Effects of Lithium Salts on the Enantioselectivity of Protonation of Enolates with Chiral Imide

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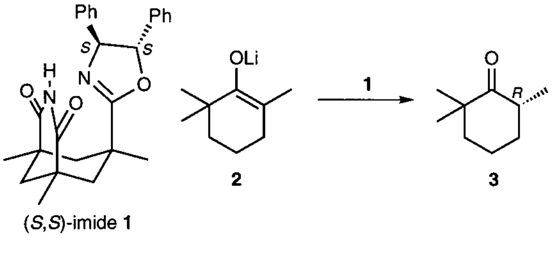
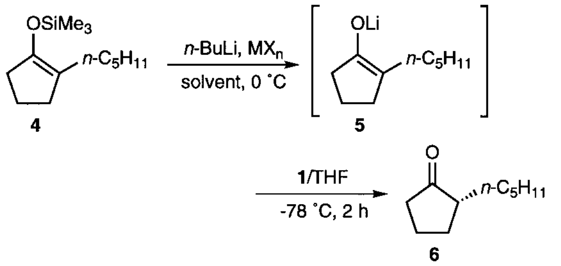
Abstract: An increase in enantioselectivity was observed in the asymmetric protonation of prochiral enolates with a chiral imide using lithium salt as an additive. For example, (*R*)-enriched 2-*n*-pentylcyclopentanone **6** was obtained in high yield with 90% ee when the silyl enol ether **4** was treated with *n*-BuLi in the presence of 5 equiv of LiBr in Et_2O and the resulting lithium enolate **5** was then protonated by a solution of (*S*,*S*)-imide **1** in THF. In contrast, the product **6** obtained without LiBr exhibited a lower enantiomeric excess (74% ee).

We have previously shown that (*S*,*S*)-imide **1**, a chiral imide with an asymmetric 2-oxazoline, is an efficient chiral proton source for asymmetric protonation of simple metal enolates.[1,2] Various enolates derived from 2-alkylcycloalkanones can be protonated with high enantioselectivity. For instance, the reaction of lithium enolate **2** with an equimolar amount of the chiral imide **1** gives (*R*)-enriched 2,2,6-trimethylcyclohexanone (**3**) with 87% ee (eq 1).[1a] We report here the asymmetric protonation of prochiral enolates in which enantioselectivity is remarkably improved using lithium bromide as an additive. Lithium salts are known to be incorporated into lithium enolate aggregates[3] and often increase the degree of asymmetric induction.[4] Thus, we examined the effect of the addition of lithium salt on the enantioselectivity of protonation with (*S*,*S*)-imide **1**.



(1)

The silyl enol ether **4**[5] was treated with a solution of *n*-BuLi/hexane[6] (1.1 equiv) in the presence of a metal salt in THF or ether at 0 °C for 2 h, and the *in situ*-generated lithium enolate **5** was then protonated with (*S*,*S*)-imide **1** (1.1 equiv) in THF at -78 °C for 2 h to give (*R*)-enriched 2-*n*-pentylcyclopentanone (**6**,[7] eq 2). The results are summarized in Table 1. In the absence of a metal salt, the reaction proceeded in THF or a mixture of ether and THF with moderate enantioselectivity (63~74% ee, entries 1 and 2). In contrast, when an equimolar amount of lithium bromide was present, higher enantiomeric excesses were obtained (entries 3 and 4). Further increases in enantioselectivity were observed under the influence of more than one equivalent of LiBr. The use of 5 equiv of the salt in ether resulted in the highest optical purity (90% ee, entry 8). Interestingly, protonation of the lithium enolate **5** gave better results in a mixture of ether and THF than in THF alone regardless of the amount of LiBr (entries 1-10).[8] Although other lithium salts, sodium bromide, and magnesium bromide were also examined as additives, they decreased the enantiomeric ratio of the ketone **6** (entries 11-17). CH_2Cl_2 and MeO^nPr were less effective solvents with respect to asymmetric induction (entries 18 and 19).



