JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

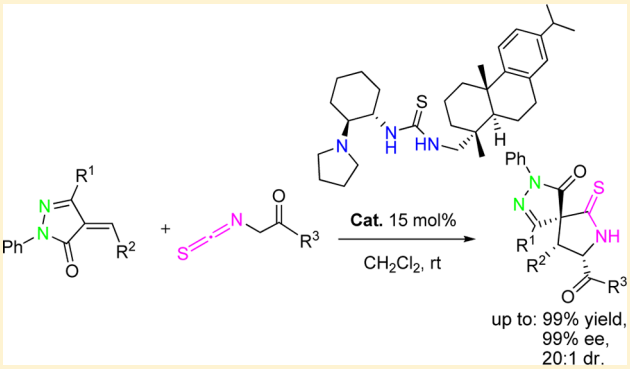
Core Scaffold-Inspired Stereoselective Synthesis of Spiropyrazolones via an Organocatalytic Michael/Cyclization Sequence

Luping Liu, Yuan Zhong, Panpan Zhang, Xianxing Jiang,* and Rui Wang*

Key Laboratory of Preclinical Study for New Drugs of Gansu Province, School of Basic Medical Sciences, Institute of Biochemistry and Molecular Biology, State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, China 730000

Supporting Information

ABSTRACT: Herein, the organocatalytic asymmetric Michael/cyclization sequence of α-isothiocyanato imides and esters with a variety of unsaturated pyrazolones is presented, in general, affording functionalized spiropyrazolones containing three contiguous stereogenic centers in high levels of diastereo- and enantioselectivity (up to 20:1 dr and 99% ee). Moreover, the current protocol provides a highly efficient and convenient strategy that allows rapid enantioselective construction of diversely spiropyrazolone skeletons with high optical purity.

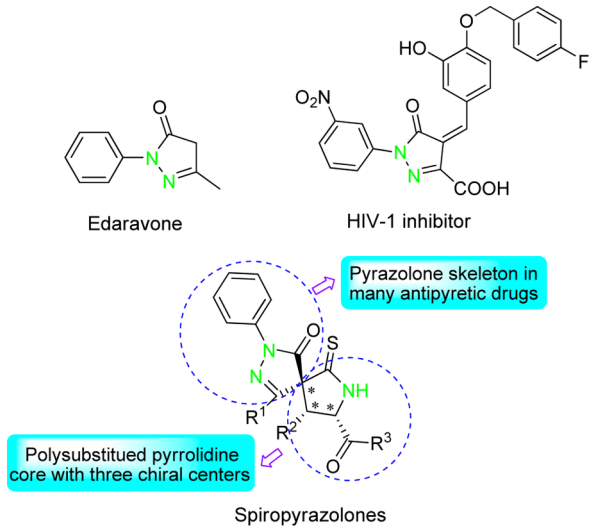


INTRODUCTION

Pyrazol-3-ones are important structural motifs in organic synthesis and have been found as key backbones, commonly shown by a series of biological assays to have potent biological and pharmaceutical activities, including anti-inflammatory, antibacterial, HIV inhibition, and clinically useful antitumor activity.[1] Significantly, optically active pyrazolone derivatives as important synthetic intermediates or products have attracted intense interest from chemists in recent years.[2] Therefore, the development of highly efficient synthetic methods to access optically active pyrazolones, in particular spiropyrazolones, would be of great utility for target-oriented organic synthesis (Scheme 1). However, this represents a considerable difficulty due to the synthetic challenges presented by spiro-motifs, including incorporating heterocycles and obtaining high enantioselectivity.

To date, although the preparation of such kinds of pyrazolone skeletons has been partly addressed in elegant works because of its significant bioactivity,[2] the asymmetric catalytic approaches to access chiral pyrazolones at the C4 position are scarce and only a few examples have been documented. Especially, the asymmetric synthesis of spiropyrazolones via a catalytic cascade approach still remains challenging. To the best of our knowledge, only one report of their efficient asymmetric synthesis via an intermolecular Michael–aldol reaction of aldehydes has been described.[2k] Inspired by Feng and co-workers' recent report on the synthesis of pyrazolone derivatives bearing a quaternary stereocenter at the C4 position[3] by using a metal/*N*,*N*′-dioxide complex, we considered whether the enantioselective construction of this new type of spiropyrazolone could be achieved via a common but more efficient bifunctional organocatalytic cascade cyclization approach,[4] thereby providing an elegant starting point to discover new reaction modes (Figure 1). For these reasons, in this text, we present our results on this topic.

Scheme 1. Biologically Active Pyrazolone Derivatives and Pyrrolidone-Type Spiropyrazolones



Recently, α-isothiocyanato imides or esters have emerged as some of the most attractive reactants in asymmetric organometallic or organocatalytic cascade reactions to furnish masked chiral β-hydroxyl-α-amino and α,β-diamino acid derivatives.[5]

Received: August 31, 2012
Published: October 16, 2012

   dx.doi.org/10.1021/jo301851a | *J. Org. Chem.* 2012, 77, 10228–10234

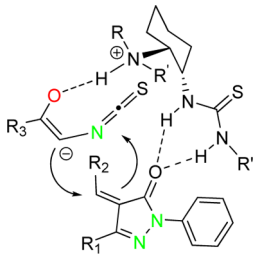


Figure 1. Proposed model for asymmetric construction of spiropyrazolones.

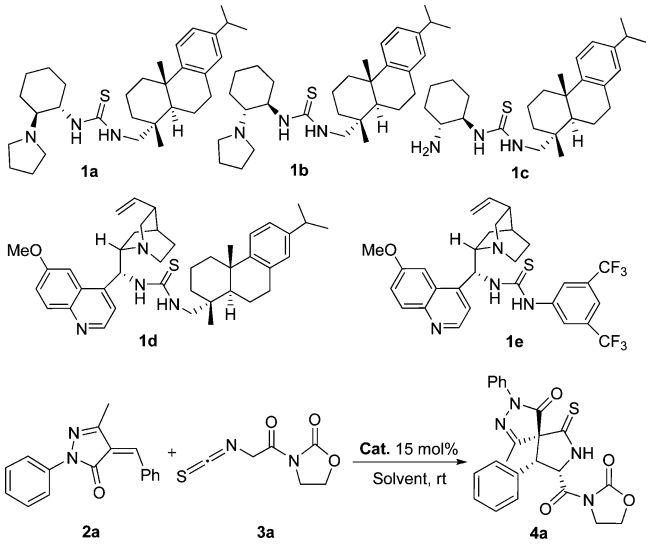
Surprisingly, among these protocols, the variant of a catalytic enantioselective Michael addition[6]/cyclization sequence of α-isothiocyanato imides showed a substrate-dependent characteristic. Notably, methyleneindolinone was employed as an exclusively suitable Michael acceptor in all of the above related asymmetric cascade cyclizations.[7] Herein, we present a highly enantioselective [3 + 2] cycloaddition of α-isothiocyanato imides with unsaturated pyrazolones by using rosin-derived tertiary amine-thiourea to form functionalized spiropyrazolones bearing three contiguous stereogenic centers with high levels of enantio- and diastereoselectivity (up to 20:1 dr and 99% ee).

RESULTS AND DISCUSSION

On the basis of our recent success with the Michael cyclization reaction of α-isothiocyanato imides **3a** by employing rosin-derived bifunctional thiourea catalysis,[8,9] and to gain a better understanding of the scope of this conceptually catalytic system, we hoped to expand our studies beyond model compounds to develop an efficient protocol for accessing functionalized spiropyrazolones.[10] We selected the unsaturated pyrazolone **2a** as a model substrate to start our investigation. Satisfyingly, we obtained the desired product **4a** in high yield and enantio- and diastereoselectivity (99% yield, 96% ee, and 10:1 dr) in the presence of 15 mol % of **1a** at room temperature in CH_2Cl_2 (entry 1, Table 1). Subsequently, other available organocatalysts **1b**–**e** were also evaluated (entries 2–5, Table 1). Although tertiary amine-thiourea **1b**, **1d**, and **1e** could provide the products, relatively low yields and enantioselectivites were observed. In contrast, thiourea catalyst **1c** proved to be essentially inactive for this transformation (entry 3, Table 1). Further screening of solvents indicated that CH_2Cl_2 proved to be the most suitable reaction media for this asymmetric process.

