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Organocatalytic Asymmetric Michael Addition of 3-Pyrrolyloxindoles to β-Phthalimidonitroethene for the Synthesis of 3,3′-Disubstituted Oxindoles Bearing Contiguous 3,α,β-Triamino Functionality

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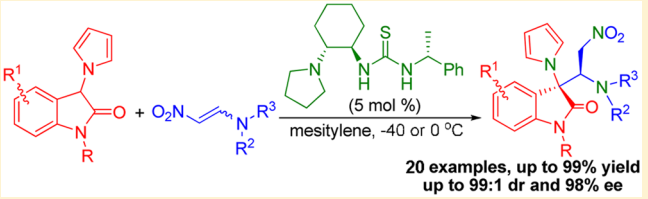
Supporting Information

ABSTRACT: An organocatalytic asymmetric Michael addition reaction of 3-pyrrolyloxindoles to β-phthalimidonitroethene has been developed with a bifunctional thiourea−tertiary amine as the catalyst. A range of 3,3′-disubstituted oxindoles bearing contiguous 3,α,β-triamino functionality could be obtained in high yields with good diastereoselectivities and high enantioselectivities (up to 99% yield, 99:1 dr, and 98% ee). The higher reactivity of β-phthalimidonitroethene compared to the reactivity of ordinary nitroalkenes in the reaction with 3-pyrrolyloxindoles was demonstrated by contrast experiments.



3,3′-Disubstituted oxindoles, containing a tetrasubstituted stereocenter at the C3-position of indolin-2-one, are privileged structural motifs presented in numerous natural products, drugs, and pharmaceutically active compounds.[1] Various asymmetric strategies for the construction of structurally diverse chiral 3,3′-disubstituted oxindole frameworks have been investigated over the past decade.[2] In particular, optically active 3,3′-disubstituted oxindoles bearing one or more nitrogen atoms have been attracting considerable attention due to their importance in the design of medicinally significant compounds and in the synthesis of alkaloid compounds.[3] Accordingly, different kinds of nitrogen-containing oxindoles have been prepared with various methods by organic chemists. In light of our literature search, we noticed that the synthesis of chiral 3,3′-disubstituted oxindoles bearing 3-amino functionality,[4] α-amino functionality,[5] β-amino functionality,[6] 3,α-diamino functionality,[7] 3,β-diamino functionality,[8] and α,β-diamino functionality[9] had been reported. However, in this research field, the generation of chiral 3,3′-disubstituted oxindoles containing contiguous 3,α,β-triamino functionality, which are useful complements to nitrogen-containing oxindoles, still remains unexploited so far (Figure 1). Therefore, the development of efficient asymmetric reactions for the preparation of such types of disubstituted oxindoles is desirable.

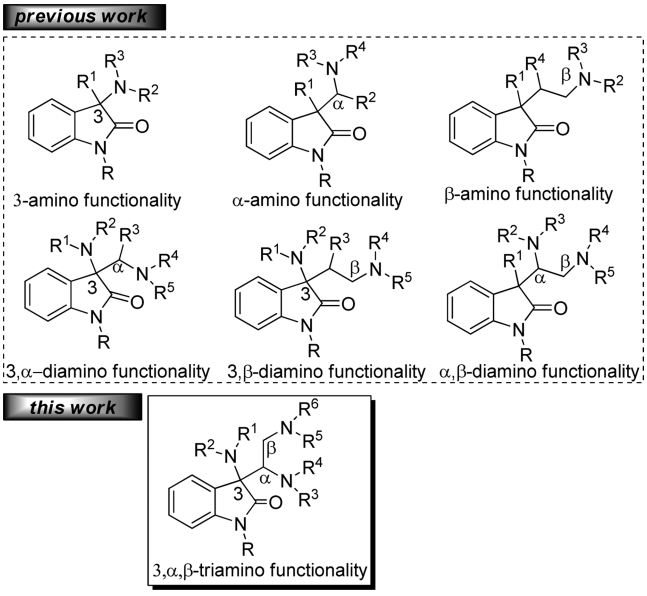


Figure 1. Diverse 3,3′-disubstituted oxindoles bearing one or more amino functionalities.

Over the past decades, asymmetric organocatalysis as a powerful and promising research area has attracted great attention in organic chemistry, which has accelerated the development of new methodologies for the synthesis of various chiral compounds.[10] In recent years, our group has developed some organocatalytic methods for the construction of diverse chiral 3,3′-disubstituted oxindoles.[11] Particularly, we used 3-pyrrolyloxindoles as efficient nucleophiles, realizing the synthesis of chiral 3,3′-disubstituted oxindoles bearing 3-amino or 3,β-diamino functionality.[12] Moreover, we also reported the

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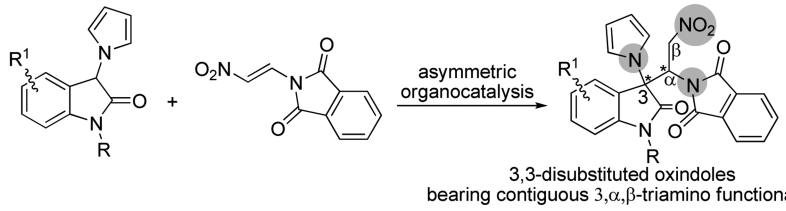
Scheme 1. Strategy for the Synthesis of 3,3′-Disubstituted Oxindoles Bearing Contiguous 3,α,β-Triamino Functionality

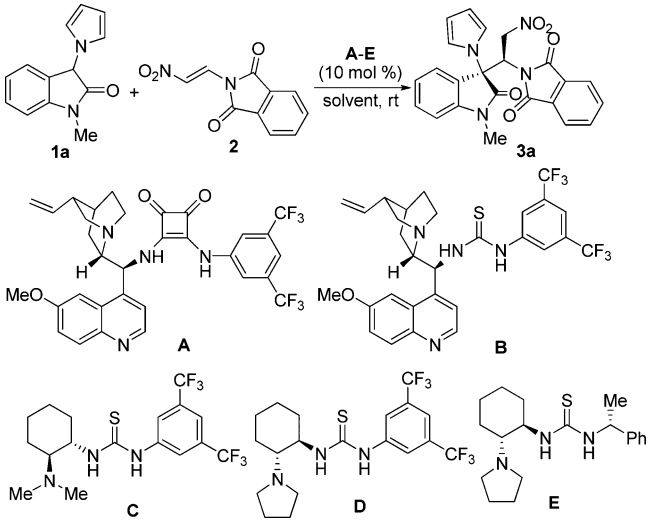


synthesis of 3,3′-disubstituted oxindoles bearing α,β-diamino functionality with the reaction of 3-substituted oxindoles and protected 2-amino-1-nitroethenes.[9] Nevertheless, we also noticed that β-phthalimidonitroethene could serve as a useful electrophile for preparing compounds containing two vicinal amino functionalities.[13] Inspired by these elegant reactions,[9,12,13] we have an interest in developing new strategies for the generation of 3,3′-disubstituted oxindoles bearing contiguous 3,α,β-triamino functionality. Herein, we report our research results with respect to the asymmetric Michael addition reaction of 3-pyrrolyloxindoles and β-phthalimidonitroethene to access this type of disubstituted oxindoles with organocatalysis (Scheme 1).

