SUPPORTING INFORMATION

Lanthanide Lewis Acid-mediated Enantioselective Conjugate Radical Additions

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Experimental Procedures. Methylene chloride and THF were dried using Solvatek solvent purification system prior to use. Flash chromatography was performed using EM Science silica gel 60 (230-400 mesh). Melting points were determined using the Fisher-Johns melting point apparatus. All glassware was oven dried, assembled hot, and cooled under a stream of dry nitrogen before use. Reactions with air sensitive materials were carried out by standard syringe techniques.

¹H NMR were recorded on a Varian Unity/Inova-500 NB (500 MHz), or a Varian Unity/Inova-400 NB (400 MHz). Chemical shifts are reported in parts per million (ppm) down field from TMS, using residual CDCl₃ (7.27 ppm) as an internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublets of doublets, m = multiplet, b = broad), coupling constant(s) and integration. ¹³C NMR were recorded on a Varian Unity/Inova-500 NB (125 MHz) or a Varian Unity/Inova-400 (100 MHz) spectrometers using broad band proton decoupling. Chemical shifts are reported in parts per million (ppm) down field from TMS, using the middle resonance of CDCl₃ (77.0 ppm) as an internal standard. HPLC analyses were carried out on a Waters 515 HPLC pump and a 2487 dual λ absorbance detector connected to a PC with Millennium³² workstation. Optical rotations were recorded on a JASCO-DIP-370 instrument. High-resolution mass spectra (HRMS) [EI⁺] were obtained at the Mass spectrometry Laboratory, Ohio State University, Columbus, OH. Lanthanide

triflates, (*S*)-Proline and acetyl oxazolidinone were purchased from Aldrich Chemical Company.

Synthesis of **3**, **13** and **14**:

The ligands **3**, **13** and **14** were prepared according to literature procedure reported for **3** as shown in scheme 1.¹

Scheme 1

Ethyl (*S*)-(-)-2-(hydroxy(diphenyl)methyl)-1-pyrrolidine carboxylate **3:** 88% yield; $[\alpha]_D^{25} -165.2$ (*c* 1.04, CHCl_3) {lit: $[\alpha]_D^{20} -146$ (*c* 1.04, CHCl_3)}²; mp: 113-114 °C [lit. mp 115-116 °C (hexane)]²; ¹H NMR (CDCl_3 , 500 MHz) δ 0.81-0.9 (m, 1H), 1.23 (t, *J* = 6.9 Hz, 3H), 1.46-1.53 (m, 1H), 1.92-1.98 (m, 1H), 2.05-2.17 (m, 1H), 2.96 (m, 1H), 3.40-3.45 (m, 1H), 4.09-4.15 (m, 2H), 4.93 (dd, *J* = 8.9 and 3.6 Hz, 1H), 6.04 (bs, 1H), 7.22-7.56 (m, 10H); ¹³C NMR (CDCl_3 , 125 MHz) δ 14.9, 23.2, 29.9, 47.9, 62.1, 66.2, 81.8, 127.3, 127.4, 127.7, 127.8, 128.1, 128.4, 143.9, 146.6.

Ethyl (*S*)-(-)-2-(hydroxy(dimethyl)methyl)-1-pyrrolidine carboxylate **13:** 73% yield; $[\alpha]_D^{25} -78.2$ (*c* 1.26, CHCl_3); ¹H NMR (CDCl_3 , 500 MHz) δ 0.99 (s, 3H), 1.07 (s, 3H), 1.18 (t, *J* = 7.14 Hz, 3H), 1.52-1.65 (m, 2H), 1.75-1.98 (m, 3H), 3.09-3.15 (m, 1H), 3.61-3.69 (m, 1H), 3.80 (t, *J* = 7.4 Hz, 1H), 4.05 (q, *J* = 7.1 Hz, 2H), 5.67 (b, 1H); ¹³C NMR (CDCl_3 , 125 MHz) δ 14.8, 23.3, 24.4, 27.8, 29.2, 48.2, 61.9, 67.9, 73.8, 158.5; HRMS Exact mass calcd for $\text{C}_{10}\text{H}_{19}\text{NO}_3\text{Na}$ [*M*+*Na*]⁺: 224.1257; Found: 224.1236.

