Note

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.0c00370 • Publication Date (Web): 07 Apr 2020

Synthesis of α-Aryl-Oxindoles by Friedel-Crafts Alkylation of Arenes

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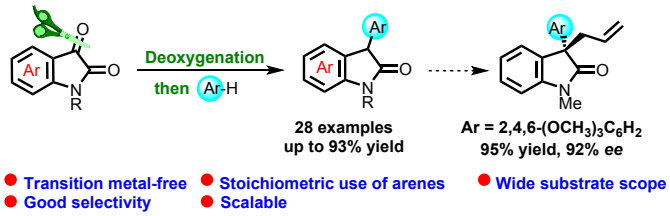
Supporting Information Placeholder



ABSTRACT: α-Aryl-oxindoles are accessed from isatin *via* a two-step procedure involving a phospha-Brook rearrangement and a Friedel-Crafts alkylation in a one-pot procedure. The use of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as solvent significantly extended the reaction substrate scope to include relatively less electron rich arenes including benzene. This new alkylation method is fast, straightforward and allows for the direct introduction of the oxindole moiety onto a range of aromatic compounds including phenols. Additionally, the application of arylated products was shown in decarboxylative asymmetric allylation and protonation.

Oxindoles are an important class of compound because of their presence in various natural products and biologically active molecules.[1] α-Aryl-oxindoles are synthetically interesting as they have found various applications in biology and pharmaceutical chemistry (Figure 1).[2] α-Aryl-oxindoles have also been employed as a substrates in various asymmetric organic transformations[3] including allylation,[3a] amination,[3b] halogenation,[3c] and thiocyantion.[3d]

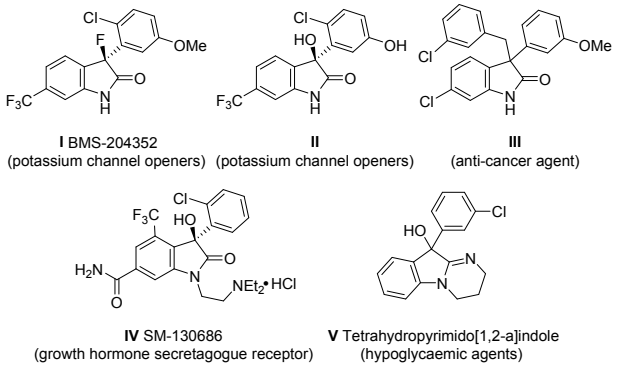


Figure 1. α-Aryl-oxindole containing pharmaceutically active molecules.

To date, various methods have been developed for the synthesis of α-aryl-oxindoles (Figure 2a). Selected existing approaches for the synthesis of α-aryl-oxindoles involve: i) the transition metal-catalysed reaction of N-substituted oxindoles with aryl halides/pseudohalides/boron reagents[4] ii) the acylation of N-substituted oxindoles with allyl chloroformate using strong base followed by arylation involving aryllead triacetate and then decarboxylative protonation;[5] iii) aryl Grignard reagent addition to isatin to generate a tertiary alcohol followed by reductive

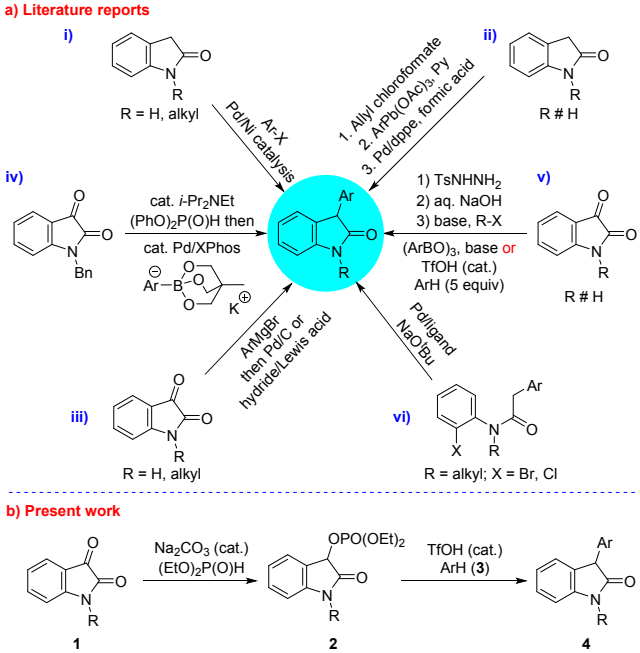
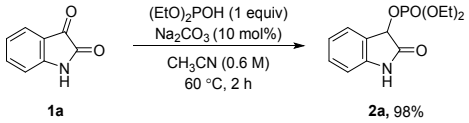


Figure 2. Strategies for the synthesis of α-aryl-oxindoles.

deoxygenation using Pd/C or hydride reagents in the presence of strong Lewis acids;[3e,6] iv) the reaction of N-substituted oxindoles with a catalytic amount of Hunig's base and diphenylphosphite followed by a Pd-catalysed reaction with aryl boron reagents;[7] v) a multistep reaction where the α-carbonyl group of isatin is converted into the corresponding diazo compound in three steps followed by base-mediated reaction with aryl boroxines or a triflic acid catalysed reaction with excess amount of electron rich arenes;[8] and vi) a metal-catalysed intramolecular cyclisation.[9] Despite these advances, the use of transition metal catalysis, aryl halides/pseudohalides/boron reagents, toxic aryllead reagents, a limited substrate scope in terms of requiring a protected N-H group and the use of the sterically bulkier aryl moiety, multistep synthesis, and the requirement of using a syringe pump - all these approaches have limitations. Bearing these factors in mind and with our interest in synthesis of α-aryl-carbonyl compounds,[10] we proposed a new catalytic method for the synthesis of α-aryl-oxindoles involving Friedel-Crafts alkylation of arene using a novel oxindole coupling partner, diethyl (2-oxoindolin-3-yl) phosphate **2**, *in situ* derived from isatin (Figure 2b).

The alkylating oxindole coupling partner **2a** was prepared by employing a base-catalysed phospha-Brook rearrangement of isatin (**1a**) with diethylphosphite (Scheme 1).[11]

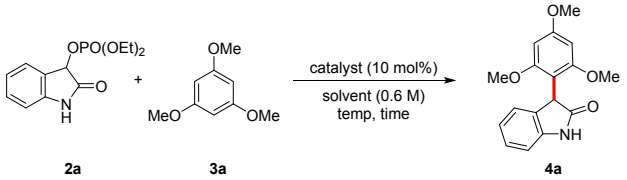
Scheme 1. Synthesis of oxindole coupling partner



1a **2a**, 98%

We then commenced the optimisation of our key step involving catalytic C-H alkylation of 1,3,5-trimethoxybenzene (**3a**) (Table 1). We realised that **2a** under Lewis or Bronsted acidic conditions would generate an electrophilic oxindole coupling partner. Lewis acids such as $FeCl_3$, $Cu(OTf)_2$, or $Zn(OTf)_2$ in dichloroethane at room temperature did not furnish the expected product after 48 h, although, we were glad to see that the use of $Sc(OTf)_2$ afforded product **4a** in 50% yield (entries 1 to 4). Increasing the reaction temperature to 60 ˚C in dichloroethane showed complete conversion to the product (entry 5). Changing the solvent to tetrahydrofuran, nitromethane or acetonitrile furnished the product **4a** quantitatively (entries 6-8). Interestingly, the use of triflic acid gave the alkylation product **4a** in 65% conversion after prolonged reaction time (48 h) at room temperature (entry 9). After heating the reaction to 60 ˚C, quantitative conversion to **4a** was achieved in 24 h. Changing the solvent to tetrahydrofuran or nitromethane showed similar results as dichloroethane (24 h for full conversion) whereas the use of acetonitrile as solvent drastically reduced the reaction time to 2 h. Subsequently, reducing the amount of 1,3,5-trimethoxybenzene from 3 to 1.5 equivalents did not have a negative impact on the conversion and product **4a** was isolated in 82% yield. However, the same reaction at room temperature dropped the conversion to 50%, even after 12 h reaction time (entry 15). Encouraged by the high catalytic activity of TfOH, we further investigated the activity of a few weaker Bronsted acids, including methanesulfonic acid (MSA), *para*-toluenesulfonic acid (*p*-TSA), camphorsulfonic acid (CSA) and trifluoroacetic acid (TFA) using CH_3CN as the solvent (entries 16-19). All of these Bronsted acids also formed the expected Friedel-Crafts alkylation product **4a** but only after relatively longer reaction times (12 to 24 h). Finally, we settled with the optimised reaction conditions which includes **2a** as limiting reagent with 1.5 equivalent of 1,3,5-trimethoxybenzene and 10 mol% TfOH in acetonitrile (0.6 M) at 60 ˚C for 2 h.

