ORGANIC LETTERS

2006
Vol. 8, No. 8
1721−1724

Catalytic Asymmetric Protonation of Lithium Enolates Using Amino Acid Derivatives as Chiral Proton Sources

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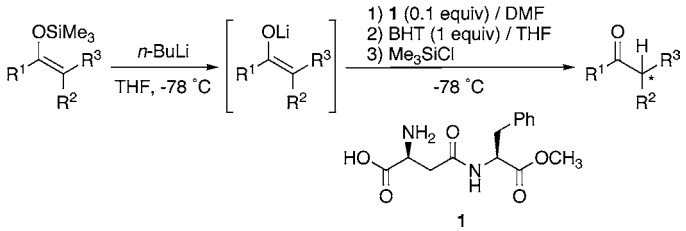
Received February 4, 2006

ABSTRACT



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Asymmetric protonation of lithium enolates was examined using commercially available amino acid derivatives as chiral proton sources. Among the amino acid derivatives tested, *Nβ*-L-aspartyl-L-phenylalanine methyl ester was found to cause significant asymmetric induction in the protonation of lithium enolates. The enantiomeric excess (up to 88% ee) of the products obtained in the presence of a catalytic amount of the chiral proton source was higher than those obtained in the stoichiometric reaction.

Asymmetric protonation of enols or enolates is an efficient route to prepare optically active carbonyl compounds that possess a tertiary asymmetric carbon at the α-position.[1,2] A number of excellent examples of asymmetric protonation using a chiral Brønsted acid have so far been reported, and some of them proceed catalytically with a stoichiometric amount of an achiral proton source;[3] however, most of these chiral Brønsted acids are expensive or require a multistep synthesis, and thus, superior chiral proton sources are desired.

Here, we wish to report a novel example of catalytic asymmetric protonation using commercially available amino acid derivatives as chiral proton sources.

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(1) For reviews, see: (a) Hünig, S. In *Houben-Weyl: Methods of Organic Chemistry*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E21, p 3851. (b) Fehr, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2566. (c) Yanagisawa, A.; Yamamoto, H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; Vol. III, p 1295. (d) Eames, J.; Weerasooriya, N. *Tetrahedron: Asymmetry* **2001**, *12*, 1. (e) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726. (f) Yanagisawa, A. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 2004; Suppl. 2, p 125. (g) Duhamel, L.; Duhamel, P.; Plaquevent, J.-C. *Tetrahedron: Asymmetry* **2004**, *15*, 3653.

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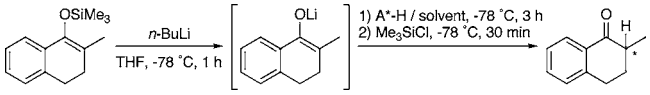
10.1021/ol0603007 CCC: $33.50
Published on Web 03/23/2006

We initially examined stoichiometric asymmetric protonation of a 2-methyl-1-tetralone-derived salt-free lithium enolate using an amino acid or its derivative as a chiral proton source (Table 1). Among the chiral Brønsted acids tested, unprotected amino acids were insoluble in THF and DMF and gave a racemic product (entries 1−3). In contrast, protected amino acid derivatives were soluble in those solvents, but the racemic product was still obtained using these chiral proton sources (entries 4 and 5). To attain significant asymmetric induction, we then used commercially available dipeptides. First, *N*α-L-aspartyl-L-phenylalanine methyl ester (aspartame) was examined, and as a result, a small extent of asymmetric induction was observed (entry 6). Furthermore, a similar dipeptide, *N*β-L-aspartyl-L-phenylalanine methyl ester, showed better enantioselectivities (8∼13% ee), though they were still unsatisfactory (entry 7). The low enantioselectivity shown by the chiral acid is probably due to its poor solubility in DMF or its tendency to aggregate.

On the basis of this consideration, we envisaged that if the reaction proceeds with a catalytic amount of the amino acid derivative and a stoichiometric amount of an achiral proton source higher enantioselectivity might be obtained. To our delight, employment of a catalytic amount of *N*β-L-aspartyl-L-phenylalanine methyl ester (**1**) as a chiral proton source and a stoichiometric amount of 2,6-di-*tert*-butyl cresol (BHT)[3f] as an achiral proton source led to a dramatic increase in enantioselectivity with good yield (76∼80% ee, 71∼79% yield, Table 2, entry 7). Interestingly, aspartame, which has a structure closely related to **1**, provided the racemic ketone (entry 6). This result indicates that the position of the amino group of **1** is crucial for the asymmetric induction. As for the achiral proton source, steric bulkiness of BHT is indispensable to achieve high enantioselectivity and simple phenol gave the product with only 7% ee (entry 8). Noteworthy was the fact that not only a bulky phenol derivative but also a bulky achiral diketone were effective in the asymmetric induction (56% ee, entry 10).

