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Cu-catalyzed asymmetric Henry reaction promoted by chiral camphor Schiff bases

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ABSTRACT

Five novel chiral camphor Schiff bases have been synthesized and utilized as ligands in asymmetric Henry reaction between nitromethane and aldehydes. The diastereoisomeric Schiff bases **5a** and **5a'** were separated successfully and gave completely different absolute configurations in the reaction. The reactions were carried out with CuCl-Schiff base **5a** complex under mild condition with good yields and enantioselectivities. This is the first time that camphor-derivated Schiff bases were used as ligands in asymmetric Henry reaction.

1. Introduction

The Henry (nitroaldol) reaction is an attractive C—C bond-forming reaction in which a nitroalkane compound is added to an aldehyde or ketone to obtain primarily a β-nitroalcohol, which may be subsequently converted into synthetically useful derivatives such as carboxylic acids, aldehydes, α-hydroxy ketones, amino alcohols, azides, sulphides and other useful compounds by FGT (functional group transformation) [1]. Significantly, chiral amino alcohols obtained by reduction of chiral β-nitroalcohols have been found widespread utility as chiral ligands in asymmetric catalysis, and as an important building block of natural products as well as pharmaceuticals [2]. Due to the importance of chiral β-nitroalcohols in organic synthesis, considerable efforts have been focused on the development of catalytic enantioselective version of the Henry reaction on the basis of the use of coordinating complexes of transition metals or lanthanides with chiral ligands [3]. In particular, chiral copper complexes have received particular attention in terms of wide structural variability of the chiral ligands (bisoxazolines [4], amino alcohols [5], diamines [6], sulfonamides [7], aminopyridines [8], Schiff bases [9] etc.) low toxicity, low cost, excellent chelating ability, ease of handling and ready availability. Chiral Schiff bases and their complexes with transition metals are one of the most studied chiral catalysts and have been extensively applied in asymmetric synthesis [10]. D-(+)-Camphor plays an important role in the asymmetric synthesis in terms of its low cost, rigid structure and convenience to transform into synthetically useful derivatives. Chiral camphor derived Schiff base has already been reported in enantioselective trimethylsilylcyanation of aldehydes [11]. But the report of chiral camphor derived Schiff bases used in enantioselective Henry reaction is still rare. We have paid much attention to modifying the novel chiral frame of camphor and studying their applications in asymmetric reaction [12]. Therefore, the development of new chiral camphor Schiff bases and investigation on its activities in Cu-catalyzed enantioselective Henry reaction are proceeding in our laboratory. The results are recorded here.

2. Experimental

2.1. General

All the starting materials and reagents were obtained from commercial sources and used directly without further purification. The solvents were purified by standard techniques. The reactions were monitored by thin layer chromatography (TLC). Flash column chromatography was carried out on silica gel (200–400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AVANCE-300 and Bruker AVANCE-400 spectrometers (with TMS as an internal standard). Melting points were recorded on a melting point apparatus

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and uncorrected. Optical rotations were measured on a Rudolph Autopol IV-T polarimeter in the indicated solvent. Enantiomeric excesses were determined using Shimadzu LC-20AT high performance liquid chromatography with a chiralcel OD-H column.

2.2. General procedure for the preparation of diastereoisomers **5a** and **5a'**

Camphor amino ketone **1** (1.53 g, 10 mmol) was added to a 50 mL round-bottomed flask containing 10 mL methanol, then cooled to −15 °C. Sodium borohydride (0.95 g, 25 mmol) was slowly added portionwise to the flask over 20 min. The mixture was stirred overnight at −15 °C, then warmed to room temperature naturally and stirred for additional 3 h, subsequently, removed the methanol under reduced pressure, added the H_2O (10 mL), and extracted with dichloromethane (3 × 10 mL). The combined organic solution was dried over Na_2SO_4, filtered and concentrated under vacuum. The mixed diastereoisomer of amino alcohol **2** was obtained (1.29 g, 83%).

