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Chiral Cinchona Alkaloid-Derived Thiourea Catalyst for Enantioselective Synthesis of Novel β-Amino Esters by Mannich Reaction

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ABSTRACT A cinchona alkaloid-derived thiourea catalyst has been designed to access new asymmetric β-amino esters bearing benzothiazole moiety by utilizing a Mannich reaction between an imine and a malonate. A simultaneous activation of the two imine functionalities and malonate by the bifunctional chiral organocatalyst is proposed to account for the good yields (71–91%) and high enantiomeric excess (89.4–98.5%) under mild conditions. *Chirality 24:223–231, 2012.*

KEY WORDS: asymmetric β-amino esters; benzothiazole moiety; chiral cinchona alkaloid-derived thiourea; enantiomeric excess

INTRODUCTION

Enantiomerically pure β-amino acid derivatives are extremely useful in life sciences as part of biologically active molecules and small molecule pharmaceuticals.[1–4] Some of these compounds can also serve as valuable intermediates in routes to novel molecules with biological and pharmacological activities. The synthetic requirement emanates from the fact that barring the only example of β-alanine, other β-amino acids and β-peptides in general do not occur in nature. Most of the reported methods predominantly rely upon classical resolution, stoichiometric use of chiral auxiliaries, or homologation of α-amino acids.[5–10] In fact, chemical synthesis of β-amino acid derivatives offers great challenge due to the wide diversity of functional groups that can be bonded to the β carbon and the necessity of preserving chirality or creating the same via stereospecific addition of reagents across flat substrates. To access optically active β-amino acid derivatives through the later method, various organocatalytic techniques promoted by small chiral organic molecules ranging from simple proline and related chiral amine derivatives to axially chiral binaphthyl-derived Bronsted acids, thioureas, and cinchona alkaloids have been reviewed.[11–21] In this context, asymmetric organocatalytic Mannich reactions, at least in principle, are perhaps one of the most powerful modern techniques that represent a direct entry into optically active β-amino carbonyl compounds.[22–25] Jacobsen's group reported organocatalytic asymmetric Mannich reaction to prepare enantioenriched β-amino acid derivatives,[26] whereas various other workers obtained similar class of compounds by cinchona alkaloid induced Mannich reaction.[27–31] Despite these reports, a reliable route to access optically active β-amino acid derivatives bearing heterocyclic pharmacophores by organocatalytic Mannich reaction still needs to be developed. Multifunctional organocatalysts having hydrogen-bond donor ability and a secondary interaction site, are able to catalyze a vast number of reactions with high enantioselectivity.[32–34] Acidic sites of chiral thioureas and phosphoric acids often bind with the nitrogen atom of the Schiff's base making the electrophilic imine susceptible to be stereoselectively attacked by the nucleophilic enolsilane,[26,35] 1,3-diketones,[36] or malonates which in turn could be activated by the Bronsted basic part of the bifunctional organocatalyst through a concerted pathway.[16,37,38] Thus, appropriate positioning of a bifunctional catalyst containing a thiourea (capable to provide activation through hydrogen bond) and a cinchona alkaloid bearing tertiary amine component in a chiral scaffold could result in potential catalysts for asymmetric Mannich transformations. Based on this concept, we explored the possibility to utilize a series of cinchona alkaloid-derived thiourea catalysts in the preparation of enantioenriched β-amino esters from imines containing a benzothiazole unit and diethyl malonate. Some novel structural catalysts were also designed by making subtle variation in the nature of substituents linked to thiourea group. The final structure in the product still retains the bioactive component of heterocyclic benzothiazole. The stereochemical outcome of the reaction can be controlled through double hydrogen bond activation of two imine groups by thiourea, while the malonate is activated by the basic nitrogen atom of cinchona alkaloid. The method was found to be suitable with different imine and good yields and high *ee* values of the target compounds were obtained. To the best of our knowledge, this is the first report for the preparation of enantioselective β-amino esters bearing benzothiazole moiety

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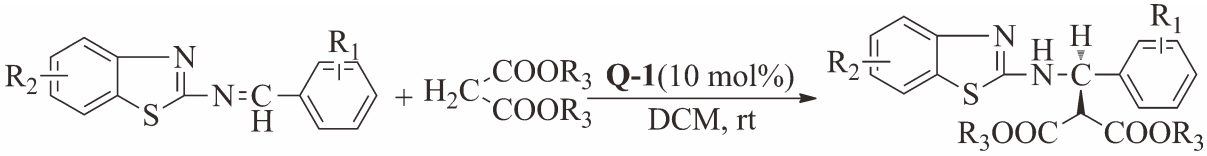
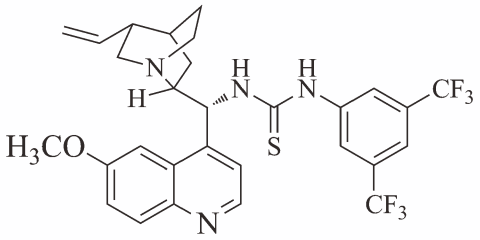


R_1=H, *p*-Cl, *o*-Cl, *p*-F, o-F, *o*-OCH_3, *p*-CH_3;
R_2=4-CH_3, 6-OCH_3;
R_3=C_2H_5, CH_3



Q-1

Scheme 1. Synthetic route to chiral β-amino esters **3**.

through simultaneous activation of two imines and malonate by the catalyst (Scheme 1).

MATERIALS AND METHODS

General

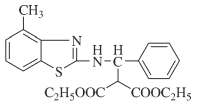
The melting points of the products were determined on a XT-4 binocular microscope (Beijing Tech Instrument Co., China) and were not corrected. The IR spectra were recorded on a Bruker VECTOR22 spectrometer in KBr disks. NMR spectra were recorded on a JEOL-ECX 500 instrument (500 MHz for ^{1}H, 125 MHz for ^{13}C, 200 MHz for ^{31}P, 470 MHz for ^{19}F) using $CDCl_3$ as a solvent, unless otherwise mentioned. Tetramethylsilane (δ = 0) served as an internal standard for ^{1}H-NMR and $CDCl_3$ was used as an internal standard (δ = 77.0) for ^{13}C-NMR. H_3PO_4 was used as an internal standard (δ = 0) for ^{31}P-NMR. CF_3COOD was used as an external standard (δ = 76.5) for ^{19}F-NMR. Elemental analysis was performed on an Elementar Vario-III CHN analyzer. The reagents were all of analytical grade or chemically pure. Analytical thin layer chromatography (TLC) was performed on silica gel GF_{254}. Organic solvents used were dried by standard methods when necessary. Purification of the products was performed by chromatographic operation on silica gel Qingdao GF_{254} under normal pressure. Reaction experiments were performed under argon atmosphere using standard double-line pipe. Catalysts **Q-1, QD-1,** and**Q-3** were prepared according to the literature procedures.[39,40] Catalysts **Q-2, Q-4**, and **Q-5** and benzothiazol-2-yl-benzylidene imines **1** were prepared as given in the Supporting Information.

The analytical high-performance liquid chromatography (HPLC) of the compounds was performed on Agilent 1100 series Apparatus composed of a quaternary pump, an auto sampler, a diode array detector (DAD) a vacuum degasser, a column oven, and Agilent Chemstation software. The two columns employed were Chiralpak AD-H-amylose tri-(3,5-dimethylphenylcarbamate) coated on 5-μm silica-gel and Chiralpak IA-amylose tri-(3,5-dimethylphenylcarbamate) immobilized on silica-gel (each of 250 mm × 4.6 mm i.d., Daicel Chemical Industries Ltd).

