Novel Chiral Bifunctional L-Thiazoline-Thiourea Derivatives: Design and Application in Enantioselective Michael Reactions

QI LAI, YANG LI, ZHIYONG GONG, QINGWEN LIU, CHIYU WEI, AND ZHIGUANG SONG*
Department of Organic Chemistry, College of Chemistry, Jilin University, Changchun, China

ABSTRACT Several novel chiral bifunctional L-thiazoline-thiourea derivatives were easily synthesized from commercially available L-cysteine in high yield. These catalysts were subsequently applied to the enantioselective Michael addition of acetylacetone to *β*-nitrostyrenes. The products with *S* configuration were obtained in 98% enantiomeric excess (*ee*) when the L-thiazoline-thiourea derivatives were used. A plausible transition state model is proposed to explain the observed enantioselectivities. *Chirality 27:979–988, 2015.* © 2015 Wiley Periodicals, Inc.

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Asymmetric organocatalytic reactions are extremely important in modern synthetic and pharmaceutical chemistry.[1–5] In this field, catalytic asymmetric Michael addition is widely regarded to be a fundamental C-C bond-forming reaction utilized in organic synthesis.[6,7] Furthermore, the enantioselective addition of 1, 3-dicarbonyl compounds onto *β*-nitrostyrenes is also regarded as one of the benchmark reactions and an attractive strategy. The reaction has become a standard for the evaluation of newly designed organocatalysts. Therefore, considerable attention has been focused on developing new effective chiral catalysts for asymmetric Michael addition.[8–14]

Among various chiral catalysts, the H-bond donor catalysts have been widely developed as a typical class of catalysts.[15–18] Of the different H-bond donor catalysts reported to date, those based on the thiourea core dominate the field. Thus, new thioureas or other hydrogen bond donors from accessible members of the chiral pool are continuously being developed.[19–29] Over the past few years, bifunctional tertiary amine-thiourea organocatalysts have emerged as new and efficient organocatalysts for asymmetric reactions.[30,31] It was found that the cinchona alkaloid family and its derivatives as the chiral amine parts of catalysts possessed high catalytic activity resulting in a high *ee* value in the asymmetric Michael addition.[32–37] However, there are only a few examples that chiral thiazoline-catalysts have been employed since they were first investigated by Helmchen et al. in 1991.[38–43] There is no report about cinchonine- and quinine-derived chiral thiazoline-containing catalysts, although the imino moiety-containing thiazoline is an efficient surrogate for the functional amino unit in some chiral catalysts. Therefore, the development of efficient new catalysts containing thiazoline for asymmetric transformations is challenging.

We recently first reported the design, synthesis, and application of a series of novel modular, thiazoline-containing N-O ligands **6** derived from L-cysteine (Scheme 1) in asymmetric addition of diethylzinc to aromatic aldehydes.[44] Encouraged by these successful efforts and aiming to demonstrate the generality of the new catalysts containing thiazoline, we fixed our attention on employing these novel catalysts **13** (Scheme 1) by tuning the thiourea moiety for enantioselective addition of 1, 3-dicarbonyl compounds onto *β*-nitrostyrenes.

EXPERIMENTAL

Materials and Instruments

All 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 ^{1}H NMR and ^{13}C NMR (Varian Mercury 300 NMR spectrometer), using tetramethylsilane (TMS) 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 from Shanghai Physical Optics Instrument Factory (China). Concentration is given as absolute values expressed in g/100 mL. High-performance liquid chromatography (HPLC) analyses were performed using a Shimadzu (Kyoto, Japan) LC-10A VP pump, SPD-10A VP UV detector, and Shimadzu CTO-10 AC VP column oven with appropriate chiral columns. Mass spectra were obtained using liquid chromatography / mass spectroscopy (LC/MS) 1100 from Agilent Technology (Palo Alto, CA) and Alltech (Deerfield, IL) ELSD 2000 instrument. High-resolution mass spectroscopic analysis (HRMS) data were measured on a Bruker (Billerica, MA) Apexll mass spectrometer by means of the electrospray ionization (ESI) technique. Melting points were determined by X-4 digital microscopy apparatus. C, H, and N elemental analyses were taken on a Perkin–Elmer (Boston, MA) 240C elemental analyzer.

Synthesis

(*R*)-tetrahydrothiazo-2-thione-4-carboxylic acid [(*R*)-TTCA] **2** was synthesized by known methods,[44] m.p. = 179–181 °C, $[\alpha]_D^{20} = -86.3$ (*c* 1.2, 0.5 N HCl).

General procedure for preparation of (3a-3c). 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 hours. Upon cooling to room temperature, the precipitate was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether: EtOAc).

*Correspondence to: Zhiguang Song, Department of Organic Chemistry, College of Chemistry, Jilin University, Changchun 130021, China. E-mail: szg@jlu.edu.cn
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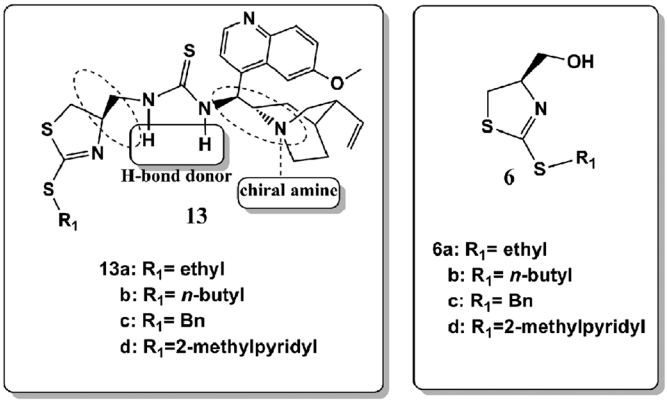


Scheme 1. Chiral Bifunctional L-Thiazoline-Thiourea catalysts.

(*R*)-2-ethylthio-4-ethyloxycarbonyl-4,5-dihydro-1,3-thiazole (3a) **3a** was obtained as a colorless oil, 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, 6H), 3.06-3.25 (m, 2H), 3.56-3.71 (m, 2H), 4.25 (q, J = 6 Hz, 2H), 5.06 (t, J = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ(ppm) 14.08, 14.41, 27.34, 37.02, 61.58, 77.23, 170.50. 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 (3b) **3b** was obtained as a colorless oil, 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), 1.39-1.44 (m, 4H), 1.64-1.69 (m, 4H), 3.08-3.23 (m, 2H), 3.59-3.66 (m, 2H, 4.19 (t, J = 6.6 Hz, 2H), 5.06 (t, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ(ppm) 13.54 , 13.63, 19.01, 21.79, 30.50, 31.13, 32.75, 37.15, 65.47, 77.25, 170.65. 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-benzylthio-4-benzyloxycarbonyl-4,5-dihydro-1,3-thiazole (3c) **3c** was obtained as a colorless oil, 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), 4.34-4.45 (m, 2H), 5.12 (m, 1 H), 5.25 (s, 2H), 7.26-7.39 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ(ppm) 37.19, 37.36, 67.20, 77.07, 127.49, 128.15, 128.36, 128.55, 129.04, 135.34, 136.28, 170.21. 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 methyl-(R)-2-thioxothiazolidine-4-carboxylate (4). To a solution of (*R*)-TTCA (**2**) (0.65 g, 4.0 mmol) in methanol (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 then was obtained as a colorless oil, 99% yield.

(*R*)-methyl-2-thioxothiazolidine-4-carboxylate (4) **4**[43] was obtained as a colorless oil, 99% yield. $[\alpha]_D^{20} = -68$ ($c = 5.5$, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm) 3.81 (d, J = 8 Hz, 2H), 3.86 (s, 3H), 4.83-4.88 (m, 1H), 8.21 (br, 1H). MS (ESI): m/z 177.1 [M + H$^+$]; Elemental analysis calculated for $C_5H_7NO_2S_2$: C, 33.88; H, 3.98; N, 7.90. Found: C, 34.69, H, 4.06, N, 7.80.

