JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

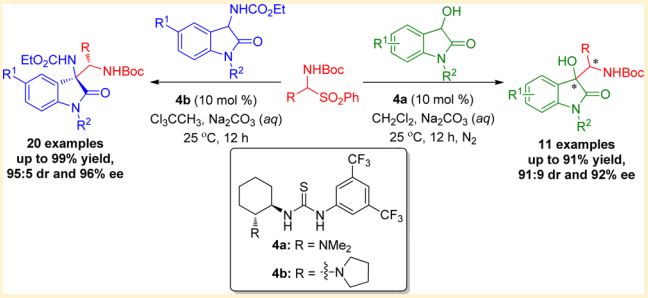
Organocatalytic Asymmetric Mannich Reaction of 3-Hydroxyoxindoles/3-Aminooxindoles with in Situ Generated *N*-Boc-Protected Aldimines for the Synthesis of Vicinal Oxindole−Diamines/Amino Alcohols

Jing Shan, Baodong Cui,* Yu Wang, Chengli Yang, Xiaojian Zhou, Wenyong Han, and Yongzheng Chen*

School of Pharmacy, Zunyi Medical University, Zunyi 563000, P. R. China

Supporting Information

ABSTRACT: A highly efficient asymmetric Mannich reaction of 3-monosubstituted 3-aminooxindoles/3-hydroxyoxindoles with in situ generated *N*-Boc-protected aldimines catalyzed by the chiral bifunctional thiourea−tertiary amine catalyst has been developed. Under mild reaction conditions, a series of structurally diverse vicinal oxindole−diamines/amino alcohols were smoothly obtained in moderate to high yields (up to 99%) with good to excellent diastereoselectivities and enantioselectivities (up to 95:5 dr and 96% ee). The synthetic application of this protocol was also demonstrated by the versatile transformation of chiral vicinal oxindole−diamine/amino alcohol into spirocyclic oxindoles.

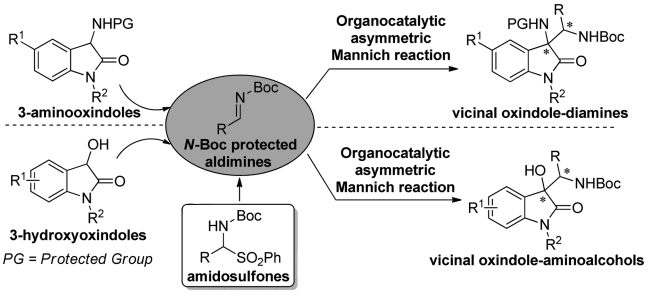


INTRODUCTION

Endeavors leading to the synthesis of structurally diverse organic molecules are of continuing interest to medicinal chemists because these efforts have the potential to generate new drug candidates.[1] Optically active disubstituted 3-aminooxindoles[2]/3-hydroxyoxindoles[3] are structural motifs that represent privileged pharmacophores found in biologically active natural products and synthetic compounds. In recent years, considerable efforts were invested in the development of creative strategies to access chiral disubstituted 3-aminooxindoles[4,5,6a−c,7]/3-hydroxyoxindoles.[6c,d,7,8] These strategies focused on catalytic, asymmetric, and synthetic methods, including the asymmetric addition reactions of nucleophiles to isatin imines[1,4a,c,d] or isatins,[4b,c,7] amination,[4a,c,5] or hydroxylation[4c,8] of 3-monosubstituted oxindoles and other reactions.[6] Despite these achievements, highly efficient and stereoselective methodologies for the expeditious construction of structurally diverse disubstituted 3-aminooxindoles and 3-hydroxyoxindoles remain desirable goals.

Some literature surveys reveal that 3-monosubstituted 3-aminooxindoles[9]/3-hydroxyoxindoles[10] can be employed as nucleophiles to react with various electrophiles for generation of chiral disubstituted 3-aminooxindoles/3-hydroxyoxindoles. Additionally, the *N*-Boc-protected aldimines have been widely used in the organocatalytic, asymmetric Mannich reaction for the amino introduction into the chemical structures.[11] However, the reaction of 3-aminooxindoles/3-hydroxyoxindoles with *N*-Boc-protected aldimines for asymmetric synthesis of vicinal oxindole−diamines/amino alcohols has not been exploited. In this context, we envisioned that the asymmetric Mannich reaction between 3-aminooxindoles/3-hydroxyoxindoles and *N*-Boc-protected aldimines would provide an important complementary way to access new structures of chiral disubstituted 3-aminooxindole/3-hydroxyoxindole (Scheme 1). Herein, we report our research results with respect to this subject by organocatalysis.

Scheme 1. Design for Synthesis of Chiral Vicinal Oxindole−Diamines/Amino Alcohols



RESULTS AND DISCUSSION

Our studies began with the model reaction of 3-aminooxindole **1a** with amidosulfone **2a**, and various chiral bifunctional thiourea−tertiary amine catalysts were screened (Figure 1). Takemoto's catalyst **4a** was first investigated in toluene with

Received: February 6, 2016
Published: June 3, 2016

DOI: 10.1021/acs.joc.6b00278
J. Org. Chem. 2016, 81, 5270−5277

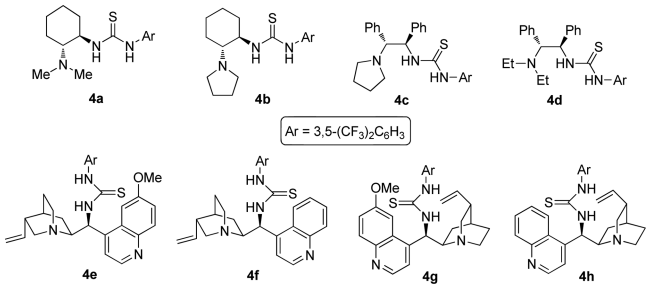
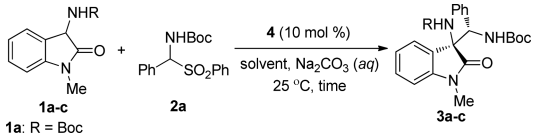


Figure 1. Chiral bifunctional thiourea–tertiary amine catalysts screened in this work.

saturated aqueous solution of Na_2CO_3. Substrate **1a** could be consumed completely at 25 °C for 12 h and gave vicinal oxindole–diamine **3a** in 94% yield with 84:16 dr and 54% ee (Table 1, entry 1). To our delight, 68% ee was obtained by using the catalyst **4b** with a pyrrolidine structure (entry 2). However, catalysts **4c** and **4d** based on the diphenylethane skeleton provided very poor ee in spite of excellent dr (entries 3 and 4). Further catalyst examination revealed that other chiral bifunctional thiourea–tertiary amines **4e–h** derived from cinchona alkaloids could not give better enantioselectivities compared with that shown in entry 2 (entries 5–8). The effects of a *N*-protected group at the C3 position of oxindole were explored. The reaction results revealed substrate **1c** with a *N*-CO_2Et substituent at the C3 position showed higher stereoselectivity (entry 10, for **3c**, 98% yield, 90:10 dr and 86% ee). The following solvent screening confirmed Cl_3CCH_3 as the optimal solvent (entry 16). Finally, lowering the reaction temperature to 0 °C was not beneficial for further improvement of stereoselectivity (entry 18).

Table 1. Optimization of Reaction Conditions[a]



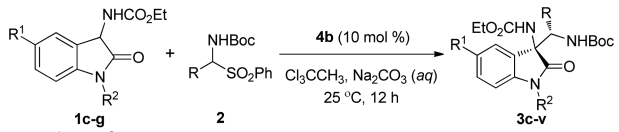
1a: R = Boc
1b: R = Cbz
1c: R = CO_2Et

entry	1	4	solvent	time (h)	3/yield[b] (%)	dr[c]	ee[d] (%)
1	**1a**	**4a**	toluene	12	**3a**/94	84:16	54
2	**1a**	**4b**	toluene	12	**3a**/97	74:26	68
3	**1a**	**4c**	toluene	24	**3a**/89	97:3	21
4	**1a**	**4d**	toluene	24	**3a**/97	99:1	6
5	**1a**	**4e**	toluene	24	**3a**/98	88:12	54
6	**1a**	**4f**	toluene	24	**3a**/89	90:10	33
7	**1a**	**4g**	toluene	24	**3a**/98	86:14	30
8	**1a**	**4h**	toluene	24	**3a**/99	92:8	48
9	**1b**	**4b**	toluene	24	**3b**/97	87:13	83
10	**1c**	**4b**	toluene	24	**3c**/98	90:10	86
11	**1c**	**4b**	mesitylene	24	**3c**/98	88:12	83
12	**1c**	**4b**	fluorobenzene	24	**3c**/98	85:15	88
13	**1c**	**4b**	CH_2Cl_2	12	**3c**/97	91:9	89
14	**1c**	**4b**	$CHCl_3$	24	**3c**/98	89:11	83
15	**1c**	**4b**	$ClCH_2CH_2Cl$	24	**3c**/98	89:11	88
16	**1c**	**4b**	Cl_3CCH_3	12	**3c**/99	90:10	91
17	**1c**	**4b**	THF	36	**3c**/82	81:19	4
18[e]	**1c**	**4b**	Cl_3CCH_3	24	**3c**/91	90:10	91

[a]Unless otherwise noted, the reactions were performed with 0.1 mmol of **1**, 0.12 mmol of **2a**, and 0.1 mL of a saturated aqueous solution of Na_2CO_3 in the presence of 10 mol % of **4** in 2.0 mL of solvent at 25 °C for the specified reaction time. [b]Isolated yields of **3**. [c]Determined by chiral HPLC analysis. [d]Enantiomeric excess for major diastereoisomers determined by chiral HPLC analysis. [e]Reaction was carried out at 0 °C.

