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Modular Amino Acids-Based Chiral Ligands for Copper-Catalyzed Enantioselective Conjugation Addition of Diethylzinc to Cyclic Enones

SHAOHUA GOU AND ZAHER M. A. JUDEH*

Division of Chemical and Biomolecular Engineering, School of Chemical and Biomedical Engineering, Nanyang Technological University, Singapore

ABSTRACT New amino acid-based modular chiral ligands were readily synthesized and used to catalyze the asymmetric conjugate addition of Et_2Zn to various cyclic enones in the presence of a variety of copper sources. Moderately high *ee* of up to 72% were obtained using ligand (*S*)-**1e** under mild conditions. *Chirality 23:105–112, 2011.* © 2010 Wiley-Liss, Inc.

KEY WORDS: alkylation; amino acids; conjugate addition; diethylzinc; enones

INTRODUCTION

The asymmetric conjugate addition of dialkylzinc reagents to α,β-unsaturated substrates is a powerful carbon–carbon bond forming reaction.[1–3] It has been successfully applied to many substrates such as cyclic and acyclic enones, nitro olefins, amides, lactones, lactams, and malonates to give desirable products useful for the synthesis of biologically active compounds.[4–9] Specifically, chiral copper complexes have proved to be very effective in the conjugate addition of dialkylzinc derivatives to cyclic and acyclic enones. Key to this success is the design and development of catalytic and highly efficient phosphorus-containing chiral ligands such as phosphites,[10–18] diphosphites,[19,20] phosphoramidites,[8,21–26] P,O-ligand,[27] and P,N-ligand.[15,28–31] However, nonphosphorus chiral ligands have been less explored and their success has remained rather limited. For example, several chiral sulfonamides,[32–36] diaminocarbenes,[37–41] oxazolines,[42] thioether-hydroxyl ligand,[43–47] N,N-ligand,[48] and N,S-ligand[48–50] have been reported to give moderate to excellent enantioselectivities depending upon the ligand, substrate, and reaction conditions. Changes in the stereoelectronic properties of chiral ligands can often lead to dramatic variation in the reactivity and enantioselectivity of reactions involving such ligands. Therefore, we are interested in new, stable, and modular chiral ligands with the aim of synthesizing a small library that can be used for efficient enantioselective copper-catalyzed 1,4-conjugate addition of dialkylzinc reagents to α,β-unsaturated compounds. To achieve this aim, cheap and readily available components that can undergo straightforward chemical modifications to give the desired chiral catalysts in high yields are needed. For this purpose, amino acids that are known to catalyze a variety of enantioselective reactions have been chosen.[51–53] The general structure of the target ligands is shown in Figure 1. These ligands are synthesized from L-phenylalanine and incorporate a sulfonamide, an amide, and a hydroxyl or an alkoxy groups. These sulfonamide ligands have the advantages of straightforward synthesis, high resistance to oxidation (normally encountered in phosphorus-containing ligands), and facile modular construction that allows for easy variation of the amine substituent and the amino acid backbone. This class of ligands has been designed to mimic the most successful nonphosphorus chiral sulfonamides that are known to give up to 90% *ee* in the conjugate addition of Et_2Zn to enones.[32–34] The results of our investigation presented here demonstrates the usefulness of these ligands in the copper-catalyzed enantioselective conjugate addition of Et_2Zn to several cyclic enones.

EXPERIMENTAL

General Remarks

All reactions were conducted in oven-dried glassware under inert atmosphere of nitrogen using anhydrous solvents unless otherwise stated. Analytical thin layer chromatography was performed on alumina- or glass-backed silica plates (F254, 250-μm thickness) and visualized under UV light. Flash column chromatography was carried out on silica gel 60 (230–400 mesh) under air pressure. Enantiomeric ratios of the products were determined using chiral GC techniques. Specific rotations were determined as $[\alpha]_D^{20}$ (c = 0.02 g/ml in CH_2Cl_2). Melting points are uncorrected. Only the more representative frequencies (cm^{-1}) are reported for IR spectra. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) chemical shifts in $CDCl_3$ are quoted as δ values relative to tetramethylsilane (δ = 0.00) and $CDCl_3$

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*Correspondence to: Zaher Judeh, School of Chemical and Biomedical Engineering, Nanyang Technological University, 62 Nanyang Drive, N1.2 B1-14, Singapore 637459. E-mail: zaher@ntu.edu.sg
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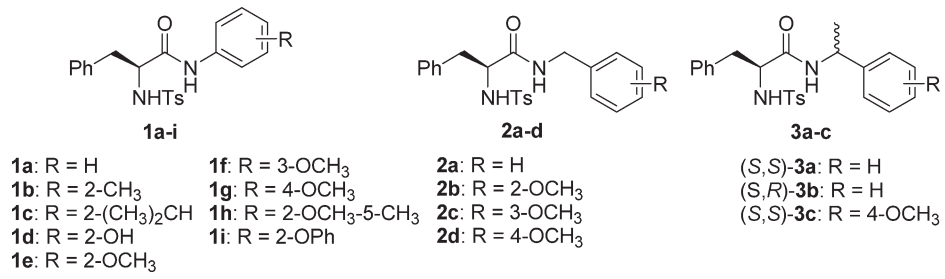


Fig. 1. Structures of ligands synthesized from L-phenylalanine.

