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Investigation of the diastereoselective Mannich reaction using imidazolidin-2-thione as a chiral auxiliary

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ABSTRACTS

Titanium mediated asymmetric Mannich reactions using imidazolidin-2-thione as a chiral auxiliary proceeded in good yields and with high diastereoselectivity to afford the *anti*-products in the presence of PPh_3 additive. A non-chelated transition state with the PPh_3-bound titanium enolate was proposed to explain the stereochemistry of the product. Alcoholysis of the adducts with methanol cleaved the imidazolidin-2-thione auxiliary to give the methyl esters in good yields and with excellent ee values.

1. Introduction

The asymmetric Mannich reaction is a powerful method in organic chemistry. It provides versatile intermediates in the syntheses of biologically important compounds containing enantiomerically enriched β-aminocarbonyl moieties.[1] Therefore, many efforts have been made to develop stereoselective Mannich-type processes.[2] Among these diverse strategies, the chiral auxiliary mediated asymmetric Mannich reaction has attracted considerable attention.[3]

Chiral auxiliaries are common construction elements in asymmetric synthesis due to their high chiral induction ability and easy cleavage from newly generated chiral compounds. Over the past few years, our group has undertaken a research program on the investigation of chiral auxiliaries[4] and their applications to synthesize insect pheromones.[5] Recently, Nair et al. reported on the preparation of (*S*)-4-isopropyl-1-phenylimidazolidin-2-thiones and their application as a chiral auxiliary in asymmetric aldol reactions providing products in good yields and with excellent diastereoselectivities.[6] Inspired by their results, we herein report an efficient system for the asymmetric Mannich reaction utilizing imidazolidin-2-thione as a chiral auxiliary and Lewis base as an additive.

2. Results and discussion

The chiral auxiliary imidazolidin-2-thiones **3** were readily prepared from L-amino acids **1** in two steps according to an established procedure (Scheme 1).[5] Acylation of **3** was then carried out to afford the N-acylated products **4**.

The Mannich reaction of *N*-propionylimidazolidin-2-thione **4a** and *N*-(4-methoxyphenyl)-benzaldimine was chosen as the model reaction to screen the reaction conditions. No reaction occurred when the reaction was conducted in the presence of LDA, and thus a Lewis acid/base reagent system was applied (Scheme 2). As can be seen from Table 1, attempts to use *n*-Bu_2BOTf or $Sn(OTf)_2$ as a Lewis acid and DIPEA as a base gave no adduct product (entries 1 and 2). It was found that $TiCl_4$ was a favorable Lewis acid of which a slight excess (1.05 equiv) was enough to complete the reaction effectively (compare entries 3–5 in Table 1). When the reaction temperature was changed from 0 °C to −78 °C, a higher yield was obtained and a better diastereomeric ratio was achieved (compare entries 3 and 6 in Table 1). Some other bases were also studied. Only 43% yield was obtained when (−)-sparteine was used as the base (entry 7, Table 1). The introduction of tetramethylethylenediamine (TMEDA) led to excellent diastereoselectivity, however the reaction yield was unsatisfactory (entry 8, Table 1).

In order to further enhance the diastereoselectivity of the titanium-mediated Mannich reaction, several additives were introduced into the reaction system (Scheme 3) since it was supposed that the additive acted as a ligand for titanium, and thus affected the stereochemical outcome.[7] The results are summarized in Table 2.

As expected, the diastereoselectivity was indeed affected by the addition of additives. Furthermore, the diastereomeric ratios were dependant upon the amounts of additives used, thus suggesting that the additive affected the enolate aggregation state and the titanium coordination sphere. A better result was observed when 1.1 equiv of additive were used (compare entries 2 and 3, and 4

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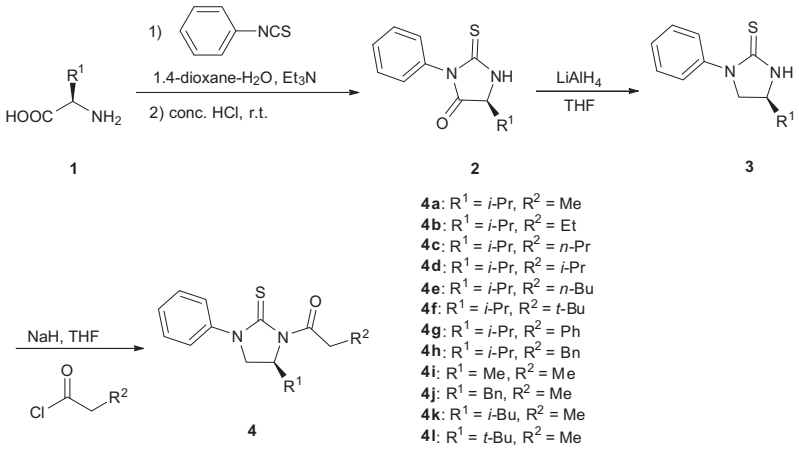
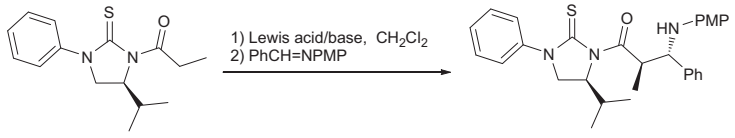


Scheme 1.

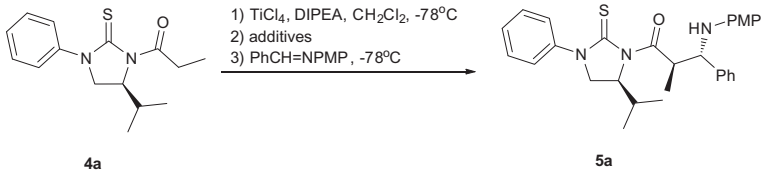


Scheme 2.

Table 1
Survey of the conditions for the Mannich reaction of **4a** and *N*-(4-methoxyphenyl)benzaldimine[a]

Entry	Lewis acid		Base	Temp (°C)	Yield[b] (%)	dr[c]
	Species	Amount (equiv)				
1	n-Bu_2BOTf	1.05	DIPEA	0	—	—
2	$Sn(OTf)_2$	1.05	DIPEA	0	—	—
3	$TiCl_4$	1.05	DIPEA	0	73	84:16
4	$TiCl_4$	1.5	DIPEA	0	75	83:17
5	$TiCl_4$	2.0	DIPEA	0	62	84:16
6	$TiCl_4$	1.05	DIPEA	−78	88	88:12
7	$TiCl_4$	1.05	(−)-sparteine	−78	43	86:14
8	$TiCl_4$	1.05	TMEDA	−78	17	98:2

[a] Reaction conditions: **4a** (1.0 equiv), *N*-(4-methoxyphenyl)benzaldimine (1.3 equiv), Lewis acid, base (1.1 equiv), CH_2Cl_2, 8 h.
[b] Isolated yield corresponds to the major adduct isomer.
[c] Determined by ^1H NMR before chromatography.



Scheme 3.

and 5 in Table 2). Surprisingly, NMP and 1,4-dioxane had no obvious influence on the process (entries 2 and 16, Table 2) while Ph_3PO gave the worst stereoselectivity (entry 12, Table 2). It was found that PPh_3 was the most suitable additive for the reaction, providing the adduct product with 97:3 dr and 90% yield (entry 7, Table 2). The other phosphine ligands including bi-dentate phosphine ligands seemed to be detrimental both for yield and diastereoselectivity (entries 8–11, Table 2). Notably, when Ph_2PCH_3, which has smaller steric size than PPh_3, was employed, an obvious decrease in dr value was observed (entry 8, Table 2). Although the addition of TMEDA resulted in excellent *anti*-diastereoselectivity, the reaction yield was unsatisfactory (entry 6, Table 2). Any attempt to improve it was unsuccessful.

With the optimal reaction conditions in hand, we next investigated the substrate scope of the asymmetric Mannich reaction with *N*-acylimidazolidin-2-thiones **4** and various aldimines (Scheme 4). The results are outlined in Table 3. The Mannich reactions proceeded with good to excellent *anti* selectivities and yields. The experimental results of entries 1–6 were comparable to, or in most cases better than, those obtained using hydantoin as an

Table 2
Influence of additives on the Mannich reaction of **4a** and *N*-(4-methoxyphenyl)benzaldimine[a]

Entry	Additive	Yield[b] (%)	dr[c]
1	None	88	88:12
2	NMP	52	89:11
3[d]	NMP	46	85:15
4	CH_3CN	86	96:4
5[e]	CH_3CN	76	94:6
6	TMEDA	8	99:1
7	PPh_3	90	98:2
8	Ph_2PCH_3	71	93:7
9	DPPF	86	95:5
10	DPPE	77	96:4
11	Xantphos	85	98:2
12	Ph_3PO	63	84:16
13	THF	70	94:6
14	Et_2O	76	94:6
15	DME	63	95:5
16	1,4-Dioxane	57	89:11

[a] Reaction conditions: **4a** (1.0 equiv), *N*-(4-methoxyphenyl)benzaldimine (1.3 equiv), $TiCl_4$ (1.05 equiv), DIPEA (1.1 equiv), additive (1.1 equiv), CH_2Cl_2, −78 °C.
[b] Isolated yield corresponds to the major adduct isomer.
[c] Determined by ^1H NMR before chromatography.
[d] 2.0 equiv of NMP were used.
[e] 2.0 equiv of CH_3CN were used.

