Asymmetric Protonation of Lithium Enolate of α-Amino Acid Derivatives using Chiral Brønsted Acids

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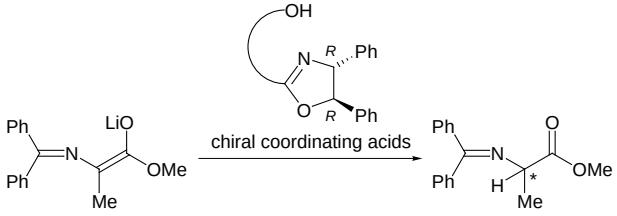
Abstract: Chiral alcohols possessing an asymmetric 2-oxazoline ring were synthesized as new chiral Brønsted acids from tetrahydro-2-furoic acid and (1*S*, 2*R*)-2-amino-1,2-diphenylethanol. These alcohols were superior to (*S*,*S*)- or (*R*,*R*)-imide reported previously as a chiral proton source for enantioselective protonation of lithium enolate of an alanine derivative.

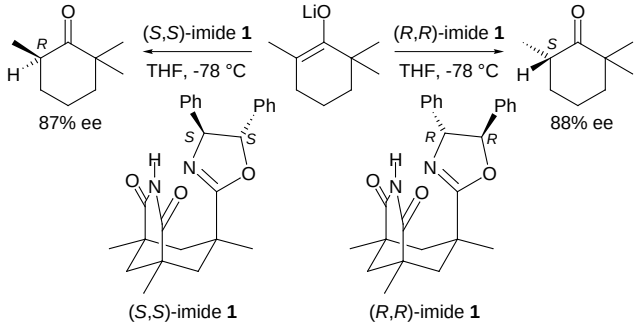
Key words: enantioselective protonation, lithium enolate, α-amino acid derivative, chiral alcohols, 2-oxazoline, asymmetric catalysis

Asymmetric protonation of prochiral metal enolates has become an efficient way of preparing nonracemic carbonyl compounds.[1] The success of this method depends upon the structure and acidity of the chiral proton source. Numerous chiral acids have been synthesized to date and have been utilized in enantioselective protonations.[1–3] However, there are few reports on the protonation of enolates of α-amino acid derivatives giving rise to high asymmetric induction.[4] We describe here a new example of enantioselective protonation of lithium enolate of an alanine derivative with chiral alcohols possessing an asymmetric 2-oxazoline ring (Equation 1).

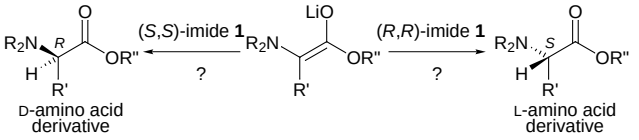


Equation 1

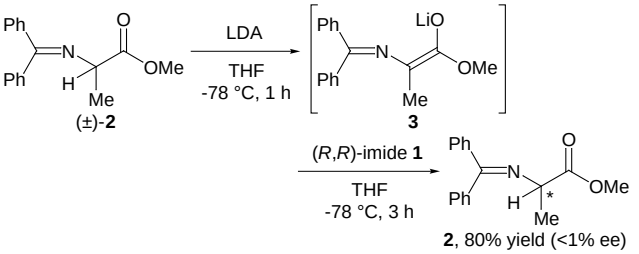
We have previously shown that (*S*,*S*)-imide **1** and related imides possessing an asymmetric 2-oxazoline are efficient chiral proton sources for asymmetric protonation of lithium enolates derived from simple ketones such as 2-alkylcycloalkanones.[5] With this imide **1**, the lithium enolate of 2,2,6-trimethylcyclohexanone can be protonated stereoselectively to give the original ketone in nearly 90% ee with an (*R*)-configuration. Use of the enantiomer (*R*,*R*)-imide **1** gave (*S*)-enriched ketone with a similar enantioselectivity (Scheme 1). We envisaged that if these chiral imides were applied to the protonation of enolates of α-amino acid derivatives, both L- and D-α-amino acids might be selectively obtained simply by changing the chiral proton source (Scheme 2). Thus, we initially examined the reaction of lithium enolate **3**, generated from racemic alanine derivative **2** and LDA in THF, with (*R*,*R*)-imide **1** at –78 °C for 3 hours, however, almost no asymmetric induction occurred in the protonation (Equation 2).



