

Defluorinative Diborasodiation of Benzotrifluorides with Bis(pinacolato)diboron and Sodium

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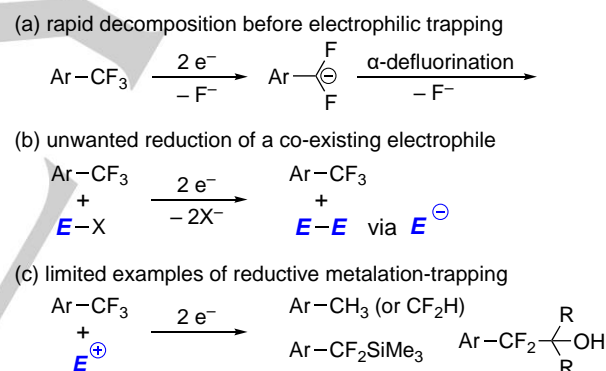
Abstract: Treatment of benzotrifluorides with sodium dispersion in the presence of bis(pinacolato)diboron results in diborative reduction to yield the corresponding diborylbenzylsodium species. The anionic species react not only with reactive organic halides but also with aromatic carbonyl compounds to yield the corresponding alkenylboron compounds via Peterson-type olefination. The success of the generation of the diborylbenzylsodium species lies in immediate capture of initially formed unstable difluorobenzylsodium with co-existing reduction-resistant bis(pinacolato)diboron.

Organofluorine compounds are useful as biologically active agents as well as key components of functional materials.^[1] Among fluorine-containing substituents, a trifluoromethyl group endows organic molecules with polarization and lipophilicity, thus occupying a unique position. Because methods to introduce a trifluoromethyl group have been actively studied, trifluoromethyl-containing compounds have nowadays become readily available.^[2]

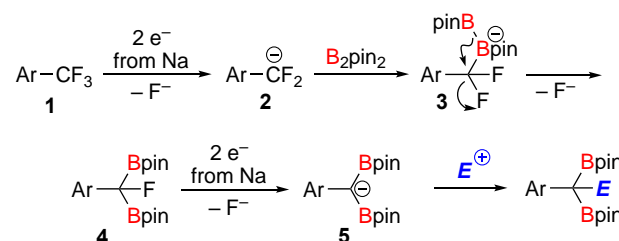
While trifluoromethyl-containing compounds are useful on their own, increasing attention has been paid to methods to transform the strong C–F bonds in a trifluoromethyl group.^[3,4] Among such transformations, reductive metalation to generate the corresponding carbanion has been expected to be promising in organic synthesis. However, the generated carbanions are unstable and decompose rapidly via α -defluorination (Scheme 1a).^[5] To avoid the rapid decomposition, the carbanion should be promptly trapped with an electrophile that is placed in the same reaction flask. However, co-existing electrophiles are generally subjected to single electron reduction under the reductive conditions and do not afford the desired products but by-products such as the dimers of electrophiles via reductive homo-coupling (Scheme 1b). Actually, reductive metalation of benzotrifluorides is applied limitedly to protonation,^[6] silylation with chlorosilanes,^[7] and hydroxyalkylation with carbonyls^[8] (Scheme 1c).^[9]

Recently we have become interested in the use of reduction-resistant electrophiles in order to trap unstable anionic intermediates generated through a reductive process.^[10] Among the reduction-resistant electrophiles, alkoxyboranes have shown high performance in the efficiency of the trapping as well as the usefulness of the borylated products in organic synthesis. Here we report that bis(pinacolato)diboron B_2pin_2 efficiently traps the corresponding carbanions that are reductively generated from benzotrifluorides to eventually generate diborylbenzyl anion species.

The mechanistic design of this new reductive diborylation is shown in Scheme 2. Efficient two-electron injection from sodium dispersion^[10,11] to benzotrifluorides **1** provides the corresponding difluorobenzyl anion **2**. The anion would be expected to react instantly with B_2pin_2 in the same pot before the undesired α -elimination. The generated borate **3** then undergoes 1,2-shift of the pinacoloboryl group to yield *gem*-difluorobenzyl species **4**.^[12] Further reduction by the remaining sodium proceeds smoothly to yield doubly boron-stabilized benzyl anion **5**.^[13] Subsequent reaction with an electrophile yields diboryl compounds of synthetic use.