We began our studies by screening some chiral organocatalysts in the model reaction between 3-pyrrolyloxindole **1a** and β-phthalimidonitroethene **2**. As shown in Table 1, with 9-squaramide quinine **A** as catalyst, the reaction gave the desired 3,3′-disubstituted oxindole **3a** in 73% yield with 91:9 diastereomeric ratio (dr) and only 10% ee after 16 h in CH_2Cl_2 at room temperature (entry 1). However, with 9-thiourea quinine **B** as the catalyst, the reaction could complete in 4 h and give **3a** in 97% yield with 92:8 dr and 55% ee (entry 2). With thiourea catalyst **C** or **D** derived from chiral diamine as the catalyst, the reaction provided **3a** with excellent yield and diastereoselectivity and only acceptable ee value (entries 3 and 4). To our delight, **3a** could be obtained in 98% yield with 92:8 dr and 85% ee with thiourea catalyst **E** derived from chiral cyclohexanediamine and phenylethylamine (Table 1, entry 5). Having identified **E** as the best candidate, we performed a screen of solvents for the model reaction. Running the reaction in acetonitrile led to a decrease in stereoselectivity, albeit without loss of chemical yield (entry 6). After we tested THF, toluene, and mesitylene (entries 7−9), excellent reactivity and high stereocontrol were obtained when mesitylene was used as the solvent (entry 9). When the temperature was decreased to 0 and −40 °C (entries 10 and 11), it was found that **3a** could be smoothly obtained with quantitative yield and excellent diastereo- and enantioselectivity, while the reaction time was extended to 10 h (entry 11). Next, we observed that the reaction also gave the same results as in entry 11 by lowering the catalyst loading to 5 mol % (entry 12). Ultimately, the ratio of **2** to **1a** was changed from 1.5:1 to 1.05:1, and the reaction also occurred successfully and afforded **3a** in 99% yield with 97:3 dr and 98% ee (entry 13).

With the optimized reaction conditions in hand, the substrate scope of the asymmetric Michael addition of various 3-pyrrolyloxindoles to β-phthalimidonitroethene **2** was explored. As shown in Table 2, besides the reaction with **1g** as the substrate, almost all of the reactions had very high reactivity and provided 3,3′-disubstituted oxindoles bearing contiguous 3,α,β-triamino functionality in excellent chemical yields. We also found that the electronic effect of the N-protecting group seems to be important to the enantioselectivity because electron-donating

Table 1. Optimizing Reaction Conditions[a]



entry	solvent	cat.	time (h)	yield (%)[b]	dr[c]	ee (%)[c]
1	CH_2Cl_2	**A**	16	73	91:9	10
2	CH_2Cl_2	**B**	4	97	92:8	55
3	CH_2Cl_2	**C**	4	98	93:7	73
4	CH_2Cl_2	**D**	4	99	93:7	71
5	CH_2Cl_2	**E**	4	98	92:8	85
6	CH_3CN	**E**	4	96	73:27	58
7	THF	**E**	4	98	93:7	87
8	toluene	**E**	4	99	94:6	89
9	mesitylene	**E**	4	99	93:7	91
10	mesitylene	**E**	6	98	95:5	94[d]
11	mesitylene	**E**	10	99	97:3	98[e]
12	mesitylene	**E**	10	99	97:3	98[e,f]
13	mesitylene	**E**	15	99	97:3	98[e,f,g]

[a]Unless otherwise noted, the reactions were carried out with **1a** (0.1 mmol), **2** (0.15 mmol), and 10 mol % of catalyst in 2.0 mL of solvent at room temperature. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Run at 0 °C. [e]Run at −40 °C. [f]5 mol % of **E** was used. [g]**1a** (0.1 mmol) and **2** (0.105 mmol) were used.

substituents led to products **3b−f** with good to excellent enantioselectivity (entries 1−5), while the *N*-H and *N*-Ac substrates **1g** and **1h** gave their corresponding products **3g** and **3h** with 77 and 56% ee (entries 6 and 7). Additionally, the 3-pyrrolyloxindoles with an electron-donating or an electron-withdrawing group at the C5-position were also tolerated and furnished the respective Michael adducts in excellent yield, dr, and ee (entries 8−11); these results suggested that the electronic property of the group at the C5-position had no obvious effects on the reactivity and stereoselectivity. Moreover, for the 3-pyrrolyloxindoles (**1l−o**) containing the same chlorine substituent at a different position, the reaction with **2** also worked well and delivered the respective product with acceptable results (entries 11−14). However, by comparison, substrate **1n** gave the

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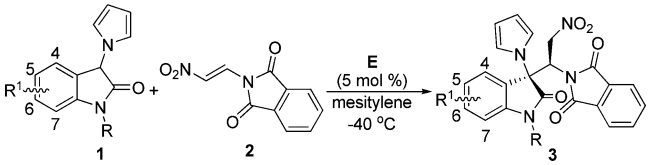
Table 2. Substrate Scope of the Asymmetric Michael Addition of 3-Pyrrolyloxindoles to 2[a]



entry	R^1/R	time (h)	3/yield (%)[b]	dr[c]	ee (%)[c]
1	H/Et (**1b**)	15	**3b**/99	97:3	98
2	H/Bn (**1c**)	15	**3c**/99	96:4[d]	94
3	H/isopropyl (**1d**)	22	**3d**/98	87:13[d]	94
4	H/allyl (**1e**)	20	**3e**/99	96:4[d]	96
5	H/Ph (**1f**)	15	**3f**/99	96:4[d]	85
6	H/H (**1g**)	20	**3g**/67	95:5	77
7	H/Ac (**1h**)	15	**3h**/97	97:3[d]	56
8	5-Me/Me (**1i**)	20	**3i**/94	97:3	97
9	5-F/Me (**1j**)	15	**3j**/99	97:3	98
10	5-Br/Me (**1k**)	20	**3k**/90	97:3	96
11	5-Cl/Me (**1l**)	15	**3l**/98	97:3	97
12	6-Cl/Me (**1m**)	15	**3m**/99	97:3	97
13[e]	4-Cl/Me (**1n**)	24	**3n**/91	98:2	81
14	7-Cl/Me (**1o**)	20	**3o**/99	99:1	96
15	7-NO_2/Me (**1p**)	15	**3p**/98	97:3[d]	86

[a]Unless otherwise noted, the reactions were conducted with **1** (0.1 mmol), **2** (0.105 mmol), and 5 mol % of **E** in 2 mL of mesitylene at −40 °C. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Determined by ^{1}H NMR. [e]Run at 0 °C.

corresponding product with relatively low yield and enantioselectivity probably due to the highly steric hindrance from the C4-position (entry 13 vs entries 11 and 12). Notably, the ee value of **3n** could be increased to 99% from 81% by one simple recrystallization from MeOH (data not shown). Furthermore, substrate **1p** containing a nitro group at the C7-position of 3-pyrrolyloxindole was also tolerated, giving **3p** with good results (entry 15).

