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Graphical Abstract

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Jasneet Kaur, Akshay Kumar, and Swapandeep Singh Chimni*

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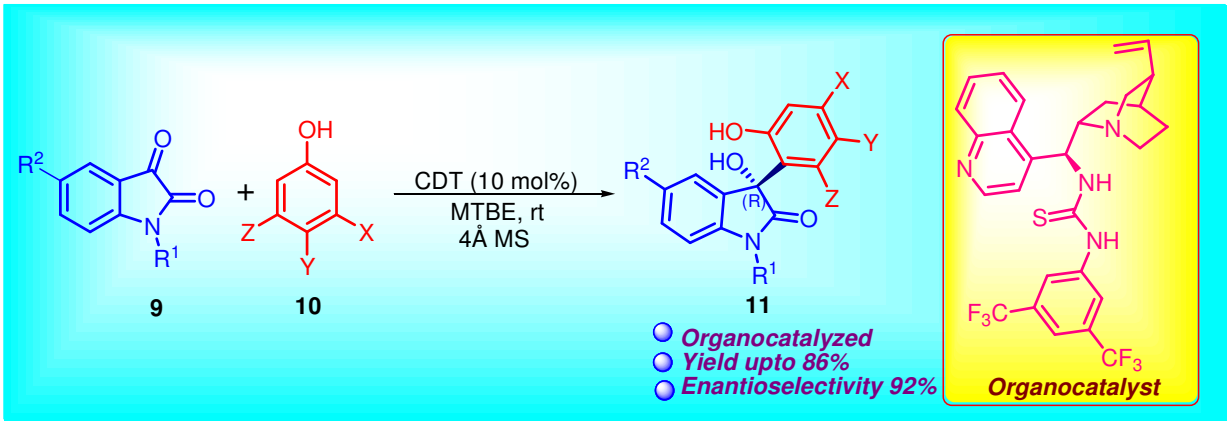

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A highly enantioselective Friedel–Crafts reaction of activated phenols with isatin derivatives has been developed employing *Cinchona*-derived thiourea as an organocatalyst. A variety of biologically important 3-aryl-3-hydroxy-2-oxindoles have been synthesized using phenols in good to excellent yield with good enantioselectivity (up to 92% ee).

Introduction

Oxindole skeleton bearing a oxygenated chiral tetrasubstituted carbon at C3 constitute a significant structural motif which occurs in large family of bioactive natural products and therapeutically useful agents.[1] In particular, 3-aryl-3-hydroxy-2-oxindole is an important structural unit found in many pharmaceutically active compounds, and is a key intermediate for the drug development programmes.[2] Owing to their biological significance, the asymmetric synthesis of 3-aryl-3-hydroxy-2-oxindoles has become an intensively investigated research area.[3] Over the years, variety of catalytic asymmetric methods[3a], including nucleophilic addition to isatins[3b-c], oxidation of 3-aryl-2-oxindoles[3d-e], and intramolecular arylation reactions[3f-h], have been developed to tackle the synthetic challenge in constructing aryl substituted chiral tertiary alcohol carbon centre at 3-position of oxindole. Among the available methods, the catalytic asymmetric arylation of isatins is one of the most efficient synthetic routes.[4-6] The asymmetric arylation of isatins, especially, the addition of an organoboronic reagent to isatins, has been well studied in the presence of chiral metal complexes.[4] However, despite various advantages associated with organocatalysis and its explosive growth, the synthesis of this subunit by organocatalyzed reactions is limited to the use of heteroarenes.[5] Recently, our group [6a-b] and Wang [6c] *et al* reported the Friedel-Crafts-type-addition of 1-naphthols and sesamol to isatins, but a systematic study of organocatalyzed asymmetric C-3 arylation of isatins with other electron-rich arenes, such as phenols is lacking.[7] In addition, the structure activity correlation shows that the biological activity of 3-aryl-3-hydroxy-2-oxindoles is sensitive to absolute stereochemistry at C-3 and substituent pattern on the aryl group.[8] Hence, Friedel-Crafts addition of phenols to isatins delivers new chiral derivatives of 3-aryl-3-hydroxy-2-oxindoles, which may possess unexplored medicinal advantage and can also be used as synthetic intermediate for the synthesis of highly potent bioactive molecules. Synthesis of similar oxindole derivatives have been achieved using multistep procedure.[8a] The novelty of present work consists of achieving this in a single step under mild conditions.

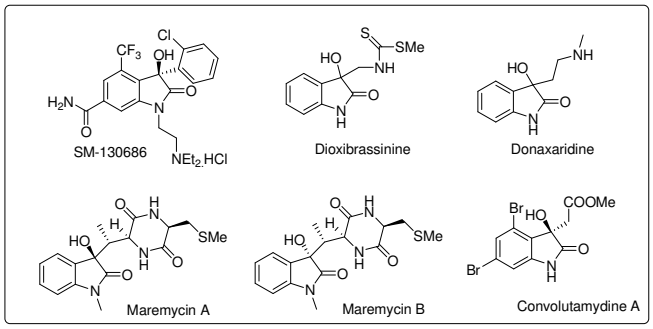
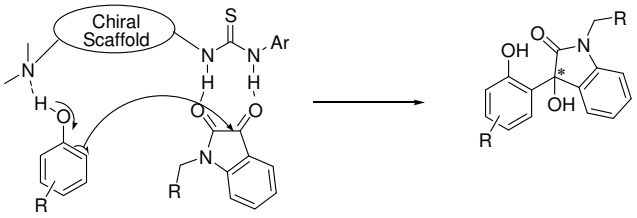


Fig. 1 Biologically active 3-hydroxy-2-oxindole derivatives.

Our group has been actively involved in the synthesis of new 3-hydroxy-2-oxindoles employing bifunctional organocatalysts.[9] Herein we report the first organocatalyzed synthesis of 3-aryl-3-hydroxy-2-oxindoles using phenols as arylating agents with isatins. The enantioinduction have been achieved in the Friedel–Crafts reaction of phenols with isatins through synergistic activation by a bifunctional *Cinchona*-thiourea organocatalyst (**Scheme 1**).



Scheme 1: Proposed dual activation for the thiourea-tertiary amine catalyzed, asymmetric Friedel-Crafts reaction of phenols with isatins.

