Chapter 3

Enantioselective Friedel-Crafts Reaction of Indoles with Isatins: Facile Synthesis of 3-Indolyl-3-hydroxyoxindole Derivatives

3.1 Introduction

The Friedel-Crafts (F-C) reaction, one of the oldest organic synthetic methods, is still one of the most powerful carbon-carbon bond forming reaction from benchtop experiments to industrial processes for procuring valuable building blocks.\(^{101}\) Although Friedel-Crafts reaction has proven its significance since its discovery in 1877,\(^{102}\) but the catalytic asymmetric versions of this methodology have been actively developed during the last decade.\(^{60}\) The first example of catalytic asymmetric Friedel-Crafts reaction was reported by Bigi \textit{et al.} in 1985, using chiral alkoxyaluminum chloride catalyst for ortho-alkylation of phenols.\(^{103}\) Since then, many groups have directed their efforts for developing new routes to devise highly efficient strategies for asymmetric Friedel-Crafts reaction. The recent upsurge in the development of asymmetric catalytic Friedel-Crafts reaction is based on the development of chiral transition metal based catalysts and organocatalysts for this transformation.\(^{60}\) While the initial examples of catalytic asymmetric Friedel-Crafts reaction describes a metal-catalyzed addition of aromatic substrates to electron deficient \(\sigma\)-((epoxide opening) and \(\pi\)-systems (1,2-carbonyl and 1,4-conjugate additions), but now-a-days, the field of organocatalysis has led to the development of new asymmetric protocols for enantioselective Friedel-Crafts reactions. Organocatalytic asymmetric Friedel-Crafts reaction provides a highly efficient method for the synthesis of valuable chiral arene derivatives that can serve as precursors for asymmetric synthesis of natural products, bioactive molecules and pharmaceuticals (Figure 5).


Indole ring is an important moiety that is present in many natural alkaloids and bioactive molecules. Since its discovery in 1869, indole has become a privileged structure in numerous research areas such as: pharmaceuticals, fragrances, agrochemicals, pigments and material science.\[104\] The importance of indole and its broad spectrum of application justify it being addressed as the “The Lord of the Rings” of aromatic compounds.\[105\] Indole is commonly referred to as an electron-rich heteroaromatic system that shows enhanced reactivity, compared to benzene, in electrophilic aromatic substitutions and addition reactions such as Friedel-Crafts reaction. The enantioselective Friedel-Crafts reactions involving indole derivatives has led to the availability of substituted enantiopure indole derivatives, which serve as precursors for bioactive molecules such as tryptamine, melatonin analogue, 1,2,3,4-tetrahydro-β-carbolines, (-)-harmicine, (-)-flustramine B, serotonin reuptake inhibitor 1 (BMS-594-726), etc. The enantioselective organocatalytic Friedel-Crafts reaction of indole derivatives with various electrophiles such as enals,\[106\] enones,\[107\] nitroalkenes,\[108\]


imines,\textsuperscript{109} \(\alpha\)-ketoesters\textsuperscript{5} and \(\beta,\gamma\)-unsaturated \(\alpha\)-ketoesters,\textsuperscript{110} are well known in the literature. Recently, isatin derivatives have emerged as powerful electrophiles in synthetic organic chemistry.\textsuperscript{111} However, the enantioselective Friedel-Crafts reaction of indole derivatives with isatin derivatives to provide 3-indolyl-3-hydroxyoxindole derivatives was not known.\textsuperscript{112}

Oxindole framework bearing a tetra-substituted carbon stereocenter at the 3-position is a privileged heterocyclic motif that is present in the large family of bioactive natural products and a series of pharmaceutically active compounds.\textsuperscript{113} Among various chiral oxindole derivatives the 3-substituted-3-hydroxyoxindole unit is encountered in a variety of alkaloids and natural products with a wide spectrum of biological activities (Figure 6).\textsuperscript{114} On the other hand, enantioselective synthesis of stereogenic quaternary carbon center by the addition of carbon nucleophiles to ketones is considered a


a formidable task.\textsuperscript{115} The low reactivity of these substrates relative to aldehydes is often a limitation. This requires the activation of both nucleophile as well as electrophile by a bifunctional organocatalyst having acidic as well as basic sites. In this regard, \textit{Cinchona} alkaloids and their modified derivatives have emerged as very efficient organocatalysts for catalyzing a variety of enantioselective transformations. Owing to the synthetic challenge associated with the development of quaternary stereocenter and the synthetic utility of indole as well as oxindole derivatives, it was planned to develop an organocatalytic methodology to synthesize enantiopure 3-indolyl-3-hydroxyoxindole derivatives bearing quaternary stereogenic center \textit{via} \textit{Cinchona} alkaloid catalyzed Friedel-Crafts reaction of indoles with isatin derivatives.

3.2 Results and Discussion

It was envisaged that 9-hydroxy-/or 6'-hydroxy-(in case of cupreine and cupreidine) group of the \textit{Cinchona} alkaloids would activate the carbonyl group of isatin through hydrogen bonding, while the quinuclidine nitrogen would activate and orient indole through the formation of hydrogen bond (Scheme 56).

Initially, Friedel-Crafts reaction of indole (95a) with isatin (21a) in the presence of 10 mol% of quinidine (QD) in THF at room temperature was investigated (Scheme 57). The progress of the reaction was monitored on TLC which showed the formation of a new product with Rf: 0.3 in hexane : ethyl acetate (4 : 6). After running the reaction for 96 hours the product was purified on silica gel column chromatography using hexane : ethyl acetate (4 : 6) as eluents. The product was isolated in 62% yield and analyzed by NMR spectroscopy. $^1$H NMR spectra in DMSO-d$_6$ at 300 MHz shows two singlet at δ 11.00 and 10.39 corresponding to two 2NH, a 4H multiplet at δ 7.39-7.25 corresponding to ArH, a 1H singlet at δ 7.14 corresponding to ArH, a 4H multiplet at δ 7.10-6.87 corresponding to ArH and a 1H singlet at δ 6.46 corresponding to OH. $^{13}$C NMR spectra in DMSO-d$_6$ at 75 MHz shows signals at δ 178.8, 141.8, 137.0, 133.6, 129.4, 125.0, 124.9, 123.8, 122.1, 121.4, 120.4, 118.8, 115.6, 111.8, 110.0, 75.2. On the basis of this data the product was identified as Friedel-Crafts product (101a).
This was further confirmed by LCMS, that gives m/z at 286.8 corresponding to \((M+Na)^+\). After the identification of product, the optical rotation of 101a was found to be \([\alpha]_{D}^{25} = +66.5\) (c 0.5 in EtOH). The racemic product was prepared by the reaction of indole (95a) with isatin (21a) in the presence of triethylamine as catalyst in ethanol. The racemic sample was resolved with chiral HPLC using Daicel Chiralpak IB column using hexane/iso-propanol (70/30) as mobile phase. Two enantiomer of 101a shows peaks at retention time 11.8 and 15.6 minutes at 217 nm (Figure 8 (a)). The chiral product (101a) shows two peaks at 11.9 and 14.3 minutes with different peak area and the enantiomeric excess was calculated to be 52% (Figure 8 (b)).

Encouraged by this result, the catalytic potential of other natural Cinchona alkaloids quinine (QN), cinchonidine (CD) and cinchonine (CN) for enantioselective Friedel-Crafts reaction of indole (95a) with isatin (21a) was evaluated. These catalysts provide the product (101a) in 61%, 32% and 33% yield and enantioselectivity of 53% ee, 60% ee and 58% ee, respectively (entries 2-4, Table 1).

