

Enantioselective nitroaldol (Henry) reaction catalyzed by chiral Schiff-base ligands

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Abstract—Chiral Schiff-bases **2**, **3**, **4** and **5** were designed for the enantioselective nitroaldol (Henry) reaction. The highest enantioselectivity was observed for ligand **4** (82% ee) when CH_2Cl_2 was used as a solvent.

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1. 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 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, until recently, the wide applicability of this transformation was impaired due to the non-availability of suitable catalysts for imparting a definite stereochemistry onto the newly generated stereogenic centres. The first asymmetric version of the Henry reaction was reported by Shibasaki in 1992.² Since then, interest in this area has been expanded upon considerably and various reports have been continuously appearing in the literature with regard to the development of various metal and non-metal based catalysts for the asymmetric Henry reaction.

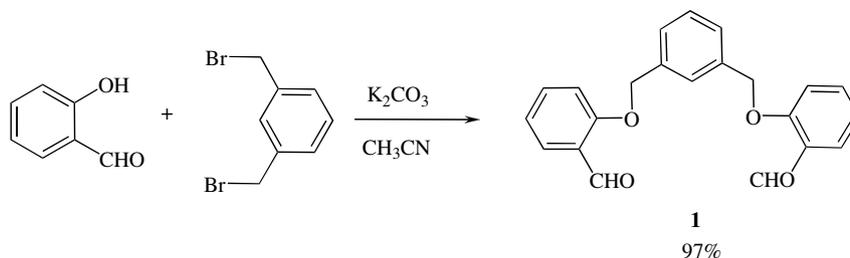
In these processes, different chiral catalysts were developed, such as those based upon BINOL by Shibasaki,² bis(oxazolines) by Evans and Jørgensen,³ cinchona alkaloid by Corey,⁴ dinuclear zinc complexes by Trost,⁵ salen-cocomplexes by Yamada⁶ and amino alcohols by Palomo.^{7,8} A chiral Schiff-base is one of the most frequently used catalysts, especially in asymmetric cyclopropanation.^{9,10} The first asymmetric Henry (nitroaldol) reaction catalyzed by chiral copper Schiff-base complexes was first reported by

Zhou.¹¹ Two reviews have already been appeared in the literature on recent advances in the asymmetric nitroaldol (Henry) reaction.^{12,13} In addition, various reports have been continuously appearing in the literature.^{14–23} We have previously reported the novel synthesis of a chiral Schiff-base and enantioselective nitroaldol reactions.²⁴ In the previous study, the observed enantioselectivities were low. As a result, we decided to improve the catalyst and began with the synthesis of a simple chiral Schiff-base with a phenol group. Finally, to explore the effect of a spacer group, we linked a simple chiral Schiff-base with a spacer group 1,3-bis(bromomethyl) benzene.

