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Enantioselective Aza-Henry Reaction of Imines Bearing a Benzothiazole Moiety Catalyzed by a *Cinchona*-Based Squaramide

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Abstract: An efficient enantioselective aza-Henry reaction of nitroalkanes to imines bearing a benzothiazole moiety catalyzed by a *Cinchona*-based squaramide has been developed. In the reaction of imines, the corresponding products were obtained in good to excellent yields (up to 99%) with excellent enantioselectivities (up to >99% *ee*) for most of the aromatic substituted imines. The imines with electron-withdrawing groups gave better yields than those bearing electron-donating groups in the aza-Henry reaction. Moreover, a one-pot three-component enantioselective aza-Henry reaction using 2-aminobenzothiazoles, aldehydes, and nitromethane was also developed. Moderate to good yields and high enantioselectivities were obtained in the one-pot cases (up to 98% *ee*).

Keywords: asymmetric catalysis; aza-Henry reaction; benzothiazoles; imines; organocatalysis; squaramides

Introduction

The aza-Henry reaction is an important and efficient method for carbon-carbon bond formation in organic chemistry.[1] The resulting β-nitro amines are useful synthetic intermidiates, which can be conveniently converted to vicinal diamines by reduction of the nitro group, or to α-amino acids derivatives through Nef reactions.[2] In recent years, many studies on the catalytic asymmetric aza-Henry reaction have been reported. Shibasaki et al. reported that heterobimetallic complexes with lanthanide BINOL systems promoted the aza-Henry reaction to give β-nitro amines with high enantioselectivity.[3] Jørgensen et al. also developed a catalytic asymmetric version of this reaction with bisoxazoline copper(II) complexes.[4] Trost et al. used dinuclear Zn as a novel catalyst in the addition of nitroalkanes to carbamate-protected imines and α,β-unsaturated imines giving α-amino products in high enantiomeric excess.[5] Various types of organocatalysts have also been developed in recent years, such as chiral thioureas,[6] chiral phase-transfer catalysts,[7] chiral proton catalysts,[8] chiral phosphoric acid[9] and other types of catalysts.[10] However, the substrates of most reports are limited to aldimines or ketoimines using simple amino counterparts.[11] The utilization of heterocyclic imines or imines containing heterocyclic amino counterparts has been rarely reported.[12] Among the heterocyclic compounds, benzothiazole is an important heterocyclic moiety found in many natural products and medically important synthetic molecules.[13] Benzothiazole derivatives often exhibit a wide spectrum of significant biological activities.[14] In this context, the syntheses of these compounds have attracted more attation, but only a few catalytic asymmetric approaches were reported.[15]

Despite the successful catalytic systems reported, the development of new and efficient ones for aza-Henry reactions is still in demand. Chiral squaramide catalysts like thiourea catalysts have great potential in catalytic asymmetric reactions. These molecules exhibit a dual donor-acceptor hydrogen bonding ability.[16] Chiral squaramides as a novel type of good hydrogen-bonding organocatalysts have been successfully applied in various asymmetric reactions.[17] Recently, our group also reported the chiral squaramide-catalyzed asymmetric Michael addition of nitroalkanes to nitroalkenes.[17g] In spite of the progress in this area, the application of this class of organocatalysts in aza-Henry reactions has never been reported. We envisioned that *Cinchona* alkaloid-based squaramides as bifunctional organocatalysts can be used to catalyze the aza-Henry reaction, because both the electrophilic and nucleophilic components in this reaction can be

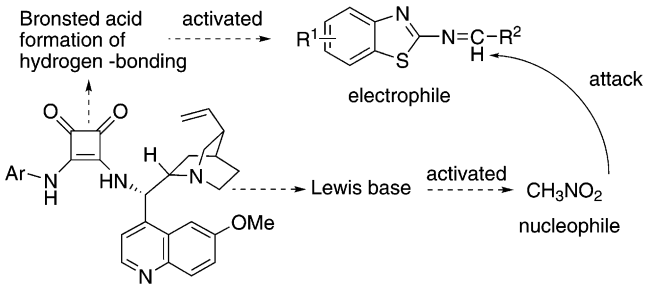


Figure 1. Activation mode of *Cinchona* alkaloid-squaramide.

activated by Brønsted acid and Lewis base functionalities of squaramide organocatalysts simultaneously (Figure 1).[18] The match of these two backbones embedded in the squaramide catalysts is critical for promoting the enantioselectivity. Based on the activation mode and previous related work, the application of *Cinchona*-based squaramides in this reaction was investigated. Herein we would like to report the first highly enantioselective aza-Henry reaction catalyzed by a *Cinchona*-based squaramide organocatalyst (Figure 2).

Results and Discussion

Initially, we selected the addition of nitromethane **2a** to imine **1a** bearing a benzothiazole moiety as a model reaction. The model reaction proceeded well in CH_2Cl_2 in the presence of 5 mol% catalyst **I** for 48 h at room temperature to furnish the corresponding adduct **3a** with very low enantioselectivity (9% *ee*) albeit with good yield (70%) (Table 1, entry 1). The primary amine catalyst **II** derived from quinine **I** also afforded very low enantioselectivity (10% yield, 8% *ee*) (Table 1, entry 2). Next, several quinine-based organocatalysts were prepared and their capacity to promote the enantioselective aza-Henry reaction was evaluated. Squaramide catalysts **III**–**V** all gave product **3a** in high yields and excellent enantioselectivities (99% *ee*). When the C_2-symmetrical quinine-based squaramide catalyst **VI** was used, high yield and enantioselectivity (91% yield, 94% *ee*) were obtained (Table 1, entry 6). In addition, a control experiment with quinine-based thiourea catalyst **VII** was performed for comparing the catalytic activity. Under otherwise identical conditions, thiourea **VII** gave the corresponding adduct **3a** in 90% yield with 97% *ee* (Table 1, entry 7). This result indicates that the squaramide catalyst exhibits a slightly higher reactivity and enantioselectivity than the corresponding thiourea. From the above evaluation, squaramide **III** was identified as the optimal catalyst.

With the optimal catalyst in hand, we investigated the effects of solvent, catalyst loading, and temperature in a search for the optimal conditions. The results are shown in Table 2. Variation of the solvents had a very limited effect on the reaction process. The common solvents such as PhMe, THF, $ClCH_2CH_2Cl$, $CHCl_3$, and CCl_4 all afforded high yields (87–92%) and excellent enantioselectivities (99% *ee*) (Table 2, entries 2–6). This observation demonstrates that the catalytic system for the aza-Henry reaction is well tolerant towrds solvent variation. The solvent CH_2Cl_2 was still the best reaction medium. Noticeably, when the reaction was carried out in neat nitromethane, the product **3a** in high yield with excellent enantioselectivity (80% yield, 99% *ee*) was achieved (Table 2, entry 7). Subsequently, the effect of catalyst loading was investigated. We chose the amount of catalyst **III** with the four gradients (10 mol%, 5 mol%, 2 mol%,

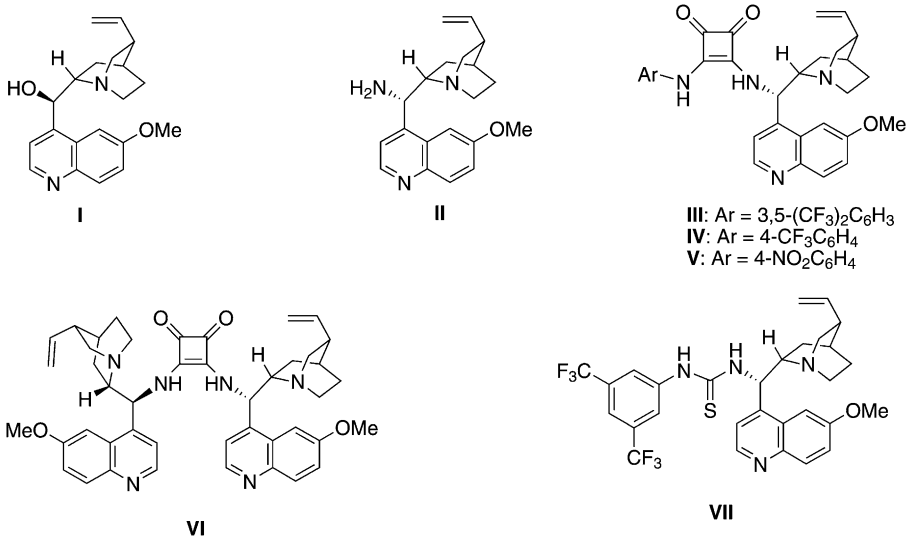
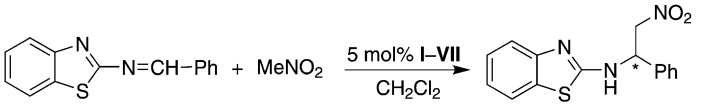


Figure 2. The screened organocatalysts.