Further, in order to find a suitable catalyst that provides 101a in high yield and enantioselectivity, it was planned to synthesize modified Cinchona alkaloids. The 6'-OH Cinchona alkaloid i.e. cupreine (CPN) was synthesized using literature procedure.35 The model reaction performed with CPN provides 101a in 82% ee and 81% yield suggesting the role of 6'-OH group in increasing the reactivity and selectivity (entry 5, Table 1). In order to further evaluate the role of phenolic hydroxyl group, the other variant of 6'-OH Cinchona alkaloid i.e. 9-O-benzylcupreine (BnCPN) was synthesized in which 9-OH was blocked with benzyl group.37 The use of BnCPN (10 mol%) as catalyst for the reaction of 95a with 21a provided 101a with enhanced...
enantioselectivity of 90% ee (entry 6, Table 1). The pseudoenantiomeric catalyst, 9-\textit{O}-benzylcupreidine (BnCPD) provided the opposite enantiomer of 101\textit{a} in 85% ee (entry 7, Table 1). The model reaction catalyzed by C9-thiourea derivative of cinchonidine (CDT) and quinine (QNT) afforded 101\textit{a} in low yield (29% and 31%, respectively) and poor enantioselectivity (31% and 29% ee, respectively) (entries 8-9, Table 1). In the catalyst screening for the Friedel-Crafts reaction of 95\textit{a} with 21\textit{a}, BnCPN was found as the best catalyst that gave product 101\textit{a} in 90% ee. So all further optimizations were carried out with BnCPN as catalyst.
Table 1 Catalyst screening for enantioselective Friedel-Crafts reaction of indole (95a) with isatin (21a).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalysts</th>
<th>Yield [%][b]</th>
<th>ee [%][c]</th>
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<tr>
<td>1</td>
<td>QD</td>
<td>62</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
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<td>3</td>
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<td>32</td>
<td>-60</td>
</tr>
<tr>
<td>4</td>
<td>CN</td>
<td>33</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td>CPN</td>
<td>81</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>BnCPN</td>
<td>83</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>BnCPD</td>
<td>82</td>
<td>-85</td>
</tr>
<tr>
<td>8</td>
<td>CDT</td>
<td>31</td>
<td>29</td>
</tr>
<tr>
<td>9</td>
<td>QNT</td>
<td>29</td>
<td>31</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 0.250 mmol isatin (21a), 0.375 mmol of indole (95a) and 10 mol% of catalyst in THF. [b] Yield refers to isolated yield after column chromatography. [c] ee refers to enantiomeric excess determined by chiral HPLC.

In order to increase the reaction rate of BnCPN catalyzed Friedel-Crafts reaction of 95a with 21a, the reaction was performed at above ambient temperatures (entries 2-3, Table 2). The model reaction performed at higher temperature (50 ºC and 40 ºC) increases the yield up to 97% but, lowers the enantioselectivity (entries 2-3,

Table 2 Optimization of reaction condition for enantioselective Friedel-Crafts reaction of indole (95a) with isatin (21a).

<table>
<thead>
<tr>
<th>Entry</th>
<th>BnCPN [x mol %]</th>
<th>Temperature [ºC]</th>
<th>Additive</th>
<th>Yield [%][b]</th>
<th>ee [%][c]</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>27</td>
<td>-</td>
<td>83</td>
<td>90</td>
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<td>6</td>
<td>5</td>
<td>27</td>
<td>-</td>
<td>63</td>
<td>85</td>
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<tr>
<td>7</td>
<td>10</td>
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<td>95</td>
</tr>
<tr>
<td>8</td>
<td>15</td>
<td>27</td>
<td>4Å MS</td>
<td>92</td>
<td>96</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: 0.250 mmol isatin (21a), 0.375 mmol of indole (95a) and x mol% of BnCPN in THF. [b] Yield refers to isolated yield after column chromatography. [c] ee refers to enantiomeric excess determined by chiral HPLC.
Increasing the catalyst loading leads to increased yield without any significant effect on the enantioselectivity of 101a (entries 4-5, Table 2). The lower catalyst loading resulted in lower yield (63%) and lower enantioselectivity (85% ee) of 101a (entry 6, Table 2). Interestingly, performing the reaction in the presence 10 mol% of BnCPN and 4Å molecular sieves (MS) results in the formation of 101a in 82% yield and increased enantioselectivity of 95% ee (entry 7, Table 2). This is probably due to the fact that molecular sieves absorb the traces of moisture in the solvent thus facilitating the hydrogen bonding of catalyst with the substrates. With 15 mol% of BnCPN as catalyst and 4Å molecular sieves as additive, 101a was isolated in 92% yield and 96% ee. Further solvent screening has been carried out using 15 mol% of BnCPN and 4Å MS as additive.

Screening of different organic solvents with 15 mol% BnCPN and 4Å MS as additive shows that the use of THF as solvent provides best enantioselectivity of 101a (entry 1, Table 3) (Figure 9 (a)). Other ethereal solvents such as diethyl ether, MTBE

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvents</th>
<th>Yield [%][b]</th>
<th>ee [%][c]</th>
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</thead>
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<tr>
<td>1</td>
<td>THF</td>
<td>92</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>Diethyl ether</td>
<td>38</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>MTBE</td>
<td>33</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>1,4-Dioxane</td>
<td>83</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>Toluene</td>
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<td>EtOAc</td>
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</tr>
<tr>
<td>12</td>
<td>DMF</td>
<td>15</td>
<td>46</td>
</tr>
<tr>
<td>13[d]</td>
<td>THF</td>
<td>93</td>
<td>-89</td>
</tr>
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</table>

[a] Reaction conditions: 0.250 mmol isatin (21a), 0.375 mmol of indole (95a), 100 mg of 4Å molecular sieves and 15 mol% of BnCPN in dry THF. [b] Yield refers to isolated yield after column chromatography. [c] ee refers to enantiomeric excess determined by chiral HPLC. [d] BnCPD was used as catalyst.
and 1,4-dioxane resulted in lower yield and lower enantioselectivity of 101a (entries 2-4, Table 3). In toluene 101a was obtained in 41% yield and 39% ee (entry 5, Table 3). In chlorinated solvents such as dichloromethane, chloroform and 1,2-dichloroethane, 101a was isolated in high yield (99%, 96% and 94%, respectively), but enantioselectivity was rather low (80% ee, 60% ee and 49% ee) (entries 6-8, Table 3). In polar protic solvents like ethanol and methanol, 101a was isolated in 94% and 95% yield; and 49% ee and 33% ee, respectively (entries 9-10, Table 3). Other solvents such as ethyl acetate (entry 11, Table 3) and DMF (entry 12, Table 3) proved to be less

**Figure 9** HPLC chromatogram of Friedel-Crafts product (101a): (a) with BnCPN and (b) with BnCPD.
efficient in term of product yield and enantio-induction. So the best optimized reaction condition for \textbf{BnCPN} catalyzed enantioselective Friedel-Crafts reaction of indole and isatin constitutes, the use of 15 mol\% of \textbf{BnCPN} organocatalyst, THF as the solvent and 4Å MS as additive at room temperature. In this reaction condition the product \textbf{101a} was isolated in 92\% yield and 96\% ee. In the optimized reaction condition, when the reaction was carried out with \textbf{BnCPD} the opposite enantiomer of \textbf{101a} was isolated in 93\% yield and 89\% ee (entry 13, Table 3) (Figure 9 (b)).

Once armed with the optimized reaction condition, the substrate scope was investigated by screening different indole and isatin derivatives. 5-Flouro, 5-chloro and 5-bromoisatins (\textbf{21b}, \textbf{21c} and \textbf{21d}) react well with indole (\textbf{95a}) yielding the corresponding 3-substituted-3-hydroxyindoles (\textbf{101b}, \textbf{101c} and \textbf{101d}) in 97\%, 98\% and 99\% yield; and 83\% ee, 90\% ee and 92\% ee, respectively (entries 2-4, Table 4). The reaction of 5-nitroisatin (\textbf{21e}) with \textbf{95a} occurs with high yield of 98\% and good enantioselectivity of 83\% ee (entry 5, Table 4). The N-alkylated isatins (\textbf{21f}, \textbf{21g} and \textbf{21h}) also reacted with indole (\textbf{95a}) to provide corresponding adducts (\textbf{101f}, \textbf{101g} and \textbf{101h}) in 89\%, 88\% and 99\% yield; and 85\% ee, 88\% ee and 88\% ee, respectively (entries 6-8, Table 4).

