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Highly enantioselective Mannich reactions of imines with *tert*-butyl acetoacetate catalyzed by squaramide organocatalyst

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ABSTRACT

Highly enantioselective Mannich reactions of imines bearing a benzothiazole moiety with *tert*-butyl acetoacetate, catalyzed by a cinchona-based squaramide organocatalyst have been developed. The corresponding benzothiazole β-keto ester derivatives were obtained in high yields (up to 99%) and with excellent enantioselectivities (up to 98% ee).

1. Introduction

Chiral heterocyclic compounds are widely present in natural products and organic materials.[1] Compounds with a benzothiazole moiety have been widely studied.[2] It is well known that benzothiazoles and their derivatives are synthetically and biologically significant molecular structures. Many compounds containing a benzothiazole ring system exhibit significant antidiabetic, antitumor, anti-inflammatory, antimicrobial, anticonvulsant, antiviral, antitubercular, antioxidant, antimalarial, antiasthmatic, anthelmintic, and analgesic activities, and are diuretic.[3] Chiral heterocyclic compounds with a benzothiazole moiety can be obtained via reactions of imines bearing a benzothiazole moiety with various types of donors including nitroalkanes,[4] malonates, etc.[5,6] It is a challenging task to develop asymmetric Mannich reactions for synthesizing these compounds with multiple stereogenic stereocenters.

In recent years, chiral squaramides[7] have been successfully applied in various asymmetric reactions for the synthesis of compounds with multiple stereogenic centers.[8] Our group has reported a series of efficient enantioselective reactions catalyzed by squaramide organocatalysts.[9] Organocatalysts containing a tertiary amine group seem to be appropriate for substrate activation and stereochemical control in the projected Mannich reaction. Until now, the utilization of imimes bearing a benzothiazole moiety in the reaction to synthesize these compounds with multiple chiral stereocenters has not been reported on.

A direct asymmetric Mannich reaction[10] is an attractive approach toward the construction of highly functionalized amine-containing building blocks.[11] In particular, the direct addition of β-keto esters to imines affords multifunctional secondary amines.[12] Herein we report on an efficient direct enantioselective Mannich reaction of imines bearing a benzothiazole moiety with *tert*-butyl acetoacetate catalyzed by a cinchona-based squaramide organocatalyst; the corresponding products could be obtained with excellent enantioselectivities (up to 98% ee).

2. Results and discussion

Our investigation began with the addition of *tert*-butyl acetoacetate **2a** to imine **1a** bearing a benzothiazole moiety using a cinchona-based squaramide as the catalyst. The reaction was performed in the presence of 5 mol % catalyst **I** in CH_2Cl_2 for 24 h at room temperature, and the corresponding products were obtained in excellent yield (99%) and with high enantioselectivities (91% and 89% ee) (Table 1, entry 1). However, the diastereoselectivity was low (60:40 dr) and the diastereomers could not be separated by column chromatography. A series of acetoacetates were evaluated under these reaction conditions. Ethyl benzoylacetate **2b** gave low enantioselectivity (7% ee, the ee of the other isomer cannot be determined), but the corresponding product **3ab** was obtained in 98% yield (Table 1, entry 2). Ethyl acetylacetate **2c** and ethyl-2-cyclohexanoncarboxylate **2e** did not afford the corresponding products (Table 1, entries 3 and 5). When ethyl 2-methylacetoacetate **2d** was used, compound **3ad** was obtained in high yield with low enantioselectivities (85% yield, 29%, and 48% ee), while the diastereoselectivity ratio was only 37:63 (Table 2, entry 4). From the above results, the reaction of *tert*-butyl acetoacetate **2a** with imines bearing a benzothiazole moiety was selected as the optimal route.

In order to improve the enantioselectivity of product **3aa**, other four squaramide catalysts **II**–**V** (Fig. 1) were evaluated using 5 mol % catalyst loading in CH_2Cl_2 for 24 h at room temperature. When mono-CF_3 substituted quinine-based squaramide catalyst

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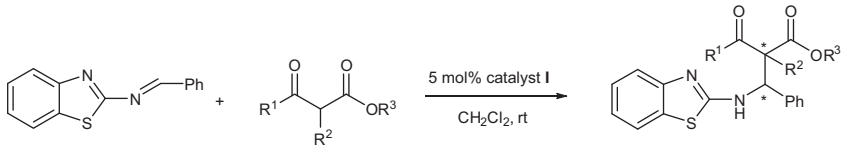
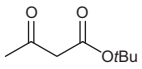
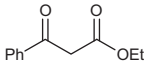
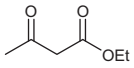
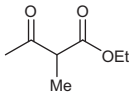
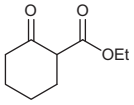
0957-4166/

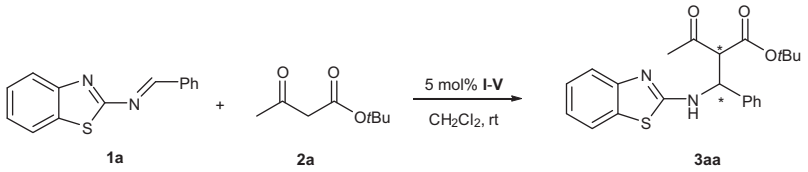
Table 1
Asymmetric Mannich reaction of imine **1a** with various acetoacetates[a]



Entry	Acetoacetate	Time (h)	Product	Yield[b] (%)	dr[c]	ee[d] (%)
1	 **2a**	18	**3aa**	99	60:40	91/89
2	 **2b**	18	**3ab**	98	51:49	7/nd
3	 **2c**	24	**3ac**	90	—	—
4	 **2e**	24	**3ad**	85	37:63	29/48
5	 **2f**	24	**3ae**	10	—	—

[a] Reaction conditions: imine **1a** (47.6 mg, 0.2 mmol) and acetoacetates **2** (0.2 mmol) in CH_2Cl_2 (1 mL) at room temperature.
[b] Isolated yield after column chromatography purification.
[c] Determined by chiral HPLC analysis.
[d] Enantiomeric excess was determined by chiral HPLC analysis using a Daicel Chiralpak IA or AD-H column. Nd: the ee cannot be determined.

