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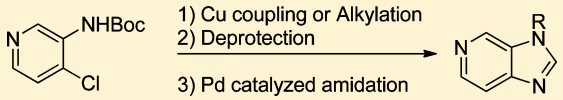
Copper- and Palladium-Catalyzed Amidation Reactions for the Synthesis of Substituted Imidazo[4,5-*c*]pyridines

Robert J. Wilson, Adam J. Rosenberg, Lauren Kaminsky, and Daniel A. Clark*

Department of Chemistry, 1-014 Center for Science and Technology, Syracuse University, Syracuse, New York 13244, United States

Supporting Information

ABSTRACT: Imidazo[4,5-*c*]pyridines were synthesized in three steps utilizing a palladium-catalyzed amidation/cyclization strategy. *N*-Aryl substrates were synthesized using copper-catalyzed amidation of 3-amino-*N*-Boc-4-chloropyridine. Complementary protocols for the selective chlorination of imidazo[4,5-*c*]pyridines at the C2 and C7 positions were also developed.



INTRODUCTION

Imidazopyridines and derivatives thereof comprise an important collection of biologically active molecules. Imidazopyridine structures are present in druglike molecules ageladine A and 3-deazaadenosine (Figure 1)[1] and are recognized by the pharmaceutical industry as valuable bioisosteres.[2] Imidazo[4,5-*c*]pyridines (IP_c) are currently being investigated for the inhibition of hepatitis C virus replication,[3,4] cyclin-dependent kinase inhibitors (i.e., grossularine 1 and 2),[5] and other biologically relevant targets.[6−15]

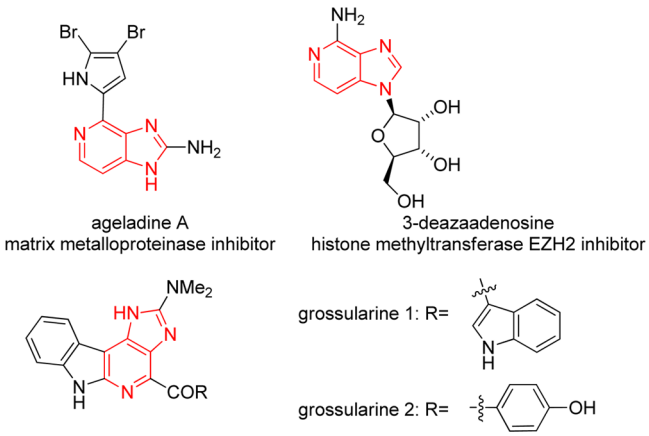


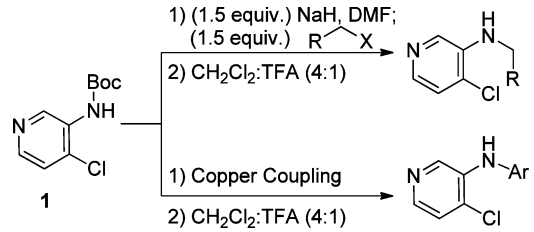
Figure 1. Biologically active compounds containing imidazo[4,5-*c*]pyridine core.

Previously imidazopyridines have been prepared from the appropriately substituted diaminopyridines; however, these compounds can be difficult to obtain in a regiospecific fashion, and mixtures often result.[8] We recently reported a new route to imidazo[4,5-*b*]pyridines (IP_b) utilizing an amide cross-coupling strategy starting from 3-amino-2-chloropyridine.[16] This method allowed for complete control of regioselectivity in the synthesis of N-1 substituted IP_b. Based on the success of this approach, investigations shifted to the 3-amino-4-chloropyridines which may be useful for the synthesis of the corresponding IP_c. This strategy provides access to substituted heterocycles that are problematic to obtain selectively using other methods.[8]

RESULTS AND DISCUSSION

In order to explore a cross-coupling route to these molecules the N-3 nitrogen of 3-amino-4-chloropyridine must first be arylated or alkylated. Alkylation has previously been accomplished with 3-amino-2-chloropyridine by reductive amination,[17] and *N*-aryl moieties were installed by Chan−Lam coupling.[18,19] However, in our hands, use of the corresponding 3-amino-4-chloropyridine provided the desired products in poor yield. Due to these unexpected difficulties, we elected to investigate known 4-chloro-3-*N*-Boc-pyridine (**1**)[20] as an entry into these analogous systems (Scheme 1). Base-mediated alkylation of the carbamate nitrogen provided *N*-alkyl and *N*-benzyl products from the corresponding alkyl or benzyl halides, and removal of the Boc group was accomplished by TFA in DCM.

Scheme 1. Substituted 3-Aminopyridines



Cognizant that installation of *N*-aryl and *N*-heteroaryl functionality by this strategy would not be practical, an alternative approach was sought. Palladium-catalyzed amidation was not explored due to the activated aryl chlorine present in **1**. Multiple unselective coupling events were envisioned, and these competitive couplings would likely limit the substrate scope. Therefore, copper-catalyzed couplings were examined to avoid the aforementioned problems; however, new questions arose

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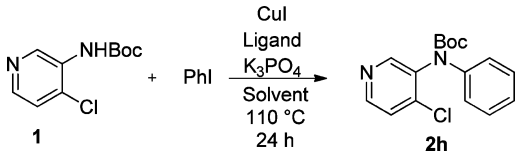
about the ability of **1** to participate in copper-catalyzed amidation. Basic pyridines are known to interfere with amidation reactions, and pyridine itself is occasionally used as a ligand.[21] Undaunted by these precedents, we investigated copper-catalyzed conditions for the desired *N*-aryl products.

Studies commenced with copper(I) iodide and diamine ligands previously used for copper-catalyzed amidation (Table 1).[22−25] None of the desired product (**2h**) was observed using

Table 1. Copper-Catalyzed Amidation Optimization[a]



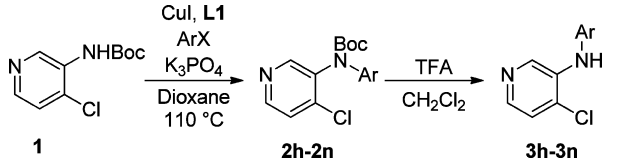
entry	ligand	solvent	conversion[b] (%)	yield[b] (%)
1	DMEDA	DMF	100	0[c]
2	DMEDA	Tol	100	0[c]
3	DMEDA	dioxane	79	43
4	EDA	dioxane	71	59
5	**L1**	Tol	70	65
6	**L1**	**dioxane**	**100**	**96**[d]
7	**L2**	dioxane	72	trace
8[e]	**L1**	dioxane	100	65
9[f]	**L1**	dioxane	77	74
10[g]	**L1**	dioxane	19	19

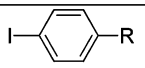
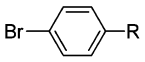
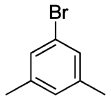
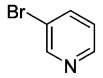
[a]Reaction conditions: 10 mol % of CuI, 20 mol % of ligand, 2 equiv of base, 0.5 M. [b]Using mesitylene as an internal standard. [c]Decomposition of **1** was observed. [d]Isolated yield. [e]20 mol % of CuI, 40 mol % of ligand. [f]Cs_2CO_3 used as the base. [g]K_2CO_3 used as the base. DMEDA = *N*,*N*′-dimethylethylenediamine. EDA = ethylenediamine. **L1** = (±) *trans*-1,2-diaminocyclohexane. **L2** = (±) *N*,*N*′-dimethyl-1,2-diaminocyclohexane.

N,*N*′-dimethylethylenediamine (DMEDA) as a ligand in either DMF or toluene, although 79% conversion and 43% yield of **2h** was obtained in 1,4-dioxane (entries 1−3). Ethylenediamine (EDA), a less encumbered ligand, gave 71% conversion and an increased 59% yield of **2h** (entry 4). The more rigid *trans*-1,2-diaminocyclohexane gave similar results when the reaction was carried out in toluene (entry 5); when 1,4-dioxane was utilized complete conversion and 96% isolated yield of **2h** was obtained (entry 6). The more electron-rich *N*,*N*′-dimethyl analogue **L2** gave moderate conversion (72%) but only a trace of **2h** (entry 7). These results support Buchwald's hypothesis that the coupling of bulky secondary amides is aided by unencumbered diamine ligands.[23,24] Attempts to further improve the coupling and shorten the reaction time by altering the base or increasing the catalyst loading were unsuccessful (entries 8−10).

With optimized copper-amidation conditions elucidated, we explored the substrate scope of the C−N coupling reaction (Table 2). As shown previously, iodobenzene gave 96% yield of **2h**, and Boc deprotection under acidic conditions provided **3h** in 97% yield (entry 1). Analogous conditions with 4-iodotoluene gave **2i** in 76% yield and **3i** in 92% yield (entry 2). Aryl bromides were also effective substrates for the copper amidation conditions. Electron-poor 4′-bromoacetophenone and 4-bromotrifluorotoluene gave **2j** in 90% and **2k** in 79%, respectively (entries 3 and 4). Electron-rich aryl bromides 4-bromoanisole (entry 5) and 3,5-dimethylbromobenzene (entry 6) gave partial conversion for the amidation, and the crude reaction mixtures were deprotected for ease of isolation to give

Table 2. Copper-Catalyzed Amidation Scope[a]



entry	ArX	yield of amidation[b] (%)	yield of deprotection[b] (%)
			
1	R=H	96 (**2h**)	97 (**3h**)
2	R=Me	76 (**2i**)	92 (**3i**)
			
3	R=Acetyl	90 (**2j**)	89 (**3j**)
4	R=CF_3	79 (**2k**)	89 (**3k**)
5	R=OMe	-	47 (**3l**)[c]
6		-	66 (**3m**)[c]
7		88 (**2n**)	89 (**3n**)

[a]Reaction conditions: (1) 1 equiv of **1**, 1.1 equiv of ArX, 10 mol % of CuI, 20 mol % of **L1**, 2 equiv of K_3PO_4, 1,4-dioxane (0.5 M); (2) 25% TFA in CH_2Cl_2. [b]Isolated yield. [c]Yield over two steps.

3l and **3m** in 47% and 66% yield, respectively, over two steps. The use of halopyridines as coupling partners did not adversely affect the amidation or deprotection reactions as 3-bromopyridine gave **2n** in 88% and Boc deprotection afforded **3n** in 89% yield (entry 8).