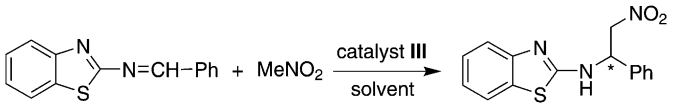
Table 1. Screening of organocatalysts for the enantioselective aza-Henry of nitromethane **2a** to imine **1a**.[a]



Entry	Catalyst	Time [h]	Yield [%][b]	*ee* [%][c]
1	**I**	48	70	9
2	**II**	72	10	8
3	**III**	48	95	99
4	**IV**	48	92	99
5	**V**	48	94	99
6	**VI**	48	91	94
7	**VII**	48	90	97

[a] Unless noted otherwise, reactions were carried out with imine **1a** (47.6 mg, 0.2 mmol) and nitromethane **2a** (122 mg, 2.0 mmol) in CH_2Cl_2 (2 mL) at room temperature.
[b] Isolated yield after column chromatographic purification.
[c] Determined by HPLC analysis using a Daicel Chiralpak IB column.

Table 2. Optimization of reaction conditions for the enantioselective aza-Henry of nitromethane **2a** to imine **1a**.[a]



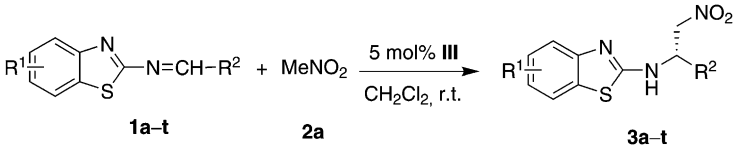
Entry	Solvent	Temperarture [°C]	Time [h]	Loading [mol%]	Yield [%][b]	*ee* [%][c]
1	CH_2Cl_2	r.t.	48	5	95	99
2	PhMe	r.t.	48	5	92	99
3	THF	r.t.	48	5	87	99
4	$(CH_2Cl)_2$	r.t.	48	5	90	99
5	$CHCl_3$	r.t.	72	5	92	99
6	CCl_4	r.t.	48	5	91	99
7	$MeNO_2$	r.t.	48	5	80	99
8	CH_2Cl_2	r.t.	48	10	94	99
9	CH_2Cl_2	r.t.	48	2	67	98
10	CH_2Cl_2	r.t.	48	1	60	96
11	CH_2Cl_2	0	72	5	88	94
12	CH_2Cl_2	40	72	5	90	98

[a] Reactions were carried out with imine **1a** (47.6 mg, 0.2 mmol) and nitromethane **2a** (122 mg, 2.0 mmol) in CH_2Cl_2 (2 mL).
[b] Isolated yield after column chromatographic purification.
[c] Determined by HPLC analysis using a Daicel Chiralpak IB column

and 1 mol%) (Table 2, entries 8–10). The presence of 10 mol% or 5 mol% catalyst almost gave the same results (Table 2, entry 8). When 2 mol% catalysts were used, the enantioselectivity was decreased to 98% *ee*. On further reduction of the catalyst loading the enantioselectivity was decreased to 96% *ee*. At the same time the yields also decreased obviously (67% and 60% yield, respectively) (Table 2, entries 9 and 10). In the asymmetric reaction, the influence of the temperature cannot be ignored. So the aza-Henry reactions were conducted at 0 °C and 40 °C, respectively. However, the enantioselectivity at 0 °C or 40 °C was lower than the one at room temperature (Table 2, entries 11 and 12). Neither high nor low temperature is favourable for this reaction. So we identified that the optimal reaction conditions were: CH_2Cl_2, in the presence of 5 mol% catalyst **III**, and at room temperature.

With the optimal reaction conditions established, we explored the scope of this aza-Henry reaction. The results are shown in Table 3. Imines **1a**–**1f** derived from aromatic aldehydes bearing electron-neutral, electron-withdrawing or electron-donating substitutions reacted smoothly with nitromethane to afford the corresponding adducts in good-to-high yields with

Table 3. Substrate scope of the enantioselective aza-Henry of nitromethane **2a** to imines **1**.[a]



1a–t **2a** **3a–t**

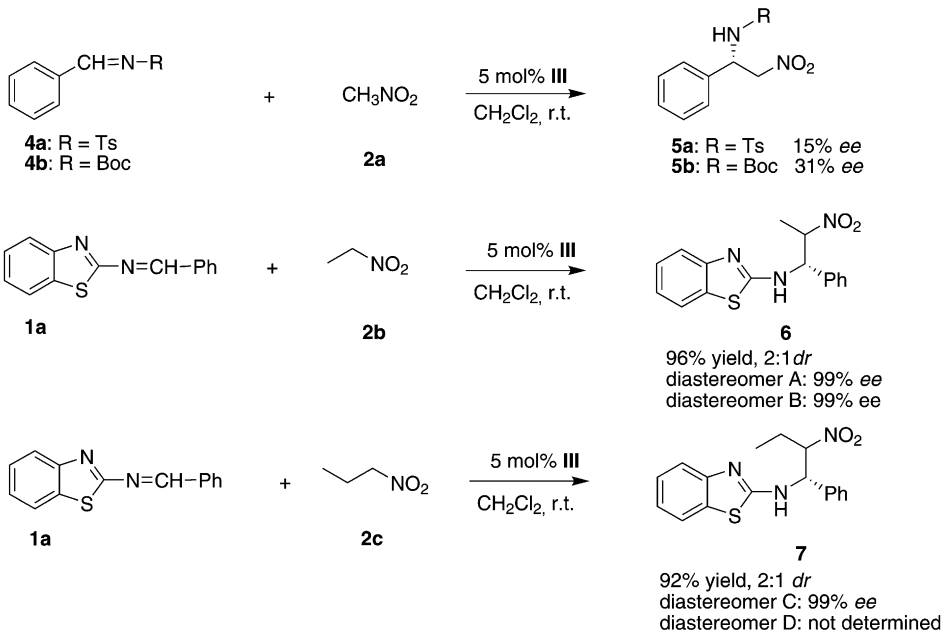
Entry	R^1	R^2	Time [h]	Product	Yield [%][b]	*ee* [%][c]
1	H	C_6H_5	48	**3a**	95	>99
2	H	4-FC_6H_4	48	**3b**	80	99
3	H	4-ClC_6H_4	48	**3c**	94	99
4	H	4-BrC_6H_4	48	**3d**	86	98
5	H	3-$O_2NC_6H_4$	24	**3e**	99	>99
6	H	2-$MeOC_6H_4$	48	**3f**	80	99
7	H	5-Cl-2-HOC_6H_3	48	**3g**	97	51
8	H	4-$(Me)_2NC_6H_4$	48	**3h**	70	87
9	H	3,5-Cl_2-2-HOC_6H_2	48	**3i**	91	80
10	H	3-pyridinyl	48	**3j**	95	99
11	H	2-furanyl	48	**3k**	90	98
12	6-Me	C_6H_5	48	**3l**	94	99
13	6-MeO	C_6H_5	24	**3m**	90	99
14	6-Cl	C_6H_5	24	**3n**	91	99
15	6-Me	3-$O_2NC_6H_4$	24	**3o**	98	99
16	6-MeO	3-$O_2NC_6H_4$	24	**3p**	92	99
17	6-Cl	3-$O_2NC_6H_4$	24	**3q**	89	97
18	6-Me	2-$MeOC_6H_4$	48	**3r**	97	99
19	6-MeO	2-$MeOeC_6H_4$	48	**3s**	90	99
20	6-Cl	2-$MeOC_6H_4$	48	**3t**	92	99

[a] Reactions were carried out with imine **1** (0.2 mmol) and nitromethane **2a** (122 mg, 2.0 mmol) in CH_2Cl_2 (2 mL).
[b] Isolated yield after column chromatographic purification.
[c] Determined by HPLC analysis.

excellent enantioselectivities (99% *ee*) (Table 3, entries 1–6). The electronic property of the substituent has a certain effect on the yield. Generally, imines with electron-withdrawing substituents gave higher yields than those with electron-donating substituents. When reactions were performed with imines **1g** and **1i** bearing a hydroxy group, the desired products were obtained with moderate enantioselectivities (51% *ee* and 80% *ee*, respectively) (Table 3, entries 7 and 9). Imine **1h** bearing strong electron-donating substitution, $N(Me)_2$, afforded the corresponding product in 70% yield with 87% *ee* (Table 3, entry 9). A significant decrease on the enantioselectivity can be attributed to strong hydrogen bond interaction between the OH or $N(Me)_2$ group and squaramide catalyst **III**. Imines **1j** and **1k** derived from heteroaromatic aldehydes were also good substrates, and the desired products were obtained in high yields with excellent enantioselectivities (95% yield, 99% *ee* and 90% yield, 98% *ee*, respectively) (Table 3, entries 10 and 11). Imines **1l**–**1t** with variations (6-Me, 6-MeO, and 6-Cl) on the benzothiazole ring were examined, and excellent yields and excellent enantioselectivities (97–99% *ee*) were achieved (Table 3, entries 12–20).

