Synthetic Methods

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Catalytic Borylation of SCF_3-Functionalized Arenes by Rhodium(I) Boryl Complexes: Regioselective C–H Activation at the *ortho*-Position**

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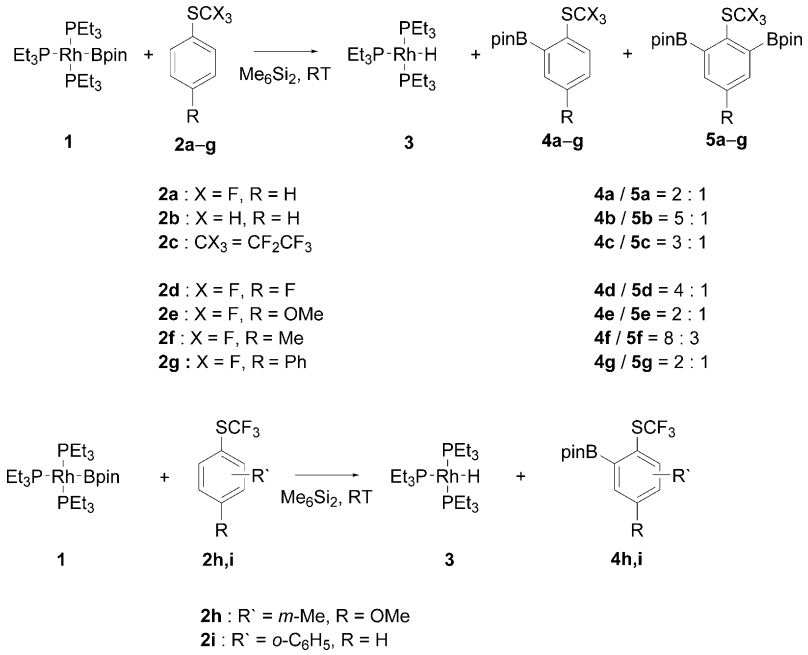
Dedicated to Professor Helmut Werner on the occasion of his 80th birthday

Abstract: *An unprecedented reaction pathway for the borylation of SCF_3-containing arenes using [Rh(Bpin)(PEt_3)$_3$] (pin = pinacolato) is reported. Catalytic processes were developed and the functionalizations proceed under mild reaction conditions. The C–H activations occur with a unique regioselectivity for the position ortho to the SCF_3 group, which apparently serves as directing group. Borylated SCF_3 compounds can serve as versatile building blocks.*

The trifluoromethylthio group is of considerable interest, because to some extent SCF_3 compounds are often characterized by a high lipophilicity, which can in turn enhance the ability of SCF_3 derivatives to cross lipid membranes and thus their biodisponibility.[1] Moreover, the high electronegativity of a SCF_3 group ensures their stability in acidic environments.[2] Thus, the use of the SCF_3-containing compounds as building blocks can lead to unique molecular properties and creates opportunities for the design of new bioactive substrates.[3,4] SCF_3-functionalized compounds are, for instance, of interest in isostere-based drug design.[5]

Numerous methods to construct the SCF_3 moiety are reported. Typical procedures involve halogen–fluorine exchange reactions at the sulfur atom or the trifluoromethylation of sulfur-containing compounds.[6] In addition, in recent years several routes to introduce a SCF_3 building block by formation of a C–S bond were developed.[1,4,7] However, an alternative route to access unique SCF_3 compounds consists of a functionalization of derivatives which already contain a SCF_3 group. Such an approach can also involve the introduction of highly valuable entities, such as boryl groups, which might be beneficial for further derivatization reactions.

Herein, we report on the catalytic borylation of SCF_3-containing arenes by C–H activation on using the highly reactive rhodium(I) boryl complex [Rh(Bpin)(PEt_3)$_3$] (**1**) (pin = pinacolato) as the catalyst.[8,9] The reactions proceed under mild reaction conditions and are distinguished by their selectivity for functionalization at the position *ortho* to the SCF_3 moiety,[7e] which presumably serves as a directing group.



