JOC Article

Functionalization of Organotrifluoroborates: Reductive Amination

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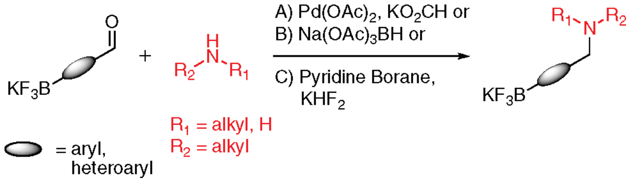


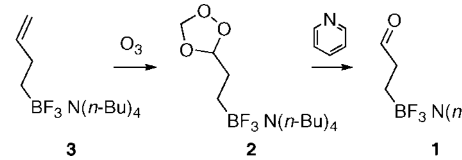
Herein we report the conversion of aldehyde-containing potassium and tetrabutylammonium organotrifluoroborates to the corresponding amines through reductive amination protocols. Potassium formate facilitated by catalytic palladium acetate, sodium triacetoxyborohydride, and pyridine borane have all served as effective hydride donors, reducing the initially formed imines or iminium ions to provide the corresponding amines.

Introduction

Owing to the existence of an empty p orbital on boron, boronic acids and, to a lesser extent, boronate esters exhibit sensitivity to several classes of useful reagents commonly employed during the course of organic synthesis. Their reactivity toward oxidants, bases, nucleophiles, and organic acids limits the conditions to which these organoboron species can be exposed, and to a great extent this dictates at which point the boron must be introduced during a synthesis campaign. Organotrifluoroborates, which lack an empty p orbital and therefore are mechanistically inhibited from reacting through modes normally observed for tricoordinate organoboron compounds, fulfill all of the criteria needed for a protected boronic acid with little cost and substantial benefits.[1] Thus, the tetracoordinate nature of these species, fortified with exceptionally strong boron−fluorine bonds, provides extraordinary opportunities for manipulation of ancillary functional groups with retention of the trifluoroborate, allowing one to make or purchase a very simple organoboron compound and build molecular complexity into the molecule from the ground up. The full development of organotrifluoroborates has the potential to liberate strategic planning in the construction of complex molecules as well as the design of scaffolds for diversity-oriented synthesis. As previously reported, we have demonstrated that alkene ozonolysis, Wittig reactions, dihydroxylations, and epoxidation reactions can be performed in the presence of the organotrifluoroborate unit, creating a novel entry to unique and potentially valuable organic synthons.[2] Herein we describe the reductive amination[3] of aldehyde-containing potassium and tetrabutylammonium organotrifluoroborates, which not only demonstrates the resistance of the carbon−boron bond to a variety of aggressive reaction conditions but also provides a unique access to amine-substituted organotrifluoroborates.

Results and Discussion

During our investigation of methods to access tetrabutylammonium 3-(trifluoroborato)propanal (**1**) by an ozonolysis protocol, it was discovered that the remarkably stable secondary ozonide **2**, formed by treatment of tetrabutylammonium 3-butenyltrifluoroborate (**3**) with ozone, could be treated with an amine base to generate the desired aldehyde product **1** (eq 1).[2e,4]



(1)

Interestingly, while the desired product was obtained in pure form when pyridine was used as the base, it was also observed

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(1) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275–286.

(2) (a) Molander, G. A.; Ribagorda, M. *J. Am. Chem. Soc.* **2003**, *125*, 11148–11149. (b) Molander, G. A.; Ellis, N. M. *J. Org. Chem.* **2006**, *71*, 7491–7493. (c) Molander, G. A.; Figueroa, R. *Org. Lett.* **2006**, *8*, 75–78. (d) Molander, G. A.; Figueroa, R. *J. Org. Chem.* **2006**, *71*, 6135–6149. (e) Molander, G. A.; Cooper, D. J. *J. Org. Chem.* **2007**, *72*, 3558–3560.

(3) (a) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A. *J. Org. Chem.* **1996**, *61*, 3849–3862. (b) Abdel-Magid, A. F.; Mehrman, S. J. *Org. Process Rev. Dev.* **2006**, *10*, 971–1031. (c) Quan, M. L.; Han, Q.; Fevig, J. M.; Lam, P. Y. S.; Bai, S.; Knabb, R. M.; Luettgen, J. M.; Wong, P. C.; Wexler, R. R. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1795–1798. (d) Baxter, E. W.; Reitz, A. B. *Organic Reactions*; Wiley: New York, 2002; Vol. 59.