To get a general sense of what this catalyst can do for the aza-Henry reaction, other imines with more typical N-substituents were investigated. The imines derived from benzaldehyde and aniline or *p*-chloroaniline cannot undergo this aza-Henry reaction, Ts-imine **4a** gave very low enantioselectivity (15% *ee*) and Boc-imine **4b** afforded the corresponding product **5b** in 90% yield with 31% *ee*. This result indicates that the presence of the N-heterocycle in the imine is necessary for high enantioselectivity. Other nitroalkanes were further investigated. The reaction of nitroethane **2b** and imine **1a** catalyzed by 5 mol% catalyst **III** was also effective to provide the corresponding product **6** in 96% yield with excellent enantioselectivities for both diastereomers (99% *ee* and 99% *ee*, respectively), albeit with low diastereoselectivity (Scheme 1). When nitropropane **2c** was used, the aza-Henry product **7** was obtained in 92% yield with excellent enantioselectivities for one diastereomer (99% *ee*). The enantioselectivity of another diastereomer cannot be determined owing to the fact that the corresponding two enantiomers cannot be separated with the series of columns in hand.

To determine the absolute configuration of the aza-Henry products, a single crystal of the product **3d**



Scheme 1. Further substrate scope of imines and nitroalkanes.

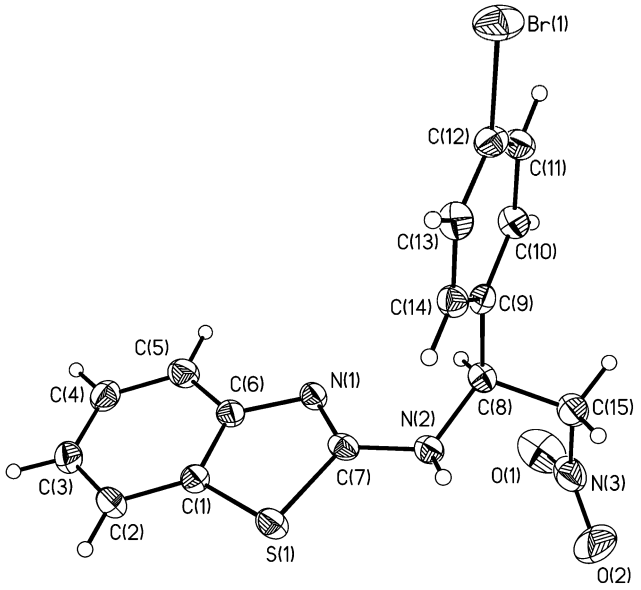
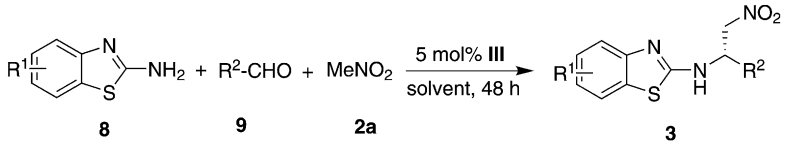


Figure 3. X-ray crystal structure of product **3d**.

suitable for X-ray crystallographic analysis was obtained by crystallization from ethanol. As shown in Figure 3, the absolute configuration of **3d** was determined to be (*S*).[19] The absolute configurations of other products were assigned by analogy.

Encouraged by the above excellent results, we tried to develop a one-pot three-component enantioselective aza-Henry reaction.[20] Following the two-component reaction conditions, the asymmetric one-pot aza-Henry reaction was performed with 2-aminobenzothiazole, benzaldehyde, and nitromethane in CH_2Cl_2 at room temperature. The desired product **3a** was obtained with excellent enantioselectivity but in low yield (20% yield, 98% *ee*) (Table 4, entry 1). For improving the yield, the reaction conditions such as solvent, temperature and additives were simply reoptimized (Table 4, entries 2–8). When the reaction temperature was increased to 60 °C, the yield was enhanced but with reduction of the enantioselectivity (Table 4, entries 2–4). No good result was obtained when the reaction was performed at 90 °C in PhMe (Table 4, entry 5). Then, we tried to evaluate the effect of additives. When 4 Å molecular sieve, anhydrous Na_2SO_4 or $MgSO_4$ was used as additive, the product was obtained with higher yield but lower enantioselectivity (Table 4, entries 6–8). The result (55% yield, 89% *ee*) achieved in toluene at 60 °C was found to be acceptable in consideration of both yield and enantioselectivity (Table 4, entry 2). Under the new optimal conditions, the scope of the one-pot three-component asymmetric aza-Henry reaction was further explored. Aromatic aldehydes **9** with electron-withdrawing or electron-donating substitutions were examined, and moderate to good yields with high enantioselectivies were obtained (Table 4, entries 9–11). 2-Aminobenzothiazoles with different substitutions (6-Me, 6-MeO, and 6-Cl) on the benzothiazole ring also gave comparable results (Table 4, entries 12–14). When the aza-Henry reaction with 2-amino-5-chlorobenzothiazole, 2-methoxybenzaldehyde, and nitromethane was performed in toluene in the presence of 5 mol% catalyst **III** at 60 °C for 90 h, the product **3t** was obtained with high yield and excellent enantioselectivity (90% yield, 94% *ee*) (Table 4, entry 15).

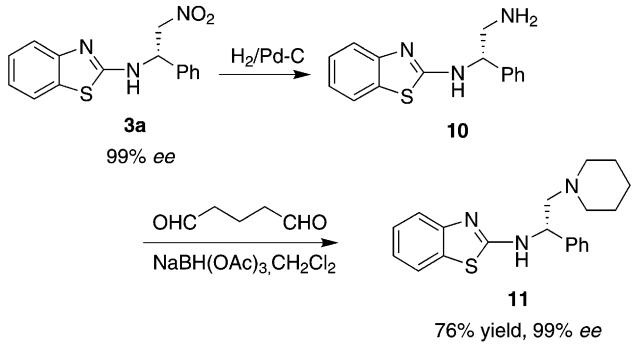
Table 4. One-pot three-component enantioselective aza-Henry reaction.[a]



Entry	R^1	R^2	Temperature [°C]	Solvent	Product	Yield [%][b]	*ee* [%][c]
1	H	C_6H_5	r.t.	CH_2Cl_2	**3a**	20	98
2	H	C_6H_5	60	PhMe	**3a**	55	89
3	H	C_6H_5	60	$CHCl_3$	**3a**	43	59
4	H	C_6H_5	60	$(CH_2Cl)_2$	**3a**	36	73
5	H	C_6H_5	90	PhMe	**3a**	57	52
6[d,e]	H	C_6H_5	60	PhMe	**3a**	90	76
7[e,f]	H	C_6H_5	60	PhMe	**3a**	65	80
8[e,g]	H	C_6H_5	60	PhMe	**3a**	75	79
9	H	4-ClC_6H_4	60	PhMe	**3c**	57	86
10	H	3-$O_2NC_6H_4$	60	PhMe	**3e**	50	94
11	H	2-$MeOC_6H_4$	60	PhMe	**3f**	71	91
12	6-Me	C_6H_5	60	PhMe	**3 L**	61	83
13	6-MeO	C_6H_5	60	PhMe	**3 m**	46	87
14	6-Cl	C_6H_5	60	PhMe	**3n**	46	94
15[h]	6-Cl	2-$MeOC_6H_4$	60	PhMe	**3t**	90	94

[a] Reactions were carried out with 2-aminobenzothiazole **8** (0.2 mmol), aldehyde **9** (0.3 mmol), and nitromethane **2a** (122 mg, 2.0 mmol) for 48 h.
[b] Isolated yield after column chromatographic purification.
[c] Determined by HPLC analysis.
[d] 4 Å molecular sieves (30 mg) were used as additive.
[e] The reaction time was 72 h.
[f] Anhydrous Na_2SO_4 (30 mg) was used as additive.
[g] Anhydrous $MgSO_4$ (30 mg) was used as additive.
[h] The reaction time was 90 h.

After obtaining products that are important intermediates for organic synthesis, we paid more attention to their derivatization. Product **10** was obtained from **3a** by palladium-catalyzed hydrogen reduction. Next, glutaraldehyde was added to product **10** (Scheme 2), and the novel compound **11** bearing two biologically active heterocycles was obtained in good yield (76%) with retained excellent enantioselectivity (99% *ee*). This demonstrates the synthetic utility of the present asymmetric methodology.



Scheme 2. The synthetic transformation of **3a**.

Conclusions

In summary, we have developed an efficient *Cinchona*-based squaramide-catalyzed efficient enantioselective aza-Henry of imines bearing a benzothiazole moiety with nitromethane. The corresponding products were obtained in good to excellent yields with excellent enantioselectivities in most cases. In addition, a one-pot three-component enantioselective aza-Henry reaction using 2-aminobenzothiazoles, aldehydes, and nitromethane was also developed. Moderate to good yields and high enantioselectivities were obtained in one-pot cases. Further studies on squaramide-catalyzed asymmetric reactions and the enantioselective synthesis of other functional chiral molecules are currently underway in our laboratory.

Experimental Section

General Remarks

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 on an XT-4 melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded with Varian Mercury-plus 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. Mass spectra were obtained on a VG-ZAB-HS (EI) mass spectrometer. The HR-MS (ESI) spectra were obtained with a Bruker APEX IV mass spectrometer. Optical rotations were measured on a WZZ-3 polarimeter at the indicated concentration with units g/100 mL. The enatiomeric excesses (*ee*) of the products were determined by chiral HPLC analysis using an Aglient HP 1200 instrument (*n*-hexane/2-propanol as eluent). The squaramide catalysts **III**–**VI** were prepared according to literature procedures.[17f,21]

Typical Procedure for the Asymmetric Aza-Henry of Nitromethane to Imines

The reaction was carried out with imine **1a** (47.6 mg, 0.2 mmol), nitromethane **2a** (122 mg, 2.0 mmol), and catalyst **III** (6.3 mg, 0.01 mmol) in CH_2Cl_2 (2 mL) at room temperature for 48 h. The mixture was separated directly by silica gel column chromatography with petroleum ether-ethyl acetate (5:1), and the product was obtained as pure form.