Scheme 1. Selective C–H borylation of phenyl sulfides at the position *ortho* to the thioether group.

Treatment of [Rh(Bpin)(PEt_3)$_3$] (**1**) with an equimolar amount of phenyltrifluoromethyl sulfide (**2a**) at room temperature resulted in the formation of [Rh(H)(PEt_3)$_3$] (**3**)[8–10] as well as the borylated aromatics **4a** and **5a**, which are functionalized at the *ortho* position to the SCF_3 group (Scheme 1). The latter were formed in a ratio of 2:1 and were identified by ^{1}H, ^{11}B, ^{13}C and ^{19}F NMR spectroscopy. The

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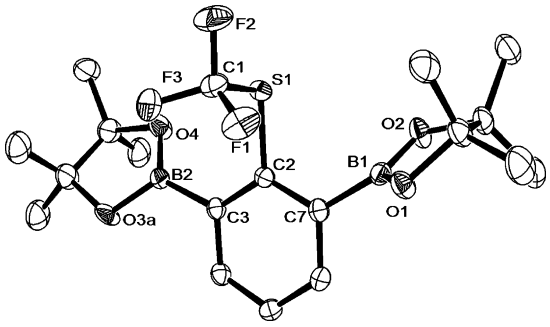


Figure 1. Molecular structure of **5a** (ORTEP, ellipsoids are set at a 50% probability).[34] All hydrogen atoms are omitted for clarity. Selected bond lengths [Å]: S1-C1 1.790(2), S1-C2 1.7932(19), B1-C7 1.571(3), B2-C3 1.576(3).

molecular structure of **5a** was determined by X-ray diffraction analysis (Figure 1).

To investigate the scope of the reaction, **1** was treated with the phenyl sulfides **2b** and **2c**, which contain a SCH_3 and a SCF_2CF_3 moiety, respectively. An excellent selectivity for a functionalization at the *ortho* positions was observed to give the mono- and bisborylated products **4b** and **5b** as well as **4c** and **5c**, along with **3** (Scheme 1). The conversion of **2c** is lower than that of either **2a** or **2b**. The *para*-substituted SCF_3 arenes **2d–f** can also be borylated with an analogous regioselectivity and the corresponding products **4d–f** and **5d–f** were obtained. The reaction of **1** with **2d**, which exhibits the electron-withdrawing fluorine atom at the *para* position, is faster than that with **2f** bearing an electron-donating group. No benzylic borylation was observed in the reaction of **2f**. Note that Marder et al. reported a rhodium-catalyzed borylation of toluene to primarily give benzyl boronate esters.[11] Although **1** was used in C–F bond-activation reactions, no C–F bond-cleavage reaction was observed, neither at the SCF_3 group nor at the aromatic C–F bond of **2d**.[8,12] The *ortho* borylation was also successful for the compounds **2h** and **2i**, bearing a methyl group at the *meta* position and a phenyl group at one *ortho* position, respectively, to the corresponding products **4h** and **4i**. Note that **2i** has no functional group at the *para* position and the selective *ortho* borylation is consistent with the results which were found for **2a–g**. For **2h** no double borylation was observed, and might be explained by the steric hindrance caused by the *meta* substituent. With the exception of **4b**[13] all the borylated compounds **4** and **5** have not been synthesized previously.[14] 4-Bpin-$C_6H_4SCF_3$, which is an isomer to **4a**, can be synthesized by Suzuki–Miyaura borylation of the aryl bromide with diboranes.[15]

A variation of the boryl group is possible, too. Comparable regioselectivities were found upon treatment of [Rh{$BO_2C_3H_4(CH_3)_2$}$(PEt_3)_3$] (**1′**)[9a] with either **2a** or **2b** which led to the formation of the corresponding boronate esters **4a′** and **5a′**, and **4b′** and **5b′** (see the Supporting Information).