Table 2
Screening of the organocatalysts for the enantioselective Mannich reaction of *tert*-butyl acetoacetate **2a** with imine **1a**[a]



Entry	Catalyst	Yield[b] (%)	dr[c]	ee[d] (%)
1	**I**	99	60:40	91/89
2	**II**	99	57:43	81/79
3	**III**	97	54:46	85/83
4	**IV**	96	49:51	59/53
5	**V**	99	49:51	86/82

[a] Reaction conditions: imine **1a** (47.6 mg, 0.2 mmol) and *tert*-butyl acetoacetate **2a** (0.2 mmol) in CH_2Cl_2 (1 mL) at room temperature.
[b] Isolated yield after column chromatography purification.
[c] Determined by chiral HPLC analysis.
[d] Enantiomeric excess was determined by chiral HPLC analysis using Daicel Chiralpak IA column.

II was used in this reaction, the corresponding product **3aa** was obtained in excellent yield (99%) and with high enantioselectivities (81% and 79% ee, 57:43 dr) (Table 2, entry 2). When C_2-symmetric quinine-based squaramide catalyst **III** was used, a high yield (97% yield) was obtained, the enantioselectivities were better than squaramide **II** (85% and 83% ee, 54:46 dr) (Table 2, entry 3).

Squaramide **IV** afforded the product in high yield, but the enantioselectivities were very low (59% and 53% ee, 49:51 dr) (Table 2, entry 4). The classical thiourea catalyst **V** was also evaluated in this reaction and afforded high enantioselectivities (86% and 82% ee, 49: 51 dr) (Table 2, entry 5). Squaramide **I** was chosen as the best catalyst for further evaluation in this Mannich reaction of imines bearing a heterocycle moiety with *tert*-butyl acetoacetate **2a**.

Next, the effect of the solvent, catalyst loading, and temperature were evaluated to find the optimal reaction conditions. The results are shown in Table 3. Five solvents were evaluated under the same reaction conditions (Table 3, entries 1–5). In $CHCl_3$ and $PhCH_3$, product **3aa** was obtained in excellent yields (99% and 98%) and with high enantioselectivities (84%, 82% ee, 58:42 dr and 86%, 80% ee, 57:43 dr) (Table 3, entries 2 and 3). When the reaction was performed in THF, the product was obtained in the same yield as with CH_2Cl_2 (99% yield), but the enantioselectivities were better

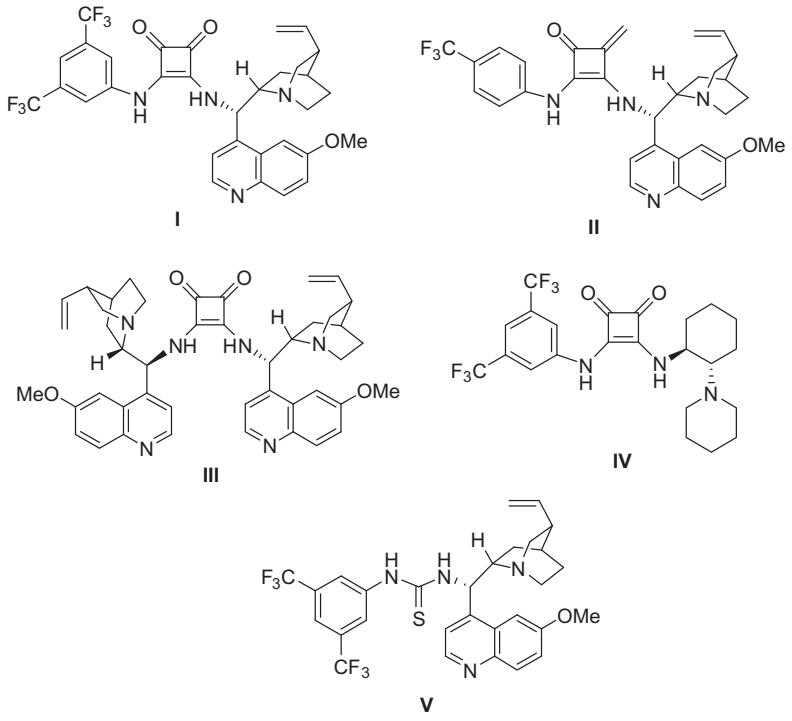
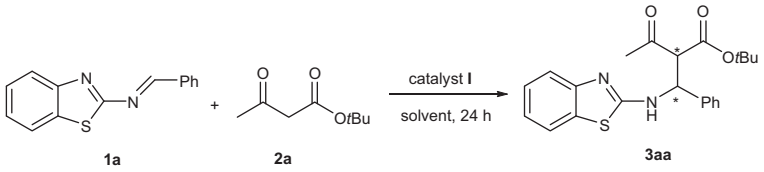


Figure 1. Organocatalysts screened.

