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Organocatalyzed Enantioselective Synthesis of Quaternary Carbon-Containing Isoindolin-1-ones

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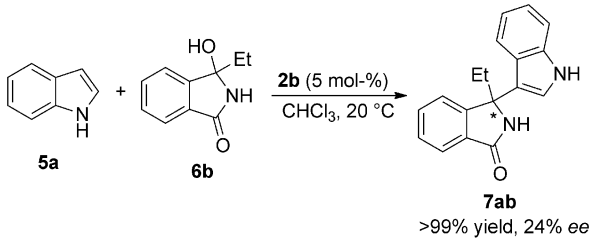
3,3′-Triphenylsilyl-substituted (*S*)-BINOL-based (1,1′-bi-2-naphthol) phosphoric acid has proven to be an effective organocatalyst for the asymmetric Friedel–Crafts alkylation of indoles with 3-substituted 3-hydroxyisoindolin-1-ones, affording the corresponding quaternary carbon-containing 3,3-disubstituted isoindolin-1-ones in good yields (up to 99%) with good to excellent enantioselectivities (up to 95% *ee*). The optical purity of the product was further improved after a single recrystallization. This protocol provides a convenient method for the catalytic asymmetric synthesis of valuable 3,3-disubstituted isoindolin-1-ones in high yields and enantioselectivities.

Introduction

Although 2,3-dihydro-1*H*-isoindol-1-ones (isoindolin-1-ones) are the key skeleton in a number of synthetic and naturally occurring bioactive molecules, the methodology for the asymmetric synthesis of simple substituted isoindolinones with a high *ee* was rarely explored, and only a few diastereoselective processes were developed during the past two decades.[1–6] The main drawback of these protocols is that stoichiometric amounts of a chiral controller derived from the natural chiral pool are required. Recently, we have developed the first catalytic asymmetric process for the preparation of enantiomerically enriched 3-substituted isoindolinones.[7] In the presence of chiral phosphoric acid[8,9] catalyst **2b**, a variety of 3-indolyl-substituted isoindolin-1-ones were obtained with moderate to good enantioselectivity by Friedel–Crafts (F–C) alkylation[10] of indoles[11] with 3-hydroxyisoindolin-1-one. However, this catalytic system failed to provide quaternary carbon-containing isoindolin-1-ones with a satisfactory *ee* value. For example, the asymmetric F–C alkylation of indole with 3-ethyl 3-hydroxyisoindolin-1-one, instead of 3-hydroxyisoindolin-1-one, led to the corresponding 3-ethyl 3-(1*H*-indol-3-yl)isoindolin-1-one with an enantioselectivity of only 24% *ee* (Scheme 1).



Scheme 1. Phosphoric acid **2b**-catalyzed asymmetric F–C alkylation of indole with 3-ethyl 3-hydroxyisoindolin-1-one.

Since the construction of chiral quaternary carbons represents one of the most challenging and demanding topics in the synthesis of natural products and chiral drugs,[12] the development of such a new catalytically enantioselective synthesis of quaternary carbon-containing isoindolin-1-ones appeared to be of great importance.[13] We report herein our further efforts on the development of an enantioselective synthesis of 3,3-disubstituted isoindolin-1-ones starting from the corresponding 3-substituted 3-hydroxyisoindolin-1-ones, which can easily be prepared from the reaction of phthalimide with various Grignard reagents.[14]

Results and Discussion

Based on the previous result, the influence of the steric and electronic properties of the 3 and 3′ substituents as well as the backbone on the catalytic performance of the chiral phosphoric acids was systematically investigated. Thus, a series of 3,3′-substituted (*S*)-BINOL-based phosphoric acids **1a**–**e**, 3,3′-substituted (*R*)-H_8-BINOL-based (5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol) phosphoric acids **2a**–**d**, and the corresponding *N*-triflylphosphoramides **3**, **4a**, and **4b** were employed as the catalyst candidates in the model reaction for the F–C alkylation of indole (**5a**) with 3-ethyl 3-hydroxyisoindolin-1-one (**6b**). All the

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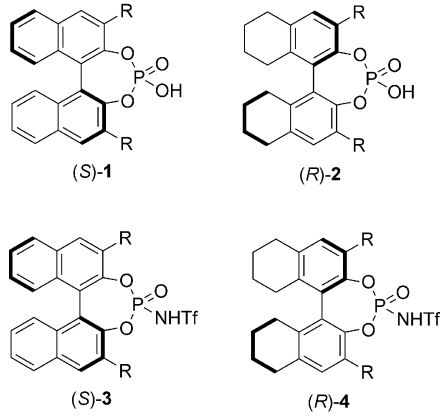
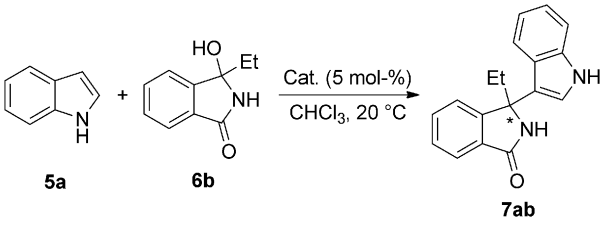
catalytic tests were conducted at room temperature in chloroform using 5 mol-% of catalyst, and the results are listed in Table 1.



The results in Table 1 clearly demonstrated that all the phosphoric acids and *N*-triflylphosphoramides catalyzed the reaction at 20 °C, affording 3-ethyl-3-(1*H*-indol-3-yl)isoindolin-1-one (**7ab**) with variable degrees of enantiomeric excess. Enantioselectivities ranging from 16% to 23%*ee* were obtained when 3,3′-aryl-substituted BINOL-based phosphoric acids (*S*)-**1a**–**c** were used (Table 1, Entries 1–3). Intriguingly, using phosphoric acids **1d** [R = $P(O)Ph_2$] and **1e** (R = $SiPh_3$) significantly improved the enantioselectivity of **7ab** to 51 and 66%*ee*, respectively, with a reverse in the absolute stereochemistry (Table 1, Entries 4 and 5). No superior results were obtained by changing the backbone from the BINOL-based to H_8-BINOL-based skeleton (Table 1, Entries 6–9). Surprisingly, *N*-triflylphosphoramide **3** led to a nearly racemic product in spite of its good performance in the nucleophilic substitution of γ-hydroxylactams with indole (Table 1, Entry 10).[15] Similarly, H_8-BINOL-based *N*-triflylphosphoramides **4** also exhibited poor stereoselectivities (Table 1, Entries 11 and 12).

Table 1. Catalyst evaluation.[a]

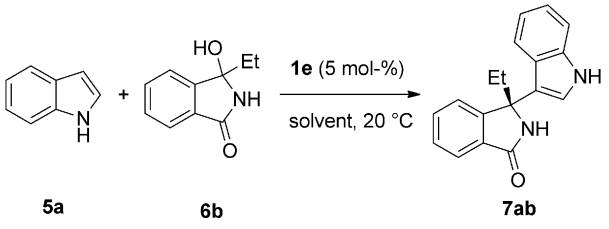


Entry	Catalyst	Time [h]	Yield [%][b]	*ee* [%][c]
1	**1a** (R = 4-ClC_6H_4)	1	94	23
2	**1b** (R = 4-PhC_6H_4)	1	82	16
3	**1c** (R = 2-naphthyl)	0.5	96	17
4	**1d** [R = $P(O)Ph_2$]	10	92	–51
5	**1e** (R = $SiPh_3$)	8	95	–66
6	**2a** (R = 4-ClC_6H_4)	1	99	–35
7	**2b** (R = 2-naphthyl)	0.5	>99	–24
8	**2c** (R = 9-phenanthryl)	0.5	92	31
9	**2d** (R = $SiPh_3$)	24	89	53
10	**3** (R = $SiPh_3$)	0.5	97	–2
11	**4a** (R = 2-naphthyl)	0.5	98	20
12	**4b** (R = 9-phenanthryl)	0.5	99	9

[a] Reagents and conditions: **5a** (0.3 mmol) and **6b** (0.2 mmol) in the presence of catalyst (5 mol-%) in chloroform (1 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis.

