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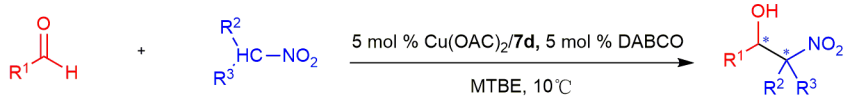
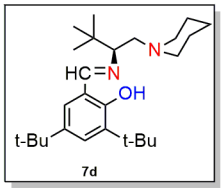


R^2 = R^3 = Me, 26 examples, up to 83% yield, 95% *ee*;
R^2 = R^3 = H, 17 examples, up to 95% yield, 99% *ee*;
R^2 = H, R^3 = Me, 16 examples, up to 95% yield, 95% *ee*, 98% *ee*, 85:15 *dr*;
R^2 = H, R^3 = Et, 17 examples, up to 96% yield, 95% *ee*, 99% *ee*, 76:24 *dr*



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A New Type of *L*-Tertiary Leucine-Derived Ligand: Synthesis and Application in Cu (II)-catalyzed Asymmetric Henry Reactions

Zedong Cai[1, a], Ting Lan[1, a], Pengfei Ma[a], Jingfang Zhang[b], Qingqing Yang[a], Wei He[*, a]

[a] *Department of Chemistry, School of Pharmacy, The Fourth Military Medical University, Xi'an, 710032, People's Republic of China.*
[b] *Key Laboratory of Functional Polymer Materials (Ministry of Education), Institute of Polymer Chemistry, College of Chemistry, Nankai University, Tianjin 300071, People's Republic of China.*

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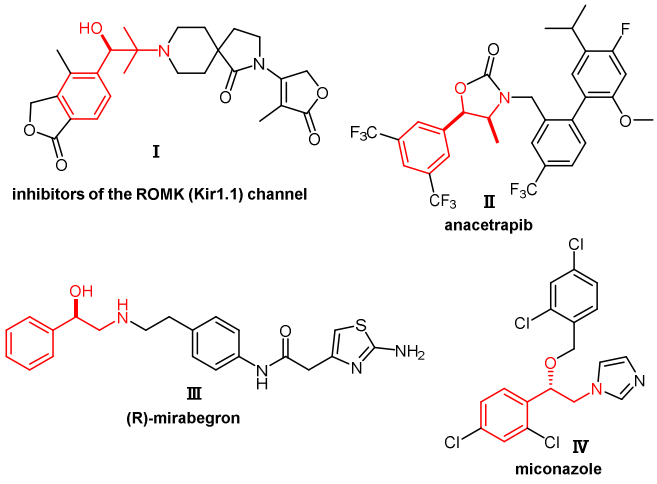
ABSTRACT

A new series of Schiff bases derived from amino acids were developed as chiral ligands for Cu (II)-catalyzed asymmetric Henry reactions. The optimum ligand **7d** exhibited outstanding catalytic efficiency in the Cu (II)-catalyzed asymmetric Henry additions of four nitroalkanes to different kinds of aldehydes to produce 76 desired adducts in high yields (up to 96%) with excellent enantioselectivities, up to 99% enantiomeric excess (*ee*).

1. Introduction

Controlling spatial selectivity and enantioselectivity is one of the most important topics in organic reactions. [1] Transition-metal catalysis is one of the most important methods to improve the enantioselectivity of the transformations. [2] Amongst these metal complexes, chiral copper complexes [3] have received particular attention due to its low toxicity, low cost, ready availability, and wide structural variability of the chiral ligands such as Schiff base, [4] salen, [5] cinchona alkaloid derivatives, [6] BINAP, [7] bisoxazolines, [8] and diamines. [9] To date, there are still very few catalytic systems available for asymmetric catalytic reactions with various substrates. Therefore, the design of new chiral catalysts to solve this problem is still a major issue.

The Henry reaction is one of the most valuable and atomic-economical reactions in the formation of carbon-carbon bonds. [10] Its resulting product, *β*-nitroalcohol, is a very vital intermediate for some biologically active natural products, medicines, chiral ligands (**Figure 1**). [11] For example, molecule **I** is a powerful inhibitor of the ROMK (kir1.1) channel and can be used as a diuretic and/or natriuretic agent for the therapy and prophylaxis of cardiovascular diseases, including hypertension, heart failure, and diseases associated with excessive salt and water retention. However, the asymmetric Henry reaction with 2-nitropropane as nucleophilic reagent has not been reported so far. Over the past several decades, with Shibasaki's groundbreaking work, [12] dozens of metal-catalyzed (Zn, [13] Cu, [6, 14] Co, [15] Mg, [16] or Cr [17]) systems have been developed for asymmetric Henry reactions to obtain high enantioselectivity and diastereoselectivity. Unlike the asymmetric Henry reaction of aldehydes with only nitromethane or/and nitroethane, [18] the asymmetric Henry reaction of aldehydes with different kinds of nitroalkanes using only the same catalytic system, including 1-nitropropane and 2-nitropropane, has not been reported systematically. [19] Based on these reasons, we have developed chiral ligands derived from amino acids to realize the asymmetric Henry reaction with various nitroalkanes.



[*] Corresponding author. Tel.: +86-29-84774470; e-mail: weihechem@fmmu.edu.cn
[1] These authors contributed equally to this work.

Figure 1. Representative bioactive compounds containing structural units of *o*-Aryl aminoalcohols from natural and synthetic sources.

2. Results and discussion

A new series of Schiff base ligands was easily prepared (see Experimental Section and Supplementary data) from commercially available amino acids and salicylaldehyde derivatives (**Figure 2**). Initially, benzaldehyde (**8a**) and 2-nitropropane (**9a**) were used as model substrates to screen these ligands.

