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Amino-Indanol-Catalyzed Asymmetric Michael Additions of Oxindoles to Protected 2-Amino-1-nitroethenes for the Synthesis of 3,3′-Disubstituted Oxindoles Bearing α,β-Diamino Functionality

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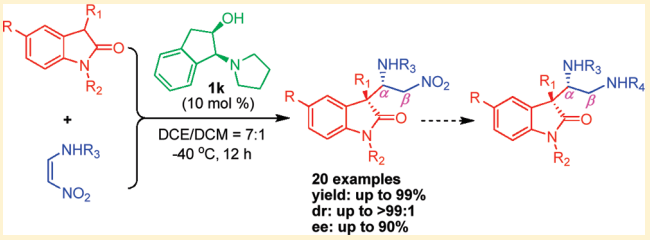
Supporting Information

ABSTRACT: An organocatalytic asymmetric Michael addition reaction of 3-substituted oxindoles to protected 2-amino-1-nitroethenes has been developed. The reaction is catalyzed by a simple and readily available amino-indanol derivative and affords the desired products in very high yields (up to 99%) with excellent diastereoselectivities (up to >99:1) and very good enantioselectivities (up to 90%). Significantly, this study provides a general catalytic method for the construction of 3,3′-disubstituted oxindoles bearing α,β-diamino functionality as well as vicinal chiral quaternary/tertiary stereocenters. The potential utility of the protocol also had been demonstrated by gram-scale reaction and the versatile conversion of product. Furthermore, On the basis of the comprehensive experimental results and the absolute configuration of one of the Michael adducts, a work model was also proposed to explain the origin of asymmetric induction.



INTRODUCTION

3,3′-Disubstituted oxindole structures are versatile synthetic motifs for biologically active natural products and pharmaceutically attractive intermediates.[1] In particular, optically active 3,3′-disubstituted oxindoles with α-amino or β-amino functionality are quite attractive and valuable synthetic targets. Consequently, substantial catalytic asymmetric approaches for these structural motifs have been reported in recent years, for example, using 3-substituted oxindoles as nucleophiles addition to imines leading to α-amino functionality[2] and addition to nitroolefins leading to β-amino functionality (Scheme 1).[3] However, in sharp contrast, the highly enantioselective and general methods for the synthesis of 3,3′-disubstituted oxindoles with α,β-diamino functionality remains elusive (Scheme 1), despite the indisputable fact that this kind of structural motif serves as a prominent feature in some biologically active natural products and several pharmaceutically active compounds, such as (+)-alantrypinone, (−)-serantrypinone, and (−)-lapatin.[4] In this context, an efficient approach for the asymmetric construction of structurally diverse 3,3′-disubstituted oxindole scaffolds bearing α,β-diamino functionality is highly desirable. To this end, one conceivable strategy could be to use the asymmetric conjugate addition reaction of 3-substituted oxindoles with 1,2-diamino-containing Michael acceptor, such as protected 2-amino-1-nitroethenes (Scheme 1).[5] If that is indeed the case, we can envision that this process will provide straightforward access to 3,3′-disubstituted oxindole motifs bearing α,β-diamino functionality as well as vicinal chiral quaternary/tertiary stereocenters, moreover, it should be a significant challenge due to the stereocontrol of both the absolute and relative configurations (Scheme 1).

The Michael addition is certainly one of the most powerful bond-forming transformations, and the diversity in donors and acceptors that can be combined is remarkable.[6] In this respect, the application of 3-substituted oxindoles as nucleophile with a diverse range of Michael acceptors has recently become the focus of research leading to various oxindoles that incorporate a chiral quaternary carbon center.[3,7] In spite of that significant progress having been made, the catalytic asymmetric Michael addition of 3-substituted oxindoles to protected 2-amino-1-nitroethenes, a class of ideal 1,2-diamino-containing Michael acceptor candidates with an easily transformable functional group, has not been realized so far (Scheme 1). To the best of our knowledge, there is only one example about the asymmetric Michael addition of aldehydes to protected 2-amino-1-nitroethenes by Ma and coworkers.[5b] In this context, as a continuing effort to develop new methodology for the construction of complex structural motifs with organocatalysts,[8] we recently realized the first catalytic asymmetric Michael addition of 3-substituted oxindoles to protected 2-amino-1-nitroethenes by a very simple and readily

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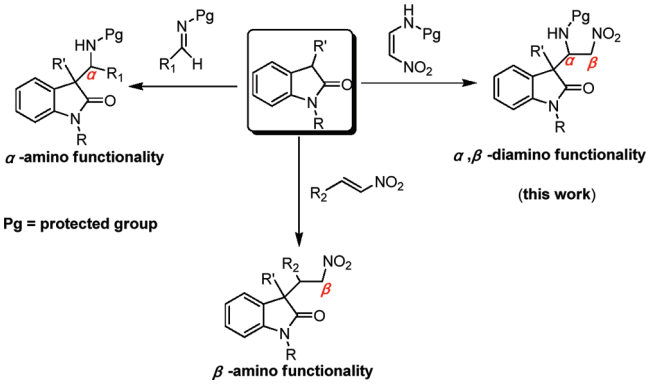
Scheme 1. Strategies for the Synthesis of 3,3′-Disubstituted Oxindoles Bearing α-Amino, β-Amino, or α,β-Diamino Functionality



available amino-indanol catalyst,[9] leading to the formation of a wide scope of 3,3′-disubstituted oxindoles bearing α,β-diamino functionality with vicinal chiral quaternary/tertiary stereocenters in up to 99% yield, 90% ee, and >99:1 dr. Herein, we wish to report our research results on this subject.

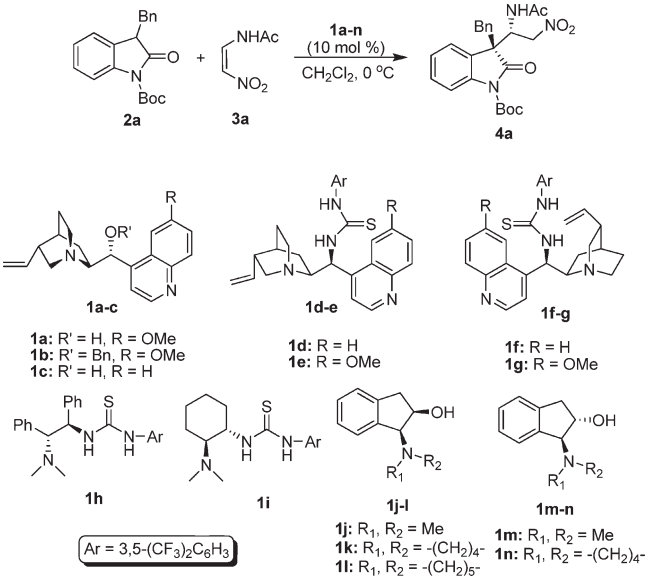
RESULTS AND DISCUSSION

Our studies commenced with a screen of organocatalysts derived from cinchona alkaloids (**1a**−**g**) and chiral 1,2-diamine compounds (**1h**,**i**) by means of the model reaction of 3-benzyl-oxindole **2a** and (*Z*)-*N*-(2-nitrovinyl)acetamide (**3a**) in CH_2Cl_2 at 0 °C (Table 1, entries 1−9). These experiments revealed that the reaction could be catalyzed by 10 mol % catalyst and afforded **4a** in excellent yields and good to excellent diastereoselectivities, but very poor enantioselectivities. However, to our delight, during the further quest for potential organocatalysts, it was observed that some simple and readily available amino-indanols **1j**,**k**, and **1m**,**n** catalyzed smoothly the model reaction, affording **4a** in excellent yields and diastereoselectivities, particularly with acceptable enantioselectivity ranging from 58% to 71% ee (Table 1, entries 10−11 and 13−14). We also noted that the relatively high ee value could be obtained with ***1l*** as catalyst, but the reactivity was unacceptable (Table 1, entry 12). By comprehensive comparison, **1k** was designated as the optimal catalyst in view of the reactivity and diastereo- and enantioselectivity (Table 1, entry 11).

