Organocatalytic Synthesis of α-Triphenylmethylamines from Diarylketimines and Phenols

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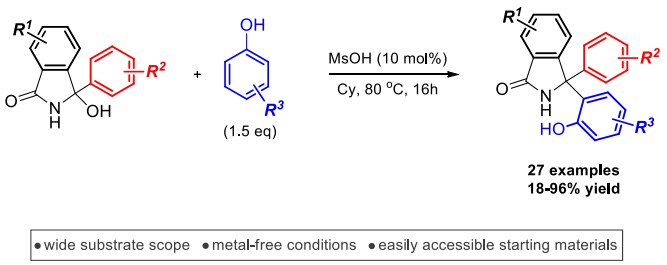
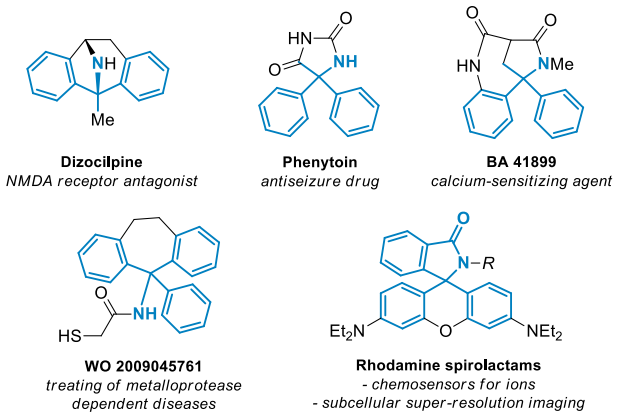
Abstract



Formal Betti reaction between variously substituted phenols and benzophenone-derived imines to afford α-triphenylmethylamines is reported. Key to success of this transformation is the *in situ* generation of the reactive benzophenone iminium species under organocatalytic conditions. Different phenols reacted smoothly enabling the synthesis of an array of α-triphenylmethylamines, which are highly valued structural motifs in bioactive molecules and chemical sensors.

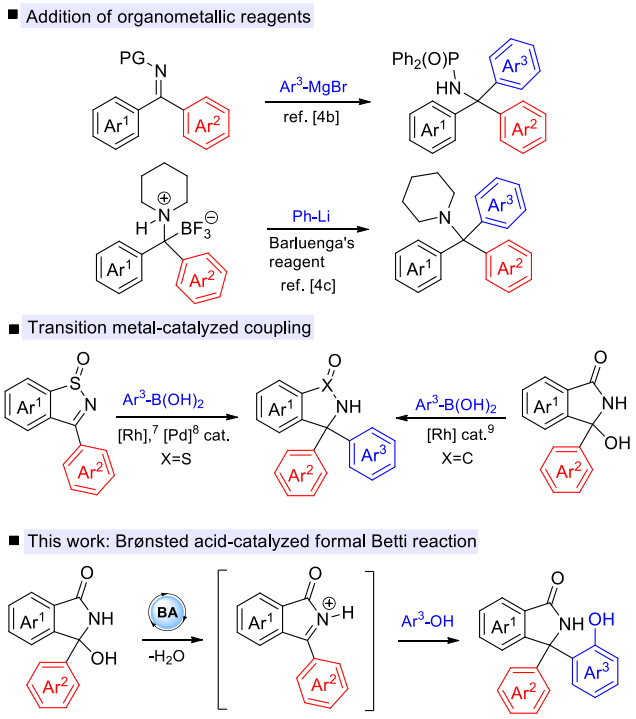
α-Tertiary amines – a class of amines adjacent to a tertiary carbon atom – are an attractive structural subunit in bioactive molecules,[1] chemical sensors[2] and molecules used for subcellular imaging[3] (Scheme 1). The usual strategy for their preparation is addition of carbon nucleophiles to ketimines. It follows that the most efficient approach for the synthesis of α-triphenylmethylamines would be the direct C-arylation of benzophenone imines, as their parent ketones are either commercially available, or can be prepared by well-known synthetic routes. Although the arylation of alkyl-aryl imines is well developed and can provide access to α-diarylalkylmethylamines,[4] methodologies employing additions to benzophenone-derived imines are few and far between.[5] The scarcity of latter methodologies stems from remarkably low reactivity of bis-aromatic ketimines, making an arylation of benzophenone imines even more challenging.



Scheme 1. α-Tertiary amines in bioactive molecules.

A few notable examples of preparation of α-triphenylmethylamines have appeared in the literature, though some of them within general studies on imine reactivity (Scheme 2). The Harutyunyan group[4b] and the Bode group[4c] reported 1,2-additions of Grignard reagents to activated benzophenone imines. During the development of radical coupling reactions between aryl halides and 2-azaallyl species, Walsh et al obtained α-triphenylmethylamine motifs in low yields as side products.[6] In rhodium-catalyzed reactions, a series of enantioenriched α-triphenylmethylamines

were prepared by employing cyclic *N*-sulfonyl benzophenone-derived imines as reactive electrophiles.[7] This concept was extended to a series of palladium-catalyzed transformations,[8] as well as to cyclic amides.[9]



Scheme 2. Strategies towards α-triphenylmethylamines.

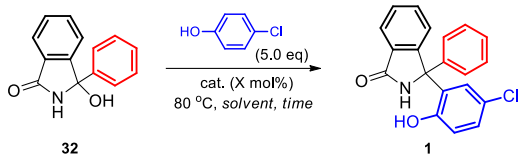
In contrast to these elegant examples, to the best of our knowledge there are no reports on the synthesis of α-triphenylmethylamines under organocatalytic conditions. Development of such protocols would add a new dimension to already existing methods, allowing more versatility in the preparation of these valuable structural units.

Herein, we report a Brønsted acid-catalyzed formal Betti reaction – a 1,2-addition of phenols to *N*-acyl benzophenone-ketimines, generated *in situ* from α^N-hydroxy amides. The Betti reaction is a Mannich-type multicomponent reaction between aldehydes, primary amines, and naphthols for the synthesis of α-secondary amines, so-called Betti bases.[10] Although phenols can be used in the Betti reaction, 2-naphthols are preffered nucleophiles because of their higher reactivity in

comparison to standard phenol derivatives, especially in rare examples describing the formation of α-diarylalkylmethylamine products.[11] In recent years, a number of methodologies were developed where reactive imine species were formed *in situ* from their stable precursors, 3-hydroxyisoindolinones, and utilized in various transformations.[12] Based on reported strategies, we reasoned that benzophenone-derived iminium species generated in this way might act as highly reactive electrophiles for poor nucleophiles, such as phenols, and enable 1,2-addition of aryl rings in a formal Betti reaction.

We started our investigations by combining 3-phenyl 3-hydroxyisoindolinone **32** with *p*-chlorophenol in the presence of various Brønsted and Lewis acids (Table 1).

Table 1. Screening of reaction conditions.[a]



Entry	Cat. (mol%)	Solvent	Time (h)	Yield (%)
1	*p*TsOH (20)	toluene	16	77
2	PhCOOH (20)	toluene	60	27
3	AcOH	toluene	60	67
4	H_2SO_4 (20)	toluene	10	50
5	MsOH (20)	toluene	12	98
6	BF_3 x OEt_2 (20)	toluene	48	43
7	$SnCl_2$ (20)	toluene	24	53
8	$Sc(OTf)_2$ (20)	toluene	24	90
9	MsOH (20)	*o*-xylene	24	82
10	MsOH (20)	cyclohexane	4	92
11	MsOH (20)	heptane	5	70
12	**MsOH (10)**	**cyclohexane**	**16**	**89**[b]
13	MsOH (5)	cyclohexane	48	traces[b]
14	MsOH (10)	cyclohexane	72	88[b,c]

[a]Reactions were carried out on 0.2 mmol scale. [b]*p*-Chlorophenol (1.5 eq). [c]60 °C.

