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Asymmetric Henry Reaction Catalyzed by Chiral Schiff Base*

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Abstract— Four chiral Schiff bases were synthesized conveniently from chiral amino alcohol and 2-hydroxynaphthalene-1-carbaldehyde. These ligands were used to catalyze the addition of nitroalkanes to aldehydes under ambient conditions in good yields with up to 91% *ee*.

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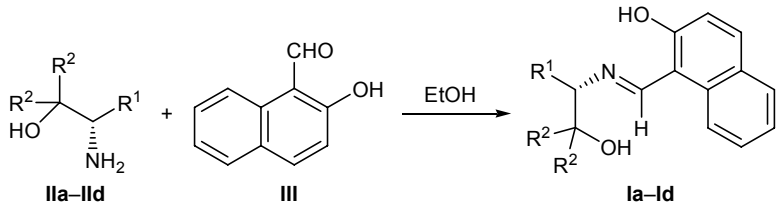
Since the first asymmetric Henry reaction reported by Shibasaki in 1992 [1], various efficient metal-based asymmetric catalysts were developed, such as bisoxazolines [2–6], cinchona alkaloid [7], dinuclear zinc complexes [8, 9], salen–Co complexes [10–12], and amino alcohols [13, 14]. After the first asymmetric Henry reaction catalyzed by chiral copper–Schiff base complexes was reported [15], a series of novel Schiff base catalysts were developed [16–22]. Most of these ligands were easily prepared from natural amino acids and salicylaldehyde. Schiff bases containing a naphthol fragment were seldom reported.

In this paper we report on the synthesis of four simple Schiff base ligands **Ia**–**Id** by reaction of chiral amino alcohols **IIa**–**IId** with 2-hydroxynaphthalene-1-carbaldehyde (**III**); Schiff bases **Ia**–**Id** were anticipated to be efficient catalysts for asymmetric Henry reaction. Amino alcohols **IIa**–**IId** were prepared according to known procedure [23–25], and their condensation with aldehyde **III** in ethanol afforded Schiff bases **Ia**–**Id** (Scheme 1). Taking into account the data of [21], we selected copper(II) salts as Lewis acids to catalyze asymmetric Henry reaction.

First, compounds **Ia**–**Id** were tested in the reaction of 4-nitrobenzaldehyde with nitromethane in the presence of $Cu(OAc)_2 \cdot 2H_2O$ at room temperature (Scheme 2). 2-Nitro-1-(4-nitrophenyl)ethanol formed in the reaction catalyzed by Schiff base **Id** was isolated in 65% yield (*ee* 76%; Table 1, run no. 4). Having selected the catalyst, we examined the effects of sol-

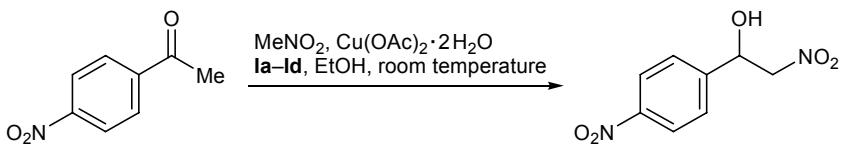
Scheme 1.



IIa–IId **III** **Ia–Id**

R^1 = Ph, R^2 = H (**a**); R^1 = R^2 = Ph (**b**); R^1 = $PhCH_2$, R^2 = H (**c**); R^1 = $PhCH_2$, R^2 = Ph (**d**).

Scheme 2.



* The text was submitted by the authors in English.

Table 1. Asymmetric Henry reaction in the presence of Schiff base ligands **Ia**–**Id**[a]

Run no.	Ligand	Yield,[b] %	*ee*, % (*S*)[c]
1	**Ia**	43	< 5
2	**Ib**	68	37
3	**Ic**	65	19
4	**Id**	65	76

[a] All reactions were carried out with 0.3 mmol of 4-nitrobenzaldehyde and 0.2 ml of nitromethane in 3 ml EtOH in the presence of 10 mol % of ligand and 10 mol % of $Cu(OAc)_2 \cdot 2H_2O$ at room temperature; hereinafter, reaction time 72 h.

