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Novel chiral thiazoline-containing N-O ligands in the asymmetric addition of diethylzinc to aldehydes: substituent effect on the enantioselectivity

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Several novel chiral thiazoline primary and tertiary alcohols were easily synthesized from commercially available L-cysteine in three steps and with high yield. These ligands were subsequently applied to the asymmetric addition of diethylzinc (Et_2Zn) to various aldehydes. Products with *S* configuration were obtained when thiazoline-containing tertiary alcohol ligands were used as catalysts. The primary alcohol induced corresponding products with *R* configuration in 68% enantiomeric excess, which was a higher value relative to other N-O ligands possessing a primary alcohol unit in the literature. Furthermore, a plausible transition state model was proposed to explain the observed enantioselectivities. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords: thiazoline; chiral ligands; imino primary alcohol; asymmetric addition; diethylzinc

Introduction

Asymmetric organic catalytic reactions are extremely important in modern synthetic and pharmaceutical chemistry.[1–6] In this field, the asymmetric addition of diethylzinc to aldehydes is an efficient and feasible reaction for obtaining chiral secondary alcohols, which are often applied in the synthesis of many biologically active compounds.[7–10] Furthermore, It is also regarded as one of the benchmark reactions for exploring the catalytic potential of new ligands. Therefore, numerous efforts have been made to develop new effective chiral ligands for asymmetric addition of diethylzinc to benzaldehyde.[11–17]

Among various chiral ligands, the chiral β-amino alcohols have been widely developed as a typical class of catalysts.[18–22] It was found that β-amino tertiary alcohol ligands possessed high catalytic activity to obtain high enantiomeric excess (ee) values in the asymmetric addition of diethylzinc to aldehydes. However, under the same condition, chiral primary alcohols always resulted in corresponding products with lower ee values.[23–27] Therefore, the development of efficient β-amino primary alcohol ligands for asymmetric transformations is a challenge.

Among the large variety of Lewis basic donor functionalities, the imino moiety containing thiazoline[28–32] was found to an efficient surrogate to the amino unit in the chiral β-amino alcohol catalyst. However, to the best of our knowledge, there is no previous report on the development of thiazoline-containing chiral β-imino primary alcohol ligand-promoted enantioselective addition of diethylzinc to aldehydes. In this study, we first disclose the design, synthesis, and application of a series of novel modular, thiazoline-containing N-O ligands derived from L-cysteine (Scheme 1) in asymmetric addition of diethylzinc to aromatic aldehydes.

Results and Discussion

Synthesis of Ligands

In our work, we report a simple three-step synthesis of a series of novel chiral N-O ligands **5** containing a primary alcohol unit (Scheme 2). First, (*R*)-tetrahydrothiazo-2-thione-4-carboxylic acid ((*R*)-TTCA) **2** was obtained by cyclization between commercial L-cysteine and carbon disulfide under basic conditions.[33] Alkyl bromide was then added *in situ* to facilitate a tandem alkylation of **2** to **3** in moderate yield (Table 1). Finally, thioether derivatives **3** were converted to chiral β-imino primary alcohols (**5a–5e**) by $NaBH_4$ treatment. Compound **6** could also be easily obtained from **4** by treatment with $NaBH_4$. The detail results are depicted in Table 1.

Conventionally, the reduction of ester to primary alcohol with lithium aluminum hydride requires a relatively longer time, avoidance from moisture, and low-temperature conditions.[34,35] Nevertheless, in our study, the use of a sodium borohydride/MeOH system at room temperature has provided a straightforward and higher-yield method for obtaining chiral imino primary alcohols **5a–5e**. This method also successfully suppresses racemization and secures the optical purity of the resulting alcohols. Furthermore, in Scheme 1, we have

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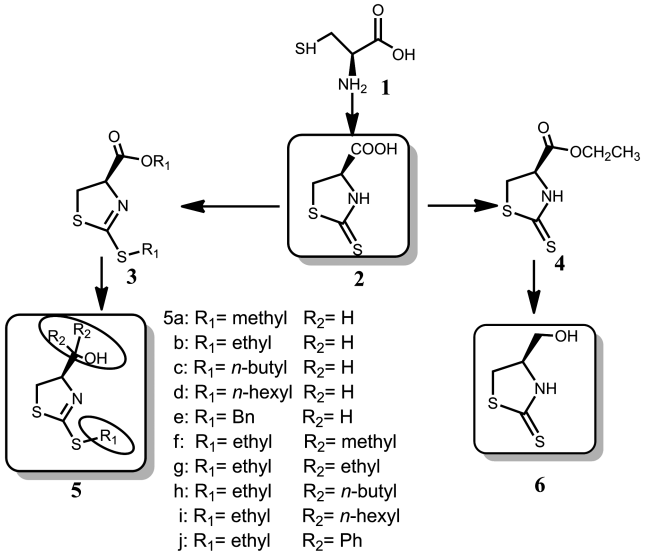
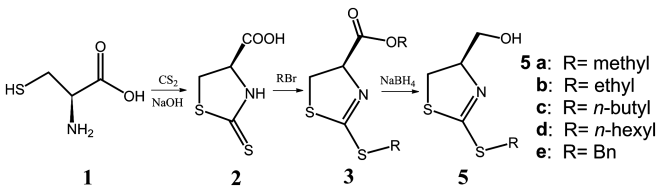


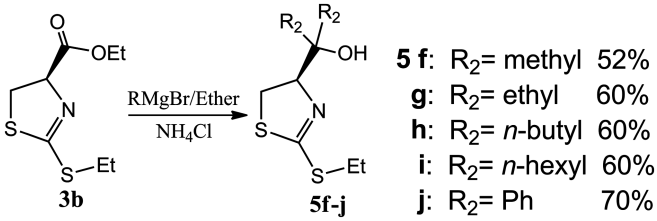
Scheme 1. Molecular structures of thiazoline ligands.



Scheme 2. The synthesis strategy for **5a–5e**.

documented a new protocol for direct esterification of **2** to obtain compound **4** at room temperature using catalytic $TiCl_4$. Compared to the conventional method with other Lewis acids,[36,37] this new method significantly improved chemoselectivity and overall efficiency, with complete retention of the original (*R*) configuration of **2**.

For comparison, we also synthesized thiazoline tertiary alcohol ligands **5f–5j** in moderate yield, which were easily formed via nucleophilic addition reaction of the ester group of **3b** by RMgBr, as shown in Scheme 3. Therefore, our chiral ligands of imino primary alcohols and imino tertiary alcohols could be easily achieved in only three steps and with high yield from commercial L-cysteine.



Scheme 3. Preparation of thiazoline ligands **5f–5j**.

Observation of Catalytic Activity

In order to detect the catalytic activity of thiazoline ligands, the asymmetric addition of Et_2Zn to benzaldehyde was chosen as a model reaction to yield chiral 1-phenyl-1-propanol **(7a)**. Our study began with the solvent and ligand loading screening (Table 2). We found that the solvent employed significantly affected the conversion and enantioselectivity. For example, in the presence of 10 mol% **5b**, the corresponding adduct **7a** was obtained in 74% yield and 41% ee in hexane with the *R* configuration. On the other hand, when the reaction was carried out in toluene, a relatively higher yield and ee (81% and 68%, respectively) were obtained. Consequently, toluene was considered as an optimized solvent in the following catalytic reactions. Moreover, we also found that **5b** loading had a significant influence on the activity of the catalyst and a slight influence on yield. For example, 2 mol% **5b** induced **7a** in only 10% ee. Decreasing the **5b** loading to 5 mol% led to lower ee (33%) However, in the presence of up to 20 mol% **5b**, only 48.4% ee was observed. Thus the optimized chiral ligand loading was confirmed at 10 mol% relative to benzaldehyde.

We next explored the influence of the thioalkyl moiety of ligands on conversion yield and enantioselectivity. Reaction conditions were set as 10 mol% ligands in toluene at room temperature, as presented in Table 3. Although all chiral primary alcohol ligands **5a–5e** resulted in moderate ee of the alcohol product with (*R*) configuration, to our delight these initial results still represented a significant improvement on the low ee obtained with other chiral β-amino primary alcohol ligands documented in the literature.[23–27] Moreover, thioethyl ligand **5b** (R_1 = Et, entry 2 in Table 3) led to the best enantioselectivity (68% ee) in high yield (81%), whereas the least hindered **5a** led to a diminished ee. Interestingly, the ligands **5c**, **5d**, **5e** with bulkier thio substituents (R_1 = *n*-butyl, *n*-hexyl and Bn, respectively) did not improve the enantioselectivity of the alcohol product as expected. The ee decreased as the function of the bulk of the thio substituents. Therefore, the 2-thio substituent group (R_1) strongly influenced the enantioselectivity of the ligand.

