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Scientific paper

Enantioselective Henry Reaction Catalyzed by Chiral Piperazine Derivatives

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Abstract

A series of novel tridentate Schiff bases is synthesized from piperazine-amine and substituted salicylaldehydes, and characterized by spectroscopic methods. These chiral ligands were used to catalyze the addition of nitromethane to various aldehydes in the presence of Cu(II) ions under ambient conditions in good yields (98%) and high enantioselectivities (9:91 *er*).

Keywords: Piperazine; Schiff base; chiral catalyst; enantioselective Henry reaction

1. Introduction

The catalytic asymmetric Henry (nitroaldol) reaction is a very efficient and atom economic method for stereoselective C–C bond formation. The resulting chiral products of this reaction, β-hydroxynitroalkanes, contain two functional groups (hydroxyl and nitro groups) and can be easily transformed into many valuable building blocks in asymmetric organic synthesis. The asymmetric Henry reaction has also been applied to the synthesis of bioactive natural products and pharmaceutical agents.[1–7] Since the Shibasaki group reported the first catalytic asymmetric Henry reaction,[8] a great deal of effort has been devoted to the development of various metal-containing catalysts.[9–13] In particular, Cu(II) complexes of various tridentate ligands have recently been used as chiral catalysts with good enantioselectivity.[14–18]

The piperazine skeleton is a unique structure often found in biologically active compounds. Piperazine based compounds are found in antihistamines, antibiotics, antidepressant and anticancer drugs. Their metal complexes are also successfully used as catalyst in different organic reactions.[19] Transition metal complexes of amine ligands containing piperazine moiety are very stabile form. However, there isn't any report that tridentate Schiff base ligands derived from piperazine are used as catalyst in the asymmetric Henry reaction.

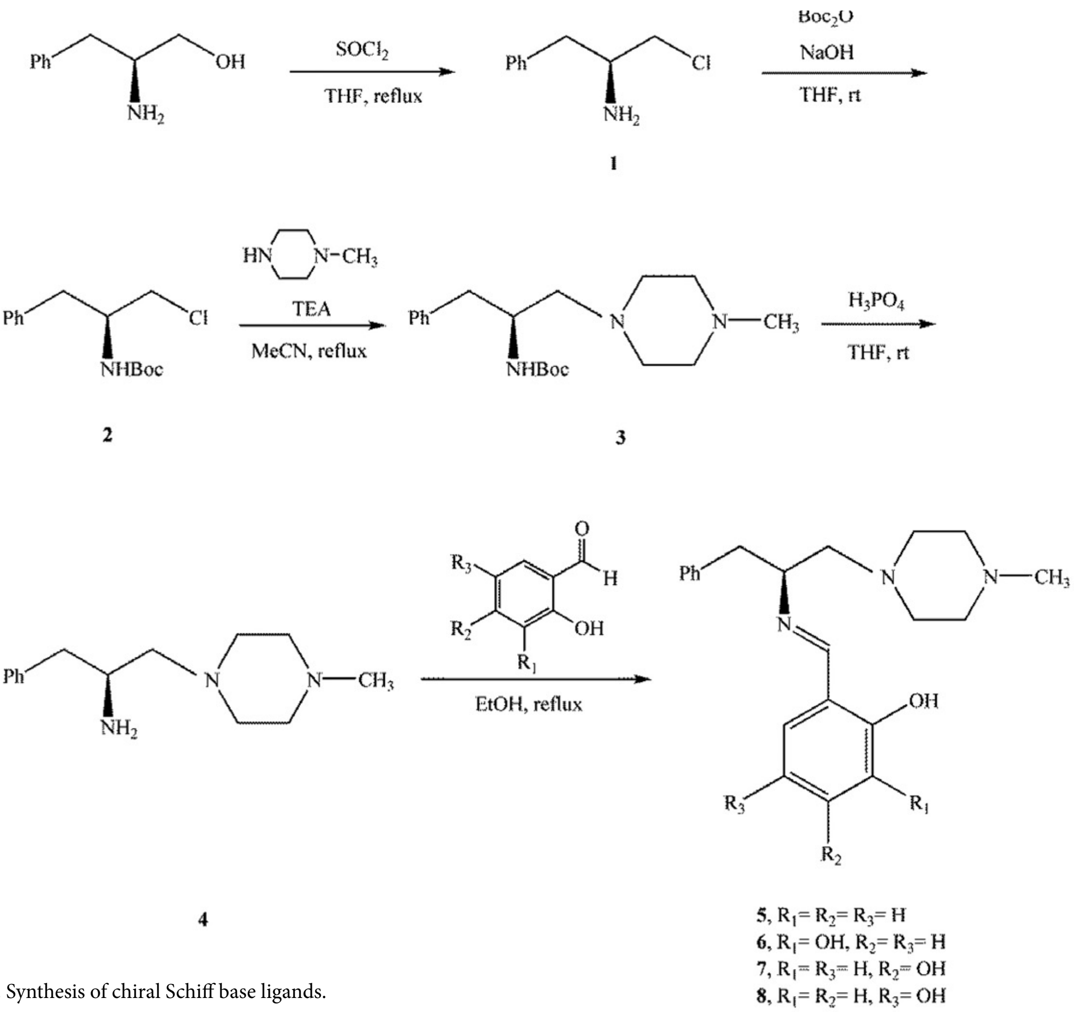
In our previous publications we reported the synthesis and catalytic activity of copper(II) complexes of tridentate Schiff base ligands derived from amino acids.[20–21] Herein, we report novel chiral tridentate Schiff bases which can be readily synthesized from piperazine-amine and can be used as catalysts in enantioselective Henry reactions under mild conditions. We thought that the N group in the ring, which is not coordinated to the metal, will increase the enantioselectivity due to the bifunctional capability of the piperazine derivatives.