Benzothiazol-2-yl-[2-nitro-1-phenylethyl]amine (3a): Compound **3a** was obtained according to the general procedure as a white solid; yield: 57 mg (95%); mp 136–138 °C. The enantiomeric excess was determined by HPLC [Daicel Chiralpak IB column (*n*-hexane-2-propanol 95:5), flow rate 1.0 mL min^{-1}, detection at 254 nm]: minor enantiomer t_R = 54.8 min, major enantiomer t_R = 59.2 min, >99% *ee*; $[\alpha]_D^{25}$: +157.7 (*c* 0.35, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (t, J = 7.0 Hz, 2H, ArH), 7.43–7.36 (m, 5H, ArH), 7.31 (t, J = 8.0 Hz, 1H, ArH), 7.13 (t, J = 7.8 Hz, 1H, ArH), 5.69 (t, J = 6.2 Hz, 1H, CH), 5.09 (dd, J_1 = 13.2 Hz, J_2 = 6.8 Hz, 1H, CH_2), 4.86 (dd, J_1 = 12.8 Hz, J_2 = 5.8 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 151.6, 136.1, 130.7, 129.3, 129.0, 126.5, 126.1, 122.4, 120.9 119.5, 76.3, 56.8; IR (KBr): ν = 3390, 3135, 3179, 2956, 2913, 2836, 1601, 1556, 1495, 1444, 1376, 1314, 1116, 1092, 753, 702 cm^{-1}; HR-MS (ESI): m/z = 300.08051, calcd. for $C_{15}H_{14}N_3O_2S$ $[M+H]^+$: 300.08012.

Benzothiazol-2-yl-[1-(4-fluorophenyl)-2-nitroethyl]amine (3b): Compound **3b** was obtained according to the general procedure as a white solid; yield: 50.7 mg (80%); mp 46–48 °C.The enantiomeric excess was determined by HPLC [Daicel Chiralpak IB column (*n*-hexane-2-propanol 90:10), flow rate 1.0 mL min^{-1}, detection at 254 nm]: minor enantiomer t_R = 22.5 min, major enantiomer t_R = 28.1 min, 99% *ee*; $[\alpha]_D^{25}$: +54.2 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (t, J = 8.8 Hz, 2H, ArH), 7.40 (dd, J_1 = 8.8 Hz, J_2 = 5.2 Hz , 2H, ArH), 7.32 (t, J = 7.6 Hz, 1H, ArH), 7.14 (t, J = 7.6 Hz, 1H, ArH), 7.08 (t, J = 8.4 Hz, 2H, ArH), 6.30 (s, 1H, NH), 5.69 (t, J = 6.2 Hz, 1H, CH), 5.08 (dd, J_1 = 13.0 Hz, J_2 = 6.6 Hz , 1H, CH_2), 4.84 (dd, J_1 = 13.2 Hz, J_2 = 5.6 Hz , 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 162.8 (d, $^1J_{C,F}$ = 246 Hz), 151.5, 132.0, 130.6, 128.5 (d, $^3J_{C,F}$ = 8.7 Hz), 126.2, 122.5, 121.0, 119.5, 116.3 (d, $^2J_{C,F}$ = 22.1 Hz), 78.2, 56.2; IR (KBr): ν = 3376, 3072, 2924, 1599, 1560, 1530, 1508, 1456, 1444, 1375, 1339, 1224, 1160, 1125, 1016, 972, 919, 834, 752, 726 cm^{-1}; HR-MS (ESI): m/z = 318.07127, calcd. for $C_{15}H_{13}FN_3O_2S$ $[M+H]^+$: 318.08012.

Benzothiazol-2-yl-[1-(4-chlorophenyl)-2-nitroethyl]amine (3c): Compound **3c** was obtained according to the general procedure as a white solid: yield: 62.4 mg (94%); mp 142–144 °C. The enantiomeric excess was determined by HPLC [Daicel Chiralpak IB column (*n*-hexane-2-propanol 90:10), flow rate 1.0 mL min^{-1}, detection at 254 nm]: minor enantiomer t_R = 23.7 min, major enantiomer t_R = 30.8 min, 99% *ee*; $[\alpha]_D^{25}$: +99.7 (*c* 0.61, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (dd, J_1 = 14.0 Hz, J_2 = 8.0 Hz, 2H, ArH), 7.35–7.29 (m, 5H, ArH), 7.14 (t, J = 7.4 Hz, 1H, ArH), 6.31 (s, 1H, NH), 5.68 (t, J = 5.8 Hz, 1H, CH), 5.06 (dd, J_1 = 13.0 Hz, J_2 = 6.6 Hz, 1H, CH_2), 4.84 (dd, J_1 = 13.2 Hz, J_2 = 5.4 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.0, 151.5, 135.0, 134.7, 130.7, 129.5, 128.0, 126.2, 122.6, 121.0, 119.6, 78.1, 56.0; IR (KBr): ν = 3390, 3072, 2963, 2911, 1594, 1556, 1527, 1502, 1457, 1442, 1431, 1379, 1335, 1271, 1247, 1226, 1185, 1096, 1087, 1010, 918, 861, 823, 755, 740 cm^{-1}; HR-MS (ESI): m/z = 334.04145, calcd. for $C_{15}H_{13}ClN_3O_2S$ $[M+H]^+$: 334.04115.

Benzothiazol-2-yl-[1-(4-bromophenyl)-2-nitroethyl]amine (3d): Compound **3d** was obtained according to the general procedure as a white solid: yield: 65 mg (86%); mp 133–135 °C. The enantiomeric excess was determined by HPLC [Daicel Chiralpak IB column (*n*-hexane-2-propanol 90:10), flow rate 1.0 mL min^{-1}, detection at 254 nm]: minor enantiomer t_R = 30.4 min, major enantiomer t_R = 36.5 min, 98% *ee*; $[\alpha]_D^{25}$: +24.4 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.60 (m, 2H, ArH), 7.52 (d, J = 8.4 Hz, 2H, ArH), 7.34–7.29 (m, 3H, ArH), 7.14 (t, J = 7.6 Hz, 1H, ArH), 6.05(s, 1H, NH), 5.69 (t, J = 5.8 Hz, 1H, CH), 5.08 (dd, J_1 = 13.2 Hz, J_2 = 6.4 Hz , 1H, CH_2), 4.86 (dd, J_1 = 13.2 Hz, J_2 = 5.6 Hz , 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 151.4, 135.2, 132.4, 130.5, 128.2, 126.2, 123.0, 122.5, 121.0, 119.4, 78.0, 56.2; IR (KBr): ν = 3383, 3070, 2923, 1632, 1594, 1557, 1525, 1501, 1488, 1442, 1430, 1378, 1335, 1270, 1246, 1225, 1184, 1128, 1070, 1007, 918, 857, 821, 754, 730 cm^{-1}; HR-MS (ESI): m/z = 377.99115, calcd. for $C_{15}H_{13}BrN_3O_2S$ $[M+H]^+$: 377.99064.

Benzothiazol-2-yl-[2-nitro-1-(3-nitrophenyl)ethyl]amine (3e): Compound **3e** was obtained according to the general procedure as a yellow solid; yield: 68.5 mg (99%); mp 50–52 °C The enantiomeric excess was determined by HPLC [Daicel Chiralpak IB column (*n*-hexane-2-propanol 90:10), flow rate 0.8 mL min^{-1}, detection at 254 nm]: minor enantiomer t_R = 44.3 min, major enantiomer t_R = 48.9 min, >99% *ee*; $[\alpha]_D^{25}$: +28.0 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (s, 1H, ArH), 8.20 (d, J = 8.0 Hz, 1H, ArH), 7.79 (d, J = 7.6 Hz, 1H, ArH), 7.60–7.53 (m, 3H, ArH), 7.31 (t, J = 7.4 Hz, 1H, ArH), 7.15 (t, J = 7.2 Hz, 1H, ArH), 6.41 (s, 1H, NH), 5.90 (br s, 1H, CH), 5.13 (dd, J_1 = 13.2 Hz, J_2 = 5.6 Hz, 1H, CH_2), 4.94 (dd, J_1 = 13.4 Hz, J_2 = 3.8 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): 164.6, 151.4, 148.6, 138.7, 132.8, 130.7, 130.3, 126.2, 123.9, 122.8, 121.6, 121.0, 119.7, 77.8, 55.6; IR (KBr): ν = 3377, 3071, 2962, 1711, 1613, 1598, 1562, 1525, 1455, 1443, 1376, 1347, 1262, 1206, 1099, 1017, 929, 896, 803, 754, 726, 686 cm^{-1}; HR-MS (ESI): m/z = 345.06495, calcd. for $C_{15}H_{13}N_4O_4S$ $[M+H]^+$: 345.06520.

