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Note

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Synthesis of *N*-Substituted-3-amino-4-halopyridines: a Sequential Boc-Removal/Reductive Amination Mediated by Brønsted and Lewis Acids

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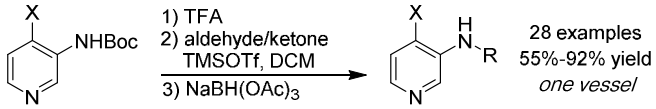


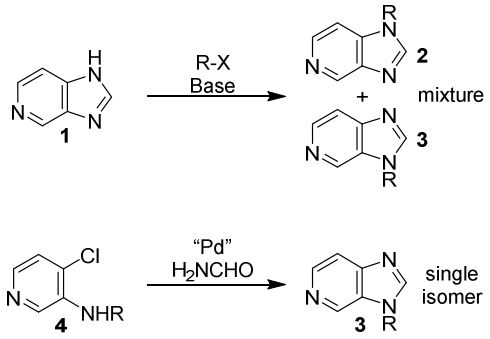
Abstract:

N-Substituted-3-amino-4-halopyridines are valuable synthetic intermediates, as they readily provide access to imidazopyridines and similar heterocyclic systems. The direct synthesis of *N*-substituted-3-amino-4-halopyridines is problematic, as reductive aminations and base promoted alkylations are difficult in these systems. A high yielding deprotection/alkylation protocol mediated by trifluoroacetic acid and trimethylsilyl trifluoromethanesulfonate is described, providing access to a wide scope of *N*-substituted-3-amino-4-halopyridines. This protocol furnishes many reaction products in high purity without chromatography. Similar reductive amination conditions were also established for deactivated anilines.

N-Substituted imidazo[4,5-*c*]pyridine derivatives have engendered notable interest in drug discovery, as they often possess significant and varied biological activity.[1] Selective approaches to *N*-substituted imidazo[4,5-*c*]pyridines are coveted,[2] as a mixture of regioisomers (Scheme 1) is typically obtained upon base promoted alkylation.[2-3] Recently a selective synthesis of *N*-substituted imidazo[4,5-*c*]pyridines employing a palladium catalyzed tandem

amidation/cyclization as the key step was developed.[4] This method utilizes *N*-substituted-3-amino-4-halopyridines as the reaction starting material, thus more effective methods to access pyridines like **4** became a priority.

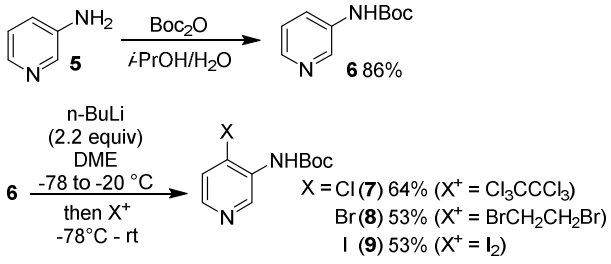
Scheme 1. Use of *N*-Substituted-3-Amino-4-Halopyridines in the Regioselective Synthesis of *N*-Substituted Imidazo[4,5-*c*]pyridines



Initially attempts were made to alkylate 3-amino-4-chloropyridine using reductive amination conditions that have provided high yields in similar pyridine systems (AcOH and $NaBH(OAc)_3$ are typically effective for 3-amino-2-chloropyridine,[5] for example), but these reactions showed poor conversion or failed completely. This lack of reactivity is attributed to the higher basicity of the 3-amino-4-chloropyridine (the pK_a of 4-chloropyridinium has been reported as 3.83,[6] while 2-chloropyridinium has a pKa of 0.75[7]), allowing it to act as a buffer, slowing imine formation or decelerating reduction of the imine by limiting protonation. Therefore a three-step procedure involving protection as a carbamate, base-promoted alkylation and acid-mediated deprotection was carried out to yield *N*-substituted 3-amino-4-chloropyridines. This alkylation protocol gave only moderate yields in most cases (typically 40-50%).[4a] An investigation was therefore initiated to expand and strengthen alkylation protocols to access *N*-alkylated-3-amino-4-halopyridines.

At first these studies were hindered by the gradual decomposition of 3-amino-4-chloropyridine under ambient conditions, forcing constant repurification to achieve meaningful isolated yields. This prompted the search for a bench stable, easily functionalized starting material that could be prepared and stored on large scale. Starting from the inexpensive 3-aminopyridine, **5**, monoprotection with di-*tert*-butyldicarbonate afforded the *N*-Boc-3-aminopyridine **6** in excellent yield on 20 g scale. This material was purified by recrystallization and could be used in the next step without chromatography (Scheme 2). The carbamate serves as a useful directing group for lithiation at the pyridine 4-position, with subsequent electrophilic halogenation (employing hexachloroethane, 1,2-dibromoethane, or iodine respectively) affording *N*-Boc-3-amino-4-halopyridines on large scale (up to 100 mmol). Quéginer and co-workers previously reported a similar directed metalation with a pivalate,[8] however the removal of the Boc group is a more facile process compared to that of pivalate and similar amide directing groups.[8-9] In addition, the Boc-protected 3-amino-4-halopyridine could be stored under ambient conditions with no special precautions for up to six months without noticeable degradation.

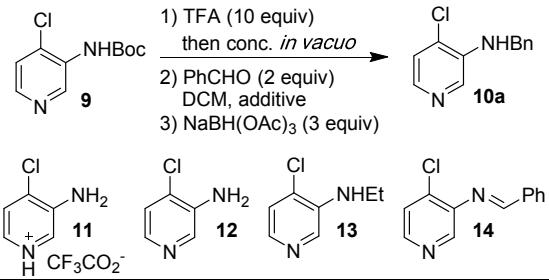
Scheme 2. Optimized Synthesis of *N*-Boc-3-Amino-4-Halopyridines



A reinvestigation of the reductive amination protocol was undertaken with the goal to improve access to *N*-substituted 3-amino-4-chloropyridine systems. Reductive amination remains one of the simplest, mildest, and most economical methods for forming C–N bonds.[1a,5b,10] However, there are still limitations to this chemistry. Generally, less nucleophilic

amines require stronger acids to facilitate the conversion to the imine/iminium.[5b,10a] Selectivity between the reduction of the imine and carbonyl reactant decreases with increased acid strength, however, which may hinder product formation.[10b] Despite this limitation, working in highly acidic media also presented an opportunity to facilitate Boc-removal *in situ*, so the reductive amination with stronger Brønsted acids was initially evaluated. Sodium triacetoxyborohydride was used as the reducing agent for its selective reactivity.[10a,10b,11] Other reducing agents such as sodium borohydride and sodium cyanoborohydride were less effective. Trifluoroacetic acid (TFA) is known to deprotect *tert*-butyl carbamates and mediate reductive amination for weakly basic amines, so it was evaluated first (Table 1).[5,9b] Boc removal from substrate **7** was complete within minutes in neat TFA (10 equiv). The corresponding pyridinium salt **11** could be isolated at this stage upon concentration *in vacuo*. Given that ammonium salts have been previously reported to facilitate reductive amination,[10a] pyridinium trifluoroacetate **11** was subjected to reductive amination conditions and provided a 45% yield of the desired product **10a** (Table 1, entry 1). The reduction of the imine was sluggish, as a significant amount of imine **14** was also detected. The addition of more TFA favored the reduction of the imine (Table 1, entries 2-4), though excess TFA led to competitive reduction of the aldehyde, leaving unreacted amine **12** along with moderate amount of desired pyridine **10a** (Table 1, entry 4) in the product mixture.

Table 1. Reaction Conditions for Deprotection and Reductive Amination of **9**



Entry	Additive (Equiv)	10a[a]	12[a]	13[a]	14[a]
1	-	45	-	-	45
2	TFA (1)	53	-	-	33
3	TFA (2)	63	-	-	28
4	TFA (10)	30	55	-	-
5[b]	BF_3•OEt_2 (5)	19	12	9	-
6[b]	$TiCl_4$ (5)	12	32	12	-
7[b]	$AlCl_3$ (5)	10	31	21	-
8[b]	TMSOTf (5)	53	15	10	-
9	TMSOTf (2)	90	-	-	4
10	TfOH (1)	50	33	-	-
11	TMSOTf (1.1)	55	-	20	-

[a]Yield as determined using ^{1}H NMR with a mesitylene internal standard. [b]Lewis acids were used to deprotect the Boc group without TFA.

