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

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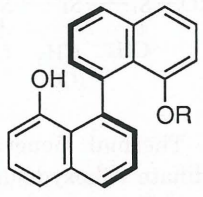
New chiral proton sources 2-4 having axial chirality were introduced. They protonate 2-alkyl a-tetralone enolates 8-10 enantioselectively. Enantiomeric excess of up to 94% was obtained on protonation of 10, when -MgI was used as a counter cation.

Keywards: Asymmetric synthesis / Protonation / Magnesium enolate

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. The acidity of the proton source plays a crucial role in achieving high enantiomeric excess (ee). Though chiral alcohols have been frequently used as a chiral proton source, they are acids too weak to complete the protonation in a limited time. Thus, high ee's cannot be obtained with chiral alcohols, because the alkoxide generated in situ acts as a base to remove the proton again. The phenolic hydroxyl group has a moderate acidity 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.[3] Here, we report structurally unique chiral proton sources derived from 1,1'-binaphthalene-8,8'-diol (1) and a remarkable effect of Mg(II) on enantioselective protonation.

We chose carbamate **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 Fig. la, because the π-π interaction of the naphthyl ring with a planar carbamoyl group is expected to be greater in the syn-form than in the anti-form (Fig. 1b).



1 : R = H
2 : R = $CONMe_2$
3 : R = $CONEt_2$
4 : R = CON^iPr_2

SYNTHETIC ORGANIC CHEMISTRY —Fine Organic Synthesis—

Scope of Research

The research interests of the laboratory include the development of new synthetic methodology, molecular recognition, and design and synthesis of biologically active compounds including functionalized DNA oligomers. Programs are active in the areas of use of chiral leaving groups for an asymmetric induction, desymmetrization of symmetrical compounds, asymmetric alkylation of carbonyl compounds based on "memory of chirality", use of binaphthalenes in the asymmetric synthesis and chiral recognition, and untitumor diterpenoids.

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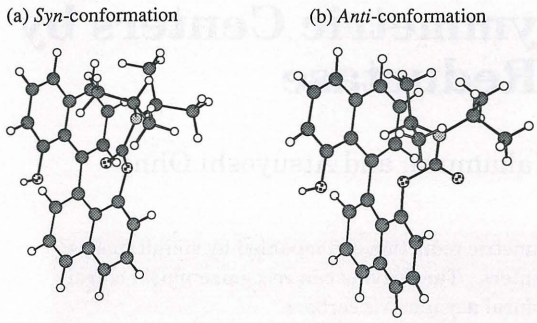
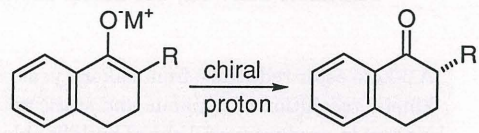


Figure 1.

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 (Fig. 1b) due to intermolecular hydrogen bonding. Molecular mechanics (MM) calculations,[4] however, predict that **4** exists in the *syn*-form as the lowest energy conformation (Fig. 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.

Pertinent results of chiral protonation of enolates **5-7** are listed in Table I. The magnesium enolates were prepared from the corresponding enol acetates 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℃ for 0.5 h followed by warming to 10℃ for 1 h. The bulkiness of the substituents on the nitrogen has little effect on ee (see entries 1, 3, and 4). The MM calculations 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.



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

A remarkable effect of a counter cation of the enolate was observed. Magnesium enolate gave a higher ee than those of lithium (entries 1 and 2, 7 and 8, 9 and 10). Although the profound effects of the counter cation on the diastereoselectivity are well known in the aldol condensations, such a marked effect of the counter cation has not been observed in the asymmetric protonation. In the case of 8, the lithium enolate gave a product with an absolute configuration opposite to that from the magnesium enolate (see entries 1 and 2). 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 Fig. 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.

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.

Table 1.

entry	enolate[a] compound	M =	proton source	product	yield[b]	% ee[c]
1	**5**	MgI	**2**	**8**	57(73)	58
2	**5**	Li	**2**	*ent*-**8**	66	10
3	**5**	MgI	**3**	**8**	72(80)	69
4	**5**	MgI	**4**	**8**	66(73)	54
5	**6**	MgI	**2**	**9**	73(84)	67
6	**6**	MgI	**3**	**9**	84(96)	75
7	**7**	Li	**2**	**10**	72	9
8	**7**	MgI	**2**	**10**	48(90)	92
9	**7**	Li	**3**	**10**	74	15
10	**7**	MgI	**3**	**10**	71(81)	90

[a]Prepared from the corresponding enol acetate with MeMgX unless otherwise stated. [b]The yield in the parenthesis is based on the recovered starting material. [c]Determined by HPLC using a chiral column (Daicel Chiralpack AS).

References

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