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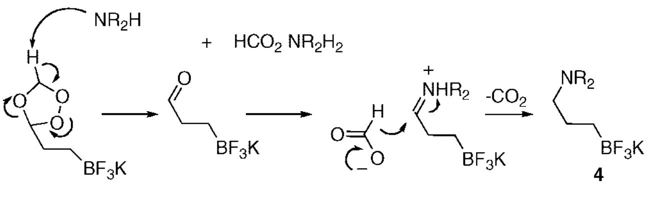
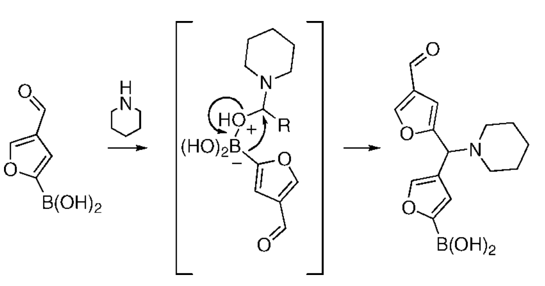
that if a secondary amine was used instead of pyridine, the corresponding tertiary amine **4** was obtained in addition to the desired aldehyde (Scheme 1). We rationalized that a process closely resembling the Leuckart reaction occurred, whereby ammonium formate was liberated during the course of the reaction and served as a reducing agent for a reductive amination process.[5] Although this reaction gave an inseparable mixture of the aldehyde and the amine as products, it foretold that conditions could be developed to access valuable amine-containing organoboron coupling partners in pure form.

There is precedent for the reductive amination of aldehyde-containing boronic acids and, in particular, (2-formylaryl)boronic acids and derivatives.[6] However, to our knowledge unless this boronic acid or structurally related ortho-substituted arylboronic acids are used, there exist few examples where the amine component is something other than an aniline derivative.[7] To fill this perceived void, a more general method for the reductive amination of aldehyde-containing organoborons was sought to provide access to nucleophilic cross-coupling partners incorporating various amine functional groups.

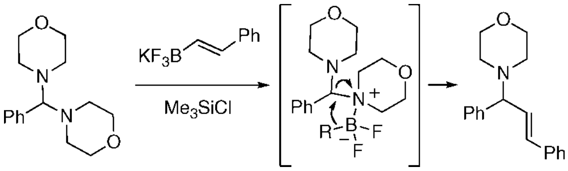
SCHEME 1



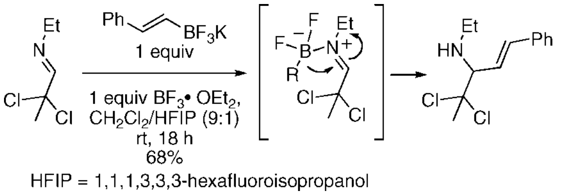
There was initially some concern that one of several different processes could result in unproductive side reactions resulting from reaction of the aldehyde-containing organotrifluoroborate with the amine. It was hoped that the tetracoordinate organotrifluoroborates, in contrast to their tricoordinate boronic acid counterparts, would prevent coordination of the boron with the oxygen atom of the intermediate hemiaminal, a necessary initial step for subsequent bond formation in the Petasis boronic acid Mannich reaction (eq 2).[8] Although this and related types of transformations have been reported using organotrifluoroborates (eqs 3 and 4),[9] it has only occurred in the presence of strong fluorophiles that generate difluoroboranes in situ.[10] Depending on the nature of the organotrifluoroborate and electrophile, several different mechanistic pathways have been proposed for these transformations,[9a,b,f,g,11] including the traditional Petasis boronic acid Mannich mechanism through an intermediate hemiaminal or aminal (eqs 2 and 3)[8,9b,11] and direct intramolecular addition via an imine-complexed RBF_2 species (eq 4).[9c]



(2)



(3)

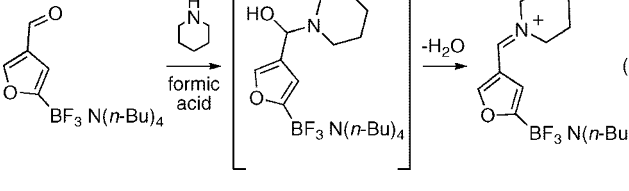


(4)

HFIP = 1,1,1,3,3,3-hexafluoroisopropanol

More relevant to the current work, during the course of our studies MacMillan et al. demonstrated that potassium aryl- and heteroaryltrifluoroborates[12] participate as nucleophiles in amine-catalyzed 1,4-additions to enals without Lewis acid activation (although in the presence of 1 equiv of HF) through a mechanism involving direct addition of the organotrifluoroborate to the intermediate conjugated iminium ions. This raised the possibility that related 1,2-additions might occur between organotrifluoroborates and iminium ions generated via Mannich-type reactions from the corresponding aldehydes (Scheme 2).

As it transpired, none of these potentially deleterious issues were validated in our studies, as under the conditions developed there was no evidence of these alternative reaction pathways. Instead, when tetrabutylammonium (4-formylfuran-2-yl)trifluoroborate (**5**) was treated with piperidine and formic acid in the presence of 4 Å molecular sieves, a near-quantitative yield of the corresponding iminium ion was isolated (eq 5).



(5)

On the basis of these initial observations, an in situ reductive amination was developed to provide the amine product **6** using potassium formate facilitated by a palladium catalyst (eq 6).[13]

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(4) Schwartz, C.; Raible, J.; Mott, K.; Dussault, P. H. *Org. Lett.* **2006**, *8*, 3199–3201.

(5) Leuckart, R. *J. Prakt. Chem.* **1890**, *41*, 33.