Having identified the best catalyst **1k**, optimization of reaction conditions was further investigated. The probe of reaction temperature was first carried out in CH_2Cl_2 (Table 2, entries 1−4). It was observed that −40 °C was the most ideal temperature for obtaining the product in view of the yield and stereoselectivity (Table 2, entry 3). Next, the effect of various solvents for the Michael addition of **2a** to **3a** was also surveyed. It was found that CH_2Cl_2 is better than the other six different solvents surveyed (Table 2, entry 3 vs entries 5−10). Delightfully, the most desired results (99% yield, 49:1 dr, and 86% ee) could be obtained smoothly in DCE and DCM mixed solvent (volume ratio 7:1) (Table 2, entry 11). An attempt to add 100 mg of 4 Å molecular sieves (MS) to the process would not result in any improvement in the reaction (Table 2, entry 12 vs entry 11). Dilution had no any improvement in the yield, dr, and ee value, and a slight extension of reaction time was required (Table 2, entry 13). On the contrary, Michael adduct **4a** could be obtained in quantitative yield with 98:2 dr and up to 90% ee after 12 h by increasing the concentration of 3-substituted oxindole **2a** to 0.12 M (Table 2, entry 14). Afterward, upon further elevating the concentration to 0.24 M, enantioselectivity was decreased to 82%, albeit without sacrificing the yield and diastereoselectivity (Table 2, entry 15).

Adopting the reaction conditions described in Table 2, entry 14 as the optimal compromise among the reactivity and diastereo- and enantioselectivity, the generality of the method was demonstrated by evaluating a variety of 3-substituted oxindoles and two protected 2-amino-1-nitroethenes (Table 3). 3-Benzyl-*N*-Boc-oxindoles **2b**−**i** tolerated substitution at any position of the aromatic ring of the benzyl group, and both electron-donating and electron-withdrawing functionalities were compatible (Table 3,

Table 1. Screening of Organocatalysts[a]



entry	1	time (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	**1a**	8	97	89:11	−20
2	**1b**	8	90	84:16	41
3	**1c**	8	96	94:6	−9
4	**1d**	8	97	98:2	3
5	**1e**	8	96	96:4	0
6	**1f**	8	97	99:1	−15
7	**1g**	8	97	94:6	−1
8	**1h**	8	95	96:4	−5
9	**1i**	8	97	90:10	4
10	**1j**	8	97	94:6	68
11	**1k**	8	98	94:6	71
12	***1l***	30	28	85:15	74
13	**1m**	8	97	94:6	58
14	**1n**	8	95	93:7	71

[a] All the reactions were carried out at 0 °C for the specified time, **2a** (0.2 mmol), **3a** (0.24 mmol), **1** (10 mol %) in CH_2Cl_2 (4.0 mL). [b] Isolated yield. [c] Diastereoisomeric ratio determined with chiral HPLC by analysis of the purified product after separating by column chromatography. [d] Determined by chiral HPLC analysis.

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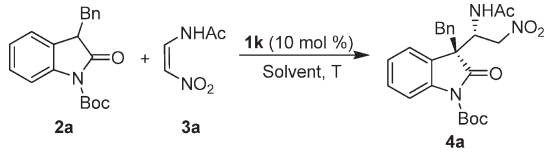
Table 2. Optimization of Reaction Conditions[a]



entry	solvent	T (°C)	time (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	DCM	rt	3	98	98:2	62
2	DCM	0	8	97	94:6	71
3	DCM	−40	15	98	97:3	84
4	DCM	−78	30	31	96:4	89
5	DCE	−34	15	99	95:5	81
6	$CHCl_3$	−40	15	83	96:4	65
7	C_6H_5Cl	−40	15	75	94:4	78
8	toluene	−40	30	34	92:8	65
9	CH_3CN	−40	30	56	93:7	71
10	THF	−40	30	44	85:15	44
11	DCE/DCM	−40	15	99	98:2	86[e]
12	DCE/DCM	−40	15	99	98:2	85[e,f]
13	DCE/DCM	−40	20	98	98:2	86[e,g,h]
14	DCE/DCM	−40	12	99	98:2	90[e,g,i]
15	DCE/DCM	−40	10	99	98:2	82[e,g,j]

[a] Unless otherwise noted, the reactions were carried out with **2a** (0.2 mmol), **3a** (0.24 mmol), and **1k** (10 mol %) in solvent (4.0 mL). [b] Isolated yield. [c] Diastereoisomeric ratio determined with chiral HPLC by analysis of the purified product after separating by column chromatography. [d] Determined by chiral HPLC analysis. [e] DCE/DCM = 7:1 (volume ratio). [f] With 100 mg of 4 Å MS as additive. [g] **2a** (0.24 mmol) and **3a** (0.20 mmol) were used. [h] 6.0 mL of solvent was used. [i] 2.0 mL of solvent was used. [j] 1.0 mL of solvent was used. DCM = dichloromethane; DCE = 1,2-dichloroethane.

entries 1−8). In these cases, the desired Michael adducts were generally obtained in excellent yields and diastereoselectivities, with good ee values ranging from 78% to 89%. Notably, with 1-naphthyl derivative **2j** as donor, excellent yield, dr, and good ee values were achieved as well (Table 3, entry 9). Similar results were observed with the thiophene counterpart **2k** (Table 3, entry 10). Moreover, 3-alkyloxindole substrates **2*l*−n** also showed very high reactivity, while the corresponding products could be obtained in high yields and diastereoselectivities and good enantioselectivities after 12 h under the optimal reaction conditions (Table 3, entries 11−13). Furthermore, the oxindole core may also be modified. Thus, both the benzo moiety (Table 3, entries 14 and 15) and the *N*-protecting group were changed (Table 3, entries 16 and 17) as well for giving access to structurally diverse products. 3-Aryloxindole **2s** gave rise to the corresponding adduct **4s** in excellent yield and diastereoselectivity, but with only 55% ee (Table 3, entry 18). On the other hand, another protecting group also could be incorporated into 2-amino-1-nitroethene, for example, (*Z*)-*N*-(2-nitrovinyl)benzamide (**3b**) and **2c** were subjected to the standard conditions and furnished the corresponding adduct with acceptable results (Table 3, entry 19).

To exploit the potential of the current catalyst system, the reaction was scaled up to using 4.8 mmol of **2f** as the starting material addition to **3a** with 10 mol % of **1k**. Product **4f** could be obtained smoothly in 93% yield, 95:5 dr, and 82% ee after 12 h, without significant deleterious effect on the reactivity and stereoselectivity (Scheme 2).

The absolute configuration of **4k** was assigned as (C8*R*,C9*S*) configuration on the basis of the X-ray crystal structure of **4k′**,[10] prepared from **4k** by removal of the Boc group with F_3CCOOH (Scheme 3). As no reaction occurred at the stereogenic center in **4k** while removing the Boc group, compound **4k** was deduced to have the same (C8*R*,C9*S*) configuration. Meanwhile, the absolute configuration of the other products were assigned by analogy.

Next, we attempted the versatile conversion of compound **4f** into other functionalized compounds, such as **5**, **6**, and **7** (Scheme 4). The Pd/C-catalyzed hydrogenation of compound **4f** proceeded smoothly in methanol, converting the nitro group into a primary amine group contained in **5**. Then, compound **6** could be obtained in 90% yield with >99:1 dr and 86% ee from **5** via the protection with $(Boc)_2O$ (Boc = *tert*-butoxycarbonyl). Eventually, we also found that compound **5** could be transformed into **7** in 62% yield with >99:1 dr and 83% ee via two sequential steps: deprotecting the Boc group with F_3CCOOH and protection of the amine group with TsCl (Scheme 4).

On the basis of experimental results and the observed absolute configuration of **4k**, we suggest Figure 1 as a proposed working model. As illustrated in Figure 1, the tertiary amine group of the catalyst activates the deprotonated enolated oxindole. Simultaneously, owing to strong intramolecular hydrogen bonding in substrate **3a**, only the *Z* isomer is formed; as a result, this probably facilitates the formation of single hydrogen bonding interaction between the hydroxyl group of the catalyst and the nitro group of substrate **3a**. Subsequently, the *si*-face of the **3a** was preferably attacked by the *re*-face of enolated oxindole, delivering the desired Michael adduct with (C8*R*,C9*S*) configuration.