Procedure for preparation of (R)-2-((pyridin-2-ylmethyl)thio)-4-methyloxycarbonyl −4, 5-dihydro-1, 3-thiazole (5). To a solution of methyl-(*R*)-2-thioxothiazolidine-4-carboxylate (**4**) (1.35 g, 7.63 mmol) in acetonitrile (20 mL), 2-(bromomethyl) pyridine hydrobromide (2.53 g, 10 mmol), anhydrous K_2CO_3 (2.8 g), and (0.1 g) KI were added at room temperature. The solution was then stirred at 40 °C for 3 h. Upon cooling to room temperature, the precipitate was removed by filtration and filtrate was then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether: EtOAc = 1:1).

(*R*)-2-((pyridin-2-ylmethyl)thio)-4-methyloxycarbonyl −4, 5-dihydro-1, 3-thiazole **5** was obtained in 86% yield after purification by column chromatography on silica gel, $[\alpha]_D^{20} = +27$ ($c = 1.3$, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm) 3.60-3.74 (m, 2H), 3.80 (s, 3H), 4.55 (q, 2H, J = 15 Hz), 5.08 (t, J = 7.5 Hz, 1H), 7.17-7.21 (m, 1H), 7.46-7.49 (m, 1H), 7.62-7.68 (m, 1 H), 8.54-8.56 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ(ppm) 37.58, 38.82, 52.69, 77.05, 122.35, 123.55, 136.67, 149.44, 156.62, 168.63 , 170.95. MS (ESI): m/z 269.2 [M + H$^+$]; Elemental analysis calculated for $C_{11}H_{12}N_2O_2S_2$: C, 49.23; H, 4.51; N, 10.44. Found: C, 49.20, H, 4.50, N, 10.48.

General procedure for preparation of (R)-2-substitutedthio-4-hydroxymethyl-4, 5-dihydro-1, 3-thiazoles (6a-6d). To a solution of **3** or **5** (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 before water was added to quench the excessive $NaBH_4$. The mixture was then extracted twice with CH_2Cl_2. The combined organic phase were washed twice with saturated brine, 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 alcohols **6a-6d**.

(*R*)-2-ethylthio-4-hydroxymethyl-4,5-dihydro-1,3-thiazole (6a) **6a** was obtained as a colorless oil, 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, 3H), 2.06 (br, 1H), 3.07-3.14 (m, 2H), 3.27 (dd, J = 8.7 Hz, J = 10.8 Hz, 1H), 3.42 (dd, J = 8.1 Hz, J = 10.8 Hz, 1H), 3.69 (dd, J = 5.7 Hz, J = 11.1 Hz, 1H), 3.88 (dd, J = 4.8 Hz, J = 11.1 Hz, 1H), 4.54-4.63 (m, 1H,); ^{13}C NMR (75 MHz, $CDCl_3$) δ(ppm) 14.39, 27.13, 35.84, 63.76, 78.39. 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 (6b) **6b** was obtained as a colorless oil, 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), 1.37-1.49 (m, 2H), 1.63-1.73 (m, 2H), 1.94 (br, 1H), 3.12 (t, J = 7.5 Hz, 2H), 3.27 (dd, J = 8.7 Hz, J = 10.8 Hz, 1H), 3.42 (dd, J = 8.4 Hz, J = 10.8 Hz, 1H), 3.69 (dd, J = 5.7 Hz, J = 11.1 Hz, 1H), 3.89 (dd, J = 4.8 Hz, J = 11.1 Hz, 1H), 4.54-4.63 (m,1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ(ppm) 13.47, 21.76, 31.24, 32.59, 35.90, 64.04, 78.46. 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-benzylthio-4-hydroxymethyl-4,5-dihydro-1,3-thiazole (6c) **6c** was obtained as a light yellow oil, 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, 1H), 3.29 (dd, J = 8.4 Hz, J = 10.5 Hz, 1H), 3.44 (dd, J = 8.1 Hz, J = 10.5 Hz, 1H), 3.65 (dd, J = 5.7 Hz, J = 11.4 Hz, 1H), 3.88 (dd, J = 4.8 Hz, J = 11.1 Hz, 1H), 4.35 (m, 2 H), 4.56-4.64 (m,1H), 7.28-7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ(ppm) 36.26, 37.06, 64.09, 78.33, 127.48, 128.52, 128.89, 136.43. 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*)-2-((pyridin-2-ylmethyl)thio)-4-hydroxymethyl-4,5-dihydro-1,3-thiazole (6d) **6d** was obtained as a light yellow solid, 88% yield after purification by column chromatography on silica gel (CH_3OH: CH_2Cl_2 = 1:20), m. p. = 60 °C, $[\alpha]_D^{20}$ = + 62 (*c* = 2.0, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ(ppm) 3.31 (dd, J = 7.5 Hz, J = 10.8 Hz, 1H), 3.45 (dd, J = 8.4 Hz, J = 10.8 Hz, 1H), 3.62 (dd, J = 5.4 Hz, J = 11.1 Hz, 1H), 3.86 (dd, J = 4.5 Hz, J = 11.1 Hz, 1H), 4.32 (d, J = 13.8 Hz, 1H), 4.65 (d, J = 13.8 Hz, 1H), 4.59-4.68 (m,1H), 7.16-7.20 (m, 1H), 7.35-7.38 (m, 1H), 7.62-7.67 (m, 1H), 8.51-8.54 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ(ppm) 36.72, 38.4, 64.36, 77.15, 122.45, 123.31, 136.91, 149.43, 157.07, 165.95. HRMS (ESI) m/z calcd for $C_{10}H_{13}N_2OS_2$ [M + H^+]: 241.0464, found 241.0463.

General procedure for preparation of (7a-7d). To a solution of **6** (3 mmol) in dry $CHCl_3$ (10 mL), triethylamine (0.83 mL, 6 mmol) and *p*-toluenesulfonyl chloride (0.86 g, 4.5 mmol) were added at 0 °C. The reaction mixture was stirred at room temperature for 60 h. Then the reaction was quenched by addition of 5% sodium bicarbonate solution and extracted with $CHCl_3$ (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-(ethylthio)-4,5-dihydrothiazol-4-yl)methyl-4-methylbenzenesulfonate (7a) **7a**[43] was obtained as a light yellow oil, 82% yield after purification by column chromatography on silica gel (petroleum ether: EtOAc = 5:1), ^1H NMR (300 MHz, $CDCl_3$) δ(ppm) 1.31 (t, J = 7.5 Hz, 3H), 2.46 (s, 3 H), 3.04 (q, J = 7.5 Hz, 2H), 3.27 (dd, J = 6.3 Hz, J = 11.1 Hz, 1H), 3.46 (dd, J = 8.1 Hz, J = 11.1 Hz, 1H), 3.99 (dd, J = 8.1 Hz, J = 9.9 Hz, 1H), 4.21 (dd, J = 4.2 Hz, J = 9.9 Hz, 1H), 4.64-4.73 (m, 1H), 7.36 (d, J = 8.1 Hz, 2H), 7.80 (d, J = 8.1 Hz, 2H).

(*R*)-(2-(butylthio)-4,5-dihydrothiazol-4-yl)methyl-4-methylbenzenesulfonate (7b) **7b**[43] was obtained as a light yellow oil, 80% yield after purification by column chromatography on silica gel (petroleum ether: EtOAc = 5:1), ^1H NMR (300 MHz, $CDCl_3$) δ(ppm) 0.91 (t, J = 7.2 Hz, 3H), 1.33-1.43 (m, 2H), 1.56-1.68 (m, 2H), 2.46 (s, 3H), 3.04 (t, J = 7.2 Hz, 2H), 3.27 (dd, J = 6.3 Hz, J = 11.1 Hz, 1H), 3.46 (dd, J = 8.1 Hz, J = 11.1 Hz, 1H), 3.98 (dd, J = 8.4 Hz, J = 9.6 Hz, 1H), 4.21 (dd, J = 4.2 Hz, J = 9.9 Hz, 1H), 4.66-4.72 (m, 1H), 7.36 (d, J = 8.1 Hz, 2H), 7.80 (d, J = 8.1 Hz, 2H).