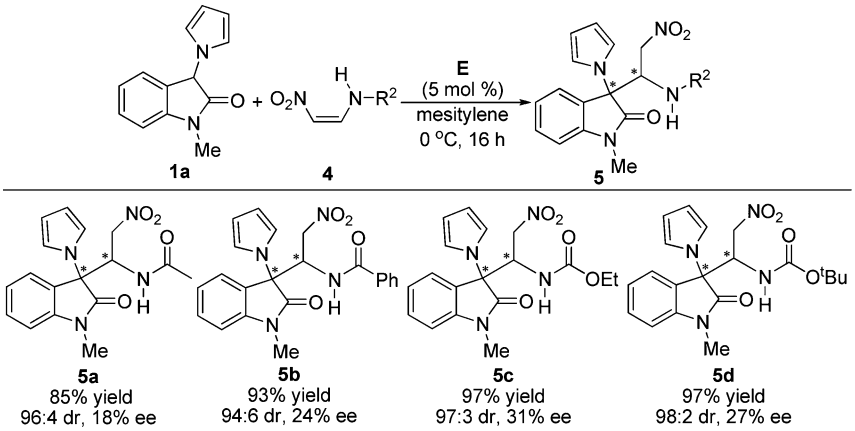
The structure and absolute configuration of **3n** could be confirmed by X-ray crystal structure analysis. It contains a (C5*R*,C6*S*) configuration.[14] Based on the assumption that product **3n** and all of the other products in Table 2 were formed via a uniform mechanism and transition state, the configurations of the other products were assigned by analogy.

Encouraged by the successful reactions of 3-pyrrolyloxindoles and *β*-phthalimidonitroethene as described above, we attempted to extend this method to the reaction of **1a** with different acyl-protected 2-amino-1-nitroethenes **4**, which were employed and reacted well with 3-substituted oxindoles in our previous work.[9] As shown in Scheme 2, the reactions proceeded well in the presence of 5 mol % of **E** in mesitylene at 0 °C, smoothly affording products **5a−d** in good to excellent yields with excellent diastereoselectivities (85−97% yield, 94:6 to 98:2 dr). However, the catalyst system demonstrated very poor enantioselective induction in the preparation of **5a−d**. In light of these results, we found that catalyst **E** for the reaction of **1a** and *β*-phthalimidonitroethene was significantly superior to the reaction of **1a** and acyl-protected 2-amino-1-nitroethenes in the enantioselectivity. It was probably because of the competition for the hydrogen bonding activity of the N−H bond in the 2-amino-1-nitroethenes with the catalyst.

In order to illustrate the synthetic utility of this methodology, the reaction of **1a** and **2** was carried out on a gram scale under the standard conditions, and **3a** could be obtained in 96% yield without loss in the diastereo- and enantioselectivity (Scheme 3). In addition, we tried to convert the Michael adduct **3a** into other 3,3′-disubstituted oxindole compounds. The nitro group of **3a** could be reduced to an amino group using Pd/C in methanol. There was no change taking place in the stereoselectivity during the above transformation (Scheme 3).

In order to gain insight into the difference of reaction properties between *β*-phthalimidonitroethene and nitroalkenes, we conducted a series of contrast experiments (Scheme 4). First, we employed an equimolar mixture of *β*-phthalimidonitroethene **2** and nitroalkene **7** reacting with 3-pyrrolyloxindole **1a** using our previous catalytic system,[12a] which is suitable for the reaction of **1a** and **7**. We found that **3a** and **8** could be obtained in a ratio of 82:18,[15] with 93:7 dr and 10% ee for **3a** and with 86:14 dr and 94% ee for **8**. These results suggested that *β*-phthalimidonitroethene **2** had a reactivity higher than that of nitroalkene **7**, and catalyst **A** possessed better enantioselective induction for the reaction of **7** and **1a** than for the reaction of **2** and **1a** (Scheme 4, eq 1). We also examined the same contrast experiment used above by using the current catalytic system, which is suitable for

Scheme 2. Reactions of 3-Pyrrolyloxindole 1a with Acyl-Protected 2-Amino-1-nitroethenes 4[a]



[a]Unless otherwise specified, the reactions were carried out with **1a** (0.1 mmol), **4** (0.15 mmol), and 5 mol % of **E** in 2 mL of mesitylene at 0 °C for 16 h. The reported yields were the isolated yield. The dr values were determined by ^{1}H NMR spectroscopy. The ee values were determined by chiral HPLC analysis.

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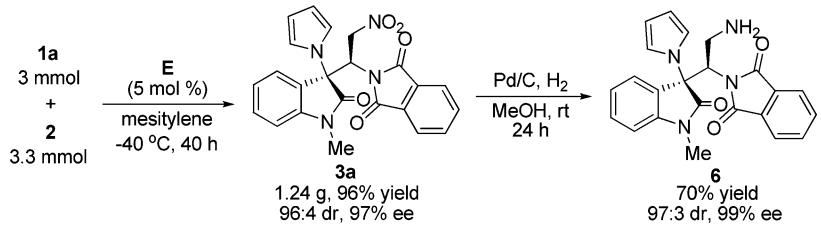
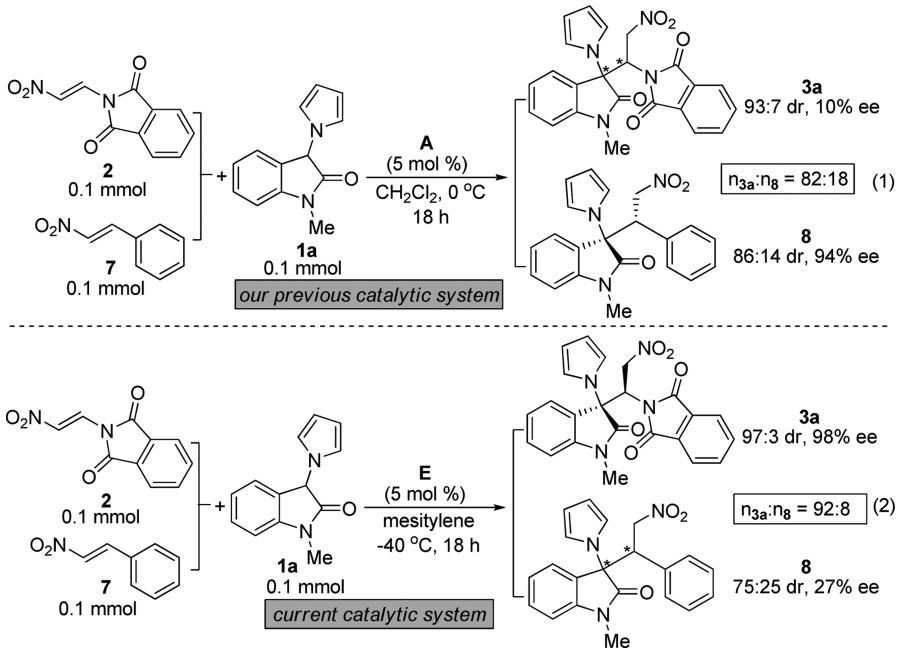
Scheme 3. Gram-Scale Experiment and Transformation of Product 3a to 6