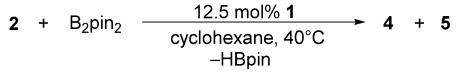
The stoichiometric C–H activation of benzene at **1** to yield PhBpin and **3** was reported before.[8] In contrast, a reaction of **1** with 2,3,5,6-tetrafluoropyridine gave [Rh(4-C_5NF_4)$(PEt_3)_3$] and HBpin. However, on treatment of **1** with phenyl sulfides we did not observe any generation of an aryl complex.

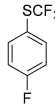
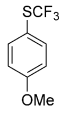
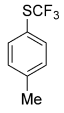
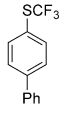
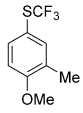
According to the literature, the regioselectivity for C–H borylation reactions is predominantly determined by steric factors.[16] Thus, the activation of monosubstituted arenes with transition-metal catalysts in the presence of B_2pin_2 or HBpin often leads to a mixture of functionalized arylboronate esters, in which *meta*-substituted aromatics are usually the main products.[16,17] However, directing groups were used to achieve a catalytic borylation at the *ortho* position.[18] These reactions involve, for instance silyl groups,[19] carbonyl moieties,[20] phosphines,[21] or nitrogen-containing directing groups.[22] The employment of the Bpin group as a traceless directing group for the borylation of nitrogen heterocycles and anilines was also demonstrated.[23] We presume that the SCX_3 moieties also serve as directing groups.[24,25] Although an initial coordination between rhodium and the SCX_3 moiety, which precedes the borylation at the *ortho* position, might be important, an interaction between the metal-bound Bpin entity and the sulfur atom of the SCX_3 group is also conceivable. Note that for the C–F activation of pentafluoropyridine a four-membered transition state, which involves an interaction of a fluorine atom with the boryl ligand, was suggested on the basis of DFT calculations.[8,26] However, we did not observe any reactivity of **1** towards anisole or trifluoromethoxy benzene at room temperature, despite the assumption that the oxygen–boron interaction might be stronger than a sulfur–boron affinity. In addition, no reaction of **1** with **2a** takes place in the presence of free phosphine, thus indicating the dissociation of phosphine from **1**, presumably after precoordination of the substrate.

Based on the stoichiometric conversions, catalytic borylation reactions were developed. Treatment of **2a** with B_2pin_2 in cyclohexane at 40 °C[27] in the presence of 12.5 mol% **1** (based on the amount of B_2pin_2) led to a mixture of **4a** and **5a**.[28] An increase in the reaction time or the amount of B_2pin_2 yielded larger amounts of **5a** (Table 1, entries 1–5). Monitoring the reaction by NMR spectroscopy revealed that the C–H borylation of **4a** starts when the concentration of **4a** is high compared to that of **2a**. A ten-times excess of **2a** over B_2pin_2 gave only **4a**.[18,20b,22d,e] The thioethers **2b** and **2c** are also viable substrates for producing *ortho*-borylated products under mild reaction conditions with excellent regioselectivities (entries 6–9). Moreover, the protocol is applicable to derivatives with functional groups at positions *ortho, meta*, or *para* to the SCF_3 group (entries 10–16). Competition experiments indicate that **2d** converts faster than **2a**, **2e**, **2f**, and **2g**, but no other relationship regarding the electronic influence of any substituent at the substrate is apparent (see the Supporting Information).

Upon using 2.5 mol% of **1** (based on the amount of B_2pin_2) as the catalyst, a three-times excess of **2a**, and cyclohexane as the solvent, the TON (based on the C–H activation steps) for the formation of **4a** and **5a** improved from 9 to 39 after 20 hours at 40 °C[29] (Scheme 2). Comparable improvements were achieved for the thioethers **2d–f** as substrates. Kinetic traces show that the conversion of **2a** is complete after 18 hours when using a 2.5 mol% catalyst

Table 1: Catalytic *ortho* borylation of **2a–i** using 12.5 mol% of the catalyst **1**.[a,b]