The results of experiments under optimized conditions that probed the scope of the reaction are summarized in Scheme 2. In general, various unsaturated aromatic pyrazolones having different electronic and steric parameters were tolerated and gave the corresponding products in good to excellent yields (71–99%, **4b**–**p**) and diastereoselectivities and high enantioselectivities (81–99% ee, **4b**–**p**). Notably, an increase in the steric hindrance of the R^2 group could markedly affect the yield and stereochemical outcome of the product. When a bulkier 1-naphthyl group was introduced into R^2, **4b** was formed with only 4:1 dr in 72% yield and 81% ee. As expected, the unsaturated heterocyclic pyrazolones have also proven to be suitable substrates for this asymmetric process. Although 2-furyl-substituted pyrazolone gave 4:1 dr, good to excellent enantioselectivities and yields were still obtained (**4l** and **4m**). Compared to the planar structure of the furan ring, the nonplanar structural nature of the thiophene ring could lead to

Table 1. Screening of Reaction Conditions[a]



entry	catalyst	solvent	yield (%)	ee (%)[b]	dr[c]
1	**1a**	CH_2Cl_2	99	96	10:1
2	**1b**	CH_2Cl_2	89	86	10:1
3	**1c**	CH_2Cl_2	trace	n.d.	n.d.
4	**1d**	CH_2Cl_2	54	65	10:1
5	**1e**	CH_2Cl_2	47	78	10:1
6	**1a**	Et_2O	95	95	10:1
7	**1a**	toluene	98	90	10:1
8	**1a**	MeOH	trace	n.d.	n.d.

[a]Unless noted, the reaction was conducted with **2a** (0.10 mmol) and **3a** (0.11 mmol) with 15 mol % catalyst at room temperature for 2 h. [b]The ee values were determined by HPLC. [c]The dr values were determined by ^{1}H NMR.

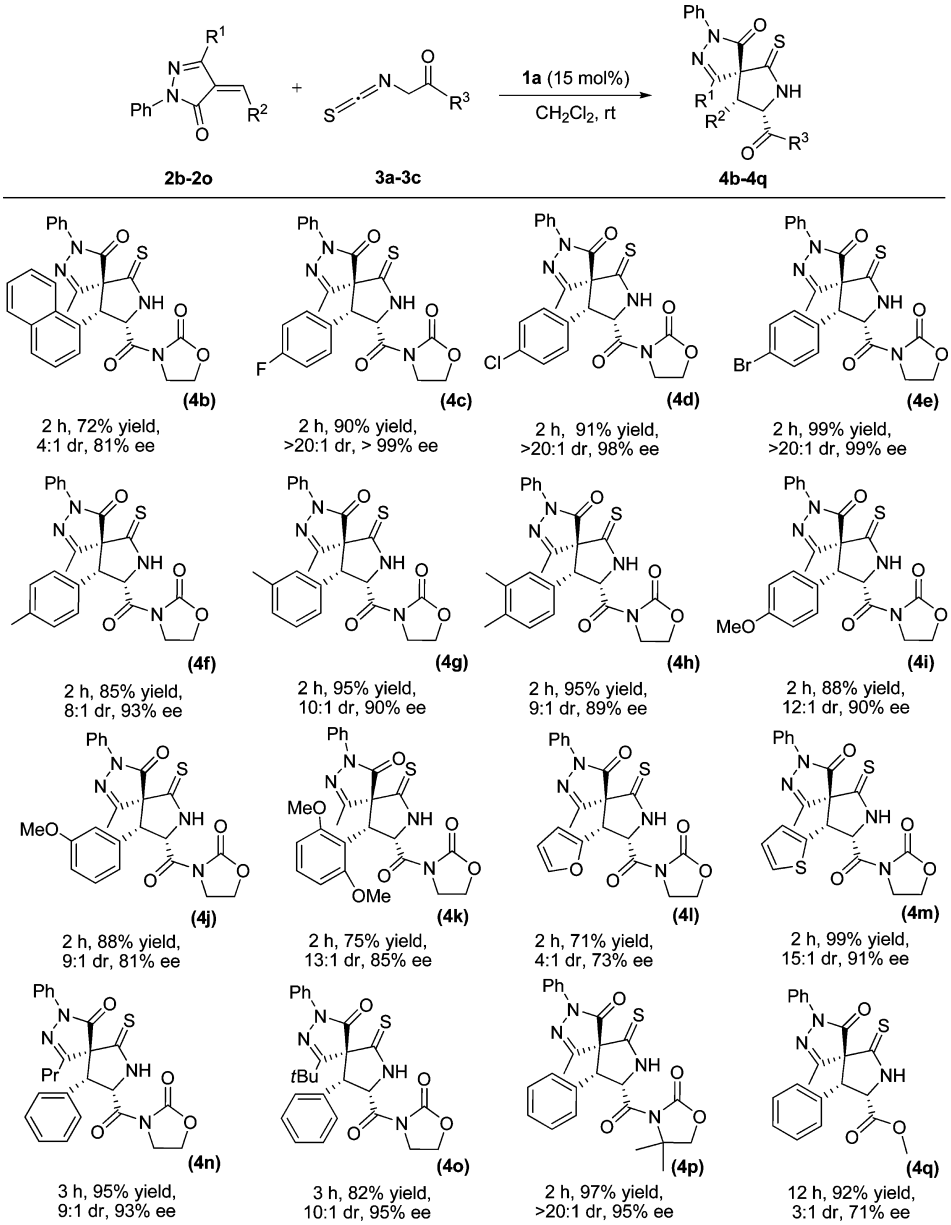
better results in terms of yield and stereochemical outcome. In addition, the results suggested that the rigid skeleton of the isoxazolidinone functional group is necesssary for stereocontrol in this reaction. When methyl isothiocyanato acetate was employed, the reaction afforded **4q** with 71% ee and 3:1 dr. The absolute and relative configurations of this kind of spiropyrazolones were unambiguously determined by X-ray crystallography of **4a** (see Supporting Information).

With the successful construction of chiral spiropyrazolone skeletons as described above, the transformation of the cycloadduct to a number of valuable compounds was performed. As illustrated in Scheme 3, product **4a** could be converted smoothly into **5a** containing three adjacent chiral centers through a simple oxidant treatment[6a] in 98% yield with a slight loss of enantioselectivity. **4a** could also be transformed to **6a** possessing a potential medical skeleton in high yield (91%) and enantioselectivity (88% ee) under the established method.[5k] In addition, conversion of the isoxazolidinone group proved straightforward. The isoxazolidinone functional group could be easily transformed into the ester by treatment of **4a** with MeMgI and ethanol in THF, affording **7a** in 93% yield and 88% ee. These representative examples demonstrate the inherent synthetic potential of this methodology.

As a preliminary study, we also decided to evaluate the biological activities[11] of this new kind of spiropyrazolone, thereby providing a basis for scaffold-inspired synthesis and further development of new types of candidates for future biomedical utilities. We chose some representative compounds

dx.doi.org/10.1021/jo301851a | J. Org. Chem. 2012, 77, 10228–10234

Scheme 2. Scope of Substrates[a]



[a]The spiropyrazolones with three adjacent stereocenters synthesized by optimal reaction conditions. The ee values were determined by chiral-phase HPLC analysis and the dr values were determined by ^{1}H NMR.

(**4a**, **4c**, **4e**, **4f**, and **4i**), which were evaluated for their cytotoxicity in vitro toward the human T-cell leukemia cell line (jurkat), human cervical cancer cell line (Hela), and human bladder cancer cell line (5637). We found that **4e** exhibited obvious antiproliferative activity, and detailed results are presented in the Supporting Information.