(6) (a) Gray, C. W.; Walker, B. T.; Brian, T.; Foley, R. A.; Houston, T. A. *Tetrahedron Lett.* **2003**, *44*, 3309–3312. (b) Johnson, L. L.; Houston, T. A. *Tetrahedron Lett.* **2002**, *43*, 8905–8908. (c) Luvino, D. *Tetrahedron Lett.* **2006**, *47*, 9253–9256.

(7) (a) Hall, D. G.; Gravel, M.; Thompson, M. Z.; Berube, C. *J. Org. Chem.* **2002**, *67*, 3–15. (b) Martin, B.; Possémé, F.; Barbier, C.; Carreaux, F.; Carboni, B.; Seiler, N.; Moulinoux, J.-P.; Delcros, J.-G. *J. Med. Chem.* **2001**, *44*, 3653. (c) Asano, T.; Nakamura, H.; Uehara, Y. Yamamoto, Y. *ChemBioChem* **2004**, *5*, 483–490. (d) Prullano, L.; Rohovec, J.; Aime, S.; Maschmeyer, T.; Prata, M. I.; Lima, J.; Geraldes, C.; Peters, J. *Chem. Eur. J.* **2004**, *10*, 5205–5217.

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(10) Exception: Kabalka, G. W.; Venkataiah, B.; Dong, G. *Tetrahedron Lett.* **2004**, *45*, 729–731.

(11) Petasis, N. A. Method for the Synthesis of Amines and Amino Acids with Organoboron Derivatives. *WO 98/00398*, January 8, 1998.

(12) MacMillan, D. W. C.; Lee, S. *J. Am. Chem. Soc.* **2007**, *129*, 15438–15439.

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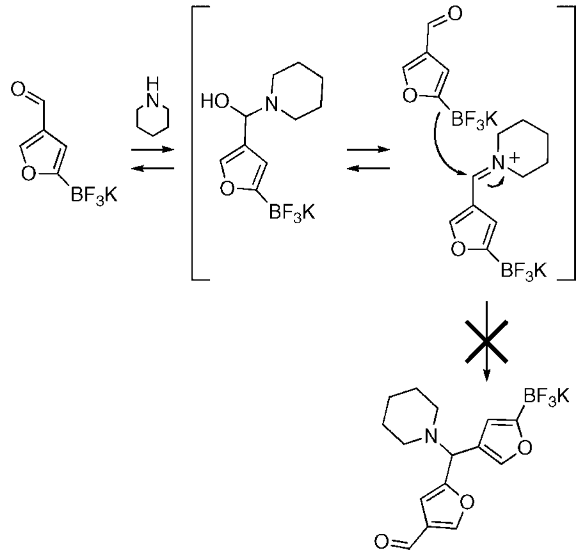
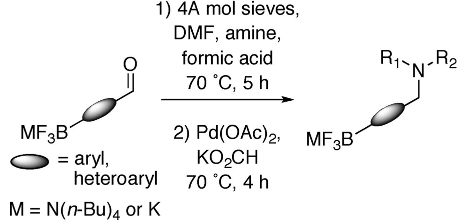
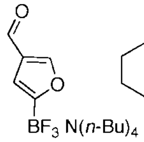
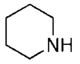
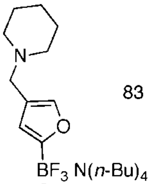
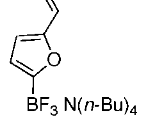
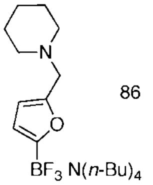
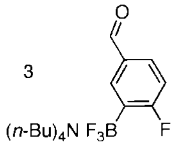
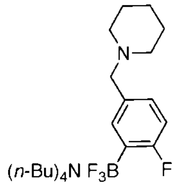
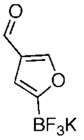
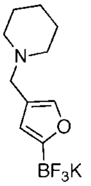
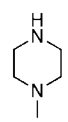
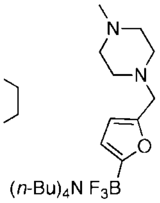
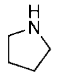
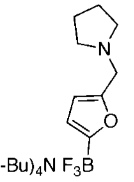
SCHEME 2



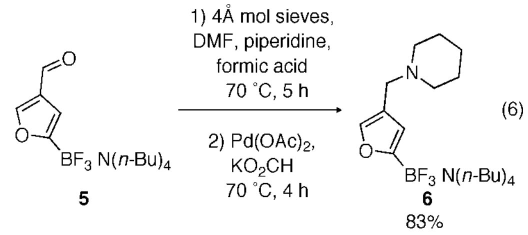
This method was optimized for **5** and applied to a variety of aldehyde-containing trifluoroborates to give the corresponding piperidinyl methylamines (Table 1). To determine the scope of the method, aldehyde **7** was then transformed using two different secondary amines, providing the corresponding tertiary amines in excellent yields (Table 1, entries 5 and 6).