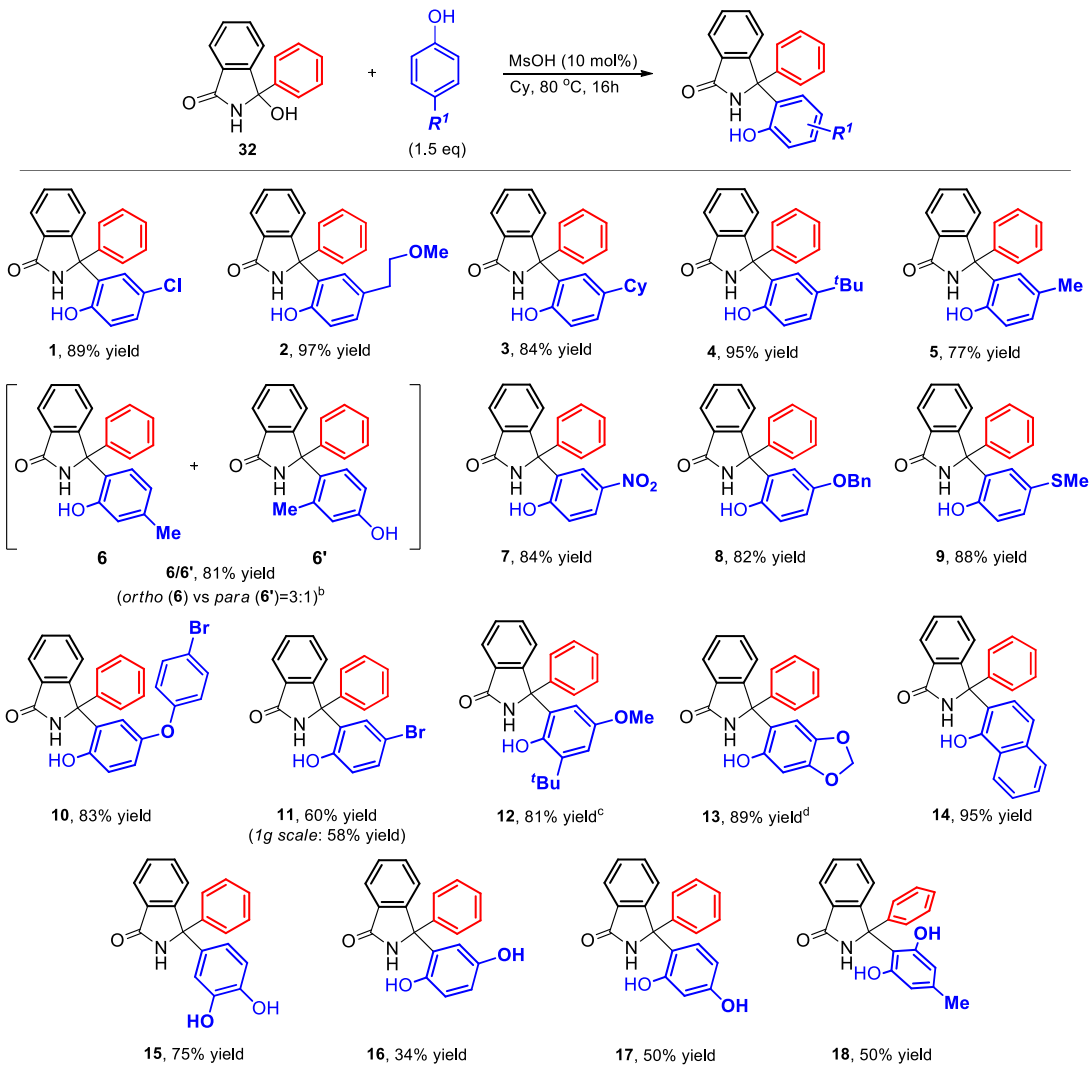
Our initial attempt with *p*-toluenesulfonic acid in toluene at 80 °C led to the desired product **1** within 16 hours (77% yield, entry 1). Employing carboxylic acids as catalysts substantially prolonged reaction time; after 60 hours, product **1** was isolated in 27% (benzoic acid, entry 2) and 67% (acetic acid, entry 3) yield, respectively. By using catalytic amount of sulfuric acid, the reaction was completed within 10 hours, though decomposition products were observed along with the product (50% yield, entry 4). On the other hand, methanesulfonic acid yielded product **1** in almost quantitative yield after 12 hours (entry 5).

Next, the catalytic efficiency of various Lewis acids was investigated. In general, reaction times were significantly prolonged. BF_3 x OEt_2 (43% yield, 48 hours, entry 6) and $SnCl_2$ (53% yield, 24 hours, entry 7) successfully catalyzed the transformation in moderate yields, while substantially better yield was obtained by employing $Sc(OTf)_2$ as catalyst (90% yield, 24 hours, entry 8).

After identifying methanesulfonic acid as the catalyst of choice for the transformation, the influence of solvent, temperature, and catalyst/reagent loading was investigated. By conducting the reaction in *o*-xylene for 24 hours at 80 °C, product **1** was isolated in 82% yield (entry 9). Significant improvements in terms of reaction times were observed when cyclohexane (92% yield, 4 hours, entry 10) and heptane (70% yield, 5 hours, entry 11) were used as solvents, respectively. The reaction maintained its effectiveness when the amount of *p*-chlorophenol was lowered to 1.5 eq, accompanied by 10 mol% catalyst loading (89% yield, 16 hours, entry 12). Further decrease of catalyst loading to 5 mol% resulted only in traces of the product, even after 48 hours (entry 13). Finally, performing the reaction under entry 11 parameters at 60 °C prolonged its time to 72 hours (entry 14). Hence, chosen reaction conditions for the formal Betti reaction include diarylketimine precursor (1.0 eq), phenol (1.5 eq) and methanesulfonic acid (10 mol%) in cyclohexane at 80 °C.

With the optimized reaction conditions in hand (in terms of ratio between the catalyst and reagent loading, and obtained yield), we turned our attention to investigate the substrate scope and reaction limitations (Table 2).

Table 2. Substrate scope I: Phenols.[a]



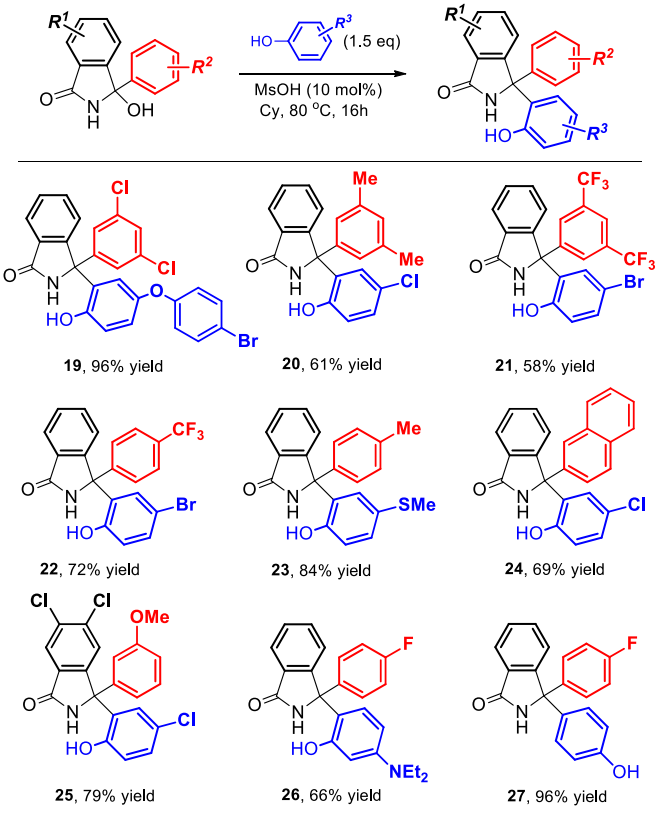
[a]Reactions were carried out on 0.2 mmol scale. [b]Inseparable mixture of *ortho* and *para* addition products with respect to hydroxy group. Ratio determined by ^{1}H NMR. [c]2-(tert-butyl)-4-methoxyphenol (5.0 eq), *p*TsOH (20 mol%), 48h. [d]Sesamol (1.5 eq), *p*TsOH (20 mol%), 16h.

