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Generation of Lithium Enolates Accelerated by Lithium Trifluoromethanesulfonate. Application to the Selective 1,4-Chiral Induction in the Aldol Reaction of *t*-Butyl δ-Hydroxy Carboxylates

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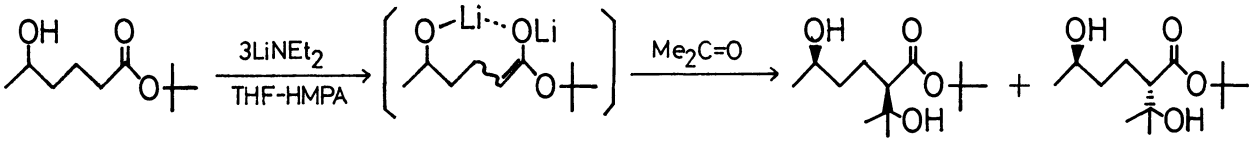
The presence of lithium trifluoromethanesulfonate accelerates the enolate formation from *t*-butyl δ-hydroxy carboxylates with lithium diethylamide. The reaction of the resulting enolates with ketones or benzaldehyde affords the corresponding α,δ-*syn* aldol adducts stereoselectively.

In the preceding communication, we reported the stereoselective 1,4-chiral induction in the alkylation reaction of lithium enolates generated from *t*-butyl δ-hydroxy carboxylates.[1] Highly selective chiral induction directed by a hydroxyl group[2] in the above reaction prompted us to apply this method to the stereoselective introduction of various electrophiles to δ-hydroxy carboxylates.

First we examined the aldol reaction of *t*-butyl 5-hydroxyhexanoate (1A). Lithiation of 1A was performed at -78 °C by the treatment with 3 molar amounts of lithium diethylamide in THF-hexamethylphosphoric triamide (HMPA). The resulting solution of the enolate 2 was treated with acetone at -100 °C to produce the aldol adducts 3a and 4a in 78% yield, however, the stereoselectivity was not sufficiently high in this reaction (3a:4a = 82:18). The generation of the enolate 2 at -100 °C for 1 h in THF-HMPA consequently enhanced the selectivity toward *syn* aldol product up to 86:14, but the yield of aldol products was decreased to 53%. The low yield suggested that the transformation of 1A to the enolate 2 was incomplete at -100 °C.



1A 2 3a 4a

In order to generate the enolate 2 smoothly even at -100 °C, the lithiation was examined in the presence of various lithium salts based on the consideration that the lithiation might be facilitated by the coordination of such Lewis acids to the ester group.[3] Finally it was noted that the addition of lithium trifluoromethanesulfonate (LiOTf) or lithium iodide enhanced the lithiation, and especially the use of excess LiOTf was found to promote the lithiation effectively

Table 1. Aldol reaction between 1A and acetone

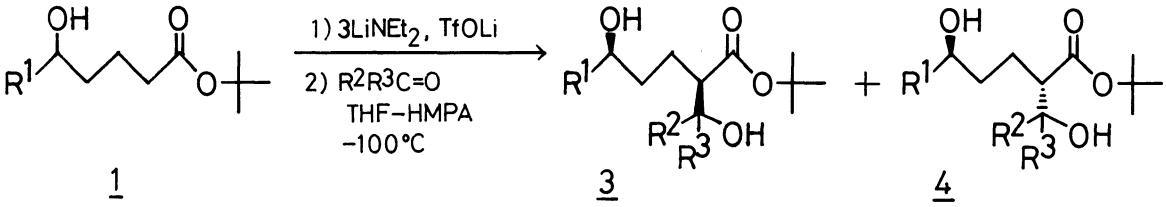
Temp of lithiation/°C	Additive[a]	3a : 4a[b]	Total yield/%
-100 → -78		82 : 18	78
-100		86 : 14	53
-100	LiI	88 : 12	79
-100	LiOTf	91 : 9	92
-100	LiOTf[c]	85 : 15	74
-100	LiOTf	87 : 13	82[d]

a) 3 molar amounts of additive were used.
b) The ratios were determined by ^{13}C NMR spectra.
c) 1 molar amount of LiOTf was used.
d) 2.2 molar amounts of lithium diethylamide were used.