Ethyl (*S*)-(-)-2-(hydroxy(di-2-naphthyl)methyl)-1-pyrrolidine carboxylate **14:** 60% yield; $[\alpha]_D^{25} -222.0$ (*c* 1.05, CHCl_3); mp: 105-106 °C (pentane); ¹H NMR (CDCl_3 ,

500 MHz) δ 0.81 (b, 1H), 1.22 (s, 3H), 1.48-1.51 (m, 1H), 2.06-2.28 (m, 2H), 3.0 (b, 1H), 3.45 (m, 1H), 4.17 (b, 2H), 5.17 (dd, J = 8.7 and 3.6 Hz, 1H), 7.46-7.59 (m, 6H), 7.78-7.92 (m, 8H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 14.8, 23.4, 30.1, 48.0, 62.3, 66.4, 82.1, 125.4, 126.1, 126.3, 126.4, 126.7, 127.2, 127.4, 127.5, 127.7, 128.1, 128.6, 128.7, 132.8, 132.9, 133.1, 141.3, 143.9; HRMS Exact mass calcd for $\text{C}_{28}\text{H}_{27}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 448.1883; Found: 448.1877.

Synthesis of 4-9:

The ligand **9** was prepared from **3** by the alkaline hydrolysis according to the literature procedure.¹ Ligands **4-8** were obtained from **9** by the treatment with the corresponding alkyl chloroformates. Di-(*t*-butyl) dicarbonate was used for **4**.

General Procedure for 4-8: To a stirred solution of **9** (500 mg, 2 mmol) and Et_3N (2.4 mmol) in dry ether or THF (10 mL) was added alkyl chloroformate (2.4 mmol) at rt. The reaction was monitored by TLC and after completion was washed with 1N HCl. The organic phase was dried over MgSO_4 , concentrated and further purified by column chromatography on silica gel to afford the pure products.

Scheme 2

tert-Butyl (S)-(-)-2-(hydroxy(diphenyl)methyl)-1-pyrrolidine carboxylate 4:

78% yield; $[\alpha]_{\text{D}}^{25} -152.9$ (c 1.06, CHCl_3) {lit. $[\alpha]_{\text{D}}^{23} +177.7$ (c 2.16, CHCl_3) for (*R*)-enantiomer}³; mp: 148-150 °C (hexane) [lit. mp 147-149 °C]³; ^1H NMR (CDCl_3 , 500 MHz) δ 0.78 (m, 1H), 1.21-1.31 (m, 1H), 1.44 (s, 9H), 1.89-1.95 (m, 1H), 2.05-2.13 (m, 1H), 2.87 (m, 1H), 3.35 (m, 1H), 4.90 (dd, J = 8.9 and 3.6 Hz), 6.47 (bs, 1H), 7.24-7.41

(m, 10H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 23.1, 28.6, 29.9, 48.1, 65.9, 80.8, 81.9, 127.2, 127.3, 127.6, 127.9, 128.1, 128.5, 144.0, 146.7.

iso-Butyl (S)-(-)-2-(hydroxy(diphenyl)methyl-1-pyrrolidine carboxylate 5: 83% yield; $[\alpha]_{\text{D}}^{25} -135.1$ (c 1.11, CHCl_3); ^1H NMR (CDCl_3 , 500 MHz) δ 0.79-0.88 (m, 1H), 0.92 (d, J = 6.8 Hz, 6H), 1.5 (m, 1H), 1.94 (m, 2H), 2.10 (m, 1H), 2.96 (m, 1H), 3.42 (dd, J = 17.4 and 8.0 Hz 1H), 3.81 (m, 1H), 3.95 (dd, J = 10.2 and 6.7 Hz, 1H), 4.95 (dd, J = 8.9 and 3.6 Hz, 1H), 6.14 (bs, 1H) 7.26-7.42 (m, 10H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 19.2, 19.4, 23.1, 28.2, 29.9, 47.9, 66.3, 72.3, 81.9, 127.3, 127.4, 127.6, 127.9, 128.1, 128.5, 143.8, 146.6; HRMS Exact mass calcd for $\text{C}_{22}\text{H}_{27}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 376.1883; Found: 376.1892.