Benzothiazol-2-yl-[(2-methoxyphenyl)-2-nitroethyl]amine (3f): Compound **3f** was obtained according to the general procedure as a yellow solid; yield: 53.1 mg (80%); mp 46–

47 °C The enantiomeric excess was determined by HPLC [Daicel Chiralpak IB column (*n*-hexane-2-propanol 90:10), flow rate 1.0 mL min^{-1}, detection at 254 nm]: minor enantiomer t_R = 27.9 min, major enantiomer t_R = 23.0 min, 99% *ee*; $[\alpha]_D^{25}$: +121.5 (*c* 1.17, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 8.0 Hz, 2H, ArH), 7.36–7.27 (m, 3H, ArH), 7.10 (t, *J* = 7.4 Hz, 1H, ArH), 6.95 (t, *J* = 8.0 Hz, 2H, ArH), 6.43 (s, 1H, NH) 5.80 (t, *J* = 6.4 Hz, 1H, CH), 5.03 (dd, J_1 = 12.4 Hz, J_2 = 7.2 Hz, 1H, CH_2), 4.87 (dd, J_1 = 12.4 Hz, J_2 = 6.4 Hz, 1H, CH_2), 3.93 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.7, 156.9, 151.9, 130.7, 130.3, 129.2, 126.0, 123.5, 122.1, 121.2, 120.8, 119.4, 111.1, 77.2, 55.5, 55.4; IR (KBr): ν = 3398, 3061, 2937, 2838, 1723, 1599, 1558, 1532, 1490, 1456, 1444, 1376, 1338, 1286, 1245, 1208, 1123, 1020, 930, 854, 790, 752, 726 cm^{-1}; HR-MS (ESI): *m*/*z* = 330.09102, calcd. for $C_{16}H_{16}N_3O_3S$ $[M+H]^+$: 330.09069.

2-[1-(Benzothiazol-2-ylamino)-2-nitroethyl]-4-chlorophenol (3g): Compound **3g** was obtained according to the general procedure as a yellow solid; yield: 67.7 mg (97%); mp 105–108 °C. The enantiomeric excess was determined by HPLC [Daicel Chiralpak AD-H column (*n*-hexane-2-propanol 70:30), flow rate 1.0 mL min^{-1}, detection at 254 nm]: minor enantiomer t_R = 5.3 min, major enantiomer t_R = 6.6 min, 51% *ee*; $[\alpha]_D^{25}$: +46.9 (*c* 0.75, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.0 Hz, 1H, ArH), 7.50 (d, *J* = 8.0 Hz, 1H, ArH), 7.33 (t, *J* = 7.8 Hz, 1H, ArH), 7.22–7.16 (m, 2H, ArH), 7.13 (d, *J* = 2.4 Hz, 1H, ArH), 6.80 (d, *J* = 8.4 Hz, 1H, ArH), 6.31 (d, *J* = 8.0 Hz, 1H, NH) 5.79 (br s, 1H, CH), 5.12 (dd, J_1 = 13.2 Hz, J_2 = 7.6 Hz, 1H, CH_2), 4.96 (dd, J_1 = 13.2 Hz, J_2 = 3.6 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0, 153.6, 149.5, 129.7, 129.4, 126.7, 126.5, 124.3, 123.2, 122.9, 121.4, 118.4, 116.7, 76.8, 54.3; IR (KBr): ν = 3423, 3359, 3060, 3029, 2954, 2782, 2710, 2572, 1706, 1603, 1570, 1558, 1539, 1522, 1499, 1490, 1449, 1347, 1328, 1270, 1246, 1204, 1172, 1122, 1106, 1020, 931, 875, 818, 750, 725 cm^{-1}; HR-MS (ESI): *m*/*z* = 350.03617, calcd. for $C_{15}H_{13}ClN_3O_3S$ $[M+H]^+$: 350.03607.

Benzothiazol-2-yl-[1-(4-dimethylaminophenyl)-2-nitroethyl]amine (3h): Compound **3h** was obtained according to the general procedure as a yellow solid; yield: 47.8 mg (70%); mp 106–108 °C. The enantiomeric excess was determined by HPLC [Daicel Chiralpak IB column (*n*-hexane-2-propanol 90:10), flow rate 0.8 mL min^{-1}, detection at 254 nm]: minor enantiomer t_R = 37.3 min, major enantiomer t_R = 44.3 min, 87% *ee*; $[\alpha]_D^{25}$: +111.3 (*c* 0.23, CH_2Cl_2); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.70 (d, *J* = 7.2 Hz, 1H, NH), 7.68 (d, *J* = 7.2 Hz, 1H, ArH), 7.42 (d, *J* = 8.0 Hz, 1H, ArH), 7.30 (d, *J* = 8.8 Hz, 2H, ArH), 7.25–7.21 (m, 1H, ArH), 7.06–7.01 (m, 1H, ArH), 6.71 (d, *J* = 8.8 Hz, 2H, ArH), 5.65–5.59 (m, 1H, CH), 5.01–4.90 (m, 2H, CH_2), 2.86 (s, 6H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.0, 151.9, 150.1, 132.0, 130.3, 127.6, 125.5, 124.5, 121.3, 120.9, 118.4, 112.2, 79.1, 78.6, 55.4; IR (KBr): ν = 3399, 3056, 2920, 1722, 1643, 1597, 1530, 1484, 1446, 1379, 1319, 1295, 1267, 1170, 1122, 1067, 968, 808, 741, 720 cm^{-1}; HR-MS (ESI): *m*/*z* = 343.12272, calcd. for $C_{17}H_{19}N_4O_2S$ $[M+H]^+$: 343.12232.

2-[1-(Benzothiazol-2-ylamino)-2-nitroethyl]-4,6-dichlorophenol (3i): Compound **3i** was obtained according to the general procedure as a yellow solid; yield: 69.7 mg (91%); mp 83–85 °C. The enantiomeric excess was determined by HPLC [Daicel Chiralpak AD-H column (*n*-hexane-2-propanol 85:15), flow rate 1.0 mL min^{-1}, detection at 254 nm]: minor enantiomer t_R = 10.3 min, major enantiomer t_R = 9.1 min, 80% *ee*; $[\alpha]_D^{25}$: −113.4 (*c* 0.94, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (t, *J* = 7.4 Hz, 2H, ArH), 7.36–7.31 (m, 2H, ArH), 7.19–7.15 (m, 2H, ArH), 5.94–5.88 (m, 1H, CH), 5.13 (dd, J_1 = 13.4 Hz, J_2 = 7.8 Hz , 1H, CH_2), 4.89 (dd, J_1 = 13.2 Hz, J_2 = 4.8 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 150.3, 149.0, 129.9, 129.7, 126.6, 126.4, 125.7, 125.4, 123.1, 121.1, 119.5, 77.2, 53.2; IR (KBr): ν = 3371, 3059, 2978, 1705, 1598, 1575, 1557, 1537, 1456, 1447, 1413, 1375, 1339, 1295, 1249, 1223, 1157, 1128, 1044, 1018, 930, 866, 752, 725 cm^{-1}; HR-MS (ESI): *m*/*z* = 383.99747, calcd. for $C_{15}H_{12}Cl_2N_3O_3S$ $[M+H]^+$: 383.99707.

Benzothiazol-2-yl-(2-nitro-1-pyridin-3-ylethyl)amine (3j): Compound **3j** was obtained according to the general procedure as a yellow solid; yield: 57 mg (95%); mp 130–133 °C. The enantiomeric excess was determined by HPLC [Daicel Chiralpak AD-H column (*n*-hexane:2-propanol 70:30), flow rate 1.0 mL min^{-1}, detection at 254 nm]: minor enantiomer t_R = 6.6 min, major enantiomer t_R = 11.8 min, 99% *ee*; $[\alpha]_D^{25}$: +79.6 (*c* 0.5, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.73 (d, *J* = 2.0 Hz, 1H, pyridine-H), 8.60 (d, *J* = 4.0 Hz , 1H, pyridine-H), 7.78–7.76 (m, 1H, ArH), 7.59–7.55 (m, 2H, ArH), 7.34–7.29 (m, 2H, ArH), 7.16–7.12 (m, 1H, ArH), 6.48 (br s, 1H, NH), 5.84 (t, *J* = 6.0 Hz, 1H, CH), 5.15 (dd, J_1 = 13.4 Hz, J_2 = 6.6 Hz, 1H, CH_2), 4.93 (dd, J_1 = 13.2 Hz, J_2 = 5.6 Hz , 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6, 151.5, 150.0, 148.3, 134.6, 132.5, 130.8, 126.1, 124.0, 122.6, 120.9, 119.7, 77.6, 54.2; IR (KBr): ν = 3197, 2961, 2759, 1598, 1565, 1534, 1476, 1455, 1443, 1424, 1377, 1338, 1316, 1240, 1205, 1124, 1026, 911, 853, 754, 724, 709, 638 cm^{-1}; HR-MS (ESI): *m*/*z* = 301.07484, calcd. for $C_{14}H_{13}N_4O_2S$ $[M+H]^+$: 301.07537.