(Table 1). Thus the hydroxy ester 1A was converted to the enolate 2 with 3 molar amounts of lithium diethylamide in the presence of 3 molar amounts of LiOTf at -100 °C for 2 h in THF-HMPA, and the reaction with acetone gave the aldol adducts 3a and 4a in 92% yield. Furthermore, the high stereoselectivity toward the *syn* aldol product was also achieved by the addition of LiOTf (3a:4a = 91:9).

The reaction of *t*-butyl 5-hydroxyhexanoate (1A) and *t*-butyl 5-hydroxynonanoate (1B) with acetone and cyclohexanone was conducted by the combined use of LiOTf with the results shown in Table 2. In all cases, the *syn* aldol products were obtained in high yield with high stereoselectivity.[4]

A typical experimental procedure is described for the reaction of 1A and acetone: To a THF (5 mL) solution of LiOTf (323 mg, 2.07 mmol) was added a THF (5 mL) solution of diethyl amine (179 mg, 2.44 mmol) under an argon atmosphere, and cooled to -78 °C. Butyllithium (1.25 mL of a 1.54 M solution in hexane) was added



1 3 4

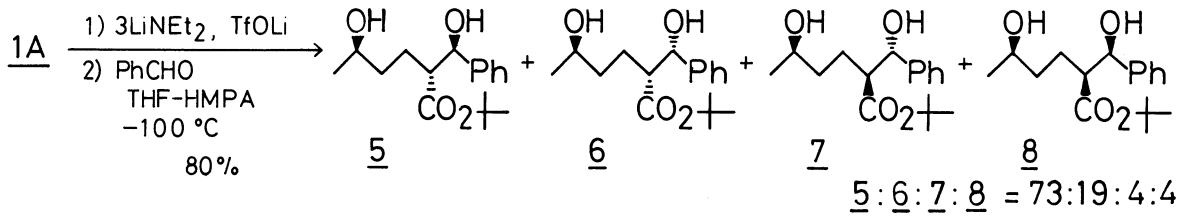
Table 2. Aldol reaction of 1 with ketones in the presence of LiOTf

	R^1	R^2	R^3	3 : 4[a]	Total yield/%
a	Me	Me	Me	91 : 9	92
b	Me	$-(CH_2)_5-$		86 : 14	99
c	n-Bu	Me	Me	91 : 9	99
d	n-Bu	$-(CH_2)_5-$		93 : 7	97

a) The ratios were determined by ^{13}C NMR spectra.

and the solution was stirred at that temperature for 15 min followed by the addition of a THF (1 mL) solution of HMPA (0.66 mL, 3.79 mmol) and then cooled to -100 °C. A THF (4 mL) solution of *t*-butyl 5-hydroxyhexanoate (119 mg, 0.63 mmol) was added to the mixture and stirred for 2 h at that temperature, and then a THF (4 mL) solution of acetone (91 mg, 1.57 mmol) was added. After being stirred for 30 min at -100 °C, the reaction was quenched with sat. aqueous NH_4Cl. Extraction with ether and purification by preparative tlc on silica gel gave *syn*-*t*-butyl 5-hydroxy-2-(1-hydroxy-1-methylethyl)hexanoate and the *anti* isomer (total 142 mg, 92%) in a ratio of 91:9, respectively.

The aldol reaction of 1A and benzaldehyde was examined and the high stereoselection between α,δ-carbons was also achieved (5+6 : 7+8 = 92 : 8), however, the stereocontrol between α,β′-relationships was not sufficient.



Thus, it was noted that LiOTf efficiently promote lithiation of esters with lithium amides and was utilized successfully to the selective 1,4-chiral induction in the aldol reaction of δ-hydroxy esters.

The authors are grateful to Professor Teruaki Mukaiyama for valuable discussion during this work.

