TITLE:
Defluorinative Diborasodiation of Benzotrifluorides with Bis(pinacolato)Diboron and Sodium

AUTHOR(S):
Ito, Shiori; Takahashi, Fumiya; Yorimitsu, Hideki

CITATION:

ISSUE DATE:
2021-06

URL:
http://hdl.handle.net/2433/268763

RIGHT:
This is the peer reviewed version of the following article: [S. Ito, F. Takahashi, H. Yorimitsu, Asian J. Org. Chem. 2021, 10, 1440.], which has been published in final form at https://doi.org/10.1002/ajoc.202100206. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions. This article may not be enhanced, enriched or otherwise transformed into a derivative work, without express permission from Wiley or by statutory rights under applicable legislation. Copyright notices must not be removed, obscured or modified. The article must be linked to Wiley’s version of record on Wiley Online Library and any embedding, framing or otherwise making available the article or pages thereof by third parties from platforms, services and websites other than Wiley Online Library must be prohibited; The full-text file will be ...
COMMUNICATION

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

Shiori Ito, Fumiya Takahashi, and Hideki Yorimitsu*^[a]

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 alkynylboron compounds via Peterson-type olefination. The success of the generation of the diborylbenzylsodium species lies in immediate capture of initially formed unstable difluorobenzylsodium with coexisting reduction-resistant bis(pinacolato)diboron.

Organofluorine compounds are useful as biologically active agents as well as key components of functional materials. 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. 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. 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). 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] 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, alkoxyporoboranes 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$_2$pin$_2$ 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$_2$pin$_2$ in the same pot before the undesired α-elimination. The generated borate 3 then undergoes 1,2-shift of the pinacolatoboryl group to yield gem-diborylfluoro 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.

Organofluorine compounds are useful as biologically active agents as well as key components of functional materials. 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. 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. 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). 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, silylation with chlorosilanes, and hydroxyalkylation with carbonyls.[8] 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, alkoxyporoboranes 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$_2$pin$_2$ 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$_2$pin$_2$ in the same pot before the undesired α-elimination. The generated borate 3 then undergoes 1,2-shift of the pinacolatoboryl group to yield gem-diborylfluoro 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.

(a) rapid decomposition before electrophilic trapping

\[
\text{Ar–CF}_3 + 2e^- \rightarrow \text{Ar}_2F_2 \rightarrow \text{Ar} + \alpha\text{-defluorination} - F^- 
\]

(b) unwanted reduction of a co-existing electrophile

\[
\text{Ar–CF}_3 + 2e^- \rightarrow \text{Ar} + \text{CF}_3 \text{F} - 2X^- \rightarrow \text{E}^\ominus \rightarrow \text{E} + \text{E}^- \text{ via } \text{E}^\ominus 
\]

(c) limited examples of reductive metalation-trapping

\[
\text{Ar–CF}_3 + 2e^- \rightarrow \text{Ar–CH}_3 \text{ (or CF}_2\text{H)} - \text{R} \rightarrow \text{Ar–CF}_2\text{SiMe}_3 - \text{Ar–CF}_2\text{OH} - \text{R} 
\]

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

\[
\text{Ar–CF}_3 + 2e^- \rightarrow \text{Ar–CF}_2\text{Bpin}_2 - \text{Bpin} \rightarrow \text{Ar-F} - \text{F}^- \rightarrow \text{Ar-F} 
\]

\[
\text{Ar–CF}_3 + 2e^- \rightarrow \text{Ar–CF}_2\text{Bpin}_2 - \text{Bpin} \rightarrow \text{Ar–CF}_2\text{Bpin} \rightarrow \text{Ar–CF}_2\text{Bpin} 
\]

Scheme 2. Mechanistic design of defluorinative diborasodiation.

Treatment of 4-trifluoromethylbiphenyl (1a) with sodium dispersion (4 equiv) in the presence of B$_2$pin$_2$ in THF afforded monoborylated product 6a in 68% NMR yield after protonolysis with isopropyl alcohol. None of the expected diborylated product
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 Bpin$_2$ should be placed during the reduction: When Bpin$_2$ 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 naphthalenide as a homogeneous reducing agent improved the yield up to 64%.

![Diagram](https://example.com/diagram.png)

**Scheme 3.** Defluorinative reaction of 1a and Bpin$_2$ 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 benzetrifluoride (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 diboration at the acetylenic carbons[10b] 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 diboration of 1 followed by methylation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>8</th>
<th>Isolated yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-Ph</td>
<td>8a</td>
<td>67 (56[16])</td>
</tr>
<tr>
<td>2</td>
<td>4-(4-FC6H4)</td>
<td>8b</td>
<td>52[14]</td>
</tr>
</tbody>
</table>

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.

![Diagram](https://example.com/diagram.png)

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

gem-Diboryl product 8a underwent selective activation of one of the two boryl groups with methylthium, 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.
In summary, we have developed a transformation of benzotrifluorides into the corresponding diboryldibenzylsodium 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(phenyl)diborane as a reduction-resistant electrophile, 3) 1,2-boryl shift from the resulting borylborane, and 4) reduction of the resulting diboryldifluorotoluene. 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

This work was supported by JSPS KAKENHI Grant Number JP19H00895 as well as JST CREST Grant Number JPMJCR19R4. F.T. acknowledges JSPS Predoctoral Fellowship (JSPS KAKENHI Grant Number JP20J22814). H.Y. thanks The Asahi Glass Foundation for financial support. We thank KOBELECO ECO-Solutions Co., Ltd. for providing sodium dispersion.

Keywords: reduction · manipulation · borylation · carbannion · defluorination


In summary, we have developed a transformation of benzotrifluorides into the corresponding diboryldibenzylsodium 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(phenyl)diborane as a reduction-resistant electrophile, 3) 1,2-boryl shift from the resulting borylborane, and 4) reduction of the resulting diboryldifluorotoluene. 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.
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, meta-thesis 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.


Terminating the reaction with CH$_3$OD 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.

Polar aprotic solvents such as DMI are common solvents in the reductive metalation of benzotrifluorides. See references 6-8.

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 B$_2$pin$_2$ in DMI led to no conversion.


Entry for the Table of Contents

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.

Institute and/or researcher Twitter usernames: @yorimitsu_lab