CONCLUSION

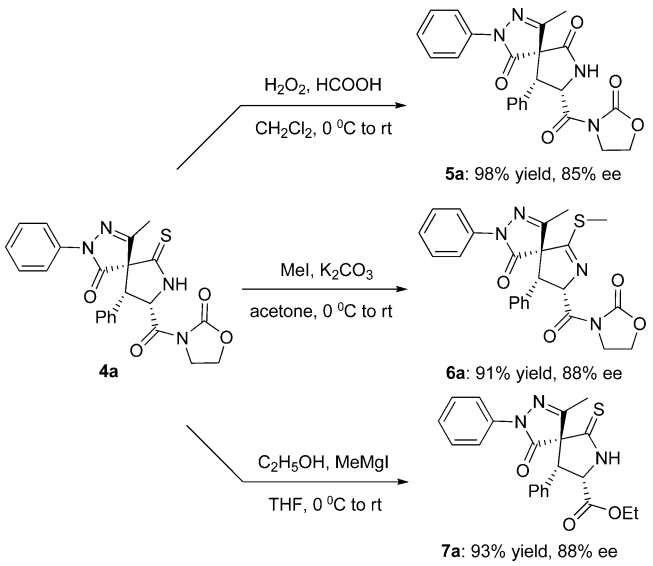
We have disclosed the synthesis of highly optically active spiropyrazolones with high levels of enantio- and diastereoselectivity (up to 20:1 dr and 99% ee) through an organocatalyzed asymmetric [3 + 2] Michael/cyclization sequence of α-isothiocyanato imides and esters with various unsaturated pyrazolones. Additional investigations involving the application of this catalytic approach and intensive studies on structure–biological activity relationships are underway in our group and will be reported in due course.

EXPERIMENTAL SECTION

General Information. All solvents were dried according to established procedures. Reactions were monitored by thin layer chromatography (TLC), and column chromatography purifications were carried out using silica gel GF254. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a 300 MHz spectrometer in $CDCl_3$, and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a 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), and coupling constant in hertz (Hz). Infrared (IR) spectra were recorded on an FT-IR spectrometer. Optical rotations were recorded on a polarimeter. HRMS was

dx.doi.org/10.1021/jo301851a | J. Org. Chem. 2012, 77, 10228–10234

Scheme 3. Construction of Other Chiral Spiropyrazolones Frameworks



measured with a mass spectrometer, and the mass analyzer type is Q-Tof. The ee value determination was carried out using chiral high-performance liquid chromatography (HPLC) with Daicel Chiracel AD-H column on Waters with a 2998 UV-detector, and the dr values were determined by 300 Hz ^{1}H NMR.

Representative Procedure for the Asymmetric Michael/Cyclization Reactions. Catalyst **1a** (0.015 mmol, 15 mol %), 4-benzylidene-3-methyl-1-phenyl-1*H*-pyrazol-5(4*H*)-one **2a** (0.1 mmol, 1.0 equiv), and α-isothiocyanato imide **3a** (0.11 mmol, 1.1 equiv) were dissolved in 1.0 mL of CH_2Cl_2 at room temperature. After the reaction was completed (monitored by TLC), the resulting mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc, 100:8) to afford the product. The enantiomeric purity of the product was determined by HPLC, and the dr value was determined by ^{1}H NMR spectroscopy (300 Hz). **4b−q** were prepared using the same method.

4a: The title compound was isolated as a mixture of diastereoisomers by column chromatography (CH_2Cl_2/EtOAc = 100/8) in 99% yield (44.5 mg). White solid, mp 139−140 °C; $[\alpha]^{20}_D$ = 2.3 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.00 (br s, 0.09 H), 8.91 (br s, 0.86 H), 7.89−7.92 (d, *J* = 9.0 Hz, 2 H), 7.40−7.43 (t, *J* = 7.5 Hz, 2 H), 7.31−7.37 (m, 3 H), 7.18−7.25 (m, 3 H), 6.41−6.47 (m, 1 H), 4.81−4.86 (m, 1 H), 4.22−4.30 (m, 1 H), 3.76−3.96 (m, 2 H), 3.16−3.25 (m, 1H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.4, 170.1, 167.6, 157.4, 152.2, 137.4, 134.2, 129.3, 129.0, 128.8, 128.6, 125.4, 118.9, 76.4, 67.8, 63.0, 53.1, 42.3, 17.3. HRMS-ESI (*m*/*z*): calcd for $C_{23}H_{20}N_4O_4S+H^+$: 449.1278; found: 449.1281, 0.7 ppm. IR: 3276.7, 2923.6, 1782.5, 1705.4, 1595.9, 1498.7, 1391.8, 1363.8, 1268.2, 1220.4, 1038.1, 758.3, 735.9, 703.8, 654.8, 553.9 cm^{-1}. HPLC: ee of major diastereoisomer was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 40/60, 1.0 mL/min, 245 nm), retention time: t_{minor} = 26.49 min, t_{major} = 16.30 min, ee = 96%.

4b: The title compound was isolated as a mixture of diastereoisomers by column chromatography (CH_2Cl_2/EtOAc = 100/8) in 72% yield (36 mg). White solid, mp 151−152 °C; $[\alpha]^{20}_D$ = 1.45 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.00 (br s, 0.19 H), 8.95 (br s, 0.68 H), 7.84−7.95 (m, 5 H), 7.62−7.64 (d, *J* = 7.2 Hz, 1 H), 7.50−7.53 (m, 2 H), 7.39−7.44 (m, 3 H), 7.19−7.24 (m, 1 H), 6.64−6.68 (m, 1 H), 5.89−5.92 (d, *J* = 6.9 Hz, 1 H), 4.07−4.15 (m, 1 H), 3.47−3.82 (m, 2 H), 3.08−3.17 (m, 1 H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.6, 170.1, 167.8, 157.4, 152.2, 137.5, 133.7, 131.1, 130.0, 129.6, 129.0, 128.9, 127.6, 126.5, 125.5, 124.9, 122.1, 119.0, 77.2, 67.9, 62.7, 46.5, 42.2, 17.1. HRMS-ESI (*m*/*z*): calcd for $C_{27}H_{22}N_4O_4S+H^+$: 499.1435; found: 499.1438, 0.6 ppm. IR: 2923.0, 1781.4, 1704.6, 1498.9, 1391.0, 1363.2, 1298.3, 1263.0, 1222.0, 1123.7, 757.9, 736.0, 695.3 cm^{-1}. HPLC: ee of major diastereoisomer was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 50/50, 1.0 mL/min, 240 nm), retention time: t_{minor} = 30.60 min, t_{major} = 37.87 min, ee = −81%.

4c: The title compound was isolated as a mixture of diastereoisomers by column chromatography (CH_2Cl_2/EtOAc = 100/8) in 90% yield (42 mg). White solid, mp 144−146 °C; $[\alpha]^{20}_D$ = 2.88 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.84 (br s, 1 H), 7.89−7.91 (d, *J* = 7.8 Hz, 2 H), 7.38−7.43 (m, 2 H), 7.18−7.26 (m, 3 H), 7.01−7.06 (m, 2 H), 6.41−6.43 (d, *J* = 6.3 Hz, 1 H), 4.84−4.86 (d, *J* = 6.3 Hz, 1 H), 4.31 (br s, 1 H), 4.04 (br s, 1 H), 3.86 (br s, 1 H), 3.31 (br s, 1 H), 1.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.3, 169.9, 167.5, 157.1, 152.2, 137.4, 130.6, 130.5, 130.2, 128.9, 125.5, 119.0, 116.3, 116.0, 76.3, 67.7, 63.1, 52.4, 42.3, 17.4. HRMS-ESI (*m*/*z*): calcd for $C_{23}H_{19}FN_4O_4S+H^+$: 467.1184; found: 467.1181, 0.6 ppm. IR: 2921.7, 1782.6, 1704.7, 1499.0, 1390.3, 1363.6, 1267.0, 1219.2, 1121.7, 1037.0, 757.5, 738.2, 693.4 cm^{-1}. HPLC: ee of major diastereoisomer was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 40/60, 1.0 mL/min, 240 nm), retention time: t_{major} = 20.38 min, ee = >99%.

