Full paper

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Synthesis and applications in Henry reactions of novel chiral thiazoline tridentate ligands

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Several novel chiral tridentate ligands containing thiazoline were efficiently synthesized from commercially available l=cysteine in high yield. These ligands were subsequently applied to the asymmetric Henry reaction of nitromethane and various aldehydes. It was found that the structures of the thiazoline ligands had a significant influence on the enantioselectivity. It was shown that the optimal catalyst for this reaction was a ligand complexed with CuCl, which was formed from chiral thiazoline with chiral aminoalcohol. At −20°C, with 10 mol% of this ligand, a product with (*S*)-configuration was isolated in 93% yield and 98% enantiomeric excess. Copyright © 2015 John Wiley & Sons, Ltd.

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Keywords: chiral thiazoline ligand; Henry reactions; asymmetric synthesis

Introduction

The asymmetric addition reaction of nitro compounds to aldehydes (Henry reaction) is an effective way of preparing chiral β-nitro-secondary alcohols.[1,2] Chiral β-nitro-secondary alcohols are not only widely present in many biologically active compounds, but also are important building blocks, which can be reduced to β-aminoalcohols, dehydrated to nitroalkenes or oxidized to nitrocarbonyl compounds. Therefore, it is essential to develop catalytic asymmetric Henry reactions of nitromethane and aldehydes with high enantioselectivity.[3–6]

In the field of catalytic asymmetric Henry reactions, a lot of typical, effective and widely used chiral catalysts have been reported. Shibasaki and co-workers in 1995 first reported an asymmetric Henry reaction catalyzed by a La(O-*t*-Bu)$_3$ and chiral (*S*)-(−)-BINOL complex.[7–15] Also, bisoxazoline ligands **1**, bisimadozoline ligands **2**, iminoalcohol ligands **3**, chiral diamine ligands **4** and quinine ligands **5** (Fig. 1) can also promote Lewis acid-catalyzed asymmetric Henry reactions. However, asymmetric Henry reactions catalyzed by chiral thiazoline ligands have seldom been reported.[16]

We first disclosed the design, synthesis and application of a series of novel modular thiazoline-containing N,O ligands derived from L-cysteine in asymmetric addition of diethylzinc to aromatic aldehydes.[17] In the reaction, the imino group of thiazoline is an effective amino unit, so iminoalcohol thiazoline could be deemed as a member of the group of chiral β-aminoalcohol ligands. Recently we reported novel thiazoline-containing amide catalysts which were applied to asymmetric aldol reaction of aromatic aldehydes with high enantioselectivity.[18] Encouraged by these successful efforts, we explored the generality of these novel chiral scaffolds containing thiazoline. To obtain more metal-bonding sites, we decided to add two more coordination sites by introducing some functional groups such as cinchona alkaloid, benzimidazole, chiral aminoalcohol and 8-aminoquinoline to form novel chiral thiazoline tridentate ligands. These chiral thiazoline tridentate ligands, namely –NH– amide tertiary amine tridentate ligands **6** and **7**, –NH– amide secondary amine tridentate ligands **8** and **9**, –NH– amide –OH tridentate ligands **10–12** and –NH– amide imine tridentate ligand **13**, are shown in Fig. 2. Furthermore, the catalytic potential of these new ligands was tested in the asymmetric Henry reaction of nitromethane and various aldehydes.

Results and discussion

(*R*)-Tetrahydrothiazo-2-thione-4-carboxylic acid (**15**) was prepared via the cyclization of L-cysteine and carbon disulfide under basic conditions, according to a previous procedure.[17] Then we synthesized a series of novel chiral thiazoline tridentate ligands (**6–14**) containing thiazoline (Scheme 1) via a two-step procedure from compound **15**. First, compound **15** was stirred with ethyl chloroformate to form the anhydride **16**, which was then reacted with compound **17**, **18**, **19**, **20**, **21**, **22**, **23** or a solution of 8-aminoquinoline (**24**) to facilitate a one-pot sequence to give ligands **6–13** in moderate yield. Ligand **14** was synthesized from compound **13** by reduction of $LiAlH_4$.

Before investigating the efficiency of the synthesized chiral ligands in the Henry reaction, we first optimized the reaction conditions, which include solvent, amount of ligand and reaction temperature. We examined these in the presence of 10 mmol% CuCl and *N*,*N*-diisopropylethylamine (DIPEA) as base. The effect of different solvents and the amount of ligand on yield and enantioselectivity was investigated (Table 1). For example, the reaction of *p*-nitrobenzaldehyde with nitromethane in the presence of

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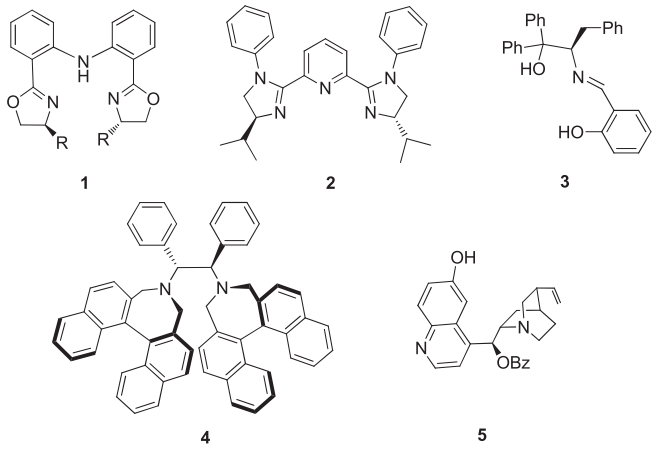


Figure 1. Chiral ligands applied to asymmetric Henry reaction.

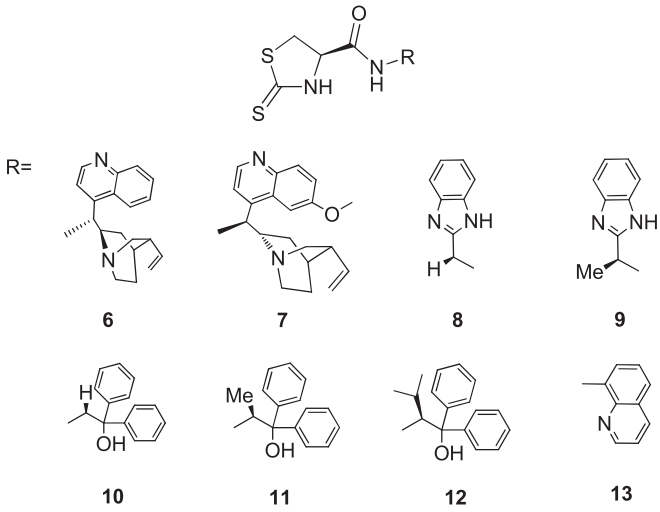


Figure 2. Novel chiral thiazoline tridentate ligands.

10 mol% ligand **12** and 10 mol% CuCl catalyst gives 70% yield with 62% enantiomeric excess (*ee*) in dichloromethane, while the reaction in ethanol gives 90% yield with 98% *ee*. Thus, ethanol is established as the best solvent for this reaction system. Also, the reaction in the presence of 20 mol% ligand **12** gives 75% *ee*, while the reaction in the presence of 10 mol% ligand **12** gives 98% *ee*. However, decreasing further the amount of ligand **12** gives a lower yield and poorer enantioselectivity. When the reaction temperature is increased from −20°C to room temperature, the reaction gives a poorer enantioselectivity than before. Therefore, the optimized conditions of the reaction are obtained: 10 mol% ligand **12**, at −20°C and ethanol as solvent.

