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Tridentate ligands derived from L-tert-Leucine for the Cu(II) mediated asymmetric Henry reaction

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Chiral tridentate Schiff base ligands were prepared from L-tert-Leucine and used as catalysts in the asymmetric Henry reaction in the presence of Cu(II) ions. Moderate enantiomeric excesses (up to 66%) and yields (up to 76%) of the desired β-nitroalcohols were obtained.

Key Words: Asymmetric Henry reaction, chiral Schiff base, L-tert-Leucine, amino alcohol, tridentate ligand

Introduction

The nitroaldol or Henry reaction is one of the classical named reactions in organic synthesis. Essentially the coupling of the nucleophile generated from a nitroalkane with a carbonyl electrophile, it has been a widely used transformation since its discovery in 1895.[1] The resulting product of this reaction is a β-nitroalcohol, which is a versatile intermediate in synthetic organic chemistry.

The Henry reaction may be catalyzed or promoted by many different catalysts, including inorganic bases[2] and organocatalysts;[3] however, much recent effort has been focused on the development of various metal-based catalysts. Included in this research effort was the first asymmetric version of the Henry reaction. This was reported by Shibasaki and coworkers in 1992 and involved a lanthanide-based catalyst.[4] Subsequent work has focused to a significant extent on chiral complexes of zinc[5,6] and copper.[7,8]

As part of an ongoing investigation into the structure and reactivity of tridentate Schiff base ligands and complexes derived from L-tert-Leucine, we recently reported the structure of a highly novel nickel complex derived from ligand **A** (Figure 1), which contained an unprecedented anti-skew carboxylate bridging group.[9]

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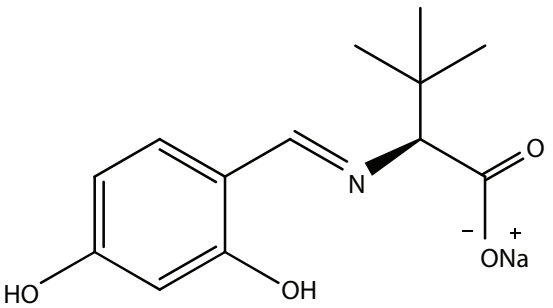
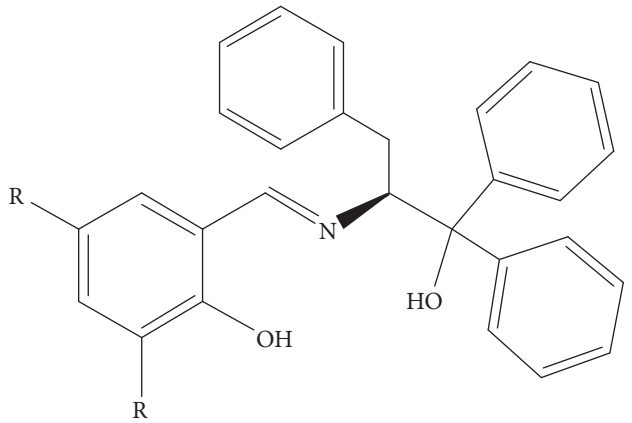


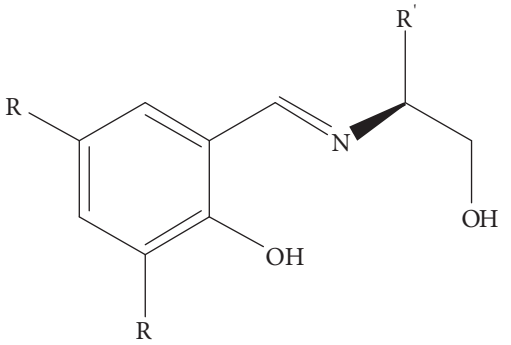
A

Figure 1. The structure of ligand A.

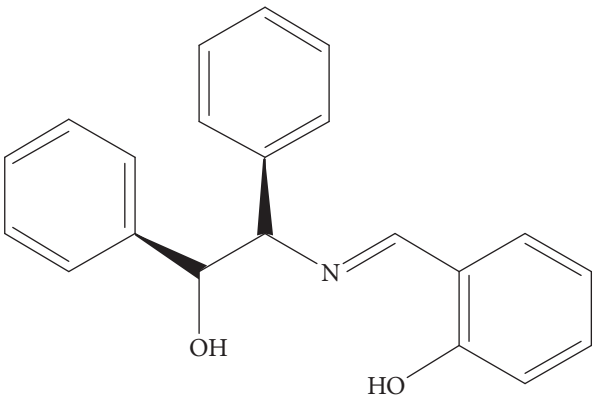
While carrying out these studies, we became aware that copper complexes of closely related Schiff bases ligands were becoming of increasing importance in the asymmetric Henry reaction.[10–15] For example, Wang (**B**),[16] Punniyamurthy (**C**),[17] and Mao (**D**)[18] (Figure 2) independently prepared tridentate amino alcohol based Schiff base



B



C



D

Figure 2. Ligands B, C, and D.

ligands starting from chiral amino acids or amino alcohols. It was determined that the solid state structure of Cu(II) complexes of ligands **B** and **C** consists of a dimeric structure where each copper center has square planar geometry and the OH groups originating from the amino alcohol moiety occupy bridging positions. We were interested in employing derivatives of ligand **A** in this reaction to see if we could utilize the bulkiness of the tert-butyl group present in L-tert-Leucine to good effect in this type of reaction. Therefore we prepared a series of ligands from L-tert-Leucine as can be seen in Figure 3.

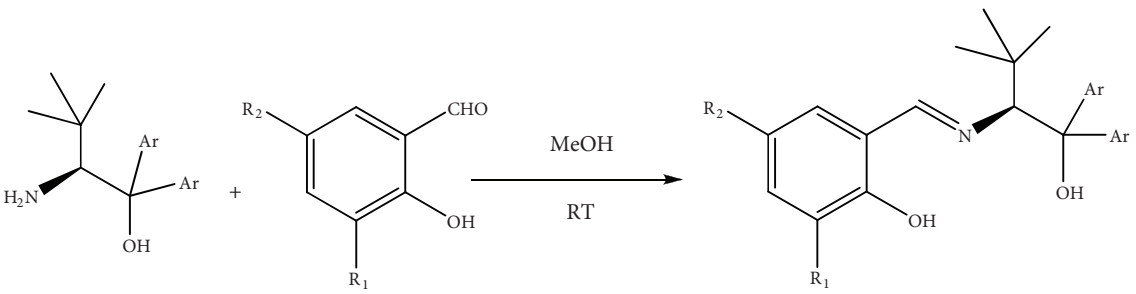


Figure 3. Preparation of Schiff base ligands.