Scheme 1



Scheme 2



Equation 2

We then investigated the possibility of benzoic acid or benzyl alcohol derivatives bearing an asymmetric 2-oxazoline ring as new chiral proton sources for the asymmet-

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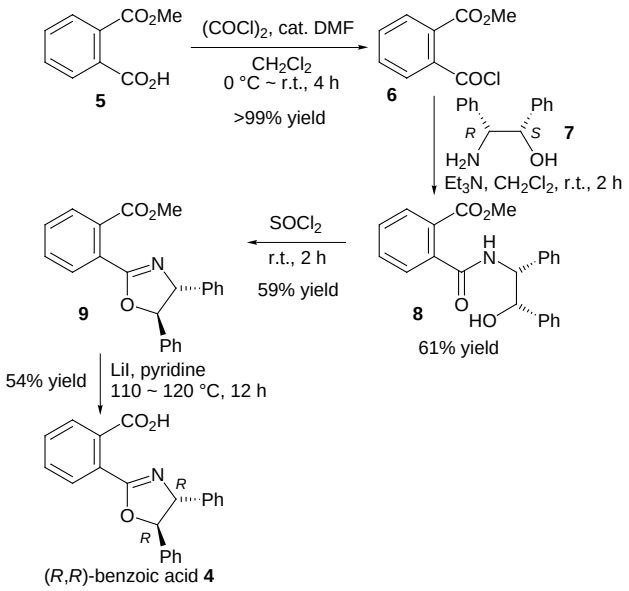
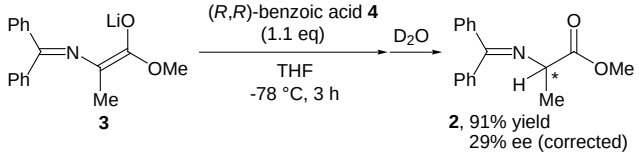
ric protonation of metal enolates of amino acid derivatives, because these chiral Brønsted acids should have similar or stronger acidity compared with that of (*R*,*R*)-imide **1**. First, chiral benzoic acid **4** was synthesized from *mono*-methyl phthalate (**5**) in four steps (Scheme 3). The monoacid **5** was converted into the acid chloride **6** (> 99% yield) followed by reaction with (1*S*,2*R*)-2-amino-1,2-diphenylethanol (**7**) leading to the amide **8** in 61% yield. Cyclization of **8** to 2-oxazoline **9** with thionyl chloride (59% yield) and subsequent cleavage of methyl ester by LiI/pyridine[6] (54% yield) furnished (*R*,*R*)-benzoic acid **4**.[7] When the lithium enolate **3** was treated with a solution of acid **4** (1.1 equiv) in THF at –78 °C for 3 hours followed by quenching with D_2O[8] at –78 °C, nonracemic alanine derivative **2** was obtained in 91% yield and 29% corrected ee[9] (Equation 3).[10]



Scheme 3



Equation 3

We further tested the ability of chiral benzyl alcohol derivatives having an asymmetric 2-oxazoline moiety to protonate the lithium enolate **3** enantioselectively. Thus, chiral benzylic alcohols **15**–**18** were prepared by treating bromo arene **14** with *n*-BuLi in THF at –78 °C followed by reaction of the resulting aryl lithium with the corresponding ketones or *t*-BuCHO. Among the chiral alcohols examined, one diastereomer of the chiral secondary alcohol **18**[11] provided a moderate enantioselectivity (49% corrected ee; 22% observed ee; 54% enolization; 44% protonation by **18**; 10% deuteration in quench), while the chiral tertiary alcohols **15**–**17** were less effective (18 ~ 4% corrected ee). The fact that an additional stereogenic center of **18** is nearer the proton source, rather than its steric hindrance, is considered to be the key to a higher level of asymmetric induction (Figure 1).