(δ = 77.0), respectively, in parts per million and coupling constants in hertz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High-resolution mass spectra (HRMS) were obtained using positive electrospray ionization (*m/z* values are given). All commercially available chemicals were used as received, unless otherwise noted. Chiral ligands **1d** and **3a** (Scheme 1) were synthesized according to published literature procedures.[54,55]

General Procedure for the Synthesis of Ligands 1, 2, and 3

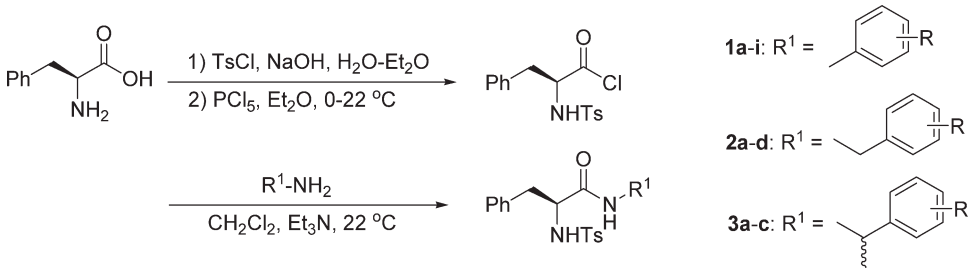
3-Phenyl-2-(toluene-4-sulfonylamino)-propionyl chloride[54,55] (405 mg, 1.2 mmol) was added to a solution of aniline or phenylamine (1 mmol) and Et_3N (0.21 ml, 1.5 mmol) in CH_2Cl_2 (10 ml) at 22°C. After stirring for 2 h, the reaction mixture was diluted with CH_2Cl_2 (50 ml), washed with aqueous HCl (1.0 M, 2 × 20 ml), aqueous K_2CO_3 or $NaHCO_3$ (1.0 M, 2 × 20 ml), and then with brine (2 × 20 ml). The organic layer was dried over $MgSO_4$, filtered, and evaporated to dryness on a rotary evaporator. The crude products were purified using column chromatography on silica gel (EA-Hexane) and recrystallized from a mixture of EA:hexane (10:1, v:v). The corresponding products were obtained as white solids in 80–95% yield.

(*S*)-*N*-(*p*-Toluenesulfonyl)-phenylalanine phenylamide (1a). White solid; 95% yield; m.p. 174–176°C; $[\alpha]_D^{20}$ −82.23 (*c* = 0.02 g/ml in CH_2Cl_2); IR ν_{max} cm^{-1} (KBr) 3335, 1538, 1436 (NHCO), 1600 (CO), 1333, 1159 (SO_2); ^1H NMR ($CDCl_3$) δ 2.39 (s, 3H), 2.99 (q, *J* = 6.3 Hz, 1H), 3.06 (q, *J* = 6.9 Hz, 1H), 3.98 (dd, *J* = 6.6 Hz, 1H), 5.04 (d, *J* = 6.6 Hz, 1H), 6.96–6.99 (m, 2H), 7.12–7.37 (m, 10H), 7.58 (q, *J* = 6.6 Hz, 2H), 7.9 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 21.6, 38.3, 58.4, 120.2, 124.9, 127.3, 127.5, 129.0, 129.1, 129.2, 130.0, 136.9, 144.2, 168.2; HRMS (ESI) calculated for $C_{22}H_{23}N_2O_3S$ 395.1429, found 395.1438.

(*S*)-*N*-(*p*-Toluenesulfonyl)-phenylalanine *o*-tolylamide (1b). White solid; 87% yield; m.p.183–185°C; $[\alpha]_D^{20}$ −91.50 (*c* = 0.02 g/ml in CH_2Cl_2); IR ν_{max} cm^{-1} (KBr) 3237, 1531, 1442 (NHCO), 1665 (CO), 1334, 1163 (SO_2); ^1H NMR ($CDCl_3$) δ 2.13 (s, 3H), 2.42 (s, 3H), 2.98 (q, *J* = 6.3 Hz, 1H), 3.09 (q, *J* = 6.9 Hz, 1H), 4.03 (dd, J_1 = 6.3 Hz, J_2 = 6.6 Hz, 1H), 5.04 (d, *J* = 6.6 Hz, 1H), 6.96–6.99 (m, 2H), 7.05–7.24 (m, 8H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 7.8 Hz, 1H), 8.03 (s,1H); ^{13}C NMR ($CDCl_3$) δ 17.49, 21.59, 38.16, 58.44, 122.63, 125.50, 126.64, 127.22, 127.47, 129.14, 129.18, 129.44, 129.97, 130.50, 134.92, 135.00, 135.30, 144.21, 168.29; HRMS (ESI) calculated for $C_{23}H_{25}N_2O_3S$ 409.1586, found: 409.1598.