Benzothiazol-2-yl-(1-furan-2-yl-2-nitroethyl)amine (3k): Compound **3k** was obtained according to the general procedure as a yellow solid; yield: 51.9 mg (90%); mp 130–132 °C. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IB column (*n*-hexane-2-propanol 80:20), flow rate 1.0 mL min^{-1}, detection at 254 nm]: minor enantiomer t_R = 9.0 min, major enantiomer t_R = 8.4 min, 98% *ee*; $[\alpha]_D^{25}$: +225.9 (*c* 1.95, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60–7.58 (m, 2H, ArH), 7.39 (d, *J* = 1.6 Hz,1H, furan-H), 7.32 (t, *J* = 8.0 Hz,1H, ArH), 7.14 (t, *J* = 7.0 Hz,1H, ArH), 6.41 (d, *J* = 3.2 Hz, 1H, furan-H), 6.36 (dd, J_1 = 3.2 Hz, J_2 = 2.0 Hz, 1H, furan-H), 6.09 (br s, 1H, NH), 5.88 (t, *J* = 5.8 Hz, 1H, CH), 5.07 (dd, J_1 = 13.2 Hz, J_2 = 5.6 Hz, 1H, CH_2), 4.92 (dd, J_1 = 13.2 Hz, J_2 = 6.0 Hz, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.7, 151.6, 148.8, 143.1, 130.8, 126.1, 122.5, 120.9, 119.7, 110.8, 108.6, 75.8, 50.6; IR (KBr): ν = 3177, 3003, 2972, 2740, 1594, 1569, 1542, 1456, 1447, 1379, 1250, 1228, 1202, 1179, 1143, 1074, 1012, 965, 832, 821, 763, 751, 726, 692, 640 cm^{-1}; HR-MS (ESI): *m*/*z* = 290.05895, calcd. for $C_{13}H_{12}N_3O_3S$ $[M+H]^+$: 290.05939.

(6-Methylbenzothiazol-2-yl)-(2-nitro-1-phenylethyl)amine (3l): Compound **3l** was obtained according to the general procedure as a white solid; yield: 58.7 mg (94%); mp 126–128 °C. The enantiomeric excess was determined by HPLC [Daicel Chiralpak IB column (*n*-hexane-2-propanol 70:30), flow rate 1.0 mL min^{-1}, detection at 254 nm]: minor enantiomer t_R = 10.1 min, major enantiomer t_R = 8.5 min, 99% *ee*; $[\alpha]_D^{25}$: +69.5 (*c* 2.29, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 8.2 Hz, 1H, ArH), 7.40–7.31 (m, 6H, ArH), 7.11 (d, *J* = 8.0 Hz, 1H, ArH), 6.37 (s, 1H, NH), 5.66 (t, *J* =

6.0 Hz, 1H, CH), 5.05 (dd, $J_1=12.8$ Hz, $J_2=6.8$ Hz, 1H, CH_2), 4.83 (dd, $J_1=13.0$ Hz, $J_2=5.8$ Hz, 1H, CH_2), 2.38 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=164.8$, 149.5, 136.2, 132.1, 130.7, 129.2, 128.9, 127.2., 126.5, 120.9, 119.0, 78.3, 56.8, 21.2; IR (KBr): $\nu=3195$, 3013, 1719, 1605, 1542, 1467, 1384, 1233, 1196, 1074, 808, 760, 694 cm^{-1}; HR-MS (ESI): $m/z=314.09591$, calcd. for $C_{16}H_{16}N_3O_2S$ $[M+H]^+$: 314.09557.

(6-Methoxybenzothiazol-2-yl)-(2-nitro-1-phenylethyl)amine (3m): Compound **3m** was obtained according to the general procedure as a white solid; yield: 58.9 mg (90%); mp 45–47 °C. The enantiomeric excess was determined by HPLC [Daicel Chiralpak AD-H column (*n*-hexane-2-propanol 70:30), flow rate 1.0 mL min^{-1}, detection at 254 nm]: minor enantiomer $t_R=13.2$ min, major enantiomer $t_R=20.2$ min, 99% *ee*; $[\alpha]_D^{25}$: +57.3 (*c* 0.45, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.45$ (d, $J=8.8$ Hz, 1H, ArH), 7.41–7.32 (m, 5H, ArH), 7.10 (d, $J=2.4$ Hz, 1H, ArH), 6.89 (dd, $J_1=8.8$ Hz, $J_2=2.4$ Hz, 1H, ArH), 5.64 (t, $J=6.4$ Hz, 1H, CH_2), 5.05 (dd, $J_1=13.0$ Hz, $J_2=7.0$ Hz, 1H, CH_2), 4.83 (dd, $J_1=13.0$ Hz, $J_2=5.8$ Hz, 1H, CH_2), 3.80 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=163.9$, 155.6, 145.7, 136.2, 131.6, 129.2, 128.9, 126.5, 119.8, 113.7, 105.3, 78.3, 56.8, 55.8; IR (KBr): $\nu=3412$, 2917, 2738, 1626, 1602, 1556, 1487, 1441, 1375, 1315, 1271, 1225, 1180, 1089, 1057, 1027, 927, 832, 765, 701, 623, 602 cm^{-1}; HR-MS (ESI): $m/z=330$. 09091, calcd. for $C_{16}H_{16}N_3O_3S$ $[M+H]^+$: 330.09069.

(6-Chlorobenzothiazol-2-yl)-(2-nitro-1-phenylethyl)amine (3n): Compound **3n** was obtained according to the general procedure as a white solid; yield: 60.9 mg (91%); mp 141–142 °C. The enantiomeric excess was determined by HPLC [Daicel Chiralpak IB column (*n*-hexane-2-propanol 70:30), flow rate 1.0 mL min^{-1}, detection at 254 nm]: minor enantiomer $t_R=10.2$ min, major enantiomer $t_R=7.7$ min, 99% *ee*; $[\alpha]_D^{25}$: +63.4 (*c* 2.72, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.55$–7.41 (m, 7H, ArH), 7.27 (d, $J=6.4$ Hz, 1H, ArH), 5.80 (br s, 1H, NH), 5.70 (t, $J=5.0$ Hz, 1H, CH), 5.10 (dd, $J_1=13.0$ Hz, $J_2=6.2$ Hz, 1H, CH_2), 4.88 (dd, $J_1=12.8$ Hz, $J_2=5.6$ Hz, 1H, CH_2); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta=165.6$, 150.7, 137.4, 132.0, 128.6, 128.1, 126.9, 125.7, 125.2, 120.7, 119.4, 78.3, 55.5; IR (KBr): $\nu=3375$, 3062, 2977, 1597, 1558, 1535, 1494, 1446, 1377, 1342, 1307, 1270, 1205, 1096, 1052, 967, 919, 816, 765, 700 cm^{-1}; HR-MS (ESI): $m/z=334.04135$, calcd. for $C_{15}H_{13}Cl\,N_3O_2S$ $[M+H]^+$: 334.04115.

(6-Methylbenzothiazol-2-yl)-[2-nitro-1-(3-nitrophenyl)ethyl]amine (3o): Compound **3o** was obtained according to the general procedure as a yellow solid; yield: 70 mg (98%); mp 131–133 °C. The enantiomeric excess was determined by HPLC [Daicel Chiralpak IA column (*n*-hexane-2-propanol 80:20), flow rate 1.0 mL min^{-1}, detection at 254 nm]: minor enantiomer $t_R=12.4$ min, major enantiomer $t_R=15.3$ min, 99% *ee*; $[\alpha]_D^{25}$: +48.4 (*c* 2.58, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.33$ (s, 1H, ArH), 8.21 (d, $J=8.0$ Hz, 1H, ArH), 7.79 (d, $J=7.6$ Hz, 1H, ArH), 7.59 (t, $J=8.0$ Hz, 1H, ArH), 7.44 (d, $J=8.4$ Hz, 1H, ArH), 7.40 (s, 1H, ArH), 7.12 (d, $J=7.6$ Hz, 1H, ArH), 6.09 (br s, 1H, NH), 5.89 (t, $J=5.8$ Hz, 1H, CH), 5.14 (dd, $J_1=13.2$ Hz, $J_2=6.4$ Hz, 1H, CH_2), 4.95 (dd, $J_1=13.4$ Hz, $J_2=5.0$ Hz, 1H, CH_2), 2.39 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=164.1$, 149.2, 148.6, 138.7, 132.9, 132.6, 130.8, 130.3, 127.4, 123.8, 121.6, 121.0, 119.2, 77.9, 55.7, 21.2; IR (KBr): $\nu=3374$, 3201, 2922, 1793, 1607, 1556, 1528, 1467, 1378, 1350, 1308, 1278, 1238, 1196, 1135, 1100, 1002, 928, 898, 814, 734, 688, 671 cm^{-1}; HR-MS (ESI): $m/z=$ 359.08098,calcd. for $C_{16}H_{15}N_4O_4S$ $[M+H]^+$: 359.08085.