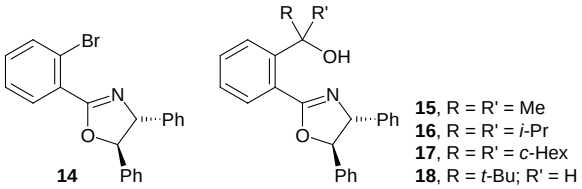
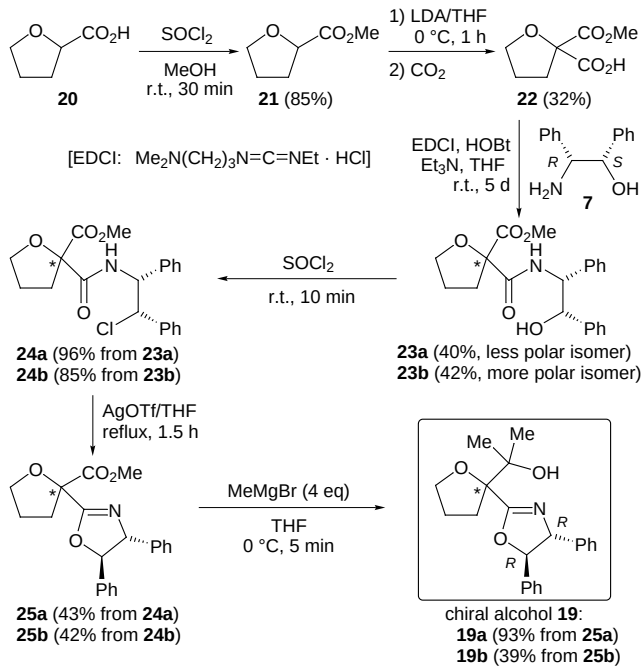


Figure 1

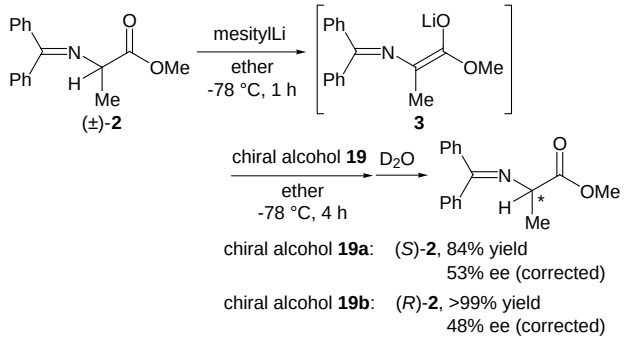
On the basis of the aforementioned results we designed the new chiral alcohol **19** which has a tetrahydrofuran (THF) ring in place of a benzene ring (Scheme 4). We were interested in using the THF ring as a backbone of chiral alcohol **19**, because its oxygen atom was expected to coordinate the lithium atom of the enolate **3** and form a more rigid transition-state structure than those of chiral alcohols **15**–**18**. The synthesis of chiral alcohol **19** was carried out starting from racemic tetrahydro-2-furoic acid (**20**). Treatment of **20** with thionyl chloride in the presence of MeOH afforded the methyl ester **21** in 85% yield. The ester **21** was converted to the monoester of dicarboxylic acid **22** in 32% yield by means of carboxylation of the lithium enolate generated from **21** with LDA in THF. The monoacid was treated with (1*S*,2*R*)-2-amino-1,2-diphenylethanol (**7**) to give amide **23** in 82% yield with an almost 1:1 diastereomeric ratio. These diastereomers were separated into **23a** (less polar isomer) and **23b** (more polar isomer) by column chromatography on silica gel. Both isomers **23a** and **23b** were transformed into the required chiral alcohols **19a** and **19b** by a three-step sequence: (1) chlorination with thionyl chloride giving **24a** (96% yield from **23a**) and **24b** (85% yield from **23b**), (2) cyclization with silver triflate to form 2-oxazolines **25a** and **25b** in 43 and 42% yields, respectively, and (3) addition of two equivalents of methyl Grignard furnishing the chiral alcohols **19a**[12] (from **25a**) and **19b**[13] (from **25b**).

Using the chiral alcohols **19a** and **19b** as chiral proton sources, we attempted the asymmetric protonation of the lithium enolate of alanine derivative **3** (Equation 4). In these experiments we employed mesityllithium[4f,h,14] instead of LDA as a base for generating enolate **3** since diisopropylamine resulting from LDA was anticipated to prevent alcohol **19** from coordinating the lithium of the enolate and thus from leading to a preferable transition-state structure. When enolate **3** was treated with a solution of alcohol **19a** in ether at –78 °C for 4 hours, (*S*)-enriched alanine derivative **2** was formed in 84% yield and 53% corrected ee (36% observed ee; 89% enolization; 67% protonation by **19a**; 22% deuteration in quench). In contrast, use of diastereomer **19b** resulted in formation of (*R*)-**2** with 48% corrected ee (42% observed ee; 90% enolization; 89% protonation by **19b**; 1.4% deuteration in quench). These results indicate that the stereochemistry at



Scheme 4

the new stereogenic center is more strongly influenced by an asymmetric tetrahydrofuran ring rather than by an asymmetric 2-oxazoline ring of the alcohols **19a** and **19b**. Although further structural modifications are necessary to obtain higher enantioselectivity, chiral alcohol **19** is a promising chiral proton source for asymmetric protonation of enolates of α-amino acid derivatives.



