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Organocatalytic asymmetric aldol reaction of ketones with isatins: straightforward stereoselective synthesis of 3-alkyl-3-hydroxyindolin-2-ones

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Abstract—An efficient asymmetric aldol condensation of ketones with isatins has been developed using an L-proline-derived bifunctional organocatalyst. This strategy allows the enantioselective synthesis of a variety of 3-alkyl-3-hydroxyindolin-2-ones with a stereogenic quaternary carbon center in excellent yields with good to excellent enantiomeric excess. The method has been applied to the enatioselective synthesis of (*S*)-convolutamydine A successfully.

1. Introduction

3-Substituted-3-hydroxyindolin-2-ones have received much attention from organic and medicinal chemists because of their key structural functionalities in natural products and drug candidates (Fig. 1),[1,2] represented by convolutamydines,[3] diazonamide A,[4a] leptosin D,[4b] 3′-hydroxyglucoisatisin,[4c] witindolinone C,[4d] TMC-95s,[5] celogentin K,[6] dioxibrassinine[7] as well as several other pharmaceutically active compounds.[8] Chiral 3-substituted-3-hydroxyindolin-2-ones are particularly important molecules in the field of medicinal chemistry since their biological activities may be derived from the substituted group at C-3 position as well as the absolute configuration of the stereogenic center. Accordingly, it is of great importance to develop efficient and practical methods to synthesize such kind of compounds. One of the most straightforward approaches to 3-substituted-3-hydroxyindolin-2-ones is obviously a nucleophilic addition of appropriate nucleophiles to isatins. Recently, several elegant approaches to 3-aryl or alkyl-3-hydroxyindolin-2-ones have been reported using metal-based catalysts.[9–12] Among them, a few enantioselective formations of a tertiary alcohol at C-3 position have been carried out with moderate to excellent enantioselectivity.[13] However, to our best knowledge, there has been rare organocatalytic enantioselective synthesis of these compounds, although organocatalysis has recently provided a new research avenue in the field of asymmetric synthesis and may reduce the operational complexity and chemical waste in comparison to metal catalysis.[14] Only very recently, Tomasini[15a,b] and Hao[15c] have reported aldol reactions of isatins and acetone, among which moderate ee (up to 77% and 79% ees, respectively) has been obtained. Therefore, the development of more efficient asymmetric organocatalyst is highly desirable.

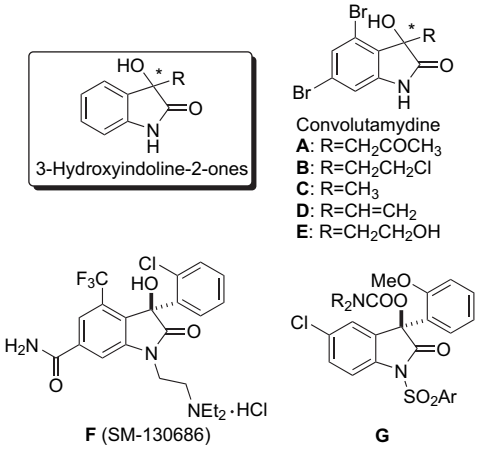

Figure 1. Representative examples of biologically active 3-substituted-3-hydroxyindoline-2-ones.

On the other hand, catalytic asymmetric construction of a stereogenic quaternary carbon center is a challenging goal, especially the addition of carbon nucleophiles to

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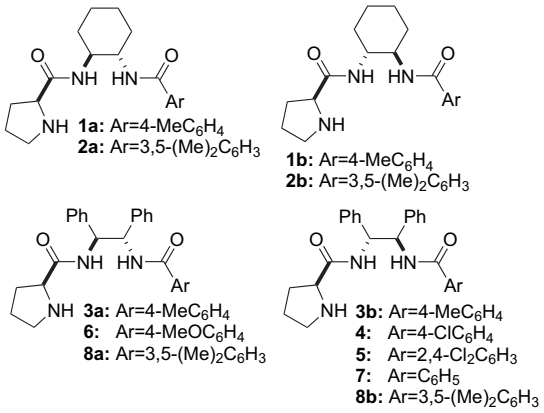
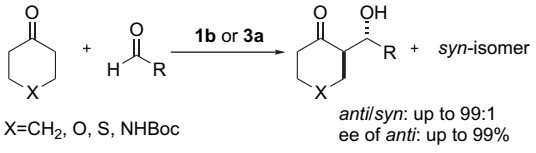


Figure 2. Tunable and bifunctional organocatalysts screened.

ketone derivatives. The activations of both substrates are necessary, because of their lower reactivity in the reaction. Recently, we have developed a series of tunable and bifunctional organocatalysts (Fig. 2) that can promote aldol reactions with broad scope of substrates (Scheme 1).[16,17] The fundamental concept of the catalyst design is that the activity and selectivity can be tuned by a simple modification of the structural motif of the catalyst, and the double H-bond and secondary amine center can activate both substrates simultaneously at defined positions in the transition states. As a logical extension of this strategy, we have investigated the direct aldol reaction of isatins with acetone and 2-butanone and herein describe our preliminary results.



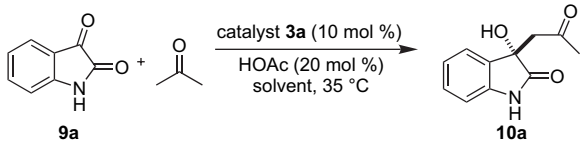
Scheme 1. Direct aldol reactions of cycloketones and aldehydes.