Result and Discussion

Initially, the catalytic ability of *Cinchona* alkaloids QD, CN, QN and CD was evaluated for the Friedel-Crafts-type-addition of 3,4-

dimethoxyphenol **10a** with *N*-benzylisatin **9a** in THF and 4Å molecular sieves at room temperature. The desired product **11a** was isolated in good yield, but with poor enantioselectivity (**Table 1, entries 1-4**). The same reaction was performed using modified *Cinchona* catalysts (CPD, CPN, BnCPD and BnCPN), the desired adduct was obtained with low level of enantioselectivity (**Table 1, entries 5-8**). Next, we studied the catalytic capability of 9-thiourea derivatives of *Cinchona* alkaloids on the same reaction (**Table 1, entries 9-16**). Among different *Cinchona*-derived thioureas (**3a**, **3b**, **4a** and **4b**) (**Table 1, entries 9-12**), the Cinchonidine thiourea **3a** provided the Friedel-Crafts adduct **11a** in good yield of 86% and good

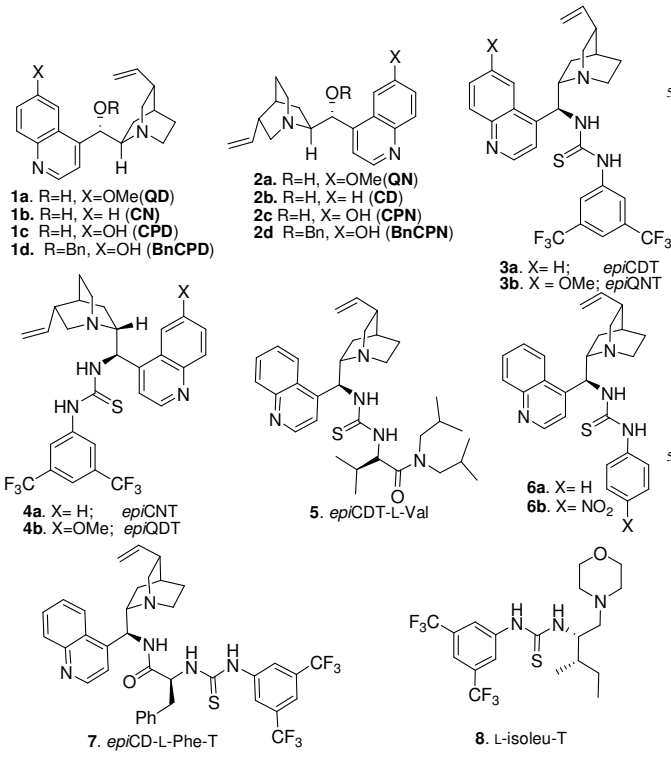
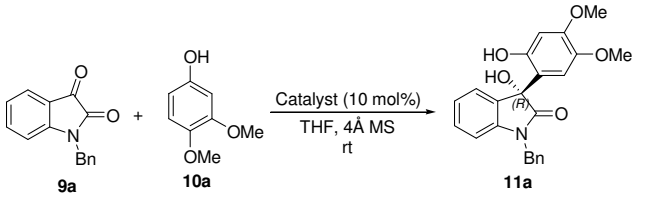


Figure 2: Structure of organocatalysts.

enantiomeric excess of 83% ee (**Table 1, entry 9**). Therefore, we planned to synthesize different cinchonidine-based thioureas (**5-7**), and evaluated their catalytic potential on the model reaction (**Table 1, entries 13-16**). The *epi*CDT-L-Val (**5**) afforded the adduct **11a** in 68% yield and 40% ee (**Table 1, entry 13**). Using thioureas **6a** and **6b** the product **11a** was isolated in good yield (80-83%) and good enantioselectivity (73-82% ee) (**Table 1, entries 14-15**). The organocatalyst **7** having thiourea group at the distance of six bonds from tertiary amine functionality, yielded adduct **11a** in moderate yield with low enantioselectivity (**Table 1, entry 16**). The amino acid, *L*-isoleucine-derived bifunctional thiourea **8** was found to be inferior catalyst for this transformation (**Table 1, entry 17**). After evaluating the catalytic power of diverse thioureas, the *epi*CDT (**3a**) emerged as the best catalyst for this reaction (**Table 1, entry 9).** Lowering the reaction temperature from room temperature to -18 °C resulted in prolonged reaction time without any enhancement in the enantioselectivity (**Table 1, entry 18**).

Further optimization of the reaction condition was performed by screening of different solvents. Variation of solvents had a pronounced effect on the enantioselectivity of the reaction (**Table 2**). In chlorinated solvents such as chloroform, dichloromethane and 1,2-dichloroethane, the product **11a** was isolated in good yield (78-84%) and low to moderate enantioselectivity (35-62% ee) (**Table 2, entries 1-3**). Non-polar solvents such as xylene and toluene proved to be inefficient in terms of enantio-induction (**Table 2, entries 4-5**). Polar aprotic solvents such as ethyl acetate provided the Friedel-Crafts adduct **11a** in good yield and good enantioselectivity (**Table 2, entry 6**). Among different etheral solvents, MTBE emerged as the best solvent because it provided **11a** in good yield (82%) and highest level of enantioselectivity (88% ee). The use of benzoic acid as an additive in the model reaction leads to decrease in the enantioselectivity (**Table 2, entry 10**). Thus, the best optimized condition consists of 10 mol% of **3a**, 4Å molecular sieves and MTBE as a solvent at ambient temperature providing Friedel-Crafts adduct **11a** in 82% yield and 88% ee.

Table 1. Catalyst Screening.[a]



Entry	Catalyst	Time (h)	Yield (%)	ee (%)[c,d]
1	**1a**	12	76	10 (+)
2	**1b**	12	80	4 (-)
3	**2a**	12	77	19 (-)
4	**2b**	12	82	30 (-)
5	**1c**	12	76	29 (-)
6	**2c**	12	80	19 (+)
7	**1d**	12	82	37 (-)
8	**2d**	12	77	24 (+)
9	**3a**	12	86	83 (+)
10	**3b**	12	80	70 (+)
11	**4a**	12	77	38 (-)
12	**4b**	12	82	15 (-)
13	**5**	110	68	40 (+)
14	**6a**	12	83	73 (+)
15	**6b**	12	80	82(+)
16	**7**	24	64	35(+)
17	**8**	12	77	20(+)
18	**3a**	24	72	82(+)

[a] Reaction conditions: 0.1 mmol of phenols **10a**, 0.1 mmol *N*-benzylisatin **9a**, 4Å molecular sieves (50 mg) and catalysts (**1-8**, 10 mol%) in dry THF. [b]Yield refers to isolated yield after column chromatography. [c]Enantiomeric excess (ee) determined by chiral HPLC. [d]The sign in parentheses indicates the sign of the optical rotation. [e]Reaction was performed at -18 °C

After optimizing the conditions, the substrate scope was evaluated by studying the Friedel-Crafts addition of phenols to isatins **9a-9z**. 5-Halogen-*N*-benzylisatins **9b-9d** reacted well with 3,4-dimethoxyphenol, yielding 3-aryl-3-hydroxy-2-oxindoles **11b-11d** in good yield (81-85%) and good enantioselectivity (86-88% ee) (**Table 3, entries 2-4**). The *N*-benzylisatins **9f** and **9g** substituted with electron donating groups in the aromatic ring provided adducts **11f** and **11g** with slight decrease in the enantioselectivity (81% ee in each case) (**Table 3, entries 6-7**). 5-

Iodo-*N*-benzylisatin gave Friedel-Crafts adduct **11e** in good yield (83%) but with moderate enantioselectivity (60% ee) (**Table 3, entry 5**). The reaction of *N*-allylisatin derivatives **9h-9k** with 3,4-dimethoxyphenol afforded Friedel-Crafts adducts **11h-11k** in good yield (79-84%) and good enantioselectivity (84-92% ee) (**Table 3, entries 8-11**). 5-Methyl-*N*-allylisatin **9m** gave product **11m** in good enantiomeric excess (83% ee) (**Table 3, entry 13**).