Scheme 1. Difficulty in reductive functionalization of benzotrifluorides and limited successful examples.



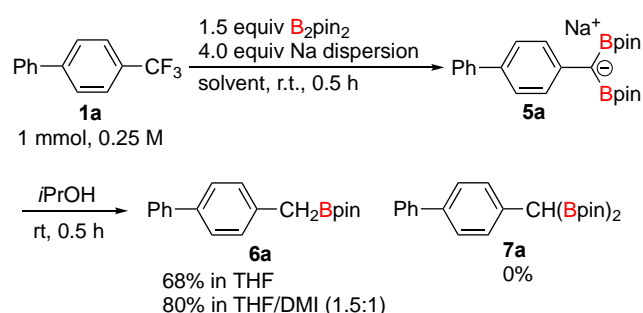
Scheme 2. Mechanistic design of defluorinative diborasodiation.

Treatment of 4-trifluoromethylbiphenyl (**1a**) with sodium dispersion (4 equiv) in the presence of B_2pin_2 in THF afforded monoborylated product **6a** in 68% NMR yield after protonolysis with isopropyl alcohol. None of the expected diborylated product

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7a was observed because the initial protonation of **5a** was followed by another protonation of one of the two C–B bonds^[14] probably promoted by an isopropoxide anion. Even though the formation of **7a** was not observed, we screened the solvent to improve the yield of **6a**. We finally found a 1.5:1 mixture of THF and 1,3-dimethyl-2-imidazolidinone (DMI) as the best solvent system (80% NMR yield, 64% isolated yield).^[15,16]

It is worth noting that B₂pin₂ should be placed during the reduction: When B₂pin₂ was added after the reduction, the reaction gave a complex mixture containing none of **6a**. Regarding the reducing agent, sodium dispersion was the best among tested: When the reaction was performed by using lithium powder, **6a** was obtained in only 16% yield along with a complex product mixture. Interestingly, the use of lithium naphthalene as a homogeneous reducing agent improved the yield up to 64%.



Scheme 3. Defluorinative reaction of **1a** and B₂pin₂ followed by protonolysis.

With the results in Scheme 3, we then examined the scope of this reaction by using iodomethane as the reaction-terminating electrophile (Table 1). The methylation afforded the *gem*-diboryl products **8** without protodeborylation occurring upon aqueous workup. The reductive transformation of biphenyl derivatives **1a–f** proceeded smoothly to yield the corresponding products **8a–f**. The transformation of **1b** proceeded with the fluoro group on the benzene ring untouched. The methoxy group in **8c** and the trimethylsilyl group in **8e** were compatible under the reaction conditions. Pristine benzotrifluoride (**1g**) bearing only one benzene ring required naphthalene as an electron-transfer catalyst to yield **8g**. This was also the case for the reactions of **1h–j**, even though their substituents might facilitate electron transfer to the substrates. Of note is that no diborylation at the acetylenic carbons^[10a] took place to yield **8i** selectively. Treatment of 1,4-bis(trifluoromethyl)benzene resulted in the formation of a complex mixture of products.^[17]

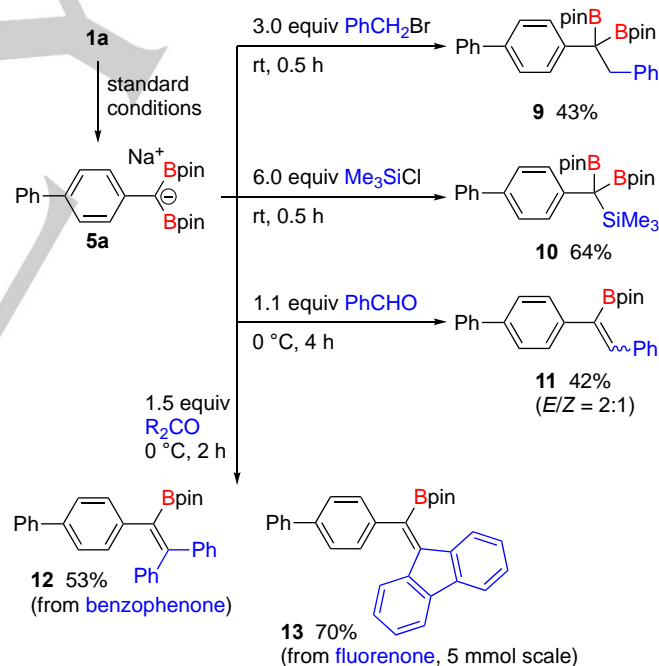
Table 1. Defluorinative diborasodiation of **1** followed by methylation.