Further optimization of reaction conditions by changing the solvent, reaction temperature, or substrate concentration, or providing an additive to the reaction mixture, was performed with catalyst **1e**. As shown in Table 2, both the catalytic efficiency and enantioselectivity are strongly dependent on the choice of solvent (Table 2, Entries 1–7). The same level of stereocontrol was almost obtained for other chlorohydrocarbons (Table 2, Entries 2 and 3 versus Entry 1). The use of toluene as an apolar solvent resulted in marked decrease in both the reaction rate and selectivity (Table 2, Entry 4). The reaction was sluggish to some extent especially using ethereal solvents (Table 2, Entries 6 and 7). Although an improved enantioselectivity of 74%*ee* was observed with THF (tetrahydrofuran), the corresponding alkylation product was obtained in only 35% yield, even with a prolonged reaction time of 5 d. Performing the reaction in ethyl acetate favored the stereocontrol of the reaction, affording product **7ab** with 70%*ee*. The highest *ee* value of 76% was achieved when the reaction was run in acetonitrile, but using other nitrile solvents such as propiononitrile and benzonitrile led to a significant erosion of enantioselectivity

Table 2. Optimization of reaction conditions.[a]



Entry	Solvent	Time [h]	Yield [%][b]	*ee* [%][c]
1	$CHCl_3$	8	95	66
2	CH_2Cl_2	12	99	63
3	$ClCH_2CH_2Cl$	36	95	63
4	$PhCH_3$	66	91	50
5	EA	66	82	70
6	Et_2O	80	87	64
7	THF	5 d	35	74
8	CH_3CN	12	89	76
9	CH_3CH_2CN	20	98	62
10	PhCN	45	85	60
11[d]	CH_3CN	26	91	70
12[e]	CH_3CN	52	89	10
13[f]	CH_3CN	60	91	66
14[g]	CH_3CN	3	94	68
15[h]	CH_3CN	45	99	60
16[i]	CH_3CN	11	91	78
17[j]	CH_3CN	20	98	75

[a] Reagents and conditions: **5a** (0.3 mmol) and **6b** (0.2 mmol) in the presence of catalyst **1e** (5 mol-%) in 1 mL of solvent (0.2 M solution of **6b**). [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] 4 Å molecular sieves (MS) were added as an additive. [e] 0.1 mL of water was added. [f] The reaction was performed at 10 °C. [g] The reaction was carried out at 40 °C. [h] Using 2 mol-% **1e**. [i] Using 0.1 M solution of **6b**. [j] Using 0.05 M solution of **6b**.

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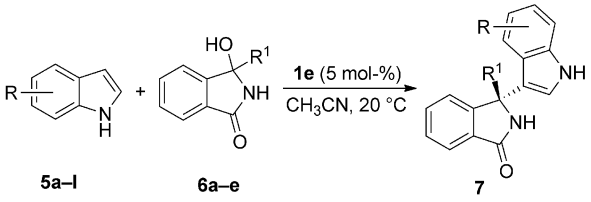
(Table 2, Entries 9 and 10 versus Entry 8). The addition of 4 Å molecular sieves as an additive to remove the trace amount of water generated from the reaction resulted in decreasing both the reaction rate and stereoselectivity (Table 2, Entry 11), which was consistent with our previous report.[7] The addition of water as an additive also had a negative effect on the outcome of the reaction (Table 2, Entry 12). The effect of temperature was also remarkable. Conducting the reaction at either a lower or higher temperature led in both cases to an obvious loss of stereocontrol (Table 2, Entries 13 and 14). Moreover, it is noteworthy that the concentration of the reaction mixture also played an important role in the reaction. Dilution of the reaction mixture (from a 0.2 to a 0.1 M solution of **6a**) led to a slight increase in enantioselectivity, furnishing the product **7ab** in 91% yield and 78%*ee* (Table 2, Entry 16). Decreasing the concentration of **6b** further from a 0.1 to a 0.05 M solution did not lead to further improvement in the enantioselectivity, but rather to the slight loss of catalytic efficiency (Table 2, Entry 17 versus Entry 16).

The scope of the substrate in the reaction was initially explored by subjecting various 3-hydroxyisoindolin-1-ones bearing different substituents at the three-position to the optimized reaction conditions with indole (**5a**). Both aliphatic and aromatic substituents for R^1 were tolerated with the 3-hydroxyisoindolin-1-ones (Table 3, Entries 1–5). Although moderate enantioselectivities were observed with methyl- and phenyl-substituted 3-hydroxyisoindolin-1-ones, the use of ethyl-, allyl-, and butyl-substituted ones led to a significant improvement in stereocontrol, generating the corresponding alkylation product with enantioselectivities of 78%, 79% and 77%*ee*, respectively.

To further demonstrate the scope of this organocatalytic F–C alkylation, a plethora of indoles **5** were evaluated for the reaction with 3-ethyl 3-hydroxyisoindolin-1-one (**6b**) under the optimal reaction conditions. As shown in Table 3, a wide range of indoles bearing either an electron-withdrawing or electron-donating substituent at various positions on the indole ring were included as the reaction partners, leading to the formation of the desired products in good to excellent yields (Table 3, Entries 6–16). Generally, electron-rich indoles exhibited a higher enantioselectivity than those of electron-poor ones. In fact, the stereocontrol was particularly favored by the introduction of an electron-donating group on the seven-position of the indole ring. The highest value of 95%*ee* was obtained with 7-methyl-substituted indole **5l** (Table 3, Entry 17). The same phenomenon was also observed when 3-allyl 3-hydroxyisoindolin-1-one (**6c**), instead of **6b**, was employed (Table 3, Entries 18–23). Similarly, 7-methyl-substituted indole **5l** was proven to be the best substrate, affording the alkylation product **7lc** with an *ee* value of 94%. Moreover, the reaction between 3-butyl 3-hydroxyisoindolin-1one (**6d**) and electron-rich indoles, such as **5h** and **5l**, also ran smoothly to afford the desired products with 85% and 95%*ee*, respectively. In addition, the reaction was repeated on a larger scale. For instance, both a comparable *ee* value and yield were observed for compound **7ac** when the reaction was performed on a 2 mmol-scale. As all the F–C alkylation products were solids with a high melting point, there was an opportunity to further improve the optical purity of the

Table 3. Substrate scope of indoles in the **1e**-catalyzed F–C reaction.[a]



5a–l 6a–e 7

Entry	Product **7** (R,R^1)	Time [h]	Yield [%][b]	*ee* [%][c]
1	**7aa** (H, Me)	12	99	56
2	**7ab** (H, Et)	11	91 (70)[d]	78 (99.8)[d]
3	**7ac** (H, allyl)	48	92	79
4[e]	**7ac** (H, allyl)	72	85	76
5	**7ad** (H, Bu)	12	93	77
6	**7ae** (H, Ph)	29	90	58
7	**7bb** (5-F, Et)	48	76	68
8	**7cb** (6-F, Et)	30	75	79
9	**7db** (5-Cl, Et)	30	79	68
10	**7eb** (6-Cl, Et)	20	66	79
11	**7fb** (5-Br, Et)	24	80	66
12	**7gb** (5-MeO, Et)	21	95	81
13	**7hb** (7-MeO, Et)	30	72	90
14	**7ib** (5-BnO, Et)	20	90	80
15	**7jb** (6-BnO, Et)	34	94	86
16	**7kb** (7-BnO, Et)	37	80	87
17	**7lb** (7-Me, Et)	25	83	95
18	**7cc** (6-F, allyl)	88	59	79
19	**7ec** (6-Cl, allyl)	74	66	66
20	**7hc** (7-MeO, allyl)	66	63	86
21	**7jc** (6-BnO, allyl)	42	80	76
22	**7kc** (7-BnO, allyl)	66	62	83
23	**7lc** (7-Me, allyl)	60	74	94
24	**7hd** (7-MeO, Bu)	24	82	85
25	**7ld** (7-Me, Bu)	24	91	95

[a] Reagents and conditions: **5** (0.3 mmol) and **6** (0.2 mmol) in the presence of catalyst **1e** (5 mol-%) in acetonitrile (2 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Data in the parentheses were obtained through a single recrystallization from methanol. [e] The reaction was carried out using a 2 mmol-scale.

