Enantioselective Protonation of Enolates: Novel Chiral Proton Sources and Remarkable Effects of the Countercation[1]

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Enantioselective protonation[2] of ketone or ester enolates constitutes an important method for the preparation of optically active α-substituted ketones or esters, complementary to the asymmetric α-alkylation of carbonyl compounds. A variety of chiral proton sources such as organic acids,[3] alcohols,[4] amides,[5] hydrochlorides of amines,[6] combinations of chiral secondary amines and chiral or achiral weak acids,[7] and chiral aniline[8] have been reported. The internal proton return process involving a chiral secondary amine and BF_3·OEt_2 opened a new avenue for asymmetric protonation.[9] Enantioselective protonation by an enzyme[10] and catalytic antibodies[11] has also been reported recently.

The acidity of the proton source plays a crucial role in achieving high enantiomeric excess (ee).[7d] Though chiral alcohols have been frequently used as a chiral proton source, they are too weak of acids to complete the protonation in a limited time. Thus, high ee's cannot be obtained with chiral alcohols,[4] because the alkoxide generated *in situ* acts as a base to remove the proton again. The phenolic hydroxyl group has a moderate acidity[12] to protonate enolates, but it is difficult to put the proton in an asymmetric microenvironment. Only an isolated example has been reported for the use of (*R*)-1,1′-binaphthalene-2,2′-diol as a chiral proton source with low ee.[4c] Here, we report structurally unique chiral proton sources derived from 1,1′-binaphthalene-8,8′-diol (**1**)[13] and a remarkable effect of Mg(II) on enantioselective protonation.

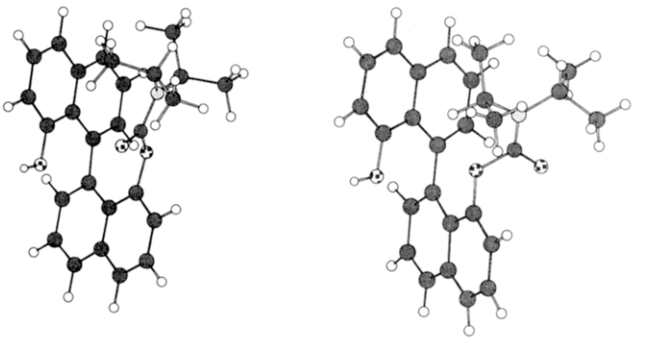
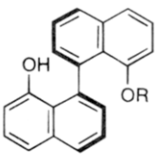


Figure 1. Conformations of (*R*)-**4**. (a) The most stable conformation calculated by MacroModel/MM2. (b) Solid state conformation determined by X-ray analysis. See ref 18.



1 : R = H
2 : R = $CONMe_2$
3 : R = $CONEt_2$
4 : R = $CONⁱPr_2$

We chose carbamates **2**−**4** as the chiral proton sources, in which the acidic hydrogen would be kept in a highly chiral microenvironment for the following reasons. Firstly, the naphthyl ring totally blocks one side of the phenolic hydroxyl group. Secondly, the carbamoyl moiety should be fixed as *syn* to the hydroxyl group as shown in Figure la, because the $\pi-\pi$ interaction of the naphthyl ring with a planar carbamoyl group is expected to be greater in the *syn*-form than in the *anti*-form (Figure 1b).[18]

Racemic **1** was resolved through the diester of (*S*)-*O*-acetylmandelic acid to give optically pure (*R*)-**1**. The desired carbamates **2**−**4** were easily prepared by condensation with the corresponding carbamyl chloride. X-ray analysis of (*R*)-**4** unexpectedly revealed that the orientation of the carbonyl group is *anti* to the hydroxyl group in the crystalline state (Figure 1b) due to intermolecular hydrogen bonding (see Figure 3 in supplementary material). Molecular mechanics (MM) calculations,[15] however, predict that **4** exists in the *syn*-form as the lowest energy conformation (Figure la), which is 4.2 kJ/mol lower than that of *anti*-form of the lowest energy. This contradiction is not surprising, because intermolecular interactions are not included in the calculations. The conformation of (*R*)-**4** in solution would be similar to that from the calculations rather than that in the crystalline state, since such a strong intermolecular hydrogen bonding observed in the crystalline state would not be expected in the solution.

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(13) Although racemic **1** was prepared,[14] optical resolution was not attempted.

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(15) The MacroModel/MM2 (version 4.0) force field was used.