Experimental

All ^{1}H-NMR and ^{13}C-NMR spectra were recorded using a Varian AS 400+ Mercury FT NMR spectrometer at ambient temperature. IR spectra were recorded on a Perkin Elmer 100 FTIR spectrometer. The enantiomeric excesses of the Henry reaction products were determined by HPLC using a chiralcel OD-H column. Optical rotations were determined using a Rudolph Research Analytical Autopol I automatic polarimeter. Absolute configurations of the product β-nitroalcohols were determined by comparison of $[\alpha]_D^{25}$ values with literature values.[7–19] Solvents were used as received from commercial sources.

Preparation of L-tert-Leucine methyl ester hydrochloride methyl *(S)*-2-amino-3,3-dimethylbutanoate hydrochloride

A solution of the L-tert-Leucine (2 mmol) in 20 mL of methanol was cooled with ice water. After cooling, 2 mL of $SOCl_2$ was added dropwise. The resulting clear solution was then refluxed for 8 h. Evaporation of the solvent gave a white solid. IR (KBr), 3344, 3085, 3083, 3057, 2948, 2904, 1583, 1492, 1473, 1447, 1376, 1167, 1057 cm^{-1}. ^{1}H-NMR (MeOH, δ ppm): 7.66 (d, J =8 Hz, 2 H), 7.55 (d, J =8 Hz, 2H), 7.30 (t, J =7.6 Hz, 2H), 7.20 (t, J =7.6 Hz, 2H), 7.01 (t, J = 7.6 Hz, 2H), 4.41 (br, 1H), 3.82 (s, 1H), 1.37 (br, 2H), 0.79 (s, 9H).

^{13}C-NMR ($CDCl_3$, δ ppm), 150.1, 145.5, 128.7, 127.9, 126.6, 126.4, 125.8, 80.1, 77.6, 77.3, 76.9, 63.9, 35.8, 29.3. Elemental analysis, calculated for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20. Found: C, 79.33; H, 8.54; N, 5.10%.

General procedure for the preparation of 1a-c

In a 2-necked round-bottomed flask fitted with a reflux condenser were placed Mg (20 mmol) and anhydrous diethyl ether (20 mL). The mixture was stirred and bromobenzene derivatives (10 mmol) were added dropwise. The reaction mixture was then refluxed for 30 min. After cooling, it was added to a mixture of methyl (*S*)−2-amino-3,3-dimethylbutanoate hydrochloride (2 mmol) in 5 mL of diethyl ether as quickly as possible. The reaction mixture was stirred for 24 h at ambient temperature and then quenched with saturated NH_4Cl in ice water. The solution was filtered and extracted with diethyl ether. The organic phase was dried using Na_2SO_4 and evaporated under vacuum and a yellow solid was obtained.

(*S*)-2-amino-3, 3-dimethyl-1,1-diphenylbutan-1-ol (1a)

The yellow solid was washed with cold hexane to give white crystals, 62% yield, mp = 130-133 °C, IR (KBr), 3344, 3085, 3083, 3057, 2948, 2904, 1583, 1492, 1473, 1447, 1376, 1167, 1057, 967 cm^{-1}. ^{1}H-NMR ($CDCl_3$, δ ppm), 7.66 (d, J =8 Hz, 2 H), 7.55 (d, J =8 Hz, 2H), 7.3 (t, J =7.6 Hz, 2H), 7.20 (t, J =7.6 Hz, 2H), 7.01 (t, J =7.6 Hz, 2H), 4.41 (br, 1H), 3.82 (s, 1H), 1.37 (br, 2H), 0.79 (s, 9H). ^{13}C-NMR ($CDCl_3$, δ ppm), 150.1, 145.5, 128.7, 127.9, 126.6, 126.4, 125.8, 80.1, 77.6, 77.3, 76.9, 63.9, 35.7, 29.3. Elemental analysis, calculated for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20. Found: C, 79.33; H, 8.54; N, 5.10%.

(*S*)-2-amino-3,3-dimethyl-1,1-di *m*-tolylbutan-1-ol (1b)

The yellow solid was purified by column chromatography using hexane:ethyl acetate (90:10). White crystals, 36% yield, mp = 127-129 °C, IR (KBr), 3408, 3337, 3036, 2954, 2948, 1602, 1480, 1447, 1381, 1301, 1167, 1137, 868 cm^{-1}. ^{1}H-NMR ($CDCl_3$, δ ppm), 7.47-6.91 (m, 8H), 3.80 (s, 1H), 2.38 (s, 3H), 2.31 (s, 3H), 1.52 (br, 2H), 0.80 (s, 9H). ^{13}C-NMR ($CDCl_3$, δ ppm), 149.9, 145.4, 138.3, 137.3, 128.5, 127.7, 127.4, 127.1, 126.8, 126.7, 123.7, 122.6, 80.1, 63.9, 35.7, 29.3, 21.9, 21.9. Elemental analysis, calculated for $C_{20}H_{27}ON$: C, 80.76; H, 9.15; N, 4.71. Found: C, 79.64; H, 8.91; N, 4.18%.

(*S*)-2-amino-3,3-dimethyl-1,1-di *p*-tolylbutan-1-ol (1c)

The yellow solid was purified by column chromatography using hexane:ethyl acetate. White crystals, 31% yield, mp = 117-120 °C, IR (KBr), 3412, 2981, 2956, 2921, 1507, 1469.3, 1410, 1376, 1183, 804 cm^{-1}. ^{1}H-NMR ($CDCl_3$, δ ppm), 7.51 (d, J= 8 Hz, 2H), 7.40 (d, J= 8 Hz, 2H), 7.09 (d, J= 8 Hz, 2H), 7.00 (d, J= 8 Hz, 2H), 3.77 (s, 1H), 2.27 (s, 3H), 2.24 (s, 3H), 1.75 (br, 1H), 0.79 (s, 9H). ^{13}C-NMR ($CDCl_3$, δ ppm), 147.3, 142.8, 136.1, 135.7, 129.4, 128.6, 126.2, 125.6, 79.9, 63.8, 35.7, 29.4, 21.2, 21.1. Elemental analysis, calculated for $C_{20}H_{27}ON$: C, 80.76; H, 9.15; N, 4.71. Found: C, 79.14; H, 8.92; N, 4.48%.

