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Note

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2-Aminopyridines via Reaction of Pyridine *N*-Oxides and Activated Isocyanides

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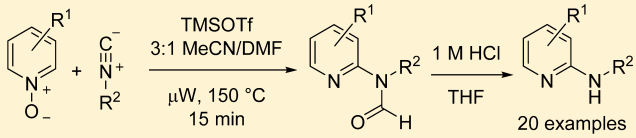
Supporting Information

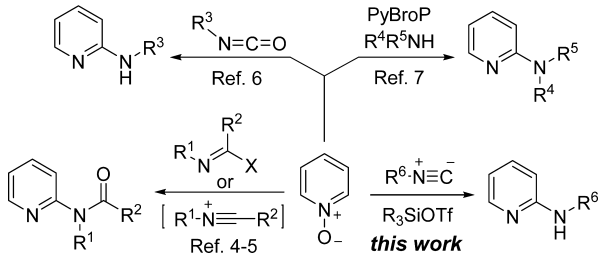
ABSTRACT: A practical and efficient method for the synthesis of substituted 2-aminopyridines from pyridine *N*-oxides is reported. Yields of purified, isolated products of up to 84% are observed for the one-pot, two-step process. The reaction involves an in situ deprotection of an isolable *N*-formylamino-pyridine intermediate and facilitates the synthesis of 2-aminopyridines for which other methods fail.



Substituted aromatic heterocycles constitute a large portion of the body of pharmaceutical agents. Within that chemical space exist aminopyridines, which serve as pharmacophores for many bioactive small molecules in their own right.[1] Whereas its carbon-analogue aniline presents a variety of problematic issues pharmacologically due to its tendency to be oxidized to a reactive and toxic nitroso species,[2] the heteroaromatic 2-aminopyridine avoids such problems due to its reduced oxidation potential, thus rendering it a safer alternative for drug design. Additionally, 2-aminopyridines possess advantageous absorption and emission spectra and thus have proven useful as fluorescent tags, particularly in the study of oligosaccharides.[3]

It has been previously shown that pyridine *N*-oxides are capable of yielding amides of 2-aminopyridines by reaction with imidoyl chlorides[4] or triflates[5] and 2-aminopyridines by reaction with isocyanates (Scheme 1).[6] Pyridine *N*-oxides

Scheme 1. Amination and Amidation of Pyridine *N*-Oxides



activated with a phosphonium coupling reagent were shown to react with amines to give 2-aminopyridines by a Reissert–Henze-type reaction.[7] Reissert–Henze-type reactions were also employed in the synthesis of *N*-unsubstituted[8] and *N*-triflyl 2-aminopyridines.[9] We were interested in investigating the unexplored interaction of pyridine *N*-oxides and isocyanides, whose unique dual nature of reactivity, their tendency to react both as nucleophilic carbanions and electrophilic carbenes, has resulted in a rich chemical history.[10] Given that some pyridine *N*-oxide derivatives have shown poor or zero reactivity in prior methods,[4a,11] or were not reported in another,[7] we sought to expand the synthetic arsenal for the synthesis of 2-aminopyridines. Also, some previously reported methods yield 2-aminopyridine amides as products that require harsh conditions to cleave the amide bond and isolate the desired 2-aminopyridine derivatives.[4,5] Thus, we report here a new method for the synthesis of 2-aminopyridines by reaction of activated isocyanides with pyridine *N*-oxides followed by mild hydrolysis of the incipient *N*-formyl-2-aminopyridines.

An initial survey of reaction conditions was conducted with commercially available methyl isonicotinate *N*-oxide (**1a**) and benzyl isocyanide (**2a**), shown in Table 1. Microwave irradiation proved superior to traditional heating in flask, with a solvent combination of acetonitrile and DMF giving the best results. Use of DMSO resulted in an isocyanide–DMSO redox reaction and no product formation (entry 7).[12] A variety of Lewis and Brønsted acids were examined for their ability to initiate the reaction, which did not occur without the action of an activator (entry 1). Acyl chlorides such as acetyl chloride (entry 2) proved only mildly effective, whereas dimethyl sulfate (entry 6) provided a good level of conversion. Strong Brønsted acids gave mixed results: while camphorsulfonic acid (CSA, entry 3) gave virtually zero product conversion, the similar, but much smaller, analogue methanesulfonic acid (MsOH, entry 4) gave more promising results. The best results were obtained with strong silylating agents like trimethylsilyl triflate (TMSOTf, entries 7–11) and triisopropylsilyl triflate (TIPSOTf, not shown). As the initial product formamide **3** was partially cleaved during workup and purification, it was fully converted to the amine **4** by mild acidic solvolysis.[13] For the purpose of comparison, the reaction was also run under

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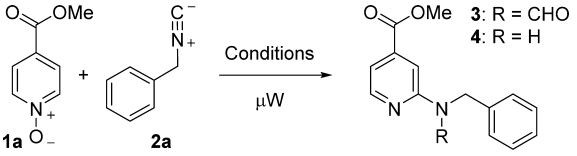
Table 1. Optimization of Reaction Conditions*



entry	activator	solvent(s)	relative conversion[e]
1	none	3:1 MeCN/DMF	0
2	AcCl	3:1 MeCN/DMF	0
3	CSA	3:1 MeCN/DMF	0
4	MsOH	3:1 MeCN/DMF	14
5	BF_3•OEt_2	3:1 MeCN/DMF	6
6[d]	Me_2SO_4	3:1 MeCN/DMF	35
7	TMSOTf	DMSO	0
8	TMSOTf	DMF	62 (32%)[f]
9	TMSOTf[a]	3:1 MeCN/DMF	23
10	TMSOTf[b]	3:1 MeCN/DMF	59 (40%)[f]
11	TMSOTf[c]	3:1 MeCN/DMF	100 (45%)[f]

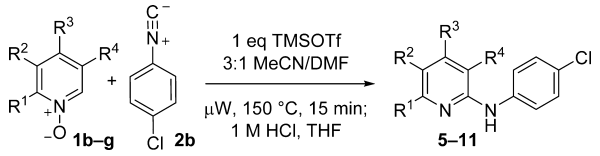
*Reaction conditions: 1 equiv of *N*-oxide, 1 equiv of isocyanide, and 1 equiv of activator in stated solvent in microwave at 150 °C for 15 min, then 1 M HCl and THF, 50 °C. [a]0.1 equiv. [b]0.5 equiv. [c]1.0 equiv. [d]Yields of the methylamide. [e]Relative HPLC yields determined by peak area analysis of product(s) and *N*-oxide in crude reaction mixture. [f]Isolated yield in parentheses.

