TÜBİTAK

Turkish Journal of Chemistry

http://journals.tubitak.gov.tr/chem/

Research Article

Turk J Chem
(2013) 37: 966 – 977
© TÜBİTAK
doi:10.3906/kim-1210-62

Asymmetric Henry reaction catalyzed by Cu(I)-based chiral amino alcohol complex

Tianhua SHEN, Quan QIN, Hang NI, Ting XIA, Xiaocong ZHOU, Funa CUI, Junqi LI, Deqiang RAN, Qingbao SONG*

The State Key Laboratory Breeding Base of Green Chemistry-Synthesis Technology,
College of Chemical Engineering and Materials Science, Zhejiang University of Technology, Hangzhou, P. R. China

Received: 31.10.2012 • **Accepted:** 11.06.2013 • **Published Online:** 04.11.2013 • **Printed:** 29.11.2013

Abstract: The Cu(I)-based complex prepared from (S)-2-(furan-2-yl-methylamino)-2-phenylethanol (**5c**) and CuCl was used as catalyst in enantioselective Henry reactions of arylaldehydes and nitromethane, which gave 89% ee and 95% yield at ambient temperature. The proposed catalytic cycle of an asymmetric Henry reaction was suggested.

Key words: Chiral amino alcohol, copper(I) salt, asymmetric catalysis, Henry reaction

1. Introduction

The Henry or nitroaldol reaction is one of the most powerful carbon–carbon bond forming reactions in organic chemistry,[1] and the CH-NO_2 moiety in nitro alcohol adducts can be subjected to subsequent reactions to afford other functionalities, for instance, ketone, aldehyde, carboxylic acid, and amino compounds,[2] which are highly valuable building blocks in asymmetric organic synthesis. Hence, the stereoselective Henry reaction has already been applied in the synthesis of various compounds.

Since the first asymmetric Henry reaction was reported by Shibasaki in 1992,[3] various versions of metal-catalyzed asymmetric Henry reactions have been reported. Because of its cheap price, low toxicity, and excellent chelating properties with ligands, copper has been widely used in organic synthesis. Copper can coordinate with many ligands,[4] such as bisoxazolines,[5] trisoxazolines,[5f] boron-bridged bisoxazoline,[6] thiaoline,[5c,d] bisoxazolidine,[7] amino alcohol,[8] imino alcohols,[9] aminopyridine,[10] iminopyridine,[11] bipiperidine,[12] camphor -imidazoline,[13] imidazole derivatives,[14] sparteine,[15] oxabispidine,[16] diamine,[17] trianglamine,[18] Schiff-base,[19] N,N'-dioxide,[20] tetrahydrosalen,[21] cinchona alkaloid,[22] and thiophene.[23] Many of these copper-based complexes catalyze the asymmetric Henry reaction with high yields and ee values.

Herein we describe the synthesis and applications of a series of copper(I) complexes prepared from (S)-amino alcohol **4**, **5**, and CuCl; the addition of nitro alkanes to aldehyde gave ee up to 89%. The aldehydes are compatible with this protocol, providing the corresponding nitroaldol products in high yields.

2. Experimental

2.1. General procedures

All solvents were dried by the standard method. Unless otherwise noted, commercially available reagents were used without further purification. All reactions were monitored by TLC with Haiyang GF254 silica gel coated

*Correspondence: qbsong@zjut.edu.cn

plates. Column chromatography was carried out using 100–200 mesh silica gel. Liquid aldehydes were freshly distilled before use.

Melting points were obtained with an X-4 micromelting point apparatus and are uncorrected. Optical rotations were determined in a solution of CH_2Cl_2 at 20 °C by using an Autopol IV polarimeter. IR spectra were recorded by a Veptor-22 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were obtained in $CDCl_3$ on a Bruker AVANCE III 500 MHz and 125 MHz spectrometers, respectively, using TMS as the internal reference. J values were given in hertz. Mass spectra were carried out on a VARIAN1200 and measured by the EI method.

Chiral HPLC analyses were performed by using a SHIMADZU LC-20AT instrument equipped with a SHIMADZU SPD-20A detector with chiral stationary phase column (Daicel Co. Chiralcel AD-H and OJ-H). Retention times are given in minutes.

2.2. Preparation of ligands' backbone

(*S*)-Phenylalanine methyl ester hydrochloride (1). $SOCl_2$ (11 mL, 155 mmol) was added dropwise to methanol (100 mL) in a 250-mL round-bottomed flask at –10 °C. After stirring for 15 min, L-phenylalanine (16.5 g, 100 mmol) was added. After being warmed up to ambient temperature and stirred for 3 h, the reaction mixture was refluxed for 2 h. Then the reaction mixture was condensed under reduced pressure; the residue was filtered and washed with ethanol to give compound **1**. Yield: 85%. mp 156–158 °C (lit.[24] = 157–158 °C).

(*S*)-2-Amino-1,1,3-triphenylpropan-1-ol (2). (S)-Phenylalanine methyl ester hydrochloride 2.16 g (10 mmol) was added portionwise to freshly prepared Grignard reagent of PhMgBr (80 mmol) in diethyl ether under an argon atmosphere at 0 °C. Then the mixture was stirred at ambient temperature overnight, and a cold saturated NH_4Cl was added into it under vigorous stirring. The mixture was extracted with ethyl acetate (50 mL × 3). The combined organic layer was washed with brine and dried with anhydrous Na_2SO_4, and then concentrated in a vacuum. This residue was recrystallized with diethyl ether and gave compound **2** as a colorless crystal. Yield: 65.3%; mp 144–145 °C (lit.[25] = 154–155 °C).

(*S*)-2-Phenylglycinol (3). A 250-mL 3-neck round-bottomed flask was fitted with a magnetic stir bar, a reflux condenser, and an addition funnel. The flask was charged with 3.31 g (91 mmol) of sodium borohydride and 100 mL of THF (predried over sodium). L-phenylglycine (5.74 g, 38 mmol) was added in one portion. The remaining neck was sealed with a septum and an argon line attached, and the flask was cooled to 0 °C in an ice bath. A solution of 9.65 g (38 mmol) of iodine dissolved in 25 mL of THF was poured into the addition funnel and added dropwise over 30 min, resulting in vigorous evolution of hydrogen. After addition, the reaction was complete and gas evolution had ceased, and the flask was heated to reflux for 18 h and then cooled to ambient temperature, and methanol was added cautiously until the mixture became clear. After stirring for 30 min, the solvent was removed by rotary evaporation, leaving a white paste, which was dissolved by adding 150 mL of 20% aqueous NaOH. The solution was stirred for 4 h and extracted with CH_2Cl_2 (50 mL × 3). The organic phase was dried with anhydrous Na_2SO_4 and concentrated in a vacuum. Then the white crude product was recrystallized in toluene to afford **3** as a colorless crystal. Yield: 65.3%; mp 72–73 °C (lit.[26] = 69–71 °C).

