The First Example of Enantioselective Protonation of Prochiral Enolates with Chiral γ-Hydroxyselenoxides

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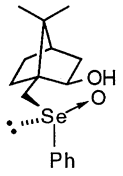
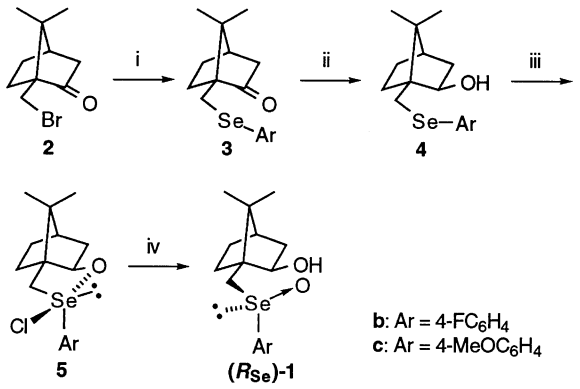
Enantioselective protonation of a simple enolate has been developed using an optically pure γ-hydroxyselenoxide **1** as a chiral proton source. Reaction of zinc bromide enolate **7b** with (S_{Se})-selenoxide (S_{Se})-**1c** gave (*S*)-2-benzylcyclohexanone (*S*)-**8** with high enantioselectivity. Intramolecular hydrogen bonding between hydroxy group and seleninyl-oxygen of **1** would contribute to this asymmetric induction.

Numerous studies have been reported on the preparation and application to asymmetric synthesis of optically active sulfoxides.[1] In contrast, relatively a few studies have been reported on those of optically active selenoxides. To the best of our knowledge, application of chiral selenoxides to asymmetric synthesis is limited to asymmetric selenoxide elimination and asymmetric [2,3]sigmatropic rearrangement.[2] The practical difficulty in studying chiral selenoxides in high enantiomeric or diastereomeric purity derives from their configurational lability. We have quite recently reported the facile synthesis of optically pure selenoxide **1a** (γ-hydroxyselenoxide) by using 2-*exo*-hydroxy-10-bornyl group as a chiral ligand.[3] We report here the first example of enantioselective protonation with the chiral γ-hydroxyselenoxide **1** as a chiral proton source to afford 2-benzylcyclohexanone up to 89% enantiomer excess (ee) and 81% chemical yield.

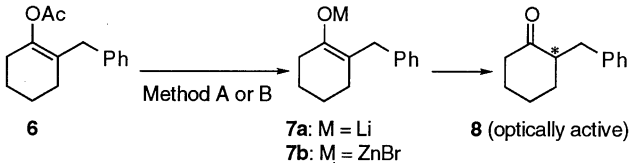


(R_{Se})-**1a**

Optically pure selenoxides **1b**,**c**[4] were prepared as shown in Scheme 1. Reaction of bromocamphor **2** with lithium arylselenolate gave camphorselenide **3** quantitatively. Reduction of carbonyl group of **3** afforded hydroxyselenide **4**. Reaction of **4** with *tert*-butyl hypochlorite gave chloroselenurane **5**, which was diastereoselectively converted to (R_{Se})-selenoxides (R_{Se})-**1b**,**c** by treatment with $NaHCO_3$ in 9 and 29% yield from **3**.



Scheme 1. *Reagent and conditions*: 1) ArSeLi, THF, reflux, ~100%. ii) $LiAlH_4$, Et_2O, -20 °C. iii) ^tBuOCl, MeOH-CH_2Cl_2, 0 °C. iv) aq. $NaHCO_3$, 9 and 29% from **3**.



Scheme 2. *Reagent and conditions*: Method A; i) 2 eq. MeLi, Et_2O, 0 °C then rt. ii) 3.3 eq. **1**, CH_2Cl_2, -100 °C. Method B; i) 4 eq. MeLi, Et_2O, 0 °C. ii) 1.5 eq. $ZnBr_2$, 0 °C then rt. iii) 4.3 eq. **1**, CH_2Cl_2, -100 °C.

Table 1. Enantioselective protonation of enolate **7a** with selenide **4a** or (R_{Se})-selenoxide (R_{Se})-**1a**[a]

chiral proton sources		**8**			
	Ar	yield (%)	$[\alpha]_D$ (°)	config.	ee (%)[b]
4a	Ph	53	+2.7	*R*	6
(R_{Se})-**1a**	Ph	51	+13.3	*R*	29

[a]Method A. [b]The enantiomer excess of the ketone **8** is calculated from $[\alpha]_D$ value.[5]

Enantioselective protonation with a simple selenium compound **1** or **4** was carried out according to the method of Matsumoto and Ohta[6] (method A) (Scheme 2 and Table 1). The ee of **8** was shown to be only 6% in the reaction with selenide **4a**, whereas that was determined to be 29% in the case of selenoxide (R_{Se})-**1a**. These results suggest that seleninyl group is responsible for asymmetric induction.

To improve the ee, we studied this asymmetric protonation reaction using selenoxides **1** which have an electron-withdrawing group or an electron-donating group. All selenoxides **1** were recovered quantitatively. When 4-fluorophenyl group was substituted instead of phenyl group, the ee of **8** decreased (Table 2). In the case of 4-anisyl group, the preferred enantiomer of **8** turned to *S* and the ee went up to 64%. Consequently, the enantioselectivity of this reaction has been improved by introduction of 4-methoxy group to benzene ring of a chiral proton source.