conventional oil bath heating and gave a slightly lower yield after 4 h.[14]

Having worked out the optimized reaction conditions, a survey of substrate scope was initiated using 4-chlorophenyl isocyanide (**2b**) and various pyridine *N*-oxides (Table 2). Yields were dependent upon the nature of the pyridine *N*-oxide, with those bearing electron-withdrawing substituents affording higher yields (products **6** and **7**) than those with less polar aliphatic groups (product **10**) or electron-donating substituents (products **8** and **11**). The low yield (19%) of 4-methoxy-substituted **8** from the electron-rich pyridine *N*-oxide **1d** is noteworthy. In addition, the attenuated yield of 3,5-dibromo-*N*-(4-chlorophenyl)pyridin-2-amine (**11**, 41%) may indicate that coordination of the reactants is sensitive to steric hindrance. The pyridine *N*-oxide **1e** possessing a 4-carboxaldehyde substituent proved unstable and/or unreactive and resulted in degradation of starting material, with reduction of the *N*-oxide and aldehyde functional groups evident by LCMS analysis.

Further elucidation of substrate scope was conducted with a variety of pyridine *N*-oxides and isocyanides (Table 3). In general, yields were good (40−76%) with regioselectivity depending on the nature of both the pyridine *N*-oxide and the isocyanide. The 2-aminopyridines arising from aromatic isocyanides (save for **2d** due to sterics) and **1h** were produced in good yields and (generally) favored the 2,3-disubstituted pyridine (i.e., **12b**−**14b**) by a slight margin (relative to 2,5-disubstituted **12a**−**14a**). The combination of 3-cyano-substituted pyridine *N*-oxide **1h** and isocyanide **2b** (entry 1) showed a particularly high bias (3:1) for the 2,3-disubstituted product **12b**, in 74% yield. In general, aliphatic isocyanides (**2a,e**−**f**) tended to give slightly lower yields than their aromatic counterparts (**2b**−**d**). Reaction efficiency also appears to be dependent upon the degree of steric congestion at the isocyanide reactive center, which is evident when comparing products **15** and **16** (entries 4 and 5); appendage of a methyl group at the benzylic position of the isocyanide resulted in a lower yield of **16** and increased propensity for the 2,5-disubstituted regioisomer. Isocyanides possessing bulky aliphatic groups proved ineffective in this procedure; *tert*-butyl isocyanide (**2g**) and diphenylmethyl isocyanide (**2h**)[15] (entries 11 and 12) yielded negligible product when reacted with pyridine *N*-oxide **1h**. It should be noted that pyridine *N*-oxides with electron-withdrawing cyano or nitro substituents, as in **1h** (Table 3), **1c** (Table 2, entry 3), and **1k** (Table 3, entry 9), have shown no reactivity in previously published methods involving isocyanates and imidoyl chlorides as dipolarophiles.[4a,11]

Table 2. Initial Pyridine *N*-Oxide Substrate Scope Survey*



Entry	Pyridine *N*-Oxide	R^1	R^2	R^3	R^4	Product
1	**1b**	H	H	H	H	**5** 71%
2	**1a**	H	H	CO_2Me	H	**6** 60%
3	**1c**	H	H	NO_2	H	**7** 67%
4	**1d**	H	H	OMe	H	**8** 19%
5	**1e**	H	H	CHO	H	**9** 0%[a]
6	**1f**	Me	H	H	H	**10** 48%
7	**1g**	H	Br	H	Br	**11** 41%

*Reaction conditions: 1 equiv of *N*-oxide, 1 equiv of isocyanide, and 1 equiv of TMSOTf in 3:1 MeCN/DMF microwaved at 150 °C for 15 min, then 1 M HCl and THF, 50 °C. [a]No product detected.

Based on the data in Table 3, some trends can be inferred concerning the regioselectivity of reaction between 3-substituted pyridine *N*-oxides and isocyanides. Pyridine *N*-oxides (**1h**−**j**) possessing electron-withdrawing substituents gave a larger proportion of the 2,3-disubstituted isomer (**12**−**14**, **18**, **19**) when reacted with an aryl isocyanide than would otherwise be expected based on steric effects alone. Additionally, yields reflected the favorability of this interaction, with the nearly 2-fold difference in yield of **18** (Table 3, entry 7) and **21** (Table 3, entry 10) proving illustrative. Regioselectivity was most pronounced for compound **19** (Table 3, entry 8), for which none of the alternative regioisomer was observed. One notable exception to the trend, however, is compound **20**

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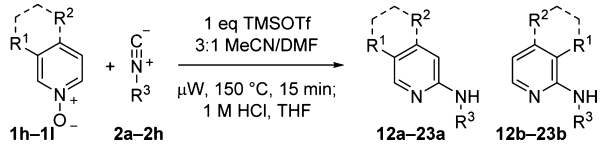
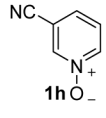
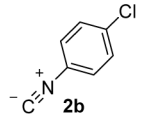
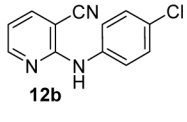
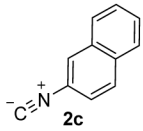
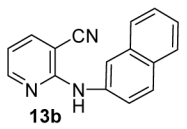
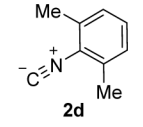
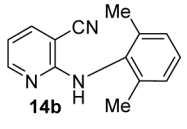
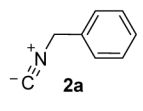
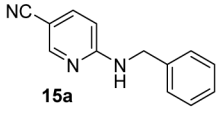
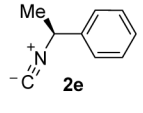
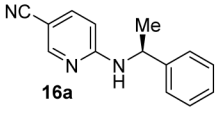
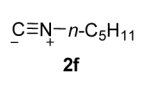
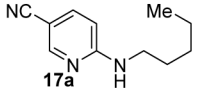
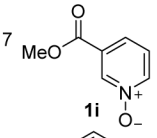
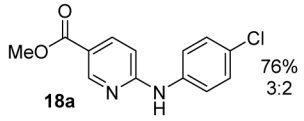
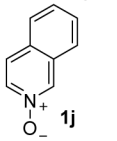
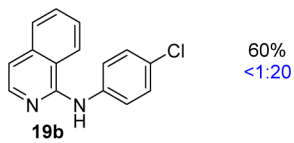
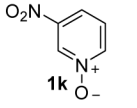
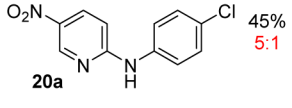
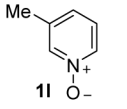
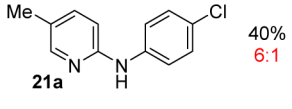
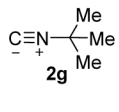
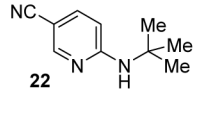
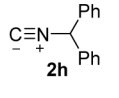
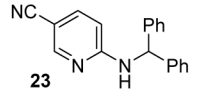
Table 3. Substrate Scope and Regiochemical Trends