Table 1. Optimisation studies[a]



2a **3a** **4a**

entry	catalyst	solvent	temp (° C)	time (h)	conversion (%)[b]
1	$FeCl_3$	DCE	rt	48	nd
2	$Cu(OTf)_2$	DCE	rt	48	nd
3	$Zn(OTf)_2$	DCE	rt	48	nd
4	$Sc(OTf)_3$	DCE	rt	48	50
5	$Sc(OTf)_3$	DCE	60	24	>99
6	$Sc(OTf)_3$	THF	60	24	>99
7	$Sc(OTf)_3$	$MeNO_2$	60	3	>99
8	$Sc(OTf)_3$	CH_3CN	60	2	>99
9	TfOH	DCE	rt	48	65
10	TfOH	DCE	60	24	>99
11	TfOH	THF	60	24	>99
12	TfOH	$MeNO_2$	60	24	>99
13	TfOH	CH_3CN	60	2	>99
14	TfOH	CH_3CN	60	2	>99(82)[c]
15	TfOH	CH_3CN	rt	12	>50
16	MSA	CH_3CN	60	12	>99
17	*p*-TSA	CH_3CN	60	12	>99
18	CSA	CH_3CN	60	24	>99
19	TFA	CH_3CN	60	24	>99[d]
20	TfOH	HFIP	60	2	>99(85)[c]
21	None	HFIP	60	5	nd

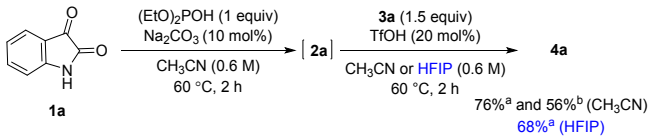
[a]Reaction conditions: **2a** (0.6 mmol), **3a** (1.8 mmol), catalyst (0.060 mmol), solvent (0.6 M). [b]Conversions were determined by ^1H NMR spectroscopic analysis of the crude reaction, isolated yields in parentheses. [c]1.5 equivalent of **3a**. [d]1.5 equivalent of TFA.

Interestingly, this optimised reaction condition was not suitable for less electron rich arene substrates such as toluene and benzene as only trace amounts of expected products were formed. Therefore, further optimisation of the reaction conditions was required to achieve the best results for such substrates. Recent reports of the use of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as a solvent in organic synthesis drew our attention.[12] The initial work of Moran showed that the application of HFIP as a solvent in catalytic reactions with TfOH drastically increased the reaction rate.[13] Interestingly, the use of HFIP as a solvent in our study provided full conversion to the expected product **4a** after 2 h, similar results to that in CH_3CN using **3a** as

the arene source (compare entries 14 and 20). Since HFIP itself can act as a strong hydrogen-bond donor, a control reaction was carried out without a catalytic amount of TfOH (entry 21). This reaction resulted in no product formation suggesting no possible background reaction without TfOH.

After optimisation of both steps independently, we decided to develop a one pot procedure for this C-H alkylation strategy wherein diethyl (2-oxoindolin-3-yl) phosphate (**2a**) was prepared *in situ* from isatin (**1a**) followed by the addition of 1,3,5-trimethoxybenzene (**3a**) and a catalytic amount of TfOH. Gratifyingly, this approach selectively furnished the product **4a** in 76% yield in CH_3CN and 68% in HFIP (Scheme 2). A similar reaction on a large scale (10 mmol, 1.47 g) in acetonitrile furnished **4a** in 56% yield.

Scheme 2. One pot procedure for the synthesis of α-aryl-oxindoles

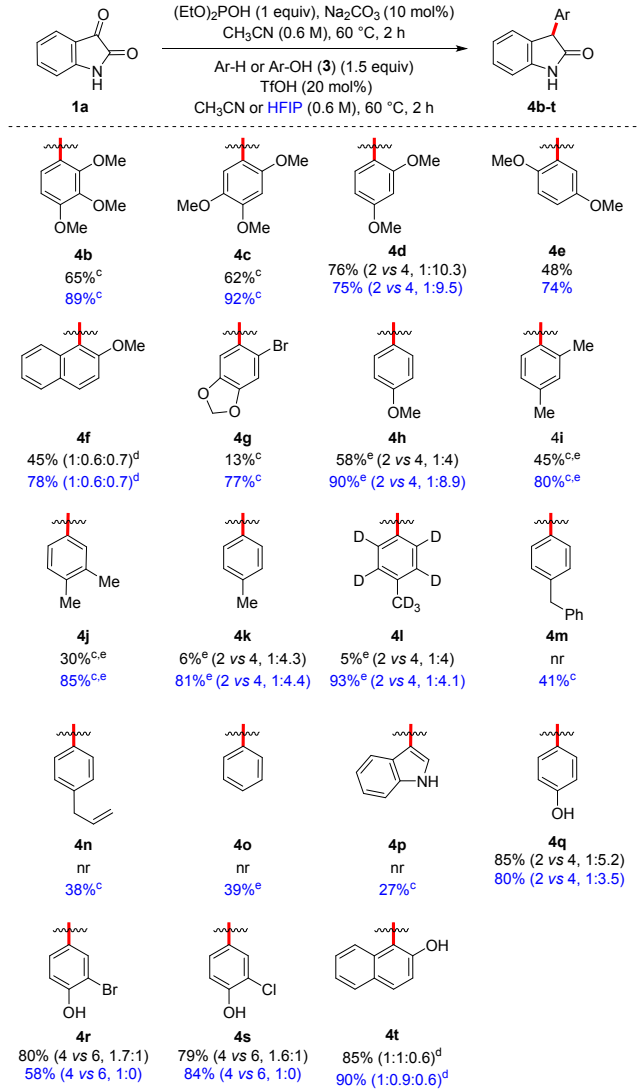


[a]Reaction performed on 0.6 mmol scale. [b]Reaction performed on 10 mmol scale.

As observed, the use of catalytic amounts of TfOH with HFIP as solvent provided improved results compared to acetonitrile with less reactive aromatic compounds. As a result, we explored a substrate scope with both solvent systems to compare their reactivity. The percentage yields quoted within the following text refers to those reactions carried out in HFIP, whereas Scheme **3** shows both results for comparison. It was also observed that the yields of the expected alkylated products dropped slightly when the reaction was carried out in one pot compared to the stepwise reaction procedure.

We investigated the scope of the reaction by reacting isatin **1a** in a one pot fashion with a range of arenes (**3b-3p**) (Scheme 3). Initially, the reaction of variously substituted methoxybenzene analogues (**3b-3h**) proceeded smoothly under the optimised reaction conditions to provide C-H alkylated products (**4b-4h**) in good to excellent yields (74-90%). It is important to note that, for a few of the arene substrates there is a possibility of forming a mixture of *ortho*- and *para*-isomers of alkylated products. The reaction of 1,2,3-trimethoxybenzene (**3b**) selectively furnished the product **4b** in 89% yield. Similarly, 1,2,4-trimethoxybenzene afforded selectively **4c** as the only isomer in 92% yield. The use of dimethoxybenzenes such as 1,3-dimethoxybenzene (**3d**) provided alkylated product **4d** in 75% yield along with a minor amount of the other regioisomer (1:9.5 ratio of 2- *vs* 4- alkylation). Later, 1,4-dimethoxybenzene (**4e**) reacted smoothly to afford the only possible isomer **4e** in 74% yield. The use of 2-methoxynaphthalene as the arene source provided the product **4f** in 78% yield as an unidentified mixture of regioisomers (1:0.6:0.7 ratio). The bromo-substituted 1,3-benzodioxole (**3g**) furnished product **4g** as a single isomer in 77% yield. The reaction of anisole (**3h**) afforded the product **4h** as a mixture of *ortho*- and *para*-isomers (1:8.9) in 90% yield. The application of 1,3- and 1,2-xylenes (**3i-3j**) afforded the products **4i** and **4j** as single isomers in 80% and 85% yields, respectively. The application of toluene (**3k**) produced **4k** in 81% yield with a 1:4.4 ratio of *ortho*- and *para*-isomers. Similarly, deuterated toluene (**3l**) afforded product **4l** in 93% yield in a 1:4.1 *ortho*:*para* ratio. The use of diphenylmethane (**3m**) and allylbenzene (**3n)** furnished the expected products **4m** and **4n**, although in moderate yields of 41% and 38%, respectively, but as single isomers. Interestingly, C-H alkylation of the less reactive aromatic compound, benzene (**3o**), furnished the expected product **4o** albeit in a 39% yield. The heterocycle indole **3p** also furnished the 3-alkylation product **4p** in a low yield of 27% using methanesulfonic acid instead of TfOH due to the decomposition of product observed subsequently. Additionally, electronically poor arenes such as bromo-, chloro- and iodobenzene were also tested which afforded arylated products in only trace amounts. The use of aniline was not successful due to the observed decomposition under the present reaction conditions.

Scheme 3. Substrate scope with various arenes[a,b]



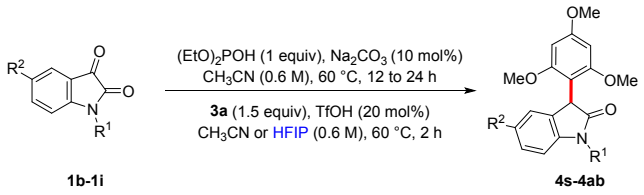
[a]Isolated yield – yield using CH_3CN or HFIP solvent. [b]Only the major isomer is illustrated where more than one product was

identified. [c]Only isomer. [d]Unidentified mixture of regioisomers [e]5 equivalent of Ar-H used.