Table 3
Mannich reactions of *N*-acyl imidazolidin-2-thiones **4** and aldimines[a]

Entry	R^1	R^2	Ar	Product	Yield[b] (%)	dr[c]
1	*i*-Pr	Me	C_6H_5	**5a**	90	98:2
2	*i*-Pr	Me	4-ClC_6H_4	**5b**	91	98:2
3	*i*-Pr	Me	3-$O_2NC_6H_4$	**5c**	86	98:2
4	*i*-Pr	Me	2,3-$(CH_3O)_2C_6H_3$	**5d**	88	98:2
5	*i*-Pr	Me	2-Furyl	**5e**	78	91:9
6	*i*-Pr	Me	2-Thienyl	**5f**	80	97:3
7	*i*-Pr	Et	C_6H_5	**5g**	88	94:6
8	*i*-Pr	*n*-Pr	C_6H_5	**5h**	94	96:4
9	*i*-Pr	*i*-Pr	C_6H_5	**5i**	65	97:3
10	*i*-Pr	*n*-Bu	C_6H_5	**5j**	92	97:3
11	*i*-Pr	*t*-Bu	C_6H_5	**5k**	trace	n.d.
12	*i*-Pr	Ph	C_6H_5	**5l**	95	94:6
13	*i*-Pr	Bn	C_6H_5	**5m**	83	94:6
14	Me	Me	C_6H_5	**5n**	87	97:3
15	Bn	Me	C_6H_5	**5o**	94	97:3
16	*i*-Bu	Me	C_6H_5	**5p**	88	98:2
17	*t*-Bu	Me	C_6H_5	**5q**	90	97:3

[a] Reaction conditions: **4** (1.0 equiv), aldimine (1.3 equiv), $TiCl_4$ (1.05 equiv), DIPEA (1.1 equiv), PPh_3 (1.1 equiv), CH_2Cl_2, −78 °C.
[b] Isolated yield corresponds to the major adduct isomer.
[c] Determined by ^1H NMR before chromatography.

Table 4
Alcoholysis of Mannich adducts **5a–f** and **5n–q**

Entry	Mannich adduct	Product	Ar	Yield[b] (%)	ee[a] (%)
1	**5a**	**6a**	C_6H_5	93	98
2	**5b**	**6b**	4-ClC_6H_4	90	99
3	**5c**	**6c**	3-$NO_2C_6H_4$	91	98
4	**5d**	**6d**	2,3-$(CH_3O)_2C_6H_3$	89	97
5	**5e**	**6e**	2-Furyl	86	97
6	**5f**	**6f**	2-Thienyl	85	97
7	**5n**	**6a**	C_6H_5	94	97
8	**5o**	**6a**	C_6H_5	92	98
9	**5p**	**6a**	C_6H_5	91	98
10	**5q**	**6a**	C_6H_5	90	98

[a] Isolated yield by silica gel chromatography.
[b] Determined by HPLC.

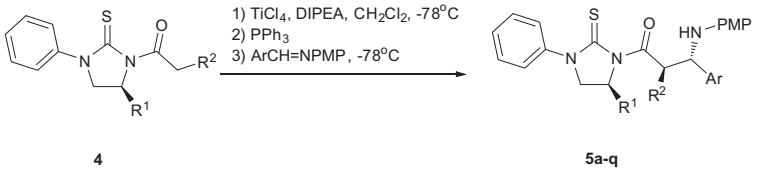
auxiliary as previously reported.[4c] *N*-Propionylimidazolidin-2-thione and 2-furyl aldimine gave the worst diastereoselectivity, with only 91:9 dr being obtained (entry 5, Table 3). Relatively low yields (65%) were obtained when R^2 was isopropyl (entries 9, Table 3). A more hindered aldimine, however, resulted in only trace amounts of product (entry 11, Table 3). It should be noted that the reaction outcome was not affected by the size of the substituent at the 4-position of the imidazolidin-2-thione ring (compare entries 1, 14–17 in Table 3), indicating that PPh_3 was the predominant factor in determining the diastereoselectivity of the reaction (see Scheme 5).

After separation from the minor diastereomer, the major adducts **5a–f** and **5n–q** were subjected to alcoholysis with methanol,[4c,8] which resulted in the quantitative recovery of chiral auxiliary **3** without a decrease of the enantiomeric purity (Scheme 4), and afforded the corresponding methyl esters **6a–f** in good yields (86–93%) and with excellent ee values (>97%) (Table 4), which were comparable to those previously reported.[4c] Almost the same enantioselectivities were obtained for different imidazolidin-2-thiones. The PPh_3 additive played a crucial role in determining the stereoselectivity of the asymmetric Mannich reaction. The absolute configuration of the Mannich adducts can be determined according to the procedure we have previously described and an *anti*-isomer was constructed to be the major product in the Mannich reaction.[4c]

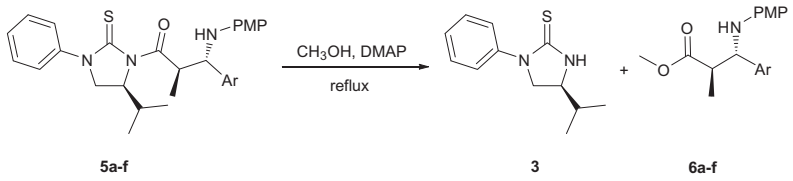
Based on the previous literature reports,[6b,10] two models can be considered to account for the observed stereoselectivity. In the absence of an additive, a coordinated chair structure involving a sulfur atom (TS-1, Scheme 6) formed which minimizes the steric interactions between aldimines and the substituents on the imidazolidin-2-thione ring, and also between the Ar and R^2 group. In the presence of PPh_3, a non-chelated configuration with the PPh_3-bound titanium enolate (TS-2, Scheme 6) was preferred which guarantees that the approach of the aldimine to the enolate is from the less hindered Re face of the carbon–carbon double bond (away from the PPh_3 ligand). Furthermore, this transition state minimizes the repulsion between the Ar and R^2 group, and most importantly between the PPh_3 and PMP group. Both of these transition states, however, afford the same stereochemical outcome.

3. Conclusions

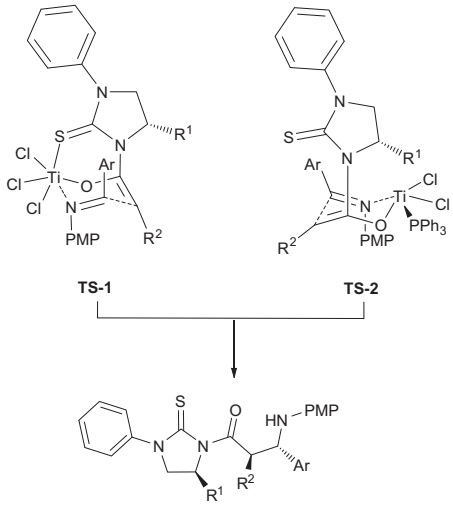
We have developed an efficient system for an asymmetric Mannich reaction, which provided access to the *anti*-isomer as the main product. The PPh_3 additive played a crucial role with regard to the stereochemical outcome of the process and a non-chelated transition state was proposed. The chiral auxiliary can



Scheme 4.



Scheme 5.



Scheme 6.

be quantitatively recovered through alcoholysis of the Mannich adducts, and afforded the corresponding methyl esters in good yields and with excellent enantiomerically selectivities.

4. Experimental

4.1. General

The aldimines were prepared by condensation of the corresponding aldehyde and *p*-methoxyphenylamine under standard conditions.[9] The solvents were dried or purified by standard procedures before use. Melting points were measured on a WRS-1A digital melting point apparatus. Optical rotations were measured using a sodium D line on WZZ-2B Automatic Polarimeter. HPLC analyses were carried out on a Dionex chromatograph (Ultimate 3000 pump, Chiralcel®OD-H or AD-H column) equipped with a diode-array UV detector. IR spectra were obtained on KBr pellets or CH_2Cl_2 solvent. NMR spectra were recorded on a Varian Unity Inova 600 spectrometer in $CDCl_3$ (^1H at 400 MHz and ^{13}C at 100 MHz) using TMS as the internal standard. High-resolution mass spectra (HRMS) were recorded on a Varian 7.0T FTMS mass spectrometer using ESI (electrospray ionization).

4.2. General procedure for preparation of 3-phenyl-2-thioxoimidazolidin-4-one

L-Amino acid (25 mmol, 1.0 equiv) was added to a solution of phenyl isothiocyanate (2.96 mL, 25 mmol, 1.0 equiv) in 1,4-dioxane–H_2O (60 mL, 1:1, v/v) and cooled to 0 °C. Then Et_3N (7.0 mL, 50 mmol, 2.0 equiv) was slowly added and the solution was stirred for 1 h, followed by the addition of concentrated HCl (6.25 mL, 75 mmol, 3.0 equiv) at 0 °C until the pH was approximately 2. The reaction mixture was stirred for another 12 h at rt, and the precipitate formed was filtered and dried to afford the desired compound.

4.2.1. (*S*)-5-Isopropyl-3-phenyl-2-thioxoimidazolidin-4-one 2a

Yield: 90%; white solid; mp 148.2–150.5 °C; $[\alpha]_D^{20} = -53.9$ (*c* 1.00, $CHCl_3$); IR: 3190, 1759, 1596, 1516, 1462, 1195 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.04 (d, J = 7.0 Hz, 3H), 1.13 (d, J = 7.0 Hz, 3H), 2.32–2.44 (m, 1H), 4.18 (d, J = 3.8 Hz, 1H), 7.23–7.32 (m, 2H), 7.41–7.56 (m, 3H), 8.29 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.34, 18.95, 31.31, 65.18, 128.40, 129.31, 129.43, 132.75, 173.15, 184.37.

4.2.2. (*S*)-5-Methyl-3-phenyl-2-thioxoimidazolidin-4-one 2b

Yield: 91%; white solid; mp 178.4–179.1 °C; $[\alpha]_D^{20} = -22.8$ (*c* 1.00, CH_2Cl_2); IR: 3178, 1748, 1593, 1530, 1455, 1193 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.51 (d, J = 6.8 Hz, 3H), 4.27 (q, J = 7.1, 7.1, 7.1 Hz, 1H), 7.32 (m, 2H), 7.48 (m, 3H), 8.52 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.91, 55.64, 128.34, 129.22, 129.36, 132.62, 174.39, 183.44; HRMS calcd for $C_{10}H_{10}N_2OS$ $[M+H]^+$: 207.0587, found 207.0579.

