One-Electron Reductive Cleavage of the C–Cl Bond of $ArCF_2Cl$: Convenient Route for the Synthesis of $ArCF_2$ Derivatives

Masato Yoshida,* Ayako Morishima, Daiki Suzuki, Masahiko Iyoda, Kozo Aoki,† and Shigeru Ikuta†

Department of Chemistry, Faculty of Science, Tokyo Metropolitan University, Hachioji, Tokyo 192-03

†Computer Center, Tokyo Metropolitan University, Hachioji, Tokyo 192-03

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When $ArCF_2Cl$ was reacted with PhSeNa in DMF in the presence of light, it was found that a $S_{RN}1$ type reaction occurred to give $ArCF_2SePh$. As the reaction did not proceed without light, the substitution reaction should be initiated by photo-induced electron transfer from $PhSe^-$ to $ArCF_2Cl$. The cleavage of the C–Cl bond of $PhCF_2Cl$ by one-electron reduction with samarium(II) iodide to give a $PhCF_2$ radical and chloride ion was also observed. The $PhCF_2$ radical, thus formed, was trapped by styrene and phenylacetylene before it was reduced to $PhCF_2$ anion. UHF/3-21G calculation demonstrated that one-electron reduction in $PhCF_2Cl$ led the spontaneous dissociation of the C–Cl bond to the $PhCF_2$ radical and Cl^-, but the $PhCF_3$ radical anion existed as a stable form.

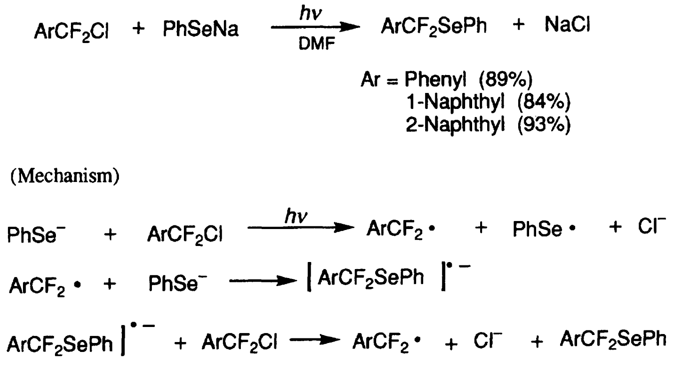
Recently, the molecules bearing a *gem*-difluoromethylene group($-CF_2-$) have attracted much interest, because the replacement of $-CH_2-$ to $-CF_2-$ brings about dramatic changes in the physical, chemical, and biological properties of the parent molecules.[1] However, convenient methods for the preparation of these molecules are limited,[2] and the development of such methodology is still an important and challenging target for organic chemists. Since there are many $ArCH_2$ branched natural and biological active compounds, a development of a convenient route for the synthesis of $ArCF_2$ derivatives is especially interesting. As a precursor for the synthesis of $ArCF_2$ derivatives, $ArCF_3$ is inconvenient due to the strong C–F bond, and little is known about the routes from $ArCF_3$; the C–F bond is too stable to replace the fluorine with other functional groups.[3] The carbon–chlorine bond is predicted to be more reactive than the C–F bond, and $ArCF_2Cl$ is, accordingly, expected to be a useful precursor for the synthesis of $ArCF_2$ derivatives. We have been exploring the chlorodifluoromethylation of aromatic rings with bis(chlorodifluoroacetyl) peroxide and successive conversion of the chlorine into other functional groups.[4] In our previous paper, we reported that the chlorine atom of $ArCF_2Cl$ was readily replaced by a hydrogen or allyl group under radical conditions.[4] We have now explored the reductive cleavage of the C–Cl bond of $ArCF_2Cl$ by a one-electron reducing agent such as $PhSe^-$ and samarium(II) iodide (SmI_2), and the results are described in this paper with theoretical considerations using ab initio molecular orbital calculation.

