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Enantioselective Synthesis of Quaternary 3-Aminooxindoles via Organocatalytic Asymmetric Michael Addition of 3-Monosubstituted 3-Aminooxindoles to Nitroolefins

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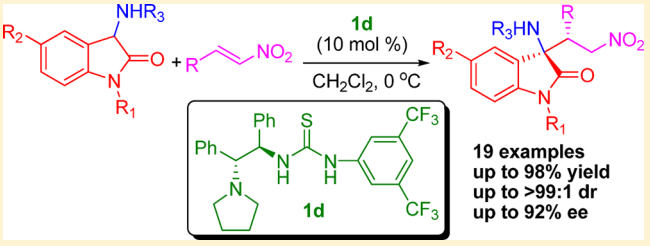
Supporting Information

ABSTRACT: An enantioselective synthesis of quaternary 3-aminooxindoles with 3-monosubstituted 3-aminooxindoles as nucleophiles is first presented. A Michael addition reaction of 3-monosubstituted 3-aminooxindoles to nitroolefins has been developed with a bifunctional thiourea-tertiary amine as a catalyst to afford a range of 3,3-disubstituted oxindoles bearing adjacent quaternary-tertiary centers in good results (up to 98% yield, >99:1 dr, and 92% ee). We also demonstrate the potential synthetic utility of this methodology by a transformation of the product into a spirocyclic oxindole compound.



Oxindoles are prominent scaffolds in natural products,[1] as well as providing valuable pharmaceutical lead compounds. Particularly, 3,3-disubstituted oxindoles ubiquitously make up the core of many natural products and pharmaceuticals.[1] Among these, quaternary 3-aminooxindole frameworks are present in a large number of bioactive, naturally occurring alkaloids and medicinally relevant compounds (Figure 1).[2] Hence numerous stereoselective processes for preparing various quaternary 3-aminooxindole derivatives have been developed.[3] The known methods for the construction of this type of fascinating frameworks include asymmetric addition to isatin imines,[4] amination of 3-monosubstituted oxindoles,[5] multicomponent reaction,[6] hydroxyamination reaction,[3a,7] and other strategies (Scheme 1).[8] Despite these achievements, given the potential bioactive and medicinal significance of the enantiomerically pure quaternary 3-aminooxindole compounds, it is still important and desirable to develop more effective and creative methods to access the compounds containing a quaternary 3-aminooxindole skeleton.

Indeed the potential clinical significance and the synthetic application of chiral 3,3-disubstituted oxindoles have led to a demand for the efficient asymmetric synthetic methods. Recently, a number of successful examples using various 3-monosubstituted oxindoles as nucleophiles reacting with diverse electrophiles to afford 3,3-disubstituted oxindoles have been reported.[1,3] However, to the best of our knowledge, no examples with 3-monosubstituted 3-aminooxindoles as nucleophiles for catalytic asymmetric transformations were reported (Scheme 1). In this context, from a synthetic point of view, we envisioned that the reaction of 3-monosubstituted 3-aminooxindoles as nucleophiles with appropriate acceptors would be an alternatively direct approach to access the quaternary 3-aminooxindole compounds (Scheme 1). As a continuation of our studies on the construction of structurally diverse 3,3-disubstituted oxindoles,[9] herein, we wish to report an unprecedented Michael addition reaction of 3-monosubstituted 3-aminooxindoles to nitroolefins with bifunctional thiourea-tertiary amine organocatalysts (Scheme 2).[10] This will complement a new strategy for the preparation of enantioenriched quaternary 3-aminooxindoles bearing adjacent quaternary-tertiary centers. Nevertheless, we also strongly believe that this study will open an opportunity for employing 3-monosubstituted 3-aminooxindoles as competent nucleophiles for various catalytic asymmetric transformations.

The studies were initiated by evaluating the reaction between ethyl 1-methyl-2-oxoindolin-3-ylcarbamate[11] **2a** and *β*-nitrostyrene **3a** using Takemoto's catalyst **1a** (Figure 2) in toluene at 0 °C. The reaction proceeded smoothly to afford the desired Michael adduct **4a** in good yield with good diastereoselectivity and moderate enantioselectivity (Table 1, entry 1). Under the analogous conditions, **1b** or **1c** was a little better than **1a** for the reaction, as **4a** could be obtained in excellent yield with good diastereoselectivity and enantioselectivity, respectively (Table 1, entries 2 and 3). These data suggest that the pyrrolidine structure of the tertiary amine in the catalyst is superior to the dimethylamine structure for the reactivity and enantioselectivity. We then conducted the reaction in the presence of catalyst

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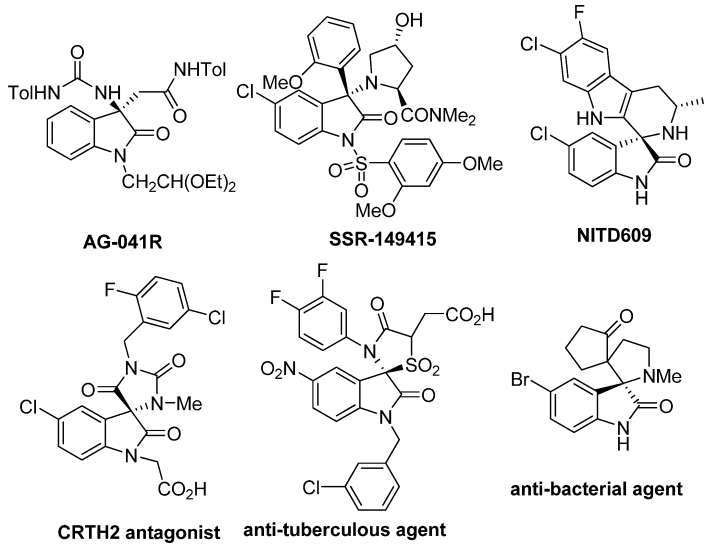
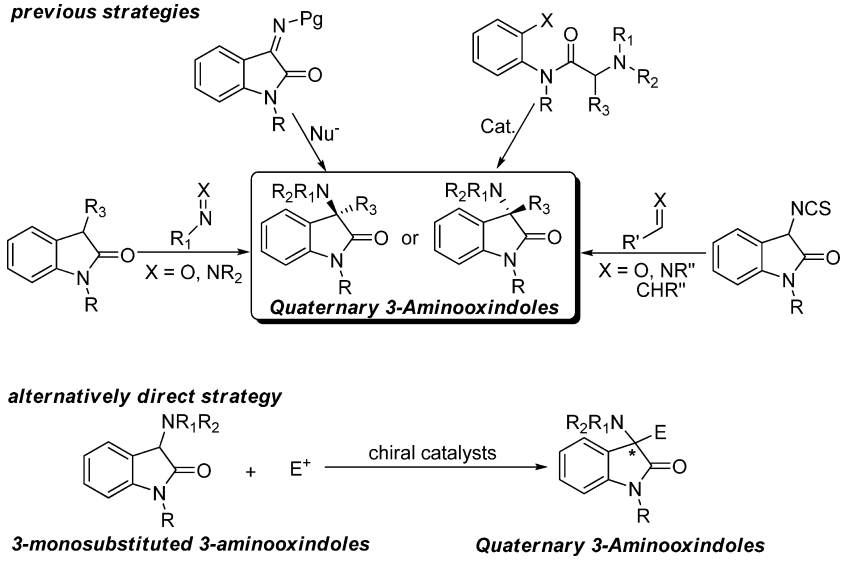
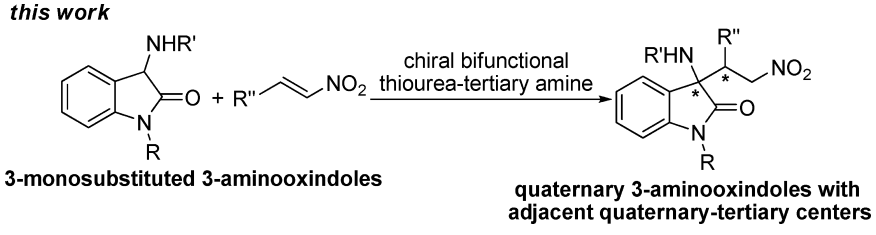