General Procedure for Enantioenriched 3a–l by Organocatalytic Mannich Reaction of Benzothiazolyl Imine 1a–l with Diethyl Malonate 2b or Dimethyl Malonate 2a

Diethyl malonate **2b** (0.30 mmol) in dichloromethane (DCM) (2.0–3.0 ml) was added in one shot to a mixture of imine **1a–l** (0.25 mmol) and chiral catalyst (10 mol %) at room temperature and stirred for 72–96 h. After the completion of the reaction (as observed by TLC), the solvent was evaporated and the product was purified by silica gel column chromatography to afford the corresponding product. The optical purity was determined by HPLC analysis using a chiral column.

Diethyl 2-((4-methylbenzo[d]thiazol-2-ylamino)(phenyl)methyl)-malonate (3a).

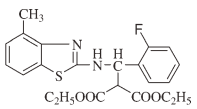


3a

(*R*)-(−)-3a, this product was obtained as a colorless oil from a reaction catalyzed by **Q-1** (10 mol %) at room temperature for 72 h; yield (92.8 mg, 90%) by preparative TLC (GF254 silica gel: hexane/ethyl ether = 5/1); 95.8% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/isopropyl alcohol (IPA) = 95/5, 1.0 ml min^{-1}, λ = 254 nm, t_r (major) = 7.85 min, t_r (minor) = 14.81 min]; $[\alpha]_D^{25} = -22.7$ (*c* = 1.10, $CHCl_3$). IR (KBr) ν: 3387, 2978, 1732, 1539, 1452, 1236, 1157, 759, 700, 480 cm^{-1}. ^{1}H-NMR (500 MHz,$CDCl_3$) δ: 1.13–1.14 (m, 6H), 2.52 (s, 3H), 4.01 (d, *J* = 5.7 Hz, 1H), 4.09–4.19 (m, 4H), 5.65 (brs, 1H), 6.95 (t, *J* = 14.9 Hz, 2H), 7.06 (d, *J* = 7.4 Hz, 1H), 7.22–7.25 (m, 1H), 7.30 (t, *J* = 14.9 Hz, 2H), 7.35 (d, *J* = 7.4 Hz, 1H), 7.41 (d, *J* = 7.4 Hz, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 168.0, 167.0, 165.5, 151.3, 138.7, 130.8, 129.2, 128.8, 126.8, 126.7, 121.7, 118.3, 62.3, 62.0, 58.4, 57.3, 18.5, 14.0. Analysis calculated for $C_{22}H_{24}N_2O_4S$: C, 64.06; H, 5.86; N, 6.79. Found: C, 63.99; H, 5.77; N, 6.53.

(*S*)-(+)-3a, this product was obtained as a colorless oil from a reaction catalyzed by **QD-1** (10 mol %) at room temperature for 72 h; yield (80%); 89.4% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH = 70/30, 1.0 ml min^{-1}, λ = 270 nm, t_r (major) = 5.05 min, t_r (minor) = 4.33 min].

Diethyl 2-((4-methylbenzo[*d*]thiazol-2-ylamino)(2-fluorophenyl)-methyl)malonate (3b).



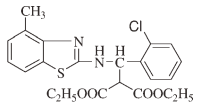
3b

(*R*)-(−)-3b, this product was obtained as a colorless oil from a reaction catalyzed by **Q**-1 (10 mol %) at room temperature for 72 h; yield (97.8 mg,

91%) by preparative TLC (GF254 silica gel: hexane/ethyl ether = 5/1); 96.0% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/IPA = 90/10, 1.0 ml min^{-1}, λ = 254 nm, t_r (major) = 7.09 min, t_r (minor) = 10.61 min]; $[\alpha]_D^{25}$ = −20.0 (*c* = 1.50, $CHCl_3$). IR (KBr) ν: 3387, 2980, 1734, 1539, 1373, 1240, 1151, 1039, 759 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.15–1.19 (m, 6H), 2.52 (s, 3H), 4.10–4.15 (m, 5H), 5.83–5.85 (m, 1H), 6.84 (d, *J* = 9.8 Hz, 1H), 6.97 (t, *J* = 7.4 Hz, 1H), 7.05–7.10 (m, 3H), 7.24–7.28 (m, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.44–7.47 (m, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 167.9, 166.7, 165.1, 161.5, 159.5, 151.3, 129.4, 129.0, 126.7, 124.4, 121.8, 118.3, 115.6, 62.3, 62.0, 55.7, 53.7, 18.4, 14.0. ^{19}F-NMR (470 MHz, $CDCl_3$) δ: −117.7. Analysis calculated for $C_{22}H_{23}N_2O_4FS$: C, 61.38; H, 5.39; N, 6.51; Found: C, 61.36; H, 5.25; N, 6.56.

(*S*)-(+)-3b, this product was obtained as a colorless oil from a reaction catalyzed by **QD-1** (10 mol %) at room temperature for 72 h; yield (85%); 90.0% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH = 70/30, 1.0 ml min^{-1}, λ = 270 nm, t_r (major) = 4.90 min, t_r (minor) = 4.27 min].

Diethyl 2-((4-methylbenzo[*d*]thiazol-2-ylamino)(2-chlorophenyl)-methyl)malonate (3c).

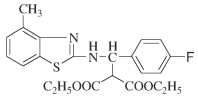


3c

(*R*)-(−)-3c, this product was obtained as a white solid from a reaction catalyzed by **Q-1** (10 mol %) at room temperature for 72 h; yield (99.4 mg, 89%) by preparative TLC (GF254 silica gel: hexane/ethyl ether = 5/1); 94.8% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/IPA = 95/5, 1.0 ml min^{-1}, λ = 254 nm, t_r (major) = 10.36 min, t_r (minor) = 16.63 min]; $[\alpha]_D^{25}$ = −120.4 (*c* = 1.00, $CHCl_3$). IR (KBr) ν: 3383, 2922, 1732, 1535, 1373, 1238, 1155, 756 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.14–1.22 (m, 6H), 2.52 (s, 3H), 4.05–4.12 (m, 1H), 4.14–4.28 (m, 4H), 5.93 (brs, 1H), 6.96 (t, *J* = 15.4 Hz, 1H), 7.06 (d, *J* = 7.4 Hz, 1H), 7.19–7.24 (m, 3H), 7.36–7.40 (m, 2H), 7.49–7.51 (m, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 168.1, 166.8, 165.2, 151.3, 135.8, 129.9, 129.4, 129.3, 128.5, 127.3, 126.7, 121.7, 118.3, 62.4, 61.9, 55.9, 54.4, 18.4, 14.0. Analysis calculated for $C_{22}H_{23}N_2O_4ClS$: C, 59.12; H, 5.19; N, 6.27; Found: C, 59.24; H, 5.11; N, 6.08.

(*S*)-(+)-3c, this product was obtained as a colorless oil from a reaction catalyzed by **QD-1** (10 mol %) at room temperature for 72 h; yield (85%); 90.0% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH = 70/30, 1.0 ml min^{-1}, λ = 270 nm, t_r (major) = 4.92 min, t_r (minor) = 4.14 min].

Diethyl 2-((4-methylbenzo[*d*]thiazol-2-ylamino)(4-fluorophenyl)-methyl)malonate (3d).

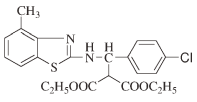


3d

(*R*)-(−)-3d, this product was obtained as a colorless oil from a reaction catalyzed by **Q-1** (10 mol %) at room temperature for 72 h; yield (95.6 mg, 89%) by preparative TLC (GF254 silica gel: hexane/ethyl ether = 5/1); 95.0% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH = 95/5, 1.0 ml min^{-1}, λ = 270 nm, t_r (major) = 8.41 min, t_r (minor) = 14.97 min]; $[\alpha]_D^{25}$ = −22.6 (*c* = 0.73, $CHCl_3$). IR (KBr) ν: 3373, 2993, 1747, 1539, 1506, 1301, 1261, 1145, 1024, 769 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.17–1.18 (m, 6H), 2.52 (s, 3H), 3.96 (d, *J* = 5.2 Hz, 1H), 4.14–4.17 (m, 4H), 5.63–5.65 (m, 1H), 6.88 (d, *J* = 8.6 Hz, 1H), 6.96–7.03 (m, 3H), 7.08 (d, *J* = 7.4 Hz, 1H), 7.38–7.42 (m, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 168.0, 166.8, 165.1, 163.4, 161.4, 151.2, 130.6, 129.3, 128.6, 126.7, 121.8, 118.3, 115.8, 115.6, 62.3, 62.1, 57.6, 57.2, 18.4, 14.0. ^{19}F-NMR (470 MHz, $CDCl_3$) δ: −114.0. Analysis calculated for $C_{22}H_{23}N_2O_4FS$: C, 61.38; H, 5.39; N, 6.51; Found: C, 61.20; H, 5.26; N, 6.41.

