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Organocatalytic One-Pot Asymmetric Synthesis of Thiolated Spiro-γ-lactam Oxindoles Bearing Three Stereocenters

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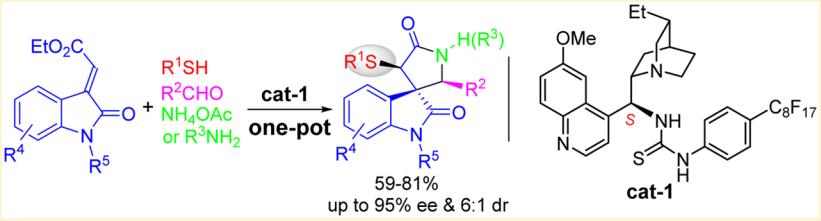
Supporting Information



ABSTRACT: The first asymmetric synthesis of spiro-γ-lactam oxindoles bearing three stereocenters is reported. One-pot thiol-Michael/Mannich/lactamization reactions promoted by a recyclable fluorous bifunctional cinchona alkaloid/thiourea organocatalyst afford products in moderate to good yields with up to 95% ee and 6:1 dr.

INTRODUCTION

The privileged γ-lactam scaffold can be found in a number of biologically active compounds[1] such as natural product lactacystin **A**,[2] synthetic p53-HDMA inhibitor **B**,[3] racemic antituberculosis agent **C**,[4] and CRTH2 receptor antagonist **D**[5] (Figure 1). These compounds are thiolated γ-lactams or have a spirooxindole skeleton.[6] The development of new methods for efficient synthesis of thiolated spiro-γ-lactam analogs bearing multiple stereocenters is desirable for both synthetic and medicinal chemistry considerations.

A number of diastereoselective[7] and enantioselective[8] methods for spiro-γ-lactam oxindoles have been reported. Among the methods for asymmetric synthesis, organocatalytic [3 + 2] annulation of imines and enals (Scheme 1, A)[9] or Michael addition-initiated cascade reactions of 3-aminooxindoles and α,β-unsaturated acyl phosphonates (Scheme 1, B)[10] are two general protocols for spiro-γ-lactam oxindoles **1** bearing two stereocenters. These methods have also been applied for asymmetric synthesis of spiroheterocyclic oxindoles including spiro-γ-thiolactam oxindoles,[11] spiro-δ-lactam oxindoles,[12] spiro-γ-lactone oxindoles,[13] spiro-δ-lactone oxindoles,[14] and spiropyrrolidine oxindoles.[15] To the best of our knowledge, there is no synthetic method for spiro-γ-lactam oxindoles bearing more than two stereocenters. Introduced in this paper is the first reaction sequence for spiro-γ-lactam oxindoles **2** bearing three contiguous stereocenters, including one quaternary and two tertiary carbons, on the γ-lactam ring.

RESULTS AND DISCUSSION

The proposed one-pot thiol-Michael/Mannich/lactamization reaction shown in Table 1 was initiated by an organocatalytic thiol-Michael addition of benzenethiol **3a** and (*E*)-ethyl 2-(1-methyl-2-oxoindolin-3-ylidene)acetate **4a**.[16] The reaction mixture containing **5a** was used directly for the Mannich reaction with an imine generated in situ from benzaldehyde **6a** and NH_4OAc. Compound **7a** resulting from the Mannich reaction was cyclized to form spiro-γ-lactam oxindole **2a**. During the method development, seven catalysts (**cat-1** to **cat-7**) including the reported recyclable fluorous catalyst **cat-1**[17] were screened for the thiol-Michael addition of 4-methylbenzenethiol **3a** and oxindole **4** using toluene as a solvent (Table 1, entries 1−7). After 3 h at room temperature, the solution of **5a** was reacted with NH_4OAc and benzaldehyde **6a** in the presence of piperidine for the Mannich reaction at 40 °C for 12 h. EtOH was used as a cosolvent to improve substrate solubility. It was found that reactions with **cat-1**, **cat-2**, **cat-5**, and **cat-7** gave product **2a** around 90% yields (Table 1, entries 1, 2, 5, and 7) with around 55% ee and >1.25:1 dr. Because **cat-1** is recyclable, it was used as the catalyst for reaction condition optimization at lower temperaure for better stereoselectivity. Different bases (piperidine, DBU, Et_3N) and cosolvents (EtOH, MePh, CH_2Cl_2, MeCN, H_2O) were tested for the Mannich reactions. It was found that the Michael addition in MePh at −20 °C followed by the Mannich/lactamization reactions at 25 °C with 0.5 equiv of piperidine and EtOH as a cosolvent gave spiro-γ-

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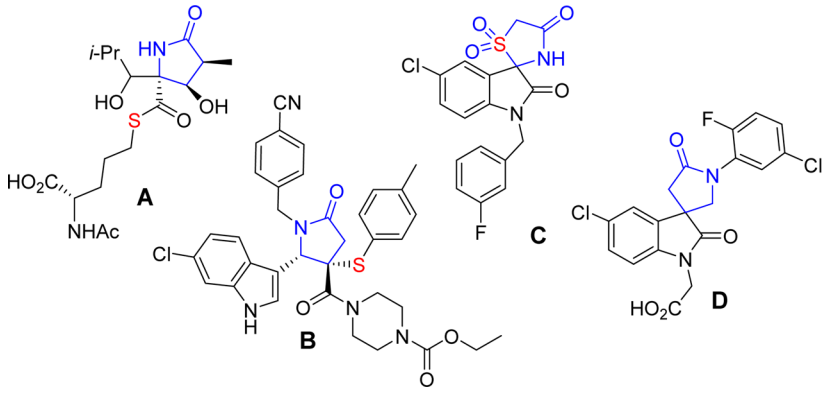
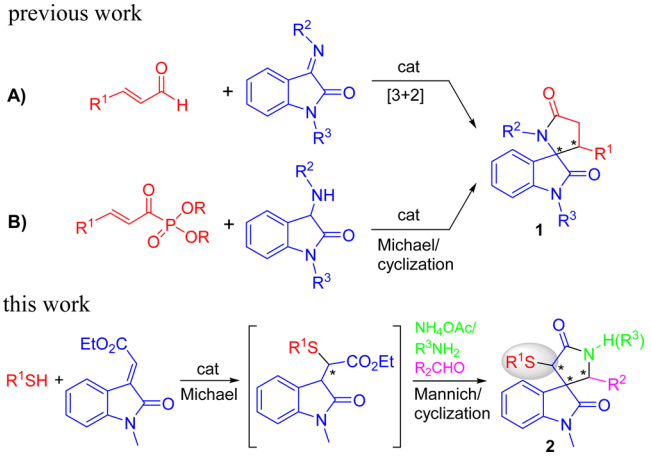


Figure 1. Biologically active γ-lactams and spirooxindoles.