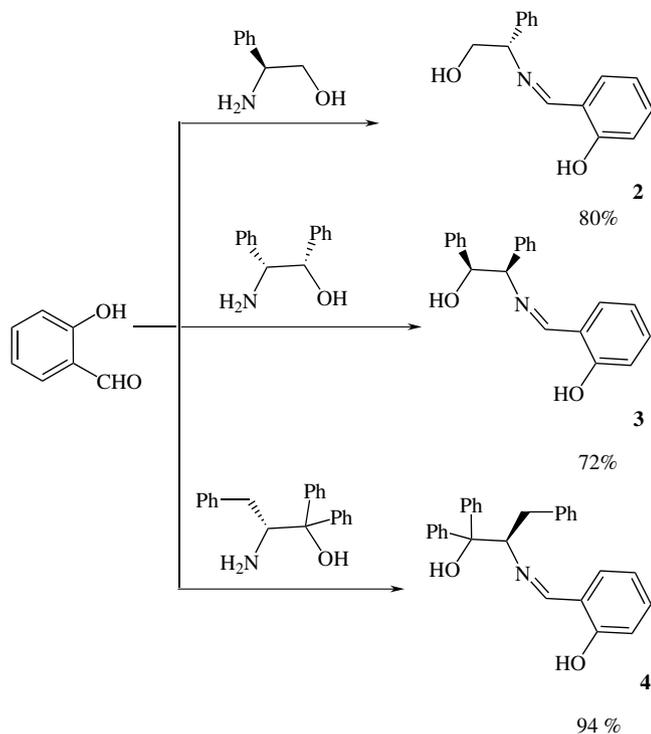
2. Results and discussion

To synthesize structurally simple, chiral Schiff-base, *o*-hydroxybenzaldehyde was chosen as an aldehyde part of the Schiff-base. To synthesize the desired simple chiral Schiff-base ligands, the three commercially available chiral amino alcohols (1*S*,2*R*)-2-amino-1,2-diphenylethanol, (*S*)-(+)-phenylglycinol and (*R*)-(+)-2-amino-1,1,3-triphenylpropanol were used as chiral sources. The amino alcohols were chosen to create a steric effect on the carbinol carbon. The reaction of *o*-hydroxybenzaldehyde with three chiral amino alcohols in EtOH gave chiral Schiff-base compounds. To explore the effect of a spacer group, the *o*-hydroxy benzaldehyde was reacted with 1,3-bis(bromomethyl) benzene in the presence of K_2CO_3 in CH_3CN . All reactions were simple and straightforward. All compounds were characterized with ¹H NMR, ¹³C NMR and elemental analysis (Schemes 1–3).

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Scheme 1.



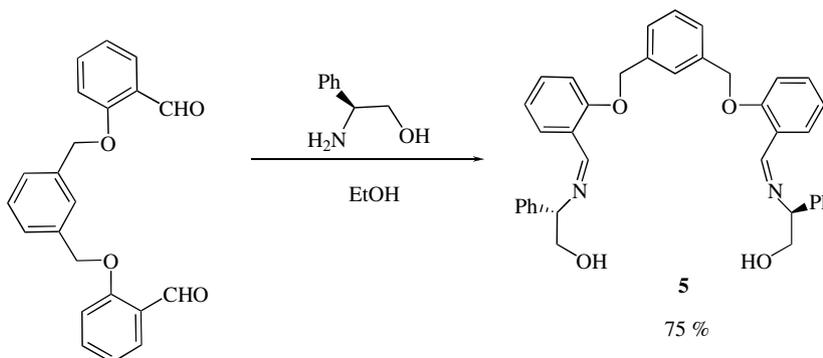
Scheme 2.

Under our previous reaction conditions,²⁴ the reaction was initially carried out at room temperature using 10 mol % catalyst and triflate as the source for metal ion and triethylamine as a promoter for 40 h. We used chiral Schiff-base ligands **2**, **3**, **4** and **5** under the above mentioned conditions

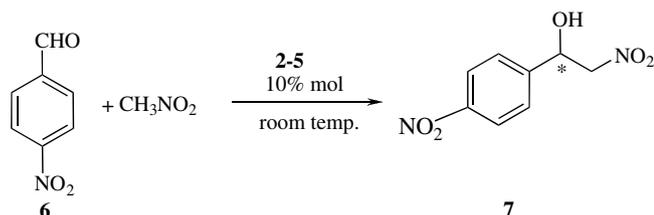
to examine the solvent effect using solvents such as ethanol, dichloromethane and toluene. Under the first experimental conditions, 10 mol % triethyl amine was added as an organic base in all the reactions (Table 1). The first experimental results show that the reaction yields were higher in all the cases when triethylamine was added to the reaction medium as a promoter. Next, CH₂Cl₂ proved to be the best solvent for the enantioselective nitroaldol reaction catalyzed by chiral Schiff-base ligands. The organic base triethylamine increased the reaction yield in all entries (Table 1); however, it caused a slight decrease in ee. The effect of organic base was shown dramatically in catalyst **4**. The enantioselectivity observed increased from 17 up to 82 ee when triethylamine was not used as a promoter. In general, the organic base increased the reaction yield, but decreased enantioselectivity. The best catalyst proved to be **3** when the organic base, triethylamine, was not added to the reaction medium. Whenever triethylamine was added to the reaction medium the best catalyst was **4**. The spacer group did not have a profound effect on selectivity but it did change the configuration of adduct meaning that it may be useful in applications for obtaining the desired configuration (Table 2).