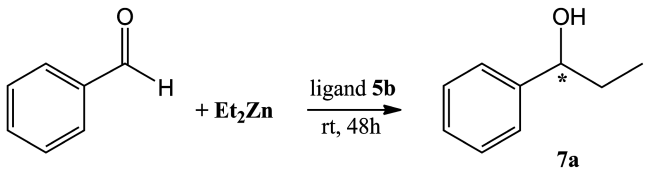
In comparison to primary alcohol ligand, the catalytic activity of thiazoline tertiary alcohol ligands **5f–5j** for asymmetric addition

Table 1. Preparation of thioether derivatives **3a–3e**, **5a–5e** and **6**[a]

Entry	R	Product	Yield (%)[b]	$[\alpha]_D^{20}$	Product	Yield (%)[b]	$[\alpha]_D^{20}$
1	Methyl	**3a**	80	+42	**5a**	88	+62.6
2	Ethyl	**3b**	88	+39	**5b**	99	+46.3
3	*n*-Butyl	**3c**	72	+29	**5c**	99	+28.4
4	*n*-Hexyl	**3d**	76	+23	**5d**	99	+24.6
5	Bn	**3e**	56	+17	**5e**	99	+21.6
6	H	**4**	99	−43	**6**	85	+20

[a]See Experimental section.
[b]Calculated in single step after column chromatography.

Table 2. Effect of amount chiral ligand **5b** and solvent on asymmetric addition of Et_2Zn to benzaldehyde[a]



Entry	Solvent	**5b** (mol%)	Yield (%)[b]	ee (%)[c]	$[\alpha]_D^{20}$	Configuration[d]
1	Hexane	10	74	41	+18.3	*R*
2	Tetrahydrofuran	10	34	3	+1.4	*R*
3	Dichloromethane	10	29	11	+4.8	*R*
4	Toluene	10	81	68	+30.0	*R*
5	Toluene	2	64.7	10	+4.5	*R*
6	Toluene	5	66.2	33	+14.6	*R*
7	Toluene	20	60	48	+21.4	*R*

[a]The reactions were run for 0.5 h at 0°C and for 48 h at room temperature.
[b]Yields after silica gel column chromatography.
[c]The ee was determined by HPLC using a Daicel Chiral OD column.
[d]The absolute configuration of the alcohol was assigned by comparison of the sign of the specific rotation to the literature value.[38–40]

Table 3. Asymmetric addition of Et_2Zn to benzaldehyde catalyzed by ligands **5** and **6**[a]

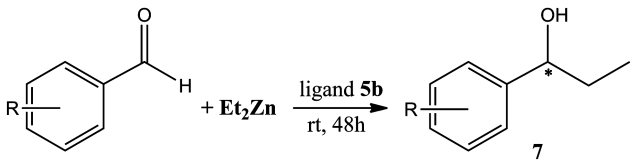
Entry	Ligand (10 mol%)	Yield (%)[b]	ee (%)[c]	$[\alpha]_D^{20}$	Configuration[d]
1	**5a**	66	44	+26.0	*R*
2	**5b**	81	68	+30.0	*R*
3	**5c**	68	47	+20.6	*R*
4	**5d**	71	42	+18.0	*R*
5	**5e**	70	34	+22.0	*R*
6	**6**	40	10	+6.0	*R*
7	**5f**	70	19	+6.0	*R*
8	**5g**	60	16	−7.0	*S*
9	**5h**	62	14	−7.2	*S*
10	**5i**	70	20	−11.9	*S*
11	**5j**	80	6	−3.0	*S*

[a]The reactions were run for 0.5 h at 0°C and for 48 h at room temperature.
[b]Yields after silica gel column chromatography.
[c]The ee was determined by HPLC using a Daicel Chiral OD column.
[d]The absolute configuration of the alcohol was assigned by comparison of the sign of the specific rotation to the literature value.[38–40]

of Et_2Zn to benzaldehyde was also determined. We found that all of the tertiary alcohol ligands promoted the production of the desired alcohol in good yield (60–80%, entries 7–11 in Table 3). However, corresponding products possessed lower enantiomeric excesses than those catalyzed by **5a–5e**. For example, **5i** led to an alcohol product with 20.2% ee in 70% yield (entry 10 in Table 3). Obviously, the thiazoline tertiary alcohol ligands are not a good template for catalyst development for the asymmetric addition of Et_2Zn to benzaldehyde. More interestingly, the favored enantiomer of the alcohol product obtained in the presence of **5g–5j** was revealed to possess an (*S*) configuration. Although there have been reports on the dependence of absolute configuration of the product on the structure of chiral ligands, especially on the steric hindrance caused by substituents near to the postulated reaction center,[41–45] our results indicate that catalytic processes in the presence of primary and tertiary alcohols must have distinct transition states.

Owing to the unproductive screening on the thiazoline tertiary alcohol catalyst, we returned to the more promising thiazoline primary alcohol catalysts. To explore the influence of electronic and steric effects of the substrate in the asymmetric addition of Et_2Zn, a series of aryl aldehydes were tested in the reactions in the presence of previously optimized primary alcohol ligand **5b** (Table 4). A general trend observed with respect to enantioselectivities of the alcohol product as the function of the electron-donating or electron-withdrawing substituents on the aryl aldehyde substrate is also shown in Fig. 1. Substrates with electron-donating groups of aryl aldehydes (entries 2–4) afforded slight lower enantioselectivities than that of benzaldehyde, but higher than those with electron-withdrawing groups (entries 5–7). On the other hand, *para*-

Table 4. Asymmetric addition of Et_2Zn to various aldehydes catalyzed by ligand **5b**[a]



Entry	R	Ligand (10 mol%)	Yield (%)[b]	ee (%)[c]	$[\alpha]_D^{20}$	Configuration[d]
1	H	**5b**	81	68	+30.0	*R*
2	*o*-OCH_3	**5b**	65	43	+7.0	*R*
3	*m*-OCH_3	**5b**	90	39	+13.0	*R*
4	*p*-OCH_3	**5b**	98	64	+27.3	*R*
5	*o*-Cl	**5b**	80	39	+15.5	*R*
6	*m*-Cl	**5b**	81	38	+10.3	*R*
7	*p*-Cl	**5b**	85	62	+23	*R*

[a]The reactions were run for 0.5 h at 0°C and for 48 h at room temperature.
[b]Yields after silica gel column chromatography.
[c]The ee was determined by HPLC using a Daicel Chiral OD or AD column.
[d]The absolute configuration of the alcohol was assigned by comparison of the sign of the specific rotation to the literature value.[38–40]

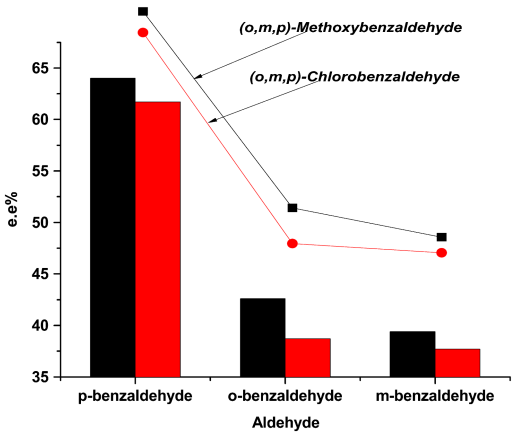


Figure 1. Effect of the asymmetric addition of Et_2Zn to various aldehydes.

substituent aldehydes led to much higher enantioselectivities than those of the *ortho*- or *meta*-aldehydes.

Finally, based on experimental observations and related mechanistic studies by other authors,[45–47] we proposed transition state models of the thiazoline alcohol ligand-promoted asymmetric diethylzinc addition to aromatic aldehydes (Fig. 2). First, Et_2Zn_A reacts rapidly with the alcohol ligand by replacing the hydrogen in the hydroxyl group to give the corresponding zinc monoalkoxide **8**. The second equivalent of Et_2Zn then comes in and coordinates with complex **8** to form the zinc monoalkoxide–diethylzinc complex **9**, which finally isomerizes to the complex **10** via thermodynamic equilibration.[48–50] The final substrate aldehyde coordination with complex **10** set up the bis six-membered ring transition states (TS), **11** and **12**, respectively.[51,52] Owing to electron density accumulation on the zinc atom with coordination of the oxygen and nitrogen atoms in the ligand, the nucleophilicity-enhanced ethyl group of Et_2Zn_A would attack the aldehyde carbonyl from either the *re* face or the *si* face.

