

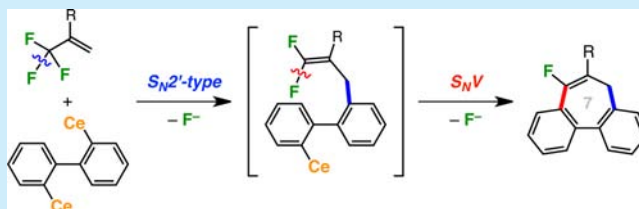
# Domino C–F Bond Activation of the CF<sub>3</sub> Group: Synthesis of Fluorinated Dibenzo[*a,c*][7]annulenes from 2-(Trifluoromethyl)-1-alkenes and 2,2'-Diceriobiaryls

Takeshi Fujita, Marina Takazawa, Kazuki Sugiyama, Naoto Suzuki, and Junji Ichikawa\*

Division of Chemistry, Faculty of Pure and Applied Sciences, University of Tsukuba, Tsukuba, Ibaraki 305-8571, Japan

**S** Supporting Information

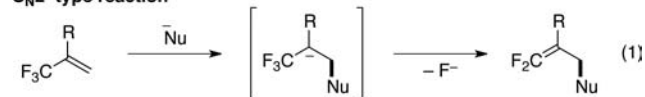
**ABSTRACT:** The construction of ring-fluorinated seven-membered carbocycles was readily achieved via the domino S<sub>N</sub>2'-type/S<sub>N</sub>V reaction between 2-(trifluoromethyl)-1-alkenes and 1,4-carbodianions. The S<sub>N</sub>2'-type reaction of 2-(trifluoromethyl)-1-alkenes with 2,2'-diceriobiaryls generated the intermediary 1,1-difluoro-1-alkenes bearing a monoceriobiaryl moiety, which in turn underwent intramolecular S<sub>N</sub>V reaction to afford fluorinated 5*H*-dibenzo[*a,c*][7]annulenes.



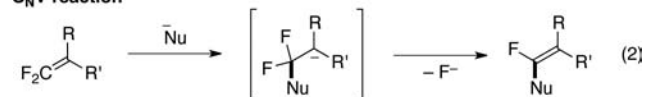
Carbon–fluorine (C–F) bonds are generally considered to be difficult to cleave because of their high bond energy,<sup>1</sup> whereas 2-(trifluoromethyl)-1-alkenes and 1,1-difluoro-1-alkenes exhibit unique reactivities in defluorinative addition–elimination processes. Nucleophilic attack to 2-(trifluoromethyl)-1-alkenes typically proceeds at the carbon atom  $\gamma$  to the fluorine substituents and is followed by fluoride elimination to afford 1,1-difluoro-1-alkenes (S<sub>N</sub>2'-type reaction, Scheme 1, eq

**Scheme 1.** Allylic and Vinylic C–F Bond Activation in S<sub>N</sub>2'-Type and S<sub>N</sub>V Reactions

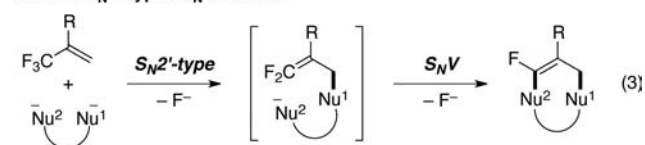
**S<sub>N</sub>2'-type reaction**



**S<sub>N</sub>V reaction**



**Domino S<sub>N</sub>2'-type / S<sub>N</sub>V reaction**



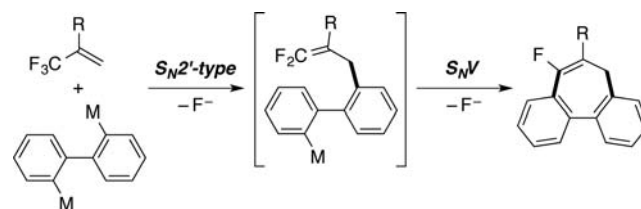
1).<sup>1,2</sup> On the other hand, 1,1-difluoro-1-alkenes are susceptible to nucleophilic substitution at the carbon atom  $\alpha$  to the fluorine substituents to give monofluoroalkenes (S<sub>N</sub>V reaction, Scheme 1, eq 2).<sup>1,3</sup>

