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Quinine-catalyzed asymmetric domino Michael-cyclization reaction for the synthesis of spirocyclic oxindoles bearing two spiro quaternary centers and three consecutive stereocenters

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ABSTRACT

An efficient organocatalytic diastereo- and enantioselective method for the construction of spirocyclic oxindole derivatives bearing two spiro quaternary centers and three consecutive stereocenters via a domino Michael/cyclization process has been developed. Using commercially available quinine as catalyst, the reactions of 3-isothiocyanato oxindoles with unsaturated pyrazolones and unsaturated isoxazolones proceeded smoothly under mild reaction conditions for giving two classes of spirocyclic oxindole compounds in high to excellent yields with moderate to good diastereoselectivities and enantioselectivities. A plausible dual activation working model was tentatively proposed to account for the stereochemistry of the domino Michael/cyclization process.

1. Introduction

The spirocyclic oxindole scaffold defines the characteristic structural core of a number of biologically active synthetic and natural products with activities in a variety of disease areas (Fig. 1).[1] Nevertheless, it has been exactly shown that the well-defined three-dimensional architecture and structural complexity of natural molecules are generally correlated with the specificity of their biological activity.[2] Therefore, the development of new methods for efficient construction of various spirocyclic oxindole structural motifs is most fascinating and significant in the potential drug development. Consequently, a variety of strategies for the enantioselective synthesis of diversely structured spirocyclic oxindole compounds have been reported in the past few years.[3] Despite the substantial advances made thus far, the synthetic challenge of the spiro motif continues to encourage the development of creative methods to access these important spirocyclic structures.[4] In this context, exploring efficient methodology for the direct generation of structurally complex spirocyclic oxindoles (particularly those that contain highly strained spiro stereocenters and several contiguous stereocenters) has remained a formidable challenge and is highly desirable.

3-Isothiocyanato oxindoles, firstly synthesized by our group,[5a] have recently emerged as versatile nucleophiles for the

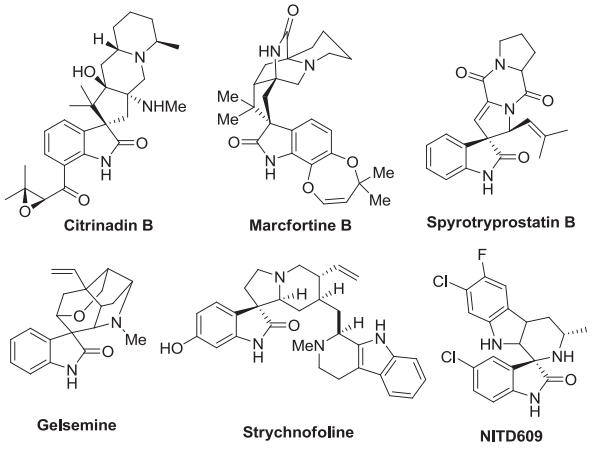

Fig. 1. Natural products and bioactive drug candidates containing spirocyclic oxindole core scaffolds.

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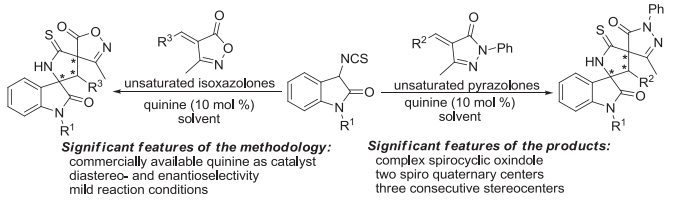
construction of diverse spirocyclic oxindoles through different catalytic asymmetric processes. These methodologies mainly relied on the nucleophilic additions of 3-isothiocyanato oxindoles to various electrophiles by aldol-,[5,6] Mannich-,[6,7] and Michael-type reaction.[4c–g,8] In parallel, a large number of organocatalytic *domino* reactions with various cinchona alkaloid derivatives as catalysts have been perceived as prospective solutions to the synthesis of enantiometrically enriched oxindole compounds.[3,9] Additionally, we also noticed that unsaturated pyrazolones had been used as a class of Michael acceptors for some asymmetric reaction.[4d,10] Encouraged by these achievements and our own laboratory's recent successes in the construction of 3,3′-disubstituted oxindole,[11] we attempted to investigate the reactions of 3-isothiocyanato oxindoles and unsaturated pyrazolones, as well as unsaturated isoxazolones. It was observed that the reactions smoothly gave rise to two classes of complex spirocyclic oxindole compounds, bearing two spiro quaternary centers and three consecutive stereocenters, with commercially available quinine as catalyst via a domino Michael/cyclization process under mild reaction conditions (Scheme 1). Herein, we wish to report the results of our endeavours on this subject.



Scheme 1. Quinine-catalyzed domino Michael/cyclization process for the synthesis of two classes of spirocyclic oxindole derivatives.

2. Results and discussion

Initially, 3-isothiocyanato oxindole **1a** and 4-benzylidene-3-methyl-1-phenyl-pyrazolone **2a** were treated with 10 mol % Takemoto catalyst **4a** (Fig. 2) in toluene at 25 °C, the desired Michael-cyclization product **3a** was observed in 83% yield, but with 77% ee and only 51:49 dr (Table 1, entry 1). However, replacement of Takemoto catalyst **4a** by quinine thiourea catalyst **4b** (Fig. 2) for the model reaction gave a significant lower yield and lower ee value, in spite of the higher diastereoselectivity (Table 1, entry 2). Nevertheless, performing the reaction with quinine derivatives **4c** and **4d** (Fig. 2), product **3a** could be obtained in excellent yield but with moderate diastereo- and enantioselectivity, respectively (Table 1, entries 3 and 4). Gratifyingly, the same reaction proceeded smoothly with commercially available quinine (**4e**) (Fig. 2) as catalyst and afforded **3a** in high to 94% yield with 88:12 dr and 90% ee (Table 1, entry 5). However, other natural cinchona alkaloids **4f**–**h** (Fig. 2) furnished lower ee value than quinine (**4e**) for the reaction of **1a** and **2a** (Table 1, entries 6–8 vs entry 5). Afterwards, using 10 mol % **4e** as catalyst, reactions run in other solvents (e.g., mesitylene, CH_2Cl_2, $CHCl_3$, THF, CH_3CN) were inferior to those performed in toluene with respect to yield or enantioselectivity (Table 1, entries 9–13 vs entry 5). Cooling the reaction to 0 °C led to a set of acceptable results, but a longer reaction time was required (Table 1, entry 14). Furthermore, lowering the reaction temperature to −20 °C resulted in a significant decrease in yield with prolonged reaction time (Table 1, entry 15). Unfortunately, further lowering to −40 °C, the reaction could hardly provide the product **3a** (Table 1, entry 16). In contrast, elevating the reaction temperature to 50 °C had a detrimental effect on the diastereo- and enantioselectivity (Table 1, entry 17). The use of 4 Å molecular sieve as additive led to slight decrease in enantioselectivity (Table 1, entry 18 vs 5). From this we speculated that the small amount water absorbed by 4 Å molecular sieve probably facilitated the stereoselectivity. Therefore, we deliberately added 0.1 mL water into the reaction system to examine the function of water in the reaction. It was observed that the desired product could be smoothly obtained in 98% yield, but with distinctly decreased level of diastereoselectivity and enantioselectivity (Table 1, entry 19).

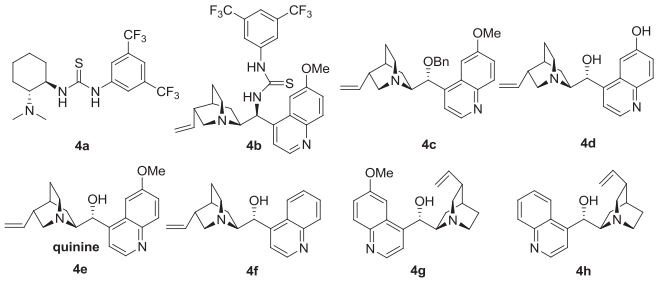
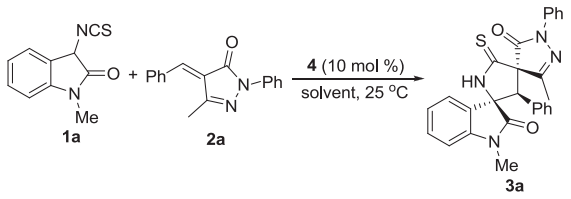


Fig. 2. Chiral organocatalysts screened in the domino reaction of **1a** and **2a** (Table 1).