CONCLUSION

In conclusion, we have developed an organocatalytic methodology for the asymmetric Michael addition of 3-substrated oxindoles to protected 2-amino-1-nitroethenes in the presence of a simple amino-indanol derivative. A wide spectrum of 3,3′-disubstituted oxindoles bearing α,β-diamino functionality and vicinal quaternary/tertiary stereocenters were smoothly obtained in excellent yields (up to 99%), virtually perfect diastereoselectivities (up to >99:1), and good enantioselectivities (up to 90%). Two points particularly noteworthy in this work include the following: (1) this is the sole example so far for the asymmetric synthesis of 3,3′-disubstituted oxindoles bearing α,β-diamino functionality; and (2) the simple and readily available amino-indanol derivative **1k** works well for this kind of asymmetric Michael addition reaction, whereas some analogous organic bifunctional catalysts derived from cinchona alkaloids or chiral 1,2-diamines are futile to control the enantioselectivity. In addition, the potential utilities of the protocol also had been demonstrated by gram-scale reaction and the versatile conversion of product.

EXPERIMENTAL SECTION

General Experimental Procedure for the Asymmetric Michael Additions of Oxindoles to Protected 2-Amino-1-nitroethenes Catalyzed by Amino-Indanol. In an ordinary vial equipped with a magnetic stirring bar, to the mixture of oxindoles **2** (0.24 mmol) and catalyst **1k** (0.02 mmol) in 2.0 mL of freshly distilled CH_2ClCH_2Cl/CH_2Cl_2 (7:1) was added protected 2-amino-1-nitroethenes **3** (0.2 mmol). The reaction mixture was stirred at −40 °C

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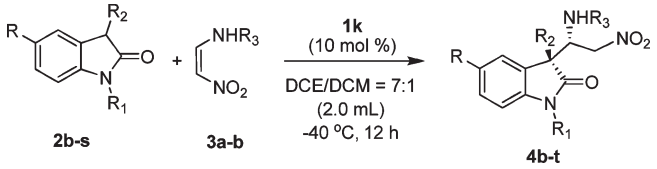
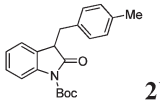
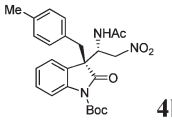
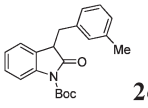
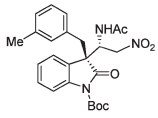
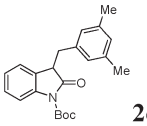
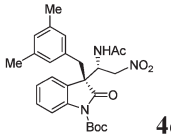
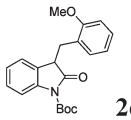
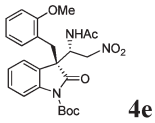
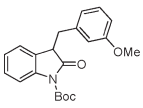
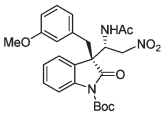
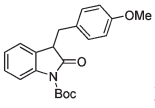
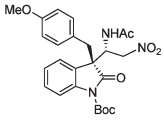
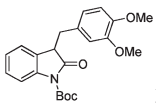
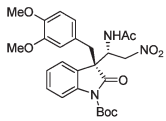
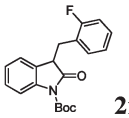
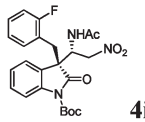
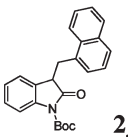
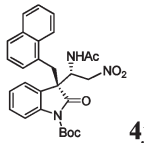
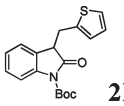
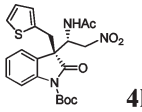
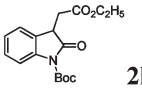
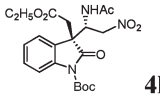
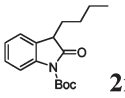
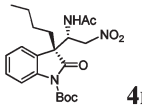
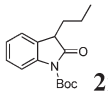
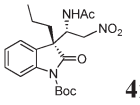
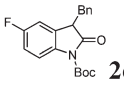
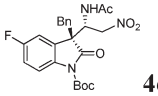
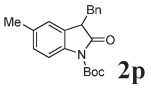
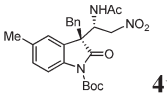
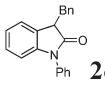
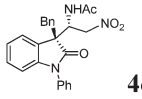
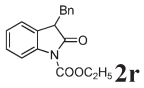
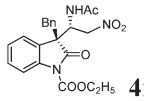
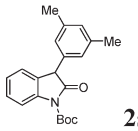
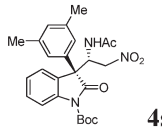
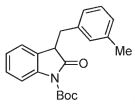
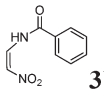
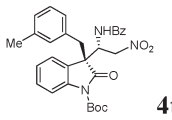
Table 3. Asymmetric Michael Addition Reaction of a Variety of 3-Substituted Oxindoles to Protected 2-Amino-1-nitroethenes[a]



entry	2	3	4	yield (%)[b]	dr[c]	ee (%)[d]
1	 **2b**	 **3a**	 **4b**	93	95:5	83
2	 **2c**	 **3a**	 **4c**	95	96:4	89
3	 **2d**	 **3a**	 **4d**	92	>99:1	82
4	 **2e**	 **3a**	 **4e**	95	97:3	84
5	 **2f**	 **3a**	 **4f**	94	98:2	84
6	 **2g**	 **3a**	 **4g**	94	96:4	78
7	 **2h**	 **3a**	 **4h**	95	95:5	81
8	 **2i**	 **3a**	 **4i**	99	97:3	85
9	 **2j**	 **3a**	 **4j**	94	97:3	86

dx.doi.org/10.1021/jo2004378 |*J. Org. Chem.* 2011, 76, 4008–4017

Table 3. Continued

entry	2	3	4	yield (%)[b]	dr[c]	ee (%)[d]
10	 **2k**	 **3a**	 **4k**	94	94:6	84[e]
11	 **2l**	 **3a**	 **4l**	92	94:6	74
12	 **2m**	 **3a**	 **4m**	91	97:3	80
13	 **2n**	 **3a**	 **4n**	93	96:4	80
14	 **2o**	 **3a**	 **4o**	90	>99:1	87
15	 **2p**	 **3a**	 **4p**	92	95:5	80
16	 **2q**	 **3a**	 **4q**	83	92:8	64[f]
17	 **2r**	 **3a**	 **4r**	99	96:4	80
18	 **2s**	 **3a**	 **4s**	92	>99:1	55[g]
19	 **2c**	 **3b**	 **4t**	85	86:14	72

[a] Unless otherwise noted, the reactions were carried out with **2** (0.24 mmol), **3** (0.20 mmol), and **1k** (10 mol %) in DCE/DCM 2.0 mL (volume ratio = 7:1) at −40 °C for 12 h. [b] Isolated yield. [c] Diastereoisomeric ratio determined with chiral HPLC by analysis of the purified product after separating by column chromatography. [d] Determined by chiral HPLC analysis. [e] The absolute configuration of **4k** was determined in view of the X-ray crystal structure of the derivative **4k′**.[10] [f] Run for 48 h. [g] Run at −78 °C for 48 h.

for 12 h and was directly loaded onto silica gel and purified by flash chromatography to give products **4**.

(*R*)-*tert*-Butyl-3-((*S*)-1-acetamido-2-nitroethyl)-3-benzyl-2-oxoindoline-1-carboxylate (4a): white solid; yield 99%, 98:2 dr, 90% ee, $[\alpha]^{20}_{D}$ +31.5 (*c* 1.35, $CHCl_3$); mp 153.3−155.6 °C; deprotected the Boc group, the ee was determined by HPLC analysis with a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; 1.0 mL/min; λ = 254 nm; t_{major} = 9.23 min; t_{minor} = 6.15 min); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.48 (s, 9H), 1.82 (s, 3H), 3.16 (d, *J* = 12.6 Hz, 1H), 3.32 (d, *J* = 12.6 Hz, 1H), 4.93−4.96 (m, 2H), 5.54−5.59 (m, 1H), 6.45 (br s, 1H), 6.70 (d, *J* = 6.9 Hz, 2H), 6.95−7.04 (m, 3H), 7.18−7.21 (m, 2H), 7.34−7.36 (m, 1H), 7.43−7.45 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.7, 27.9, 42.7, 51.5, 58.0, 75.5, 84.7, 114.6, 124.3, 124.5, 126.3, 127.0, 127.7, 129.0, 129.7, 133.3, 139.6, 148.0, 170.0, 176.1; IR (KBr) ν 3339, 3032, 2931, 1662, 1558, 1245, 841, 752, 567 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{27}N_3NaO_6$ $[M + Na]^+$ 476.1792, found 476.1798.