(*R*)-(2-(benzylthio)-4,5-dihydrothiazol-4-yl)methyl-4-methylbenzenesulfonate (7c) **7c** was obtained as a yellow oil, 84% yield after purification by column chromatography on silica gel (petroleum ether: EtOAc = 5:1), ^1H NMR (300 MHz, $CDCl_3$) δ(ppm) 2.45 (s, 3H), 3.28 (dd, J = 6.3 Hz, J = 11.1 Hz, 1H), 3.47 (dd, J = 8.1 Hz, J = 11.1 Hz, 1H), 3.98 (dd, J = 8.1 Hz, J = 9.9 Hz, 1H), 4.20 (dd, J = 4.2 Hz, J = 9.9 Hz, 1H), 4.27 (s, 2H), 4.65-4.74 (m, 1H), 7.27-7.32 (m, 5H), 7.36 (d, J = 8.1 Hz, 2H), 7.81 (d, J = 8.4 Hz, 2H).

(*R*)-(2-((pyridin-2-ylmethyl)thio)-4,5-dihydrothiazol-4-yl)methyl-4-methylbenzenesulfonate (7d) **7d** was obtained as a yellow oil, 90% yield after purification by column chromatography on silica gel (petroleum ether: EtOAc = 1:1), ^1H NMR (300 MHz, $CDCl_3$) δ(ppm) 2.45 (s, 3H), 3.27 (dd, J = 6.6 Hz, J = 11.1 Hz, 1H), 3.47 (dd, J = 8.1 Hz, J = 11.1 Hz, 1H), 3.97 (dd, J = 8.1 Hz, J = 9.9 Hz, 1H), 4.17 (dd, J = 4.5 Hz, J = 9.9 Hz, 1H), 4.42 (s, 2H), 4.64-4.73 (m, 1H), 7.16-7.21 (m, 1H), 7.35-7.38 (m, 1H), 7.36 (d, J = 8.1 Hz, 2H), 7.62-7.68 (m, 1H), 7.80 (d, J = 8.4 Hz, 2H), 8.53-8.55 (m, 1H).

General procedure for preparation of (8, 9). To a solution of **7** (3 mmol) in dry DMSO (20 mL), sodium azide (1.95 g, 30 mmol) was added at room temperature The reaction mixture was stirred at room temperature for 24 h. Then the reaction was quenched by addition of water and extracted with $CHCl_3$ (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 **8** obtained was used directly in the next step without purification.

To a solution of the crude product **8** (2 mmol) in THF (20 mL), triphenylphosphine (1.05 g, 4 mmol) and water (0.08 mL, 4 mmol) were added at room temperature. The reaction mixture was stirred at room temperature for 24 h. Then the reaction was quenched by addition of water, neutralized with 1 M hydrochloric acid to pH = 2 at 0 °C, and extracted with ethyl acetate. Then the aqueous phase was neutralized to pH = 12 with sodium hydroxide solution at 0 °C, and then extracted with ethyl acetate (20 mL × 3). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product **9** obtained and purified by column chromatography on silica gel.

(*R*)-(2-(ethylthio)-4,5-dihydrothiazol-4-yl)methanamine (9a) **9a** was obtained as a yellow oil, 90% yield after purification by column chromatography on silica gel (CH_2Cl_2: CH_3OH = 9:1), ^1H NMR (400 MHz, $CDCl_3$) δ(ppm) 1.36 (t, J = 7.2 Hz, 3H), 2.88 (q, J = 6.4 Hz, 1H), 2.97 (dd, J = 5.2 Hz, J = 12.8 Hz, 1H), 3.08-3.11 (m, 1H), 3.18 (dd, J = 8.0 Hz, J = 14.4 Hz, 1H), 3.42-3.47 (m, 2H), 4.44-4.51 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 9.42, 21.94, 31.89, 40.61, 74.14, 159.96; MS (ESI): m/z 177.0 [M + H^+].

(*R*)-(2-(butylthio)-4,5-dihydrothiazol-4-yl)methanamine (9b) **9b** was obtained as a colorless oil, 89% yield after purification by column chromatography on silica gel (CH_2Cl_2: CH_3OH = 9:1), ^1H NMR (300 MHz, $CDCl_3$) δ(ppm) 0.93 (t, J = 7.5 Hz, 3H), 1.39-1.47 (m, 2H), 1.63-1.73 (m, 2H), 1.91 (br, 2H), 2.85-2.96 (m, 2H), 3.07-3.13 (m, 2H), 3.17 (dd, J = 8.4 Hz, J = 10.8 Hz, 1H), 3.43 (dd, J = 8.4 Hz, J = 10.8 Hz, 1H), 4.54-4.63 (m,1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ(ppm) 13.61, 21.86, 31.39, 32.56, 37.17, 45.94, 79.46, 165.52; MS (ESI): m/z 205.2 [M + H^+].

(*R*)-(2-(benzylthio)-4,5-dihydrothiazol-4-yl)methanamine (9c) **9c** was obtained as a light yellow oil, 86% yield after purification by column chromatography on silica gel (CH_2Cl_2: CH_3OH = 9:1), ^1H NMR (300 MHz, DMSO) δ(ppm) 2.64-2.78 (m, 2 H), 3.33 (dd, J = 7.5 Hz, J = 11.8 Hz, 1H), 3.49 (dd, J = 8.1 Hz, J = 11.8 Hz, 1H), 4.35 (d, J = 3 Hz, 2H), 4.38-4.46 (m,1H), 7.26-7.37 (m, 5H); ^{13}C NMR (75 MHz, DMSO) δ(ppm) 35.86, 37.17, 44.90, 79.32, 127.27, 128.40, 128.94, 129.36, 137.28, 162.15; MS (ESI): m/z 239.1 [M + H^+].

(*R*)-(2-((pyridin-2-ylmethyl)thio)-4,5-dihydrothiazol-4-yl)metha-namine (9d) **9d** was obtained as a light yellow oil, 88% yield after purification by column chromatography on silica gel (CH_2Cl_2: CH_3OH = 9:1), ^1H NMR (300 MHz, DMSO) δ(ppm) 2.63-2.75 (m, 1H), 3.33 (dd, J = 7.5 Hz, J = 10.8 Hz, 1H), 3.86 (dd, J = 4.5 Hz, J = 11.1 Hz, 1H), 4.35-4.42 (m, 1H), 4.46 (d, J = 5.1 Hz, 2H), 7.26-7.30 (m, 1H), 7.35-7.46 (d, J = 7.8 Hz, 1H), 7.72-7.78 (m, 1H), 8.50-8.51 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ(ppm) 32.43, 33.35, 40.76, 74.04, 117.02, 117.99, 131.36, 144.23, 151.72, 159.22; MS (ESI): m/z 241.1 [M + H^+].

General procedure for preparation of (11a-11b). A cinchona alkaloid (2.5 mmol) and triphenylphosphine (0.8 g, 3 mmol) were dissolved in THF (25 mL) and the solution was cooled to 0 °C. Diethylazodicarboxylate (3 mmol, 0.6 mL) was subsequently added. To the resulting solution was added dropwise the solution of diphenyl phosphoryl azide (0.65 mL, 3 mmol) in THF (10 mL) at 0 °C. The mixture was allowed to warm to room temperature. After being stirred for 24 h, it was heated to 50 °C and stirred for 3 h. Triphenylphosphine (0.85 g, 3.3 mmol) was added again, and the mixture was stirred at 50 °C for an additional 3 h. After the solution was cooled to room temperature, H_2O (3 mL) was added, and the solution was stirred for 12 h. Then the reaction was quenched by addition of water, neutralized with 1 M hydrochloric acid to pH = 2 at 0 °C, and extracted with ethyl acetate. Then the aqueous phase was neutralized to pH = 12 with sodium hydroxide solution at 0 °C, and then extracted with ethyl acetate (20 mL × 3). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, and

concentrated in vacuo. Purification by silica gel column chromatography using EtOAc: CH_3OH: $(Et)_3N$ =100:100:1) as an eluent gave the corresponding amine.

11a was obtained as a light yellow oil, 76% yield after purification by column chromatography on silica gel, $[\alpha]_D^{20}$ = +110 (*c* = 1.0, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ(ppm) 0.94-1.05 (m, 1H), 1.43-1.48 (m, 3H), 2.18-2.26 (m, 2H), 2.88-2.96 (m, 5H), 4.71 (d, J = 10.2 Hz, 1H), 5.04-5.13 (m, 2H), 5.84-5.95 (m, 1H), 7.60-7.68 (m, 2H), 7.72-7.77 (m, 1H), 8.03 (d, J = 5.4 Hz, 1H), 8.50-8.52 (m, 1H), 8.86 (d, J = 4.2 Hz, 1H).

