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Chiral Phosphoric Acid Catalyzed Asymmetric Friedel–Crafts Alkylation of Indole with 3-Hydroxyisoindolin-1-one: Enantioselective Synthesis of 3-Indolyl-Substituted Isoindolin-1-ones

Xiaolei Yu,[a] Aidang Lu,[a] Youming Wang,*[a] Guiping Wu,[a] Haibin Song,[a] Zhenghong Zhou,*[a] and Chuchi Tang[a]

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Chiral phosphoric acids have been proven to be effective organocatalysts for the asymmetric Friedel–Crafts alkylation of indoles with 3-hydroxyisoindolin-1-ones. The corresponding products were obtained in excellent chemical yields (up to 99 %) with moderate to excellent enantioselectivities (up to >99 % *ee* after a single recrystallization). This is the first example of the catalytic asymmetric synthesis of valuable 3-substituted isoindolin-1-ones in high yields and enantioselectivities.

Introduction

Currently, the chemistry of chiral nonracemic 3-substituted 2,3-dihydro-1*H*-isoindol-1-ones (isoindolin-1-ones) has attracted much attention from many research groups, as they are the key skeleton of a number of synthetic and naturally occurring bioactive molecules. For example, (*S*)-PD172938 (**1**)[1] is a dopamine D4 receptor antagonist, (*R*)-pazinaclone (**2**)[2] possesses anxiolytic activity and is of interest as a sedative, hypnotic, and muscle relaxant, and (+)-lennoxamine (**3**)[3] is a naturally occurring isoindolobenzazepine alkaloid (Figure 1).

Although there are several methods available to make racemic 3-substituted isoindolinones, in contrast to the great progress made in asymmetric synthesis during the past three decades, the methodology for the asymmetric synthesis of simple 3-substituted isoindolinones with high enantioselectivity has been rarely explored. These methods involve an intramolecular Heck reaction of chiral *N*-vinyl *o*-iodobenzamide,[4] a tandem nucleophilic 1,2-addition/ring-closure procedure from SAMP or RAMP [(S)- or (*R*)-1-amino-2-methoxymethylpyrrolidine] hydrazones,[5] radical cyclization of allenamide containing a chiral auxiliary,[6] anionic cyclization and re-aromatization of *N*-benzylbenzamide derivatives in the presence of a chiral base,[7] nucleophilic addition or hydride reduction of chiral acyliminium ion,[8] as well as chiral auxiliary mediated carbocation methods.[9] The main drawback of these protocols is that all of them need a chiral auxiliary derived from the natural chiral pool to control the diastereoselectivity of the reaction. In some cases, the cleavage of the chiral appendage is quite harsh and tedious. To the best of our knowledge, there is no catalytic asymmetric process for the preparation of enantiomerically enriched 3-substituted isoindolinones, and the development of such a new catalytic enantioselective synthesis of these compounds appears to be of great importance.

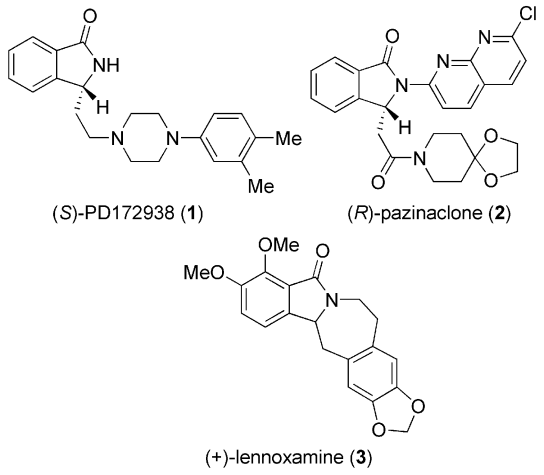

Figure 1. Different pyrrolidine-based organocatalysts.

The formation of new carbon–carbon bonds through the catalytic asymmetric Friedel–Crafts (F–C) alkylation reaction has recently made a great impact on stereoselective synthesis.[10] It has potential application in the synthesis of molecules with the indole framework or pharmacophore, which is found in a range of natural products and medicinal compounds of diverse therapeutic actions.[11] On the other

[a] State Key Laboratory of Elemento-Organic Chemistry, Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, P. R. China
Fax: +86-22-23508939
E-mail: z.h.zhou@nankai.edu.cn

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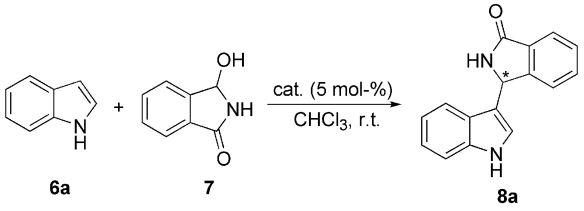
hand, in the past few years, chiral phosphoric acids as chiral Brønsted acids have attracted considerable attention in organocatalyzed asymmetric organic transformations.[12,13] These results opened the way for the use of these types of organocatalysts in asymmetric F–C alkylation reactions. As part of our ongoing studies on organocatalyzed asymmetric transformations,[14] we reported herein the first example of the asymmetric, organocatalytic synthesis of these valuable enantiopure 3-indolyl-substituted isoindolin-1-ones through a chiral phosphoric acid catalyzed enantioselective F–C alkylation of indoles with 3-hydroxyisoindolin-1-one.[15]