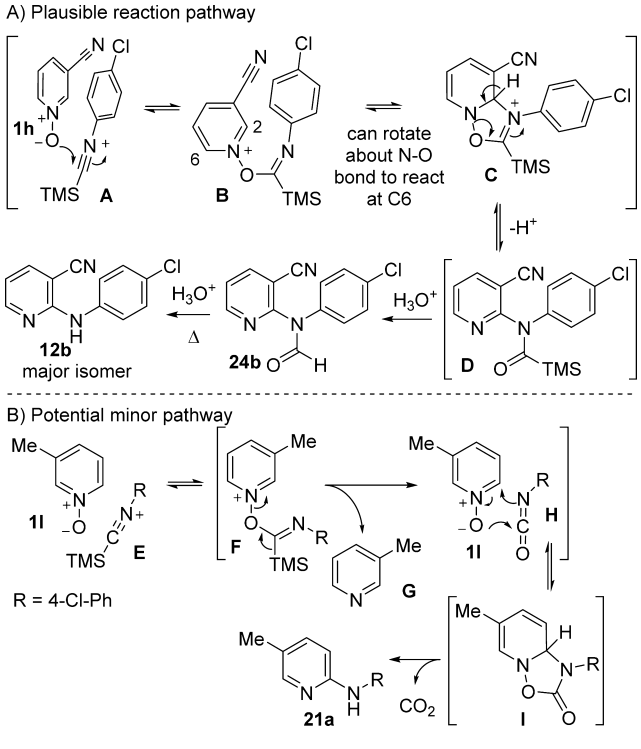
Entry	*N*-Oxide	Isocyanide	Major Product Isomer	Yield a:b
1	 **1h**	 **2b**	 **12b**	74% 1:3
2	**1h**	 **2c**	 **13b**	84% 2:3
3	**1h**	 **2d**	 **14b**	45% 1:1
4	**1h**	 **2a**	 **15a**	61% 5:3
5	**1h**	 **2e**	 **16a**	54% 4:1
6	**1h**	 **2f**	 **17a**	45% 3:1
7	 **1i**	**2b**	 **18a**	76% 3:2
8	 **1j**	**2b**	 **19b**	60% <1:20
9	 **1k**	**2b**	 **20a**	45% 5:1
10	 **1l**	**2b**	 **21a**	40% 6:1
11	**1h**	 **2g**	 **22**	0%[a]
12	**1h**	 **2h**	 **23**	0%[a]

[a]Minor amount of product detected after workup, which was not isolated.

(Table 3, entry 9), which favored by a 5:1 margin the 2,5-disubstituted isomer.

A plausible reaction mechanism is presented in Scheme 2A. Addition of the *N*-oxide to the activated isocyanide **A**[16] would give imidate intermediate **B**, from which further reaction can occur at either C2 or C6 of the activated aromatic ring to give oxadiazoline **C** (by reaction at C2). The regioselectivity of this addition can be rationalized as a balance between the partial charge distribution about the aromatic ring and steric effects imposed by the 3-substituent. The nitrile group in the 3-position of intermediate C has a relatively minor steric impact (given its linear geometry) on attack of the nucleophile at the 2-position. Thus, given that there is a larger accumulation of partial positive charge at C2 relative to C6, electrostatic effects dictate selective formation of the 2,3-isomer **12b**. For product **18**, although the electron-withdrawing ability of the 3-carbomethoxy group places a larger partial positive charge at C2, its greater steric demand (relative to nitrile) shifts the regioselectivity to favor 2,5-isomer **18a**. A similar charge distribution calculation for the intermediate leading to **21** reveals a much narrower gap between the C2−C6 partial charges, increasing the importance of the steric effect of the 3-methyl group and leading to the highest ratio of 2,5-isomer (**21a**) in Table 3. A more detailed analysis of these factors is included as Figure SI-1 in the Supporting Information. The impact of the size of the isocyanide must be taken into account as well; a trend in entries 1−6 can be seen such that larger bulk about the isocyanide reactive center equates to a larger ratio of

Scheme 2. Possible Reaction Pathways



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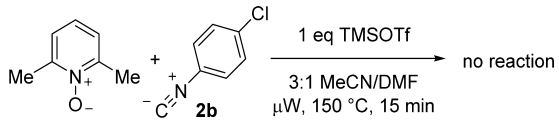
the 2,5-isomer. Rearomatization would give **D**, and hydrolysis[17] would lead to 2-aminopyridine **12b**. Interestingly, the order of reagent addition proved inconsequential; identical results were obtained even when the pyridine *N*-oxide and TMSOTf were premixed. Also, no reaction was observed at the 4-position of the pyridine *N*-oxide, as was demonstrated with the example shown in Scheme 3.

Scheme 3. Failure of a 2,6-Disubstituted Pyridine *N*-Oxide To React



An alternative reaction pathway, which consumes 0.5 equiv of pyridine *N*-oxide **1l** through oxidation of the isocyanide to isocyanate via **F**,[12,18] could be a minor source of product formation (Scheme 2B). This pathway would proceed through cycloaddition with the isocyanate **H** to ultimately give 2-aminopyridine **21a** after decarboxylation of cycloadduct **I**. Side product **G**, resulting from reduction of the *N*-oxide, was observed by LCMS in cases of poor reactivity. However, it is notable that the use of 2 equiv of pyridine *N*-oxide in our reaction afforded no improvement in yield. Also, this alternative pathway does not give rise to the formamide (ie. **24b**, Scheme 2A), which we observed as the major initial product in every instance (see Figure SI-2A, Supporting Information). Thus, this pathway is not a major contributor to product formation.

In conclusion, a new method for the synthesis of 2-aminopyridines from pyridine *N*-oxides and activated isocyanides has been developed. Isolated yields of purified products were generally good and a variety of functional groups were tolerated. Importantly, in contrast with previously reported methods, substituted pyridines bearing strongly electron-withdrawing substituents (-NO_2, −CN) reacted efficiently to provide the desired products in good yield. Reaction output, yield, and regioselectivity were dependent upon the nature of the starting materials (aliphatic vs aromatic, presence of electron-donating vs -withdrawing substituents, substitution pattern), with regioselectivity being controlled by a combination of steric and electronic factors in the imidate intermediate.