The reaction maintained its effectiveness upon changing the halogen atom in *para* position of the phenol to alkyl groups (**2**–**5**). In order to investigate regioselectivity of the reaction, *m*-cresol was employed as a nucleophile. Under the same reaction conditions, products **6** and **6'** were isolated in

81% yield as an inseparable mixture of *ortho* (**6**) vs *para* (**6'**) addition products (with respect to hydroxy group) in 3:1 ratio. The ratio between two regioisomers did not significantly change when the reaction was performed at 60 °C, or at 100 °C, respectively (see Supporting Information for details). Introduction of activating and deactivating groups in *para* position had little or no influence on product yield or the reaction course (**7**–**10**, >80% yield). In comparison to *p*-chlorophenol, the reaction with *p*-bromophenol resulted in significantly lower yield (**11**, 60% yield), however, the reaction did not lose its effectiveness when performed on a 1.0 gram scale. Under the same conditions, the reaction with 2,4-disubstituted phenol afforded complex reaction mixture in which product **12** was not detected. The reason most likely lies in the cleavage of aryl-methyl ethers with methanesulfonic acid under elevated temperatures.[13] By switching the catalyst to *p*-toluenesulfonic acid and by increasing the amount of phenol to 5.0 eq, product **12** was obtained in 81% yield. Following the same reasoning, the reaction conditions used for the formation of **12** were also employed in the synthesis of **13**, and sesamol succesfully reacted with 3-hydroxyisoindolinone **32** (**13**, 89% yield). Under the standard reaction conditions, the reaction with 1-naphthol resulted in almost quantitative yield of product **14**.

Reactions with different dihydroxybenzenes were investigated next. Employing catechol as a nucleophile resulted in addition through *para* position with respect to one of hydroxy groups, generating more favorable 1,2,5-trisubstituted product **15** in 75% yield. In reactions with quinol and resorcinol, products **16** and **17** were isolated in low yields (34% and 50% yield, respectively). Since starting isoindolinone alcohol **32** was completely consumed in both reactions, this observation can be attributed to problems encountered during the isolation of products. By conducting the reaction with orcinol, the addition occured almost exclusively through carbon positioned between two hydroxy groups, with only traces of the other regioisomer visible in NMR spectra (**18**, 50% yield).

Table 3. Substrate scope II: Imine precursors.[a]



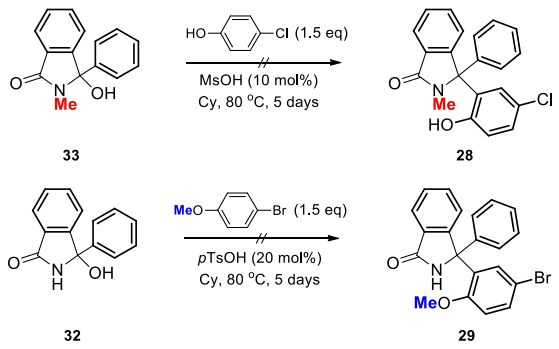
[a]Reactions were carried out on 0.2 mmol scale unless otherwise noted (see Experimental section).

Next, various imine precursors were submitted to the reaction with a range of phenol derivatives (Table 3). In general, introduction of different substituents in *para* and *meta* positions on the 3-aryl ring of 3-hydroxyisoindolinone provided products in good to excellent yields, regardless of the type of phenol derivative used. The reaction was tolerant of chloro, methyl, and trifluoromethyl substituents on both *meta* positions of the 3-phenyl ring (**19**–**21**), as well as with *para* substitutions on 3-phenyl ring (**22** and **23**). Placement of 2-naphtyl substituent also had no significant influence on the reaction outcome (**24**, 69% yield), and similar trend was observed with imine precursor possessing substituted isoindolinone benzene ring (**25**,

79% yield). Employing *m*-diethylamino phenol as a nucleophile provided only one regioisomer **26** in 66% yield, most likely because of increased steric hindrance around *para* position (with respect to hydroxy group). Finally, we investigated regioselectivity of the reaction when unsubstituted phenol was used, and only *para* regioisomer **27** was isolated in 96% yield.

On the other hand, the transformation did not proceed with *ortho* substituted 3-aryl substituents on the imine precursor. With mesityl substitution, only starting materials were retrieved, and the same result was obtained with 3-(*o*-methoxylphenyl) substituent. This limitation most likely stems from the increased steric hindrance around the reactive center.

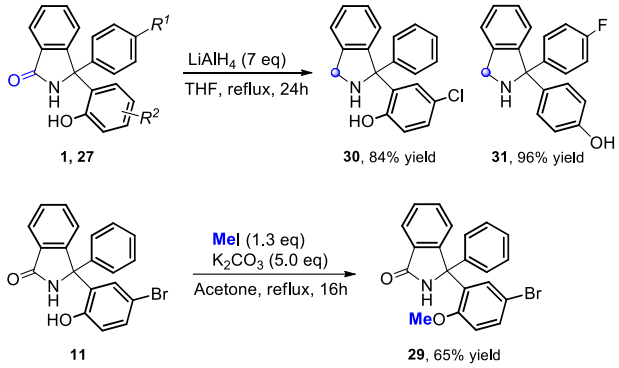
In order to get a better insight on the reactivity of both reaction partners, experiments with *N*-protected isoindolinone alcohol and *O*-protected phenol were performed (Scheme 3).



Scheme 3. Control experiments.

When *N*-methyl 3-hydroxyisoindolinone **33** and *p*-chlorophenol were submitted to reaction conditions, product **28** was not observed even after substantially prolonged reaction time. Likewise, in a reaction between isoindolinone alcohol **32** and *p*-bromoanisole catalyzed by *p*-toluenesulfonic acid, only starting materials were isolated from the reaction mixture. These experiments indicate that N*H* is required for the generation of reactive benzophenone iminium species, and that O*H* plays an important role in the nucleophilicity of the phenyl ring.

Finally, we explored possibilities of synthetic utility of obtained products (Scheme 4). In addition to the successful scale-up reaction (**11**, Table 2), products of the formal Betti reaction were used in further transformations. Thus, $LiAlH_4$-mediated reduction of amide group afforded products bearing α,α-disubstituted isoindoline core in very good and excellent yields (**30**, 84% yield, **31**, 96% yield). Since one of the control experiments showed that the transformation does not proceed with anisole derivatives as nucleophiles, access to these compounds was demonstrated by employing standard *O*-alkylation (**29**, 65% yield).



Scheme 4. Demonstration of synthetic utility.

In conclusion, we have developed a Brønsted acid-catalyzed formal Betti reaction between phenols and *in situ* generated diarylketimines from 3-aryl 3-hydroxyisoindolinones. The transformation proceeds smoothly with a broad range of phenols and benzophenone-derived imines to afford α-triphenylmethylamines in good to excellent yields. Development of the stereoselective variant of this transformation is currently under way, and will be reported in due course.

Experimental Section

General Information. Chemicals and solvents were purchased from commercial suppliers and used as received. Unless otherwise noted, all compounds were prepared according to the General procedure. Flash column chromatography was carried out using silica gel (Merck, 40−63 μm

particle size). NMR spectra were recorded on Bruker Avance 600 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 nondeuterated solvent peak. If not otherwise noted, spectra were acquired at 298 K. Structural assignment were made with additional information from HMQC and HMBC experiments. Infrared spectra were recorded on a Varian UV/vis Cary 4000 spectrometer equipped with an attenuated total reflectance attachment with internal calibration. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}). High resolution mass spectrometry (HRMS) was performed on a 4800 Plus MALDI TOF/TOF Analyzer. Melting points were determined using an Electrothermal 9100 apparatus in open capillaries and are uncorrected. Substrates, 3-aryl 3-hydroxyisoindolinones **32−41** (see Supporting Information), were synthesized in high yields from readily available starting materials, by employing addition of a Grignard or organolithium reagent to phthalimide.[14]

General procedure. To a suspension of 3-aryl 3-hydroxyisoindolinone (0.2 mmol) in cyclohexane (2.0 mL) was added MsOH (19 mg, 14 μL, 0.02 mmol) at 25 °C. After stirring for 10 min, phenol derivative (0.3 mmol) was added, and the resulting reaction mixture was stirred in an oil bath for 16 hours at 80 °C. Full consumption of the starting material was confirmed by TLC, and the crude reaction mixture was directly purified by column chromatography on silica gel.

