boost the yield at room temperature. At elevated temperature, the reaction mixture is a translucent pale yellow solution; while at room temperature the mixture is opaque dark green, implying that the catalyst may be insoluble at room temperature. We proposed the idea that a counter ion with a long alkyl chain might improve the solubility of the copper catalyst thus boosting the yield. We synthesized copper(II) *n*-hexanoate as Figure 2-2 and tested its performance. Copper(II) *n*-hexanoate (Table 2-11, entry 1) and

commercial copper(II) 2-ethylhexanoate (Table 2-11, entry 2) were examined, however copper(II) *n*-hexanoate only showed comparable yield to $CuCl_2$.

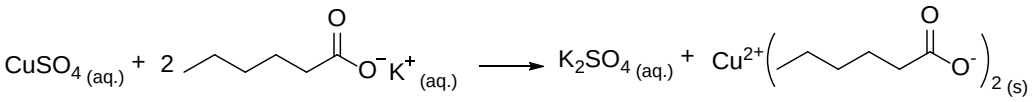


Figure 2-2. Synthesis of copper(II) hexanoate.

Table 2-11. Comparison between $CuCl_2$ and Cu catalysts with long alkyl chain.

Entry	Oxidant	**Cat.**	**Solv.**	**Temp./°C**	**Time/h**	**GC Yield/%**
1	$PhI(OAc)_2$	Cu(II) *n*-hexanoate	DCE	r.t.	0.25	55
2	$PhI(OAc)_2$	Cu(II) 2-ethylhexanoate	DCE	r.t.	0.25	38
3	$PhI(OAc)_2$	$CuCl_2$	DCE	r.t.	0.25	54

Working on improving the solubility of the catalyst to boost the yield, we further tested the use of crown ethers to see if they can bind to copper(II) ion and better solvate the metal center. Three crown ethers, namely 12-Crown-4, 15-Crown-5 and 18-Crown-6, were investigated, but none gave positive feedback. The binding of the metal center to the ether might be too strong, leading to the loss of available vacant sites for catalysis or too much steric hindrance.

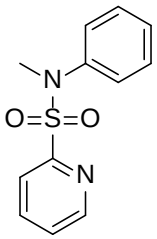
Table 2-12. Addition of crown ether.

Entry	Oxidant	Cat.	Additive	Solv.	Temp./°C	Time/h	GC Yield/%
1	$PhI(OAc)_2$	$CuCl_2$	12-Crown-4	DCE	r.t.	0.25	40
2	$PhI(OAc)_2$	$CuCl_2$	15-Crown-5	DCE	r.t.	0.25	29
3	$PhI(OAc)_2$	$CuCl_2$	18-Crown-6	DCE	r.t.	0.25	23

Preliminary mechanistic investigation: necessity to bind as an amidate

Based on the aforementioned investigations, the optimal conditions of amination of *N*-(2-pyridyl)sulfonyl-directed benzene were determined to be: 20 mol % of $CuCl_2$, 20 mol % of $MgCl_2$, 2 equivalent of $PhI(OAc)_2$, 2 equivalent of morpholine in dichloroethane at room temperature for 15 min.

To briefly probe into the reaction mechanism, *N*-methylated substrate **2** (Figure 2-3) was submitted to the optimal conditions. After 12 h of reaction, nearly all the substrate was recovered from the reaction mixture. (Table 2-13) It was therefore postulated that the coordination of the substrate to Cu^{II} as an amidate occurs prior to C-H activation and amination, without which the formation of amination product is impossible. (Figure 2-4)



2

Figure 2-3. Structure of *N*-methyl-*N*-phenylpyridine-2-sulfonamide

Table 2-13. Reaction of *N*-methylated substrate.

Entry	Oxidant	Cat./eq.	Additive/eq.	Solv.	Temp./°C	Time/h	GC Yield/%
1	$PhI(OAc)_2$	0.2 $CuCl_2$	0.2 $MgCl_2$	DCE	r.t.	12	--