Results and Discussion

We first performed the F–C alkylation of indole (**6a**) with 3-hydroxyisoindolin-1-one (**7**) in the presence of binol phosphate **4a** as the catalyst. Gratifyingly, that the reaction ran smoothly to give the corresponding F–C alkylation product 3-(1*H*-indol-3-yl)isoindolin-1-one in excellent yield, albeit with quite low enantioselectivity. This result prompted us to improve the catalytic performance of the phosphoric acids by tuning the steric and electronic properties of the 3,3′-substituents and the backbone of the scaffold. Then, a series of 3,3′-substituted (*S*)-binol or (*R*)-H_8-binol-based (H_8-binol = 5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol) phosphoric acids **4b**–**g** and **5a**–**c** was employed to perform the F–C alkylation. All the catalytic tests were conducted at room temperature in chloroform by using 5 mol-% of the catalyst, and the results are listed in Table 1.

Table 1. Catalyst evaluation.[a]

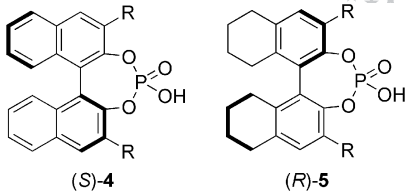


6a **7** **8a**

Entry	Catalyst **4** or **5**	Time [d]	Yield [%][b]	*ee* [%][c]
1	**4a** (R = H)	6.5	89	3
2	**4b** (R = Ph)	5	99	39
3	**4c** (R = 4-MeC_6H_4)	5.5	73	–33
4	**4d** (R = 2,4,6-*i*Pr$_3C_6H_2$)	7	34	7
5	**4e** (R = 2-naphthyl)	5	91	47
6	**4f** (R = 9-anthryl)	5.5	65	63
7	**4g** (R = Ph_3Si)	5.5	56	27
8	**5a** (R = Ph)	4	80	–47
9	**5b** (R = 2-naphthyl)	3.5	99	–83
10	**5c** (R = 9-phenanthryl)	10	58	–42

[a] Reaction conditions: **6a** (0.3 mmol) and **7** (0.2 mmol) in the presence of catalyst (5 mol-%) in chloroform (1 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis.

The results in Table 1 clearly show that variation of the substituents at the 3,3′-positions of the binaphthyl scaffold significantly affect the enantioselectivities of the reaction (Table 1, Entry 1 vs. Entries 2–7). For example, the introduction of a variety of substituted phenyl moieties resulted

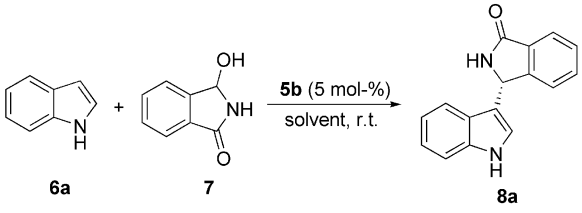


(*S*)-**4** (*R*)-**5**

in enantioselectivities ranging from 7 to 39% (Table 1, Entries 2–4). Fused aromatic substituents, such as 2-naphthyl and 9-anthryl, at the 3,3′-positions of the phosphoric acids (i.e., **4e** and **4f**) are favorable for the stereocontrol of the reaction, which provide the F–C alkylation product with 47 and 63%*ee*, respectively (Table 1, Entries 5 and 6). Interestingly, by tuning the 3,3′-disubstituents of the phosphoric acids, the stereochemistry of the F–C alkylation reaction can be reversed. For instance, chiral phosphoric acids **4b** and **4c**, both derived from (*S*)-binol, led to **8a** with opposite optical rotation (Table 1, Entry 2 vs. 3). Moreover, investigation of the backbone effect of the binaphthyl skeleton indicated that H_8-binol-derived phosphoric acids **5a** and **5b** generally demonstrated higher enantioselectivities (Table 1, Entries 8 and 9) than their corresponding binol-derived analogues (Table 1, Entries 2 and 5). 3-(1*H*-Indol-3-yl)isoindolin-1-one (**8a**) was obtained in up to 83%*ee* with catalyst **5b**, which bears 2-naphthyl groups at the 3,3′-positions of the catalyst.

Further optimization of the reaction conditions by changing the solvent, additive, or reaction temperature was performed with catalysts **5b**. The results are listed in Table 2.

Table 2. Optimization of reaction conditions.



6a **7** **8a**

Entry	Solvent	Time [d]	Yield [%][a]	*ee* [%][b]
1	$CHCl_3$	3.5	99	83
2	CH_2Cl_2	3.5	96	71
3	$ClCH_2CH_2Cl$	2.5	96	48
4	THF	5	72	45
5	$PhCH_3$	5.5	66	42
6	Et_2O	5	70	56
7	CH_3CN	4	98	52
8[c]	$CHCl_3$	6	64	19
9[d]	$CHCl_3$	6	66	46
10[e]	$CHCl_3$	6	56	49
11[f]	$CHCl_3$	6	27	49
12[g]	$CHCl_3$	0.71	94	43

[a] Isolated yield. [b] Determined by chiral HPLC analysis. [c] 3 Å MS were added as additive. [d] 4 Å MS were added as additive. [e] 5 Å MS were added as additive. [f] The reaction was carried out at 0 °C. [g] The reaction was at 40 °C.

