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Hydride reduction of *o*-(fluorosilyl)benzodifluorides for subsequent C–F transformations†‡

Rika Idogawa,[a] Akihiro Kobayashi,[ab] Youngchan Kim,[a] Ken Shimomori,[a]
Takamitsu Hosoya[a] and Suguru Yoshida*[b]

An efficient method for sequential C–F transformations of *o*-hydrosilyl-substituted benzotrifluorides is disclosed. A key to the success is hydride reduction of *o*-fluorosilyl-substituted difluoromethylenes prepared by a single C–F transformation of *o*-hydrosilyl-substituted benzotrifluorides. We succeeded in further C–F transformations *via* hydride abstraction of the resulting *o*-hydrosilyl group, enabling us to synthesize a wide variety of organofluorine compounds.

Organofluorine compounds are of great importance in broad research fields including pharmaceutical sciences, agrochemistry, and materials chemistry.[1] A wide variety of fluorinating reagents have been developed so far for synthesizing a wide range of organofluorines from halides and alcohols (Fig. 1A).[2] Despite the remarkable improvements in organofluorine chemistry enhancing the availability of organofluorines, it is not easy to synthesize highly functionalized benzyl fluoride derivatives due to the limited fluorination reactions.[3]

Modern studies of selective C–F transformations significantly expanded the accessibility of organofluorines (Fig. 1B and C).[4,5] For example, in 2018, Young and coworkers succeeded in a single C–F transformation of α,α-difluorotoluene (**1**) with a frustrated Lewis pair between tri(*o*-tolyl)phosphine and tris(pentafluorophenyl)borane realizing facile synthesis of phosphonium salt **2**, which served in the preparation of fluoroalkenes by the Wittig reaction with aldehydes (Fig. 1B).[6] Our recent achievements from 2016 on single C–F transformations of benzotrifluorides **4** enabled to synthesize difluoromethylenes **5** through hydride abstraction of *o*-hydrosilyl group (Fig. 1C).[7] Herein, we disclose a new method to synthesize highly functionalized benzyl fluorides **8** from *o*-fluorosilyl-substituted difluoromethylenes **5** by C–F and C–Si transformations (Fig. 1D). A key to the success was efficient reconstruction of hydrosilyl group from fluorosilyl groups, which allowed

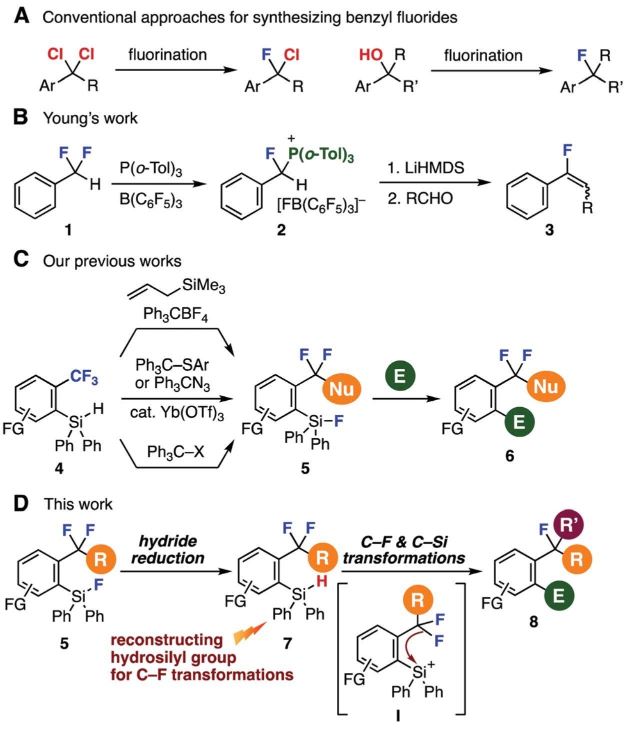

Fig. 1 Backgrounds and an abstract of this study. (A) Conventional methods to synthesize benzyl fluorides. (B) Young's work. (C) Our previous studies. (D) This work.

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[a] Laboratory of Chemical Bioscience, Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University (TMDU), 2-3-10 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-0062, Japan

[b] Department of Biological Science and Technology, Faculty of Advanced Engineering, Tokyo University of Science, 6-3-1 Niijuku, Katsushika-ku, Tokyo 125-8585, Japan. E-mail: s-yoshida@rs.tus.ac.jp

† Dedicated to Professor Koichi Narasaka with Gratitude on the Occasion of his 77th Birthday (Kiju).

