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Natural amino acid salt catalyzed aldol reactions of isatins with ketones: highly enantioselective construction of 3-alkyl-3-hydroxyindolin-2-ones

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ABSTRACT

The asymmetric synthesis of 3-alkyl-3-hydroxyindolin-2-ones via direct aldol reaction of isatin with ketones catalyzed by natural amino acid salts is described, in which the phenylalanine lithium salt was found to be the best catalyst. This strategy was then applied to a variety of isatin and ketone substrates and the corresponding aldol products were obtained in excellent yields (up to 97%) with good to excellent enantioselectivities (up to 90%).

1. Introduction

3-Alkyl-3-hydroxyindolin-2-ones, key structural features of many bioactive compounds,[1] can be found in convolutamydines,[2] celogentin K,[3] TMC-95s,[4] 3′-hydroxyglucoisatisin,[5] diazonamide A,[6] dioxibrassinine[7] as well as several other pharmaceutically active compounds.[8] Due to the fact that biologically active compounds containing the 3-substituted-3-hydroxyoxindole moiety are inherently asymmetric, many approaches have been developed to construct the stereogenic center at the C-3 position.[9] One of the most straightforward approaches to 3-substituted-3-hydroxyindolin-2-ones is the C–C bond formation of appropriate nucleophiles to the isatin C-3 position. Among the most fundamental and important measures for constructing carbon–carbon bonds are the aldol reaction, and many efforts have been made in the asymmetric synthesis of 3-alkyl-3-hydroxyindolin-2-ones by employing this reaction.[10] In 2005, the first enantioselective aldol reaction of isatin with acetone was reported by Tomasini et al. using a dipeptide-based organocatalyst.[11] Later on, Zhao et al. successfully developed a quinidine thiourea, which was used as the organocatalyst in the asymmetric aldol reaction of inactivated ketones and activated carbonyl compounds.[12] Chen et al. reported an example of carbohydrate-derived alcohols as organocatalysts in enantioselective aldol reactions of isatins with ketones.[13] Recently, Nuclease p1, an enzyme from *Penicillium citrinum*, was successfully used to directly catalyze asymmetric aldol reactions between isatin derivatives and cyclic ketones under mild conditions.[14] Despite the above success, finding new catalysts with operation simplicity and catalyst efficiency for the asymmetric synthesis of this structural moiety still attracts considerable interest.

Over the past few decades, the catalytic performance of amino acid metal salts, which take advantage of organocatalysis and Lewis acid catalysis in asymmetric synthesis, has been intensively studied. As pioneering works in this field, Yamaguchi et al. reported that L-proline rubidium salt catalyzed the Michael addition of simple malonates to enones.[15] Since then, as an ideal alternative to organocatalysts and other metal based catalysts, the catalytic activity of amino acid metal salts has been demonstrated in many different reactions.[16] In 2005, Liu et al. reported an example of chiral amino acid salts as a new type of catalyst, in which highly enantioselective cyanosilylations of ketones were promoted by L-phenylglycine sodium salt.[17] Not long ago, Kang described a straightforward synthesis of Phaitanthrin A and its derivatives by employing L-phenylalanine potassium salt to catalyze this asymmetric aldol reaction.[18] Very recently, Chanda disclosed the utilization of potassium salt of phenylalanine for the construction of structurally valuable alkyl/aryl/hetaryl substituted and spirocyclic 3-hydroxyindanone frameworks.[19] In continuation of our previous efforts on asymmetric direct aldol reaction of functionalized ketones catalyzed by amine organocatalysts based on bispidine,[20] we herein investigate the possibility of adopting natural amino acid salts as new agents to catalyze the synthesis of 3-alkyl-3-hydroxyindolin-2-ones via the direct aldol reactions of isatin and its derivatives with ketones with high enantioselectivity.

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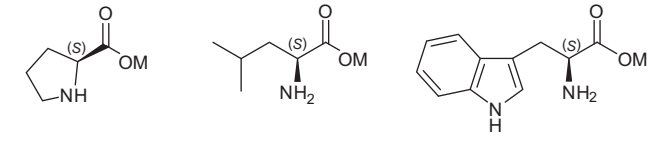
2. Results and discussion

Initially, the amino acid salts were synthesized employing a simple reaction protocol described by Liu with some modifications.[17] Accordingly, the corresponding amino acids were added to the alkali metal hydroxide in methanol at 0 °C and stirring at 25 °C for 4 h. The solvent was then evaporated off at 25 °C in vacuum, and the salts were directly used without further purification. The chemical structures of the amino acids and their salts are shown in Scheme 1.