11b was obtained as a light yellow oil, 80% yield after purification by column chromatography on silica gel, $[\alpha]_D^{20}$ = + 80 (*c* 1.0, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ(ppm) 0.65-0.72 (m, 1H), 1.16-1.25 (m, 1H), 1.52 (m, 3H), 2.24 (m, 2H), 2.64-2.69 (m, 2H), 2.91-2.99 (m, 1H), 3.141-3.22 (m, 1H), 3.93 (s, 3H), 4.62 (d, J = 10.2 Hz, 1H, 4.91-5.02 (m, 2H), 5.77-5.88 (m, 1H), 7.40 (dd, J = 2.7 Hz, J = 8.7 Hz, 1H), 7.59 (d, J = 5.4 Hz, 1 H), 7.92 (d, J = 9.3 Hz, 1H), 8.33 (m, 1H), 8.70 (d, J = 4.5 Hz, 1H).

General procedure for preparation of (12a-12b). To a solution of the corresponding primary amine **11** (1.55 mmol) in dry THF (10 mL) at −10 °C were added CS_2 (9.3 mmol, 0.56 mL) and DCC (1.55 mmol, 0.32 g). The reaction mixture was warmed slowly to room temperature over a period of 3 h and then stirred 48 h at room temperature. The solvent was subsequently removed under vacuum. The residue was purified by chromatography on silica gel.

12a[45] was obtained as a white solid, 80% yield after purification by column chromatography on silica gel (EtOAc: CH_3OH = 10:1), $[\alpha]_D^{20}$ = +117.6 (c = 1.0, $CHCl_3$), m.p. = 176–180 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ(ppm) 1.86-1.96 (m, 4H), 2.07 (brs, 1H), 2.62-2.70 (m, 1H), 3.14-3.33 (m, 3H), 3.52-3.56 (m, 1H), 3.81-3.88 (m, 1H), 5.19-5.32 (m, 2H), 5.51 (d, J = 10.2 Hz, 1H), 5.84-5.95 (m, 1H), 7.56 (d, J = 4.5 Hz, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.75 (t, J = 7.5 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 8.16 (d, J = 8.4 Hz, 1H), 8.90 (dd, J = 4.2 Hz, J = 11.7 Hz, 1H). HRMS (ESI) m/z calcd for $C_{20}H_{22}N_3S$ $[M + H^+]$: 336.1529, found 336.1521.

12b[46] was obtained as a white solid, 84% yield after purification by column chromatography on silica gel (EtOAc: CH_3OH = 10:1), $[\alpha]_D^{20}$ = +15 (c = 1.0, $CHCl_3$), m.p. = 86–88 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ(ppm) 1.52-1.59 (m, 1H), 1.84-1.92 (m, 3H), 2.07 (brs, 1H), 2.65 (m, 1H), 3.10-3.17 (m, 1H), 3.22-3.31 (m, 2H), 3.49-3.52 (m, 1H), 3.70-3.72 (m, 1H), 3.93 (s, 3H), 5.04-5.12 (m, 2H), 5.38 (d, J = 10.2 Hz, 1H), 5.63-5.74 (m, 1H), 7.28 (d, J = 2.7 Hz, 1H), 7.34 (dd, J = 2.7 Hz, J = 9.0 Hz, 1H), 7.38 (d, J = 4.5 Hz, 1H), 7.99 (d, J = 9.3 Hz, 1H), 8.70 (d, J = 4.5 Hz, 1H). HRMS (ESI) m/z calcd for $C_{21}H_{24}N_3OS$ $[M + H^+]$: 366.1635, found 366.1636.

General procedure for preparation of (13a-13e). To a solution of chiral amine **9** (2.7 mmol) in anhydrous CH_2Cl_2 (20 mL) was added isothiocyanate **12** (2.7 mmol) at room temperature. The solution was stirred overnight. Thin-layer chromatography (TLC) indicated completion of the reaction. The reaction mixture was concentrated under vacuum. The residue was purified by silica gel chromatography to afford the pure product **13**.

13a was obtained as a white solid, 83% yield after purification by column chromatography on silica gel (CH_2Cl_2: CH_3OH = 9:1), $[\alpha]_D^{20}$ = −90.9 (*c* = 1.0, $CHCl_3$), m.p. = 100–102 °C . ^1H NMR (300 MHz, $CDCl_3$) δ(ppm) 0.88-0.99 (m, 1H), 1.28 (t, J = 7.2 Hz, 3H), 1.34-1.45 (m, 1H), 1.64-1.74 (m, 3H), 2.33 (brs, 1H), 2.72-2.88 (m, 2H), 2.91-3.05 (m, 3H), 3.22-3.32 (m, 4H), 3.52-3.56 (m, 1H), 3.80-3.84 (m, 2H), 4.00 (s, 3H), 4.42-4.52 (m, 1H), 4.95-5.02 (m, 2H), 5.64-5.75 (m, 1H), 7.37-7.47 (m, 2H), 7.87 (brs, 1H), 8.02 (d, J = 9.3 Hz, 1H), 8.72-8.75 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ(ppm) 14.71, 25.53, 26.88, 27.22 , 27.46, 37.03, 38.76, 41.86, 47.98, 55.16, 56.14 , 60.78, 75.93, 102.76, 115.63, 120.36, 122.41, 128.39, 131.47, 140.06, 144.73, 147.72 , 158.20, 167.53, 182.92. HRMS (ESI) m/z calcd for $C_{27}H_{36}N_5OS_3$ $[M + H^+]$: 542.2076, found 542.2073.

13b was obtained as a white solid, 80% yield after purification by column chromatography on silica gel (CH_2Cl_2: CH_3OH = 9:1), $[\alpha]_D^{20}$ = −67 (*c* = 1.0, $CHCl_3$), m.p. = 120–122 °C ^1H NMR (300 MHz, $CDCl_3$) δ(ppm) 0.91 (t, J = 7.2 Hz, 3H), 1.02-1.08 (m, 1H), 1.21-1.67 (m, 6H, thiazoline), 1.82 (brs, 3H), 2.45 (brs, 1H), 2.91-3.05 (m, 4H), 3.07-3.13 (m, 1H), 3.31-3.43 (m, 2H), 3.55-3.68 (m, 3H), 3.83-3.90 (m, 1H), 4.00 (s, 3H), 4.52-4.59 (m, 1H), 5.02-5.08 (m, 2H), 5.63-5.74 (m, 1H), 7.37-7.41 (m, 1H), 7.50-7.52 (m, 1H), 7.84 (brs, 1H), 8.02 (d, J = 9.0 Hz, 1H), 8.75-8.76 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ(ppm) 14.01, 22.27, 25.32, 26.60, 27.55, 31.76, 33.23, 37.47 (−S$\underline{C}$H$_2$CHN=), 38.48, 41.86, 48.51, 55.12, 56.41 , 60.80, 76.34, 102.68, 1$\underline{1}$6.66, 121.19, 122.71 , 128.19, 132.34, 139.19, 145.51, 148.10, 158.73, 167.80, 183.40. HRMS (ESI) m/z calcd for $C_{29}H_{40}N_5OS_3$ $[M + H^+]$: 570.2389, found 570.2387.

13c was obtained as a white solid, 85% yield after purification by column chromatography on silica gel (CH_2Cl_2: CH_3OH = 9:1), $[\alpha]_D^{20}$ = −92.9 (*c* = 1.0, $CHCl_3$), m.p. = 98–100 °C, ^1H NMR (300 MHz, $CDCl_3$) δ(ppm) 0.88-0.97 (m, 1H), 1.30-1.41 (m, 1H), 1.62-1.69 (m, 3H), 2.31 (brs, 1H), 2.71-2.88 (m, 3H), 3.02-3.30 (m, 5H,), 3.54-3.68 (m, 1H), 3.78-3.90 (m, 1H), 3.97 (s, 3 H), 4.19 (d, J = 6.9 Hz, 2H), 4.38-4.53 (m, 1H), 4.93-5.00 (m, 2H), 5.61-5.73 (m, 1H), 7.26-7.39 (m, 7H), 7.74 (brs, 1H), 8.00 (d, J = 9.3 Hz, 1H), 8.70-8.72 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ(ppm) 26.07, 27.64, 27.83, 37.38, 37.48, 39.54 , 41.56 , 48.55, 55.77, 56.26, 60.91, 76.19, 102.60, 115.43, 120.55, 122.48, 127.99, 129.01, 129.40, 129.47 , 132.12, 136.76, 140.99, 145.17,148.03, 158.38, 167.40, 183.30. HRMS (ESI) m/z calcd for $C_{32}H_{38}N_5OS_3$ $[M + H^+]$: 604.2233, found 604.2231.