Table 1
Optimization of reaction conditions[a]



Entry	Solvent	4	Yield[b] (%)	dr[c]	ee[d] (%)
1	Toluene	**4a**	83	51:49	77
2	Toluene	**4b**	40	82:18	30
3	Toluene	**4c**	95	87:13	47
4	Toluene	**4d**	95	74:26	45
5	Toluene	**4e**	94	88:12	90
6	Toluene	**4f**	96	89:11	60
7	Toluene	**4g**	97	88:12	81
8	Toluene	**4h**	95	93:7	46
9	Mesitylene	**4e**	88	85:15	90
10	CH_2Cl_2	**4e**	94	88:12	88
11	$CHCl_3$	**4e**	96	78:22	63
12	THF	**4e**	80	88:12	78
13	CH_3CN	**4e**	96	78:22	63
14	Toluene	**4e**	90	88:12	90[e]
15	Toluene	**4e**	42	—	—[f]
16	Toluene	**4e**	Trace	—	—[g]
17	Toluene	**4e**	96	70:30	71[h]
18	Toluene	**4e**	97	88:12	85[i]
19	Toluene	**4e**	98	56:44	46[j]

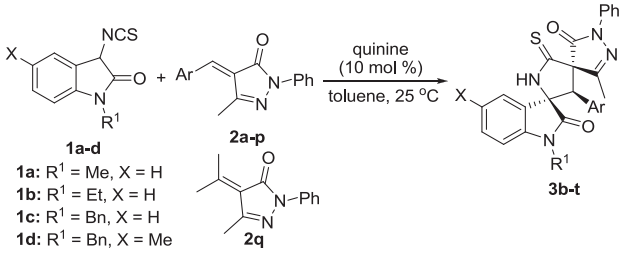
[a] Unless otherwise noted, the reactions were performed with 0.1 mmol **1a** and 0.12 mmol **2a** in the presence of 10 mol % catalyst in 5.0 mL solvent at 25 °C for 0.5 h.
[b] Isolated yields of **3a**.
[c] Determined by HPLC analysis.
[d] Enantiomeric excess for major diastereoisomers determined by chiral HPLC analysis.
[e] The reaction was performed at 0 °C for 3.0 h.
[f] The reaction was performed at −20 °C for 12.0 h.
[g] The reaction was performed at −40 °C for 24.0 h.
[h] The reaction was performed at 50 °C for 0.5 h.
[i] 50 mg 4 Å molecular sieve was used.
[j] 0.1 mL water was added into the reaction system.

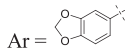
With optimized reaction conditions in hand (Table 1, entry 5), the reaction scope was examined next (Table 2). Firstly, with 3-isothiocyanato oxindole **1b** as nucleophilic reagent, diverse unsaturated pyrazolones **2a**–**g** were investigated to examined the effects of the electronic properties and the steric hindrance of the aromatic group on reactivity, diastereoselectivity and enantioselectivity (Table 2, entries 1–7). Regardless of electron-donating

groups or electron-withdrawing groups on the phenyl ring of unsaturated pyrazolones **2**, all the reactions proceeded smoothly to afford the desired products **3b**–**g** in 90–95% yield with 76–92% ee (Table 2, entries 1–6). Moreover, a 1-naphthyl-based unsaturated pyrazolones **2g** also gave rise to the corresponding spirocyclic oxindole **3h** in high yield with moderate diastereoselectivity and excellent enantioselectivity (Table 2, entry 7). Subsequently, replacing the *N*-ethyl oxindole **1b** with *N*-benzyl oxindole **1c** as nucleophilic reagent for further examining the scope and limitation of the substrate, it was observed that different β-aryl-substituted α,β-unsaturated pyrazolones, including a variation of substituents containing electron-donating as well as electron-withdrawing functionalities on the aryl moiety, also could be smoothly transformed into the corresponding spirocyclic oxindoles **3i**–**p** in acceptable results (Table 2, entries 8–15). Furthermore, two heteroaromatic pyrazolones **2o** and **2p** were successfully employed for reacting with 3-isothiocyanato oxindole **1c** under the standard conditions, giving the expected products **3q** and **3r** in excellent yield with good enantioselectivity, respectively, and thereby broadening the scope of the reaction (Table 2, entry 16 and 17). Ultimately, when a methyl group was introduced in the 5-position of the oxindole ring, there was no effect on the reactivity and selectivity of the reaction (Table 2, entry 18). Note that the β-alkyl-substituted α,β-unsaturated pyrazolones (**2q**) could also participate in the reaction with oxindole **1a** to afford the corresponding product **3t** in excellent yield and diastereoselectivity, but with hardly any enantioselectivity (Table 2, entry 19).

To further expand the substrate scope, a series of β-aryl-substituted α,β-unsaturated isoxazolones[12] were selected as electrophilic reagent by reacting with 3-isothiocyanato oxindoles to generate another class of spirocyclic oxindoles (Table 3). The reaction between *N*-methyl 3-isothiocyanato oxindole **1a** and β-phenyl-α,β-unsaturated isoxazolone **5a** proceeded smoothly in CH_2Cl_2 at −40 °C in the presence of 10 mol % quinine as catalyst, providing the corresponding product **6a** in 95% yield with 90:10 dr and 74% ee (Table 3, entry 1). Similar results also could be obtained with *N*-benzyl 3-isothiocyanato oxindole **1c** as nucleophilic regent (Table 3, entry 2). Further studies demonstrated that the electronic properties of the aromatic group in unsaturated isoxazolone had little or no effect on the reactivity and stereoselectivity (Table 3, entries 3–5). The reaction also took place with heteroaromatic substituents as thiophene in unsaturated isoxazolone in high yield with good selectivity (Table 3, entry 6). A bulkier group, such as 2-naphthyl group, also could be incorporate in to the unsaturated isoxazolone and gave the corresponding optically active product **6g** with good results (Table 3, entry 7).

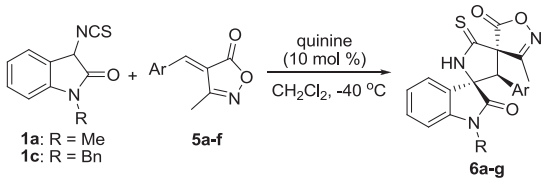
Table 2
Scope of the domino reaction of 3-isothiocyanato oxindoles **1** and unsaturated pyrazolones **2**[a]



Entry	1	2	Time (h)	3/Yield[b] (%)	dr[c]	ee[d] (%)
1	**1b**	Ar=Ph (**2a**)	0.5	**3b**/92	83:17	91
2	**1b**	Ar=3-MeC_6H_4 (**2b**)	0.5	**3c**/95	83:17	92
3	**1b**	Ar=3,4-Me$O_2C_6H_3$ (**2c**)	0.5	**3d**/92	84:16	86
4	**1b**	Ar =  (**2d**)	0.5	**3e**/95	88:12	88
5	**1b**	Ar=3-BrC_6H_4 (**2e**)	0.5	**3f**/94	87:13	76
6	**1b**	Ar=2,4-$Cl_2C_6H_3$ (**2f**)	3.0	**3g**/90	50:50	91/75
7	**1b**	Ar=1-naphthyl (**2g**)	0.5	**3h**/92	65:35	98/91
8	**1c**	Ar=Ph (**2a**)	1.0	**3i**/93	87:13	94
9	**1c**	Ar=4-MeC_6H_4 (**2h**)	0.5	**3j**/96	86:14	87
10	**1c**	Ar=3-MeOC_6H_4 (**2i**)	0.5	**3k**/95	83:17	88
11	**1c**	Ar=4-MeOC_6H_4 (**2j**)	0.5	**3l**/94	82:18	91
12	**1c**	Ar=2,4-Me$O_2C_6H_3$ (**2k**)	2.0	**3m**/95	77:23	94
13	**1c**	Ar=4-ClC_6H_4 (**2l**)	0.5	**3n**/94	81:19	95
14	**1c**	Ar=2-BrC_6H_4 (**2m**)	3.0	**3o**/90	63:37	89/91
15	**1c**	Ar=4-BrC_6H_4 (**2n**)	0.5	**3p**/95	83:17	80
16	**1c**	Ar=2-furyl (**2o**)	1.0	**3q**/95	56:44	87/82
17	**1c**	Ar=2-thienyl (**2p**)	1.0	**3r**/96	86:14	85
18	**1d**	Ar=Ph (**2a**)	1.0	**3s**/95	88:12	93
19	**1a**	**2q**	3.0	**3t**/98	>99:1[e]	2

[a] Unless otherwise noted, the reactions were performed with 0.1 mmol **1** and 0.12 mmol **2** in the presence of 10 mol % quinine in 5.0 mL toluene at 25 °C for the specified reaction time.
[b] Isolated yields of **3**.
[c] Determined by HPLC analysis.
[d] Enantiomeric excess for major diastereoisomers determined by chiral HPLC analysis, and the results in parentheses for minor diastereoisomers also determined by chiral HPLC analysis.
[e] Determined by ^1H NMR of the crude reaction mixture.

