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Promotion of Henry reactions using $Cu(OTf)_2$ and a sterically hindered Schiff base: access to enantioenriched β-hydroxynitroalkanes

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ABSTRACT

The steric and electronic properties of chiral Schiff base ligands derived from *cinchona* alkaloids were evaluated in asymmetric Henry reactions. Amongst these, the sterically hindered ligand **2** showed outstanding catalytic efficiency in the Cu(II) catalyzed asymmetric addition of nitroalkanes to a variety of aldehydes to afford the desired adducts in high yields (up to 97%) with excellent enantioselectivities (up to 99% ee) and moderate to good diastereoselectivities (up to 84:16 dr).

1. Introduction

Strategies for controlling the regio- and stereoselectivity of reactions are at the heart of modern organic chemistry research.[1] To obtain high selectivity in these reactions, an empirical approach to ligand design remains a powerful protocol.[2] New ligands are usually based on some well-designed structures, which have the desired steric and electronic features, or are based on well-known chirality inducers, such as BINAP,[3] BINOL,[4] BOX,[2d,5] TADDOL,[6] *cinchona* alkaloid derivatives,[7] and salen complexes[8] etc. Some ligands have been designed by combining two or more of these moieties, and others by subtle modification of existing ligands to optimize their properties. With respect to the latter strategy, the steric and electronic factors of existing ligands are basic considerations in the development of more efficient ligands. Amongst the groups used as substitutes, *tert*-butyl[9] finds use as a bulky substituent with electron-donating properties, which exhibits excellent activity and selectivity in many transformations.

The Henry (Nitroaldol) reaction constitutes one of the most useful methodologies for carbon–carbon bond formation.[10] Owing to the chemical versatility of the nitro group, the resulting β-hydroxynitroalkanes, especially in an optically active form, are useful fragments in the synthesis of biologically active compounds and polyfunctionalized molecules.[11] In the last two decades, since the pioneering work of Shibasaki,[12] where a heterobimetallic lanthanoid catalyst was used, various versions of metal-catalyzed (Zn,[13] Cu,[14] Co,[15] Mg,[16] or Cr[17]) asymmetric Henry reactions have been developed. Amongst these metal complexes, Cu-catalyzed Henry reactions have received much attention since copper is cheap and of low toxicity, and also it has excellent chelating properties to coordinate with bidentate as well as polydentate ligands. Our previous study has revealed a Cu-catalyzed enantioselective addition of nitroalkanes to aldehydes using a novel type of Schiff base ligand based on the *cinchona* alkaloids.[18] It is the first report of successful use of *cinchona*-based Schiff base ligands in asymmetric catalysis. However, only moderate conversions were obtained and high ligand loading (20 mol %) were required. To further improve this highly enantioselective catalytic system, we have varied the steric and electronic properties of the *cinchona*-based ligands. Herein, we report a number of new Schiff base ligands (Fig. 1) and their activities in Cu(II)-catalyzed Henry reactions. The *tert*-butyl group has proven to be able to increase the catalytic efficiency dramatically.

The methodology herein provides several practical advantages: (1) The most efficient Schiff base ligand **2** is easily synthesized in two steps and in an overall 85% yield. (2) The method also features a lower catalyst and ligand loading (both 5 mol %). (3) The scope of the present catalytic system is quite extensive; It demonstrates high efficiency in enantioselective Henry reactions of both aromatic and aliphatic aldehydes with nitromethane or nitroethane.

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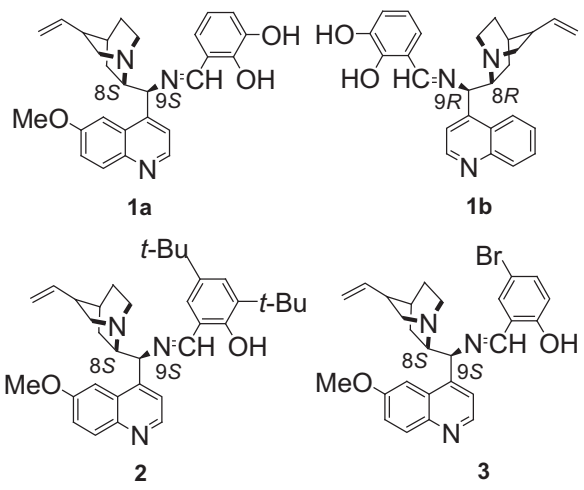


Fig. 1. The Schiff base ligands screened in asymmetric Henry reactions.