Scheme 1. Asymmetric Synthetic Methods for Spiro-γ-lactam Oxindoles



lactam oxindole **2a** in 77% yield with 83% ee and 6:1 dr (Table 1, entry 12). An improved ee of 93% was obtained using a modified reaction procedure of mixing **4** and **cat-1** under −20 °C for 1 h before dropwise addition of ice-cold 4-methylbenzenethiol **3** solution in MePh (Table 1, entry 13). This process allows better interaction of oxindole **4** with **cat-1** before the addition of **3**. Without using a base for the Mannich reaction, product yield dropped to 17% (Table 1, entry 16). Using CH_2Cl_2, MeCN, or H_2O as a cosolvent for the Mannich reaction, product yields decreased to 23−65%, but it has no significant impact on ee and dr (Table 1, entries 17−20). It is noteworthy that a control reaction without **cat-1** for the Mannich/cyclization reactions gave **2a** in slightly lower yield of 73% (entry 21) but with similar 92% ee and 6:1 dr as that of the reaction of with **cat-1** shown in entry 13. The result indicates that for the second step of the Mannich reaction the stereochemistry was controlled by asymmetric coumpound **5** instead of **cat-1**. Catalyst recovery was carried out by loading the concentrated reaction mixture onto a fluorous silica gel cartridge for solid-phase extraction (F-SPE).[18] There was an 80:20 MeOH/H_2O fraction for the product and a 100% MeOH fraction for fluorous catalyst **cat-1**. The catalyst recovered from the concentrated MeOH fraction has an average yield of 91% and a purity >97%.

The scope of the cascade thiol-Michael/Mannich/cyclization reactions was investigated by synthesizing 14 analogues of **2** using different thiols as Michael donors and different amines and aldehydes for the Mannich reactions (Table 2). The reactions proceeded smoothly to afford products **2a−n** in moderate to good yields and stereoselectivities. Reactions with both electron-withdrawing (F, CF_3) and electron-donating (*t*-Bu, SMe) groups at the *para*-position of benzaldehydes **6** gave products **2b−f** in 68−81% yields with >87% ee and >4:1 dr. A reaction with a heterocyclic aldehyde gave **2g** in 75% yield with good stereoselectivity. The reactions of aliphatic aldehydes such as cyclopropanecarbaldehyde and acetaldehyde gave products **2h** and **2i** in moderate yields and >83% ee, but the dr was <3:1. The low diastereoselectivity may result from the small steric hindrance of cyclopropyl and methyl groups of the aldehydes. The reaction of *N*-unsubstituted oxindole gave **2j** in 57% yield with 1.5:1 dr. Benzylic thiol was also used as the nucleophile, which gave products **2k** in good yield and ee, but the dr value was only 2:1. Interestingly, when an aliphatic thiol was used as a nucleophile for **2l**, the ee of the major diastereomer was only 33%, but the ee of the minor isomer was still as high as 86%. Reactions with substituted substrates **4** were also studied, and the resulting product **2m** and **2n** gave moderate yields and good ee. A scale up reaction using 0.5 g of **4** was carried out under slightly revised conditions (Scheme 2) to give **2a** in a consistent yield of 82% and 6:1 dr but a lower ee value of 72% compared with that of a small-scale reaction shown in Table 2. Further optimization might be needed to improve the ee of the scale-up reaction. The reaction using formaldehyde and allylamine was attempted. Highly reactive formaldehyde reduced the time of the Mannich reaction to 3 h to afford *N*-allylated product **2o** in 87% yield with 89% ee and 4:1 dr (Scheme 3). The relative configuration of spiro-γ-lactam oxindole products **2** was determined on the basis of the NOE experiment of the major diastereomer of **2e** (see the Supporting Information) and also by obtaining the X-ray structure of **2d** (Figure 2, CCDC 1452249). Our attempt at introducing an amino acid as a chiral auxiliary to **2d** was not successful. We have to rely on literature information to determine the absolute configuration of **2d**. It was found that a similar thiol-Michael addition of oxindole **4** using a catalyst with an inversed (*R*)-C9 stereocenter has been reported by the Zhao group.[16g] The absolute configuration of thiolated stereocenter was assigned as *S* via the XRD study. On the basis of this information, we determined the absolute configuration of thiolated stereocenter of **2d** as *R*, and the other two stereocenters were demetrmined by the X-ray structure of **2d**.

A possible organocatalytic reaction mechanism for the one-pot Michael/Mannich/lactamization process is proposed in Scheme 4. Fluorous **cat-1** bearing an (*S*)-C9 stereocenter forms

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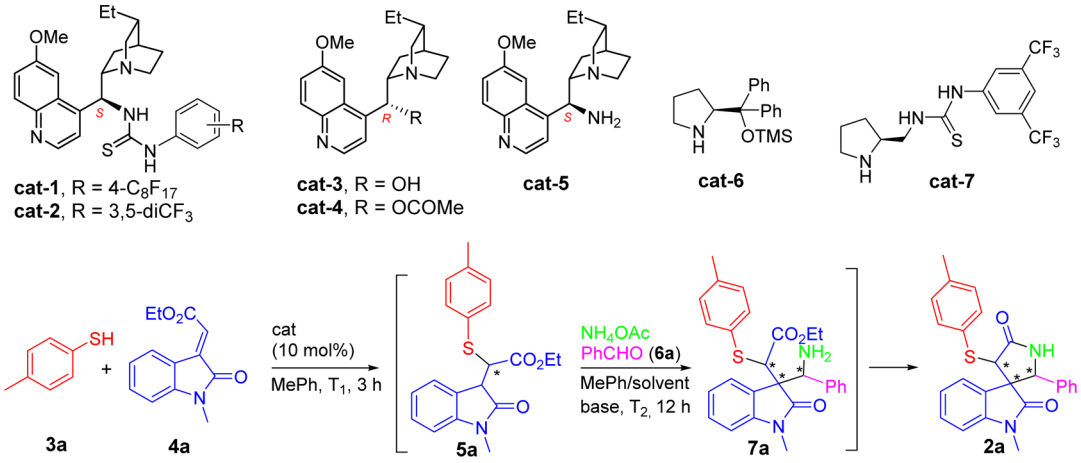
Table 1. Optimization of One-Pot Thiol-Michael/Mannich/Cyclization Reactions[a]