EXPERIMENTAL SECTION

General Procedure for the 2-Amination of Pyridine *N*-Oxides: Synthesis of Methyl 2-(Benzylamino)isonicotinate (4). Pyridine *N*-oxide **1a** (30 mg, 0.196 mmol, 1.0 equiv) benzyl isocyanide (**2a**, 24 μL, 0.196 mmol, 1.0 equiv), and TMSOTf (19 μL, 0.196 mmol, 1.0 equiv) were mixed in MeCN/DMF (3:1, 0.1 M based on *N*-oxide) in a 10 mL capped microwave reaction tube. The contents were stirred and microwave-irradiated to a set temperature of 150 °C for 15 min. The crude reaction mixture was concentrated to remove volatile organics (DMF remains), 1 M HCl (5 mL) and THF (5 mL) were added, and the mixture was stirred at 50 °C until complete conversion of formamide **3** to aminopyridine **4**. Saturated aqueous sodium bicarbonate (10 mL) was added to neutralize the solution to approximately pH 7, and then the volatile organics were removed. Ethyl acetate (15 mL) was added, and the organics were washed with water (2 × 10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. For some aminopyridines (see particular examples below), purification can be accomplished by dissolving in a hexane/EtOAc mixture (using highest ratio possible of hexane allowing solubility) and washing with water (3 × 10 mL), followed by a quick Florisil column if necessary (the product tends to elute last on this adsorbent). Otherwise, the crude product was purified by flash chromatography on Florisil to yield **4**. See specific examples for purification conditions. In some cases, preparative TLC was used to separate the 2,3- from the 2,5-isomer. It is possible to substitute 7 M NH_3 in MeOH to cleave the formamide **3** to give **4**.

In-Flask Procedure for the 2-Amination of Pyridine *N*-Oxides. Pyridine *N*-oxide **1a** (30 mg, 0.196 mmol, 1.0 equiv), benzyl isocyanide (**2a**, 24 μL, 0.196 mmol, 1.0 equiv), and TMSOTf (19 μL, 0.196 mmol, 1.0 equiv) in MeCN/DMF (3:1, 0.1 M based on *N*-oxide) were heated to 105 °C for 4 h under nitrogen atmosphere. The crude reaction mixture was concentrated to remove volatile organics (DMF remains), then 1 M HCl (5 mL) and THF (5 mL) were added, and the mixture was stirred at 50 °C until complete conversion of formamide **3** to aminopyridine **4** (see below for analytical data). Ethyl acetate (15 mL) was added, and the organics were washed with water (2 × 10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification involved flash chromatography on Florisil (DCM → 5% EtOAc/DCM) to give **4** (15 mg, 37%).

Methyl 2-(Benzylamino)isonicotinate (4). 0.196 mmol scale: 21 mg, 45% yield. Purification involved flash chromatography on Florisil (DCM→5% EtOAc/DCM) to give **4** as a crystalline solid (mp = 118−120 °C). R_f = 0.24 (5:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, CD_3CN) δ: 8.12 (d, 1H, *J* = 5.6 Hz), 7.36−7.30 (m, 5H), 7.25 (d, 1H, *J* = 6.8 Hz), 6.99 (s, 1H), 6.98 (d, 1H, *J* = 2.0 Hz), 5.94 (bs, 1H), 4.55 (d, 2H, *J* = 6.4 Hz), 3.84 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ: 166.9, 160.4, 149.8, 141.1, 139.5, 129.4, 128.2, 127.8, 111.9, 108.4, 53.0, 45.8. HRMS calcd for $C_{14}H_{15}N_2O_2$ $[M + H]^+$: 243.1128, found 243.1112.

***N*-(4-Chlorophenyl)pyridin-2-amine (5).** 0.557 mmol scale: 81 mg, 71% yield. Purification involved addition of 5:1 hexanes/EtOAc and washing with water (3 × 10 mL) and brine (10 mL) The organics were dried over sodium sulfate and concentrated in vacuo to give **5** as an amorphous solid. R_f = 0.28 (5:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, CD_3CN) δ: 8.16 (dd, 1H, *J* = 2.0, 5.6 Hz), 7.63 (d, 2H, *J* = 8.8 Hz), 7.55 (td, 1H, *J* = 2.0, 8.0 Hz), 7.50 (bs, 1H), 7.27 (d, 2H, *J* = 8.8 Hz), 6.79−6.75 (m, 2H). ^{13}C NMR (100 MHz, CD_3CN) δ: 156.7, 148.3, 141.5, 138.4, 129.4, 125.9, 120.7, 116.0, 111.4. HRMS calcd for $C_{11}H_{10}ClN_2$ $[M + H]^+$: 205.0527, found 205.0518.

Methyl 2-((4-Chlorophenyl)amino)isonicotinate (6). 0.326 mmol scale: 51 mg, 60% yield. Purification involved addition of 5:1 hexanes/EtOAc with 5% DCM (just enough to dissolve) and washing with water (3 × 10 mL) and brine (10 mL). The organics were dried over sodium sulfate and concentrated in vacuo to give **6** as an amorphous solid. R_f = 0.38 (5:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, CD_3CN) δ: 8.29 (dd, 1H, *J* = 0.4, 5.2 Hz), 7.74 (bs, 1H), 7.65 (d, 2H, *J* = 9.2 Hz), 7.29 (d, 1H, *J* = 8.8 Hz), 7.26 (dd, 1H, *J* = 0.8 1.2 Hz), 7.21 (dd, 1H, *J* = 1.6, 5.2 Hz), 3.89 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ: 166.6, 157.3, 149.5, 140.9, 139.9, 129.5, 126.6, 121.0, 114.3, 111.1, 53.2. HRMS calcd for $C_{13}H_{12}ClN_2O_2$ $[M + H]^+$: 263.0582, found 263.0578.