With the desired N-substituted 3-amino-4-chloropyridine substrates in hand, the palladium-catalyzed formation of the desired IP_c commenced. Substrate **3h** (3-amino-*N*-phenyl-4-chloropyridine) was chosen to evaluate conditions for the synthesis of IP_c (Figure 2, Table 3). The newly developed Me_3(OMe)-*t*-BuXPhos[26] ligand was utilized in place of the Me_4-*t*-BuXPhos or *t*-BuBrettPhos ligands previously employed.[16] This ligand performed well giving the desired IP_c

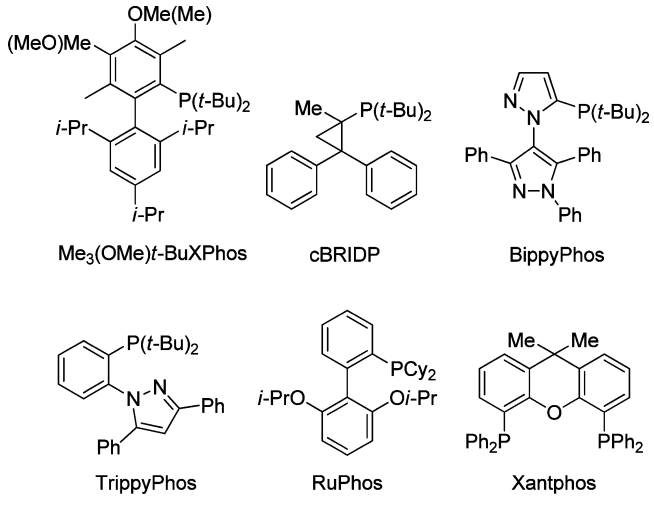


Figure 2. Ligand structures.

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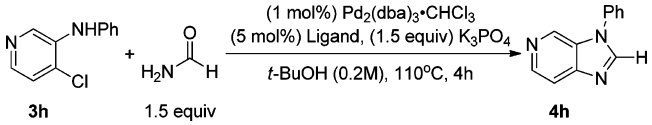
Table 3. Ligand Screen



3h 1.5 equiv 4h

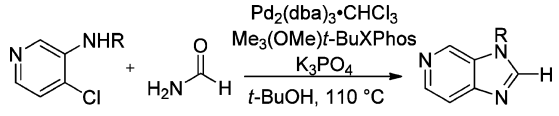
entry	ligand	conversion (%)	yield[a] (%)
1	Me_3(MeO)-*t*-BuXPhos	100	90[b]
2	cBRIDP	100	81
3	BippyPhos	100	87
4	TrippyPhos	10	trace
5	RuPhos	15	0
6	(*t*-Bu_3PH)BF_4	17	0
7	(Cy_3PH)BF_4	18	0
8	XantPhos	17	0

[a]Determined by ^{1}H NMR using mesitylene as an internal standard. [b]Isolated yield.

4h in 90% yield. The cBRIDP[27] ligand developed by Takasago afforded 81% yield, and Singer's BippyPhos[28] gave 87% yield of the desired IP_c **4h**. TrippyPhos[29] furnished only trace amounts of **4h**. No product was observed for other ligands, for example, RuPhos, tri-*tert*-butylphosphine, tricyclohexylphosphine, and XantPhos.

With useful palladium-catalyzed amidation conditions in hand, attention turned to examining the reaction scope. As illustrated in Table 4, benzyl derivitives **3a**–**e** performed well

Table 4. Palladium-Catalyzed Amidation/Cyclization[a]



3a-3n 4a-4n

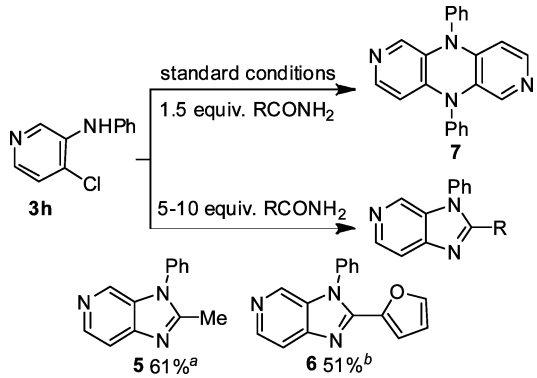
entry	R	yield[b] (%)	product
1	**3a**, $CH_2(C_6H_5)$	84	**4a**
2	**3b**, CH_2(2,5-OMe-C_6H_3)	85	**4b**
3	**3c**, CH_2(3,5-OMe-C_6H_3)	52	**4c**
4	**3d**, CH_2(4-F-C_6H_4)	75	**4d**
5	**3e**, CH_2(4-Ph-C_6H_4)	75	**4e**
6	**3f**, Me	58	**4f**
7	**3g**, *n*-Pr	85	**4g**
8	**3h**, Ph	90	**4h**
9	**3i**, 4-Me-Ph	89	**4i**
10	**3j**, 4-Ac-Ph	87	**4j**
11	**3k**, 4-CF_3-Ph	91	**4k**
12	**3l**, 4-OMe-Ph	80	**4l**
13	**3m**, 3,5-xylyl	90	**4m**
14	**3n**, 3-pyridyl	86	**4n**

[a]Reaction conditions: 1 equiv of **3**, Pd (1 mol %), ligand (5 mol %), 1.5 equiv of formamide, 1.5 equiv of K_3PO_4, 0.2 M *t*-BuOH, 110 °C, 4 h. [b]Isolated yield.

(52–85% yield), with electron-donating, electron-withdrawing, aryl, and fluorine substitution all being tolerated (entries 1–5). Methyl (**3f**) and *n*-propyl (**3g**) substitution gave **4f** in 58% and **4g** in 85% yield, respectively (entries 6 and 7). The aryl-substituted derivatives provided the cyclized products **4h**–**m** in excellent 80–91% yields, with both electron-poor and electron-rich systems performing admirably (entries 8–13). Additionally, bis-pyridine moiety **3n** was well tolerated under the reaction conditions giving **4n** in 86% yield (entry 14).

The use of substituted amides under conditions optimized for formamide only lead to the formation of dimer **7**. Since amides are less nucleophilic than anilines,[30] substrate **3h** must out-compete the amide for binding to palladium, leading to a facile dimerization. In the absence of amide under otherwise identical reaction conditions, we also observed the formation of **7**. This unwanted dimerization could be thwarted by increasing the amount of amide from 1.5 to ≥5 equiv (Scheme 2). Using these slightly modified conditions, C2-substituted IP_c **5** and **6** could be obtained in 61% and 51% yields, respectively.

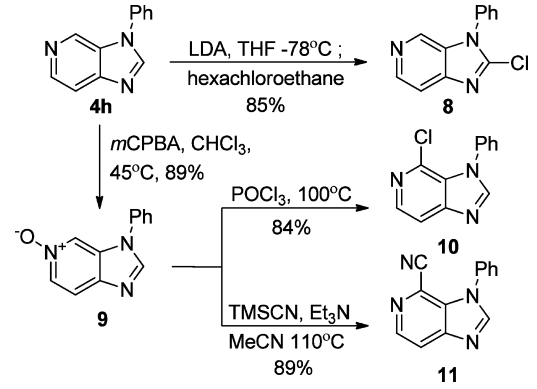
Scheme 2. Amide Scope[a]



[a]Conditions: 1 equiv of **3h**, Pd (2 mol %), ligand (10 mol %), 2 equiv of K_3PO_4, (a) 10 equiv of acetamide, (b) 5 equiv of furanamide, 0.2 M *t*-BuOH, 110 °C, 4 h.

We sought to demonstrate the utility of the IP_c system by further elaboration of the reaction products (Scheme 3).

Scheme 3. Functionalization Reactions



Selective deprotonation of **4h** at C2 with LDA and quenching the resulting lithiate with hexachloroethane produced compound **8** in 85% yield. Alternatively, *m*-CPBA can be used to oxidize **4h** to pyridine-*N*-oxide **9** in 89% yield. Pyridine *N*-oxide **9** was subsequently treated with $POCl_3$ at 120 °C for 2 h to form aryl chloride **10** regioselectively in 84% yield.[31] Thus, we have demonstrated complementary regioselective chlorination protocols to obtain functionalized chloro-IP_c **8** and **10**. Additionally, treatment of **9** with TMSCN and triethylamine in acetonitrile[32] gave the Reissert–Henze product **11** in 89% yield as a single regioisomer.

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CONCLUSION

In summary, we have utilized copper-catalyzed conditions for the arylation of 3-amino-4-chloropyridine **1** with aryl and heteroaryl halides, providing a high-yielding and direct route to monoarylated 3-amino-4-chloropyridines. Subsequent palladium-catalyzed amidation produced imidazo[4,5-*c*]pyridines in excellent yields using amide coupling partners. Further functionalization of the IP_c by halogenation and cyanation was demonstrated yielding IP_c primed for further manipulation.

EXPERIMENTAL SECTION

General Procedures. Unless otherwise indicated, all reactions were conducted in oven (140 °C) or flame-dried glassware using distilled and degassed solvents under a positive pressure of dry argon with standard Schlenk techniques. All air-sensitive reagents were stored in a glovebox containing dry argon gas. Dry tetrahydrofuran (THF), toluene, acetonitrile (CH_3CN), and methylene chloride (DCM) were obtained by passing commercially available predried, oxygen-free formulations through two activated alumina columns. Stainless steel syringes or cannulae that had been oven-dried (140 °C) and cooled under an argon atmosphere or in a desiccator were used to transfer air- and moisture-sensitive liquids. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on precoated glass plates of silica gel (0.25 mm) using the indicated solvent system. Visualization was accomplished with ultraviolet light (254 nm) or by treatment with one of the following solutions and carefully heating with a hot-air gun (450 °C): 10% phosphomolybdic acid in ethanol, 1% potassium permanganate/7% potassium carbonate/0.5% sodium hydroxide aqueous solution, or anisaldehyde in ethanol with 10% sulfuric acid. Flash column chromatography was performed using silica gel (40−63 μm). All workup and purification procedures were carried out with reagent grades solvents in air.

General Experimental A: Copper Coupling. To an oven-dried Schlenk tube equipped with a stir bar were added copper(I) iodide (10 mol %), potassium phosphate (2 equiv), *tert*-butyl-4-chloropyridin-3-yl carbamate **1** (1 equiv), and the haloarene (1.1 equiv) (if a solid). The reaction tube was evacuated and refilled with $Ar_{(g)}$. (±)-*trans*-1,2-Diaminocyclohexane (**L1**) (20 mol %) was added, followed by 1,4-dioxane (0.5 M) and the haloarene (1.1 equiv) (if a liquid). The reaction was degassed with three vacuum/$Ar_{(g)}$ purge cycles, equipped with a coldfinger, and placed in a preheated 110 °C oil bath. The reaction mixture was stirred for the time indicated, cooled to room temperature, and diluted with EtOAc. The reaction mixture was then filtered through a Celite plug, concentrated in vacuo, and applied to a silica gel column eluted with the indicated solvent mixture(s) to give the *N*-aryl product.

General Experimental B: Boc Deprotection. To an oven-dried round-bottom flask equipped with a stir bar was added Boc-pyridine **2h**−**n** (1 equiv) and DCM (0.5 M). The reaction was cooled to 0 °C (ice−water bath), and trifluoroacetic acid (TFA) (0.17 M) was added. The reaction was allowed to warm to room temperature and stirred until TLC analysis indicated consumption of the starting material (**2h**−**n**). The reaction was then poured into satd $NaHCO_{3(aq)}$ and diluted with DCM, and the layers were separated. The aqueous layer was extracted with DCM. The combined organic layers were dried over sodium sulfate, decanted, and concentrated in vacuo to give the desired deprotected product.

