JOC The Journal of Organic Chemistry

Note

Chiral Brønsted Acid-Catalyzed Enantioselective aza-Friedel-Crafts Reaction of Cyclic #-Diaryl N-Acyl Imines With Indoles

Danijel Glava#, Chao Zheng, Irena Dokli, Shu-Li You, and Matija Gredi#ak

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b01420 • Publication Date (Web): 25 Jul 2017

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society.
1155 Sixteenth Street N.W., Washington, DC 20036

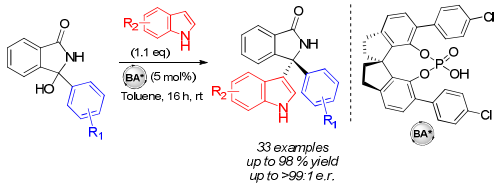
Chiral Brønsted Acid-Catalyzed Enantioselective aza-Friedel-Crafts Reaction of Cyclic *α*-Diaryl *N*-Acyl Imines With Indoles

Danijel Glavač,[a] Chao Zheng,[b] Irena Dokli,[a] Shu-Li You[b*] and Matija Gredičak[a*]

[a] *Division of Organic Chemistry and Biochemistry, Ruđer Bošković Institute, Bijenička c. 54, 10 000 Zagreb, Croatia. Email: matija.gredicak@irb.hr*

[b] *State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China. Email: slyou@sioc.ac.cn*

Abstract



Asymmetric addition of indoles to cyclic *α*-diaryl-substituted *N*-acyl imines, which are generated *in situ* from 3-aryl 3-hydroxyisoindolinones, is described. The transformation proceeds smoothly with a broad range of indoles and isoindolinone alcohols using a SPINOL-derived chiral Brønsted acid catalyst to afford *α*-tetrasubstituted (3-indolyl)(diaryl)methanamines in excellent yields and enantioselectivities (up to 98 % yield, up to >99:1 e.r.). The origin of stereochemical induction is supported by DFT calculations and experimental data.

The asymmetric addition of indoles to imines is the most straightforward synthetic approach for the preparation of 3-indolyl methanamines, structural motifs embedded in numerous indole alkaloids and synthetic indole derivatives.[1] The most common strategies for the construction of such optically active stereocentres employ organocatalytic asymmetric aza-Friedel-Crafts reactions.[2] In Lewis acid catalyzed protocols, Cu(I) complexes are usually employed for the generation of chiral 3-indolyl methanamines in high yields and enantioselectivities,[3] though their efficiency depends on the electronic properties of the indoles.[4] Due to the ability to activate a large spectrum of substrates, asymmetric Brønsted acid catalysis has become a method of choice for this transformation. In 2004, Terada reported first chiral phosphoric acid-catalyzed aza-Friedel-Crafts reaction of furan with imines.[5] Terada's seminal work gave raise to the development of numerous protocols for the preparation of chiral 3-indolyl methanamines using chiral Brønsted acid catalysts.[6]

However, these methodologies result in methanamines with chiral α-tertiary centres, and in recent years significant, progress has been made in the construction of chiral α-tetrasubstituted methanamines. Nishibayashi[6] and Watson[7] groups reported asymmetric copper-catalyzed alkynylation of ketimines to deliver α-diaryl quaternary stereogenic centres. Chiral phosphoric acid-catalyzed asymmetric aza-Friedel-Crafts reactions developed by Nakamura,[9] Rueping,[10] Wang[11] and Maruoka[12] furnished tetrasubstituted α-keto(diaryl) methanamines. Although elegant and versatile, these protocols result in products in the form of chiral α-(diaryl)alkyl-, rather than chiral α-(triaryl)-substituted methanamines. Only a handful of reports tackled the organocatalytic asymmetric catalytic aza-Friedel-Crafts addition for the generation of α-triaryl methanamines. In 2011, Wang and Zhou reported an enantioselective aza-Friedel-Crafts reaction of indoles with *N*-acyl imines, affording isoindolinones with quaternary stereogenic centres in high yields, but moderate enantioselectivities.[13] Among a range of obtained (diaryl)methanamines, the substrate scope

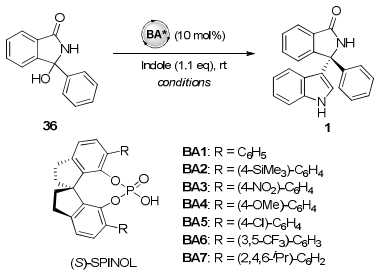
included only one example of chiral α-(3-indolyl)(diaryl)methanamine product. In 2012, Lete et al reported an asymmetric addition of indoles to isoindoloquinolines.[14] The authors obtained desired products in very good yields, but low enantiomeric ratios. To the best of our knowledge, there are currently no effective protocols for the organocatalytic asymmetric aza-Friedel-Crafts reaction for the preparation of chiral α-(3-indolyl)(diaryl) methanamines.

Herein, we report a chiral phosphoric acid-catalyzed enantioselective addition of indoles to cyclic α-diaryl-substituted *N*-acyl imines, generated *in situ* from 3-aryl 3-hydroxyisoindolinones. These heterocycles have recently been succesfully employed as substrates in various asymmetric metallo- and organocatalytic transformations. Nishimura and Hayashi developed rhodium-catalyzed asymmetric Friedel-Crafts additions to *N*(sulfonyl)-imines[15] and *N*(acyl)-imines,[16] resulting in α-(triaryl)-substituted methanamines. Nishimura expanded this protocol to iridium-catalyzed arylations of *N*(acyl)-ketimines,[17] while Hayashi successfully employed modified amino acid-derived phosphine-imine ligands for palladium-catalyzed asymmetric arylations of *N*(sulfonyl)-imines.[18] Along with aforementioned aza-Friedel-Crafts reaction described by Wang and Zhou,[13] various organocatalytic transformations of 3-hydroxyisoindolinones have also been developed. In 2012, Zhou et al reported asymmetric hydrogenolysis of racemic tertiary alcohols, 3-substituted 3-hydroxyisoindolinones with Hantzsch's esters.[19] The following year, Jia et al reported the same transformation by employing benzothiazolines as hydrogen source.[20] Recently, Singh et al developed enantioselective hydrophosphonylation of α-(diaryl)-substituted 3-hydroxyisoindolinones,[21] while the Singh group[22] and our group[23] independently reported asymmetric addition of thiols to form *N*(acyl),*S*-acetals derived from these heterocycles comprising newly-formed quaternary stereogenic centres.

Since our preliminary results showed that BINOL-derived chiral phosphoric acids are not appropriate catalysts for these transformations (see Supporting Information), we turned our

attention to SPINOL-derived catalysts.[6e,24] We started our investigations by combining 3-phenyl 3-hydroxyisoindolinone with indole in the presence of various chiral Brønsted acids (**BA***) (Table 1).

Table 1. Enantioselective reaction optimization[a]



Entry	Cat.	Solvent	Time (h)	Yield (%)	e.r.
1	**BA1**	Toluene	5	95	87:13
2	**BA2**	Toluene	5	97	92:8
3	**BA3**	Toluene	5	98	93:7
4	**BA4**	Toluene	5	95	86:14
5	**BA5**	Toluene	5	97	97:3
6	**BA6**	Toluene	5	98	78:22
7	**BA7**	Toluene	5	98	79:21
8	**BA5**	Fluorobenzene	5	95	91:9
9	**BA5**	*p*-Xylene	5	92	92:8
10	**BA5**	Chloroform	5	89	95:5
11	**BA5**	DCM	5	91	93:7
12	**BA5**	**Toluene**	**16**	**97**	**97:3**[b]
13	**BA5**	Toluene	168	53	96:4[c]
14	**BA5**	Toluene	16	92	96:4[d]

[a] Reactions performed on 0.2 mmol scale. e.r. determined by the chiral HPLC. [b] **BA5** (5 mol%). [c] –10 °C. [d] Additive: $MgSO_4$.

Our initial attempt with phenyl-substituted chiral phosphoric acid **BA1** in toluene led to the complete conversion to the desired product **1** within 5 hours at room temperature, and with the observed enantioselectivity of 87:13 e.r. (Entry 1). Introduction of the TMS group on the phenyl ring of the acid (**BA2**) lead to the increase of the enantiomeric purity in the product (Entry 2). When electron-withdrawing (**BA3**) and electron-donating (**BA4**) groups were placed on the catalyst, the reaction maintained its level of enantioselectivity (Entries 3 and 4). However, the introduction of *p*-chlorophenyl substitutent on the SPINOL backbone resulted

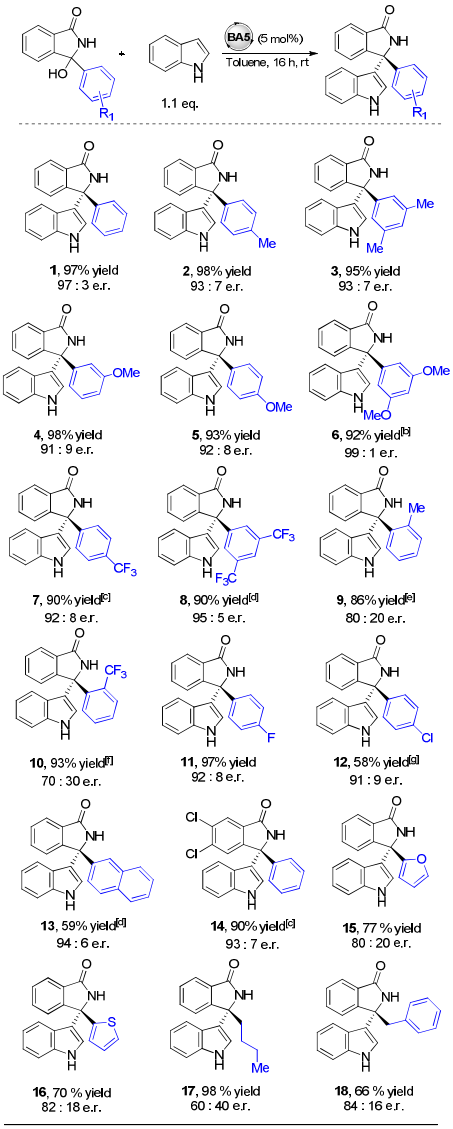
in substantially higher enantiomeric ratio in the product (97:3 e.r., Entry 5). On the other hand, introduction of bulkier substituents on the flanking aromatic rings of the catalyst resulted in significant drop in the enantioselectivities (Entries 6 and 7).