13d was obtained as a white solid, 87% yield after purification by column chromatography on silica gel (CH_2Cl_2: CH_3OH = 9:1), $[\alpha]_D^{20}$ = −69 (*c* = 1.0, $CHCl_3$), m.p. = 104–106 °C, ^1H NMR (300 MHz, $CDCl_3$) δ(ppm) 0.95-1.00 (m, 1H), 1.36-1.45 (m, 1H), 1.73 (brs, 3H), 2.36 (brs, 1H), 2.73-2.88 (m, 3H), 3.09-3.36 (m, 5H), 3.54-3.68 (m, 1 H), 3.80-3.95 (m, 1H), 3.99 (s, 3H), 4.31-4.55 (m, 3H), 4.96-5.02 (m, 2H), 5.61-5.73 (m, 1H), 7.13-7.19 (m, 1H), 7.32-7.37 (m, 2H), 7.39-7.45 (m, 1H), 7.59-7.64 (m, 1H), 7.84 (brs, 1H), 7.99-8.03 (m, 1H), 8.51-8.54 (m, 1H), 8.72 (t, J = 4.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ(ppm) 25.48, 27.03, 27.21, 37.27, 38.26, 38.86, 41.11, 47.78, 55.19, 55.64, 60.49, 75.47, 102.31, 114.70, 119.91 , 121.82, 122.21, 123.16, 127.93, 131.25, 136.68 , 140.41, 144.44, 147.30, 149.00, 156.38, 157.68, 165.68, 182.85. HRMS (ESI) m/z calcd for $C_{31}H_{37}N_6OS_3$ $[M + H^+]$: 605.2185, found 605.2182.

13e was obtained as a white solid, 60% yield after purification by column chromatography on silica gel (CH_2Cl_2: CH_3OH = 9:1), $[\alpha]_D^{20}$ = +116 (*c* = 1.0, $CHCl_3$), m.p. = 58–60 °C, ^1H NMR (400 MHz, $CDCl_3$) δ(ppm) 1.00-1.03 (m, 1H), 1.14-1.40 (m, 2H), 1.60-1.76 (m, 3H), 2.32-2.46 (m, 2H), 2.58-2.67 (m, 2H), 3.01-3.21 (m, 4H), 3.35-3.41 (m, 1H), 3.68-3.78 (m, 1H), 3.87-3.91 (m, 1H), 4.37-4.41 (m, 1H), 4.48-4.60 (m, 1H), 4.79-4.82 (m, 1H), 5.09-5.14 (m, 1H), 5.20-5.27 (m, 1H), 5.87-5.95 (m, 1H), 7.21-7.22 (m, 1 H), 7.41-7.42 (m, 1H), 7.51 (m, 1H), 7.58-7.67 (m, 2H), 7.73-7.77 (m, 1H), 8.15-8.17 (m, 1H), 8.35-8.45 (m, 1H), 8.59 (m, 1H), 8.93 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) 24.92, 25.68, 26.44, 27.21, 29.68 , 37.56 , 38.57, 39.37, 47.33, 48.08, 53.51, 58.04, 75.70, 100.00, 114.81, 119.91, 122.42, 123.47, 126.68, 130.39, 136.92, 140.24, 148.55, 147.30, 150.24, 156.67, 156.81, 166.09, 183.29. HRMS (ESI) m/z calcd for $C_{30}H_{35}N_6S_3$ $[M + H^+]$: 575.2080, found 575.2087.

General procedure for the Michael addition. 1, 3-dicarbonyl compound (1 mmol) was added to a mixture of catalyst **13** (5 mol%) and the corresponding nitroolefin (0.20 mmol) in toluene (2 mL). The reaction mixture was stirred at room temperature for 48 h. The mixture was concentrated in vacuum. The residue was purified by chromatography on silica gel using ethyl acetate / hexanes (1:5) as the eluent to give the adduct. The enantiomeric excess (*ee*) of the products was determined by chiral HPLC analysis using chiral columns.

(*S*)-3-(2-nitro-1-phenylethyl)-pentane-2, 4-dione (**14a**) 99% yield, 97% *ee*, by HPLC analysis (Daicel Chiralcel AD column, hexane: 2-propanol = 90:10, 0.7 mL/min, 254 nm UV detector), t_R = 16.5 min for (major) and t_R = 22.2 min for (minor). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.94 (s, 3H), 2.30 (s, 3H), 4.21-4.28 (m, 1H), 4.38 (d, J = 10.8 Hz, 1H), 4.62-4.68 (m, 2H), 7.17-7.20 (m, 2H), 7.29-7.37 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 29.62, 30.47, 42.82, 70.70, 78.19, 127.97, 128.56, 129.35, 136.03, 201.03, 201.77.

(*S*)-3-[1-(4-chlorophenyl)-2-nitroethyl]-pentane-2, 4-dione (**14b**) 85% yield, >99% *ee*, by HPLC analysis (Daicel Chiralcel AD column, hexane: 2-propanol = 80:20, 1.0 mL/min, 215 nm UV detector), t_R = 12.68 min for (major) and t_R = 30.0 min for (minor). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.00 (s, 3H), 2.32 (s, 3H), 4.28-4.30 (m, 1H), 4.34 (d, J = 10.8 Hz, 1H), 4.63-4.64 (m, 2H), 7.16 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H).

(*S*)-3-[1-(4-fluorophenyl)-2-nitroethyl]-pentane-2, 4-dione (**14c**) 90% yield, 84% *ee*, by HPLC analysis (Daicel Chiralcel AD column, hexane: 2-propanol = 90:10, 0.7 mL/min, 210 nm UV detector), t_R = 20.95 min for (major) and t_R = 41.1 min for (minor). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.97 (s, 3H), 2.30 (s, 3H), 4.23-4.27 (m, 1H), 4.33 (d, J = 10.8 Hz, 1H), 4.61 (d, J = 6.0 Hz, 2H), 7.01-7.05 (m, 2H), 7.16-7.19 (m, 2H).

(*S*)-3-[1-(4-bromophenyl)-2-nitroethyl]-pentane-2, 4-dione (**14d**) 99% yield, 98% *ee*, by HPLC analysis (Daicel Chiralcel OD column, hexane: 2-propanol = 90:10, 0.8 mL/min, 230 nm UV detector), t_R = 36.85 min for (major) and t_R = 40.88 min for (minor). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.99 (s, 3H), 2.30 (s, 3H), 4.22-4.26 (m, 1H), 4.34 (d, J = 10.8 Hz, 1H), 4.62 (d, J = 6.0 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H).

(*S*)-3-[1-(3-bromophenyl)-2-nitroethyl]-pentane-2, 4-dione (**14e**) 97% yield, 98% *ee*, by HPLC analysis (Daicel Chiralcel AD column, hexane: 2-propanol = 95:5, 1.0 mL/min, 230 nm UV detector), t_R = 18.32 min for (major) and t_R = 19.55 min for (minor). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.02 (s, 3H), 2.31 (s, 3H), 4.23-4.24 (m, 1H), 4.36 (d, J = 10.8 Hz, 1H), 4.64 (d, J = 6.0 Hz, 2H), 7.14 (d, J = 8.4 Hz, 1H), 7.22 (t, J = 8.4 Hz, 1H), 7.38 (s, 1H), 7.45 (d, J = 8.4 Hz, 2H).

