Homoaldol and Aldol Reactions from Common Enolates and Oxiranes: Reaction of Reductively Generated Chromium Enolates through Cationic Rearrangement

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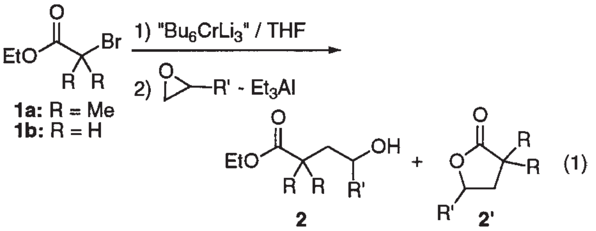
Enolates generated from α-bromo esters by the reduction with "Bu_6CrLi_3" react with oxiranes to afford γ-hydroxy esters and β-hydroxy esters, depending on the Lewis acid used as a promoter.

Enolates are a fundamental species for organic synthesis, and the aldol reaction is a representative reaction of enolates, where both the carbon-carbon bond formation and the creation of a functional hydroxy group for the further synthetic manipulations are achieved in a single event.[1] As for the homologue, homoaldol reaction, synthetic equivalents of homoenolates are usually used as nucleophiles toward carbonyl compounds.[2]

We recently found that α-halo carbonyl compounds reacted with an equimolar amount of "Bu_6CrLi_3"[3] to generate enolates under mild conditions.[4] These enolates reacted chemoselectively with the electrophiles added afterward, in contrast to reactions with Cr(II) reagents as reductants, where only by the Barbier-type procedure, enolates reacted with electrophiles. This stepwise and so-called Grignard-type procedure revealed an interesting feature in the reactivity of the enolates.

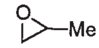
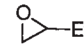
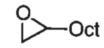
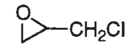
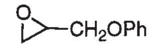
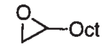
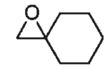
We report herein two reactions, homoaldol and aldol reactions of the common enolates and oxiranes, depending on the Lewis acid used as a promoter (eqs 1 and 2).



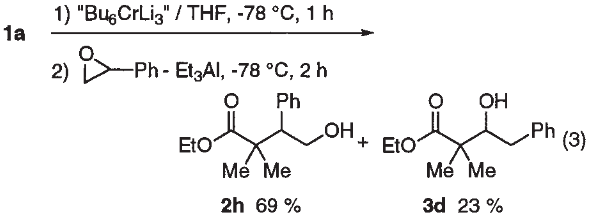
The enolate reductively generated from ethyl α-bromoisobutyrate (**1a**) with "Bu_6CrLi_3" did not react with propylene oxide. When a solution of propylene oxide-Et_3Al in THF prepared in advance at −78 °C was transferred to the solution of the enolate at −78 °C, and the temperature of the resultant mixture was raised to room temperature, a mixture of γ-hydroxy ester **2a** and its cyclized γ-lactone **2a′** was obtained in 76% combined yield. The results of the straightforward homoaldol reaction are summarized in Table 1.

Both enolates derived from **1a** and **1b** reacted with some types of oxiranes to afford homoaldol products in good yields. Functionalized oxiranes bearing a chlorine atom and a phenoxy group also provided the corresponding homoaldol products (entries 4 and 5). In the reaction of **1a** with styrene oxide, regioisomeric homoaldol product **2h** (69%) and β-hydroxy ester **3d** (23%) were obtained (eq 3).

Table 1. Reaction of bromo ester **1** with oxiranes in the presence of Et_3Al[a]

Entry	Bromo Ester **1**	Oxirane	Product	Yield of **2** + **2'** / %[b]
1	**1a**		**2a** + **2a'**	76
2	**1a**		**2b** + **2b'**	90
3	**1a**		**2c** + **2c'**	86
4	**1a**		**2d** + **2d'**	90
5	**1a**		**2e** + **2e'**	77
6	**1b**		**2f** + **2f'**	72
7	**1b**		**2g** + **2g'**	72

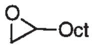
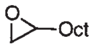
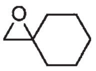
[a]A solution of "Bu_6CrLi_3" in THF was prepared from BuLi (3.12 mmol) and $CrCl_3$ (0.52 mmol) in THF (4 mL) at -78 °C for 30 min. Bromo ester **1** (0.5 mmol) was added to the solution and the mixture was stirred for 1 h (**1a**: at -78 °C, **1b**: at -20 °C). THF (2 mL), oxirane (3.69 mmol), and Et_3Al (3.64 mmol) were mixed at -78 °C in another flask, and the solution was transferred to the solution of enolate. The temperature of the resultant mixture was raised to room temperature and the mixture was stirred for 2 h.
[b]Isolated yield.



We were interested in the formation of β-hydroxy ester **3d** in eq 3, and found that on using $EtAlCl_2$ as the Lewis acid, the course of the reaction dramatically changed, and only β-hydroxy ester **3** was obtained. These results are shown in Table 2.

