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Novel bifunctional thiourea–ammonium salt catalysts derived from amino acids: application to highly enantio- and diastereoselective aza-Henry reaction

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ABSTRACT

The development of new efficient and easily accessible catalysts has been one of the focuses in asymmetric phase-transfer catalysis. In this paper, a novel class of chiral bifunctional thiourea–ammonium phase-transfer catalysts were synthesized from commercially available α-amino acids. The structural modularity of these catalysts permits facile tunings to achieve optimum results, which was demonstrated in catalyzing the aza-Henry reaction with excellent enantioselectivities (up to 99.5% ee) and diastereoselectivities (up to >25:1 dr).

1. Introduction

As an inexpensive and readily accessible chiral source, chiral α-amino acids have attracted much interest as an arsenal for the development of diverse organocatalysts, which have found extensive applications in asymmetric synthesis.[1] One of the recent remarkable advances in this field is the development of novel bifunctional or multifunctional organocatalysts based on simple chiral acyclic α-amino acids.[2] Representative catalysts including primary-secondary diamines,[3] tertiary amine-thioureas,[4] and aminophosphines[5] have been successfully applied to a variety of reactions. The success of these catalysts is closely related to the two obvious advantages endowed with chiral α-amino acids as a chiral pool: ready availability at affordable costs and modular structures enabling facile fine tunings.

The catalytic asymmetric phase-transfer catalysis has been well-established as one of the major commonly utilized methodology for the synthesis of kinds of organic compounds.[6] In this realm, while most catalysts are derived from cinchona alkaloids[6g,h] (Scheme 1, **I**), chiral binols[6i,j] (Scheme 1, II) or chiral guanidines[6k] (Scheme 1, III) with great success achieved, the development and applications of novel catalytic systems are still of key importance for the continuing advancement of this methodology.

Our group have focused on the development of novel bifunctional chiral organocatalysts from simple acyclic α-amino acid.[7] Bi- or multifunctionality, especially with an emphasis on H-bond interaction, has been one of the key concepts with great success in the design of new organocatalysts for asymmetric catalysis.[8] However, the application of such a concept in the development of new chiral phase-transfer catalysts has been still rather limited,[9] especially in the case of amino acid-based phase-transfer catalysts. Notably, Ooi and co-workers have developed a new family of chiral 1,2,3-triazoliums using α-amino acids over 10 steps, and applied them to some reactions with excellent results.[10] Our previous good results obtained with the bifunctional primary–tertiary diamine catalysts have inspired us to the development of structurally-related novel bifunctional ammonium salt phase-transfer catalysts (Fig. 1).[11] The highly modular structures of these bifunctional catalysts allow for easy fine tunings at different positions for efficiency improvement. To demonstrate the great potential of these new catalysts for applications in asymmetric phase-transfer catalysis, we applied them to catalyze the aza-Henry reaction as a model, which is an important method for the synthesis of numerous biologically active compounds and building blocks of natural products, such as vicinal diamines and α-amino acids.[12]

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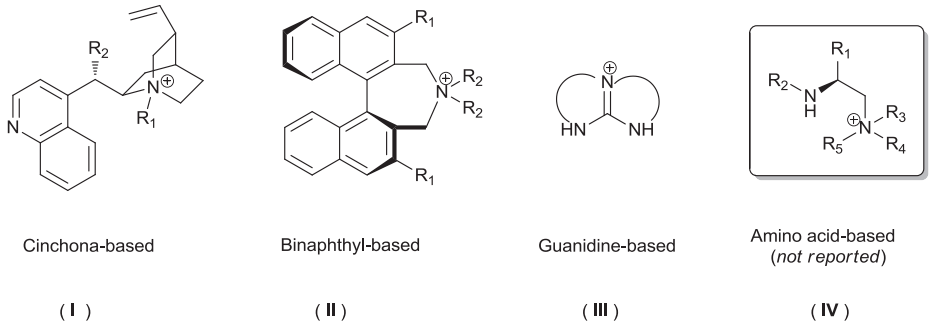


Scheme 1. Chiral quaternary ammonium catalysts (anions are omitted).

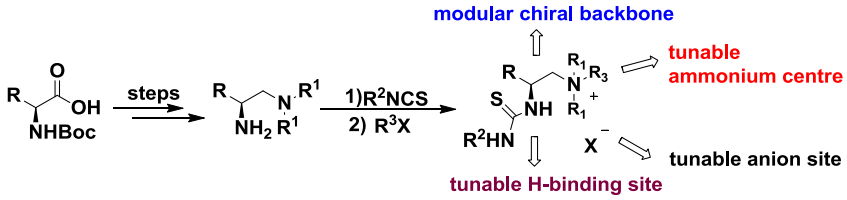


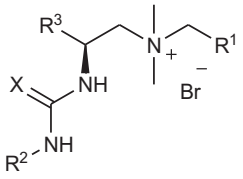
Fig. 1. Design and synthesis of bifunctional thiourea–ammonium salt catalysts.

2. Results and discussion

The *N*-Boc imines used in the aza-Henry reaction for this study were in situ generated from amidosulfones.[9c,f,13] The results of the optimization of the reaction condition parameters, such as screenings of catalysts (Fig. 2), solvents were listed in Table 1. We chose the reaction between amidosulfone **2a** and nitromethane **4a** in the presence of 5 equiv of KOH at −20 °C in toluene as a model reaction for catalyst evaluation (entries 1–8). Firstly, catalysts **1a**–**e** derived from L-leucine and L-isoleucine with different substitutions at the ammonium centre (R^1) and thiourea moieties (R^2) were tested (entries 1–5). The enantioselectivity of the reaction seemed susceptible to changes on both sites and a suitable combination of the substituent groups was identified as in the catalyst **1d** (R^1=4-BrC_6H_4, R^2=4-$NO_2C_6H_4$, entry 4). Subsequent examination of the chiral backbones of these ammonium salts revealed a superior catalyst **1f** derived from *tert*-butyl leucine (entry 6). The ensuing investigation of solvent effect indicated that this reaction gave a higher level of enantiocontrol in CH_2Cl_2 (entry 9), with the best ee value (92%) obtained at −30 °C (entry 13). The use of weaker bases led to inferior results (entries 14–17).

tolerated in the reaction to give the desired products in high yields and with good to excellent enantioselectivities (entries 1–9). While substrates with electron-donating groups on the benzene ring are favoured over those with electron-withdrawing ones in terms of yield and ee value, the influence of the positions of these substituents seemed negligible. However, a significant drop in enantioselectivity was observed with the aliphatic substrate **2j**, while the yield remained excellent (entry 10). To our delight, the employment of nitroethane **4b** also provided excellent yields and ee values, although the dr values were sensitive to the substitution changes of the aryl groups, fluctuating between moderate to excellent (entries 11 and 13–15). The 1-nitropropane **4c** bearing a longer alkyl chain also gave an excellent yield, high ee value and a moderate dr value (entry 12). Notably, the reaction between **2a** and nitromethane **4a** could be performed on a gram-scale with only a slight decrease in the yield and enantioselectivity (entry 16).

