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# LEWIS ACID-CATALYZED BORONO-MINISCI REACTIONS OF ARYLBORONIC ACIDS AND HETEROCYCLES

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**Abstract** – A Lewis acid-catalyzed Minisci reaction between arylboronic acids and heterocycles has been developed. This radical-coupling reaction was demonstrated employing several different heterocycles as well as electron-rich arylboronic acids. Quinoline substrates afforded modest regioselectivity for substitution at the 4-position under the reaction conditions, in contrast to previously reported Brønsted acid-mediated reactions with quinoline substrates that favored substitution at the 2-position.

The Minisci reaction has been a powerful reaction for the derivatization of heterocycles.[1] The Minisci reaction is broadly defined as the addition of a radical to a heterocycle and subsequent rearomatization of the heterocycle. While many radical precursors have been demonstrated to work in this reaction, arylboronic acids have only recently been identified as convenient sources of aryl radical precursors.[2] One of the remaining drawbacks to the Minisci reaction is the lack of regioselectivity. The regioselectivity in these radical reactions is determined by the inherent reactivity of the substrate.[3] We hypothesized that Lewis acids could promote regioselective Minisci reactions by sterically blocking access to the electrophilic 2-position of heterocycles.

Alternative methods have been developed to provide heterocycle-aryl coupling.[4-7] An approach that attracted our interest was precoordination of a Lewis acid to the heterocycle followed by addition of a Grignard or zinc ionic nucleophile that provided one regioisomer of the coupled product.[8] Typically in a Minisci reaction the heterocycle is activated by a Brønsted acid. We sought to examine whether Lewis acids would be effective catalysts in radical Minisci reactions and to evaluate the regioselectivity in these reactions to determine if the Lewis acid coordination could overcome the inherent reactivity of the heterocycle.

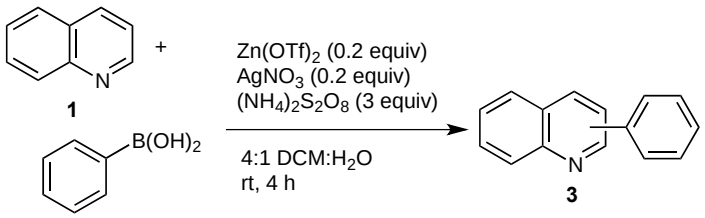
Lewis acids have previously been employed in Minisci reactions.[9,10] These reactions occur under forcing thermal conditions, making the possibility for a regioselective reaction unlikely. The coupling between

arylboronic acids and heterocycles would provide a reaction system that favors monoarylation and proceeds under mild reaction conditions, creating the possibility of a Lewis acid-catalyzed regioselective Minisci reaction.

In order for this approach to work, the Lewis acid must be effective in an aqueous solvent mixture. There have been reports of Lewis acids being effective in aqueous solvent mixtures which was a concern given that a biphasic reaction medium is required for the Brønsted acid-mediated Minisci coupling between heterocycles and arylboronic acids.[11,12,2a] Baran's coupling of zinc sulphinate salts with heterocycles that generate alkyl radicals does not require the addition of Brønsted acids in biphasic solvent systems, suggesting the Zn metal may be activating the heterocycle as a Lewis acid.[13] Given this precedent, Lewis acids were considered to be a viable activator for the electron deficient heterocycles in Minisci reactions in biphasic solvent systems.

We started our investigations by examining quinoline and phenylboronic acid with the use of zinc triflate ($Zn(OTf)_2$) as a catalyst using similar biphasic conditions to those developed by Baran (Scheme 1).[2] $Zn(OTf)_2$ (0.2 equiv) was found to promote the reaction in 4 h at room temperature, providing the product in 68% yield. Encouragingly, this reaction favored the 4-substituted product (1.5:1, C4:C2), in contrast to the Brønsted acid-mediated reaction that favored the 2-substituted product reported by Baran (61%, 2:1 C2:C4). Control experiments revealed that catalytic amounts of zinc triflate and silver nitrate were both required to maintain the reaction efficiency (entries 2 and 3). Next, the counterion on the Lewis acid catalyst was substituted to determine if a more tightly coordinating counterion would improve the regioselectivity in the reaction. In the reaction with $ZnBr_2$, no product was observed after 12 h, indicating that the $ZnBr_2$ inhibits the $AgNO_3$-catalyzed background reaction. The reaction employing $Zn(OAc)_2$ as a catalyst produced a 35% yield (1.5:1 C4:C2), but required 12 h to reach completion. These results suggest a strongly coordinating counterion interfers with the Zn cation's ability to coordinate and activate the nitrogen heterocycle for radical addition. Transition metal cations of different sizes were then examined to determine the effect on the yield and regioselectivity of the reaction. $Sc(OTf)_3$ ($Sc^{3+}$, 88.5 pm) and $La(OTf)_3$ ($La^{3+}$, 117.2 pm) were competent catalysts under the reaction conditions providing the products in 67% and 63% yields, respectively (entries 7 and 8) but both catalysts provided the same regioselectivity (1.5:1, C4:C2) as the $Zn(OTf)_2$-catalyzed reaction. A control experiment using a catalytic amount of trifluoromethanesulfonic acid (0.4 equiv) revealed that it could not function as a catalyst, providing only a 27% yield of the product. While the nature of the activation of the heterocycle by the $Zn(OTf)_2$ catalyst remains unclear at this time, this experiment demonstrates that $Zn(OTf)_2$ was an effective catalyst and superior in efficiency to catalytic amounts of the related Brønsted acid in the biphasic solvent system. Given the success of $Zn(OTf)_2$, AgOTf was evaluated as a catalyst to see if it could serve the dual purpose of radical initiator and Lewis acid. While the reaction with just AgOTf

