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Perfluorinated pinacol promotes efficient amidination of 2-aminophenylboronic acid

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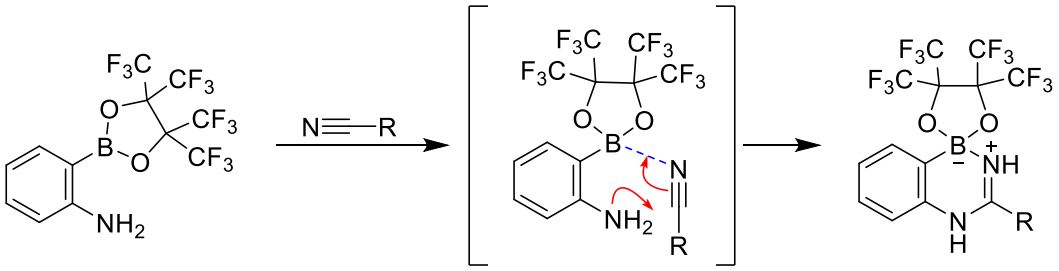
Abstract

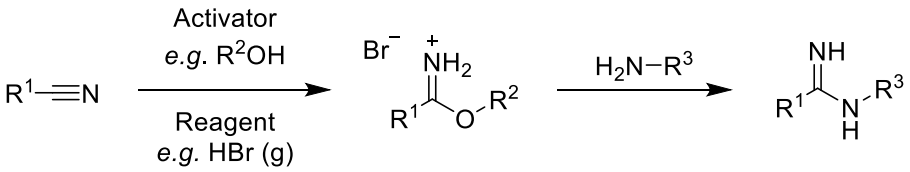
This work reports the use of halogenated alcohols in catalyzing a unique amidination reaction using 2-aminophenylboronic acid. Trials using acetonitrile as the reactant nitrile showed that the amidination efficiency increased from 33% with salicylic acid, to 78% with 2,2,2-trifluoroethanol and finally quantitative yields with perfluorinated pinacol. This protecting group proved to be highly efficient for amidination of several different nitrile groups with only mild heating.



Keywords: Amidination, boronic acid, fluorine, Lewis acid, nitrile

Introduction

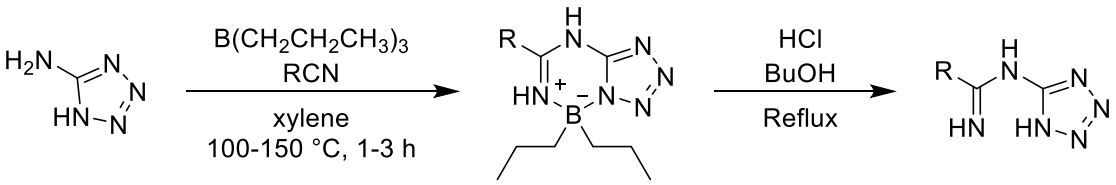
Amidines are found in a number of biologically active molecules, but this molecular structure is underused when compared to the structurally analogous amide bonds. This can best be attributed to the lack of mild but effective ways to install this functionality. Many amidination methods have been developed, but often they require specific precursors limiting the utility of these methods. A review by Granik provides a summary of traditional methodologies,[1] many of which invoke activating the nitriles before the introduction of the amine. Several groups have done this using the Pinner reaction, which works by converting the nitrile into a protonated alkyl iminoester intermediate that is more vulnerable to nucleophilic amines.[1,2] These iminoesters have been produced using simple alcohols reacting with gaseous HCl or HBr, methyl sulfofluoridate, boron trifluoride or methanol at high pressures.[3] An example of this can be seen in **Error! Reference source not found.**.



Scheme 1. Typical Pinner reaction showing the progression of nitriles to amidines.

This two-step synthesis has been used widely since the 1960's and is robust enough to accept both primary and secondary amines. The many problems with the Pinner system and its immediate derivatives are that the reagents used are quite harsh potentially causing secondary side reactions. Significant research has gone into developing new methods that either minimise the use of the harsh reagents or eliminate their use altogether by employing powerful catalysts. Another common method is the use of strong Lewis acids as electron withdrawing groups to catalyse amidine synthesis. In this case, Lewis acids like $AlCl_3$ and $FeCl_3$ are used as electron withdrawing groups when interacting with the nitrile nitrogen, the amine then readily attacks the nitrile in a simple one step reaction. However, this reaction can require temperatures in excess of 150 °C and even then, it is sometimes inefficient.