4d: The title compound was isolated as a mixture of diastereoisomers by column chromatography (CH_2Cl_2/EtOAc = 100/8) in 91% yield (44 mg). White solid, mp 124−126 °C; $[\alpha]^{20}_D$ = 4.00 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.85 (br s, 1 H), 7.88−7.91 (d, *J* = 8.7 Hz, 2 H), 7.38−7.43 (t, *J* = 15.9 Hz, 2 H), 7.30−7.33 (m, 2 H), 7.19−7.23 (m, 3 H), 6.40−6.43 (d, *J* = 6.9 Hz, 1 H), 4.82−4.85 (d, *J* = 6.6 Hz, 1 H), 4.27−4.35 (m, 1 H), 4.02−4.11 (m, 1 H), 3.79−3.88 (m, 1H), 3.29−3.37 (m, 1H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.2, 169.9, 167.4, 157.0, 152.2, 137.4, 135.3, 132.7, 130.0, 129.3, 128.9, 125.5, 118.9, 76.2, 67.6, 63.0, 53.5, 42.3, 17.4. HRMS-ESI (*m*/*z*): calcd for $C_{23}H_{19}ClN_4O_4S+H^+$: 483.0888; found: 483.0891, 0.5 ppm. IR: 3277.2, 2921.9, 1781.4, 1703.3, 1497.6, 1390.7, 1364.6, 1267.7, 1218.5, 1122.4, 1095.7, 1036.5, 757.7, 690.2 cm^{-1}. HPLC: ee of major diastereoisomer was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 40/60, 1.0 mL/min, 255 nm), retention time: t_{minor} = 18.47 min, t_{major} = 11.63 min, ee = 98%.

4e: The title compound was isolated as a mixture of diastereoisomers by column chromatography (CH_2Cl_2/EtOAc = 100/8) in 99% yield (52 mg). White solid, mp 181−183 °C; $[\alpha]^{20}_D$ = 2.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.89 (br s, 1 H), 7.88−7.91 (d, *J* = 8.4 Hz, 2 H), 7.38−7.49 (m, 4 H), 7.13−7.23 (m, 3 H), 6.41−6.43 (d, *J* = 6.6 Hz, 1 H), 4.81−4.84 (d, *J* = 6.6 Hz, 1 H), 4.27−4.32 (m, 1 H), 4.02−4.11 (m, 1 H), 3.82−3.88 (m, 1 H), 3.29−3.38 (m, 1 H), 1.42 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.1, 169.9, 167.4, 157.0, 152.2, 137.3, 133.2, 132.3, 130.3, 128.8, 125.5, 123.4, 118.9, 76.1, 67.5, 63.0, 52.5, 42.3, 17.5. HRMS-ESI (*m*/*z*): calcd for $C_{23}H_{19}BrN_4O_4S+H^+$: 527.0383; found: 527.0388, 0.9 ppm. IR: 3279.6, 2922.1, 1782.2, 1703.5, 1595.2, 1498.3, 1390.9, 1364.8, 1268.1, 1218.5, 1123.1, 1036.8, 758.0, 708.7, 690.3 cm^{-1}. HPLC: ee of major diastereoisomer was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 40/60, 1.0 mL/min, 240 nm), retention time: t_{minor} = 25.65 min, t_{major} = 17.26 min, ee = 99%.

4f: The title compound was isolated as a mixture of diastereoisomers by column chromatography (CH_2Cl_2/EtOAc = 100/8) in 85% yield (46 mg). White solid, mp 138−140 °C; $[\alpha]^{20}_D$ = 4.1 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.99 (br s, 0.11 H), 8.90 (br s, 0.88 H), 7.89−7.92 (d, *J* = 7.5 Hz, 2 H), 7.37−7.42 (t, *J* = 15.9 Hz, 2 H), 7.17−7.22 (m, 1 H), 7.11 (br s, 4 H), 6.39−6.45 (m, 1 H), 4.77−4.82 (m, 1 H), 4.23−4.28 (m, 1 H), 3.78−3.97 (m, 2 H), 3.21−3.29 (m, 1 H), 2.32 (s, 3 H), 1.38 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.5, 170.1, 167.7, 157.6, 152.2, 139.2, 137.5, 131.1, 129.6, 128.8, 128.4, 125.3, 118.9, 76.5, 67.8, 63.0, 52.9, 42.3, 21.2, 17.3. HRMS-ESI (*m*/*z*): calcd for $C_{24}H_{22}N_4O_4S+H^+$: 463.1435; found: 463.1436, 0.4 ppm. IR: 3277.2, 2923.1, 1783.1, 1705.0, 1595.3, 1499.2, 1391.1, 1363.7, 1267.3, 1218.8, 1122.3, 1037.1, 758.1, 737.7, 693.0 cm^{-1}. HPLC: ee of major diastereoisomer was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 40/60, 1.0 mL/

dx.doi.org/10.1021/jo301851a | J. Org. Chem. 2012, 77, 10228−10234

min, 238 nm), retention time: Retention time: t_{minor} = 33.72 min, t_{major} = 15.62, ee = 93%.

4g: The title compound was isolated as a mixture of diastereoisomers by column chromatography (CH_2Cl_2/EtOAc = 100/8) in 95% yield (44.5 mg). White solid, mp 103−104 °C; $[\alpha]^{20}_D$ = 3.2 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.92 (br s, 0.08 H), 8.82 (br s, 0.82 H), 7.89−7.91 (d, *J* = 7.8 Hz, 2 H), 7.37−7.42 (t, *J* = 15.9 Hz, 2 H), 7.12−7.22 (m, 3 H), 7.01−7.04 (m, 2 H), 6.38−6.43 (m, 1 H), 4.76−4.80 (m, 1 H), 4.23−4.31 (m, 1 H), 3.80−3.95 (m, 2 H), 3.17−3.26 (m, 1 H), 2.30 (s, 3 H), 1.37 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.4, 170.1, 167.6, 157.5, 152.2, 138.9, 137.4, 134.1, 129.9, 129.2, 128.9, 128.8, 125.4, 125.3, 118.9, 76.4, 67.8, 63.0, 53.1, 42.3, 21.3, 17.2. HRMS-ESI (*m*/*z*): calcd for $C_{24}H_{22}N_4O_4S$+H$^+$: 463.1435; found: 463.1438, 0.7 ppm. IR: 3283.9, 2922.1, 1782.5, 1705.3, 1595.8, 1498.4, 1391.0, 1364.1, 1267.4, 1220.0, 1038.0, 757.7, 705.7 cm^{-1}. HPLC: ee of major diastereoisomer was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 40/60, 1.0 mL/min, 255 nm), retention time: t_{minor} = 43.20 min, t_{major} = 13.85 min, ee = 90%.

4h: The title compound was isolated as a mixture of diastereoisomers by column chromatography (CH_2Cl_2/EtOAc = 100/8) in 95% yield (45 mg). White solid, mp 132−134 °C; $[\alpha]^{20}_D$ = 3.1 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.96 (br s, 0.10 H), 8.84 (br s, 0.85 H), 7.89−7.92 (d, *J* = 7.8 Hz, 2 H), 7.37−7.42 (t, *J* = 15.9 Hz, 2 H), 7.19−7.22 (t, *J* = 7.5 Hz, 1 H), 7.04−7.07 (d, *J* = 7.5 Hz, 1 H), 6.93−6.96 (d, *J* = 8.1 Hz, 2 H), 6.37−6.43 (m, 1 H), 4.73−4.78 (m, 1 H), 4.23−4.31 (m, 1 H), 3.77−3.97 (m, 2 H), 3.21−3.29 (m, 1 H), 2.21−2.22 (d, *J* = 5.1 Hz, 6 H), 1.37 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.4, 170.2, 167.6, 157.7, 152.2, 137.7, 137.5, 137.3, 131.4, 130.1, 129.7, 128.8, 125.7, 125.3, 118.9, 77.2, 67.8, 63.0, 52.9, 42.3, 19.6, 19.5, 17.3. HRMS-ESI (*m*/*z*): calcd for $C_{25}H_{24}N_4O_4S$+H$^+$: 477.1591; found: 477.1593, 0.4 ppm. IR: 3281.5, 2923.0, 1783.1, 1705.0, 1595.7, 1500.1, 1391.6, 1364.2, 1267.9, 1220.1, 1123.2, 1038.4, 757.8, 737.1, 695.2, 651.8 cm^{-1}. HPLC: ee of major diastereoisomer was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 40/60, 1.0 mL/min, 255 nm), retention time: t_{minor} = 33.39 min, t_{major} = 9.64 min, ee = 89%.