Methyl (S)-(-)-2-(hydroxy(diphenyl)methyl-1-pyrrolidine carboxylate 6: 90% yield; $[\alpha]_{\text{D}}^{25} -150.0$ (c 1.0, CHCl_3); mp: 162-164 °C (hexane); ^1H NMR (CDCl_3 , 500 MHz) δ 0.81-0.89 (m, 1H), 1.48-1.52 (m, 1H), 1.92-1.98 (m, 1H), 2.05-2.14 (m, 1H), 2.98 (bm, 1H), 3.40-3.42 (m, 1H). 3.66 (s, 3H), 4.94 (dd, J = 8.7 and 3.4 Hz), 5.9 (bs, 1H), 7.26-7.41 (m, 10H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 23.2, 29.8, 48.0, 53.3, 66.2, 81.8, 127.4, 127.7, 127.8, 127.9, 128.1, 128.4, 143.9, 146.6; HRMS Exact mass calcd for $\text{C}_{19}\text{H}_{21}\text{NO}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 334.1413; Found: 334.1406.

Butyl (S)-(-)-2-(hydroxy(diphenyl)methyl-1-pyrrolidine carboxylate 7: 90% yield; $[\alpha]_{\text{D}}^{25} -141.0$ (c 1.41, CHCl_3); ^1H NMR (CDCl_3 , 400 MHz) δ 0.79-0.87 (m, 1H), 0.93 (t, 7.45 Hz, 3H), 1.31-1.40 (m, 2H), 1.43-1.53 (m, 2H), 1.55-1.62 (m, 2H), 1.90-1.98 (m, 1H), 2.04-2.14 (m, 1H), 2.94 (m, 1H), 3.40 (dd, J = 18.0 and 8.1 Hz), 4.03-4.15 (m, 2H), 4.92 (dd, J = 8.8 and 3.8 Hz), 7.24-7.41 (m, 10H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 13.9, 19.3, 23.2, 29.9, 30.7, 31.2, 47.9, 66.1, 66.2, 81.8, 127.3, 127.4, 127.6, 127.9, 128.1,

128.4, 143.9, 146.6; HRMS Exact mass calcd for $C_{22}H_{27}NO_3Na$ $[M+Na]^+$: 376.1883; Found: 376.1902.

Benzyl (S)-(-)-2-(hydroxy(diphenyl)methyl)-1-pyrrolidine carboxylate 8⁴: 80% yield; 1H NMR ($CDCl_3$, 500 MHz) δ 0.88-0.94 (b, 1H), 1.51-1.54 (m, 1H), 1.96-2.02 (m, 1H), 2.07-2.16 (m, 1H), 3.05 (b, 1H), 3.5-3.52 (b, 1H), 5.00 (dd, J = 8.9 and 3.6 Hz, 1H), 5.22 (m, 2H), 6.06 (b, 1H), 7.62-7.45 (m, 15H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 23.2, 29.9, 48.1, 66.5, 67.7, 81.9, 127.4, 127.5, 127.8, 127.9, 128.1, 128.2, 128.3, 128.4, 128.8, 136.8, 143.9, 146.6, 159.0.

(S)-(-)-Diphenyl(pyrrolidin-2-yl)methanol 9⁵: 90% yield; 1H NMR ($CDCl_3$, 500 MHz) δ 1.55-1.79 (m, 4H), 2.93-2.97 (m, 1H), 3.02-3.06 (m, 1H), 4.26 (t, J = 7.6 Hz, 1H), 7.16-7.20 (m, 1H), 7.26-7.32 (m, 2H), 7.52 (d, J = 7.9 Hz, 1H), 7.59 (d, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.7, 26.5, 47.0, 64.7, 77.3, 125.8, 126.1, 126.6, 126.7, 128.2, 128.5, 145.7, 148.4.

Synthesis of Ligands 10-12: These were prepared in a similar procedure as described above for **4-8**.

Scheme 3

(S)-N-(Dimethylcarbonyl)- α,α -diphenylpyrrolidine-2-methanol 10: 66% yield; $[\alpha]_D^{25}$ 38.0 (c 1.0, $CHCl_3$); mp: 187-190 °C; 1H NMR ($CDCl_3$, 500 MHz) δ 1.6-1.7 (m, 2H), 1.74-1.83 (m, 1H), 1.87-2.02 (m, 1H), 2.63 (s, 6H), 3.03-3.09 (m, 1H), 3.23-3.27 (m, 1H), 5.23 (t, J = 8.3 Hz, 1H), 7.19-7.54 (m, 10H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 25.7, 29.7, 38.2, 52.4, 67.0, 82.0, 127.0, 127.2, 127.6, 127.7, 127.8, 128.0, 144.1, 146.2, 165.8; HRMS Exact mass calcd for $C_{20}H_{24}N_2O_2Na$ $[M+Na]^+$: 347.1729; Found: 347.1740.