In the case that R_2 in the ligand is a small group such as a hydrogen atom or methyl group, the phenyl group in the substrate prefers to be in equatorial position because of weak steric hindrance between the phenyl unit and small R_2 (TS **11**). Thus, a preferable *re*-face attack of the ethyl group of Zn_A to the carbonyl and lead to the formation of the *R* enantiomer of the alcohol product. On the other hand, with the increase in bulkiness of the 2-thio-substituent (R_1) in the ligand, more steric factors have to be taken into consideration. In the presence a larger R_1, it is more difficult to pose the phenyl group in an equatorial position. Therefore, a gradual decrease of enantioselectivity in the catalytic reactions was observed from **5b** to **5e**.

When R_2 is a larger group, such as an ethyl, *n*-butyl, *n*-hexyl or phenyl group, the phenyl group in the substrate is forced to dispose in the axial position to avoid steric interaction with R_2. Eventually, the ethyl group of Zn_A is transferred from the *si*-face of the benzaldehyde to form the *S* enantiomer of the product (TS **12**). Moreover, in the presence of these tertiary alcohol ligands the energy difference between TS **11** and TS **12** is small because the substrate phenyl group is disposed equatorially in **11**. Therefore, these thiazoline tertiary ligands only led to adduct products with poor ee values.

Experimental

Materials and Instruments

Toluene, hexane and ethyl ether (Na, benzophenone) were dried by distillation; other analytical-grade reagents were purchased from Beijing Chemical Reagent Co. (China) and used without further purification. The products were purified by neutral column chromatography on silica gel (300–400 mesh). The structures of chiral thiazoline ligands were identified by ^1H NMR and ^{13}C NMR (Varian Mercury 300 NMR spectrometer), using tetramethylsilane as an internal standard. Chemical shifts (δ) are given in parts per million and coupling constants are given as absolute values expressed in hertz. Optical rotations were measured with a WZZ-1S digital automatic polarimeter (Shanghai Physical Optics Instrument Factory). Concentration is given as absolute values expressed in g 100 ml^{-1}. High-performance liquid chromatographic analyses (HPLC) were performed using Shimadzu LC-10A VP pump, SPD-10A VP UV detector,

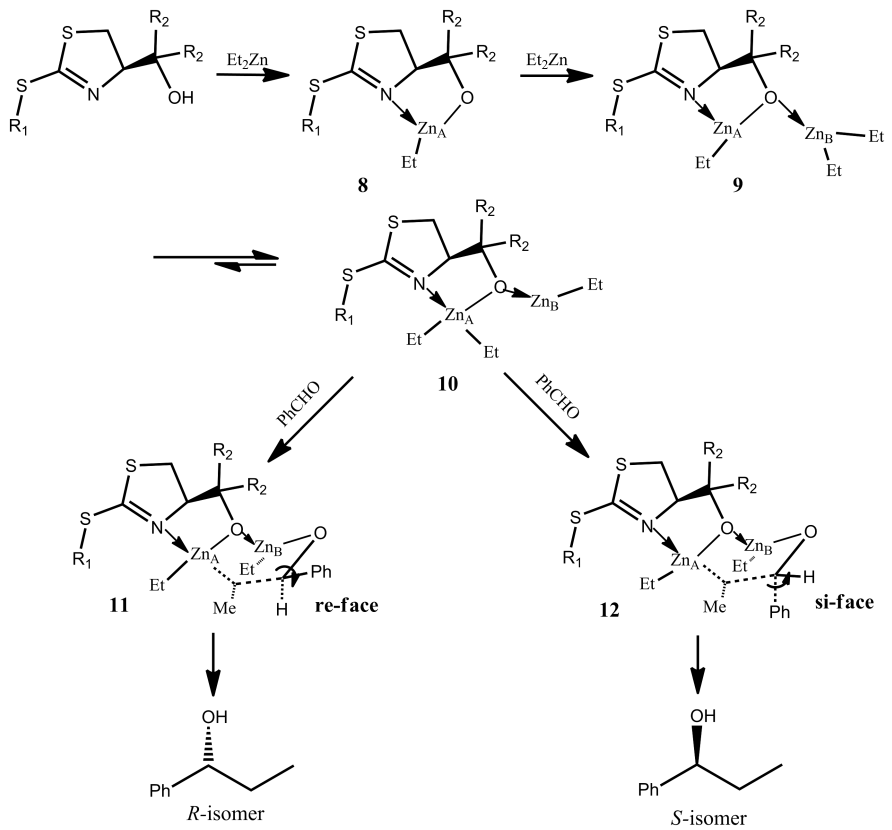


Figure 2. A tentative mechanism for asymmetric addition of Et_2Zn to aldehydes.

and Shimadzu CTO-10AC VP column oven with appropriate chiral columns. Mass spectra were obtained using an LC/MS 1100 of Agilent Technology Corp. and an Alltech ELSD 2000 instrument. Melting points were determined using an X-4 digital microscopy apparatus. C, H, and N elemental analyses were taken on a PerkinElmer 240C elemental analyzer.x

Synthesis

(*R*)-Tetrahydrothiazo-2-thione-4-carboxylic acid [(*R*)-TTCA] **2** was synthesized by known methods;[33] m.p. 179–181°C, $[\alpha]_D^{20} = -86.3$ (*c* 1.2, 0.5 N HCl).

*General Procedure for Preparation of **3a–3e***

To a solution of (*R*)-TTCA (**2**) (2.0 g, 12.3 mmol) in acetonitrile (40 ml), the corresponding halide (37.5 mmol) and anhydrous K_2CO_3 (3.4 g) were added at room temperature. The solution was then stirred at 55°C for 6 h. After cooling to room temperature, the precipitate was removed by filtration, and acetonitrile was then removed under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether:EtOAc).

(*R*)-2-Methylthio-4-methyloxycarbonyl-4,5-dihydro-1,3-thiazole (**3a**) was obtained as a colorless oil, with 80% yield after purification by column chromatography on silica gel (petroleum ether:EtOAc = 3:1), $[\alpha]_D^{20} = +42$ (*c* 3.1, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.59 (s, 3H, -SCH_3), 3.62–3.71 (m, 2H, -SCH_2-), 3.81 (s, 3H, -OCH_3), 5.07 (t, J = 8.7 Hz, 1H, =N-CH-); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 15.56 (-SCH_3), 37.27 (-SCH_2-), 52.65 (-OCH_3), 77.14 (N-CH-), 170.93 (-C = O). MS (electrospray ionization (ESI)): *m/z* 192.2 [M + H$^+$]. Elemental analysis calculated for $C_6H_9NO_2S_2$: C, 37.68; H, 4.74; N, 7.32. Found: C, 37.70, H, 4.70, N, 7.29.

(*R*)-2-Ethylthio-4-ethyloxycarbonyl-4,5-dihydro-1,3-thiazole (**3b**) was obtained as a colorless oil, with 88% yield after purification by column chromatography on silica gel (petroleum ether:EtOAc = 3:1), $[\alpha]_D^{20} = +38.8$ (*c* 6.4, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.29–1.41 (m, 6 H, -CH_3), 3.06–3.25 (m, 2H, -SCH_2CH_3), 3.56–3.71 (m, 2H, -SCH_2CHN), 4.25 (q, J = 6 Hz, 2H, -OCH_2-), 5.06 (t, J = 7.2 Hz, 1 H, N-CH-); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 14.08 (-SCH_2CH_3), 14.41 (-OCH_2CH_3), 27.34 (-SCH_2CH_3), 37.02 (-SCH_2CHN), 61.58 (-OCH_2-), 77.23 (N-CH-), 170.50 (-C = O). MS (ESI): *m/z* 220.3 [M + H$^+$]. Elemental analysis calculated for $C_8H_{13}NO_2S_2$: C, 43.81; H, 5.97; N, 6.39. Found: C, 43.83, H, 5.96, N, 6.36.