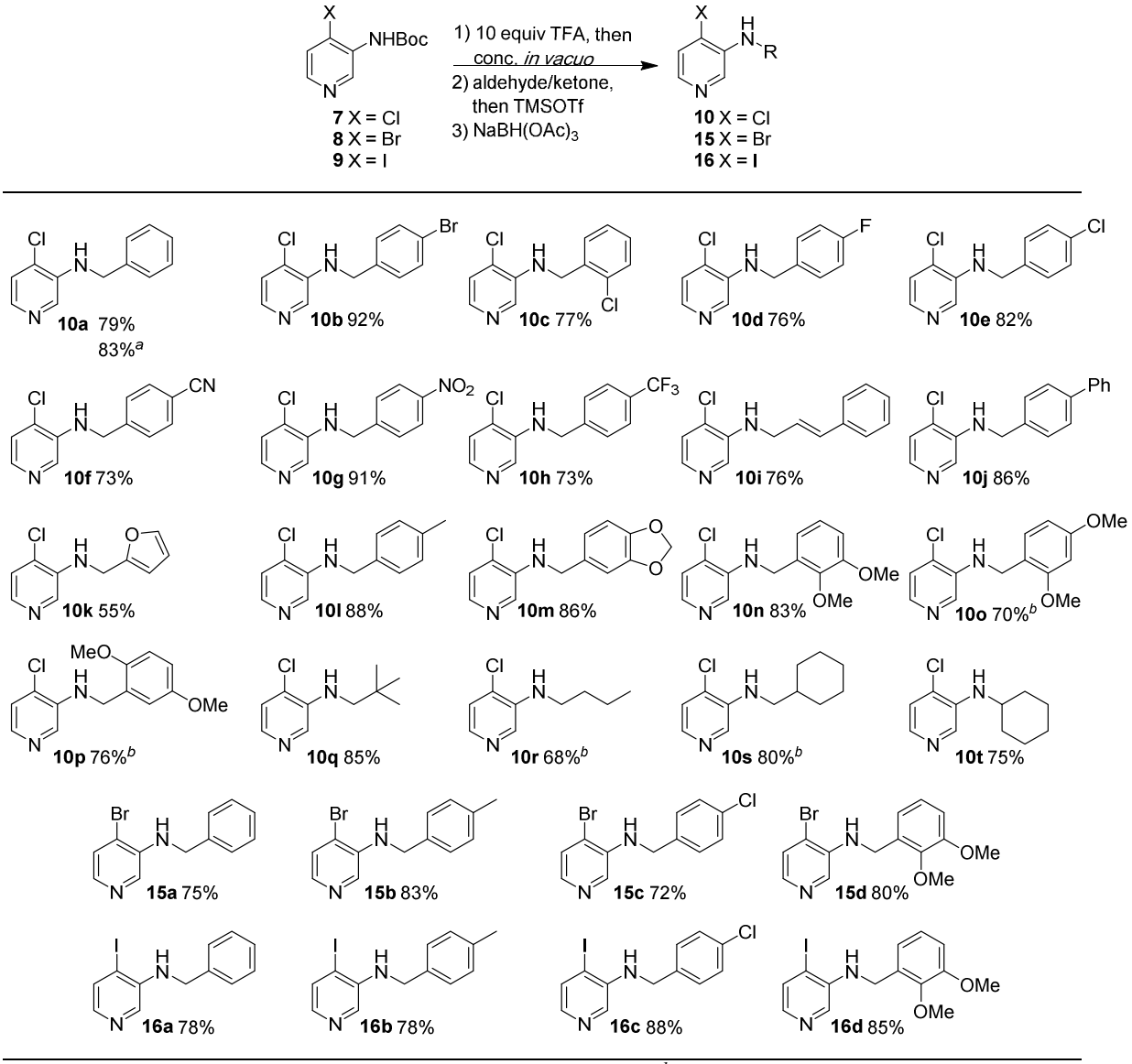
Attention became focused on the use of Lewis acids for both deprotection and reductive amination. Presumably, a more oxophilic Lewis acid would preferentially activate the carbonyl partner in the presence of the basic pyridine. Several strong Lewis acids that have been reported to both cleave Boc groups[12] and facilitate reductive aminations[13] were screened to mediate conversion of **9** to **10a** (Table 1, entries 5-8). Boc removal was rapid with boron trifluoride diethyl etherate, titanium (IV) chloride, and aluminum trichloride, being complete in minutes. However, these Lewis acids were ineffective at mediating the reductive amination. Instead, competitive reduction of the aldehyde occurred with benzyl alcohol being observed by TLC and crude ^{1}H NMR. Interestingly, an ethylated byproduct **13** was observed in some cases, evidently resulting from reaction with decomposing sodium triacetoxyborohydride.[10b,11b,13d]

Further screening revealed that TMSOTf demonstrated promising reactivity (Table 1, entry 8) in the reductive amination, providing 53% yield of **10a**. Presumably TMSOTf facilitates condensation of the amine and the carbonyl partner while minimizing the reversibility of imine formation (a similar argument has been adopted when TMSOAc was employed in reductive amination[10d]). An even better result was obtained when the pyridinium trifluoroacetate was used as the starting material, with a 90% yield of **10a** being observed. Experiments employing TfOH (Table 1, entry 11) provided a lower yield than with TMSOTf (Table 1, entry 10), likely because the water generated by imine formation is not effectively scavenged. Excess of both TMSOTf and the aldehyde was required to prevent competitive ethylation (Table 1, entry 11).

Under the optimized conditions a 79% isolated yield with the benzyl substituted amine **10a** (Table 2) was achieved. A large scale reaction using this substrate was performed on a 15 mmol scale, which provided an 83% isolated yield of pyridine **10a** without column chromatography. This protocol demonstrated excellent substrate tolerance. High yields were obtained with halo-substituted aryl aldehydes (Table 2, **10b-e**) and with electron-deficient aldehydes (Table 2 **10f-h**). Cinnamyl substrate **10i** was isolated with a 76% yield and the *trans*-olefin was maintained during the reduction. Biphenyl functionality was introduced with an 86% isolated yield of **10j**. Numerous electron rich carbonyl substrates (Table 2, **10k-t**) were also evaluated with good results. The furfuryl substrate, **10k**, showed tolerance of acidic reaction conditions and acidic purification conditions (55% isolated yield). *p*-Tolyl, piperonyl, and 2,3-dimethoxybenzyl (DMB) substrates (Table 2, **10l-n**) also gave product in excellent yields. Acid labile substrates 2,4- (**10o**) and 2,5-DMB (**10p**),[9b] were obtained without the addition of TMSOTf in a reduced reaction time of 1 hour. The sterically encumbering neopentyl amine, **10q**, was obtained in 85% yield from pivaldehyde. Enolizable aliphatic aldehydes (Table 2, **10r-s**)

also participate and gave good to moderate yields without using TMSOTf. These substrates are often prone to overalkylation[10f] in reductive aminations and require chromatography. Cyclohexanone also performed well under the reaction conditions, providing a 75% yield of cyclohexylamine **10t**. In addition, 4-bromo-3-aminopyridine and 4-iodo-3-aminopyridine gave good yields with a variety of carbonyl substrates under analogous conditions (Table 2, **15a-d** and **16a-d**). Most benzylic amine products are accessed with greater than 95% purity (as determined by ^{1}H NMR) without chromatography.

Table 2. Substrate scope for one-pot Boc-removal/Reductive amination

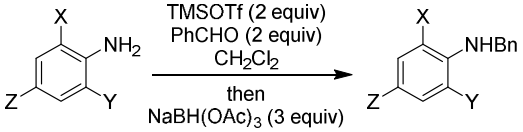


[a]Reaction performed on a 15 mmol scale. [b]No TMSOTf was added.

Given the excellent yields obtained with the 4-halo-3-aminopyridines, the optimized conditions were also evaluated with some aniline substrates that have been reported[10b,13d] to be slow to undergo reductive amination due to electronic and/or steric reasons (Table 3). Tribromoaniline provided the benzylated product **17** in 96% yield under these conditions. Reductive amination of 2,4-dinitroaniline provided 63% yield of **18**, while 2,6-diisopropylaniline

proceeded, yielding 70% of **19**. The excellent yield with these difficult substrates is again attributed to the use of TMSOTf, which facilitates imine formation, removes water, and produces the strong acid TfOH, activating the imine for reduction. TMSOTf has only rarely been utilized in reductive amination reactions,[13d,13e] but these results indicate that this Lewis acid should be investigated in difficult cases where the amine partner is deactivated and/or significantly hindered.