The 5-substituted indoles also reacted efficiently with isatin derivatives in the presence of \textbf{BnCPN}. The reactions of 5-methoxyindole (\textbf{95b}) with isatin derivatives (\textbf{21a}, \textbf{21d} and \textbf{21g}) provide corresponding oxindole derivatives (\textbf{101i}, \textbf{101j} and \textbf{101k}) in 97\%, 99\% and 95\% yield; and 97\% ee, 99\% ee and 93\% ee, respectively (entry 9-11, Table 4). 5-Bromoindole (\textbf{95c}) and 5-nitroindole (\textbf{95d}) reacts with isatin (\textbf{21a}) providing \textbf{101l} and \textbf{101m} in 92\% and 90\% yield; and 80\% ee and 79\% ee, respectively (entries 12-13, Table 4). 2-Methylindole (\textbf{95e}) reacts with isatin (\textbf{21a}) to provide \textbf{101n} in 96\% yield and only in 17\% ee (entry 14, Table 4). Enantiomeric excess of the Friedel-Crafts adducts could be enriched to >99\% after crystallization from \textit{iso}-propanol (entries, 1 and 9, Table 4).

To demonstrate the practical utility of this method, the Friedel-Crafts reaction of isatin (\textbf{21a}) and indole (\textbf{95a}) was performed at 10 mmol scale, using 10 mol\% of \textbf{BnCPN} (Scheme 58). The desired product (\textbf{101a}) was formed in 91\% yield and 95\% ee. After crystallization from \textit{iso}-propanol, 81\% of \textbf{101a} was isolated in >99\% ee.
Table 4 Substrate scope for BnCPN catalyzed Friedel-Crafts reaction of indole derivatives (95) with isatin derivatives (21).[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>95 (R¹, R²)</th>
<th>21(R³, R⁴)</th>
<th>101</th>
<th>Yield [%][b]</th>
<th>ee [%][c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>95a (R¹ = H, R² = H)</td>
<td>21a (R³ = H, R⁴ = H)</td>
<td>101a</td>
<td>92</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(&gt;99)[d]</td>
</tr>
<tr>
<td>2</td>
<td>95a (R¹ = H, R² = H)</td>
<td>21b (R³ = H, R⁴ = F)</td>
<td>101b</td>
<td>97</td>
<td>83</td>
</tr>
<tr>
<td>3</td>
<td>95a (R¹ = H, R² = H)</td>
<td>21c (R³ = H, R⁴ = Cl)</td>
<td>101c</td>
<td>98</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>95a (R¹ = H, R² = H)</td>
<td>21d (R³ = H, R⁴ = Br)</td>
<td>101d</td>
<td>99</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>95a (R¹ = H, R² = H)</td>
<td>21e (R³ = H, R⁴ = NO₂)</td>
<td>101e</td>
<td>98</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>95a (R¹ = H, R² = H)</td>
<td>21f (R³ = Me, R⁴ = H)</td>
<td>101f</td>
<td>89</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>95a (R¹ = H, R² = H)</td>
<td>21g (R³ = Bn, R⁴ = H)</td>
<td>101g</td>
<td>88</td>
<td>88</td>
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<tr>
<td>8</td>
<td>95a (R¹ = H, R² = H)</td>
<td>21h (R³ = Me, R⁴ = Br)</td>
<td>101h</td>
<td>99</td>
<td>88</td>
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<tr>
<td>9</td>
<td>95b (R¹ = MeO, R² = H)</td>
<td>21a (R³ = H, R⁴ = H)</td>
<td>101i</td>
<td>97</td>
<td>97</td>
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<td>(&gt;99)[d]</td>
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<td>10</td>
<td>95b (R¹ = MeO, R² = H)</td>
<td>21d (R³ = H, R⁴ = Br)</td>
<td>101j</td>
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<td>11</td>
<td>95b (R¹ = MeO, R² = H)</td>
<td>21g (R³ = Bn, R⁴ = H)</td>
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<tr>
<td>13</td>
<td>95d (R¹ = NO₂, R² = H)</td>
<td>21a (R³ = H, R⁴ = H)</td>
<td>101m</td>
<td>90</td>
<td>79</td>
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<tr>
<td>14</td>
<td>95e (R¹ = H, R² = Me)</td>
<td>21a (R³ = H, R⁴ = H)</td>
<td>101n</td>
<td>96</td>
<td>17</td>
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</tbody>
</table>

[a] Reaction conditions: 0.250 mmol isatins (21), 0.375 mmol of indoles (95), 15 mol% of BnCPN and 100 mg of 4Å molecular sieves in dry THF at rt. [b] Yield refers to isolated yield after column chromatography. [c] ee refers to enantiomeric excess determined by chiral HPLC. [d] ee value after crystallization from iso-propanol.

The absolute configuration of stereogenic center in the adduct (101) has been assigned as (S) on the basis of the X-ray structure of 101a (Figure 10).[116] The single crystal X-ray structure of 101a indicates that the crystal has an orthorhombic crystalline state with symmetrical space group P 2₁ 2₁ 2₁.

[116] CCDC 874066 contains the supplementary crystallographic data of 101a.
In order to demonstrate the bifunctional mode of catalysis by 9-O-benzylcupreine (BnCPN), where the quinuclidine moiety interacts with NH of indole and the C6' hydroxyl group activates the isatin carbonyl via hydrogen bond interactions, the catalysis by 9-O-benzylcinchonidine (BnCD) and 9-O-benzylquinine (BnQN) having no free OH group were studied (Scheme 59). The reactions performed with these catalysts did not yield Friedel-Crafts adduct even after eight days. Similar observation was made on running the reaction with catalyst 185, where quinuclidine tertiary amine is converted to quaternary salt. These results indicate that the simultaneous activation of both reactants by the quinuclidine moiety and 6'-OH of the catalyst is required for the success of the reaction. This point was further proved by the fact that no product formation was observed in BnCPN catalyzed reaction of N-methylindole (95f) with isatin where the NH hydrogen is not available for hydrogen bonding interaction with quinuclidine moiety. In addition to activation, the bifunctional catalyst also provides the favorable orientation for the adduct formation in high enantioselectivity.

Based on these observations a transition state involving a ternary complex between the catalyst, isatin and indole has been proposed (Figure 11). In the transition
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Scheme 59 Reactions performed for the elucidation of bifunctional mode of catalysis for enantioselective Friedel-Crafts reaction of indole with isatin.

Figure 11 Plausible transition state for the enantioselective synthesis of 3-indolyl-3-hydroxyoxindole.
3.3 Conclusions
In conclusion, the catalytic potential of bifunctional Cinchona-derived organocatalyst for the enantioselective Friedel-Crafts reaction of indoles with isatins has been explored for the first time. The easily available 9-O-benzylcupreine (BnCPN) catalyzes the enantioselective synthesis of 3-indolyl-3-hydroxyoxindole derivatives in good to excellent yield (up to 99%) and high enantioselectivity (up to 99% ee). On the basis of experimental observations the bifunctional mode of catalysis with BnCPN has been demonstrated.