Figure 1. Biologically active compounds based on the quaternary 3-aminooxindole frameworks.

Scheme 1. Catalytic Methods for the Asymmetric Synthesis of Quaternary 3-Aminooxindoles



Scheme 2



1d containing a pyrrolidine structure and chiral DPEN scaffold, providing **4a** in 97% yield with 87:13 dr and up to 81% ee, but with a prolonged reaction time (Table 1, entry 4). Further screening of the catalysts **1e–h** were carried out under the analogue conditions as used in entry 1 (Table 1, entries 5–8). The results revealed that catalysts **1e–h** were inferior to **1d** in every respect (Table 1, entries 5–8 vs 4). Then **1d** was chosen for optimization studies. We further explored the effects of the nitrogen protecting group of the C3-position of oxindole. A similar yield and diastereoselectivity as in entry 4 could be achieved for **2b** bearing the *N*-Boc group, but the corresponding **4b** was obtained with only 70% ee (Table 1, entry 9). Meanwhile, similar results were observed for **2c** bearing the *N*-Cbz group (Table 1, entry 10, for **4c**, 95% yield, 89:11 dr and 71% ee). Screening of the solvent identified dichloromethane to be the best solvent for the reaction (Table 1, entry 12). Slight improvements in diastereo- and enantioselectivity accompanied the substrate ratio changes from 1:1.2 to 1:1.5 regarding **2a**:**3a** (Table 1, entry16 vs 12).

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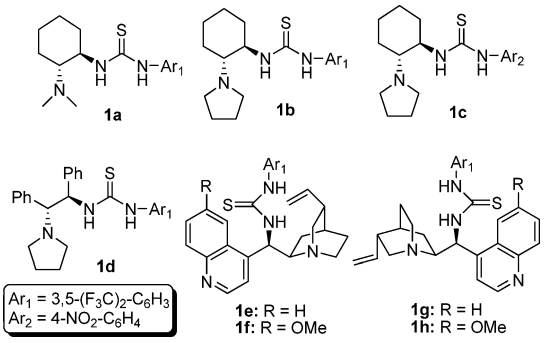
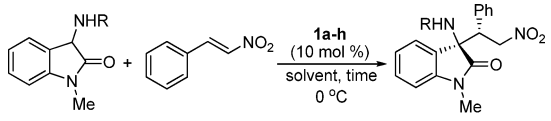


Figure 2. Chiral organocatalysts examined in this work.

Table 1. Representative Screening Results for the Michael Addition of 3-Monosubstituted 3-Aminooxindoles to Nitroolefins[a]



2a-c
2a: R = CO_2Et
2b: R = Boc
2c: R = Cbz

3a

4a-c

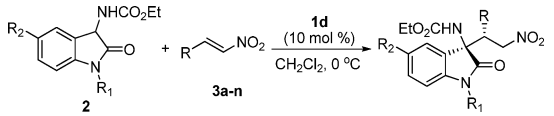
entry	1	2	solvent	time (h)	4/yield (%)[b]	dr[c]	ee (%)[d]
1	1a	2a	toluene	24	4a/70	89:11	61
2	1b	2a	toluene	24	4a/97	90:10	75
3	1c	2a	toluene	24	4a/96	79:21	71
4	1d	2a	toluene	48	4a/97	87:13	81
5	1e	2a	toluene	30	4a/85	81:19	67
6	1f	2a	toluene	24	4a/82	86:14	66
7	1g	2a	toluene	30	4a/86	85:15	66
8	1h	2a	toluene	24	4a/80	75:25	62
9	1d	2b	toluene	36	4b/96	85:15	70
10	1d	2c	toluene	36	4c/95	89:11	71
11	1d	2a	mesitylene	96	4a/98	86:14	75
12	1d	2a	CH_2Cl_2	72	4a/98	90:10	86
13	1d	2a	$CHCl_3$	72	4a/98	85:15	82
14	1d	2a	THF	96	4a/72	89:11	78
15	1d	2a	CH_3CN	120	4a/78	90:10	78
16	1d	2a	CH_2Cl_2	72	4a/98	95:5	88[e]
17	1d	2a	CH_2Cl_2	40	4a/97	90:10	86[f]
18	1d	2a	CH_2Cl_2	120	4a/98	88:12	86[g]

[a]Unless otherwise noted, reactions were carried out with **2a** (0.1 mmol), **3a** (0.12 mmol), and **1** (0.01 mmol) in solvent (1.0 mL) at 0 °C. [b]Isolated yield. [c]Determined by HPLC analysis. [d]Major diastereoisomer determined by chiral HPLC analysis. [e]The ratio of **2a**:**3a** was 1:1.5. [f]Reaction was conducted at 15 °C. [g]Reaction was conducted with 20 mol % **1d** at −40 °C.

Finally, changes in temperature did not positively effect the results (Table 1, entries 17−18).