(*S*)-*N*-(*p*-Toluenesulfonyl)-phenylalanine 2-isopropylphenylamide (1c). White solid; 85% yield; m.p.160–162°C; $[\alpha]_D^{20}$ −67.47 (*c* = 0.02 g/ml in CH_2Cl_2); IR ν_{max} cm^{-1} (KBr) 3312, 1522, 1436 (NHCO), 1665 (CO), 1332, 1156 (SO_2); ^1H NMR ($CDCl_3$) δ 1.19 (t, *J* = 6.9, 6H), 2.43 (s, 3H), 2.95 (q, *J* = 6.0 Hz, 1H), 3.15 (q, *J* = 6.6 Hz, 1H), 3.15 (dd, J_1 = J_2 = 6.3 Hz, 1H), 4.96 (d, *J* = 6.6 Hz, 1H), 6.98 (t, *J* = 5.4 Hz, 2H), 7.17–7.28 (m, 9H), 7.59 (d, *J* = 7.8 Hz, 3H), 8.07 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.61, 22.94, 23.04, 27.67, 30.96, 38.02, 58.34, 124.02, 125.63, 126.25, 126.30, 127.22, 127.48, 129.15, 129.20, 130.00, 133.37, 134.95, 135.44, 140.55, 168.56; HRMS (ESI) calculated for $C_{25}H_{29}N_2O_3S$ 437.1899, found 437.1907.

(*S*)-*N*-(*p*-Toluenesulfonyl)-phenylalanine 2-methoxyphenylamide (1e). White solid; 83% yield; m.p.166–168°C; $[\alpha]_D^{20}$ −56.79 (*c* = 0.02 g/ml in CH_2Cl_2); IR ν_{max} cm^{-1} (KBr) 3242, 1541, 1481 (NHCO), 1661 (CO), 1330, 1159 (SO_2); ^1H NMR ($CDCl_3$) δ 2.36 (s, 3H), 2.98 (q, *J* =



Scheme 1. Synthesis of amino acid-based ligands.

6.6 Hz, 1H), 3.09 (q, J = 6.3 Hz, 1H), 3.80 (s, 3H), 4.04 (d, J = 6.6 Hz, 1H), 5.04 (d, J = 6.6 Hz, 1H), 6.82–7.07 (m, 5H), 7.18–7.22 (m, 4H), 7.59 (d, J = 8.4 Hz, 2H), 8.19–8.22 (m, 1H), 8.39 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.50, 38.72, 55.77, 58.67, 110.09, 119.74, 120.91, 122.45, 124.32, 127.20, 128.96, 129.28, 129.78, 135.15, 143.93, 167.86; HRMS (ESI) calculated for $C_{23}H_{25}N_2O_4S$ 425.1535, found 425.1549.

(*S*)-*N*-(*p*-Toluenesulfonyl)-phenylalanine 3-methoxyphenylamide (1f). White solid; 88% yield; m.p. 145–147°C; $[\alpha]_D^{20}$ −76.95 (c = 0.02 g/ml in CH_2Cl_2); IR ν_{max} cm^{-1} (KBr) 3242, 1541, 1487 (NHCO), 1661 (CO), 1330, 1159 (SO_2); ^{1}H NMR ($CDCl_3$) δ 2.41 (s, 3H), 2.96 (q, J = 6.6 Hz, 1H), 3.09 (q, J = 6.9 Hz, 1H), 3.79 (s, 3H), 3.97 (q, J = 6.9 Hz, 1H), 5.03 (d, J = 6.9 Hz, 1H), 6.66–6.83 (m, 1H), 6.84–6.87 (m, 1H), 6.88–6.99 (m, 2H), 7.08–7.23 (m, 7H), 7.57 (d, J = 8.4 Hz, 2H), 7.95 (s, 1H);^{13}C NMR ($CDCl_3$) δ 21.54, 38.29, 55.32, 58.45, 105.84, 110.75, 112.36, 127.24, 127.46, 129.13, 129.19, 129.63, 129.95, 138.04, 144.23, 160.08, 168.14; HRMS (ESI) calculated for $C_{23}H_{25}N_2O_4S$, 425.1535, found 425.1546.

(*S*)-*N*-(*p*-Toluenesulfonyl)-phenylalanine 4-methoxyphenylamide (1g). White solid; 90% yield; m.p. 144–146°C; $[\alpha]_D^{20}$ −78.66 (c = 0.02 g/ml in CH_2Cl_2); IR ν_{max} cm^{-1} (KBr) 3330, 1533, 1411 (NHCO), 1660 (CO), 1334, 1250 (SO_2); ^{1}H NMR ($CDCl_3$) δ 2.17 (s, 3H), 2.93 (q, J = 6.3 Hz, 1H), 3.10 (q, J = 6.9 Hz, 1H), 3.79 (s, 3H), 3.96 (q, J_1 = 13.5 Hz, J_1 = 6.6 Hz, 1H), 4.96 (d, J = 6.6 Hz, 1H), 6.81–6.85 (m, 2H), 6.86–6.99 (m, 2H), 7.17–7.25 (m, 9H), 7.58 (d, J = 8.1 Hz, 2H), 7.79 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.55, 38.41, 55.48, 58.43, 114.10, 122.10, 127.25, 127.43, 129.08, 129.21, 129.92, 144.15, 156.84, 167.98; HRMS (ESI) calculated for $C_{23}H_{25}N_2O_4S$, 425.1535, found 425.1547.

