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Synthesis of Acyltrifluoroborates

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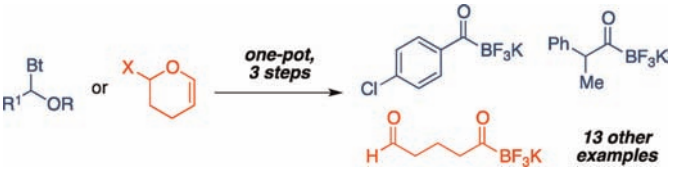
ABSTRACT



Acylboranes are among the most elusive boron-containing organic functional groups, a fact that has impeded development of new reactions employing them as substrates. A new synthesis of acyltrifluoroborates from benzotriazole (Bt)-based *N,O*-acetals has been developed. Two other routes provide acyltrifluoroborates containing alcohols, aldehydes, and carbamates. The ketone-like reactivity of the acyltrifluoroborate functional group is demonstrated, and the first X-ray structure of an acyltrifluoroborate is reported.

The current practice of synthetic organic chemistry relies heavily on the use of general, predictable coupling reactions of functionalized building blocks. Boronic acids and their derivatives are perhaps the most successful class of prefunctionalized reagents, as they are both amenable to a wide range of transformations and generally stable toward a variety of reaction conditions and unprotected functional groups. This has led to a large and ever growing number of commercially available boronic acids and their derivatives as well as creative new reactions that employ them as substrates.[1] Besides the common aryl and alkenylboronic acids, recent work has provided routes to previously inaccessible derivatives including those containing enantioenriched alkyl,[2] heteroaryl,[3] alkynyl,[4] and α-amino and α-alkoxy functional groups.[5]

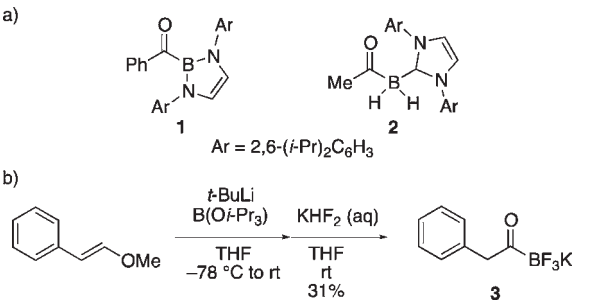


Figure 1. (a) Known acylboranes. (b) Previous synthesis of an acyltrifluoroborate.

In contrast, *acyl*boronic acids are currently considered esoteric compounds that are difficult to prepare, and only five derivatives have been reported.[6] Nozaki prepared the amino-stabilized acylborane **1** in 2007 by nucleophilic addition of an anionic boron reagent,[7] and Lacôte,

(1) Hall, D. G., Ed. *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials*, 2nd ed.; WILEY-VCH: Weinheim, 2011.

(2) For recent examples of their synthesis, see: (a) Lee, J. C. H.; McDonald, R.; Hall, D. G. *Nat. Chem.* **2011**, *3*, 894–899. (b) Bagutski, V.; Elford, T. G.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 1080–1083. (c) Schiffner, J. A.; Müther, K.; Oestreich, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1194–1196. (d) Kliman, L. T.; Mlynarski, S. N.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 13210–13211. For stereoretentive cross-couplings, see: (e) Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024–5025. (f) Taylor, B. L. H.; Jarvo, E. R. *J. Org. Chem.* **2011**, *76*, 7573–7576.

(3) For solutions to the instability of 2-pyridyl boronic acid derivatives in cross-coupling reactions, see: (a) Billingsley, K. L.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4695–4698. (b) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961–6963. (c) Dick, G. R.; Woerly, E. M.; Burke, M. D. *Angew. Chem., Int. Ed.* **2012**, *51*, 2667–2672.

(4) For syntheses of ethynyl boronic acid derivatives, see: (a) Struble, J. R.; Lee, S. J.; Burke, M. D. *Tetrahedron* **2010**, *66*, 4710–4718. (b) Yamamoto, Y.; Hattori, K.; Ishii, J.-i.; Nishiyama, H. *Tetrahedron* **2006**, *62*, 4294–4305.

