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Asymmetric Protonation of Ketone Enolates Using Chiral β-Hydroxyethers: Acidity-Tuned Enantioselectivity

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Abstract: New chiral hydroxyethers **1a**−**f** were prepared for asymmetric protonation of achiral enolates prepared from prochiral ketones. The enantioselectivity of protonation was highly dependent upon the acidity of the chiral alcohols, the highest enantioselectivity (90% ee) being achieved with 3,5-dichloro-substituted β-hydroxyether **1c**. A salt-free enolate generated from trimethylsilyl enol ether **4** provided product of the highest ee. Unlike other reagents, chloro-substituted alcohols provided almost consistent enantioselections throughout the reaction temperatures examined (−25 to −98 °C). Protonation of other aromatic ketones showed selectivity similar to that of 2-methyl-1-tetralone.

Enantioselective protonation is one of the most efficient approaches for obtaining optically active α-substituted carbonyl compounds since a chiral proton source can be recovered and reused.[1] Many stoichiometric and catalytic chiral proton donors for enantioselective protonation of prochiral enolates have been developed. Among many reagents used for the asymmetric protonation, chiral alcohols and amines have been employed most frequently. As depicted in Figure 1, most chiral alcohols contain various functional groups such as carbonyl (**A**),[2−5] amino (**B**),[6−8] sulfinyl (**C**),[9,10] and selenoxy (**D**)[11] groups adjacent to the hydroxyl moiety to assist in better chelation of the metal from the enolate. Among these, the sulfinyl directing group (**C**) has proven to be most effective, allowing for exceedingly enantioselelctive (up to 99% ee's) protonation.[9,10] It appears that these groups

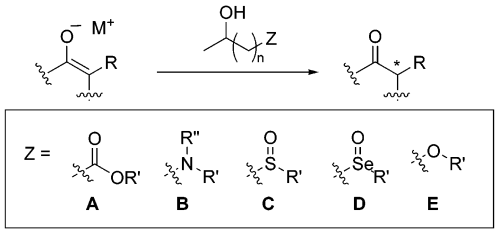

FIGURE 1. Asymmetric protonation of enolates using various chiral alcohols as proton donors.

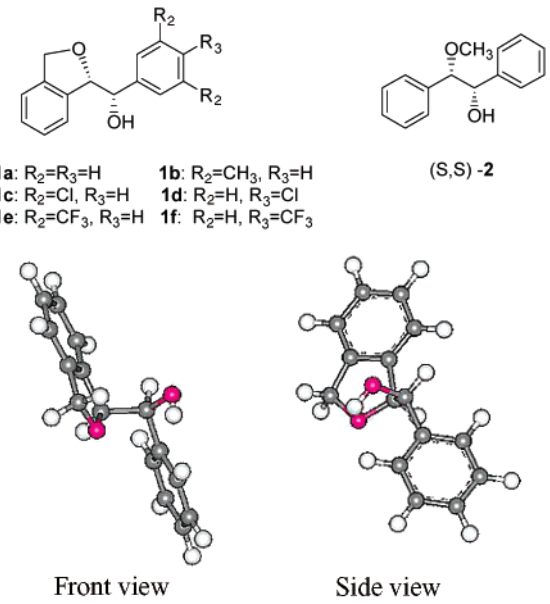

FIGURE 2. Chiral hydroxyethers **1a**−**f** and **2** and Molecular modeling of (*S*,*S*)-**1a**. Geometry was optimized at PM3 using the PC Spartan Pro program.

coordinate to the metal of the enolate and discriminate two enantiotopic faces in the protonation step. However, proton donors composed of chiral β-hydroxy ethers (**E**) are rare,[12] presumably due to the common acceptance that the ether functionality is not effective as a ligand for metals.

We envisioned that if both the alcohol and the ether oxygen atoms of **1a**[13] are employed to bind a metal, a

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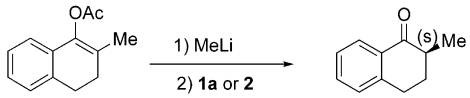
TABLE 1. Asymmetric Protonation of the Enolate Generated from Enol Acetete 3 Using MeLi in the Presence of Chiral β-Hydroxy Ether 1a or 2 at Various Temperatures[a]



3 **5**

entry	proton source	temp (°C)	% ee of (*S*)-**5**
1	(*S*,*S*)-**2**	−78	28
2	(*S*,*S*)-**1a**	0	46
3	(*S*,*S*)-**1a**	−25	67
4	(*S*,*S*)-**1a**	−42	71
5	(*S*,*S*)-**1a**	−78	72
6	(*S*,*S*)-**1a**	−98	56

[a] MeLi in diethyl ether was added to the enol acetate in dichloromethane.