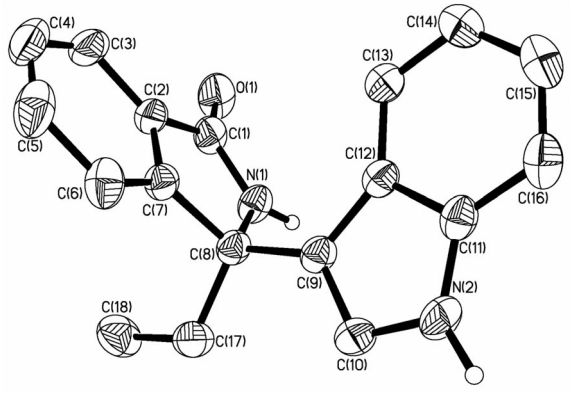


Figure 1. X-ray crystal structure determination of the F–C alkylation product **7ab**. The solvent and most of the hydrogen atoms have been omitted for clarity.

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products through recrystallization. For example, the optical purity of **7ab** was dramatically improved by a single recrystallization from methanol, affording an almost optically pure alkylation product in an acceptable yield (Table 3, Entry 2, 99.8%*ee*). An X-ray crystal structure determination of enantiopure **7ab** was obtained, which enabled the absolute configuration of the product to be assigned as *R* (Figure 1).[16] The stereochemistry of the other products was assigned by analogy.

Similar to Rueping's[15] and our previous report,[7] the reaction is believed to occur by an in situ generated cyclic acyl iminium ion upon treatment of 3-substituted 3-hydroxyisoindolin-1-ones with the chiral phosphoric acid.

Conclusions

In conclusion, we have successfully developed the first organocatalytic enantioselective synthesis of quaternary carbon-containing isoindolin-1-ones through a chiral phosphoric acid-catalyzed asymmetric F–C alkylation of indoles with 3-substituted 3-hydroxyisoindolin-1-ones. The corresponding products were obtained in excellent chemical yields with good to excellent enantioselectivities. Moreover, almost enantiomerically pure isoindolin-1-ones was attained through a simple recrystallization. The protocol described herein provides an efficient access to biologically valuable quaternary carbon-containing isoindolin-1-ones in high yields and enantioselectivities.

Experimental Section

General Methods: All reagents and solvents were commercial grade and purified prior to use when necessary. NMR spectra were recorded with a Varian 400 MHz instrument. Chemical shifts are measured relative to the residual solvent peaks with an internal standard set to δ = 2.50 and δ = 39.43 ([D$_6$]DMSO). Specific rotations were measured with a Perkin–Elmer 341MC polarimeter. Enantiomeric excesses were determined using a HP-1100 instrument (chiral column; mobile phase, hexane/*i*PrOH). HRMS was performed with a Varian QFT-ESI instrument. Melting points were measured with a Taike X-4 melting point apparatus.

General Procedure for 1e-Catalyzed Asymmetric F–C Alkylation of Indoles with 3-Substituted 3-Hydroxyisoindolin-1-one: In a dry Schlenk tube, indoles **5** (0.30 mmol), 3-substituted 3-hydroxyisoindolin-1-ones **6** (0.20 mmol) and phosphoric acid (*S*)-**1e** (8.7 mg, 0.01 mmol) were dissolved in CH_3CN (2.0 mL) at room temperature under a nitrogen atmosphere. The solution was stirred after the total consumption of **7** (monitored by TLC). After removal of the solvent under reduced pressure, the residue was purified by flash chromatography (ethyl acetate/dichloromethane, 1:8) to afford the desired product.

(*R*)-3-(1*H*-Indol-3-yl)-3-methylisoindolin-1-one (7aa): White solid, 51.9 mg, 99% yield, m.p. 209–210 °C, $[\alpha]_D^{20}$ = +7.8 (*c* = 1.0, MeOH), 56%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.92 (s, 3 H, CH_3), 6.74–6.84 (m, 2 H, Ar-H), 6.99 (t, *J* = 7.2 Hz, 1 H, Ar-H), 7.31–7.35 (m, 2 H, Ar-H), 7.47 (t, *J* = 7.2 Hz, 2 H, Ar-H), 7.54 (s, 1 H, Ar-H), 7.74 (d, *J* = 6.8 Hz, 1 H, Ar-H), 8.98 (s, 1 H, NH), 11.10 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 26.9, 59.8, 111.6, 116.0, 118.5, 119.0, 120.9, 122.2, 122.7, 123.3, 124.6, 127.8, 131.2, 130.8, 136.8, 153.0, 168.3 ppm. HRMS (ESI): calcd. for $C_{17}H_{14}N_2O$ [M – H]$^-$ 261.1033; found 261.1035. HPLC analysis (Chiralpak AD-H column; hexane/2-propanol, 70:30; flow rate: 1.0 mL/min; wavelength: 220 nm): *R*t (retention time) = 5.46 (minor) and 10.53 min (major).

(*R*)-3-Ethyl-3-(1*H*-indol-3-yl)isoindolin-1-one (7ab): White solid, 50.3 mg, 91% yield, m.p. 195–197 °C, $[\alpha]_D^{20}$ = +39.8 (*c* = 1.0, MeOH), 78%*ee* (99.8%*ee* after a single recrystallization from methanol). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.65 (t, *J* = 7.2 Hz, 3 H, CH_3), 2.33–2.47 (m, 2 H, CH_2), 6.80 (t, *J* = 7.2 Hz, 1 H, Ar-H), 6.99–7.01 (m, 2 H, Ar-H), 7.33 (t, *J* = 7.2 Hz, 2 H, Ar-H), 7.41–7.49 (m, 3 H, Ar-H), 7.72 (d, *J* = 6.8 Hz, 1 H, Ar-H), 8.90 (s, 1 H, NH), 11.09 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 7.7, 30.4, 63.5, 111.6, 115.9, 118.5, 119.2, 120.9, 122.3, 122.5, 123.0, 124.8, 127.8, 131.7, 132.1, 136.7, 151.2, 169.1 ppm. HRMS (ESI): calcd. for $C_{18}H_{16}N_2O$ [M – H]$^-$ 275.1190; found 275.1192. HPLC analysis (Chiralpak AD-H column; hexane/2-propanol, 75:25; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 6.00 (minor) and 12.13 min (major).

(*R*)-3-Allyl-3-(1*H*-indol-3-yl)isoindolin-1-one (7ac): White solid, 53.1 mg, 92% yield, m.p. 173–175 °C, $[\alpha]_D^{20}$ = +52.6 (*c* = 1.0, MeOH), 79%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.13–3.24 (m, 2 H, CH_2), 4.94 (d, *J* = 10.0 Hz, 1 H, vinyl), 5.05 (d, *J* = 17.2 Hz, 1 H, vinyl), 5.37–5.47 (m, 1 H, vinyl), 6.79 (t, *J* = 7.6 Hz, 1 H, Ar-H), 6.94 (d, *J* = 7.6 Hz, 1 H, Ar-H), 7.00 (t, *J* = 7.6 Hz, 1 H, Ar-H), 7.35 (d, *J* = 8.4 Hz, 2 H, Ar-H), 7.43 (t, *J* = 7.2 Hz, 1 H, Ar-H), 7.49 (t, *J* = 7.2 Hz, 1 H, Ar-H), 7.55 (s, 1 H, Ar-H), 7.70 (d, *J* = 7.2 Hz, 1 H, Ar-H), 8.96 (s, 1 H, NH), 11.12 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 42.0, 62.7, 111.6, 115.5, 118.5, 119.0, 119.2, 121.0, 122.5, 122.6, 123.3, 124.7, 127.8, 131.6, 132.0, 132.5, 136.7, 150.9, 168.8 ppm. HRMS (ESI): calcd. for $C_{19}H_{16}N_2O$ [M – H]$^-$ 287.1190; found 287.1190. HPLC analysis (Chiralpak AD-H column; hexane/2-propanol, 70:30; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 5.55 (minor) and 112.57 min (major).