Thus, appropriate choice of binucleophiles enables straightforward ring construction via double activation of C–F bonds by the sequential S<sub>N</sub>2'-type/S<sub>N</sub>V process (Scheme 1, eq 3). This protocol enables selective activation of two C–F bonds in

a CF<sub>3</sub> group and retention of one C–F bond, which has long been considered troublesome because of the shielding effect of the CF<sub>3</sub> group.<sup>4</sup> In fact, we have reported 2-fluoroquinoline synthesis from 2-(trifluoromethyl)-1-alkenes via the S<sub>N</sub>2'-type/S<sub>N</sub>V sequence, initiated by treatment with *ortho*-lithiated aniline derivatives.<sup>5</sup> Similarly, we have also achieved 3-fluoropyrazole synthesis via the formal [3 + 2]-cyclization between 2-(trifluoromethyl)-1-alkenes and hydrazines, in which the ring closure was not completed by a simple S<sub>N</sub>V reaction.<sup>6</sup> Most recently, following our results, Xiao and Zhang et al. reported a one-pot synthesis of 2-fluoro-4*H*-pyrans in which 1,3-dicarbonyl compounds were used as binucleophiles in the presence of K<sub>2</sub>CO<sub>3</sub>.<sup>7</sup>

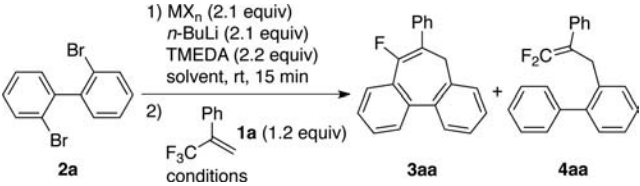
To take full advantage of the sequence, we embarked on the construction of seven-membered carbocycles by using binucleophiles containing two carbanion moieties (Scheme 2). As a result, we succeeded in a one-pot synthesis of 7-fluoro-5*H*-dibenzo[*a,c*][7]annulenes<sup>8</sup> by treatment of 2-(trifluoromethyl)-1-alkenes with 2,2'-dimetallobiaryls.<sup>9</sup> The cycloheptatriene core is widely used in bioactive agents<sup>10</sup> and functional materials.<sup>11</sup> In spite of their utility, their conventional synthetic methods typically required harsh conditions, expensive

**Scheme 2.** Seven-Membered Carbocycle Construction via Domino S<sub>N</sub>2'-Type/S<sub>N</sub>V Reactions



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Table 1. Screening of Conditions for Domino  $S_N2'$ -Type/ $S_NV$  Reaction between **1a** and **2a**


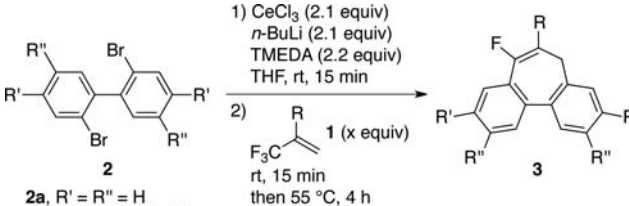
entry	MXn	solvent	conditions	3aa <sup>a</sup> (%)	4aa <sup>a</sup> (%)
1		THF	55 °C, 4 h	58	27
2	MgBr <sub>2</sub>	THF	55 °C, 4 h	ND <sup>b</sup>	ND <sup>b</sup>
3	ZnCl <sub>2</sub>	THF	55 °C, 4 h	N.D. <sup>b</sup>	ND <sup>b</sup>
4	CuBr	THF	55 °C, 4 h	ND <sup>b</sup>	ND <sup>b</sup>
5	CeCl <sub>3</sub>	THF	55 °C, 4 h	82	7
6	CeCl <sub>3</sub>	Et <sub>2</sub> O	40 °C, 5 h	71	16
7	CeCl <sub>3</sub>	1,4-dioxane	55 °C, 6 h	29	22
8	CeCl <sub>3</sub>	THF	−78 °C, 15 min then 55 °C, 4 h	40	trace
9	CeCl <sub>3</sub>	THF	0 °C, 15 min then 55 °C, 4 h	37	12
10	CeCl <sub>3</sub>	THF	rt, 15 min then 55 °C, 4 h	91 (90)	6

<sup>a</sup>Yield was determined by <sup>19</sup>F NMR measurement using PhCF<sub>3</sub> as an internal standard. Isolated yield is given in parentheses. <sup>b</sup>ND = not detected.

reagents, and/or multiple steps.<sup>8</sup> In contrast, our approach enables a short-step synthesis of dibenzo[7]annulenes by using readily available substrates and reagents.