2. Results and discussion

Initially, we conducted a reaction of isatin **9a** with acetone with the use of **3a** (10 mol %) as the catalyst in the presence of HOAc (20 mol %) without additional solvent to examine the feasibility of the process. It was found that the reaction afforded the aldol adduct in almost quantitative yield with 64% ee (Table 1, entry 1). Although the enantiomeric excess of the desired product was moderate, we were nevertheless encouraged and examined the reaction in detail under a variety of conditions in an attempt to increase the enantioselectivity. Thus, the optimal catalyst **3a**, employed previously for the aldol reaction of cyclic ketones,[16b] was used to examine the effects of additional solvents on the reaction, and the results are summarized in Table 1.

The results shown in Table 1 indicate that the enantioselectivity of the reaction of isatin and acetone is sensitive to the solvent. An enantioselectivity/solvent profile documented that the reaction in DMF occurred with higher enantioselectivity than in other solvents (entries 2–7 in Table 1). Interestingly, this reaction can also proceed smoothly in more environmentally friendly solvent brine with 59% ee (entry 7 in Table 1). Basically, the reaction was run with excess acetone. The optimal enantiocontrol in the presence of **3a** was achieved when acetones were used as both the substrate and the solvent (entry 1 in Table 1).

Table 1. Effects of reaction conditions on the direct aldol reaction of isatin **9a** with acetone[a]

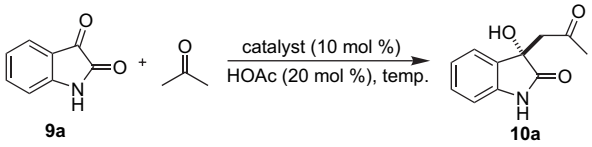


Entry	Solvent	Temp (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	Acetone	35	54	99	64
2	THF	35	24	99	44
3	Dioxane	35	22	94	60
4	CH_2Cl_2	35	22	96	58
5	Toluene	35	5	99	57
6	DMF	35	11	94	61
7	Brine	35	20	99	59

[a] Unless otherwise noted, reactions were carried out with 0.3 mmol of **9a** and 1 mL of acetone in 1 mL of solvent in the presence of 20 mol % of catalyst **3a** and 40 mol % of HOAc.
[b] Isolated yield.
[c] Determined by chiral HPLC.

Then, we screened a small library of bifunctional organocatalysts **1**–**8** derived from L-proline and chiral diamines (Fig. 2 and Table 2) at 10 °C. As shown in Table 2, the reaction using L-proline as the catalyst provided the desired aldol adduct **10a** in high yield but with low enantioselectivity (entry 1 in Table 2). The bifunctional L-prolinamides **1**–**3**, which catalyzed highly diastereo- and enantioselective aldol

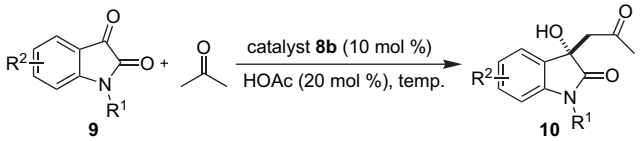
Table 2. Direct aldol reaction of isatin **9a** with acetone catalyzed by catalysts **1**–**8**[a]



Entry	Catalyst	Acetone (mL)	Temp (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	L-Pro	2	10	77	91	25
2	**1a**	2	10	90	93	37
3	**1b**	2	10	90	99	36
4	**2a**	2	10	62	99	31
5	**2b**	2	10	64	83	32
6	**3a**	2	10	54	99	64
7	**3b**	2	10	71	99	62
8	**4**	2	10	54	99	59
9	**5**	2	10	54	99	54
10	**6**	2	10	69	86	54
11	**7**	2	10	71	99	65
12	**8a**	2	10	69	99	45
13	**8b**	2	10	39	99	67
14	**8b**	0.6	−15	3	99	74
15	**8b**	0.6	−40	18	99	83
16[d]	**8b**	0.6	−40	70	89	81
17	**8b**	0.3	−50	41	99	88

[a] Unless otherwise noted, reactions were carried out with 0.3 mmol of **9a** in acetone with 10 mol % of catalyst and 20 mol % of HOAc.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] Compound **8b** (5 mol %) was used.

Table 3. Aldol reaction of isatins with acetone catalyzed by organocatalyst **8b**[a]



Entry	R^1	R^2	Product	Temp (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	H	H	**10a**	−50	41	99	88
2	H	H	**10a**	−60	94	98	89
3[d]	H	H	**10a**	−60	30	99	90
4	Me	H	**10b**	−45	50	85	88
5	Allyl	H	**10c**	−40	48	94	85
6	$PhCH_2$	H	**10d**	−45	50	99	87
7	H	5-Br	**10e**	−50	144	98	80
8	H	5-F	**10f**	−40	144	89	79
9	H	5-Me	**10g**	−50	96	99	88
10[d]	H	5-CF_3O	**10h**	−40	54	99	80
11	H	6-Br	**10i**	−40	42	98	77
12[d,e]	H	6-Cl	**10j**	−60	96	90	78

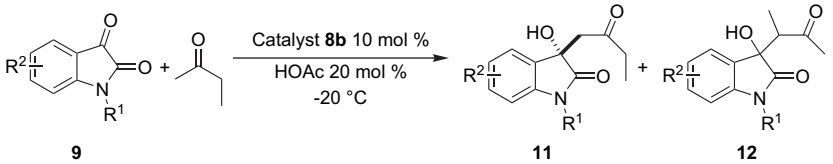
[a] Unless otherwise noted, reactions were carried out with 0.3 mmol of **9** in 0.3 mL of acetone with 10 mol % of catalyst **8b** and 20 mol % of HOAc.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] Compound **8b** (20 mol %) and 40 mol % HOAc were used.
[e] Acetone (0.6 mL) was used.