2. Results and discussion

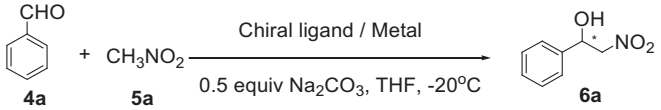
The Schiff base ligands were readily prepared in high yields from commercially available *cinchona* alkaloids and salicylaldehyde derivatives (Fig. 1). Reaction between benzaldehyde (**4a**) and nitromethane (**5a**) was carried out as the model reaction to screen these ligands.

The pseudoenantiomeric *cinchona* alkaloid derivatives **1a** and **1b** were first explored as the chiral sources in the model reaction. As depicted in Table 1, the absolute configuration of the product was highly dependent upon the configuration at C8- and C9- of the *cinchona* alkaloids. Also, the presence of a methoxy group at the 6-position of quinine alkaloids resulted in a higher ee value (Table 1, entries 1 and 2). However, the performances of these two ligands were not satisfactory. On one hand, the electron-donating hydroxy group at the 3-position of salicylaldehyde moiety in both of ligands gave no benefits to activity or selectivity, while on the other, despite the fact that the hydroxy group might coordinate well to Cu(II), it failed to affect the possible transition state when compared to our previous research. We then turned to ligands **2** and **3**, which have significantly different steric and electronic properties to **1a** and **1b**. Ligand **2**, with two hindered *tert*-butyl substituents, exhibited a promising catalytic activity in the reaction (entry 3), while ligand **3**, bearing an electron withdrawing group, was less efficient with respect to both the yield and ee value of the model reaction (entry 4). Both the yield and ee value were maintained when the catalyst loading of ligand **2** was further reduced to 5 mol % (entry 5 vs entry 3). Thus, it was notable that both the nature of the chiral backbones and the substituents on the moieties are pivotal elements for the asymmetric induction in the reaction, which again provided solid evidence to the importance of steric and electronic factors in the activity of the ligands.

Encouraged by the preliminary results, our attention was next focused on the screening of a series of transition metal salts with 5 mol % catalyst loading. Generally, Cu salts demonstrated better results than the others, and the enantioselectivity was dependent on the counterions (Table 1). Amongst them, $Cu(OTf)_2$ proved to be the best choice, affording the Henry adduct in high yield with an excellent ee value (entry 11). Although other Cu salts like $Cu(OAc)_2\cdot 2H_2O$, CuCl, CuBr, and CuI gave promising ee values, the reactions were sluggish (entries 5 and 8–10). In contrast, other metals, such as Zn, Ag, Co, and Ni, showed inferior performances both in activity and selectivity (entries 12–15). Furthermore, we found no effect of the ligand **2**/$Cu(OTf)_2$ ratio on either the yield or ee value (entry 16 vs entry 11). Thus, 5 mol % of ligand **2**/$Cu(OTf)_2$ 1:1 complex was selected as the most efficient catalyst for the model reaction.

As the reaction temperature typically plays a significant role in determining the ee values of adducts in asymmetric catalysis, the optimization of the temperature was then carried out. The catalytic reaction performed at room temperature only resulted in moderate ee value though the yield reached 96% (Table 2, entry 1). On

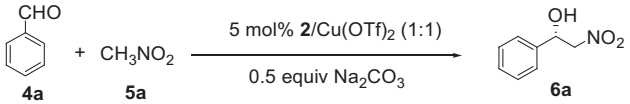
Table 1
Evaluation of chiral Schiff base ligands and central metals in the asymmetric Henry reaction[a]



Entry	Metal	Ligand	Ratio of metal:ligand	Yield[b] (%)	ee (%)[c]
1[e]	$Cu(OAc)_2\cdot H_2O$	**1a**	1:2	61	70 (*S*)[d]
2	$Cu(OAc)_2\cdot H_2O$	**1b**	1:2	53	43 (*R*)
3	$Cu(OAc)_2\cdot H_2O$	**2**	1:2	86	87 (*S*)
4	$Cu(OAc)_2\cdot H_2O$	**3**	1:2	73	73 (*S*)
5[f]	$Cu(OAc)_2\cdot H_2O$	**2**	1:2	85	87 (*S*)
6	$CuCl_2\cdot 2H_2O$	**2**	1:2	13	18 (*S*)
7	$CuBr_2$	**2**	1:2	63	51 (*S*)
8	CuCl	**2**	1:1	65	68 (*S*)
9	CuBr	**2**	1:1	52	73 (*S*)
10	CuI	**2**	1:1	73	73 (*S*)
11	$Cu(OTf)_2$	**2**	1:2	92	87 (*S*)
12	$Zn(OTf)_2$	**2**	1:2	13	18 (*S*)
13	AgOTf	**2**	1:1	27	7 (*S*)
14	$CoCl_2\cdot 2H_2O$	**2**	1:2	76	39 (*S*)
15	$NiCl_2\cdot 6H_2O$	**2**	1:2	72	19 (*S*)
16	$Cu(OTf)_2$	**2**	1:1	92	88 (*S*)