After identifying **BA5** catalyst as the optimal catalyst for the transformation, the influence of solvent, temperature, catalyst loading, and the addition of additives was investigated. By conducting the reaction in other common solvents, the product was obtained with slightly lower enantioselectivities (Entries 8–11). Next, we examined the chiral catalyst loading. 5 mol% of the catalyst led to the same enantioselectivity as with 10 mol% loading, though the reaction time was prolonged to 16 hours (Entry 12). Cooling the reaction to –10 °C led to an incomplete conversion after 7 days, but the enantioselectivity of the reaction was not improved (Entry 13). Lastly, we investigated the addition of a drying agent, but the enantiomeric ratio remained the same (Entry 14). Hence, the optimized procedure employed 5 mol% of **BA5** catalyst in toluene at room temperature.

With optimized reaction conditions in hand, we turned our attention to investigate the substrate scope and reaction limitations. Initially, we examined asymmetric (3-indolyl)(diaryl)methanamine formation with various 3-aryl 3-hydroxyisoindolinones[23] (Table 2). Indole reacted efficiently with a range of different 3-aryl 3-hydroxyisoindolinones and provided high yields and enantioselectivities. When alkyl groups were placed around the 3-aryl substituent, a small drop in enantiomeric ratios was observed, and products **2** and **3** were furnished in very good yields and enantioselectivities. By introducing electron-donating groups on the *meta* and *para* positions of the 3-aryl ring, the reaction maintained its effectiveness, and no significant change in enantiomeric ratios was observed (**4**, 98% yield, 91:9 e.r., and **5**, 93% yield, 92:8 e.r.). However, when methoxy substitutents were placed in both *meta* positions of the 3-aryl, the enantioselectivity of the reaction was dramatically improved (**6**, 92% yield, 99:1 e.r.). Trifluoromethyl groups on the 3-aryl substituent were also

well tolerated, furnishing products **7** and **8** in high yields and enantioselectivities, though the reactions had to be performed at elevated temperatures.

Table 2. Substrate scope: isoindolinone alcohols[a]



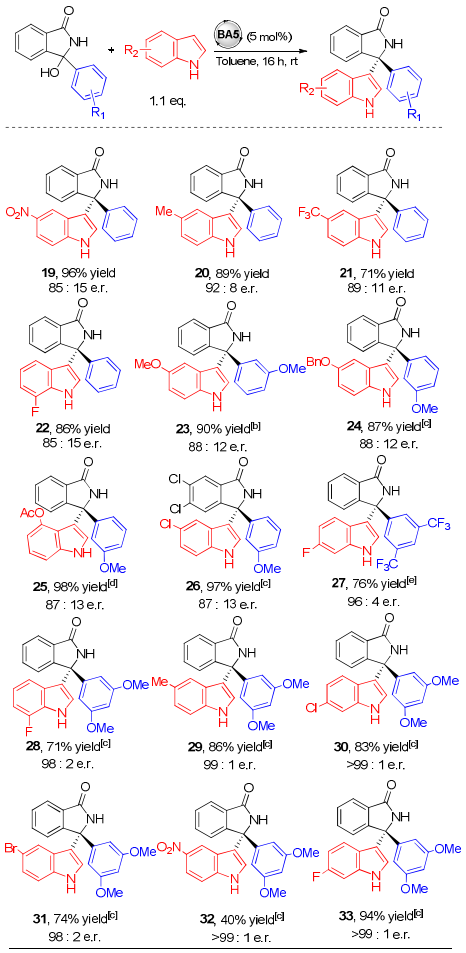
[a] Isolated yields. Reactions performed on 0.2 mmol scale. [b] 40 °C. [c] 50 °C. [d] 60 °C. [e] 96 h. [f] 40 °C, 60 h. [g] 6 days.

When *ortho*-methyl and *ortho*-trifluoromethyl substituents were introduced, the reaction times were significantly prolonged, and moderate enantioselectivities were observed (**9**, 86% yield, 80:20 e.r., and **10**, 93% yield, 70:30 e.r.). The most probable explanation for this observation is that the increased steric hidrance around the reaction centre overrides the steric influence of the chiral phosphoric acid catalyst. Introduction of the halogen-containing 3-aryl substituent (**11** and **12**), 3-naphtyl substituent (**13**), and phthalimide aromatic ring substitutions (**14**) did not change the efficiency of the reaction. When smaller aromatic systems were employed as 3-aryl groups, a significant drop in enantioselectivity was observed (**15**, 77% yield, 80:20 e.r., and **16**, 70% yield, 82:18 e.r.).

Although the aim of this study was the preparation of (3-indolyl)(diaryl)methanamines, we investigated whether 3-alkyl substituents were also tolerated. Submitting 3-butyl 3-hydroxyisoindolinone substrate to the optimized reaction conditions resulted in product **17** in high yield, but poor enantioselectivity (98% yield, 60:40 e.r.). By utilizing 3-benzyl substituent on the isoindolinone alcohol, the enantiomeric ratio in the product was substantially higher, though still moderate (**18**, 84:16 e.r.). Poor or moderate enantioselectivities in examples with smaller aromatic rings and alkyl chains as 3-substituents are most likely due to their size; these groups are probably not big enough to successfully create a differentiation between the enantiotopic faces of the *N*-acyl iminium intermediate when binding to the catalyst.

Furthermore, we turned our attention to investigating the scope and limitations of the reaction with various indoles (Table 3).

Table 3. Substrate scope: indoles[a]



[a] Isolated yields. Reactions performed at 0.2 mmol scale. [b] 80 °C. [c] 50 °C. [d] 36 h. [e] 50 °C, 72 h.

Initially, we chose 3-phenyl and 3-(*m*-methoxy)phenyl 3-hydroxyisoindolinones as model alcohols for the investigation of the influence of indole substituents on the reaction outcome (entries **19**–**25**). In general, enantioselectivities slightly dropped regardless of the position and nature of the substituent on the indole. *α*-Chiral methanamine products were isolated in excellent yields and in enantioselectivities ranging from 85:15 e.r. to 92:8 e.r. The reaction maintained moderate effectiveness when 3-hydroxyisoindolinone with substituted phthalimide

ring was reacted with 5-chloroindole (**26**, 97% yield, 87:13 e.r.). Better level of enantioselectivity was obtained when 3-(3,5-ditrifluoromethyl)phenyl 3-hydroxyisoindolinone was combined with 6-fluoroindole (**27**, 76% yield, 96:4 e.r.). Next, we screened 3-(3,5-dimethoxy)phenyl 3-hydroxyisoindolinone, the alcohol that yielded the best enantiomeric ratio in the reaction with unsubstituted indole. Corresponding products **28**–**33** were isolated in very good yields and excellent enantioselectivities (>99:1 e.r.), regardless of the position and nature of the substituents on indole. This result indicates that 3,5-dimethoxy substitution on 3-phenyl ring is alone responsible for the extraordinary high enenatiomeric ratios in products, as observed in metal-catalyzed reactions investigated by Nishimura et al.[17]

By comparing HPLC traces of product **1** with HPLC traces of a known compound (see Supporting information),[13] the absolute configuration was assigned to be (*S*), and the absolute configurations of the remaining products were assigned by analogy. In order to investigate the origin of the observed enantioselectivity, we performed mechanistic investigation experiments. First, DFT calculations were performed at B3LYP-D3(BJ)/6-311+G** level of theory on a model reaction. Two transition states (**TS-*R*** and **TS-*S***) leading to the products in (*R*) and (*S*) configurations, respectively were located (Figure 1).

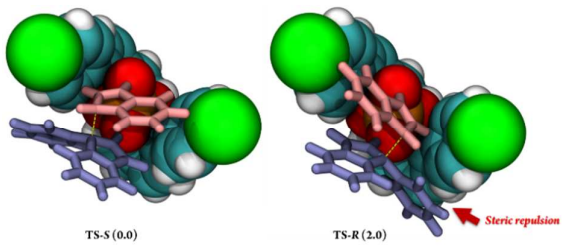
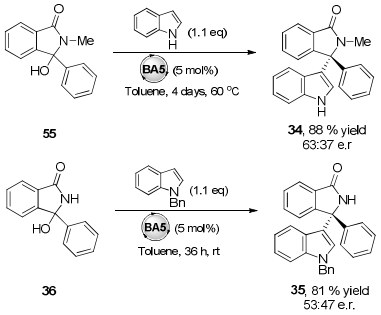


Figure 1. The optimized structures and the relative Gibbs free energies (in kcal/mol) of the two key transition states. The catalyst **BA5** is represented with VDW model. The indole and isoindolinone *N*-acyl iminium ion are represented with stick models in pink and purple, respectively. The yellow dashlines show the forming C–C bonds.

The calculated Gibbs free energy of **TS-*R*** is 2 kcal/mol higher than that of **TS-*S***, indicating the product in (*S*) configuration should be formed predominantly, which is consistent with the experimental results. In the unfavorable **TS-*R***, significant steric repulsion is established between the phenyl group of the isoindolinone and the lower 4-ClC_6H_4 group on the chiral phosphoric acid catalyst, which is the main reason that accounts for the higher energetic barrier of this transition state.

In order to further elucidate stereochemical induction of the reaction, experiments with *N*-protected isoindolinone alcohol and *N*-protected indole were performed, respectively (Scheme 1).



Scheme 1. Reactions with *N*-protected isoindolinone alcohol, and *N*-protected indole.