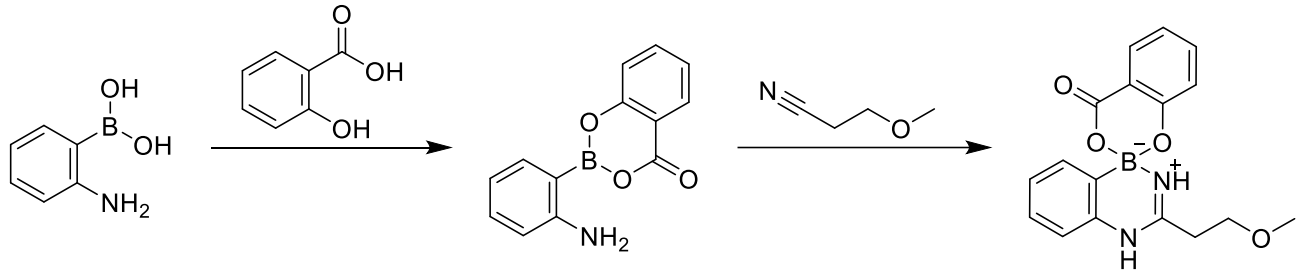
Prior to our work, only one group had used organoboron compounds for the synthesis of amidines, this work was shown across two articles in 1987 and 1989.[4,5] In their first publication, Dorokhov *et al*. described the synthesis of *N*-(5-tetrazolyl)amidines from 5-aminotetrazole through a borane-promoted amidination reaction (Scheme 2).[4] This reaction used an organoborane rather than the Pinner conditions due to the low basicity of the compound and the lower potential for side products.



Scheme 2. Amindination by activation using boranes.

In this two-step reaction, the organoborane activates the nitrile through its Lewis acidity and coordinates this activated nitrile with the 5-aminotriazole after extrusion of a propyl group. The organoborane was cleaved by HCl-promoted solvolysis with butanol, and after column chromatography pure product was isolated.

Common nitriles were tried including *p*-toluenenitrile, *o*-toluenenitrile, phenylnitrile and acetonitrile achieving 67-85% yields. Their next report was similar, this time toward synthesis of *N*-(1,2,4-triazol-5-yl)amidines.[5] For optimum reaction efficiency, the final borane cleavage should be conducted in a sealed ampule which increased the cleavage from 42 to 92%.[5] This method was able to produce yields of between 54-92% for the same nitriles used in the previous study. Finally, our group has previously investigated the use of boronate protecting groups to promote amidination of 2-aminophenylboronic acid (**2-APB**).[6] An example of this chemistry can be seen below in Scheme 3.



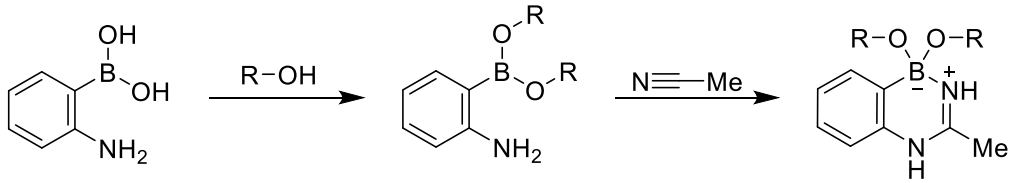
Scheme 3. Amidination reaction promoted by salicylic acid protecting group.

We reported that boronate esters can facilitate amidination of proximal amines under mild conditions initially discovered by reaction with MeCN as solvent. This reaction was similar to an unexpected amidation in this system involving EtOAc as solvent.[7] The presence of the salicylate ester promotes B–N coordination that both enables the reaction and allows crystal formation in many of the products even on 20 mg scale reactions. The chemistry was best suited to the use of aliphatic nitriles, furthermore, reactive functionalities such as bromides can be tolerated. One significant limitation of this method was the inability to readily remove the salicylate ester. Herein, we expand on our prior research to further improve both the efficiency and utility of this amidination reaction.

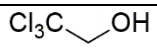
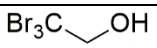
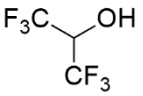
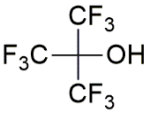
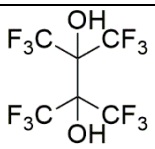
Results and Discussion

Previosuly, we demonstrated that the amidination efficiency of **2-APB** was primarily altered by the electron withdrawing effect of the bound substituent on the boronate ester. To advance this idea, we attempted to synthesise **1** using halogenated alcohols to increase the Lewis acidity of the resultant boronate ester. This reaction and the tested alcohols with their relative conversion efficiencies can be seen in Table 1.

Table 1. Amidination reaction trialing a variety of halogenated alcholols (ROH) ability to promote amidination of **2-APB** with acetonitrile.