References

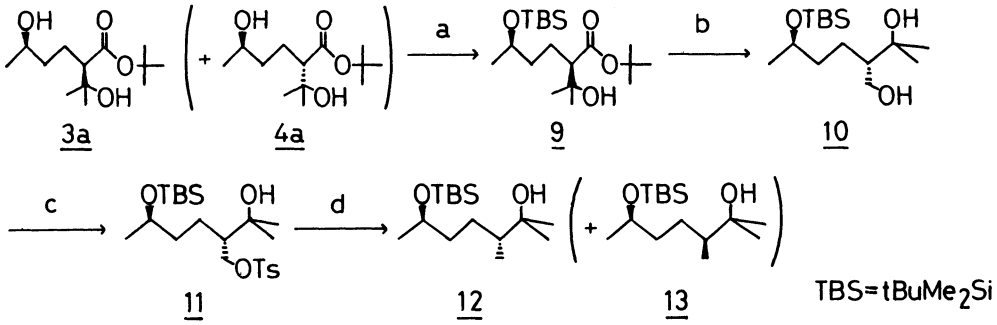
1) K. Narasaka and Y. Ukaji, Chem. Lett., 1986, 81: Our intial report that *syn* stereoselection is controlled by the addition of HMPA without regard to the configuration of the generating lithium enolate, was noted to be incorrect due to our experimental error. By some experiments of the reproducibility, it was confirmed that the selectivity was found to mainly depend on the geometry of the lithium enolate. The trapping of the generated enolate with *t*-butyldimethylsilyl chloride[5] suggested us that the geometry of the enolate generated in THF was mainly *trans*.[6] On the other hand, when the co-solvent HMPA was present during deprotonation, the *cis* enolate was supposed to be as a predominant isomer. Consequently, it is considered that the lithium enolate does not form the lithium-olefin π coordination in this alkylation reaction. The detail will be published in a full paper.

2) The 1,2-chiral induction in the alkylation of enolates of β-hydroxy esters is also well regulated by a hydroxyl group via the chelate formation: G. Fráter, U. Müller, and W. Günther, Tetrahedron, 40, 1269 (1984) and the references cited therein; D. Seebach, H. F. Chow, R. F. W. Jackson, K. Lawson, M. A. Sutter, S. Thaisrivongs, and J. Zimmermann, J. Am. Chem. Soc., 107, 5292 (1985).

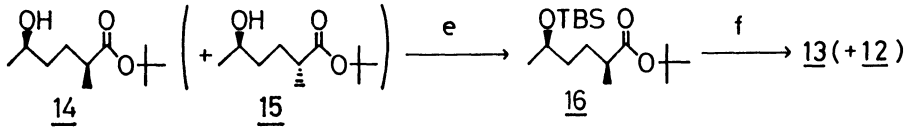
3) Recently Masamune, Roush, and Rathke reported that lithium halides are

effective for the generation of carbanions in Horner-Wadsworth-Emmons reaction using weak bases such as amines: M. A. Blanchette, W. Choy, J. T. Davis, A. P. Essenfeld, S. Masamune, W. R. Roush, and T. Sakai, Tetrahedron Lett., 25, 2183 (1984); M. W. Rathke and M. Nowak, J. Org. Chem., 50, 2624 (1985).

4) The stereochemistry of 3a was confirmed by the transformation of 3a to 12, which was compared with the authentic 12 derived from 15. That is, a ca. 4:1 mixture of 3a and 4a was converted to 12 and 13 as shown in Shceme 1. On the other hand, a mixture of 13 and 12 were derived from a ca. 4:1 mixture of 14 and 15[1] (Scheme 2). The ^{13}C NMR spectra of the main product 12 obtained from a mixture of 3a and 4a and the minor product 12 derived from a mixture of 14 and 15 were identical each other. The ^{13}C NMR spectrum of the minor product 13 produced from a mixture of 3a and 4a also agreed with that of the major product 13 from a mixture of 14 and 15. Furthermore, in ^{13}C NMR spectra, all the chemical shifts of α-carbons (-CH(COO^{t}Bu)-) and δ-carbons (-CH(OH)-) of the *syn* isomers 3 appear at lower fields about 0.4-0.7 ppm and 0.5-1.0 ppm than those of the *anti* isomers 4, respectively.



Scheme 1. (a): TBSCl, Et_3N; 90%, (b): $LiAlH_4$; 76%, (c): *p*-TsCl, pyridine; 94%, (d): $LiAlH_4$; 69%.



Scheme 2. (e): TBSCl, Et_3N; 90%, (f): MeLi; 89%.

5) R. E. Ireland, R. H. Mueller, and A. K. Willard, J. Am. Chem. Soc., 98, 2868 (1976).

6) The geometry of the ester enolates is presented according to the Heathcock's nomenclature using *cis* and *trans* terms; C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, J. Org. Chem., 45, 1066 (1980).

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