With optimal reaction conditions in hand, the substrate scope was explored by the reactions of ethyl 1-methyl-2-oxoindolin-3-ylcarbamate **2a** with various nitroolefins **3a−l** (Table 2, entries 1−12). No obvious impact on efficiency as well as diastereo- and enantioselectivity was observed, regardless of the electronic nature, bulkiness, or position of the substituent in the phenyl ring of nitroolefins. Nevertheless, the sterically demanding nitroolefin **3j** was also successfully employed in the reaction (Table 2, entry 10). In addition to

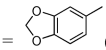
Table 2. Scope of 1d-Catalyzed Asymmetric Michael Addition of 3-Monosubstituted 3-Aminooxindoles 2 to Nitroolefins 3[a]



2
2a: R_1 = Me, R_2 = H
2d: R_1 = Me, R_2 = Me
2e: R_1 = Me, R_2 = F
2f: R_1 = Et, R_2 = H

3a-n

4a, 4d-s

entry	2	3	time (h)	4/yield (%)[b]	dr[c]	ee (%)[d]
1	2a	R = Ph (**3a**)	72	**4a**/98	95:5	88
2	2a	R = 2-$MeOC_6H_4$ (**3b**)	72	**4d**/98	>99:1[e]	82
3	2a	R = 3-$MeOC_6H_4$ (**3c**)	120	**4e**/97	85:15	79
4	2a	R =  (**3d**)	120	**4f**/93	95:5[e]	84
5	2a	R = 2-ClC_6H_4 (**3e**)	72	**4g**/97	87:13	69
6	2a	R = 4-ClC_6H_4 (**3f**)	72	**4h**/90	90:10	80
7	2a	R = 2-BrC_6H_4 (**3g**)	72	**4i**/96	94:6	69
8	2a	R = 4-BrC_6H_4 (**3h**)	72	**4j**/98	88:12	79
9	2a	R = 4-FC_6H_4 (**3i**)	72	**4k**/96	91:9	83
10	2a	R = 2-naphthyl (**3j**)	72	**4l**/95	79:21	79
11	2a	R = 2-thienyl (**3k**)	72	**4m**/98	92:8[f]	77[f]
12	2a	R = cyclohexyl (**3l**)	120	**4n**/30	>99:1[e]	87
13	2d	R = Ph (**3a**)	72	**4o**/91	86:14	92
14	2d	R = 3-BrC_6H_4 (**3m**)	72	**4p**/94	85:15	75
15	2d	R = 2-furyl (**3n**)	41	**4q**/95	93:7	80
16	2e	R = Ph (**3a**)	72	**4r**/97	94:6	88
17	2f	R = Ph (**3a**)	72	**4s**/96	92:8[e]	84

[a]Unless otherwise noted, reactions were carried out with **2** (0.1 mmol), **3** (0.15 mmol), and **1d** (0.01 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C. [b]Isolated yield. [c]Determined by HPLC analysis. [d]Major diastereoisomer determined by chiral HPLC analysis. [e]Determined by ^1H NMR. [f]The dr and ee values of **4m** could be readily improved to >99:1 dr and >99% ee by recrystallizing from ethanol.

aromatic groups, heterocyclic analogue **3k** was used to acquire the corresponding quaternary 3-aminooxindole product with acceptable results (Table 2, entry 11). Under the same conditions, the aliphatic nitroolefin **3l** gave the expected product **4n** only in 30% yield with >99:1 dr and 87% ee (Table 2, entry 12). Afterward, further exploration of the substrate scope was focused on 3-monosubstituted 3-aminooxindoles.[11] It was observed that the oxindole substrates bearing both an electron-donating (Table 2, entries 13−15) and electron-withdrawing substituent (Table 2, entry 16) could effectively react with diversely nitroolefins. Ultimately, replacing the methyl moiety on the *N*-1 of **2a** with an ethyl group had no significant detrimental effect on the reaction in every respect, the corresponding product **4s** also could be obtained in 96% yield, 92:8 dr, and 84% ee (Table 2, entry 17).

In order to illustrate the synthetic utility of this methodology, we attempted to convert the product **4a** into a spiro[tetrahydropyrimidin-one-3-oxindole] compound (Scheme 3). First, the nitro group of **4a** was easily reduced to a primary amine by $NaBH_4$ with $NiCl_2$ as a Lewis acid. And then, the unpurified compound **5** was directly subjected to a NaOH aqueous solution with ethanol as solvent, giving the spiro[tetrahydropyrimidin-one-3-oxindole] product **6** in 90% yield for two steps with 93:7 dr and 91% ee. Notably, the spirocyclic oxindole compound as **6** was previously not accessible via the asymmetric catalysis process. Consequently, our approach

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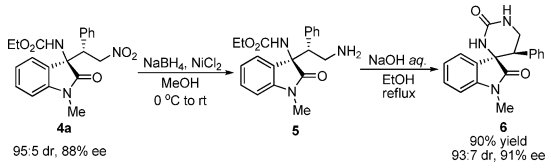
Scheme 3. Transformation of 4a into Spiro[tetrahydropyrimidin-one-3-oxindole] Compound



should add a new aspect for the enantioselective synthesis of quaternary 3-aminooxindoles.

Additionally, we fortunately found that the dr and ee values of product **4m** (Table 2, entry 11) could be readily improved to >99:1 dr and >99% ee by recrystallizing from ethanol. Based on this observation, single crystals suitable for X-ray crystallographic analysis were obtained from the enantiopure **4m**. Consequently, the relative and absolute stereochemistry for the major diastereoisomer of **4m** was unambiguously assigned as (*C4R*, *C5R*) by single crystal X-ray diffraction.[12] Other compounds in a series were assigned analogously.

According to the observed stereochemistry of the product **4m** and referring to the related dual activation model reports,[13] a transition state involving simultaneous activation by chiral bifunctional thiourea-tertiary amine catalyst **1d** for the Michael addition process was proposed (Figure 3). It can be assumed

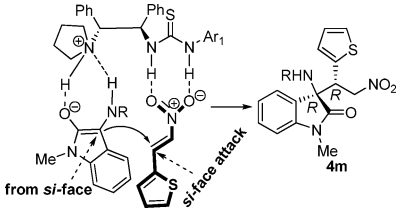


Figure 3. Proposed transition state for the Michael addition of 3-monosubstituted 3-aminooxindoles to nitroolefins.

that nitroolefin was activated by the H-bonding to the thiourea moiety of the catalyst; meanwhile, deprotonation/enolization of 3-monosubstituted 3-aminooxindole was facilitated by the tertiary amine moiety of **1d**. The *si*-face attack of enolate to the *si*-face of nitroolefin led to the formation of the desired Michael adduct **4m** with an (*R*,*R*)-configuration bearing adjacent quaternary-tertiary centers.

In conclusion, we have developed a new method to synthesize optically active quaternary 3-aminooxindoles from 3-monosubstituted 3-aminooxindoles and nitroolefins by a bifunctional thiourea-tertiary amine-catalyzed Michael addition under mild conditions. A range of quaternary 3-aminooxindoles bearing adjacent quaternary-tertiary centers could be smoothly obtained in good yields (up to 98%) with high levels of diastereoselectivities (up to >99:1 dr) and enantioselectivities (up to 92% ee). The potential synthetic utility of the optically active Michael addition product was demonstrated by the transformation of one product into the spiro-[tetrahydropyrimidin-one-3-oxindole] compound. A plausible transition state model was also brought forward. Notably, this represents the first example about 3-monosubstituted 3-aminooxindoles serving as nucleophiles for the catalytic asymmetric transformation.

