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The First Generation and Stereospecific Alkylation of α-Trifluoromethyl Oxiranyl Anion

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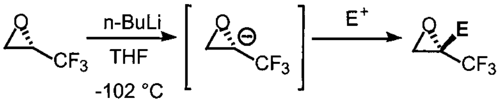
ABSTRACT



Generation and reactions of oxiranyl anion 2 stabilized by a trifluoromethyl group are described. Treatment of (*S*)-2,3-epoxy-1,1,1-trifluoropropane (75% ee) with *n*-BuLi followed by electrophiles gave corresponding 2-alkylated epoxide 3 with retention of stereochemistry in moderate to good yields. The reaction is applicable for a general synthesis of optically active trifluoromethylated tertiary alcohols.

For the past 2 decades, preparations of optically active fluorinated compounds have been the subject of many reported studies.[1] Although many methodologies for the preparation of optically active fluorinated compounds have been developed and reported, there has been no report, to the authors' knowledge, on the preparation and utilization of optically active α-trifluoromethylated carbanions. The problem with the generation and reactions of α-trifluoromethylated carbanions is mainly due to their unstable nature, because the carbanions readily undergo defluorination to the corresponding difluoroolefins.[2] Thus, the previous studies were focused on the prevention of this unwanted defluorination of the delicate carbanions.

To date, some successful preparation of α-trifluoromethylated carbanions, avoiding unwanted defluorinations, has been reported (Scheme 1). The first category of the α-trifluoromethylated carbanion is the preparation of organometallics, where the metal is attached to an sp^2 carbon (**A**),[3] and the second category is the carbanion stabilized by π-conjugation (**B**)[4] or by geminal chlorines (**C**).[5] This

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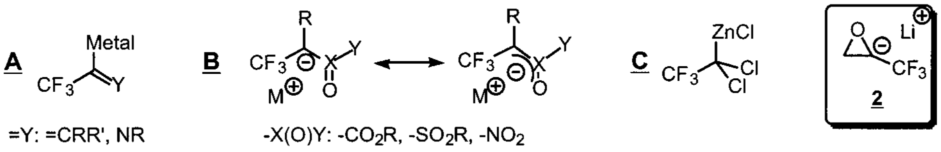
Scheme 1



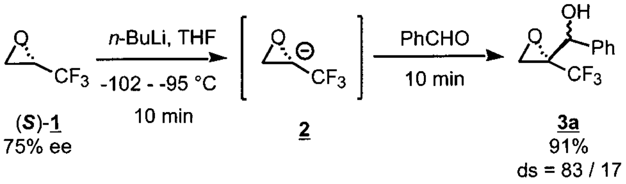
categorization implies that the α-trifluoromethylated carbanion centers ought to have the sp^2 nature of the carbon orbital or the chlorine atoms' field effects in stabilizing the carbanions. In the second case, the carbanion would have the lone pair electrons in the p-orbital or sp^3-orbital and thus could be alkylated stereospecifically. However, there has been no report on the stereospecific alkylation of α-trifluoromethylated carbanion, which would be potentially useful for the synthesis of optically active trifluoromethylated compounds.

In the present study we considered that a utilization of oxiranyl moiety would stabilize the α-trifluoromethylated carbanion. Oxiranyl anion has been known as a reactive species prepared from epoxide with a strong base, and the anion has conformationally restricted sp^3-like carbon.[6] Thus the trifluoromethylated oxiranyl anion **2** could be a stereochemically stable α-trifluoromethylated carbanion.

To date, many oxiranyl anions with various anion-stabilizing groups have been reported.[7] However, there has been no report on the oxiranyl anion with a trifluoromethyl group. Those reported oxiranyl anions have their anion center just at the α-position of the anion stabilizing groups. Of course, the trifluoromethyl group is highly electron-withdrawing so as to induce regioselective generation of α-trifluoromethylated oxiranyl carbanion.

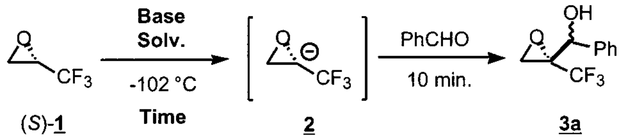
Very fortunately, 2-trifluoromethyl oxirane, 2,3-epoxy-1,1,1-trifluoropropane (TFPO) is a compound with high availability. The compound with 75% ee (*S*) is commercially available; also some laboratory-scale preparations of optically pure TFPO have been reported.[8] Thus, the generation and stereospecific alkylation of optically active oxiranyl anion from optically active TFPO would lead to the general method for preparation of optically active trifluoromethylated *tert*-alcohols, which would be a series of key building blocks for trifluoromethylated compounds with quaternary carbon.