TABLE 1. Organotrifluoroborate Substrates Subjected to Palladium-Catalyzed Reductive Amination Using Various Amines



entry	aldehyde	amine	product	% yield
1	 **5**		 **6**	83
2	 **7**		 **8**	86
3	 **9**		 **10**	70
4	 **11**		 **12**	74
5	**7**		 **13**	92
6	**7**		 **14**	100

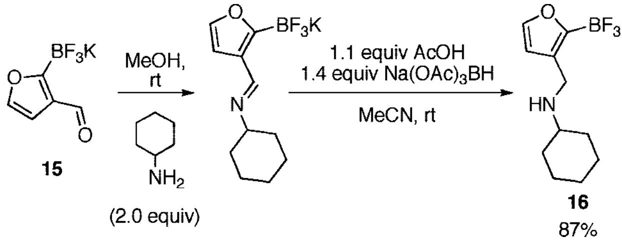
[a] Greater than 5% impurity from DMF.


(6)

Unfortunately, this first reductive amination protocol suffered in several respects. Although it proved effective for access to pure amine-containing trifluoroborates in high yields when applied to the furanyl substrates **5** (83%) and (5-formylfuran-2-yl)trifluoroborate (**7**) (86%), the substrate scope was limited. When the protocol was extended to a variety of activated and nonactivated benzaldehydes, it gave either an inseparable impurity that appeared to derive from a side reaction with DMF or a mixture of the aldehyde starting material, the corresponding imine, and the amino product. This method was also determined to be effective almost exclusively for tetrabutylammonium trifluoroborate substrates, with only one of the potassium trifluoroborates surveyed, (4-formylfuran-2-yl)trifluoroborate (**11**) (74%), giving the desired product (Table 1, entry 4). Furthermore, following the survey of a variety of primary amines including aniline, benzylamine, *n*-butylamine, *tert*-butylamine, and cyclohexylamine, the method was determined to be ineffective in the installation of secondary amines into the trifluoroborate substrates examined. Thus, in an effort to expand this chemistry to include a range of potassium organotrifluoroborates and primary amines as effective partners, other protocols for the reductive amination were considered.

Sodium triacetoxyborohydride (STAB) seemed an obvious choice as a selective reducing agent. In addition to its high level of selectivity, reactions utilizing STAB with acetonitrile as a solvent have also been well-developed.[14] This was encouraging to us, as we expected many of the iminium ion intermediates to be soluble in acetonitrile. With this in mind, a variety of conditions for the reductive amination of aldehyde **15** and cyclohexylamine using STAB were explored.

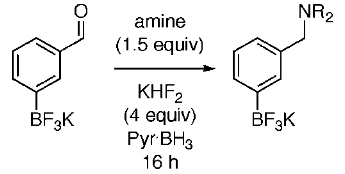
There was some anxiety concerning a single-step protocol, wherein the reduction took place on an imine or iminium ion derived in situ, because it could result in the formation of a mixture of amine and alcohol products.[12] Because such a mixture could prove difficult to separate, a two-step, one-pot reductive amination process was utilized whereby addition of the reducing agent was delayed until complete conversion to the imine or iminium ion had occurred. Thus, the overall conversion from aldehyde to amine was considered in two stages, examining first the conversion of the aldehyde to the corresponding imine. When **15** and cyclohexylamine were stirred with anhydrous methanol as a solvent, conversion to the imine was realized in 20 min without the use of acetic acid (eq 7). The second stage, reduction of the imine using STAB, was conducted in acetonitrile and proceeded smoothly using 1.4 equiv of STAB and 1.1 equiv of acetic acid at ambient temperature to give the desired methylaminofuran **16**. Although this new method did allow the reductive amination of the potassium salt **15**, the method demonstrated significant substrate dependence, and obtaining reasonable yields of pure material with other substrates proved difficult.

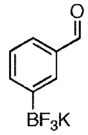
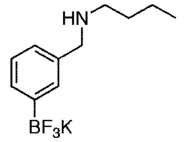
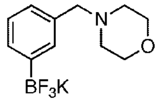
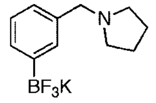
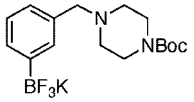
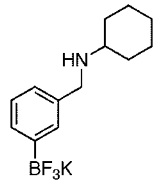
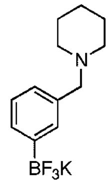
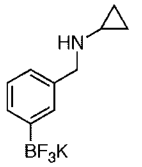


(7)

Other selective reducing agents were examined to solve this problem. Because borane–amine complexes allow the use of methanol, a solvent that had proven very effective in the conversion of formyltrifluoroborates to the corresponding imines, and because these reducing agents demonstrate a high degree of selectivity for reduction of the iminium ion over the aldehyde,[15] use of these reagents would allow the entire sequence to be run in methanol.[11] After several boranes were screened, including *tert*-butylamine–borane, picoline–borane, and triethylamine–borane, pyridine–borane (pyr•BH_3) was found to reduce the iminium ion generated from aldehyde **17** and cyclohexylamine most efficaciously. Furthermore, while acetic acid can be used in conjunction with these boranes to protonate the imine, giving the reactive iminium ion,[16] inexpensive KHF_2 was used instead. This served double duty. Acting as an acid, the KHF_2 activated the imine. Additionally, the KHF_2 appeared to serve as a fluoride source, allowing removal of borane byproducts that otherwise contaminated the desired organotrifluoroborates.