3.4 Experimental
General Methods:
All reactions were performed in oven-dried glassware. The solvents were dried with conventional methods. The molecular sieves were activated at 300 °C for 2 hours in an oven. NMR spectra were obtained at 300 MHz (JEOL AL-300) and 500 MHz (Bruker Avance 500 MHz) for $^1$H NMR and at 75 MHz (JEOL AL-300) and 100 MHz (Bruker Avance 400 MHz) for $^{13}$C NMR with TMS (in CDCl$_3$ or DMSO-d$_6$) as internal standard. The chemical shifts are reported in δ values relative to TMS and coupling constants ($J$) are expressed in Hz. Spectral patterns are designated as s = singlet; d = doublet; dd = doublet of doublet, t = triplet; br = broad; m = multiplet. IR spectra were obtained with FT-IR Bruker 270-30 spectrophotometer and Varian 660-IR FT-IR spectrometer and expressed in wave numbers (cm$^{-1}$). Mass spectra were recorded on Bruker Esquire 300 LC Mass spectrometer and JEOL AccuTOF DART mass spectrometer. Optical rotations were noted on JASCO DIP-360 digital polarimeter. HPLC analyses were performed on a Shimadzu LC-20AD using Daicel Chiralpak AD-H, and IB columns. The column chromatography was carried out on a column packed with silica gel (60-120 mesh). Melting points were recorded in glass capillaries using melting point apparatus and were uncorrected.

Materials:
Catalysts 1a, 1b were purchased from Merck (India), 2a was purchased from Spectrochem Pvt. Ltd. India and 2b was purchased from Sigma-Aldrich and used as such without any purification. Isatin derivatives 21a and 21d were purchased from Spectrochem Pvt. Ltd. India, 21c was purchased from s.d. fine-chem Ltd. India, 21b was purchased from Sigma-Aldrich and 23e-23h were prepared according to the
procedures known in literature.\textsuperscript{117} Indoles 95a-95e were purchased from Spectrochem Pvt. Ltd. India and 95f was purchased from Sigma-Aldrich.

**Procedure for the synthesis of 9-O-benzylcinchonidine (BnCD) and 9-O-benzylquinine (BnQN) (Scheme 60).\textsuperscript{37}**

To the solution of cinchonidine (CD) or quinine (QN) (3.1 mmol) in DMF (10 mL, freshly distilled from a suspension of CaH\textsubscript{2} in DMF) was added NaH (57 % suspension in mineral oil, 7.7 mmol). The resulting mixture was stirred at room temperature for 2 hours. Then, benzylchloride [3.4 mmol, 431 mg (392 \textmu L)] was added dropwisely via a syringe over a period of 10 minutes. The resulting mixture was stirred overnight. After the completion of reaction, brine (10 mL) was added carefully and the resulting mixture was extracted with ethyl acetate (50 mL). The organic phase was washed with brine (3×25 mL), dried over anhydrous Na\textsubscript{2}SO\textsubscript{4} and concentrated \textit{in vacuo}. The product was purified on a silica gel column using chloroform : methanol (95: 5) as eluents.

\[
\begin{align*}
1a, \text{CD} \quad (X = \text{H}) & \quad \text{BnCl, NaH} \\
1b, \text{QN} \quad (X = \text{OMe}) & \quad \text{DMF, rt}
\end{align*}
\]

**Scheme 60**

**9-O-Benzylcinchonidine (BnCD).**

White wax; R\textsubscript{f}: 0.4 (chloroform : methanol, 9 : 1); 91% yield; \([\alpha]^{25}\text{D} = -92.5 (c, 1.0 \text{ EtOH}); \) \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \(\delta 8.91 (d, J = 4.5 \text{ Hz}, 1\text{H}), 8.25-8.16 (m, 2\text{H}), 7.77-7.72 (m, 1\text{H}), 7.64-7.59 (m, 1\text{H}), 7.55 (d, J = 4.5 \text{ Hz}, 1\text{H}), 7.36-7.27 (m, 5\text{H}), 5.76-5.64 (m, 1\text{H}), 5.52 (br s, 1\text{H}), 4.99-4.90 (m, 2\text{H}), 4.46 (br s, 2\text{H}), 3.55-3.47 (m, 1\text{H}), 3.19-3.12 (m, 2H), 2.79-2.69 (m, 2H), 2.36-2.31 (m, 1\text{H}), 1.90-1.84 (m, 3\text{H}), 1.60-1.56 (m, 2\text{H});

\begin{itemize}
\end{itemize}
$^{13}$C NMR (75 MHz, CDCl$_3$) δ 150.0, 148.5, 140.9, 137.5, 130.4, 128.4, 127.8, 127.6, 126.9, 126.3, 123.2, 118.4, 114.7, 79.7, 71.3, 60.5, 56.4, 43.2, 39.4, 27.7, 27.1, 21.8; m/z (ESI): 385.2260 (M+1)$^+$. 

9-0-Benzylinquinine (BnQN).

Light yellow wax; R$_f$ 0.4 (chloroform : methanol, 9 : 1); 90% yield; [α]$^D_{25}$ = -121.9 (c, 0.7 EtOH); $^1$H NMR (300 MHz, CDCl$_3$) δ 8.75 (d, $J$ = 3.3 Hz, 1H, ArH), 8.05 (d, $J$ = 6.9 Hz, 1H), 7.48 (d, $J$ = 3.3 Hz 1H) 7.40-7.26 (m, 7H), 5.78-5.69 (m, 1H), 5.22 (br s, 1H), 4.97-4.89 (m, 2H), 4.47-4.39 (m, 2H), 3.91 (s, 3H), 3.15 (br s, 1H), 3.15-3.05 (m, 2H), 2.26-2.23 (m, 2H), 1.80-1.50 (m, 5H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 157.8, 147.6, 144.7, 141.9, 137.9, 131.9, 128.5, 127.6, 127.5, 121.8, 119.0, 101.2, 80.4, 71.2, 60.3, 57.1, 55.7, 43.2, 40.0, 27.9, 27.8, 22.6; m/z (ESI): 415.2375 (M+1)$^+$. 

General procedure for the synthesis of cupreine (CPN)$^{35}$ and 9-0-benzylocupreine (BnCPN)$^{37}$ (Scheme 61):

A suspension of the starting Cinchona alkaloid derivative (QN or BnQN) (2.0 mmol) and NaSEt (8.0 mmol, 672 mg) was stirred in dry DMF (15 mL, freshly distilled from the suspension of CaH$_2$ in DMF) at 110 °C under an atmosphere of nitrogen, until the TLC analysis showed that the starting material was completely consumed (10-12 hours). The reaction mixture was allowed to cool down to room temperature and then saturated NH$_4$Cl (10 mL) was added to it followed by the addition of water (15 mL). The pH value of the solution was maintained around 7 and resulting mixture was extracted with ethyl acetate (2×50 mL) and the organic phase was washed with brine.
(4×15 mL), dried over anhydrous Na$_2$SO$_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography using chloroform : methanol (9 : 1) as eluents to obtain the desired product.

**Cupreine (CPN).**

Light brown solid; mp: 168-170 °C $R_f$: 0.3 (chloroform : methanol, 9 : 1); 90% yield; $[\alpha]_D^{25} = -163.0$ (c, 1.0 EtOH); $^1$H NMR (500 MHz, CDCl$_3$): δ 8.56 (d, $J = 4.5$ Hz, 1H), 7.93 (d, $J = 9.1$ Hz, 1H), 7.57 (d, $J = 4.5$ Hz, 1H), 7.33-7.31 (m, 2H), 7.14 (d, $J = 2.3$ Hz, 1H), 5.78 (s, 1H), 5.57-5.53 (m, 1H) 4.89-4.84 (m, 2H), 3.97-3.90 (m, 2H), 3.07-2.92 (m, 2H), 2.72-2.70 (m, 1H), 2.55-2.58 (m, 1H), 2.29-2.31 (m, 1H), 1.95-1.83 (m, 3H), 1.55-1.56 (m, 1H), 1.23-1.25 (m, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ 157.5, 146.4, 146.1, 142.7, 139.8, 131.1, 126.4, 123.2, 118.1, 115.4, 104.0, 69.2, 59.5, 55.5, 43.4, 38.6, 27.3, 26.0, 18.8; m/z (ESI): 311.1731 (M+1)$^+$. 