The subsequent investigations of the steric and electronic effects of the ligands **6–14** show that the reactivity and enantioselectivity are closely related to the chiral backbone and the substituents of the ligand moiety. Reactions were carried out using 10 mol% ligand and CuCl in ethanol at −20°C (Table 2). The reaction in the presence of ligand **12** gives 93% yield with 98% *ee*, while the reaction in the presence of less sterically hindered ligands **10** and **11** provides a poorer enantioselectivity. The reaction in the presence of benzimidazole ligands **8** and **9** gives good enantioselectivity, and sterically hindered ligands lead to higher *ee* values (Table 2, entries 3 and 4). But in the presence of quinine ligands **6** and **7** the reaction gives poorer *ee* values but higher yield. Different configurations of the metal-bonding site lead to the same configuration of product, thus indicating that the configuration of thiazoline not the configuration of substituents on amide group controls the configuration of the product (Table 2, entries 1 and 2). Among the ligands **6–14**, ligands **13** and **14** prepared from chiral thiazoline and 8-aminoquinoline provide the poorest enantioselectivity (Table 2, entries 8 and 9). Ligand **14**, whose amide is reduced to amine, does not give good enantioselectivity. Possible reasons are that there is no chiral backbone in 8-aminoquinoline and the coordination activity of nitrogen atoms in amide is better than that in amine.

The effects of different copper sources (Table 2, entries 7–9) were also examined with the most efficient ligand **12**. The results reveal that CuCl gives better yield and enantioselectivity than $Cu(OAc)_2 \cdot H_2O$. Thus CuCl is chosen for further reactions.

With the optimized conditions in hand, the scope of the substrate was extended. A variety of aldehydes were employed as substrates to react with nitromethane, giving the corresponding products with high yields and *ee* values (Table 3). The data clearly show that electron-withdrawing substituents exhibit higher *ee* than electron-donating substituents. The substrates with *ortho*-substituent give lower enantioselectivities than others (Table 3, entries 1 and 2 versus 3). An aliphatic aldehyde also reacts well with nitromethane and gives the corresponding products with high yield and *ee* value (Table 3, entry 9).

According to the literature[20–22] and the stereochemistry of the products, a plausible transition state is proposed, as shown in Scheme 2. When copper coordinates with ligands, the configuration of complex is tetrahedral. Two nitrogen and one oxygen anion are bonded to copper(I). The last metal-bonding site is connected with the oxygen of nitroalkane to activate the nitroalkane. The R group of the aldehyde is located far away from benzene and isopropyl. The methylene of the nitroalkane attacks the *Si* face of the aldehyde. Therefore, the configuration of the product is *S* which corresponds to our result.

Experimental

General remarks

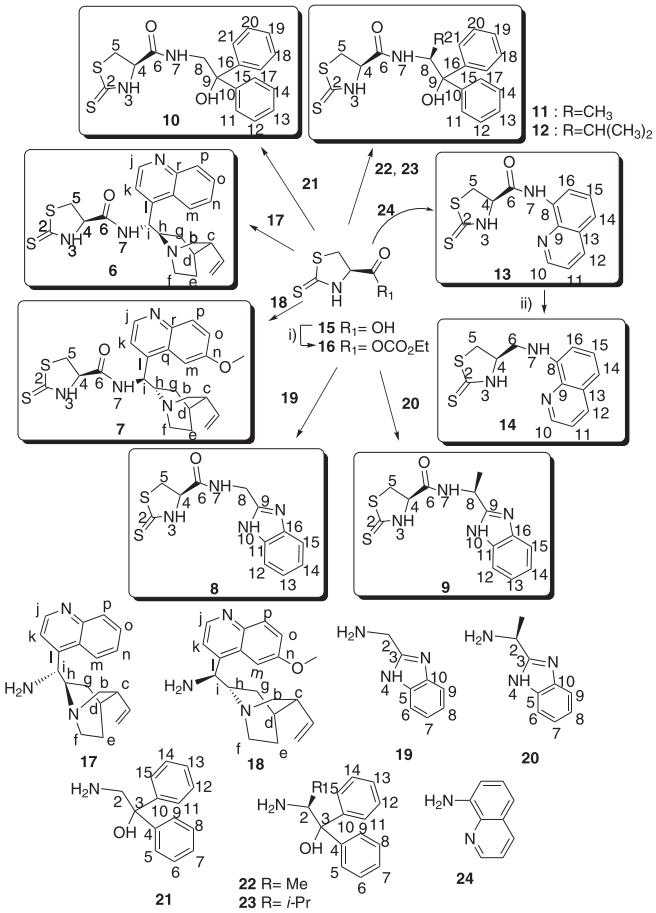
^1H NMR and ^{13}C NMR spectra were recorded with a Varian Mercury 300 MHz NMR spectrometer or a Bruker AVANCE 400 MHz NMR spectrometer, using tetramethylsilane as an internal standard. Mass spectra were obtained using an LC/MS 1100 (Agilent Technology Corp.). A WZZ-1S digital automatic polarimeter (Shanghai Physical Optics Instrument Factory) was used, with concentrations given as absolute values expressed in grams per 100 ml. Melting points were determined with an X-4 digital microscope. HPLC analyses were performed using a Shimadzu LC-10A VP pump, SPD-10A VP UV detector and Shimadzu CTO-10AC VP column oven with appropriate chiral columns.

All commercial chemicals were of analytical grade, purchased from Beijing Chemical Reagent Co. (China) and used without further purification. Compound **24** was purchased from J&K Company. Column chromatography was generally performed on silica gel (300–400 mesh) and TLC on silica gel GF_{254} plates.

Syntheses

*Synthesis of compound **15***

Compound **15** was produced as described previously.[17] M.p. 179–181°C; $[\alpha]_D^{20} = -86.3°$ (*c* 1.2, 0.5 N HCl).



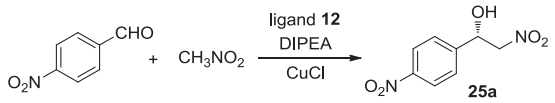
Scheme 1. Synthesis of chiral thiazoline tridentate ligands.

*Synthesis of aminoquinine (**17**, **18**)*

Quinine (2.5 mmol) and triphenylphosphane (0.8 g, 3 mmol) were mixed in anhydrous tetrahydrofuran, and the whole mixture was cooled to 0°C, and treated dropwise with diisopropyl azodicarboxylate (0.6 ml, 3 mmol) and a solution of diphenylphosphorylazide (0.65 ml, 3 mmol) in anhydrous tetrahydrofuran (10 ml). After the addition, the mixture was heated to room temperature for 24 h and then the mixture was warmed to 50°C for another 3 h. Triphenylphosphane (0.85 g, 3.3 mmol) was then added, and the mixture was stirred until no gas was released (about 3 h). After cooling the mixture to room temperature, 3 ml of water was added and the mixture was stirred at the same temperature for 12 h. At 0°C, 1 M HCl was added slowly to neutralize the mixture until pH = 2, after which it was extracted with ethyl acetate three times. At 0°C, to the aqueous phase was added aqueous NaOH until pH = 10 and subsequently extracted with ethyl acetate three times. The combined organic layer was dried with Na_2SO_4 and the solvent was removed by evaporation under reduced pressure. The crude product was purified using column chromatography (ethyl acetate–methanol–triethylamine, 100:100:1 by volume) to afford **17** and **18** as a yellow oil.