Scheme 4. Contrast Experiments of β-Phthalimidonitroethene and Nitroalkene with 1a



the reaction of **1a** and **2**. Surely, the reaction gave **3a** and **8** in a ratio of 92:8,[15] with 97:3 dr and 98% ee for **3a** and with 75:25 dr and 27% ee for **8**. These results further revealed that the reaction rate of **1a** and **2** was faster than that of **1a** and **7**, but catalyst **E** showed better enantioselective induction for the reaction of **2** and **1a** than for **7** and **1a** (Scheme 4, eq 2). Regarding the relatively higher reactivity of β-phthalimidonitroethene **2**, we think it may be due to the strong electron-withdrawing feature of the phthaloyl group at the β-position of **2**. The phthaloyl group makes the β-phthalimidonitroethene substrates more electron-deficient than ordinary nitroalkene **7**, thereby leading to the higher reactivity of β-phthalimidonitroethene **2** compared to the reactivity of substrate **7**.

In conclusion, we have developed an efficient asymmetric Michael addition reaction of 3-pyrrolyloxindoles to β-phthalimidonitroethene with a bifunctional thiourea−tertiary amine catalyst. This method opened up a new way for the construction of 3,3′-disubstituted oxindoles bearing a contiguous 3,α,β-triamino functionality. Using the developed protocol, a range of 3,3′-disubstituted oxindoles were smoothly obtained in high yields with good diastereoselectivities and high enantioselectivities (up to 99% yield, 99:1 dr, and 98% ee). The potential synthetic utility of this protocol was demonstrated by the reduction of the Michael adduct and a gram-scale experiment. The higher reactivity of β-phthalimidonitroethene compared to the reactivity of ordinary nitroalkenes in the reaction with 3-pyrrolyloxindoles was demonstrated by contrast experiments.

EXPERIMENTAL SECTION

General Information. Reagents were purchased from commercial sources and were used as received unless mentioned otherwise. Reactions were monitored by thin-layer chromatography (TLC). ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6. ^{1}H NMR chemical shifts are reported in parts per million relative to tetramethylsilane (TMS) with the solvent resonance employed as the internal standard ($CDCl_3$ at 7.26 ppm, DMSO-d_6 at 2.50 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. ^{13}C NMR chemical shifts are reported in parts per million from TMS with the solvent resonance as the internal standard ($CDCl_3$ at 77.20 ppm, DMSO-d_6 at 39.51 ppm). Melting points were recorded on a melting point apparatus.

General Procedure for the Synthesis of Compounds 3a−p. In an ordinary vial equipped with a magnetic stirring bar, the 3-pyrrolyloxindoles **1** (0.1 mmol, 1.0 equiv), β-phthalimidonitroethene **2** (0.105 mmol, 1.05 equiv), and catalyst **E** (5 mol %) were dissolved in 2.0 mL of mesitylene at −40 or 0 °C, and then the mixture was stirred for the indicated time. After completion of the reaction, as indicated by TLC, products **3** were isolated by flash chromatography on silica gel (petroleum ether/ethyl acetate = 6/1−2/1).

*2-((R)-1-((S)-1-Methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)-2-nitroethyl)isoindoline-1,3-dione (**3a**):* White solid, 42.1 mg, 98% yield; 97:3 dr; 98% ee; $[\alpha]_D^{20} = -119.3$ (*c* 1.1, CH_2Cl_2); mp 178.7−180.5 °C; the ee was determined by HPLC (Chiralpak AS-H, *i*-PrOH/hexane = 20/80, flow rate = 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 16.6 min, t_{major} = 18.9 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major diastereomer) 7.70−7.62 (m, 4H), 7.47 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.20 (t, *J* = 2.2 Hz, 2H), 7.15 (m, 1H), 6.98−6.87 (m, 1H), 6.69 (d, *J* = 7.9 Hz, 1H), 6.26 (t, *J* = 2.2 Hz, 2H), 6.12 (dd, *J* = 11.0, 2.5 Hz, 1H), 5.73 (dd, *J* =

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14.7, 11.0 Hz, 1H), 5.01 (dd, J = 14.6, 2.5 Hz, 1H), 3.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major diastereomer) 170.9, 166.4, 142.9, 134.5, 130.7, 130.5, 125.2, 124.9, 123.6, 122.9, 119.1, 110.3, 108.8, 71.3, 66.8, 52.6, 26.7; HRMS (ESI-TOF) calcd for $C_{23}H_{18}N_4NaO_5$ $[M + Na]^+$ 453.1169, found 453.1171.

*2-((R)-1-((S)-1-Ethyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)-2-nitroethyl)isoindoline-1,3-dione (**3b**):* White solid, 44.0 mg, 99% yield; 97:3 dr; 98% ee; $[\alpha]_D^{20} = -67.5$ (c 2.2, CH_2Cl_2); mp 170.6−172.3 °C; the ee was determined by HPLC (Chiralpak AD-H, i-PrOH/hexane = 30/70, flow rate = 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 14.8 min, t_{major} = 15.7 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major diastereomer) 7.76−7.61 (m, 4H), 7.49 (d, J = 7.6 Hz, 1H), 7.20 (t, J = 2.2 Hz, 2H), 7.17−7.12 (m, 1H), 6.97−6.88 (m, 1H), 6.70 (d, J = 7.9 Hz, 1H), 6.26 (t, J = 2.2 Hz, 2H), 6.12 (dd, J = 11.1, 2.5 Hz, 1H), 5.82 (dd, J = 14.7, 11.0 Hz, 1H), 4.99 (dd, J = 14.7, 2.5 Hz, 1H), 3.90−3.71 (m, 2H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major diastereomer) 170.5, 166.7, 142.0, 134.5, 130.6, 125.5, 125.2, 123.7, 122.8, 119.3, 119.0, 110.3, 108.8, 71.1, 66.9, 52.6, 35.4, 11.9; HRMS (ESI-TOF) calcd for $C_{24}H_{20}N_4NaO_5$ $[M + Na]^+$ 467.1326, found 467.1324.

