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Preparation of Optically Active Ketones *via* Enantioface-Differentiating Protonation of Prochiral Enolates

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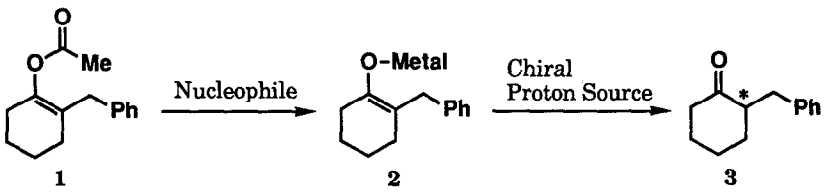
Summary: Enantioselective protonation of the prochiral lithium enolate (**2**) of 2-benzylcyclohexanone (**3**) was developed. Reaction of **2** with methyl (*S*)-α-hydroxyisocaproate (**15**) as a chiral proton source afforded (*R*)-**3** in a high optical yield. This reaction is widely applicable to the preparation of various α-substituted optically active ketones.

Optically active α-substituted ketones are versatile intermediates in asymmetric synthesis, and hence a number of methods for stereoselective α-alkylation have been developed.[1,2] On the other hand, in spite of its potential usefulness,[3] only a relatively few studies have been reported on enantioselective protonation of prochiral enolates.[4] Recently, we have reported such kind of reactions by the aid of enzymes, *i.e.*, enantioselective hydrolysis of enol esters.[5] Herein, reported the results of enantioface-differentiating protonation by non-enzymatic method with a chiral proton source (Scheme 1).



1 2 3

Scheme 1.

1-Acetoxy-2-benzylcyclohexene (**1**) was chosen as the representative precursor of prochiral enolate (**2**) because the enantiomeric excess of the expected product 2-benzylcyclohexanone (**3**) is easily determined by HPLC analysis (CHIRALCEL OJ, Daicel Chemical Industries, Ltd.) and its optical rotation is known.[6] Ester **1** was converted to lithium enolate (**2**) by addition of MeLi (1.9 eq., Et_2O solution)[7] to **1** in Et_2O, and treated with various chiral proton sources at -78 °C. Because the rate of protonation should be far smaller than that of diffusion, the proton source must be a weak acid. Thus, we expected chiral alcohols to result better discrimination between enantiotopic faces. As shown in Table 1, ethyl (*S*)-lactate (**10a**) gave the highest e.e. Examination of reaction conditions using (*S*)-**10a**, it was found that the best results were obtained when the reaction was carried out in Et_2O at low temperature without any additives (DMPU, TMEDA),[8] starting from lithium enolate (**2**).

Table 1. Enantioselective Protonation of Enolate **2** with Chiral Alcohols.

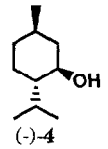
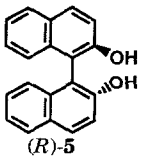
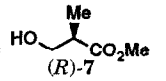
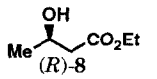
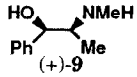
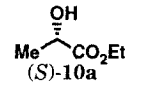
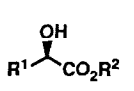
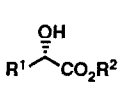
entry	R*OH	yield/%	e.e./%	config.
1	 (-)-**4**	74	0	
2	 (*R*)-**5**	74	22	*R*
3	 (*S*)-**6**	62	0	
4	 (*R*)-**7**	77	19	*S*
5	 (*R*)-**8**	72	6	*S*
6	 (+)-**9**	85	36	*S*
7	 (*S*)-**10a**	80	62	*R*

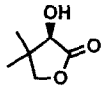
Table 2. Enantioselective Protonation of Enolate **2** with α-Hydroxy Esters.

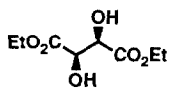
entry	R*OH	temperature/°C	yield/%	e.e./%	config.
1	(*S*)-**10a**	0	84	0	
2	(*S*)-**10a**	-45	80	33	*R*
3	(*S*)-**10a**	-100	73	73	*R*
4	(*S*)-**10b**	-78	73	61	*R*
5	(*R*)-**10c**	-78	71	46	*S*
6	(*R*)-**11**	-78	80	45	*S*
7	(*S*)-**12**	-78	67	67	*R*
8	(*S*)-**13**	-78	74	54	*R*
9	(*R*)-**14**	-78	67	77	*S*
10	(*S*)-**15**	-78	74	80	*R*
11	(*S*)-**15**	-100	87	83	*R*
12	(*R*)-**15**	-100	79	79	*S*
13	(*R*)-**16**	-78	69	3	*R*
14	(*R,R*)-**17**	-78	65	10	*R*
15	(*2S,3R*)-**18**	-78	73	47	*R*