2.3. General procedure of the preparation for ligands 4a–4e

To a solution of an aldehyde (3.0 mmol) and **2** (0.91 g, 3.0 mmol) in 10 mL of CH_2Cl_2 was added anhydrous $MgSO_4$ (1.0 g), and the mixture was stirred at ambient temperature until the reaction was complete (monitored by TLC). Then the reaction mixture was filtered, and the filtrate was distilled under reduced pressure. Then

the Schiff base was obtained and dissolved in MeOH (10 mL) and THF (10 mL). After cooling to 0 °C, $NaBH_4$ (0.23 g, 6.0 mmol) was added in portions; then the mixture was stirred at ambient temperature until the reaction was complete. After the removal of the solvent, aqueous hydrochloric acid (1 N) was added until pH 8–9. Then the mixture was extracted with CH_2Cl_2 (20 mL × 3), and the organic phase washed with brine, dried with anhydrous Na_2SO_4, and evaporated to give the crude product. Then the residue was purified on silica gel column chromatography.

(*S*)-2-(3,4-Dimethoxybenzylamino)-1,1,3-triphenylpropan-1-ol (4a). 78% yield; mp 129–130 °C; $[\alpha]_D^{20}$ = –313 (c = 0.010, CH_2Cl_2), ^{1}H NMR (δ, ppm): 7.80–7.13 (15H, m, Ph-H), 6.61 (1H, d, J = 8.5 Hz, Ar-H), 6.17 (1H, dd, J = 8.0, 1.5 Hz, Ar-H), 6.11 (1H, d, J = 1.5 Hz, Ar-H), 3.97 (1H, dd, J = 11.0, 3.0 Hz, C*HN), 3.81 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 2.97–2.88 (3H, m, J = 14.5, 11.0, 3.0 Hz, CH_2N, $PhCH_2$), 2.36 (1H, dd, J = 14.5, 10.5 Hz, $PhCH_2$); ^{13}C NMR (δ, ppm): 148.62, 147.89, 144.62, 139.34, 132.28, 129.05, 128.56, 128.20, 128.09, 126.62, 126.47, 126.41, 126.05, 125.62, 120.08, 111.28, 110.71, 78.17, 77.03, 76.78, 65.50, 58.36, 55.81, 55.63, 53.63, 37.58; IR (KBr, cm^{-1}): 3451.2, 3322.6, 3003.6, 2907.1, 2853.5, 1581.0, 1494.0, 1370.2, 1158.3, 797.7, 768.4, 701.6; MS (m/z, %): 454 ((M + 1)$^+$, 12.6), 362 (5.1), 270 (99.9), 183 (18.2), 151 (99.3), 105 (98.2), 91 (45.7), 77 (88.6).

(S)-2-((4-Bromothiophen-2-yl)methylamino)-1,1,3-triphenylpropan-1-ol (4b). 85% yield; mp 200–201 °C; $[\alpha]_D^{20}$ = –150 (c = 0.023, CH_2Cl_2); ^{1}H NMR (δ, ppm): 7.44–7.11 (15H, m, Ph-H), 7.00 (1H, d, J = 1.0 Hz, thiophene-H), 6.89 (1H, d, J = 1.4 Hz, thiophene-H), 3.12–3.00 (2H, m, CH_2N), 2.87–2.79 (2H, m, $PhCH_2$), 2.75 (1H, dd, J = 3.5, 13.8 Hz, C*HN); ^{13}C NMR (δ, ppm): 145.66, 142.76, 140.36, 138.22, 130.88, 130.54, 129.47, 129.35, 128.93, 128.21, 126.34, 126.12, 121.44, 89.91, 77.82, 73.65, 47.45, 34.51; IR (KBr, cm^{-1}): 3492.1, 2961.0, 2893.0, 1600.8, 1491.5, 1448.5, 1365.4, 1156.9, 811.4, 750.9, 699.0, 579.8; MS (m/z, %): 478 ((M + 1)$^+$, 2.5), 386 (2.4), 296 (30.8), 183 (99.9), 176 (17.2), 105 (95.9), 91 (97.4), 77 (99.9).

(*S*)-2-(Furan-2-ylmethylamino)-1,1,3-triphenylpropan-1-ol (4c). 60% yield; mp 80–81 °C; $[\alpha]_D^{20}$ = –52.3 (c = 0.022, CH_2Cl_2); ^{1}H NMR (δ, ppm): 7.73–7.02 (16H, m, Ph-H, furan-H), 6.14 (1H, dd, J = 2.5, 2.0 Hz, furan-H), 5.69 (1H, d, J = 3.0 Hz, furan-H), 4.80 (1H, br, NH), 3.97 (1H, dd, J = 10.5, 2.8 Hz, C*HN), 3.13 (1H, d, J = 14.5 Hz, CH_2N), 2.92–2.86 (2H, m, CH_2NH, $PhCH_2$), 2.35 (1H, dd, J = 14.5, 10.5 Hz, $PhCH_2$), 1.62 (1H, br, OH); ^{13}C NMR (δ, ppm): 152.93, 147.47, 145.05, 141.74, 139.12, 128.90, 128.58, 128.20, 126.73, 126.46, 126.25, 126.00, 125.62, 109.62, 106.96, 78.05, 77.29, 77.03, 76.78, 63.85, 44.81, 37.48; IR (KBr, cm^{-1}): 3340.2, 3022.3, 2922.5, 1599.6, 1492.5, 1449.1, 1366.8, 1212.7, 1147.5, 802.0, 740.8, 699.2; MS (m/z, %): 384 ((M + 1)$^+$, 3.1), 200 (99.9), 183 (13.6), 105 (99.0), 91 (75.2), 77 (97.3).