2. Results and Discussion

For the purpose of creating structurally different chiral tridentate Schiff bases, (*S*)-1-(4-methylpiperazin-1-yl)-3-phenylpropan-2-amine **4** was reacted with a variety of 2-hydroxybenzaldehydes. Our preparative routes to the piperazine-amine involved protection of amino alcohol derivative followed by addition of piperazine ring and deprotection of Boc group as can be seen in Scheme 1. Subsequent reaction with different aldehydes afforded the desired chiral Schiff base ligands **5–8** in high yields.

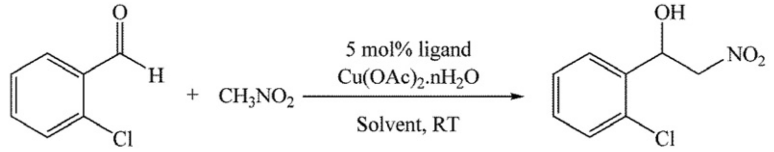
Initial studies were focused on the effect of these ligands **5–8** on the asymmetric Henry reaction by carrying out reactions between 2-chlorobenzaldehyde as a model substrate and nitromethane in the presence of $Cu(OAc)_2 \cdot nH_2O$. The results are summarized in Table 1.

The first experimental results showed that substituents in aromatic ring of the ligand had a significant effect on the enantioselectivity. Ligand **5** was expressly superior



Scheme 1. Synthesis of chiral Schiff base ligands.

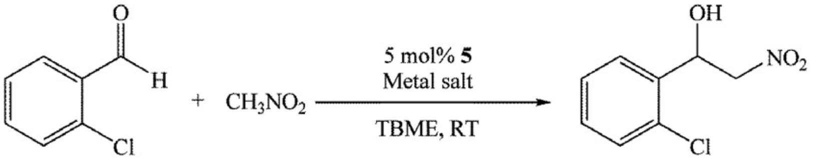
Table 1. Reaction of 2-chlorobenzaldehyde: screening of ligands and solvent effect