9-Aminodeoxycinchonine (**17**). The crude product was purified using column chromatography (ethyl acetate–methanol–triethylamine, 100:100:1 by volume) to afford **17** as a yellow oil (76% yield). $[\alpha]_D^{20}$ = +110° (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO, δ, ppm): 0.94–1.05 (m, 1 H, C^g*H*), 1.43–1.48 (m, 3H, C^g*H*, C^e*H*$_2$), 2.18–2.26 (m, 2 H, C^c*H*, C^d*H*), 2.88–2.96 (m, 5 H, C^h*H*, C^b*H*$_2$, C^f*H*$_2$), 4.71 (d, *J* = 9.9 Hz, 1 H, C^i*H*), 5.04–5.13 (m, 2 H, –CH=C*H*$_2$), 5.84–5.95 (m, 1 H, –C*H*=CH$_2$), 7.60–7.68 (m, 2 H, C^o*H*, C^k*H*), 7.72–7.77 (td, J_1 = 8.3, J_2 = 1.3 Hz, 1 H, C^n*H*), 8.03 (dd, J_1 = 8.3, J_2 = 1.3 Hz, 1 H, C^p*H*), 8.51 (brs, 1 H, C^m*H*), 8.86 (d, *J* = 4.2 Hz, 1 H, C^j*H*).

Table 1. Screening of solvents and catalyst loading for diastereoselective Henry reaction[a]



Entry	Solvent	**12** (mol%)	Temp. (°C)	Yield (%)[b]	*ee* (%)[c]	Configuration[d]
1	Ethanol	10	−20	90	98	*S*
2	Dichloromethane	10	−20	70	62	*S*
3	Tetrahydrofuran	10	−20	86	78	*S*
4	Ethanol	20	−20	95	75	*S*
5	Ethanol	5	−20	55	73	*S*
6	Ethanol	10	25	96	82	*S*

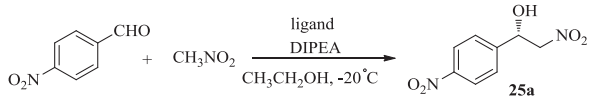
[a]Reactions were carried out using *p*-nitrobenzaldehyde (1 mmol), nitromethane (10mmol), CuCl (0.1 mmol), DIPEA (0.1 mmol) and ligand **12** (0.1 mmol) in solvent (2 ml) in nitrogen atmosphere for 48 h.

[b]Isolated yield after column purification.

[c]Enantiomeric excess values were determined by HPLC using Chiralcel OD.

[d]The absolute configuration of the products was assigned by comparison with retention time from the literature.[19]

Table 2. Screening of ligands **6–14** and copper sources for the diastereoselective Henry reaction[a]



Entry	Ligand (10 mol%)	Yield (%)[b]	*ee* (%)[c]	Configuration[d]
1	**6** + CuCl	85	75	*S*
2	**7** + CuCl	70	68	*S*
3	**8** + CuCl	92	80	*S*
4	**9** + CuCl	93	88	*S*
5	**10** + CuCl	86	86	*S*
6	**11** + CuCl	90	90	*S*
7	**12** + CuCl	93	98	*S*
8[e]	**12** + $Cu(OAc)_2 \cdot H_2O$	85	96	*S*
9[e]	**12** + $CuCl_2 \cdot 2H_2O$	86	70	*S*
10	**13** + CuCl	81	67	*S*
11	**14** + CuCl	70	52	*S*

[a]Reactions were carried out using *p*-nitrobenzaldehyde (1 mmol), nitromethane (10 mmol), copper salt (0.1 mmol), DIPEA (0.1 mmol) and ligand (0.1 mmol) in ethanol (2 ml) at −20°C in nitrogen atmosphere for 48 h.

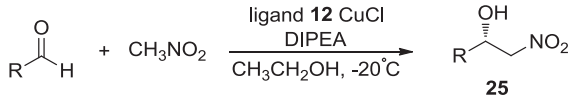
[b]Isolated yield after column purification.

[c]Enantiomeric excess values were determined by HPLC using Chiralcel OD.

[d]The absolute configuration of the products was assigned by comparison with retention time from the literature.[19]

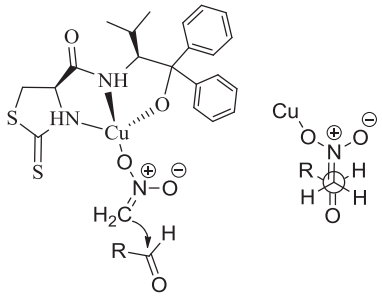
[e]The reaction was conducted in air.

Table 3. Diastereoselective Henry reaction of aldehydes with nitromethane catalyzed by ligand **12**/CuCl[a]



Entry	R	Yield (%)[b]	*ee* (%)[c]	Configuration[d]
1	4-$NO_2C_6H_4$ (a)	93	98	*S*
2	3-$NO_2C_6H_4$ (b)	91	98	*S*
3	2-$NO_2C_6H_4$ (c)	89	89	*S*
4	2-$OCH_3C_6H_4$ (d)	68	82	*S*
5	4-ClC_6H_4 (e)	94	72	*S*
6	3-ClC_6H_4 (f)	71	67	*S*
7	4-FC_6H_4 (g)	85	86	*S*
8	4-BrC_6H_4 (h)	91	85	*S*
9	$PhCH_2$ (i)	92	83	*S*
10	$(CH_3)_2CHCH_3$ (j)	82	86	*S*
11	Cyclohexyl (k)	70	90	*S*

[a]Reactions were carried out using aldehydes (1 mmol), nitromethane (10mmol), CuCl (0.1 mmol), DIPEA (0.1 mmol) and ligand **12** (0.1 mmol) in solvent (2 ml) in nitrogen atmosphere for 48 h.
[b]Isolated yield after column purification.
[c]Enantiomeric excess values were determined by HPLC using Chiralcel OD, AD-H.
[d]The absolute configuration of the products was assigned by comparison with retention time from the literature.[19]



Scheme 2. Plausible transition state for the Henry reaction.

9-Aminodeoxyquinine (**18**). The crude product was purified using column chromatography (ethyl acetate–methanol–triethylamine, 100:100:1 by volume) to afford **18** as a yellow oil (80% yield). $[\alpha]_D^{20}$ = +80° (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO, δ, ppm): 0.65–0.72 (m, 1 H, C^gH), 1.16–1.25 (m, 1 H, C^gH), 1.52 (m, 3 H, C^eH_2, C^dH), 2.24 (m, 2 H, C^bH_2), 2.64–2.69 (m, 2 H, C^fH_2), 2.91–2.99 (m, 1 H, C^cH), 3.141–3.22 (m, 1 H, C^hH), 3.93 (s, 3 H, –OCH_3), 4.62 (d, *J* = 10.2 Hz, 1 H, C^iH), 4.91–5.02 (m, 2 H, –CH=CH_2), 5.77–5.88 (m, 1 H, –CH=CH_2), 7.40 (dd, *J* = 2.7 Hz, *J* = 9.3 Hz, 1 H, C^oH), 7.59 (d, *J* = 4.5 Hz, 1 H, C^kH), 7,80 (brs, 1 H, C^mH) 7.92 (d, *J* = 9.3 Hz, 1 H, C^pH), 8.70 (d, *J* = 4.5 Hz, 1 H, C^jH).