(*R*)-*tert*-Butyl-3-((*S*)-1-acetamido-2-nitroethyl)-3-(4-methylbenzyl)-2-oxoindoline-1-carboxylate (4b): white solid; yield 93%; 95:5 dr, 83% ee, $[\alpha]^{20}_{D}$ +23.3 (*c* 1.63, $CHCl_3$); mp 92.3−93.9 °C; deprotected the Boc group, the ee was determined by HPLC analysis with a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; 1.0 mL/min; λ = 254 nm; t_{major} = 10.41 min; t_{minor} = 6.44 min); ^{1}H NMR ($CDCl_3$,

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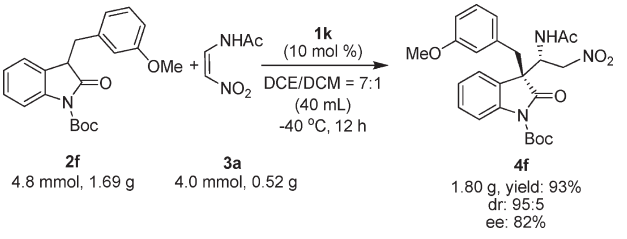
300 MHz) δ 1.47 (s, 9H), 1.79 (s, 3H), 2.14 (s, 3H), 3.13 (d, J = 12.9 Hz, 1H), 3.27 (d, J = 12.9 Hz, 1H), 4.92−4.95 (m, 2H), 5.54−5.58 (m, 1H), 6.57 (d, J = 7.8 Hz, 2H), 6.63−6.65 (m, 1H), 6.77 (d, J = 7.8 Hz, 2H), 7.18−7.21 (m, 2H), 7.36−7.39 (m, 1H), 7.43−7.46 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.8, 22.6, 27.8, 42.3, 51.4, 58.0, 75.5, 84.5, 114.6, 124.3, 124.4, 126.5, 128.4, 128.9, 129.5, 130.1, 136.5, 139.5, 148.0, 170.2, 176.2; IR (KBr) ν 3337, 2981, 1783, 1734, 1668, 1558, 1252, 1150, 1105, 756 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{29}N_3NaO_6$ $[M + Na]^+$ 490.1949, found 490.1967.

(*R*)-*tert*-Butyl-3-((*S*)-1-acetamido-2-nitroethyl)-3-(3-methylbenzyl)-2-oxoindoline-1-carboxylate (4c). white solid; yield 95%; 96:4 dr, 89% ee, $[\alpha]^{20}_D$ +50.1 (c 1.40, $CHCl_3$); mp 162.1−164.5 °C; deprotected the Boc group, the ee was determined by HPLC analysis with a Chiralpak AD-H column (90/10 hexane/*i*-PrOH; 1.0 mL/min; λ = 254 nm; t_{major} = 27.45 min; t_{minor} = 15.95 min); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.50 (s, 9H), 1.76 (s, 3H), 2.08 (s, 3H), 3.11 (d, J = 12.6 Hz, 1H), 3.26 (d, J = 12.6 Hz, 1H), 4.93−4.96 (m, 2H), 5.53−5.57 (m, 1H), 6.21−6.32 (m, 1H), 6.48−6.51 (m, 2H), 6.84−6.86 (m, 2H), 7.18−7.21 (m, 2H), 7.38−7.44 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.0, 22.7, 27.9, 42.7, 51.5, 58.0, 75.6, 84.6, 114.5, 124.3, 124.4, 126.5, 126.7, 127.6, 127.7, 129.0, 130.4, 133.1, 137.3, 139.6, 148.0, 169.9, 176.2; IR (KBr) ν 3380, 3034, 1785, 1736, 1558, 1252, 1149, 706 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{29}N_3NaO_6$ $[M + Na]^+$ 490.1949, found 490.1965.

(*R*)-*tert*-Butyl-3-((*S*)-1-acetamido-2-nitroethyl)-3-(3,5-dimethylbenzyl)-2-oxoindoline-1-carboxylate (4d). white solid; yield 92%; >99:1 dr, 82% ee, $[\alpha]^{20}_D$ +26.2 (c 1.75, $CHCl_3$); mp 171.4−173.6 °C; deprotected the Boc group, the ee was determined by HPLC analysis with a Chiralpak OJ-H column (90/10 hexane/*i*-PrOH; 1.0 mL/min; λ = 254 nm; t_{major} = 33.31 min; t_{minor} = 41.97 min); ^{1}H

Scheme 2. The Asymmetric Michael Addition Reaction of 2f to 3a in Gram-Scale



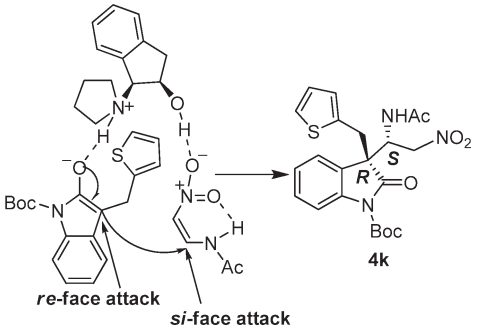
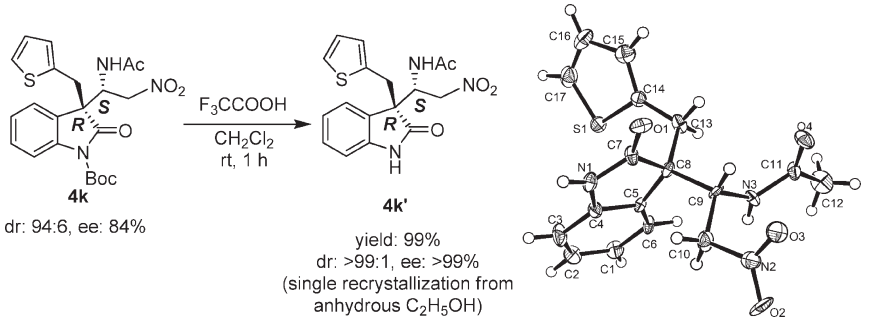
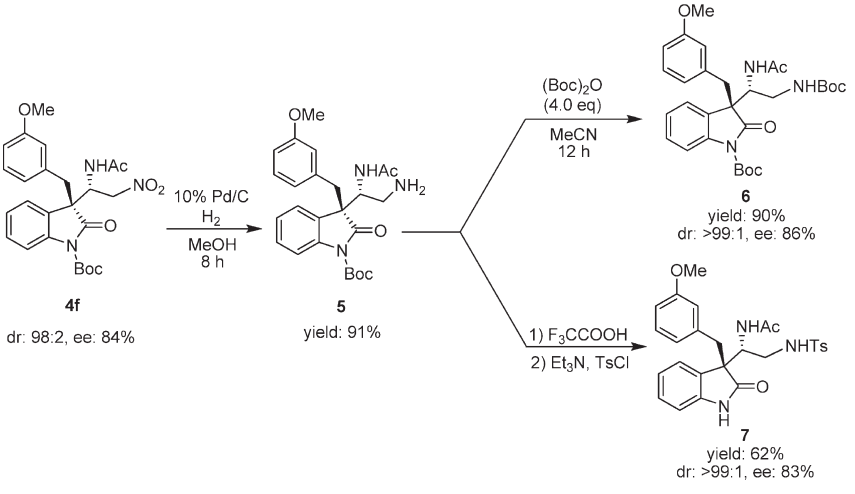


Figure 1. Proposed working model for the asymmetric Michael addition of 3-substituted oxindoles to protected 2-amino-1-nitroethene.