reactions of cycloketones with aldehydes (Scheme 1),[16] did show excellent activities for the model reaction, but the enantioselectivities were not satisfactory (entries 2–7 in Table 2). We believe that a small variation in the structure motif of the catalyst can greatly affect the stereoselectivity of the reaction. Thus, we further examined the catalyst by changing the substitution pattern of phenyl group at the NH (entries 8–13 in Table 2) and the ee was improved to 67% when catalyst **8b** was employed (entry 13 in Table 2). It is noteworthy that the catalysts derived from L-proline and (*R*,*R*)-diamine showed a superior level of enantiocontrol to their diastereomers derived from L-proline and (*S*,*S*)-diamine (entries 5, 7, 13 vs 4, 6, 12 in Table 2). These results indicate that careful and precise tuning of the structure of the catalyst is essential to maximize the catalytic efficiency. The reaction temperature is another critical factor for the enantioselective aldol reaction (entries 13–17 in Table 2), with the best result (99% yield, 88% ee) being attained at −50 °C (entry 17 in Table 2). Significantly, when the catalyst loading was reduced to 5 mol %, the reaction still took place in high yield with a little loss in the ee, though a longer reaction time was needed (entry 16 vs 15 in Table 2).

With the optimized conditions in hand, the scope of the reaction was examined with a variety of isatins (Table 3). As shown in Table 3, isatin substrates bearing electron-withdrawing and electron-donating substituents could be employed in the direct organocatalytic aldol reaction. The 3-hydroxyindolin-2-one derivatives were isolated in 85–99% yields. The reaction exhibits good to excellent enantioselectivities (77–90% ee). The reaction of free isatins gave the same enantioselectivity as the reaction of *N*-methyl isatins did (entries 1 vs 4 in Table 3). Incorporation of methyl, allyl, and benzyl substituents at the N-1 position revealed that electronic and steric modifications could be accomplished with no big influence on the reaction selectivity (entries 4–6 in Table 3). As shown in entries 7–12, incorporation of substituents at the C-5 and C-6 positions showed obvious influence on the enantioselectivity of the reaction. In general, the substituent at C-5 proved to be superior to C-6 substituted analogues (entries 7 vs 11 in Table 3). In the case of 5-methylisatin, the product was obtained in almost quantitative yield with 88% ee (entry 9 in Table 3). Significantly, F-, Cl-, and Br-substituted isatins worked as well for this reaction (entries 7, 8, and 10–12 in Table 3). Such chloro- and bromo-oxindoles could be valuable for some transition-metal-catalyzed transformation,[18] and the fluorine-containing products could be useful in the fields of medicinal and material sciences.[19]

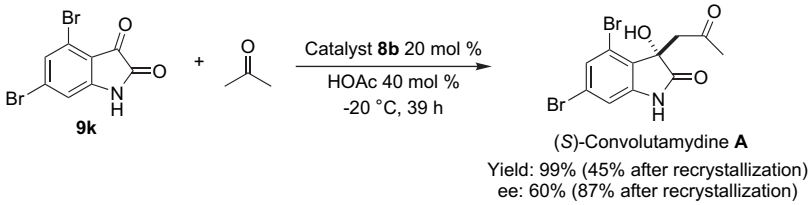
We next examined the ability of diamide catalyst **8b** to catalyze direct aldol reactions of isatins with 2-butanone. As shown in Table 4, this process was also very efficient, providing the aldol adducts in excellent chemical yields with reasonable enantioselectivities. The reaction exhibits high regioselectivity, and affords the products of C–C bond formation at the methyl group, the less substituted C1-position of butanone as the major regioisomers (entries 1–4 in Table 4). Because the aldol adducts **11** are generally solids, it is possible to obtain excellent enantiomeric excesses after a single recrystallization (entry 3 in Table 4, 95% ee).

Table 4. Aldol reaction of isatins with 2-butanone catalyzed by organocatalyst **8b**[a]



Entry	R^1	R^2	**9**	Time (h)	Yield (**11**/**12**)[b,c] (%)	ee[d] (**11**) (%)
1	H	H	**a**	46	98 (9/1)	74
2	H	5-Me	**g**	18	99 (7/1)	72
3	H	5-CF_3O	**h**	46	99 (12/1)	75 (95)[e]
4	H	6-Cl	**j**	46	99 (8/1)	70

[a] Unless otherwise noted, reactions were carried out with 0.3 mmol of **9** in 0.3 mL of 2-butanone with 10 mol % of catalyst **8b** and 20 mol % of HOAc.
[b] Isolated yield of mixture of **11** and **12**.
[c] Determined by ^{1}H NMR.
[d] Determined by chiral HPLC.
[e] After one recrystallization.



Scheme 2. Synthesis of (*S*)-convolutamydine A.

An application of this organocatalytic aldol reaction of isatin with ketones is represented in a simple synthesis of (*S*)-convolutamydine A. Convolutamydines A–E (Fig. 1), isolated from the Floridian marine bryozoan Amathia convolute by Kanano et al. in 1995, are members of a class of oxindole alkaloids containing 4,6-dibromo-3-hydroxy-oxindole as a common structural motif.[3a] A few racemic syntheses of these alkaloids have already been reported by several groups,[3b,20] and recently Kobayashi and co-workers reported enantioselective synthesis of convolutamydines B and E via Mukaiyama aldol reaction.[9b] Tomasini and co-workers presented the first organocatalytic asymmetric synthesis of (*R*)-convolutamydine A with 68% ee.[15b] We applied the catalyst **8b** in the synthesis of (*S*)-convolutamydine A and 60% ee was obtained (87% ee after a single recrystallization) (Scheme 2).

The absolute configuration of the aldol product **10a** was determined to be *S* by comparing our experimental results with those in the literature.[15] The absolute configuration of **10j** was unambiguously determined to be *S* by single-crystal X-ray analysis (Fig. 3).[21] Accordingly, we hypothesized that enantiofacial discrimination might be governed by the control of catalyst in enamine geometry and orientation of the isatins. A possible transition state is proposed in Figure 4, which is in accordance with previously proposed L-proline-based aldol transition-state model.[22] The configuration of other products could be tentatively assigned by assuming an analogous enantioinduction.