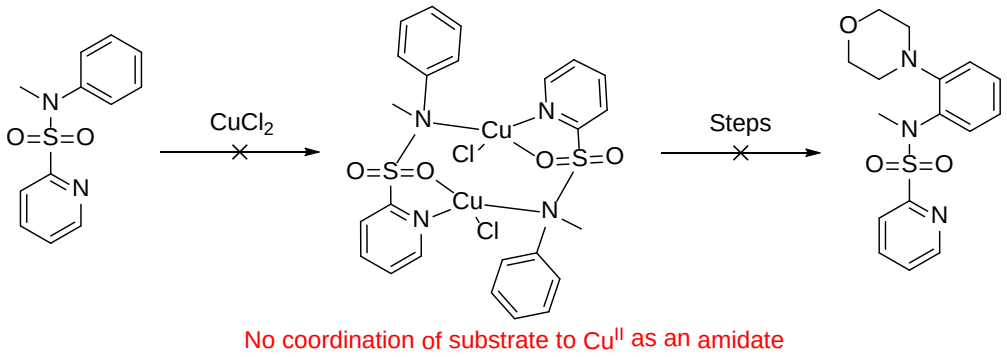
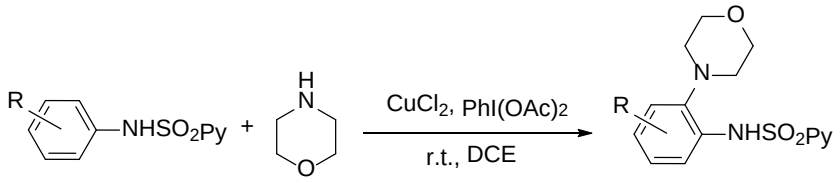


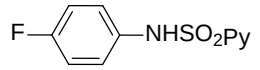
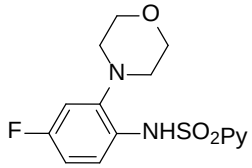
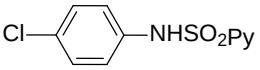
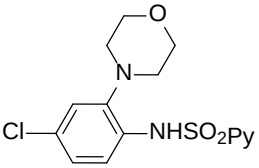
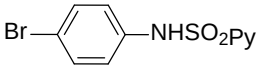
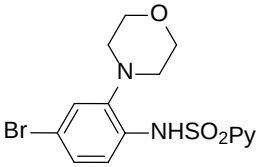
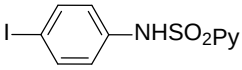
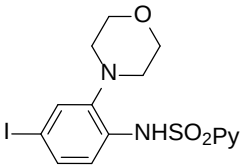
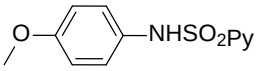
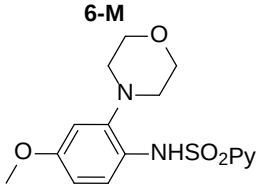
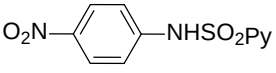
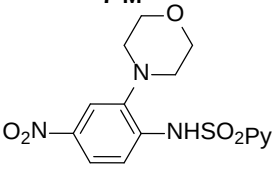
Figure 2-4. Proposed explanation for inactivity of *N*-methylated substrate

2.2 – Scope of Substrates

With the optimal conditions, we then examined *N*-(2-pyridyl)sulfonyl-directed arene substrates with different electron-withdrawing and electron-donating groups. We found the *ortho*-C-H amination under *N*-(2-pyridyl)sulfonyl direction is strongly affected by electronic properties. In general, electron-poor substrates (Table 2-14, entry 1-4 & 6) are more reactive than electron-rich substrate (Table 2-14, entry 5), while different halogen-substituted substrates showed similar reactivity.

Table 2-14. Scope of substrate.



Entry	Substrate	Product	Yield
1	 **3**	 **3-M**	54 %
2	 **4**	 **4-M**	50 %
3	 **5**	 **5-M**	47 %
4	 **6**	 **6-M**	51 %
5	 **7**	 **7-M**	22 %
6	 **8**	 **8-M**	46 %

Conditions: Morpholine (2 equiv.), $PhI(OAc)_2$ (2 equiv.), $CuCl_2$ (20 mol %), $MgCl_2$ (20 mol %) room temperature, 15 min. Isolated yields

Chapter 3

Directions for Mechanistic Studies

This chapter will deal with two proposed mechanisms, namely a traditional organometallic pathway and a single-electron-transfer (SET) pathway, for the directed C-H amination based on published studies. Experiments that can help identify the mechanism are discussed in future work.

3.1 – Proposed Mechanisms

The mechanism of the copper catalyzed *N*-(2-pyridyl)sulfonyl-directed amination remains unclear though the optimal conditions were determined. The reaction could possibly occur via a traditional organometallic pathway or a single-electron-transfer (SET) pathway. Ribas *et al* has reported stoichiometric C-H activation for macrocyclic substrate as in Figure 3-1[18], a similar mechanism of disproportionation may be present in the amination reaction to induce a Cu(I)/Cu(III) catalytic cycle. Yu *et al* in their report of chelate-directed aerobic aryl C-H functionalization proposed a single-electron-transfer mechanism as in Figure 3-2, which could also be the key to this amination reaction.[19]

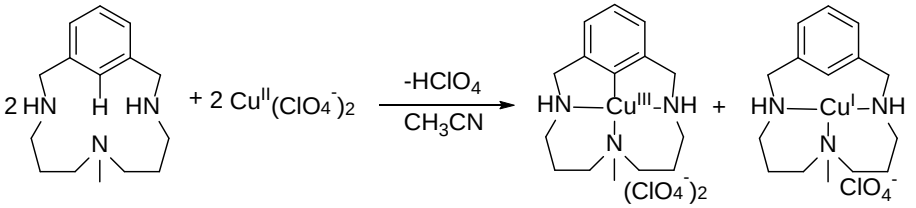


Figure 3-1. Disproportionation of Cu^{II} under macrocyclic condition.

