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Novel Schiff base ligands derived from *Cinchona* alkaloids for Cu(II)-catalyzed asymmetric Henry reaction

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ABSTRACT

A new series of Schiff bases derived from *Cinchona* alkaloids were developed as chiral ligands for the copper(II)-catalyzed asymmetric Henry reaction. The optimized catalyst can promote the Henry reaction of both aromatic and aliphatic aldehydes with nitromethane or nitroethane. Those reactions can afford the chiral β-nitro alcohol adducts with high enantioselectivities.

1. Introduction

The Henry (nitro-aldol) reaction[1] is one of the most important and versatile C–C bond forming reactions in organic synthesis. Because the resulting β-nitro alcohol adducts can be transformed into important building blocks of natural products or pharmaceuticals, such as β-amino alcohols, α-hydroxy ketones, aldehydes, carboxylic acids, azides, and sulfides,[2] great efforts have been devoted toward the implementation of asymmetric versions of the Henry reaction. Indeed, significant progress has been achieved in the last few years.[3–10] Since Shibasaki reported the first successful enantioselective Henry reaction,[3] various types of chiral metal catalysts, containing chiral ligands with metal atoms (such as copper,[5] zinc,[2d,6] chromium,[2b,7] magnesium,[8] cobalt,[9] and rare earth,[3,10]), and organocatalysts[4] have been developed. Among them, the Cu-catalyzed asymmetric Henry reaction has received much attention in recent years. However, despite the significant progress achieved, most of these methods suffer from some limitations, such as the use of preformed silyl nitronates as nucleophiles, narrow substrate scope, relatively high catalyst loading, low reaction temperatures, multistep synthetic procedures for ligand preparation, or demanding the use of additives. Therefore, the development of readily available, highly stereoselective, and practical chiral catalysts for Henry reaction with a broad range of substrates is still highly desirable.

Chiral ligand design has played a pivotal role in the development of efficient metal-catalyzed asymmetric reactions. A large number chiral ligands, such as bisoxazoline,[5a–c] bisthiazoline,[5d] bis(imidazoline),[5h] BINOL-oxazoline,[5q] salen,[5g,k,7,9] *N*,*N*′-dioxides,[5j] aminopyridine,[5l] bipiperidine,[5p] amino alcohol,[6c] *Cinchona* alkaloids,[5m] and nanocrystalline[8] have been used in the metal-catalyzed asymmetric Henry reaction. Recently, the economic and environmental friendly chiral Schiff base ligands have frequently used in asymmetric catalysis, including Henry reaction.[5e,k,s,9,11] In asymmetric Henry reaction, some of chiral Schiff base-metal complexes give excellent results with aromatic aldehydes, but the yields and ee values are often decreased dramatically for the aliphatic aldehydes. *Cinchona* alkaloids are classified as the most 'privileged organic chirality inducers', owing to the advantages of being inexpensive, structurally tunable and both enantiomers easily available according to the need.[12] They and their derivatives have been widely used in asymmetric catalysis.[2b,5m] In our previous study, *Cinchona* alkaloids derived chiral quaternary salts and thiourea organocatalysts have been successfully employed in the asymmetric alkylation and Michael reaction, respectively.[11]

Herein, we report a series of novel *Cinchona* alkaloids derived Schiff bases and their application in the Cu-catalyzed asymmetric Henry reaction. To the best of our knowledge, no *Cinchona* alkaloids derived Schiff base ligand has been reported. Eight new chiral Schiff

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base ligands were prepared from *Cinchona* alkaloids with salicylaldehyde and its derivatives in high yields under mild conditions. They were then applied in the Cu(II)-catalyzed asymmetric Henry reaction. Under the optimized conditions, the range of substrates was successfully expanded to both aromatic and aliphatic aldehydes with high enantioselectivities and good yields. Moreover, when nitroethane instead of nitromethane was used in the Henry reaction, products with two chiral centers were also obtained successfully.