(*S*)-2-((1*H*-pyrrol-2-yl)methyleneamino)-1,1,3-triphenylpropan-1-ol (4d). The title compound was prepared according to the general procedure without the reduction with $NaBH_4$ and purified by recrystallization from ethanol. 65% yield; mp 196–197 °C; $[\alpha]_D^{20}$ = –178 (c = 0.015, CH_2Cl_2); ^{1}H NMR (δ, ppm): 7.68–6.94 (16H, m, Ph-H, CH = N), 6.64 (1H, s, pyrrol-H), 6.16 (1H, d, J = 2.5 Hz, pyrrol-H), 6.07 (1H, dd, J = 3.5, 3.0 Hz, pyrrol-H), 4.36 (1H, dd, J = 13.5, 6.0 Hz, C*HN), 2.84 (2H, d, J = 6.0 Hz, $PhCH_2$); ^{13}C NMR (δ, ppm): 152.76, 139.50, 129.98, 128.41, 128.15, 126.64, 126.37, 126.24, 126.06, 125.59, 114.69, 114.67, 109.57, 79.64, 77.38, 77.29, 77.03, 76.78, 37.17; IR (KBr, cm^{-1}): 3411.4, 3025.1, 2934.1, 1636.2, 1602.0, 1493.2, 1449.9, 1366.7, 1176.0, 808.9, 750.5, 700.8; MS (m/z, %): 381 ((M + 1)$^+$, 3.4), 197 (99.9), 183 (49.0), 105 (99.1), 91 (77.5), 77 (97.9).

(*S*)-2-(Naphthalen-2-ylmethylamino)-1,1,3-triphenylpropan-1-ol (4e). 85% yield; mp 196–197

°C; $[\alpha]_D^{20}$ = –61.0 (c = 0.020, CH_2Cl_2); ^{1}H NMR (δ, ppm): 7.77–6.86 (22H, m, Ar-H), 4.87 (1H, br, NH), 3.98 (1H, dd, J = 11.0, 3.0 Hz, C*HN), 3.12 (1H, d, J = 13.0 Hz, CH_2N), 3.22 (1H, d, J = 13.0 Hz, CH_2N), 2.96 (1H, dd, J = 14.5, 2.8 Hz, $PhCH_2$), 2.38 (1H, dd, J = 14.5, 11.0 Hz, $PhCH_2$), 1.54 (1H, br, OH); ^{13}C NMR (δ, ppm): 147.65, 145.06, 139.39, 137.02, 133.14, 132.49, 129.15, 128.72, 128.23, 127.83, 127.67, 127.53, 126.53, 126.47, 126.35, 126.07, 125.84, 125.64, 125.58, 78.17, 77.30, 77.05, 77.03, 76.80, 65.42, 53.60, 37.73; IR (KBr, cm^{-1}): 3408.7, 3023.5, 2958.2, 1600.2, 1493.8, 1447.3, 1377.7, 1174.1, 861.5, 790.6, 697.9; MS (m/z, %): 444 ($(M + 1)^+$, 2.2), 260 (66.6), 183 (15.1), 105 (99.9), 91 (56.9), 77 (98.3).

2.4. General procedure of the preparation for ligands 5a–5e

To a solution of aldehyde 3.0 mmol and **3** (0.411 g, 3.0 mmol) in 10 mL of CH_2Cl_2 was added anhydrous $MgSO_4$ (1.0 g), and the mixture was stirred at ambient temperature until the reaction completed (monitored by TLC). After the solid material was removed by filtration the solvent was distilled under reduced pressure. Then the Schiff base was obtained and dissolved in MeOH (10 mL) and THF (10 mL). After cooling to 0 °C, $NaBH_4$ (0.23 g, 6.0 mmol) was added in portions; then the mixture was stirred at room temperature until the reaction was over (monitored by TLC). After the removal of the solvent, aqueous hydrochloric acid (1 N) was added until pH 8–9. Then the resulting mixture was extracted with CH_2Cl_2 (20 mL × 3), and the organic phase was washed with brine, dried with anhydrous Na_2SO_4, and evaporated to give the crude product. Then the residue was purified on silica gel column chromatography. Amino alcohols **5a**[27], **5c**[28], **5d**[29], and **5e**[30] are known compounds.

(*S*)-2-(3,4-Dimethoxybenzylamino)-2-phenylethanol (5a). 79% yield; $[\alpha]_D^{20}$ = + 58.1 (c = 0.015, CH_2Cl_2); ^{1}H NMR (δ, ppm): 7.38–7.30 (5H, m, Ph-H), 6.82–6.78 (3H, m, Ph-H), 3.85 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 3.80 (1H, dd, J = 9.0, 4.2 Hz, C*HN), 3.69 (1H, d, J = 11.0 Hz, CH_2N), 3.68 (1H, d, J = 12.5 Hz, CH_2O), 3.57 (1H, d, J = 10.5 Hz, CH_2N), 3.54 (1H, d, J = 13.0 Hz, CH_2O), 2.51 (2H, br, NH, OH); IR (KBr, cm^{-1}): 3406.3, 3001.9, 2935.0, 2834.8, 1582.3, 1515.9, 1453.8, 1344.9, 1156.6, 854.5, 808.0, 762.6, 703.0. MS (m/z, %): 196 (74.5), 104 (24.5), 91 (99.9).

(*S*)-2-((4-Bromothiophen-2-yl)methylamino)-2-phenylethanol (5b). 80% yield; $[\alpha]_D^{20}$ = + 68.6 (c = 0.010, CH_2Cl_2); ^{1}H NMR (δ, ppm): 7.39–7.28 (5H, m, Ph-H), 7.10 (1H, d, J = 1.5 Hz, thiophene-H), 6.77 (1H, d, J = 1.0 Hz, thiophene-H), 3.88 (1H, dd, J = 14.5, 0.5 Hz, CH_2N), 3.83 (1H, dd, J = 9.5, 4.2 Hz, C*HN), 3.76 (1H, dd, J = 14.5, 0.5 Hz, CH_2N), 3.70 (1H, dd, J = 11.0, 4.5 Hz, CH_2O), 3.57 (1H, dd, J = 11.0, 4.5 Hz, CH_2O), 2.81 (2H, br, NH, OH); IR (KBr, cm^{-1}): 3417.9, 3027.8, 2926.1, 2869.4, 1635.1, 1528.4, 1453.6, 1345.8, 1153.2, 857.4, 758.7, 701.4, 583.9; MS (m/z, %): 312 ($(M + 1)^+$, 0.9), 280 (61.2), 175 (99.9), 104 (12.6).

