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Halogen–lithium exchange versus deprotonation: synthesis of diboronic acids derived from aryl–benzyl ethers

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Abstract—Lithiation of a series of aryl benzyl ethers containing halogen substituents (–F, –Br, –I) was investigated. The resultant mono- and diorganolithium intermediates were converted into the corresponding aldehydes or diboronic acids in good yields. The dilithiation of aryl benzyl ethers containing a reactive hydrogen atom and halogen atom capable of halogen–lithium exchange proceeds quantitatively in THF at −50 °C. It was found that mono aryllithiums formed in the reaction can remove the reactive hydrogen atom from a molecule of aryl benzyl ether thus decreasing the yield of dilithiated species. This effect does not occur when *t*-BuLi is used instead of *n*-BuLi.

The formation of dilithiated organometallic compounds is interesting for two reasons: they can be used as starting materials for the synthesis of more advanced organic compounds and studying their formation can reveal knowledge about the mechanism of lithiation. In this Letter, we present the results of our studies on lithiation of aryl benzyl ethers (ABEs) containing –F, –Br and –I substituents. The successful dilithiation of ABEs opens the way to the synthesis of diboronic acids, a group of compounds which have found many applications in organic synthesis and in analytical chemistry.[1–3] Lithiation of organic compounds can occur via deprotonation (*ortho* lithiation) or via a halogen–lithium exchange (HLE) mechanism. It is generally accepted that fluorine atoms accelerate *ortho* lithiation and Br or I atoms undergo HLE easily. Ziegler showed that amongst butyl halides only iodine and bromine derivatives underwent rapid halogen–lithium exchange with *n*-butyllithium in diethyl ether.[4] The presence of an activating group is essential for both *ortho* lithiation and HLE. The activating group increases the acidity of the *ortho* hydrogen as in fluorobenzenes, forming entropy saving complexes like in anisoles or stabilizing the newly formed organolithium compound (e.g., 2,5-dibromonitrobenzene) which undergoes HLE to give the more stable 2-lithio species.[5] It was found recently that fluorine activates bromine more strongly than a methoxy group, however, nonactivated iodine undergoes HLE easier than an activated bromine atom.[6] Our previous work on metallation of fluorinated ABEs possessing reactive hydrogen atoms at different positions confirmed that the acidity of the hydrogen was the most important factor directing the regioselectivity rather than –O–Li–Bu complex formation.[7] The presence of other factors such as temperature and solvent is also crucial for selective lithiation.[8] The ABEs used for this study can be lithiated in more than one position and depending on the structure, the reaction can occur via HLE or a deprotonation mechanism, but in some cases both the mechanisms occur simultaneously. Our work demonstrates that a small change in the structure of the ABE requires completely different conditions to obtain dilithiated species selectively. The resultant lithiated ABEs were converted into the corresponding benzaldehydes or diboronic acids.

Regioselective bromine–lithium exchange in 2-bromoanisole as well as in 2-bromotoluene is well known.[9,10] It was interesting to determine the regioselectivity of the HLE in **1** as this compound contains both 2-bromoanisole and 2-bromotoluene moieties. These two bromine atoms should demonstrate different reactivities as only one of them is activated by an oxygen atom. ABE **1** was subjected to the HLE reactions (Table 1, entries 1 and 2). We found that in diethyl ether solvent

