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Carbohydrate-derived alcohols as organocatalysts in enantioselective aldol reactions of isatins with ketones

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ABSTRACT

The catalytic activity of carbohydrate-derived amino alcohols in the enantioselective aldol reaction of ketones with isatin and its derivatives has been examined for the first time. The carbohydrate-derived amino alcohols **5** were found to be efficient organocatalysts for asymmetric aldol reactions. A variety of isatins were used as substrates and the corresponding aldol products were obtained in high yields (up to 99%) and with moderate enantioselectivities (up to 75%).

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1. Introduction

3-Alkyl-3-hydroxyindolin-2-ones are encountered in a large variety of natural and artificial bioactive compounds and can be used for the total synthesis of natural products and pharmaceutically active compounds.[1] Compounds containing the 3-substituted 3-hydroxyoxindole moiety are inherently asymmetric,[2] and the influence of the absolute configuration at the stereogenic center at the C-3 position of the oxindole on the biological activity has been investigated extensively.[3] In recent years, a variety of catalytic asymmetric methods have been developed for the construction of 3-alkyl-3-hydroxyindolin-2-ones.[4] In 2005, Tomasini and co-workers reported the first enantioselective aldol reaction of isatin with acetone catalyzed by dipeptide-based organocatalysts.[5] Malkov et al. have described the synthesis of (*R*)-convolutamydine A with high enantiomeric excess by using 20 mol % of vicinal amino alcohols prepared from leucinol and valinol.[6] Nakamura et al. reported that natural *N*-heteroarylsulfonylprolinamide acted as a highly efficient organocatalyst for the reaction of acetone or aldehydes with isatin derivatives with low catalyst loadings.[7] Very recently, a quinidine thiourea was used as the organocatalyst in the asymmetric aldol reaction of inactivated ketones and activated carbonyl compounds, which was carried out by Zhao and co-workers.[8] Asymmetric organocatalysis has attracted considerable interest as a new, powerful, and environmentally friendly methodology for the catalytic production of enantiomerically pure organic compounds. Therefore, the design of new effective organocatalysts for asymmetric synthesis is of great importance.

Carbohydrates have been widely used in organic synthesis and have only recently shown their huge potential as a source of highly effective chiral auxiliaries, ligands, and catalysts.[9] The design and fine-tuning of carbohydrate-based catalyst is facilitated by the multiple functional groups present within this class of compounds.[10] This allows a systematic regio- and stereoselective introduction of different functionalities in the synthesis of a series of chiral ligands that can be screened in the search for high activities and enantioselectivities.[11] Enantioselective aldol reactions using carbohydrate-derived amino alcohols as organocatalysts are rare and represent a significant challenge.[12] Following our interest in carbohydrates as inexpensive and highly modular chiral sources for asymmetric reactions,[13] we herein report the first example of a catalytic asymmetric aldol reaction between isatins and ketones using various carbohydrate-derived amino alcohols.

2. Results and discussion

2.1. Synthesis of carbohydrate-derived organocatalyst 2–6

In only three steps from the known glucosamine **1**, conveniently functionalized D-glucosamine-derived compounds **2** and **3** can be obtained, then the protection at C-2 can be removed to give amino alcohols **4** and **5** easily, which after reaction of 1 equiv of 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene affords the desired carbohydrate-derived organocatalyst **6** in 92% yield (Fig. 1, Scheme 1). The structures of the synthesized compounds were established by spectroscopic methods and elemental analysis.

2.2. Catalytic activities of carbohydrate-derived organocatalysts in enantioselective aldol reactions

With these organocatalysts in hand, we then examined their efficiency in enantioselective aldol reactions with isatin **7a** and acetone **8a** as the model substrates. The results of the catalyst screening and optimizations are presented in Table 1.

