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Palladium-catalyzed picolinamide-directed halogenation of ortho C–H bonds of benzylamine substrates

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ABSTRACT

We report a new set of methods for the halogenation of the ortho C–H bonds of *N*-benzyl picolinamides under palladium-catalyzed conditions. These reactions feature the use of a unique combination of K(Na)XO_3 and $K_2S_2O_8$ reagents, which enables the installation of iodo, bromo, and chloro groups onto the ortho position of *N*-benzyl picolinamides in a unified fashion. A variety of benzylamine products bearing complex halogen substitution can be quickly prepared from much simpler precursors in good yield and selectivity.

1. Introduction

Halogenated arenes are versatile building blocks in organic synthesis.[1] Synthetic methods based on metal-catalyzed halogenation of the ortho C–H bonds of arene substrates have been quickly advanced over the past decade.[2–8] These methods provide unique synthesis solutions that can complement conventional methods based on electrophilic aromatic substitution (S_EAr) and directed metalation.[9] Like directed lithiation chemistry, heteroatom-based directing groups are typically required to achieve the desired selectivity and reactivity. Among metal catalysts, Pd-catalyzed C–H halogenation reactions have been most investigated.[10] In 1970, Fahey pioneered Pd-catalyzed ortho C–H chlorination and bromination of azobenzenes using chlorine and bromine.[2] In 2004, Sanford reported Pd-catalyzed ortho C–H chlorination and bromination of benzoquinoline using *N*-halosuccinimides.[3a] In 2006, Shi and co-workers reported Pd-catalyzed ortho C–H chlorination of acetanilides using $Cu(OAc)_2$/$CuCl_2$.[4] In 2008, Yu reported Pd-catalyzed ortho C–H iodination of triflamide protected 2-arylehtylamines using I_2/$PhI(OAc)_2$.[5a] Enantioselective, triflamide-directed iodination of symmetric diarylmethylamines with I_2 has also been reported.[5b] More recently, Rao further expanded the scope of directing groups such that a range of common ester and amide-based directing groups can be utilized to facilitate Pd-catalyzed ortho C–H chlorination and bromination using *N*-halosuccinimides/$Na_2S_2O_8$.[6] Notably, most of these reaction systems have been tailored to achieve halogenation with only one or two of the halogens; there are few unified sets of conditions capable of introducing Cl, Br, and I.[3b]

Recently, our laboratory has become interested in investigating the picolinamide (PA) directing group for use in C–H functionalization reactions.[11] The PA group, first introduced by the Daugulis laboratory,[12] has demonstrated excellent capability for a variety of Pd-catalyzed C–H functionalizations, forming both C–C and C–heteroatom bonds.[13] Last year, we reported that the PA group can facilitate mono-selective iodination of ε ortho C–H bonds of γ-arylpropylamines under Pd-free conditions (Eq. 1, Scheme 1).[14,15] These reactions proceed through a rarely observed intramolecular directed electrophilic aromatic substitution (S_EAr) pathway with high efficiency and ortho selectivity. Subsequent Cu-catalyzed intramolecular C–N coupling of the iodinated intermediates afforded tetrahydroquinoline products with various substitution patterns. In contrast, bromination, and chlorination of γ-arylpropylamine substrates under similar conditions with NBS or NCS was non-selective. Furthermore, while PA-coupled β-phenylethylamines substrates were ortho-iodinated with excellent mono and ortho selectivity, iodination of PA-coupled benzylamine substrates generated a mixture of ortho and para-iodinated products via non-directed S_EAr (Eq. 2). Prompted by the importance and abundance of benzylamine compounds in organic synthesis, we began to investigate whether we can achieve the ortho halogenation of benzylamines under metal catalysis. Herein, we report a new set of Pd-

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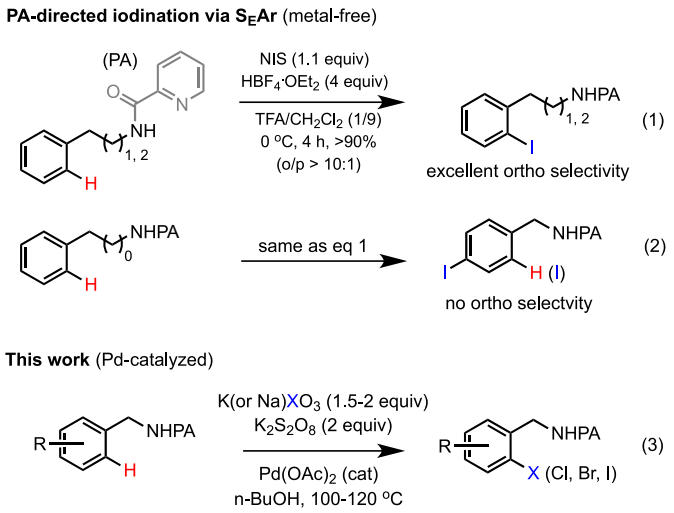
catalyzed ortho C–H halogenation reactions of *N*-benzyl picolinamides. A unified set of reaction conditions featuring the use of K(Na)XO_3 and $K_2S_2O_8$ allows the ortho halogenation of benzylamines with iodo, bromo, and chloro groups.



Scheme 1. PA-directed halogenation of ortho C–H bonds of benzylamines.

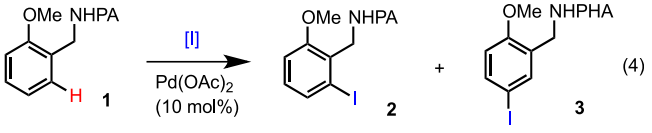
2. Results and discussion

Our previous studies have shown that the ortho C–H bonds of benzyl picolinamides can be readily transformed into various carbon–carbon and carbon–heteroatom bonds under Pd-catalyzed conditions.[11] Encouraged by these earlier successes, we anticipated that Pd-catalyzed C–H functionalization of benzyl picolinamides with halides under suitable oxidative conditions would give ortho halogenated products through the similar catalytic manifold. However, unlike Pd-catalyzed ortho C–C bond forming reactions, halogenation via non-directed S_EAr pathways often undermines regio-control due to the involvement of highly reactive halonium ion intermediates. We commenced our study with the Pd-catalyzed ortho iodination of electron-rich 2-methoxybenzyl picolinamide **1** (Table 1). As shown in entry 1 of Table 1, iodination of **1** under our previously reported NIS/HBF_4 conditions gave predominately non-directed product **3**. Iodination of **1** with NIS alone in TFA/DCM also gave **3** selectively in lower yield (entry 2). Reaction of **1** in the presence of 10 mol % of $Pd(OAc)_2$ and 2 equiv of NIS in CH_3CN at 110 °C gave a mixture of ortho product **2** in 28% yield and **3** in 63% yield, presumably via non-directed S_EAr (entry 3).[3c] Interestingly, the yield and selectivity of the reaction were significantly improved by applying Cl–Ph solvent (entry 4).