(*S*)-2-(Furan-2-ylmethylamino)-2-phenylethanol (5c). 60% yield; mp 69–70 °C; $[\alpha]_D^{20}$ = + 98.8 (c = 0.015, CH_2Cl_2); ^{1}H NMR (δ, ppm): 7.40–7.30 (5H, m, Ph-H), 7.29 (1H, d, J = 2.0 Hz, furan-H), 6.29 (1H, dd, J = 3.0, 2.0 Hz, furan-H), 6.11 (1H, d, J = 3.5 Hz, furan-H), 3.79 (1H, dd, J = 8.5, 4.0 Hz, C*HN), 3.74 (1H, d, J = 14.5 Hz, CH_2N), 3.70 (1H, dd, J = 11.0, 4.5 Hz, CH_2O), 3.60 (1H, d, J = 14.0 Hz, CH_2N), 3.58 (1H, dd, J = 11.0, 8.5 Hz, CH_2O), 2.37 (2H, br, NH, OH); IR (KBr, cm^{-1}): 3265.6, 3031.0, 2919.1, 2864.1, 1602.2, 1493.7, 1454.0, 1337.4, 1196.9, 1145.6, 807.7, 763.2, 703.8; MS (m/z, %): 218 ($(M + 1)^+$, 9.8), 186 (99.9), 81 (99.8), 77 (96.6).

(*S*)-2-((1*H*-pyrrol-2-yl)methyleneamino)-2-phenylethanol (5d). This compound was prepared

according to the general procedure without the reduction with $NaBH_4$ and purified by recrystallization from ethanol. 60% yield; mp 196–197 °C; $[\alpha]_D^{20}$ = + 156 (c = 0.018, CH_2Cl_2); IR (KBr, cm^{-1}): 3331.3, 3061.3, 2857.7, 1640.6, 1489.0, 1448.5, 1366.7, 1180.1, 813.2, 736.5, 700.8; MS (m/z, %): 214 (M^+, 21.0), 183 (99.9), 79 (37.3), 77 (48.9).

(*S*)-2-(Naphthalen-2-ylmethylamino)-2-phenylethanol (5e). 75% yield; $[\alpha]_D^{20}$ = + 43.6 (c = 0.015, CH_2Cl_2); ^1H NMR (δ, ppm): 7.82–7.28 (12H, m, Ar-H), 3.89 (1H, d, J = 13.5 Hz, CH_2N), 3.83 (1H, dd, J = 8.5, 4.2 Hz, C*HN), 3.73 (1H, d, J = 12.5 Hz, CH_2N), 3.70 (1H, dd, J = 10.8, 4.0 Hz, CH_2O), 3.57 (1H, dd, J = 11.0, 8.5 Hz, CH_2O), 2.26 (2H, br, NH, OH); IR (KBr, cm^{-1}): 3284.7, 3028.4, 2926.0, 2852.9, 1944.8, 1600.7, 1491.8, 1452.9, 1366.3, 1175.0, 870.4, 825.9, 700.1; MS (m/z, %): 278 ($(M + 1)^+$, 1.2), 246 (99.9), 105 (93.0), 81 (99.8), 77 (29.6).

2.5. General procedure of the asymmetric Henry reaction

The chiral ligand (0.03 mmol) and CuCl (0.03 mmol) were put in a 10-mL round-bottomed flask. Ethanol (1.5 mL) was added and the mixture was stirred for 1 h at ambient temperature (18 °C). Usually a color change from colorless to greenish was observed during this time. Subsequently, the desired aldehyde (0.3 mmol) was added, followed by slow addition of 0.16 mL (3 mmol) of nitromethane via syringe. The reaction was monitored by TLC until completed. The volatile components were removed in vacuo and the crude product was purified by preparative TLC with petroleum ether/ethyl acetate to afford the desired β-nitroalcohol. Enantiomeric excess was determined by using HPLC with Chiracel OJ-H or Chiralpak AD-H chiral columns.

2-Nitro-1-phenylethanol. Chiral HPLC (Daicel Chiralpak AD-H), n-hexane: i-PrOH = 95:5; flow rate: 0.5 mL/min; λ = 230 nm; t_{minor} = 36.46 min, t_{major} = 37.66 min; 55% ee. Corresponding racemic compound's retention time: τ_1 = 34.59 min, τ_2 = 35.73 min.

2-Nitro-1-(4-Nitrophenyl)ethanol. Chiral HPLC (Daicel Chiralpak AD-H), n-hexane: i-PrOH = 65:35; flow rate: 1.0 mL/min; λ = 254 nm; t_{major} = 10.23 min, t_{minor} = 13.04 min; 89% ee. Corresponding racemic compound's retention time: τ_1 = 10.08 min, τ_2 = 12.73 min.

2-Nitro-1-(3-Nitrophenyl)ethanol. Chiral HPLC (Daicel Chiralpak AD-H), n-hexane: i-PrOH = 68:32; flow rate: 0.7 mL/min; λ = 254 nm; t_{minor} = 7.91 min, t_{major} = 8.68 min; 76% ee. Corresponding racemic compound's retention time: τ_1 = 7.89 min, τ_2 = 8.67 min.

2-Nitro-1-(2-Nitrophenyl)ethanol. Chiral HPLC (Daicel Chiralpak AD-H), n-hexane: i-PrOH = 70:30; flow rate: 0.5 mL/min; λ = 254 nm; t_{minor} = 11.70 min, t_{major} = 12.25 min; 88% ee. Corresponding racemic compound's retention time: τ_1 = 11.81 min, τ_2 = 12.34 min.

2-Nitro-1-(4-Chlorophenyl)ethanol. Chiral HPLC (Daicel Chiralpak Chiralcel OJ-H), n-hexane: i-PrOH = 85:15; flow rate: 1.0 mL/min; λ = 220 nm; t_{major} = 6.08 min, t_{minor} = 12.91 min; 86% ee. Corresponding racemic compound's retention time: τ_1 = 5.49 min, τ_2 = 12.26 min.

2-Nitro-1-(3-Chlorophenyl)ethanol. Chiral HPLC (Daicel Chiralpak AD-H), n-hexane: i-PrOH = 85:15; flow rate: 0.5 mL/min; λ = 215 nm; t_{minor} = 13.71 min, t_{major} = 14.89 min; 41% ee. Corresponding racemic compound's retention time: τ_1 = 13.19 min, τ_2 = 14.28 min.

2-Nitro-1-(2-Chlorophenyl)ethanol. Chiral HPLC (Daicel Chiralpak Chiralcel OJ-H), n-hexane: i-PrOH = 95:5; flow rate: 0.8 mL/min; λ = 215 nm; t_{major} = 27.11 min, t_{minor} = 28.04 min; 36% ee. Corresponding racemic compound's retention time: τ_1 = 26.53 min, τ_2 = 27.49 min.

1-(2,5-Dimethoxyphenyl)-2-nitroethanol. Chiral HPLC (Daicel Chiralpak AD-H), n-hexane: i-PrOH = 90:10; flow rate: 0.7 mL/min; λ = 215 nm; t_{minor} = 24.72 min, t_{major} = 25.79 min; 71% ee. Corresponding racemic compound's retention time: τ_1 = 24.33 min, τ_2 = 25.33 min.