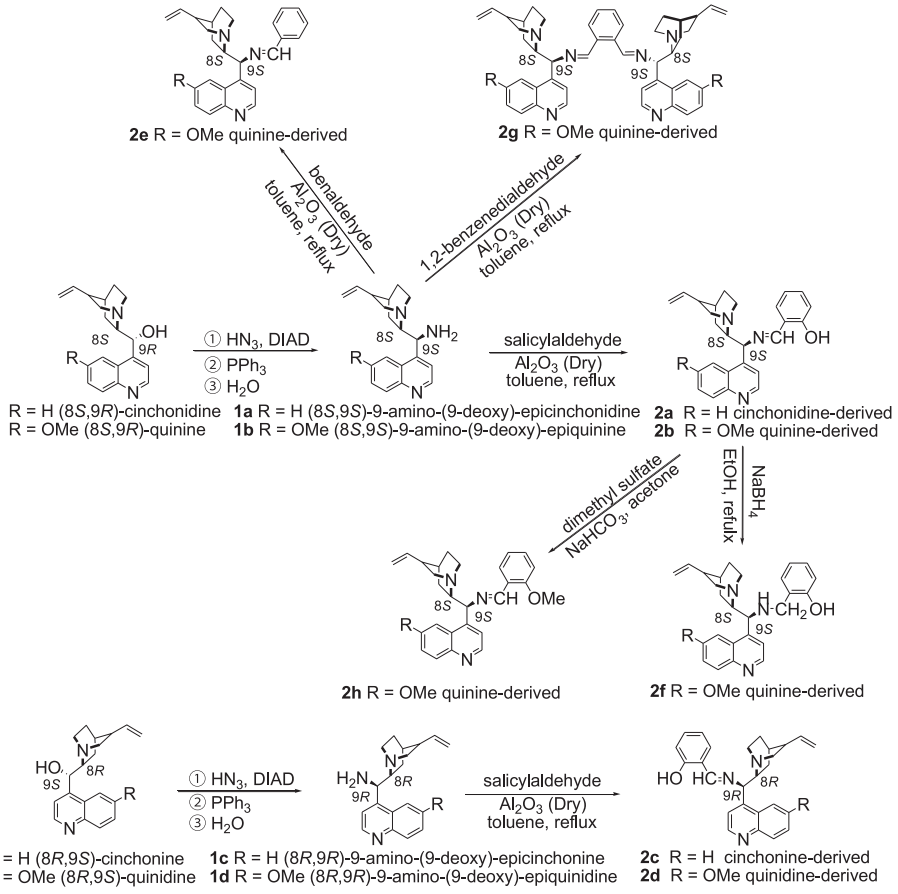
2. Results and discussion

2.1. Synthesis of ligands

A series of new chiral Schiff base ligands derived from *Cinchona* alkaloids were prepared in high yield (Scheme 1). Thus, four different *pseudo*enantiomeric of *Cinchona* alkaloids were transformed into corresponding 9-amino compounds **1a**–**d**,[13] followed by condensation with salicylaldehyde to give Schiff bases **2a**–**d** in high yield (75–84%). To investigate the influence of the different function group of the ligands on chiral induction and catalytic activity, ligands **2e**, **2f**, **2g**, and **2h** were prepared. Ligand **2e**, without hydroxyl group, was simply synthesized by condensation of benzaldehyde with (8*S*,9*S*)-9-amino-(9-deoxy)-epiquinine **1b**. The hydrogenated Schiff base ligand **2f** was prepared by reducing **2b** with $NaBH_4$. C_2-Symmetric dimeric Schiff base **2g** was obtained by reaction of **1b** with 1,2-benzenedialdehyde. Finally, to decide the role of the hydroxyl group on **2b**, it was methylated with dimethyl sulfate to afford the corresponding methyl ether **2h**.

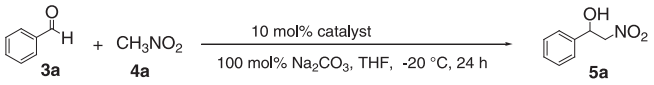
2.2. Initial screening

Initially the reactivity and enantioselectivity of various alkaloids derived Schiff bases complexes for the Henry reaction were investigated. The reaction between benzaldehyde and nitromethane in the presence of 10 mol % of catalyst, generated in situ from metal source (10 mol %) and ligand (20 mol %), and Na_2CO_3 (100 mol %) in THF at −20 °C was chosen as a model system; the results are summarized in Table 1. $Cu(OAc)_2\cdot H_2O$ proved to be the most suitable metal sources as other metal salts, such as $CuCl_2\cdot 2H_2O$, CuCl, $Cu(OTf)_2$, $NiCl_2\cdot 6H_2O$, AgOTf, YiOTf, $Pb(OAc)_2$, $Zn(OAc)_2$, and $Zn(OTf)_2$ gave lower reactivities and enantioselectivities. The absolute configuration of the product is decided by the C_8-position and C_9-position configuration of *Cinchona* alkaloids (entries 1–4). Unsurprisingly, the *pseudo*enantiomeric derived catalyst pairs induced opposite enantioselectivity in the Henry reaction. Comparing entries 2 and 4 with 1 and 3, it can be seen that the additional methoxy group at the 6-position of the *Cinchona* alkaloids is benefit for the enantioselectivity. Notably, the hydroxyl group on the phenyl of aldehyde is very important. Without the hydroxyl group (ligand **2e**), the ee value decreased from 79% to 61%, and the yield decreased straightly from 79% to 23% (entry 5 vs entry 2). Importantly, the hydrogenated Schiff base ligand **2f** gave excellent yield but poor enantioselectivity (entry 6). It indicates the carbon–nitrogen double bond of the Schiff base ligand is crucial for high enantioselectivity. The C_2-symmetric dimeric Schiff base ligand **2g** did not improve the performance (entry 7). The results obtained with different Schiff bases showed that ligand **2b**, derived from quinine, was most effective. The most suitable ratio of $Cu(OAc)_2\cdot H_2O$ to ligand **2b** proved to be 1:2 (Table 1, entry 2 vs



Scheme 1. Synthesis of Schiff base ligands **2a**–**h**.

Table 1
Screening of the Schiff base ligands and central metals in the asymmetric Henry reaction[a]



3a 4a 5a

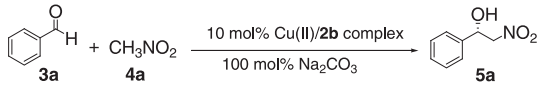
Entry	Metal	Ligand	Ratio of metal/ligand	Yield[b] (%)	ee[c] (%)	Config.[d]
1	$Cu(OAc)_2·H_2O$	**2a**	1:2	32	43	*S*
2	$Cu(OAc)_2·H_2O$	**2b**	1:2	79	79	*S*
3	$Cu(OAc)_2·H_2O$	**2c**	1:2	30	31	*R*
4	$Cu(OAc)_2·H_2O$	**2d**	1:2	56	58	*R*
5	$Cu(OAc)_2·H_2O$	**2e**	1:2	23	61	*S*
6	$Cu(OAc)_2·H_2O$	**2f**	1:2	95	8	*S*
7	$Cu(OAc)_2·H_2O$	**2g**	1:2	20	58	*R*
8	$CuCl_2·2H_2O$	**2b**	1:2	23	64	*S*
9	CuCl	**2b**	1:1	25	76	*S*
10	$Cu(OTf)_2$	**2b**	1:2	10	68	*S*
11	$Zn(OAc)_2$	**2b**	1:1	NR	—	—
12	$Zn(OTf)_2$	**2b**	1:1	NR	—	—
13	$NiCl_2·6H_2O$	**2b**	1:2	11	42	*S*
14	AgOTf	**2b**	1:1	7	4	*S*
15	YiOTf	**2b**	1:1	Trace	ND	—
16	$Pb(OAc)_2$	**2b**	1:2	Trace	ND	—
17	$Cu(OAc)_2·H_2O$	**2b**	1:1	48	74	*S*
18	$Cu(OAc)_2·H_2O$	**2b**	1:3	76	78	*S*

[a] All reactions were carried out with 0.25 mmol of benzaldehyde and 1.25 mmol of nitromethane in 1 mL THF in the presence of 10 mol % catalyst, 100 mol % Na_2CO_3 at −20 °C for 20 h.
[b] Isolated yield.
[c] Determined by HPLC analysis (Chiralcel OD-H column).
[d] By comparison with the literature data.[5,10]

entries 17 and 18). Based on the data summarized in Table 1, $Cu(OAc)_2·H_2O$ and ligand **2b**, which gave the best results, were chosen for subsequent studies.