[a] All reactions were carried out with 0.5 mmol of benzaldehyde, 5 mmol of nitromethane and 50 mol % Na_2CO_3 in 2 mL of THF in the presence of 5 mol % of catalyst at −20 °C. All the catalysts were formed in situ, about 1 h before addition of benzaldehyde.
[b] Isolated yield.
[c] Determined by HPLC analysis (Chiralcel OD-H column).
[d] By comparison of the HPLC elution order of the enantiomers with the literature data.[14]
[e] With 10 mol % of catalyst loading in entries 1–4.
[f] With 5 mol % of catalyst loading in entries 5–16.

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



Entry	Solvent	Temp (°C)	Yield[b] (%)	ee (%)[c]
1	THF	rt	96	51
2	THF	0	96	64
3	THF	−10	94	72
4	THF	−20	92	88
5	THF	−40	52	78
6	Toluene	−20	81	66
7	MeOH	−20	96	22
8	EtOH	−20	93	62
9	*i*-PrOH	−20	90	68
10	Neat	−20	NR	—
11	CH_3CN	−20	82	76
12	TBME	−20	83	62
13	CH_2Cl_2	−20	68	46
14	$CHCl_3$	−20	76	58

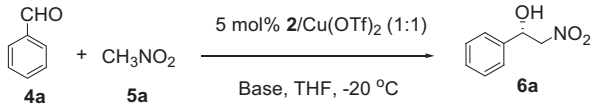
[a] All reactions were carried out with 0.5 mmol of benzaldehyde and 5 mmol of nitromethane in 2 mL of solvent in the presence of 5 mol % of catalyst.
[b] Isolated yield.
[c] Determined by HPLC analysis (Chiralcel OD-H column).

lowering the temperature, the ee value increased, accompanied by a slight decrease in yield. However, at −40 °C, the selectivity was not further improved as expected (entry 5). It was obvious that −20 °C was the most suitable temperature in view of both the yield and the ee value (entry 4).

In addition, a series of solvents (e.g., methanol, ethanol, isopropanol, nitromethane, THF, TBME, acetonitrile, toluene, dichloromethane, and chloroform) were also tested in the catalytic enantioselective Henry reaction between benzaldehyde and nitromethane in combination with ligand **2**, $Cu(OTf)_2$, and Na_2CO_3 (Table 2, entries 4 and 6–14). Generally, nonprotonic solvents were found to be superior to protonic and halogenated ones, and among the different solvents tested, THF was clearly the best choice for this reaction, with 92% yield and 88% ee (entry 4).

It is believed that the deprotonation of nucleophiles is necessary for the proceeding of Henry reaction, which has also been clearly demonstrated in our case (Table 3, entry 1).[19] To increase the reactivity, a series of Brønsted bases were tested in the reaction between benzaldehyde and nitromethane in the presence of 5 mol % of ligand **2**/$Cu(OTf)_2$ 1:1 complex and 50 mol % of base. As illustrated in Table 3, KOH, K_2CO_3, DBU, $CsCO_3$, Et_3N gave good yields but poor enantioselectivities (entries 4–8). DIPEA, DMAP gave lower yields and the ee values were moderate (entries 9 and 10). In addition, use of the much weaker base 2,2′-bipyridine gave no reaction even with a longer reaction time (>72 h) (entry 11). Amongst the bases evaluated, Na_2CO_3 and DABCO showed the best activities and ee values (entries 2 and 3). Using Na_2CO_3, we also tested the effect of reducing its loading to 20 mol %; the yield decreased dramatically, albeit with a maintained ee value (entry 12).