In addition to organic iodonium precursors, we also evaluated simple alkali metal iodides as iodo donors under oxidative conditions, in order to develop more economical iodination conditions. In recent years, a variety of cheap inorganic iodonium donating reagents have been applied for the non-catalytic oxidative halogenation of arenes, such as iodine–nitrogen dioxide,[16] $I_2/Na_2S_2O_8$,[17] $I_2/(NH_4)_2S_2O_8$,[18] KI/oxone,[19] NaI/NaOCl,[20] KI/KO_3,[21] and NH_4I/H_2O_2.[22] However, these reagents have not been widely applied for Pd-catalyzed C–H iodination. We first attempted Pd-catalyzed iodinations of **1** with $I_2/K_2S_2O_8$ or NaI/$K_2S_2O_8$ at 110 °C, which provided trace amount of the ortho-iodinated product **2** (entries 6 and 7). Interestingly, KIO_3[23]/$K_2S_2O_8$[24] afforded **2** in much greater yield; *n*-BuOH gave notably better results than other solvents (entry 8). Reaction of **1** with KIO_3 alone did not yield **2** (entry 9). Addition of 1.5 equiv of NaI to $KIO_3/K_2S_2O_8$ dramatically decreased the yield of **2** (entry 10). No formation of **2** was observed in the absence of $Pd(OAc)_2$ or $K_2S_2O_8$ (entries 11, 12).

The substrate scope of this Pd-catalyzed PA-directed ortho iodination with $KIO_3/K_2S_2O_8$ (conditions **A**) was examined next (Scheme 2). In general, electron-rich arenes were more reactive and gave higher iodination yields than electron-poor substrates. It should be noted that electron-poor substrates (see **6** and **9**) are usually unreactive under the typical S_EAr halogenation conditions. The Pd-catalyzed iodinations were generally clean and contained only product and unreacted starting material. Halogenation of the PA directing group was not observed presumably due to the electron-deficiency of the pyridine ring. Reactions of benzylamines bearing 2 equiv ortho C–H bonds gave a mixture of mono and di-iodinated products (see **4**). Similar to our previously reported PA-directed ortho C–H functionalization of benzylamines, less hindered ortho C–H positions were selectively iodinated (see **5** and **7**). Iodination of a naphthalene substrate selectively occurred at the 2 position to give **8**, illustrating the favorability of five-membered palladacycle intermediate over larger metallacycle.

Table 1
Ortho C–H iodination of benzylamine **1**

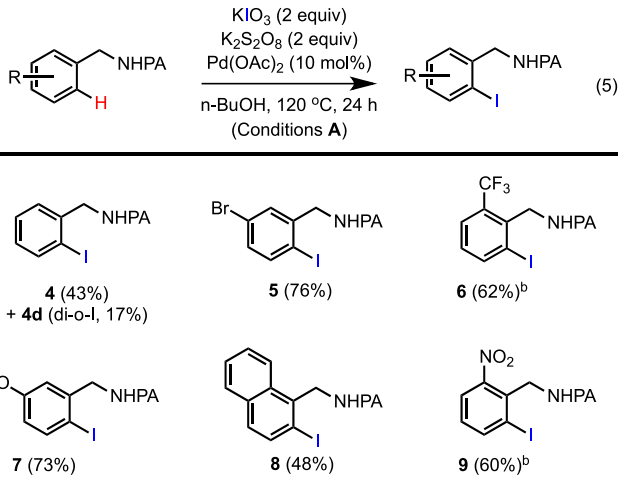


Entry	Reagents (equiv)	Solvents/ temp (°C) time/h	Yield (%)[a]	
			2	3
1	NIS (1.1), HBF_4OEt_2 (3)	TFA/DCM (1/9) 0/4	<4	60
2	NIS (1.5)	TFA/DCM (1/9) 0/4	<4	27
3	Pd, NIS (1.5)	CH_3CN 110/24	28	63
4	Pd, NIS (1.5)	Cl–Ph 110/24	91	<2
5	Pd, I_2 (1.5), PIDA (1.5) $NaHCO_3$ (1)	DMF 120/24	<2	18
6	Pd, I_2 (1.5) $K_2S_2O_8$ (1.5)	*n*-BuOH 120/24	<2	<2
7	Pd, NaI (1.5) $K_2S_2O_8$ (2)	*n*-BuOH 120/24	<2	<2
8	Pd KIO_3 (2), $K_2S_2O_8$ (2)	*n*-BuOH 120/24	85 (80)[b]	<2
9	Pd KIO_3 (2)	*n*-BuOH 120/24	<2	<2
10	Pd, NaI (1.5) KIO_3 (2), $K_2S_2O_8$ (2)	*n*-BuOH 120/24	<2	<2
11	Pd, NaI (1.5) KIO_3 (2)	*n*-BuOH 120/24	<2	<2
12	KIO_3 (2), $K_2S_2O_8$ (2)	*n*-BuOH 120/24	<2	<2

TFA: trifluoroacetic acid, DCM: dichloromethane, DMF: dimethylformamide. PIDA: phenyliodine diacetate.

[a] Yields are based on ^1H NMR analysis of screening reactions on a 0.2 mmol scale under Ar.

[b] Isolated yield.

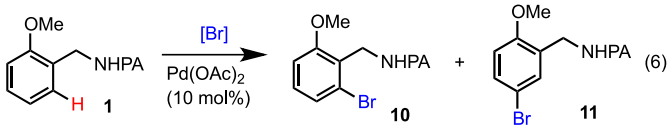


a) Isolated yield on a 0.2 mmol scale. b) 36 h.

Scheme 2. Substrate scope of PA-directed ortho iodination of benzylamines.

Encouraged by the success of the PA-directed ortho iodination reaction, we next explored Pd-catalyzed ortho C–H bromination of benzylamines (Table 2). S_EAr bromination of **1** under the NBS-mediated conditions in TFA/DCM predominantly gave the non-directed bromination product **11** (entries 1, 2). Unlike iodination, Pd-catalyzed bromination of **1** using 10 mol % of $Pd(OAc)_2$ and 1.5 equiv of NBS in Cl–Ph at 110 °C gave the non-directed **11** in 28% yield (entry 3). Pd-catalyzed bromination of **1** with $Cu(OAc)_2/CuBr_2$ gave little product (entry 4). Finally, we found that Pd-catalyzed bromination of **1** with $KBrO_3/K_2S_2O_8$ gave the ortho-directed product **10** in 84% yield (entry 5).[25] In contrast with the iodination reaction, addition of 1.5 equiv of NaBr further improved the bromination yield (entry 9). No bromination occurred in the absence of either $K_2S_2O_8$ or Pd (entries 9, 12).