As shown in Table 2, both the catalytic efficiency and asymmetric induction are strongly dependent on the solvents used (Table 2, Entries 1–7). Among the variety of solvents examined for the catalysis, originally chosen chloroform is the best choice in terms of the enantioselectivity. The effect of temperature on the reaction is also remarkable. Both the reaction rate and the enantiomeric excess of product **8a** were markedly decreased when the reaction temperature was reduced to 0 °C (Table 2, Entry 11). Although a dramatic rate acceleration was observed, performing the reaction at 40 °C led to an obvious loss of stereocontrol (Table 2, Entry 12). Because water is generated during the F–C reaction with the hydroxy group, the influence of the addition of molecular sieves as additive to remove the traces amounts of water generated from the reaction was further examined (Table 2, Entries 8–10). In general, the presence of molecular sieves is detrimental to the reaction, which resulted in sharp decreases in reaction rate and stereoselectivity.

Having established the optimal conditions, we next investigated the effect of indoles in the reaction with 3-hydroxyisoindolin-1-one **7** (Table 3). A wide range of indoles could be tolerated, leading to the formation of desired adducts in excellent yields. The highest *ee* value of 83%*ee* (Table 3, Entry 1) was obtained with unsubstituted indole (**6a**). The introduction of halogen, alkyl, or alkoxy substituents onto the indolyl rings all resulted in some loss of stereocontrol, in which the enantiomeric excess values ranged from 32 to 72% (Table 3, Entries 2–12). Because all of the F–C alkylation products were solids with high melting points, in some cases, the optical purity of the product could be dramatically improved by a single recrystallization from methanol (Table 3, Entries 1, 5, 6, and 11). An X-ray structure of enantiopure **8a** was obtained, which enabled the absolute configuration of the product to be assigned as *R* (Figure 2).[16] The stereochemistry of the other products was assigned by analogy.

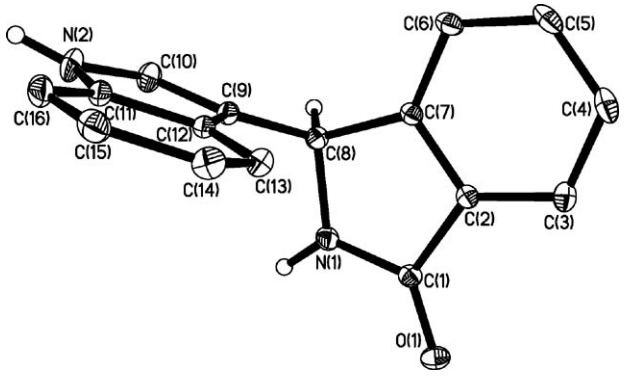
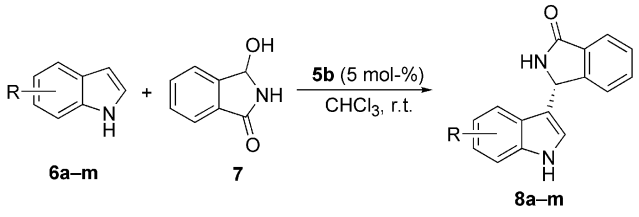


Figure 2. X-ray crystal structure of F–C alkylation product **8a**. Most of hydrogen atoms have been omitted for clarity.

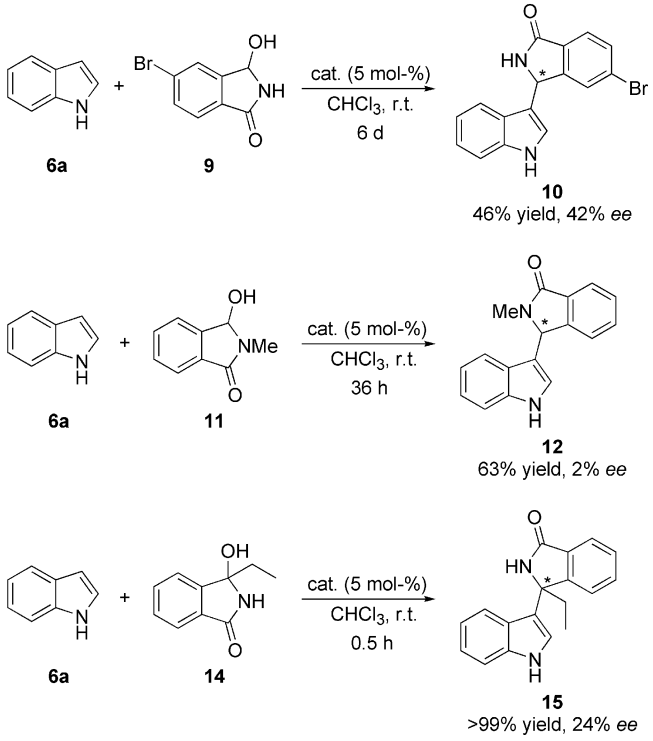
The substrate scope of the reaction was also preliminarily explored by subjecting different 3-hydroxyisoindolin-1-ones to the optimized reaction conditions with indole (**6a**) (Scheme 1). The reaction of 5-bromo-3-hydroxyisoindolin-1-one (**9**) was to some extent sluggish and afforded the desired alkylation product in 46% yield with 42%*ee*. When using 3-hydroxy-2-methylisoindolin-1-one (**11**) as the reactant, although the corresponding product could be obtained in quantitative yield, the enantioselectivity eroded