Results and Discussion

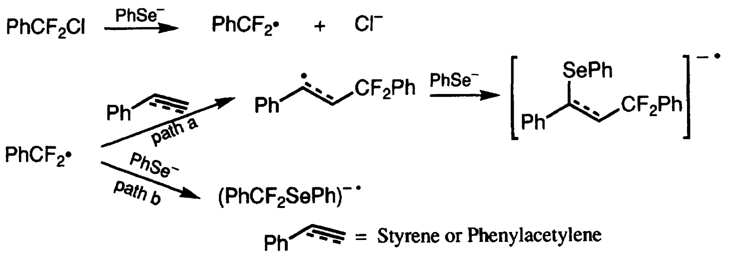
It is known that the C–Cl bond in chlorofluorocarbons is usually inert to normal nucleophilic attack due to the strong electron-withdrawing power of fluorine. The atomic charge of Cl in $PhCF_2Cl$ was calculated by UHF/3-21G to be -0.0137; this means that the C–Cl bond in $PhCF_2Cl$ is little polarized and therefore nonreactive to nucleophilic attack. In fact, $PhCF_2Cl$ was found to be resistant to the usual nucleophiles, such as alkyllithium and alkylmagnesium halide. However, the replacement of the chlorine of $ArCF_2Cl$ with $PhSe^-$ was observed in the reaction of $PhCF_2Cl$ with PhSeNa. As the reaction did not proceed without light, the substitution reaction is probably initiated by a photo-induced electron transfer from $PhSe^-$ to $ArCF_2Cl$ as shown in Scheme 1. In this reaction, $PhSe^-$ did not act as a nucleophile but as a one-electron reducing agent. PhS^- and $PhSe^-$ have been reported to act as a one-electron reducing agent in the $S_{RN}1$ type reactions of halofluoro compounds.[5,6]

Thus, the C–Cl bond of $ArCF_2Cl$ was found to be readily dissociated by one-electron reduction to give a $ArCF_2$ radical and chloride ion.[7] Uneyama et al. have reported perfluoroalkyl-chalcogenations (sulfenylation, selenenylation, and tellurenylation) of olefins and acetylenes by the reaction of PhX^-($X = S$, Se, and Te) with perfluoroalkyl halide. The reaction is initiated by a one-electron transfer from PhX^- to perfluoroalkyl halide to give a perfluoroalkyl radical followed by a radical chain reaction via addition to olefin or acetylene.[8] We therefore investigated the reaction of $PhCF_2Cl$ with PhSeNa in the presence of styrene or phenylacetylene to introduce the $PhCF_2$ unit into an unsaturated bond. However, the desired adduct of $PhCF_2$ and PhSe to styrene was not obtained but only $PhSeCF_2Ph$ was produced; this means that the $PhCF_2$ radical reacted with $PhSe^-$ (path b in Scheme 2) prior to styrene and phenylacetylene (path a in Scheme 2).

Samarium(II) iodide (SmI_2) was investigated as an alternative agent for one-electron reduction of $PhCF_2Cl$. SmI_2 has recently attracted much attention as a very useful and facile one-electron reducing reagent[9] and already been used



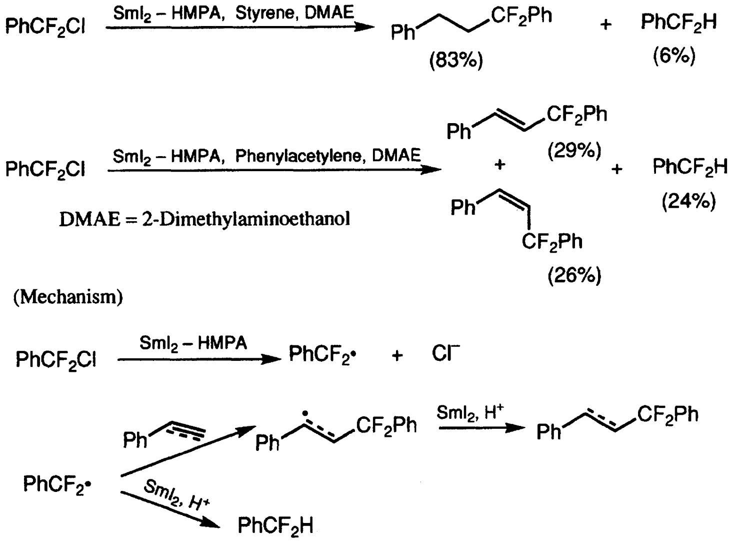
Scheme 1.