Solvent always plays an important role in various catalytic processes. A series of reaction solvents, such as THF, toluene, diethyl ether, hexane, methanol, ethanol, isopropanol, acetonitrile, acetone, dichloromethane, DMF, and dioxane, were tested in the catalytic enantioselective Henry reaction between benzaldehyde and nitromethane in combination with $Cu(OAc)_2·H_2O$, ligand **2b**, and Na_2CO_3 (Table 2). Of the different solvents tested, THF was clearly the best choice for this reaction in terms of yield and enantioselectivity (entry 1). Using the nonpolar solvents, such as ether, hexane, and toluene, both the enantioselectivities and the chemical yields were inferior to THF (entry1 vs entries 2–4). With the polar protonic solvents methanol or ethanol as solvents, good yields could be obtained, but the enantioselectivities were poor (entries 5 and 6). Strangely, when acetone or CH_2Cl_2 was used as solvents, only trace product could be observed (entries 9 and 10). Using dioxane (entry 12) as solvent, 64% ee and 74% yield were obtained after 12 h at 12 °C (the melting point of dioxane is 11.8 °C).

Table 2
Screening the solvents in the asymmetric Henry reaction[a]



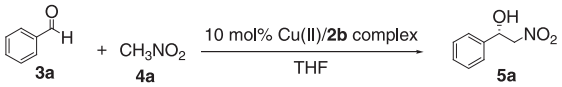
3a 4a 5a

Entry	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	THF	24	79	79
2	Toluene	24	41	56
3	Et_2O	24	20	56
4	Hexane	24	13	48
5	MeOH	12	92	16
6	EtOH	12	87	40
7	*i*-PrOH	12	30	39
8	CH_3CN	12	60	52
9	Acetone	24	Trace	ND[d]
10	CH_2Cl_2	24	Trace	ND[d]
11	DMF	24	8	22
12[e]	Dioxane	12	74	64

[a] All reactions were carried out with 0.25 mmol of benzaldehyde and 1.25 mmol of nitromethane in the intend solvent (1 mL) at the presence of 10 mol % $Cu(OAc)_2·H_2O$/**2b** (1:2), 100 mol % of Na_2CO_3 at −20 °C for intend time.
[b] Isolated yield.
[c] Determined by HPLC analysis (Chiralcel OD-H column).
[d] Not detected.
[e] Reaction was carried out at 12 °C.

The basic additives were believed to deprotonate the nucleophiles in the Henry reaction.[4c] Indeed, the reaction did not occur in absence of base (Table 3, entry 1). Subsequently, the influence of different bases on the reactivity and stereoselectivity was studied. DABCO (entries 2 and 3), DIPEA (entry 4), Et_3N (entry 7), KOH (entry 12), K_2CO_3 (entry 13), and Na_2CO_3 (entries 15–18) gave moderate to good enantioselectivities and yields. DBU (entry 5), $CsCO_3$ (entry 11), and NaOH (entry 14) were good bases in terms of yields, but the enantioselectivities were disappointing. 2,2′-bipyridine (entry 9–10) afforded excellent enantioselectivity (98% ee) but with a slightly low yield. Of the bases tested, DABCO, Na_2CO_3, and 2,2′-bipyridine are most promising. The optimum amount of bases that is needed to achieve good conversion and enantioselectivity was 50 mol % relative to the substrate (entries 3 and 17) for DABCO and Na_2CO_3, respectively, and 300 mol % for 2,2′-bipyridine.

Table 3
Effects of basic additives on the Cu(II)/**2b** complex catalyzed enantioselective Henry reaction[a]



3a 4a 5a

Entry	Base	Loading of base (mol %)	Temperature (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	—	—	−20	24	NR	—
2	DABCO	100	−20	24	81	70
3	DABCO	50	−20	24	67	80
4	DIPEA	100	−20	12	53	52
5	DBU	100	−20	12	86	15
6	DMAP	100	−20	12	72	62
7	Et_3N	100	−20	12	55	62
8	Pyridine	100	−20	24	9	72
9	2,2′-Bipyridine	100	−20	24	37	98
10	2,2′-Bipyridine	300	−20	48	57	95
11	$CsCO_3$	100	−20	12	73	27
12	KOH	100	−20	12	62	62
13	K_2CO_3	100	−20	12	45	53
14	NaOH	100	−20	12	82	39
15	Na_2CO_3	200	−20	24	83	76
16	Na_2CO_3	100	−20	24	79	79
17	Na_2CO_3	50	−20	24	75	84
18	Na_2CO_3	40	−20	24	60	85
19	Na_2CO_3	30	−20	24	25	87
20	Na_2CO_3	50	0	24	85	70
21	Na_2CO_3	50	−10	24	78	76
22	Na_2CO_3	50	−30	24	57	79

[a] All reactions were carried out with 0.25 mmol of benzaldehyde and 1.25 mmol of nitromethane in 1 mL of THF in the presence of 10 mol % catalyst, at intend temperature.
[b] Isolated yield.
[c] Determined by HPLC analysis (Chiralcel OD-H column).

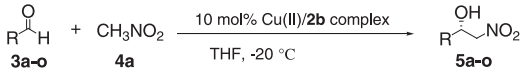
The effects of temperature on the reaction were also tested (Table 3, entries 17 and 20–22). As the temperature increased from −20 °C to 0 °C, ee decreased significantly with an increase in the yield. Strangely, both yield and ee decreased obviously when the temperature decreased from −20 °C to −30 °C.

