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Highly Enantiofacial Protonation of Prochiral Lithium Enolates with Chiral ß-Hydroxy Sulfoxides[1]

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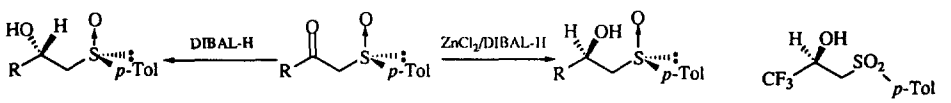
Abstract: Highly enantioselective protonation of prochiral lithium enolates is disclosed. The present method employed (S,R_S)-CF_3-hydroxy sulfoxide (**3b**) as the chiral protonating agent, and the protonation of lithium enolates of cyclohexanone derivatives with **3b** proceeded with high enantioselectivities. © 1997 Elsevier Science Ltd.

The enantioface selective protonation of prochiral enolates is a very simple and attractive route for the preparation of optically active carbonyl compounds and is of current interest.[2-4] It is, however, surprising that very few methods have been developed for achieving high levels of enantioselectivity in these transformations. Here we report that highly enantiofacial protonation of prochiral lithium enolates of cyclohexanone derivatives can be accomplished by using chiral ß-hydroxy sulfoxides.

Previously we and Solladié have independently demonstrated that the carbonyl reduction of enantiomerically pure (R)-ß-keto sulfoxides (**1**) proceeds highly diastereoselectively to give diastereomeric ß-hydroxy sulfoxides, (R,R_S)-**2** or (S,R_S)-**3** based on the reducing agent employed.[5] These ß-hydroxy sulfoxides are synthetically valuable intermediates for the preparation of enantiomerically pure hydroxy compounds because of the ready elaboration of the residual functionalities.[5] Furthermore, these type of compounds are also quite promising as a chiral ligand or ligated agent since the ß-hydroxy sulfinyl moiety is able to bind strongly to alkali or alkaline earth metal ions via a six-membered chelation form.[6] In order to evaluate such an ability of ß-hydroxy sulfoxides in asymmetric synthesis, we chose to examine the protonation of lithium enolates.



3a,b **1a**: R=*i*-Bu, **1b**: R=CF3 **2a,b** **4**

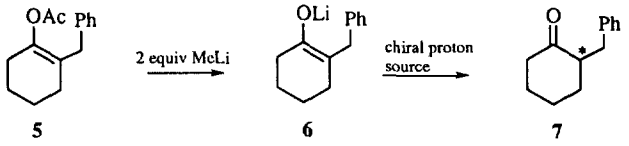


Table I. Asymmetric Protonation of **6** by Chiral Protonating Reagents **2**, **3**, and **4**.

entry	chiral source	conditions	isolated yield (%)	ee(%)[a]	confign
1	**2a**	THF (-100 - 0°C)	78	13	(*R*)
2	**2a**	Et_2O (-100 - 0°C)	77	43	(*R*)
3	**2a**	Et_2O-CH_2Cl_2 (-100 - 0°C)	87	26	(*S*)
4	**2b**	Et_2O-CH_2Cl_2 (-100 - -50°C)	84	79	(*R*)
5	**3a**	Et_2O-CH_2Cl_2 (-100 - 0°C)	81	90	(*S*)
6	**3b**	Et_2O-CH_2Cl_2 (-100 - 0°C)	94	92	(*S*)
7	**3b**	Et_2O-CH_2Cl_2 (-100 - -50°C)	93	97	(*S*)
8	**3b**	Et_2O-CH_2Cl_2 (-100 - -90°C)	95	72	(*S*)
9	**3b**	Et_2O (-100 - -50°C)	81	87	(*S*)
10	**4**	Et_2O-CH_2Cl_2 (-100 - -50°C)	88	52	(*S*)

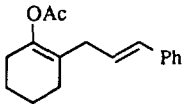
[a] Determined by HPLC analysis (column, CHIRALCEL OJ).

In an initial experiment, 1-acetoxy-2-benzyl-1-cyclohexene (**5**) was treated with 2 equiv of MeLi in ether at 0 °C, generating the regiochemically pure lithium enolate **6**[2f, 7] ; the protonation was conducted under a variety of conditions using chiral ß-hydroxy sulfoxides (2.5 equiv). The enantiomeric excesses (ee's) were directly determined by HPLC using a chiral stationary phase column and some of the results are summarized in Table I.[8] From these experiments, some characteristic features of the reaction appeared. First, the asymmetric induction is dependant upon the choice of the diastereomeric alcohols **2** or **3**; the use of the (S,R_S)-isomers **3** shows much higher ee than the case of (R,R_S)-isomers **2**. Second, the appropriate combination of the solvents is essential in realizing of a high level of asymmetric induction. The combination of Et_2O-CH_2Cl_2 afforded the maximum ee, while the use of THF or Et_2O as a solvent resulted in the poor ee's. Third, the larger size of the side chain in ß-hydroxy sulfoxides **3** did not cause significant improvement of the enantiostereoselection.[8] Finally and most importantly, virtually complete asymmetric induction was accomplished using (S,R_S)-CF_3-substituted derivative **3b**[9] to afford (*S*)-**7** with 97% ee. The reaction of **6** using (R,R_S)-isomer **2b** as protonating reagent gave (*R*)-**7** with 79% ee. It is noted that the protonation with **2b** and **3b** is complete below -50 °C. This remarkable effect may result as a consequence of considerably high acidity of the alcoholic proton induced by the strong electron-withdrawing CF_3 group. Using these conditions, some lithium enolates were investigated as shown in Table II. All cases examined show satisfactory results and the absolute configurations of the products indicate that the protonation occurred preferentially from the same enantioface of the enolates when **3b** was employed. In the present work, the proton source can be completely recovered without any loss of the optical purity.