[b] Hereinafter, the yield of isolated product is given.

[c] Hereinafter, the fraction of the *S* isomer was determined by HPLC on a chiral column (AD-H); the absolute configuration was determined by comparing the order of elution with an authentic sample according to [2, 8, 9]; conditions of HPLC analyses for adducts of 4-nitrobenzaldehyde with nitromethane: eluent hexane–*i*-PrOH (65 : 35), flow rate 1.0 ml/min; λ 254 nm; t_{minor} = 6.9 min, t_{major} = 8.7 min.

Table 2. Effect of solvent on the enantioselectivity of asymmetric Henry reaction[a]

Run no.	Solvent	Yield, %	*ee*, % (*S*)
1	EtOH	65	76
2	MeOH	60	67
3	PrOH	58	78
4	*i*-PrOH	50	71
5	BuOH	69	85

[a] All reactions were carried out with 0.3 mmol of 4-nitrobenzaldehyde and 0.2 ml of nitromethane in the presence of 10 mol % of ligand **Id** and 10 mol % of $Cu(OAc)_2 \cdot 2H_2O$ at room temperature using 3 ml of solvent.

Table 3. Effect of copper salts on the enantioselectivity of asymmetric Henry reaction[a]

Run no.	Copper salt	Yield, %	*ee*, % (*S*)
1	$Cu(OAc)_2 \cdot 2H_2O$	69	81
2	$CuSO_2 \cdot 5H_2O$	23	31
3	$CuCl_2 \cdot 2H_2O$	30	59
4	$Cu(OTf)_2$	15	31

[a] All reactions were carried out with 0.3 mmol of 4-nitrobenzaldehyde and 0.2 ml of nitromethane in the presence of 10 mol % of ligand **Id** and 10 mol % of copper salt in 3 ml of BuOH at room temperature.

vent, copper salt, and amount of nitromethane on the asymmetric Henry reaction with 4-nitrobenzaldehyde. Insofar as protic solvents are superior to aprotic ones [18, 26], the reaction was carried out in different alcohols (Table 2). Enhanced enantioselectivity (85%) was observed using butan-1-ol as solvent (run no. 5). A number of copper(II) salts were also tested (Table 3), and $Cu(OAc)_2 \cdot 2H_2O$ turned out to be the most efficient (run no. 1).

The amount of nitromethane was also important (Table 4). The yield and *ee* values were considerably improved when the amount of nitromethane was increased from 0.1 ml (1.8 mmol) to 0.4 ml (7.5 mmol). No appreciable improvement was achieved by further raising the amount of nitromethane.

Thus the optimal conditions are as follows: Schiff base **Id** and $Cu(OAc)_2 \cdot 2H_2O$ as catalyst, butan-1-ol as solvent, and excess of nitromethane (25 equiv, 0.4 ml, 7.5 mmol). To extend the scope of the reaction under study, various aldehydes were brought into reaction with nitromethane under the optimal conditions. The corresponding products were obtained in moderate to good yields with high *ee* values (Table 5). For example, the reaction of nitromethane with 3-nitrobenzaldehyde afforded the corresponding adduct in 95% yield with *ee* 91% (run no. 8).

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded from solutions in $CDCl_3$ on a Bruker Avance III spectrometer operating at 500 and 125 MHz, respectively; tetramethylsilane was used as internal reference. Chiral HPLC analyses were performed on a Shimadzu LC-20AT instrument equipped with a Shimadzu SPD-20A detector and a Chiralcel AD-H column (Daicel Co.). The melting points were determined using an X-4 micro-melting point apparatus and were not corrected. All reactions were monitored by TLC. Silica gel (100–200 mesh) was used for column chromatography. All solvents were dried by standard methods. Commercially available reagents were used without additional purification, unless otherwise stated.

Amino alcohols **IIa**, **IIb** [23], **IIc** [24], and **IId** [25] were synthesized by known methods from L-phenylglycine methyl ester hydrochloride or L-phenylalanine methyl ester hydrochloride.