(*S*)-*N*-(*p*-Toluenesulfonyl)-phenylalanine 2-methoxy-5-methyl-phenylamide (1h). White solid; 92% yield; m.p. 186–189°C; $[\alpha]_D^{20}$ −54.45 (c = 0.02 g/ml in CH_2Cl_2); IR ν_{max} cm^{-1} (KBr) 3367, 1541, 1491 (NHCO), 1664 (CO), 1330, 1162 (SO_2); ^{1}H NMR ($CDCl_3$) δ 2.29 (s, 3H), 2.36 (s, 3H), 2.97 (q, J = 6.6 Hz, 1H), 3.10 (q, J = 6.6 Hz, 1H), 3.76 (s, 3H), 4.04 (d, J = 6.0 Hz, 1H), 5.11 (d, J = 6.0 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 6.92 (d, J = 9.6 Hz, 2H), 6.99–7.20 (m, 5H), 7.60 (d, J = 8.1 Hz, 2H), 8.04 (s, 1H), 8.36 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.95, 21.52, 55.90, 58.65, 109.96, 120.35, 124.54, 127.20, 128.98, 129.09, 129.80, 130.39, 135.13, 143.92, 167.81; HRMS (ESI) calculated for $C_{24}H_{27}N_2O_4S$ 439.1692, found 139.1702.

(*S*)-*N*-(*p*-Toluenesulfonyl)-phenylalanine 2-phenoxylphenylamide (1i). White solid; 87% yield; m.p. 103–105°C; $[\alpha]_D^{20}$ −56.13 (c = 0.02 g/ml in CH_2Cl_2); IR ν_{max} cm^{-1} (KBr) 3256, 1535, 1451 (NHCO), 1663 (CO), 1329, 1218 (SO_2); ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H), 2.98 (d, J = 6.6 Hz, 2H), 3.98 (d, J = 6.6 Hz, 1H), 4.00 (d, J_1 = J_2 = 6.6 Hz, 1H), 4.89 (d, J = 6.3 Hz, 1H), 6.83–7.37 (m, 14H), 7.55 (d, J = 8.4 Hz, 2H), 8.28 (d, J_2 = 6.3 Hz, 1H), 8.42 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.53, 38.43, 58.54, 101.80, 117.90, 118.63, 120.98, 123.87, 123.91, 124.69, 127.00, 127.37, 128.74, 128.99, 129.15, 129.81, 129.91, 134.85, 143.98, 146.01, 156.24, 168.19; HRMS (ESI) calculated for $C_{28}H_{27}N_2O_4S$ 487.1692, found 487.1706.

(*S*)-*N*-(*p*-Toluenesulfonyl)-phenylalanine benzylamide (2a). White solid; 87% yield; m.p. 138–140°C; $[\alpha]_D^{20}$ −12.03 (c = 0.02 g/ml in CH_2Cl_2); IR ν_{max} cm^{-1} (KBr) 3253, 1542, 1437 (NHCO), 1654 (CO), 1332, 1160 (SO_2); ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H), 2.94 (q, J = 6.0 Hz, 1H), 3.02 (q, J = 6.6 Hz, 1H), 4.32–4.37 (m, 1H), 4.99 (q, J = 7.2 Hz, 1H), 6.66 (d, J = 4.8 Hz, 1H), 6.89 (d, J = 6.3 Hz, 2H), 7.01–7.04 (m, 2H), 6.92–7.31 (m, 10H), 7.56 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.53,38.49, 43.50, 58.10, 127.04, 127.07, 127.38, 217.55, 128.55, 128.75, 129.24, 129.74, 135.40, 136.04, 137.51, 143.68, 170.36; HRMS (ESI) calculated for $C_{23}H_{25}N_2O_3S$ 409.1586 found 409.1599.

(*S*)-*N*-(*p*-Toluenesulfonyl)-phenylalanine 2-methoxybenzylamide (2b). White solid; 83% yield; m.p. 106–108°C; $[\alpha]_D^{20}$ −12.15 (c = 0.02 g/ml in CH_2Cl_2); IR ν_{max} cm^{-1} (KBr) 3244, 1542, 1439 (NHCO), 1641 (CO), 1258, 1161 (SO_2); ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H), 2.80 (q, J = 6.9 Hz, 1H), 3.02 (q, J = 6.6 Hz, 1H), 3.55 (s, 3H), 3.74 (s, 1H), 4.32 (d, J = 6.0 Hz, 2H), 4.91 (s, 1H), 6.65 (s, 1H), 6.83–6.92 (m, 4H), 7.07–7.33 (m, 7H), 7.56 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.60, 38.46, 39.60, 55.24, 57.78, 110.23, 120.54, 127.12, 128.82, 128.92, 129.21, 129.55, 129.80, 135.18, 143.84, 157.49, 169.45; HRMS (ESI) calculated for $C_{24}H_{27}N_2O_4S$ 439.1692 found 439.1703.

(*S*)-*N*-(*p*-Toluenesulfonyl)-phenylalanine 3-methoxybenzylamide (2c). White solid; 86% yield; m.p. 107–109°C; $[\alpha]_D^{20}$ −5.28 (c = 0.02 g/ml in CH_2Cl_2); IR ν_{max} cm^{-1} (KBr) 3248, 1541, 1490 (NHCO), 1654 (CO), 1339, 1157 (SO_2); ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3H), 2.89–3.02 (m, 2H), 3.79 (s, 3H), 3.90 (d, J = 6.3 Hz, 1H), 4.33 (d, J = 6.0 Hz, 2H), 4.95 (s, 1H), 6.62–6.92 (m, 6H), 7.12–7.24 (m, 6H), 7.53 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.60, 38.27, 43.63, 55.29, 57.92, 64.40, 113.03, 113.23, 119.84, 127.14, 127.39, 128.96, 129.17, 129.67, 129.86, 135.10, 143.97, 159.86; HRMS (ESI) calculated for $C_{24}H_{27}N_2O_4S$ 439.1692 found 439.1705.