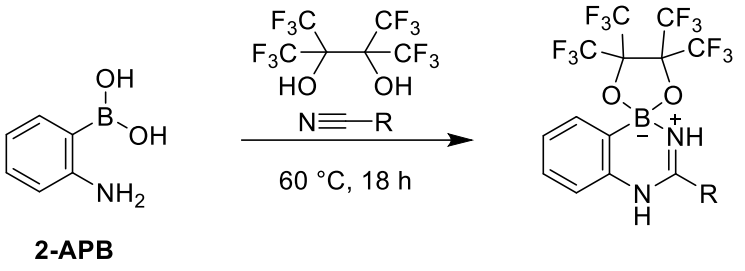
2-APB **1**

Alcohol Name (IUPAC)	Chemical structure	Reactant abbreviation	Reaction efficiency
2,2,2-Trifluoroethanol		TFE	71%
2,2,2-Trichloroethanol		TCE	<1%
2,2,2-Tribromoethanol		TBE	<1%
1,1,1,3,3,3-Hexafluoropropan-2-ol		F_6-OH	4%
1,1,1,3,3,3-Hexafluoro-2-(trifluoromethyl)propan-2-ol		F_9-OH	N.D.
1,1,1,4,4,4-Hexafluoro-2,3-bis (trifluoromethyl)butane-2,3-diol		F_{12}-$(OH)_2$	≈100%

N.D. = not detected

Among trifluoro-, trichloro- and tribromoethanol, only TFE showed significant conversion to amidine when used in excess. There are two possible explanations for this change in reaction efficiency. The first is electronic, F (3.98 χ_p) has a greater Pauling electronegativity, *i.e*., greater electron withdrawing potential, than Cl (3.16 χ_p) and Br (2.96 χ_p) which would decrease the electropositivity of the boron moving from TCE to TBE thereby decreasing the reaction efficiency.[8] The second difference is steric, F is smallest halogen with a radius of only 64 pm and it possible that the larger Cl (99 pm) and Br (114 pm) increased steric hindrance limiting the reaction.[9] Importantly, it was also possible to readily convert the TFE ester back to the free boronic acid after amidination by simple hydrolysis.

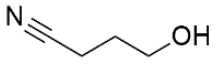
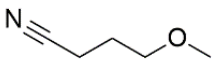
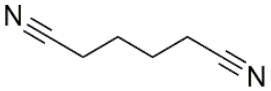
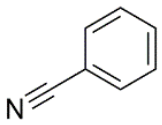
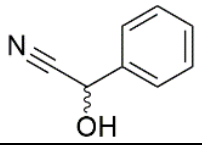
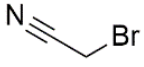
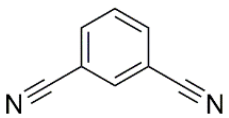
With the results clearly favoring fluorine-substituted alcohols, additional more complex fluorinated alcohols were tested. These results clearly depict perfluoropinacol [F_{12}-$(OH)_2$] being the most efficient protecting group for promoting amidination. While hexafluoroisopropanol [F_6-OH] did produce product, it was limited whereas perfluoro-*t*-butanol [F_9-OH] failed to produce any product. Both F_6-OH and F_9-OH had low boiling points of just 59 and 45 °C, respectively, limiting the amount the reaction could be heated at standard pressure. The other contributing factor that could cause lower yields is the electronic repulsion of these highly fluorinated compounds if both OH groups of the boronic acid became substituted; whereas the full protected form of F_{12}-$(OH)_2$ likely increases the reactivity of the boron ester due to enhanced inductive effect and ring strain. Distortion of a neutral boron atom out of plane can increase its Lewis acidity.[10] As synthesis of amidine **1** using F_{12}-$(OH)_2$ proved to be very efficient, additional nitriles were explored. One uniform method was developed for this comparative study shown in Scheme .



2-APB

Scheme 4. Amidination of **2-APB** using a perfluoropinacol protecting group.

In the F_{12}-$(OH)_2$ trial, the temperature was placed at 60 °C to provide sufficient activation energy and each reaction was performed for 18 h. An excess of the nitrile and F_{12}-$(OH)_2$ was used and where available, the liquid nitrile was used as the solvent to help drive the reaction. In reactions with solid nitriles, 4 equivalents were used; in these cases, toluene was used as the solvent. To ensure sufficient boronate ester formation, 4 equivalents of the F_{12}-$(OH)_2$ was also used. In reactions where dinitrile compounds were used, an additional variation was performed reacting **2-APB** in a 2:1 ratio with the nitrile to attempt to create di-amidine compounds. These variations and their reaction efficiencies (determined by NMR) can be seen in
Table 2. Amidination of **2APB** and various nitriles using a F_{12}-$(OH)_2$ protecting group.

No.	Nitrile Name (IUPAC)	Nitrile Chemical structure	MW	Boiling point (°C)	Reaction efficiency
2	3-Hydroxypropionitrile		71.08	163	56%[a]
3	3-Methoxypropionitrile		85.10	228	100%[a] (50%)[b]
4	Adiponitrile		108.14	295.1	28%[a]
5	Benzonitrile		103.12	188	53%[a]
6	Mandelonitrile		66.06	220	0%[a]
7	Acetonitrile		41.06	81	>98%[a]
8	Bromoacetonitrile		119.95	148	>98%[a]
9	1,3-Dicyanobenzene		128.13	288	0%[a]