Schiff bases Ia–Id (*general procedure*). A mixture of 5 mmol of aldehyde **III** and 5 mmol of (*S*)-amino alcohol **IIa**–**IId** in 30 ml of ethanol was stirred for 12 h at room temperature. The solvent was removed, and the residue was purified by column chromatography on silica gel using ethyl acetate–petroleum ether (1 : 10) as eluent or by recrystallization from ethanol.

(*S*)-1-{[(2-Hydroxy-1-phenylethyl)imino]methyl}-naphthalen-2-ol (Ia) was purified by recrystallization from ethanol. Yield 1.07 g (85%), yellow crystals, mp 187°C. The NMR spectrum of **Ia** coincided with that reported in [27].

(*S*)-1-{[(2-Hydroxy-1,2,2-triphenylethyl)imino]-methyl}naphthalen-2-ol (Ib) was purified by column chromatography on silica gel. Yield 1.75 g (77%), yellow crystals, mp 128–130°C. The NMR spectrum of **Ib** coincided with that given in [23].

(*S*)-1-{[(1-Hydroxy-3-phenylpropan-2-yl)imino]-methyl}naphthalen-2-ol (Ic) was purified by recrystallization from ethanol. Yield 1.3 g (85%), yellow crystals, mp 178–180°C. ^{1}H NMR spectrum, δ, ppm: 2.92 d.d (1H, PhC**H**$_2$, J = 13.78, 7.62 Hz), 3.02 d.d (1H, PhC**H**$_2$, J = 13.79, 4.23 Hz), 3.72 m (2H, HOC**H**$_2$), 3.92 d.d (1H, NCH), 5.11 br (1H, CH_2O**H**), 6.62–7.50 m (11H, H_{arom}), 8.37 s (1H, N=CH), 14.13 br (1H, 2-OH). ^{13}C NMR spectrum, δ_C, ppm: 175.62, 158.59, 137.19, 136.99, 133.56, 129.43, 129.10, 128.75, 127.71, 126.91, 126.07, 123.96, 122.51, 117.90, 106.36, 68.24, 65.23, 38.64. Found, %: C 78.56; H 6.26; N 4.57. $C_{20}H_{19}NO_2$. Calculated, %: C 78.66; H 6.27; N 4.59.

(*S*)-1-{[(1-Hydroxy-1,3,3-triphenylpropan-2-yl)-imino]methyl}naphthalen-2-ol (Id) was purified by column chromatography on silica gel. Yield 2.1 g (92%) (cf. [28], no analytical data were given), yellow solid, mp 159–160°C. ^{1}H NMR spectrum, δ, ppm: 3.03 d.d (1H, PhC**H**$_2$, J = 13.98, 10.63 Hz), 3.18 d.d (1H, PhC**H**$_2$, J = 13.92, 1.35 Hz), 4.00 br (1H, CH_2O**H**), 4.48 d.d (1H, NCH, J = 10.75, 1.37 Hz), 6.85–7.75 m (21H, H_{arom}), 7.97 s (1H, N=CH), 14.31 br (1H, 2-OH). ^{13}C NMR spectrum, δ_C, ppm: 37.75, 74.60, 80.08, 106.60, 118.07, 122.58, 124.01, 126.16, 126.24, 126.32, 126.68, 127.22, 127.40, 127.58, 128.40, 128.66, 128.67, 128.98, 129.64, 136.67, 133.65, 138.55, 144.28, 144.63, 158.99, 173.84. Found, %: C 83.92; H 5.94; N 3.04. $C_{32}H_{27}NO_2$. Calculated, %: C 84.00; H 5.95; N 3.06.