Entry	Ligand	Solvent	Time (h)	Yield[a] (%)	*er*[b,c]
1	**5**	TBME	48	98	9:91
2	**5**	*i*-PrOH	48	73	20:80
3	**5**	THF	48	49	41:59
4	**6**	TBME	48	84	10:90
5	**6**	*i*-PrOH	48	67	14:86
6	**6**	THF	48	38	39:61
7	**7**	TBME	48	60	22:78
8	**7**	*i*-PrOH	48	49	24:76
9	**7**	THF	48	45	24:76
10	**8**	TBME	48	n.d.	–
11	**8**	*i*-PrOH	48	50	15:75
12	**8**	THF	48	42	28:72

[a] Isolated yieds after column chromatography; [b] enantiomeric ratio (*er*) determined by HPLC analysis using a Chiralcel OD-H column; [c] the absolute configuration of the major product was assigned as *S* by comparison with the literature values;[22–24] n.d.: not determined.

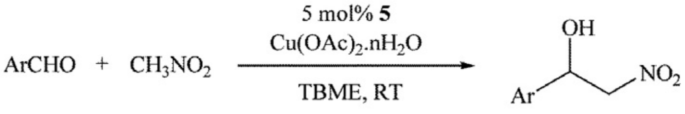
Table 2. Optimization of the reaction conditions



Entry	Metal Salt	Temp. (°C)	Time (h)	Yield[a] (%)	*er*[b,c]
1	Copper(II) benzoate	RT	48	75	9:91
2	Copper(II) formate	RT	48	n. d.	–
3	Copper(II) acetate	RT	48	98	9:91
4	Copper(II) acetate	0	48	52	27:73
5[d]	Copper(II) acetate	RT	48	74	42:58

[a] Isolated yieds after column chromatography; [b] enantiomeric ratio (*er*) determined by HPLC analysis using a Chiralcel OD-H column; [c] the absolute configuration of the major product was assigned as *S* by comparison with the literature values;[22–24] [d] with 10 mol% ligand and $Cu(OAc)_2$ loading; n.d.: not determined.

Table 3. Substrate scope



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Entry	ArCHO	Product	Time (h)	Yield[a]	*er*[b]	Config.[c]
1	2-Chlorobenzaldehyde	**9a**	48	98	9:91	*S*
2	2-Bromobenzaldehyde	**9b**	48	83	15:85	*S*
3	2-Methoxybenzaldehyde	**9c**	48	89	10:90	*S*
4	3-Nitrobenzaldehyde	**9d**	48	71	51:49	*S*
5	Benzaldehyde	**9e**	96	92	21:79	*S*
6	4-Methylbenzaldehyde	**9f**	120	85	35:65	*S*
7	4-Ethylbenzaldehyde	**9g**	120	60	24:76	n. d.
8	4-Methoxybenzaldehyde	**9h**	120	68	64:36	*R*
9	4-Chlorobenzaldehyde	**9i**	48	88	13:87	*S*

[a] Isolated yieds after column chromatography; [b] enantiomeric ratio (*er*) determined by HPLC analysis using a Chiralcel OD-H column; [c] the absolute configuration of the major product was assigned by comparison with the literature values;[22–24] n.d.: not determined.

among the other ligands **6–8** in terms of *er* values. Next, *tert*-butyl methyl ether was found to be the best solvent for enantioselective nitroaldol reaction. The best results were observed when substrate was stirred for 48 h in the presence of 5 mol% **5** and $Cu(OAc)_2{\cdot}nH_2O$ at room temperature in TBME (Table 1, entry 1).

After the selection of the ligand for the catalyst system and the solvent, the reaction parameters, including copper salt, temperature and catalyst loading, were optimised. As can be seen from Table 2, surprisingly, when the reaction was performed using copper(II) formate, product formation was not observed (entry 2). However, when copper(II) benzoate and copper(II) acetate were used in the reaction, high *er* values were observed (entries 1, 3). These results show that carboxylate counter ion in copper salt is very effective in the copper(II) catalysed enantioselective Henry reaction. Afterward, the catalyst loadings were tested (entries 3, 5) and 5 mol% was found to afford the best results. In addition, room temperature is an optimal reaction temperature (entries 3, 4).

