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Synthesis of novel chiral Schiff-base ligands and their application in asymmetric nitro aldol (Henry) reaction

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Abstract—Chiral Schiff-bases prepared from chiral amino alcohols catalyze the enantioselective Henry (nitro aldol) reaction between nitromethane and *p*-nitrobenzaldehyde in the presence of $Cu(OTf)_2$ and $Zn(OTf)_2$. $Zn(OTf)_2$ promoted the reaction yield, while $Cu(OTf)_2$ promoted the enantiomeric excess. The highest enantioselectivities were observed with ligand **3** (44% ee) and ligand **5** (47% ee).

1. Introduction

Among the various C–C bond forming reactions, the nitro aldol 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 is 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. However, the wide applicability of this transformation, until recently, was impaired due to the unavailability of suitable catalysts for imparting a definite stereochemistry to the newly generated stereogenic centers. The first asymmetric version of the Henry reaction was reported by Shibasaki in 1992.[2] Since then, interest in this area has been considerably expanded upon with various reports continuously appearing in the literature on the development of various metal and nonmetal based catalysts for the asymmetric Henry reaction.

In these processes, different chiral catalysts were developed, such as those based upon BINOL by Shibasaki,[2] bis(oxazoline) by Evans and Jørgensen,[3] cinchona alkaloids by Corey,[4] dinuclear zinc complexes by Trost,[5] Salen co-complexes by Yamada[6] and amino alcohols by Palomo.[7,8] A chiral Schiff-base is one of the more frequently used catalysts, especially in asymmetric cyclopropanation.[9,10] The first asymmetric Henry (nitro aldol) reaction catalyzed by chiral copper Schiff-base complexes was first reported by Zhou.[11] Two reviews have appeared in the recent literature based on recent advances in the asymmetric nitro aldol (Henry) reaction.[12,13] Herein we report the novel synthesis of chiral Schiff-base and enantioselective nitro aldol reactions.

2. Result and discussion

In order to create a structurally different chiral Schiff-base, *p*-hydroxy benzaldehyde was reacted with diethyleneglycolditosylate and 1,4-bis(bromomethyl)benzene in CH_3CN/K_2CO_3 (Scheme 1). To synthesize the desired chiral Schiff-base ligand (Schemes 2 and 3) the two chiral amino alcohols [(1*S*,2*R*)-2-amino-1,2-diphenylethanol and (*R*)-(−)-phenylglycinol] were used as a chiral source. The reaction of the dialdehyde with the two chiral amino alcohols in EtOH gave chiral Schiff-base compounds. All compounds were characterized with ^1H NMR, ^{13}C NMR and elemental analysis.

According to reaction conditions described by Zhou[11] and Feng[14] for the chiral Schiff-base-copper catalyzed Henry reaction, the reaction was initially carried out at room temperature in ethanol using 10 mol % catalyst and triflate as the source for metal ion for 40 h; these reaction conditions were applied to all entries. When Zn(II) triflate was used the reaction yield was higher than with copper(II) triflate, although the enantiomeric excess did decrease. The results showed that copper(II) was the best promoter. In two cases, the reaction gave the corresponding nitroalkene, resulting in elimination. Ligands **3** and **5** were found to be superior