Scheme 3. Transformation of 4k to 4k′ and the X-ray Crystallographic Structure of 4k′



Scheme 4. Transformation of 4f to Other Compounds



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NMR ($CDCl_3$, 300 MHz) δ 1.46 (s, 9H), 1.77 (s, 3H), 2.02 (s, 6H), 3.08 (d, J = 12.6 Hz, 1H), 3.22 (d, J = 12.6 Hz, 1H), 4.91−5.01 (m, 2H), 5.55−5.59 (m, 1H), 6.28 (s, 2H), 6.65 (s, 1H), 6.80−6.84 (m, 1H), 7.17−7.21 (m, 2H), 7.34−7.37 (m, 1H), 7.44−7.47 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.8, 22.6, 27.8, 42.6, 51.3, 58.0, 75.5, 84.4, 114.3, 124.3, 124.4, 126.6, 127.5, 128.4, 128.7, 133.0, 137.0, 139.5, 147.9, 170.2, 176.3; IR (KBr) ν 3325, 2926, 1786, 1736, 1559, 1251, 1148, 841, 759 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{31}N_3NaO_6$ [M + Na]$^+$ 504.2105, found 504.2112.

(*R*)-*tert*-Butyl-3-((*S*)-1-acetamido-2-nitroethyl)-3-(2-methoxybenzyl)-2-oxoindoline-1-carboxylate (4e). white solid; yield 95%; 97:3 dr, 84% ee, $[\alpha]^{20}_D$ −17.4 (c 1.75, $CHCl_3$); mp 138.1−139.9 °C; deprotected the Boc group, the ee was determined by HPLC analysis with a Chiralpak OD-H column (80/20 hexane/*i*-PrOH; 1.0 mL/min; λ = 254 nm; t_{major} = 23.45 min; t_{minor} = 15.55 min); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.60 (s, 9H), 1.66 (s, 3H), 3.08 (d, J = 13.2 Hz, 1H), 3.47 (d, J = 13.2 Hz, 1H), 3.58 (s, 3H), 5.04−5.12 (m, 2H), 5.33−5.53 (m, 1H), 5.73−5.92 (m, 1H), 6.60 (d, J = 8.4 Hz, 1H), 6.64−6.69 (m, 1H), 6.75 (d, J = 7.2 Hz, 1H), 7.00−7.17 (m, 4H), 7.49 (d, J = 8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.7, 28.1, 35.8, 51.6, 54.7, 57.3, 75.6, 84.7, 110.0, 114.1, 119.9, 122.4, 123.5, 125.5, 126.5, 128.6, 128.7, 131.5, 139.4, 148.5, 157.2, 169.5, 176.7; IR (KBr) ν 3339, 3055, 2934, 1783, 1733, 1557, 1250, 1150, 755 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{29}N_3NaO_7$ [M + Na]$^+$ 506.1898, found 506.1922.

(*R*)-*tert*-Butyl-3-((*S*)-1-acetamido-2-nitroethyl)-3-(3-methoxybenzyl)-2-oxoindoline-1-carboxylate (4f). white solid; yield 94%; 98:2 dr, 84% ee, $[\alpha]^{20}_D$ −88.7 (c 1.38, $CHCl_3$); mp 112.2−114.9 °C; deprotected the Boc group, the ee was determined by HPLC analysis with a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; 1.0 mL/min; λ = 254 nm; t_{major} = 11.64 min; t_{minor} = 7.52 min); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.50 (s, 9H), 1.79 (s, 3H), 3.12 (d, J = 12.6 Hz, 1H), 3.29 (d, J = 12.6 Hz, 1H), 3.54 (s, 3H), 4.90−4.94 (m, 2H), 5.54−5.56 (m, 1H), 6.20−6.21 (m, 2H), 6.31 (d, J = 7.5 Hz, 1H), 6.58−6.61 (m, 1H), 6.87−6.92 (m, 1H), 7.20−7.23 (m, 2H), 7.42−7.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.6, 27.7, 42.6, 51.4, 54.8, 57.8, 75.4, 84.6, 113.3, 114.3, 114.6, 122.0, 124.1, 124.3, 126.3, 128.6, 129.0, 134.6, 139.6, 147.9, 158.8, 169.8, 175.9; IR (KBr) ν 3336, 2929, 1788, 1668, 1560, 1253, 1166, 1040, 757, 697 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{29}N_3NaO_7$ [M + Na]$^+$ 506.1898, found 506.1902.

(*R*)-*tert*-Butyl-3-((*S*)-1-acetamido-2-nitroethyl)-3-(4-methoxybenzyl)-2-oxoindoline-1-carboxylate (4g). white solid; yield 94%; 96:4 dr, 78% ee, $[\alpha]^{20}_D$ +44.1 (c 1.50, $CHCl_3$); mp 161.4−163.2 °C; deprotected the Boc group, the ee was determined by HPLC analysis with a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; 1.0 mL/min; λ = 254 nm; t_{major} = 13.95 min; t_{minor} = 7.69 min); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.50 (s, 9H), 1.76 (s, 3H), 3.10 (d, J = 12.9 Hz, 1H), 3.26 (d, J = 12.9 Hz, 1H), 3.65 (s, 3H), 4.90−4.94 (m, 2H), 5.51−5.55 (m, 1H), 6.24−6.28 (m, 1H), 6.51 (d, J = 8.7 Hz, 2H), 6.61 (d, J = 8.7 Hz, 2H), 7.18−7.25 (m, 2H), 7.40−7.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.7, 27.9, 41.9, 51.4, 55.0, 58.1, 75.6, 84.7, 113.2, 114.7, 124.2, 124.5, 125.5, 126.5, 129.0, 130.7, 139.6, 148.0, 158.6, 169.9, 176.2; IR (KBr) ν 3275, 2930, 1785, 1735, 1557, 1513, 1251, 1149, 1106, 1033, 838, 754 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{29}N_3NaO_7$ [M + Na]$^+$ 506.1898, found 506.1913.

(*R*)-*tert*-Butyl-3-((*S*)-1-acetamido-2-nitroethyl)-3-(3,4-dimethoxybenzyl)-2-oxoindoline-1-carboxylate (4h). white solid; yield 95%; 95:5 dr, 81% ee, $[\alpha]^{20}_D$ +35.1 (c 1.50, $CHCl_3$); mp 134.1−136.8 °C; deprotected the Boc group, the ee was determined by HPLC analysis with a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; 1.0 mL/min; λ = 254 nm; t_{major} = 14.06 min; t_{minor} = 8.22 min); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.49 (s, 9H), 1.77 (s, 3H), 3.10 (d, J = 12.6 Hz, 1H), 3.26 (d, J = 12.6 Hz, 1H), 3.53 (s, 3H), 3.72 (s, 3H), 4.91−4.94 (m, 2H), 5.51−5.55 (m, 1H), 6.08 (s, 1H), 6.25−6.35 (m, 2H), 6.51 (d, J = 8.1 Hz, 1H), 7.20−7.23 (m, 2H), 7.41−7.44 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.7, 27.9, 42.3, 51.4, 55.4, 55.6, 58.1, 75.5, 84.7, 110.4, 112.5, 114.8, 122.1, 124.2, 124.4, 125.6, 126.6, 129.0, 139.8, 148.0, 169.9, 176.2; IR (KBr) ν 3341, 2979, 1784, 1733, 1557, 1516, 1261, 1150, 1027, 766 cm^{-1}; HRMS (ESI) calcd for $C_{26}H_{31}N_3NaO_8$ [M + Na]$^+$ 536.2003, found 536.2024.