(*R*)-3-Butyl-3-(1*H*-indol-3-yl)isoindolin-1-one (7ad): White solid, 56.6 mg, 93% yield, m.p. 202–204 °C, $[\alpha]_D^{20}$ = +48.0 (*c* = 1.0, MeOH), 77%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.80 (t, *J* = 6.8 Hz, 3 H, CH_3), 1.20–1.25 (m, 4 H, 2 CH_2), 2.30–2.46 (m, 2 H, CH_2), 6.80 (t, *J* = 7.6 Hz, 1 H, Ar-H), 7.00 (t, *J* = 7.6 Hz, 2 H, Ar-H), 7.34 (d, *J* = 7.6 Hz, 2 H, Ar-H), 7.41–7.49 (m, 3 H, Ar-H), 7.70 (d, *J* = 7.2 Hz, 1 H, Ar-H), 8.92 (s, 1 H, NH), 11.09 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 13.9, 22.2, 25.2, 37.4, 63.1, 111.6, 116.0, 118.5, 119.2, 120.9, 122.3, 122.5, 123.0, 124.7, 127.7, 131.7, 131.9, 136.7, 151.6, 169.0 ppm. HRMS (ESI): calcd. for $C_{20}H_{20}N_2O$ [M + Na]$^+$ 327.1468; found 327.1468. HPLC analysis (Chiralpak AD-H column; hexane/2-propanol, 70:30; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 5.72 (minor) and 12.00 min (major).

(*R*)-3-(1*H*-Indol-3-yl)-3-phenylisoindolin-1-one (7ae): White solid, 58.4 mg, 90% yield, m.p. 237–239 °C, $[\alpha]_D^{20}$ = –35.0 (*c* = 1.0, MeOH), 58%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.77–6.83 (m, 2 H, Ar-H), 6.88 (d, *J* = 2.4 Hz, 1 H, Ar-H), 7.02–7.06 (m, 1 H, Ar-H), 7.27–7.35 (m, 3 H, Ar-H), 7.38 (d, *J* = 8.0 Hz, 1 H, Ar-H), 7.47–7.53 (m, 3 H, Ar-H), 7.55–7.63 (m, 2 H, Ar-H), 7.75 (d, *J* = 7.2 Hz, 1 H, Ar-H), 9.65 (s, 1 H, NH), 11.08 (d, *J* = 2.0 Hz, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 66.2, 111.7, 116.7, 118.6, 119.9, 121.3, 123.1, 124.1, 124.2, 125.1, 126.4, 127.4, 128.3, 131.0, 131.9, 137.0, 142.7, 150.8, 168.5 ppm. HRMS (ESI): calcd. for $C_{22}H_{16}N_2O$ [M – H]$^-$ 323.1190; found 323.1195. HPLC analysis (Chiralpak AD-H column; hexane/2-propanol, 70:30; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 14.08 (major) and 21.00 min (minor).

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(*R*)-3-Ethyl-3-(5-fluoro-1*H*-indol-3-yl)isoindolin-1-one (7bb): White solid, 44.7 mg, 76% yield, m.p. 217–219 °C, $[\alpha]_D^{20}$ = +21.6 (*c* = 1.0, MeOH), 68%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.64 (t, *J* = 7.2 Hz, 3 H, CH$_3$), 2.30–2.39 (m, 1 H, one proton of CH$_2$), 2.41–2.48 (m, 1 H, one proton of CH$_2$), 6.63 (dd, *J* = 2.0 and 10.8 Hz, 1 H, Ar-H), 6.86 (dt, *J* = 2.0 and 9.2 Hz, 1 H, Ar-H), 7.33 (d, *J* = 6.0 Hz, 2 H, Ar-H), 7.45 (t, *J* = 7.2 Hz, 1 H, Ar-H), 7.51 (t, *J* = 7.2 Hz, 1 H, Ar-H), 7.58 (d, *J* = 2.0 Hz, 1 H, Ar-H), 7.72 (d, *J* = 7.2 Hz, 1 H, Ar-H), 8.90 (s, 1 H, NH), 11.21 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 7.6, 30.3, 63.3, 103.7 (d, *J* = 23.7 Hz), 109.1 (d, *J* = 26.1 Hz), 112.5 (d, *J* = 9.9 Hz), 116.1 (d, *J* = 4.6 Hz), 122.3, 122.5, 124.7 (d, *J* = 10.1 Hz), 125.1, 127.8, 131.8, 132.0, 133.3, 150.9, 156.3 (d, *J* = 231.0 Hz), 169.0 ppm. HRMS (ESI): calcd. for C$_{18}$H$_{15}$FN$_2$O [M – H]$^-$ 317.1061; found 317.1064. HPLC analysis (Chiralpak AD-H column; hexane/2-propanol, 70:30; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 5.17 (minor) and 8.64 min (major).

(*R*)-3-Ethyl-3-(6-fluoro-1*H*-indol-3-yl)isoindolin-1-one (7cb): White solid, 44.1 mg, 75% yield, m.p. 220–221 °C, $[\alpha]_D^{20}$ = +29.8 (*c* = 1.0, MeOH), 79%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.62 (t, *J* = 7.2 Hz, 3 H, CH$_3$), 2.27–2.38 (m, 1 H, one proton of CH$_2$), 2.40–2.47 (m, 1 H, one proton of CH$_2$), 6.68 (dt, *J* = 2.0 and 9.2 Hz, 1 H, Ar-H), 6.92 (dd, *J* = 5.6 and 8.8 Hz, 1 H, Ar-H), 7.10 (dd, *J* = 2.0 and 10.0 Hz, 1 H, Ar-H), 7.31 (d, *J* = 7.6 Hz, 1 H, Ar-H), 7.44 (t, *J* = 7.6 Hz, 1 H, Ar-H), 7.45–7.52 (m, 2 H, Ar-H), 7.70 (d, *J* = 7.2 Hz, 1 H, Ar-H), 8.88 (s, 1 H, NH), 11.15 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 7.6, 30.3, 63.2, 97.4 (d, *J* = 25.3 Hz), 107.0 (d, *J* = 24.1 Hz), 116.1, 120.0 (d, *J* = 10.0 Hz), 122.3, 122.5, 123.7 (d, *J* = 2.9 Hz), 127.8, 131.7, 132.0, 136.6 (d, *J* = 12.6 Hz), 151.0, 158.5 (d, *J* = 234.8 Hz), 168.9 ppm. HRMS (ESI): calcd. for C$_{18}$H$_{15}$FN$_2$O [M + Na]$^+$ 317.1061; found 317.1068. HPLC analysis (Chiralpak AD-H column; hexane/2-propanol, 70:30; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 5.49 (minor) and 7.39 min (major).

(*R*)-3-(5-Chloro-1*H*-indol-3-yl)-3-ethylisoindolin-1-one (7db): White solid, 49.1 mg, 79% yield, m.p. 157–159 °C, $[\alpha]_D^{20}$ = +15.0 (*c* = 1.0, MeOH), 68%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.63 (t, *J* = 6.8 Hz, 3 H, CH$_3$), 2.31–2.37 (m, 1 H, one proton of CH$_2$), 2.42–2.47 (m, 1 H, one proton of CH$_2$), 6.95 (s, 1 H, Ar-H), 7.01 (d, *J* = 8.4 Hz, 1 H, Ar-H), 7.32 (d, *J* = 7.2 Hz, 1 H, Ar-H), 7.36 (d, *J* = 8.8 Hz, 1 H, Ar-H), 7.45 (t, *J* = 7.2 Hz, 1 H, Ar-H), 7.51 (t, *J* = 7.2 Hz, 1 H, Ar-H), 7.60 (s, 1 H, Ar-H), 7.73 (d, *J* = 7.2 Hz, 1 H, Ar-H), 8.94 (s, 1 H, NH), 11.32 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 7.6, 30.5, 63.2, 113.1, 115.8, 118.3, 120.9, 122.3, 122.6, 123.1, 124.9, 125.8, 127.9, 131.8, 131.9, 135.1, 150.8, 169.0 ppm. HRMS (ESI): calcd. for C$_{18}$H$_{15}$ClN$_2$O [M + Na]$^+$ 333.0765; found 333.0768. HPLC analysis (Chiralpak AD-H column; hexane/2-propanol, 70:30; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 4.87 (minor) and 8.89 min (major).

