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Facile Synthesis of Diverse Multisubstituted *ortho*-Silylaryl Triflates via C–H Borylation

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Diverse multisubstituted *ortho*-silylaryl triflates were efficiently synthesized from simple *ortho*-silylaryl triflates via iridium-catalyzed regioselective C–H borylation and subsequent deborylative functionalizations. An azidoaryne precursor synthesized by this method served as a useful bis-reactive platform molecule, thus demonstrating the utility of the method for preparing diverse aromatic compounds.

With the increasing demands of chemical libraries that facilitate efficient drug discovery, new synthetic methodologies such as "diversity-oriented synthesis"[1] and "multicomponent reactions,"[2] which enable expeditious preparation of vast numbers of diversified compounds, are growing increasingly important. An aryne serves as a favorable platform intermediate for this purpose because it is capable of transforming into a wide range of aromatic compounds via various types of reactions, i.e., cycloadditions with arynophiles or reactions with nucleophiles and electrophiles (Figure 1A).[3,4] Several methods for generating arynes, including precursors, have been developed and applied to the synthesis of a diverse array of aromatic compounds. *ortho*-Silylaryl triflate **1** is one of the most widely used precursors because of the mild conditions required for aryne generation, which has prompted the development of numerous transformations mediated by an aryne.[5] However, the preparation of multisubstituted *ortho*-silylaryl triflates is not always easy, particularly for substrates with a base-sensitive function, because representative synthetic methods require multiple steps, including a silylation step via a carbanion species (Figure 1B).[6] To render multisubstituted *ortho*-silylaryl triflates more accessible, we hypothesized that derivatization of simple *ortho*-silylaryl triflates would be a practical approach (Figure 1C). Herein, we demonstrate a facile method of synthesizing diverse multisubstituted *ortho*-silylaryl triflates via the C–H borylation of simple *ortho*-silylaryl triflates.

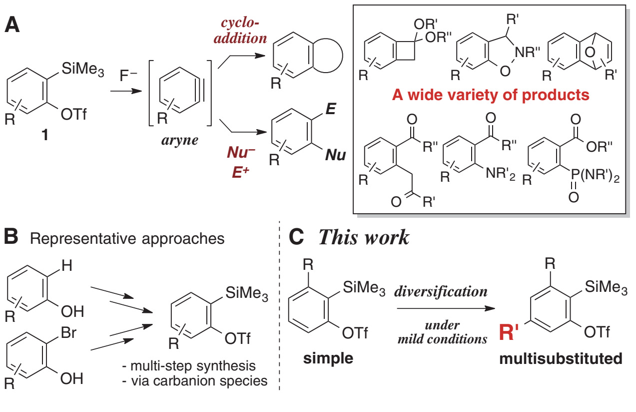
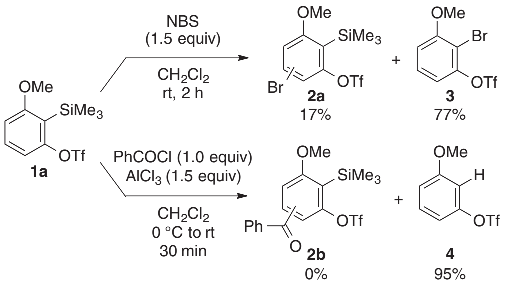


Figure 1. (A) Generation of arynes from *ortho*-silylaryl triflates and examples of available products via diverse transformations. (B) Representative synthetic methods for *ortho*-silylaryl triflate. (C) The strategy used in this work. Tf: CF_3SO_2, Nu: nucleophile, E: electrophile.

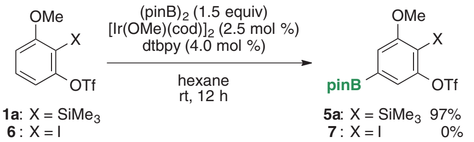
Our initial attempts to modify 3-methoxy-2-(trimethylsilyl)phenyl triflate (**1a**) directly by classical electrophilic substitution reactions were unsuccessful. For example, neither bromination nor Friedel–Crafts acylation of **1a** efficiently afforded **2a** or **2b**, and the cleavage of the C–Si bond proceeded instead, providing predominantly **3** or **4** (Scheme 1).