provided the desired product and complete consumption of starting material, the yield was greatly reduced (entry 10). The $Zn(OTf)_2$-catalyzed reaction proved very sensitive to solvent, requiring both dichloromethane and water. Use of more coordinating organic solvents such as DMSO and acetonitrile completely shut down the reaction.



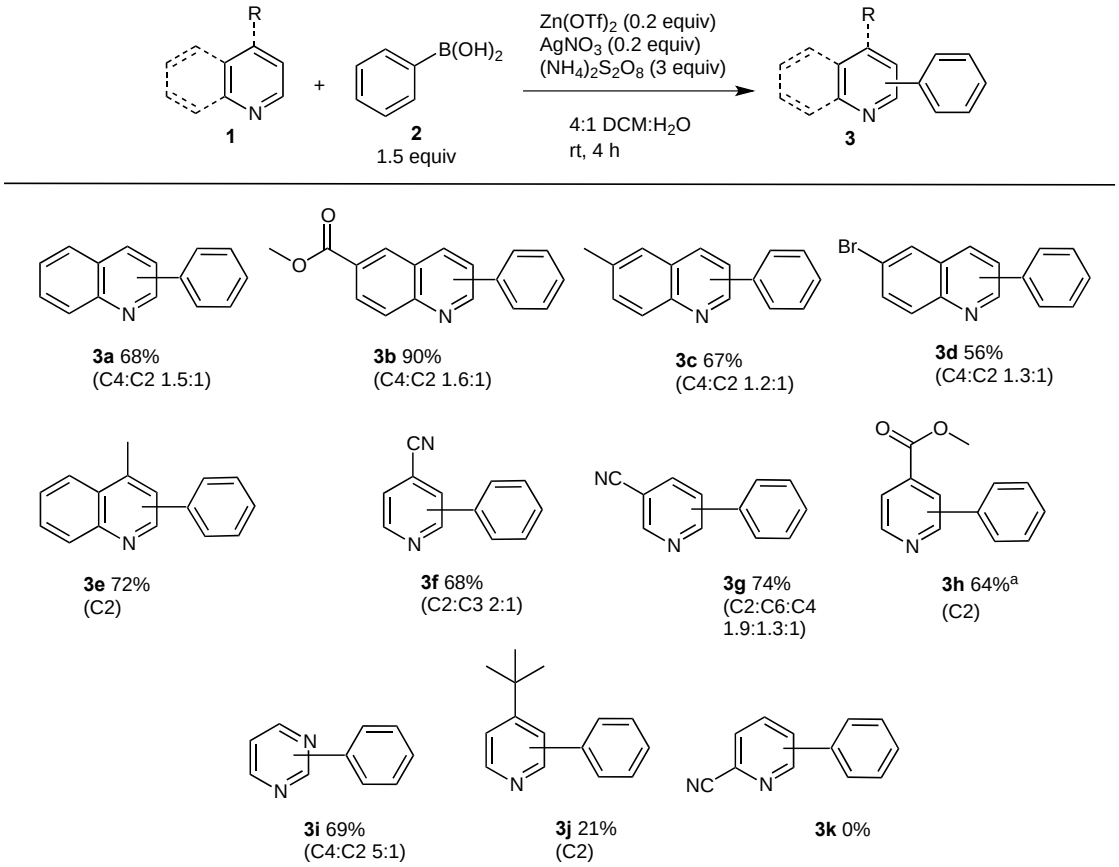

| Entry | Change from Standard Conditions | C4:C2 ratio | Yield (%) |
|---|---|---|---|
| 1 | none | 1.5:1 | 68 |
| 2 | no $AgNO_3$ | NA | 0 |
| 3 | no $Zn(OTf)_2$ | 1:1 | 35 |
| 4 | $ZnBr_2$ (0.2 equiv) and no $Zn(OTf)_2$ | NA | 0 |
| 5 | $Zn(OAc)_2$ (0.2 equiv) and no $Zn(OTf)_2$ | 1.5:1 | 35 [a] |
| 6 | $Zn(OTf)_2$ (0.3 equiv) | 1.5:1 | 61 [a,b] |
| 7 | $Sc(OTf)_3$ (0.2 equiv) and no $Zn(OTf)_2$ | 1.5:1 | 67 [b] |
| 8 | $La(OTf)_3$ (0.2 equiv) and no $Zn(OTf)_2$ | 1.5:1 | 63 [b] |
| 9 | $CF_3SO_3H$ (0.4 equiv) and no $Zn(OTf)_2$ | 1:1 | 27 [c] |
| 10 | AgOTf (0.2 equiv) and no $Zn(OTf)_2$ and no $AgNO_3$ | 2:1 | 35 |
| 11 | AgOTf (0.2 equiv) and no $Zn(OTf)_2$ | 2:1 | 15 [b] |
| 12 | $Zn(OTf)_2$ (0.1 equiv) | 1.5:1 | 34 |
| 13 | only DCM as solvent | NA | 0 |
| 14 | DMSO instead of DCM | NA | 0 |
| 15 | MeCN instead of DCM | NA | 0 |

[a]Reaction time 12 h. [b] $^1H$ NMR yield using 1,4-dimethoxybenzene as an internal standard.
[c]15% of the starting material was also recovered.