Table 3
Optimization of reaction conditions for the enantioselective Mannich reaction of *tert*-butyl acetoacetate **2a** with imine **1a**[a]



1a **2a** **3aa**

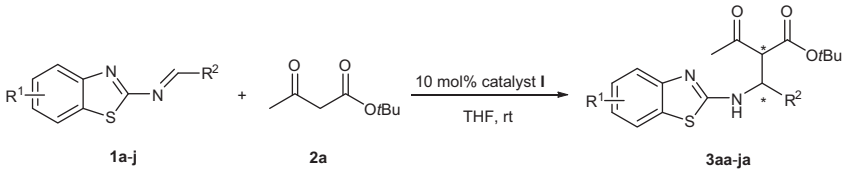
Entry	Solvent	Time (h)	Product	Yield[b] (%)	dr[c]	ee[d] (%)
1	CH_2Cl_2	rt	5	99	60:40	91/89
2	$CHCl_3$	rt	5	99	58:42	84/82
3	PhMe	rt	5	98	57:43	86/80
4	THF	rt	5	99	57:43	97/96
5	$ClCH_2CH_2Cl$	rt	5	99	56:44	70/67
6	THF	rt	2	98	54:46	94/93
7	THF	rt	1	96	55:45	80/79
8	THF	rt	10	99	58:42	98/98
9	THF	rt	15	99	52:48	98/98
10	THF	rt	20	99	56:44	98/98
11	THF	−15	10	0	—	—

[a] Reaction conditions: imine **1a** (47.6 mg, 0.2 mmol) and *tert*-butyl acetoacetate **2a** (0.2 mmol) in solvent (1 mL) for 24 h.
[b] Isolated yield after column chromatography purification.
[c] Determined by chiral HPLC analysis.
[d] Enantiomeric excess was determined by chiral HPLC analysis using Daicel Chiralpak IA column.

(97% and 96% ee, 57:43 dr) (Table 3, entry 4). In $ClCH_2CH_2Cl$, the product was obtained in 99% yield, but the enantioselectivities were reduced to 70% and 67% ee (56:44 dr) (Table 3, entry 5). Hence THF was selected as the best reaction medium. Catalyst loadings of 1, 2, 5, 10, 15, and 20 mol % were evaluated in the same reaction (Table 3, entries 4 and 6–10). The results indicated that 10 mol % catalyst loading was suitable for obtaining the best enantioselectivities (98% and 98% ee) (Table 3, entry 8). When the catalyst loading was enhanced to 15 and 20 mol %, the yields and enantioselectivities remained the same (Table 3, entries 9 and 10). Increasing the catalyst loading further had no beneficial effect on the enantioselectivity and diastereoselectivity. The catalyst loading was reduced to 2 and 1 mol %, which led to a decrease in the yields and enantioselectivities (Table 3, entries 6 and 7). When the reaction was performed at −15 °C, the product was not obtained. This suggests that the reaction temperature plays an important role in this catalytic asymmetric reaction. From the above evaluation, the optimal reaction conditions were determined as: 10 mol % catalyst **I**, in THF, at room temperature (Table 3, entry 8).

We next investigated the scope of this direct Mannich reaction. The results are shown in Table 4. Imines **1b**, **1c,** and **1d** bear differ-

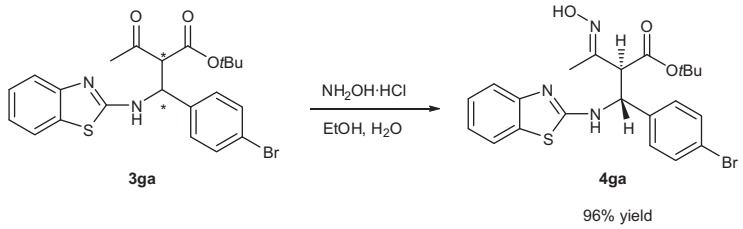
Table 4
Substrate scope of the enantioselective Mannich reaction of *tert*-butyl acetoacetate **2a** with imines **1**[a]



1a-j **2a** **3aa-ja**

Entry	R^1	R^2	Time (h)	Product	Yield[b] (%)	dr[c]	ee[d] (%)
1	H	C_6H_5	24	**3aa**	99	58:42	98/98
2	6-Me	C_6H_5	24	**3ba**	99	58:42	97/95
3	6-Cl	C_6H_5	24	**3ca**	98	48:52	98/97
4	6-MeO	C_6H_5	24	**3da**	99	59:41	95/96
5	H	4-$O_2NC_6H_4$	24	**3ea**	99	64:36	89/95
6	H	4-MeC_6H_4	24	**3fa**	98	64:36	92/92
7	H	4-BrC_6H_4	24	**3ga**	94	59:41	92/95
8	6-Cl	4-$O_2NC_6H_4$	48	**3ha**	92	57:43	95/95
9	6-Me	4-$O_2NC_6H_4$	48	**3ia**	90	64:36	94/94
10	6-MeO	2-$MeOC_6H_4$	48	**3ja**	97	98:2	83/nd

[a] Reaction conditions: imine **1a** (47.6 mg, 0.2 mmol) and *tert*-butyl acetoacetate **2a** (0.2 mmol) in THF (1 mL) at room temperature.
[b] Isolated yield after column chromatography purification.
[c] Determined by chiral HPLC analysis.
[d] Enantiomeric excess was determined by chiral HPLC analysis.



