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In Situ Generation of Silyl Anion Species through Si–B Bond Activation for the Concerted Nucleophilic Aromatic Substitution of Fluoroarenes

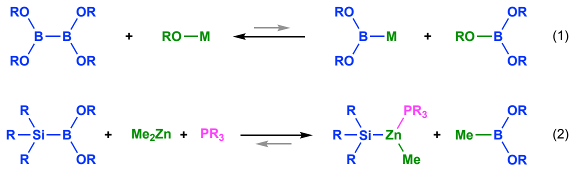
Kumiko Kojima,[a] Yuki Nagashima,[a] Chao Wang,*[ab] and Masanobu Uchiyama.*[ab]

Dedication ((optional))

Abstract: *In situ* generated silyl anion species enable the concerted nucleophilic aromatic substitution of fluoroarenes. Model DFT calculations indicated that addition of a base to a silylborane would thermodynamically form a silyl-borate complex and then kinetically release a silyl anion species thorough Si–B bond cleavage, and that the *in situ* generated silyl anion equivalent would further react with a fluoroarene through a concerted nucleophilic aromatic substitution pathway with an activation barrier of ca. 20 kcal/mol to afford the silylated product with a large energy gain. Experiments confirmed that the defluorosilylation reaction took place smoothly at room temperature simply upon mixing fluoroarenes with commercially available silylborane and NaO^{t}Bu. Radical scavenger and radical clock reaction experiments provide further evidence for the *in situ* generation of the silyl anion.

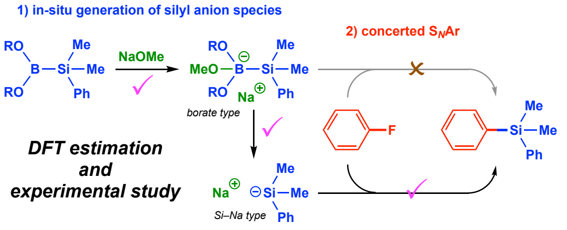
Trialkylsilyl anion species (denoted as silyl anion or R_3Si^-) have long been used as highly reactive silylation reagents.[1] However, they have serious limitations. Firstly, conventional silyl anion reagents ([R_3Si–M]; M = Li, Na, Mg, K) are thermally labile, leading to difficulty in storage and safety issues. Thus, most silyl anions are not suitable for reactions that require heating; indeed, they sometimes decompose even at room temperature. To overcome this problem, *in situ* transmetalation of the highly instable [R_3Si–M] species into more stable R_3Si–metal complexes has been developed. For example, silylzincates, which are easily prepared from [R_3Si–M] and dialkylzinc, show satisfactory reactivity and good stability.[2-3] However, the preparation and generation of [R_3Si–M] generally involve the use of highly inflammable alkali metals such as Li, Na, and K, with strict requirements for the reaction conditions,[1] such as extremely low temperature. Here, we present a protocol for *in situ* generation of silyl anion equivalent from readily available, storable, easy-to-handle silylboranes *via* Si–B bond activation[4] with alkoxide anion *under mild conditions*. This in turn enables concerted nucleophilic aromatic substitution reaction of fluoroarenes simply by mixing fluoroarenes with commercially available silylborane and NaO^{t}Bu at room temperature.

Previously, in 2013, one of our group reported a B–B bond activation of diborons with metal alkoxide, but the *in situ* generation of boryl anion is thermodynamically difficult, even though it is kinetically favorable (Scheme 1-1).[5] On the other hand, we very recently established a protocol for *in situ* direct preparation of silylzinc species (Si–Zn) *via* activation of the Si–B bond of stable silylboranes with dialkylzinc and phosphine, enabling stereoselective silylzincation of terminal alkynes (Scheme 1-2).[6] The facile Si–B bond cleavage and quantitative formation of Si–Zn species prompted us to consider whether this protocol could be also used for the *in situ* generation of [R_3Si–M] or silyl anion equivalent.



Scheme 1. In-situ generation of boryl and silyl anion.