entry	catalyst	T_1 (°C)	T_2 (°C)	base (0.5 equiv)	solvent[b]	**2a** (%)[c]	ee[d] (%)	dr[e]
1	**cat-1**	25	40	piperidine	EtOH	90	56 (43)	1.5:1
2	**cat-2**	25	40	piperidine	EtOH	91	57 (40)	1.25:1
3	**cat-3**	25	40	piperidine	EtOH	87	−17 (−33)	1.25:1
4	**cat-4**	25	40	piperidine	EtOH	83	−32 (−35)	1.25:1
5	**cat-5**	25	40	piperidine	EtOH	90	21 (9)	1.25:1
6	**cat-6**	25	40	piperidine	EtOH	79	3 (8)	2:1
7	**cat-7**	25	40	piperidine	EtOH	92	55 (47)	1.5:1
8	**cat-1**	25	25	piperidine	EtOH	87	54 (45)	2:1
9	**cat-1**	25	0	piperidine	EtOH	35	89 (82)	2:1
10	**cat-1**	0	25	piperidine	EtOH	89	69	3:1
11	**cat-1**	−10	25	piperidine	EtOH	80	72	6:1
12	**cat-1**	−20	25	piperidine	EtOH	77	83	6:1
13	**cat-1**	**−20**	**25**	**piperidine**	**EtOH**	**78**	**93**[f]	**6:1**
14	**cat-1**	−20	25	DBU	EtOH	37	79 (82)	1.25:1
15	**cat-1**	−20	25	Et_3N	EtOH	59	87	4:1
16	**cat-1**	−20	25	none	EtOH	17		1.25:1
17	**cat-1**	−20	25	piperidine	CH_2Cl_2	57	91	6:1
18	**cat-1**	−20	25	piperidine	CH_3CN	65	90	5:1
19	**cat-1**	−20	25	piperidine	MePh	55	93	5:1
20	**cat-1**	−20	25	piperidine	H_2O	23	93	5:1
21[g]	**cat-1**	−20	25	piperidine	EtOH	73	92	6:1

[a]Reaction of 0.1 mmol of **4** in 0.5 mL of MePh, 1:1:1:1.2 of **3a**:**4**:**6a**:NH_4OAc. [b]1:1.5 MePh/solvent. [c]Isolated yield for both diastereomers. [d]ee determined by HPLC on a Venusil Chiral CA column with a mobile phase of 90:10 hexane/*i*-PrOH; ee of the minor diastereomer is in parentheses; negative ee for opposite ratio of the enantiomers. [e]Determined by ^{1}H NMR. [f]Mixing **4** and **cat-1** for 1 h before addition of ice-cold **3a** in toluene. [g]After the thiol-Michael addition reaction, **cat-1** was removed by F-SPE.

a complex with the substrates to induce the *Re* face Michael addition to form **5**. This step is similar to that reported by the Zhao group.[16g] The formation of a (*R*)-thiolated stereocenter of **5** is highly selective, and 1:1−1:1.5 dr of **5** result from the α-carbon of the carbonyl. The Mannich reaction of **5** with an in situ generated imine to form **7** and **7′**, which then cyclize to form spiro-γ-lactam oxindoles **2** (major) and its diasmereomer **2′** (minor), each bearing three stereocenters. A control reaction without using **cat-1** (Table 1, entry 21) indicated that the stereocontrol of the Mannich/cyclization reactions resulted from the enantioenriched intermediate **5** instead of **cat-1**. We believe the spirocarbon is responsible for the formation two diastereomers (1.2:1−6:1 dr) of the final products. Good evidence was obtained from **2o** as shown in Scheme 3. This compound only has two stereocenters but also has two diastereomers in 4:1 ratio. This result eliminates the possibility of the carbon connected to R^2 for forming diastereomers. The stereochemistry of spiro-δ-lactam oxindoles reported in our previous work also supports the diastereomer assigments for products **2**.[12a]

In summary, the first asymmetric synthesis of substituted spiro-γ-lactam oxindoles through a thiol-Michael/Mannich/lactamization sequence is developed. The one-pot reaction promoted by a recyclable fluorous organocatalyst efficiently generates four bonds and three contiguous stereocenters in diastereo- and enantiocontrolled manners. This method could be used for making novel spiro-γ-lactam oxindoles for biological screening. Extension of this method for other thiolated spiroheterocyclic oxindoles is under investigation and will be reported in due course.

EXPERIMENTAL SECTION

General Information. Chemicals and solvents were purchased from commercial suppliers and used as received. Final products were purified on a pre-LC system with a C18 column. All isolated products were characterized on the basis of ^{1}H NMR and ^{13}C NMR spectroscopic data and HRMS data. ^{1}H NMR and ^{13}C NMR chemical

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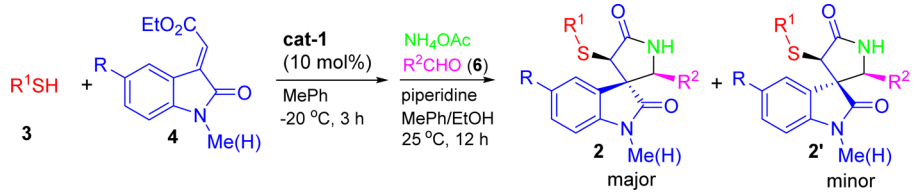
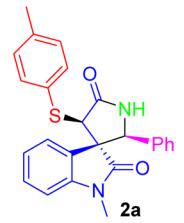
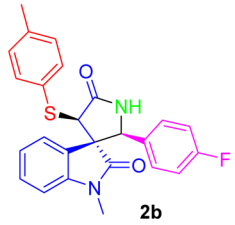
Table 2. One-Pot Synthesis of Spiro-γ-lactam Oxindoles[a,b]