General procedure for the preparation of the chiral Schiff bases

The solution of aldehyde (1 mmol) in MeOH was added dropwise into the solution of amino alcohol (1 mmol) in 5 mL of MeOH. The reaction mixture was stirred for 2-10 h at room temperature. Evaporation of the solvent provided a residue, which was crystallized from CH_2Cl_2:hexane to give yellow or orange crystals (59%-98% yields).

(*S*)-2-[(1-hydroxy-3,3-dimethyl-1,1-diphenylbutan-2-ylimino)methyl]phenol (3a)

Yellow crystals, 97% yield, mp = 174.6-176.1 °C, IR (KBr), 3054, 2955, 2871, 1627, 1582, 1491, 1448, 1275, 1151, 750 cm^{-1}. 1H-NMR ($CDCl_3$, δ ppm) 12.85 (s, 1H), 8.12 (s, 1H), 7.23 (d, J= 7.6 Hz, 2H), 7.53 (d, J= 8 Hz, 2H), 7.29-7.14 (m, 6H), 7.09 (dd, J= 1.6 Hz, 7.6 Hz, 2H), 7.03 (t, J= 7.6 Hz, 2H), 6.87 (d, J= 8.4 Hz, 1H), 6.81 (t, J= 7.6 Hz, 1H), 4.08 (s, 1H), 2.83 (s, 1H), 0.85 (s, 9H). ^{13}C-NMR ($CDCl_3$, δ ppm) 166.9, 155.8, 148.1, 131.9, 129.9, 128.4, 128.2, 127.3, 127.0, 126.8, 126.3, 126.1, 125.9, 120.9, 118.6, 117.7, 115.6. Elemental analysis, calculated for $C_{25}H_{27}O_2N$: C, 80.40; H, 7.29; N, 3.75. Found: C, 79.50; H, 7.22; N, 3.80%. $[\alpha]_D^{25}$= +52.8 (c 0.8, CH_2Cl_2).

(*S*)-4-tert-butyl-2-[(1-hydroxy-3,3-dimethyl-1,1-diphenylbutan-2-ylimino)methyl]phenol (3b)

Yellow crystals, 90% yield, mp = 161-162 °C, IR (KBr), 3599, 3054, 3033, 2960, 2901, 2871, 1633, 1594, 1493, 1449, 1265, 1184, 1059, 705 cm^{-1}. ^{1}H-NMR ($CDCl_3$, δ ppm), 8.15 (s, 1H), 7.66 (dd, J= 1.2 Hz, 7.6 Hz, 2H), 7.54 (dd, J= 1.2 Hz, 8.8 Hz, 2H), 7.31-7.02 (m, 7H), 6.81 (d, J= 8.4, 1H), 4.09 (s, 1H), 2.88 (br, 1H), 1.27 (s, 9H), 0.85 (s, 9H). ^{13}C-NMR ($CDCl_3$, δ ppm), 167.5, 158.5, 147.6, 145.2, 141.6, 130.1, 128.4, 128.2, 126.8, 126.6, 126.3, 125.9, 117.9, 116.5, 83.9, 80.8, 36.6, 34.1, 31.6, 29.8. Elemental analysis, calculated for $C_{29}H_{35}O_2N$: C, 81.08; H, 8.21; N, 3.26. Found: C, 82.05; H, 8.09; N, 3.33%. $[\alpha]_D^{25}$= -27.5 (c 0.36, CH_2Cl_2).

(*S*)-4-bromo-2-[(1-hydroxy-3,3-dimethyl-1,1-diphenylbutan-2-ylimino)methyl]phenol (3c)

Yellow crystals, 92% yield, mp = 185-186 °C, IR (KBr), 3601, 3062, 2947, 2868, 1630, 1572, 1479, 1449, 1357, 1274, 1057, 705 cm^{-1}. ^{1}H-NMR ($CDCl_3$, δ ppm), 12.87 (br, 1H), 7.99 (s, 1H), 7.64 (dd, J= 1.2 Hz, 8 Hz, 2H), 7.49 (dd, J= 1.2 Hz, 8.8 Hz, 2H), 7.32-7.15 (m, 7H), 7.06 (td, J= 1.2 Hz, 7.6 Hz, 1H), 6.76 (d, J= 8.8 Hz, 1H), 4.05 (s, 1H), 2.73 (br, 1H), 0.85 (s, 9H). ^{13}C-NMR ($CDCl_3$, δ ppm), 165.5, 160.1, 146.9, 145.0, 135.3, 133.7, 128.5, 128.0, 127.0, 126.9, 126.2, 125.8, 119.9, 119.1, 110.3, 96.4, 84.2, 80.9, 36.5, 29.8. Elemental analysis, calculated for $C_{25}H_{26}O_2NBr$: C, 66.37; H, 5.79; N, 3.10. Found: C, 65.71; H, 5.70; N, 3.17%. $[\alpha]_D^{25}$= -2.4 (c 0.83, CH_2Cl_2).