Table 3. Substrate scope of indoles in the **5b**-catalyzed F–C reaction.[a]



Entry	R	Time [d]	Yield [%][b]	*ee* [%][c]
1	H (**a**)	3.5	99 (80)[d]	83 (>99)[d]
2	5-F (**b**)	2.5	98	65
3	6-F (**c**)	2.0	98	72
4	5-Cl (**d**)	2.0	99	59
5	6-Cl (**e**)	2.5	97 (77)[d]	57 (93)[d]
6	5-Br (**f**)	2.0	96 (75)[d]	66 (92)[d]
7	4-OBn (**g**)	3.0	90	32
8	5-OBn (**h**)	3.0	93	57
9	6-OBn (**i**)	2.5	90	43
10	5-MeO (**j**)	4.0	95	50
11	2-Me (**k**)	2.0	94 (70)[d]	68 (97)[d]
12	7-Me (**l**)	2.5	97	51
13	1-Me (**m**)	3.0	98	42

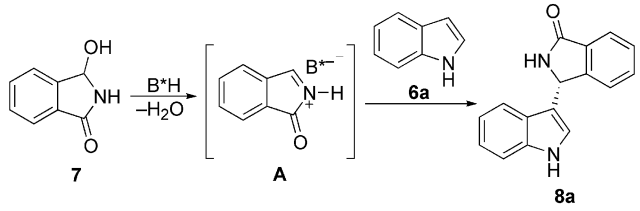
[a] Reaction conditions: **6** (0.3 mmol) and **7** (0.2 mmol) in the presence of catalyst **5b** (5 mol-%) in chloroform (1 mL). [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Data in parentheses were obtained through a single recrystallization from methanol.



Scheme 1. Reaction of other 3-hydrxoyisoindolin-1-ones.

dramatically. The reaction of 3-hydroxy-2-phenylisoindolin-1-one (**13**) failed to give the F–C alkylation product. 3-Substituted 3-hydroxyisoindolin-1-one, such as 3-ethyl-3-hydroxyisoindolin-1-one (**14**), exhibited much higher reactivity under identical conditions relative to 3-hydroxyisoindolin-1-one (**7**). The reaction was complete within 30 min to provide quantitatively the corresponding product **15** containing a quaternary carbon center with 24%*ee* (Scheme 1).

The proposed mechanism for the reaction course of this F–C alkylation is depicted in Scheme 2. The exposure of 3-hydroxyisoindolin-1-one (**7**) to the chiral phosphoric acid leads to the formation of close counterion **A**, in which the chiral phosphate anion creates a chiral environment to control the enantioselectivity of the F–C reaction.



Scheme 2. Proposed mechanism.

Conclusions

In conclusion, we have successfully developed the first organocatalytic enantioselective synthesis of 3-substituted isoindolin-1-ones through the chiral phosphoric catalyzed asymmetric F–C alkylation of indoles with 3-hydroxyisoindolin-1-ones. The corresponding products were obtained in excellent chemical yields with moderate to good enantioselectivities. Enantiomerically pure 3-indolylisoindolin-1-ones can be attained through simple recrystallization. The organocatalytic transformation described herein provides efficient access to valuable 3-substituted 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 acquired with a Varian 400 MHz instrument. Chemical shifts are measured relative to residual solvent peaks as an internal standard set to δ = 2.50 ppm and δ = 39.43 ppm ([D$_6$]DMSO). Specific rotations were measured with a Perkin–Elmer 341MC polarimeter. Enantiomeric excess values were determined with an HP-1100 instrument (chiral column; mobile phase: hexane/*i*PrOH). HRMS was performed with a Varian QFT-ESI instrument. Melting points were determined with a Taike X-4 melting point apparatus.

General Procedure for 5b-Catalyzed Asymmetric F–C Alkylation of Indoles with 3-Hydroxyisoindolin-1-one: In a dry Schlenk tube, indole (**6**; 0.30 mmol), 3-hydroxyisoindolin-1-one (**7**; 0.20 mmol), and phosphoric acid (*R*)-**5b** (6.0 mg, 0.01 mmol) were dissolved in $CHCl_3$ (1.0 mL) at room temperature under a nitrogen atmosphere. The solution was stirred until complete consumption of **7** (monitored by TLC). After removal of the solvent under reduced pressure, the residue was purified by flash chromatography (ethyl acetate/dichloromethane, 1:5) to afford the desired product.