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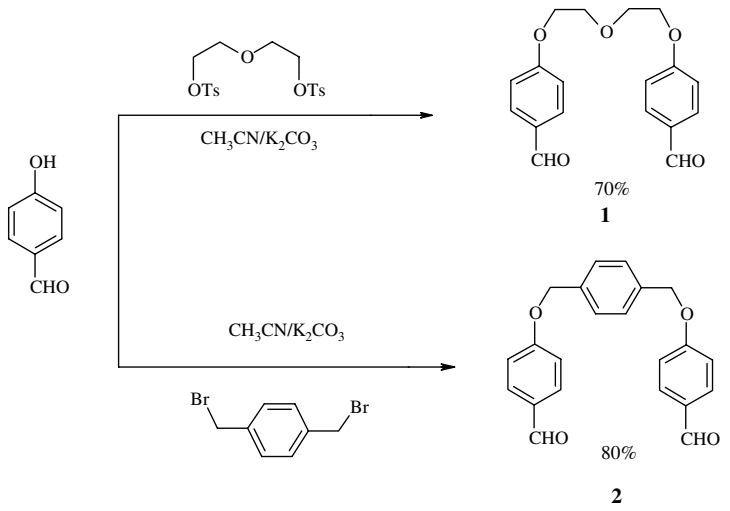
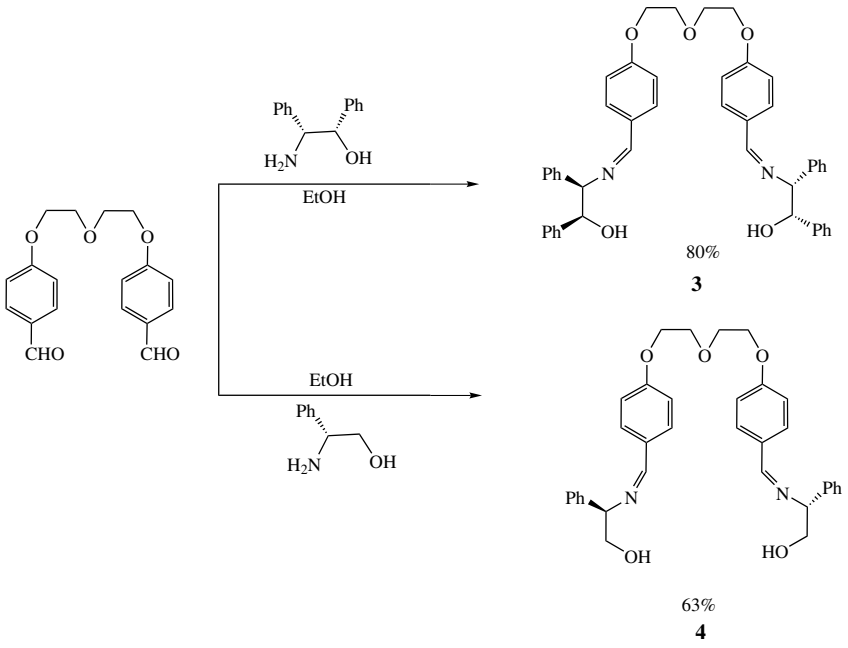


Scheme 1.



Scheme 2.

to other ligands tested (entries 1 and 5). This may be attributed to the steric hindrance of two phenyl groups on the ligands. Furthermore, this characteristic feature may also effect the configuration of adducts (*R*) (Table 1).

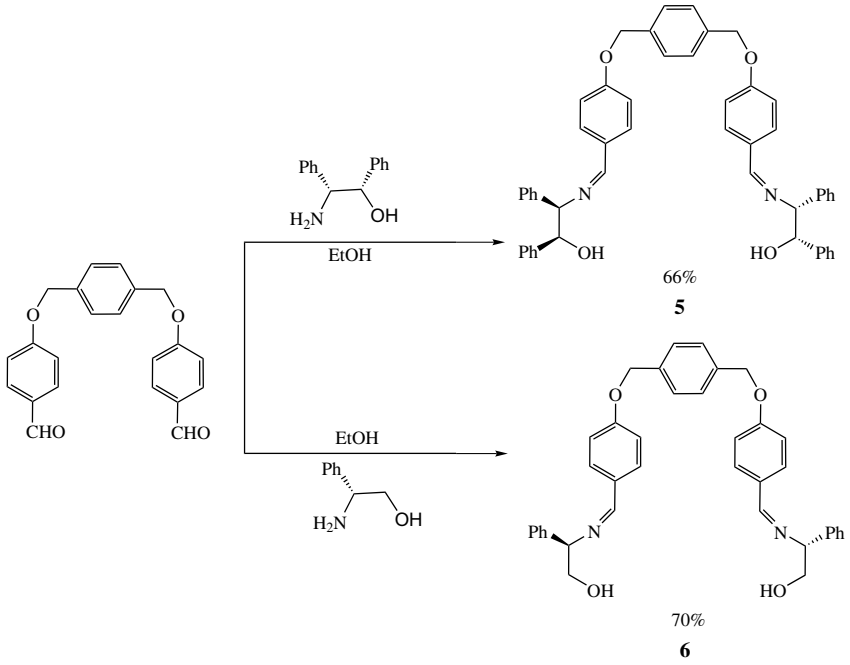
3. Conclusion

In conclusion, we have synthesized novel chiral Schiff-base ligands which can be used in enantioselective metal-catalyzed reactions. The study of the scope of this reaction, the preparation of new ligands and their application to the Henry reaction is currently in progress.