(*S*)-3-[(1-hydroxy-3,3-dimethyl-1,1-diphenylbutan-2-ylimino)methyl]benzene-1,2-diol (3d)

Yellow crystals, 97% yield, mp = 99-102 °C, IR (KBr), 3420, 3059, 3035, 2958, 1635, 1599, 1543, 1516, 1464, 1449, 1239, 742 cm^{-1}. 1H-NMR ($CDCl_3$, δ ppm), 7.91 (s, 1H), 7.67-7.65 (m, 2H), 7.52-7.50 (m, 2H), 7.32-7.28 (m, 2H), 7.25-7.17 (m, 3H), 7.07-7.03 (m, 1H), 6.88 (dd, J= 2 Hz, 6.4 Hz, 1H), 6.56 (m, 2H), 4.13 (s, 1H), 3.06 (br, 1H), 0.88 (s, 9H). ^{13}C-NMR ($CDCl_3$, δ ppm), 166.2, 155.5, 146.6, 146.5, 144.9, 128.6, 128.3, 127.2,

127.0, 126.2, 125.7, 122.5, 116.9, 116.6, 81.2, 81.2, 36.6, 31.8, 22.9, 14.3. Elemental analysis, calculated for $C_{25}H_{27}O_3N$: C, 77.09; H, 6.99; N, 3.60. Found: C, 76.97; H, 7.58; N, 3.26%. $[\alpha]_D^{25}$ = -211.9 (c 0.71, CH_2Cl_2).

(*S*)-2-(benzyloxy)-6-[(1-hydroxy-3,3-dimethyl-1,1-diphenylbutan-2-ylimino)methyl]phenol (3e)

Yellow crystals, 59% yield, mp = 139-142 °C, IR (KBr), 3581, 3061, 3027, 2932, 2871, 1627, 1583, 1495, 1450, 1250, 1061, 749 cm^{-1}. ^{1}H-NMR ($CDCl_3$, δ ppm), 8.12 (s, 1H), 7.67 (dd, J= 0.8 Hz, 7.2 Hz, 2H), 7.53 (dd, J= 0.8 Hz, 7.6 Hz, 2H), 7.44 (d, J= 7.2 Hz, 2H), 7.38-7.14 (m, 8H), 7.03 (td, J= 1.2 Hz, 7.2 Hz, 1H), 6.88 (d, J= 7.6 Hz, 1H), 6.74-6.65 (m, 2H), 5.13 (s, 2H), 4.09 (s, 1H), 2.87 (br, 1H), 0.85 (s, 9H). ^{13}C-NMR ($CDCl_3$, δ ppm), 167.1, 151.9, 147.5, 147.4, 145.1, 137.2, 128.8, 128.4, 128.1, 127.7, 126.9, 126.7, 126.3, 125.9, 123.9, 118.7, 118.2, 116.9, 83.8, 80.9, 71.4, 36.5, 29.8. Elemental analysis, calculated for $C_{32}H_{33}O_3N$: C, 80.14; H, 6.94; N, 2.92. Found: C, 79.05; H, 6.91; N, 2.92%. $[\alpha]_D^{25}$= +84.5 (c 0.69, CH_2Cl_2).

(*S*)-2-[(1-hydroxy-3,3-dimethyl-1,1-diphenylbutan-2-ylimino)methyl]-6-methoxyphenol (3f)

Yellow crystals, 98% yield, mp = 182-184 °C, IR (KBr), 3590, 3054, 2961, 2874, 1627, 1492, 1448, 1469, 1362, 1259, 1080 cm^{-1}. ^{1}H-NMR ($CDCl_3$, δ ppm), 13.53 (br, 1H), 8.09 (s, 1H), 7.66 (dd, J= 1.2 Hz, 7.6 Hz, 2H), 7.53 (dd, J= 1.2 Hz, 7.6 Hz, 2H), 7.29-7.14 (m, 5H), 7.05-7.01 (m, 1H), 6.87-6.85 (m, 1H), 6.75-6.70 (m, 2H), 4.08 (s, 1H), 3.86 (s, 3H), 2.82 (br, 1H), 1.57 (br, 1H), 0.85 (s, 9H). ^{13}C-NMR ($CDCl_3$, δ ppm), 166.9, 151.7, 148.5, 147.1, 145.1, 128.4, 128.2, 126.9, 126.7, 126.3, 125.9, 123.3, 118.3, 118.2, 114.1, 83.7, 80.9, 56.2, 36.5, 29.8. Elemental analysis, calculated for $C_{26}H_{28}O_3N$: C, 77.39; H, 7.24; N, 3.47. Found: C, 76.46; H, 7.06; N, 3.47%. $[\alpha]_D^{25}$ = +73.8 (c 1.22, CH_2Cl_2).

(*S*)-2-[(1-hydroxy-3,3-dimethyl-1,1-diphenylbutan-2-ylimino)methyl]benzene-1,4-diol (3g)

Orange crystals, 61% yield, mp = 179-180 °C, IR (KBr), 3309, 3082, 2961, 2933, 2868, 1633, 1596, 1489, 1478, 1376, 1159, 1058, 702 cm^{-1}. ^{1}H-NMR ($CDCl_3$, δ ppm), 8.03 (s, 1H), 7.67 (dd, J= 1.2 Hz, 7.6 Hz, 2H), 7.52 (dd, J= 1.2 Hz, 7.2 Hz, 2H), 7.29-7.14 (m, 6H), 7.03 (t, J= 7.6 Hz, 1H), 6.76 (d, J= 2.8 Hz, 1H), 6.58 (d, J= 2.8 Hz, 1H), 4.07 (s, 1H), 2.88 (br, 1H) 0.85 (s, 9H). ^{13}C-NMR ($CDCl_3$, δ ppm), 166.5, 154.9, 147.87, 147.3, 145.1, 128.4, 128.2, 126.9, 126.7, 126.3, 125.9, 120.5, 118.4, 117.7, 117.3, 84.1, 80.9, 36.5, 29.8. Elemental analysis, calculated for $C_{25}H_{27}O_3N$: C, 77.09; H, 6.99; N, 3.60. Found: C, 76.34; H, 6.86; N, 3.51%. $[\alpha]_D^{25}$ = +27.0 (c 0.30, CH_2Cl_2).