Scheme 2.

as a catalyst to promote the radical addition of perfluoroalkyl iodide to olefins and acetylenes.[10] $PhCF_2Cl$ underwent one-electron reduction with SmI_2 in the presence of HMPA to give the $PhCF_2$ radical and chloride ion, and the resulting $PhCF_2$ radical was trapped by styrene and phenylacetylene (Scheme 3).[11] 2-Dimethylaminoethanol (DMAE) was added as a proton source; in the absence of a proton source the yield of the adduct was very low and considerable amounts of polymeric compounds were produced. When a radical trapping reagent did not exist in the reaction system, $PhCF_2H$ was obtained as a sole product. In the presence of CH_3OD, $PhCF_2D$ was obtained almost selectively. This means that the reduction proceeds on the ionic path; the $PhCF_2$ radical is further reduced with SmI_2 to a $PhCF_2$ anionic species (Scheme 3).

UHF/3-21G calculation demonstrated that reduction in $PhCF_2Cl$ led the spontaneous and selective dissociation of the C–Cl bond to the $PhCF_2$ radical and Cl^- (Fig. 1). The selective reduction of the C–Cl bond in $PhCF_2Cl$ has also been indicated by an electrochemical study using cyclic voltammetry; the difference in reduction potential between that of the C–Cl bond and that of the C–F bond was reported to be about 0.7 V, sufficiently for a selective reduction.[7] On the contrary, benzylidyne trifluoride ($PhCF_3$) did not undergo one-electron reductive cleavage of the C–F bond with either $PhSe^-$ or SmI_2, and UHF/3-21G calculation also indicated that the $PhCF_3$ radical anion existed as a stable form without



Scheme 3.

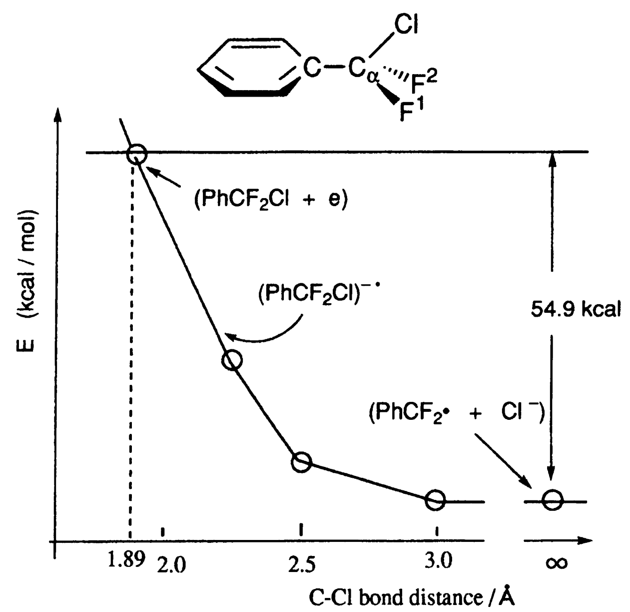
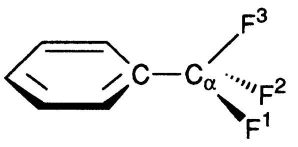


Fig. 1. Energy diagram for dissociation of $PhCF_2Cl$ radical anion calculated by UHF/3-21G; C–Cl bond distance is fixed and the other internal coordinates (bond distance, angle, and dihedral angle) are optimized for each of a series of specified C–Cl bond distances.



	neutral molecule	radical anion
C-F¹ (Å)	1.352	1.377
C-F² (Å)	1.352	1.377
C-F³ (Å)	1.355	1.406
$\angle CC_\alpha F^3$ (deg)	112.9	118.4

$E_{HF}\{(PhCF_3)^{-\bullet}\} = -563.1695$ (Hartrees)

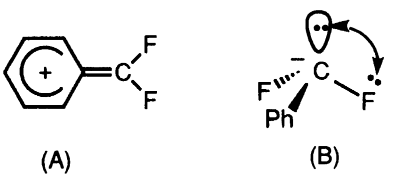
$E_{HF}(PhCF_2\bullet) + E_{HF}(F^-) = -563.0567$ (Hartrees)

Fig. 2. UHF/3-21G optimized structures of $PhCF_3$ and its radical anion.

the C–F bond dissociation (Fig. 2).