To get some insights into the catalytic mechanism of the reaction, we performed two control experiments to test the role of the H-bond sites (the thiourea moiety) and the quaternary ammonium centre of the bifunctional phase-transfer catalysts (Scheme 2). When we employed the thiourea-tertiary amine cata-



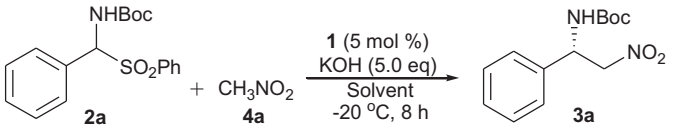
1a : R^1 = Ph, R^2 = 4-$NO_2C_6H_3$, R^3 = *i*-Bu, X = S
1b : R^1 = 4-BrC_6H_4, R^2 = 3,5-$(CF_3)_2C_6H_3$, R^3 = *i*-Bu, X = S
1c : R^1 = 4-BrC_6H_4, R^2 = 3,5-$(CF_3)_2C_6H_3$, R^3 = *i*-Bu, X = O
1d : R^1 = 4-BrC_6H_4, R^2 = 4-$NO_2C_6H_4$, R^3 = *i*-Bu, X = S
1e : R^1 = 4-$NO_2C_6H_4$, R^2 = 4-$NO_2C_6H_4$, R^3 = 2-(*S*)-Bu, X = S
1f : R^1 = 4-BrC_6H_4, R^2 = 4-$NO_2C_6H_4$, R^3 = *t*-Bu, X = S
1g : R^1 = 4-BrC_6H_4, R^2 = 4-$NO_2C_6H_4$, R^3 = Bn, X = S
1h : R^1 = 4-BrC_6H_4, R_2 = 4-$NO_2C_6H_4$, R^3 = 2-(*S*)-Bu, X = S

Fig. 2. Catalysts screened in this study.

Under these optimized reaction conditions, we then surveyed the substrate scope of this reaction with different amidosulfones and nitroalkanes (Table 2). With nitromethane **4a**, in general, various amidosulfones with diverse aromatic groups (Rx) were well

lyst **1l**, which lacks the quaternary ammonium centre compared to **1b** (Table 1, entry 1), the enantioselectivity slumped to 3% ee, though the yield was excellent. Similarly, the use of catalyst **1m** with one blocked H-donor site also gave much inferior results.

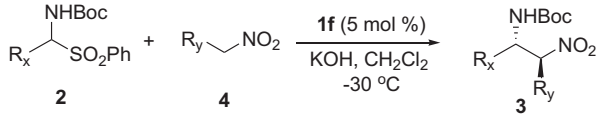
Table 1
Screening of phase-transfer catalysts[a]



Entry	Catalyst	Solvent	Base	Yield[b] (%)	ee[c] (%)
1	**1a**	Toluene	KOH	85	75
2	**1b**	Toluene	KOH	90	77
3	**1c**	Toluene	KOH	80	62
4	**1d**	Toluene	KOH	81	80
5	**1e**	Toluene	KOH	73	65
6	**1f**	Toluene	KOH	78	87
7	**1g**	Toluene	KOH	85	73
8	**1h**	Toluene	KOH	80	80
9	**1f**	CH_2Cl_2	KOH	85	90
10	**1f**	$CHCl_3$	KOH	80	70
11	**1f**	$PhCF_3$	KOH	88	79
12	**1f**	TBME	KOH	85	70
13[d]	**1f**	CH_2Cl_2	KOH	94	92
14[d]	**1f**	CH_2Cl_2	NaOH	85	84
15[d]	**1f**	CH_2Cl_2	Cs_2CO_3	40	56
16[d]	**1f**	CH_2Cl_2	K_2CO_3	Trace	nd
17[d]	**1f**	CH_2Cl_2	Na_2CO_3	Trace	nd

[a] Unless otherwise noted, the reaction was carried out with **2a** (0.2 mmol) and CH_3NO_2 (1.0 mmol) in CH_2Cl_2.
[b] Yield of the isolated product.
[c] Determined by HPLC analysis.
[d] At −30 °C.

Table 2
Substrate scope study of the asymmetric aza-Henry reaction[a]

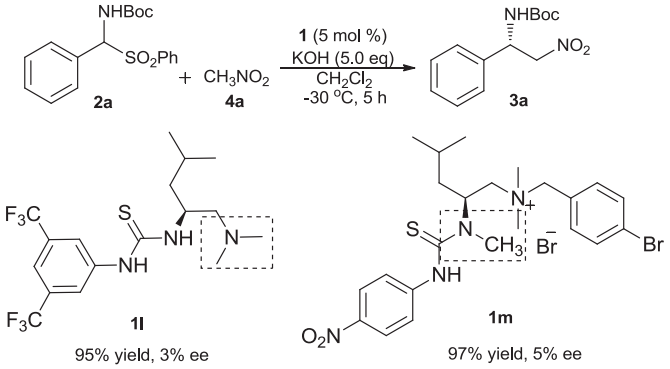


Entry	**2** (Rx)	**4** (Ry)	**3**	Yield[b] (%)	ee[c] (%)	dr[d]
1	**2a** (Ph)	**4a** (H)	**3a**	94	92	—
2	**2b** (4-FC_6H_4)	**4a** (H)	**3b**	80	89	—
3	**2c** (4-MeC_6H_4)	**4a** (H)	**3c**	92	93	—
4	**2d** (4-$CF_3C_6H_4$)	**4a** (H)	**3d**	85	89	—
5	**2e** (4-$MeOC_6H_4$)	**4a** (H)	**3e**	90	94	—
6	**2f** (3-$MeOC_6H_4$)	**4a** (H)	**3f**	90	96	—
7	**2g** (2-$MeOC_6H_4$)	**4a** (H)	**3g**	98	94	—
8	**2h** (1-Naphthyl)	**4a** (H)	**3h**	99	91	—
9	**2i** (2-Furyl)	**4a** (H)	**3i**	80	88	—
10	**2j** ($PhCH_2CH_2$)	**4a** (H)	**3j**	98	68	—
11	**2a** (Ph)	**4b** (Me)	**3k**	99	96	20:1
12	**2a** (Ph)	**4c** (Et)	**3l**	99	89	8:1
13	**2b** (4-FC_6H_4)	**4b** (Me)	**3m**	99	99	6:1
14	**2d** (4-$MeOC_6H_4$)	**4b** (Me)	**3n**	99	97	>25:1
15	**2f** (3-$MeOC_6H_4$)	**4b** (Me)	**3o**	99	99.5	9:1
16	**2a** (Ph)	**4a** (H)	**3a**	92	89	—

[a] Unless otherwise noted, all reactions were carried out with **2** (0.2 mmol) and **4** (1.0 mmol) in CH_2Cl_2 (8 mL) catalyzed by **1f** (5 mol %) at −30 °C.
[b] Isolated yield.
[c] Determined by ^1H NMR or chiral HPLC analysis.
[d] The reaction was run on a gram scale of **2a** (1.8 g, 5.2 mmol).