(*R*)-3-(6-Chloro-1*H*-indol-3-yl)-3-ethylisoindolin-1-one (7eb): White solid, 41.0 mg, 66% yield, m.p. 219–220 °C, $[\alpha]_D^{20}$ = +18.4 (*c* = 1.0, MeOH), 79%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.63 (t, *J* = 6.8 Hz, 3 H, CH$_3$), 2.30–2.36 (m, 1 H, one proton of CH$_2$), 2.41–2.48 (m, 1 H, one proton of CH$_2$), 6.84 (d, *J* = 8.8 Hz, 1 H, Ar-H), 6.96 (d, *J* = 8.4 Hz, 1 H, Ar-H), 7.32 (d, *J* = 7.2 Hz, 1 H, Ar-H), 7.38 (s, 1 H, Ar-H), 7.44 (t, *J* = 7.2 Hz, 1 H, Ar-H), 7.50 (t, *J* = 7.2 Hz, 1 H, Ar-H), 7.54 (s, 1 H, Ar-H), 7.70 (d, *J* = 7.2 Hz, 1 H, Ar-H), 8.91 (s, 1 H, NH), 11.23 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 7.6, 30.4, 63.2, 111.1, 116.2, 118.8, 120.4, 122.2, 122.5, 123.5, 124.2, 125.8, 127.8, 131.8, 131.9, 137.1, 150.9, 169.0 ppm. HRMS (ESI): calcd. for C$_{18}$H$_{15}$ClN$_2$O [M + Na]$^+$ 333.0765; found 333.0768. HPLC analysis (Chiralpak AD-H column; hexane/2-propanol, 70:30; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 5.42 (minor) and 7.74 min (major).

(*R*)-3-(5-Bromo-1*H*-indol-3-yl)-3-ethylisoindolin-1-one (7fb): White solid, 56.8 mg, 80% yield, m.p. 155–156 °C, $[\alpha]_D^{20}$ = –14.0 (*c* = 1.0, MeOH), 66%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.63 (t, *J* = 7.2 Hz, 3 H, CH$_3$), 2.29–2.38 (m, 1 H, one proton of CH$_2$), 2.40–2.47 (m, 1 H, one proton of CH$_2$), 7.09 (s, 1 H, Ar-H), 7.12 (d, *J* = 8.4 Hz, 1 H, Ar-H), 7.31 (d, *J* = 8.8 Hz, 2 H, Ar-H), 7.46 (t, *J* = 7.2 Hz, 1 H, Ar-H), 7.52 (t, *J* = 7.2 Hz, 1 H, Ar-H), 7.58 (d, *J* = 2.4 Hz, 1 H, Ar-H), 7.72 (d, *J* = 7.2 Hz, 1 H, Ar-H), 8.94 (s, 1 H, NH), 11.33 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]-DMSO): δ = 7.6, 30.5, 63.2, 111.2, 113.6, 115.7, 121.3, 122.3, 122.5, 123.4, 124.8, 126.5, 127.9, 131.8, 131.9, 135.3, 150.8, 169.0 ppm. HRMS (ESI): calcd. for C$_{18}$H$_{15}$BrN$_2$O [M + Na]$^+$ 377.0260; found 377.0261. HPLC analysis (Chiralpak AD-H column; hexane/2-propanol, 70:30; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 4.85 (minor) and 9.08 min (major).

(*R*)-3-Ethyl-3-(5-methoxy-1*H*-indol-3-yl)isoindolin-1-one (7gb): White solid, 58.2 mg, 95% yield, m.p. 269–271 °C, $[\alpha]_D^{20}$ = –32.0 (*c* = 0.2, MeOH), 81%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.64 (t, *J* = 6.8 Hz, 3 H, CH$_3$), 2.33–2.37 (m, 1 H, one proton of CH$_2$), 2.44–2.47 (m, 1 H, one proton of CH$_2$), 3.53 (s, 3 H, CH$_3$), 6.40 (s, 1 H, Ar-H), 6.67 (d, *J* = 8.4 Hz, 1 H, Ar-H), 7.21 (d, *J* = 8.4 Hz, 1 H, Ar-H), 7.33 (d, *J* = 7.2 Hz, 1 H, Ar-H), 7.43–7.46 (m, 2 H, Ar-H), 7.51 (t, *J* = 7.2 Hz, 1 H, Ar-H), 7.72 (d, *J* = 7.2 Hz, 1 H, Ar-H), 8.90 (s, 1 H, NH), 10.95 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 7.7, 30.2, 55.0, 63.4, 101.6, 110.5, 112.1, 115.4, 122.5, 123.7, 125.1, 127.8, 131.8, 131.9, 132.3, 151.0, 152.6, 169.0 ppm. HRMS (ESI): calcd. for C$_{19}$H$_{18}$N$_2$O$_2$ [M + Na]$^+$ 329.1260; found 329.1268. HPLC analysis (Chiralpak AD-H column; hexane/2-propanol, 70:30, flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 7.05 (minor) and 29.76 min (major).

(*R*)-3-Ethyl-3-(7-methoxy-1*H*-indol-3-yl)isoindolin-1-one (7hb): White solid, 44.1 mg, 72% yield, m.p. 234–236 °C, $[\alpha]_D^{20}$ = +64.0 (*c* = 1.0, MeOH), 90%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.63 (t, *J* = 7.2 Hz, 3 H, CH$_3$), 2.29–2.38 (m, 1 H, one proton of CH$_2$), 2.41–2.48 (m, 1 H, one proton of CH$_2$), 3.86 (s, 3 H, CH$_3$), 6.58 (t, *J* = 8.0 Hz, 2 H, Ar-H), 6.72 (t, *J* = 8.0 Hz, 1 H, Ar-H), 7.32 (t, *J* = 8.0 Hz, 1 H, Ar-H), 7.35 (s, 1 H, Ar-H), 7.42 (t, *J* = 7.2 Hz, 1 H, Ar-H), 7.48 (t, *J* = 7.2 Hz, 1 H, Ar-H), 7.68 (d, *J* = 7.2 Hz, 1 H, Ar-H), 7.72 (d, *J* = 7.2 Hz, 1 H, Ar-H), 8.84 (s, 1 H, NH), 11.16 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 7.7, 30.4, 55.0, 63.4, 101.4, 112.5, 116.5, 119.1, 122.2, 122.4, 126.3, 126.8, 127.6, 131.6, 132.0, 151.2, 169.0 ppm. HRMS (ESI): calcd. for C$_{19}$H$_{18}$N$_2$O$_2$ [M + Na]$^+$ 329.1260; found 329.1261. HPLC analysis (Chiralpak AD-H column; hexane/2-propanol, 70:30; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 7.92 (minor) and 41.49 min (major).

(*R*)-3-(5-Benzyloxy-1*H*-indol-3-yl)-3-ethylisoindolin-1-one (7ib): White solid, 68.8 mg, 90% yield, m.p. 215–216 °C, $[\alpha]_D^{20}$ = –10.0 (*c* = 0.5, MeOH), 80%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.64 (t, *J* = 6.8 Hz, 3 H, CH$_3$), 2.29–2.34 (m, 1 H, one proton of CH$_2$), 2.42–2.47 (m, 1 H, one proton of CH$_2$), 4.87 (d, *J* = 18.8 Hz, 1 H, one proton of CH$_2$), 4.91 (d, *J* = 18.4 Hz, 1 H, one proton of CH$_2$), 6.61 (s, 1 H, Ar-H), 6.74 (d, *J* = 7.6 Hz, 1 H, Ar-H), 7.22 (d, *J* = 8.4 Hz, 1 H, Ar-H), 7.31–7.36 (m, 7 H, Ar-H), 7.43–7.51 (m, 2 H, Ar-H), 7.71 (d, *J* = 6.8 Hz, 1 H, Ar-H), 8.85 (s, 1 H, NH), 10.89 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 7.7, 30.4, 63.5, 69.5, 103.2, 111.4, 112.1, 115.5, 122.3, 122.5, 123.6, 125.0, 127.5, 127.6, 127.7, 128.3, 131.6, 132.0, 132.1, 137.4, 151.0, 151.5, 169.0 ppm. HRMS (ESI): calcd. for C$_{25}$H$_{22}$N$_2$O$_2$ [M + Na]$^+$ 405.1573; found 405.1568. HPLC analysis (Chiralpak AD-H

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column; hexane/2-propanol, 70:30; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 8.96 (minor) and 25.01 min (major).