Entry	R	8	Isolated yield / %
1	4-Ph	8a	67 (56 ^[9])
2	4-(4-FC ₆ H ₄)	8b	52 ^[b,c]

3	4-(4-MeOC ₆ H ₄)	8c	53
4	4-(4-MeC ₆ H ₄)	8d	40
5	4-(4-Me ₃ SiC ₆ H ₄)	8e	43
6	3-Ph	8f	61
7	H	8g	39 ^[d]
8	3-MeO	8h	38 ^[d]
9	4-C ₄ H ₉ C≡C	8i	48 ^[b,c,d]
10	4-pinB	8j	48 ^[b,d]

[a] 5-mmol scale. [b] 6.0 equiv MeI. [c] 60 °C for the methylation. [d] 0.4 equiv naphthalene was used as an additive.

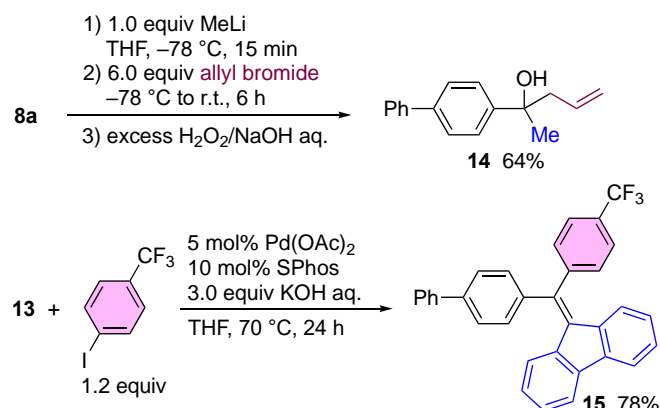
Not only the methylation but also benzylation and silylation occurred to yield **9** and **10** (Scheme 4). However, simple alkyl halides were not suitable as electrophiles, probably because the anionic intermediate **5a** is bulky and is stabilized by the two boryl and the biphenyl groups. Instead of the alkylation, we found that Peterson-type olefination reaction of carbonyl compounds with **5a** proceeds smoothly to yield alkenylborons **11–13**.^[18] Although the stereoselectivity in the reaction of benzaldehyde was low, the olefination represents an interesting transformation from benzotrifluorides to alkenylboron compounds in one-pot.



Scheme 4. Reactions of anion **5a** with other electrophiles.

gem-Diboryl product **8a** underwent selective activation of one of the two boryl groups with methyllithium, which was followed sequentially by trapping with allyl bromide and by oxidation to yield **14**^[19] (Scheme 5). The Suzuki-Miyaura cross-coupling reaction of olefinated product **13** proceeded smoothly^[20] to yield tetraarylethene **15** in high yield.

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Scheme 5. Transformations of diborylated product **8a** and alkenylboron **13**.

In summary, we have developed a transformation of benzotrifluorides into the corresponding diborylbenzylsodium species, which will find applications as interesting reagents in organic synthesis. The generation of the anion would be achieved by the following reaction sequence: 1) reduction of benzotrifluorides with sodium to yield unstable difluorobenzylsodium, 2) instant capture of the anion with bis(pinacolato)diboron as a reduction-resistant electrophile, 3) 1,2-boryl shift from the resulting borylborate, and 4) reduction of the resulting diborylfluorotoluene. The key to the success is the use of the reduction-resistant electrophile. Further investigation about combined use of alkali-metal reduction and reduction-resistant electrophiles are ongoing in our laboratory.