(*S*)-(+)-3d, this product was obtained as a colorless oil from a reaction catalyzed by **QD-1** (10 mol %) at room temperature for 72 h; yield (80%); 90.2% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH = 70/30, 1.0 ml min^{-1}, λ = 270 nm, t_r (major) = 5.85 min, t_r (minor) = 4.32 min].

Diethyl 2-((4-methylbenzo[*d*]thiazol-2-ylamino)(4-chlorophenyl)-methyl)malonate (3e).

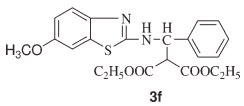


3e

(*R*)-(−)-3e, this product was obtained as a colorless oil from a reaction catalyzed by **Q-1** (10 mol %) at room temperature for 72 h; yield (100.0 mg, 89%) by preparative TLC (GF254 silica gel: hexane/ethyl ether = 5/1); 95.2% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH = 95/5, 1.0 ml min^{-1}, λ = 270 nm, t_r (major) = 8.72 min, t_r (minor) = 15.41 min]; $[\alpha]_D^{25}$ = −7.2 (*c* = 0.77, $CHCl_3$). IR (KBr) ν: 3361, 2980, 1743, 1533, 1489, 1344, 1238, 1149, 1039, 756, 744 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.18 (s, 6H), 2.51 (s, 3H), 3.96 (d, *J* = 5.2 Hz, 1H), 4.09–4.23 (m, 4H), 5.65 (brs, 1H), 6.88 (brs, 1H), 6.98 (t, *J* = 7.4 Hz, 1H), 7.08 (d, *J* = 6.8 Hz, 1H), 7.30 (d, *J* = 8.6 Hz, 2H), 7.36–7.39 (m, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 168.0, 166.8, 165.0, 151.2, 137.4, 133.9, 129.3, 128.9, 128.2, 126.7, 121.8, 118.3, 62.4, 62.1, 57.6, 57.0, 18.4, 14.0. Analysis calculated for $C_{22}H_{23}N_2O_4ClS$: C, 59.12; H, 5.19; N, 6.27; Found: C, 59.01; H, 5.08; N, 6.17.

(*S*)-(+)-3e, this product was obtained as a colorless oil from a reaction catalyzed by **QD-1** (10 mol %) at room temperature for 72 h; yield (80%); 85.9% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH = 70/30, 1.0 ml min^{-1}, λ = 270 nm, t_r (major) = 6.11 min, t_r (minor) = 4.42 min].

Diethyl 2-((6-methoxybenzo[d]thiazol-2-ylamino)(phenyl) methyl)malonate (3f).

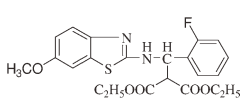


3f

(*R*)-(−)-3f, this product was obtained as a colorless oil from a reaction catalyzed by **Q-1** (10 mol %) at room temperature for 96 h; yield (86.8 mg, 81%) by preparative TLC (GF254 silica gel: hexane/ethyl ether = 3/1); 98.5% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH = 70/30, 1.0 ml min^{-1}, λ = 270 nm, t_r (major) = 8.35 min, t_r (minor) = 10.23 min]; $[\alpha]_D^{25}$ = −13.8 (*c* = 1.40, $CHCl_3$). IR (KBr) ν: 3371, 2980, 1734, 1604, 1545, 1471, 1222, 1157, 1028, 833, 700 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.14–1.16 (m, 6H), 3.78 (s, 3H), 4.00 (d, *J* = 4.6 Hz,1H), 4.14–4.16 (m, 4H), 5.69 (brs, 1H), 6.84–6.90 (m, 2H), 7.08 (d, *J* = 2.8 Hz,1H), 7.24–7.26 (m, 1H), 7.32 (t, *J* = 14.8 Hz, 2H), 7.39–7.42 (m, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 168.2, 167.0, 164.6, 155.3, 146.4, 138.7, 131.8, 128.8, 128.0, 126.6, 119.7, 113.6, 105.3, 62.3, 61.9, 57.9, 57.2, 55.9, 14.0, 13.9. Analysis calculated for $C_{22}H_{24}N_2O_5S$: C, 61.67; H, 5.65; N, 6.54. Found: C, 61.55; H, 5.48; N, 6.66.

(*S*)-(+)-3f, this product was obtained as a colorless oil from a reaction catalyzed by **QD-1** (10 mol %) at room temperature for 96 h; yield (72%); 95.8% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH = 70/30, 1.0 ml min^{-1}, λ = 270 nm, t_r (major) = 10.20 min, t_r (minor) = 8.35 min].

Diethyl 2-((6-methoxybenzo[*d*]thiazol-2-ylamino)(2-fluorophenyl)methyl)malonate (3g).



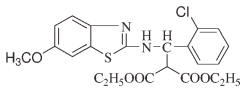
3g

(*R*)-(−)-3g, this product was obtained as a colorless oil from a reaction catalyzed by **Q-1** (10 mol %) at room temperature for 96 h; yield (95.5 mg, 86%) by preparative TLC (GF254 silica gel: hexane/ethyl ether = 3/1); 98.2% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH =

70/30, 1.0 ml min^{-1}, λ = 270 nm, t_r (major) = 8.64 min, t_r (minor) = 7.02 min]; $[\alpha]_D^{25}$ = −15.2 (*c* = 1.00, $CHCl_3$). IR (KBr) ν: 3383, 1741, 1606, 1548, 1489, 1219, 1155, 1037, 763 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.13–1.17 (m, 6H), 3.79 (s, 3H), 4.10–4.16 (m, 5H), 5.86–5.88 (m, 1H), 6.78 (brs, 1H), 6.86 (dd, *J* = 2.3 Hz, *J* = 2.8 Hz, 1H), 7.05–7.10 (m, 3H), 7.24–7.28 (m, 1H), 7.40–7.44 (m, 2H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 168.1, 166.8, 164.2, 161.4, 159.4, 146.4, 131.8, 129.4, 129.9, 128.7, 124.4, 119.9, 115.9, 115.6, 113.6, 105.3, 62.3, 61.9, 55.9, 55.6, 53.4, 14.0, 13.9. ^{19}F-NMR (470 MHz, $CDCl_3$) δ: −117.4. Analysis calculated for $C_{22}H_{23}N_2FO_5S$: C, 59.18; H, 5.19; N, 6.27; Found: C, 59.04; H, 5.19; N, 6.28.

(*S*)-(+)-3g, this product was obtained as a colorless oil from a reaction catalyzed by **QD-1** (10 mol %) at room temperature for 96 h; yield (74%); 96.0% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH = 70/30, 1.0 ml min^{-1}, λ = 270 nm, t_r (major) = 8.65 min, t_r (minor) = 7.12 min].

Diethyl 2-((6-methoxybenzo[*d*]thiazol-2-ylamino)(2-chlorophenyl) methyl)malonate (3h).