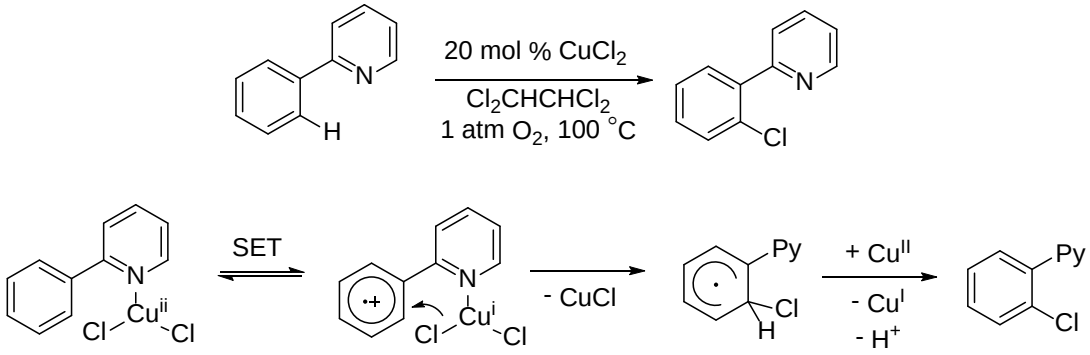


Figure 3-2. Proposed SET mechanism of Cu catalyzed C-H functionalization.

Based on these studies, a traditional organometallic pathway was proposed as in Figure 3-3. In this pathway, a Cu^{III} / Cu^{I} catalytic cycle is present to afford the amination product through oxidative addition and reductive elimination. The bimetallic catalytic center was proposed based on previous study on palladium-catalyzed *N*-(2-pyridyl)sulfonyl-directed gamma-arylation of amino acid derivatives.[15]

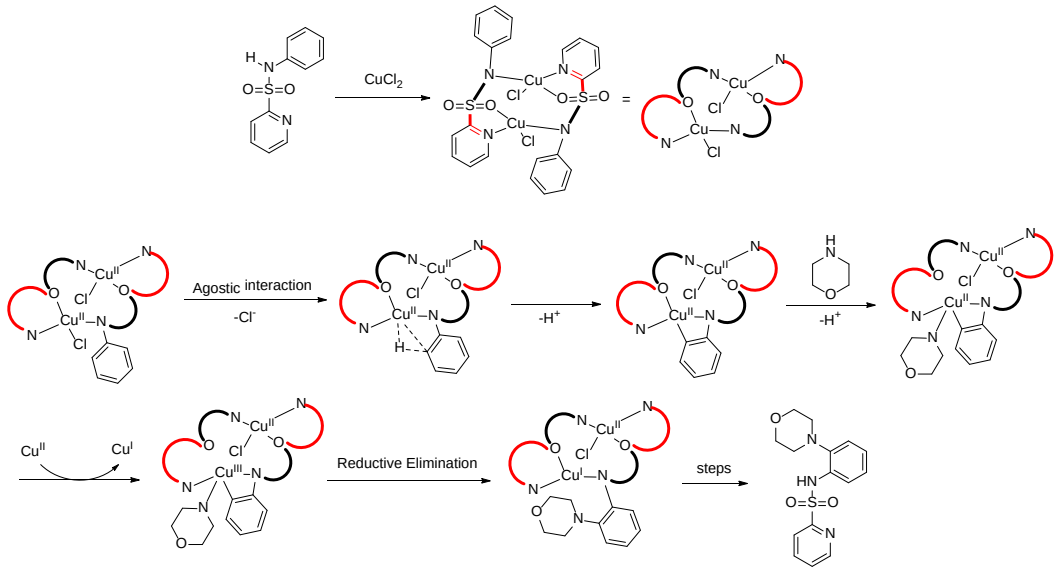


Figure 3-3. Proposed traditional organometallic pathway for copper-catalyzed *N*-(2-pyridyl)sulfonyl directed aryl C(sp^2)-H amination.

A single-electron-transfer pathway was also proposed featuring a SET process between the Cu^{II} center and benzene moiety. This pathway, on the other hand, does not involve a rate-limiting C-H activation step as illustrated in Figure 3-4.