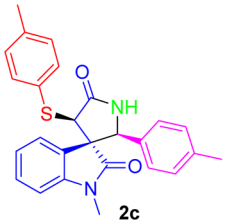




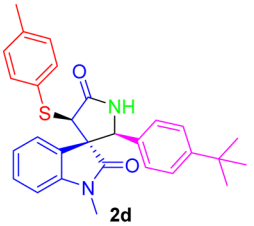
78%, 93% ee, 6:1 dr



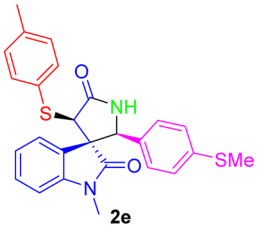
79%, 87% ee, 6:1 dr



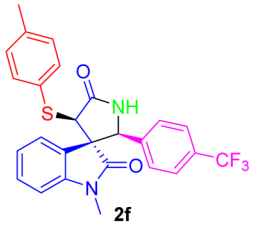
72%, 94% ee, 4:1 dr



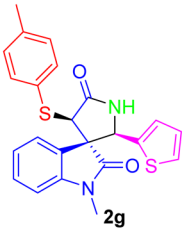
68%, 94% ee, 5:1 dr



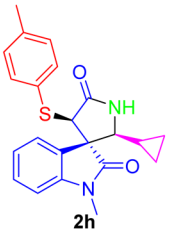
71%, 91% ee, 5:1 dr



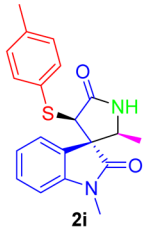
81%, 89% ee, 6:1 dr



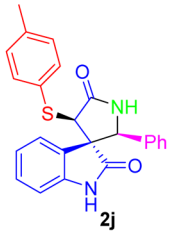
75%, 82% ee, 6:1 dr



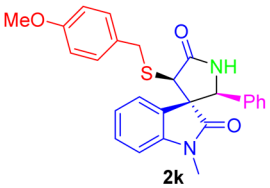
67%, 85% (71%)[c] ee, 3:1 dr



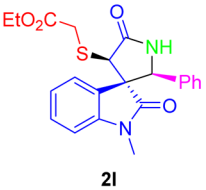
59%, 83% (80%)[c] ee
2.5:1 dr



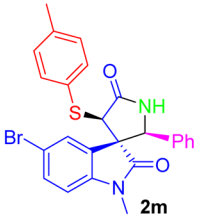
57%, 95% (73%)[c] ee
1.5:1 dr



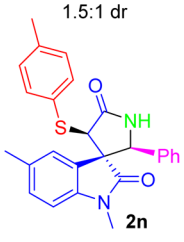
73%, 87% ee, 2:1 dr



78%, 33% (86%)[c] ee
1.2:1 dr



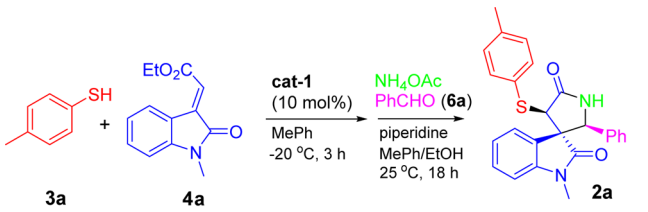
62%, 86% ee, 5:1 dr



71%, 83% ee, 4:1 dr

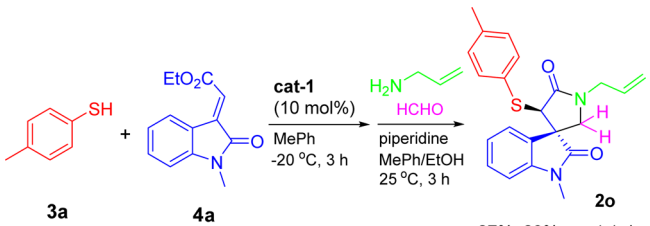
[a]See the Supporting Information for the one-pot reaction procedure. [b]Islotaled yield of diastereomeric mixture. [c]ee of the minor diastereomer is in parentheses.

Scheme 2. Scale-up Reaction for Asymmetric Synthesis of 2a



82%, 6:1 dr, 72% ee

Scheme 3. Synthesis of *N*-Allyl Product 2o



87%, 89% ee, 4:1 dr

shifts are reported in ppm using tetramethylsilane (TMS) as an internal standard. The enantiomeric excess (ee) values of products were determined by HPLC with different chiral columns.

General Procedure for the Synthesis of Racemic Spirocylic Oxindoles 2. To a solution of **3** (0.1 mmol) and oxindole **4** (0.1 mmol, 1.0 equiv) in 0.5 mL of toluene was added Et_3N (0.05 mmol, 0.5 equiv). After the reaction mixture was stirred at 25 °C for 1 h, a

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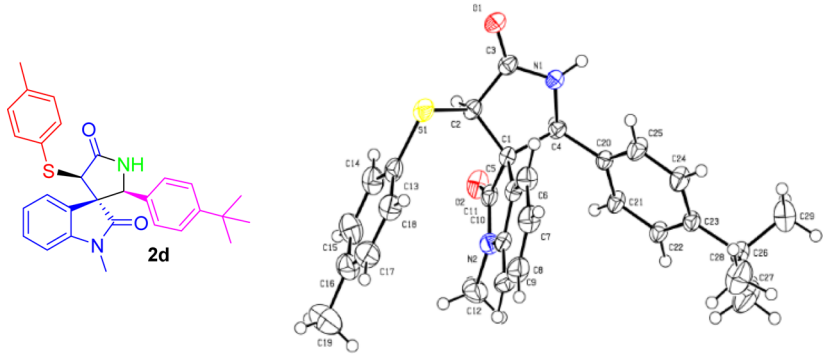
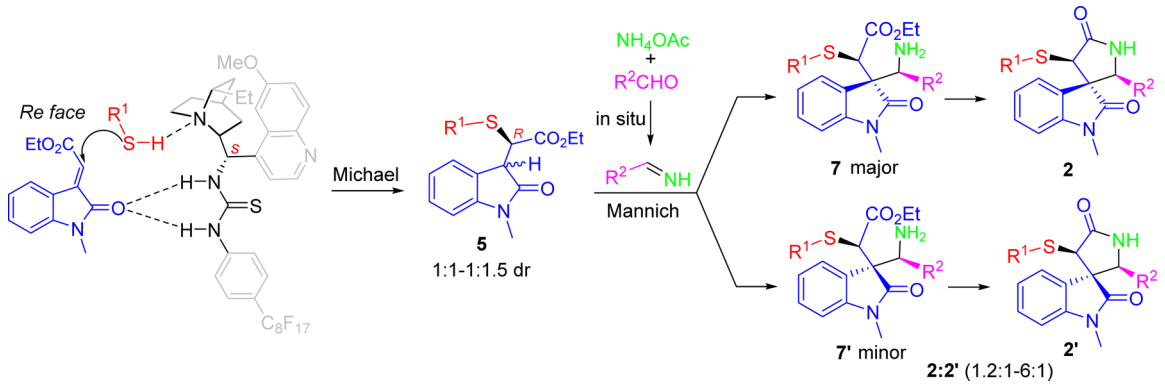


Figure 2. X-ray crystallographic structure of **2d**. Thermal ellipsoids were shown at 50% probability.

Scheme 4. Stereochemistry of the One-Pot Reaction



solution of aldehyde 6 (0.1 mmol, 1.0 equiv), NH_4OAc (0.12 mmol, 1.2 equiv), and piperidine (5 mg, 0.5 equiv) in 1 mL of ethanol was added. The reaction mixture was stirred at room temperature for 12 h. The concentrated reaction mixture was purified by prep-LC to give racemic product **2**. The dr values of racemic samples were also observed at LC−MS in ratios of 1:1−2:1.

General Procedure for the Synthesis of Enantioenriched Spirocylic Oxindoles 2 and Catalyst Recovery. To a solution of fluorous catalyst **cat-1** (6 mg, 0.01 mmol) in 0.5 mL of toluene was added oxindole **4** (0.1 mmol, 1.0 equiv). After the reaction mixture was stirred at −20 °C for 1 h, ice-cold thiol (0.1 mmol in 1 mL of toluene) was added dropwise in 10 min. After the mixture was stirred at −20 °C for 3 h, aldehyde **6** (0.1 mmol, 1.0 equiv), NH_4OAc (0.12 mmol, 1.2 equiv), and piperidine (5 mg, 0.5 equiv) in 1 mL of ethanol were added. The reaction mixture was then stirred at 25 °C for 12 h. The concentrated reaction mixture was loaded onto a fluorous solid-phase extraction (F-SPE) cartridge and eluted with 80:20 MeOH/H_2O and then MeOH. The MeOH fraction was concentrated to recover the purified **cat-1**. The concentrated MeOH/H_2O fraction was purified by Angela HP-100 prep-LC to give chiral product **2**.