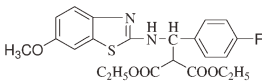


3h

R)-(−)-3h, this product was obtained as a colorless oil from a reaction catalyzed by **Q-1** (10 mol %) at room temperature for 96 h; yield (99.2 mg, 86%) by preparative TLC (GF254 silica gel: hexane/ethyl ether = 3/1); 97.9% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH = 70/30, 1.0 ml min^{-1}, λ = 270 nm, t_r (major) = 6.51 min, t_r (minor) = 7.79 min]; $[\alpha]_D^{25}$ = −106.5 (*c* = 0.90, $CHCl_3$). IR (KBr) ν: 3387, 2974, 1749, 1604, 1533, 1473, 1226, 1151, 1031, 765 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.13 (t, *J* = 38.4 Hz, 3H), 1.20 (t, *J* = 13.8 Hz, 3H), 3.78 (s, 3H), 4.03–4.09 (m, 1H), 4.12–4.28 (m, 4H), 5.90–5.91 (m, 1H), 6.85 (dd, *J* = 2.3 Hz, *J* = 2.2 Hz, 1H), 7.07 (d, *J* = 2.3 Hz, 1H), 7.14–7.24 (m, 3H), 7.38–7.48 (m, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 168.2, 166.9, 164.3, 155.3, 146.5, 135.8, 132.8, 131.9, 129.4, 129.9, 129.5, 128.4, 127.3, 119.9, 105.3, 62.4, 61.9, 55.9, 55.8, 54.3, 14.1, 13.9. Analysis calculated for $C_{22}H_{23}N_2ClO_5S$: C, 57.08; H, 5.01; N, 6.05; Found: C, 57.07; H, 4.99; N, 6.01.

(*S*)-(+)-3h, this product was obtained as a colorless oil from a reaction catalyzed by **QD-1** (10 mol %) at room temperature for 96 h; yield (73%); 96.3% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH = 70/30, 1.0 ml min^{-1}, λ = 270 nm, t_r (major) = 7.88 min, t_r (minor) = 7.07 min].

Diethyl 2-((6-methoxybenzo[*d*]thiazol-2-ylamino)(4-fluorophenyl)methyl)malonate (3i).

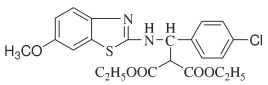


3i

(*R*)-(−)-3i, this product was obtained as a colorless oil from a reaction catalyzed by **Q-1** (10 mol %) at room temperature for 96 h; yield (90.3 mg, 81%) by preparative TLC (GF254 silica gel: hexane/ethyl ether = 3/1); 98.5% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH = 70/30, 1.0 ml min^{-1}, λ = 270 nm, t_r (major) = 11.55 min, t_r (minor) = 7.80 min]; $[\alpha]_D^{25}$ = −20.1 (*c* = 1.30, $CHCl_3$). IR (KBr) ν: 3371, 2993, 1751, 1604, 1548, 1474, 1263, 1159, 1022, 817, 567 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.15–1.16 (m, 6H), 3.79 (s, 3H), 3.96 (d, *J* = 5.2 Hz, 1H), 4.09–4.19 (m, 4H), 5.68 (brs, 1H), 6.85–6.91 (m, 2H), 6.99–7.02 (m, 2H), 7.08 (d, *J* = 2.8 Hz, 1H), 7.37–7.42 (m, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 168.1, 166.8, 164.3, 163.4, 161.4, 155.4, 146.4, 134.5, 131.8, 128.4, 128.3, 119.8, 115.8, 115.6, 113.6, 105.3, 62.3, 62.0, 57.2, 55.9, 14.1, 13.9; ^{19}F-NMR (470 MHz, $CDCl_3$) δ: −114.2; Analysis calculated for $C_{22}H_{23}N_2FO_5S$: C, 59.18; H, 5.19; N, 6.27. Found: C, 59.30; H, 5.27; N, 6.27.

(*S*)-(+)-3i, this product was obtained as a colorless oil from a reaction catalyzed by **QD-1** (10 mol %) at room temperature for 96 h; yield (66%); 91.5% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH = 70/30, 1.0 ml min^{-1}, λ = 270 nm, t_r (major) = 11.50 min, t_r (minor) = 7.89 min].

Diethyl 2-((6-methoxybenzo[*d*]thiazol-2-ylamino)(4-chlorophenyl)methyl)malonate (3j).

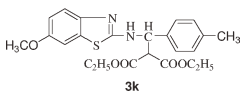


3j

(*R*)-(−)-3j, this product was obtained as a colorless oil from a reaction catalyzed by **Q-1** (10 mol %) at room temperature for 96 h; yield (93.6 mg, 81%) by preparative TLC (GF254 silica gel: hexane/ethyl ether = 3/1); 98.1% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH = 70/30, 1.0 ml min^{-1}, λ = 270 nm, t_r (major) = 7.98 min, t_r (minor) = 12.40 min]; $[\alpha]_D^{25}$ = −15.0 (*c* = 1.25, $CHCl_3$). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: (ppm) 1.21 (s, 6H), 3.81 (s, 3H), 3.96 (s, 1H), 4.15–4.18 (m, 4H), 5.69 (brs, 1H), 6.87 (s, 1H), 7.28 (s, 1H), 7.30–7.41 (m, 5H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ (ppm): 168.0, 166.8, 164.2, 155.4, 146.3, 137.4, 133.8, 131.8, 128.9, 128.1, 119.9, 113.6, 105.3, 62.0, 57.2, 57.0, 55.9, 54.3, 14.1, 13.9; IR(KBr, cm^{-1}) ν: 3364, 2980, 1734, 1605, 1498, 1476, 1223, 1091, 1028, 829. Analysis calculated for $C_{22}H_{23}N_2ClO_5S$: C, 57.08; H, 5.01; N, 6.05. Found: C, 57.00; H, 5.18; N, 5.99.

(*S*)-(+)-3j, this product was obtained as a colorless oil from a reaction catalyzed by **QD-1** (10 mol %) at room temperature for 96 h; yield (65%); 95.6% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH = 70/30, 1.0 ml min^{-1}, λ = 270 nm, t_r (major) = 12.39 min, t_r (minor) = 8.11 min].

Diethyl 2-((6-methoxybenzo[*d*]thiazol-2-ylamino)(*p*-tolyl)methyl)-malonate (3k).

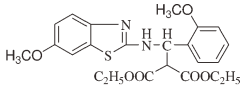


3k

(*R*)-(−)-3k, this product was obtained as a colorless oil from a reaction catalyzed by **Q-1** (10 mol %) at room temperature for 96 h; yield (77.5 mg, 70%) by preparative TLC (GF254 silica gel: hexane/ethyl ether = 3/1); 98.4% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH = 70/30, 1.0 ml min^{-1}, λ = 270 nm, t_r (major) = 7.93 min, t_r (minor) = 10.85 min]; $[\alpha]_D^{25}$ = −14.7 (*c* = 1.40, $CHCl_3$). IR (KBr) ν: 3366, 2980, 1732, 1604, 1548,1469, 1223, 1157, 1029, 814, 563 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.13–1.16 (m, 3H), 2.28 (m, 3H), 3.77 (s, 3H), 3.96 (d, *J* = 5.2 Hz, 1H), 4.09–4.18 (m, 4H), 5.61 (brs, 1H), 6.83–6.87 (m, 2H), 7.06–7.12 (m, 3H), 7.25–7.28 (m, 2H), 7.39 (d, *J* = 9.2 Hz, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 168.2, 167.0, 164.8, 155.3, 146.5, 137.8, 135.6, 131.8, 129.5, 126.5, 119.7, 113.5, 105.3, 62.2, 61.9, 57.3, 55.9, 21.2, 14.1, 13.9. Analysis calculated for $C_{23}H_{26}N_2O_5S$: C, 62.42; H, 5.92; N, 6.33. Found: C, 62.50; H, 5.87; N, 6.25.

(*S*)-(+)-3k, this product was obtained as a colorless oil from a reaction catalyzed by **QD-1** (10 mol %) at room temperature for 96 h; yield (66%); 97.7% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH = 70/30, 1.0 ml min^{-1}, λ = 270 nm, t_r (major) = 9.34 min, t_r (minor) = 7.14 min].