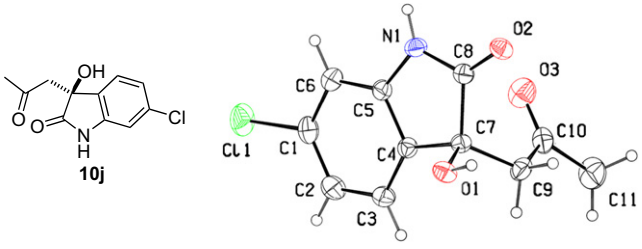


Figure 3. ORTEP drawing of the (*S*)-enantiomer of **10j**.

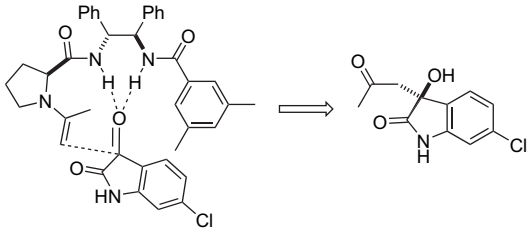


Figure 4. A proposed transition state.

3. Conclusions

In summary, we have described a direct catalytic asymmetric aldol reaction of acetone and butanone with isatins using L-proline-derived bifunctional organocatalysts. This method represents a general approach to 3-alkyl-3-hydroxyindolin-2-ones with a quaternary stereocenter. Yields of products are excellent (85–99%). The reaction exhibits good to excellent enantioselectivities (up to 90% ee).

4. Experimental

4.1. General

Unless otherwise noted, material were purchased from commercial suppliers and used without further purification. Dichloromethane, dimethyl sulfoxide (DMSO), and *N*,*N*-dimethyl formamide (DMF) were freshly distilled from calcium hydride. Tetrahydrofuran (THF), dioxane, and toluene were distilled from sodium/benzophenone. Flash column chromatography was performed using 200–300 mesh silica gel. ^{1}H NMR spectra were recorded on 400 MHz spectrophotometers. Solvent for NMR is DMSO-*d*, unless the otherwise noted. Chemical shifts are reported in delta (δ) units in parts per million (ppm) relative to the singlet (0 ppm) for tetramethylsilane (TMS). Data are reported as follows: chemical shift, multiplicity (s=single, d=doublet, t=triplet, q=quartet, br=broad, and m=multiplet), coupling constants (Hz) and integration. ^{13}C NMR spectra were recorded on 100 MHz. Chemical shifts are reported in parts per million relative to the central line of the heptet at 39.5 ppm for DMSO-*d*. Chiral HPLC was performed with chiral columns (Chiralpak AD and OJ columns).

4.1.1. General procedure for the aldol reaction of isatin 9 with acetone. The organocatalyst **8b** (0.03 mmol) and HOAc (0.06 mmol) were stirred in 0.3 mL acetone for 10 min at −50 °C. The corresponding isatin **9a** (0.3 mmol) was added and the mixture was stirred for 41 h. Then acetone was removed under reduced pressure and the mixture was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate (2/1)). Organocatalysts **1**–**8** were prepared according to the previously reported procedure.[16a–c] Catalysts **1**–**3** are known compounds.[16a–c]

4.1.1.1. Catalyst 4. ^{1}H NMR δ 1.44–1.58 (m, 2H), 1.61–1.69 (m, 1H), 1.90 (br s, 1H), 1.96–2.05 (m, 1H), 2.82–2.96 (m, 2H), 3.71 (q, *J*=4.8, 9.2 Hz, 1H), 5.24 (dd, *J*=8.0, 10.8 Hz, 1H), 5.34 (dd, *J*=7.2, 11.2 Hz, 1H), 7.09–7.23 (m, 10H), 7.38 (d, *J*=8.8 Hz, 2H), 7.82 (d, *J*=8.4 Hz, 2H), 8.39 (d, *J*=6.8 Hz, 1H), 8.53 (d, *J*=8.0 Hz, 1H); ^{13}C NMR δ 25.7, 30.6, 46.9, 58.2, 60.1, 61.1, 127.2, 127.3, 127.8,

128.0, 128.3, 128.5, 128.6, 131.9, 137.4, 137.9, 139.2, 165.4, 176.9; MS (EI) *m/z* 448 (rel intensity) (M^++1). Analysis calculated for $C_{26}H_{26}ClN_3O_2$: C, 69.71; H, 5.85; N, 9.38. Found: C, 69.67; H, 5.88; N, 9.35.

4.1.1.2. Catalyst 5. ^{1}H NMR δ 1.60–1.62 (m, 3H), 1.83–1.94 (m, 1H), 2.24 (br s, 1H), 2.87–2.99 (m, 2H), 3.5 (q, *J*=4.8, 9.2 Hz, 1H), 5.31 (dd, *J*=8.8, 10.4 Hz, 1H), 5.42 (dd, *J*=7.6, 10.4 Hz, 1H), 7.14–7.23 (m, 11H), 7.38 (d, *J*=2.0 Hz, 1H), 7.43 (d, *J*=8.0 Hz, 1H), 8.26 (d, *J*=7.6 Hz, 1H), 8.55 (d, *J*=8.0 Hz, 1H); ^{13}C NMR δ 26.0, 30.6, 47.1, 58.0, 60.2, 60.4, 127.0, 127.4, 127.5, 127.7, 127.8, 128.2, 128.4, 128.5, 129.9, 130.4, 131.9, 133.4, 136.3, 138.2, 138.9, 165.3, 176.1; MS (EI) *m/z* 482 (rel intensity) (M^+). Analysis calculated for $C_{26}H_{25}Cl_2N_3O_2$: C, 64.73; H, 5.22; N, 8.71. Found: C, 64.79; H, 5.25; N, 8.67.