**Scheme 1. Optimization of Reaction Conditions**

With optimized conditions in hand, we examined other heterocycles in this reaction (Scheme 2).[14] Given the regioselectivity obtained in the reaction of quinoline, several 6-substituted quinolines were employed as substrates. The 6-substituted methyl ester provided an excellent yield (90%) of the product **3b** and a ratio of 1.6:1 C4:C2 regioselectivity, similar to that observed with quinoline. The 6-methyl and 6-bromoquinoline substrates also provided modest regioselectivity for the C4-substituted products **3c** and **3d**. Examination of substituted pyridines revealed that electron-deficient pyridines performed best in this Lewis acid-catalyzed reaction. Reactions employing 4-cyano and 3-cyanopyridines both provided the desired products in good yields. A limitation was that 2-substituted pyridines such as 2-cyanopyridine provided none of the desired product under the standard conditions, similar to previous findings.[2] Despite the altered regioselectivity observed with quinoline and substituted quinolines, the regioselectivity observed with substituted pyridines was similar to that reported with Brønsted acid-mediated coupling, indicating that the Lewis acid was unable to overcome the inherent selectivity in pyridine substrates.[3] The reaction using 4-*tert*-butylpyridine did not go to completion under these conditions and provided only a

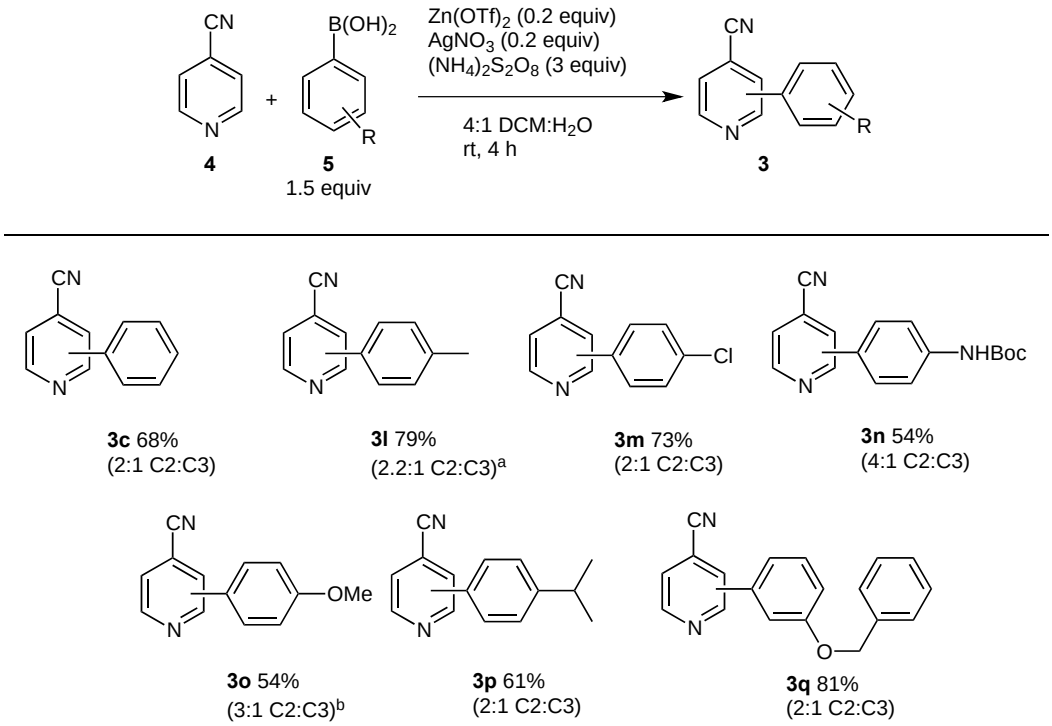
21% yield of product **3j**, showing the limitations of this $Zn(OTf)_2$-catalyzed reaction.