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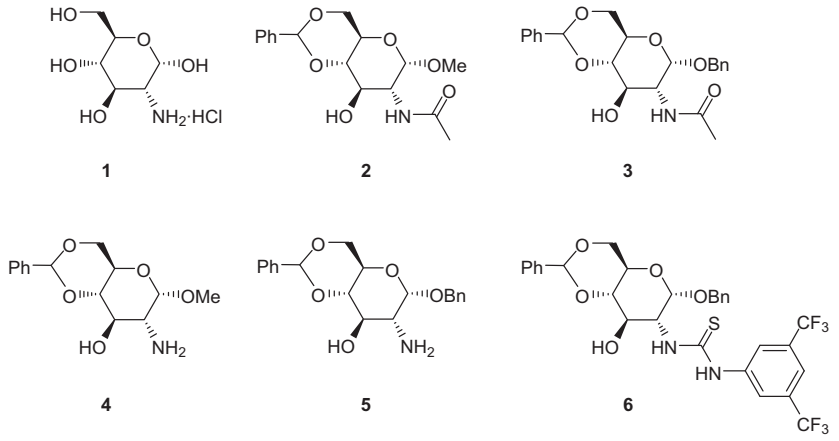
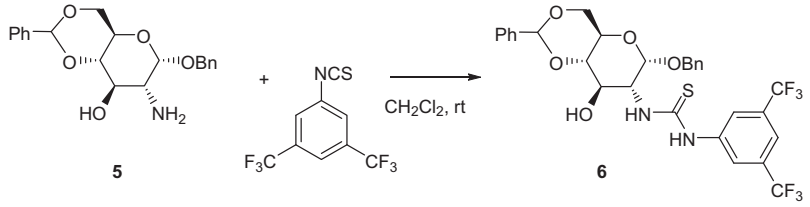


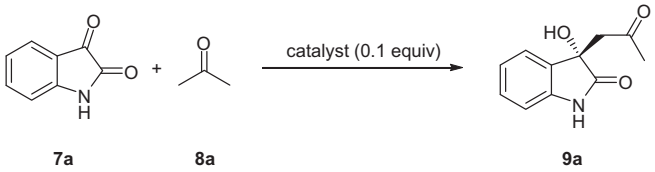
Figure 1. Various carbohydrate-derived catalysts screened for aldol reaction.



Scheme 1. Synthesis of chiral thiourea organocatalysts **6**.

Initially, the reaction was performed in the presence of D-glucosamine hydrochloride (10 mol %) and a catalytic amount of Et_3N as an additive in acetone to give a good yield of the desired compound **9a** at room temperature, but the ee value obtained was poor (Table 1, entry 1). Accordingly, intermediates **2** and **3** failed to catalyze the reaction, showing the key importance of the primary amino group. In contrast, amino alcohols **4** gave much improved yields and ee values for the (*S*)-enantiomer (Table 1, entry 4). By using amino alcohols **5** instead of **4**, the enantioselectivity of **9a** increased to 41% ee (entry 4). However, with carbohydrate-derived organocatalyst **6**, only a trace amount of **9a** was formed (Table 1, entry 3). The ee value was improved to 55% when the reaction was carried out at 0 °C and prolonging the reaction time to 72 h. As expected, amino alcohols **5** (20 mol %) exhibited excellent reactivity but some loss in enantioselectivity at 0 °C over 24 h occurred. However, a further decrease in the catalyst loading to 5 mol % rendered the reaction unacceptably slow. When the reaction was carried out at −25 °C, the ee value increased but the reaction rate decreased to 30% (entry 5). Thus, the optimized catalyst loading was chosen as 10 mol % of **5**. The absolute configuration of the product **9a** was determined to be (*S*) by comparing the specific rotation with the literature values.[5]

Table 1
Enantioselective aldol reaction of isatin with acetone catalyzed by carbohydrate-derived catalysts[a]



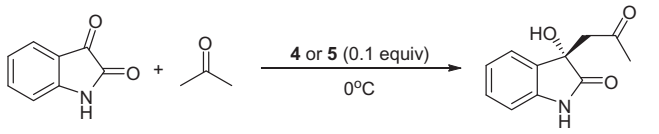
Entry	Catalyst (%)	Temp (°C)	Time (days)	Yield[b] (%)	ee[c] (%) Config.[d]
1	1 (10)	rt	1	99	10 (*S*)[e]
2	2 (10)	rt	1	30	5 (*S*)
3	3 (10)	rt	1	85	<3
4	4 (10)	rt	1	95	15 (*S*)
5	5 (10)	rt	1	99	41 (*S*)
7	6 (10)	rt	2	90	<3 [f]
8	5 (10)	0	4	99	55 (*S*)
9	5 (20)	0	2	95	50 (*S*)
10	5 (5)	0	4	36	54 (*S*)[f]
11	5 (10)	−25	4	12	60 (*S*)

[a] The reactions were carried out with isatin (0.10 mmol) and the catalyst (0.01 mmol, 10 mol %) in the 10 mol % H_2O in 1.0 mL acetone.
[b] Isolated yields.
[c] Determined by chiral HPLC using a Chiralpak OJ-H column (eluent: hexane/2-propanol = 80:20, 1.0 mL/min.).
[d] The absolute configuration was determined by comparison of the specific rotation with that of the literature value.[5]
[e] 10 mol % of Et_3N was used as an additive.
[f] 10 mol % of PhCOOH was used as an additive.