By setting up a template reaction with acetone **8a** as the donor substrate and isatin **7a** as the acceptor using 20 mol % of the catalyst at room temperature, the catalytic performance of these catalysts for asymmetric aldol reactions was evaluated and the results are shown in Table 1. As evident from Table 1, the reaction proceeded well with all 18 chiral amino acid salts; the most studied proline lithium salt **1a** showed a good yield of 87% albeit with a low ee value of 15% (Table 1, entry 1). The effects of either amino acid or the cation species on the yield and ee values are summarized in Table 1. For a specific type of amino acid, when the alkali metal species was changed, we found that the lithium salt of the amino acid usually led to a higher enantioselectivity of the product than other two cation salts. Conversely, some sterically hindered amino acid salts gave better results than others when they were in the same type of alkali metal salt. Three different salts of previously reported phenylalanine all had relatively good catalytic activities than others (Table 1, entries 10–12). Also, we found the lithium salt **4a** rather than the previously reported potassium salt **4c**,[18] that showed a higher activity in this template reaction, with an ee value up to 49% (entry 10 vs 12) with a high yield of 95%. Hence, the phenylalanine lithium salt **4a** was chosen for further investigation.

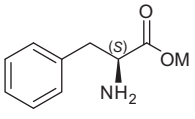
In a second step, we investigated the different ratios of the mixed catalysts and catalysts loading, as well as the temperature with the aim of improving the catalytic activity. Inspired by the previous report that a mixed catalyst consisting of the salt of the amino acid and its original amino acid can be more effective than using these catalysts individually in the Michael addition of malonates to enones,[16e] we examined the activity of catalysts prepared with different ratios of phenylalanine and lithium hydroxide (Table 2, entries 1–4). The results shows that catalyst $\mathbf{4a_2}$ prepared in a ratio of phenylalanine/lithium hydroxide 1:0.9 was



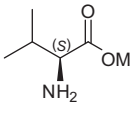
1a M = Li
1b M = Na
1c M = K

2a M = Li
2b M = Na
2c M = K

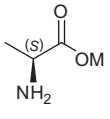
3a M = Li
3b M = Na
3c M = K



4a M = Li
4b M = Na
4c M =K



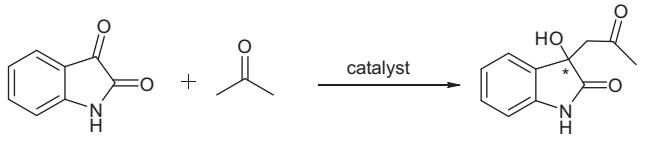
5a M = Li
5b M = Na
5c M = K



6a M = Li
6b M = Na
6c M = K

Scheme 1. Various amino acid salts catalysts screened for aldol reaction.

Table 1
Enantioselective aldol reaction of isatin with acetone catalyzed by amino acid salts

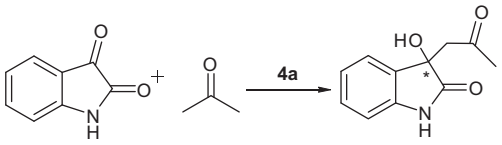


7a **8a** **9a**

Entry[a]	Catalyst	Yield[b] (%)	ee[c] (%) config.[d]
1	**1a**	87	15 (*S*)
2	**1b**	49	16 (*S*)
3	**1c**	95	16 (*S*)
4	**2a**	86	10 (*S*)
5	**2b**	75	33 (*S*)
6	**2c**	98	22 (*S*)
7	**3a**	96	41 (*S*)
8	**3b**	95	34 (*S*)
9	**3c**	68	37 (*S*)
10	**4a**	95	49 (*S*)
11	**4b**	81	45 (*S*)
12	**4c**	92	35 (*S*)
13	**5a**	96	43 (*S*)
14	**5b**	81	32 (*S*)
15	**5c**	95	33 (*S*)
16	**6a**	98	35 (*S*)
17	**6b**	91	15 (*S*)
18	**6c**	90	10 (*S*)