Table 3
Effects of the base additives in the asymmetric Henry reaction[a]

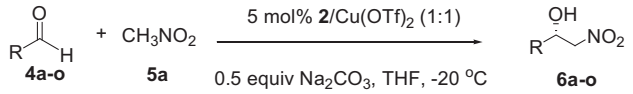


Entry	Base additive	Loading of base (mol %)	Yield[b] (%)	ee (%)[c]
1	—	—	NR	ND
2	Na_2CO_3	50	92	88
3	DABCO	50	88	87
4	KOH	50	93	52
5	K_2CO_3	50	87	38
6	DBU	50	91	25
7	$CsCO_3$	50	97	45
8	Et_3N	50	83	45
9	DIPEA	50	63	49
10	DMAP	50	47	76
11[d]	2,2′-Bipyridine	50	NR	ND
12	Na_2CO_3	20	56	87

[a] All reactions were carried out with 0.5 mmol of benzaldehyde and 5 mmol of nitromethane in 2 mL of THF in the presence of 5 mol % of catalyst at −20 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis (Chiralcel OD-H column).
[d] After 72 h.

With the optimized conditions in hand, the scope of the catalytic enantioselective nitroaldol reaction was demonstrated by treatment of various aldehydes with nitromethane in the presence of 5 mol % of the ligand **2**/$Cu(OTf)_2$ 1:1 complex and 50 mol % of Na_2CO_3 in THF at −20 °C. As illustrated in Table 4, all the Henry reactions with aromatic and aliphatic aldehydes gave adducts in good yields and enantioselectivities. For the aromatic aldehydes, substrates with electron-donating groups or electron-withdrawing groups at the phenyl ring demonstrated no significant differences (Table 4, entries 1–9). The position of the substituent on the phenyl ring of aromatic aldehydes also showed little effect on the ee value (entries 2–4 and entries 7–8). The bulky aldehyde 1-naphthaldehyde **4j** afforded the

Table 4
Ligand **2**/$Cu(OTf)_2$ complex catalyzed enantioselective Henry reactions of nitromethane with different aldehydes[a]



Entry	Aldehyde	Time (h)	Yield[b] (%)	ee (%)[c]
1	Benzaldehyde (**4a**)	20	92	88
2	4-Chlorobenzaldehyde (**4b**)	12	92	85
3	3-Chlorobenzaldehyde (**4c**)	12	93	84
4	2-Chlorobenzaldehyde (**4d**)	12	95	88
5	4-Bromobenzaldehyde (**4e**)	12	94	90
6	4-Methylbenzaldehyde (**4f**)	10	97	88
7	2-Methoxybenzaldehyde (**4g**)	10	95	93
8	4-Methoxybenzaldehyde (**4h**)	10	96	99
9	4-Fluorbenzaldehyde (**4i**)	10	96	90
10	1-Naphthaldehyde (**4j**)	10	96	91
11	3-Phenylpropanal (**4k**)	24	91	99
12	Furan-2-carbaldehyde (**4l**)	24	89	99
13	Cyclohexanecarbaldehyde (**4m**)	24	83	98
14	Isovaleraldehyde (**4n**)	30	85	87
15	Butyraldehyde (**4o**)	28	89	85

[a] All reactions were carried out with 0.5 mmol of the aldehyde and 5 mmol of nitromethane in 2 mL of THF in the presence of 5 mol % of catalyst, 50 mol % of Na_2CO_3 at −20 °C.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis using Chiralcel OD-H, OJ-H or Chiralpak AD-H column.

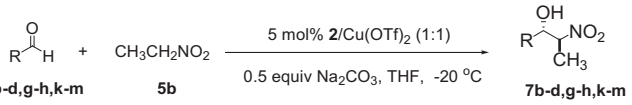
corresponding adduct in excellent yield and with a high ee (entry 10). The heteroaromatic aldehyde furan-2-carbaldehyde **4l** also furnished the adduct with 99% ee (entry 12). Most remarkably, all aliphatic aldehydes investigated, (cyclic, branched and nonbranched) reacted smoothly with nitromethane under mild conditions to afford the optically active Henry adducts **6k**, **6m**, **6n**, and **6o** in reasonable yields with excellent enantioselectivities (entries 11 and 13–15).