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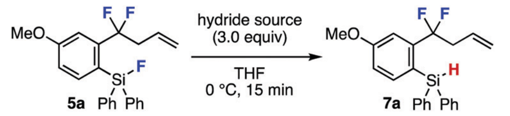
Table 1 Screening of the reaction conditions



Entry	Hydride source	Yield (%)
1	$LiAlH_4$	Quant[a]
2	$NaBH_4$	0
3	$i\text{-}Bu_2AlH$	0
4	$Li[i\text{-}Bu_3BH]$	0
5	$Li[Et_3BH]$	0

[a] Isolated yield (1.0 mmol scale).

further C–F transformations *via* silyl cation intermediate **I** generated by hydride abstraction.

First, we examined hydride reduction of *o*-fluorosilyl-substituted difluoromethylene **5a** using various metal hydrides (Table 1).[8] As a result, *o*-hydrosilyl-substituted benzodifluoride **7a** was synthesized quantitatively with lithium aluminum hydride (LAH) without damaging labile difluoromethylene moiety[8] and C–Si cleavage (entry 1). In sharp contrast, hydride reduction of fluorosilane **5a** resulted in failure when using sodium borohydride, diisobutylaluminum hydride, lithium triisobutylborohydride, or lithium triethylborohydride due to undesired decomposition (entries 2–5). The efficient LAH reduction of fluorosilane **7a** took place in 1.0 mmol scale, clearly showing the good scalability.

A wide range of *o*-fluorosilyl-substituted benzodifluorides **5** successfully participated in the hydride reduction to afford *o*-(hydrosilyl)benzodifluorides **7** (Fig. 2). For example, hydrosilanes **7b** and **7c** having electron-rich thienyl and electron-deficient 4-(trifluoromethyl)phenyl group, respectively, were efficiently prepared by LAH reduction. Hydride reduction furnishing bromo-substituted silane **7d** also proceeded smoothly leaving the bromo group untouched. The reduction of fluorodimethylsilyl group instead of fluorodiphenylsilyl group proceeded and required longer reaction time affording hydrosilane **7e** in good yield,[9] where the dimethylsilyl group can serve in the C–F transformations.[7a] Furthermore, efficient synthesis of **7f** bearing an acidic allylic proton was achieved without damaging difluoromethylene moiety. We succeeded in the preparation of difluorobenzyl sulfide **7g** and chlorides **7h** and **7i** in good yields. Also, difluorobenzyl bromide **7j** was synthesized in moderate yield. Unfortunately, the synthesis of difluorobenzyl *p*-toluenesulfonate **7k** resulted in failure due to the labile sulfonate ester moiety.

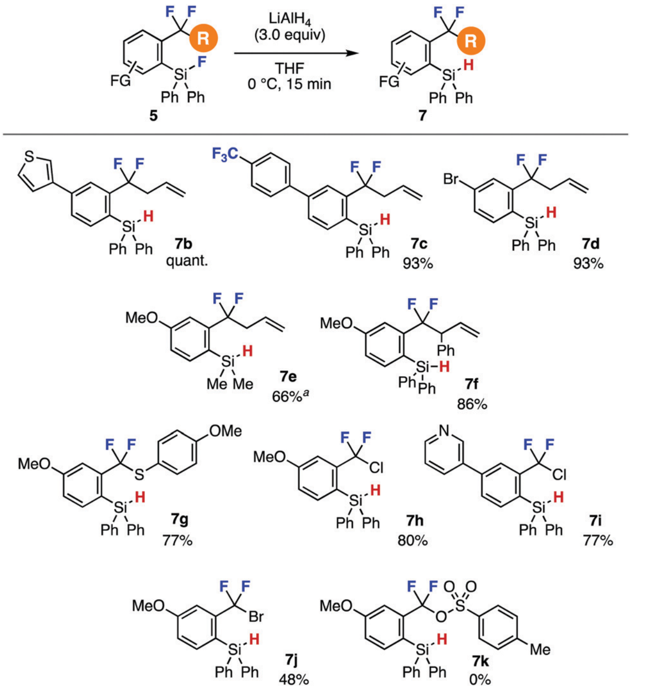


Fig. 2 Syntheses of *o*-(hydrosilyl)benzodifluorides **7**. See the ESI‡ for details. [a]The reaction time was 2 h.