Table 2. Solvent Screening.[a]

Entry	Solvent	Time (h)	Yield (%)[b]	ee (%)[c]
1	Chloroform	12	78	35
2	DCM	12	84	46
3	DCE	12	80	62
4	Xylene	12	75	57
5	Toluene	12	74	47
6	Ethyl acetate	12	74	74
7	THF	12	86	83
8	MTBE	12	82	88
9	Dioxane	12	78	77
10[d]	MTBE	12	84	70

[a]Reaction conditions: 0.1 mmol of phenols **10**, 0.1 mmol *N*-benzylisatin **9a**, 4Å molecular sieves (50 mg), additive (10 mol%) and catalysts **3a** (10 mol%) in dry solvent. [b]Yield refers to isolated yield after column chromatography. [c]Enantiomeric excess (*ee*) determined by chiral HPLC. [d]Reaction was performed using benzoic acid as an additive. MTBE = Methyl *tert*-butyl ether

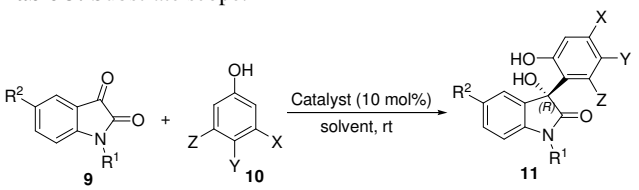
The *N*-methylisatins **9n** afforded the Friedel-Crafts adduct **11n** in good yield (83%) and good enantioselectivity (85% ee) (**Table 3, entry 14**). The Friedel-Crafts addition of 3,4-dimethoxyphenol to *N*-propargylisatins **9o** provided the corresponding product **11o** in 83% yield and 70% ee (**Table 3, entry 15**)

Next, we screened different derivatives of phenols (**10b-10c**) with isatins. The Friedel-Crafts addition of 3-methoxyphenol (**10b**) to 5-substituted *N*-benzylisatins **9b-9d** provided the corresponding products **11p-11r** in good yield (83-86%) and good enantioselectivity (77-84% ee) (**Table 3, entries 16-18**).

The reaction of 3-methoxyphenol with *N*-benzylisatins bearing the electron releasing groups provides the desired adduct in good yield (82%) but with moderate enantioselectivity (63% ee) (**Table 3, entry 19**). Using *N*-allylisatin **9t**, the Friedel-Crafts adduct **11t** was isolated in good yield (81%) and good enantioselectivity (85% ee), whereas *N*-propargylisatin **9u** provided the adduct **11u** in good yield (73%) but with moderate enantioselectivity (59% ee) (**Table 3, entries 20-21**). The *N*-methylisatin afforded the Friedel-Crafts adduct in 79% yield and 69% ee (**Table 3, entry 22**).

Further, we have studied the Friedel-Crafts reaction of 3,5-dimethoxyphenol (**10c**) with different derivatives of isatin (**9b**, **9i** and **9u**). The reaction proceeds smoothly providing desired Friedel-Crafts adducts (**11w-11z**) in good yield and good enantioselectivity (**Table 3, entries 23-25**). The *N*-unprotected isatin **9z** react very slowly with 3,4-dimethoxyphenol providing the adduct **11z** in good yield (78%) and good enantioselectivity (80% ee) (**Table 3, entry 26**).

Table 3: Substrate scope.[a]



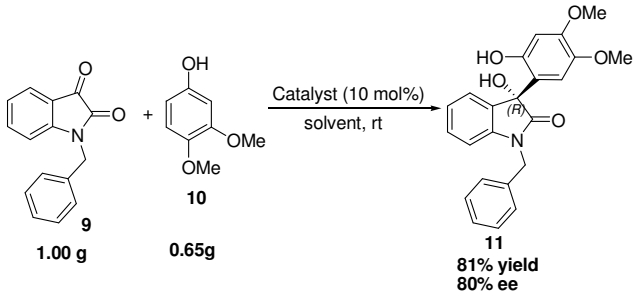
10a X= OMe, Y= OMe, Z=H
10b X= OMe, Y= H, Z= H
10c X = OMe, Y= H, Z= OMe

Entry	10	9 (R_1, R_2)	11	Time (h)	Yield[b] (%)	ee[c] (%)
1	**10a**	**9a** (R_1=Bn, R_2=H)	**11a**	12	82	88
2	**10a**	**9b** (R_1= Bn, R_2=F)	**11b**	12	82	86
3	**10a**	**9c**(R_1=Bn, R_2=Cl)	**11c**	12	85	88
4	**10a**	**9d**(R_1=Bn, R_2=Br)	**11d**	12	81	87
5	**10a**	**9e** (R_1= Bn, R_2=I)	**11e**	12	83	60
6	**10a**	**9f**(R_1=Bn, R_2=Me)	**11f**	12	79	81
7	**10a**	**9g**(R_1=Bn, R_2=OMe)	**11g**	12	80	81
8	**10a**	**9h**(R_1= CH_2CHCH_2 , R_2=F)	**11h**	12	83	84
9	**10a**	**9i**(R_1=CH_2CHCH_2 , R_2=Cl)	**11i**	12	81	92
10	**10a**	**9j**(R_1=CH_2CHCH_2 , R_2=Br)	**11j**	12	79	84
11	**10a**	**9k**(R_1=CH_2CHCH_2, R_2=I)	**11k**	12	84	90
12	**10a**	**9l**(R_1=$CH_2CHCHCH_3$, R_2=Cl)	**11l**	12	80	75
13	**10a**	**9m** (R_1=CH_2CHCH_2, R_2=Me)	**11m**	12	82	83
14	**10a**	**9n**(R_1=Me, R_2=Cl)	**11n**	12	83	85
15	**10a**	**9o** (R_1= CH_2CCH, R_2=H)	**11o**	12	83	70
16	**10b**	**9b** (R_1= Bn, R_2=F)	**11p**	12	85	77
17	**10b**	**9c**(R_1 Bn, R_2=Cl)	**11q**	12	83	82
18	**10b**	**9d** (R_1= Bn R_2=Br)	**11r**	12	86	84
19	**10b**	**9g**(R_1=Bn, R_2=OMe)	**11s**	12	82	63
20	**10b**	**9i**(R_1=CH_2CHCH_2 , R_2=Cl)	**11t**	12	81	85
21	**10b**	**9u** (R_1= CH_2CCH, R_2=H)	**11u**	12	73	59
22	**10b**	**9v** (R_1= CH_3, R_2=H)	**11v**	12	79	69
23	**10c**	**9b** (R_1=Bn, R_2=F)	**11w**	12	87	71
24	**10c**	**9i**(R_1=CH_2CHCH_2 , R_2=Cl)	**11x**	12	83	76
25	**10c**	**9u**(R_1=CH_2CCH, R_2=H)	**11y**	12	82	68
26	**10a**	**9z**(R_1=H, R_2=H)	**11z**	96	78	80

[a]Reaction conditions: 0.1 mmol of isatin derivatives **9**, 0.1 mmol phenols **10**, 4Å molecular sieves (50 mg) and catalysts **3a** (10 mol%) in dry MTBE.[b] Yield refers to isolated yield after column chromatography. [c]Enantiomeric excess (*ee*) determined by chiral HPLC.