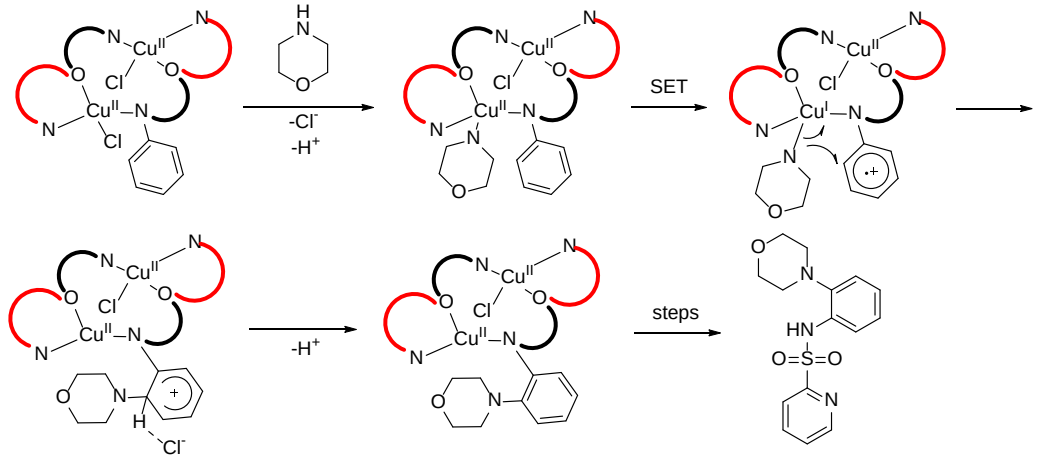


Figure 3-4. Proposed single-electron-transfer pathway for copper-catalyzed *N*-(2-pyridyl)sulfonyl directed aryl C(sp^2)-H amination.

3.2 – Future Work

Mechanism interpretation

Provided that SET mechanism strongly favors electron-rich substrates while such trend is less likely for the organometallic pathway, a Hammet plot for the synthesized substrates can be constructed to provide an insight into a possible mechanism. If the calculated rho value is higher than 1, it is likely that the reaction adopts a SET pathway; if the rho value is higher than 0 but lower than 1, it is likely that reaction adopts a traditional organometallic pathway.

A kinetic isotope effect (KIE) can also be calculated in intramolecular competition experiments with substrate **9**, intermolecular competition experiments with a 1:1 mixture of substrate **1** and substrate **10**, as well as experiments comparing independent rates of H- (**1**) and D-labeled (**11**) substrates. (Figure 3-5) The lack of KIE (KIE ≈ 1) would support the SET pathway while the existence would support the traditional organometallic pathway.

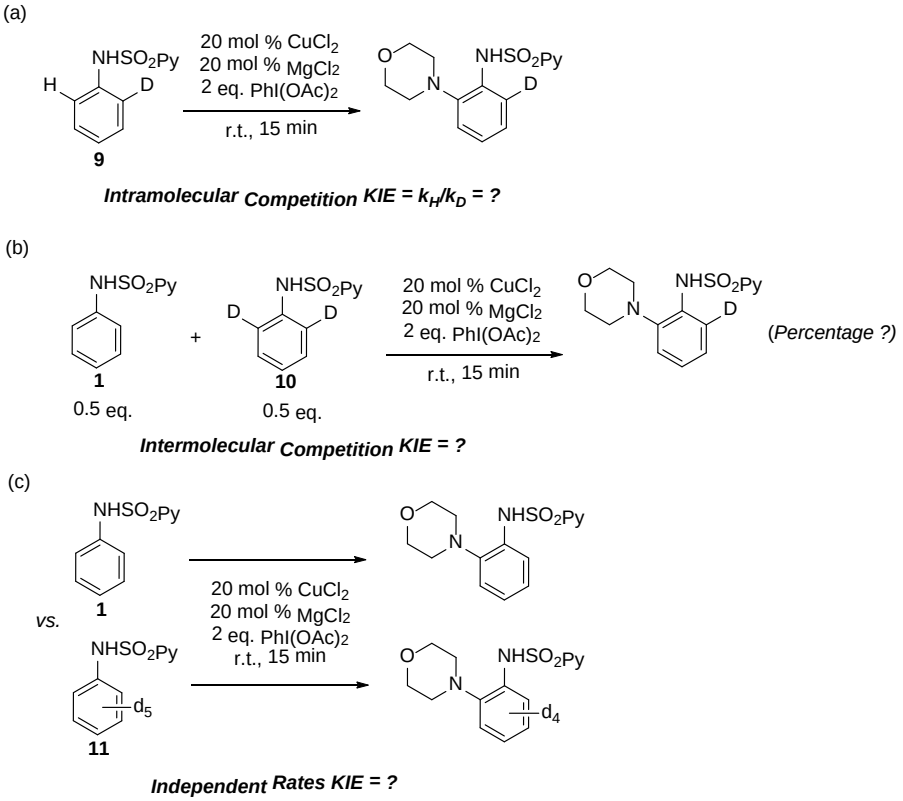


Figure 3-5. Possible kinetic isotope experiments for mechanism interpretation.