After investigating the scope of various aromatic compounds, we turned our attention towards selective C-H alkylation of phenols (**3q-3t**) with isatin (**1a**) (Scheme 3). The reaction of **1a** with phenol (**3q**) furnished the C-H alkylation product **4q** in 80% yield as a mixture of *ortho*- and *para*-isomers in a 1:3.5 ratio. Next, *ortho*-substituted bromophenol (**3r**) and chlorophenol (**3s**), yielded selective *para* C-H alkylation products (**4r-4s**) in good to excellent yields (58-84%). The use of 2-naphthol (**3t**) furnished product **4t** in 90% yield as an unidentified mixture of regioisomers in a 1:0.9:0.6 ratio. Finally, it is important to note that the yield of products (**4b-4t**) were consistently better (except **4d**, **4q**, and **4r**) with HFIP as a solvent compared to when acetonitrile was employed as solvent.

After exploring the reaction of a wide range of aromatic compounds (**3b-3t**) with isatin (**1a)**, we turned our attention to study the effect of employing different N-substituted isatin derivatives (**1b-1e**, Scheme 4). The reaction of 1,3,5-trimethoxybenzene (**3a**) with N-benzylated (**1b**), N-allylated (**1c**), N-propargylated (**1d**) and N-methylated (**1e**) analogues of isatin furnished the expected alkylated products (**4u-4x**) in good to moderate yields (52-64%). Similarly, the effect of various substitutions at the 5-position of isatin was also studied (**1f-1i**, Scheme 4). The isatins with 5-halo substituents such as bromo (**1f**), chloro (**1g**) and fluoro (**1h**) reacted smoothly with **3a** to furnish the expected alkylated products (**4y-4aa**) in 62%, 67% and 56% yields, respectively. Finally, 5-methoxyisatin (**1i**) upon reaction with **3a** afforded product (**4ab**) in excellent yield (88%).

Scheme 4. Substrate scope with various N-alkylated and 5-substituted isatins[a]

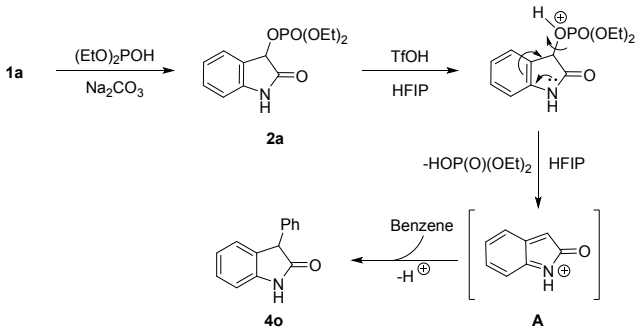


4u, R^1 = Bn, R^2 = H; 50% (60%)
4v, R^1 = Allyl, R^2 = H; 71% (64%)
4w, R^1 = Propargyl, R^2 = H; 65% (52%)
4x, R^1 = Methyl, R^2 = H; 52% (60%)
4y, R^1 = H, R^2 = Br; (62%)
4z, R^1 = H, R^2 = Cl; (67%)
4aa, R^1 = H, R^2 = F; (56%)
4ab, R^1 = H, R^2 = OMe; (88%)

[a]Isolated yield – yield using CH_3CN (HFIP) as solvent.

We propose the following reaction mechanism for this novel two step aromatic C-H alkylation (Scheme 5). Initially diethylphosphite reacts with isatin (**1a**) in the presence of a catalytic amount of Na_2CO_3 (10 mol%) to generate

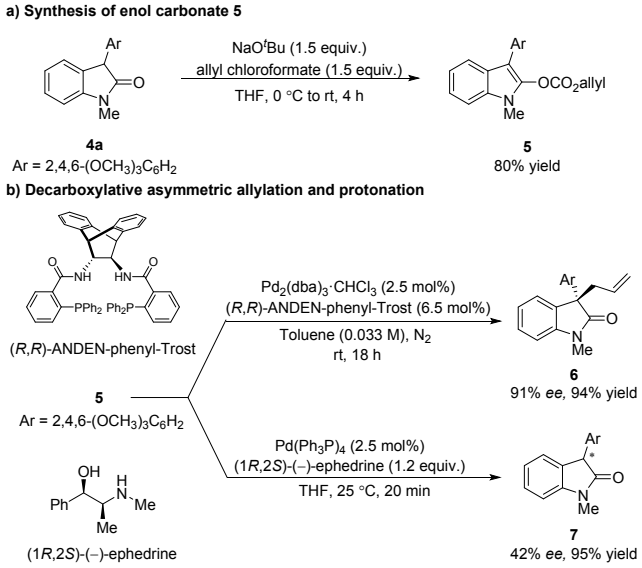
Scheme 5. Proposed reaction mechanism



diethyl-(2-oxoindolin-3-yl)-phosphate (**2a**). This intermediate is then activated in the presence of catalytic amounts of TfOH (20 mol%) to generate the electrophilic oxindole species (**A**) which subsequently reacts with benzene to generate 3-phenyl-oxindole (**4o**). We believe that HFIP plays an important role in stabilising the electrophilic oxindole intermediate (**A**) due to its high ionising power with low nucleophilicity.[12,13]

Additionally, the synthetic utility of arylated products was shown in the synthesis of quaternary and tertiary arylated chiral products (Scheme 6). The starting material, enol carbonate **5**, required for palladium-catalysed decarboxylative asymmetric allylation and protonation was prepared from **4a** in 80% yield (Scheme 6a). The enol carbonate **5** upon reaction with catalytic amounts of $Pd(dba)_3.CHCl_3$ and (*R,R*)-ANDEN-phenyl-Trost ligand furnished product **6** with a quaternary chiral center in an excellent *ee* of 91% and 94% yield (Scheme 6b).[3a,5,14] Similarly, **5** when reacted under palladium catalysis using (1*R*,2*S*)-(-)-ephedrine as a chiral proton source furnished a α-aryl-oxindole **7** in 42% *ee* and 95% yield (Scheme 6b).[15]

Scheme 6. Synthetic applications



To conclude, we report an efficient, easy and versatile method for the synthesis of α-aryl-oxindoles by using Friedel-Crafts alkylation of aromatic compounds with an electrophilic alkylating oxindole coupling partner. The alkylating oxindole precursor was synthesised by using a base-catalysed phospha-Brook rearrangement of readily available isatin with diethylphosphite. This methodology allows for the selective installation of the oxindole moiety

onto aromatic compounds, including phenols, with good levels of regioselectivity.

EXPERIMENTAL SECTION

1. General Information

Unless otherwise noted, all commercial reagents were used as received without further purification. Tetrahydrofuran (THF) were obtained from a PureSolv-300-3-MD dry solvents dispenser. Acetonitrile and toluene were dried using standard protocols. Standard Schlenk techniques were employed for moisture sensitive reactions. Column chromatography was performed on Davisil LC60A 40-63 micron silica gel. Thin-layer chromatography (TLC) was performed on aluminium-backed sheets purchased from Merck pre-coated with silica gel 60 F254. NMR spectra were recorded in deuterated chloroform ($CDCl_3$) or deuterated dimethylsulfoxide (DMSO-D_6). ^1H NMR spectra were recorded on VarianInova spectrometers (300, 400 and 500 MHz). ^{13}C NMR spectra were recorded on 300, 400, 500 and 600 MHz Varian-Inova spectrometers (75, 101,125 and 150 MHz). HRMS were measured on a Micromass/Waters LCT mass spectrometer. Infrared spectra were recorded on a FT-IR spectrometer and are reported in terms wavenumbers (ν max) with units of reciprocal centimetres (cm^{-1}). Supercritical fluid chromatography (SFC) was performed on a Waters Acquity UPC2 ® instrument with Chiralpak® IA-3 and IB-3 columns. Optical rotation measurements were recorded using a Schmidt-Haensch Unipol L2000 polarimeter at 589 nm and are quoted in units of deg dm^{-1} cm^3 g^{-1} (concentration c is given in g/100 mL).

2. Experimental Procedures

2.1 Synthesis of 2a from 1a

In a 10 mL screw-cap glass vial equipped with a magnetic stirrer, isatin (**1a**, 0.6 mmol), Na_2CO_3 (0.06 mmol) and diethylphosphite (0.6 mmol) were added, followed by CH_3CN (1 mL, 0.6 M). The reaction mixture was stirred at 60 ° C in preheated oil bath until the completion of reaction (2 h). The crude reaction mixture was directly purified by flash column chromatography on silica gel to get the product **2a**.

2.2 Synthesis of 4a from 2a

In a 10 mL screw-cap glass vial equipped with a magnetic stirrer, diethyl (2-oxoindolin-3-yl) phosphate (**2a**, 0.60 mmol), arene (**3a**, 0.90 mmol) and TfOH (20 mol%) were added, followed by CH_3CN or hexafluoroisopropanol (HFIP) (1 mL, 0.6 M). The reaction mixture was stirred at 60 °C in preheated oil bath until the completion of reaction (2 h). The crude reaction mixture was directly purified by flash column chromatography on silica gel to get the product.