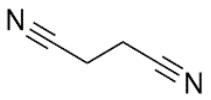
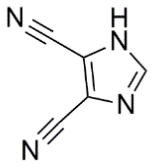
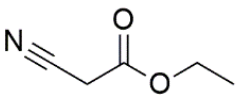
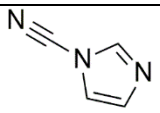
10	Succinonitrile		80.09	266.1	20%[c] (N.D.)[d]
11	4,5-Dicyanoimidazole		118.10	569.3	69%[c] (60%)[d]
12	Ethyl Cyanoacetate		113.12	209	51%[a]
13	1-Cyanoimidazole		93.09	60	0%[d]

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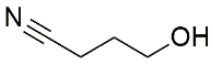
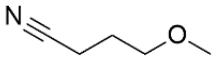
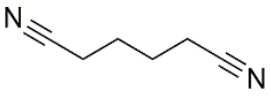
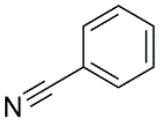
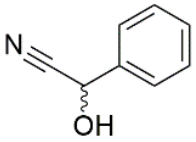
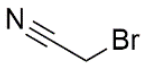
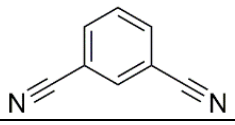
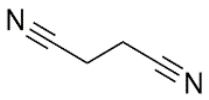
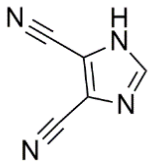
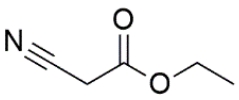
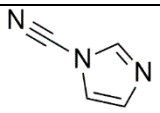
Table 2. Amidination of **2APB** and various nitriles using a F_{12}-$(OH)_2$ protecting group.

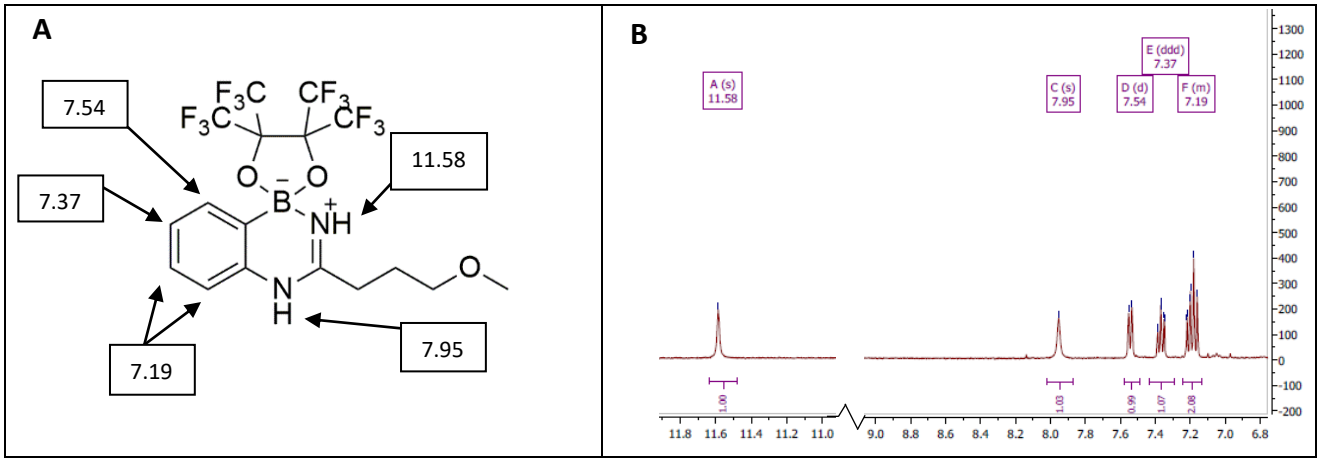
No.	Nitrile Name (IUPAC)	Nitrile Chemical structure	MW	Boiling point (°C)	Reaction efficiency
2	3-Hydroxypropionitrile		71.08	163	56%[a]
3	3-Methoxypropionitrile		85.10	228	100%[a] (50%)[b]
4	Adiponitrile		108.14	295.1	28%[a]
5	Benzonitrile		103.12	188	53%[a]
6	Mandelonitrile		66.06	220	0%[a]
7	Acetonitrile		41.06	81	>98%[a]
8	Bromoacetonitrile		119.95	148	>98%[a]
9	1,3-Dicyanobenzene		128.13	288	0%[a]

10	Succinonitrile		80.09	266.1	20%[c] (N.D.)[d]
11	4,5-Dicyanoimidazole		118.10	569.3	69%[c] (60%)[d]
12	Ethyl Cyanoacetate		113.12	209	51%[a]
13	1-Cyanoimidazole		93.09	60	0%[d]

[a] Reaction: Excess nitrile (1 mL) used as solvent
[b] Reaction: Excess nitrile (1 mL) used as solvent, reaction was left at r.t.
[c] Reaction: Solid nitriles (4 equiv.) and toluene was used as solvent
[d] Reaction: For solid mono-nitriles (1 equiv.) or di-nitriles (0.5 equiv.) toluene was used as solvent

This method proved significantly more efficient than our previous protocol, often delivering quantitative yields. Separation of products was simple, as most recrystalised in both the nitrile solvents and toluene. The most efficient was 3-methoxypropionitrile (**3**) mirroring the previous work[6] with quantitative yields; this nitrile even displayed 50% conversion at room temperature. By removing the ether linkage, 3-hydroxypropionitrile (**2**) had approximately half the conversion, and this may be owed to the alcohol competing with the F_{12}-$(OH)_2$ for boronic acid binding. Among the other products linear, non-aromatic reactions appeared to be favored, but dinitrile molecules had lower reactivity. This was likely attributed to the electron withdrawing effect of the second nitrile reducing the nucleophilicity of the other nitrile toward boron.