*Synthesis of alkylamino-1-H-benzimidazole (**19**, **20**)*

o-Phenylenediamine and excess amino acid (1:1.2) were mixed and refluxed in 6 mol l^{-1} aqueous HCl. The course of the reaction was confirmed using TLC. After the reaction completed, the resulting solution was cooled until crystals began to form. The crude product was recrystallized from ethanol.

H-benzimidazole-2-methylamine dihydrochloride (**19**). Yield 60%; m.p. 264–266°C. ^{1}H NMR (300 MHz, DMSO, δ, ppm): 4.56 (s, 2 H, C^2H_2), 7.50 (q, *J* = 3.0 Hz, 2 H, C^7H, C^8H), 7.82 (q, *J* = 3.0 Hz, 2 H, C^6H, C^9H), 9.21 (brs, 3 H, C^1H, –N*H*, –NH_2).

1-*H*-benzimidazole-2-(*S*)-ethylamine dihydrochloride (**20**). Yield 50%; m.p. 130–132°C. ^{1}H NMR (300 MHz, DMSO, δ, ppm): 1.82 (dd, *J* = 1.5 Hz, *J* = 6.9 Hz, 3 H, CH_3), 4.95–4.98 (m, 1 H, C^2H), 7.49–7.53 (m, 2 H, C^7H, C^8H), 7.80–7.84 (m, 2 H, C^6H, C^9H), 9.29 (brs, 3 H, –N*H*, –NH_2).

*Synthesis of L-amino tertiary alcohols (**21–23**)*

To a solution of amino acid (50 mmol) in 2 mol l^{-1} aqueous NaOH (20 ml), benzyl chloroformate (CbzCl; 50 mmol) and 2 mol l^{-1} aqueous NaOH were added at 0°C. The solution was kept at pH = 9–10 and stirred vigorously for 1 h. Then the solution was stirred at room temperature for 1 h. The mixture was then extracted with diethyl ether (2 × 15 ml). Then the aqueous phase was added to 20 ml of ethyl acetate and treated with 2 mol l^{-1} aqueous HCl until pH = 1. The combined organic phase was washed with saturated brine twice, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was used directly for subsequent steps without further purification.

At −10°C, 3.8 ml of thionyl chloride was added dropwise to 35 ml of anhydrous methanol and treated with a solution of 50 mmol of amino acid protected by Cbz in anhydrous methanol (10 ml). The solution was stirred at this temperature for 0.5 h. Then the mixture was stirred at room temperature for 12 h. After that the solution was poured into ice and then treated with 2 mol l^{-1} aqueous NaOH until pH = 9. The resulting solution was extracted with ethyl acetate three times. The organic layers were combined, washed with brine, dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to afford the amino acid esters protected by Cbz, which were used directly for subsequent steps without further purification.

Magnesium powder and 0.1 g of iodine were added to 10 ml of anhydrous tetrahydrofuran and treated dropwise with a solution of bromobenzene (12 mmol) in anhydrous tetrahydrofuran (10 ml), keeping the mixture refluxed. After the addition, the mixture was refluxed for 0.5 h. At 0°C, a solution of Cbz-amino acid esters (3 mmol) in anhydrous tetrahydrofuran (10 ml) was added dropwise, and then the mixture was stirred at room temperature for 12 h. The reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with diethyl ether, washed with brine, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The crude product was purified using column chromatography (ethyl acetate–petroleum ether, 1:3 v/v) to afford Cbz-protected amino tertiary alcohols.

Cbz-2-amino-1,1-diphenylethanol. White solid, 90% yield. ^{1}H NMR (300 MHz, DMSO, δ, ppm): 3.85 (d, *J* = 5.4 Hz, 2 H, –NHCH_2–), 4.98 (s, 2 H, –CH_2Ph), 5.84 (s, 1 H, –O*H*), 6.83 (d, *J* = 5.4 Hz, 1 H, N*H*), 7.17–7.24 (m, 4 H, –Ph), 7.26–7.31 (m, 7 H, –Ph), 7.42–7.46 (m, 4 H, –Ph).

(*S*)-Cbz-(*R*)-2-amino-1,1-diphenylpropan-1-ol. White solid, 87% yield. ^{1}H NMR (300 MHz, DMSO, δ, ppm): 0.92 (d, *J* = 6.3 Hz, 3 H, –CH_3), 4.72–4.82 (m, 1 H, –*CH*–), 4.90 (d, *J* = 12.9 Hz, 1 H, –CH_2Ph), 5.10 (d, *J* = 12.9 Hz, 1 H, –CH_2Ph), 5.23 (s, 1 H, –O*H*), 6.86 (d, *J* = 6.3 Hz, 1 H, N*H*), 7.24–7.32 (m, 4 H, –Ph), 7.24–7.32 (m, 7 H, –Ph), 7.46–7.52 (m, 4 H, –Ph).

(*S*)-Cbz-(*R*)-2-amino-3-methy-1,1-diphenylbutyl-1-ol. White solid, 93% yield. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 0.87 (d, *J* = 6.9 Hz, 3 H, –CH_3), 0.92 (d, *J* = 6.9 Hz, 3 H, –CH_3), 1.78–1.88 (m, 1 H, –*CH*(CH_3)$_2$), 3.48 (s, 1 H, –O*H*), 4.67 (d, *J* = 10.2 Hz, 1 H, –*CH*–), 4.95 (d, *J* = 12.3 Hz,

1 H, –CH_2Ph), 5.06 (d, J = 12.3 Hz, 1 H, –CH_2Ph), 5.27 (d, J = 10.2 Hz, 1 H, –N*H*), 7.17–7.23 (m, 5 H, –Ph), 7.28–7.34 (m, 6 H, –Ph), 7.43–7.49 (m, 4 H, –Ph).

To Cbz-amino tertiary alcohol in 50 ml of anhydrous methanol was added 2.0 g of Pd/C (5%), in hydrogen atmosphere, and stirred at 50°C until the reaction completed. Pd/C was removed by filtration and the solvent was removed under reduced pressure. The crude product was recrystallized from petroleum ether to obtain the amino tertiary alcohol **13**.

2-Amino-1,1-diphenylethanol (**21**). White solid, 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 3.40 (s, 2 H, C^2H_2), 7.21–7.27 (m, 2 H, C^7H, $C^{13}H$), 7.31–7.35 (m, 4 H, C^6H, C^8H, $C^{12}H$, $C^{14}H$), 7.36–7.47 (m, 4 H, C^5H, C^9H, $C^{11}H$, $C^{15}H$).

(*S*)-2-Amino-1,1-diphenylpropan-1-ol (**22**). White solid, 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 0.94 (d, J = 6.3 Hz, 3 H, –CH_3), 4.14 (q, J = 6.3 Hz, 1 H, C^2H), 7.13–7.21 (m, 2 H, C^7H, $C^{13}H$), 7.24–7.34 (m, 4 H, C^6H, C^8H, $C^{12}H$, $C^{14}H$), 7.47 (d, J = 6.6 Hz, 2 H, C^5H, C^9H), 7.61 (d, J = 6.6 Hz, 2 H, $C^{11}H$, $C^{15}H$).