[a]1.3 equivalents of phenylboronic acid were employed to avoid double addition.

**Scheme 2. Scope of Heterocycles**

Next, varying the arylboronic acid component was examined. 4-Cyanopyridine was chosen as the heterocycle to evaluate different arylboronic acids in this reaction (Scheme 3). Electron-rich substituents were well tolerated. The regioselectivity with all substrates favored the 2-substituted product. Notably, 4-(*N*-Boc-amino)phenylboronic acid was effective in this reaction providing product **3n** in 54% yield. The Boc protecting group would potentially be incompatible with the TFA-mediated reaction conditions Baran reported. *p*-Methoxyphenylboronic acid provided a 6% yield of an unusual minor side product, the 2,3-disubstituted cyanopyridine. Reactions employing less *p*-methoxyphenylboronic acid (1.2 equiv) reduced but did not eliminate the presence of this side product. When using *p*-tolylboronic acid, a small amount of the 2-substituted product was isolated as the 4-formylphenyl-substituted cyanopyridine. When 0.1 equiv of $Zn(OTf)_2$ was employed, this side product was reduced, indicating the zinc catalyst was responsible for this additional oxidation. No benzylic oxidation products were observed in the reaction with 4-isopropylphenylboronic acid.




[a]16% of the 2-substituted product was isolated as the 4-formylphenyl addition product.
[b]6% was the 2,3-disubstituted product.

**Scheme 3. Scope of Arylboronic Acids**

We have developed a Lewis acid-catalyzed Minisci reaction between arylboronic acids and heterocycles. Reactions employing quinoline substrates exhibited modest regioselectivity favoring the C4-substituted products that is different than previously reported examples with stoichiometric Brønsted acid mediators of this reaction that favor the C2-substituted products. A range of heterocycles as well as electron-rich arylboronic acids including 4-(*N*-Boc-amino)phenylboronic acid were found to work in this reaction.

## EXPERIMENTAL

**Standard Procedure:** Ammonium persulfate (3 equiv, 342 mg), phenylboronic acid (1.5 equiv, 91 mg), silver nitrate (0.2 equiv, 17 mg), and zinc trifluoromethanesulfonate (0.2 equiv, 36 mg) were combined in a 10 mL round bottom flask. A heterocycle (1 equiv, 0.5 mmol) was then added to the same flask and solvated with water (0.4 mL) and $CH_2Cl_2$ (1.6 mL). The resulting mixture was sonicated for 10 sec and placed on a stir plate to stir vigorously at room temperature for 4 h. The reaction was quenched with 28% ammonium hydroxide (2 mL), diluted with water (10 mL), and extracted with $CH_2Cl_2$ (3 x 10 mL). The organic layer was dried over sodium sulfate, filtered through cotton, and evaporated en vacuo. The products were purified by column chromatography ($SiO_2$, 5-20% EtOAc/hexanes). Products **3b**, **3c**, and **3d** required further purification by crystallization as the trifluoromethanesulfonic acid salts and recrystallization from THF/hexanes.

**3a** 42 mg of 4-phenylquinoline as a colorless solid and 28 mg of 2-phenylquinoline as an orange oil were isolated providing a combined yield of 68% in a 1.5:1 ratio (C4:C2). **2-phenylquinoline:**[14] $^1$H NMR (400 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 8.6, 0.8 Hz, 1H), 8.20 – 8.15 (m, 2H), 7.89 (d, *J* = 8.6 Hz, 1H), 7.83 (d, *J* = 1.6 Hz, 1H), 7.74 (d, *J* = 1.6 Hz, 1H), 7.59 – 7.42 (m, 4H); **4-phenylquinoline:**[15] $^1$H NMR (400 MHz, $CDCl_3$) δ 8.95 (d, *J* = 4.4 Hz, 1H), 8.21 – 8.15 (m, 1H), 7.96 – 7.89 (m, 1H), 7.73 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.59 – 7.43 (m, 6H), 7.34 (d, *J* = 4.4 Hz, 1H).