General Experimental C: Alkylation/Deprotection. To an oven-dried round-bottom flask equipped with a stir bar were added pyridine **1** (1 equiv) and DMF (0.5 M). The reaction mixture was cooled to 0 °C (ice−water bath), and sodium hydride (60 wt % in mineral oil) (1.5 equiv) was added in small portions over a period of ∼2 min. The reaction mixture was stirred for 1 h at 0 °C, at which time the appropriate benzyl or alkyl halide (1.5 equiv) was added dropwise as a solution in DMF. The reaction was allowed to warm to room temperature and stirred until TLC analysis indicated consumption of the starting material. The reaction was quenched by the addition of H_2O and diluted with EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to give the crude alkylated product which was used without further purification.

The crude alkylated substrate was dissolved in DCM (0.5 M) and added to an oven-dried round-bottom flask equipped with a stir bar. TFA (0.17−0.25 M) was added dropwise and the reaction stirred at room temperature until TLC analysis indicated consumption of the starting material. The reaction was quenched with satd $NaHCO_{3(aq)}$, and the layers were separated. The organic layer was dried over Na_2SO_4, concentrated in vacuo, and applied to a silica gel column to give the desired product.

General Experimental D: Palladium Amidation of 3-Amino-4-chloropyridines. To an oven-dried 25 mL Schlenk tube equipped with a stirbar were added $Pd_2(dba)_3{\cdot}CHCl_3$ (1 mol %), $Me_3(OMe)$*t*-BuXPhos (5 mol %), K_3PO_4 (1.5 equiv), and pyridine **3** (1 equiv). The reaction vessel was evacuated under vacuum and refilled with $Ar_{(g)}$. *t*-BuOH (0.2 M) and formamide (1.5 equiv) were then added via syringe, and the reaction mixture was degassed by three vacuum/$Ar_{(g)}$ purge cycles. The reaction vessel was then equipped with a coldfinger condenser, placed in a preheated 110 °C oil bath, and stirred for the specified time. Upon consumption of pyridine **3** (as judged by TLC analysis), the reaction mixture was allowed to cool to room temperature. The reaction mixture was diluted with methanol and passed through a Celite plug. The crude mixture was concentrated in vacuo and applied to a silica gel column eluted with the indicated solvent mixture(s) to give the desired product.

Pyridine ***2h.*** Following general experimental procedure A: Copper(I) iodide (83 mg, 0.44 mmol), potassium phosphate (1.86 g, 8.74 mmol), pyridine **1** (1.0 g, 4.37 mmol), diamine **L1** (0.11 mL, 0.87 mmol), iodobenzene (0.54 mL, 4.81 mmol), and 1,4-dioxane (0.5 M) were combined and stirred for 18 h. Purification via flash column chromatography, eluted with 30% EtOAc/hexanes, gave 1.28 g of pyridine **2h** (96%) as a light yellow solid: mp 85−87 °C; R_f = 0.39 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.50 (s, 1H), 8.39 (d, J = 5.4 Hz, 1H), 7.39 (d, J = 5.1 Hz, 1H), 7.33−7.21 (m, 4H), 7.18−7.11 (m, 1H), 1.42 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 152.8, 151.6, 148.9, 143.0, 141.3, 137.3, 128.9, 126.0, 125.6, 125.0, 82.1, 28.1; FT-IR (NaCl, thin film) ν = 2977, 2932, 1719, 1559, 1319, 1160, 691 cm^{-1}. Anal. Calcd for $C_{16}H_{17}ClN_2O_2$: C, 63.05; H, 5.62; N, 9.19. Found: C, 63.29; H, 5.45; N, 9.39

Pyridine ***2i.*** Following general experimental procedure A: Copper(I) iodide (43 mg, 0.22 mmol), potassium phosphate (955 mg, 4.50 mmol), pyridine **1** (500 mg, 2.18 mmol), diamine **L1** (0.06 mL, 0.44 mmol), 4-iodotoluene (539 mg, 2.48 mmol), and 1,4-dioxane (0.5 M) were combined and stirred for 22 h. Purification via flash column chromatography, eluted with 20% EtOAc/hexanes, gave 540 mg of pyridine **2i** (76%) as an off-white solid: mp 98−100 °C; R_f = 0.64 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.50 (s, 1H), 8.40 (d, J = 5.1 Hz, 1H), 7.40 (d, J = 5.4 Hz, 1H), 7.16−7.09 (m, 4H), 2.31 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 153.0, 151.6, 148.8, 142.9, 138.8, 137.5, 129.5, 125.7, 125.0, 82.0, 28.1, 21.0; FT-IR (NaCl, thin film) ν = 3036, 2979, 1715, 1554 cm^{-1}. Anal. Calcd for $C_{17}H_{19}ClN_2O_2$: C, 64.05; H, 6.01; N, 8.79. Found: C, 64.12; H, 6.04; N, 8.99.

Pyridine ***2j.*** Following general experimental procedure A: Copper(I) iodide (43 mg, 0.22 mmol), potassium phosphate (955 mg, 4.5 mmol), pyridine **1** (500 mg, 2.18 mmol), diamine **L1** (0.06 mL, 0.45 mmol), 4-trifluoromethylbromobenzene (0.35 mL, 2.48 mmol), and 1,4-dioxane (0.5 M) were combined and stirred for 22 h. Purification via flash column chromatography, eluted with 20% EtOAc/hexanes, gave 640 mg of pyridine **2j** (79%) as a yellow oil: R_f = 0.69 (30% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.50 (s, 1H), 8.48 (d, J = 5.4 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 5.1 Hz, 1H), 7.36 (d, J = 8.7 Hz, 2H), 1.43 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 152.3, 151.6, 149.5, 144.3, 143.2, 136.5, 127.4 (q, J_{C-F} = 32.7 Hz), 126.0 (q, J_{C-F} = 3.6 Hz), 125.1, 124.6, 124.0 (q, J_{C-F} = 272.8 Hz), 83.0, 28.0; ^{19}F NMR (282.3 MHz, $CDCl_3$) δ = −62.8; FT-IR (NaCl,

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thin film) ν = 2982, 1722, 1615, 1161 cm^{-1}. Anal. Calcd for $C_{17}H_{16}ClF_3N_2O_2$: C, 54.77; H, 4.33; N, 7.51. Found: C, 54.69; H, 4.10; N, 7.27.

Pyridine ***2k***. Following general experimental procedure A: Copper(I) iodide (42 mg, 0.22 mmol), potassium phosphate (929 mg, 4.38 mmol), pyridine **1** (500 mg, 2.18 mmol), diamine **L1** (0.06 mL, 0.44 mmol), 4′-bromoacetophenone (480 mg, 2.41 mmol), and 1,4-dioxane (0.5 M) were combined and stirred for 24 h. Purification via flash column chromatography, eluted with 30% EtOAc/hexanes, gave 686 mg of pyridine **2k** (90%) as a yellow oil: R_f = 0.27 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.45 (s, 1H), 8.43 (d, J = 5.4 Hz, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 5.4 Hz, 1H), 7.26 (d, J = 8.7 Hz, 2H), 2.50 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 196.9, 152.1, 151.6, 149.5, 145.4, 143.1, 136.5, 133.7, 129.1, 125.1, 123.9, 82.9, 28.0, 26.5; FT-IR (NaCl, thin film) ν = 2982, 1722, 1615, 1161 cm^{-1}. Anal. Calcd for $C_{18}H_{19}ClN_2O_3$: C, 62.34; H, 5.52; N, 8.08. Found: C, 61.95; H, 5.28; N, 7.71.

Pyridine ***2n***. Following general experimental procedure A: Copper(I) iodide (42 mg, 0.22 mmol), potassium phosphate (929 mg, 4.38 mmol), pyridine **1** (500 mg, 2.18 mmol), diamine **L1** (0.06 mL, 0.44 mmol), 3-bromopyridine (0.24 mL, 2.41 mmol), and 1,4-dioxane (0.5 M) were combined and stirred for 24 h. Purification via flash column chromatography, eluted with 35% EtOAc/hexanes, gave 590 mg of pyridine **2n** (88%) as a yellow solid: mp 55−57 °C; R_f = 0.14 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.53 (s, 1H), 8.47 (d, J = 5.4 Hz, 1H), 8.47 (s, 1H), 8.40 (dd, J = 4.7, 1.4 Hz, 1H), 7.66 (d, J = 7.5 Hz, 1H), 7.45 (d, J = 5.4 Hz, 1H), 7.27 (dd, J = 8.3, 4.8 Hz, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.4, 151.5, 149.5, 146.6, 143.0, 137.9, 136.2, 132.3, 125.0, 123.3, 82.9, 29.9; FT-IR (NaCl, thin film) ν = 2980, 1716 cm^{-1}. Anal. Calcd for $C_{15}H_{16}ClN_3O_2$: C, 58.92; H, 5.27; N, 13.74. Found: C, 58.94; H, 4.98; N, 14.01.

Pyridine ***3b***. Following general experimental procedure C: Pyridine **1** (228 mg, 1 mmol), DMF (4 mL), and sodium hydride (60 wt % in mineral oil) (60 mg, 1.5 mmol) were combined and stirred for 1 h, then 1-(chloromethyl)-2,5-dimethoxybenzene[33] (224 mg, 1.2 mmol) was added, and the reaction mixture was stirred for 14 h. Subsequent workup gave the crude alkylated product, which was dissolved in DCM (5 mL) and TFA (2.5 mL) and stirred for 4 h. Purification via flash column chromatography, eluted with 20% EtOAc/hexanes, gave 174 mg of pyridine **3b** (40% over two steps) as a light brown solid: mp 65−68 °C; R_f = 0.55 (5% MeOH/DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.03 (s, 1H), 7.84 (d, J = 5.4 Hz, 1H), 7.14 (d, J = 5.4 Hz, 1H), 6.85−6.73 (m, 3H), 4.77 (bs, NH), 4.41 (d, J = 6.0 Hz, 2H) 3.81 (s, 3H) 3.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 153.6, 151.5, 140.5, 138.6, 134.1, 127.7, 127.0, 123.7, 115.2, 112.5, 111.3, 55.8, 55.7, 42.9; FT-IR (NaCl, thin film) ν = 3293, 2914, 1582 cm^{-1}. Anal. Calcd for $C_{14}H_{15}ClN_2O_2$: C, 60.33; H, 5.42; N, 10.05. Found: C, 60.73; H, 5.33; N, 9.68.