After establishment of the optimal reaction conditions, the nonchiral diastereoselectivities of products **3c–v** (for **3c**, dr 62:38; for **3d**, dr 77:23; for **3e**, dr 77:23; for **3f**, dr 70:30; for **3g**, dr 53:47; for **3h**, dr 72:28; for **3i**, dr 79:21; for **3j**, dr 70:30; for **3k**, dr 77:23; for **3l**, dr 72:28; for **3m**, dr 76:24; for **3n**, dr 65:35; for **3o**, dr 71:29; for **3p**, dr 57:43; for **3q**, dr 65:35; for **3r**, dr 72:28; for **3s**, dr 69:31; for **3t**, dr 68:32; for **3u**, dr 69:31; for **3v**, dr 56:44) were obtained by using DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as base. Then the asymmetric reaction of 3-aminooxindole **1c** with various amidosulfones **2b–j** was investigated. Whether the substituent on the phenyl ring was an electron-donating (**2c–e** and **2g**) or electron-withdrawing (**2h–j**) substituent of amidosulfones, all reactions proceeded smoothly to give the desired vicinal oxindole–diamines **3e–g,i,j–l** in 83–99% yields with up to 92% ee (Table 2, entries 3–5, 7, and 8–10). It is noteworthy that using

Table 2. Scope of Asymmetric Mannich Reaction of 3-Aminooxindoles 1 with Amidosulfones 2[a]



1c: R^1 = H, R^2 = Me
1d: R^1 = Me, R^2 = Me
1e: R^1 = F, R^2 = Me
1f: R^1 = H, R^2 = Et
1g: R^1 = H, R^2 = Bn

entry	1	2	3/yield[b] (%)	dr[c]	ee[d] (%)
1	**1c**	R = Ph (**2a**)	**3c**/99	90:10	91
2	**1c**	R = 2-$MeOC_6H_4$ (**2b**)	**3d**/99	77:23	77
3	**1c**	R = 3-MeC_6H_4 (**2c**)	**3e**/99	90:10	92
4	**1c**	R = 3-$MeOC_6H_4$ (**2d**)	**3f**/98	90:10	91
5	**1c**	R = 3,4-$(MeO)_2C_6H_3$ (**2e**)	**3g**/90	90:10[e]	92
6	**1c**	R = 3-$NO_2C_6H_4$ (**2f**)	**3h**/83	86:14	82
7	**1c**	R = 4-MeC_6H_4 (**2g**)	**3i**/93	89:11	92
8	**1c**	R = 4-FC_6H_4 (**2h**)	**3j**/96	90:10	91
9	**1c**	R = 4-ClC_6H_4 (**2i**)	**3k**/99	92:8	91
10	**1c**	R = 4-BrC_6H_4 (**2j**)	**3l**/83	91:9	92
11	**1c**	R = 2-furyl (**2k**)	**3m**/98	86:14	86
12	**1c**	R = 2-thienyl (**2l**)	**3n**/72	88:12	90
13	**1d**	R = Ph (**2a**)	**3o**/99	89:11	89
14	**1e**	R = Ph (**2a**)	**3p**/99	87:13	89
15	**1f**	R = Ph (**2a**)	**3q**/98	79:21	90
16	**1g**	R = Ph (**2a**)	**3r**/98	94:6	96
17	**1g**	R = 4-$MeOC_6H_4$ (**2m**)	**3s**/98	95:5	92
18	**1g**	R = 3-ClC_6H_4 (**2n**)	**3t**/98	94:6	96
19	**1g**	R = 3-BrC_6H_4 (**2o**)	**3u**/99	94:6	95
20	**1g**	R = 1-naphthyl (**2p**)	**3v**/79	73:27	85

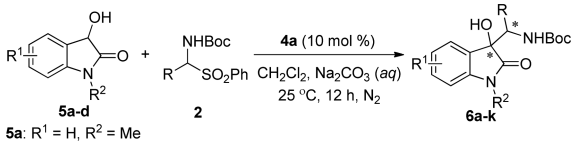
[a]Unless otherwise noted, the reactions were performed with 0.1 mmol of **1**, 0.12 mmol of **2**, and 0.1 mL of a saturated aqueous solution of Na_2CO_3 in the presence of 10 mol % of **4b** (4.4 mg, 0.01 mol) in 2.0 mL of Cl_3CCH_3 at 25 °C for 12 h. [b]Isolated yields of **3**. [c]Determined by chiral HPLC analysis. [d]Enantiomeric excess for major diastereoisomers determined by chiral HPLC analysis. [e]Determined by ^1H NMR analysis of the mixture of two diastereoisomers.

DOI: 10.1021/acs.joc.6b00278
J. Org. Chem. 2016, 81, 5270–5277

the sterically demanding **2b** and **2f** with strong electron-withdrawing nitro group on the phenyl ring as substrates gave rise to the products **3d** and **3h** in lower ee (entries 2 and 6). In addition, two heteroaromatic amidosulfones **2k** and **2l** were also successfully employed in the reaction and afforded the corresponding products **3m** and **3n** with good results (entries 11 and 12). The absolute configuration of the major stereoisomer **3n** was determined as (C5*R*,C11*S*) by X-ray crystallographic analysis (see the Supporting Information). The stereochemistry of other compounds **3** and **8** was identified by analogy. Furthermore, examination of the substituent on the phenyl ring and N-1 position of 3-aminooxindole indicated *N*-benzyl-substituted 3-aminooxindole **1g** could give higher enantioselectivity (entries 13−16). To further explore the substrate scope of the asymmetric Mannich reaction, 3-aminooxindole **1g** was subsequently used as the nucleophile to react with other four amidosulfones **2m−p**. It was observed that amidosulfones **2m−o** could offer the corresponding products **3s−u** in good yields with excellent stereoselectivities (entries 17−19) except for the bulky 1-naphthyl-substituted amidosulfone **2p** (entry 20). Finally, the point was that compounds **3c** and **3e−v** showed remarkable enhancement in diastereoselectivity from the chiral catalyst with the exception of compound **3d** through comparison of the nonchiral diastereoselectivities and chiral diastereoselectivities.

On the basis of the synthesis of a series of chiral vicinal oxindole−diamines **3**, the asymmetric Mannich reaction between 3-hydroxyoxindoles **5** and amidosulfones **2** was also explored for the purpose of producing a variety of chiral vicinal oxindole−amino alcohols **6**. Initially, the nonchiral diastereoselectivities of products **6a−k** (for **6a**, dr 68:32; for **6b**, dr 48:52; for **6c**, dr 33:67; for **6d**, dr 38:62; for **6e**, dr 45:55; for **6f**, dr 35:65; for **6g**, dr 46:54; for **6h**, dr 41:59; for **6i**, dr 52:48; for **6j**, dr 41:59; for **6k**, dr 52:48) were obtained by using DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as base. Subsequently, with Takemoto's catalyst **4a** and dichloromethane as solvent, the reaction of *N*-methyl-substituted 3-hydroxyoxindole **5a** with amidosulfone **2a** proceeded smoothly to afford the corresponding vicinal oxindole−amino alcohol **6a** in 75% yield with good enantioselectivity (Table 3, entry 1). However, other solvents (CH_3CCl_3: 62% yield, 89:11 dr and 84% ee; toluene: 76% yield, 91:9 dr and 81% ee; THF: 77% yield, 71:29 dr and 1% ee; CH_3CN: 69% yield, 51:49 dr and 8% ee) could not provide preferable results. In contrast, *N*-benzyl-substituted substrate **5b** gave better results (entry 2 vs entry 1). Thus, it was next employed as the nucleophile to react with various amidosulfones **2**. Investigation showed amidosulfones **2c**, **2g**, **2m**, and **2e** with an electron-donating substituent on phenyl ring could provide the desired products **6c−f** in 72−90% yields with up to 92% ee (entries 3−6). However, inferior enantioselectivities were obtained from substrates **2i** and **2j** with electron-withdrawing substituents on the phenyl ring (entries 7 and 8). Additionally, 2-thienyl-substituted substrate **2l** was also applicable to the asymmetric Mannich reaction process and gave the product **6i** in good results (entry 9). Examination of the substituent on the phenyl ring of 3-hydroxyoxindole indicated there were no significant effects on the reaction stereoselectivities (entries 10 and 11). Eventually, it was emphasized that compounds **6b−h** and **6j** showed remarkable enhancement and a reversal in diastereoselectivity from the chiral catalyst with the exception of compounds **6a**, **6i**, and **6k** through the comparasion of the nonchiral diastereoselectivities and chiral diastereoselectivities.

Table 3. Scope of Asymmetric Mannich Reaction of 3-Hydroxyoxindoles 5 with Amidosulfones 2[a]



5a-d 2 6a-k

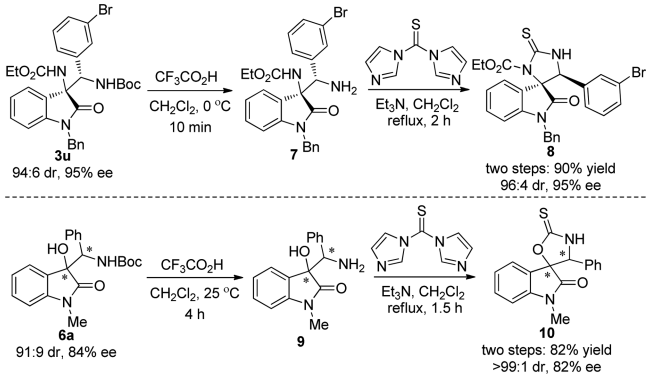
5a: R^1 = H, R^2 = Me
5b: R^1 = H, R^2 = Bn
5c: R^1 = 5-OMe, R^2 = Bn
5d: R^1 = 7-F, R^2 = Bn

entry	5	2	6/yield[b] (%)	dr[c]	ee[d] (%)
1	**5a**	R = Ph (**2a**)	**6a**/75	91:9	84
2	**5b**	R = Ph (**2a**)	**6b**/91	90:10	87
3	**5b**	R = 3-MeC_6H_4 (**2c**)	**6c**/80	90:10	87
4	**5b**	R = 4-MeC_6H_4 (**2g**)	**6d**/78	91:9	88
5	**5b**	R = 4-$MeOC_6H_4$ (**2m**)	**6e**/74	82:18	88
6	**5b**	R = 3,4-$(MeO)_2C_6H_3$ (**2e**)	**6f**/72	84:16	92
7	**5b**	R = 4-ClC_6H_4 (**2i**)	**6g**/77	82:18	80
8	**5b**	R = 4-BrC_6H_4 (**2j**)	**6h**/69	83:17	78
9	**5b**	R = 2-thienyl (**2l**)	**6i**/84	90:10	85
10	**5c**	R = Ph (**2a**)	**6j**/89	91:9	86
11	**5d**	R = Ph (**2a**)	**6k**/37	88:12	90

[a]Unless otherwise noted, the reactions were performed with 0.1 mmol of **5**, 0.12 mmol of **2**, and 0.1 mL of a saturated aqueous solution of Na_2CO_3 in the presence of 10 mol % of **4a** (4.1 mg, 0.01 mmol) in 2.0 mL of CH_2Cl_2 at 25 °C under N_2 atmosphere for 12 h. [b]Isolated yields of **6**. [c]Determined by chiral HPLC analysis. [d]Enantiomeric excess for major diastereoisomers determined by chiral HPLC analysis.