3ga **4ga**

96% yield

Scheme 1. The transformation of **3ga** to oxime **4ga**.

ent substituent (6-Me, 6-Cl, and 6-MeO) on the benzothiazole ring. The desired products were obtained in excellent yields and with excellent enantioselectivities (98–99% yield and 95–98% ee, respectively) (Table 4, entries 2–4). Imines **1e**–**1g** with various substituent groups (4-NO_2, 4-Me, 4-Br) on the benzene ring, gave slightly lower enantioselectivities compared with the imines substituted on the benzothiazole ring (94–99% yield and 89–95% ee, respectively) (Table 4, entries 5–7). Imines **1h** and **1i** have the same substituent (4-NO_2) on the benzene ring; the former gave slightly better results than the latter (92% yield and 95% ee vs 90% yield and 94% ee) (Table 4, entries 8 and 9). When the benzothiazole ring and benzene ring had the same substituent (MeO–), the corresponding product was obtained in excellent yield (99%) and with moderate enantioselectivities (83% ee, the ee of another isomer could not be determined) (Table 4, entry 10). The excellent diastereoselectivity (98:2 dr) may be ascribed to the steric hindrance of the 2-MeO substituent.

In order to ascertain the absolute configuration of these Mannich compounds with multiple stereogenic centers, product **3ga** was treated with hydroxylammonium chloride in aqueous EtOH to afford the corresponding oxime **4ga** (Scheme 1).[13] The major diastereomer of the product **4ga** was separated directly by silica gel column chromatography and its absolute configuration was determined as (*R*,*S*) on the basis of X-ray crystal structure analysis (Fig. 2).[14]

On the basis of the activation mode and previous related work on this Mannich reaction, we have proposed a possible mechanism for this reaction (Fig. 3). The enol form of *tert*-butyl acetoacetate **2a** is activated and deprotonated by the basic nitrogen atom of the tertiary amine Lewis base in the squaramide organocatalyst **I**. The heteroaromatic imine is activated through double hydrogen bonding between the two N atoms in the imine and the two NH group in the squaramide. The nucleophilic attack of the active methylene of *tert*-butyl acetoacetate on imine **1a** in the most favored direction via the following transition state, and product **3aa** is obtained with excellent enantioselectivities.

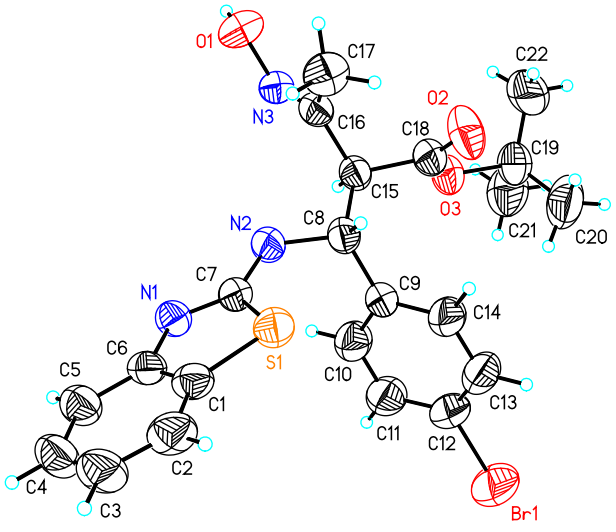


Figure 2. X-ray crystal structure of the major diastereomer of **4ga**.

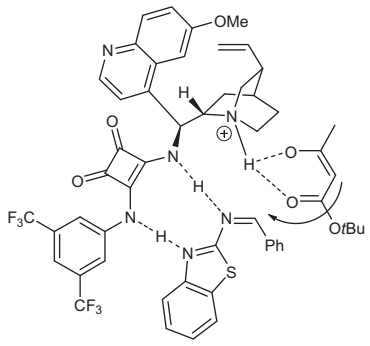


Figure 3. Proposed transition state for the asymmetric Mannich reaction of *tert*-butyl acetoacetate **2a** with imine **1a**.

3. Conclusion

In conclusion, a highly enantioselective Mannich reaction of *tert*-butyl acetoacetate with imines bearing a benzothiazole has been developed using a squaramide as organocatalyst. The corresponding benzothiazole keto ester derivatives were obtained in high to excellent yields and with high to excellent enantioselectivities in most cases. The squaramide catalyst proved to be better than the corresponding thiourea catalyst for this reaction. Further studies on squaramide-catalyzed asymmetric reactions are currently underway in our laboratory.

4. Experimental

4.1. General methods

Commercially available compounds were used without further purification. Solvents were dried according to standard procedures. Column chromatography was carried out using silica gel (200–300 mesh). Melting points were measured with a XT-4 melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded with Varian Mercury-plus 400 or Bruker AVIII 400 MHz spectrometers, while the ^{13}C NMR spectra were recorded at 100 MHz. Infrared spectra were obtained with a Perkin Elmer Spectrum One FT-IR spectrometer. Optical rotations were measured with a WZZ-3 or Krüss P8000 polarimeter at the indicated concentration with unit g/100 mL. The enantiomeric excesses (ee) of the products were determined by chiral HPLC analysis using Aglient HP 1200 instrument (*n*-hexane-2-propanol as eluent).

4.2. Materials

Squaramide catalysts **I**–**III**,[9a] **IV**[9c] were prepared according to the literature.

4.3. General procedure for the asymmetric Mannich reaction

Imine **1a** (47.6 mg, 0.2 mmol), *tert*-butyl acetoacetate (31.6 mg, 0.2 mmol), and catalyst **I** (12.6 mg, 0.02 mmol) in THF (1 mL) were stirred at room temperature for 24–48 h. After the reaction was complete, the mixture was separated directly by silica gel column chromatography with petroleum ether–ethyl acetate (5:1) as the eluant, and a pure product was obtained.