(*S*)-2,4-di-tert-butyl-6-[(1-hydroxy-3,3-dimethyl-1,1-diphenylbutan-2-ylimino)methyl]phenol (3h)

Yellow crystals 59% yield, mp = 155-157 °C, IR (KBr), 3581, 3061, 3027, 2932, 2871, 1627, 1583, 1495, 1450, 1250, 1061, 749 cm^{-1}. ^{1}H-NMR ($CDCl_3$, δ ppm), 8.13 (s, 1H), 7.65 (dd, J= 1.2 Hz, 8.8 Hz, 2H), 7.53 (dd, J= 1.2 Hz, 8.4 Hz, 2H), 7.30-7.12 (m, 7H), 7.02 (t, J= 7.6 Hz, 1H), 6.87 (d, J= 2.4 Hz, 1H), 4.06 (s, 1H), 2.92 (br, 1H), 1.39 (s, 9H), 1.27 (s, 9H), 0.85 (s, 9H). ^{13}C-NMR ($CDCl_3$, δ ppm), 167.1, 151.9, 147.5, 147.4, 145.1, 137.2, 128.8, 128.4, 128.12, 127.7, 126.9, 126.7, 126.3, 125.9, 123.9, 118.7, 118.2, 116.9, 83.8, 80.9, 71.4, 36.5, 29.8. Elemental analysis, calculated for $C_{33}H_{41}O_2N$: C, 80.14; H, 6.94; N, 2.92. Found: C, 79.05; H, 6.91; N, 2.92%. $[\alpha]_D^{25}$ = +23.7 (c 0.84, CH_2Cl_2).

(*S*)-2-[(1-hydroxy-3,3-dimethyl-1,1-dim-tolylbutan-2-ylimino)methyl]phenol (3i)

Yellow crystals, 78% yield, mp = 138-141 °C, IR (KBr), 3598, 3038, 2956, 2869, 1628, 1603, 1582, 1480, 1463, 1276, 1151, 753 cm^{-1}. ^{1}H-NMR ($CDCl_3$, δ ppm), 8.08 (s, 1H), 7.47-6.77 (m, 13H), 4.02 (s, 1H), 2.77 (br, 1H), 2.33 (s, 3H), 2.24 (s, 3H), 0.86 (s, 9H). ^{13}C-NMR ($CDCl_3$, δ ppm), 166.8, 160.9, 147.3, 145.1, 137.8, 137.5, 132.5, 131.6, 128.0, 127.9, 127.6, 127.4, 126.8, 126.7, 123.6, 123.0, 118.8, 118.6, 117.1, 96.4, 84.1, 80.8, 36.5, 29.9, 21.8, 21.9. Elemental analysis, calculated for $C_{27}H_{31}O_2N$: C, 80.76; H, 7.78; N, 3.49. Found: C, 79.98; H, 7.78; N, 3.21%. $[\alpha]_D^{25}$ = +61.2 (c 0.59, CH_2Cl_2).

(*S*)-2-[(1-hydroxy-3,3-dimethyl-1,1-dip-tolylbutan-2-ylimino)methyl]phenol (3j)

Yellow crystals, 63% yield, mp = 175-177 °C, IR (KBr), 3559, 3024, 2957, 2868, 2730, 1628, 1582, 1508, 1478, 1463, 1369, 1275, 1065, 754 cm^{-1}. ^{1}H-NMR ($CDCl_3$, δ ppm), 12.86 (br, 1H), 8.11 (s, 1H), 7.48 (dd, J= 2 Hz, 8.4 Hz, 2H), 7.37 (dd, J= 2 Hz, 8.8 Hz, 2H), 7.25-7.21 (m, 2H), 7.09-6.98 (m, 4H), 6.86 (d, J= 7.6 Hz, 2H), 6.79 (td, J= 0.8 Hz, 7.6 Hz, 2H), 4.01 (s, 1H), 2.70 (br, 1H), 2.69 (s, 3H), 2.18 (s, 3H), 0.84 (s, 9H). ^{13}C-NMR ($CDCl_3$, δ ppm), 166.8, 160.9, 144.6, 142.5, 136.3, 136.1, 132.6, 131.8, 129.1, 128.8, 126.1, 125.8, 118.8, 118.7, 117.1, 83.9, 80.74, 77.5, 77.2, 76.9, 36.5, 29.8, 21.1, 21.0. Elemental analysis, calculated for $C_{27}H_{31}O_2N$: C, 80.76; H, 7.78; N, 3.49. Found: C, 80.05; H, 7.64; N, 3.43%. $[\alpha]_D^{25}$ = -58.0 (c 0.55, CH_2Cl_2).

(S)-1-[(1-hydroxy-3,3-dimethyl-1,1-diphenylbutan-2-ylimino)methyl]naphthalen-2-ol (3k)

Yellow crystals, 84% yield, mp = 151-154 °C, IR (KBr), 3197, 3054, 2960, 1626, 1596, 1543, 1524, 1493, 1368, 1349, 1194, 739, 697 cm^{-1}. 1H-NMR ($CDCl_3$, δ ppm), 8.43 (s, 1H), 7.71 (dd, J= 1.2 Hz, 8.8 Hz, 2H), 7.60 (dd, J= 1.2 Hz, 8.8 Hz, 2H), 7.56 (d, J= 8 Hz, 1H), 7.39 (td, J= 1.2 Hz, 8 Hz, 1H), 7.32 (t, J= 7.2 Hz, 2H), 7.25-7.19 (m, 4H), 7.01 (t, J= 7.2 Hz, 1H), 6.85 (d, J= 9.2 Hz, 1H). ^{13}C-NMR ($CDCl_3$, δ ppm) 174.0, 159.7, 146.1, 145.0, 136.9, 133.9, 129.3, 128.6, 128.3, 127.9, 127.3, 127.2, 126.6, 126.4, 125.9, 124.2, 122.9, 118.2, 106.9, 81.5, 79.6, 77.6, 77.2, 76.9, 36.8, 29.8. Elemental analysis, calculated for $C_{29}H_{29}O_2N$: C, 82.24; H, 6.90; N, 3.31. Found: C, 78.05; H, 6.70; N, 3.16%. $[\alpha]_D^{25}$ = -9.15 (c 0.66, CH_2Cl_2).

General procedure for the asymmetric Henry reaction

To a solution of ligand **3a-k** (0.01 mmol) and 1 mL of TBME at the given temperature was added $Cu(OAc)_2.nH_2O$ (0.01 mmol). The mixture was allowed to stir for 5 h. The aldehyde (0.1 mmol) and nitromethane (10 mmol) were added into the solution. The progress of the reaction was monitored by TLC. After completion, the solvent was evaporated and the residue was purified by column chromatography using hexane:ethyl acetate (5:1) to afford the desired Henry product **4a-j**. The enantiomeric excess values were determined by HPLC using a Chiralcel OD-H column.