**3b** 73 mg of methyl 4-phenylquinoline-6-carboxylate as a colorless solid and 46 mg of methyl 2-phenylquinoline-6-carboxylate as a colorless solid were isolated providing a combined yield of 90% in a 1.6:1 ratio (C4:C2). **methyl 4-phenylquinoline-6-carboxylate:**[16] $^1$H NMR (400 MHz, $CDCl_3$) δ 9.01 (d, *J* = 4.4 Hz, 1H), 8.68 (dd, *J* = 1.9, 0.6 Hz, 1H), 8.30 (dd, *J* = 8.8, 1.9 Hz, 1H), 8.20 (dd, *J* = 8.8, 0.6 Hz, 1H), 7.59 – 7.49 (m, 5H), 7.40 (d, *J* = 4.4 Hz, 1H), 3.92 (s, 3H); **methyl 2-phenylquinoline-6-carboxylate:**[17] $^1$H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 1.9 Hz, 1H), 8.33 – 8.29 (m, 2H), 8.21 – 8.18 (m, 3H), 7.95 (d, *J* = 8.6 Hz, 1H), 7.59 – 7.47 (m, 3H), 4.01 (s, 3H).

**3c** 40 mg of 6-methyl-4-phenylquinoline as a colorless solid and 33 mg of 6-methyl-2-phenylquinoline as a colorless solid were isolated providing a combined yield of 67% in a 1.2:1 ratio (C4:C2). **6-methyl-4-phenylquinoline:**[18] $^1$H NMR (400 MHz, Chloroform-d) δ 8.87 (d, *J* = 4.4 Hz, 1H), 8.07 (d, *J* = 8.6 Hz, 1H), 7.69 – 7.64 (m, 1H), 7.59 – 7.46 (m, 6H), 7.29 (d, *J* = 4.4 Hz, 1H), 2.47 (s, 3H); **6-methyl-2-phenylquinoline:**[19] $^1$H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.12 (m, 3H), 8.08 (d, *J* = 8.6 Hz, 1H), 7.84 (d, *J* = 8.6 Hz, 1H), 7.60 – 7.49 (m, 4H), 7.45 (t, *J* = 6.7 Hz, 1H), 2.55 (s, 3H).

**3d** 45 mg of 6-bromo-4-phenylquinoline as a colorless solid and 35 mg of 6-bromo-2-phenylquinoline as a colorless solid were isolated providing a combined yield of 56% in a 1.3:1 ratio (C4:C2). **6-bromo-4-phenylquinoline:**[20] $^1$H NMR (400 MHz, $CDCl_3$) δ 8.95 (d, *J* = 4.4 Hz, 1H), 8.07 – 8.02 (m, 2H), 7.80 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.59 – 7.46 (m, 5H), 7.36 (d, *J* = 4.4 Hz, 1H); **6-bromo-2-phenylquinoline:**[21] $^1$H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.12 (m, 3H), 8.04 (d, *J* = 9.0 Hz, 1H), 7.99 (d, *J* = 2.2 Hz, 1H), 7.91 (d, *J* = 8.7 Hz, 1H), 7.79 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.56 – 7.46 (m, 3H).

**3e** 79 mg of 4-methyl-2-phenylquinoline as a yellow solid was isolated providing a 72% yield. **4-methyl-2-phenylquinoline:**[15] $^1$H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.0 Hz, 1H), 8.05 – 7.94 (m, 1H), 7.72 (d, *J* = 1.2 Hz, 1H), 7.53 (s, 1H), 2.77 (d, *J* = 1.0 Hz, 2H).

**3f** 43 mg of 4-cyano-2-phenylpyridine and 22 mg of 4-cyano-3-phenylpyridine were isolated as pale yellow solids providing a combined yield of 68% in a 2:1 ratio (C2:C3). **4-cyano-2-phenylpyridine:**[2b] $^1$H NMR (400 MHz, $CDCl_3$) δ 8.85 (dd, *J* = 4.9, 1.0 Hz, 1H), 8.04 – 7.96 (m, 2H), 7.94 (t, *J* = 1.2 Hz, 1H), 7.57 – 7.47 (m, 3H), 7.44 (dd, *J* = 5.0, 1.4 Hz, 1H). **4-cyano-3-phenylpyridine:**[2b] $^1$H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.75 (d, *J* = 5.0 Hz, 1H), 7.63 (d, *J* = 5.0 Hz, 1H), 7.61 – 7.49 (m, 5H).