4i: The title compound was isolated as a mixture of diastereoisomers by column chromatography (CH_2Cl_2/EtOAc = 100/8) in 88% yield (42 mg). White solid, mp 123−124 °C; $[\alpha]^{20}_D$ = 6.0 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.06 (br s, 0.07 H), 9.00 (br s, 0.87 H), 7.89−7.92 (d, *J* = 7.8 Hz, 2 H), 7.37−7.42 (t, *J* = 15.6 Hz, 2 H), 7.15−7.22 (m, 3 H), 6.82−6.85 (d, *J* = 8.7 Hz, 2 H), 6.39−6.45 (m, 1 H), 4.78−4.83 (m, 1 H), 4.24−4.31 (m, 1 H), 3.95−4.03 (m, 1 H), 3.78−3.87 (m, 1 H), 3.78 (s, 3 H), 3.24−3.33 (m, 1 H), 1.42 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.4, 170.1, 167.7, 159.9, 157.7, 152.2, 137.5, 129.9, 128.8, 126.0, 125.3, 118.9, 114.2, 77.2, 67.8, 63.0, 55.2, 52.5, 42.3, 17.4. HRMS-ESI (*m*/*z*): calcd for $C_{24}H_{22}N_4O_5S$+H$^+$: 479.1384; found: 479.1386, 0.5 ppm. IR: 3054.3, 2926.5, 1786.8, 1706.1, 1595.9, 1497.8, 1390.4, 1364.6, 1265.1, 1122.0, 1035.2, 896.0, 739.8, 705.7 cm^{-1}. HPLC: ee of major diastereoisomer was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 40/60, 1.0 mL/min, 255 nm), retention time: t_{minor} = 33.14 min, t_{major} = 15.66 min, ee = 90%.

4j: The title compound was isolated as a mixture of diastereoisomers by column chromatography (CH_2Cl_2/EtOAc = 100/8) in 88% yield (42 mg). White solid, mp 109−111 °C; $[\alpha]^{20}_D$ = 3.2 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.00 (br s, 0.09 H), 8.90 (br s, 0.87 H), 7.89−7.91 (d, *J* = 7.8 Hz, 2 H), 7.37−7.42 (t, *J* = 15.9 Hz, 2 H), 7.12−7.22 (m, 3 H), 6.99−7.04 (m, 2 H), 6.38−6.44 (m, 1 H), 4.76−4.81 (m, 1 H), 4.22−4.30 (m, 1 H), 3.76−3.95 (m, 2 H), 3.17−3.25 (m, 1 H), 2.30 (s, 3 H), 1.37 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.3, 170.1, 167.6, 159.7, 157.4, 152.3, 137.4, 135.6, 130.1, 128.8, 125.4, 120.6, 118.9, 115.0, 113.7, 76.3, 67.7, 63.0, 53.3, 53.1, 42.3, 17.2.HRMS-ESI (*m*/*z*): calcd for $C_{24}H_{22}N_4O_5S$ +H$^+$: 479.1384; found: 479.1387, 0.6 ppm. IR: 3280.8, 2923.9, 1782.2, 1705.3, 1597.0, 1497.0, 1391.4, 1364.3, 1265.8, 1122.7, 1038.7, 757.5, 737.0, 703.5 cm^{-1}. HPLC: ee of major diastereoisomer was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 40/60, 1.0 mL/min, 240 nm), retention time: t_{minor} = 32.52 min, t_{major} = 15.00 min, ee = 81%.

4k: The title compound was isolated as a mixture of diastereoisomers by column chromatography (CH_2Cl_2/EtOAc = 100/8) in 75% yield (38 mg). White solid, mp 179−181 °C; $[\alpha]^{20}_D$ = 2.2 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.56 (br s, 1 H), 8.46 (br s, 1 H), 7.91−7.94 (d, *J* = 7.8 Hz, 2 H), 7.38−7.42 (t, *J* = 15.9 Hz, 2 H), 7.17−7.22 (t, *J* = 14.7 Hz, 1 H), 6.77−6.86 (m, 3 H), 6.34−6.38 (m, 1 H), 5.17−5.19 (d, *J* = 7.5 Hz, 1 H), 4.25−4.34 (m, 1 H), 3.68−3.97 (m, 2 H), 3.72 (s, 3 H), 3.68 (s, 3 H), 3.26−3.33 (m, 1 H), 1.55 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.1, 170.6, 167.7, 157.3, 153.1, 152.0, 151.4, 137.6, 128.8, 125.3, 123.5, 118.9, 115.6, 111.9, 77.20, 75.8, 67.0, 62.9, 55.8 55.4, 42.4, 16.6. HRMS-ESI (*m*/*z*): calcd for $C_{25}H_{24}N_4O_6S$+H$^+$: 509.1489; found: 509.1491, 0.3 ppm. IR: 2923.6, 1785.4, 1706.9, 1501.4, 1389.8, 1364.2, 1265.6, 1229.5, 1122.4, 1040.8, 740.4, 704.0 cm^{-1}. HPLC: ee of major diastereoisomer was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 40/60, 1.0 mL/min, 240 nm), retention time: t_{minor} = 40.62 min, t_{major} = 17.13 min, ee = 85%.

4l: The title compound was isolated as a mixture of diastereoisomers by column chromatography (CH_2Cl_2/EtOAc = 100/8) in 71% yield (31 mg). White solid, mp 125−126 °C; $[\alpha]^{20}_D$ = 2.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.67 (br s, 1 H), 7.87−7.90 (d, *J* = 7.8 Hz, 2 H), 7.37−7.42 (t, *J* = 15.9 Hz, 3 H), 7.17−7.22 (t, *J* = 14.7 Hz, 1 H), 6.25−6.35 (m, 2 H), 6.21−6.23 (m, 1 H), 5.00−5.04 (m, 1 H), 4.34−4.42 (m, 1 H), 4.13−4.22 (m, 1 H), 3.95−4.01 (m, 1 H), 3.52−3.61 (m, 1 H), 1.60 (br s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.8, 169.9, 167.2, 157.5, 152.5, 147.6, 143.1, 137.4, 128.9, 125.5, 119.0, 111.1, 110.6, 77.2, 75.5, 65.5, 63.2, 46.3, 42.6, 15.3. HRMS-ESI (*m*/*z*): calcd for $C_{21}H_{18}N_4O_5S$+H$^+$: 439.1071; found: 439.1072, 0.3 ppm. IR: 2922.7, 1781.8, 1707.2, 1500.5, 1392.0, 1365.8, 1264.5, 1222.4, 1122.9, 1036.6, 738.2, 701.6 cm^{-1}. HPLC: ee of major diastereoisomer was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 40/60, 1.0 mL/min, 255 nm), retention time: t_{minor} = 26.38 min, t_{major} = 21.55 min, ee = 73%.