These results suggested that both the quaternary ammonium centre and the double H-bond donors were crucial for the asymmetric induction.

On the basis of our experiment results and previous relevant studies,[9c] we proposed a possible transition state model to rationalize the stereochemical results of the reaction (Fig. 3) (see the SD for more details). Its assumed that the in situ generated imine might have H-bonding interaction with the thiourea moiety of the catalyst, while the nitro group anion of the nucleophile



Scheme 2. Control experiments for mechanistic study.

nitromethane would be directed by the quaternary ammonium centre by the Coulomb force (static interaction). Such an assembly would make the *Re*-face attack of the nucleophile more favourable.

To extend the utility of this reaction, we studied some useful transformations of the products **3** (Scheme 3). Firstly, we developed a four-step transformation of the product **3a** to the chiral compound **5** in high yields (56% over four steps) while maintaining the optical purity of the product. Using a known method, compound **5** could be transformed into taurine,[14] which belongs to a family of molecules with useful pharmaceutical values. Then we achieved the conversion of **3k** into chiral amine **6**,[15] which is an important building block in organic synthesis,[16] by a radical process to get rid of the nitro group. The stereochemical integrity was also well maintained in this process.

3. Conclusion

In conclusion, we have developed a novel family of bifunctional (thio)urea–ammonium salts as chiral phase-transfer catalysts based on simple acyclic α-amino acids. These new catalysts demonstrated high efficiency in the aza-Henry reaction between amidosulfones and nitroalkanes, in which H-bond and ammonium salts are crucial to achieve excellent enantioselectivities and diastereoselectivities. Highly modular structures as well as their ready accessibility render them promising catalysts in organic catalysis. Efforts towards a deep understanding of the reaction mechanism as well as the application of these catalysts to other relevant reactions are currently underway in our laboratories.

4. Experimental

4.1. General

The ^1H NMR spectra were recorded on a Bruker (400 MHz). All chemical shifts (δ) were given in parts per million. Data were reported as follows: chemical shift, integration, multiplicity (s=single, d=doublet, t=triplet, q=quartet, br=broad, m=multiplet) and coupling constants hertz (Hz). ^{13}C NMR spectra were recorded on a DPX-400 (400 MHz). Flash column chromatography was performed using H silica gel. For thin-layer chromatography (TLC), silica gel plates (HSGF 254) were used and compounds were visualized by irradiation with UV light. Analytical high performance liquid chromatography (HPLC) was carried out on SHIMADZU equipment using chiral columns. Melting points were determined on an SGW X-4 melting point and were uncorrected. Optical rotations were measured on a JASCO P-1010 Polarimeter at λ=589 nm. IR spectra were recorded on a Perkin–Elmer 983G instrument. Mass spectra analysis was performed on API 200 LC/MS system (Applied Biosystems Co. Ltd.).

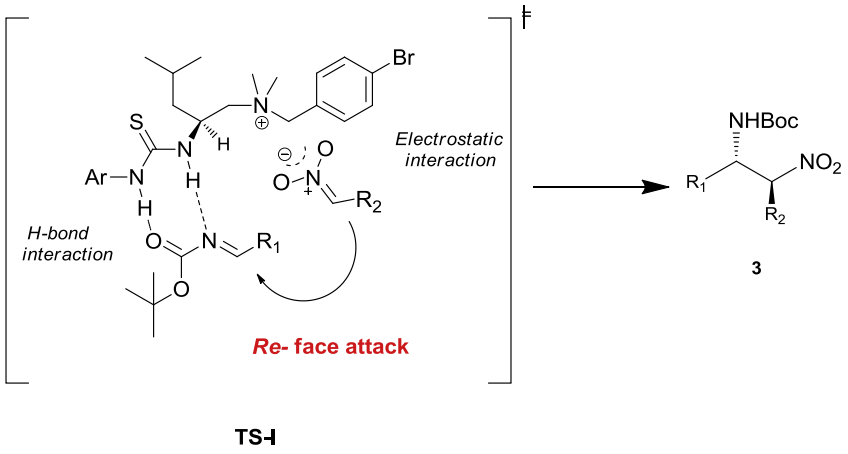
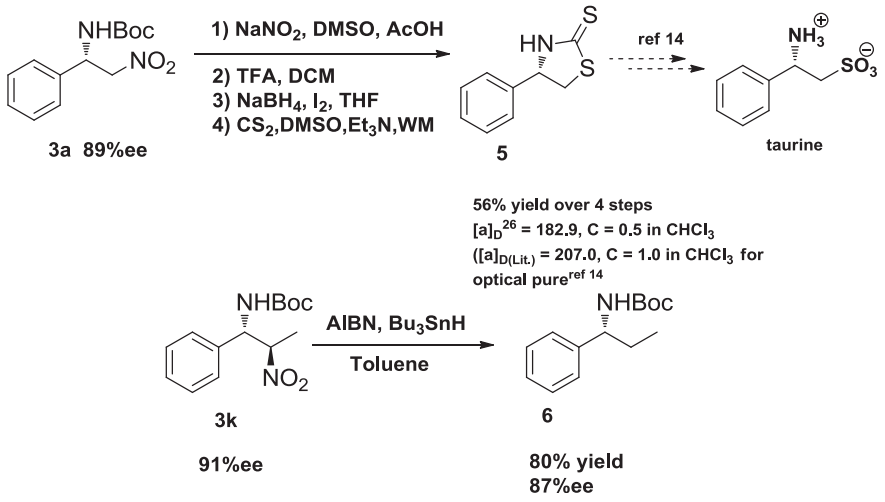


Fig. 3. A possible transition state.



Scheme 3. Useful transformation of the products **3**.

All reagents purchased from commercial sources were used as sold and purified by standard techniques. All starting amidosulfones were synthesized by condensation of the corresponding aldehyde with *tert*-butyl carbamate and benzenesulfinic acid sodium salt mediated by formic acid in an aqueous media.

