The Pennsylvania State University

The Graduate School

Eberly College of Science

PALLADIUM-CATALYZED HALOGENATION OF ORTHO-C-H BONDS OF BENZYLAMINE PICOLINAMIDES AND ARYLETHYLAMINE PICOLINAMIDES

A Thesis in

Chemistry

by

Chengxi Lu

Submitted in Partial Fulfillment
of the Requirements
for the Degree of

Master of Science

August 2014

The thesis of Chengxi Lu was reviewed and approved* by the following:

Gong Chen
Assistant Professor of Chemistry
Thesis Advisor

Kenneth S. Feldman
Professor of Chemistry
Graduate Program Chire

Yanming Wang
Associate Professor of Biochemistry and Molecular Biology

*Signatures are on file with The Graduate School

ABSTRACT

A new Pd-catalyzed picolinamide-directed halogenation reaction of *ortho*-C(sp^2)-H bonds is discussed. The usage of inexpensive inorganic salt ($KBrO_3$, $NaClO_3$/$NaClO_2$ and KIO_3) as halide source and $K_2S_2O_8$ as oxidant offer a more practical method to introduce halide atoms onto aromatic organic compound. This method is effective on benzylamine picolinamides and arylethylamine picolinamides.

TABLE OF CONTENTS

LIST OF SCHEMES

LIST OF FIGURES

LIST OF TABLES

ACKNOWLEDGEMENTS

First I'd like to thank my research advisor, Professor Gong Chen, for accepting me to study in his group. It's a priceless opportunity for me to learn and involve in the cutting-edge research. I would like to particularly thank him for training and guiding me with great patience. I would not be half as proficient as I am today without his help and guidance.

I must thank Professor Kenneth S. Feldman and Professor Alexander Radosevich for navigating me. The rewarding talks with them help me find the direction of my research, as well as my life.

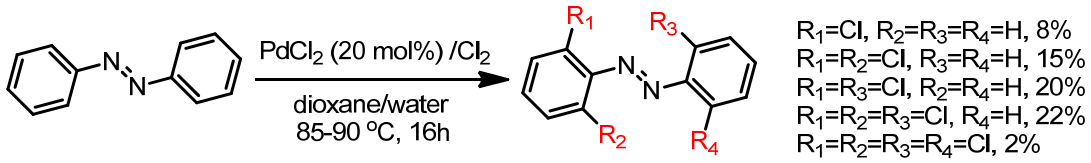
I would also like to thank the members of the Chen group, particularly Dr. Gang He and Dr. Shuyu Zhang. His advice and guidance helped me overcome so many difficulties in my research. I really appreciate the selfless sharing of experience between all the members of Chen group. Everyone's wisdom and experience promote and inspire each other.

Finally, I must thank my parents. Since I made my decision to study abroad, they gave me unconditional support. Although they are thousands miles away, I can feel surrounded by their love every second.

Introduction

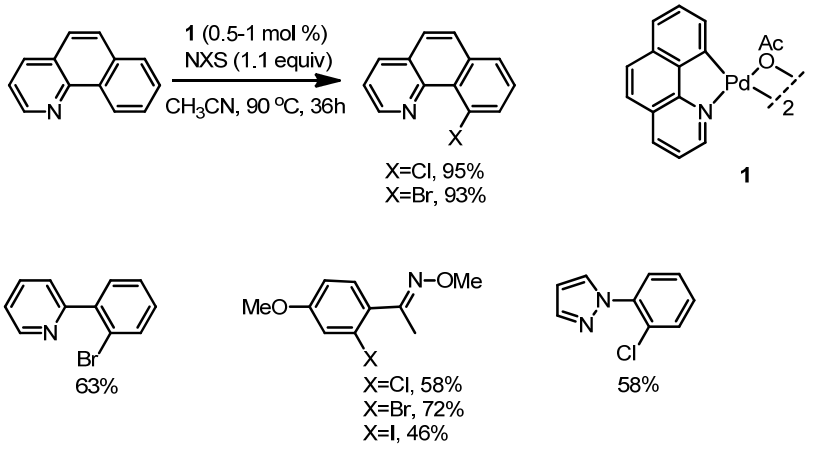
Carbon-halogen bonds are prevalent in a variety of biologically active molecules and pharmaceutical agents.[1] Aryl, vinyl, and benzylic halides also can serve as important precursors to Grignard[2] and organolithium reagents.[3] Additionally, aryl halides have found widespread application in a variety of cross-coupling reactions.[4] As a result of the diverse synthetic utility of organic halides, the regioselective introduction of halogen atoms into organic molecules is of fundamental importance in organic synthesis.

Historically, such transformations generally were performed by electrophilic aromatic substitution (EAS)[5] or directed *ortho*-lithiation (DoL) reactions followed by halogen quenching. EAS uses reagents such as *N*-halosuccinimides,[6a] X_2,[6b] peroxides/HX,[6c] peroxides/MX[6d] or hypervalent iodine reagents.[6e] Although the EAS methods have been widely used, they also suffer from several disadvantages: (i) the substrate scope is often limited to arenes activated by electron-donating substituents, (ii) side reactions, including benzylic halogenation and overhalogenation of the arene, are common, (iii) only a limited set of arene substitution patterns can be accessed, and (iv) multiple regioisomeric products are frequently obtained, resulting in decreased yields and the requirement for tedious separation.[7] DoL reactions are limited by the requirement for strong bases and by the relatively narrow scope of suitable directing groups. [8]



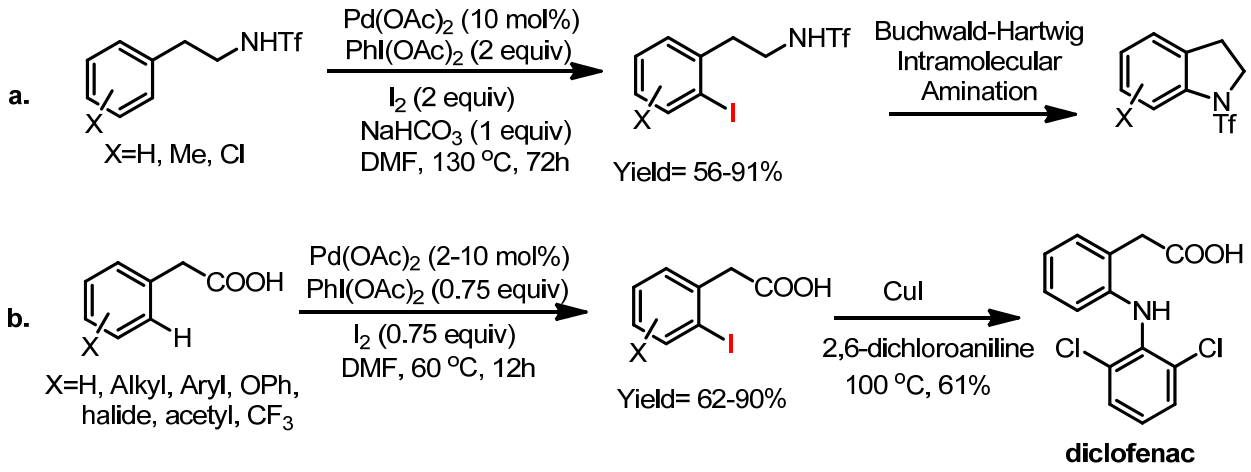
Scheme 1. Chlorination of azobenzene reported by Fahey

The development of new transition metal-catalyzed reactions for the selective halogenation of arenes is needed due to these limitations. The Pd-catalyzed *ortho*-C− H halogenation of arenes has been greatly advanced since the pioneering discovery by Fahey in the 1970s.[9] In Fahey's study, azobenzene was used in this reaction and *ortho*-chlorinated azobenzenes were produced when Cl_2 were mixed with the dioxane/water solution of azobenzene and $PdCl_2$ at 85-90 °C (Scheme 1). A mixture of mono- and multiply-chlorinated products was obtained and the combined yields of different chlorinated products were in the range of 2-22%. With more $PdCl_2$ catalyst, mono-, di-, and trichloroazobenzene could be transformed further into tetrachlorozaobenzene. Bromination reaction was achieved only in stoichiometric fashion, and produced 2-bromoazobenzene in 29% yield.



Scheme 2. Halogenation of benzo[*h*]quinoline and other related substrates

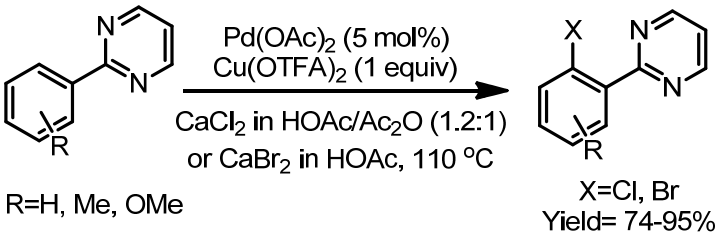
In 2003, Sanford and coworkers reported the Pd-catalyzed chlorination and bromination of benzo[*h*]quinoline with NBS/NCS (Scheme 2).[10a] Palladium complex **1** was used as catalyst. When a mixture of benzo[*h*]quinoline, NXS (X=Br, Cl), and complex **1** were heated in CH_3CN at 90 ^oC for 36h, the desired halogenated product was obtained in excellent yield (Scheme 2a). A series of arene substrates were halogenated in good yield (Scheme 2b).[10b] Mechanistic studies clearly supported a $Pd^{II/IV}$ catalytic manifold for these reactions.[10c]



Scheme 3. Iodination of phenylethylamine (a) and phenylacetic acid (b) and transformations

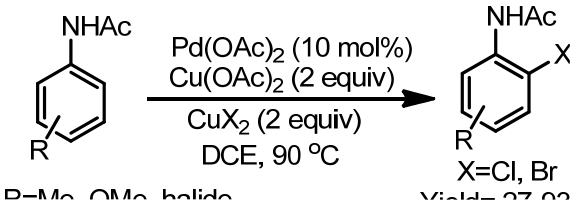
In 2008, Yu and coworkers disclosed the Pd-catalyzed *ortho*-iodination reactions of β-phenylethylamine and β-phenylpropylamine substrates (Scheme 3a).[11a] They found that the trifluoromethylsulfonamide (triflamide, NHTf) moiety worked as a good directing group. A subsequent Buchwald-Hartwig intramolecular amination reaction allowed for the facile synthesis of indolines and tetrahydroquinolines. They also reported the Pd-catalyzed *ortho*-iodination reactions of benzoic acid and phenylacetic acid substrates under similar conditions (Scheme 3b).[11b] They proposed that IOAc, generated *in situ* from I_2 and $Ph(IOAc)_2$, oxidized an aryl Pd(II)

intermediate to an aryl Pd(IV) species, which underwent reductive elimination to give the iodinated product. To demonstrate the utility of this methodology, a concise synthesis of diclofenac was achieved *via* Pd-catalyzed *ortho*-iodination followed by an Ullmann coupling reaction.