4.2.3. (*S*)-5-Benzyl-3-phenyl-2-thioxoimidazolidin-4-one 2c

Yield: 92%; white solid; mp 189.1–190.4 °C; $[\alpha]_D^{20} = -245.8$ (*c* 0.16, CH_2Cl_2); IR: 3164, 1747, 1598, 1518, 1454, 1190 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.11 (dd, J = 6.9, 14 Hz, 1H), 3.29 (dd, J = 14, 3.6 Hz, 1H), 4.50 (dd, J = 6.8, 4.0 Hz, 1H), 7.01 (m, 2H), 7.21–7.52 (m, 8H), 8.13 (br s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.55, 60.97, 127.89, 128.26, 129.01, 129.23, 129.36, 129.35, 132.54, 183.70; HRMS calcd for $C_{16}H_{14}N_2OS$ $[M+H]^+$: 283.0900, found 289.0901.

4.2.4. (*S*)-5-((*S*)-*sec*-Butyl)-3-phenyl-2-thioxoimidazolidin-4-one 2d

Yield: 95%; white solid; mp 160.1–161.6 °C; $[\alpha]_D^{20} = -47.0$ (*c* 0.14, CH_2Cl_2); IR: 3193, 1754, 1595, 1515, 1455, 1171 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, J = 7.4, 7.4 Hz, 3H), 1.13 (d, J = 6.9 Hz, 3H), 1.36–1.51 (m, 1H), 1.53–1.63 (m, 1H), 2.06–2.21 (m, 1H), 4.25 (d, J = 3.6 Hz, 1H), 7.32–7.37 (m, 2H), 7.45–7.60 (m, 3H), 8.86 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.60, 23.85, 37.69, 64.73, 128.32, 129.20, 129.32, 132.63, 173.23, 183.92; HRMS calcd for $C_{13}H_{16}N_2OS$ $[M+H]^+$: 249.1056, found 249.1055.

4.2.5. (*S*)-5-(*tert*-Butyl)-3-phenyl-2-thioxoimidazolidin-4-one 2e

Yield: 93%; white solid; mp 148.2–148.9 °C; $[\alpha]_D^{20} = -390.5$ (*c* 0.14, CH_2Cl_2); IR: 3197, 1754, 1595, 1515, 1455, 1197 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.11 (s, 9H), 3.90 (s, 1H), 7.25–7.33 (m, 2H), 7.39–7.53 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.59 (3C), 36.01, 68.28, 128.39, 129.22, 129.33, 132.69, 172.42, 183.77; HRMS calcd for $C_{13}H_{16}N_2OS$ $[M+H]^+$: 249.1056, found 249.1053.

4.3. General procedure for 1-phenylimidazolidin-2-thione

To a stirred solution of **2** (20.0 mmol, 1.0 equiv) in anhydrous THF (100 mL) under an N_2 atmosphere was added $LiAlH_4$ (4.55 g,

120.0 mmol, 6.0 equiv) portionwise at 0 °C. The reaction mixture was stirred at reflux for 12 h, cooled, and slowly quenched with aqueous NaOH (1 M, 30 mL, 3.0 mmol) to form a slurry, which was filtered through a Celite bed. The filtrate was taken in EtOAc (100 mL), washed with brine (50 mL), dried over anhydrous $MgSO_4$, and evaporated under vacuum to give a crude solid. The crude product was purified by column chromatography on silica gel (300–400 mesh) by eluting with a mixture of *n*-hexane /EtOAc (5:1,v/v) to give the title compound.

4.3.1. (*S*)-4-Isopropyl-1-phenylimidazolidin-2-thione 3a

Yield: 60%; white solid; mp 62.8–64.1 °C; $[\alpha]_D^{20} = -36.1$ (*c* 1.00, CH_2Cl_2); IR: 3209, 1595, 1494, 1452, 1248 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.95 (d, *J* = 4.5 Hz, 3H), 1.00 (d, *J* = 4.4 Hz, 3H), 1.77–1.90 (m, 1H), δ 3.74 (dd, *J* = 11.2, 4.8 Hz 1H), 3.82 (dd, *J* = 6.4, 5.2 Hz, 1H), 4.15–4.21 (m, 1H), 7.19–7.30 (m, 1H), 7.33–7.48 (m, 2H), 7.52–7.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.01, 18.22, 32.81, 55.56, 59.65, 124.49, 126.33, 128.82, 139.96, 181.47.

4.3.2. (*S*)-4-Methyl-1-phenylimidazolidin-2-thione 3b

Yield: 65%; white solid; mp 108.9–109.7 °C; $[\alpha]_D^{20} = -183.9$ (*c* 0.16, CH_2Cl_2); IR: 3181, 1596, 1505, 1455, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.29 (d, *J* = 3.5 Hz 3H), 3.62 (dd, *J* = 12.2, 7.3 Hz, 1H), 3.96–4.08 (m, 1H), 4.14 (dd, *J* = 9.8, 7.2 Hz, 1H), 7.13–7.24 (m, 1H), 7.30–7.44 (m, 2H), 7.48–7.63 (m, 2H), 7.94 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.27, 49.09, 58.38, 123.93, 125.65, 128.26, 139.63, 180.55; HRMS calcd for $C_{10}H_{12}N_2S$ $[M+H]^+$: 193.0794, found 193.0787.

4.3.3. (*S*)-4-Benzyl-1-phenylimidazolidin-2-thione 3c

Yield: 64%; yellow sticky solid; $[\alpha]_D^{20} = -127.6$ (*c* 0.24, CH_2Cl_2); IR: 3340, 1600, 1505, 1455, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.94 (dd, *J* = 9.6, 2.3 Hz, 1H), 2.95 (dd, *J* = 13.2, 6.2 Hz, 1H), 3.84 (dd, *J* = 9.0, 5.5 Hz, 1H), 4.17 (dd, *J* = 12.3, 3.4 Hz, 1H), 4.21–4.25 (m, 1H), 7.00 (s, 1H), 7.11–7.69 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.29, 55.05, 57.15, 124.56, 126.50, 127.38, 128.88, 129.13, 129.22, 136.16, 140.03, 182.04; HRMS calcd for $C_{16}H_{16}N_2S$ $[M+H]^+$: 269.1107, found 269.1104.

4.3.4. (*S*)-4-((*S*)-*sec*-Butyl)-1-phenylimidazolidin-2-thione 3d

Yield: 66%; white solid; mp 111.6–111.8 °C; $[\alpha]_D^{20} = -70.8$ (*c* 0.16, CH_2Cl_2); IR: 3219, 1596, 1505, 1455, 1044 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.87–1.01 (m, 6H), 1.13–1.28 (m, 1H), 1.45–1.59 (m, 1H), 1.60–1.71 (m, 1H), 3.79–3.91 (m, 2H), 4.11–4.23 (m, 1H), 7.11 (br s, 1H), 7.19–7.30 (m, 1H), 7.35–7.45 (m, 2H), 7.50–7.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.14, 14.08, 25.16, 39.00, 55.13, 58.32, 124.47, 126.28, 128.78, 139.98, 181.43; HRMS calcd for $C_{13}H_{18}N_2S$ $[M+H]^+$: 235.1263, found 235.1256.

4.3.5. (*S*)-4-(*tert*-Butyl)-1-phenylimidazolidin-2-thione 3e

Yield: 68%; white solid; mp 101.1–102.5 °C; $[\alpha]_D^{20} = -189.4$ (*c* 0.15, CH_2Cl_2); IR: 3198, 1595, 1488, 1455, 1046 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.95 (s, 9H), 3.69 (dd, *J* = 10.7, 7.3 Hz, 1H), 3.84 (dd, *J* = 9.4, 6.8 Hz, 1H), 4.07–4.21 (m, 1H), 7.19–7.27 (m, 1H), 7.33–7.42 (m, 2H), 7.52–7.60 (m, 2H), 7.75 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.11 (3C), 33.81, 53.52, 62.68, 124.47, 126.18, 128.71, 139.91, 181.16; HRMS calcd for $C_{13}H_{18}N_2S$ $[M+H]^+$: 235.1263, found 235.1256.

4.4. General procedure for the preparation of *N*-acyl imidazolidin-2-thione 4

To a stirred solution of **3** (8.0 mmol, 1.0 equiv) in anhydrous THF (40 mL) under an N_2 atmosphere was added NaH (0.38 g, 9.6 mmol, 1.2 equiv) portionwise at 0 °C. After 1 h, the corresponding acyl chloride (9.6 mmol, 1.2 equiv) was added dropwise and the mixture was stirred for 1 h. The reaction mixture was washed with aqueous $NaHCO_3$ (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification of the crude product by silica gel column chromatography (*n*-hexane/EtOAc, 8:1, v/v) gave the desired compounds **4a**–**4l**.

4.4.1. (*S*)-*N*-Propionyl-4-isopropyl-1-phenylimidazolidin-2-thione 4a

Yield: 90%; sticky orange solid; $[\alpha]_D^{20} = +98.9$ (*c* 1.00, $CHCl_3$); IR: 1683, 1597, 1498, 1456, 1200 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.81–1.06 (m, 6H), 1.20 (t, *J* = 7.3 Hz, 3H), 2.38–2.48 (m, 1H), 3.33 (dq, *J* = 17.9, 7.2 Hz, 1H), 3.51 (dq, *J* = 17.9, 7.3 Hz, 1H), 3.64 (dd, *J* = 10.6, 2.2 Hz, 1H), 4.05 (dd, *J* = 10.6, 9.2 Hz, 1H), 4.73 (dt, *J* = 9.2, 3.2 Hz, 1H), 7.32–7.40 (m, 3H), 7.43–7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.19, 15.20, 18.31, 29.73, 31.93, 50.51, 60.47, 126.27, 127.97, 129.45, 140.18, 175.95, 179.38.