Table 2
Ortho C–H bromination of benzylamine **1**

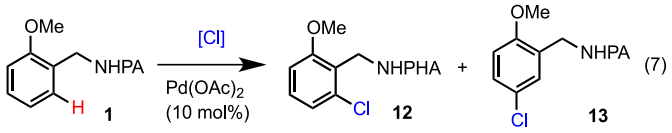


Entry	Reagents (equiv)	Solvents/temp (°C)/ time (h)	Yield (%)[a]	
			10	**11**
1	NBS (1.1), HBF_4OEt_2 (3)	TFA/DCM (1/9), 0/1	<2	53
2	NBS (1.5)	TFA/DCM (1/9), 0/1	<2	70
3	Pd, NBS (1.5)	Cl–Ph 120/24	<2	28
4	Pd, $Cu(OAc)_2$ (1.5) $CuBr_2$ (1.5)	DCE 110/24	<2	<2
5	Pd $KBrO_3$ (1.5), $K_2S_2O_8$ (2)	*n*-BuOH 100/24	84	<2
6	Pd, NaBr (0.5) $KBrO_3$ (1.5), $K_2S_2O_8$ (2)	*n*-BuOH 100/24	90	<2
7	Pd, NaBr (1) $KBrO_3$ (1.5), $K_2S_2O_8$ (2)	*n*-BuOH 100/24	91	<2
8	Pd, NaBr (1.5) $KBrO_3$ (1.5), $K_2S_2O_8$ (2)	*n*-BuOH 100/24	95 (89)[b]	<2
9	Pd, NaBr (1.5) $KBrO_3$ (1.5)	*n*-BuOH 100/24	<2	<2
10	Pd, NaBr (1.5) $K_2S_2O_8$ (2)	*n*-BuOH 100/24	<2	<2
11	Pd, KBr (1.5) $KBrO_3$ (1.5), $K_2S_2O_8$ (2)	*n*-BuOH 100/24	66	<2
12	NaBr (1.5) $KBrO_3$ (1.5), $K_2S_2O_8$ (2)	*n*-BuOH 100/24	<2	<2

[a] Yields are based on ^1H NMR analysis of reactions on a 0.2 mmol scale.
[b] Isolated yield.

Next, we examined the ortho C–H chlorination of **1** (Table 3). Only small amount of non-directed S_EAr chlorination product **13** was formed under the NCS/HBF_4-mediated conditions in TFA/DCM (entry 1). Pd-catalyzed chlorination with NCS gave the non-directed product **13** (entries 3, 4). Pd-catalyzed chlorination with chloramine-T, $Cu(OAc)_2/CuCl_2$, or $CaCl_2/K_2S_2O_8$ gave poor results (entries 5–7). To our delight, Pd-catalyzed chlorination using a combination of $NaClO_3/K_2S_2O_8$ in *n*-BuOH at 110 °C gave the ortho-directed product **12** in significantly improved yield (entry 8).[26] An 80% isolated yield was obtained when 1.5 equiv of NaCl, 1.5 equiv of $NaClO_3$, and 2 equiv of $K_2S_2O_8$ were used (entry 9). No ortho C–H chlorination occurred in the absence of Pd (entry 12).

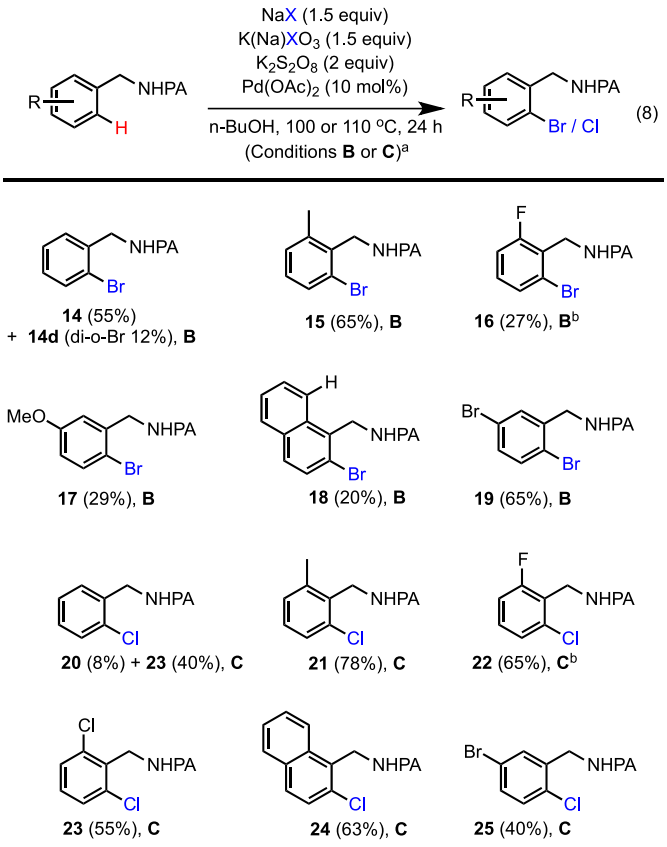
Table 3
Ortho C–H chlorination of benzylamine **1**



Entry	Reagents (equiv)	Solvents/temp (°C)/ time (h)	Yield (%)[a]	
			12	**13**
1	NCS (1.1), HBF_4OEt_2 (3)	TFA/DCM (1/9) 0/1	<2	10
2	NCS (1.5)	TFA/DCM (1/9) 0/1	<2	<2
3	Pd, NCS (1.5)	Cl–Ph 120/24	<2	6
4	Pd, NCS (1.5)	CH_3CN 120/24	<2	71
5	Pd, Chloramine-T (1.5)	AcOH 120/24	<2	<2
6	Pd, $Cu(OAc)_2$ (2), $CuCl_2$ (2)	DCE 110/24	<2	<2
7	Pd, $CaCl_2$ (1.5), $K_2S_2O_8$ (2)	AcOH 110/24	9	<2
8	Pd $NaClO_3$ (1.5), $K_2S_2O_8$ (2)	*n*-BuOH 110/24	72	<2
9	Pd, NaCl (1.5) $NaClO_3$ (1.5), $K_2S_2O_8$ (2)	*n*-BuOH 110/24	83 (80)[b]	<2
10	Pd, NaCl (1.5) $NaClO_2$ (1.5), $K_2S_2O_8$ (2)	*n*-BuOH 110/24	35	<2
11	Pd, KCl (1.5), $NaClO_3$ (1.5), $K_2S_2O_8$ (2)	*n*-BuOH 110/24	75	<2
12	NaCl (1.5) $NaClO_3$ (1.5), $K_2S_2O_8$ (2)	*n*-BuOH 110/24	<2	<2

[a] Yields are based on ^1H NMR analysis of reactions on a 0.2 mmol scale.
[b] Isolated yield.