Table 3. Reductive Aminations with Hindered Aniline Substrates



Entry	X	Y	Z	% Yield
1	Br	Br	Br	96 (**17**)
2	NO_2	H	NO_2	63 (**18**)
3	*i*-Pr	*i*-Pr	H	70 (**19**)

In summary, an efficient, general procedure for the reductive amination of 3-amino-4-halo-pyridines is disclosed. A useful single vessel protocol has been devised using *N*-Boc-3-amino-4-halopyridines as the starting materials. Acid-mediated precipitation followed by formation of the free base provided the mono-alkylated amines in high purity. This protocol was used in the efficient synthesis of *N*-alkylated 3-amino-4-halopyridines, and may be of use in similar systems which resist reductive amination under standard conditions.

Experimental Section

General procedure A

To a round bottom flask equipped with a magnetic stir bar and rubber septum, was added, *N*-Boc-3-amino-4-halopyridine (1 equiv) followed by neat TFA (10 equiv.) via syringe.

CAUTION: Vigorous gas evolution and an exothermic reaction occurs. The Boc-removal was monitored by thin layer chromatography (3-amino-4-halopyridines have an R_f = 0.20 in 1:1 ethyl acetate: hexanes). The reaction mixture was concentrated *in vacuo* and the crude oil was dissolved in ethyl acetate and concentrated *in vacuo* three times to yield the solid pyridinium trifluoroacetate salt. DCM (0.5 M) was added to form a slurry to which the carbonyl (2 equiv) and TMSOTf (2 equiv) were added, sequentially. The mixture was stirred for 1 hour at ambient temperature before sodium triacetoxyborohydride (3 equiv) was added as a single portion. The mixture was allowed to stir at rt for 24 hours. The reaction mixture was quenched by the addition of 20 mL of $NaOH_{(aq)}$ (20% w/v) and 20 mL of DCM. The resulting two layers were separated and the aqueous layer was extracted with DCM (3 x 15 mL). The combined organic layers were washed with 30 mL of brine, dried over magnesium sulfate, filtered through a coarse porosity fritted funnel and concentrated *in vacuo*. The crude material was dissolved in 25 mL of diethyl ether and 2 mL of 1M HCl in ether (2 equivalents) was added dropwise to the vigorously stirring ether solution at room temperature. The resulting slurry was allowed to stir for 1 hour in a 0 °C (ice/water) and solvent was removed by needle filtration. The resulting solid was washed with an additional 25 mL of diethyl ether and needle filtered again. The resulting salt was treated with 20 mL of (20% w/v) $NaOH_{(aq)}$ and 20 mL of DCM. The aqueous layer was extracted with 15mL DCM and the combined organic layers were dried over anhydrous magnesium sulfate, filtered through a coarse porosity fritted funnel and concentrated *in vacuo* to yield pure product.

General Procedure B

To a round bottom flask equipped with a magnetic stir bar and rubber septum, was added, *N*-Boc-3-amino-4-halopyridine (1 equiv) then added TFA (10 equiv) via syringe, neat. CAUTION: Vigorous gas evolution and an exothermic reaction occurs. The Boc-removal was monitored by

thin layer chromatography (3-amino-4-halopyridines have an R_f = 0.20 in 1:1 ethyl acetate: hexanes). The reaction mixture was concentrated *in vacuo*. The crude oil was dissolved in ethyl acetate and concentrated *in vacuo* three times to yield the solid pyridinium trifluoroacetate salt. DCM (0.5 M) then the carbonyl (2 equiv) were added to form a slurry mixture. Reaction stirred for 1 hour before adding sodium triacetoxyborohydride (2 equiv). Reduction was allowed to occur for 1 hour. The reaction was quenched and collected with (20% w/v) $NaOH_{(aq)}$ and DCM. The resulting two layers were separated and the aqueous layer was extracted with DCM (3 x 15 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered through a coarse porosity fritted funnel and concentrated *in vacuo*.

General Procedure C

To a round bottom flask equipped with a magnetic stir bar and rubber septum, was added, *N*-Boc-3-amino-4-halopyridine (1 equiv) then added TFA (10 equiv) via syringe, neat. CAUTION: Vigorous gas evolution and an exothermic reaction occurs. The Boc-removal was monitored by thin layer chromatography (3-amino-4-halopyridines have an R_f = 0.20 in 1:1 ethyl acetate: hexanes). The reaction mixture was concentrated *in vacuo*. The crude oil is dissolved in ethyl acetate and concentrated *in vacuo* three times to yield the solid pyridinium trifluoroacetate salt. DCM (0.5 M) then the carbonyl (1.1 equiv) were added to form a slurry mixture. Reaction was stirred for 1 hour before adding sodium triacetoxyborohydride (3 equiv). Reduction was allowed to occur for 24 hours. The reaction was quenched and collected with 20% (w/v) NaOH aqueous solution and DCM. The resulting two layers were separated and the aqueous layer was extracted three times with DCM (3 x 15 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered through a coarse porosity fritted funnel and concentrated *in vacuo*. The crude mixture was dissolved in 25 mL of diethyl ether. 2 mL of 1M ethereal

hydrogen chloride (2 equivalents) was added dropwise to the vigorously stirring ether solution at room temperature. The resulting slurry was allowed to stir for 1 hour in a 0 °C ice-water bath. Slurry was removed from ice bath and stirring, and was subject to needle filtration. The resulting solid was treated with an additional 25 mL of diethyl ether and needle filtered again. The resulting wash was discarded and the pyridinium salt was collected with 20 mL (20% w/v) $NaOH_{(aq)}$ and 20 mL DCM. The aqueous layer was extracted once more with 15 mL DCM. The combined organics were dried over anhydrous magnesium sulfate, filtered through a coarse porosity fritted funnel and concentrated *in vacuo*.

General Procedure for directed metalation

A flame-dried 3 neck round bottom flask equipped with a magnetic stir bar, addition funnel, immersion thermometer, and septum was charged with *N*-Boc-3-aminopyridine and 1,2 dimethoxyethane (~0.3 M). The reaction mixture was cooled to -78 °C (dry ice/acetone) and *n*-BuLi (2.4 eq, hexanes solution) was added dropwise to yield an opaque mixture that was allowed to warm to -20 °C and stir for 2 hours. The reaction mixture was again cooled to -78 °C and a solution of electrophilic halogen source (1.5 eq) in 1,2 dimethoxyethane (~1.6 M) was added dropwise. The resulting solution was allowed to warm to room temperature with removal of cooling bath and stir overnight. The reaction was quenched by the addition of saturated ammonium chloride and the layers were separated. The aqueous layer was extracted 3 times with methyl *tert*-butyl ether. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered through a coarse porosity fritted filter, and then concentrated *in vacuo*. The crude material was adsorbed onto silica gel and loaded directly onto silica gel column, eluting with 30% ethyl acetate: hexanes.

***N*-Boc-3-Aminopyridine (6).** A 250 mL, 3-neck round bottom flask equipped with 100 mL addition funnel and magnetic stir bar was charged with 3-aminopyridine (20 g, 213 mmol), isopropanol (60 mL), and water (23 mL), and the mixture was cooled to 0 °C in an ice-water bath. The addition funnel was charged with a solution of di-*tert*-butyl dicarbonate (53 g, 244 mmol) in isopropanol (30 mL). Gas evolution occurred during the dropwise addition. Upon completion of the dropwise addition, the reaction was removed from ice bath, allowed to warm to room temperature and stirred overnight. Reaction was concentrated *in vacuo* and the resulting thick oil was dissolved in methyl *tert*-butyl ether. The resulting two layers were separated with a separatory funnel. The aqueous layer was extracted with methyl *tert*-butyl ether three times. The collected organic was washed with brine, dried over anhydrous magnesium sulfate, filtered through a coarse porosity fritted filter, then concentrated *in vacuo* to yield 35.5 grams of white solid (86%): Compared to literature data[14] mp 115-117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 2.4 Hz, 1H), 8.28 (dd, J = 4.7, 1.4 Hz, 1H), 7.97 (d, J = 7.0 Hz, 1H), 7.24 (dd, J = 8.4, 4.7 Hz, 1H), 6.57 (bs, 1H), 1.53 (s, 9H).