When *N*-methylated 3-hydroxyisoindolinone **55** was submitted to aza-Friedel-Crafts reaction with indole, the product **34** was obtained in high yield and low enantioselectivity (88% yield, 63:37 e.r.) after performing the reaction at 60 °C for 4 days. Similarly, in the reaction of isoindolinone alcohol **36** and *N*-benzylated indole under optimized reaction conditions, product **35** was obtained practically as a racemate (81% yield, 53:47 e.r.). These experiments indicate that chiral phosphoric acid binds to both substrates in the transition state *via* their respective N*H* atoms, which is in accordance with the generally accepted mechanism.[6e]

In conclusion, we have developed a chiral Brønsted acid-catalyzed asymmetric aza-Friedel-Crafts reaction between indoles and *in situ* generated cyclic *α*-diaryl-substituted *N*-acyl imines. The reaction proceeds smoothly with a broad range of indoles and isoindolinone alcohols to afford chiral *α*-tetrasubstituted (3-indolyl)(diaryl)methanamines in high yields and enantioselectivities. The origin of the enantioselectivity was supported by DFT calculations and experimental data. We anticipate that the utility of the developed asymmetric aza-Friedel-Crafts reaction as a central component in the construction of complex heterocyclic cores will be further explored.

Experimental Section

General Information

Chemicals and solvents were purchased from commercial suppliers and used as received. Flash column chromatography was carried out using silica gel (Merck, 40−63 μm particle size). NMR spectra were recorded on Bruker Avance 600 MHz and 300 MHz spectrometers, operating at 150.92 or 75.47 MHz for ^{13}C and 600.13 or 300.13 MHz for ^{1}H nuclei. Chemical shifts are quoted in ppm, and are referenced to the residual non-deuterated solvent peak. Spectra were acquired at 298 K. Infra-red spectra were recorded on a Varian Uv/Vis Cary 4000 spectrometer equipped with an attenuated total reflectance attachment with internal calibration. Absorbtion maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). Mass spectrometry measurements were performed on HPLC system coupled with triple quadrupole mass spectrometer, operating in a positive electrospray ionization (ESI) mode. High resolution mass spectrometry (HRMS) was performed on a 4800 Plus MALDI TOF/TOF Analyzer. Mps were determined using an Electrothermal 9100 apparatus in open capillaries and are uncorrected. Substrates, 3-aryl 3-hydroxyisoindolinones, (**36**–**55** in SI) were

synthesized in high yields from readily available starting materials, by employing addition of Grignard or organolithium reagent to phthalimide.[25] Chiral phosphoric acids **BA1–BA7** have been prepared according to known procedures, and obtained data corresponds to data reported therein.[26] Racemic standards were prepared by using *p*-toluenesulfonic acid (10 mol%) instead of a chiral catalyst.

General Procedure

To a flame-dried Schlenk tube containing a solution of 3–aryl 3–hydroxyisoindolinone (0.2 mmol) in toluene (2 mL) was added indole (0.22 mmol) and chiral phosphoric acid **BA5** (5 mol%). The reaction mixture was stirred at room temperature until substrate was fully consumed according to HPLC. The crude reaction mixture was directly purified by column chromatography on silica gel.

(*S*)-3-(1H-indol-3-yl)-3-phenylisoindolin-1-one (1).[13] White solid. Yield: 70 mg (97 %), 97:3 e.r. Column chromatography eluents: dichloromethane-methanol 40:1. ^{1}H NMR (600 MHz, DMSO) δ 11.04 (s, 1H), 9.59 (s, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.58 (dd, *J* = 10.6, 4.1 Hz, 1H), 7.52 (t, *J* = 7.3 Hz, 1H), 7.47 (d, *J* = 7.3 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.29 (t, *J* = 7.2 Hz, 1H), 7.07 – 7.00 (m, 1H), 6.87 (d, *J* = 2.5 Hz, 1H), 6.84 – 6.73 (m, 2H). ^{13}C NMR (75 MHz, DMSO) δ 168.9, 151.3, 143.3, 137.5, 132.3, 131.6, 128.7, 127.9, 126.9, 125.6, 124.7, 124.6, 123.6, 121.7, 120.3, 119.1, 117.2, 112.2, 66.7. ESI–MS: 325 $[M+H]^{+}$. t_{R1} = 11.6 min (major), t_{R2} = 19.6 min (minor) (Daicel Chiralpack IC-3, 20% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(1H-indol-3-yl)-3-(*p*-tolyl)isoindolin-1-one (2). White solid. Yield: 69 mg (98 %), 93:7 e.r. Column chromatography eluents: dichloromethane-methanol 40:1. ^{1}H NMR (600 MHz, DMSO) δ 11.00 (s, 1H), 9.52 (s, 1H), 7.70 (d, *J* = 7.4 Hz, 1H), 7.59 – 7.52 (m, 2H), 7.50 – 7.46 (m, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.10 (t, *J* = 9.0 Hz, 2H), 7.04

– 6.97 (m, 1H), 6.88 – 6.71 (m, 3H), 2.25 (s, 3H). ^{13}C NMR (75 MHz, DMSO) δ 168.9, 151.5, 140.3, 137.5, 136.9, 132.3, 131.5, 129.30, 128.6, 126.8, 125.6, 124.6, 123.6, 121.7, 120.4, 119.1, 117.3, 112.2, 66.5, 21.0. mp 265.9–267.3 °C. ν_{max} (neat): 3289, 1676, 1352, 1107, 812, 736, 541 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{19}N_2O$ 339.1497; Found 339.1486. t_{R1} = 12.2 min (major), t_{R2} = 22.6 min (minor) (Daicel Chiralpack IC-3, 20% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(3,5-dimethylphenyl)-3-(1H-indol-3-yl)isoindolin-1-one (3). White solid. Yield: 66 mg (95 %), 93:7 e.r. Column chromatography eluents: petroleum ether-ethyl acetate 2:1. ^{1}H NMR (300 MHz, DMSO) δ 11.03 (s, 1H), 9.52 (s, 1H), 7.73 (d, *J* = 7.1 Hz, 1H), 7.64 – 7.46 (m, 3H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.08 (s, 2H), 7.06 – 6.99 (m, 1H), 6.95 – 6.75 (m, 4H), 2.20 (s, 6H). ^{13}C NMR (151 MHz, DMSO) δ 168.9, 151.4, 143.2, 137.6, 137.5, 132.2, 131.5, 129.3, 128.6, 125.6, 124.7, 124.6, 123.6, 121.7, 120.4, 119.1, 117.3, 112.2, 66.6, 21.6. mp 181.3–186.0 °C. ν_{max} (neat): 3233, 2918, 1681, 1465, 1245, 1014, 739 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{21}N_2O$ 353.1654; Found 353.1671. t_{R1} = 11.1 min (major), t_{R2} = 17.1 min (minor) (Daicel Chiralpack IC-3, 20% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(1H-indol-3-yl)-3-(3-methoxyphenyl)isoindolin-1-one (4). White solid. Yield: 68 mg (98 %), 91:9 e.r. Column chromatography eluents: dichloromethane-methanol 40:1. ^{1}H NMR (300 MHz, DMSO) δ 11.07 (s, 1H), 9.61 (s, 1H), 7.75 (d, *J* = 7.1 Hz, 1H), 7.66 – 7.49 (m, 3H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.27 (t, *J* = 7.9 Hz, 1H), 7.10 – 7.00 (m, 3H), 6.93 – 6.76 (m, 4H), 3.70 (s, 3H). ^{13}C NMR (75 MHz, DMSO) δ 168.9, 159.5, 151.1, 144.9, 137.5, 132.3, 131.5, 129.9, 128.8, 125.5, 124.7, 123.6, 121.7, 120.3, 119.3, 119.1, 117.1, 113.3, 112.6, 112.2, 66.6, 55.5. mp 144.1–145.5 °C. ν_{max} (neat): 3273, 1677, 1289, 1246, 1037, 703 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{19}N_2O_2$ 355.1447; Found 355.1433. t_{R1} = 15.8 min (major), t_{R2} = 24.5 min (minor) (Daicel Chiralpack IC-3, 20% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(1H-indol-3-yl)-3-(4-methoxyphenyl)isoindolin-1-one (5). White solid. Yield: 65 mg (94 %), 92:8 e.r. Column chromatography eluents: dichloromethane-methanol 40:1. ^{1}H NMR (600 MHz, DMSO) δ 11.01 (s, 1H), 9.52 (s, 1H), 7.72 (d, *J* = 7.5 Hz, 1H), 7.60 – 7.54 (m, 2H), 7.52 – 7.47 (m, 1H), 7.35 (t, *J* = 7.5 Hz, 3H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.92 – 6.82 (m, 4H), 6.79 (t, *J* = 7.4 Hz, 1H), 3.73 (s, 3H). ^{13}C NMR (151 MHz, DMSO) δ 168.8, 158.9, 151.7, 137.5, 135.1, 132.2, 131.5, 128.6, 128.1, 125.6, 124.6, 124.5, 123.5, 121.7, 120.4, 119.1, 117.5, 114.0, 112.2, 66.3, 55.5. mp 208.7–213.4 °C. ν_{max} (neat): 3250, 1671, 1509, 1248, 1033, 740, 542 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{19}N_2O_2$ 355.1447; Found 355.1456. t_{R1} = 20.2 min (major), t_{R2} = 35.0 min (minor) (Daicel Chiralpack IC-3, 20% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(3,5-dimethoxyphenyl)-3-(1H-indol-3-yl)isoindolin-1-one (6). White solid. Yield: 62 mg (92 %), 99:1 e.r. Column chromatography eluents: petroleum ether-ethyl acetate 2:1. ^{1}H NMR (300 MHz, DMSO) δ 11.04 (s, 1H), 9.55 (s, 1H), 7.73 (d, *J* = 7.1 Hz, 1H), 7.65 – 7.49 (m, 3H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.06 – 6.99 (m, 1H), 6.88 (d, *J* = 2.5 Hz, 1H), 6.87 – 6.74 (m, *J* = 13.1, 6.4 Hz, 2H), 6.60 (d, *J* = 2.2 Hz, 2H), 6.45 (t, *J* = 2.1 Hz, 1H), 3.69 (s, 6H). ^{13}C NMR (151 MHz, DMSO) δ 168.9, 160.8, 150.9, 145.7, 137.5, 132.3, 131.6, 128.8, 125.6, 124.7, 124.7, 123.6, 121.7, 120.3, 119.1, 116.9, 112.2, 105.7, 98.9, 66.7, 55.6. mp 162.1–166.4 °C. $[\alpha]_D$= +222° (*c* 0.5, MeOH). ν_{max} (neat): 3233, 1683, 1591, 1456, 1152, 739 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{21}N_2O_3$ 385.1552; Found 385.1534. t_{R1} = 17.8 min (major), t_{R2} = 24.2 min (minor) (Daicel Chiralpack IC-3, 20% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(1H-indol-3-yl)-3-(4-(trifluoromethyl)phenyl)isoindolin-1-one (7). White solid. Yield: 61 mg (90 %), 92:8 e.r. Column chromatography eluents: dichloromethane-methanol 40:1. ^{1}H NMR (600 MHz, DMSO) δ 11.16 (s, 1H), 9.77 (s, 1H), 7.77 (d, *J* = 7.5 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.63 – 7.59 (m,