Diethyl 2-((6-methoxybenzo[*d*]thiazol-2-ylamino)(2-methoxyphenyl)methyl)malonate (3l).



3l

R)-(−)-3l, this product was obtained as a colorless oil from a reaction catalyzed by **Q-1** (10 mol %) at room temperature for 96 h; yield (81.3 mg, 71%) by preparative TLC (GF254 silica gel: hexane/ethyl ether = 3/1); 89.4% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH = 95/5, 1.0 ml min^{-1}, λ = 270 nm, t_r (major) = 22.01 min, t_r (minor) = 24.44 min]; $[\alpha]_D^{25}$= −59.2 (*c* = 0.80, $CHCl_3$). IR (KBr) ν: 3200, 2982, 1726, 1605, 1554, 1475, 1230, 1030, 815, 760 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 1.12–1.14 (m, 6H), 3.78 (s, 3H), 3.94 (m, 3H), 4.10–4.11 (m, 4H), 4.26

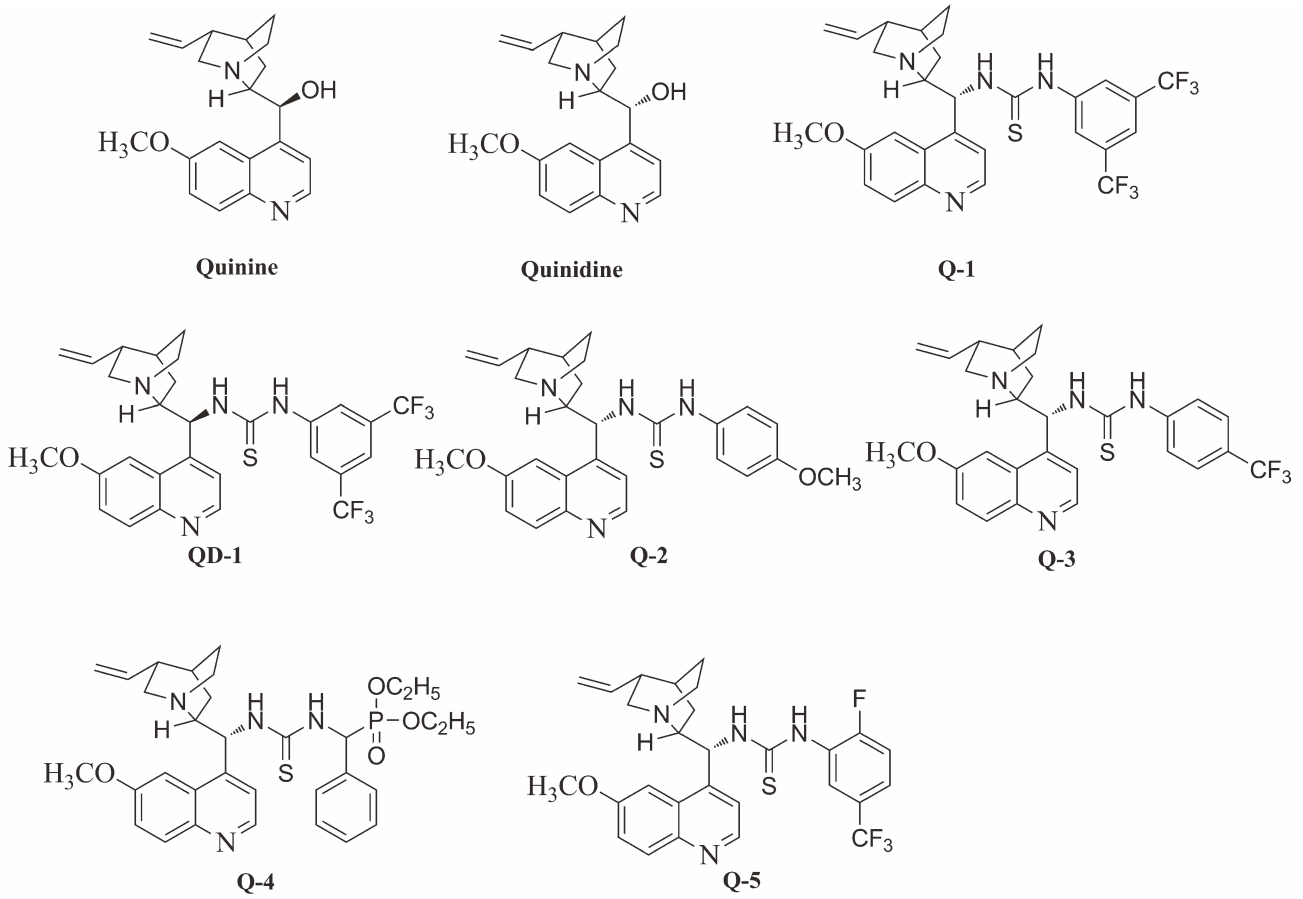


Fig. 1. Cinchona alkaloid-derived thiourea catalysts and commercial quinine and quinidine.

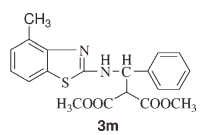
(d, J = 6.9 Hz, 1H), 5.62–5.64 (m, 1H), 6.77 (d, J = 10.3 Hz, 1H), 6.84–6.90 (m, 3H), 7.08 (d, J = 2.8 Hz, 1H), 7.23–7.25 (m, 1H) 7.34–7.36 (m, 1H), 7.40 (d, J = 9.2 Hz, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 168.1, 167.2, 165.2, 156.8, 155.2, 146.5, 131.8, 129.4, 128.9, 125.8, 120.7, 119.6, 113.5, 110.6, 105.3, 61.9, 61.8, 55.9, 55.6, 55.3, 14.0. Analysis calculated for $C_{23}H_{26}N_2SO_6$: C, 60.25; H, 5.72; N, 6.11. Found: C, 60.31; H, 5.35; N, 6.17.

(*S*)-(+)-3l, this product was obtained as a colorless oil from a reaction catalyzed by **QD-1** (10 mol %) at room temperature for 96 h; yield (65%); 98.2% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH = 95/5, 1.0 ml min^{-1}, λ = 270 nm, t_r (major) = 23.86 min, t_r (minor) = 22.06 min].

General Procedure for Enantioenriched 3m–r by Organocatalytic Mannich Reaction of Benzothiazolyl Imine with dimethyl Malonate 2a

Similar procedure as described with diethyl malonate **2a** was adopted. The enantioenriched **3m–r** was obtained by reaction of diethyl malonate **2a** and benzothiazolyl imine **1a–c** and **1i–k** catalyzed by **Q-1** (10 mol %) at room temperature for 72–96 h.

Dimethyl 2-((4-methylbenzo[*d*]thiazol-2-ylamino)(phenyl)methyl) malonate (3m).



(*R*)-(−)-3m, this product was obtained as a colorless oil from a reaction catalyzed by **Q-1** (10 mol %) at room temperature for 72 h; yield (71.0 mg, 74%) by preparative TLC (GF254 silica gel: hexane/ethyl ether = 5/1); 95.3% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH = 80/20, 1.0 ml min^{-1}, λ = 270 nm, t_r (major) = 5.20 min, t_r (minor) = 5.76 min]; $[\alpha]_D^{25} = -21.8$ (c = 1.47, $CHCl_3$). IR (KBr) ν: 3334, 2949, 1720, 1539, 1340, 1267, 1024, 769, 700 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.52 (s, 3H), 3.68 (s, 6H), 4.03–4.04 (m, 1H), 5.63–5.64 (m, 1H), 6.86 (br, 1H), 6.96 (t, J = 7.4 Hz, 1H), 7.07 (d, J = 6.9 Hz, 1H), 7.27 (t, J = 12.6 Hz, 1H), 7.33 (t, J = 15.5 Hz, 2H), 7.31–7.41 (m,3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 168.3, 167.3, 165.4, 151.2, 138.6, 129.2, 128.9, 128.2, 126.7, 126.6, 121.7, 118.3, 58.4, 57.0, 53.2, 52.9, 18.4. Analysis calculated for $C_{20}H_{20}N_2O_4S$: C, 62.48; H, 5.24; N, 7.29. Found: C, 62.43; H, 5.27; N, 7.40.