Table 3
Scope of the domino reaction of 3-isothiocyanato oxindoles **1** and unsaturated isoxazolones **5**[a]

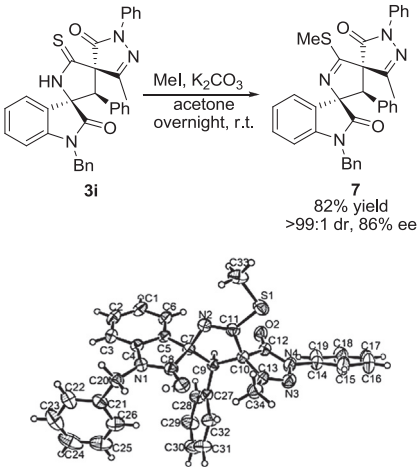


Entry	1	5	Time (h)	6/Yield[b] (%)	dr[c]	ee[d] (%)
1	**1a**	Ar=Ph (**5a**)	1	**6a**/95	90:10	74
2	**1c**	Ar=Ph (**5a**)	1	**6b**/96	94:6	77
3	**1c**	Ar=4-MeC_6H_4 (**5b**)	1	**6c**/93	93:7	77
4	**1c**	Ar=4-MeOC_6H_4 (**5c**)	2	**6d**/94	92:8	73
5	**1c**	Ar=4-FC_6H_4 (**5d**)	1	**6e**/94	92:8	67
6	**1c**	Ar=2-thienyl (**5e**)	2	**6f**/92	89:11	68
7	**1c**	Ar=2-naphthyl (**5f**)	2	**6g**/93	60:40	64

[a] Unless otherwise noted, the reactions were performed with 0.1 mmol **1** and 0.12 mmol **5** in the presence of 10 mol % quinine in 5.0 mL CH_2Cl_2 at −40 °C for the specified reaction time.
[b] Isolated yields of **6**.
[c] Determined by HPLC analysis.
[d] Enantiomeric excess for major diastereoisomers determined by chiral HPLC analysis.

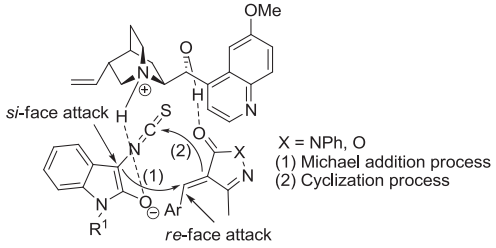
Scheme 2 outlines one transformation of the chiral product **3i** into another spirocyclic oxindole **7**. By reacting **3i** with methyl iodide and K_2CO_3 in acetone at room temperature for overnight, compound **7** could be accessed in 82% yield with >99:1 dr and 86% ee. And then, we determined the relative and absolute configuration of the major stereoisomer b single-crystal X-ray analysis of the compound **7**, where the chiral centers were determined as (*R*,*R*,*R*)-configuration (Scheme 2). Assuming a common reaction pathway, the stereochemistry of the other compounds was tentatively assigned by analogy.

Additionally, based on previous studies about the α-isothiocyanato imides or esters applied in the organocatalytic asymmetric transformations[4c–g,5,6,8,13] and our experimental results, a dual activation working model is tentatively suggested in Scheme 3 to account for the stereochemistry of the domino Michael/cyclization process. During the catalytic process, the two substrates involved in the reaction are activated simultaneously by the tertiary amine moiety (for 3-isothiocyanato oxindole) and 9-OH moiety (for unsaturated pyrazolones or unsaturated isoxazolones) of the



Scheme 2. Transformation of product **3i** into compound **7** and the X-ray structure of compound **7**.

catalyst quinine. In the first Michael addition step, the activated 3-isothiocyanato oxindole (from the *si*-face) attacks the β-position (to the *re*-face) of the unsaturated pyrazolones or unsaturated isoxazolones. In the succedent cyclization step, the α-position of the unsaturated pyrazolones or unsaturated isoxazolones approaches the −NCS group of the 3-isothiocyanato oxindole resulting in the desired spirocyclic oxindole derivatives with determinate stereochemistry.



Scheme 3. Proposed working model for the domino Michael/cyclization process.

3. Conclusion

In conclusion, we have developed an organocatalytic diastereo- and enantioselective method for the construction of spirocyclic oxindole derivatives bearing two spiro quaternary centers and three consecutive stereocenters via a domino Michael/cyclization process. The reaction utilizes 3-isothiocyanato oxindoles as nucleophilic reagents addition to unsaturated pyrazolones, as well as unsaturated isoxazolones with commercially available quinine as catalyst under mild reaction conditions, affording two classes of spirocyclic oxindole compounds in high to excellent yields (90–96%) with moderate to good diastereoselectivities (up to 94:6 dr) and enantioselectivities (64–98% ee). Furthermore, a plausible working model was also proposed on the basis of previous literature and our own investigation to account for the stereochemistry of the domino Michael/cyclization process. We believe that this methodology will be useful in diversity-oriented library synthesis and the subsequent biological evaluation of its members for medicinal chemistry.

4. Experimental section

4.1. General

Reagents were purchased from commercial sources and were used as received unless mentioned otherwise. Reactions were monitored by TLC. ^{1}H NMR and ^{13}C NMR (300 and 75 MHz, respectively) spectra were recorded in $CDCl_3$ and DMSO-d_6. ^{1}H NMR chemical shifts are reported in ppm relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard. Data are reported as follows: chemical shift, multiplicity (s=singlet, br s=broad singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constants (Hertz) and integration. ^{13}C NMR chemical shifts are reported in parts per million from tetramethylsilane (TMS) with the solvent resonance as the internal standard. Melting points were recorded on a Buchi Melting Point B-545.

4.2. General procedure for the synthesis of products 3

In an ordinary vial equipped with a magnetic stirring bar, the compounds **2** (0.12 mmol, 1.2 equiv) and quinine (3.24 mg, 10 mol %, 0.01 mmol) was dissolved in 5.0 mL of freshly distilled toluene at 25 °C, and then oxindoles **1** (0.1 mmol) was added. After completion of the reaction, as monitored by TLC, the reaction mixture was directly purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=10:1∼3:1) to yield products **3**.

4.3. General procedure for the synthesis of products 6

In an ordinary vial equipped with a magnetic stirring bar, the compounds **5** (0.12 mmol, 1.2 equiv) and quinine (3.24 mg, 10 mol %, 0.01 mmol) was dissolved in 5.0 mL of freshly distilled CH_2Cl_2 at −40 °C, and then oxindoles **1** (0.1 mmol) was added. After completion of the reaction, as monitored by TLC, the reaction mixture was directly purified by flash chromatography on silica gel (petroleum ether/ethyl acetate=10:1∼3:1) to yield products **6**.

4.4. Transformation of product 3i into compound 7

To the mixture of **3i** (54.2 mg, 0.1 mmol) and anhydrous K_2CO_3 (15.3 mg, 0.11 mmol) in 5 mL acetone was added CH_3I (6.9 μL, 0.11 mmol) at 0 °C. The resulting mixture was stirred overnight at room temperature and then concentrated in vacuo. The residue was directly purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 3.5:1) to give the compound **7** as white solid.

4.5. Characterization data and HPLC conditions of products 3, 6 and 7

*4.5.1. Compound **3a**.* White solid, 94% yield; 88:12 dr, 90% ee; $[\alpha]_D^{20}$ +17.9 (*c* 1.07, $CHCl_3$); mp 139.2–140.5 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane=30:70, flow rate 1.0 mL/min, λ=254 nm, major diastereomer: t_{minor}=18.4 min, t_{major}=5.7 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major) 2.58 (s, 3H), 3.12 (s, 3H), 4.93 (s, 1H), 6.79 (d, *J*=7.8 Hz, 1H), 6.94 (d, *J*=6.9 Hz, 2H), 7.13–7.22 (m, 5H), 7.36–7.41 (m, 3H), 7.72 (d, *J*=7.5 Hz, 1H), 7.88 (d, *J*=7.8 Hz, 2H), 8.71 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 16.9, 26.6, 61.3, 73.5, 77.5, 108.9, 119.2, 124.2, 124.4, 125.4, 126.3, 127.8, 128.4, 128.5, 128.8, 128.9, 129.6, 130.8, 131.3, 137.5, 143.1, 158.7, 171.3, 173.3, 197.9; IR (KBr): ν 3062, 2962, 1709, 1613, 1596, 1498, 1471, 1365, 1263, 1157, 1100, 1023, 752, 733, 690, 591 cm^{-1}; HRMS (ESI): Calculated for $C_{27}H_{22}N_4NaO_2S$ $[M+Na]^+$: 489.1356, found: 489.1356.

*4.5.2. Compound **3b**.* White solid, 92% yield; 83:17 dr, 91% ee; $[\alpha]_D^{20}$ +23.0 (*c* 1.06, $CHCl_3$); mp 228.9–230.3 °C; the ee was determined by HPLC (Chiralpak AD-H, EtOH/hexane=30:70, flow rate 1.0 mL/min, λ=254 nm, major diastereomer: t_{minor}=10.5 min, t_{major}=5.8 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major) 0.99 (t, *J*=7.2 Hz, 3H), 2.62 (s, 3H), 3.43–3.52 (m, 1H), 3.74–3.83 (m, 1H), 4.90 (s, 1H), 6.77 (d, *J*=7.8 Hz, 1H), 6.91 (d, *J*=7.2 Hz, 2H), 7.08–7.20 (m, 5H), 7.34–7.40 (m, 3H), 7.71 (d, *J*=6.9 Hz, 1H), 7.87–7.90 (m, 2H),

8.63 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 12.0, 17.0, 35.2, 61.8, 73.6, 77.3, 108.9, 119.1, 124.0, 124.6, 125.4, 126.5, 128.0, 128.3, 128.6, 128.7, 128.8, 129.6, 130.7, 131.3, 137.6, 142.2, 158.7, 171.3, 172.7, 198.0; IR (KBr): ν 3123, 2964, 1728, 1613, 1596, 1499, 1468, 1369, 1264, 1216, 1153, 1120, 749, 689, 589 cm^{-1}; HRMS (ESI): Calculated for $C_{28}H_{24}N_4NaO_2S$ $[M+Na]^+$: 503.1512, found: 503.1519.

