Chiral Cinchona Alkaloid-Thiourea Catalyzed Mannich Reaction for Enantioselective Synthesis of β-Amino Ketones Bearing Benzothiazol Moiety

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Mannich reactions of imine with acetylacetone were effectively catalyzed by the modified chiral cinchona alkaloid-derived thiourea. The reactions led to chiral *β*-amino carbonyl compounds in high yields and good enantioselectivities. The study demonstrated for the first time that Mannich reactions of unmodified acetylacetone with heterocyclic imine derived from benzothiazole can be promoted by chiral bifunctional organocatalyst.

Keywords asymmetric addition, *β*-amino ketones, Mannich reaction, chiral cinchona alkaloid-derived thiourea

Introduction

Enantiomerically pure *β*-amino ketones are valuable and widely used chiral building blocks for the asymmetric synthesis of nitrogen-containing biologically active molecules and natural products.[1] For example, *β*-amino ketones not only can serve as key precursors of 1,3-amino alcohols,[2] *γ*-aryl amines[3] and 1,3-diamines,[4] but also can be employed in the synthesis of various alklaloids through the intramolecular Mannich cyclization reactions.[5] Moreover, it is worth noting that the introduction of benzothiazole units into a molecule often produces significant changes in its chemical, and biological properties,[6] and some of them are commercially used for plant protection *e.g.* benthiazole as an agricultural fungicide, mefenacet as a potent herbicide and dufulin as an anti-plant virus agent. In this context, the design of new synthetic methodologies for the asymmetric synthesis of *β*-amino ketones is of considerable current interest. The Mannich reactions, a typical carbon-carbon bond forming reaction, involving aldehydes, amines (or directly imines), and enolizable ketones are widely utilized chemical transformations for constructing *β*-amino ketones,[7] which can be realized via chiral metal complex catalysis and small chiral organic molecules ranging from simple proline and its related derivatives to axially chiral binaphthyl derived Bronsted acids, thioureas, and cinchona alkaloids.[8] Among various asymmetric organocatalysts, chiral thiourea hydrogen-bond donors as well as the cinchona alkaloids and their derivatives have been found to be effective catalysts for the activation of imines for different enantioselective nucleophilic Mannich additions.[9]

In our previous publication,[10] we have developed a highly enantioselective cinchona alkaloid thiourea-catalyzed Mannich reaction to obtain novel *β*-amino ester derivatives containing benzoxazol units. In the present work, we report the application of cinchona alkaloid thiourea catalyst to asymmetric Mannich reaction of acetylacetone using the heterocyclic imine bearing benzothiazole unit.

Results and discussion

Based on these reports, we studied the role of bifunctional cinchona alkaloid-derived thiourea catalyst in an asymmetric Mannich reaction of acetylacetone with heterocyclic imine bearing benzothiazole unit. To our delight, the Mannich reaction proceeded smoothly in the presence of newly prepared catalyst **Q-1** at room temperature to afford the desired *β*-amino ketone **3a** with a benzothiazole unit in high yield and enantiomeric excess (97%, 83% respectively; Table 1, Entry 2). Among the tested catalysts, quinine (Table 1, Entry 1) which does not have any thiourea group, was found to be less effective compared to the synthetically prepared cinchona alkaloid-derived thiourea catalysts **Q-1** and **Q-2**.[11] It is worth noting that when cinchona alkaloid-derived thiourea catalysts **Q-1** and **Q-2** bear both hydrogen-bond donor thiourea and hydrogen-bond ac-

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ceptor tertiary amine groups, they are superior catalysts compared to quinine. Furthermore, the new catalyst **Q-1** was also proved to be superior compared to the previously known catalyst **Q-2** (Table 1, Entry 3) in terms of enantioselectivity.