[a] All the reactions were carried out with 0.1 mmol (14.71 mg, 1 equiv) isatin **7a**, 1.0 mL of acetone **8a**, and 0.02 mmol catalyst (20 mol %) at room temperature for 12 h.
[b] Isolated yields after purification by flash column.
[c] Determined by HPLC on CHIRALPAK AD-3 column after purification (eluent: hexane/2-propanol = 80:20, 1.0 mL/min).
[d] The absolute configuration was determined by comparison of the specific rotation with that previously reported.[11]

Table 2
Effect of the reaction conditions for the enantioselective aldol reaction

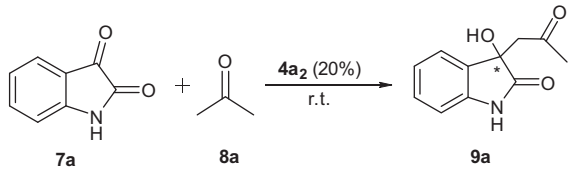


7a **8a** **9a**

Entry[a]	Catalyst	Time (h)	Yield[b] (%)	ee[c] (%) config.[d]
1	$\mathbf{4a_1}$[e]	12	89	Racemic
2	$\mathbf{4a_2}$[f]	12	94	56 (*S*)
3	$\mathbf{4a_3}$[g]	12	92	48 (*S*)
4	$\mathbf{4a_4}$[h]	12	93	41 (*S*)
5	$\mathbf{4a_2}$ (30%)	12	87	57 (*S*)
6	$\mathbf{4a_2}$ (25%)	12	91	56 (*S*)
7	$\mathbf{4a_2}$ (20%)	12	93	56 (*S*)
8	$\mathbf{4a_2}$ (15%)	12	82	53 (*S*)
9	$\mathbf{4a_2}$ (10%)	12	85	46 (*S*)
10	$\mathbf{4a_2}$ (5%)	12	87	32 (*S*)
11	$\mathbf{4a_2}$[i]	24	82	21 (*S*)
12	$\mathbf{4a_2}$[i]	36	95	15 (*S*)
13	$\mathbf{4a_2}$[j]	48	32	16 (*S*)
14	$\mathbf{4a_2}$[j]	84	58	21 (*S*)

[a] Unless specified otherwise, all the reactions were carried out with 0.1 mmol (14.71 mg, 1 equiv) isatin **7a**, 1 mL of acetone **8a**, and 0.02 mmol catalyst $\mathbf{4a_2}$ (20 mol %) at room temperature for 12 h.
[b] Isolated yields after purification by flash column.
[c] Determined by HPLC on CHIRALPAK AD-3 column after purification (eluent: hexane/2-propanol = 80:20, 1.0 mL/min).
[d] The absolute configuration was determined by comparison of the specific rotation with that previously reported.[11]
[e] The ratio of the catalyst is phenylalanine/lithium hydroxide 1:1.2.
[f] The ratio of the catalyst is phenylalanine/lithium hydroxide 1:0.9.
[g] The ratio of the catalyst is phenylalanine/lithium hydroxide 1:0.8.
[h] The ratio of the catalyst is phenylalanine/lithium hydroxide 1:0.6.
[i] Temperature at 0 °C.
[j] Temperature at −20 °C.

Table 3
Optimization of the solvent for the enantioselective aldol reaction



Entry[a]	Solvents	Yield[b] (%)	ee[c] (%) config.[d]
1	CH_2Cl_2	79	71 (*S*)
2	PhMe	35	67 (*S*)
3	$CHCl_3$	48	69 (*S*)
4	xylene	49	65 (*S*)
5	PhOMe	86	61 (*S*)
6	CH_3CN	53	49 (*S*)
7	MTBE	60	54 (*S*)
8[e]	CH_2Cl_2/PhOMe	86	70 (*S*)

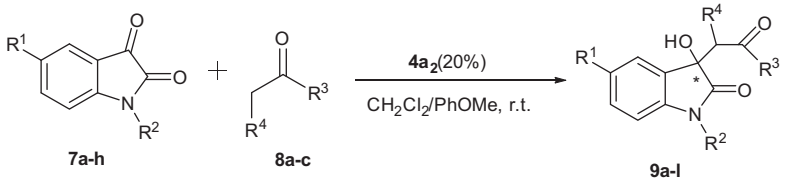
[a] Unless specified otherwise, all the reactions were carried out with 0.1 mmol (14.71 mg, 1 equiv) isatin **7a**, 0.2 mL acetone **8a**, and 0.02 mmol catalyst **4a$_2$** (20 mol %) in 0.8 mL certain solvents at room temperature for 12 h.
[b] Isolated yields after purification by flash column.
[c] Determined by HPLC on CHIRALPAK AD-3 column after purification (eluent: hexane/2-propanol = 80:20, 1.0 mL/min).
[d] The absolute configuration was determined by comparison of the specific rotation with that previously reported.[11]
[e] 0.4 mL of CH_2Cl_2 and 0.4 mL of PhOMe were used as cosolvents.