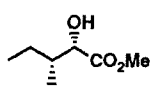

(*R*)


(*S*)

10 ~ 15

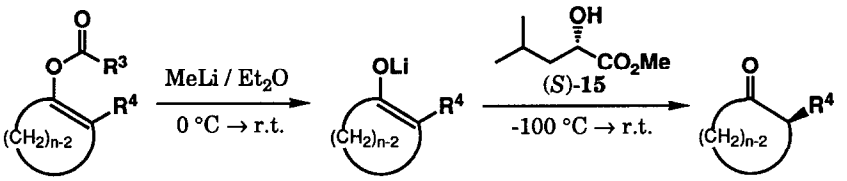

(*R*)-**16**


(*R,R*)-**17**


(*2S,3R*)-**18**

	10a	**10b**	**10c**	**11**	**12**	**13**	**14**	**15**
R^1	Me	Me	Me	Ph	*i*-Pr	*t*-Bu	PhC_2H_4	*i*-Bu
R^2	Et	Me	*i*-Bu	Et	Me	Me	Et	Me

Table 3. Enantioselective Protonation of Various Enolates.



entry	n	R^3	R^4	yield/%	$[\alpha]_D$/°(c, solvent, temp.)	e.e./%	config.
1	6	Et	$PhCH_2$	82		82[a]	*R*
2	6	*i*-Pr	$PhCH_2$	80		83[a]	*R*
3	6	Ph	$PhCH_2$	87		82[a]	*R*
4	5	Et	$PhCH_2$	86	+50.3 (1.20, MeOH, 24)	34[a]	*R*
5	6	Et	Me	83[b]	+ 8.3 (1.06, MeOH, 25)	58[c]	*S*
6	6	Et	Pr	82	+19.8 (1.05, MeOH, 25)	65[c]	*S*
7	6	Et	C_7H_{15}	88	+17.8 (1.11, $CHCl_3$, 25)	60[c]	*S*
8	6	Et	*i*-Bu	81	+32.7 (1.10, $CHCl_3$, 20)	71[c]	*S*
9	6	Et	CH_2=$CHCH_2$	75	+ 9.2 (1.24, MeOH, 28)	72[c]	*R*

a) Determined by HPLC analysis with CHIRALCEL OJ. b) Determined by GLC analysis. c) Determined by capillary GLC analysis of the corresponding MTPA ester of the reduced alcohol using PEG 20M (Gasukuro Kogyo Inc.). Reduction of ketone was performed with DIBAL in THF.

As the experiments so far suggested that an α-hydroxy ester would work well as chiral proton donor, variations of the structure were examined (Table 2). While the steric bulkiness of alkoxy part showed no favorable effect (entry 4, 5), the acyl part of the ester had a serious effect to the enantioselectivity. As is apparent from the Table, methyl (*S*)-α-hydroxyisocaproate (**15**) gave the best result (entry 11). Under an argon atmosphere, MeLi (0.608 mmol) was added to a solution of **1** (73.6 mg, 0.320 mmol) in Et_2O (5 ml) at 0 °C and the solution was stirred at room temperature. To this solution, was added slowly (*S*)-**15** (96% e.e., 1.05 mmol)[9] in Et_2O (3 ml) at -100 °C, followed by stirring for 10 min. The mixture was gradually warmed to room temperature during 1 h and quenched with a buffer (pH 6.8). After usual work up, the product was purified by flash column chromatography on silica-gel to give (*R*)-**3** in 87% chemical and 83% optical yield, $[\alpha]_D^{25}$ +38.3° (c 1.17, MeOH); lit.[6] $[\alpha]_D$ +41.4° (c 5, MeOH), (*R*)-form (88% e.e.). The chiral source (*S*)-**15** could be easily recovered without any racemization. When (*R*)-**15** (92% e.e.)[9] was used instead of (*S*)-enantiomer, (*S*)-ketone **3** was reasonably obtained (79%, 79% e.e.), $[\alpha]_D^{27}$ -36.0° (c 1.26, MeOH).