(5) (a) Beenen, M. A.; An, C.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 6910–6911. (b) Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 11036–11037. (c) Molander, G. A.; Sandrock, D. L. *Org. Lett.* **2007**, *9*, 1597–1600.

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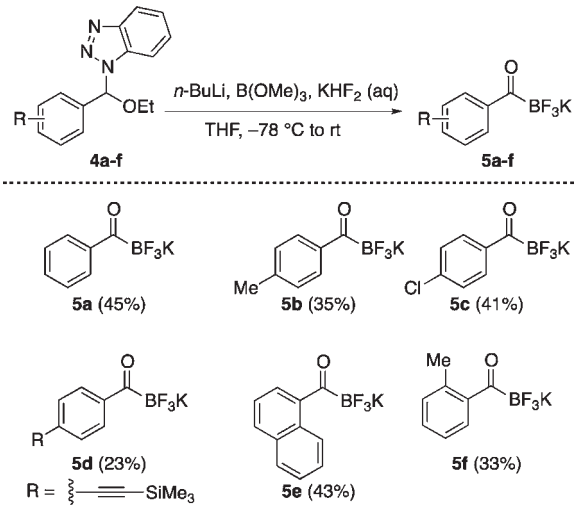
Curran, and co-workers reported NHC-stabilized acylborane **2** in 2010 (Figure 1a).[8] Recently, Molander described the synthesis of a single acyltrifluoroborate, **3**, by hydrolysis/fluorination of an intermediate α-borylvinyl ether (Figure 1b), but was not able to extend this route to other examples.[9] The lack of access to acylboronic acid derivatives has impeded a thorough investigation of their chemistry.

Prompted by our finding that **3** undergoes rapid and clean amide-forming ligations with *O*-Bz hydroxylamines in water,[10] we have identified new approaches to the synthesis of acyltrifluoroborates. This work primarily takes advantage of Katritzky's benzotriazole-based *N,O*-acetals as acyl-anion equivalents.[12,15] By combining this chemistry with in situ formation of the acyltrifluoroborate from the intermediate boronate ester, we have prepared a dozen new examples. Two other approaches were used to prepare acyltrifluoroborates bearing amine, alcohol, and aldehyde functional groups. These synthetic routes make acyltrifluoroborates available as starting materials for the amide-forming ligation and for further explorations of their properties and chemical reactivity.

At the outset, we considered that an ideal starting material for acyltrifluoroborates would be an acyl-anion equivalent that was easily prepared, readily deprotonated, and which regenerated the carbonyl under mild conditions, preferably with the aqueous acid of the boron fluorination step.[11] Based on these criteria, the benzotriazole-ethoxy *N,O*-acetals **4** developed by Katritzky were selected as possible precursors to benzoyltrifluoroborates.[12] These *N,O*-acetals are prepared directly from the corresponding aldehydes, lithiated rapidly at −78 °C, and hydrolyzed by a mild acid. They have also been used to prepare acylsilanes, demonstrating their suitability to form unconventional carbonyl-containing molecules.[13]

Scheme 1. Benzoyltrifluoroborates from *N,O*-Acetals **4a**−**f**



We found that quenching the anion of **4a** with $B(OMe)_3$ followed by the addition of aqueous KHF_2 gave benzoyltrifluoroborate **5a** in 45% yield (Scheme 1). *n*-BuLi was used as the limiting reagent to avoid the formation of trace amounts of $BuBF_3K$ that were difficult to separate from the desired product. It was also crucial to trap with $B(OMe)_3$ rather than $B(O\textit{i}\text{-Pr})_3$ as the latter led only to the formation of decomposed products, presumably from inefficient quenching of the relatively unstable benzyl anion. Substituted benzoyltrifluoroborates **5b**−**5f** were prepared according to the same procedure. Of the *N,O*-acetals used, only the 2-methoxyphenyl group proved problematic, as no trifluoroborate was observed in that reaction. Although the overall yields were modest, they were acceptable considering that the synthesis comprises a three-step, one-pot sequence as well as the isolation of the potassium trifluoroborate salt without any chromatography.[14] Further, the scale was sufficiently large that a single reaction produced > 300 mg of each example, providing ample material for further studies.