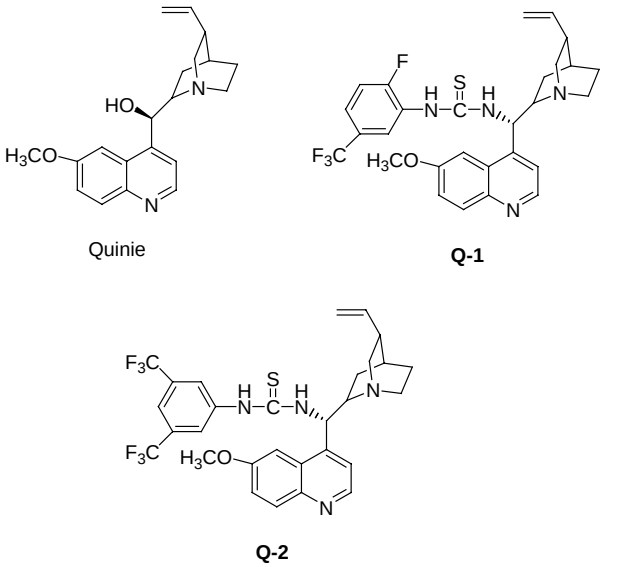
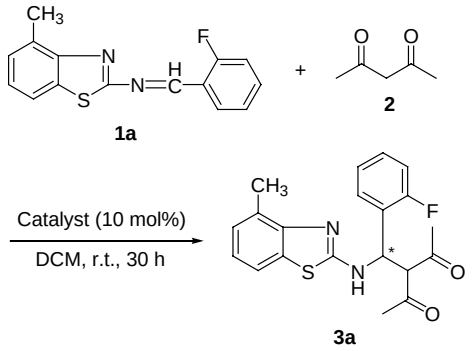


Figure 1 Commercial quinine and cinchona alkaloid derived thiourea catalysts.

Table 1 Catalyst evaluation for the direct addition of acetylacetone **2** to imine **1a**[a]

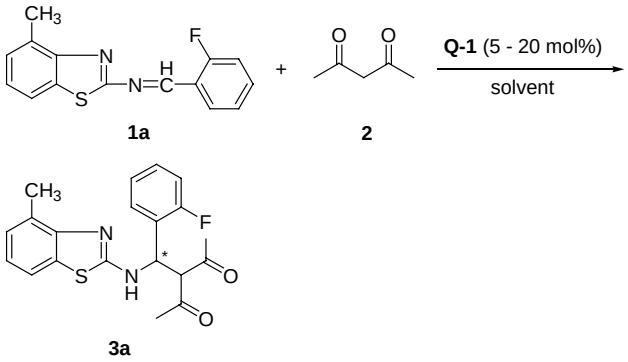


Entry	Catalyst	Solvent	Yield[b]/%	*ee*[c]/%
1	Quinine	DCM	93	71
2	**Q-1**	DCM	97	83
3	**Q-2**	DCM	98	74

[a] Reactions were run with **1a** (0.25 mmol) and **2** (0.30 mmol) in methylene chloride (2.0 mL) using 10 mol% of catalyst at room temperature for 30 h. [b] Isolated yield after chromatographic purification. [c] Determined by HPLC analysis (Chiralpak IA).

Therefore, a survey of the reaction parameters was conducted with the ideal catalyst **Q-1** at room temperature in various solvents such as acetone, THF, toluene and DCM. It can be observed that DCM afforded the product in better enantioselectivity and yield under the comparable conditions (Table 2, Entry 4). Next, catalyst loading was eventually reduced to 5 mol% in the same solvent with a slight rise in enantioselectivity (Table 2, Entry 5), whereas increasing catalyst loading to 20 mol% did not influence the outcome to a great extent (Table 2, Entry 6). Similarly, when the reaction temperature was lowered to 0 ℃, it took much longer time for its completion without any significant improvement in enantioselectivity (Table 2, Entry 7).

Table 2 Optimization of reaction conditions using catalyst **Q-1**[a]



Entry	Q-1/mol%	Solvent	Temperature/℃	Time/h	Yield[b]/%	*ee*[c]/%
1	10	acetone	r.t.	30	83	63
2	10	THF	r.t.	30	95	23
3	10	toluene	r.t.	30	94	82
4	10	DCM	r.t.	30	97	83
5	5	DCM	r.t.	30	95	84
6	20	DCM	r.t.	30	97	83
7	5	DCM	0	42	95	84

[a] Unless otherwise stated, reactions were run with **1a** (0.25 mmol) and **2** (0.30 mmol) in solvent (2.0 mL) using **Q-1**. [b] Isolated yields after chromatographic purification. [c] Determined by chiral HPLC analysis (Chiralpak IA).