The synthetic application of this protocol was demonstrated by the versatile transformation of chiral vicinal oxindole−diamine **3u** and oxindole−amino alcohol **6a** into the spirocyclic oxindoles **8** and **10** (Scheme 2). At the beginning, the Boc

Scheme 2. Transformation of Products 3u and 6a into Spirocyclic Oxindoles 8 and 10

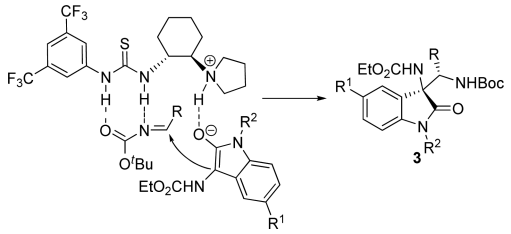


group of **3u**/**6a** was easily removed by CF_3CO_2H to give the primary amine **7**/**9**. When Et_3N was used as base, the unpurified primary amine **7**/**9** was used to react with di(1*H*-imidazol-1-yl)methanethione, giving the spirocyclic oxindoles **8** and **10** in good yields and without reduced stereoselectivities for two steps.

According to the previous report[11e] and established stereochemistry of major stereoisomer **3n**, a possible reaction mechanism involving dual activation of catalyst **4b** was proposed (Scheme 3). 3-Aminooxindoles **1** were enolized by the tertiary amine moiety though the deprotonation. Simultaneously, *N*-Boc-protected aldimines in situ generated were

DOI: 10.1021/acs.joc.6b00278
J. Org. Chem. 2016, 81, 5270−5277

Scheme 3. Proposed Transition State for Production of Compounds 3



activated by thiourea moiety through the hydrogen-bonding interaction. The *Si*-face attack of enolized 3-aminooxindole to the *Re*-face of aldimines then led to the production of vicinal oxindole−diamine **3**.

In conclusion, we have developed an efficient complementary methodology for stereoselective synthesis of disubstituted 3-aminooxindole/3-hydroxyoxindole via the asymmetric Mannich reaction of 3-monosubsituted 3-aminooxindoles/3-hydroxyoxindoles with in situ generated *N*-Boc protected aldimines catalyzed by the chiral bifunctional thiourea−tertiary amine catalyst. Under mild reaction conditions, a wide range of vicinal oxindole−diamines/amino alcohols were obtained in up to 99% yield with 95:5 dr and 96% ee. The synthetic application of this protocol was also demonstrated by the versatile transformation of chiral vicinal oxindole−diamine **3u** and oxindole−amino alcohol **6a** into the spirocyclic oxindole compounds.

EXPERIMENTAL SECTION

General Methods. ^{1}H NMR and ^{13}C NMR (300, 400, and 75, 100 MHz, respectively) spectra were recorded in $CDCl_3$. ^{1}H NMR chemical shifts are reported in ppm relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ($CDCl_3$ at 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet and m = multiplet), coupling constants (Hz), and integration. ^{13}C NMR chemical shifts are reported in ppm relative to tetramethylsilane (TMS) with the solvent resonance as the internal standard ($CDCl_3$ at 77.16 ppm).

General Procedure for the Synthesis of Vicinal Oxindole−Diamines 3. In an ordinary vial equipped with a magnetic stirring bar, 3-aminooxindoles **1** (0.1 mmol, 1 equiv), amidosulfones **2** (0.12 mmol, 1.2 equiv), and catalyst **4b** (4.4 mg, 0.01 mmol) were dissolved in 2.0 mL of Cl_3CCH_3, and then 0.1 mL of a saturated aqueous solution of Na_2CO_3 was added into the solution. The resulting mixture was stirred at 25 °C for 12 h. After completion of the reaction, as indicated by TLC, the reaction mixture was directly purified by flash chromatography (petroleum ether/ethyl acetate = 5/1−2/1) to furnish the corresponding products **3**.

*(S,S)-tert-Butyl ((3-((Ethoxycarbonyl)amino)-1-methyl-2-oxoindolin-3-yl)(phenyl)methylcarbamate (**3c**).* White solid; 43.5 mg, yield 99%; 90:10 dr, 91% ee. $[\alpha]_D^{25}$ = −36.6 (*c* 1.00, $CHCl_3$). Mp: 116.5−117.5 °C. The ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 10/90, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 15.1 min, t_{major} = 17.3 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.18 (br s, 3H), 1.44 (s, 9H), 2.87 (s, 3H), 3.99 (s, 2H), 5.14 (d, *J* = 9.8 Hz, 1H), 6.24 (br s, 1H), 6.38 (d, *J* = 7.6 Hz, 1H), 6.49 (d, *J* = 9.4 Hz, 1H), 6.81 (d, *J* = 7.3 Hz, 2H), 6.97−7.07 (m, 4H), 7.11−7.15 (m, 1H), 7.38 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 14.5, 26.0, 28.4, 59.3, 61.5, 64.4, 80.7, 108.0, 122.9, 127.4, 127.5, 127.9, 129.5, 134.9, 143.3, 155.0, 156.3, 174.8. HRMS (ESI-TOF): calcd for $C_{24}H_{29}N_3NaO_5$ $[M + Na]^+$ 462.1999, found 462.2014.

*(S,S)-tert-Butyl ((3-((Ethoxycarbonyl)amino)-1-methyl-2-oxoindolin-3-yl)(2-methoxylphenyl)methyl)carbamate (**3d**).* White solid; 46.5 mg, yield 99%; 77:23 dr, 77% ee. $[\alpha]_D^{25}$ = +6.8 (*c* 1.00, $CHCl_3$). Mp: 117.8−119.2 °C. The ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 10/90, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 13.2 min, t_{major} = 19.1 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.16−1.20 (m, 3H), 1.43 (s, 9H), 3.00 (s, 3H), 3.54 (s, 3H), 3.97 (s, 2H), 5.85 (br s, 1H), 6.39 (d, *J* = 7.6 Hz, 2H), 6.45 (d, *J* = 8.0 Hz, 1H), 6.71−6.74 (m, 2H), 6.91−7.09 (m, 4H), 7.32 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 14.5, 26.1, 28.4, 54.9, 55.3, 61.3, 64.7, 80.4, 107.3, 110.0, 119.7, 121.7, 124.1, 127.2, 129.1, 129.3, 129.7, 143.3, 154.9, 156.0, 156.4, 175.3. HRMS (ESI-TOF): calcd for $C_{25}H_{31}N_3NaO_6$ $[M + Na]^+$ 492.2105, found 492.2091.

*(S,S)-tert-Butyl ((3-((Ethoxycarbonyl)amino)-1-methyl-2-oxoindolin-3-yl)(3-methylphenyl)methyl)carbamate (**3e**).* White solid; 44.9 mg, yield 99%; 90:10 dr, 92% ee. $[\alpha]_D^{25}$ = −26.5 (*c* 1.00, $CHCl_3$). Mp: 123.1−124.6 °C. The ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 10/90, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 11.6 min, t_{major} = 13.8 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.17 (br s, 3H), 1.45 (s, 9H), 2.09 (s, 3H), 2.87 (s, 3H), 3.99 (s, 2H), 5.09 (d, *J* = 9.6 Hz, 1H), 6.23 (br s, 1H), 6.38 (d, *J* = 7.5 Hz, 1H), 6.44 (d, *J* = 9.4 Hz, 1H), 6.58 (s, 1H), 6.62 (d, *J* = 7.0 Hz, 1H), 6.86−6.90 (m, 2H), 7.02−7.06 (m, 1H), 7.10−7.14 (m, 1H), 7.37 (d, *J* = 7.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 14.5, 21.2, 25.9, 28.5, 59.3, 61.4, 64.5, 80.7, 108.0, 122.8, 122.9, 123.4, 124.5, 127.2, 128.4, 128.6, 129.4, 134.7, 137.1, 143.3, 155.0, 156.4, 174.8. HRMS (ESI-TOF): calcd for $C_{25}H_{31}N_3NaO_5$ $[M + Na]^+$ 476.2156, found 476.2139. Anal. calcd for $C_{25}H_{31}N_3O_5$: C, 66.21; H, 6.89; N, 9.27. Found: C, 66.03; H, 6.89; N, 9.07.

*(S,S)-tert-Butyl ((3-((Ethoxycarbonyl)amino)-1-methyl-2-oxoindolin-3-yl)(3-methoxylphenyl)methyl)carbamate (**3f**).* White solid; 46.0 mg, yield 98%; 90:10 dr, 91% ee. $[\alpha]_D^{25}$ = −20.2 (*c* 1.00, $CHCl_3$).Mp: 122.5−124.0 °C. The ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 10/90, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 16.0 min, t_{major} = 19.8 min); ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.17 (br s, 3H), 1.45 (s, 9H), 2.88 (s, 3H), 3.52 (s, 3H), 3.99 (s, 2H), 5.11 (d, *J* = 9.7 Hz, 1H), 6.22 (s, 2H), 6.41−6.50 (m, 3H), 6.59 (d, *J* = 8.1 Hz, 1H), 6.92−6.96 (m, 1H), 7.04−7.08 (m, 1H), 7.13−7.17 (m, 1H), 7.38 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 14.5, 26.0, 28.5, 55.2, 59.2, 61.5, 64.3, 80.7, 108.2, 112.8, 114.4, 119.5, 122.8, 122.9, 123.4, 128.4, 129.5, 136.5, 143.5, 154.9, 156.3, 158.6, 174.8. HRMS (ESI-TOF): calcd for $C_{25}H_{31}N_3NaO_6$ $[M + Na]^+$ 492.2105, found 492.2095.

*(S,S)-tert-Butyl ((3-((Ethoxycarbonyl)amino)-1-methyl-2-oxoindolin-3-yl)(3,4-dimethoxylphenyl)methyl)carbamate (**3g**).* White solid; 45.0 mg, yield 90%; 90:10 dr, 92% ee. $[\alpha]_D^{25}$ = −33.9 (*c* 1.00, $CHCl_3$). Mp: 127.9−129.5 °C. The ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 10/90, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 34.2 min, t_{major} = 27.8 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.18 (br s, 3H), 1.45 (s, 9H), 2.88 (s, 3H), 3.53 (s, 3H), 3.75 (s, 3H), 3.99 (s, 2H), 5.07 (d, *J* = 9.7 Hz, 1H), 6.13 (s, 1H), 6.17 (br s, 1H), 6.43−6.56 (m, 4H), 7.06−7.09 (m, 1H), 7.14−7.17 (m, 1H), 7.40 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 14.4, 26.0, 28.4, 55.6, 55.8, 58.8, 61.4, 64.3, 80.6, 108.3, 109.8, 110.9, 119.3, 122.7, 122.8, 127.4, 128.5, 129.5, 143.5, 147.6, 148.3, 154.9, 156.1, 174.9. HRMS (ESI-TOF) calcd for $C_{26}H_{33}N_3NaO_7$ $[M + Na]^+$ 522.2211, found 522.2198.