Pyridine ***3c***. Following general experimental procedure C: Pyridine **1** (1.85 g, 8.09 mmol), DMF (33 mL), and sodium hydride (60 wt % in mineral oil) (483 mg, 12.1 mmol) were combined and stirred for 1 h, then 1-(chloromethyl)-3,5-dimethoxybenzene[34] (1.81 g, 9.71 mmol) was added, and the reaction mixture was allowed to stir overnight. Subsequent workup gave the crude alkylated product, which was dissolved in DCM (27 mL) and TFA (9 mL) and stirred for 3 h. Purification via flash column chromatography, eluted with 30−70% EtOAc/hexanes (20% gradient elution), gave 1.85 g of pyridine **3c** (82% over two steps) as an orange solid: mp 44−47 °C; R_f = 0.10 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.00 (s, 1H), 7.89 (d, J = 5.1 Hz, 1H), 7.19 (d, J = 5.1 Hz, 1H), 6.52 (d, J = 2.4 Hz, 2H), 6.39 (t, J = 2.4 Hz, 1H), 4.64 (bs, 1H), 4.40 (d, J = 5.7 Hz, 2H), 3.79 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 161.2, 140.4, 140.2, 138.7, 133.7, 127.5, 123.7, 105.1, 99.2, 55.2, 47.6; FT-IR (NaCl, thin film) ν = 3414, 2837, 1622, 1504, 1328, 1205, 1156, 1068 cm^{-1}. Anal. Calcd for $C_{14}H_{15}ClN_2O_2$: C, 60.33; H, 5.42; N, 10.05. Found: C, 60.62; H, 5.13; N, 10.22.

Pyridine ***3d***. Following general experimental procedure C: Pyridine **1** (457 mg, 2 mmol), DMF (4 mL), and sodium hydride (60 wt % in mineral oil) (120 mg, 3 mmol) were combined and stirred for 1 h, then 1-(chloromethyl)-4-fluorobenzene[35] (432 mg, 3 mmol) was added, and the reaction mixture was stirred for an additional 2 h. Subsequent workup gave the crude alkylated product, which was dissolved in DCM (5 mL) and TFA (1 mL) and stirred for 4 h. Purification via flash column chromatography, eluted with 25% EtOAc/hexane, gave 236 mg of pyridine **3d** (50% over two steps) as a pale yellow solid: mp 78−79 °C; R_f = 0.71 (50% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.98 (s, 1H), 7.90 (d, J = 5.1 Hz, 1H), 7.35−7.31 (m, 2H), 7.20 (d, J = 5.1 Hz, 1H), 7.08−7.02 (m, 2H), 4.61 (bs, NH), 4.43 (d, J = 5.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 162.3 (d, J_{C-F} = 244.5 Hz), 140.1, 139.0, 133.7 (d, J_{C-F} = 9 Hz), 133.5, 128.9 (d, J_{C-F} = 8.25 Hz), 127.6, 123.8, 115.7 (d, J_{C-F} = 21.75 Hz), 46.9; ^{19}F NMR (282.3 MHz, $CDCl_3$) δ = [(−115.1)−(−115.2)] (m); FT-IR (NaCl, thin film) ν = 3424, 1603 cm^{-1}. Anal. Calcd for $C_{12}H_{10}ClFN_2$: C, 60.90; H, 4.26; N, 11.84. Found: C, 61.23; H, 4.19; N, 12.02.

Pyridine ***3e***. Following general experimental procedure C: Pyridine **1** (457 mg, 2 mmol), DMF (4 mL), and sodium hydride (60 wt % in mineral oil) (120 mg, 3 mmol) were combined and stirred for 1 h, then 4-(chloromethyl)-1,1′-biphenyl[36] (606 mg, 3 mmol) was added, and the reaction mixture was stirred for an additional 2 h. Subsequent workup gave the crude alkylated product, which was dissolved in DCM (7 mL) and TFA (1 mL) and stirred for 4 h. Purification via flash column chromatography, eluted with 25% EtOAc/hexanes, gave 240 mg of pyridine **3e** (45% over two steps) as a pale yellow solid: mp 99−101 °C; R_f = 0.5 (50% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.06 (s, 1H), 7.91 (d, J = 5.1 Hz, 1H), 7.61−7.56 (m, 4H), 7.47−7.41 (m, 4H), 7.38−7.32 (m, 1H), 7.21 (d, J = 4.8 Hz, 1H), 4.67 (t, J = 5.1 Hz, NH), 4.51 (d, J = 5.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 140.7, 140.7, 140.3, 139.0, 137.0, 133.9, 128.9, 127.8, 127.7, 127.5, 127.1, 123.8, 47.4; FT-IR (NaCl, thin film) ν = 3417, 1579 cm^{-1}. Anal. Calcd for $C_{18}H_{15}ClN_2$: C, 73.34; H, 5.13; N, 9.50. Found: C, 73.27; H, 4.88; N, 9.18.

Pyridine ***3f***. Following general experimental procedure C: Pyridine **1** (708 mg, 3.09 mmol), DMF (7 mL), and sodium hydride (60 wt % in mineral oil) (223 mg, 5.57 mmol) were combined and stirred for 1 h, then iodomethane (0.58 mL, 9.28 mmol) was added, and the reaction mixture was stirred for an additional 2 h. Subsequent workup gave the crude alkylated product, which was dissolved in DCM (15 mL) and TFA (5 mL) and stirred for 4 h. Purification via flash column chromatography, eluted with 20% EtOAc/hexanes, gave 174 mg of pyridine **3f** (40% over two steps) as a light brown solid: mp 54−55 °C; R_f = 0.42 (5% MeOH/DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.02 (s, 1H), 7.89 (d, J = 4.8 Hz, 1H), 7.17 (d, J = 5.1 Hz, 1H), 4.25 (bs, NH), 2.97 (d, J = 5.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 141.3, 138.5, 132.9, 127.4, 123.6, 30.2; FT-IR (NaCl, thin film) ν = 3293, 2914, 1582 cm^{-1}. Anal. Calcd for $C_6H_7ClN_2$: C, 50.54; H, 4.95; N, 19.65. Found: C, 50.57; H, 5.18; N, 19.45.

Pyridine ***3g***. To an oven-dried 100 mL round-bottom flask equipped with a stirbar were added 3-amino-4-chloropyridine (2.0 g, 15.6 mmol), EtOAc (24 mL), propionaldehyde (1.2 mL, 17.1 mmol), and TFA (2.3 mL, 31.1 mmol). The reaction mixture was stirred for 5 min before sodium triacetoxyborohydride (3.95 g, 18.7 mmol) was added in three portions over 2 min. The reaction mixture was stirred for 15 min and judged complete by TLC analysis. The reaction mixture was poured into 100 mL of satd $NaHCO_{3(aq)}$ and diluted with EtOAc (25 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (25 mL). The combined organics were washed with brine (25 mL), dried over $MgSO_4$, filtered, concentrated in vacuo, and applied directly to a silica gel column eluted with 30% EtOAc/hexanes to give 2.05 g of pyridine **3g** (77%) as yellow oil. Upon cooling to −20 °C, this compound solidified to give a slightly yellow solid: mp 28−29 °C; R_f = 0.69 (5% MeOH/DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.01 (s, 1H), 7.84 (d, J = 5.1 Hz, 1H), 7.15 (d, J = 5.1 Hz, 1H), 4.18 (bs, 1H), 3.19 (m, 2H), 1.69 (sext, J = 7.5 Hz, 2H), 1.02 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 140.7, 138.3, 133.4, 127.4, 123.8, 45.2, 22.6, 11.6; FT-IR (NaCl, thin film) ν = 2992, 2938, 1543, 1471, 973, 855, 691 cm^{-1}. Anal. Calcd for $C_8H_{11}ClN_2$: C, 56.31; H, 6.50; N, 16.42. Found C, 56.66; H, 6.39; N, 16.65.

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Pyridine ***3h***. Following general experimental procedure B: Pyridine **2h** (1.12 g, 3.67 mmol), DCM (7.3 mL), and TFA (2.45 mL) were combined and stirred for 24 h to give 732 mg (97%) of pyridine **3h** as a tan microcrystalline solid: mp 107−109 °C; R_f = 0.39 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.56 (s, 1H), 8.02 (d, J = 5.1 Hz, 1H), 7.39−7.31 (m, 2H), 7.28 (d, J = 5.1 Hz, 1H), 7.21−7.17 (m, 2H), 7.15−6.95 (m, 1H), 5.98 (br s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 141.2, 140.5, 138.0, 137.6, 130.0, 129.8, 124.4, 123.7, 120.6; FT-IR (NaCl, thin film) ν = 3106, 3031, 1596, 1560, 1496, 1406, 1328, 1233, 1075, 816, 755, 696 cm^{-1}. Anal. Calcd for $C_{11}H_9ClN_2$: C, 64.56; H, 4.43; N, 13.69. Found: C, 64.86; H, 4.66; N, 13.86.

Pyridine ***3i***. Following general experimental procedure B: Pyridine **2i** (436 mg, 1.4 mmol), DCM (3 mL), and TFA (1.5 mL) were combined and stirred for 24 h to give 280 mg (92%) of pyridine **3i** as a yellow solid: mp 59−60 °C; R_f = 0.39 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.45 (s, 1H), 7.98 (d, J = 5.1 Hz, 1H), 7.25 (d, J = 5.1 Hz, 1H), 7.16 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 5.90 (br s, 1H), 2.34 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 140.5, 138.2, 137.6, 137.2, 133.7, 130.3, 129.3, 124.3, 121.5, 20.9; FT-IR (NaCl, thin film) ν = 3401, 3233, 3030, 2920, 1571, 1517, 809 cm^{-1}. Anal. Calcd for $C_{12}H_{11}ClN_2$: C, 65.91; H, 5.07; N, 12.81. Found: C, 65.76; H, 4.71; N, 12.55.

Pyridine ***3j***. Following general experimental procedure B: Pyridine **2j** (520 mg, 1.4 mmol), DCM (3 mL) and TFA (1.5 mL) were combined and stirred for 24 h to give 340 mg (89%) of pyridine **3j** as a yellow solid. R_f = 0.21 (30% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.67 (s, 1H), 8.15 (d, J = 4.8 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 5.1 Hz, 1H), 7.14 (d, J = 8.7 Hz, 2H), 6.10 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 144.5, 143.3, 140.5, 135.9, 132.7, 127 (q, J_{C-F} = 3.8 Hz), 124.7, 124.3 (q, J_{C-F} = 271.0 Hz), 124.2 (q, J_{C-F} = 32.6 Hz), 117.6; ^{19}F NMR (282.3 MHz, $CDCl_3$) δ= −62.2; FT-IR (NaCl, thin film) ν = 3249, 2988, 1616, 1111 cm^{-1}. Anal. Calcd for $C_{12}H_8ClF_3N_2$: C, 52.86; H, 2.96; N, 10.27. Found: C, 52.88; H, 2.98; N, 10.07.

Pyridine ***3k***. Following general experimental procedure B: Pyridine **2k** (440 mg, 1.27 mmol), DCM (3 mL), and TFA (1.5 mL) were combined and stirred for 24 h to give 280 mg (89%) of pyridine **3k** as a yellow solid: mp 115−116 °C; R_f = 0.12 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.72 (s, 1H), 8.17 (d, J = 5.1 Hz, 1H), 7.93 (d, J = 8.7 Hz, 2H), 7.36 (d, J = 5.1 Hz, 1H), 7.11 (d, J = 8.7 Hz, 2H), 6.22 (br s, 1H), 2.56 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 196.6, 146.0, 143.8, 141.3, 135.5, 133.3, 131.2, 130.7, 124.9, 116.6, 26.5; FT-IR (NaCl, thin film) ν = 3247, 3172, 3049, 1667, 1604, 1565, 813 cm^{-1}. Anal. Calcd for $C_{13}H_{11}ClN_2O$: C, 63.29; H, 4.49; N, 11.36. Found: C, 63.31; H, 4.14; N, 11.71.