Scheme 2



The typical procedure for generation of oxiranyl anion **2** from (*S*)-TFPO **1** and reaction of **2** with benzaldehyde is illustrated in Scheme 2. Treatment of (*S*)-TFPO **1** with 1.1 equiv of *n*-BuLi in THF at −102 to −95 °C for 10 min led to regioselective generation of trifluoromethylated oxiranyl anion **2**. Then, oxiranyl anion **2** was allowed to react with benzaldehyde at the temperature for 10 min to give corresponding epoxy alcohol **3a** in 91% isolated yield (diastereoselectivity = 83/17). The optical purity of **3a** was found to be 75% ee, which was the same as that of the starting TFPO. This fact suggested that the reaction proceeded without epimerization at the chiral center. Surprisingly, possible side reactions, such as defluorination, Payne rearrangement,[9] or intra-[10] and intermolecular ring openings, did

Table 1. Optimization of the Reaction Conditions, Base, and Solvent



entry[a]	base	solvent	time [min]	yield of **3a**[c] (recovery of **1**)	ds[d]
1	*n*-BuLi	THF	10	99	83/17
2	*n*-BuLi	THF	10	95	81/19
3	LDA	THF	60	87	81/19
4	*t*-BuOK	THF	60	nr[e] (>99)	
5	*n*-BuLi	ether	60	tr (99)	
6	*n*-BuLi	hexane	60	nr[e] (>99)	
7[b]	*n*-BuLi	ether−TMEDA	10	32 (72)	nd[f]
8[b]	*n*-BuLi	hexane−TMEDA	10	40 (37)	69/31
9[b]	*n*-BuLi	THF−HMPA	10	72 (11)	69/31

[a] Compound **1** (1 mmol) with base (1.1 equiv) in dry solvent (5 mL), −102 °C. [b] Additives (1.1 equiv). [c] Yield by ^{19}F NMR. 1,3-Bis(trifluoromethy)benzene was used as internal standard. [d] Diastereoselectivity was determined by ^{19}F NMR. [e] No reaction. [f] Not detected.

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(8) This optically active TFPO (*S*-rich, 75% ee) is commercially available from Japan Energy Corporation. For a recent review on preparation and reaction of optically active TFPO, see: (a) Katagiri, T. *Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemical Challenges and Biomedical Targets*; Soloshonok, V. A., Ed.; John Wiley & Sons: Chichester, 1999; pp 161. Optically pure (*R*)- and (*S*)-TFPO have also been prepared in laboratory scale; see: (b) Von dem Bussche-Hunnefeld, C.; Cescato, C.; Seebach, D. *Chem. Ber.* **1992**, *125*, 2795. (c) Ramachandran, P. V.; Gong, B.; Brown, H. C. *J. Org. Chem.* **1995**, *60*, 41. (d) Shimizu, M.; Sugiyama, K.; Fujisawa, T. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2655. (e) Katagiri, T.; Obara, F. Japan Energy Corp., *Jpn. Kokai Tokkyo Koho JP*06-247953 1994; *Chem. Abstr. 122*, 9847b.

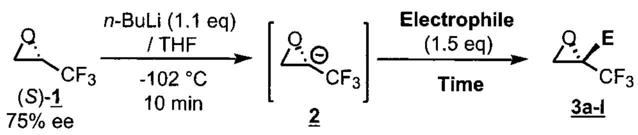
not occur at the temperature. The stability of this oxiranyl anion **2** is, thus, of interest. This carbanion **2** was found to be stable even at −78 °C for 1 h and gave product **3a** in excellent yield, but the anion seemed to start to decompose at around −70 °C, and **3a** was not obtained above −40 °C.

The combination of base and solvent was examined to optimize the yield of **3a**, as shown in Table 1.

Common Li bases such as *n*-BuLi, *s*-BuLi, and LDA gave good results (entries 1−3), while the reaction conducted by ^{t}BuOK resulted in no reaction (entry 4), which could be due to low solubility of the base at the low temperature. Choice of solvent was of critical importance in this reaction. The reaction in THF gave the product almost quantitatively (entry 1). Although ether or hexane solvent did not give product **3a** at all (entries 5 and 6), the addition of TMEDA enabled the reaction even in these solvents (entries 7 and 8); however, the yields remained moderate. Addition of HMPA to THF solvent to stabilize the anion simply resulted in a lower yield of the product and lower diastereoselectivity than that in THF only (entry 9).