Scale-up Reaction for Enantioenriched 2a. To a solution of fluorous catalyst **cat-1** (200 mg) in 12 mL of toluene was added oxindole **4a** (500 mg). After the reaction mixture was stirred at −20 °C for 1 h, ice-cold thiol (270 mg in 25 mL of toluene) was slowly added over 30 min. After the mixture was stirred at −20 °C for 3 h, aldehyde **6a** (230 mg), NH_4OAc (200 mg, 1.2 equiv), and piperidine (120 mg, 0.5 equiv) in 15 mL of ethanol were added. The reaction mixture was then stirred at 25 °C for 18 h. The concentrated reaction mixture was loaded on to a fluorous solid-phase extraction (F-SPE) cartridge and eluted with 80:20 MeOH/H_2O and then MeOH. The MeOH fraction was concentrated to recover the purified **cat-1**. The concentrated MeOH/H_2O fraction was purified by Angela HP-100 prep-LC (70:30 MeOH/H_2O, 30 min) to give chiral product **2a**.

*(2′S,3R,4′R)-1-Methyl-2′-phenyl-4′-(p-tolylthio)spiro[indoline-3,3′-pyrrolidine]-2,5′-dione (**2a**).* White solid, 78% yield (32 mg). Mp: 193−195 °C. $[\alpha]_D^{20}$ = +25.3 (*c* = 0.70, $CHCl_3$), 6:1 dr (2:1 for racemic reaction), 93% ee. The ee was determined by HPLC analysis (Venusil Chiral CA column, 90:10 hexane/*i*-PrOH, 1.0 mL/min, λ = 254 nm): t_{minor} = 12.380 min, t_{major} = 11.136 min. ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (ddd, *J* = 7.4, 1.2, 0.5 Hz, 1H), 7.13 (td, *J* = 7.7, 1.2 Hz, 1H), 7.10−7.05 (m, 5H), 7.01−6.92 (m, 5H), 6.51−6.46 (m, 1H), 6.10 (s, 1H), 5.22 (s, 1H), 4.81 (s, 1H), 2.91 (s, 3H), 2.26 (s, 3H), 1.58 (s, H_2O). ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.4, 173.4, 143.4, 137.8, 134.3, 133.0, 129.4, 129.0, 128.9, 128.3, 128.1, 126.0, 125.6, 124.6, 121.8, 107.9, 63.3, 62.4, 57.2, 26.1, 21.0. HRMS (EI-TOF, *m*/*z*): calcd for $C_{25}H_{22}N_2O_2S$ 414.1402 $[M]^+$, found 414.1400.

*(2′S,3R,4′R)-2′-(4-Fluorophenyl)-1-methyl-4′-(p-tolylthio)spiro-[indoline-3,3′-pyrrolidine]-2,5′-dione (**2b**).* White solid, 79% yield (34 mg). Mp: 204−205 °C. $[\alpha]_D^{20}$ = +15.6 (*c* = 0.32, $CHCl_3$), 6:1 dr (1.75:1 for racemic reaction), 87% ee. The ee was determined by HPLC analysis (Venusil Chiral CA column, 90:10 hexane/*i*-PrOH, 1.0 mL/min, λ = 254 nm): t_{minor} = 14.152 min, t_{major} = 8.992 min. ^1H NMR (400 MHz, $CDCl_3$): δ 7.32−7.21 (m, 3H), 7.09−7.02 (m, 3H), 6.94 (dd, *J* = 8.6, 5.3 Hz, 2H), 6.87−6.80 (m, 4H), 6.62 (d, *J* = 7.7 Hz, 1H), 6.28 (s, 1H), 4.94 (s, 1H), 4.28 (s, 1H), 2.81 (s, 3H), 2.20 (s, 3H), 1.58 (brs, H_2O). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.5, 172.4, 164.0 (d, 1JC-F = 248.5 Hz), 144.6, 137.9, 133.2, 130.7, 129.7, 129.4, 128.0, 127.9, 125.8, 122.6, 122.6, 115.2, 115.0, 108.1, 103.8, 63.2, 62.8, 58.4, 25.6, 20.9. HRMS (ESI-TOF, *m*/*z*): calcd for $C_{25}H_{21}FN_2O_2S$ 433.1386 $[M + H]^+$, found 433.1378.

*(2′S,3R,4′R)-1-Methyl-2′-(p-tolyl)-4′-(p-tolylthio)spiro[indoline-3,3′-pyrrolidine]-2,5′-dione (**2c**).* White solid, 72% yield (30.8 mg). Mp: 222−224 °C. $[\alpha]_D^{20}$ = −11.1 (*c* = 0.75, $CHCl_3$), 4:1 dr (1.75:1 for racemic reaction), 94% ee. The ee was determined by HPLC analysis (Venusil Chiral CA column, 95:5 hexane/*i*-PrOH, 1.0 mL/min, λ = 254 nm): t_{minor} = 68.72 min, t_{major} = 19.024 min. ^1H NMR (400 MHz, $CDCl_3$): δ 7.39−7.21 (m, 3H), 7.10−7.00 (m, 3H), 6.94 (d, *J* = 7.9 Hz, 2H), 6.84 (dd, *J* = 7.9, 5.7 Hz, 4H), 6.61 (d, *J* = 7.8 Hz, 1H), 6.14 (s, 1H), 4.93 (s, 1H), 4.28 (s, 1H), 4.19 (q, impurity from **4**), 3.22 (s, impurity from **4**), 2.80 (s, 3H), 2.22 (s, 3H), 2.20 (s, 3H), 1.59 (brs, H_2O), 1.22 (impurity from **4**). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.6, 172.3, 144.7, 138.4, 137.8, 133.2, 130.8, 130.8, 129.8,

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129.4, 129.2, 128.8, 126.1, 126.1, 122.6, 122.5, 108.1, 63.5, 62.8, 58.5, 25.6, 21.1, 21.0. HRMS (ESI-TOF, m/z): calcd for $C_{26}H_{24}N_2O_2S$ 429.1636 $[M + H]^+$, found 429.1634.

*(2′S,3R,4′R)-2′-(4-tert-Butylphenyl)-1-methyl-4′-(p-tolylthio)-spiro[indoline-3,3′-pyrrolidine]-2,5′-dione (**2d**).* White solid, 68% yield (32 mg). Mp: 202−204 °C. $[\alpha]_D^{20}$ = +41.5 (c = 1.45, $CHCl_3$), 5:1 dr (2:1 for racemic reaction), 94% ee. The major diastereomer was recrystallized with CH_2Cl_2/hexane for X-ray analysis. The ee was determined by HPLC analysis (Venusil Chiral CA column, 75:25 hexane/*i*-PrOH, 1.0 mL/min, λ = 254 nm): t_{minor} = 8.423 min, t_{major} = 6.892 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33−7.21 (m, 2H), 7.19−7.12 (m, 2H), 7.12−6.98 (m, 3H), 6.89−6.82 (m, 4H), 6.62 (d, J = 7.7 Hz, 1H), 6.09 (s, 1H), 4.93 (s, 1H), 4.29 (s, 1H), 2.75 (s, 3H), 2.20 (s, 3H), 1.20 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.6, 172.3, 151.7, 144.7, 137.8, 133.2, 130.9, 130.8, 129.4, 129.3, 126.1, 125.8, 125.0, 122.6, 122.5, 108.1, 63.5, 62.9, 58.4, 34.5, 31.1, 25.5, 21.0. HRMS (ESI-TOF, m/z): calcd for $C_{29}H_{30}N_2O_2S$ 471.2106 $[M + H]^+$, found 471.2094.