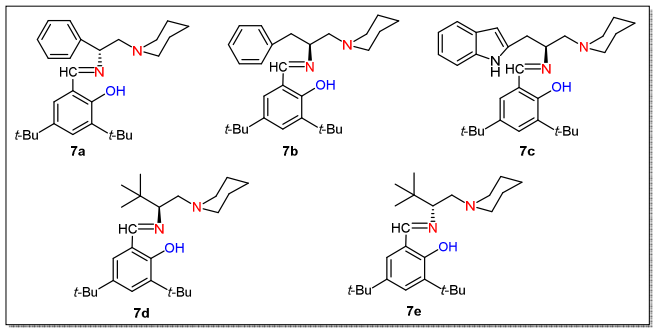
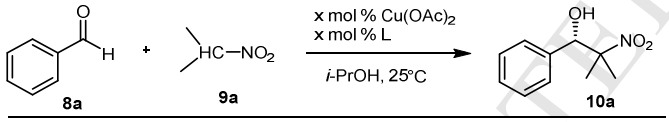


Figure 2. The Schiff base ligands screened in asymmetric Henry reactions.

First, the reaction [6b] was performed in *i*-PrOH at 25°C using 10 mol% of various Schiff base ligands in combination with copper acetate (**Table 1**, entries 1–4). To our delight, **7d** proved to be the most suitable ligand for this reaction. When the loading of the catalyst was reduced to 5 mol%, the yield and *ee* value were still maintained (**Table 1**, entries 4–6). From entry 7, we can see that the absolute configuration of amino acids determined the absolute configuration of products (**Table 1**, entry 7). Reactions did not occur when only ligand was used instead of Cu (II)-complex (**Table 1**, entry 8).

Table 1. Evaluation of chiral Schiff base ligands and their loading in the asymmetric Henry reaction.[a)]

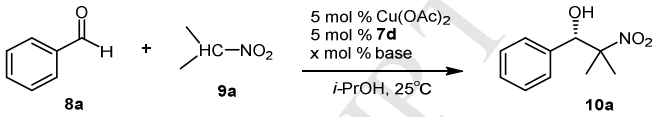


Entry	Ligand	Loading of Cat. (mol %)	Yield (%)[b)]	*ee* (%)[c)]
1	**7a**	10	trace	n.d.[d)]
2	**7b**	10	13	68 (S)[e)]
3	**7c**	10	trace	n.d.
4	**7d**	10	35	85 (S)
5	**7d**	8	34	84 (S)
6	**7d**	5	33	85 (S)
7	**7e**	5	33	73 (R)
8[f)]	**7d**	5	trace	n.d.

[a)] All of the reactions were carried out with 0.2 mmol of benzaldehyde and 2 mmol of 2-nitropropane in 1 mL of *i*-PrOH in the presence of x mol% of catalyst at 25°C. All of the catalysts were formed in situ, about 0.5 h before addition of benzaldehyde. [b)] Isolated yield. [c)] Determined by HPLC analysis (Chiralcel OD-H column, Hex:*i*-Pro = 90:10, 1.0 mL·min^{-1}, 25□, 210 nm) t_R (minor)=9.725 min, t_R(major)=14.165 min. [d)] n.d. = not detected. [e)] By comparison of the HPLC elution order of the enantiomers with the literature data. [19h] [f)] Without metal.

To increase the reaction yield of the catalytic system, different kinds of basic additives were tested (**Table 2**, entries 1–11). As desired, the addition of a basic additive did increase the yield of the reaction; however, the *ee* value decreased. The addition of bipyridine, potassium hydroxide, sodium carbonate, cesium carbonate, and potassium fluoride dihydrate gave low ee values (**Table 2**, entries 2–5, 7). DABCO significantly increased the yield, such that 77% *ee* and 83% yield were achieved using 5 mol% of DABCO as additive (**Table 2**, entries 11–14).

Table 2. Effects of the base additives in the asymmetric Henry reaction.[a)]



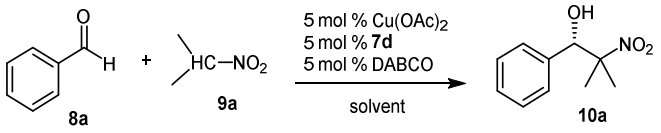
Entry	Base	Loading of base (mol %)	Yield (%)[b)]	*ee* (%)[c)]
1	DMAP	100	78	39
2	2,2'-bipyridine	100	41	0
3	KOH	100	82	3
4	Na_2CO_3	100	81	8
5	Cs_2CO_3	100	78	3
6	K_2CO_3	100	85	15
7	$KF{\cdot}2H_2O$	100	83	0
8	NaF	100	67	47
9	Li_2CO_3	100	65	25
10	bipyridine	100	38	81
11	DABCO	100	93	51
12	DABCO	10	85	74
13	DABCO	8	83	74
14	DABCO	5	83	77

[a)] All of the reactions were carried out with 0.2 mmol of benzaldehyde and 2 mmol of 2-nitropropane in 1 mL of *i*-PrOH in the presence of 5 mol% of catalyst at 25°C. [b)] Isolated yield. [c)] Determined by HPLC analysis (Chiralcel OD-H column, Hex:*i*-Pro = 90:10, 1.0 mL·min^{-1}, 25□, 210 nm) t_R (minor)=9.725 min, t_R(major)=14.165 min.