(*R*)-1-(4-nitrophenyl)-2-nitroethanol (4a)

White crystals, 76% yield, 1H-NMR ($CDCl_3$, δ ppm), 3.17 (br, 1H), 4.58 (d, J= 2 Hz, 1H), 4.60 (d, J= 6 Hz, 1H), 5.61 (m, 1H), 7.63 (m, 2H), 8.26 (m, 2H). HPLC: Chiralcel OD-H column, hexane:isopropanol (90:10), 1

mL/min, 267 nm, major enantiomer t_r = 29.4 min, minor enantiomer t_r = 37.6 min, 63% ee, $[\alpha]_D^{25}$ = -21.2 (c 1.23, CH_2Cl_2).

(*R*)-1-(3-nitrophenyl)-2-nitroethanol (4b)

Yellow oil, 63% yield, 1H-NMR ($CDCl_3$, δ ppm), 3.51 (br, 1H), 4.63 (m, 2H), 5.61 (dd, J= 4.4, 7.6 Hz, 1H), 7.61 (t, J= 7.6 Hz, 1H), 7.78 (m, 1H), 8.19 (m, 1H), 8.30 (m, 1H). HPLC: Chiralcel OD-H column, hexane:isopropanol (90:10), 1 mL/min, 267 nm, major enantiomer t_r = 28.1 min, minor enantiomer t_r = 32.5 min, 52% ee, $[\alpha]_D^{25}$= -7.34 (c 1.1, CH_2Cl_2).

(*R*)-1-(2-nitrophenyl)-2-nitroethanol (4c)

Brown crystals, 54% yield, 1H-NMR ($CDCl_3$, δ ppm), 3.35 (br, 1H), 4.56 (dd, J= 9.2, 13.6 Hz, 1H), 4.85 (dd, J= 2.4, 14 Hz, 1H), 6.03 (d, J= 8 Hz, 1H), 7.55 (td, J= 1.6, 8.4 Hz, 1H), 7.75 (td, J= 0.8, 7.6 Hz, 1H), 7.95 (d, J= 8 Hz, 1H), 8.06 (dd, J= 1.2, 8 Hz, 1H). HPLC: Chiralcel OD-H column, hexane:isopropanol (90:10), 1 mL/min, 267 nm, major enantiomer t_r = 15.9 min, minor enantiomer t_r = 18.3 min, 48% ee, $[\alpha]_D^{25}$= +123.9 (c 0.9, CH_2Cl_2).

(*R*)-1-(2-chlorophenyl)-2-nitroethanol (4d)

Colorless oil, 25% yield, 1H-NMR ($CDCl_3$, δ ppm), 4.36 (dd, J= 9.6, 13.6 Hz, 1H), 4.57 (dd, J= 2.4, 13.6 Hz, 1H), 5.75 (m, 1H), 7.24 (m, 3H), 7.56 (dd, J= 2, 7.6 Hz, 1H). HPLC: Chiralcel OD-H column, hexane:isopropanol (95:5), 1 mL/min, 267 nm, major enantiomer t_r = 14.6 min, minor enantiomer t_r = 15.6 min, 49% ee, $[\alpha]_D^{25}$= -32.9 (c 0.61, CH_2Cl_2).

(*R*)-1-(4-methylphenyl)-2-nitroethanol (4e)

Yellow oil, 18% yield, 1H-NMR ($CDCl_3$, δ ppm), 2.36 (s, 3H), 2.74 (br, 1H), 4.48 (dd, J= 2.8, 13.2 Hz, 1H), 4.60 (dd, J= 10.4, 13.6 Hz, 1H), 5.42 (d, J= 9.2 Hz, 1H), 7.26 (m, 4H). HPLC: Chiralcel OD-H column, hexane:isopropanol (90:10), 1 mL/min, 267 nm, major enantiomer t_r = 13.5 min, minor enantiomer t_r = 17.09 min, 58% ee, $[\alpha]_D^{25}$= -28.1 (c 0.5, CH_2Cl_2).

(*R*)-1-(4-ethylphenyl)-2-nitroethanol (4f)

Yellow oil, 20% yield, 1H-NMR ($CDCl_3$, δ ppm), 1.23 (t, J= 7.6 Hz, 3H), 2.65 (q, J= 7.6 Hz, 2H), 2.86 (d, J= 3.6 Hz, 1H), 4.48 (dd, J= 3.2, 13.2 Hz, 1H), 4.50 (dd, J= 9.6, 13.2 Hz, 1H), 5.42 (m, 1H), 7.22 (m, 2H), 7.29 (m, 2H). HPLC: Chiralcel OD-H column, hexane:isopropanol (90:10), 1 mL/min, 267 nm, major enantiomer t_r = 12.3 min, minor enantiomer t_r = 15.9 min, 59% ee, $[\alpha]_D^{25}$= -26.2 (c 0.53, CH_2Cl_2).

(*R*)-1-(4-methoxyphenyl)-2-nitroethanol (4g)

Yellow oil, 48% yield, 1H-NMR ($CDCl_3$, δ ppm), 2.84 (br, 1H), 3.81 (s, 3H), 4.46 (dd, J= 2.8, 12.8 Hz, 1H), 4.59 (dd, J= 9.6, 13.2 Hz, 1H), 5.39 (m, 1H), 6.91 (d, J= 8.8 Hz, 2H), 7.30 (d, J= 8.8 Hz, 2H). HPLC:

Chiralcel OD-H column, hexane:isopropanol (90:10), 1 mL/min, 267 nm, major enantiomer t_r = 20.6 min, minor enantiomer t_r = 26.06 min, 52% ee, $[\alpha]_D^{25}$= -0.9 (c 2.19, CH_2Cl_2).

(*R*)-1-phenyl-2-nitroethanol (4h)

Yellow oil, 29% yield, 1H-NMR ($CDCl_3$, δ ppm), 3.08 (br, 1H), 4.49 (dd, J= 2.8, 13.2 Hz, 1H), 4.59 (dd, J= 9.6, 13.6 Hz, 1H), 5.43 (dd, J= 2.8, 9.6 Hz, 1H), 7.38 (m, 5H). HPLC: Chiralcel OD-H column, hexane:isopropanol (90:10), 1 mL/min, 267 nm, major enantiomer t_r = 14.1 min, minor enantiomer t_r = 16.4 min, 51% ee, $[\alpha]_D^{25}$ = -25.8 (c 1.0, CH_2Cl_2).