Active Structural Motif

The 8-aminoquinoline (AQ) and picolinamide (PA) directing groups, first introduced by the Daugulis group in 2005[20], have proved to possess superior directing capabilities in a number of Pd-catalyzed C-H functionalizations.[21] The 2-aminomethylpyridine (MP) moiety, mentioned in the same seminal work by Daugulis *et al*, also showed directing ability to some extent, though it is not synthetically satisfying. Together with the currently addressed *N*-(2-pyridyl)sulfonyl group, it is obvious that all directing groups bear the same active motif as depicted in Figure 3-6. We can postulate that many structures possessing the same active motif may have certain capability of C-H functionalization. Structure **12** and adenine in Figure 3-7 can be tested for their activities, though adenine might not give regioselective results due to too many coordinating

nitrogen atoms. In addition, density functional theory (DFT) studies can be conducted to compare reactivities and delve into the directing mechanism.

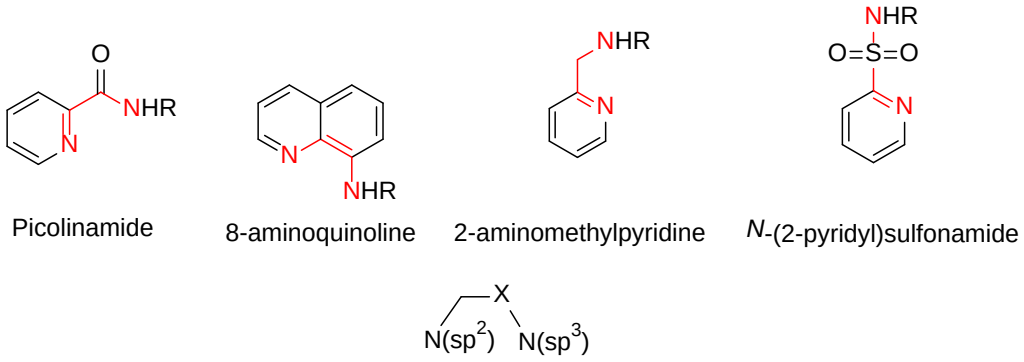


Figure 3-6. Effective directing groups for C-H functionalization and common structure moiety.

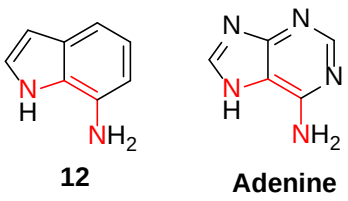


Figure 3-7. Potential directing group candidates.

3.3 – Conclusion

In conclusion, we have introduced a new method of aryl amination under the direction of the *N*-(2-pyridyl)sulfonyl group using inexpensive copper catalyst $CuCl_2$ and $MgCl_2$ as auxiliary agent. All reactions can be carried out at room temperature in 15 min and are oxygen-tolerant, giving moderate to good yields. The ease of operation (no heating required) and fast nature of this approach are economical and may find its use in the industry.

Chapter 4

Experimental Section

4.1 – General Information: Materials and Method

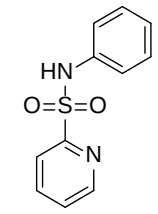
Reagent

Toluene, *p*-dioxane, THF, DMF, DMSO and acetonitrile were obtained from a JC Meyer solvent dispensing system without further purification. Chromatography was performed using 230-400 mesh SilicaFlash 60R silica gel (Silicycle Inc.). All other materials were obtained from commercial sources and used as received unless otherwise noted.

Instrument

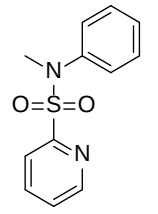
NMR spectra were obtained on Bruker AV-360, CDPX-300 or DPX-300 using $CDCl_3$ as solvent. Spectra were calibrated using residual solvent peaks as internal standard. Multiplicities were recorded as: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, dt = doublet of triplets, td = triplet of doublets, ddd = doublet of doublet of doublets, br = broad singlet, m = multiplet. GC-MS experiments were conducted on Agilent 7820A GC and 5975 series MSD system. *N*-phenylpyridine-2-sulfonamide was used as internal standard for GC yield determination.