(*R*)-2-Butylthio-4-butyloxycarbonyl-4,5-dihydro-1,3-thiazole (**3c**) was obtained as a colorless oil, with 72% yield after purification by column chromatography on silica gel (petroleum ether:EtOAc = 5:1), $[\alpha]_D^{20} = +28.5$ (*c* 6.7, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.92–0.95 (m, 6H, -CH_3), 1.39–1.44 (m, 4 H, -CH_2), 1.64–1.69 (m, 4H, -CH_2), 3.08–3.23 (m, 2H, -SCH_2CH_2-), 3.59–3.66 (m, 2H, -SCH_2CHN), 4.19 (t, J = 6.6 Hz, 2H, -OCH_2-), 5.06 (t, J = 8.1 Hz, 1H, N-CH-); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 13.54 (-CH_3), 13.63 (-CH_3), 19.01 (-CH_2), 21.79 (-CH_2), 30.50 (-SCH_2CH_2-), 31.13 (-CH_2), 32.75 (-CH_2), 37.15 (SCH_2CHN), 65.47 (-OCH_2-), 77.25 (N-CH-), 170.65 (-C = O). MS (ESI): *m/z* 276.3 [M + H$^+$]. Elemental analysis calculated for $C_{12}H_{21}NO_2S_2$: C, 52.33; H, 7.68; N, 5.09. Found: C, 52.36, H, 7.69, N, 5.06.

(*R*)-2-Hexylthio-4-hexyloxycarbonyl-4,5-dihydro-1,3-thiazole (**3d**) was obtained as a colorless oil, with 76% yield after purification by column chromatography on silica gel (petroleum ether:EtOAc = 5:1), $[\alpha]_D^{20} = +23.2$ (*c* 3.5, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm)

0.86–0.89 (m, 6H, -CH_3), 1.29–1.31 (m, 12H, -CH_2), 1.65–1.71 (m, 4H, -CH_2), 3.08–3.20 (m, 2H, -SCH_2CH_2-), 3.56–3.70 (m, 2H, -SCH_2CHN), 4.16–4.21 (m, 2H, -OCH_2-), 5.04–5.09 (m, 1H, NCH-); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 13.95 (-CH_3), 22.46 (-CH_2), 22.48 (-CH_2), 25.43 (-CH_2), 28.36 (-CH_2), 28.43 (-CH_2), 29.02 (-CH_2), 31.24 (-CH_2), 31.34 (-CH_2), 33.09 (-CH_2), 37.15 (-SCH_2CHN), 65.78 (-OCH_2-), 77.19 (NCH-), 170.69 (-C=O). MS (ESI): *m/z* 332.4 [M + H^+]. Elemental analysis calculated for $C_{16}H_{29}NO_2S_2$: C, 57.96; H, 8.82; N, 4.22. Found: C, 57.97, H, 8.80, N, 4.20.

(*R*)-2-Benzylthio-4-benzyloxycarbonyl-4,5-dihydro-1,3-thiazole (**3e**) was obtained as a colorless oil, with 56% yield after purification by column chromatography on silica gel (petroleum ether:EtOAc = 5:1), $[\alpha]_D^{20}$ = +17 (*c* 3.1, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.59–3.62 (m, 2H, -SCH_2CHN), 4.34–4.45 (m, 2 H, -SCH_2-Ph), 5.12 (m, 1H, NCH-), 5.25 (s, 2 H, -OCH_2-Ph), 7.26–7.39 (m, 10 H, -Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 37.19 (-SCH_2CHN), 37.36 (-SCH_2-Ph), 67.20 (-OCH_2-) , 77.07 (NCH-), 127.49 (-Ph), 128.15 (-Ph), 128.36 (-Ph), 128.55 (-Ph), 129.04 (-Ph), 135.34 (-Ph), 136.28 (-Ph), 170.21 (-C=O). MS (ESI): *m/z* 344.2 [M + H^+]. Elemental analysis calculated for $C_{18}H_{17}NO_2S_2$: C, 62.94; H, 4.99; N, 4.08. Found: C, 62.97, H, 4.97, N, 4.07.

Procedure for preparation of (R)-4-ethyloxycarbonyl-1,3-thiazoline-2-thione (**4**)

To a solution of (*R*)-TTCA (**2**) (0.65 g, 4.0 mmol) in ethanol (10 ml), $TiCl_4$ (0.1 ml, 1.0 mmol) was added at 0°C. The solution was then stirred at room temperature for 12 h. Then the solution was neutralized with 5% sodium bicarbonate solution to pH 8 at 0°C. The mixture was then extracted twice with CH_2Cl_2. The combined organic phase were washed with saturated brine twice, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether:EtOAc = 3:2) and was obtained as colorless a oil, with 99% yield.

(*R*)-4-Ethyloxycarbonyl-1, 3-thiazoline-2-thione (**4**) was obtained as a colorless oil, with 99% yield. $[\alpha]_D^{20}$ = −42.9 (*c* 5.5, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.34 (t, *J* = 7.2 Hz, 3 H, -CH_3), 3.80 (d, *J* = 3 Hz, 1H, -SCH_2CHNH), 3.82 (d, *J* = 3 Hz, 1H, -SCH_2CHNH), 4.27–4.34 (m, 2H, -OCH_2-), 4.83–4.88 (m, 1H, -SCH_2CHNH), 8.21 (br, 1H, -NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 14.02 (-CH_3), 35.41 (-SCH_2CHNH), 62.78 (-OCH_2-), 63.82 (-SCH_2CHNH), 168.28 (-C=O). MS (ESI): *m/z* 192.1 [M + H^+]. Elemental analysis calculated for $C_6H_9NO_2S_2$: C, 37.68; H, 4.74; N, 7.32. Found: C, 37.69, H, 4.76, N, 7.30.

General procedure for preparation of (*R*)-2-substituted thio-4-hydroxymethyl-4,5-dihydro-1,3-thiazoles (**5a–5e**) and (*R*)-4-hydroxymethyl-1,3-thiazoline-2-thione (**6**)

To a solution of **3** or **4** (5.0 mmol) in methanol (15 ml), $NaBH_4$ (0.57 g, 15.0 mmol) was added. The solution was then stirred at room temperature for 0.5 h. When thin-layer chromatography revealed that the reaction was completed, water was added to remove excessive $NaBH_4$. The mixture was then extracted twice with CH_2Cl_2. 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 purified by column chromatography on silica gel to give the alcohol **5a–5e** or **6**.

(*R*)-2-Methylthio-4-hydroxymethyl-4,5-dihydro-1,3-thiazole (**5a**) was obtained as a colorless oil, with 88% yield after purification by column chromatography on silica gel (petroleum ether:EtOAc = 1:3), $[\alpha]_D^{20}$ = +62.6 (*c* 3.9, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.03 (s, 1 H, -OH), 2.55 (s, 3H, -SCH_3), 3.31 (dd, *J* = 8.7 Hz, *J* = 10.5 Hz, 1H, -SCH_2CHN), 3.45 (dd, *J* = 8.4 Hz, *J* = 10.5 Hz, 1H, -SCH_2CHN), 3.69 (dd, *J* = 5.7 Hz, *J* = 11.1 Hz, 1H, -CH_2OH), 3.91 (dd, *J* = 4.8 Hz, *J* = 11.1 Hz, 1 H, -CH_2OH), 4.57–4.62 (m, 1H, -SCH$_2$CHN); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 15.48 (-SCH_3), 36.26 (-SCH_2CHN), 64.09 (-CH_2OH), 78.43 (-SCH$_2$CHN). MS (ESI): *m/z* 165.0 [M + H^+]. Elemental analysis calculated for $C_5H_9NOS_2$: C, 36.78; H, 5.56; N, 8.58. Found: C, 36.72, H, 5.58, N, 8.56.