Next, we examined the substrate scope of Pd-catalyzed PA-directed ortho C–H bromination and chlorination under the standard conditions **B** and **C** using $NaX/K(Na)XO_3/K_2S_2O_8$ (Scheme 3). We observed patterns of reactivity and selectivity similar to the C–H iodination reactions. The less hindered ortho C–H bonds of asymmetric substrates are selectively halogenated under the standard conditions (see **17** and **25**). A variety of benzylamine products carrying complex halogen substitution (e.g., **19** and **22**) were obtained from easily accessible starting materials.



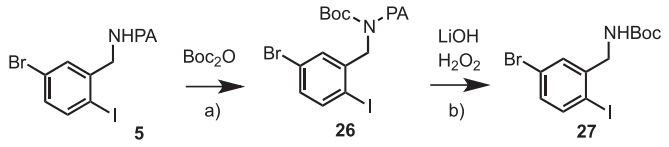
a) Isolated yields of reactions on a 0.2 mmol scale. Conditions **B**: X=Br, Conditions **C**: X=Cl. b) 36 h.

Scheme 3. Substrate scope of PA-directed ortho-bromination and chlorination of benzylamines.

These $K(Na)XO_3/K_2S_2O_8$-mediated halogenation reactions likely share a similar catalytic cycle. First, C–H palladation forms Pd^{II} palladacycle intermediates, then oxidative addition yields higher valent palladium intermediates, and finally C–X reductive elimination forms the halogenated products. While a $Pd^{II/IV}$ manifold has been invoked to explain many Pd-catalyzed oxidative halogenation systems, a catalytic manifold involving Pd^{III} intermediates could also be operative.[18] The identity of the active halogenating and oxidizing species is elusive due to the involvement of multiple reagents. The application of $K_2S_2O_8$, which is the sole oxidant in

several Pd-catalyzed C–H functionalization systems,[24] is critical for our halogenation reactions. We suspect that X_2 is possibly formed in situ, either from reaction of $NaXO_3$ with NaX[25,26] or from disproportionation of $K(Na)XO_3$, and plays a critical role in these reaction systems. While Cl_2, Br_2, and I_2 are known to oxidize Pd^{II},[2,5b,12b] they may also react with $K_2S_2O_8$ to form new oxidative halogenating species for these Pd-catalyzed reactions.[17,18]

The PA group of the halogenated products obtained above can be removed under mild conditions (Scheme 4). For instance, compound **5** was first reacted with Boc_2O/DMAP at room temperature to give *N*-Boc protected intermediate **26**, which was deprotected with $LiOH/H_2O_2$ at room temperature to give Boc protected benzylamine product **27** in good yield.[11f]



a) Boc_2O, DMAP, CH_3CN, rt, 88%; b) $LiOH \cdot H_2O$, H_2O_2, rt, 57%.

Scheme 4. Removal of the PA group.

In summary, we have developed a new set of methods to halogenate the ortho C–H bonds of *N*-benzyl picolinamides under palladium-catalyzed conditions. These reactions feature the use of a unique combination of $K(Na)XO_3$ and $K_2S_2O_8$ reagents, which can enable the installation of iodo, bromo, and chloro groups on the ortho position of benzylamines in a unified fashion. A variety of benzylamine products bearing complex halogen substitution can be quickly prepared from much simpler precursors in good yield and selectivity.

3. Experimental sections

3.1. General conditions

All commercial materials were used as received unless otherwise noted. All solvents were obtained from a JC Meyer solvent dispensing system and used without further purification. Flash chromatography was performed using 230–400 mesh SiliaFlash 60® silica gel (Silicycle Inc.). $PhI(OAc)_2$ (98%, Aldrich), $Pd(OAc)_2$ (98%, Aldrich) were used in the Pd-catalyzed reactions. NMR spectra were recorded on Bruker CDPX-300, DPX-300, DPX-400 instruments, and calibrated by using residual solvent peaks as the internal reference. Multiplicities are recorded as: s=singlet, d=doublet, t=triplet, dd=doublet of doublets, m=multiplet. High-resolution ESI mass experiments were operated on a Waters LCT Premier instrument.

3.2. Standard procedure for the preparation of *N*-benzyl picolinamide[11f]

2-Methoxybenzylamine (0.68 g, 5 mmol), 2-picolinic acid (0.74 g, 6 mmol), EDCI (1.16 g, 6 mmol), HOBt (0.92 g, 6 mmol), and DIPEA (2.2 mL, 13 mmol) were dissolved in 20 mL of anhydrous DMF. The mixture was stirred at room temperature for 24 h. 200 mL water was then added to quench the reaction and the mixture was extracted with EtOAc. The combined organic layers was washed with H_2O and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica-gel flash chromatography (EtOAc/Hex: 1/15) to give the desired product **1** (1.10 g, 90%). ^1H NMR ($CDCl_3$, 400 MHz) δ 8.57–8.54 (m, 1H), 8.47 (br, 1H), 8.23 (dd, J=0.8, 7.8 Hz, 1H), 7.85 (td, J=7.7, 2.0 Hz, 1H), 7.43–7.39 (m, 1H), 7.37 (dd, J=1.2, 7.4 Hz, 1H), 7.28 (td, J=9.5, 1.5 Hz, 1H), 6.96–6.91 (m, 2H), 4.69 (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. HRMS calcd for $C_{15}H_{15}N_2O_2$ $[M+H^+]$: 255.1134, Found: 255.1116.

