Tetrahedron Letters xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

D-Mannitol-derived novel chiral thioureas: Synthesis and application in asymmetric Henry reactions

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ARTICLE INFO

Article history:
Received 6 December 2017
Revised 19 January 2018
Accepted 26 January 2018
Available online xxxx

Keywords:
Asymmetric catalysis
Oxaziridination
Cinchonaalkaloids
Organic catalysis

ABSTRACT

Five novel thioureas have been obtained through multi-step reactions from D-Mannitol as starting material and applied as catalysts in the asymmetric Henry reaction. Using catalyst **7a**, (1*S*,2*R*)-2-nitro-1-phenylpropan-1-ol containing two chiral centers was obtained in high yield and with high selectivity (up to 95% yield, 87% ee, 91:9 dr). This catalyst also retained activity in the presence of water, affording a up to 93% yield, 88% ee, and 94:6 dr.

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Introduction

The Henry (nitroaldol) reaction is a versatile and important reaction for the formation of carbon–carbon bonds in organic synthesis.[1,2] The nitroalcohol adducts, especially the optically active adducts produced by the asymmetric version of this reaction can be conveniently transformed into many important biologically active compounds or building blocks for several natural products, such as β-amino alcohols, nitroolefins, and nitro carbonyl compounds.[3–5] Accordingly, the design of powerful and novel catalysts to produce high selectivity in the asymmetric Henry reaction has attracted increasing attention.[6–8] In recent decades, some metal complex catalysts have been developed for use in the asymmetric Henry reaction.[9–11] But as other transformation, both metal-catalysis and organocatalysis have a place in this area.

Organocatalysts have received increasing attention recently because they are environmentally friendly and have been used to achieve various powerful asymmetric transformations.[12–16] Among these organocatalysts, chiral ureas or thioureas containing multiple hydrogen bonding sites are of particular interest.[17–19] Since the pioneering work of Jacobsen,[20] chiral thiourea catalysts have been successfully applied to many transformations, such as catalytic asymmetric Michael addition reactions,[21,22] asymmetric hydrogenation,[23] and asymmetric epoxidation.[24] However, despite excellent work in diverse asymmetric reactions, only limited success has been reported for chiral thiourea-catalyzed asymmetric Henry reactions.[25–28]

In many of these important asymmetric reactions, solvents have been shown to have an interesting influence. Therefore, screening different solvents is an important part of methodology development. Compared with reactions in organic solvents, aqueous phase reactions have lower toxicity and are more environmentally friendly. Therefore, simultaneously creating novel chiral thiourea catalysts that are highly efficient, showing high enantioselectivity and diastereoselectivity in aqueous-phase Henry reactions, remains a synthetic challenge.

In our previous study, we reported several novel chiral catalysts derived from *Cinchona* alkaloids that have been successfully applied to asymmetric Azy-Henry[29] and Michael addition reactions.[30] Based on these successes, we aimed to design and apply new chiral thiourea catalysts and extend their synthetic potential. Herein, we report a series of novel D-Mannitol-derived chiral thiourea catalysts and their application to the asymmetric Henry reaction in both organic solvent and water.

Results and discussion

D-Mannitol has attracted considerable research interest regarding its applications in the pharmaceutical and industrial sectors, and is found in a wide range of land and marine plants. Using

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https://doi.org/10.1016/j.tetlet.2018.01.082
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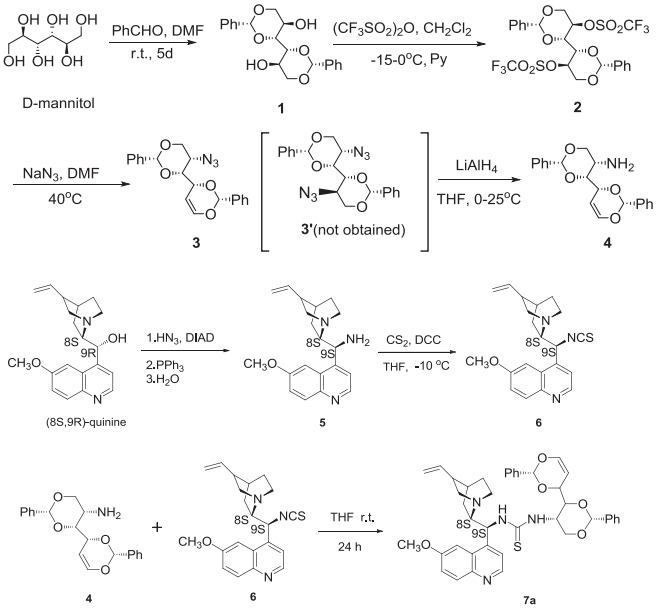
D-Mannitol as the starting material, catalysts **7a**–**7e** were synthesized following the steps shown in Scheme 1.