Under optimized reaction conditions, we further enlarged the scope of this transformation using various combinations of heterocyclic imines bearing benzothiazole unit with acetylacetone. A series of enantioenriched title compounds were prepared as shown in Table 3. Substituent effects of different groups in the benzene ring of the heterocyclic imine bearing benzothiazole unit **1** were usually insignificant on enantioselectivity. As expected, heterocyclic imine bearing benzothiazole unit **1** bearing strongly electron-withdrawing groups in the benzene ring improved the rate and yields of the reaction due to excellent enantioselectivities, whereas the benzene ring possessing electron-donating groups afforded the corresponding *β*-amino carbonyl compounds in slightly lower yields and enantioselectivities. It is worth noting that when heterocyclic imines bearing benzothiazole unit **1** bear *ortho*-substituted benzene ring group, they afford addition products **3** in slightly higher enantioselectivities compared to those bearing *para*-substituted benzene ring group.

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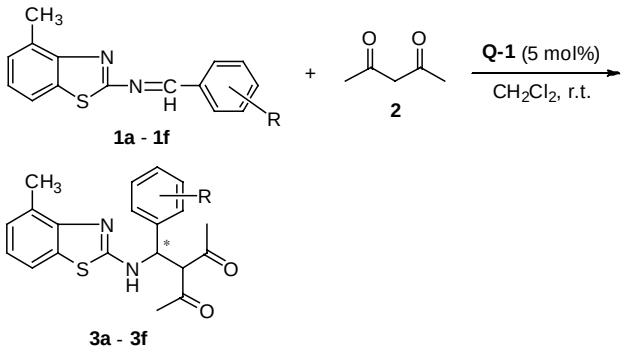
Table 3 Cinchona alkaloid-thiourea (**Q-1**) catalyzed asymmetric addition of acetylacetone **2** to imines **1a**—**1f**[a]



Entry	R	Adduct	Time/h	Yield[b]/%	*ee*[c]/%
1	*o*-F	**3a**	30	95	84
2	*o*-Cl	**3b**	42	94	80
3	*p*-F	**3c**	48	94	79
4	*p*-Cl	**3d**	60	91	72
5	*o*-OCH_3	**3e**	96	90	75
6	*o*-NO_2	**3f**	30	94	80

[a] Unless otherwise stated, reactions were run with **1a**—1**f** (0.25 mmol) and **2** (0.30 mmol) in methylene chloride (2.0 mL) using 5 mol% of **Q-1** at room temperature. [b] Isolated yields after chromatographic purification. [c] Determined by chiral HPLC analysis (Chiralpak IA).