First, we sought suitable conditions for the domino  $S_N2'$ -type/ $S_NV$  reaction using  $\alpha$ -(trifluoromethyl)styrene (**1a**) and 2,2'-dibromobiphenyl (**2a**) as model substrates (Table 1). Dibromobiphenyl **2a** was treated with 2.1 equiv of *n*-BuLi and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) in THF at room temperature for 15 min. Then, the mixture was reacted with (trifluoromethyl)styrene **1a** at 55 °C for 4 h to give dibenzo[7]annulene **3aa** in 58% yield, as well as difluoroalkene **4aa**, formed only by the  $S_N2'$ -type reaction, in 27% yield (entry 1). To improve the reactivities of the intermediary di- and monometallobiphenyls, several other metallic species were examined (entries 2–5). When MgBr<sub>2</sub>, ZnCl<sub>2</sub>, or CuBr was employed for transmetalation, the reaction was seriously inhibited (entries 2–4). However, the use of CeCl<sub>3</sub>, which would generate 2,2'-diceribiphenyl, drastically promoted the domino  $S_N2'$ -type/ $S_NV$  reaction to afford **3aa** in 82% yield, suppressing the formation of **4aa** (entry 5).<sup>12</sup> Since cerium reagents generally exhibit reduced basicity along with substantial nucleophilicity, the reaction of 2,2'-diceribiphenyl with **1a** seems to proceed as expected, suppressing deprotonation of the solvent. Although the solvent effects of other ether solvents, such as diethyl ether and 1,4-dioxane, were examined, THF served as the best medium (entries 6 and 7). For further improvement in the yield of **3aa**, we changed the temperature at the initial stage of the reaction between **1a** and the diceribiphenyl, as that is less stable to heating (entries 8–10). After addition of **1a**, stirring at −78 or 0 °C for 15 min followed by raising the temperature to 55 °C retarded the reaction (entries 8 and 9). Finally, when the temperature was kept at room temperature for 15 min to consume the diceribiphenyl and then raised to 55 °C, **3aa** was obtained in 90% isolated yield (entry 10).

With the optimized conditions in hand, we have investigated the scope of 2-(trifluoromethyl)-1-alkenes **1** and 2,2'-dibromobiphenyls **2** (Table 2). Trifluoromethylstyrenes **1b** and **1c**, bearing a methyl group on the phenyl group, effectively underwent the domino reaction with the in situ generated diceribiphenyl derived from **2a**, regardless of the position of

Table 2. Synthesis of Dibenzo[7]annulenes **3**


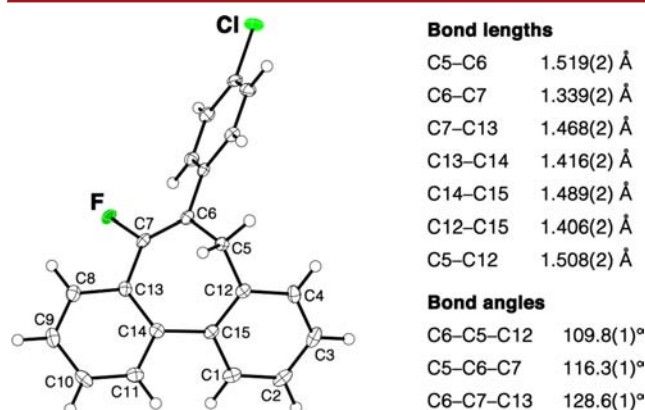
entry	1, R	x (equiv)	2	3 (yield, <sup>a</sup> %)
1	<b>1a</b> , Ph	1.2	<b>2a</b>	<b>3aa</b> (90)
2	<b>1b</b> , 4-MeC <sub>6</sub> H <sub>5</sub>	1.3	<b>2a</b>	<b>3ba</b> (77)
3	<b>1c</b> , 3-MeC <sub>6</sub> H <sub>5</sub>	1.2	<b>2a</b>	<b>3ca</b> (72)
4	<b>1d</b> , 4-FC <sub>6</sub> H <sub>5</sub>	1.2	<b>2a</b>	<b>3da</b> (78)
5	<b>1e</b> , 3-FC <sub>6</sub> H <sub>5</sub>	1.4	<b>2a</b>	<b>3ea</b> (80)
6	<b>1f</b> , 4-ClC <sub>6</sub> H <sub>5</sub>	1.1	<b>2a</b>	<b>3fa</b> (83)
7	<b>1g</b> , 3-ClC <sub>6</sub> H <sub>5</sub>	1.4	<b>2a</b>	<b>3ga</b> (80)
8 <sup>b</sup>	<b>1h</b> , 4-MeOC <sub>6</sub> H <sub>5</sub>	1.0	<b>2a</b>	<b>3ha</b> (44)
9 <sup>b</sup>	<b>1i</b> , 3-MeOC <sub>6</sub> H <sub>5</sub>	1.2	<b>2a</b>	<b>3ia</b> (44)
10 <sup>b</sup>	<b>1j</b> , 4-CF <sub>3</sub> C <sub>6</sub> H <sub>5</sub>	1.2	<b>2a</b>	<b>3ja</b> (57)
11 <sup>b</sup>	<b>1k</b> , SiMe <sub>2</sub> Ph	1.4	<b>2a</b>	<b>3ka</b> (79)
12	<b>1a</b> , Ph	1.2	<b>2b</b>	<b>3ab</b> (80)
13 <sup>b</sup>	<b>1k</b> , SiMe <sub>2</sub> Ph	1.4	<b>2b</b>	<b>3kb</b> (72)
14	<b>1a</b> , Ph	1.2	<b>2c</b>	<b>3ac</b> (80)
15 <sup>b</sup>	<b>1k</b> , SiMe <sub>2</sub> Ph	2.0	<b>2c</b>	<b>3kc</b> (70)