**9-O-Benzylcupreine (BnCPN).**

White solid; mp: 208-210 $R_f$: 0.3 (chloroform : methanol, 9 : 1); 85% yield; $[\alpha]_D^{25} = -79.0$ (c, 1.0 EtOH); $^1$H NMR (300 MHz, DMSO-d$_6$) δ 10.03 (br s, 1H), 8.63 (d, $J = 4.4$ Hz, 1H), 7.89 (d, $J = 9.2$ Hz, 1H), 7.70-7.15 (m, 8H), 5.92-5.77 (m, 1H), 5.14-4.82 (m, 3H), 4.34 (d, $J = 11.6$ Hz, 1H), 4.27 (d, $J = 11.6$ Hz, 1H), 3.30-2.94 (m, 2H), 2.88-2.70 (m, 1H), 2.50-2.10 (m, 3H), 1.94-1.32 (m, 5H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 155.8, 146.2, 143.3, 143.0, 140.7, 134.4, 131.1, 127.9, 127.2, 121.7, 114.2, 103.9, 70.6, 59.2, 55.9, 42.6, 40.1, 27.5, 27.4, 26.6; m/z (ESI): 401.2204 (M+1)$^+$. 

**Procedure for the synthesis of 9-O-Benzylcupreine (BnCPD)$^{35}$ (Scheme 62):**

To the solution of quinidine (QD) (3.1 mmol, 1.006 g) in DMF (10 mL, freshly distilled from a suspension of CaH$_2$ in DMF) was added NaH (57% suspension in mineral oil, 7.7 mmol). The resulting mixture was stirred at room temperature for 2 hours. Then, benzyl chloride [3.4 mmol, 431 mg (392 μL)] was added dropwisely via a syringe over a period of 10 minutes. The resulting mixture was stirred overnight at room temperature. After the completion of reaction brine (10 mL) was added carefully
and the resulting mixture was extracted with ethyl acetate (50 mL). The organic phase was washed with brine (3×25 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo to obtain crude 9-O-benzylquinidine. The suspension of the crude 9-O-benzylquinidine and NaSEt (12.4 mmol, 1.05 g) was stirred in dry DMF (15 mL, freshly distilled from the suspension of CaH₂ in DMF) at 110 °C under an atmosphere of nitrogen, until the TLC analysis showed that the starting material was completely consumed (12 hours). The reaction mixture was allowed to cool down to room temperature and then saturated NH₄Cl (15 mL) was added to it, followed by the addition of water (20 mL). The pH value of the solution was maintained around 7 and the resulting mixture was extracted with ethyl acetate (2×50 mL) and the organic phase was washed with brine (4×15 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo. The crude product was purified on column chromatography using chloroform : methanol (9 : 1) as eluents to obtain pure 9-O-benzylcupreidine.

\[ \text{Scheme 62} \]

**9-O-Benzylcupreidine (BnCPD).**

White solid; mp: 125-127 °C; Rf: 0.3 (chloroform : methanol, 9 : 1); 85% yield; [α]_D^{25} = +154.3 (c, 1.0, CHCl₃); \(^1\)H NMR (300 MHz, CDCl₃): \( \delta \) 10.92 (br s, 1H), 8.67 (d, \( J = 4.4 \) Hz, 1H), 8.01(d, \( J = 9.2 \) Hz, 1H), 7.86 (s, 1H), 7.44 (br s, 1H), 7.35 (dd, \( J = 2.4 \) Hz, 8.8 Hz, 1H), 7.24-7.28 (m, 5H), 6.97-5.89 (m, 1H), 5.53 (br, s 1H), 4.97 (d, \( J = 10.0 \) Hz, 1H), 4.94 (s, 1H), 4.34-4.25 (m, 2H), 3.56 (br s, 1H), 3.05-3.03 (m, 2H), 2.87-2.78 (m, 2H), 2.26-2.24 (m, 2H), 1.74 (br s, 1H), 1.52-1.39 (m, 2H), 1.13 (br s, 1H); \(^{13}\)C NMR (75 MHz, CDCl₃): \( \delta \) 157.0, 146.5, 143.6, 139.9, 137.7, 131.3, 128.3, 127.9, 127.8, 127.7, 127.6, 123.4, 114.9, 106.7, 79.0, 71.2, 59.0, 49.7, 49.2, 39.6, 28.0, 25.9; m/z (ESI): 401.2201 (M+1)^+. 

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General procedure for the synthesis of CDT (184a) and QNT (184b) (Scheme 63): 118

To a solution of Cinchona-derived amine (CDA or QNA)118 (1.0 mmol) in dry DCM (2 mL), a solution of 3,5-bis(trifluoromethyl)phenyl isothiocyanate [1.1 mmol, 298 mg (201μL)] in dry DCM (1 mL) was added slowly at room temperature. The mixture was stirred overnight and after the completion of reaction, the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel using chloroform : methanol (95 : 5) as eluents to obtain corresponding thiourea derivatives.

![Scheme 63](image)

1-(3,5-Bis(trifluoromethyl)phenyl)-3-(S)-(quinolin-4-yl)(8-vinylquinuclidin-2-yl)methyl thiourea (CDT).

Yellow solid; mp: 122-123 °C; Rf: 0.5 (chloroform : methanol, 95 : 5); 92% yield; [a]D25 = -53.7 (c 0.37, CHCl3); 1H NMR (300 MHz, CHCl3): δ 8.80 (br s, 1H), 8.35 (br s, 1H), 8.14 (d, J = 8.5 Hz, 1H), 7.80 (s, 2H), 7.74 (dd, J = 8.0 and 7.5 Hz, 1H), 7.69 (s, 1H), 7.67 (dd, J = 8.0 and 7.5 Hz, 1H), 7.27 (br s, 1H), 5.78 (br s, 1H), 5.67 (m, 1H), 4.98 (m, 2H), 3.26 (m, 1H), 3.20 (m, 1H), 3.17 (dd, J = 13.5 and 10.5 Hz, 1H), 2.78 (m, 2H), 2.33 (br s, 1H), 1.70 (m, 2H), 1.63 (m, 1H), 1.33 (m, 1H), 0.93 (br s, 1H); 13C NMR (75 MHz, CHCl3): δ 180.8, 149.8, 148.4, 139.3, 132.5, 132.2, 131.9, 130.2, 129.5, 127.0, 124.3, 123.4, 122.8, 121.6, 118.8, 118.6, 115.4, 61.5, 48.4, 47.0, 38.8, 27.2, 25.9, 25.5, 24.9; m/z (ESI): 565.1 (M+).

1-[3,5-Bis(trifluoromethyl)phenyl]-3-[(S)-(6-methoxyquinolin-4-yl)(8-vinylquinuclidin-2-yl)methyl]thiourea (QNT).

Yellow solid; mp: 120-121 °C; Rf: 0.5 (chloroform : methanol, 95 : 5); 93% yield; [α]D 25 = −127.0 (c 0.5, CHCl3); 1H NMR (300 MHz, CDCl3): δ 8.60 (br s, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.82 (br s, 2H), 7.68 (s, 1H), 7.62 (br s, 1H), 7.39 (d, J = 8.5 Hz, 1H), 7.18 (br s, 1H), 5.84 (br s, 1H), 5.70 (m, 1H), 5.01 (m, 2H), 3.96 (s, 3H), 3.37 (br s, 1H), 3.30 (br s, 1H), 3.18 (m, 1H), 2.79 (br s, 2H), 2.35 (br s, 1H), 1.72 (s, 1H), 1.68 (m, 2H), 1.41 (m, 1H), 0.92 (br s, 1H); 13C NMR (75 MHz, CDCl3): δ 180.8, 158.3, 147.5, 144.8, 140.3, 139.9, 132.6, 132.1, 131.8, 124.9, 123.4, 122.2, 121.2, 118.5, 115.6, 102.3, 61.2, 55.9, 54.9, 41.6, 38.7, 30.9, 27.1, 25.5; IR (KBr): ν 3244, 1634, 752, 681 cm⁻¹; HRMS (ESI): calced for [C29H28F6N4OS]⁺: 594.1882; found: 594.1876.