4.2. Typical procedure for the preparation of bifunctional ammonium salts 1

With a modified method according to the Ref. 4: to a stirred solution of Boc-protected α-amino acid (2.0 mmol) in CH_2Cl_2 (10.0 mL) were added HBTU (3.0 mmol) and DIPEA (4.0 mmol) at 0 °C. Then dimethylamine (2 mmol) was added and the reaction mixture was vigorously stirred at room temperature and monitored by TLC. After 2 h, the resulting solution was poured into 100 mL of H_2O, the organic layer was separated, washed with 1.0 M HCl, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was dissolved into a mixture of TFA (4.0 mmol)/CH_2Cl_2 (20 mL), and the resulting mixture was stirred at room temperature overnight. The mixture was extracted by water firstly and then the combined aqueous layer was basified with satd aq $NaHCO_3$ solution, which was then extracted with CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. After that, the crude product was added dropwise into a suspension of $LiAlH_4$ (6.0 mmol) in dried THF (30 mL) at 0 °C, when finished, the mixture was stirred at 75 °C for 24 h before being carefully quenched by sequential addition of water until the stop of gas evolution. Then anhydrous Na_2SO_4 was added into the mixture, then the mixture was filtered through silica gel and the filtrate was concentrated under reduced pressure. The crude product was then dissolved into CH_2Cl_2, and the isothiocyanate or isocyanate was added into this solution, and stirred overnight. Then the solvent was removed in vacuo to afford the crude product, which could be used directly in the next step. The crude product was dissolved in a solution of CH_3CN (5.0 mL)/R′Br (2 equiv), and the resulting mixture was stirred at room temperature overnight and monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure using a rotary evaporator and the residue was purified by silica gel chromatography (CH_2Cl_2, CH_2Cl_2/methanol as the eluent) to afford the desired products **1**.

*4.2.1. (S)-N-Benzyl-2-(3-(3,5-bis(trifluoromethyl)phenyl)thioureido)-N,N,4-trimethylpentan-1-ammonium bromide (**1a**).* Yield: 60%; yellow solid; $[\alpha]_D^{26}$ −20.6 (*c* 3.5, $CHCl_3$); mp=107–109 °C; IR (neat): 2958, 1552, 1511, 1329, 1255, 730; ^1H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1H), 9.34–9.32 (d, *J*=8.0 Hz, 1H), 8.12–8.10 (d, *J*=8 Hz, 2H), 8.03–8.00 (d, *J*=12 Hz, 2H), 7.56–7.53 (m, 1H), 7.49–7.48 (d, *J*=4.0 Hz, 4H), 5.55–5.48 (m, 1H), 4.87–4.84 (d, *J*=12.0 Hz, 1H),

4.70–4.67 (d, *J*=12.0 Hz, 1H), 4.35–4.29 (m, 1H), 3.27–3.23 (br, 7H), 1.85–1.76 (m, 2H), 1.38–1.31 (m, 1H), 1.07–1.05 (d, *J*=8 Hz, 3H), 0.99–0.97 (d, *J*=8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.42, 145.81, 142.95, 132.88, 131.19, 129.44, 128.90, 128.81, 128.62, 126.56, 124.22, 121.23, 69.68, 68.45, 51.20, 50.21, 47.75, 43.86, 24.33, 23.14, 22.66; HRMS (ESI): calcd for $[M-Br]^+$ ($C_{22}H_{31}N_4O_2S$) requires 415.2168, found 415.2171.

*4.2.2. (S)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)thioureido)-N-(4-bromobenzyl)-N,N,4-trimethylpentan-1-ammonium bromide (**1b**).* Yield: 70%; white solid; $[\alpha]_D^{26}$ −30.5 (*c* 2.0, $CHCl_3$); mp=113–116 °C; IR (neat): 2960, 1593, 1544, 1473, 1383, 1133, 885, 738; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 8.82–8.79 (d, *J*=8.0 Hz, 1H), 8.24 (s, 2H), 7.59–7.55 (t, *J*=8.0 Hz, 3H), 7.39–7.37 (d, *J*=8.0 Hz, 2H), 5.56–5.48 (m, 1H), 4.95–4.92 (d, *J*=12.0 Hz, 1H), 4.69–4.66 (d, *J*=12.0 Hz, 1H), 4.51–4.44 (dd, *J*=8.0, 4.0 Hz, 1H), 3.35–3.31 (d, *J*=12.0 Hz, 1H), 3.23 (s, 6H), 1.89–1.82 (m, 1H), 1.81–1.74 (m, 1H), 1.40–1.43 (m, 1H), 1.05–1.04 (d, *J*=4.0 Hz, 3H), 0.97–0.96 (d, *J*=4.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.06, 140.74, 134.45, 134.40, 132.72, 131.73, 131.44 (q, J_{C-F}=33.0 Hz), 130.62, 130.57, 126.06, 125.43, 124.58 (q, J_{C-F}=279.0 Hz), 123.02, 121.64, 117.66, 70.07, 67.35, 51.04, 50.34, 48.15, 43.84, 24.37, 23.06, 22.63; HRMS (ESI): calcd for $[M-Br]^+$ ($C_{24}H_{29}BrF_6N_3S$) requires 584.1170, found 584.1167.

*4.2.3. (S)-2-(3-(3,5-Bis(trifluoromethyl)phenyl)ureido)-N-(4-bromobenzyl)-N,N,4-trimethylpentan-1-ammonium bromide (**1c**).* Yield: 65%; white solid; $[\alpha]_D^{26}$ −77.8 (*c* 1.0, $CHCl_3$); mp=106–107 °C; IR(neat): 2962, 1698, 1573, 1474, 1277, 1131, 881, 738, 703; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.31 (s, 1H), 8.03 (s, 2H), 7.61–7.59 (d, *J*=8.0 Hz, 2H), 7.50–7.48 (d, *J*=8.0 Hz, 1H), 7.44 (s, 2H), 7.42 (s, 1H), 4.91–4.88 (d, *J*=12.0 Hz, 1H), 4.77–4.74 (d, *J*=12.0 Hz, 1H), 4.58–4.51 (m, 1H), 4.24–4.18 (br, 1H), 3.34–3.31 (d, *J*=12.0 Hz, 1H), 3.27 (s, 3H), 3.23 (s, 3H), 1.85–1.81 (m, 1H), 1.78–1.70 (m, 1H), 1.29–1.22 (m, 1H), 0.96–0.93 (br, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 140.9, 134.4, 132.7, 131.9 (q, *J*=33.0 Hz), 126.1, 125.3, 124.5 (q, *J*=271.0 Hz), 117.8, 115.1, 69.3, 67.8, 50.8, 50.2, 43.9, 43.2, 24.2, 23.0, 21.4; HRMS (ESI): calcd for $[M-Br]^+$ ($C_{24}H_{29}BrF_6N_3O$) requires 568.1398, found 584.1383.