(6-Methoxybenzothiazol-2-yl)-[2-nitro-1-(3-nitrophenyl)-ethyl]amine (3p): Compound **3p** was obtained according to the general procedure as a yellow solid; yield: 68.7 mg (92%); mp 48–50 °C. The enantiomeric excess was determined by HPLC [Daicel Chiralpak AD-H column (*n*-hexane-2-propanol 70:30 v/v), flow rate 1.0 mL min^{-1}, detection at 254 nm]: minor enantiomer $t_R=13.2$ min, major enantiomer $t_R=14.6$ min, 99% *ee*; $[\alpha]_D^{25}$: +27.4 (*c* 1.93, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.32$ (s, 1H, ArH), 8.20 (d, $J=8.4$ Hz, 1H, ArH), 7.79 (d, $J=7.6$ Hz, 1H, ArH), 7.58 (t, $J=8.0$ Hz,1H, ArH), 7.44 (d, $J=8.8$ Hz, 1H, ArH), 7.12 (d, $J=1.6$ Hz, 1H, ArH), 6.90 (dd, $J_1=2.4$ Hz, $J_2=8.8$ Hz,1H, ArH), 5.86 (t, $J=5.6$ Hz, 1H, CH), 5.12 (dd, $J_1=13.6$ Hz, $J_2=6.8$ Hz, 1H, CH_2), 4.93 (dd, $J_1=13.2$ Hz, $J_2=5.2$ Hz, 1H, CH_2), 3.81 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=163.2$, 155.8, 148.5, 145.4, 138.7, 132.9, 131.8, 130.2, 123.7, 121.6, 120.0, 113.9, 105.3, 77.8, 55.8, 55.7; IR (KBr): $\nu=3462$, 3385, 3088, 2925, 1619, 1597, 1561, 1526, 1446, 1376, 1350, 1271, 1245, 1206, 1098, 1051, 906, 858, 817, 733, 687 cm^{-1}; HR-MS (ESI): $m/z=375.07562$, calcd. for $C_{16}H_{15}N_4O_5S$ $[M+H]^+$: 375.07577.

(6-Chlorobenzothiazol-2-yl)-[2-nitro-1-(3-nitrophenyl)-ethyl]amine (3q): Compound **3q** was obtained according to the general procedure as a white solid; yield: 67.1 mg (89%); mp 54–56 °C. The enantiomeric excess was determined by HPLC [Daicel Chiralpak IB column (*n*-hexane-2-propanol 80:20), flow rate 1.0 mL min^{-1}, detection at 254 nm]: minor enantiomer $t_R=17.3$ min, major enantiomer $t_R=15.5$ min, 97% *ee*; $[\alpha]_D^{25}$: +36.8 (*c* 1.88, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.33$ (s, 1H, ArH), 8.22 (d, $J=7.2$ Hz, 1H, ArH), 7.79 (d, $J=7.6$ Hz, 1H, ArH), 7.60 (t, $J=8.0$ Hz, 2H, ArH), 7.55 (d, $J=1.2$ Hz, 1H, ArH), 7.44 (d, $J=8.8$ Hz, 1H, ArH), 7.26 (d, $J_1=2.6$ Hz, $J_2=8.6$ Hz, 1H, ArH), 6.33 (br s, 1H, NH), 5.90 (t, $J=5.6$ Hz, 1H, CH), 5.13 (dd, $J_1=13.8$ Hz, $J_2=6.6$ Hz, 1H, CH_2), 4.96 (dd, $J_1=13.4$ Hz, $J_2=5.4$ Hz, 1H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=164.7$, 150.0, 148.6, 138.5, 132.9, 132.0, 130.4, 128.0, 126.7, 123.9, 121.6, 120.6, 120.4, 77.8, 55.5; IR (KBr): $\nu=3369$, 3088, 2924, 1705, 1597, 1560, 1531, 1447, 1402, 1377, 1350, 1270, 1204, 1097, 1052, 904, 858, 816, 733, 687 cm^{-1}; HR-MS (ESI): $m/z=379.02622$, calcd. for $C_{15}H_{12}ClN_3O_2S$ $[M+H]^+$: 379.02623.

[1-(2-Methoxyphenyl)-2-nitroethyl]-(6-methylbenzothiazol-2-yl)amine (3r): Compound **3r** was obtained according to the general procedure as a white solid; yield: 66.5 mg (97%); mp 45–47 °C. The enantiomeric excess was determined by HPLC [Daicel Chiralpak IB column (*n*-hexane-2-propanol 70:30), flow rate 0.8 mL min^{-1}, detection at 254 nm]: minor enantiomer $t_R=17.7$ min, major enantiomer $t_R=13.6$ min, 99% *ee*; $[\alpha]_D^{25}$: +100.0 (*c* 0.68, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.45$ (d, $J=8.8$ Hz, 1H, ArH), 7.37–7.31 (m, 3H, ArH), 7.10 (d, $J=8.0$ Hz, 1H, ArH), 6.95 (t, $J=7.4$ Hz, 2H, ArH), 6.26 (br s, 1H, NH), 5.77 (br s, 1H, CH), 5.03 (dd, $J_1=12.4$ Hz, $J_2=7.2$ Hz, 1H, CH_2), 4.86 (dd, $J_1=12.4$ Hz, $J_2=6.4$ Hz, 1H, CH_2), 3.94 (s, 3H, OCH_3), 2.38 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=165.0$, 156.9, 149.8, 131.9, 130.7, 130.2, 129.3, 127.1, 123.6, 121.2, 120.8, 119.0, 111.1, 77.3, 55.5, 55.4, 21.2; IR (KBr): $\nu=3374$, 3070, 2964, 2942,. 2836, 1604, 1550, 1541,

1496, 1471, 1439, 1388, 1344, 1285, 1242, 1224, 1189, 1119, 1056, 1030, 1015, 857, 829, 817, 768, 758, 737, 636, 627 cm^{-1}; HR-MS (ESI): $m/z = 344.10657$, calcd. for $C_{17}H_{18}N_3O_3S$ $[M+H]^+$: 344.10634.

(6-Methoxybenzothiazol-2-yl)-[1-(2-methoxyphenyl)-2-nitroethyl]amine (3s): Compound **3s** was obtained according to the general procedure as a white solid; yield: 64.7 mg (90%); mp 50–52 °C. The enantiomeric excess was determined by HPLC [Daicel Chiralpak IB column (*n*-hexane-2-propanol 70:30 v/v), flow rate 0.8 mL min^{-1}, detection at 254 nm]: minor enantiomer $t_R = 13.9$ min, major enantiomer $t_R = 11.1$ min, 99% *ee*; $[\alpha]_D^{25}$: +133.1 (*c* 2.88, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.46$ (d, $J = 9.2$ Hz, 1H, ArH), 7.36–7.30 (m, 2H, ArH), 7.10 (d, $J = 2.4$ Hz, 1H, ArH), 6.97–6.92 (m, 2H, ArH), 6.89 (dd, $J_1 = 2.6$ Hz, $J_2 = 8.8$ Hz, 1H, ArH), 6.32 (br s, 1H, NH), 5.77 (br s, 1H, CH), 5.01 (dd, $J_1 = 12.6$ Hz, $J_2 = 7.0$ Hz, 1H, CH_2), 4.85 (dd, $J_1 = 12.6$ Hz, $J_2 = 6.2$ Hz, 1H, CH_2), 3.92 (s, 3H, OCH_3) 3.80 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.1$, 156.8, 155.4, 146.0, 131.6, 130.2, 129.1, 123.6, 121.1, 119.7, 113.6, 111.0, 105.2, 77.2, 55.8, 55.4, 55.3; IR (KBr): $\nu = 3310$, 2921, 1613, 1557, 1533, 1489, 1462, 1376, 1338, 1276, 1245, 1219, 1163, 1123, 1048, 1023, 907, 869, 816, 789, 753, 730 cm^{-1}; HR-MS (ESI): $m/z = 360.10126$, calcd. for $C_{17}H_{18}N_3O_4S$ $[M+H]^+$: 360.10125.

(6-Chlorobenzothiazol-2-yl)-[1-(2-methoxyphenyl)-2-nitroethyl]amine (3t): Compound **3t** was obtained according to the general procedure as a white solid; yield: 66.9 mg (92%); mp 59–62 °C. The enantiomeric excess was determined by HPLC [Daicel Chiralpak IB column (*n*-hexane-2-propanol 70:30 v/v), flow rate 1.0 mL min^{-1}, detection at 254 nm]: minor enantiomer $t_R = 15.9$ min, major enantiomer $t_R = 11.3$ min, 99% *ee*; $[\alpha]_D^{25}$: +161.8 (*c* 0.56, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.54$ (s, 1H, ArH), 7.46 (d, $J = 8.0$ Hz, 2H, ArH),7.34 (t, $J = 7.4$ Hz, 2H, ArH), 7.25 (d, $J = 7.2$ Hz, 1H, ArH), 6.96 (t, $J = 8.4$ Hz, 2H, ArH), 5.79 (t, $J = 6.4$ Hz, 1H, CH), 5.02 (dd, $J_1 = 12.6$ Hz, $J_2 = 7.4$ Hz, 1H, CH_2), 4.85 (dd, $J_1 = 12.4$ Hz, $J_2 = 5.6$ Hz, 1H, CH_2), 3.94 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 165.7$, 156.9, 150.6, 131.9, 130.4, 129.3, 127.3, 126.5, 123.3, 121.3, 120.5, 120.2, 111.2, 77.2, 55.6, 55.4; IR (KBr): $\nu = 3357$, 3069, 2938, 2840, 1717, 1596, 1550, 1534, 1489, 1447, 1419, 1376, 1336, 1306, 1250, 1216, 1119, 1021, 917, 859, 812, 798, 752 cm^{-1}; HR-MS (ESI): $m/z = 364.05189$, calcd. for $C_{16}H_{15}ClN_3O_3S$ $[M+H]^+$: 364.05172.