(*S*)-*N*-(*p*-Toluenesulfonyl)-phenylalanine 4-methoxybenzylamide (2d). White solid; 91% yield; m.p. 129–131°C; $[\alpha]_D^{20}$ −6.09 (c = 0.02 g/ml in CH_2Cl_2); IR ν_{max} cm^{-1} (KBr) 3251, 1541, 1513 (NHCO), 1652 (CO), 1328, 1161 (SO_2); ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3H), 2.88 (q, J = 6.3 Hz, 1H), 2.99 (q, J = 6.9 Hz, 1H), 3.79 (s, 3H), 3.90 (d, J = 6.6 Hz, 1H), 4.25 (d, J = 5.4 Hz, 2H), 4.98 (d, J = 6.3 Hz, 1H), 6.49 (s, 1H), 6.80 (d, J = 6.9 Hz, 2H), 6.91 (d, J = 7.5 Hz, 2H), 7.03–7.27 (m, 7H), 7.54 (d, J = 6.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.56, 34.60, 38.34, 40.99, 55.28, 57.88, 114.08, 127.16, 127.30, 128.94, 129.18, 129.66, 129.82, 130.49, 135.24, 143.92, 169.82; HRMS (ESI) calculated for $C_{24}H_{27}N_2O_4S$ 439.1692 found 439.1702.

***N*-(*p*-Toluenesulfonyl)-L-phenylalanine (*R*)-1-(4-methoxyphenyl)-ethylamide (3b).** White solid; 91% yield; m.p. 125–217°C; $[\alpha]_D^{20}$ +16.02 (c = 0.02 g/ml in CH_2Cl_2); IR ν_{max} cm^{-1} (KBr) 3264, 1541, 1514 (NHCO), 1652 (CO), 1330, 1240 (SO_2); ^{1}H NMR ($CDCl_3$) δ 1.32 (d, J = 6.9 Hz, 3H), 2.42 (s, 3H), 2.83 (q, J = 6.9 Hz, 1H), 3.03 (q, J = 6.6 Hz, 1H), 3.79 (s, 3H), 3.84 (d, J = 8.1 Hz, 1H), 4.87–4.96 (m, 2H), 6.29 (d, J = 7.2 Hz, 1H), 6.81–6.91 (m,

4H), 7.06 (d, J = 8.7 Hz, 2H), 7.13–7.22 (m, 5H), 7.55 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.41, 21.60, 38.51, 48.53, 55.32, 57.75, 113.93, 127.13, 127.32, 128.98, 129.26, 129.86, 134.71, 135.21, 125.82, 143.92, 158.83, 168.88; HRMS (ESI) calculated for $C_{25}H_{29}N_2O_4S$ 453.1848 found 453.1856.

General Procedure for Catalytic Asymmetric Conjugate Addition

A mixture of copper source (0.03 mmol) and ligand (0.03 mmol) in an appropriate solvent (1.0 ml) was stirred under nitrogen atmosphere at 22°C for 10 min and then cooled to 0°C. Et_2Zn (0.44 mmol, solution in toluene) was added dropwise and the mixture was stirred for 1 h. Enone (0.20 mmol) was then added and the resulting mixture was stirred for 24 h before being quenched by aqueous HCl (1.0 M). The mixture was extracted with Et_2O (3 × 20 ml), the organic phases were combined, dried over Na_2SO_4, filtered, and evaporated to dryness using rotary evaporator. The crude product was purified by column chromatography on silica gel (EA-hexane). The *ee* values of the products were determined by chiral GC G-TA as follows.

3-(*S*)-Ethyl-cyclohexanone (5a). A 72% *ee* by GC analysis (Chiracel G-TA column, 110°C, and flow: 2.0 ml/min). Retention times, t_1 = 5.4 (minor), t_2 = 5.6 min (major).[56]

3-(*R*)-Ethyl-4,4-dimethyl-cyclohexanone (5b). A 56% *ee* by GC analysis (Chiracel G-TA column, 100°C, and flow: 1.0 ml/min). Retention times, t_1 = 33.3 (minor), t_2 = 34.2 min (major).[8]

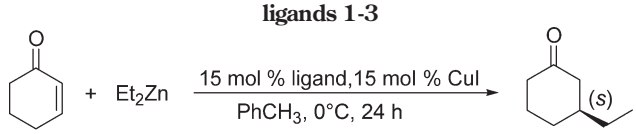
3-(S)-Ethyl-cycloheptanone (5c). A 52% *ee* by GC analysis (Chiracel G-TA column, 100°C, and flow: 1.0 ml/min). Retention times, t_1 = 26.7 (major), t_2 = 27.2 min (minor).[56]

RESULTS AND DISCUSSION

The ligands were synthesized by reacting L-phenylalanine with tosyl chloride to give the tosyl-L-phenylalanine, which upon reaction with PCl_5 gave the tosyl-L-phenylalanine acid chloride (Scheme 1).[54,55] Condensation of this acid chloride with an appropriate amine nucleophile gave the respective ligands **1–3** in 80–98% yield (Fig. 1). Substituted and unsubstituted aniline **1a–i**, benzylamine **2a–d**, and (*R*)- and (*S*)-α-methyl benzylamine **3a–c** nucleophiles were used. The ligands **1–3** were designed in such a way to probe the effects of (i) different substituents at the amide nitrogen, (ii) various substituents at the aromatic ring (iii), the substitution pattern at the aromatic ring, and (iv) match/mismatch characteristics due to additional chirality.