1-(Naphthalen-2-yl)-2-nirtoethanol. Chiral HPLC (Daicel Chiralpak AD-H), n-hexane: i-PrOH = 85:15; flow rate: 0.5 mL/min; λ = 230 nm; t_{minor} = 31.96 min, t_{minor} = 33.99 min; 55% ee. Corresponding racemic compound's retention time: τ_1 = 31.45 min, τ_2 = 33.12 min.

1-(Furan-2-yl)-2-nitroethanol. Chiral HPLC (Daicel Chiralpak AD-H), n-hexane: i-PrOH = 85:15; flow rate: 1.0 mL/min; λ = 225 nm; t_{major} = 15.62 min, t_{minor} = 16.35 min; 58% ee. Corresponding racemic compound's retention time: τ_1 = 16.02 min, τ_2 = 16.72 min.

1-(4-Bromothiophen-2-yl)-2-nitroethanol. Chiral HPLC (Daicel Chiralpak AD-H), n-hexane: i-PrOH = 95:5; flow rate: 1.0 mL/min; λ_{max} = 230 nm; t_{minor} = 17.01 min, t_{major} = 19.51 min; 86% ee. Corresponding racemic compound's retention time: τ_1 = 17.19 min, τ_2 = 19.83 min.

2.6. General procedure for preparation of the racemic Henry reaction products

The aldehyde (0.3 mmol) was added to a 10-mL round-bottomed flask. Then ethanol (1.5 mL) was added at ambient temperature (18 °C). Subsequently, nitromethane (0.16 mL, 3 mmol) was injected via syringe. The reaction was monitored by TLC until complete conversion was achieved (about 8 h). The volatile components were removed in vacuo and the crude product was purified by preparative TLC with petroleum ether/ethyl

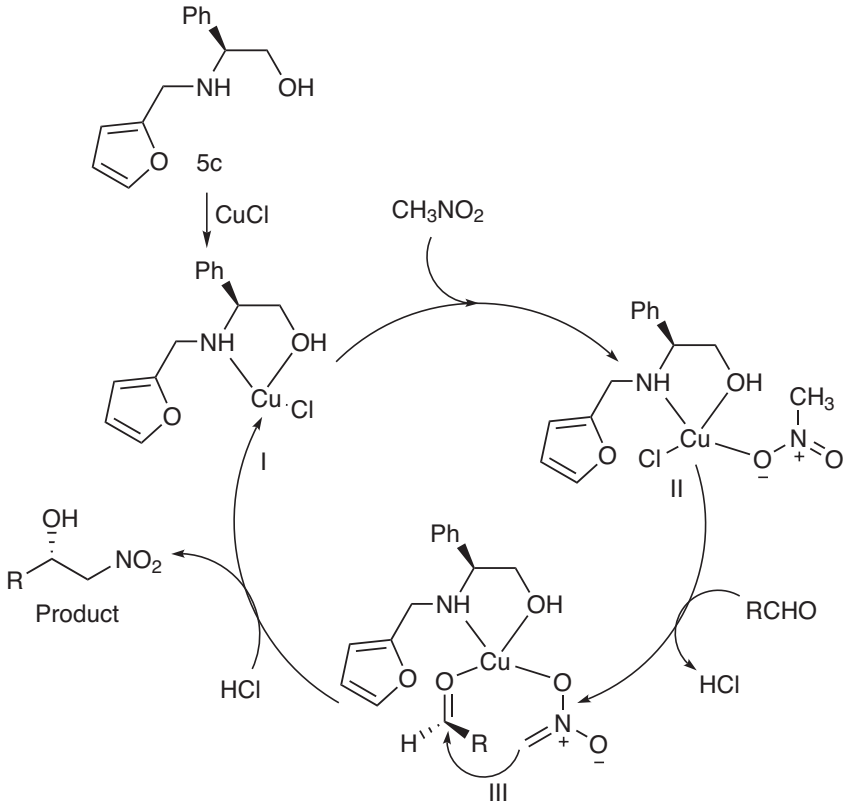


Figure. Proposed catalytic cycle for the enantioselective Henry reaction.

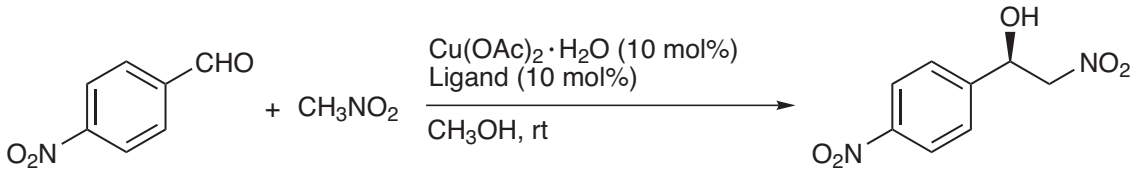
acetate, which gave the racemic β-nitroalcohol. Retention time was determined by using HPLC with Chiracel OJ-H or Chiralpak AD-H chiral columns.

3. Results and discussion

The L-phenylalaninol ligands **4a**–**e** were synthesized from L-phenylalanine as a starting material through 4 simple steps and the L-2-phenylglycinol ligands **5a-e** were synthesized from L-phenylglycine through 3 steps (Scheme).

With these series of amino alcohols in hand, we began to evaluate these ligands for the enantioselective Henry reaction. During our initial experiments, ligands **4a**–**e** were used in the additive reaction of nitromethane to*p*-nitrobenzaldehyde at ambient temperature in methanol (Table 1). This type of ligand showed poor catalytic activity and enantio- selectivity in this reaction (Table 1, entries 1–5). It is possible that the phenyl rings on the α-carbon atom of the hydroxyl group gave significant steric hindrance, and so the substrate was too hard to combine with the copper complex. Then we changed the backbone of the ligand. The L-2-phenylglycinol type ligand **5b** showed the best enantioselectivity (Table 1, entry 7). Although the enantiomeric excess was enhanced to 44%, the yield was still moderate. When triethylamine was added, the reaction was complete in 12 h with good yields, but the products were almost racemic (Table 1, entries 11 and 12).

Table 1. The model enantioselective Henry reactions of *p*-nitrobenzaldehyde with nitromethane using different ligands.