4.5.3. Compound ***3c***. White solid, 95% yield; 83:17 dr, 92% ee; $[\alpha]_D^{20}$ +17.9 (*c* 1.07, $CHCl_3$); mp 156.3–157.5 °C; the ee was determined by HPLC (Chiralpak AD-H, EtOH/hexane=30:70, flow rate 1.0 mL/min, λ=254 nm, major diastereomer: t_{minor}=7.8 min, t_{major}=5.1 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major) 1.02 (t, *J*=7.2 Hz, 3H), 2.11 (s, 3H), 2.59 (s, 3H), 3.44–3.52 (m, 1H), 3.76–3.85 (m, 1H), 4.86 (s, 1H), 6.68 (s, 1H), 6.76–6.79 (m, 2H), 6.97–7.00 (m, 2H), 7.16–7.21 (m, 2H), 7.34–7.40 (m, 3H), 7.71 (d, *J*=7.5 Hz, 1H), 7.88 (d, *J*=7.8 Hz, 2H), 8.70 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 12.0, 17.0, 21.2, 35.2, 61.6, 73.5, 77.4, 108.9, 119.1, 124.0, 124.6, 124.8, 125.4, 126.4, 126.5, 128.6, 128.7, 128.8, 129.3, 130.4, 130.5, 131.2, 137.5, 138.4, 142.2, 158.8, 171.3, 172.8, 198.0; IR (KBr): ν 3227, 2926, 1721, 1612, 1596, 1490, 1468, 1368, 1215, 1156, 1129, 1101, 754, 689, 656 cm^{-1}; HRMS (ESI): Calculated for $C_{29}H_{26}N_4NaO_2S$ $[M+Na]^+$: 517.1669, found: 517.1669.

4.5.4. Compound ***3d***. White solid, 92% yield; 84:16 dr, 86% ee; $[\alpha]_D^{20}$ +32.7 (*c* 1.20, $CHCl_3$); mp 177.8–178.8 °C; the ee was determined by HPLC (Chiralpak AD-H, EtOH/hexane=20:80, flow rate 1.0 mL/min, λ=254 nm, major diastereomer: t_{minor}=22.7 min, t_{major}=11.7 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major) 0.93 (t, *J*=6.9 Hz, 3H), 2.66 (s, 3H), 3.35–3.42 (m, 1H), 3.50 (s, 3H), 3.56–3.63 (m, 1H), 3.69 (s, 3H), 4.79 (s, 1H), 6.37 (s, 1H), 6.50–6.55 (m, 2H), 6.70 (d, *J*=7.8 Hz, 1H), 7.14–7.19 (m, 2H), 7.32–7.38 (m, 3H), 7.69 (d, *J*=7.5 Hz, 1H), 7.85–7.88 (m, 2H), 8.77 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 12.1, 17.0, 35.1, 55.4, 55.5, 62.3, 73.7, 77.4, 108.8, 111.0, 111.1, 119.0, 120.5, 122.6, 122.7, 123.9, 124.5, 125.4, 126.7, 128.7, 131.1, 137.5, 142.2, 148.6, 149.0, 158.7, 171.4, 172.7, 198.1; IR (KBr): ν 3263, 2931, 1721, 1612, 1595, 1489, 1367, 1270, 1215, 1149, 1026, 755, 690, 656 cm^{-1}; HRMS (ESI): Calculated for $C_{30}H_{28}N_4NaO_4S$ $[M+Na]^+$: 563.1723, found: 563.1706.

4.5.5. Compound ***3e***. Light yellow solid, 95% yield; 88:12 dr, 88% ee; $[\alpha]_D^{20}$ +13.9 (*c* 1.40, $CHCl_3$); mp 148.3–149.7 °C; the ee was determined by HPLC (Chiralpak AD-H, EtOH/hexane=30:70, flow rate 1.0 mL/min, λ=254 nm, major diastereomer: t_{minor}=15.2 min, t_{major}=8.3 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major) 1.05 (t, *J*=6.9 Hz, 3H), 2.63 (s, 3H), 3.45–3.52 (m, 1H), 3.77–3.84 (m, 1H), 4.76 (s, 1H), 5.82 (s, 2H), 6.38–6.51 (m, 3H), 6.77 (d, *J*=7.8 Hz, 1H), 7.15–7.19 (m, 2H), 7.30–7.39 (m, 3H), 7.68 (d, *J*=7.2 Hz, 1H), 7.87 (d, *J*=7.8 Hz, 2H), 8.70 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 12.1, 17.0, 35.2, 62.2, 73.7, 77.6, 101.2, 108.4, 108.9, 119.0, 122.3, 123.7, 124.0, 124.5, 125.4, 126.4, 128.8, 131.3, 137.5, 142.2, 147.9, 158.5, 171.2, 172.9, 198.0; IR (KBr): ν 3243, 2926, 1723, 1612, 1596, 1492, 1366, 1258, 1239, 1106, 1040, 755, 691 cm^{-1}; HRMS (ESI): Calculated for $C_{29}H_{24}N_4NaO_4S$ $[M+Na]^+$: 547.1410, found: 547.1417.

4.5.6. Compound ***3f***. White solid, 94% yield; 87:13 dr, 76% ee; $[\alpha]_D^{20}$ +14.7 (*c* 1.08, $CHCl_3$); mp 145.3–146.8 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane=30:70, flow rate 1.0 mL/min, λ=254 nm, major diastereomer: t_{minor}=13.7 min, t_{major}=5.0 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major) 1.07 (t, *J*=7.2 Hz, 3H), 2.58 (s, 3H), 3.45–3.54 (m, 1H), 3.81–3.88 (m, 1H), 4.83 (s, 1H), 6.80–6.86 (m, 2H), 6.97–7.00 (m, 1H), 7.07 (s, 1H), 7.17–7.22 (m, 2H), 7.29–7.32 (m, 1H), 7.36–7.41 (m, 3H), 7.70 (d, *J*=7.2 Hz, 1H), 7.87 (d, *J*=7.8 Hz, 2H), 8.76 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 12.2, 17.0, 35.3, 60.6, 73.3, 77.1, 109.1, 119.2, 122.8, 124.2, 124.6, 125.6, 126.0, 126.7, 128.8, 130.4, 130.7, 131.5, 131.7, 133.0, 137.4, 142.2, 158.4, 171.0, 172.5, 197.5; IR (KBr): ν 3240, 2977, 2934, 1717, 1613, 1596, 1498, 1469, 1368, 1315, 1215, 1156, 1132, 1100, 754, 690 cm^{-1}; HRMS (ESI): Calculated for $C_{28}H_{23}BrN_4NaO_2S$ $[M+Na]^+$: 581.0617, found: 581.0606.

4.5.7. Compound ***3g***. White solid, 90% yield; 50:50 dr, 91%, 75% ee; $[\alpha]_D^{20}$ +116.2 (*c* 1.00, $CHCl_3$); mp 143.4–144.8 °C; the ee was determined by HPLC (Chiralpak AD-H, EtOH/hexane=20:80, flow rate 1.0 mL/min, λ=254 nm, one diastereomer: t_{minor}=4.7 min, t_{major}=6.7 min; the other diastereomer: t_{minor}=9.3 min, t_{major}=9.8 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ (one diastereomer) 1.11 (t, *J*=7.2 Hz, 3H), 2.44 (s, 3H), 3.48–3.57 (m, 1H), 3.73–3.82 (m, 1H), 5.51 (s, 1H), 6.68 (d, *J*=7.8 Hz, 1H), 6.78–6.82 (m, 1H), 7.19–7.23 (m, 3H), 7.28–7.39 (m, 3H), 7.53 (d, *J*=8.7 Hz, 1H), 7.73 (d, *J*=8.1 Hz, 2H), 8.27 (s, 1H), 8.62 (d, *J*=7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (one diastereomer) 12.2, 14.1, 35.5, 49.8, 73.5, 76.9, 108.7, 119.7, 123.3, 124.6, 125.9, 126.3, 126.8, 128.9, 129.0, 129.2, 131.1, 132.9, 135.4, 135.9, 137.2, 142.2, 158.6, 169.0, 174.0, 196.5; IR (KBr): ν 3204, 2925, 2854, 1716, 1700, 1612, 1595, 1497, 1462, 1366, 1292, 1151, 1128, 1105, 753, 687 cm^{-1}; HRMS (ESI): Calculated for $C_{28}H_{22}Cl_2N_4NaO_2S$ $[M+Na]^+$: 571.0733, found: 571.0742.

