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Halogen–lithium exchange versus deprotonation: regioselective mono- and dilithiation of aryl benzyl sulfides. A simple approach to α,2-dilithiotoluene equivalents

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ABSTRACT

Halogen–lithium exchange and deprotonation reactions between aryl benzyl sulfides and alkyllithiums were investigated. The resultant mono- and dilithiated intermediates were converted into the corresponding aldehydes and boronic, or carboxylic acids in good yields. It was found that diethyl ether stabilizes the *ortho*-lithiated compounds toward isomerisation to the benzylic derivatives. The process occurs easily in THF at low temperature and is a facile route to the α,2-dilithiotoluene derivative which can be transformed into a dicarboxylic acid on treatment with CO_2.

Directed metalation of substituted arenes has been studied over many years and has become a powerful method for the functionalization of aromatic systems. However, many reports on the lithiation of sulfides are concerned only with the deprotonation mechanism. We report an investigation in which the competition between two mechanisms (halogen–lithium exchange and deprotonation) has been studied for the first time.[1] Compared with our previous studies on lithiation of aryl benzyl ethers where the benzylic position was rather unreactive, here it becomes the important factor influencing the reaction selectivity.[2] Sulfur is an element known to promote both α and *ortho* lithiation. In α lithiation the effect is generally considered to be a result of sulfur polarizability and of hyperconjugation with the anitperiplanar S–C σ^* orbital.[3] This fact has led to interesting applications in the synthesis of various benzo- and naphthothiophenes via intramolecular ring closure of α-lithiated sulfides.[4] However, the stability of α-lithiated species can be a problem in the synthesis of *ortho*-lithiated sulfides because they can isomerize to the more stable α-lithiated derivatives.[5] The *ortho*-directing power of sulfur is relatively weak. Whereas thiophene can be lithiated to give 2-lithiothiophene, diaryl sulfides undergo lithiation less efficiently than diaryl ethers.[6] Molecules containing both sulfur and oxygen atoms are lithiated *ortho* to oxygen.[1d] The present Letter is concerned with the lithiation of aryl benzyl sulfides (ABSs) containing halogen substituents. Lithiation of these compounds can proceed either via halogen–lithium exchange (HLE) or a deprotonation mechanism. We have demonstrated that a careful choice of the reagents and reaction conditions is required to obtain the desired product selectively. The new functionalized organolithium compounds can react with various electrophilic compounds such as CH_3I, DMF, $B(OEt)_3$, $B(OMe)_3$, and CO_2 to give, after hydrolysis, the functionalized ABSs.

We were interested in comparing the selectivity of the lithiation of substrates **1–3** with respect to the solvent (Table 1). The reaction of **1** or **2** with *n*-BuLi proceeds cleanly in THF as well as in diethyl ether to give the monolithiated species which were next reacted with $B(OMe)_3$ to give the respective arylboronic acids **1a** and **2a** after hydrolysis (entries 1 and 2). However, lithiation of **3** with *n*-BuLi in THF gave exclusively **3a** (entry 3) as a result of the rearrangement of *ortho*-lithiated **3** to the more stable benzylic derivative which reacts with butyl bromide. In a competition experiment where **3** was treated with 3 equiv of *t*-BuLi we isolated **3b** exclusively (entry 4) after a CH_3I quench of the formed organolithium compound. These results revealed that isomerisation of *ortho*-lithiated **3** to the benzylic derivative is preferred over deprotonation with *t*-BuLi. The use of diethyl ether as a solvent stabilizes *ortho*-lithiated **3** at −78 °C, however, it rearranges to the benzylic derivative on heating to −20 °C. The reaction with $B(OMe)_3$ at −78 °C and its subsequent hydrolysis gave the respective boronic acid **3c** (entry 5). The molecular structure of **3c** was determined using X-ray analysis (Fig. 1). Koh has patented the *ortho* lithiation of 2-bromophenyl 2,4,6-trimethoxyphenylbenzyl sulfide which proceeds in moderate yield (46%) at −78 °C using THF as the solvent.[7] This result shows that the stability of the *ortho*-lithiated ABSs to-

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Table 1
Preparation of functionalized ABSs via halogen–lithium exchange or deprotonation and subsequent treatment with various electrophiles