To examine the feasibility of this idea, we performed DFT calculations[7-10] using $PhMe_2Si$–$B(OCH_2CH_2O)$ and NaOMe as chemical models of silylboranes and metal alkoxides (Scheme 2). It has been reported that R_3Si–B(pin) can efficiently form a silyl-borate complex with alkoxides, but it was not clear whether a highly reactive silyl anion equivalent could be generated from the silyl-borate species and practically utilized. We selected the defluorosilylation reaction[11-12] of Ph–F as a model reaction, based on the experimental observation by Würthwein and Studer that the S_NAr (nucleophilic aromatic substitution) reaction of unactivated fluoroarenes with silyllithiums proceeds smoothly without any transition metal (TM) catalyst.[13] S_NAr reaction has long been considered to proceed in a stepwise manner *via* the Meisenheimer intermediate,[14] though more recently an in-depth mechanistic study by Jacobsen[15] demonstrated that S_NAr reaction also occurs via a concerted pathway.[16]



Scheme 2. Features of this defluorosilylation reaction.

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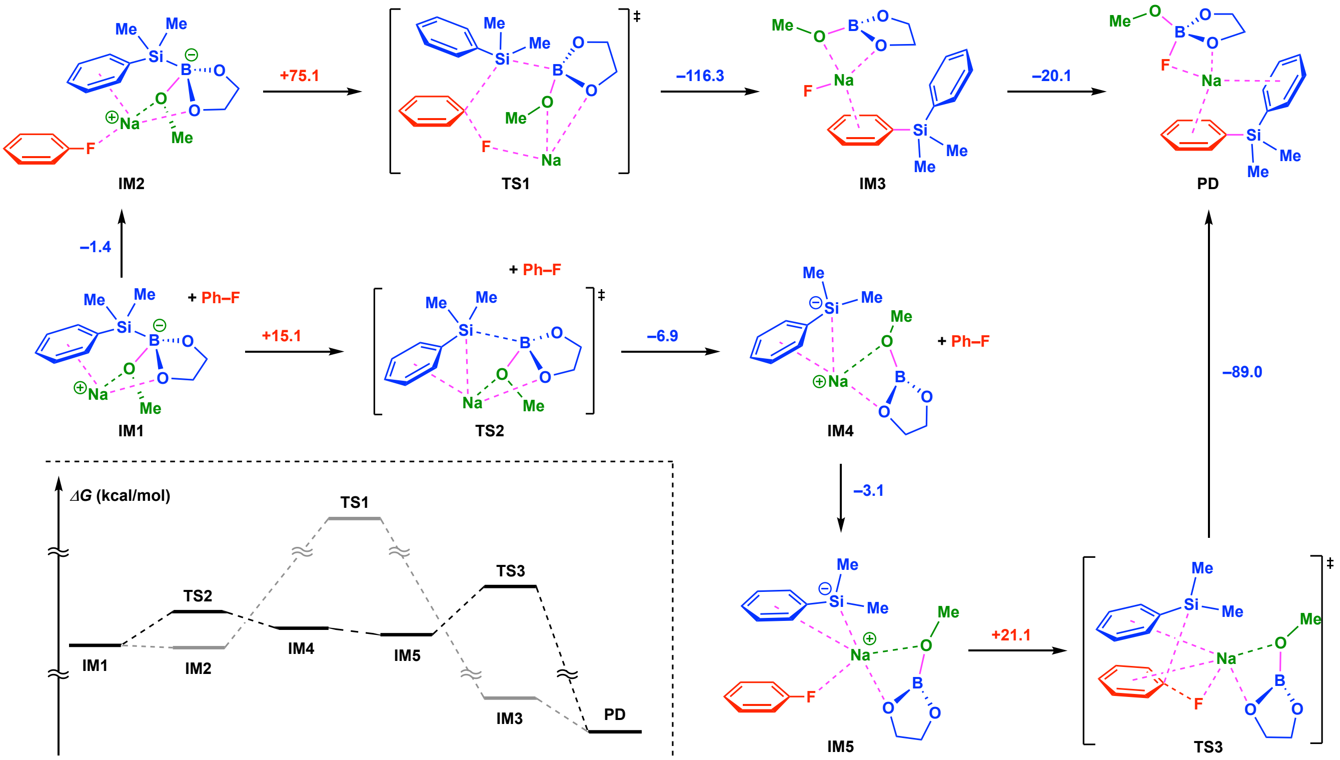