To date, although various highly efficient catalytic systems have been developed for enantioselective Henry reactions, nitroalkanes other than nitromethane have been less explored.[14p,20] Therefore, to further evaluate our catalytic system, we examined nitroethane as the nucleophile in diastereoselective Henry reactions. As showed in Table 5, in most cases, the reactions were carried out with moderate to good diastereoselectivities, and both the *anti* and *syn* products could be obtained with high enantioselectivity. For the benzaldehyde derivatives investigated, the ee values of the *syn* products reached up to 99% (entries 1–5). The aryl substituted aliphatic aldehyde 3-phenylpropanal **4k** and the heteroaryl aldehyde furan-2-carbaldehyde **4l** afforded products with moderate diastereoselectivities, while the ee values of the both *anti* and *syn* products were excellent (entries 6 and 7). Gratifyingly, the mainly *anti* adduct (*anti*/*syn*=84:16) with up to 99% ee was obtained when the aliphatic aldehyde cyclohexanal **4m** reacted with nitroethane (entry 8).

To account for the stereochemical outcome of the reaction, the absolute configuration of ligand **2** was identified by its crystal structure (Fig. 2). Unfortunately, despite many efforts, we could not obtain the X-ray crystal structure of the ligand **2**/Cu(II) complex. However, the stereochemistry of ligand **2** revealed that the atoms O1, N1, and N2 could all potentially coordinate to the copper center. In addition, other efforts were made to elucidate a possible transition state. Initially, the formation of the ligand **2**/Cu(II) 1:1 complex was evidenced by MS (ES, M+H) calcd for: $C_{35}H_{46}N_3O_2Cu(OTf)_2$ 901.42, found: 901.28. Furthermore, IR spectra of both ligand **2** and its Cu(II) complex (see Supplementary data) showed the disappearance of the hydroxyl signal in the latter, suggesting coordination of the deprotonated hydroxyl on the salicylaldehyde moiety to the copper center.

On the basis of the preliminary experimental investigations and previously mentioned steric and electronic considerations, we

Table 5
Ligand **2**/$Cu(OTf)_2$ complex catalyzed diastereoselective Henry reactions of nitroethane with different aldehydes[a]



Entry	Aldehyde	Time (h)	Yield (%)[b]	*anti*/*syn*[c]	ee (%)[d]	
					anti	*syn*
1	4-Chlorobenzaldehyde (**4b**)	20	92	58:42	74	99
2	3-Chlorobenzaldehyde (**4c**)	20	95	57:43	99	99
3	2-Chlorobenzaldehyde (**4d**)	20	91	84:16	76	99
4	2-Methoxybenzaldehyde (**4g**)	18	96	75:25	73	99
5	4-Methoxybenzaldehyde (**4h**)	18	87	42:58	75	99
6	3-Phenylpropanal (**4k**)	30	81	44:56	99	99
7	Furan-2-carbaldehyde (**4l**)	36	86	41:59	99	82
8	Cyclohexanecarbaldehyde (**4m**)	48	83	84:16	99	70

[a] All reactions were carried out with 0.5 mmol of the aldehyde and 5 mmol of nitroethane in 2 mL of THF in the presence of 5 mol % of catalyst, 50 mol % of Na_2CO_3 at −20 °C.
[b] Isolated yield.
[c] By comparison with literature data.[20]
[d] Determined by chiral HPLC analysis using Chiralcel OD-H, OJ-H or Chiralpak AD-H column.

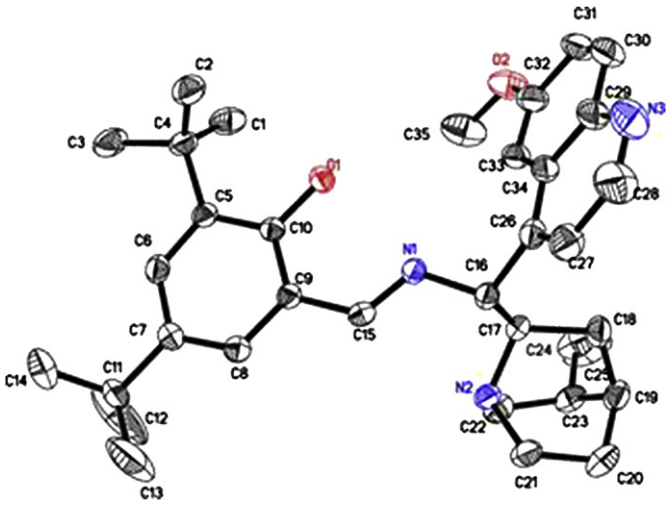


Fig. 2. X-ray crystal structure of ligand **2**.[21]

propose the possible transition state illustrated in Fig. 3. In the assumed active species, the carbonyl oxygen atom of the electrophile is coordinated at one of the more Lewis acidic equatorial sites for maximum activation. Thus, the deprotonated nitromethane as nucleophile binds its oxygen atom to the metal center from the axial side favoring *Re*-face attack at the aldehyde, affording the adduct with the *S* configuration, while *Si*-face attack of nitromethane to the aldehyde is hindered by steric repulsion between the phenyl ring of the aldehyde and the *tert*-butyl substituent on the ligand.