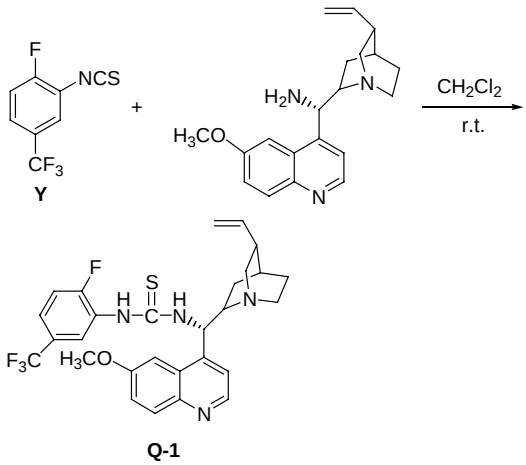
Experimental section

All reagents were used as received from commercial sources. IR spectra (KBr disks) were recorded on a Bruker Vector 22 spectrometer and reported in frequency of absorption (cm^{-1}). Proton, carbon and fluorine nuclear magnetic resonance (^1H, ^{19}F and ^{13}C NMR) spectra were recorded at room temperature on a JEOL-ECX 500 NMR spectrometer operating at 500, 470 and 125 MHz, respectively, using TMS as an internal standard. Elemental analysis was performed on an Elementar Vario-III CHN analyzer. High performance liquid chromatography (HPLC) analysis was performed on an Agilent 1100/1200 series instrument equipped with a quaternary pump, using a Daicel Chiralpak IA Column (250 mm×4.6 mm). UV absorption was monitored at 270 nm. Specific rotations were measured on a WZZ-2S digital polarimeter with a sodium lamp. Analytical TLC was performed on silica gel GF254. Column chromatographic purification was carried out using silica gel.

Preparation of catalyst Q-1 (Scheme 1)

To a mixture of 9-amino (9-deoxy) quinine (1.62 g, 5.0 mmol) and 5.0 mL of dry DCM, a solution of isothiocyanate (**Y** 1.10 g, 5.0 mmol) in 5.0 mL of dry DCM was added drop wise at room temperature. The reaction mixture was stirred for 10 h, the solvent was removed *in vacuo* and the residue was purified by column chromatography (Silica gel: Ethyl acetate/Methanol/aq. NH_4OH=300/10/1) to yield an amorphous solid, 70% yield, m.p. 124—126 ℃; $[\alpha]_D^{25}$ −111.6 (*c* 0.52, $CH_3CO_2C_2H_5$); ^1H NMR ($CDCl_3$, 500 MHz) δ: 8.65 (s, 1H), 8.01 (d, J = 24.6 Hz, 2H), 7.60 (brs, 1H), 7.37—7.43 (m, 2H), 7.19—7.27 (m, 2H), 5.67—5.71 (m, 1H), 4.97 (t, J=24.6 Hz, 2H), 3.96 (s, 3H), 3.16—3.24 (m, 3H), 2.74 (s, 2H), 2.32 (s, 1H), 1.64—1.69 (m, 2H), 1.37 (t, J=21.8 Hz, 1H), 1.25—1.26 (m, 1H), 0.94 (s, 1H); ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −61.8, −118.4; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 181.6, 158.0, 156.0, 147.5, 144.8, 140.8, 131.8, 124.5, 124.1, 121.9, 116.8, 114.9, 102.0, 60.4, 55.7, 54.9, 41.0, 39.1, 27.6, 27.2, 25.6; IR (KBr) v: 3223, 2927, 1622, 1508, 1332, 1261, 1124, 1029, 827, 717 cm^{-1}. Anal. calcd for $C_{28}H_{28}F_4N_4OS$: C 61.75, H 5.18, N 10.29; found C 61.38, H 4.84, N 10.03.

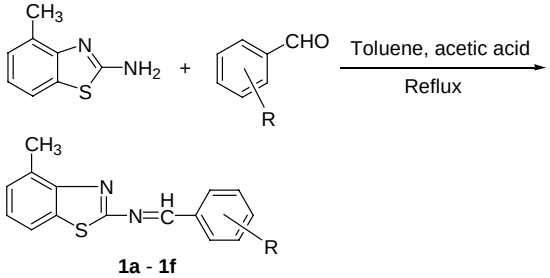
Scheme 1



Preparation of heterocyclic imines 1a—1f derived from benzothiazole (Scheme 2)

Substituted benzaldehyde (6 mmol) in 5 mL of toluene was added slowly with constant stirring to a 50 mL three necked round bottom flask containing 2-amino-4-methylbenzothiazole (0.82 g, 5 mmol), acetic acid (1 mL) and anhydrous toluene (10 mL). The reaction mixture was refluxed for 8 to 10 h, then cooled down to room temperature. The resulting precipitate was filtered, washed with petroleum ether, and recrystallized from a mixture solvent of ethanol and petroleum ether (3/1) to afford a yellow solid **1**.