Pyridine ***3l***. Following general experimental procedure A: Copper(I) iodide (20 mg, 0.11 mmol), K_3PO_4 (465 mg, 2.18 mmol), pyridine **1** (250 mg, 1.09 mmol), diamine **L1** (27 μL, 0.22 mmol), 4-bromoanisole (0.15 mL, 1.2 mmol), and 1,4-dioxane (0.5 M) were combined and stirred for 29 h, cooled to room temperature, diluted with EtOAc, filtered through a Celite plug, and concentrated in vacuo. The crude mixture was dissolved in DCM (3 mL) and TFA (1.5 mL) and stirred for 24 h. The reaction was poured into satd $NaHCO_{3(aq)}$ and diluted with DCM, and the layers were separated. The aqueous layer was extracted with DCM, and the combined organic layers were dried over Na_2SO_4, decanted, and concentrated in vacuo to give a brown oil. Purification via flash column chromatography, eluted with 20% EtOAc/hexanes, gave 120 mg of pyridine **3l** (47% over two steps) as a brown solid: mp 59−60 °C; R_f = 0.24 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.26 (s, 1H), 7.94 (d, J = 5.1 Hz, 1H), 7.24 (d, J = 5.1 Hz, 1H), 7.16 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 9.0 Hz, 2H), 5.82 (br s, 1H), 3.82 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 157.1, 140.0, 139.3, 136.3, 132.7, 128.4, 124.9, 124.2, 115.1, 55.7; FT-IR (NaCl, thin film) ν = 3234, 3041, 2933, 2835, 1513, 1244 cm^{-1}. Anal. Calcd for $C_{12}H_{11}ClN_2O$: C, 61.41; H, 4.72; N, 11.94. Found: C, 61.48; H, 4.97; N, 11.67.

Pyridine ***3m***. Following general experimental procedure A: Copper(I) iodide (20 mg, 0.11 mmol), K_3PO_4 (465 mg, 2.18 mmol), pyridine **1** (250 mg, 1.09 mmol), diamine **L1** (27 μL, 0.22 mmol), 5-bromo-*m*-xylene (0.17 mL, 1.2 mmol), and 1,4-dioxane (0.5 M) were combined and stirred for 29 h, cooled to room temperature, diluted with EtOAc, filtered through a Celite plug, and concentrated in vacuo. The crude mixture was dissolved in DCM (3 mL) and TFA (1.5 mL) and stirred for 24 h. The reaction was poured into satd $NaHCO_{3(aq)}$ and diluted with DCM, the layers were separated, and the aqueous layer was extracted with DCM. The combined organic layers were dried over Na_2SO_4, decanted, and concentrated in vacuo to give a brown oil. Purification via flash column chromatography, eluted with 20% EtOAc/hexanes, gave 168 mg of pyridine **3m** (66% over two steps) as an off-white solid: mp 127−128 °C; R_f = 0.42 (30% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.58 (s, 1H), 8.01 (s, 1H), 7.27 (d, J = 3.9 Hz, 1H), 6.81 (s, 2H), 6.74 (s, 1H), 5.88 (s, 1H), 2.30 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 140.9, 140.3, 139.6, 138.2, 137.7, 129.8, 125.5, 124.4, 118.3, 21.4; FT-IR (NaCl, thin film) ν = 3402, 1606, 1571, 1075 cm^{-1}. Anal. Calcd for $C_{13}H_{13}ClN_2$: C, 67.10; H, 5.63; N, 12.04. Found: C, 67.17; H, 5.88; N, 11.93.

Pyridine ***3n***. Following general experimental procedure B: Pyridine **2n** (168 mg, 0.55 mmol), DCM (2 mL), and TFA (1 mL) were combined and stirred for 6 h to give 100 mg (89%) of pyridine **3n** as a yellow solid: mp 117−118 °C; R_f = 0.06 (30% EtOAc/hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.49 (s, 1H), 8.46 (d, J = 2.1 Hz, 1H), 8.29 (d, J = 4.5 Hz, 1H), 8.07 (d, J = 5.1 Hz, 1H), 7.48 (d, J = 5.1 Hz, 1H), 7.30 (d, J = 5.1 Hz, 1H), 7.24 (dd, J = 8.1, 4.8 Hz, 1H), 6.28 (br s, 1H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 144.3, 142.4, 142.3, 138.5, 137.5, 136.7, 131.4, 126.4, 124.6, 124.0; FT-IR (NaCl, thin film) ν = 3172, 3042, 1588, 1326 cm^{-1}. Anal. Calcd for $C_{10}H_8ClN_3$: C, 58.41; H, 3.92; N, 20.43. Found: C, 58.36; H, 4.14; N, 20.39.

3-Benzyl-3H-imidazo[4,5-c]pyridine ***(4a)***.[37] Following general procedure D: Pyridine **3a** (88 mg, 0.4 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (4.14 mg, 0.004 mmol), Me_3(OMe)-*tert*-butyl-XPhos[26] (10 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), and formamide (0.024 mL, 0.6 mmol) were combined with 2 mL of *tert*-butyl alcohol in a 25 mL Schlenk tube. After 4 h, TLC analysis indicated the reaction was complete. The reaction mixture was cooled to rt, filtered through Celite, concentrated in vacuo, and purified on a silica gel column, eluted with 3% MeOH/DCM, to give 70 mg of pyridine **4a** (84%) as a light brown solid: mp 134−135 °C (lit.[37] 133−136 °C); R_f = 0.4 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.75 (s, 1H), 8.45 (d, J = 5.7 Hz, 1H), 8.08 (s, 1H), 7.75 (dd, J = 5.7 Hz, 1H), 7.40−7.34 (m, 3H), 7.25−7.21 (m, 2H), 5.44 (s, 2H).

3-(2,5-Dimethoxybenzyl)-3H-imidazo[4,5-c]pyridine ***(4b)***. Following general procedure D: Pyridine **3b** (111 mg, 0.4 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (4 mg, 0.004 mmol), Me_3(OMe)-*tert*-butyl-XPhos[26] (10 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), and formamide (0.024 mL, 0.6 mmol) were combined with 2 mL of *tert*-butyl alcohol in a 25 mL Schlenk tube. After 6.5 h, TLC analysis indicated the reaction was complete. The reaction mixture was cooled to rt, filtered through Celite, concentrated in vacuo, and purified on a silica gel column, eluted with 3% MeOH/DCM, to give 92 mg of pyridine **4b** (85%) as a light brown solid: mp 125 °C dec; R_f = 0.25 (5% MeOH/DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.83 (d, J = 0.6 Hz, 1H), 8.38 (d, J = 5.4 Hz, 1H), 8.06 (s, 1H), 7.65 (dd, J = 5.7 Hz, 0.9 Hz, 1H), 6.79 (app d, J = 1.5 Hz, 2H), 6.73 (app t, J = 1.5 Hz, 1H), 5.32 (s, 2H), 3.75 (s, 3H), 3.68 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 153.6, 151.5, 138.8, 146.3, 141.8, 133.9, 131.8, 123.7, 116.2, 115.0, 114.1, 111.7, 55.8, 55.8, 45.0; FT-IR (NaCl, thin film) ν = 2968, 2936, 2878, 1650, 1610, 1492, 1461, 1383, 1309, 1264, 1211, 907, 826 cm^{-1}. Anal. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.79; H, 5.24; N, 15.59.

3-(3,5-Dimethoxybenzyl)-3H-imidazo[4,5-c]pyridine ***(4c)***. Following general procedure D: Pyridine **3c** (110 mg, 0.4 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (4 mg, 0.004 mmol), Me_3(OMe)-*tert*-butyl-XPhos[26] (10 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), and formamide (0.024 mL, 0.6 mmol) were combined with 2 mL of *tert*-butyl alcohol in a 25 mL Schlenk tube. After 19 h, TLC analysis indicated the reaction was complete. The reaction mixture was cooled to rt, filtered through Celite, concentrated in vacuo, and purified on a silica gel column, eluted with 1−5% MeOH/DCM (2% gradient elution), to give 54 mg of pyridine **4c** (52%) as an orange solid: mp 98−100 °C; R_f = 0.20

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(5% MeOH/DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.69 (s, 1H), 8.39 (d, J = 5.7 Hz, 1H), 8.01 (s, 1H), 7.65 (dd, J = 5.7 Hz, 1.2 Hz, 1H), 6.35 (t, J = 2.1 Hz, 1H), 6.28 (d, J = 2.1 Hz, 2H), 5.28 (s, 2H), 3.66 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 161.4, 149.0, 145.8, 142.1, 136.7, 133.9, 115.1, 105.5, 100.0, 55.4, 49.5; FT-IR (NaCl, thin film) ν = 3482, 2799, 1644, 1455, 1374, 1159, 1067 cm^{-1}. Anal. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.80; H, 5.69; N, 15.63.

*3-(4-Fluorobenzyl)-3H-imidazo[4,5-c]pyridine (**4d**).* Following general procedure D: Pyridine **3d** (95 mg, 0.4 mmol), $Pd_2(dba)_3$·$CHCl_3$ (4 mg, 0.004 mmol), Me_3(OMe)-*tert*-butyl-XPhos[26] (10 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), and formamide (0.024 mL, 0.6 mmol) were combined with 2 mL of *tert*-butyl alcohol in a 25 mL Schlenk tube. After 4 h, TLC analysis indicated the reaction was complete. The reaction mixture was cooled to rt, filtered through Celite, concentrated in vacuo, and purified on a silica gel column, eluted with 3% MeOH/DCM, to give 68 mg of pyridine **4d** (75%) as a pale yellow solid: mp 107−110 °C; R_f = 0.31 (5% MeOH/DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.65 (d, J = 0.6 Hz, 1H), 8.39 (d, J = 5.4 Hz, 1H), 8.00 (s, 1H), 7.66 (dd, J = 5.7, 0.9 Hz, 1H), 7.18−7.13 (m, 2H), 7.09−6.96 (m, 2H), 5.34 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 162.7 (d, J_{C-F} = 246.75 Hz), 149.1, 145.7, 142.2, 133.7, 131.5, 130.4 (d, J_{C-F} = 3.45 Hz), 129.2 (d, J_{C-F} = 7.95 Hz), 116.3 (d, J_{C-F} = 21.75 Hz), 115.1, 48.8; ^{19}F NMR (282.3 MHz, $CDCl_3$) δ= −113.0 (m); FT-IR (NaCl, thin film) ν = 1608 cm^{-1}. Anal. Calcd for $C_{13}H_{10}FN_3$: C, 68.71; H, 4.44; N, 18.49. Found: C, 68.54; H, 4.36; N, 18.32.