2.3 One pot procedure for synthesis of 4a from 1a

In a 10 mL screw-cap glass vial equipped with a magnetic stirrer, isatin (**1a**, 0.6 mmol), Na_2CO_3 (0.06 mmol) and diethylphosphite (0.6 mmol) were added, followed by CH_3CN (1 mL, 0.6 M). The reaction mixture was stirred at 60 ° C in preheated oil bath until the disappearance of isatin (**1a**) (2 to 12 h). Then 1,3,5-trimethoxybenzene (**3a**, 0.90 mmol) and TfOH (20 mol%) were added, followed by CH_3CN or hexafluoroisopropanol (HFIP) (1 mL, 0.6 M). The reaction mixture was stirred at the same temperature (60 ° C) until the completion of reaction (2 h). The crude reaction mixture was directly purified by flash column chromatography on silica gel to get the product.

(**Note**: It is important to note that the complete removal of acetonitrile from the first step is necessary before adding HFIP and TfOH to obtain better yields of the products)

2.4 General procedure for synthesis of 4 from 1

In a 10 mL screw-cap glass vial equipped with a magnetic stirrer, isatin (**1**, 0.6 mmol), Na_2CO_3 (0.06 mmol) and diethylphosphite (0.6 mmol) were added, followed by CH_3CN (1 mL, 0.6 M). The reaction mixture was stirred at 60 ° C in preheated oil bath until the disappearance of isatin (**1**) (2 to 12 h). Then Ar-H or Ar-OH (**3**, 0.90 mmol) and TfOH (20 mol%) were added, followed by CH_3CN or hexafluoroisopropanol (HFIP) (1 mL, 0.6 M). The reaction mixture was stirred at the same temperature (60 °C) until the completion of reaction (2 h). The crude reaction mixture was directly purified by flash column chromatography on silica gel to get the product.

2.5 Procedure for synthesis of enol carbonate 5

In a 25 mL round bottom flask equipped with a magnetic stirrer, arylated oxindole (**4a**, 0.415 mmol, 1 equiv.) and NaOtBu (0.622 mmol, 1.5 equiv.) was added in dry THF (5 mL) and reaction mixture stirred at 0 °C for 15 minutes. At this point allylchloroformate (0.622 mmol, 1.5 equiv.) is added to the reaction mixture and it was stirred at room temperature until the completion of reaction (4 h). Then reaction was quenched with small amount of water followed by work up with EtOAc (50 mL) and purification by flash column chromatography on silica gel resulted the product enol carbonate **5** as a white solid.

2.6 Procedure for palladium-catalysed decarboxylative asymmetric allylation

To a mixture of arylated enol carbonate (**5**, 25 mg, 0.0629 mmol, 1 equiv.), $Pd_2(dba)_3 \cdot CHCl_3$ (1.62 mg, 0.00157 mmol, 2.5 mol%), and (*R*,*R*)-ANDEN-Phenyl-Trost ligand (3.3 mg, 0.00408 mmol, 6.5 mol%) under N_2 was added toluene (0.033 M). The mixture was allowed to stir at room temperature for 24 h. The solution was reduced in vacuo and purified by flash column chromatography to yield (*R*)-**6** as a white solid (21 mg, 94% yield, 91% *ee*).

2.7 Procedure for palladium-catalysed decarboxylative asymmetric protonation

[$Pd(PPh_3)_4$] (1.8 mg, 2.5 mol%), (1*R*,2*S*)-(–)-ephedrine (12.5 mg, 1.2 eq.) and arylated enol carbonate (**5**, 0.0844 mmol, 25 mg, 1 eq.) were added to a flame dried Schlenk flask (10 mL) followed by anhydrous THF (2.5 mL). The reaction mixture was stirred at 25 ° C for 20 min after which reaction was quenched and the solvent was removed in vacuo and the resulting residue purified by flash column chromatography to obtain protonated product **7** as a white solid in 95% yield and 45% *ee*.

(**Note:** Racemisation of chiral centre was observed over the time or when reaction was kept for longer time due to the highly acidic α-proton of arylated oxindole product)

3. Characterisation of products

Diethyl (2-oxoindolin-3-yl) phosphate (2a)[16]

The title compound was prepared according to the general procedure 2.1.

Colourless oil. Yield = 168 mg, 98%. R_f = 0.30 (50 % ethyl acetate/cyclohexane). ^{1}H NMR (300 MHz, Chloroform-*d*) δ 9.00 (s, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.31 – 7.20 (m, 1H), 7.03 (td, *J* = 7.6, 1.1 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 5.57 (d, *J* = 13.0 Hz, 1H), 4.38 – 4.02 (m, 4H), 1.35 (dtd, *J* = 11.1, 7.1, 1.2 Hz, 6H). ^{31}P NMR (121 MHz, Chloroform-*d*) δ -1.17.

3-(2,4,6-Trimethoxyphenyl)indolin-2-one (4a)

The title compound was prepared according to the general procedure 2.3.

Yellowish solid. Melting point = 219-221 ˚C. Yield = 147 mg, 82% in CH_3CN and 153 mg, 85% in HFIP. R_f = 0.25 (50% ethyl acetate/cyclohexane). IR (neat, cm^{-1}): 3205, 2935, 2839, 1703, 1608, 1594, 1469, 1418, 1329, 1206, 1149, 1057. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.16 (s, 1H), 7.14 (tt, *J* = 7.5, 1.2 Hz, 1H), 6.98 – 6.84 (m, 3H), 6.24 (d, *J* = 2.2 Hz, 1H), 6.07 (d, *J* = 2.2 Hz, 1H), 5.15 (s, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 3.49 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, Chloroform-*d*) δ 180.9, 160.9, 159.5, 159.0, 141.8, 130.9, 127.1, 123.5, 121.8, 109.2, 106.5, 91.7, 91.0, 56.0 (d), 55.8 (d), 55.4 (d), 42.7. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{17}H_{17}NO_4Na$ 322.1050; Found 322.1041.

3-(2,3,4-Trimethoxyphenyl)indolin-2-one (4b)

The title compound was prepared according to the general procedure 2.4.

Yellowish solid. Melting point = 162-164 ˚C. Yield = 117 mg, 65% in CH_3CN and 160 mg, 89% in HFIP. R_f = 0.40 (50% ethyl acetate/cyclohexane). IR (neat, cm^{-1}): 3253, 2940, 1704, 1618, 1601, 1494, 1469, 1418, 1327, 1276, 1234, 1205, 1094. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.89 (s, 1H), 7.19 (td, *J* = 7.7, 1.2 Hz, 1H), 7.01 (d, *J* = 7.3 Hz, 1H), 6.96 (td, *J* = 7.5, 1.1 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 1H), 6.65 (d, *J* = 8.5 Hz, 1H), 4.69 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.63 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, Chloroform-*d*) δ 179.6, 153.7, 152.0, 142.5, 141.6, 130.8, 127.9, 124.8, 124.3, 123.4, 122.3, 109.6, 107.3, 60.7, 60.6, 56.0, 49.1. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{17}H_{17}NO_4Na$ 322.1050; Found 322.1050.

3-(2,4,5-Trimethoxyphenyl)indolin-2-one (4c)

The title compound was prepared according to the general procedure 2.4.

Brown solid. Melting point = 183-185 ˚C. Yield = 108 mg, 62% in CH_3CN and 165 mg, 92% in HFIP. R_f = 0.25 (50% ethyl acetate/cyclohexane). IR (neat, cm^{-1}): 2941, 2838, 1708, 1594, 1458, 1424, 1324, 1204, 1149, 1116, 1066. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.46 (s, 1H), 7.20 (tt, *J* = 7.6, 1.1 Hz, 1H), 7.06 – 7.01 (m, 1H), 6.97 (td, *J* = 7.4, 1.0 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 6.64 (s, 1H), 6.58 (s, 1H), 4.83 (s, 1H), 3.89 (s, 3H), 3.79 (s, 3H), 3.72 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, Chloroform-*d*) δ 179.3, 152.0, 149.4, 143.4, 141.3, 130.6, 127.80, 124.4, 122.4, 116.9, 113.9, 109.4, 98.7, 56.9, 56.7, 56.2, 48.1. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{17}H_{17}NO_4Na$ 322.1050; Found 322.1064.

3-(2,6-Dimethoxyphenyl)indolin-2-one (4d)[8b]

The title compound was prepared according to the general procedure 2.4.

Yellow solid. Melting point = 162-164 ˚C. Yield = 123 mg, 76% in CH_3CN (2 *vs* 4, 1:10.3) and 121 mg, 75% in HFIP (2 *vs* 4, 1:9.5). R_f = 0.45 (50% ethyl acetate/cyclohexane). IR (neat, cm^{-1}): 3212, 2928, 1705, 1614, 1588, 1508, 1470, 1328, 1292, 1209, 1157, 1035. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 7.22 – 7.14 (m, 1H), 7.03 (dd, *J* = 7.9, 1.9 Hz, 2H), 6.95 (td, *J* = 7.5, 1.0 Hz, 1H), 6.90 (d, *J* = 7.9 Hz, 1H), 6.50 (d, *J* = 2.4 Hz, 1H), 6.47 (dd, *J* = 8.3, 2.5 Hz, 1H), 4.84 (s, 1H), 3.80 (s, 3H), 3.73 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, Chloroform-*d*) δ 179.6, 160.5, 158.5, 141.4, 130.8, 130.6, 127.7, 124.3, 122.3, 118.0, 109.4, 104.8, 99.4, 55.7, 55.4, 47.9. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{16}H_{16}NO_3$ 270.1125; Found 270.1124.