4.4.2. (*S*)-*N*-Butyryl-4-isopropyl-1-phenylimidazolidin-2-thione 4b

Yield: 84%; orange sticky solid; $[\alpha]_D^{20} = +79.4$ (*c* 0.17, CH_2Cl_2); IR: 1681, 1596, 1499, 1455, 1188 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.94 (d, *J* = 4.8 Hz, 3H), 0.95 (d, *J* = 4.7 Hz, 3H), 0.99 (t, *J* = 7.4 Hz, 3H), 1.66–1.84 (m, 2H), 2.35–2.48 (m, 1H), 3.27 (ddd, *J* = 16.6, 8.3, 6.6 Hz, 1H), 3.51 (ddd, *J* = 16.6, 8.4, 6.2 Hz, 1H), 3.63 (dd, *J* = 10.7, 2.2 Hz, 1H), 4.04 (dd, *J* = 10.4, 9.6 Hz, 1H), 4.73 (dt, *J* = 9.8, 2.5 Hz, 1H), 7.31–7.39 (m, 3H), 7.42–7.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.74, 14.99, 18.18, 18.52, 29.50, 39.87, 50.22, 60.21, 126.13, 127.86, 129.31, 139.91, 174.85, 179.07; HRMS calcd for $C_{16}H_{22}N_2OS$ $[M+H]^+$: 291.1526, found 291.1527.

4.4.3. (*S*)-*N*-Valeryl-4-isopropyl-1-phenylimidazolidin-2-thione 4c

Yield: 80%; sticky orange solid; $[\alpha]_D^{20} = +92.2$ (*c* 0.15, CH_2Cl_2); IR: 1682, 1597, 1499, 1465, 1189 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.88–1.00 (m, 9H), 1.34–1.47 (m, 2H), 1.60–1.81 (m, 2H), 2.34–2.47 (m, 1H), 3.29 (ddd, *J* = 16.6, 8.7, 6.3 Hz, 1H), 3.53 (ddd, *J* = 16.2, 8.8, 6.1 Hz, 1H), 3.61 (dd, *J* = 10.7, 2.2 Hz, 1H), 4.03 (dd, *J* = 10.7, 9.2 Hz, 1H), 4.72 (dt, *J* = 9.3, 2.3 Hz, 1H), 7.29–7.39 (m, 3H), 7.40–7.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.91, 14.90, 18.09, 22.22, 27.11, 29.41, 37.62, 50.11, 60.12, 126.03, 127.73, 129.20, 139.83, 174.91, 178.94; HRMS calcd for $C_{17}H_{24}N_2OS$ $[M+H]^+$: 305.1682, found 305.1671.

4.4.4. (*S*)-*N*-Isovaleryl-4-isopropyl-1-phenylimidazolidin-2-thione 4d

Yield: 74%; sticky orange solid; $[\alpha]_D^{20} = +57.9$ (*c* 0.19, CH_2Cl_2); IR: 1681, 1597, 1499, 1466, 1196 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.93 (d, *J* = 3.9 Hz, 3H), 0.95 (d, *J* = 3.6 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), 2.22–2.34 (m, 1H), 2.35–2.47 (m, 1H), 3.16 (dd, *J* = 15.9, 7.5 Hz, 1H), 3.48 (dd, *J* = 15.9, 6.3 Hz, 1H), 3.61 (dd, *J* = 10.8, 2.3 Hz, 1H), 4.02 (dd, *J* = 10.8, 9.2 Hz, 1H), 4.73 (dt, *J* = 9.3, 3.2 Hz, 1H), 7.29–7.39 (m, 3H), 7.40–7.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.87, 18.14, 22.31, 22.55, 25.56, 29.42, 46.25, 50.08, 60.10, 126.09, 127.78, 129.24, 139.88, 174.14, 178.99; HRMS calcd for $C_{17}H_{24}N_2OS$ $[M+H]^+$: 305.1682, found 305.1672.

4.4.5. (*S*)-*N*-Hexanoyl-4-isopropyl-1-phenylimidazolidin-2-thione 4e

Yield: 54.6%; sticky orange solid; $[\alpha]_D^{20} = +54.6$ (*c* 0.20, CH_2Cl_2); IR: 1681, 1597, 1498, 1465, 1186 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.79–1.03 (m, 9H), 1.23–1.45 (m, 4H), 1.56–1.85 (m, 2H), 2.28–2.54 (m, 1H), 3.29 (ddd, *J* = 16.5, 8.7, 6.3 Hz, 1H), 3.52 (ddd, *J* = 16.4, 8.8, 6.1 Hz, 1H), 3.61 (dd, *J* = 10.7, 2.3 Hz, 1H), 4.03

(dd, J = 10.6, 9.3 Hz, 1H), 4.72 (dt, J = 9.3, 2.4 Hz, 1H), 7.29–7.39 (m, 3H), 7.41–7.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.96, 14.92, 18.11, 22.47, 24.72, 29.43, 31.30, 37.89, 50.13, 60.15, 126.05, 127.76, 129.23, 139.85, 174.97, 178.97; HRMS calcd for $C_{18}H_{26}N_2OS$ $[M+H]^+$: 319.1839, found 319.1832.

4.4.6. (*S*)-*N*-*tert*-Butylacetyl-4-isopropyl-1-phenylimidazolidin-2-thione 4f

Yield: 77%; sticky orange solid; $[\alpha]_D^{20}$ = +92.6 (c 0.17, CH_2Cl_2); IR: 1681, 1597, 1499, 1465, 1162 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (d, J = 6.5 Hz, 3H), 0.97 (d, J = 6.0 Hz, 3H), 1.11 (s, 9H), 2.37–2.47 (m, 1H), 3.41 (d, J = 15.6 Hz, 1H), 3.56–3.64 (m, 2H), 4.00 (dd, J = 10.6, 9.2 Hz, 1H), 4.74 (dt, J = 9.7, 2.5 Hz, 1H), 7.31–7.38 (m, 3H), 7.41–7.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.05, 18.26, 29.74, 31.73, 47.82, 50.07, 60.35, 126.24, 127.89, 129.33, 140.01, 173.61, 179.44; HRMS calcd for $C_{18}H_{26}N_2OS$ $[M+H]^+$: 319.1839, found 319.1825.

4.4.7. (*S*)-*N*-Phenylacetyl-4-isopropyl-1-phenylimidazolidin-2-thione 4g

Yield: 72%; sticky orange solid; $[\alpha]_D^{20}$ = +107.7 (c 0.22, CH_2Cl_2); IR: 1681, 1597, 1487, 1416, 1179 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H), 2.33–2.49 (m, 1H), 3.60 (dd, J = 10.8, 2.1 Hz, 1H), 4.00 (dd, J = 10.7, 9.3 Hz, 1H), 4.70 (dt, J = 9.2, 2.2 Hz, 1H), 4.77 (d, J = 16.6 Hz, 1H), 4.93 (d, J = 16.6 Hz, 1H), 7.19–7.26 (m, 1H), 7.27–7.48 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.90, 18.12, 29.39, 43.86, 50.15, 60.58, 126.07, 126.70, 127.95, 128.29, 129.33, 129.87, 134.92, 139.72, 172.91, 178.93; HRMS calcd for $C_{20}H_{22}N_2OS$ $[M+H]^+$: 339.1526, found 339.1516.

4.4.8. (*S*)-*N*-(3-Phenylpropionyl)-4-isopropyl-1-phenylimidazolidin-2-thione 4h

Yield: 76%; sticky orange solid; $[\alpha]_D^{20}$ = +87.5 (c 0.14, CH_2Cl_2); IR: 1681, 1597, 1479, 1463, 1189 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (d, J = 1.6 Hz, 3H), 0.91 (d, J = 1.5 Hz, 3H), 2.32–2.43 (m, 1H), 2.96–3.13 (m, 2H), 3.57 (dd, J = 10.8, 2.4 Hz, 1H), 3.69 (ddd, J = 16.4, 8.8, 6.6 Hz, 1H), 3.85 (ddd, J = 16.7, 8.9, 6.1 Hz, 1H), 3.94 (dd, J = 10.7, 9.2 Hz, 1H), 4.66 (dt, J = 9.8, 2.5 Hz, 1H), 7.12–7.19 (m, 1H), 7.22–7.36 (m, 7H), 7.38–7.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.94, 18.13, 29.44, 31.07, 33.17, 39.37, 50.17, 60.29, 125.95, 126.04, 127.85, 128.29, 128.58, 129.28, 139.75, 141.00, 173.98, 178.86; HRMS calcd for $C_{21}H_{24}N_2OS$ $[M+H]^+$: 353.1682, found 353.1675.

4.4.9. (*S*)-*N*-Propionyl-4-methyl-1-phenylimidazolidin-2-thione 4i

Yield: 89%; white solid; mp 86.4–87.6 °C; $[\alpha]_D^{20}$ = +225.7 (c 0.11, CH_2Cl_2); IR: 1681, 1596, 1498, 1456, 1195 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (t, J = 7.3, 7.3 Hz, 3H), 1.46 (d, J = 6.2 Hz, 3H), 3.30 (dq, J = 17.8, 7.3 Hz, 1H), 3.41–3.53 (m, 2H), 4.18 (dd, J = 10.1, 8.6 Hz, 1H), 4.85 (dt, J = 8.5, 6.0 Hz, 1H), 7.32–7.43 (m, 3H), 7.43–7.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.02, 19.78, 31.96, 52.24, 56.69, 126.73, 127.99, 129.40, 139.99, 175.65, 178.33; HRMS calcd for $C_{13}H_{16}N_2OS$ $[M+H]^+$: 249.1056, found 249.1051.

4.4.10. (*S*)-*N*-Propionyl-4-benzyl-1-phenylimidazolidin-2-thione 4j

Yield: 90%; white solid; mp 85.9–87.2 °C; $[\alpha]_D^{20}$ = +93.9 (c 0.43, CH_2Cl_2); IR: 1681, 1596, 1488, 1455, 1156 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (t, J = 7.2 Hz, 3H), 3.01 (dd, J = 13.5, 8.0 Hz, 1H), 3.13 (dd, J = 13.5, 3.2 Hz, 1H), 3.35 (dq, J = 17.7, 7.3 Hz, 1H), 3.56 (dq, J = 17.9, 7.3 Hz, 1H), 3.60 (dd, J = 10.5, 1.1 Hz, 1H), 3.99 (dd, J = 16.4, 7.0 Hz, 1H), 4.98–5.02 (m, 1H), 7.07 (m, 2H), 7.21–7.26 (m, 2H), 7.26–7.35 (m, 3H), 7.36–7.41 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.09, 32.00, 38.34, 53.21, 56.92, 126.24, 127.25, 127.94, 128.90, 129.27, 129.71, 135.91, 139.73, 175.81, 178.59; HRMS calcd for $C_{19}H_{20}N_2OS$ $[M+H]^+$: 325.1369, found 325.1370.