3. Conclusion

In conclusion we have synthesized simple chiral Schiff-base ligands, which can be used in enantioselective metal-catalyzed reactions. The experimental results show that simple chiral Schiff-base ligands catalyze the enantioselective nitroaldol reaction. The spacer group has the potential to alter the configuration of the adduct which may be useful for that application.



Scheme 3.

Table 1. Asymmetric nitroaldol (Henry) reaction between nitromethane and *p*-nitrobenzaldehyde in the presence of triethylamine as the base catalyzed by a chiral Schiff-base^a

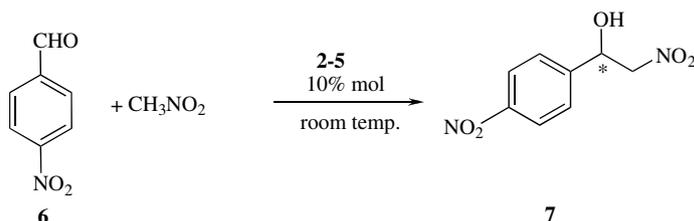
Entry	Cat.	M(OTf) ₂	Time (h)	Solvent	Yield ^b	ee ^c (%)	Config. ^d
1	2	Cu(OTf) ₂	40	EtOH	62	8	(R)
2	2	Cu(OTf) ₂	40	PhMe	68	17	(R)
3	2	Cu(OTf) ₂	40	CH ₂ Cl ₂	73	16	(R)
4	3	Cu(OTf) ₂	40	EtOH	61	5	(S)
5	3	Cu(OTf) ₂	40	PhMe	65	4	(S)
6	3	Cu(OTf) ₂	40	CH ₂ Cl ₂	72	58	(S)
7	4	Cu(OTf) ₂	40	EtOH	56	17	(S)
8	4	Cu(OTf) ₂	40	PhMe	69	11	(S)
9	4	Cu(OTf) ₂	40	CH ₂ Cl ₂	67	22	(S)
10	5	Cu(OTf) ₂	40	EtOH	63	45	(S)
11	5	Cu(OTf) ₂	40	PhMe	66	15	(S)
12	5	Cu(OTf) ₂	40	CH ₂ Cl ₂	64	57	(S)

^a All reactions were performed on a 0.2 mmol scale of 4-nitrobenzaldehyde, 0.6 mL of nitromethane and 10 mol % triethylamine as a base.

^b After purification with TLC ethylacetate/petroleum ether (30:70), *R*_f: 0.36, lit.:²⁶ 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 literature²⁵ and also determined by HP Chiral Detector.

Table 2. Asymmetric nitroaldol (Henry) reaction between nitromethane and *p*-nitrobenzaldehyde in the absence of triethylamine catalyzed by a chiral Schiff-base^a

Entry	Cat.	M(OTf) ₂	Time (h)	Solvent	Yield ^b	ee ^c (%)	Config. ^d
1	2	Cu(OTf) ₂	40	EtOH	53	4	(S)
2	2	Cu(OTf) ₂	40	PhMe	55	15	(S)
3	2	Cu(OTf) ₂	40	CH ₂ Cl ₂	61	24	(S)
4	3	Cu(OTf) ₂	40	EtOH	46	14	(R)
5	3	Cu(OTf) ₂	40	PhMe	49	44	(R)
6	3	Cu(OTf) ₂	40	CH ₂ Cl ₂	52	62	(R)
7	4	Cu(OTf) ₂	40	EtOH	48	73	(R)
8	4	Cu(OTf) ₂	40	PhMe	50	36	(R)
9	4	Cu(OTf) ₂	40	CH ₂ Cl ₂	53	82	(R)
10	5	Cu(OTf) ₂	40	EtOH	54	54	(R)
11	5	Cu(OTf) ₂	40	PhMe	51	24	(R)
12	5	Cu(OTf) ₂	40	CH ₂ Cl ₂	56	65	(R)

^a All reactions were performed on a 0.2 mmol scale of 4-nitrobenzaldehyde, 0.6 mL of nitromethane.

