

A Facile Approach to 2-CF₃-Substituted Seven-membered Oxacycles via Stereoselective Preparation and Cope Rearrangement of 2-CF₃-*cis*-2,3-Bis(alkenyl)oxiranes

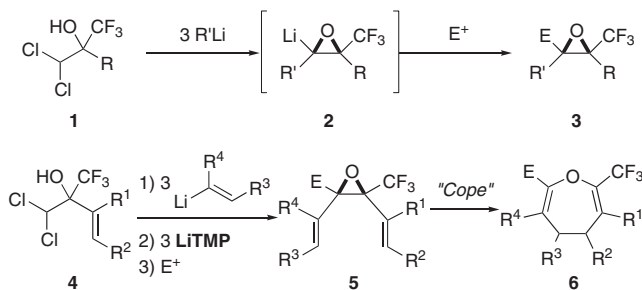
Masaki Shimizu,* Takuya Fujimoto, Xinyu Liu, and Tamejiro Hiyama
 Department of Material Chemistry, Graduate School of Engineering, Kyoto University,
 Katsura Campus, Nishikyo-ku, Kyoto 615-8510

(Received January 6, 2004; CL-040017)

Stereoselective preparation and Cope rearrangement of 2-CF₃-substituted *cis*-2,3-bis(alkenyl)oxiranes provides a convenient route to a diverse of 2-CF₃-4,5-dihydrooxepins. The reaction sequence followed by reduction or oxidation provides 2-CF₃-substituted oxepanes or oxepins, respectively.

Incorporation of a trifluoromethyl group in biologically active compounds can alter chemical properties as well as biological activities of parent compounds, so that trifluoromethylated compounds are of great significance in pharmaceutical and agrochemical research.¹ Meanwhile, much attention is focused on such seven-membered oxacycles as oxepanes and oxepins owing to their occurrence in biologically active natural products.² From such viewpoints, development of facile synthetic methods for CF₃-substituted seven-membered oxacycles, a novel class of CF₃-containing compounds, is of particular interest for exploration of potent biologically active substances.

We have recently reported that CF₃-containing dichlorohydrins **1** (R = aryl, alkyl, alkenyl, alkynyl) react with 3 molar amounts of R'Li (R' = alkyl, aryl, vinyl) at -98 °C to give *cis*-2,3-disubstituted 2-lithio-3-trifluoromethyloxiranes **2**, which react with various electrophiles (E⁺) to give CF₃-containing tri- and tetrasubstituted oxiranes **3** stereoselectively (Scheme 1).³ We envisioned that 2-CF₃-substituted 4,5-dihydrooxepins **6** could be easily prepared if stereoselective preparation of *cis*-bis(alkenyl)oxiranes **5** from alkenyl-substituted dichlorohydrins **4** with alkenyllithiums and subsequent Cope rearrangement were feasible.



Scheme 1. A facile route to 2-CF₃-substituted 4,5-dihydrooxepins **6**.

At first we applied the sequence of operations to synthesis of **5** and found that the original reaction protocol totally failed to give the expected products. Considering the fact that reaction of **4** (R¹ = H, R² = Ph) with BuLi or of **1** (R = C≡CPh) with vinylolithium generated the corresponding lithio-oxirane (**2**), we ascribed the failure to not only lower basicity of vinylolithium but also lower acidity of a methine proton of **4**. After many

screening experiments, use of lithium 2,2,6,6-tetramethylpiperide (LiTMP, 3 molar amounts) in addition to vinylolithium was found highly effective to give rise to the corresponding oxiranyl-lithiums,⁴ which could be trapped with a variety of electrophiles (E⁺) to give **5**. The lithium amide base could deprotonate and vinylolithium could behave as a nucleophile as we expected. The modified procedure was applied to synthesis of various kinds of **5** as summarized in Table 1. Generally, *cis*-**5** was produced as a single diastereomer except for **5e** (*cis/trans* = 92:8), **5i** (89:11), and **5q** (78:22).⁵

Table 1. Preparation of 2-CF₃-*cis*-2,3-bis(alkenyl)oxirane **5**^a

Entry	5	R ¹	R ²	R ³	R ⁴	E	Yield/% ^b
1	5a	H	Ph	H	H	H	77
2	5b	H	Ph	H	H	Me	72
3	5c	H	Ph	H	H	Me ₃ Sn	64
4	5d	H	Ph	H	H	Me ₃ Si	77
5	5e	H	Ph	H	H	MeO ₂ C	70 ^c
6	5f	H	Ph	H	H	(Me ₂ CO) ₂ B	72
7	5g	H	Ph	H	H	Ph ₂ C(OH)	62
8	5h	H	Ph	H	H	TBS	- ^d
9	5i	H	Ph	H	Ph	H	86 ^c
10	5j	H	Ph	H	Ph	Me ₃ Si	75
11	5k	H	H	H	Ph	Me ₃ Si	71
12	5l	Ph	H	H	H	H	80
13	5m	H	H	H	H	PhCH ₂	60
14	5n	H	H	H	H	Me ₃ Sn	56
15	5o	H	H	H	H	TBS	46
16	5p	H	Ph	-(CH ₂) ₃ O-	H	H	25
17	5q	-O(CH ₂) ₃ -	H	H	H	Me ₃ Si	69 ^c