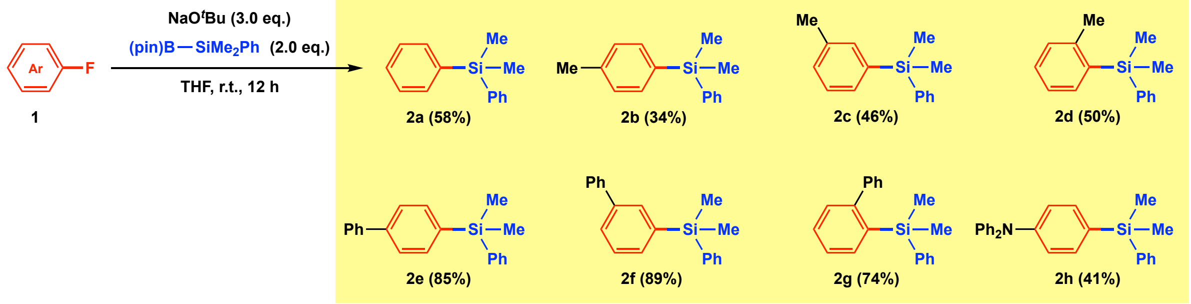
Figure 1. DFT calculation at the M06L/6-31+G* level. ΔG: Gibbs free energy in kcal/mol.

The possible S$_N$Ar reaction pathways of Ph–F are shown in Figure 1. Although we must keep in mind the possibility that the simplification inherent in these models may lead to underestimation of the steric/electronic interactions, the model calculation provides a valuable starting point for considering 1) whether the silyl anion equivalent can be generated from a mixture of silylborane and alkoxide[17] and 2) whether the *in-situ*-generated silyl anion equivalent has sufficient reactivity for the defluorosilylation of fluoroarene. The reactants (silylborane and NaOMe) first form an association borate complex **IM1** with a large energy gain (–34.8 kcal/mol). The Si-borate formation causes the O–B–O angle (104.6°) to be deformed by 8.3° and the Si–B bond length (2.10 Å) to be elongated by more than 3% as compared with those in the starting silylborane (see Supporting Information). Two types of silyl anions are *a priori* possible for the potential active species, the Si-borate (itself) and other silyl anion equivalents. We will discuss the S$_N$Ar reactions of Ph–F with borate-type species first.

Initial electrostatic coordination of a lone pair of Ph–F to Na cation results in the formation of a complex (**IM2**) with a stabilization energy of 1.4 kcal/mol. To reach the TS of the defluorosilylation (S$_N$Ar) reaction, the Si-borate structure changes drastically, so that the Si atom can approach the *ipso*-carbon of Ph–F. The C–Si bond formation and C–F bond cleavage take place as a single event at **TS1** to produce **IM3**. The stabilization energy is very large (–116.3 kcal/mol) because of the formation of stable C–Si, B–O and Na–F bonds. However, the activation energy is extremely high (+75.1 kcal/mol), mainly because of the steric bulkiness of the Si-borate moiety and its low nucleophlicity due to delocalization of negative charge over the borate structure. Obviously, such a transformation would not take place under normal conditions.

Of several possible TSs for the generation of silyl anion equivalent from **IM1**, we could identify one, **TS2**. The activation energies are reasonably low (15.1 kcal/mol), and then a rather endothermic process leads to **IM4**, which can be further stabilized through the formation of **IM5** with Ph–F. This is in good accordance with the experimental findings. Then, concerted S$_N$Ar reaction *via* C–F bond cleavage occurs *via* **TS3** with an activation barrier of 21.1 kcal/mol to give **PD**. Overall, this route is energetically more favorable than the Si-borate pathway. These results suggested that 1) *in situ* generation of the silyl anion reagent would be kinetically favorable, and 2) defluorosilylation by the *in-situ*-generated silyl anion *via* the concerted substitution route is feasible even at room temperature.

