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Enantioselective Synthesis of Cyclic Thioureas *via* Mannich Reaction and Concise Synthesis of Highly Optically Active Methylthioimidazolines: Discovery of a More Potent Antipyretic Agent

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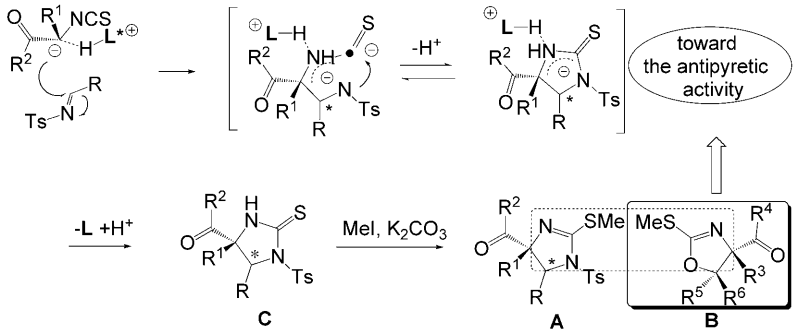
Abstract: Drug lead synthesis by the rapid construction of chiral molecular complexity around the biologically relevant framework using a highly efficient strategy is a key goal of organic synthesis. Herein, a highly efficient and convenient strategy that allows the rapid synthesis of highly optically active methylthioimidazolines through the novel rosin-derived thiourea-catalyzed asymmetric synthesis of cyclic thioureas with high levels of enantio- and diastereoselectivity (up to 99% *ee*, and 20:1 *dr*) *via* Mannich reaction is described fior the first time. Several of the new methylthioimidazolines showed extremely promising antipyretic activity in the development of neuroinflammation through preliminary biological studies. Additionally, to gain a better understanding of the structural stability-activity relationships, explicit molecular dynamics (MD) simulations in water at room temperature and at body temperature were investigated.

Keywords: antipyretic agents; asymmetric synthesis; methylthioimidazolines; tertiary amine-thiourea catalysts

Introduction

Drug-lead organic synthesis, in particular the highly enantioselective construction of target-oriented chiral molecular complexity, is recognized as one of the most challenging subjects for synthetic chemists[1] and, furthermore, searching for a proper efficient biological model for the screening evaluation of structurally diverse chiral targets is a difficult task. Therefore, although there has been great demand, the development of efficient synthetic methodologies in this area of research and finally their contribution to the discovery of new therapeutic agents still remains scarce to date. Antipyretic drugs against neuroinflammation[2] are an important but expensive class of clinical therapeutic agents, which can be used as a therapeutic strategy to prevent and treat brain diseases closely associated with neuroinflammation, such as multiple sclerosis[3a] and Alzheimer's disease.[3b] Epidemiological and clinical evidence[4] suggests that long-term use of anti-inflammatory drugs may impede the onset and slow the progression of Alzheimer's disease. For these reasons, we recently first presented our contribution on the successful synthesis of a new kind of spirooxazoline, which revealed promising biological activity with an antipyretic action against the development of neuroinflammation.[5] Nevertheless, this significant research remains a much less developed field, and catalytic enantioselective synthesis and preliminary biological studies would still be highly valuable in both pharmaceutical and organic chemistry. Inspired by our recent elegant advances in this field, we ques-



Scheme 1. Strategy for the synthesis of chiral methylthioimidazolines by tertiary amine-thiourea-cataylzed reactions and similar cores in spirooxazolines.

tioned whether other structurally similar molecules or analogues such as methylthioimidazoline[6] (**A**, Scheme 1) would show more powerful antipyretic activity to thereby provide an opportunity to discover new antipyretic agents. In this text, we wish to present our results on this topic.

Results and Discussion

During our recent research interests in the catalytic enantioselective synthesis of biological and pharmaceutical precedents by using rosin-derived thiourea catalysts[7,8] and to further expand the synthetic utility of this conceptually new catalytic system, we envisioned that the optically active methylthioimidazoline **A** could analogously be obtained through methylation of the cyclic thiourea **C**, which might be generated *via* a catalytic enantioselective intramolecular Mannich[9] cyclization reaction of α-isothiocyanato imides[10] to *N*-tosylimines in the presence of a tertiary amine-thiourea[11] (Scheme 1). To the best of our knowledge, to date, the catalytic asymmetric synthesis and preliminary biological studies of highly enantiomerically enriched methylthioimidazolines have not been reproted, and thus remains an important challenge. We first reveal herein an asymmetric synthetic approach to such compounds and their extremely promising antipyretic activity in the development of neuroinflammation through preliminary biological studies.

Subsequently, our attention was especially focused on the catalytic highly enantioselective synthesis of cyclic thioureas because several very practical tertiary amine-thiourea catalysts **3a**–**3c** (Figure 1) proved to be inefficient for this catalytic asymmetric reaction in previous studies reported by Seidel[10b] and Zhong[10c] independently. It is important to note that, except for the first reported example using a metallic catalyst,[10e] almost the same small molecules were employed as exclusive efficient catalysts in the aforementioned two organocatalytic versions. Even so, we still believe that our rosin-derived thiourea catalyst might perform

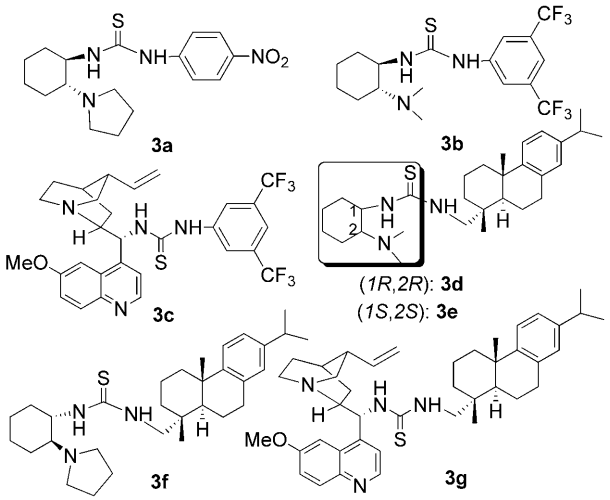
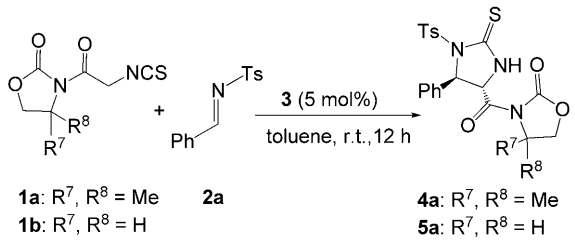


Figure 1. Structure of thiourea catalysts.

well in the reaction owing to its excellent structural backbone and well-defined stereocenters. To explore the efficacy of rosin-derived tertiary amine-thiourea system for the proposed Mannich cyclization process, the model reaction of isothiocyanate **1a** with *N*-tosylimine **2a** was performed in toluene at room temperature in the presence of 5.0 mol% of ligand loading (Table 1). The results showed that tertiary amine-thioureas **3d**–**3f** gave poor results in terms of yield and stereochemical outcome (entries 1–3). Interestingly, a significant enhancement of yield and stereoselectivity was achieved when using **3g** (93% yield, 9:1 *dr* and 96% *ee*, entry 4), and the further solvent optimization indicated that a remarkable decrease of *ee* values was observed in CH_2Cl_2, Et_2O and $CHCl_3$ while the reactions afforded the products with high yields (entries 6–8). Gratifyingly, we further lowered the temperature to −15 °C, and better enantioselectivity was obtained without a significant decrease in yield (97% *ee* and 90% yield, entry 9).