1H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.08 – 7.03 (m, 1H), 6.92 (d, *J* = 2.5 Hz, 1H), 6.85 – 6.81 (m, 2H). ^{13}C NMR (151 MHz, DMSO) δ 168.9, 150.6, 148.0, 137.6, 132.6, 131.5, 129.1, 128.5 (q, *J* = 31.8 Hz), 127.7, 125.8 (q, *J* = 3.7 Hz), 125.4, 124.9, 124.7 (q, *J* = 271.9 Hz), 124.6, 123.8, 121.9, 120.2, 119.3, 116.4, 112.3, 66.5. mp 285.9–288.6 °C. ν_{max} (neat): 3292, 1674, 1325, 1132, 1068, 737, 595 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{16}F_3N_2O$ 393.1215; Found 393.1215. t_{R1} = 7.8 min (major), t_{R2} = 13.2 min (minor) (Daicel Chiralpack IC-3, 20% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(3,5-bis(trifluoromethyl)phenyl)-3-(1H-indol-3-yl)isoindolin-1-one (8). White solid. Yield: 57 mg (90 %), 95:5 e.r. Column chromatography eluents: petroleum ether-ethyl acetate 2:1. ^{1}H NMR (600 MHz, DMSO) δ 11.23 (s, 1H), 9.85 (s, 1H), 8.15 – 8.09 (m, *J* = 17.3 Hz, 3H), 7.80 (d, *J* = 7.7 Hz, 1H), 7.76 (d, *J* = 7.7 Hz, 1H), 7.68 – 7.63 (m, 1H), 7.60 – 7.57 (m, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.96 – 6.89 (m, *J* = 9.7 Hz, 1H), 6.83 (t, *J* = 7.6 Hz, 1H), 6.72 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 168.8, 149.7, 146.7, 137.5, 133.0, 131.4, 130.9 (q, *J* = 32.9 Hz), 129.5, 127.5 (q, *J* = 3.2 Hz), 125.5, 125.0, 124.6, 124.0, 123.6 (q, *J* = 273.0 Hz), 122.3, 122.1, 119.6, 119.5, 115.7, 112.5, 66.2. mp 259.5–263.4 °C. ν_{max} (neat): 3337, 1676, 1278, 1171, 1117, 743, 702, 680 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{15}F_6N_2O$ 461.1089; Found 461.1106. t_{R1} = 6.9 min (major), t_{R2} = 9.6 min (minor) (Daicel Chiralpack IC-3, 10% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(1H-indol-3-yl)-3-(*o*-tolyl)isoindolin-1-one (9). White solid. Yield: 61 mg (86 %), 80:20 e.r. Column chromatography eluents: dichloromethane-methanol 40:1. ^{1}H NMR (600 MHz, DMSO) δ 11.03 (s, 1H), 9.46 (s, 1H), 7.75 (d, *J* = 7.4 Hz, 1H), 7.60 – 7.56 (m, *J* = 10.8, 4.0 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.17 – 7.10 (m, 4H), 7.08 (t, *J* = 7.8 Hz, 1H), 6.96 (d, *J* = 2.4 Hz, 1H), 6.87 (t, *J* = 7.6 Hz, 1H), 1.95 (s, 3H). ^{13}C NMR (151 MHz, DMSO) δ 169.4, 151.6, 139.7, 137.6, 133.0, 132.2, 131.5, 128.6, 128.5, 128.4, 126.2, 125.5, 124.6, 123.6, 122.9, 121.8, 120.4, 119.1, 118.4, 112.3, 67.5,

21.4. mp 186.8–190.1 °C. ν_{max} (neat): 3222, 1666, 1343, 1105, 732 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{19}N_2O$ 339.1497; Found 339.1497. t_{R1} = 9.3 min (major), t_{R2} = 11.7 min (minor) (Daicel Chiralpack IC-3, 20% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(1H-indol-3-yl)-3-(2-(trifluoromethyl)phenyl)isoindolin-1-one (10). White solid. Yield: 62 mg (93 %), 70:30 e.r. Column chromatography eluents: dichloromethane-methanol 40:1. ^{1}H NMR (300 MHz, DMSO) δ 11.05 (s, 1H), 9.22 (s, 1H), 7.89 – 7.70 (m, 2H), 7.63 – 7.32 (m, 7H), 7.06 (t, *J* = 7.4 Hz, 1H), 7.00 – 6.80 (m, 2H), 6.71 (d, *J* = 1.9 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 169.6, 150.5, 141.1, 137.6, 132.7, 132.4, 132.2, 131.8, 128.9, 128.8, 128.4 (q, *J* = 6.8 Hz), 127.0 (q, *J* = 31.0 Hz), 125.2, 124.5 (q *J* = 274.1 Hz), 124.4, 123.7, 123.4, 121.9, 120.8, 119.5, 119.1, 112.2, 67.0. mp 274.7–278.0 °C. ν_{max} (neat): 3292, 1679, 1308, 1152, 1128, 1111, 1037, 789, 739, 694 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{16}F_3N_2O$ 393.1215; Found 393.1200. t_{R1} = 31.2 min (major), t_{R2} = 35.3 min (minor) (Daicel Chiralpack IC-3, 10% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(4-fluorophenyl)-3-(1H-indol-3-yl)isoindolin-1-one (11). White solid. Yield: 68 mg (97 %), 92:8 e.r. Column chromatography eluents: dichloromethane-methanol 40:1. ^{1}H NMR (600 MHz, DMSO) δ 11.06 (s, 1H), 9.61 (s, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.64 – 7.56 (m, *J* = 7.7 Hz, 2H), 7.55 – 7.51 (m, 1H), 7.48 (dd, *J* = 8.8, 5.4 Hz, 2H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.16 (t, *J* = 8.8 Hz, 2H), 7.07 – 7.01 (m, *J* = 8.2, 5.7, 2.5 Hz, 1H), 6.87 (d, *J* = 2.5 Hz, 1H), 6.85 – 6.76 (m, 2H). ^{13}C NMR (151 MHz, DMSO) δ 168.9, 161.9 (d, *J* = 243.8 Hz), 151.2, 139.5 (d, *J* = 2.9 Hz), 137.5, 132.4, 131.5, 129.0 (d, *J* = 8.2 Hz), 128.8, 125.4, 124.7, 124.5, 123.7, 121.8, 120.3, 119.2, 117.1, 115.5 (d, *J* = 21.4 Hz), 112.3, 66.2. mp 216.3–219.9 °C. ν_{max} (neat): 3293, 1673, 1505, 1226, 739, 586 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{16}FN_2O$ 343.1247; Found 343.1237. t_{R1} = 11.8 min (major), t_{R2} = 18.4 min (minor) (Daicel Chiralpack IC-3, 20% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(4-chlorophenyl)-3-(1H-indol-3-yl)isoindolin-1-one (12). White solid. Yield: 40 mg (58 %), 91:9 e.r. Column chromatography eluents: dichloromethane-methanol 40:1. ^{1}H NMR (300 MHz, DMSO) δ 11.08 (s, 1H), 9.62 (s, 1H), 7.75 (d, *J* = 7.2 Hz, 1H), 7.65 – 7.57 (m, 2H), 7.53 – 7.33 (m, 6H), 7.09 – 6.99 (m, 1H), 6.93 – 6.78 (m, 3H). ^{13}C NMR (75 MHz, DMSO) δ 168.9, 150.9, 142.4, 137.6, 132.6, 132.5, 131.5, 128.9, 128.8, 128.7, 125.4, 124.7, 124.5, 123.7, 121.8, 120.3, 119.2, 116.7, 112.3, 66.2. mp 256.3–259.9 °C. ν_{max} (neat): 3273, 1670, 1333, 1013, 740, 539 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{16}ClN_2O$ 359.0951; Found 359.0963. t_{R1} = 32.0 min (major), t_{R2} = 61.4 min (minor) (Daicel Chiralpack IC-3, 10% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(1H-indol-3-yl)-3-(naphthalen-2-yl)isoindolin-1-one (13). White solid. Yield: 40 mg (59 %), 94:6 e.r. Column chromatography eluents: petroleum ether-ethyl acetate 2:1. ^{1}H NMR (600 MHz, DMSO) δ 11.10 (s, 1H), 9.71 (s, 1H), 7.97 (s, 1H), 7.91 – 7.86 (m, 2H), 7.86 – 7.81 (m, 1H), 7.78 (d, *J* = 10.4 Hz, 1H), 7.72 (d, *J* = 7.7 Hz, 1H), 7.66 – 7.58 (m, 2H), 7.56 – 7.46 (m, 3H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.07 – 7.00 (m, 1H), 6.93 (d, *J* = 2.6 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.79 – 6.73 (m, 1H). ^{13}C NMR (151 MHz, DMSO) δ 169.0, 151.2, 140.8, 137.5, 132.9, 132.7, 132.4, 131.6, 128.8, 128.5, 128.4, 127.9, 126.8, 126.7, 125.9, 125.6, 124.8, 124.7, 124.6, 123.7, 121.8, 120.3, 119.1, 117.1, 112.2, 66.8. mp 299.3–302.1 °C. ν_{max} (neat): 3180, 3053, 1671, 1242, 1107, 742, 478 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{26}H_{19}N_2O$ 375.1497; Found 375.1515. t_{R1} = 8.8 min (major), t_{R2} = 12.8 min (minor) (Daicel Chiralpack IC-3, 20% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-5,6-dichloro-3-(1H-indol-3-yl)-3-phenylisoindolin-1-one (14). White solid. Yield: 66 mg (90 %), 93:7 e.r. Column chromatography eluents: dichloromethane-methanol 40:1. ^{1}H NMR (300 MHz, DMSO) δ 11.12 (s, 1H), 9.88 (s, 1H), 7.94 (s, 1H), 7.90 (s, 1H), 7.52 – 7.48 (m, 2H), 7.40 – 7.32 (m, 4H), 7.05 (ddd, *J* = 8.2, 6.2, 1.9 Hz, 1H), 6.94 (d, *J* = 2.6 Hz, 1H), 6.87 – 6.76 (m, 2H). ^{13}C NMR (75 MHz, DMSO) δ 166.7, 151.2, 142.2, 137.5, 135.3, 132.3,