Table II. Asymmetric Protonation of Some Enolates with **3b**.

entry	substrate	isolated yield(%)	ee(%)[a]	confign
1	**8**	93	92	(*S*)
2	**9a**	94	94	(*R*)[b]
3	**9b**	94	78	(*S*)
4	**9c**	97	87	(*S*)

a) Determined by HPLC analysis with CHIRALCEL OJ.
b) Determined by comparing the value of optical rotation (Murakata, M.; Nakajima, M.;Koga, K. *J. Chem. Soc., Chem. Commun.* **1990**, 1657).



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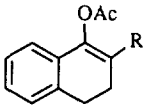
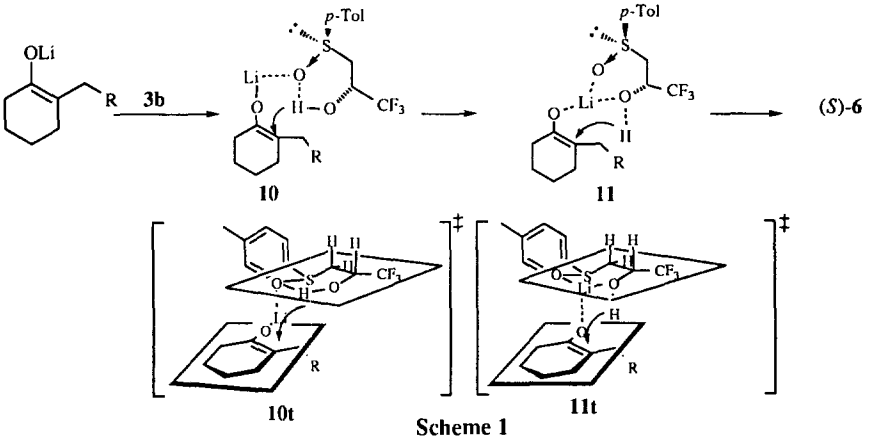


9 a: R=CH_3
b: R=CH_2Ph
c: R=(*E*)CH_2CH=CHPh

In order to get further information, the asymmetric protonation of **6** using chiral (*R*)-hydroxy sulfone **4** was examined and it showed that the sense of asymmetric induction was reverse (entry 10 vs. entry 4 of Table I) compared with the case of **2b** and the ee was only 52%. Accordingly, it is clear that both the hydroxyl and sulfinyl groups are crucial for the present enantiofacial discrimination.

These results represent the highest ee yet reported for enantioselective enolate protonation and the remarkably high stereocontrol can be considered as a result of the conformationally rigid transition state. As mentioned earlier, we have established that the enantioselectivity is governed by the nature of the ß-hydroxy sulfoxides used as the proton source; (R,R_S)-isomers **2** are less efficient for the enantioselective protonation of lithium enolates than (S,R_S)-isomers **3**. We assumed that the higher selectivity of these latter reagents was due to the proximity of the boat-like conformation that is more topologically different from the chair-like conformation found in (R,R_S)-isomers.[10] For the present reaction, the product-determining step is presumably the proton transfer from either the coordinated form of the lithium enolate to **3b** or the six-membered chelation intermediate involving the Li (such as **10** and **11**, respectively, in Scheme 1). Given the assumption that the proton is delivered axially from the one face of the enolate carbon,[11, 12] then both of the



Scheme 1

steric approach models (**10t** and **11t** in Scheme 1), wherein the chiral recognition is primarily determined by evaluating the non-bonded interactions between the cyclohexene ring of the enolate and the hydroxy sulfoxide skeleton in the transition state, provide a useful rationale for the product stereochemistry. At present, it is premature to present a more detailed mechanistic rationale for the observed enantioselectivity; nevertheless, it is evident that the present system should provide some insights to the long-standing enantiofacial protonation of achiral enolates.

In conclusion, we have shown that the high level of enantiofacial protonation of prochiral lithium enolates can be accomplished by using chiral ß-hydroxy sulfoxides. The studies on the scope and limitations of the present asymmetric protonation as well as its application are underway and the results will be reported in due course.

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