(*S*)-3-[1-(4-nitrophenyl)-2-nitroethyl]-pentane-2, 4-dione (**14f**) 80% yield, 86% *ee*, by HPLC analysis (Daicel Chiralcel AD column, hexane: ethanol = 80:20, 1.0 mL/min, 254 nm UV detector), t_R = 17.53 min for (major) and t_R = 20.32 min for (minor). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.04 (s, 3H), 2.33 (s, 3H), 4.40 (m, 2H), 4.69 (m, 2H), 7.42 (d, J = 8.4 Hz, 2H), 8.21 (d, J = 8.4 Hz, 2H).

(*S*)-3-[1-(3-nitrophenyl)-2-nitroethyl]-pentane-2, 4-dione (**14 g**) 85% yield, >99% *ee*, by HPLC analysis (Daicel Chiralcel AS column, hexane: 2-propanol = 80:20, 0.8 mL/min, 215 nm UV detector), t_R = 34.52 min for (major) and t_R = 50.32 min for (minor). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.06 (s, 3H), 2.34 (s, 3H), 4.43 (m, 2H), 4.70 (m, 2H), 7.55 (d, J = 8.4 Hz, 2H), 8.12 (s, 1H), 8.17 (d, J = 8.4 Hz, 1H).

(*S*)-3-[1-(2-nitrophenyl)-2-nitroethyl]-pentane-2, 4-dione (**14 h**) 84% yield, 96% *ee*, by HPLC analysis (Daicel Chiralcel AS column, hexane: 2-propanol = 80:20, 0.8 mL/min, 215 nm UV detector), t_R = 29.85 min for (major) and t_R = 32.35 min for (minor). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.14 (s, 3H), 2.31 (s, 3H), 4.67 (d, J = 8.4 Hz, 2H), 4.72-4.77 (m, 1H), 4.84 (dd, J = 3.6 Hz, J = 13.2 Hz, 1H), 4.98 (dd, J = 7.2 Hz, J = 13.2 Hz, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.49 (t, J = 8.4 Hz, 1H), 7.59 (t, J = 8.4 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H).

(*S*)-3-[1-(4-methoxyphenyl)-2-nitroethyl]-pentane-2, 4-dione (**14i**) 94% yield, 74% *ee*, by HPLC analysis (Daicel Chiralcel AD column, hexane: 2-propanol = 85:15, 0.65 mL/min, 210 nm UV detector), t_R = 18.15 min for (major) and t_R = 27.65 min for (minor). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.94 (s, 3H), 2.29 (s, 3H), 3.77 (s, 3H), 4.16-4.22 (m, 1H), 4.33 (d, J = 10.8 Hz, 1H), 4.59 (d, J = 6.0 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H).

(*S*)-3-[1-(2-methoxyphenyl)-2-nitroethyl]-pentane-2, 4-dione (**14j**) 90% yield, 80% *ee*, by HPLC analysis (Daicel Chiralcel AS column, hexane: 2-propanol = 80:20, 0.8 mL/min, 215 nm UV detector), t_R = 14.10 min for (major) and t_R = 15.92 min for (minor). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.95 (s, 3H), 2.29 (s, 3H), 3.90 (s, 3H), 4.98-4.52 (m, 1H), 4.60 (t, J = 6.0, 1H), 4.80 (t, J = 10.8 Hz, 2H), 6.90 (d, J = 7.2 Hz, 2H), 7.09 (d, J = 7.2 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H).

(*S*)-3-[1-(furan-2-yl)-2-nitroethyl]-pentane-2, 4-dione (**14 k**) 95% yield, 88% *ee*, by HPLC analysis (Daicel Chiralcel AD column, hexane: 2-propanol = 90:10, 1.0 mL/min, 220 nm UV detector), t_R = 11.92 min for (major) and t_R = 14.03 min for (minor). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.10 (s, 3H), 2.30 (s, 3H), 4.37-4.42 (m, 2H), 4.68 (d, J = 4.8 Hz, 2H), 6.19 (s, 1H), 6.32 (s, 1H), 7.38 (s, 1H).

(*S*)-3-[1-(naphthalen-2-yl)-2-nitroethyl]-pentane-2, 4-dione (**14 l**) 99% yield, 86% *ee*, by HPLC analysis (Daicel Chiralcel AD column, hexane: 2-propanol = 90:10, 0.7 mL/min, 210 nm UV detector), t_R = 25.27 min for (major) and t_R = 32.78 min for (minor). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.94 (s, 3H), 2.32 (s, 3H), 4.41-4.49 (m, 1H), 4.50 (d, J = 10.8 Hz, 1H), 4.67-4.77 (m, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.48-7.51 (m, 1H), 7.65 (s, 1H), 7.78-7.84 (m, 3H).

(3*S*)-ethyl-2-acetyl-4-nitro-3-phenylbutyrate (**14 m**) 99% yield, HPLC analysis (Daicel Chiralcel AD column, hexane: 2-propanol = 95:5, 0.8 mL/min, 220 nm UV detector), *dr* = 80:20, major diastereomer: t_R = 15.23 min for (major) and t_R = 23.23 min for (minor), 89% *ee*; minor diastereomer: t_R = 49.05 min for (major) and t_R = 25.58 min for (minor), 43% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.00-1.28 (t, J = 7.2 Hz, 3H), 2.05-2.30 (t, J = 7.2 Hz, 3H), 3.96 (q, J = 7.2 Hz, 1H), 4.03-4.12 (d, J = 9.9 Hz, 1H), 4.17-4.27 (m, 2H), 4.75 (d, J = 6.6 Hz, 1H), 4.82-4.85 (m, 1H), 7.19-7.22 (m, 2H), 7.27-7.31 (m, 3H).

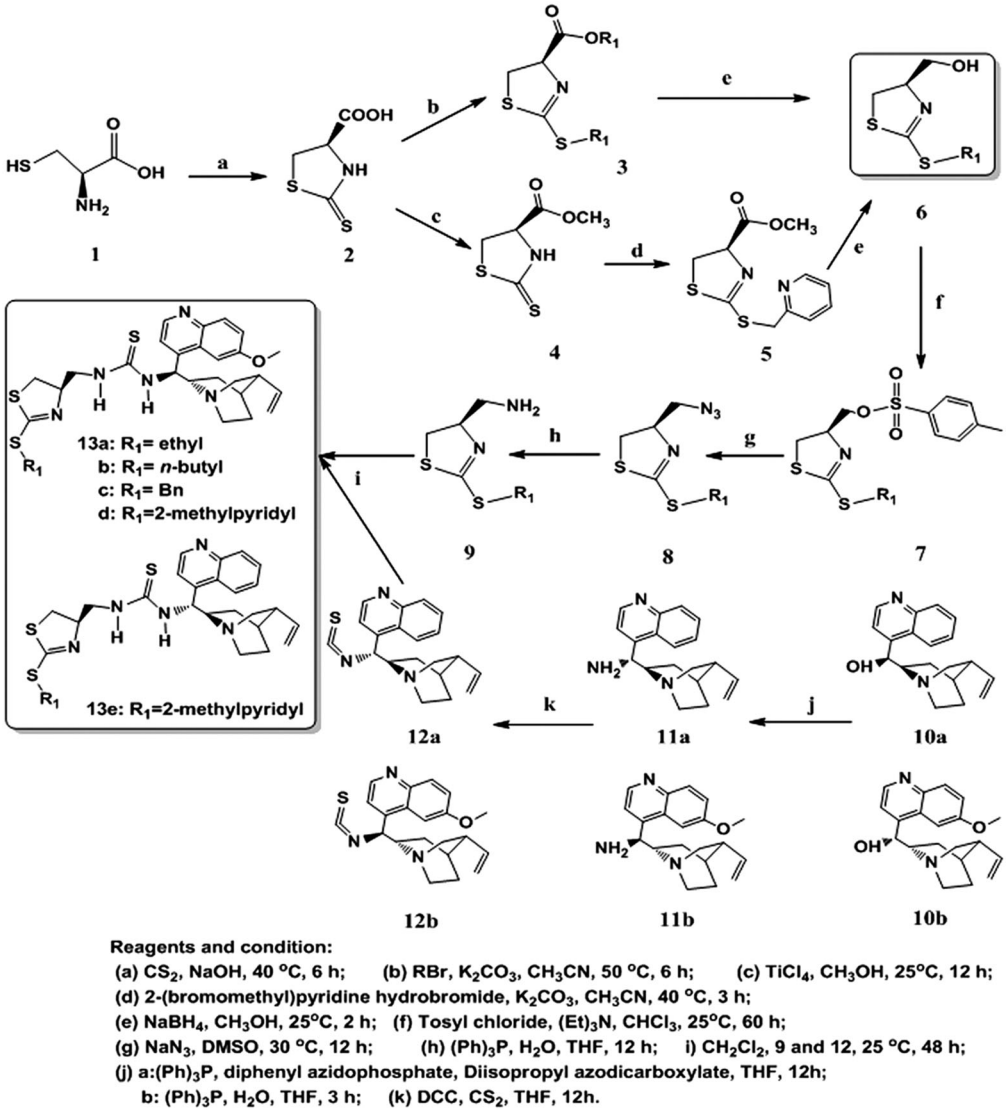
(3*S*)-ethyl-2-benzoyl-4-nitro-3-phenylbutanoate (**14n**) 99% yield, HPLC analysis (Daicel Chiralcel AD column, hexane: 2-propanol = 95:5, 1.0 mL/min, 245 nm UV detector), *dr* = 94:6, major diastereomer: t_R = 17.53 min for (major) and t_R = 40.05 min for (minor), 83% *ee*; minor diastereomer: t_R = 33.17 min for (major) and t_R = 16.02 min for (minor), 67% *ee*. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 0.90 (t, J = 7.2 Hz, 3 H, $-CH_2\underline{CH_3}$), 3.87 (q, J = 7.2 Hz, 1H), 4.47-4.50 (m, 1H), 4.79-4.80 (m, 1H), 4.94-4.97 (m, 2H), 7.21 (m, 3H), 7.31 (m, 2H), 7.49 (t, J = 7.2 Hz, 2H), 7.60-7.62 (m, 1H), 8.05 (d, J = 8.4 Hz, 2H).