<sup>a</sup>Isolated yield. <sup>b</sup>BF<sub>3</sub>·OEt<sub>2</sub> (2.0 equiv) was added 5 min after addition of **1**. After being stirred at room temperature for 10 min, the mixture was heated to 55 °C.

the substituent, leading to the corresponding dibenzo[7]-annulenes **3ba** and **3ca** in 77% and 72% yields, respectively (entries 2 and 3). Reactions of (trifluoromethyl)styrenes **1d–g** bearing a fluorine or chlorine substituent also proceeded without loss of the C–F or C–Cl bond on the benzene ring (entries 4–7). Methoxy-bearing (trifluoromethyl)styrenes **1h** and **1i**, (trifluoromethyl)styrene **1j** bearing another CF<sub>3</sub> group, and 2-silylated trifluoropropene **1k** participated in the reaction with the aid of BF<sub>3</sub>·Et<sub>2</sub>O (entries 8–11). Not only **2a** but also di-*tert*-butylated and tetramethylated biphenyls **2b** and **2c** underwent diceriation followed by the domino  $S_N2'$ -type/ $S_NV$

reaction with (trifluoromethyl)alkenes **1a** and **1k** to afford the corresponding dibenzo[7]annulenes **3ab**, **3kb**, **3ac**, and **3kc** in high yields (entries 12–15).

Unambiguous structural characterization of dibenzo[7]-annulenes **3** was achieved by X-ray crystallographic analysis of **3fa** (Figure 1). The bond lengths of C5–C6 and C6–C7 are

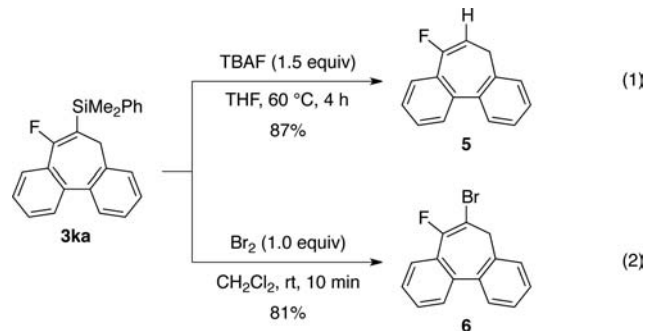


**Figure 1.** ORTEP drawing of dibenzo[7]annulene **3fa** with 50% ellipsoid probability.

1.519(2) and 1.339(2) Å, respectively. Moreover, the bond angles of C6–C5–C12, C5–C6–C7, and C6–C7–C13 are 109.8(1)°, 116.3(1)°, and 128.6(1)°, respectively. These data indicate that the hybridization modes of C5, C6, and C7 are  $sp^3$ ,  $sp^2$ , and  $sp^2$ , respectively, and C6–C7 is a double bond. Thus, in the domino  $S_N2'$ -type/ $S_NV$  reaction of trifluoromethylalkenes **1** with diceriobiaryls, the latter  $S_NV$  reaction proceeded without migration of C–C double bonds.

Further transformations of dibenzo[7]annulene **3ka** bearing a silyl group were achieved by treatment with electrophiles (Scheme 3, eqs 1 and 2). Desilylation of **3ka** proceeded by

**Scheme 3.** Chemical Transformation of **3ka**



addition of tetrabutylammonium fluoride in THF to afford protodesilylation product **5** in 87% yield (Scheme 3, eq 1). In addition, **3ka** also underwent electrophilic substitution with  $Br_2$  in  $CH_2Cl_2$  to give brominated dibenzo[7]annulene **6** in 81% yield (Scheme 3, eq 2). Bromo[7]annulene **6** serves as a platform for further functionalized cycloheptatrienes via transition-metal-catalyzed coupling reactions.

In conclusion, we have established a one-pot synthesis of fluorinated dibenzo[7]annulenes that involves sequential activation of two C–F bonds of the  $CF_3$  group in 2-(trifluoromethyl)-1-alkenes. Our current protocol provides ready access to valuable cycloheptatriene derivatives. Further-

more, the obtained fluorine-containing dibenzo[7]annulenes are less accessible by other methods.<sup>13</sup>

## ■ ASSOCIATED CONTENT

### § Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03743.

Experimental details, characterization data, and NMR spectra (PDF)

X-ray crystallographic data of **3fa** (CIF)

## ■ AUTHOR INFORMATION

### Corresponding Author

\*E-mail: junji@chem.tsukuba.ac.jp.

### ORCID

Junji Ichikawa: 0000-0001-6498-326X

### Notes

The authors declare no competing financial interest.

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