It is interesting to note that the optimized structure of the $PhCF_2$ radical is nonplanar. The optimized structures of the $PhCF_2$ radical, cation, and anion, and those of $PhCH_2$ calculated by UHF/3-21G are shown in Fig. 3.

The $PhCH_2$ radical, cation, and anion have planar structures and are stabilized by delocalization of non-bonding orbitals to the benzene ring. However, in the series of $PhCF_2$, calculated structures of the radical and anion were nonplanar. The $PhCF_2$ cation is stabilized by resonance effect with a benzene ring as shown in Scheme 4 (A); meanwhile, in the $PhCF_2$ anion, repulsion between the anionic charge on the benzylic carbon and the lone-pair of fluorine (Scheme 4 (B)) leads the structure to a nonplanar form. The long carbon-fluorine bond (1.45 Å) in the $PhCF_2$ anion reflects the contribution of the repulsion. In the $PhCF_2$ radical, the repulsion of the unpaired electron for the lone pair of fluorines also predominates, thus leading to a nonplanar structure, though the effect is less than in $PhCF_2$ anion. As the unpaired electron is localized on the benzylic carbon, the reactivity of the $PhCF_2$ radical is predicted to be higher than that of the $PhCH_2$ radical where the unpaired electron is delocalized to the benzene ring. In fact, the $ArCF_2$ radical was experimentally shown in our previous work to be moderately reactive and useful for the synthesis of $ArCF_2$ derivatives.[5]



Scheme 4.

Thus, in this study, the importance of one-electron reduction of the C–Cl bond of $ArCF_2Cl$ as a convenient route for the synthesis of $ArCF_2$ derivatives is shown experimentally and theoretically.

Experimental

Melting points were measured with Yanaco MP-500D melting point apparatus, and are uncorrected. ^1H, ^{13}C, and ^{19}F NMR spectra were taken with a JEOL JNM EX400 (400 MHz ^1H, 100 MHz ^{13}C, and 376 MHz ^{19}F NMR) spectrometer. Fluorine chemical shifts are given in ppm from external CF_3CO_2H. Mass spectra were obtained with a JEOL JMS AX-505W spectrometer with a JEOL JMA 5000 mass data system using an electron-impact (EI) ionization technique at 70 eV. Gel-permeation chromatography (GPC) was done with a JAI model LC-908 liquid chromatograph with two JAIGEL-1H columns (20 mm×600 mm) with chloroform as eluent. Standard ab initio molecular orbital calculations were done with the GAUSSIAN 90 program[12] using IBM 3090/30J Computer.

Materials. $PhCF_2Cl$ was prepared by the reaction of benzene with bis(clorodifluoroacetyl) peroxide as described in our previous paper.[4] 1-(Chlorodifluoromethyl)- and 2-(chlorodifluoromethyl)naphthalenes were obtained by the reaction of naphthalene with bis(chlorodifluoroacetyl) peroxide, and the respective isomers were separated by GPC.[4] Diphenyl diselenide was available from Nacalai Tesque, Inc. and recrystallized from hexane before use. Samarium(II) iodide (SmI_2) was used as a THF solution (0.1 mol dm^{-3}); it was synthesized from samarium powder by the reaction with I_2 in THF under nitrogen according to the literature,[13] or obtained from Aldrich Co., Ltd., as a THF solution (0.1 mol dm^{-3}). The concentration of SmI_2 was measured by iodometry before use as described in the literature.[13]

Reaction of $ArCF_2Cl$ with $PhSe^-$. Diphenyl diselenide (0.4 mmol) was treated with $NaBH_4$ (1.2 mmol) in ethanol (0.2 cm^3) at room temperature under nitrogen to give PhSeNa, and then $PhCF_2Cl$ (0.4 mmol) in DMF (3 cm^3) was added. The resulting solution was allowed to react at 100 °C under visible light. The reaction mixture was worked up with water (25 cm^3), and organic products were extracted with ether (20 cm^3×2). The combined organic layer was washed with water, and then dried over $MgSO_4$. After removal of the ether, the residue was purified by GPC to give $PhCF_2SePh$.