Overall, the optimized reaction conditions were 10 mol % of $Cu(OAc)_2·H_2O$/**2b** (1:2) complex as catalyst, THF as solvent, 50 mol % Na_2CO_3, DABCO or 300 mol % 2,2′-bipyridine as basic additives, −20 °C as reaction temperature.

2.3. Reaction with nitromethane

With the optimized reaction conditions in hand, the scope of Henry reaction with nitromethane was explored (Table 4). Aromatic aldehydes in general gave good yields (63–82%) and high enantioselectivities (78–98% ee). Importantly, although the highest enantiomeric excesses were obtained with electron-rich 4-methoxybenzaldehyde and 2-furaldehyde (entries 7 and 11, 98% ee), reactions with electron-deficient aromatic 4-nitrobenzaldehyde also gave high enantioselectivity (entry 9, 85% ee). More importantly, unlike most of other chiral copper catalysts, aliphatic cyclic, branched or unbranched aldehydes were also excellent substrates in our catalytic system, affording nitroaldol adducts in good yields and high enantioselectivities (entries 12–15, 62–67% yield, 81–99% ee). In particular, 3-phenylpropanal gave almost optically pure β-nitro alcohol adduct with 50 mol % of DABCO as basic additive (entry 12).

Table 4
Cu(II)/**2b** complex catalyzed enantioselective Henry reaction[a]



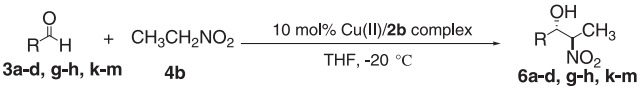
Entry	Substrate		Time (h)	Yield[b] (%)	ee[c] (%)
1		**3a** Y=H	20	75	84 (*S*)[d]
2		**3b** Y=4-Cl	20	65	85 (*S*)
3[e]		**3c** Y=2-Cl	20	73	86 (*S*)
4[f]		**3d** Y=4-Br	20	70	80 (*S*)
5[e]		**3e** Y=4-F	20	64	81 (*S*)
6[e]		**3f** Y=4-Me	28	73	84 (*S*)
7[f]		**3g** Y=4-OMe	28	63	98 (*S*)
8[e]		**3h** Y=2-OMe	28	82	78 (*S*)
9[f]		**3i** Y=4-NO_2	20	66	85 (*S*)
10[e]		**3g**	20	81	80 (*S*)
11[e]		**3k**	20	72	98 (*S*)
12[f]		**3l**	32	62	99 (*S*)
13[f]		**3m**	32	67	81 (*S*)
14		**3n**	32	66	86 (*S*)
15[f]		**3o**	32	65	87 (*S*)

[a] All reactions were carried out with 0.25 mmol of benzaldehyde and 1.25 mmol of nitromethane in 1 mL THF in the presence of 10 mol % Cu(II)/**2b** complex, 50 mol % of Na_2CO_3 at −20 °C.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis using Chiralcel OD-H or Chiralpak AD-H column.
[d] By comparison with the literature data.[5,10]
[e] 2,2′-Bipyridine (300 mol %) was used as a base.
[f] DABCO (50 mol %) was used as basic additive.

2.4. Reaction with nitroethane

A highly enantioselective Henry reaction using nitromethane as a nucleophile has been well documented. However, highly diastereo- and enantioselective Henry reactions that use nitroethane to form two stereocenters simultaneously still remain challenging and less explored compare to the reaction of nitromethane.[5b,14] The promising results obtained with nitromethane above prompted us to further evaluate the ligand **2b** in the Henry reaction with nitroethane. The preliminary results were summarized in Table 5. Under the optimized reaction conditions, all aldehydes (both aromatic and aliphatic) tested gave good yields (68–91%) and high enantioselectivities (up to 99% ee), although the diastereoselectivities were rather low. The best result was obtained with electron-rich 2-methoxybenzaldehyde (entry 6, *anti*/*syn*=73:27, *anti*: 85% ee, *syn*: 99% ee).

Table 5
Cu(II)/**2b** complex catalyzed diastereoselective Henry reaction[a]



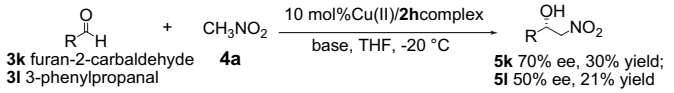
Entry	Substrate		Time (h)	Yield[b] (%)	*anti*/*syn*	ee[c] (%)	
						anti	*syn*[d]
1		**3a** YH	20	72	67:33	79	76
2[e]		**3b** Y=4-Cl	20	77	61:39	68	72
3		**3c** Y=2-Cl	20	71	72:28	72	56
4[e]		**3d** Y=4-Br	20	84	68:32	73	66
5		**3g** Y=4-OMe	28	69	70:30	77	74
6		**3h** Y=2-OMe	28	72	73:27	85	99
7		**3k**	20	68	48:52	99	68
8		**3l**	32	60	53:47	74	73
9		**3m**	32	61	62:38	91	59

[a] All reactions were carried out with 0.25 mmol of aldehydes and 1.25 mmol of nitroethane in 1 mL THF in the presence of 10 mol % Cu(II)/**2b** complex, 50 mol % of Na_2CO_3 at −20 °C.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis using Chiralcel OD-H or Chiralpak AD-H column.
[d] By comparison with the literature data.[5b,14]
[e] DABCO (50 mol %) was used as a base.

These results, together with those of reactions with nitromethane, have shown that the new quinine derived Schiff base **2b** is a useful chiral ligand for the Cu-catalyzed asymmetric Henry reaction of both aromatic and aliphatic aldehydes.