132.1, 128.9, 128.2, 126.9, 126.7, 125.5, 125.4, 125.2, 121.9, 120.1, 119.3, 116.0, 112.3, 66.6. mp 268.0–269.7 °C. ν_{max} (neat): 3249, 1683, 1398, 1101, 782, 740 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{15}Cl_2N_2O$ 393.0561; Found 393.0542. t_{R1} = 16.6 min (major), t_{R2} = 21.6 min (minor) (Daicel Chiralpack IC-3, 30% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(furan-2-yl)-3-(1H-indol-3-yl)isoindolin-1-one (15). Brown solid. Yield: 56 mg (77 %), 80:20 e.r. Column chromatography eluents: petroleum ether-ethyl acetate 2:1. ^{1}H NMR (600 MHz, DMSO) δ 11.07 (s, 1H), 9.59 (s, 1H), 7.74 (d, *J* = 7.4 Hz, 1H), 7.68 – 7.61 (m, 1H), 7.61 – 7.54 (m, 2H), 7.54 – 7.49 (m, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.06 – 6.97 (m, *J* = 8.1, 6.2, 1.9 Hz, 1H), 6.93 (d, *J* = 2.6 Hz, 1H), 6.85 – 6.74 (m, 2H), 6.43 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.32 (d, *J* = 3.0 Hz, 1H). ^{13}C NMR (75 MHz, DMSO) δ 168.9, 155.2, 149.4, 143.6, 137.2, 132.5, 131.6, 129.2, 125.2, 124.5, 124.4, 123.5, 121.7, 119.5, 119.3, 114.9, 112.3, 110.7, 107.3, 62.6. mp 237.2–240.4 °C. ν_{max} (neat): 3187, 1670, 1352, 1011, 736 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{15}N_2O_2$ 315.1134; Found 315.1127. t_{R1} = 11.7 min (major), t_{R2} = 23.8 min (minor) (Daicel Chiralpack IC-3, 20% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(1H-indol-3-yl)-3-(thiophen-2-yl)isoindolin-1-one (16). White solid. Yield: 50 mg (70 %), 82:18 e.r. Column chromatography eluents: petroleum ether-ethyl acetate 2:1. ^{1}H NMR (600 MHz, DMSO) δ 11.13 (s, 1H), 9.74 (s, 1H), 7.77 (d, *J* = 7.4 Hz, 1H), 7.65 – 7.60 (m, *J* = 7.6 Hz, 2H), 7.58 – 7.53 (m, *J* = 10.3, 3.9 Hz, 1H), 7.45 (d, *J* = 4.8 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.12 (d, *J* = 2.7 Hz, 1H), 7.08 – 7.01 (m, 3H), 6.87 – 6.82 (m, *J* = 8.3 Hz, 2H). ^{13}C NMR (75 MHz, DMSO) δ 168.7, 151.4, 147.9, 137.4, 132.6, 131.1, 129.1, 127.5, 126.1, 125.6, 125.4, 124.8, 124.3, 123.6, 121.8, 120.1, 119.3, 116.6, 112.3, 64.3. mp 285.6–289.4 °C. ν_{max} (neat): 3182, 1679, 1339, 1077, 740, 596 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{15}N_2OS$ 331.0905; Found 331.0908. t_{R1} = 12.3 min (major), t_{R2} = 23.5 min (minor) (Daicel Chiralpack IC-3, 20% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-butyl-3-(1H-indol-3-yl)isoindolin-1-one (17).[13] White solid. Yield: 73 mg (98 %), 60:40 e.r. Column chromatography eluents: petroleum ether-ethyl acetate 2:1. ^{1}H NMR (600 MHz, DMSO) δ 11.04 (s, 1H), 8.86 (s, 1H), 7.69 (d, *J* = 7.4 Hz, 1H), 7.50 – 7.41 (m, *J* = 14.7, 7.4, 0.9 Hz, 3H), 7.33 (dd, *J* = 12.1, 7.9 Hz, 2H), 7.02 – 6.94 (m, 2H), 6.81 – 6.76 (m, 1H), 2.47 – 2.41 (m, 1H), 2.34 – 2.27 (m, *J* = 13.5, 4.5 Hz, 1H), 1.30 – 1.16 (m, *J* = 18.5, 12.5, 6.6 Hz, 4H), 0.80 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, DMSO) δ 169.4, 152.1, 137.2, 132.4, 132.2, 128.2, 125.2, 123.5, 123.0, 122.8, 121.4, 119.7, 118.9, 116.5, 112.1, 63.6, 37.9, 25.7, 22.7, 14.4. ESI–MS: 305 [M+H^{+}]. t_{R1} = 8.2 min (major), t_{R2} = 17.0 min (minor) (Daicel Chiralpack AD, 20% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-benzyl-3-(1H-indol-3-yl)isoindolin-1-one (18). White solid. Yield: 47 mg (66 %), 84:16 e.r. Column chromatography eluents: petroleum ether-ethyl acetate 2:1. ^{1}H NMR (600 MHz, DMSO) δ 11.13 (s, 1H), 8.92 (s, 1H), 7.67 (d, *J* = 2.5 Hz, 1H), 7.52 – 7.45 (m, *J* = 14.6, 7.5 Hz, 2H), 7.37 (dd, *J* = 19.9, 7.8 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.01 (dd, *J* = 8.7, 3.9 Hz, 4H), 6.94 – 6.87 (m, 3H), 6.78 (t, *J* = 7.5 Hz, 1H), 3.86 (d, *J* = 13.2 Hz, 1H), 3.67 (d, *J* = 13.1 Hz, 1H) ^{13}C NMR (75 MHz, DMSO) δ 169.0, 150.6, 137.2, 135.8, 132.8, 131.6, 131.1, 128.1, 127.5, 126.5, 125.3, 123.7, 123.6, 122.6, 121.5, 119.7, 119.0, 116.7, 112.1, 63.9, 43.5. mp 211.0–213.0 °C. ν_{max} (neat): 3192, 1673, 1455, 1120, 739, 697 cm^{-1}. HRMS (ESI-TOF) m/z: [M+H]$^{+}$ Calcd for $C_{23}H_{19}N_2O$ 338.1419; Found 338.1426. t_{R1} = 12.2 min (minor), t_{R2} = 39.7 min (major) (Daicel Chiralpack IC-3, 20% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(5-nitro-1H-indol-3-yl)-3-phenylisoindolin-1-one (19). Yellow solid. Yield: 79 mg (96 %), 85:15 e.r. Column chromatography eluents: dichloromethane-methanol 40:1. ^{1}H NMR (300 MHz, DMSO) δ 11.81 (s, 1H), 9.82 (s, 1H), 7.96 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.83 – 7.73 (m, 2H), 7.66 – 7.59 (m, 2H), 7.59 – 7.52 (m, 2H), 7.52 – 7.44 (m, *J* = 8.1, 1.4 Hz, 2H), 7.42 – 7.28 (m, 3H), 7.16 (d, *J* = 2.2 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 169.0, 150.7, 142.8, 140.8, 140.7, 132.6, 131.4, 129.1, 129.0, 128.6, 128.2, 126.7, 124.8, 124.6, 123.8,