*(S,S)-tert-Butyl ((3-((Ethoxycarbonyl)amino)-1-methyl-2-oxoindolin-3-yl)(3-nitrophenyl)methyl)carbamate (**3h**).* White solid; 40.2 mg, yield 83%; 86:14 dr, 82% ee. $[\alpha]_D^{25}$ = −11.3 (*c* 1.00, $CHCl_3$). Mp: 132.7−134.3 °C. The ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 10/90, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 19.1 min, t_{major} = 24.8 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.15 (br s, 3H), 1.44 (s, 9H), 2.89 (s, 3H), 3.99 (s, 2H), 5.26 (d, *J* = 9.0 Hz, 1H), 6.13 (s, 1H), 6.39 (d, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 8.8 Hz, 1H), 7.07−7.16 (m, 2H), 7.21 (s, 2H), 7.43 (d, *J* = 7.0 Hz, 1H), 7.67 (s, 1H), 7.93 (d, *J* = 5.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 14.4, 26.1, 28.4, 58.7, 61.7, 63.5, 81.1, 108.4, 122.7, 123.0, 123.2, 123.5,

DOI: 10.1021/acs.joc.6b00278
J. Org. Chem. 2016, 81, 5270−5277

127.3, 128.3, 130.1, 133.5, 137.9, 142.9, 147.3, 154.9, 155.8, 174.5. HRMS (ESI-TOF): calcd for $C_{24}H_{28}N_4NaO_7$ $[M + Na]^+$ 507.1850, found 507.1840.

(S,S)-tert-Butyl ((3-((Ethoxycarbonyl)amino)-1-methyl-2-oxoindolin-3-yl)(4-methylphenyl)methyl)carbamate ***(3i)***. White solid; 42.2 mg, yield 93%; 89:11 dr, 92% ee. $[\alpha]_D^{25}$ = −33.0 (*c* 1.00, $CHCl_3$). Mp: 110.9−112.0 °C. The ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 10/90, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 11.7 min, t_{major} = 14.0 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.17 (br s, 3H), 1.45 (s, 9H), 2.09 (s, 3H), 2.87 (s, 3H), 3.98 (s, 2H), 5.10 (d, *J* = 9.6 Hz, 1H), 6.29 (br s, 1H), 6.38 (d, *J* = 7.6 Hz, 1H), 6.46 (d, *J* = 9.6 Hz, 1H), 6.58 (s, 1H), 6.63 (d, *J* = 7.0 Hz, 1H), 6.86−6.90 (m, 2H), 7.02−7.06 (m, 1H), 7.10−7.14 (m, 1H), 7.36 (d, *J* = 7.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 14.4, 21.2, 25.9, 28.4, 59.2, 61.4, 64.5, 80.6, 108.0, 122.8, 122.9, 124.5, 127.2, 128.4, 128.6, 129.3, 134.8, 137.0, 143.3, 155.0, 156.3, 174.8. HRMS (ESI-TOF): calcd for $C_{25}H_{31}N_3NaO_5$ $[M + Na]^+$ 476.2156, found 476.2161.

(S,S)-tert-butyl ((3-((Ethoxycarbonyl)amino)-1-methyl-2-oxoindolin-3-yl)(4-fluorophenyl)methyl)carbamate ***(3j)***. White solid; 43.9 mg, yield 96%; 90:10 dr, 91% ee. $[\alpha]_D^{25}$ = −37.3 (*c* 1.00, $CHCl_3$). Mp: 124.7−125.9 °C. The ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 10/90, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 15.0 min, t_{major} = 23.6 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.15 (br s, 3H), 1.44 (s, 9H), 2.89 (s, 3H), 3.97 (s, 2H), 5.12 (d, *J* = 9.5 Hz, 1H), 6.19 (br s, 1H), 6.42 (d, *J* = 7.7 Hz, 1H), 6.53 (d, *J* = 9.4 Hz, 1H), 6.66−6.70 (m, 2H), 6.77−6.80 (m, 2H), 7.03−7.07 (m, 1H), 7.13−7.17 (m, 1H), 7.36 (d, *J* = 7.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 14.4, 26.0, 28.4, 58.6, 61.5, 64.1, 80.8, 108.2, 114.3 (d, *J* = 21.4 Hz, 1C), 122.9, 123.1, 128.0, 129.2 (d, *J* = 8.1 Hz, 1C), 129.6, 131.0, 143.2, 154.9, 156.1, 162.2 (d, *J* = 245.7 Hz, 1C), 174.8. HRMS (ESI-TOF): calcd for $C_{24}H_{28}FN_3NaO_5$ $[M + Na]^+$ 480.1905, found 480.1903.

(S,S)-tert-Butyl ((3-((Ethoxycarbonyl)amino)-1-methyl-2-oxoindolin-3-yl)(4-chlorophenyl)methyl)carbamate ***(3k)***. White solid; 46.9 mg, yield 99%; 92:8 dr, 91% ee. $[\alpha]_D^{25}$ = −40.1 (*c* 1.00, $CHCl_3$). Mp: 128.7−129.6 °C. The ee was determined by HPLC (Chiralpak OD-H, *i*-PrOH/hexane = 8/92, flow rate 0.5 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 34.3 min, t_{major} = 17.4 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.14 (br s, 3H), 1.43 (s, 9H), 2.90 (s, 3H), 3.97 (s, 2H), 5.11 (d, *J* = 9.4 Hz, 1H), 6.17 (br s, 1H), 6.44 (d, *J* = 7.7 Hz, 1H), 6.54 (d, *J* = 6.9 Hz, 1H), 6.75 (d, *J* = 8.2 Hz, 2H), 6.97 (d, *J* = 8.2 Hz, 2H), 7.03−7.07 (m, 1H), 7.14−7.18 (m, 1H), 7.36 (d, *J* = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 14.4, 26.0, 28.4, 58.6, 61.5, 63.9, 80.8, 108.3, 122.9, 123.1, 127.6, 128.1, 128.9, 129.7, 133.8, 133.9, 143.3, 155.0, 156.0, 174.8. HRMS (ESI-TOF): calcd for $C_{24}H_{28}ClN_3NaO_5$ $[M + Na]^+$ 496.1610, found 496.1611.

(S,S)-tert-Butyl ((3-((Ethoxycarbonyl)amino)-1-methyl-2-oxoindolin-3-yl)(4-bromophenyl)methyl)carbamate ***(3l)***. White solid; 43.0 mg, yield 83%; 91:9 dr, 92% ee. $[\alpha]_D^{25}$ = −49.0 (*c* 1.00, $CHCl_3$). Mp: 128.1−129.5 °C. The ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 10/90, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 21.8 min, t_{major} = 38.9 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.16 (br s, 3H), 1.43 (s, 9H), 2.91 (s, 3H), 3.98 (s, 2H), 5.09 (d, *J* = 9.2 Hz, 1H), 6.12 (br s, 1H), 6.44−6.48 (m, 1H), 6.52−6.58 (m, 1H), 6.69 (d, *J* = 7.7 Hz, 2H), 7.04−7.08 (m, 1H), 7.11−7.19 (m, 3H), 7.37 (d, *J* = 7.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 14.4, 26.1, 28.4, 58.7, 61.6, 63.9, 80.9, 108.4, 122.1, 122.9, 123.1, 129.2, 129.5, 129.8, 130.6, 134.4, 143.2, 154.9, 156.0, 174.8. HRMS (ESI-TOF): calcd for $C_{24}H_{28}BrN_3NaO_5$ $[M + Na]^+$ 540.1105, found 540.1094.

(S,R)-tert-Butyl ((3-((Ethoxycarbonyl)amino)-1-methyl-2-oxoindolin-3-yl)(2-furyl)methyl)carbamate ***(3m)***. White solid; 42.1 mg, yield 98%; 86:14 dr, 86% ee. $[\alpha]_D^{25}$ = −10.9 (*c* 1.00, $CHCl_3$). Mp: 107.9−109.1 °C. The ee was determined by HPLC (Chiralpak OD-H, *i*-PrOH/hexane = 3/97, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 71.6 min, t_{major} = 22.3 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.14 (br s, 3H), 1.46 (s, 9H), 3.06 (s, 3H), 3.97 (s, 2H), 5.30 (d, *J* = 11.0 Hz, 1H), 5.69 (s, 1H), 6.03 (s, 1H), 6.13 (d, *J* = 11.0 Hz, 1H), 6.27 (br s, 1H), 6.59 (d, *J* = 7.6 Hz, 1H), 7.02−7.06 (m, 1H), 7.09 (s, 1H), 7.19−7.22 (m, 1H), 7.28−7.31 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 14.4, 26.4, 28.4, 53.7, 61.4, 63.7, 81.0, 108.0, 108.4, 110.1, 123.0, 128.0, 129.6, 142.1, 142.4, 143.7, 148.6, 154.9, 156.5, 174.6. HRMS (ESI-TOF): calcd for $C_{22}H_{27}N_3NaO_6$ $[M + Na]^+$ 452.1792, found 452.1792.

(S,R)-tert-Butyl ((3-((Ethoxycarbonyl)amino)-1-methyl-2-oxoindolin-3-yl)(2-thienyl)methyl)carbamate ***(3n)***. White solid; 32.1 mg, yield 72%; 88:12 dr, 90% ee. $[\alpha]_D^{25}$ = −6.6 (*c* 1.00, $CHCl_3$). Mp: 95.8−97.3 °C. The ee was determined by HPLC (Chiralpak OD-H, *i*-PrOH/hexane = 10/90, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 26.6 min, t_{major} = 8.7 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.15 (br s, 3H), 1.47 (s, 9H), 2.96 (s, 3H), 3.99 (s, 2H), 5.44 (d, *J* = 9.6 Hz, 1H), 6.16 (s, 1H), 6.41 (d, *J* = 9.2 Hz, 2H), 6.55 (d, *J* = 7.4 Hz, 1H), 6.66 (s, 1H), 6.98 (d, *J* = 4.2 Hz, 1H), 7.08−7.11 (m, 1H), 7.22 (d, *J* = 7.4 Hz, 1H), 7.38 (d, *J* = 6.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 14.5, 26.2, 28.4, 55.4, 61.5, 64.1, 81.0, 108.3, 123.0, 123.2, 125.0, 125.6, 126.0, 126.1, 129.8, 138.3, 144.1, 154.9, 156.2, 174.7. HRMS (ESI-TOF): calcd for $C_{22}H_{27}N_3NaO_5S$ $[M + Na]^+$ 468.1564, found 468.1563.