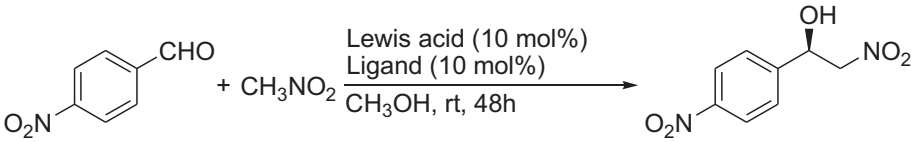


Entry[a]	Ligand	t (h)	Yield (%) [b]	Ee (%) [c]
1	4a	48	28	<5
2	4b	48	30	<5
3	4c	48	35	15
4	4d	48	20	<5
5	4e	48	33	<5
6	5a	48	65	30
7	5b	48	60	44
8	5c	48	70	37
9	5d	48	40	7
10	5e	48	80	24
11	5b	12	90	<5
12	5c	12	93	<5

[a] Reactions were performed on a 0.3 mmol scale of aldehyde and 0.16 mL (3 mmol) of nitromethane. [b] Chromatogram yield. [c] Enantiomeric excesses were determined by HPLC using a Chiral AD-H column. [d] Et_3N of 10 mol % was used as the additive.

From Table 2, several kinds of copper salt as Lewis acid were selected and evaluated for the enantioselective Henry reaction at ambient temperature. CuCl was found to be the best copper salt for this reaction, with high enantiomeric excess and moderate yield (Table 2, entries 3 and 4). CuBr showed the best enantiomeric excess, but with low yield (Table 2, entry 8). A similar moderate yield was obtained by using CuI as Lewis acid, but the products were almost racemic (Table 2, entries 9 and 10).

Table 2. Effect of Lewis acid on the enantioselectivity.

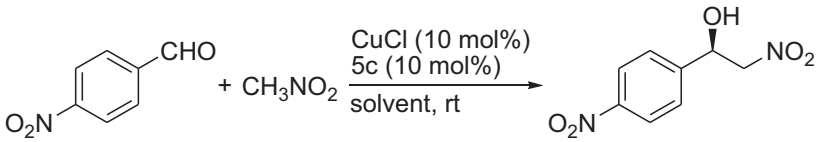


Entry [a]	Ligand	Lewis acid	Yield (%) [b]	Ee (%) [c]
1	5b	$Cu(OAc)_2 \cdot H_2O$	65	44
2	5c	$Cu(OAc)_2 \cdot H_2O$	70	37
3	5b	CuCl	83	69
4	5c	CuCl	80	74
5	5b	$CuCl_2 \cdot 2H_2O$	20	39
6	5c	$CuCl_2 \cdot 2H_2O$	20	41
7	5b	CuBr	30	69
8	5c	CuBr	35	77
9	5b	CuI	77	<5
10	5c	CuI	86	<5

[a] Reactions were performed on a 0.3 mmol scale of aldehyde and 0.16 mL (3 mmol) of nitromethane. [b] Chromatogram yield. [c] Enantiomeric excesses were determined by HPLC using a Chiral AD-H column.

As shown in Table 3, it is clear that protic alcoholic solvents were superior to aprotic solvents (entries 1 and 2). The enantioselectivity was enhanced to 89% when using ethanol as the solvent (entry 2), and the reaction rate became fast (entry 2). Coordinative solvents like alcohols might coordinate with copper ion, which would enhance the enantioselectivity[9] (entries 3, 4, and 6).

Table 3. Effect of solvent on the enantioselective Henry reaction.

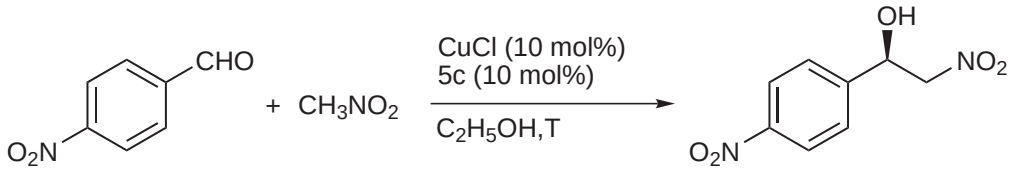


Entry [a]	Solvent	t (h)	Yield (%) [b]	Ee (%) [c]
1	MeOH	24	80	74
2	EtOH	18	95	89
3	CH_2Cl_2	48	30	63
4	PhMe	48	15	55
5	CH_3NO_2	48	17	55
6	THF	48	35	56

[a] Reactions were performed on a 0.3 mmol scale of aldehyde and 0.16 mL (3 mmol) of nitromethane. [b] Chromatogram yield. [c] Enantiomeric excesses were determined by HPLC using a Chiral AD-H column.

Reaction temperature was the last optimized factor of the enantioselective Henry reaction (Table 4). At –20 °C, no corresponding product was checked by TLC (Table 4, entry 1). Then we conducted the reaction under warm temperature, and both the yields and enantioselectivity were improved (Table 4, entries 2–4). When the temperature was increased to 35 °C, the reaction was faster than that at 18 °C, but the ee value of the product dropped (Table 4, entry 4).

Table 4. Effect of temperature on the enantioselective Henry reaction.

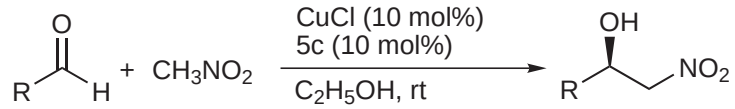


Entry [a]	T (°C)	t (h)	Yield (%) [b]	Ee (%) [c]
1	–20	24	–	nd
2	0	24	88	90
3	18	24	97	89
4	35	6	98	83

[a] Reactions were performed on a 0.3 mmol scale of aldehyde and 0.16 mL (3 mmol) of nitromethane. [b] Chromatogram yield. [c] Enantiomeric excesses were determined by HPLC using a Chiral AD-H column.

Under optimal condition, several arylaldehydes were found to be suitable substrates (Table 5). A variety of aromatic, heteroaromatic aldehydes provided nitroalcohol products with good yields (up to 95%) and good enantiomeric excesses in the range of 36% to 89%. It might be noted that the electronic character of the substituent as well as its steric hindrance had rather slight influence on the enantioselectivities. The enantioselectivities of the chiral products with para-substituents had a significant increase compared with ortho- and meta-substituents (Table 5, entries 2–7), and these results correlated with the increased electrophilicity of the substrates. Heteroaromatic aldehydes also gave nitroaldol products with good ee values (Table 5, entries 10 and 11).

Table 5. Scope of aldehydes in the enantioselective Henry reaction with nitromethane.