4.2 – General procedures for synthesis of *N*-(2-pyridyl)sulfonyl aniline derivatives



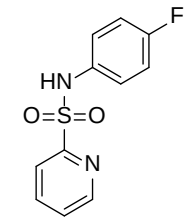
Compound **1**

***N*-phenylpyridine-2-sulfonamide (1)**: To a solution of aniline (1.31 g, 14.1 mmol, 1 equiv.) in THF (anhydrous, 140 ml) cooled in ice bath under N_2 atmosphere, pyridine (2.28 ml, 28.2 mmol, 2 equiv.) and pyridine-2-sulfonyl chloride (3 g, 16.9 mmol, 1.2 equiv.) were successfully added dropwise. The resulting reaction mixture was allowed to reach room temperature and stirred overnight when a precipitate formed. The mixture was then filtered and the precipitate was discarded. Distilled water (60 ml) was added to the filtrate and THF was later removed by rotovap, yielding a suspension in water. The white solid was filtered off, washed with toluene (2 × 5 ml) and dried *in vacuo* to give **1** as a white powder; yield: 2.48 g (75%). ^{1}H NMR ($CDCl_3$, 360 MHz) δ: 9.18 (s, 1H), 8.68 (dd, *J* = 4.6, 1.2 Hz, 1H), 8.05 – 7.97 (m, 1H), 7.58 – 7.49 (m, 1H), 7.32 – 7.13 (m, 4H), 7.02 (t, *J* = 7.2 Hz, 1H).



Compound **2**

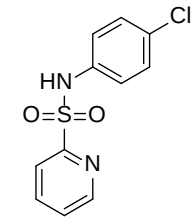
Compound **2** was prepared following the general procedure from *N*-methylaniline (1 g, 9.33 mmol) to give **2** as a white solid; yield: 1.65 g (71%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.76 (dd, *J* = 4.7, 0.8 Hz, 1H), 8.00 (td, *J* = 7.8, 1.7 Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.64 (ddd, *J* = 7.7, 4.7, 1.2 Hz, 1H), 7.34 – 7.14 (m, 5H), 3.46 (s, 3H).



Compound **3**

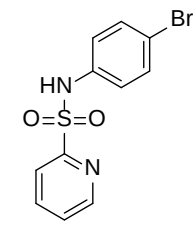
Compound **3** was prepared following the general procedure from 4-fluoroaniline (395 mg, 3.56 mmol) to give **3** as a grey solid; yield: 431 mg (48%). ^{1}H NMR ($CDCl_3$, 360 MHz) δ: 9.20 (s, 1H), 8.69 (ddd, *J* = 4.7, 1.7, 0.9

Hz, 1H), 8.00 (td, *J* = 7.7, 1.7 Hz, 1H), 7.91 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.59 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 7.35 – 7.21 (m, 2H), 7.00 (t, *J* = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75MHz) δ: 160.9, 157.9, 150.9, 139.1, 134.7, 127.9, 124.8, 123.5, 116.4.



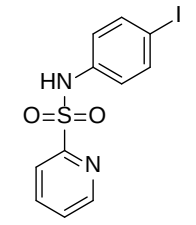
Compound **4**

Compound **4** was prepared following the general procedure from 4-chloroaniline (1 g, 7.85 mmol) to give **4** as a white solid; yield: 949 mg (45%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 9.34 (s, 1H), 8.70 (dd, *J* = 4.5, 1.0 Hz, 1H), 8.11 – 8.01 (m, 1H), 8.01 – 7.95 (m, 1H), 7.62 (ddd, *J* = 7.3, 4.7, 1.4 Hz, 1H), 7.38 – 7.21 (m, 4H). ^{13}C NMR ($CDCl_3$, 75MHz) δ: 157.8, 151.0, 139.2, 137.6, 130.1, 129.8, 128.1, 123.5, 123.4, 123.4.



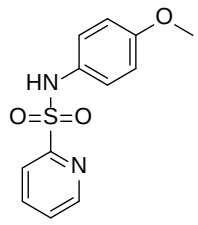
Compound **5**

Compound **5** was prepared following the general procedure from 4-bromoaniline (1 g, 5.76 mmol) to give **5** as a grey solid; yield: 920 mg (51%). ^{1}H NMR ($CDCl_3$, 360 MHz) δ: 9.32 (s, 1H), 8.67 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.02 (td, *J* = 7.6, 1.7 Hz, 1H), 7.96 (dt, *J* = 7.9, 1.2 Hz, 1H), 7.59 – 7.49 (m, 1H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 8.8Hz, 2H). ^{13}C NMR ($CDCl_3$, 75MHz) δ: 157.8, 151.0, 139.2, 138.2, 138.1, 132.8, 128.1, 123.6, 123.6, 123.5, 117.7.