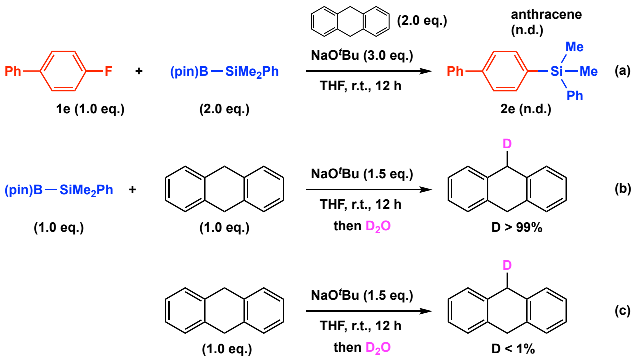
Inspired by these theoretical results, we carried out “proof-of-concept” experiments. We found that the use of NaO^{t}Bu as a base in THF solution with commercially available PhMe$_2$Si–B(pin) resulted in a smooth reaction with various aryl fluorides, such as Ph–F **1a**, *para*-, *meta*-, and *ortho*-fluorotoluenes **1b-d**, *para*-, *meta*-, and *ortho*-fluorobiphenyls **1e-g** to afford the corresponding defluorosilylation products **2a-g** in moderate to good yields. It is noteworthy that no regioisomers of these silylated products were detected by GC–MS or NMR analysis, indicating that aryne intermediates was not involved in these



Scheme 3. Substrate scope of the reaction.

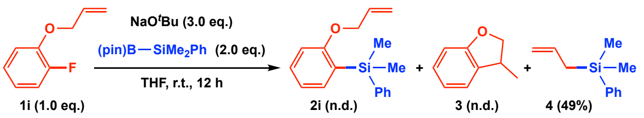
reactions.[18] Remarkably, even 4-fluoroaniline derivative **1h**, which has a very electron-rich aryl group, could be used in this protocol, albeit with a reduced yield (**2h**, 41%). These results are consistent with a concerted S_NAr reaction.

To confirm the reaction mechanism, we carried out a series of control experiments. First, to examine whether radical route was involved, the current reaction was performed with adding 9,10-dihydroanthracene. We found that addition of 9,10-dihydroanthracene blocked the reaction of **1e**, though no formation of anthracene was detected (Scheme 4a). Next, when 9,10-dihydroanthracene was treated under the standard reaction conditions in the absence of **1e** followed by quenching with D_2O, deuterated anthracene was obtained (Scheme 4b). This means that deprotonation reaction of 9,10-dihydroanthracene proceeds under the standard reaction conditions. However, deprotonation of 9,10-dihydroanthracene with NaO^{t}Bu was not successful in the absence of silylborane (Scheme 4c). These results support the involvement of *in situ* generation of silyl anion, which would act as a strong base to abstract the active benzyl proton of 9,10-dihydroanthracene.[19]



Scheme 4. Control experiments with 9,10-dihydroanthracene (n.d.: not detected).

We also tested the reaction of fluoroarene **1i** as a radical-clock substrate under the standard conditions (Scheme 5). Neither defluorosilylation product **2i** nor cyclization product **3** was detected, but instead, allylation product **4** was observed, indicating that the silyl anion attacks the allyl ether moiety rather than the C(aryl)–F bond. Overall, these experimental observations rule out a radical mechanism for this reaction.



Scheme 5. Control experiment with **1i** (n.d.: not detected).