***N*-Boc-3-Amino-4-chloropyridine (7).** Following the general procedure for directed metalation using hexachloroethane as the electrophile on a 100 mmol (19.43 gram) scale, a yield of 14.55 grams of an pale yellow solid was obtained (64%): mp:105-106 °C; R_f 0.52 (1:1 ethyl acetate:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 8.20 (d, J = 5.2 Hz, 1H), 7.29 (d, J = 5.2, 1H), 6.83 (bs, 1H), 1.55 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 144.2, 142.2, 132.7, 131.1, 123.8, 82.1, 28.4. IR (KBr pellet) ν = 3224, 3135, 2973, 1725, 1573, 1085 cm^{-1}; Anal. Calcd for $C_{10}H_{13}ClN_2O_2$: C, 52.52; H, 5.73; N, 12.25; Found: C, 52.45; H, 5.47; N, 12.32.

***N*-Boc-3-Amino-4-bromopyridine (8).** Following the general procedure for directed metalation using 1,2-dibromoethane as the electrophile on a 60 mmol (11.66 gram) scale, a yield of 8.63

grams of a white solid was obtained (53%): mp 108-109 °C; R_f 0.41 (1:1 ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (s, 1H), 8.10 (d, J =5.2 Hz, 1H), 7.45 (d, J =5.2 Hz, 1H), 6.83 (bs, 1H), 1.54 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 144.3, 142.3, 133.9, 127.1, 122.2, 82.1, 28.4; IR (KBr pellet) 3228, 3125, 1974, 1727, 1568, 1456, 1164 cm^{-1}; Anal. Calcd for $C_{10}H_{13}BrN_2O_2$: C, 43.97; H, 4.80; N, 10.26. Found: C, 43.78; H, 4.81; N, 10.00.

***N*-Boc-3-Amino-4-iodopyridine (9).** Following the general procedure for directed metalation using iodine as the electrophile on a 60 mmol (11.66 gram) scale, a yield of 10.23 grams of a pale yellow solid was obtained (53%): mp: 87-88 °C; R_f 0.41 (1:1 ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (s, 1H), 7.91 (d, J =5.1 Hz, 1H), 7.69 (d, J =5.1 Hz, 1H), 6.66 (bs, 1H), 1.55 (s, 9H); **^{13}**C NMR (100 MHz, $CDCl_3$) δ 152.2, 144.6, 142.1, 136.6, 133.7, 99.7, 82.0, 28.4; IR (KBr pellet) 3381, 3068, 2980, 1726, 1561, 1509, 1250 cm^{-1}; Anal. Calcd for $C_{10}H_{13}N_2IO_2$: C, 37.52; H, 4.09; N, 8.75. Found: C, 37.78; H, 4.05; N, 8.74;

3-Amino-4-chloropyridinium trifluoroacetate (11). A 25 mL round bottom flask and magnetic stir bar was charged with *N*-Boc-3-amino-4-chloropyridine (228mg, 1.0 mmol) and TFA (741 μL, 10 mmol). Upon completion of the Boc-removal, the yellow solution was concentrated *in vacuo* to yield 231 mg of a pale yellow solid (95%): mp 134-135 °C; R_f 0.12 (50% ethyl acetate : hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.91 (d, J = 5.8 Hz, 1H), 7.58 (d, J = 5.84 Hz, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ 159.2 (q, $J_{C\text{-}F}$ = 34.1 Hz), 144.2, 131.0, 130.4, 129.7, 126.6, 116.6 (q, $J_{C\text{-}F}$ = 293.4 Hz); ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -76.2; IR (KBr, pellet) 3375, 3196, 3044, 2644, 2112, 1675, 1560, 1489, 1206; Anal. Calcd for $C_7H_6ClF_3N_2O_2$: C, 34.66; H, 2.49; N, 11.55. Found: C, 34.63; H, 2.65; N, 11.51.

***N*-(Ethyl)-3-amino-4-chloropyridine (13).** To a 100 mL flame-dried round-bottom flask equipped with a magnetic stir was charged with *N*-Boc-3-amino-4-chloropyridine (1.14 grams, 5

mmol) and DMF (0.5M). The resulting mixture was cooled to 0 °C (ice-water) and sodium hydride (60% by wt, 300 mg, 7.5 mmol) was added (CAUTION: gas evolution). After 1 hour, bromoethane (0.56 mL, 7.5 mmol) was added dropwise via syringe at 0 °C. After addition was complete the cooling bath was removed and the reaction mixture was allowed to warm to room temperature. After 30 minutes at room temperature the reaction mixture was quenched with 10 mL water. The resulting layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 15 ml). The organic layers were collected, washed with 30 mL brine, dried over anhydrous magnesium sulfate, filtered through a coarse porosity fritted funnel and concentrated *in vacuo* to yield a yellow oil. The crude mixture was diluted in 10 mL DCM and 3.5 mL of TFA was added dropwise via syringe. The reaction was monitored by TLC and upon completion the reaction was quenched with water and (20% w/v) $NaOH_{(aq)}$ was added until the aqueous layer was pH 8. The aqueous layer was extracted with DCM (3 x 15 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered through a coarse porosity fritted funnel, and concentrated *in vacuo*. The crude material was subjected to flash column chromatography (2.5cm x 15cm) eluted with 1L 10% ethyl acetate: hexanes solution to yield 224 mg of white solid (29%). mp 26-27 °C; R_f = 0.4 (1:1 ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.87 (d, J = 4.8 Hz, 1H), 7.17 (d, J = 5.2 Hz, 1H), 4.09 (s, 1H), 3.29-3.26 (m, 2H), 1.34 (t, J = 14.4 Hz, 3H) ^{13}C NMR δ (100 MHz, $CDCl_3$) δ 140.6, 138.4, 133.4, 127.3, 123.7, 38.0, 14.7; IR (KBr, pellet) 3410, 2969, 1579, 1507, 1414, 1325 cm^{-1}; Anal. Calcd for $C_7H_9ClN_2$: C, 53.68; H, 5.79; N, 17.89. Found: C, 53.72; 5.74; N, 17.88.

***N*-(Benzyl)-3-amino-4-chloropyridine (10a).** Following general procedure A: 193 mg of pale yellow solid containing 5% of pyridine **A** was collected. **10a** could be further purified via flash

column chromatography, eluting with 3% ethyl acetate: 3% triethylamine: 3% benzene: 91% hexanes to yield 173 mg of pale yellow crystalline solid (79%). mp 100-103 °C; R_f 0.42 (50% ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.90 (d, J = 5.1 Hz, 1H), 7.38 - 7.29 (m, 5H), 7.20 (d, J = 5.1 Hz, 1H), 4.62 (bs, 1H), 4.46 (d, J = 5.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 138.9, 137.9, 133.8, 128.9, 127.7, 127.6, 127.4, 123.8, 47.7; IR (KBr, pellet) 3428, 1636, 1579, 1259; Anal. Calcd for $C_{12}H_{11}ClN_2$: C, 65.91; H, 5.07; N, 12.81. Found. C, 65.79; H, 5.08; N, 12.80.

In addition, a 15 mmol scale reaction for **10a** was performed following general procedure A: Following the work-up and purification via general procedure A: product was recrystallized in 10% methanol: hexanes solution to yield 2.73 g of pale yellow solid (83%).

Following the Boc-removal protocol to yield 3-aminopyridinium trifluoroacetate, the salt was recrystallized using ethyl acetate and subject to conditions following general procedure A: pyridinium salt (121 mg, 0.5 mmol), DCM (0.5 M), benzaldehyde (102 μL, 1 mmol), then TMSOTf (181 μL, 1 mmol) were combined in a 25 mL round-bottom flask, equipped with stir bar and rubber septum, and allowed to stir for 1 hr at rt. Sodium triacetoxyborohydride (318 mg, 1.5 mmol) was added in one portion and allowed to stir for 24 hr. Following the work-up and purification via general procedure A, 90 mg of white solid was obtained (83%).