Unlike the NMR data previously obtained for the salicylate derivatives,[6] the perfluoropinacol protecting group caused the two signature peaks to shift from 9.5 and 11 ppm to 7.5-8 and 11.5-12 ppm, respectively. This provided a unique avenue to evaluate which amine was responsible for which of the two proton peaks using 2D NMR. The 3-methoxypropionitrile amidine product was chosen for this analysis due its high purity and clean integration. The proton, HSQC and HMQC NMR data for this compound are shown in Figure .



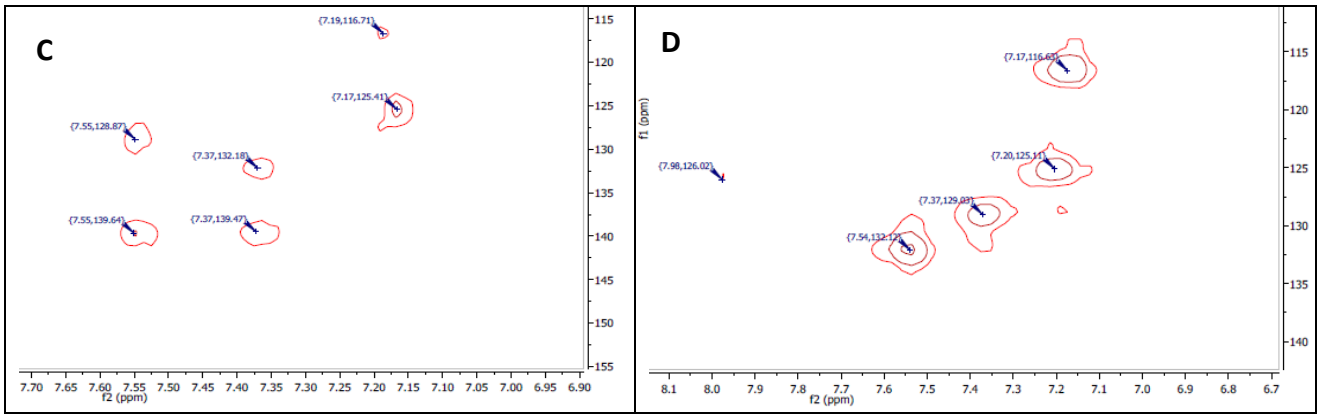
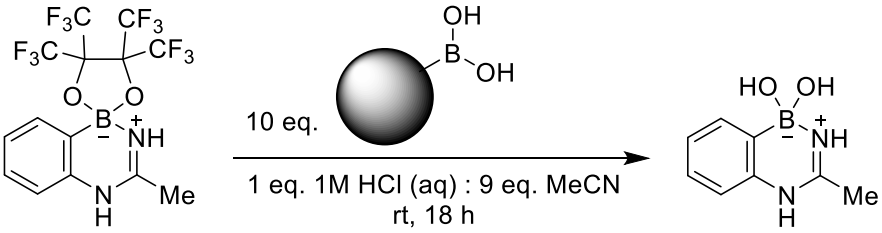


Figure 1. Amidination of 3-methoxypropionitrile using F_{12}-$(OH)_2$ (A: Amidination with assigned aromatic peaks, B: ^{1}H NMR of aromatic regions, C: HSQC of the aromatic regions and D: HMQC of the aromatic regions).

The HMQC provides the best evidence as the location of the 7.95 ppm proton, when looking at the peak (*δ* 7.96, 126.02) it is clear that this proton is two bonds away from an aromatic carbon which could only be the secondary amine. When comparing the molecules shown below, the significant shift from 9.37 to 7.95 ppm indicates that the change in the boronic acid protecting group caused the largest shift observed.

One apparent problem that surfaced with this perfluoropinacol method was the boronate deprotection; unlike the other fluorinated compounds, F_{12}-$(OH)_2$ could not be removed through hydrolysis and application of strong vacuum. Like the previous salicylic acid examples, it was resistant to the application of acids and bases owing to strong coordination by the amidine. One final option was explored using transesterification of polymer bound boronic acid shown in **Error! Reference source not found.**.



Scheme 5. Deprotection via transesterification of perfluoropinacol boronate.