***N*-(4-Chlorophenyl)-4-nitropyridin-2-amine (7).** 0.500 mmol scale: 83 mg, 67% yield. Purification involved addition of 5:1 hexanes/EtOAc and washing with water (3 × 10 mL) and brine (10 mL). The organics were dried over sodium sulfate and concentrated in vacuo. The mostly pure material was then subjected to flash chromatography on Florisil (DCM→5% EtOAc/DCM) to give **7** as a crystalline solid (mp = 168−170 °C). R_f = 0.40 (5:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, CD_3CN) δ: 8.41 (dd, 1H, *J* = 0.4, 5.6 Hz), 8.00 (bs, 1H), 7.64 (d, 2H, *J* = 9.2 Hz), 7.41 (dd, 1H, *J* = 0.8, 2.0 Hz), 7.39 (dd, 1H, *J* = 2.0, 5.2 Hz), 7.33 (d, 2H, *J* = 8.8 Hz). ^{13}C NMR (100 MHz, CD_3CN) δ: 158.1, 156.2, 151.1, 140.2, 129.7, 127.6, 121.6, 107.7, 104.3. HRMS calcd for $C_{11}H_9ClN_3O_2$ $[M + H]^+$: 250.0378, found 250.0379.

***N*-(4-Chlorophenyl)-4-methoxypyridin-2-amine (8).** 0.426 mmol scale: 19 mg, 19% yield. Purification involved addition of 5:1 hexanes/EtOAc and washing with water (3 × 10 mL) and brine (10 mL). The organics were dried over sodium sulfate, concentrated in vacuo, and then subjected to flash chromatography on silica gel (DCM→5% EtOAc/DCM) to give **8** as an amorphous solid. R_f = 0.37 (3:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, CD_3CN) δ: 7.98 (d, 1H, *J*

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= 6.0 Hz), 7.59 (d, 2H, J = 9.2 Hz), 7.43 (bs, 1H), 7.26 (d, 1H, J = 8.8 Hz), 6.41 (dd, 1H, J = 2.0, 5.6 Hz), 6.28 (d, 1H, J = 2.0 Hz), 3.80 (s, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ: 167.02, 157.46, 148.65, 140.65, 128.56, 125.11, 120.03, 103.84, 93.86, 54.88. HRMS calcd for $C_{12}H_{11}ClN_2O$ $[M + H]^+$: 235.0633, found 235.0632.

***N*-(4-Chlorophenyl)-6-methylpyridin-2-amine (10).** 0.596 mmol scale: 63 mg, 48% yield. Purification involved addition of 5:1 hexanes/EtOAc with 5% DCM (just enough to dissolve) and washing with water (3 × 10 mL) and brine (10 mL). The organics were dried over sodium sulfate and concentrated in vacuo. The semipure material was then subjected to flash chromatography on Florisil (DCM → 5% EtOAc/DCM) to give **10** as an amorphous solid. R_f = 0.36 (5:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, CD_3CN) δ: 7.66 (d, 2H, J = 8.8 Hz), 7.46−7.41 (m, 2H), 7.25 (d, 2H, J = 8.8 Hz), 6.65 (dd, 1H, J = 0.4, 7.2 Hz), 6.58 (d, 1H, J = 8.0 Hz), 2.39 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ: 157.4, 156.1, 141.7, 138.8, 129.4, 125.7, 120.6, 115.0, 108.1, 24.4. HRMS calcd for $C_{12}H_{12}ClN_2$ $[M + H]^+$: 219.0684, found 219.0670.

3,5-Dibromo-*N*-(4-chlorophenyl)pyridin-2-amine (11). 0.316 mmol scale: 47 mg, 41% yield. Purification involved addition of 5:1 hexanes/EtOAc and washing with water (3 × 10 mL) and brine (10 mL). The organics were dried over sodium sulfate and concentrated in vacuo. The mostly pure material was then subjected to flash chromatography on Florisil (DCM → 5% EtOAc/DCM) to give **11** as a crystalline solid (mp = 98−100 °C). R_f = 0.69 (5:1 hexanes/EtOAc). ^{1}H NMR (400 MHz, CD_3CN) δ: 8.17 (d, 1H, J = 2.4 Hz), 8.03 (d, 1H, J = 2.0 Hz), 7.59 (d, 2H, J = 8.8 Hz), 7.37 (bs, 1H), 7.32 (d, 2H, J = 9.2 Hz). ^{13}C NMR (100 MHz, CD_3CN) δ: 152.0, 147.6, 143.2, 139.6, 129.4, 128.2, 123.3, 123.3, 109.1, 107.4. HRMS calcd for $C_{11}H_8Br_2ClN_2$ $[M + H]^+$: 362.8716, found 362.8714.

6-((4-Chlorophenyl)amino)nicotinonitrile and 2-((4-Chlorophenyl)amino)nicotinonitrile (12a and 12b). 0.666 mol scale: 111 mg, 73% combined yield. Purification involved addition of 5:1 hexanes/EtOAc and washing with water (3 × 10 mL) and brine (10 mL). The organics were dried over sodium sulfate and concentrated in vacuo. Compound **12a** is an amorphous solid and **12b** is a crystalline solid (mp = 129−131 °C). If any minor impurities remain flash chromatography on Florisil (DCM→5% EtOAc/DCM) can be used. R_f = (**12a**) 0.14 and (**12b**) 0.40 (5:1 hexanes/EtOAc). **12a**. ^{1}H NMR (400 MHz, CD_3CN) δ: 8.48 (d, 1H, J = 2.4 Hz), 8.04 (bs, 1H), 7.75 (dd, 1H, J = 2.4, 8.8 Hz), 7.62 (d, 2H, J = 8.8 Hz), 7.33 (d, 2H, J = 8.8 Hz), 6.81 (d, 1H, J = 8.8 Hz). ^{13}C NMR (100 MHz, CD_3CN) δ: 158.4, 153.5, 140.7, 139.6, 129.7, 128.1, 122.4, 119.0, 111.1, 99.9. **12b**. ^{1}H NMR (400 MHz, CD_3CN) δ: 8.33 (dd, 1H, J = 2.0, 4.8 Hz), 7.92 (dd, 1H, J = 2.0, 7.6 Hz), 7.59 (d, 2H, J = 8.8 Hz), 7.33 (d, 2H, J = 8.8 Hz), 6.88 (dd, 1H, J = 4.8, 7.6 Hz). ^{13}C NMR (100 MHz, CD_3CN) δ: 156.9, 153.0, 143.6, 139.2, 129.4, 128.7, 123.9, 116.9, 115.7, 94.7. HRMS calcd for $C_{12}H_9ClN_3$ $[M + H]^+$: 230.0480, found 230.0480.