4.5.8. Compound ***3h***. White solid, 92% yield; 65:35 dr, 98%, 91% ee; $[\alpha]_D^{20}$ +66.6 (*c* 0.60, $CHCl_3$); mp 228.8–230.3 °C; the ee was determined by HPLC (Chiralpak AD-H, EtOH/hexane=10:90, flow rate 1.0 mL/min, λ=254 nm, major diastereomer: t_{minor}=13.6 min, t_{major}=19.8 min; minor diastereomer: t_{minor}=25.6 min, t_{major}=17.1 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major+minor) 0.58 (t, *J*=7.2 Hz, 2H), 0.86 (t, *J*=7.2 Hz, 1H), 2.42 (s, 2H), 2.78 (s, 1H), 3.21–3.42 (m, 1H), 3.50–3.66 (m, 0.7H), 3.69–3.81 (m, 0.3H), 5.78 (s, 0.7H), 5.92 (s, 0.3H), 6.48–6.53 (m, 1H), 7.02–7.08 (m, 1H), 7.18–7.36 (m, 6.7H), 7.56 (d, *J*=8.1 Hz, 1H), 7.68–7.81 (m, 5H), 8.15 (d, *J*=8.7 Hz, 0.7H), 8.72–8.83 (m, 1.6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major+minor) 11.6, 12.0, 14.3, 17.0, 35.1, 35.2, 49.2, 55.9, 74.3, 74.6, 77.6, 78.0, 108.5, 108.8, 119.1, 119.8, 121.3, 123.4, 124.7, 125.3, 125.5, 125.6, 125.7, 127.2, 128.6, 128.7, 128.8, 129.1, 129.2, 129.3, 130.5, 133.5, 141.8, 158.2, 158.5, 169.8, 171.2, 173.6, 174.4, 197.2, 198.7; IR (KBr): ν 3227, 2926, 1717, 1612, 1596, 1498, 1365, 1215, 1158, 1127, 791, 755, 690 cm^{-1}; HRMS (ESI): Calculated for $C_{32}H_{26}N_4NaO_2S$ $[M+Na]^+$: 553.1669, found: 553.1677.

4.5.9. Compound ***3i***. Light yellow solid, 93% yield; 87:13 dr, 94% ee; $[\alpha]_D^{20}$ −20.1 (*c* 1.10, $CHCl_3$); mp 142.1–143.2 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane=30:70, flow rate 1.0 mL/min, λ=254 nm, major diastereomer: t_{minor}=55.2 min, t_{major}=6.5 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major) 2.69 (s, 3H), 4.50 (d, *J*=15.9 Hz, 1H), 4.97 (s, 1H), 5.11 (d, *J*=15.9 Hz, 1H), 6.62 (d, *J*=7.5 Hz, 1H), 6.81 (d, *J*=6.6 Hz, 2H), 6.97 (d, *J*=7.5 Hz, 2H), 7.11–7.23 (m, 9H), 7.34–7.40 (m, 2H), 7.74 (d, *J*=7.2 Hz, 1H), 7.89 (d, *J*=8.1 Hz, 2H), 8.77 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 17.1, 44.4, 62.1, 73.8, 77.5, 110.0, 119.1, 124.2, 124.5, 125.4, 126.3, 126.6, 126.9, 127.6, 127.7, 128.4, 128.5, 128.6, 128.7, 128.8, 129.0, 130.0, 130.5, 131.3, 134.3, 137.6, 142.5, 158.6, 171.2, 173.2, 198.0; IR (KBr): ν 3245, 2925, 1724, 1613, 1595, 1497, 1363, 1178, 1158, 1130, 1078, 754, 693 cm^{-1}; HRMS (ESI): Calculated for $C_{33}H_{26}N_4NaO_2S$ $[M+Na]^+$: 565.1669, found: 565.1658.

4.5.10. Compound ***3j***. Light yellow solid, 96% yield; 86:14 dr, 87% ee; $[\alpha]_D^{20}$ −28.6 (*c* 1.04, $CHCl_3$); mp 148.3–149.5 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane=30:70, flow rate 1.0 mL/min, λ=254 nm, major diastereomer: t_{minor}=23.3 min, t_{major}=6.0 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major) 2.25 (s, 3H), 2.71 (s, 3H), 4.49 (d, *J*=15.9 Hz, 1H), 4.92 (s, 1H), 5.12 (d, *J*=15.9 Hz, 1H), 6.58 (d, *J*=7.5 Hz, 1H), 6.80 (d, *J*=7.2 Hz, 2H), 6.87–6.93 (m, 4H), 7.13–7.23 (m, 6H), 7.34–7.39 (m, 2H), 7.73 (d, *J*=6.9 Hz, 1H), 7.88 (d, *J*=8.1 Hz, 2H), 8.81 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 17.1, 21.0, 44.3, 62.2, 73.9, 77.6, 109.9, 119.0, 124.1, 124.5, 125.3, 126.3,

126.5, 126.8, 127.2, 127.6, 128.4, 128.5, 128.6, 128.7, 129.2, 129.7, 131.1, 134.3, 137.5, 138.5, 142.4, 158.6, 171.2, 173.3, 198.2; IR (KBr): ν 3228, 2923, 1724, 1613, 1596, 1497, 1468, 1366, 1158, 1126, 755, 732, 691, 667 cm^{-1}; HRMS (ESI): Calculated for $C_{34}H_{28}N_4NaO_2S$ $[M+Na]^+$: 579.1825, found: 579.1807.

*4.5.11. Compound **3k**.* White solid, 95% yield; 83:17 dr, 88% ee; $[\alpha]_D^{20}$ −26.4 (*c* 0.80, $CHCl_3$); mp 123.6–124.8 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane=30:70, flow rate 1.0 mL/min, λ=254 nm, major diastereomer: t_{minor}=17.8 min, t_{major}=6.9 min); ^1H NMR (300 MHz, $CDCl_3$) δ (major) 2.70 (s, 3H), 3.48 (s, 3H), 4.50 (d, *J*=15.9 Hz, 1H), 4.94 (s, 1H), 5.11 (d, *J*=15.9 Hz, 1H), 6.50 (s, 1H), 6.54–6.61 (m, 2H), 6.77–6.84 (m, 3H), 6.98–7.01 (m, 1H), 7.17–7.24 (m, 6H), 7.35–7.40 (m, 2H), 7.74 (d, *J*=7.2 Hz, 1H), 7.89 (d, *J*=7.8 Hz, 2H), 8.84 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 17.1, 44.4, 55.0, 62.0, 73.8, 77.4, 110.0, 113.4, 114.8, 119.1, 120.4, 124.2, 124.5, 125.4, 126.3, 126.6, 126.8, 127.7, 128.8, 130.0, 130.8, 131.3, 131.8, 134.3, 137.5, 142.6, 158.7, 159.7, 171.2, 173.2, 198.0; IR (KBr): ν 3226, 2927, 1718, 1612, 1596, 1485, 1365, 1162, 1131, 1034, 750, 730, 689, cm^{-1}; HRMS (ESI): Calculated for $C_{34}H_{28}N_4NaO_3S$ $[M+Na]^+$: 595.1774, found: 595.1786.

*4.5.12. Compound **3l**.* White solid, 94% yield; 82:18 dr, 91% ee; $[\alpha]_D^{20}$ −19.5 (*c* 1.04, $CHCl_3$); mp 156.3–157.5 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane=30:70, flow rate 1.0 mL/min, λ=254 nm, major diastereomer: t_{minor}=29.5 min, t_{major}=8.4 min); ^1H NMR (300 MHz, $CDCl_3$) δ (major) 2.74 (s, 3H), 3.69 (s, 3H), 4.45 (d, *J*=15.9 Hz, 1H), 4.88 (s, 1H), 5.12 (d, *J*=15.9 Hz, 1H), 6.55–6.63 (m, 3H), 6.73 (d, *J*=6.9 Hz, 2H), 6.91 (d, *J*=8.7 Hz, 2H), 7.15–7.24 (m, 6H), 7.34–7.39 (m, 2H), 7.72–7.76 (m, 1H), 7.86–7.89 (m, 2H), 8.61 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 17.1, 44.3, 55.1, 62.4, 74.0, 77.6, 109.9, 114.4, 119.1, 122.1, 124.2, 124.4, 125.3, 126.4, 126.6, 126.8, 127.7, 128.6, 128.7, 130.0, 131.2, 131.3, 134.3, 137.6, 142.5, 158.5, 159.8, 171.3, 173.3, 198.4; IR (KBr): ν 3244, 2928, 1724, 1612, 1596, 1516, 1488, 1364, 1255, 1181, 1119, 1031, 754, 691 cm^{-1}; HRMS (ESI): Calculated for $C_{34}H_{28}N_4NaO_3S$ $[M+Na]^+$: 595.1774, found: 595.1788.