The most important part of this work was the synthesis of the chiral amine intermediate. This was achieved from D-Mannitol via a four-step process, comprising condensation, esterification, azidation, and reduction steps, affording the chiral amine in high yield. Our initial goal was to synthesize a bisazide product containing two 1,4-dioxane skeletons (structure shown as **3′**), but only monoazide **3** was obtained as a side product. The absolute configuration of azide intermediate **3** (determined by X-ray crystallographic, see Supporting information) suggested that only one methanesulfonyl fluoride group had undergone azidation, while the other had been eliminated. Azide intermediate **3** was then reduced with lithium aluminum hydride to afford key intermediate **4**. (8*S*,9*S*)-9-amino-(9-deoxy)-epiquinine **5** was prepared from quinine according to the literature.[31–33]

Chiral amine **5** was then treated with carbon disulfide and dicyclohexylcarbodiimide (DCC) in THF to obtain isothiocyanate **6**.[29] Finally, **6** and **4** were condensed to afford the organocatalyst **7a** in a high yield (90%).

Catalysts **7b**, **7c**, and **7d** were synthesized according to the same synthetic route using different starting materials, namely quinidine, hydroquinine, and cinchonine, respectively. Catalyst **7e** was prepared from 3,5-bis-(trifluoromethyl)-phenyl isothiocyanate and **4**. The structures shown in Fig. 1 were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and HRMS.

Organocatalysts **7a**–**7e** were tested in the Henry reaction of nitromethane and benzaldehyde (**8a**) for the synthesis of 1-phenyl-2-nitro-ethanol (**9aa**). Table 1 shows that **7a**–**7d**, which were derived from *Cinchona* alkaloids, afforded better chiral induction than **7e**, which did not have a *Cinchona* skeleton (Table 1, entries 1–4 vs entry 5). Therefore, the *Cinchona* skeleton played a decisive role in controlling chiral induction. Moreover, the configurations of C8 and C9 in *Cinchona*-derived catalysts **7a**–**7d** played an important role in enantioselective control. Catalysts **7a** and **7c**, with an 8*S*/9*S* configuration, afforded the product with an *S* configuration (Table 1, entries 1 and 3). Meanwhile, catalysts **7b** and **7d**, with an 8*R*/9*R* configuration, afforded the product with an *R* configuration (Table 1, entries 2 and 4). However, we believe that the Mannitol moiety was also valuable, providing a large obstructed skeleton that might be beneficial for chiral induction. Next, we selected **7a** as the organocatalyst for screening different conditions for the catalytic Henry reaction.



Scheme 1. General synthetic route toward organocatalyst **7a**.

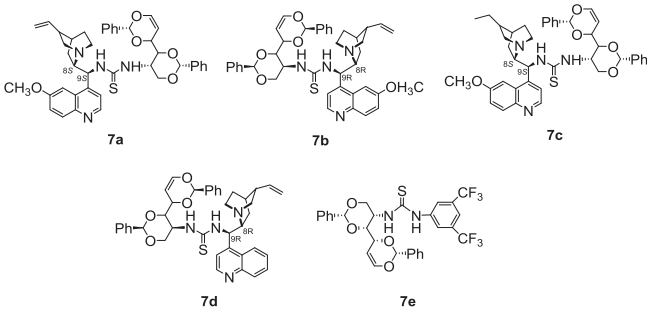
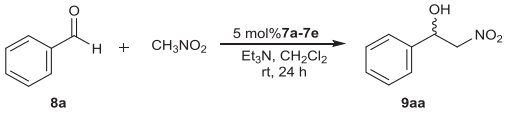


Fig. 1. Structures of the chiral thiourea organocatalysts.

Table 1
Catalyst screening results.