TABLE 2. Organotrifluoroborate Substrates Subjected to Reductive Amination Using Pyridine–Borane and Various Amines



entry	aldehyde	product	yield
1	 **17**	 **18**	76[a]
2	**17**	 **19**	89
3	**17**	 **20**	76
4	**17**	 **21**	73
5	**17**	 **22**	91
6	**17**	 **23**	76
7	**17**	 **24**	100

[a] Product exists as greater than 5% internal ammonium salt.

A variety of amines were then used with **17** to determine the scope of this protocol (Table 2). We were delighted to discover that good to excellent yields could be achieved for a wide range of amines. Although application of this method to benzaldehyde **17** and *n*-butylamine gave a mixture of the aminomethyl product **18** and the corresponding internal ammonium salt, other primary amines, including cyclopropylamine and cyclohexylamine, gave the desired products in pure form (entries 5 and 7). Furthermore, the method was successfully applied to a variety of amine-containing heterocycles to give the corresponding tertiary amine products. Pyrrolidine, piperidine, morpholine, and even Boc-protected piperazine could be used to give the corresponding boron-containing amines in good yield and in high purity (Table 2, entries 2–4 and 6).

Cyclohexylamine and piperidine were then used to show that the method could be applied to a variety of aryl and heteroaryl

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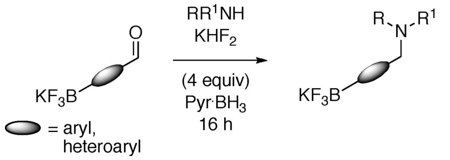
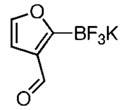
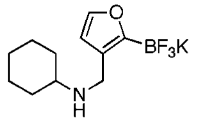
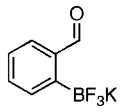
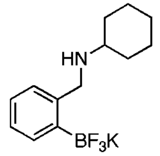
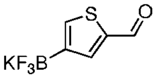
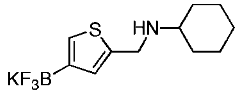
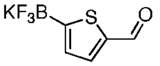
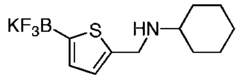
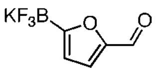
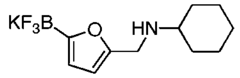
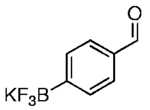
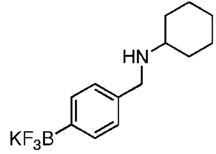
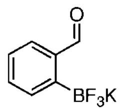
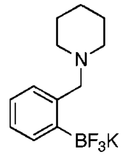
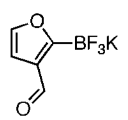
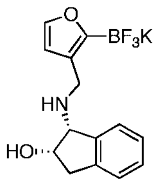
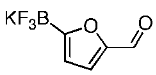
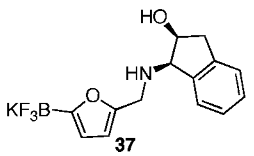
(14) Abdel-Magid, A. F.; Maryanoff, C. A. *Org. Process Res. Dev.* **2006**, *10*, 971–1031.

(15) Domannn, M. D.; Guch, I. C.; DiMare, M. *J. Org. Chem.* **1995**, *60*, 5995–5996.

(16) Pelter, A.; Rosser, R. M.; Mills, S. *J. Chem. Soc., Perkin Trans. 1* **1984**, *4*, 717–720.

TABLE 3. Organotrifluoroborate Substrates Subjected to Reductive Amination Using Pyridine−Borane



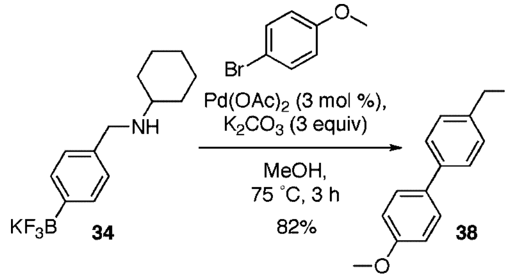
entry	aldehyde	product	yield
1	 **15**	 **16**	82
2	 **25**	 **26**	48
3	 **27**	 **28**	71
4	 **29**	 **30**	75
5	 **31**	 **32**	91
6	 **33**	 **34**	90 (70^a)
7	 **25**	 **35**	67^b
8	 **15**	 **36**	97^c
9	 **31**	 **37**	86^c

^{a} Gram scale reaction. ^{b} Product exists as greater than 5% internal ammonium salt. ^{c} Performed in two stages with no KHF$_2$.

aldehydes (Table 3, entries 1−7). Although the majority of the aminomethyl-substituted organotrifluoroborates synthesized were easily purified by precipitation from acetone using diethyl ether, those derived from substrates with an ortho relationship between the aldehyde and trifluoroborate functional groups (**16**, **26**, and **35**) had to be further dried by azeotropically removing the water with toluene and placing the resulting powders under vacuum (0.01 Torr).