Next, the catalytic activity of organocatalyst **5** was evaluated in the catalytic asymmetric aldol reaction at 0 °C and the results are summarized in Table 2. Six different solvents with organocatalyst **5** were examined to determine the optimum reaction media. When the reaction was carried out in CH_2Cl_2, the enantioselectivity that was obtained was higher than CH_3CN, AcOEt, Et_2O, and PhMe (entry 5 vs entries 1–4, and 7). However, a racemic product was obtained in CH_3OH. Thus, CH_2Cl_2 was selected as the solvent for the aldol reaction. In addition, it seemed that the amino alcohols **5** derived from benzyl α-D-glucosides tended to give higher catalytic enantioselectivities than the amino alcohols **4** derived from methyl α-D-glucosides. The size of the alkyl group (methyl or benzyl) seems to have some influence on the catalytic activity (entry 5 vs 8).

In a third study, the scope of this reaction was studied and the results are summarized in Table 3. As shown in Table 3, with acetone as the substrate, various substituted isatins may be applied in this reaction. The protecting group of isatin **2** (either methyl or benzyl) had little effect on the ee of the corresponding products. Because the *N*-methyl- and *N*-benzyl-protected isatins **7b** and **7c** had good solubility in CH_2Cl_2, the corresponding products **9b** and

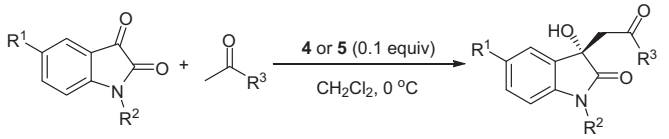
Table 2
Optimization of the solvent for the enantioselective aldol reaction[a]



Entry	Catalyst	Solvent	Time (days)	Yield[b] (%)	ee[c] (%)
1	5	CH_3CN	2	99	40
2	5	AcOEt	4	45	25
3	5	Et_2O	4	60	38
4	5	CH_3OH	1	99	Racemic
5	5	CH_2Cl_2	4	91	67
6	5	$PhCH_3$	2	99	30
7	5	THF	1	99	45
8	4	CH_2Cl_2	4	48	50

[a] The reactions were carried out with isatin (0.10 mmol) , acetone (8.0 mmol), and the catalyst (0.01 mmol, 10 mol %) in 2 ml of the specified solvent at 0 °C.
[b] Isolated yields.
[c] Determined by chiral HPLC using a Chiralpak OJ-H column (eluent: hexane/2-propanol = 80:20, 1.0 mL/min.)

Table 3
Organocatalytic enantioselective aldol reaction addition of ketones **8a**–**b** to various isatins **7a**–**g** promoted by organocatalyst **5**[a]



7a-g **8a,b** **9a-g**

Entry	Catalyst	R^1	R^2	R^3	Time (days)	Yield[b] (%)	ee[c] (%) Config.[d]
1	5	H	H	Me	4	99	67 (*S*)
2	5	H	Me	Me	1	97	65 (*S*)
3	5	H	Bn	Me	1	95	60 (*S*)
4	5	H	H	Ph	4	99	<3
5	5	Cl	H	Me	4	95	72 (*S*)
6	5	Br	H	Me	4	82	75 (*S*)
7	5	CH_3	H	Me	4	80	63 (*S*)
8	4	Cl	H	Me	4	88	55 (*S*)

[a] The reactions were carried out with isatin (0.10 mmol), ketone (8.0 mmol for acetone or 3.0 mmol for other ketones), and the catalyst (0.01 mmol, 10 mol %) in 1.0 mL of CH_2Cl_2 at 0 °C.
[b] Isolated yields.
[c] Determined by chiral HPLC using a Chiralpak OJ-H or AD-H column.
[d] The absolute configuration was determined by comparison of the specific rotation with that of a literature value.