**3g** 21 mg of 6-phenylnicotinonitrile (white solid), 30 mg of 2-phenylnicotinonitrile (white solid) and 16 mg of 4-phenylnicotinonitrile (white solid) were isolated providing a 67% combined yield of the products in a 1.9:1.3:1 ratio (C2:C6:C4). **6-phenylnicotinonitrile:**[22] $^1$H NMR (400 MHz, $CDCl_3$) δ 8.94 (d, *J* = 1.3 Hz, 1H), 8.08 – 8.02 (m, 2H), 8.00 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.85 (dd, *J* = 8.3, 0.9 Hz, 1H), 7.54 – 7.48 (m, 3H). **2-phenylnicotinonitrile:**[23] $^1$H NMR (400 MHz, $CDCl_3$) δ 8.88 (dd, *J* = 4.9, 1.8 Hz, 1H), 8.08 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.96 – 7.91 (m, 2H), 7.58 – 7.51 (m, 3H), 7.38 (dd, *J* = 7.9, 4.8 Hz, 1H). **4-phenylnicotinonitrile:**[24] $^1$H NMR (400 MHz, $CDCl_3$) δ 8.96 (s, 1H), 8.82 (d, *J* = 5.2 Hz, 1H), 7.68 – 7.59 (m, 2H), 7.57 – 7.53 (m, 3H), 7.48 (d, *J* = 5.2 Hz, 1H).

**3h** Employing 1.3 equivalents (79 mg) of phenylboronic acid, 68 mg of methyl 2-phenylisonicotinate as a colorless oil was isolated providing a 64% yield. **methyl 2-phenylisonicotinate:**[25] $^1$H NMR (400 MHz, $CDCl_3$) δ 8.84 (dd, *J* = 5.0, 0.9 Hz, 1H), 8.30 (dd, *J* = 1.5, 0.9 Hz, 1H), 8.12 – 7.99 (m, 2H), 7.77 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.62 – 7.35 (m, 3H), 3.99 (s, 3H).

**3i** 50 mg of 4-phenylpyrimidine and 4 mg of 2-phenylpyrimidine as colorless oil were isolated providing a 69% yield of products in a 5:1 ratio (C4:C2). **4-phenylpyrimidine:**[2b] $^1$H NMR (400 MHz, $CDCl_3$) δ 9.27 (d, *J* = 1.4 Hz, 1H), 8.76 (d, *J* = 5.3 Hz, 1H), 8.24 – 8.01 (m, 2H), 7.72 (dd, *J* = 5.4, 1.5 Hz, 1H), 7.60 – 7.46 (m, 3H). **2-phenylpyrimidine:**[2b] $^1$H NMR (400 MHz, $CDCl_3$) δ 8.82 (d, *J* = 4.9 Hz, 2H), 8.45 (ddt, *J* = 4.8, 3.6, 1.4 Hz, 2H), 7.59 – 7.44 (m, 3H), 7.22 – 7.15 (m, 1H).

**3j** 22 mg of 2-phenyl-4-*tert*-butylpyridine as a clear oil (21% yield) was isolated along with 7 mg of recovered starting material (10%). **2-phenyl-4-*tert*-butylpyridine:**[2a] $^1$H NMR (400 MHz, $CDCl_3$) δ 8.62 – 8.59 (m, 1H), 8.02 – 7.94 (m, 2H), 7.71 (dd, *J* = 1.8, 0.6 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.45 – 7.38 (m, 1H), 7.25 (dd, 1H), 1.38 (s, 9H).

**3l** 45 mg of 2-(*p*-tolyl)isonicotinonitrile as a pale yellow solid and 33 mg of an inseparable mixture of 3-(*p*-tolyl)isonicotinonitrile and 2-(4-formylphenyl)isonicotinonitrile were isolated in a 1:0.4 ratio providing a combined yield of 79%. **2-(*p*-tolyl)isonicotinonitrile:**[2b] $^1$H NMR (400 MHz, $CDCl_3$) δ 8.82 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.91 – 7.89 (m, 2H), 7.88 (d, *J* = 1.9 Hz, 1H), 7.39 (dd, *J* = 4.9, 1.4 Hz, 1H), 7.33 – 7.28 (m, 2H), 2.42 (s, 3H); **3-(*p*-tolyl)isonicotinonitrile and 2-(4-formylphenyl)-isonicotinonitrile:**[2b] $^1$H NMR (400 MHz, $CDCl_3$) δ 10.11 (s, 0.4H), 8.91 (dd, *J* = 5.0, 0.9 Hz, 0.4H), 8.85 (d, *J* = 0.9 Hz, 1H), 8.72 (d, *J* = 5.0 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 0.8H), 8.06 – 7.99 (m, 1.2H), 7.60 (dd, *J* = 5.0, 0.8 Hz, 1H), 7.53 (dd, *J* = 4.9, 1.4 Hz, 0.4H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.35 (dt, *J* = 7.8, 0.8 Hz, 2H), 2.44 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 191.8, 157.4, 151.1, 151.0, 148.5, 142.7, 139.9, 138.9, 137.4, 131.7, 130.4, 130.0, 128.8, 127.7, 126.2, 124.3, 122.7, 121.7, 118.8, 116.6, 116.5, 21.4; IR (neat) ν = 3790, 3662, 2254, 1709, 1596, 1548, 1479, 1382, 903, 722, 649 cm$^{-1}$.

