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Enantioselective [3 + 2] annulation of 4-isothiocyanato pyrazolones and alkynyl ketones under organocatalysis†

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An asymmetric [3 + 2] annulation reaction of 4-isothiocyanato pyrazolones with alkynyl ketones in the presence of an organic catalyst derived from a cinchona alkaloid under mild conditions is realized. This protocol provides unprecedented expeditious access to a wide range of optically active spiro[pyrroline–pyrazolones] with various electronic properties in high yields with good to excellent enantioselectivities.

Introduction

Pyrazolones and their derivatives, featuring two adjacent nitrogen atoms within a pentacyclic heterocycle, have drawn considerable attention from organic and medicinal chemists owing to their important synthetic and pharmaceutical potential.[1] In particular, spiropyrazolones have recently risen to prominence because of their significant medicinal relevance.[2] As exemplified by the entities in Fig. 1, spiropyrazolone derivatives exhibit diverse medicinal potential ranging from antitumor, antibacterial to analgesic activities and can serve as a type-4-phosphodiesterase inhibitor.[2a,3] Thus, the development of methods that provide efficient access to these core structures has triggered vast investigation. Over the last few years, some elegant studies have been published on the asymmetric synthesis of spiropyrazolones bearing an all-carbon ring.[4] However, there exist only a handful of reports on the efficient synthesis of optically active spiropyrazolones with a five-membered N-heterocyclic ring,[5] especially with the nitrogen atom at the C4 position of the pyrazolone unit.[6] For example, in 1994, Ronald Grigg developed an elegant [3 + 2] annulation of maleimide with an azomethine ylide for the synthesis of spiropyrazolones (Scheme 1a).[6a] Later, Javier Agejas reported a two-step reaction to construct spiro[pyrrolidine–pyrazolones] (Scheme 1b).[6e] To date, asymmetric approaches to access these special chiral spiro[pyrroline–pyrazolones] have been less explored, especially *via* a catalytic cascade approach.[7] Hence, it is valuable to develop a novel strategy to construct this core structure efficiently.

As part of our research into the asymmetric synthesis and modification of pharmaceutically relevant heterocycles,[2b,8] very recently, we developed a series of 4-isothiocyanato pyrazolones and successfully used them as ambiphilic synthons to react with imines[9] and activated alkenes[10] for the asymmetric synthesis of a range of spirocyclic pyrazolone derivatives in high yields with excellent diastereoselectivity and enantioselectivity. Our results indicated that the readily achieved novel 4-isothiocyanato pyrazolones were powerful synthons to construct

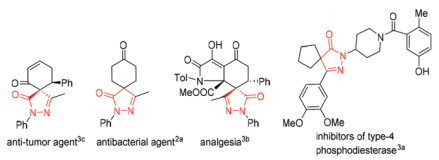
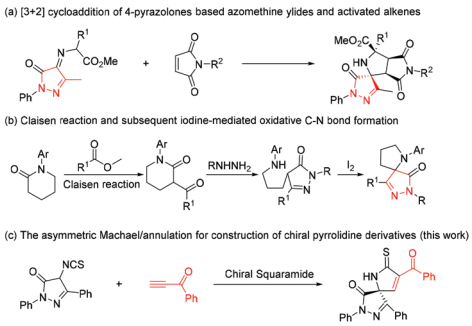


Fig. 1 Biologically active spiropyrazolone derivatives.



Scheme 1 Previous synthesis of spiro[pyrrolidine–pyrazolones] and our asymmetric [3 + 2] annulation.

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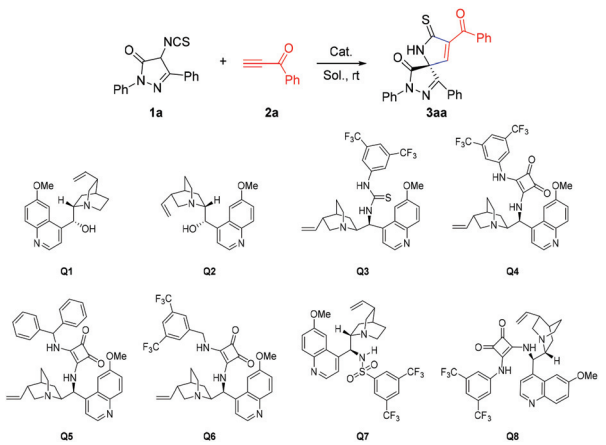
4-nitrogen attached chiral spirocyclic pyrazolones. Aiming to develop a new strategy for the construction of spiro[pyrroline–pyrazolones] with high levels of enantiocontrol, herein, we present the organocatalytic asymmetric Michael/annulation of 4-isothiocyanato pyrazolones and alkynyl ketones with bifunctional chiral squaramide as a catalyst, providing spiro[pyrroline–pyrazolone] core structures in high yields with excellent enantioselectivities.

Results and discussion

Initially, the reaction of 4-isothiocyanato pyrazolone **1a** and alkynyl ketone **2a** was selected as the model reaction with natural quinine (**Q1**) as the catalyst in dichloromethane (DCM) at room temperature (Table 1). The cascade annulation reaction proceeded rapidly to give the product **3aa** in 87% yield with 37% ee (entry 1), and similar enantioselectivity was obtained when quinidine (**Q2**) was used (entry 2). Encouraged by these results, further trials of quinine-derived hydrogen-bonding catalysts (**Q3–6**) were conducted (entries 3–6). While all could smoothly catalyze the model reaction, delivering the spiroannulation product in a high yield, the quinine squaramide catalyst **Q4** exhibited superior stereocontrol, affording the dispirocyclic product with 90% ee (entry 4). When *N*-tosylsulfonamide **Q7** was used, very low enantioselectivity was obtained (entry 7). With **Q4** as the most optimal catalyst, the effect of solvents was investigated (entries 8–14). The results showed that the enantioselectivity of this annulation varied less in similar solvents chloroform and 1,2-dichloroethane (entries 8 and 9) but decreased greatly in other solvents, especially acetonitrile and diethyl ether (entries 11 and 12). With the initially used DCM as the solvent of choice, the decrease of the amount of alkynyl ketone from 1.2 to 1.1 equivalent improved the isolated yield to 91% and ee to 93% (entry 15). With quinidine squaramide **Q8**, the enantiomer of **3aa** could also be obtained conveniently in 83% yield with 92% ee. Reducing the catalyst loading or cooling the reaction resulted in reduced enantioselectivities (entries 17–19).