Finally, with the optimised conditions, the scope of the substrate was investigated using a variety of aromatic aldehydes (Table 3). Moderate to good enantiomeric ratio and yield of the desired β-hydroxynitroalkanes were obtained. The data clearly showed that the substrates with *ortho*-substituent (entries 1–3) gave seriously higher enantioselectivities than other. These increases in enantioselectivity are possibly due to the geometry of the substrate having a great and important role in the mechanism.

3. Experimental

All chemicals were purchased from Merck, Sigma-Aldirch, Alfa Aesar, or Fluka and were used without any purification. Silica gel F_{254} (Merck 5554) precoated plates were used for thin layer chromatography. For column chromatography, silica gel 60 (Merck 7743) was used. IR spectra were recorded using a Perkin Elmer 100 FTIR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were obtained by using a 400 MHz Varian NMR spectrometer at ambient temperature. Optical rotations were determined using a Rudolph Research Analytical AUTOPOL I automatic polarimeter. HPLC analysis was carried out on Agilent Technologies 1200 series with chiral stationary phase column (Chiralcel OD-H). Elemental analyses were performed on a Leco CHNS-932 elemental analyzer. High resolution mass spectra (HRMS) were measured on a Waters Synapt G1 mass spectrometer using ESI-TOF ionization. Compound **2** was prepared according to the literature method.[25]

Preparation of (*S*)-*tert*-butyl (1-benzyl-2-chloroethyl) carbamate (2). $SOCl_2$ (0.3 mL, 4 mmol) was added dropwise to a solution of (*S*)-2-amino-3-phenyl-1-propanol (150 mg, 1 mmol) in THF (10 mL) at 0 °C and the resulting solution was refluxed for 12 h. Then the solvent was evaporated in vacuo and the residue **1** was used without purification. To a solution of **1** and NaOH (88 mg, 2.2 mmol) in THF (10 mL) was added di-*tert*-butyl dicarbonate (Boc_2O) (240 mg, 1.1 mmol). The reaction mixture was stirred at room temperature for 24 h. Evaporation of the solvent gave a residue that was purified with column chromatography (1:8 ethyl acetate:hexane) to give the title compound as light yellow crystals. Yield 94%, mp 83–84 °C. IR (KBr) ν 3339, 2978, 1691, 1528, 1169 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.24 (m, 5H), 4.80 (br s, 1H), 4.12 (br s, 1H), 3.63–3.47 (dd, J = 3.6, 11.2 Hz, 2H), 2.93–2.85 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 154.98, 137.01, 129.16, 128.58, 126.82, 79.76, 51.90, 46.88, 37.77, 28.32. Anal. Calcd for $C_{14}H_{20}ClNO_2$: C, 62.33; H, 7.47; N, 5.19. Found: C, 61.40; H, 7.17; N, 5.13.

Preparation of (*S*)-*tert*-butyl [1-(4-methylpiperazin-1-yl)-3-phenylpropan-2-ylcarbamate] (3). To a solution of **2** (50 mg, 0.185 mmol) in acetonitrile under nitrogen atmosphere was added triethylamine (0.078 mL, 0.555 mmol) and 1-methylpiperazine (185.3 mg, 1.85 mmol). The reaction mixture was refluxed for 12 h. After completion of the reaction (as monitored by TLC), the solvent was evaporated in vacuo. The residue was purified with column chromatography (1:1 ethyl acetate:hexane) to give the title compound as an off-white solid. Yield 86%, mp 125–127 °C. IR (KBr) ν 3385, 2944, 1681, 1508, 1166 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29–7.16 (m, 5H), 4.58 (br s, 1H), 3.92 (br s, 1H), 2.85 (d, J = 6 Hz, 2H), 2.41–2.26 (m, 10H), 2.24 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 155.54, 137.77, 129.65, 128.21, 126.22, 79.06, 60.44, 55.13, 53.28, 48.54, 45.99, 28.40. Anal. Calcd for $C_{19}H_{31}N_3O_2$: C, 68.43; H, 9.37; N, 12.60. Found: C, 66.42; H, 8.92; N, 12.74.