TABLE 2. Asymmetric Protonation of Enolate Generated from Enol Acetate 3 Using MeLi at −78 °C[a]

entry	proton source	% ee of ketone (*S*)-**5**
1	(*S*,*S*)-**1a**	72
2	(*S*,*S*)-**1b**	39
3	(*S*,*S*)-**1c**	78

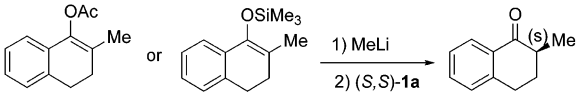
[a] MeLi in diethyl ether was added to the enol acetate in dichloromethane.

pseudo-C_2-symmetric alignment could be constructed as shown in Figure 2. This conformational rigidity may be exploited in asymmetric protonation of prochiral enolates. It is also of note that, by changing substituents at the phenyl ring connected to the carbinol, various steric and electronic influences on the reaction enantioselectivity could be examined. Herein we report on the efficient asymmetric protonation of lithium enolates generated from α-substituted ketone derivatives employing novel chiral β-hydroxyethers **1a**−**f**.

Synthesis of β-hydroxy ether analogues equipped with various substituents (**1b**−**f**) has been accomplished accordingly to the reported method.[13] As a control experiment, protonation of an enolate prepared from enol acetate **3** using (*S*,*S*)-2-methoxy-1,2-diphenyl-ethanol **2**[14] was carried out, and ketone (*S*)-**5** of only 28% ee was obtained (Table 1, entry 1). The low enantioselectivity might be due to a large degree of freedom around the acyclic ether moiety of compound **2**. When the conformationally constrained cyclic ether **1a** was employed, however, a significant improvement of enantioselection was observed as summarized in Table 1. It is interesting to note that, as the reaction temperature was lowered, the enantioselectivity of the protonation using **1a** increased, peaking at −78 °C (entry 5), and then decreased as the temperature was decreased further.[15]

Then we examined three electronically dissimilar chiral β-hydroxy ethers **1a**−**c**. As summarized in Table 2, when the reactions were carried out at −78 °C, the 3,5-dichloro-substituted alcohol **1c** exhibited the best enantioselection (78% ee, entry 3). Even though **1b** is similar in structure to **1c**, protonation with **1b** proceeded with strikingly low enantioselectivity (39% ee, entry 2). This strongly indicates that the asymmetric protonation is closely related to the acidity of the proton donor alcohol.[10c,16]

TABLE 3. Effect of Additives in Asymmetric Protonation from Enolates Generated from 3 or 4[a]



3 **4** **5**

entry	enolate source	temp (°C)	salts present or added	% ee of ketone (*S*)-**5**
1	**3**	−78	LiO^{t}Bu	72
2	**3**	−78	LiO^{t}Bu/LiBr	24
3	**3**	−42	LiO^{t}Bu/LiBr	14
4	**4**	−78	none	81
5	**4**	−78	LiBr	75

[a] MeLi in diethyl ether was added to the enolate precursor in dichloromethane.

The presence of metal salts has been known to change the enolate structure,[17] and improved enantioselectivities have often been observed with added metal salts such as lithium in asymmetric protonation.[10,18] To examine the effect of lithium salts in our protonation, reactions were examined in the presence/absence of LiBr as outlined in Table 3. Contrary to the previously reported cases, the addition of lithium bromide to the enolate generated from **10** resulted in a precipitous drop of the enantioselectivity regardless of reaction temperature (entries 2 and 3, Table 3). Since the generation of lithium enolate from the enol acetate **3** is inevitably accompanied with lithium *tert*-butoxide, also a lithium salt, we examined the reaction of salt-free lithium enolate. For this purpose, the silyl enol ether **4** was selected as a precursor for the generation of the enolate. As can be seen in Table 3, protonation of the enolate generated from **4** proceeded with the highest enantioselectivity, yielding product of 81% ee (entry 4). However, addition of lithium bromide to the salt-free enolate had a deleterious effect on enantioselectivity (entry 5).

To examine the effect of the reaction media on enantioselectivity, reactions in various solvents have been carried out, and the results are summarized in Table 4. The enantioselection was found to be extremely sensitive to the solvents, and the best result was achieved when the reaction was carried out in dichloromethane using MeLi in ether (entry 1).