6-(Naphthalen-2-ylamino)nicotinonitrile and 2-(Naphthalen-2-ylamino)nicotinonitrile (13a and 13b). 0.458 mmol scale: 94 mg, 84% combined yield. Purification involved addition of 5:1 hexanes/EtOAc and washing with water (3 × 10 mL) and brine (10 mL). The organics were dried over sodium sulfate and concentrated in vacuo. Both isomers were isolated as amorphous solids and could be separated by flash chromatography on Florisil (DCM5% EtOAc/DCM). R_f = (**13a**) 0.12 and (**13b**) 0.38 (5:1 hexanes/EtOAc). **13a**. ^{1}H NMR (400 MHz, CD_3CN) δ: 8.54 (d, 1H, J = 2.4 Hz), 8.28 (d, 1H, J = 2.4 Hz), 8.19 (bs, 1H), 7.83 (apparent q, 3H, J = 8.0 Hz), 7.77 (dd, 1H, J = 2.4, 9.2 Hz), 7.59 (dd, 1H, J = 2.4, 8.8 Hz), 7.40 (td, 1H, J = 1.2, 7.6 Hz), 6.91 (dd, 1H, J = 0.4, 8.8 Hz). ^{13}C NMR (100 MHz, CD_3CN) δ: 158.7, 153.6, 140.6, 138.2, 135.0, 131.0, 129.5, 128.5, 128.1, 127.5, 125.5, 121.9, 119.1, 116.8, 111.0, 99.8. **13b**. ^{1}H NMR (400 MHz, CD_3CN) δ: 8.39 (dd, 1H, J = 2.0, 5.2 Hz), 8.18 (d, 1H, J = 1.6 Hz), 7.95 (ddd, 1H, J = 0.4, 2.0, 7.6 Hz), 7.86−7.80 (m, 3H), 7.69 (bs, 1H), 7.65 (dd, 1H, J = 2.4, 8.8 Hz), 7.48 (t, 1H, J = 8.0 Hz), 7.42 (t, 1H, J = 6.8 Hz), 6.90 (ddd, 1H, J = 0.8, 4.8, 7.6 Hz). ^{13}C NMR (100 MHz, CD_3CN) δ: 157.1, 153.1, 143.6, 138.0, 134.8, 131.2, 129.0, 128.4, 128.1, 127.3, 125.7, 123.1, 117.1, 115.6, 94.7. HRMS calcd for $C_{16}H_{12}N_3$ $[M + H]^+$: 246.1026, found 246.1030.

6-((2,6-Dimethylphenyl)amino)nicotinonitrile and 2-((2,6-Dimethylphenyl)amino)nicotinonitrile (14a and 14b). 0.500 mmol scale: 50 mg, 45% combined yield. Purification involved flash chromatography on Florisil (DCM → 5% EtOAc/DCM) to give **14a** as a crystalline solid (mp = 117−119 °C) and **14b** as an amorphous solid. R_f = (**14a**) 0.22 and (**14b**) 0.31 (5:1 hexanes/EtOAc). **14a**. ^{1}H NMR (400 MHz, CD_3CN) δ: 8.35 (bs, 1H), 7.65 (dd, 1H, J = 2.0, 8.8 Hz), 7.34 (bs, 1H), 2.15 (s, 6H). ^{13}C NMR (100 MHz, CD_3CN) δ: 160.6, 154.2, 141.1, 137.7, 129.3, 128.9, 128.3, 119.3, 100.9, 98.1, 18.3. **14b**. ^{1}H NMR (400 MHz, CD_3CN) δ: 8.14 (dd, 1H, J = 1.6, 4.8 Hz), 7.86 (dd, 1H, J = 2.0, 7.6 Hz), 7.13 (s, 3H), 7.09 (bs, 1H), 6.72 (dd, 1H, J = 4.8, 7.6 Hz), 2.16 (s, 6H). ^{13}C NMR (100 MHz, CD_3CN) δ: 158.8, 153.7, 143.4, 138.0, 137.0, 128.9, 128.1, 117.4, 113.9, 92.2, 18.5. HRMS calcd for $C_{14}H_{14}N_3$ $[M + H]^+$: 224.1182, found 224.1177.

6-(Benzylamino)nicotinonitrile and 2-(Benzylamino)-nicotinonitrile (15a and 15b). 0.416 mmol scale: 53 mg, 61% combined yield. Purification involved addition of 5:1 hexanes/EtOAc with 5% DCM (just enough to dissolve) and washing with water (3 × 10 mL) and brine (10 mL). The organics were dried over sodium sulfate and concentrated in vacuo. The isomers were separated by flash chromatography on Florisil (DCM→5% EtOAc/DCM) to give **15a** as a crystalline solid (mp = 105−107 °C) and **15b** as an amorphous solid. R_f = (**15a**) 0.18 and (**15b**) 0.44 (5:1 hexanes/EtOAc). **15a**. ^{1}H NMR (400 MHz, CD_3CN) δ: 8.33 (d, 1H, J = 2.4 Hz), 7.59 (dd, 1H, J = 2.0, 8.8 Hz), 7.35−7.32 (m, 4H), 7.26 (sext, 1H, J = 4.4 Hz), 6.53 (d, 1H, J = 8.8 Hz), 6.43 (bs, 1H), 4.57 (d, 2H, J = 6.0 Hz). ^{13}C NMR (100 MHz, CD_3CN) δ: 161.1, 154.1, 141.2, 140.1, 129.4, 128.2, 128.0, 119.5, 97.2, 45.4. **15b**. ^{1}H NMR (400 MHz, CD_3CN) δ: 8.21 (dd, 1H, J = 1.6, 4.8 Hz), 7.77 (dd, 1H, J = 2.0, 7.6 Hz), 7.36−7.29 (m, 4H), 7.26−7.21 (m, 1H), 6.64 (dd, 1H, J = 5.2, 7.6 Hz), 6.28 (bs, 1H), 4.67 (d, 2H, J = 6.0 Hz). ^{13}C NMR (100 MHz, CD_3CN) δ: 159.3, 153.5, 142.9, 140.9, 129.3, 128.1, 127.8, 117.4, 113.1, 92.4, 45.0. HRMS calcd for $C_{13}H_{12}N_3$ $[M + H]^+$: 210.1026, found 210.1015.