The scope of the reaction of oxiranyl anion **2** is summarized in Table 2. The anion **2** reacted smoothly with both aromatic and aliphatic aldehydes to give products in excellent yields (entries 1−4). The reaction with α,*β*-unsaturated aldehyde provided 1,2-adduct in a good yield (entry 5). The reactions of **2** with aromatic and aliphatic ketones also led to excellent yields of products (entries 6−8). Though the reaction with benzoyl chloride or several chloroformates gave unidentified products, the reaction with Weinreb amide gave a corresponding 2-benzoylated oxirane in good yield (entry 9). The reactions of **2** with triarylorganometallic halides led to excellent yields of products (entries 10 and 11). The trifluoromethylated silyl and stannyl oxiranes would be alternative reactive species for further synthetic applications, which will be reported elsewhere. The reaction of **2** with MeI proceeded successfully (Table 2, entry 12 and Scheme 3), although the reactions with other organic halides such as vinyl, allyl, and benzyl have not succeeded yet. Unfortunately, the product **3l** is highly volatile, and thus the **3l** was ring opened by (*S*)-1-phenethylamine to the corresponding amino alcohol **4a**, which was isolated in 75% yield (Scheme 3).

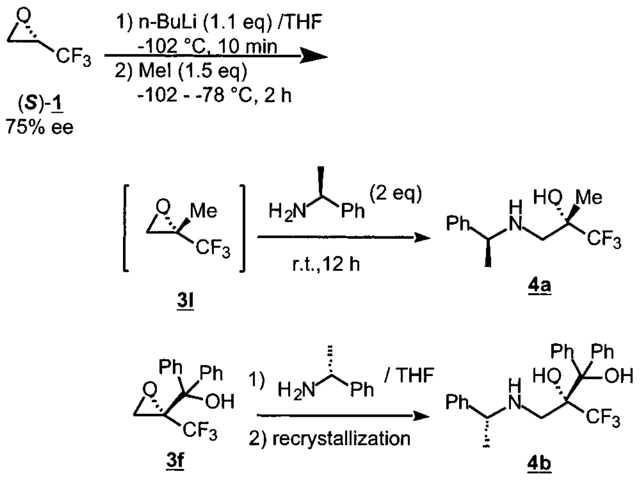
Table 2. Scope of the Reaction of Oxiranyl Anion **2**



entry	eletrophile	time [min]	products (yields [%])[a]	ds[b]
1	PhCHO	10	**3a**, 91	83/17
2	*p*-CNC$_6$H$_4$CHO	10	**3b**, 88	78/22
3	p-CH$_3$OC$_6$H$_4$CHO	10	**3c**, 99	85/15
4	PhCH$_2$CH$_2$CHO	10	**3d**, 85	51/49
5	*trans*-PhCH═CHCHO	10	**3e**, 77	81/19
6	PhCOPh	10	**3f**, 85	
7	CH$_3$COPh	10	**3g**, 78	84/16
8	*tert*-butylcyclohexanone	10	**3h**, 87	*d*
9	PhCON(OMe)Me	10	**3i**, 82	
10	Ph$_3$SiCl	30	**3j**, 70	
11	Ph$_3$SnCl	30	**3k**, 87	
12	CH$_3$I	120[e]	**3l**, [82][f]	

[a] Isolated yield. [b] Diastereoselectivity was determined by ^{19}F NMR and GC analysis. [c] Benzoylated product. [d] Ratio of cis and trans stereoisomer between −OH and −^{t}Bu was 83/17. [e] Temperature was raised from −102 to −78 °C. [f] Conversion of starting material was determined by ^{19}F NMR analysis.

Scheme 3



To confirm the stereochemistry of the product **3f**, we submitted amino alcohol **4b**, which was obtained by the ring opening reaction of **3f** with (*R*)-1-phenethylamine and isolated as the major diastereomer by recrystallizations of diastereo mixture, to X-ray crystallographic analysis. The result of the analysis showed the absolute configuration at α-carbon to the trifluoromethyl group to be *R*; that is, the stereochemistry of the anion center was retained throughout the reaction.[11]

In conclusion, we succeeded in the first generation of α-trifluoromethylated oxiranyl anion. The oxiranyl anion was found to be applicable to the synthesis of a variety of 2-substituted-2-trifluoromethyl oxiranes, which would be general precursors for functionalized trifluoromethylated *tert*-alcohols, of which two examples are shown in Scheme 3. Further synthetic applications of **3** are now in progress.

Acknowledgment. We thank SC-NMR Laboratory of Okayama University for ^{19}F and ^{1}H NMR analyses and the

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(11) Crystallographic data and CIF for compound **4b** have been reported as Supporting Information.

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Supporting Information Available: Full experimental details and characterization data for compounds and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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