*2-((R)-1-((S)-1-Benzyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)-2-nitroethyl)isoindoline-1,3-dione (**3c**):* White solid, 50.1 mg, 99% yield; 96:4 dr; 94% ee; $[\alpha]_D^{20} = -27.0$ (c 2.5, CH_2Cl_2); mp 184.7−186.5 °C; the ee was determined by HPLC (Chiralpak AD-H, i-PrOH/hexane = 25/75, flow rate = 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 42.8 min, t_{major} = 39.6 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major diastereomer) 7.78−7.61 (m, 4H), 7.51 (d, J = 7.6 Hz, 1H), 7.32−7.29 (m, 5H), 7.23 (t, J = 2.2 Hz, 2H), 7.07−7.01 (m, 1H), 6.94−6.88 (m, 1H), 6.58 (d, J = 7.8 Hz, 1H), 6.29 (t, J = 2.2 Hz, 2H), 6.19 (dd, J = 11.1, 2.4 Hz, 1H), 5.85 (dd, J = 14.7, 11.1 Hz, 1H), 5.27 (d, J = 15.8 Hz, 1H), 5.01 (dd, J = 14.7, 2.5 Hz, 1H), 4.67 (d, J = 15.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major diastereomer) 171.2, 166.9, 142.3, 134.8, 134.5, 130.6, 128.9, 127.9, 127.3, 125.4, 125.0, 123.9, 123.6, 123.0, 119.1, 110.5, 109.8, 71.2, 67.0, 52.7, 44.7; HRMS (ESI-TOF) calcd for $C_{29}H_{22}N_4NaO_5$ $[M + Na]^+$ 529.1482, found 529.1484.

*2-((R)-1-((S)-1-Isopropyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)-2-nitroethyl)isoindoline-1,3-dione (**3d**):* White solid, 44.9 mg, 98% yield; 87:13 dr; 94% ee; $[\alpha]_D^{20} = -62.9$ (c 2.3, CH_2Cl_2); mp 193.0−194.7 °C; the ee was determined by HPLC (Chiralpak AS-H, i-PrOH/hexane = 10/90, flow rate = 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 16.3 min, t_{major} = 19.2 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major diastereomer) 7.73−7.63 (m, 4H), 7.50−7,45 (m, 1H), 7.20−7.17 (m, 2H), 7.14−7.08 (m, 1H), 6.96−6.80 (m, 2H), 6.33−6.23 (m, 2H), 6.14 (dd, J = 11.0, 2.4 Hz, 1H), 5.84 (dd, J = 14.8, 11.1 Hz, 1H), 5.00 (dd, J = 14.7, 2.5 Hz, 1H), 4.74−4.62 (m, 1H), 1.52−1.48 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major diastereomer) 170.5, 166.7, 141.5, 134.5, 130.5, 130.3, 125.8, 125.1, 123.5, 122.4, 118.9, 110.3, 110.3, 71.1, 66.7, 52.4, 44.6, 19.2, 18.4; HRMS (ESI-TOF) calcd for $C_{25}H_{22}N_4NaO_5$ $[M + Na]^+$ 481.1482, found 481.1483.

*2-((R)-1-((S)-1-Allyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)-2-nitroethyl)isoindoline-1,3-dione (**3e**):* White solid, 45.1 mg, 99% yield; 96:4 dr; 96% ee; $[\alpha]_D^{20} = -85.0$ (c 2.3, CH_2Cl_2); mp 159.1−160.7 °C; the ee was determined by HPLC (Chiralpak AS-H, i-PrOH/hexane = 20/80, flow rate = 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 14.2 min, t_{major} = 17.4 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major diastereomer) 7.73−7.62 (m, 4H), 7.49 (dd, J = 7.6, 1.2 Hz, 1H), 7.20 (t, J = 2.2 Hz, 2H), 7.14−7.09 (m, 1H), 6.95−6.90 (m, 1H), 6.70 (d, J = 7.9 Hz, 1H), 6.27 (t, J = 2.2 Hz, 2H), 6.15 (dd, J = 11.0, 2.5 Hz, 1H), 5.94−5.75 (m, 2H), 5.29−5.22 (m, 2H), 5.01 (dd, J = 14.7, 2.5 Hz, 1H), 4.52−4.43 (m, 1H), 4.35−4.27 (m, 1H); ^{13}C NMR (75 MHz, CDCl3) δ (major diastereomer) 170.7, 167.1, 142.2, 134.5, 130.7, 130.5, 125.3, 124.9, 123.5, 122.9, 119.1, 118.4, 110.4, 109.7, 71.1, 66.9, 52.6, 43.1; HRMS (ESI-TOF) calcd for $C_{25}H_{20}N_4NaO_5$ $[M + Na]^+$ 479.1326, found 479.1327.

*2-((R)-2-Nitro-1-((S)-2-oxo-1-phenyl-3-(1H-pyrrol-1-yl)indolin-3-yl)ethyl)isoindoline-1,3-dione (**3f**):* White solid, 49 mg, 99% yield; 96:4 dr; 85% ee; $[\alpha]_D^{20} = -6.5$ (c 1.3, CH_2Cl_2); mp 194.2−195.9 °C; the ee was determined by HPLC (Chiralpak AD-H, i-PrOH/hexane = 15/85, flow rate = 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 43.2 min, t_{major} = 39.8 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major diastereomer) 7.79−7.72 (m, 2H), 7.69−7.65 (m, 2H), 7.63−7.44 (m, 6H), 7.29 (t, J = 2.2 Hz, 2H), 7.10−7.04 (m, 1H), 6.98−6.93 (m, 1H), 6.63 (d, J = 7.9 Hz, 1H), 6.32 (t, J = 2.2 Hz, 2H), 6.21 (dd, J = 11.1, 2.5 Hz, 1H), 5.84 (dd, J = 14.6, 11.1 Hz, 1H), 5.12 (dd, J = 14.6, 2.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major diastereomer) 170.3, 167.1, 143.1, 134.6, 133.4, 130.6, 130.6, 129.9, 129.8, 128.8, 126.6, 125.1, 123.8, 123.4, 119.1, 110.6, 110.1, 71.4, 67.1, 52.7; HRMS (ESI-TOF) calcd for $C_{28}H_{20}N_4NaO_5$ $[M + Na]^+$ 515.1326, found 515.1324.

*2-((R)-2-Nitro-1-((S)-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)ethyl)-isoindoline-1,3-dione (**3g**):* White solid, 27.9 mg, 67% yield; 95:5 dr; 77% ee; $[\alpha]_D^{20} = -17.4$ (c 1.4, CH_2Cl_2); mp 204.5−206.2 °C; the ee was determined by HPLC (Chiralpak AD-H, i-PrOH/hexane = 30/70, flow rate = 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 31.0 min, t_{major} = 22.1 min); ^{1}H NMR (300 MHz, DMSO-d_6) δ (major diastereomer) 11.17 (s, 1H), 7.85−7.81 (m, 4H), 7.58 (d, J = 7.6 Hz, 1H), 7.22−7.10 (m, 3H), 6.96−6.91 (m, 1H), 6.79 (d, J = 7.8 Hz, 1H), 6.12 (t, J = 2.2 Hz, 2H), 5.97 (dd, J = 10.0, 3.2 Hz, 1H), 5.53 (dd, J = 14.7, 10.0 Hz, 1H), 5.13 (dd, J = 14.7, 3.2 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ (major diastereomer) 172.5, 166.4, 141.7, 135.3, 130.8, 125.7, 125.4, 123.7, 123.5, 122.0, 119.2, 110.5, 109.7, 71.6, 66.6, 51.9; HRMS (ESI-TOF) calcd for $C_{22}H_{16}N_4NaO_5$ $[M + Na]^+$ 439.1013, found 439.1007.