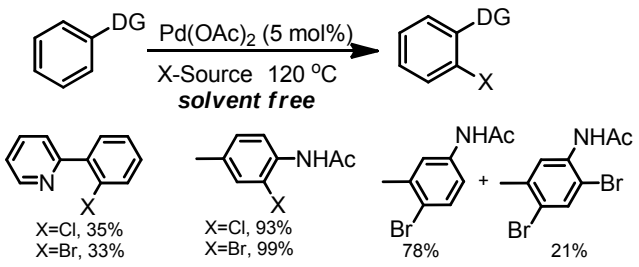
Scheme 4. Mono-selective halogenation of arylpyrimidines

Xu and coworkers reported a Pd-catalyzed monoselective halogenation reaction of arylpyrimidines (Scheme 4).[12] Mono-chlorinated or brominated arylpyrimidines could be produced using $CaCl_2$ or $CaBr_2$ as the halogen source and $Cu(OTFA)_2$ as the oxidant at 110 ^oC. The monohalogenated products could be isolated in > 74% yield along with small amounts of dihalogenated products (<10%).



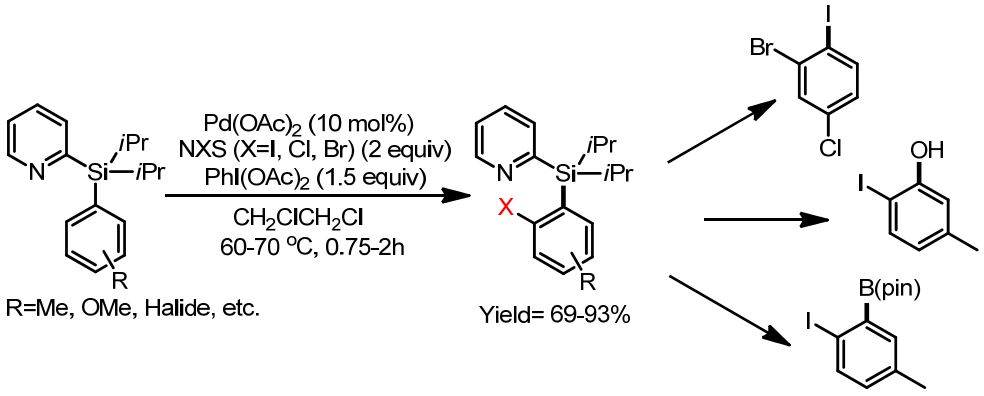
Scheme 5. *Ortho*-halogenation of acetanilides

In 2006, Shi and coworkers reported a highly selective *ortho*-chlorination reaction of acetanilide substrates (Scheme 5).[13] $CuCl_2$ was used as the chlorine source. The bromination reaction of relatively electron-rich acetanilides also was achieved under similar condition.



Scheme 6. Webster's solvent-free halogenation reactions

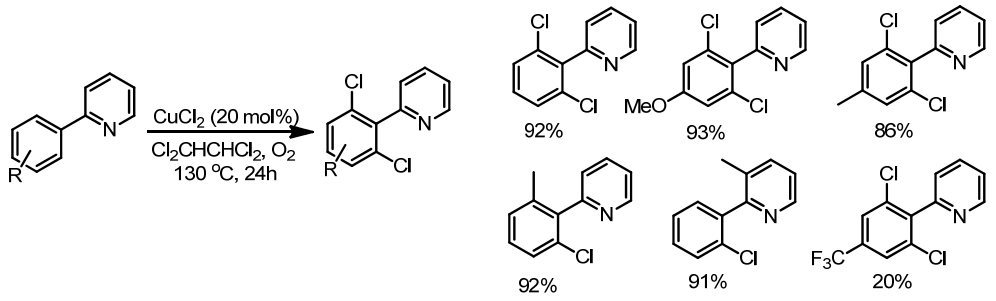
In 2010, Webster and coworkers reported a solvent-free protocol for *ortho*-bromination and chlorination reactions for substrates previously used by the Sanford and Shi laboratory (Scheme 6).[14] In some substrates, the non-directed *para*-halogenated product was also obtained.



Scheme 7. Halogenation of PyDipSi-arenes and subsequent transformations

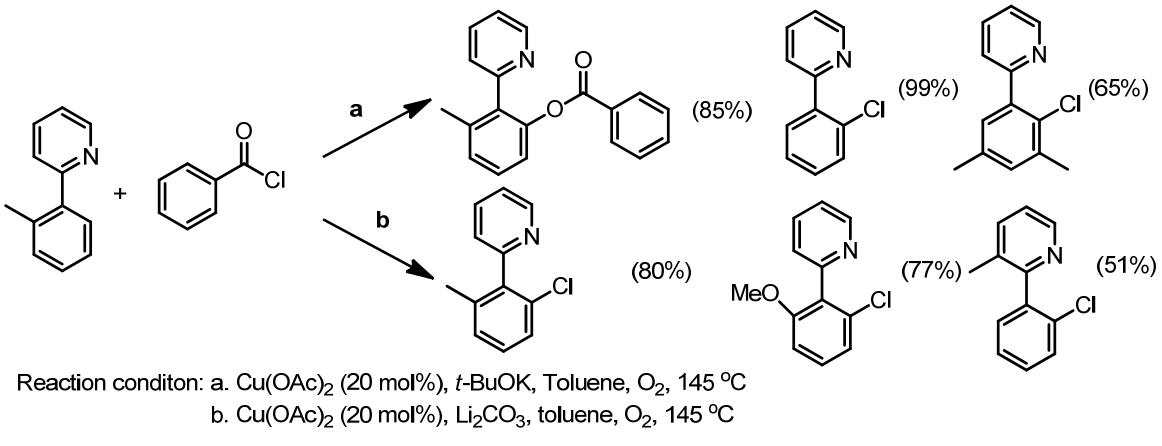
In 2010, Gevorgyan and coworkers reported the Pd-catalyzed *ortho*-halogenation reactions of pyridyldiisopropylsilyl (PyDipSi) arenes.[15] NXS (X=Cl, Br or I) was used as the

halogen source and $PhI(OAc)_2$ served as oxidant (Scheme 7). The PyDipSi directing group could be readily converted into a variety of functional groups through further transformations.



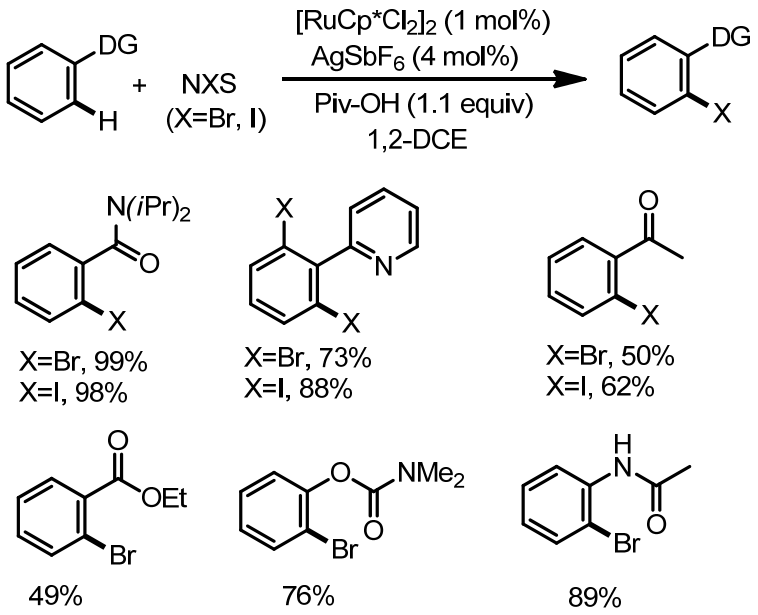
Scheme 8. Cu-catalyzed chlorination reaction of phenylpyridine

In addition to palladium, other metal catalysts also were found capable of facilitating *ortho*-halogenations of arene substrates. In 2006, Yu disclosed the first Cu-catalyzed *ortho*-chlorination reaction of 2-phenylpyridine.[16] The reaction was carried out with 20 mol % $CuCl_2$ in $Cl_2CHCHCl_2$ solvent under O_2 at 130 °C (Scheme 8). The $Cl_2CHCHCl_2$ was believed to be partially converted to $Cl_2C{=}CHCl$ and HCl, providing the chlorine source.



Scheme 9. Cheng's Cu-catalyzed benzoxylation and chlorination of phenylpyridine

In 2011, Cheng reported an interesting $Cu(OAc)_2$ catalyzed *ortho*-chlorination of 2-arylpyridine (Scheme 9).[17] When 2-arylpyridine was heated with benzoyl chloride in toluene in the presence t-BuOK, *ortho*-benzoxylation products were obtained. However, when Li_2CO_3 instead of *t*-BuOK was used, *ortho*-chlorination predominated.



Scheme 10. Glorius' Ru-catalyzed bromination and iodination of diverse arenes

In 2012, Glorius and coworkers reported the first Ru-catalyzed *ortho*-bromination and iodination reactions of a large range of arenes (Scheme 10).[18] Low loading of $[RuCp^*Cl_2]_2$ catalyst (1 mol%) was required; NBS and NIS was used as the halogen source. A number of carbonyl-based functional groups were employed successfully as directing groups, and moderate-to-excellent yields were obtained.

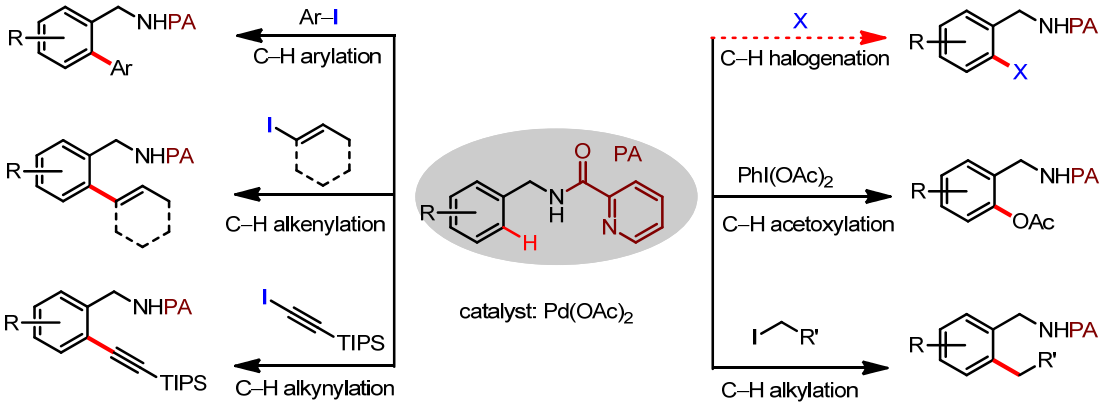


Figure 1. Pd-catalyzed PA-directed *ortho*-C(sp^2)–H bond functionalization

The picolinamide group, first introduced by the Daugulis laboratory in 2005,[19] has demonstrated unique directing abilities for a number of Pd-catalyzed C−H functionalization reactions in recent investigations.[20] Prompted by our interest in heterocycle synthesis, we investigated the utility of simple benzylamines as an entry point to multiply substituted *N*-containing scaffolds. Benzylamines can be easily accessed through various preparative methods. In recent studies, our laboratory has demonstrated that the *ortho*-C−H bonds of picolinamide (PA) protected benzylamines can be efficiently alkenylated, alkynylated[21a] and even alkylated[21b] with suitable halide reagents under Pd catalysis (Figure 1). Encouraged by these successes, we have proceeded to investigate whether *ortho*-C−H bonds of benzylamine picolinamides could be halogenated to provide useful intermediates for further transformations.