Keywords: Lithiation; Aryl–benzyl ethers; Butyllithium; Diboronic acid.
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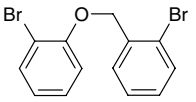
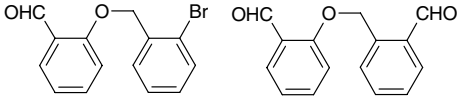
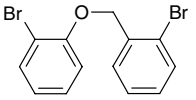
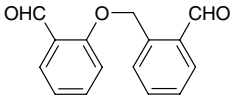
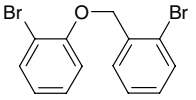
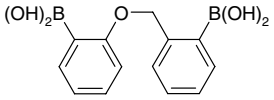
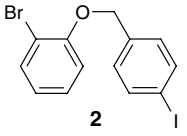
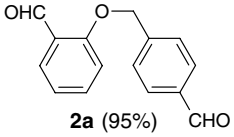
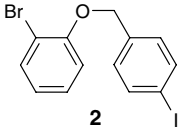
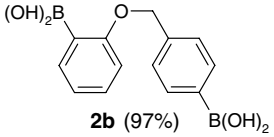
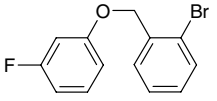
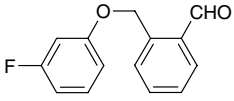
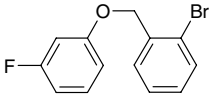
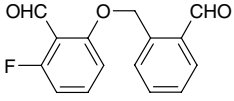
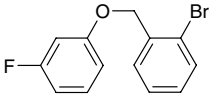
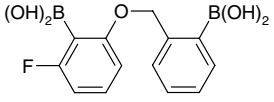
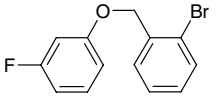
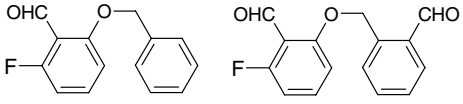
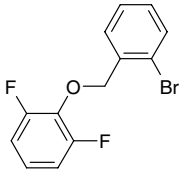
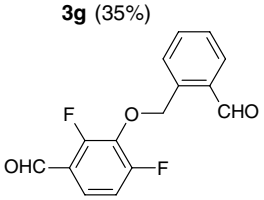
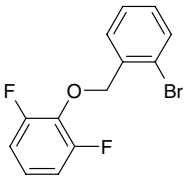
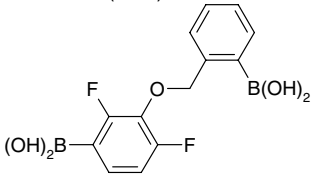
Table 1. Preparation of functionalized ABEs via halogen–lithium exchange or deprotonation and subsequent DMF or $B(OEt)_3$ quench

Entry	ABE	RLi	Solvent, temperature (°C)	Products
1	 **1**	*n*-BuLi	Et_2O, −60	 **1a** (87%) **1b** (13%)
2	 **1**	2*n*-BuLi	THF, −40	 **1b** (98%)
3	 **1**	2*n*-BuLi	THF, −40	 **1c** (96%)
4	 **2**	2*n*-BuLi	Et_2O, −60	 **2a** (95%)
5	 **2**	2*n*-BuLi	Et_2O, −60	 **2b** (97%)
6	 **3**	*n*-BuLi	Et_2O, −40	 **3h** (95%)
7	 **3**	3*t*-BuLi	THF, −50	 **3f** (96%)
8	 **3**	3*t*-BuLi	THF, −50	 **3i** (95%)
9	 **3**	2*n*-BuLi	THF, −50	 **3g** (35%) **3f** (45%)
10	 **4**	2*n*-BuLi	THF, −50	 **4a** (92%)
11	 **4**	2*n*-BuLi	THF, −50	 **4b** (71%)