Having established the best reaction conditions for the protonation using chiral hydroxyether **1a**, we examined

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TABLE 4. Solvent Effects on the Protonation of Enolates Generated from Silyl Enol Ether 4 Using β-Hydroxyether 1a or 1c

entry	proton donor	temp (°C)	solvent (MeLi/reaction)[a]	% ee of ketone (*S*)-**5**
1	(*S*,*S*)-**1a**	−78	Et_2O/CH_2Cl_2	81
2	(*S*,*S*)-**1a**	−78	Et_2O/toluene	30
3	(*S*,*S*)-**1c**	−78	Et_2O/toluene	72
4	(*S*,*S*)-**1a**	−42	Et_2O/Et_2O	45
5	(*S*,*S*)-**1a**	−25	THF/THF	2

[a] MeLi in the first solvent was added to the silyl enol ether in the second solvent.

various chiral hydroxyethers **1a**−**f** at four different temperatures in order to further examine the influence of the alcohol's acidity toward the reaction enantioselectivity. Relative acidities of these halogenated hydroxyethers have been evaluated using computational methods, and the electrostatic potential, which is believed to be correlated to the acidity,[19] was in the order of **1a**, **1b** < **1c**, **1d** < **1e**, **1f**.[20] As summarized in Table 5, while protonation using **1a** and **1b** exhibited variation of enantioselectivities according to the reaction temperature (entries 2−5 and 6−9, respectively), reactions using 3,5-dichlorobenzyl- and 4-chlorobenzyl alcohol derivatives **1c** and **1d** showed much improved and almost constant enantioselectivities regardless of the reaction temperature (entries 10−14 and 15−18, respectively). Of the two chlorinated alcohols, 3,5-dichlorinated alcohol **1c** provided the better enantioselection (90% ee, entries 11−13), and the same magnitude of asymmetric induction was obtained using either (*S*,*S*)-**1c** or (*R*,*R*)-**1c** at −78 °C. Reactions employing **1d** exhibited uniformly lower (74−78% ees) enantioselection than those using **1c** (88−90% ees), indicating that a steric factor may play a role in the case of alcohols of similar acidity. To examine the effect of still more acidic alcohols, we have carried out reactions using 3,5-bis(trifluoromethyl)benzyl- and 4-(trifluoromethyl)benzyl alcohol derivatives **1e** and **1f**, respectively. However, neither of the fluorinated alcohols showed better enantioselection than those obtained with chloro-substituted hydroxyethers **1c** and they exhibited somewhat fluctuating enantioselectivities according to the reaction temperature (entries 19−26).

A few structurally related aromatic prochiral ketones have been examined employing **1c** under the most selective asymmetric protonation conditions (Table 6). Enantioselectivity (87% ee, entry 1) comparable to the case of 2-methyltetralone was observed in the production of 2(*S*)-benzyl-1-tetralone; however, slightly diminished enantioselectivity (79% ee, entry 2) was obtained in the protonation of enolates derived from 2-methyl-1-indanone. Aliphatic ketones such as 2,2,6-trimethylcyclohexanone turned out to be very poor substrates for asymmetric protonation using **1c**. Almost negligible asymmetric induction (3% ee) was observed.

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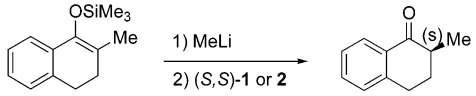
(20) Energy of a hypothetical proton removal process is given by the electrostatic potential at the site of the acidic proton in neutral acid. The values for **1a**−**f** are 44.46, 44.82, 49.22, 49.19, 56.70, and 53.44 kcal/mol, respectively. Calculations were performed at HF/6-31G** level using the PC Spartan Pro program.

TABLE 5. Asymmetric Protonation of a Salt-Free Enolate Generated from Silyl Enol Ether 4 Using β-Hydroxyether 1a−f or 2 at Various Temperatures

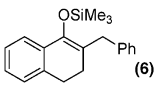
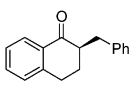
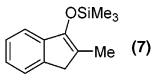
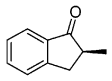
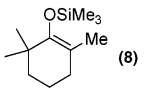
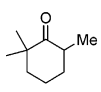