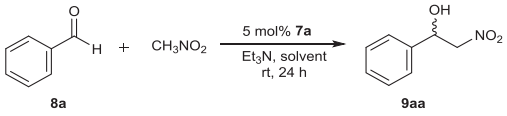


Entry[a]	Catalyst	Yield[b] (%)	ee[c] (%)	Config.[d]
1	**7a**	80	35	(S)
2	**7b**	68	−30	(R)
3	**7c**	70	28	(S)
4	**7d**	75	−25	(R)
5	**7e**	68	6	(S)

[a] Performed on benzaldehyde (0.2 mmol) and nitromethane (2 mmol, 10 eq.) at room temperature for 24 h in dichloromethane (1 mL) using 5 mol% catalyst.
[b] Isolated yield.
[c] Determined by HPLC analysis (Chiralcel OD-H column).
[d] Absolute configurations were established by comparison with literature data.[34]

Solvents play an important role in asymmetric catalysis. To explore the solvent effect in this reaction, several solvents were screened. Table 2 shows that using ethanol, acetonitrile, dichloromethane, and chloroform gave high yields, but low ee values (Table 2, entries 1, 2, 5, and 6). Toluene gave better results than tetrahydrofuran and acetone (Table 2, entries 3, 4, and 7). To

Table 2
Solvent screening in the asymmetric Henry reaction.[a]

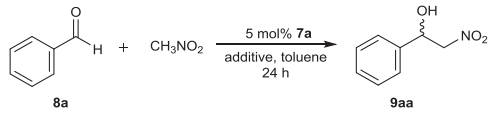


Entry[a]	Solvent	Yield[b] (%)	ee[c] (%)
1	Ethanol	90	4
2	Acetonitrile	80	10
3	THF	40	60
4	Acetone	40	40
5	CH_2Cl_2	80	42
6	$CHCl_3$	90	48
7	Toluene	85	63
8	Trifluorotoluene	87	52
9	Benzene	85	64

[a] All reactions were performed using benzaldehyde (0.2 mmol), nitromethane (2 mmol), catalyst **7a** (5 mol%), and Et_3N (20 mol%) in different solvents (1 mL) at 0 °C for 24 h.
[b] Isolated yield.
[c] Determined by HPLC analysis (Chiralcel OD-H column).

further increase the ee values, we tried using aromatic solvents. Interestingly, benzene gave similar results to toluene, but trifluorotoluene gave a lower ee (Table 1, entries 8 and 9). Therefore, toluene was the solvent of choice for subsequent experiments.

Table 3
Screening of additives and temperature in the asymmetric Henry reaction.[a]



8a 9aa

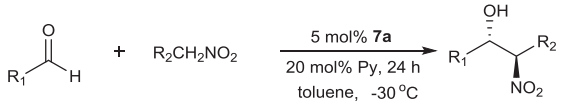
Entry[a]	Additive	Temp. (°C)	Yield[b] (%)	ee[c] (%)
1	Na_2CO_3	0	65	67
2	K_2CO_3	0	65	10
3	NaOH	0	68	51
4	Et_3N	0	77	56
5	DIPEA	0	75	56
6	DABCO	0	70	58
7	DMAP	0	43	71
8	Pyridine	0	90	70
9	Pyridine	25	92	40
10	Pyridine	−20	88	71
11	Pyridine	−30	85	78
12	Pyridine	−40	50	73
13[d]	Pyridine	−30	90	76
14[e]	Pyridine	−30	70	62

[a] All reaction were performed using benzaldehyde (0.2 mmol), nitromethane (2 mmol), catalyst **7a** (5 mol%), and additive (20 mol%) in toluene (1 mL) at different temperatures for 24 h.
[b] Isolated yield.
[c] Determined by HPLC analysis (Chiralcel OD-H column).
[d] 10 mol% **7a** was used.
[e] 3 mol% **7a** was used.

In asymmetric catalytic reactions, additives have often been shown to have a positive effect on both yield and ee. According to the literature, alkaline additives can improve reactivity and enantioselectivity significantly in asymmetric Henry reactions.[18,27] Therefore, a series of alkaline additives were tested in our synthesis (Table 3). Table 3 shows that pyridine and DMAP gave better enantioselectivity, but pyridine afforded better conversion (Table 3, entries 7 and 8). We then investigated the effect of temperature on yield and ee. At room temperature, the ee decreased from 70 to 40, but a good yield was retained (Table 3, entry 9). At −30 °C, the product ee was increased to 78 with an 85% yield (Table 3, entry 11). Further reducing the temperature to −40 °C slowed down the reaction and gave no further improvements in ee (Table 3, entry 12). Therefore, −30 °C was selected as the optimal temperature. We then investigated the amount of catalyst used, finding that a 10% catalyst loading did not improve the enantioselectivity (Table 3, entry 13), while a 3% catalyst loading reduced the catalytic efficiency, producing a lower ee value (Table 3, entry 14).