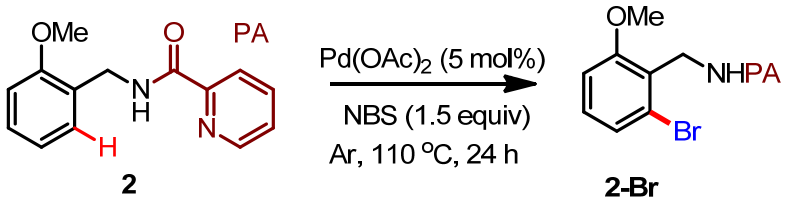
In this thesis research, we studied the *ortho*-C(sp^2)−H bond halogenation reactions of both benzylamine and β-arylethylamine picolinamides under $Pd(OAc)_2$ catalysis. Inexpensive inorganic salts ($KBrO_3$, $NaClO_3$/$NaClO_2$ and KIO_3 along with $K_2S_2O_8$ oxidant can be effectively used as the halogen sources in this procedure. All reactions provided arylhalide products in moderate-to-good yield, suggesting a potentially more economical method for the introduction of regioselective halogen into aromatic molecules.

Halogenation Reactions of Benzylamine Picolinamides

Bromination Reaction

We began our study of the bromination reaction of PA-protected benzylamine substrate **2** with NBS, a widely used brominating reagent. The initial reaction conditions examined under the similar condition reported in literature with NBS as brominating reagent. After screening various combination of solvents and halogen sources, only trace amount of product (<3%) was detected by GC-MS (Table 1).

Table 1. Pd-catalyzed bromination of compound **2** with NBS



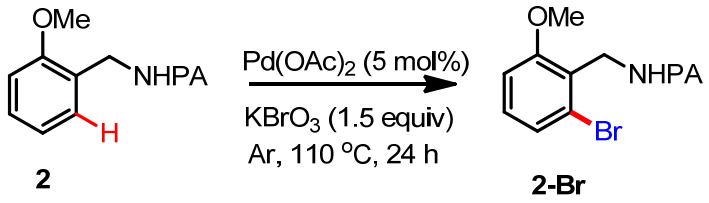
2 **2-Br**

entry	solvent	additive (equiv)	yield[a] (%)
1	toluene	–	--
2	Ph-Cl	--	--
3	Ph-Cl/NMP(9:1)	--	–
4	toluene	Ad-COOH (1)	--
5	toluene	Piv-COOH (1)	–
6	toluene	K_2CO_3 (2)	--
7	toluene	$PhI(OAc)_2$ (2)	trace

a. Yield was determined by GC-MS.

Inspired by its usage as oxidant in the preparation of $PhI(OAc)_2$, we evaluated $KBrO_3$ as the brominating reagent in this reaction system. $KBrO_3$ has not been employed in any metal-catalyzed bromination reactions in literature. Some common non-polar solvents did not give any desired product, presumably due to the poor solubility of the inorganic salt in those solvents (Table 2, entries 1-2). Among the polar solvents examined, we were delighted to find that *n*-butanol significantly promoted the reaction and only the *ortho*-brominated product was formed (Table 2, entries 3-6). Addition of acid or base additives were examined, but these trials showed little improvement (Table 2, entries 7-10).

Table 2. Pd-catalyzed bromination of compound **2** with $KBrO_3$ in different solvents



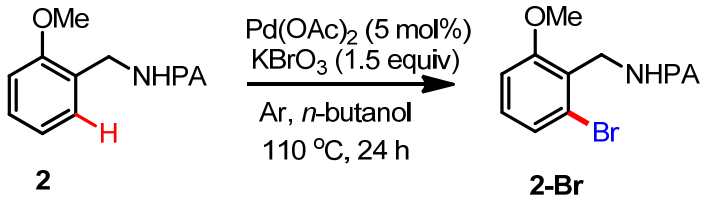
2 **2-Br**

entry	solvent	additive (equiv)	yield[a] (%)
1	toluene	--	--
2	Ph-Cl	--	--
3	DMF	--	trace
4	*n*-propanol	--	6
5	***n*-butanol**	**--**	**35**
6	*t*-butanol	--	--
7	*n*-butanol	Ad-COOH (1)	--
8	*n*-butanol	Piv-COOH (1)	11
9	*n*-butanol	2-Biphenylacetic acid (1)	15
10	*n*-butanol	Cs_2CO_3 (1)	--

a. Yield was determined by GC-MS.

Assuming that the reaction proceeds through a Pd(II)/(IV) catalytic cycle, we realized that $KBrO_3$ must to act as both a bromine source and an oxidant in this reaction. Additional oxidant might be able to improve the bromination process. Different oxidants then were examined (Table 3). The commonly-used hypervalent iodine-based oxidant $PhI(OAc)_2$ resulted in only a trace amount of product, while others like oxone and DDQ completely suppressed the reaction (Table 3, entries 1, 3 & 4). We were delighted to find that the addition of $K_2S_2O_8$ improved the yield of **2a.** Furthermore, addition of 0.5 equiv of NaBr with $K_2S_2O_8$ present improved the yield to 79% (Table 3, entry 5).

Table 3. Pd-catalyzed bromination of compound **2** with additional oxidant



2 **2-Br**

entry	oxidant (equiv)	additive (equiv)	yield[a] (%)
1	$PhI(OAc)_2$ (2)	--	trace
2	$K_2S_2O_8$ (2)	--	66
3	Oxone (2)	–	--
4	DDQ (2)	–	–
5	**$K_2S_2O_8$ (2)**	**NaBr (0.5)**	**79**

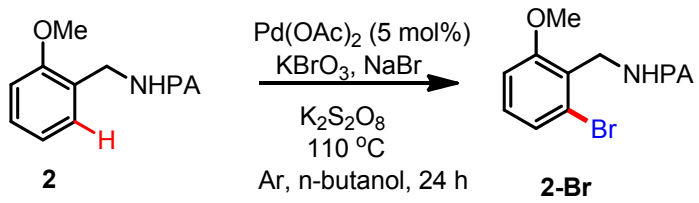
a. Yield was determined by GC-MS.

Since three inorganic reagents were involved in the reaction system, we then tested the effect of each reagent (Table 4). In the absence of $K_2S_2O_8$ oxidant, the yield was below 35%

(Table 4, entry 1). NaBr alone could not act as the bromine source in the absence of $KBrO_3$ (Table 4, entry 2). More than 1 equiv of $K_2S_2O_8$ was required for the optimal yield (Table 4, entries 3 & 4). 1.5 equiv of NaBr was also required for the optimal yield (Table 4, entries 4-6). The best reaction temperature was determined to be 100 ^oC, as $K_2S_2O_8$ started to decompose above 100 ^oC under the reaction conditions. When the reaction time was extended to 36 hours, complete conversion of **2** was observed and an excellent yield of **2-Br** was obtained (Table 4, entry 7). If the temperature dropped to 90 ^oC, the reaction slowed down dramatically (Table 4, entry 8). When the loading of $Pd(OAc)_2$ was reduced to 2 mol%, the yield also dropped (Table 4, entry 9). When the reaction was carried out without $Pd(OAc)_2$ as catalyst, no desired product could be observed, which proved that $Pd(OAc)_2$ did catalyze this bromination reaction.

Based on the above investigation, the optimal conditions for the bromination reaction were determined to be: $Pd(OAc)_2$ (5 mol%), $KBrO_3$ (1.5 equiv), $K_2S_2O_8$ (1.5 equiv), NaBr (1.5 equiv), in *n*-butanol (0.1 mM) at 100^oC for 36 hours.

Table 4. Pd-catalyzed bromination of compound **2** in the presence of NaBr



2 **2-Br**

entry	$KBrO_3$ (equiv)	$K_2S_2O_8$ (equiv)	NaBr (equiv)	yield[a] (%)
0	1.5	2.0	--	66
1	1.5	--	1.5	33
2	--	2.0	1.5	--
3	1.5	0.5	0.5	45
4	1.5	1.5	0.5	60
5	1.5	1.5	1.0	68
6	1.5	1.5	1.5	83
7	**1.5**	**1.5**	**1.5**	**94[b] (85)[f]**
8	1.5	1.5	1.5	73[c]
9	1.5	1.5	1.5	77[d]
10	1.5	1.5	1.5	--[e]

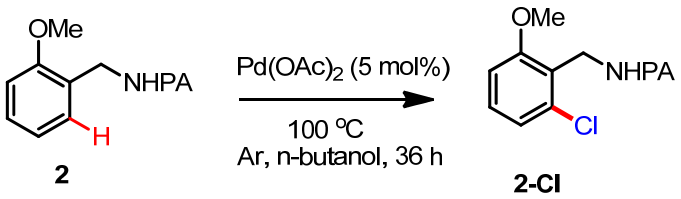
a. Yield was determined by GC-MS. b. 100 °C, 36h. c. 90 °C, 48h. d. $Pd(OAc)_2$ 2 mol%, 48h.
e. 100 oC, 18h, without $Pd(OAc)_2$. f. isolated yield

Chlorination Reaction

Encouraged by the success with the bromination reactions, we went on to investigate the corresponding chlorination reaction. Initial chlorination reactions were carried out using the similar conditions as established for the bromination reaction. To our delight, these reactions provided promising yields with little optimization (Table 5). Both $NaClO_3$ and $NaClO_2$ were evaluated as chlorine sources, $NaClO_3$ was found to be considerably more effective than $NaClO_2$ (Table 5, entries 2 & 3). At 110 °C, an 86% yield was obtained (Table 5, entry 4). Knowing that

$K_2S_2O_8$ decomposes at 110 °C, we used 2 equiv of $K_2S_2O_8$ for the reaction. A 90% yield of **2-Cl** was obtained (Table 5, entry 5).

Table 5. Pd-catalyzed chlorination of compound **2**



2 **2-Cl**

entry	Cl-source (equiv)	$K_2S_2O_8$ (equiv)	NaCl (equiv)	yield[a] (%)
1	$NaClO_2$ (1.5)	1.5	–	32
2	$NaClO_2$ (1.5)	1.5	1.5	52
3	$NaClO_3$ (1.5)	1.5	1.5	84
4	$NaClO_3$ (1.5)	1.5	1.5	86[b]
5	**$NaClO_3$ (1.5)**	**2.0**	**1.5**	**90[b] (81)[c]**

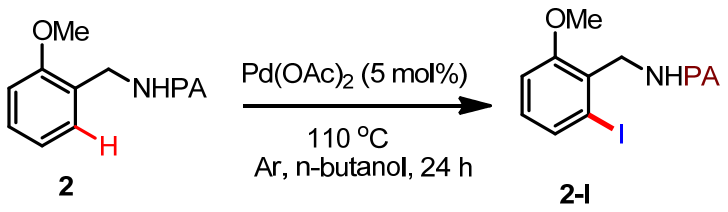
a. Yield was determined by GC-MS. b. 110 °C c. isolated yield

The optimal conditions for the PA-directed chlorination were determined to be: $Pd(OAc)_2$ (5 mol%), $NaClO_3$ (1.5 equiv), $K_2S_2O_8$ (2.0 equiv), NaCl (1.5 equiv), *n*-butanol as solvent (0.1 mM) at 110 °C for 36 hour.