The reconstructed hydrosilyl group of difluoromethylenes served in further C–F transformations (Fig. 3). Indeed, single C–F chlorination of difluoromethylene **7a** with trityl chloride in chlorobenzene and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP)[10] through benzyl cation intermediate **II** proceeded efficiently to afford highly functionalized benzyl fluoride **8a** in good yield (Fig. 3A).[7c] Various benzyl fluorides **8b–8e** were synthesized through single C–F transformations of difluoromethylenes **7a–7d** having a range of functional groups (Fig. 3B). For instance, C–F chlorination products **8b–8d** were prepared from **7b–7d** with trityl chloride in moderate to good yields without damaging a wide variety of functionalities such as fluoro, chloro, allyl, fluorosilyl, trifluoromethyl, thienyl, and bromo groups. It is worth noting that benzyl chloride **8c** was prepared selectively without C–F chlorination of trifluoromethyl group. Further C–F allylation of benzodifluoride **7a** also took place to afford **8e** in moderate yield.[7a] When we attempted Yb-catalyzed C–F thiolation of benzodifluoride **7a** with 4-tolyl trityl sulfide,[7b] benzyl fluoride **8f** was not obtained, showing the different reactivity of fluorobenzyl cation **II** generated from **7a** to difluorobenzyl cation intermediates in our previous reports.[7] Owing to the great importance of organofluorine chemistry, successes in the synthesis of highly functionalized benzyl fluorides **8a–8e** obviously indicated the significant potential of sequential transformations *via* reconstruction of the hydrosilyl group.

Facile synthesis of α,α-difluorobenzyl chloride **7h** by a single C–F chlorination and subsequent LAH reduction was achieved from benzotrifluoride **4a** in a one-pot manner *via* removal of solvents under reduced pressure (Fig. 3C). Benzyl fluoride **8a** was prepared in good yield also from α,α-difluorobenzyl chloride **7h** by a single C–F allylation provably *via* α-chloro-α-fluorobenzyl cation **III**. Second C–F chlorination took place smoothly to provide α,α-dichlorobenzyl fluoride **8g** in moderate yield. Moreover, we succeeded in the preparation of benzyl fluoride **8a** from benzotrifluoride **4a** in a three-step, single purification procedure (Fig. 3D). Indeed, C–F allylation of **4a** followed by LAH reduction using the crude product and subsequent C–F chlorination provided benzyl fluoride **8a** in moderate yield.

Succeeding transformations of highly functionalized benzyl fluoride **8a** realized facile synthesis of organofluorines