*4.2.4. (S)-N-(4-Bromobenzyl)-N,N,4-trimethyl-2-(3-(4-nitrophenyl) thioureido)pentan-1-ammonium bromide (**1d**).* Yield: 77%; yellow solid; $[\alpha]_D^{26}$ −54.5 (*c* 0.5, $CHCl_3$); mp=111–114 °C; IR (neat): 2960, 1593, 1544, 1383, 1277, 1133, 885, 847; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.26 (s, 1H), 9.34–9.31 (d, *J*=8.0 Hz, 1H), 8.14–8.12 (d, *J*=8.0 Hz, 2H), 8.02–8.00 (d, *J*=8.0 Hz, 2H), 7.65–7.63 (d, *J*=8.0 Hz, 2H), 7.40–7.38 (d, *J*=8.0 Hz, 2H), 5.54–5.47 (br, 1H), 4.95–4.91 (d, *J*=12.0 Hz, 1H), 4.70–4.67 (d, *J*=12.0 Hz, 1H), 4.40–4.34 (m, 1H), 3.32–3.26 (br, 6H), 3.20–3.18 (d, *J*=8.0 Hz, 1H), 1.83–1.75 (m, 2H), 1.37–1.30 (m, 1H), 1.06–1.05 (d, *J*=4.0 Hz, 3H), 0.99–0.98 (d, *J*=4.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.38, 145.54, 143.16, 134.44, 132.81, 131.69, 130.58, 126.17, 125.47, 125.03, 124.29, 124.25, 121.38, 121.29, 69.83, 67.44, 51.17, 50.41, 47.75, 43.93, 24.38, 23.14, 22.63; HRMS (ESI): calcd for $[M-Br]^+$ ($C_{22}H_{30}BrN_4O_2S$) requires 493.1273, found 493.1283.

*4.2.5. (2S,3S)-N,N,3-Trimethyl-N-(4-nitrobenzyl)-2-(3-(4-nitrophenyl) thioureido)pentan-1-ammonium bromide (**1e**).* Yield: 80%; yellow solid; $[\alpha]_D^{26}$ −18.0 (*c* 0.5, $CHCl_3$); mp=119–121 °C; IR (neat): 2964, 1524, 1329, 1251, 1110, 852, 732; ^{1}H NMR (400 MHz, CD_3CN) δ 11.19 (s, 1H), 9.52–9.49 (d, *J*=8.0 Hz, 1H), 8.31–8.29 (d, *J*=8.0 Hz, 2H), 8.15–8.12 (d, *J*=8.0 Hz, 2H), 8.10–8.07 (d, *J*=8.0 Hz, 2H), 7.85–7.83 (d, *J*=8.0 Hz, 2H), 5.41–5.35 (m, 1H), 4.93–4.90 (d, *J*=12.0 Hz, 1H), 4.83–4.80 (d, *J*=12.0 Hz, 1H), 3.93–3.87 (m, 1H), 3.66–3.63 (d, *J*=12.0 Hz, 1H), 3.19–3.18 (br, 6H), 1.84–1.79 (m, 1H), 1.58–1.51 (m, 1H), 1.45–1.35 (m, 1H), 1.07–1.05 (d, *J*=8.0 Hz, 3H), 0.99–0.96 (t, *J*=8.0 Hz, 3H); ^{13}C NMR (100 MHz, CD_3CN) δ 180.7, 149.3, 146.2, 142.9, 134.6, 134.1, 129.7, 124.8, 124.2, 124.0, 121.6, 120.7, 117.3, 67.3, 66.8, 62.2, 60.7, 60.5, 40.2, 24.6, 14.4, 11.2; HRMS (ESI): calcd for $[M-Br]^+$ ($C_{22}H_{30}N_5O_4S$) requires 460.2019, found 460.2008.

*4.2.6. (S)-N,N,3,3-Tetramethyl-N-(4-bromobenzyl)-2-(3-(4-nitrophe nyl)thioureido)butan-1-ammonium bromide (**1f**).* Yield: 76%; yellow solid; $[\alpha]_D^{26}$ −119.9 (*c* 1.0, $CHCl_3$); mp=112–114 °C; IR (neat): 2963, 1575, 1508, 1330, 1257, 1109, 851, 727; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.54 (s, 1H), 9.43–9.40 (d, *J*=12.0 Hz, 1H), 8.13–8.11 (d, *J*=8.0 Hz, 2H), 8.05–8.02 (d, *J*=12.0 Hz, 2H), 7.63–7.61 (d, *J*=8.0 Hz, 2H), 7.42–7.40 (d, *J*=8.0 Hz, 2H), 5.26–5.21 (t, *J*=12.0 Hz, 1H), 4.97–4.93 (d, *J*=16.0 Hz, 1H), 4.65–4.62 (d, *J*=12.0 Hz, 1H), 4.41–4.35 (m, 1H), 3.61–3.58 (d, *J*=12.0 Hz, 1H), 3.25 (s, 3H), 3.18 (s, 3H), 1.13 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.20, 145.66, 143.13, 134.55, 132.74, 131.72, 131.71, 130.73, 130.64, 126.11, 125.51, 124.25, 121.26, 67.83, 67.56, 56.35, 50.69, 49.86, 37.15, 26.44; HRMS (ESI): calcd for $[M-Br]^+$ ($C_{22}H_{30}BrN_4O_2S$) requires 493.1273, found 493.1261.

*4.2.7. (S)-N-(4-Bromobenzyl)-N,N-dimethyl-2-(3-(4-nitrophenyl)thioureido)-3-phenylpropan-1-ammonium bromide (**1g**).* Yield: 70%; yellow solid; $[\alpha]_D^{26}$ −53.3 (*c* 3.5, $CHCl_3$); mp=113–116 °C; IR (neat): 2964, 1510, 1329, 1253, 1110, 850; ^{1}H NMR (400 MHz, CD_3CN) δ 10.10 (s, 1H), 9.56–9.53 (d, *J*=8.0 Hz, 1H), 8.14–8.12 (d, *J*=8.0 Hz, 2H), 8.00–7.98 (d, *J*=8.0 Hz, 2H), 7.53–7.51 (d, *J*=8.0 Hz, 2H), 7.36–7.30 (br, 5H), 7.17–7.15 (d, *J*=8.0 Hz, 2H), 5.64–5.56 (br, 1H), 4.70–4.67 (d, *J*=12.0 Hz, 1H), 4.51–4.47 (br, 1H), 4.43–4.39 (d, *J*=12.0 Hz, 1H), 3.32–3.29 (br, 1H), 3.27–3.23 (d, *J*=12.0 Hz, 1H), 3.07 (br, 4H), 2.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.0, 145.4, 143.0, 135.7, 134.3, 132.6, 131.6, 130.5, 129.4, 127.5, 126.0, 125.1, 124.3, 121.3,67.9, 66.3, 51.1, 51.0, 50.2, 40.4; HRMS (ESI): calcd for $[M-Br]^+$ ($C_{25}H_{28}BrN_4O_2S$) requires 527.1116, found 527.1099.