EXPERIMENTAL SECTION

Procedure for the Synthesis of Ethyl 1-Methyl-2-oxoindolin-3-ylcarbamate (2a). To a solution of 3-amino-1-methylindolin-2-one hydrochloride (1.0 g, 5.0 mmol) in $CHCl_3$ (20 mL) was added Et_3N (1.1 mL, 7.5 mmol) at 0 °C under a N_2 atmosphere. The resulting mixture was vigorously stirred for 15 min, and then ethyl carbonochloridate (0.55 mL, 5.5 mmol) was added slowly via syringe to the mixture. The resultant mixture was allowed to stir for 1 h and concentrated, and the residue was purified by flash chromatography to furnish product **2a** as a white solid in 0.8 g. 68% yield; mp 165.8−167.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (s, 3H), 3.19 (s, 3H), 4.05−4.16 (m, 2H), 5.05 (d, J = 7.5 Hz, 1H), 5.37 (d, J = 6.9 Hz, 1H), 6.80 (d, J = 7.8 Hz, 1H), 7.02−7.07 (m, 1H), 7.24−7.36 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 26.4, 53.8, 61.5, 108.2, 122.9, 124.3, 126.5, 129.2, 143.6, 156.5, 174.3; HRMS (ESI-TOF): calcd for $C_{12}H_{14}N_2NaO_3$ [M + Na]$^+$, 257.0897; found, 257.0899.

Ethyl 1,5-Dimethyl-2-oxoindolin-3-ylcarbamate (2d). The method for the synthesis of **2d** was similar to that of **2a**. Product **2d** could be obtained in 0.45 g as a white solid from 3-amino-1,5-dimethylindolin-2-one hydrochloride (0.6 g, 2.83 mmol). 64% yield; mp 143.5−144.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (s, 3H), 2.32 (s, 3H), 3.19 (s, 3H), 4.15 (q, J = 6.9 Hz, 2H), 5.05 (d, J = 6.0 Hz, 1H), 5.35 (d, J = 5.7 Hz, 1H), 6.70 (d, J = 7.8 Hz, 1H), 7.10 (d, J = 7.8 Hz, 1H), 7.19 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 21.0, 26.5, 53.8, 61.6, 108.0, 125.2, 126.5, 129.5, 132.6, 141.3, 156.6, 174.2; HRMS (ESI-TOF): calcd for $C_{13}H_{16}N_2NaO_3$ [M + Na]$^+$, 271.1053; found, 271.1060.

Ethyl 5-Fluoro-1-methyl-2-oxoindolin-3-ylcarbamate (2e). The method for the synthesis of **2e** was similar to that of **2a**. Product **2e** could be obtained in 0.47 g as a white solid from 3-amino-5-fluoro-1-methylindolin-2-one hydrochloride (0.61 g, 2.83 mmol). 66% yield; mp 170.2−171.6 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (s, 3H), 3.21 (s, 3H), 4.11−4.15 (m, 2H), 5.00 (d, J = 6.3 Hz, 1H), 5.49 (s, 1H), 6.73−6.77 (m, 1H), 6.98−7.04 (m, 1H), 7.14 (d, J = 6.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.4, 26.6, 54.0, 61.7, 108.8 (d, J = 8.0 Hz, 1C), 112.7 (d, J = 25.4 Hz, 1C), 115.5 (d, J = 23.5 Hz, 1C), 128.1 (d, J = 8.2 Hz, 1C), 139.6, 156.4, 159.4 (d, J = 240.2 Hz, 1C), 174.0; HRMS (ESI-TOF): calcd for $C_{12}H_{13}FN_2NaO_3$ [M + Na]$^+$, 275.0802; found, 275.0804.

Ethyl 1-Ethyl-2-oxoindolin-3-ylcarbamate (2f). The method for the synthesis of **2f** was similar to that of **2a**. Product **2f** could be obtained in 0.36 g as a white solid from 3-amino-1-ethylindolin-2-one hydrochloride (0.6 g, 2.83 mmol). 51% yield; mp 122.5−123.8 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26−1.30 (m, 6H), 3.73−3.81 (m, 2H), 4.15 (d, J = 6.6 Hz, 2H), 5.06 (br s, 1H), 5.47 (d, J = 7.2 Hz, 1H), 6.85 (d, J = 7.8 Hz, 1H), 7.04−7.08 (m, 1H), 7.28−7.33 (m, 1H), 7.39 (d, J = 6.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.4, 14.4, 34.9, 53.8, 61.4, 108.3, 122.6, 124.5, 126.7, 129.1, 142.7, 156.4, 173.9; HRMS (ESI-TOF): calcd for $C_{13}H_{16}N_2NaO_3$ [M + Na]$^+$, 271.1053; found, 271.1052.

General Experimental Procedure for the Asymmetric Michael Addition Reaction between 3-Amino-3-Monosubstituted Oxindoles and Nitroolefins Catalyzed by 1d. A solution of 3-amino-3-monosubstituted oxindoles **2** (0.1 mmol), nitroolefins **3** (0.15 mmol, 1.5 equiv) and catalyst **1d** (5.4 mg, 10 mol %, 0.01 mmol) in CH_2Cl_2 (1.0 mL) was stirred at 0 °C for specified time. After completion of the reaction, the mixture was directly purified by flash chromatography to furnish the corresponding products **4**.

Ethyl ((*R*)-1-Methyl-3-((*R*)-2-nitro-1-phenylethyl)-2-oxoindolin-3-yl)carbamate (4a). White solid; 37.6 mg, yield 98%; 95:5 dr, 88% ee; $[\alpha]_D^{20}$ = −6.3 (c 0.35, EtOH); mp 203.4−205.1 °C; the ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 6.9 min, t_{major} = 8.2 min); ^{1}H NMR (300 MHz, DMSO-d_6) for (major diastereomer): δ 1.10 (s, 3H), 2.85 (s, 3H), 3.84 (s, 2H), 4.13 (d, J = 5.1 Hz, 1H), 5.39 (s, 2H), 6.51 (d, J = 7.2 Hz, 1H), 6.79−6.81 (m, 2H), 6.97−7.05 (m, 5H), 7.35 (d, J = 6.6 Hz, 1H), 8.54 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) (for major diastereomer): δ 14.4, 25.8, 47.9, 60.4, 63.2, 74.2, 107.8, 122.3, 122.5, 127.4, 127.7, 128.6, 128.9, 129.1, 133.2, 142.9, 154.7, 173.8; HRMS

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(ESI-TOF): calcd for $C_{20}H_{21}N_3NaO_5$ $[M + Na]^+$, 406.1373; found, 406.1384.