Preparation of (*S*)-1-(4-methylpiperazin-1-yl)-3-phenylpropan-2-amine (4). The compound **3** (100 mg, 0.3 mmol) was dissolved in 3 mL THF and 3 mL 85% H_3PO_4 was added dropwise to the solution. The reaction was stirred overnight at room temperature. To terminate the reaction, 5 mL distilled water was added and the reaction mixture was neutralized with saturated NaOH. The solution was extracted with ethyl acetate. The organic phase was dried using Na_2SO_4 and evaporated in vacuo. The residue was purified with column chromatography (1:1 methanol:ethyl acetate) to give the title compound as a yellow oil. Yield 95%. IR (NaCl) ν 3362, 2800, 1601 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.19 (m, 5H), 3.22–3.15 (m, 1H), 2.74–2.71 (dd, J = 4.8, 13.6 Hz, 1H), 2.50–2.29 (m, 11H), 2.27 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 139.18, 129.22, 128.38, 126.23, 64.71, 55.21, 53.42, 49.22, 45.91, 42.07.

General Procedure for The Preparation of Chiral Schiff Bases 5–8

A solution of **4** (1 mmol) and the appropriate aldehyde (1 mmol) in 10 mL ethanol was refluxed until the aldehyde has been consumed. The solvent was evaporated in vacuo and crude product was purified with flash chromatography.

2-((*E*)-{[(1*S*)-1-Benzyl-2-(4-methylpiperazin-1-yl) ethyl]imino}methyl)phenol (5). Yellow crystals, yield 96%, mp 88–90 °C, = $[\alpha]^{19}_{D}$ –120 (*c* 0.25, CH_3OH). IR (KBr) ν 3213, 2796, 1630, 1581 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.28–7.13 (m, 7H), 6.82 (d, J = 8 Hz, 1H), 6.77 (t, J = 7.6 Hz, 1H), 3.71–3.64 (m, 1H), 3.07–3.02 (dd, J = 4, 16 Hz, 1H), 2.84–2.79 (dd, J = 8, 12 Hz, 1H), 2.65–2.62 (dd, J = 4, 8 Hz, 2H), 2.55–2.34 (m, 8H) 2.23 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 165.22, 162.38, 138.17, 132.29, 131.42, 129.30, 128.85, 127.90, 125.95, 118.32, 117.79, 116.74, 67.67, 62.61, 54.20, 52.54, 44.76, 40.41. HRMS ESI-TOF (*m/z*): $[M + H]^+$ calcd for $C_{21}H_{28}N_3O$: 338.2232. Found: 338.2229. HPLC (hexane:*i*-PrOH (95:15), wavelength: 267 nm, flow rate: 1.0 mL/min): t_r = 10.627 min.

3-((*E*)-{[(1*S*)-1-Benzyl-2-(4-methylpiperazin-1-yl) ethyl]imino}methyl)benzene-1,2-diol (6). Yellow solid, yield 87%, mp 101–102 °C, = $[\alpha]^{19}_{D}$–102 (*c* 0.26, CH_3OH). IR (KBr) ν 3439, 2808, 1632, 1540 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.24–7.14 (m, 5H), 6.83–6.81 (dd, J = 1.6, 7.6 Hz, 1H), 6.65–6.63 (dd, J = 1.6, 8 Hz, 1H), 6.57 (t, J = 8 Hz, 1H), 3.75–3.68 (m, 1H), 3.07–3.03 (dd, J = 4, 12 Hz, 1H), 2.86–2.80 (dd, J = 8, 12 Hz, 1H), 2.65–2.62 (dd, J = 2.8, 5.2 Hz, 2H), 2.56–2.37 (m, 8H), 2.23 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 165.43, 153.26, 146.04, 138.02, 129.32, 128.00, 126.06, 122.14, 117.55, 117.04, 116.94, 66.87, 62.53, 54.45, 52.69, 44.54, 40.24. HRMS ESI-TOF (*m/z*): $[M + H]^+$ calcd for $C_{21}H_{28}N_3O_2$: 354.2182. Found: 354.2177. HPLC (hexane:*i*-PrOH (95:15), wavelength: 267 nm, flow rate: 1.0 mL/min): t_r = 15.218 min.