(*S*)-3-(1*H*-Indol-3-yl)isoindolin-1-one (8a): Yield: 49 mg, 99%. White solid, m.p. 225–227 °C. $[\alpha]_D^{20}$ = +33.6 (*c* = 1.0, DMSO), 83%*ee* (>99%*ee* after a single recrystallization). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 5.96 (s, 1 H, CH), 6.81 (t, *J* = 7.2 Hz, 1 H, Ar-H), 6.88 (d, *J* = 7.2 Hz, 1 H, Ar-H), 7.03 (t, *J* = 7.2 Hz, 1 H, Ar-H), 7.28–7.36 (m, 2 H, Ar-H), 7.44–7.51 (m, 3 H, Ar-H), 7.74–7.76 (m, 1 H, Ar-H), 8.93 (s, 1 H, NH), 11.07 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 53.7, 111.7, 118.4, 118.6, 121.2, 122.6, 123.4, 124.3, 125.0, 127.8, 128.6, 131.5, 132.1, 136.7, 148.3, 169.2 ppm. HRMS (ESI): calcd. for $C_{16}H_{12}N_2O$ [M – H]$^-$ 247.0877; found 247.0879. HPLC (Chiralpak AD-H column, hexane/2-propanol = 75:25, flow rate = 1.0 mL/min, wavelength = 220 nm): t_R = 679 (minor), 11.84 min (major).

(*R*)-3-(5-Fluoro-1*H*-indol-3-yl)isoindolin-1-one (8b): Yield: 52 mg, 98%. White solid, m.p. 215–217 °C. $[\alpha]_D^{20}$ = +30.0 (*c* = 1.0, DMSO), 65%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 5.97 (s, 1 H, CH), 6.59 (d, *J* = 10.0 Hz, 1 H, Ar-H), 6.89 (dt, *J* = 9.2, 2.0 Hz, 1 H, Ar-H), 7.31 (d, *J* = 7.2 Hz, 1 H, Ar-H), 7.36 (dd, *J* = 8.8, 4.8 Hz, 1 H, Ar-H), 7.48–7.55 (m, 3 H, Ar-H), 7.77 (d, *J* = 6.8 Hz, 1 H, Ar-H), 8.96 (s, 1 H, NH), 11.21 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 53.4, 102.8, 103.1, 109.3, 109.6, 112.0, 112.7, 112.8, 122.7, 123.4, 125.1, 125.2, 126.2, 126.3, 128.0, 131.7, 132.0, 133.2, 133.3, 147.9, 155.2, 157.5, 169.2 ppm. HRMS (ESI): calcd. for $C_{16}H_{11}FN_2O$ [M + H]$^+$ 267.0928; found 267.0933. HPLC (Chiralpak AD-H column, hexane/2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 220 nm): t_R = 5.52 (minor), 8.61 min (major).

(*R*)-3-(6-Fluoro-1*H*-indol-3-yl)isoindolin-1-one (8c): Yield: 52 mg, 98%. White solid, m.p. 224–226 °C. $[\alpha]_D^{20}$ = +32.3 (*c* = 1.0, DMSO), 72%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 5.96 (s, 1 H, CH), 6.72 (dt, *J* = 9.6, 2.4 Hz, 1 H, Ar-H), 6.86 (dd, *J* = 8.4, 2.4 Hz, 1 H, Ar-H), 7.15 (dd, *J* = 10.0, 1.6 Hz, 1 H, Ar-H), 7.30 (d, *J* = 6.8 Hz, 1 H, Ar-H), 7.47 (s, 1 H, Ar-H), 7.49–7.54 (m, 2 H, Ar-H), 7. 76 (d, *J* = 6.4 Hz, 1 H, Ar-H), 8.99 (s, 1 H, NH), 11.16 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 53.5, 97.5, 97.8, 107.1, 107.3, 112.0, 119.3, 119.4, 121.8, 122.7, 123.4, 124.9, 125.0, 127.9, 131.6, 132.0, 136.6, 148.1, 157.6, 159.9, 169.2 ppm. HRMS (ESI): calcd. for $C_{16}H_{11}FN_2O$ [M – H]$^-$ 265.0783; found 265.0791. HPLC (Chiralpak AD-H column, hexane/2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 220 nm): t_R = 5.90 (minor), 7.82 min (major).

(*R*)-3-(5-Chloro-1*H*-indol-3-yl)isoindolin-1-one (8d): Yield: 56 mg, 99%. White solid, m.p. 214–216 °C. $[\alpha]_D^{20}$ = +21.6 (*c* = 1.0, DMSO), 59%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 5.98 (s, 1 H, CH), 6.91 (s, 1 H, Ar-H), 7.05 (dd, *J* = 8.8, 1.2 Hz, 1 H, Ar-H), 7.31 (d, *J* = 6.8 Hz, 1 H, Ar-H), 7.40 (d, *J* = 8.8 Hz, 1 H, Ar-H), 7.49–7.54 (m, 3 H, Ar-H), 7. 78 (d, *J* = 7.2 Hz, 1 H, Ar-H), 9.00 (s, 1 H, NH), 11.32 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 53.3, 111.7, 113.3, 117.5, 121.2, 122.7, 123.2, 123.4, 126.1, 126.2, 128.0, 131.7, 131.9, 135.2, 147.9, 169.2 ppm. HRMS (ESI): calcd. for $C_{16}H_{11}ClN_2O$ [M – H]$^-$ 281.0487; found 281.0490. HPLC (Chiralpak AD-H column, hexane/2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 220 nm): t_R = 5.42 (minor), 8.80 min (major).