(*R*)-3-(6-Benzyloxy-1*H*-indol-3-yl)-3-ethylisoindolin-1-one (7jb): White solid, 71.9 mg, 94% yield, m.p. 191–192 °C, $[\alpha]_D^{20}$ = +25.2 (*c* = 0.5, MeOH), 86%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.62 (t, *J* = 7.2 Hz, 3 H, CH_3), 2.27–2.39 (m, 1 H, one proton of CH_2), 2.40–2.46 (m, 1 H, one proton of CH_2), 5.05 (s, 2 H, CH_2), 6.56 (dd, *J* = 1.6 and 8.8 Hz, 1 H, Ar-H), 6.85–6.88 (m, 2 H, Ar-H), 7.28–7.51 (m, 9 H, Ar-H), 7.69 (d, *J* = 7.2 Hz, 1 H, Ar-H), 8.86 (s, 1 H, NH), 10.87 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]-DMSO): δ = 7.7, 30.4, 63.4, 69.3, 95.9, 109.3, 115.9, 119.3, 119.8, 121.7, 122.2, 122.5, 127.3, 127.5, 127.7, 128.3, 131.6, 132.0, 137.3, 137.4, 151.2, 154.2, 169.0 ppm. HRMS (ESI): calcd. for $C_{25}H_{22}N_2O_2$ [M + Na]$^+$ 405.1573; found 405.1573. HPLC analysis (Chiralpak AD-H column; hexane/2-propanol, 70:30; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 11.36 (minor) and 23.15 min (major).

(*R*)-3-(7-Benzyloxy-1*H*-indol-3-yl)-3-ethylisoindolin-1-one (7kb): White solid, 61.2 mg, 80% yield, m.p. 112–113 °C, $[\alpha]_D^{20}$ = +44.6 (*c* = 1.0, MeOH), 87%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.63 (t, *J* = 7.2 Hz, 3 H, CH_3), 2.29–2.38 (m, 1 H, one proton of CH_2), 2.41–2.47 (m, 1 H, one proton of CH_2), 5.22 (s, 2 H, CH_2), 6.60 (d, *J* = 7.6 Hz, 1 H, Ar-H), 6.64–6.71 (m, 2 H, Ar-H), 7.30–7.54 (m, 9 H, Ar-H), 7.68 (d, *J* = 7.2 Hz, 1 H, Ar-H), 8.87 (s, 1 H, NH), 11.20 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 7.7, 30.5, 63.5, 69.0, 102.8, 112.3, 116.5, 119.0, 122.3, 122.5, 122.7, 126.5, 127.1, 127.5, 127.8, 128.3, 131.7, 132.1, 137.3, 145.0, 151.3, 169.0 ppm. HRMS (ESI): calcd. for $C_{25}H_{22}N_2O_2$ [M + Na]$^+$ 405.1573; found 405.1564. HPLC analysis (Chiralpak OD-H column; hexane/2-propanol, 70:30; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 15.46 (minor) and 42.03 min (major).

(*R*)-3-Ethyl-3-(7-methyl-1*H*-indol-3-yl)isoindolin-1-one (7lb): White solid, 48.2 mg, 83% yield, m.p. 212–214 °C, $[\alpha]_D^{20}$ = +50.8 (*c* = 1.0, MeOH), 95%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.65 (t, *J* = 6.8 Hz, 3 H, CH_3), 2.33–2.48 (m, 2 H, CH_2), 2.42 (s, 3 H, CH_3), 6.71 (t, *J* = 7.6 Hz, 1 H, Ar-H), 6.80–6.85 (m, 2 H, Ar-H), 7.32 (d, *J* = 7.2 Hz, 1 H, Ar-H), 7.41–7.48 (m, 3 H, Ar-H), 7.70 (d, *J* = 7.2 Hz, 1 H, Ar-H), 8.91 (s, 1 H, NH), 11.07 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 7.7, 16.8, 30.5, 63.5, 116.3, 116.9, 118.7, 120.7, 121.4, 122.3, 122.5, 122.7, 124.5, 127.8, 131.7, 132.6, 136.2, 151.3, 169.1 ppm. HRMS (ESI): calcd. for $C_{19}H_{18}N_2O$ [M + Na]$^+$ 313.1311; found 313.1315. HPLC analysis (Chiralpak AD-H column; hexane/2-propanol, 70:30; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 5.38 (minor) and 13.23 min (major).

(*R*)-3-Allyl-3-(6-fluoro-1*H*-indol-3-yl)isoindolin-1-one (7cc): White solid, 36.1 mg, 59% yield, m.p. 199–200 °C, $[\alpha]_D^{20}$ = +50.2 (*c* = 1.0, MeOH, 79%*ee*). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.10–3.20 (m, 2 H, CH_2), 4.93 (d, *J* = 10.0 Hz, 1 H, vinyl), 5.03 (d, *J* = 17.2 Hz, 1 H, vinyl), 5.33–5.43 (m, 1 H, vinyl), 6.68 (t, *J* = 9.2 Hz, 1 H, Ar-H), 6.84 (dd, *J* = 6.0 and 8.4 Hz, 1 H, Ar-H), 7.10 (d, *J* = 9.6 Hz, 1 H, Ar-H), 7.34 (d, *J* = 7.2 Hz, 1 H, Ar-H), 7.43 (t, *J* = 7.2 Hz, 1 H, Ar-H), 7.48 (t, *J* = 7.2 Hz, 1 H, Ar-H), 7.54 (s, 1 H, Ar-H), 7.68 (d, *J* = 7.2 Hz, 1 H, Ar-H), 8.97 (s, 1 H, NH), 11.19 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 41.9, 62.5, 97.4 (d, *J* = 26.9 Hz), 107.1 (d, *J* = 25.7 Hz), 115.7, 119.0, 120.0 (d, *J* = 10.2 Hz), 121.5, 122.5, 124.0, 127.9, 131.7, 131.9, 132.3, 136.6 (d, *J* = 13.4 Hz), 150.7, 158.5 (d, *J* = 249.3 Hz), 168.7 ppm. HRMS (ESI): calcd. for $C_{19}H_{15}FN_2O$ [M + Na]$^+$ 329.1061; found 329.1059. HPLC analysis (Chiralpak AD-H column; hexane/2-propanol, 70:30; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 5.46 (minor) and 7.25 min (major).

(*R*)-3-Allyl-3-(6-chloro-1*H*-indol-3-yl)isoindolin-1-one (7ec): White solid, 42.6 mg, 66% yield, m.p. 220–222 °C, $[\alpha]_D^{20}$ = +36.2 (*c* = 1.0, MeOH), 66%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.10–3.20 (m, 2 H, CH_2), 4.93 (d, *J* = 10.0 Hz, 1 H, vinyl), 5.04 (d, *J* = 17.2 Hz, 1 H, vinyl), 5.33–5.43 (m, 1 H, vinyl), 6.83 (d, *J* = 8.4 Hz, 1 H, Ar-H), 6.88 (d, *J* = 8.4 Hz, 1 H, Ar-H), 7.35 (t, *J* = 7.2 Hz, 2 H, Ar-H), 7.44 (d, *J* = 7.2 Hz, 1 H, Ar-H), 7.50 (t, *J* = 7.2 Hz, 1 H, Ar-H), 7.59 (s, 1 H, Ar-H), 7.68 (d, *J* = 7.2 Hz, 1 H, Ar-H), 8.97 (s, 1 H, NH), 11.25 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 42.0, 62.5, 111.2, 115.9, 118.9, 119.2, 120.4, 122.6, 123.5, 124.5, 125.9, 127.9, 131.8, 131.9, 132.3, 137.1, 150.6, 168.8 ppm. HRMS (ESI): calcd. for $C_{19}H_{15}ClN_2O$ [M + Na]$^+$ 345.0765; found 345.0759. HPLC analysis (Chiralpak AD-H column; hexane/2-propanol, 70:30; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 5.44 (minor) and 7.80 min (major).