3.3. Standard procedure for the Pd-catalyzed ortho C–H iodination reaction

A mixture of picolinamide **1** (48 mg, 0.2 mmol, 1 equiv), $Pd(OAc)_2$ (4.4 mg, 0.02 mmol, 0.1 equiv), $K_2S_2O_8$ (108 mg, 0.4 mmol, 2 equiv), and KIO_3 (86 mg, 0.4 mmol, 2.0 equiv) in *n*-butanol (2 mL) in a 10 mL glass vial (purged with Ar, sealed with PTFE cap) was heated at 120 °C for 24 h. The reaction mixture was filtered through a pad of Celite and concentrated in vacuo. The resulting residue was purified by silica-gel flash chromatography (hexanes/DCE 1:10) to give product **2** as a pale solid (78 mg, 82%).

*3.3.1. N-(2-Methoxy-6-iodo)-benzyl picolinamide (**2**).* ^1H NMR (300 MHz, $CDC1_3$) δ 8.51 (d, J=4.0 Hz, 1H), 8.23 (br, 2H), 7.85 (t, J=7.8 Hz, 1H), 7.48 (d, J=7.8 Hz, 1H), 7.40–7.38 (m, 1H), 6.97 (t, J=8.0 Hz, 1H), 6.88 (d, J=7.7 Hz, 1H), 4.88 (d, J=5.6 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 158.7, 150.4, 148.4, 137.6, 132.1, 130.8, 129.5, 126.4, 122.6, 111.2, 102.1, 56.4, 43.9. HRMS calcd for: $C_{14}H_{14}IN_2O_2$ $[M+H^+]$: 369.0100, Found: 369.0101.

*3.3.2. N-(2-Methoxy-5-iodo)-benzyl picolinamide (**3**).* ^1H NMR (300 MHz, $CDC1_3$) δ 8.55 (d, J=4.2 Hz, 1H), 8.42 (br, 1H), 8.21 (d, J=7.8 Hz, 1H), 7.87–7.82 (m, 1H), 7.60 (d, J=2.1 Hz, 1H), 7.54 (dd, J=2.4, 8.7 Hz, 1H), 7.44–7.40 (m, 1H), 6.65 (d, J=8.7 Hz, 1H), 4.61 (d, J=6.3 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 157.9, 138.1, 137.8, 137.7, 129.1, 126.5, 122.8, 113.0, 83.1, 55.9, 38.7 HRMS calcd for: $C_{14}H_{14}IN_2O_2$ $[M+H^+]$: 369.0100, Found: 369.0110.

*3.3.3. N-(2-Iodo)-benzyl picolinamide (**4**).* ^1H NMR (300 MHz, $CDC1_3$) δ 8.56 (br, 2H), 8.22 (d, J=7.8 Hz, 2H), 7.86–7.83 (m, 2H), 7.45–7.43 (m, 2H), 7.32 (t, J=7.5 Hz, 1H), 6.98 (t, J=3.5 Hz, 1H), 4.70 (d, J=6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 150.1, 148.6, 140.8, 139.9, 137.8, 129.9, 129.7, 129.0, 126.70, 122.8, 99.5, 48.6. HRMS calcd for: $C_{13}H_{12}IN_2O$ $[M+H^+]$: 338.9994, Found: 339.0001.

*3.3.4. N-(2,6-Diiodo)-benzyl picolinamide (**4d**).* ^1H NMR (300 MHz, CDC13) δ 8.54 (d, J=4.2 Hz, 1H), 8.25 (d, J=7.8 Hz, 1H), 8.19 (br, 1H), 7.90–7.82 (m, 3H), 7.44–7.40 (m, 1H), 6.34 (t, J=7.8 Hz, 1H), 5.06 (d, J=5.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 143.6, 141.9, 141.7, 139.2, 131.6, 126.6, 122.8, 100.5, 54.8. HRMS calcd for: $C_{13}H_{11}I_2N_2O$ $[M+H^+]$: 464.8961, Found: 464.8995.

*3.3.5. N-(2-Iodo-5-bromo)-benzyl picolinamide (**5**).* ^1H NMR (300 MHz, $CDC1_3$) δ 8.56–8.55 (br, 2H), 8.20 (d, J=7.8 Hz, 1H), 7.88–7.82 (m, 1H), 7.66 (d, J=8.1 Hz, 1H), 7.51 (s, 1H), 7.46–7.41 (m, 1H), 7.10 (dd, J=2.1, 8.4 Hz, 1H), 4.64 (d, J=6.3 Hz, 2H); ^{13}C NMR (75 MHz, CDCl3) δ 164.7, 149.8, 148.6, 142.8, 141.0, 137.8, 132.7, 132.4, 126.8, 123.3, 122.8, 97.1, 48.2. HRMS calcd for: $C_{13}H_{11}BrIN_2O$ $[M+H^+]$: 416.9099, Found: 418.9100.

*3.3.6. N-(2-Trifluoromethyl-6-iodo)-benzyl picolinamide (**6**).* ^1H NMR (300 MHz, $CDC1_3$) δ 8.50 (d, J=4.8 Hz, 1H), 8.24 (d, J=7.8 Hz, 1H), 8.12 (d, J=7.8 Hz, 1H), 8.01 (br, 1H), 7.88–7.82 (m, 1H), 7.72 (d, J=8.1 Hz), 7.43–7.39 (m, 1H), 7.14 (t, J=7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 149.9, 148.5, 144.5, 138.3, 137.8, 130.0, 126.9, 126.8, 126.7, 122.8, 104.48, 45.7. HRMS calcd for: $C_{14}H_{11}F_3IN_2O$ $[M+H^+]$: 406.9868, Found: 406.9886.

*3.3.7. N-(3-Methoxy-6-iodo)-benzyl picolinamide (**7**).* ^1H NMR (300 MHz, $CDC1_3$) δ 8.56–8.54 (br, 2H), 8.22 (d, J=7.8 Hz, 1H), 7.87–7.82 (m, 1H), 7.69 (d, J=8.4 Hz, 1H), 7.45–7.43 (m, 1H), 7.01 (d, J=2.8 Hz, 1H), 6.58 (dd, J=3.0, 8.7 Hz, 1H), 4.65 (d, J=6.3 Hz, 2H),

3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 160.6, 150.1, 148.6, 141.8, 140.3, 138.8, 126.73, 122.8, 116.0, 115.5, 87.6, 55.8, 48.5; HRMS calcd for: $C_{14}H_{14}IN_2O_2$ [M+H$^+$]: 369.0100, Found: 369.0110.

*3.3.8. N-(1-(2-Iodo)-naphthyl)-methyl picolinamide (**8**).* ^{1}H NMR (300 MHz, $CDC1_3$) δ 8.45 (d, J=3.9 Hz, 1H), 8.33–8.24 (m, 3H), 7.92–7.80 (m, 3H), 7.58–7.48 (m, 3H), 7.39–7.36 (m, 1H), 5.34 (d, J=5.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 150.0, 148.5, 137.7, 136.9, 136.4, 133.8, 133.0, 130.6, 129.0, 128.2, 127.0, 126.6, 125.1, 122.8, 101.3, 46.1. HRMS calcd for: $C_{17}H_{14}IN_2O$ [M+H$^+$]: 389.0151, Found: 389.0164.