Further, we have performed the reactions of *N*-benzylisatin with 2-chlorophenol, 4-chlorophenol, 2-bromophenol, 4-bromophenol, 4-iodophenol under the similar conditions but no product was formed even after 72 hrs. In addition to this, we have tried 4-bromo-3-methoxyphenol, 3-methoxy-5-methylphenol and 3,5-dimethylphenol but no product formation was observed even after two days.

A gram-scale reaction was performed to demonstrate the practical utility of this process. (**Scheme 2**) The reaction of 3,4-dimethoxyphenol (**10**) with *N*-benzylisatin (**9**) on a 4.5 mmol scale with 10 mol-% of the catalyst resulted in the formation of **11** in 81% yield after 18 h with a small loss in enantioselectivity (80%).



Scheme 2. Gram-scale preparation of 3-substituted 3-hydroxyoxindole.

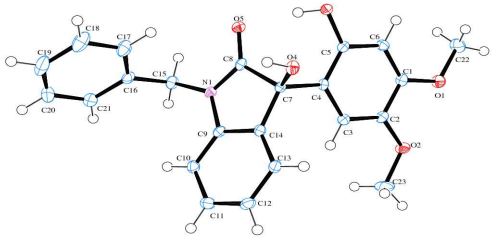


Figure 2 ORTEP diagram of the molecule (**11a**) at 30% probability.

The (*R*) absolute configuration of adducts was assigned on the basis of single-crystal X-ray diffraction analysis of compound **11a** (**Figure 2**). A transition state model can be proposed to rationalize the stereochemistry of the product (**11**). The thiourea moiety of the catalyst activates and orients isatin through double H-bonding, while the phenol is activated by the tertiary amine of the catalyst which undergoes *Re* face addition to the activated isatin via transition state A resulting in the formation of (*R*)-**11**. On the other hand, the transition state B results in unfavourable interaction between isatin aromatic ring and the phenol derivative. (**Figure 3**)

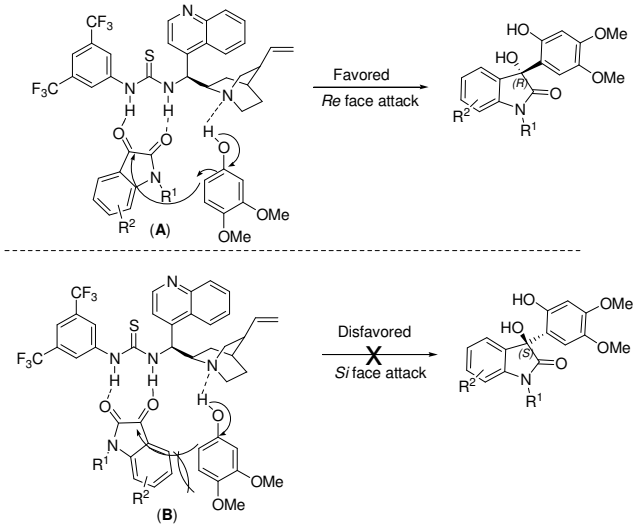


Figure 3. Proposed Transition State

Conclusions

We have developed an organocatalytic enantioselective Friedel-Crafts reaction of phenols with isatins employing chiral thiourea-tertiary amine as catalyst. Through this methodology, a wide variety of biologically relevant 3-aryl-3-hydroxy-2-oxindolins were synthesized in good yield (upto 86%) and good enantioselectivity (upto 92% ee).

Experimental

All reactions were performed in oven-dried glassware. All solvents and commercially available chemical were used without further purification. The molecular sieves were activated at 200 ˚C for 2 hours in an oven. The column chromatography was carried out on a column packed with silica gel 60-120 using mixtures of hexane and ethyl acetate as an eluents. ^{1}H NMR spectra were recorded in $CDCl_3$ on a BRUKER AVANCE III (500 MHz), JNM-ECS400 (400 MHz), BRUKER AVANCE II (400 MHz) and JEOL (300 MHz) spectrometer. ^{13}C NMR spectra were recorded in $CDCl_3$ on BRUKER AVANCE III (125 MHz), JNM- ECS400 (100 MHz), BRUKER AVANCE II (100 MHz) and JEOL (75 MHz). Chemical shifts (δ) are expressed in ppm downfield from internal TMS. MS were recorded on micrOTOF-Q II 10356 Mass Spectrometer. Optical rotation was determined with AUTOPOL IV polarimeter at 25 ˚C using sodium D light. Enantiomeric excess was determined by using Shimadzu LC-20AD using Daicel Chiralpak IA, IB and IC column.

General Procedure

To a solution of isatin derivatives (0.1 mmol), phenols (0.1 mmol), 4Å MS (50 mg) in 0.3 mL of MTBE, the catalyst epi*CDT* (**3a**, 10 mol%) was added at 25 °C. The reaction mixture was stirred for 12–96 hours and the progress of the reaction was monitored at regular intervals by thin layer chromatography (tlc). After the completion of reaction, the crude reaction mixture was purified by column chromatography on silica gel (mesh 60–120) using hexane–ethyl acetate (1:1) as eluent. The enantiomeric excess of the purified Friedel-Crafts adducts **11** were determined using Diacel Chiralpak columns. The racemic standards were prepared using triethylamine (10 mol%) as a catalyst.

(*R*)-1-Benzyl-3-hydroxy-3-(2-hydroxy-4,5-dimethoxyphenyl) indolin-2-one (11a): Brown solid; m.p.=109-110 °C; 82% yield; $[\alpha]_{20}^{D}$= +7.19 (c 0.25, $CHCl_3$); 88% ee; HPLC [Chiralpak IA, hexane/i-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 9.04 min (major) and t_R = 16.6 min (minor)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.23 (s, 1H, OH), 7.20-7.56 (m, 8H, ArH), 6.84 (d, J= 5.0 Hz, 1H, ArH), 6.68 (s, 1H, ArH),6.33 (s, 1H, ArH), 4.93 (dd, J= 65.0 Hz, J= 15.0 Hz, 2H, CH_2), 4.38 (s, 1H, OH), 3.88 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.08, 55.94, 56.59, 79.31, 104.1, 110.3, 111.3, 115.6, 123.9, 125.9, 127.2, 127.9, 128.9, 129.3, 130.4, 134.9, 142.4, 142.6, 150.8, 151.3, 179.1. HRMS calcd. for $C_{23}H_{21}NO_5$ $[M + Na]^+$ 414.1372; found 414.1384.