The produced diastereoisomeric amino alcohol **2** (0.78 g, 5 mmol), the 4-hydroxy-salicylaldehyde **4a** (0.69 g, 5 mmol) and anhydrous sodium sulfate (1.42 g, 10 mmol) were suspended in dry ethanol (35 mL). The mixture was stirred at reflux for 12 h, and then the solvent was evaporated under reduced pressure to obtain crude product. Diastereoisomer **5a** and **5a'** were obtained in 74% (1.02 g) and 20% (0.28 g) yield by purification the crude product through flash column chromatography on a silica gel using petroleum ether and ethyl acetate as eluent.

2.2.1. 4-(((1S,2R,4R)-2-Hydroxy-7,7-dimethylbicyclo[2.2.1]heptan-1-ylimino)methyl)benzene-1,3-diol **5a**

Pale yellow solid, 1.02 g, yield: 74%, mp: 220–221.8 °C, $[\alpha]_D^{20}$ = −174.59°(c0.09, CH_2Cl_2); ^{1}H NMR (400 MHz, DMSO) δ 14.63 (s, 1H), 9.90 (d, J = 22.4 Hz, 1H), 8.26 (d, J = 6.0 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 6.09 (dd, J = 8.8, 2.0 Hz, 1H), 5.98 (d, J = 2 Hz, 1H), 5.24–5.25 (m, 1H), 3.75–3.78 (m, 1H), 1.91–1.94 (m, 1H), 1.76–1.83 (m, 4H), 1.19–1.31 (m, 2H), 1.12 (s, 3H), 0.81 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 171.6, 163.0, 162.2, 134.2, 111.2, 105.9, 103.6, 75.6, 71.4, 47.3, 42.4, 40.4, 28.44, 26.6, 19.7, 19.7. HRMS (ESI, M + H$^+$) calcd. for $C_{16}H_{22}NO_3$ 276.1594, found 276.1599.

2.2.2. 4-(((1S,2S,4R)-2-Hydroxy-7,7-dimethylbicyclo[2.2.1]heptan-1-ylimino)methyl)benzene-1,3-diol **5a'**

Pale yellow solid, 0.28 g, yield: 20%, mp: 226.4–227.8 °C, $[\alpha]_D^{20}$ = −216°(c1.0, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO) δ 14.65 (s, 1H), 9.92 (s, 1H), 8.24 (s, 1H), 7.21 (d, J = 8.4 Hz, 1H), 6.24 (dd, J = 8.4, 2.3 Hz, 1H), 6.14 (d, J = 2.2 Hz, 1H), 4.97(d, J = 5.3 Hz, 1H), 4.15 (t, J = 4.9 Hz, 1H), 2.25–2.31 (m, 2H), 1.75–1.90 (m, 1H), 1.69–1.71 (m, 1H), 1.42–1.49 (m, 2H), 1.08 (d, J = 3.4 Hz, 1H), 1.05 (s, 3H), 0.85 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 166.1, 163.9, 162.1, 133.8, 112.1, 106.9, 103.1, 74.8, 73.3, 49.1, 42.9, 40.6, 28.1, 21.9, 20.2, 18.9. HRMS (ESI, M + H$^+$) calcd. for $C_{16}H_{22}NO_3$ 276.1600, found 276.1599.

2.3. General procedure for the preparation of the chiral camphor amino alcohol **2a** [12]

Solid $CeCl_3{\cdot}7H_2O$ (2.60 g, 7 mmol) was added to a solution of the chiral camphor isocyanate **3** (5.01 g, 28 mmol) in 100 mL of dry methanol in 250 mL single-necked flask at 0 °C. The mixture was cooled to −78 °C, slowly added solid sodium borohydride (5.30 g, 140 mmol) portionwise over 1 h, then continuously stirred at −78 °C for one more hour. After that, the reaction mixture was warmed to −40 °C and continuously stirred for 2 h, then naturally warmed to 25 °C. 6 N KOH (50 mL) was added to the remaining slurry which was obtained by removing the methanol from the reaction mixture under reduced rotation. The resulting mixture was heated to reflux for 3 h, cooled to room temperature, and extracted with dichloromethane (100 mL) for three times. The combined organic phases were dried over anhydrous sodium sulfate, filtered, concentrated to obtain a white crude camphor amino alcohol. The optically pure camphor amino alcohol **2a** (2.83 g, 65%) was obtained after separating the crude camphor amino alcohol by column chromatography.