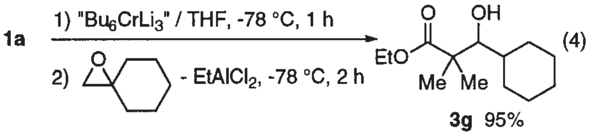
The rearrangement of oxiranes to aldehydes catalyzed by a Lewis acid was previously reported.[5] Although this sort of rearrangement is possibly involved in the present reaction, it is worthy of note that the cationic rearrangement took place in the presence of a nucleophilic enolate, and the enolate reacted only with the rearranged aldehyde selectively.[6] In the reaction with styrene oxide, the produced aldol **3d** is identical with the product from a reaction of the enolate with highly enolizable phenylace-

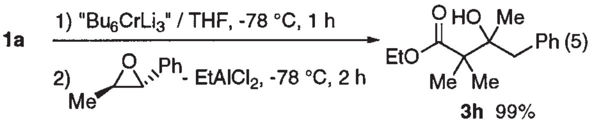
Table 2. Reaction of bromo ester **1** with oxiranes in the presence of $EtAlCl_2$[a]

Entry	Bromo Ester **1**	Oxirane	Product	Yield of **3** / %[b]
1	**1a**		**3a**	93
2	**1a**		**3b**	81
3	**1a**		**3c**	85
4[c]	**1a**		**3d**	95
5	**1b**		**3e**	75 (88/ 12)[d]
6	**1b**		**3f**	81 (80/ 20)[d]

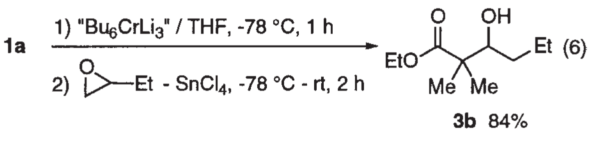
[a] A solution of "Bu_6CrLi_3" in THF was prepared from BuLi (3.12 mmol) and $CrCl_3$ (0.52 mmol) in THF (4 mL) at -78 °C for 30 min. Bromo ester **1** (0.5 mmol) was added to the solution and the mixture was stirred for 1 h (**1a**: at -78 °C, **1b**: at -40 °C). THF (2 mL), oxirane (3.69 mmol), and $EtAlCl_2$ (3.64 mmol) were mixed at -78 °C in another flask, and the solution was transferred to the solution of enolate. The mixture was stirred at -78 °C for 2 h. [b] Isolated yield. [c] Et_2AlCl was used instead of $EtAlCl_2$. [d] *Syn*/*anti* ratio.

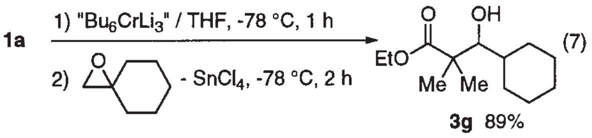
toaldehyde (entry 4). Unfortunately, epichlorohydrin and glycidyl phenyl ether did not provide the desired aldol products, while from 1,1- and 1,2-disubstituted oxiranes, aldol products were obtained in high yields (eqs 4 and 5); the latter reaction corresponds to the reaction between the enolate derived from ethyl isobutyrate and methyl benzyl ketone.

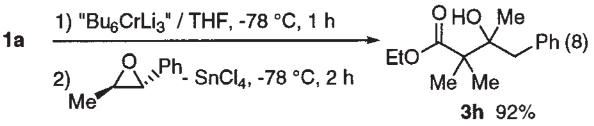




Reactions with other Lewis acids were briefly examined, and we found that $SnCl_4$ also promoted the reactions giving β-hydroxy esters **3** (eqs 6–8).[7] Further synthetic application is now under investigation.







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Dedicated to Prof. Teruaki Mukaiyama on the occasion of his 75th birthday.

References and Notes

† A visiting researcher from Xinjiang Institute of Chemistry, Chinese Academy of Sciences.

1 T. Mukaiyama, in "Organic Reactions," ed. by W. G. Dauben, John Wiley & Sons, New York (1982), Vol. 28, Chap. 3, p 203.

2 D. Hoppe, *Angew. Chem., Int. Ed. Engl.* **23**, 932 (1984).

3 A tentatively used formula "Bu_6CrLi_3" expresses only the molar ratio of butyllithium employed to chromium(III) salt, since the structure of the species is not clear at present.

4 M. Hojo, K. Sakata, N. Ushioda, T. Watanabe, H. Nishikori, and A. Hosomi, *Organometallics*, **20**, 5014 (2001).

5 B. Rickborn, in "Comprehensive Organic Synthesis," ed. by B. M. Trost and I. Fleming, Pergamon, Oxford (1991), Vol. 3, Chap. 3, p 733; K. Maruoka, T. Ooi, S. Nagahara, and H. Yamamoto, *Tetrahedron*, **47**, 6983 (1991); K. Maruoka, N. Murase, R. Bureau, T. Ooi, and H. Yamamoto, *Tetrahedron*, **50**, 3663 (1994).

6 Products derived from the rearrangements of other groups, such as alkyls and halogen of the Lewis acid used were not detected.

7 When $BF_3{\cdot}OEt_2$ and $ZnCl_2$ were used in the reaction of **1a** with ethyloxirane (corresponds to eq 6), yields of aldol **3b** were 67% and 28%, respectively. In the reaction of **1a** with octyloxirane using $ZnBr_2$, 74% yield of homoaldol products **2c** + **2c′** were obtained.