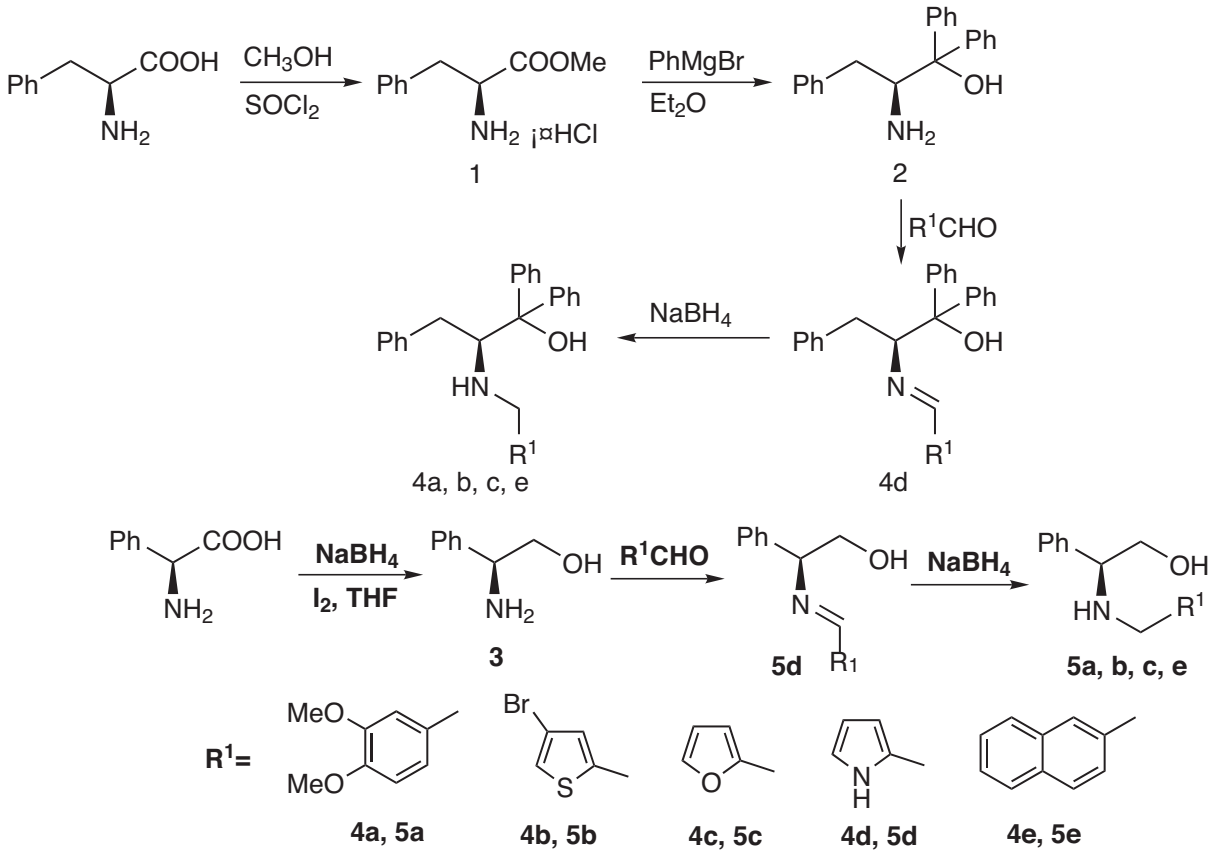


Entry [a]	Aldehydes	t (h)	Yield (%) [b]	Ee (%) [c]
1	Benzaldehyde	120	35	55
2	4-Nitrobenzaldehyde	18	95	89
3	3-Nitrobenzaldehyde	48	75	76
4	2-Nitrobenzaldehyde	30	90	88
5	4-Chlorobenzaldehyde	120	50	86
6	3-Chlorobenzaldehyde	120	35	41
7	2-Chlorobenzaldehyde	120	30	36
8	2,5-Dimethoxylbenzaldehyde	96	45	71
9	2-Naphthyl-aldehyde	48	69	55
10	Furan-2-carbaldehyde	120	30	58
11	4-Bromothiophene-2-carbaldehyde	41	75	86

[a] Reactions were performed on a 0.3 mmol scale of aldehyde and 0.16 mL (3 mmol) of nitromethane. [b] Chromatogram yield. [c] Enantiomeric excesses were determined by HPLC using a Chiral AD-H or a Chiral OJ-H column.

Based on the previous results and relevant mechanism suggested by Evans,[5e] the proposed catalytic cycle is shown in the Figure. The complex **I** was formed by the reaction from ligand **5c** and CuCl. Due to

the strong coordination ability of the nitro group to the center metal, nitromethane was activated through a possible complex **II**. Then the aldehyde bonded to the copper ion to form the transition state **III,** and the nitromethane was deprotonated to generate the active nucleophile simultaneously. Eventually, the product was obtained through the attack of nucleophile.



Scheme. Preparation of chiral amino alcohol type ligands **4** and **5**.

4. Conclusion

The results of the experiment showed that the Cu(I)-based complex was prepared from (S)-2-(furan-2-ylmethylamino)-2-phenylethanol (**5c**) with CuCl used as catalyst in the enantioselective Henry reaction of arylaldehydes and nitromethane with up to 89% ee values and 95% yield at ambient temperature. Under optimal conditions, several arylaldehydes were found to be suitable substrates. The proposed catalytic cycle of the asymmetric Henry reaction was suggested. Further studies about amino alcohols on asymmetric synthesis are currently being undertaken by our group.

Acknowledgments

This work was financially supported by the National Science Foundation of Zhejiang Province (LY12B02016) and the State Key Laboratory Breeding Base of Green Chemistry-Synthesis Technology, Zhejiang University of Technology (People's Republic of China).