This deprotection was adapted from Pennington *et al.* who used polystyrene-bound boronate which allowed for the separation of the deprotected product by simple filtration.[11] There was a minor loss in product with the deprotection recovering 98% of the expected yield, but the product was pure and there was no trace of F_{12}-$(OH)_2$ detectable by ^{19}F NMR. Based on this reaction, not only is this a viable amidination method, but the deprotection allows it to be used in the production of free boronic acids for testing as potential carbohydrate sensors, the ultimate goal of our work.[12]

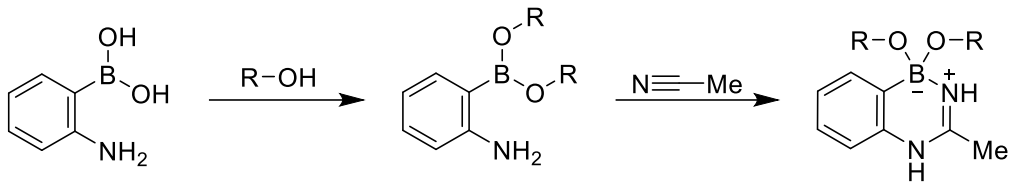
Conclusions

This work has identified a new method to produce amidines and, through initial optimization, is a viable method for a variety of nitriles. Compared to the traditional Pinner synthesis, the new method described herein is more efficient, likely due to interactions between the boronic acid and the activated nitrile. It is a

one-step reaction that can be completed using simple conditions compared to methods which require preparatory steps that use strong acids or metal activation of nitriles.[13,14] While a significant amount of optimization has been performed on the amidination, further improvements can be proposed. One option is to test how amidination is affected by dehydration methods to enable boronate ester formation as this was driven only by heating for operational simplicity. Nevertheless, the amidination method developed here is effective under mild conditions with a number of nitrile substrates, and adds to the broad arsenal of boron-mediated reactions.[15-18]

Experimental Section

Synthesis of 1,1-dihydroxy-3-methyl-1,4-dihydrobenzo[*c*][1,5,2]diazaborinin-2-ium-1-uide (1)



2-APB **1**

Solvent comparison

TFE. 2-APB (25 mg, 1.825 × 10^{-4} mol) was dissolved in MeCN (10 mL) and 2,2,2-trifluoroethanol (7 mL). The reaction was heated to 60 °C for 24 h, then H_2O (5 mL) and MeOH (5 mL) were added and the mixture was concentrated in vacuo to yield 42.5 mg with the NMR showing a 71% amidination efficiency as a mixture of boronate esters/hemiesters. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.78 (s, 1H), 10.44 (s, 1H), 8.76 (s, 1H), 8.57 (s, 1H), 7.57–7.37 (m, 3H), 7.37–7.31 (m, 1H), 7.27–6.96 (m, 7H), 6.07 (s, 2H), 3.88 (q, *J* 9.7 Hz, 5H), 3.62-3.49 (m, 7H).

F_6-OH. 2-APB (50 mg, 3.65 × 10^{-4} mol) was dissolved in MeCN (4 mL) and 1,1,1,3,3,3-hexafluoropropan-2-ol (2 mL). The reaction was heated to 50 °C for 18 h, then H_2O (5 mL) and MeOH (5 mL) were added and the mixture was concentrated in vacuo. 43.3 mg of solid was isolated with the NMR showing trace amidination. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.90 (s, 1H), 8.98 (s, 1H), 8.49 (s, 1H), 7.73 (ddd, *J* 17.1, 7.5, 1.6 Hz, 2H), 7.42 (ddd, *J* 8.5, 7.2, 1.7 Hz, 1H), 7.23 (d, *J* 8.1 Hz, 1H), 7.12 (ddd, *J* 8.4, 7.0, 1.6 Hz, 1H), 6.94 (dd, *J* 7.2, 1.0 Hz, 1H), 6.62 (dd, *J* 8.2, 1.0 Hz, 1H), 6.58–6.46 (m, 1H), 5.88 (s, 2H).

F_9-OH. 2-APB (50 mg, 3.65 × 10^{-4} mol) was dissolved in MeCN (15 mL) and 1,1,1,3,3,3-hexafluoro-2-(trifluoromethyl)propan-2-ol (2 mL). The reaction was heated to 40 °C for 18 h, then H_2O (5 mL) and MeOH (5 mL) were added and the mixture was concentrated in vacuo. 46.5 mg of solid was isolated with the NMR showing no amidination.

F_{12}-$(OH)_2$. 2-APB (50 mg, 3.65 × 10^{-4} mol) was dissolved in MeCN (15 mL) and 1,1,1,4,4,4-hexafluoro-2,3-bis(trifluoromethyl)butane-2,3-diol (1 mL). The reaction was heated at 60 °C for 18 h, then H_2O (5 mL) and MeOH (5 mL) were added and the mixture was concentrated in vacuo. 232.1 mg of solid was isolated with the NMR showing complete amidination. ^{1}H NMR (400 MHz, Methanol-d_4) δ 12.37 (s, 1H), 8.51 (s, 1H), 8.30 (d, *J* 7.5 Hz, 1H), 8.16–8.09 (m, 1H), 7.88 (dd, *J* 26.1, 8.1 Hz, 2H), 3.20 (s, 3H).