4 **5**

entry	proton donor[a]	temp (°C)	conversion[b] (%)	% ee of ketone (*S*)-**5**
1	(*S*,*S*)-**2**	−78	90[c]	3
2	(*S*,*S*)-**1a**	−98	90	70
3	(*S*,*S*)-**1a**	−78	99	81
4	(*S*,*S*)-**1a**	−42	64[c]	73
5	(*S*,*S*)-**1a**	−25	93[c]	52
6	(*S*,*S*)-**1b**	−98	96	43
7	(*S*,*S*)-**1b**	−78	97[c]	56
8	(*S*,*S*)-**1b**	−42	75[c]	38
9	(*S*,*S*)-**1b**	−25	98[c]	64
10	(*S*,*S*)-**1c**[d]	−98	95	88
11	(*S*,*S*)-**1c**[d]	−78	87	90
12	(*R*,*R*)-**1c**	−78	97	−90[e]
13	(*S*,*S*)-**1c**[d]	−42	88[c]	90
14	(*S*,*S*)-**1c**[d]	−25	80[c]	88
15	(*S*,*S*)-**1d**	−98	82	74
16	(*S*,*S*)-**1d**	−78	97	77
17	(*S*,*S*)-**1d**	−42	88	75
18	(*S*,*S*)-**1d**	−25	99	78
19	(*S*,*S*)-**1e**	−98	89	84
20	(*S*,*S*)-**1e**	−78	97	82
21	(*S*,*S*)-**1e**	−42	95	70
22	(*S*,*S*)-**1e**	−25	76	78
23	(*S*,*S*)-**1f**	−98	92	72
24	(*S*,*S*)-**1f**	−78	99	79
25	(*S*,*S*)-**1f**	−42	97	85
26	(*S*,*S*)-**1f**	−25	85	77

[a] Reagents of >99% ee were used unless otherwise noted. [b] Determined through ^{1}H NMR analysis unless otherwise noted. [c] Determined through HPLC analysis. [d] (*S*,*S*)-**1c** of 96% ee was used, and the product ee was corrected for the purity of (*S*,*S*)-**1c**. [e] Ketone (*R*)-**5** was obtained.

TABLE 6. Asymmetric Protonation of Salt-Free Enolates Generated from Silyl Enol Ethers 6−8 Using β-Hydroxyether 1c at −78 °C

Entry	Substrates	Conversion[a] (%)	Product ketone	Ee (%)[b]
1	 (**6**)	79		87
2	 (**7**)	97		79
3	 (**8**)	-		3[c]

[a] Determined through ^{1}H NMR analysis. [b] Ee values were determined through HPLC analysis using a Daicel Chiralcel OD-H column. [c] Ee value was determined through GC analysis using a chiral column (SUPELCO, γ-DEX).

As for the transition state model for the asymmetric protonation using (*S*,*S*)-**1c**, four possible approaches are postulated as shown in Figure 3. Though lithium enolates may exist primarily as tetrameric and diametric aggregates in ethereal solution,[17] we focused on the monomeric structure to clarify the origin of stereoselectivity. First, due to the steric interaction between the α-methyl

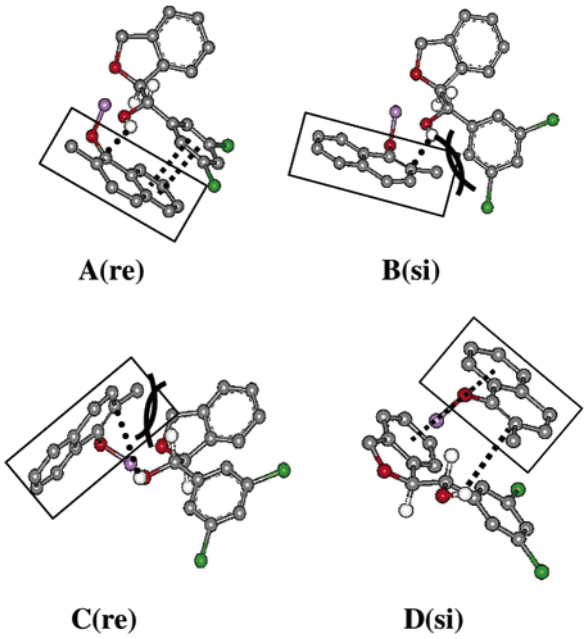


FIGURE 3. Four possible transition-state approach models for the asymmetric protonation of α-methyltetralone using (*S*,*S*)-**1c**.

group of the enolate and the chiral hydroxy ether, models **A(re)** and **D(si)** would be more favorable than **B(si)** and **C(re)**. Second, though similar attractive $\pi-\pi$ interactions are considered to exist between the chiral hydroxyether and the lithium enolate in **A(re)** and **D(si)**, due to electronegative substituents of the chiral hydroxyether, the chlorinated phenyl ring would decrease the energy level of the HOMO−LUMO interaction. Consequently, among the four possible approaches, **A(re)** appears to be the most preferable one, producing the experimentally observed (*S*)-ketone. Calculated energy values of HOMO−LUMO of **1a**−**d** were shown in the order of **1a**, **1b** > **1c**, **1d** > **1e**, **1f**,[21] which is in accordance with the previous calculation of relative acidities.