2.5. Mechanism study

To elucidate the pathway of the Cu(II)/**2b** complex catalyzed asymmetric Henry reaction, we further investigated the role of the hydroxy group in the catalysis by using the hydroxyl protected ligand **2h**. It was tested in the asymmetric Henry reaction of two selected substrates under the same reaction conditions as Table 4 (Scheme 2). We can see that both yield and ee value decreased dramatically in two occasions. By compared the infrared spectrums of ligand **2b** with the one of Cu(II)/**2b** complex, we also found that the signal of hydroxyl group on **2b** disappeared when it coupled with $Cu(OAc)_2 \cdot H_2O$.[15] Those help us to confirm the belief that the hydroxyl group of the ligand takes part in the formation of the catalyst complex.



Scheme 2. Asymmetric Henry reaction under Cu(II)/**2h** complex.

Based on the experiment results all above, two possible six coordinate Cu(II) transition[5d,16] states (TS **A** and TS **B**) are shown in Fig. 1. The uncovered hydroxyl group and the carbon–nitrogen double bond of Schiff base may coordinate with the central copper. The phenyl ring of salicylaldehyde was on a totally different dimensional direction with the part of *Cinchona* alkaloids's backbone. In the proposed working model for the Henry reaction of aldehyde with nitromethane, TS **A** generated favoring *Re*-face attack of the nitronate anion to aldehyde, which explained the Henry products with *S* configurations. *Si*-face attack of nitromethane to aldehyde leading to TS **B** is disfavored due to steric repulsion between the substrate aldehyde and the catalyst backbone as shown in Fig. 1.

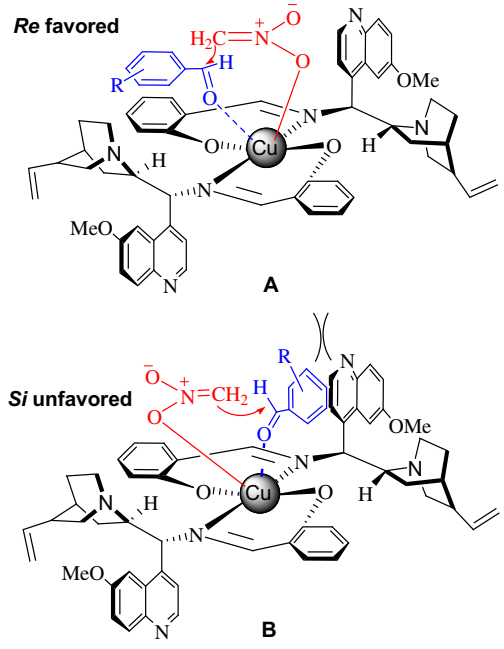


Fig. 1. Proposed working model for the Henry reaction of aldehyde with nitromethane.

3. Conclusion

In conclusion, a novel chiral Schiff base (**2b**)/Cu(II) system has been developed for the diastereo and enantioselective Henry reaction. The reactions proceeded smoothly to provide the corresponding adducts in high enantioselectivities for a wide range of substrates. This is the first time *Cinchona* alkaloids derived Schiff base ligands are used as ligands in asymmetric catalysis. A transition state model has also been proposed to account for the good stereocontrol. Cu(II)/**2b** complex, being air stable, easily available, and high enantioselectivity, is a promising catalyst for the development of synthesis of chiral β-nitro alcohols.

4. Experimental section

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on Mercury 400 MHz or JEOL JNM-LA 400 MHz spectrometers. Chemical shifts are expressed in parts per million downfield from TMS as internal standard, and coupling constants are reported in hertz. Mass spectrometric analyses were done on Waters Q Tof Premier Micromass (ESI) spectrometer. Routine monitoring of reactions was performed by TLC, using 0.2 mm Kieselgel 60 F_{254} precoated aluminum sheets, commercially available from Merck. Visualization was done by fluorescence quenching at 254 nm, exposure to iodine vapor, and/or 2,4-dinitrophenylhydrazine solution. All the column chromatographic separations were done by using silica gel (Acme, 60–120 mesh). HPLC was done on a Daicel chiral column having 0.46 cm internal diameter×25 cm length. Petroleum ether used was of boiling range 60–90 °C. Reactions that needed anhydrous conditions were run under an atmosphere of nitrogen or argon using flame dried glassware. The organic extracts were dried over anhydrous sodium sulfate. Evaporation of solvents was performed at reduced pressure. THF and diethyl ether were distilled from sodium metal/benzophenone. CH_2Cl_2 and $CHCl_3$ were distilled from CaH_2.

4.2. Preparation of the ligands (Scheme 1)

4.2.1. (8S,9S)-9-Amino(9-deoxy)-epicinchonidine ***1a****, (8S,9S)-9-amino(9-deoxy)-epiquinine* ***1b****, (8R,9R)-9-amino(9-deoxy)-epicinchonine* ***1c****, and (8R,9R)-9-amino(9-deoxy)-epiquinidine* ***1d****.* The compounds **1a**–**d** were prepared according to the literature.[13]

4.2.2. Synthesis of Schiff base ligand ***2b****.* In a flask, a solution of salicylaldehyde (0.24 mL, 2.3 mmol) and (8S,9S)-9-amino-(9-deoxy)-epiquinine (0.513 g, 1.588 mmol) in toluene (40 mL) was heated to reflux. After that, two scoops of Al_2O_3 (about 1.5 g, dried at 110 °C for 2 h before use) were added to the solution. And then added one more scoop each hour.