Scheme 2



N-(2-Fluorobenzylidene)-4-methylbenzo[*d*]thiazol-2-amine (1a)

Reaction time 8 h, 64% yield, m.p. 101—102 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 9.30 (s, 1H, CH), 8.33—8.36 (m, 1H, ArH), 7.66—7.69 (m, 1H, ArH), 7.54—7.58 (m, 1H, ArH), 7.26—7.30 (m, 3H, ArH), 7.18 (t, J=9.2 Hz, 1H, ArH), 2.77 (s, 3H, CH_3); ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −118.6; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 170.4, 164.7, 162.7, 159.7, 151.2, 135.2, 133.6, 128.8, 127.2, 125.5, 124.9, 124.8, 119.2, 116.1, 18.6; IR (KBr) v: 2920, 1596, 1486, 1145, 768 cm^{-1}.

N-(2-Chlorobenzylidene)-4-methylbenzo[*d*]thiazol-2-amine (1b)

Reaction time 8 h, 60% yield, m.p. 106—108 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 9.43 (s, 1H, CH), 8.42 (d, J = 10.0 Hz, 1H, ArH), 7.65—7.68 (m, 1H, ArH), 7.46—7.50 (m, 2H, ArH), 7.38—7.41 (m, 1H, ArH), 7.28 (d, J=5.0 Hz, 2H, ArH), 2.77 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 170.2, 163.1, 151.2, 137.6, 134.0, 133.7, 130.3, 129.7, 127.4, 127.2, 125.6, 119.2, 18.6; IR (KBr) v: 2918, 1604, 1458, 1155, 758 cm^{-1}.

N-(4-Fluorobenzylidene)-4-methylbenzo[*d*]thiazol-2-amine (1c)

Reaction time 8 h, 62% yield, m.p. 99—100 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.96 (s, 1H, CH), 8.05—8.08 (m, 2H, ArH), 7.64—7.67 (m, 1H, ArH), 7.25—7.29 (m, 2H, ArH), 7.20 (t, J=8.6 Hz, 2H, ArH), 2.76 (s, 3H, CH_3); ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −104.3; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 170.3, 166.9, 164.9, 164.8, 151.2, 134.1, 133.4, 132.6, 132.5, 127.2, 125.4, 119.2, 116.5, 116.4, 18.6; IR (KBr) v: 2862, 1581, 1482, 1145, 837, 762 cm^{-1}.

N-(4-Chlorobenzylidene)-4-methylbenzo[*d*]thiazol-2-amine (1d)

Reaction time 9 h, 58% yield, m.p. 118—120 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.90 (s, 1H, CH), 7.98 (d, J=8.6 Hz, 2H, ArH), 7.65—7.67 (m, 1H, ArH), 7.49 (d, J=8.6 Hz, 2H, ArH), 7.26—7.28 (m, 2H, ArH), 2.76 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 170.1, 164.8, 151.1, 139.5, 134.2, 133.5, 133.3, 131.4, 129.5, 127.2, 125.4, 119.2, 18.6; IR (KBr) v: 2914, 1589, 1487, 1147, 837, 764 cm^{-1}.

N-(2-Methoxybenzylidene)-4-methylbenzo[*d*]thiazol-2-amine (1e)

Reaction time 10 h, 56% yield, m.p. 124—125 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 9.41 (s, 1H, CH), 8.36 (d, J=7.5 Hz, 2H, ArH), 7.66 (t, J=3.5 Hz, 1H, ArH), 7.55 (d, J=7.5 Hz, 1H, ArH), 7.27—7.25 (m, 2H, ArH), 7.09 (t, J=6.9 Hz, 1H, ArH), 6.99 (d, J=7.5 Hz, 1H, ArH), 3.96 (s, 3H, CH_3), 2.78 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 171.3, 162.7, 160.6, 151.2, 134.9, 133.8, 133.3, 128.8, 126.9, 125.1, 123.2, 121.0, 119.0, 111.2, 55.7, 18.6; IR (KBr) v: 2921, 1591, 1487, 1360, 1252, 1153, 837, 746 cm^{-1}.