^aTo a solution of an alkenyllithium (3.0 mmol) in THF (5 mL) was added dichlorohydrin **4** (1.0 mmol) at -98 °C and then LiTMP (3.0 mmol, 0.67 M in THF) at -98 °C. The resulting solution was stirred at -98 °C for 3–6 h and then treated with an electrophile [MeOH (entries 1, 9, 12, and 16); MeI (Entry 2); Me₃SnCl (Entries 3 and 14); Me₃SiCl (Entries 4, 10, 11, and 17); CO₂/Me₃SiCHN₂ (Entry 5); (Me₂CO)₂B(OⁱPr) (Entry 6); Ph₂C=O (Entry 7); TBSOTf (Entries 8 and 15); BnBr (Entry 13)] at -98 °C. The solution was warmed gradually to -78 °C before quenching with saturated aqueous NH₄Cl solution. ^bIsolated yields. ^cIsolated yields of a *cis/trans* mixture. ^dProduct **5h** rearranged even at room temperature.

With *cis*-bis(alkenyl)oxiranes **5** in hand, we next studied the Cope rearrangement.⁶ At first, 2-phenylethenyl- and vinyl-substituted oxiranes **5a–h** were selected as a typical model and heated in CCl₄ solutions. The rearrangement of **5a** and **5b** proceeded in high yields at 100 °C in 12 and 8 h, respectively, as shown in Entries 1 and 2 of Table 2. *cis*-Bis(alkenyl)oxiranes **5c–e** with Me₃Sn, Me₃Si, or MeO₂C reacted at lower temperatures in shorter times (Entries 3–5). In case of **5e**, *trans* isomer did not

Table 2. Cope rearrangement of **5a–h**^a

Entry	5	Temp/°C	Time/h	6	Yield/% ^b
1	5a	100	12	6a	93
2	5b	100	8	6b	85
3	5c	80	4	6c	88
4	5d	80	2	6d	92
5	5e	80	2	6e	96 ^[c]
6	5f	60	3	6f	99
7	5g	60	3	6g	95
8	5h	60	2	6h	55 ^[d]

^aA solution of oxirane **5** (0.5 mmol) in CCl₄ (3 mL) was heated in a sealed tube. The progress of the reaction was monitored by ¹⁹F NMR. ^bIsolated yields. ^cIsolated yield based on reacted *cis*-diastereomer of **5**. ^dIsolated yield based on the corresponding dichlorohydrin.

undergo the rearrangement at all under the conditions and was recovered quantitatively. Furthermore, the reaction was markedly accelerated by a large group like (pinacolato)boryl or hydroxydiphenylmethyl (Entries 6 and 7). Noteworthy is that *tert*-butyldimethylsilyl (TBS)-substituted oxirane **5h** rearranged even at room temperature to prevent the isolation. Thus, bulkiness of substituent E appears to force two terminal sp² carbons to locate close each other and to accelerate the Cope rearrangement.

The scope of this approach to **6** is readily seen in Table 3. The isolated yields of **6** were generally high. Rate-enhancement of the rearrangement by incorporation of a silyl or stannyl group was again observed (Entries 2, 3, 6, 7, and 9). An enol moiety also could participate in the rearrangement (Entries 8 and 9). Thus, bicyclic oxepins **6p**⁷ and **6q** were isolated in high yields after purification by silica gel column chromatography.

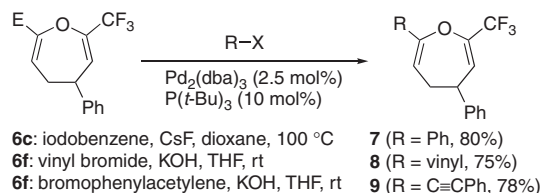
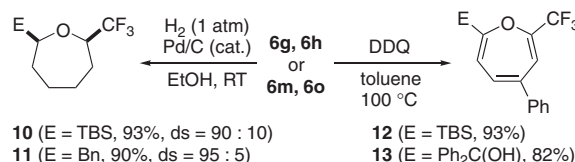
Table 3. Synthesis of 2-CF₃-4,5-dihydrooxepins **6**^a

Entry	5	Temp/°C	Time/h	6	Yield/% ^b
1	5i	120	4	6i	89 ^c
2	5j	85	2	6j	92
3	5k	85	2	6k	95
4	5l	100	48	6l	93
5	5m	80	5	6m	100
6	5n	80	3	6n	89
7	5o	60	3	6o	94
8	5p	140	6	6p	90
9	5q	100	18	6q	86 ^c

^aA solution of oxirane **5** (0.5 mmol) in CCl₄ (3 mL) was heated in a sealed tube. The progress of the reaction was monitored by ¹⁹F NMR. ^bIsolated yields. ^cIsolated yields based on reacted *cis*-diastereomer of **5**.