^b After purification with TLC ethyl acetate/petroleum ether (30:70), *R*_f: 0.36, lit.:²⁵ 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 literature²⁴ and also determined by HP Chiral Detector.

4. Experimental

4.1. General information

All chemicals were 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. ¹H (400 MHz) and ¹³C (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. *J* values are given in Hertz. Optical rotations were recorded using an PERKIN ELMER Model 341 polarimeter. HPLC measurements were performed with BIORAD instrument. Separation was carried out on Chiralcel OD column (250 × 4.60 mm) with hexane/2-propanol (85:15) as an eluent. TLC plates were purchased from Fluka.

4.1.1. Synthesis of dialdehyde 1

4.1.1.1. Compound 1. To a solution of *o*-hydroxybenzaldehyde (8 g, 0.07 mol) in 200 mL of CH₃CN were added anhydrous K₂CO₃ (38.4 g, 0.28 mol) and 1,3-bis(bromomethyl) benzene (6.86 g, 0.026 mol). The reaction was heated at reflux for 24 h. Then, CH₃CN was removed and the residue was partitioned between CH₂Cl₂ and

H₂O. The layers were separated and the organic phase was washed sequentially with H₂O, 1 M aq NaOH solution, H₂O and brine. After drying over MgSO₄, concentration in vacuo gave a white solid (8.7 g, 97%), mp = 117–118 °C; ¹H NMR (400 MHz, CDCl₃) δ 5.243 (s, 4H), 7.058–7.093 (q, 4H, *J* 4 Hz), 7.469–7.580 (m, 6H), 7.867–7.891 (q, 2H, *J* 4 Hz), 10.567 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 70.25, 113.04, 121.18, 125.23, 126.06, 127.18, 128.64, 129.23, 135.94, 136.77, 160.88, 189.61; IR: ν 3078 3043, 3012, 2935, 2877, 2765, 1666, 1601, 1481, 1458, 1400, 1369, 1304, 1288, 1234, 1165, 1103, 1007, 895, 845, 822, 791, 752, 710, 660, 509. Anal. Calcd for C₂₂H₁₈O₄: C, 76.29; H, 5.24. Found: C, 76.22; H, 5.31.

4.1.2. Synthesis of chiral Schiff-base ligands 2–5

4.1.2.1. Ligand 2. To a solution of *o*-hydroxybenzaldehyde (1.83 g, 15 mmol) in 100 mL of EtOH was added (*S*)-(+)-phenylglycinol (2.47 g, 18 mmol). The reaction was then heated at reflux for 16 h. The EtOH was removed and the residue was washed with ether three times and then crystallized from ethylacetate to give a solid (2.89 g, 80%), mp: 87–88 °C; [α]_D²⁰ = +99.3 (*c* 2, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 2.69 (br s, 1H), 3.911–3.927 (d, 2H, *J* 4 Hz), 4.462–4.495 (t, 1H, *J* 4 Hz), 6.889–7.425 (m, 9H), 8.47 (s, 1H), 13.45 (br s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 67.61, 75.79, 117.05, 118.74, 118.91, 127.13, 127.90, 128.86, 131.79, 132.71, 139.35, 161.05, 166.28; IR:

ν 3203, 3029, 2914, 2852, 1624, 1586, 1497, 1466, 1412, 1389, 1316, 1278, 1216, 1158, 1124, 1066, 1047, 1035, 985, 927, 854, 812, 758, 700, 642. Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.61; H, 6.33; N, 5.74.