*2-((R)-1-((S)-1-Acetyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)-2-nitroethyl)isoindoline-1,3-dione (**3h**):* White solid, 44.5 mg, 97% yield; 97:3 dr; 56% ee; $[\alpha]_D^{20} = -16.4$ (c 2.2, CH_2Cl_2); mp 199.8−201.4 °C; the ee was determined by HPLC (Chiralpak AD-H, EtOH/hexane = 35/65, flow rate = 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 10.4 min, t_{major} = 12.5 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major diastereomer) 8.07 (d, J = 8.2 Hz, 1H), 7.73−7,64 (m, 4H), 7.42 (dd, J = 7.7, 1.2 Hz, 1H), 7.22−7.16 (m, 1H), 7.09 (t, J = 2.3 Hz, 2H), 7.05 (dd, J = 7.6, 1.1 Hz, 1H), 6.31 (t, J = 2.3 Hz, 2H), 6.20 (dd, J = 11.0, 2.4 Hz, 1H), 5.64 (dd, J = 14.5, 11.0 Hz, 1H), 5.15 (dd, J = 14.5, 2.4 Hz, 1H), 2.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major diastereomer) 172.4, 170.7, 167.4, 139.4, 135.8, 134.7, 131.0, 130.4, 125.5, 124.8, 124.2, 123.9, 118.8, 116.9, 111.0, 71.5, 67.5, 52.2, 26.7; HRMS (ESI-TOF) calcd for $C_{24}H_{18}N_4NaO_6$ $[M + Na]^+$ 481.1119, found 481.1113.

*2-((R)-1-((S)-1,5-Dimethyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)-2-nitroethyl)isoindoline-1,3-dione (**3i**):* White solid, 41.8 mg, 94% yield; 97:3 dr; 97% ee; $[\alpha]_D^{20} = -76.5$ (c 2.1, CH_2Cl_2); mp 184.0−185.7 °C; the ee was determined by HPLC (Chiralpak AD-H, EtOH/hexane = 10/90, flow rate = 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 35.9 min, t_{major} = 52.2 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major diastereomer) 7.81−7.60 (m, 4H), 7.27−7.26 (m, 1H), 7.20 (t, J = 2.2 Hz, 2H), 6.94−6.91 (m, 1H), 6.57 (d, J = 8.0 Hz, 1H), 6.26 (t, J = 2.2 Hz, 2H), 6.10 (dd, J = 11.0, 2.5 Hz, 1H), 5.73 (dd, J = 14.6, 11.1 Hz, 1H), 5.01 (dd, J = 14.6, 2.5 Hz, 1H), 3.23 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major diastereomer) 170.9, 166.9, 140.5, 134.5, 132.7, 130.9, 130.6, 125.7, 125.3, 123.5, 119.1, 110.3, 108.5, 71.4, 67.0, 52.7, 26.8, 20.9; HRMS (ESI-TOF) calcd for $C_{24}H_{20}N_4NaO_5$ $[M + Na]^+$ 467.1326, found 467.1321.

*2-((R)-1-((S)-5-Fluoro-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)-2-nitroethyl)isoindoline-1,3-dione (**3j**):* White solid, 44.4 mg, 99% yield; 97:3 dr; 98% ee; $[\alpha]_D^{20} = -87.8$ (c 2.2, CH_2Cl_2); mp 183.1−184.9 °C; the ee was determined by HPLC (Chiralpak AD-H, i-PrOH/hexane = 30/70, flow rate = 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 16.3 min, t_{major} = 17.6 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major diastereomer) 7.80−7.63 (m, 4H), 7.29−7.21 (m, 1H), 7.15 (t, J = 2.2 Hz, 2H), 6.91−6.85 (m, 1H), 6.64 (dd, J = 8.6, 4.1 Hz, 1H), 6.28 (t, J = 2.2 Hz, 2H), 6.13 (dd, J = 11.0, 2.5 Hz, 1H), 5.72 (dd, J = 14.7, 11.0 Hz, 1H), 4.98 (dd, J = 14.7, 2.5 Hz, 1H), 3.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major diastereomer) 170.7, 166.9, 158.7 (d, J = 243.8 Hz, 1C), 138.9, 134.7, 130.5, 126.7 (d, J = 7.8 Hz, 1C), 123.9, 119.0, 117.2 (d, J = 23.5 Hz, 1C), 113.3 (d, J = 25.9 Hz, 1C), 110.7, 109.5 (d, J = 8.0 Hz, 1C), 71.0, 67.0, 52.3, 26.9; HRMS (ESI-TOF) calcd for $C_{23}H_{17}FN_4NaO_5$ $[M + Na]^+$ 471.1075, found 471.1074.

*2-((R)-1-((S)-5-Bromo-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)-2-nitroethyl)isoindoline-1,3-dione (**3k**):* White solid, 45.7 mg, 90% yield; 97:3 dr; 96% ee; $[\alpha]_D^{20} = -107.0$ (c 2.3, CH_2Cl_2); mp 209.0−210.7 °C; the ee was determined by HPLC (Chiralpak AD-H, i-PrOH/hexane = 30/70, flow rate = 1.0 mL/min, λ = 254 nm, major

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J. Org. Chem. 2016, 81, 5759−5765

diastereomer: t_{minor} = 14.6 min, t_{major} = 15.6 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major diastereomer) 7.82−7.63 (m, 4H), 7.59 (d, J = 1.9 Hz, 1H), 7.31−7.26 (m, 1H), 7.14 (t, J = 2.3 Hz, 2H), 6.58 (d, J = 8.4 Hz, 1H), 6.34−6.25 (m, 2H), 6.12 (dd, J = 11.0, 2.5 Hz, 1H), 5.70 (dd, J = 14.7, 11.0 Hz, 1H), 4.98 (dd, J = 14.7, 2.5 Hz, 1H), 3.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major diastereomer) 170.5, 166.8, 141.9, 134.7, 133.5, 130.5, 128.2, 127.1, 123.7, 119.0, 115.6, 110.7, 110.2, 71.0, 66.9, 52.4, 26.9; HRMS (ESI-TOF) calcd for $C_{23}H_{17}BrN_4NaO_5$ [M + Na]$^+$ 531.0275, found 531.0278.

*2-((R)-1-((S)-5-Chloro-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)-2-nitroethyl)isoindoline-1,3-dione (**3l**):* White solid, 45.5 mg, 98% yield; 97:3 dr; 97% ee; $[\alpha]_D^{20}$ = −100.5 (c 2.3, CH_2Cl_2); mp 219.2−220.6 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 30/70, flow rate = 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 15.0 min, t_{major} = 16.4 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major diastereomer) 7.80−7.64 (m, 4H), 7.46 (d, J = 2.1 Hz, 1H), 7.18−7.09 (m, 3H), 6.63 (d, J = 8.4 Hz, 1H), 6.28 (t, J = 2.3 Hz, 2H), 6.12 (dd, J = 10.9, 2.5 Hz, 1H), 5.71 (dd, J = 14.7, 11.0 Hz, 1H), 4.97 (dd, J = 14.7, 2.5 Hz, 1H), 3.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major diastereomer) 170.6, 166.8, 141.4, 134.7, 130.7, 130.5, 128.5, 126.8, 125.4, 123.8, 119.0, 110.7, 109.7, 71.0, 66.9, 52.4, 26.9; HRMS (ESI-TOF) calcd for $C_{23}H_{17}ClN_4NaO_5$ [M + Na]$^+$ 487.0780, found 487.0776.