the most effective for this template reaction, with an ee value up to 56% without a loss of yield when compared with the original catalyst **4a**. However, if the lithium hydroxide was in excess at all, the product would be formed in a racemic state (Table 2, entry 1). The effect of different catalyst loading of **4a$_2$** was tested by altering the catalyst loading in a wide range from 5 mol % to 30 mol % (Table 2, entries 5–10). When the catalyst loading was decreased from 30 mol % to 20 mol %, the ee value was almost unchanged while the yield increased slowly from 87% to 93%. But when the catalyst loading decreased down below to 15 mol %, the ee value down to 53%, so we chose 20 mol % of **4a$_2$** as the best catalyst loading. Then, we altered the temperature and prolonged the reaction time. It seems that alteration of neither the reaction time nor temperature could bring satisfying results (Table 2, entries 11–14). On the contrary, they may hinder the enantioselective synthesis of the product. So, 25 °C (rt) was selected as the best reaction temperature.

In continuation of the screening studies, we conducted experiments with different solvents to establish the optimal reaction conditions of catalyst **4a$_2$**. As summarized in Table 3, seven different polar and non-polar solvents were examined. Variation of the reaction media had a significant effect on the reaction. When the reaction was carried out in CH_2Cl_2, the enantioselectivity obtained was higher than in $CHCl_3$, xylene, PhOMe, PhMe, CH_3CN or MTBE (entry 1 vs entries 2–7), although its yield was lower compared with PhOMe. Thus, as the optimal compromise between reactivity and stereoselectivity, a mixture of CH_2Cl_2 and PhOMe was tested as the reaction media, affording **9a** in a relatively high yield while the enantioselectivity was almost unchanged (Table 2, entry 8). Hence, a mixture of CH_2Cl_2 and PhOMe was chosen as the best solvent combination.

Thus, using the optimized conditions, the scope of this reaction was studied and the results are reported in Table 4. With acetone as the donor substrate, various substituted isatins were applied in this reaction. The different *N*-substituted group of isatin **7** (either methyl or benzyl or PMB) had a positive effect on the ee value of the corresponding product; the corresponding products of *N*-methyl, *N*-benzyl and *N*-PMB-protected isatins **9b**, **9c,** and **9d** were obtained in better yields and with higher ee (Table 4, entries 2–4). This revealed that the steric modification at the *N*-1 position did have a positive influence on the reaction selectivity. Conversely, isatin substrates bearing electron-withdrawing and electron-donating groups had little influence on the results (Table 4, entries 5–8). In general, electron-withdrawing substituted analogues were superior to electron-donating substituted analogues (Table 4, entries 5, 6 vs 8). In the case of 5-bromine isatin, the reactivity is low due to the poor solubility in the cosolvents. When compared with no substituent at the 5-position of isatin **7a**, it seems that an electron-donating substituted group methyl

Table 4
Substrate scope with various isatins and ketones



Entry[a]	Product	R^1	R^2	R^3	R^4	Time (h)	Yield[b] (%)	ee[c] (%)
1	**9a**	H	H	Me	H	12	86	70
2	**9b**	H	Me	Me	H	12	91	81
3	**9c**	H	Bn	Me	H	12	90	87
4	**9d**	H	PMB	Me	H	16	87	87
5	**9e**	F	H	Me	H	16	89	77
6	**9f**	Cl	H	Me	H	22	97	78
7	**9g**	Br	H	Me	H	48	nd	nd
8	**9h**	Me	H	Me	H	48	73	66
9	**9i**	H	H	$-CH_2CH_2CH_2-$		16	87	79
10	**9j**	H	Bn	$-CH_2CH_2CH_2-$		24	96	80
11	**9k**	H	Bn	$-CH_2CH_2CH_2CH_2-$		12	97	83
12	**9l**	H	PMB	$-CH_2CH_2CH_2-$		24	96	90

[a] Unless specified otherwise, all the reactions were carried out with 0.1 mmol isatin derivatives **7**, 0.2 mL of ketone derivatives **8**, and 0.02 mmol catalyst **4a$_2$** (20 mol %) in co-solvent of 0.4 mL of CH_2Cl_2 and 0.4 mL of PhOMe.
[b] Isolated yields after purification by flash column.
[c] Determined by HPLC on CHIRALPAK columns after purification.