4.3.1. *tert*-Butyl 2-((benzo[*d*]thiazol-2-ylamino)(phenyl)methyl)-3-oxobutanoate 3aa

Compound **3aa** was obtained according to the general procedure as a yellow solid (78.0 mg, 99% yield); mp 42–43 °C. It was analyzed to determine the diastereoselectivity and enantioselectivity of the reaction (58:42 dr, 98% ee (major), 98% ee (minor)) by HPLC (IA column, *n*-hexane-2-propanol 80:20, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: t_{major} = 10.6 min, t_{minor} = 8.8 min; minor diastereomer: t_{major} = 16.6 min, t_{minor} = 15.1 min; $[\alpha]_D^{25}$ = +9.6 (*c* 1.03, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major + minor) = 7.53 (d, *J* = 7.6 Hz, 1H, ArH), 7.50 (d, *J* = 8.4 Hz, 1H, ArH), 7.42–7.38 (m, 2H, ArH), 7.30 (t, *J* = 7.4 Hz, 2H, ArH), 7.26–7.22 (m, 2H, ArH), 7.07–7.03 (m, 1H, ArH), 5.74 (d, *J* = 5.6 Hz, 0.5H, CH), 5.60 (d, *J* = 6.8 Hz, 0.5H, CH), 4.13 (d, *J* = 5.6 Hz, 0.5H, CH), 3.98 (d, *J* = 5.6 Hz, 0.5H, CH), 2.27 (s, 1.5H, CH_3), 2.19 (s, 1.5H, CH_3), 1.33 (s, 4.5H, CH_3), 1.30 (s, 4.5H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ (major + minor) = 203.5, 200.9, 167.9, 166.5, 166.2, 165.9, 152.0, 138.8, 130.7, 128.6, 127.8, 126.9, 126.6, 125.8, 121.7, 121.6, 120.7, 119.2, 119.1, 83.1, 65.3, 64.5, 58.4, 57.3, 30.8, 29.1, 27.7, 27.6 ppm. IR (KBr): *v* 3357, 3063, 2978, 2931, 1718, 1599, 1540, 1496, 1454, 1445, 1394, 1369, 1249, 1147, 1079, 1017, 883, 839, 753, 725, 699 cm^{-1}.

4.3.2. *tert*-Butyl 2-(((6-methylbenzo[*d*]thiazol-2-yl)amino)(phenyl)methyl)-3-oxobutanoate 3ba

Compound **3ba** was obtained according to the general procedure as a yellow solid (81.1 mg, 99% yield); mp 53–55 °C. It was analyzed to determine the diastereoselectivity and enantioselectivity of the reaction (58:42 dr, 97% ee (major), 95% ee (minor)) by HPLC (AD-H column, *n*-hexane-2-propanol 80:20, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: t_{major} = 16.0 min, t_{minor} = 11.7 min; minor diastereomer: t_{major} = 27.8 min, t_{minor} = 20.6 min; $[\alpha]_D^{25}$ = +5.3 (*c* 1.28, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major + minor) = 7.32 (t, *J* = 8.8 Hz, 3H, ArH), 7.26–7.20 (m, 3H, ArH), 7.18–7.14 (m, 1H, ArH), 6.98 (d, *J* = 8.0 Hz, 1H, ArH), 5.65 (d, *J* = 5.2 Hz, 0.5H, CH), 5.49 (d, *J* = 6.4 Hz, 0.5H, CH), 4.05 (d, *J* = 6.4 Hz, 0.5H, CH), 3.90 (d, *J* = 5.6 Hz, 0.5H, CH), 2.28 (s, 3H, CH_3), 2.20 (s, 1.5H, CH_3), 2.11 (s, 1.5H, CH_3), 1.26 (s, 4.5H, CH_3), 1.23 (s, 4.5H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ (major + minor) = 203.6, 176.9, 168.0, 166.0, 165.7, 165.5, 162.3, 150.0, 139.0, 138.9, 131.5, 130.8, 128.6, 127.8, 127.1, 126.92, 126.82, 126.6, 120.8, 118.83, 118.75, 83.0, 65.3, 64.4, 58.4, 57.3, 30.8, 29.1, 27.7, 27.6, 21.1 ppm. IR (KBr): *v* 3404, 2966, 2922, 1713, 1608, 1572, 1540, 1470, 1454, 1369, 1261, 1146, 1096, 1028, 809, 698 cm^{-1}.

4.3.3. *tert*-Butyl 2-(((6-chlorobenzo[*d*]thiazol-2-yl)amino)(phenyl)methyl)-3-oxobutanoate 3ca

Compound **3ca** was obtained according to the general procedure as a yellow solid (84.2 mg, 98% yield); mp 44–46 °C. It was analyzed to determine the diastereoselectivity and enantioselectivity of the reaction (52:48 dr, 97% ee (major), 98% ee (minor)) by HPLC (AD-H column, *n*-hexane-2-propanol 80:20, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: t_{major} = 21.0 min, t_{minor} = 18.2 min; minor diastereomer: t_{major} = 12.2 min, t_{minor} = 11.7 min; $[\alpha]_D^{25}$ = +11.5 (*c* 1.26, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major + minor) = 7.40–7.36 (m, 1H, ArH), 7.33–7.28 (m, 3H, ArH), 7.22 (t, *J* = 7.4 Hz, 2H, ArH), 7.16 (t, *J* = 7.2 Hz, 1H, ArH), 7.12–7.09 (m, 1H, ArH), 5.63 (d, *J* = 5.6 Hz, 0.5H, CH), 5.52 (d, *J* = 6.4 Hz, 0.5H, CH), 4.05 (d, *J* = 6.8 Hz, 0.5H, CH), 3.89 (d, *J* = 6.0 Hz, 0.5H, CH), 2.19 (s, 1.5H, CH_3), 2.12 (s, 1.5H, CH_3), 1.26 (s, 4.5H, CH_3), 1.22 (s, 4.5H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ (major + minor) = 204.4, 200.7, 167.6, 166.7, 165.6, 138.4, 138.3, 128.64, 128.62, 128.1, 128.0, 127.0, 126.9, 126.7, 126.35, 126.27, 120.43, 120.40, 119.5, 119.2, 114.2, 83.21, 83.15, 65.3, 64.7, 58.6, 57.7, 30.6, 29.4, 27.9, 27.7, 27.5, 21.5 ppm. IR (KBr): *v* 3385, 2979, 1713, 1599, 1540, 1494, 1447, 1394, 1369, 1258, 1146, 1094, 1051, 1026, 969, 918, 813, 753, 699 cm^{-1}.