Acknowledgements

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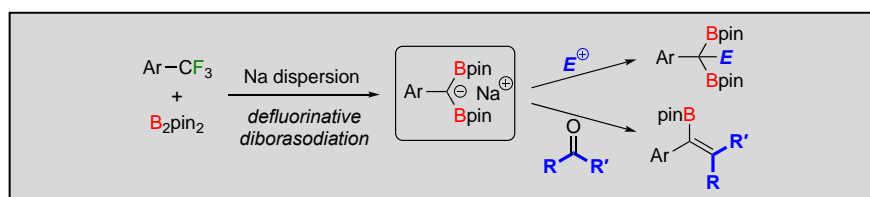
Keywords: reduction • metalation • borylation • carbanion • defluorination

- [1] a) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881-1886; b) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320-330; c) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359-4369; d) R. Berger, G. Resnati, P. Metrangolo, E. Weberd, J. Hulliger, *Chem. Soc. Rev.* **2011**, *40*, 3496-3508; e) J.-M. Vincent, *Chem. Commun.* **2012**, *48*, 11382-11391; f) T. Fujiwara, D. O'Hagan, *J. Fluorine Chem.* **2014**, *167*, 16-29; g) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Rev.* **2014**, *114*, 2432-2506; h) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315-8359; i) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa, H. Liu, *Chem. Rev.* **2016**, *116*, 422-518; j) N. A. Meanwell, *J. Med. Chem.* **2018**, *61*, 5822-5880.
- [2] a) O. A. Tomashenko, V. V. Grushin, *Chem. Rev.* **2011**, *111*, 4475-4521; b) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470-477; c) Y. Macé, E. Magnier, *Eur. J. Org. Chem.* **2012**, 2479-2494; d) P. Chen, G. Liu, *Synthesis* **2013**, *45*, 2919-2939; e) G. Landelle, A. Panossian, S.