We then investigated the generality of the protocol with respect to the synthesis of a variety of cyclic thioureas under the optimized reaction conditions

Table 1. Catalyst screening and optimization of reaction conditions.[a]



1a: R^7, R^8 = Me **2a** **4a**: R^7, R^8 = Me
1b: R^7, R^8 = H **5a**: R^7, R^8 = H

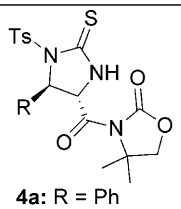
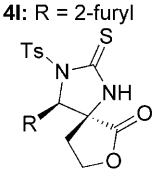
Entry	Catalyst	Substrate	Yield [%][b]	*dr*[c]	*ee* [%][d]
1	**3d**	**1a**	(**4a**) 37	4:1	33
2	**3e**	**1a**	(**4a**) 40	4:1	34
3	**3f**	**1a**	(**4a**) 49	5:1	67
4	**3g**	**1a**	(**4a**) 93	9:1	88
5	**3g**	**1b**	(**4b**) 89	4:1	80
6[e]	**3g**	**1a**	(**4b**) 92	5:1	51
7[f]	**3g**	**1a**	(**4a**) 79	5:1	42
8[g]	**3g**	**1a**	(**4a**) 91	5:1	65
9[h]	**3g**	**1a**	(**4a**) 90	9:1	97

[a] Unless noted otherwise, the reaction was carried out with **1** (0.20 mmol) and **2a** (0.30 mmol) in toluene (1.5 mL) for 12 h at room temperature.
[b] Isolated yield of the mixture of diastereomers.
[c] Determined by ^{1}H NMR.
[d] The *ee* values of the major diastereomer were determined by HPLC, and the configuration was assigned by comparison of HPLC data and X-ray crystal data of **TID-1**.
[e] In CH_2Cl_2 (1.0 mL).
[f] In Et_2O (1.0 mL).
[g] In $CHCl_3$ (1.0 mL).
[h] The reaction was performed for 18 h at −15 °C .

(Table 2). It is seen that a variety of aromatic *N*-tosylimines bearing various types of substituents underwent the reaction to afford the desired products with excellent enantioselectioselectivities (91%–99% *ee*) in good to high diastereoselectivities (6:1–20:1 *dr*) and yields (79–94%, entries 1–12). Encouraged by the outstanding results achieved above, we decided to carry out some more challenging studies, such as the construction of spirocyclic[12] thioureas considering their potential versatility. Gratifyingly, although low diastereoselectivities were observed in phenyl and *ortho*-F-substituted aromatic *N*-tosylimines (entries 13 and 14), in general, the catalytic system also proved to be efficient for the enantioselective construction of spirocyclic thioureas, again leading to high yields (81–90%) and excellent enantioselectivities (90–96% *ee*, entries 13–17).

The proposed possible model to account for the high enantioselectivity is shown in Figure 2. In light of the experimental results described above and recent studies,[5] the tertiary amine-thiourea would act in a bifunctional fashion. The α-carbon atom of isothio-

Table 2. Cyclic thioureas formed by rosin-derived tertiary amine-thiourea-catalyzed asymmetric Mannich reaction.[a]

Entry	Time [h]	Product[b]	Yield [%][c]	*dr*[d]	*ee* [%][e]
					
1	18	**4a:** R = Ph	90	9:1	97%
2	36	**4b:** R = 1-naphthyl	79	13:1	91%
3	36	**4c:** R = 2-naphthyl	90	11:1	98%
4	18	**4d:** R = 4-FC_6H_4	92	10:1	96%
5	18	**4e:** R = 4-ClC_6H_4	85	9:1	99%
6	18	**4f:** R = 4-BrC_6H_4	87	10:1	98%
7	18	**4g:** R = 2-FC_6H_4	90	15:1	97%
8	18	**4h:** R = 2-ClC_6H_4	83	20:1	99%
9	18	**4i:** R = 4-MeC_6H_4	91	12:1	99%
10	18	**4j:** R = 3-MeC_6H_4	94	13:1	96%
11	18	**4k:** R = 2-MeC_6H_4	84	16:1	97%
12	18	**4l:** R = 2-furyl	87	6:1	98%
					
13	6	**4m:** R = Ph	89	2:1	90%
14	6	**4n:** R = 2-FC_6H_4	84	3:1	95%
15	6	**4o:** R = 4-ClC_6H_4	90	8:1	93%
16	6	**4p:** R = 3-MeC_6H_4	81	10:1	96%
17	6	**4q:** R = 4-MeC_6H_4	83	8:1	n.d.

[a] Unless noted, the reaction was carried out with isothiocyanates (0.20 mmol) and *N*-tosylimines (0.30 mmol) in toluene (1.5 mL) at −15 °C in the presence of 5.0 mol% of **3g**. For experimental details, see the Supporting Information.
[b] The configuration was assigned by comparison of HPLC data and X-ray crystal data of **TID-1**.
[c] Isolated yield of the mixture of diastereomers.
[d] Determined by ^{1}H NMR and chiral HPLC.
[e] The *ee* values of the major diastereomer were determined by HPLC.

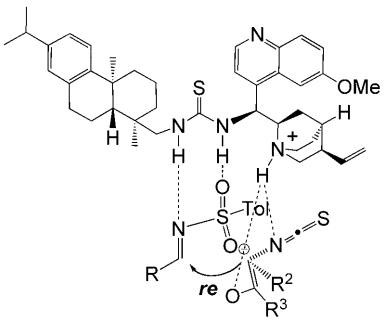
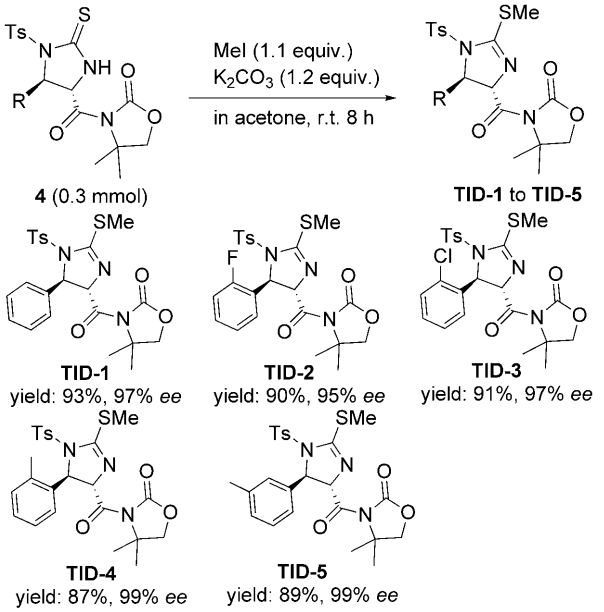


Figure 2. Proposed model of the reaction transition state.

cyanate could be activated *via* enolate anion by an interaction between the neighboring tertiary amine moiety of the catalyst and isothiocyanate, alongside which the *N*-tosylimine is fixed and activated by the two thiourea hydrogen atoms through weak hydrogen bonds. Subsequently the attack of the incoming nucleophile to the *re*-face of *N*-tosylimine takes place (attack on the *si*-face of the *N*-tosylimine is restricted by the quinine scaffold of the catalyst), which is consistent with the experimental results. In previous studies,[8c,d] we also tried to explain the role of the rosin amine moiety of the catalyst for obtaining high enantioselectivities and diastereoselectivities by carrying out reaction with catalysts having different configuration of the chiral scaffold moiety in the catalyst. The investigation proved that the two chiral moieties of the thiourea are mutually reinforcing for the high efficacy of the catalyst. The catalytic activity depends mainly on the remaining chiral scaffold moiety of the thiourea (the inherent property of the stereochemical structure of the dehydroabietic amine moiety of the thiourea) and also on the suitable matching of the stereochemical features of the remaining quinine scaffold moiety. The stereochemical control of the reaction is mainly provided by the quinine moiety of the thiourea. In addition, the excellent structural backbone and well-defined stereocenters of the dehydroabietic amine moiety of **3g** also have an important effect on the high enantioselectivity for the formation of adduct.