$PhCF_2SePh$: Colorless crystals (from hexane); mp 75.4—

76.1 °C; ^{1}H NMR ($CDCl_3$) $\delta = 7.22$—7.66 (m, 10H); ^{13}C NMR ($CDCl_3$) $\delta = 122.40$ (t, $J_{CF} = 289$ Hz), 125.00, 125.75, 128.27, 129.11, 129.48, 130.38, 136.94 (t, $J_{CCF} = 20.1$ Hz), 137.16; ^{19}F NMR ($CDCl_3$) $\delta = 5.4$; MS *m/z* 284 (M^+ for ^{80}Se), 157, 128. Found: C, 55.30; H, 3.40%. Calcd for $C_{13}H_{10}F_5Se$: C, 55.14; H, 3.56%.

Similarly, the reactions of 1-(chlorodifluoromethyl)naphthalene and 2-(chlorodifluoromethyl)naphthalene with PhSeNa in DMF were done.

PhSeCF₂Np-1: Colorless crystals (from hexane); mp 75.0—76.0 °C; ^{1}H NMR ($CDCl_3$) $\delta = 7.29$ (m, 2H), 7.38 (m, 2H), 7.52—7.65 (m, 5H), 7.89 (m, 2H), 8.56 (d, $J = 8.3$ Hz, 1H); ^{13}C NMR ($CDCl_3$) $\delta = 123.92$ (t, $J_{CCCF} = 8.3$ Hz), 124.19 (2C), 125.55, 125.77 (t, $J_{CF} = 286.7$ Hz), 126.08, 126.17, 128.64, 128.91, 129.00, 129.41, 131.56, 131.84 (t, $J_{CCF} = 20.1$ Hz), 134.01, 137.12; ^{19}F NMR ($CDCl_3$) $\delta = 8.8$; MS *m/z* 334 (M^+ for ^{80}Se), 178, 128. Found: C, 61.25; H, 3.56%. Calcd for $C_{17}H_{12}F_2Se$: C, 61.27; H, 3.62%.

PhSeCF₂Np-2: Colorless crystals (from hexane); mp 127.6—130.0 °C; ^{1}H NMR ($CDCl_3$) $\delta = 7.28$—7.49 (m, 2H), 7.38 (m, 1H), 7.49—7.67 (m, 5H), 7.79—7.91 (m, 4H); ^{13}C NMR $\delta = 122.00$ (t, $J_{CCCF} = 3.7$ Hz), 124.47 (t, $J_{CF} = 294.4$ Hz), 124.80 (t, $J_{CCCF} = 5.5$ Hz), 125.79, 126.79, 127.45, 127.74, 128.33, 128.75, 129.08, 129.39, 132.22, 133.89, 134.05 (t, $J_{CCF} = 23.8$ Hz), 137.12; ^{19}F NMR ($CDCl_3$) $\delta = 5.5$; MS *m/z* 334 (M^+), 178, 157, 127. Found: C, 61.09; H, 3.39%. Calcd for $C_{17}H_{12}F_2Se$: C, 61.27; H, 3.62%.