(*S*)-6-((1-Phenylethyl)amino)nicotinonitrile and (*S*)-2-((1-Phenylethyl)amino)nicotinonitrile (16a and 16b). 0.333 mmol scale: 40 mg, 54% combined yield. Purification involved addition of 5:1 hexanes/EtOAc with 5% DCM (just enough to dissolve) and washing with water (3 × 10 mL) and brine (10 mL). The organics were dried over sodium sulfate and concentrated in vacuo. The mostly pure material was then subjected to flash chromatography on Florisil (DCM → 5% EtOAc/DCM) to give the isomer mixture as an amorphous solid. R_f = (**16a**) 0.23 and (**16b**) 0.53 (5:1 hexanes/EtOAc). **16a**. ^{1}H NMR (400 MHz, CD_3CN) δ: 8.27 (d, 1H, J = 2.4 Hz), 7.55 (dd, 1H, J = 2.4, 8.8 Hz), 7.38−7.30 (m, 4H), 7.25−7.21 (m, 1H), 6.47 (d, 1H, J = 8.8 Hz), 6.40 (bs, 1H), 5.04 (bs, 1H), 1.49 (d, 3H, J = 6.8 Hz). ^{13}C NMR (100 MHz, CD_3CN) δ: 160.4, 154.0, 145.8, 140.1, 129.5, 127.9, 126.9, 119.5, 100.9, 97.2, 51.7, 23.6. **16b**. ^{1}H NMR (400 MHz, CD_3CN) δ: 8.16 (dd, 1H, J = 2.0, 5.2 Hz), 7.76 (dd, 1H, J = 2.0, 7.6 Hz), 7.41−7.38 (m, 2H), 7.34−7.30 (m, 2H), 7.22 (tt, 1H, J = 1.2, 7.2 Hz), 6.62 (dd, 1H, J = 4.8, 7.6 Hz), 5.88 (bs, 1H), 5.31 (quint, 1H, J = 6.8 Hz), 1.55 (d, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, CD_3CN) δ: 158.6, 153.5, 146.0, 143.0, 129.4, 127.8, 127.0, 117.4, 113.2, 92.5, 51.5, 23.1. HRMS calcd for $C_{14}H_{14}N_3$ $[M + H]^+$: 224.1182, found 224.1144.

6-(Pentylamino)nicotinonitrile and 2-(Pentylamino)-nicotinonitrile (17a and 17b). 0.500 mmol scale: 53 mg, 56% combined yield. Purification involved addition of 5:1 hexanes/EtOAc and washing with water (3 × 10 mL) and brine (10 mL). The organics were dried over sodium sulfate and concentrated in vacuo. The individual isomers were separated by preparative TLC to give both as amorphous solids. R_f = (**17a**) 0.23 and (**17b**) 0.53 (5:1 hexanes/EtOAc). **17a**. ^{1}H NMR (400 MHz, CD_3CN) δ: 8.31 (d, 1H, J = 2.0 Hz), 7.56 (d, 1H, J = 8.0 Hz), 6.46 (d, 1H, J = 8.8 Hz), 5.95 (bs, 1H), 3.31 (q, 2H, J = 6.4 Hz), 1.57 (q, 2H, J = 7.2 Hz), 1.35−1.31 (m, 4H), 0.90 (t, 3H, J = 6.4 Hz). ^{13}C NMR (100 MHz, CD_3CN) δ: 161.3, 154.1, 139.9, 139.9, 119.7, 96.4, 42.0, 29.8, 29.5, 23.1, 14.3. **17b**. ^{1}H NMR (400 MHz, CD_3CN) δ: 8.24 (dd, 1H, J = 1.6, 4.8 Hz), 7.72 (dd, 1H, J = 1.6, 7.6 Hz), 6.60 (dd, 1H, J = 4.8, 7.6 Hz), 5.71 (bs, 1H), 3.44 (d, 2H, J = 6.0, 10.0 Hz), 1.60 (quint, 2H, J = 7.2 Hz), 1.36−1.31 (m, 4H), 0.90 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, CD_3CN) δ: 159.6,

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153.6, 142.8, 117.6, 112.4, 92.0 41.8, 29.8, 29.8, 23.1, 14.3. HRMS calcd for $C_{11}H_{16}N_3$ $[M + H]^+$: 190.1339, found 190.1315.

Methyl 6-((4-Chlorophenyl)amino)nicotinate and Methyl 2-((4-Chlorophenyl)amino)nicotinate (18a and 18b). 0.307 mmol scale: 61 mg, 76% combined yield. Purification involved addition of 5:1 hexanes/EtOAc and washing with water (3 × 10 mL) and brine (10 mL). The organics were dried over sodium sulfate and concentrated in vacuo. Preparative TLC was used to separate the isomers. Compound **18a** is a crystalline solid (mp = 179−180 °C), and **18b** is an amorphous solid. R_f = (**18a**) 0.19 and (**18b**) 0.53 (5:1 hexanes/EtOAc). **18a**. ^{1}H NMR (400 MHz, CD_3CN) δ: 8.76 (d, 1H, J = 2.4 Hz), 8.02 (dd, 1H, J = 2.4, 8.8 Hz), 7.95 (bs, 1H), 7.66 (d, 2H, J = 8.8 Hz), 7.32 (d, 2H, J = 8.8 Hz), 6.78 (d, 1H, J = 8.8 Hz), 3.84 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ: 166.7, 159.3, 151.2, 140.1, 138.9, 129.6, 127.6, 122.0, 118.1, 110.5, 52.3. **18b**. ^{1}H NMR (400 MHz, CD_3CN) δ: 10.20 (bs, 1H), 8.37 (dd, 1H, J = 2.0, 4.4 Hz), 8.28 (dd, 1H, J = 2.0, 8.0 Hz), 7.75 (d, 2H, J = 8.8 Hz), 7.32 (d, 2H, J = 8.8 Hz), 6.85 (dd, 1H, J = 4.4, 7.6 Hz), 3.91 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ: 168.8, 156.6, 153.8, 141.2, 139.9, 129.4, 127.5, 122.8, 115.1, 108.6, 53.1. HRMS calcd for $C_{13}H_{12}ClN_2O_2$ $[M + H]^+$: 263.0582, found 263.0580.

***N*-(4-Chlorophenyl)isoquinolin-1-amine (19b).** 0.413 mmol scale: 63 mg, 60% yield. Purification involved subjection to flash chromatography on Florisil (DCM → 5% EtOAc/DCM) to give **19b** as a crystalline solid (mp = 129−131 °C) and the only observable product. R_f = (**19b**) 0.47 (5:1 hexanes/EtOAc). **19b**. ^{1}H NMR (400 MHz, CD_3CN) δ: 8.19 (d, 1H, J = 8.4 Hz), 7.99 (d, 1H, J = 5.6 Hz), 7.92 (bs, 1H), 7.81 (d, 2H, J = 8.4 Hz), 7.78 (d, 1H, J = 7.6 Hz), 7.67 (td, 1H, J = 1.2, 7.2 Hz); 7.58 (td, 1H, J = 1.2, 7.6 Hz), 7.31 (d, 2H, J = 8.8 Hz), 7.16 (d, 1H, J = 6.0 Hz). ^{13}C NMR (100 MHz, CD_3CN) δ: 153.3, 141.4, 141.1, 138.4, 131.1, 129.3, 128.0, 127.5, 127.0, 123.3, 122.8, 119.7, 114.3. HRMS calcd for $C_{15}H_{12}ClN_2$ $[M + H]^+$: 255.0684, found 255.0694.