*4.2.8. (2S,3S)-N-(4-Bromobenzyl)-N,N,3-trimethyl-2-(3-(4-nitrophe nyl)thioureido)pentan-1-ammonium bromide (**1h**).* Yield: 69%; yellow solid; $[\alpha]_D^{26}$ −30.3 (*c* 3.5, $CHCl_3$); mp=105–106 °C; IR (neat): 2964, 1572, 1508, 1328, 1253, 1110, 1013, 851, 734; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.32 (s, 1H), 9.39–9.37 (d, *J*=8.0 Hz, 1H), 8.14–8.12 (d, *J*=8.0 Hz, 2H), 8.03–8.01 (d, *J*=8.0 Hz, 2H), 7.63–7.61 (d, *J*=8.0 Hz, 2H), 7.42–7.39 (d, *J*=8.0 Hz, 2H), 5.42–5.36 (m, 1H), 4.94–4.91 (d, *J*=12.0 Hz, 1H), 4.66–4.63 (d, *J*=12.0 Hz, 1H), 4.42–4.36 (m, 1H), 3.46–3.43 (d, *J*=12.0 Hz, 1H), 3.24 (s, 3H), 3.19 (s, 3H), 1.57–1.48 (m, 1H), 1.39–1.30 (m, 1H), 1.09 (d, *J*=8.0 Hz, 3H), 0.99–0.96 (t, *J*=8.0 Hz, 3H), 0.87–0.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.47, 145.69, 143.03, 134.56, 132.68, 131.66, 130.58, 126.03, 125.59, 124.26, 121.17, 52.45, 50.71, 50.02, 40.15, 36.82, 36.78, 25.10, 15.10, 11.89; HRMS (ESI): calcd for $[M-Br]^+$ ($C_{22}H_{30}BrN_4O_2S$) requires 493.1273, found 493.1289.

4.3. Preparation of 1m

To a stirred solution of Boc-protected α-amino acid (2.0 mmol) in CH_2Cl_2 (10.0 mL) were added HBTU (3.0 mmol) and DIPEA (4.0 mmol) at 0 °C. Then dimethylamine (2 mmol) was added and the reaction mixture was vigorously stirred at room temperature and monitored by TLC. After 2 h, the resulting solution was diluted with 100 mL of H_2O, the organic layer was separated, washed with 1.0 M HCl and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was added dropwise into a suspension of $LiAlH_4$ (6 mmol) in dried THF (30 mL) at 0 °C. The resulting mixture was stirred at 75 °C for 24 h, and was then carefully quenched by sequential addition of water until the stop of gas evolution. Anhydrous Na_2SO_4 was added into the mixture and after filtration through silica gel, the filtrate was concentrated under reduced pressure. The crude product was then dissolved in CH_2Cl_2 to form a solution, to which the isothiocyanate was added and followed by stirring overnight. Then the solvent was removed in vacuo to afford the crude product, which was used directly in the next step.

The crude product was dissolved in a solution of 1-bromo-4-(bromomethyl)benzene (2.0 equiv) in CH_3CN (5.0 mL) and then the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure using a rotary evaporator and the residue was purified by silica gel chromatography (CH_2Cl_2, CH_2Cl_2/methanol as the eluent) to afford the desired product **1m**.

*4.3.1. (S)-N-(4-Bromobenzyl)-N,N,4-trimethyl-2-(1-methyl-3-(4-nitrophenyl)thioureido)-pentan-1-ammonium bromide (**1m**).* Yield: 70%; yellow solid; $[\alpha]_D^{26}$ −33.1 (*c* 3.5, $CHCl_3$); mp=112–115 °C; IR (neat): 2958, 1594, 1510, 1326, 1110, 1074, 854; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 8.16–8.13 (d, *J*=12.0 Hz, 2H), 7.83–7.80 (d, *J*=12.0 Hz, 2H), 7.61–7.59 (d, *J*=8.0 Hz 2H), 7.49–7.47 (d, *J*=8.0 Hz, 2H), 6.51–6.45 (m, 1H), 5.25–5.22 (d, *J*=12.0 Hz, 1H), 5.00–4.94 (dd, *J*=16.0, 12 Hz, 1H), 4.90–4.87 (d, *J*=12.0 Hz, 1H), 3.58 (s, 3H), 3.34–3.31 (d, *J*=12.0 Hz, 6H), 3.14–3.11 (d, *J*=12.0 Hz, 1H), 1.68–1.60 (m, 1H), 1.52–1.46 (m, 1H), 1.35–1.28 (m, 1H), 1.06–1.04 (d, *J*=8.0 Hz, 3H), 0.98–0.96 (d, *J*=8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.21, 146.26, 144.10, 134.60, 132.60, 125.84, 125.46, 123.77, 66.68, 53.51, 50.27, 49.61, 41.50, 33.29, 24.54, 23.04, 22.98; HRMS (ESI): calcd for $[M-Br]^+$ ($C_{23}H_{32}BrN_4O_2S$) requires 507.1429, found 507.1427.

4.4. General procedure for the asymmetric aza-Henry reaction

To a stirred solution of the corresponding amidosulfone (0.2 mmol) in CH_2Cl_2 (8.0 mL) were added nitroalkane (1.0 mmol) and catalyst **1** at −30 °C under argon. The reaction mixture was vigorously stirred and then grounded KOH (1.0 mmol) was added. After 8 h (monitored by TLC), 10 mL of satd aq $NaHCO_3$ was added and the mixture was allowed to warm to ambient temperature and extracted with CH_2Cl_2. The combined organic extracts were concentrated under reduced pressure using a rotary evaporator and the residue was purified by silica gel chromatography (hexane/EtOAc as the eluent) to afford the desired products **3**.

*4.4.1. (S)-tert-Butyl 2-nitro-1-phenylethylcarbamate (**3a**).* Yield: 94%; White solid; $[\alpha]_D^{25}$ +20.5 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.26 (m, 5H), 5.37 (br, 1H), 5.27 (br, 1H), 4.85 (br, 1H), 4.73–4.68 (m, 1H), 1.44 (s, 9H); Enantiomeric excess: 92%, determined by HPLC (Chiralpak PC-II column, hexane/*i*-PrOH 90:10, λ=214 nm, flow rate 0.7 mL/min; t_{major}=17.9 min; t_{minor}=15.5 min).