After 4 h, the temperature was slowly cooled down to room temperature. Then the mixture was filtrated and the residue was washed with Et_2O. The combined organic layers were removed under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/methanol/Et_3N 30:1:1) to afford Schiff base ligand **2b** (570 mg, 84% yield) as a yellow solid. $[\alpha]_D^{25}$ −76.2 (*c* 1.0, CH_2Cl_2). Mp 165–166 °C. IR (KBr) ν_{max}: 3427, 2937, 2864, 1627, 1278 cm^{-1}. ^{1}H NMR (400 MHz, DMSO) δ=13.5 (s, 1H, OH), 8.75 (t, *J*=3.6, 14.0 Hz, 2H, ArH), 7.98 (d, *J*=8.8 Hz, 1H, *CH*=N), 7.72 (t, *J*=21.6, 3.6 Hz, 2H, ArH), 7.43 (dd, *J*=10.0, 7.2 Hz, 2H, ArH), 7.30 (t, *J*=7.2, 7.6 Hz, 1H, ArH), 6.86 (dd, *J*=7.2, 8.8, 8.4 Hz, 2H, ArH), 5.89–5.80 (m, 1H, CH_2=C*H*), 5.24 (d, *J*=8 Hz, 1H, CH), 5.01–4.90 (m, 2H, *C*H_2=CH), 3.99 (s, 3H, OCH_3), 3.63–3.34 (m, 2H, CH_2), 3.07 (t, *J*=12, 10.8 Hz, 1H, CH), 2.64 (d, *J*=12.8 Hz, 2H, CH_2), 2.21 (s, 1H, CH), 1.52 (d, *J*=28.8 Hz, 3H, CH), 1.30 (s, 1H, CH), 0.75 (q, *J*=7.2, 4.0, 7.2 Hz, 1H, CH). ^{13}C NMR (100 MHz, DMSO) δ=165.7, 160.2, 157.3, 147.7, 144.3, 142.2, 132.4, 131.6, 131.5, 127.5, 121.4, 121.3, 118.7, 118.6, 116.4, 114.1, 102.2, 59.7, 55.6, 39.9, 39.5, 27.5, 27.4, 25.5 ppm. HRMS (ESI, M+H) calcd for $C_{27}H_{30}N_3O_2$ 428.2338, found 428.2333.

4.2.3. Synthesis of Schiff base ligand ***2a****.* Ligand **2a** was prepared in the same way as **2b** from (8S,9S)-9-amino(9-deoxy)-epicinchonidine with salicylaldehyde. The product was obtained as a yellow solid, 75% yield. $[\alpha]_D^{25}$ −88.4 (*c* 1.0, CH_2Cl_2). Mp 87–88 °C. IR (KBr) ν_{max}: 3429, 2939, 2864, 1627, 1278 cm^{-1}. ^{1}H NMR (400 MHz, DMSO) δ=13.4 (s, 1H, OH), 8.93 (s, 1H, ArH), 8.71(s, 1H, *CH*=N), 8.59 (d, *J*=8.4 Hz, 1H, ArH), 8.06 (t, *J*=8.4, 9.2 Hz, 1H, ArH), 7.75 (dd, *J*=18.8, 7.2 Hz, 2H, ArH), 7.29–7.44 (m, 3H, ArH), 6.86 (dd, *J*=6.8, 7.6, 8.4 Hz, 2H, ArH), 5.92–5.83 (m, 1H, CH_2=C*H*), 5.37 (d, *J*=8.8 Hz, 1H, CH), 4.97 (dd, *J*=17.6, 13.2 Hz, 2H, *C*H_2=CH), 3.06–3.53 (m, 3H, CH), 2.65 (d, *J*=11.6 Hz, 2H, CH_2), 2.24 (s, 1H, CH), 1.32 (m, 3H, CH), 1.22–1.09 (m, 1H, CH), 0.84 (m, 1H, CH). ^{13}C NMR (100 MHz, DMSO) δ=165.7, 160.2, 150.4, 148.1, 145.8, 142.2, 131.7, 130.0, 129.3, 126.9, 126.6, 123.8, 120.8, 118.7, 118.6, 102.2, 117.2, 116.3, 114.3, 59.8, 55.6,

39.9, 27.4, 25.6 ppm. HRMS (ESI, M+H) calcd for $C_{26}H_{28}N_3O$ 398.2232, found 398.2227.

*4.2.4. Synthesis of Schiff base ligand **2c**.* Ligand **2c** was prepared in the same way as **2b** from (8*R*,9*R*)-9-amino(9-deoxy)-epicinchonine with salicylaldehyde. The product was obtained as a yellow solid, 78% yield. $[\alpha]_D^{25}$ +65.5 (*c* 1.0, CH_2Cl_2). Mp 88–89 °C. IR (KBr) ν_{max}: 3444, 2927, 2862, 1627, 1278 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ=9.91 (s, 1H, OH), 8.79 (d, *J*=4.4 Hz, 1H, ArH), 8.46 (d, *J*=9.20 Hz, 1H, C*H*=N), 8.08 (d, *J*=11.20 Hz, 1H, ArH), 7.70–7.42 (m, 7H, ArH), 7.01 (t, *J*=10.80 Hz, 1H, ArH), 5.92 (s, 1H, CH_2=C*H*), 5.45 (s, 1H, CH), 5.13–5.07 (m, 2H, CH_2=CH), 3.55 (d, *J*=9.60 Hz, 1H, CH), 3.00 (m, 4H, CH), 2.31 (s, 1H, CH), 1.65 (s, 1H, CH), 1.54 (s, 1H, CH), 1.41–1.35 (m, 2H, CH), 1.00–0.87 (m, 1H, CH). ^{13}C NMR (100 MHz, MeOD) δ=163.4, 151.0, 148.9, 137.9, 134.0, 133.9, 133.6, 133.4, 130.8, 130.2, 129.9, 129.7, 129.6, 129.2, 127.9, 122.9, 120.5, 118.6, 115.4, 54.5, 49.7, 47.2, 40.5, 29.0, 27.3 ppm. HRMS (ESI, M+H) calcd for $C_{26}H_{28}N_3O$ 3398.2232, found 398.2227.

