

Supporting Information for

A Novel Synthesis of α -Amino Acid Derivatives through Catalytic, Enantioselective Ene Reactions of α -Imino Esters

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General. Unless otherwise stated, all reactions were carried out under strictly anhydrous, air-free conditions. Formation of all ligand-metal complexes was done in a glove box under N₂. All solvents were dried and distilled by standard procedures. The ¹H and ¹³C NMR spectra were acquired on a Varian Unity 400 MHz Spectrometer. The ¹H (400 MHz) and ¹³C chemical shifts (101 MHz) are given in parts per million (δ) with respect to internal TMS standards or residual solvent peaks. FTIR spectra were recorded on a Bruker IFS-55 spectrometer and optical rotations were recorded on a Perkin Elmer 120 polarimeter at room temperature. When possible, enantiomeric ratios were obtained using a Chiralcel OD chiral HPLC column. The enantiomeric ratio of compound **4e** was determined with the chiral shift reagent preseodymium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate].¹ The title α -imino ester **1** was made from ethyl glyoxylate² and N-toluenesulfonylisocyanate (Aldrich) by Weinreb's procedure.³ The Cu(I)(CH₃CN)₄ClO₄ was made according to the Kubas procedure.⁴ The olefins **2b**,⁵ **2d**,⁶ **2e**,⁷ and **2f**,⁸ were prepared by known methods. All other starting materials were purchased from Lancaster Synthesis Inc., except for (R)-Tol-BINAP and (R)-BINAP which were purchased from Strem Chemical and acetophenone-*methyl-d*₃ which was purchased from Aldrich chemical corporation.

¹ Parker, D. *Chem. Rev.* **1991**, 1441.

² Kelly, T. R.; Schmidt, T. E.; Haggerty, J. G. *Synthesis* **1972**, 544.

³ Tschaen, D. H.; Turos, E.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 5058.

⁴ Kubas, G. J. *Inorg. Synth.*, Vol. XIX, Shriver, D. F., Ed.; Plenum, p 90, 1979.

⁵ Ohta, T.; Ikegami, H.; Miyake, T.; Takaya, H. *J. Organomet. Chem.* **1995**, *502*, 169.

⁶ Harada, T.; Karaswa, A.; Oku, A. *J. Org. Chem.* **1986**, *51*, 842.

⁷ Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584.

⁸ Miles, W. H.; Berreth, C. L.; Smiley, P. M. *Tetrahedron Lett.* **1993**, *34*, 5221.

General ene procedure. The Cu(I) phosphine complexes were formed by dissolving (*R*)-Tol-BINAP (20.4 mg, 0.030 mmol) with Cu(I)(CH₃CN)₄ClO₄ (8.2 mg, 0.025 mmol) in benzotrifluoride (1 mL) and stirring at room temperature for 30 min to give a pale yellow solution. The α -imino ester **1** (128 mg, 0.50 mmol) was added to the metal complex solution. The mixture was placed under nitrogen at room temperature and a solution of the olefin **2a** (R = Me, R' = Ph) (118 mg, 1.00 mmol) in BTF (0.5 mL) was added to the reaction mixture. The reaction was allowed to stir for 18 h at rt to ensure completion. The reaction was quenched with water (5 mL) and extracted with CH₂Cl₂ (2 x 5 mL). The combined organic layers were dried over MgSO₄ and the solvent was removed under reduced pressure. The crude residue was subjected to column chromatography (5-20% EtOAc/hexanes) on a small silica gel plug (2.5 x 3 cm) yielding 171.5 mg of **4a** (92% yield).

(2S)-4-Phenyl-2-(toluene-4-sulfonylamino)-pent-4-enoic Acid Ethyl Ester (4a). White crystalline solid recrystallized from Et₂O: mp = 91-93 °C; [α]_D = +17.4° (c = 0.0245, CH₂Cl₂); ¹H NMR (CDCl₃) δ 7.63 (d, 2H), 7.26 (m, 5H), 7.21 (d, 2H), 5.32 (s, 1H), 5.11 (s, 1H), 5.09 (s, 1H), 3.98 (m, 1H), 3.70 (m, 2H), 2.91 (m, 3H), 2.38 (s, 3H), 1.02 (t, 2H) ppm; ¹³C NMR (CDCl₃) δ 170.9, 143.5, 142.5, 139.4, 136.6, 129.5, 128.3, 127.8, 127.2, 126.3, 117.2, 61.5, 54.5, 39.3, 21.5, 13.8 ppm; IR (CH₂Cl₂): 3353, 2958, 2932, 1735, 1345, 1183, 1092 cm⁻¹; HPLC (6.25% iPrOH/Hexane, 1.0 mL/min) (*R*) = 22.03, (*S*) = 24.02 min. Anal. Calcd for C₂₀H₂₃NO₄S: C, 64.32; H, 6.21; N, 3.75. Found C, 64.06; H, 6.24; N, 3.90.