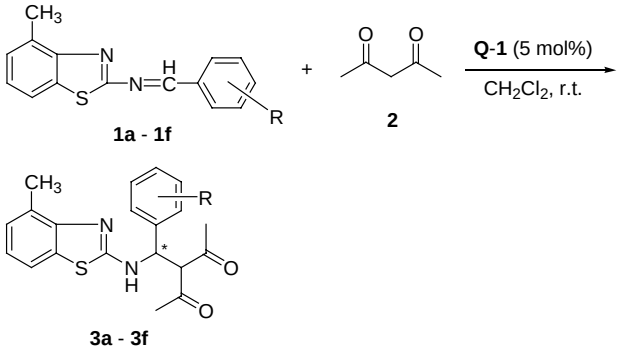
N-(2-Nitrobenzylidene)-4-methylbenzo[*d*]thiazol-2-amine (1f)

Reaction time 8 h, 72% yield, m.p. 171—172 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 9.53 (s, 1H, CH), 8.52 (d, J=7.5 Hz, 1H, ArH), 8.16 (d, J=8.0 Hz, 1H, ArH), 7.81 (t, J=7.5 Hz, 1H, ArH), 7.74—7.69 (m, 2H, ArH), 7.32 (d, J=5.8 Hz, 2H, ArH), 2.78 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 169.3, 161.7, 151.1, 149.8, 134.5, 133.9, 133.7, 132.8, 130.3, 129.4, 127.2, 125.8, 124.9, 119.2, 18.5; IR (KBr) v: 2961, 1566, 1521, 1331, 1167, 1138, 762 cm^{-1}.

General procedure for the enantioselective organocatalytic Minnich reaction of acetylacetone 2 with *N*-(substituted benzylidene)-4-methylbenzo[*d*]thiazol-2-amines 1a—1f (Scheme 3)

Acetylacetone (30.0 mg, 0.30 mmol) in DCM (2.0 mL) was added in one shot to a mixture of heterocyclic imine derived from benzothiazole **1a**—**1f** (0.25 mmol) and chiral catalyst **Q-1** (6.8 mg, 0.0125 mmol) at room temperature and stirred for 30—96 h. After completion of the reaction (as observed by TLC), the mixture was purified directly by preparative thin layer chromatography (GF254 silica gel: petroleum ether∶ethyl ether= 3∶7, V∶V) to yield **3a**—**3f**.

Scheme 3



3-{(2-Fluorophenyl)[(4-methylbenzo[*d*]thiazol-2-yl)-amino]methyl}pentane-2,4-dione (3a)

White solid, 95% yield, m.p. 115—116 ℃; 84% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH=99/1, 1.0 mL•min^{-1}, λ=270 nm, t_R(major)= 16.49 min, t_R(minor)=19.93 min], $[\alpha]_D^{25}$ +40.1 (c 1.04, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.46—7.43 (m, 1H, ArH), 7.40 (d, J=8.0 Hz, 1H, ArH), 7.27—7.23 (m, 1H, ArH), 7.11—7.05 (m, 1H, ArH), 7.00 (t, J=7.5 Hz, 1H, ArH), 6.48 (d, J=9.8 Hz, 1H, NH), 6.02 (t, J=9.2 Hz, 1H, CH), 4.48 (d, J=6.9 Hz, 1H, CH), 2.52 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.17 (s, 3H, CH_3); ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −118.1; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 204.3, 202.0, 164.4, 161.2, 159.3, 151.0, 130.5, 129.8, 129.7, 129.5, 126.6, 125.9, 125.8, 124.5, 122.0, 118.2, 115.8, 115.6, 70.1, 53.5, 30.5, 29.9, 18.3; IR (KBr) v: 3335, 2914, 1722, 1707, 1533, 1217, 1204, 765 cm^{-1}. Anal. calcd for $C_{20}H_{19}FN_2O_2S$: C 64.85, H 5.17,

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N 7.56; found C 64.92, H 5.32, N 7.68.