***N*-(4-Bromobenzyl)-3-amino-4-chloropyridine (10b).** Following general procedure A: 273 mg of pale orange crystalline solid was obtained (92%): mp 104-105 °C; R_f 0.65 (50% ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.91 (d, J = 4.8 Hz, 1H), 7.50-7.47 (m, 2H), 7.23-7.19 (m, 2H), 7.20 (d, J = 5.1 Hz, 1H), 4.63 (bs, 1H), 4.43 (d, J = 5.8 Hz, 2H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 140.2, 139.4, 137.0, 133.9, 132.2, 129.1, 127.9, 124.0, 121.7, 47.2; IR (KBr, pellet) 3244, 1577, 1512, 1407, 1329, 1234, 1073 cm^{-1}; Anal. Calcd for $C_{12}H_{10}BrClN_2$: C, 48.43; H, 3.39; N, 9.41. Found. C, 48.43; H, 3.49; N, 9.58.

***N*-(2-Chlorobenzyl)-3-amino-4-chloropyridine (10c).** Following general procedure A: **10c** was further purified via flash column chromatography eluted with 3% ethyl acetate: 3% triethylamine: 3% benzene: 91% hexanes afforded 196 mg of pale yellow crystalline solid (77%): mp 81-83 °C; R_f 0.47 (50% ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.93 (d, J = 5.1 Hz, 1H), 7.46-7.38 (m, 2H), 7.30-7.27 (m, 2H), 7.23 (d, J = 5.1 Hz, 1H), 4.79 (bs, 1H), 4.61 (d, J = 6.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 139.3, 135.2, 134.0, 133.6, 130.0, 129.1, 129.0, 127.9, 127.3, 124.0, 45.5; IR (KBr, pellet) 3245, 3068, 2955, 1583, 1558, 1509, 1417, 1330, 1259, 1069 cm^{-1}; Anal. Calcd for $C_{12}H_{10}Cl_2N_2$: C, 56.94; H, 3.98; N, 11.07. Found. C, 56.91; H, 3.98; N, 11.09.

***N*-(4-Fluorobenzyl)-3-amino-4-chloropyridine (10d).** Following general procedure A: **10d** was recrystallized in 30:1 hexanes: ethyl acetate afforded 180 mg of slight yellow crystalline solid (76%): mp 80-83 °C; R_f 0.37 (50% ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.90 (d, J = 5.1 Hz, 1H), 7.35-7.31 (m, 2H), 7.20 (d, J = 5.1 Hz, 1H), 7.07-7.03 (m, 2H), 4.60 (bs, 1H), 4.43 (d, J = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5 (d, $J_{C\text{-}F}$= 244.8 Hz), 140.2, 139.2, 133.9, 133.7 (d, $J_{C\text{-}F}$= 3.2 Hz), 129.1 (d, $J_{C\text{-}F}$= 8.0 Hz), 127.8, 123.9, 115.9 (d, $J_{C\text{-}F}$= 21.6 Hz), 47.2; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -115.3; IR (KBr, pellet) 3321, 3054, 2913, 1579, 1506, 1325, 1228, 1070 cm^{-1}; Anal. Calcd for $C_{12}H_{10}ClFN_2$: C, 60.90; H, 4.26; N, 11.84. Found. C, 60.92; H, 4.31; N, 11.87.

***N*-(4-Chlorobenzyl)-3-amino-4-chloropyridine (10e)**. Following general procedure A: **10e** was further purified via flash column chromatography eluted with 3% acetone: 3% triethylamine: 3%

benzene: 91% hexanes afforded 208 mg of slight orange crystalline solid (82%): mp 93-95 °C; R_f 0.50 (50% ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.90 (d, J = 5.1 Hz, 1H), 7.35-7.30 (m, 4H), 7.20 (d, J = 5.1 Hz, 1H), 4.63 (bs, 1H), 4.44 (d, J = 5.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 139.3, 136.5, 133.9, 133.6, 129.2, 128.7, 127.9, 124.0, 47.2; IR (KBr, pellet) 3436, 3235, 2847, 1578, 1513, 1489, 1416, 1330, 1089 cm^{-1}; Anal. Calcd for $C_{12}H_{10}Cl_2N_2$: C, 56.94; H, 3.98; N, 11.07. Found: C, 57.08; H, 4.03; N, 10.75.

***N*-(4-Cyanobenzyl)-3-amino-4-chloropyridine (10f).** Following general procedure A: **10f** was further purified via flash column chromatography eluted with 3% ethyl acetate: 3% triethylamine: 3% benzene: 91% hexanes, then recrystallized in hexanes to afford 178 mg of pale yellow crystalline solid (73%): mp 107-108 °C; R_f 0.20 (50% ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.87 (m, 2H), 7.65 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 5.0 Hz, 1H), 4.79 (bs, 1H), 4.56 (d, J = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 139.7, 133.8, 132.8, 128.1, 127.7, 124.1 (2 overlapping), 118.7, 111.8, 47.3; IR (KBr, pellet) 3236, 3055, 2226, 1577, 1508, 1327, 1239, 1069, 823, 692, 556 cm^{-1}; Anal. Calcd for $C_{13}H_{10}ClN_3$: C, 64.07; H, 4.14; N, 17.24. Found. C, 64.07; H, 4.16; N, 17.43.

***N*-(4-Nitrobenzyl)-3-amino-4-chloropyridine (10g).** Following general procedure A: **10g** was further purified via silica plug eluted with 50% ethyl acetate: hexanes afforded 240 mg of green solid (91%): mp 118-119 °C; R_f 0.28 (50% ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24-8.21 (m, 2H), 7.93 (d, J = 5.1 Hz, 1H), 7.88 (s, 1H), 7.54-7.52 (m, 2H), 7.23 (d, J = 5.1 Hz, 1H), 4.81 (bs, 1H), 4.61 (d, J = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 145.7, 139.9, 139.8, 133.7, 128.2, 127.8, 124.3, 124.1, 47.2; IR (KBr, pellet) 3221, 3071, 2925, 1579, 1516, 1345, 1069 cm^{-1}; Anal. Calcd for $C_{12}H_{10}ClN_3O_2$: C, 54.66; H, 3.82; N, 15.94. Found. C, 54.63; H, 3.84; N, 16.14.

***N*-(4-(Trifluoromethyl)benzyl)-3-amino-4-chloropyridine (10h).** Following general procedure A: **10h** was further purified via flash column chromatography eluted with a gradient elution of 10% to 30% ethyl acetate: hexanes, affording 209 mg of white crystalline solid (73%): mp 94-96 °C; R_f 0.31 (50% ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.91 (d, J = 5.1 Hz, 1H), 7.61 (d, J = 8.1 Hz, 2H), 7.48 (d, J = 8.1 Hz, 2H), 7.21 (d, J = 5.1 Hz, 1H), 4.73 (bs, 1H), 4.55 (d, J = 5.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 142.2 (q, J_{C-F} = 1.4 Hz), 140.0, 139.5, 133.9, 130.2 (q, J_{C-F} = 32.3 Hz), 128.0, 127.5, 126.0 (q, J_{C-F}= 3.8 Hz), 124.2 (q, J_{C-F} = 270.4 Hz), 124.0, 47.3; ^{19}F NMR (376.5 MHz, $CDCl_3$) δ -63.1; IR (KBr, pellet) 3272, 3054, 2942, 1619, 1582, 1507, 1414 cm^{-1}; Anal. Calcd for $C_{13}H_{10}ClF_3N_2$: C, 54.47; H, 3.52; N, 9.77. Found. C, 54.23; H, 3.49; N, 9.90.

***N*-Cinnamyl-3-amino-4-chloropyridine (10i).** Following general procedure A: **10i** was further purified via flash column chromatography eluted with 3% ethyl acetate: 3% triethylamine: 3% benzene: 91% hexanes afforded 185 mg of white solid (76%): mp 65-67 °C; R_f 0.28 (50% ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.91 (d, J =5.1 Hz, 1H), 7.39-7.36 (m, 2H), 7.34-7.30 (m, 2H), 7.27-7.23 (m, 1H), 7.20 (d, J =5.1 Hz, 1H), 6.66 (d, J =15.9 Hz, 1H), 6.31 (dt, J =15.9, 5.8 Hz, 1H), 4.44 (bs, 1H), 4.08 (td, J =5.8, 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.4, 139.0, 136.6, 134.0, 132.7, 128.8, 128.0, 127.8, 126.6, 125.5, 123.9, 45.7; IR (KBr, pellet) 3274, 3055, 3020, 2936, 1576, 1552, 1071 cm^{-1}; Anal. Calcd for $C_{14}H_{13}ClN_2$: C, 68.71; H, 5.35; N, 11.45. Found: C, 68.75; H, 5.41; N, 11.46.