References

1. Henry, L. *C. R. Hebd. Seances Acad. Sci.* **1895**, *120*, 1265.
2. a) Coppola, G. M.; Schuster, H. F. *α-Hydroxy Acids in Enantioselective Syntheses*, VCH, Weinheim, **1997**. b) Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017–1047. c) Narayana, C.; Reddy, N. K.; Kabalka, G. W. *Synth. Commun.* **1992**, *22*, 2587–2592. d) Matt, C.; Wagner, A.; Mioskowski, C. *J. Org. Chem.* **1997**, *62*, 234–235. e) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561–2576. f) Poupart, M.-A.; Fazal, G.; Goulet, S.; Mar, L. T. *J. Org. Chem.* **1999**, *64*, 1356–1361.
3. a) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418–4420; b) Sasai, H.; Tokunaga, T.; Watenabe, S.; Suzuki, T.; Itoh, N.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 7388–7389.
4. For a review see: Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, 2561–2574.
5. a) Christensen, C.; Juhl, K.; Jørgensen, K. A. *Chem. Commun.* **2001**, 2222–2223; b) Christensen, C.; Juhl, K.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4875–4881. c) Lu, S.-F.; Du, D.-M.; Zhang, S.-W.; Xu, J. *Tetrahedron: Asymmetry* **2004**, *15*, 3433–3441; d) Du, D.-M.; Lu, S.-F.; Fang, T.; Xu, J. *J. Org. Chem.* **2005**, *70*, 3712–3715. e) Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T. Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692–12693. f) Gaab, M.; Bellemin-Laponnaz, S.; Gade, L. H. *Chem. Eur. J.* **2009**, *15*, 5450–5462.
6. Toussaint, A.; Pfaltz, A. *Eur. J. Org. Chem.* **2008**, 4591–4597.
7. Spangler, K. Y.; Wolf, C. *Org. Lett.* **2009**, *11*, 4724–4727.
8. a) Mansawat, W.; Saengswang. I.; U-prasitwong, P.; Bhanthumnavin, W.; Vilaivan, T. *Tetrahedron Lett.* **2007**, *48*, 4235–4238. b) Kim, H. U.; Oh, K. *Org. Lett.* **2009**, *11*, 5682–5685.
9. a) Gan, C.; Lai, G.; Zhang, Z.; Wang, Z.; Zhou, M.-M. *Tetrahedron: Asymmetry* **2006**, *17*, 725–728. b) Jammi, S.; Punniyamurthy, T. *Eur. J. Inorg. Chem.* **2009**, 2508–2511. c) Guo, J.; Mao, J. *Chirality* **2009**, *21*, 619–627.
10. Blay, G.; Domingo, L. R.; Hernández-Olmos, V.; Pedro, J. R. *Chem. Eur. J.* **2008**, *14*, 4725–4730.
11. a) Blay, G.; Climent, E.; Fernández, I.; Hernández-Olmos, V.; Pedro, J. R. *Tetrahedron: Asymmetry* **2006**, *17*, 2046–2049. b) Blay, G.; Climent, E.; Fernández, I.; Hernández-Olmos, V.; Pedro, J. R. *Tetrahedron: Asymmetry* **2007**, *18*, 1603–1612. c) Blay, G.; Hernández-Olmos, V.; Pedro, J. R. *Org. Biomol. Chem.* **2008**, *6*, 468–476.
12. Noole, A.; Lippur, K.; Metsala, A.; Lopp, M.; Kanger, T. *J. Org. Chem.* **2010**, *75*, 1313–1316.
13. Bureša, F.; Kulhánek, J.; Růžička, A. *Tetrahedron Lett.* **2009**, *50*, 3042–3045.
14. Bureš, F.; Szotkowski, T.; Kulhánek, J.; Pytela, O.; Ludwiga, M.; Holčapek, M. *Tetrahedron: Asymmetry* **2006**, *17*, 900–907.
15. Maheswaran, H.; Prasanth, K. L.; Krishna, G. G.; Ravikumar, K.; Sridhar, B.; Kantam, M. L. *Chem. Commun.* **2006**, 4066–4068.
16. Breuning, M.; Hein, D.; Steiner, M.; Gessner, V. H.; Strohmann, C. *Chem. Eur. J.* **2009**, *15*, 12764–12769.
17. a) Arai, T.; Watanabe, M.; Fujiwara, A.; Yokoyama, N.; Yanagisawa, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 5978–5981. b) Bandini, M.; Benaglia, M.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *Org. Lett.* **2007**, *9*, 2151–2153. c) Bandini, M.; Piccinelli, F.; Tommasi, S.; Umani-Ronchi, A.; Ventrici, C. *Chem. Commun.* **2007**, 616–618. d) Kowalczyk, R.; Sidorowicz, Ł.; Skarżewski, J. *Tetrahedron: Asymmetry* **2008**, *19*, 2310–2315. e) Arai, T.; Takashita, R.; Endo, Y.; Watanabe, M.; Yanagisawa, A. *J. Org. Chem.* **2008**, *73*, 4903–4906. f) Kowalczyk, R.; Skarżewski, J. *Tetrahedron: Asymmetry* **2009**, *20*, 2467–2473. g) Selvakumar, S.; Sivasankarana, D.; Singh, V. K. *Org. Biomol. Chem.* **2009**, *7*, 3156–3162. h) Zhang, G.; Yashima, E.; Woggona, W. D. *Adv. Synth. Catal.* **2009**, *351*, 1255–1262.
18. Tanaka, K.; Hachiken, S.; *Tetrahedron Lett.* **2008**, *49*, 2533–2536.
19. Jammi, S.; Saha, P.; Sanyashi, S.; Sakthivel, S.; Punniyamurthy, T. *Tetrahedron* **2008**, *64*, 11724–11731.
20. Qin, B.; Xiao, X.; Liu, X.; Huang, J.; Wen, Y.; Feng, X. *J. Org. Chem.* **2007**, *72*, 9323–9328.

21. a) Xiong, Y.; Wang, Fei.; Huang, X.; Wen, Y.; Feng, X. *Chem. Eur. J.* **2007**, *13*, 829–833. b) Constable, E. C.; Zhang, G.; Housecroft, C. E.; Neuburger, M.; Schaffner, S.; Woggon, W. D.; Zampese, J. A. *New J. Chem.* **2009**, *33*, 2166–2173.

22. Zielińska-Błajet, M.; Skarżewski, J. *Tetrahedron: Asymmetry* **2009**, *20*, 1992–1998.

23. Bandini, M.; Cabiddu, S.; Cadoni, E.; Olivelli, P.; Sinisi, R.; Umani-Ronchi, A.; Usai, M. *Chirality* **2009**, *21*, 239–244.

24. Cristiane, F. D. C.; Alessandra, C. P. *Chem. Biol. Drug. Des.* **2012**, *79*, 216-222.

25. Da, C.; Han, Z.; Ni, M.; Yang, F.; Liu, D.; Zhou, Y.; Wang, R. *Tetrahedron: Asymmetry* **2003**, *14*, 659–665.

26. Giannis, A.; Sandhoff, K. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 218–219.

27. Carrillo, L.; Badía, D.; Domínguez, E.; Ortega, F.; Tellitu, I. *Tetrahedron Asymmetry* **1998**, *9*, 151–155.

28. Benningshof, J. C. R.; Blaauw, R. H.; Ginkel, A. E.; Maarseveen, J. H.; Rutjes, F. P. J. T.; Hiemstra, H. *J. Chem. Soc. Perkin Trans. I* **2002**, 1693–1700.

29. Alvaro, G.; Fabio, R. D.; Gualandi, A.; Savoia, D. *Eur. J. Org. Chem.* **2007**, 5573–5582.

30. Hiroshi, K.; Mikio, S.; Yoshio, O. *PCT. Int. Appl.* 9417079, **1994**.