Reaction of PhCF₂Cl with SmI₂ in the Presence of Styrene and Phenylacetylene. To a solution of $PhCF_2Cl$ in benzene (0.15 mol dm^{-3}) in the presence of HMPA (3 mol amt. to SmI_2), 2-PrOH, and styrene (25 mol amt. to $PhCF_2Cl$), a THF solution of SmI_2 (3—4 mol amt. to $PhCF_2Cl$) was added at room temperature under nitrogen. The reaction completed at once. $PhCF_3$ was added to the reaction mixture as an internal standard, and the yields of the products were measured by ^{19}F NMR; $PhCF_2Cl$ was completely consumed under these conditions, and the production of $PhCF_2CH_2CH_2Ph$ and $PhCF_2H$ was recognized. However, $PhCF_2Cl$ remained when a theoretical amount of SmI_2 (2 mol amt. to $PhCF_2Cl$) was used, and excess SmI_2 was required to consume $PhCF_2Cl$ completely. After the workup with aq-HCl (1 mol dm^{-3}), organic products were extracted with ether (3 × 10 cm^3), and the combined organic layer was washed with water. The solution was dried over $MgSO_4$, and then the solvent was removed. The purification of the residue by GPC gave pure $PhCF_2CH_2CH_2Ph$.

PhCF₂CH₂CH₂Ph: Colorless oil; ^{1}H NMR ($CDCl_3$) $\delta =$ 2.37—2.45 (m, 2H), 2.78 (t, $J = 8.3$ Hz, 2H), 7.15—7.20 (m, 2H), 7.25—7.29 (m, 2H), 7.42—7.45 (m, 3H), 7.49—7.52 (m, 2H); ^{13}C NMR ($CDCl_3$) $\delta = 28.77$, 40.95 (t, $J_{CCF} = 27.6$ Hz), 124.93, 126.19, 128.23, 128.46, 128.97, 129.74, 137.16, 140.43; ^{19}F NMR ($CDCl_3$) $\delta = -20.8$; MS *m/z* 232 (M^+), 127, 105. Exact MS: Found: *m/z* 232.1054. Calcd for $C_{15}H_{14}F_2$: 232.1063.

Similarly, the reaction in the presence of phenylacetylene was done. *E* and *Z* isomers of the adducts were separated by GPC.

***E*-PhCH=CHCF₂Ph:** Colorless oil; ^{1}H NMR ($CDCl_3$) $\delta = 6.44$ (d, t $J_{HH} = 16.1$ Hz, $J_{HF} = 9.8$ Hz, 1H), 6.82 (d, $J = 16.1$ Hz, 1H), 7.28—7.60 (m, 10H); ^{13}C NMR ($CDCl_3$) $\delta = 119.96$ (t, $J_{CF} = 239$ Hz), 124.29, (t, $J_{CCF} = 29.4$ Hz), 125.52, 127.20, 128.44, 128.72, 129.05, 129.91, 134.28, 134.74, 136.66; ^{19}F NMR ($CDCl_3$) $\delta = -15.6$; MS *m/z* 127 (M^+), 103. Exact MS: Found: *m/z* 230.0872. Calcd for $C_{15}H_{12}F_2$: M, 230.0907.

***Z*-PhCH=CHCF₂Ph:** Colorless oil; ^{1}H NMR ($CDCl_3$) $\delta = 6.01$ (q, $J_{HH} = J_{HF} = 12.7$ Hz, 1H), 6.83 (d, $J_{HH} = 12.7$ Hz, 1H), 7.25—7.55 (m, 10H); ^{13}C NMR ($CDCl_3$) $\delta = 119.36$ (t, $J_{CF} = 238$ Hz), 125.44, 125.96 (t, $J_{CCF} = 29.4$ Hz), 127.80, 128.33, 129.10, 129.87, 134.92, 136.07, 137.17; ^{19}F NMR ($CDCl_3$) $\delta = -7.3$.

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	Cation	Radical	Anion
θ (deg.)	0	20.1	65.5
∠FC$_\alpha$F (deg.)	112.6	112.1	103.2
C$_\alpha$-F (Å)	1.29	1.34	1.45
C$_\alpha$-C (Å)	1.36	1.40	1.49

	Cation	Radical	Anion
θ (deg.)	0	0	0
∠HC$_\alpha$H (deg.)	116.9	117.8	117.1
C$_\alpha$-H (Å)	1.07	1.07	1.08
C$_\alpha$-C (Å)	1.36	1.42	1.39

Fig. 3. Optimized structures for cation, radical, and anion of $PhCX_2$ (X = F and H) calculated by UHF/3-21G.

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