9c were obtained in good yield and ee in a shorter reaction time (Table 3, entries 2 and 3). When acetophenone **8b** was used as a substrate under the optimized conditions, the ee value was generally very poor. The electronic nature of the substituent on the isatin phenyl ring showed some influence on the enantioselectivities. It was found that substrates with electron-donating substituents tended to give higher catalytic activities and enantioselectivities than those with electron-withdrawing groups (Table 3, entries 4, 5 and 6). All of these substrates afforded the same configuration in the end product, namely the (*S*)-enantiomer. During the course of our study, Ricci et al. reported the application of similar chiral amino alcohol organocatalysts derived from Chitosan aerogel in asymmetric direct aldol reaction in water, providing the products in high yields and with good stereoselectivity. However, the reaction with water miscible acetone yielded (*S*)-3-hydroxy-3-(2-oxopropyl)indolin-2-one in good yields but not with synthetically useful enantioselectivities (ee: 25%).[12]

When cyclohexanone **8c** was used instead of **8a**, the reaction with isatin gave the corresponding products in moderate yields with low enantioselectivities (yield: 80%; ee: 11%; dr: 52%;) in 1.0 mL of CH_2Cl_2 at 0 °C. It is noteworthy that when the reactions were carried out with 0.5 ml of H_2O as a solvent at 0 °C products in good yields and with moderate enantioselectivities were obtained (yield: 99%; ee: 63%; dr: 81%) (Scheme 2).

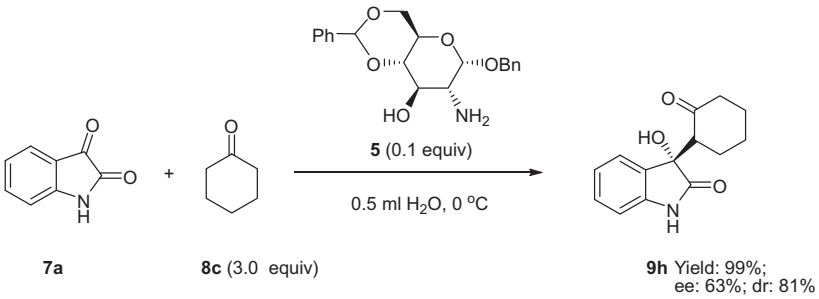
3. Conclusion

In conclusion, we have described the first application of amino alcohols as organocatalysts in the enantioselective aldol reactions of ketones with isatin and its derivatives. The advantage of these organocatalysts is that they are easily prepared in a few steps from commercial D-glucosamine, an inexpensive natural chiral feedstock. The influence of the D-glucosamine moiety on the enantioselectivity of the product of the aldol reaction was studied by modifying the size of the alkyl group at the anomeric position. Further investigations of the efficacy of these organocatalysts in other catalytic asymmetric reactions will be reported in due course.

4. Experimental

4.1. General

Solvents were commercially obtained at the highest commercial quality and used without further purification. Column chromatography was performed on silica gel grade 60 (230–400 mesh). Analytical TLC: Silica Gel 60, F254 plates from Merck, which were visualized by UV and phosphomolybdic acid staining. Optical rotation values were measured on a PerkinElmer P241 polarimeter. Enantiomeric excesses (% ee) were determined by HPLC (Agilent 1100 series) analysis using Chiralcel OD column or ChiraCel AD-H column. The ^1H, ^{13}C NMR spectra were recorded on a Bruker Avance DRX-400 spectrometer; chemical shifts (δ) are given in ppm and are referenced to residual solvent peaks (^1H NMR and



7a **8c** (3.0 equiv) **9h** Yield: 99%; ee: 63%; dr: 81%

Scheme 2. Asymmetric direct aldol reaction for the synthesis of 3-cyclohexanone-3-hydroxy-2-oxindoles.