(*R*)-1-Benzyl-5-fluoro-3-hydroxy-3-(2-hydroxy-4,5-dimethoxyphenyl)indolin-2-one (11b): Brown semi-solid; 82% yield; $[\alpha]_{20}^{D}$ = +6.28 (c 0.25, $CHCl_3$); 86% ee; HPLC [Chiralpak IA, hexane/i-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 8.09 min (major) and t_R = 15.5 min (minor)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.03 (s, 1H, OH), 7.28-7.34 (m, 8H, ArH), 6.68 (s, 1H, ArH), 6.33 (s, 1H, ArH), 4.84-5.00 (m, 2H, CH_2), 4.45 (s, 1H, OH), 3.88 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.23, 56.00, 56.74, 79.10, 104.2, 111.0, 111.3, 126.4, 127.2, 128.1, 129.0, 129.4, 130.3, 134.5, 150.9, 151.1, 178.6. HRMS calcd. for $C_{23}H_{20}FNO_5$ $[M + Na]^+$ 432.1231; found 432.1238.

(*R*)-1-Benzyl-5-chloro-3-hydroxy-3-(2-hydroxy-4,5-dimethoxyphenyl)indolin-2-one (11c): Semi-solid; yield 85%; $[\alpha]_{20}^{D}$= +8.46 (c 0.25, $CHCl_3$); 88% ee; HPLC [Chiralpak IA, hexane/i-PrOH, 70:30, 1.0 mL/min, 254 nm, t_R = 7.19 min (major) and t_R = 9.01 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.84 (s, 1H, OH), 7.25-7.51 (m, 8H, ArH), 6.65-6.73 (m, 1H, ArH), 6.31 (s, 1H, ArH), 4.91 (dd, J= 40.8 Hz, J= 15.6 Hz, 2H, CH_2), 4.35 (s, 1H, OH), 3.86 (s, 3H, OCH_3), 3.64 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 45.24, 57.01, 57.75, 80.11, 105.2, 112.1, 112.3, 116.3, 127.4, 128.2, 129.1, 130.1, 130.4, 131.3, 135.5, 141.9, 143.9, 151.9, 152.1, 179.6. HRMS calcd. for $C_{23}H_{20}ClNO_5$ $[M + Na]^+$ 426.1143; found 426.1141.

(*R*)-1-Benzyl-5-bromo-3-hydroxy-3-(2-hydroxy-4,5-dimethoxyphenyl)indolin-2-one (11d): Brown semi-solid; yield 81%; $[\alpha]_{20}^{D}$= +9.26 (c 0.25, $CHCl_3$); 87% ee; HPLC [Chiralpak IA, hexane/i-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 7.74 min (minor) and t_R = 8.50 min (major)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.50 (s, 1H, OH), 7.09-7.36 (m, 6H, ArH), 6.66-6.93 (m, 2H, ArH), 6.16 (s, 1H, ArH), 6.15 (s, 1H, ArH), 4.81-5.89 (m, 3H), 3.74 (s, 3H, OCH_3), 3.27 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.27, 55.32, 55.81, 78.13, 92.00, 95.65, 103.9, 109.9, 110.0, 112.6, 112.8, 116.2, 116.3, 127.7, 127.9, 128.8, 135.5, 157.2, 159.3, 161.4, 176.5. HRMS calcd. for $C_{23}H_{20}BrNO_5$ $[M + H]^+$ 470.0603; found 470.0630

(*R*)-1-Benzyl-3-hydroxy-3-(2-hydroxy-4,5-dimethoxyphenyl)-5-iodoindolin-2-one (11e): Brown semi-solid; yield 83%; $[\alpha]_{20}^{D}$= +11.6 (c 0.25, $CHCl_3$); 60% ee; HPLC [Chiralpak IC, hexane/i-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 10.9 min (major) and t_R = 14.6 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.46 (s, 1H, OH), 7.11-7.37 (m, 6H, ArH), 6.67-6.91 (m, 2H, ArH), 6.17 (d, J= 3.0 Hz, 1H, ArH), 5.89 (d, J= 3.0 Hz, 1H, ArH), 4.90(dd, J = 30.0 Hz, J = 15.0 Hz, 2H, CH_2), 4.57 (s, 1H, OH), 3.75 (s, 3H, OCH_3), 3.28 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.10, 55.96, 56.60, 78.45, 79.31, 104.2, 110.3, 111.4, 115.7, 123.9, 125.9, 127.2, 127.9, 128.9, 129.1, 130.4, 134.8, 142.4, 142.6, 150.9, 151.3, 179.1. HRMS calcd. for $C_{23}H_{20}INO_5$ $[M + Na]^+$ 540.0283; found 540.0272.

(*R*)-1-Benzyl-3-hydroxy-3-(2-hydroxy-4,5-dimethoxyphenyl)-5-methylindolin-2-one (11f): Brown semi-solid; yield 79%; $[\alpha]_{20}^{D}$=+2.36 (c 0.25, $CHCl_3$); 81% ee; HPLC [Chiralpak IC, hexane/i-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 7.56 min (major) and t_R = 9.15 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H, OH), 6.91-7.35 (m, 6H, ArH), 6.65-6.89 (m, 2H, ArH), 5.87-6.14 (m, 2H, ArH), 4.97 (s, 1H, OH), 4.09-4.92 (m, 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 1.76 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.13, 44.09, 55.96, 56.69, 79.44, 104.1, 110.1, 111.6, 115.8, 126.6, 127.2, 127.9, 128.9, 129.1, 130.7, 133.7, 134.9, 139.9, 142.6, 150.9, 151.3, 178.9. HRMS calcd. for $C_{24}H_{23}NO_5$ $[M + Na]^+$ 428.1473 ; found 428.1483.

(*R*)-1-Benzyl-3-hydroxy-3-(2-hydroxy-4,5-dimethoxyphenyl)-5-methoxyindolin-2-one (11g): Brown oil; yield 80%; $[\alpha]_{20}^{D}$= +3.29 (c 0.25, $CHCl_3$); 81% ee; HPLC [Chiralpak IA, hexane/i-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 11.6 min (major) and t_R = 19.1 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.24 (s, 1H, OH), 7.07-7.35 (m, 7H, ArH), 6.65-6.70 (m, 2H, ArH), 6.32 (d, J= 1.8 Hz, 1H, ArH), 4.88 (dd, J= 42.4 Hz, J= 15.3 Hz, 2H, CH_2), 4.37 (s, 1H, OH), 3.85 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 2.34 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.32, 44.28, 56.14, 56.88, 79.63, 104.3, 110.2, 111.7, 116.0, 126.8, 127.4, 128.1, 129.1, 130.8, 133.8, 135.1, 140.1, 142.8, 151.1, 151.5, 179.2. HRMS calcd. for $C_{24}H_{23}NO_6$ $[M+Na]^+$ 444.1423 ; found 428.1439

(*R*)-1-Allyl-5-fluoro-3-hydroxy-3-(2-hydroxy-4,5-dimethoxyphenyl)indolin-2-one (11h): Brown oil, yield 83 %; $[\alpha]_{20}^{D}$= +12.3 (c 0.25, $CHCl_3$); 84% ee; HPLC [Chiralpak IA, hexane/i-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 6.07 min (major) and t_R = 8.36 min (minor)]; ^{1}H NMR (300 MHz,$CDCl_3$) δ 9.48 (s, 1H, OH), 6.85-7.41 (m, 4H, ArH), 6.18 (d, J= 2.4 Hz, 1H, ArH), 5.89-5.95 (m, 2H), 5.28-5.40 (m, 2H, CH_2), 4.25-4.54 (m, 2H, CH_2), 3.75 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.64, 55.99, 56.72, 78.76, 86.29, 104.1, 111.1, 112.1, 115.2, 118.3, 130.2, 131.4, 134.0, 139.1, 142.1, 142.8, 150.8, 150.9, 177.9. HRMS calcd. for $C_{19}H_{18}FNO_5$ $[M + Na]^+$ 382.1066 ; found 382.4695.