(S,S)-tert-Butyl ((3-((Ethoxycarbonyl)amino)-1,5-dimethyl-2-oxoindolin-3-yl)(phenyl)methyl)carbamate ***(3o)***. White solid; 44.9 mg, yield 99%; 89:11 dr, 89% ee. $[\alpha]_D^{25}$ = −60.5 (*c* 1.00, $CHCl_3$). Mp: 112.6−113.8 °C. The ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 10/90, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 12.3 min, t_{major} = 10.9 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.21 (br s, 3H), 1.44 (s, 9H), 2.33 (s, 3H), 2.84 (s, 3H), 4.00 (s, 2H), 5.11 (d, *J* = 9.7 Hz, 1H), 6.22 (br s, 1H), 6.26 (d, *J* = 7.9 Hz, 1H), 6.50 (d, *J* = 9.7 Hz, 1H), 6.80 (d, *J* = 7.4 Hz, 2H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.97−7.07 (m, 3H), 7.19 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 14.4, 21.4, 26.0, 28.4, 59.2, 61.4, 64.4, 80.6, 107.8, 123.7, 127.4, 127.5, 127.8, 129.7, 132.4, 135.0, 140.9, 155.0, 156.3, 174.7. HRMS (ESI-TOF): calcd for $C_{25}H_{31}N_3NaO_5$ $[M + Na]^+$ 476.2156, found 476.2152.

(S,S)-tert-Butyl ((3-((Ethoxycarbonyl)amino)-1-methyl-5-fluoro-2-oxoindolin-3-yl)(phenyl)methyl)carbamate ***(3p)***. White solid; 45.3 mg, yield 99%; 87:13 dr, 89% ee. $[\alpha]_D^{25}$ = −24.8 (*c* 1.00, $CHCl_3$). Mp: 111.3−112.6 °C. The ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 8/92, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 16.5 min, t_{major} = 12.5 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.18 (br s, 3H), 1.44 (s, 9H), 2.86 (s, 3H), 3.99 (s, 2H), 5.13 (d, *J* = 9.4 Hz, 1H), 6.29−6.31 (m, 1H), 6.44 (br s, 1H), 6.49 (d, *J* = 9.6 Hz, 1H), 6.80−6.86 (m, 3H), 7.02−7.13 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 14.5, 26.1, 28.4, 59.1, 61.6, 64.6, 80.8, 108.7, 111.1 (d, *J* = 25.1 Hz, 1C), 115.7 (d, *J* = 23.4 Hz, 1C), 127.4, 127.5, 127.6, 128.0, 128.1, 134.7, 139.2, 155.0, 156.2, 159.4 (d, *J* = 240.6 Hz, 1C), 174.6. HRMS (ESI-TOF): calcd for $C_{24}H_{28}FN_3NaO_5$ $[M + Na]^+$ 480.1905, found 480.1898.

(S,S)-tert-Butyl ((3-((Ethoxycarbonyl)amino)-1-ethyl-2-oxoindolin-3-yl)(phenyl)methyl)carbamate ***(3q)***. White solid; 44.4 mg, yield 98%; 79:21 dr, 90% ee. $[\alpha]_D^{25}$ = −31.0 (*c* 1.00, $CHCl_3$). Mp: 246.9−247.5 °C. The ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 10/90, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 16.2 min, t_{major} = 17.2 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 0.88 (t, *J* = 7.1 Hz, 3H), 1.16 (br s, 3H), 1.44 (s, 9H), 3.33−3.38 (m, 1H), 3.56−3.60 (m, 1H), 3.97 (s, 2H), 5.16 (d, *J* = 9.6 Hz, 1H), 6.22 (br s, 1H), 6.44 (d, *J* = 7.6 Hz, 1H), 6.54−6.60 (m, 1H), 6.83 (d, *J* = 6.8 Hz, 2H), 6.97−7.06 (m, 4H), 7.12−7.16 (m, 1H), 7.39 (d, *J* = 7.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 12.0, 14.4, 28.4, 34.7, 59.0, 61.4, 63.9, 80.6, 108.2, 122.7, 123.3, 127.5, 127.7, 127.8, 128.2, 129.4, 135.0, 142.7, 154.9, 156.2, 174.5. HRMS (ESI-TOF): calcd for $C_{25}H_{31}N_3NaO_5$ $[M + Na]^+$ 476.2156, found 476.2141. Anal. Calcd for $C_{25}H_{31}N_3O_5$: C, 66.21; H, 6.89; N, 9.27. Found: C, 66.07; H, 6.88; N, 9.12.

DOI: 10.1021/acs.joc.6b00278
J. Org. Chem. 2016, 81, 5270−5277

*(S,S)-tert-Butyl ((3-((Ethoxycarbonyl)amino)-1-benzyl-2-oxoindolin-3-yl)(phenyl)methyl)carbamate (**3r**).* White solid; 50.5 mg, yield 98%; 94:6 dr, 96% ee. $[\alpha]_D^{25}$ = −17.5 (*c* 1.00, $CHCl_3$). Mp: 117.8−118.3 °C. The ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 10/90, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 25.5 min, t_{major} = 19.9 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.19 (br s, 3H), 1.47 (s, 9H), 4.02 (s, 2H), 4.55 (d, *J* = 16.0 Hz, 1H), 4.72 (d, *J* = 16.0 Hz, 1H), 5.26 (d, *J* = 8.9 Hz, 1H), 6.23 (s, 1H), 6.43 (br s, 1H), 6.60 (d, *J* = 9.7 Hz, 1H), 6.86−6.91 (m, 4H), 6.99−7.02 (m, 4H), 7.10−7.14 (m, 1H), 7.19−7.20 (m, 3H), 7.39−7.41 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 14.4, 28.4, 44.1, 58.9, 61.4, 64.1, 80.6, 109.4, 122.9, 123.1, 127.0, 127.3, 127.7, 127.9, 128.2, 128.7, 129.1, 129.4, 129.8, 135.0, 143.0, 154.9, 156.2, 175.3. HRMS (ESI-TOF): calcd for $C_{30}H_{33}N_3NaO_5$ $[M + Na]^+$ 538.2312, found 538.2311.

*(S,S)-tert-Butyl ((3-((Ethoxycarbonyl)amino)-1-benzyl-2-oxoindolin-3-yl)(4-methoxylphenyl)methyl)carbamate (**3s**).* White solid; 53.5 mg, yield 98%; 95:5 dr, 92% ee. $[\alpha]_D^{25}$ = −49.4 (*c* 1.00, $CHCl_3$). Mp: 123.7−124.6 °C. The ee was determined by HPLC (Chiralpak OD-H, *i*-PrOH/hexane = 5/95, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 26.4 min, t_{major} = 19.5 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.18 (br s, 3H), 1.46 (s, 9H), 3.70 (s, 3H), 4.01 (s, 2H), 4.67 (s, 2H), 5.21 (d, *J* = 9.3 Hz, 1H), 6.27 (s, 1H), 6.38 (br s, 1H), 6.51−6.53 (m, 3H), 6.76−6.78 (m, 2H), 6.90 (s, 2H), 7.04 (d, *J* = 3.6 Hz, 2H), 7.19−7.20 (m, 3H), 7.39 (d, *J* = 3.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 14.4, 28.4, 44.1, 55.2, 58.3, 61.4, 64.2, 80.6, 109.5, 113.1, 122.9, 123.0, 127.0, 127.1, 127.4, 128.4, 128.6, 128.8, 129.4, 135.0, 143.1, 154.9, 156.2, 159.1, 175.4. HRMS (ESI-TOF): calcd for $C_{31}H_{35}N_3NaO_6$ $[M + Na]^+$ 568.2418, found 568.2434.

*(S,S)-tert-Butyl ((3-((Ethoxycarbonyl)amino)-1-benzyl-2-oxoindolin-3-yl)(3-chlorophenyl)methyl)carbamate (**3t**).* White solid; 53.9 mg, yield 98%; 94:6 dr, 96% ee. $[\alpha]_D^{25}$ = −27.0 (*c* 1.00, $CHCl_3$). Mp: 115.3−116.8 °C. The ee was determined by HPLC (Chiralpak OD-H, *i*-PrOH/hexane = 3/97, flow rate 0.5 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 56.3 min, t_{major} = 27.2 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.18 (br s, 3H), 1.47 (s, 9H), 4.02 (s, 2H), 4.56 (d, *J* = 15.9 Hz, 1H), 4.75 (d, *J* = 15.8 Hz, 1H), 5.23 (d, *J* = 9.4 Hz, 1H), 6.29 (s, 1H), 6.33 (br s, 1H), 6.64 (d, *J* = 9.3 Hz, 1H), 6.72 (d, *J* = 7.7 Hz, 1H), 6.89−6.92 (m, 2H), 6.96 (d, *J* = 6.4 Hz, 2H), 7.04−7.11 (m, 3H), 7.22−7.23 (m, 3H), 7.37−7.39 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 14.4, 28.4, 44.2, 58.5, 61.5, 63.8, 80.9, 109.6, 123.1, 123.2, 126.0, 126.9, 127.5, 127.8, 128.1, 128.6, 128.8, 128.9, 129.7, 133.8, 135.0, 137.4, 143.0, 154.8, 156.0, 175.1. HRMS (ESI-TOF): calcd for $C_{30}H_{32}ClN_3NaO_5$ $[M + Na]^+$ 572.1923, found 572.1919.