Table 1 Optimization of the reaction conditions[a]



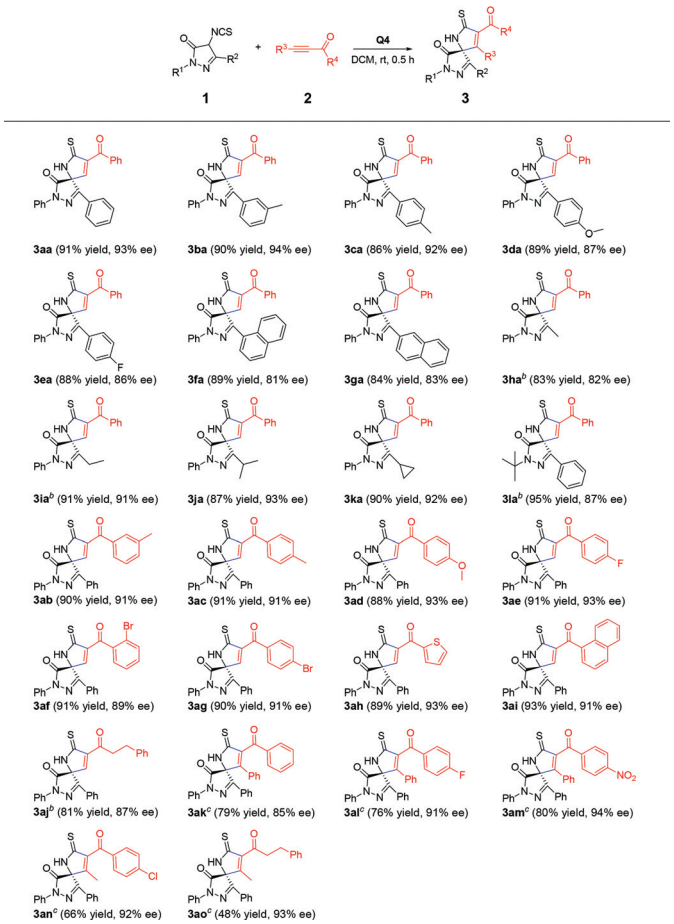
Entry	Cat.	Solvent	*t* [h]	Yield[b] [%]	ee [%]
1	**Q1**	DCM	0.5	87	37
2	**Q2**	DCM	0.5	88	−21
3	**Q3**	DCM	0.5	89	86
4	**Q4**	DCM	0.5	88	90
5	**Q5**	DCM	1	85	80
6	**Q6**	DCM	1	93	71
7	**Q7**	DCM	1.5	86	13
8	**Q4**	DCE	1	89	82
9	**Q4**	$CHCl_3$	1	90	89
10	**Q4**	Toluene	1	91	55
11	**Q4**	CH_3CN	1	86	33
12	**Q4**	Et_2O	1	89	15
13	**Q4**	THF	1.5	86	27
14	**Q4**	1,4-Dioxane	1.5	90	45
15[f]	**Q4**	DCM	0.5	91	93
16[f]	**Q8**	DCM	0.5	83	−92
17[c,f]	**Q4**	DCM	0.5	87	89
18[d,f]	**Q4**	DCM	0.5	90	92
19[e,f]	**Q4**	DCM	3	86	82

[a] Unless otherwise noted, the reaction was performed on a 0.1 mmol scale with **1a** (1.0 equiv.), **2a** (1.2 equiv.), and a catalyst (10 mol%) in a solvent (1 mL). [b] Isolated yield. [c] Catalyst (5 mol%). [d] The reaction was carried out at 0 °C. [e] The reaction was carried out at −20 °C. [f] The amount of **2a** was 1.1 equiv.

With the optimal reaction conditions being identified (Table 1, entry 15), the generality of the annulation reaction was investigated. First, the scope of 4-isothiocyanato pyrazolones **1** that participated in the asymmetric annulation is shown in Table 2. Generally, a broad spectrum of 4-isothiocyanato pyrazolones reacted well with phenyl alkynyl ketone **2a**, delivering a diverse array of [3 + 2] derivatives in high yields with excellent stereocontrol. Various electron-donating and electron-withdrawing substituents such as methyl, methoxyl and fluorine groups on the phenyl group at the C3 position of pyrazolones afforded the [3 + 2] annulation products **3ba–3ea** in high yields (86–90%) with excellent enantioselectivities (86–94% ee). Additionally, this procedure was also applicable to 4-isothiocyanato pyrazolones with 1-naphthyl (**3fa**, 89% yield, 81% ee) and 2-naphthyl (**3ga**, 84% yield, 83% ee) at the C3 position of the pyrazolones. Substrates bearing methyl, ethyl, isopropyl and cyclopropyl at the C3 position of pyrazolones were also investigated under the standard conditions. It turned out that all alkyl substituents had no influence on this reaction affording products **3ia–3ka** in good yields (87–91%) with high enantioselectivities (91–93% ee) except for **3ha**, probably due to the low steric hindrance of the methyl group. Besides, the *N*-*tert*-butyl group at the N1 position of the pyrazolone was also well accommodated to provide the desired product **3la** in 95% yield with 87% ee.

Subsequently, the scope of alkynyl ketones **2** was investigated (Table 2). Alkynyl ketones **2** bearing various electron-donating groups at the *para*- and *meta*-positions on the aromatic ring such as methoxy and methyl were amenable for the [3 + 2] annulation reactions, providing the corresponding desired products (**3ab–3ad**) in high yields (88–91%) with high enantioselectivities (91–93% ee). Besides, alkynyl ketones **2** bearing electron-withdrawing halogens such as F and Br proceeded smoothly, affording products (**3ae–3ag**) in high yields

Table 2 Generality of the asymmetric [3 + 2] annulation reaction[a]



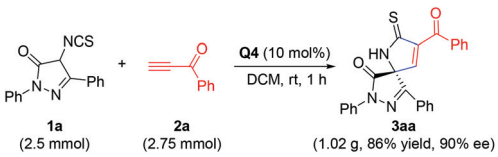
[a] The reactions were conducted with **1** (0.2 mmol) and **Q4** (10 mol%) in DCM (2.0 mL) at rt for 5 minutes. Then alkynyl ketones **2** (0.22 mmol) were added into the reaction mixture. The yields of the isolated products are given. The ee was determined by chiral HPLC. [b] The reaction time was 1 h. [c] The reaction time was 72 h.

(90–91%) with high enantioselectivities (89–93% ee). It turned out that the electronic properties of alkynyl ketones had no pronounced influence on the yields and stereoselectivities. In addition, asymmetric [3 + 2] annulation of alkynyl ketones with a heteroaryl substituent or a naphthyl substituent proceeded smoothly, delivering the corresponding chiral products in 89% yield with 93% ee and 93% yield with 91% ee (**3ah** and **3ai**), respectively. The aliphatic alkynyl ketone was also accommodated, providing **4aj** in 81% yield with 87% ee. Changing terminal alkynones to internal α,β-ynones had no obvious effect on the enantioselectivity of the annulation product (**3ak–3ao**). Due to the conjugate and steric effects of aryl with alkynones, the reactivity of α,β-ynones was suppressed (**3ak–3ao**) and the reaction time was prolonged to 72 h, but the enantioselectivities remained high (85–94% ee).