4.3.4. *tert*-Butyl 2-(((6-methoxybenzo[*d*]thiazol-2-yl)amino)(phenyl)methyl)-3-oxobutanoate 3da

Compound **3da** was obtained according to the general procedure as a yellow solid (84.3 mg, 99% yield); mp 45–47 °C. It was analyzed to determine the diastereoselectivity and enantioselectivity of the reaction (59:41 dr, 95% ee (major), 96% ee (minor)) by HPLC (AD-H column, *n*-hexane-2-propanol 80:20, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: t_{major} = 16.9 min, t_{minor} = 14.4 min; minor diastereomer: t_{major} = 39.9 min, t_{minor} = 36.3 min; $[\alpha]_D^{25}$ = +11.3 (*c* 1.44, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major + minor) = 7.34–7.30 (m, 3H, ArH), 7.23 (t, *J* = 7.4 Hz, 2H, ArH), 7.16 (t, *J* = 7.0 Hz, 1H, ArH), 7.00 (dd, J_1 = 5.2 Hz, J_2 = 2.4 Hz, 1H, ArH), 6.77 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H, ArH), 5.63 (d, *J* = 5.6 Hz, 0.5H, CH), 5.47 (d, *J* = 6.8 Hz, 0.5H, CH), 4.05 (d, *J* = 6.4 Hz, 0.5H, CH), 3.89 (d, *J* = 5.6 Hz, 0.5H, CH), 3.75–3.65 (m, 4H, CH and OCH_3), 2.20 (s, 1.5H, CH_3), 2.12 (s, 1.5H, CH_3), 1.26 (s, 4.5H, CH_3), 1.23 (s, 4.5H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ (major + minor) = 203.3, 201.0, 167.9, 165.9, 165.1, 164.6, 155.3, 146.0, 138.8, 131.5, 128.6, 127.9, 127.8, 127.0, 126.6, 119.5, 119.2, 113.5, 105.2, 83.1, 65.3, 64.6, 58.5, 57.4, 55.8, 30.7, 29.2, 27.7, 27.6 ppm. IR (KBr): ν 3366, 3063, 2978, 2934, 2871, 1717, 1605, 1576, 1545, 1471, 1439, 1393, 1369, 1261, 1223, 1146, 1056, 1028, 833, 810, 754, 699 cm^{-1}.

4.3.5. *tert*-Butyl 2-((benzo[*d*]thiazol-2-ylamino)(4-nitrophenyl)methyl)-3-oxobutanoate 3ea

Compound **3ea** was obtained according to the general procedure as a yellow solid (87.3 mg, 99% yield); mp 54–55 °C. It was analyzed to determine the diastereoselectivity and enantioselectivity of the reaction (64:36 dr, 89% ee (major), 95% ee (minor)) by HPLC (AD-H column, *n*-hexane-2-propanol 80:20, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: t_{major} = 18.9 min, t_{minor} = 20.9 min; minor diastereomer: t_{major} = 39.1 min, t_{minor} = 43.7 min; $[\alpha]_D^{25}$ = +21.0 (*c* 2.50, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major + minor) = 8.07 (d, *J* = 8.4 Hz, 2H, ArH), 7.54 (d, *J* = 8.4 Hz, 1H, ArH), 7.51 (d, *J* = 8.4 Hz, 1H, ArH), 7.46 (t, *J* = 8.0 Hz, 1H, ArH), 7.40 (d, *J* = 8.4 Hz, 1H, ArH), 7.17 (t, *J* = 7.8 Hz, 1H, ArH), 7.02–6.98 (m, 1H, ArH), 5.83 (d, *J* = 5.6 Hz, 0.5H, CH), 5.73 (d, *J* = 6.4 Hz, 0.5H, CH), 4.12 (d, *J* = 6.4 Hz, 0.5H, CH), 3.93 (d, *J* = 5.2 Hz, 0.5H, CH), 2.24 (s, 1.5H, CH_3), 2.16 (s, 1.5H, CH_3), 1.28 (s, 4.5H, CH_3), 1.25 (s, 4.5H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ (major + minor) = 203.2, 200.1, 167.6, 165.6, 165.4, 151.7, 147.3, 146.6, 130.6, 128.0, 127.8, 125.9, 123.7, 122.2, 122.1, 120.8, 119.3, 119.2, 83.8, 64.6, 63.8, 57.4, 56.5, 30.7, 29.1, 27.7, 27.6 ppm. IR (KBr): ν 3369, 3063, 2978, 2933, 1713, 1598, 1524, 1538, 1456, 1445, 1369, 1347, 1288, 1249, 1146, 1015, 841, 754, 726, 700 cm^{-1}.