Iodination Reaction

We then went on to investigate the PA-directed iodination reaction under similar condition. Initial trial offered promising results (Table 6). KIO_3 was found to be an effective iodinating reagent. Surprisingly, addition of NaI (1.5 equiv) shut down the reaction (Table 6, entry 1). When the reaction was carried out with 2 equiv of KIO_3 and 2 equiv of $K_2S_2O_8$ at 120 °C, the yield was significantly improved (Table 6, entry 4).

Table 6. Pd-catalyzed iodination of compound **2**



entry	KIO_3 (equiv)	$K_2S_2O_8$ (equiv)	NaI (equiv)	yield[a] (%)
1	1.5	1.5	1.5	--
2	1.5	1.5	--	18
3	2.0	2.0	--	63
4	2.0	2.0	--	89[b](81)[c]

a. Yield was determined by GC-MS. b. 120 °C, 36h c. isolated yield

The optimal conditions for iodination reaction were determined to be: of $Pd(OAc)_2$ (5 mol%), KIO_3 (2.0 equiv), $K_2S_2O_8$ (2.0 equiv), *n*-butanol (0.1 mM) as solvent, at 120 °C for 36 hour.

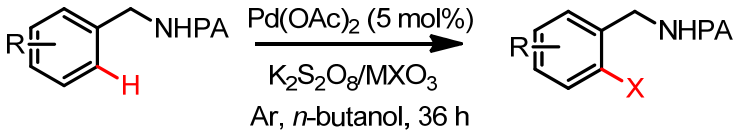
The Scope of Substrates

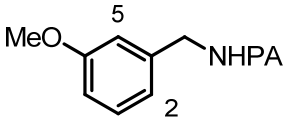
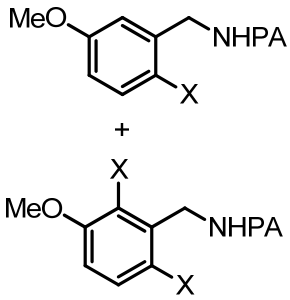
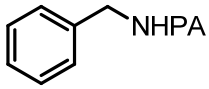
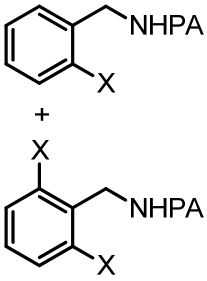
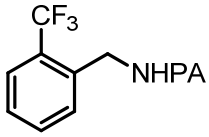
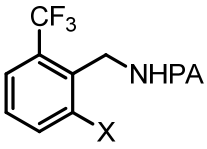
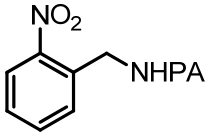
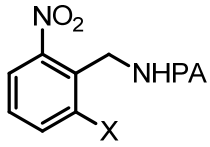
With the optimized conditions in hand, we then examined the substrate scope of the halogenation reactions. Both electron-rich and electron-poor arene substrates were evaluated and moderate to good yield were obtained (Table 7).

In general, the electron-rich arenes were more reactive and offered higher yields than the electron-poor substrates (Table 7, entries 1 and 3&4). When two *ortho* positions were available, the ratio of mono- to di- halogenation products could be influenced by the amount of halogenating reagent. The halogenation of **3** showed this selectivity. When 1.3 equiv of $KBrO_3$

was used, the ratio of mono- to dibrominated products of **3** was larger than 10:1 (Table 7, entry 2). However, when a large excess of iodinating reagent was used, the formation of dihalogenated product of **3** predominated. Steric hindrance also played a role in controlling the regioselectivity. Comparing the bromination of **3** and **4** (Table 4, entries 1 & 2), substrate **4** offered more dibrominated product than the more electron-rich **3** under the same conditions. The less hindered 2 position of **3** was more readily halogenated than the more hindered 5 position of **3**.

Table 7. Pd-catalyzed halogenation of PA-protected benzylamine substrates



entry	Substrate	Product	Yield(%)
1	 **3**		X=Br, **3-Br1**, 62 **3-Br2**, <5[a] X=I, **3-I1**, 12 **3-I2**, 72[b]
2	 **4**		X=Br, **4-Br1,** 51 **4-Br2**, 17[a]
3	 **5**		X=Cl, **5-Cl**, 50[c] X=I, **5-I,** 55[d]
4	 **6**		X=I, **6-I**, 45[d]

Reagents and conditions: a. $K_2S_2O_8$ (1.5 equiv), $KBrO_3$ (1.3 equiv), NaBr (0.5 equiv), 100 °C. b. $K_2S_2O_8$ (3.0 equiv), KIO_3 (3.0 equiv), 120 °C. c. $K_2S_2O_8$ (2.0 equiv), $NaClO_3$ (1.5 equiv), NaCl (1.5 equiv), 110 °C, 48h. d. $K_2S_2O_8$ (2 equiv), KIO_3 (2.0 equiv), 120 °C, 48h.

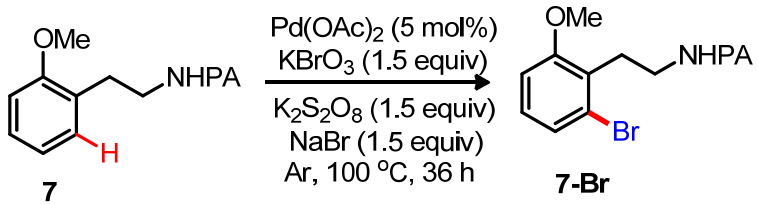
Halogenation Reactions of Substituted *β*-Arylethylamine Picolinamides

Bromination Reaction

The successful halogenation of the benzylamine picolinamides substrates prompted us to examine the halogenation reactions of β-arylethylamine picolinamide substrates under the similar conditions.

We began the study with the bromination reaction of β-phenethylamine picolinamide **7**. To our disappointment, the simple implantation of the previous conditions did not provide the desired product in satisfying yield (Table 8, entry 1). A screening of solvents revealed that DMF was more suitable for this reaction than *n*-butanol (Table 8, entry 4). None of the other solvents or mixed solvents were as effective as DMF.

Table 8. Pd-catalyzed bromination of compound **7** in different solvents



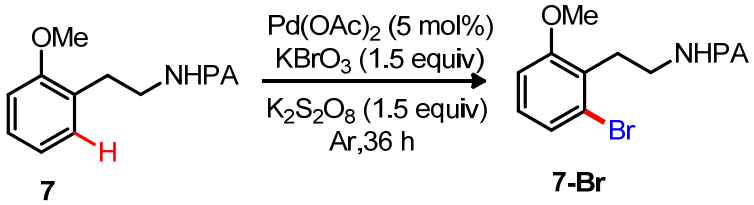
7 **7-Br**

entry	solvent	yield[a] (%)
1	*n*-butanol	32
2	*n*-propanol	--
3	*i*-propanol	--
4	**DMF**	**64**
5	*n*-butanol/xylene(1:1)	–
6	*n*-butanol/DMF(1:1)	trace

a. Yield was determined by GC-MS.

Using DMF as the solvent, we then examined the effect of different additives and different temperatures on the yield and regioselectivity of halogenation (Table 9). Without any additive, only trace amount of brominated product was observed with substrate **7** (Table 9, entry 1). The addition of stoichiometric amount of NaBr was necessary for obtaining a high yield (Table 9, entries 2 & 3). Other bromine sources were also evaluated, but gave a lower yield than NaBr (Table 9, entries 4-6). A lower reaction temperature (80 ^{o}C) resulted in lower yield, and a higher temperature (120 ^{o}C) did not provide any improvement (Table 9, entries 7 & 8).

Table 9. Pd-catalyzed bromination of compound **7** with different additives



7 **7-Br**

entry	Additive (equiv)	Temperature (^{o}C)	yield[a] (%)
1	--	100	trace
2	NaBr (1.0)	100	45
3	**NaBr (1.5)**	**100**	**64 (45)[b]**
4	CuBr (1.5)	100	38
5	$CuBr_2$ (1.5)	100	33
6	NBS (1.5)	100	21
7	NaBr (1.5)	80	trace
8	NaBr (1.5)	120	62

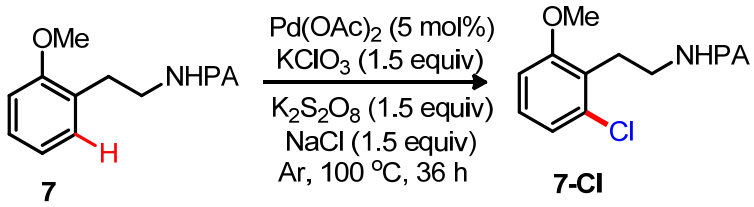
a. Yield was determined by GC-MS. b. isolated yield

Based on the above experiments, the optimal conditions for the bromination reaction of β-phenylethylpicolinamide were determined to be: $Pd(OAc)_2$ (5 mol%), $KBrO_3$ (1.5 equiv), $K_2S_2O_8$ (1.5 equiv), NaBr (1.5 equiv), in DMF (0.1 mM), at 100 ^{o}C for 36 hours.

Chlorination Reaction

Similar to the bromination of β-phenethylamine picolinamide, the chlorination reaction of **7** did not proceed well in *n*-butanol (Table 10, entry 1). No improvement was obtained in DMF (Table 10, entry 1). Other aprotic solvents were examined, but none of them offered a satisfying result.

Table 10. Pd-catalyzed chlorination of compound **7** in different solvents



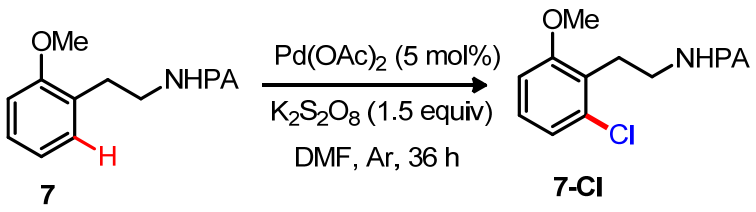
7 **7-Cl**

entry	solvent	yield[a] (%)
1	*n*-butanol	18
2	DMF	trace
3	NMP	--
4	DMPU	–
5	HMPA	--

a. Yield was determined by GC-MS.

Surprisingly, the use of $NaClO_2$ provided excellent results for the chlorination of phenethylamine substrate **7**. In our earlier studies, $NaClO_2$ was found to be inferior to $NaClO_3$ in the chlorination of benzylamine substrates (Table 11, entry 2). An acceptable yield (63%) was obtained when the reaction temperature was dropped to 40 °C (Table 11, entries 3-7).