Next, we set out to examine reaction conditions using the

Table 2. Enantioselective protonation of enolate **7a** with (R_{Se})-selenoxides (R_{Se})-**1a-c**[a]

chiral proton sources		**8**			
	Ar	yield (%)	$[\alpha]_D$ (°)	config.	ee (%)[b]
(R_{Se})-**1a**	Ph	51	+13.3	*R*	29
(R_{Se})-**1b**	4-FC_6H_4	68	-0.2	—	0
(R_{Se})-**1c**	4-$MeOC_6H_4$	47[c]	-29.9	*S*	64

[a]Method A. [b]The ee was determined by HPLC analysis[6] and/or optical rotation.[5] [c]A mixture of unidentified compounds was also obtained.

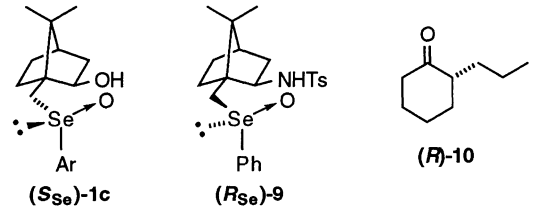
Table 3. Enantioselective protonation of enolates **7a,b** with (R_{Se})- or (S_{Se})-selenoxide (**R_{Se})-** or (**S_{Se})-1c**

chiral proton sources	method	**8** yield (%)	config.	ee (%)[a]
(**R_{Se})-1c**	A	47[e]	*S*	64
(**S_{Se})-1c**[b]	A	35[e]	*S*	62
(**R_{Se})-1c**[c]	B	82	*S*	62
(**S_{Se})-1c**[d]	B	81	*S*	89

[a]The ee was determined by optical rotation[5] and HPLC analysis.[6] [b]R_{Se} : S_{Se} = 5 : 95. [c]R_{Se} : S_{Se} = 95 : 5. [d]R_{Se} : S_{Se} = 3 : 97. [e]A mixture of unidentified compounds was also obtained.

chiral proton source **1c**. Fortunately, we obtained (S_{Se})-selenoxide (**S_{Se})-1c** by recrystallization of the crude selenoxide mixture from acetone in more than 90% de and the isolated yield was 12%. In order to check the influence of chirality of the seleninyl group on enantioface-differentiation, we carried out the protonation reaction with (**S_{Se})-1c**. Unexpectedly, the reaction also gave (***S*)-8** and showed about the same degree of enantioface-differentiation (62% ee). That is, both chirality of the seleninyl group and bornyl group influenced on this asymmetric induction. In the case of (**R_{Se})-1c**, changing lithium of the enolate to zinc bromide[7] (method B), chemical yield of **8** was improved to be 82%. Both ee and chemical yield went up to 89% and 81%, respectively, in the reaction with (**S_{Se})-1c** and zinc bromide enolate **7b**. Consequently, this enantioselective protonation is available for a practical use.

Typical procedure for Method B was as follows: 4 Equivalents of MeLi in Et_2O was added to a solution of enolacetate **6** in Et_2O at 0 °C and the reaction mixture was stirred at 0 °C for 5 min. To this was added 1.5 equivalents of $ZnBr_2$ at 0 °C and the whole mixture was stirred at 0 °C for 5 min and then at room temperature for 20 min to form zinc bromide enolate **7b**. After cooling to -100 °C, a solution of 4.3 equivalents of a chiral proton source in CH_2Cl_2 was added to the mixture. After 10 min stirring at -100 °C, the reaction temperature was allowed to warm to -10 °C. The reaction was quenched by addition of 0.2 mol dm^{-3} pH 6.8-phosphate buffer solution at 0 °C. Usual work-up and purification gave 2-benzylcyclohexanone **8**.



(**S_{Se})-1c** (**R_{Se})-9** (***R*)-10**

Ar = 4-$MeOC_6H_4$

The exact course of the reaction is not certain yet. Intramolecular hydrogen bonding between hydroxy group and seleninyl-oxygen as well as π–π stacking between benzene rings in selenoxide and substrate might contribute to this asymmetric induction. In order to support our working hypothesis, we carried out the protonation reaction with zinc bromide enolate **7b** and (R_{Se})-4-toluenesulfonamide (**R_{Se})-9**. By IR spectra, intramolecular hydrogen bonding of the N-H group of (**R_{Se})-9** was shown to be weaker than that of the O-H group. As expected, the ee decreased to 4%. With regard to π–π stacking, we investigated the protonation reaction with zinc bromide enolate of 2-*n*-propylcyclohexanone. When (S_{Se})-selenoxide (**S_{Se})-1c** was used as a chiral proton source, the ee and chemical yield of (*R*)-2-*n*-propylcyclohexanone (***R*)-10**[8] were 88% and 76%, respectively. These results suggested that the asymmetric induction did not derive from π–π stacking between benzene rings in selenoxide and substrate.

Recently, much attention has been paid on an enantioselective protonation and there have been some reports which succeeded in the asymmetric induction of simple enolates.[6,9] Our methodology will provide a new entry to this research field. Application of our method to other substrates and detailed mechanistic work are now in progress in our group.

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References and Notes

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