Preliminary screening involved the addition of 2-cyclohexen-1-one **4a** to a complex of ligands **1**, **2**, or **3** (15 mol %) and CuI (15 mol %) with Et_2Zn (2.2 equiv) in dry toluene at 0°C (Table 1). The results in Table 1 show a strong influence of the ligand structure on the enantioselectivity of **5a**. Ligand **1a** (R = H) gave **5a** in 88% yield and 40% *ee* (Table 1, entry 1). More sterically demanding ligands **1b** (R = 2-methyl) and **1c** (R = 2-isopropyl; Table 1, entries 2 and 3) gave similar *ee*s to **1a** indicating the insignificant steric effects exerted by the alkyl substituents. This expected outcome can be explained by free rotation of the aniline aromatic ring of ligands **1a–1c**. We then thought of introducing a substituent at the aromatic ring to eliminate the free rotation and form a "handle" where copper and zinc can coordinate. Unfortunately, introduction of a 2-OH group as in **1d** did not improve the *ee* (35%) but instead led to a decrease in the yield of **5a** to 54% (Table 1, entry 4). Gratifyingly, significant improvements in the *ee* to 72% and in the yield to 77% were achieved when ligand **1e** with a 2-OMe was used (Table 1, entry 5). The use of ligands **1f** (having a 3-OMe substituent) and **1g** (having a 4-OMe substituent) led to the formation of **5a** in lower *ee*s of 31% and 17%, respectively (Table 1, entries 6 and 7). The higher *ee* obtained using **1e** indicated a better coordination between the metal center and the 2-OMe substituent. Interestingly, when ligand **1h** with a 2-OMe and a 5-methyl substituents was used, a decrease in the *ee* to 48% was observed (Table 1, entry 8 vs. entry 5). To investigate the effect of bulkier and coordinating ortho-substituents, ligand **1i** with a 2-OPh substituent was synthesized and when used gave moderate 55% *ee* and 53% yield (Table 1, entry 9). We then investigated the effect of increasing the coordination sphere by using benzylamines (ligands **2** and **3**; Table 1, entries 10–16) instead of aniline. Similar trends to ligand **1** were observed in this case. Ligand **2a**, with no substituents on the aromatic ring, gave the lowest *ee* of

TABLE 1. Asymmetric conjugate addition of Et_2Zn to 2-cyclohexen-1-one 4a catalyzed by CuI complexes of ligands 1-3



4a **5a**

Entry[a]	Ligand	Yield (%)[b]	*ee* (%)[c]
1	**1a**	88	40
2	**1b**	84	39
3	**1c**	61	37
4	**1d**	54	35
5	**1e**	77	72
6	**1f**	70	31
7	**1g**	80	17
8	**1h**	83	48
9	**1i**	53	55
10	**2a**	73	19
11	**2b**	62	63
12	**2c**	90	31
13	**2d**	83	20
14	**3a**	87	35
15	**3b**	73	38
16	**3c**	43	10

[a]Conditions: 2.2 equiv Et_2Zn ($PhCH_3$ solution), 2-cyclohexen-1-one concentration 0.2 M in $PhCH_3$.
[b]The yield of the 1,2-product was not determined.
[c]Determined by chiral GC (G-TA column). Absolute configuration was assigned by comparison with the literature values.[56]

TABLE 2. Effects of different copper sources on the addition of Et_2Zn to 2-cyclohexen-1-one

Entry[a]	Ligand	Copper source	Yield (%)	*ee* (%)[b]
1	**1e**	CuI	77	72
2	**1e**	CuBr	49	29
3	**1e**	CuCl	54	51
4	**1e**	CuCN	92	47
5	**1e**	$CuCl_2$	41	5
6	**1e**	$CuSO_4{\cdot}5H_2O$	62	41
7	**1e**	$CuNO_3{\cdot}5H_2O$	59	12
8	**1e**	$Cu(acac)_2$	38	12
9	**1e**	$Cu(OAc)_2{\cdot}H_2O$	71	7
10	**1e**	PhSCu	62	15
11	**1i**	CuI	53	55
12	**1i**	CuCl	64	55
13	**1i**	CuCN	56	38
14	**1i**	$CuSO_4{\cdot}5H_2O$	69	40
15	**2b**	CuI	62	63
16	**2b**	CuCl	88	27
17	**2b**	CuBr	88	33
18	**2b**	$CuSO_4{\cdot}5H_2O$	75	55
19	**2b**	$Cu(acac)_2$	38	31
20	**2b**	PhCuS	82	14
21	**2b**	$Cu(OAc)_2$	80	19

[a]Conditions: 2.2 equiv Et_2Zn ($PhCH_3$ solution), 2-cyclohexen-1-one concentration 0.2 M in $PhCH_3$.
[b]Determined by chiral GC (G-TA column). Absolute configuration was assigned by comparison with the literature values.[8]

19% (Table 1, entry 10), whereas **2b** with a 2-OMe gave the best *ee* of 63% (Table 1, entry 11). Ligands **2c** with a 3-OMe substituent and **2d** with a 4-OMe substituent gave lower *ee*s of 31% and 20%, respectively (Table 1, entries 12 and 13). Ligand **3** with (*R*)- and (*S*)-α-methyl benzylamine side chains was also examined to probe the effect of additional chirality (Table 1, entries 14–16). Again, similar trends to ligands **1** and **2** were observed. Ligand (*S*,*S*)-**3a** (R = H) gave 35% *ee* while ligand **3c** (R = 4-OMe) gave 10% *ee* (Table 1, entries 14 and 16). To determine whether there is a cooperative effect between the stereocenters of the ligand backbone, (*S*,*R*)-**3b** was examined. Unfortunately, no significant effect was observed and the *ee* obtained was 38% (Table 1, entry 15).