4-((*E*)-{[(1*S*)-1-Benzyl-2-(4-methylpiperazin-1-yl)ethyl] imino}methyl)benzene-1,3-diol (7). Pale yellow solid, yield 92%, mp 112–114 °C, = $[\alpha]_D^{19}$ −104 (*c* 0.25, CH_3OH). IR (KBr) *ν* 3384, 2811, 1624, 1601 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.80 (s, 1H), 7.29–7.15 (m, 6H), 6.92 (d, *J* = 12 Hz, 1H), 6.11 (d, *J* = 8 Hz, 1H), 3.80–3.75 (m, 1H), 3.06–3.01 (dd, *J* = 8, 16 Hz, 1H), 2.88–2.82 (dd, *J* = 8, 12 Hz, 1H), 2.64–2.54 (m, 10H), 2.31 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 174.16, 162.85, 137.45, 134.61, 129.20, 128.11, 126.23, 109.91, 107.82, 62.62, 61.82, 54.53, 52.64, 44.54, 39.53. HRMS ESI-TOF (*m/z*): $[M + H]^+$ calcd for $C_{21}H_{28}N_3O_2$: 354.2182. Found: 354.2165. HPLC (hexane:*i*-PrOH (95:15), wavelength: 267 nm, flow rate: 1.0 mL/min): t_r = 15.302 min.

2-((*E*)-{[(1*S*)-1-Benzyl-2-(4-methylpiperazin-1-yl) ethyl]imino}methyl)benzene-1,4-diol (8). Light brown solid, yield 79%, mp 142–144 °C, = $[\alpha]_D^{19}$ −112 (*c* 0.25, CH_3OH). IR (KBr) *ν*: 3193, 2810, 1636, 1591 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.94 (s, 1H), 7.24–7.13 (m, 5H), 6.78–6.75 (dd, *J* = 4, 8 Hz, 1H), 6.69 (d, *J* = 8 Hz, 1H), 6.58 (d, *J* = 4 Hz, 1H), 3.66–3.60 (m, 1H), 3.05–3.01 (dd, *J* = 4, 12 Hz, 1H), 2.82–2.76 (dd, *J* = 8, 12 Hz, 1H), 2.65–2.62 (dd, *J* = 2.8, 5.2 Hz, 2H), 2.60–2.44 (m, 8H), 2.30 s (3H). ^{13}C NMR (400 MHz, $CDCl_3$) *δ* 164.91, 154.20, 149.03, 138.35, 129.37, 128.99, 127.90, 125.93, 119.65, 118.49, 116.74, 116.23, 68.52, 62.88, 54.41, 54.13, 52.74, 44.54, 40.60, 40.31. HRMS ESI-TOF (*m/z*): $[M + H]^+$ calcd for $C_{21}H_{28}N_3O_2$: 354.2182. Found: 354.2180. HPLC (hexane:*i*-PrOH (95:15), wavelength: 267 nm, flow rate: 1.0 mL/min): t_r = 17.391 min.

General Procedure for the Asymmetric Henry Reaction

The chiral Schiff base ligand **5–8** (0.01 mmol) and $Cu(OAc)_2 \cdot nH_2O$ (0.01 mmol) were allowed to stir in 2 mL of solvent at room temperature for 2 h. A color of solution change from light green to dark green was observed during this time. Subsequently, the appropriate aldehyde (0.2 mmol) and nitromethane (2 mmol) were added into the solution. The reaction mixture was stirred until most of the aldehyde has been consumed. The volatile components were evaporated in vacuo and the crude product was purified with column chromatography (1:5 ethyl acetate:hexane) to give the desired β-hydroxynitroalkane. Enantiomeric ratio (*er*) was determined by using HPLC with Chiracel OD-H column.