(S)-N-(Phenylsulfonyl)- α,α -diphenylpyrrolidine-2-methanol 11: 76% yield; $[\alpha]_D^{25}$ -89.9 (c 1.04, CHCl_3); mp: 118-120 °C; ^1H NMR (CDCl_3 , 500 MHz) δ 0.77-0.85 (m, 1H), 1.18-1.28 (m, 1H), 1.78-1.92 (m, 2H), 2.79-2.84 (m, 1H), 3.28-3.33 (m, 1H), 4.43 (s, 1H), 4.88 (dd, J = 8.9 and 3.6 Hz, 1H), 7.26-7.45 (m, 10H), 7.54 (m, 2H), 7.62 (m, 1H), 7.78-7.81 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 24.1, 29.9, 50.2, 67.7, 80.1, 127.5, 127.7, 127.8, 127.9, 128.3, 128.5, 129.5, 133.2, 138.3, 143.8, 145.8; HRMS Exact mass calcd for $\text{C}_{23}\text{H}_{23}\text{NO}_3\text{SNa}$ $[\text{M}+\text{Na}]^+$: 416.1291; Found: 416.1262.

(S)-N-(Pivaloyl)- α,α -diphenylpyrrolidine-2-methanol 12: 93% yield; $[\alpha]_D^{25}$ -97.9 (c 1.06, CHCl_3); mp: 132-133 °C; ^1H NMR (CDCl_3 , 500 MHz) δ 1.11 (s, 9H), 1.37-1.44 (m, 1H), 1.49-1.59 (m, 1H), 1.77-1.84 (m, 1H), 2.04-2.10 (m, 1H), 2.66-2.72 (m, 1H), 3.67-3.72 (m, 1H), 5.23-5.29 (m, 1H), 7.19-7.49 (m, 10H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 24.9, 27.8, 29.3, 39.4, 49.3, 69.1, 82.6, 127.3, 127.4, 127.5, 128.1, 128.3, 143.2, 146.1, 180.1; HRMS Exact mass calcd for $\text{C}_{22}\text{H}_{27}\text{NO}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 360.1934; Found: 360.1939.

N-Cinnamoyl oxazolidinone 1: This was prepared as reported in literature.⁶ Under N_2 , to a flask containing 2-oxazolidinone (0.87 g, 1.0 mmol) and THF (20 mL), was added NaH (60% in mineral oil, 0.48 g, 12 mmol) in portions at 0 °C. After complete addition, the solution was stirred for 0.5 h at 0 °C. A solution of cinnamoyl chloride (1.83 g, 11 mmol) in 5 mL THF was then added dropwise at 0 °C over 10 minutes and the mixture was stirred at rt for 10 h. The reaction was quenched with 1 mL of saturated NH_4Cl solution and extracted with EtOAc (3 x 30 mL). The extracts were combined, washed with brine (2 x 5 mL), dried over MgSO_4 and concentrated. The crude product was purified by chromatography on silica gel using hexane/EtOAc (3:1) as eluent to yield 2.0 g of **1** (92%) as colorless solid. Mp: 150-151 °C (EtOH) [lit. 151-152.5 °C]¹; ^1H NMR

(400 MHz, CDCl₃) δ 4.14 (t, J = 8.0 Hz, 2H), 4.46 (t, J = 8.0 Hz, 2H), 7.40 (m, 3H), 7.60 (m, 2H), 7.85 (d, J = 15.8 Hz, 1H), 7.92 (d, J = 15.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 42.9, 62.2, 100.0, 116.6, 128.7, 129.0, 130.8, 134.6, 153.7, 165.5.