*3.3.9. N-(2-Nitro-6-iodo)-benzyl picolinamide (**9**).* ^{1}H NMR (300 MHz $CDC1_3$) δ 8.52–8.51 (br, 2H), 7.18–7.10 (m, 2H), 7.84–7.79 (m, 2H), 7.42–7.38 (m, 1H), 7.15 (t, J=7.8 Hz, 1H), 3.93 (d, J=6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.46, 151.5, 149.7, 148.6, 144.7, 137.7, 134.6, 130.4, 126.8, 124.9, 122.8, 103.3, 45.5. HRMS calcd for $C_{13}H_{11}IN_3O_3$ [M+H$^+$]: 383.9845, Found: 383.9859.

3.4. Standard procedure for the Pd-catalyzed ortho C–H bromination reaction

A mixture of picolinamide **1** (48 mg, 0.2 mmol, 1 equiv), $Pd(OAc)_2$ (4.4 mg, 0.01 mmol, 0.05 equiv), $K_2S_2O_8$ (108 mg, 0.4 mmol, 2 equiv), $KBrO_3$ (50 mg, 0.3 mmol, 1.5 equiv), and NaBr (31 mg, 0.3 mmol, 1.5 equiv) in *n*-butanol (2 mL) in a 10 mL glass vial (purged with Ar, sealed with PTFE cap) was heated at 100 °C for 24 h. The reaction mixture was filtered through a short pad of Celite and concentrated in vacuo. The resulting residue was purified by silica-gel flash chromatography (hexanes/DCE 1:10) to give the product **10** as a pale white solid (57 mg, 89%).

*3.4.1. N-(2-Methoxy-6-bromo)-benzyl picolinamide (**10**).* ^{1}H NMR (300 MHz $CDC1_3$) δ 8.50 (d, J=4.2 Hz, 1H), 8.27 (br, 1H), 8.22 (d, J=7.8 Hz, 1H), 7.84–7.79 (m, 1H), 7.40–7.36 (m, 1H), 7.20–7.10 (m, 2H), 6.85 (d, J=7.8 Hz, 1H), 4.88 (d, J=5.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 159.5, 150.4, 148.4, 137.6, 130.2, 126.4, 126.2, 125.4, 122.7, 110.27, 56.5, 38.8, 30.1. HRMS calcd for: $C_{14}H_{14}BrN_2O_2$ [M+H$^+$]: 321.0239, Found: 321.0236.

*3.4.2. N-(2-Methoxy-5-bromo)-benzyl picolinamide (**11**).* ^{1}H NMR (300 MHz, $CDC1_3$) δ 8.52 (d, J=3.9 Hz, 1H), 8.44 (br, 1H), 7.84–7.79 (m, 1H), 7.42–7.30 (m, 3H), 7.30 (d, J=8.4 Hz, 1H), 4.61 (d, J=6.3 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 157.0, 150.3, 148.5, 137.7, 132.3, 131.7, 129.0, 126.6, 122.7, 113.1, 112.4, 56.1, 38.8. HRMS calcd for: $C_{14}H_{14}BrN_2O_2$ [M+H$^+$]: 321.0239, Found: 321.0240.

3.5. Standard procedure for the Pd-catalyzed ortho C–H chlorination reaction

A mixture of picolinamide **1** (48 mg, 0.2 mmol, 1 equiv), $Pd(OAc)_2$ (4.4 mg, 0.01 mmol, 0.05 equiv), $K_2S_2O_8$ (108 mg, 0.4 mmol, 2 equiv), $NaClO_3$ (32 mg, 0.3 mmol, 1.5 equiv), and NaCl (18 mg, 0.3 mmol, 1.5 equiv) in *n*-butanol (2 mL) in a 10 mL glass vial (purged with Ar, sealed with PTFE cap) was heated at 100 °C for 24 h. The reaction mixture was filtered through a short pad of Celite and concentrated in vacuo. The resulting residue was purified by silica-gel flash chromatography (hexanes/DCE 1:10) to give the product **12** as a pale white solid (57 mg, 80%).

*3.5.1. N-(2-Methoxy-6-chloro)-benzyl picolinamide (**12**).* ^{1}H NMR (300 MHz, $CDC1_3$) δ 8.50 (d, J=3.9 Hz, 1H), 8.23 (br, 1H), 8.21 (d, J=7.8 Hz, 1H), 7.81 (t, J=7.2 Hz, 1H), 7.39–7.36 (m, 1H), 7.19 (t, J=8.1 Hz, 1H), 7.00 (d, J=7.8 Hz, 1H), 6.81 (d, J=8.4 Hz, 1H), 4.87 (d, J=5.7 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.1, 158.7, 150.4, 148.4, 137.6, 132.1, 130.8, 129.5, 126.4, 122.7, 111.2, 102.1, 56.4, 43.9, 30.1. HRMS calcd for: $C_{14}H_{14}ClN_2O_2$ [M+H$^+$]: 277.0744, Found: 277.0745.

*3.5.2. N-(2-Methoxy-5-chloro)-benzyl picolinamide (**13**).* ^{1}H NMR (300 MHz, $CDC1_3$) δ 8.52 (d, J=4.2 Hz, 1H), 8.45 (br, 1H), 7.82–7.79 (m, 1H), 7.41–4.39 (m, 1H), 7.29 (s, 1H), 7.17 (dd, J=2.4, 8.7 Hz, 1H), 6.77 (d, J=8.7 Hz, 1H), 4.61 (d, J=6.3 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 156.5, 150.2, 148.5, 137.7, 129.4, 128.5, 128.5, 126.5, 125.8, 122.7, 111.8, 56.1, 38.8. HRMS calcd for: $C_{14}H_{14}ClN_2O_2$ [M+H$^+$]: 277.0744, Found: 276.7182.

*3.5.3. N-(2-Bromo)-benzyl picolinamide (**14**).* ^{1}H NMR (300 MHz, $CDC1_3$) δ 8.56–8.54 (br, 2H), 8.21 (d, J=7.8 Hz, 1H), 7.88–7.82 (m, 1H), 7.56 (d, J=7.8 Hz, 1H), 7.48–7.41 (m, 2H), 7.30–7.26 (m, 1H), 7.14 (td, J=1.5, 7.8 Hz, 1H), 4.75 (d, J=6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 150.1, 148.6, 137.8, 137.7, 133.2, 130.5, 129.5, 128.1, 126.7, 124.2, 122.7, 44.1. HRMS calcd for $C_{13}H_{12}BrN_2O$ [M+H$^+$]: 291.0133, Found: 291.0129.