Table 11. Pd-catalyzed chlorination of compound **7** with $NaClO_2$



7 **7-Cl**

entry	Cl-source (equiv)	NaCl (equiv)	Temperature (^oC)	yield[a] (%)
1	NCS (1.5)	1.5	100	--
2	$NaClO_2$ (1.5)	1.5	100	86
3	$NaClO_2$ (1.5)	0.5	100	88
4	**$NaClO_2$ (1.5)**	**0.5**	**80**	**87(80)[b]**
5	$NaClO_2$ (1.5)	0.5	60	82
6	$NaClO_2$ (1.5)	0.5	40	63
7	$NaClO_2$ (1.5)	0.5	25	32

a. Yield was determined by GC-MS. b. isolated yield

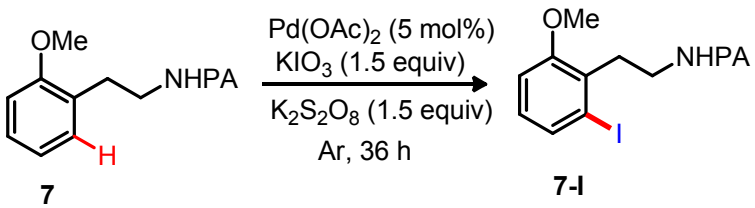
The optimal conditions for the chlorination of phenethylamine picolinamide were determined to be use of $Pd(OAc)_2$ (5 mol%), $NaClO_2$ (1.5 equiv), $K_2S_2O_8$ (1.5 equiv), NaCl (0.5 equiv), in DMF (0.1 mM) at 80 ^oC for 36 hours.

Iodination Reaction

Similar to the bromination and chlorination of phenethylamine picolinamide **7**, DMF was also found to be more effective than *n*-butanol for the iodination reaction (Table 12, entries 1 & 2). Raising the temperature from 100 ^oC to 120 ^oC gave marginal improvement (Table 12, entry 3). To our surprise, addition of 0.5 equiv of NaI significantly improved the reaction yield to 86% yield (Table 12, entry 4). The promoting effect was not observed in the iodination of

benzylamine substrates. Furthermore, 56% yield was obtained when the reaction was performed at 40 °C. Complete consumption of starting materials was observed when the reaction was conducted at 60 °C for 36 hours.

Table 12. Pd-Catalyzed Iodination of compound **7**



7 **7-I**

entry	Solvent	Additive (equiv)	Temperature (°C)	yield[a] (%)
1	*n*-butanol	--	100	32
2	DMF	--	100	52
3	DMF	--	120	57
4	DMF	NaI (0.5)	100	86
5	DMF	NaI (0.5)	80	85
6	**DMF**	**NaI (0.5)**	**60**	**90(83)[b]**
7	DMF	NaI (0.5)	40	56
8	DMF	NaI (0.5)	25	--

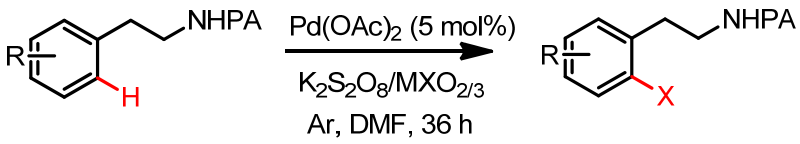
a. Yield was determined by GC-MS. b. 110°C c. isolated yield

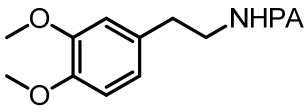
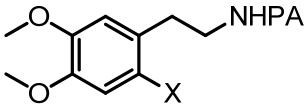
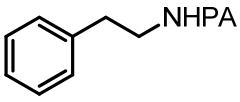
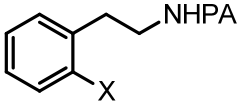
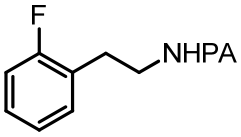
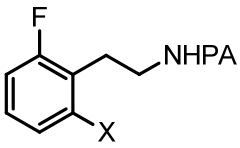
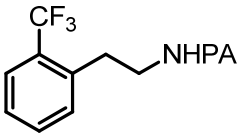
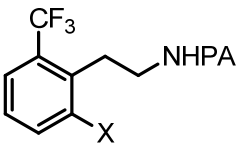
Based on the above experiments, the optimal conditions for the iodination reaction of phenethylamine picolinamides were determined to be: $Pd(OAc)_2$ (5 mol%), KIO_3 (1.5 equiv), $K_2S_2O_8$ (1.5 equiv), NaI (0.5 equiv) in DMF (0.1 mM) at 80 °C for 36 hours.

Scope of substrates

With the optimized conditions in hand, we went on to examine β-arylethylamine picolinamide substrates with different electron-donating and electron-withdrawing substituents. (Table 13).

Table 13. Pd-catalyzed *ortho*-C−H halogenation of phenylethylamine substrates



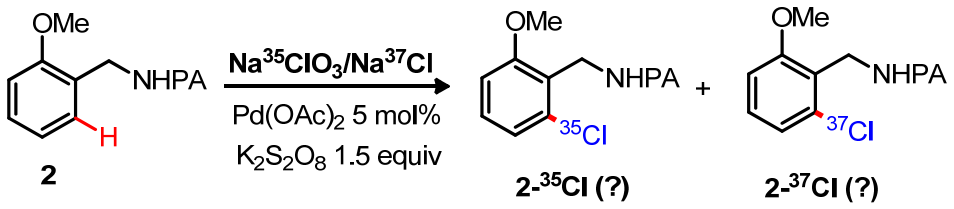
entry	Substrate	Product	Yield(%)
1	 **8**		X=Br, **8-Br**, 25[a] X=Cl, **8-Cl**, 27[b] X=I, **8-I**, 42[c]
2	 **9**		X=Cl, **9-Cl1**, 20[b] X=**I**, **9-I1**, 25 **9-I2**, <5[c]
3	 **10**		X=**I**, **10-I**, 17[d]
4	 **11**		X=I, **11-I**, 12[d]

Reagents and conditions: a. $K_2S_2O_8$ (2.5 equiv), $KBrO_3$ (2.5 equiv), KBr (2.5 equiv), 100 °C. b. $K_2S_2O_8$ (2.5 equiv), $NaClO_2$ (2.5 equiv), NaCl (1.0 equiv), 80 °C. c. $K_2S_2O_8$ (2.5 equiv), KIO_3 (2.5 equiv), NaI (1.0 equiv), 60 °C. e. $K_2S_2O_8$ (1.5 equiv), KIO_3 (1.5 equiv), NaI (0.5 equiv), 80 °C.

We found the *ortho*-C− H halogenation reactions were strongly influenced by the electronic properties of the substrates (Table 13). The electron-rich substrate **8** can be halogenated with all three halogen (Cl, Br, I) (Table 13, entry 1). However, the bromination product of the unsubstituted substrate **9** cannot be produced, and the yields for the corresponding chlorinated and iodinated products were significantly lower (Table 13, entry 2). Only the iodination reaction was successful with electron-deficient substrates **10** and **11** (Table 13, entries 3 & 4). Clearly, these Pd-catalyzed halogenation reactions were much more effective for electron-rich phenylethylamine picolinamide substrates than the electron-deficient substrates.

Future directions

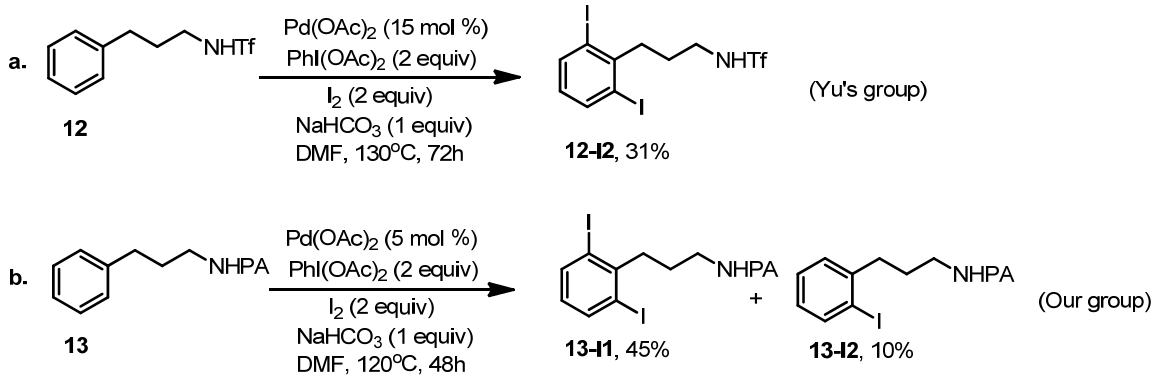
The mechanism of this Pd-catalyzed C−H halogenation reaction remains unclear. We have demonstrated that halogen ions of high oxidation state are required for the reaction, but the role of the halogen anions in enhancing yield is not well understood. Isotope labeling experiments might be helpful in revealing the functional roles of these halogen sources. For example, $Na^{35}ClO_3$ and $Na^{37}Cl$ could be employed in the chlorination reaction. If only ^{35}Cl-labeled product is isolated, the Cl anions might not be involved in the key steps of the catalytic cycle. If both ^{35}Cl- and ^{37}Cl- labeled products are isolated, the ratio of two products could provide potentially useful information about the mechanism (Scheme 11).



Scheme 11. Proposed mechanistic study by isotopic labeling.

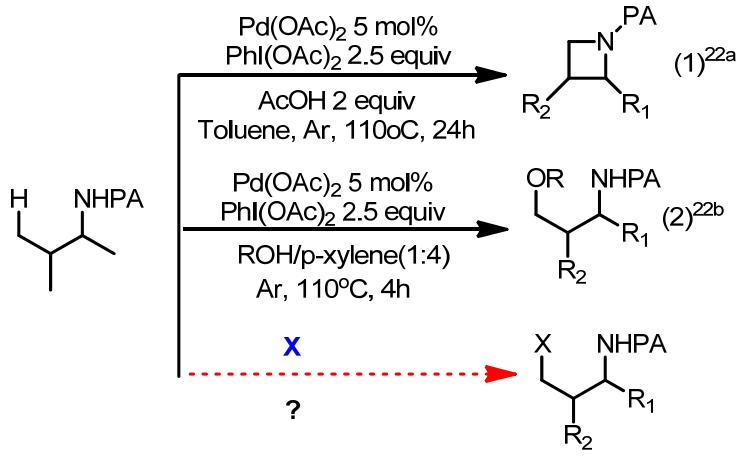
The picolinamide directing group might be utilized to enable halogenation of even more remote C(sp^2)−H bonds. The Yu laboratory recently demonstrated that the TfNH group (Scheme 12a) could promote the iodination of the ε-C−H bond of a phenylpropylamine substrate.[11b] Using the same conditions, we also successfully achieved a similar ε-C−H iodination reaction using a PA protected substrate (Scheme 12b). With lower catalyst loading and reduced reaction temperature, a higher yield and a much cleaner conversion were observed. We are optimistic that

such ε-C− H iodination could be improved to a synthetically useful level upon further optimization of the reaction condition.



Scheme 12. Remote iodination the ε-C−H of phenylpropyl- trifluoroacetamides and picolinamides.

Finally, PA-directed halogenation of γ-C(sp^3) − H bonds will also be investigated to provide alkyl halide products(Scheme 13).



Scheme 13. Pd-catalyzed PA-directed fuctionalization of γ-C(sp^3)−H bonds

Conclusion

In conclusion, we have developed a new set of conditions for Pd-catalyzed regioselective C−H halogenation reactions using cheap inorganic salts as halogen sources. All the reactions were carried out under relatively mild conditions. Moderate to excellent yields were obtained. These findings provide a more economical method to introduce halogens into aromatic organic molecules.