With optimal conditions in hand, the substrate scope of the enantioselective Henry reaction of nitroalkanes and aldehydes using catalyst **7a** was investigated. A broad range of nitroalkanes and aldehydes were tested (Table 4). In general, all the reactions performed well under the optimized conditions, with most affording good yields with moderate to good ee values. Table 4 clearly shows that, as nucleophilic reagents, nitroethane and nitropropane better assisted chiral induction than nitromethane, and usually provided the corresponding products with better ee values (e.g. Table 4, entries 2, 4 vs entry 1; entry 6 vs entry 5; entry 8 vs entry 7 etc). This was due to the low steric hindrance of nitromethane, which was not sufficient for improving chiral induction. Notably, in the literature, reports of nitroalkanes improving chiral induction in asymmetric Henry reactions are rare. When using nitromethane as the nucleophilic reagent, substrates with electron-donating

Table 4
Scope of nitroalkanes and aldehydes in the asymmetric Henry reaction.



8 9

Entry[a]	R_1	R_2	Product	Yield[b] (%)	d.r.[d]	ee[c] (%)
1	Ph (**8a**)	H	9aa	85	–	78
2	Ph (**8a**)	CH_3	9ab	95	91:9	87
3[e]	Ph (**8a**)	CH_3	9ab	83	94:6	87
4	Ph (**8a**)	CH_3CH_2	9ac	70	86:14	87
5	3-ClC_6H_4 (**8b**)	H	9ba	85	–	48
6	3-ClC_6H_4 (**8b**)	CH_3	9bb	75	90:10	76
7	4-BrC_6H_4 (**8c**)	H	9ca	85	–	73
8	4-BrC_6H_4 (**8c**)	CH_3	9cb	80	86:14	81
9[e]	4-BrC_6H_4 (**8c**)	CH_3	9cb	93	92:8	88
10	4-FC_6H_4 (**8d**)	H	9da	90	–	34
11	4-FC_6H_4 (**8d**)	CH_3	9db	85	85:15	79
12	4-$MeOC_6H_4$ (**8e**)	H	9ea	80	–	66
13	4-$MeOC_6H_4$ (**8e**)	CH_3	9eb	68	88:12	80
14[e]	4-$MeOC_6H_4$ (**8e**)	CH_3	9eb	85	91:9	85
15	3-$MeOC_6H_4$ (**8f**)	H	9fa	85	–	81
16	2-Naphthyl (**8g**)	H	9ga	85	–	78
17	2-Naphthyl (**8g**)	CH_3	9gb	60	70:30	71
18	1-Naphthyl (**8h**)	H	9ha	78	–	73
19	$PhCH_2$– (**8k**)	H	9ka	80	–	21
20	$PhCH_2$– (**8k**)	CH_3	9kb	80	61:39	68

[a] All reactions were carried out with **8** (0.2 mmol) and $R_2CH_2NO_2$ (2 mmol, 10 eq.) in toluene (1 mL) at −30 °C for 24 h.
[b] Isolated yield.
[c] Enantiomeric excess of **9**, determined by chiral HPLC analysis (Chiralpak OD-H and AD-H columns).
[d] Absolute configuration of **9** was established according to literature data.[34]
[e] Reaction performed in toluene/water (7:3).

Please cite this article in press as: Liu M., et al. Tetrahedron Lett. (2018), https://doi.org/10.1016/j.tetlet.2018.01.082

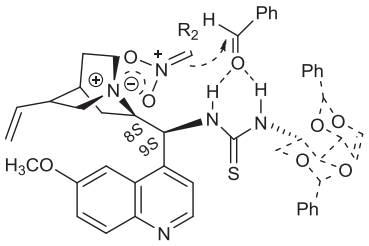


Fig. 2. Proposed reaction transition state.

groups gave better results than those with electron-withdrawing groups (Table 4, entries 5, 7, 10, 12 and 15). Benzaldehyde and 2-naphthyl formaldehyde gave similar results (Table 4, entries 15, 16). The reaction of aliphatic substrate **8k** with nitromethane gave relatively poor results (Table 4, entry 19). However, we were pleased to see that the ee value reached up to 68% when nitroethane was used as the nucleophile (Table 4, entries 19 and 20).