(*S*)-2-Amino-3-methy-1,1-diphenylbutyl-1-ol (**23**). White solid, 95% yield. ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 0.88 (d, J = 6.9 Hz, 3 H, –CH_3), 0.92 (d, J = 6.9 Hz, 3 H, –CH_3), 1.70–1.80 (m, 1 H, –$CH(CH_3)_2$), 3.84 (d, J = 2.1 Hz, 1 H, C^2H), 7.13–7.20 (m, 2 H, C^7H, $C^{13}H$), 7.25–7.33 (m, 4 H, C^6H, C^8H, $C^{12}H$, $C^{14}H$), 7.48–7.51 (m, 2 H, C^5H, C^9H), 7.60–7.63 (m, 2 H, $C^{11}H$, $C^{15}H$).

*Synthesis of chiral thiazoline tridentate ligands (**6–13**)*

Compound **15** (3.26 g, 20 mmol) and *N*-methylmorpholine (2.5 ml, 21 mmol) were dissolved in 20 ml of anhydrous tetrahydrofuran and cooled to −10°C. Then the mixture was treated dropwise with a solution of ethyl chloroformate (1.9 ml, 20 mmol) in tetrahydrofuran (5 ml) and stirred for 0.5 h. Compound **17**, **18**, **19**, **20**, **21**, **22**, **23**, or a solution of **24** (20 mmol) in tetrahydrofuran (10 ml) was added dropwise, and then the mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with ethyl acetate three times, washed with brine, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The crude product was purified using column chromatography to afford compounds **6–13**.

(4*R*)-*N*-((1*R*)-quinolin-4-yl(5-vinylquinuclidin-2-yl)methyl)-2-thioxothiazolidine-4-carboxamide (**6**). The crude product was purified using column chromatography (dichloromethane–methanol, 9:1 v/v) to afford a white solid, 80% yield, $[\alpha]_D^{20}$ = +48° (*c* 1.0, $CHCl_3$), m.p. 198–202°C. ^{1}H NMR (300 MHz, DMSO, δ, ppm): 0.83–0.92 (m, 1 H, C^gH), 0.97–1.06 (m, 1 H, C^gH), 1.48–1.53 (m, 3 H, C^dH, C^eH_2), 2.25 (m, 1 H, C^cH), 2.82–2.98 (m, 4 H, C^bH_2, C^fH_2), 3.14–3.19 (m, 3 H, C^hH, C^5H_2), 3.75 (dd, J_1 = 9.3, J_2 = 11.4 Hz, 1 H, C^4H), 5.01–5.15 (m, 2 H, –CH=CH_2), 5.92 (ddd, J_1 = 17.0, J_2 = 10.2, J_3 = 6.9 Hz, 1 H, –CH=CH_2), 7.57 (d, J = 4.4 Hz, 1 H, C^kH), 7.65–7.69 (td, J_1 = 1.5, J_2 = 8.2 Hz, 1 H, C^nH), 7.75–7.80 (td, J_1 = 1.5, J_2 = 8.2 Hz, 1 H, C^oH), 8.04 (dd, J_1 = 1.5, J_2 = 8.2 Hz, 1 H, C^pH), 8.36 (dd, J_1 = 1.5, J_2 = 8.2 Hz, 1 H, C^mH), 8.62 (d, J = 5.9Hz, 1 H, N^7H), 8.89 (d, J = 4.4 Hz, 1 H, C^jH). ^{13}C NMR (75 MHz, DMSO, δ, ppm): 24.90 (C^g), 25.80 (C^e), 27.09 (C^d), 35.91 (C^c), 46.57 (C^5), 48.57 (C^f), 55.94 (C^i), 58.47 (C^b), 64.70 (C^h), 114.52 (–CH=CH_2), 119.60 (C^m), 123.46 (C^k), 126.51 (C^o), 126.71 (C^p), 129.07 (C^n), 129.74 (C^l), 140.70 (-CH=CH_2), 146.29 (C^q), 147.82 (C^r), 150.11 (C^j), 167.93 (C^6), 199.62 (C^2). MS (ESI): *m/z* 438.8 [M + H$^+$].

(4*R*)-*N*-((1*S*)-(6-methoxyquinolin-4-yl)((5*R*)-5-vinylquinuclidin-2-yl)methyl)-2-thioxothiazolidine-4-carboxamide (**7**). The crude product was purified using column chromatography (dichloromethane–methanol, 9:1 v/v) to afford a yellow solid, 85% yield, $[\alpha]_D^{20}$ = −123.4° (*c* 1.0, $CHCl_3$), m.p. 142–144°C. ^{1}H NMR (300 MHz, DMSO, δ, ppm): 0.71–0.72 (m, 1 H, C^gH), 1.54–1.59 (m, 4 H, C^gH, C^dH, C^eH_2), 2.25–2.37 (m, 3 H, C^bH_2, C^cH), 2.67–2.72 (m, 2 H, C^fH), 3.18–3.37 (m, 2 H, C^5H_2), 3.51–3.55 (m, 1 H, C^hH), 3.78–3.85 (m, 1 H, C^4H), 3.95 (s, 3 H, –OCH_3), 4.69–4.72 (m, 1 H, C^iH), 4.98–5.08 (m, 2 H, –CH=CH_2), 5.89–5.99 (m, 1 H, –CH=CH_2), 7.43 (d, J = 8.7 Hz, 1 H, C^oH), 7.51 (d, J = 3.6 Hz, 1 H, C^kH), 7.73 (s, 1 H, C^mH), 7.94–7.97 (d, J = 9.3 Hz, 1 H, C^pH), 7.84 (brs, 1 H, N^7H), 8.73–8.75 (d, J = 3.6 Hz, 1 H, C^jH). ^{13}C NMR (75 MHz, DMSO, δ, ppm): 26.12 (C^e), 27.03 (C^d), 36.08 (C^g), 40.78 (C^c), 55.37 (C^5), 55.66 (C^f), 58.23 (–OCH_3), 64.79 (C^i), 102.45 (C^m), 114.33 (–CH=CH_2), 120.03 (C^o), 121.34 (C^k), 128.07 (C^p), 131.23 (C^l), 141.93 (–CH=CH_2), 144.09 (C^r), 147.54 (C^j), 157.41 (C^n), 168.17 (C^6), 199.85 (C^2). MS (ESI): *m/z* 469.1 [M + H$^+$].

(*R*)-*N*-((1*H*-benzo[*d*]imidazol-2-yl)methyl)-2-thioxothiazolidine-4-carboxamide (**8**). The crude product was purified using column chromatography (dichloromethane–methanol, 9:1 v/v) to afford a white solid, 83% yield, $[\alpha]_D^{20}$ = −10.2° (*c* 1.0, CH_3OH), m.p. 224–226°C. ^{1}H NMR (300 MHz, DMSO, δ, ppm): 3.63 (q, J = 6.0 Hz, 1 H, C^5H), 3.81 (dd, J = 9.0 Hz, J = 11.4 Hz, 1 H, C^5H), 4.48–4.63 (m, 2 H, C^8H_2), 4.85 (dd, J = 6.0 Hz, J = 9.0 Hz, 1 H, C^4H), 7.15 (m, 2 H, $C^{13}H$, $C^{14}H$), 7.52 (m, 2 H, $C^{12}H$, $C^{15}H$), 8.87 (t, J = 5.7 Hz, 1 H, –N^7H), 10.26 (s, 1 H, –S*H*), 12.28 (s, 1 H, –$N^{10}H$). ^{13}C NMR (75 MHz, DMSO, δ, ppm): 35.82 (C^8), 37.43 (C^5), 65.07 (C^4), 121.59 (C^{12}, C^{15}), 151.34 (C^{13}, C^{14}), 168.62 (C^6), 199.67 (C^2). MS (ESI): *m/z* 293.1 [M + H$^+$].