(2)

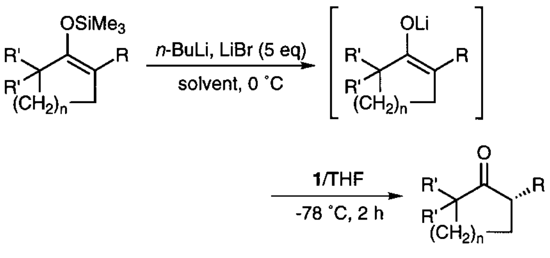
Table 1. Influence of salts on the enantioselectivity of protonation of the lithium enolate **5** with (*S*,*S*)-imide **1**[a]

Entry	MX_n (equiv)	solvent[b]	% ee[c]
1	—	THF	63
2	—	Et_2O	74
3	LiBr (1)	THF	79
4	LiBr (1)	Et_2O	83
5	LiBr (2)	THF	79
6	LiBr (2)	Et_2O	85
7	LiBr (5)	THF	77
8	LiBr (5)	Et_2O	90
9	LiBr (10)	THF	78
10	LiBr (10)	Et_2O	88
11	LiCl (5)	THF	80
12	LiCl (5)	Et_2O	77
13	$LiClO_4$ (5)	THF	58
14	$LiClO_4$ (5)	Et_2O	72
15	LiI (5)	THF	40
16	NaBr (5)	THF	65
17	$MgBr_2$ (5)	THF	1[d]
18[e]	LiBr (5)	Et_2O	60
19[f]	LiBr (5)	MeO^nPr	71

[a] Unless otherwise noted, the lithium enolate **5** was generated from the silyl enol ether **4** (1 equiv) and a solution of *n*-BuLi/hexane (1.1 equiv) in the presence of metal salt in the specified solvent at 0 °C for 2 h. The enolate **5** was then protonated with (*S*,*S*)-imide **1** (1.1 equiv) in THF at -78 °C for 2 h. Unreacted enolate **5** was recovered as the silyl enol ether **4** by quenching with TMSCl at -78 °C. Yields of the isolated product **6** were >99~78%. [b] A small amount of hexane (ca. 6%) was contained in each solvent. [c] Determined by GC analysis with chiral column (Chiraldex™ B-TA, astec). (*R*)-Enriched ketone **6** was obtained in each case except for entry 17. [d] (*S*)-Enriched product was obtained. [e] A solution of (*S*,*S*)-imide **1** in CH_2Cl_2 was used. [f] A solution of (*S*,*S*)-imide **1** in MeO^nPr was used

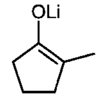
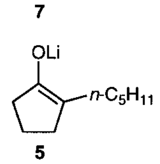
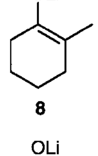
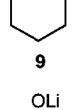
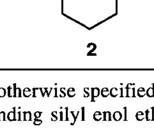
We then studied the enantioselective protonation of various enolates **2**, **5**, and **7**-**9**[9] with (*S*,*S*)-imide **1** in the presence of 5 equiv of LiBr (eq 3). Some examples are listed in Table 2. These reactions have the following characteristics: (1) the addition of LiBr had a positive effect for all of the enolates tested, with the exception of the lithium enolate **2** (entries 9 and 10); (2) higher enantioselectivity was attained when a lithium enolate was generated in ether rather than THF,[8] except in the case of **2**, which gave the best ee in the reaction without LiBr in THF (entry 9); and (3) a lithium enolate of 2-alkylcyclopentanone is superior to that of

2-alkylcyclohexanone with regard to the enantioselectivity of protonation with **1** (compare entries 1, 2, 5, and 6).