*3-(5-Chloro-2-hydroxyphenyl)-3-phenylisoindolin-1-one (**1**)*. Colorless solid. Yield: 66 mg (89%). Column chromatography eluents: dichloromethane−acetone 20:1. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.09 (s, 1H), 9.10 (s, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 7.2 Hz, 1H), 7.63 (t, J = 7.8 Hz, 1H), 7.53 (t, J = 7.2 Hz, 1H), 7.28-7.26 (m, 2H), 7.24-7.21 (m, 2H), 7.17-7.14 (m, 3H), 6.84 (d, J = 8.4 Hz, 1H). $^{13}C\{1H\}$ NMR (151 MHz, DMSO-d_6) δ 168.2, 154.3, 149.2, 143.0, 132.0, 131.1, 130.2, 128.9, 128.6, 128.3, 126.9, 126.7, 125.3 (overlapping another signal), 123.4, 121.9, 118.0,

68.7 - signals of the residual solvents (acetone and DCM) are visible in spectra. Mp 299.8–305.3 °C. ν_{max} (neat): 3370, 3178, 2955, 2359, 1676, 1468, 1316, 1075, 756, 695, 599, 533 cm^{-1}. HRMS (MALDI TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{15}ClNO_2$ 336.0713; found 336.0726.

*3-(2-Hydroxy-5-(2-methoxyethyl)phenyl)-3-phenylisoindolin-1-one (**2**).* Colorless solid. Yield: 77 mg (97%). Column chromatography eluents: dichloromethane−acetone 20:1. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.58 (s, 1H), 8.90 (s, 1H), 7.72 (t, *J* = 6.6 Hz, 2H), 7.61 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.27-7.19 (m, 3H), 7.15-7.13 (m, 2H), 7.06-7.01 (m, 2H), 6.76 (d, *J* = 8.1 Hz, 1H), 3.41 (t, *J* = 6.9 Hz, 2H), 3.18 (s, 3H), 2.64 (t, *J* = 6.9 Hz, 2H). ^{13}C{1H} NMR (300 MHz, DMSO-d_6) δ 9.58 (s, 1H), 8.90 (s, 1H), 7.72 (t, *J* = 6.6 Hz, 2H), 7.61 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.27-7.19 (m, 3H), 7.15-7.13 (m, 2H), 7.06-7.01 (m, 2H), 6.76 (d, *J* = 8.1 Hz, 1H), 3.41 (t, *J* = 6.9 Hz, 2H), 3.18 (s, 3H), 2.64 (t, *J* = 6.9 Hz, 2H). Mp 237.1–240.9 °C. ν_{max} (neat): 3403, 2360, 1672, 1248, 1112, 699, 606 cm^{-1}. HRMS (MALDI TOF) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{22}NO_3$ 360.1600; found 360.1584.

*3-(5-Cyclohexyl-2-hydroxyphenyl)-3-phenylisoindolin-1-one (**3**).* Colorless solid. Yield: 71 mg (84%). Column chromatography eluents: dichloromethane−acetone 20:1. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.52 (s, 1H), 8.91 (s, 1H), 7.74 (d, *J* = 12.6 Hz, 1H), 7.72 (d, *J* = 12.3 Hz, 1H), 7.62 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.50 (dt, *J* = 7.5, 0.9 Hz, 1H), 7.27-7.18 (m, 3H), 7.14-7.12 (m, 2H), 7.05-7.00 (m, 2H), 6.75 (d, *J* = 8.1 Hz, 1H), 2.35-2.28 (m, 1H), 1.73-1.63 (m, 5H), 1.32-1.12 (m, 5H) - signals of the residual solvents (acetone and DCM) are visible in spectra. ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 168.5, 153.2, 150.0, 143.9, 137.5, 131.9, 131.1, 128.5, 128.3, 127.5, 127.1, 126.9, 125.6, 125.5, 125.3, 123.4, 116.4, 69.3, 43.1, 34.4, 26.4, 25.7. Mp 305.8–307.0 °C. ν_{max} (neat): 3424, 2924, 2360, 1662, 1428, 1359, 1246, 1117, 750, 696, 579 cm^{-1}. HRMS (MALDI TOF) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{26}NO_2$ 384.1964; found 384.1952.

*3-(5-(tert-Butyl)-2-hydroxyphenyl)-3-phenylisoindolin-1-one (**4**).* Colorless solid. Yield: 75 mg (95%). Column chromatography eluents: dichloromethane−acetone 20:1. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.52 (s, 1H), 8.91 (s, 1H), 7.75-7.70 (m, 2H), 7.69 (dt, J = 7.5, 1.2 Hz, 1H), 7.51 (t, J = 8.1 Hz, 1H), 7.28-7.13 (m, 8H), 6.76 (d, J = 8.1 Hz, 1H), 1.16 (s, 9H). ^{13}C{1H} NMR (75 MHz, DMSO-d_6) δ 168.6, 152.9, 150.0, 144.0, 140.5, 131.8, 131.1, 128.5, 128.3, 127.0, 126.9, 126.6, 125.6, 125.3, 124.1, 123.5, 116.0, 69.4, 34.0, 31.5. Mp 284.1–285.0 °C. ν_{max} (neat): 3407, 2962, 2360, 1681, 1416, 1373, 1265, 1127, 823, 702, 608 cm^{-1}. HRMS (MALDI TOF) *m/z*: [M + H]$^{+}$ calcd for $C_{24}H_{25}NO_2$ 358.1807; found 358.1817.

*3-(2-Hydroxy-5-methylphenyl)-3-phenylisoindolin-1-one (**5**).* Colorless solid. Yield: 53 mg (77%). Column chromatography eluents: dichloromethane−acetone 50:1. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.51 (s, 1H), 8.88 (s, 1H), 7.73 (d, J = 14.3 Hz, 1H), 7.71 (d, J = 14.1 Hz, 1H), 7.61 (t, J = 15.0 Hz, 1H), 7.50 (t, J = 15.0 Hz, 1H), 7.26-7.23 (m, 2H), 7.20-7.15 (m, 3H), 7.00 (s, 1H), 6.97 (d, J = 7.8 Hz, 1H), 6.73 (d, J = 7.8 Hz, 1H), 2.15 (s, 3H). ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 168.2, 152.9, 149.8, 143.9, 131.7, 131.1, 129.5, 128.3, 128.1, 127.7, 127.5, 126.72, 126.67, 125.5, 125.2, 123.2, 116.3, 69.0, 20.4 - signals of the residual solvents (acetone and DCM) are visible in spectra. Mp 302.6–305.3 °C. ν_{max} (neat): 3401, 2360, 1673, 1418, 1369, 1249, 1059, 759, 697, 566 cm^{-1}. HRMS (MALDI TOF) *m/z*: [M + H]$^{+}$ calcd for $C_{21}H_{18}NO_2$ 316.1338; found 316.1350.

*3-(2-Hydroxy-4-methylphenyl)-3-phenylisoindolin-1-one (**6**)* and *3-(4-Hydroxy-2-methylphenyl)-3-phenylisoindolin-1-one (**6'**).* Inseparable mixture of regioisomers **6** and **6'** in in 3:1 relative ratio as colorless solid. Regioisomers and their ratio was determined on the basis of ^{1}H, HSQC and HMBC NMR experiments (see Supporting Information). Yield: 56 mg (81%). Column chromatography eluents: dichloromethane−acetone 50:1. **6:** ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.63 (s, 1H), 8.86 (s, 1H), 7.69 (d, J = 7.2 Hz, 1H), 7.66 (d, J = 7.2 Hz, 1H), 7.59 (t, J = 7.2 Hz, 1H),

7.49 (t, *J* = 6.6 Hz, 1H), 7.32 (d, *J* = 4.2 Hz, 1H), 7.23 (d, *J* = 7.2 Hz, 2H), 7.17 (d, *J* = 7.2 Hz, 2H), 7.02 (d, *J* = 7.8 Hz, 1H), 6.64 (s, 1H), 6.57 (d, *J* = 9.0 Hz, 1H), 2.20 (s, 3H). ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 168.3, 155.1, 149.9, 143.9, 138.7, 131.7, 131.1, 128.6, 128.1, 127.1, 126.7, 125.4, 125.2, 125.1, 123.2, 119.0, 117.0, 68.8, 20.6 - signals of the residual solvents (acetone and DCM) are visible in spectra. **6':** ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.40 (s, 1H), 9.36 (s, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 6.72 (d, *J* = 8.4 Hz, 1H), 6.47 (dd, *J* = 9.0, 3.0 Hz, 1H), 1.76 (s, 3H) - rest of the signals are overlapped by the signals of the major regioisomer. ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.1, 156.9, 150.8, 144.5, 138.5, 131.9, 130.7, 129.0, 125.3, 125.3, 125.1, 123.3, 119.4, 111.8, 70.4, 30.7, 21.4 - rest of the signals are overlapped by the signals of the major regioisomer. Mp 256.3–257.3 °C. ν_{max} (neat): 3410, 3050, 1672, 1240, 695 cm^{-1}. HRMS (MALDI TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{18}NO_2$ 316.1338; found 316.1332.