4.1.1.3. Catalyst 6. ^{1}H NMR δ 1.52–1.64 (m, 2H), 1.76–1.82 (m, 1H), 2.07–2.14 (m, 1H), 2.62 (br s, 1H), 2.72–2.77 (m, 1H), 2.89–2.95 (m, 1H), 3.73 (q, *J*=5.6, 9.2 Hz, 1H), 3.8 (s, 1H), 5.28 (dd, *J*=8.0, 10.0 Hz, 1H), 5.41 (dd, *J*=8.0, 10.4 Hz, 1H), 6.91 (d, *J*=8.8 Hz, 2H), 7.12–7.23 (m, 10H), 7.81 (d, *J*=8.8 Hz, 2H), 8.10 (d, *J*=7.6 Hz, 1H), 8.56 (d, *J*=8.0 Hz, 1H); ^{13}C NMR δ 25.8, 30.4, 46.9, 55.2, 58.5, 60.1, 60.7, 113.5, 126.1, 127.2, 127.3, 127.7, 128.1, 128.5, 128.9, 138.0, 139.4, 161.9, 166.4, 176.1; MS (EI) *m/z* 444 (rel intensity) (M^++1). Analysis calculated for $C_{27}H_{29}N_3O_3$: C, 73.11; H, 6.59; N, 9.47. Found: C, 73.05; H, 6.69; N, 9.41.

4.1.1.4. Catalyst 7. ^{1}H NMR δ 1.42–1.54 (m, 2H), 1.63–1.71 (m, 1H), 1.92 (br s, 1H), 1.94–2.02 (m, 1H), 2.82–2.88 (m, 1H), 2.89–2.95 (m, 1H), 3.71 (q, *J*=5.2, 9.2 Hz, 1H), 5.28 (dd, *J*=8.4, 11.2 Hz, 1H), 5.40 (dd, *J*=7.2, 11.2 Hz, 1H), 7.10–7.24 (m, 10H), 7.41–7.50 (m, 3H), 7.87–7.89 (m, 2H), 8.23 (d, *J*=7.2 Hz, 1H), 8.54 (d, *J*=8.0 Hz, 1H); ^{13}C NMR δ 25.8, 30.6, 47.0, 58.1, 60.2, 61.2, 127.1, 127.2, 127.4, 127.5, 127.9, 128.1, 128.3, 128.6, 131.3, 133.5, 137.9, 139.4, 166.4, 176.9; MS (EI) *m/z* 414 (rel intensity) (M^++1). Analysis calculated for $C_{26}H_{27}N_3O_2$: C, 75.52; H, 6.58; N, 10.16. Found: C, 75.49; H, 6.60; N, 10.21.

4.1.1.5. Catalyst 8a. ^{1}H NMR δ 1.48–1.60 (m, 2H), 1.73–1.81 (m, 1H), 2.00–2.09 (m, 1H), 2.31 (s, 6H), 2.45 (br s, 1H), 2.71–2.77 (m, 1H), 2.86–2.92 (m, 1H), 3.65 (q, *J*=5.6, 9.2 Hz, 1H), 5.30 (dd, *J*=8.8, 10.0 Hz, 1H), 5.44 (dd, *J*=8.0, 10.4 Hz, 1H), 7.08–7.19 (m, 11H), 7.41 (s, 2H), 7.97 (d, *J*=8.0 Hz, 1H), 8.53 (d, *J*=8.8 Hz, 1H); ^{13}C NMR δ 21.1, 25.8, 30.4, 46.9, 58.3, 60.2, 60.5, 124.7, 127.3, 127.6, 128.1, 128.4, 132.9, 133.9, 137.9, 138.0, 138.2, 139.3, 167.3, 176.1; MS (EI) *m/z* 441 (rel intensity) (M^+). Analysis calculated for $C_{28}H_{31}N_3O_2$: C, 76.16; H, 7.08; N, 9.52. Found: C, 76.21; H, 7.14; N, 9.45.

4.1.1.6. Catalyst 8b. ^{1}H NMR δ 1.46–1.52 (m, 2H), 1.69–1.77 (m, 1H), 1.93–2.01 (m, 1H), 2.06 (br s, 1H), 2.34 (s, 6H), 2.81–2.86 (m, 1H), 2.88–2.94 (m, 1H), 3.70 (q, *J*=4.8, 9.2 Hz, 1H), 5.28 (dd, *J*=8.4, 10.4 Hz, 1H), 5.40 (dd, *J*=7.6, 10.8 Hz, 1H), 7.10–7.22 (m, 11H), 7.44 (s, 2H), 7.94 (d, *J*=7.6 Hz, 1H), 8.53 (d, *J*=8.4 Hz, 1H); ^{13}C NMR δ 21.0, 25.7, 30.3, 46.8, 58.0, 60.1, 60.5, 124.7, 127.0, 127.3, 127.4, 127.6, 127.9, 128.4, 132.7, 133.5, 137.7, 138.1, 139.3, 166.9, 176.3; MS (EI) *m/z* 441 (rel intensity) (M^+). Analysis calculated for $C_{28}H_{31}N_3O_2$: C, 76.16; H, 7.08; N, 9.52. Found: C, 76.10; H, 7.16; N, 9.47.