(*R)*1-(4-chlorophenyl)-2-nitroethanol (4i)

Colorless oil, 42% yield, ^{1}H-NMR ($CDCl_3$, δ ppm), 2.96 (br, 1H), 4.49 (dd, J= 9.2, 13.2 Hz, 1H), 4.57 (dd, J = 9.2, 13.6 Hz, 1H), 5.44 (dd, J= 2.8, 9.6 Hz, 1H), 7.33 (m, 4H). HPLC: Chiralcel OD-H column, hexane:isopropanol (90:10), 1 mL/min, 267 nm, major enantiomer t_r = 13.8 min, minor enantiomer t_r = 17.4 min, 51% ee, $[\alpha]_D^{25}$= -22.1 (c 1.45, CH_2Cl_2).

(*R*)1-(2-methoxyphenyl)-2-nitroethanol (4j)

Yellow oil, 40% yield, ^{1}H-NMR ($CDCl_3$, δ ppm) 3.15 (d, J= 6 Hz, 1H), 3.88 (s, 3H), 4.57 (dd, J= 9.2, 13.2, 1H), 4.64 (dd, J= 3.2, 13.2 Hz, 1H), 5.65-5.61 (m, 1H), 6.91 (d, J = 8.8 Hz, 1H), 7.01 (td, J= 0.8, 7.6 Hz, 1H), 7.33 (td, J = 0.8, 1.6 Hz, 1H), 7.44 (dd, J = 0.8, 7.2 Hz, 1H). HPLC: Chiralcel OD-H column, hexane:isopropanol (90:10), 1 mL/min, 267 nm, major enantiomer t_r = 11.3 min, minor enantiomer t_r = 12.9 min, 53% ee, $[\alpha]_D^{25}$ = -26.4 (c 1.51, CH_2Cl_2).

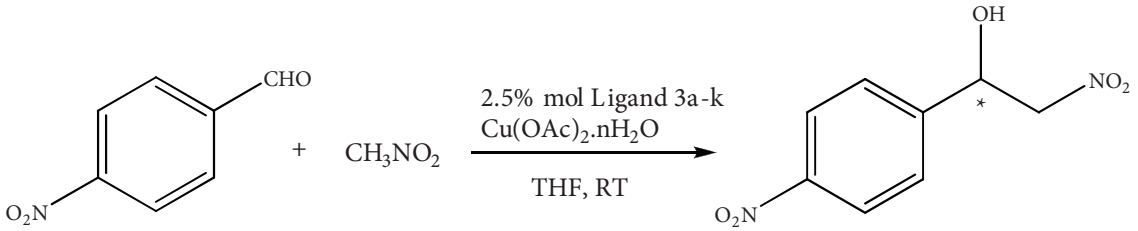
Results and discussion

Amino alcohols (**1a-c**) derived from the chiral amino acid L-tert-Leucine were obtained by addition of a Grignard reagent to the methyl ester of the amino acid. These chiral amino alcohols were reacted with different aldehydes to give Schiff base ligands (**3a-k**) in high yields. The ligands were appraised as catalysts for the Henry reaction by carrying out reactions between 4-nitrobenzaldehyde and nitromethane in THF solvent in the presence of $Cu(OAc)_2.nH_2O$. It was determined that the desired β-nitroalcohol was obtained in these reactions. However, we were surprised to observe that for all our ligands the R enantiomer of the product β-nitroalcohol was the major stereoisomer formed. By contrast, ligands **B**-**D** had all afforded the S enantiomer as the major stereoisomer. Yields and observed enantiomeric excesses of the products are given in Table 1.

The experimental results (Table 1) showed that substitution on the phenol ring had a significant influence on the enantioselectivity and the reaction yield. The best results were obtained when an alkoxy group such as methoxy (Table 1, Entry 6) or benzyloxy (Table 1, Entry 5) was present in the 3-position of the phenol ring. Surprisingly, replacing this alkoxy group with a hydroxyl group (Table 1, Entry 4) afforded a decrease in both yield and enantiomeric excess. Introduction of a substituent at the 5-position of the aromatic ring also led to

surprising effects, for example ligand **3b**, which contained a tert-butyl group in this position, afforded only a very low enantiomeric excess (Table 1, Entry 2).

Table 1. Optimization of catalytic ligands (3a-k) effect on the asymmetric Henry reaction.



Entry	Ligand	Time (h)	Yield[b] (%)	ee[c] (%)	Config[d]
1	3a	24	47	16	*R*
2	3b	24	25	2	*R*
3	3c	24	52	25	*R*
4	3d	24	31	9	*R*
5	3e	24	70	38	*R*
6	3f	24	72	47	*R*
7	3g	24	35	12	*R*
8	3h	24	70	15	*R*
9	3i	24	38	10	*R*
10	3j	24	52	12	*R*
11	3k	24	46	19	*R*

[a] All reactions were performed with 0.5 mmol 4-Nitro-benzaldehyde, 2.5% mol ligand and $Cu(OAc)_2.nH_2O$, and 5 mmol nitromethane in 1 mL of THF at room temperature.

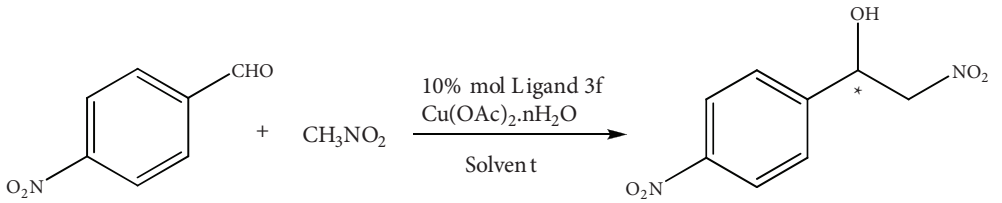
[b] Isolated yields by column chromatography using 5:1 hexane:ethyl acetate.

[c] Determined by HPLC with OD-H column using hexane:isopropanol (90:10).