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group at C-5 position may work against the catalyst efficiency (Table 4, entry 8 vs 1). Cyclohexanone and cyclopentanone were tested as donor substrates for their effects in this reaction. As shown in Table 4, these substrates were also very efficient, affording the relevant adducts in excellent chemical yields and with reasonable enantioselectivities. Along with previous results, the reaction exhibits higher enantioselectivity when some sterically hindered substrates were adopted (entries 10–12 vs entry 9).

3. Conclusion

In conclusion, we have demonstrated the successful application of phenylalanine lithium salt as an effective novel catalyst for highly enantioselective aldol reactions of acetone with isatin and its derivatives. The advantage of these catalysts is that they are easily prepared from inexpensive natural chiral amino acids. The influence of different groups substituted on the isatin on the enantioselectivity of the product of the aldol reaction was primarily studied. Further investigations into the application of these catalysts to other reactions and toward the synthesis of active pharmaceutical motifs are currently underway in our laboratory.

4. Experimental

4.1. General methods

All solvents and reagents were of analytical reagents and used without further purification. Crude products were purified by column chromatography on silica gel of 300–400 mesh. TLC analysis was performed on Silica Gel 60, F254 plates, which were visualized by UV at 254 nm. Chiral High-performance liquid chromatography (HPLC) analyses were conducted with a Waters Alliance 2695 instrument, using a UV–visible light (Vis) Waters PDA 2998 detector and working at 254 nm. The chromatographic grade isopropanol and hexane were used as eluents. ^{1}H NMR and ^{13}C NMR and ^{19}F NMR spectra were recorded on a Bruker Avance (Varian Unity Inova) 400 MHz spectrometer using TMS as internal reference chemical shift in δ, ppm. Solvent for NMR is DMSO-d_6. Low-resolution mass spectrometry (LR-MS) was carried out on an AB/MDS Sciex 3200 QTRAP mass spectrometer (AB SCIEX, USA) equipped with electro-spray ionization (ESI) source. Optical rotations were measured on Anton Paar MCP 200 at λ = 589 nm, D = 1 dm. All aldol reactions were carried out under an atmosphere of air in a closed system.

4.2. General procedure for the aldol reaction of isatins with ketones

The organic salts were directly added to a stirred solution of isatin **7** (0.10 mmol) and ketone **8** (1 mL or 0.2 mL) in the corresponding solvent, then sealed and stirred for the corresponding time and at the temperature given in Tables 1–4. The solvent was then removed under reduced pressure and the mixture was purified by flash chromatography on silica gel (PE and EA as eluents) to give the desired aldol products.

4.2.1. (*S*)-3-(2-Oxopropyl)-3-hydroxyindolin-2-one 9a

Pale yellow solid, 86% yield, 70% ee. Mp: 167–169 °C; $[\alpha]_D^{25}$ = −11.0 (*c* 1.0, MeOH); ^{1}H NMR: δ 10.23 (s, 1H), 7.24 (d, *J* = 7.2 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 6.90 (t, *J* = 7.6 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 5.99 (s, 1H), 3.28 (d, *J* = 16.8 Hz, 1H), 3.05 (d, *J* = 16.8 Hz, 1H), 1.99 (s, 3H); ^{13}C NMR: δ 205.2, 178.1, 142.5, 131.5, 128.9, 123.6, 121.2, 109.4, 72.6, 50.6, 30.5; MS (ESI): *m*/*z* 206 (M^++1); The ee was determined by HPLC using Chiralpak AD-3 column (80:20 hexane/*i*-PrOH at 1 mL/min): t_{maj} = 11.6 min, t_{min} = 15.0 min, λ = 254 nm.