4. Experimental

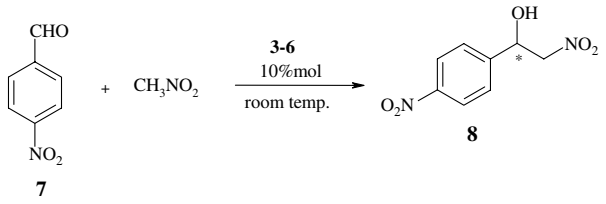
4.1. General information

All chemicals were of reagent grade unless otherwise specified. Melting points were determined with a GALLENKAMP Model apparatus with open capillaries and are uncorrected. Infrared spectra were recorded on a MATTSON Model 1000 spectrophotometer. The elemental analyses were obtained with CARLO-ERBA Model 1108 apparatus. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker DPX-400 high performance digital FT-NMR spectrometer, with tetramethylsilane as the internal standard for solutions in deuteriochloroform.



Scheme 3.

Table 1. Asymmetric nitro aldol (Henry) reaction between nitromethane and *p*-nitrobenzaldehyde catalyzed by chiral Schiff-base[a]



Entry	Cat.	$M(OTf)_2$	Time (h)	Solvent	Yield[b]	ee[c] (%)	Config.[d]
1	**3**	$Cu(OTf)_2$	40	EtOH	56	44	(*R*)
2	**3**	$Zn(OTf)_2$	40	EtOH	62	8	(*S*)
3	**4**	$Cu(OTf)_2$	40	EtOH	45	30	(*S*)
4	**4**	$Zn(OTf)_2$	40	EtOH	57	18	(*S*)
5	**5**	$Cu(OTf)_2$	40	EtOH	56	47	(*R*)
6	**5**	$Zn(OTf)_2$	40	EtOH	63	11	(*S*)
7	**6**	$Cu(OTf)_2$	40	EtOH	54	27	(*S*)
8	**6**	$Zn(OTf)_2$	40	EtOH	64	17	(*S*)

[a] All reactions were performed on a 0.2 mmol scale of 4-nitrobenzaldehyde in the mixture of 0.8 mL of ethanol and 0.6 mL of nitromethane.
[b] After purification with TLC ethyl acetate/petroleum ether (30:70) R_f: 0.36, lit.:[15] 0.34.
[c] Determined by chiral HPLC using an OD column.
[d] Determined by comparing the HPLC elution order of the enantiomers with an authentic sample according to the literature[14] and also determined by HP Chiral Detector.

J values are given in hertz. Optical rotations were recorded using a PERKIN ELMER Model 341 polarimeter. HPLC measurements were performed with BIORAD instrument. Separations were carried out on Chiralcel OD column (250 × 4.60 mm) with hexane/2-propanol (85:15) as eluent. TLC plates were purchased from Fluka.

4.2. Synthesis of dialdehydes 1 and 2

4.2.1. Compound 1. To a solution of *p*-hydroxybenzaldehyde (8.50 g, 0.07 mol) in 200 mL of CH_3CN were added anhydrous K_2CO_3 (38.4 g, 0.28 mol) and diethyleneglycol ditosylate (10 g, 0.02 mol). The reaction mixture was heated at reflux for 24 h. The CH_3CN was removed and the residue partitioned between CH_2Cl_2 and H_2O. The layers were separated and the organic phase washed sequentially with H_2O, 1 N aq NaOH solution, H_2O, and brine. After drying over $MgSO_4$ and concentration in vacuo, we obtained a white solid (4.8 g, 70%). Mp: 125–127 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 3.98–4.00 (t, 4H, *J* 4.60 Hz), 4.25–4.27 (t, 4H, *J* 4.60 Hz), 7.02–7.04 (d, 4H, *J* 8.40 Hz), 7.83–7.85 (d, 4H, *J* 8.80 Hz), 9.90 (s, 2H); ^{13}C

NMR (100 MHz, $CDCl_3$): δ 67.75, 69.78, 114.86, 130.18, 131.97, 163.71, 190.78; IR: ν 3069, 2947, 2934, 2903, 2889, 2838, 2748, 2638, 2582, 1863, 1683, 1606, 1573, 1510, 1459, 1426, 1266, 1150, 1061, 933, 849, 803, 656, 521; Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.54; H, 5.72.