General procedure for the synthesis of N-benzylcinchoninium bromide (185) (Scheme 64): 119

To a 100 mL round bottom flask equipped with a magnetic stirring bar and a reflux condenser, cinchonine (CN) (3.4 mmol, 1.0 g), THF (50 mL), and benzylbromide (3.4 mmol, 582 mg (404 μL)) were added. The mixture was heated to reflux until the reaction was completed as judged to be complete by TLC analysis and the reaction mixture was then cooled to room temperature and poured into diethyl ether (150 mL) with stirring. The resulting suspension was stirred for 1 hour and the precipitated solids were isolated by filtration, which was recrystallized from methanol/diethyl ether to afford pure 185.

\[ \text{CN} \xrightarrow{\text{BnBr, THF, reflux}} \text{185} \]

\[ \text{Scheme 64} \]

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N-benzylecinchoninium bromide (185).

White solid; mp: 259-261 °C; Rf: 0.5 (chloroform : methanol, 90 : 10); 85% yield; [α]D^25 = +151 (c 0.5, CHCl₃); \(^1\)H NMR (300 MHz, CHCl₃): δ 8.84 (d, J = 4.6 Hz, 1H), 8.34 (d, J = 8.3 Hz, 1H), 7.93 (d, J = 4.4 Hz, 1H), 7.64 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 7.0 Hz, 2H), 7.22 -6.98 (m, 5H), 6.83-6.70 (m, 1H), 6.50 (br s, 1H), 6.18-6.03 (m, 1H), 5.89-5.76 (m, 1H), 5.41-5.26 (m, 1H), 5.26-5.11 (m, 2H), 4.49-4.38 (m, 1H), 4.20-4.02 (m, 2H), 3.29 (t, J = 11.7 Hz, 1H), 2.74 (dd, J = 21.4 and 9.8 Hz, 1H), 2.27 (dd, J = 17.1 and 8.9 Hz, 1H), 2.13 -2.01 (m, 1H), 1.82 -1.63 (m, 3H), 0.77 – 0.63 (m, 1H); \(^{13}\)C NMR (75 MHz, CDCl₃): δ 149.1, 146.6, 144.9, 135.2, 134.0, 129.9, 129.2, 128.6, 128.5, 127.3, 126.9, 123.5, 123.3, 119.7, 118.1, 66.7, 65.7, 61.4, 56.2, 53.6, 53.4, 38.0, 27.2, 23.8, 21.8; HRMS calced for [C\(_{26}\)H\(_{29}\)N\(_2\)OBr-Br] \(^+\): 385.2280, found: 385.2262.

General procedure for the synthesis of racemic adducts:

A mixture of indole (0.375 mmol), triethylamine (20 mol%) and isatin (0.250 mmol) in ethanol (1 mL) was stirred at room temperature until the TLC shows the completion of the reaction. The product was isolated by purifying on a column packed with silica gel (60-120 mesh) using hexane : ethyl acetate (4 : 6) as eluents.

General procedure for the organocatalytic enantioselective Friedel-Crafts reaction of indole with isatin:

To a stirred solution of indole (95) (0.375 mmol) and BnCPN (15 mol%) in dry THF (1 mL) containing molecular sieves (100 mg), isatin (21) (0.25mmol) was added. After stirring the reaction at room temperature for 96 hours, pure 3-substitued-3-hydroxyoxindole was isolated by purifying on a column packed with silica gel (60-120 mesh) using hexane : ethyl acetate (4 : 6) as eluents.
(S)-3-Hydroxy-3-((1H-indol-3-yl)indolin-2-one (101a).

White solid; mp: 295-296 °C; R<sub>f</sub>: 0.3 (hexane : ethyl acetate, 4 : 6); 92% yield; [α]_{D}^{25} = +123.6 (c 0.5, EtOH); 96% ee [Chiralpak IB column, hexane/i-PrOH = 70/30, 1.0 mL/min, 217 nm, tR = 11.8 min (minor) and 14.1 min (major)]; <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>): δ 11.00 (s, 1H, NH), 10.39 (s, 1H, NH), 7.39-7.25 (m, 4H, ArH), 7.14 (d, J = 2.4 Hz, 1H, ArH), 7.10-6.87 (m, 4H, ArH), 6.46 (s, 1H, OH); <sup>13</sup>C NMR (75 MHz, DMSO-d<sub>6</sub>): δ 178.8, 141.8, 137.0, 133.6, 129.4, 125.0, 124.9, 123.8, 122.1, 121.4, 120.4, 118.8, 115.6, 111.8, 110.0, 75.2; IR (CHCl<sub>3</sub>): ν (cm<sup>-1</sup>) 3386, 1713; m/z (ESI): 286.8 (M+Na)<sup>+</sup>.

(S)-5-Fluoro-3-hydroxy-3-((1H-indol-3'-yl)indolin-2-one (101b).

White solid; mp: 210-212 °C; R<sub>f</sub>: 0.2 (hexane : ethyl acetate, 4 : 6); 97% yield; [α]_{D}^{25} = +160.6 (c 0.4, EtOH); 83% ee [Chiralpak AD-H column, hexane/i-PrOH = 70/30, 1.0 mL/min, 217 nm, tR = 11.6 min (minor) and 12.7 min (major)]; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 10.50 (s, 1H, NH), 10.07 (s, 1H, NH), 7.56 (d, J = 7.8 Hz, 1H, ArH), 7.34 (d, J = 8.1 Hz, 1H, ArH), 7.13-7.07 (m, 3H, ArH), 6.96-6.88 (m, 3H, ArH), 6.31 (s, 1H, OH); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub> + DMSO-d<sub>6</sub>): δ 177.4, 136.2, 133.6, 135.5, 123.4, 122.1, 119.8, 119.0, 117.4, 113.7, 113.4, 111.1, 110.7, 110.1, 109.0, 74.0; m/z (ESI): 305.1 (M+Na)<sup>+</sup>.

(S)-5-Chloro-3-hydroxy-3-((1H-indol-3-yl)indolin-2-one (101c).

White solid; mp: 115-116 °C (blackening); R<sub>f</sub>: 0.2 (hexane : ethyl acetate, 4 : 6); 98% yield; [α]_{D}^{25} = +180.6 (c 0.3, EtOH); 90% ee [Chiralpak IB column, hexane/i-PrOH = 70/30, 1.0 mL/min, 217 nm, tR = 9.7 min (minor) and 12.4 min (major)]; <sup>1</sup>H NMR (500 MHz, DMSO-d<sub>6</sub>): δ 11.05 (s, 1H, NH), 10.07 (s, 1H, NH), 7.56 (d, J = 7.8 Hz, 1H, ArH), 7.21 (d, J = 2.0 Hz, 1H, ArH), 7.10 (d, J = 2.45 Hz, 1H, ArH), 7.06-7.03 (m, 1H, ArH), 6.93-6.88 (m, 2H, ArH), 6.53 (s, 1H, OH); <sup>13</sup>C NMR (125 MHz, DMSO-d<sub>6</sub>): δ 178.0,
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140.5, 136.8, 135.4, 128.9, 125.6, 124.7, 124.6, 123.6, 121.2, 120.0, 118.6, 114.6, 111.6, 111.2, 74.9; IR (CHCl$_3$): $\nu$ (cm$^{-1}$) 3414, 3336, 1724; m/z (ESI): 320.8 (M+Na)$^+$. (S)-5-Bromo-3-hydroxy-3-(1H-indol-3-yl)indolin-2-one (101d).