(*R*)-*tert*-Butyl-3-((*S*)-1-acetamido-2-nitroethyl)-3-(2-fluorobenzyl)-2-oxoindoline-1-carboxylate (4i). white solid; yield 99%; 97:3 dr, 85% ee, $[\alpha]^{20}_D$ +16.3 (c 1.50, $CHCl_3$); mp 153.1−155.3 °C; deprotected the Boc group, the ee was determined by HPLC analysis with a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; 1.0 mL/min; λ = 254 nm; t_{major} = 11.14 min; t_{minor} = 6.91 min); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.54 (s, 9H), 1.78 (s, 3H), 3.25 (d, J = 13.2 Hz, 1H), 3.41 (d, J = 13.2 Hz, 1H), 4.86−4.90 (m, 2H), 5.50−5.56 (m, 1H), 6.36−6.38 (m, 1H), 6.72−6.77 (m, 1H), 6.81−6.86 (m, 2H), 7.12−7.13 (m, 1H), 7.15−7.19 (m, 2H), 7.39−7.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.7, 27.9, 34.7, 51.6, 57.3, 75.4, 84.9, 114.3, 115.0 (d, J_{CF} = 22.6 Hz), 121.0 (d, J_{CF} = 15.2 Hz), 123.5 (d, J_{CF} = 3.5 Hz), 124.4, 124.8, 125.7, 129.1, 129.3, 131.3 (d, J_{CF} = 3.7 Hz), 139.3, 148.1, 160.5 (d, J_{CF} = 245.3 Hz), 170.0, 176.2; IR (KBr) ν 3275, 2950, 1763, 1725, 1661, 1558, 1153, 1101, 750, 702 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{26}FN_3NaO_6$ [M + Na]$^+$ 494.1698, found 494.1705.

(*R*)-*tert*-Butyl-3-((*S*)-1-acetamido-2-nitroethyl)-3-(naphthalen-1-ylmethyl)-2-oxoindoline-1-carboxylate (4j). white solid; yield 94%; 97:3 dr, 86% ee, $[\alpha]^{20}_D$ +41.4 (c 1.50, $CHCl_3$); mp 121.1−124.2 °C; deprotected the Boc group, the ee was determined by HPLC analysis with a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; 1.0 mL/min; λ = 254 nm; t_{major} = 11.30 min; t_{minor} = 8.25 min); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.32 (s, 9H), 1.72 (s, 3H), 3.58 (d, J = 13.2 Hz, 1H), 3.95 (d, J = 13.2 Hz, 1H), 5.13−5.16 (m, 2H), 5.73−5.77 (m, 1H), 6.32−6.34 (m, 1H), 6.80 (d, J = 7.2 Hz, 1H), 7.03−7.06 (m, 3H), 7.23−7.43 (m, 4H), 7.56 (d, J = 8.1 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.88 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.7, 27.7, 38.1, 51.6, 57.9, 75.7, 84.4, 114.3, 123.9, 124.3, 124.4, 124.6, 125.4, 125.6, 126.4, 128.0, 128.2, 128.3, 128.9, 129.7, 131.7, 133.4, 139.5, 147.8, 170.0, 176.5; IR (KBr) ν 3339, 2980, 1784, 1735, 1558, 1251, 1149, 1100, 772 cm^{-1}; HRMS (ESI) calcd for $C_{28}H_{29}N_3NaO_6$ [M + Na]$^+$ 526.1949, found 526.1964.

(*R*)-*tert*-Butyl-3-((*S*)-1-acetamido-2-nitroethyl)-2-oxo-3-(thiophen-2-ylmethyl)indoline-1-carboxylate (4k). white solid; yield 94%; 94:6 dr, 84% ee, $[\alpha]^{20}_D$ +27.6 (c 1.25, $CHCl_3$); mp 158.1−160.3 °C; deprotected the Boc group, the ee was determined by HPLC analysis with a Chiralpak OD-H column (85/15 hexane/*i*-PrOH; 1.0 mL/min; λ = 254 nm; t_{major} = 23.97 min; t_{minor} = 20.68 min); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.54 (s, 9H), 1.82 (s, 3H), 3.38 (d, J = 14.1 Hz, 1H), 3.59 (d, J = 14.1 Hz, 1H), 4.75−7.81 (m, 2H), 5.46−5.53 (m, 1H), 6.24−6.27 (m, 1H), 6.52 (d, J = 3.0 Hz, 1H), 6.68−6.71 (m, 1H), 6.94 (d, J = 5.1 Hz, 1H), 7.20−7.32 (m, 2H), 7.41 (d, J = 7.2 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.8, 28.0, 36.6, 51.5, 57.6, 75.3, 84.9, 114.9, 124.2, 124.8, 125.0, 126.2, 126.3, 127.6, 129.5, 134.7, 140.1, 148.2, 170.0, 175.7; IR (KBr) ν 3285, 2980, 1785, 1756, 1558, 1148, 1203, 1105, 767, 701 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{25}N_3NaO_6S$ [M + Na]$^+$ 482.1356, found 482.1363.

(*R*)-*tert*-Butyl-3-((*S*)-1-acetamido-2-nitroethyl)-3-(2-ethoxy-2-oxoethyl)-2-oxoindoline-1-carboxylate (4*l*). colorless oil; yield 92%; 94:6 dr, 74% ee, $[\alpha]^{20}_D$ +25.7 (c 1.88, $CHCl_3$); deprotected the Boc group, the ee was determined by HPLC analysis with a Chiralpak OJ-H column (80/20 hexane/*i*-PrOH; 0.8 mL/min; λ = 254 nm; t_{major} = 29.45 min; t_{minor} = 38.05 min); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, J = 7.2 Hz, 3H), 1.62 (s, 9H), 1.83 (s, 3H), 3.01 (d, J = 16.2 Hz, 1H), 3.18 (d, J = 16.2 Hz, 1H), 3.79−3.87 (m, 2H), 4.31−4.39 (m, 1H), 4.75−4.53 (m, 1H), 5.25−5.28 (m, 1H), 6.78 (d, J = 9.6 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 7.25−7.36 (m, 2H), 7.75 (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.5, 22.6, 28.0, 39.8, 52.0, 52.9, 61.0, 74.4, 85.1, 115.0, 123.6, 124.7, 125.7, 129.6, 140.1, 148.5, 168.5, 170.6, 175.5; IR (KBr) ν 3338, 2982, 2934, 1730, 1669, 1253,

1150, 1030, 841, 775, 680 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{27}N_3NaO_8$ $[M + Na]^+$ 472.1690, found 472.1708.

(*R*)-*tert*-Butyl-3-((*S*)-1-acetamido-2-nitroethyl)-3-butyl-2-oxoindoline-1-carboxylate (4m). white solid; yield 91%; 97:3 dr, 80% ee, $[\alpha]^{20}_D$ +24.6 (*c* 2.00, $CHCl_3$); mp 75.4−77.1 °C; deprotected the Boc group, the ee was determined by HPLC analysis with a Chiralpak OD-H column (80/20 hexane/*i*-PrOH; 1.0 mL/min; λ = 254 nm; t_{major} = 14.46 min; t_{minor} = 6.86 min); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.75 (t, *J* = 7.2 Hz, 3H), 0.75−0.78 (m, 1H), 0.88−1.21 (m, 1H), 1.15−1.23 (m, 2H), 1.61 (s, 9H), 1.68 (s, 3H), 1.89−2.06 (m, 2H), 4.71−4.79 (m, 2H), 5.28−5.36 (m, 1H), 6.35−6.38 (m, 1H), 7.16−7.21 (m, 1H), 7.25−7.33 (m, 2H), 7.69 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.5, 22.5, 22.6, 25.8, 28.0, 35.7, 52.0, 56.2, 75.2, 85.2, 114.6, 124.0, 124.8, 127.3, 128.9, 139.5, 148.5, 169.9, 176.8; IR (KBr) ν 3297, 2959, 1785, 1736, 1558, 1150, 763, 694 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{29}N_3NaO_6$ $[M + Na]^+$ 442.1949, found 442.1952.

(*R*)-*tert*-Butyl-3-((*S*)-1-acetamido-2-nitroethyl)-2-oxo-3-propylindoline-1-carboxylate (4n). white solid; yield 93%; 80% ee, 96:4 dr, $[\alpha]^{20}_D$ +79.9 (*c* 1.31 $CHCl_3$); mp 93.1−96.2 °C; deprotected the Boc group, the ee was determined by HPLC analysis with a Chiralpak OD-H column (80/20 hexane/*i*-PrOH; 1.0 mL/min; λ = 254 nm; t_{major} = 22.22 min; t_{minor} = 8.93 min); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.74−0.79 (m, 4H), 0.82−0.87 (m, 1H), 1.59 (s, 9H), 1.69 (s, 3H), 1.86−1.95 (m, 2H), 4.68−4.77 (m, 2H), 5.29−5.36 (m, 1H), 6.64−6.67 (m, 1H), 7.14−7.19 (m, 1H), 7.25−7.34 (m, 2H), 7.65−7.70 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.8, 17.2, 22.4, 27.9, 38.1, 52.0, 56.3, 75.1, 85.1, 114.6, 123.9, 124.8, 127.2, 128.8, 139.4, 148.4, 170.2, 176.8; IR (KBr) ν 3280, 2964, 1784, 1732, 1558, 1149, 754 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{27}N_3NaO_6$ $[M + Na]^+$ 428.1792, found 428.1809.