*3-(2-Hydroxy-5-nitrophenyl)-3-phenylisoindolin-1-one (**7**).* Yellow solid. Yield: 64 mg (84%). Column chromatography eluents: dichloromethane−acetone 10:1. ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.53 (brs, 1H), 9.33 (s, 1H), 8.13 (dd, *J* = 8.4, 2.4 Hz, 1H), 8.12 (d, *J* = 3.0 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.67 (dt, *J* = 7.8, 0.6 Hz, 1H), 7.56 (dt, *J* = 7.8, 0.6 Hz, 1H), 7.30-7.27 (m, 2H), 7.25-7.23 (m, 1H), 7.21-7.19 (m, 2H), 6.97 (d, *J* = 9.0 Hz, 1H) - signal of the residual solvent (acetone) is visible in spectrum. ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 168.4, 148.9, 142.6, 138.6, 132.2, 131.2, 129.3, 128.9, 128.4, 127.1, 126.0, 125.2, 125.1, 123.5, 123.3, 116.8, 68.6 - one signal in aromatic region is overlapped. Mp 275.7–277.2 °C. ν_{max} (neat): 3432, 3395, 2721, 2358, 1584, 1334, 1079, 695 cm^{-1}. HRMS (MALDI TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{14}N_2O_4$ 347.1032; found 347.1047.

*3-(5-(Benzyloxy)-2-hydroxyphenyl)-3-phenylisoindolin-1-one (**8**).* Colorless solid. Yield: 73 mg (82%). Column chromatography eluents: dichloromethane−acetone 20:1. ^{1}H NMR (600 MHz,

DMSO-d_6) δ 9.34 (s, 1H), 8.88 (s, 1H), 7.71 (d, J = 11.0 Hz, 1H), 7.66 (d, J = 11.7 Hz, 1H), 7.60 (dt, J = 7.5, 1.2 Hz, 1H), 7.51 (dt, J = 7.2 Hz, 1.2 Hz, 1H), 7.36-7.14 (m, 10H), 6.88-6.73 (m, 3H), 4.93 (s, 2H). ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 168.3, 150.4, 149.5, 149.1, 143.6, 137.2, 131.9, 131.0, 128.7, 128.41, 128.36, 128.2, 127.7 (two signals overlapping), 126.8, 125.4, 125.2, 123.3, 116.8, 115.0, 114.6, 69.8, 68.9. Mp 243.8–245.6 °C. ν_{max} (neat): 3396, 2360, 1674, 1428, 1210, 1025, 696, 593 cm^{-1}. HRMS (MALDI TOF) *m/z*: [M + H]$^+$ calcd for $C_{27}H_{22}NO_3$ 408.1600; found 408.1586.

*3-(2-Hydroxy-5-(methylthio)phenyl)-3-phenylisoindolin-1-one (**9**).* Colorless solid. Yield: 67 mg (88%). Column chromatography eluents: dichloromethane−acetone 20:1. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.84 (s, 1H), 9.02 (s, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 7.2 Hz, 1H), 7.62 (dt, J = 7.8, 1.2 Hz, 1H), 7.52 (d, J = 7.2 Hz, 1H), 7.27-7.15 (m, 7H), 6.83 (d, J = 8.4 Hz, 1H), 2.34 (s, 3H)) - signal of the residual solvent (acetone) is visible in spectrum. ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 168.2, 153.7, 149.5, 143.4, 131.8, 131.1, 129.3, 128.9, 128.5, 128.2, 127.4, 126.8, 125.7, 125.4, 125.2, 123.3, 117.4, 68.9, 17.0. Mp 267.3–269.5 °C. ν_{max} (neat): 3406, 2360, 1683, 1408, 1269, 696, 586 cm^{-1}. HRMS (MALDI TOF) *m/z*: [M + H]$^+$ calcd for $C_{21}H_{18}NO_2S$ 348.1058; found 348.1068.

*3-(5-(4-Bromophenoxy)-2-hydroxyphenyl)-3-phenylisoindolin-1-one (**10**).* Colorless solid. Yield: 86 mg (83%). Column chromatography eluents: dichloromethane−acetone 20:1. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.80 (s, 1H), 9.04 (s, 1H), 7.75-7.69 (m, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.52-7.46 (m, 3H), 7.30-7.17 (m, 5H), 6.89-6.84 (m, 5H). ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 168.2, 157.4, 152.0, 149.4, 146.7, 143.3, 132.6, 131.9, 131.1, 129.5, 128.5, 128.2, 126.9, 125.3, 125.2, 123.3, 120.4, 119.1, 117.4, 113.9, 68.8 - one signal in aromatic region is overlapped. Mp

155.5–156.8 °C. ν_{max} (neat): 3417, 3058, 2342, 1670, 1480, 1219, 697, 581 cm^{-1}. HRMS (MALDI TOF) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{19}BrNO_3$ 472.0548; found 472.0546.

*3-(5-Bromo-2-hydroxyphenyl)-3-phenylisoindolin-1-one (**11**).* Colorless solid. Yield: 50 mg (60%). Gram scale reaction: 3-hydroxy-3-phenylisoindolin-1-one **32** (1.0 g, 4.44 mmol) afforded 0.97 g (58%) of the title compound. Column chromatography eluents: dichloromethane−acetone 10:1. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.11 (s, 1H), 9.11 (s, 1H), 7.79 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 7.2 Hz, 1H), 7.63 (dt, J = 7.8, 0.6 Hz, 1H), 7.53 (dt, J = 7.2, 0.6 Hz, 1H), 7.35 (dd, J = 8.4, 2.4 Hz, 1H), 7.28-7.26 (m, 3H), 7.23-7.21 (m, 1H), 7.16-7.15 (m, 2H), 6.79 (d, J = 9.0 Hz, 1H). ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 168.2, 154.8, 149.3, 143.0, 132.0, 131.9, 131.1, 130.7, 129.5, 128.7, 128.3, 127.0, 125.3, 125.2, 123.4, 118.6, 109.5, 68.6. Mp 299.8–305.3 °C. ν_{max} (neat): 3167, 1682, 1217, 1289, 962, 707 cm^{-1}. HRMS (MALDI TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{15}BrNO_2$ 402.0106; found 402.0110.

*3-(3-(tert-Butyl)-2-hydroxy-5-methoxyphenyl)-3-phenylisoindolin-1-one (**12**).* To a suspension of 3-hydroxy-3-phenylisoindolin-1-one **32** (50 mg, 0.22 mmol) in cyclohexane (2.0 mL) was added *p*-TsOH (8.4 mg, 0.04 mmol) at 25 °C. After stirring for 10 min, 2-(*tert*-butyl)-4-methoxyphenol (60 mg, 0.33 mmol) was added, and the resulting reaction mixture was stirred in an oil bath for 48 hours at 80 °C. Full consumption of the starting material was confirmed by TLC and direct flash column chromatography of the reaction mixture (DCM/acetone 10:1) afforded 69 mg (81%) of the title compound as colorless solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.97 (s, 1H), 7.72 (d, J = 7.2 Hz, 1H), 7.61 (dt, J = 7.2 1.2 Hz, 1H), 7.52-7.48 (m, 2H), 7.26-7.24 (m, 2H), 7.20-7.16 (m, 3H), 6.81 (d, J = 3.0 Hz, 1H), 6.69 (s, 1H), 6.44 (d, J = 3.0 Hz, 1H), 3.58 (s, 3H), 1.31 (s, 9H). ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 168.8, 152.5, 150.2, 146.5, 144.0, 143.0, 134.4, 131.9, 130.4, 128.4, 128.3, 126.7, 125.6, 124.4, 123.4, 112.0, 111.4, 69.5, 54.9, 34.8, 29.9. Mp 257.4–258.6 °C. ν_{max}

(neat): 3479, 2947, 2360, 1687, 1198, 1053, 695 cm^{-1}. HRMS (MALDI TOF) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{26}NO_3$ 388.1913; found 388.1913.