*4.5.13. Compound **3m**.* White solid, 95% yield; 77:23 dr, 94% ee; $[\alpha]_D^{20}$ +34.8 (*c* 0.80, $CHCl_3$); mp 231.2–232.5 °C; the ee was determined by HPLC (Chiralpak AD-H, EtOH/hexane=30:70, flow rate 1.0 mL/min, λ=254 nm, major diastereomer: t_{minor}=16.7 min, t_{major}=11.2 min); ^1H NMR (300 MHz, $CDCl_3$) δ (major) 2.41 (s, 3H), 3.23 (s, 3H), 3.68 (s, 3H), 4.61 (d, *J*=15.6 Hz, 1H), 5.18 (d, *J*=15.6 Hz, 1H), 5.37 (s, 1H), 6.10–6.13 (m, 1H), 6.17 (d, *J*=2.4 Hz, 1H), 6.69 (d, *J*=7.8 Hz, 1H), 7.01–7.04 (m, 2H), 7.12–7.25 (m, 7H), 7.35–7.40 (m, 2H), 7.73–7.75 (m, 1H), 7.94–7.97 (m, 2H), 8.48 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 16.7, 44.4, 52.8, 55.0, 55.1, 73.0, 98.4, 103.9, 109.6, 111.8, 118.5, 123.9, 124.8, 125.1, 126.2, 126.3, 127.3, 127.5, 127.8, 128.6, 128.7, 128.8, 128.9, 130.9, 131.8, 134.5, 138.0, 142.6, 158.4, 158.7, 160.6, 172.1, 174.1, 198.7; IR (KBr): ν 3255, 2937, 1721, 1613, 1597, 1499, 1468, 1364, 1299, 1210, 1159, 1121, 1032, 754, 692 cm^{-1}; HRMS (ESI): Calculated for $C_{35}H_{30}N_4NaO_4S$ $[M+Na]^+$: 625.1880, found: 625.1897.

*4.5.14. Compound **3n**.* White solid, 94% yield; 81:19 dr, 95% ee; $[\alpha]_D^{20}$ −35.1 (*c* 0.70, $CHCl_3$); mp 139.0–140.3 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane=30:70, flow rate 1.0 mL/min, λ=254 nm, major diastereomer: t_{minor}=21.6 min, t_{major}=6.4 min); ^1H NMR (300 MHz, $CDCl_3$) δ (major) 2.71 (s, 3H), 4.46 (d, *J*=15.9 Hz, 1H), 4.89 (s, 1H), 5.10 (d, *J*=15.9 Hz, 1H), 6.63 (d, *J*=7.5 Hz, 1H), 6.76–6.78 (m, 2H), 6.90 (d, *J*=8.4 Hz, 2H), 7.07 (d, *J*=8.4 Hz, 2H), 7.19–7.25 (m, 6H), 7.35–7.40 (m, 2H), 7.73 (d, *J*=6.6 Hz, 1H), 7.86 (d, *J*=7.8 Hz, 2H), 8.74 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 17.1, 44.4, 61.8, 73.8, 77.3, 110.0. 119.1, 124.3, 124.5, 125.5, 126.0, 126.8, 127.8, 127.9, 128.7, 128.8, 128.9, 129.0, 129.3, 130.0, 131.4, 134.2, 135.0, 137.4, 142.5, 158.2, 171.0, 173.0, 197.9; IR (KBr): ν 3338, 2924, 1721, 1613, 1598, 1496, 1469, 1366, 1159, 1123, 1096, 1015, 754, 690 cm^{-1}; HRMS (ESI): Calculated for $C_{33}H_{25}ClN_4NaO_2S$ $[M+Na]^+$: 599.1279, found: 599.1269.

*4.5.15. Compound **3o**.* White solid, 90% yield; 63:37 dr, 89%, 91% ee; $[\alpha]_D^{20}$ +50.9 (*c* 1.00, $CHCl_3$); mp 209.6–210.8 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane=30:70, flow rate 1.0 mL/min, λ=254 nm, major diastereomer: t_{minor}=25.6 min, t_{major}=7.4 min; minor diastereomer: t_{minor}=18.9 min, t_{major}=11.5 min); ^1H NMR (300 MHz, $CDCl_3$) δ (major) 2.56 (s, 3H), 4.50 (d, *J*=15.9 Hz, 1H), 5.17 (d, *J*=15.9 Hz, 1H), 5.68 (s, 1H), 6.50–6.52 (m, 1H), 6.88–6.97 (m, 4H), 7.16–7.21 (m, 6H), 7.34–7.39 (m, 2H), 7.47 (d, *J*=7.8 Hz, 1H), 7.61 (d, *J*=7.8 Hz, 1H), 7.73 (d, *J*=7.8 Hz, 2H), 8.37 (s, 1H), 8.69–8.72 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 14.6, 44.3, 53.2, 68.1, 73.9, 109.6, 119.7, 123.4, 124.7, 125.7, 126.6, 126.7, 127.1, 127.7, 128.7, 128.8, 129.1, 129.2, 130.3, 130.9, 132.6, 132.9, 134.3, 137.2, 142.4, 158.6, 169.0, 174.7, 197.0; IR (KBr): ν 3336, 2924, 1721, 1613, 1596, 1498, 1469, 1368, 1296, 1158, 1128, 1028, 755, 693 cm^{-1}; HRMS (ESI): Calculated for $C_{33}H_{25}BrN_4NaO_2S$ $[M+Na]^+$: 643.0774, found: 643.0799.

*4.5.16. Compound **3p**.* White solid, 95% yield; 83:17 dr, 80% ee; $[\alpha]_D^{20}$ −20.3 (*c* 1.00, $CHCl_3$); mp 139.5–140.7 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane=30:70, flow rate 1.0 mL/min, λ=254 nm, major diastereomer: t_{minor}=23.1 min, t_{major}=6.3 min); ^1H NMR (300 MHz, $CDCl_3$): δ (major) 2.71 (s, 3H), 4.46 (d, *J*=15.9 Hz, 1H), 4.86 (s, 1H), 5.11 (d, *J*=15.9 Hz, 1H), 6.63 (d, *J*=7.5 Hz, 1H), 6.76–6.78 (m, 2H), 6.84 (d, *J*=8.4 Hz, 2H), 7.19–7.24 (m, 8H), 7.35–7.40 (m, 2H), 7.72–7.75 (m, 1H), 7.86 (d, *J*=7.8 Hz, 2H), 8.76 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 17.1, 44.4, 61.9, 73.7, 77.2, 110.0. 119.1, 123.2, 124.3, 124.5, 125.5, 126.0, 126.8, 127.9, 128.7, 128.8, 128.9, 129.4, 130.3, 131.4, 131.6, 131.7, 132.2, 134.2, 137.4, 142.5, 158.2, 171.0, 173.0, 197.8; IR (KBr): ν 3335, 2925, 1721, 1613, 1596, 1491, 1468, 1366, 1158, 1128, 1079, 1011, 753, 692 cm^{-1}; HRMS (ESI): Calculated for $C_{33}H_{25}BrN_4NaO_2S$ $[M+Na]^+$: 643.0774, found: 643.0749.

*4.5.17. Compound **3q**.* White solid, 95% yield; 56:44 dr, 87%, 82% ee; $[\alpha]_D^{20}$ +66.8 (*c* 0.55, $CHCl_3$); mp 141.7–142.9 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane=30:70, flow rate 1.0 mL/min, λ=254 nm, major diastereomer: t_{minor}=24.4 min, t_{major}=8.1 min; minor diastereomer: t_{minor}=10.0 min, t_{major}=8.8 min); ^1H NMR (300 MHz, $CDCl_3$) δ (major) 2.39 (s, 3H), 4.70 (d, *J*=15.6 Hz, 1H), 4.92 (s, 1H), 5.17 (d, *J*=15.6 Hz, 1H), 5.73 (d, *J*=3.3 Hz, 1H), 5.97–5.98 (m, 1H), 6.68 (d, *J*=7.8 Hz, 1H), 7.00 (s, 1H), 7.09–7.14 (m, 1H), 7.18–7.29 (m, 7H), 7.38–7.43 (m, 2H), 7.83–7.86 (m, 2H), 8.37 (br s, 1H), 8.55 (d, *J*=7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 13.6, 44.5, 49.5, 72.5, 75.0, 109.5, 110.6, 119.5, 123.8, 124.6, 125.6, 127.1, 127.9, 128.8, 128.9, 129.0, 130.8, 134.6, 137.5, 142.3, 144.9, 158.0, 168.6, 174.5, 195.7; IR (KBr): ν 3212, 2923, 1724, 1613, 1596, 1498, 1469, 1365, 1317, 1157, 1125, 1020, 755, 690 cm^{-1}; HRMS (ESI): Calculated for $C_{31}H_{24}N_4NaO_3S$ $[M+Na]^+$: 555.1461, found: 555.1467.