Versatility of the present approach is demonstrated by one-pot synthesis of **6o** from 1,1-dichloro-3,3,3-trifluoropropan-2-one as well as facile and diverse transformations of **6c** and **6f**. Thus, treatment of the ketone with vinyl lithium (4 equiv.), LiTMP (3 equiv.), and then TBSOTf (3 equiv.) followed by quenching with MeOH and heating the mixture at 60 °C gave **6o** in 36% yield all in one-pot. Aryl, alkenyl, or alkynyl group was easily introduced on the oxepin ring of **6c** and **6f**, to give **7–9** in good yields via the Pd-catalyzed cross-coupling reaction with the corresponding halides (Scheme 2).

Finally, reduction and oxidation of **6** led to 2-CF₃-substituted oxepanes and oxepins, respectively, as shown in Scheme 3. Hydrogenation of **6m** and **6o** with Pd/C under H₂ (1 atm) pro-

**Scheme 2.** Synthetic utility of metalated products**Scheme 3.** Conversion of **6** to oxepanes and oxepins.

ceeded stereoselectively to give **10** and **11**, respectively, with high *cis* selectivity,⁸ while **6g** and **6h** were dehydrogenated efficiently to afford **12** and **13** in good yields when DDQ was employed as an oxidant in toluene.

In summary, we have developed a facile synthetic route to 2-CF₃-substituted seven-membered oxacycles, which involves *cis*-selective preparation of 2,3-bis(alkenyl)oxiranes substituted by a CF₃ group and an arbitrarily incorporated substituent E followed by the Cope rearrangement. In particular, the rearrangement is found remarkably accelerated by such a metal substituent E as a boryl, silyl, or stannyl group that can act as a versatile functional group for further transformation. This methodology allows us to obtain diverse kinds of 2-trifluoromethylated oxepanes and oxepins.

This work was supported by Grant-in-Aid for COE Research on Elements Science, no. 12CE2005, from Ministry of Education, Culture, Sports, Science and Technology, Japan. 1,1-Dichloro-3,3,3-trifluoropropan-2-one was kindly donated by Central Glass Co. Ltd.

References and Notes

- a) T. Hiyama, "Organofluorine Compounds. Chemistry and Applications," Springer-Verlag, Berlin (2000). b) M. Hudlicky and A. E. Pavlath, "Chemistry of Organic Fluorine Compounds II. A Critical Review," American Chemical Society, Washington, DC (1995). c) J. T. Welch, *Tetrahedron*, **43**, 3123 (1987).
- a) D. R. Boyd, in "Comprehensive Heterocyclic Chemistry," ed. by A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford (1984), Vol. 7, p 547. b) L. I. Belen'kii, in "Comprehensive Heterocyclic Chemistry II," ed. by A. R. Katritzky, C. W. Rees, and E. F. V. Scriven, Pergamon Press, Oxford (1996), Vol. 9, p 45. c) J. O. Hoberg, *Tetrahedron*, **54**, 12631 (1998).
- a) M. Shimizu, T. Fujimoto, H. Minezaki, T. Hata, and T. Hiyama, *J. Am. Chem. Soc.*, **123**, 6947 (2001). b) M. Shimizu, T. Fujimoto, X. Liu, H. Minezaki, T. Hata, and T. Hiyama, *Tetrahedron*, **59**, 9811 (2003).
- Treatment of **4** with LiTMP followed by the addition of vinyl lithium resulted in the production of complex mixture.
- Cis/trans* isomers of **5e**, **5i**, and **5q** were not separable by column chromatography on silica gel or gel permeation chromatography.
- Review on Cope rearrangement of bis(alkenyl)oxiranes: a) T. Hudlicky, R. Fan, J. W. Reed, and K. G. Gadamasetti, in "Org. React.," John Wiley & Sons, Inc., New York (1992), Vol. 41, p 1. Examples: b) P. v. Zezschwitz, K. Voigt, A. Lansky, M. Noltemeyer, and A. d. Meijere, *J. Org. Chem.*, **64**, 3806 (1999). c) W.-N. Chou, J. B. White, and W. B. Smith, *J. Am. Chem. Soc.*, **114**, 4658 (1992).
- Stereochemistry of **6p** was not determined at present.
- cis*-Stereochemistry was assigned by NOE experiment.