(2S)-2-(Toluene-4-sulfonylamino)-3-(3,4-dehydronaphthalen-1-yl)-propionic Acid Ethyl Ester (4b). White crystalline solid recrystallized from Et₂O: mp = 132-134 °C; [α]_D = +33.2° (c = 0.010, CH₂Cl₂); ¹H NMR (CDCl₃) δ 7.60 (d, 2H), 7.15 (m, 6H), 5.87 (t, 1H), 5.03 (d, 1H), 4.04 (q, 1H), 3.84 (q, 2H), 2.83 (m, 2H), 2.62 (t, 2H), 2.35 (s, 3H), 2.19 (q, 2H), 1.06 (t, 3H) ppm; ¹³C NMR (CDCl₃) δ 171.5, 143.4, 136.6, 136.5, 133.2, 130.9, 129.5, 129.4, 127.7, 127.0, 126.4, 122.2, 61.5, 54.7, 36.8, 29.7, 28.0, 23.0, 21.4, 13.8 ppm; IR (CH₂Cl₂): 3342, 2927, 2853, 1737, 1344, 1266, 1161, 1092; HPLC (5.0% iPrOH/Hexane, 1.0 mL/min) (*R*) = 46.55, (*S*) = 56.28 min. Anal. Calcd for C₂₂H₂₅NO₄S: C, 66.14; H, 6.28; N, 3.51. Found C, 65.67; H, 6.33; N, 3.52.

(2S)-3-Cyclohex-1-enyl-2-(toluene-4-sulfonylamino)-propionic Acid Ethyl Ester (4c). White crystalline solid recrystallized from Et₂O: mp = 93-95 °C; [α]_D = +3.49° (c = 0.0175, CH₂Cl₂); ¹H NMR (CDCl₃) δ 7.68 (d, 2H), 7.24 (d, 2H), 5.38 (s, 1H), 4.95 (d, 1H), 3.89 (m, 3H), 3.37 (s, 3H), 2.24 (m, 2H), 1.90 (bs, 2H), 1.75 (m, 2H), 1.46 (m, 4H), 1.08 (t, 3H) ppm; ¹³C NMR (CDCl₃) δ 171.7, 143.5, 136.8, 131.8, 129.5, 127.3, 126.5, 61.4, 54.3, 42.0, 27.7, 25.2, 22.5, 21.9, 21.5, 13.9 ppm; IR (CH₂Cl₂): 3344, 2932, 1739, 1597, 1345, 1163, cm⁻¹.

1092; HPLC (5.0% iPrOH/Hexane, 0.8 mL/min) (*R*) = 28.37, (*S*) = 30.16 min. Anal. Calcd for C₁₈H₂₅NO₄S: C, 61.51; H, 7.18; N, 3.99. Found C, 61.29; H, 7.33; N, 4.00.

(2*S*)-2-(Toluene-4-sulfonylamino)-4-phenylsulfanyl-pent-4-enoic Acid Ethyl Ester (4d). White crystalline solid recrystallized from Et₂O/Hexanes: mp = 107-109 °C; [α]_D = +20.6 ° (c = 0.0293, CH₂Cl₂); ¹H NMR (CDCl₃) δ 7.78 (d, 2H), 7.35 (m, 7H), 5.38 (d, 1H), 5.21 (s, 1H), 4.98 (s, 1H), 4.21 (m, 1H), 3.89 (m, 2H), 2.63 (m, 2H), 2.42 (s, 3H), 1.05 (t, 3H) ppm; ¹³C NMR (CDCl₃) δ 170.67, 143.60, 139.4, 136.8, 133.2, 132.1, 129.6, 129.3, 128.2, 127.3, 117.6, 61.7, 54.7, 39.9, 21.5, 13.9 ppm; IR (CH₂Cl₂): 3344, 2967, 2926, 1740, 1344, 1163, 1093, 1023; HPLC (7.0% iPrOH/Hexane, 1.0 mL/min) (*R*) = 34.36, (*S*) = 39.80 min. Anal. Calcd for C₂₀H₂₃NO₄S₂: C, 59.24; H, 5.72; N, 3.46. Found C, 59.11; H, 5.76; N, 3.55.