*4.5.18. Compound **3r**.* White solid, 96% yield; 86:14 dr, 85% ee; $[\alpha]_D^{20}$ −3.9 (*c* 1.00, $CHCl_3$); mp 118.5–119.8 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane=30:70, flow rate 1.0 mL/min, λ=254 nm, major diastereomer: t_{minor}=39.3 min, t_{major}=7.8 min); ^1H NMR (300 MHz, $CDCl_3$) δ (major) 2.71 (s, 3H), 4.59 (d, *J*=15.9 Hz, 1H), 5.04 (d, *J*=15.9 Hz, 1H), 5.17 (s, 1H), 6.62 (d, *J*=7.8 Hz, 1H), 6.71 (d, *J*=3.3 Hz, 1H), 6.76–6.80 (m, 1H), 6.86–6.88 (m, 2H), 7.10–7.12 (m, 1H), 7.18–7.29 (m, 6H), 7.36–7.41 (m, 2H), 7.70 (d, *J*=7.2 Hz, 1H), 7.89–7.92 (m, 2H), 8.79 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 17.2, 44.4, 57.4, 73.8, 77.4, 110.0, 119.1, 124.2, 124.5, 125.4, 125.8, 126.4, 126.9, 127.1, 127.7, 127.9, 128.7,

128.8, 131.2, 131.4, 134.3, 137.5, 142.8, 158.4, 170.9, 172.9, 197.6; IR (KBr): ν 3336, 2924, 1721, 1613, 1596, 1497, 1469, 1364, 1316, 1156, 1125, 753, 698 cm^{-1}; HRMS (ESI): Calculated for $C_{31}H_{24}N_4NaO_2S_2$ $[M+Na]^+$: 571.1233, found: 571.1216.

4.5.19. Compound ***3s***. Light yellow solid, 95% yield; 88:12 dr, 93% ee; $[\alpha]_D^{20}$ −38.4 (*c* 1.26, $CHCl_3$); mp 119.7–121.3 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane=30:70, flow rate 1.0 mL/min, λ=254 nm, major diastereomer: t_{minor}=20.8 min, t_{major}=5.0 min); ^1H NMR (300 MHz, $CDCl_3$) δ (major) 2.35 (s, 3H), 2.67 (s, 3H), 4.49 (d, *J*=15.9 Hz, 1H), 4.97 (s, 1H), 5.09 (d, *J*=15.9 Hz, 1H), 6.50 (d, *J*=7.8 Hz, 1H), 6.81 (d, *J*=6.3 Hz, 2H), 6.97 (d, *J*=7.5 Hz, 2H), 7.03–7.23 (m, 8H), 7.36–7.41 (m, 2H), 7.55 (s, 1H), 7.92 (d, *J*=7.8 Hz, 2H), 8.74 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 17.0, 21.0, 44.4, 61.8, 73.8, 77.5, 109.8, 119.1, 125.1, 125.4, 126.2, 126.9, 127.6, 128.3, 128.5, 128.6, 128.7, 128.8, 129.0, 130.0, 130.7, 131.6, 134.2, 134.4, 137.6, 140.1, 158.7, 171.3, 173.2, 197.9; IR (KBr): ν 3255, 2923, 2854, 1715, 1613, 1597, 1499, 1363, 1178, 1131, 818, 751, 696, 595 cm^{-1}; HRMS (ESI): Calculated for $C_{34}H_{28}N_4NaO_2S$ $[M+Na]^+$: 579.1825, found: 579.1828.

4.5.20. Compound ***3t***. White solid, 98% yield; >99:1 dr, 2% ee; mp 215.8–217.2 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane=30:70, flow rate 1.0 mL/min, λ=254 nm, t_{minor}=9.6 min, t_{major}=7.2 min); ^1H NMR (300 MHz, DMSO-d_6) δ 1.02 (s, 3H), 1.32 (s, 3H), 2.35 (s, 3H), 3.13 (s, 3H), 7.06–7.25 (m, 3H), 7.38–7.47 (m, 3H), 7.77–7.85 (m, 3H), 11.21 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 18.1, 26.4, 26.6, 26.7, 48.2, 77.7, 80.4, 109.1, 118.6, 122.3, 125.3, 125.8, 127.1, 129.0, 130.4, 137.1, 143.7, 158.7, 170.2, 174.4, 196.5; IR (KBr): ν 3125, 3055, 2975, 1728, 1615, 1532, 1490, 1471, 1371, 1352, 1273, 1186, 1152, 1113, 1088, 1047, 761, 752, 690 cm^{-1}; HRMS (ESI): Calculated for $C_{23}H_{22}N_4NaO_2S$ $[M+Na]^+$: 441.1356, found: 441.1356.

4.5.21. Compound ***6a***. White solid, 95% yield; 90:10 dr, 74% ee; $[\alpha]_D^{20}$ −1.1 (*c* 1.10, $CHCl_3$); mp 110.2–111.7 °C; the ee was determined by HPLC (Chiralpak AS-H, *i*-PrOH/hexane=50:50, flow rate 1.0 mL/min, λ=254 nm, major diastereomer: t_{minor}=39.2 min, t_{major}=13.3 min); ^1H NMR (300 MHz, $CDCl_3$) δ (major) 2.43 (s, 3H), 3.13 (s, 3H), 4.75 (s, 1H), 6.81 (d, *J*=7.8 Hz, 1H), 6.92 (d, *J*=7.2 Hz, 2H), 7.08–7.23 (m, 4H), 7.35–7.43 (m, 1H), 7.63 (d, *J*=7.2 Hz, 1H), 8.56 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 14.8, 26.7, 61.5, 73.5, 74.1, 109.3, 124.2, 124.4, 125.3, 127.7, 128.8, 129.0, 129.2, 129.4, 129.5, 131.7, 143.1, 164.9, 172.9, 176.5, 195.3; IR (KBr): ν 3205, 2937, 1787, 1728, 1613, 1506, 1376, 1353, 1197, 1157, 1101, 875, 750, 699 cm^{-1}; HRMS (ESI): Calculated for $C_{21}H_{17}N_3NaO_3S$ $[M+Na]^+$: 414.0883, found: 414.0883.

4.5.22. Compound ***6b***. White solid, 96% yield; 94:6 dr, 77% ee; $[\alpha]_D^{20}$ −18.6 (*c* 1.10, $CHCl_3$); mp 110.5–111.9 °C; the ee was determined by HPLC (Chiralpak OD-H, *i*-PrOH/hexane=10:90, flow rate 1.0 mL/min, λ=254 nm, major diastereomer: t_{minor}=11.7 min, t_{major}=16.6 min); ^1H NMR (300 MHz, $CDCl_3$) δ (major) 2.56 (s, 3H), 4.53 (d, *J*=15.9 Hz, 1H), 4.79 (s, 1H), 5.07 (d, *J*=15.9 Hz, 1H), 6.65 (d, *J*=7.8 Hz, 1H), 6.84 (d, *J*=6.9 Hz, 2H), 6.94 (d, *J*=7.5 Hz, 2H), 7.09–7.31 (m, 8H), 7.65 (d, *J*=6.9 Hz, 1H), 8.66 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 14.9, 44.4, 62.3, 73.8, 74.0, 110.2, 124.3, 124.4, 125.4, 126.9, 127.8, 128.3, 128.8, 128.9, 129.0, 129.2, 129.3, 129.7, 131.6, 134.1, 142.5, 164.9, 172.9, 176.4, 195.4; IR (KBr): ν 3317, 3062, 3032, 2926, 1790, 1728, 1613, 1487, 1469, 1367, 1178, 1120, 1081, 1013, 877, 748, 697 cm^{-1}; HRMS (ESI): Calculated for $C_{27}H_{21}N_3NaO_3S$ $[M+Na]^+$: 490.1196, found: 490.1195.

4.5.23. Compound ***6c***. White solid, 93% yield; 93:7 dr, 77% ee; $[\alpha]_D^{20}$ −33.8 (*c* 0.40, $CHCl_3$); mp 136.2–137.6 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane=30:70, flow rate 1.0 mL/min, λ=254 nm, major diastereomer: t_{minor}=7.3 min, t_{major}=5.0 min); ^1H NMR (300 MHz, $CDCl_3$) δ (major) 2.28 (s, 3H), 2.56 (s, 3H), 4.52 (d, *J*=15.9 Hz, 1H), 4.74 (s, 1H), 5.08 (d, *J*=15.9 Hz, 1H), 6.63 (d, *J*=7.8 Hz, 1H), 6.82–6.85 (m, 3H), 6.95 (d, *J*=8.1 Hz, 2H), 7.15–7.27 (m, 6H), 7.64 (d, *J*=7.2 Hz, 1H), 8.66 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 15.0, 21.0, 44.4, 62.4, 73.9, 74.1, 110.2, 124.3, 124.4, 125.4, 126.0, 126.9, 127.8, 128.3, 128.7, 128.9, 129.3, 130.0, 131.6, 134.1, 139.2, 142.5, 165.0, 172.9, 176.5, 195.6; IR (KBr): ν 3332, 2923, 1790, 1727, 1613, 1488, 1469, 1369, 1179, 1116, 1080, 1013, 877, 752, 696 cm^{-1}; HRMS (ESI): Calculated for $C_{28}H_{23}N_3NaO_3S$ $[M+Na]^+$: 504.1352, found: 504.1350.