(*R*)-*N*-((*S*)-1-(1*H*-benzo[*d*]imidazol-2-yl)ethyl)-2-thioxothiazolidine-4-carboxamide (**9**). The crude product was purified using column chromatography (dichloromethane–methanol, 9:1 v/v) to afford a white solid, 80% yield, $[\alpha]_D^{20}$ = −15° (*c* 1.0, CH_3OH), m.p. 150–152°C. ^{1}H NMR (300 MHz, DMSO, δ, ppm): 1.54 (d, J = 6.9 Hz, 3 H, –CH_3), 3.63 (q, J = 6.3 Hz, 1 H, C^5H), 3.81 (dd, J = 9.0 Hz, J = 11.4 Hz, 1 H, C^5H), 4.82 (dd, J = 6.9 Hz, J = 9.0 Hz, 1 H, C^8H), 5.13–5.23 (dd, J = 6.3 Hz, J = 9.0 Hz, 1 H, C^4H), 7.14–7.18 (m, 2 H, $C^{13}H$, $C^{14}H$), 7.45 (d, J = 7.2 Hz, 1 H, $C^{12}H$), 7.57 (d, J = 7.2 Hz, 1 H, $C^{15}H$), 8.79 (d, J = 7.8 Hz, 1 H, –N^7H), 10.26 (s, 1 H, –S*H*), 12.28 (s, 1 H, –$N^{10}H$). ^{13}C NMR (75 MHz, DMSO, δ, ppm): 19.77 (–CH_3), 35.68 (C^5), 43.78 (C^8), 65.16 (C^4), 121.56 (C^{12}, C^{15}), 155.17 (C^{13}, C^{14}), 167.82 (C^6), 199.71 (C^2). MS (ESI): *m/z* 307.1 [M + H$^+$].

(*R*)-*N*-(2-hydroxy-2,2-diphenylethyl)-2-thioxothiazolidine-4-carboxamide(**10**). The crude product was purified using column chromatography (ethyl acetate–petroleum ether, 9:1 v/v) to afford a white solid, 90% yield, $[\alpha]_D^{20}$ = −44° (*c* 1.0, CH_3OH), m.p. 52–53°C. ^{1}H NMR (300 MHz, DMSO, δ, ppm): 2.85 (q, J = 5.7 Hz, 1 H, C^5H), 3.53 (dd, J = 9.3 Hz, J = 11.4 Hz, 1 H, C^5H), 3.71 (dd, J = 4.2 Hz, J = 13.8 Hz, 1 H, C^8H), 4.21 (dd, J = 6.9 Hz, J = 13.5 Hz, 1 H, C^8H), 4.71 (dd, J = 5.7 Hz, J = 9.3 Hz, 1 H, C^4H), 7.16–7.23 (m, 2 H, $C^{13}H$, $C^{19}H$), 7.26–7.33 (m, 4 H, $C^{12}H$, $C^{14}H$, $C^{18}H$, $C^{20}H$), 7.40–7.44 (m, 4 H, $C^{11}H$, $C^{15}H$, $C^{17}H$, $C^{21}H$), 7.88–7.92 (m, 1 H, N^7H), 10.21 (s, 1 H, –S*H*). ^{13}C NMR (75 MHz, DMSO, δ, ppm): 35.88 (C^5), 48.04 (C^8), 64.71 (C^4), 76.96 (C^9), 125.91 (C^{19}), 125.98 (C^{13}), 126.56 (C^{17}, C^{21}), 126.75 (C^{11}, C^{15}), 127.81 (C^{18}, C^{20}), 127.99 (C^{12}, C^{14}), 145.36 (C^{16}), 145.92 (C^{10}), 168.54 (C^6), 199.59 (C^2). MS (ESI): *m/z* 357.2 [M − H$^+$].

(*R*)-*N*-((*S*)-1-hydroxy-1,1-diphenylpropan-2-yl)-2-thioxothiazolidine-4-carboxamide (**11**). The crude product was purified using column chromatography (ethyl acetate–petroleum ether, 1:1 v/v) to afford a white solid, 89% yield, $[\alpha]_D^{20}$ = −20° (*c* 1.0, CH_3OH), m.p. 48–50°C. ^{1}H NMR (300 MHz, DMSO, δ, ppm): 0.96 (d, J = 6.9 Hz, 3 H, –CH_3), 3.04 (q, J = 6.3 Hz, 1 H, C^5H), 3.66 (dd, J = 9.0 Hz, J = 11.1 Hz, 1 H, C^5H), 4.57–4.64 (dd, J = 6.9 Hz, J = 9.0 Hz, 1 H, C^8H), 4.95–5.07 (dd, J = 6.3 Hz, J = 9.0 Hz, 1 H, C^4H), 7.15–7.30 (m, 6 H, $C^{13}H$, $C^{19}H$, $C^{12}H$, $C^{14}H$, $C^{18}H$, $C^{20}H$), 7.43–7.51 (m, 4 H, $C^{11}H$, $C^{15}H$, $C^{17}H$, $C^{21}H$), 7.64 (d, J = 9.0 Hz, 1 H, N^7H), 10.29 (s, 1 H, –S*H*). ^{13}C

NMR (75 MHz, DMSO, δ, ppm): 15.57 (–CH_3), 35.86 (C^5), 50.21 (C^8), 64.54 (C^4), 79.14 (C^9), 125.35 (C^{19}), 125.46 (C^{13}), 126.08 (C^{17}, C^{21}), 126.25 (C^{11}, C^{15}), 127.55 (C^{18}, C^{20}), 127.87 (C^{12}, C^{14}), 145.58 (C^{16}), 145.98 (C^{10}), 167.32 (C^6), 199.49 (C^2). MS (ESI): *m/z* 371.0 [M − H^+].

(*R*)-*N*-((*S*)-1-hydroxy-3-methyl-1,1-diphenylbutan-2-yl)-2-thioxothiazolidine-4-carboxamide (**12**). The crude product was purified using column chromatography (ethyl acetate–petroleum ether, 1:1 v/v) to afford a white solid, 86% yield, $[\alpha]_D^{20} = -56.5°$ (*c* 1.0, CH_3OH), m.p. 58–60°C. ^{1}H NMR (300 MHz, DMSO, δ, ppm): 0.77 (d, *J* = 6.9 Hz, 3 H, –CH_3), 0.91 (d, *J* = 6.9 Hz, 3 H, –CH_3), 1.75–1.82 (m, 1 H, –$CH(CH_3)_2$), 2.33 (dd, *J* = 5.1 Hz, *J* = 11.4 Hz, 1 H, C^5H), 3.34 (q, *J* = 9.3 Hz, 1 H, C^5H), 4.66 (dd, *J* = 5.1 Hz, *J* = 9.3 Hz, 1 H, C^4H), 4.85 (m, 1 H, C^8H), 7.08–7.34 (m, 6 H, $C^{13}H$, $C^{19}H$, $C^{12}H$, $C^{14}H$, $C^{18}H$, $C^{20}H$), 7.51 (t, *J* = 7.5 Hz, 4 H, $C^{11}H$, $C^{15}H$, $C^{17}H$, $C^{21}H$), 7.63 (d, *J* = 10.4 Hz, 1 H, N^7H). ^{13}C NMR (75 MHz, DMSO, δ, ppm): 17.04 (–CH_3), 23.54 (–$CH(CH_3)_2$), 36.28 (C^5), 60.45 (C^8), 65.45 (C^4), 81.34 (C^9), 125.73 (C^{19}), 126.20 (C^{13}), 126.48 (C^{17}, C^{21}), 126.57 (C^{11}, C^{15}), 128.27 (C^{18}, C^{20}), 128.46 (C^{12}, C^{14}), 147.16 (C^{16}), 148.89 (C^{10}), 169.01 (C^6), 200.10 (C^2). MS (ESI): *m/z* 422.9 [M + Na^+], 382.8 [M + H^+ − 18].