(*R*)-3-(6-Chloro-1*H*-indol-3-yl)isoindolin-1-one (8e): Yield: 55 mg, 97%. White solid, m.p. 229–231 °C. $[\alpha]_D^{20}$ = +23.0 (*c* = 1.0, DMSO), 57%*ee* (93%*ee* after a single recrystallization). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 5.97 (s, 1 H, CH), 6.88 (s, 1 H, Ar-H), 7.29 (d, *J* = 6.8 Hz, 2 H, Ar-H), 7.42 (s, 1 H, Ar-H), 7.48–7.53 (m, 3 H, Ar-H), 7. 76 (d, *J* = 6.4 Hz, 1 H, Ar-H), 8.97 (s, 1 H, NH),

11.23 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 53.4, 111.3, 112.1, 119.0, 119.7, 122.7, 123.4, 123.8, 125.5, 126.0, 128.0, 131.6, 132.0, 137.1, 148.0, 169.2 ppm. HRMS (ESI): calcd. for $C_{16}H_{11}ClN_2O$ [M – H]$^-$ 281.0487; found 281.0491. HPLC (Chiralpak AD-H column, hexane/2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 220 nm): t_R = 6.40 (minor), 8.99 min (major).

(*R*)-3-(5-Bromo-1*H*-indol-3-yl)isoindolin-1-one (8f): Yield: 63 mg, 96%. White solid, m.p. 191–192 °C. $[\alpha]_D^{20}$ = +26.9 (*c* = 1.0, DMSO), 66%*ee* (92%*ee* after a single recrystallization). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 5.98 (s, 1 H, CH), 7.07 (s, 1 H, Ar-H), 7.16 (d, *J* = 8.8 Hz, 1 H, Ar-H), 7.31 (d, *J* = 6.8 Hz, 1 H, Ar-H), 7.35 (d, *J* = 7.2 Hz, 1 H, Ar-H), 7.49–7.56 (m, 3 H, Ar-H), 7. 78 (d, *J* = 6.4 Hz, 1 H, Ar-H), 8.99 (s, 1 H, NH), 11.32 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 53.3, 111.2, 111.6, 113.8, 120.6, 122.7, 123.4, 123.7, 125.9, 126.8, 128.0, 131.7, 131.9, 135.41, 147.9, 169.2 ppm. HRMS (ESI): calcd. for $C_{16}H_{11}BrN_2O$ [M – H]$^-$ 324.9982; found 324.9986. HPLC (Chiralpak AD-H column, hexane/2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 220 nm): t_R = 5.49 (minor), 9.21 min (major).

(*R*)-3-(4-Benzyloxy-1*H*-indol-3-yl)isoindolin-1-one (8g): Yield: 64 mg, 90%. White solid, m.p. 222–224 °C. $[\alpha]_D^{20}$ = +27.5 (*c* = 1.0, DMSO), 32%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 5.20 (d, *J* = 4.8 Hz, 2 H, CH$_2$), 6.22 (s, 1 H, CH), 6.59–6.60 (m, 1 H, Ar-H), 6.99–7.00 (m, 3 H, Ar-H), 7.24–7.31 (m, 3 H, Ar-H), 7.41–7.49 (m, 5 H, Ar-H), 7. 67 (d, *J* = 7.2 Hz, 1 H, Ar-H), 8.85 (s, 1 H, NH), 11.08 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 53.9, 69.0, 100.5, 105.2, 113.0, 115.9, 120.8, 120.9, 122.2, 122.5, 123.7, 127.3, 127.5, 128.2, 128.3, 131.3, 131.8, 137.3, 138.1, 138.2, 149.0, 152.3, 169.4 ppm. HRMS (ESI): calcd. for $C_{23}H_{18}N_2O_2$ [M – H]$^-$ 353.1296; found 353.1292. HPLC (Chiralpak AD-H column, hexane/2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 220 nm): t_R = 12.37 (minor), 25.74 min (major).

(*R*)-3-(5-Benzyloxy-1*H*-indol-3-yl)isoindolin-1-one (8h): Yield: 66 mg, 93%. White solid, m.p. 179–181 °C. $[\alpha]_D^{20}$ = +30.1 (*c* = 1.0, DMSO), 57%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 4.91 (d, *J* = 4.0 Hz, 2 H, CH$_2$), 5.94 (s, 1 H, CH), 6.57 (s, 1 H, Ar-H), 6.78 (dd, *J* = 8.8, 2.0 Hz, 1 H, Ar-H), 7.24–7.30 (m, 3 H, Ar-H), 7.34–7.35 (m, 5 H, Ar-H), 7.49–7.51 (m, 2 H, Ar-H), 7.75–7.77 (m, 1 H, Ar-H), 8.92 (s, 1 H, NH), 10.92 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 53.3, 69.5, 102.3, 111.4, 111.7, 112.2 122.6, 123.4, 124.5, 124.7, 125.4, 127.5, 127.6, 127.8, 128.3, 131.5, 131.8, 132.0, 137.4, 148.1, 151.7, 169.2 ppm. HRMS (ESI): calcd. for $C_{23}H_{18}N_2O_2$ [M + Na]$^+$ 377.1260; found 377.1257. HPLC (Chiralpak AD-H column, hexane/2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 220 nm): t_R = 10.75 (minor), 24.87 min (major).