3-{(2-Chlorophenyl)[(4-methylbenzo[*d*]thiazol-2-yl)-amino]methyl}pentane-2,4-dione (3b)

White solid, 94% yield, m.p. 126—127 ℃; 80% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH=99/1, 1.0 mL•min^{-1}, λ=270 nm, t_R(major)=13.77 min, t_R(minor)=15.05 min], $[\alpha]_D^{25}$ +81.6 (*c* 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.49 (t, *J*=4.6 Hz, 1H, ArH), 7.40 (t, *J*=8.6 Hz, 2H, ArH), 7.23 (t, *J*=4.0 Hz, 2H, ArH), 7.08 (d, *J*=6.9 Hz, 2H, ArH), 6.98 (t, *J*=7.5 Hz, 1H, NH), 6.13 (dd, *J*=4.6, 9.2 Hz, 1H, CH), 4.51 (d, *J*=4.6 Hz, 1H, CH), 2.50 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.07 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 206.0, 202.7, 164.6, 151.3, 136.4, 132.6, 130.8, 130.1, 129.6, 129.5, 129.4, 127.6, 126.9, 122.1, 118.5, 67.5, 55.6, 32.4, 29.5, 18.5; IR (KBr) *v*: 3422, 2914, 1721, 1705, 1539, 1472, 1200, 770, 744 cm^{-1}. Anal. calcd for $C_{20}H_{19}ClN_2O_2S$: C 62.09, H 4.95, N 7.24; found C 62.13, H 5.21, N 7.34.

3-{(4-Fluorophenyl)[(4-methylbenzo[*d*]thiazol-2-yl)-amino]methyl}pentane-2,4-dione (3c)

White solid, 94% yield, m.p. 120—121 ℃; 79% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH=99/1, 1.0 mL•min^{-1}, λ=270 nm, t_R(major)=20.59 min, t_R(minor)=23.25 min], $[\alpha]_D^{25}$ +46.1 (*c* 1.06, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.40—7.37 (m, 3H, ArH), 7.09—6.97 (m, 4H, ArH), 6.57 (brs, 1H, NH), 5.72 (d, *J*=8.0 Hz, 1H, CH), 4.36 (d, *J*=8.1 Hz, 1H, CH), 2.50 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.19 (s, 3H, CH_3); ^{19}F NMR ($CDCl_3$, 470 MHz) δ: −113.6; ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 204.1, 204.0, 201.8, 164.5, 163.3, 161.3, 134.8, 130.5, 130.4, 129.3, 128.7, 128.6, 126.7, 122.0, 118.3, 115.9, 115.7, 72.3, 57.4, 30.4, 30.2, 18.3; IR (KBr) *v*: 3314, 2913, 1724, 1694, 1537, 1508, 1246, 843, 771 cm^{-1}. Anal. calcd for $C_{20}H_{19}FN_2O_2S$: C 64.85, H 5.17, N 7.56; found C 64.96, H 5.32, N 7.68.

3-{(4-Chlorophenyl)[(4-methylbenzo[*d*]thiazol-2-yl)-amino]methyl}pentane-2,4-dione (3d)

White solid, 91% yiled, m.p. 110—111 ℃; 72% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH=99/1, 1.0 mL•min^{-1}, λ=270 nm, t_R(major)=21.00 min, t_R(minor)=24.14 min], $[\alpha]_D^{25}$ −176.8 (*c* 1.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.39—7.26 (m, 5H, ArH), 7.09—6.97 (m, 2H, ArH), 6.52 (brs, 1H, NH), 5.77 (d, *J*=7.5 Hz, 1H, CH), 4.35 (d, *J*=7.5 Hz, 1H, CH), 2.50 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 2.21 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 204.3, 202.0, 164.7, 151.1, 137.8, 134.2, 130.7, 129.6, 129.2, 128.6, 127.0, 122.3, 118.5, 72.3, 57.6, 30.7, 30,4, 18.6; IR (KBr) *v*: 3360, 2916, 1722, 1697, 1533, 1487, 1200, 761, 745 cm^{-1}. Anal. calcd for $C_{20}H_{19}ClN_2O_2S$: C 62.09, H 4.95, N 7.24; found C 62.36, H 5.11, N 7.32.