Equation 4

A representative experimental procedure is given by the reaction of lithium enolate **3** with chiral alcohol **19a** (Equation 4). To a solution of 2-bromomesitylene (0.067 mL, 0.44 mmol) in dry ether (2 mL) at –78 °C was added a solution of *t*-BuLi (1.45 M, 0.61 mL, 0.88 mmol) in pentane under an argon atmosphere. After the reaction mixture had been stirred for 1 hour at –78 °C, a solution of racemic alanine derivative **2** (110 mg, 0.40 mmol) in dry ether (4 mL) was added at –78 °C. The reaction mixture was held at this temperature for 1 hour, then divided into two equal parts. A half of the resulting reaction mixture was quenched by D_2O (0.3 mL) and the rate of enolization was determined to be 89% by ^1H NMR analysis (a 11% reduction of a peak at δ = 4.18 ppm was observed for the product **2**). To the other half of the mixture was added dropwise a solution of chiral alcohol **19a** (77 mg, 0.22 mmol) in ether (4 mL) at –78 °C. After being stirred for 4 hours, D_2O (0.3 mL) was added to determine the percentage of the unreacted lithium enolate **3** (22% deuteration in quench) and the mixture was gradually warmed to room temperature. A saturated NH_4Cl solution (10 mL) was then added, and the organic material was extracted twice with ether (10 mL each). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel to give the (*S*)-enriched alanine derivative **2** (46 mg, 84% isolated yield) with 53% ee [corrected value based on the percentage (67%) of protonation by **19a** and observed ee (36% ee)] which showed the appropriate spectral data.[15] The enantiomeric ratio was determined by HPLC analysis using a chiral column (Chiralcel OJ, Daicel Chemical Industries, Ltd., hexane/*i*-PrOH = 20/1, flow rate = 0.2 mL/min): t_R = 62.5 min (*S*-isomer); t_R = 86.2 min (*R*-isomer). The absolute configuration was determined by comparison of its optical rotation with published data.[16] Alcohol **19a** was recovered (> 90% yield) without a noticeable loss of optical purity.

Acknowledgement

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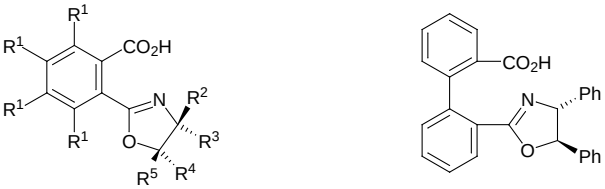
(7) Spectral data of **4**: TLC R_f = 0.05 (1:2 ethyl acetate/hexane); IR (KBr): 3200–2250, 3040, 1709, 1653, 1495, 1456, 1283 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 5.46 (d, 1 H, *J* = 8.1 Hz, CH), 5.58 (d, 1 H, *J* = 8.4 Hz, CH), 7.24–7.68 (m, 10 H, aromatic), 7.67 (dt, 1 H, *J* = 1.5, 7.5 Hz, aromatic), 7.76 (dt, 1 H, *J* = 1.5, 7.5 Hz, aromatic), 8.24 (dd, 1 H, *J* = 1.5, 7.5 Hz, aromatic), 8.67 (dt, 1 H, *J* = 1.2, 7.5 Hz, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 76.3, 77.7, 89.9, 123.4, 126.0 (2 C), 126.3 (2 C), 128.6, 129.2 (2 C), 129.3 (2 C), 129.4, 131.0, 132.0, 133.1, 135.6, 137.9, 139.1, 166.8 (2 C); $[\alpha]^{23}_D$ +70.7 (c 1.0, $CHCl_3$).

(8) D_2O was added as a quencher to determine a percentage of the unreacted enolate **3**. As for an experimental procedure for the D_2O quench, see the representative experimental procedure in the text.

(9) Corrected value based on the percentage of the protonated product. The details of the protonation are as follows: 13% observed ee; 54% enolization; 44% protonation by **4**; 10% deuteration in quench.