In view of the next preliminary biological evaluation, several synthesis-oriented optically active methylthioimidazolines were synthesized under the asymmetric protocol established (Scheme 2). A variety of substituted methylthioimidazolines with different steric and electronic parameters (**TID-1** to **TID-5**) were smoothly formed with excellent enantioselectivities (90% to 99% *ee*) in yields ranging from 87% to 93%. With these novel chiral molecules in hand, the aim of the present report was to investigate their antipyretic activity on the fever provoked by intracerebroventricular (icv) injection of lipopolysaccharide (LPS) a component of the outer membrane of Gram-negative bacteria. The injection of LPS directly into the brain has been recognized as an animal model for the study of neuroinflammation.[13] (Figure 3). Excitingly, several of the compounds, including **TID-1** and **TID-2**, were found to attenuate the fever caused by the icv injection of LPS in a dose-dependent manner. As shown in Figure 3, the fever induced by LPS (125.0 ng) is significantly reduced by coinjection of **TID-1** or **TID-2** (20.0 nmol) ($P < 0.05$) at 240 min. Compared to saline, the central injection of **TID-1** or **TID-2** (20.0 nmol) did not change the body temperature. In addition, **TID-1** or **TID-2** (2.0 and 10.0 nmol) slightly, but not significantly, decreased LPS-induced fever at 240 min. Fever is part of the acute-phase reaction to inflammation. The pivotal role of these methylthioimidazolines in the control of the process of neuroinflammation may help to prevent and treat neuroinflammation diseases.



Scheme 2. Synthesis of biologically active chiral methylthioimidazolines (synthetic details are given in the Experimental Section).

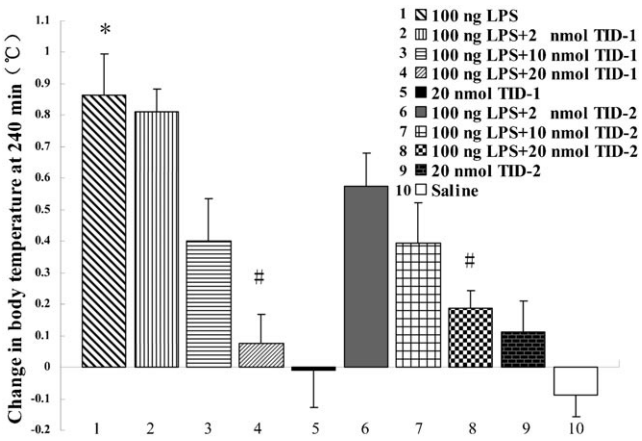


Figure 3. Antipyretic activity of **TID-1** and **TID-2** in neuroinflammation. The change of body temperature induced by LPS in the absence or presence of **TID-1** or **TID-2** injected into the third ventricle at 240.0 min in mice. The rectal temperature was recorded after injection of saline, LPS, or the co-application of LPS and **TID-1** or **TID-2**. Each data point represents the mean ± standard error of the mean from experiments conducted on 6–8 mice per group. Points labeled with # were significantly different ($p < 0.05$) from the corresponding points for LPS alone; * significantly different from saline ($p < 0.05$) (For experimental details, see the Supporting Information).

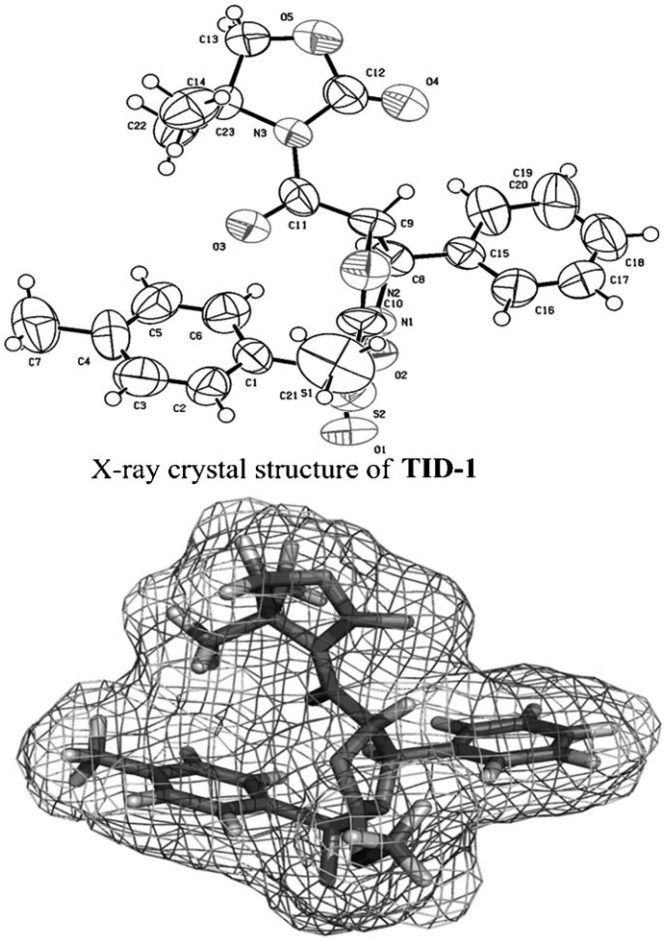


Figure 4. X-ray crystal structure of **TID-1** and the conformations obtained after explicit MD simulations in water at 300 K and 315 K. The atoms C, N, S, O and H are colored in gray with 90%, 70%, 50%, 30%, 10%. Figure was drawn by means of PyMol (A colored version of this figure is shown in the Supporting Information).[16]

In light of the potent biological activities *in vivo*, we sought to determine the conformation of **TIDs** in a simulated body environment which is surrounded by water at 315 K. To investigate the explicit conformation of the TIDs in water, the crystal 3D model of **TID-1** (Figure 4) was embedded in a water box and we performed 20.0 ns unrestrained molecular dynamics (MD) simulations at 300 K (body temperature) and 315 K (room temperature, compared with the body environment). The time evolutions of the total energy and RMSD (root mean square deviation) of **TID-1** were analyzed to evaluate the stability of each system. The average structure of the last 5.0 ns trajectory was considered as the typical structure of the **TID-1** model. Finally, two identical structures of the **TID-1** at different temperatures were obtained (all atom RMSD = 0.026). During explicit MD simulations in water, a noteworthy phenomenon is that **TID-1** exhibited a strong structural stability and identical conformations were observed at temperatures of 300 K and 315 K. The results obtained suggest that the stability of the conformation depends on the overall interaction energy involved in the electrostatic force and Van der Waals force.[14] In addition, the stacking interactions[15] may also play an important role in stabilizing the orientation of **TID-1** (for details, see the Supporting Information).

Conclusions

In conclusion, we have disclosed the synthesis of highly optically active methylthioimidazolines through the novel rosin-derived thiourea-catalyzed asymmetric synthesis of cyclic thioureas with high levels of enantio- and diastereoselectivity (up to 99% *ee*, and 20:1 *dr*) *via* Mannich reaction. Several of the new methylthioimidazolines showed extremely promising antipyretic activity in the development of neuroinflammation through preliminary biological studies. Additionally, to gain a better understanding of the structural stability-activity relationships, the explicit molecular dynamics (MD) simulations in water at room temperature and body temperature were investigated.