*(2′S,3R,4′R)-1-Methyl-2′-(4-(methylthio)phenyl)-4′-(p-tolylthio)-spiro[indoline-3,3′-pyrrolidine]-2,5′-dione (**2e**).* White solid, 71% yield (32.6 mg). Mp: 179−180 °C. $[\alpha]_D^{20}$ = +25.3 (c = 0.70, $CHCl_3$), 5:1 dr (1.5:1 for racemic reaction), 91% ee. The ee was determined by HPLC analysis (Venusil Chiral CD column, 90:10 hexane/*i*-PrOH, 1.0 mL/min, λ = 254 nm): t_{minor} = 10.348 min, t_{major} = 7.924 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, J = 6.5 Hz, 1H), 7.14 (td, J = 7.7, 1.2 Hz, 1H), 7.05 (d, J = 8.3 Hz, 2H), 6.98−6.87 (m, 8H), 6.51 (d, J = 7.8 Hz, 1H), 6.35 (s, 1H), 5.16 (s, 1H), 4.77 (s, 1H), 2.89 (s, 3H), 2.32 (s, 3H), 2.24 (s, 3H), 1.58 (s, H_2O). ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.3, 173.5, 143.3, 138.7, 137.8, 133.0, 130.9, 129.4, 129.1, 128.8, 126.2, 125.9, 125.8, 124.6, 121.9, 108.1, 63.1, 62.4, 57.4, 26.2, 21.0, 15.3. HRMS (ESI-TOF, m/z): calcd for $C_{26}H_{24}N_2O_2S_2$ 461.1357 $[M + H]^+$, found 461.1346.

*(2′S,3R,4′R)-1-Methyl-4′-(p-tolylthio)-2′-(4-(trifluoromethyl)-phenyl)spiro[indoline-3,3′-pyrrolidine]-2,5′-dione (**2f**).* White solid, 81% yield (39 mg). Mp: 175−177 °C. $[\alpha]_D^{20}$ = +9.54 (c = 0.60, $CHCl_3$), 6:1 dr (2:1 for racemic reaction), 89% ee. The ee was determined by HPLC analysis (Venusil Chiral CD column, 90:10 hexane/*i*-PrOH, 1.0 mL/min, λ = 254 nm): t_{minor} = 12.54 min, t_{major} = 9.520 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, J = 8.4 Hz, 2H), 7.30 (t, J = 4.3 Hz, 2H), 7.11−7.07 (m, 3H), 7.06−7.02 (m, 2H), 7.00 (s, 1H), 6.87−6.81 (m, 2H), 6.64 (d, J = 7.6 Hz, 1H), 5.06 (s, 1H), 4.33 (s, 1H), 3.22 (s, impurity from **4**), 2.78 (s, 3H), 2.20 (s, 3H), 1.58 (s, H_2O), 1.22 (t, impurity from **4**). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.8, 172.3, 144.5, 138.3, 137.9, 133.1, 130.5, 129.6, 129.4, 126.6, 125.7, 125.1, 125.1, 122.8, 122.7, 122.4, 108.3, 77.3, 77.0, 76.6, 63.3, 62.5, 58.5, 25.6, 20.9. HRMS (ESI-TOF, m/z): calcd for $C_{26}H_{22}F_3N_2O_2S$ 483.1354 $[M + H]^+$, found 483.1338.

*(2′R,3R,4′R)-1-Methyl-2′-(thiophene-2-yl)-4′-(p-tolylthio)spiro-[indoline-3,3′-pyrrolidine]-2,5′-dione (**2g**).* White solid, 75% yield (32 mg). Mp: 182−184 °C. $[\alpha]_D^{20}$ = +8.02 (c = 0.80, $CHCl_3$), 6:1 dr (2:1 for racemic reaction), 82% ee. The ee was determined by HPLC analysis (Venusil Chiral CA column, 95:5 hexane/*i*-PrOH, 1.0 mL/min, λ = 254 nm): t_{minor} = 30.724 min, t_{major} = 7.000 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.32 (m, 1H), 7.23−7.19 (m, 1H), 7.09−7.04 (m, 2H), 7.03−6.98 (m, 2H), 6.97−6.93 (m, 2H), 6.79−6.76 (m, 1H), 6.73−6.69 (m, 1H), 6.61−6.56 (m, 1H), 6.40−6.35 (m, 1H), 5.51−5.39 (m, 1H), 4.81−4.69 (m, 1H), 2.93 (dd, J = 7.3, 1.3 Hz, 3H), 2.27 (t, J = 10.0 Hz, 3H), 1.58 (s, H_2O). ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.0, 173.0, 143.7, 137.9, 137.2, 133.0, 129.5, 129.3, 128.8, 126.4, 126.2, 125.6, 125.6, 124.5, 122.0, 108.1, 77.3, 77.0, 76.6, 62.4, 60.0, 57.1, 26.3, 21.0. HRMS (ESI-TOF, m/z): calcd for $C_{23}H_{20}N_2O_2S_2$ 421.1044 $[M + H]^+$, found 421.1052.

*(2′S,3R,4′R)-2′-Cyclopropyl-1-methyl-4′-(p-tolylthio)spiro-[indoline-3,3′-pyrrolidine]-2,5′-dione (**2h**).* White solid, 67% yield (25 mg). Mp: 223−225 °C. $[\alpha]_D^{20}$ = +51.9 (c = 0.58, $CHCl_3$), 3:1 dr (1.2:1 for racemic reaction), 85% ee (91% for minor isomer). The ee was determined by HPLC analysis (Venusil Chiral CA column, 92.5:7.5 hexane/*i*-PrOH, 1.0 mL/min, λ = 254 nm): major diastereomer: t_{minor} = 15.740 min, t_{major} = 14.368 min; minor diastereomer: t_{minor} = 10.348 min, t_{major} = 7.924 min. Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29−7.25 (m, 1H), 7.06−6.90 (m, 3H), 6.84−6.76 (m, 2H), 5.97 (s, 1H), 4.13 (s, 1H), 3.25 (s, 2H), 2.97 (d, J = 9.7 Hz, 1H), 2.18 (s, 2H), 1.58 (s, H_2O), 1.15−0.98 (m, 1H), 0.52−0.37 (m, 1H), 0.22−0.01 (m, 2H), −0.47 (ddd, J = 6.9, 6.0, 3.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.9, 171.3, 144.6, 137.6, 133.0, 130.6, 129.3, 128.9, 127.8, 122.6, 122.2, 108.1, 65.3, 60.6, 58.8, 26.1, 20.9, 10.1, 2.8, 0.5. Minor diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40−7.34 (m, 2H), 7.14−7.08 (m, 1H), 7.07−7.02 (m, 2H), 6.98−6.91 (m, 2H), 6.81 (dt, J = 7.5, 0.9 Hz, 1H), 6.00 (s, 1H), 4.61 (s, 1H), 3.14 (d, J = 9.7 Hz, 1H), 2.98 (s, 3H), 2.25 (s, 3H), 0.43 (dtdd, J = 7.7, 4.5, 4.0, 2.5 Hz, 2H), 0.22−0.15 (m, 1H), 0.07− −0.08 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 175.1, 172.5, 144.1, 137.7, 132.9, 129.3, 129.1, 129.0, 126.0, 125.3, 122.2, 108.3, 77.3, 76.9, 76.6, 65.3, 60.4, 57.3, 26.2, 21.0, 10.3, 3.2, 0.6. HRMS (ESI-TOF, m/z): calcd for $C_{22}H_{22}N_2O_2S$: 379.1480 $[M + H]^+$, found 379.1480.