Ethyl ((*R*)-3-((*R*)-1-(2-Methoxyphenyl)-2-nitroethyl)-1-methyl-2-oxoindolin-3-yl)carbamate (4d). White solid; 40.5 mg, yield 98%; >99:1 dr (determined by ^{1}H NMR of chiral compound), 82% ee; $[\alpha]_D^{20}$ = +27.4 (*c* 0.88, $CHCl_3$); mp 175.2−176.6 °C; the ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 9.1 min, t_{major} = 11.1 min); ^{1}H NMR (300 MHz, $CDCl_3$) for (major diastereomer): δ 1.13 (s, 3H), 3.17 (s, 3H), 3.79 (s, 3H), 3.94 (d, *J* = 6.6 Hz, 2H), 4.69 (s, 1H), 5.00−5.04 (m, 2H), 6.45 (s, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 6.74 (d, *J* = 8.1 Hz, 1H), 6.83−6.91 (m, 3H), 6.94−6.96 (br, 1H), 7.17−7.20 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) (for major diastereomer): δ 14.3, 26.3, 39.4, 55.4, 61.3, 63.7, 74.3, 107.7, 111.0, 120.3, 121.7, 122.0, 124.8, 127.6, 129.5, 129.7, 143.3, 154.6, 156.8, 175.1; HRMS (ESI-TOF): calcd for $C_{21}H_{23}N_3NaO_6$ $[M + Na]^+$, 436.1479; found, 436.1491.

Ethyl ((*R*)-3-((*R*)-1-(3-Methoxyphenyl)-2-nitroethyl)-1-methyl-2-oxoindolin-3-yl)carbamate (4e). White solid; 40.1 mg, yield 97%; 85:15 dr, 79% ee; $[\alpha]_D^{20}$ = −13.9 (*c* 1.03, $CHCl_3$); mp 129.7−131.4 °C; the ee was determined by HPLC analysis (Chiralpak AD-H, ethanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 20.9 min, t_{major} = 16.3 min); ^{1}H NMR (300 MHz, $CDCl_3$) (for major diastereomer): δ 1.07−1.14 (m, 3H), 3.05 (s, 3H), 3.63 (s, 3H), 3.97−4.02 (m, 2H), 4.32 (d, *J* = 5.7 Hz, 1H), 5.03 (dd, *J* = 9.6 Hz, 14.1 Hz, 1H), 5.21 (dd, *J* = 4.2 Hz, 14.1 Hz, 1H), 5.80 (br, 1H), 6.44 (s, 1H), 6.54−6.60 (m, 2H), 6.68 (d, *J* = 8.1 Hz, 1H), 7.01−7.08 (m, 2H), 7.17−7.22 (m, 1H), 7.47 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) for (major diastereomer): δ 14.3, 26.2, 48.7, 55.1, 61.6, 63.2, 74.5, 108.1, 114.2, 114.5, 120.7, 122.8, 124.2, 127.9, 129.1, 129.7, 134.4, 143.0, 159.2, 174.3; HRMS (ESI-TOF): calcd for $C_{21}H_{23}N_3NaO_6$ $[M + Na]^+$, 436.1479; found, 436.1488.

Ethyl ((*R*)-3-((*R*)-1-(Benzo[*d*][1,3]dioxol-5-yl)-2-nitroethyl)-1-methyl-2-oxoindolin-3-yl)carbamate (4f). White solid; 39.7 mg, yield 93%; 95:5 dr (determined by ^{1}H NMR of chiral compound), 84% ee; $[\alpha]_D^{20}$ = −20.8 (*c* 1.05, $CHCl_3$); mp 187.6−189.1 °C; the ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane =30/70, flow rate 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 8.8 min, t_{major} = 9.8 min); ^{1}H NMR (300 MHz, $CDCl_3$) for (major diastereomer): δ 1.14 (s, 3H), 3.10 (s, 3H), 3.94−4.01 (m, 2H), 4.26 (d, *J* = 6.0 Hz, 1H), 4.95 (dd, *J* = 9.9 Hz, 13.8 Hz, 1H), 5.13 (dd, *J* = 4.2 Hz, 14.1 Hz, 1H), 5.80 (br, 1H), 5.85−5.87 (m, 2H), 6.45−6.47 (m, 2H), 6.54−6.62 (m, 2H), 7.03−7.08 (m, 1H), 7.19−7.24 (m, 1H), 7.44 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) (for major diastereomer): δ 14.3, 26.3, 48.5, 61.6, 63.2, 74.8, 101.2, 107.9, 108.2. 108.9, 122.6, 123.0, 124.2, 126.4, 127.8, 129.7, 143.0, 147.4, 147.5, 154.7, 174.4; HRMS (ESI-TOF): calcd for $C_{21}H_{21}N_3NaO_7$ $[M + Na]^+$, 450.1272; found, 450.1270.

Ethyl ((*R*)-3-((*R*)-1-(2-Chlorophenyl)-2-nitroethyl)-1-methyl-2-oxoindolin-3-yl)carbamate (4g). White solid; 40.5 mg, yield 97%; 87:13 dr, 69% ee; $[\alpha]_D^{20}$ = +24.8 (*c* 1.15, $CHCl_3$); mp 156.3−157.5 °C; the ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 12.9 min, t_{major} = 14.1 min); ^{1}H NMR (300 MHz, $CDCl_3$) for (major diastereomer): δ 1.15 (s, 3H), 3.13 (s, 3H), 3.99−4.06 (m, 2H), 5.04 (dd, *J* = 9.6 Hz, 13.8 Hz, 1H), 5.19 (dd, *J* = 3.3 Hz, 9.3 Hz, 1H), 5.42 (dd, *J* = 3.3 Hz, 14.1 Hz, 1H), 6.00 (br, 1H), 6.49 (d, *J* = 7.8 Hz, 1H), 6.96−7.16 (m, 6H), 7.59 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) (for major diastereomer): δ 14.2, 26.3, 43.2, 61.7, 63.5, 75.1, 107.5, 122.6, 124.6, 126.3, 127.2, 129.5, 129.7, 129.8, 129.9, 131.7, 135.2, 142.5, 154.7, 174.3; HRMS (ESI-TOF): calcd for $C_{20}H_{20}ClN_3NaO_5$ $[M + Na]^+$, 440.0984; found, 440.0990.