Experimental Section

General Procedure of the Synthesis

All reactions were carried out under an argon atmosphere condition unless otherwise noted and solvents were dried according to established procedures. Reactions were monitored by thin layer chromatography (TLC), column chromatography purifications were carried out using silica gel GF254. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker 300 MHz spectrometer in $CDCl_3$ unless otherwise noted and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker 300 MHz spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as internal standard unless otherwise noted. Data are presented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, cm = complex multiplet) and coupling constant in Hertz (Hz). Infrared (IR) spectra were recorded on an FT-IR spectrometer. Optical rotations were recorded on a Perkin–Elmer 341 polarimeter. HR-MS were measured with an APEX II 47e mass spectrometer. Melting points were measured on an XT-4 melting point apparatus and are uncorrected. The *ee* values determination was carried out using chiral high-performance liquid chromatography (HPLC) with a Daicel Chiracel AD-H column on a Waters apparatus with a 2996 UV-detector and the *dr* values were determined by 300 Hz ^{1}H NMR.

General Procedure for the Biological Studies

Male Kunming mice weighting 27–30 g were used. The experiments were performed between 10:00 and 17:00. All

mice were housed one per cage in a room maintained at 22 ± 0.5 °C and relative humidity of 52 ± 2% with free access to food and water. The mice were placed in the specially designed restraining device as described by Rosow et al., with their tails taped lightly to horizontal posts.[17] Rectal temperature was measured with a thermistor probe (Machine Equipment Corporation of GaoBeiDian, China) inserted to a depth of 2.5 cm into the rectum, which was linked to a recorder system (model BL-420E+, Taimeng Technology Corporation of Chengdu, China). The icv administration into the third ventricle was performed following the method described by Francés et al.[18] The drugs were coinjected to investigate whether the fever of LPS could be antagonized by **TIDs**. Body temperature was recorded before injection and then at 120, 180, 240 and 300 min after icv in the third ventricle or various treatments and controls. Changes in body temperature after injection and before drug administration were calculated for each animal. The time courses of change in body temperature of mice subjected to different treatments are shown in Figure 3. Data are given as means ± S.E.M. One-way ANOVA followed by the Bonferroni's post-hoc test was used to establish statistical significance; a probability level of $P < 0.05$ was considered to be significant.

The Experiments of Dynamics (MD) Simulations

The crystal 3D model of **TID-1** was embedded in a water box. The topologies were generated by PRODRG. MD simulations were performed with the GROMACS 4.5.1 package employing NPT and periodic boundary conditions. A modification of GROMOS96 force field is applied for the system. A twin cutoff of 10 Å was used for the short-range interaction and a cutoff of 12 Å was used for the Lennard–Jones interaction. The Particle Mesh Ewald (PME) algorithm was used for the calculation of electrostatic contributions to energies and forces. Bond length was constrained using the LINCS algorithm. Two systems were coupled to a temperature bath at 300 K and 315 K, with a coupling constant of 0.1 ps. Isotropic coupling with time constant of 1.0 ps was applied to keep the pressure at 1.0 bar. The systems were first energy minimized using the steepest descent integrator for about 6000 steps. Then a 20.0 ns simulation was performed with a time step of 2.0 fs. The time evolutions of the total energy and RMSD of **TID-1** were analyzed to evaluate the stability of each system.

Thiourea catalyst (3 g) was synthesized according to the literature procedures.[8]

1-{[(1*R*,4a*S*,10a*R*)-7-Isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl]methyl}-3-{[(*S*)-(6-methoxyquinolin-4-yl)-[(2*S*,4*S*,8*R*)-8-vinylquinuclidin-2-yl]methyl}thiourea (3g): $[\alpha]_D^{20}$: −70 (*c* 1.0, $CHCl_3$); mp 163 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 8.67 (s, 1H), 7.89–7.92 (m, 2H), 7.37–7.44 (m, 2H), 7.10–7.13 (d, *J* = 8.1 Hz, 1H), 6.83–6.95 (m, 2H), 5.72–5.83 (m, 2H), 4.87–4.98 (m, 2H), 3.90 (s, 3H), 3.55–3.58 (d, *J* = 10.5 Hz, 1H), 3.04–3.14 (m, 4H), 2.75–2.80 (m, 3H), 2.51–2.58 (m, 2H), 2.22 (m, 2H), 1.81 (br, 1H), 1.38–1.54 (m, 7H), 1.15–1.18 (m, 11H), 1.09 (m, 3H), 0.78 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 157.9, 148.5, 148.1, 145.9, 145.2, 142.9, 135.7, 132.2, 128.9, 127.4, 125.0, 124.5, 122.2, 115.2, 104.2, 56.6, 56.3, 45.1, 41.8, 38.9, 38.4, 37.9, 36.8, 33.9, 30.5, 28.4, 28.1, 26.6, 26.1, 25.1, 24.9, 21.8, 19.8, 19.6, 19.2; IR: ν = 3271, 3069, 2931, 2866, 2212, 1915, 1735, 1622, 1539, 1472, 1363, 1292, 1234, 11362, 1032, 911, 824, 732 cm^{-1}; HR-MS (ESI): *m/z* = 651.4079, calcd for $C_{41}H_{54}N_4OS + H^+$: 651.4091; Δ = 1.8 ppm.

General Procedure for the Organocatalytic Asymmetric Synthesis of Cyclic Thioureas *via* Mannich Reaction of Isothiocyanate (1a) with *N*-Tosylimines

To a stirred solution of **3g** (0.006 mmol, 3.0 mol%) and *N*-tosylimine (0.30 mmol) in dry toluene (1.5 mL), isothiocyanate **1a** (0.20 mmol) was added under argon, The solution was stirred at −15 °C for 18–36 h. After the reaction was completed (monitored by TLC), the resulting mixture was concentrated under reduced pressure and the residue was purified through column chromatography on silica gel to give the optical pure products (see Supporting Information).

4,4-Dimethyl-3-[(4*S*,5*R*)-5-phenyl-2-thioxo-1-tosylimidazolidine-4-carbonyl]oxazolidin-2-one (4a): Colorless needles; $[\alpha]_D^{20}$: −74 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54–7.52 (d, *J* = 8.4 Hz, 2H), 7.36–7.34 (m, 5H), 7.22 (br, 1H), 7.11–7.09 (d, *J* = 8.1 Hz, 1H), 6.24–6.23 (d, *J* = 1.8 Hz, 1H), 4.89 (d, *J* = 1.8 Hz, 1H), 4.13 (s, 2H), 2.35 (s, 3H), 1.62 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.9, 167.2, 154.2, 144.8, 138.3, 134.8, 129.5, 129.1, 129.0, 128.7, 127.0, 76.1, 66.0, 64.7, 61.4, 24.6, 24.5, 21.6. IR: ν = 3381, 2976, 1779, 1601, 1470, 1397, 1310, 1244, 1168, 1094, 1046, 761, 698, 670, 578, 544 cm^{-1}; ESI-MS: *m/z* = 474 [M$^+$]. *Major diastereomer*: *ee* was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 30/70, 1.0 mL min^{-1}, 245 nm): retention times t_{minor} = 12.99 min, t_{major} = 18.93 min, *ee* 97%.