Amino alcohols can be utilized as substrates in the reductive amination. Thus, it was shown that the method could be employed using the chiral *cis*-aminoindanols in reactions with aldehydes **15** and **31** (entries 8 and 9). Optimal experimental conditions in these two cases required that 1 equiv of *cis*-aminoindanol and no acid be used in the reaction mixture to obtain pure product. Thus, good yields of the chiral products **36** and **37** were obtained by the method, which remained one-pot but which was conducted in two steps to ensure that the aldehyde was completely converted to the corresponding imine prior to introduction of pyridine−borane.

Finally, we demonstrated that the amine-substituted organotrifluoroborates formed in these reductive aminations could be coupled in high yields to aryl halide partners. In an adaptation of conditions developed by our group, the coupled product was realized by employing 3 mol % Pd(OAc)$_2$ under ligandless conditions (eq 8).[17] In this variation, K$_2$CO$_3$ (3.0 equiv) was utilized as the base and the reaction was performed in MeOH at 75 °C for 3 h. Under these conditions, no column chromatography was required and the coupled product was isolated in 82% yield.



(8)

In summary, protocols for the reductive amination of aldehyde-containing organotrifluoroborates using potassium formate facilitated by catalytic palladium acetate (Table 1), sodium triacetoxyborohydride (eq 2), and pyridine−borane (Tables 2 and 3) have been developed. These methods offer access to valuable amine-containing organoborons and provide another example of the complementarity between organotrifluoroborates (which allow functionalization of ancillary carbonyls) and boronic acids. Use of organotrifluoroborates provides access to both trifluoroborato-substituted imines and iminium ions, where under similar reaction conditions boronic acids might be expected to undergo the Petasis boronic acid Mannich or related reactions. Reduction of the imine and iminium ion substituted organotrifluoroborates generated in situ affords the corresponding trifluoroborato-functionalized amines in a one-pot process. The amino-substituted organotrifluoroborates thus generated can be cross-coupled under ligandless conditions, affording high yields of a biaryl product wherein no chromatography is utilized at any point in the multistep process.

Experimental Section

General Procedure for Preparation of Tetrabutylammonium (Formylaryl)trifluoroborates. Tetrabutylammonium (4-

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[17] Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302–4314.

Formylfuran-2-yl)trifluoroborate (5). To a slurry of potassium (4-formylfuran-2-yl)trifluoroborate (101 mg, 0.50 mmol) in H_2O (1 mL) and CH_2Cl_2 (5 mL) was added an aqueous solution of (*n*-Bu)$_4$NOH (0.32 mL, 0.50 mmol, 1.6 M in water) with stirring. The biphasic solution was stirred for 0.5 h. The layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL), after which the combined organic layers were washed with H_2O, dried ($MgSO_4$), and concentrated under high vacuum to give the product as a colorless oil (154 mg, 76%). IR: 1673 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.89 (t, $J = 8$ Hz, 12H), 1.25−1.36 (m, 8H), 1.45−1.55 (m, 8H), 3.08 (t, $J = 9$ Hz, 8H), 6.56 (s, 1H), 8.0 (s, 1H), 9.82 (s, 1H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.5, 19.5, 23.7, 58.5, 107.5, 129.1, 152.8, 185.5. ^{19}F NMR (471 MHz, $CDCl_3$): δ −142.5. ^{11}B NMR (128 MHz, $CDCl_3$): δ −0.42. HRMS (ESI): *m/z* calcd for $C_5H_3BF_3O_2$ $[M - C_{16}H_{36}N]^-$ 163.0178, found 163.0222.

General Procedure A for the Reductive Amination of Tetrabutylammonium (Formylaryl)trifluoroborates using Palladium-Catalyzed Formate. Tetrabutylammonium (4-((Piperidin-1-yl)methyl)furan-2-yl)trifluoroborate (6). A test tube containing activated 4 Å molecular sieves and tetrabutylammonium (4-formylfuran-2-yl)trifluoroborate (**5**) was evacuated under vacuum (0.01 Torr) for 15 min. DMF (1 mL), piperidine (60 mg, 0.71 mmol), and formic acid (28 mg, 0.61 mmol) were then added with stirring. The solution was heated under nitrogen for 5 h at 70 °C, after which potassium formate (100 mg, 1.19 mmol) and palladium acetate (5 mg, 0.02 mmol, 6 mol %) were added, and stirring was continued for an additional 4 h. Heat was removed, and the reaction mixture was cooled to room temperature. Aqueous KHF_2 (1 mL, 4.5 M) was then added, and the solution was stirred for 20 min. The mixture was filtered, and the white solid was rinsed with CH_2Cl_2 (2 × 5 mL). The filtrate was washed with H_2O, 3 M NaOH, and brine, and dried ($MgSO_4$), and the solvent was removed to give the product as a deep yellow oil (130 mg, 83%). IR: 2933, 1669 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.81 (t, $J = 8$ Hz, 12H), 1.17−1.26 (m, 10H), 1.35−1.44 (m, 12H), 2.23 (s, 4H), 2.98 (t, $J = 9$ Hz, 8H), 3.32 (s, 2H), 6.11 (s, 1H), 7.09 (s, 1H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 13.6, 19.5, 23.7, 24.2, 26.1, 53.9, 56.0, 58.3, 107.8, 111.7, 151.0. ^{19}F NMR (471 MHz, $CDCl_3$): δ −141.2. ^{11}B NMR (128 MHz, $CDCl_3$): δ 0.164. HRMS (ESI): *m/z* calcd for $C_{10}H_{14}BF_3NO$ $(M - C_{16}H_{36}N)$ 232.1121, found 232.1131.