Ethyl ((*R*)-3-((*R*)-1-(4-Chlorophenyl)-2-nitroethyl)-1-dimethyl-2-oxoindolin-3-yl)carbamate (4h). White solid; 37.6 mg, yield 90%; 90:10 dr, 80% ee; $[\alpha]_D^{20}$ = −30.9 (*c* 1.13, $CHCl_3$); mp 148.0−149.3 °C; the ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 5.4 min, t_{major} = 6.2 min); ^{1}H NMR (300 MHz, $CDCl_3$) for (major diastereomer): δ 1.05−1.14 (m, 3H), 3.03 (s, 3H), 3.99−4.06 (m, 2H), 4.40 (s, 1H), 5.13 (dd, *J* = 9.6 Hz, 14.1 Hz, 1H), 5.31 (dd, *J* = 4.2 Hz, 14.1 Hz, 1H), 5.90 (br s, 1H), 6.52 (d, *J* = 7.8 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 7.08−7.21 (m, 2H), 7.53 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) for (major diastereomer): δ 14.2, 26.2, 48.1, 61.7, 63.3, 74.4, 108.2, 122.9, 124.0, 128.2, 129.8, 130.0, 131.5, 134.2, 142.7, 154.9, 173.9; HRMS (ESI-TOF): calcd for $C_{20}H_{20}ClN_3NaO_5$ $[M + Na]^+$, 440.0984; found, 440.0981.

Ethyl ((*R*)-3-((*R*)-1-(2-Bromophenyl)-2-nitroethyl)-1-methyl-2-oxoindolin-3-yl)carbamate (4i). White solid; 44.4 mg, 96% yield; 94:6 dr, 69% ee; $[\alpha]_D^{20}$ = +37.4 (*c* 1.35, $CHCl_3$); mp 188.7−190.1 °C; the ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 13.7 min, t_{major} = 16.0 min); ^{1}H NMR (300 MHz, $CDCl_3$) for (major diastereomer): δ 1.06−1.15 (m, 3H), 3.14 (s, 3H), 4.03 (q, *J* = 6.9 Hz, 2H), 5.01 (dd, *J* = 9.6 Hz, 14.1 Hz, 1H), 5.18 (dd, *J* = 3.6 Hz, 9.3 Hz, 1H), 5.42 (dd, *J* = 3.6 Hz, 14.1 Hz, 1H), 6.00 (br s, 1H), 6.50 (d, *J* = 7.5 Hz, 1H), 6.95−7.01 (m, 2H), 7.10−7.17 (m, 3H), 7.30 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) (for major diastereomer): δ 14.3, 26.3, 46.0, 61.7, 63.5, 75.3, 107.6, 122.6, 124.9, 126.5, 126.8, 127.0, 127.4, 129.7, 129.8, 133.3, 133.4, 142.5, 154.7, 174.3; HRMS (ESI-TOF): calcd for $C_{20}H_{20}BrN_3NaO_5$ $[M + Na]^+$, 484.0479; found: 484.0485.

Ethyl ((*R*)-3-((*R*)-1-(4-Bromophenyl)-2-nitroethyl)-1-dimethyl-2-oxoindolin-3-yl)carbamate (4j). White solid; 45.3 mg, yield 98%; 88:12 dr, 79% ee; $[\alpha]_D^{20}$ = −32.9 (*c* 1.13, $CHCl_3$); mp 150.2−151.3 °C; the ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 5.7 min, t_{major} = 6.6 min); ^{1}H NMR (300 MHz, $CDCl_3$) (for major diastereomer): δ 1.05−1.14 (m, 3H), 3.03 (s, 3H), 4.03 (q, *J* = 6.9 Hz, 2H), 4.38 (d, *J* = 5.4 Hz, 1H), 5.12 (dd, *J* = 9.6 Hz, 14.1 Hz, 1H), 5.31 (dd, *J* = 4.2 Hz, 14.1 Hz, 1H), 5.85 (br s, 1H), 6.52 (d, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 2H), 7.03−7.08 (m, 1H), 7.16−7.25 (m, 3H), 7.53 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) for (major diastereomer): δ 14.2, 26.2, 48.2, 61.7, 63.3, 74.4, 108.3, 122.4, 123.1, 124.1, 127.9, 129.8, 130.1, 131.1, 132.1, 142.7, 154.9, 173.9; HRMS (ESI-TOF): calcd for $C_{20}H_{20}BrN_3NaO_5$ $[M + Na]^+$, 484.0479; found, 484.0472.

Ethyl ((*R*)-3-((*R*)-1-(4-Fluorophenyl)-2-nitroethyl)-1-dimethyl-2-oxoindolin-3-yl)carbamate (4k). White solid; 38.5 mg, yield 96%; 91:9 dr, 83% ee; $[\alpha]_D^{20}$ = −30.8 (*c* 0.90, $CHCl_3$); mp 168.1−169.3 °C; the ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 5.2 min, t_{major} = 5.9 min); ^{1}H NMR (300 MHz, $CDCl_3$) (for major diastereomer): δ 1.06−1.15 (m, 3H), 3.02 (s, 3H), 4.03 (q, *J* = 6.9 Hz, 2H), 4.39 (d, *J* = 5.1 Hz, 1H), 5.13 (dd, *J* = 9.6 Hz, 14.1 Hz, 1H), 5.31 (dd, *J* = 4.2 Hz, 14.1 Hz, 1H), 5.90 (br s, 1H), 6.50 (d, *J* = 7.8 Hz, 1H), 6.73−6.78 (m, 2H), 6.87−6.92 (m, 2H), 7.03−7.08 (m, 1H), 7.15−7.20 (m, 1H), 7.53 (d, *J* = 6.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) for (major diastereomer): δ 14.3, 26.1, 48.1, 61.7, 63.5, 74.6, 108.2, 115.0 (d, *J* = 21.5 Hz, 1C), 123.1, 124.1, 128.0, 128.8 (d, *J* = 3.2 Hz, 1C), 129.7, 130.4 (d, *J* = 8.3 Hz, 1C), 142.7, 154.9, 162.3 (d, *J* = 246.6 Hz, 1C), 174.0; HRMS (ESI-TOF): calcd. for $C_{20}H_{20}FN_3NaO_5$ $[M + Na]^+$, 424.1279; found, 424.1270.

Ethyl ((*R*)-1-Methyl-3-((*R*)-1-(naphthalen-1-yl)-2-nitroethyl)-2-oxoindolin-3-yl)carbamate (4l). White solid; 41.2 mg, yield 95%; 79:21 dr, 79% ee; $[\alpha]_D^{20}$ = +120.5 (*c* 0.40, EtOH); mp 207.3−208.6 °C; the ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 8.4 min, t_{major} = 10.6 min); ^{1}H NMR (300 MHz, DMSO-d_6) for (major diastereomer): δ 1.12 (br s, 3H), 2.96 (s, 3H), 3.86 (br s, 2H), 5.44−5.60 (m, 3H), 6.37 (d, *J* = 7.5 Hz, 1H), 6.48−6.53 (m, 1H), 6.70−6.75 (m, 1H), 7.28−7.37 (m, 4H), 7.47−7.52 (m, 1H), 7.60−7.66 (m, 2H), 8.18 (d, *J* = 8.7 Hz, 1H), 8.58 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) (for major diastereomer): δ 14.4, 25.9, 40.1, 60.5, 63.6, 75.8, 107.3, 121.6, 122.9, 123.4, 123.5, 124.2, 125.3, 125.7, 128.2, 128.4, 128.6, 130.5, 132.0, 132.9, 142.6, 154.7, 174.1; HRMS (ESI-TOF): calcd for $C_{24}H_{23}N_3NaO_5$ $[M + Na]^+$, 456.1530; found, 456.1532.