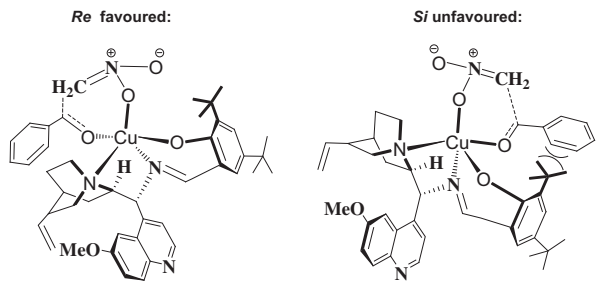


Fig. 3. Plausible transition state for the enantioselective Henry reaction.

3. Conclusion

In summary, the new Schiff base **2**, which was easily prepared from *cinchona* alkaloids, together with $Cu(OTf)_2$, showed high efficiency in enantioselective Henry reactions between nitroalkanes and a wide range of aromatic and aliphatic aldehydes. Furthermore, the reaction proceeded with a low catalyst loading (5 mol %). A possible transition state was also proposed based on the X-ray crystal structure of ligand **2** and the absolute configuration of the β-nitro alcohol adduct. The exploration of these chiral skeletons in other asymmetric reactions is ongoing in our laboratory.

4. Experimental section

4.1. General

All the starting materials and reagents were purchased from commercial suppliers and used without further purification. Solvents were purified by standard procedures. Routine monitoring of reactions was performed by TLC, visualization was done by fluorescence quenching at 254 nm or exposure to iodine vapor. Flash chromatography was carried out on silica gel (Acme, 60–120 mesh). Melting points were determined using YG252A apparatus and were uncorrected. Optical rotations were measured on a Perkin–Elmer 343 polarimeter in the solvent indicated. NMR spectra were recorded on INOVA 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) spectrometers (with TMS as an internal standard), and coupling constants are reported in hertz. High-resolution mass spectra (HRMS) were carried out on a BRUKER APEX-II. IR spectra were recorded as KBr disks on a FTIR-8400S (CE). High performance liquid chromatography (HPLC) was performed by an Agilent 1100 interfaced to an HP 71 series computer workstation with Daicel Chiralcel OD-H, OJ-H column or Chiralpak AD-H column.

4.2. Preparation of the ligands

(8*S*, 9*S*)-9-amino(9-deoxy)-epiquinine and (8*R*,9*R*)-9-amino(9-deoxy)-epicinchonine were prepared according to the literature.[22]

*4.2.1. Synthesis of ligand **2**.* A solution of 3,5-di-*tert*-butyl-salicylaldehyde (257 mg, 1.1 mmol) and (8*S*,9*S*)-9-amino-(9-deoxy)-epiquinine (323.4 mg, 1.0 mmol) in absolute ethanol (20 mL) was heated to reflux. After that, 1.5 g $MgSO_4$ (dried at 110 °C for 2 h before use) was added to the solution.

After 8 h, the mixture was slowly cooled down to room temperature and filtrated. The solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel (petroleum ether/CH_2Cl_2 1:0 to 1:1) to afford the Schiff base ligand **2** as a yellow solid (501 mg, 93% yield). $[\alpha]_D^{25}=-55$ (*c* 0.5, CH_2Cl_2); mp 122–123 °C; IR (KBr) ν_{max}: 3403, 2962, 2864, 1627, 1278 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.49 (s, 1H, OH), 8.76 (d, *J*=6 Hz, 1H, ArH), 8.41 (s, 1H, C*H*=N), 8.05 (d, *J*=12 Hz, 1H, ArH), 7.66 (d, *J*=2.4 Hz, 1H, ArH), 7.47 (d, *J*=5.6 Hz, 1H, ArH), 7.40 (dd, *J*=2.8, 3.2 Hz, 1H, ArH), 7.33 (d, *J*=2.4 Hz, 1H, ArH), 7.04 (d, *J*=2.8 Hz, 1H, ArH), 5.83–5.76 (m, 1H, CH_2=C*H*), 4.99 (dd, *J*=16.8, 7.2 Hz, 2H, C*H*$_2$=CH), 4.86 (d, *J*=12.8 Hz, 1H, CH), 4.03 (s, 3H, OCH_3), 3.62 (q, *J*=11.6 Hz, 1H, CH), 3.27–3.19 (m, 2H, CH_2), 2.84–2.80 (m, 2H, CH_2), 2.27 (br s, 1H, CH), 1.67 (br s, 1H, CH), 1.62–1.54 (m, 2H, CH_2), 1.40 (s, 9H, *t*-Bu), 1.26 (s, 9H, *t*-Bu), 0.91–0.84 (m, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 157.4, 157.3, 147.1, 144.8, 143.9, 141.3, 139.6, 136.0, 131.6, 127.2, 126.6, 125.8, 121.2, 120.9, 120.8, 117.4, 113.8,