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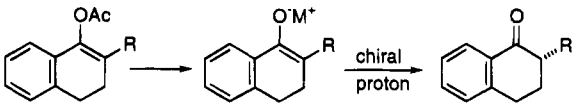
Table 1. Enantioselective Protonation of Enolates 8–10

entry	enolate[a] compd	(M =)	proton source	product	yield[b] (%)	ee[c]
1	**8**	MgCl	**2**	**11**	33 (37)	9
2	**8**	MgBr	**2**	**11**	49 (69)	49
3	**8**	MgI	**2**	**11**	57 (73)	58
4	**8**[d]	Li	**2**	*ent*-**11**	66	10
5	**8**	MgI	**3**	**11**	72 (80)	69
6	**8**[e]	Li	**3**	*ent*-**11**	76	55
7	**8**	MgI	**4**	**11**	66 (73)	54
8	**9**	MgI	**2**	**12**	73 (84)	68
9	**9**	MgI	**3**	**12**	84 (96)	75
10	**10**[f]	Li	**2**	**13**	72	9
11	**10**	MgI	**2**	**13**	48 (90)	92
12	**10**[g]	MgI	**2**	**13**	52 (94)	94
13	**10**[f]	Li	**3**	**13**	74	15
14	**10**	MgI	**3**	**13**	71 (81)	90
15	**10**[g]	MgI	**3**	**13**	66 (87)	93

[a] Prepared from the corresponding enol acetate with MeMgX unless otherwise stated. [b] The yield in the parentheses is based on the recovered starting material. [c] Determined by HPLC using a chiral column (Daicel Chiralpack AS). [d] Prepared from **5** with MeLi. [e] Prepared from the corresponding trimethylsilyl enol ether with MeLi/LiBr. [f] Prepared from **7** with MeLi/LiBr. [g] Prepared from the corresponding enol benzoate with MeMgI.

Scheme 1



5 : R = Me **8** : R = Me **11** : R = Me
6 : R = Et **9** : R = Et **12** : R = Et
7 : R = ^{i}Pr **10** : R = ^{i}Pr **13** : R = ^{i}Pr

Pertinent results of chiral protonation of enolates **8–10** are listed in Table 1. The magnesium enolates were prepared from the corresponding enol acetates **5–7** with methyl Grignard reagent in ether at room temperature. The enolates were protonated with a suspension of optically active carbamates **2–4** in ether at −78 °C for 0.5 h followed by warming to 10 °C for 1 h. Bromide and iodide gave a moderate ee, while chloride gave poor ee (see entries 1–3). The bulkiness of the substituents on the nitrogen has little effect on ee (see entries 3, 5, and 7). The MM calculations[15] indicated that carbamates **2** and **3** exist in essentially the same conformation as that of **4**. This might support the observed results of the small effect of the substituents on the nitrogen atom.

A remarkable effect of a countercation of the enolate was observed. Magnesium enolate gave a higher ee than those of lithium (entries 3 and 4, 10 and 11, 13 and 14). Although the profound effects of the countercation on the diastereoselectivity are well known in the aldol condensations,[16] such a marked effect of the counter cation has not been observed in the asymmetric protonation.[17] In the case of **8**, the lithium enolate gave a product with an absolute configuration opposite to that from the magnesium enolate (see entries 4 and 6). It is clear that the aggregation state of lithium enolate is different from that of magnesium, which should play a key role toward the observed effects. Although more detailed studies are necessary to gain insight into the precise mechanism, the transition model shown in Figure 2a accounts for the observed *S*-configuration of product **13**. Another transition state 2b giving *ent*-**13** would be highly unfavorable due to a severe repulsive interaction between the isopropyl group and the naphthyl moiety.

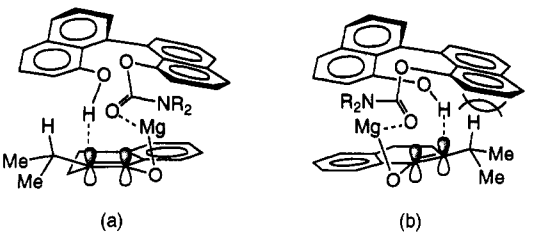


Figure 2. Possible models for the transition state of the asymmetric protonation leading to (a) **13** and (b) *ent*-**13**.

In conclusion, we have introduced novel chiral proton sources with unique structural features and shown that they can protonate the magnesium enolate of 2-alkyltetralones with moderate to high ee. The present studies raise the important suggestion that a change in the counter cation might be the way to achieve a high degree of enantioselective protonation, even though structural modification of chiral proton sources is very important.

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Supplementary Material Available: Full experimental details including optical resolution of **1**, spectroscopic data for **2–4**, and crystal structure of **4** showing intermolecular hydrogen bonding (Figure 3) (3 pages).

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(17) A remarkable increase in the ee was observed by using a combination of lithium and magnesium as countercations. See ref 4b.

(18) The author has deposited atomic coordinates for (*R*)-**4** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.