3-(2,5-Dimethoxyphenyl)indolin-2-one (4e)

The title compound was prepared according to the general procedure 2.4.

Yellow solid. Melting point = 151-152 ˚C. Yield = 78 mg, 48% in CH_3CN and 119 mg, 74% in HFIP. R_f = 0.45 (50% ethyl acetate/cyclohexane). IR (neat, cm^{-1}): 3207, 2968, 2834, 1699, 1618, 1499, 1469, 1227, 1042. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.30 (s, 1H), 7.20 – 7.13 (m, 1H), 7.05 – 6.99 (m, 1H), 6.93 (td, *J* = 7.5, 1.0 Hz, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 8.9 Hz, 1H), 6.78 (dd, *J* = 8.9, 2.9 Hz, 1H), 6.67 (d, *J* = 3.0 Hz, 1H), 4.84 (s, 1H), 3.72 (s, 3H), 3.68 (s, 3H). ^{13}C {^{1}H} NMR (101 MHz, Chloroform-*d*) δ 178.7, 153.8, 151.8, 141.3, 130.2, 127.8, 126.7, 124.4, 122.4, 116.4, 113.3, 112.8, 109.3, 56.5, 55.7, 48.5. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{16}H_{16}NO_3$ 270.1125; Found 270.1118.

3-(2-Methoxynaphthalen-1-yl)indolin-2-one (4f)

The title compound was prepared according to the general procedure 2.4.

Yellow solid. Melting point = 196-198 ˚C. Yield = 78 mg, 45% in CH_3CN (mixture of regioisomers in 1:0.6:0.7 ratio) and 135 mg, 78% in HFIP (mixture of regioisomers in 1:0.6:0.7 ratio). R_f = 0.30 (50% ethyl acetate/cyclohexane). IR (neat, cm^{-1}): 3213, 2925, 2853, 1708, 1620, 1602, 1512, 1470, 1391, 1326, 1265, 1218, 1030. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.83 (s, 1H), 10.56 (s, 1H), 10.46 (s, 1H), 8.33 (dt, *J* = 8.5, 0.9 Hz, 1H), 7.99 – 7.90 (m, 3H), 7.89 – 7.84 (m, 1H), 7.78 (q, *J* = 9.0 Hz, 2H), 7.64 (d, *J* = 1.7 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.44 (ddd, *J* = 7.9, 6.8, 1.0 Hz, 1H), 7.38 (d, *J* = 9.0 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.27 – 7.18 (m, 3H), 7.18 – 7.09 (m, 3H), 7.06 (dd, *J* = 7.2, 1.2 Hz, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.95 (t, *J* = 7.4 Hz, 2H), 6.91 – 6.79 (m, 3H), 6.76 (td, *J* = 7.5, 1.1 Hz, 2H), 6.66 – 6.59 (m, 1H), 5.67 (t, *J* = 1.1 Hz, 1H), 5.45 (s, 1H), 4.86 (s, 1H), 4.01 (s, 2H), 3.86 (s, 3H), 3.55 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, DMSO-d_6) δ 178.9, 178.3, 177.8, 157.7, 156.7, 155.2, 143.5, 143.2, 142.4, 134.2, 133.8, 133.2, 132.3, 131.1, 130.9, 130.7, 130.3, 129.6, 129.5, 129.5, 129.2, 129.0, 128.9, 128.6, 128.2, 127.7, 127.6, 127.5, 127.4, 127.2, 127.1, 125.3, 124.0, 123.8, 123.8, 123.7, 123.4, 123.2, 123.0, 122.2, 122.1, 121.4, 120.6, 119.3, 117.7, 115.5, 114.6, 110.2, 109.9, 109.2, 106.2, 57.7, 56.8, 55.6, 52.3, 45.0, 44.5. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{19}H_{16}NO_2$ 290.1176; Found 290.1173.

3-(6-Bromobenzo[d][1,3]dioxol-5-yl)indolin-2-one (4g)

The title compound was prepared according to the general procedure 2.4.

Yellow solid. Melting point = 206-208 ˚C. Yield = 26 mg, 13% in CH_3CN and 153 mg, 77% in HFIP. R_f = 0.55 (50% ethyl acetate/cyclohexane). IR (neat, cm^{-1}): 3210, 3011, 2898, 1704, 1618, 1502, 1472, 1407, 1326, 1235, 117, 1036. ^1H NMR (500 MHz, Chloroform-*d*) δ 8.08 (s, 1H), 7.25 (dt, *J* = 7.7, 1.1 Hz, 1H), 7.22 – 7.08 (m, 2H), 7.02 (td, *J* = 7.5, 1.0 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.36 (s, 1H), 5.95 (s, 2H), 5.28 (s, 1H). ^{13}C {^1H} NMR (151 MHz, Chloroform-*d*) δ 177.8, 148.0, 141.1, 129.8, 129.6, 128.5, 124.9, 122.8, 116.1, 112.8, 109.9, 108.3, 101.9, 51.9, 29.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{11}NO_3Br$ 331.9917; Found 331.9936.

3-(4-Methoxyphenyl)indolin-2-one (4h)[4a]

The title compound was prepared according to the general procedure 2.4.

Yellow solid. Melting point = 166-168 ˚C. Yield = 83 mg, 58% in CH_3CN (2 *vs* 4, 1:4) and 129 mg, 90% in HFIP (2 *vs* 4, 1:8.9). R_f = 0.55 (50% ethyl acetate/cyclohexane). IR (neat, cm^{-1}): 3209, 2960, 2930, 2836, 1702, 1617, 1510, 1485, 1470, 1247, 1216, 1179, 1031. ^1H NMR (400 MHz, Chloroform-*d*) δ 9.05 (s, 1H), 7.24 – 7.18 (m, 1H), 7.16 – 7.06 (m, 3H), 7.00 (td, *J* = 7.5, 1.1 Hz, 1H), 6.95 – 6.83 (m, 3H), 4.57 (s, 1H), 3.77 (s, 3H). ^{13}C {^1H} NMR (101 MHz, Chloroform-*d*) δ 179.2, 159.1, 141.7, 129.9, 129.5, 128.4, 128.3, 125.2, 122.6, 114.4, 110.0, 55.3, 51.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{14}NO_2$ 240.1019; Found 240.1015.

3-(2,4-Dimethylphenyl)indolin-2-one (4i)[17]

The title compound was prepared according to the general procedure 2.4.

Yellow solid. Melting point = 171-173 ˚C. Yield = 64 mg, 45% in CH_3CN and 114 mg, 80% in HFIP. R_f = 0.75 (50% ethyl acetate/cyclohexane). IR (neat, cm^{-1}): 3210, 2971, 1699, 1617, 1470, 1327, 1214, 1093, 1046. ^1H NMR (500 MHz, Chloroform-*d*) δ 9.40 (s, 1H), 7.23 (tt, *J* = 7.7, 1.2 Hz, 1H), 7.14 – 6.67 (m, 6H), 4.85 (s, 1H), 2.32 (s, 6H). ^{13}C {^1H} NMR (126 MHz, Chloroform-*d*) δ 179.5, 141.7, 137.4, 136.9, 131.9, 130.1, 128.1, 127.1, 124.7, 122.6, 110.0, 49.1, 26.9, 21.0 (d) (Due to broadening some of the peaks are missing). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{16}NO$ 238.1226; found 238.1239.

3-(3,4-Dimethylphenyl)indolin-2-one (4j)

The title compound was prepared according to the general procedure 2.4.

Red solid. Melting point = 178-180 ˚C. Yield = 43 mg, 30% in CH_3CN and 121 mg, 85% in HFIP. R_f = 0.75 (50% ethyl acetate/cyclohexane). IR (neat, cm^{-1}): 3206, 2969, 2920, 1702, 1618, 1470, 1326, 1232, 1215, 1193, 1096. ^1H NMR (500 MHz, Chloroform-*d*) δ 9.43 (d, *J* = 30.6 Hz, 1H), 7.24 (tt, *J* = 7.7, 1.1 Hz, 1H), 7.16 – 7.10 (m, 2H), 7.06 – 6.99 (m, 2H), 6.96 (dd, *J* = 11.8, 8.0 Hz, 2H), 4.59 (s, 1H), 2.26 (s, 3H), 2.25 (s, 3H). ^{13}C {^1H} NMR (126 MHz, Chloroform-*d*) δ 179.5 (d), 141.8 (d), 137.2, 136.1, 133.9, 130.2, 130.1, 129.7, 128.2, 125.9, 125.1, 122.6, 110.1 (d), 52.6, 19.8, 19.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{16}NO$ 238.1226; Found 238.1234.

3-(*p*-Tolyl)indolin-2-one (4k)[17]

The title compound was prepared according to the general procedure 2.4.