(*R*)-*tert*-Butyl-3-((*S*)-1-acetamido-2-nitroethyl)-3-benzyl-5-fluoro-2-oxoindoline-1-carboxylate (4o). white solid; yield 90%; >99:1 dr, 87% ee, $[\alpha]^{20}_D$ +38.9 (*c* 1.63, $CHCl_3$); mp 114.2−116.1 °C; deprotected the Boc group, the ee was determined by HPLC analysis with a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; 1.0 mL/min; λ = 254 nm; t_{major} = 9.57 min; t_{minor} = 11.36 min); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.46 (s, 9H), 1.83 (s, 3H), 3.17 (d, *J* = 12.6 Hz, 1H), 3.36 (d, *J* = 12.6 Hz, 1H), 4.83−5.00 (m, 2H), 5.54−5.57 (m, 1H), 6.73 (d, *J* = 6.9 Hz, 2H), 6.88−6.91 (s, 1H), 6.96−7.05 (m, 3H), 7.14 (d, *J* = 9.6 Hz, 1H), 7.31−7.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.5, 27.8, 42.6, 51.5, 58.2, 75.1, 84.8, 111.9 (d, J_{CF} = 24.6 Hz), 115.5 (d, J_{CF} = 22.8 Hz), 115.9 (d, J_{CF} = 8.0 Hz), 127.1, 127.8, 128.4 (d, J_{CF} = 8.2 Hz), 129.5, 133.1, 135.5, 147.8, 160.0 (d, J_{CF} = 242.6 Hz), 170.7, 175.8; IR (KBr) ν 3283, 2925, 2854, 1785, 1734, 1556, 1479, 1250, 1150, 1095, 1037, 841, 757 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{26}FN_3NaO_6$ $[M + Na]^+$ 494.1698, found 494.1704.

(*R*)-*tert*-Butyl-3-((*S*)-1-acetamido-2-nitroethyl)-3-benzyl-5-methyl-2-oxoindoline-1-carboxylate (4p). white solid; yield 92%; 95:5 dr, 80% ee, $[\alpha]^{20}_D$ +42.0 (*c* 1.68, $CHCl_3$); mp 132.1−133.9 °C; deprotected the Boc group, the ee was determined by HPLC analysis with a Chiralpak OD-H column (80/20 hexane/*i*-PrOH; 1.0 mL/min; λ = 254 nm; t_{major} = 17.90 min; t_{minor} = 13.90 min); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.46 (s, 9H), 1.79 (s, 3H), 2.36 (s, 3H), 3.13 (d, *J* = 12.6 Hz, 1H), 3.29 (d, *J* = 12.6 Hz, 1H), 4.90−4.93 (m, 2H), 5.51−5.58 (m, 1H), 6.55 (d, *J* = 10.2 Hz, 1H), 6.68 (d, *J* = 7.2 Hz, 2H), 6.94−7.06 (m, 4H), 7.22 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.1, 22.7, 27.9, 42.6, 51.6, 57.9, 75.5, 84.4, 114.4, 124.5, 124.6, 126.3, 126.9, 127.6, 127.7, 129.4, 129.6, 133.4, 134.2, 137.1, 148.0, 170.0, 176.2; IR (KBr) ν 3328, 3034, 1779, 1663, 1555, 1186, 1120, 819, 699 cm^{-1}. HRMS (ESI) calcd for $C_{25}H_{29}N_3NaO_6$ $[M + Na]^+$ 490.1949, found 490.1970.

***N*-((*S*)-1-((*R*)-3-Benzyl-2-oxo-1-phenylindolin-3-yl)-2-nitroethyl)acetamide (4q).** white solid; yield 83%; 92:8 dr, 64% ee, $[\alpha]^{20}_D$ +20.0 (*c* 1.50, $CHCl_3$); mp 65.2−67.8 °C; the ee was determined by HPLC analysis with a Chiralpak OD-H column (80/20 hexane/*i*-PrOH; 1.0 mL/min; λ = 254 nm; t_{major} = 12.77 min; t_{minor} = 19.84 min); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.93 (s, 3H), 3.26 (d, *J* = 12.6 Hz, 1H), 3.42 (d, *J* = 12.6 Hz, 1H), 4.73−4.78 (m, 2H), 5.53−5.57 (m, 1H), 6.43 (d, *J* = 7.2 Hz, 1H), 6.44−6.55 (m, 1H), 6.80 (d, *J* = 6.9 Hz, 2H), 6.87 (d, *J* = 6.9 Hz, 2H), 7.04−7.19 (m, 5H), 7.38−7.44 (m, 3H), 7.53−7.55 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.9, 41.9, 51.7, 57.4, 75.6, 109.4, 110.0, 123.1, 123.8, 124.6, 126.5, 126.8, 126.9, 127.1, 127.7, 127.8, 128.5, 128.6, 129.1, 129.3, 129.6, 130.0, 133.5, 134.0, 143.9, 170.2, 175.7; IR (KBr) ν 3281, 2924, 1710, 1664, 1556, 1376, 1240, 1109, 756, 698 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{23}N_3NaO_4$ $[M + Na]^+$ 452.1581, found 452.1591.

(*R*)-3-((*S*)-1-Acetamido-2-nitroethyl)-3-benzyl-2-oxoindolin-1-ylpropionate (4r). white solid; yield 99%; 96:4 dr, 80% ee, $[\alpha]^{20}_D$ +29.0 (*c* 2.50, $CHCl_3$); mp 158.9−162.3 °C; the ee was determined by HPLC analysis with a Chiralpak AD-H column (90/10 hexane/*i*-PrOH; 1.0 mL/min; λ = 254 nm; t_{major} = 23.52 min; t_{minor} = 15.80 min); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.24−1.37 (m, 3H), 1.77 (s, 3H), 3.20 (d, *J* = 12.6 Hz, 1H), 3.34 (d, *J* = 12.6 Hz, 1H), 4.17−4.31 (m, 2H), 4.95 (d, *J* = 6.9 Hz, 2H), 5.50−5.56 (m, 1H), 6.69−6.75 (m, 3H), 6.95−7.03 (m, 3H), 7.21−7.26 (m, 2H), 7.46−7.49 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 22.5, 42.5, 51.8, 58.0, 63.4, 75.3, 114.6, 124.5, 124.7, 126.4, 127.1, 127.8, 129.1, 129.6, 133.2, 139.2, 149.7, 170.3, 176.0; IR (KBr) ν 3266, 2927, 1789, 1663, 1554, 1284, 1239, 1162, 1027, 765, 701 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{23}N_3NaO_6$ $[M + Na]^+$ 448.1479, found 448.1495.

(*R*)-*tert*-Butyl-3-((*S*)-1-acetamido-2-nitroethyl)-3-(3,5-dimethylphenyl)-2-oxoindoline-1-carboxylate (4s). white solid; yield 92%; >99:1 dr, 55% ee, $[\alpha]^{20}_D$ −87.8 (*c* 1.63, $CHCl_3$); mp 114.2−117.1 °C; deprotected the Boc group, the ee was determined by HPLC analysis with a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; 1.0 mL/min; λ = 254 nm; t_{major} = 5.91 min; t_{minor} = 5.21 min); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.67 (s, 9H), 2.31 (s, 6H), 4.51−4.56 (m, 1H), 5.02−5.10 (m, 1H), 6.05−6.14 (m, 1H), 6.15−6.23 (m, 1H), 6.94 (s, 1H), 7.11 (s, 2H), 7.15−7.21 (m, 1H), 7.25−7.31 (m, 1H), 7.64−7.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.4, 22.6, 28.0, 52.0, 60.9, 75.8, 85.4, 114.4, 123.8, 124.8, 125.1, 128.5, 128.8, 130.2, 136.4, 138.6, 139.2, 148.5, 169.8, 176.0; IR (KBr) ν 3283, 2925, 1785, 1734, 1556, 1250, 1150, 1095, 841, 757, 702 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{29}N_3NaO_6$ $[M + Na]^+$ 490.1949, found 490.1951.