(10) We studied the enantioselectivity of the protonation of other chiral benzoic acids **10**–**13** derived from various amino alcohols and diacids, however, no results better than those with acid **4** were obtained (Figure 2).



10, R^1 = Cl; R^2 = R^4 = H; R^3 = R^5 = Ph
11, R^1 = H; R^2 = R^4 = 2-MeC_6H_4; R^3 = R^5 = H
12, R^1 = H; R^2 = R^4 = 3,5-$tBu_2C_6H_3$; R^3 = R^5 = H

13

Figure 2

(11) Spectral data of one diastereomer of **18** (less polar isomer): TLC R_f = 0.14 (1:2 ether/hexane); IR ($CHCl_3$): 3900–3150, 3013, 2975, 1690, 1509, 1472, 1397, 1225 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 0.86 (s, 9 H, 3 CH_3), 4.00 (s, 1 H, OH), 4.95–4.97 (m, 3 H, 3 CH), 7.13–7.49 (m, 13 H, aromatic), 7.93 (m, 1 H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2 (3 C), 35.9, 67.6, 78.4, 91.0, 122.7, 123.4, 126.7 (2 C), 127.1, 127.8 (4 C), 127.9 (3 C), 128.5, 131.0, 131.6, 142.0, 142.1, 144.7, 161.4; $[\alpha]^{30}_D$ –85.4 (c 1.0, $CHCl_3$).

(12) Spectral data of **19a**: TLC R_f = 0.43(ether); IR ($CHCl_3$): 3700–3200, 3019, 2982, 1653, 1497, 1456, 1374, 1215 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.38 (s, 3 H, CH_3), 1.42 (s, 3 H, CH_3), 2.05 (m, 2 H, CH_2), 2.41 (m, 2 H, CH_2), 3.71 (s, 1 H, OH), 4.04 (dd, 1 H, *J* = 6.9, 13.5 Hz, one proton of CH_2), 4.14 (dd, 1 H, *J* = 7.2, 14.4 Hz, one proton of CH_2), 5.10 (d, 1 H, *J* = 7.8 Hz, CH), 5.26 (d, 1 H, *J* = 8.1 Hz, CH), 7.20–7.40 (m, 10 H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.2, 25.3, 26.2, 32.2, 70.1, 73.6, 78.2, 88.2, 89.2, 125.8 (2 C), 126.5 (2 C), 127.8, 128.5, 128.8 (2 C), 128.9 (2 C), 139.9, 141.6, 170.1; $[\alpha]^{30}_D$ +40.2 (c 1.0, $CHCl_3$).

(13) Spectral data of **19b**: TLC R_f = 0.53(ether); IR ($CHCl_3$): 3650–3200, 3017, 2982, 1649, 1495, 1456, 1374, 1215 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.37 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 2.05 (m, 2 H, CH_2), 2.40 (m, 2 H, CH_2), 3.81 (s, 1 H, OH), 4.09 (m, 2 H, CH_2), 5.13 (d, 1 H, *J* = 8.7 Hz, CH), 5.28 (d, 1 H, *J* = 8.4 Hz, CH), 7.21–7.41 (m, 10 H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.0, 25.3, 26.2, 32.2, 70.1, 73.5, 78.4, 88.1, 89.2, 126.0 (2 C), 126.5 (2 C), 127.8, 128.6, 128.8 (2 C), 129.0 (2 C), 139.9, 141.5, 170.1; $[\alpha]^{30}_D$ +108.9 (c 1.0, $CHCl_3$).

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(15) Spectral data of **2**:[16] TLC R_f = 0.30 (1:2 ether/hexane); IR(neat): 2990, 2950, 1742, 1624, 1599, 1578, 1491, 1447, 1287, 1206 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.42 (d, 3 H, *J* = 6.9 Hz, CH_3), 3.72 (s, 3 H, CH_3), 4.18 (q, 1 H, *J* = 6.9 Hz, CH), 7.17–7.21 (m, 2 H, aromatic), 7.30–7.49 (m, 6 H, aromatic), 7.62–7.66 (m, 2 H, aromatic); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2, 52.1, 60.6, 127.6 (2 C), 128.0 (2 C), 128.6 (3 C), 128.7 (2 C), 130.3, 136.2, 139.4, 169.7, 173.4. Observed $[\alpha]_D$ value of (*R*)-**2** (42% ee) obtained in the protonation with **19b**: $[\alpha]^{28}_D$ +24.8 (c 1.0, $CHCl_3$).

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