Having demonstrated that Bt-acetals could serve as acyl-anion equivalents leading to acyltrifluoroborates, we wished to also prepare non-benzoyl products. Katritzky had previously shown that replacing ethoxy with phenoxy allowed lithiation of alkyl-substituted *N,O*-acetals such as **7**.[15] Furthermore, **7** can be prepared from the readily available benzotriazole derivative **6**, which would then be the common precursor to acyltrifluoroborates if the phenoxy-acetal could be hydrolyzed effectively in aqueous KHF_2. This was indeed the case, and a variety of new acyltrifluoroborates were prepared by the two-step method outlined in Scheme 2.

The first lithiation/alkylation reaction was performed with both both primary benzyl and alkyl as well as secondary benzyl bromides as electrophiles and gave **7a**−**f** in 73−85% yield. Although one-pot sequential double lithiation/alkylation sequences for disubstitution of **6** have been

(6) (a) A titanium organometallic complex containing a carbonyl tris(pentafluorophenyl)borate has been isolated; see: Hair, G. S.; Jones, R. A.; Cowley, A. H.; Lynch, V. *Organometallics* **2000**, *20*, 177–181. (b) A phosphine−borane complex similar to **2** has been prepared; see: Imamoto, T.; Hikosaka, T. *J. Org. Chem.* **1994**, *59*, 6753–6759. We thank a referee for pointing us to this reference.

(7) (a) Yamashita, M.; Suzuki, Y.; Segawa, Y.; Nozaki, K. *J. Am. Chem. Soc.* **2007**, *129*, 9570–9571. (b) Segawa, Y.; Suzuki, Y.; Yamashita, M.; Nozaki, K. *J. Am. Chem. Soc.* **2008**, *130*, 16069–16079.

(8) Monot, J.; Solovyev, A.; Bonin-Dubarle, H.; Derat, É.; Curran, D. P.; Robert, M.; Fensterbank, L.; Malacria, M.; Lacôte, E. *Angew. Chem., Int. Ed.* **2010**, *49*, 9166–9169.

(9) (a) Molander, G. A.; Raushel, J.; Ellis, N. M. *J. Org. Chem.* **2010**, *75*, 4304–4306. (b) Ellis, N. M., PhD thesis, University of Pennsylvania, Philadelphia, USA, 2009.

(10) Dumas, A. M.; Molander, G. A.; Bode, J. W. *Angew. Chem., Int. Ed.*, in press (DOI: 10.1002/anie.201201077).

(11) Lithiated dithianes have been trapped with $B(OMe)_3$ and converted to the corresponding trifluoroborates with aqueous KHF_2; however their conversion into acyltrifluoroborates has not been reported. See: Vieira, A. S.; Fiorante, P. F.; Zukerman-Schpector, J.; Alves, D.; Botteselle, G. V.; Stefani, H. A. *Tetrahedron* **2008**, *64*, 7234–7241.

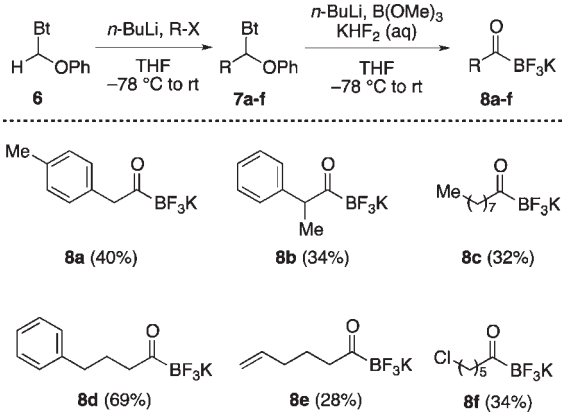
(12) Katritzky, A. R.; Lang, H.; Wang, Z.; Zhang, Z.; Song, H. *J. Org. Chem.* **1995**, *60*, 7619–7624.

(13) Katritzky, A. R.; Wang, Z.; Lang, H. *Organometallics* **1996**, *15*, 486–490.

(14) One-pot syntheses of aryltrifluoroborates commonly give yields of ∼50−60%. For examples, see Schemes 11 and 12 in Darses, S.; Genet, J.-P. *Chem. Rev.* **2007**, *108*, 288–325.

(15) Katritzky, A. R.; Lang, H.; Wang, Z.; Lie, Z. *J. Org. Chem.* **1996**, *61*, 7551–7557.