[d] Absolute configurations were determined by comparison of the values with the literature values.[7–19]

After the selection of the catalyst, the effect of solvent was investigated (Table 2, Entries 1-12). It can be seen that ethereal solvents such as THF, ether, and dioxane gave reasonable yields and enantiomeric excesses. However, when alcohols were used as solvents disappointing enantiomeric excesses were obtained. The optimum solvent was determined to be tert-butylmethylether (TBME). This result contrasts with previous studies where alcoholic solvents[16–18] or CH_2Cl_2[17] were found to afford higher enantiomeric excesses. Subsequently, the catalyst loadings were tested (Table 2, Entries 14-16) and 10 mol % was found to afford the best results. In addition, to observe the effect of temperature on the process, one reaction was carried out at 0 °C. Although a slight increase in enantiomeric excess was obtained, the reaction took a longer time and gave a lower yield (Table 2, Entry 13).

Table 2. The solvent effect on the asymmetric Henry reaction between nitromethane and 4-nitrobenzaldehdye in the presence of 10% mol ligand 3f and $Cu(OAc)_2.nH_2O$.



Entry	Solvent	T (°C)	Time (day)	Yield[b] (%)	ee[c] (%)	Config
1	THF	rt	2	44	47	*R*
2	Ethanol	rt	2	60	31	*R*
3	CH_2Cl_2	rt	2	25	37	*R*
4	Et_2O	rt	2	50	49	*R*
5	Methanol	rt	2	52	14	*R*
6	Iso-propanol	rt	2	56	27	*R*
7	Dioxane	rt	2	54	35	*R*
8	TBME	rt	2	55	55	*R*
9	EtOAc	rt	2	37	41	*R*
10	Hexane	rt	2	40	30	*R*
11	CH_3CN	rt	2	40	39	*R*
12	Toluene	rt	2	22	39	*R*
13	TBME	0 °C	6	61	66	*R*
14[d]	TBME	rt	2	68	58	*R*
15[e]	TBME	rt	2	76	63	*R*
16[f]	TBME	rt	2	65	48	*R*

[a] Reactions were performed with 0.5 mmol 4-nitro-benzaldehyde, 10% mol ligand and $Cu(OAc)_2.nH_2O$, and 5 mmol nitromethane in 1 mL of solvent.

[b] Isolated yields by the column chromatography using 5:1 hexane:ethyl acetate.

[c] Determined by HPLC with OD-H column using hexane:isopropanol (90:10).

[d] 5 mol % of ligand and $Cu(OAc)_2.nH_2O$ were used.

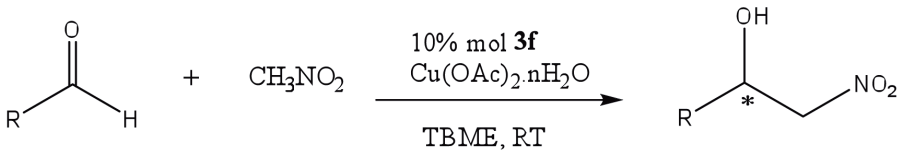
[e] 10 mol % of ligand and $Cu(OAc)_2.nH_2O$ were used.

[f] 1.25 mol % of ligand and $Cu(OAc)_2.nH_2O$ were used.

Finally, using the optimized conditions, a variety of aromatic aldehydes were employed as substrates (Table 3, Entries 1-10). Using these conditions, the expected products were obtained with moderate to good enantiomeric excesses (48%-63%) and yields (18%-76%). These enantiomeric excesses and yields are comparable to those obtained by Mao[18] using ligand **D** and superior to those obtained by Punniyamurthy[17] using ligand **C**. However, Wang,[16] using ligand **B**, had obtained even better enantioselectivity. These results suggest that it is important to have substituents at both carbons of the amino alcohol functionality and that substituents containing aromatic groups may be the preferred options. Consistent with this suggestion, Ma and

coworkers[14] very recently reported the preparation of a series of interesting ligands (**E**) (Figure 4) containing a paracyclophane group attached to a tridentate ONO Schiff base functionality. When applied to the Henry reaction in the presence of $Cu(OAc)_2.nH_2O$, good enantiomeric excesses of the desired β-nitroalcohol could be obtained. In these cases, CH_2Cl_2 was determined to be the optimum solvent, and, as in our results, the R enantiomer was the major stereoisomer formed. However, enantiomeric excesses were found to be strongly dependent on the nature of the R group present on the cyclophane group.

Table 3. Range of the aldehydes used in the Henry reactions in the presence of 10% mol ligand 3f and $Cu(OAc)_2.nH_2O$.



a: R= 4-NO_2Ph **b:** R= 3-NO_2Ph
c: R= 2-NO_2Ph **d:** R= 2-ClPh
e: R= 4-MePh **f:** R= 4-EtPh
g: R= 4-OMePh **h:** R= Ph
i: R= 4-ClPh **j:** R= 2-OMePh

4a-j

Entry	Product	T (°C)	Time (Day)	Yield (%)	ee (%)	Config
1	4a	rt	2	76	63	*R*
2	4b	rt	2	63	52	*R*
3	4c	rt	2	54	48	*R*
4	4d	rt	3	25	49	*R*
5	4e	rt	5	18	58	*R*
6	4f	rt	5	20	59	*R*
7	4g	rt	3	48	52	*R*
8	4h	rt	4	29	51	*R*
9	4i	rt	4	42	51	*R*
10	4j	rt	5	40	53	*R*

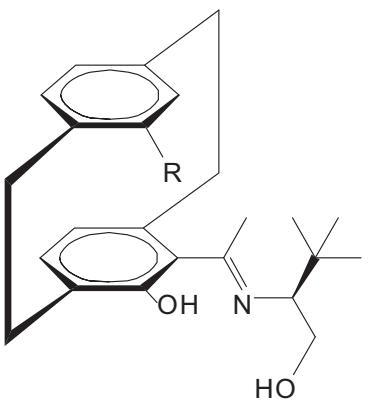


Figure 4. The structure of ligand **E**.

Conclusion

Schiff base ligands **3a-k** were synthesized that contain a tert-butyl group and their effects on the asymmetric Henry reaction as a catalyst were studied. Moderate to good enantiomeric excesses (up to 66%) of the products were obtained.

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