(*R*)-3-(6-Benzyloxy-1*H*-indol-3-yl)isoindolin-1-one (8i): Yield: 64 mg, 90%. White solid, m.p. 212–214 °C. $[\alpha]_D^{20}$ = +29.4 (*c* = 1.0, DMSO), 43%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 5.06 (s, 2 H, CH$_2$), 5.90 (s, 1 H, CH), 6.58 (dd, *J* = 8.8, 1.6 Hz, 1 H, Ar-H), 6.74 (d, *J* = 8.8 Hz, 1 H, Ar-H), 6.91 (d, *J* = 1.6 Hz, 1 H, Ar-H), 7.28–7.30 (m, 3 H, Ar-H), 7.37 (t, *J* = 7.6 Hz, 2 H, Ar-H), 7.42 (d, *J* = 7.2 Hz, 2 H, Ar-H), 7.50 (t, *J* = 7.2 Hz, 2 H, Ar-H), 7.74 (d, *J* = 6.8 Hz, 1 H, Ar-H), 8.91 (s, 1 H, NH), 10.87 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 53.8, 69.4, 96.3, 109.6, 111.7, 119.1, 119.5, 122.7, 123.2, 123.4, 127.5, 127.6, 127.6, 127.9, 128.4, 131.7, 132.0, 137.5, 148.3, 154.5, 169.4 ppm. HRMS (ESI): calcd. for $C_{23}H_{18}N_2O_2$ [M – H]$^-$ 353.1296; found 353.1290. HPLC (Chiralpak AD-H column, hexane/2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 220 nm): t_R = 12.28 (minor), 20.93 min (major).

(*R*)-3-(5-Methoxy-1*H*-indol-3-yl)isoindolin-1-one (8j): Yield: 53 mg, 95%. White solid, m.p. 157–159 °C. $[\alpha]_D^{20}$ = +28.0 (*c* = 1.0, DMSO), 50%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.57 (s, 3 H, OCH$_3$), 5.97 (s, 1 H, CH), 6.44 (s, 1 H, Ar-H), 6.72 (dd, *J* = 8.8, 1.6 Hz, 1 H, Ar-H), 7.28 (d, *J* = 8.8 Hz, 1 H, Ar-H), 7.33–7.36 (m, 2 H, Ar-H), 7.51 (t, *J* = 6.8 Hz, 2 H, Ar-H), 7.78 (d, *J* = 6.8 Hz, 1 H, Ar-H), 8.96 (s, 1 H, NH), 10.94 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 53.6, 55.0, 100.7, 110.9, 111.4, 122.5, 123.5, 124.6, 124.7, 125.5, 127.8, 131.5, 131.7, 131.8, 132.1, 148.2, 152.8, 169.2 ppm. HRMS (ESI): calcd. for $C_{17}H_{14}N_2O_2$ [M – H]$^-$ 277.0982; found 277.0974. HPLC (Chiralpak AD-H column, hexane/2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 220 nm): t_R = 7.54 (minor), 20.99 min (major).

(*R*)-3-(2-Methyl-1*H*-indol-3-yl)isoindolin-1-one (8k): Yield: 49 mg, 94%. White solid, m.p. 274–276 °C. $[\alpha]_D^{20}$ = +22.6 (*c* = 1.0, DMSO), 68%*ee* (92%*ee* after a single recrystallization). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.46 (s, 3 H, CH$_3$), 6.00 (s, 1 H, CH), 6.59 (s, 1 H, Ar-H), 6.71 (t, *J* = 6.4 Hz, 1 H, Ar-H), 6.93 (t, *J* = 6.8 Hz, 1 H, Ar-H), 7.26 (d, *J* = 6.8 Hz, 2 H, Ar-H), 7.50 (s, 2 H, Ar-H), 7.78 (s, 1 H, Ar-H), 8.86 (s, 1 H, NH), 11.02 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 11.3, 52.8, 106.5, 110.6, 117.5, 118.4, 120.2, 122.5, 123.5, 126.1, 127.8, 131.5, 132.4, 134.0, 134.2, 135.1, 135.3, 148.4, 169.3 ppm. HRMS (ESI): calcd. for $C_{17}H_{14}N_2O$ [M + H]$^+$ 263.1179; found 263.1187. HPLC (Chiralpak AD-H column, hexane/2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 220 nm): t_R = 5.64 (minor), 10.20 min (major).

(*R*)-3-(7-Methyl-1*H*-indol-3-yl)isoindolin-1-one (8l): Yield: 51 mg, 97%. White solid, m.p. 203–205 °C. $[\alpha]_D^{20}$ = +21.4 (*c* = 1.0, DMSO), 51%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.43 (s, 3 H, CH$_3$), 5.96 (s, 1 H, CH), 6.72 (d, *J* = 4.4 Hz, 2 H, Ar-H), 6.83 (t, *J* = 4.0 Hz, 1 H, Ar-H), 7.28 (d, *J* = 6.4 Hz, 1 H, Ar-H), 7.44 (s, 1 H, Ar-H), 7.49–7.50 (m, 2 H, Ar-H), 7.74–7.77 (m, 1 H, Ar-H), 8.93 (s, 1 H, NH), 11.05 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]-DMSO): δ = 16.6, 53.8, 112.1, 116.1, 118.8, 120.8, 121.7, 122.6 123.4, 123.8, 124.0, 124.7, 127.8, 131.5, 132.1, 136.2, 148.3, 169.2 ppm. HRMS (ESI): calcd. for $C_{17}H_{14}N_2O$ [M – H]$^-$ 261.1033; found 261.1041. HPLC (Chiralpak AD-H column, hexane/2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 220 nm): t_R = 5.77 (minor), 10.02 min (major).