*(S,S)-tert-Butyl ((3-((Ethoxycarbonyl)amino)-1-benzyl-2-oxoindolin-3-yl)(3-bromophenyl)methyl)carbamate (**3u**).* White solid; 58.9 mg, yield 99%; 94:6 dr, 95% ee. $[\alpha]_D^{25}$ = −33.2 (*c* 1.00, $CHCl_3$). Mp: 120.3−121.3 °C. The ee was determined by HPLC (Chiralpak OD-H, *i*-PrOH/hexane = 3/97, flow rate 0.5 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 52.4 min, t_{major} = 27.3 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.18 (br s, 3H), 1.47 (s, 9H), 4.02 (s, 2H), 4.54 (d, *J* = 16.0 Hz, 1H), 4.77 (d, *J* = 16.0 Hz, 1H), 5.22 (d, *J* = 9.4 Hz, 1H), 6.28 (s, 1H), 6.36 (br s, 1H), 6.64 (d, *J* = 9.4 Hz, 1H), 6.78 (d, *J* = 7.7 Hz, 1H), 6.83−6.87 (m, 1H), 6.96 (d, *J* = 6.8 Hz, 2H), 7.04−7.07 (m, 3H), 7.22−7.26 (m, 4H), 7.36−7.38 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 14.4, 28.4, 44.2, 58.5, 61.5, 63.8, 80.9, 109.6, 121.8, 123.1, 123.2, 126.5, 126.9, 127.5, 127.8, 128.8, 129.2, 129.7, 130.7, 131.0, 134.9, 137.7, 142.9, 154.8, 155.9, 175.1. HRMS (ESI-TOF): calcd for $C_{30}H_{32}BrN_3NaO_5$ $[M + Na]^+$ 616.1418, found 616.1416.

*(S,S)-tert-Butyl ((3-((Ethoxycarbonyl)amino)-1-benzyl-2-oxoindolin-3-yl)(1-naphthyl)methyl)carbamate (**3v**).* Colorless oil; 44.7 mg, yield 79%; 73:27 dr, 85% ee. $[\alpha]_D^{25}$ = +106.3 (*c* 1.00, $CHCl_3$). The ee was determined by HPLC (Chiralpak OD-H, *i*-PrOH/hexane = 5/95, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 47.4 min, t_{major} = 20.9 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.20 (br s, 3H), 1.44 (s, 9H), 4.05 (s, 2H), 4.59 (d, *J* = 15.8 Hz, 1H), 4.91 (d, *J* = 15.7 Hz, 1H), 6.13 (d, *J* = 7.2 Hz, 1H), 6.35 (d, *J* = 9.4 Hz, 1H), 6.45 (br s, 1H), 6.58 (d, *J* = 9.5 Hz, 1H), 6.65−6.73 (m, 2H), 7.10−7.21 (m, 3H), 7.25−7.42 (m, 7H), 7.59−7.62 (m, 2H), 8.13 (d, *J* = 8.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 14.5, 28.4, 44.3, 52.4, 61.4, 64.8, 80.7, 108.8, 122.4, 123.3, 124.0, 124.3, 124.5, 125.5, 125.9, 126.9, 127.4, 127.5, 128.4, 128.7, 128.8, 129.1, 131.0, 132.3, 133.1, 135.2, 142.4, 154.9, 156.5, 175.8. HRMS (ESI-TOF) calcd for $C_{34}H_{35}N_3NaO_5$ $[M + Na]^+$ 588.2469, found 588.2460.

General Procedure for the Synthesis of Vicinal Oxindole−Amino Alcohols 6. In an ordinary vial equipped with a magnetic stirring bar were dissolved 3-hydroxyoxindoles **5** (0.1 mmol, 1 equiv), amidosulfones **2** (0.12 mmol, 1.2 equiv), and catalyst **4a** (4.1 mg, 0.01 mmol) in 2.0 mL of CH_2Cl_2, and then 0.1 mL of a saturated aqueous solution of Na_2CO_3 was added into the solution. The resulting mixture was stirred at 25 °C under N_2 atmosphere for 12 h. After completion of the reaction, as indicated by TLC, the reaction mixture was directly purified by flash chromatography (petroleum ether/ethyl acetate = 5/1−2/1) to furnish the corresponding products **6**.

*tert-Butyl ((3-Hydroxy-1-methyl-2-oxoindolin-3-yl)(phenyl)methyl)carbamate (**6a**).* Colorless oil; 27.6 mg, yield 75%; 91:9 dr, 84% ee. $[\alpha]_D^{25}$ = +9.0 (*c* 1.00, $CHCl_3$). The ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 10/90, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 22.6 min, t_{major} = 20.4 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.42 (s, 9H), 2.87 (s, 3H), 4.10−4.12 (m, 1H), 5.25 (d, *J* = 9.4 Hz, 1H), 6.45 (d, *J* = 7.5 Hz, 1H), 6.52 (d, *J* = 9.3 Hz, 1H), 6.90 (d, *J* = 6.1 Hz, 2H), 7.02−7.12 (m, 4H), 7.17−7.20 (m, 1H), 7.52 (d, *J* = 6.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 25.8, 28.5, 61.2, 77.3, 80.4, 108.3, 123.3, 124.4, 127.4, 127.6, 127.7, 128.0, 130.1, 136.1, 143.3, 156.1, 176.6. HRMS (ESI-TOF) calcd for $C_{21}H_{24}N_2NaO_4$ $[M + Na]^+$ 391.1628, found 391.1620.

*tert-Butyl ((1-Benzyl-3-hydroxy-2-oxoindolin-3-yl)(phenyl)methyl)carbamate (**6b**).* Light yellow solid; 40.5 mg, yield 91%; 90:10 dr, 87% ee. $[\alpha]_D^{25}$ = −9.5 (*c* 1.00, $CHCl_3$). Mp: 101.7−103.2 °C. The ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 10/90, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 32.6 min, t_{major} = 51.9 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.45 (s, 9H), 4.23−4.25 (m, 1H), 4.45 (d, *J* = 15.9 Hz, 1H), 4.84 (d, *J* = 16.2 Hz, 1H), 5.39 (d, *J* = 9.8 Hz, 1H), 6.34 (d, *J* = 6.2 Hz, 1H), 6.60 (d, *J* = 9.6 Hz, 1H), 6.74 (d, *J* = 6.2 Hz, 2H), 6.97 (d, *J* = 7.1 Hz, 2H), 7.03−7.10 (m, 4H), 7.12−7.20 (m, 4H), 7.56 (d, *J* = 5.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 28.5, 43.7, 60.6, 77.0, 80.5, 109.7, 123.4, 124.6, 126.9, 127.5, 127.7, 128.1, 128.2, 128.5, 128.7, 130.2, 134.7, 136.0, 142.9, 156.1, 176.8. HRMS (ESI-TOF): calcd for $C_{27}H_{28}N_2NaO_4$ $[M + Na]^+$ 467.1941, found 467.1925.

*tert-Butyl ((1-Benzyl-3-hydroxy-2-oxoindolin-3-yl)(m-tolyl)methyl)carbamate (**6c**).* Light yellow oil; 36.7 mg, yield 80%; 90:10 dr, 87% ee. $[\alpha]_D^{25}$ = −0.6 (*c* 1.00, $CHCl_3$). The ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 10/90, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 23.3 min, t_{major} = 33.4 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.46 (s, 9H), 2.11 (s, 3H), 4.22 (s, 1H), 4.43 (d, *J* = 16.0 Hz, 1H), 4.88 (d, *J* = 16.0 Hz, 1H), 5.37 (d, *J* = 9.7 Hz, 1H), 6.32 (d, *J* = 5.8 Hz, 1H), 6.57 (d, *J* = 9.6 Hz, 1H), 6.70 (d, *J* = 6.2 Hz, 2H), 6.76−6.79 (m, 2H), 6.92−7.00 (m, 2H), 7.05−7.09 (m, 2H), 7.13−7.19 (m, 3H), 7.57 (d, *J* = 4.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 21.4, 28.5, 43.7, 60.5, 77.1, 80.5, 109.8, 123.3, 124.6, 124.8, 126.7, 127.5, 127.9, 128.1, 128.4, 128.5, 128.7, 130.1, 134.7, 135.9, 137.7, 143.0, 156.1, 176.8. HRMS (ESI-TOF): calcd for HRMS (ESI-TOF) calcd for $C_{28}H_{30}N_2NaO_4$ $[M + Na]^+$ 481.2098, found 481.2082.

*tert-Butyl ((1-Benzyl-3-hydroxy-2-oxoindolin-3-yl)(p-tolyl)methyl)carbamate (**6d**).* Colorless oil; 35.8 mg, yield 78%; 91:9 dr, 88% ee. $[\alpha]_D^{25}$ = −0.5 (*c* 1.00, $CHCl_3$). The ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 10/90, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 23.3 min, t_{major} = 33.3 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.46 (s, 9H), 2.11 (s, 3H), 4.06 (s, 1H), 4.44 (d, *J* = 16.0 Hz, 1H), 4.87 (d, *J* = 16.0 Hz, 1H), 5.34 (d, *J* = 9.9 Hz, 1H), 6.32 (d, *J* = 4.6 Hz, 1H), 6.54 (d, *J* = 10.0 Hz, 1H), 6.61−6.77 (m, 4H), 6.92−7.00 (m, 2H), 7.08−

DOI: 10.1021/acs.joc.6b00278
J. Org. Chem. 2016, 81, 5270−5277

7.21 (m, 5H), 7.57 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 21.4, 28.5, 43.7, 60.6, 77.1, 80.5, 109.8, 123.3, 124.6, 124.8, 126.7, 127.5, 128.0, 128.4, 128.5, 128.7, 130.2, 134.7, 135.8, 137.7, 143.1, 156.1, 176.9. HRMS (ESI-TOF): calcd for $C_{28}H_{30}N_2NaO_4$ $[M + Na]^+$ 481.2098, found 481.2083.

*tert-Butyl ((1-Benzyl-3-hydroxy-2-oxoindolin-3-yl)(4-methoxyphenyl)methyl)carbamate (**6e**).* Light yellow solid; 35.1 mg, yield 74%; 82:18 dr, 88% ee. $[\alpha]_D^{25} = -0.5$ (c 1.00, $CHCl_3$). Mp: 116.9−118.4 °C. The ee was determined by HPLC (Chiralpak AD-H, i-PrOH/hexane = 10/90, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 44.3 min, t_{major} = 78.1 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.45 (s, 9H), 3.70 (s, 3H), 4.08 (s, 1H), 4.44 (d, J = 16.0 Hz, 1H), 4.89 (d, J = 16.0 Hz, 1H), 5.32 (d, J = 9.8 Hz, 1H), 6.36 (d, J = 6.7 Hz, 1H), 6.51 (d, J = 9.9 Hz, 1H), 6.57 (d, J = 8.2 Hz, 2H), 6.72−6.76 (m, 2H), 6.86 (d, J = 7.8 Hz, 2H), 7.06−7.11 (m, 2H), 7.13−7.20 (m, 3H), 7.55 (d, J = 6.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 28.5, 43.7, 55.2, 60.0, 77.0, 80.5, 109.8, 113.5, 123.4, 124.5, 126.7, 126.9, 127.6, 128.0, 128.7, 128.8, 129.4, 130.2, 134.7, 143.1, 156.1, 159.0, 176.9. HRMS (ESI-TOF): calcd for $C_{28}H_{30}N_2NaO_5$ $[M + Na]^+$ 497.2047, found 497.2042. Anal. Calcd for $C_{28}H_{30}N_2O_5$: C, 70.87; H, 6.37; N, 5.90. Found: C, 69.56; H, 6.37; N, 5.91.