4,4-Dimethyl-3-[(4*S*,5*R*)-5-(naphthalen-1-yl)-2-thioxo-1-tosylimidazolidine-4-carbonyl]oxazolidin-2-one (4b): White solid; $[\alpha]_D^{20}$: −30 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95–7.86 (m, 5H), 7.58–7.44 (m, 4H), 7.33 (br, 1H) 7.23–7.17 (m, 2H), 4.61 (s, 1H), 4.08 (s, 2H), 2.41 (s, 3H), 1.66 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.3, 167.3, 154.1, 145.0, 134.8, 134.1, 129.6, 129.4, 128.9, 127.1, 126.1, 125.7, 123.7, 121.8, 76.1, 64.9, 62.3, 61.4, 24.5, 24.4, 21.7; IR: ν = 3368, 3041, 1797, 1702, 1488, 1411, 1369, 1267, 1218, 1170, 1121, 1088, 726, 570 cm^{-1}; anal. calcd. for $C_{26}H_{25}N_3O_5S_2$: C 59.64, H 4.81, N 8.02; found: C 59.84, H 4.66, N, 8.12. *Major diastereomer: ee* was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 30/70, 1.0 mL min^{-1}, 245 nm): retention times t_{minor} = 12.02 min, t_{major} = 13.56 min, *ee* 91%.

4,4-Dimethyl-3-[(4*S*,5*R*)-5-(naphthalen-2-yl)-2-thioxo-1-tosylimidazolidine-4-carbonyl]oxazolidin-2-one (4c): White solid; $[\alpha]_D^{20}$: +35 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83–7.78 (m, 4H), 7.55–7.51 (m, 4H), 7.38–7.35 (d, *J* = 8.4 Hz, 2H), 7.21 (s, 1H), 6.98–6.95 (d, *J* = 8.1 Hz, 1H), 6.45–6.44 (d, *J* = 1.8 Hz, 1H), 4.94–4.93 (d, *J* = 2.1 Hz, 1H), 4.13 (s, 2H), 2.29 (s, 3H), 1.64 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.0, 167.2, 154.2, 114.8, 135.4, 134.8, 134.4, 133.4, 133.0, 129.4, 128.6, 128.3, 127.7, 126.8, 126.7, 123.8, 76.1, 66.1, 64.7, 61.4, 24.6, 24.5, 21.6; IR: ν = 3366, 3038, 1802, 1711, 1486, 1411, 1368, 1256, 1210, 1172, 1124, 1098, 745, 571 cm^{-1}; anal. calcd. for $C_{26}H_{25}N_3O_5S_2$: C 59.64, H 4.81, N 8.02; found: C 59.75, H 4.70, N 8.16. *Major diastereomer: ee* was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 30/70,

1.0 mL min^{-1}, 245 nm): retention times t_{minor} = 16.49 min, t_{major} = 18.98 min, *ee* 98%.

3-[(4*S*,5*R*)-5-(4-Fluorophenyl)-2-thioxo-1-tosylimidazolidine-4-carbonyl]-4,4-dimethyloxazolidin-2-one (4d): Colorless needles; $[\alpha]_D^{20}$: −17 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.44 (d, *J* = 7.5 Hz, 2H), 7.38–7.36 (m, 2H), 7.22–7.06 (m, 5H), 6.65 (d, *J* = 2.1 Hz, 1H), 4.82–4.81 (d, *J* = 1.8 Hz, 1H), 4.13 (s, 2H), 2.40 (s, 3H), 1.63 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.4, 166.8, 161.1, 154.3, 145.0, 134.7, 130.6, 129.5, 128.9, 124.9, 124.9, 116.0, 115.7, 76.1, 64.0, 61.3, 60.5, 24.5, 21.7; IR: ν = 3344, 3041, 2969, 1748, 1611, 1509, 1370, 1227, 1094, 841, 756, 728, 682, 591, 572 cm^{-1}; anal. calcd. for $C_{22}H_{22}FN_3O_5S_2$: C 53.75, H 4.51, N 8.55; found: C 53.61, H 4.40, N 8.66. *Major diastereomer: ee* was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 30/70, 1.0 mL min^{-1}, 245 nm): retention times t_{minor} = 11.55 min, t_{major} = 12.62 min, *ee* 96%.

3-[(4*S*,5*R*)-5-(4-Chlorophenyl)-2-thioxo-1-tosylimidazolidine-4-carbonyl]-4,4-dimethyloxazolidin-2-one (4e): Colorless needles; $[\alpha]_D^{20}$: +55 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60–7.57 (d, *J* = 8.4 Hz, 2H), 7.36–7.27 (m, 5H), 7.16–7.13 (d, *J* = 8.4 Hz, 2H), 6.12 (d, *J* = 1.2 Hz, 1H), 4.89 (d, *J* = 1.8 Hz, 1H), 4.14 (s, 2H), 2.38 (s, 3H), 1.62 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.2, 167.3, 154.2, 145.1, 136.8, 135.0, 134.7, 129.3, 129.2, 128.8, 128.5, 76.1, 65.6, 64.4, 61.4, 24.6, 24.4, 21.7. IR: ν = 3348, 3046, 2972, 1746, 1640, 1510, 1374, 1225, 1098, 841, 759, 727, 679, 588, 570 cm^{-1}; anal. calcd. for $C_{22}H_{22}ClN_3O_5S_2$: C 52.01, H 4.36, N 8.27; found: C 52.31, H 4.39, N 8.06. *Major diastereomer: ee* was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 30/70, 1.0 mL min^{-1}, 245 nm): retention time t_{major} = 14.62 min, *ee* 99%.

3-[(4*S*,5*R*)-5-(4-Bromophenyl)-2-thioxo-1-tosylimidazolidine-4-carbonyl]-4,4-dimethyloxazolidin-2-one (4f): Colorless solid; $[\alpha]_D^{20}$: +18 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62–7.59 (d, *J* = 8.4 Hz, 2H), 7.48–7.46 (d, *J* = 8.4 Hz, 2H), 7.24–7.21 (d, *J* = 8.4 Hz, 2H), 7.17–7.14 (d, *J* = 8.4 Hz, 2H), 6.17 (d, *J* = 1.2 Hz, 1H), 4.84 (d, *J* = 1.8 Hz, 1H), 4.15 (s, 2H), 2.39 (s, 3H), 1.64 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.0, 167.1, 154.2, 145.1, 137.3, 134.7, 132.2, 129.4, 128.8, 128.7, 123.3, 76.2, 65.5, 64.5, 61.4, 24.7, 24.5, 21.7; IR: ν = 3357, 3059, 2988, 1794, 1705, 1489, 1394, 1264, 1214, 1168, 1114, 755, 725, 688, 614, 570 cm^{-1}; anal. calcd. for $C_{22}H_{22}BrN_3O_5S_2$: C 47.83, H 4.01, N 7.61; found: C 48.03, H 4.18, N 7.54. *Major diastereomer: ee* was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 30/70, 1.0 mL min^{-1}, 245 nm): retention times t_{major} = 15.40 min, t_{minor} = 20.80 min, *ee* 98%.

3-[(4*S*,5*R*)-5-(2-Fluorophenyl)-2-thioxo-1-tosylimidazolidine-4-carbonyl]-4,4-dimethyloxazolidin-2-one (4g): Colorless needles; $[\alpha]_D^{20}$: +11 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58–7.55 (d, *J* = 8.4 Hz, 2H), 7.36–7.31 (m, 2H), 7.23 (br, 1H), 7.15–7.12 (d, *J* = 8.4 Hz, 2H), 7.05–6.99 (m, 2H), 6.19–6.18 (d, *J* = 1.2 Hz, 1H), 4.88 (d, *J* = 1.8 Hz, 1H), 4.14 (s, 2H), 2.37 (s, 3H), 1.63 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.0, 167.2, 154.2, 145.0, 134.8, 134.3, 129.4, 129.1, 128.9, 128.8, 116.1, 115.8, 76.1, 65.4, 64.6, 61.4, 24.7, 24.4, 21.6; IR: 3346, 3046, 2971, 1746, 1622, 15010, 1228, 1085, 840, 758, 724, 682, 579, 570 cm^{-1}; anal. calcd. for $C_{22}H_{22}FN_3O_5S_2$: C 53.75, H 4.51, N 8.55; found: C 54.01, H 4.58, N 8.32. *Major diastereomer: ee* was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 30/70, 1.0 mL min^{-1}, 245 nm): retention times t_{minor} = 11.63 min, t_{major} = 13.77 min, *ee* 97%.