*Imidazo[4,5-c]pyridine (**4e**).* Following general procedure D: Pyridine **3e** (95 mg, 0.4 mmol), $Pd_2(dba)_3$·$CHCl_3$ (4 mg, 0.004 mmol), Me_3(OMe)-*tert*-butyl-XPhos[26] (10 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), and formamide (0.024 mL, 0.6 mmol) were combined with 2 mL of *tert*-butyl alcohol in a 25 mL Schlenk tube. After 4.5 h, TLC analysis indicated the reaction was complete. The reaction mixture was cooled to rt, filtered through Celite, concentrated in vacuo, and purified on a silica gel column, eluted with 4% MeOH/DCM, to give 86 mg of pyridine **4e** (75%) as an off-white solid: mp 189−191 °C; R_f = 0.34 (5% MeOH/DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.76 (s, 1H), 8.46 (d, J = 5.7 Hz, 1H), 8.07 (s, 1H), 7.73 (dd, J = 5.7, 1.2 Hz, 1H), 7.58−7.51 (m, 4H), 7.45−7.26 (m, 5H), 5.44 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 149.1, 145.8, 142.2, 141.8, 140.1, 133.9, 133.4, 131.6, 128.9, 127.9, 127.8, 127.7, 127.1, 115.1, 49.2; FT-IR (NaCl, thin film) ν = 1602 cm^{-1}. Anal. Calcd for $C_{19}H_{15}N_3$: C, 79.98; H, 5.30; N, 14.73. Found: C, 79.96; H, 5.56; N, 14.39.

*3-Methyl-3H-imidazo[4,5-c]pyridine (**4f**).*[38] Following general procedure D: Pyridine **3f** (57 mg, 0.4 mmol), $Pd_2(dba)_3$·$CHCl_3$ (4 mg, 0.004 mmol), Me_3(OMe)-*tert*-butyl-XPhos[26] (10 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), and formamide (0.024 mL, 0.6 mmol) were combined with 2 mL of *tert*-butyl alcohol in a 25 mL Schlenk tube. After 5 h, TLC analysis indicated the reaction was complete. The reaction mixture was cooled to rt, filtered through Celite, concentrated in vacuo, and purified on a silica gel column, eluted with 4% MeOH/DCM, to give 31 mg of pyridine **4f** (58%) as a pale yellow solid: mp 95−97 °C; R_f = 0.17 (5% MeOH/DCM); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.80 (d, J = 0.6 Hz, 1H), 8.42 (d, J = 5.4 Hz, 1H), 7.91 (s, 1H), 7.65 (dd, J = 5.7 Hz, 0.9 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 148.7, 146.2, 142.0, 133.2, 132.3, 114.9, 31.5.

*3-Propyl-3H-imidazo[4,5-c]pyridine (**4g**).* Following general procedure D: Pyridine **3e** (68 mg, 0.4 mmol), $Pd_2(dba)_3$·$CHCl_3$ (4 mg, 0.004 mmol), Me_3(OMe)-*tert*-butyl-XPhos[26] (10 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), and formamide (0.024 mL, 0.6 mmol) were combined with 2 mL of *tert*-butyl alcohol in a 25 mL Schlenk tube. After 6.5 h, TLC analysis indicated the reaction was complete. The reaction mixture was cooled to rt, filtered through Celite, concentrated in vacuo, and purified on a silica gel column, eluted with 3% MeOH/DCM, to give 55 mg of pyridine **4e** (85%) as a light brown solid: mp 75−78 °C; R_f = 0.22 (5% MeOH/DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.85 (s, 1H), 8.43 (d, J = 5.7 Hz, 1H), 7.98 (s, 1H), 7.69 (dd, J = 5.4 Hz, 0.9 Hz, 1H), 4.21 (t, J = 6.9 Hz, 2H), 1.95 (sext, J = 7.2 Hz, 2H), 0.95 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 149.0, 145.8, 141.9, 133.5, 131.7, 115.2, 47.4, 23.4, 11.4; FT-IR (NaCl, thin film) ν = 2969, 2880, 1655, 1609, 1492, 1460, 1383, 1309, 1264, 1211, 1166, 1126, 1027, 906, 825 cm^{-1}. Anal. Calcd for $C_9H_{11}N_3$: C, 67.06; H, 6.88; N, 26.07. Found: C, 67.10; H, 6.99; N, 26.06.

*3-Phenyl-3H-imidazo[4,5-c]pyridine (**4h**).* Following general procedure D: Pyridine **3h** (82 mg, 0.4 mmol), $Pd_2(dba)_3$·$CHCl_3$ (4 mg, 0.004 mmol), Me_3(OMe)-*tert*-butyl-XPhos[26] (10 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), and formamide (0.024 mL, 0.6 mmol) were combined with 2 mL of *tert*-butyl alcohol in a 25 mL Schlenk tube. After 6.5 h, TLC analysis indicated the reaction was complete. The reaction mixture was cooled to rt, filtered through Celite, concentrated in vacuo, and purified on a silica gel column, eluted with 3% MeOH/DCM, to give 70 mg of pyridine **4h** (85%) as a light brown solid: mp 149−150 °C; R_f = 0.26 (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.91 (s, 1H), 8.46 (d, J = 5.7 Hz, 1H), 8.19 (s, 1H), 7.72 (dd, J = 5.4 Hz, 0.6 Hz, 1H), 7.61−7.41 (m, 5H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 149.1, 144.8, 142.5, 135.4, 134.2, 131.4, 130.3, 128.7, 123.8, 115.2; FT-IR (NaCl, thin film) ν = 3177, 1597, 1503, 1480, 1304, 1233, 761, 696 cm^{-1}. Anal. Calcd for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.80; H, 4.90; N, 21.28.

*3-(p-Tolyl)-3H-imidazo[4,5-c]pyridine (**4i**).* Following general procedure D: Pyridine **3i** (87 mg, 0.4 mmol), $Pd_2(dba)_3$·$CHCl_3$ (4 mg, 0.004 mmol), Me_3(OMe)-*tert*-butyl-XPhos[26] (10 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), and formamide (0.024 mL, 0.6 mmol) were combined with 2 mL of *tert*-butyl alcohol in a 25 mL Schlenk tube. After 6 h, TLC analysis indicated the reaction was complete. The reaction mixture was cooled to rt, filtered through Celite, concentrated in vacuo, and purified on a silica gel column, eluted with 4% MeOH/DCM, to give 72 mg of pyridine **4i** (86%) as a light brown solid: mp 108−109 °C; R_f = 0.33 (5% MeOH/DCM); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.90 (s, 1H), 8.48 (d, J = 5.7 Hz, 1H), 8.17 (s, 1H), 7.74 (dd, J = 5.7 Hz, 0.6 Hz, 1H), 7.40−7.36 (m, 4H), 2.43 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ= 149.1, 145.0, 142.6, 139.1, 134.3, 133.0, 131.7, 131.0, 123.9, 115.3, 21.2; FT-IR (NaCl, thin film) ν = 3051, 2924, 1518, 1480, 821 cm^{-1}. Anal. Calcd for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.66; H, 5.54; N, 19.97.

*3-(4-(Trifluoromethyl)phenyl)-3H-imidazo[4,5-c]pyridine (**4j**).* Following general procedure D: Pyridine **3j** (108 mg, 0.4 mmol), $Pd_2(dba)_3$·$CHCl_3$ (4 mg, 0.004 mmol), Me_3(OMe)-*tert*-butyl-XPhos[26] (10 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), and formamide (0.024 mL, 0.6 mmol) were combined with 2 mL of *tert*-butyl alcohol in a 25 mL Schlenk tube. After 6 h, TLC analysis indicated the reaction was complete. The reaction mixture was cooled to rt, filtered through Celite, concentrated in vacuo, and purified on a silica gel column, eluted with 4% MeOH/DCM, to give 96 mg of pyridine **4j** (91%) as a pale yellow solid: mp 166−167 °C; R_f = 0.30 (5% MeOH/DCM); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.97 (s, 1H), 8.52 (d, J = 5.7 Hz, 1H), 8.25 (s, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 5.7 Hz, 1H), 7.69 (d, J = 8.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 149.4, 144.4, 143.1, 138.5, 133.9, 131.0, 130.8 (q, J_{C-F} = 33.3 Hz), 127.8 (q, J_{C-F} = 3.7 Hz), 123.9, 123.5 (q, J_{C-F} = 272.9 Hz), 115.5; ^{19}F NMR (282.3 MHz, $CDCl_3$) δ = −63.0; FT-IR (NaCl, thin film) ν = 3056, 1606, 1334, 1106 cm^{-1}. Anal. Calcd for $C_{13}H_8F_3N_3$: C, 59.32; H, 3.06; N, 15.96. Found: C, 59.04; H, 2.77; N, 15.67.

*Imidazo[4,5-c]pyridine (**4k**).* Following general procedure D: Pyridine **3k** (98 mg, 0.4 mmol), $Pd_2(dba)_3$·$CHCl_3$ (4 mg, 0.004 mmol), Me_3(OMe)-*tert*-butyl-XPhos[26] (10 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), and formamide (0.024 mL, 0.6 mmol) were combined with 2 mL of *tert*-butyl alcohol in a 25 mL Schlenk tube. After 4 h, TLC analysis indicated the reaction was complete. The reaction mixture was cooled to rt, filtered through Celite, concentrated in vacuo, and purified on a silica gel column, eluted with 4% MeOH/DCM, to give 83 mg of pyridine **4k** (87%) as a pale yellow solid: mp 199−201 °C; R_f = 0.33 (5% MeOH/DCM); ^{1}H NMR (600 MHz, $CDCl_3$) δ= 8.99 (s, 1H), 8.51 (d, J = 5.7 Hz, 1H), 8.26 (s, 1H), 8.18 (d, J = 8.7 Hz, 2H), 7.76 (dd, J = 5.7 Hz, 0.9 Hz, 1H), 7.65 (d, J = 8.7 Hz, 2H), 2.65 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 196.3, 149.3, 144.3, 143.0, 139.1, 136.8, 134.0, 130.9, 130.5, 123.3, 115.4, 26.6; FT-IR (NaCl, thin film) ν = 1677, 1601, 1353, 816 cm^{-1}. Anal. Calcd for

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$C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.50; H, 4.76; N, 17.43.

*3-(4-Methoxyphenyl)-3H-imidazo[4,5-c]pyridine (**4l**).* Following general procedure D: Pyridine **3l** (93 mg, 0.4 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (4 mg, 0.004 mmol), Me_3(OMe)-*tert*-butyl-XPhos[26] (10 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), and formamide (0.024 mL, 0.6 mmol) were combined with 2 mL of *tert*-butyl alcohol in a 25 mL Schlenk tube. After 6.5 h, TLC analysis indicated the reaction was complete. The reaction mixture was cooled to rt, filtered through Celite, concentrated in vacuo, and purified on a silica gel column, eluted with 3% MeOH/DCM, to give 69 mg of pyridine **4l** (77%) as a pale yellow solid: mp 105−106 °C; R_f = 0.30 (5% MeOH/DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.86 (s, 1H), 8.49 (d, J = 5.7 Hz, 1H), 8.14 (s, 1H), 7.75 (d, J = 5.4 Hz, 1H), 7.42 (d, J = 8.7 Hz, 2H), 7.08 (d, J = 9.0 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ = 159.9, 149.0, 145.2, 142.5, 134.3, 132.1, 128.3, 125.7, 115.5, 115.2, 55.8; FT-IR (NaCl, thin film) ν = 2839, 1517, 1253 cm^{-1}. Anal. Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.44; H, 5.05; N, 18.75.