*3.5.4. N-(2,6-Dibromo)-benzyl picolinamide (**14d**).* ^{1}H NMR (300 MHz, $CDC1_3$) δ 8.52 (d, J=3.9 Hz, 1H), 8.31 (br, 1H), 8.23 (d, J=7.8 Hz, 1H), 7.87–7.81 (m, 1H), 7.56 (d, J=8.1 Hz, 2H), 7.43–7.41 (m, 1H), 7.03 (t, J=8.1 Hz, 1H), 5.03 (d, J=5.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 150.1, 148.6, 137.7, 136.7, 133.0, 130.8, 128.1, 126.7, 126.6, 122.8, 45.03. HRMS calcd for $C_{13}H_{11}Br_2N_2O$ [M+H$^+$]: 368.9238, Found: 368.9247.

*3.5.5. N-(2-Methyl-6-bromo)-benzyl picolinamide (**15**).* ^{1}H NMR (300 MHz, $CDC1_3$) δ 8.52 (d, J=3.6 Hz, 1H), 8.23–8.20 (br, 2H), 7.86–7.81 (m, 1H), 7.72 (d, J=7.8 Hz, 1H), 7.42–4.38 (m, 1H), 7.16 (d, J=7.2 Hz, 1H), 6.89 (t, J=7.2 Hz, 1H), 4.84 (d, J=7.2 Hz, 2H), 2.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3, 150.1, 148.5, 140.3, 137.7, 135.7, 131.1, 130.3, 129.6, 126.5, 126.4, 122.6, 41.3, 21.0. HRMS calcd for: $C_{14}H_{14}BrN_2O$ [M+H$^+$]: 305.0290, Found: 305.0291.

*3.5.6. N-(2-Bromo-6-fluoro)-benzyl picolinamide (**16**).* ^{1}H NMR (300 MHz, $CDC1_3$) δ 8.52 (d, J=4.5 Hz, 1H), 8.36 (br, 1H), 8.21 (d, J=8.1 Hz, 1H), 7.86–7.80 (m, 1H), 7.43–7.38 (m, 2H), 7.16 (q, J=7.2 Hz, 1H), 7.06 (t, J=8.4 Hz, 1H), 4.86 (d, J=5.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3, 150.1, 148.5, 137.7, 130.7, 130.5, 129.1, 129.1, 126.6, 122.82, 115.6, 115.3. HRMS calcd for: $C_{13}H_{11}BrFN_2O$ [M+H$^+$]: 309.0039, Found: 309.0045.

*3.5.7. N-(2-Bromo-5-methoxy)-benzyl picolinamide (**17**).* ^{1}H NMR (300 MHz, $CDC1_3$) δ 8.55–8.51 (br, 2H), 8.21 (d, J=7.8 Hz, 1H), 7.87–7.81 (m, 1H), 7.45–7.40 (m, 2H), 7.00 (d, J=3.0 Hz, 1H), 6.69 (dd, J=3.0, 8.7 Hz, 1H), 4.70 (d, J=7.2 Hz, 2H), 3.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 259.5, 150.1, 148.6, 138.6, 137.8, 133.8, 126.7, 122.8, 116.2, 115.09, 114.4, 55.9, 44.2. HRMS calcd for: $C_{14}H_{14}BrN_2O_2$ [M+H$^+$]: 321.0239, Found: 321.0238.

*3.5.8. N-(1-(2-Bromo)-naphthyl)-methyl picolinamide (**18**).* ^{1}H NMR (300 MHz, $CDC1_3$) δ 8.44 (d, J=5.2 Hz, 1H), 8.34 (d, J=8.1 Hz, 1H), 8.25 (d, J=7.8 Hz, 1H), 7.85–7.80 (m, 2H), 7.70–7.63 (m, 2H), 7.60 (t, J=7.2 Hz, 1H), 7.50 (t, J=7.2 Hz, 1H), 7.38–7.34 (m, 1H), 5.32 (d, J=5.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3, 150.0, 148.5, 137.7, 133.4, 133.2, 133.0, 130.4, 129.0, 128.2, 126.7, 124.9, 124.5, 122.8, 40.7. HRMS calcd for: $C_{17}H_{14}BrN_2O$ [M+H$^+$]: 341.0290, Found: 341.0296.

*3.5.9. N-(3,6-Dibromo)-benzyl picolinamide (**19**).* ^{1}H NMR (300 MHz, $CDC1_3$) δ 8.61–8.56 (br, 2H), 8.25 (d, J=7.8 Hz, 1H), 7.93–7.88 (m, 1H), 7.59 (d, J=2.1 Hz, 1H), 7.51–7.45 (m, 2H), 7.32 (m, 1H), 4.74 (d, J=6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 148.7,

139.8, 137.9, 134.6, 133.0, 132.5, 126.9, 122.9, 122.6, 122.0, 110.0, 43.8. HRMS calcd for $C_{13}H_{11}Br_2N_2O$ [M+H$^+$]: 368.9238, Found: 368.9250.

*3.5.10. N-(2-Chloro)-benzyl picolinamide (**20**).* ^{1}H NMR (300 MHz, $CDC1_3$) δ 8.55 (d, J=6.4 Hz, 1H), 8.50 (br, 1H), 8.21 (d, J=7.8 Hz, 1H), 7.88–7.82 (m, 1H), 7.48–7.37 (m, 3H), 7.26–7.21 (m, 2H), 7.70 (d, J=5.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 150.1, 148.5, 137.8, 136.0, 134.1, 130.4, 129.9, 129.3, 127.5, 126.7, 122.7, 41.7. HRMS calcd for $C_{13}H_{12}ClN_2O$ [M+H$^+$]: 247.0638, Found: 247.0627.

*3.5.11. N-(2-Methyl-6-chloro)-benzyl picolinamide (**21**).* ^{1}H NMR (300 MHz, $CDC1_3$) δ 8.52 (d, J=4.5 Hz, 1H), 8.33 (br, 1H), 8.23 (d, J=7.8 Hz, 1H), 7.87–7.82 (m, 1H), 7.43–7.39 (m, 1H), 7.27 (d, J=6.9 Hz, 1H), 7.18–7.10 (m, 2H), 4.85 (d, J=5.7 Hz, 2H), 2.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 150.2, 148.5, 140.2, 137.8, 135.9, 134.2, 129.7, 129.2, 127.8, 126.6, 122.7, 38.8, 20.7. HRMS calcd for: $C_{14}H_{14}ClN_2O$ [M+H$^+$]: 261.0795, Found: 261.0790.