General Procedure for Preparation of Potassium (Formylaryl)trifluoroborates. Potassium (4-Formylfuran-2-yl)trifluoroborate (11). To (4-formylfuran-2-yl)boronic acid (5.0 g, 3.57 mmol) in MeOH (20 mL) was added dropwise a solution of KHF_2 (13.65 g, 0.175 mol) in H_2O (40 mL) using an addition funnel. The mixture was stirred for 2 h and then concentrated under high vacuum. The residual solids were extracted with 20% MeOH in acetone (4 × 10 mL). The combined extracts were concentrated close to the saturation point. Et_2O (20 mL) was then added until no more precipitation was observed. The solids were collected, washed with Et_2O (2 × 10 mL), and dried under high vacuum to afford the product as a white crystalline solid (4.78 g, 66%). Mp: >200 °C. IR (KBr): 1687 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.29 (d, $J = 20$ Hz, 1H), 8.34 (s, 1H), 9.81 (s, 1H); ^{13}C NMR (125.8 MHz, DMSO-d_6): δ 106.8, 128.9, 154.3, 186.3. ^{19}F NMR (471 MHz, DMSO-d_6): δ −140.5. ^{11}B NMR (128 MHz, DMSO-d_6): δ −0.225. HRMS (ESI): *m/z* calcd for $C_5H_3BF_3O_2$ $(M - K)$ 163.0178, found 163.0176.

Potassium (4-((Piperidin-1-yl)methyl)furan-2-yl)trifluoroborate (12). A test tube containing activated 4 Å molecular sieves (400 mg) and potassium (4-formylfuran-2-yl)trifluoroborate (192 mg, 0.95 mmol) was evacuated under vacuum (0.01 Torr) for 15 min. DMF (1 mL), piperidine (212 mg, 2.49 mmol), and formic acid (69 mg, 1.5 mmol) were added with stirring, and the solution was then heated under nitrogen for 5 h at 70 °C. Palladium acetate (22 mg, 0.10 mmol, 10 mol %) and potassium formate (195 mg, 2.32 mmol) were then added, and stirring was continued for an additional 4 h. Heat was removed, the reaction mixture was filtered, and the white solid was rinsed with MeOH (3 × 5 mL). To the filtrate was added an aqueous solution of KHF_2 (1 mL, 4.4 M) with stirring, which was continued for 1 h. The solution was then concentrated under vacuum. The resulting yellow solid was extracted with 10% MeOH in acetone (3 × 5 mL). This was concentrated and precipitated with Et_2O (10 mL) to give the title compound as a yellow solid (190 mg, 74%). Mp: >200 °C. IR: 2933, 1669 cm^{-1}. ^{1}H NMR (500 MHz, acetone-d_6): δ 1.38−1.44 (m, 2H), 1.52−1.60 (m, 4H), 2.10−2.16 (m, 4H), 3.44 (s, 2H), 6.21 (s, 1H), 7.30 (s, 1H). ^{13}C NMR (125.8 MHz, acetone-d_6): δ 23.7, 25.1, 53.1, 53.1, 113.1, 140.8. ^{19}F NMR (471 MHz, acetone-d_6): δ −142.1. ^{11}B NMR (128 MHz, acetone-d_6): δ 0.662. HRMS (ESI): *m/z* calcd for $C_{10}H_{14}BF_3NO$ $(M - K)$ 232.1121, found 232.1129.

Potassium (3-((Cyclohexylamino)methyl)furan-2-yl)trifluoroborate (16). To a sealed test tube containing potassium (3-formylfuran-2-yl)trifluoroborate (110 mg, 0.54 mmol) in MeOH (4 mL) was added cyclohexylamine (198 mg, 2.0 mmol) with stirring. Stirring was continued for 1 h, and then the solvent was removed to give a yellow solid. This was taken up into acetonitrile (4 mL). Acetic acid (40 mg, 0.67 mmol) and sodium triacetoxyborohydride (150 mg, 0.71 mmol) were added, and the test tube was resealed. This mixture was stirred for 16 h at room temperature. KOH (168 mg, 1.5 mmol) was then added, followed by H_2O (2 mL). This mixture was stirred for 20 min, KHF_2 (421 mg, 5.4 mmol) was then added, and this solution was stirred for an additional 30 min. The solution was then concentrated under vacuum. The resulting yellow solid was extracted with 10% MeOH in acetone (3 × 5 mL). This was concentrated and precipitated with Et_2O (5 mL) to give the product as a yellow solid (135 mg, 87%). Mp: >200 °C. IR (KBr): 2939 cm^{-1}. ^{1}H NMR (500 MHz, acetone-d_6): δ 1.06−1.31 (m, 5H), 1.60 (d, $J = 12$ Hz, 1H), 1.74 (dd, $J = 9, 4$ Hz, 2H), 1.99−2.19 (m, 3H), 2.83−2.87 (m, 1H), 3.95 (s, 2H), 6.28 (d, $J = 1$ Hz, 1H), 7.31 (d, $J = 1$ Hz, 1H). ^{13}C NMR (125.8 MHz, acetone-d_6): δ 24.4, 25.4, 30.6, 40.9, 55.6, 110.3, 141.4. ^{19}F NMR (471 MHz, acetone-d_6): δ −139.7. ^{11}B NMR (128 MHz, acetone-d_6): δ 1.61. HRMS (ESI): *m/z* calcd for $C_{11}H_{16}BF_3NO$ $(M - K)$ 246.1277, found 246.1281.