Generally, the solvent has significant effects on the enantioselectivity in catalytic asymmetric reactions. Therefore, solvents were screened systematically (**Table 3**, entries 1-15). As shown in **Table 3**, alcohols and ethers improved the enantioselectivity of the reaction. Among the selected solvents, *n*-propanol, 1, 4-dioxane and methyl *tert*-butyl ether all showed excellent effects. After comprehensive consideration, we chose methyl *tert*-butyl ether as the optimal reaction solvent. The reaction temperature was further optimized (**Table 3**, entries 15-19). The enantioselectivity of the reaction was greatly improved

when the temperature was reduced from room temperature to 10°C, and it reached 88% *ee*. The yield of the reaction was maintained at a relatively high level. The enantioselectivity increased slightly when the reaction temperature was further lowered, but the yield seriously decreased. Therefore, we decided to choose 10°C as the optimum reaction temperature.

Table 3. Screening the solvents and temperature in the asymmetric Henry reaction.[a)]



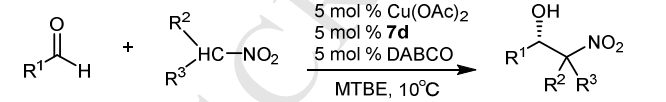
Entry	Solvent	Temp. (°C)	Yield (%)[b)]	*ee* (%)[c)]
1	THF	25	89	77
2	toluene	25	78	61
3	DMSO	25	81	50
4	*i*-PrOH	25	85	77
5	DCM	25	56	49
6	Et_2O	25	78	70
7	*n*-Hex	25	54	43
8	DMF	25	83	65
9	MeOH	25	84	77
10	CH_3CN	25	78	66
11	EtOH	25	83	73
12	*n*-PrOH	25	87	79
13	$(CH_2OH)_2$	25	trace	n.d.
14	1,4-dioxane	25	85	80
15	MTBE	25	88	80
16	MTBE	10	85	88
17	MTBE	0	69	89
18	MTBE	-10	51	90
19	MTBE	-20	32	92

[a)] All of the reactions were carried out with 0.2 mmol of benzaldehyde, 2 mmol of 2-nitropropane, and 5 mol% DABCO in 1 mL of solvent in the presence of 5 mol% of catalyst. [b)] Isolated yield. [c)] Determined by HPLC analysis (Chiralcel OD-H column, Hex:*i*-Pro = 90:10, 1.0 mL·min^{-1}, 25□, 210 nm) t_R (minor)=9.725 min, t_R(major)=14.165 min.

In general, the optimum reaction conditions were 5 mol% **7d**/Cu $(OAc)_2$ (1:1) complex as catalyst, MTBE as solvent, 5 mol% DABCO as basic additive, 10°C as reaction temperature, and a reaction time of 12 hours.

With the optimal reaction conditions in hand, the substrates involved in the asymmetric Henry reaction were systematically extended. Primarily, we extended the asymmetric Henry reaction with 2-nitropropane (**Table 4**, entries 1-26). For benzaldehyde substrates, no matter the electron-donating or electron-withdrawing substituents on the benzene ring, and the different positions of substituents, these substrates are applicable to the catalytic system indiscriminately (**Table 4**, entries 1-11). To our surprise, we found that benzaldehyde substrates with 2, 4-substituents can also achieve excellent catalytic effects (**Table 4**, entries 12-20). Heterocycles, fused rings, and different cinnamaldehydes have also been proven to be suitable for the catalytic system and have achieved excellent catalytic performance (**Table 4**, entries 22-26). For single chiral centers, we also attempted to expand Henry reactions using nitromethane as a substrate (**Table 4**, entries 27-43). Unsurprisingly, excellent catalytic effects were obtained. Remarkably, under this catalytic system, many aldehydes can obtain more than 95% *ee*, and even isobutyraldehyde (**Table 4**, entry 39) and cyclopropionaldehyde (**Table 4**, entry 43) can produce almost chiral pure nitroalcohols.

Table 4. Asymmetric Henry reaction with a single chiral center catalyzed by **7d**/Cu $(OAc)_2$.[a)]



Entry	Aldehyde	Nitroalkane	Product	Yield (%)[b)]	*ee* (%)[c)]
1	Ph **(8a)**	**9a** R_2=R_3=Me	**10a**	71	90
2	2-MeC_6H_4 **(8b)**	**9a** R_2=R_3=Me	**10b**	70	93
3	2-$MeOC_6H_4$ **(8c)**	**9a** R_2=R_3=Me	**10c**	72	95
4	3-$MeOC_6H_4$ **(8d)**	**9a** R_2=R_3=Me	**10d**	73	91
5	4-$MeSC_6H_4$ **(8e)**	**9a** R_2=R_3=Me	**10e**	75	89
6	2-FC_6H_4 **(8f)**	**9a** R_2=R_3=Me	**10f**	83	95
7	2-ClC_6H_4 **(8g)**	**9a** R_2=R_3=Me	**10g**	79	94
8	4-ClC_6H_4 **(8h)**	**9a** R_2=R_3=Me	**10h**	81	93
9	2-BrC_6H_4 **(8i)**	**9a** R_2=R_3=Me	**10i**	79	92
10	4-BrC_6H_4 **(8j)**	**9a** R_2=R_3=Me	**10j**	81	93
11	2-IC_6H_4 **(8k)**	**9a** R_2=R_3=Me	**10k**	72	91
12	2,4-diFC_6H_4 **(8l)**	**9a** R_2=R_3=Me	**10l**	85	93
13	2,4-diClC_6H_4 **(8m)**	**9a** R_2=R_3=Me	**10m**	81	94
14	2,4-diBrC_6H_4 **(8n)**	**9a** R_2=R_3=Me	**10n**	81	94
15	4-Br-2-FC_6H_4 **(8o)**	**9a** R_2=R_3=Me	**10o**	83	93
16	4-Br-2-ClC_6H_4 **(8p)**	**9a** R_2=R_3=Me	**10p**	83	95
17	2-Br-4-ClC_6H_4 **(8q)**	**9a** R_2=R_3=Me	**10q**	83	93
18	2-F-4-MeC_6H_4 **(8r)**	**9a** R_2=R_3=Me	**10r**	77	94
19	2-Cl-4-MeC_6H_4 **(8s)**	**9a** R_2=R_3=Me	**10s**	73	94
20	2-Br-4-MeC_6H_4 **(8t)**	**9a** R_2=R_3=Me	**10t**	77	91
21	2-PhC_6H_4 **(8u)**	**9a** R_2=R_3=Me	**10u**	71	90
22	PhC=C **(8v)**	**9a** R_2=R_3=Me	**10v**	77	89