(*R*)-*N*-(quinolin-8-yl)-2-thioxothiazolidine-4-carboxamide (**13**). The crude product was purified using column chromatography (ethyl acetate–petroleum ether, 1:1 v/v) to afford a yellow solid, 88% yield, $[\alpha]_D^{20} = -62°$ (*c* 1.0, $CHCl_3$), m.p. 98–100°C. ^{1}H NMR (300 MHz, DMSO, δ, ppm): 3.71 (dd, *J* = 4.8 Hz, *J* = 11.4 Hz, 1 H, C^5H), 4.00 (dd, *J* = 9.0 Hz, *J* = 11.7 Hz, 1 H, C^5H), 5.32 (dd, *J* = 4.8 Hz, *J* = 9.0 Hz, 1 H, C^4H), 7.60–7.65 (m, 1 H, $C^{11}H$), 7.67 (m, 1 H, $C^{15}H$), 7.74 (dd, *J* = 1.2 Hz, *J* = 8.1 Hz, 1 H, $C^{14}H$), 8.44 (d, *J* = 1.5 Hz, *J* = 8.4 Hz, 1 H, $C^{12}H$), 8.66 (d, *J* = 1.2 Hz, *J* = 8.1 Hz, 1 H, $C^{16}H$), 8.96 (m, 1 H, $C^{10}H$), 10.59 (s, 2 H, N^3H, N^7H). ^{13}C NMR (75 MHz, DMSO, δ, ppm): 32.23 (C^5), 60.88 (C^4), 111.93 (C^{11}), 116.68 (C^{16}), 117.63 (C^{14}), 121.81 (C^{15}), 122.53 (C^{13}), 127.64 (C^{12}), 131.14 (C^8), 132.91 (C^9), 143.41 (C^{10}), 161.54 (C^6), 198.54 (C^2). MS (ESI): *m/z* 290.2 [M + H^+].

Synthesis of chiral thiazoline tridentate ligand ***14***

At 0°C, a solution of ligand **13** (0.6 g, 2 mmol) in anhydrous tetrahydrofuran (10 ml) was added slowly to a suspension of lithium aluminium hydride (0.3 g, 6 mmol) in anhydrous tetrahydrofuran (10 ml), under nitrogen atmosphere, and refluxed with stirring for 24 h at this temperature. The reaction mixture was quenched with saturated aqueous Na_2SO_4, extracted with diethyl ether, washed with brine, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The crude product was purified using column chromatography (ethyl acetate–petroleum ether, 1:2 v/v) to afford compound **14**.

(*R*)-4-((Quinolin-8-ylamino)methyl)thiazolidine-2-thione (**14**). Yellow solid, 78% yield, $[\alpha]_D^{20} = -11°$ (*c* 1.0, $CHCl_3$), m.p. 144–146°C. ^{1}H NMR (300 MHz, DMSO, δ, ppm): 3.45–3.57 (m, 3 H, C^5H_2, C^6H), 3.66–3.73 (m, 1 H, C^6H), 4.48–4.57 (m, 1 H, C^4H), 6.78 (d, *J* = 7.5 Hz, 1 H, N^3H), 6.94 (m, 1 H, $C^{11}H$), 7.10 (d, *J* = 8.1 Hz, 1 H, $C^{15}H$), 7.38 (d, *J* = 8.1 Hz, 1 H, $C^{14}H$), 7.51 (q, *J* = 4.2 Hz, 1 H, $C^{12}H$), 8.22 (d, *J* = 8.1 Hz, 1 H, $C^{16}H$), 8.75–8.76 (m, 1 H, $C^{10}H$), 10.35 (s, 1 H, –SH). ^{13}C NMR (75 MHz, DMSO, δ, ppm): 35.89 (C^5), 44.50 (C^6), 62.52 (C^4), 104.25 (C^{11}), 113.74 (C^{16}), 121.77 (C^{14}), 127.72 (C^{15}), 128.35 (C^{13}), 135.97 (C^{12}), 137.45 (C^8), 144.13 (C^9), 146.94 (C^{10}), 198.54 (C^2). MS (ESI): *m/z* 276.1 [M + H^+].

General Procedure for Enantioselective Henry Reactions Catalyzed by Novel Chiral Thiazoline Tridentate Ligands

At room temperature, CuCl (0.01 g, 0.1 mmol) was added to a solution of chiral ligand (0.1 mmol, 10 mol%) in ethanol (2 ml) in nitrogen atmosphere and stirred for 0.5 h. Then the solution was cooled to −20°C, treated with aldehyde (1 mmol), nitromethane (0.54 ml, 10 mmol) and DIPEA (0.018 ml, 0.1 mmol) and stirred at this temperature for 48 h. The reaction mixture was quenched with saturated aqueous NH_4Cl, extracted with dichloromethane, washed with brine, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The crude product was purified using column chromatography (ethyl acetate–petroleum ether, 1:3 v/v) to afford chiral secondary alcohol **25**. Enantiomeric excess was determined using HPLC with a Chiralcel column.

(*S*)-2-Nitro-1-(4-nitrophenyl)ethanol (**25a**). Yield 93%, 98% *ee*, by HPLC analysis (Daicel Chiralcel OD column, hexane–2-propanol = 85:15, 0.5 ml min^{-1}, 215 nm UV detector), t_R = 23.75 min (for minor) and t_R = 34.35 min (for major). ^{1}H NMR (300 MHz, $CDCl_3$, δ, ppm): 3.24 (s, 1 H, –OH), 4.57–4.61 (m, 2 H, –CH_2NO_2), 5.60–5.64 (m, 1 H, –CH–), 7.63 (d, *J* = 8.4 Hz, 2 H, –Ph), 8.26 (d, *J* = 8.4 Hz, 2 H, –Ph). ^{13}C NMR (75 MHz, $CDCl_3$, δ, ppm): 70.03 (–CHOH), 80.70 (–CH_2NO_2), 124.13 (–Ph), 127.06 (–Ph), 145.42 (–Ph), 147.97 (–Ph).

(*S*)-2-Nitro-1-(3-nitrophenyl)ethanol (**25b**). Yield 91%, 98% *ee*, by HPLC analysis (Daicel Chiralcel OD column, hexane–2-propanol = 85:15, 0.8 ml min^{-1}, 250 nm UV detector), t_R = 17.90 min (for minor) and t_R = 20.28 min (for major). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.16 (brs, 1 H, –OH), 4.60–4.69 (m, 2 H, –CH_2NO_2), 5.63 (d, *J* = 8.0 Hz, 1 H, –CH–), 7.64 (d, *J* = 8.0 Hz, 1 H, –Ph), 7.79 (d, *J* = 8.0 Hz, 1 H, –Ph), 8.25 (d, *J* = 8.0 Hz, 1 H, –Ph), 8.35 (s, 1 H, –Ph).