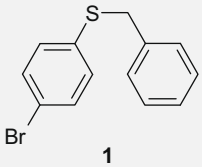
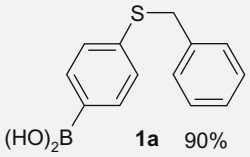
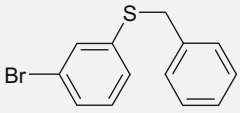
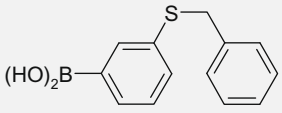
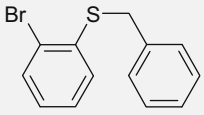
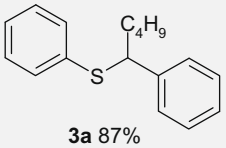
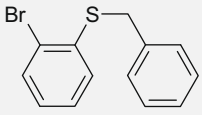
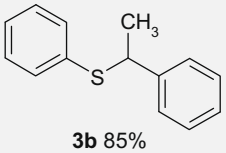
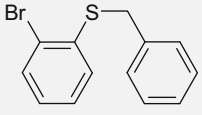
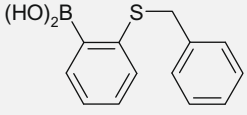
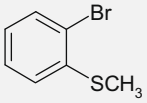
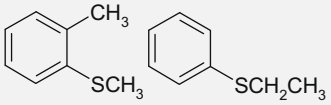
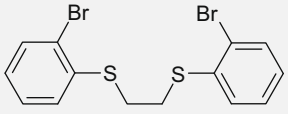
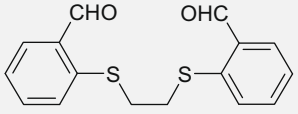
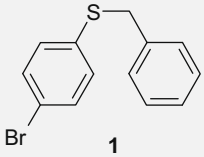
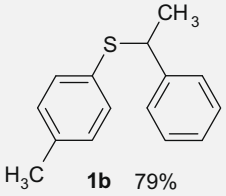
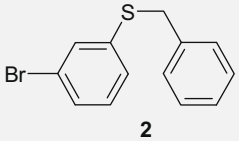
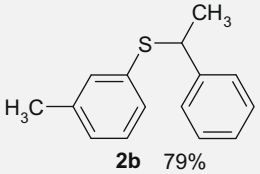
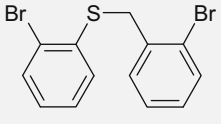
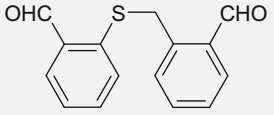
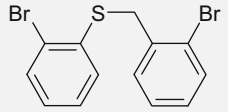
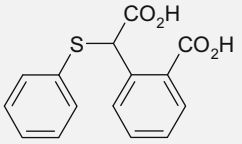
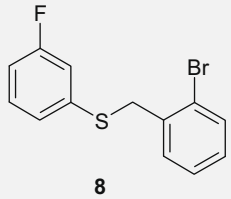
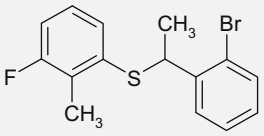
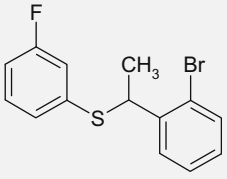
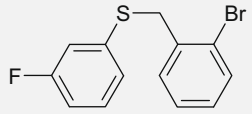
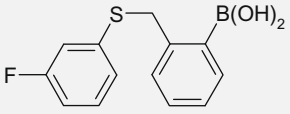
Entry	Starting material	RLi, solvent, temperature, electrophile	Product
1	 **1**	1. *n*-BuLi, THF, −78 °C 2. $B(OEt)_3$ 3. H_2O, HCl	 **1a** 90%
2	 **2**	1. *n*-BuLi, THF, −78 °C 2. $B(OEt)_3$ 3. H_2O, HCl	 **2a** 94%
3	 **3**	1. *n*-BuLi, THF, −78 °C	 **3a** 87%
4	 **3**	1. 3 *t*-BuLi, THF, −78 °C 2. CH_3I	 **3b** 85%
5	 **3**	1. *n*-BuLi, Et_2O, −78 °C 2. $B(OMe)_3$ 3. H_2O, HCl	 **3c** 88%
6	 **4**	1. 2 *t*-BuLi, THF, −78 °C 2. CH_3I	 **4a** 96% [a] **4b** 4% [a]
7	 **5**	1. 2 *n*-BuLi, THF, −78 °C 2.DMF 3.H_2O, HCl	 **5a** 85%
8	 **1**	1. 3 *t*-BuLi, THF, −78 °C 2. CH_3I 3. H_2O	 **1b** 79%
9	 **2**	1. 3 *t*-BuLi, THF, −78 °C 2. CH_3I 3. H_2O	 **2b** 79%
10	 **6**	1. 4 *t*-BuLi, Et_2O, −78 °C 2. DMF 3. H_2O, HCl	 **6a** 81%