*2-((R)-1-((S)-6-Chloro-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)-2-nitroethyl)isoindoline-1,3-dione (**3m**):* White solid, 46.0 mg, 99% yield; 97:3 dr; 97% ee; $[\alpha]_D^{20}$ = −55.8 (c 2.3, CH_2Cl_2); mp 201.4−203.2 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 30/70, flow rate = 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 15.2 min, t_{major} = 17.9 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major diastereomer) 7.78−7.67 (m, 4H), 7.40 (d, J = 8.1 Hz, 1H), 7.14 (t, J = 2.3 Hz, 2H), 6.91 (dd, J = 8.1, 1.9 Hz, 1H), 6.71 (d, J = 1.9 Hz, 1H), 6.27 (t, J = 2.3 Hz, 2H), 6.11 (dd, J = 11.0, 2.5 Hz, 1H), 5.71 (dd, J = 14.7, 11.0 Hz, 1H), 4.98 (dd, J = 14.7, 2.5 Hz, 1H), 3.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major diastereomer) 170.9, 166.5, 144.2, 136.6, 134.7, 130.5, 125.9, 123.8, 123.7, 122.9, 119.0, 110.6, 109.6, 71.1, 66.5, 52.4, 26.9; HRMS (ESI-TOF) calcd for $C_{23}H_{17}ClN_4NaO_5$ [M + Na]$^+$ 487.0780, found 487.0776.

*2-((R)-1-((S)-4-Chloro-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)-2-nitroethyl)isoindoline-1,3-dione (**3n**):* White solid, 42.2 mg, 91% yield; 98:2 dr; 81% ee; $[\alpha]_D^{20}$ = −73.2 (c 2.1, CH_2Cl_2); mp 175.8−177.4 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 25/75, flow rate = 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 24.3 min, t_{major} = 19.5 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major diastereomer) 7.79−7.63 (m, 4H), 7.10 (t, J = 8.1 Hz, 1H), 6.99 (t, J = 2.3 Hz, 2H), 6.84−6.81 (m, 1H), 6.70−6.57 (m, 2H), 6.27 (t, J = 2.2 Hz, 2H), 5.57 (dd, J = 13.9, 10.7 Hz, 1H), 5.41 (dd, J = 13.9, 2.2 Hz, 1H), 3.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major diastereomer) 171.8, 166.9, 145.0, 134.6, 132.4, 131.7, 130.5, 124.7, 123.8, 123.2, 119.7, 109.9, 107.2, 72.6, 67.7, 50.2, 27.1; HRMS (ESI-TOF) calcd for $C_{23}H_{17}ClN_4NaO_5$ [M + Na]$^+$ 487.0780, found 487.0771.

*2-((R)-1-((S)-7-Chloro-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)-2-nitroethyl)isoindoline-1,3-dione (**3o**):* White solid, 46.0 mg, 99% yield; 99:1 dr; 96% ee; $[\alpha]_D^{20}$ = −63.3 (c 2.3, CH_2Cl_2); mp 171.6−173.2 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 30/70, flow rate = 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 16.5 min, t_{major} = 14.4 min); ^{1}H NMR (300 MHz, CDCl3) δ (major diastereomer) 7.78−7.64 (m, 4H), 7.35 (dd, J = 7.5, 1.2 Hz, 1H), 7.13 (t, J = 2.2 Hz, 2H), 7.07 (dd, J = 8.3, 1.2 Hz, 1H), 6.84 (dd, J = 8.3, 7.5 Hz, 1H), 6.28 (t, J = 2.2 Hz, 2H), 6.14 (dd, J = 11.0, 2.4 Hz, 1H), 5.71 (dd, J = 14.7, 11.0 Hz, 1H), 5.02 (dd, J = 14.7, 2.4 Hz, 1H), 3.64 (s, 3H); ^{13}C NMR (75 MHz, CDCl3) δ (major diastereomer) 171.34, 166.74, 138.84, 134.68, 132.90, 130.48, 128.07, 123.80, 123.69, 123.23, 118.91, 116.02, 110.71, 71.16, 66.37, 52.28, 30.33; HRMS (ESI-TOF) calcd for $C_{23}H_{17}ClN_4NaO_5$ [M + Na]$^+$ 487.0780, found 487.0782.

*2-((R)-1-((S)-1-Methyl-7-nitro-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)-2-nitroethyl)isoindoline-1,3-dione (**3p**):* Pale yellow solid, 46.5 mg, 98% yield; 97:3 dr; 86% ee; $[\alpha]_D^{20}$ = +24.4 (c 2.4, CH_2Cl_2); mp 186.5−188.2 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 20/80, flow rate = 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 41.5 min, t_{major} = 37.0 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major diastereomer) 7.76−7.68 (m, 4H), 7.65 (dd, J = 7.5, 1.2 Hz, 1H), 7.52 (dd, J = 8.4, 1.2 Hz, 1H), 7.12 (t, J = 2.2 Hz, 2H), 7.01 (dd, J = 8.4, 7.5 Hz, 1H), 6.32 (t, J = 2.2 Hz, 2H), 6.19 (dd, J = 10.9, 2.4 Hz, 1H), 5.70 (dd, J = 14.8, 10.9 Hz, 1H), 5.02 (dd, J = 14.8, 2.4 Hz, 1H), 3.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 167.0, 136.5, 135.2, 134.9, 130.3, 129.0, 128.2, 126.2, 124.0, 122.7, 118.9, 111.2, 70.8, 65.4, 52.1, 30.6; HRMS (ESI-TOF) calcd for $C_{23}H_{18}N_5O_7$ [M + H]$^+$ 476.1201, found 476.1212.

General Procedure for the Synthesis of Compounds 5a−d. In an ordinary vial equipped with a magnetic stirring bar, the 3-pyrrolyloxindole **1a** (0.1 mmol, 1.0 equiv), compounds **4** (0.15 mmol, 1.5 equiv), and catalyst **E** (5 mol %) were dissolved in 2.0 mL of mesitylene at 0 °C, and the mixture was stirred for the indicated time. After completion of the reaction, as indicated by TLC, products **5** were isolated by flash chromatography on silica gel (petroleum ether/ethyl acetate = 6/1−2/1).