4.2.2. (*S*)-1-Methyl-3-(2-oxopropyl)-3-hydroxyindolin-2-one 9b

White solid, 91% yield, 81% ee. Mp: 155–157 °C; $[\alpha]_D^{25}$ = −15.2 (*c* 2.4, MeOH); ^{1}H NMR: δ 7.28 (m, 2H), 6.98 (q, *J* = 8.0 Hz, *J* = 15.6 Hz, 2H), 6.06 (s, 1H), 3.37 (d, *J* = 6.4 Hz, 2H), 3.10 (s, 3H), 1.99 (s, 3H); ^{13}C NMR: δ 205.1, 176.5, 143.9, 130.9, 129.1, 123.2, 121.9, 108.2, 72.3, 50.4, 30.4, 25.8; MS (ESI): *m*/*z* 220 (M^++1); The ee was determined by HPLC using Chiralpak AS-H column (80:20 hexane/*i*-PrOH at 1 mL/min): t_{maj} = 26.6 min, t_{min} = 31.2 min, λ = 254 nm.

4.2.3. (*S*)-1-Benzyl-3-(2-oxopropyl)-3-hydroxyindolin-2-one 9c

Pale yellow solid, 90% yield, 87% ee; Mp: 161–163 °C; $[\alpha]_D^{25}$ = −16.4 (*c* 2.8, MeOH); ^{1}H NMR: δ 7.43 (d, *J* = 7.2 Hz, 1H), 7.33 (t, *J* = 7.2 Hz, 3H), 7.26 (t, *J* = 7.2 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 6.97 (t, *J* = 7.2 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 6.21 (s, 1H), 4.87 (q, *J* = 16.0 Hz, *J* = 20.0 Hz, 2H), 3.46 (d, *J* = 16.0 Hz, 1H), 3.19 (d, *J* = 16.0 Hz, 1H), 2.03 (s, 3H); ^{13}C NMR: δ 205.2, 176.7, 143.1, 136.3, 130.9, 129.0, 128.4, 127.2, 123.4, 122.0, 108.9, 72.3, 50.3, 42.6, 30.4; MS (ESI): *m*/*z* 296 (M^++1); The ee was determined by HPLC using Chiralpak AS-H column (80:20 hexane/*i*-PrOH at 1 mL/min): t_{min} = 14.7 min, t_{maj} = 16.5 min, λ = 254 nm.

4.2.4. (*S*)-1-(4-Methoxybenzyl)-3-(2-oxopropyl)-3-hydroxyindolin-2-one 9d

White solid, 87% yield, 87% ee. Mp: 114–116 °C; $[\alpha]_D^{25}$ = −16.3 (*c* 3.7, MeOH); ^{1}H NMR: δ 7.36 (d, *J* = 8.4, 2H), 7.32 (d, *J* = 7.2, 1H), 7.17 (t, *J* = 7.6, 1H), 6.96 (t, *J* = 7.2 Hz, 1H), 6.89 (d, *J* = 4.8 Hz, 2H), 6.76 (d, *J* = 7.6, 1H), 6.18 (s, 1H), 4.79 (q, *J* = 15.6 Hz, *J* = 37.6 Hz, 2H), 3.72 (s, 3H), 3.43 (d, *J* = 16.8 Hz, 1H), 3.16 (d, *J* = 17.2 Hz, 1H), 2.03 (s, 3H); ^{13}C NMR: δ 205.2, 176.6, 158.4, 143.1, 128.9, 128.6, 128.1, 121.9, 113.8, 109.0, 72.3, 55.0, 50.3, 42.1, 30.4; MS (ESI): *m*/*z* 326 (M^++1). The ee was determined by HPLC using Chiralpak AS-H column (80:20 hexane/*i*-PrOH at 1 mL/min): t_{maj} = 13.6 min, t_{min} = 14.1 min, λ = 254 nm).