*4.2.5. Synthesis of Schiff base ligand **2d**.* Ligand **2d** was prepared in the same way as **2b** from (8*R*,9*R*)-9-amino(9-deoxy)-epiquinidine with salicylaldehyde. The product was obtained as a yellow solid, 81% yield. $[\alpha]_D^{25}$ +70.0 (*c* 1.0, CH_2Cl_2). Mp 165–166 °C. IR (KBr) ν_{max}: 3425, 2983, 2958, 1622, 1255 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ=10.00 (s, 1H, OH), 8.70 (d, *J*=5.60 Hz, 1H, ArH), 8.36 (s, 1H, C*H*=N), 8.01 (d, *J*=12.00 Hz, 1H, ArH), 7.92 (s, 1H, ArH), 7.83 (d, *J*=10.00 Hz, 1H, ArH), 7.77 (m, 2H, ArH), 7.55 (d, *J*=5.2 Hz, 1H, ArH), 7.38 (m, 2H, ArH), 5.77–5.72 (m, 1H, CH_2=C*H*), 5.50 (s, 1H, CH), 5.01–4.88 (m, 2H, CH_2=CH), 4.01 (s, 3H, OCH_3), 3.66 (t, *J*=11.6 Hz, 1H, CH), 3.52 (s, 1H, CH), 3.27–3.21 (m, 1H, CH), 2.76 (d, *J*=15.60 Hz, 2H, CH_2), 2.26 (s, 1H, CH), 1.62 (d, *J*=34.8 Hz, 2H, CH_2), 1.45–1.40 (m, 1H, CH), 1.26 (s, 1H, CH), 0.97–0.90 (m, 1H, CH). ^{13}C NMR (100 MHz, MeOD) δ=162.1, 160.0, 148.4, 146.6, 145.4, 140.5, 134.9, 133.3, 132.1, 131.9, 130.1, 129.6, 124.0, 120.0, 118.6, 117.7, 116.0, 102.8, 62.9, 60.2, 50.3, 47.6, 39.8, 28.8, 26.6, 25.4 ppm. HRMS (ESI, M+H) calcd for $C_{27}H_{30}N_3O_2$ 428.2338, found 428.2333.

*4.2.6. Synthesis of Schiff base ligand **2e**.* Ligand **2e** was prepared in the same way as **2b** from (8*S*,9*S*)-9-amino(9-deoxy)-epiquinine with benzaldehyde. The product was obtained as a light brown oil, 79% yield. $[\alpha]_D^{25}$ −46.4 (*c* 1.0, CH_2Cl_2). IR (KBr) ν_{max}: 2939, 2864, 1627, 1278 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ=8.77 (d, *J*=5.2, 1H, ArH), 8.38 (s, 1H, C*H*=N), 8.06 (d, *J*=12.4 Hz, 1H, ArH), 7.58 (s, 1H, ArH), 7.47–7.40 (m, 2H, ArH), 7.22 (d, *J*=6.4 Hz, 1H, ArH), 6.92 (d, *J*=10.8 Hz, 1H, ArH), 6.84 (t, *J*=10.0 Hz, 1H, ArH), 5.79 (m, 1H, CH_2=C*H*), 5.03–5.48 (m, 3H, CH_2=CH and CH), 4.01 (s, 3H, OCH_3), 3.59 (d, *J*=11.6 Hz, 1H, CH), 3.27–3.16 (m, 2H, CH_2), 2.82–2.78 (m, 2H, CH_2), 2.28 (s, 1H, CH), 1.68 (s, 1H, CH), 1.59 (m, 2H, CH_2), 1.43 (m, 1H, CH), 0.89–0.84 (m, 1H, CH). ^{13}C NMR (100 MHz, MeOD) δ=169.7, 164.1, 148.3, 145.3, 142.7, 142.6, 137.4, 132.7, 132.1, 131.5, 129.7, 129.5, 128.0, 123.8, 123.3, 115.1, 104.3, 103.3, 65.2, 61.5, 56.9, 49.3, 41.5, 40.7, 29.0, 28.7, 26.7 ppm. HRMS (ESI, M+H) calcd for $C_{27}H_{30}N_3O$ 412.2389, found 412.2383.

*4.2.7. Ligand **2f** was prepared as following step.* A solution of **2b** (202 mg, 0.47 mmol) and $NaBH_4$ (114 mg, 2.8 mmol) in absolute ethanol (15 mL) was refluxed with stirring for 24 h. The solution was cooled to room temperature and H_2O (10 mL) was added to destroy excessive $NaBH_4$. The mixture solution was extracted with CH_2Cl_2 (3×30 mL). The combined extracts were washed with a saturated NH_4Cl solution (3×10 mL), water (3×10 mL) and the organic layer was dried over anhydrous $MgSO_4$. After filtered and removed the solvent under reduced pressure, white solid product was obtained and purified by recrystallization with methanol as a fawn-colored solid **2f**, 92% yield. $[\alpha]_D^{25}$ +36.0 (*c* 1.0, CH_2Cl_2). Mp 134–135 °C. IR (KBr) ν_{max}: 3261, 2939, 2864, 1622, 1240 cm^{-1}. ^1H NMR (400 MHz, DMSO) δ=13.5 (s, 1H, OH), 8.78 (s, 1H, ArH), 7.97 (d, *J*=8.4 Hz, 1H, ArH), 7.77 (s, 1H, ArH), 7.54 (s, 1H, ArH), 7.43 (t, *J*=7.6, 14.8 Hz, 1H, ArH), 6.99 (d, *J*=29.6 Hz, 2H, ArH), 6.60 (d, *J*=38.8 Hz, 2H, ArH), 5.79–5.67 (m, 1H, CH_2=C*H*), 5.05–4.86 (m, 2H, CH_2=CH), 4.63 (s, 1H, CH), 3.91 (s, 3H, OCH_3), 3.85 (s, 2H, CH_2), 3.49–3.30 (m, 3H, CH), 2.82 (s, 2H, CH_2), 2.39 (s, 1H, CH), 1.61 (m, 3H, CH), 1.22 (s, 2H, CH_2), 0.76 (s, 1H, CH). ^{13}C NMR (100 MHz, DMSO) δ=157.3, 155.7, 147.8, 143.8, 131.3, 129.3, 129.2, 127.9, 125.5, 121.4, 119.7, 118.3, 114.9, 101.6, 60.6, 55.5, 45.9, 40.0, 38.1, 26.6, 24.4 ppm. HRMS (ESI, M+H) calcd for $C_{27}H_{32}N_3O_2$ 430.2400, found 430.2377.