Grey solid; mp: 120 °C (blackening); $R_f$: 0.2 (hexane : ethyl acetate, 4 : 6); 99% yield; $[\alpha]_D^{25} = +162.4$ (c 0.5, EtOH); 92% ee [Chiralpak IB column, hexane/$i$-PrOH = 70/30, 1.0 mL/min, 217 nm, $t_R = 9.7$ min (minor) and 12.1 min (major)]; $^1$H NMR (500 MHz, DMSO-d$_6$): $\delta$ 11.05 (s, 1H, NH) 10.51 (s, 1H, NH), 7.45-7.43 (m, 1H, ArH), 7.36-7.31 (m, 3H, ArH), 7.10 (d, $J = 2.51$ Hz, 1H, ArH), 7.08-7.03 (m, 1H, ArH), 6.91-6.85 (m, 2H, ArH), 6.53 (s, 1H, OH); $^{13}$C NMR (125 MHz, DMSO-d$_6$): $\delta$ 177.6, 139.4, 136.9, 135.4, 133.1, 126.1, 122.8, 122.4, 120.0, 118.8, 117.7, 116.3, 113.4, 112.7, 110.5, 73.7; IR (CHCl$_3$): $\nu$ (cm$^{-1}$) 3390, 1715; m/z (ESI): 364.8 (M+Na)$^+$. (S)-3-Hydroxy-3-(1H-indol-3-yl)-5-nitroindolin-2-one (101e).

Yellow solid; mp: 118-120 °C (blackening); $R_f$: 0.2 (hexane : ethyl acetate, 4 : 6); 98% yield; $[\alpha]_D^{25} = +218.6$ (c 0.36, EtOH); 83% ee [Chiralpak IB column, hexane/$i$-PrOH = 70/30, 0.5 mL/min, 217 nm, $t_R = 24.4$ min (minor) and 29.7 min (major)]; $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 11.10 (s, 1H, NH), 11.07 (s, 1H, NH), 8.24 (dd, $J = 2.4$ and 8.7 Hz, 1H, ArH), 8.03 (d, $J = 2.4$ Hz, 1H, ArH), 7.47 (d, $J = 8.1$ Hz, 1H, ArH), 7.34 (d, $J = 8.1$ Hz, 1H, ArH), 7.11-7.02 (m, 3H, ArH), 6.94-6.88 (m, 1H, ArH), 6.75 (s, 1H, OH); $^{13}$C NMR (125 MHz, DMSO-d$_6$): $\delta$ 179.0, 148.6, 142.8, 137.4, 134.7, 126.9, 125.2, 124.4, 121.8, 120.7, 120.5, 119.3, 114.4, 112.2, 110.5, 75.0; IR (CHCl$_3$): $\nu$ (cm$^{-1}$) 3355, 1727; m/z (ESI): 331.9 (M+Na)$^+$. HRMS (ESI): calced for [C$_{16}$H$_{11}$N$_3$O$_4$Na]: 332.0656, found: 332.0647.
(S)-3-Hydroxy-3-(1H-indol-3-yl)-1-methylindolin-2-one (101f).

White solid; mp: 115-116 °C; Rf: 0.3 (hexane : ethyl acetate, 4 : 6); 89% yield; [α]D25 = +136.1 (c 0.5, EtOH); 85% ee [Chiralpak AD-H column hexane/i-PrOH = 70/30, 1.0 mL/min, 217 nm, tR = 9.6 min (major) and 12.7 min (minor)]; 1H NMR (300 MHz, CDCl3): δ 8.31 (s, 1H, NH), 7.49 (d, J = 8.4 Hz, 1H, ArH), 7.42 (d, J = 7.5 Hz, 1H, ArH), 7.36-7.30 (m, 1H, ArH), 7.26 (d, J = 7.5 Hz, 1H, ArH), 7.14-7.01 (m, 1H, ArH); 7.04 (t, J = 7.3 Hz, 2H, ArH), 6.99-6.96 (m, 1H, ArH) 6.84 (d, J = 7.8 Hz, 1H, ArH), 3.89 (s, 1H, OH) 3.22 (s, 3H, CH3); 13C NMR (75 MHz, CDCl3): δ 177.3, 143.1, 136.9, 131.1, 129.7, 124.9, 124.7, 123.3, 122.3, 120.3, 120.0, 115.1, 111.5, 108.5, 75.6, 26.4. IR (CHCl3): ν (cm⁻¹) 3346, 1720; m/z (ESI): 300.8 (M+Na)+; HRMS (ESI): calced for [C17H14N2O2Na]+: 301.0954, found: 301.0953.

(S)-1-Benzyl-3-hydroxy-3-(1H-indol-3-yl)indolin-2-one (101g).

White solid; mp: 122-125 °C; Rf: 0.4 (hexane : ethyl acetate, 4 : 6); 88% yield; [α]D25 = +58.6 (c 0.7, acetone); 88% ee [Chiralpak AD-H column, hexane/i-PrOH = 70/30, 1.0 mL/min, 217 nm, tR = 10.1 min (major) and 14.4 min (minor)]; 1H NMR (500 MHz, DMSO-d6): δ 11.04 (s, 1H, NH), 7.36-7.24 (m, 9H, ArH), 7.11 (d, J = 2.0 Hz, 1H, ArH), 7.03-7.96 (m, 3H, ArH), 6.82 (t, J = 7.5 Hz, 1H, ArH); 6.59 (s, 1H, OH) 4.91 (s, 2H, CH2); 13C NMR (125 MHz, DMSO-d6): δ 176.8, 142.1, 136.8, 136.4, 132.7, 129.1, 128.5, 127.4, 124.8, 124.6, 123.6, 122.5, 121.1, 120.3, 118.5, 115.1, 111.5, 109.2, 74.7, 42.7; IR (CHCl3): ν (cm⁻¹) 3399, 1720; m/z (ESI): 376.9 (M+Na)+.

(S)-5-Bromo-3-hydroxy-3-(1H-indol-3-yl)-1-methylindolin-2-one (101h).

White solid; mp: 99-101 °C; Rf: 0.4 (hexane : ethyl acetate, 4 : 6); 99% yield; [α]D25 = +190.7 (c 0.4, EtOH); 88% ee [Chiralpak AD-H column, hexane/i-PrOH = 70/30, 1.0 mL/min, 217 nm, tR = 8.8 min (major) and 13.9 min (minor)]; 1H NMR (300 MHz, CDCl3 + DMSO-d6): δ 10.37 (s, 1H, NH), 7.52-7.49 (m, 2H, ArH), 7.44 (dd, J = 2.1 and
8.25 Hz, 1H, ArH), 7.35 (d, J = 10.8 Hz, 1H, ArH), 7.13 (d, J = 2.7 Hz, 1H, ArH), 7.11-7.05 (m, 1H, ArH), 6.99-6.94 (m, 1H, ArH), 6.82 (d, J = 8.1 Hz, 1H, ArH), 6.34 (s, 1H, OH), 3.21 (s, 3H, CH$_3$); $^{13}$C NMR (125 MHz, DMSO-d$_6$): δ 176.1, 142.3, 136.8, 135.1, 131.8, 126.9, 124.6, 123.7, 121.2, 120.0, 118.8, 114.4, 114.2, 111.7, 110.7, 74.6, 26.1; IR (CHCl$_3$): ν (cm$^{-1}$) 3346, 1710; m/z (ESI): 378.8 (M+Na)$^+$. 

(S)-3-Hydroxy-3-(5-methoxy-1H-indol-3-yl)indolin-2-one (101i).

White solid; mp: 197-199 °C; Rf: 0.2 (hexane : ethyl acetate, 4 : 6); 97% yield; [α]$_D^{25}$ = +178.9 (c 0.5, EtOH); 97% ee [Chiralpak IB column, hexane/i-PrOH = 70/30, 0.5 mL/min, 217 nm, tR = 29.3 min (minor) and 41.8 min (major)]; $^1$H NMR (300 MHz, DMSO-d$_6$): δ 10.81 (s, 1H, NH), 10.30 (s, 1H, NH), 7.27-7.18 (m, 3H, ArH), 6.98-6.87 (m, 4H, ArH), 6.69-6.65 (m, 1H, ArH), 3.60 (s, 3H, OCH$_3$); $^{13}$C NMR (75 MHz, DMSO-d$_6$): δ 178.5, 152.8, 141.7, 133.4, 132.1, 129.2, 125.4, 124.9, 124.3, 121.8, 115.1, 112.1, 110.9, 109.7, 102.7, 75.0, 55.2; IR (CHCl$_3$): ν (cm$^{-1}$) 3344, 1705: m/z (ESI): 316.8 (M+Na)$^+$. 