Interestingly, the presence of the Mannitol moiety gave catalyst **7a** good solubility and provided the possibility of developing an asymmetric reaction under aqueous conditions. Therefore, the catalytic reactions were also conducted in water using the model substrate. However, in most cases, the ee value was decreased dramatically when using either pure water or brine as solvent. When adjusting the water phase to use toluene and water (7:3) as cosolvent, some substrates gave better results. For example, the reactions of *p*-bromobenzaldehyde and *p*-methoxybenzaldehyde with nitroethane both gave better yields and higher ee values (Table 4, entries 2, 3, 8, 9, 13 and 14).

Based on the preliminary experimental results and those of previous mechanistic studies,[34,35] a plausible transition state model for this transformation was proposed (Fig. 2). The carbonyl oxygen atom of the electrophile was activated by the multiple hydrogen bonding interactions of the thiourea moiety. Meanwhile, considering the electronic influence, the basic quinuclidine nitrogen activated the nitroparaffin via static interactions. The activated nucleophile favored *Si*-face attack to the aldehyde, affording the desired asymmetric Henry reaction adducts with an S configuration.

Conclusion

In summary, five novel chiral thiourea organocatalysts have been synthesized from D-Mannitol and *Cinchona* alkaloids or 3,5-bis (trifluoromethyl) aniline, which were applied into the asymmetric Henry reaction of nitroalkanes and aldehydes. Catalyst **7a** not only showed good catalytic activity in the organic phase, but also successfully catalyzed the reaction in the presence of water. A series of chiral nitroalcohols were prepared using this methodology with yields of up to 95%, ee values up to 88%, and diastereomeric ratios of up to 94:6. Further investigations into the reaction mechanism and applications of these new organocatalysts to other asymmetric reactions are ongoing in our laboratory.

Experimental section

General

All the starting materials and reagents were purchased from commercial suppliers and used without further purification. Solvents were purified by standard procedures. DCM, toluene and benzene were freshly distilled prior to use, non-dried toluene and DCM were also used in the experimental section. The reactions were monitored by thin layer chromatography (TLC) and analysis of TLCs was done either via UV light (254 nm) or phosphomolybdic acid. Melting points were determined using a standard melting point apparatus and were uncorrected. NMR spectra were recorded in $CDCl_3$ solution on a Varian INOVA-400 MHz instrument. The ^1H NMR chemical shifts are reported as δ value in parts per million (ppm) relative to tetramethylsilane (TMS, $\delta = 0.00$)/$CHCl_3$ ($\delta = 7.26$) as internal standard. The ^{13}C NMR chemical shifts are reported as δ values in parts per million (ppm) downfield from TMS and referenced with respect to the $CDCl_3$ signal (triplet, centerline $\delta = 77.0$ ppm). High-resolution mass spectra (HRMS) were measured on a Bruker micrOTOF-QII. IR spectra were recorded as KBr disks on a FTIR-8400S(CE). The yields are of materials isolated by column chromatography. Enantiomeric excess (ee) determination was carried out on an Agilent 1260 interfaced to a HP 71 series computer workstation with Chiralcel OD-H or AD-H column.

General procedure for the preparation of chiral thiourea catalysts

Compound ***1*** was prepared from D-Mannitol and benzaldehyde according to the literature method.[36]

*Preparation of **2**:* Under N_2 in −10 °C, a mixture of 28.64 g (80 mmol) of **1**, 400 mL of methylene chloride and 52 mL (640 mmol) of anhydrous pyridine was added to a 1000 mL three-necked reaction flask. 36 mL trifluoromethanesulfonic anhydride (214 mmol) in DCM was added in 30 min. The solution was warmed to 0 °C and stirred for 3 h. After completion of the reaction, the reaction solution was washed with saturated copper sulfate and saturated brine, dried over anhydrous magnesium sulfate, purified by flash chromatography (dichloromethane: *n*-hexane was used as eluent). 48.5 g of white solid **2** was obtained in a yield of 97%. m.p. 86.9 °C–87.8 °C; $[\alpha]_D^{25} = -34.1°$ ($c = 1.0$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.40–7.50(m, 4H), 7.40(t, $J = 3.2$ Hz, 6H), 5.67(s, 2H), 5.22–5.28(m, 2H), 4.52–4.56(m, 2H), 4.34(d, $J = 9.2$ Hz, 2H), 4.18(t, $J = 10.4$ Hz, 2H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 134.61, 128.53, 127.33, 125.17, 118.85, 115.68, 100.94, 73.53, 71.01, 66.44: IR ν: 1628, 1508, 1458, 1385, 1277, 1177, 1130, 972, 760, 698 cm^{-1}.