(S)-1-(2-Chlorophenyl)-2-nitroethanol (9a).[22] Colorless oil, yield 98%. HPLC conditions: hexane:*i*-PrOH (93:7), wavelength: 267 nm, flow rate: 0.8 mL/min, t_{minor} = 14.3 min, t_{major} = 14.8 min, 9:91 *er*.

(S)-1-(2-Bromophenyl)-2-nitroethanol (9b).[22] Colorless oil, yield 83%. HPLC conditions: hexane:*i*-PrOH (85:15), wavelength: 267 nm, flow rate: 1.0 mL/min, t_{minor} = 9.2 min, t_{major} = 9.7 min, 15:85 *er*.

(S)-1-(2-Methoxyphenyl)-2-nitroethanol (9c).[22] Yellow oil, yield 89%. HPLC conditions: hexane:*i*-PrOH (90:10), wavelength: 267 nm, flow rate: 1.0 mL/min, t_{minor} = 11.8 min, t_{major} = 12.7 min, 10:90 *er*.

(S)-1-(3-Nitrophenyl)-2-nitroethanol (9d).[24] Yellow oil, yield 71%. HPLC conditions: hexane:*i*-PrOH (90:10), wavelength: 267 nm, flow rate: 1.0 mL/min, t_{major} = 28.2 min, t_{minor} = 31.0 min, 51:49 *er*.

(S)-1-Phenyl-2-nitroethanol (9e).[23] Yellow oil, yield 92%. HPLC conditions: hexane:*i*-PrOH (90:10), wavelength: 267 nm, flow rate: 1.0 mL/min, t_{minor} = 14.1 min, t_{major} = 15.1 min, 21:79 *er*.

(S)-1-(4-Methylphenyl)-2-nitroethanol (9f).[22] Yellow crystals, yield 85%. HPLC conditions: hexane:*i*-PrOH (90:10), wavelength: 267 nm, flow rate: 1.0 mL/min, t_{minor} = 12.9 min, t_{major} = 15.4 min, 35:65 *er*.

(S)-1-(4-Ethylphenyl)-2-nitroethanol (9g).[22] Yellow oil, yield 60%. HPLC conditions: hexane:*i*-PrOH (90:10), wavelength: 267 nm, flow rate: 1.0 mL/min, t_{minor} = 11.6 min, t_{major} = 14.2 min, 24:76 *er*.

(R)-1-(4-Methoxyphenyl)-2-nitroethanol (9h).[22] Yellow oil, yield 68%. HPLC conditions: hexane:*i*-PrOH (90:10), wavelength: 267 nm, flow rate: 1.0 mL/min, t_{major} = 19.9 min, t_{minor} = 24.3 min, 64:36 *er*.

(S)-1-(4-Chlorophenyl)-2-nitroethanol (9i).[22] Colorless oil, yield 88%. HPLC conditions: hexane:*i*-PrOH (90:10), wavelength: 267 nm, flow rate: 1.0 mL/min, t_{minor} = 14.0 min, t_{major} = 16.7 min, 13:87 *er*.

4. Conclusions

Four novel tridentate Schiff bases have been prepared from a chiral (*S*)-2-amino-3-phenyl-1-propanol, which can be used in the asymmetric Henry reaction. Compared with other catalytic systems, the advantages of our method are mild reaction conditions, low loading of the catalyst (5 mol %) necessary, no need for additives and without any precautions against the presence of air and moisture needed.

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Supplementary Data

^{1}H and ^{13}C NMR spectra of compounds **2–8** and HPLC chromatograms of compounds **5–8**.

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Povzetek

Iz piperazin-aminov in substituiranih salicilaldehidov smo sintetizirali novo serijo tridentatnih Schiffovih baz ter jih karakterizirali s spektroskopskimi metodami. Tako pripravljene kiralne ligande smo uporabili kot katalizatorje za adicijo nitrometana na različne aldehide, ki smo jo izvedli ob dodatku Cu(II) ionov pri sobnih pogojih, produkte pa smo pripravili z dobrimi izkoristki (98 %) in visokimi enantioselektivnostmi (9:91 *er*).