(*R*)-1-Allyl-5-chloro-3-hydroxy-3-(2-hydroxy-4,5-dimethoxyphenyl)indolin-2-one (11i): Brown semi-solid; yield 81%; $[\alpha]_{20}^{D}$= +11.5 (c 0.25, $CHCl_3$); 92% ee; HPLC [Chiralpak IA, hexane/i-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 8.84 min (major) and t_R = 11.8 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (s, 1H, OH), 7.26-7.52 (m, 2H, ArH), 6.84 (d, J= 9.0 Hz, 1H, ArH), 6.63 (d, J = 6.0 Hz, 1H, ArH), 6.33 (d, J = 6.0 Hz, 1H, ArH), 5.79-5.85 (m, 1H, CH), 5.19-5.77 (m, 2H, CH_2), 4.28-4.44 (m, 2H, CH_2), 3.87 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.72, 55.97, 56.80, 78.97, 104.1, 111.1, 111.2, 115.2, 118.3, 126.3, 129.3, 130.2, 130.3, 130.8, 140.9, 142.8, 150.9, 151.1, 178.3. $C_{19}H_{18}ClNO_5$ $[M+Na]^+$ 398.0767 ; found 398.0829.

(*R*)-1-Allyl-5-bromo-3-hydroxy-3-(2-hydroxy-4,5-dimethoxyphenyl)indolin-2-one (11j): Semi-solid; yield 79%; [α]20D= +12.8 (c 0.25, CHCl3); 84% ee; HPLC [Chiralpak IA, hexane/i-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 10.2 min (major)

and t_R = 13.6 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.35 (s, 1H, OH), 7.23-7.36 (m, 3H, ArH), 6.17-6.79 (m, 2H, ArH), 5.85-5.94 (m, 2H), 5.28-5.41 (m, 2H, CH_2), 4.22-4.51 (m, 2H, CH_2), 4.11 (s, 1H, OH), 3.76 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.69, 55.98, 56.78, 78.90, 104.1, 111.1, 111.6, 115.2, 116.5, 118.3, 129.1, 130.2, 131.2, 133.1, 141.4, 142.8, 150.9, 151.0, 178.1. HRMS calcd. for $C_{19}H_{18}BrNO_5$ $[M+Na]^+$ 442.0261 ; found 442.0320.

(*R*)-1-Allyl-3-hydroxy-3-(2-hydroxy-4,5-dimethoxyphenyl)-5-iodoindolin-2-one (11k): Semi-solid; yield 84%; $[\alpha]_{20}^{D}$= +15.6 (c 0.25, $CHCl_3$); 90% ee; HPLC [Chiralpak IA, hexane/i-PrOH, 70/30, 1 mL/min, 254 nm, t_R = 6.53 min (major) and t_R = 9.83 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.56 (s, 1H, OH), 7.11-7.38 (m, 3H, ArH), 6.69-6.71 (m, 2H, ArH), 5.87-5.89 (m, 3H), 4.86-4.98 (m, 2H, CH_2), 3.78 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.64, 55.98, 56.73, 78.76, 86.27, 104.1, 111.1, 112.1, 115.2, 118.3, 130.2, 131.4, 134.7, 139.1, 142.1, 142.8, 150.8, 151.0, 177.9. HRMS calcd. for $C_{19}H_{18}INO_5$ $[M + Na]^+$ 490.0127 ; found 490.0121.

(*R*)-1-((*E*)-But-2-enyl)-5-chloro-3-hydroxy-3-(2-hydroxy-4,5-dimethoxyphenyl)indolin-2-one (11l): Light brown oil; yield 80%; $[\alpha]_{20}^{D}$= +5.69 (c 0.25, $CHCl_3$); 75% ee; HPLC [Chiralpak IC, hexane/i-PrOH, 70/30, 1 mL/min, 254 nm, t_R = 7.76 min (major) and t_R = 10.0 min (minor)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.94 (s, 1H, OH), 7.28-7.52 (m, 2H, ArH), 6.87 (d, J= 10.0 Hz, 1H, ArH), 6.63 (s, 1H, ArH), 6.33 (s, 1H, ArH), 5.37-5.75 (m, 2H, CH_2), 4.49 (s, 1H, OH), 4.19-4.28 (m, 2H, CH_2), 3.86 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 1.69 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.65, 42.23, 55.95, 56.80, 79.00, 104.1, 111.1, 115.2, 122.8, 123.0, 126.3, 129.2, 130.2, 130.3, 131.0, 141.0, 142.7, 151.0, 178.1. HRMS calcd. for $C_{20}H_{20}ClNO_5$ $[M+Na]^+$ 412.0922; found 412.0934.

(*R*)-1-Allyl-3-hydroxy-3-(2-hydroxy-4,5-dimethoxyphenyl)-5-methylindolin-2-one (11m): Brown semi-solid; yield 82%; $[\alpha]_{20}^{D}$= +14.8 (c 0.25, $CHCl_3$); 83% ee; HPLC [Chiralpak IA, hexane/i-PrOH, 70/30, 1 mL/min, 254 nm, t_R = 6.08 min (major) and t_R = 7.01 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.40 (s, 1H, OH), 6.43-7.44 (m, 5H, ArH), 5.85-5.96 (m, 1H, CH), 5.27-5.33 (m, 2H, CH_2), 4.32-4.50 (m, 3H), 3.94 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 2.47 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.16, 42.63, 55.94, 56.73, 79.32, 104.1, 109.9, 111.6, 115.8, 117.9, 126.6, 129.1, 130.6, 133.6, 139.9, 142.6, 150.8, 151.3, 178.7.

(*R*)-5-Chloro-3-hydroxy-3-(2-hydroxy-4,5-dimethoxyphenyl)-1-methylindolin-2-one (11n): Brown semi-solid; yield 83%; $[\alpha]_{20}^{D}$= +7.32 (c 0.25, CHCl3); 85% ee; HPLC [Chiralpak IA, hexane/i-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 7.57 min (minor) and t_R = 8.08 min (major)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (s, 1H, OH), 7.26-7.48 (s, 2H, ArH), 6.79-6.86 (s, 1H, ArH), 6.58 (s, 1H, ArH), 6.31 (s, 1H, ArH), 4.67 (s, 1H, OH), 3.83 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 1.67 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.84, 56.13, 56.88, 78.23, 104.5, 110.5, 111.4, 112.4, 113.9, 125.6, 126.6, 130.6, 151.2, 178.4. HRMS calcd. for $C_{17}H_{16}ClNO_5$ $[M+Na]^+$ 372.0609 ; found 372.0644.