Experimental Section

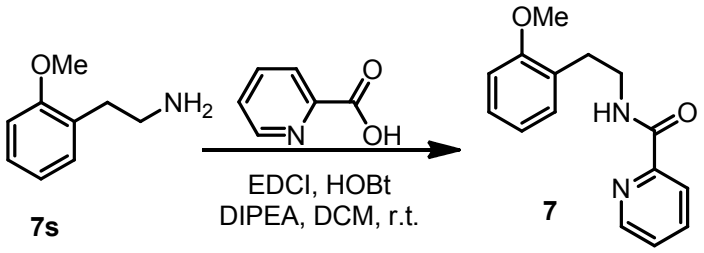
General Information:

1. Reagents: All commercial materials were used as received unless otherwise noted. DMF was obtained from a JC Meyer solvent dispensing system and used without further purification. Flash chromatography was performed using 230-400 mesh SiliaFlash 60R silica gel (Silicycle Inc.).

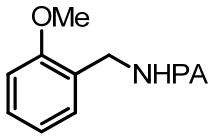
2. Instrument: NMR spectra were recorded on Bruker CDPX-300, DPX-300, DPX-400 instruments and calibrated using residual solvent peaks as internal reference. Multiplicities were recorded as: s = singlet, d = doublet, t= triplet, dd = doublet of doublets, td = triplet of dounlets, br s = broad singlet, m = multipet. High resolution ESI mass experiments were operated on a Waters LCT Premier instrument. GC-MS experiments were operated on Agilent 7820A GC and 5975 series MSD system. N-benzyl-2-pyridinecarboxamide (in chapter 1) and N-phenylethyl-2-pyridinecarboxamide (in chapter 2) were used as internal standard to determine GC yield.

3. General procedure for the preparation of picolinamide substrates

3.1 General procedure A for the preparation of picolinamide substrates **2-10**



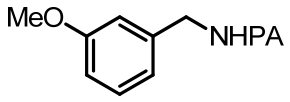
A mixture of amine (1.0 eq.), picolinic acid (1.1 eq.), EDCI (1.1 eq.), HOBt•H_2O (1.1 eq.), and DIPEA (3.0 eq.) in anhydrous DCM (0.2 M) was stirred at room temperature overnight. Water was added and the mixture was extracted with DCM. The combined organic layers was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The resulting residue was purified by silica gel flash chromatography to give the desired picolinamide product.



2

Compound **2** (Known compound)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.55-8.51 (m, 1H), 8.49-8.45 (br, 1H), 8.21 (dd, *J* = 0.8, 7.8 Hz, 1H), 7.83 (td, *J* = 2.0, 7.7 Hz, 1H), 7.43-7.33 (m, 2H), 7.29-7.25 (m, 1H), 6.96-6.91 (m, 2H), 4.67 (d, *J* = 6.2 Hz, 2H), 3.9 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.5, 158.0, 150.6, 148.5, 137.7, 130.0, 129.2, 126.7, 126.4, 122.7, 121.0, 110.8, 55.8, 39.5.

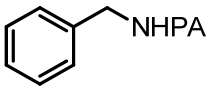


3

Compound **3** (Known compound)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.53- 8.50 (m, 1H), 8.31 (br, 1H), 8.22 (d, *J* = 7.8 Hz, 1H), 7.83 (td, *J* = 1.7, 7.7 Hz, 1H), 7.43-7.35 (m, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.93 (d, *J* = 2.5 Hz, 1H),

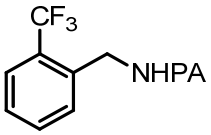
6.78 (dd, J = 2.6, 8.4 Hz, 1H), 5.65-5.60 (m, 1H), 4.64 (d, J = 5.9 Hz, 2H), 3.77 (s, 3H), 2.22-2.14 (m, 4H), 1.78-1.65 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.1, 158.4, 150.0, 148.1, 137.4, 137.1, 136.4, 129.9, 127.0, 126.2, 122.3, 114.1, 112.7, 55.3, 41.7, 31.1, 25.5, 23.2, 22.1; HRMS Calcd for $C_{20}H_{23}N_2O_2$ [M+H$^+$]: 323.1760, Found: 323.1758.



4

Compound **4** (Known compound)

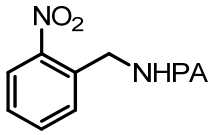
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.53-8.50 (m, 1H), 8.47-8.40 (br, 1H), 8.24 (d, J = 7.7 Hz, 1H), 7.86-7.81 (m, 1H), 7.42-7.28 (m, 6H), 4.68 (d, J = 5.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.7, 150.3, 148.5, 138.7, 137.8, 129.1, 128.2, 127.8, 126.6, 122.7, 43.9.



5

Compound **5** (Known compound)

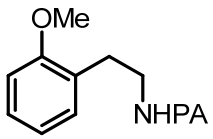
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.53 (dd, J = 0.7, 3.9 Hz, 1H), 8.56-8.41 (br, 1H), 8.21 (d, J = 7.8 Hz, 1H), 7.84 (td, J = 1.7, 7.7 Hz, 1H), 7.69-7.60 (m, 2H), 7.53-7.48 (m, 1H), 7.44-7.34 (m, 2H), 4.85 (d, J = 6.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.5, 149.7, 148.3, 137.5, 136.8, 132.4, 130.5, 127.6, 126.4, 126.1, 126.0, 122.5, 40.6; HRMS Calcd for $C_{14}H_{12}IN_2O$ [M+H$^+$]: 338.9994, Found: 339.0018.



6

Compound **6**

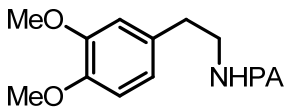
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.80-8.95 (br, 1H), 8.58 (d, *J* = 3.9 Hz, 1H), 8.18 (dd, *J* = 0.7, 7.8 Hz, 1H), 7.86 (td, *J* = 1.7, 7.7 Hz, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.53-7.48 (td, J = 1.7, 7.7, 1H), 7.47-7.43 (m, 2H), 4.94 (d, *J* = 6.3 Hz, 2H); HRMS Calcd for $C_{13}H_{11}N_3O_3$ [M+H$^+$]: 258.0800, Found: 258.0878



7

Compound **7** (Known coumpound)

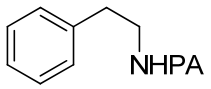
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.52 (d, *J* = 4.7 Hz, 1H), 8.32 (s, 1H), 8.20 (d, *J* = 7.8 Hz, 1H), 7.84 (td, *J* = 7.6, 1.6 Hz, 1H), 7.41-7.37 (m, 1H), 7.25-7.18 (m, 2H), 6.92-6.85 (m, 2H), 3.86 (s, 3H), 3.73 (q, *J* = 6.7 Hz, 2H), 2.99 (t, *J* = 6.9 Hz, 2H); ^{13}C NMR (CDCl3, 75.5 MHz) δ 164.72, 157.95, 150.56, 148.38, 137.60, 130.97, 128.25, 127.91, 126.34, 122.45, 121.02, 110.61, 55.61, 40.46, 30.69; HRMS Calcd for $C_{15}H_{17}N_2O_2$ [M+H+]:257.1290; Found: 257.1265.



8

Compound **8** (Known compound)

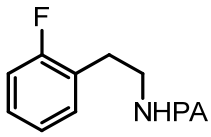
^{1}H NMR (400 MHz, CDCl3) δ 8.48 (d, *J* = 4.4 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 8.13 (bs, 1H), 7.81 (dt, *J* = 7.6 Hz, *J*= 1.6 Hz, 1H), 7.39-7.36 (m, 1H), 6.79-6.76 (m, 4H), 3.84 (s, 3H), 3.82 (s, 3H), 3.69 (q, *J* = 6.4 Hz, 2H), 2.86 (t, *J* = 7.2 Hz, 2H). ^{13}C NMR (100 MHz, CDCl3) δ (ppm) 164.3, 150.0, 149.0, 148.1, 147.7, 137.4, 131.6, 126.1, 122.2, 120.7, 112.1, 111.5, 56.0, 55.8, 40.9, 35.6. $C_{16}H_{18}N_2O_3$ [M+Na^+]; calculated 309.1215, found 309.1321.



9

Compound 9 (Known Compound)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.51 (d, J = 4.3 Hz, 1H), 8.21 (d, J = 7.8 Hz, 1H), 8.14 (s, 1H), 7.85 (td, J = 7.7, 1.5 Hz, 1H), 7.41-7.38 (m, 1H), 7.33-7.30 (m, 2H), 7.26-7.21 (m, 3H), 3.76 (q, J = 6.8 Hz, 2H), 2.97 (t, J = 7.3 Hz, 2H); ^{13}C NMR (CDCl3, 75.5 MHz) δ 164.75, 150.30, 148.47, 139.39, 137.67, 129.17, 128.99, 126.85, 126.51, 122.51, 41.20, 36.30; HRMS Calcd for $C_{14}H_{15}N_2O$ [M+H^+]: 227.1184; Found: 227.1179.

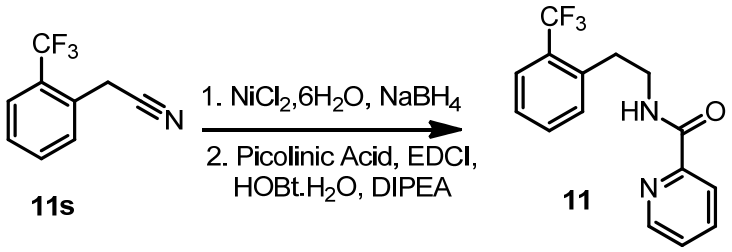


10

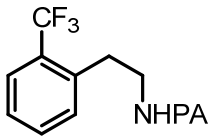
Compound **10** (Known compound)

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.56 (d, *J* = 4.0 Hz, 1H), 8.24 (d, *J* = 7.7 Hz, 2H), 7.89 (t, *J* = 7.8 Hz, 1H), 7.46 (m, 1H), 7.29-7.21 (m, 2H), 7.12-7.04 (m, 2H), 3.80 (q, *J* = 6.9 Hz, 2H), 3.05 (t, *J* = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.79, 163.32, 160.07, 150.29, 148.46, 137.67, 131.52, 131.45, 128.74, 128.63, 126.51, 126.36, 126.15, 124.59, 124.55, 122.52, 115.88, 115.59, 39.92, 29.72; HRMS Calcd for $C_{14}H_{14}FN_2O$ [M+H$^+$]: 245.1090; Found: 245.1071.

3.1 General procedure B for the preparation of picolinamide substrates **11**



To a stirred solution of benzonitrile (1.0 eq) in dry methanol (0.2M), cooled to 0 oC, was added $NiCl_2 \cdot 6H_2O$ (0.5 eq). $NaBH_4$ (7.0 eq) was then added in small portions over 30 min. The resulting reaction mixture was allowed to warm to room temperature and left to stir for a further 1 h, at which point diethylenetriamine (1.0 eq) was added. The mixture was allowed to stir for 30 min before solvent evaporation. The residue was dissolved in EtOAc and washed with saturated $NaHCO_3$. The organic layer was over anhydrous Na_2SO_4, and concentrated *in vacuo*.