*3-(3,5-Dimethylphenyl)-3H-imidazo[4,5-c]pyridine (**4m**).* Following general procedure D: Pyridine **3m** (93 mg, 0.4 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (4 mg, 0.004 mmol), Me_3(OMe)-*tert*-butyl-XPhos[26] (10 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), and formamide (0.024 mL, 0.6 mmol) were combined with 2 mL of *tert*-butyl alcohol in a 25 mL Schlenk tube. After 4 h, TLC analysis indicated the reaction was complete. The reaction mixture was cooled to rt, filtered through Celite, concentrated in vacuo, and purified on a silica gel column, eluted with 4% MeOH/DCM, to give 80 mg of pyridine **4m** (90%) as a pale yellow solid: mp 144−146 °C; R_f = 0.33 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.96 (s, 1H), 8.51 (d, J = 5.4 Hz, 1H), 8.19 (s, 1H), 7.77 (d, J = 5.6 Hz, 1H), 7.14 (s, 3H), 2.43 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 149.2, 144.9, 142.6, 140.5, 135.4, 134.6, 131.6, 130.5, 121.7, 115.3, 21.5; FT-IR (NaCl, thin film) ν = 3060, 2919, 1602, 1494, 1231 cm^{-1}. Anal. Calcd for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.64; H, 5.59; N, 18.66.

*3-(Pyridin-3-yl)-3H-imidazo[4,5-c]pyridine (**4n**).* Following general procedure D: Pyridine **3n** (95 mg, 0.4 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (4 mg, 0.004 mmol), Me_3(OMe)-*tert*-butyl-XPhos[26] (10 mg, 0.02 mmol), K_3PO_4 (128 mg, 0.6 mmol), and formamide (0.024 mL, 0.6 mmol) were combined with 2 mL of *tert*-butyl alcohol in a 25 mL Schlenk tube. After 5 h, TLC analysis indicated the reaction was complete. The reaction mixture was cooled to rt, filtered through Celite, concentrated in vacuo, and purified on a silica gel column, eluted with 4% MeOH/DCM, to give 67 mg of pyridine **4n** (86%) as a yellow solid: mp 138−140 °C; R_f = 0.57 (4% MeOH/DCM); ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.94 (s, 1H), 8.88 (d, J = 2.4 Hz, 1H), 8.78 (dd, J = 4.8 Hz, 1.2 Hz, 1H), 8.55 (d, J = 5.4 Hz, 1H), 8.23 (s, 1H), 7.91 (ddd, J = 8.0 Hz, 2.4 Hz, 1.2 Hz, 1H), 7.80 (d, J = 5.4 Hz, 1H), 7.58 (dd, J = 8.0 Hz, 4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ= 150.2, 149.4, 145.3, 144.5, 143.3, 133.8, 132.5, 131.4, 131.4, 124.8, 115.6; FT-IR (NaCl, thin film) ν = 3351, 3058, 2928, 1496, 1249 cm^{-1}. Anal. Calcd for $C_{11}H_8N_4$: C, 67.34; H, 4.11; N, 28.55. Found: C, 67.40; H, 4.15; N, 28.21.

*2-Methyl-3-phenyl-3H-imidazo[4,5-c]pyridine (**5**).* To an oven-dried 50 mL Schlenk tube were added pyridine **3h** (82 mg, 0.4 mmol), $Pd_2(dba)_3CHCl_3$ (8 mg, 0.008 mmol), Me_3(OMe)*t*BuXPhos[26] (20 mg, 0.04 mmol), K_3PO_4 (170 mg, 0.8 mmol), and acetamide (236 mg, 4.0 mmol); the reaction vessel was sealed, evacuated under vacuum, and purged with $Ar_{(g)}$. *t*-BuOH (2.0 mL) was added, and the reaction mixture was degassed with three vacuum/$Ar_{(g)}$ purge cycles, equipped with a coldfinger condenser, and placed in a preheated 110 °C oil bath. After 4 h, TLC analysis indicated the complete consumption of pyridine **3h**. The reaction mixture was cooled to rt, filtered through Celite, concentrated in vacuo, and purified on a silica gel column, eluted with 2% MeOH/DCM, to give 51 mg of pyridine **5** (61%) as a yellow solid: mp 104−107 °C; R_f = 0.26 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.50 (s, 1H), 8.42 (d, J = 5.6 Hz, 1H), 7.63−7.53 (m, 4H), 7.39−7.36 (m, 2H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.0, 147.9, 142.6, 135.2, 134.3, 133.3, 130.3, 129.5, 126.8, 113.9, 14.5; FT-IR (NaCl, thin film) ν = 3407, 3048, 2926, 1596, 1501, 1392, 822 cm^{-1}. Anal. Calcd for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.77; H, 5.32; N, 19.85.

*2-(Furan-2-yl)-3-phenyl-3H-imidazo[4,5-c]pyridine (**6**).* To an oven-dried 50 mL Schlenk tube were added pyridine **3h** (82 mg, 0.4 mmol), $Pd_2(dba)_3CHCl_3$ (8 mg, 0.008 mmol), Me_3(OMe)-*t*-BuXPhos[26] (20 mg, 0.04 mmol), K_3PO_4 (170 mg, 0.8 mmol), and furanamide (222 mg, 2.0 mmol); the reaction vessel was sealed, evacuated under vacuum, and purged with $Ar_{(g)}$. *t*-BuOH (2.0 mL) was added, and the reaction mixture was degassed with three vacuum/$Ar_{(g)}$ purge cycles, equipped with a coldfinger condenser, and placed in a preheated 110 °C oil bath. After 5 h, TLC analysis indicated the complete consumption of pyridine **3h**. The reaction mixture was cooled to rt, filtered through Celite, concentrated in vacuo, and purified on a silica gel column, eluted with 2% MeOH/DCM, to give 53 mg of pyridine **6** (51%) as a yellow solid: mp 153−155 °C; R_f = 0.21 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.47 (s, 1H), 8.47 (d, J= 5.6 Hz, 1H), 7.72 (dd, J = 5.6, 1.2 Hz, 1H), 7.63−7.59 (m, 3H), 7.50 (dd, J=1.2, 0.8 Hz, 1H), 7.45−7.41 (m, 2H), 6.37 (dd, J = 3.6, 1.6 Hz, 1H), 6.29 (dd, J= 3.6, 0.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 147.9, 146.6, 145.2, 144.3, 143.7, 142.9, 135.4, 134.7, 133.6, 130.2, 130.0, 127.6, 114.2, 111.8; FT-IR (NaCl, thin film) ν = 3049, 2924, 2222, 1591, 1502, 1416, 1267, 905, 819 cm^{-1}. Anal. Calcd for $C_{16}H_{11}N_3O$: C, 73.55; H, 4.24; N, 16.08. Found: C, 73.48; H, 4.28; N, 15.94.

*5,10-Diphenyl-5,10-dihydrodipyrido[3,4-b:3′,4′-e]pyrazine (**7**).* Pyridine **3h** (82 mg, 0.4 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (4 mg, 0.004 mmol), Me_3(OMe)-*tert*-butyl-XPhos[26] (10 mg, 0.02 mmol), and K_3PO_4 (128 mg, 0.6 mmol), were combined with 2 mL of *tert*-butyl alcohol in a 25 mL Schlenk tube. The reaction mixture was degassed with three vacuum/$Ar_{(g)}$ purge cycles, equipped with a coldfinger condenser, and placed in a preheated 110 °C oil bath. After 16.5 h, the reaction mixture was cooled to rt, filtered through Celite, concentrated in vacuo, and purified on a silica gel column, eluted with 5% MeOH/DCM, to give 26 mg of pyrazine **7** (39%) as a yellow solid: mp 168−170 °C; R_f = 0.05 (10% *i*-PrOH/DCM); ^{1}H NMR (400 MHz, CD_3OD) δ = 7.68 (d, J= 1.5 Hz, 1H), 7.48 (dd, J= 6.8, 1.5 Hz, 1H), 7.21−7.17 (m, 2H), 7.05−7.02 (m, 2H), 6.86−6.83 (m, 1H), 6.38 (d, J= 6.8 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ = 173.0, 143.4, 136.4, 134.9, 130.7, 122.9, 119.8, 119.3, 113.1; FT-IR (NaCl, thin film) ν = 2928, 2858, 1625, 1590, 1458, 1173, 824 cm^{-1}. Anal. Calcd for $C_{22}H_{16}N_4$: C, 78.55; H, 4.79; N, 16.66. Found: C, 78.28; H, 4.84; N, 16.75;

*2-Chloro-3-phenyl-3H-imidazo[4,5-c]pyridine (**8**).* Chloride **8** was prepared following a literature procedure.[39] To an oven-dried 25 mL Schlenk tube were added pyridine **4h** (49 mg, 0.25 mmol) and 1.0 mL of THF. The reaction mixture was cooled to −78 °C (CO_2/acetone bath), lithium diisopropylamide (2.0 M in THF, 0.19 mL) was added dropwise, and the reaction mixture was allowed to stir for 1 h. Hexachloroethane (89 mg, 0.375 mmol) was added as a solution in THF (0.25 mL), and the reaction mixture was warmed to rt over 45 min. The reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride (4 mL), diluted with 5 mL of water, and poured into 10 mL of EtOAc. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over magnesium sulfate, filtered, concentrated in vacuo, and purified on a silica gel column, eluted with 5% MeOH/DCM, to afford 48 mg of chloride **8** (84%) as a yellow solid: mp 110 °C dec; R_f = 0.40 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.58 (s, 1H), 8.52 (d, J= 5.7 Hz, 1H), 7.68 (dd, J = 6.9, 0.9 Hz, 1H), 7.66−7.60 (m, 3H), 7.49−7.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 146.8, 144.4, 143.0, 134.1, 133.6, 133.2, 130.1, 130.0, 126.9, 114.0; FT-IR (NaCl, thin film) ν = 1638, 1498, 1437, 1366, 1285 cm^{-1}. Anal. Calcd for $C_{12}H_8ClN_3$: C, 62.76; H, 3.51; N, 18.30. Found: C, 62.94; H, 3.67; N, 18.66.