After several attempts, we determined that iridium-catalyzed Smith/Miyaura–Ishiyama–Hartwig C–H borylation[7] suited our purpose. The reaction of *ortho*-silylaryl triflate **1a** with bis(pinacolato)diboron in the presence of a catalytic amount of iridium complex and 4,4′-di-*tert*-butyl-2,2′-bipyridyl (dtbpy) afforded borylated *ortho*-silylaryl triflate **5a** in excellent yield (Scheme 2). In common with reported examples, the borylation proceeded regioselectively at a sterically unhindered position of **1a** without damaging the silyl or the triflyloxy group. However, borylation of *ortho*-iodoaryl triflate **6**, another type of aryne precursor,[8] did not proceed under the same conditions and starting material **6** was recovered.

The borylation conditions were applicable to various 3- or 6-substituted 2-(trimethylsilyl)phenyl triflates **1** (Table 1). Electron-donating methyl- and trimethylsilyl-substituted *ortho*-silylaryl triflates were borylated to afford **5b** and **5c**, respectively, in high yields, demonstrating that the substitution positions of the

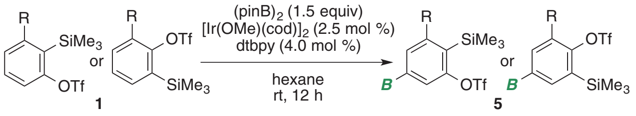


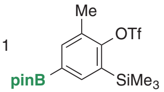
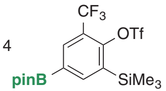
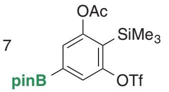
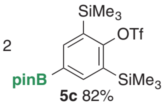
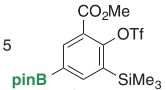
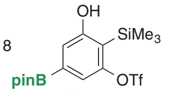
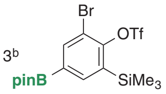
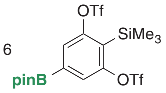
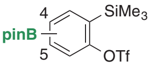
Scheme 1. Initial attempts to modify *ortho*-silylaryl triflate **1a** by classical electrophilic substitution reactions. NBS: *N*-bromosuccinimide.



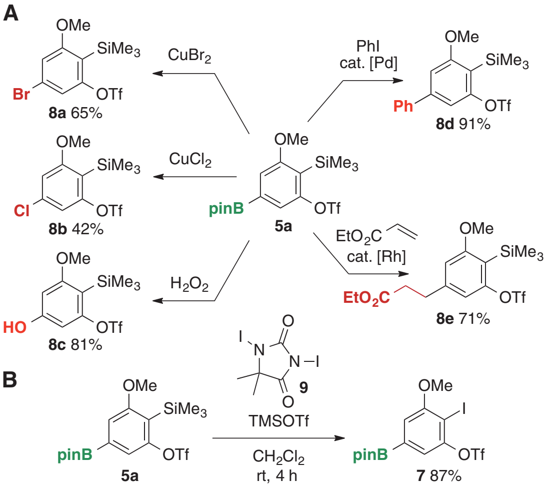
Scheme 2. Borylation of aryne precursors **1a** and **6** using an iridium catalyst. Bpin: 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl, cod: 1,4-cyclooctadiene, dtbpy: 4,4′-di-*tert*-butyl-2,2′-bipyridyl.

Table 1. Borylation of various *ortho*-silylaryl triflates

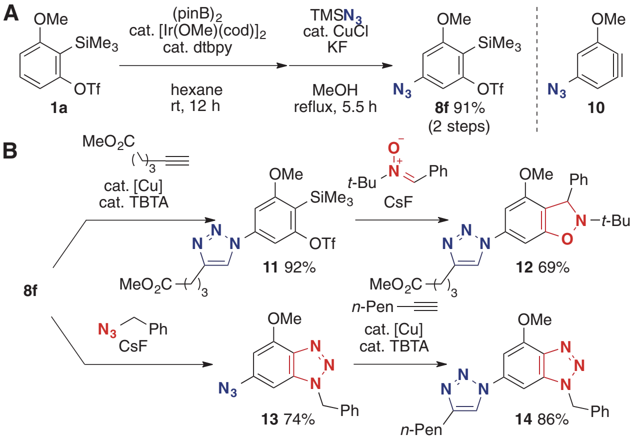


Entry	5, yield[a]	Entry	5, yield[a]	Entry	5, yield[a]
1	 **5b** 87%	4	 **5e** 82%	7	 **5h** 65%
2	 **5c** 82%	5	 **5f** 68%	8	 **5i** 40%
3[b]	 **5d** 87%	6	 **5g** 78%	9	 **5j** 87% (4-:5- = 13:87)

[a]Isolated yields. [b]Instead of dtbpy, tmphen was used.