We then studied the influence of solvent on the product yield and enantioselectivity (Table 3). As a result, the solvents of choice were DMF for **1** and THF for BHT (entry 1). So, we further used an increased amount of DMF as a solvent for **1**; however, the enantiomeric excess of the product decreased drastically (entry 6).

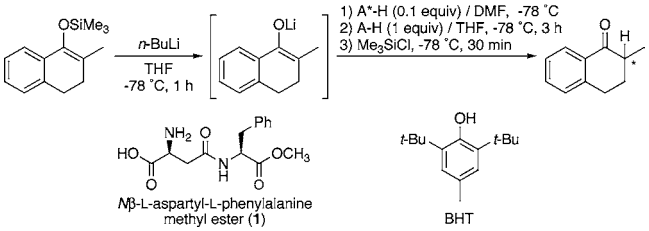
Table 1. Stoichiometric Asymmetric Protonation of a Lithium Enolate of 2-Methyl-1-tetralone Using Various Chiral Brønsted Acids[a]



entry	A*−H/solvent	yield (%)[b]	ee (%)[c]
1	L-proline/THF	66	<1
2	L-aspartic acid/DMF	41	<1
3	L-arginine/DMF	14	<1
4	*N*-Cbz-L-aspartic acid/THF	66	<1
5	*N*-Boc-L-aspartic acid/THF	83	<1
6	*N*α-L-aspartyl-L-phenylalanine methyl ester (aspartame)/DMF	77	2
7	*N*β-L-aspartyl-L-phenylalanine methyl ester (**1**)/DMF	62	8 ∼ 13 (*S*)

[a] The lithium enolate was generated from the corresponding silyl enolate (1 equiv) and a hexane solution of *n*-BuLi (1.1 equiv) in THF at −78 °C for 1 h. The following protonation was carried out using a chiral Brønsted acid (1.1 equiv) in a specified solvent at −78 °C for 3 h. The reaction was quenched with Me_3SiCl at −78 °C to remove the unreacted enolate. [b] Isolated yield. [c] The enantioselectivity was determined by HPLC analysis on a chiral column (OD-H). Parentheses indicate the absolute configuration of the product.

Table 2. Catalytic Asymmetric Protonation of a Lithium Enolate of 2-Methyl-1-tetralone Catalyzed by Various Chiral Brønsted Acids[a]

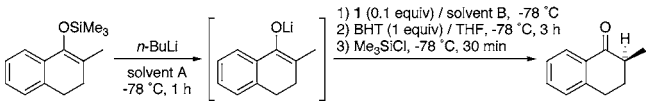


entry	A*−H	A−H	yield (%)[b]	ee (%)[c]
1	L-proline	BHT	65	<1
2	L-aspartic acid	BHT	46	<1
3	L-glutamic acid	BHT	30	<1
4	L-glutamic acid 5-methyl ester	BHT	50	<1
5	glutathione	BHT	28	<1
6	*N*α-L-aspartyl-L-phenylalanine methyl ester (aspartame)	BHT	62	<1
7	*N*β-L-aspartyl-L-phenylalanine methyl ester (**1**)	BHT	71 ∼ 79	76 ∼ 80 (*S*)
8	**1**	phenol	56	7 (*S*)
9	**1**	(*S*)-BINOL	77	9 (*S*)
10	**1**	2,2,6,6-tetramethyl-3,5-heptadione	76	56 (*S*)

[a] The lithium enolate was generated from the corresponding silyl enolate (1 equiv) and a hexane solution of *n*-BuLi (1.1 equiv) in THF at −78 °C for 1 h. The following protonation was carried out using a chiral Brønsted acid (0.1 equiv) in DMF at −78 °C for 5 min. Then, a solution of an achiral proton source (1 equiv) in THF was added (over a period of 2 h) at −78 °C. After the mixture was stirred for 1 h, the reaction was quenched with Me_3SiCl at −78 °C to remove the unreacted enolate. [b] Isolated yield. [c] The enantioselectivity was determined by HPLC analysis on a chiral column (OD-H). Parentheses indicate the absolute configuration of the product.