(S)-5-Bromo-3-hydroxy-3-(5-methoxy-1H-indol-3-yl)indolin-2-one (101j).

White solid, mp: 227-230 °C; Rf: 0.4 (hexane : ethyl acetate, 4 : 6); 99% yield; [α]$_D^{25}$ = +217.5 (c 0.5, EtOH); 99% ee [Chiralpak IB column, hexane/i-PrOH = 70/30, 0.5 mL/min, 217 nm, tR = 26.3 min (minor) and 39.2 min (major)]; $^1$H NMR (300 MHz, CDCl$_3$ and DMSO-d$_6$): δ 10.44 (s, 1H, NH), 10.21 (s, 1H, NH), 7.43-7.21 (m, 3H, ArH), 7.05 (s, 2H, ArH), 6.37 (s, 1H, OH), 3.72 (s, 3H, OCH$_3$); $^{13}$C NMR (125 MHz, DMSO-d$_6$): δ 175.1, 152.3, 137.6, 134.2, 131.3, 127.4, 126.3, 124.6, 122.5, 113.9, 112.8, 112.2, 112.0, 111.4, 109.3, 69.4, 55.2; IR (CHCl$_3$): ν (cm$^{-1}$) 3386, 3277, 3210, 1708; m/z (ESI): 394.8 (M+Na)$^+$; HRMS (ESI): calced for [C$_{17}$H$_{13}$BrN$_2$O$_3$Na]$^+$: 395.0009, found 395.0007.
(S)-1-Benzyl-3-hydroxy-3-(5-methoxy-1H-indol-3-yl)indolin-2-one (101k).

White solid; mp: 85-87 °C; R$_f$: 0.4 (hexane : ethyl acetate, 4 : 6); 95% yield; $[\alpha]_D^{25} = +150.8$ (c 0.5, EtOH); 93% ee [Chiralpak IB column, hexane/i-PrOH = 70/30, 0.5 mL/min, 217 nm; tR = 29.8 min (major) and 42.2 min (minor)]; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 8.23 (s, 1H, NH), 7.47-7.45 (m, 1H, ArH), 7.28-7.16 (m, 7H, ArH), 7.05-7.00 (m, 2H, ArH), 6.91-6.90 (m, 1H, ArH), 6.81-6.76 (m, 2H, ArH); 5.03 (d, $J = 15.6$ Hz, 1H, CH$_2$) 4.78 (d, $J = 15.9$ Hz, 1H, CH$_2$), 3.69 (s, 1H, OH) 3.59 (s, 3H, OCH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$ + DMSO-d$_6$): $\delta$ 176.0, 151.8, 141.0, 134.6, 131.4, 130.9, 127.9, 127.3, 126.2, 126.0, 124.0, 123.6, 123.3, 121.5, 113.2, 111.0, 110.4, 107.8, 100.9, 73.8, 53.9, 42.0; IR (CHCl$_3$): $\nu$ (cm$^{-1}$) 3423, 1707; m/z (ESI): 407.0 (M+Na)$^+$. 

(S)-3-(5-bromo-1H-indol-3-yl)-3-hydroxyindolin-2-one (101l).

Grey solid; mp: $>300$ °C; R$_f$: 0.3 (hexane : ethyl acetate, 4 : 6); 92% yield; $[\alpha]_D^{25} = +159.8$ (c 0.5, EtOH); 80% ee [Chiralpak AD-H column, hexane/i-PrOH = 70/30, 1.0 mL/min, 217 nm; tR = 8.9 min (major) and 9.1 min (minor)]; $^1$H NMR (500 MHz, DMSO-d$_6$): 11.01 (s, 1H, NH), 10.37 (s, 1H, NH) 7.75 (d, $J = 1.58$ Hz, 1H, CH$_2$) 4.78 (d, $J = 15.9$ Hz, 1H, CH$_2$), 3.69 (s, 1H, OH) 3.59 (s, 3H, OCH$_3$); $^{13}$C NMR (125 MHz, DMSO-d$_6$): $\delta$ 177.7, 141.3, 135.2, 132.6, 128.7, 126.6, 124.6, 124.3, 123.2, 122.7, 121.3, 115.1, 113.0, 110.8, 109.3, 74.3; IR (CHCl$_3$): $\nu$ (cm$^{-1}$) 3378, 1720; m/z (ESI): 366.7 (M+Na)$^+$. 

(S)-3-Hydroxy-3-(5-nitro-1H-indol-3-yl)indolin-2-one (101m).

Yellow solid; mp : $>300$ °C; R$_f$: 0.3 (hexane : ethyl acetate, 4 : 6); 90% yield; $[\alpha]_D^{25} = +141.5$ (c 0.4, EtOH); 79% ee [Chiralpak AD-H column, hexane/i-PrOH = 70/30, 1.0 mL/min, 211 nm; tR = 18.1 min (major) and 19.6 min (minor)]; $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ 11.36 (s, 1H, NH), 10.17 (s, 1H, NH) 8.77 (s, 1H, ArH),
8.01-7.97 (m, 1H, ArH), 7.49-7.24 (m, 3H, ArH), 7.10-6.94 (m, 3H, ArH), 6.47 (s, 1H, OH); $^{13}$C NMR (75 MHz, DMSO-d$_6$) : δ 178.5, 152.8, 141.7, 133.4, 132.0, 129.2, 125.4, 124.9, 124.3, 121.8, 115.0, 112.1, 110.9, 109.7, 102.7, 75.0; m/z (ESI): 331.9 (M+Na).

(S)-3-Hydroxy-3-(2-methyl-1H-indol-3-yl)indolin-2-one (101n).

White solid; mp: 182-183 °C; 96% yield; [$\alpha$]$_D^{25}$ = -16.0 (c 0.5, EtOH); 17% ee [Chiralpak IB column, hexane/i-PrOH = 70/30, 0.5 mL/min, 211 nm, tR = 20.9 min (minor) and 23.9 min (major)]; $^1$H NMR (500 MHz, DMSO-d$_6$): δ 10.64 (s, 1H, NH), 10.11 (s, 1H, NH) 7.01-6.94 (m, 3H, ArH), 6.72-6.65 (m, 4H, ArH), 6.51-6.46 (m, 1H, ArH), 6.04 (s, 1H, OH) 2.17 (s, 3H, CH$_3$), $^{13}$C NMR (125 MHz, DMSO-d$_6$): δ 179.2, 142.2, 135.4, 134.6, 133.9, 129.5, 127.1, 125.4, 122.2, 120.3, 119.7, 118.6, 110.7, 110.1, 109.9, 67.3, 13.8; IR (CHCl$_3$): ν (cm$^{-1}$) 3349, 2924 1737; m/z (ESI): 301.2 (M+Na)$^+$.}

**Procedure for gram scale organocatalytic enantioselective Friedel-Crafts reaction of indole with isatin:**

To a stirred solution of indole (95a) (15 mmol) and BnCPN (15 mol%) in dry THF (10 mL) containing 4Å molecular sieves (1.0 g), isatin (21a) (10 mmol) was added. After stirring the reaction at room temperature for 96 hours the reaction mixture was filtered and the filtrate was evaporated under vacuum. The crude mixture was dissolved in ethanol (10 mL) and then precipitated with ice cold water (25 mL). The spectroscopically pure product was isolated in 91% yield by filtration and washing with ethyl acetate : hexane (3 : 7) mixture.