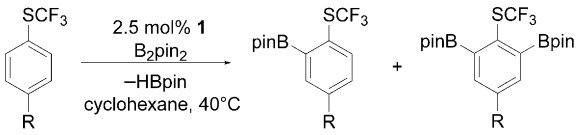


Entry	Substrate	B_2pin_2/**2**	*t*	Yield [%][28,c] (**4** + **5**)	**4**/**5**	TON[d]
1		1:1	20 h	57 + 21	11:4	6
2	 **2a**	1:1	2 d	56 + 25	9:4	8
3		1:10	20 h	94	**4a** only	8
4		1:3	20 h	94 + 9	31:3	9
5		3:1	20 h	14 + 71	1:5	12
6		1:3	20 h	94 + 9	10:1	9
7	 **2b**	1:1	20 h	56 + 25	9:4	7
8		1:3	20 h	30[e]	**4c** only	2
9	 **2c**	1:2	16 h[f]	76 + 5[e]	14:1	7
10		1:8	14 h	94	**4d** only	8
11	 **2d**	1:3	11 h	91 + 5	18:1	8
12	 **2e**	1:3	20 h	99 + 5	20:1	9
13	 **2f**	1:3	20 h	99 + 13	15:2	10
14	 **2g**	1:1	20 h	60 + 14	17:4	7
15	 **2h**	1:1	20 h	86	**4h** only	7
16	 **2i**	1:1	20 h	87	**4i** only	7

[a] Reactions were performed in a NMR tube which was equipped with a PFA inliner. [b] Yields and ratios were determined by ^{19}F NMR spectroscopy; except for entries 6 and 7 for which by ^{1}H NMR spectroscopy was used. [c] Yields are based on the amount of B_2pin_2, except that for entry 5.[28] [d] Turnover number = number of borylation steps per mole of **1**.[28] [e] Reaction mixture also contains traces of PhBpin. [f] Reaction was performed at 50°C.

loading, whereas a higher loading led to completion after 8 hours.

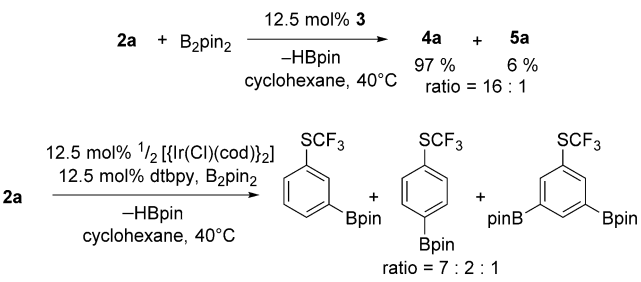
Because [Rh(H)(PEt_3)$_3$] (**3**) was formed in the stoichiometric C–H activation reactions (Scheme 1), its capability for C–H activation at room temperature was also tested, but treatment of **3** with **2a** did not lead to any C–H bond cleavage. However, **3** is presumably an intermediate in a putative catalytic cycle and might, therefore, serve as a catalytic precursor. Indeed, **3** catalyzed the borylation of **2a** with *ortho*



2a,d–f **4a,d–f** **5a,d–f**

2a : R = H **4a** / **5a** = 32 : 3 yield: 82 + 8 % TON: 39
2d : R = F **4d** / **5d** = 17 : 1 yield: 100 + 6 % TON: 45
2e : R = OMe **4e** / **5e** = 16 : 1 yield: 97 + 6 % TON: 44
2f : R = Me **4f** / **5f** = 11 : 1 yield: 92 + 8 % TON: 44

Scheme 2. Catalytic borylation of phenyltrifluoromethyl sulfides.