4.2.2. Compound 2. This compound was prepared in a similar method that was used in compound **1** from *p*-hydroxybenzaldehyde (6.1 g, 0.05 mol), K_2CO_3 (27.6 g, 0.2 mol), and 1,4-bis(bromomethyl) benzene (5.6 g, 0.02 mol) to give a white solid (5.5 g, 80%), mp: 163–165 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.10 (s, 4H), 7.08–7.10 (d, 4H, *J* 8.00 Hz), 7.48–7.49 (d, 4H, *J* 8.00 Hz), 7.85–7.87 (d, 4H, *J* 8.00 Hz), 9.90 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 69.90, 115.15, 127.84, 130.26, 132.01, 136.17, 163.60, 190.74; IR: ν 3082, 2947, 2883, 2826, 2806, 2735, 1683, 1616, 1573, 1510, 1426, 1253, 1163, 996, 894, 829, 803, 650, 616, 560, 503; Anal. Calcd for $C_{22}H_{18}O_4$: C, 76.29; H, 5.24. Found: C, 76.33; H, 5.31.

4.3. Synthesis of chiral Schiff-base ligands 3–6

4.3.1. Ligand 3. To a solution of **1** (0.63 g, 2mmol) in 100 mL of EtOH was added (1*S*,2*R*)-2-amino-1,2-diphenylethanol (1.065 g, 5 mmol). The reaction mixture was heated at reflux for 16 h. The EtOH was removed and the residue washed with ether three times and then crystallized from ethyl acetate to give a solid (2.84 g, 80%), mp: 125–127 °C, $[\alpha]_D^{20} = +12.2$ (*c* 2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.34 (br s, 2H), 3.94–3.96 (t, 4H, *J* 4 Hz), 4.18–4.20 (t, 4H, *J* 4 Hz), 4.47–4.49 (d, 2H, *J* 4 Hz), 5.06–5.07 (d, 2H, *J* 8 Hz), 6.92–6.94 (d, 4H, *J* 8 Hz), 7.25–7.37 (m, 20H), 7.64–7.66 (d, 4H, *J* 8 Hz), 8.04 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 67.55, 69.89, 78.27, 80.90, 126.97, 127.19, 127.45, 127.62, 127.77, 128.17, 128.30, 128.44, 129.38, 129.87, 140.36, 140.75, 160.91, 161.04; IR: ν 3409, 3063, 3031, 2921, 2870, 1946, 1882, 1817, 1754, 1638, 1606, 1516, 1452, 1420, 1382, 1305, 1253, 1170, 1124, 1030, 913, 829, 765, 708, 534; Anal. Calcd for $C_{46}H_{44}N_2O_5$: C, 78.38; H, 6.29; N, 3.97. Found: C, 78.31; H, 6.21; N, 3.84.

4.3.2. Ligand 4. This compound was prepared in a similar method to that used for ligand **3**, from **1** (0.785 g, 2.5 mmol) and (*R*)-(−)-phenylglycinol (0.825 g, 6 mmol), to give the product (1.980 g, 63%). Mp: 121–122 °C, $[\alpha]_D^{20} = +103.2$ (*c* 2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) ppm: δ 2.15 (br s, 2H), 3.88–4.00 (m, 8H), 4.20–4.23 (t, 4H, *J* 4.00 Hz, Ar–OCH_2), 4.46–4.91 (m, 2H), 6.94–6.96 (d, 4H, *J* 8.00 Hz), 7.28–7.48 (m, 10H), 7.72–7.74 (d, 4H, *J* 8 Hz), 8.32 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 67.58, 67.81, 69.91, 76.09, 114.65, 127.39, 127.42, 128.45, 129.15, 130.06, 140.93, 161.04, 162.05; IR: ν 3198, 3055, 3031, 2928, 2877, 2838, 1745, 1638, 1606, 1500, 1465, 1305, 1266, 1170, 1138, 1054, 829, 759, 694, 528; Anal. Calcd for $C_{34}H_{36}N_2O_5$: C, 73.89; H, 6.57; N,5.07. Found: C, 73.94; H, 6.47; N, 5.13.