***N*-(4-Phenylbenzyl)-3-amino-4-chloropyridine (10j).** Following general procedure A: **10j** was further purified via flash column chromatography eluted with 3% ethyl acetate: 3% triethylamine: 3% benzene: 91% hexanes afforded 220 mg of off-white crystalline solid (87%): mp 98-100 °C; R_f 0.53 (50% ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H),

7.91 (d, *J* = 5.1 Hz, 1H), 7.60-7.57 (m, 4H), 7.47-7.43 (m, 4H), 7.38-7.33 (m, 1H), 7.21 (d, *J* = 5.1 Hz, 1H), 4.66 (bs, 1H), 4.43 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 140.7, 140.3, 139.9 136.9, 133.8, 128.8, 128.0, 127.8, 127.6, 127.4, 127.1, 123.8, 47.4; IR (KBr, pellet) 3270, 1581, 1514, 1487, 1418, 1259 cm^{-1}; Anal. Calcd for $C_{18}H_{15}ClN_2$: C, 73.34; H, 5.13; N, 9.50. Found: C, 73.45; H, 5.15; N, 9.83.

***N*-(Furfuryl)-3-amino-4-chloropyridine (10k).** Following general procedure A: **10k** was further purified via flash column chromatography eluted with 1% ethyl acetate: 1% triethylamine: 1% benzene: 97% hexanes then crystallized in of hexanes to afford 114 mg of off white solid (55%): mp 59-61 °C; R_f 0.47 (50% ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.92 (d, *J* = 5.1 Hz, 1H), 7.39 (dd, *J* = 1.8 Hz, 0.8 Hz, 1H), 7.19 (d, *J* = 5.1 Hz, 1H), 6.34 (dd, *J* = 3.2 Hz, 1.8 Hz, 1H), 6.29 (dd, *J* = 3.2 Hz, 0.8 Hz, 1H), 4.60 (bs, 1H), 4.45 (d, *J* = 5.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 142.6, 140.1, 139.4, 134.0, 128.1, 124.0, 110.6, 107.9, 40.9; IR (KBr, pellet) 3431, 3199, 3075, 3014, 2953, 1581, 1556, 1517, 1438 cm^{-1}; Anal. Calcd for $C_{10}H_9ClN_2O$: C, 57.57; H, 4.35; N, 13.43. Found: C, 57.51; H, 4.35; N, 13.68.

***N*-(4-Methylbenzyl)-3-amino-4-chloropyridine (10l).** Following general procedure A: 204 mg of **10l** was obtained as a pale orange crystalline solid (88%): mp 80-82 °C; R_f 0.50 (50% ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.88 (d, *J* = 5.1 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.20-7.16 (m, 3H), 4.57 (bs, 1H), 4.41 (d, *J* = 5.6 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.5, 138.9, 137.6, 134.9, 133.9, 129.7, 127.7, 127.5, 123.9, 47.6, 21.2; IR (KBr, pellet) 3238, 3079, 3018, 2930, 2850, 1577, 1512, 1415, 1332, 1262 cm^{-1}; Anal. Calcd for $C_{13}H_{13}ClN_2$: C, 67.10; H, 5.63; N, 12.04. Found: C, 67.21; H, 5.61; N, 12.19.

***N*-(Piperonyl)-3-amino-4-chloropyridine (10m).** Following general procedure A: **10m** was purified via flash column chromatography eluted with 3% ethyl acetate: 3% triethylamine: 3% benzene: 91% hexanes to afford 224 mg of white crystalline solid (86%): mp 88-92 °C; R_f 0.52 (50% ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.89 (d, J = 5.1 Hz, 1H), 7.19 (d, J = 5.1 Hz, 1H), 6.87-6.77 (m, 3H), 5.96 (d, J = 1.7 Hz, 2H), 4.57 (bs, 1H), 4.36 (d, J = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 147.3, 140.3, 139.1, 134.0, 131.8, 127.8, 123.9, 120.8, 108.7, 108.0, 101.3, 47.7; IR (KBr, pellet) 3412, 2901, 1578, 1501, 1416, 1245 cm^{-1}; Anal. Calcd for $C_{13}H_{11}ClN_2O_2$: C, 59.44; H, 4.22; N, 10.66. Found. C, 59.36; H, 4.25; N, 10.65.

***N*-(2,3-Dimethoxybenzyl)-3-amino-4-chloropyridine (10n).** Following general procedure A: **10n** was further purified via flash column chromatography eluted with 10% ethyl acetate: hexanes, then 20% ethyl acetate: hexanes to afford 232 mg of pale yellow crystalline solid (83%): mp 76-79 °C; R_f 0.44 (50% ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.88 (d, J = 5.1 Hz, 1H), 7.17 (d, J = 5.1 Hz, 1H), 7.03 (t, J = 7.9 Hz, 1H), 6.91 (dd, J = 7.7 Hz, 1.5 Hz, 1H), 6.88 (dd, J = 8.1 Hz, 1.5 Hz, 1H), 4.67 (bs, 1H), 4.47 (d, J = 6.0 Hz, 2H), 3.90 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 147.4, 140.5, 138.8, 134.0, 131.6, 127.8, 124.4, 123.9, 120.8, 112.3, 61.0, 55.9, 43.0; IR (KBr, pellet) 3387, 2997, 2964, 2933, 2831, 1582, 1510, 1480, 1449, 1418 cm^{-1}; Anal. Calcd for $C_{14}H_{15}ClN_2O_2$: C, 60.33; H, 5.42; N, 10.05. Found. C, 60.10; H, 5.59; N, 9.90.

***N*-(2,4-Dimethoxybenzyl)-3-amino-4-chloropyridine (10o).** Following general procedure B: **10o** was further purified via flash column chromatography eluted with 10% ethyl acetate: hexanes to afford 97 mg of slight yellow crystalline solid (70%): mp 70-71 °C; R_f 0.37 (50% ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.85 (d, J = 5.1 Hz, 1H),

7.18 (d, *J* = 8.9 Hz, 1H), 7.15 (d, *J* = 5.1 Hz, 1H), 6.48 (d, *J* = 2.3 Hz, 1H), 6.44 (dd, *J* = 8.2 Hz, 2.4 Hz, 1H), 4.67 (brth, *J* = 5.4 Hz, 1H), 4.38 (d, *J* = 6.1 Hz, 2H), 3.85 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 158.7, 140.8, 138.6, 134.3, 129.9, 127.8, 123.8, 118.5, 104.2, 98.9, 55.5, 55.5, 42.9; IR (KBr, pellet) 3246, 1620, 1582, 1510, 1209 cm^{-1}; Anal. Calcd for $C_{14}H_{15}ClN_2O_2$: C, 60.33; H, 5.42; N, 10.05. Found: C, 59.99; H, 5.52; N, 9.97.

***N*-(2,5-Dimethoxybenzyl)-3-amino-4-chloropyridine (10p).** Following general procedure B: **10p** was further purified via flash column chromatography eluted with 10% ethyl acetate: hexanes to afford 106 mg of slight yellow crystalline solid (76%): mp 70-71 °C; R_f 0.37 (50% ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.86 (d, *J* = 5.1 Hz, 1H), 7.16 (d, *J* = 5.1 Hz, 1H), 6.86 (d, *J* = 2.8 Hz, 1H), 6.83 (d, *J* = 8.8 Hz, 1H), 6.77 (dd, *J* = 8.8 Hz, 3.0 Hz, 1H), 4.76-4.73 (m, 1H), 4.43 (d, *J* = 6.2 Hz, 2H), 3.84 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 151.6, 140.5, 138.7, 134.1, 127.7, 127.1, 123.7, 115.3, 112.6, 111.3, 55.8, 55.7, 43.0; IR (KBr, pellet) 3278, 3063, 2997, 2956, 2836, 1577, 1501, 1417, 1270, 1235 cm^{-1}; Anal. Calcd for $C_{14}H_{15}ClN_2O_2$: C, 60.33; H, 5.42; N, 10.05. Found. C, 60.28; H, 5.42; N, 9.95.