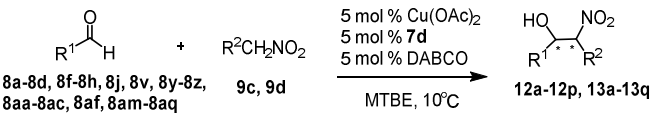
23	2-NO_2PhC=C **(8w)**	**9a** R_2=R_3=Me	**10w**	78	91
24	4-BrPhC=C **(8x)**	**9a** R_2=R_3=Me	**10x**	82	89
25	1-naphthyl **(8y)**	**9a** R_2=R_3=Me	**10y**	77	93
26	2-thienyl **(8z)**	**9a** R_2=R_3=Me	**10z**	79	89
27	Ph **(8a)**	**9b** R_2=R_3=H	**11a**	95	96
28	2-MeC_6H_4 **(8b)**	**9b** R_2=R_3=H	**11b**	91	95
29	4-$MeOC_6H_4$ **(8aa)**	**9b** R_2=R_3=H	**11c**	92	93
30	2-FC_6H_4 **(8f)**	**9b** R_2=R_3=H	**11d**	92	88
31	2-thienyl **(8z)**	**9b** R_2=R_3=H	**11e**	93	96
32	4-indolyl **(8ab)**	**9b** R_2=R_3=H	**11f**	88	96
33	1-naphthyl **(8y)**	**9b** R_2=R_3=H	**11g**	89	98
34	2-naphthyl **(8ac)**	**9b** R_2=R_3=H	**11h**	87	95
35	2-MeO-1-naphthyl **(8ad)**	**9b** R_2=R_3=H	**11i**	85	86
36	1-pyrenyl **(8ae)**	**9b** R_2=R_3=H	**11j**	89	94
37	Et **(8af)**	**9b** R_2=R_3=H	**11k**	92	91
38	*n*-Pr **(8ag)**	**9b** R_2=R_3=H	**11l**	91	91
39	*i*-Pr **(8ah)**	**9b** R_2=R_3=H	**11m**	91	>99
40	*n*-Bu **(8ai)**	**9b** R_2=R_3=H	**11n**	91	95
41	*t*-Bu **(8aj)**	**9b** R_2=R_3=H	**11o**	89	91
42	cyclohexyl **(8ak)**	**9b** R_2=R_3=H	**11p**	93	95
43	epoxy **(8al)**	**9b** R_2=R_3=H	**11q**	95	99

[a)] All of the reactions were carried out with 0.2 mmol of benzaldehyde and 2 mmol of nitroalkane and 5 mol% DABCO in 1 mL of MTBE in the presence of 5 mol% of catalyst at 10°C. [b)] Isolated yield. [c)] Determined by HPLC analysis (Chiralcel OD-H, OJ-H, or Chiralpak AD-H, AS-H column).

Afterwards, the nitroalkanes that can produce two chiral center products were also systematically investigated (**Table 5**). First, nitroethane was used as a substrate to expand aldehydes. To our delight, both of the two diastereomers caused excellent enantioselectivity, although the diastereoselectivity of the products was not good.It seems that there is no difference between the type of substituents on benzaldehyde substrates (electron-donating or electron-withdrawing) and the position of substituents (**Table 5**, entries 1-11). Similarly, nitroethane can be extended to fused-ring, heterocyclic, fused-heterocyclic, and cinnamaldehyde substrates with good-to-excellent performance (**Table 5**, entries 12-16).

Second, the previously unexplored substrates, such as 1-nitropropane, were expanded with different aldehydes (**Table 5**, entries 17-33). It was anticipated that, like nitroethane, the products with 1-nitropropane as a nucleophilic reagent would also cause very excellent enantioselectivity, which would also be applicable to aldehydes with different substituents on the benzene ring (**Table 5**, entries 17-26). Therefore, we also extended the types of aldehydes to fused ring, heterocycle, fused heterocycle, aliphatic aldehyde, and cinnamaldehyde substrates and obtained excellent catalytic selectivity (**Table 5**, entries 27-33).