TABLE 1. Catalyst screening[a]

Entry	Cat.	Temp (°C)	Yield[b]	*ee*[c]
1	Quinine	rt	85%	79.1%
2	Quinidine	rt	85%	76.0%
3	**Q-1**	rt	90%	95.7%
4	**QD-1**	rt	85%	90.0%
5	**Q-2**	rt	85%	88.8%
6	**Q-3**	rt	90%	95.1%
7	**Q-4**[d]	rt	30%	21.2%
8	**Q-5**	rt	85%	92.6%

[a]Unless otherwise noted, reactions were carried out with 0.25 mmol of **1b**, 0.30 mmol of **2b** in 2.0 ml of methylene chloride using 10 mol % of catalyst at room temperature for 72 h.
[b]Isolated yield after chromatographic purification.
[c]Determined by HPLC analysis (Chiralpak IA).
[d]Reaction was carried out with 10 mol % of catalyst at room temperature for 96 h.

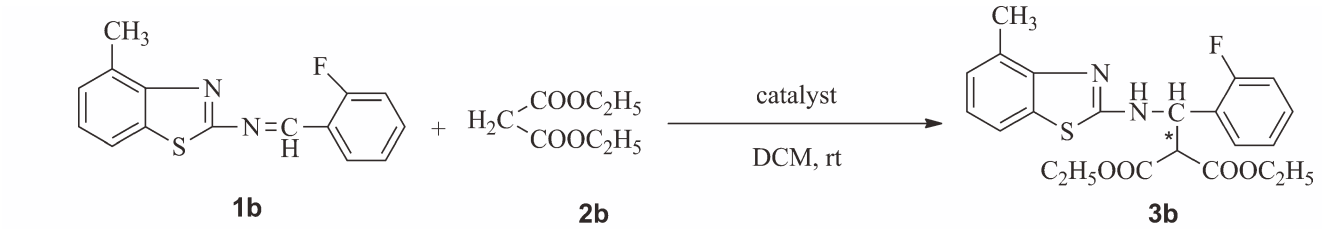
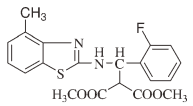


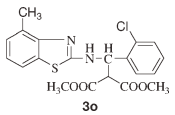
Fig. 2. Catalyst screening.

Dimethyl 2-((4-methylbenzo[*d*]thiazol-2-ylamino)(2-fluorophenyl) methyl)malonate (3n).



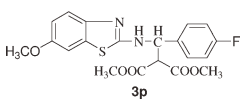
(*R*)-(−)-3n, this product was obtained as a colorless oil from a reaction catalyzed by **Q-1** (10 mol %) at room temperature for 72 h; yield (85.4 mg, 85%) by preparative TLC (GF254 silica gel: hexane/ethyl ether = 5/1); 95.3% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH = 80 /20, 1.0 ml min^{-1}, λ = 270 nm, t_r (major) = 5.04 min, t_r (minor) = 5.47 min]; $[\alpha]_D^{25}$ = −17.5 (*c* = 1.29, $CHCl_3$). IR (KBr) ν: 3360, 2955, 1745, 1593, 1535, 1360, 1165, 762, 744, 525 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.52 (s, 3H), 3.68 (s, 3H), 3.70 (m, 3H), 4.14 (d, *J* = 5.7 Hz, 1H), 5.83–5.85 (m, 1H), 6.81 (d, *J* = 9.2 Hz, 1H), 6.97 (t, *J* = 8.0 Hz, 1H), 7.08 (q, *J* = 7.4 Hz, 3H), 7.24–7.28 (m, 1H), 7.38 (m, *J* = 7.8 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 168.3, 167.1, 165.0, 161.5, 159.5, 151.2, 128.9, 126.7, 124.5, 121.9, 118.3, 115.8, 115.6, 53.6, 53.2, 18.4; ^{19}F-NMR (470 MHz, $CDCl_3$) δ: −117.8. Analysis calculated for $C_{20}H_{19}FN_2SO_4$: C, 59.69; H, 4.76; N, 6.96. Found: C, 59.59; H, 4.52; N, 6.91.

Dimethyl 2-((4-methylbenzo[*d*]thiazol-2-ylamino)(2-chlorophenyl)methyl)malonate (3o).



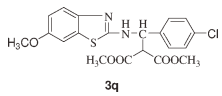
(*R*)-(−)-3o, this product was obtained as a colorless oil from a reaction catalyzed by **Q-1** (10 mol %) at room temperature for 72 h; yield (85.8 mg, 82%) by preparative TLC (GF254 silica gel: hexane/ethyl ether = 5/1); 96.9% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH = 80/20, 1.0 ml min^{-1}, λ = 270 nm, t_r (major) = 4.78 min, t_r (minor) = 5.44 min]; $[\alpha]_D^{25}$ = −122.7 (*c* = 1.34, $CHCl_3$). IR (KBr) ν: 3367, 2951, 1745, 1539, 1492, 1355, 1251, 761, 586 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.52 (s, 3H), 3.66 (s, 3H), 3.76 (m, 3H), 4.18 (d, *J* = 4.6 Hz, 1H), 5.92 (q, *J* = 4.6 Hz, 1H), 6.96 (t, *J* = 7.4 H z, 1H), 7.06 (d, *J* = 7.4 Hz, 1H), 7.20–7.25 (m, 3H), 7.36–7.40 (m, 2H), 7.40–7.48 (m, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 168.5, 167.2, 165.1, 151.3, 129.9, 129.5, 128.3, 127.3, 126.7, 121.8, 118.3, 55.9, 54.1, 52.8, 18.4. Analysis calculated for $C_{20}H_{19}ClN_2SO_4$: C, 57.34; H, 4.57; N, 6.69. Found: C, 57.29; H, 4.46; N, 6.69.

Dimethyl 2-((6-methoxybenzo[*d*]thiazol-2-ylamino)(4-fluorophenyl)methyl)malonate (3p).



(*R*)-(−)-3p, this product can be obtained as a colorless oil from a reaction catalyzed by **Q-1**(10 mol %) at room temperature for 96 h; yield (84.6 mg, 81%) by preparative TLC (GF254 silica gel: hexane/ethyl ether = 3/1); 97.1% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH = 70/30, 1.0 ml min^{-1}, λ = 270 nm, t_r (major) = 7.96 min, t_r (minor) = 10.17 min]; $[\alpha]_D^{25}$ = −17.7 (*c* = 0.90, $CHCl_3$). IR (KBr) ν: 3373, 2953, 1755, 1602, 1539, 1438, 1222, 1157, 844, 812, 584 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.67 (s, 3H), 3.70 (s, 3H), 3.78 (m, 3H), 3.98 (d, *J* = 5.2 Hz, 1H), 5.64–5.67 (m, 1H), 6.84–6.87 (m, 2H), 7.00 (t, *J* = 8.6 Hz, 2H), 7.08 (d, *J* = 2.9 Hz, 1H), 7.35–7.41 (m, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 168.4, 167.2, 164.3, 163.4, 161.4, 155.5, 146.3, 134.4, 131.8, 128.4, 128.3, 119.8, 115.9, 115.7, 113.7, 105.3, 57.0, 56.0, 53.2, 52.9; ^{19}F-NMR (470 MHz, $CDCl_3$) δ: −113.9. Analysis calculated for $C_{20}H_{19}FN_2SO_5$: C, 57.41; H, 4.58; N, 6.69. Found: C, 57.45; H, 4.57; N, 6.79.

Dimethyl 2-((6-methoxybenzo[*d*]thiazol-2-ylamino)(4-chlorophenyl)methyl)malonate (3q).