4.3.3. Ligand 5. This compound was prepared in a similar method to that used in ligand **3** from **2** (0.7 g, 2 mmol) and (1*S*,2*R*)-2-amino-1,2-diphenylethanol (1.0224 g, 4.8 mmol) to give the product (0.7 g, 46%) mp: 122–123 °C, $[\alpha]_D^{20} = +50$ (*c* 2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.76 (br s, 2H), 4.47–4.49 (d, 2H, *J* 8 Hz), 5.06–5.19 (m, 6H, Ar–CH_2, Ar–CHOH), 6.97–6.99 (d, 4H, *J* 8 Hz), 7.24–7.67 (m, 24H), 7.85–7.87 (d, 4H, *J* 8 Hz), 8.05 (s 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 69.73, 78.26, 80.86, 114.82, 127.18, 127.46, 127.74, 127.78, 128.18, 128.24, 128.30, 128.42, 128.50, 129.43, 129.92, 136.53, 140.31, 140.71, 160.85, 161.02; IR: ν 3563, 3409, 3063, 3031, 2908, 2883, 2838, 1882, 1645, 1606, 1516, 1459, 1426, 1387, 1310, 1253, 1170, 1112, 1022, 836, 765, 708, 617, 521; Anal. Calcd for $C_{50}H_{44}N_2O_4$: C, 81.50; H, 6.02; N, 3.80. Found: C, 81.58; H, 6.1; N, 3.72.

4.3.4. Ligand 6. This compound was prepared in a similar method that was used in ligand **3** from **2** (1.73 g, 5 mmol) and (*R*)-(−)phenylglycinol (1.644 g, 12 mmol) to give the product (1.94 g, 70%), mp: 138–140 °C, $[\alpha]_D^{20} = +102.9$ (*c* 2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20 (br s, 2H), 3.89–4.02 (m, 4H), 4.47–4.50 (m, 2H), 5.13 (s, 4H), 6.98–7.01 (d, 4H, *J* 8 Hz), 7.27–7.48 (m, 14H), 7.72–7.74 (d, 4H, *J* 8 Hz), 8.30 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 67.81, 69.73, 76.09, 114.91, 127.38, 127.43, 127.73, 128.55, 129.20, 130.11, 136.52, 140.91, 160.93, 162.06; IR: ν 3178, 3060, 3037, 2934, 2864, 1908, 1645, 1606, 1516, 1459, 1426, 1394, 1317, 1259, 1199, 1073, 1047, 906, 826, 708, 637, 515; Anal. Calcd for $C_{38}H_{36}N_2O_4$: C, 78.06; H, 6.21; N, 4.79. Found: C, 78.12; H, 6.14; N, 4.73.

4.3.5. Typical procedure for the asymmetric Henry reaction. Ligand **5** (14.7 mg, 0.02 mmol) and $Cu(OTf)_2$ (7.2 mg, 0.02 mmol) were added to absolute ethanol (0.8 mL) at room temperature. Stirring was continued for 1 h and then 4-nitrobenzaldehyde (30.2 mg, 0.2 mmol) and nitromethane (0.6 mL) were added to the resulting green solution and stirring continued for 40 h at room temperature. The mixture was concentrated in vacuo. CH_2Cl_2 (2 mL) and HCl (1 M, 5 mL) were added and stirring continued until the green color had disappeared. The mixture was then extracted with CH_2Cl_2 (3 × 10 mL) and the organic extract combined, dried over $MgSO_4$, and evaporated in vacuo. The residue was purified by TLC by using EtOAc/PE (30:70, R_f: 0.36, lit.:[12] 0.34) to afford **8** as a white solid (23.76 mg, 56% yield, 47% ee; Chiralcel OD, hexane/*i*-PrOH 85:15, 0.8 mL min^{-1}, (*R*): t_R(major) = 21.6 min, lit.:[14] 19.7 min, (*S*): t_R(minor) = 26.7 min, lit.:[14] 24.23 min).

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