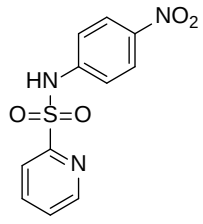
Compound **6**

Compound **6** was prepared following the general procedure from 4-iodoaniline (1 g, 4.56 mmol) to give **6** as a pale brown solid; yield: 920 mg (56%). ^{1}H NMR ($CDCl_3$, 360 MHz) δ: 9.31 (s, 1H), 8.66 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.02 (td, *J* = 7.6, 1.7 Hz, 1H), 7.95 (ddd, *J* = 7.9, 1.5, 0.9 Hz, 1H), 7.64 – 7.52 (m, 3H), 7.09 (d, *J* = 8.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75MHz) δ: 157.8, 151.0, 139.2, 138.8, 128.1, 123.7, 123.6, 123.5, 88.3.



Compound **7**

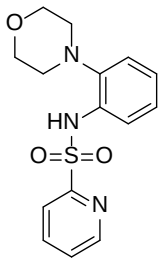
Compound **7** was prepared following the general procedure from 4-methoxyaniline (1 g, 8.11 mmol) to give **7** as a grey solid; yield: 643 mg (30%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.96 (s, 1H), 8.74 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 7.99 (td, *J* = 7.7, 1.7 Hz, 1H), 7.89 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.61 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 7.18 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 9.0 Hz, 2H), 3.72 (s, 3H). ^{13}C NMR ($CDCl_3$, 75MHz) δ: 158.3, 158.1, 150.8, 139.0, 130.8, 127.7, 125.5, 123.5, 114.9, 55.6.



Compound **8**

Compound **8** was prepared following the general procedure from 4-nitroaniline (1 g, 7.24 mmol) to give **8** as a yellow solid; yield: 890 mg (44%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.66 (dt, *J* = 4.7 Hz, 1.3, 1H), 8.13 (d, *J* = 9.3 Hz, 2H), 8.10 (d, *J* = 1.4 Hz, 1H), 8.09 (t, *J* = 1.4 Hz, 1H), 7.69 – 7.59 (m, 1H), 7.52 (d, *J* = 9.3 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75MHz) δ: 157.5, 151.2, 145.1, 144.4, 139.6, 128.6, 125.8, 123.5, 119.6.

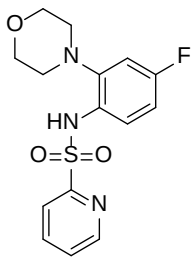
4.3 – General procedures for synthesis of *N*-(2-morpholinophenyl)pyridine-2-sulfonamide derivatives



Compound **1-M**

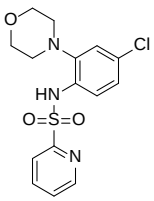
***N*-(2-morpholinophenyl)pyridine-2-sulfonamide (1-M):** To a stirred solution of *N*-phenylpyridine-2-sulfonamide (118.64 mg, 0.5 mmol, 1 equiv.), (diacetoxyiodo)benzene (322.10 mg, 1 mmol, 2 equiv.), copper(II) chloride (13.44 mg, 0.1 mmol, 0.2 equiv.) and magnesium chloride (9.52 mg, 0.1 mmol, 0.2 equiv.) in DCE (1 ml), a solution of morpholine (86.5 µL, 1 mmol, 2 equiv.) in DCE (1 ml) was added dropwise at room temperature and further stirred for 15 min. Distilled water (30 ml) was added and the mixture was extracted with DCM (3 × 15 ml). The combined

organic phase was washed with saturated brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The resulting mixture was purified with column chromatography using silica gel to give the desired product (ethyl acetate: hexane = 1:1). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.61 (d, *J* = 4.0 Hz, 1H), 8.50 (br, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.87 (td, *J* = 7.8, 1.5 Hz, 1H), 7.60 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.44 (dd, *J* = 7.1, 5.0 Hz, 1H), 7.15 – 6.99 (m, 3H), 3.88 (t, *J* = 4.4 Hz, 4H), 2.76 (t, *J* = 4.2 Hz, 4H).



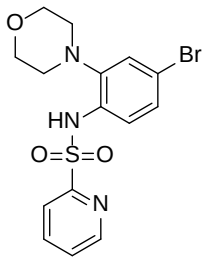
Compound **3-M**

Compound **3-M** was prepared following the general procedure from **3**. ^{1}H NMR ($CDCl_3$, 360 MHz) δ: 8.62 (d, *J* = 4.2 Hz, 1H), 8.18 (br, 1H), 8.02 (d, *J* = 7.7 Hz, 1H), 7.88 (t, *J* = 6.3 Hz, 1H), 7.58 (dd, *J* = 7.4, 4.7 Hz, 1H), 7.46 (t, *J* = 4.7 Hz, 1H), 6.86 – 6.76 (m, 2H). 3.87 (t, *J* = 3.6 Hz, 4H), 2.73 (t, *J* = 3.4 Hz, 4H). ^{13}C NMR ($CDCl_3$, 75MHz) δ: 161.5, 157.0, 150.6, 143.1, 138.5, 129.4, 127.6, 123.5, 120.1, 113.3, 110.0, 67.6, 53.1