4m: The title compound was isolated as a mixture of diastereoisomers by column chromatography (CH_2Cl_2/EtOAc = 100/8) in 99% yield (45 mg). White solid, mp 128−130 °C; $[\alpha]^{20}_D$ = −2.1 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.87 (br s, 0.07 H), 8.76 (br s, 0.94 H), 7.89−7.91 (d, *J* = 7.8 Hz, 2 H), 7.38−7.43 (t, *J* = 15.9 Hz, 2 H), 7.18−7.24 (m, 2 H), 7.02−7.03 (m, 1 H), 6.96−6.99 (m, 1 H), 6.43−6.49 (m, 1 H), 5.13−5.18 (m, 1 H), 4.30−4.38 (m, 1 H), 4.06−4.15 (m, 1 H), 3.85−3.94 (m, 1 H), 3.39−3.47 (m, 1 H), 1.49 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.7, 169.4, 167.2, 157.3, 152.4, 137.4, 135.0, 128.8, 127.8, 125.7, 125.5, 119.0, 76.2, 67.6, 63.1, 48.0, 42.4, 16.6. HRMS-ESI (*m*/*z*): calcd for $C_{21}H_{18}N_4O_4S_2$+H$^+$: 455.0842; found: 455.0847, 0.9 ppm. IR: 3281.4, 2921.0, 1780.6, 1703.5, 1594.9, 1498.1, 1391.2, 1363.8, 1299.6, 1259.7, 1219.9, 1122.0, 1036.7, 757.7, 694.9 cm^{-1}. HPLC: ee of major diastereoisomer was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 40/60, 1.0 mL/min, 255 nm), retention time: t_{minor} = 23.13 min, t_{major} = 29.29 min, ee = 91%.

4n: The title compound was isolated as a mixture of diastereoisomers by column chromatography (CH_2Cl_2/EtOAc = 100/8) in 95% yield (45 mg). White solid, mp 93−95 °C; $[\alpha]^{20}_D$ = 2.7 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.95 (br s, 1 H), 7.91−7.94 (d, *J* = 7.8 Hz, 1.83 H), 7.69−7.71 (d, *J* = 7.8 Hz, 0.18 H),7.28−7.43 (m, 5 H), 7.07−7.24 (m, 3 H), 6.40−6.46 (m, 0.9 H), 5.96−5.98 (m, 0.1 H), 4.80−4.85 (m, 0.9 H), 4.60−4.63 (m, 0.1 H), 4.21−4.31 (m, 1 H), 3.76−3.94 (m, 2 H), 3.16−3.24 (m, 1 H), 1.34−1.61 (m, 2 H), 0.93−0.99 (t, *J* = 15.3 Hz, 0.18 H), 0.75−0.86 (m, 1 H), 0.68−0.73 (t, *J* = 14.7 Hz, 2.74 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.8, 170.2, 167.7, 160.1, 152.2, 137.7, 134.4, 129.2, 128.9, 128.8, 128.7, 125.2, 118.8, 76.6, 67.8, 63.0, 53.3, 42.3, 32.8, 18.1, 13.6. HRMS-ESI (*m*/*z*): calcd for $C_{25}H_{24}N_4O_4S$+H$^+$: 477.1591; found: 477.1607, 3.3 ppm. IR: 3287.6, 2963.6, 2929.9, 1783.8, 1704.8, 1597.0, 1498.4, 1390.9, 1359.9, 1268.4, 1220.2, 1124.4, 1037.1, 909.4, 733.8, 703.2, 649.1 cm^{-1}. HPLC: ee of major diastereoisomer was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane =

40/60, 1.0 mL/min, 240 nm.) t_{minor} = 28.99 min, t_{major} = 14.64 min, ee = 93%.

4o: The title compound was isolated as a mixture of diastereoisomers by column chromatography (CH_2Cl_2/EtOAc = 100/8) in 82% yield (40 mg). White solid, mp 114−116 °C; $[\alpha]^{20}_D$ = 0.9 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.12 (br s, 1 H), 7.55−7.57 (d, *J* = 8.4 Hz, 2 H), 7.29−7.33 (m, 3 H), 7.22−7.24 (m, 4 H), 7.06−7.11 (t, *J* = 14.7 Hz, 1 H), 6.15−6.22 (m, 1 H), 4.92−4.97 (m, 1 H), 4.00−4.23 (m, 2 H), 3.55−3.80 (m, 2 H), 1.51 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.2, 168.5, 168.4, 165.9, 152.6, 137.4, 131.9, 130.6, 128.7, 128.5, 127.8, 125.1, 119.3, 77.4, 77.2, 66.3, 63.0, 50.0, 42.4, 36.7, 30.4. HRMS-ESI (*m*/*z*): calcd for $C_{26}H_{26}N_4O_4S$ +H^+: 491.1748; found: 491.1767, 4.0 ppm. IR: 3282.9, 2964.4, 2925.1, 1780.2, 1715.9, 1596.3, 1499.3, 1392.8, 1366.6, 1283.1, 1222.6, 1119.3, 1037.0, 911.5, 756.8, 733.5, 703.8 cm^{-1}. HPLC: ee of major diastereoisomer was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 40/60, 1.0 mL/min, 240 nm), retention time: t_{minor} = 14.80 min, t_{major} = 48.49 min, ee = 95%.

4p: The title compound was isolated as a mixture of diastereoisomers by column chromatography (CH_2Cl_2/EtOAc = 100/8) in 97% yield (46 mg). White solid, mp 115−117 °C; $[\alpha]^{20}_D$ = 3.9 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.51 (br s, 1 H), 7.89−7.92 (d, *J* = 7.8 Hz, 2 H), 7.31−7.42 (m, 5 H), 7.17−7.25 (m, 3 H), 6.45−6.47 (d, *J* = 6.6 Hz, 1 H), 4.70−4.72 (d, *J* = 6.6 Hz, 1 H), 3.86−3.89 (d, *J* = 8.4 Hz, 1 H), 3.50−3.53 (d, *J* = 8.7 Hz, 1 H), 1.45 (s, 3 H), 1.37 (s, 3H), 0.68 (s, 3 H),; ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.3, 169.8, 167.9, 157.1, 152.7, 137.5, 134.6, 129.3, 129.2, 128.8, 128.7, 125.3, 119.0, 76.2, 75.7, 68.3, 60.6, 53.2, 24.8, 22.9, 17.4. HRMS-ESI (*m*/*z*): calcd for $C_{25}H_{24}N_4O_4S$+H^+: 477.1591; found: 477.1593, 0.5 ppm. IR: 2925.2, 1777.4, 1706.7, 1596.1, 1498.5, 1364.0, 1305.5, 1248.6, 1179.7, 1099.1, 1032.6, 759.8, 736.0, 703.4 cm^{-1}. HPLC: ee of major diastereoisomer was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 40/60, 1.0 mL/min, 240 nm), retention time: t_{minor} = 15.29 min, t_{major} = 10.87 min, ee = 95%.

4q: The title compound was isolated as a mixture of diastereoisomers by column chromatography (CH_2Cl_2/EtOAc = 100/8) in 92% yield (36 mg). White solid, mp 162−164 °C; $[\alpha]^{20}_D$ = 0.5 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.73 (br s, 0.24 H), 8.62 (br s, 0.74 H), 7.89−7.91 (d, *J* = 7.8 Hz, 2 H), 7.38−7.44 (m, 2 H), 7.33−7.35 (m, 3 H), 7.21−7.23 (m, 3 H), 5.83−5.87 (m, 1 H), 4.29−4.32 (m, 1 H), 3.38 (s, 3 H), 1.29 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.5, 170.0, 168.9, 168.1, 157.8, 137.4, 134.7, 131.0, 129.2, 129.1, 128.9, 128.7, 128.0, 127.8, 126.8, 125.5, 119.5, 119.2, 120.0, 77.2, 65.0, 53.5, 53.2, 53.0, 52.5, 16.8. HRMS-ESI (*m*/*z*): calcd for $C_{21}H_{19}N_3O_3S$+H^+: 394.1220; found: 394.1227, 1.8 ppm. IR: 3436.1, 2924.1, 2853.7, 1702.5, 1640.0, 1498.4, 1364.4, 1299.7, 1228.4, 758.3, 697.5 cm^{-1}. HPLC: ee of major diastereoisomer was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 40/60, 1.0 mL/min, 240 nm), retention time: t_{minor} = 13.38 min, t_{major} = 9.64 min, ee = 71%.

General Procedure for Synthesis of 5a. **4a** (0.1 mmol, 44.8 mg) was dissolved in CH_2Cl_2 (3 mL), and the solution was cooled in an ice bath. Then H_2O_2 (30%, 1.0 mL) and formic acid (80%, 1.0 mL) were added, respectively, to the solution dropwise. The reaction was then warmed to room temperature and stirred for 5 min. After the reaction was completed (monitored by TLC), CH_2Cl_2 (50 mL) was added, and the organic phase was washed with water (×3). The organic layer was dried over Na_2SO_4 and then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc, 100:8) to afford the product **5a**.