Representative experimental procedure for chiral Lewis acid catalyzed conjugate addition of radicals to enoate 1 (Table 1, entry 3): Under N₂, a mixture of Sm(OTf)₃ (0.06 mmol) and ligand **3** (0.06 mmol) in CH₂Cl₂ (1 mL) was stirred at rt for 45 min and cooled to -78 °C. N-cinnamoyl oxazolidinone **1** (0.2 mmol) (in 1 mL CH₂Cl₂) was added and the mixture was allowed to stir for an additional 30 min at this temperature. The reaction was initiated by sequential addition of 2-iodo propane (2 mmol), *n*-Bu₃SnH (0.4 mmol), Et₃B (0.6 mmol, 1M solution in hexanes) and oxygen (introduced via syringe). The reaction was monitored by TLC (30% EtOAc in hexane) and when judged complete was quenched with silica gel, concentrated, washed with hexanes and extracted with ether. The ether extract was concentrated over silica gel and purified by silica gel chromatography (hexane-ethyl acetate) to give 44 mg (84%) of **2** as colorless solid. The enantiomeric purity was determined by HPLC t_R 21.0 min (*S* enantiomer); t_R 27.5 min (*R* enantiomer) [Chiralcel OD (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 93/7, 1.0 mL/min] as 79% ee (*S* enantiomer). Mp: 77-79 °C; ¹H NMR (400 MHz, CDCl₃) δ 0.74 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.7 Hz, 3H), 1.91 (m, 1H), 2.98 (ddd, J = 10.2, 5.0, 2.4 Hz, 1H), 1.91 (m, 1H), 3.21 (dd, J = 16.6, 4.8 Hz, 1H), 3.51 (dd, J = 16.4, 10.2 Hz, 1H), 3.76-3.87 (m, 2H), 4.22 (td, J = 8.8, 7.2 Hz, 1H), 4.31 (td, J = 8.8, 7.2 Hz, 1H), 7.19 (m, 3H), 7.25 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 20.6, 20.9, 33.3, 38.7, 42.6, 48.5, 62.0, 126.3, 128.1, 128.5, 143.1, 153.6, 172.6.

Representative experimental procedure for chiral Lewis acid catalyzed conjugate addition of radicals to enoate 1 with additives (Table 2, entry 9): Under

N₂, a mixture of Sm(OTf)₃ (0.06 mmol), ligand **3** (0.06 mmol) and **15** (0.132 mmol) in CH₂Cl₂ (1 mL) was stirred at rt for 45 min and cooled to -78 °C. *N*-cinnamoyl oxazolidinone **1** (0.2 mmol) (in 1 mL CH₂Cl₂) was added and the mixture was allowed to stir for an additional 30 min at this temperature. The reaction was initiated by sequential addition of 2-iodo propane (2 mmol), *n*-Bu₃SnH (0.4 mmol), Et₃B (0.6 mmol, 1M solution in hexanes) and oxygen (introduced via syringe). The reaction was monitored by TLC (30% EtOAc in hexane) and when judged complete was quenched with silica gel, concentrated, washed with hexanes and extracted with ether. The ether extract was concentrated over silica gel and purified by silica gel chromatography (hexane-ethyl acetate) to give 35 mg (67%) of **2** as colorless solid. The enantiomeric purity was determined by HPLC t_R 21.0 min (*S* enantiomer); t_R 27.5 min (*R* enantiomer) [Chiralcel OD (0.46 cm x 25 cm) (from Daicel Chemical Ind., Ltd.) hexane/*i*-PrOH, 93/7, 1.0 mL/min] to be 89% (*S* enantiomer).

Calculation of product ee from experimental ee for table 2, entry 6:

$$(R_{\text{product}} + R_{\text{additive}} / S_{\text{product}} + S_{\text{additive}}) = 1.84 \quad (1)$$

Since 0.132 mmol of racemic product was used as additive, R_{additive} = 0.066 and S_{additive} = 0.066.

$$R_{\text{product}} + S_{\text{product}} = 0.2 \text{ mmol} \quad (2)$$

Solving equations (1) and (2), R_{product} = 0.1491 and S_{product} = 0.0509 and hence the product obtained from the reaction of the substrate **1** has 49% ee.

References

- (1) Bhaskar Kanth, J. V.; Periasamy, M. *Tetrahedron* **1993**, *49*, 5127-5132.
- (2) Gibson, C. L. *Tetrahedron: Asymmetry* **1999**, *10*, 1551-1561.
- (3) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231-3239.
- (4) Takahashi, H.; Kawabata, A.; Higashiyama, K. *Chem. Pharm. Bull.* **1987**, *35*, 1604-1607.

- (5) Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Jones, E. T. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751-762.
- (6) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340-5345.