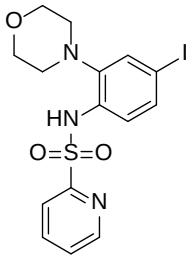
Compound **4-M**

Compound **4-M** was prepared following the general procedure from **4**. ^{1}H NMR ($CDCl_3$, 360 MHz) δ: 8.62 (d, *J* = 7.7 Hz, 1H), 8.33 (br, 1H), 8.04 (d, *J* = 7.7 Hz, 1H), 7.89 (td, *J* = 6.4, 1.4 Hz, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.48 (dd, *J* = 3.9, 0.8 Hz, 1H), 7.09 (d, *J* = 7.7 Hz, 1H), 7.05 (dd, *J* = 7.3, 2.0 Hz, 1H), 3.88 (t, *J* = 3.8 Hz, 4H), 2.76 (t, *J* = 3.7 Hz, 4H). ^{13}C NMR ($CDCl_3$, 75MHz) δ: 156.9, 150.6, 142.6, 138.5, 132.0, 129.8, 127.6, 126.8, 123.4, 122.9, 119.6, 67.5, 53.2.



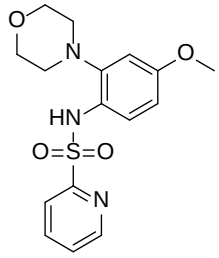
Compound **5-M**

Compound **5-M** was prepared following the general procedure from **5.** ^{1}H NMR ($CDCl_3$, 360 MHz) δ: 8.61 (d, *J* = 7.7 Hz, 1H), 8.31 (br, 1H), 8.04 (d, *J* = 7.7 Hz, 1H), 7.89 (td, *J* = 6.5, 1.4 Hz, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.47 (dd, *J* = 6.2, 4.2 Hz, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 7.18 (dd, *J* = 7.2, 1.8 Hz, 1H), 3.87 (t, *J* = 3.8 Hz, 4H), 2.75 (t, *J* = 3.7 Hz, 4H). ^{13}C NMR ($CDCl_3$, 75MHz) δ: 156.8, 150.6, 142.8, 138.6, 132.6, 129.7, 127.7, 125.9, 123.3, 119.8, 117.2, 67.6, 53.1.



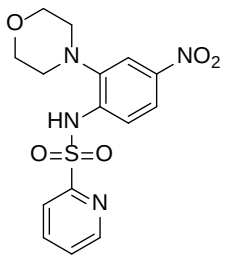
Compound **6-M**

Compound **6-M** was prepared following the general procedure from **6.** ^{1}H NMR ($CDCl_3$, 360 MHz) δ: 8.62 (d, *J* = 7.7 Hz, 1H), 8.30 (br, 1H), 8.05 (d, *J* = 7.7 Hz, 1H), 7.90 (td, *J* = 6.5, 1.4 Hz, 1H), 7.48 – 7.46 (m, 1H), 7.38-7.37 (m, 3H), 3.87 (t, *J* = 3.8 Hz, 4H), 2.75 (t, *J* = 3.7 Hz, 4H).



Compound **7-M**

Compound **7-M** was prepared following the general procedure from **7.** ^{1}H NMR ($CDCl_3$, 360 MHz) δ: 8.62 (d, *J* = 7.7 Hz, 1H), 8.10 (br, 1H), 7.98 (d, *J* = 7.7 Hz, 1H), 7.84 (td, *J* = 6.5, 1.2 Hz, 1H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.43 (dd, *J* = 6.2, 4.2 Hz, 1H), 6.67 (d, *J* = 7.7 Hz, 1H), 6.62 (dd, *J* = 7.4, 2.2 Hz, 1H), 3.84 (t, *J* = 3.4 Hz, 4H), 2.68 (t, *J* = 3.3 Hz, 4H).



Compound **8-M**

Compound **8-M** was prepared following the general procedure from **8.** ^{1}H NMR ($CDCl_3$, 360 MHz) δ: 8.62 (d, *J* = 7.7 Hz, 1H), 8.57 (br, 1H), 8.13 (d, *J* = 7.7 Hz, 1H), 8.03 – 7.93 (m, 3H), 7.75 (d, *J* = 7.7 Hz, 1H), 7.52 (dd, *J* = 8.0, 4.0 Hz 1H), 3.92 (t, *J* = 3.8 Hz, 4H), 2.88 (t, *J* = 3.8 Hz, 4H).

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