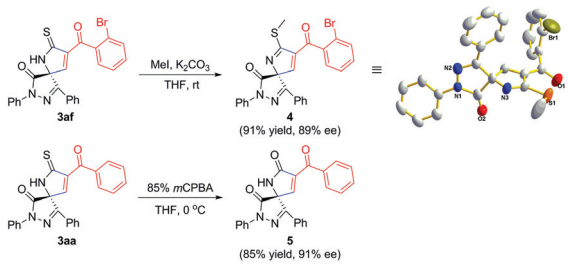
To confirm the practicability of the [3 + 2] annulation process, the gram-scale synthesis of compound **3aa** was facilely achieved. **1a** (2.5 mmol) and **2a** (2.75 mmol) were treated in the presence of 10 mol% of **Q4** in DCM; the reaction also worked well without any loss in the efficiency and stereochemical outcome of the reaction (Scheme 2). The desired product **3aa** could be obtained in 86% yield with excellent enantioselectivity (90% ee).

Next, the versatility of spiro[pyrroline–pyrazolones] **3** was analyzed. As shown in Scheme 3, **3af** could be further transformed into spiro[2*H*-pyrrole-pyrazolone] derivative **4** in 91% yield with 89% ee through direct methylation. The absolute configuration of the product was unambiguously determined to be *R* by X-ray crystallographic analysis of a single crystal of **4**. To obtain the pyrrolin-2-one derivatives, **3aa** was directly subjected to an oxidation reaction with *m*CPBA in THF, and pyrrolin-2-thione could be converted into pyrrolin-2-one, giving compound **5** in 85% yield with 91% ee.

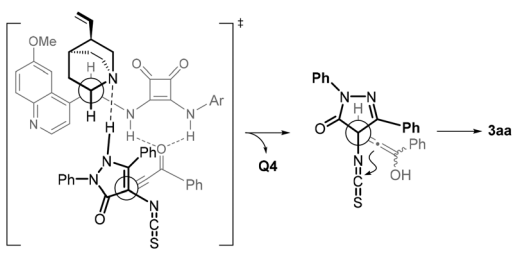
Based on the result and previously reported dual activation mode,[10,11] a plausible working model was proposed, as shown in Scheme 4. 4-Isothiocyanato pyrazolone **1a** was deprotonated to form the enamine tautomer of 4-isothiocyanato pyrazolone,[12] and alkynyl ketone **2a** was activated *via* double hydrogen bonding. Then, the Michael addition/cyclization of **1a** and alkynyl ketone **2a** gave the product **3aa**.



Scheme 2 Gram-scale synthesis of **3aa**.



Scheme 3 Diversification of **3af** and **3aa**.



Scheme 4 Proposed transition state working model for the [3 + 2] annulation.

Conclusions

In summary, we have developed an asymmetric [3 + 2] annulation reaction between 4-isothiocyanato pyrazolones and alkynyl ketones for the first time in the presence of an organocatalyst. This reaction provided an efficient protocol for the enantioselective synthesis of spiro[pyrroline–pyrazolones] in high yields with excellent enantioselectivities and allows the use of a wide range of 4-isothiocyanato pyrazolones while tolerating a considerable degree of variations of alkynyl ketones under mild conditions.

Experimental

General information

Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. Column chromatography was performed on silica gel (200–300 mesh). Enantiomeric excesses (ee) were determined by HPLC using the corresponding commercial chiral columns as stated at 30 °C with a UV detector at 254 nm. Optical rotations were reported as follows: $[\alpha]_D^T$ (c g per 100 mL, solvent). All ^{1}H NMR and ^{19}F NMR spectra were recorded on Bruker Avance II 400 MHz and Bruker Avance III 471 MHz spectrometers, respectively, ^{13}C NMR spectra were recorded on a Bruker Avance II 101 MHz spectrometer or a Bruker Avance III 126 MHz spectrometer with chemical shifts reported in ppm (in $CDCl_3$, with TMS as an internal standard). The data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad singlet, dd = double doublet, coupling constants in Hz, integration). HRMS (ESI) was performed with an HRMS/MS instrument (LTQ Orbitrap XL™).

General procedure for the synthesis of compounds 3

A tube equipped with a magnetic stir bar was charged with 4-isothiocyanato pyrazolone **1** (0.2 mmol), **Q4** (0.02 mmol), and DCM (2 mL). After stirring for 5 min, alkynyl ketone **2** (0.22 mmol) was added in one portion. The reaction was monitored by TLC. After 0.5–1 h, the mixture was purified by column chromatography on silica gel (unless otherwise noted, petroleum ether/EtOAc = 8 : 1 was used as the eluent) directly to give the product **3**.

Compound 3aa. Yellow solid (77.1 mg, 91% yield). Mp 111.5–114.5 °C; $[\alpha]_D^{20}$ = +35.00 (c 0.30, CH_2Cl_2), ^{1}H NMR (400 MHz, chloroform-d) δ 8.06 (s, 1H), 8.02 (s, 1H), 7.99 (dd, J = 4.4, 1.4 Hz, 2H), 7.97 (s, 1H), 7.75 (dd, J = 8.0, 1.6 Hz 2H), 7.63 (t, J = 7.4 Hz, 1H), 7.51–7.46 (m, 7H), 7.30 (t, J = 7.5 Hz, 1H), 7.17 (s, 1H); ^{13}C NMR (101 MHz, chloroform-d) δ 196.8, 189.7, 164.9, 151.6, 146.6, 141.3, 137.3, 135.8, 134.4, 131.9, 130.1, 129.4, 129.2, 128.9, 128.8, 126.4, 126.1, 118.9, 78.9; HRMS (ESI) m/z calcd for $C_{25}H_{17}N_3O_2S$ ($[M + H]^+$) 424.1114, found 424.1114; the enantiomeric excess was determined to be 93% (determined by HPLC using a chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 15.2 min, t_{minor} = 12.7 min).

Compound *ent*-3aa. Yellow solid (35.0 mg, 83% yield). Mp 110.9–113.5 °C; $[\alpha]_D^8$ = −12.50 (c 0.12, CH_2Cl_2), ^{1}H NMR (400 MHz, chloroform-d) δ 8.37 (s, 1H), 8.00–7.90 (m, 4H), 7.76–7.67 (m, 2H), 7.63–7.54 (m, 1H), 7.45 (dtd, J = 8.1, 5.4, 3.3 Hz, 7H), 7.28 (d, J = 7.5 Hz, 1H), 7.09 (s, 1H); ^{13}C NMR (101 MHz, chloroform-d) δ 196.9, 151.6, 146.7, 141.2, 137.3, 135.8, 134.4, 132.0, 130.1, 129.4, 129.2, 129.0, 128.8, 126.4, 126.1, 119.0, 78.8; the enantiomeric excess was determined to be −92% (determined by HPLC using a chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 18.4 min, t_{minor} = 14.0 min).