(*R*)-3-(1-Methyl-1*H*-indol-3-yl)isoindolin-1-one (8m): Yield: 51 mg, 98%. White solid, m.p. 208–210 °C. $[\alpha]_D^{20}$ = +27.1 (*c* = 1.0, DMSO), 42%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.75 (s, 3 H, NCH$_3$), 5.97 (s, 1 H, CH), 6.89 (t, *J* = 7.6 Hz, 1 H, Ar-H), 6.99 (d, *J* = 8.0 Hz, 1 H, Ar-H), 7.12 (t, *J* = 7.6 Hz, 1 H, Ar-H), 7.30–7.32 (m, 1 H, Ar-H), 7.39–7.41 (m, 2 H, Ar-H), 7.50 (t, *J* = 3.6 Hz, 2 H, Ar-H), 7.77–7.79 (m, 1 H, Ar-H), 8.98 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 32.3, 53.4, 109.9, 111.0, 118.6, 121.4, 122.7, 123.4, 125.4, 127.9, 128.4, 131.6, 132.0, 137.1, 148.2, 169.3 ppm. HRMS (ESI): calcd. for $C_{17}H_{14}N_2O$ [M + H]$^+$ 263.1179; found 263.1177. HPLC (Chiralpak AD-H column, hexane/2-propanol = 70:30, flow rate = 1.0 mL/min, wavelength = 220 nm): t_R = 6.73 (minor), 10.54 min (major).

5-Bromo-3-(1*H*-indol-3-yl)isoindolin-1-one (10): Yield: 30 mg, 46%. White solid, m.p. 195 °C. $[\alpha]_D^{20}$ = +24.5 (*c* = 1.0, DMSO), 42%*ee*. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.00 (s, 1 H, CH), 6.85 (t, *J* = 7.2 Hz, 1 H, Ar-H), 6.93 (d, *J* = 8.0 Hz, 1 H, Ar-H), 7.05 (t, *J* = 7.6 Hz, 1 H, Ar-H), 7.39 (d, *J* = 8.0 Hz, 1 H, Ar-H), 7.46–7.49 (m, 2 H, Ar-H), 7.67–7.72 (m, 2 H, Ar-H), 9.01 (s, 1 H, NH), 11.16 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 53.5,

110.9, 111.9, 118.3, 121.4, 124.6, 124.7, 124.8, 125.3, 126.4, 131.2, 131.3, 136.7, 150.6, 168.3 ppm. HRMS (ESI): calcd. for $C_{16}H_{11}BrN_2O$ [M – H]$^-$ 324.9982; found 324.9987. HPLC (Chiralpak AD-H column, hexane/2-propanol = 75:25, flow rate = 1.0 mL/min, wavelength = 220 nm): t_R = 7.70 (minor), 10.27 min (major).

3-(1*H*-Indol-3-yl)-2-methylisoindolin-1-one (12): Yield: 33 mg, 63%. White solid, m.p. 203–205 °C, 2%*ee*. ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 2.82 (s, 3 H, CH$_3$), 5.86 (s, 1 H, CH), 6.62 (t, J = 7.2 Hz, 1 H, Ar-H), 6.77 (t, J = 7.60 Hz, 1 H, Ar-H), 7.05 (t, J = 7.6 Hz, 1 H, Ar-H), 7.38 (d, J = 8.0 Hz, 1 H, Ar-H), 7.48–7.50 (m, 2 H, Ar-H), 7.60 (s, 1 H, Ar-H), 7.78–7.80 (m, 1 H, Ar-H), 11.24 (s, 1 H, NH) ppm. ^{13}C NMR (100.6 MHz, [D$_6$]DMSO): δ = 26.8, 59.3, 109.1, 111.9, 117.9, 118.9, 121.3, 122.4, 123.2, 124.8, 126.1, 128.0, 131.5, 131.8, 136.8, 146.2, 166.9 ppm. HRMS (ESI): calcd. for $C_{17}H_{14}N_2O$ [M – H]$^-$ 261.1033; found 261.1041. HPLC (Chiralpak OD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 220 nm): t_R = 29.79 (minor), 33.90 min (major).

3-Ethyl-3-(1*H*-indol-3-yl)isoindolin-1-one (15): Yield: 55 mg, >99%. White solid, m.p. 195–197 °C. $[\alpha]_D^{20}$ = –19.0 (c = 1.0, DMSO), 24%*ee*. ^{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 (Chiralpak AD-H column, hexane/2-propanol = 75:25, flow rate = 1.0 mL/min, wavelength = 210 nm): t_R = 6.73 (minor), 13.88 min (major).

Supporting Information (see footnote on the first page of this article): Copies of the NMR and HRMS spectra as well as chiral HPLC traces of the prepared 3-indolyl isoinlolin-1-ones.

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