Table 5. Diastereoselective Henry reactions catalyzed by **7d**/Cu (OAc) $_2$.[a)]



8a-8d, 8f-8h, 8j, 8v, 8y-8z, 8aa-8ac, 8af, 8am-8aq + $R^2CH_2NO_2$ **9c, 9d** → **12a-12p, 13a-13q**

Entry	Aldehyde	Nitroalkane	Product	Yield (%)[b)]	*anti:syn*[c)]	*ee* (%)[c)] anti	*ee* (%)[c)] syn
1	Ph **(8a)**	**9c** R_2= Me	**12a**	95	85:15	95	98
2	2-MeC_6H_4 **(8b)**	**9c** R_2= Me	**12b**	90	85:15	90	93
3	3-MeC_6H_4 **(8am)**	**9c** R_2= Me	**12c**	92	80:20	92	91
4	4-MeC_6H_4 **(8an)**	**9c** R_2= Me	**12d**	94	80:20	93	94
5	2-$MeOC_6H_4$ **(8c)**	**9c** R_2= Me	**12e**	89	85:15	96	95
6	3-$MeOC_6H_4$**(8d)**	**9c** R_2= Me	**12f**	91	21:79	94	94
7	4-$MeOC_6H_4$ **(8aa)**	**9c** R_2= Me	**12g**	94	81:19	96	96
8	4-*i*-PrC_6H_4 **(8ao)**	**9c** R_2= Me	**12h**	92	74:26	95	98
9	2-FC_6H_4**(8f)**	**9c** R_2= Me	**12i**	92	83:17	93	88
10	4-FC_6H_4 **(8ap)**	**9c** R_2= Me	**12j**	97	78:22	92	91
11	2-ClC_6H_4 **(8g)**	**9c** R_2= Me	**12k**	91	83:17	86	96
12	1-naphthyl**(8y)**	**9c** R_2= Me	**12l**	88	67:33	84	91
13	2-naphthyl **(8ac)**	**9c** R_2= Me	**12m**	91	74:26	93	94
14	4-indolyl **(8ab)**	**9c** R_2= Me	**12n**	90	76:24	87	93
15	2-thienyl **(8z)**	**9c** R_2= Me	**12o**	91	77:23	95	94
16	PhC=C **(8v)**	**9c** R_2= Me	**12p**	91	64:36	94	91
17	Ph **(8a)**	**9d** R_2= Et	**13a**	95	71:29	94	97
18	2-MeC_6H_4 **(8b)**	**9d** R_2= Et	**13b**	92	69:31	90	99
19	3-MeC_6H_4 **(8am)**	**9d** R_2= Et	**13c**	93	68:32	91	93
20	4-MeC_6H_4 **(8an)**	**9d** R_2= Et	**13d**	94	66:34	94	92
21	2-$MeOC_6H_4$ **(8c)**	**9d** R_2= Et	**13e**	93	65:35	95	99
22	4-$MeOC_6H_4$ **(8aa)**	**9d** R_2= Et	**13f**	94	76:24	95	97
23	2-FC_6H_4 **(8f)**	**9d** R_2= Et	**13g**	94	73:27	92	94
24	4-FC_6H_4 **(8ap)**	**9d** R_2= Et	**13h**	96	68:32	93	92
25	4-ClC_6H_4 **(8h)**	**9d** R_2= Et	**13i**	95	71:29	92	95
26	4-BrC_6H_4 **(8j)**	**9d** R_2= Et	**13j**	96	66:34	92	92
27	1-naphthyl **(8y)**	**9d** R_2= Et	**13k**	91	68:32	93	96
28	2-naphthyl **(8ac)**	**9d** R_2= Et	**13l**	92	70:30	91	93
29	4-indolyl **(8ab)**	**9d** R_2= Et	**13m**	87	71:29	92	94
30	2-thienyl **(8z)**	**9d** R_2= Et	**13n**	90	72:28	96	98
31	2-furyl **8aq**	**9d** R_2= Et	**13o**	91	69:31	91	91

32	PhC=C (**8v**)	**9d** R_2= Et	**13p**	91	51:49	93	91
33	Et (**8af**)	**9d** R_2= Et	**13q**	93	41:59	94	97

[a] All of the reactions were carried out with 0.2 mmol of benzaldehyde, 2 mmol of nitroalkane, and 5 mol% DABCO in 1 mL of MTBE in the presence of 5 mol% of catalyst at 10°C. [b] Isolated yield. [c] Determined by HPLC analysis (Chiralcel OD-H, OJ-H, or Chiralpak AD-H, AS-H column), by comparison of the HPLC elution order of the enantiomers with the literature data for the absolute configuration. [14f, 6b]

In order to elucidate the reaction mechanism of the catalytic system, the absolute configuration of ligand **7d** was identified by X-ray single crystal diffraction (**Figure 3**). The spatial configuration of ligand **7d** shows that both the O1 and N1 atoms may potentially coordinate with the copper center. [18]

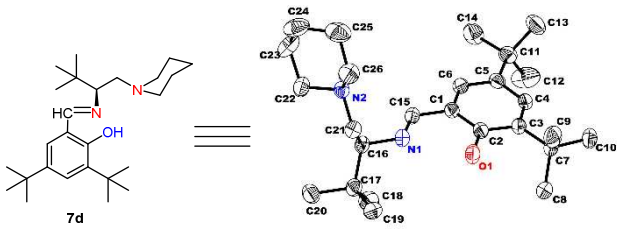


Figure 3. X-ray crystal structure of ligand **7d**. (CCDC 1888078).

Based on the experimental investigations above and previous mechanistic studies, [6b, 18c] we proposed a possible transition state as shown in **Figure 4**. From the single crystal structure of ligand **7d** and the coplanarity of the entire structure of phenol and phenylimine, we speculated that the phenolic hydroxyl oxygen and the phenylimine nitrogen participate in the coordination of the metal copper. The tertiary leucine derivative is partially perpendicular to the salicylaldehyde moiety. The quaternized piperidine forms an ion pair with the deprotonated nitromethane, while another oxygen of the nitro group coordinates with the metal copper. The carbonyl oxygen of the substrate aldehyde is also coordinated to the metal copper. It is favorable that the nitromethane attacks the carbonyl carbon from the *Re* face.