*3-(6-Hydroxybenzo[d][1,3]dioxol-5-yl)-3-phenylisoindolin-1-one (**13**).* To a suspension of 3-hydroxy-3-phenylisoindolin-1-one **32** (50 mg, 0.22 mmol) in cyclohexane (2.0 mL) was added *p*-TsOH (8.4 mg, 0.04 mmol) at 25 °C. After stirring for 10 min, sesamol (46 mg, 0.33 mmol, 1.5 eq) was added and the resulting reaction mixture was stirred in an oil bath for 16 hours at 80 °C. Full consumption of the starting material was confirmed by TLC and direct flash column chromatography of the reaction mixture (DCM/acetone 10:1) afforded 68 mg (89%) of the title compound as colorless solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.53 (s, 1H), 8.87 (s, 1H), 7.68 (d, *J* = 8.1 H, 2H), 7.60 (t, *J* = 7.2 Hz, 1H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.25-7.18 (m, 5H), 6.65 (s, 1H), 6.45 (s, 1H), 5.91 (d, *J* = 3.9 Hz, 2H); ^{13}C{1H} NMR (75 MHz, DMSO-d_6) δ 168.2, 150.4, 149.9, 147.2, 144.0, 139.0, 131.8, 131.0, 128.3, 128.1, 126.7, 125.4, 125.2, 123.3, 119.8, 107.1, 101.0, 98.6, 68.8; Mp 192.6-194.9 °C. ν_{max} (neat): 3246, 1681, 1439, 1183, 831, 700, 557; HRMS (MALDI-TOF) m/z: $[M+H]^+$ calcd. for $C_{21}H_{16}NO_4$ 346.1079; found 346.1080.

*3-(1-Hydroxynaphthalen-2-yl)-3-phenylisoindolin-1-one (**14**).* Colorless solid. Yield: 76 mg (95%). Column chromatography eluents: dichloromethane−acetone 5:1. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.77 (s, 1H), 9.13 (s, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.79 (d, *J* = 7.8 Hz, 1H), 7.73 (d, *J* = 7.2 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 1H), 7.49-7.44 (m, 2H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 1H), 7.28-7.26 (m, 2H), 7.23-7.20 (m, 3H); ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 168.5, 150.8, 150.2, 144.6, 134.1, 131.9, 131.2, 128.4, 128.3, 127.8, 126.8, 126.3, 125.5, 125.4, 125.22, 125.18, 125.16, 123.6, 123.3, 121.9, 118.8, 69.4; Mp 258.4–259.1 °C. ν_{max} (neat): 3446, 2359, 1673, 1349, 1195, 750, 580 cm^{-1}; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd. for $C_{24}H_{18}NO_2$ 352.1338; found 352.1331.

*3-(3,4-Dihydroxyphenyl)-3-phenylisoindolin-1-one (**15**).* Colorless solid. Yield: 56 mg (75 %). Column chromatography eluents: dichloromethane−acetone 10:1. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.56 (s, 1H), 8.91 (brs, 2H), 7.68 (d, J = 7.2 Hz, 1H), 7.61(t, J = 7.2 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.49 (t, J = 7.2 Hz, 1H), 7.34-7.26 (m, 5H), 6.64 (d, J = 7.8 Hz, 1H), 6.61 (d, J = 2.4 Hz, 1H), 6.44 (dd, J = 8.4, 2.4 Hz, 1H); ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 168.3, 150.4, 144.9, 144.7, 143.6, 134.0, 131.8, 131.1, 128.2, 127.3, 126.9, 124.7, 123.1, 118.0, 115.1, 114.8, 79.2, 69.8; Mp 162.2-163.0 °C. ν_{max} (neat): 3522, 3354, 3039, 1655, 1283, 1115, 748, 450 cm^{-1}. HRMS (MALDI-TOF) m/z: $[M+H]^+$ calcd. for $C_{20}H_{16}NO_3$ 318.1130; found 318.1134. Regiochemistry of the reaction was confirmed on the basis of 2D NMR spectra (see Supporting Information for details).

*3-(2,5-Dihydroxyphenyl)-3-phenylisoindolin-1-one (**16**).* Colorless solid. Yield: 24 mg (34 %). Column chromatography eluents: dichloromethane−acetone 3:1. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.02 (s, 1H), 8.80 (s, 1H), 8.75 (s, 1H), 7.72-7.66 (m, 2H), 7.62 (t, J = 6.3 Hz, 1H), 7.51 (t, J = 7.2 Hz, 1H), 7.28-7.15 (m, 5H), 6.67-6.55 (m, 3H); ^{13}C{1H} NMR (75 MHz, DMSO-d_6) δ 168.3, 149.8, 149.2, 147.5, 143.8, 131.7, 131.0, 128.4, 128.3, 128.1, 126.7, 125.5, 125.2, 123.2, 117.0, 115.2, 114.5, 68.9; Mp 238.4-239.4 °C. ν_{max} (neat): 3203, 1650, 1424, 1247, 1212, 1112, 695, 589 cm^{-1}. HRMS (MALDI-TOF) m/z: $[M+H]^+$ calcd. for $C_{20}H_{16}NO_3$ 318.1130; found 318.1125.

*3-(2,4-Dihydroxyphenyl)-3-phenylisoindolin-1-one (**17**).* Colorless solid. Yield: 36 mg (50 %). Column chromatography eluents: dichloromethane−acetone 3:1. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.58 (s, 1H), 9.34 (s, 1H), 8.77 (s, 1H), 7.68 (t, J = 7.5 Hz, 1H), 7.62-7.55 (m, 2H), 7.50-7.45 (m, 1H), 7.27-7.16 (m, 5H), 6.89 (d, J = 8.4 Hz, 1H), 6.31 (d, J = 2.4 Hz, 1H), 6.16 (dd, J = 8.7, 2.4 Hz, 1H); ^{13}C{1H} NMR (75 MHz, DMSO-d_6) δ 168.3, 158.2, 156.2, 150.2, 144.3, 131.6, 131.1, 128.1, 127.9, 126.6, 125.4, 125.2, 123.2, 118.8, 105.1, 103.6, 79.2, 68.7; Mp 287.8-289.0 °C. ν_{max} (neat): 3204, 1651, 1424, 1210, 1132, 1112, 901, 695 cm^{-1}. HRMS (MALDI-TOF) m/z:

$[M+H]^+$ calcd. for $C_{20}H_{16}NO_3$ 318.1130; found 318.1128. Regiochemistry of the reaction was confirmed on the basis of 2D NMR spectra (see Supporting Information for details).

*3-(2,6-Dihydroxy-4-methylphenyl)-3-phenylisoindolin-1-one (**18**).* Colorless solid. Yield: 36 mg (50 %). Column chromatography eluents: dichloromethane−acetone 5:1. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.20 (s, 2H), 8.46 (s, 1H), 7.55 (d, J = 7.2 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H), 7.37 (t, J = 8.4 Hz, 1H), 7.32 (t, J = 6.6 Hz, 1H), 7.23-7.19 (m, 4H), 7.14-7.10 (m, 1H), 6.07 (s, 2H), 2.08 (s, 3H); ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 168.7, 156.3, 152.1, 146.7, 137.9, 130.0, 129.9, 128.0, 127.9, 126.9, 125.9, 125.4, 124.1, 121.6, 111.4, 108.2, 79.1, 67.9, 20.61; Mp 165.1-165.3 °C. ν_{max} (neat): 3169, 2360, 1651, 1501, 1420, 1059, 694, 567 cm^{-1}. HRMS (MALDI-TOF) m/z: $[M+H]^+$ calcd. for $C_{21}H_{18}NO_3$ 332.1287; found 332.1277. Regiochemistry of the reaction was confirmed on the basis of 2D NMR spectra (see Supporting Information for details).