***N*-(2,2-Dimethylpropyl)-3-amino-4-chloropyridine (10q).** Following general procedure A: **10q** was further purified via flash column chromatography eluted with 1% ethyl acetate: 1% triethylamine: 1% benzene: 97% hexanes to afford 136 mg of pale yellow crystalline solid (68%): mp 35-37 °C; R_f 0.51 (50% ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.84 (d, *J* = 5.1 Hz, 1H), 7.15 (d, *J* = 5.1 Hz, 1H), 4.21 (bs, 1H), 3.01 (d, *J* = 6.0 Hz, 2H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 138.2, 133.6, 127.4, 123.8, 55.2, 32.2, 27.6; IR (KBr, pellet) 3427, 3224, 2961, 2864, 2502, 1580, 1517, 1417 cm^{-1}; Anal. Calcd for $C_{10}H_{15}ClN_2$: C, 60.45; H, 7.61; N, 14.10. Found: C, 60.43; H, 7.50; N, 14.17.

***N*-(*n*-Butyl)-3-amino-4-chloropyridine (10r).** Following general procedure C: **10r** was further purified via flash column chromatography eluted with 1% ethyl acetate: 1% triethylamine: 1% benzene: 97% hexanes to afford 125 mg of off-white crystalline solid (68%): mp 38-39 °C; R_f 0.43 (50% ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.86 (d, J = 4.6 Hz, 1H), 7.16 (d, J = 5.0 Hz, 1H), 4.15 (bs, 1H), 3.25-3.21 (m, 2H), 1.71-1.64 (m, 2H), 1.50-1.41 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 138.2, 133.4, 127.2, 123.7, 43.1, 31.4, 20.2, 13.8; IR (KBr, pellet) 3309, 2953, 2935, 2868, 1580, 1555, 1484, 1410 cm^{-1}; Anal. Calcd for $C_9H_{13}ClN_2$: C, 58.54; H, 7.10; N, 15.17. Found C, 58.54; H, 7.11; N, 15.22.

***N*-(Cyclohexylmethyl)-3-amino-4-chloropyridine (10s).** Following general procedure C: **10s** was further purified via flash column chromatography eluted with 10% ethyl acetate: hexanes to afford 180 mg of slight yellow crystalline solid (80%): mp 67-70 °C; R_f 0.59 (50% ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.83 (d, J = 5.1 Hz, 1H), 7.14 (d, J = 5.1, 1H), 4.25 (brs, 1H), 3.06 (t, J = 6.2 Hz, 2H), 1.86-1.57 (m, 6H), 1.32-1.12 (m, 3H), 1.06-0.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 138.1, 133.5, 127.3, 123.8, 50.0, 37.5, 31.2, 26.6, 26.0; IR (KBr, pellet) 3383, 3054, 2923, 2845, 1577, 1508, 1459 cm^{-1}; Anal. Calcd for $C_{12}H_{17}ClN_2$: C, 64.14; H, 7.63; N, 12.47. Found. C, 64.12; H, 7.54; N, 12.18.

***N*-(Cyclohexyl)-3-amino-4-chloropyridine (10t).** Following general procedure A: **10t** was further purified via flash column chromatography eluted with 3% acetone: 3% triethylamine: 3% benzene: 91% hexanes afforded 79 mg of white crystalline solid (75%): mp 64-65 °C; R_f 0.68 (50% ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.82 (d, J = 5.1 Hz, 1H), 7.15 (d, J = 5.1 Hz, 1H), 4.09 (d, J = 7.1 Hz, 1H), 3.41-3.38 (m, 1H), 2.09-2.05 (m, 2H), 1.81-1.76 (m, 2H), 1.69-1.64 (m, 1H), 1.44-1.37 (m, 2H), 1.31-1.20 (m, 3H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 139.9, 138.0, 134.1, 127.4, 124.1, 51.4, 33.3, 25.9, 24.9; IR (KBr, pellet) 3410, 3051, 2932, 2852, 1578, 1506, 1449, 1414 cm^{-1}; Anal. Calcd for $C_{11}H_{15}ClN_2$: C, 62.70; H, 7.18; N, 13.30. Found. C, 62.84; H, 7.18; N, 13.29.

***N*-(Benzyl)-3-amino-4-bromopyridine (15a).** Following general procedure A: **15a** was further purified via flash column chromatography, eluted with 10% ethyl acetate: 90% hexanes to yield 197 mg of pale purple crystalline solid (75%): mp 102-103 °C; R_f 0.44 (50% ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.79 (d, J =5.1 Hz, 1H), 7.38-3.36 (m, 5H), 7.34-7.28 (m, 1H), 4.65 (bt, 1H), 4.46 (d, J =5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 139.2, 138.0, 133.8, 129.0, 127.9, 127.5, 127.2, 118.6, 48.0; IR (KBr, pellet) 3331, 3051, 2360, 1577, 1508, 1453, 1413, 1256 cm^{-1}; Anal. Calcd for $C_{12}H_{11}BrN_2$: C, 54.77; H, 4.21; N, 10.65; Found: C, 54.79; H, 4.21; N, 10.66.

***N*-(4-Methylbenzyl)-3-amino-4-bromopyridine (15b).** Following general procedure A: **15b** was recrystallized in hexanes to afford 229 mg of pale orange crystalline solid (83%): mp 85-86 °C; R_f 0.44 (50% ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.79 (d, J = 5.0 Hz, 1H), 7.35 (d, J = 5.1 Hz, 1H), 7.26 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 4.60 (bs, 1H), 4.41 (d, J = 5.6 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 139.0, 137.6, 134.9, 133.8, 129.7, 127.5, 127.2, 118.6, 47.7, 21.3; IR (KBr, pellet) 3424, 3250, 3055, 3020, 2935, 2850, 1575, 1550, 1508, 1452, 1412 cm^{-1}; Anal. Calcd for $C_{13}H_{13}BrN_2$: C, 56.34; H, 4.73; N, 10.11. Found: C, 56.40; H, 4.74; N, 10.04.

***N*-(4-Chlorobenzyl)-3-amino-4-bromopyridine (15c).** Following general procedure A: **15c** was further purified via silica plug eluted with 50% ethyl acetate: hexanes, then recrystallized with hexanes afforded 213 mg of an off-white crystalline solid (72%): mp 87-88 °C; R_f 0.40 (50% ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.80 (d, J = 5.1 Hz, 1H),

7.37 (d, *J*=5.1 Hz, 1H), 7.34 (d, *J*=8.7 Hz, 2H), 7.30 (d, *J*=8.7 Hz, 2H), 4.66 (bs, 1H), 4.44 (d, *J* = 5.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 139.4, 136.5, 133.8, 133.6, 129.2, 128.7, 127.3, 118.8, 47.3; IR (KBr, pellet) 3241, 3055, 2934, 2896, 2848, 1574, 1551, 1508, 1488, 1413 cm^{-1}; Anal. Calcd for $C_{12}H_{10}BrClN_2$: C, 48.43; H, 3.39; N, 9.41. Found: C, 48.41; H, 3.43; N, 9.36.

***N*-(2,3-Dimethoxybenzyl)-3-amino-4-bromopyridine (15d).** Following general procedure A: **15d** was further purified via silica plug eluted with 50% ethyl acetate: hexanes, then recrystallized in hexanes to afford 257 mg of pale orange solid (80%): mp 83-85 °C; R_f 0.32 (50% ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.77 (d, *J* = 5.1 Hz, 1H), 7.33 (d, *J* = 5.1 Hz, 1H), 7.03 (t, *J* = 7.9 Hz, 1H), 6.92-6.87 (m, 2H), 4.69 (bs, 1H), 4.48 (d, *J* = 5.9 Hz, 2H), 3.90 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 147.4, 141.6, 138.9, 133.9, 131.6, 127.2, 124.3, 120.8, 118.6, 112.3, 61.0, 56.0, 43.1; IR (KBr, pellet) 3260, 3086, 2955, 2932, 1573, 1544, 1480, 1413, 1274 cm^{-1}; Anal. Calcd for $C_{14}H_{15}BrN_2O_2$: C, 52.03; H, 4.68; N, 8.67. Found: C, 52.14; H, 4.81; N, 8.84.

***N*-(Benzyl)-3-amino-4-iodopyridine (16a).** Following general procedure A: **16a** was further purified via flash column chromatography, eluted with 10% ethyl acetate: 90% hexanes to yield 238 mg of off-white crystalline solid (77%): mp 90-92 °C; R_f 0.44 (50% ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.60 (d, *J*=4.8 Hz, 1H), 7.58 (d, *J*=5.2 Hz, 1H), 7.38-3.36 (m, 4H), 7.34-7.28 (m, 1H), 4.53 (bs, 1H), 4.46 (d, *J* =5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 139.4, 137.9, 133.8, 132.8, 129.0, 127.8, 127.4, 95.1, 48.2; IR (KBr, pellet) 3328, 3061, 3015.6, 2908, 1564, 1540, 1502, 1452, 1409 cm^{-1}; Anal. Calcd for $C_{12}H_{11}IN_2$: C, 46.47; H, 3.58; N, 9.03. Found: C, 46.46; H, 3.61; N, 9.02.