(2*S*)-2-(Toluene-4-sulfonylamino)-3-(1-(toluene-4-sulfonyl)-1*H*-indol-3-yl)-proprionic Acid Ethyl Ester (4e). White crystalline solid recrystallized from EtOAc/Hexanes: mp = 179-182 °C; [α]_D = +5.91 ° (c = 0.01045, CH₂Cl₂); ¹H NMR (CDCl₃) : δ 7.92 (d, 1H), 7.73 (d, 2H), 7.56 (d, 2H), 7.41 (d, 2H), 7.28-7.14 (m, 6H), 5.17 (d, 1H), 4.21 (m, 1H), 3.88 (t, 2H), 3.08 (qd, 2H), 2.37 (s, 3H), 2.33 (s, 3H), 1.00 (t, 3H) ppm; ¹³C NMR (CDCl₃) δ 170.7, 144.9, 143.7, 136.3, 135.1, 134.2, 130.4, 129.9, 129.5, 127.0, 126.8, 124.8, 123.119.3, 116.3, 113.6, 61.9, 55.5, 29.7, 29.1, 21.5, 21.4, 13.8 ppm; IR (CH₂Cl₂): 3342, 2932, 2858, 1737, 159.1366, 1166, 1092; Anal. Calcd for C₂₇H₂₈N₂O₆S₂: C, 59.98 ;H, 5.22; N, 5.18 Found C, 59.78; H, 5.02; N, 5.67.

(2*S*)-2-(Toluene-4-sulfonylamino)-3-furan-3-yl-proprionic Acid Ethyl Ester (4f). White crystalline solid recrystallized from Et₂O: mp = 78-80 °C; [α]_D = +13.5 ° (c = 0.010, CH₂Cl₂); ¹H NMR (CDCl₃) δ 7.68 (d, 2H), 7.29 (m, 3H), 7.18 (s, 1H), 6.18 (s, 1H), 5.17 (d, 1H), 4.09 (m, 1H), 3.88 (q, 2H), 2.86 (d, 2H), 2.38 (s, 3H), 1.02 (t, 3H) ppm; ¹³C NMR (CDCl₃) δ 170.6, 143.7, 143.0, 140.6, 136.7, 129.6, 127.2, 118.1, 111.2, 61.8, 55.7, 28.9, 21.5, 13.9 ppm; IR (CH₂Cl₂): 3339, 2928, 1732, 1344, 1260, 1159; HPLC (10.0% iPrOH/Hexane, 1.0 mL/min) (*R*) = 13.38, (*S*) = 14.17 min. Anal. Calcd for C₁₆H₁₉NO₅S: C, 56.96; H, 5.68; N, 4.15. Found C, 56.77; H, 5.69; N, 4.28.

Determination of absolute stereochemistry of 4a.

(2*S*)-3-Benzoyl-2-(toluene-4-sulfonylamino)-proprionic Acid Ethyl Ester (5) was generated by a modification of the method of Viski *et al.*⁹ To a solution of (2*S*)-4-phenyl-2-(toluene-4-sulfonylamino)-pent-4-enoic acid ethyl ester **4a** (70 mg, 0.19 mmol) in 1.5 mL THF was added 52 mg of KMnO₄ in 1 mL of water

⁹ Viski, P.; Szeverényi, Z.; Simándi, L. *J. Org. Chem.* **1986**, *51*, 3213.

over 30 min. The mixture was heated to 45°C for 30 min. The brown precipitate was filtered and the filtrate was extracted with diethyl ether. The organic phase was concentrated and chromatographed (25% EtOAc/Hexanes) to yield pure (2S)-5 in 30% yield (20 mg). The optical rotation and spectral data were analogous to the known literature compound.¹⁰

Deprotection of 4a.¹¹ (2S)-4-Phenyl-2-(toluene-4-sulfonylamino)-pent-4-enoic Acid Ethyl Ester (400 mg, 1.07 mmol) and phenol (302 mg, 3.21 mmol) were dissolved in 8 mL of HBr/HOAc (33%) and heated in a sealed tube at 75 °C for 12 h. The reaction was cooled to rt and quenched with H₂O (8 mL). The reaction mixture was heated to 50 °C for 1 h and successively extracted with hexanes (10 mL) and Et₂O (2 x 10 mL). The aqueous layer was concentrated and the resulting crystals (220 mg, 75% yield) were identified as the amino acid prepared by literature methods.¹²

Determination of absolute stereochemistry of 4c.