4.4.11. (*S*)-*N*-Propionyl-4-((*S*)-*sec*-butyl)-1-phenylimidazolidin-2-thione 4k

Yield: 88%; yellow gum; $[\alpha]_D^{20}$ = +91.3 (c 0.65, CH_2Cl_2); IR: 1688, 1596, 1488, 1455, 1196 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88–1.04 (m, 6H), 1.13–1.27 (m, 4H), 1.28–1.42 (m, 1H), 2.09–2.28 (m, 1H), 3.33 (dq, J = 17.9, 7.2 Hz, 1H), 3.51 (dq, J = 17.8, 7.3 Hz, 1H), 3.63 (dd, J = 10.6, 2.5 Hz 1H), 4.83 (dt, J = 9.4, 2.8 Hz, 1H), 7.31–7.39 (m, 3H), 7.41–7.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.96, 11.71, 12.15, 25.56, 31.89, 35.93, 50.09, 59.12, 126.08, 127.83, 129.27, 139.80, 175.63, 179.09; HRMS calcd for $C_{16}H_{22}N_2OS$ $[M+H]^+$: 291.1526, found 291.1523.

4.4.12. (*S*)-*N*-Propionyl-4-(*tert*-butyl)-1-phenylimidazolidin-2-thione 4l

Yield: 91%; white solid; mp 71.1–71.7 °C; $[\alpha]_D^{20}$ = +45.2 (c 0.56, CH_2Cl_2); IR: 1682, 1596, 1485, 1455, 1180 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (s, 9H), 1.20 (t, J = 7.3 Hz, 3H), 3.31 (dq, J = 17.4, 7.2 Hz, 1H), 3.50 (dq, J = 17.2, 7.3 Hz, 1H), 3.66 (dd, J = 10.9, 1.4 Hz, 1H), 4.13 (dd, J = 10.9, 8.4 Hz, 1H), 4.82 (dd, J = 8.4, 1.4 Hz, 1H), 7.29–7.37 (m, 1H), 7.37–7.49 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.41, 25.87, 31.76, 36.43, 52.25, 62.20, 125.71, 127.76, 129.32, 139.82, 175.97, 179.86; HRMS calcd for $C_{16}H_{22}N_2OS$ $[M+H]^+$: 291.1526, found 291.1525.

4.5. General procedure for the preparation of *N*-acyl imidazolidin-2-thione 4

To a stirred solution of **3** (8 mmol, 1.0 equiv) in anhydrous THF (40 mL) under an N_2 atmosphere was added NaH (0.38 g, 9.6 mmol, 1.2 equiv) portionwise at 0 °C. After 1 h, the corresponding acyl chloride (9.6 mmol, 1.2 equiv) was added dropwise and the mixture was stirred for 1 h. The reaction mixture was washed with aqueous $NaHCO_3$ (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated. Purification of the crude product by silica gel column chromatography (n-hexane/EtOAc, 8:1, v/v) gave the desired compound **4a**–**4h**.

4.5.1. (*S*)-*N*-Propionyl-4-isopropyl-1-phenylimidazolidin-2-thione 4a

Yield: 90%; sticky orange solid; $[\alpha]_D^{20}$ = +98.9 (c 1.00, $CHCl_3$); IR: 1683, 1597, 1498, 1456, 1200 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81–1.06 (m, 6H), 1.20 (t, J = 7.3 Hz, 3H), 2.38–2.48 (m, 1H), 3.33 (dq, J = 17.9, 7.2 Hz, 1H), 3.51 (dq, J = 17.9, 7.3 Hz, 1H), 3.64 (dd, J = 10.6, 2.2 Hz, 1H), 4.05 (dd, J = 10.6, 9.2 Hz, 1H), 4.73 (dt, J = 9.2, 3.2 Hz, 1H), 7.32–7.40 (m, 3H), 7.43–7.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.19, 15.20, 18.31, 29.73, 31.93, 50.51, 60.47, 126.27, 127.97, 129.45, 140.18, 175.95, 179.38.

4.5.2. (*S*)-*N*-Butyryl-4-isopropyl-1-phenylimidazolidin-2-thione 4b

Yield: 84%; sticky orange solid; $[\alpha]_D^{20}$ = +79.4 (c 0.17, CH_2Cl_2); IR: 1681, 1596, 1499, 1455, 1188 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (d, J = 4.8 Hz, 3H), 0.95 (d, J = 4.7 Hz, 3H), 0.99 (t, J = 7.4 Hz, 3H), 1.66–1.84 (m, 2H), 2.35–2.48 (m, 1H), 3.27 (ddd, J = 16.6, 8.3, 6.6 Hz, 1H), 3.51 (ddd, J = 16.6, 8.4, 6.2 Hz, 1H), 3.63 (dd, J = 10.7, 2.2 Hz, 1H), 4.04 (dd, J = 10.4, 9.6 Hz, 1H), 4.73 (dt, J = 9.8, 2.5 Hz, 1H), 7.31–7.39 (m, 3H), 7.42–7.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.74, 14.99, 18.18, 18.52, 29.50, 39.87, 50.22, 60.21, 126.13, 127.86, 129.31, 139.91, 174.85, 179.07; HRMS calcd for $C_{16}H_{22}N_2OS$ $[M+H]^+$: 291.1526, found 291.1527.

4.5.3. (*S*)-*N*-Valeryl-4-isopropyl-1-phenylimidazolidin-2-thione 4c

Yield: 80%; sticky orange solid; $[\alpha]_D^{20}$ = +92.2 (*c* 0.15, CH_2Cl_2); IR: 1682, 1597, 1499, 1465, 1189 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.88–1.00 (m, 9H), 1.34–1.47 (m, 2H), 1.60–1.81 (m, 2H), 2.34–2.47 (m, 1H), 3.29 (ddd, *J* = 16.6, 8.7, 6.3 Hz, 1H), 3.53 (ddd, *J* = 16.2, 8.8, 6.1 Hz, 1H), 3.61 (dd, *J* = 10.7, 2.2 Hz, 1H), 4.03 (dd, *J* = 10.7, 9.2 Hz, 1H), 4.72 (dt, *J* = 9.3, 2.3 Hz, 1H), 7.29–7.39 (m, 3H), 7.40–7.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.91, 14.90, 18.09, 22.22, 27.11, 29.41, 37.62, 50.11, 60.12, 126.03, 127.73, 129.20, 139.83, 174.91, 178.94; HRMS calcd for $C_{17}H_{24}N_2OS$ $[M+H]^+$: 305.1682, found 305.1671.

4.5.4. (*S*)-*N*-Isovaleryl-4-isopropyl-1-phenylimidazolidin-2-thione 4d

Yield: 74%; sticky orange solid; $[\alpha]_D^{20}$ = +57.9 (*c* 0.19, CH_2Cl_2); IR: 1681, 1597, 1499, 1466, 1196 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.93 (d, *J* = 3.9 Hz, 3H), 0.95 (d, *J* = 3.6 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), 2.22–2.34 (m, 1H), 2.35–2.47 (m, 1H), 3.16 (dd, *J* = 15.9, 7.5 Hz, 1H), 3.48 (dd, *J* = 15.9, 6.3 Hz, 1H), 3.61 (dd, *J* = 10.8, 2.3 Hz, 1H), 4.02 (dd, *J* = 10.8, 9.2 Hz, 1H), 4.73 (dt, *J* = 9.3, 3.2 Hz, 1H), 7.29–7.39 (m, 3H), 7.40–7.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.87, 18.14, 22.31, 22.55, 25.56, 29.42, 46.25, 50.08, 60.10, 126.09, 127.78, 129.24, 139.88, 174.14, 178.99; HRMS calcd for $C_{17}H_{24}N_2OS$ $[M+H]^+$: 305.1682, found 305.1672.

4.5.5. (*S*)-*N*-Hexanoyl-4-isopropyl-1-phenylimidazolidin-2-thione 4e

Yield: 54.6%; sticky orange solid; $[\alpha]_D^{20}$ = +54.6 (*c* 0.20, CH_2Cl_2); IR: 1681, 1597, 1498, 1465, 1186 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.79–1.03 (m, 9H), 1.23–1.45 (m, 4H), 1.56–1.85 (m, 2H), 2.28–2.54 (m, 1H), 3.29 (ddd, *J* = 16.5, 8.7, 6.3 Hz, 1H), 3.52 (ddd, *J* = 16.4, 8.8, 6.1 Hz, 1H), 3.61 (dd, *J* = 10.7, 2.3 Hz, 1H), 4.03 (dd, *J* = 10.6, 9.3 Hz, 1H), 4.72 (dt, *J* = 9.3, 2.4 Hz, 1H), 7.29–7.39 (m, 3H), 7.41–7.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.96, 14.92, 18.11, 22.47, 24.72, 29.43, 31.30, 37.89, 50.13, 60.15, 126.05, 127.76, 129.23, 139.85, 174.97, 178.97; HRMS calcd for $C_{18}H_{26}N_2OS$ $[M+H]^+$: 319.1839, found 319.1832.