2.4. General procedure for the preparation of the chiral camphor Schiff base ligands

Chiral camphor amino alcohol **2a** (0.62 g, 4 mmol), the corresponding salicylaldehyde derivatives **4a**–**4f** (4 mmol) and anhydrous sodium sulfate (1.14 g, 8 mmol) were dissolved in dry ethanol (30 mL). The mixture was stirred at reflux for 12 h, and then the solvent was evaporated under reduced pressure. The crude product was purified to obtain the final product by flash column chromatography on a silica gel using petroleum ether and ethyl acetate as eluent.

2.4.1. 4-(((1S,2R,4R)-2-Hydroxy-7,7-dimethylbicyclo[2.2.1]heptan-1-ylimino)methyl)benzene-1,3-diol **5a**

Pale yellow solid, 0.83 g, yield: 75%.

2.4.2. (1S,2R,4R)-1-(4-Butoxy-2-hydroxybenzylideneamino)-7,7-dimethylbicyclo-[2.2.1]heptan-2-ol **5b**

Yellow solid, 1.03 g, yield: 78%, mp: 78–79.2 °C, $[\alpha]_D^{20}$ = −197.67°(c1.0, CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.21 (s, 1H), 7.54 (s, 1H), 6.61–6.64 (m, 1H), 5.98–6.01 (m, 2H), 5.12 (s, 1H), 3.83–3.89 (m, 3H), 1.94–1.96 (m, 1H), 1.66–1.85 (m, 6H), 1.39–1.44 (m, 2H), 1.15–1.20 (m, 5H), 0.86–0.90 (m, 3H), 0.70–0.73 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 164.5, 159.8, 133.3, 110.1, 105.1, 102.0, 75.9, 70.4, 66.5, 47.0, 41.9, 38.9, 30.1, 26.5, 25.8, 18.7, 18.5, 18.2, 12.8. HRMS (ESI, M + H$^+$) calcd. for $C_{20}H_{30}NO_3$ 332.2220, found 332.2225.

2.4.3. (1S,2R,4R)-1-(3,5-Di-tert-butyl-2-hydroxybenzylideneamino)-7,7-dimethylbicyclo[2.2.1]heptan-2-ol **5c**

Yellow solid, 1.28 g, yield: 86%, mp: 149–150 °C, $[\alpha]_D^{20}$ = −51.34°(c0.4, CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.97 (s, 1H), 8.46 (s, 1H), 7.40 (s, 1H), 7.14 (s, 1H), 3.85 (d, J = 6.0 Hz, 1H), 2.15 (s, 1H), 1.88–2.10 (m, 5H), 1.45 (s, 9H), 1.32 (s, 9H), 1.25–1.30 (m, 5H), 0.86 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 158.6, 140.0, 137.1, 127.1, 126.2, 118.1, 78.8, 74.8, 48.1, 43.7, 39.8, 35.1, 34.2, 31.5, 29.5, 28.0, 27.1, 20.2, 20.0. HRMS (ESI, M + H$^+$) calcd. for $C_{24}H_{38}NO_2$ 372.2897, found 372.2906.

2.4.4. (1S,2R,4R)-1-(5-Bromo-2-hydroxybenzylideneamino)-7,7-dimethylbicyclo[2.2.1]heptan-2-ol **5d**

Yellow solid, 1.12 g, yield: 83%, mp: 101.4–105 °C, $[\alpha]_D^{20}$ = −74.56°(c0.98, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.22 (s, 1H), 8.27 (s, 1H), 7.34–7.38 (m, 2H), 6.81 (d, J = 8.8 Hz, 1H), 3.90 (dd, J = 8.0, 3.6 Hz, 1H), 2.46 (s, 1H), 2.04–2.10 (m, 1H), 1.88–2.00 (m, 4H), 1.23–1.34 (s, 5H), 0.84 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.4, 163.0, 139.7, 135.6, 133.8, 120.4, 119.8, 108.7, 78.3, 74.4, 48.4, 43.5, 40.1, 27.7, 27.0, 19.8. HRMS (ESI, M + H$^+$) calcd. for $C_{16}H_{21}BrNO_2$ 338.0750, found 338.0755.