(*R*)-2-Ethylthio-4-hydroxymethyl-4,5-dihydro-1,3-thiazole (**5b**) was obtained as a colorless oil, with 99% yield after purification by column chromatography on silica gel (petroleum ether:EtOAc = 1:2), $[\alpha]_D^{20}$ = +46.3 (*c* 2.8, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.36 (t, *J* = 7.2 Hz, 3 H, -CH_3), 2.06 (br, 1H, -OH), 3.07–3.14 (m, 2 H, -SCH_2CH_3), 3.27 (dd, *J* = 8.7 Hz, *J* = 10.8 Hz, 1H, -SCH_2CHN), 3.42 (dd, *J* = 8.1 Hz, *J* = 10.8 Hz, 1 H, -SCH_2CHN), 3.69 (dd, *J* = 5.7 Hz, *J* = 11.1 Hz, 1H, -CH_2OH), 3.88 (dd, *J* = 4.8 Hz, *J* = 11.1 Hz, 1 H, -CH_2OH), 4.54–4.63 (m, 1 H, -SCH$_2$CHN); ^{13}C NMR (75MHz, $CDCl_3$) δ (ppm) 14.39 (-CH_3), 27.13 (-SCH_2CH_3), 35.84 (-SCH_2CHN), 63.76 (-CH_2OH), 78.39 (-SCH$_2$CHN). MS (ESI): *m/z* 179.0 [M + H^+]. Elemental analysis calculated for $C_6H_{11}NOS_2$: C, 40.65; H, 6.25; N, 7.90. Found: C, 40.67, H, 6.23, N, 7.93.

(*R*)-2-Butylthio-4-hydroxymethyl-4,5-dihydro-1,3-thiazole (**5c**) was obtained as a colorless oil, with 99% yield after purification by column chromatography on silica gel (petroleum ether:EtOAc = 1:2), $[\alpha]_D^{20}$ = +28.4 (*c* 3.9, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.93 (t, *J* = 7.5 Hz, 3H, -CH_3), 1.37–1.49 (m, 2 H, -CH_2-), 1.63–1.73 (m, 2 H, -CH_2-), 1.94 (br, 1 H, -OH), 3.12 (t, *J* = 7.5 Hz, 2 H, -SCH_2-), 3.27 (dd, *J* = 8.7 Hz, *J* = 10.8 Hz, 1H, -SCH_2CHN), 3.42 (dd, *J* = 8.4 Hz, *J* = 10.8 Hz, 1H, -SCH_2CHN), 3.69 (dd, *J* = 5.7 Hz, *J* = 11.1 Hz, 1 H, -CH_2OH), 3.89 (dd, *J* = 4.8 Hz, *J* = 11.1 Hz, 1H, -CH_2OH), 4.54–4.63 (m, 1H, -SCH$_2$CHN); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 13.47 (-CH_3), 21.76 (-CH_2-), 31.24 (-CH_2-), 32.59 (-SCH_2-), 35.90 (-SCH_2CHN), 64.04 (-CH_2OH), 78.46 (-SCH$_2$CHN). MS (ESI): *m/z* 206.2 [M + H^+]. Elemental analysis calculated for $C_8H_{15}NOS_2$: C, 46.79; H, 7.36; N, 6.82. Found: C, 46.75, H, 7.38, N, 6.86.

(*R*)-2-Hexylthio-4-hydroxymethyl-4,5-dihydro-1,3-thiazole (**5d**) was obtained as a light-yellow oil, with 99% yield after purification by column chromatography on silica gel (petroleum ether:EtOAc = 1:3), $[\alpha]_D^{20}$ = +24.6 (*c* 3.3, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.89 (t, *J* = 6.9 Hz, 3 H, -CH_3), 1.26–1.43 (m, 6H, -CH_2-), 1.64–1.73 (m, 2H, -CH_2-), 1.94 (br, 1 H, -OH), 3.09 (t, *J* = 7.5 Hz, 2H, -SCH_2-), 3.27 (dd, *J* = 8.7 Hz, *J* = 10.8 Hz, 1H, -SCH_2CHN), 3.42 (dd, *J* = 8.4 Hz, *J* = 10.8 Hz, 1H, -SCH_2CHN), 3.64–3.73 (m, 1H, -CH_2OH), 3.89 (dd, *J* = 4.8 Hz, *J* = 11.1 Hz, 1H, -CH_2OH), 4.54–4.63 (m, 1H, -SCH$_2$CHN); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 13.93 (-CH_3), 22.43 (-CH_2-), 28.34 (-CH_2-), 29.16 (-CH_2-), 31.21 (-CH_2-), 32.94 (-SCH_2-), 35.92 (-SCH_2CHN), 64.11 (-CH_2OH), 78.47 (-SCH$_2$CHN). MS (ESI): *m/z* 234.2 [M + H^+]. Elemental analysis calculated for $C_{10}H_{19}NOS_2$: C, 51.46; H, 8.21; N, 6.00. Found: C, 51.42, H, 8.22, N, 6.05.

(*R*)-2-Benzylthio-4-hydroxymethyl-4,5-dihydro-1,3-thiazole (**5e**) was obtained as light-yellow oil, with 98% yield after purification by column chromatography on silica gel (petroleum ether:EtOAc = 1:2), $[\alpha]_D^{20}$ = +21.6 (*c* 2.2, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.86 (s, 1 H, -OH), 3.29 (dd, *J* = 8.4 Hz, *J* = 10.5 Hz, 1H, -SCH_2CHN), 3.44 (dd, *J* = 8.1 Hz, *J* = 10.5 Hz, 1H, -SCH_2CHN), 3.65 (dd, *J* = 5.7 Hz, *J* = 11.4 Hz, 1H, -CH_2OH), 3.88 (dd, *J* = 4.8 Hz, *J* = 11.1 Hz, 1H, -CH_2OH), 4.35 (m, 2H, -SCH_2-Ph), 4.56–4.64 (m,1H, -SCH$_2$CHN), 7.28–7.38 (m, 5H, -Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 36.26 (-SCH_2CHN), 37.06 (-SCH_2-Ph), 64.09 (-CH_2OH), 78.33 (-SCH$_2$CHN), 127.48 (-Ph), 128.52 (-Ph), 128.89 (-Ph), 136.43 (-Ph). MS (ESI): *m/z* 240.1 [M + H^+]. Elemental analysis calculated for $C_{11}H_{13}NOS_2$: C, 55.20; H, 5.47; N, 5.85. Found: C, 55.26, H, 5.44, N, 5.88.

(*R*)-4-Hydroxymethyl-1,3-thiazoline-2-thione (**6**) was obtained as a white solid, with 85% yield after purification by column chromatography on silica gel (petroleum ether:EtOAc = 1:4), $[\alpha]_D^{20}$ = +20.0 (*c* 2.4, MeOH), ^{1}H NMR (300 MHz, DMSO) δ (ppm) 3.36 (dd, *J* = 6 Hz,

J = 11.1 Hz, 1H, -SCH$_2$CHN), 3.43–3.51 (m, 2H, -CH$_2$OH), 3.56 (dd, J = 5.4 Hz, J = 11.1 Hz, 1H, -SCH$_2$CHN), 4.16–4.25 (m, 1H, -SCH$_2$CHN), 7.02 (br, 1H, -NH); ^{13}C NMR (75 MHz, DMSO) δ (ppm) 34.47 (-SCH$_2$CHN), 61.08 (-CH$_2$OH), 66.01 (-SCH$_2$CHN), 197.72 (-C = S). MS (ESI): *m/z* 150.0 [M + H$^+$]. Elemental analysis calculated for $C_4H_7NOS_2$: C, 32.19; H, 4.73; N, 9.39. Found: C, 32.19, H, 4.77, N, 9.36.

General procedure for preparation of ***5f–5j***

To magnesium (0.288 g) and a small piece of iodine in dry ethyl ether (5 ml), a solution of RBr or ArBr (12 mmol) in dry ethyl ether (10 ml) was added dropwise to keep the mixture at gentle reflux. When the addition was completed, the reaction mixture was kept refluxing for 1 h. The RMgBr or ArMgBr solution obtained was then stored at 0°C. To RMgBr or ArMgBr (12 mmol), a solution of **3a** (0.657 g, 3 mmol) in dry ethyl ether (10 ml) was added at 0°C. The reaction mixture was stirred at room temperature for 12 h. Then the reaction was quenched by addition of saturated aqueous NH_4Cl and extracted with ethyl ether (20 ml × 3). The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure. The crude product was purified by column chromatography on silica gel.