*4.4.2. (S)-tert-Butyl 1-(4-fluoropenyl)-2-nitrothylcarbamate (**3b**).* Yield: 80%; White solid; $[\alpha]_D^{25}$ +19.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.29 (d, *J*=5.2 Hz, 1H), 7.28–7.27 (d, *J*=8.0 Hz, 1H)7.10–7.05 (t, *J*=8.4 Hz, 3H), 5.34 (br, 1H), 5.27 (br, 1H), 4.84 (br, 1H), 4.71–4.66 (m, 1H), 1.44 (s, 9H); Enantiomeric excess: 89%, determined by HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 90:10, λ=214 nm, flow rate 0.7 mL/min; t_{major}=17.4 min; t_{minor}=23.5 min).

*4.4.3. (S)-tert-Butyl 1-(4-fluoropenyl)-2-nitrothylcarbamate (**3c**).* Yield: 92%; White solid; $[\alpha]_D^{25}$ +30.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 4H), 5.33 (br, 1H), 5.21 (br, 1H), 4.83 (br, 1H), 4.70–4.66 (m, 1H), 2.34 (s, 1H), 1.44 (s, 9H); Enantiomeric excess: 93%, determined by HPLC (Chiralpak PC-II column, hexane/*i*-PrOH 90:10, λ=214 nm, flow rate 0.7 mL/min; t_{major}=17.4 min; t_{minor}=15.2 min).

*4.4.4. (S)-tert-Butyl 1-(4-fluoropenyl)-2-nitrothylcarbamate (**3d**).* Yield: 85%; White solid; $[\alpha]_D^{25}$ +12.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.64 (d, *J*=8.0 Hz, 2H), 7.46–7.44 (d, *J*=8.0 Hz, 2H), 5.47 (br, 2H), 4.89 (br, 1H), 4.75 (m, 1H), 1.44 (s, 9H); Enantiomeric excess: 89%, determined by HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 90:10, λ=214 nm, flow rate 0.7 mL/min; t_{major}=14.1 min; t_{minor}=23.2 min).

*4.4.5. (S)-tert-Butyl 1-(4-fluoropenyl)-2-nitrothylcarbamate (**3e**).* Yield: 90%; White solid; $[\alpha]_D^{25}$ +37.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.21 (d, *J*=8.0 Hz, 2H), 6.91–6.89 (d, *J*=8.0 Hz, 2H), 5.30 (br, 1H), 5.16 (br, 1H), 4.85 (br, 1H), 4.69–4.64 (m, 1H), 3.80 (s, 3H), 1.44 (s, 9H); Enantiomeric excess: 94%, determined by HPLC (Chiralpak OD-H column, hexane/*i*-PrOH 90:10, λ=214 nm, flow rate 0.7 mL/min; t_{major}=46.6 min; t_{minor}=40.9 min).

*4.4.6. (S)-tert-Butyl 1-(4-fluoropenyl)-2-nitrothylcarbamate (**3f**).* Yield: 90%; White solid; $[\alpha]_D^{25}$ +39.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.28 (t, *J*=8.0 Hz, 1H), 6.87–6.83 (m, 3H), 5.34 (br, 1H), 5.25 (br, 1H), 4.83 (br, 1H), 4.71–4.67 (m, 1H), 3.81 (s, 3H), 1.44 (s, 9H); Enantiomeric excess: 96%, determined by HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 90:10, λ=214 nm, flow rate 0.7 mL/min; t_{major}=27.9 min; t_{minor}=42.1 min).

*4.4.7. (S)-tert-Butyl 1-(4-fluoropenyl)-2-nitrothylcarbamate (**3g**).* Yield: 98%; White solid; $[\alpha]_D^{25}$ +48.9 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.29 (t, *J*=8.0 Hz, 1H), 7.24 (br, 1H), 6.97–6.93 (t, *J*=7.6 Hz, 1H), 6.92–6.90 (d, *J*=8.0 Hz, 1H), 5.71 (br, 1H), 5.56 (br, 1H), 4.79 (m, 1H), 4.69 (m, 1H), 3.90 (s, 3H), 1.44 (s, 9H); Enantiomeric excess: 94%, determined by HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 90:10, λ=214 nm, flow rate 0.7 mL/min; t_{major}=23.4 min; t_{minor}=22.0 min).

*4.4.8. (S)-tert-Butyl 1-(4-fluoropenyl)-2-nitrothylcarbamate (**3h**).* Yield: 99%; White solid; $[\alpha]_D^{25}$ +11.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13–8.11 (d, *J*=8.0 Hz, 1H), 7.91–7.89 (d, *J*=8.0 Hz, 1H), 7.86–7.83 (m, 1H), 7.63–7.59 (t, *J*=7.2 Hz, 1H), 7.56–7.54 (d, *J*=8.0 Hz, 1H), 7.46–7.44 (m, 2H), 6.28 (br, 1H), 5.36 (br, 1H), 4.89 (br, 1H), 1.43 (s, 9H); Enantiomeric excess: 91%, determined by HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 90:10, λ=214 nm, flow rate 0.7 mL/min; t_{major}=24.2 min; t_{minor}=44.1 min).

*4.4.9. (S)-tert-Butyl 1-(4-fluoropenyl)-2-nitrothylcarbamate (**3i**).* Yield: 80%; White solid; $[\alpha]_D^{25}$ +37.9 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (br, 1H), 6.35 (m, 1H), 6.32 (m, 1H), 5.46 (br, 1H), 5.27 (br, 1H), 4.85 (br, 1H), 4.75–4.71 (m, 1H), 1.46 (s, 9H); Enantiomeric excess: 88%, determined by HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 90:10, λ=214 nm, flow rate 0.7 mL/min; t_{major}=14.5 min; t_{minor}=13.5 min).

*4.4.10. (S)-tert-Butyl 1-(4-fluoropenyl)-2-nitrothylcarbamate (**3j**).* Yield: 98%; White solid; $[\alpha]_D^{25}$ −29.9 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.28 (t, *J*=8.0 Hz, 2H), 7.23–7.21 (d, *J*=8.0 Hz, 1H), 7.18–7.16 (d, *J*=8.0 Hz, 2H), 4.87 (br, 1H), 4.54 (br, 2H), 4.10 (m, 1H), 2.77–2.65 (m, 2H), 1.93–1.89 (m, 2H), 1.46 (s, 9H); Enantiomeric excess: 68%, determined by HPLC (Chiralpak PC-II column, hexane/*i*-PrOH 90:10, λ=214 nm, flow rate 0.7 mL/min; t_{major}=7.8 min; t_{minor}=8.4 min).