4.1.2.2. Ligand 3. To a solution of *o*-hydroxybenzaldehyde (1.83 g, 15 mmol) in 100 mL of EtOH was added (1*S*,2*R*)-2-amino-1,2-diphenylethanol (3.84 g, 18 mmol). The reaction was then heated at reflux for 16 h. The EtOH was removed and the residue was washed with ether three times and then crystallized from ethyl acetate to give a solid (3.531 g, 72%), mp: 144–145 °C; $[\alpha]_D^{20} = -11.4$ (*c* 2, CH_2Cl_2); 1H NMR (400 MHz, $CDCl_3$) δ 2.19 (br s, 1H), 4.536–4.553 (d, 1H, *J* 8 Hz), 5.056–5.072 (d, 1H, *J* 8 Hz), 6.824–7.412 (m, 14H), 8.097 (s, 1H), 13.190 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 78.35, 80.16, 116.92, 118.69, 127.21, 128.06, 128.08, 128.11, 128.17, 128.42, 128.78, 131.68, 132.55, 139.49, 140.18, 160.88, 165.94; IR: ν 3949, 3084, 3064, 2872, 1632, 1582, 1497, 1459, 1428, 1351, 1278, 1201, 1158, 1120, 1093, 1062, 1027, 989, 908, 854, 816, 766, 700, 643, 585, 535, 465. Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.53; H, 6.11; N, 4.36.

4.1.2.3. Ligand 4. To a solution of *o*-hydroxybenzaldehyde (0.16 g, 0.13 mmol) in 100 mL of EtOH was added 1,1,3-triphenyl-(*R*)-(+)-2-amino propanol (0.4 g, 0.13 mmol). The reaction was heated to reflux for 16 h. The EtOH was removed and the residue was washed with ether three times and then crystallized from ethylacetate to give a solid (0.51 g, 94%), mp: 159–161 °C, $[\alpha]_D^{20} = +169.4$ (*c* 2, CH_2Cl_2); 1H NMR (400 MHz, $CDCl_3$) δ 2.868–2.902 (q, 1H, *J* 8 Hz), 3.071–3.105 (d, 2H, *J* 12 Hz), 4.307–4.422 (d, 1H, *J* 8 Hz), 6.763–7.678 (m, 19H), 7.697 (s, 1H), 12.651 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 37.40, 78.54, 79.77, 116.85, 118.16, 118.73, 126.01, 126.19, 126.42, 127.03, 127.18, 128.35, 128.42, 128.53, 129.76, 131.69, 132.73, 138.81, 143.99, 145.27, 160.68, 166.64; IR: ν 3571, 3062, 3029, 2890, 2374, 1959, 1628, 1588, 1496, 1450, 1158, 1053, 954, 755, 696, 558. Anal. Calcd. for $C_{28}H_{25}NO_2$ C, 82.53; H, 6.18; N, 3.44. Found: C, 82.28; H, 6.26; N, 3.36.

4.1.2.4. Ligand 5. To a solution of **1** (1.384 g, 4 mmol) in 100 mL of EtOH was added *S*-(+)-phenylglycinol (1.207 g, 8 mmol). The reaction was heated at reflux for 16 h. The EtOH was removed and the residue was washed with ether three times and then hexane to give a yellow oil (1.752 g, 75%); $[\alpha]_D^{20} = +40.2$ (*c* 2, CH_2Cl_2); 1H NMR (400 MHz, $CDCl_3$) δ 2.997 (br s, 2H), 3.863–3.991 (m, 4H), 4.433–4.465 (q, 2H, *J* 4 Hz), 5.148 (s, 4H), 6.963–6.984 (d, 2H, *J* 8 Hz), 7.036–7.491 (m, 18H), 8.128–8.147 (d, 2H, *J* 8 Hz), 8.902 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 67.73, 70.25, 76.72, 112.69, 121.27, 124.89, 126.03, 126.90, 127.35, 127.43, 127.86, 128.52, 129.03, 132.28, 137.25, 141.10, 158.13, 158.70; IR: ν 3375, 3066, 3031, 2931, 2877, 1639, 1604, 1489, 1458, 1388, 1295, 1245, 1160, 1118, 1052, 910, 755, 736, 705, 647, 532. Anal. Calcd for $C_{38}H_{36}N_2O_4$: C, 78.06; H, 6.21; N, 4.79. Found: C, 78.01; H, 6.31; N, 4.73.

4.1.2.5. Typical procedure for the asymmetric Henry reaction. Asymmetric Henry reaction was performed according to our previous method.²⁴

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