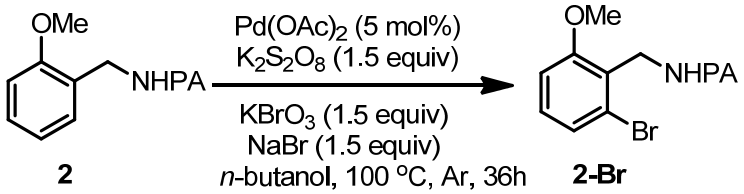
11

Compound **11** (Known compound)

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.54 (d, *J* = 4.7 Hz, 1H), 8.21 (d, *J* = 7.8 Hz, 2H), 7.86 (td, *J* = 7.7, 1.5 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.50-7.40 (m, 3H), 7.34 (t, *J* = 7.5 Hz, 1H), 3.76 (q, *J* = 6.7 Hz, 2H), 3.15 (t, *J* = 7.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 164.79, 150.21, 148.43, 137.90, 137.64, 132.27, 131.94, 129.28, 128.89, 126.94, 126.51, 126.43, 126.35, 123.14, 122.48, 40.90, 33.05; HRMS Calcd for $C_{15}H_{14}F_3N_2O$ [M+H$^+$]: 295.1053; Found: 295.1047.

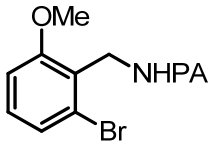
4. General procedure for Pd-catalyzed halogenation.

4.1 General procedure for Pd-catalyzed bromination of benzylamine picolinamide



2 **2-Br**

A mixture of picolinamide (0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 5 mol%), $K_2S_2O_8$ (81 mg, 0.3 mmol, 1.5 eq), and $KBrO_3$ (50 mg, 0.3 mmol, 1.5 eq) and NaBr (31 mg, 0.3 mmol, 1.5 eq) in n-butanol (2.0 mL) in a 10 mL glass vial (purged with Ar, sealed with PTFE cap) was heated at 100oC for 36 hours. The reaction mixture was cooled to RT, and concentrated in vacuo. The resulting residue was purified by silica gel flash chromatography to give brominated product.

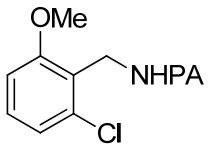


2-Br

Compound **2-Br**

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.53 (d, *J* = 3.9 Hz, 1H), 8.21 (br, 2H), 7.84 (td, *J* = 5.7, 1.1 Hz, 1H), 7.41 (d, *J* = 1.7 Hz, 1 H), 7.25 (m, 2H), 6.88 (d, *J* = 7.9 Hz, 1H), 4.91 (d, *J* = 5.4 Hz, 2H),

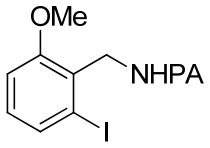
3.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 164.20, 159.51, 150.50, 148.46, 137.6i8, 130.24, 126.43, 126.36, 126.22, 125.50, 122.77, 110.27, 56.50, 38.84.; HRMS Calcd for $C_{14}H_{13}BrN_2O_2$ [M+H$^+$]: 321.0160; Found: 321.0236



2-Cl

Compound **2-Cl**

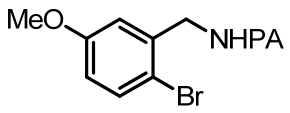
^{1}H NMR ($CDCl_3$, 400MHz) δ 8.50 (s, 1H), 8.28 (br, 1H), 8.21 (d, *J* = 8.0 Hz, 1H), 7.81 (t, *J* = 7.4 Hz, 1H), 7.37 (s, 1H), 7.18 (d, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 8.0 Hz, 1H), 6.86 (d, *J* = 8.0 Hz 1H), 4.90 (d, *J* = 5.3 Hz, 2H), 3.90 (s, 3H). HRMS Calcd for $C_{14}H_{13}ClN_2O_2$ [M+H$^+$]: 277.0738; Found: 277.0745



2-I

Compound **2-I**

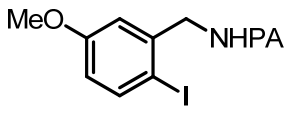
^{1}H NMR ($CDCl_3$, 400MHz) δ 8.77 (s, 1H), 8.25 (d, *J* = 7.6 Hz, 2H), 7.82 (t, *J* = 7.2 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.38 (s, 1H), 6.97 (t, *J* = 7.8 Hz, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 4.87 (d, *J* = 5.4 Hz, 2H), 3.87 (s, 3H). HRMS Calcd for $C_{14}H_{13}IN_2O_2$ [M+H$^+$]: 369.0094; Found: 369.0101



3-Br1

Compound **3-Br1**

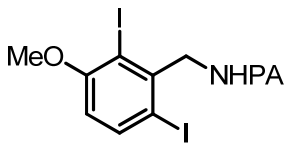
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.51-8.56 (br, 2H), 8.21 (d, *J* = 7.8 Hz, 1H), 7.84 (t, *J* = 6.3 Hz, 1H), 7.42 (d, *J* = 5.4 Hz, 2 H), 7.00 (s, 1H), 6.89 (dd, *J* = 6.0, 3.0 Hz, 1H), 4.69 (d, *J* = 6.3 Hz, 2H), 3.75 (s, 3H); HRMS Calcd for $C_{14}H_{13}BrN_2O_2$ [M+H$^+$]: 321.0233; Found: 321.0238



3-I1

Compound **3-I1**

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.52-8.58 (br, 2H), 8.22 (d, *J* = 7.8 Hz, 1H), 7.85 (t, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 8.7 Hz, 1H), 7.43 (t, *J* = 1.5 Hz, 1H), 7.00 (d, *J* = 2.7 Hz, 1H), 6.58 (dd, *J* = 7.8, 3.0 Hz, 1H), 4.66 (d, *J* = 6.3 Hz, 2H), 3.76 (s, 3H)

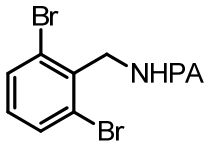


3-I2

Compound **3-I2**

^{1}H NMR ($CDCl_3$, 300MHz) δ 8.51 (d, *J* = 4.8 Hz, 1H), 8.24 (d, *J* = 8.1 Hz, 1H), 8.16 (br, 1H), 7.40 (td, *J* = 1.7 Hz, 1H), 6.51 (d, *J* = 8.4 Hz, 1H), 5.13 (d, *J* = 5.4 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHZ) δ 164.15, 159.36, 150.04, 148.53, 143.14, 140.61, 137.71, 133.89,

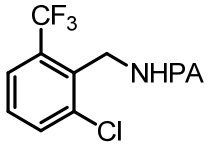
130.12, 126.59, 122.72, 112.61, 112.02, 94.09, 89.19, 57.27, 54.97.; HRMS Calcd for $C_{14}H_{12}I_2N_2O_2$, [M+H$^+$]: 494.8988



4-Br2

Compund **4-Br2**

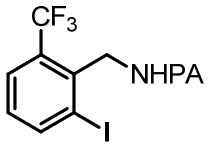
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.53 (d, *J* = 4.8 Hz, 1H), 8.26-8.32 (br, 1H), 8.24 (d, *J* = 7.6 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.40 (m, 1H), 7.13 (t, *J* = 7.8 Hz, 1H), 4.93 (d, *J* = 5.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 164.25,150.11, 148.60, 137.78, 136.79, 133.99, 130.88, 130.52, 129.54, 126.70, 110.95, 45.03



5-Cl

Compound **5-Cl**

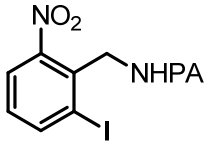
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.48 (d, *J* = 4.8 Hz, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 8.06-8.16 (br, 1H), 7.84 (t, *J* = 6.4 Hz, 1H), 7.62 (d, *J* = 12.0 Hz, 2H), 7.39 (t, *J* = 7.2 Hz, 1H), 4.95 (d, *J* = 5.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 163.99, 149.94, 148.49, 138.05, 137.76, 133.98, 132.25, 131.85, 129.62, 126.66, 125.85, 125.27, 122.81, 38.23



5-I

Compound **5-I**

^{1}H NMR ($CDCl_3$, 300MHz) δ 8.48 (d, *J* = 3.8 Hz, 1H), 8.23 (d, *J* = 7.8 Hz, 1H), 8.11 (d, *J* = 7.8 1H), 8.02-8.08 (br, 1H), 7.83 (t, *J* = 1.7 Hz, 1H), 6.51 (d, *J* = 8.4 Hz, 1H), 5.13 (d, *J* = 5.4 Hz, 2H), 3.88 (s, 3H). ^{13}C NMR ($CDCl_3$, 75.5 MHZ) δ 164.02, 149.88, 148.52, 144.50, 138.33, 137.76, 131.74, 130.00, 126.95, 125.67, 122.79, 104.44, 45.64

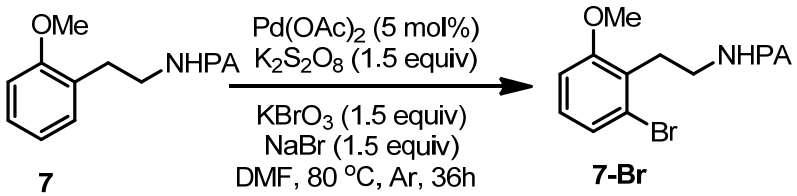


6-I

Compound **6-I**

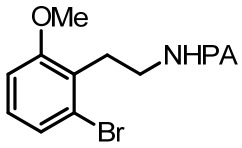
^{1}H NMR ($CDCl_3$, 300MHz) δ 8.46-8.53 (br, 2H), 8.17 (d, *J* = 7.8 Hz, 1H), 8.12 (d, *J* = 7.8 1H), 7.81 (d, *J* = 6.0 Hz, 1H), 7.41 (m, 1H), 7.15 (t, *J* = 5.4 Hz, 1H), 4.94 (d, *J* = 6.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHZ) δ 164.58, 149.79, 148.65, 144.76, 137.75, 134.72, 130.45, 126.78, 124.96, 122.82, 116.17, 103.30, 45.56

4.2 General procedure of Pd-catalyzed bromination of phenylethylamine picolinamide



7 **7-Br**

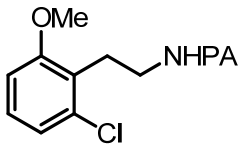
A mixture of picolinamide (0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 5 mol%), $K_2S_2O_8$ (81 mg, 0.3 mmol, 1.5 eq), and $KBrO_3$ (50 mg, 0.3 mmol, 1.5 eq) and NaBr (31 mg, 0.3 mmol, 1.5 eq) in DMF (2.0 mL) in a 10 mL glass vial (purged with Ar, sealed with PTFE cap) was heated at 100°C for 36 hours. The reaction mixture was cooled to RT, and concentrated in vacuo. The resulting residue was purified by silica gel flash chromatography to give brominated product.



7-Br

Compound **7-Br**

^{1}H NMR ($CDCl_3$, 400MHz) δ 8.50 (d, *J* = 4.2 Hz, 1H), 8.22 (br, 1H), 8.15 (d, *J* = 7.8 Hz, 1H), 7.80 (t, *J* = 7.7 Hz, 1H), 7.37 (t, *J* = 4.2 Hz, 1H), 7.26 (d, *J* = 11.5 Hz, 2H), 6.70 (d, *J* = 8.3 Hz, 1H), 3.80 (s, 3H), 3.65 (q, *J* = 6.7 Hz, 2H), 2.89 (t, *J* = 7.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHZ) δ 164.80, 157.14, 150.42, 148.32, 137.74, 133.67, 130.87, 130.26, 126.49, 122.57, 113.13, 112.33, 66.95, 40.14, 30.60.