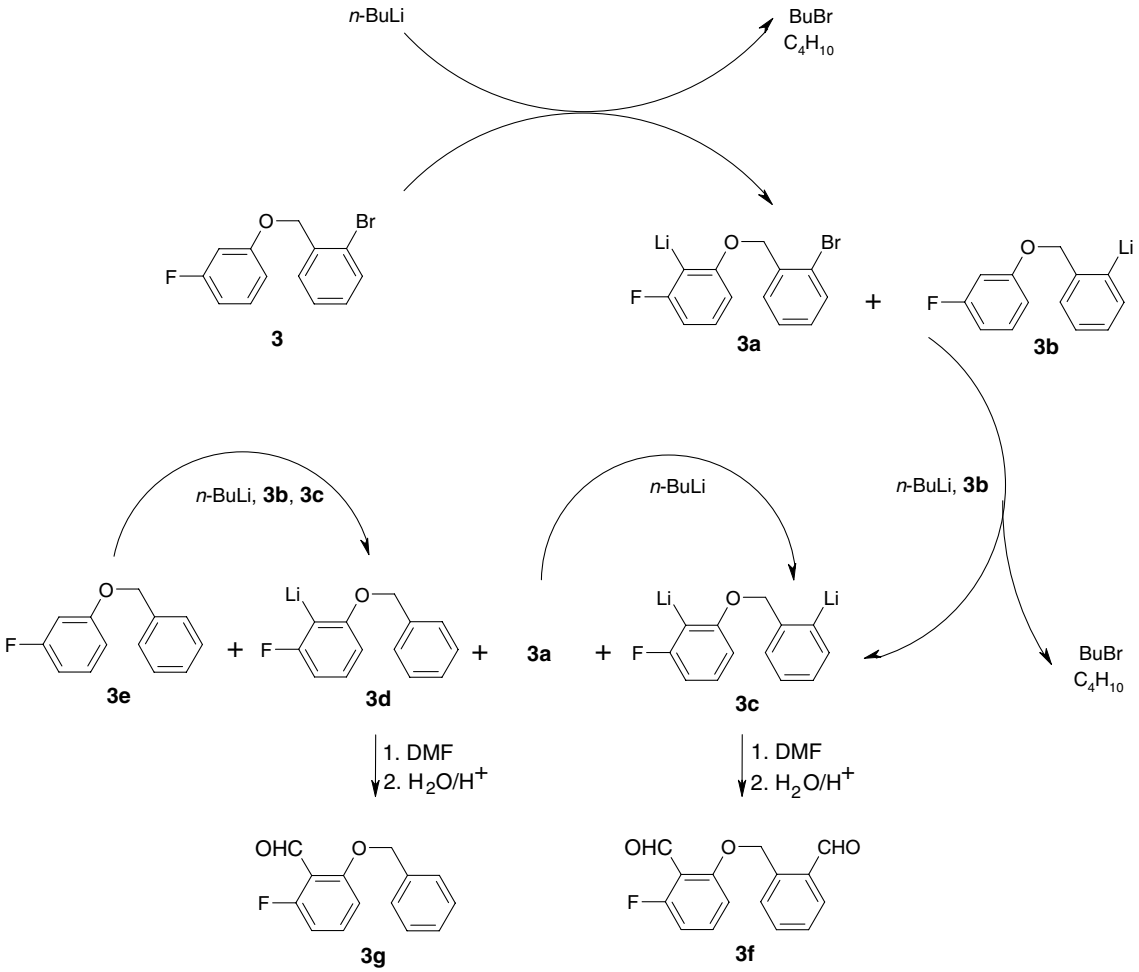
both bromines compete for *n*-BuLi but mainly the bromine *ortho* to the oxygen atom (87%) is replaced with lithium to give the corresponding aldehyde after DMF quench. However, the nonactivated bromine atom *ortho* to the methylene group also undergoes HLE providing the dilithiated species which gives the respective dialdehyde (13%) after DMF quench. Similar results were obtained with 2 mol of *n*-BuLi. Attempted application of THF as solvent and increasing the temperature to −40 °C activated the bromine atom on the benzylic aromatic of **1** and the reaction with 2 mol equiv of *n*-BuLi gave the dialdehyde exclusively after DMF quench. The use of $B(OEt)_3$ as an electrophile resulted in the respective diboronic acid in excellent yield (entry 3). We also investigated the HLE of **2** using 2 equiv of *n*-BuLi, and in this case, quantitative replacement of the bromine and iodine atoms was observed in diethyl ether at −60 °C and the respective dialdehyde or diboronic acid was isolated following DMF or $B(OEt)_3$ quench (Table 1, entries 4 and 5). At this point, we can state that the selective dilithiation of **1** and **2** via HLE is feasible and depends on the correct choice of solvent and temperature.

We were next interested in comparing the relative directing potential of fluorine and oxygen with respect to the nonactivated bromine atom. We employed ABE **3**, where one of the hydrogen atoms is flanked by fluorine and oxygen atoms and can be removed by deprotonation while the bromine atom can undergo HLE.[11,12] The reaction of **3** with *n*-BuLi in diethyl ether at −40 °C followed by DMF quench afforded the respective monoaldehyde (entry 6). This result shows that in diethyl ether only the HLE occurs at a reasonable rate. Surprisingly, treatment of **3** with 2 equiv of *n*-BuLi in THF at −50 °C followed by DMF quench did not give the pure dialdehyde, instead a mixture of two products was formed (entry 9) as confirmed by analysis of the ^1H NMR spectrum where two methylene singlets at 5.13 and 5.24 ppm were observed. The mass spectrum showed the presence of two molecular ions: $m/z = 230$ and $m/z = 258$ which correspond to structures **3f** and **3g**. However, application of *t*-BuLi (1:3) as base at −50 °C yielded **3f** quantitatively (entry 7) and the use of $B(OEt)_3$ as an electrophile gave the respective diboronic acid (entry 8). The lithiation of **4** can also occur via HLE or deprotonation because of the presence of the strongly activating fluorine atoms and the bromine. Contrary to lithiation of **3**, treatment of **4** with 2 equiv of *n*-BuLi followed by DMF quench occurred cleanly to give **4a** in satisfactory yield (entry 10). The difference between the reactivity of **3** and **4** with *n*-butyllithium is caused most probably by the presence of the reactive hydrogen atom flanked by fluorine and oxygen atoms in **3**. According to our hypothesis, this atom shows such high reactivity that it can be removed not only by *n*-butyllithium but also by the intermediates **3b** or **3c** containing C–Li bonds. As a result, the reactions provide a mixture of **3f** and **3g** (Scheme 1). The reaction of **3** with *t*-BuLi proceeds cleanly as *t*-BuLi is a stronger base than **3b** and removes the reactive hydrogen atom more rapidly. The reaction of **4** with *n*-BuLi occurs cleanly because the hydrogen atoms *ortho* to the fluorine are not reactive enough to be removed by intermediates analogous to **3b**. The successful dilithiation of **4** enabled the synthesis of the respective diboronic acid **4b** using $B(OEt)_3$ as an electrophile (entry 11). It should be noted that the temperature for lithiation of **3** and **4** should not be higher than −50 °C because of the potential decomposition of the lithiated species via an aryne.[13]