Table 1 (*continued*)

Entry	Starting material	RLi, solvent, temperature, electrophile	Product
11	 **6**	1. 4 *t*-BuLi, THF, −78 °C 2. CO_2 3. H_2O,HCl	 **6f** 82%
12	 **8**	1. 2 LTMP, THF, −78 °C 2. CH_3I	 **8a** 15% [a]  **8b** 85% [a]
13	 **8**	1. 2 *t*-BuLi, THF, −78 °C 2. $B(OEt)_3$ 3. H_2O, HCl	 **8c** 79%

[a] Yields calculated from the ^1H NMR spectra.

ward isomerisation also depends on the stability of the benzylic carbanion which can be moderated by the substituents on the phenyl ring. A detailed study on this effect is in progress and will be published elsewhere.

It was interesting to compare the reactivity of the α-hydrogen atoms in ABSs with anisole. In the lithiation of 2-bromothioanisole **4** with 2 equiv of *t*-BuLi in THF at −78 °C we found that the rearrangement of the *ortho*-lithioanisole to the α-lithio derivative was very slow. After quenching with CH_3I we obtained **4a** (96%) and **4b** (4%) (entry 6). The stability of *ortho*-lithiated anisole enabled dilithiation of **5** using *n*-BuLi in THF. The reaction afforded **5a** after treatment of the formed organolithium compound with DMF (entry 7). The above results suggest that rearrangement of *ortho*-lithiated ABSs to the benzylic derivatives is kinetically driven.

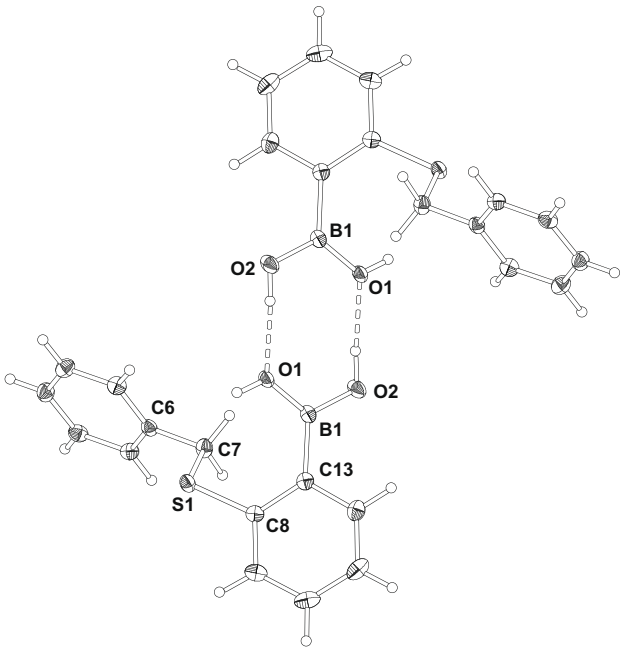
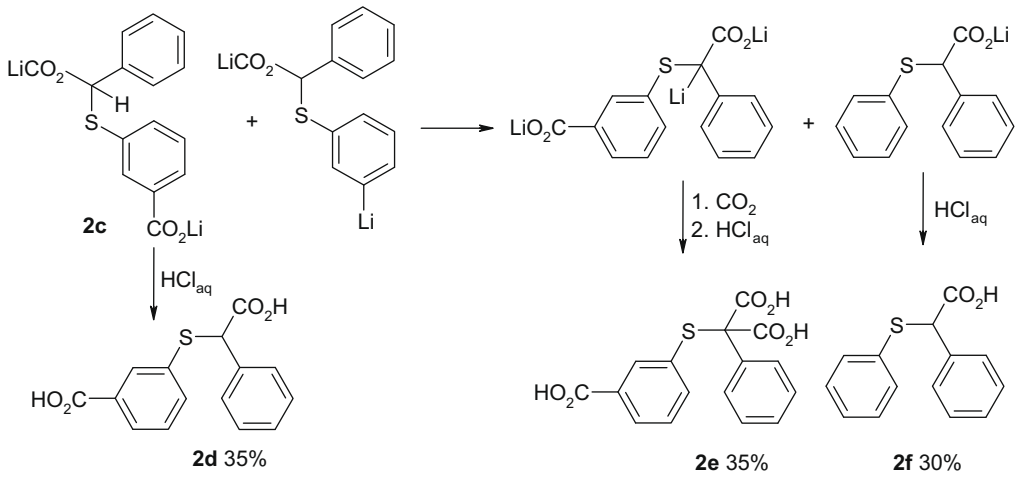