(3) (a) Fehr, C.; Galindo, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1888. (b) Yanagisawa, A.; Kikuchi, T.; Watanabe, T.; Kuribayashi, T.; Yamamoto, H. *Synlett* **1995**, 372. (c) Nakamura, Y.; Takeuchi, S.; Ohira, A.; Ohgo, Y. *Tetrahedron Lett.* **1996**, *37*, 2805. (d) Riviere, P.; Koga, K. *Tetrahedron Lett.* **1997**, *38*, 7589. (e) Vedejs, E.; Kruger, A. W. *J. Org. Chem.* **1998**, *63*, 2792. (f) Takeuchi, S.; Nakamura, Y.; Ohgo, Y.; Curran, D. P. *Tetrahedron Lett.* **1998**, *39*, 8691. (g) Yanagisawa, A.; Watanabe, T.; Kikuchi, T.; Yamamoto, H. *J. Org. Chem.* **2000**, *65*, 2979. (h) Nishimura, K.; Ono, M.; Nagaoka, Y.; Tomioka, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 440. (i) Asensio, G.; Gil, J.; Alemán, P.; Medio-Simón, M. *Tetrahedron: Asymmetry* **2001**, *12*, 1359. See also: (j) Yasukata, T.; Koga, K. *Tetrahedron: Asymmetry* **1993**, *4*, 35. (k) Eames, J.; Weerasooriya, N. *Chirality* **1999**, *11*, 787. (l) Flinois, K.; Yuan, Y.; Bastide, C.; Harrison-Marchand, A.; Maddaluno, J. *Tetrahedron* **2002**, *58*, 4707.

Table 3. Solvent Effect on Catalytic Asymmetric Protonation of a Lithium Enolate of 2-Methyl-1-tetralone Catalyzed by **1**[a]

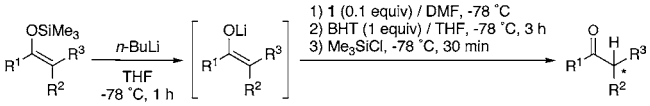


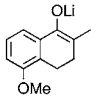
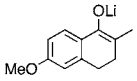
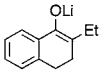
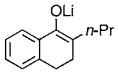
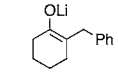
entry	solvent A	solvent B	yield (%)[b]	ee (%)[c]
1	THF	DMF	71 ~ 79	76 ~ 80
2	ether	DMF	22	22
3	cyclopentyl methyl ether	DMF	40	17
4	THF	DMI	76	71
5	THF	DMSO	70	42
6	THF[d]	DMF	72	10

[a] The lithium enolate was generated from the corresponding silyl enolate (1 equiv) and a hexane solution of *n*-BuLi (1.1 equiv) in solvent A (4 mL) at −78 °C for 1 h. The following protonation was carried out using **1** (0.1 equiv) in solvent B (0.5 mL) at −78 °C for 5 min. Then, a solution of BHT (1 equiv) in solvent A (5 mL) was added (over a period of 2 h) at −78 °C. After the mixture was stirred for 1 h, the reaction was quenched by Me_3SiCl at −78 °C to remove the unreacted enolate. [b] Isolated yield.[c] The enantioselectivity was determined by HPLC analysis on a chiral column (OD-H). (*S*)-Enriched product was obtained in every entry. [d] An increased amount (6 mL) of DMF was used as solvent B.

Under the optimized reaction conditions, we carried out the catalytic asymmetric protonation of various lithium enolates (Table 4). In general, tetralone derivatives besides

Table 4. Catalytic Asymmetric Protonation of Various Lithium Enolates[a]



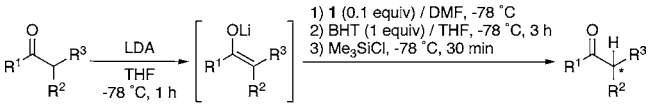
entry	lithium enolate	yield (%)[b]	ee (%)[c]
1		71~79	76~80 (*S*)
2		85	70
3		91	45
4		59	88
5		83	24
6		65	69 (*S*)

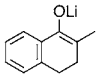
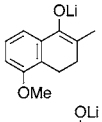
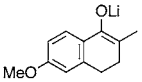
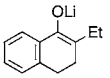
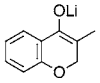
[a] The lithium enolate was generated from the corresponding silyl enolate (1 equiv) and a hexane solution of *n*-BuLi (1.1 equiv) in THF at −78 °C for 1 h. The following protonation was carried out using **1** (0.1 equiv) in DMF at −78 °C for 5 min. Then, a solution of BHT (1 equiv) in THF was added (over a period of 2 h) at −78 °C. After the mixture was stirred for 1 h, the reaction was quenched by Me_3SiCl at −78 °C to remove the unreacted enolate. [b] Isolated yield. [c] The enantioselectivity was determined by HPLC analysis on a chiral column (OD-H, OJ-H, or OB). Parentheses indicate the absolute configuration of the product.

a 2-*n*-propyl-1-tetralone derivative gave good results in terms of chemical yield and enantioselectivity, and among them, a lithium enolate of 2-ethyl-1-tetralone gave the best result (88% ee, 59% yield, entry 4). A 2-benzylcyclohexanone-derived lithium enolate also showed moderate enantioselectivity (69% ee, entry 6).