Yellow solid. Melting point = 157-159 ˚C. Yield = 8 mg, 6% in CH_3CN (2 *vs* 4, 1:4.3) and 108 mg, 81% in HFIP (2 *vs* 4, 1:4.4). R_f = 0.70 (50% ethyl acetate/cyclohexane). IR (neat, cm^{-1}): 3210, 2922, 2853, 1704, 1618, 1511, 1471, 1327, 1297, 1220. ^1H NMR (500 MHz, Chloroform-*d*) δ 9.60 (s, 1H), 7.24 (ddd, *J* = 8.8, 7.1, 1.2 Hz, 1H), 7.19 (d, *J* = 7.8 Hz, 2H), 7.17 – 7.11 (m, 3H), 7.03 (td, *J* = 7.5, 1.0 Hz, 1H), 6.94 (d, *J* = 7.7 Hz, 1H), 4.63 (s, 1H), 2.36 (s, 3H). ^{13}C {^1H} NMR (126 MHz, Chloroform-*d*) δ 179.5 (d), 141.9 (d), 137.4, 133.5, 129.9, 129.7, 128.4, 128.3, 125.1, 122.6, 110.2 (d), 52.5, 21.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{16}NO$ 238.1232; Found 238.1239.

3-(4-(Methyl-d3)phenyl-2,3,5,6-d4)indolin-2-one (4l)

The title compound was prepared according to the general procedure 2.4.

Yellow solid. Melting point = 155-157 ˚C. Yield = 7 mg, 5% in CH_3CN (2 *vs* 4, 1:4) and 128 mg, 93% in HFIP (2 *vs* 4, 1:4.1). R_f = 0.70 (50% ethyl acetate/cyclohexane). IR (neat, cm^{-1}): 3207, 2268, 1699, 1618, 1470, 1325, 1214. ^1H NMR (400 MHz, Chloroform-*d*) δ 9.49 (s, 1H), 7.24 – 7.18 (m, 1H), 7.10 (d, *J* = 7.4 Hz, 1H), 7.00 (td, *J* = 7.6, 1.1 Hz, 1H), 6.94 – 6.88 (m, 1H), 4.60 (s, 1H). ^{13}C {^1H} NMR (101 MHz, Chloroform-*d*) δ 179.4, 141.9, 141.8, 137.1, 133.3, 129.9, 128.3, 128.1, 125.1, 122.6, 110.1 (d), 52.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_7D_7NO$ 231.1509; Found 231.1523.

3-(4-Benzylphenyl)indolin-2-one (4m)

The title compound was prepared according to the general procedure 2.4.

Yellow solid. Melting point = 178-180 ˚C. Yield = 74 mg, 41% in HFIP. R_f = 0.75 (50% ethyl acetate/cyclohexane). IR (neat, cm^{-1}): 3209, 3026, 2920, 1707, 1619, 1453, 1297, 1186. ^1H NMR (500 MHz, Chloroform-*d*) δ 9.34 (s, 1H), 7.35 – 7.15 (m, 10H), 7.13 (d, *J* = 7.4 Hz, 1H), 7.03 (td, *J* = 7.5, 1.1 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 4.63 (s, 1H), 3.99 (s, 2H). ^{13}C {^1H} NMR (126 MHz, Chloroform-*d*) δ 179.2, 141.8, 140.8, 140.6, 134.2, 129.7, 129.5, 129.0, 128.6, 128.5, 128.3, 126.1, 125.2, 122.6, 110.1, 52.4, 41.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{18}NO$ 300.1383; Found 300.1399.

3-(4-Allylphenyl)indolin-2-one (4n)

The title compound was prepared according to the general procedure 2.4.

Yellow gum. Yield = 57 mg, 38% in HFIP. R_f = 0.75 (50% ethyl acetate/cyclohexane. IR (neat, cm^{-1}): 3257, 2972, 2924, 1702, 1619, 1471, 1326, 1218, 1086, 1046. ^1H NMR (500 MHz, Chloroform-*d*) δ 9.38 (s, 1H), 7.27 – 7.11 (m, 6H), 7.03 (td, *J* = 7.6, 1.0 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.01 – 5.93 (m, 1H), 5.16 – 5.06 (m, 2H), 4.63 (s, 1H), 3.40 (d, *J* = 6.9 Hz, 2H). ^{13}C {^1H} NMR (126 MHz, Chloroform-*d*) δ 179.2 (d), 141.8 (d), 139.5, 137.2, 134.2 (d), 129.8 (d), 129.2, 128.5, 128.3, 125.2 (d), 122.6, 116.0, 110.1 (d), 52.5 (d), 39.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{16}NO$ 250.1226; Found 250.1227.

3-Phenylindolin-2-one (4o)[17]

The title compound was prepared according to the general procedure 2.4.

White solid. Melting point = 189-191 ˚C. Yield = 49 mg, 39% in HFIP. R_f = 0.70 (50% ethyl acetate/cyclohexane. IR (neat, cm^{-1}): 3212, 2923, 2853, 1709, 1618, 1471, 1325, 1219. ^1H NMR (500 MHz, Chloroform-*d*) δ 9.31 (s, 1H), 7.40 – 7.34 (m, 2H), 7.34 – 7.29 (m, 1H), 7.28 – 7.21 (m, 3H), 7.14 (d, *J* = 7.4 Hz, 1H), 7.04 (td, *J* = 7.5, 0.9 Hz, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 4.66 (s, 1H). ^{13}C {^1H} NMR (126 MHz, Chloroform-*d*) δ 179.1, 141.8 (t), 136.5 (t), 129.7, 129.6, 129.0, 128.5 (t), 127.7, 125.2 (t), 122.7, 110.1 (t), 52.8 (t). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{14}H_{11}NONa$ 232.0733; Found 232.0746.

3-(1H-Indol-3-yl)indolin-2-one (4p)[18]

The title compound was prepared according to the general procedure 2.4.

Red gum. Yield = 40 mg, 27% in HFIP. R_f = 0.30 (50% ethyl acetate/cyclohexane). ^1H NMR (500 MHz, Chloroform-*d*) δ 8.80 (s, 1H), 8.28 (s, 1H), 7.34 – 7.33 (m, 1H), 7.28 – 7.26 (m, 1H), 7.24 – 7.21 (m, 1H), 7.18 – 7.14 (m, 2H), 7.07 (d, *J* = 2.4 Hz, 1H), 7.02 (m, 1H), 6.98 (m, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 4.92 (s, 1H).

3-(4-Hydroxyphenyl)indolin-2-one (4q)[4a]

The title compound was prepared according to the general procedure 2.4.

White solid. Melting point = 226-228 ˚C. Yield = 114 mg, 85% in CH_3CN (2 *vs* 4, 1:5.2) and 108 mg, 80% in HFIP (2 *vs* 4, 1:3.5). R_f = 0.45 (50% ethyl acetate/cyclohexane. IR (neat, cm^{-1}): 3251, 2500, 1696, 1618, 1514, 1471, 1334, 1216. ^1H NMR (500 MHz, DMSO-d_6) δ 10.42 (s, 1H), 9.35 (s, 1H), 7.19 (tt, *J* = 7.7, 1.1 Hz, 1H), 7.16 – 7.06 (m, 1H), 7.00 (d, *J* = 7.4 Hz, 1H), 6.96 – 6.66 (m, 8H), 4.58 (s, 1H). ^{13}C {^1H} NMR (126 MHz, DMSO-d_6) δ 178.2, 178.1, 156.9, 155.8, 143.2, 143.1, 131.2, 130.9, 129.8, 128.7, 128.3, 128.2, 127.9, 125.1, 125.0, 124.2, 122.0, 121.6, 119.4, 115.8, 115.8, 109.8, 109.4, 51.5, 48.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{12}NO_2$ 226.0863; Found 226.0868.

3-(3-Bromo-4-hydroxyphenyl)indolin-2-one (4r)

The title compound was prepared according to the general procedure 2.4.

Yellow solid. Melting point = 250-252 ˚C. Yield = 146 mg, 80% in CH_3CN (4 *vs* 6, 1.7:1) and 105 mg, 58% in HFIP (4 *vs* 6, 1:0). R_f = 0.40 (50% ethyl acetate/cyclohexane. IR (neat, cm^{-1}): 3219, 2923, 1703, 1620, 1471, 1293, 1220, 1152. ^1H NMR (500 MHz, DMSO-d_6) δ 10.48 (s, 1H), 10.22 (s, 1H), 7.25 – 7.19 (m, 2H), 7.06 – 7.01 (m, 1H), 6.95 (td, *J* = 7.5, 1.1 Hz, 1H), 6.92 – 6.87 (m, 3H), 4.66 (s, 1H). ^{13}C {^1H} NMR (126 MHz, DMSO-d_6) δ 177.6, 153.6, 143.1, 132.9, 130.3, 130.0, 128.9, 128.6, 125.2, 122.2, 117.0, 109.9, 109.6, 50.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{11}NO_2Br$ 303.9968; Found 303.9965.

3-(3-Chloro-4-hydroxyphenyl)indolin-2-one (4s)

The title compound was prepared according to the general procedure 2.4.