120.1, 117.6, 117.2, 112.8, 66.1. mp 318.8–323.1 °C. ν_{max} (neat): 3203, 1667, 1332, 1254, 1048, 738, 692 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{16}N_3O_3$ 370.1192; Found 370.1193. t_{R1} = 59.8 min (major), t_{R2} = 72.0 min (minor) (Daicel Chiralpack IC-3, 20% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(5-methyl-1H-indol-3-yl)-3-phenylisoindolin-1-one (20). White solid. Yield: 67 mg (89 %), 92:8 e.r. Column chromatography eluents: dichloromethane-methanol 40:1. ^{1}H NMR (300 MHz, DMSO) δ 10.92 (s, 1H), 9.57 (s, 1H), 7.73 (d, *J* = 7.2 Hz, 1H), 7.63 – 7.39 (m, 5H), 7.38 – 7.20 (m, *J* = 22.1, 9.2, 5.4 Hz, 4H), 6.86 (dd, *J* = 8.3, 1.2 Hz, 1H), 6.81 (d, *J* = 2.6 Hz, 1H), 6.65 (s, 1H), 2.16 (s, 3H). ^{13}C NMR (151 MHz, DMSO) δ 169.0, 151.4, 143.3, 135.9, 132.3, 131.5, 128.7, 128.7, 127.8, 127.4, 126.9, 125.8, 124.7, 124.6, 123.6, 123.4, 120.1, 116.6, 111.9, 66.7, 21.8. mp 239.1–240.3 °C. ν_{max} (neat): 3272, 1669, 1315, 1030, 697, 539 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{19}N_2O$ 339.1497; Found 339.1497. t_{R1} = 10.3 min (major), t_{R2} = 21.2 min (minor) (Daicel Chiralpack IC-3, 20% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-phenyl-3-(5-(trifluoromethyl)-1H-indol-3-yl)isoindolin-1-one (21). White solid. Yield: 62 mg (71 %), 89:11 e.r. Column chromatography eluents: dichloromethane-methanol 40:1. ^{1}H NMR (300 MHz, DMSO) δ 11.52 (s, 1H), 9.79 (s, 1H), 7.76 (d, *J* = 7.3 Hz, 1H), 7.64 – 7.43 (m, 6H), 7.40 – 7.27 (m, 4H), 7.13 (s, 1H), 7.05 (s, 1H). ^{13}C NMR (151 MHz, DMSO) δ 169.0, 150.9, 142.9, 139.0, 132.5, 131.4, 128.9, 128.9, 128.1, 127.1, 126.7, 125.8 (q, *J* = 271.4 Hz), 124.8, 124.6, 123.7, 119.9 (q, *J* = 30.9 Hz), 118.2 (q, *J* = 3.2 Hz), 113.1, 66.3. mp 275.3–277.5 °C. ν_{max} (neat): 3270, 1670, 1329, 1108, 746, 699, 589 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{16}F_3N_2O$ 393.1215; Found 393.1216. t_{R1} = 13.2 min (major), t_{R2} = 19.2 min (minor) (Daicel Chiralpack IC-3, 10% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(7-fluoro-1H-indol-3-yl)-3-phenylisoindolin-1-one (22). White solid. Yield: 65 mg (86 %), 85:15 e.r. Column chromatography eluents: dichloromethane-methanol 40:1. ^{1}H NMR (300 MHz, DMSO) δ 11.61 (s, 1H), 9.66 (s, 1H), 7.75 (d, *J* = 7.1 Hz, 1H), 7.65 – 7.44 (m, 5H), 7.39 – 7.27 (m, 3H), 6.94 – 6.84 (m, 2H), 6.82 – 6.73 (m, 1H), 6.63 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (151 MHz, DMSO) δ 168.9, 151.0, 149.6 (d, *J* = 243.3 Hz), 142.9, 132.4, 131.5, 129.5 (d, *J* = 5.6 Hz), 128.9, 128.8, 127.9, 126.8, 125.7, 125.4 (d, *J* = 13.5 Hz), 124.6, 123.7, 119.5 (d, *J* = 6.0 Hz), 118.6, 116.6 (d, *J* = 3.1 Hz), 106.6 (d, *J* = 15.7 Hz), 66.4. mp 261.6–264.6 °C. ν_{max} (neat): 3254, 1670, 1321, 1235, 1031, 696 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{16}FN_2O$ 343.1260; Found 343.1247. t_{R1} = 9.8 min (major), t_{R2} = 16.2 min (minor) (Daicel Chiralpack IC-3, 20% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(5-methoxy-1H-indol-3-yl)-3-(3-methoxyphenyl)isoindolin-1-one (23). White solid. Yield: 68 mg (90 %), 89:11 e.r. Column chromatography eluents: dichloromethane-methanol 40:1. ^{1}H NMR (600 MHz, DMSO) δ 10.87 (s, 1H), 9.60 (s, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.59 – 7.55 (m, 1H), 7.51 (dd, *J* = 10.8, 4.0 Hz, 1H), 7.27 – 7.23 (m, 2H), 7.04 – 7.01 (m, *J* = 2.1 Hz, 1H), 6.86 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.83 (d, *J* = 2.6 Hz, 1H), 6.69 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.26 (d, *J* = 2.2 Hz, 1H), 3.68 (s, 3H), 3.48 (s, 3H). ^{13}C NMR (75 MHz, DMSO) δ 169.0, 159.6, 153.2, 151.1, 144.8, 132.6, 132.3, 131.6, 129.8, 128.8, 126.0, 125.3, 124.7, 123.5, 119.2, 116.6, 113.3, 112.7, 112.6, 111.5, 102.7, 66.6, 55.5, 55.4. mp 203.4–207.8 °C. ν_{max} (neat): 3233, 1681, 1465, 1215, 1034, 740 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{20}F_3N_2O_3$ 385.1552; Found 385.1550. t_{R1} = 13.5 min (major), t_{R2} = 31.1 min (minor) (Daicel Chiralpack IC-3, 30% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(5-(benzyloxy)-1H-indol-3-yl)-3-(3-methoxyphenyl)isoindolin-1-one (24). White solid. Yield: 78 mg (87 %), 88:12 e.r. Column chromatography eluents: dichloromethane-methanol 40:1. ^{1}H NMR (300 MHz, DMSO) δ 10.90 (s, 1H), 9.62 (s, 1H), 7.74 (dd, *J* = 6.1, 1.9 Hz, 1H), 7.58 – 7.48 (m, 3H), 7.37 – 7.23 (m, 7H), 7.04 – 6.96 (m, 2H), 6.88 (dd, *J* = 9.3,

2.3 Hz, 2H), 6.77 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.44 (d, *J* = 2.3 Hz, 1H), 4.84 (dd, *J* = 27.7, 12.2 Hz, 2H), 3.69 (s, 3H). ^{13}C NMR (151 MHz, DMSO) δ 169.0, 159.6, 152.1, 151.1, 144.8, 137.9, 132.8, 132.3, 131.5, 129.9, 128.8, 128.7, 128.0, 125.9, 125.1, 124.6, 123.6, 119.2, 116.7, 113.3, 112.8, 112.7, 112.4, 104.3, 70.1, 66.6, 55.5. mp 129.1–133.1 °C. ν_{max} (neat): 3225, 1683, 1465, 1254, 1038, 782, 737, 696, 593 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{30}H_{25}F_3N_2O_3$ 461.1865; Found 461.1846. t_{R1} = 10.3 min (major), t_{R2} = 22.1 min (minor) (Daicel Chiralpack IC-3, 30% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(1-(3-methoxyphenyl)-3-oxoisoindolin-1-yl)-1H-indol-4-yl acetate (25). White solid. Yield: 79 mg (98 %), 87:13 e.r. Column chromatography eluents: dichloromethane-methanol 40:1. ^{1}H NMR (300 MHz, DMSO) δ 11.33 (s, 1H), 8.49 (s, 1H), 7.75 (d, *J* = 7.3 Hz, 1H), 7.65 – 7.47 (m, 3H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.21 – 7.06 (m, 3H), 6.99 – 6.88 (m, 1H), 6.77 – 6.64 (m, 3H), 3.61 (s, 3H), 1.67 (s, 3H). ^{13}C NMR (75 MHz, DMSO) δ 169.0, 168.7, 159.7, 151.6, 145.8, 143.2, 140.3, 132.6, 130.9, 130.2, 128.8, 125.7, 124.7, 123.9, 122.4, 118.6, 117.9, 114.4, 113.2, 112.7, 112.5, 109.8, 66.7, 55.4, 21.0. mp 252.7–256.2 °C. ν_{max} (neat): 3324, 1681, 1323, 1195, 1040, 750, 583 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{25}H_{21}F_3N_2O_4$ 413.1501; Found 413.1490. t_{R1} = 21.4 min (major), t_{R2} = 25.0 min (minor) (Daicel Chiralpack IC-3, 20% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-5,6-dichloro-3-(5-chloro-1H-indol-3-yl)-3-(3-methoxyphenyl)isoindolin-1-one (26). White solid. Yield: 68 mg (97 %), 87:13 e.r. Column chromatography eluents: petroleum ether-ethyl acetate 2:1. ^{1}H NMR (300 MHz, DMSO) δ 11.37 (s, 1H), 9.99 (s, 1H), 7.96 (d, *J* = 3.7 Hz, 2H), 7.42 (d, *J* = 8.7 Hz, 1H), 7.30 (t, *J* = 7.9 Hz, 1H), 7.11 – 6.99 (m, 4H), 6.97 – 6.86 (m, 2H), 3.74 (s, 3H). ^{13}C NMR (75 MHz, DMSO) δ 166.7, 159.7, 150.6, 143.6, 136.0, 135.5, 132.4, 131.9, 130.3, 126.9, 126.8, 126.4, 125.6, 123.9, 122.0, 119.4, 119.1, 115.8, 113.9, 113.1, 66.2, 55.6. mp 165.8–169.3 °C. ν_{max} (neat): 3177, 1693, 1239, 893, 773, 466 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{16}N_2O_2$ 457.0277; Found 457.0269. t_{R1} =