4.5.6. (*S*)-*N*-*tert*-Butylacetyl-4-isopropyl-1-phenylimidazolidin-2-thione 4f

Yield: 77%; sticky orange solid; $[\alpha]_D^{20}$ = +92.6 (*c* 0.17, CH_2Cl_2); IR: 1681, 1597, 1499, 1465, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.94 (d, *J* = 6.5 Hz, 3H), 0.97 (d, *J* = 6.0 Hz, 3H), 1.11 (s, 9H), 2.37–2.47 (m, 1H), 3.41 (d, *J* = 15.6 Hz, 1H), 3.56–3.64 (m, 2H), 4.00 (dd, *J* = 10.6, 9.2 Hz, 1H), 4.74 (dt, *J* = 9.7, 2.5 Hz, 1H), 7.31–7.38 (m, 3H), 7.41–7.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.05, 18.26, 29.74, 31.73, 47.82, 50.07, 60.35, 126.24, 127.89, 129.33, 140.01, 173.61, 179.44; HRMS calcd for $C_{18}H_{26}N_2OS$ $[M+H]^+$: 319.1839, found 319.1825.

4.5.7. (*S*)-*N*-Phenylacetyl-4-isopropyl-1-phenylimidazolidin-2-thione 4g

Yield: 72%; sticky orange solid; $[\alpha]_D^{20}$ = +107.7 (*c* 0.22, CH_2Cl_2); IR: 1681, 1597, 1487, 1416, 1179 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.89 (d, *J* = 7.0 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 3H), 2.33–2.49 (m, 1H), 3.60 (dd, *J* = 10.8, 2.1 Hz, 1H), 4.00 (dd, *J* = 10.7, 9.3 Hz, 1H), 4.70 (dt, *J* = 9.2, 2.2 Hz, 1H), 4.77 (d, *J* = 16.6 Hz, 1H), 4.93 (d, *J* = 16.6 Hz, 1H), 7.19–7.26 (m, 1H), 7.27–7.48 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.90, 18.12, 29.39, 43.86, 50.15, 60.58, 126.07, 126.70, 127.95, 128.29, 129.33, 129.87, 134.92, 139.72, 172.91, 178.93; HRMS calcd for $C_{20}H_{22}N_2OS$ $[M+H]^+$: 339.1526, found 339.1516.

4.5.8. (*S*)-*N*-(3-Phenylpropionyl)-4-isopropyl-1-phenylimidazolidin-2-thione 4h

Yield: 76%; sticky orange solid; $[\alpha]_D^{20}$ = +87.5 (*c* 0.14, CH_2Cl_2); IR: 1681, 1597, 1479, 1463, 1189 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.90 (d, *J* = 1.6 Hz, 3H), 0.91 (d, *J* = 1.5 Hz, 3H), 2.32–2.43 (m, 1H), 2.96–3.13 (m, 2H), 3.57 (dd, *J* = 10.8, 2.4 Hz, 1H), 3.69 (ddd, *J* = 16.4, 8.8, 6.6 Hz, 1H), 3.85 (ddd, *J* = 16.7, 8.9, 6.1 Hz, 1H), 3.94 (dd, *J* = 10.7, 9.2 Hz, 1H), 4.66 (dt, *J* = 9.8, 2.5 Hz, 1H), 7.12–7.19 (m, 1H), 7.22–7.36 (m, 7H), 7.38–7.45 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.94, 18.13, 29.44, 31.07, 33.17, 39.37, 50.17, 60.29, 125.95, 126.04, 127.85, 128.29, 128.58, 129.28, 139.75, 141.00, 173.98, 178.86; HRMS calcd for $C_{21}H_{24}N_2OS$ $[M+H]^+$: 353.1682, found 353.1675.

4.5.9. General procedure for the Mannich reactions

A solution of *N*-acyl imidazolidin-2-thione **4a**–**4h** (1.0 mmol) in anhydrous CH_2Cl_2 (6 mL) was cooled to −78 °C under an N_2 atmosphere, and $TiCl_4$ (0.12 ml, 1.05 mmol) was added dropwise. The mixture was stirred at −78 °C for 15 min, then DIPEA (0.19 ml, 1.1 mmol) was slowly added. The dark red solution was stirred at −78 °C for another 30 min, and a solution of Ph_3P (0.289 g, 1.1 mmol) in CH_2Cl_2 (2 mL) was slowly added. The mixture was stirred for 10 min at −78 °C, then a solution of the corresponding aldimine (1.3 mmol) in anhydrous CH_2Cl_2 (3 mL) was added dropwise. The reaction was quenched after 8 h by the addition of saturated aqueous NH_4Cl (3 ml). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (20 mL × 3). The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated. ^1H NMR analysis of the crude mixture revealed the diastereoselectivity. Purification of the crude product by silica gel column chromatography (*n*-hexane/EtOAc, 10:1, v/v) gave the major Mannich adducts **5b**–**5m**.

4.5.10. (5*S*,2′*R*,3′*S*)-5-Isopropyl-3-phenyl-1-[2′-methyl-3′-(*p*-methoxyphenylamino)-3′-phenyl-propionyl]imidazolidin-2-thione 5a

Yield: 90%; white solid; mp 69.6–70.8 °C; $[\alpha]_D^{20}$ = +123.5 (*c* 0.28, CH_2Cl_2); IR: 3307, 1681, 1597, 1514, 1456, 1185 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (d, *J* = 2.0 Hz, 3H), 0.88 (d, *J* = 2.6 Hz, 3H), 1.04 (d, *J* = 6.5 Hz, 3H), 2.29–2.46 (m, 1H), 3.61–3.68 (m, 4H), 4.04 (dd, *J* = 10.8, 9.1 Hz, 1H), 4.49 (d, *J* = 9.8 Hz, 1H), 4.76 (dq, *J* = 9.0, 2.2 Hz, 1H), 5.75 (dt, *J* = 15.9, 6.8 Hz, 1H), 6.49 (d, *J* = 8.4 Hz, 2H), 6.62 (d, *J* = 8.2 Hz, 2H), 7.15–7.26 (m, 2H), 7.28–7.52 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.07, 16.13, 18.16, 29.67, 42.55, 50.40, 55.75, 61.27, 64.36, 114.60, 114.64, 126.41, 127.92, 128.36, 128.50, 129.58, 139.78, 139.82, 151.97, 177.78, 179.56; HRMS calcd for $C_{29}H_{33}N_3O_2S$ $[M+H]^+$: 488.2366, found: 488.2360.

4.5.11. (5*S*,2′*R*,3′*S*)-5-Isopropyl-3-phenyl-1-[2′-methyl-3′-(*p*-methoxyphenylamino)-3′-(*p*-chloro-phenyl)-propionyl]imidazolidin-2-thione 5b

Yield: 91%; white solid; mp 78.2–78.9 °C; $[\alpha]_D^{20}$ = +95.2 (*c* 0.14, CH_2Cl_2); IR: 3303, 1682, 1596, 1513, 1488, 1186 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.83–0.91 (m, 6H), 1.05 (d, *J* = 6.6 Hz, 3H), 2.30–2.40 (m, 1H), 3.61–3.69 (m, 4H), 3.96–4.11 (m, 1H), 4.48 (d, *J* = 9.6 Hz, 1H), 4.72–4.80 (m, 1H), 5.73 (dt, *J* = 16.0, 6.6 Hz, 1H), 6.48 (d, *J* = 8.4 Hz, 2H), 6.63 (d, *J* = 8.6 Hz, 2H), 7.21–7.27 (m, 1H), 7.34–7.55 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.12, 16.09, 18.18, 29.81, 42.47, 50.54, 55.84, 61.33, 63.92, 114.86, 115.61, 126.42, 128.40, 128.61, 128.74, 129.34, 129.61, 133.17, 139.88, 140.25, 152.46, 177.46, 179.59; HRMS calcd for $C_{29}H_{32}ClN_3O_2S$ $[M+H]^+$: 522.1977, found: 522.1985.

4.5.12. (5*S*,2′*R*,3′*S*)-5-Isopropyl-3-phenyl-1-[2′-methyl-3′-(*p*-methoxyphenylamino)-3′-(*m*-nitro-phenyl)-propionyl]imidazolidin-2-thione 5c

Yield: 86%; yellow solid; mp 88.7–89.4 °C; $[\alpha]_D^{20}$ = +155.1 (*c* 0.13, CH_2Cl_2); IR: 3300, 1682, 1598, 1530, 1486, 1188 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.92 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 7.2 Hz, 3H), 1.14 (d, *J* = 6.3 Hz, 3H), 2.34–2.51 (m, 1H), 3.67–3.76 (m, 4H), 4.08–4.16 (m, 1H), 4.69 (d, *J* = 9.2 Hz, 1H), 4.77–4.85 (m, 1H), δ 5.88 (dt, *J* = 15.7, 7.2 Hz, 1H), 6.55 (d, *J* = 8.4 Hz, 2H), 6.69 (d, *J* = 8.4 Hz, 2H), 7.41–7.59 (m, 6H), 7.88 (d, *J* = 7.6 Hz, 1H), 8.11 (d, *J* = 8.3 Hz, 1H), 8.34 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.11, 16.14, 18.16, 29.84, 42.27, 50.60, 55.81, 61.42, 63.62, 114.97, 115.11, 122.57, 122.85, 126.39, 128.51, 129.58, 129.66, 133.86, 139.76, 140.47, 144.74, 148.64, 152.39, 176.95, 179.58; HRMS calcd for $C_{29}H_{32}N_4O_4S$ $[M+H]^+$: 533.2217, found: 533.2226.