Perfluoronated Pinacol Amidinations

General Method for Liquid Nitriles. 2-APB (20.0 mg, 1.46 × 10^{-4} mol) was added to perfluorinated pinacol (100 μL). The reactant liquid nitrile (1 mL) was added, and the mixture was left at 60 °C for 18 h. The mixture was concentrated in vacuo but due to the high boiling point of the reactants only some of the solvent was removed. A crude NMR was performed on this mixture, integrations shown as relative ratios rounded to the nearest integer.

3. (3-Methoxypropionitrile). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.60 (s, 1H), 7.95 (s, 1H), 7.57–7.50 (m, 1H), 7.37 (dd, *J* 7.5, 1.5 Hz, 1H), 7.24–7.13 (m, 2H), 3.70 (t, *J* 5.6 Hz, 2H), 3.30 (s, 3H), 3.17 (s, 2H), 2.96 (t, *J* 5.6 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.9, 139.6, 132.2, 129.0, 125.2, 123.7, 120.3, 116.5, 69.1, 58.5, 49.1, 33.0.

^{11}B NMR (128 MHz, DMSO-d_6) δ 5.91. ^{19}F NMR (376 MHz, DMSO-d_6) δ -67.9 (dsex). MS +ve ion mode (MeOH): *m/z*: observed 519.0, calculated 520.1 [$C_{16}H_{13}BF_{12}N_2O_3$]. Boron Isotopes: ^{10}B 22% and ^{11}B 78%.

5. (Benzonitrile). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 9.50 (s, 1H), 8.18 (s, 1H), 7.89–7.65 (m, 12H), 7.64–7.54 (m, 5H), 7.48–7.30 (m, 2H), 7.27 (ddd, *J* 8.0, 6.0, 2.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 159.0, 140.1, 131.5, 130.8, 129.0, 128.8, 123.7, 119.3, 111.8. ^{11}B NMR (128 MHz, DMSO-d_6) δ 11.63. ^{19}F NMR (376 MHz, DMSO-d_6) δ -67.40 (p), -67.96 (p), -68.60, -69.28. MS +ve ion mode (MeOH): *m/z*: observed 539.1, calculated 538.1 [$C_{19}H_{11}BF_{12}N_2O_2$]. Boron Isotopes: ^{10}B 22% and ^{11}B 78%.

7. (Acetonitrile). ^{1}H NMR (400 MHz, Methanol-d_4) δ 12.37 (s, 1H), 8.51 (s, 1H), 8.30 (d, *J* 7.5 Hz, 1H), 8.16–8.09 (m, 1H), 7.88 (dd, *J* 26.1, 8.1 Hz, 2H), 3.20 (s, 3H). ^{13}C NMR (101 MHz, MeOD) δ 161.3, 140.4, 132.8, 130.8, 129.8, 125.8, 124.5, 124.1, 121.6, 121.2, 117.0, 21.1. ^{11}B NMR (128 MHz, MeOD) δ 12.01, 6.29. ^{19}F NMR (376 MHz, MeOD) δ -66.96 (q), -67.09 (q), -67.79, -68.47. MS +ve ion mode (MeOH): *m/z*: observed 475.9, calculated 476.0 [$C_{14}H_9BF_{12}N_2O_2$]. Boron Isotopes: ^{10}B 22% and ^{11}B 78%.

8. (Bromoacetonitrile). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.07 (s, 1H), 8.15 (s, 1H), 7.55 (d, *J* 7.5 Hz, 1H), 7.40 (td, *J* 7.6, 1.5 Hz, 1H), 7.30–7.15 (m, 2H), 4.62 (s, 2H), 4.50 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 163.0, 158.6, 139.6, 139.4, 132.0, 129.1, 129.1, 125.7, 120.8, 116.8, 57.9, 26.5. ^{11}B NMR (128 MHz, DMSO-d_6) δ 5.78. ^{19}F NMR (376 MHz, DMSO-d_6) δ -67.78 (dd), -68.05 (p), -69.24.

General Method for Solid Nitriles: 2-APB (20.0 mg, 1.46 × 10^{-4} mol) was dissolved in toluene (3 mL), then perfluorinated pinacol (100 μL) was added. The reactant solid nitrile (5.84 × 10^{-4} mol) was added, and the mixture was left at 60 °C for 18 h. The mixture was concentrated in vacuo but due to the high boiling point of the reactants only some of the solvent was removed. A crude NMR was performed on this mixture, and for dinitriles only mono-amidination was observed (if any).

11. (4,5-Dicyanoimidazole). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.15 (s, 1H), 8.37 (s, 1H), 8.31 (s, 10H), 7.63–7.55 (m, 1H), 7.49–7.39 (m, 6H), 7.35–7.20 (m, 8H), 7.21–7.10 (m, 2H), 2.30 (s, 2H), 2.09 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 141.1, 139.5, 132.1, 130.1, 129.1, 126.0, 123.4, 120.8, 120.5, 117.7, 49.0, 40.6. ^{11}B NMR (128 MHz, DMSO-d_6) δ 11.30. ^{19}F NMR (376 MHz, DMSO-d_6) δ -69.13. MS +ve ion mode (MeOH): *m/z*: observed 554.0, calculated 553.1 [$C_{17}H_8BF_{12}N_5O_2$]. Boron Isotopes: ^{10}B 22% and ^{11}B 78%.