Scheme 2. Synthesis of Acyltrifluoroborates **8a**–**f**

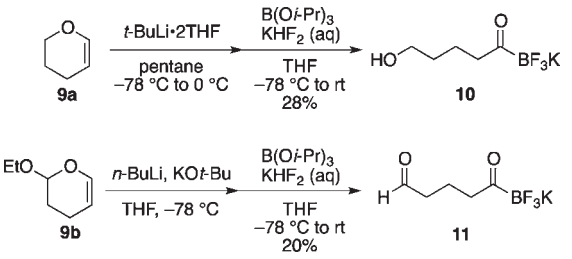


described, preparation of acyltrifluoroborates was infeasible with this approach as they were difficult to isolate from the accumulated byproducts. However, starting from pure **7**, one-pot deprotonation/borylation and fluorination/hydrolysis gave acyltrifluoroborates **8a**–**f** in yields similar to those obtained from *N*,*O*-acetals **4**. Phenylacetyltrifluoroborates **8a**–**b** are similar to the example previously prepared by Molander,[9a] however derived from a route that is more amenable to product diversity. Non-benzylic examples could also be prepared, including those with aromatic (**8d**) and alkenyl (**8e**) groups. Terminal alkyl chloride **8f** was formed equally well, despite some competitive cyclization during the lithiation/borylation stage of the reaction.

During our attempts to develop a general synthesis of structurally diverse acyltrifluoroborates, we also explored several other routes to specific substrates. Cyclic vinyl boronic esters proved particularly valuable for the preparation of acyltrifluoroborates bearing functional groups (Scheme 3). Cyclic vinyl ethers are known to be easily lithiated to give relatively stable anions, which could be trapped with electrophilic boron reagents.[16] Starting from 2,3-dihydropyran **9a**, a one-pot sequence of deprotonation, borylation, and treatment with aqueous KHF_2 gave acyltrifluoroborate **10**.

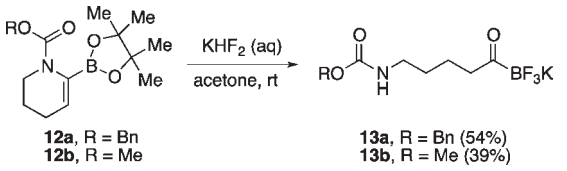
Similarly, the reaction of ethoxy-substituted dihydropyran **9b** gave acyltrifluoroborate **11** by spontaneous loss of ethanol during the hydrolysis step.[17] It is likely that

Scheme 3. Acyltrifluoroborates from Cyclic Vinyl Ethers



direct preparation of the vinyl boronic esters by Ir-catalyzed C–H functionalization will provide another entry into the requisite starting materials.[18]

Scheme 4. Synthesis of *N*-Protected δ-Amino Acyltrifluoroborates



12a, R = Bn
12b, R = Me

13a, R = Bn (54%)
13b, R = Me (39%)

Another route to functionalized acyltrifluoroborates was achieved from cyclic carbamates **12a**–**b**, which were easily prepared from the corresponding vinyl triflates by Pd-catalyzed cross-coupling with B_2pin_2.[19] Treatment of an acetone solution of the vinyl boronate with aqueous KHF_2 gave acyltrifluoroborates **13a**–**b** in 54% and 39% yield, respectively (Scheme 4).

The first structure determination of an acyltrifluoroborate was obtained by X-ray analysis of a single crystal of **5c** (Figure 2), grown by vapor diffusion of hexane into a solution of **5c** in acetone. The C=O bond length of 1.24 Å suggested that the carbonyl was ketone-like; the IR frequency of 1636 cm^{-1} was lower than that of a typical ketone or aldehyde, but close to that reported for other acylboranes such as **1**, **2**, and **3**.[7–9]

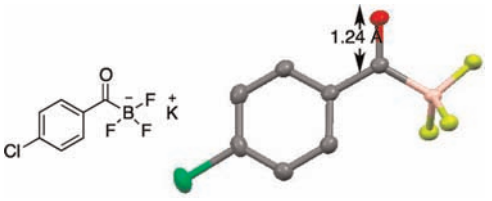


Figure 2. X-ray crystal structure of acyltrifluorobate **5c**.