The present catalytic system is further applied to lithium enolates generated from the corresponding racemic ketones by their treatment with LDA. This procedure is superior to the method via a silyl enolate from the viewpoint of efficiency and atom economy. However, the former method has a disadvantage in that the coexisting diisopropylamine might prevent the catalyst **1** from coordinating to a lithium enolate.[4] In fact, although lithium enolates derived from 2-methyl-1-tetralone and its derivatives showed enantioselectivity similar to those given by the method via a silyl enolate (entries 1−3, Table 5), a lithium enolate of sterically

Table 5. Catalytic Asymmetric Protonation of Various Lithium Enolates Directly Generated from Ketones[a]



entry	lithium enolate	yield (%)[b]	ee (%)[c]
1		65	81[d] (80)[d]
2		86	64 (70)
3		94	41 (45)
4		61	13 (88)
5		67	20 (15)

[a] The lithium enolate was generated from the corresponding ketone (1 equiv) and LDA (1.1 equiv) in THF at −78 °C for 1 h. The following protonation was carried out using **1** (0.1 equiv) in DMF at −78 °C for 5 min. Then, a solution of BHT (1 equiv) in THF was added (over a period of 2 h) at −78 °C. After the mixture was stirred for 1 h, the reaction was quenched by Me_3SiCl at −78 °C to remove the unreacted enolate. [b] Isolated yield. [c] The enantioselectivity was determined by HPLC analysis on a chiral column (OD-H, OJ-H, or OB). Values in parentheses are ee's of products from the corresponding silyl enolates. [d] (*S*)-Enriched product was obtained.

bulkier 2-ethyl-1-tetralone was protonated with lower ee (entry 4).

Asymmetric protonation of a metal enolate takes place catalytically if a coexisting achiral proton source reacts with a deprotonated chiral proton source faster than with the metal enolate, a concept first introduced by Fehr and co-workers.[5]

(4) For a study of an influence of diisopropylamine on enantioselective protonation of a lithium enolate, see: Yanagisawa, A.; Kikuchi, T.; Kuribayashi, T.; Yamamoto, H. *Tetrahedron* **1998**, *54*, 10253.

(5) Fehr, C.; Stempf, I.; Galindo, J. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1044.

A hypothesis for the catalytic mechanism is shown in Figure 1. Reaction of a lithium enolate with the chiral proton source

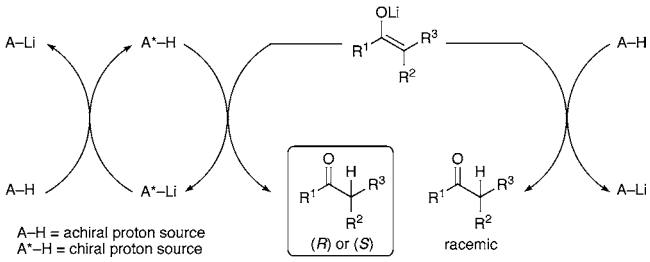


Figure 1. Plausible catalytic cycle.

A*−H yields (*R*)- or (*S*)-ketone and the lithiated chiral proton source A*−Li. Subsequent protonation of A*−Li with the achiral proton source A−H enables the chiral proton source A*−H to be reproduced. Higher reactivity of A*−Li than that of the lithium enolate toward A−H is the key to success in the catalytic cycle. Because both the catalyst **1** and BHT possess appropriate pK_a values and BHT also has enough steric bulkiness to avoid the quick reaction with the lithium enolate, the catalytic cycle is considered to take place smoothly.

In conclusion, we have developed a catalytic asymmetric protonation using an amino acid derivative as a chiral proton source. The combination of the catalyst **1** and BHT was the most effective in providing various nonracemic ketones with enantiomeric excesses up to 88%. In addition, lithium enolates directly generated from racemic ketones have also been successfully applied to the catalytic asymmetric protonation. Further study on the application of the present catalytic reaction to other substrates is now in progress.

Acknowledgment. We gratefully acknowledge financial support from the Graduate School of Science and Technology, Chiba University.

Supporting Information Available: Experimental procedures and spectral data for all products in Tables 4 and 5. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0603007