(*S*)-2-Nitro-1-(2-nitrophenyl)ethanol (**25c**). Yield 89%, 89% *ee*, by HPLC analysis (Daicel Chiralcel OD column, hexane–2-propanol = 90:10, 0.9 ml min^{-1}, 215 nm UV detector), t_R = 16.12 min (for minor) and t_R = 18.27 min (for major). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.24 (brs, 1 H, –OH), 4.55-4.61 (m, 1 H, –CH–), 4.90 (d, *J* = 8.0 Hz, 1 H, –CH_2NO_2), 6.08 (d, *J* = 8.8 Hz, 1 H, –CH_2NO_2), 7.58 (t, *J* = 8.0 Hz, 1 H, –Ph) 7.77 (t, *J* = 8.0 Hz, 1 H, –Ph), 7.98 (d, *J* = 8.0 Hz, 1 H, –Ph), 8.10 (d, *J* = 8.0 Hz, 1 H, –Ph).

(*S*)-2-Nitro-1-(2-methoxyphenyl)ethanol (**25d**). Yield 68%, 82% *ee*, by HPLC analysis (Daicel Chiralcel OD column, hexane–2-propanol = 85:15, 0.8 ml min^{-1}, 215 nm UV detector), t_R = 17.90 min (for minor) and t_R = 20.28 min (for major). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.16 (brs, 1 H, –OH), 3.91 (s, 3 H, –OCH_3), 4.58–4.70 (m, 2 H, –CH_2NO_2), 5.66 (d, *J* = 8.0 Hz, 1 H, –CH–), 6.94 (d, *J* = 8.0 Hz, 1 H, –Ph), 7.04 (d, *J* = 8.0 Hz, 1 H, –Ph) 7.36 (d, *J* = 8.0 Hz, 1 H, –Ph), 7.47 (d, *J* = 8.0 Hz, 1 H, –Ph).

(*S*)-2-Nitro-1-(4-chlorophenyl)ethanol (**25e**). Yield 94%, 72% *ee*, by HPLC analysis (Daicel Chiralcel OD column, hexane–2-propanol = 85:15, 0.8 ml min^{-1}, 215 nm UV detector), t_R = 12.82 min (for minor) and t_R = 15.90 min (for major). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.90 (brs, 1 H, –OH), 4.50–4.63 (m, 2 H, –CH_2NO_2), 5.47 (d, *J* = 9.2 Hz, 1 H, –CH–), 7.36–7.42 (m, 4 H, –Ph).

(*S*)-2-Nitro-1-(3-chlorophenyl)ethanol (**25f**). Yield 71%, 67% *ee*, by HPLC analysis (Daicel Chiralcel OD column, hexane–2-propanol = 85:15, 0.5 ml min^{-1}, 215 nm UV detector), t_R = 20.88 min (for minor) and t_R = 26.42 min (for major). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.59 (brs, 1 H, –OH), 4.52–4.63 (m, 2 H, –CH_2NO_2), 5.47 (d, *J* = 8.0 Hz, 1 H, –CH–), 7.29–7.37 (m, 1 H, –Ph), 7.36 (m, 2 H, –Ph) 7.46 (s, 1 H, –Ph).

(*S*)-2-Nitro-1-(4-fluorophenyl)ethanol (**25g**). Yield 85%, 86% *ee*, by HPLC analysis (Daicel Chiralcel OD column, hexane–2-propanol = 90:10, 0.5 ml min^{-1}, 215 nm UV detector), t_R = 22.58 min (for minor) and t_R = 26.87 min (for major). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.91 (brs, 1 H, –OH), 4.50–4.64 (m, 2 H, –CH_2NO_2), 5.47 (d, *J* = 9.2 Hz, 1 H, –CH–), 7.12 (t, *J* = 8.0 Hz, 2 H, –Ph), 7.40–7.43 (m, 2 H, –Ph).

(*S*)-2-Nitro-1-(4-bromophenyl)ethanol (**25h**). Yield 91%, 85% *ee*, by HPLC analysis (Daicel Chiralcel OD column, hexane–2-propanol

= 85:15, 0.9 ml min^{-1}, 250 nm UV detector), t_R = 11.47 min (for minor) and t_R = 13.03 min (for major). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 3.19 (brs, 1 H, –O*H*), 4.48–4.61 (m, 2 H, –CH_2NO$_2$), 5.42 (d, *J* = 8.8 Hz, 1 H, –C*H*–), 7.29 (d, *J* = 8.0 Hz, 2 H, –Ph), 7.54 (d, *J* = 8.0 Hz, 2 H, –Ph).

(*S*)-1-Nitro-3-phenylpropan-2-ol (**25i**). Yield 92%, 83% *ee*, by HPLC analysis (Daicel Chiralcel OD column, hexane–2-propanol = 90:10, 0.5 ml min^{-1}, 215 nm UV detector), t_R = 38.25 min (for minor) and t_R = 50.25 min (for major). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.34 (brs, 1 H, –O*H*), 2.87–2.92 (m, 2 H, –CH_2Ph), 4.39–4.48 (m, 2 H, –CH_2NO$_2$), 4.59–4.60 (m, 1 H, –C*H*–), 7.24–7.38 (m, 5 H, –Ph).

(*S*)-4-Methyl-1-nitropentan-2-ol (**25j**). Yield 82%, 86% *ee*, by HPLC analysis (Daicel Chiralcel AD-H column, hexane–2-propanol = 95:5, 0.5 ml min^{-1}, 210 nm UV detector), t_R = 27.42 min (for minor) and t_R = 37.22 min (for major). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 0.95–1.01 (m, 6 H, –CH(CH_3)$_2$), 1.21–1.30 (m, 1 H, –CH_2–), 1.50–1.56 (m, 1 H, –CH_2–), 1.81–1.91 (m, 1 H, –C*H*–), 2.50 (brs, 1 H, –O*H*), 4.37–4.45 (m, 3 H, –CH_2NO$_2$, –C*H*OH–).

(*S*)-1-Cyclohexyl-2-nitroethanol (**25k**). Yield 70%, 90% *ee*, by HPLC analysis (Daicel Chiralcel AD-H column, hexane–2-propanol = 95:5, 0.5 ml min^{-1}, 210 nm UV detector), t_R = 27.45 min (for minor) and t_R = 31.94 min (for major). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.11–1.85 (m, 11 H, cyclohexyl), 2.35 (brs, 1 H, –O*H*), 4.08–4.11 (m, 1 H, –C*H*–), 4.20–4.50 (m, 2 H, –CH_2NO$_2$).

Conclusions

We synthesized a series of chiral thiazoline-type tridentate ligands with L-cysteine, and introduced various functional groups, such as cinchona alkaloid, benzimidazole, chiral amino alcohol and 8-aminoquinoline, to produce a series of novel chiral thiazoline tridentate ligands. These ligands, together with CuCl, were able to promote a highly enantioselective Henry reaction between nitromethane and various aldehydes. The study showed that the optimal catalyst for this reaction was that with ligand **12**, which was formed from chiral thiazoline with chiral amino alcohol. At −20°C, with 10 mol% of ligand **12** complexed with CuCl, in ethanol, the product was obtained with *S* configuration and stereoselectity up to 98% *ee*.

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