Having realized the potential of ligands **1–3** in the asymmetric copper-catalyzed 1,4-conjugate addition of Et_2Zn to 2-cyclohexen-1-one **4a**, the effect of several reaction parameters such as copper source, catalyst loading, ligand-to-copper ratio, and reaction solvent were studied with the aim of optimizing the reaction conditions and developing more efficient ligands.

Initially, the effects of various copper sources such as CuBr, CuCl, CuCN, $CuCl_2$, $CuSO_4{\cdot}5H_2O$, $CuNO_3{\cdot}5H_2O$, $Cu(acac)_2$, $Cu(OAc)_2{\cdot}H_2O$, and PhSCu[57] were investigated using the most promising ligands **1e**, **1i**, and **2b** under the same reaction conditions mentioned in Table 1 (Table 2). In all cases, except in entries 16 and 17, a combination between **1e**, **1i**, or **2b** and CuI, CuCl, CuCN, or $CuSO_4{\cdot}5H_2O$ gave the best *ee*s (Table 2, entries 1, 3, 4, 6, 11–15, and 18). Ligands **1e**, **1i**, and **2b** with CuI showed the highest *ee*s of up to 72% (Table 2, entries 1, 11, and 13). Other copper sources such as CuBr, $CuCl_2$, $CuNO_3{\cdot}5H_2O$, $Cu(acac)_2$, $Cu(OAc)_2{\cdot}H_2O$, and PhCuS gave *ee*s between 5 and 33% (Table 2, entries 2, 5, 7–10, 20, and 21).

The effects of catalyst loading and optimum mole ratio of ligand-to-CuI were investigated using **1e** (Table 3). The best catalyst loading was found to be 15 mol %; higher or lower catalyst loadings afforded inferior *ee* (Table 3, entries 2–6 vs. entry 1). The highest *ee* of 72% was obtained when the mole ratio ligand-to-CuI was 1:1 (Table 3, entry 1). Higher (Table 3, entry 2) or lower (Table 3, entries 3 and 5) mole ratio of CuI versus **1e** led to the formation of **5a** in lower *ee* and yield.

Next, we investigated the effect of various coordinating and noncoordinating solvents ($PhCH_3$, CH_2Cl_2, THF, Et_2O, and hexane) using complexes of ligands **1e** and **2b** with CuI and $CuSO_4{\cdot}5H_2O$ (Table 4 entries 1–15). Complexes of ligands **1e** and **2b** with CuI gave cloudy solutions. These complexes showed similar *ee* trends in various solvents (Table 4, entries 1–9) except with hexane where **1e** gave *ee* of 43% while **2b** afforded only 8% (Table 4, entry 10). Generally, $PhCH_3$ and Et_2O gave the highest *ee*s (Table 4, entries 1, 4, 6, and 9), CH_2Cl_2 gave moderate *ee*s (Table 4, entries 2 and 7), whereas THF gave very low *ee*s (Table 4, entries 3 and 8). No clear distinction between the effects of coordinating and noncoordinating solvents could be obtained. In comparison, complexes of **2b** with CuI (Table 4, entries 6 and 10) and $CuSO_4{\cdot}5H_2O$ (Table 4, entries 11 and 15) showed a significant increase in the yield of **5a** but no clear trends in the *ee*s. The highest *ee* of 55% was obtained in $PhCH_3$, whereas the lowest *ee* of 18% was obtained in CH_2Cl_2.

To examine the scope and limitation of ligands **1e** and **2b**, the enantioselective 1,4-conjugate addition of Et_2Zn to other cyclic enones was examined under the optimized reaction conditions mentioned in Table 1. Conjugate addition of Et_2Zn to 4,4-dimethyl-cyclohex-2-enone **4b** using CuI, CuCN, and $CuSO_4{\cdot}5H_2O$ complexes of **1e** or **2b** resulted in the formation of **5b** in very moderate *ee*s of 12–42% (Table 5, entries 1–7). The highest *ee* of 42% was obtained with a **1e**-CuCN complex (Table 5, entry 3). Interestingly, when this reaction was performed at −20°C, an increase in the *ee* of **5b** to 56% was observed indicating the scope for further optimization (Table 5, entry 4).