*(2′S,3R,4′R)-1,2′-Dimethyl-4′-(p-tolylthio)spiro[indoline-3,3′-pyrrolidine]-2,5′-dione (**2i**).* White solid, 59% yield (21 mg), mp 157−159 °C, $[\alpha]_D^{20}$ = +47.6 (c = 0.42, $CHCl_3$), 2.5:1 dr (1:1 for racemic reaction), 83% ee (80% for minor isomer). The ee was determined by HPLC analysis (Venusil Chiral CA column, 90:10 hexane/*i*-PrOH, 1.0 mL/min, λ = 254 nm): major diastereomer: t_{minor} = 11.700 min, t_{major} = 10.064 min; minor diastereomer: t_{minor} = 12.600 min, t_{major} = 20.052 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (td, J = 7.7, 1.3 Hz, 1H), 7.08 (dd, J = 7.5, 0.8 Hz, 1H), 7.04−6.96 (m, 3H), 6.83 (dt, J = 8.3, 4.2 Hz, 3H), 6.19 (s, 1H), 4.18 (s, 1H), 4.00 (q, J = 6.5 Hz, 1H), 3.26 (s, 3H), 2.20 (s, 3H), 1.58 (brs, H_2O), 1.10 (d, J = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 173.5, 171.8, 144.6, 137.7, 133.1, 130.5, 129.3, 129.1, 126.5, 122.7, 108.2, 60.9, 59.1, 55.0, 26.0, 21.0, 14.8. HRMS (ESI-TOF, m/z): calcd for $C_{20}H_{20}N_2O_2S$: 353.1323 $[M + H]^+$, found 353.1326.

*(2′S,3R,4′R)-2′-Phenyl-4′-(p-tolylthio)spiro[indoline-3,3′-pyrrolidine]-2,5′-dione (**2j**).* Colorless oil, 57% yield (22.8 mg), 1.5:1 dr (1:1 for racemic reaction), 95% ee for major diastereomer, 72% ee for minor diastereomer. The ee was determined by HPLC analysis (Regis (*R*,*R*)-Whelk-O1column, 80:20 hexane/*i*-PrOH, 1.0 mL/min, λ = 254 nm): t_{minor} = 9.632 min, t_{major} = 6.940 min. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.52 (s, 1H, major), 10.02 (s, 1H, minor), 8.88 (s, 1H, major), 8.61 (s, 1H, minor), 7.31−6.90 (m, 20H, major + minor), 6.87−6.71 (m, 3H, major), 6.63−6.48 (m, 3H, minor), 5.06 (s, 2H, major + mimor), 4.72 (s, 1H, minor), 4.52 (s, 1H, major), 2.22 (s, 3H, major), 2.17 (s, 3H, minor). ^{13}C NMR (101 MHz, DMSO-d_6): δ 176.2, 175.0, 173.0, 172.6, 143.2, 142.35, 136.8, 136.5, 135.9, 135.8, 132.5, 131.6, 130.8, 130.6, 129.8, 129.7, 129.3, 129.2, 128.3, 128.2, 128.1, 127.7, 126.7, 126.3, 126.0, 125.4, 124.4, 122.0, 121.2, 109.9, 109.4, 63.1, 62.7, 62.6, 62.3, 57.5, 57.1, 21.0, 20.9. HRMS (ESI-TOF, m/z): calcd for $C_{24}H_{20}N_2O_2S$ 401.1323 $[M + H]^+$, found 401.1341.

*(2′S,3R,4′R)-4′-((4-Methoxybenzyl)thio)-1-methyl-2′-phenylspiro-[indoline-3,3′-pyrrolidine]-2,5′-dione (**2k**).* Colorless oil, 73% yield (32.4 mg), 2:1 dr (1.25:1 for racemic reaction), 87% ee. The ee was determined by HPLC analysis (Regis (*R*,*R*)-Whelk-O1 column, 80:20 hexane/*i*-PrOH, 1.0 mL/min, λ = 254 nm): t_{minor} = 12.640 min, t_{major} = 15.832 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (ddd, J = 7.7, 7.2, 1.7 Hz, 1H), 7.20−7.10 (m, 3H), 7.07−6.99 (m, 4H), 6.90 (dd, J = 7.2, 1.6 Hz, 2H), 6.75−6.69 (m, 2H), 6.62 (d, J = 7.8 Hz, 1H), 6.19 (s, 1H), 4.89 (s, 1H), 3.84 (s, 1H), 3.80 (s, 3H), 3.72 (d, J = 13.7 Hz, 1H), 3.53 (d, J = 13.6 Hz, 1H), 2.74 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 172.6, 158.7, 144.5, 134.0, 130.2, 129.3, 128.9, 128.6, 128.1, 126.0, 125.9, 122.5, 122.5, 113.7, 107.9, 63.8, 62.3, 55.2, 50.7, 35.9, 25.5. HRMS (ESI-TOF, m/z): calcd for $C_{26}H_{24}N_2O_3S$ 445.1586 $[M + H]^+$, found 445.1552.