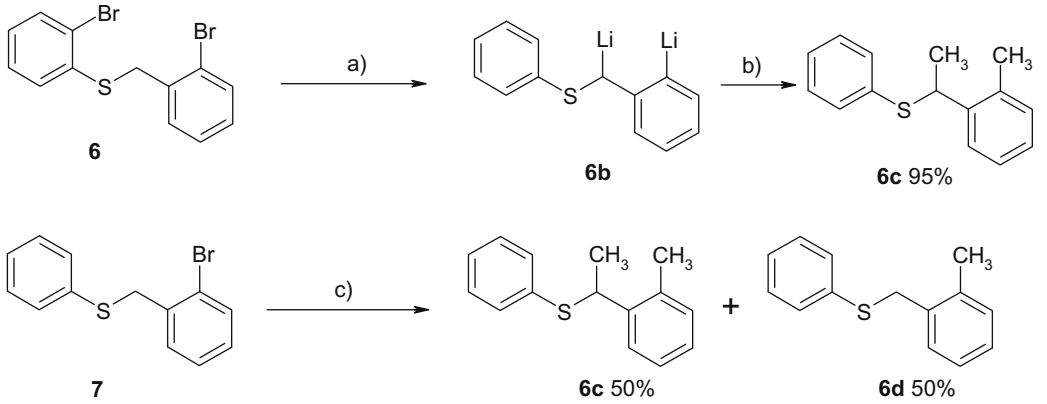
Figure 1. ORTEP drawing of **3c** (dimer) with thermal ellipsoid plot (50% probability). Selected bond lengths (Å) and angles (°): B1–O1 1.370(2), B1–C13 1.575(2), O1–H2–O2 171.28(2), O1–B1–C13–C8 30.95(2). Crystallographic data for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 746938.

Dilithiated compounds are valuable reagents which have found many applications in the synthesis of complex molecules.[8] The presence of two types of reactive centers in ABSs opens the possibility to synthesize the respective dilithiated derivatives. Compounds **1** and **2** can be lithiated according to the HLE and deprotonation mechanism. The use of *n*-BuLi is not a good method to form dilithiated derivatives because butyl bromide formed in the process reacts at the benzylic carbon atom at −78 °C. However, **1** and **2** can be dilithiated selectively using *t*-BuLi in THF. The obtained dilithiated derivatives are stable in THF at low temperature. They were kept at −78 °C for two hours and then reacted with CH_3I to give **1b** and **2b**, respectively (entries 8 and 9). However, the use of CO_2 as the electrophile resulted in significant amounts of **2e** and **2f** apart from the expected bis-carboxylic acid **2d** (Scheme 1).[9] An explanation relies on the activation of the benzylic hydrogen in **2c** toward deprotonation as a result of CO_2 adduct formation.

In continuation of our studies we tried to replace selectively two bromine atoms with lithium in compound **6**. The lithiation was carried out using 2 equiv of *n*-BuLi in diethyl ether at −60 °C. However, this temperature was too low to exchange the bromine atom in the benzylic part of the molecule and a complicated mixture of products formed after treatment of the organolithium derivatives with DMF. The use of *t*-BuLi as the base enabled selective formation of the respective aldehyde **6a** (entry 10). We have already revealed that THF destabilizes *ortho*-lithiated **3**. Hence, the dilithiation of **6** in THF afforded **6b** (Scheme 2) which was quenched with CH_3I to give **6c**. This reaction proceeds smoothly and can be used as a general route to synthesize α,2-dilithiotoluene derivatives. Contrary to this result, di-lithiation of **7** with *t*-BuLi proceeds sluggishly and gives a 1:1 mixture of **6c** and **6d**. These results suggest that intramolecular benzylic lithiation is preferred over the intermolecular process. Compared with the reaction with **1** and **2**, quenching of the dilithiated **6** with



Scheme 1. The possible lithiation sequence providing the mixture of **2d**, **2e,** and **2f**.