4.5.13. (5*S*,2′*R*,3′*S*)-5-Isopropyl-3-phenyl-1-[2′-methyl-3′-(*p*-methoxyphenylamino)-3′-(2″,3″-dimethoxyphenyl)-propionyl] imidazolidin-2-thione 5d

Yield: 88%; white solid; mp 82.6–83.7 °C; $[\alpha]_D^{20}$ = +85.1 (*c* 0.58, CH_2Cl_2); IR: 3312, 1682, 1596, 1514, 1480, 1185 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (d, *J* = 1.9 Hz, 3H), 0.89 (d, *J* = 1.6 Hz, 3H), 1.04 (d, *J* = 6.6 Hz, 3H), 2.31–2.45 (m, 1H), 3.62–3.67 (m, 4H), 3.81 (s, 3H), 3.92 (s, 3H), 4.04 (dd, *J* = 10.7, 9.1 Hz, 1H), 4.78 (dq, *J* = 9.1, 2.1 Hz, 1H), 5.03 (d, *J* = 10.2 Hz, 1H), 5.78 (dt, *J* = 16.8, 6.5 Hz, 1H), 6.59 (d, *J* = 9.0 Hz, 2H), 6.63 (d, *J* = 8.9 Hz, 2H), 6.71–7.13 (m, 3H), 7.35–7.56 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.03, 15.93, 18.16, 29.56, 42.38, 550.33, 55.68, 55.71, 61.08, 61.19, 111.25, 114.54, 114.57, 115.31, 120.11, 124.16, 126.44, 128.26, 129.53, 129.56, 139.91, 147.83, 151.92, 152.35, 178.12, 179.56; HRMS calcd for $C_{31}H_{37}N_3O_4S$ $[M+H]^+$: 548.2578, found: 548.2590.

4.5.14. (5*S*,2′*R*,3′*S*)-5-Isopropyl-3-phenyl-1-[2′-methyl-3′-(*p*-methoxyphenylamino)-3′-(2″-furyl)-propionyl]imidazolidin-2-thione 5e

Yield: 68%; white solid; mp 76.2–77.4 °C; $[\alpha]_D^{20}$ = +148.3 (*c* 0.15, CH_2Cl_2); IR: 3297, 1680, 1596, 1513, 1499, 1191 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.92 (d, *J* = 1.4 Hz, 3H), 0.94 (d, *J* = 1.0 Hz, 3H), 1.25 (d, *J* = 6.6 Hz, 1H), 2.36–2.47 (m, 1H), 3.71–3.76 (m, 4H), 4.05 (dd, *J* = 9.7, 9.6 Hz, 1H), 4.81 (dq, *J* = 9.0, 2.0 Hz, 1H), 4.87 (d, *J* = 9.5 Hz, 1H), 5.95 (dt, *J* = 16.0, 6.6 Hz, 1H), 6.64 (d, *J* = 8.8 Hz, 2H), 6.74 (d, *J* = 8.8 Hz, 2H), 6.89–7.23 (m, 3H), 7.38–7.59 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.97, 16.03, 18.04, 29.42, 43.01, 50.08, 55.51, 59.52, 60.94, 114.45, 115.01, 126.21, 126.44, 129.35, 139.57, 140.89, 141.60, 146.75, 146.89, 151.90, 152.13, 177.06, 179.20; HRMS calcd for $C_{27}H_{31}N_3O_3S$ $[M+H]^+$: 478.2159, found: 478.2147.

4.5.15. (5*S*,2′*R*,3′*S*)-5-Isopropyl-3-phenyl-1-[2′-methyl-3′-(*p*-methoxyphenylamino)-3′-(2″-thienyl)-propionyl]imidazolidin-2-thione 5f

Yield: 80%; white solid; mp 74.6–76.0 °C; $[\alpha]_D^{20}$ = +133.3 (*c* 0.40, CH_2Cl_2); IR: 3307, 1682, 1597, 1514, 1486, 1187 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.86 (d, *J* = 5.6 Hz, 3H), 0.88 (d, *J* = 5.4 Hz, 3H), 1.13 (d, *J* = 6.6 Hz, 1H), 2.27–2.43 (m, 1H), 3.62–3.70 (m, 4H), 4.02 (dd, *J* = 10.7, 9.2 Hz, 1H), 4.67 (d, *J* = 9.7 Hz, 1H), 4.75 (dq, *J* = 9.2, 2.2 Hz, 1H), 5.87 (dt, *J* = 16.4, 8.0 Hz, 1H), 6.20–6.26 (m, 2H), 6.59 (d, *J* = 8.6 Hz, 2H), 6.67 (d, *J* = 9.0 Hz, 2H), 7.28–7.30 (m, 1H), 7.33–7.50 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.04, 15.50, 17.99, 29.37, 41.23, 50.16, 55.69, 57.87, 60.93, 107.77, 110.13, 114.54, 114.63, 115.72, 126.32, 128.20, 129.48, 139.77, 141.85, 152.46, 154.42, 177.22, 179.24; HRMS calcd for $C_{27}H_{31}N_3O_2S_2$ $[M+H]^+$: 494.1930, found: 494.1931.

4.5.16. (5*S*,2′*R*,3′*S*)-5-Isopropyl-3-phenyl-1-[2′-methyl-3′-(*p*-methoxyphenylamino)-3′-phenyl-butyryl]imidazolidin-2-thione 5g

Yield: 88%; white solid; mp 137.6–138.4 °C; $[\alpha]_D^{20}$ = +165.2 (*c* 0.11, CH_2Cl_2); IR: 3308, 1681, 1596, 1514, 1463, 1180 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.70–0.93 (m, 9H), 1.19–1.33 (m, 1H), 1.68–1.83 (m, 1H), 2.31–2.43 (m, 1H), 3.57–3.65 (m, 4H), 3.99 (dd, *J* = 10.8, 8.9 Hz, 1H), 4.54 (d, *J* = 9.7 Hz, 1H), 4.75 (dq, *J* = 8.9, 1.8 Hz, 1H), 5.73 (dt, *J* = 15.6, 4.3 Hz, 1H), 6.49 (d, *J* = 8.8 Hz, 2H), 6.60 (d, *J* = 8.9 Hz, 2H), 7.13–7.19 (m, 1H), 7.22–7.28 (m, 2H), 7.32–7.50 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.71, 14.91, 17.95, 24.36, 29.68, 49.74, 50.41, 55.66, 61.24, 62.66, 114.53, 114.89, 126.28, 127.17, 127.78, 128.20, 128.39, 129.44, 139.65, 140.95, 142.02, 151.64, 177.13, 179.46; HRMS calcd for $C_{30}H_{35}N_3O_2S$ $[M+H]^+$: 502.2523, found 502.2504.

4.5.17. (5*S*,2′*R*,3′*S*)-5-Isopropyl-3-phenyl-1-[2′-methyl-3′-(*p*-methoxyphenylamino)-3′-phenyl-valeryl]imidazolidin-2-thione 5h

Yield: 94%; white solid; mp 140.6–141.5 °C; $[\alpha]_D^{20}$ = +123.6 (*c* 0.24, CH_2Cl_2); IR: 3310, 1681, 1596, 1514, 1463, 1184 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.78 (t, *J* = 7.0, 7.0 Hz, 3H), 0.82–0.90 (m, 6H), 1.11–1.31 (m, 3H), 1.70–1.84 (m, 1H), 2.31–2.46 (m, 1H), 3.57–3.65 (m, 4H), 3.98 (dd, *J* = 10.8, 8.9 Hz, 1H), 4.54 (d, *J* = 9.8 Hz, 1H), 4.73 (dq, *J* = 8.9, 1.8 Hz, 1H), 5.78 (dt, *J* = 16.8, 3.6 Hz, 1H), 6.49 (d, *J* = 8.8 Hz, 2H), 6.60 (d, *J* = 8.9 Hz, 2H), 7.12–7.19 (m, 1H), 7.22–7.28 (m, 2H), 7.32–7.49 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.21, 15.15, 18.13, 20.60, 29.69, 33.23, 47.97, 50.39, 55.61, 61.28, 62.94, 114.49, 114.99, 126.25, 127.17, 127.80, 128.19, 128.37, 129.41, 139.61, 140.80, 141.90, 151.68, 177.17, 179.41; HRMS calcd for $C_{31}H_{37}N_3O_2S$ $[M+H]^+$: 516.2679, found 516.2655.

4.5.18. (5*S*,2′*R*,3′*S*)-5-Isopropyl-3-phenyl-1-[2′-methyl-3′-(*p*-methoxyphenylamino)-3′-phenyl-isovaleryl]imidazolidin-2-thione 5i

Yield: 65%; white solid; mp 87.9–89.2 °C; $[\alpha]_D^{20}$ = +196.7 (*c* 0.21, CH_2Cl_2); IR: 3310, 1681, 1597, 1513, 1463, 1183 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.63 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 1H), 1.85–1.98 (m, 1H), 2.14–2.26 (m, 1H), 3.50 (dd, *J* = 10.9, 1.9 Hz, 1H), 3.61 (s, 3H), 3.88 (dd, *J* = 10.8, 8.8 Hz, 1H), 4.64–4.71 (m, 1H), 4.77 (d, *J* = 8.3 Hz, 1H), 6.12 (dt, *J* = 14.2, 5.8 Hz, 1H), 6.49 (d, *J* = 8.9 Hz, 2H), 6.62 (d, *J* = 8.9 Hz, 2H), 7.09–7.16 (m, 1H), 7.19–7.46 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.56, 18.01, 18.90, 20.71, 29.06, 29.54, 49.87, 51.69, 55.44, 59.03, 60.66, 114.22, 114.54, 126.14, 126.87, 127.55, 127.91, 128.18, 129.21, 139.57, 141.24, 141.58, 151.31, 176.14, 179.17; HRMS calcd for $C_{31}H_{37}N_3O_2S$ $[M+H]^+$: 516.2679, found 516.2659.

4.5.19. (5*S*,2′*R*,3′*S*)-5-Isopropyl-3-phenyl-1-[2′-methyl-3′-(*p*-methoxyphenylamino)-3′-phenyl-hexanoyl]imidazolidin-2-thione 5j

Yield: 92%; white solid; mp 162.1–162.9 °C; $[\alpha]_D^{20}$ = +157.1 (*c* 0.13, CH_2Cl_2); IR: 3311, 1681, 1597, 1514, 1464, 1182 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.76 (t, *J* = 4.7, 4.7 Hz, 3H), 0.83–0.90 (m, 6H), 1.09–1.24 (m, 5H), 1.70–1.84 (m, 1H), 2.32–2.45 (m, 1H), 3.59–3.66 (m, 4H), 4.00 (dd, *J* = 10.9, 8.9 Hz, 1H), 4.53 (d, *J* = 9.8 Hz, 1H), 4.74 (dq, *J* = 9.0, 1.8 Hz, 1H), 5.76 (dt, *J* = 17.2, 2.9 Hz, 1H), 6.49 (d, *J* = 8.9 Hz, 2H), 6.60 (d, *J* = 8.9 Hz, 2H), 7.12–7.18 (m, 1H), 7.22–7.29 (m, 2H), 7.34–7.51 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.90, 15.13, 17.98, 22.56, 29.45, 30.81, 48.04, 50.43, 55.56, 61.29, 62.59, 114.52, 114.96, 126.25, 127.15, 127.81, 128.21, 128.36, 129.41, 139.65, 140.91, 142.00, 151.68, 177.20, 179.46; HRMS calcd for $C_{32}H_{39}N_3O_2S$ $[M+H]^+$: 530.2836, found 530.2832.