Scheme 3. Various transformations of borylated *ortho*-silylaryl triflate **5a** (see Supporting Information for details of the conditions).



Scheme 4. (A) Formal C–H azidation of *ortho*-silylaryl triflate **1a**. (B) Two types of sequential cycloadditions from azidoaryne precursor **8f** (see Supporting Information for details of the conditions).

silyl and triflyloxy groups are interchangeable (Entries 1 and 2). For bromo-substituted *ortho*-silylaryl triflate, the use of 3,4,7,8-tetramethyl-1,10-phenanthroline (tmphen)[9] as a ligand rather than dtbpy afforded a higher yield of product **5d** (Entry 3). *ortho*-Silylaryl triflates bearing an electron-withdrawing group were also capable of borylating with high efficiency while leaving the triflyloxy group untouched (Entries 4–6). The method was also applicable to the borylation of *ortho*-silylaryl triflates with a base-sensitive acetoxy group and an unprotected hydroxy group, affording the corresponding products **5h** and **5i**, respectively, in moderate yields (Entries 7 and 8). Incidentally, borylation of unsubstituted *ortho*-(trimethylsilyl)phenyl triflate provided a mixture of regioisomers with moderate selectivity (Entry 9).[10]

The boryl group of *ortho*-silylaryl triflate **5a** was transformable into a wide variety of substituents without the loss of the silyl and triflyloxy groups (Scheme 3A). Various oxidative transformations[11] of **5a** occurred to furnish brominated, chlorinated, and hydroxylated derivatives **8a**–**8c** in moderate to good yields. C–C bond formations of **5a**, such as Suzuki–Miyaura coupling[12] with phenyl iodide and rhodium-catalyzed 1,4-addition[13] to ethyl acrylate, also proceeded to yield **8d** and **8e**, respectively. However, treatment of **5a** with iodination reagent **9**[14] did not afford the iododeborylated product but instead provided *ortho*-iodoaryl triflate **7** (Scheme 3B), which we failed to obtain by the direct borylation of *ortho*-iodoaryl triflate **6** (Scheme 2). This approach will be useful in preparing diverse multisubstituted *ortho*-iodoaryl triflate-type aryne precursors.

The utility of borylation-mediated derivatization of simple *ortho*-silylaryl triflate was demonstrated in the diversity-oriented synthesis of heteroaromatic compounds using an azidated *ortho*-silylaryl triflate **8f** as a platform molecule (Scheme 4). Azide **8f**, which was designed as a precursor of azidoaryne **10**, was prepared efficiently by formal aromatic C–H azidation[15,16] of **1a** without isolation of the borylated product **5a**. Azidoaryne precursor **8f** served as a compact bis-reactive platform molecule, which was derivatized by the sequential use of aryne and click chemistries (Scheme 4B). For example, copper-catalyzed azide–alkyne cycloaddition followed by aryne–nitrone cycloaddition[4d,8b] afforded triazoylbenzoisoxazole **12**. Furthermore, the order of click reaction and aryne-mediated transformation was exchangeable: reaction of azidoaryne **10**, generated in situ from **8f** by treatment with fluoride, with benzyl azide proceeded smoothly to provide benzotriazole **13**[17] with good azido-type selectivity, and subsequent copper-catalyzed cycloaddition[18] with 1-heptyne resulted in the efficient formation of bistriazole **14**.[8g] The combinatorial use of different azidophiles and arynophiles in the reaction with **8f** can easily produce a chemical library that consists of highly diverse compounds.

In summary, we have shown that the iridium-catalyzed C–H borylation of simple *ortho*-silylaryl triflates, followed by transformation of boryl groups into other functional groups, makes multisubstituted *ortho*-silylaryl triflates readily available. The utility of the method for preparing diverse aromatic compounds has been finely demonstrated using an azidated substrate, which served as a bis-reactive azidoaryne precursor. Because *ortho*-

silylaryl triflates can be used for other transformations besides those via aryne, such as thia-Fries rearrangement,[4j] borylated *ortho*-silylaryl triflates should serve as useful platforms to efficiently expand the range of available aromatic compounds. Further studies, including the construction of a unique chemical library, are now in progress.

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Supporting Information for characterization of new compounds is available electronically on J-STAGE.

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