(*S*)-diethyl-2-(2-nitro-1-phenylethyl)malonate (**14o**) 99% yield, 46 *ee*, by HPLC analysis (Daicel Chiralcel AD column, hexane:ethanol = 90:10, 1.0 mL/min, 254 nm UV detector), t_R = 10.13 min for (major) and t_R = 14.83 min for (minor). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.05 (t, J = 7.2, 3H), 1.26 (t, J = 7.2 Hz, 3H), 3.82 (d, J = 9.3 Hz, 1H), 4.01 (q, J = 7.2 Hz, 2H), 4.17-4.28 (m, 3H), 4.82-4.96 (m, 2H), 7.23-7.34 (m, 5H).

RESULTS AND DISCUSSION

Synthesis of Catalysts

We synthesized a series of novel chiral thiazoline-containing catalysts **13** in high yield (Scheme 2). First, (*R*)-tetrahydrothiazo-2-thione-4-carboxylic acid [(*R*)-TTCA] **2** was obtained by cyclization between L-cysteine and carbon disulfide under basic condition. Then alkyl bromide was added in situ to facilitate a tandem alkylation of **2** to afford **3** in moderate yield. Finally, thioether derivatives **3** and **5** were converted to chiral *β*-imino primary alcohols (**6a-6d**) upon $NaBH_4$ treatment. Conventionally, the reduction of ester to primary alcohol with lithium aluminum hydride requires a relatively longer time, as well as moisture-free and low-temperature conditions.[47,48] Nevertheless, in this study the use of sodium borohydride/MeOH system at room temperature provided a straightforward and more efficient method for synthesizing the chiral imino primary alcohols **6a-6d**. This method also successfully suppressed the racemization and maintained the optical purity of the resulting alcohols.



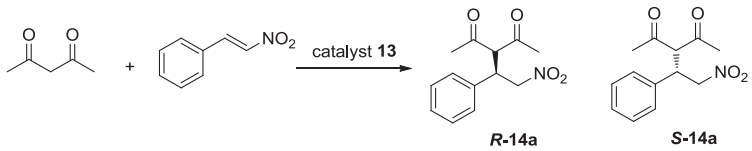
Scheme 2. The synthesis strategy for **13a-13e**.

Furthermore, we have documented a new protocol for the direct esterification of **2** to afford compound **4** at room temperature using catalytic $TiCl_4$. Compared with the conventional method using other Lewis acids, this new modification significantly improved the chemoselectivity and overall efficiency with complete retention of the original (*R*) configuration of **2**.[49] Then the thiazoline primary alcohols **6a-6d** were converted to the thiazoline primary amines **9a-9d** in moderate yield. For preliminary investigations, we selected cinchonine and quinine as representatives of the cinchona alkaloid family. After the cinchonine and quinine were reacted in THF in the presence of triphenylphosphine, diphenyl azidophosphate, and diisopropyl azodicarboxylate (DIAD), the cinchonine and quinine primary amines **11a-11b** were obtained. Then the cinchonine and quinine primary amines **11a-11b** were converted to isothiocyanate **12a-12b**. Lastly, the chiral bifunctional L-thiazoline-thiourea catalysts **13** could be easily synthesized from these chiral thiazoline primary amines and the isothiocyanates in high yield. So there are three chiral building blocks in these catalysts as shown in Scheme 1. With this consideration in mind, we designed and synthesized chiral bifunctional L-thiazoline-thiourea catalysts **13**, which consist of these functional groups. The catalyst structure was slightly changed to investigate the strength of H-bondings, catalytic activity, and selectivity.

Observation of Catalytic Activity

In order to detect the catalytic activity of L-thiazoline-thiourea catalysts derivatives, the asymmetric Michael reaction of *β*-nitrostyrene and acetylacetone was chosen as the model reaction (Table 1). First, the solvents, catalyst loading and temperature were screened. We found that the solvent employed significantly affected the conversion and enantioselectivity. Among the solvents tested, CH_2Cl_2 was identified to lead to the corresponding product (***S*-14a**) in 96% yield, 86% *ee* in the presence of 10 mol% **13d**. Further studies showed that the optimal solvent for this reaction was toluene, which could provide a relatively higher yield and *ee* (98% and 90%, respectively) of the product ***S*-14a** in the presence of 10 mol% **13d**. We also found that the catalyst

TABLE 1. Effect of the amount of catalyst 13 and solvent on asymmetric Michael reaction[a]



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Entry	Solvent	Temperature (°C)	13 (mol%)	Yield (%)[b]	*ee* (%)[c]	Configuration[d]
1	*n*-hexane	25	**13d** (10)	80	82	*S*
2	CH_2Cl_2	25	**13d** (10)	96	86	*S*
3	brine	25	**13d** (10)	85	70	*S*
4	Toluene	25	**13d** (10)	98	90	*S*
5	Toluene	−20	**13d** (5)	83	85	*S*
6	Toluene	25	**13d** (5)	99	97	*S*
7	Toluene	25	**13a** (5)	94	80	*S*
8	Toluene	25	**13b** (5)	99	84	*S*
9	Toluene	25	**13c** (5)	99	87	*S*
10	Toluene	25	**13e** (5)	99	95	*R*
11	Toluene	25	**13d** (5) + AcOH	96	77	*S*

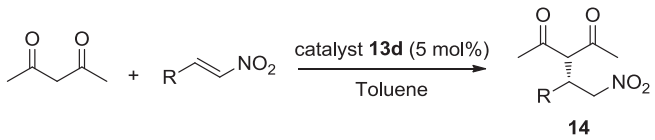
[a]The reactions were conducted with *β*-nitrostyrene (0.2 mmol) and acetylacetone (1 mmol) in 2 mL solvent for 48 h.
[b]Yields after silica gel column chromatography.
[c]*ee* was determined by HPLC using a Daicel Chiral AD column.
[d]The absolute configurations of the products were assigned by comparing the retention times in HPLC with those reported in the literature.[50]

13d loading had a significant influence on stereoselectivity but a slight influence on yield of the model reaction. Decreasing the **13d** loading from 10 mol% to 5 mol% relative to *β*-nitrostyrene could enhance the *ee* of the product (***S*-14a**) from 90% to 97%. Higher catalyst loading resulted in a slight decrease of the *ee* of the product. Temperature also significantly affected the yield, but only slightly influenced the stereoselectivity of the reaction (Table 1, entries 5 and 6). At −20 °C and 5 mol% of **13d** in toluene, the product (***S*-14a**) was obtained with only 83% yield and 85% *ee*. However, when the temperature was elevated to 25 °C the product was isolated in 99% yield and a higher 97% *ee*.