(*R*)-2-(2-(Ethylthio)-4,5-dihydrothiazol-4-yl) propan-2-ol (**5f**) was obtained as a light-yellow oil, with 52% yield after purification by column chromatography on silica gel (petroleum ether:EtOAc = 4:1), $[\alpha]_D^{20}$ = +26.0 (*c* 11.8, CHCl$_3$), ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 1.21 (s, 3 H, -SCH$_2$CH$_3$), 1.37 (dd, J = 7.5 Hz, J = 10.2 Hz, 6 H, -C(CH$_3$)$_2$OH), 1.99 (br, 1 H, -OH), 3.08–3.16 (m, 2 H, -SCH$_2$-), 3.25–3.39 (m, 2 H, -SCH$_2$CHN), 4.32 (dd, J = 8.4 Hz, J = 10.5 Hz, 1H, -SCH$_2$CHN); ^{13}C NMR (75 MHz, CDCl$_3$) δ (ppm) 14.64 (-CH$_3$), 25.16 (-C(CH$_3$)$_2$OH), 27.17 (-SCH$_2$-), 27.29 (-SCH$_2$-), 35.29 (-SCH$_2$CHN), 72.37 (-C(CH$_3$)$_2$OH), 86.35 (-SCH$_2$CHN). MS (ESI): *m/z* 206.0 [M + H$^+$], 188.1 [M + H$^+$ − 18]. Elemental analysis calculated for $C_8H_{15}NOS_2$: C, 46.79; H, 7.36; N, 6.82. Found: C, 46.72, H, 7.38, N, 6.88.

(*R*)-3-(2-(Ethylthio)-4,5-dihydrothiazol-4-yl) pentan-3-ol (**5g**) was obtained as a light-yellow oil, with 60% yield after purification by column chromatography on silica gel (petroleum ether:EtOAc = 6:1), $[\alpha]_D^{20}$ = +7.8 (*c* 12.8, CHCl$_3$), ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 0.94 (dd, J = 7.5 Hz, J = 15.9 Hz, 6 H, -CH$_3$), 1.36 (t, J = 7.2 Hz, 3 H, -SCH$_2$CH$_3$), 1.40–1.47 (m, 1 H, -CH$_2$-), 1.53–1.61 (m, 1 H, -CH$_2$-), 1.74–1.83 (m, 2 H, -CH$_2$-), 3.06–3.14 (m, 2 H, -SCH$_2$-), 3.26 (dd, J = 8.1 Hz, J = 10.5 Hz, 1 H, -SCH$_2$CHN), 3.37 (t, J = 11.1 Hz, 1H, -SCH$_2$CHN), 4.38 (dd, J = 8.4 Hz, J = 11.1 Hz, 1H, -SCH$_2$CHN); ^{13}C NMR (75 MHz, CDCl$_3$) δ (ppm) 7.63 (-CH$_3$), 7.84 (-CH$_3$), 14.66 (-SCH$_2$CH$_3$), 26.88 (-CH$_2$-), 27.23 (-CH$_2$-), 29.49 (-CH$_2$-), 34.88 (-SCH$_2$CHN), 75.91 (-C(C$_2$H$_5$)$_2$OH), 83.27 (-SCH$_2$CHN). MS (ESI): *m/z* 233.8 [M + H$^+$], 215.8 [M + H$^+$ − 18]. Elemental analysis calculated for $C_{10}H_{19}NOS_2$: C, 51.46; H, 8.21; N, 6.00. Found: C, 51.44, H, 8.23, N, 6.09.

(*R*)-5-(2-(Ethylthio)-4,5-dihydrothiazol-4-yl) nonan-5-ol (**5h**) was obtained as a yellow oil, with 60% yield after purification by column chromatography on silica gel (petroleum ether:EtOAc = 10:1), $[\alpha]_D^{20}$ = +6.1 (*c* 14.8, CHCl$_3$), ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 0.89–0.95 (m, 6 H, -CH$_3$), 1.26–1.49 (m, 15 H, -CH$_2$- and -SCH$_2$CH$_3$), 1.76 (s, 1 H, -C(C$_4$H$_9$)$_2$OH)), 3.05–3.13 (m, 2 H, -SCH$_2$-), 3.25 (dd, J = 8.1 Hz, J = 10.5 Hz, 1H, -SCH$_2$CHN), 3.37 (t, J = 11.4 Hz, 1 H, -SCH$_2$CHN), 4.34 (dd, J = 8.1 Hz, J = 11.4 Hz, 1H, -SCH$_2$CHN); ^{13}C NMR (75 MHz, CDCl$_3$) δ (ppm) 14.03 (-CH$_3$), 14.07 (-CH$_3$), 14.68 (-SCH$_2$CH$_3$), 23.32 (-CH$_2$-), 23.38 (-CH$_2$-), 25.47 (-CH$_2$), 25.73 (-CH$_2$-), 27.23 (-CH$_2$-), 34.73 (-SCH$_2$-), 34.95 (-SCH$_2$-), 37.47 (-SCH$_2$CHN), 75.66 (-C(C$_4$H$_9$)$_2$OH), 83.88 (-SCH$_2$CHN). MS (ESI): *m/z* 289.9 [M + H$^+$], 271.9 [M + H$^+$ − 18]. Elemental analysis calculated for $C_{14}H_{27}NOS_2$: C, 58.08; H, 9.40; N, 4.84. Found: C, 58.09, H, 9.45, N, 4.82.

(*R*)-7-(2-(Ethylthio)-4,5-dihydrothiazol-4-yl) tridecan-7-ol (**5i**) was obtained as a yellow oil, with 60% yield after purification by column chromatography on silica gel (petroleum ether:EtOAc = 6:1), $[\alpha]_D^{20}$ = +6.7 (*c* 14.8, CHCl$_3$), ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 0.87–0.91 (m, 6 H, -CH$_3$), 1.29–1.38 (m, 20 H, -CH$_2$-), 1.67–1.76 (m, 3 H, -SCH$_2$CH$_3$), 3.02–3.13 (m, 2H, -SCH$_2$-), 3.22–3.40 (m, 2H, -SCH$_2$CHN), 4.35 (dd, J = 8.1 Hz, J = 11.4 Hz, 1H, -SCH$_2$CHN); ^{13}C NMR (75 MHz, CDCl$_3$) δ (ppm) 14.00 (-CH$_3$), 14.66 (-SCH$_2$CH$_3$), 22.58 (-CH$_2$), 23.24 (-CH$_2$-), 23.48 (-CH$_2$), 27.22 (-CH$_2$), 29.91 (-CH$_2$), 29.99 (-CH$_2$), 31.75 (-CH$_2$), 31.78 (-CH$_2$), 34.96(-SCH$_2$CH$_3$), 35.16 (-SCH$_2$CH$_3$), 37.77 (-SCH$_2$CHN), 75.74 (-C(C$_6$H$_{13}$)$_2$OH), 83.95 (-SCH$_2$CHN). MS (ESI): *m/z* 345.9 [M + H$^+$], 327.9 [M + H$^+$ − 18]. Elemental analysis calculated for $C_{18}H_{35}NOS_2$: C, 62.55; H, 10.21; N, 4.05. Found: C, 62.54, H, 10.22, N, 4.07.

(*R*)-(2-(Ethylthio)-4,5-dihydrothiazol-4-yl) diphenylmethanol (**5j**) was obtained as a yellow oil, with 70% yield after purification by column chromatography on silica gel (petroleum ether:EtOAc = 4:1), $[\alpha]_D^{20}$ = −31.9 (*c* 5.5, CHCl$_3$), ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 1.29 (t, J = 7.2 Hz, 3H, -CH$_3$), 2.65 (s, 1H, (-C(Ph)$_2$OH)), 2.87–2.94 (m, 1H, -SCH$_2$CH$_3$), 2.99–3.06 (m, 1H, -SCH$_2$CH$_3$), 3.35 (t, J = 11.4 Hz,1H, -SCH$_2$CHN), 3.47 (dd, J = 7.2 Hz, J = 14.1 Hz, 1H, -SCH$_2$CHN), 5.45 (dd, J = 7.8 Hz, J = 11.4 Hz, 1H, -SCH$_2$CHN), 7.19–7.25(m, 2H, -Ph), 7.29–7.31 (m, 4 H, -Ph), 7.42–7.45 (m, 2H, -Ph), 7.57–7.59 (m, 2H, -Ph); ^{13}C NMR (75 MHz, CDCl$_3$) δ (ppm) 14.46 (-CH$_3$), 27.32 (-SCH$_2$CH$_3$), 36.16 (-SCH$_2$CHN), 78.68 (-C(Ph)$_2$OH), 83.16 (-SCH$_2$CHN), 125.78 (-Ph), 126.82 (-Ph), 126.88 (-Ph), 127.06 (-Ph), 127.91 (-Ph), 128.09 (-Ph), 128.15 (-Ph), 130.45 (-Ph), 132.76 (-Ph), 144.24 (-Ph), 146.71 (-Ph). MS (ESI): *m/z* 329.8 [M + H$^+$], 312.8 [M + H$^+$ − 18]. Elemental analysis calculated for $C_{18}H_{19}NOS_2$: C, 65.62; H, 5.81; N, 4.25. Found: C, 65.67, H, 5.83, N, 4.23.