Compound 3ba. Yellow solid (78.7 mg, 90% yield). Mp 111.5–114.5 °C, $[\alpha]_D^{23}$ = −4.8 (c 0.25, CH_2Cl_2); ^{1}H NMR (400 MHz, chloroform-d) δ 8.44 (s, 1H), 7.93 (t, J = 7.5 Hz, 4H), 7.61–7.52 (m, 2H), 7.47–7.38 (m, 5H), 7.32–7.25 (m, 2H), 7.24 (s, 1H), 7.02 (s, 1H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, chloroform-d) δ 196.8, 189.6, 164.9, 151.7, 146.7, 141.2, 139.2, 137.3, 135.8, 134.4, 132.8, 130.1, 129.4, 129.2, 128.9, 128.8, 126.6, 126.4, 123.3, 118.9, 78.9, 21.5. HRMS (ESI) m/z calcd for $C_{26}H_{19}N_3O_2S$ ($[M + H]^+$) 438.1271, found 438.1286; the enantiomeric excess was determined to be 94% (determined by HPLC using a chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 14.8 min, t_{minor} = 12.6 min).

Compound 3ca. Yellow solid (75.2 mg, 86% yield). Mp 121.5–124.5 °C; $[\alpha]_D^{20}$ = −11.33 (c 0.07, CH_2Cl_2); ^{1}H NMR (400 MHz, chloroform-d) δ 8.43 (s, 1H), 7.99–7.88 (m, 4H), 7.62–7.51 (m, 3H), 7.42 (q, J = 7.3 Hz, 4H), 7.25 (s, 1H), 7.20 (d, J = 8.1 Hz, 2H), 7.02 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (101 MHz, chloroform-d) δ 196.8, 189.7, 164.9, 151.7, 146.6, 142.7, 141.4, 137.4, 135.8, 134.4, 130.1, 130.1, 129.2, 128.8, 126.3, 126.2, 126.1, 118.9, 78.9, 21.7; HRMS (ESI) m/z calcd for $C_{25}H_{18}N_3O_2S$ ($[M + H]^+$) 438.1271, found 438.1286; the enantiomeric excess was determined to be 92% (determined by HPLC using a chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 11.3 min, t_{minor} = 10.1 min).

Compound 3da. Yellow solid (80.6 mg, 89% yield). Mp 124.5–125.5 °C; $[\alpha]_D^{20}$ = +35.00 (c 0.12, CH_2Cl_2); ^{1}H NMR (400 MHz, chloroform-d) δ 8.52 (s, 1H), 7.94 (dd, J = 16.2, 8.0 Hz, 4H), 7.63 (dd, J = 9.0, 2.7 Hz, 2H), 7.58 (d, J = 7.3 Hz, 1H), 7.43 (q, J = 8.0 Hz, 4H), 7.25 (d, J = 3.0 Hz, 1H), 7.06 (d, J = 4.5 Hz, 1H), 6.92 (d, J = 8.9 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (101 MHz, chloroform-d) δ 196.8, 189.7, 164.8, 162.5, 151.3, 146.6, 141.4, 137.4, 135.8, 134.4, 130.1, 129.1, 128.7, 127.9, 126.2, 121.6, 118.9, 114.9, 79.0, 55.5; HRMS (ESI) m/z calcd for $C_{26}H_{19}N_3O_3S$ ($[M + H]^+$) 454.1220, found 454.1237; the enantiomeric excess was determined to be 87% (determined by HPLC using a chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 17.2 min, t_{minor} = 14.5 min).

Compound 3ea. Yellow solid (77.6 mg, 88% yield). Mp 124.5–126.5 °C; $[\alpha]_D^{20}$ = +10.88 (c 0.22, CH_2Cl_2); ^{1}H NMR (400 MHz, chloroform-d) δ 8.68 (s, 1H), 7.90 (dd, J = 12.5, 7.8 Hz, 4H), 7.69 (dd, J = 8.9, 5.2 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H),

7.42 (q, J = 8.4 Hz, 4H), 7.25 (s, 1H), 7.10 (t, J = 8.6 Hz, 2H), 7.06 (s, 1H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −107.12; ^{13}C NMR (101 MHz, chloroform-d) δ 196.8, 189.7, 164.9, 164.7 (d, J = 254.5 Hz), 150.7, 146.8, 141.1, 137.2, 135.7, 134.5, 130.1, 129.2, 128.8, 128.4 (d, J = 8.8 Hz), 126.5, 125.3 (d, J = 3.4 Hz), 118.9, 116.7 (d, J = 22.3 Hz), 78.8; HRMS (ESI) m/z calcd for $C_{25}H_{18}N_3O_2FS$ ([M + H]$^+$) 442.1020, found 442.1034, the enantiomeric excess was determined to be 86% (determined by HPLC using a chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 17.8 min, t_{minor} = 13.8 min).

Compound 3fa. Yellow solid (84.2 mg, 89% yield). Mp 158.5–160.0 °C; $[\alpha]_D^{19}$ = +16.00 (c 0.62, CH_2Cl_2); ^{1}H NMR (400 MHz, chloroform-d) δ 8.98 (d, J = 8.6 Hz, 1H), 8.41 (s, 1H), 8.01 (d, J = 7.7 Hz, 2H), 7.95 (d, J = 8.2 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 6.9 Hz, 2H), 7.70–7.62 (m, 1H), 7.63–7.53 (m, 3H), 7.53–7.46 (m, 3H), 7.40 (t, J = 7.7 Hz, 2H), 7.31 (t, J = 7.5 Hz, 1H), 7.15 (s, 1H); ^{13}C NMR (101 MHz, chloroform-d) δ 196.8, 189.6, 164.5, 152.4, 146.6, 141.2, 137.4, 135.8, 134.3, 134.2, 132.6, 130.4, 130.0, 129.3, 129.2, 128.7, 128.4, 127.5, 126.7, 126.4, 125.5, 125.3, 125.1, 119.0, 80.3; HRMS (ESI) m/z calcd for $C_{29}H_{19}N_3O_2S$ ([M + H]$^+$) 474.1271, found 474.1284; the enantiomeric excess was determined to be 81% (determined by HPLC using a chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 16.6 min, t_{minor} = 14.1 min).

Compound 3ga. Yellow solid (79.5 mg, 84% yield). Mp 110.5–112.5 °C; $[\alpha]_D^{20}$ = +42.33 (c 0.15, CH_2Cl_2); ^{1}H NMR (400 MHz, chloroform-d) δ 8.23 (s, 1H), 8.03–7.95 (m, 6H), 7.85 (dd, J = 18.5, 9.1 Hz, 3H), 7.64–7.40 (m, 8H), 7.29 (t, J = 7.4 Hz, 1H), 7.16 (s, 1H); ^{13}C NMR (101 MHz, chloroform-d) δ 196.9, 189.6, 164.9, 151.5, 146.7, 141.2, 137.3, 135.8, 134.7, 134.4, 132.8, 130.0, 129.4, 129.3, 129.2, 128.8, 128.3, 127.8, 127.2, 127.1, 126.4, 126.3, 122.2, 118.9, 78.8; HRMS (ESI) m/z calcd for $C_{29}H_{19}N_3O_2S$ ([M + H]$^+$) 474.1271, found 474.1284; the enantiomeric excess was determined to be 83% (determined by HPLC using a chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 21.4 min, t_{minor} = 14.8 min).