*Ethyl 2-((2′S,3R,4′R)-1-Methyl-2,5′-dioxo-2′-phenylspiro-[indoline-3,3′-pyrrolidin]-4′-yl)thio)acetate (**2l**).* Colorless oil, 78% yield (32 mg), 1.2:1 dr (1:1 for racemic reaction), 33% ee (86% for minor isomer). The ee was determined by HPLC analysis (Regis (*R*,*R*)-Whelk-O1 column, 80:20 hexane/*i*-PrOH, 1.0 mL/min, λ = 254 nm): major diastereomer: t_{minor} = 23.080 min, t_{major} = 13.780 min; minor diastereomer: t_{minor} = 27.928 min, t_{major} = 17.884 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58−6.84 (m, 16H, major + minor), 6.64 (d, J = 7.7 Hz, 1H, minor), 6.57 (d, J = 7.8 Hz, 1H, major), 5.27 (s, 1H,

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SCH, major), 5.03 (s, 1H, SCH, minor), 4.58 (s, 1H, CH, minor), 4.55 (s, 1H, CH, major), 4.13 (q, J = 7.1 Hz, 2H, CH_2CH_3, major), 3.95 (q, J = 7.2 Hz, 2H, CH_2CH_3, minor) 3.33 (dd, J = 15.0, 14.6 Hz, 2H, CH_2, major), 3.17 (s, NCH_3, 3H, major), 2.99 (dd, J = 14.6, 15.0 Hz, 2H, CH_2, minor), 2.71 (s, 3H, NCH_3, minor), 1.24 (t, J = 7.1 Hz, 3H, CH_2CH_3, major), 1.11 (t, J = 7.1 Hz, 3H, CH_2CH_3, minor). ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.7, 174.4, 173.0, 172.4, 170.0, 169.6, 144.6, 143.3, 134.4, 133.8, 129.6, 129.2, 128.6, 128.2, 128.1, 128.1, 126.1, 125.9, 125.6, 125.6, 124.2, 123.0, 122.7, 121.9, 108.1, 64.2, 63.22, 62.3, 61.6, 61.3, 61.3, 52.0, 51.3, 33.9, 33.2, 26.5, 25.5, 14.0, 13.9. HRMS (EI-TOF, m/z): calcd for $C_{22}H_{22}N_2O_4S$ 410.1300 $[M]^+$, found 410.1294.

*(2′S,3R,4′R)-5-Bromo-1-methyl-2′-phenyl-4′-(p-tolylthio)spiro-[indoline-3,3′-pyrrolidine]-2,5′-dione (**2m**).* Colorless oil, 62% yield (30.5 mg), 5:1 dr (1.25:1 for racemic reaction), 86% ee. The ee was determined by HPLC analysis (Regis (*R*,*R*)-Whelk-O1 column, 80:20 hexane/*i*-PrOH, 1.0 mL/min, λ = 254 nm): t_{minor} = 14.880 min, t_{major} = 10.292 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40−7.33 (m, 1H, major + minor), 7.25−7.21 (m, 3H, major + minor), 7.13−7.03 (m, 5H, major + minor), 7.00−6.92 (m, 4H, major + minor), 6.46 (d, J = 8.3 Hz, minor), 6.33 (d, J = 8.3 Hz, 1H, major), 6.09 (s, 1H), 5.19 (s, 1H, major), 4.91 (s, minor), 4.81 (s, 1H, major), 4.32 (s, minor), 2.85 (s, 3H, major), 2.76 (s, minor), 2.25 (s, 3H, major), 2.24 (s, minor). ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.9, 172.9, 142.3, 138.1, 133.9, 133.4, 133.1, 131.7, 129.5, 129.4, 129.1, 128.5, 128.3, 128.3, 126.6, 126.1, 125.5, 114.5, 109.2, 63.2, 62.5, 56.9, 26.2, 21.0. HRMS (ESI-TOF, m/z): calcd for $C_{25}H_{21}BrN_2O_2S$ 493.0585 $[M + H]^+$, found 493.0579.

*(2′S,3R,4′R)-1,5-Dimethyl-2′-phenyl-4′-(p-tolylthio)spiro-[indoline-3,3′-pyrrolidine]-2,5′-dione (**2n**).* White solid, 71% yield (30 mg). Mp: 178−180 °C. $[\alpha]_D^{20}$ = +13.2 (c = 0.38, $CHCl_3$), 4:1 dr (2:1 for racemic reaction), 83% ee. The ee was determined by HPLC analysis (Regis (*R*,*R*)-Whelk-O1 column, 80:20 hexane/*i*-PrOH, 1.0 mL/min, λ = 254 nm): t_{minor} = 14.368 min, t_{major} = 12.988 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21−7.12 (m, 3H), 7.11−7.04 (m, 3H), 7.01−6.98 (m, 1H), 6.97−6.92 (m, 2H), 6.88−6.83 (m, 2H), 6.49 (d, J = 7.9 Hz, 1H), 6.00 (s, 1H), 4.93 (s, 1H), 4.28 (s, 1H), 2.75 (s, 3H), 2.30 (s, 3H), 2.22 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.4, 172.2, 142.3, 137.7, 133.9, 133.2, 132.1, 130.8, 129.5, 129.3, 128.6, 128.4, 128.1, 126.1, 125.8, 123.3, 107.8, 77.3, 76.9, 76.6, 63.7, 62.9, 58.4, 25.6, 21.0, 20.9, 0.02. HRMS (ESI-TOF, m/z): calcd for $C_{26}H_{24}N_2O_2S$ 429.1636 $[M + H]^+$, found 429.1631.

*(3R,4′R)-1′-Allyl-1-methyl-4′-(p-tolylthio)spiro[indoline-3,3′-pyrrolidine]-2,5′-dione (**2o**).* Colorless oil, 87% yield (32.8 mg), 4:1 dr (1.5:1 for racemic reaction), 89% ee. The ee was determined by HPLC analysis (Regis (*R*,*R*)-Whelk-O1column, 80:20 hexane/*i*-PrOH, 1.0 mL/min, λ = 254 nm): t_{minor} = 12.536 min, t_{major} = 9.392 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (td, J = 7.8, 1.3 Hz, 1H), 7.28−7.23 (m, 2H), 7.10 (td, J = 7.6, 1.0 Hz, 1H), 7.07−7.03 (m, 2H), 6.97−6.92 (m, 2H), 6.79−6.74 (m, 1H), 5.77 (dddd, J = 16.9, 10.1, 6.7, 6.2 Hz, 1H), 5.24 (ddd, J = 7.9, 5.7, 1.3 Hz, 2H), 4.62 (s, 1H), 4.15 (ddt, J = 14.9, 6.1, 1.3 Hz, 1H), 3.92 (ddd, J = 15.0, 6.8, 0.9 Hz, 1H), 3.71 (d, J = 9.5 Hz, 1H), 3.30 (d, J = 9.5 Hz, 1H), 2.95 (s, 3H), 2.25 (s, 3H), 1.58 (s, H_2O). ^{13}C NMR (101 MHz, $CDCl_3$): δ 175.6, 169.8, 143.4, 137.7, 132.9, 131.4, 129.4, 129.3, 129.1, 129.0, 123.8, 122.8, 119.6, 108.3, 57.5, 53.4, 53.1, 46.1, 26.3, 21.0. HRMS (EI-TOF, m/z): calcd for $C_{22}H_{22}N_2O_2S$ 378.1402 $[M]^+$, found 378.1400.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00653.

Experimental details and analytical data for all new compounds; ^{1}H, ^{13}C NMR and HPLC spectra for the products (PDF)

Single-crystal X-ray crystallography data for product **2d** (CIF)

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Notes

The authors declare no competing financial interest.

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