Scheme 2. Reagents and conditions: (a) 4 *t*-BuLi, THF, −78 °C; (b) CH_3I; (c) 3 *t*-BuLi, THF, −78 °C then CH_3I.

CO_2 afforded diacid **6f** (entry 11) in high yield and we observed only small amounts (less than 5 mol %) of side products. This result suggests that the benzylic hydrogen atom gains some protection from the *ortho*-carboxylithium group.

It was interesting to study the lithiation ability of a hydrogen atom flanked by sulfur and fluorine atoms and to compare it with the reactivity of the benzylic hydrogen atom. For this purpose, compound **8** was reacted with 2 equiv of lithium 2,2,6,6-tetramethylpiperidine (LTMP) in THF and the organolithium compound obtained was quenched with CH_3I. Analysis of the reaction mixture revealed that the conversion into the corresponding dilithiated compound was not quantitative, as apart from **8a**, a substantial amount of **8b** was detected (entry 12). However, the lithiation of **8** with *n*-BuLi in THF proceeded selectively according to the HLE mechanism to give **8c** after reaction with $B(OEt)_3$ (entry 13).

In conclusion, the lithiation of ABSs occurs easily both on the aromatic ring and at the benzylic position, hence the reaction requires careful choice of the organolithium reagent, solvent, and temperature to introduce the lithium atom selectively. The obtained organolithium reagents are stable at low temperature, however, when the lithium atom is *ortho* to sulfur, isomerisation to a benzylic derivative can take place. This process occurs easily in THF at −78 °C, but it can be avoided using diethyl ether as the solvent. On the other hand, the isomerisation gives access to the respective α,2-dilithiotoluene derivatives. The synthetic potential of these compounds was demonstrated in the reaction with CO_2 leading to the respective dicarboxylic acid.

Typical procedure for lithiation of ABSs: In a typical lithiation, *t*-BuLi (1.7 M solution in pentane, 24 mL, 40 mmol) was added at −78 °C to a solution of 2-bromobenzyl-2-bromophenyl sulfide (3.58 g, 10 mmol) in Et_2O (40 mL). The resultant slurry was stirred for 2.5 h followed by slow addition of DMF (1.46 g, 20 mmol). The mixture was stirred overnight and then hydrolyzed with dilute aq H_2SO_4. The organic phase was separated and the aq phase was extracted with Et_2O (20 mL). Evaporation of the combined organic solutions left a solid which was washed with H_2O and recrystallized from hexane (20 mL) to give **6a** as yellow crystals, mp 98–99 °C. Yield: 2.07 g, 81%; ^1H NMR (400 MHz, $CDCl_3$): δ 10.17 (1H, s, C*H*O), 10.14 (1H, s, C*H*O), 7.80 (2H, m, Ph), 7.46 (4H, m, Ph), 7.34 (1H, m, Ph), 7.20 (1H, m, Ph), 4.55 (2H, s, CH_2); $^{13}C\{^1H\}$ NMR (100.6 MHz, $CDCl_3$): δ 192.23, 191.42, 140.10, 138.10, 135.11, 134.00, 133.94, 133.62, 133.50, 131.24, 131.20, 131.13, 128.15, 126.72, 35.93. Anal. Calcd for $C_{15}H_{12}SO_2$: C, 70.29; H, 4.72. Found: C, 70.34; H, 4.75.

Compound **1a**: mp 148–149 °C. Yield: 2.20 g, 90%; ^1H NMR (400 MHz, acetone-d_6): δ 7.76 (2H, d, *J*= 8.0 Hz, Ph), 7.39 (2H, d, *J* = 8.0 Hz, Ph), 7.29 (4H, m, Ph), 7.22 (1H, m, Ph), 7.17 (2H, s, –OH), 4.24 (2H, s, CH_2); $^{13}C\{^1H\}$ NMR (100.6 MHz, acetone-d_6): δ 140.38, 138.43, 135.44, 129.69, 129.21, 127.89, 127.79, 37.63. Anal. Calcd for $C_{13}H_{13}BSO_2$: C, 63.96; H, 5.37. Found: C, 63.98; H, 5.40.