Compound 3ha. Yellow solid (59.9 mg, 83% yield). Mp 115.5–116.5 °C; $[\alpha]_D^{20}$ = −152.50 (c 0.20, CH_2Cl_2); ^{1}H NMR (400 MHz, chloroform-d) δ 8.17 (s, 1H), 8.01–7.92 (m, 2H), 7.85 (dd, J = 8.7, 1.2 Hz, 2H), 7.67–7.58 (m, 1H), 7.49 (t, J = 7.8 Hz, 2H), 7.47–7.38 (m, 1H), 7.25 (t, J = 7.4 Hz, 1H), 6.96 (s, 1H), 2.18 (s, 3H); ^{13}C NMR (101 MHz, chloroform-d) δ 197.3, 189.7, 165.0, 154.8, 147.1, 139.4, 137.3, 135.7, 134.5, 130.0, 129.1, 128.8, 126.1, 118.9, 80.0, 14.2; HRMS (ESI) m/z calcd for $C_{20}H_{15}N_3O_2S$ ([M + H]$^+$) 362.0958, found 362.0969; the enantiomeric excess was determined to be 82% (determined by HPLC using a chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 10.8 min, t_{minor} = 9.3 min).

Compound 3ia. Yellow solid (68.3 mg, 91% yield). Mp 95.0–97.0 °C; $[\alpha]_D^{19}$ = −151.11 (c 0.36, CH_2Cl_2); ^{1}H NMR (400 MHz, chloroform-d) δ 8.77 (s, 1H), 7.93 (d, J = 7.0 Hz, 2H), 7.82 (d, J = 7.5 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 7.39 (t, J = 7.8 Hz, 2H), 7.21 (t, J = 7.4 Hz, 1H), 6.93 (s, 1H), 2.59–2.33 (m, 2H), 1.25 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, chloroform-d) δ 197.3, 189.7, 165.1, 158.8, 146.9, 139.7, 137.4, 135.7, 134.5, 130.0, 129.1, 128.8, 126.1, 118.9, 80.0, 22.2, 10.0; HRMS (ESI) m/z calcd for $C_{21}H_{17}N_3O_2S$ ([M + H]$^+$) 376.1114, found 376.1126; the enantiomeric excess was determined to be 91% (determined by HPLC using a chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 13.0 min, t_{minor} = 9.3 min).

Compound 3ja. Yellow solid (67.7 mg, 87% yield). Mp 88.0–89.0 °C; $[\alpha]_D^{18}$ = −168.04 (c 0.51, CH_2Cl_2); ^{1}H NMR (400 MHz, chloroform-d) δ 8.95 (s, 1H), 7.93 (d, J = 7.0 Hz, 2H), 7.82 (d, J = 7.4 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.44 (t, J = 7.8 Hz, 2H), 7.38 (t, J = 7.8 Hz, 2H), 7.21 (t, J = 7.4 Hz, 1H), 6.95 (s, 1H), 2.72 (hept, J = 6.9 Hz, 1H), 1.28 (d, J = 6.9 Hz, 3H), 1.23 (d, J = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, chloroform-d) δ 197.2, 189.8, 165.2, 161.9, 146.6, 140.2, 137.4, 135.7, 134.5, 130.1, 130.0, 129.1, 128.8, 126.1, 118.9, 80.1, 29.6, 20.9, 20.3; HRMS (ESI) m/z calcd for $C_{22}H_{19}N_3O_2S$ ([M + H]$^+$) 390.1271, found 390.1282; the enantiomeric excess was determined to be 93% (determined by HPLC using a chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 10.8 min, t_{minor} = 8.5 min).

Compound 3ka. Yellow solid (69.7 mg, 90% yield). Mp 99.0–102.0 °C; $[\alpha]_D^{18}$ = −96.10 (c 0.41, CH_2Cl_2); ^{1}H NMR (400 MHz, chloroform-d) δ 8.80 (s, 1H), 7.95 (d, J = 7.0 Hz, 2H), 7.79 (d, J = 7.6 Hz, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.8 Hz, 2H), 7.37 (t, J = 8.2 Hz, 2H), 7.20 (t, J = 7.4 Hz, 1H), 6.97 (d, J = 1.5 Hz, 1H), 1.59 (tt, J = 8.0, 5.1 Hz, 1H), 1.16–1.04 (m, 4H); ^{13}C NMR (101 MHz, chloroform-d) δ 197.4, 189.7, 164.9, 159.7, 146.8, 139.8, 137.4, 135.8, 134.5, 130.1, 129.1, 128.8, 128.7, 126.0, 118.8, 80.2, 10.0, 9.8, 9.4; HRMS (ESI) m/z calcd for $C_{22}H_{17}N_3O_2S$ ([M + H]$^+$) 388.1114, found 388.1128; the enantiomeric excess was determined to be 92% (determined by HPLC using a chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 16.2 min, t_{minor} = 10.3 min).

Compound 3la. Yellow oil (76.6 mg, 95% yield). $[\alpha]_D^{8}$ = +56.14 (c 0.61, CH_2Cl_2); ^{1}H NMR (400 MHz, chloroform-d) δ 7.98–7.90 (m, 2H), 7.63–7.55 (m, 3H), 7.38–7.32 (m, 3H), 7.41–7.30 (m, 3H), 7.04 (s, 1H), 1.58 (s, 9H); ^{13}C NMR (101 MHz, chloroform-d) δ 196.8, 189.8, 166.4, 149.2, 146.7, 141.7, 136.0, 134.2, 131.1, 130.1, 129.7, 129.2, 128.7, 125.6, 79.5, 59.9, 28.2; HRMS (ESI) m/z calcd for $C_{23}H_{22}N_3O_2S$ ([M + H]$^+$) 404.1427, found 404.1428; the enantiomeric excess was determined to be 87% (determined by HPLC using a chiral IC-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 9.8 min, t_{minor} = 13.2 min).

