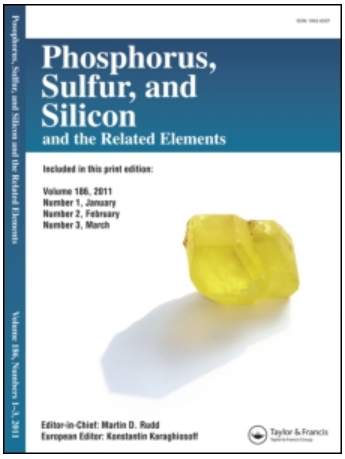

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β-Hydroxy Sulfoxide Derivatives as a Powerful Chiral Protonating Reagent

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β-HYDROXY SULFOXIDE DERIVATIVES AS A POWERFUL CHIRAL PROTONATING REAGENT

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Abstract Highly enantioselective protonation of prochiral lithium enolates using enantiomerically pure β-hydroxy sulfoxides are described.

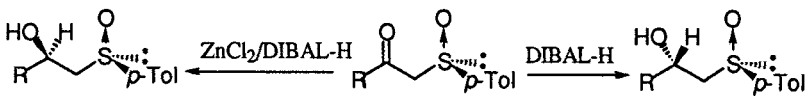
INTRODUCTION

Enantiomerically pure β-hydroxy sulfoxides, readily obtainable by the highly diastereoselective carbonyl reduction of β-keto sulfoxides, are synthetically valuable intermediates for the preparation of enantiomerically pure hydroxy compounds because of the ready elaboration of the residual functionalities. In addition, it is anticipated that these chiral β-hydroxy sulfinyl compounds could be employed as a chiral ligand or a chiral reagent in asymmetric synthesis. In order to evaluate such an ability of β-hydroxy sulfoxides, we chose to examine the protonation of lithium enolates.

RESULTS AND DISCUSSION

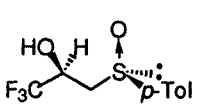
Synthesis of Chiral β-Hydroxy Sulfoxides

Both enantiomerically pure diastereomers of β-hydroxy sulfoxides used here were readily prepared by highly stereoselective reduction of the corresponding β-keto sulfoxides (**1**) (eq. 1).[1] We have also found that the reaction is quite general and the stereochemical course is not influenced even by dialkyl substituents α,α to the sulfinyl group.[2]

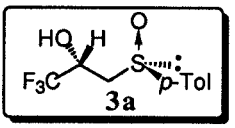


(1)

2 **1** **3**



2a



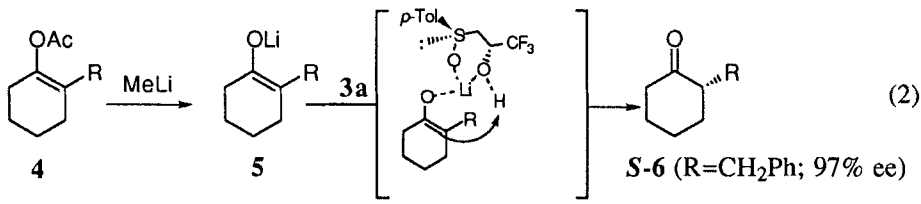
3a

Asymmetric Protonation of Prochiral Lithium Enolates

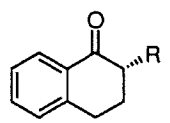
The protonations of the lithium enolate **5**, generated from 1-acetoxy-2-substituted-2-cyclohexene (**4**), were examined using the chiral β-hydroxy sulfoxides (**2** or **3**) under a variety of conditions. From these experiments, some characteristic features of the reaction appeared:

(1) An opposite sense of asymmetric induction is found by the choice of the diastereomeric alcohols **2** or **3**. Furthermore, the use of the (S,R_S)-isomers **3** shows much higher ee than the case of (R,R_S)-isomers **2**.
(2) 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 as a solvent resulted in the poor ee's.
(3) The larger size of the side chain (R) in β-hydroxy sulfoxides **3** did not cause significant improvement of the enantiostereoselection.
(4) Finally and most importantly, virtually complete asymmetric induction (R=CH_2Ph; 97% ee) was accomplished using (S,R_S)-CF_3-substituted derivative **3a**[3] (eq. 2); even when the (R,R_S)-isomer **2a** was used as protonating reagent, much higher ee (*R*-**6**; 79% ee) was attained compared with the cases of the corresponding alkyl derivative **2** (e.g. R=*i*-Bu, 43% ee).

With **3a**, protonation of some other lithium enolates also proceeds with high enantioselectivities. All cases examined show satisfactory results and the absolute configurations of the products indicate that the protonation with **3a** occurred preferentially from the same enantioface of the enolates, regardless of the nature of the α-substituent. In the present work, the proton source can be completely recovered without any loss of the optical purity.



4 **5** ***S*-6** (R=CH_2Ph; 97% ee) (2)



7a~c

7a	R=Me;	94% ee
7b	R=CH_2Ph;	87% ee
7c	R=CH_2CH=$CHPh$ (*E*)	78% ee

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 which involves a six-membered ring formation between the lithium enolate and β-hydroxy sulfoxide as shown in eq 2. As mentioned above, the enantioselectivity is governed by the nature of the β-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 attribute the higher selectivity of these latter reagents to the proximity of the boat-like conformation that is more topologically different from the chair-like conformation found in (R,R_S)-isomers. Given the reasonable assumption that the coordinated proton is delivered axially from the one face of the enolate carbon, then the steric approach model may provide a useful rationale for the present product stereochemistry.

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