*Preparation of **3**:* Dissolved compound **2** (17.6 g, 27 mmol) and sodium azide (21.06 mg, 324 mmol) in *N,N*-dimethylformamide (140 mL), after stir for 4 h under 40 °C, then the water (150 mL) was poured to quench the reaction. Phases were separated, water layer was washed with petroleum ether, dried over magnesium sulfate. The crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 100:1 to 60:1) to afford a yellow solid, the yellow solid was further recrystallize to afford a white solid **3** 2.85 g, and the yield was 26%. m.p. 105.5–106.5 °C; $[\alpha]_D^{25} = +23.5°$ ($c = 1.0$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.36–7.53(m, 10H), 6.78(d, $J = 6.4$ Hz, 1H), 5.94(s, 1H), 5.65(s, 1H), 5.05(d, $J = 7.2$ Hz, 1H), 5.99(d, $J = 6.4$ Hz, 1H), 4.54(d, $J = 12.4$ Hz, 1H), 4.23–4.27(m, 1H), 4.19(t, $J = 16.8$ Hz, 1H), 4.11(t, $J = 6.8$ Hz, 1H), 3.09(s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 144.9, 137.3, 136.8, 129.3, 128.4, 128.4, 126.5, 126.4, 102.2, 100.8, 98.4, 82.0, 77.4, 77.1, 76.8, 74.7, 71.0, 53.2 ppm; IR ν: 3416, 2112, 1639, 1616, 1400, 1224, 1124, 758, 698 cm^{-1}; HRMS *m/z:* Calcd for $C_{20}H_{19}N_3O_4$[M+Na]$^+$} 388.1274, found 388.1286.

*Preparation of **4**:* 0.5 g (13.3 mmol) of lithium aluminum tetrahydrate and 20 mL of anhydrous THF were added to a 50 mL three-necked reaction flask and stirred to a suspension. Under N_2, a solution of 1.85 g (4.5 mmol) of compound **3** in THF was added dropwise over 10 min. The reaction was continued for 3 h at room temperature, monitored by TLC. The work-up process was: 15 mL of saturated KF solution was added dropwise to the reaction flask while stirring. The THF in the reaction solution was distilled off. The organic phase was washed by water and saturated brine, washed with anhydrous magnesium sulfate and filtered. The crude product was purified by flash chromatography to give 1.31 g

as a white solid **4**, yield 81%. m.p. 97 °C–98.5 °C; $[\alpha]_D^{25}$ = +90° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.52(t, *J* = 4.0 Hz, 4H), 7.37(s, 6H), 7.26(s, 1H), 6.78(d, *J* = 6.4 Hz, 1H), 5.94(s, 1H), 5.66(s, 1H), 5.00(d, *J* = 7.2 Hz, 1H), 5.08(d, *J* = 6.4 Hz, 1H),4.53(d, *J* = 12.4 Hz, 1H), 4.19–4.27(m, 2H), 3.09(s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 145.4, 136.9, 129.2, 128.9, 128.3, 128.3, 126.3, 126.1, 101.8, 101.6, 98.3, 81.6, 74.9, 74.5, 46.6 ppm; IR *v*: 3474, 3416, 1635, 1618, 1400, 1221, 1121, 771, 698 cm^{-1}; ESI-MS *m*/*z*: Calcd for $C_{20}H_{24}N_2O_4$[M^+]340.15, found 340.10.

(8*S*,9*S*)-9-amino-(9-deoxy)-epiquinine **5**[31–33] and isothiocyanate **6** was prepared according to the literatures.[29]