Compound **2a**: mp 137–138 °C. Yield: 2.29 g, 94%; ^1H NMR (400 MHz, acetone-d_6): δ 7.85 (1H, br s, Ph), 7.65 (1H, m, Ph), 7.36–7.17 (7H, m, Ph), 4.18 (2H, s, CH_2), 3.50 (2H, s, –OH); $^{13}C\{^1H\}$ NMR (100.6 MHz, acetone-d_6): δ 138.63, 136.37, 135.71,

132.73, 131.76, 129.61, 129.10, 128.85, 127.77, 38.66. Anal. Calcd for $C_{13}H_{13}BSO_2$: C, 63.96; H, 5.37. Found: C, 63.99; H, 5.43.

Compound **3c**: mp 115–117 °C. Yield: 2.14 g, 88%; ^{1}H NMR (400 MHz, acetone-d_6): δ 7.71 (1H, m, Ph), 7.37 (1H, m, Ph), 7.31–7.17 (7H, m, Ph), 4.13 (2H, s, CH_2), 3.42 (2H, s, –OH); ^{13}C{^{1}H} NMR (100.6 MHz, acetone-d_6): δ 140.08, 138.36, 135.75, 133.24, 130.87, 129.67, 129.10, 127.85, 127.47, 41.32. Anal. Calcd for $C_{13}H_{13}BSO_2$: C, 63.96; H, 5.37. Found: C, 63.97; H, 5.38.

Compound **5a**: mp 135–136 °C. Yield: 2.55 g, 85%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.37 (2H, s, C*H*O), 7.87 (2H, m, Ph), 7.51 (2H, m, Ph), 7.36 (4H, m, Ph), 3.19 (4H, s, CH_2); ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$): δ 191.43, 139.75, 134.47, 134.13, 132.40, 128.67, 126.21, 32.10. Anal. Calcd for $C_{16}H_{14}S_2O_2$: C, 63.55; H, 4.67. Found: C, 63.90; H, 4.71.

Compound **6f**: mp 148–149 °C. Yield: 2.36 g, 82%; ^{1}H NMR (400 MHz, acetone-d_6): δ 8.00 (1H, m, Ph), 7.77 (1H, m, Ph), 7.59 (1H, m, Ph), 7.40 (3H, m, Ph), 7.32–7.23 (3H, m, Ph), 6.52 (1H, s, CH); ^{13}C{^{1}H} NMR (100.6 MHz, acetone-d_6): δ 171.46, 168.64, 139.04, 135.58, 133.17, 132.18, 131.69, 130.82, 130.20, 129.74, 128.69, 128.18, 51.91. Anal. Calcd for $C_{15}H_{12}SO_4$: C, 62.49; H, 4.20. Found: C, 62.55; H, 4.23.

Compound **8c**: mp 135–136 °C. Yield: 2.07 g, 79%; ^{1}H NMR (400 MHz, acetone-d_6): δ 7.66 (1H, m, Ph), 7.30–7.23 (3H, m, Ph), 7.18 (1H, m, Ph), 7.13 (1H, m, Ph), 7.08 (1H, m, Ph), 6.89 (1H, s, Ph), 4.55 (2H, s, CH_2), 3.17 (s, 2H, OH) ; ^{13}C{^{1}H} NMR (100.6 MHz, acetone-d_6): δ 163.53 (d, J = 244 Hz), 142.55, 141.02 (d, J = 8.3 Hz), 135.44, 131.15 (d, J = 9.1 Hz), 130.12 (d, J = 6.9 Hz), 127.12, 125.00, 124.98, 115.50 (d, J = 13.8 Hz), 113.07 (d, J = 21.2 Hz), 38.09. Anal. Calcd for $C_{13}H_{12}BFSO_2$: C, 59.57; H, 4.61. Found: C, 59.64; H, 4.65.

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9. Formation of compounds **2d**–**f** was confirmed by GC/MS analysis after silylation with bis(trimethylsilyl)acetamide.