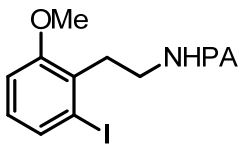


7-Cl

Compound **7-Cl**

^{1}H NMR ($CDCl_3$, 400MHz) δ 8.53 (d, *J* = 3.0 Hz, 1H), 8.29 (br, 1H), 8.19 (d, *J* = 7.6 Hz, 1H), 7.84 (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 5.6 Hz, 1H), 7.16 (s, 2H), 6.78 (d, *J* = 9.2 Hz, 1H), 3.84 (s, 3H), 3.69 (q, *J* = 6.4 Hz, 2H), 2.97 (t, *J* = 7.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHZ) δ 164.77,

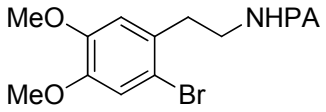
156.61, 150.41, 148.40, 137.66, 130.92, 129.76,127.96, 126.58, 125.72, 122.55.13, 111.75, 56.05, 40.10, 30.61. ; HRMS Calcd for $C_{15}H_{15}ClN_2O_2$ [M+H$^+$]: 291.0895; Found: 321.0908



7-I

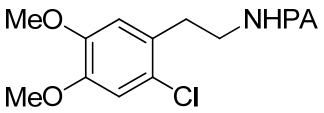
Compound **7-I**

^{1}H NMR ($CDCl_3$, 400MHz) δ 8.52 (d, *J* = 4.4 Hz, 1H), 8.25-8.29 (br, 1H), 8.17 (d, *J* = 7.8 Hz, 1H), 7.82 (t, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 12.4 Hz, 2H), 7.40 (t, *J* = 5.6 Hz, 2H), 6.62 (d, *J* = 8.0 Hz, 1H), 3.81 (s, 3H), 3.66 (q, *J* = 6.8 Hz, 2H), 2.96 (t, *J* = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHZ) δ 164.76, 157.94, 150.42, 148.42, 139.70, 137.66, 137.07, 136.88, 130.72, 126.58, 122.55, 113.02, 83.19, 40.11, 30.42.; HRMS Calcd for $C_{15}H_{15}IN_2O_2$ [M+H$^+$]: 383.0251; Found: 383.0273



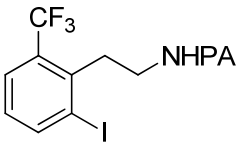
8-Br

^{1}H NMR ($CDCl_3$, 300MHz) δ 8.51 (d, *J* = 4.2 Hz, 1H), 8.20-8.24 (m, 2H), 7.82 (t, *J* = 4.8 Hz, 1H), 7.41-7.43 (m, 1H), 7.02 (s, 1H), 6.77 (s, 1H), 3.84 (s, 3H), 3.72 (s, 3H), 3.69 (dd, *J* = 6.9 Hz, 2H), 3.01 (t, *J* = 7.2 Hz, 2H) ^{13}C NMR ($CDCl_3$, 75.5 MHZ) δ 164.81, 150.28, 148.79, 148.66, 148.48, 137.83, 130.55, 126.64, 122.61, 115.99, 114.61, 113.88,56.58, 56.40, 39.66, 36.14



8-Cl

^{1}H NMR ($CDCl_3$, 300MHz) δ 8.65 (s, 1H), 8.31-8.17 (m, 2H), 8.21 (t, *J* = 4.8 Hz, 1H), 7.56-7.51 (m, 1H), 6.89 (s, 1H), 6.78 (s, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.73 (dd, *J* = 6.9 Hz, 2H), 3.03 (t, *J* = 7.2 Hz, 2H) ^{13}C NMR ($CDCl_3$, 75.5 MHZ) δ 164.79, 150.32, 148.60, 148.48, 148.21, 137.81, 128.68, 126.61, 125.32, 122.60, 113.83, 113.03, 56.56, 56.46, 39.58, 33.72

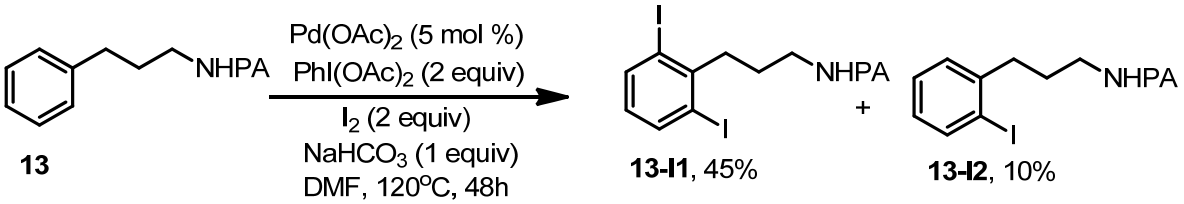


11-I

Compound **11-I**

^{1}H NMR ($CDCl_3$, 400MHz) δ 8.56 (d, *J* = 4.4 Hz, 1H), 8.20-8.24 (br, 2H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.84 (t, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.42 (t, *J* = 6.0 Hz, 2H), 7.03 (t, *J* = 8.0 Hz, 1H), 3.70 (dd, *J* = 15.6, 6.8 Hz, 2H), 3.29 (t, *J* = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHZ) δ 164.70, 150.25, 148.44, 144.27, 140.06, 137.81, 131.12, 130.72, 129.54, 128.64, 127.00, 122.70, 122.27, 104.31, 39.28, 28.30

4.3 Procedure of Pd-catalyzed bromination of phenylpropylamine picolinamide

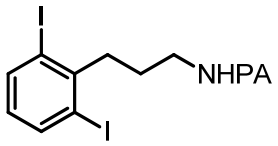


13

13-I1, 45%

13-I2, 10%

A mixture of phenylpropylamine picolinamide (0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 5 mol%), $PhI(OAc)_2$ (128 mg, 0.4 mmol, 2.0 eq), I_2 (101 mg, 0.4 mmol, 2.0 eq) and $NaHCO_3$ (20 mg, 0.2 mmol, 1.0 eq) in DMF (2.0 mL) in a 10 mL glass vial (purged with Ar, sealed with PTFE cap) was heated at 120°C for 48 hours. The reaction mixture was cooled to RT, and concentrated in vacuo. The resulting residue was purified by silica gel flash chromatography to give brominated product.



13-I2

Compound **13-I2**

^{1}H NMR ($CDCl_3$, 400MHz) δ 8.54 (d, *J* = 4.4 Hz, 1H), 8.15-8.26 (br, 2H), 7.84 (t, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.40 (t, *J* = 6.4 Hz, 1H), 6.48 (t, *J* = 7.6 Hz, 1H), 3.63 (dd, *J* = 15.6, 6.8 Hz, 2H), 3.16 (t, *J* = 8.8 Hz, 2H), 1.91 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHZ) δ 164.81, 148.45, 145.64, 140.51, 137.76, 129.92, 126.50, 122.63, 128.64, 99.37, 44.76, 39.47, 28.67

References

1. Butler, A.; Walker, J. V. *Chem. Rev*. **1993**, *93*, 1937-1944.

2.; Silverman, G. S., Rakita, P.E., Eds.; Dekker *Handbook of Grignard reagents*: New York, NY **1996**.

3. Sotomayor, N.; Lete, E. Curr. *Org. Chem*. **2003**, *7*, 275-300.

4. (a); Dieterich, F., Stang, P.J., Eds. *Metal Catalyzed Cross Coupling Reactions*; Wiley-VCH: New York, NY, **1998**; (b) Hartwig, J.F. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.i., Ed.; Wiley Interscience: New York, NY **2002**; pp 1097-1106

5. (a) Taylor, R. *Electrophilic Aromatic Substitution*; John Wiley: New York, **1990**. (b) De la Mare, P. B. *Electrophilic Halogenation*; Cambridge University Press: Cambridge, **1976** Chapter 5. (c) Merkushev, E. B. *Synehesis*, **1988**, 923.

6. (a) Zhang, Y.; Shibatomi, K.; Yamamoto, H. *Synlett* **2005**, *18*, 2837 and references therein. (b) Firouzabadi, H.; Iranpoor, N.; Shiri, M. *Tetrahedron Lett*. **2003**, *44*, 8781. (c) Vyas, P.V.l Bhatt, A. K.; Ramachandraiah, G.; Bedekar, A. V. *Tetrahedron Lett*. **2003**, *44*, 4085. (d) Iskra, J.; Stavber, S.; Zupan, M. *Synthesis* **2004**, *11*, 1869. (e) Braddock, D. C.; Cansell, G.; Hermitage, S. A. *Synlett* **2004**, *3*, 461.

7. Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Org Lett***. 2006**, *8*, 2523-2526.

8. Snieckus, V. *Chem. Rev*. **1990**, *90*, 879.

9. Fahey, D. R.; J. *Organomet. Chem*. **1971**, *27*, 283-292

10. (a) Dick, A. R.; Hull, K. L., Sanford, M. S. *J. Am. Chem. Soc*. **2004**, *126*, 2300-2301. (b) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Tetrohedron* **2006**, *6*2, 11483-11498. (c) Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc*. **2007**, *129*, 15142.

11. (a). Li, J.; Mei, T.; Yu, J. *Angew. Chem. Int. Ed*. **2008**, *47*, 6452-6455. (b) Mei, T.; Wang, D.; Yu, J. *Org. Lett*. **2010**, *12*, 3140-3143.

12. Song, B.; Zheng, X.; Mo, J.; Xu, B. *Adv. Synth. Catal*. **2010**, *352*, 329-335.

13. Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. *J. Am. Chem. Soc*. **2006**, *128*, 7416-7417.

14. Bedford, R. B.; Mitchell, C. J.; Webster, R. L. *Chem. Commun*. **2010**, *46*, 3095-3097

15. Dudnik, A. S.; Chernyak, N.; Huang, C.; Gevorgyan, V. *Angew. Chem. Int. Ed*. **2010**, *49*, 8729-8732.

16. Chen, X.; Hao, X.; Goodhue, C. E.; Yu, J. *J. Am. Chem. Soc*. **2006**, *128*, 7890-6781.

17. Wang, W.; Pan, C.; Chen, F.;Cheng, *J. Chem. Commun*. **2011**, *47*, 3978-3980.

18. Schroder, N.; Wencel-Delord, J.; Glorius, F. *J. Am. Chem. Soc*. **2012**, *134*, 8289-8310.

19. Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc*. **2005**, *127*, 13154-13155.

20. (a) Zhang, S.; He, G.; Zhao, Y.; Wright, K.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.*, **2012,** *134*, 7313-7316. (b) He, G.; Lu, C.; Zhao, Y.; Nack, W. A.; Chen, G. *Org. Lett*. **2012**, *14*, 2944-2947.

21. (a) Zhao, Y.; He, G.; Nack, W. A.; Chen, G. *Org. Lett*. **2012**, *14*, 2948. (b) Zhao, Y.; Chen, G. *Org. Lett*. **2011**, *13*, 4850-4853.