Preparation of ***7a****:* A solution of **4** (272.7 mg, 2.25 mmol) was added to stirred solution **5** (550.2 mg, 1.50 mmol) in THF (5 mL) at room temperature. After 24 h, the solvent was removed under reduced pressure. The residue was purified by recrystallization to afford the product **7a** (517.8 mg. 71% yield). m.p. 125 °C–127 °C; $[\alpha]_D^{25}$ = +106° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.99(d, *J* = 9.2 Hz, 1H), 7.53–7.57(m, 5H), 7.35–7.41(m, 12H), 6.70 (d, *J* = 6.4 Hz, 1H), 5.90(s, 1H), 5.59–5.68(m, 1H), 5.53(s, 1H), 5.35 (s, 1H), 4.90–4.97(m, 2 H), 4.73(t, *J* = 10.2 Hz, 2 H), 4.02(d, *J* = 8.8 Hz, 2 H), 3.95(s, 3 H), 2.90–3.22(m, 3 H), 2.65–2.73(m, 2 H), 2.24 (s, 1H), 1.48–1.63(m, 3 H), 0.83–0.89(m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) *δ:* 171.20, 157.91, 147.63, 145.73, 141.07, 137.43, 136.95, 132.01, 129.21, 128.99, 128.77, 128.30, 128.10, 126.32, 126.04, 125.71, 121.88, 114.78, 101.84, 100.80, 98.31, 97.99, 81.76, 74.52, 71.43, 55.71, 55.50, 50.28, 46.53, 40.59, 39.44, 27.65, 27.32, 21.07 ppm, 14.19; IR *v*: 1647, 1620, 1508, 1358, 1227, 1126, 1088, 1030, 760, 698 cm^{-1}; HRMS *m*/*z*: Calcd for $C_{41}H_{44}N_4O_5S$[[M +H]$^+$} 705.3111; found 705.3102.

Preparation of ***7b****:* The synthesis route was as the same as **7a**, except the starting material was *quinidine*. The spectra data for **7b** was: m.p. 104 °C–106 °C; $[\alpha]_D^{25}$ = +231° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.02(d, *J* = 9.2 Hz, 1H), 7.46–7.75 (m, 7H), 7.36–7.41(m, 10H), 6.64(d, *J* = 6.0 Hz, 1H), 5.85(s, 1H), 5.56–5.64(m, 2H), 4.93–5.03(m, 2H), 4.72(d, *J* = 6.8 Hz, 2H), 4.05 (t, *J* = 7.2 Hz, 2H), 4.00(s, 3H), 3.39–3.52(m, 2H), 3.21(m, 2H), 3.83 (t, *J* = 5.0 Hz, 2H), 2.32(s, 1H), 1.61–1.71(m, 3H), 1.36–1.43(m, 1H), 0.88–0.98 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 192.51, 182.20, 158.16, 147.81, 145.66, 144.91, 137.50, 136.91, 134.50, 131.91, 129.77, 129.16, 128.98, 128.24, 126.36, 122.13, 102.08, 101.44, 98.04, 81.67, 74.47, 71.30, 55.93, 53.50, 49.87, 41.43, 36.01, 29.71, 26.71, 24.75, 11.71 ppm; IR *v*: 2931, 2869, 1643, 1620, 1527, 1523, 1261, 1226, 1091, 1029, 918, 759, 696 cm^{-1}; HRMS *m*/*z*: Calcd for $C_{41}H_{44}N_4O_5S$[[M+H]$^+$} 705.3111, found 705.3104.

Preparation of ***7c****:* The synthesis route was as the same as 7a, except the starting material was *hydroquinine*. The spectra data for **7c** was: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.01(d, *J* = 9.2 Hz, 1H), 7.81(t, *J* = 1.2 Hz, 1H), 7.34–7.50(m, 14H), 6.60(d, *J* = 5.6 Hz, 1H), 5.82(s, 1H), 5.54(s, 1H), 5.14–5.16(m, 1H), 4.70(t, *J* = 16.4 Hz, 2H), 4.05(d, *J* = 7.6 Hz, 1H), 4.00(s, 3H), 3.53(d, *J* = 8.8 Hz, 1H), 3.35(d, *J* = 11.4 Hz, 1H), 2.87(t, *J* = 2.8 Hz, 1H), 2.65–2.67(m, 1H), 2.04(s, 2H), 1.74(s, 2H), 1.21–1.30(m, 5H), 1.03–1.07(m, 1H), 1.00–1.03(m 1H), 0.79(t, *J* = 7.4 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 182.13, 158.21, 147.79, 145.66, 144.96, 137.45, 136.91, 131.95, 129.13, 128.96, 128.22, 126.35, 122.16, 102.02, 101.69, 101.44, 98.05, 81.62, 74.43, 71.26, 65.28, 56.47, 55.94, 49.86, 41.98, 41.41, 30.14, 29.12, 29.67, 24.78, 23.35, 23.10, 14.10, 11.65, 11.10 ppm; IR *v*: 3301, 2981, 2931, 2873, 1693, 1504, 1411, 1373, 1257, 1211, 968, 763 cm^{-1}. HRMS *m*/*z*: Caled for $C_{41}H_{46}N_4O_5S$[[M+H]$^+$} 707.3268, found 707.3258.