*tert-Butyl ((1-Benzyl-3-hydroxy-2-oxoindolin-3-yl)(3,4-dimethoxyphenyl)methyl)carbamate (**6f**).* Light yellow solid; 36.3 mg, yield 72%; 84:16 dr, 92% ee. $[\alpha]_D^{25} = -13.1$ (c 1.00, $CHCl_3$). Mp: 123.4−124.9 °C. The ee was determined by HPLC (Chiralpak IA3, i-PrOH/hexane = 10/90, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 52.6 min, t_{major} = 28.5 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.45 (s, 9H), 3.43 (s, 3H), 3.78 (s, 3H), 4.12 (s, 1H), 4.42 (d, J = 16.0 Hz, 1H), 4.86 (d, J = 16.0 Hz, 1H), 5.32 (d, J = 9.7 Hz, 1H), 6.28 (s, 1H), 6.35−6.42 (m, 1H), 6.49−6.60 (m, 3H), 6.69 (d, J = 6.4 Hz, 2H), 7.10−7.17 (m, 5H), 7.59 (d, J = 3.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 28.5, 43.7, 55.6, 55.7, 60.2, 77.0, 80.5, 109.9, 110.5, 111.2, 119.2, 123.2, 124.5, 126.6, 126.7, 127.6, 128.3, 128.7, 130.2, 134.4, 143.2, 148.0, 148.4, 156.1, 176.9. HRMS (ESI-TOF): calcd for $C_{29}H_{32}N_2NaO_6$ $[M + Na]^+$ 527.2153, found 527.2155.

*tert-Butyl ((1-Benzyl-3-hydroxy-2-oxoindolin-3-yl)(4-chlorophenyl)methyl)carbamate (**6g**).* Colorless oil; 36.9 mg, yield 77%; 82:18 dr, 80% ee. $[\alpha]_D^{25} = -13.1$ (c 1.00, $CHCl_3$). The ee was determined by HPLC (Chiralpak AD-H, i-PrOH/hexane = 10/90, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 26.5 min, t_{major} = 45.6 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.44 (s, 9H), 4.06 (s, 1H), 4.42 (d, J = 15.9 Hz, 1H), 4.91 (d, J = 16.4 Hz, 1H), 5.34 (d, J = 9.3 Hz, 1H), 6.42 (d, J = 7.2 Hz, 1H), 6.60 (s, 1H), 6.74 (s, 2H), 6.87 (d, J = 7.4 Hz, 2H), 6.99 (d, J = 7.2 Hz, 2H), 7.09−7.15 (m, 2H), 7.20−7.23 (m, 3H), 7.55 (d, J = 6.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 28.5, 43.8, 60.0, 76.7, 80.7, 109.9, 123.6, 124.6, 126.7, 126.9, 127.7, 128.3, 128.8, 129.1, 130.5, 133.7, 134.6, 134.7, 143.0, 155.9, 176.6. HRMS (ESI-TOF): calcd for $C_{27}H_{27}ClN_2NaO_4$ $[M + Na]^+$ 501.1552, found 501.1541.

*tert-Butyl ((1-Benzyl-3-hydroxy-2-oxoindolin-3-yl)(4-bromophenyl)methyl)carbamate (**6h**).* Light yellow solid; 36.1 mg, yield 69%; 83:17 dr, 78% ee. $[\alpha]_D^{25} = -0.6$ (c 1.00, $CHCl_3$). Mp: 123.5−125.1 °C. The ee was determined by HPLC (Chiralpak AD-H, i-PrOH/hexane = 10/90, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 29.0 min, t_{major} = 55.6 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.44 (s, 9H), 4.14 (s, 1H), 4.41 (d, J = 15.9 Hz, 1H), 4.91 (d, J = 16.2 Hz, 1H), 5.33 (d, J = 9.6 Hz, 1H), 6.42 (d, J = 7.4 Hz, 1H), 6.60 (d, J = 9.2 Hz, 1H), 6.74 (s, 2H), 6.82 (d, J = 7.6 Hz, 2H), 7.08−7.15 (m, 4H), 7.21−7.26 (m, 3H), 7.55 (d, J = 6.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 28.5, 43.9, 60.1, 76.6, 80.7, 109.9, 121.9, 123.5, 124.6, 126.9, 127.6, 127.7, 128.8, 129.4, 130.5, 131.2, 134.6, 135.3, 143.0, 155.9, 176.6. HRMS (ESI-TOF): calcd for $C_{27}H_{27}BrN_2NaO_4$ $[M + Na]^+$ 545.1046, found 545.1030.

*tert-Butyl ((1-Benzyl-3-hydroxy-2-oxoindolin-3-yl)(thiophene-2-yl)methyl)carbamate **6i**.* White solid; 37.8 mg, yield 84%; 90:10 dr, 85% ee. $[\alpha]_D^{25} = -0.5$ (c 1.00, $CHCl_3$). Mp: 114.1−115.6 °C. The ee was determined by HPLC (Chiralpak IC3, i-PrOH/hexane = 10/90, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 61.5 min, t_{major} = 50.2 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.48 (s, 9H), 4.11 (s, 1H), 4.45 (d, J = 15.8 Hz, 1H), 4.97 (d, J = 16.2 Hz, 1H), 5.64 (d, J = 9.2 Hz, 1H), 6.49−6.55 (m, 3H), 6.76 (s, 3H), 7.04 (s, 1H), 7.10−7.12 (m, 1H), 7.19 (s, 4H), 7.51 (d, J = 6.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 28.5, 43.8, 56.8, 76.4, 80.8, 109.9, 123.6, 124.6, 125.1, 125.7, 126.6, 126.8, 127.5, 127.7, 128.8, 130.6, 134.7, 139.8, 143.7, 156.0, 176.5. HRMS (ESI-TOF): calcd for $C_{25}H_{26}N_2NaO_4S$ $[M + Na]^+$ 473.1505, found 473.1508.

*tert-Butyl ((1-Benzyl-3-hydroxy-5-methoxy-2-oxoindolin-3-yl)-(phenyl)methyl)carbamate (**6j**).* Light yellow solid; 42.2 mg, yield 89%; 91:9 dr, 86% ee. $[\alpha]_D^{25} = -48.2$ (c 1.00, $CHCl_3$). Mp: 116.5−117.8 °C. The ee was determined by HPLC (Chiralpak AD-H, i-PrOH/hexane = 10/90, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 41.8 min, t_{major} = 37.1 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.45 (s, 9H), 3.75 (s, 3H), 4.11 (s, 1H), 4.42 (d, J = 16.0 Hz, 1H), 4.81 (d, J = 16.2 Hz, 1H), 5.37 (d, J = 10.0 Hz, 1H), 6.23 (d, J = 8.5 Hz, 1H), 6.57−6.63 (m, 2H), 6.71 (d, J = 6.8 Hz, 2H), 6.99 (d, J = 7.4 Hz, 2H), 7.06−7.09 (m, 2H), 7.14−7.19 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 28.5, 43.8, 55.9, 60.6, 77.3, 80.6, 110.5, 111.0, 115.4, 126.7, 126.9, 127.5, 127.7, 127.8, 128.1, 128.7, 134.8, 136.0, 136.2, 156.1, 156.5, 176.6. HRMS (ESI-TOF): calcd for $C_{28}H_{30}N_2NaO_5$ $[M + Na]^+$ 497.2047, found 497.2037.

*tert-Butyl ((1-Benzyl-7-fluoro-3-hydroxy-2-oxoindolin-3-yl)-(phenyl)methyl)carbamate (**6k**).* Light yellow oil; 17.1 mg, yield 37%; 88:12 dr, 90% ee. $[\alpha]_D^{25} = +1.1$ (c 1.00, $CHCl_3$). The ee was determined by HPLC (Chiralpak IA3, i-PrOH/hexane = 10/90, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 16.2 min, t_{major} = 17.9 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 1.44 (s, 9H), 4.21 (s, 1H), 4.73 (d, J = 15.5 Hz, 1H), 4.81 (d, J = 16.1 Hz, 1H), 5.32 (d, J = 9.9 Hz, 1H), 6.51 (d, J = 9.8 Hz, 1H), 6.91 (d, J = 8.1 Hz, 4H), 6.99−7.06 (m, 3H), 7.10−7.14 (m, 2H), 7.19−7.23 (m, 3H), 7.37 (d, J = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 28.5, 45.4, 60.7, 77.0, 80.7, 118.4 (d, J = 19.5 Hz, 1C), 120.6, 124.2, 126.8, 127.2, 127.5, 127.6, 128.0, 128.1, 128.2, 128.6, 128.9, 130.9 (d, J = 2.9 Hz, 1C), 135.5, 136.0, 147.3 (d, J = 244.2 Hz, 1C), 156.1, 176.5. HRMS (ESI-TOF): calcd for $C_{27}H_{27}FN_2NaO_4$ $[M + Na]^+$ 485.1847, found 485.1855.

Procedure for the Synthesis of Compound 8. To the solution of **3u** (159.0 mg, 0.27 mmol) in CH_2Cl_2 (1.5 mL) was slowly added CF_3CO_2H (0.5 mL) at 0 °C. The resulting mixture was subsequently stirred at 0 °C for 10 min and concentrated, and the residue was dissolved in CH_2Cl_2 (5.0 mL). Then the mixture was adjusted to pH 10 with saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to give the crude primary amine 7 (131.0 mg). Then the mixture of 7 (131.0 mg), di(1*H*-imidazol-1-yl)methanethione (57.0 mg, 32.0 mmol), and Et_3N (7 μL) in CH_2Cl_2 (6.0 mL) was refluxed for 2 h. The mixture was adjusted to pH 2 with 2 M HCl and extracted with CH_2Cl_2 (3 × 5 mL). After being dried over anhydrous Na_2SO_4, the mixture was concentrated, and the residue was purified by flash column chromatography (petroleum ether/ethyl acetate = 5/1−2/1) to give the product **8** as a white solid (130.0 mg).