(*R*)-3-Hydroxy-3-(2-hydroxy-4,5-dimethoxyphenyl)-1-(prop-2-ynyl)indolin-2-one (11o): Brown oil; yield 83%; $[\alpha]_{20}^{D}$= +18.3 (c 0.25, $CHCl_3$); 70% ee; HPLC [Chiralpak IA, hexane/i-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 7.39 min (major) and t_R = 10.4 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.84 (s, 1H, OH), 7.10-7.49 (m, 3H, ArH), 6.55 (s, 1H, ArH), 6.28 (s, 1H, ArH), 4.69 (s, 1H, OH), 4.46 (dd, J= 42.6 Hz, J= 17.7 Hz, 2H, CH_2), 3.79 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 2.26 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.64, 36.72, 56.03, 56.71, 73.14, 79.23, 103.8, 106.1, 110.2, 111.5, 124.2, 129.4, 130.2, 130.5, 142.6, 150.8, 151.2, 162.8, 177.9. HRMS calcd. for $C_{19}H_{17}NO_5$ $[M+Na]^+$ 362.0999 ; found 362.1049.

(*R*)-1-Benzyl-5-fluoro-3-hydroxy-3-(2-hydroxy-4-methoxyphenyl)indolin-2-one (11p): Brown semi-solid; yield 85%; $[\alpha]_{20}^{D}$= +3.11 (c 0.25, $CHCl_3$); 77% ee; HPLC [Chiralpak IA, hexane/i-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 11.2 min (major) and t_R = 14.6 min (minor)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.13 (s, 1H, OH), 7.24-7.62 (m, 7H, ArH), 6.61-6.75 (m, 3H, ArH), 6.38-6.41 (m, 1H, ArH), 4.89 (dd, J= 50.0 Hz, J= 20.0 Hz, 2H, CH_2), 4.43 (s, 1H, OH), 3.79 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.18, 55.38, 79.08, 104.8, 106.8, 111.7, 116.6, 127.1, 128.1, 128.2, 129.0, 129.2, 133.0, 134.4, 141.4, 157.6, 161.8, 178.6. HRMS calcd. for $C_{22}H_{18}FNO_4$ $[M+Na]^+$ 402.1112 ; found 402.1149.

(*R*)-1-Benzyl-5-chloro-3-hydroxy-3-(2-hydroxy-4-methoxyphenyl)indolin-2-one (11q): Brown oil; yield 83%; $[\alpha]_{20}^{D}$= +0.79 (c 0.25, $CHCl_3$); 82% ee; [Chiralpak IA, hexane/i-PrOH, 80:20, 1 mL/min, 254 nm, t_R = 17.5 min (major) and t_R = 25.9 min (minor)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.34 (s, 1H, OH), 7.00-7.33 (m, 8H, ArH), 6.70-6.99 (m, 2H, ArH), 6.34-6.40 (m, 1H, ArH), 4.90 (dd, J= 55.0 Hz, J= 15.0 Hz, 2H, CH_2), 4.48 (s, 1H, OH), 3.78 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.24, 55.37, 79.33, 104.9, 106.8, 110.9, 111.0, 114.1, 114.2, 116.5, 116.7, 116.8, 127.1, 128.0, 128.1, 129.0, 130.9, 131.0, 134.5, 138.2, 157.7, 158.8, 160.7, 161.8, 178.9. HRMS calcd. for $C_{22}H_{18}ClNO_4$ $[M + Na]^+$ 418.0822; found 418.0836.

(*R*)-1-Benzyl-5-bromo-3-hydroxy-3-(2-hydroxy-4-methoxyphenyl)indolin-2-one (11r): Semi-solid; yield 86%; $[\alpha]_{20}^{D}$= +2.39 (c 0.25, $CHCl_3$); 84% ee; [Chiralpak IC, hexane/i-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 7.39 min (major) and t_R = 8.75 min (minor)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.48 (m, 7H, ArH), 6.62-6.76 (m, 3H, ArH), 6.38-6.41 (m, 1H, ArH), 4.90 (dd, J= 45.0 Hz, J= 15.0 Hz, 2H, CH_2), 3.79 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.14, 55.36, 79.03, 104.5, 104.6, 106.6, 106.7, 110.2, 111.6, 116.5, 116.6, 127.1, 127.2, 128.0, 129.0, 131.8, 132.9, 134.4, 141.3, 157.5, 157.9, 161.7, 178.5. HRMS calcd. for $C_{22}H_{18}BrNO_4$ $[M+Na]^+$ 462.0311 ; found 462.0298.

(*R*)-1-Benzyl-3-hydroxy-3-(2-hydroxy-4-methoxyphenyl)-5-methoxyindolin-2-one (11s): Brown oil; yield 82%; $[\alpha]_{20}^{D}$= +5.69 (c 0.25, $CHCl_3$); 63% ee; [Chiralpak IC, hexane/i-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 7.51 min (minor) and t_R = 8.09 min (major)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.71 (s, 1H, OH), 7.25-7.34 (m, 6H, ArH), 7.13 (d, J= 5.0 Hz, 1H, ArH), 6.37-6.82 (m, 4H, ArH), 4.90 (dd, J= 35.0 Hz, J= 15.0 Hz, 2H, CH_2), 3.80 (s, 6H, 2 X OCH_3), ^{13}C NMR (125 MHz, $CDCl_3$) δ 44.18, 55.37, 55.87, 79.68, 105.1, 106.8, 110.8, 113.0, 115.0, 117.4, 127.1, 127.9, 128.6, 128.9, 130.2, 134.8, 135.5, 156.7, 158.1, 161.7, 179.1. HRMS calcd. for $C_{23}H_{21}NO_5$ $[M+Na]^+$ 414.1312 ; found 414.1340.

(*R*)-1-Allyl-5-chloro-3-hydroxy-3-(2-hydroxy-4-methoxyphenyl)indolin-2-one (11t): Brown oil; yield 81%;

$[\alpha]_{20}^{D}$= +11.9 (c 0.25, $CHCl_3$); 85% ee; [Chiralpak IC, hexane/i-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 7.58 min (major) and t_R = 9.58 min (minor)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.49 (m, 2H, ArH), 6.85 (d, J= 10.0 Hz, 2H, ArH), 6.72 (d, J= 10.0 Hz, 1H, ArH), 6.61 (d, J= 5.0 Hz, 1H, ArH), 6.39 (s, 1H, OH), 5.79-5.83 (m, 1H, CH), 5.21-5.27 (m, 2H, CH_2), 4.25-4.42 (m, 2H, CH_2), 3.78 (s, 3H, OCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.73, 55.38, 79.08, 104.9, 106.8, 111.1, 116.7, 118.4, 126.5, 128.1, 129.3, 130.2, 130.3, 130.9, 140.8, 157.7, 161.8, 178.4. HRMS calcd. for $C_{18}H_{16}ClNO_4$ $[M+Na]^+$ 368.0660; found 368.0715.