4.3.6. *tert*-Butyl 2-((benzo[*d*]thiazol-2-ylamino)(*p*-tolyl)methyl)-3-oxobutanoate 3fa

Compound **3fa** was obtained according to the general procedure as a yellow solid (80.3 mg, 98% yield); mp 54–56 °C. It was analyzed to determine the diastereoselectivity and enantioselectivity of the reaction (64:36 dr, 92% ee (major), 92% ee (minor)) by HPLC (AD-H column, *n*-hexane-2-propanol 80:20, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: t_{major} = 12.4 min, t_{minor} = 11.2 min; minor diastereomer: t_{major} = 19.2 min, t_{minor} = 13.9 min; $[\alpha]_D^{25}$ = −9.7 (*c* 1.62, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major + minor) = 8.22 (d, *J* = 9.2 Hz, 1H, ArH), 8.04 (d, *J* = 6.0 Hz, 1H, ArH), 7.73 (t, *J* = 7.0 Hz, 1H, ArH), 7.49–7.41 (m, 3H, ArH), 7.20–7.16 (m, 1H, ArH), 7.01 (t, *J* = 7.6 Hz, 1H, ArH), 5.87 (d, *J* = 5.2 Hz, 0.5H, CH), 5.76 (d, *J* = 6.0 Hz, 0.5H, CH), 4.14 (d, *J* = 6.4 Hz, 0.5H, CH), 3.94 (d, *J* = 5.2 Hz, 0.5H, CH), 2.26 (s, 1.5H, CH_3), 2.16 (s, 1.5H, CH_3), 1.29 (s, 4.5H, CH_3), 1.26 (s, 4.5H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ (major + minor) = 203.3, 200.2, 167.8, 165.7, 165.5, 165.4, 151.8, 148.3, 141.6, 141.5, 133.2, 129.6, 125.9, 122.9, 122.8, 122.2, 122.1, 122.0, 121.7, 120.85, 120.81, 119.42, 119.35, 83.9, 64.6, 63.8, 57.2, 56.2, 30.8, 29.0, 27.72, 27.65 ppm. IR (KBr): ν 3369, 3066, 2978, 2931, 1713, 1599, 1532, 1480, 1456, 1444, 1369, 1350, 1284, 1249, 1146, 1098, 1017, 929, 901, 839, 806, 754, 726, 692 cm^{-1}.

4.3.7. *tert*-Butyl 2-((benzo[*d*]thiazol-2-ylamino)(4-bromophenyl)methyl)-3-oxobutanoate 3ga

Compound **3ga** was obtained according to the general procedure as a yellow solid (89.3 mg, 94% yield); mp 68–70 °C. It was analyzed to determine the diastereoselectivity and enantioselectivity of the reaction (65:35 dr, 90% ee (major), 96% ee (minor)) by HPLC (IA column, *n*-hexane-2-propanol 80:20, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: t_{major} = 9.1 min, t_{minor} = 10.7 min; minor diastereomer: t_{major} = 20.4 min, t_{minor} = 22.4 min; $[\alpha]_D^{25}$ = +29.4 (*c* 2.31, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major + minor) = 7.48–7.41 (m, 2H, ArH), 7.37–7.32 (m, 2H, ArH), 7.23–7.16 (m, 3H, ArH), 7.01–6.96 (m, 1H, ArH), 5.61 (d, *J* = 5.6 Hz, 0.5H, CH), 5.50 (d, *J* = 6.8 Hz, 0.4H, CH), 4.02 (d, *J* = 6.8 Hz, 0.5H, CH), 3.86 (d, *J* = 5.2 Hz, 0.5H, CH), 2.19 (s, 1.5H, CH_3), 2.13 (s, 1.5H, CH_3), 1.28 (s, 4.5H, CH_3), 1.24 (s, 4.5H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ (major + minor) = 203.3, 200.5, 167.7, 166.1, 165.9, 165.8, 151.9, 151.8, 138.1, 131.7, 128.7, 128.4, 125.9, 121.9, 121.8, 120.8, 119.2, 119.1, 83.4, 65.1, 64.3, 57.8, 56.8, 30.7, 29.2, 27.7, 27.6 ppm. IR (KBr): ν 3362, 2979, 2934, 1901, 1709, 1599, 1532, 1488, 1444, 1408, 1394, 1369, 1248, 1147, 1073, 1011, 829, 817, 755, 726, 668, 541 cm^{-1}.

4.3.8. *tert*-Butyl 2-((6-chlorobenzo[*d*]thiazol-2-ylamino)(4-nitrophenyl)methyl)-3-oxobutanoate 3ha

Compound **3ha** was obtained according to the general procedure as a yellow solid (87.4 mg, 92% yield); mp 70–72 °C. It was analyzed to determine the diastereoselectivity and enantioselectivity of the reaction (57:43 dr, 95% ee (major), 95% ee (minor)) by HPLC (IA column, *n*-hexane-2-propanol 80:20, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: t_{major} = 13.4 min, t_{minor} = 20.7 min; minor diastereomer: t_{major} = 30.3 min, t_{minor} = 27.5 min; $[\alpha]_D^{25}$ = +21.8 (*c* 2.34, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): (major + minor) = 8.17 (dd, J_1 = 8.4 Hz, J_2 = 4.0 Hz, 2H, ArH), 7.60 (dd, J_1 = 8.4 Hz, J_2 = 5.6 Hz, 2H, ArH), 7.51–7.50 (m, 1H, ArH), 7.36 (dd, J_1 = 8.8 Hz, J_2 = 4.0 Hz, 1H, ArH), 7.20 (d, *J* = 8.4 Hz, 1H, ArH), 5.91 (d, *J* = 4.8 Hz, 0.5H, CH), 5.84 (d, *J* = 5.6 Hz, 0.5H, CH), 4.20 (d, *J* = 6.0 Hz, 0.5H, CH), 3.99 (d, *J* = 5.2 Hz, 0.5H, CH), 2.34 (s, 1.5H, CH_3), 2.22 (s, 1.5H, CH_3), 1.35 (s, 9H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ (major + minor) = 203.6, 200.0, 167.8, 165.5, 165.4, 150.4, 147.4, 146.4, 131.9, 131.8, 127.8, 127.7, 127.3, 126.5, 126.4, 123.8, 120.4, 120.03, 119.95, 84.0, 77.2, 64.4, 63.4, 57.3, 56.3, 31.0, 29.0, 28.1, 27.6 ppm. IR (KBr): ν 3369, 2979, 2934, 1713, 1598, 1540, 1492, 1447, 1394, 1369, 1347, 1252, 1146, 1052, 1014, 964, 855, 816, 767, 749, 700 cm^{-1}.