*3-(5-(4-Bromophenoxy)-2-hydroxyphenyl)-3-(3,5-dichlorophenyl)isoindolin-1-one (**19**).*

Colorless solid. Yield: 114 mg (96%). Column chromatography eluents: dichloromethane−acetone 5:1. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.95 (s, 1H), 9.26 (s, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 7.2 Hz, 1H), 7.64 (dt, J = 7.2, 1.2 Hz, 1H), 7.54 (t, J = 7.2 Hz, 1H), 7.50 (t, J = 1.8 Hz, 1H), 7.48-7.46 (m, 2H), 7.161 (s, 1H), 7.158 (s, 1H), 6.95-6.85 (m, 5H) - signal of the residual solvent (acetone) is visible in spectrum. ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 168.1, 157.1, 151.7, 148.04, 147.97, 147.0, 134.0, 132.6, 132.4, 130.9, 129.1, 128.4, 126.8, 125.1, 124.1, 123.6, 120.8, 119.3, 118.7, 117.6, 114.1, 68.0. Mp 287.8–288.2 °C. ν_{max} (neat): 3186, 2360, 1671, 1223, 576 cm^{-1}. HRMS (MALDI TOF) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{17}BrCl_2NO_3$ 539.6769; found 539.6768.

*3-(5-Chloro-2-hydroxyphenyl)-3-(3,5-dimethylphenyl)isoindolin-1-one (**20**).* Colorless solid. Yield: 48 mg (61%). Column chromatography eluents: dichloromethane−acetone 5:1. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.06 (s, 1H), 8.97 (s, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.70 (d, J = 7.2 Hz,

1H), 7.63 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.23 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.10 (d, *J* = 2.4 Hz, 1H), 6.85 (s, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 6.78 (s, 2H), 2.17 (s, 6H). ^{13}C{1H} NMR (75 MHz, DMSO-d_6) δ 168.3, 154.4, 149.3, 143.0, 137.2, 132.0, 131.1, 130.4, 128.9, 128.6, 128.5, 126.8, 125.3, 123.4, 122.9, 121.9, 118.0, 68.6, 21.1. Mp 287.3–289.2 °C. ν_{max} (neat): 3066, 1675, 1269, 695 cm^{-1}. HRMS (MALDI TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{19}ClNO_2$ 364.1104; found 364.1088.

*3-(3,5-Bis(trifluoromethyl)phenyl)-3-(5-bromo-2-hydroxyphenyl)isoindolin-1-one (**21**)*. Colorless solid. 3-(3,5-bis(trifluoromethyl)phenyl)-3-hydroxyisoindolin-1-one **36** (20 mg, 0.055 mmol) afforded 16 mg (58%) of the title compound. Column chromatography eluents: dichloromethane−acetone 10:1. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.34 (brs, 1H), 9.49 (s, 1H), 8.03 (s, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 7.2 Hz, 1H), 7.74 (s, 2H), 7.69 (t, *J* = 7.2 Hz, 1H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.38 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.27 (d, *J* = 2.4 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H) - signal of the residual solvent (acetone) is visible in spectrum. ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 168.4, 148.0, 147.2, 133.1, 133.0, 131.3, 130.6 (q, *J* = 32.9 Hz), 129.9, 129.8, 129.6, 126.1, 125.3, 124.4, 124.2, 122.6, 121.5, 119.0, 110.1, 68.3. Mp 298.5–299.7 °C. ν_{max} (neat): 3709, 3042, 2360, 1660, 1276, 681 cm^{-1}. HRMS (MALDI TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{13}BrF_6NO_2$ 516.0034; found 516.0054.

*3-(5-Bromo-2-hydroxyphenyl)-3-(4-(trifluoromethyl)phenyl)isoindolin-1-one (**22**)*. Colorless solid. Yield: 71 mg (72%). Column chromatography eluents: dichloromethane−acetone 5:1. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.21 (s, 1H), 9.27 (s, 1H), 7.82 (d, *J* = 7.2 Hz, 1H), 7.75 (d, *J* = 7.2 Hz, 1H), 7.68-7.65 (m, 3H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.39-7.36 (m, 3H), 7.27 (d, *J* = 2.4 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 1H) - signal of the residual solvent (acetone) is visible in spectrum. ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 168.2, 154.6, 148.4, 147.9, 132.4, 132.2, 131.0, 130.2,

129.2, 129.0, 127.5 (q, *J* = 31.7 Hz), 126.0, 125.32, 125.29, 125.1, 123.6, 118.7, 109.7, 68.3. Mp 198.0–199.6 °C. ν_{max} (neat): 3184, 2361, 1668, 1229, 577 cm^{-1}. HRMS (MALDI TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{14}BrF_3NO_2$ 448.0160; found 448.0150.

*3-(2-Hydroxy-5-(methylthio)phenyl)-3-(p-tolyl)isoindolin-1-one (**23**)*. Colorless solid. Yield: 66 mg (84%). Column chromatography eluents: dichloromethane−acetone 5:1. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.80 (s, 1H), 8.95 (s, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 7.2 Hz, 1H), 7.61 (dt, *J* = 7.2, 1.2 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.18-7.13 (m, 2H), 7.07-7.02 (m, 4H), 6.81 (d, *J* = 8.4 Hz, 1H), 2.33 (s, 3H), 2.23 (s, 3H) - signal of the residual solvent (acetone) is visible in spectrum. ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 168.2, 153.8, 149.7, 140.4, 135.9, 131.8, 131.1, 129.2, 129.0, 128.7, 128.4, 127.4, 125.6, 125.3, 125.2, 123.2, 117.3, 68.7, 20.5, 17.0. Mp 235.2–237.2 °C. ν_{max} (neat): 3074, 2358, 1680, 1237, 697 cm^{-1}. HRMS (MALDI TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{20}NO_2S$ 362.1215; found 362.1211.

*3-(5-Chloro-2-hydroxyphenyl)-3-(naphthalen-2-yl)isoindolin-1-one (**24**)*. Colorless solid. Yield: 58 mg (69%). Column chromatography eluents: dichloromethane−acetone 20:1. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.07 (s, 1H), 9.22 (s, 1H), 7.87-7.84 (m, 5H), 7.69-7.62 (m, 2H), 7.55 (dt, *J* = 7.2, 0.9 Hz, 1H), 7.49-7.43 (m, 2H), 7.33 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.26 (dd, *J* = 8.4, 2.7 Hz, 1H), 7.19 (d, *J* = 2.4 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 1H). ^{13}C{1H} NMR (75 MHz, DMSO-d_6) δ 168.4, 154.5, 149.3, 140.5, 132.7, 132.2, 132.1, 131.2, 130.1, 129.1, 128.8, 128.00, 128.95, 127.4, 126.9, 126.3, 126.0, 125.3, 124.1, 123.5, 123.4, 122.1, 118.2, 68.9. Mp 283.6–286.5 °C. ν_{max} (neat): 3053, 1659, 1416, 1118, 700, 556 cm^{-1}. HRMS (MALDI TOF) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{17}ClNO_2$ 386.0870; found 386.0879.

*5,6-Dichloro-3-(5-chloro-2-hydroxyphenyl)-3-(3-methoxyphenyl)isoindolin-1-one (**25**)*. Colorless solid. Yield: 75 mg (79%). Column chromatography eluents: dichloromethane−acetone 20:1. ^{1}H

NMR (600 MHz, DMSO-d_6) δ 10.8 (brs, 1H), 9.54 (s, 1H), 8.20 (s, 1H), 7.90 (s, 1H), 7.23 (dt, *J* = 8.1, 2.1 Hz, 2H), 7.15 (d, *J* = 2.7 Hz, 1H), 6.87 (dd, *J* = 8.1, 2.4 Hz, 1H), 6.83 (d, *J* = 9.6 Hz, 1H), 6.76 (dd, *J* = 7.8, 0.9 Hz, 1H), 6.70 (t, *J* = 1.8 Hz, 1H), 3.68 (s, 3H). ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 166.3, 159.3, 154.3, 149.5, 143.4, 135.1, 132.3, 132.1, 129.8, 129.5, 129.3, 127.2, 127.1, 125.3, 122.4, 118.3, 118.2, 112.4, 112.3, 68.6, 55.2. Mp 151.7–153.6 °C. ν_{max} (neat): 2996, 2360, 1597, 1411, 1253, 776, 682, 466 cm^{-1}. HRMS (MALDI TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{15}Cl_3NO_3$ 434.0039; found 434.0029.