4.1.1.7. Compound 10a: 3-(2-oxopropyl)-3-hydroxyindolin-2-one. The ee was determined by HPLC (Chiralpak AD column, hexane/*i*-PrOH 70:30, flow rate 1 mL/min; t_R (major)=7.1 min; t_R (minor)=9.5 min, λ=254 nm). ^{1}H NMR δ 2.00 (s, 3H), 3.01 (d, *J*=16.4 Hz, 1H), 3.28 (d, *J*=16.8 Hz, 1H), 6.00 (br s, 1H), 6.79 (d, *J*=7.6 Hz, 1H), 6.91 (t, *J*=7.6 Hz, 1H), 7.17 (t, *J*=8.0 Hz, 1H), 7.25 (d, *J*=7.6 Hz, 1H), 10.22 (br s, 1H); ^{13}C NMR δ 30.7, 50.4, 72.8, 109.6, 121.4, 123.8, 129.1, 131.6, 142.6, 178.3, 205.3; MS (EI) *m/z* 206 (rel intensity) (M^++1). Analysis calculated for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.15; H, 5.59; N, 6.77.

4.1.1.8. Compound 10b: 1-methyl-3-(2-oxopropyl)-3-hydroxyindolin-2-one. The ee was determined by HPLC (Chiralpak OJ column, hexane/*i*-PrOH 70:30, flow rate 1 mL/min; t_R (minor)=8.7 min; t_R (major)=10.3 min, λ=254 nm). ^{1}H NMR δ 1.98 (s, 3H), 3.07 (d, *J*=16.4 Hz, 1H), 3.09 (s, 3H), 3.34 (d, *J*=16.8 Hz, 1H), 6.05 (br s, 1H), 6.95 (d, *J*=8.0 Hz, 1H), 6.99 (t, *J*=7.6 Hz, 1H), 7.26–7.30 (m, 2H), 10.22 (br s, 1H); ^{13}C NMR δ 25.8, 30.5, 50.4, 72.3, 108.2, 121.9, 123.2, 129.1, 130.9, 144.0, 176.5, 205.1; MS (EI) *m/z* 219 (rel intensity) (M^+). Analysis calculated for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.63; H, 6.14; N, 6.42.

4.1.1.9. Compound 10c: 1-allyl-3-(2-oxopropyl)-3-hydroxyindolin-2-one. The ee was determined by HPLC (Chiralpak AD column, hexane/*i*-PrOH 90:10, flow rate 1 mL/min; t_R (minor)=17.4 min; t_R (major)=19.0 min, λ=254 nm). ^{1}H NMR δ 1.99 (s, 3H), 3.12 (d, *J*=16.8 Hz, 1H), 3.39 (d, *J*=17.2 Hz, 1H), 4.21 (dd, *J*=4.8, 16.4 Hz, 1H), 4.31 (dd, *J*=4.4, 16.8 Hz, 1H), 5.16 (d, *J*=10.4 Hz, 1H), 5.35 (d, *J*=17.2 Hz, 1H), 5.79–5.88 (m, 1H), 6.09 (br s, 1H), 6.86 (d, *J*=7.6 Hz, 1H), 6.98 (t, *J*=7.6 Hz, 1H), 7.24 (t, *J*=8.0 Hz, 1H), 7.31 (d, *J*=7.2 Hz, 1H); ^{13}C NMR δ 30.4, 41.4, 50.3, 72.2, 108.9, 116.7, 121.9, 123.3, 129.0, 130.9, 131.9, 143.2, 176.3, 205.1; MS (EI) *m/z* 245 (rel intensity) (M^+). Analysis calculated for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.34; H, 6.28; N, 5.78.

4.1.1.10. Compound 10d: 1-benzyl-3-(2-oxopropyl)-3-hydroxyindolin-2-one. The ee was determined by HPLC (Chiralpak AD column, hexane/*i*-PrOH 90:10, flow rate 1 mL/min; t_R (minor)=29.8 min; t_R (major)=31.9 min, λ=254 nm). ^{1}H NMR δ 2.02 (s, 3H), 3.18 (d, *J*=16.8 Hz, 1H), 3.44 (d, *J*=16.8 Hz, 1H), 4.82 (d, *J*=16.0 Hz, 1H), 4.91 (d, *J*=16.0 Hz, 1H), 6.19 (br s, 1H), 6.73 (d, *J*=7.6 Hz, 1H), 6.96 (t, *J*=7.6 Hz, 1H), 7.16 (d, *J*=7.6 Hz, 1H), 7.25 (t, *J*=7.2 Hz, 1H), 7.33 (t, *J*=7.2 Hz, 3H), 7.43 (d, *J*=7.2 Hz, 1H); ^{13}C NMR δ 30.4, 42.7, 50.3, 72.3, 108.9, 122.0, 123.4, 127.2, 128.4, 129.0, 130.9, 136.3, 143.1, 176.7, 205.2; MS (EI) *m/z* 296 (rel intensity) (M^++1). Analysis calculated for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.59; H, 8.45; N, 4.92.

4.1.1.11. Compound 10e: 5-bromo-3-(2-oxopropyl)-3-hydroxyindolin-2-one. The ee was determined by HPLC (Chiralpak AD column, hexane/*i*-PrOH 70:30, flow rate 1 mL/min; t_R (major)=6.6 min; t_R (minor)=9.3 min,

λ=254 nm). ^{1}H NMR δ 2.02 (s, 3H), 3.07 (d, J=17.2 Hz, 1H), 3.39 (d, J=17.2 Hz, 1H), 6.09 (br s, 1H), 6.75 (d, J=8.0 Hz, 1H), 7.35 (d, J=8.0 Hz, 1H), 7.43 (s, 1H), 10.36 (br s, 1H); ^{13}C NMR δ 30.3, 50.0, 72.6, 111.4, 113.0, 126.7, 131.6, 134.2, 142.0, 177.8, 205.3; MS (EI) m/z 285 (rel intensity) (M^++1). Analysis calculated for $C_{11}H_{10}BrNO_3$: C, 46.50; H, 3.55; N, 4.93. Found: C, 45.95; H, 3.63; N, 4.95.