Yellow solid. Melting point = 204-206 ˚C. Yield = 123 mg, 79% in CH_3CN (4 *vs* 6, 1.6:1) and 131 mg, 84% in HFIP (4 *vs* 6, 1:0). R_f = 0.40 (50% ethyl acetate/cyclohexane. IR (neat, cm^{-1}): 3263, 2920, 2850, 1703, 1620, 1501, 1472, 1293, 1219, 1046. ^1H NMR (500 MHz, DMSO-d_6) δ 10.48 (s, 1H), 10.14 (s, 1H), 7.21 (tt, *J* = 7.7, 1.1 Hz, 1H), 7.09 (d, *J* = 2.1 Hz, 1H), 7.04 (d, *J* = 7.4 Hz, 1H), 6.98 – 6.85 (m, 4H), 4.66 (s, 1H). ^{13}C {^1H} NMR (126 MHz, DMSO-d_6) δ 177.6, 152.6, 143.1, 130.2, 130.0, 129.6, 128.6, 128.3, 125.2, 122.1, 120.0, 117.3, 109.9, 50.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{14}H_{11}NO_2Cl$ 260.0473; Found 260.0487.

3-(2-Hydroxynaphthalen-1-yl)indolin-2-one (4t)

The title compound was prepared according to the general procedure 2.4.

Yellow solid. Melting point = 247-249 ˚C. Yield = 140 mg, 85% in CH_3CN (mixture of regioisomers in 1:1:0.6 ratio) and 149 mg, 90% in HFIP (mixture of regioisomers in 1:0.9:0.6 ratio). R_f = 0.30 (50% ethyl acetate/cyclohexane. IR (neat, cm^{-1}): 3164, 1703, 1620, 1514, 1470, 1329, 1289, 1219, 1205, 1023, 1002. *Mixture of regiosomers:* ^1H NMR (500 MHz, DMSO-d_6) δ 10.78 (s, 1H), 10.54 (s, 1H), 10.40 (s, 1H), 10.15 (s, 1H), 9.72 (s, 1H), 9.59 (s, 1H), 8.26 (d, *J* = 8.5 Hz, 1H), 7.85 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.80 – 7.68 (m, 4H), 7.68 – 7.56 (m, 2H), 7.52 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.38 – 7.29 (m, 2H), 7.27 – 6.91 (m, 12H), 6.88 – 6.71 (m, 5H), 6.64 (d, *J* = 7.3 Hz, 1H), 5.61 (s, 1H), 5.39 (s, 1H), 4.83 (s, 1H). ^{13}C {^1H} NMR (126 MHz, DMSO-d_6) δ 178.8, 178.5, 177.8, 154.9, 153.2, 143.7, 143.2, 142.5, 134.9, 132.9, 132.2, 131.2, 131.0, 129.7, 129.6, 129.1, 129.1, 129.0, 128.9, 128.5, 128.5, 128.4, 128.1, 128.1, 127.4, 127.2, 127.0, 127.0, 126.8, 125.3, 123.9, 123.3, 122.9, 122.8, 122.7, 122.1, 122.1, 121.3, 119.3, 118.6, 118.4, 116.5, 114.5, 110.1, 109.9, 109.1, 109.0, 52.3, 45.0, 44.5. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{18}H_{13}NO_2Na$ 298.0838; Found 298.0844.

1-Benzyl-3-(2,4,6-trimethoxyphenyl)indolin-2-one (4u)

The title compound was prepared according to the general procedure 2.4.

Brown gum. Yield = 117 mg, 50% in CH_3CN and 140 mg, 60% in HFIP. R_f = 0.70 (50% ethyl acetate/cyclohexane. IR (neat, cm^{-1}): 3006, 2939, 2839, 1704, 1608, 1594, 1487, 1464, 1341, 1204, 1149, 1113. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.47 – 7.41 (m, 2H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.30 – 7.25 (m, 1H), 7.15 – 7.09 (m, 1H), 6.97 (dt, *J* = 7.3, 1.3 Hz, 1H), 6.91 (td, *J* = 7.4, 1.0 Hz, 1H), 6.75 (d, *J* = 7.8 Hz, 1H), 6.26 (d, *J* = 2.2 Hz, 1H), 6.06 (d, *J* = 2.2 Hz, 1H), 5.22 (d, *J* = 1.0 Hz, 1H), 5.16 (d, *J* = 15.6 Hz, 1H), 4.85 (d, *J* = 15.6 Hz, 1H), 3.91 (s, 3H), 3.82 (s, 3H), 3.34 (s, 3H). ^{13}C {^1H} NMR (126 MHz, Chloroform-*d*) δ 177.6, 160.9, 159.5, 158.9, 143.5, 136.6, 130.2, 128.5, 127.7, 127.4, 127.0, 123.3, 121.9, 108.3, 106.5, 91.6 (d), 90.9 (d), 56.1 (d), 55.6 (d), 55.4 (d), 43.9, 42.1 (d). HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{24}H_{24}NO_4$ 390.1700; Found 390.1723.

1-Allyl-3-(2,4,6-trimethoxyphenyl)indolin-2-one (4v)

The title compound was prepared according to the general procedure 2.4.

Yellow solid. Melting point = 107-109 ˚C. Yield = 144 mg, 71% in CH_3CN and 130 mg, 64% in HFIP. R_f = 0.65 (50% ethyl acetate/cyclohexane. IR (neat, cm^{-1}): 3399, 2940, 1697, 1609, 1595, 1488, 1465, 1359, 1341, 1205, 1150, 1115, 1047. ^1H NMR (500 MHz, Chloroform-*d*) δ 7.23 – 7.15 (m, 1H), 7.00 – 6.89 (m, 2H), 6.83 (d, *J* = 7.7 Hz, 1H),

6.24 (d, *J* = 2.3 Hz, 1H), 6.06 (d, *J* = 2.2 Hz, 1H), 5.92 (ddt, *J* = 17.2, 10.5, 5.3 Hz, 1H), 5.34 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.26 (dd, *J* = 10.4, 1.5 Hz, 1H), 5.13 (s, 1H), 4.56 (ddt, *J* = 16.3, 5.2, 1.7 Hz, 1H), 4.32 (ddt, *J* = 16.3, 5.5, 1.6 Hz, 1H), 3.90 (s, 3H), 3.80 (s, 3H), 3.47 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, Chloroform-*d*) δ 177.4, 160.8, 159.5, 158.8, 143.5, 132.2 (d), 130.1, 127.0, 123.3, 121.9, 117.2 (d), 108.2, 106.7, 91.6 (d), 90.9 (d), 56.0 (d), 55.7 (d), 55.4 (d), 42.4, 42.0 (d). HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{22}NO_4$ 340.1543; Found 340.1543.

1-(Prop-2-yn-1-yl)-3-(2,4,6-trimethoxyphenyl)indolin-2-one (4w)

The title compound was prepared according to the general procedure 2.4.

Brown solid. Melting point = 154-156 ˚C. Yield = 131 mg, 65% in CH_3CN and 105 mg, 52% in HFIP. R_f = 0.70 (50% ethyl acetate/cyclohexane. IR (neat, cm^{-1}): 3281, 2965, 2939, 2839, 1711, 1592, 1488, 1464, 1418, 1339, 1228, 1203, 1188, 1148, 1111, 1053, 1037. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.29 – 7.22 (m, 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 7.02 – 6.94 (m, 2H), 6.23 (d, *J* = 2.3 Hz, 1H), 6.04 (d, *J* = 2.2 Hz, 1H), 5.10 (d, *J* = 1.2 Hz, 1H), 4.81 (dd, *J* = 17.6, 2.6 Hz, 1H), 4.41 (dd, *J* = 17.6, 2.5 Hz, 1H), 3.90 (s, 3H), 3.80 (s, 3H), 3.50 (s, 3H), 2.25 (t, *J* = 2.5 Hz, 1H). ^{13}C {^{1}H} NMR (126 MHz, Chloroform-*d*) δ 177.0, 160.9, 159.3, 158.8, 142.4, 129.9, 127.1, 123.5, 122.3, 108.3, 106.7, 91.5 (d), 90.9 (d), 77.9, 71.6 (d), 56.0 (d), 55.8 (d), 55.4 (d), 41.9 (d), 29.7. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{20}H_{20}NO_4$ 338.1387; Found 338.1382.

1-Methyl-3-(2,4,6-trimethoxyphenyl)indolin-2-one (4x)

The title compound was prepared according to the general procedure 2.4.

Yellow solid. Melting point = 126-128 ˚C. Yield = 98 mg, 52% in CH_3CN and 113 mg, 60% in HFIP. R_f = 0.45 (50% ethyl acetate/cyclohexane. IR (neat, cm^{-1}): 3003, 2940, 2839, 1702, 1608, 1593, 1493, 1466, 1417, 1375, 1339, 1204, 1193, 1146, 1113. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.31 – 7.19 (m, 1H), 7.03 – 6.90 (m, 2H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.25 (d, *J* = 2.3 Hz, 1H), 6.05 (d, *J* = 2.3 Hz, 1H), 5.09 (s, 1H), 3.91 (s, 3H), 3.81 (s, 3H), 3.47 (s, 3H), 3.30 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, Chloroform-*d*) δ 177.9, 160.8, 159.4, 158.8, 144.5, 130.2, 127.2, 123.3, 121.9, 107.2, 106.9, 91.7, 91.0, 56.0, 55.4, 42.0, 26.3. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{20}NO_4$ 314.1387; Found 314.1380.