*3.5.12. N-(2-Fluoro-6-chloro)-benzyl picolinamide (**22**).* ^{1}H NMR (300 MHz, $CDC1_3$) δ 8.15 (d, J=4.2 Hz, 1H), 8.35 (br, 1H), 8.20 (d, J=7.5 Hz, 1H), 7.84–7.79 (m, 1H), 7.41–7.37 (m, 1H), 7.23–7.20 (m, 2H), 7.04–6.98 (m, 1H), 4.84 (d, J=5.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3, 163.7, 160.4, 150.0, 148.4, 137.7, 136.1, 136.1, 130.1, 126.6, 125.8, 125.8, 122.7, 114.9, 114.6, 35.1, 35.1. HRMS calcd for $C_{13}H_{11}ClFN_2O$ [M+H$^+$]: 265.0544, Found: 265.0538.

*3.5.13. N-(2,6-Dichloro)-benzyl picolinamide (**23**).* ^{1}H NMR (300 MHz, $CDC1_3$) 8.52 (d, J=4.5 Hz, 1H), 8.32 (br, 1H), 8.22 (d, J=7.8 Hz, 1H), 7.86–7.81 (m, 1H), 7.42–7.39 (m, 1H), 7.33 (d, J=8.1 Hz, 2H), 7.18 (t, J=7.8 Hz, 1H), 4.99 (d, J=6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 150.0, 148.4, 137.7, 136.7, 133.9, 130.0, 128.9, 126.6, 122.8, 39.52. HRMS calcd for $C_{13}H_{11}Cl_2N_2O$ [M+H$^+$]: 281.0248, Found: 281.0244.

*3.5.14. N-(1-(2-Chloro)-naphthyl)-methyl picolinamide (**24**).* ^{1}H NMR (300 MHz, $CDC1_3$) δ 8.43 (d, J=3.9 Hz, 1H), 8.32 (d, J=8.1 Hz, 2H), 8.24 (d, J=7.5 Hz, 1H), 7.83–7.74 (m, 3H), 7.59 (t, J=7.8 Hz, 1H), 7.51–7.47 (m, 2H), 7.38–7.34 (m, 1H), 5.30 (d, J=5.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3, 150.0, 148.4, 137.7, 133.5, 133.2, 132.8, 131.0, 130.2, 128.9, 128.18, 127.5, 126.5, 126.5, 124.6, 122.7, 37.7. HRMS calcd for: $C_{17}H_{14}ClN_2O$ [M+H$^+$]: 297.0795, Found: 297.0789.

*3.5.15. N-(2-Chloro-4-bromo)-benzyl picolinamide (**25**).* ^{1}H NMR (300 MHz, $CDC1_3$) δ 8.56–8.52 (br, 2H), 8.21 (d, J=7.8 Hz, 1H), 7.88–7.83 (m, 1H), 7.55 (s, 1H), 7.46–7.42 (m, 1H), 7.33 (d, J=8.1 Hz, 1H), 7.23 (d, J=8.4 Hz, 1H), 4.72 (d, J=6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 149.8, 148.6, 138.1, 137.8, 132.9, 132.8, 132.2, 131.3, 126.8, 122.8, 121.16. HRMS calcd for: $C_{13}H_{11}BrClN_2O$ [M+H$^+$]: 324.9743, Found: 324.9747.

3.6. Revomal of the picolinamide group

Step a: A mixture of picolinamide **3** (41.7 mg, 0.1 mmol, 1 equiv), $(Boc)_2O$ (43.6 mg, 0.2 mmol, 2 equiv), and DMAP (2.5 mg, 0.02 mmol, 0.2 equiv) in anhydrous MeCN (0.3 mL) in a 10 mL glass vial was stirred at room temperature for 12 h. The reaction mixture was diluted with dichloromethane, filtered through a short pad of Celite, and concentrated in vacuo. The resulting residue was purified by silica-gel flash chromatography (hexanes/EtOAc 10:1) to give the Boc protected product **26** as a white solid (45.5 mg, 88%).

*3.6.1. N-Boc-N-(2-iodo-5-bromo)-benzyl picolinamide (**26**).* ^{1}H NMR (300 MHz, $CDC1_3$) δ 8.64 (d, J=4.5 Hz, 1H), 7.86–7.81 (m, 1H), 7.77 (d, J=7.8 Hz, 1H), 7.68–7.62 (m, 2H), 7.45–7.41 (m, 1H), 7.08 (dd, J=2.1, 8.1 Hz, 1H), 4.96 (s, 2H), 1.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 154.3, 153.3, 148.7, 141.9, 140.9, 137.4, 132.2, 129.9, 126.1, 123.5, 123.5, 95.5, 84.1, 53.9, 27.7. HRMS calcd for: $C_{18}H_{19}BrIN_2O_3$ [M+H$^+$]: 516.9624, Found: 516.9664.

Step b: Boc protected picolinamide **26** (41 mg, 0.08 mmol, 1 equiv) was dissolved in 1 mL of THF/H_2O (4:1) at 0 °C. $LiOH\cdot H_2O$ (13 mg, 0.25 mmol), 30% H_2O_2 (55 μL, 0.4 mmol) were added. Reaction was stirred at room temperature for 6 h. The reaction mixture was filtered through a short pad of Celite and concentrated in vacuo. The resulting residue was purified by silica-gel flash chromatography (hexanes/EtOAc: 20:1) to give the product **27** as a white solid (18.8 mg, 57%).

*3.6.2. Boc-N-(2-iodo-5-bromo)-benzylamine (**27**).* ^{1}H NMR (300 MHz, $CDC1_3$) δ 7.54 (d, J=8.4 Hz, 1H), 7.45 (d, J=2.1 Hz, 1H), 7.10 (dd, J=2.1, 8.4 Hz, 1H), 5.03 (br, 2H), 4.28 (d, J=8.0 Hz, 2H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 141.0, 132.5, 131.9, 96.6, 49.3, 28.8. HRMS calcd for: $C_{12}H_{16}BrINO_2$ [M+H$^+$]: 411.9409, Found: 411.9415.

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Supplementary data

^{1}H and ^{13}C NMR spectra for all new compounds are available. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.02.070.

References and notes

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