(*R*)-*tert*-Butyl-3-((*S*)-1-benzamido-2-nitroethyl)-3-(3-methylbenzyl)-2-oxoindoline-1-carboxylate (4t). white solid; yield 85%; 86:14 dr, 72% ee, $[\alpha]^{20}_D$ +26.6 (*c* 2.13, $CHCl_3$); mp 102.2−104.3 °C; deprotected the Boc group, the ee was determined by HPLC analysis with a Chiralpak OD-H column (80/20 hexane/*i*-PrOH; 1.0 mL/min; λ = 254 nm; t_{major} = 21.66 min; t_{minor} = 16.96 min); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.53 (s, 9H), 2.10 (s, 3H), 3.20 (d, *J* = 12.6 Hz, 1H), 3.38 (d, *J* = 12.6 Hz, 1H), 4.95−4.99 (m, 2H), 5.70−5.76 (m, 1H), 6.55 (d, *J* = 5.4 Hz, 2H), 6.87 (d, *J* = 6.3 Hz, 1H), 6.89−6.93 (m, 2H), 7.14−7.18 (m, 2H), 7.29−7.33 (m, 2H), 7.42−7.51 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.0, 27.9, 42.6, 52.2, 58.0, 75.5, 84.6, 114.7, 124.3, 124.4, 126.2, 126.7, 126.9, 127.3, 127.5, 127.7, 128.3, 128.5, 128.8, 129.1, 130.5, 131.8, 133.2, 133.5, 137.3, 139.7, 148.1, 167.5, 176.0; IR (KBr) ν 3342, 2937, 1784, 1734, 1558, 1487, 1251, 1149, 1038, 931, 770 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{31}N_3NaO_6$ $[M + Na]^+$ 552.2105, found 552.2111.

(*R*)-*tert*-Butyl-3-((*S*)-1-acetamido-2-aminoethyl)-3-(3-methoxybenzyl)-2-oxoindoline-1-carboxylate (5). To a stirred solution of compound **4f** (483 mg, 1 mmol) in CH_3OH (20 mL) was added Pd/C (w/w 10%, 212 mg, 20 mol %) at room temperature. The reaction mixture was stirred under H_2 atmosphere (1 atm) for 8 h at room temperature. Then, it was filtered through Celite and washed with ethyl acetate. The filtrates were concentrated and purified by column chromatography (hexane/ethyl acetate 2:1) to give **5** as a white solid

(412 mg, 91% yield). Mp 114.1−116.9 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.35 (s, 9H), 1.43 (s, 3H), 3.00 (d, J = 6.3 Hz, 2H), 3.36 (d, J = 12.3 Hz, 1H), 3.63 (d, J = 12.3 Hz, 1H), 3.76 (s, 3H), 5.06−5.11 (m, 1H), 6.85 (d, J = 7.2 Hz, 2H), 6.95 (s, 1H), 7.05 (d, J = 7.2 Hz, 1H), 7.14−7.27 (m, 3H), 7.33−7.35 (m, 2H), 7.54−7.57 (m, 1H), 10.51 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.1, 28.2, 42.3, 45.8, 52.8, 55.3, 55.6, 81.7, 114.0, 115.2, 123.3, 128.2, 128.6, 128.8, 129.4, 131.5, 135.2, 136.3, 137.1, 156.9, 159.7, 169.9, 170.6; IR (KBr) ν 3274, 3060, 2977, 1702, 1490, 1368, 1158, 1053, 726, 612 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{31}N_3NaO_6$ $[M + NaO]^+$ 492.2105, found 492.2120.

(*R*)-*tert*-Butyl-3-((*S*)-1-acetamido-2-(*tert*-butoxycarbonylamino)ethyl)-3-(3-methoxybenzyl)-2-oxoindoline-1-carboxylate (6). To a stirred solution of compound **5** (1.0 mmol) in CH_3CN (25 mL) was added $(Boc)_2O$ (4.0 mmol) at room temperature. After the mixture was stirred for 12 h at room temperature, the mixture was concentrated in vacuo and purified by silica gel column chromatography (hexane/ethyl acetate = 2/1) to afford **6** (497 mg, 90% yield). Colorless oil, >99:1 dr, 86% ee, $[\alpha]^{20}_D$ −88.7 (c 1.38, $CHCl_3$); the ee was determined by HPLC analysis with a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; 1.0 mL/min; λ = 254 nm; t_{major} = 4.58 min; t_{minor} = 4.27 min); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.50 (s, 9H), 1.52 (s, 9H), 1.59 (s, 3H), 3.14 (d, J = 5.7 Hz, 2H), 3.46 (d, J = 12.6 Hz, 1H), 3.59 (d, J = 12.6 Hz, 1H), 3.78 (s, 3H), 5.11−5.18 (m, 1H), 6.82 (d, J = 2.1 Hz, 1H), 6.84−6.85 (m, 1H), 6.92 (br s, 2H), 7.00 (d, J = 7.5 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 7.27−7.33 (m, 3H), 7.58 (d, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.3, 27.5, 28.2, 42.4, 46.5, 51.7, 54.1, 55.1, 80.9, 86.0, 114.0, 115.5, 123.2, 127.6, 128.8, 128.9, 129.4, 130.9, 135.3, 136.0, 136.3, 150.7, 156.8, 159.6, 170.7, 171.1; HRMS (ESI) calcd for $C_{30}H_{39}N_3NaO_8$ $[M + NaO]^+$ 592.2629, found 592.2639.

***N*-((*S*)-1-((*R*)-3-(3-Methoxybenzyl)-2-oxoindolin-3-yl)-2-(4-methylphenylsulfonamido)ethyl)acetamide (7).** Compound **5** (0.5 mmol) was dissolved in F_3CCOOH (1.3 mL) at 0 °C, and the solution was stirred for about 30 min at 0 °C. It was then concentrated in vacuo to afford the crude product. To a solution of the crude product (0.56 mmol) in dry CH_2Cl_2 (5 mL) at 0 °C was added Et_3N (1.40 mmol) under an argon atmosphere. The resulting mixture was stirred at 0 °C for 10 min, then a solution of TsCl (0.84 mmol) in dry CH_2Cl_2 (1.5 mL) was added dropwise. The resulting solution was stirred at 0 °C for 30 min, then allowed to warm to room temperature; stirring was then continued for about 4 h. The reaction mixture was concentrated in vacuo and purified by silica gel column chromatography (hexane/AcOEt = 10/1) to afforde7 (62%). White soild; >99:1 dr, 83% ee, $[\alpha]^{20}_D$ −5.7 (c 1.5, $CHCl_3$); mp 128.4−131.9 °C; the ee was determined by HPLC analysis with a Chiralpak AD-H column (80/20 hexane/*i*-PrOH; 1.0 mL/min; λ = 254 nm; t_{major} = 11.95 min; t_{minor} = 9.28 min); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.83 (s, 3H), 2.42 (s, 3H), 3.05−3.23 (m, 3H), 3.56 (s, 3H), 3.74 s, 1H), 5.07 (s, 1H), 6.36−6.41 (m, 2H), 6.61 (d, J = 7.8 Hz, 1H), 6.71 (d, J = 7.8 Hz, 1H), 6.92−7.12 (m, 4H), 7.25−7.36 (m, 3H), 7.79 (d, J = 7.5 Hz, 2H), 9.08 (br s, 1H), 9.57 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.6, 22.9, 40.9, 51.3, 53.5, 54.9, 57.4, 110.1, 112.8, 114.8, 122.4, 122.5, 124.0, 128.4, 128.5, 129.5, 129.6, 129.7, 130.0, 136.1, 141.1, 144.8, 158.6, 172.4, 180.1; HRMS (ESI) calcd for $C_{27}H_{29}N_3NaO_6S$ $[M + NaO]^+$ 546.1669, found 546.1680.

■ ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures, detailed spectral data for products, and X-ray crystal structure (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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