3-[(4*S*,5*R*)-5-(2-Chlorophenyl)-2-thioxo-1-tosylimidazolidine-4-carbonyl]-4,4-dimethyloxazolidin-2-one (4h): Colorless needles; $[\alpha]_D^{20}$: +12 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62–7.59 (d, *J* = 8.4 Hz, 2H), 7.34–7.30 (m, 4H), 7.17–7.14 (d, *J* = 8.1 Hz, 2H), 7.11 (br, 1H), 6.20 (d, *J* = 1.2 Hz, 1H), 4.84–4.83 (d, *J* = 1.8 Hz, 1H), 4.15 (s, 2H), 2.39 (s, 3H), 1.64 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.9, 167.1, 154.2, 145.1, 136.9, 135.1, 134.7, 129.4, 129.3, 128.8, 128.4, 76.2, 65.4, 64.5, 61.4, 24.7, 24.5, 21.7; IR: ν = 3346, 3052, 2971, 1720, 1641, 1515, 1374, 1227, 1097, 840, 759, 682, 588, 570 cm^{-1}; anal. calcd. for $C_{22}H_{22}ClN_3O_5S_2$: C 52.01, H 4.36, N 8.27; found: C 52.22, H 4.43, N 8.08. *Major diastereomer: ee* was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 30/70, 1.0 mL min^{-1}, 245 nm): retention time: t_{major} = 19.77 min, *ee* 99%.

4,4-Dimethyl-3-[(4*S*,5*R*)-2-thioxo-5-*p*-tolyl-1-tosylimidazolidine-4-carbonyl]oxazolidin-2-one (4i): Colorless solid; $[\alpha]_D^{20}$: −67 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58–7.55 (d, *J* = 8.4 Hz, 2H), 7.25–7.16 (m, 5H), 7.12–7.10 (d, *J* = 8.4 Hz, 2H), 6.21 d, *J* = 1.2 Hz, 1H), 4.87 (d, *J* = 1.8 Hz, 1H), 4.13 (s, 2H), 2.37 (s, 3H), 1.63 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.9, 167.2, 154.2, 144.7, 139.1, 135.4, 134.9, 129.6, 129.4, 128.6, 126.9, 76.1, 65.8, 64.7, 61.3, 24.6, 24.4, 21.6, 14.2; IR: ν = 3348, 2975, 1698, 1606, 1468, 1399, 1321, 1247, 1168, 1094, 1048, 760, 701, 658, 572 cm^{-1}; anal. calcd. for $C_{23}H_{25}N_3O_5S_2$: C 56.66, H 5.17, N 8.62; found: C 56.39, H 5.34, N 8.68. *Major diastereomer: ee* was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 30/70, 1.0 mL min^{-1}, 245 nm): retention times t_{major} = 14.12 min, t_{minor} = 23.21 min, *ee* 99%.

4,4-Dimethyl-3-[(4*S*,5*R*)-2-thioxo-5-*m*-tolyl-1-tosylimidazolidine-4-carbonyl]oxazolidin-2-one (4j): White solid; $[\alpha]_D^{20}$: −21 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.57–7.54 (d, *J* = 8.1 Hz, 2H), 7.37 (br, 1H), 7.23–7.12 (m, 5H), 7.09–7.06 (d, *J* = 8.4 Hz, 2H), 6.21 (d, *J* = 1.2 Hz, 1H), 4.89 (d, *J* = 1.8 Hz, 1H), 4.14 (s, 2H), 2.36 (s, 3H), 2.28 (s, 3H), 1.62 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.0, 167.2, 154.2, 144.7, 138.9, 138.2, 134.9, 129.9, 129.5, 129.0, 128.6, 127.4, 124.2, 76.1, 66.0, 64.7, 61.4, 24.6, 24.4, 21.6, 21.4; IR: ν = 3346, 2981, 1694, 1610, 1454, 1386, 1248, 1153, 1095, 1037, 761, 698, 642, 571 cm^{-1}; anal. calcd. for $C_{23}H_{25}N_3O_5S_2$: C 56.66, H 5.17, N 8.62; found: C 56.90, H 5.30, N, 8.71. *Major diastereomer: ee* was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 30/70, 1.0 mL min^{-1}, 245 nm): retention times t_{minor} = 9.32 min, t_{major} = 11.39 min, *ee* 96%.

4,4-Dimethyl-3-[(4*S*,5*R*)-2-thioxo-5-*o*-tolyl-1-tosylimidazolidine-4-carbonyl]oxazolidin-2-one (4k): White solid; $[\alpha]_D^{20}$: −33 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66–7.63 (d, *J* = 8.1 Hz, 2H), 7.22–7.20 (m, 4H), 7.17–7.14 (d, *J* = 8.1 Hz, 2H), 6.69–6.68 (d, *J* = 1.8 Hz, 1H), 4.69 (d, *J* = 1.8 Hz, 1H), 4.12 (s, 2H), 2.41 (s, 3H), 2.38 (s, 3H), 1.61 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.5, 167.0, 154.3, 144.9, 136.9, 134.9,131.0, 129.6, 128.9, 128.8, 127.0, 76.1, 64.7, 62.2, 61.4, 24.5, 24.4, 21.7, 19.3; IR: ν = 3426, 3191, 3058, 2979, 1746, 1478, 1369, 1266, 1175, 1090, 1066, 1024, 740 cm^{-1}; anal. calcd. for $C_{23}H_{25}N_3O_5S_2$: C 56.66, H 5.17, N 8.62; found: C 56.94, H 5.07, N 8.33. *Major diastereomer: ee* was determined by HPLC analysis (Chiralcel AD-H, *i*-

PrOH/hexane = 30/70, 1.0 mL min^{-1}, 245 nm): retention times t_{minor} = 7.83 min, t_{major} = 11.47 min, *ee* 97%.

3-[(4*S*,5*S*)-5-(Furan-2-yl)-2-thioxo-1-tosylimidazolidine-4-carbonyl]-4,4-dimethyloxazolidin-2-one (4l): Colorless solid; $[\alpha]_D^{20}$: +39 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61–7.59 (d, *J* = 8.1 Hz, 2H), 7.34 (br, 1H), 7.21–7.20 (m, 1H), 7.19–7.17 (d, *J* = 8.1 Hz, 2H), 6.62–6.61 (d, *J* = 3.3 Hz, 1H), 6.43–6.41 (m, 2H), 5.06 (d, *J* = 2.1 Hz, 1H), 4.14 (s, 2H), 2.38 (s, 3H), 1.62 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.2, 166.6, 154.2, 149.8, 144.8, 143.4, 134.8, 129.3, 128.9, 110.8, 110.7, 76.1, 61.6, 61.4, 58.9, 24.6, 24.5, 21.7. IR: ν = 3412, 1781, 1698, 1478, 1392, 1365, 1266, 1230, 1171, 1092, 748 cm^{-1}; anal. calcd. for $C_{20}H_{21}N_3O_6S_2$: C 51.82, H 4.57, N 9.07; found: C 52.03, H 4.48, N 9.33. *Major diastereomer: ee* was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 30/70, 1.0 mL min^{-1}, 245 nm): retention times t_{minor} = 12.12 min, t_{major} = 22.57 min, *ee* 98%.

