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Asymmetric Synthesis of α -Amino Acids via Chiral *N*-Alkylidenesulfinamides

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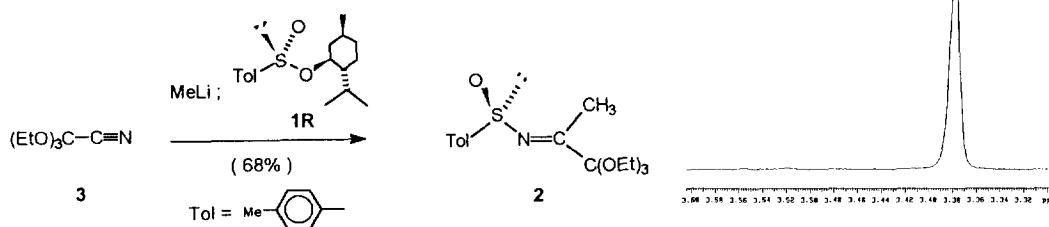
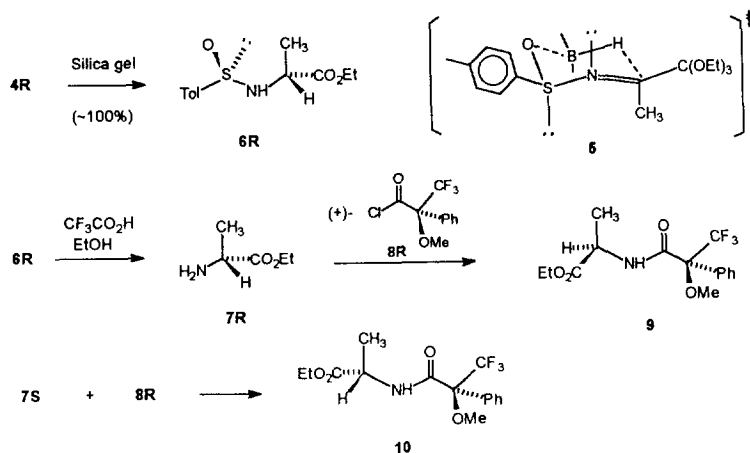
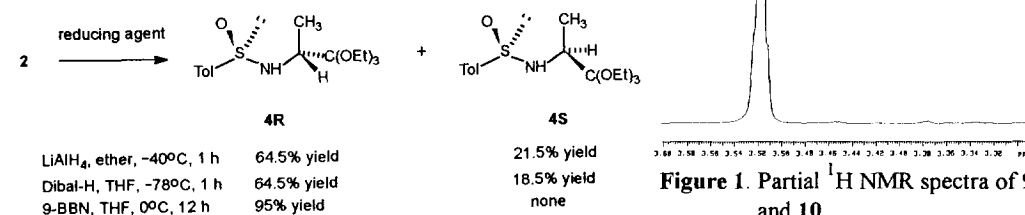
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Abstract: (*SR*)-(-)-*N*-[1-(Triethoxymethyl)ethylidene]-*p*-toluenesulfinamide (**2**) was synthesized from the addition reaction of triethoxyacetonitrile with MeLi followed by (+)-(*R*)-*d*-menthyl *p*-toluenesulfinate (**1R**). Sulfinimine **2** underwent complete stereoselective reduction with 9-BBN and addition reaction with allylmagnesium bromide. Optically pure α -amino acids were synthesized from these adducts by simple hydrolysis.

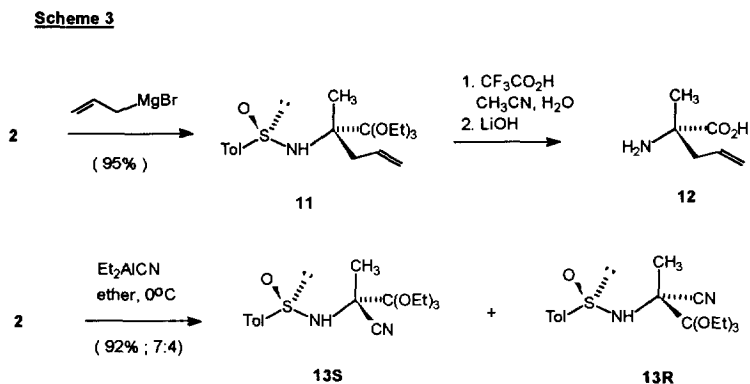
Chiral *N*-benzylidene- and *N*-alkylidenesulfinamides have been synthesized by four different methods:

(i) reactions of organometallic reagents with benzonitrile followed by (-)-*l*-menthyl (*S*)-*p*-toluenesulfinate (**1S**);¹ (ii) oxidation of sulfenimines with chiral oxaziridines;^{2a} (iii) reduction of benzonitriles or α,β -unsaturated nitriles with Dibal-H followed by treatment with methyllithium and sulfinate **1S**;^{2b} and (iv) displacement of sulfinate **1S** with lithiated hexamethyldisilazide followed by condensation with aryl aldehydes or α,β -unsaturated aldehydes.^{2b} However, with the first three methods, the preparation of only *N*-benzylidene- and *N*-(2-propenylidene)sulfinamides was reported and in the latter, *n*-pentanal afforded only a 30% yield of the corresponding sulfinimine. Several syntheses of β - and γ -amino acids had been reported utilizing *N*-benzylidenesulfinamides.¹⁻³ However, there is only one report on this class of reactions relating to the synthesis of an α -amino acid methyl ester, methyl (2*S*,3*R*)-2-amino-3-hydroxy-3-phenylpropanoate.⁴ That work involved the hydrolysis of an aziridine derived from the addition reaction of a *N*-benzylidenesulfinamide with lithiated methyl bromoacetate. Continuing our studies of chiral *N*-alkylidenesulfinamide,¹ we report herein the synthesis of a chiral *N*-[1-(triethoxymethyl)ethylidene]sulfinamide, **2**, and its use in the asymmetric synthesis of optically pure α -amino acids.⁵

In a direct and simple synthesis of α -amino acids via chiral sulfinimines, a carboxylic acid moiety or its equivalent would be introduced at the α -carbon (the imino carbon) of the sulfinimine. Sulfinimine **2** was, therefore, synthesized through our reported methodology.¹ The addition reaction of methyllithium with triethoxyacetonitrile (**3**) followed by treatment with (+)-(*R*)-*d*-menthyl *p*-toluenesulfinate (**1R**) gave a 68% yield of **2** (based on 26% recovery of **1R**) (Scheme 1).⁶ Nitrile **3** was prepared according to the reported procedures from either the reaction of trichloroacetonitrile with sodium ethoxide in heptane at 90 °C^{7a} or the reaction of tetraethoxymethane with trimethylsilyl cyanide and tin tetrachloride.^{7b}

Scheme 1**Scheme 2**

Reduction of sulfinimine **2** was carried out with various reducing agents as outlined in Scheme 2. Lithium aluminum hydride as well as diisobutylaluminum hydride gave both diastereomers, **4R** and **4S**, in ratios close to 3:1. On the other hand, 9-borabicyclo[3.3.1]nonane (9-BBN) yielded exclusively **4R**.⁸ Ortho ester **4R** was hydrolyzed on a silica gel column overnight to give a quantitative yield of ester **6R**. A six-membered-ring transition state for this stereoselective reduction reaction is proposed and depicted in **5**. The boron chelates with oxygen of sulfinamide **2**; therefore, approach of the hydride reagent occurs from the *si* face⁹ of the sulfinimine. The absolute configuration of **4R** was determined through ethanolysis of **6R** with 2 equiv of trifluoroacetic acid in ethanol at 25 °C for 12 h to give (*D*)-(*R*)-alanine ethyl ester (**7R**). The ¹H and ¹³C NMR