Compound 3ab. Yellow solid (78.7 mg, 90% yield). Mp 215.0–217.0 °C; $[\alpha]_D^{20}$ = −10.69 (c 0.29, CH_2Cl_2); ^{1}H NMR (400 MHz, acetone-d6) δ 10.20 (s, 1H), 8.01 (dd, J = 8.7, 1.2 Hz, 2H), 7.86 (dd, J = 7.6, 2.1 Hz, 2H), 7.84–7.81 (m, 2H), 7.78 (s, 1H), 7.62–7.57 (m, 3H), 7.56–7.50 (m, 3H), 7.45 (t, J = 8.0 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, acetone-d6) δ 205.3, 197.4, 189.8, 165.6, 151.8, 147.5, 141.4, 138.6, 1378.0, 136.4, 134.9, 131.6, 130.0, 129.9, 129.3, 129.1,

128.7, 127.0, 126.0, 125.9, 118.7, 79.4, 20.5; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{19}N_3O_2S$ ($[M + H]^+$) 438.1271, found 438.1276; the enantiomeric excess was determined to be 91% (determined by HPLC using a chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 14.6 min, t_{minor} = 13.0 min).

Compound 3ac. Yellow solid (79.5 mg, 91% yield). Mp 110.0–111.0 °C; $[\alpha]_D^{20}$ = −11.43 (*c* 0.14, CH_2Cl_2); ^1H NMR (400 MHz, chloroform-d) δ 8.27 (s, 1H), δ 7.96 (d, *J* = 8.1 Hz, 2H), 7.89 (d, *J* = 7.9 Hz, 2H), 7.74 (d, *J* = 7.5 Hz, 2H), 7.46 (m, 5H), 7.27 (d, *J* = 8.8 Hz, 3H), 7.10 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (101 MHz, chloroform-d) δ 197.1, 189.1, 165.0, 151.6, 147.0, 145.6, 140.7, 137.4.0, 133.4, 131.9, 130.2, 129.5, 129.4, 129.2, 129.0, 126.4, 126.1, 119.0, 78.8, 21.9; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{19}N_3O_2S$ ($[M + H]^+$) 438.1271, found 438.1276; the enantiomeric excess was determined to be 91% (determined by HPLC using a chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 18.1 min, t_{minor} = 12.5 min).

Compound 3ad. Yellow solid (79.7 mg, 88% yield). Mp 235.0–236.0 °C; $[\alpha]_D^{19}$ = −49.75 (*c* 0.40, CH_2Cl_2); ^1H NMR (400 MHz, acetone-d6) δ 10.17 (s, 1H), 8.00 (t, *J* = 7.6 Hz, 4H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.73 (s, 1H), 7.61–7.54 (m, 3H), 7.53 (t, *J* = 8.0 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.08 (d, *J* = 9.0 Hz, 2H), 3.92 (s, 3H); ^{13}C NMR (101 MHz, acetone-d6) δ 205.3, 197.7, 188.1, 165.7, 164.6, 151.9, 147.8, 140.9, 138.0, 132.0, 131.6, 129.9, 129.4, 129.3, 129.1, 126.0, 125.9, 118.7, 114.0, 79.4, 55.3; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{19}N_3O_3S$ ($[M + H]^+$) 454.1220, found 454.1228; the enantiomeric excess was determined to be 93% (determined by HPLC using a chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 23.5 min, t_{minor} = 16.8 min).

Compound 3ae. Yellow solid (80.3 mg, 91% yield). Mp 108.0–110.0 °C; $[\alpha]_D^{17}$ = −23.33 (*c* 0.42, CH_2Cl_2); ^1H NMR (400 MHz, chloroform-d) δ 8.59 (s, 1H), 7.97 (dd, *J* = 8.8, 5.4 Hz, 2H), 7.90 (d, *J* = 7.7 Hz, 2H), 7.67 (d, *J* = 6.9 Hz, 2H), 7.46 (d, *J* = 7.3 Hz, 1H), 7.44–7.38 (m, 4H), 7.26 (t, *J* = 7.4 Hz, 1H), 7.09 (t, *J* = 8.5 Hz, 2H), 7.05 (s, 1H); ^{19}F NMR (377 MHz, chloroform-d) δ −102.42; ^{13}C NMR (101 MHz, chloroform-d) δ 196.6, 188.3, 166.5 (d, *J* = 257.4 Hz), 165.0, 151.6, 146.7, 141.2, 137.3, 132.9 (d, *J* = 9.8 Hz), 132.2 (d, *J* = 2.9 Hz), 132.0, 129.4, 129.2, 128.9, 126.5, 126.1, 118.9, 116.1 (d, *J* = 22.2 Hz), 79.0; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{16}FN_3O_2S$ ($[M + H]^+$) 442.1020, found 442.1025; the enantiomeric excess was determined to be 93% (determined by HPLC using a chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 15.0 min, t_{minor} = 11.3 min).

Compound 3af. Yellow solid (91.4 mg, 91% yield). Mp 114.0–116.0 °C; $[\alpha]_D^{17}$ = +14.17 (*c* 0.15, CH_2Cl_2); ^1H NMR (400 MHz, chloroform-d) δ 8.13 (s, 1H), 7.93 (d, *J* = 7.5 Hz, 2H), 7.72 (d, *J* = 7.2 Hz, 2H), 7.56 (dd, *J* = 17.1, 7.6 Hz, 2H), 7.52–7.37 (m, 7H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.18–7.05 (m, 1H); ^{13}C NMR (101 MHz, chloroform-d) δ 195.6, 189.4, 164.7, 151.4, 146.0, 145.3, 138.6, 137.3, 133.6, 132.8, 131.9, 131.1, 129.3, 129.2, 128.9, 127.4, 126.4, 126.2, 120.7, 118.9, 78.3; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{16}BrN_3O_2S$ ($[M + H]^+$) 502.0219, found 502.0227; the enantiomeric excess was determined to be 89% (determined by HPLC using a chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 19.1 min, t_{minor} = 15.7 min).

Compound 3ag. Yellow solid (90.2 mg, 90% yield). Mp 97.0–98.0 °C; $[\alpha]_D^{20}$ = −40.65 (*c* 1.23, CH_2Cl_2); ^1H NMR (400 MHz, chloroform-d) δ 8.74 (s, 1H), 7.86 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 7.5 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 6.9 Hz, 4H), 7.24 (s, 1H), 6.99 (s, 1H); ^{13}C NMR (101 MHz, chloroform-d) δ 196.5, 188.9, 164.9, 151.6, 146.5, 141.7, 137.2, 134.4, 132.1, 132.0, 131.5, 129.9, 129.5, 129.3, 128.9, 126.5, 126.1, 118.9, 79.1; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{16}BrN_3O_2S$ ($[M + H]^+$) 504.0204, found 504.0196; the enantiomeric excess was determined to be 91% (determined by HPLC using a chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 19.7 min, t_{minor} = 12.1 min).