Hydrogenation¹³ and deprotection¹¹ of 4c. To a test tube loaded with PtO₂ (60 mg, 0.26 mmol) was added as solution of (2S)-3-Cyclohex-1-enyl-2-(toluene-4-sulfonylamino)-propionic Acid Ethyl Ester **4c** (375 mg, 1.0 mmol) in glacial acetic acid/ethanol/con. HCl (5 mL /1.5 mL/ 0.5 mL). The test tube was pressurized with 30 psi H₂ and shaken at 25°C overnight. The reaction mixture was concentrated to 2 mL, taken up in 10 mL EtOAc and 10 mL sat NaHCO₃ and filtered through a pad of celite. The organic layer was separated and the aqueous phase extracted with 2x10 mL EtOAc. The organic extracts were combined dried over MgSO₄ and concentrated to give 247 mg of the crude reduced material which was used without further purification.

A borosilicate pressure tube was charged with the crude hydrogenation residue (247 mg ≈ 0.69 mmol), phenol (94 mg 310 mmol), 33% HBr in Acetic Acid (6.6 mL) and a Teflon stir bar. The tube was sealed with a Teflon-lined cap and immersed in a oil bath heated to 75°C. The solution was stirred at this temperature for 12 h during which time it darkens from light brown to black. The solution was cooled and following solvent removal *in vacuo*, the residue was taken up in 15 mL H₂O and heated in the oil bath to 50°C for 1 h. The

¹⁰ Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548..

¹¹ Li, G.; Sharpless, K. B. *Acta Chem. Scand.* **1996**, *50*, 649.

¹² Kopola, N.; Friess, B.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1989**, *30*, 3963.

¹³ Hoekstra, W. J.; Sunder, S. S.; Cregge, R. J.; Ashton, L. A.; Stewart, K. T.; King, C. R. *Tetrahedron* **1992**, *48*, 307.

solution was cooled, washed with 1x25 mL and 2x5 mL CH₂Cl₂, neutralized with 1.5% aqueous NH₄OH and concentrated to 3 mL. The solution was purified by ion-exchange chromatography [Amberlite IR-120 (plus) resin 1x10 cm]¹⁴ eluting with 100 mL H₂O followed by 100 mL portions of 1, 1.5, 2 and finally 3% aqueous NH₄OH. Fractions were collected and those containing the amino acid (TLC: SiO₂/MeOH, visualized with ninhydrin, R_f = 0.55-0.6) were evaporated *in vacuo* to give 79 mg (0.46 mmol, 46% yield over two steps) of (S)-cyclohexylalanine spectroscopically identical to commercial material (Fluka Chemical Corp.). The observed optical rotation $[\alpha]_D = +0.183^\circ$ (c=0.018 in 1M HCl) indicates that the deprotection has occurred without epimerization.

Kinetic Isotope Experiments.

The previously reported¹⁵ α -methyl-d₃-styrene (**2a-d₃**) was prepared by Tebbe methylenation of acetophenone-methyl-d₃ with freshly prepared reagent in dichloromethane solvent according to the procedure of Pine.¹⁶ The **2a-d₃** thus generated was found to be >98% D by ¹H NMR. Furthermore, ²H NMR indicated none of the vinylic deuterium isomer. The KIE experiments were conducted by using 2 mmol of a 1:1 mixture of **2a:2a-d₃** in our general procedure in BFT and THF, but the reactions were quenched with methanol after approximately 5% conversion. Following a standard workup and purification by preparative thin layer chromatography, the product which contained a mixture of **4a** and **4a-d₂** was analyzed by CI-MS with ammonia as the carrier gas. The pure sample of **4a** under these conditions was found to cleanly produce an M+18 peak with no attendant M+17 peak visible. The ratio of **4a:4a-d₂** produced in both trials was determined to be 80:20 by the method of Biemann,¹⁷ which leads to a k_H/k_D = 4.4 in both solvents after extrapolation to zero time.

¹⁴ For best results the resin should be soaked in water for at least 3 h to remove impurities. Prior to loading, the water should be decanted and replaced.

¹⁵ Volger, H. C. *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 677.

¹⁶ Pine, S. H.; Pettit, R. J.; Geib, G. D.; Cruz, S. G.; Gallego, C. H.; Tijerina, T.; Pine, R. D. *J. Org. Chem.* **1985**, *50*, 1212.

¹⁷ Biemann, K. *Mass Spectrometry: Organic Chemical Applications* McGraw-Hill: New York, 1962; Chapter 5.