Somewhat to our surprise, the acyltrifluoroborates maintained typical carbonyl reactivity and behaved in

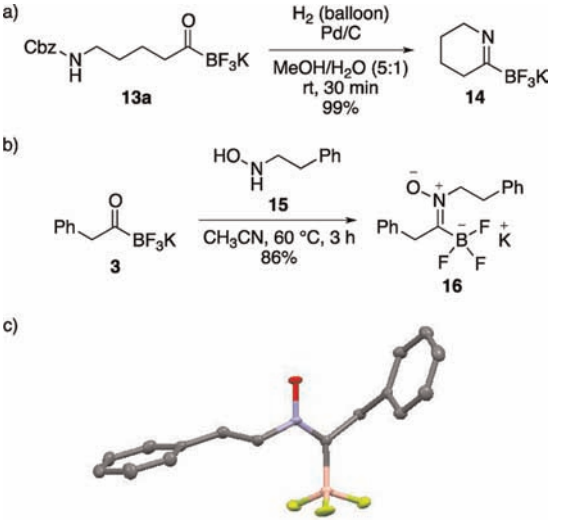
(16) Boeckman, R. K., Jr.; Bruza, K. J. *Tetrahedron* **1981**, *37*, 3997–4006.
(17) For the use of Schlosser's base to deprotonate alkoxydihydropyrans, see: Yu, C.-M.; Jung, W.-H.; Choi, H.-S.; Lee, J.; Lee, J.-K. *Tetrahedron Lett*. **1995**, *36*, 8255–8258.
(18) (a) Kikuchi, T.; Takagi, J.; Isou, H.; Ishiyama, T.; Miyaura, N. *Chem.—Asian. J*. **2008**, *3*, 2082–2090. (b) Kikuchi, T.; Takagi, J.; Ishiyama, T.; Miyaura, N. *Chem. Lett*. **2008**, *37*, 664–665.
(19) Occhiato, E. G.; Lo Galbo, F.; Guarna, A. *J. Org. Chem*. **2005**, *70*, 7324–7330.
(20) (a) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; WILEY-VCH: Weinheim, 1999. (b) Otera, J. *Modern Carbonyl Chemistry*; WILEY-VCH: Weinheim, 2000.
(21) For the preparation of a boryloxime in a carborane, see: Herzog, A.; Knobler, C. B.; Hawthorne, M. F. *Angew. Chem., Int. Ed*. **1998**, *37*, 1552–1556.

many case like ketones or aldehydes (Scheme 5).[20] Hydrogenolysis of the Cbz group in **13a** with H_2 and Pd/C did not affect the trifluoroborate moiety and revealed the primary amine, which underwent immediate cyclization to give imine **14** in quantitative yield (Scheme 5a). Similarly, trifluoroborate **3** condensed with hydroxylamine **15** to form nitrone **16** as a single isomer in 86% yield (Scheme 5b).[21] The configuration was determined by an X-ray crystal structure (Scheme 5c); the *Z* arrangement is presumably preferred in order to maximize the distance between the two anionic centers. In preliminary studies, this nitrone was reluctant to undergo either [3 + 2] dipolar cycloadditions or amide formation as we had initially expected by analogy to the chemistry of α-ketoacids.[22,23]

Our results establish acyltrifluoroborates as a new, readily accessible carbonyl-based functional group. From a practical standpoint, they were prepared on a useful laboratory scale, are air and water stable, and can be stored for at least a year in a refrigerator. Current efforts are aimed at discovering new methods for the preparation of more elaborately functionalized examples. We have shown that they possess a reactivity typical of carbonyls, such as imine and nitrone formation and, in separate work,[10] that they undergo remarkably rapid and clean amide-forming ligations with *O*-Bz hydroxylamines. Having taken steps toward making the acylborane functional group more than a rare curiousity, we hope that they will be exploited for the development of new methods that take advantage of their unique properties and reactivity.

(22) Bode, J. W.; Fox, R. M.; Baucom, K. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1248–1252.
(23) Pusterla, I.; Bode, J. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 513–516.

Scheme 5. Reactions of Acyltrifluoroborates



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Supporting Information Available. Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.