*3-Phenyl-3H-imidazo[4,5-c]pyridine 5-Oxide (**9**).* To a flame-dried 25 mL round-bottom flask containing a stir bar were added pyridine **4h** (150 mg, 0.77 mmol) and chloroform (16 mL). After complete dissolution, *m*-CPBA (85%, 390 mg, 1.93 mmol) was added as a single portion, and the reaction mixture was warmed to 45 °C for 2 h. The reaction mixture was cooled to rt, concentrated in vacuo, and then

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purified on a silica gel column, eluted with 10% MeOH/DCM, to afford 145 mg of *N*-oxide **9** (89%) as a white powder: mp 174−175 °C; R_f = 0.02 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.56 (d, J = 1.0 Hz, 1H), 8.17 (s, 1H), 8.14 (dd, J = 6.9, 1.6 Hz, 1H), 7.65 (d, J = 6.9 Hz, 1H), 7.57−7.52 (m, 2H), 7.50−7.46 (m, 1H) 7.41−7.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 146.2, 141.9, 135.7, 134.4, 132.1, 130.6, 129.5, 124.6, 123.7, 117.0; FT-IR (NaCl, thin film) ν = 3379, 1506, 1463, 1446, 1204 cm^{-1}. Anal. Calcd for $C_{12}H_9N_3O$: C, 68.24; H, 4.29; N, 19.89. Found: C, 67.93; H, 4.50; N, 19.56.

*4-Chloro-3-phenyl-3H-imidazo[4,5-c]pyridine (**10**).* To a 25 mL Schlenk tube containing a stir bar were added *N*-oxide **9** (42 mg, 0.2 mmol) and 0.2 mL of $POCl_3$. The reaction mixture was heated in a 120 °C oil bath for 2 h and then cooled to rt. The reaction mixture was diluted with 5 mL of H_2O and made basic with 1.5 mL of ammonium hydroxide. The aqueous layer was extracted with DCM (3 × 10 mL), and the combined organic layers were dried over $MgSO_4$, filtered, concentrated in vacuo, and then purified on a silica gel column, eluted with 10% MeOH/DCM, to afford 38 mg of chloride **10** (84%) as an off-white solid: mp 148−151 °C; R_f = 0.50 (5% MeOH/DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.27 (d, J = 5.5 Hz, 1H), 8.10 (s, 1H), 7.73 (d, J = 5.7 Hz, 1H), 7.57−7.53 (m, 3H), 7.46−7.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 150.9, 147.1, 141.5, 134.9, 134.3, 129.7, 129.1, 128.7, 127.7, 115.0; FT-IR (NaCl, thin film) ν = 3054, 1605, 1556, 1240, 980, 821 cm^{-1}. Anal. Calcd for $C_{12}H_8ClN_3$: C, 62.76; H, 3.51; N, 18.30. Found: C, 62.54; H, 3.66; N, 18.26.

*3-Phenyl-3H-imidazo[4,5-c]pyridine-4-carbonitrile (**11**).* To an oven-dried 15 mL pressure tube containing a stir bar were added *N*-oxide **9** (53 mg, 0.25 mmol), acetonitrile (0.5 mL), Et_3N (0.05 mL, 0.375 mmol), and trimethylsilyl cyanide (0.11 mL, 0.9 mmol). The reaction vessel was sealed with a Teflon screw cap and heated in an oil bath at 110 °C for 12 h. The reaction mixture was cooled to rt, diluted with 10 mL of DCM, and washed with 10 mL of $NaHCO_3$ (satd aq). The organic layer was dried over $MgSO_4$, filtered, concentrated in vacuo, purified on a silica gel column, and eluted with 5% MeOH/DCM to afford 49 mg of nitrile **11** (89%) as an off-white solid: mp 179−181 °C; R_f = 0.50 (5% MeOH/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.63 (d, J = 5.6 Hz, 1H), 8.24 (s, 1H), 8.02 (d, J = 5.6 Hz, 1H), 7.66−7.63 (m, 3H), 7.52−7.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 150.1, 147.9, 143.4, 133.5, 133.4, 130.7, 130.0, 127.1, 119.2, 117.4, 114.2; FT-IR (NaCl, thin film) ν = 3115, 3057, 2222, 1595, 1501, 1222 cm^{-1}. Anal. Calcd for $C_{13}H_8N_4$: C, 70.90; H, 3.66; N, 25.44. Found: C, 70.81; H, 3.59; N, 25.07.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: daclar01@syr.edu.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Dyminska, L.; Weglinski, Z.; Gagor, A.; Hanuza, J. *J. Nat. Prod.* **2013**, *76* (9), 1637−1646.
(2) Brown, N. *Bioisosteres in Medicinal Chemistry*; Wiley-VCH Verlag: Weinheim, 2012.
(3) Puerstinger, G.; Paeshuyse, J.; Heinrich, S.; Mohr, J.; Schraffl, N.; De Clercq, E.; Neyts, J. *Bioorg. Med. Chem. Lett.* **2007**, *17* (18), 5111−5114.
(4) Vliegen, I.; Paeshuyse, J.; De Burghgraeve, T.; Lehman, L. S.; Paulson, M.; Shih, I. H.; Mabery, E.; Boddeker, N.; De Clercq, E.; Reiser, H.; Oare, D.; Lee, W. A.; Zhong, W.; Bondy, S.; Purstinger, G.; Neyts, J. *J. Hepatol.* **2009**, *50* (5), 999−1009.
(5) Schneider, C.; Goyard, D.; Gueyrard, D.; Joseph, B.; Goekjian, P. G. *Eur. J. Org. Chem.* **2010**, *2010* (34), 6665−6677.
(6) Temple, C.; Rose, J. D.; Comber, R. N.; Rener, G. A. *J. Med. Chem.* **1987**, *30* (10), 1746−1751.
(7) Sahli, S.; Frank, B.; Schweizer, W. B.; Diederich, F.; Blum-Kaelin, D.; Aebi, J. D.; Böhm, H.-J.; Oefner, C.; Dale, G. E. *Helv. Chim. Acta* **2005**, *88* (4), 731−750.
(8) Caron, S.; Do, N. M.; McDermott, R. E.; Bahmanyar, S. *Org. Process Res. Dev.* **2006**, *10* (2), 257−261.
(9) Jiang, B. *Org. Process Res. Dev.* **1998**, *2* (6), 425−427.
(10) Mayorov, A. V.; Willis, B.; Di Mola, A.; Adler, D.; Borgia, J.; Jackson, O.; Wang, J.; Luo, Y.; Tang, L.; Knapp, R. J.; Natarajan, C.; Goodnough, M. C.; Zilberberg, N.; Simpson, L. L.; Janda, K. D. *ACS Chem. Biol.* **2010**, *5* (12), 1183−1191.
(11) Frohn, M.; Viswanadhan, V.; Pickrell, A. J.; Golden, J. E.; Muller, K. M.; Burli, R. W.; Biddlecome, G.; Yoder, S. C.; Rogers, N.; Dao, J. H.; Hungate, R.; Allen, J. R. *Bioorg. Med. Chem. Lett.* **2008**, *18* (18), 5023−5026.
(12) Cai, J.; Baugh, M.; Black, D.; Long, C.; Jonathan Bennett, D.; Dempster, M.; Fradera, X.; Gillespie, J.; Andrews, F.; Boucharens, S.; Bruin, J.; Cameron, K. S.; Cumming, I.; Hamilton, W.; Jones, P. S.; Kaptein, A.; Kinghorn, E.; Maidment, M.; Martin, I.; Mitchell, A.; Rankovic, Z.; Robinson, J.; Scullion, P.; Uitdehaag, J. C. M.; Vink, P.; Westwood, P.; van Zeeland, M.; van Berkom, L.; Bastiani, M.; Meulemans, T. *Bioorg. Med. Chem. Lett.* **2010**, *20* (15), 4350−4354.
(13) Gautam, R. K.; Fujii, S.; Nishida, M.; Kimoto, H.; Cohen, L. A. *J. Heterocycl. Chem.* **1994**, *31* (2), 453−455.
(14) Khanna, I. K.; Weier, R. M. *Tetrahedron Lett.* **1993**, *34* (12), 1885−1888.
(15) Vallee, F.; Carrez, C.; Pilorge, F.; Dupuy, A.; Parent, A.; Bertin, L.; Thompson, F.; Ferrari, P.; Fassy, F.; Lamberton, A.; Thomas, A.; Arrebola, R.; Guerif, S.; Rohaut, A.; Certal, V.; Ruxer, J.-M.; Delorme, C.; Jouanen, A.; Dumas, J.; Gracpin, C.; Combeau, C.; Goulaouic, H.; Dereu, N.; Mikol, V.; Mailliet, P.; Minoux, H. *J. Med. Chem.* **2011**, *54* (20), 7206−7219.
(16) Rosenberg, A. J.; Zhao, J.; Clark, D. A. *Org. Lett.* **2012**, *14* (7), 1764−1767.
(17) McLaughlin, M.; Palucki, M.; Davies, I. W. *Org. Lett.* **2006**, *8* (15), 3307−3310.
(18) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39* (19), 2933−2936.
(19) Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39* (19), 2937−2940.
(20) Lach, F.; Koza, P. *ACS Comb. Sci.* **2012**, *14* (9), 491−495.
(21) Billingsley, K. L.; Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45* (21), 3484−3488.
(22) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123* (31), 7727−7729.
(23) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124* (25), 7421−7428.
(24) Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127* (12), 4120−4121.
(25) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2010**, *1* (1), 13−31.
(26) Ueda, S.; Ali, S.; Fors, B. P.; Buchwald, S. L. *J. Org. Chem.* **2012**, *77* (5), 2543−2547.
(27) Suzuki, K.; Hori, Y.; Kobayashi, T. *Adv. Synth. Catal.* **2008**, *350* (5), 652−656.
(28) Withbroe, G. J.; Singer, R. A.; Sieser, J. E. *Org. Process Res. Dev.* **2008**, *12* (3), 480−489.
(29) Singer, R. A.; Caron, S.; McDermott, R. E.; Arpin, P.; Do, N. M. *Synthesis* **2003**, *2003* (11), 1727−1731.

(30) Hicks, J. D.; Hyde, A. M.; Cuezva, A. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131* (46), 16720−16734.
(31) Yamanaka, H.; Araki, T.; Sakamoto, T. *Chem. Pharm. Bull.* **1988**, *36* (6), 2244−2247.
(32) Vorbruggen, H.; Krolikiewicz, K. *Synthesis* **1983**, *1983* (4), 316−319.
(33) Rosowsky, A.; Papoulis, A. T.; Forsch, R. A.; Queener, S. F. *J. Med. Chem.* **1999**, *42* (6), 1007−1017.
(34) Weist, S.; Kittel, C.; Bischoff, D.; Bister, B.; Pfeifer, V.; Nicholson, G. J.; Wohlleben, W.; Sussmuth, R. D. *J. Am. Chem. Soc.* **2004**, *126* (19), 5942−5943.
(35) Bennett, G. M.; Jones, B. *J. Chem. Soc.* **1935**, 1815−1819.
(36) DasGupta, S.; Murumkar, P. R.; Giridhar, R.; Yadav, M. R. *Biorg. Med. Chem.* **2009**, *17* (10), 3604−3617.
(37) Kelley, J. L.; Linn, J. A.; Hideout, J. L.; Soroko, F. E. *J. Heterocycl. Chem.* **1988**, *25* (4), 1255−1258.
(38) Katner, A. S.; Brown, R. F. *J. Heterocycl. Chem.* **1990**, *27* (3), 563−566.
(39) Rosenberg, A. J.; Williams, T. M.; Jordan, A. J.; Clark, D. A. *Org. Biomol. Chem.* **2013**, *11* (18), 3064−3072.