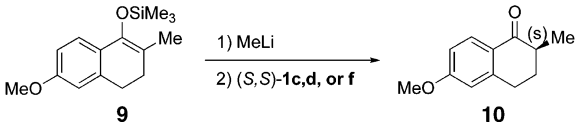
According to the proposed transition state model, an increase in the enantioselectivity could be expected from attractive $\pi-\pi$ interaction improving the HOMO−LUMO interaction. To see if the increased electron density of the enolate has a positive effect on enantioselectivity, protonation of an enolate derived from 6-methoxy-2-methyltetralone (**9**) was examined, and the results are summarized in Table 7.[22] When alcohol **1d** was used as a proton source, a significant increase (from 78 to 92% ee) in enantioselectivity was observed compared to the reaction of 2-methyltetralone. However, in the case of protonation using **1c** or **1f**, decreased enantioselectivity was observed, indicating a repulsive interaction between the substituted aryl groups due to steric interaction.

(21) Energy levels of HOMO/LUMO of the enolate from ketone **12** and **1a**−**f**. Calculations were performed at the HF/6-31G* level using the PC Spartan Pro program.

	enolate from ketone **5**	**1a**	**1b**	**1c**	**1d**	**1e**	**1f**
HOMO (eV)	−6.63	−8.65	−8.54	−8.91	−8.69	−9.12	−8.93
LUMO (eV)	0.024	3.50	3.54	3.02	3.29	2.32	2.90

(22) Authors thank one of the reviewers for the suggestion on the experiment with 6-methoxy-2-methyltetralone.

TABLE 7. Results of the Protonation of the Enolate Derived from 6-Methoxy-2-methyltetralone



9 **10**

entry	proton donors	temp (°C)	conversion (%)[a]	ee (%)[b] of 2-methyl-tetralone	ee (%)[b] of 6-methoxy-2-methyl-tetralone
1	(*S*,*S*)-**1c**	−78	84	90	80
2	(*S*,*S*)-**1d**	−78	85	78	92
3	(*S*,*S*)-**1f**	−78	72	79	70

[a] Determined through ^{1}H NMR analysis. [b] Ee values were determined through HPLC analysis using a Daicel Chiralcel OD-H column.

In conclusion, we have designed new chiral hydroxy-ethers **1a**−**f** for asymmetric protonation of achiral enolates prepared from prochiral ketones and the enantioselectivity of reactions employing these hydroxy ethers were found to be highly dependent upon the acidity of the chiral alcohols. Compounds **1b** and **1c**, though similar in structure, exhibited a dramatic difference in the enantioselectivity in the protonation of enolate generated from **3**. It was found that a salt-free enolate generated from trimethylsilyl enol ether **4** provided product of the highest enantiomeric excess, contrary to the previously reported systems. Reaction media were also found to drastically influence the results, and careful selection of solvents was essential to ensure high enantioselectivity of the reaction. With a variety of chiral alcohols **1a**−**f**, product of 90% ee was achieved using 3,5-dichloro-substituted β-hydroxyether **1c**. Reagents with methyl or trifluoromethyl substituents exhibited fluctuating selectivity depending upon the reaction temperature; however, chloro-substituted reagents provided almost consistent enantioselections throughout the reaction temperatures examined (−25 to −98 °C). Protonations of other aromatic ketones were examined, and they showed selectivity similar or slightly inferior to that of 2-methyl-1-tetralone. Almost negligible asymmetric induction was observed with aliphatic ketone precursor **8**. A transition state model involving attractive $\pi-\pi$ interaction between the enolate and the chiral proton source is proposed. A ketone with increased electron density, 6-methoxy-2-methyl-tetralone, exhibited a preference for chiral alchol **1d** rather than **1c**, showing 92% ee with **1d**.

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Supporting Information Available: A reaction scheme for the preparation of and characterization data for compounds **1a**−**f**, and a representative procedure for asymmetric protonation. This material is available free of charge via the Internet at http://pubs.acs.org.

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