*4.2.8. Synthesis of Schiff base ligand **2g**.* Ligand **2g** was prepared in the same way as **2b** from (8*S*,9*S*)-9-amino(9-deoxy)-epiquinine with 1,2-benzenedialdehyde. The product was obtained as a yellow solid, 54% yield. $[\alpha]_D^{25}$ −65.0 (*c* 1.0, CH_2Cl_2). Mp 176–178 °C. IR (KBr) ν_{max}: 3413, 2972, 2860, 1622, 1226 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ=8.74 (d, *J*=4 Hz, 2H, ArH), 8.01 (d, *J*=9.2 Hz, 4H, ArH), 7.54 (d, *J*=1.2 Hz, 2H, ArH), 7.38–7.33 (m, 6H, ArH), 7.12 (s, 2H, ArH), 5.90–5.59 (m, 2H, CH_2=C*H*), 5.05–4.91 (m, 4H, CH_2=CH), 4.67 (d, *J*=20 Hz, 2H, CH), 3.85 (s, 6H, OCH_3), 3.15–3.10 (dd, *J*=10.4, 4, 9.6 Hz, 2H, CH), 2.85–2.60 (m, 10H, CH), 1.83–1.26 (m, 10H, CH). ^{13}C NMR (100 MHz, $CDCl_3$) δ=157.7, 147.6, 142.0, 141.4, 129.3, 126.6, 120.9, 118.5, 114.7, 106.3, 101.2, 71.3, 56.7, 55.8, 43.2, 42.0, 27.8, 27.3, 21.5 ppm. HRMS (ESI, M+H) calcd for $C_{48}H_{53}N_6O_2$ 745.4230, found 745.4225.

*4.2.9. Ligand **2h** was prepared as following step.* Ligand **2b** (128 mg, 0.3 mmol) and $NaHCO_3$ were dissolved in 10 mL acetone. Dimethyl sulfate (34 μL, 0.36 mmol) dissolved in 2 mL acetone was added into the above solution drop by drop at 0 °C. Then the mixture was stirred at room temperature for 6 h. After that, 1 M NaOH (5 mL) was added and stirred vigorously for 10 min to destruct the remnant dimethyl sulfate. The aqueous phase was washed with ethyl acetate (3×20 mL). The combined organic layers were removed under reduced pressure. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/methanol/Et_3N 50:1:1) to afford yellow solid (2 h, 55 mg, 41% yield). $[\alpha]_D^{25}$ −35.5 (*c* 1.0, CH_2Cl_2). Mp 183–184 °C. IR (KBr) ν_{max}: 2970, 2937, 2793, 2761, 2681, 1450 cm^{-1}. ^1H NMR (400 MHz, $CHCl_3$) δ=8.77 (s, 1H, ArH), 8.39 (s, 1H, ArH), 8.05 (d, *J*=9.2 Hz, 1H, ArH), 7.74 (s, 1H, ArH), 7.58 (d, *J*=2.0 Hz, 1H, ArH), 7.47 (d, *J*=4.0 Hz, 2H, ArH), 7.41 (d, *J*=6.8 Hz, 2H, ArH), 7.22 (d, *J*=8.0 Hz, 1H, ArH), 6.91 (d, *J*=8.0 Hz, 1H, ArH), 6.84 (m, 1H, CH_2=C*H*), 5.82–5.74 (m, 1H, CH_2=CH), 5.03–4.99 (m, 1H, CH_2=CH), 4.96 (s, 1H, CH), 4.01 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.40–3.36 (m, 1H, CH), 3.02 (s, 1H, CH), 2.94 (s, 1H, CH), 2.09 (s, 2H, CH_2), 1.97 (s, 1H, CH), 1.68 (s, 1H, CH), 1.59–1.57 (m, 1H, CH), 0.97–0.95 (m, 1H, CH). ^{13}C NMR (100 MHz, DMSO) δ=165.7, 160.2, 159.3, 118.7, 116.3, 114.2, 102.2, 64.9, 56.1, 56.0, 55.5, 27.5, 27.4, 25.3 ppm. Anal. Calcd for $C_{28}H_{31}N_3O_2$: C, 76.16; H, 7.08; N, 9.52. Found: C, 76.11; H, 7.15; N, 9.47. LC-MS (ES, M+H) calcd for $C_{28}H_{32}N_3O_2$ 442.24, found 442.24.

*4.2.10. Preparation of Cu(II)/**2b** catalyst.* To a solution of Schiff base ligand **2b** (201 mg, 0.5 mmol) in EtOH (10 mL), $Cu(OAc)_2 \cdot H_2O$ (50 mg, 0.25 mmol) in water (1.5 mL) was added and the mixture was stirred for 3 h under reflux. After cooling down to 0 °C, the Cu/Schiff base **2b** complex was collected and dried under reduced pressure to afford the dark green solid (152 mg). The complex can be stored under air at room temperature.

4.3. General procedure for the asymmetric Henry reaction

The metal/Schiff base catalyst (0.025 mmol) was dissolved in solvent (1 mL). Then, the corresponding aldehyde (0.25 mmol) was added. After stirring for 1 h at room temperature, the mixture was cool down to −20 °C (or to indicated temperature). Then nitroalkane (1.25 mmol) and the corresponding basic additive were added. The stirring was continued for indicated time and after that

the reaction mixture was diluted with ether (3 mL). The resulting mixture suspension was filtered through a pad of Celite to remove the catalyst, and the filtrate solution was evaporated under reduced pressure. The resulting residue was purified by silica gel flash column chromatography (hexane/ether=9:1) to afford the product.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.08.076. These data include MOL files and InChIKeys of the most important compounds described in this article.

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