Likewise, moderate *ee*s (29–50%) of **5d** using CuI, CuCN, and $CuSO_4{\cdot}5H_2O$ complexes of ligands **1e** and **2b** were used for addition to cyclohept-2-enone **4c** (Table 6,

TABLE 3. The effect of catalyst loading and ratio of ligand-to-CuI on the conjugate addition of Et_2Zn to 2-cyclohexen-1-one 4a

Entry[a]	**1e** (mol %)	CuI (mol %)	Yield (%)	*ee* (%)[b]
1	15	15	77	72
2	10	15	65	49
3	20	5	40	18
4	30	30	45	35
5	15	10	54	40
6	7.5	7.5	57	62

[a]Conditions: 2.2 equiv Et_2Zn ($PhCH_3$ solution), 2-cyclohexen-1-one concentration 0.2 M in $PhCH_3$.
[b]Determined by chiral GC (G-TA column). Absolute configuration was assigned by comparison with the literature values.[56]

TABLE 4. Effect of different solvents on the addition of Et_2Zn to 2-cyclohexen-1-one 4a

Entry[a]	Ligand	Copper source	Solvent	Yield (%)	*ee* (%)[b]
1	**1e**	CuI	$PhCH_3$	77	72
2	**1e**	CuI	CH_2Cl_2	57	54
3	**1e**	CuI	THF	86	6
4	**1e**	CuI	Et_2O	73	65
5	**1e**	CuI	Hex	76	43
6	**2b**	CuI	$PhCH_3$	62	63
7	**2b**	CuI	CH_2Cl_2	67	43
8	**2b**	CuI	THF	67	7
9	**2b**	CuI	Et_2O	74	60
10	**2b**	CuI	Hex	80	8
11	**2b**	$CuSO_4{\cdot}5H_2O$	$PhCH_3$	75	55
12	**2b**	$CuSO_4{\cdot}5H_2O$	CH_2Cl_2	60	18
13	**2b**	$CuSO_4{\cdot}5H_2O$	THF	97	35
14	**2b**	$CuSO_4{\cdot}5H_2O$	Et_2O	98	38
15	**2b**	$CuSO_4{\cdot}5H_2O$	Hex	90	49

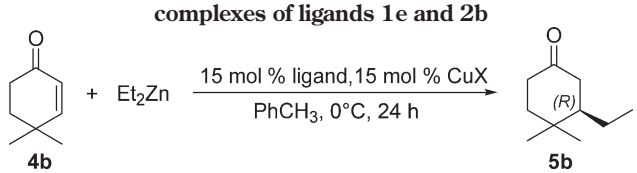
[a]Conditions: 2.2 equiv Et_2Zn ($PhCH_3$ solution), 2-cyclohexen-1-one concentration 0.2 M in $PhCH_3$.
[b]Determined by chiral GC (G-TA column). Absolute configuration was assigned by comparison with the literature values.[56]

entries 1–6). The highest *ee* of 50% was obtained when **1e**–CuCN complex was used (Table 6, entry 2).

It is well established that sulfur can strongly coordinate to late transition metals[58] and that olefins and sulfur atom have greater affinity for Cu(I) atom.[59] Noyori and coworkers[60,61] reported that *N*-benzylbenzenesulfonamide catalyzed the 1,4-addition of dialkylzincs to enones smoothly. In catalytic cycle proposed by them, oxygen atom on sulfonamide coordinated to Cu(I) center. In this case, although the real active species is not fully understood, we believe that coordination using the present bidentate ligands can happen in a similar fashion.[59–61]

In summary, we have synthesized a new class of amino acid-based modular ligands and used them for the enantio-

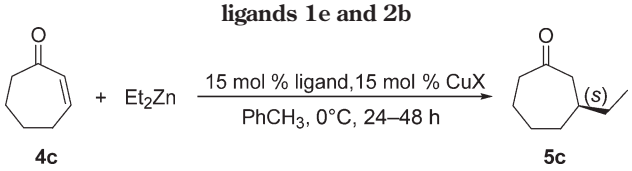
TABLE 5. Asymmetric conjugate addition of Et_2Zn to 4,4-dimethyl-cyclohex-2-enone catalyzed by copper complexes of ligands 1e and 2b



Entry[a]	Ligand	Copper source	Yield (%)	*ee* (%)[b]
1	**1e**	CuI	54	12
2	**1e**	$CuSO_4{\cdot}5H_2O$	26	21
3	**1e**	CuCN	98	42
4	**1e**	CuCN	48	56[c]
5	**2b**	CuI	48	23
6	**2b**	$CuSO_4{\cdot}5H_2O$	45	32
7	**2b**	CuCN	70	15

[a]Conditions: 2.2 equiv Et_2Zn ($PhCH_3$ solution), 2-cyclohexen-1-one concentration 0.2 M in $PhCH_3$.
[b]Determined by chiral GC (G-TA column).
[c]Reaction performed at −20°C for 7 days.

TABLE 6. Asymmetric conjugate addition of Et_2Zn to cyclohept-2-enone catalyzed by copper complexes of ligands 1e and 2b



Entry[a]	Ligand	Copper source	Yield (%)	*ee* (%)[b]
1	**1e**	CuI	58	40
2	**1e**	CuCN	78	50
3	**1e**	$CuSO_4{\cdot}5H_2O$	53	24
4	**2b**	CuI	51	29
5	**2b**	CuCN	79	36
6	**2b**	$CuSO_4{\cdot}5H_2O$	66	41

[a]Conditions: 2.2 equiv Et_2Zn ($PhCH_3$ solution), 2-cyclohexen-1-one concentration 0.2 M in $PhCH_3$.
[b]Determined by chiral GC (G-TA column).

selective copper-catalyzed 1,4-conjugate addition of Et_2Zn to various cyclic enones. These chiral ligands are inexpensive, very stable, and readily synthesized in excellent yields by reacting tosyl-L-phenylalanine acid chloride with various chiral and achiral amines. Ligand **1e**, with 2-OMe substituent, catalyzed the addition of Et_2Zn to enones to give up to 72% *ee*. This work paves the way for synthesis and evaluation of larger libraries based on the same general structure.

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