4.1.1.12. Compound 10f: 5-fluoro-3-(2-oxopropyl)-3-hydroxyindolin-2-one. The ee was determined by HPLC (Chiralpak pre-AD column, hexane/*i*-PrOH 70:30, flow rate 1 mL/min; t_R (major)=6.5 min; t_R (minor)=8.7 min, λ=254 nm). ^{1}H NMR δ 2.02 (s, 3H), 3.06 (d, J=16.8 Hz, 1H), 3.35 (d, J=17.2 Hz, 1H), 6.10 (br s, 1H), 6.77 (dd, J=4.4, 8.4 Hz, 1H), 6.97–7.03 (m, 1H), 7.16 (dd, J=2.4, 8.4 Hz, 1H), 10.36 (br s, 1H); ^{13}C NMR δ 30.4, 50.0, 72.9, 110.0, 110.1, 111.5, 111.8, 114.9, 115.1, 133.3, 133.4, 138.8, 156.7, 159.0, 178.2, 205.2; MS (EI) m/z 223 (rel intensity) (M^+). Analysis calculated for $C_{11}H_{10}FNO_3$: C, 59.19; H, 4.52; N, 6.28. Found: C, 59.17; H, 4.53; N, 6.11.

4.1.1.13. Compound 10g: 5-methyl-3-(2-oxopropyl)-3-hydroxyindolin-2-one. The ee was determined by HPLC (Chiralpak AD column, hexane/*i*-PrOH 70:30, flow rate 1 mL/min; t_R (major)=6.9 min; t_R (minor)=8.8 min, λ=254 nm). ^{1}H NMR δ 2.00 (s, 3H), 2.22 (s, 3H), 2.99 (d, J=16.8 Hz, 1H), 3.24 (d, J=16.8 Hz, 1H), 5.92 (br s, 1H), 6.66 (d, J=7.2 Hz, 1H), 6.97 (d, J=7.6 Hz, 1H), 7.06 (s, 2H), 10.11 (br s, 1H); ^{13}C NMR δ 20.7, 30.6, 50.3, 72.7, 109.1, 124.3, 129.1, 129.9, 131.6, 140.0, 178.1, 205.1; MS (EI) m/z 219 (rel intensity) (M^+). Analysis calculated for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.48; H, 6.24; N, 6.28.

4.1.1.14. Compound 10h: 5-trifluoromethoxy-3-(2-oxopropyl)-3-hydroxyindolin-2-one. The ee was determined by HPLC (Chiralpak AD column, hexane/*i*-PrOH 70:30, flow rate 1 mL/min; t_R (major)=4.8 min; t_R (minor)=6.0 min, λ=254 nm). ^{1}H NMR δ 2.00 (s, 3H), 3.07 (d, J=17.2 Hz, 1H), 3.41 (d, J=17.2 Hz, 1H), 6.17 (br s, 1H), 6.86 (d, J=8.4 Hz, 1H), 7.18 (d, J=8.4 Hz, 1H), 7.30 (s, 2H), 10.42 (br s, 1H); ^{13}C NMR δ 30.4, 49.9, 72.8, 110.2, 117.7, 118.9, 121.5, 122.2, 133.4, 141.9, 142.9, 178.2, 205.3; MS (EI) m/z 290 (rel intensity) (M^++1). Analysis calculated for $C_{12}H_{10}F_3NO_4$: C, 49.84; H, 3.49; N, 4.84. Found: C, 49.99; H, 3.52; N, 4.82.

4.1.1.15. Compound 10i: 6-bromo-3-(2-oxopropyl)-3-hydroxyindolin-2-one. The ee was determined by HPLC (Chiralpak AD column, hexane/*i*-PrOH 70:30, flow rate 1 mL/min; t_R (major)=7.1 min; t_R (minor)=9.2 min, λ=254 nm). ^{1}H NMR δ 2.00 (s, 3H), 3.07 (d, J=17.2 Hz, 1H), 3.34 (d, J=17.2 Hz, 1H), 6.07 (br s, 1H), 6.93 (s, 1H), 7.10 (d, J=8.0 Hz, 1H), 7.20 (d, J=8.0 Hz, 1H), 10.37 (br s, 1H); ^{13}C NMR δ 30.4, 50.0, 72.2, 112.2, 121.6, 123.8, 125.5, 131.0, 144.4, 178.0, 205.3; MS (EI) m/z 285 (rel intensity) (M^++1). Analysis calculated for $C_{11}H_{10}BrNO_3$: C, 46.50; H, 3.55; N, 4.93. Found: C, 46.60; H, 3.48; N, 5.02.

4.1.1.16. Compound 10j: 6-chloro-3-(2-oxopropyl)-3-hydroxyindolin-2-one. The ee was determined by HPLC (Chiralpak AD column, hexane/*i*-PrOH 70:30, flow rate 1 mL/min; t_R (major)=7.0 min; t_R (minor)=9.4 min, λ=254 nm). ^{1}H NMR δ 2.00 (s, 3H), 3.08 (d, J=16.8 Hz, 1H), 3.35 (d, J=17.2 Hz, 1H), 6.08 (br s, 1H), 6.81 (d, J=1.6 Hz, 1H), 6.96 (dd, J=1.6, 8.0 Hz, 1H), 7.26 (d, J=7.6 Hz, 1H), 10.39 (br s, 1H); ^{13}C NMR δ 30.4, 50.1, 72.2, 109.5, 120.9, 125.2, 130.6, 133.2, 144.3, 178.2, 205.3; MS (EI) m/z 241 (rel intensity) (M^++1). Analysis calculated for $C_{11}H_{10}ClNO_3$: C, 55.13; H, 4.21; N, 5.84. Found: C, 55.47; H, 4.24; N, 5.84.