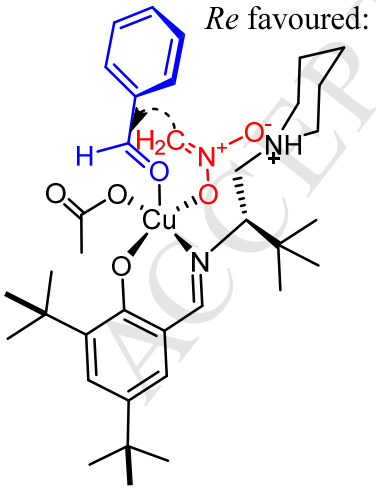
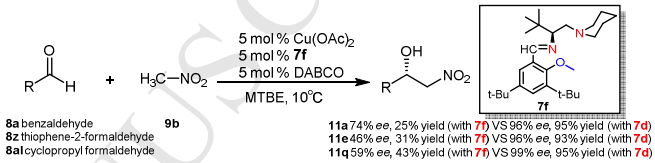
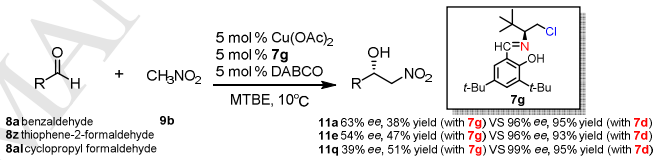


Figure 4. Plausible transition state for the enantioselective Henry reaction.

Regrettably, we have not been able to cultivate the single crystal structure of ligand **7d**/Cu $(OAc)_2$ complex. However, the formation of ligand **7d**/Cu(II) (1:1) complex was confirmed by HRMS (ESI) for $C_{26}H_{44}N_2O$ $Cu(OAc)_2$ $[M-H]^-$: calcd 580.2943, and we found 580.2947 (see Supplementary data). To elucidate the pathway of **7d**/Cu (II) complex catalyzing asymmetric Henry reactions, we further studied the role of hydroxy moiety by using the hydroxyl-protected ligand **7f** in catalytic reactions. The asymmetric Henry reaction of three selected substrates was tested under the same reaction conditions as **Table 4** (**Scheme 1**). We can see that compared with the reaction using **7d**, both the yield and *ee* value decreased significantly when **7f** was used. In addition, a new ligand **7g** without piperidine structure was synthesized to verify whether the quaternary ammonium ion of piperidine structure participates in the formation of ion pairs. The asymmetric Henry reaction of three selected substrates was tested under the same reaction conditions as **Table 4** (**Scheme 1**). The results showed that under the same conditions, the ligand **7g** without piperidine structure was inferior to ligand **7d** (**Scheme 2**) in both yield and enantioselectivity, indicating that piperidine did play a key role in the transition state. Furthermore, the ^{1}H NMR spectra of ligand **7d** and Cu (II)/ **7d** complex were obtained in THF substituted by deuterium (see Supplementary data). By comparing the two NMR spectra, we found the change of hydroxyl hydrogen signal at 13.96 ppm, which indicates that hydroxyl is involved in the formation of metal complexes.

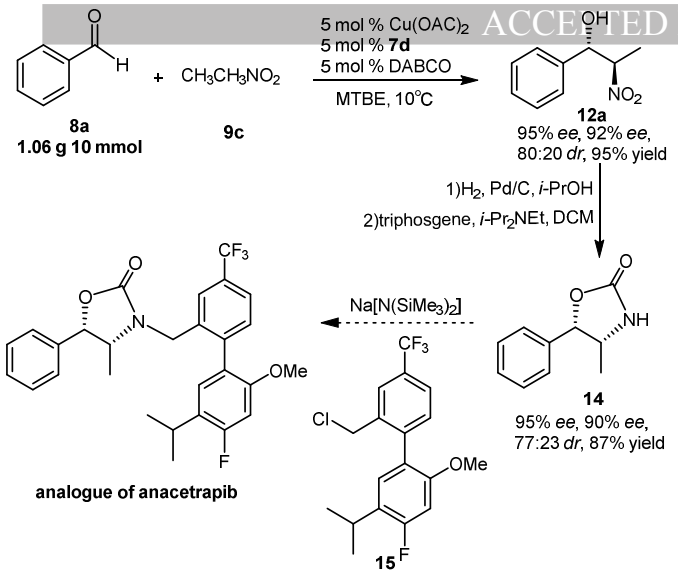


Scheme 1. Control experiments for the investigation of **7d**'s hydroxy moiety.

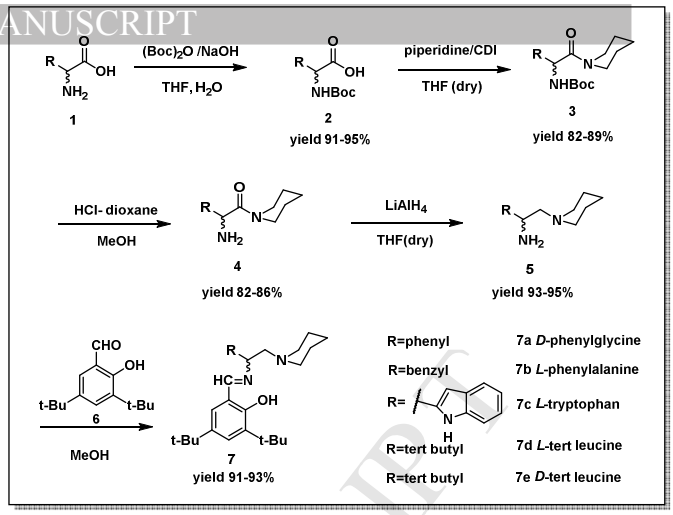


Scheme 2. Control experiments for the investigation of **7d**'s piperidine moiety.