(*R*)-3-Allyl-3-(7-methoxy-1*H*-indol-3-yl)isoindolin-1-one (7hc): White solid, 40.1 mg, 63% yield, m.p. 216–218 °C, $[\alpha]_D^{20}$ = +66.0 (*c* = 0.5, MeOH), 86%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.10–3.20 (m, 2 H, CH_2), 3.86 (s, 3 H, CH_3), 4.92 (d, *J* = 10.0 Hz, 1 H, vinyl), 5.03 (d, *J* = 16.8 Hz, 1 H, vinyl), 5.34–5.44 (m, 1 H, vinyl), 6.51 (d, *J* = 8.0 Hz, 1 H, Ar-H), 6.57 (d, *J* = 7.6 Hz, 1 H, Ar-H), 6.70 (t, *J* = 7.6 Hz, 1 H, Ar-H), 7.35 (d, *J* = 7.2 Hz, 1 H, Ar-H), 7.40 (s, 1 H, Ar-H), 7.42 (t, *J* = 7.2 Hz, 1 H, Ar-H), 7.48 (t, *J* = 7.2 Hz, 1 H, Ar-H), 7.66 (d, *J* = 7.6 Hz, 1 H, Ar-H), 8.91 (s, 1 H, NH), 11.19 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 42.0, 55.0, 62.6, 101.4, 112.0, 116.1, 118.9, 119.1, 122.4, 122.5, 122.8, 126.2, 126.8, 127.7, 131.6, 132.0, 132.5, 146.1, 150.9, 168.8 ppm. HRMS (ESI): calcd. for $C_{20}H_{18}N_2O_2$ [M + Na]$^+$ 341.1261; found 341.1257. HPLC analysis (Chiralpak AD-H column; hexane/2-propanol, 65:35; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 6.63 (minor) and 44.91 min (major).

(*R*)-3-Allyl-3-(6-benzyloxy-1*H*-indol-3-yl)isoindolin-1-one (7jc): White solid, 63.1 mg, 80% yield, m.p. 188–190 °C, $[\alpha]_D^{20}$ = +38.0 (*c* = 1.0, MeOH), 76%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.08–3.18 (m, 2 H, CH_2), 4.92 (d, *J* = 10.0 Hz, 1 H, vinyl), 5.03 (d, *J* = 17.2 Hz, 1 H, vinyl), 5.05 (s, 2 H, OCH_2), 5.34–5.44 (m, 1 H, vinyl), 6.55 (dd, *J* = 2.0 and 8.8 Hz, 1 H, Ar-H), 6.80 (d, *J* = 8.8 Hz, 1 H, Ar-H), 6.88 (d, *J* = 1.6 Hz, 1 H, Ar-H), 7.29–7.50 (m, 9 H, Ar-H), 7.67 (d, *J* = 7.2 Hz, 1 H, Ar-H), 8.92 (s, 1 H, NH), 10.89 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 41.9, 62.7, 69.3, 96.0, 109.4, 115.6, 118.9, 119.3, 119.7, 122.0, 122.5, 127.3, 127.5, 127.7, 128.3, 131.6, 132.0, 132.5, 137.3, 137.4, 150.9, 154.2, 168.8 ppm. HRMS (ESI): calcd. for $C_{26}H_{22}N_2O_2$ [M + Na]$^+$ 417.1573; found 417.1575. HPLC analysis (Chiralpak AD-H column; hexane/2-propanol, 70:30; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 11.94 (minor) and 22.21 min (major).

(*R*)-3-Allyl-3-(7-benzyloxy-1*H*-indol-3-yl)isoindolin-1-one (7kc): White solid, 48.9 mg, 62% yield, m.p. 90–92 °C, $[\alpha]_D^{20}$ = +54 (*c* = 1.0, MeOH), 83%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.11–3.21 (m, 2 H, CH_2), 4.93 (d, *J* = 10.4 Hz, 1 H, vinyl), 5.04 (d, *J* = 16.4 Hz, 1 H, vinyl), 5.22 (s, 2 H, OCH_2), 5.35–5.45 (m, 1 H, vinyl), 6.53 (d, *J* = 7.2 Hz, 1 H, Ar-H), 6.64–6.70 (m, 2 H, Ar-H), 7.30–7.54 (m, 9 H, Ar-H), 7.67 (d, *J* = 7.2 Hz, 1 H, Ar-H), 8.91 (s, 1 H, NH), 11.21 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]-DMSO): δ = 42.0, 62.6, 69.0, 102.9, 112.2, 116.1, 118.8, 119.0, 122.4, 122.5, 122.8, 126.3, 127.0, 127.4, 127.6, 127.7, 128.2, 131.5, 132.0, 132.5, 137.2, 145.0, 150.9, 168.7 ppm. HRMS (ESI): calcd. for $C_{26}H_{22}N_2O_2$ [M + Na]$^+$ 417.1573; found 417.1571. HPLC analysis (Chiralpak OD-H column; hexane/2-propanol, 65:35; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 10.73 (minor) and 30.29 min (major).

(*R*)-3-Allyl-3-(7-methyl-1*H*-indol-3-yl)isoindolin-1-one (7lc): White solid, 44.8 mg, 74% yield, m.p. 215–216 °C, $[\alpha]_D^{20}$ = +90.2 (*c* = 1.0,

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MeOH), 94%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.41 (s, 3 H, 3 H, CH$_3$), 3.12–3.23 (m, 2 H, CH$_2$), 4.93 (d, J = 10.0 Hz, 1 H, vinyl), 5.04 (d, J = 17.2 Hz, 1 H, vinyl), 5.35–5.45 (m, 1 H, vinyl), 6.68 (t, J = 7.6 Hz, 1 H, Ar-H), 6.74 (d, J = 7.6 Hz, 1 H, Ar-H), 6.79 (d, J = 6.4 Hz, 1 H, Ar-H), 7.33 (d, J = 7.2 Hz, 1 H, Ar-H), 7.42 (t, J = 7.2 Hz, 1 H, Ar-H), 7.48 (t, J = 7.2 Hz, 1 H, Ar-H), 7.52 (s, 1 H, Ar-H), 7.67 (d, J = 7.2 Hz, 1 H, Ar-H), 8.94 (s, 1 H, NH), 11.07 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]-DMSO): δ = 16.7, 42.0, 62.8, 115.9, 116.9, 118.8, 119.0, 120.7, 121.5, 122.5, 122.6, 123.0, 124.4, 127.8, 131.6, 132.1, 132.6, 136.2, 151.0, 168.9 ppm. HRMS (ESI): calcd. for $C_{20}H_{18}N_2O$ [M + Na]$^+$ 325.1311; found 325.1311. HPLC analysis (Chiralpak AD-H column; hexane/2-propanol, 70:30; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 5.29 (minor) and 17.30 min (major).

(*R*)-3-Butyl-3-(7-methoxy-1*H*-indol-3-yl)isoindolin-1-one (7hd): White solid, 54.8 mg, 82% yield, m.p. 253–255 °C, $[\alpha]_D^{20}$ = +51.0 (c = 0.2, MeOH), 85%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.79 (t, J = 7.2 Hz, 3 H, CH$_3$), 1.14–1.28 (m, 4 H, 2 CH$_2$), 2.25–2.32 (m, 1 H, one proton of CH$_2$), 2.39–2.46 (m, 1 H, one proton of CH$_2$), 3.86 (s, 3 H, CH$_3$), 6.57 (d, J = 8.0 Hz, 1 H, Ar-H), 6.59 (d, J = 8.0 Hz, 1 H, Ar-H), 6.72 (t, J = 8.0 Hz, 1 H, Ar-H), 7.32–7.34 (m, 2 H, Ar-H), 7.42 (t, J = 7.2 Hz, 1 H, Ar-H), 7.48 (t, J = 7.2 Hz, 1 H, Ar-H), 7.67 (d, J = 7.2 Hz, 1 H, Ar-H), 8.86 (s, 1 H, NH), 11.15 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 13.8, 22.1, 25.2, 37.4, 55.0, 63.1, 101.4, 112.1, 116.6, 119.0, 122.2, 122.3, 122.4, 126.2, 126.8, 127.6, 131.6, 131.8, 146.0, 151.6, 168.8 ppm. HRMS (ESI): calcd. for $C_{21}H_{22}N_2O_2$ [M – H]$^-$ 333.1609; found 333.1614. HPLC analysis (Chiralpak AD-H column; hexane/2-propanol, 65:35; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 6.01 (minor) and 30.43 min (major).