Preparation of ***7d****:* The synthesis route was as the same as 7a, except the starting material was *cinchonine*. The spectra data for 7d was: m.p. 126.2 °C–127.4 °C; $[\alpha]_D^{25}$ = +155.9° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.16(d, *J* = 8.4 Hz, 1H), 7.72(s, 1H), 7.39–7.50(m, 12H), 6.99(d, *J* = 7.6 Hz, 1H), 6.54(t, *J* = 2 Hz, 1H), 5.79–5.88(m, 1H), 5.49(s, 1H), 4.05–5.14(m, 2 H), 4.81(s, 1H), 4.61(d, *J* = 7.6 Hz, 1H), 4.23(d, *J* = 11.2 Hz, 1H), 3.98(d, *J* = 11.6 Hz, 1H), 3.78(s, 1H), 3.46(s, 3H), 2.90–3.03(m, 5H), 2.22(d, *J* = 7.2 Hz, 2H), 1.61(s, 1H), 1.47–1.48(m, 2 H), 1.40–1.45(m, 2H), 0.88(s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 180.82, 150.45, 145.59, 139.68, 137.65, 136.94, 130.76, 129.99, 129.11, 128.83, 128.30, 128.09, 127.74, 126.27, 125.87, 115.23, 110.51, 97.72, 81.21, 74.09, 70.99, 50.80, 50.21, 48.91, 46.85, 39.02, 27.39, 26.23, 25.05, 24.51 ppm; IR *v*: 3294, 2935, 2869, 1650, 1523, 1508, 1454, 1226, 1126, 1096, 748, 696 cm^{-1}, HRMS *m*/*z*: Caled for $C_{40}H_{42}N_4O_4S$[[M+H]$^+$} 675.3006, found 675.3009.

Preparation of ***7e****:* 1.07 g (3 mmol) of **4**, 20 mL of freshly distilled tetrahydrofuran was added to the reaction flask and stirred completely to dissolve. A solution of 438 μL of 3,5-bis (trifluoromethyl) phenyl was added, The reaction was carried out in 3 h at room temputure. The solvent was subsequently removed. The residue was purified by flash chromatography on silica gel (PE/EA = 20:1) to afford product **7e** (1.33 g, 71% yield) as a white solid. m.p. 72.5 °C–74.5 °C; $[\alpha]_D^{25}$ = +90° (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.20(s, 1H), 7.44–7.52(m, 5H), 7.33–7.36(m, 2H), 7.10–7.21(m, 6H), 6.75(d, *J* = 6.4 Hz, 1H), 6.58(s, 1H), 5.70(s, 1H), 5.19(d, *J* = 6.4 Hz, 1H), 5.04(d, *J* = 8.4 Hz, 1H), 4.92(d, *J* = 7.6 Hz, 1H), 4.39(d, *J* = 12.4 Hz, 1H), 3.32(d, *J* = 6.8 Hz, 1H), 4.24(d, *J* = 12.0 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 179.38, 146.71, 139.16, 135.92, 135.56, 131.77, 131.43, 130.06, 129.38, 128.41, 128.30, 126.18, 124.26, 121.88, 121.55, 117.84, 103.67, 100.36, 98.76, 82.08, 74.65, 71.72, 49.07, 29.71 ppm; IR *v*: 1628, 1508, 1458, 1385, 1277, 1177, 1130, 972, 760, 698 cm^{-1}; HRMS *m*/*z*: Caled for $C_{29}H_{24}N_2O_4SF_6$ {[M+Na]$^+$} 633.1259, found 633.1260.

Typical catalytic asymmetric Henry reaction of nitroalkane to aldehyde

Aldehyde (0.2 mmol), nitroalkane (2 mmol), thiourea catalyst **7a** (0.01 mmol, 7.2 mg) were dissolved in toluene (1 mL) (or in toluene/H_2O 7:3) at room temperature. The mixture was stirred at room temperature for 0.5 h. Then, the pyridine (0.04 mmol, 3.2 μL) were added sequentially at room temperature. The mixture was stirred for 24 h at −30 °C, and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate) to provide the desired 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.[34]

Acknowledgments

We thank the National Natural Science Foundation of China (21172261) and Natural Science Basic Research Plan in Shaanxi Province of China (2017JM8060) for financial support.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.01.082.

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Please cite this article in press as: Liu M., et al. Tetrahedron Lett. (2018), https://doi.org/10.1016/j.tetlet.2018.01.082