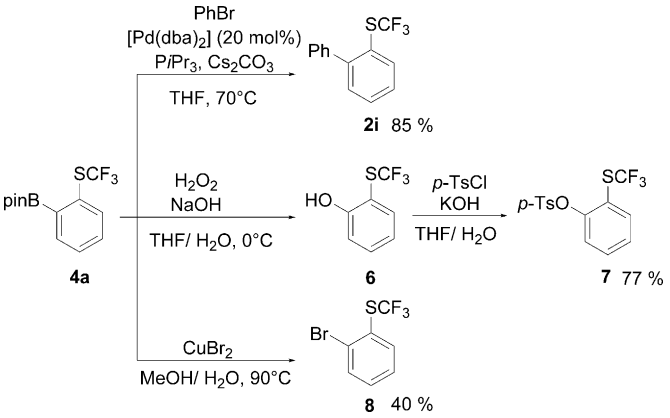


Scheme 3. Catalytic borylation of **2a** using **3** or [{Ir(Cl)(cod)}$_2$] as the catalyst.

selectivity (Scheme 3). Possibly, **1** as an active species can be generated from *fac*-[Rh(H)(Bpin)$_2$(PEt_3)$_3$], which can be furnished from **3** and B_2pin_2.[8,9a]

The applicability of the catalytic system [{Ir(μ-Cl)(cod)}$_2$]/dtbpy (dtbpy = 4,4-di-*tert*-butylbipyridine, cod = 1,5-cyclooctadiene) in C–H borylation reactions is well known.[16] Therefore, for comparison, its catalytic activity towards the borylation of **2a** with B_2pin_2 under the same reaction conditions was investigated. A mixture of three borylated products in a ratio of 7:2:1 was generated, and contained the *meta*-borylated arene as the major compound (Scheme 3). Interestingly, with **2b** no reaction was observed under these reaction conditions. These results with iridium are in sharp contrast to those of the borylation reactions with **1** as the catalyst, and indicate an influence of the CF_3 group. There is also no *ortho*-directed reaction step operating.

Further transformations of **4a** demonstrate its potential to serve as a building block (Scheme 4). Thus, a Suzuki–Miyaura



Scheme 4. Transformations of **4a**.

cross-coupling[30] of **4a** with PhBr in the presence of [Pd(dba)$_2$] (dba = dibenzylideneacetone), P*i*Pr$_3$, and Cs_2CO_3 to give 2-Ph-$C_6H_4SCF_3$ (**2i**) was achieved. Moreover, the boronate ester **4a** was converted into the alcohol **6** by oxidation with H_2O_2. The compound **6** was treated in situ with *para*-toluenesulfonyl chloride under basic conditions to afford the tosylate **7**. The latter is presumably also a useful substrate for further reactions. In addition, it was shown that the Bpin moiety of **4a** can be replaced by a bromine atom on using $CuBr_2$.

In conclusion, a remarkable reaction route to access a range of SCF_3 aromatics which are borylated at the *ortho* position was developed. Doubly borylated compounds are also accessible, and are versatile building blocks.[22g,31] The conversions impart catalytic borylation reactions of aromatic thioethers by C–H activation under mild reaction conditions. The boryl complex [Rh(Bpin)(PEt$_3$)$_3$] (**1**) serves as a catalyst and the SCX_3 groups presumably function as directing groups. Although rhodium-catalyzed arene borylation reactions are known,[11a,32] they usually require fairly harsh reaction conditions, in contrast to iridium-catalyzed conversions.[17,33] Moreover, the regioselectivities which were observed with **1** as catalyst are in sharp contrast to those which are typically found for iridium- or rhodium-catalyzed borylation reactions. In general, the conversions enable access to rare SCF_3 aromatics which were demonstrated to be useful starting compounds for further transformations.

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[28] Note that the rhodium complex **1** is also a Bpin source which leads to higher yields. In addition HBpin might in principle act as a borylation agent, although the conversion is very low. Treatment of **3** with one equivalent **2a** and HBpin revealed the formation of **4a** in yield of 5 % after 20 h at 40 °C.

[29] The reactions can be run at considerably lower temperatures in comparison to most other *ortho* C–H borylation protocols which are described in the literature (typically 70–100 °C).[19b,20b,22c,d,g,23]

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[34] CCDC 990620 (**5a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