(*R*)-3-Butyl-3-(7-methyl-1*H*-indol-3-yl)isoindolin-1-one (7ld): White solid, 58.0 mg, 91% yield, m.p. 233–235 °C, $[\alpha]_D^{20}$ = +70.6 (c = 1.0, MeOH), 95%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.80 (t, J = 7.2 Hz, 3 H, CH$_3$), 1.16–1.30 (m, 4 H, 2 CH$_2$), 2.27–2.34 (m, 1 H, one proton of CH$_2$), 2.40 (s, 3 H, CH$_3$), 2.44–2.48 (m, 1 H, one proton of CH$_2$), 6.70 (t, J = 7.2 Hz, 1 H, Ar-H), 6.79 (d, J = 6.8 Hz, 1 H, Ar-H), 6.83 (d, J = 8.0 Hz, 1 H, Ar-H), 7.33 (d, J = 7.6 Hz, 1 H, Ar-H), 7.40–7.44 (m, 2 H, Ar-H), 7.48 (dt, J = 0.8 and 7.2 Hz, 1 H, Ar-H), 7.68 (t, J = 7.2 Hz, 1 H, Ar-H), 8.86 (s, 1 H, NH), 11.01 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 13.8, 16.6, 22.1, 25.2, 37.4, 63.1, 116.4, 116.9, 118.6, 120.6, 121.3, 122.2, 122.4, 122.5, 124.4, 127.6, 131.6, 131.9, 136.2, 151.6, 168.9 ppm. HRMS (ESI): calcd. for $C_{21}H_{22}N_2O$ [M + Na]$^+$ 341.1624; found 341.1625. HPLC analysis (Chiralpak AD-H column; hexane/2-propanol, 65:35; flow rate: 1.0 mL/min; wavelength: 220 nm): R_t = 4.44 (minor) and 9.95 min (major).

Supporting Information (see footnote on the first page of this article): Copies of NMR and HRMS spectra as well as the chiral HPLC chromatograms of the prepared quaternary carbon-containing optically active isoindolin-1-ones.

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[1] R. Grigg, M. J. R. Dorrity, J. F. Malone, T. Mongkolaus-savaratana, W. D. J. A. Norbert, V. Sridharan, *Tetrahedron Lett.* **1990**, *31*, 3075–3076.
[2] D. Enders, V. Braig, G. Raabe, *Can. J. Chem.* **2001**, *79*, 1528–1535.
[3] L. Shen, R. P. Hsung, *Org. Lett.* **2005**, *7*, 775–778.
[4] J. Clayden, C. J. Menet, *Tetrahedron Lett.* **2003**, *44*, 3059–3062.
[5] a) S. M. Allin, C. J. Northfield, M. I. Page, A. M. Z. Slawin, *Tetrahedron Lett.* **1997**, *38*, 3627–3630; b) S. M. Allin, C. J. Northfield, M. I. Page, A. M. Z. Slawin, *Tetrahedron Lett.* **1998**, *39*, 4905–4908; c) S. M. Allin, C. J. Northfield, M. I. Page, A. M. Z. Slawin, *Tetrahedron Lett.* **1999**, *40*, 141–142; d) S. M. Allin, C. J. Northfield, M. I. Page, A. M. Z. Slawin, *Tetrahedron Lett.* **1999**, *40*, 143–146; e) S. M. Allin, C. J. Northfield, M. I. Page, A. M. Z. Slawin, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1715–1721; f) E. Deniau, D. Enders, A. Couture, P. Grandclaudon, *Tetrahedron: Asymmetry* **2003**, *14*, 2253–2258; g) A. A. Bahajaj, J. M. Vernon, G. D. Wilson, *Tetrahedron* **2004**, *60*, 1247–1253; h) M.-D. Chen, X. Zhou, M.-Z. He, Y.-P. Ruan, P.-Q. Huang, *Tetrahedron* **2004**, *60*, 1651–1657; i) E. Diniau, A. Couture, P. Grandclaudon, *Tetrahedron: Asymmetry* **2008**, *19*, 2735–2740.
[6] a) J. Pérard-Viret, T. Prangé, A. Tomas, J. Royer, *Tetrahedron* **2002**, *58*, 5103–5108; b) D. L. Comins, S. Schilling, Y. Zhang, *Org. Lett.* **2005**, *7*, 95–98; c) M. Lamblin, A. Couture, E. Deniau, P. Grandclaudon, *Tetrahedron: Asymmetry* **2008**, *19*, 111–123.
[7] X. L. Yu, A. D. Lu, Y. M. Wang, G. P. Wu, H. B. Song, Z. H. Zhou, C. C. Tang, *Eur. J. Org. Chem.* **2011**, 892–897.
[8] For pioneering works, see: a) T. Akiyama, J. Itoh, K. Yokota, K. Fuchibe, *Angew. Chem. Int. Ed.* **2004**, *43*, 1566–1568; b) D. Uraguchi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 5356–5357.
[9] For reviews on phosphoric acid catalysts, see: a) M. Terada, *Synthesis* **2010**, 1929–1982; b) M. Terada, *Chem. Commun.* **2008**, 4097–4112; c) T. Akiyama, *Chem. Rev.* **2007**, *107*, 5744–5758; d) S. J. Connon, *Angew. Chem. Int. Ed.* **2006**, *45*, 3909–3912; e) T. Akiyama, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2006**, *348*, 999–1010.
[10] a) M. Bandini, A. Melloni, S. Tommasi, A. Umani-Ronchi, *Synlett* **2005**, 1199–1222; b) S.-L. You, Q. Cai, M. Zeng, *Chem. Soc. Rev.* **2009**, *38*, 2190–2201; c) M. Zeng, S.-L. You, *Synlett* **2010**, 1289–1301; d) V. Terrasson, R. M. de Figueiredo, J. M. Campagne, *Eur. J. Org. Chem.* **2010**, 2635–2655.
[11] For review on catalytic functionalization of indoles, see: M. Bandini, A. Eichholzer, *Angew. Chem. Int. Ed.* **2009**, *48*, 9608–9644.
[12] For reviews, see a) K. Fuji, *Chem. Rev.* **1993**, *93*, 2037–2066; b) E. J. Corey, A. Guzman-Perez, *Angew. Chem. Int. Ed.* **1998**, *37*, 388–401; c) J. Christoffers, A. Mann, *Angew. Chem. Int. Ed.* **2001**, *40*, 4591–4597; d) I. Denissova, L. Barriault, *Tetrahedron* **2003**, *59*, 10105–10146; e) J. Christoffers, A. Baro, *Adv. Synth. Catal.* **2005**, *347*, 1473–1482; f) P. G. Cozzi, R. Hilgraf, N. Zimmermann, *Eur. J. Org. Chem.* **2007**, 5969–5994; g) J. Christoffers, A. Baro (Ed.), *Quaternary Stereocenters*, Wiley-VCH, **2005**.
[13] For catalytic asymmetric synthesis of oxoindoles bearing a tetrasubstituted stereocenters at the C-3 position, see: F. Zhou, Y.-L. Liu, J. Zhou, *Adv. Synth. Catal.* **2010**, *352*, 1381–1407.
[14] Y.-P. Ruan, M.-D. Chen, M.-Z. He, X. Zhou, P.-Q. Huang, *Synth. Commun.* **2004**, *34*, 853–861.
[15] M. Rueping, B. J. Nachtsheim, *Synlett* **2010**, 119–122.
[16] CCDC-813725 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.

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