4.3.9. *tert*-Butyl 2-(((6-methylbenzo[*d*]thiazol-2-yl)amino)(4-nitrophenyl)methyl)-3-oxobutanoate 3ia

Compound **3ia** was obtained according to the general procedure as a yellow solid (81.9 mg, 90% yield); mp 67–69 °C. It was analyzed to determine the diastereoselectivity and enantioselectivity of the reaction (64:36 dr, 94% ee (major), 94% ee (minor)) by HPLC (AD-H column, *n*-hexane-2-propanol 80:20, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: t_{major} = 24.0 min, t_{minor} = 21.5 min; minor diastereomer: t_{major} = 44.5 min, t_{minor} = 35.7 min; $[\alpha]_D^{25}$ = +39.0 (*c* 1.18, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major + minor) = 8.15 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 2H, ArH), 7.60 (t, *J* = 8.8 Hz, 2H, ArH), 7.38–7.34 (m, 2H, ArH), 7.06 (d, *J* = 8.4 Hz, 1H, ArH), 5.90 (d, *J* = 5.2 Hz, 0.5H, CH), 5.80 (d, *J* = 6.0 Hz, 0.5H, CH), 4.20 (d, *J* = 6.4 Hz, 0.5H, CH), 4.00 (d, *J* = 5.6 Hz, 0.5H, CH), 2.36 (s, 3H, CH_3), 2.32 (s, 1.5H, CH_3), 2.22 (s, 1.5H, CH_3), 1.35 and 1.34 (s, 9H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ (major + minor) = 203.1, 200.1,

167.6, 165.6, 164.9, 164.7, 149.6, 147.3, 146.7, 132.0, 131.9, 128.0, 127.8, 127.1, 123.7, 120.8, 119.0, 118.9, 83.8, 64.6, 63.8, 57.4, 56.4, 30.7, 29.0, 27.72, 27.65, 21.1 ppm. IR (KBr): ν 3369, 3203, 2979, 2930, 1713, 1608, 1571, 1538, 1526, 1467, 1394, 1369, 1347, 1281, 1254, 1147, 1014, 964, 855, 815, 752, 738, 700 cm^{-1}.

4.3.10. *tert*-Butyl 2-(((6-methoxybenzo[*d*]thiazol-2-yl)amino)(2-methoxyphenyl)methyl)-3-oxobutanoate 3ja

Compound **3ja** was obtained according to the general procedure as a yellow solid (88.4 mg, 97% yield); mp 55–57 °C. It was analyzed to determine the diastereoselectivity and enantioselectivity of the reaction (major 83% ee, the ee of minor diastereomer cannot be determined) by HPLC (AD-H column, *n*-hexane-2-propanol 80:20, flow rate 1.0 mL/min, detection at 254 nm): major diastereomer: t_{major} = 14.7 min, t_{minor} = 11.0 min; minor diastereomer: t_R = 6.6 min; $[\alpha]_D^{25}$: +21.4 (*c* 1.02, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ (major + minor) = 7.40–7.33 (m, 3H, ArH), 7.22 (t, *J* = 7.2 Hz, 1H, ArH), 7.04 (d, *J* = 7.6 Hz, 1H, ArH), 6.88 (t, *J* = 7.6 Hz, 2H, ArH), 5.74 (t, *J* = 7.2 Hz, 0.5H, CH), 5.54 (t, *J* = 8.0 Hz, 0.5H, CH), 4.35 (d, *J* = 8.0 Hz, 0.5H, CH), 4.21 (d, *J* = 6.4 Hz, 0.5H, CH), 3.91 and 3.89 (s, 3H, OCH_3), 2.34 (s, 3H, OCH_3), 2.24 (s, 1.5H, CH_3), 2.22 (s, 1.5H, CH_3), 1.32 (s, 4.5H, CH_3), 1.25 (s, 4.5H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ (major + minor) = 203.0, 201.3, 167.8, 166.1, 165.7, 156.8, 156.3, 150.0, 149.9, 131.2, 130.7, 129.8, 129.2, 129.0, 128.5, 126.8, 126.2, 125.9, 120.7, 120.6, 118.7, 110.7, 110.4, 82.6, 82.4, 63.4, 62.9, 57.1, 55.4, 54.8, 30.2, 28.9, 27.7, 27.5, 21.1 ppm. IR (KBr): ν 3377, 2977, 2930, 2839, 1713, 1607, 1571, 1543, 1491, 1466, 1394, 1369, 1281, 1245, 1147, 1024, 840, 814, 753, 563, 516 cm^{-1}.

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14. CCDC-978450 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.