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Ethyl ((*R*)-1-Methyl-3-((*R*)-2-nitro-1-(thiophen-2-yl)ethyl)-2-oxoindolin-3-yl)carbamate (4m). White solid; 38.2 mg, yield 98%; 92:8 dr, 77% ee; $[\alpha]_D^{25}$ = −18.1 (*c* 0.51, $CHCl_3$); mp 194.8−196.1 °C; the ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 8.7 min, t_{major} = 12.7 min); ^{1}H NMR (300 MHz, DMSO-d_6) (for major diastereomer): δ 1.09 (br s, 3H), 2.90 (s, 3H), 3.84 (d, *J* = 6.6 Hz, 2H), 4.47 (dd, *J* = 3.0 Hz, 11.4 Hz, 1H), 5.19−5.27 (m, 1H), 5.42 (dd, *J* = 3.3 Hz, 14.4 Hz, 1H), 6.59 (d, *J* = 2.7 Hz, 1H), 6.64−6.71 (m, 2H), 6.99−7.04 (m, 1H), 7.12−7.19 (m, 2H), 7.35 (d, *J* = 7.2 Hz, 1H), 8.53 (br s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) for (major diastereomer): δ 14.4, 26.0, 43.4, 60.5, 63.3, 75.6, 108.0, 122.5, 122.6, 126.0, 126.1, 126.7, 129.2, 135.5, 143.4, 154.7, 173.5; HRMS (ESI-TOF): calcd for $C_{18}H_{19}N_3NaO_5S$ $[M + Na]^+$, 412.0938; found, 412.0923.

Ethyl ((*R*)-3-((*R*)-1-Cyclohexyl-2-nitroethyl)-1-methyl-2-oxoindolin-3-yl)carbamate (4n). White solid; 11.7 mg, yield 30%; >99:1 dr (determined by ^{1}H NMR of chiral compound), 87% ee; $[\alpha]_D^{20}$ = −2.1 (*c* 0.38, $CHCl_3$); mp 179.7−181.2 °C; the ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 6.7 min, t_{major} = 7.2 min); ^{1}H NMR (300 MHz, $CDCl_3$) for (major diastereomer): δ 0.75−1.27 (m, 11H), 1.47−1.63 (m, 3H), 2.84 (s, 1H), 3.20 (s, 3H), 3.96 (q, *J* = 6.9 Hz, 2H), 4.60 (dd, *J* = 4.2 Hz, 15.3 Hz, 1H), 5.53 (dd, *J* = 3.0 Hz, 15.3 Hz, 1H), 6.00 (s, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 7.10−7.15 (m, 1H), 7.33−7.38 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) (for major diastereomer): δ 14.3, 25.6, 26.1, 26.4, 27.8, 32.9, 37.3, 49.6, 61.4, 72.2, 108.2, 122.8, 123.4, 128.9, 129.7, 143.9, 154.5, 175.2; HRMS (ESI-TOF): calcd for $C_{20}H_{27}N_3NaO_5$ $[M + Na]^+$, 412.1843; found, 412.1845.

Ethyl ((*R*)-1,5-Dimethyl-3-((*R*)-2-nitro-1-phenylethyl)-2-oxoindolin-3-yl)carbamate (4o). White solid; 36.2 mg, yield 91%; 86:14 dr, 92% ee; $[\alpha]_D^{20}$ = −38.8 (*c* 1.00, $CHCl_3$); mp 195.3−196.4 °C; the ee was determined by HPLC analysis (Chiralpak AD-H, ethanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 15.7 min, t_{major} = 12.9 min); ^{1}H NMR (300 MHz, $CDCl_3$) for (major diastereomer): δ 1.08−1.15 (m, 3H), 2.32 (s, 3H), 3.00 (s, 3H), 3.96−4.05 (m, 2H), 4.32 (d, *J* = 5.1 Hz, 1H), 5.05 (dd, *J* = 9.3 Hz, 14.1 Hz, 1H), 5.25 (dd, *J* = 4.5 Hz, 14.1 Hz, 1H), 5.80 (br, 1H), 6.39 (d, *J* = 7.8 Hz, 1H), 6.93−6.98 (m, 3H), 7.07−7.14 (m, 3H), 7.27 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) (for major diastereomer): δ 14.3, 21.2, 26.2, 48.8, 61.6, 63.3, 74.6, 107.8, 124.9, 127.8, 128.0, 128.3, 128.8, 129.8, 132.5, 133.0, 140.5, 154.8, 174.1; HRMS (ESI-TOF): calcd for $C_{21}H_{23}N_3NaO_5$ $[M + Na]^+$, 420.1530; found, 420.1540.

Ethyl ((*R*)-3-((*R*)-1-(3-Bromophenyl)-2-nitroethyl)-1,5-dimethyl-2-oxoindolin-3-yl)carbamate (4p). Colorless oil; 44.8 mg, yield 94%; 85:15 dr, 75% ee; $[\alpha]_D^{20}$ = −42.8 (*c* 0.90, $CHCl_3$); the ee was determined by HPLC analysis (Chiralpak AD-H, ethanol/hexane = 20/80, flow rate 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 6.4 min, t_{major} = 5.4 min); ^{1}H NMR (300 MHz, $CDCl_3$) for (major diastereomer): δ 1.14−1.18 (m, 3H), 2.33 (s, 3H), 3.00 (s, 3H), 4.00−4.08 (m, 2H), 4.37 (d, *J* = 5.4 Hz, 1H), 5.09 (dd, *J* = 9.6 Hz, 14.1 Hz, 1H), 5.26 (dd, *J* = 4.5 Hz, 14.1 Hz, 1H), 5.75 (br, 1H), 6.41 (d, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 2H), 6.98 (d, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.35 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) (for major diastereomer): δ 14.3, 21.2, 26.2, 48.2, 61.7, 63.3, 74.5, 108.0, 122.4, 125.0, 127.8, 130.1, 130.4, 131.1, 131.3, 132.3, 132.8, 140.4, 154.9, 173.8; HRMS (ESI-TOF): calcd for $C_{21}H_{22}BrN_3NaO_5$ $[M + Na]^+$, 498.0635; found, 498.0630.