General Procedure for the Organocatalytic Asymmetric Synthesis of Spirocyclic Thioureas *via* Mannich Reaction of Isothiocyanate (1c) with *N*-Tosylimines

To a stirred solution of **3g** (0.006 mmol, 3.0 mol%) and *N*-tosylimine (0.30 mmol) in dry toluene (1.5 mL), isothiocyanate **1c** (0.20 mmol) was added under argon, The solution was stirred at −15 °C for 6 h. After the reaction was completed (monitored by TLC), the resulting mixture was concentrated under reduced pressure and the residue was purified through column chromatography on silica gel to give the optical pure spirocyclic products.

(4*R*,5*S*)-4-Phenyl-2-thioxo-3-tosyl-7-oxa-1,3-diazaspiro [4.4]nonan-6-one (4m): White solid; $[\alpha]_D^{20}$: −17 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.12 (br, 1H), 7.81–7.84 (d, *J* = 7.8 Hz, 1H), 7.61–7.64 (d, *J* = 8.1 Hz, 1H), 7.29–7.41 (m, 7H), 6.16 (s, 1H), 4.18–4.54 (m, 2H), 2.38–2.41 (m, 5H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 178.7, 174.4, 171.0, 144.9, 136.2, 135.2, 129.1, 128.9, 128.8, 128.4, 126.6, 70.9, 68.0, 65.4, 64.3, 35.5, 28.9, 21.1; IR: ν = 3337, 2921, 2853, 2527, 1777, 1473, 1365, 1165, 1084, 1018, 667, 583 cm^{-1}; HR-MS (ESI): *m/z* = 403.0778, calcd. for $C_{19}H_{18}N_2O_4S_2+H^+$: 403.0781; Δ = 0.7 ppm. *Major diastereomer: ee* was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 30/70, 1.0 mL min^{-1}, 245 nm): retention times t_{minor} = 12.05 min, t_{major} = 19.12 min, *ee* 90%.

(4*R*,5*S*)-4-(2-Fluorophenyl)-2-thioxo-3-tosyl-7-oxa-1,3-diazaspiro[4.4]nonan-6-one (4n): White solid; $[\alpha]_D^{20}$: +5 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.96–7.99 (d, *J* = 7.8 Hz, 1H), 7.70–7.73 (d, *J* = 8.1 Hz, 1H), 7.20–7.71 (m, 6H), 6.08 (s, 1H), 4.11–4.50 (m, 2H), 1.85–2.42 (m, 5H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 178.6, 174.7, 145.4, 144.9, 135.4, 135.3, 134.1, 132.0, 129.7, 129.5, 129.3, 129.2, 128.8, 116.5, 67.9, 67.4, 66.3, 65.9, 64.9, 35.8, 29.7, 21.5. IR: ν = 3416, 3366, 2922, 2846, 1776, 1455, 1357, 1163, 1069, 1019, 666, 586 cm^{-1}; HR-MS (ESI): *m/z* = 421.0685, calcd. for $C_{19}H_{17}FN_2O_4S_2+H^+$: 421.0687; Δ = 0.5 ppm. *Major diastereomer: ee* was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 30/70, 1.0 mL min^{-1}, 245 nm): retention times t_{minor} = 4.99 min, t_{major} = 11.64 min, *ee* 95%.

(4*R*,5*S*)-4-(4-Chlorophenyl)-2-thioxo-3-tosyl-7-oxa-1,3-diazaspiro[4.4]nonan-6-one (4o): White solid; $[\alpha]_D^{20}$: +6 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.85–7.88 (d, *J* = 8.4 Hz, 1H), 7.71–7.73 (d, *J* = 8.1 Hz, 1H), 7.27–7.53 (m, 6H), 6.19 (s, 1H), 4.33–4.56 (m, 2H), 2.37–2.41 (m, 5H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 179.1, 174.8, 171.6, 145.6, 142.3, 135.7, 135.4, 133.9, 129.7, 129.3, 129.3, 128.9, 126.1, 70.6, 64.9, 35.8, 21.5; IR: ν = 3289, 3060, 2920, 2853, 1364, 1491, 1338, 1157, 1090, 1014, 665, 542 cm^{-1}; HR-MS (ESI): *m/z* = 437.0396, calcd. for $C_{19}H_{17}ClN_2O_4S_2+H^+$: 437.0391; Δ = 1.1 ppm. *Major diastereomer: ee* was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 30/70, 1.0 mL min^{-1}, 245 nm): retention times: t_{minor} = 10.71 min, t_{major} = 13.16 min, *ee* 93%.

(4*R*,5*S*)-2-Thioxo-4-*m*-tolyl-3-tosyl-7-oxa-1,3-diazaspiro [4.4]nonan-6-one (4p): White solid; $[\alpha]_D^{20}$: −11 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.79–7.81 (d, *J* = 8.1 Hz, 1H), 7.70–7.73 (d, *J* = 8.1 Hz, 1H), 7.14–7.39 (m, 6H), 6.09 (s, 1H), 4.39–4.56 (m, 2H), 3.38 (s, 3H), 2.26–2.40 (m, 5H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 179.3, 171.5, 145.4, 142.9, 137.9, 135.5, 129.7, 129.5, 128.5, 127.1, 126.8, 126.1, 71.5, 68.1, 64.8, 63.3, 36.1, 21.5; IR: ν = 3321, 3064, 2924, 2855, 1777, 1491, 1351, 1209, 1160, 1021, 664, 541 cm^{-1}; HR-MS (ESI): *m/z* = 417.0942, calcd. for $C_{20}H_{20}N_2O_4S_2+H^+$: 417.0937; Δ = 1.2 ppm. *Major diastereomer: ee* was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 30/70, 1.0 mL min^{-1}, 245 nm): retention times t_{minor} = 5.47 min, t_{major} = 12.21 min, *ee* 96%.

(4*R*,5*S*)-2-Thioxo-4-*p*-tolyl-3-tosyl-7-oxa-1,3-diazaspiro-[4.4]nonan-6-one (4q): White solid; $[\alpha]_D^{20}$: −15 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.80–7.83 (d, *J* = 8.4 Hz, 1H), 7.38–7.40 (d, *J* = 8.1 Hz, 1H), 7.17–7.32 (m, 6H), 6.09 (s, 1H), 4.48–4.50 (m, 2H), 3.35 (s, 3H), 2.31–2.41 (m, 5H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 171.1, 144.9, 142.5, 138.1, 135.1, 133.1, 129.1, 128.9, 127.9, 126.6, 70.9, 67.6, 64.2, 62.8, 35.5, 21.1; IR: ν = 3320, 3058, 2912, 2853, 1690, 1511, 1491, 1356, 1204, 1160, 1021, 661, 541 cm^{-1}; HR-MS (ESI): *m/z* = 417.0932, calcd. for $C_{20}H_{20}N_2O_4S_2+H^+$: 417.0937; Δ = 1.2 ppm.

General Procedure for Synthesis of Biologically Active Chiral Methylthioimidazolines

To a stirred solution of **3g** (0.006 mmol, 3.0 mol%) and *N*-tosylimine (0.30 mmol) in dry toluene (1.5 mL), isothiocyanate **1a** (0.20 mmol) was added under argon, The solution was stirred at −15 °C for 18 h. After the reaction was completed (monitored by TLC), the resulting mixture was concentrated under reduced pressure and the residue was purified through column chromatography on silica gel to give the optical pure pruducts. To a mixture of the cyclic thioureas and anhydrous K_2CO_3 (1.20 equiv.) in 2.5 mL acetone was added MeI (1.10 equiv.) dropwise at 0 °C. Then the reaction was stirred for 8 h. and concentrated under vacuum. The mixture was applied to chromatography to afford the purified methylthioimidazoline products. The enantiomeric purity of the product was determined by using HPLC.