4.2.5. (*S*)-5-Fluoro-3-(2-oxopropyl)-3-hydroxyindolin-2-one 9e

Pale yellow solid, 89% yield, 77% ee. Mp: 183–185 °C; $[\alpha]_D^{25}$ = −17.0 (*c* 1.0, MeOH); ^{1}H NMR: δ 10.25 (s, 1H), 7.16 (dd, *J* = 2.4, *J* = 8.4 Hz, 1H), 7.03–6.98 (m, 1H), 6.77 (dd, *J* = 4.0, *J* = 8.4 Hz, 1H), 6.10 (s, 1H), 3.35 (d, *J* = 17.2 Hz, 1H), 3.05 (d, *J* = 17.2 Hz, 1H), 2.02 (s, 3H); ^{13}C NMR: δ 205.2, 178.2, 158.3 (d, *J* = 235.2 Hz), 139.2, 133.8 (d, *J* = 7.0 Hz), 115.5 (d, *J* = 23.4 Hz), 112.1 (d, *J* = 24.6 Hz), 110.6 (d, *J* = 8.3 Hz), 72.8, 50.0, 30.4; ^{19}F NMR: δ −122.40; MS (ESI): *m*/*z* 224 (M^++1). The ee was determined by HPLC using Chiralpak AS-H column (80:20 hexane/*i*-PrOH at 1 mL/min): t_{maj} = 29.2 min, t_{min} = 36.3 min, λ = 254 nm.

4.2.6. (*S*)-5-Chloro-3-(2-oxopropyl)-3-hydroxyindolin-2-one 9f

Pale yellow solid, 97% yield, 78% ee. Mp: 168–169 °C; $[\alpha]_D^{25}$ = −22.0 (*c* 1.0, MeOH); ^{1}H NMR: δ 10.36 (s, 1H), 7.32 (d, *J* = 2.0, 1H), 7.23 (d, *J* = 6.4, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6. 11 (s, 1H), 3.42 (d, *J* = 10.8 Hz, 1H), 3.07 (d, *J* = 17.2 Hz, 1H), 2.09 (s, 3H); ^{13}C NMR: δ 205.3, 177.8, 141.6, 133.7, 125.2, 124.0, 110.8, 72.6, 49.9, 30.3; MS (ESI): *m*/*z* 240 (M^++1). The ee was determined by using HPLC Chiralpak IA column (80:20 hexane/*i*-PrOH at 1 mL/min): t_{maj} = 11.1 min, t_{min} = 15.6 min, λ = 254 nm.

4.2.7. 5-Bromo-3-(2-oxopropyl)-3-hydroxyindolin-2-one 9g

Compound **9g** was not obtained due to the poor solubility of 5-bromine isatin in the cosolvents of CH_2Cl_2 and PhOMe.

4.2.8. (*S*)-5-Methyl-3-(2-oxopropyl)-3-hydroxyindolin-2-one 9h

Pale yellow solid, 73% yield, 66% ee. Mp: 158–160 °C; $[\alpha]_D^{25}$ = −13.0 (*c* 1.0, MeOH); ^{1}H NMR: δ 10.12 (s, 1H), 7.06

(s, 1H), 6.98 (d, J = 7.6 Hz, 1H), 6.67 (d, J = 8.4 Hz, 1H), 5.94 (s, 1H), 3.24 (d, J = 16.8 Hz, 1H), 3.00 (d, J = 16.4 Hz, 1H), 2.23 (s, 3H), 2.01 (s, 3H); ^{13}C NMR: δ 205.2, 178.2, 140.0, 131.6, 129.9, 129.1, 124.3, 109.2, 72.7, 50.3, 30.5, 20.7; MS (ESI): m/z 220 (M^++1). The ee was determined by HPLC using Chiralpak IA column (80:20 hexane/i-PrOH at 1 mL/min): t_{maj} = 11.5 min, t_{min} = 14.4 min, λ = 254 nm.

4.2.9. 3-Hydroxy-3-(2-oxocyclopentyl)indolin-2-one 9i

Pale yellow solid, 87% yield, 79% ee. Mp: 140–142 °C; $[\alpha]_D^{25}$ = −85.0 (c 1.0, MeOH); ^{1}H NMR: δ 10.33 (s, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.19 (t, J = 7.6 Hz, 1H), 6.90 (t, J = 7.2 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 5.97 (s, 1H), 2.89 (t, J = 9.6 Hz, 1H), 2.24–1.70 (m, 6H); ^{13}C NMR: δ 216.4, 178.3, 142.8, 129.9, 129.2, 124.6, 121.2, 109.5, 74.9, 54.9, 41.4, 24.5, 20.0. MS (ESI): m/z 232 (M^++1). The ee was determined by chiral HPLC analysis using a ChiralPak AD-H column (85:15 hexane/i-PrOH at 0.8 mL/min): major diastereoisomer: t_{maj} = 29.5 min, t_{min} = 27.4 min, 79% ee; minor diastereoisomer: t_{maj} = 20.9 min, t_{min} = 23.6 min, 52% ee, λ = 254 nm.