Ethyl ((*R*)-3-((*R*)-1-(Furan-2-yl)-2-nitroethyl)-1,5-dimethyl-2-oxoindolin-3-yl)carbamate (4q). Colorless oil; 36.8 mg, yield 95%; 93:7 dr, 80% ee; $[\alpha]_D^{20}$ = −8.6 (*c* 0.70, $CHCl_3$); the ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane = 85/15, flow rate 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 12.7 min, t_{major} = 15.4 min); ^{1}H NMR (300 MHz, $CDCl_3$) for (major diastereomer): δ 1.13 (s, 3H), 2.31 (s, 3H), 3.17 (s, 3H), 3.93−4.01 (m, 2H), 4.46 (dd, *J* = 5.7 Hz, 8.1 Hz, 1H), 4.62−4.73 (m, 2H), 5.81 (br s, 1H), 6.10 (d, *J* = 3.0 Hz, 1H), 6.25−6.26 (m, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 7.05−7.09 (m, 2H), 7.33 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) (for major diastereomer): δ 14.2, 21.1, 26.6, 42.7, 61.6, 62.3, 72.9, 108.0, 110.4, 110.6, 125.3, 126.9, 130.2, 132.7, 141.0, 143.2, 147.5, 154.5, 174.2; HRMS (ESI-TOF): calcd for $C_{19}H_{21}N_3NaO_6$ $[M + Na]^+$, 410.1323; found, 410.1321.

Ethyl ((*R*)-5-Fluoro-1-methyl-3-((*R*)-2-nitro-1-phenylethyl)-2-oxoindolin-3-yl)carbamate (4r). White solid; 38.9 mg, yield 97%; 94:6 dr, 88% ee; $[\alpha]_D^{20}$ = −19.1 (*c* 0.90, $CHCl_3$); mp 194.6−195.8 °C; the ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 5.4 min, t_{major} = 4.8 min); ^{1}H NMR (300 MHz, $CDCl_3$) (for major diastereomer): δ 1.17 (br s, 3H), 3.01 (s, 3H), 4.04 (q, *J* = 6.9 Hz, 2H), 4.34 (d, *J* = 4.5 Hz, 1H), 5.10 (dd, *J* = 9.3 Hz, 14.4 Hz, 1H), 5.33 (dd, *J* = 4.2 Hz, 14.4 Hz, 1H), 5.86 (br, 1H), 6.38−6.42 (m, 1H), 6.83−6.95 (m, 3H), 7.10−7.12 (m, 3H), 7.30 (d, *J* = 6.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) (for major diastereomer): δ 14.3, 26.3, 48.7, 61.8, 63.6, 74.5, 108.6 (d, *J* = 8.1 Hz 1C), 112.5 (d, *J* = 25.0 Hz, 1C), 115.8 (d, *J* = 23.6 Hz, 1C), 128.2, 128.3, 128.4, 128.7, 132.8, 138.9, 154.8, 159.2 (d, *J* = 240.6 Hz, 1C), 174.0; HRMS (ESI-TOF): calcd for $C_{20}H_{20}FN_3NaO_5$ $[M + Na]^+$, 424.1279; found, 424.1284.

Ethyl ((*R*)-1-Ethyl-3-((*R*)-2-nitro-1-phenylethyl)-2-oxoindolin-3-yl)carbamate (4s). White solid; 38.2 mg, yield 96%; 92:8 dr (determined by ^{1}H NMR of chiral compound), 84% ee; $[\alpha]_D^{20}$ = −42.9 (*c* 0.90, $CHCl_3$); mp 165.1−166.2 °C; the ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 7.5 min, t_{major} = 9.4 min); ^{1}H NMR (300 MHz, $CDCl_3$) (for major diastereomer): δ 1.08−1.13 (m, 6H), 3.54−3.68 (m, 2H), 3.95−4.03 (m, 2H), 4.38 (d, *J* = 5.4 Hz, 1H), 5.15 (dd, *J* = 9.6 Hz, 14.1 Hz, 1H), 5.30 (dd, *J* = 4.5 Hz, 14.1 Hz, 1H), 5.85 (br s, 1H), 6.54 (d, *J* = 7.8 Hz, 1H), 6.95−6.98 (m, 2H), 7.03−7.17 (m, 5H), 7.53 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) (for major diastereomer): δ 11.9, 14.3, 34.9, 48.6, 61.5, 63.1, 74.6, 108.2, 122.5, 122.7, 124.5, 128.1, 128.2, 129.0, 129.5, 132.8, 142.1, 154.8, 173.8; HRMS (ESI-TOF): calcd for $C_{21}H_{23}N_3NaO_5$ $[M + Na]^+$, 420.1530; found, 420.1535.

(3*R*,5′*R*)-1-Methyl-5′-phenyl-5′,6′-dihydro-1′*H*-spiro[indoline-3,4′-pyrimidine]-2,2′(3′*H*)-dione (6). To the solution of **4a** (100 mg, 0.26 mmol) and $NiCl_2$ (34 mg, 0.26 mmol) in MeOH (10 mL) was added to $NaBH_4$ (12 equiv, 12 mg) at 0 °C. The resulting mixture was warmed to room temperature and vigorously stirred for 1 h. After the reaction was quenched with a saturated NH_4Cl solution, the mixture was extracted with CH_2Cl_2, and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated to furnish the crude product **5** (90 mg). Then the mixture of **5** (90 mg) and a saturated NaOH solution (4 mL) in EtOH (8 mL) was refluxed for 3.5 h. The mixture was added to water (20 mL) and extracted with CH_2Cl_2. After being dried over anhydrous Na_2SO_4, the mixture was concentrated, and the residue was purified by flash column chromatography (MeOH/ethyl acetate = 1:20) to give the product **6** as a white solid in 72 mg. 90% yield; 93:7 dr, 91% ee; $[\alpha]_D^{20}$ = +130.2 (*c* 0.70, EtOH); mp 236.8−237.9 °C; the ee was determined by HPLC analysis (Chiralpak AD-H, *i*-PrOH/hexane = 30/70, flow rate 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 12.5 min, t_{major} = 8.4 min); ^{1}H NMR (300 MHz, DMSO-d_6) (for major diastereomer): δ 2.79 (s, 3H), 3.04−3.11 (m, 1H), 3.47 (dd, *J* = 4.5 Hz, 12.3 Hz, 1H), 4.17 (t, *J* = 12.0 Hz, 1H), 6.62 (d, *J* = 7.5 Hz, 1H), 6.74 (s, 1H), 6.81 (d, *J* = 6.0 Hz, 2H), 6.88 (s, 1H), 7.00−7.09 (m, 4H), 7.12−7.18 (m, 1H), 7.49 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) (for major diastereomer): δ 25.7, 39.8, 45.4, 63.4, 108.1, 122.4, 123.8, 127.4, 127.6, 128.2, 129.1, 129.2, 135.3, 142.8, 155.6, 176.3; HRMS (ESI-TOF): calcd for $C_{18}H_{17}N_3NaO_2$ $[M + Na]^+$, 330.1213; found, 330.1218.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed spectral data for new compounds, X-ray crystal structure and the CIF files of **4m**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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