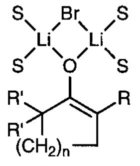
(3)

Table 2. Enantioselective protonation of various enolates with (*S*,*S*)-imide **1** in the presence of LiBr[a]

Entry	Lithium enolate	solvent[b]	% ee[c]
1	 **7**	THF	86[d] (59)[d]
2		Et_2O	92[d] (51)[d]
3	 **5**	THF	77 (63)
4		Et_2O	90 (74)
5	 **8**	THF	50 (24)
6		Et_2O	68 (33)
7	 **9**	THF	65 (52)
8		Et_2O	73 (62)
9	 **2**	THF	88[e] (88)[e]
10		Et_2O	79[e] (87)[e]

[a] Unless otherwise specified, a lithium enolate was generated from the corresponding silyl enol ether (1 equiv) and a solution of *n*-BuLi/hexane (1.1 equiv) in the presence of LiBr (5 equiv) in THF or Et_2O at 0 °C for 2 h. The following protonation was carried out using (*S*,*S*)-imide **1** (1.1 equiv) in THF at -78 °C for 2 h. An unreacted enolate was recovered as a silyl enol ether by quenching with TMSCl at -78 °C. Yields of the isolated product were >99~73%. [b] A small amount of hexane (ca. 6%) was contained in each solvent. [c] Determined by GC analysis with chiral column (Chiraldex™ B-TA, astec). Parentheses indicate the enantioselectivities of the reaction in the absence of LiBr. (*R*)-Enriched ketone was obtained in each case. [d] Determined by GC analysis with chiral column (Chiraldex™ B-TA, astec) of the acetate ester of *cis*-2-methylcyclopentanol derived from the corresponding ketone by reduction (L-Selectride®/THF, -78 °C) and acetylation (Ac_2O, Et_3N/CH_2Cl_2, r.t.). [e] Determined by GC analysis with chiral column (Chiraldex™ G-TA, astec)

It is not yet clear why LiBr increases the enantioselectivity of protonation. However, a mixed aggregate might be formed, such as **10**, consisting of a lithium enolate and LiBr, and this could participate in the reaction.[3] In fact, it has been reported that LiBr suppresses the concentration of a monomeric lithium enolate, and that a lithium enolate-LiBr mixed aggregate is the dominant reactant at higher concentrations of LiBr.[10] We have described above an improved method for the enantioselective protonation of simple prochiral enolates with (*S*,*S*)-imide **1** in the presence of LiBr as an additive.



10 (S = solvent)

A representative experimental procedure is given by the reaction of lithium enolate **5** with (*S*,*S*)-imide **1** (entry 8 in Table 1 and entry 4 in Table 2). Silyl enol ether **4** was prepared from 2-*n*-pentyl-2-cyclopentenone.[5] To a mixture of **4** (226 mg, 1.0 mmol) and LiBr (434 mg, 5.0 mmol) in dry Et_2O (5 mL) at 0 °C was added a solution of *n*-BuLi (1.65 M, 0.67 mL, 1.1 mmol) in hexane under argon.[6] After the reaction mixture had been stirred for 2 h at 0 °C, a solution of (*S*,*S*)-imide **1** (443 mg, 1.1 mmol) in dry THF (5 mL) was added dropwise at -78 °C. After being stirred for 2 h, TMSCl (0.13 mL, 1.0 mmol) was added, and stirring continued for another 30 min at this temperature. A saturated NH_4Cl solution (10 mL) was then added, and the organic material was extracted twice with Et_2O (2 x 10 mL). The combined organic extracts were washed with saturated brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (pentane/Et_2O, 5/1 to hexane/EtOAc, 1:2) to give the (*R*)-enriched ketone **6** (155 mg, >99% isolated yield) with 90% ee as a colorless oil which showed the appropriate spectral data.[11] The enantiomeric ratio was determined by GC analysis using a chiral column (astec, Chiraldex™ B-TA, 80 °C, 70 Pa): t_R = 23.9 min (*R*-isomer); t_R = 24.7 min (*S*-isomer). The imide **1** was recovered (>90% yield) without a noticeable loss of optical purity.

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References and Notes

(1) (a) Yanagisawa, A.; Kuribayashi, T.; Kikuchi, T.; Yamamoto, H. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 107. (b) Yanagisawa, A.; Kikuchi, T.; Watanabe, T.; Kuribayashi, T.; Yamamoto, H. *Synlett* **1995**, 372. (c) Yanagisawa, A.; Ishihara, K.; Yamamoto, H. *Synlett* **1997**, 411. (d) Yanagisawa, A.; Watanabe, T.; Kikuchi, T.; Kuribayashi, T.; Yamamoto, H. *Synlett* **1997**, 956.