In conclusion, the dilithiation of ABEs is efficient provided that precautions are observed concerning the choice of solvent, alkyllithium reagent and temperature. ABEs containing a nonactivated bromine atom can be dilithiated selectively via bromine–lithium exchange in THF at −40 °C. On the other hand, replacement of the nonactivated bromine with iodine enables HLE in diethyl ether at −60 °C. ABEs which can be lithiated simultaneously by deprotonation and HLE, require the use of THF to obtain the dilithiated compound and the temperature must not be higher than −50 °C to avoid aryne formation. In ABEs containing very reactive hydrogen atoms, *t*-BuLi should be used as the lithiating reagent to avoid deprotonation by the newly formed aryllithiums. The dilithiated ABEs obtained can be easily converted into diboronic acids using $B(OEt)_3$. Obviously, the synthetic potential of all the described lithiation experiments is not limited to the examples presented in this Letter and appears to be an interesting synthetic tool for the synthesis of other diboronic acids.

A typical procedure for dilithiation of ABEs and reaction with $B(OEt)_3$: To a cooled (−68 °C) solution of *n*-butyllithium (0.05 mol) in 100 mL of THF, **1** (0.025 mol) dissolved in 20 mL of THF was added dropwise with stirring while maintaining the temperature below −60 °C. The reaction mixture was slowly warmed to −40 °C and maintained at this temperature for 20 min. The resultant solution was cooled to −68 °C and then $B(OEt)_3$ (0.05 mol) was added maintaining the temperature below −60 °C. Following addition, the reaction mixture was allowed to warm to −40 °C and water (100 mL) and 3 M sulfuric acid (20 mL) were added to make the mixture slightly acidic. The organic phase was separated and the aqueous phase was extracted with ether (30 mL). Drying followed by evaporation of the combined organic solutions left a solid which was washed with water and hexane to give **1c** as colourless powder, mp 151–152 °C. ^1H NMR (400 MHz, acetone-d_6) δ 7.78 (m, 3H), 7.49 (m, 2H), 7.39 (m, 2H), 7.31 (m, 2H), 7.11 (m, 2H), 6.95 (m, 1H), 5.45 (s, 2H). ^{13}C NMR (100 MHz, acetone-d_6) δ 164.87, 142.03, 137.27, 135.52, 132.99, 130.54, 129.15, 128.06, 121.45, 112.41, 71.05. ^{11}B NMR (200 MHz) δ 29.5. Analysis: Anal. Calcd for $C_{13}H_{14}B_2O_5$: C, 57.43; H, 5.17. Found: C, 57.59, H, 5.24.

Compound **1b**: mp 117–119 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 10.62 (s, 1H), 10.17 (s, 1H), 7.86 (m, 3H), 7.69 (m, 1H), 7.56 (m, 2H), 7.10 (m, 2H), 5.66 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.43, 189.51, 160.58, 138.43, 136.04, 134.93, 132.69, 128.92, 128.07, 127.07, 125.03, 121.13, 113.05, 67.98. Analysis: Anal. Calcd



Scheme 1. The sequence of lithiations providing the mixture of **3f** and **3g**.

for $C_{15}H_{12}O_3$: C, 75.01; H, 5.00. Found: C, 74.66; H, 5.01.

Compound **2a**: mp 126–128 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.67 (s, 1H), 10.02 (s, 1H), 7.92 (m, 2H), 7.86 (m, 1H), 7.62 (m, 2H), 7.54 (m, 1H), 7.07 (m, 1H), 7.02 (m, 1H), 5.28 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.65, 189.29, 160.36, 142.78, 136.04, 135.89, 130.02, 128.73, 127.27, 125.02, 121.29, 112.73, 69.48. Analysis: Anal. Calcd for $C_{15}H_{12}O_3$: C, 75.01; H, 5.00. Found: C, 74.92; H, 4.98.