5a: The title compound was isolated as a mixture of diastereoisomers by column chromatography (CH_2Cl_2/EtOAc = 100/8) in 98% yield (42 mg). White solid, mp 133−135 °C; $[\alpha]^{20}_D$ = 2.2 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87−7.90 (m, 2 H), 7.27−7.42 (m, 7 H), 7.09−7.21 (m, 2 H), 6.13−6.16 (d, *J* = 6.9 Hz, 1 H), 4.75−4.77 (d, *J* = 6.9 Hz, 1 H), 4.22−4.30 (m, 1 H), 3.77−3.95 (m, 2 H), 3.16−3.25 (m, 1H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 168.7, 168.2, 156.7, 152.2, 137.4, 134.6, 129.2, 129.0, 128.8, 128.6, 125.3, 118.9, 68.4, 62.9, 61.3, 51.2, 42.3, 17.3. HRMS-ESI (*m*/*z*): calcd for $C_{23}H_{20}N_4O_5$+H^+: 433.1506; found: 433.1508, 0.3 ppm. IR: 3309.1, 2920.5, 1779.1, 1682.9, 1594.0, 1495.7, 1392.7, 1361.8, 1300.1, 1231.6, 1206.3, 1127.8, 1106.9, 1036.5, 731.5, 701.1 cm^{-1}. HPLC: ee of major diastereoisomer was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 50/50, 1.0 mL/min, 240 nm), retention time: t_{minor} = 28.73 min, t_{major} = 15.63 min, ee = 85%.

General Procedure for the Synthesis of 6a. To a mixture of **4a** (0.1 mmol, 44.8 mg) and anhydrous K_2CO_3 (1.10 equiv, 60 mg) in 2.5 mL of acetone was added MeI (2.0 equiv, 12.0 μL) at 0 °C. Then the reaction was left overnight. After the reaction was completed (monitored by TLC), the resulting mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc, 100:8) to afford the product **6a**.

6a: The title compound was isolated as a mixture of diastereoisomers by column chromatography (CH_2Cl_2/EtOAc = 100/8) in 91% yield (42 mg). White solid, mp 61−63 °C; $[\alpha]^{20}_D$ = 1.1 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70−7.88 (d, *J* = 6.0 Hz, 1.47 H), 7.67−7.70 (d, *J* = 7.8 Hz, 0.65 H), 7.11−7.29 (m, 8 H), 6.53−6.56 (d, *J* = 7.2 Hz, 0.68 H), 6.27−6.29 (d, *J* = 8.4 Hz, 0.30 H), 4.82−4.85 (d, *J* = 7.5 Hz, 0.68 H), 4.53−4.56 (d, *J* = 8.4 Hz, 0.36 H), 4.21−4.30 (m, 1 H), 3.82−3.98 (m, 2 H), 3.23−3.37 (m, 1 H), 2.65 (s, 3 H), 2.25 (s, 0.96 H), 1.48 (s, 2.32 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 170.2, 169.5, 169.2, 168.6, 166.8, 157.1, 155.9, 153.0, 152.5, 137.5, 134.5, 132.2, 130.1, 129.1, 128.8, 128.7, 128.6, 128.5, 127.6, 125.3, 125.2, 118.9, 118.7, 79.0, 78.5, 76.6, 75.1, 62.5, 62.4, 57.8, 55.8, 42.4, 42.3, 17.5, 14.3, 14.2, 13.9. HRMS-ESI (*m*/*z*): calcd for $C_{24}H_{22}N_4O_4S$+H^+: 463.1453; found: 463.1436, 0.2 ppm. IR: 3418.2, 2957.0, 2925.5, 1826.7, 1752.8, 1715.7, 1595.4, 1553.0, 1498.1, 1439.4, 1409.2, 1365.7, 1314.2, 1265.5, 1121.1, 1051.2, 758.9, 736.7, 699.2 cm^{-1}. HPLC: ee of major diastereoisomer was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 40/60, 1.0 mL/min, 240 nm), retention time: t_{minor} = 13.85 min, t_{major} = 9.57 min, ee = 88%.

General Procedure for Synthesis of 7a. **4a** (0.1 mmol, 44.8 mg) was dissolved in dry THF (2.0 mL) and then cooled in an ice bath. A solution of methylmagnesium iodine (2 M in diethyl ether, 0.25 mmol) in ethanol (1.0 mL) was added at dropwise at 0 °C. The reaction was then warmed to room temperature and stirred for 2 h. After the reaction was complete (monitored by TLC), the reaction was quenched by aqueous phosphate buffer solution. The mixture was concentrated under reduced pressure, and the residue was taken up in 2 M HCl and CH_2Cl_2. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (×3). The organic phases were combined, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc, 100:2) to afford the product **7a**.

7a: The title compound was isolated as a mixture of diastereoisomers by column chromatography (CH_2Cl_2/EtOAc = 100/2) in 93% yield (38 mg). Yellow oily solid; $[\alpha]^{20}_D$ = 1.5 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.65 (br s, 0.16 H), 8.56 (br s, 0.74 H), 7.89−7.91 (d, *J* = 7.8 Hz, 1.91 H), 7.79−7.82 (d, *J* = 7.8 Hz, 0.19 H),7.38−7.44 (t, *J* = 15.9 Hz, 2 H), 7.29−6.34 (m, 3.31 H), 7.19−7.25 (m, 2.72 H), 5.80−5.84 (m, 1 H), 4.29−4.32 (d, *J* = 6.6 Hz, 1 H), 3.81−3.97 (m, 2 H), 1.29 (s, 3 H), 0.72−0.77 (t, *J* = 14.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.5, 170.0, 167.6, 157.8, 137.4, 134.8, 129.1, 128.9, 128.2, 125.5, 119.0, 118.9, 64.9, 61.8, 53.6, 16.9, 13.4. HRMS-ESI (*m*/*z*): calcd for $C_{22}H_{21}N_3O_3S$+H^+: 408.1376; found: 408.1384, 1.8 ppm. IR: 3271.5, 2925.6, 1740.9, 1707.8, 1596.0, 1498.1, 1462.0, 1363.1, 1298.5, 1224.6, 1021.7, 758.0, 736.2, 699.3, 657.6 cm^{-1}. HPLC: ee of major diastereoisomer was determined by HPLC analysis (Chiralcel AD-H, *i*-PrOH/hexane = 30/70, 1.0 mL/min, 230 nm), retention time: t_{minor} = 16.14 min, t_{major} = 10.13 min, ee = 88%.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: (R.W.) wangrui@lzu.edu.cn, bcrwang@polyu.edu.hk; (X.J.) xianxingjiang@163.com.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful for the grants from the National Natural Science Foundation of China (nos. 90813012, 20932003, and 21202072) and the Key National S&T Program "Major New Drug Development" of the Ministry of Science and Technology of China (2012ZX09504-001-003).

REFERENCES

(1) (a) Akbas, E.; Berber, I. *Eur. J. Med. Chem.* **2005**, *40*, 401. (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (c) Rostom, S. A. F.; Shalaby, M. A.; El-Demellawy, M. A. *Eur. J. Med. Chem.* **2003**, *38*, 959. (d) Cottineau, B.; Toto, P.; Marot, C.; Pipaud, A.; Chenault, J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2105. (e) Lee, K. Y. J.; Kim, M.; Kim, J. N. *Tetrahedron Lett.* **2003**, *44*, 6737. (f) Rostom, S. A. F.; Shalaby, M. A.; El-Demellawy, M. A. *Eur. J. Med. Chem.* **2003**, *38*, 959. (g) Yamamoto, H.; Asai, H. *Chem. Pharm. Bull.* **1986**, *34*, 3844.