General Procedure B for the Reductive Amination of Potassium (Formylaryl)trifluoroborates using Pyridine−Borane. Potassium (3-((Pyrrolidin-1-yl)methyl)phenyl)trifluoroborate (20). To a test tube containing potassium (3-formylphenyl)trifluoroborate (106 mg, 0.50 mmol) and KHF_2 (156 mg, 2.00 mmol) in MeOH (2 mL) was added pyrrolidine (53 mg, 0.75 mmol). This was stirred for 2 h at room temperature. Pyridine−borane (46 mg, 0.5 mmol) was then added, and stirring was continued for 16 h. The solvent was then removed, and the resulting white solid was rinsed with Et_2O (2 × 5 mL). The resulting solid was then extracted with 10% MeOH/acetone (3 × 5 mL), after which the combined extracts were concentrated and precipitated with Et_2O (10 mL) to give potassium 3-((pyrrolidin-1-yl)methyl)phenyltrifluoroborate (102 mg, 76%). (For some substrates it proved necessary to add solid $KHCO_3$ (50 mg, 0.5 mmol) to the MeOH/acetone extracts to neutralize the product.) Mp: >200 °C. IR (KBr): 2975 cm^{-1}. ^{1}H NMR (500 MHz, acetone-d_6): δ 1.66−1.77 (m, 4H), 2.52 (s, 4H), 3.63 (s, 2H), 7.05 (d, $J = 5$ Hz, 2H), 7.37 (t, $J = 4$ Hz, 1H), 7.47 (s, 1H). ^{13}C NMR (125.8 MHz, acetone-d_6): δ 23.2, 53.7, 60.5, 126.3, 126.4, 130.7, 132.4, 135.7. ^{19}F NMR (471 MHz, acetone-d_6): δ −142.4. ^{11}B NMR (128 MHz, acetone-d_6): δ 3.95. HRMS (ESI): *m/z* calcd for $C_{11}H_{14}BF_3N$ $(M - K)$ 228.1171, found 228.1173.

***N*-((4′-Methoxybiphenyl-4-yl)methyl)cyclohexanamine (38) Using Ligandless Conditions.** A sealed microwave vial containing potassium (4-((cyclohexylamino)methyl)phenyl)trifluoroborate (**34**; 89 mg, 0.30 mmol), *p*-bromoanisole (58 mg, 0.31 mmol), $Pd(OAc)_2$ (2 mg, 3 mol %), and K_2CO_3 (124 mg, 0.90 mmol) was placed under vacuum (0.01 Torr) for 30 min, after which MeOH (1 mL) was added with stirring. The reaction mixture was heated at 75 °C for 3 h and then cooled to room temperature. Water (1 mL) was added, resulting in the formation of a white precipitate. This was filtered, and the white solid was then rinsed with water (2 × 1 mL). The white solid was taken up in EtOAc (5 mL), and the organic phase was washed with H_2O (3 × 3 mL) and brine (1 mL), dried ($MgSO_4$), and filtered to give title compound **38** (73 mg, 82%) as a solid following solvent removal. Mp: 65−70 °C. IR (KBr): 2918, 2845 cm^{-1}. ^{1}H NMR (500 MHz, methanol-d_4): δ 1.12−1.26 (m, 6H), 1.57 (d, $J = 12$ Hz, 1H), 1.73 (d, $J = 9$ Hz, 2H), 1.96 (d, $J = 10$ Hz, 2H), 2.42−2.47 (m, 1H), 3.77 (s, 2H), 3.80 (s, 3H), 6.95 (d, $J = 8$ Hz, 2H), 7.36 (d, $J = 8$ Hz, 2H), 7.51 (dd, $J = 11$, 2 Hz, 4 H). ^{13}C NMR (125.8 MHz, methanol-d_4): δ 24.7, 25.8, 32.3, 49.5, 54.3, 55.7, 113.9, 126.2, 127.5, 128.5, 133.3, 137.8, 139.6, 159.4. HRMS (ESI): calcd for $C_{20}H_{26}NO$ (M + H) 296.2014, found 296.2014.

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Supporting Information Available: Text and figures giving full experimental details and copies of all pertinent NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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