4.1.1.17. Compound 11a: 3-(2-oxobutyl)-3-hydroxyindolin-2-one. The ee was determined by HPLC (Chiralpak AD column, hexane/*i*-PrOH 70:30, flow rate 1 mL/min; t_R (major)=7.4 min; t_R (minor)=8.3 min, λ=254 nm). ^{1}H NMR δ 0.74 (t, J=7.2 Hz, 3H), 2.34 (dd, J=17.6, 7.2 Hz, 2H), 2.98 (dd, J=16.4 Hz, 1H), 3.26 (d, J=16.4 Hz, 1H), 5.97 (br s, 1H), 6.76 (d, J=7.6 Hz, 1H), 6.87 (t, J=7.6, 8.0 Hz, 1H), 7.14 (t, J=8.0 Hz, 1H), 7.21 (d, J=7.2 Hz, 1H), 10.20 (br s, 1H); ^{13}C NMR δ 7.3, 35.7, 49.2, 72.7, 109.4, 121.2, 123.7, 129.0, 131.5, 142.6, 178.3, 207.5; MS (EI) m/z 219 (rel intensity) (M^+). Analysis calculated for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.69; H, 5.94; N, 6.45.

4.1.1.18. Compound 11g: 5-methyl-3-(2-oxobutyl)-3-hydroxyindolin-2-one. The ee was determined by HPLC (Chiralpak AD column, hexane/*i*-PrOH 90:10, flow rate 1 mL/min; t_R (major)=26.3 min; t_R (minor)=29.0 min, λ=254 nm). ^{1}H NMR δ 0.81 (t, J=7.2 Hz, 3H), 2.26 (s, 3H), 2.40 (dd, J=16.4, 7.6 Hz, 2H), 3.03 (d, J=16.4 Hz, 1H), 3.28 (d, J=16.4 Hz, 1H), 5.97 (br s, 1H), 6.71 (d, J=7.6 Hz, 1H), 7.01 (t, J=8.0 Hz, 1H), 7.10 (s, 1H), 10.15 (br s, 1H); ^{13}C NMR δ 7.3, 20.7, 35.6, 49.2, 72.8, 109.2, 124.4, 129.1, 130.0, 131.6, 140.1, 178.3, 207.4; MS (EI) m/z 234 (rel intensity) (M^++1). Analysis calculated for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.80; H, 6.55; N, 6.35.

4.1.1.19. Compound 11h: 5-trifluoromethoxy-3-(2-oxobutyl)-3-hydroxyindolin-2-one. The ee was determined by HPLC (Chiralpak AS column, hexane/*i*-PrOH 85:15, flow rate 1 mL/min; t_R (minor)=41.2 min; t_R (major)=47.3 min, λ=254 nm). ^{1}H NMR δ 0.78 (t, J=7.2 Hz, 3H), 2.37 (dd, J=10.4, 7.2 Hz, 2H), 3.06 (d, J=17.2 Hz, 1H), 3.41 (d, J=16.8 Hz, 1H), 6.19 (br s, 1H), 6.88 (d, J=8.4 Hz, 1H), 7.18 (q, J=1.6, 8.4 Hz, 1H), 7.32 (s, 1H), 10.44 (br s, 1H); ^{13}C NMR δ 7.2, 35.6, 48.8, 77.9, 110.2, 117.7, 119.0, 121.6, 122.2, 133.4, 141.9, 143.0, 178.3, 207.7; MS (EI) m/z 303 (rel intensity) (M^+). Analysis calculated for $C_{13}H_{12}F_3NO_4$: C, 51.49; H, 3.99; N, 4.62. Found: C, 51.55; H, 3.90; N, 4.65.

4.1.1.20. Compound 11j: 6-chloro-3-(2-oxobutyl)-3-hydroxyindolin-2-one. The ee was determined by HPLC (Chiralpak AD column, hexane/*i*-PrOH 90:10, flow rate 1 mL/min; t_R (major)=26.9 min; t_R (minor)=31.4 min, λ=254 nm). ^{1}H NMR δ 0.78 (t, J=7.2 Hz, 3H), 2.37 (dd, J=16.8, 7.2 Hz, 2H), 3.09 (d, J=16.8 Hz, 1H), 3.36 (d, J=16.8 Hz, 1H), 6.12 (br s, 1H), 6.84 (s, 1H), 6.95 (d, J=8.0 Hz, 1H), 7.27 (d, J=7.6 Hz, 1H), 10.40 (br s, 1H); ^{13}C NMR δ 7.4, 35.6, 49.1, 72.4, 109.7, 121.0, 125.2, 130.0, 133.4, 144.3, 178.4, 207.7; MS (EI) m/z 253

(rel intensity) (M^+). Analysis calculated for $C_{12}H_{12}ClNO_3$: C, 51.49; H, 3.99; N, 4.62. Found: C, 51.55; H, 3.90; N, 4.70.

4.1.1.21. Compound A: 5,7-dibromo-3-(2-oxopropyl)-3-hydroxyindolin-2-one. The ee was determined by HPLC (Chiralpak AD column, hexane/*i*-PrOH 70:30, flow rate 1 mL/min; t_R (major)=7.9 min; t_R (minor)=10.1 min, λ=254 nm). ^{1}H NMR δ 2.02 (s, 3H), 3.15 (d, J=17.6 Hz, 1H), 3.73 (d, J=18.0 Hz, 1H), 6.21 (br s, 1H), 6.94 (s, 1H), 7.28 (s, 1H), 10.62 (s, 1H); ^{13}C δ NMR 30.0, 48.3, 111.8, 119.0, 122.4, 126.7, 128.7, 146.4, 177.3, 205.3; MS (EI) *m/z* 364 (rel intensity) (M^++1). Analysis calculated for $C_{11}H_9Br_2NO_3$: C, 36.40; H, 2.50; N, 3.86. Found: C, 36.26; H, 2.47; N, 3.88.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.08.003.

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