4,4-Dimethyl-3-[(4*S*,5*R*)-2-(methylthio)-5-phenyl-1-tosyl-4,5-dihydro-1*H*-imidazole-4-carbonyl]oxazolidin-2-one (TID-1): Colorless solid; $[\alpha]_D^{20}$: −17 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69–7.67 (d, *J* = 8.4 Hz, 2H), 7.29–7.23 (m, 5H), 7.22–7.19 (d, *J* = 8.4 Hz, 2H), 5.64–5.62 (d, *J* = 4.2 Hz, 1H), 5.56–5.55 (d, *J* = 4.2 Hz, 1H), 3.99 (s, 2H), 2.50 (s, 3H), 2.39 (s, 3H), 1.47 (s, 3H, 1.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.7, 160.6, 153.2, 144.4, 139.8, 135.4,

129.4, 128.7, 128.3, 128.0, 126.9, 75.8, 75.3, 66.7, 60.6, 24.8, 24.0, 21.6, 15.5; IR: ν = 3394, 2972, 2930, 2256, 1779, 1706, 1571, 1363, 1306, 1162, 1093, 672 cm^{-1}; HR-MS (ESI): m/z = 488.1305, calcd. for $C_{23}H_{25}N_3O_5S_2+H^+$: 488.1308; Δ = 0.6 ppm. *Major diastereomer: ee* was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 30/70, 1.0 mL min^{-1}, 245 nm): retention times t_{minor} = 13.74 min, t_{major} = 19.27 min, *ee* 97%.

3-[(4*S*,5*R*)-5-(2-Fluorophenyl)-2-(methylthio)-1-tosyl-4,5-dihydro-1*H*-imidazole-4-carbonyl]-4,4-dimethyloxazolidin-2-one (TID-2): Colorless needles; $[\alpha]_D^{20}$: −50 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83–7.80 (d, *J* = 8.4 Hz, 2H), 7.40–7.30 (m, 4H), 7.16–7.11 (m, 1H), 7.03–6.97 (m, 1H), 5.75–5.74 (d, *J* = 4.5 Hz, 1H), 5.69–5.67 (d, *J* = 4.5 Hz, 1H), 3.99 (s, 2H), 2.50 (s, 3H), 2.42 (s, 3H), 1.45 (s, 3H, 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.6, 160.6, 158.0, 153.2, 144.7, 134.6, 129.9, 129.8, 129.6, 128.1, 127.6, 127.4, 124.6, 124.6, 115.6, 115.3, 75.3, 74.8, 60.9, 60.6, 24.6, 24.0, 21.6, 15.5; IR: ν = 3396, 2972, 2931, 2957, 1779, 1708, 1574, 1366, 1306, 1176, 1093, 671 cm^{-1}; HR-MS (ESI): m/z = 506.1209, calcd. for $C_{23}H_{24}FN_3O_5S_2+H^+$: 506.1214; Δ = 1.0 ppm. *Major diastereomer: ee* was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 30/70, 1.0 mL min^{-1}, 245 nm): retention times t_{minor} = 9.89 min, t_{major} = 12.56 min, *ee* 95%.

3-[(4*S*,5*R*)-5-(2-Chlorophenyl)-2-(methylthio)-1-tosyl-4,5-dihydro-1*H*-imidazole-4-carbonyl]-4,4-dimethyloxazolidin-2-one (TID-3): Colorless needles; $[\alpha]_D^{20}$: −90 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91–7.89 (d, *J* = 8.4 Hz, 2H), 7.46–7.27 (m, 4H), 7.26–7.23 (m, 2H), 5.93–5.92 (d, *J* = 3.9 Hz, 1H), 5.66–5.64 (d, *J* = 3.9 Hz, 1H), 3.98 (s, 2H), 2.48 (s, 3H), 2.44 (s, 3H), 1.46 (s, 3H, 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.5, 160.6, 153.1, 144.8, 134.6, 131.5, 129.6, 129.6, 129.3, 128.3, 127.5, 75.2, 65.8, 63.8, 60.6, 24.6, 24.1, 21.6, 15.5; IR: ν = 3398, 2971, 2932, 2256, 1779, 1707, 1574, 1365, 1305, 1163, 1092, 670 cm^{-1}; HR-MS (ESI): m/z = 522.0929, calcd. for $C_{23}H_{24}ClN_3O_5S_2+H^+$: 522.0919; Δ = 1.9 ppm. *Major diastereomer: ee* was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 30/70, 1.0 mL min^{-1}, 245 nm): retention times t_{minor} = 11.24 min, t_{major} = 14.39 min, *ee* 97%.

4,4-Dimethyl-3-[(4*S*,5*R*)-2-(methylthio)-5-*o*-tolyl-1-tosyl-4,5-dihydro-1*H*-imidazole-4-carbonyl]oxazolidin-2-one (TID-4): Colorless solid; $[\alpha]_D^{20}$: −23 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69–7.66 (d, *J* = 8.1 Hz, 2H), 7.23–7.20 (d, *J* = 8.4 Hz, 2H), 7.16–7.09 (m, 4H), 5.95–5.94 (d, *J* = 4.2 Hz, 1H), 5.57–5.55 (d, *J* = 4.5 Hz, 1H), 4.00 (s, 2H), 2.51 (s, 3H), 2.40 (s, 3H), 2.32 (s, 3H), 1.50 (s, 3H, 1.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.7, 160.2, 153.1, 144.4, 138.1, 135.4, 134.8, 130.6, 129.4, 128.0, 128.0, 126.7, 75.9, 75.3, 65.9, 60.6, 24.8, 23.8, 21.6, 19.3, 15.5; IR: ν = 3393, 2968, 2929, 2256, 1780, 1706, 1571, 1365, 1305, 1166, 1092, 673 cm^{-1}; HR-MS (ESI): m/z = 502.1461, calcd. for $C_{24}H_{27}N_3O_5S_2+H^+$: 502.1465; Δ = 0.8 ppm. *Major diastereomer: ee* was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 30/70, 1.0 mL min^{-1}, 245 nm): retention times t_{minor} = 9.37 min, t_{major} = 14.62 min, *ee* 99%.

4,4-Dimethyl-3-[(4*S*,5*R*)-2-(methylthio)-5-*m*-tolyl-1-tosy l-4,5-dihydro-1*H*-imidazole-4-carbonyl]oxazolidin-2-one (TID-5): Colorless solid; $[\alpha]_D^{20}$: −15 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.64 (d, *J* = 8.1 Hz, 2H), 7.21–7.18 (d, *J* = 8.1 Hz, 2H), 7.17–7.03 (m, 3H), 6.97 (s, 1H), 5.62–5.60 (d, *J* = 4.5 Hz, 1H), 5.56–5.55 (d, *J* = 4.2 Hz, 1H), 4.00 (s, 2H), 2.52 (s, 3H), 2.39 (s, 3H), 2.26 (s, 3H),1.49 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.6, 160.3, 153.2, 144.3, 139.4, 138.4, 135.5, 129.7, 129.3, 129.2, 128.6, 128.0, 127.4, 126.5, 124.2, 75.7, 75.3, 66.7, 60.7, 24.7, 24.0, 21.6, 21.3, 15.6; IR: ν = 3384, 2971, 2928, 2252, 1779, 1706, 1570, 1362, 1306, 1165, 1092, 672 cm^{-1}; HR-MS (ESI): m/z = 502.1470, calcd. for $C_{24}H_{27}N_3O_5S_2+H^+$: 502.1465; Δ = 1.0 ppm. *Major diastereomer: ee* was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 30/70, 1.0 mL min^{-1}, 245 nm): retention times t_{minor} = 12.41 min, t_{major} = 13.25 min, *ee* 99%.

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