Since *β*-nitroalcohols are very important raw materials for synthetic drug intermediates and natural active molecules, the asymmetric Henry reaction of benzaldehyde and nitroethane was performed on a gram scale, and the desired product (**12a**) was obtained with 95% yield and 95% *ee* (*anti*), 92% *ee* (*syn*), and 80:20 *dr* (**Scheme 3**). As illustrated in **Scheme 3**, product **12a** obtained by this method was converted into oxazolidinone **14**. First, *β*-nitroalcohols were reduced to primary amines in hydrogen/palladium-carbon. Subsequently, compound **14** was obtained by triphosgene treatment. Diaryl **15** was synthesized according to the reported method and further combined with **14** to obtain an analogue of anacetrapib. [21] Ancetrapib, identified by Merck as an effective CETP inhibitor, has shown good safety and no targeting effect in clinical trials for hypercholesterolemia (phase III). [21]



Scheme 3. Gram-scale experiment and conversion of the *β*-nitroalcohol product to construct biologically active molecules.



Scheme 4. The synthetic route of the ligands **7**.

3. Conclusion

In conclusion, the new Schiff base ligand **7d**, which is easily prepared from *L*-tert-leucine, after complexing with copper acetate, exhibits excellent catalytic efficiency in the enantioselective Henry reaction of four nitroalkanes with different kinds of aldehydes, and it resulted in 76 types of *β*-nitroalcohol, with up to 99% *ee* and 96% yield. A possible transition state was proposed based on X-ray single crystal diffraction of ligand **7d**, control experiments, and absolute configurations of nitroalcohols. With our own catalytic system, we further converted the synthesized nitroalcohols to vital intermediate of anacetrapib analogues. Further investigations on the reaction mechanism and the use of these *β*-nitroalcohols in other transformations are underway in our laboratory.

4. Experimental Section

4.1 General Information

All starting materials and reagents for synthesis were purchased from suppliers without any further purification. All solvents are treated without water according to standard operation. The reaction process was monitored by thin layer chromatography (TLC), and the TLC results were analyzed by ultraviolet lamp or phosphomolybdic acid. The optical rotation of the product was measured by Perkin Elmer 343 polarimeter. High resolution mass spectrometry (HRMS) was measured on Bruer-McToof QII. Infrared spectra were recorded on FTIR-8400S (CE) as KBr discs. Using $CDCl_3$ (7.26 ppm, ^{1}H; 77.00 ppm, ^{13}C) as solvent and TMS as internal standard, NMR spectra were determined on Bruker Avance (400 MHz) spectrometer. Represent multiplicity in NMR spectra with the following abbreviations:s = singlet; d =doublet; t = triplet; q = quartet; dd = double doublet; ddd = double doublet of doublet; m =multiplet. Enantiomeric excess was determined by HPLC analysis on Daicel Chiralcel OD-H, OJ-H or Chiralpak AD-H, AS-H column.

4.2 General procedure for the preparation of Chiral Schiff base ligands 7

The primary amine **5** were synthesized from Amino acids according to the reported literature. [22-24]

4.2.1 **Preparation of 7a:** To a stirred 40 mL methanol solution of **5a** (1.63 g, 8 mmol) in a 100 mL round-bottom flask equipped with a magnetic stirring bar was added 3, 5-di-*tert*-butyl salicylaldehyde **6** (2.06 g, 8.8 mmol) portionwise, and the reaction was refluxed at 70°C. When the reaction was complete, the mixture was filtrated. After concentration of the filtrate, methanol was added to recrystallize it. After being filtrated, the filtrate was concentrated and recrystallized again. We combined three crystals, washed them with a small amount of methanol, and then dried them in vacuum. Finally, yellow crystal **7a** (3.06 g, yield 91%) was obtained. m.p. 69.5 °C–70.9 °C; $[\alpha]_D^{25}$ = -1.331° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, Methanol-*d*) δ 8.50 (s, 1H), 7.47 – 7.32 (m, 5H), 7.30 – 7.24 (m, 1H), 7.22 – 7.15 (m, 1H), 4.65 – 4.55 (m, 1H), 2.99 – 2.85 (m, 1H), 2.75 – 2.65 (m, 1H), 2.58 (s, 1H), 2.55 – 2.41 (m, 2H), 1.60 – 1.51 (m, 4H), 1.50 – 1.35 (m, 13H), 1.33 – 1.25 (m, 9H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 165.82, 158.07, 142.37, 139.97, 136.54, 128.57, 127.22, 127.09, 126.86, 126.10, 118.14, 71.65, 66.78, 55.06, 35.05, 34.14, 31.53, 29.48, 26.02, 24.27; HRMS (ESI) for $C_{28}H_{40}N_2O$ $[M + H]^+$: calcd 421.3213, found 421.3209.

4.2.2 **Preparation of 7b**: The synthetic route is the same as **7a** except that the starting material is *L*- phenylalanine. **7b** is yellow oil and the characterization data is: $[\alpha]_D^{25}$ = -0.622° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz,) δ 8.07 (s, 1H), 7.38 (s, 1H), 7.30 – 7.15 (m, 5H), 6.97 (s, 1H), 4.15 (q, *J* = 7.2 Hz, 1H), 3.63 (s, 1H), 3.10 (dd, *J* = 14.00 Hz, *J* = 4.40 Hz, 1H), 2.87 (dd, *J* = 13.6 Hz, *J* = 8.4 Hz, 1H), 2.71 – 2.64 (m, 1H), 2.48 (s, 3H), 2.07 (s, 1H), 1.65 – 1.55 (m, 4H), 1.50 – 1.41 (m, 12H), 1.35 – 1.25 (m, 10H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 165.57, 158.25, 139.06, 136.54, 129.73, 128.31, 126.72, 126.16, 125.92, 117.96, 69.06, 64.25, 55.21, 41.15, 35.10, 34.16, 31.59, 29.55, 26.11, 24.40; HRMS (ESI) for $C_{29}H_{42}N_2O$ $[M + H]^+$: calcd 435.3370, found 435.3361.