- Pazenok, J. Vors, F. R. Leroux, *Beilstein J. Org. Chem.* **2013**, *9*, 2476-2536; f) L. Chu, F. Qing, *Acc. Chem. Res.* **2014**, *47*, 1513-1522; g) C. Alonso, E. M. Marigorta, G. Rubiales, F. Palacios, *Chem. Rev.* **2015**, *115*, 1847-1935; h) X. Liu, C. Xu, M. Wang, Q. Liu, *Chem. Rev.* **2015**, *115*, 683-730; i) J. Charpentier, N. Früh, A. Togni, *Chem. Rev.* **2015**, *115*, 650-682; j) Q. Liu, C. Ni, J. Hu, *Natl. Sci. Rev.* **2017**, *4*, 303-325.
- [3] a) H. Amii, K. Uneyama, *Chem. Rev.* **2009**, *109*, 2119-2183; b) T. Stahl, H. F. T. Klare, M. Oestreich, *ACS Catal.* **2013**, *3*, 1578-1587; c) Q. Shen, Y.-G. Huang, C. Liu, J.-C. Xiao, Q.-Y. Chen, Y. Guo, *J. Fluorine Chem.* **2015**, *179*, 14-22; d) F. Jaroschik, *Chem. Eur. J.* **2018**, *24*, 14572-14582; e) J.-D. Hamel, J.-F. Paquin, *Chem. Commun.* **2018**, *54*, 10224-10239; f) X. Ma, Q. Song, *Chem. Soc. Rev.* **2020**, *49*, 9197-9219; g) R. Gupta, A. K. Jaiswal, D. Mandal, R. D. Young, *Synlett* **2020**, *31*, 933-937; h) Y. Kim, K. Kanemoto, K. Shimomori, T. Hosoya, S. Yoshida, *Chem. Eur. J.* **2020**, *26*, 6136-6140 and references cited therein.
- [4] Additional reviews about C-F bond activation: a) T. Ahrens, J. Kohlmann, M. Ahrens, T. Braun, *Chem. Rev.* **2015**, *115*, 931-972; b) T. Fujita, K. Fuchibe, J. Ichikawa, *Angew. Chem. Int. Ed.* **2019**, *58*, 390-402; *Angew. Chem.* **2019**, *131*, 396-408; c) T. Niwa, T. Hosoya, *Bull. Chem. Soc. Jpn.* **2020**, *93*, 230-248.
- [5] a) A. Streitwieser Jr., F. Mares, *J. Am. Chem. Soc.* **1968**, *90*, 2444-2445; b) J. B. Geri, M. M. W. Wolfe, N. K. Szymczak, *J. Am. Chem. Soc.* **2018**, *140*, 9404-9408; c) P. R. Blakemore, R. W. Hoffmann, *Angew. Chem. Int. Ed.* **2018**, *57*, 390-407; *Angew. Chem.* **2018**, *130*, 396-413.
- [6] a) J. P. Coleman, M. G. Gilde, J. H. P. Utley, B. C. L. Weedon, L. Ebersson, *J. Chem. Soc., Perkin Trans. 2* **1973**, 1903-1908; b) H. Lund, N. J. Jensen, *Acta Chem. Scand., Ser. B* **1974**, *28*, 263-265; c) C. P. Andrieux, C. Combellas, F. Kanoufi, J.-M. Savéant, A. Thiébaud, *J. Am. Chem. Soc.* **1997**, *119*, 9527-9540; d) S. B. Munoz, C. Ni, Z. Zhang, F. Wang, N. Shao, T. Mathew, G. A. Olah, G. K. S. Prakash, *Eur. J. Org. Chem.* **2017**, 2322-2326.
- [7] a) P. Clavel, M. P. Léger-Lambert, C. Biran, F. Serein-Spirau, M. Bordeau, N. Roques, H. Marzouk, *Synthesis* **1999**, 829-834; b) P. Clavel, G. Lessene, C. Biran, M. Bordeau, N. Roques, S. Trévin, D. Montauzon, *J. Fluorine Chem.* **2001**, *107*, 301-310; c) H. Amii, Y. Hatamoto, M. Seo, K. Uneyama, *J. Org. Chem.* **2001**, *66*, 7216-7218; d) S. Utsumi, T. Katagiri, K. Uneyama, *Tetrahedron* **2012**, *68*, 1085-1091; e) S. Utsumi, T. Katagiri, K. Uneyama, *J. Fluorine Chem.* **2013**, *152*, 84-89.
- [8] a) C. Saboureau, M. Troupel, S. Sibille, J. Périchon, *J. Chem. Soc., Chem. Commun.* **1989**, 1138-1139; b) Y. Yamauchi, T. Fukuhara, S. Hara, H. Senboku, *Synlett* **2008**, 438-442.
- [9] For recent examples of reductive transformations of C(sp³)-F bond of benzotrifluorides via radical species under photoredox catalysis, see: a) K. Chen, N. Berg, R. Gschwind, B. König, *J. Am. Chem. Soc.* **2017**, *139*, 18444-18447; b) H. Wang, N. T. Jui, *J. Am. Chem. Soc.* **2018**, *140*, 163-166; c) D. B. Vogt, C. P. Seath, H. Wang, N. T. Jui, *J. Am. Chem. Soc.* **2019**, *141*, 13203-13211; d) J. B. I. Sap, N. J. W. Straathof, T. Knauber, C. F. Meyer, M. Médebielle, L. Buglioni, C. Genicot, A. A. Trabanco, T. Noël, C. W. em Ende, V. Gouverneur, *J. Am. Chem. Soc.* **2020**, *142*, 9181-9187.
- [10] a) F. Takahashi, K. Nogi, T. Sasamori, H. Yorimitsu, *Org. Lett.* **2019**, *21*, 4739-4744; b) M. Fukazawa, F. Takahashi, K. Nogi, T. Sasamori, H. Yorimitsu, *Org. Lett.* **2020**, *22*, 2303-2307; c) S. Ito, M. Fukazawa, F. Takahashi, K. Nogi, H. Yorimitsu, *Bull. Chem. Soc. Jpn.* **2020**, *93*, 1171-1179; d) S. Wang, A. Kaga, H. Yorimitsu, *Synlett* **2021**, *32*, 219-223; e) S. Wang, A. Kaga, H. Yorimitsu, *Heterocycles* **2021**, *103*, in press (DOI: 10.3987/COM-20-S(K)59).
- [11] a) J. An, D. N. Work, C. Kenyon, D. J. Procter, *J. Org. Chem.* **2014**, *79*, 6743-6747; b) M. Han, X. Ma, S. Yao, Y. Ding, Z. Yan, A. Adijiang, Y. Wu, H. Li, Y. Zhang, P. Lei, Y. Ling, J. An, *J. Org. Chem.* **2017**, *82*, 1285-1290; c) H. Li, B. Zhang, Y. Dong, T. Liu, Y. Zhang, H. Nie, R. Yang, X. Ma, Y. Ling, J. An, *Tetrahedron Lett.* **2017**, *58*, 2757-2760; d) M. Han, Y. Ding, Y. Yan, H. Li, S. Luo, A. Adijiang, Y. Ling, J. An, *Org. Lett.* **2018**, *20*, 3010-3013; e) P. Lei, Y. Ding, X. Zhang, A. Adijiang, H. Li, Y. Ling, J. An, *Org. Lett.* **2018**, *20*, 3439-3442; f) B. Zhang, H. Li, Y. Ding, Y. Yan, J. An, *J. Org. Chem.* **2018**, *83*, 6006-6614; g) Y. Ding, S. Luo, A. Adijiang, H. Zhao, J. An, *J. Org. Chem.* **2018**, *83*, 12269-12274; h) R. Inoue, M. Yamaguchi, Y. Murakami, K. Okano, A. Mori, *ACS Omega*, **2018**, *3*, 12703-12706; i) S. Asako, H. Nakajima, K. Takai, *Nat. Catal.* **2019**, *2*,