3-{(2-Methoxyphenyl)[(4-methylbenzo[*d*]thiazol-2-yl)-amino]methyl}pentane-2,4-dione (3e)

White solid, 90% yiled, m.p. 119—120 ℃; 75% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH=99/1, 1.0 mL•min^{-1}, λ=270 nm, t_R(major)=16.91 min, t_R(minor)=18.46 min], $[\alpha]_D^{25}$ +93.2 (*c* 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.39 (t, *J*=8.0 Hz, 1H, ArH), 7.36 (dd, *J*=1.8, 8.1 Hz, 1H, ArH), 7.25 (dd, *J*=1.2, 7.5 Hz, 1H, ArH), 7.08 (d, *J*=6.9 Hz, 1H, ArH), 6.98 (t, *J*=7.5 Hz, 1H, ArH), 6.93—6.90 (m, 2H, ArH), 6.59 (d, *J*=10.3 Hz, 1H, NH), 5.77 (t, *J*=9.8 Hz, 1H, CH), 4.62 (d, *J*=8.0 Hz, 1H, CH), 3.97 (s, 3H, OCH_3), 2.53 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 2.13 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 204.1, 202.3, 165.4, 156.5, 151.1, 130.4, 130.0, 129.4, 129.1, 126.6, 125.8, 121.7, 121.0, 118.2, 110.9, 70.5, 56.8, 55.6, 30.2, 29.9, 18.3; IR (KBr) *v*: 3306, 3022, 1722, 1701, 1541, 1244, 766, 752 cm^{-1}. Anal. calcd for $C_{21}H_{22}N_2O_3S$: C 65.95, H 5.80, N 7.32; found C 66.26, H 5.91, N 7.62.

3-{(2-Nitrophenyl)[(4-methylbenzo[*d*]thiazol-2-yl)-amino]methyl}pentane-2,4-dione (3f)

Light yellow solid, 94% yiled, m.p. 118—120 ℃; 80% *ee* as determined by HPLC [Daicel Chiralpak IA, hexane/EtOH = 99/1, 1.0 mL•min^{-1}, λ = 270 nm, t_R(major) = 26.21 min, t_R(minor) = 30.80 min], $[\alpha]_D^{25}$ −223.3 (*c* 1.10, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.03 (dd, *J*=1.7, 8.6 Hz, 1H, ArH), 7.72 (dd, *J*=1.2 Hz, *J*=8.1 Hz, 1H, ArH), 7.58—7.54 (m, 1H, ArH), 7.44—7.41 (m, 1H, ArH), 7.36 (d, *J*=8.0 Hz, 1H, ArH), 7.29 (t, *J*=8.0 Hz, 1H, ArH), 7.05 (d, *J*=7.5 Hz, 1H, ArH), 6.98 (t, *J*=7.5 Hz, 1H, NH), 6.41 (dd, *J*=4.0, 9.2 Hz, 1H, CH), 4.61 (d, *J*=3.5 Hz, 1H, CH), 2.48 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 2.12 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 206.8, 202.9, 163.6, 150.8, 148.8, 135.3, 133.9, 130.5, 129.9, 129.7, 128.8, 126.6, 125.0, 122.1, 118.2, 67.2, 53.6, 32.9, 29.0, 18.0; IR (KBr) *v*: 3387, 2914, 1719, 1705, 1541, 1524, 1342, 745 cm^{-1}. Anal. calcd for $C_{20}H_{19}N_3O_4S$: C 60.44, H 4.82, N 10.57; found C 60.85, H 4.93, N 10.78.

Conclusions

We have developed an efficient catalytic Mannich reaction of heterocyclic imines derived from benzothiazole with acetylacetone in the presence of a chiral bifunctional organocatalyst **Q-1**. The resulting novel *β*-amino ketones bearing benzothiazole moiety are obtained in high yields (90%—95%) and good enantioselectivities (72%—84% *ee*). We anticipate that this method would be useful in the preparation of bioactive chiral *β*-amino ketone derivatives containing benzothiazole group, the availability of which should aid medicinal and chemical studies. Further studies on the scope of the new catalyst **Q-1** in other asymmetric transformations and anti-plant viral activity of the Mannich products are currently underway.

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