101.6, 60.1, 56.0, 55.0, 40.4, 39.4, 34.5, 33.7, 30.9, 28.9, 27.6, 27.3, 25.5. HRMS (ESI, M+H) calcd for $C_{35}H_{46}N_3O_2$ 540.3590, found 540.3591.

*4.2.2. Synthesis of ligand **1a**.* Ligand **1a** was prepared in the same way as ligand **2** from (8*S*,9*S*)-9-amino-(9-deoxy)-epiquinine and 2,3-dihydroxybenzaldehyde. The product was obtained as a yellow solid (394 mg, 89% yield). $[\alpha]_D^{25}=-74.0$ (*c* 1.0, CH_2Cl_2); mp 102–103 °C; IR (KBr) ν_{max}: 3423, 2935, 2864, 1722, 1623, 1272, 1240 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.80 (d, *J*=5.2 Hz, 1H, ArH), 8.19 (s, 1H, C*H*=N), 8.09 (d, *J*=12.4 Hz, 1H, ArH), 7.51 (br s, 1H, ArH), 7.47–7.42 (m, 2H, ArH), 6.87 (d, *J*=9.6 Hz, 1H, ArH), 6.66 (d, *J*=9.6 Hz, 1H), 6.59 (t, *J*=10.4 Hz, 1H, ArH), 5.86–5.75 (m, 1H, CH_2=C*H*), 5.05–4.99 (m, 2H, CH_2=CH), 3.98 (s, 3H, OCH_3), 3.62–3.57 (m, 1H, CH), 3.33–3.20 (m, 2H, CH_2), 3.07 (q, *J*=9.6 Hz, 1H, CH), 2.91–2.86 (m, 2H, CH_2), 2.32 (br s, 1H, OH), 1.71 (br s, 1H, OH), 1.64–1.59 (m, 2H, CH_2), 1.51–1.46 (m, 1H, CH), 1.42–1.37 (m, 2H, CH_2), 0.92–0.85 (m, 1H, CH); ^{13}C NMR (100 MHz, DMSO) δ 165.9, 157.4, 150.4, 147.7, 145.7, 144.3, 142.2, 131.5, 127.5, 121.7, 121.5, 118.3, 117.9, 114.1, 102.2, 59.7, 55.6, 51.9, 45.6, 39.6, 33.2, 27.4, 25.5, 22.6. HRMS (ESI, M+H) calcd for $C_{27}H_{30}N_3O_3$ 444.2242, found 444.2270.