Compound **2b**: mp 150–152 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 7.91 (m, 2H), 7.82 (m, 1H), 7.49 (m, 2H), 7.40 (m, 1H), 7.11 (m, 1H), 6.98 (m, 1H), 5.24 (s, 2H), 3.06 (d, 4H). ^{13}C NMR (100 MHz, acetone-d_6) δ 164.65, 139.61, 137.39, 135.36, 133.13, 127.73, 121.76, 112.42, 70.94. ^{11}B NMR (200 MHz) δ 29.1. Analysis: Anal. Calcd for $C_{13}H_{14}B_2O_5$: C, 57.43; H, 5.17. Found: C, 57.46; H, 5.20.

Compound **3f**: mp 161–163 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.57 (s, 1H), 10.14 (s, 1H), 8.03 (m, 1H), 7.90 (m, 1H), 7.73 (m, 1H), 7.58 (m, 1H), 7.52 (m, 1H), 6.95 (m, 1H), 6.79 (m, 1H), 5.64 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.65, 186.83, 163.99 (d, $J = 260$ Hz), 160.50, 138.02, 136.25, 135.16, 134.46, 132.44, 128.04, 127.11, 114.28, 108.86, 108.66, 68.72. Analysis: Anal. Calcd for $C_{15}H_{11}FO_3$: C, 69.78; H, 4.26. Found: C, 69.51; H, 4.30.

Compound **3h**: mp 42–44 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (s, 1H), 7.90 (s, 1H), 7.78 (m, 1H), 7.65 (m, 1H), 7.55 (m, 1H), 7.25 (m, 1H), 6.80 (m, 1H), 6.70 (m, 2H), 5.52 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.20, 163.61 (d, $J = 243$ Hz), 159.72, 138.91, 134.22, 134.09, 132.92, 130.29, 127.99, 127.47, 110.53, 107.96, 102.69, 67.95. Analysis: Anal. Calcd for $C_{14}H_{11}FO_2$: C, 73.06; H, 4.78. Found: C, 72.45; H, 4.91.

Compound **3i**: mp 142–144 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 7.73 (m, 1H), 7.55 (m, 1H), 7.38 (m, 1H), 7.29 (m, 2H), 6.85 (d, 1H), 6.65 (t, $J = 8.4$ Hz, 1H), 5.35 (s, 2H), 3.09 (s, 2H), 3.07 (s, 2H). ^{13}C NMR (100 MHz, acetone-d_6) δ 166.83 (d, $J = 240$ Hz), 163.87, 142.03, 135.22, 132.37, 130.45, 128.60, 127.77, 108.49, 108.34, 71.52. ^{11}B NMR (200 MHz) δ 29.3. Analysis: Anal. Calcd for $C_{13}H_{13}FB_2O_5$: C, 53.89; H, 4.49. Found: C, 53.96, H, 4.59.

Compound **4a**: mp 106–108 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.26 (s, 1H), 10.22 (s, 1H), 7.90 (m, 2H), 7.69 (m, 1H), 7.59 (m, 2H), 7.04 (m, 1H), 5.67 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.88, 185.69, 163.61 (d, $J = 243$ Hz), 159.72, 138.27, 134.12, 133.78, 133.08, 128.50, 128.05, 123.10, 121.79, 113.02, 73.69. Analysis: Anal. Calcd for $C_{15}H_{10}F_2O_3$: C, 65.23; H, 3.62. Found: C, 65.16; H, 3.72.

Compound **4b**: mp 142–143 °C. ^{1}H NMR (400 MHz, acetone-d_6) δ 7.74 (m, 1H), 7.51 (m, 1H), 7.38 (m, 2H), 7.28 (m, 1H), 6.97 (m, $J = 9.4$ Hz, 1H), 5.42 (s, 2H), 3.19 (s, 4H). ^{13}C NMR (100 MHz, acetone-d_6) δ 160.95 (m, $J = 250$ Hz), 158.34 (m, $J = 248$ Hz), 142.03, 135.34, 130.47, 130.31, 129.40, 129.00, 123.30, 112.61, 77.01. ^{11}B NMR (200 MHz) δ 29.0. Analysis: Anal. Calcd for $C_{13}H_{12}F_2B_2O_5$: C, 50.73; H, 3.90. Found: C, 50.93; H, 3.94.

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