Asymmetric Henry reaction (*typical procedure*). A 10-ml round-bottom flask was charged with a mixture of 0.03 mmol of chiral ligand **I** and 0.03 mol of copper(II) salt, 3 ml of the corresponding solvent was added, and the mixture was stirred for 3 h at room temperature. Aldehyde, 0.3 mmol, and nitromethane were then added, and the mixture was stirred until the reaction was complete (TLC). Volatile components were removed under reduced pressure, and the crude product was purified by preparative TLC using petro-

Table 4. Effect of the amount of nitromethane on the enantioselectivity of asymmetric Henry reaction[a]

Run no.	$MeNO_2$, mol (ml)	Yield, %	*ee*, % (*S*)
1	1.8 (0.1)	40	65
2	3.7 (0.2)	69	82
3	7.5 (0.4)	83	83
4	11.0 (0.4)	82	85
5	15.0 (0.8)	83	86
6	18.0 (1.0)	83	82

[a] All reactions were carried out with 0.3 mmol of 4-nitrobenzaldehyde in the presence of 10 mol % of ligand **Id** and 10 mol % of $Cu(OAc)_2 \cdot 2H_2O$ in 3 ml of BuOH at room temperature.

Table 5. Asymmetric Henry reaction of nitromethane with various aldehydes under the optimal conditions[a]

Run no.	Aldehyde	Yield, %	*ee*, %	Configuration
1	Benzaldehyde	73	59[b]	*S*
2	Naphthalene-2-carbaldehyde	68	66[c]	*S*
3	2,4-Dichlorobenzaldehyde	87	89[d]	ND
4	(4-Formylphenyl)-acetyl fluoride	54	69[e]	*S*
5	4-Bromothiophene-2-carbaldehyde	82	77[f]	ND
6	2,5-Dimethoxybenzaldehyde	83	70[g]	*S*
7	2-Nitrobenzaldehyde	93	90[h]	*S*
8	3-Nitrobenzaldehyde	95	91[i]	*S*

[a] All reactions were carried out with 0.3 mmol of aldehyde and 0.4 ml of nitromethane in the presence of 10 mol % of ligand **Id** and 10 mol % of $Cu(OAc)_2 \cdot 2H_2O$ in 3 ml of BuOH at room temperature.

[b] HPLC conditions: hexane–*i*-PrOH, 95:5, flow rate 0.5 ml/min, λ 254 nm, t_{major} = 37.2 min, t_{minor} = 39.5 min.

[c] HPLC conditions: hexane–*i*-PrOH, 95:5, flow rate 1.0 ml/min, λ 254 nm, t_{major} = 33.7 min, t_{minor} = 36.4 min.

[d] HPLC conditions: hexane–*i*-PrOH, 95:5, flow rate 1.0 ml/min, λ 254 nm, t_{minor} = 14.1 min, t_{major} = 17.8 min.

[e] HPLC conditions: hexane–*i*-PrOH, 95:5, flow rate 1.0 ml/min, λ 254 nm, t_{major} = 18.2 min, t_{minor} = 29.4 min.

[f] HPLC conditions: hexane–*i*-PrOH, 95:5, flow rate 1.0 ml/min, λ 230 nm, t_{major} = 22.1 min, t_{minor} = 27.2 min.

[g] HPLC conditions: hexane–*i*-PrOH, 95:5, flow rate 0.8 ml/min, λ 215 nm, t_{major} = 49.5 min, t_{minor} = 51.5 min.

[h] HPLC conditions: hexane–*i*-PrOH, 85:15, flow rate 1.0 ml/min, λ 254 nm, t_{major} = 11.3 min, t_{minor} = 12.2 min.

[i] HPLC conditions: hexane–*i*-PrOH, 85:15, flow rate 1.0 ml/min, λ 254 nm, t_{major} = 11.9 min, t_{minor} = 14.1 min.

leum ether–ethyl acetate as eluent. Enantiomeric excess (*ee*) was determined by HPLC using a Chiralpak AD-H column.

Preparation of racemic Henry reaction products (*general procedure***).** A 10-ml round-bottom flask was charged with 1 mmol of aldehyde, 5 ml of ethanol was added at room temperature, and 0.16 ml (3 mmol) of nitromethane and 5 drops of triethylamine were then injected via a syringe. The mixture was stirred until complete conversion was achieved (8 h, TLC). Volatile components were removed under reduced pressure, and the crude product was purified by preparative TLC using petroleum ether–ethyl acetate as eluent. The retention times of racemic β-nitro alcohols were determined by HPLC using a Chiralpak AD-H column.

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