5-Bromo-3-(2,4,6-trimethoxyphenyl)indolin-2-one (4y)

The title compound was prepared according to the general procedure 2.4.

Brown solid. Melting point = 213-215 ˚C. Yield = 140 mg, 62% in HFIP. R_f = 0.25 (50% ethyl acetate/cyclohexane. IR (neat, cm^{-1}): 3194, 2967, 2839, 1703, 1609, 1593, 1500, 1205, 1113. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.75 (s, 1H), 7.29 – 7.25 (m, 1H), 7.04 (s, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.23 (d, *J* = 2.2 Hz, 1H), 6.07 (d, *J* = 2.3 Hz, 1H), 5.13 (s, 1H), 3.90 (s, 3H), 3.82 (s, 3H), 3.51 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, Chloroform-*d*) δ 180.0, 161.2, 159.4, 158.8, 140.6, 133.0, 130.0, 126.7, 114.6, 110.5, 105.4, 91.5, 90.9, 56.0, 55.7, 55.4, 42.5. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{17}NO_4Br$ 378.0335; Found 378.0352.

5-Chloro-3-(2,4,6-trimethoxyphenyl)indolin-2-one (4z)

The title compound was prepared according to the general procedure 2.4.

Brown solid. Melting point = 218-220 ˚C. Yield = 134 mg, 67% in HFIP. R_f = 0.25 (50% ethyl acetate/cyclohexane). IR (neat, cm^{-1}): 3203, 2967, 2939, 2840, 1705, 1609, 1594, 1499, 1476, 1324, 1305, 1205, 1151, 1114. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.76 (s, 1H), 7.12 (ddd, *J* = 8.3, 2.2, 1.0 Hz, 1H), 6.91 (t, *J* = 1.6 Hz, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.24 (d, *J* = 2.3 Hz, 1H), 6.07 (d, *J* = 2.2 Hz, 1H), 5.13 (s, 1H), 3.90 (s, 3H), 3.82 (s, 3H), 3.51 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, Chloroform-*d*) δ 180.1, 161.2, 159.4, 158.8, 140.2, 132.6, 127.2, 127.1, 124.0, 109.9, 105.5, 91.5, 90.9, 56.0, 55.7, 55.4, 42.6. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{17}H_{17}NO_4Cl$ 334.0841; Found 334.0860.

5-Fluoro-3-(2,4,6-trimethoxyphenyl)indolin-2-one (4aa)

The title compound was prepared according to the general procedure 2.4.

Brown solid. Melting point = 226-228 ˚C. Yield = 107 mg, 56% in HFIP. R_f = 0.25 (50% ethyl acetate/cyclohexane). IR (neat, cm^{-1}): 3214, 2939, 2841, 1706, 1609, 1595, 1484, 1458, 1418, 1205, 1190, 1153, 1115, 1038. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.65 (s, 2H), 6.84 (tdd, *J* = 8.5, 2.6, 1.3 Hz, 1H), 6.78 (dd, *J* = 8.5, 4.3 Hz, 1H), 6.69 (ddd, *J* = 8.1, 2.7, 1.2 Hz, 1H), 6.23 (d, *J* = 2.2 Hz, 1H), 6.07 (d, *J* = 2.2 Hz, 1H), 5.13 (d, *J* = 1.2 Hz, 1H), 3.90 (s, 3H), 3.82 (s, 3H), 3.51 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, Chloroform-*d*) δ 180.4, 161.1, 159.4, 159.0 (d, *J* = 237.5 Hz), 158.9, 137.5, 132.6 (d, *J* = 7.5 Hz), 113.3 (d, *J* = 23.7 Hz), 111.5 (d, *J* = 25 Hz), 109.3 (d, *J* = 7.5 Hz), 105.6, 91.6, 90.9, 56.0, 55.7, 55.4, 43.0 (d, *J* = 1.2 Hz). HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{17}H_{16}NO_4FNa$ 340.0956; Found 340.0953.

5-Methoxy-3-(2,4,6-trimethoxyphenyl)indolin-2-one (4ab)

The title compound was prepared according to the general procedure 2.4.

Brown solid. Melting point = 175-177 ˚C. Yield = 174 mg, 88% in HFIP. R_f = 0.20 (50% ethyl acetate/cyclohexane). IR (neat, cm^{-1}): 3216, 2967, 2939, 2838, 1698, 1592, 1486, 1455, 1417, 1306, 1203, 1191, 1151, 1112, 1031. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.85 (s, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.68 (ddd, *J* = 8.4, 2.6, 0.9 Hz, 1H), 6.55 (dd, *J* = 2.6, 1.3 Hz, 1H), 6.24 (d, *J* = 2.3 Hz, 1H), 6.08 (d, *J* = 2.2 Hz, 1H), 5.12 (s, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 3.71 (s, 3H), 3.51 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, Chloroform-*d*) δ 180.5, 160.9, 159.4, 159.0, 155.4, 135.3, 132.3, 111.7, 110.8, 109.3, 106.4, 91.7, 91.0, 56.0, 55.8, 55.7, 55.4, 43.1. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for $C_{18}H_{20}NO_5$ 330.1336; Found 330.1350.

Allyl (1-methyl-3-(2,4,6-trimethoxyphenyl)-1H-indol-2-yl) carbonate (5)[5]

The title compound was prepared according to the general procedure 2.5.

White solid. Melting point = 116-118 ˚C. Yield = 98 mg, 80%. R_f = 0.40 (50 % ethyl acetate/cyclohexane). IR (neat,

cm^{-1}): 2937, 2838, 1772, 1607, 1581, 1456, 1218, 1158, 1125. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.34 – 7.28 (m, 2H), 7.21 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.08 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 6.27 (s, 2H), 5.95 (ddt, *J* = 17.1, 10.4, 5.8 Hz, 1H), 5.40 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.32 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.74 (dt, *J* = 5.8, 1.3 Hz, 2H), 3.89 (s, 3H), 3.72 (s, 6H), 3.68 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, Chloroform-*d*) δ 160.7, 159.1, 152.1, 139.6, 132.7, 130.9, 125.6, 121.2, 121.1, 119.5, 119.5, 109.0, 102.4, 94.3, 91.0, 69.5, 55.7, 55.4, 28.8. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{22}H_{23}NO_6Na$ 420.1418; Found 420.1434.

(*R*)-3-Allyl-1-methyl-3-(2,4,6-trimethoxyphenyl)indolin-2-one (6)[5]

The title compound was prepared according to the general procedure 2.6.

Colourless oil. Melting point = 135-137 ˚C. Yield = 21 mg, 94% and *ee* = 91%. R_f = 0.60 (50% ethyl acetate/cyclohexane). $[\alpha]^{20}{}_D$ = +185.95 (c = 1.0 in $CHCl_3$). Note: The absolute configuration was determined by comparing the sign of the optical rotation to that of a known sample.[5a] SFC (Chiralpak IA, CO_2(l)/IPA, 99:1 to 60:40 over 5 minute, 3 mL min^{-1}), temp. 35 ˚C, 3.639 (minor), 3.907 (major) min. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.24 – 7.13 (m, 2H), 6.94 (td, *J* = 7.5, 1.0 Hz, 1H), 6.78 (d, *J* = 7.7 Hz, 1H), 6.13 (s, 2H), 5.53 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1H), 4.96 – 4.79 (m, 2H), 3.77 (s, 3H), 3.68 (s, 6H), 3.25 (s, 3H), 3.22 (ddt, *J* = 7.2, 2.5, 1.2 Hz, 2H). ^{13}C {^{1}H} NMR (126 MHz, Chloroform-*d*) δ 180.1, 160.1, 143.5, 134.2, 133.9, 127.2, 123.1, 122.0, 117.4, 109.9, 106.9, 92.6, 56.0, 55.3, 54.0, 41.7, 25.9.

1-Methyl-3-(2,4,6-trimethoxyphenyl)indolin-2-one (7)[5b]

The title compound was prepared according to the general procedure 2.7.

Yield = 25 mg, 95%, 43% *ee*. SFC (Chiralpak IB-3, CO_2(l)/IPA, 99:1 to 60:40 over 5 minute, 3 mL min^{-1}), temp. 35 ˚C, 3.767 (major), 4.024 (minor) min. All other physical and spectroscopic data were in complete agreement with racemic product **4x.** Note: Due to high acidity of α-proton in product **7**, slow racemisation was observed over the time.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
SFC traces and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This publication has emanated from research conducted with the financial support of the Synthesis and Solid State Pharmaceutical Centre (SSPC), funded by Science Foundation Ireland (SFI) under grant numbers 12/RC/2275. BVR is grateful for the award of a BEACON postdoctoral fellowship (16/RC/23889). BVR also thanks to the SSPC and Irish Research Council (IRC) for the award of a postdoctoral fellowship (GOIPD/2015/453).
We acknowledge facilities provided by the Centre for Synthesis and Chemical Biology (CSCB), funded by the Higher Education Authority's PRTLI. We thank Dr. Yannick Ortin for NMR spectroscopic experiments and Dr. Jimmy Muldoon for mass spectroscopic analysis

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