4.5.24. Compound ***6d***. Yellow solid, 94% yield; 92:8 dr, 73% ee; $[\alpha]_D^{20}$ −38.4 (*c* 1.13, $CHCl_3$); mp 108.5–109.8 °C; the ee was determined by HPLC (Chiralpak OD-H, *i*-PrOH/hexane=10:90, flow rate 1.0 mL/min, λ=254 nm, major diastereomer: t_{minor}=15.1 min, t_{major}=19.8 min); ^1H NMR (300 MHz, $CDCl_3$) δ (major) 2.60 (s, 3H), 3.72 (s, 3H), 4.48 (d, *J*=15.9 Hz, 1H), 4.71 (s, 1H), 5.08 (d, *J*=15.9 Hz, 1H), 6.60–6.66 (m, 3H), 6.77 (d, *J*=7.2 Hz, 2H), 6.87 (d, *J*=8.7 Hz, 2H), 7.13–7.27 (m, 5H), 7.63 (d, *J*=7.2 Hz, 1H), 8.63 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 15.0, 44.3, 55.1, 62.6, 74.0, 74.2, 110.1, 114.6, 114.7, 120.7, 124.2, 124.3, 125.4, 126.8, 127.8, 128.7, 129.9, 131.5, 134.1, 137.0, 142.5, 149.6, 160.1, 165.0, 172.9, 176.5, 195.7; IR (KBr): ν 3249, 2926, 1790, 1727, 1612, 1587, 1516, 1488, 1469, 1369, 1257, 1181, 1119, 1030, 878, 754, 699 cm^{-1}; HRMS (ESI): Calculated for $C_{28}H_{23}N_3NaO_4S$ $[M+Na]^+$: 520.1301, found: 520.1296.

4.5.25. Compound ***6e***. White solid, 94% yield; 92:8 dr, 67% ee; $[\alpha]_D^{20}$ −26.8 (*c* 1.00, $CHCl_3$); mp 192.5–193.8 °C; the ee was determined by HPLC (Chiralpak OD-H, *i*-PrOH/hexane=10:90, flow rate 1.0 mL/min, λ=254 nm, major diastereomer: t_{minor}=13.0 min, t_{major}=18.1 min); ^1H NMR (300 MHz, $CDCl_3$) δ (major) 2.59 (s, 3H), 4.51 (d, *J*=15.9 Hz, 1H), 4.73 (s, 1H), 5.06 (d, *J*=15.9 Hz, 1H), 6.67 (d, *J*=7.8 Hz, 1H), 6.80–6.85 (m, 3H), 6.90–6.93 (m, 2H), 7.17–7.31 (m, 6H), 7.65 (d, *J*=7.2 Hz, 1H), 8.63 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 14.9, 44.4, 62.1, 73.8, 74.0, 110.2, 116.4 (d, *J*=21.5 Hz, 1C), 124.3, 124.4, 125.2, 126.7, 126.9, 128.0, 128.7, 128.8, 128.9, 130.5 (d, *J*=8.3 Hz, 1C), 131.8, 134.1, 136.7, 142.5, 148.4, 163.1 (d, *J*=250.1 Hz, 1C), 164.7, 172.7, 176.3, 195.3; IR (KBr): ν 3198, 3063, 2922, 1794, 1732, 1612, 1512, 1490, 1470, 1366, 1237, 1202, 1163, 1126, 1105, 1080, 1013, 880, 753, 698 cm^{-1}; HRMS (ESI): Calculated for $C_{27}H_{20}FN_3NaO_3S$ $[M+Na]^+$: 508.1102, found: 508.1094.

4.5.26. Compound ***6f***. Light yellow solid, 92% yield; 89:11 dr, 68% ee; $[\alpha]_D^{20}$ −1.9 (*c* 1.20, $CHCl_3$); mp 158.7–160.2 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane=30:70, flow rate 1.0 mL/min, λ=254 nm, major diastereomer: t_{minor}=10.4 min, t_{major}=6.4 min); ^1H NMR (300 MHz, $CDCl_3$) δ (major) 2.61 (s, 3H), 4.61 (d, *J*=15.9 Hz, 1H), 4.95 (d, *J*=15.9 Hz, 1H), 5.03 (s, 1H), 6.67 (d, *J*=7.8 Hz, 1H), 6.72 (d, *J*=3.0 Hz, 1H), 6.80–6.90 (m, 3H), 7.17–7.31 (m, 6H), 7.64 (d, *J*=7.5 Hz, 1H), 8.40 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major) 15.1, 44.4, 57.9, 73.8, 74.0, 110.2, 124.3, 124.4, 126.7, 127.0, 127.1, 127.3, 127.9, 128.6, 128.8, 128.9, 129.2, 129.8, 131.8, 134.1, 142.8, 164.7, 172.5, 176.2, 195.1; IR (KBr): ν 3106, 2954, 1793, 1713, 1614, 1498, 1433, 1378, 1331, 1304, 1199, 1158, 1125, 1084, 1015, 888, 756, 702 cm^{-1}; HRMS (ESI): Calculated for $C_{25}H_{19}N_3NaO_3S_2$ $[M+Na]^+$: 496.0760, found: 496.0752.

4.5.27. Compound ***6g***. Light yellow solid, 93% yield; 60:40 dr, 64%, 53% ee; $[\alpha]_D^{20}$ −18.3 (*c* 1.00, $CHCl_3$); mp 136.2–137.5 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane=30:70, flow rate 1.0 mL/min, λ=254 nm, minor diastereomer: t_{minor}=12.2 min, t_{major}=19.6 min; major diastereomer: t_{minor}=10.4 min, t_{major}=5.7 min); ^1H NMR (300 MHz, $CDCl_3$) δ (major+minor) 2.36 (s, 2.2H), 2.74 (s, 0.8H), 4.28 (d, *J*=15.9 Hz, 0.7H), 4.42 (d, *J*=15.9 Hz, 0.3H), 4.99 (d, *J*=15.9 Hz, 0.7H), 5.08 (d, *J*=15.9 Hz, 0.3H), 5.79 (s,

0.7H), 5.89 (s, 0.3H), 6.31–6.41 (m, 2.4H), 6.61 (d, J=7.5 Hz, 0.6H), 6.72–6.77 (m, 1.4H), 6.96–7.01 (m, 0.6H), 7.07–7.38 (m, 4.3H), 7.48–7.59 (m, 2.3H), 7.66 (d, J=8.4 Hz, 1H), 7.75–7.87 (m, 2H), 8.12 (d, J=8.4 Hz, 0.7H), 8.46 (s, 0.3H), 8.53 (s, 0.7H), 8.61–8.64 (m, 0.7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major+minor) 12.5, 15.0, 44.3, 44.4, 48.9, 55.9, 74.3, 74.5, 74.7, 109.9, 110.2, 120.9, 121.7, 123.8, 124.2, 124.3, 124.5, 124.9, 125.0, 125.1, 125.3, 126.1, 126.2, 126.5, 127.1, 127.4, 127.5, 127.7, 127.8, 128.1, 128.5, 128.6, 128.8, 128.9, 129.0, 129.5, 129.9, 130.3, 131.1, 131.6, 132.1, 132.2, 133.6, 133.8, 133.9, 140.0, 142.2, 142.5, 164.6, 164.9, 173.6, 174.3, 174.4, 176.4, 194.9, 196.2; IR (KBr): ν 3224, 3062, 2926, 1787, 1727, 1613, 1490, 1371, 1204, 1158, 1119, 1079, 1011, 877, 751, 697 cm^{-1}; HRMS (ESI): Calculated for $C_{31}H_{23}N_3NaO_3S$ $[M+Na]^+$: 540.1352, found: 540.1350.

4.5.28. Compound ***7****.*[4d] White solid, 82% yield; >99:1 dr, 86% ee; $[\alpha]_D^{20}$ +33.5 (c 1.00, $CHCl_3$); the ee was determined by HPLC (Chiralpak AD-H, i-PrOH/hexane=40:60, flow rate 1.0 mL/min, λ=254 nm, t_{minor}=16.6 min, t_{major}=6.3 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.52 (s, 3H), 2.64 (s, 3H), 4.60 (d, J=15.9 Hz, 1H), 4.98 (s, 1H), 5.21 (d, J=15.9 Hz, 1H), 6.72 (d, J=7.5 Hz, 1H), 6.94 (d, J=7.5 Hz, 2H), 7.00–7.03 (m, 2H), 7.09 (t, J=7.5 Hz, 2H), 7.15–7.25 (m, 7H), 7.45 (t, J=7.8 Hz, 2H), 7.64 (d, J=6.9 Hz, 1H), 8.01 (d, J=8.1 Hz, 2H).

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.01.036.

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