(2) Reviews of asymmetric protonations: (a) Duhamel, L.; Duhamel, P.; Launay, J.-C.; Plaquevent, J.-C. *Bull. Soc. Chim. Fr.* **1984**, II-421. (b) Fehr, C. *Chimia* **1991**, *45*, 253. (c) Waldmann, H. *Nachr. Chem., Tech. Lab.* **1991**, *39*, 413. (d) Hünig, S. In *Houben-Weyl: Methods of Organic Chemistry*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1995; Vol. E 21, p 3851. (e) Fehr, C. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2566.

(3) (a) Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, T.; Simson, M.; Seebach, D. *Synthesis* **1993**, 1271. (b) Henderson, K. W.; Dorigo, A. E.; Liu, Q.-Y.; Williard, P. G.; Schleyer, P. v. R.; Bernstein, P. R. *J. Am. Chem. Soc.* **1996**, *118*, 1339.

(4) Protonation: (a) Yasukata, T.; Koga, K. *Tetrahedron: Asymmetry* **1993**, *4*, 35. (b) Gerlach, U.; Haubenreich, T.; Hünig, S. *Chem.*

Ber. **1994**, *127*, 1981. Alkylation: (c) Murakata, M.; Nakajima, M.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1990**, 1657. (d) Hasegawa, Y.; Kawasaki, H.; Koga, K. *Tetrahedron Lett.* **1993**, *34*, 1963. (e) Imai, M.; Hagihara, A.; Kawasaki, H.; Manabe, K.; Koga, K. *J. Am. Chem. Soc.* **1994**, *116*, 8829.

(5) The silyl enol ether **4** was prepared by treating 2-*n*-pentyl-2-cyclopentenone with L-Selectride® in THF followed by silylation (TMSCl, Et_3N). Selective 1,4-reduction by L-Selectride®, see: Fortunato, J. M.; Ganem, B. *J. Org. Chem.* **1976**, *41*, 2194.

(6) *n*-BuLi can be used for cleavage of the Si-O bond of silyl enol ether **4** instead of MeLi. Generation of lithium enolates: Colvin, E. W. *Silicon in Organic Synthesis*; Butterworth: London, 1981; p 217.

(7) The absolute configuration of **6** was determined by comparison of its optical rotation with published data: Ohta, T.; Miyake, T.; Seido, N.; Kumobayashi, H.; Akutagawa, S.; Takaya, H. *Tetrahedron Lett.* **1992**, *33*, 635.

(8) A small amount of hexane (ca. 6%) was also contained in each solvent. Hünig and coworkers have reported a similar solvent effect, see reference 4b.

(9) The silyl enol ether of **7** was prepared from 2-methyl-2-cyclopentenone according to a method similar to that for **4**.[5] The silyl enol ethers of **8** and **9** were prepared by treating the corresponding ketones with bromomagnesium diisopropylamide in ether followed by silylation (TMSCl, Et_3N, HMPA): Krafft, M. E.; Holton, R. A. *Tetrahedron Lett.* **1983**, *24*, 1345.

(10) Abu-Hasanayn, F.; Streitwieser, A. *J. Am. Chem. Soc.* **1996**, *118*, 8136.

(11) TLC R_f 0.28 (1:10 ethyl acetate/hexane); IR (neat) 2959, 2930, 2872, 2859, 1740, 1468, 1456, 1408, 1379, 1333, 1271, 1154, 1092, 1003, 930, 831, 727 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3 H, J = 6.9 Hz, CH_3), 1.16-1.41 (m, 7 H, one proton of CH_2 and 3 CH_2), 1.42-1.60 (m, 1 H, one proton of CH_2), 1.67-1.89 (m, 2 H, CH_2), 1.92-2.37 (m, 5 H, CH and 2 CH_2); $[\alpha]^{24}_D$ -114.9 (c 2.1, CH_3OH).