(2) For selected examples of the construction of pyrazolone derevatives, see: (a) Field, J. B.; Dolendo, E. C.; Mireles, A.; Ershoff, B. H. *Cancer Res.* **1966**, *26*, 1371. (b) Foth, B. *Cancer Res.* **1972**, *32*, 804. (c) Ghosh, C. K.; Mukhopadhyay, K. K. *Synthesis* **1978**, 779. (d) Chantegrel, B.; Gelin, S. *Synthesis* **1985**, 548. (e) Mariappan, G.; Saha, B. P.; Bhuyan, N. R.; Bharti, P. R.; Kumar, D. J. *Adv. Pharm. Technol. Res.* **2010**, *1*, 260. (f) Ma, R.; Zhu, J.; Liu, J.; Chen, L.; Shen, X.; Jiang, H.; Li, J. *Molecules* **2010**, *15*, 3593. (g) Liao, Y.-H.; Chen, W.-B.; Wu, Z.-J.; Du, X.-L.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Adv. Synth. Catal.* **2010**, *352*, 827. (h) Gogoi, S.; Zhao, C.-G. *Tetrahedron Lett.* **2009**, *50*, 2252. (i) Gogoi, S.; Zhao, C.-G.; Ding, D. *Org. Lett.* **2009**, *11*, 2249. (j) Alba, A.-N. R.; Zea, A.; Valero, G.; Calbet, T.; Font-Bardía, M.; Mazzanti, A.; Moyano, A.; Rios, R. *Eur. J. Org. Chem.* **2011**, *7*, 1318. (k) Zea, A.; Alba, A.-N. R.; Mazzanti, A.; Moyano, A.; Rios, R. *Org. Biomol. Chem.* **2011**, *9*, 6519.

(3) (a) Yang, Z.; Wang, Z.; Bai, S.; Liu, X.; Lin, L.; Feng, X.-M. *Org. Lett.* **2011**, *13*, 596. (b) Wang, Z.; Yang, Z.-G.; Chen, D.-H.; Liu, X.-H.; Lin, L.-L.; Feng, X.-M. *Angew. Chem., Int. Ed.* **2011**, *50*, 4928.

(4) For recent reviews, see: (a) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638. (b) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037. (c) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (d) Erkkilä, A.; Majander, I.; Pihko, P. M. *Chem. Rev.* **2007**, *107*, 5416. (e) Guillena, G.; Ramon, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2007**, *18*, 693. (f) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (g) Tietze, L. F.; Brasche, G.; Gerike, K. *Domino Reactions in Organic Chemistry*; Wiley-VCH: Weinheim, 2006. (h) Pellissier, H. *Tetrahedron* **2006**, *62*, 1619. (i) Pellissier, H. *Tetrahedron* **2006**, *62*, 2143.

(5) (a) Willis, M. C.; Cutting, G. A.; Piccio, V. J.-D.; Durbin, M. J.; John, M. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 1543. (b) Li, L.; Klauber, E. G.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 12248. (c) Yoshino, T.; Morimoto, H.; Lu, G.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 17082. (d) Vecchione, M. K.; Li, L.; Seidel, D. *Chem. Commun.* **2010**, *46*, 4604. (e) Chen, X.-H.; Zhu, Y.; Qiao, Z.; Xie, M.-S.; Lin, L.-L.; Liu, X.-H.; Feng, X.-M. *Chem.—Eur. J.* **2010**, *16*, 10124. (f) Cutting, G. A.; Stainforth, N. E.; John, M. P.; Kociok-Kchn, G.; Willis, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 10632. (g) Li, L.; Ganesh, M.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 11648. (h) Lu, G.; Yoshino, T.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 4382. (i) Shi, Z.-G.; Yu, P.-Y.; Chua, P. J.; Zhong, G. F. *Adv. Synth. Catal.* **2009**, *351*, 2797. (j) Chen, X.-H.; Dong, S.-X.; Qiao, Z.; Zhu, Y.; Xie, M.-S.; Lin, L.-L.; Liu, X.-H.; Feng, X.-M. *Chem.—Eur. J.* **2011**, *17*, 2583. (k) Jiang, X.-X.; Cao, Y.-M.; Wang, Y.-Q.; Liu, L.-P.; Shen, F.-F.; Wang, R. *J. Am. Chem. Soc.* **2010**, *132*, 15328. (l) Chen, W.-B.; Wu, Z.-J.; Hu, J.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2011**, *13*, 2472.

(6) For a recent review on the Michael addition, see: Vicario, J. L.; Badía, D.; Carrillo, L.; Reyes, E. In *Organocatalytic Enantioselective Conjugate Addition Reactions*; Spivey, J. J., Ed.; The Royal Society of Chemistry: Cambridge, 2010.

(7) For recent examples Michael reactions of α-isothiocyanato imides, see: (a) Cao, Y.-M.; Jiang, X.-X.; Liu, L.-P.; Shen, F.-F.; Zhang, F.-T.; Wang, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 9124. (b) Tan, B.; Zeng, X.-F.; Leong, W. W. Y.; Shi, Z.-G.; Barbas, C. F., III; Zhong, G.-F. *Chem.—Eur. J.* **2012**, *18*, 63.

(8) For selected examples of bifunctional amine-thiourea catalyst reviews, see: (a) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (b) Connon, S. J. *Chem.—Eur. J.* **2006**, *12*, 5418. For selected recent examples, see: (c) Tan, K. L.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2007**, *46*, 1315. (d) Pan, S. C.; Zhou, J.; List, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 612. (e) Yamaoka, Y.; Miyabe, H.; Takemoto, Y. *J. Am. Chem. Soc.* **2007**, *129*, 6686. (f) Zu, L. S.; Wang, J.; Li, H.; Xie, H. X.; Jiang, W.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 1036. (g) Tsogoeva, S. B.; Wei, S. *Chem. Commun.* **2006**, 1451. (h) Yalalov, D. A; Tsogoeva, S. B.; Schmatz, S. *Adv. Synth. Catal.* **2006**, *348*, 826. (i) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6576. (j) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367.

(9) For examples of rosin-derived thiourea catalysis, see: (a) Jiang, X. X.; Zhang, G.; Fu, D.; Cao, Y. M.; Shen, F. F.; Wang, R. *Org. Lett.* **2010**, *12*, 1544. (b) Jiang, X. X.; Zhang, Y. F.; Chan, A. S. C.; Wang, R. *Org. Lett.* **2009**, *11*, 153.

(10) For selected recent examples of spiro skeletons, see: (a) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2011**, *133*, 4672. (b) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *Nat. Chem.* **2011**, *3*, 473. (c) Antonchick, A. P.; Gerding-Reimers, C.; Catarinella, M.; Schürmann, M.; Preut, H.; Ziegler, S.; Rauh, D.; Waldmann, H. *Nat. Chem.* **2010**, *2*, 735. (d) Bencivenni, G.; Wu, L.-Y.; Mazzanti, A.; Giannichi, B.; Pesciaioli, F.; Song, M.-P.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7200. (e) Chen, X.-H.; Wei, Q.; Luo, S.-W.; Xiao, H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 13819. (f) Trost, B. M.; Cramer, N.; M. Silverman, S. *J. Am. Chem. Soc.* **2007**, *129*, 12396. (g) Kobbelgaard, S.; Bella, M.; Jøgensen, K. A. *J. Org. Chem.* **2006**, *71*, 4980. (h) Bella, M.; Kobbelgaard, S.; Jøgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 3670. (i) Sebahar, P. R.; Williams, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 5666.

(11) For examples, see: (a) Yan, K.; Zhang, C.; Feng, J.; Hou, L.; Yan, L.; Zhou, Z.; Liu, Z.; Liu, C.; Fan, Y.; Zheng, B.; Xu, Z. *Eur. J. Pharmacol.* **2011**, *661*, 1. (b) Patil, J. B.; Kim, J.; Jayaprakasha, G. K. *Eur. J. Pharmacol.* **2010**, *645*, 70. (c) Baviskar, A. T.; Madaan, C.; Preet, R.; Mohapatra, P.; Jain, V.; Agarwal, A.; Guchhait, S. K.; Kundu, C. N.; Banerjee, U. C.; Bharatam, P. V. *J. Med. Chem.* **2011**, *54*, 5013.