This reaction could be applied to various substrates (Table 3). Displacement of acetate with propionate, isobutyrate and benzoate (entry 1-3) had no effect on the enantioselectivity indicating that the resulting lithium *tert*-alkoxide does not perticipate in this reaction. The asymmetric protonation of other enolates proceeded to afford optically active ketones having various substituents on the α-position. The absolute configuration of the products indicates that the proton attack always occurs on the same enantioface of the enolates.

Though the mechanism of the enantioselective protonation remains obscure at present, it is clear that α-hydroxy carbonyl moiety plays a crucial role in asymmetric induction. Thus, lithium cation

probably chelates to these oxygen atoms as well as enolate oxygen to make the transition state fairly rigid. As a result, when methyl (S)-α-hydrtoxyisocaproate (**15**) is employed as the chiral proton source, the attack of proton to double bond from its *re*-face is unfavored because of steric repulsion between the side chain of the proton donor and the α-substituent of the enolate (Figure 1b). On the other hand, *si*-face attack is free from such steric interaction, resulting in the preferential formation of (*R*)-**3** (Figure 1a).

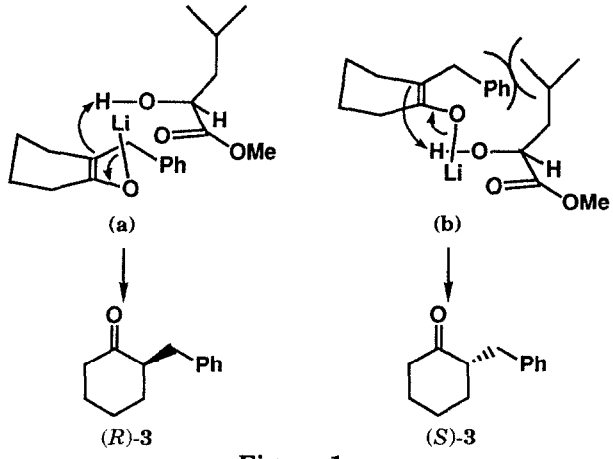


Figure 1.

In conclusion, a simple and efficient approach to optically active ketones by enantioface-differentiating protonation of prochiral enolates has been developed. This method is applicable for various compounds and is expected to be a potentially useful tool for organic synthesis.

References and Notes

1) Reviews: *Asymmetric Synthesis*, J. D. Morrison Ed., Academic Press, New York, **1983**, vol. 2 and **1984**, vol. 3.
2) Recent example of asymmetric alkylation: a) A. Ando, and T. Shioiri, *J. Chem. Soc., Chem. Commun.*,**1987**, 656; b) K. Tomioka, M. Shindo, and K. Koga, *Chem. Pharm. Bull.*, **37**, 1120 (1989); c) M. Murakata, M. Nakajima, and K. Koga, *J. Chem. Soc., Chem. Commun.*, **1990**, 1657.
3) Review: L. Duhamel, P. Duhamel, J. -C. Launay, and J. -C. Plaquevent, *Bull. Soc. Chim. Fr.*, **1984**, II-421.
4) Representative example: a) M. B. Eleveld, and H. Hogeveen, *Tetrahedron Lett.*, **27**, 631 (1986); b) L. Duhamel, S. Fouquay, and J. -C. Plaquevent, *Tetrahedron Lett.*, **27**, 4975 (1986); c) U. Gerlach, and S. Hünig, *Angew. Chem., Int. Ed. Engl.*, **26**, 1283 (1987); d) C. Fehr, and J. Galindo, *J. Am. Chem. Soc.*, **110**, 6909 (1988); e) O. Piva, and J. -P. Pete, *Tetrahedron Lett.*, **31**, 5157 (1990).
5) a) H. Ohta, K. Matsumoto, S. Tsutsumi, and T. Ihori, *J. Chem. Soc., Chem. Commun.*, **1989**, 485; b) K. Matsumoto, and H. Ohta, *Chem. Lett.*, **1989**, 1589; c) K. Matsumoto, S. Tsutsumi, T. Ihori, and H. Ohta, *J. Am. Chem. Soc.*, **112**, 9614 (1990).
6) A. I. Meyers, D. R. Williams, G. W. Erickson, S. White, and M. Druelinger, *J. Am. Chem. Soc.*, **103**, 3081 (1981).
7) H. O. House, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **36**, 2361 (1971).
8) DMPU: *N,N'*-dimethylpropyleneurea, TMEDA: *N,N,N',N'*-tetramethylethylenediamine.
9) The optical purities of (*S*)- and (*R*)-**15** were determined by HPLC analysis of the corresponding MTPA esters with Zorbax-SIL (Du Pont Instruments).

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