**3m** 50 mg of 2-(4-chlorophenyl)isonicotinonitrile and 28 mg of 3-(4-chlorophenyl)isonicotinonitrile were isolated as yellow solids providing a combined yield of 73% in a 2:1 ratio (C2:C3).

**2-(4-chlorophenyl)isonicotinonitrile:**[2b] $^1$H NMR (400 MHz, $CDCl_3$) δ 8.83 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.98 – 7.91 (m, 2H), 7.89 (t, *J* = 1.2 Hz, 1H), 7.47 (s, 1H), 7.46 – 7.41 (m, 2H). **3-(4-chlorophenyl)-isonicotinonitrile:**[2b] $^1$H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.77 (d, *J* = 5.0 Hz, 1H), 7.63 (dd, *J* = 5.0, 0.8 Hz, 1H), 7.52 (s, 4H).

**3n** 63.6 mg of *tert*-butyl (4-(4-cyanopyridin-2-yl)phenyl)carbamate as an off-white solid and 16.6 mg of *tert*-butyl (4-(4-cyanopyridin-3-yl)phenyl)carbamate as a brown oil were isolated for a combined yield of 54%. ***tert*-butyl (4-(4-cyanopyridin-2-yl)phenyl)carbamate:** $^1$H NMR (400 MHz, $CDCl_3$) δ 8.72 (dd, *J* = 5.0, 0.9 Hz, 1H), 7.89 δ 7.84 (m, 2H), 7.80 (t, *J* = 1.2 Hz, 1H), 7.43 (d, *J* = 8.7 Hz, 2H), 7.30 (dd, *J* = 5.0, 1.4 Hz, 1H), 6.66 (s, 1H), 1.46 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 158.2, 152.4, 150.6, 140.6, 131.8, 127.9, 122.9, 121.5, 121.2, 118.6, 116.9, 81.1, 28.4. IR (neat) ν = 3790, 3661, 2254, 1597, 1548, 1526, 1502, 1467, 1385, 903, 722, 650 cm$^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{17}H_{17}N_3O_2Na$, 318.1219; found, 318.1227. ***tert*-butyl (4-(4-cyanopyridin-3-yl)phenyl)carbamate:** $^1$H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 0.8 Hz, 1H), 8.63 (d, *J* = 5.0 Hz, 1H), 7.52 (dd, *J* = 5.0, 0.8 Hz, 1H), 7.47 (d, *J* = 4.8 Hz, 3H), 6.69 (s, 1H), 1.47 (s, 10H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 152.6, 151.0, 148.4, 140.0, 138.4, 129.7, 128.8, 126.2, 118.9, 118.6, 116.6, 81.2, 28.4; IR (neat) ν = 3791, 3662, 2254, 1588, 1529, 1480, 1382, 902, 722, 650 cm$^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{17}H_{17}N_3O_2Na$, 318.1219; found, 318.1229.

**3o** 38.9 mg of 2-(4-methoxyphenyl)isonicotinonitrile as a yellow-orange solid and 21.4 mg of an inseparable mixture of 3-(4-methoxyphenyl)isonicotinonitrile and 2,3-bis(4-methoxyphenyl)-isonicotinonitrile were isolated as a light-yellow solid in a 2:1 ratio for a combined 54% yield in a 3:1 ratio (C2:C3) with the double addition by-product comprising 6% of the total yield. **2-(4-methoxyphenyl)isonicotinonitrile:**[2b] $^1$H NMR (400 MHz, $CDCl_3$) δ 8.73 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.89 (d, *J* = 8.9 Hz, 2H), 7.80 (t, *J* = 1.2 Hz, 1H), 7.30 (dd, *J* = 5.0, 1.4 Hz, 1H), 6.95 (d, *J* = 8.9 Hz, 2H), 3.81 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 161.6, 158.5, 150.6, 130.0, 128.5, 122.4, 121.4, 121.2, 117.0, 114.6, 55.6; IR (neat) ν = 3791, 3662, 2254, 1599, 1530, 1468, 1382, 902, 722, 650 cm$^{-1}$; LC-MS Expected $[M + H]^+$ 211 found 211. **3-(4-methoxyphenyl)isonicotinonitrile**[2b] **and 2,3-bis(4-methoxyphenyl)isonicotinonitrile:** $^1$H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.76 (d, *J* = 4.9 Hz, 0.5H), 8.69 (d, *J* = 5.1 Hz, 1H), 7.59 (dd, *J* = 5.0, 0.8 Hz, 1H), 7.56 – 7.47 (m, 2.5H), 7.25 (d, *J* = 8.9 Hz, 1.5H), 7.16 (d, *J* = 8.7 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 1.5H), 3.78 (s, 1.5H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 160.9, 160.02, 159.98, 159.0, 151.0, 148.5, 148.2, 138.6, 137.2, 131.4, 131.3, 130.6, 130.3, 128.0, 126.8, 126.2, 124.0, 122.3, 118.6, 116.8, 116.7, 114.8, 114.4, 113.6, 55.6, 55.39, 55.36; IR (neat) ν = 3791, 3662, 2254, 1610, 1516, 1479, 1382, 1252, 903, 722, 650 cm$^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{20}H_{16}N_2O_2Na$, 339.1110; found, 339.1098.