*(+)-N-(1-(1-Methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)-2-nitroethyl)acetamide (**5a**):* White solid, 29.0 mg, 85% yield; 96:4 dr; 18% ee; $[\alpha]_D^{20}$ = +6.5 (c 1.5, CH_2Cl_2); mp 205.8−207.7 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 5/95, flow rate = 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 147.8 min, t_{major} = 60.5 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major diastereomer) 7.67 (d, J = 7.8 Hz, 1H), 7.41−7.35 (m, 1H), 7.20−7.14 (m, 1H), 7.03 (t, J = 2.3 Hz, 2H), 6.86 (d, J = 7.8 Hz, 1H), 6.23 (t, J = 2.2 Hz, 2H), 5.89−5.97 (m, 1H), 5.59 (d, J = 9.9 Hz, 1H), 4.95 (dd, J = 13.1, 10.6 Hz, 1H), 4.21 (dd, J = 13.1, 3.2 Hz, 1H), 3.30 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major diastereomer) 171.8, 169.2, 143.0, 130.7, 125.9, 125.6, 123.8, 118.9, 110.3, 108.8, 74.5, 67.6, 51.7, 26.7, 22.7; HRMS (ESI-TOF) calcd for $C_{17}H_{18}N_4NaO_4$ [M + Na]$^+$ 365.1220, found 365.1223.

*(−)-N-(1-(1-Methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)-2-nitroethyl)benzamide (**5b**):* White solid, 37.6 mg, 93% yield; 94:6 dr; 24% ee; $[\alpha]_D^{20}$ = −13.3 (c 1.1, CH_2Cl_2); mp 199.2−200.8 °C; the ee was determined by HPLC (Chiralpak AS-H, *i*-PrOH/hexane = 20/80, flow rate = 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 12.8 min, t_{major} = 38.1 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major diastereomer) 7.79−7.74 (m, 1H), 7.45−7.27 (m, 6H), 7.21−7.08 (m, 3H), 6.82 (d, J = 7.8 Hz, 1H), 6.38−6.23 (m, 3H), 6.18−6.10 (m, 1H), 5.16−5.07 (m, 1H), 4.36−4.30 (m, 1H), 3.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major diastereomer) 171.8, 167.0, 143.0, 133.2, 132.0, 130.8, 128.6, 126.7, 125.7, 123.8, 119.0, 110.3, 108.9, 74.5, 67.8, 52.2, 26.7; HRMS (ESI-TOF) calcd for $C_{22}H_{20}N_4NaO_4$ [M + Na]$^+$ 427.1377, found 427.1382.

*(+)-Ethyl (1-(1-Methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)-2-nitroethyl)carbamate (**5c**):* White solid, 36.1 mg, 97% yield; 97:3 dr; 31% ee; $[\alpha]_D^{20}$ = +33.6 (c 1.3, CH_2Cl_2); mp 184.7−186.4 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 25/75, flow rate = 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 13.1 min, t_{major} = 8.4 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major diastereomer) 7.66 (d, J = 7.6 Hz, 1H), 7.41−7.35 (m, 1H), 7.19−7.14 (m, 1H), 7.03 (t, J = 2.2 Hz, 2H), 6.87 (d, J = 7.8 Hz, 1H), 6.23 (t, J = 2.2 Hz, 2H), 5.70−5.49 (m, 1H), 5.02−4.73 (m, 2H), 4.21 (d, J = 13.2 Hz, 1H), 3.89 (q, J = 7.2 Hz, 2H), 3.29 (s, 3H),1.10−0.93 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major diastereomer) 171.6, 155.1, 143.1, 130.7, 125.8, 125.5, 123.6, 118.9, 110.2, 108.9, 74.6, 67.7, 61.6, 54.0, 26.7, 14.2; HRMS (ESI-TOF) calcd for $C_{18}H_{20}N_4NaO_5$ [M + Na]$^+$ 395.1326, found 395.1316.

*(+)-tert-Butyl (1-(1-Methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)-2-nitroethyl)carbamate (**5d**):* White solid, 38.8 mg, 97% yield; 98:2 dr; 27% ee; $[\alpha]_D^{20}$ = +13.0 (c 1.9, CH_2Cl_2); mp 180.5−182.4 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 25/75, flow rate = 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 7.0 min, t_{major} = 6.1 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ (major diastereomer) 7.65 (d, J = 7.5 Hz, 1H), 7.36 (t, J = 7.8 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.02 (t, J = 2.2 Hz, 2H), 6.86 (d, J = 7.8 Hz, 1H), 6.23 (t, J = 2.2 Hz, 2H), 5.63−5.48 (m, 1H), 5.07−4.61 (m, 2H), 4.30−4.21 (m, 1H), 3.29 (s, 3H), 1.35 (s, 2H), 1.17 (s, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (major diastereomer) 171.7, 154.0, 143.1, 130.4, 126.0, 125.7,

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J. Org. Chem. 2016, 81, 5759−5765

123.5, 118.8, 110.1, 108.7, 80.6, 74.5, 68.0, 53.6, 27.8, 26.7; HRMS (ESI-TOF) calcd for $C_{20}H_{24}N_4NaO_5$ $[M + Na]^+$ 423.1639, found 423.1646.

Procedure for the Synthesis of Compound 6. A mixture of **3a** (215 mg, 0.5 mmol) and 5% Pd/C (53.7 mg, 25%, w/w) in MeOH (10 mL) was stirred vigorously under an atmosphere of hydrogen at room temperature for 24 h. Next, the mixture was filtered through a Celite plug and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 2/1−1/1) to furnish the compound **6** as a white solid.

*2-((R)-2-Amino-1-((S)-1-methyl-2-oxo-3-(1H-pyrrol-1-yl)indolin-3-yl)ethyl)isoindoline-1,3-dione (**6**):* White solid, 139.4 mg, 70% yield; 97:3 dr; 99% ee; $[\alpha]_D^{20}$ = +9.9 (*c* 1.8, CH_2Cl_2); mp 145.6−147.2 °C; the ee was determined by HPLC (Chiralpak AD-H, *i*-PrOH/hexane = 35/65, flow rate = 1.0 mL/min, λ = 254 nm, major diastereomer: t_{minor} = 21.9 min, t_{major} = 24.2 min); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73−7.59 (m, 5H), 7.23−7.17 (m, 1H), 7.10 (t, *J* = 2.2 Hz, 2H), 7.01−6.95 (m, 1H), 6.73 (d, *J* = 7.7 Hz, 1H), 6.11 (t, *J* = 2.2 Hz, 2H), 5.77 (dd, *J* = 9.5, 4.7 Hz, 1H), 5.17 (br s, 2H), 3.75 (dd, *J* = 14.1, 9.5 Hz, 1H), 3.56 (dd, *J* = 14.1, 4.8 Hz, 1H), 3.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 168.0, 143.4, 134.0, 130.1, 126.2, 125.9, 123.4, 123.0, 122.6, 119.5, 109.1, 108.6, 67.5, 52.3, 49.9, 26.7; HRMS (ESI-TOF) calcd for $C_{23}H_{21}N_4O_3$ $[M + H]^+$ 401.1608, found 401.1592.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00896.

Copies of ^{1}H NMR, ^{13}C NMR, chiral HPLC spectra for new products (PDF)

X-ray data for **3n** (CIF)

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Notes

The authors declare no competing financial interest.

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(14) For details, see the Supporting Information. CCDC 1445221 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(15) The ratio of **3a** to **8** refers to their mole ratio based on the amount of 3-pyrrolyloxindole **1a**.

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