General procedure for the addition of Et$_2$Zn to aldehydes

To a solution of chiral ligand **5a** (1 mmol) in toluene (1.5 ml) at 0°C, a 1.0 M solution of diethylzinc in hexane (1.5 ml, 1.5 mmol) was added. After stirring the mixture for 30 min, aldehyde (1 mmol) was added to the reaction solution at 0°C. The reaction mixture was stirred for 48 h at room temperature. The reaction was quenched by the addition of a saturated solution of ammonium chloride (10 ml) and the mixture was extracted with diethyl ether (20 ml × 2). The combined organic extracts were washed with brine (30 ml × 2), dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by chromatography on silica gel using ethyl acetate–hexanes (1:5) as the eluent to give the product alcohol.

1-Phenyl-1-propanol (**7a**) 81% yield, $[\alpha]_D^{20}$ = +30 (*c* 4.8, CHCl$_3$), 68% ee by HPLC (Daicel Chiralcel OD column, hexane:2-propanol = 97:3, 1 ml min^{-1}, 254 nm UV detector), t_R = 10.42 min for (*R*) and t_S = 12.13 min for (*S*). ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 0.91 (t, J = 7.5 Hz, 3 H, -CH$_3$), 1.72–1.82 (m, 2 H, -CH$_2$), 1.89 (s, 1 H, -OH), 4.58 (t, J = 6.6 Hz, 1 H, -CHOH), 7.25–7.37 (m, 5 H, -Ph). ^{13}C NMR (75 MHz, CDCl$_3$) δ (ppm) 10.00 (-CH$_3$), 31.76 (-CH$_2$), 75.88 (-CHOH), 125.90 (-Ph), 127.36 (-Ph), 128.28 (-Ph), 144.57 (-Ph).

1-(2-Methoxyphenyl)-1-propanol (**7b**) 65% yield, $[\alpha]_D^{20}$ = +7.0 (*c* 5.4, CHCl$_3$), 42.5% ee by HPLC (Daicel Chiralcel OD column, hexane:ethanol = 97:3, 0.5 ml min^{-1}, 254 nm UV detector), t_R = 23.43 min for (*R*) and t_S = 22.08 min for (*S*). ^{1}H NMR (300 MHz, CDCl$_3$) δ (ppm) 0.95 (t, J = 7.5 Hz, 3H, -CH$_3$), 1.77–1.87 (m, 2H, -CH$_2$), 2.51 (br, 1 H, -OH), 3.85 (s, 3H, -OCH$_3$), 4.79 (t, J = 6.6 Hz, 1H, -CHOH), 6.87–6.98 (m, 2H, -Ph), 7.21–7.24 (m, 1H, -Ph), 7.26–7.31 (m, 1H, -Ph). ^{13}C NMR (75 MHz, CDCl$_3$) δ (ppm) 10.40 (-CH$_3$), 30.11 (-CH$_2$), 55.20 (-CHOH), 72.40 (-OCH$_3$), 110.50 (-Ph), 120.66 (-Ph), 127.02 (-Ph), 128.14 (-Ph), 132.35 (-Ph), 156.61 (-Ph).

1-(3-Methoxyphenyl)-1-propanol (**7c**) 90% yield, $[\alpha]_D^{20}$ = +13.0 (*c* 28.0, $CHCl_3$), 39.3% ee by HPLC (Daicel Chiralcel OD column, hexane:ethanol = 97:3, 1 ml min^{-1}, 254 nm UV detector), t_R = 18.19 min for (*R*) and t_S = 21.13 min for (*S*) ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.92 (t, *J* = 7.5 Hz, 3H, -CH_3), 1.72–1.82 (m, 2H, -CH_2), 3.81 (s, 3H, -OCH_3), 4.57 (t, *J* = 6.6 Hz, 1H, -CHOH), 6.79–6.83 (m, 1H, -Ph), 6.90–6.93 (m, 2H, -Ph), 7.23–7.28 (m, 1H, -Ph) ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 10.05 (-CH_3), 31.79 (-CH_2), 55.16 (-OCH_3), 75.87 (-CHOH), 111.45 (-Ph), 112.89 (-Ph), 118.29 (-Ph), 129.33 (-Ph), 146.34 (-Ph), 159.72 (-Ph).

1-(4′-Methoxyphenyl)-1-propanol (**7d**) 98% yield, $[\alpha]_D^{20}$ = +27.3 (*c* 28.8, $CHCl_3$), 64% ee by HPLC (Daicel Chiralcel OD column, hexane:2-propanol = 97:3, 1 ml min^{-1}, 254 nm UV detector), t_R = 13.68 min for (*R*) and t_S = 16.43 min for (*S*) ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.89 (t, *J* = 7.5 Hz, 3H, -CH_3), 1.74–1.82 (m, 2 H, -CH_2), 3.80 (s, 3 H, -OCH_3), 4.54 (t, *J* = 6.6 Hz, 1H, -CHOH), 6.86–6.89 (m, 2H, -Ph), 7.25–7.28 (m, 2H, -Ph). ^{13}C NMR (75 MHz, CDCl3) δ (ppm) 10.12 (-CH_3), 31.74 (-CH_2), 55.24 (-OCH_3), 75.61 (-CHOH), 113.78 (-Ph), 127.15 (-Ph), 136.79 (-Ph), 159.02 (-Ph).

1-(2′-Chlorophenyl)-1-propanol (**7e**) 80% yield, $[\alpha]_D^{20}$ = +15.5 (*c* 2.6, $CHCl_3$), 38.7% ee by HPLC (Daicel Chiralcel AD column, hexane:ethanol = 97:3, 1 ml min^{-1}, 254 nm UV detector), t_R = 9.35 min for (*R*) and t_S = 10.63 min for (*S*) ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.99 (t, *J* = 7.5 Hz, 3H, -CH_3), 1.76–1.82 (m, 2H, -CH_2), 5.05–5.05 (m, 1H, -CHOH), 7.16–7.22 (m, 1H, -Ph), 7.26–7.34 (m, 2H, -Ph), 7.53–7.56 (m, 1H, -Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 10.00 (-CH_3), 30.45 (-CH_2), 71.97 (-CHOH), 126.98 (-Ph), 127.12 (-Ph), 128.31 (-Ph), 129.34 (-Ph), 131.98 (-Ph), 141.96 (-Ph).

1-(3′-Chlorophenyl)-1-propanol (**7f**) 81% yield, $[\alpha]_D^{20}$ = +10.3 (*c* 2.7, $CHCl_3$), 37.7% ee by HPLC (Daicel Chiralcel OD column, hexane:2-propanol = 97:3, 0.5 ml min^{-1}, 254 nm UV detector), t_R = 20.83 min for (*R*) and t_S = 20.19 min for (*S*) ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.92 (t, *J* = 7.5 Hz, 3H, -CH_3), 1.71–1.78 (m, 2H, -CH_2), 1.80 (s, 1H, -OH), 4.59 (t, *J* = 6.6 Hz, 1H, -CHOH), 7.19–7.23 (m, 1H, -Ph), 7.24–7.30 (m, 2H, -Ph), 7.34–7.35 (m, 1H, -Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 9.91, 31.90, 75.29, 124.07 (-Ph), 126.12 (-Ph), 127.53 (-Ph), 129.62 (-Ph), 134.29 (-Ph), 146.63 (-Ph).

1-(4′-Chlorophenyl)-1-propanol (**7g**) 85% yield, $[\alpha]_D^{20}$ = +23 (*c* 2.9, $CHCl_3$), 61.7% ee by HPLC (Daicel Chiralcel OD column, hexane:2-propanol = 97:3, 0.5 ml min^{-1}, 254 nm UV detector), t_R = 20.21 min for (*R*) and t_S = 19.49 min for (*S*) ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.90 (t, *J* = 7.5 Hz, 3H, -CH_3), 1.72–1.80 (m, 2H, -CH_2), 4.59 (t, *J* = 6.6 Hz, 1H, -CHOH), 7.26–7.34 (m, 4H, -Ph). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 9.88, 31.90, 75.23, 127.30 (-Ph), 128.47 (-Ph), 133.07 (-Ph), 143.07 (-Ph).