12.3 min (major), t_{R2} = 14.2 min (minor) (Daicel Chiralpack IC-3, 10% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(3,5-bis(trifluoromethyl)phenyl)-3-(6-fluoro-1H-indol-3-yl)isoindolin-1-one (27). White solid. Yield: 50 mg (76 %), 96:4 e.r. Column chromatography eluents: petroleum ether-ethyl acetate 2:1. ^{1}H NMR (300 MHz, DMSO) δ 11.28 (s, 1H), 9.86 (s, 1H), 8.15 – 8.05 (m, *J* = 12.8 Hz, 3H), 7.83 – 7.57 (m, 4H), 7.18 (dd, *J* = 9.9, 2.0 Hz, 1H), 6.92 (d, *J* = 2.2 Hz, 1H), 6.80 – 6.60 (m, 2H). ^{13}C NMR (151 MHz, DMSO) δ 168.8, 159.3 (d, *J* = 235.6 Hz), 149.5, 146.5, 137.5 (d, *J* = 12.7 Hz), 133.1, 131.3, 130.9 (q, *J* = 32.8 Hz), 129.6, 127.5 (q, *J* = 3.0 Hz), 124.1, 123.6 (q, *J* = 273.0 Hz), 121.9, 120.7 (d, *J* = 10.1 Hz), 116.0, 108.2 (d, *J* = 24.4 Hz), 98.4 (d, *J* = 25.4 Hz), 66.1. mp 316.4–318.9 °C. $[\alpha]_D$= +125° (*c* 1, MeOH). ν_{max} (neat): 3329, 1674, 1278, 1121, 807, 699 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{14}F_7N_2O$ 479.0994; Found 479.1001. t_{R1} = 6.9 min (major), t_{R2} = 9.0 min (minor) (Daicel Chiralpack IC-3, 10% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(3,5-dimethoxyphenyl)-3-(7-fluoro-1H-indol-3-yl)isoindolin-1-one (28). White solid. Yield: 50 mg (71 %), 98:2 e.r. Column chromatography eluents: petroleum ether-ethyl acetate 2:1. ^{1}H NMR (600 MHz, DMSO) δ 11.56 (s, 1H), 9.57 (s, 1H), 7.75 – 7.70 (m, 1H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.60 – 7.55 (m, 1H), 7.54 – 7.49 (m, 1H), 6.92 – 6.84 (m, 2H), 6.81 – 6.75 (m, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 6.60 – 6.56 (m, 2H), 6.47 – 6.42 (m, 1H), 3.66 (s, 6H). ^{13}C NMR (151 MHz, DMSO) δ 168.9, 160.8, 150.7, 149.6 (d, *J* = 243.2 Hz), 145.4, 132.4, 131.5, 129.4 (d, *J* = 5.5 Hz), 128.9, 125.7, 125.3 (d, *J* = 13.4 Hz), 124.7, 123.6, 119.6 (d, *J* = 5.9 Hz), 118.3, 116.5 (d, *J* = 2.8 Hz), 106.6 (d, *J* = 15.8 Hz), 105.6, 99.0, 66.4, 55.6. mp 222.1–226.8 °C. $[\alpha]_D$= +159° (*c* 1, MeOH). ν_{max} (neat): 3259, 1676, 1422, 1154, 697, 537 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{20}FN_2O_3$ 403.1458; Found 403.1454. t_{R1} = 13.8 min (major), t_{R2} = 20.4 min (minor) (Daicel Chiralpack IC-3, 20% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(3,5-dimethoxyphenyl)-3-(5-methyl-1H-indol-3-yl)isoindolin-1-one (29). White solid. Yield: 60 mg (86 %), 99:1 e.r. Column chromatography eluents: petroleum ether-ethyl acetate 2:1. ^{1}H NMR (300 MHz, DMSO) δ 10.89 (s, 1H), 9.51 (s, 1H), 7.73 (d, *J* = 7.3 Hz, 1H), 7.63 – 7.48 (m, 3H), 7.25 (d, *J* = 8.3 Hz, 1H), 6.92 – 6.80 (m, 2H), 6.71 (s, 1H), 6.59 (d, *J* = 2.1 Hz, 2H), 6.49 – 6.41 (m, 1H), 3.69 (s, 6H), 2.19 (s, 3H). ^{13}C NMR (75 MHz, DMSO) δ 169.0, 160.7, 151.0, 145.8, 135.8, 132.2, 131.5, 128.7, 127.4, 125.8, 124.8, 124.7, 123.6, 123.4, 119.9, 116.3, 111.9, 105.7, 98.9, 66.7, 55.6, 21.8. mp 142.4–145.7 °C. $[\alpha]_D$= +170° (*c* 1, MeOH). ν_{max} (neat): 3235, 2929, 1683, 1423, 1154, 724, 593 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{25}H_{23}N_2O_3$ 399.1709; Found 399.1727. t_{R1} = 16.4 min (major), t_{R2} = 26.0 min (minor) (Daicel Chiralpack IC-3, 10% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(6-chloro-1H-indol-3-yl)-3-(3,5-dimethoxyphenyl)isoindolin-1-one (30). White solid. Yield: 61 mg (83 %), 99.5:0.5 e.r. Column chromatography eluents: petroleum ether-ethyl acetate 2:1. ^{1}H NMR (300 MHz, DMSO) δ 11.19 (s, 1H), 9.62 (s, 1H), 7.74 (d, *J* = 7.2 Hz, 1H), 7.66 – 7.49 (m, 3H), 7.42 (s, 1H), 6.95 (d, *J* = 2.4 Hz, 1H), 6.85 (s, 2H), 6.58 (d, *J* = 2.1 Hz, 2H), 6.47 (d, *J* = 2.0 Hz, 1H), 3.70 (s, 6H). ^{13}C NMR (75 MHz, DMSO) δ 168.9, 160.8, 150.7, 145.4, 137.9, 132.4, 131.4, 128.9, 126.6, 125.9, 124.6, 124.4, 123.7, 121.6, 119.5, 117.3, 111.8, 105.6, 99.0, 66.4, 55.6. mp 334.8–338.4 °C. $[\alpha]_D$= +169° (*c* 1, MeOH). ν_{max} (neat): 3262, 1680, 1455, 1154, 699, 582 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{20}ClN_2O_3$ 419.1162; Found 419.1181. t_{R1} = 43.8 min (major), t_{R2} = 55.7 min (minor) (Daicel Chiralpack IC-3, 10% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(5-bromo-1H-indol-3-yl)-3-(3,5-dimethoxyphenyl)isoindolin-1-one (31). White solid. Yield: 60 mg (74 %), 98:2 e.r. Column chromatography eluents: petroleum ether-ethyl acetate 2:1. ^{1}H NMR (600 MHz, DMSO) δ 11.26 (s, 1H), 9.65 (s, 1H), 7.74 (d, *J* = 7.4 Hz, 1H), 7.65 – 7.58 (m, 2H), 7.57 – 7.50 (m, 1H), 7.35 (d, *J* = 8.6 Hz, 1H), 7.17 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.03 (d, *J* = 1.6 Hz, 1H), 6.95 (d, *J* = 2.4 Hz, 1H), 6.58 (d, *J* = 2.2 Hz, 2H), 6.47 (t, *J*

= 2.1 Hz, 1H), 3.69 (s, 6H). ^{13}C NMR (151 MHz, DMSO) δ 169.0, 160.8, 150.7, 145.4, 136.1, 132.4, 131.4, 129.0, 127.3, 126.4, 124.7, 124.4, 123.7, 122.4, 116.7, 114.3, 111.9, 105.6, 99.0, 66.3, 55.7. mp 303.2–305.9 °C. Solution of the sample is too opaque for $[\alpha]_D$ measurement. ν_{max} (neat): 3287, 1677, 1315, 1158, 697, 590 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{20}BrN_2O_3$ 463.0657; Found 463.0640. t_{R1} = 11.8 min (major), t_{R2} = 18.2 min (minor) (Daicel Chiralpack IC-3, 20% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(3,5-dimethoxyphenyl)-3-(5-nitro-1H-indol-3-yl)isoindolin-1-one (32). Yellow solid. Yield: 30 mg (40 %), >99.5:0.5 e.r. Column chromatography eluents: petroleum ether-ethyl acetate 2:1. ^{1}H NMR (600 MHz, DMSO) δ 11.80 (s, 1H), 9.77 (s, 1H), 7.96 (dd, *J* = 9.0, 2.3 Hz, 1H), 7.85 (d, *J* = 2.2 Hz, 1H), 7.79 – 7.75 (m, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.62 (td, *J* = 7.5, 1.2 Hz, 1H), 7.59 – 7.54 (m, 2H), 7.18 (s, 1H), 6.61 (d, *J* = 2.2 Hz, 2H), 6.49 (t, *J* = 2.2 Hz, 1H), 3.69 (s, 6H). ^{13}C NMR (75 MHz, DMSO) δ 169.0, 160.9, 150.4, 145.1, 140.8, 140.6, 132.6, 131.3, 129.2, 128.7, 124.7, 123.8, 119.7, 117.4, 117.3, 112.8, 105.5, 99.2, 66.1, 55.7. mp 134.5–138.7 °C. $[\alpha]_D$= –27° (*c* 1, MeOH). ν_{max} (neat): 3208, 2931, 1687, 1332, 1052, 742, 598 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{20}N_3O_5$ 430.1403; Found 430.1382. t_{R1} = 33.5 min (major), t_{R2} = 61.6 min (minor) (Daicel Chiralpack IC-3, 30% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(3,5-dimethoxyphenyl)-3-(6-fluoro-1H-indol-3-yl)isoindolin-1-one (33). White solid. Yield: 66 mg (94 %), 99.5:0.5 e.r. Column chromatography eluents: petroleum ether-ethyl acetate 2:1. ^{1}H NMR (300 MHz, DMSO) δ 11.09 (s, 1H), 9.58 (s, 1H), 7.74 (d, *J* = 7.3 Hz, 1H), 7.65 – 7.49 (m, 3H), 7.14 (dd, *J* = 10.0, 2.2 Hz, 1H), 6.93 – 6.78 (m, 2H), 6.71 (td, *J* = 9.5, 2.3 Hz, 1H), 6.59 (d, *J* = 2.1 Hz, 2H), 6.51 – 6.41 (m, 1H), 3.68 (s, 6H). ^{13}C NMR (75 MHz, DMSO) δ 168.9, 159.2 (d, *J* = 235.9 Hz), 150.8, 145.5, 137.4 (d, *J* = 12.6 Hz), 132.3, 131.5, 128.9, 125.4, 124.6, 123.6, 122.4, 121.3 (d, *J* = 10.0 Hz), 117.2, 107.7 (d, *J* = 24.2 Hz), 105.6, 99.0, 98.1 (d, *J* = 25.4 Hz), 66.5, 55.6. mp 244.5–247.0 °C. Solution of the sample is

too opaque for $[\alpha]_D$ measurement. ν_{max} (neat): 3321, 1677, 1589, 1312, 1157, 800, 697 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{24}H_{20}FN_2O_3$ 403.1458; Found 403.1475. t_{R1} = 42.8min (major), t_{R2} = 50.3 min (minor) (Daicel Chiralpack IC-3, 20% IPA in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(1H-indol-3-yl)-2-methyl-3-phenylisoindolin-1-one (34). White solid. Yield: 62 mg (88 %), 63:37 e.r. Column chromatography eluents: petroleum ether-ethyl acetate 2:1. ^1H NMR (300 MHz, DMSO) δ 11.29 (s, 1H), 7.83 – 7.77 (m, 1H), 7.54 – 7.48 (m, 3H), 7.44 – 7.34 (m, 6H), 7.09 – 7.01 (m, 2H), 6.83 – 6.75 (m, 1H), 6.45 (d, *J* = 8.1 Hz, 1H), 2.79 (s, 3H). ^{13}C NMR (75 MHz, DMSO) δ 167.4, 151.3, 140.7, 137.4, 132.5, 130.6, 129.2, 128.8, 128.3, 127.3, 126.7, 125.8, 124.1, 123.4, 121.7, 119.9, 119.5, 113.2, 112.6, 71.5, 26.3. mp 244.5–247.0 °C. ν_{max} (neat): 3260, 1671, 1380, 818, 759 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{19}N_2O$ 339.1497; Found 339.1501. t_{R1} = 21.4 min (major), t_{R2} = 29.5 min (minor) (AD, 10% EtOH in hexane, 1.0 mL/min, 220 nm).