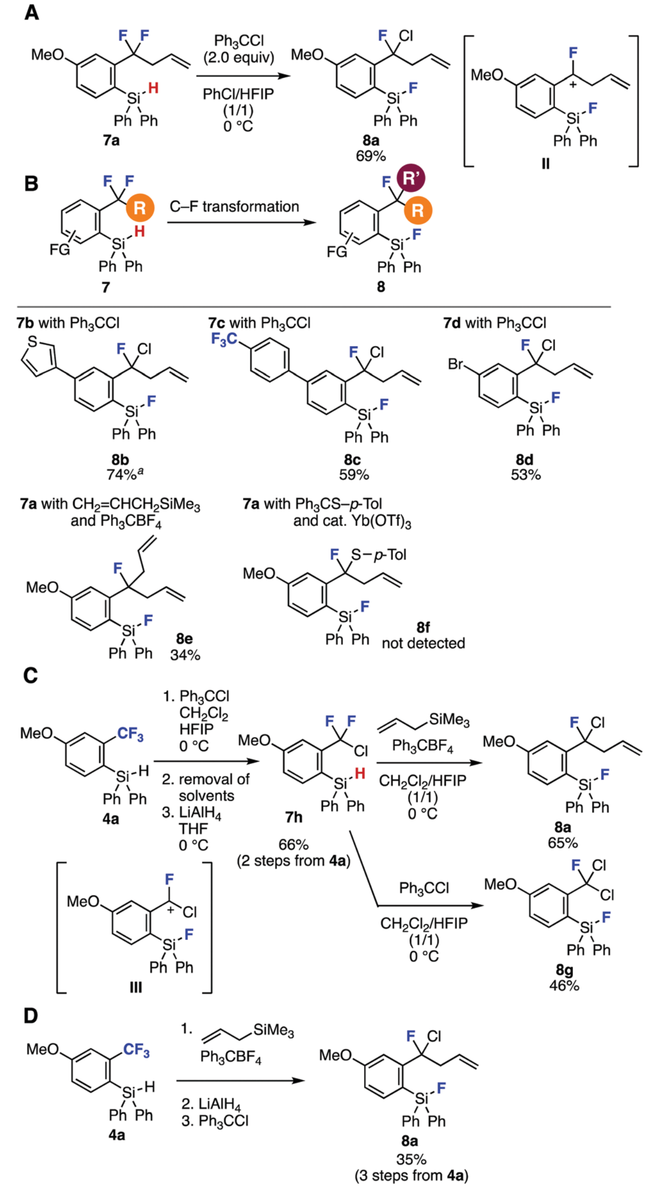


Fig. 3 Transformations of *o*-(hydrosilyl)benzodifluorides **7**. See the ESI‡ for details. Isolated yields are shown otherwise noted. [a]NMR yield. (A) C–F chlorination of **7a**. (B) Scope of benzyl fluoride synthesis. (C) Sequential C–F transformations of **4a** *via* difluorobenzyl chloride **7h**. (D) C–F transformations of **4a** with a single silica-gel column chromatography purification.

involving 1-aryl-1-fluoro-1,3-butadiene **10a** (Fig. 4A). For example, silver mediated C–Si bromination[11] of fluorosilane **8a** furnished bromide **9a** in moderate yields leaving various reactive functional groups intact (Fig. 4A, upper). Treatment of **9a** with cesium carbonate in dimethyl sulfoxide (DMSO) at 120 °C provided 1,3-butadiene **10a** in high yield with good *Z* selectivity.[12] Although 1,3-butadiene **10a** was found to be labile under various conditions such as acidic or basic aqueous conditions, it is worthy to note that 1,3-butadiene **10a** was synthesized by heating **9a** in DMSO in the presences of cesium carbonate in high yield.[13] In contrast, no diene formation was observed when boiling benzyl fluoride **9a** in the presence of cesium carbonate in toluene. When we treated *o*-fluorosilyl-substituted benzyl fluoride **8a** with 4-iodotoluene in the presence of silver oxide and a catalytic amount of palladium catalyst, biaryl **11** was obtained in good yield *via* the Hiyama cross-coupling and dehydrochlorination (Fig. 4A, lower).[14]

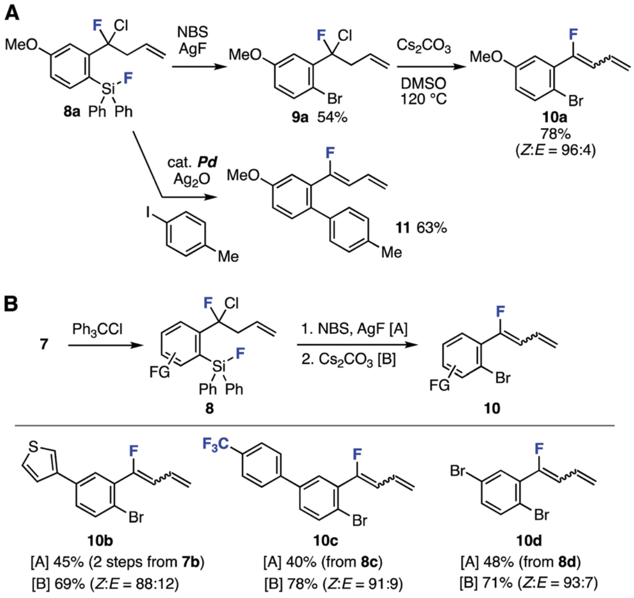


Fig. 4 Transformations of benzyl fluorides **8**. (A) Synthesis of various organofluorines from **8a**. (B) Fluorobutadiene synthesis.

A range of 1-aryl-1-fluoro-1,3-butadiens **10b–10d** were successfully prepared from **8b–8d** by C–Si bromination and following 1,3-butadiene formation (Fig. 4B). Desilylbromination of benzyl fluoride **8b** prepared by C–F chlorination of difluoromethylene **7b** and following dehydrochlorination furnished thienyl-substituted 1-fluoro-1,3-butadiene **10b**. Also, fluorobutadienes **10c** and **10d** were successfully synthesized from difluoromethylenes **7c** and **7d** having electron-deficient aromatic ring and transformable bromo group, respectively, in good yields. Since 1,3-butadienes are versatile building blocks in synthetic organic chemistry,[15] this unique method to prepare functionalized fluorobutadienes will serve to synthesize a broad range of organofluorines.

In summary, we accomplished the synthesis of a wide variety of organofluorines through LAH reduction of *o*-(fluorosilyl)benzodifluorides. A broad range of benzyl fluorides and 1-aryl-1-fluoro-1,3-butadienes were successfully prepared by C–F transformations of *o*-(fluorosilyl)benzodifluorides and following transformations. Further studies such as diversifications of 1-aryl-1-fluoro-1,3-butadienes are ongoing in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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