*3-(4-(Diethylamino)-2-hydroxyphenyl)-3-(4-fluorophenyl)isoindolin-1-one (**26**)*. Colorless solid. Yield: 56 mg (66%). Column chromatography eluents: dichloromethane−acetone 50:1. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.32 (s, 1H), 8.75 (s, 1H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.62 (d, *J* = 7.2 Hz, 1H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.48 (t, *J* = 7.2 Hz, 1H), 7.19 (dt, *J* = 5.4, 3.0 Hz, 2H), 7.06 (t, *J* = 9.0 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 1H), 6.16 (d, *J* = 1.8 Hz, 1H), 6.03 (dd, *J* = 9.0, 1.8 Hz, 1H), 3.23 (q, *J* = 7.2 Hz, 4H), 1.05 (t, *J* = 6.6 Hz, 6H). ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 168.2, 161.1 (d, *J* = 242 Hz), 156.06, 150.4, 148.5, 140.7, 131.6, 131.0, 128.1, 127.9, 127.4 (d, *J* = 8.0 Hz), 125.3, 123.2, 114.7, 114.6, 101.6, 99.4, 68.2, 43.6, 12.5. Mp 269.9–298.3 °C. ν_{max} (neat): 3422, 3154, 1685, 1323, 1220, 1071, 927, 845, 708 cm^{-1}. HRMS (MALDI TOF) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{24}FN_2O_2$ 391.1822; found 391.1827.

*3-(4-Fluorophenyl)-3-(4-hydroxyphenyl)isoindolin-1-one (**27**)*. Colorless solid. 3-(4-fluorophenyl)-3-hydroxyisoindolin-1-one **41** (150 mg, 0.66 mmol) afforded 202 mg (96%) of the title compound. Column chromatography eluents: dichloromethane−acetone 5:1. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.58 (s, 1H), 9.45 (brs, 1H), 7.70 (d, *J* = 7.2 Hz, 1H), 7.63-7.57 (m, 2H), 7.51 (t, *J* = 7.2 Hz, 1H), 7.30 (m, 2H), 7.15 (t, *J* = 9.0 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.72 (d, *J* = 8.4 Hz, 2H). ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 168.1, 162.1, 160.5, 156.7, 150.2, 139.8 (d, *J* =

3.0 Hz), 133.1, 131.9, 131.0, 128.9 (d, J = 8.3 Hz), 128.3, 128.0, 124.5, 123.1, 115.0, 114.8, 69.2 - signal of the residual solvent (acetone) is visible in spectra. Mp 144.0–144.9 °C. ν_{max} (neat): 3167, 1682, 1289, 1217, 962, 708 cm^{-1}. HRMS (MALDI TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{15}FNO_2$ 320.1087; found 320.1052.

*3-(5-Bromo-2-methoxyphenyl)-3-phenylisoindolin-1-one (**29**).* Prepared according to a modified known procedure.[15] To a solution of **11** (100 mg, 0.26 mmol) in acetone (2.0 mL), K_2CO_3 (180 mg, 1.3 mmol) and MeI (21 μL, 0.34 mmol) were added and the resulting mixture was refluxed for 24 hours in an oil bath. Then, the solvent was evaporated and column chromatography of the residue on silica gel (DCM/acetone 90:1) afforded 67 mg (65%) of the title compound as colorless solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.29 (s, 1H), 7.74-7.68 (m, 2H), 7.64 (dt, J = 7.8, 1.2 Hz, 1H), 7.56-7.51 (m, 2H), 7.32-7.21 (m, 4H), 7.15-7.12 (m, 2H), 7.05 (d, J = 8.7 Hz, 1H), 3.47 (s, 3H). ^{13}C{1H} NMR (75 MHz, DMSO-d_6) δ 168.3, 156.6, 148.9, 143.1, 132.7, 132.2, 132.1, 131.1, 129.4, 128.8, 128.3, 127.0, 125.2, 124.8, 123.5, 115.1, 111.5, 68.6, 55.74 - signals of inseparable impurities are visible in spectra. Mp 263.1–265.0 °C. ν_{max} (neat): 3166, 1682, 1289, 1217, 938, 707 cm^{-1}. HRMS (MALDI TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{17}BrNO_2$ 394.0443; found 394.0454.

*4-Chloro-2-(1-phenylisoindolin-1-yl)phenol (**30**).* $LiAlH_4$ (26 mg, 0.07 mmol) was added to a solution of compound **1** (35 mg, 0.10 mmol) in freshly distilled THF (2.0 mL) at 0 °C. After 24 hours at reflux in an oil bath, reaction mixture was quenched with saturated aqueous solution of Rochelle salt (5 mL) and extracted with DCM (3 x 20 mL). Organic layers were collected, dried over Na_2SO4, filtered and evaporated under reduced pressure. Column chromatography of the residue on silica gel (DCM/acetone 5:1) afforded 27 mg (84%) of the title compound as colorless solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.41-7.40 (m, 1H), 7.37-7.30 (m, 6H), 7.14-7.12 (m, 2H),

7.07-7.06 (m, 3H), 4.10 (dd, *J* = 19.8, 14.4 Hz, 2H) - N*H* and O*H* protons are observable in ^{1}H NMR spectrum but have low intensity. ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 157.9, 144.5, 143.3, 141.1, 128.5, 128.4, 128.4, 127.8, 127.7, 127.6, 127.2, 124.5, 122.9, 121.1, 118.8, 76.5, 48.8 - one signal in aromatic region is overlapped. Mp 177.1–179.0 °C. ν_{max} (neat): 3167, 1682, 1289 1217, 938, 707 cm^{-1}. HRMS (MALDI TOF) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{17}ClNO_2$ 322.0999; found 322.0985.

*4-(1-(4-Fluorophenyl)isoindolin-1-yl)phenol (**31**).* $LiAlH_4$ (26 mg, 0.07 mmol) was added to a solution of compound **27** (32 mg, 0.10 mmol) in freshly distilled THF (2.0 mL) at 0 °C. After 24 hours at reflux in an oil bath, reaction mixture was quenched with saturated aqueous solution of Rochelle salt (5 mL) and extracted with DCM (3 x 20 mL). Organic layers were collected, dried over Na_2SO4, filtered and evaporated under reduced pressure. Column chromatography of the residue on silica gel (DCM/acetone 5:1) afforded 29 mg (96%) of the title compound as colorless solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.33 (s, 1H), 7.36-7.34 (m, 2H), 7.28-7.26 (m, 1H), 7.23-7.21 (m, 3H), 7.10-7.07 (m, 2H), 7.01-6.99 (m, 2H), 6.68-6.65 (m, 2H), 4.08 (dd, *J* = 27.6, 14.4 Hz, 2H) - N*H* signal is not visible in ^{1}H NMR spectrum. ^{13}C{1H} NMR (151 MHz, DMSO-d_6) δ 160.9 (d, *J* = 243.0 Hz), 156.1, 147.6, 143.3 (d, *J* = 2.7 Hz), 142.3, 136.9, 129.4 (d, *J* = 8.0 Hz), 128.6, 126.8, 126.6, 124.2, 122.4, 115.2, 114.6, 114.5 (d, *J* = 20.9 Hz), 74.9, 50.2. Mp 183.1–184.2 °C. ν_{max} (neat): 2584, 2015, 1506, 1313, 1256, 852, 827, 603 cm^{-1}. HRMS (MALDI TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{17}FNO$ 306.1294; found 306.1295.

Associated content

Supporting Information: NMR spectra, list of starting 3-aryl 3-hydroxyisoindolinones, 2D NMR experiments, temperature variation experiments for compound **6**.

FAIR Data is available as Supporting Information for Publication and includes the primary NMR FID files for all synthesized compounds.

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Notes

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. The authors declare no competing financial interest.

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Acknowledgements

Financial support was provided by the Croatian Science Foundation (grant no. IP-2018-01-4053).

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