spectra of the *N*-acetyl derivative of **7R**, obtained from the treatment of **7R** and acetic anhydride in triethylamine and CH₂Cl₂ at 25 °C, are identical to those derived from (*L*)-(*S*)-alanine ethyl ester (**7S**; commercial material) and acetic anhydride; the rotations have opposite sign. The optical purity of **4R** was determined by ¹H NMR studies of the Mosher derivative, **9** [prepared by reaction of **7R** with (+)-(*R*)- α -methoxy- α -(trifluoromethyl)phenylacetyl chloride (**8R**)¹⁰ and Et₃N in CH₂Cl₂ at 25 °C for 19 h], to be >98% ee; **7R** was not detected [see Figure 1, upper spectrum: the quartet at δ 3.38 ppm belongs to the OMe protons coupled with CF₃ (J = 1.5 Hz) of **9**]. The Mosher derivative **10**, prepared from diastereomer **7S** with **8R**, showed a different chemical shift for the quartet of its OMe group (Figure 1, bottom spectrum; δ 3.52 ppm). Sulfinimine **2** also underwent a complete stereoselective addition reaction with allylmagnesium bromide in ether at 0 °C to give **11** in 95% yield (based on 48% recovery of **2**);¹¹ no other isomer was detected. The absolute configuration at the newly formed carbon center of **11** was determined by converting it into (*S*)-2-amino-2-methyl-4-butenoic acid (**12**), a known α -amino acid,¹² by a two-step sequence: (i) hydrolysis of the sulfinamide and ortho ester moieties of **11** with CF₃CO₂H in CH₃CN-H₂O (95% yield); and (ii) basic hydrolysis of the ester function with LiOH-H₂O-THF at 80 °C (96% yield; after Rexyn 101 ion exchange resin column chromatographic separation). Treatment of **2** with diethylaluminum cyanide in ether at 0 °C gave a 92% yield of **13S** and **13R** (7:4), which were separated by silica gel column chromatography.¹³ The absolute configurations of **13** were tentatively assigned from the chemistry described above.

In summary, optically pure α -amino acids were synthesized efficiently from a chiral *N*-[1-(triethoxymethyl)ethylidene]sulfinamide by stereoselective reduction with 9-BBN and addition reaction with allylmagnesium bromide. Cyanide was also added to the sulfinimine but with low stereoselectivity. Syntheses of various α -amino acids containing organometallic species are being studied.