4.5.20. (5*S*,2′*R*,3′*S*)-5-Isopropyl-3-phenyl-1-[2′-methyl-3′-(*p*-methoxyphenylamino)-3′-phenyl-phenylacetyl]imidazolidin-2-thione 5l

Yield: 95%; white solid; mp 84.6–85.2 °C; $[\alpha]_D^{20}$ = +138.3 (*c* 0.15, CH_2Cl_2); IR: 3311, 1681, 1597, 1513, 1463, 1177 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.84 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 2.38–2.50 (m, 1H), 3.51 (dd, *J* = 10.9, 1.9 Hz, 1H), 3.58 (s, 3H), 3.81 (dd, *J* = 10.9, 8.9 Hz, 1H), 4.59–4.62 (m, 1H), 4.99–5.14 (m, 1H), 6.27–6.38 (m, 1H), 6.53 (d, *J* = 8.9 Hz, 1H), 6.61 (d, *J* = 8.9 Hz, 1H), 6.92–6.99 (m, 1H), 6.99–7.79 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.17, 18.02, 29.62, 50.26, 53.38, 55.64, 61.65, 64.41, 114.63, 115.23, 126.30, 126.92, 127.41, 127.60, 128.06, 128.29, 128.74, 129.49, 130.10, 136.61, 139.67, 141.10, 141.65, 151.94, 174.80, 179.50; HRMS calcd for $C_{34}H_{35}N_3O_2S$ $[M+H]^+$: 550.2523, found 550.2510.

4.5.21. (5*S*,2′*R*,3′*S*)-5-Isopropyl-3-phenyl-1-[2′-methyl-3′-(*p*-methoxyphenylamino)-3′-phenyl-(3-phenylpropionyl)]imidazolidin-2-thione 5m

Yield: 63%; white solid; mp 143.6–144.8 °C; $[\alpha]_D^{20}$ = +112.1 (*c* 0.35, CH_2Cl_2); IR: 3318, 1682, 1597, 1514, 1464, 1190 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.80 (d, *J* = 6.9 Hz, 6H), 2.17–2.27 (m, 1H), 2.49 (dd, *J* = 12.7, 4.4 Hz, 1H), 2.83 (dd, *J* = 13.5, 11.4 Hz, 1H), 3.14 (dd, *J* = 10.6, 8.4 Hz, 1H), 3.27 (dd, *J* = 10.6, 1.7 Hz, 1H), 4.06 (dq, *J* = 8.4, 1.6 Hz, 1H), 4.69 (d, *J* = 10.0 Hz, 1H), 5.98 (dt, *J* = 16.6, 4.8 Hz, 1H), 6.49 (d, *J* = 8.9 Hz, 2H), 6.60 (d, *J* = 8.9 Hz, 2H), 7.11–7.23 (m, 8H), 7.26–7.34 (m, 3H), 7.38–7.53 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.50, 17.99, 29.37, 41.23, 50.16, 55.61, 55.69, 57.87, 60.93, 107.75, 110.13, 114.54, 114.63, 115.72, 126.32, 128.20, 129.48, 139.77, 139.82, 141.78, 141.85, 152.46, 154.42, 175.87, 177.22, 178.50, 179.42; HRMS calcd for $C_{35}H_{37}N_3O_2S$ $[M+H]^+$: 564.2679, found 564.2655.

4.6. General procedure for alcoholysis of the Mannich adducts

To a solution of Mannich adducts **5a–f** (1.0 mmol) in methanol (50 mL) was added DMAP (0.244 g, 2.0 mmol), and the reaction mixture refluxed for 8 h. The mixture was concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (*n*-hexane/EtOAc, 6:1, v/v) recovered the chiral auxiliary **3** and gave the β-amino esters **6a–f**.

4.6.1. (2*R*,3*S*)-Methyl 2-methyl-3-(*p*-methoxyphenylamino)-3-phenylpropanoate 6a

Yield: 93%; colorless oil; $[\alpha]_D^{20}$ = −51.1 (*c* 1.05, CH_2Cl_2); IR: 3370, 1731, 1597, 1511, 1455 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.13 (d, *J* = 7.0 Hz, 3H), 2.84 (m, 1H), 3.63 (s, 3H), 3.66 (s, 3H), 4.43 (d, *J* = 7.5 Hz, 1H), 6.51 (d, *J* = 8.0 Hz, 2H), 6.65 (d, *J* = 8.9 Hz, 2H), 7.26–7.30 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 15.37, 46.80, 51.96, 55.72, 61.85, 114.71, 115.16, 126.99, 127.53, 128.55, 128.67, 141.19, 152.19, 175.64.

4.6.2. (2*R*,3*S*)-Methyl 2-methyl-3-(*p*-methoxyphenylamino)-3-(*p*-chloro-phenyl) propanoate 6b

Yield: 90%; colorless oil; $[\alpha]_D^{20}$ = −42.9 (*c* 0.55, CH_2Cl_2); IR: 3393, 1731, 1597, 1513, 1457 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.15 (d, *J* = 7.0 Hz, 3H), 2.81 (m, 1H), 3.64 (s, 3H), 3.67 (s, 3H), 4.41 (d, *J* = 6.8 Hz, 1H), 6.47 (d, *J* = 7.6 Hz, 2H), 6.67 (d, *J* = 8.9 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 15.37, 46.63, 52.04, 55.76, 61.18, 114.79, 115.09, 128.37, 128.87, 133.16, 139.92, 140.16, 152.34, 175.36.

4.6.3. (2*R*,3*S*)-Methyl 2-methyl-3-(*p*-methoxyphenylamino)-3-(*m*-nitro-phenyl)propanoate 6c

Yield: 91%; yellow oil; $[\alpha]_D^{20}$ = −48.1 (*c* 1.10, CH_2Cl_2); IR: 3398, 1733, 1582, 1513, 1457 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.21 (d, *J* = 7.0 Hz, 3H), 2.95 (m, 1H), 3.65 (s, 3H), 3.68 (s, 3H), 4.58 (d, *J* = 7.8 Hz, 1H), 6.48 (d, *J* = 7.8 Hz, 2H), 6.68 (d, *J* = 8.4 Hz, 2H), 7.49–8.21 (m, 4H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 15.38, 46.30, 52.27, 55.79, 61.27, 114.85, 115.19, 122.05, 122.82, 129.68, 133.31, 139.92, 143.46, 148.59, 152.70, 174.83.

4.6.4. (2*R*,3*S*)-Methyl 2-methyl-3-(*p*-methoxyphenylamino)-3-(2′,3′-dimethoxyphenyl)propanoate 6d

Yield: 89%; pale-yellow oil; $[\alpha]_D^{20}$ = −53.2 (*c* 2.01, CH_2Cl_2); IR: 3390, 1733, 1586, 1514, 1479 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.11 (d, *J* = 7.0 Hz, 3H), 2.96 (m, 1H), 3.61 (s, 3H), 3.65 (s, 3H), 3.81 (s, 3H), 3.88 (s, 3H), 4.75 (d, *J* = 7.8 Hz, 1H), 6.45–6.97 (m, 7H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 15.75, 45.77, 51.87, 55.66, 55.71, 57.61, 60.80, 111.46, 114.69, 119.78, 120.38, 123.67, 123.97, 146.60, 147.06, 152.20, 152.55, 176.15.

4.6.5. (2*R*,3*S*)-Methyl 2-methyl-3-(*p*-methoxyphenylamino)-3-(2′-furyl)-propanoate 6e

Yield: 86%; colorless oil; $[\alpha]_D^{20}$ = −47.9 (*c* 1.10, CH_2Cl_2); IR: 3372, 1732, 1593, 1513, 1456 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.12 (d, *J* = 7.0 Hz, 3H), 3.03 (m, 1H), 3.67 (s, 3H), 3.69 (s, 3H), 4.61 (d, *J* = 7.9 Hz, 1H), 6.15 (d, *J* = 3.0 Hz, 1H), 6.24 (dd, *J* = 3.1, 1.8 Hz, 1H), 6.61 (d, *J* = 8.7 Hz, 2H), 6.72 (d, *J* = 8.9 Hz, 2H), 7.31 (d, *J* = 1.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.38, 44.33, 51.98, 55.66, 56.10, 107.54, 110.15, 114.68, 115.84, 140.69, 141.96, 152.74, 153.59, 175.27.

4.6.6. (2*R*,3*S*)-Methyl 2-methyl-3-(*p*-methoxyphenylamino)-3-(2′-thienyl)-propanoate 6f

Yield: 85%; colorless oil; $[\alpha]_D^{20}$ = −45.6 (*c* 1.06, CH_2Cl_2); IR: 3384, 1732, 1592, 1513, 1456 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.19 (d, *J* = 7.0 Hz, 3H), 2.92 (m, 1H), 3.67 (s, 3H), 3.69 (s, 3H), 4.76 (d, *J* = 7.2 Hz, 1H), 6.60 (d, *J* = 7.9 Hz, 2H), 6.70 (d, *J* = 8.8 Hz, 2H), 6.89–6.92 (m, 2H), 7.15 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.95, 46.98, 52.15, 55.75, 58.00, 114.76, 115.53, 124.46, 125.06, 126.88, 140.63, 145.91, 152.64, 175.26.

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