General Method for Deprotection of Boronate Esters. Protected boronic acid (25 mg) was dissolved in a 90:10 MeCN/1M $HCl_{(aq)}$ solution. To this 500 mg of boronate polymer (1.4-2.2 mmol/g boronic acid-impregnated polystyrene) was added and the sample was left to mix for 18 h. The polymer was filtered out and the liquid was concentrated to furnish a near quantitative yield of the expected deprotected product. While the proton NMR becomes quite complex due to mixtures of hydrated/dehydrated and cyclic/acyclic forms,[19] no signal in ^{19}F NMR could be detected from these products.

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Supplementary Material

Proton, C-13, B-11, and F-19 NMR spectra for amidine derivatives of acetonitrile, bromoacetonitrile, and 3-methoxypropionitrile are included.

References

1. Granik, V. G. *Russ. Chem. Rev.* **1983**, *52*, 377-393. https://doi.org/10.1070/RC1983v052n04ABEH002824
2. Pinner, A.; Klein, F. *Chem. Ber.* **1877**, *10*, 1889-1897. https://doi.org/10.1002/cber.187701002154
3. Rauws, T. R.; Maes, B. U. *Chem. Soc. Rev.* **2012**, *41*, 2463-2497. https://doi.org/10.1039/c1cs15236j
4. Dorokhov, V.; Amamchyan, A.; Bogdanov, V.; Shchegoleva, T. *Russ. Chem. Bull.* **1987**, *36*, 2436-2438. https://doi.org/10.1007/BF00957344
5. Dorokhov, V.; Amamchyan, A.; Bogdanov, V. *Russ. Chem. Bull.* **1989**, *38*, 2165-2167. https://doi.org/10.1007/BF00962135
6. Pappin, B. B.; Garget, T. A.; Healy, P. C.; Simone, M. I.; Kiefel, M. J.; Houston, T. A. *Org. Biomol. Chem.* **2019**, *17*, 803-806. https://doi.org/10.1039/c8ob02696c
7. Pappin, B. B.; Levonis, S. M.; Healy, P. C.; Kiefel, M. J.; Simone, M. I.; Houston, T. A. *Heterocycl. Commun.* **2017**, *23*, 167-169. https://doi.org/10.1515/hc-2017-0023
8. Murphy, L. R.; Meek, T. L.; Allred, A. L.; Allen, L. C. *J. Phys. Chem. A* **2000**, *104*, 5867-5871. https://doi.org/10.1021/jp000288e
9. Pyykkö, P. *J. Phys. Chem. A* **2014**, *119*, 2326-2337. https://doi:10.1021/jp5065819
10. Yasuda, M.; Yoshioka, S.; Hideto, N.; Chiba, K.; Baba, A. *Org. Lett.* **2008**, *10*, 929-932. https://doi.org/10.1021/ol7030944
11. Pennington, T. E.; Kardiman, C.; Hutton, C. A. *Tetrahedron Lett.* **2004**, *45*, 6657-6660. https://doi.org/10.1016/j.tetlet.2004.07.014
12. Garget, T. A.; Kiefel, M. J.; Houston, T. A. *Tetrahedron Lett.* **2022**, *94*, 153698. https://doi.org/10.1016/j.tetlet.2022.153698
13. Kukushkin, V. Y.; Pombeiro, A. J. L. *Chem. Rev.* **2002**, *102*, 1771–1802. https://doi.org/10.1021/cr0103266
14. Aly, A. A.; Bräse, S.; Gomaa, M. A.-M. *Arkivoc* **2018**, (vi), 85-138. https://doi.org/10.24820/ark.5550190.p010.607
15. Pal, R. *Arkivoc* **2018**, (i), 346-371. https://doi.org/10.24820/ark.5550190.p010.462
16. Hall, D. G. *Chem. Soc. Rev.* **2019**, *48*, 3475-3496. https://doi.org/10.1039/C9CS00191C
17. Yeung, K.; Mykura, R. C.; Aggarwal, V. K. *Nat. Synth.* **2022**, *1*, 117-126. https://doi.org/10.1038/s44160-021-00012-1
18. For an interesting mechanism of catalysis involving a mixed boronate ester of perfluoropinacol and hexafluoroisopropanol, see: Ang, H. T.; Rygas, J. P. G.; Hall, D. G. *Org. Biomol. Chem.* **2019**, *17*, 6007-6014. https://doi.org/10.1039/c9ob01043b
19. Groziak, M. P.; Ganguly, A. D.; Robinson, P. D. *J. Am. Chem. Soc.* **1994**, *116*, 7597-7605. https://doi.org/10.1021/ja00096a017