**3p** 45 mg of 2-(4-isopropylphenyl)isonicotinonitrile as a pale yellow solid and 23 mg of 3-(4-isopropylphenyl)isonicotinonitrile as an orange oil were isolated providing a combined yield of 61%. **2-(4-isopropylphenyl)isonicotinonitrile:** $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.82 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.94 (s, 1H), 7.93 – 7.89 (m, 2H), 7.40 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.38 – 7.35 (m, 2H), 3.15 – 2.85 (m, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 158.9, 151.5, 150.6, 135.0, 127.3, 127.1, 122.9, 121.9, 121.2, 116.9, 34.1, 23.9; IR (neat) v = 3774, 3662, 2964, 2254, 1710, 1595, 1546, 1468, 1389, 903, 831, 723, 649, 545, 479 cm$^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{15}H_{14}N_2Na$, 245.1055; found, 245.1051. **3-(4-isopropylphenyl)isonicotinonitrile:** $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.86 (d, *J* = 0.9 Hz, 1H), 8.72 (d, *J* = 5.0 Hz, 1H), 7.61 (dd, *J* = 5.0, 0.8 Hz, 1H), 7.54 – 7.50 (m, 2H), 7.43 – 7.38 (m, 2H), 3.08 – 2.90 (m, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 151.1, 150.7, 148.5, 138.9, 132.0, 128.9, 127.4, 126.2, 118.8, 116.7, 34.1, 24.0; IR (neat) v = 3791, 3662, 2254, 1584, 1479, 1382, 903, 832, 722, 650, 591 cm$^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{15}H_{14}N_2Na$, 245.1055; found, 245.1064.

**3q** 71.2 mg of 2-(3-(benzyloxy)phenyl)isonicotinonitrile as a white solid and 45.2 mg of 3-(3-benzyloxy)phenyl)isonicotinonitrile as a brown oil were isolated for a combined 81% yield. **2-(3-(benzyloxy)phenyl)isonicotinonitrile:** $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.74 (dd, *J* = 4.9, 1.0 Hz, 1H), 7.81 (t, *J* = 1.2 Hz, 1H), 7.59 (dd, *J* = 2.6, 1.7 Hz, 1H), 7.46 (ddd, *J* = 7.7, 1.7, 1.0 Hz, 1H), 7.41 – 7.34 (m, 2H), 7.36 – 7.26 (m, 4H), 7.29 – 7.20 (m, 1H), 7.00 (ddd, *J* = 8.2, 2.6, 1.0 Hz, 1H), 5.06 (s, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 159.6, 158.5, 150.6, 138.8, 136.8, 130.2, 128.7, 128.2, 127.6, 123.4, 122.3, 121.3, 119.6, 117.1, 116.8, 113.4, 70.6; IR (neat) v = 3791, 3662, 2254, 1591, 1548, 1468, 1443, 1381, 1291, 1229, 1026, 902, 788, 722, 649 cm$^{-1}$; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{19}H_{15}N_2O$, 287.1184; found, 287.1191. **3-(3-benzyloxy)phenyl)isonicotinonitrile:** $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.67 (d, *J* = 5.0 Hz, 1H), 7.54 (dd, *J* = 5.0, 0.8 Hz, 1H), 7.42 – 7.28 (m, 5H), 7.31 – 7.22 (m, 1H), 7.12 – 7.07 (m, 2H), 7.07 – 7.02 (m, 1H), 5.07 (s, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 159.4, 151.0, 148.9, 138.7, 136.7, 135.8, 130.4, 128.8, 128.3, 127.7, 126.2, 121.6, 119.0, 116.4, 116.3, 115.4, 70.5; IR (neat) v = 3791, 3662, 2254, 1710, 1600, 1480, 1382, 903, 786, 722, 650 cm$^{-1}$; HRMS-ESI (*m/z*) $[M + Na]^+$ calcd for $C_{19}H_{14}N_2ONa$, 309.1004; found, 309.0994.

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