4.2.3 **Preparation of 7c**: The synthetic route is the same as **7a** except that the starting material is *L*- tryptophan. **7c** is yellow crystal and the spectra data for **7c** is: m.p. 114.2 °C–115 °C; $[\alpha]_D^{25}$ = -1.146° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, Methanol-*d*) δ 8.00 (s, 1H), 7.61 – 7.52 (m, 1H), 7.38 – 7.28 (m, 2H), 7.10 – 7.03 (m, 1H), 7.02 – 6.91 (m, 3H), 4.12 (q, *J* = 7.2 Hz, 1H), 3.78 – 3.70 (m, 1H), 3.19 (dd, *J* = 14.4 Hz, *J* = 5.2 Hz, 1H), 2.91 (dd, *J* = 14.0 Hz, *J* = 8.0 Hz, 1H), 2.85 – 2.70 (m, 2H), 2.49 (s, 2H), 2.03 (s, 1H), 1.62 – 1.52 (m, 4H), 1.48 – 1.41 (m, 11H), 1.36 (s, 1H), 1.33 – 1.22 (m, 10H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 165.36, 158.28, 139.70, 136.50, 136.16, 127.70,

126.62, 125.85, 123.05, 121.80, 119.22, 118.85, 117.92, 112.84, 111.06, 67.82, 64.49, 55.26, 35.05, 34.11, 31.52, 30.52, 29.50, 26.07, 24.37; HRMS (ESI) for $C_{31}H_{43}N_3O$ [M + H]$^+$: calcd 474.3479, found 474.3474.

4.2.4 **Preparation of 7d**: The synthetic route is the same as **7a** except that the starting material is *L*-tertleucine. **7d** is yellow crystal and the spectra data for **7d** is: m.p. 107.9 °C–108.6 °C; $[\alpha]_D^{25}$ = 52.122° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 14.09 (s, 1H), 8.26 (s, 1H), 7.39 – 7.35 (m, 1H), 7.20 – 7.10 (m, 1H), 2.90 – 2.87 (m, 1H), 2.60 – 2.50 (m, 1H), 2.46 (s, 2H), 2.42 – 2.36 (m, 1H), 2.26 (s, 2H), 1.50 – 1.48 (m, 1H), 1.46 (s, 9H), 1.42 – 1.35 (m, 1H), 1.33 (s, 9H), 0.96 (s, 9H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 165.10, 158.40, 139.58, 136.50, 126.39, 125.83, 118.14, 76.21, 60.32, 55.21, 35.08, 34.16, 33.52, 31.60, 29.52, 26.99, 26.23, 24.45; HRMS (ESI) for $C_{26}H_{44}N_2O$ [M + H]$^+$: calcd 401.3526, found 401.3519.

4.2.5 **Preparation of 7e**: The synthetic route is the same as **7a** except that the starting material is *D*- tertleucine. **7e** is yellow crystal and the spectra data for **7e** is: m.p. 108.3 °C–109.1 °C; $[\alpha]_D^{25}$ = -49.683° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 14.09 (s, 1H), 8.26 (s, 1H), 7.38 (d, *J* = 2.4 Hz, 1H), 7.11 (d, *J* = 2.4 Hz, 1H), 2.87 (d, *J* = 8.8 Hz, 1H), 2.57 (d, *J* = 13.2 Hz, 1H), 2.47 (s, 2H), 2.26 (s, 1H), 1.49 (s, 4H), 1.46 (s, 9H), 1.44 (s, 1H), 1.41 – 1.35 (m, 2H), 1.33 (s, 9H), 1.32 – 1.31 (m, 1H), 0.96 (s, 9H); ^{13}C NMR (100 MHz, Chloroform-*d*) δ 165.09, 158.39, 139.57, 136.48, 126.39, 125.84, 118.12, 76.18, 60.31, 55.21, 35.07, 34.15, 33.52, 31.59, 29.50, 26.98, 26.21, 24.44; HRMS (ESI) for $C_{26}H_{44}N_2O$ [M + H]$^+$: calcd 401.3526, found 401.3524.

4.3 Typical catalytic asymmetric Henry reaction

A solution of anhydrous Cu $(OAc)_2$(1.8 mg, 0.01 mmol) and ligand **7d** (4.0 mg, 0.01 mmol) in MTBE (1 mL) in a 10 mL test tube equipped with a magnetic stirring bar was stirred at room temperature for 30 min. Next, 20 ul DABCO (5 M dissolved in *n*-propanol) was added, followed by stirring for 5 minutes. After the aldehyde (0.2 mmol) was added to the reaction mixture, we stirred the mixture at 10°C for 2 minutes, and then 2-nitropropane (180 ul, 2 mmol) was added to the tube. The reaction was stirred at 10°C and monitored by TLC. After the complete reaction, the chiral product was separated by flash column chromatography (PE/EA=9/1). Enantiomeric excesses were determined by HPLC chiral column.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, athttp://dx.doi.org/10.1002/j.tet.201######.

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- The new Schiff bases derived from amino acids were synthesized with simple methods.
- A wide-range of substrates was examed to obtain 76 β-nitroalcohols with high yields and excellent enantioselectivities.
- The transition state was initially verified by some mechanistic investigations.