*(3′S,5S)-Ethyl 1′-Benzyl-5-(3-bromophenyl)-2′-oxo-2-thioxospiro-[imidazolidine-4,3′-indoline]-3-carboxylate (**8**).* Yield 90%; 96:4 dr, 95% ee. $[\alpha]_D^{25} = -68.4$ (c 1.00, $CHCl_3$). Mp: 138.9−140.2 °C. The ee was determined by HPLC (Chiralpak IA3, i-PrOH/hexane = 10/90, flow rate 0.8 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 74.3 min, t_{major} = 46.4 min). ^{1}H NMR (300 MHz, $CDCl_3$): δ (major diastereomer) 0.87 (t, J = 7.1 Hz, 3H), 3.89−4.00 (m, 1H), 4.05−4.13 (m, 1H), 4.21 (d, J = 15.6 Hz, 1H), 4.89 (d, J = 15.6 Hz, 1H), 5.21 (s, 1H), 6.60 (d, J = 7.7 Hz, 1H), 6.65−6.68 (m, 2H), 7.12−7.20 (m, 7H), 7.25−7.30 (m, 1H), 7.45−7.50 (m, 2H), 7.78 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (major diastereomer) 13.6, 44.2, 63.5, 66.7, 73.5, 109.7, 122.7, 123.0, 123.7, 126.3, 126.9, 127.0, 127.7, 128.9, 130.4, 130.5, 130.8, 132.8, 134.3, 135.0, 143.4 150.5, 171.2, 181.7. HRMS

DOI: 10.1021/acs.joc.6b00278
J. Org. Chem. 2016, 81, 5270−5277

(ESI-TOF) calcd for $C_{26}H_{22}BrN_3NaO_3S$ $[M + Na]^+$ 558.0457, found 558.0462.

Procedure for the Synthesis of Compound 10. To the solution of **6a** (48.0 mg, 0.13 mmol) in CH_2Cl_2 (5.0 mL) was added CF_3CO_2H (0.3 mL). The resulting mixture was subsequently stirred at room temperature for 4 h and concentrated, and the residue was dissolved in CH_2Cl_2 (5.0 mL). Then the mixture was adjusted to pH 10 with saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to give the crude product **9** (34.0 mg). Then the mixture of **9** (34.0 mg), di(1*H*-imidazol-1-yl)methanethione (28.0 mg, 0.16 mmol), and Et_3N (4 μL) in CH_2Cl_2 (5.0 mL) was refluxed for 1.5 h. The mixture was adjusted to pH 2 with 2 M HCl and extracted with CH_2Cl_2 (3 × 5 mL). After being dried over anhydrous Na_2SO_4, the mixture was concentrated, and the residue was purified by flash column chromatography (petroleum ether/ethyl acetate = 5/1−1/1) to give the product **10** as a yellow oil (33.0 mg).

*1-Methyl-4′-phenyl-2′-thioxospiro[indoline-3,5′-oxazolidin]-2-one (**10**).* Yield 82%; > 99:1 dr, 82% ee. $[\alpha]_D^{25} = -22.3$ (*c* 1.00, $CHCl_3$). The ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 32.3 min, t_{major} = 26.1 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ (major diastereomer) 2.80 (s, 3H), 5.54 (s, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 6.4 Hz, 2H), 7.19−7.25 (m, 2H), 7.26−7.29 (m, 2H), 7.42−7.46 (m, 1H), 7.65 (d, *J* = 7.4 Hz, 1H), 8.25 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (major diastereomer) 26.1, 68.3, 89.3, 108.9, 123.5, 123.8, 125.3, 126.5, 126.7, 128.8, 129.0, 129.5, 131.2, 132.2, 144.7, 169.7, 189.7. HRMS (ESI-TOF): calcd for $C_{17}H_{14}N_2NaO_2S$ $[M + Na]^+$ 333.0668, found 333.0682.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00278.

^{1}H, ^{13}C NMR and HPLC spectra for the new products (PDF)

Single-crystal X-ray crystallography data for product **3n** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: cuibd@zmc.edu.cn.

*E-mail: yzchen@zmc.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the financial support from New Century Excellent Talents in University of Ministry of Education of China (NCET-2013-1069) and The Science and Technology Department of Guizhou Province (QKHSY[2015]3030 and QKHRC[2016]4029).

■ REFERENCES

(1) Bao, X.; Wang, B.; Cui, L.; Zhu, G.; He, Y.; Qu, J.; Song, Y. *Org. Lett.* **2015**, *17*, 5168.

(2) For selected examples, see: (a) Ochi, M.; Kawasaki, K.; Kataoka, H.; Uchio, Y.; Nishi, H. *Biochem. Biophys. Res. Commun.* **2001**, *283*, 1118. (b) Bernard, K.; Bogliolo, S.; Ehrenfeld, J. *Br. J. Pharmacol.* **2005**, *144*, 1037. (c) Rottmann, M.; McNamara, C.; Yeung, B. S. K.; Lee, M. C. S.; Zou, B.; Russell, B.; Seitz, P.; Plouffe, D. M.; Dharia, N. V.; Tan, J.; Cohen, S. B.; Spencer, K. R.; Gonzalez-Paez, G.; Lakshminarayana, L.; Goh, A.; Suwanarusk, R.; Jegla, T.; Schmitt, E. K.; Beck, H.-P.; Brun, R.; Nosten, F.; Renia, L.; Dartois, V.; Keller, T. H.; Fidock, D. A.; Winzeler, E. A.; Diagana, T. T. *Science* **2010**, *329*, 1175.

(3) For selected examples, see: (a) Vintonyak, V. V.; Warburg, K.; Kruse, H.; Grimme, S.; Hubel, K.; Rauh, D.; Waldmann, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 5902. (b) Koguchi, Y.; Kohno, J.; Nishio, M.; Takahashi, K.; Okuda, T.; Ohnuki, T.; Komatsubara, S. *J. Antibiot.* **2000**, *53*, 105. (c) Lin, S.; Yang, Z.-Q.; Kwok, B. H. B.; Koldobskiy, K. M.; Crews, C. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 6347. (d) Balk-Bindseil, W.; Helmke, E.; Weyland, H.; Laatsch, H. *Liebigs Ann.* **1995**, *1995*, 1291. (e) Nagamine, J.; Nagata, R.; Seki, H.; Nomura-Akimaru, N.; Ueki, Y.; Kumagai, K.; Taiji, M.; Noguchi, H. *J. Endocrinol.* **2001**, *171*, 481.

(4) For reviews, see: (a) Chauhan, P.; Chimni, S.-S. *Tetrahedron: Asymmetry* **2013**, *24*, 343. (b) Han, W.-Y.; Zhao, J.-Q.; Zuo, J.; Xu, X.-Y.; Zhang, X.-M.; Yuan, W.-C. *Adv. Synth. Catal.* **2015**, *357*, 3007. (c) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381. (d) Chen, D.; Xu, M.-H. *Chem. Commun.* **2013**, *49*, 1327.

(5) For selected examples, see: (a) Cheng, L.; Liu, L.; Wang, D.; Chen, Y.-J. *Org. Lett.* **2009**, *11*, 3874. (b) Mouri, S.; Chen, Z.; Mitsunuma, H.; Furutachi, M.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 1255. (c) Bui, T.; Hernández-Torres, G.; Milite, C.; Barbas, C. F., III. *Org. Lett.* **2010**, *12*, 5696.

(6) For selected examples, see: (a) Shen, K.; Liu, X.; Wang, G.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 4684. (b) Companyó, X.; Valero, G.; Pineda, O.; Calvet, T.; Font-Bardía, M.; Moyano, A.; Rios, R. *Org. Biomol. Chem.* **2012**, *10*, 431. (c) Jia, Y.-X.; Hillgren, J. M.; Watson, E. L.; Marsden, S. P.; Kündig, E. P. *Chem. Commun.* **2008**, 4040. (d) Shirai, T.; Ito, H.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 2658.

(7) Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104.

(8) (a) Ishimaru, T.; Shibata, N.; Nagai, J.; Nakamura, S.; Toru, T.; Kanemasa, S. *J. Am. Chem. Soc.* **2006**, *128*, 16488. (b) Sano, D.; Nagata, K.; Itoh, T. *Org. Lett.* **2008**, *10*, 1593. (c) Zhang, Z.; Zheng, W.; Antilla, J. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 1135.

(9) (a) Cui, B.-D.; Han, W.-Y.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. *J. Org. Chem.* **2013**, *78*, 8833. (b) Jiang, D.; Dong, S.; Tang, W.; Lu, T.; Du, D. *J. Org. Chem.* **2015**, *80*, 11593. (c) Chen, L.; Wu, Z.-J.; Zhang, M.-L.; Yue, D.-F.; Zhang, X.-M.; Xu, X.-Y.; Yuan, W.-C. *J. Org. Chem.* **2015**, *80*, 12668. (d) Zhu, G.; Wang, B.; Bao, X.; Zhang, H.; Wei, Q.; Qu, J. *Chem. Commun.* **2015**, *51*, 15510.

(10) For selected examples, see: (a) Wang, Q.-L.; Peng, L.; Wang, F.-Y.; Zhang, M.-L.; Jia, L.-N.; Tian, F.; Xu, X.-Y.; Wang, L.-X. *Chem. Commun.* **2013**, *49*, 9422. (b) Silvi, M.; Chatterjee, I.; Liu, Y.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 10780. (c) Retini, M.; Bergonzini, G.; Melchiorre, P. *Chem. Commun.* **2012**, *48*, 3336. (d) Trost, B. M.; Hirano, K. *Org. Lett.* **2012**, *14*, 2446. (e) Yamaguchi, E.; Mowat, J.; Luong, T.; Krische, M. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 8428.

(11) For selected examples, see: (a) Johnson, K. M.; Rattley, M. S.; Sladojevich, F.; Barber, D. M.; Nuñez, M. G.; Goldys, A. M.; Dixon, D. J. *Org. Lett.* **2012**, *14*, 2492. (b) Wang, B.; Liu, Y.; Sun, C.; Wei, Z.; Cao, J.; Liang, D.; Lin, Y.; Duan, H. *Org. Lett.* **2014**, *16*, 6432. (c) DiRocco, D. A.; Rovis, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 5904. (d) Chuan, Y.-M.; Chen, G.-H.; Gao, J.-Z.; Zhang, H.; Peng, Y.-G. *Chem. Commun.* **2011**, *47*, 3260. (e) Wang, H.-Y.; Zhang, K.; Zheng, C.-W.; Chai, Z.; Cao, D.-D.; Zhang, J.-X.; Zhao, G. *Angew. Chem., Int. Ed.* **2015**, *54*, 1775.

DOI: 10.1021/acs.joc.6b00278
J. Org. Chem. 2016, 81, 5270−5277