*4.4.11. (S)-tert-Butyl 1-(4-fluoropenyl)-2-nitrothylcarbamate (**3k**).* Yield: 99%; White solid; $[\alpha]_D^{25}$ +19.1 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.33 (m, 3H), 7.24–7.22 (m, 2H), 5.30 (br, 1H), 5.19–5.17 (m, 1H), 4.93 (br, 1H), 1.54–1.52 (d, *J*=8.0 Hz, 3H), 1.43 (s, 9H); Enantiomeric excess: 96%, determined by HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 90:10, λ=214 nm, flow rate 0.7 mL/min; t_{major}=15.6 min; t_{minor}=21.4 min).

*4.4.12. (S)-tert-Butyl 1-(4-fluoropenyl)-2-nitrothylcarbamate (**3l**).* Yield: 99%; White solid; $[\alpha]_D^{25}$ +33.1 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.32 (m, 3H), 7.24–7.22 (m, 2H), 5.14 (br, 2H), 4.74 (br, 1H), 2.10–2.00 (m, 1H), 1.91–1.85 (m, 1H), 1.43 (s, 9H), 1.00–0.97 (t, *J*=7.2 Hz, 3H); Enantiomeric excess: 89%, determined by HPLC (Chiralpak AS-H column, hexane/*i*-PrOH 90:10, λ=214 nm, flow rate 0.7 mL/min; t_{major}=83.4 min; t_{minor}=5.3 min).

*4.4.13. (S)-tert-Butyl 1-(4-fluoropenyl)-2-nitrothylcarbamate (**3m**).* Yield: 99%; White solid; $[\alpha]_D^{25}$ +23.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23–7.20 (br, 2H), 7.07–7.03 (t, *J*=8.8 Hz, 2H), 5.36 (br, 1H), 5.16–5.12 (m, 1H), 4.90 (br, 1H), 1.54–1.52 (d, *J*=8.0 Hz, 3H), 1.43 (s, 9H); Enantiomeric excess: 99%, determined by HPLC (Chiralpak AD-H column,

hexane/*i*-PrOH 90:10, λ=214 nm, flow rate 0.7 mL/min; t_{major}=13.4 min; t_{minor}=15.4 min).

*4.4.14. (S)-tert-Butyl 1-(4-fluoropenyl)-2-nitrothylcarbamate (**3n**).* Yield: 99%; White solid; $[\alpha]_D^{25}$ +36.8 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.16–7.13 (d, *J*=8.0 Hz, 2H), 6.88–6.86 (d, *J*=8.0 Hz, 2H), 5.25 (br, 1H), 5.12–5.08 (br, 1H), 4.90 (br, 1H), 3.76 (s, 3H), 1.53–1.52 (d, *J*=4.0 Hz, 3H), 1.43 (s, 9H); Enantiomeric excess: 97%, determined by HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 90:10, λ=214 nm, flow rate 0.7 mL/min; t_{major}=19.5 min; t_{minor}=21.4 min).

*4.4.15. (S)-tert-Butyl 1-(4-fluoropenyl)-2-nitrothylcarbamate (**3o**).* Yield: 99%; White solid; $[\alpha]_D^{25}$ 22.3 (*c* +0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.25 (t, *J*=8.0 Hz, 1H), 6.87–6.84 (dd, *J*=8.0, 1.2 Hz, 1H), 6.82–6.80 (d, *J*=8.0 Hz, 1H), 6.76 (br, 1H), 5.26 (br, 1H), 5.20–5.16 (m, 1H), 4.90 (br, 1H), 3.80 (s, 3H), 1.54–1.52 (d, *J*=8.0 Hz, 3H), 1.43 (s, 9H); Enantiomeric excess: 99.5%, determined by HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 80:20, λ=214 nm, flow rate 0.7 mL/min; t_{major}=12.0 min; t_{minor}=7.8 min).

4.5. Preparation of 6

The method of Barber was employed: a mixture of **3k** (0.4 mmol) in toluene was degassed and flushed with nitrogen several times before AIBN (0.08 mmol) and $(Bu)_3SnH$ (0.8 mmol) were added, followed by heating at reflux for 4 h. The reaction mixture was allowed to cool to room temperature and then directly purified by flash column chromatography (hexane/EtOAc as the eluent) to afford the desired product **6** as a colourless oil. On standing the product crystallized in to a white solid.

*4.5.1. (R)-tert-Butyl 1-phenylpropylcarbamate (**6**).* Yield: 80%; White solid; $[\alpha]_D^{25}$ +72.9 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.22 (m, 5H), 4.81 (br, 1H), 4.52 (br, 1H), 1.78–1.76 (m, 2H), 1.41 (s, 9H), 0.90–0.87 (t, *J=7.4* Hz, 3H); Enantiomeric excess: 87%, determined by HPLC (Chiralpak AD-H column, hexane/*i*-PrOH 90:10, λ=214 nm, flow rate 0.7 mL/min; t_{major}=7.8 min; t_{minor}=8.4 min).

4.6. Preparation of 5

According to the reported methods:[17] a solution of the nitro compound **1a** (5.0 mmol, 1.3 g, 89% ee), sodium nitrite (700 mg, 10 mmol) and acetic acid (50 mmol) in DMSO (30 mL) was heated at 40 °C for 1 day. After cooling to room temperature, 1.0 M HCl (50 mL) was added and the aqueous phase was extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography, followed by treatment with TFA in CH_2Cl_2 (10 mL) with stirring at room temperature for 24 h. Then satd aq Na_2CO_3 was added to adjust the pH value to around 9, followed by extraction with CH_2Cl_2, and the combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was added to a suspension of $NaBH_4$ (3 equiv) in THF (10 mL), followed by dropwise addition of a solution of I_2 in THF (5 mL) over 1 h at 0 °C. When finished, the solution was refluxed for 18 h before being cooled to room temperature. Methanol (10 mL) and aqueous NaOH (20%, 10 mL) were added, and the resulting mixture was extracted with CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was mixed with Et_3N (2.5 equiv), CS_2 (3 equiv) in 10 mL of DMSO and the mixture was warmed to 100 °C with irradiation at 40 W of power for 2 h. Then water was added and the resulting mixture was extracted with EtOAc, dried over Na_2SO_4, concentrated and purified by silica gel chromatography to afford **5**.

*4.6.1. (S)-4-Phenylthiazolidine-2-thione (**5**).* Yield: 56%; White solid; $[\alpha]_D^{26}$ +182.9, *c* 0.5 in $CHCl_3$ ($[\alpha]_{D(Lit.)}$ 207.0, *c* 1.0 in $CHCl_3$ for optical pure); ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (br, 1H), 7.42–7.37 (m, 5H), 5.33–5.29 (t, *J*=8.0 Hz, 1H), 3.87–3.82 (dd, *J*=11, 8.0 Hz, 1H), 3.53–3.48 (dd, *J*=11.0, 8.0 Hz, 1H).

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Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2013.04.079.

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