Compound 3ah. Yellow solid (76.4 mg, 89% yield). Mp 120.0–121.0 °C; $[\alpha]_D^{21}$ = +4.17 (*c* 0.24, CH_2Cl_2); ^1H NMR (400 MHz, acetone-d6) δ 10.19 (s, 1H), 8.07 (dd, *J* = 4.9, 1.1 Hz, 1H), 8.02 (s, 1H), 8.00 (d, *J* = 4.0 Hz, 1H), 7.89 (s, 1H), 7.86–7.79 (m, 3H), 7.60–7.56 (m, 3H), 7.58–7.49 (m, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.29 (dd, *J* = 4.9, 3.9 Hz, 1H); ^{13}C NMR (101 MHz, acetone-d6) δ 205.3, 196.8, 181.2, 165.5, 151.7, 146.6, 143.6, 141.9, 138.0, 136.5, 136.2, 131.6, 129.9, 129.3, 129.1, 128.7, 126.0, 125.9, 118.7, 79.2; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{15}N_3O_2S_2$ ($[M + H]^+$) 430.0678, found 430.0684; the enantiomeric excess was determined to be 93% (determined by HPLC using a chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 18.9 min, t_{minor} = 14.9 min).

Compound 3ai. Yellow solid (88.0 mg, 93% yield). Mp 230.0–231.0 °C; $[\alpha]_D^{18}$ = −39.35 (*c* 0.31, CH_2Cl_2); ^1H NMR (400 MHz, acetone-d6) δ 10.21 (s, 1H), 9.01 (d, *J* = 8.6 Hz, 1H), 8.20 (d, *J* = 8.3 Hz, 1H), 8.13 (d, *J* = 7.2 Hz, 1H), 8.02 (t, *J* = 7.0 Hz, 3H), 7.88–7.84 (m, 3H), 7.71 (t, *J* = 7.7 Hz, 1H), 7.65–7.57 (m, 5H), 7.52 (t, *J* = 8.0 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 1H); ^{13}C NMR (101 MHz, acetone-d6) δ 205.4, 197.4, 191.7, 165.6, 151.8, 148.6, 142.4, 138.0, 134.5, 134.1, 133.0, 133.0, 131.6, 130.7, 30.0, 129.3, 129.1, 128.6, 128.5, 126.7, 126.1, 125.9, 125.8, 124.5, 118.8, 79.3; HRMS (ESI) *m*/*z* calcd for $C_{29}H_{19}N_3O_2S$ ($[M + H]^+$) 474.1271, found 474.1279; the enantiomeric excess was determined to be 91% (determined by HPLC using a chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 20.1 min, t_{minor} = 23.7 min).

Compound 3aj. Yellow solid (73.0 mg, 81% yield). Mp 161.3–163.5 °C; $[\alpha]_D^{5}$ = +55.00 (*c* 0.16, CH_2Cl_2); ^1H NMR (400 MHz, chloroform-d) δ 8.26 (s, 1H), 7.95–7.82 (m, 2H), 7.62–7.53 (m, 2H), 7.49–7.33 (m, 6H), 7.26 (d, *J* = 7.4 Hz, 2H), 7.24 (s, 1H), 7.23–7.12 (m, 3H), 3.57 (dt, *J* = 18.1, 7.5 Hz, 1H), 3.40 (dt, *J* = 18.1, 7.5 Hz, 1H), 2.95 (t, *J* = 7.6 Hz, 2H); ^{13}C NMR (151 MHz, chloroform-d) δ 195.9, 164.5, 151.2, 146.2, 146.0, 140.6, 137.3, 132.0, 129.4, 129.3, 129.0, 128.5, 126.5, 126.2, 126.0, 118.9, 77.8, 44.0, 29.5; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{22}N_3O_2S$ ($[M + H]^+$) 452.1427, found 452.1423; the enantio-

meric excess was determined to be 87% (determined by HPLC using a chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 31.9 min, t_{minor} = 26.7 min).

Compound 3ak. Yellow solid (78.8 mg, 79% yield). Mp 104.0–105.0 °C; $[\alpha]_D^{18}$ = +38.67 (*c* 0.15, CH_2Cl_2); ^{1}H NMR (400 MHz, chloroform-d) δ 8.14 (s, 1H), 8.07 (d, *J* = 7.0 Hz, 2H), 7.93 (d, *J* = 7.7 Hz, 2H), 7.79 (d, *J* = 6.1 Hz, 2H), 7.58–7.52 (m, 1H), 7.51–7.41 (m, 7H), 7.30 (t, *J* = 7.4 Hz, 1H), 7.20 (td, *J* = 6.1, 2.5 Hz, 1H), 7.17–7.09 (m, 4H); ^{13}C NMR (101 MHz, chloroform-d) δ 195.6, 189.4, 164.7, 151.4, 146.0, 145.3, 138.6, 137.3, 133.6, 132.8, 131.9, 131.1, 129.3, 129.2, 128.9, 127.4, 126.4, 126.2, 120.7, 118.9, 78.3; HRMS (ESI) *m*/*z* calcd for $C_{31}H_{21}N_3O_2S$ ([M + H]$^+$) 500.1427, found 500.1434; the enantiomeric excess was determined to be 85% (determined by HPLC using a chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 13.9 min, t_{minor} = 12.1 min).

Compound 3al. Yellow solid (78.6 mg, 76% yield). Mp 114.0–115.0 °C; $[\alpha]_D^{20}$ = +25.59 (*c* 0.17, CH_2Cl_2); ^{1}H NMR (400 MHz, chloroform-d) δ 8.66 (s, 1H), 8.08 (dd, *J* = 8.6, 5.5 Hz, 2H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.78–7.69 (m, 2H), 7.44 (td, *J* = 7.7, 2.0 Hz, 6H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.19 (h, *J* = 4.2 Hz, 1H), 7.11 (d, *J* = 4.4 Hz, 4H), 7.07 (t, *J* = 8.6 Hz, 2H); ^{19}F NMR (470 MHz, $CDCl_3$) δ −102.23; ^{13}C NMR (101 MHz, chloroform-d) δ 197.0, 190.0, 166.5 (d, *J* = 257.3 Hz), 166.0, 152.7, 152.6, 142.2, 137.1, 132.7, 132.7, 132.2 (d, *J* = 2.3 Hz), 131.9, 131.1, 129.5, 129.3, 129.3, 128.6 (d, *J* = 58.8 Hz), 127.3, 126.6, 126.2, 119.4, 116.2 (d, *J* = 22.1 Hz), 80.4; HRMS (ESI) *m*/*z* calcd for $C_{31}H_{20}N_3O_2S$ ([M + H]$^+$) 518.1333, found 518.1337; the enantiomeric excess was determined to be 91% (determined by HPLC using a chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 11.3 min, t_{minor} = 9.9 min).