(*R*)-(−)-3q, this product was obtained as a colorless oil from a reaction catalyzed by **Q-1** (10 mol %) at room temperature for 96 h; yield (85.8 mg, 79%) by preparative TLC (GF254 silica gel: hexane/ethyl ether = 3/1); 97.4% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH = 70/30, 1.0 ml min^{-1}, λ = 270 nm, t_r (major) = 8.16 min, t_r (minor) = 11.11 min]; $[\alpha]_D^{25}$ = −21.9 (*c* = 0.99, $CHCl_3$). IR (KBr) ν: 3346, 2951, 1747, 1607, 1543, 1435, 1151, 837, 825, 549 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.67 (s, 3H), 3.70 (s, 3H), 3.78 (s, 3H), 3.98 (d, *J* = 5.2 Hz, 1H), 5.66 (br, 1H), 5.85 (dd, *J* = 2.8 Hz, *J* = 1.5 Hz, 2H), 7.08 (d, *J* = 2.9 Hz, 1H), 7.25–7.34 (m, 4H), 7.40 (d, *J* = 8.6 Hz, 1H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 168.4, 167.2, 164.2, 155.5, 146.3, 137.2, 134.0, 131.8, 129.0, 128.0, 113.7, 105.3, 56.8, 55.6, 56.0, 53.2. Analysis calculated for $C_{20}H_{19}ClN_2O_5S$: C, 55.24; H, 4.40; N, 6.44. Found: C, 55.12; H, 4.36; N, 6.29.

Dimethyl 2-((6-methoxybenzo[*d*]thiazol-2-ylamino)(*p*-tolyl) methyl)malonate (3r).

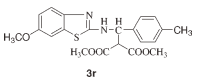


TABLE 2. Optimization of reaction conditions using catalyst Q-1[a]

Entry	**Q-1** (*x*mol %)	Temp (°C)	Solvent	Yield[b] (%)	*ee*[c] (%)
1	10	rt	THF	60	80.5
2	10	rt	Acetone	90	91.9
3	5	rt	DCM	85	95.9
4	10	rt	DCM	90	95.7
5	20	rt	DCM	90	96.4
[d] 6	10	−20	DCM	90	96.2

[a]Unless noted, reactions were run with 0.25 mmol of **1b**, 0.30 mmol of **2b** in 2.0 ml of solvent using 10 mol % of catalyst at room temperature for 60–72 h.
[b]Isolated yield after chromatographic purification.
[c]Determined by HPLC analysis (Chiralpak IA).
[d]Reaction was carried out for 72 h.

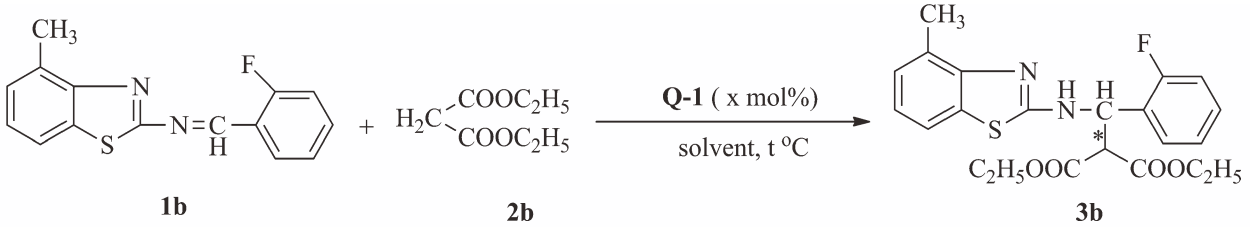


Fig. 3. Optimization of reaction condition using catalyst **Q-1**.

(*R*)-(−)-3r, this product was obtained as a colorless oil from a reaction catalyzed by **Q-1** (10 mol %) at room temperature for 96 h; yield (77.6 mg, 75%) by preparative TLC (GF254 silica gel: hexane/ethyl ether = 3/1); 97.1% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH = 70/30, 1.0 ml min^{-1}, λ = 270 nm, t_r (major) = 7.92 min, t_r (minor) = 9.52 min]; $[\alpha]_D^{25} = -18.6$ (c = 1.00, $CHCl_3$). IR (KBr) ν: 3346, 2999, 1747, 1607, 1541, 1494, 1149, 827, 561 cm^{-1}. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.28 (s, 3H), 3.64 (s, 3H), 3.67 (s, 3H), 3.78 (s, 3H), 4.00 (br, 1H), 5.59 (s, 1H), 6.84–6.85 (m, 1H), 7.06–7.11 (m, 3H), 7.26 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.6 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 168.4, 167.4, 164.8, 155.3, 146.4, 137.9, 135.5, 131.8, 129.5, 126.5, 119.7, 113.6, 105.3, 58.0, 55.9, 53.1, 52.8, 21.2. Analysis calculated for $C_{21}H_{22}N_2O_5S$: C, 60.85; H, 5.35; N, 6.76. Found: C, 60.75; H, 5.22; N, 6.79.

RESULTS AND DISCUSSION

For the initial exploration, we studied the role of various cinchona alkaloid-derived thiourea catalysts and commercial quinine and quinidine (Fig. 1) in a model asymmetric Mannich reaction of the imine **1b** with diethyl malonate **2b** to obtain β-amino ester **3b** (Table 1, Fig. 2) . The reason for employing imines derived from benzothiazole was to generate enantioenriched Mannich adducts with potent anti-plant viral activity. The importance of the heterocyclic benzothiazole unit in agricultural application was brought out explicitly in our recently written book in this field.[41] It may clearly be noted that presence of strong electron withdrawing substituent in the phenyl ring of the catalysts is a prerequisite to achieve high enantioselectivity through H-bond activation of the substrate. Thus, the newly prepared electron deficient catalysts (entries 5 and 8) and all the previously known catalysts (entries 3, 4, and 6) afforded high enantiomeric excess of the target ester with a slightly improved value being recorded for **Q-1**. The catalyst **Q-4** (entry 7), where the thiourea is not directly conjugated to the phenyl ring, offered much lower yield and enantioselectivity. Quite expectedly, both quinine and qunidine (entries 1 and 2), bearing single H-bond donor part, displayed inferior results compared to thiourea-derived catalysts **Q-1**,[32]**QD-1**,[32] **Q-2–Q-3**, and **Q-5**. The catalyst **Q-1** was selected for further investigation to optimize the reaction temperature, solvent, and catalyst loading and the results are provided in Table 2 and Figure 3.

TABLE 3. Asymmetric Mannich reaction of diethyl malonate 2b with benzothiazol-2-yl-benzylidene imines 1a-l catalyzed by Q-1 and QD-1[a]

Entry	R_1	R_2	Adduct	Time (h)	Yield (%)[b]	*ee* (%)[c]
1	H	4-CH_3	**3a**	72	90(80)	95.8(89.4)
2	*o*-F	4-CH_3	**3b**[d]	72	91(85)	96.0(90.0)
3	*o*-Cl	4-CH_3	**3c**	72	89(85)	94.8(90.0)
4	*p*-F	4-CH_3	**3d**	72	89(80)	95.0(90.2)
5	*p*-Cl	4-CH_3	**3e**	72	85(80)	95.2(85.9)
6	H	6-OCH_3	**3f**	96	81(72)	98.5(95.8)
7	*o*-F	6-OCH_3	**3g**	96	86(74)	98.2(96.0)
8	*o*-Cl	6-OCH_3	**3h**	96	86(73)	97.9(96.3)
9	*p*-F	6-OCH_3	**3i**	96	81(66)	98.5(91.5)
10	*p*-Cl	6-OCH_3	**3j**	96	81(65)	98.1(95.6)
11	*p*-CH_3	6-OCH_3	**3k**	96	70(66)	98.4(97.7)
12	*o*-OCH_3	6-OCH_3	**3l**	96	71(65)	89.4(98.2)

[a]Unless otherwise stated, reactions were conducted with 0.25 mmol of **1a–l** and 0.30 mmol of **2b** in 2.0–3.0 ml of DCM in the presence of 10 mol % catalyst at room temperature for 72–96 h. The results (ee and yield) in parentheses were obtained with **QD-1**.
[b]Isolated yields after chromatographic purification.
[c]Determined by chiral HPLC analysis (Chiralpak IA).
[d]Absolute configuration of **(−)-3b** obtained in presence of **Q-1** was determined to be *R* by single crystal X-Ray structure analysis.