4.2.10. 1-Benzyl-3-hydroxy-3-(2-oxocyclopentyl)indolin-2-one 9j

Brown solid, 96% yield, 80% ee. Mp: 166–168 °C; $[\alpha]_D^{25}$ = −75.0 (c 1.0, MeOH); ^{1}H NMR: δ 7.45 (t, J = 7.2 Hz, 1H), 7.35–7.16 (m, 6H), 6.98 (m, 1H), 6.78 (dd, J = 8.0 Hz, J = 38.4 Hz, 1H), 6.19 (d, J = 26.4 Hz, 1H), 4.86 (m, 2H), 3.00 (m, 1H), 2.23–1.65 (m, 6H); ^{13}C NMR: δ 216.5, 216.2, 176.9, 176.1, 143.4, 142.8, 136.2, 129.2, 128.4, 124.5, 122.0, 109.0, 74.6, 74.5, 55.3, 54.1, 25.0, 24.6, 20.1, 19.6. MS (ESI): m/z 322 (M^++1). The ee was determined by chiral HPLC analysis using a ChiralCel AD-H column (85:15 hexane/i-PrOH at 0.8 mL/min): major diastereoisomer: t_{maj} = 29.9 min, t_{min} = 35.3 min, 80% ee; minor diastereoisomer: t_{maj} = 41.6 min, t_{min} = 32.7 min, 55% ee, λ = 254 nm.

4.2.11. 1-Benzyl-3-hydroxy-3-(2-oxocyclohexyl)indolin-2-one 9k

Pale white solid, 97% yield, 83% ee. Mp: 163–165 °C; $[\alpha]_D^{25}$ = −42.0 (c 1.0, MeOH); ^{1}H NMR: δ 7.45 (d, J = 7.6 Hz, 2H), 7.28 (m, 4H), 7.18 (t, J = 14.8 Hz, 1H), 6.92 (t, J = 7.2 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H), 6.04 (s, 1H), 4.85 (q, J = 8.0 Hz, J = 36.4 Hz, 2H), 3.22 (dd, J = 4.4 Hz, J = 12.8 Hz, 1H), 2.23–1.44 (m, 8H), ^{13}C NMR: δ 209.3, 177.3, 143.9, 136.4, 130.2, 128.6, 128.4, 127.7, 127.1, 124.6, 121.6, 108.9, 73.6, 57.6, 42.8, 41.3, 26.8, 26.6, 24.4. MS (ESI): m/z 336 (M^++1). The ee was determined by chiral HPLC analysis using a ChiralCel OD-H column (85:15 hexane/i-PrOH at 0.5 mL/min): major diastereoisomer: t_{maj} = 33.0 min, t_{min} = 25.7 min, 83% ee; minor diastereoisomer: t_{maj} = 42.7 min, t_{min} = 25.7 min, 52% ee, λ = 254 nm.

4.2.12. 3-Hydroxy-1-(4-methoxybenzyl)-3-(2-oxocyclopentyl)indolin-2-one 9l

Brown solid, 96% yield, 90% ee. Mp: 118–120 °C; $[\alpha]_D^{25}$ = −51.0 (c 1.0, MeOH); ^{1}H NMR: δ 7.43–6.74 (m, 8H), 6.15 (d, J = 25.6, 1H), 4.77 (m, 2H), 3.72 (s, 3H), 2.96 (m, 1H), 2.77–1.64 (m, 6H), ^{13}C NMR: δ 216.4, 176.8, 158.6, 143.4, 130.4, 128.7, 128.0, 124.4, 123.9, 122.3, 121.9, 113.8, 109.1, 74.6, 55.1, 53.9, 42.3, 25.0, 24.6, 19.6. MS (ESI): m/z 352 (M^++1). The ee was determined by chiral HPLC analysis using a ChiralCel OD-H column (90:10 hexane/i-PrOH at 0.5 mL/min for 40 min, then up to 85:15 hexane/i-PrOH in 50 min at 0.5 mL/min): major diastereoisomer: t_{maj} = 83.0 min, t_{min} = 78.9 min, 90% ee; minor diastereoisomer: t_{maj} = 95.0 min, t_{min} = 69.8 min, 65% ee, λ = 254 nm.

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