(*S*)-3-(1-benzyl-1H-indol-3-yl)-3-phenylisoindolin-1-one (35). White solid. Yield: 75 mg (81 %), 47:53 e.r. Column chromatography eluents: petroleum ether-ethyl acetate 2:1. ^1H NMR (300 MHz, DMSO) δ 9.64 (s, 1H), 7.76 (d, *J* = 7.2 Hz, 1H), 7.69 – 7.45 (m, 5H), 7.43 – 7.20 (m, 7H), 7.20 – 7.10 (m, 3H), 7.09 – 6.99 (m, 1H), 6.87 – 6.74 (m, 2H), 5.39 (s, 2H). ^{13}C NMR (75 MHz, DMSO) δ 168.9, 151.2, 143.2, 138.6, 137.3, 132.4, 131.5, 129.0, 128.8, 128.6, 127.9, 127.8, 127.4, 126.8, 126.3, 124.6, 123.7, 122.0, 120.8, 119.4, 117.0, 110.9, 66.6, 49.5. mp 244.5 – 247.0 °C. ν_{max} (neat): 3058, 1684, 1351, 1175, 739, 690 cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{29}H_{23}N_2O$ 415.1810; Found 415.1805. t_{R1} = 16.6 min (major), t_{R2} = 17.0 min (minor) (Daicel Chiralpack IC-3, 20% IPA in hexane, 1.0 mL/min, 220 nm).

Acknowledgements

This work was supported by the Abbvie-Croatian Science Foundation Young Researcher Grant 2015 and Science and Technology Commission of Shanghai Municipality (16490712200). We are grateful to the Croatian Academy of Sciences and Arts, and to the Chinese Academy of Sciences.

Supporting Information: ^{1}H and ^{13}C NMR spectra, HPLC traces, the assignation of absolute stereochemistry, complete catalyst screening, and DFT calculation parameters.

References

(1) (a) Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach*; Wiley: Chichester, 2009. (b) Sidhu, P. S.; Nassif, N.; McCallum, M. M.; Teske, K.; Feleke, B.; Yuan, N. Y.; Nandhikonda, P.; Cook, J. M.; Singh, R. K.; Bikle, D. D.; Arnold, L. A. *ACS Med. Chem. Lett.* **2014**, *5*, 199–204. (c) Sidhu, P. S.; Teske, K.; Feleke, B.; Yuan, N. Y.; Guthrie, M. L.; Fernstrum, G. B.; Vyas, N. D.; Han, L.; Preston, J.; Bogart, J. W.; Silvaggi, N. R.; Cook, J. M.; Singh, R. K.; Bikle, D. D.; Arnold, L. A. *Cancer Chemother. Pharmacol.* **2014**, *74*, 787–798. (d) Zhu, J.; Chen, H.; Guo, X. E.; Qiu, X.-L.; Hu, C.-M.; Chamberlin, A. R.; Lee, W.-H. *Eur. J. Med. Chem.* **2015**, *96*, 196–208. (e) Atta-ur-Rahman; Basha, A. *Indole Alkaloids*; Harwood Academic: Chichester, 1998.

(2) For reviews on asymmetric aza-Friedel-Crafts reaction, see: (a) Poulsen, T. B.; Jørgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903–2915. (b) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626–2704. (c) You, S.-L.; Cai, Q.; Zeng, M. *Chem. Soc. Rev.* **2009**, *38*, 2190–2201. (d) Zeng, M.; You, S.-L. *Synlett* **2010**, *9*, 1289–1301. (e) Vesely, J.; Rios, R. *Chem. Soc. Rev.* **2014**, *43*, 611–630.

(3) (a) Wu, L.; Liu, R.; Zhang, G.; Wang, D.; Wu, H.; Gao, J.; Jia, Y. *Adv. Synth. Catal.* **2015**, 709–713. (b) Kumari, P.; Bera, P. K.; Khan, N.; Kureshy, R.; Abdi, S.; Bajaj, H. C. *Catal. Sci. Technol* **2014**, *4*, 563–568. (c) Jia, Y. X.; Xie, J. H.; Duan, H. F.; Wang, L. X.; Zhou, Q. L. *Org. Lett.* **2006**, *8*, 1621–1624. (d) Johannsen, M. *Chem. Commun.* **1999**, 2233-2234. (e) Saaby, S.; Fang, X.; Gathergood, N.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 4114–4116. (f) Saaby, S.; Bayon, P.; Aburel, P. S.; Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4352–4361.

(4) Wang, Y. Q.; Song, J.; Hong, R.; Li, H.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156–8157.

(5) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804–11805.

(6) (a) Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, 292–293. (b) Kang, Q.; Zhao, Z.; You, S.-L. *J. Am. Chem. Soc.* **2007**, *129*, 1484–1485. (c) Rowland, G. B.; Rowland, E. B.; Liang, Y.; Perman, J. A.; Antilla, J. C. *Org. Lett.* **2007**, *9*, 2609–2611. (d) Kang, Q.; Zheng, X. J.; You, S.-L. *Chem. Eur. J.* **2008**, *14*, 3539–3542. (e) Osorio-Planes, L.; Rodríguez-Escrich, C.; Pericàs, M. A. *Chem. Eur. J.* **2014**, *20*, 2367–2372. (f) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047–9153.

(7) Tsuchida, K.; Senda, Y.; Nakajima, K.; Nishibayashi, Y. *Angew. Chem. Int. Ed.* **2016**, *8656*, 9880–9884.

(8) Dasgupta, S.; Liu, J.; Shoffler, C. A.; Yap, G. P. A.; Watson, M. P. *Org. Lett.* **2016**, *18*, 6006–6009.

(9) Nakamura, S.; Matsuda, N.; Ohara, M. *Chem. Eur. J.* **2016**, *22*, 9478–9482.

(10) Rueping, M.; Raja, S.; Núñez, A. *Adv. Synth. Catal.* **2011**, *353*, 563–568.

(11) Feng, J.; Yan, W.; Wang, D.; Li, P.; Sun, Q.; Wang, R. *Chem. Commun.* **2012**, *48*, 8003–8005.

(12) Kano, T.; Takechi, R.; Kobayashi, R.; Maruoka, K. *Org. Biomol. Chem.* **2014**, *12*, 724–727.

(13) Yu, X.; Wang, Y.; Wu, G.; Song, H.; Zhou, Z.; Tang, C. *Eur. J. Org. Chem.* **2011**, 3060–3066.

(14) Aranzamendi, E.; Sotomayor, N.; Lete, E. *J. Org. Chem.* **2012**, *77*, 2986–2991.

(15) Nishimura, T.; Noishiki, A.; Tsui, G. C.; Hayashi, T. *J. Am. Chem. Soc.* **2012**, *134*, 5056–5059.

(16) Nishimura, T.; Noishiki, A.; Ebe, Y.; Hayashi, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 1777–1780.

(17) Nagamoto, M.; Yamauchi, D.; Nishimura, T. *Chem. Commun.* **2016**, *52*, 5876–5879.

(18) Zhou, B.; Li, K.; Jiang, C.; Lu, Y.; Hayashi, T. *Adv. Synth. Catal.* **2017**, *359*, 1969–1975.

(19) Chen, M.-W.; Chen, Q.-A.; Duan, Y.; Ye, Z.-S.; Zhou, Y.-G. *Chem. Commun.* **2012**, *48*, 1698–1700.

(20) Zhou, J. Q.; Sheng, W. J.; Jia, J. H.; Ye, Q.; Gao, J. R.; Jia, Y. X. *Tetrahedron Lett.* **2013**, *54*, 3082–3084.

(21) Suneja, A.; Unhale, R. A.; Singh, V. K. *Org. Lett.* **2017**, *19*, 476–479.

(22) Unhale, R. A.; Molleti, N.; Rana, N. K.; Dhanasekaran, S.; Bhandary, S.; Singh, V. K. *Tetrahedron Lett.* **2017**, *58*, 145–151.

(23) (a) Sućˊ, J.; Dokli, I.; Gredičak, M. *Chem. Commun.* **2016**, *52*, 2071–2074. (b) Glavač, D.; Gredičak, M. *Synlett* **2017**, *28*, 889–897.

(24) Xu, F.; Huang, D.; Han, C.; Shen, W.; Lin, X.; Wang, Y. *J. Org. Chem.* **2010**, *75*, 8677–8680.

(25) Glavač, D.; Dokli, I.; Gredičak, M. *Curr. Org. Chem.* **2017**, *21*, 1335–1340.

(26) (a) Yang, Y.; Zhu, S.-F.; Duan, H.-F.; Zhou, C.-Y.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 2248–2249. (b) Xing, C.-H.; Liao, Y.-X.; Ng, J.; Hu, Q.-S. *J. Org. Chem.* **2011**, *76*, 4125–4131.