Out of the three solvents (THF, acetone, and DCM) selected for the study, DCM afforded better selectivity and yield to the product. The optimal result could be achieved at room temperature with 10 mol % catalyst loading. The reaction at lower temperature took much longer reaction time without significant gain on enantioselectivity.

Having established the proper reaction conditions, different imines **1a–l** bearing benzothiazole moiety were reacted with diethyl malonate by using 10 mol % of **Q-1** or **QD-1** as chiral catalyst in methylene chloride at room temperature for 72–96 h to provide the title β-amino esters **3a–l** in excellent yields and high enantioselectivity (Table 3 and Fig. 4) . Similar to our observation with the pair of enantiomers quinine and quinidine (Table 1, entries 1 and 2), **Q-1** was found more effective compared to **QD-1** in terms of yield and *ee* values. The enantioenriched β-amino esters can easily be converted into their corresponding β-amino acids without any significant loss of enantioselectivity by following standard procedures.[19,21]

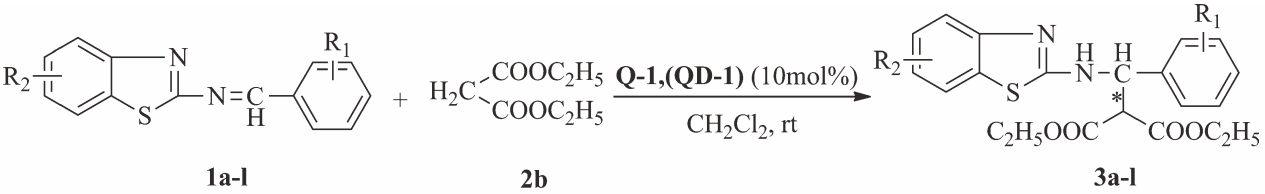


Fig. 4. Asymmetric Mannich reaction of diethyl malonate **2b** with benzothiazol-2-yl-benzylidene imines **1a–l** catalyzed by **Q-1** and **QD-1**.

TABLE 4. Enantioselective Mannich reaction of dimethyl malonate 2a with heterocyclic imines (1a-c, 1i-k) catalyzed by Q-1[a]

Entry	R_1	R_2	Adduct	Time (h)	Yield (%)[b]	*ee* (%)[c]
1	H	4-CH_3	**3m**	72	74	95.3
2	*o*-F	4-CH_3	**3n**	72	85	95.3
3	*o*-Cl	4-CH_3	**3o**	72	82	96.9
4	*p*-F	6-OCH_3	**3p**	96	81	97.1
5	*p*-Cl	6-OCH_3	**3q**	96	79	97.4
6	*p*-CH_3	6-OCH_3	**3r**	96	75	97.1

[a]Unless otherwise noted, reactions were run with 0.25 mmol of **1a–c, 1i–k,** and 0.30 mmol of **2a** in 2.0–3.0 ml of DCM in the presence of 10 mol % catalyst **Q-1** at room temperature for 72–96 h.
[b]Isolated yields after chromatographic purification.
[c]Determined by chiral HPLC analysis (Chiralpak IA).

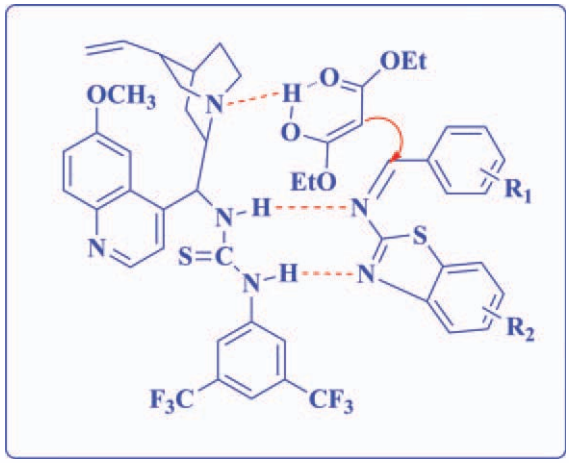


Fig. 6. Proposed stereochemical mode. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

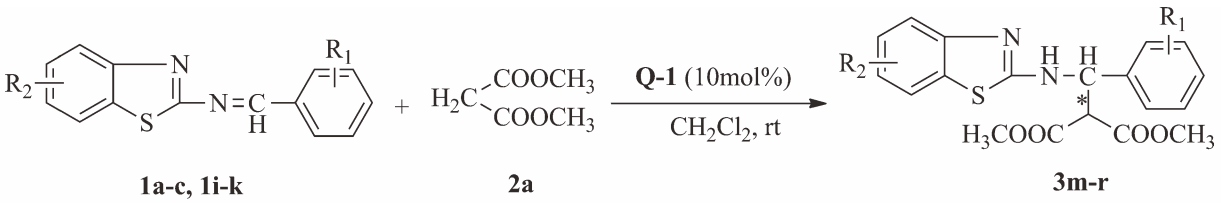


Fig. 5. Enantioselective Mannich reaction of dimethyl malonate **2a** with heterocyclic imines (**1a–c**, **1i–k**) catalyzed by **Q-1**.

Substituent effects of different groups (R_1) in the aromatic ring of the aldehydic part of the imine were usually insignificant on enantioselectivity, whereas imines derived from 2-amino-4-methylbenzothiazole displayed slightly higher reactivity compared to the one obtained from 2-amino-6-methoxybenzothiazole.

Six different benzothiazol-2-yl-benzylidene imines (**1a–c, 1i–k**) were then subjected to catalytic Mannich reaction with dimethyl malonate **2a** affording **3m–r** in excellent yields (74–85%) and high enantiomeric excess (95.3–97.4%) as shown in Table 4 and Figure 5. The chiral HPLC chromatograms of the title α-aminophosphonates are provided in Supporting Information.

Furthermore, the absolute configuration of the Mannich reaction product **(−)-3b** was unambiguously confirmed as *R* by X-ray crystallographic, which was reported in our Previous work.[42] Crystallographic data for the structure reported in this article have been deposited with the Cambridge Crystallographic Data Centre (CCDC-781779).

Based on the observed stereochemistry and previously reported modes of activation through bifunctional cinchona based thiourea catalysts, a simultaneous activation model of two imine functionalities and the enol form of the malonate is proposed. The nucleophilic attack of the active methylene on the electrophilic carbon of imine via six membered stable enol form is facilitated through hydrogen bond interaction by the tertiary amine part of the catalyst. At the same time, synergistic activation of the imines through H-bond donor thiourea leading to an eight membered cyclic transition state appears to control the stereochemical outcome of the reaction (Fig. 6).

In conclusion, suitably designed cinchona alkaloid-derived thiourea catalysts have been found highly effective in the enantioselective Mannich reaction of benzothiazol-2-yl-benzylidene imines with malonates. The resulting novel β-amino esters bearing benzothiazole moiety are obtained in high yields and excellent enantioselectivities (up to 98% *ee*). The reaction itself features simple experimental procedures under benign conditions and is completely atom-economic in character. We believe that this method provides an efficient route for the preparation of chiral β-amino esters derivatives, and the availability of these compounds should facilitate medicinal chemical studies in various fields. Simultaneous activation of both the imine groups and malonate by the bifunctional catalyst seems to control the sterochemical outcome. Further studies on the scope of new catalyst **Q-5** in other asymmetric transformations and anti-plant viral activities of the Mannich products are currently underway.

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