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References and notes

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6. All new compounds displayed satisfactory ^1H (400 MHz) and ^{13}C (100 MHz) NMR, UV, IR, and mass spectra (EI and CI). Compound **2**: $[\alpha]_{\text{D}}^{22} = -6.8$ (c 1.4, CH_2Cl_2); ^1H NMR (CDCl_3) δ 7.68 (d, $J = 8$ Hz, 2 H, Tol), 7.30 (d, $J = 8$ Hz, 2 H, Tol), 3.47 (m, 6 H, 3 CH_2O), 2.40 (s, 3 H, Me), 2.37 (s, 3 H, Me), 1.15 (t, $J = 7$ Hz, 9 H, 3 Me); ^{13}C NMR (CDCl_3) δ 174.16 (s, CN), 142.98 (s, Ar), 141.68 (s, Ar), 129.55 (d, 2 C, Ar), 125.09 (d, 2 C, Ar), 111.55 (s, CO), 58.20 (t, 3 C, CO), 21.24 (q, Me), 18.16 (q, Me), 14.81 (q, 3 C, Me).
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8. Compound **4R**: $[\alpha]_{\text{D}}^{22} = -51$ (c 0.2, CH_2Cl_2); ^1H NMR (CDCl_3) δ 7.60 (d, $J = 8$ Hz, 2 H, Tol), 7.29 (d, $J = 8$ Hz, 2 H, Tol), 4.33 (d, 1 H, NH), 3.70 (m, 1 H, CHN), 3.62-3.45 (m, 6 H, CH_2O), 2.41 (s, 3 H, *p*-Me), 1.38 (d, $J = 7$ Hz, 3 H, Me), 1.16 (m, 9 H, 3 Me); ^{13}C NMR (CDCl_3) δ 142.21 (s, Ar), 141.08 (s, Ar), 129.60 (s, 2 C, Ar), 125.85 (d, 2 C, Ar), 112.97 (s, CO), 58.27 (t, 3 C, CO), 52.56 (d, CN), 26.3 (q, Me), 21.31 (q, Me), 15.48 (q, 3 C, Me). Compound **4S**: $[\alpha]_{\text{D}}^{22} = -53$ (c 0.2, CH_2Cl_2); ^1H NMR (CDCl_3) δ 7.61 (d, $J = 8$ Hz, 2 H, Tol), 7.28 (d, $J = 8$ Hz, 2 H, Tol), 4.29 (m, 2 H, NH, CHN), 3.66 (m, 2 H, CH_2O), 3.47 (m, 4 H, CH_2O), 2.41 (s, 3 H, *p*-Me), 1.29 (d, $J = 7$ Hz, 3 H, Me), 1.17 (m, 9 H, 3 Me); ^{13}C NMR (CDCl_3) δ 142.26 (s, Ar), 141.18 (s, Ar), 129.44 (d, 2 C, Ar), 125.77 (d, 2 C, Ar), 104.79 (s, CO), 63.86 (t, CH_2O), 63.26 (t, 2 C, CH_2O), 51.67 (s, CN), 29.67 (q, Me), 21.30 (q, Me), 16.09 (q, Me), 15.22 (q, 2 C, Me).
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11. Compound **11**: $[\alpha]_{\text{D}}^{22} = -80.8$ (c 0.25, CH_2Cl_2); ^1H NMR (CDCl_3) δ 7.64 (d, $J = 8$ Hz, 2 H, Tol), 7.27 (d, $J = 8$ Hz, 2 H, Tol), 5.98 (m, 1 H, CH=), 5.09 (m, 2 H, CH_2 =), 4.26 (s, 1 H, NH), 3.68 (m, 6 H, CH_2O), 2.49 (m, 2 H, CH_2), 2.40 (s, 3 H, *p*-Me), 1.44 (s, 3 H, Me), 1.18 (t, $J = 7$ Hz, 9 H, 3 Me); ^{13}C NMR (CDCl_3) δ 144.84 (s, Ar), 140.60 (s, Ar), 134.83 (d, CH=), 129.32 (d, 2 C, Ar), 125.68 (d, 2 C, Ar), 117.85 (t, CH_2 =), 113.44 (s, CO), 65.72 (s, CN), 59.50 (t, 3 C, CO), 42.53 (t), 21.24 (q, Me), 19.53 (q, Me), 15.32 (q, 3 C, Me).
12. Belokon, Y. N.; Chernoglazova, N. I.; Kochetkov, C. A.; Garbalinskaya, N. S.; Belikov, V. M. *J. Chem. Soc. Chem. Commun.* **1985**, 171-172. Amino acid **12**: $[\alpha]_{\text{D}}^{22} = -14.6$ (c 1.3, HCl salt in D_2O); lit.¹⁰ -14.4 (*S* configuration; c 1.3, HCl in D_2O); ^1H NMR (D_2O) δ 5.80 (ddt, $J = 15.2, 12, 8$ Hz, 1 H, CH=), 5.34 (d, $J = 12$ Hz, 1 H, CH_2 =), 5.33 (d, $J = 15.2$ Hz, 1 H, CH_2 =), 2.75 (dd, $J = 14.4, 6.8$ Hz, 1 H, CH_2), 2.58 (dd, $J = 14.4, 8$ Hz, 1 H, CH_2), 1.59 (s, 3 H, Me); ^{13}C NMR (D_2O) δ 177.52 (s, C=O), 132.67 (d, CH=), 124.84 (t, CH_2 =), 94.46 (s, CN), 43.87 (t, CH_2), 24.40 (q, Me).
13. Compound **13S**: $[\alpha]_{\text{D}}^{22} = -76.7$ (c 0.15, CH_2Cl_2); ^1H NMR (CDCl_3) δ 7.59 (d, $J = 8$ Hz, 2 H, Tol), 7.31 (d, $J = 8$ Hz, 2 H, Tol), 4.60 (s, 1 H, NH), 3.78 (m, 6 H, CH_2O), 2.42 (s, 3 H, *p*-Me), 1.82 (s, 3 H, Me), 1.22 (t, $J = 7$ Hz, 9 H, Me); ^{13}C NMR (CDCl_3) δ 142.70 (s, Ar), 141.69 (2, Ar), 129.70 (d, 2 C, Ar), 125.42 (d, 2 C, Ar), 120.32 (s, CN), 111.31 (s, CO), 60.39 (t, 3 C, CO), 60.01 (s, CN), 21.34 (q, Me), 20.58 (q, Me), 15.21 (q, 3 C, Me). Compound **13R**: $[\alpha]_{\text{D}}^{22} = -50.5$ (c 0.2, CH_2Cl_2); ^1H NMR (CDCl_3) δ 7.63 (d, $J = 8$ Hz, 2 H, Tol), 7.33 (d, $J = 8$ Hz, 2 H, Tol), 4.65 (s, 1 H, NH), 3.77 (m, 6 H, CH_2O), 2.43 (s, *p*-Me), 1.88 (s, 3 H, Me), 1.22 (t, 9 H, 3 Me); ^{13}C NMR (CDCl_3) δ 142.60 (s, Ar), 141.80 (s, Ar), 129.77 (d, 2 C, Ar), 125.38 (d, 2 C, Ar), 120.14 (s, CN), 111.00 (s, CO), 60.53 (s, CN), 60.34 (t, CO), 22.43 (q, Me), 21.36 (q, Me), 15.19 (q, 3 Me).

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