***N*-(4-Chlorophenyl)-3-nitropyridin-2-amine and *N*-(4-Chlorophenyl)-5-nitropyridin-2-amine (20a and 20b).** 0.314 mmol scale: 35 mg, 45% combined yield. Purification involved subjection to flash chromatography on Florisil (DCM → 5% EtOAc/DCM) to give **20a** as a crystalline solid (mp = 152−154 °C) and **20b** as a crystalline solid (mp = 126−127 °C). R_f = (**20a**) 0.14 and (**20b**) 0.49 (5:1 hexanes/EtOAc). **20a**. ^{1}H NMR (400 MHz, CD_3CN) δ: 9.04 (d, 1H, J = 2.8 Hz), 8.31 (bs, 1H), 8.24 (dd, 1H, J = 2.8, 9.2 Hz), 7.67 (d, 2H, J = 8.8 Hz), 7.37 (d, 2H, J = 9.2 Hz), 6.82 (d, 1H, J = 0.8, 9.2 Hz). ^{13}C NMR (100 MHz, CD_3CN) δ: 159.9, 146.7, 139.2, 133.6, 129.8, 129.5, 128.8, 122.8, 110.5. **20b**. ^{1}H NMR (400 MHz, CD_3CN) δ: 9.93 (bs, 1H), 8.54 (dd, 1H, J = 2.0, 8.4 Hz), 8.47 (dd, 1H, J = 4.6, 4.4 Hz), 7.68 (d, 2H, J = 8.8 Hz), 7.38 (d, 2H, J = 8.8 Hz), 6.94 (dd, 1H, J = 4.4, 8.0 Hz). ^{13}C NMR (100 MHz, CD_3CN) δ: 155.9, 150.9, 138.40, 136.5, 134.7, 129.7, 129.6, 125.2, 115.6. HRMS calcd for $C_{11}H_9ClN_3O_2$ $[M + H]^+$: 250.0378, found 250.0376.

***N*-(4-Chlorophenyl)-5-methylpyridin-2-amine and *N*-(4-Chlorophenyl)-3-methylpyridin-2-amine (21a and 21b).** 0.577 mmol scale: 51 mg, 40% combined yield. Purification involved addition of 5:1 hexanes/EtOAc and washing with water (3 × 10 mL) and brine (10 mL). The organics were dried over sodium sulfate and concentrated in vacuo. The semipure material was then subjected to flash chromatography on Florisil (DCM → 5% EtOAc/DCM) to give **21a** as a crystalline solid (mp = 122−123 °C) and **21b** as an amorphous solid. R_f = **21a**: 0.38 and **21b**: 0.53 (5:1 hexanes/EtOAc). **21a**. ^{1}H NMR (400 MHz, CD_3CN) δ: 8.00 (s, 1H), 7.59 (d, 2H, J = 8.8 Hz), 7.39 (dd, 1H, J = 2.8, 6.8 Hz), 7.25 (d, 2H, J = 8.8 Hz), 6.71 (d, 1H, J = 8.8 Hz), 2.20 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ: 166.7, 159.3, 151.2, 140.1, 138.9, 129.6, 127.6, 122.0, 118.1, 110.5, 52.3. **21b**. ^{1}H NMR (400 MHz, CD_3CN) δ: 8.01 (dd, 1H, J = 1.6, 4.8 Hz), 7.68 (d, 2H, J = 8.8 Hz), 7.43 (dd, 1H, J = 0.8, 7.6 Hz), 7.27 (d, 2H, J = 8.8 Hz), 6.83 (bs, 1H), 6.75 (dd, 1H, J = 5.2, 7.6 Hz), 2.25 (s, 3H). ^{13}C NMR (100 MHz, CD_3CN) δ: 154.9, 145.5, 141.5, 138.9, 129.2, 126.2, 121.9, 120.0, 116.4, 17.5. HRMS calcd for $C_{12}H_{12}ClN_2$ $[M + H]^+$: 219.0684, found 219.0670.

3-(Methoxycarbonyl)pyridine 1-Oxide (1i). The compound was prepared as previously described. Oxidation of methyl nicotinate was accomplished with *m*-CPBA.[19]

3-Nitropyridine Oxide (1k). The procedure was based on a previous reaction.[20] To 3-nitropyridine (2.0 g, 16.1 mmol, 1 equiv) and sodium bicarbonate (4.33 g, 51.6 mmol, 3.2 equiv) in MeOH (100 mL) flushed with nitrogen was added Oxone (11.14 g, 18.1 mmol, 1.125 equiv) and then water (50 mL). The mixture was heated to 47 °C under nitrogen for 20 h. The reaction was stopped at partial completion; the solid was filtered off and washed with MeOH. The filtrate was concentrated, leaving only water, which was extracted with DCM (3 × 50 mL) and EtOAc (3 × 30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Ether was added, and the resulting orange amorphous solid was collected as product **1k** (396 mg, 18%). Note: a more efficient method for product isolation may involve simply concentrating all solvent after filtration, including water, and purifying the crude product as some product seems to be lost to the aqueous layer during extraction. R_f = 0.31 (7% MeOH/DCM). ^{1}H NMR (400 MHz, CD_3OD) δ: 9.12 (s, 1H), 8.61 (dquint, 1H, J = 0.8, 6.8 Hz), 8.31 (dquint, 1H, J = 0.8, 8.4 Hz), 7.74 (t, 1H, J = 7.6 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ: 148.6, 145.2, 136.8, 128.1, 123.8. HRMS calcd for $C_5H_5N_2O_3$ $[M + H]^+$: 141.0295, found 141.0262.

1-Chloro-4-isocyanobenzene (2b). To a solution of commercially available *N*-(4-chlorophenyl)formamide (4.0 g, 25.7 mmol, 1.0 equiv) in DCM (200 mL) at 0 °C was added Et_3N (10.71 mL, 77.1 mmol, 3 equiv) followed by phosphorus oxychloride (2.83 mL, 30.9 mmol, 1.2 equiv). The mixture was warmed to 23 °C and stirred for 14 h, at which time it was poured into saturated aqueous sodium bicarbonate (200 mL) and extracted with DCM (2 × 200 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to yield **2b**[21] (2.93 g, 83%) as a tan amorphous solid. NMR data matched those from ref 21.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds. Partial charge data for selected intermediates and X-ray structures for **SI-6** and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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