(*R*)-3-Hydroxy-3-(2-hydroxy-4-methoxyphenyl)-1-(prop-2-ynyl)indolin-2-one (11u): Brownish semisolid; yield 73%; $[\alpha]_{20}^{D}$= +13.6 (c 0.25, $CHCl_3$); 59% ee; [Chiralpak IC, hexane/i-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 10.8 min (major) and t_R = 14.3 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.18 (s, 1H, OH), 7.11-7.49 (m, 4H, ArH), 6.28-6.67 (m, 3H, ArH), 4.47 (dd, J= 30.9 Hz, J= 17.7 Hz, 2H, CH_2), 3.74 (s, 3H, OCH_3), 2.26 (s, 1H, CH) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.83, 55.50, 77.48, 104.8, 106.7, 107.5, 109.6, 110.3, 116.8, 124.3, 126.2, 128.9, 130.5, 141.4, 157.9, 161.8, 178.0. HRMS calcd. for $C_{18}H_{15}NO_4$ $[M+Na]^+$ 332.0893 ; found 332.0869.

(*R*)-3-Hydroxy-3-(2-hydroxy-4-methoxyphenyl)-1-methylindolin-2-one (11v): Viscous oil; yield 79%; $[\alpha]_{20}^{D}$= +2.89 (c 0.25, $CHCl_3$); 69% ee; [Chiralpak IC, hexane/i-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 14.8 min (major) and t_R = 22.8 min (minor)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.70 (s, 1H, OH), 7.24-7.53 (m, 3H, ArH), 6.94 (d, J= 10.0 Hz, 1H, ArH), 6.65 (d, J= 5.0 Hz, 1H, ArH), 6.33-6.35 (m, 1H, ArH), 4.05 (s,1H,OH), 3.79 (s, 3H, OCH_3), 3.25 (s, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.69, 55.36, 79.06, 105.1, 106.7, 109.2, 123.9, 126.2, 128.6, 130.4, 158.2, 161.8, 179.2. HRMS calcd. for $C_{16}H_{15}NO_4$ $[M+Na]^+$ 308.0893; found 308.0930.

(*R*)-1-Benzyl-5-fluoro-3-hydroxy-3-(2-hydroxy-4,6-dimethoxyphenyl)indolin-2-one (11w): Semi-solid; yield 87%; $[\alpha]_{20}^{D}$= +0.49 (c 0.25, $CHCl_3$); 71% ee; [Chiralpak IA, hexane/i-PrOH, 90:10, 1 mL/min, 254 nm, t_R = 17.0 min (major) and t_R = 28.1 min (minor)]; ^{1}H NMR (300 MHz,$CDCl_3$) δ 9.55 (s, 1H, OH), 7.09-7.38 (m, 5H, ArH), 6.66-6.92 (m, 3H, ArH), 6.14 (d, J= 2.1 Hz, 1H, ArH), 5.88 (d, J=2.1 Hz, 1H, ArH), 4.88 (dd, J=36.9 Hz, J=15.6 Hz, 2H, CH_2), 3.74 (s, 3H, OCH_3), 3.26 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.34, 55.36, 55.85, 78.92, 103.9, 110.0, 110.1, 112.5, 112.7, 127.5, 127.7, 127.9, 128.4, 128.9, 129.3, 135.5, 138.5, 157.3, 159.4, 160.7, 161.3, 176.9. HRMS calcd. for $C_{23}H_{20}FNO_5$ $[M + Na]^+$ 432.1231; found 432.1244.

(*R*)-1-Allyl-5-chloro-3-hydroxy-3-(2-hydroxy-4,6-dimethoxyphenyl)indolin-2-one (11x): Brown semi-solid; yield 83%; $[\alpha]_{20}^{D}$= +8.76 (c 0.25, $CHCl_3$); 76% ee; [Chiralpak IA, hexane/i-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 9.67 min (major) and t_R = 10.5 min (minor)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.38 (s, 1H, OH), 7.28-7.38 (m, 3H, ArH), 6.81 (d, J=5.0 Hz, 1H, ArH), 6.21 (d, J= 5.0 Hz, 1H, ArH), 5.87-5.94 (m, 1H), 5.32-5.39 (m, 2H, CH_2), 4.27-4.50 (m, 2H, CH_2), 4.21 (s, 1H, OH), 3.67 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.36, 56.08, 56.22, 78.94, 104.1, 110.9, 111.2, 111.3, 123.1, 126.4, 129.3, 130.3, 130.4, 131.1, 141.0, 141.1, 151.0, 151.1, 178.3. HRMS calcd. for $C_{19}H_{18}ClNO_5$ $[M+Na]^+$ 398.0766 ; found 398.0813.

(*R*)-3-Hydroxy-3-(2-hydroxy-4,6-dimethoxyphenyl)-1-(prop-2-ynyl)indolin-2-one (11y): Brown semi-solid; yield 82%; $[\alpha]_{20}^{D}$= +5.19 (c 0.25, $CHCl_3$); 68% ee; [Chiralpak IC, hexane/i-PrOH, 80:20, 1 mL/min, 254 nm, t_R = 26.5 min (major) and t_R = 43.9 min (minor)]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.44 (s, 1H, OH), 7.07-7.41 (m, 4H, ArH), 6.19 (d, J = 5.0 Hz, 1H, ArH), 5.93 (d, J = 5.0 Hz, 1H, ArH), 4.30-4.87 (m, 2H, CH_2), 3.90 (s, 1H, OH), 3.56 (s, 3H, OCH_3), 2.33 (s, 1H, CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 29.40, 55.30, 55.89, 77.27, 78.18, 91.79, 95.41, 104.4, 109.3, 123.5, 124.6, 129.9, 130.1, 141.5, 157.2, 159.1, 161.3, 175.6. HRMS calcd. for $C_{19}H_{17}NO_5$ $[M+Na]^+$ 362.0999 ; found 362.1055.

(*R*)-3-Hydroxy-3-(2-hydroxy-4,5-dimethoxyphenyl)indolin-2-one (11z): Brown semi-solid; yield 78%; $[\alpha]_{20}^{D}$= +10.2 (c 0.25, MeOH); 80% ee; [Chiralpak IA, hexane/i-PrOH, 70:30, 1 mL/min, 254 nm, t_R = 6.88 min (major) and t_R = 9.64 min (minor)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91 (s, 1H, NH), 8.26 (s, 1H, OH), 7.09-7.58 (m, 2H, ArH), 6.54-6.88 (m, 3H, ArH), 6.28 (d, J = 6.1 Hz, 1H, ArH), 4.67 (s, 1H, OH), 3.89 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.10, 56.22, 78.92, 104.3, 110.0, 111.3, 111.4, 115.3, 126.5, 129.3, 130.3, 130.4, 130.9, 141.2, 151.1, 151.2, 178.4. . HRMS calcd. for $C_{16}H_{15}NO_5$ [M + Na]$^+$ 324.0847; found 324.0869.

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Notes and references

[a]*Department of Chemistry, U.G.C. Centre of Advance Studies in Chemistry, Guru Nanak Dev University, Amritsar, India.*
Fax: (+)91-183-2258820
E-mail: sschimni@yahoo.com, sschimni.chem@gndu.ac.in

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‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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