*4.2.3. Synthesis of ligand **1b**.* Ligand **1b** was prepared in the same way as ligand **2** from (8*S*,9*S*)-9-amino-(9-deoxy)-epicinchonine with 2,3-dihydroxybenzaldehyde. The product was obtained as a yellow solid (347 mg, 84% yield). $[\alpha]_D^{25}=+62.32$ (*c* 1.0, CH_2Cl_2); mp 71–73 °C; IR (KBr) ν_{max}: 3060, 2935, 2869, 1627, 1463, 1272 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.97 (d, *J*=4.4 Hz, 1H, ArH), 8.36–834 (m, 1H, ArH), 8.23 (s, 1H, C*H*=N), 8.28 (d, *J*=8.4 Hz, 1H, ArH), 7.78 (t, *J*=7.6 Hz, 1H, ArH), 7.67 (t, *J*=8 Hz, 1H, ArH), 7.57 (br s, 1H, ArH), 6.80 (dd, *J*=1.2, 1.2 Hz, 1H, ArH), 6.65–6.62 (m, 1H, ArH), 6.55 (t, *J*=7.6 Hz, 1H, ArH), 5.92–5.83 (m, 1H, CH_2=C*H*), 5.14–5.09 (m, 2H, CH_2=CH), 3.59 (br s, 1H, CH), 3.16–3.10 (m, 2H, CH_2), 3.01–2.92 (m, 2H, CH_2), 2.32 (q, *J*=7.2 Hz, 1H, CH), 1.68 (br s, 1H, CH), 1.61–1.58 (m, 2H, CH_2), 1.25–1.18 (m, 2H, CH_2), 1.07–1.00 (m, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 160.2, 148.7, 145.5, 139.9, 130.8, 129.3, 128.8, 128.7, 123.3, 123.2, 122.1, 120.8, 117.9, 117.5, 114.9, 49.2, 47.1, 39.1, 27.6, 26.1, 24.9. HRMS (ESI, M+H) calcd for $C_{26}H_{28}N_3O_2$ 414.2182, found 414.2177.

*4.2.4. Synthesis of ligand **3**.* Ligand **3** was prepared in the same way as ligand **2** from (8*S*,9*S*)-9-amino-(9-deoxy)-epiquinine with 5-bromosalicylaldehyde. The product was obtained as a yellow solid (419 mg, 83% yield). $[\alpha]_D^{25}=-48.6$ (*c* 0.5, CH_2Cl_2); mp 87–88 °C; IR (KBr) ν_{max}: 3392, 2987, 2948, 1618, 1456 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 8.78 (d, *J*=4.4 Hz, 1H, ArH), 8.31 (s, 1H, C*H*=N), 8.07 (d, *J*=9.2 Hz, 1H, ArH), 7.53 (d, *J*=2.4 Hz, 1H, ArH), 7.46–7.45 (m, 2H, ArH), 7.37–7.35 (m, 2H, ArH), 6.83 (d, *J*=9.2 Hz, 1H, ArH), 5.83–5.875 (m, 1H, CH_2=C*H*), 5.00 (t, *J*=10 Hz, 2H, CH_2=CH), 4.92 (br s, 1H, CH), 4.01 (s, 3H, OCH_3), 3.26–3.15 (m, 2H, CH_2), 2.85–2.78 (m, 2H, CH_2), 2.34 (br s, 1H, CH), 1.69 (br s, 2H, CH_2), 1.46–1.43 (m, 2H, CH_2), 1.27 (t, *J*=7.2 Hz, 1H, CH), 0.89–0.84 (m, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 154.3, 152.3, 142.0, 139.3, 137.9, 135.8, 129.4, 128.2, 126.5, 121.9, 116.0, 114.5, 113.3, 108.9, 104.4, 96.1, 55.7, 54.9, 50.5, 49.9, 22.4, 21.9, 20.2. Anal. Calcd for $C_{27}H_{28}BrN_3O_2$: C 64.03, H 5.57, N 8.30; found C 64.10, H 5.59, N 8.27.

4.3. Preparation of ligand 2/Cu(OTf)$_2$ complex

A solution of Schiff base ligand **2** (377.8 mg, 0.7 mmol) and $Cu(OTf)_2$ (253 mg, 0.7 mmol) in EtOH (15 mL) was stirred for 3 h under reflux. After cooling down to room temperature, the ligand **2**/Cu(II)complex was collected and dried under reduced pressure to afford a dark green solid with a quantitative yield. The complex can be stored under air at room temperature.

4.4. General procedure for asymmetric Henry reaction

The ligand **2** (13.5 mg, 0.025 mmol), and $Cu(OTf)_2$ (9.1 mg, 0.025 mmol) were suspended in THF (2 mL). After stirring for 1 h at room temperature, aldehyde (53 mg, 0.5 mmol) and nitroalkane (325 mg, 5 mmol) were added, the mixture was cooled down to −20 °C and Na_2CO_3 (26.5 mg, 0.25 mmol) was added. The stirring was continued for the indicated time and the reaction mixture was then diluted with ether (6 mL). The resulting mixture was filtered through a pad of Celite, and the solution was evaporated under reduced pressure. The residue was purified by silica gel flash column chromatography (petroleum ether/ethyl acetate=5:1) to afford the corresponding product. The enantiomeric purity of the product was determined by HPLC analysis. The absolute configurations of the products were assigned by comparison to literature data.

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Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.08.029.

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