4-Methyl-*N*-(2-nitro-1-phenylethyl)benzenesulfonamide (5a):[22] Compound **5a** was obtained according to the general procedure as a white solid; yield: 52.1 mg (80%); mp 154–156 °C. The enantiomeric excess was determined by HPLC [Daicel Chiralpak IB column (*n*-hexane-2-propanol 70:30), flow rate 1.0 mL·min^{-1}, detection at 254 nm]: minor enantiomer $t_R = 9.8$ min, major enantiomer $t_R = 10.8$ min, 15% ee; $[\alpha]_D^{25}$: +12.3 (*c* 0.65, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.64$ (d, $J = 8.4$ Hz, 2H, ArH), 7.26–7.21 (m, 5H, ArH), 7.10–7.07 (m, 2H, ArH), 5.65 (d, $J = 7.6$ Hz, 1H, NH), 5.00 (dd, $J_1 = 13.6$ Hz, $J_2 = 6.8$ Hz , 1H, CH_2), 4.82 (dd, $J_1 = 13.2$ Hz, $J_2 = 6.8$ Hz , 1H, CH_2) , 4.66 (dd, $J_1 = 13.2$ Hz, $J_2 = 6.4$ Hz , 1H, CH_2), 2.40 (s, 3H, CH_3).

***tert*-Butyl 2-nitro-1-phenylethyl carbamate (5b):**[6j] Compound **5b** was obtained according to the general procedure as a white solid; yield: 47.8 mg (90%); mp 108–110 °C. The enantiomeric excess was determined by HPLC [Daicel Chiralpak OJ-H column (*n*-hexane-2-propanol 85:15), flow rate 1.0 mL·min^{-1}, detection at 254 nm]: minor enantiomer $t_R = 13.6$ min, major enantiomer $t_R = 11.4$ min, 31% *ee*; $[\alpha]_D^{25}$: +10.7 (*c* 1.5, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.40$–7.27 (m, 5H), 5.38 (br s, 2H, CH+NH), 4.85 (br s, 1H, CH), 4.70 (d, $J = 9.2$, 1H, CH), 1.44 (s, 9H, CH_3).

Benzothiazol-2-yl-(2-nitro-1-phenylpropyl)amine (6): Compound **5** was obtained according to the general procedure as a white solid; yield: 60.2 mg (96%); mp 55–57 °C. The enantiomeric excess was determined by HPLC [Daicel Chiralpak IA column (*n*-hexane-2-propanol 80:20), flow rate 1.0 mL min^{-1}, detection at 254 nm]: diastereomer A: $t_{minor} = 8.2$ min, $t_{major} = 11.1$ min, 99% *ee*; diastereomer B: $t_{minor} = 13.7$ min, $t_{major} = 18.5$ min, 99% *ee*; $[\alpha]_D^{25}$: +36.9 (*c* 2.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.56$–7.50 (m, 2H, ArH), 7.34–7.25 (m, 6H, ArH), 7.12–7.06 (m, 1H, ArH), 6.06 (br s, 1H, NH), 5.42–5.35 (m, 1H, CH), 5.14–5.07 (m, 1H, CH), 1.62–1.55 (m, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 166.3$, 151.4, 136.3, 135.6, 129.1, 129.0, 128.9, 128.8, 127.0, 126.9, 126.0, 122.2, 122.1, 120.8, 119.2, 86.7, 85.3, 62.0, 61.8, 17.1, 15.2; IR (KBr): $\nu = 3369$, 3195, 3062, 3031, 2991, 2940, 2903, 1702, 1599, 1535, 1495, 1444, 1389, 1358, 1310, 1287, 1262, 1247, 1204, 1157, 1069, 1028, 1017, 931, 883, 753, 725, 700 cm^{-1}; HR-MS (ESI): $m/z = 314.09570$, calcd. for $C_{16}H_{16}N_3O_2S$ $[M+H]^+$: 314.09577.

Benzothiazol-2-yl-(2-nitro-1-phenylbutyl)amine (7): Compound **7** was obtained according to the general procedure as a white solid; yield: 60.1 mg (92%); mp 60–62 °C. The enantiomeric excess was determined by HPLC [Daicel Chiralpak IA column (*n*-hexane-2-propanol 80:20), flow rate 1.0 mL min^{-1}, detection at 254 nm]: diastereomer C: $t_{minor} = 7.3$ min, $t_{major} = 11.4$ min, 99% *ee*; diastereomer D, $t_R = 18.5$ min, enantiomers cannot be separated; $[\alpha]_D^{25}$: +26.3 (*c* 3.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.57$–7.50 (m, 2H, ArH), 7.32–7.25 (m, 6H, ArH), 7.13–7.06 (m, 1H, ArH), 6.44 (br s, 1H, NH), 5.40–5.31 (m, 1H, CH), 4.95–4.83 (m, 1H, CH), 2.17–1.99 (m, 2H, CH), 1.78–1.75 (m, 1H, CH), 0.98–0.95 (m, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 166.3$, 151.5, 136.6, 135.9, 130.4, 129.1, 129.0, 128.7, 127.0, 126.7, 126.1, 126.0, 122.2, 122.1, 120.9, 120.8, 119.2, 119.1, 93.7, 92.6, 61.4, 60.9, 24.9, 23.7, 10.3; IR (KBr): $\nu = 3366$, 3211, 3026, 2975, 2937, 2879, 1701, 1598, 1552, 1535, 1496, 1455, 1372, 1310, 1285, 1246, 1202, 1126, 1081, 1070, 1018, 930, 909, 884, 806, 754, 725, 698 cm^{-1}; HR-MS (ESI): $m/z = 328.11128$, calcd. for $C_{17}H_{18}N_3O_2S$ $[M+H]^+$: 328.11142.

Synthesis of Benzolthiazol-2-yl-(1-phenyl-2-piperidin-1-ylethyl)-amine (11)

To a solution of the adduct **3a** (299 mg, 1 mmol, 99% *ee*) in MeOH (25 mL) was added 10 wt% Pd-C (106 mg, 10 mol%). The mixture was placed under an atmosphere of H_2 in a rubber balloon and stirred for 12 h at room temperature. After filtration, the solvent was concentrated and the residue was separated by silica gel column chromatography with methanol-dichloromethane (1:10) as eluent, and the product **10** was obtained as yellow liquid; yield: 200.2 mg (74%).

Glutaraldehyde (50 wt% in H_2O, 0.1 mL) was added dropwise into a mixture of **10** (80.7 mg, 0.3 mmol) and $NaBH(OAc)_3$ (424 mg, 2 mmol) in $ClCH_2CH_2Cl$ (3 mL) at room

temperature. The resulting mixture was stirred at room temperature for 13 h, and quenched with aqueous NaOH solution (10%, 5 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were concentrated. The residue was dissolved in CH_2Cl_2 (20 mL), washed with brine (10 mL), and dried over anhydrous Na_2SO_4. Then, the solution was filtered and concentrated, the residue was separated by silica gel column chromatography with methanol-dichloromethane (1:40) as eluent, and the product **11** was obtained as a yellow liquid; yield: 76.8 mg (76%). The enantiomeric excess was determined by HPLC [Daicel Chiralpak IA column (*n*-hexane-2-propanol 75:25 v/v), flow rate 1.0 mL min^{-1}, detection at 254 nm]: minor enantiomer t_R = 4.8 min, major enantiomer t_R = 8.0 min, 99% *ee*; $[\alpha]_D^{25}$: +37 (*c* 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.26 (m, 7H, ArH), 7.02–6.99 (m, 2H, ArH) 4.57 (s, 1H, CH), 2.59–2.55 (m, 4H, CH_2), 2.33 (s, 2H, CH_2), 1.60–1.45 (m, 6H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 151.8, 140.2, 131.1, 128.7, 127.8, 126.9, 125.7, 121.3, 120.6, 118.9, 65.4, 56.5, 54.2, 25.8, 24.2; IR (KBr): ν = 3265, 3065, 3029, 2937, 2852, 2803, 1722, 1676, 1599, 1533, 1493, 1444, 1374, 1356, 1306, 1285, 1212, 1156, 1122, 1098, 1074, 1029, 995, 981, 962, 943, 908, 865, 778, 752, 726, 696 cm^{-1}; HR-MS (ESI): *m*/*z* = 338.16825, calcd. for $C_{20}H_{24}N_3S$ $[M+H]^+$: 338.16854.

General Procedure for the One-Pot Asymmetric Aza-Henry Reaction

The mixture of 2-aminobenzothiazole **8** (0.2 mmol), aromatic aldehyde **9** (0.3 mmol), and catalyst **III** (6.3 mg, 0.01 mmol) in toluene (2 mL) was stirred for 5 min, then nitromethane **2a** (122 mg, 104 μL, 2.0 mmol) was added. After stirring at 60 °C for 48 h, the reaction mixture was separated directly by silica gel column chromatography to afford the corresponding product with petroleum ether-ethyl acetate (5:1) as eluent.

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