Very recently, Martin reported an elegant protocol for defluorosilylation with Et_3Si–B(pin) and LiHDMS, enabling both C(sp2)–F and C(sp3)–F bond cleavage.[20] This protocol was successfully applied for late-stage derivatization of several functional fluoroarenes, demonstrating potential synthetic utility. Martin also suggested a mechanism involving a concerted S_NAr reaction route. We compared the reactivities of Et_3Si^- and $PhMe_2Si^-$ by means of DFT calculation (see Supporting Information). As expected, the calculated pathways were very similar, and we identified the TS for the concerted S_NAr process with Et_3Si^-, **TS3(Et_3Si^-)**, which is analogous to $PhMe_2Si^-$. The calculations indicate that **TS3(Et_3Si^-)** is energetically more favorable than **TS3** by 2.8 kcal/mol, probably due to the more electron-donating character of alkyl (Et) than aryl (Ph), in good agreement with Martin's results.[21]

In summary, based on DFT calculations, we designed an efficient protocol for *in-situ* generation of highly active silyl anion species, and predicted its applicability for inert C–F bond activation. We experimentally confirmed that the expected defluorosilylation reaction took place smoothly at room temperature simply upon mixing fluoroarenes with commercially available silylborane and NaO^{t}Bu. Radical scavenger and radical clock reaction experiments supported *in situ* generation of the silyl anion. Such an *in situ* preparation method for silyl anion equivalent from readily available silylboranes under mild conditions opens up new possibilities for the practical and synthetic use of silyl anions. Investigations to expand the scope of this protocol, as well as to establish synthetic applications, are in progress.

Experimental Section

To a THF solution (0.4 M) of fluoroarene **1** (0.2 mmol) were added $PhMe_2Si–B(pin)$ (0.4 mmol) and NaO^tBu (0.6 mmol). The mixture was stirred in an argon atmosphere for 12 h, then water was added, and the aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by chromatography (silica gel) to give silylated product **2**.

Acknowledgements

This work was supported by a JSPS Grant-in-Aid for Scientific Research on Innovative Areas (No. 17H05430), JSPS KAKENHI (S) (No. 17H06173) (to M. U.), and Grant-in-Aid for Scientific Research (C) (No. 18K06544, C.W.).

Keywords: C–F bond cleavage • organicsilicon compounds • silylation • silyl anions • nucleophilic aromatic substitution

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[21] Organosodium compounds exhibit stronger carbanionic nature than organolithium due to the lower electronegativity of sodium than lithium and hence have extremely high reactivity and low stability. On the other hand, organosodium compounds are less commercially available compared with organolithium. These issues limited the application of organosodium chemistry. Similar differences/problems also occur in the silyl anion chemistry. As reflected in the structure of Si-Na in current DFT calculation, Si and Na are more separated (compared with the computation results in ref. 13), and Na^+ shows a strong π-cation interaction with Ph ring, indicating a strong anionic nature of Si. Hence, it is known that Si-Na is less stable than Si-Li species, which

cause some difficulty for preparation and storage. By using the current *in situ* protocol, Si-Na could be smoothly generated from commercially available and bench-stable base (NaO^{t}Bu), and thus facilitate further synthetic utilization of highly active Si-Na species. Further, according to our current results, when R_3Si-SiR_3 was used as the Si-Na precursor, no silylated product was observed, indicating that R_3Si–B(pin) has higher reactivity under the current reaction condition.

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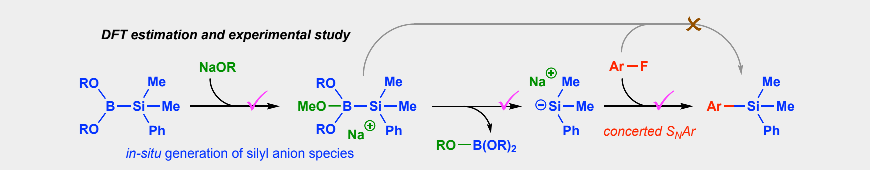

DFT calculations indicate that addition of base to silylborane can kinetically release silyl anion species thorough Si–B bond cleavage, and the anion can further react with fluoroarene through a concerted S_NAr pathway with an activation barrier of *ca.* 20 kcal/mol, with a large energy gain. Experimentally, this defluorosilylation reaction took place smoothly at room temperature simply upon mixing fluoroarenes with commercially available silylborane and NaO^{t}Bu.

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