We then explored the influence of thio-alkyl moiety of the catalysts on enantioselectivity. The catalysts **13a–13e** were screened with the model reaction under optimized conditions using 5 mol% catalysts loading in toluene at 25 °C (Table 1, entries 6–10). The catalyst **13d** exhibited the best catalytic efficiency, resulting in 99% yield and good stereoselectivity (97% *ee*) of ***S*-14a** (Table 1, entry 6). The catalyst **13b** (R_1 = *n*-butyl, Table 1, entry 8) exhibited 84% *ee* of ***S*-14a**, whereas the least hindered **13a** exhibited a lower *ee*. The *ee* increased as the function of the bulk of the thio-substituents. Similarly with catalyst **13d**, thio-2-pyridylmethyl substitution on catalyst based cinchonine **13e** (Table 1, entry 10) exhibited an effect on the enantioselectivity of the reaction (95% *ee* of ***R*-14a**). The best amine part for the catalyst was based on quinine. We also found that carboxylic acid additives could not enhance the catalytic activity and stereoselectivity with **13d**. Addition of AcOH and **13d** in a 1:1 ratio decreased enantioselectivity but only slightly affected yield (Table 1, entry 6 vs. entry 11). Therefore, catalyst **13d** was used for further study on the enantioselective Michael reaction.

To explore the influence of the electronic and steric effects of the substrate in the asymmetric Michael addition of acetylacetone onto *β*-nitrostyrenes, a series of aryl *β*-nitrostyrenes were tested under optimized conditions with catalyst **13d** (Table 2). A general trend was observed in the reaction between acetylacetone and substituted *β*-nitrostyrenes with respect

TABLE 2. Asymmetric Michael reaction of various substrates catalyzed by 13[a]



Entry	Product	Yield (%)[b]	*ee* (%)[c]	Configuration[d]
1	**14a** (R = Ph)	99	97	*S*
2	**14b** (R = 4-ClC_6H_4)	85	>99	*S*
3	**14c** (R = 4-FC_6H_4)	90	84	*S*
4	**14d** (R = 4-BrC_6H_4)	99	98	*S*
5	**14e** (R = 3-BrC_6H_4)	97	98	*S*
6	**14f** (R = 4-$NO_2C_6H_4$)	80	86	*S*
7	**14g** (R = 3-$NO_2C_6H_4$)	85	>99	*S*
8	**14h** (R = 2-$NO_2C_6H_4$)	84	96	*S*
9	**14i** (R = 4-$OCH_3C_6H_4$)	94	74	*S*
10	**14j** (R = 2-$OCH_3C_6H_4$)	90	80	*S*
11	**14k** (R = furan-2-yl)	95	88	*S*
12	**14l** (R = naphthalen-2-yl)	99	86	*S*

[a]The reactions were conducted with *β*-nitrostyrene (0.2 mmol) and acetylacetone (1 mmol) in 2 mL toluene at 25 °C for 48 h.
[b]Yields after silica gel column chromatography.
[c]*ee* was determined by HPLC using a Daicel Chiral column.
[d]The absolute configurations of the products were assigned by comparing retention times in HPLC with those reported in the literature.[50]

to the enantioselectivities of the adduct as a function of the electron-withdrawing abilities of the substituents. The substrates with electron-withdrawing groups on the β-nitrostyrene aromatic ring (entries 2–8) exhibited higher enantioselectivity than those with electron-donating groups (entries 9 and 10). Furthermore, the enantioselectivity was significantly affected by the nature of the electron-withdrawing group (entries 3 and 6) and, in some cases, by the substituent position (entries 6 vs. 7, 8). The other aromatic styrenes, such as furan-2-yl- and naphthalen-2-yl-*β*-nitrostyrene underwent the asymmetric Michael addition with acetylacetone, generating the corresponding adducts in 95% and 99% yield and 88% and 86% *ee* (Table 2, entries 11 and 12).

The asymmetric Michael addition of other nucleophiles to *β*-nitrostyrene as catalyzed by **13d** was also investigated to determine the scope of nucleophile donors. As shown in Scheme 3, the 1, 3-dicarbonyl compound ethyl acetoacetate generated the desired product **14m** in high yield and with good diastereoselectivity (80:20) and enantioselectivity (89% and 43% *ee* for the major and minor diastereomers, respectively). Significantly, the reaction generated **14n** as the major product with remarkably high diastereoselectivity (94:6) and enantioselectivity (83% and 67% *ee* for the major and minor diastereomers, respectively). However, in the case of diethyl malonate the reaction produced the adduct **14o** with *S* configuration in high yield but poor enantioselectivity (46% *ee*).

Finally, based on experimental observations and related mechanistic studies by Takemoto and colleagues,[26,51] we proposed a transition state model for the asymmetric Michael addition of acetylacetone onto *β*-nitrostyrenes as catalyzed by chiral bifunctional L-thiazoline-thiourea catalysts **13** (Fig. 1). The thiourea moiety of catalyst **13d** interacts through H-bonding with the *β*-nitro group of the nitroalkene and enhances the electrophilicity of the α-alkene carbon, while the tertiary amine deprotonates an acidic proton of the 2, 4-pentandione, generating a ternary complex. The synergistic steric hindrance from the chiral moiety of the bifunctional catalyst **13d** may be responsible for the increased stereocontrol of the Michael addition reaction.

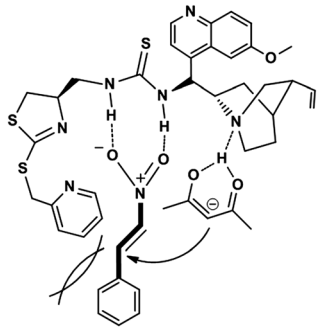


Fig. 1. A possible transition state for asymmetric Michael addition reaction.

CONCLUSION

In summary, a series of novel chiral bifunctional L-thiazoline-thiourea catalysts were facilely synthesized from L-cysteine in high yield. These compounds were found to efficiently catalyze enantioselective Michael reactions of 1, 3-dicarbonyl compounds onto *β*-nitrostyrenes in excellent enantioselectivity. This result represented a significant improvement on this type reaction mediated by quinine derivatives. Furthermore, a plausible transition state model was proposed to elucidate the observed diverse stereoselectivity. The thiazoline-thiourea scaffold studied may provide a promising route for designing new chiral catalysts for this type of reaction. The catalytic activities of the synthesized thiazoline-thiourea in other asymmetric reactions are under study and will be disclosed in due course.

ACKNOWLEDGMENTS

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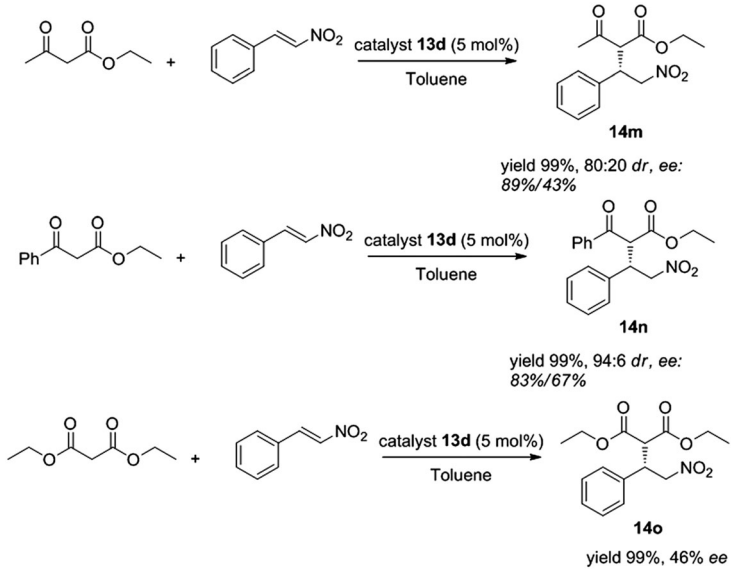

Scheme 3. Michael addition reaction of various carbonyl compounds onto β-nitrostyrenes.

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