***N*-(4-Methylbenzyl)-3-amino-4-iodopyridine (16b).** Following general procedure A: **16b** was further purified via silica plug eluted with 50% ethyl acetate: hexanes, then recrystallized in hexanes to afford 253 mg of a pale orange crystalline solid (78%): mp 65-66 °C; R_f 0.47 (50% ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.60 (d, *J*=4.8 Hz, 1H), 7.57 (d, *J*=4.8 Hz, 1H), 7.25 (d, *J* = 7.9 Hz, 2H), 7.17 (d, *J* = 7.9 Hz, 2H), 4.46 (bs, 1H), 4.41 (d, *J* = 5.4 Hz, 2H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 139.3, 137.5, 134.9, 133.8, 132.9, 129.7, 127.5, 95.1, 48.1, 21.3; IR (KBr, pellet) 3396, 3034, 2908, 2855, 1564, 1503, 1417 cm^{-1}; Anal. Calcd for $C_{13}H_{13}IN_2$: C, 48.17; H, 4.04; N, 8.64. Found: C, 48.16; H, 3.93; N, 8.53.

***N*-(4-Chlorobenzyl)-3-amino-4-iodopyridine (16c).** Following general procedure A: 303 mg of **16c** was obtained as a white crystalline solid (88%): mp 107-114 °C; R_f 0.40 (50% ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.61 (d, *J*=4.8 Hz, 1H), 7.59 (d, *J*=5.2 Hz, 1H), 7.34 (d, *J*=8.6 Hz, 2H), 7.29 (d, *J*=8.6 Hz, 2H), 4.52 (bs, 1H), 4.44 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 139.7, 136.5, 133.8, 133.6, 132.8, 129.2, 128.7, 95.3, 47.7; IR (KBr, pellet) 3389, 3043, 2929, 2868, 1559, 1497, 1446 cm^{-1}; Anal. Calcd for $C_{12}H_{10}ClIN_2$: C, 41.83; H, 2.93; N, 8.13. Found: C, 41.76; H, 2.98; N, 8.05.

***N*-(2,3-Dimethoxybenzyl)-3-amino-4-iodopyridine (16d).** Following general procedure A: 317 mg of **16d** was obtained as a brown/red solid (85%): mp 118-120 °C; R_f 0.35 (50% ethyl acetate: hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.58 (d, *J*= 5.0 Hz, 1H), 7.56 (d, *J*=5.0 Hz, 1H), 7.03 (t, *J* = 8.0 Hz, 1H), 6.89 (td, *J*=8.9, 1.5 Hz, 2H), 4.57 (bs, 1H), 4.47 (d, *J* = 5.8 Hz, 2H), 3.91 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 147.4, 144.0, 139.2, 133.8, 131.5, 124.3, 120.7, 112.3, 95.1, 61.0, 56.0, 43.5; IR (KBr, pellet) 3413, 3001, 2970, 2935, 2834, 1561, 1479, 1410, 1270 cm^{-1}; Anal. Calcd for $C_{14}H_{15}IN_2O_2$: C, 45.42; H, 4.08; N, 7.57. Found: C, 45.50; H, 4.09; N, 7.55.

***N*-Benzyl-2,4,6-tribromoaniline (17)**: An oven-dried 10 mL round bottom flask with magnetic stir bar was charged with 2,4,6-tribromoaniline (330 mg, 1 mmol), benzaldehyde (0.20 mL, 2 mmol), and CH_2Cl_2 (2 mL, 0.5 M). Trimethylsilyl trifluoromethanesulfonate (0.36 mL, 2 mmol) was added in one portion and the mixture was stirred for 1 hour. To the mixture was added sodium triacetoxyborohydride (636 mg, 3 mmol) and the reaction was stirred 18 hours, before diluting with 10 mL CH_2Cl_2 and quenching with 20 mL of 20% (m/v) $NaOH_{(aq)}$. The aqueous layer was extracted 3 times with 10 mL portions of CH_2Cl_2. The combined organics were dried with $MgSO_4$, filtered and concentrated *in vacuo*. The resulting oil was further purified via flash column chromatography (silica deactivated with a 1% triethylamine : 99% hexanes solution), eluting 402 mg of **17** with hexanes as a clear oil (96%): R_f 0.59 (10% ethyl acetate:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 2H), 7.40-7.27 (m, 5H), 4.41 (s, 2H), 4.15 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2, 139.1, 135.1, 128.8, 128.3, 127.8, 117.7, 114.4, 52.2; IR (NaCl, thin film) ν = 3051, 2983, 1264 cm^{-1}; Anal. Calcd for $C_{13}H_{10}Br_3N$: C, 37.18; H, 2.40; N, 3.34. Found: C, 37.04; H, 2.44; N, 3.30.

***N*-Benzyl-2,4-dinitroaniline (18)**: An oven-dried 10 mL round bottom flask with magnetic stir bar was charged with 2,4-dinitroaniline (183 mg, 1 mmol), benzaldehyde (0.20 mL, 2 mmol), and CH_2Cl_2 (2 mL, 0.5 M). Trimethylsilyl trifluoromethanesulfonate (0.36 mL, 2 mmol) was added in one portion and the mixture was stirred for 1 hour. To the mixture was added sodium triacetoxyborohydride (636 mg, 3 mmol) and the reaction was stirred 18 hours, before diluting with 10 mL CH_2Cl_2 and quenching with 20 mL of 20% (m/v) $NaOH_{(aq)}$. The aqueous layer was extracted 3 times with 10 mL portions of CH_2Cl_2. The combined organics were dried with $MgSO_4$, filtered and concentrated *in vacuo*. The resulting crude solid was triturated with 10 mL

of Et_2O and 171 mg of **18** was collected by filtration as a yellow solid (63%): Compared to literature data[15] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (d, *J* = 2.6 Hz, 1H), 8.91 (bs, 1H), 8.24 (dd, *J* = 9.5, 2.6 Hz, 1H), 7.43-7.33 (m, 5H), 6.91 (d, *J* = 9.5 Hz, 1H), 4.65 (d, *J* = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 136.7, 135.7, 131.0, 130.5, 129.5, 128.5, 127.2, 124.4, 114.5, 47.7.

***N*-Benzyl-2,6-diisopropylaniline (19)**: An oven-dried 10 mL round bottom flask with magnetic stir bar was charged with 2,4-dinitroaniline (183 mg, 1 mmol), benzaldehyde (0.20 mL, 2 mmol), and CH_2Cl_2 (2 mL, 0.5 M). Trimethylsilyl trifluoromethanesulfonate (0.36 mL, 2 mmol) was added in one portion and the mixture was stirred for 1 hour. To the mixture was added sodium triacetoxyborohydride (636 mg, 3 mmol) and the reaction was stirred 18 hours, before diluting with 10 mL CH_2Cl_2 and quenching with 20 mL of 20% (m/v) $NaOH_{(aq)}$. The aqueous layer was extracted 3 times with 10 mL portions of CH_2Cl_2. The combined organics were dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude oil was further purified via flash column chromatography (silica deactivated with a 1% triethylamine : 99% hexanes solution), eluting a mixture of benzyl alcohol: **19**, which was purified further through the acidification/freebase method in General procedure A. This yielded 187 mg of **19** as a clear oil (70%): Compared to literature data[16] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.28 (m, 5H), 7.12 (m, 3H), 4.05 (s, 2H), 3.31 (sept, *J* = 6.2 Hz, 2H), 3.15 (bs, 1H), 1.23 (d, *J* = 6.2 Hz, 12H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 142.9, 140.3, 128.7, 128.1, 127.6, 124.2, 123.8, 56.2, 27.9, 24.4.

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Associated Content

Supporting Information

^{1}H and ^{13}C NMR spectra available for compounds **7**, **8**, **9**, **10a-10t**, **11**, **13**, **15a-15d**, **16a-16d**, **17**, **18** (^{1}H NMR only), and **19** (^{1}H NMR only)

^{19}F NMR spectra available for compounds **10d**, **10h,** and **11**

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