Compound 3am. Yellow solid (87.0 mg, 80% yield). Mp 124.0–125.0 °C; $[\alpha]_D^{14}$ = +10.88 (*c* 0.62, CH_2Cl_2); ^{1}H NMR (400 MHz, chloroform-d) δ 8.46 (s, 1H), 8.23 (q, *J* = 8.7 Hz, 4H), 7.91 (d, *J* = 8.0 Hz, 2H), 7.76 (d, *J* = 6.8 Hz, 2H), 7.51–7.43 (m, 5H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.18–7.08 (m, 4H); ^{13}C NMR (101 MHz, chloroform-d) δ 196.5, 190.1, 165.9, 154.0, 152.4 150.8, 141.4, 139.9, 137.0, 132.1, 131.4, 130.7, 129.5, 129.5, 129.3, 128.8, 127.9, 127.3, 126.7, 126.1, 124.1, 119.3, 80.6; HRMS (ESI) *m*/*z* calcd for $C_{31}H_{20}N_4O_4S$ ([M + H]$^+$) 545.1278, found 545.1286; the enantiomeric excess was determined to be 94% (determined by HPLC using a chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 16.0 min, t_{minor} = 19.0 min).

Compound 3an. Yellow solid (62.0 mg, 66% yield). Mp 117.5–119.8 °C; $[\alpha]_D^{8}$ = −36.67 (*c* 0.50, CH_2Cl_2); ^{1}H NMR (400 MHz, chloroform-d) δ 8.43 (s, 1H), 8.01–7.86 (m, 4H), 7.75–7.64 (m, 2H), 7.52–7.40 (m, 7H), 7.29 (t, *J* = 7.5 Hz, 1H), 1.79 (s, 3H); ^{13}C NMR (101 MHz, chloroform-d) δ 197.7, 189.9, 165.9, 154.1, 152.5, 142.5, 141.0, 137.2, 134.4, 132.1, 131.3, 129.6, 129.3, 128.6, 126.6, 126.4, 119.0, 81.5, 11.4; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{19}N_3O_2SCl$ ([M + H]$^+$) 472.0881, found 472.0879; the enantiomeric excess was determined to be 92% (determined by HPLC using a chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 20.3 min, t_{minor} = 13.7 min).

Compound 3ao. Yellow solid (45.0 mg, 48% yield). Mp 161.3–163.5 °C; $[\alpha]_D^{5}$ = +55.00 (*c* 0.16, CH_2Cl_2); ^{1}H NMR (400 MHz, chloroform-d) δ 8.03–7.86 (m, 3H), 7.68–7.56 (m, 2H), 7.55–7.37 (m, 5H), 7.29 (t, *J* = 7.1 Hz, 1H), 7.27 (s, 1H), 7.24 (d, *J* = 2.3 Hz, 3H), 7.17 (t, *J* = 6.7 Hz, 1H), 3.64 (dt, *J* = 17.3, 7.8 Hz, 1H), 3.50 (dt, *J* = 17.4, 7.4 Hz, 1H), 3.02 (t, *J* = 7.6 Hz, 2H), 1.83 (s, 3H); ^{13}C NMR (101 MHz, chloroform-d) δ 198.9, 197.4, 165.4, 158.4, 141.9, 140.5, 137.2, 132.0, 129.5, 129.2, 128.6, 128.5, 128.4, 126.5, 126.1, 125.9, 119.0, 80.8, 44.7, 29.8, 11.6; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{24}N_3O_2S$ ([M + H]$^+$) 466.1584, found 466.1578; the enantiomeric excess was determined to be 93% (determined by HPLC using a chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 14.9 min, t_{minor} = 16.4 min).

The procedure for the synthesis of compounds 4

To a solution of **3af** (50.1 mg, 0.1 mmol, 1.0 equiv.) in THF (2.0 mL) were added K_2CO_3 (16.6 mg, 0.12 mmol, 1.2 equiv.) and iodomethane (17.0 mg, 0.12 mmol, 1.2 equiv.) in sequence. The reaction mixture was stirred at rt for 6 h. The solvent was evaporated, and then the crude mixture was purified by silica gel column chromatography (EtOAc/petroleum ether = 1/5) to give **4** as a light yellow solid (47.0 mg, 91% yield). Mp 150–153 °C; $[\alpha]_D^{17}$ = +31.00 (*c* 0.20, CH_2Cl_2); ^{1}H NMR (400 MHz, chloroform-d) δ 7.94 (d, *J* = 8.1 Hz, 2H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.2 Hz, 2H), 7.46 (s, 1H), 7.43 (t, *J* = 8.1 Hz, 3H), 7.41–7.27 (m, 5H), 7.26–7.21 (m, 1H), 2.62 (s, 3H); ^{13}C NMR (101 MHz, chloroform-d) δ 189.4, 177.8, 164.2, 157.4, 152.8, 143.9, 139.7, 137.8, 133.5, 132.1, 131.2, 130.4, 129.1, 129.0, 128.9, 127.5, 126.1, 125.9, 119.2, 119.1, 90.0, 14.4; HRMS (ESI) *m*/*z* calcd for $C_{26}H_{18}BrN_3O_2S$ ([M + H]$^+$) 518.0361, found 518.0354; the enantiomeric excess was determined to be 89% (determined by HPLC using a chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 13.5 min, t_{minor} = 12.4 min).

The procedure for the synthesis of compounds 5

To a solution of **3aa** (42.3 mg, 0.1 mmol, 1.0 equiv.) in THF (1.0 mL) was added 85% *m*CPBA (21.3 mg, 0.105 mmol, 1.05 equiv.) at 0 °C. The reaction mixture was stirred at 0 °C for 5 h and then the mixture was diluted with DCM (10 mL). The reaction was quenched with saturated $NaHCO_3$ aqueous (2 mL). The organic phase was separated and washed with saturated $NaHCO_3$ aqueous and brine, dried over Na_2SO_4, and concentrated. The crude mixture was purified by silica gel column chromatography (EtOAc/petroleum ether = 1/3) to give **5** as a white solid (34.6 mg, 85% yield). Mp 150–153 °C; $[\alpha]_D^{17}$ = −50.00 (*c* 0.10, CH_2Cl_2); ^{1}H NMR (400 MHz, chloroform-d) δ 7.96 (d, *J* = 7.5 Hz, 2H), 7.88 (d, *J* = 6.9 Hz, 2H), 7.76 (d, *J* = 7.1 Hz, 2H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.51–7.36 (m, 8H), 7.27 (t, *J* = 7.4 Hz, 1H), 7.24 (d, *J* = 1.7 Hz, 1H); ^{13}C NMR (101 MHz, chloroform-d) δ 188.4, 170.4, 166.3, 152.6, 145.9, 138.9, 137.5, 135.9, 134.2, 131.7, 129.8, 129.7, 129.2, 129.2, 129.1, 128.8,

126.2, 126.1, 118.9, 71.5; HRMS (ESI) m/z calcd for $C_{25}H_{17}N_3O_3$ ($[M + H]^+$) 408.1343, found 408.1343; the enantiomeric excess was determined to be 91% (determined by HPLC using a chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL min^{-1}, t_{major} = 25.4 min, t_{minor} = 15.1 min).

Conflicts of interest

There are no conflicts to declare.

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