Conclusion

In summary, a series of modular, thiazoline-containing N-O ligands were easily synthesized from L-cysteine in three steps and with high yield. These compounds could be used as chiral ligands to catalyze the asymmetric addition of diethylzinc (Et_2Zn) to various aromatic aldehydes. The configuration of the products could be tunable by simple modification of the structures of thiazoline ligands. Products with *S* configuration were obtained when the thiazoline tertiary alcohol ligands were used as catalyst. Conversely, thiazoline primary alcohol induced corresponding products with *R* configuration in 68% ee. This represented a significant improvement on this type reaction mediated by other primary amino alcohol catalysts in the literature. Furthermore, plausible transition state models were proposed to explain the observed diverse stereoselectivities. This work could be extended to other catalytic asymmetric reactions and provide a promising route for designing novel chiral thiazoline ligands.

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References

[1] B. List, Asymmetric Organocatalysis, Springer, Heidelberg, **2010**.
[2] S. Bertelsen, K. A. Jogensen, *Chem. Soc. Rev.* **2009**, *38*, 2178.
[3] D. W. C. MacMillan, *Nature* **2008**, *455*, 304.
[4] A. Dondoni, A. Massi, *Angew. Chem. Int. Ed.* **2008**, *48*, 4638.
[5] M. J. Gaunt, C. C. C. Johansson, A. McNally, N. T. Vo, *Drug Discov. Today* **2007**, *12*, 8.
[6] R.-X. Lin, C. Chen, *J. Mol. Catal. A: Chem.* **2006**, *243*, 89.
[7] Y. Li, W. P. Li, R. Wang, *J. Org. Chem.* **2010**, *75*, 6869.
[8] G. Qi, Z. M. A. Judeh, *Tetrahedron: Asymmetry* **2010**, *21*, 429.
[9] A. R. Abreu, M. Lourenc, D. Peral, M. T. S. Rosadoa, M. E. S. Eusebio, O. Palacios, J. C. Bayon, M. M. Pereira, *J. Mol. Catal. A: Chem.* **2010**, *325*, 91.
[10] L. F. Tietze, T. Kinzel, C. C. Brazel, *Acc. Chem. Res.* **2009**, *42*, 367.
[11] R. Von Roenn, J. Christoffers, *Tetrahedron* **2011**, *67*, 334.
[12] S. Banerjee, A. J. Camodeca, G. G. Griffin, C. G. Hamaker, S. R. Hitchcock, *Tetrahedron: Asymmetry* **2010**, *21*, 549.
[13] T. Bauer, S. Smolinski, *Appl. Catal. A: Gen.* **2010**, *5*, 247.
[14] V. Coeffard, H. Muller-Bunz, P. J. Guiry, *Org. Biomol. Chem.* **2009**, *7*, 1723.
[15] J.-W. Ruan, G. Lu, L.-J. Xu, Y.-M. Li, A. S. C. Chan, *Adv. Synth. Catal.* **2008**, *350*, 76.
[16] L. Pu, H.-B. Yu, *Chem. Rev.* **2001**, *101*, 757.
[17] K. Soai, S. Niwa, *Chem. Rev.* **1992**, *92*, 833.
[18] S.-H. Gou, Z.-B. Ye, G.-J. Gou, M.-M. Feng, J. Chang, *Appl. Organomet. Chem.* **2011**, *25*, 110.
[19] M. N. Patil, R. G. Gonnade, N. N. Joshi, *Tetrahedron* **2010**, *66*, 5036.
[20] N. Shibata, M. Okamoto, Y. Yamamoto, S. Sakaguchi, *J. Org. Chem.* **2010**, *75*, 5707.
[21] R. W. Parrott, S. R. Hitchcock, *Tetrahedron: Asymmetry* **2008**, *19*, 19.
[22] J. Huang, J. C. Ianni, J. E. Antoline, R. P. Hsung, M. C. Kozlowski, *Org. Lett.* **2006**, *8*, 1565.
[23] R. Dave, N. A. Sasaki, *Tetrahedron: Asymmetry* **2006**, *17*, 388.
[24] Z. Szakonyi, A. Balazs, T. A. Martinek, F. Fulop, *Tetrahedron: Asymmetry* **2006**, *17*, 199.
[25] Y. Kawanami, T. Mitsuie, M. Miki, T. Sakamoto, K. Nishitani, *Tetrahedron* **2000**, *56*, 175.
[26] Y.-J. Wu, H.-Y. Yun, Y.-S. Wu, K.-L. Dong, Y. Zhou, *Tetrahedron: Asymmetry* **2000**, *11*, 3543.
[27] R. Noyori, S. Suga, K. Kawai, S. Okad, Y. Kitamura, *J. Organomet. Chem.* **1990**, *382*, 19.
[28] A.-C. Gaumont, M. Gulea, J. Levillain, *J. Chem. Rev.* **2009**, *109*, 1371.
[29] S. C. McKeon, H. Mueller-Bunz, P. J. Guiry, *Eur. J. Org. Chem.* **2009**, *28*, 4833.
[30] A. Osorio-Lozada, H. F. Olivo, *Org. Lett.* **2008**, *10*, 617.
[31] I. Abrunhosa, M. Gulea, J. Levillain, S. Masson, *Tetrahedron: Asymmetry* **2001**, *12*, 2851.
[32] G. Helmchen, A. Krotz, K.-T. Ganz, D. Hansen, *Synlett* **1991**, 257.
[33] Y.-Z. Li, X.-S. Hu, H.-M. Huang, *Chin. Inv. Patent Bull.* **1996**.
[34] J. Kim, K. A. De Castro, M. Lim, H. Rhee, *Tetrahedron* **2010**, *66*, 3995.
[35] K. A. De Castro, H. Rhee, *Synthesis* **2008**, 1841.
[36] Y.-M. Shang, J. Li, Z.-G. Song, Y.-Z. Li, H.-M. Huang, *Chem. Res. Chin. Univ.* **2007**, *23*, 430.
[37] C.-T. Chen, Y. S. Munot, *J. Org. Chem.* **2005**, *70*, 8625.
[38] Y.-J. Chen, R.-X. Lin, C. Chen, *Tetrahedron: Asymmetry* **2004**, *15*, 3561.
[39] S.-W. Kang, D.-H. Ko, K. H. Kim, D.-C. Ha, *Org. Lett.* **2003**, *5*, 4517.
[40] S. Vyskocil, S. Jaracz, M. Smrcina, M. Sticha, V. Hanus, M. Polasek, P. Kocovsky, *J. Org. Chem.* **1998**, *63*, 7727.
[41] E. Blocka, M. Jaworska, A. Kozakiewicz, M. Welniak, A. Wojtczak, *Tetrahedron: Asymmetry* **2010**, *21*, 571.

[42] M. A. Dean, S. R. Hitchcock, *Tetrahedron: Asymmetry* **2009**, *20*, 2351.
[43] F. Lutz, L. Takashi, T. Kawasaki, K. Soai, *J. Am. Chem. Soc.* **2005**, *127*, 12206.
[44] F. Lutz, I. Sato, K. Soai, *Org. Lett.* **2004**, *6*, 1613.
[45] K. Soai, S. Yokoyama, T. Hayasaka, *J. Org. Chem.* **1991**, *56*, 4264.
[46] M. Kitamura, S. Okada, S. Suga, R. Noyori, *J. Am. Chem. Soc.* **1989**, *111*, 4028.
[47] E. J. Corey, F. J. Hannon, *Tetrahedron Lett.* **1987**, *28*, 5233.
[48] M. Kitamura, M. Yamakawa, H. Oka, S. Suga, R. Noyori, *Chem. Eur. J.* **1996**, *2*, 1173.
[49] X. Yang, J. Shen, C. Da, R. Wang, M. C. K. Choi, L. Yang, K.-Y. Wong, *Tetrahedron: Asymmetry* **1999**, *10*, 133.
[50] E. J. Corey, F. J. Hannon, *Tetrahedron Lett.* **1987**, *28*, 5237.
[51] M. Falorni, C. Collu, S. Conti, G. Giacomelli, *Tetrahedron: Asymmetry* **1996**, *7*, 293.
[52] S. Conti, M. Falorni, G. Giacomelli, F. Soccolini, *Tetrahedron* **1992**, *48*, 8993.