- 297-303; j) S. Asako, M. Kodera, H. Nakajima, K. Takai, *Adv. Synth. Catal.* **2019**, *361*, 3120-3123; k) H. Li, Z. Lai, A. Adijiang, H. Zhao, J. An, *Molecules* **2019**, *24*, 459; l) Y. Ding, S. Luo, L. Ma, J. An, *J. Org. Chem.* **2019**, *84*, 15827-15833; m) J. Q. Zhang, J. J. Ye, T. Huang, H. Shinohara, H. Fujino, L.-B. Han, *Commun. Chem.* **2020**, *3*, 1-9; n) J. Ye, J. Q. Zhang, Y. Saga, S. Onozawa, S. Kobayashi, K. Sato, N. Fukaya, L.-B. Han, *Organometallics* **2020**, *39*, 2682-2694.
- [12] The 1,2-borate shift from **3** was calculated to be reasonable, with an activation free energy of 22.3 kcal/mol. As a possible different mechanism, metathesis from **3** via a four-membered transition state proceeds with a computed activation free energy of 28.2 kcal/mol. Computational details are in Supporting Information.
- [13] Other methods to generate diborylbenzylic anion: a) S. H. Cho, J. F. Hartwig, *Chem. Sci.* **2014**, *5*, 694-698; b) W. N. Palmer, C. Zarate, P. J. Chirik, *J. Am. Chem. Soc.* **2017**, *139*, 2589-2592; c) B. Lee, P. J. Chirik, *J. Am. Chem. Soc.* **2020**, *142*, 2429-2437. The formation of **5** was monitored by ¹¹B NMR analysis. For details, see Supporting Information.
- [14] Terminating the reaction with CH₃OD resulted in the formation of doubly deuterated **6a**. The use of acetic acid afforded **7a** in 27% yield along with **6a** in 27% yield. Details are described in Supporting Information.
- [15] Details of the optimization study are described in Supporting Information.
- [16] Polar aprotic solvents such as DMI are common solvents in the reductive metalation of benzotrifluorides. See references 6–8.
- [17] This result is in sharp contrast to the successful reductive metalation-silylation process using magnesium powder and chlorotrimethylsilane in reference 7c. Also notably, the reaction of 1,4-bis(trifluoromethyl)benzene with magnesium in the presence of B₂pin₂ in DMF led to no conversion.
- [18] a) D. S. Matteson, R. J. Moody, P. K. Jesthi, *J. Am. Chem. Soc.* **1975**, *97*, 5608-5609; b) D. S. Matteson, R. J. Moody, *J. Org. Chem.* **1980**, *45*, 1091-1095; c) J. R. Coombs, L. Zhang, J. P. Morken, *Org. Lett.* **2015**, *17*, 1708-1711.
- [19] A. J. Wommack, J. S. Kingsbury, *Tetrahedron Lett.* **2014**, *55*, 3163-3166.
- [20] T. Tani, Y. Sawatsugawa, Y. Sano, Y. Hirataka, N. Takahashi, S. Hashimoto, T. Sugiura, T. Tsuchimoto, *Adv. Synth. Catal.* **2019**, *361*, 1815-1834.

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Reductive metalation of benzotrifluorides with sodium dispersion in the presence of reduction-resistant bis(pinacolato)diboron affords the corresponding diborylbenzylsodium species with elimination of the three fluoride anions. The anionic species react with electrophiles, such as aromatic carbonyl compounds to yield multi-substituted alkenylboron compounds.

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