^{13}C NMR). Elemental analyses were performed on Carlo-Erba 1106. Compounds **2** and **3** and amino alcohols **4** and **5** were prepared by previously described methods.[10,13]

4.2. General procedure for the synthesis of carbohydrate-derived organocatalyst 6

To a suspension of amino alcohols **5** (0.686 g, 2.0 mmol) in CH_2Cl_2 (10 ml) was added 1-isothiocyanato-3,5-bis(trifluoromethyl)benzene (2.2 mmol), and the reaction mixture was refluxed for 2.5 h to give a clear solution. The reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (5:1 hexane/ethyl acetate) to give the desired product. White solid, 92% yield, mp: 85–87 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.81 (s, 1H), 7.58 (s, 1H), 7.42 (s, 2H), 7.31–7.24 (m, 9H), 6.80 (d, J = 7.6 Hz, 1H), 5.51 (s, 1H), 5.07 (d, J = 3.2 Hz, 1H), 4.71 (d, J = 11.6 Hz, 1H), 4.54 (d, J = 11.6 Hz, 1H), 4.20 (t, J = 4.8 Hz, 1H), 4.08 (t, J = 4.8 Hz, 1H), 3.83 (m, 1H), 3.71 (t, J = 10.4 Hz, 1H), 3.60 (t, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 178.2, 137.6, 133.2, 131.4, 128.6, 124.5, 123.6, 121.5, 119.0, 109.3, 99.5, 81.5, 79.8, 79.5, 77.2, 77.1, 77.0, 76.4, 75.2, 75.2, 69.5, 69.1, 63.5; Anal. Calcd for $C_{29}H_{26}F_6N_2O_5S$: C, 55.43; H, 4.16; N, 4.40. Found: C, 55.47; H, 4.11; N, 4.43.

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

The organocatalyst **5** (5.9 mg, 0.01 mmol, 10 mol %) and isatin **7** (0.10 mmol) were stirred in CH_2Cl_2 (2.0 mL) for 15 min at 0 °C. The corresponding ketone **8** (8.0 mmol for acetone or 3.0 mmol for other ketones) was added and the mixture was stirred at 0 °C for the time given in the Tables. The solvent was then removed under reduced pressure and the mixture was purified by flash column chromatography on silica gel (1:5 hexane/ethyl acetate) to give the desired aldol product.

4.3.1. (*S*)-3-(2-Oxopropyl)-3-hydroxyindolin-2-one 9a[5]

Pale yellow solid, 99% yield, 67% ee. Mp: 166–168 °C; $[\alpha]_D^{25} = -18.4$ (c 0.82, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.00 (s, 3H), 3.01 (d, J = 12.8 Hz, 1H), 3.28 (d, J = 11.2 Hz, 1H), 5.99 (br s, 1H), 6.78 (d, J = 7.2 Hz, 1H), 6.90 (t, J = 7.2 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.26 (d, J = 7.2 Hz, 1H), 10.23 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 205.6, 178.5, 142.8, 131.4, 128.9, 123.6, 121.5, 109.3, 72.8, 50.2, 30.7; MS (EI) m/z 206 (M^++1); the enantiomeric excess of the product was measured by chiral stationary phase HPLC analysis using a ChiraCel OJ-H column (80:20 hexanes/i-PrOH at 1.0 mL/min): major enantiomer: t_R = 13.9 min; minor enantiomer: t_R = 16.7 min.

4.3.2. (*S*)-1-Methyl 3-(2-oxopropyl)-3-hydroxyindolin-2-one 9b[5]

White solid, 97% yield, 65% ee. Mp: 153–155 °C; $[\alpha]_D^{25} = -11.4$ (c 0.65, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.14 (s, 3H), 2.99 (d, 1H, J = 17.1 Hz), 3.18 (s, 3H), 3.22 (d, 1H, J = 17.1 Hz), 4.64 (s, 1H), 6.83 (d, 1H, J = 7.5 Hz), 7.05 (d, 1H, J = 7.8 Hz), 7.27–7.37 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 207.3, 176.5, 143.6, 129.7, 123.7, 108.3, 74.2, 49.0, 31.3, 26.2; MS (EI) m/z 220 (M^++1); the enantiomeric excess of the product was measured by chiral stationary phase HPLC analysis using a ChiraCel OJ-H column (85:15 hexanes/i-PrOH at 1.0 mL/min): major enantiomer: t_R = 13.9 min; minor enantiomer: t_R = 15.6 min.

4.3.3. (*S*)-1-Benzyl 3-(2-oxopropyl)-3-hydroxyindolin-2-one 9c[5]

White solid, 95% yield, 60% ee. Mp: 178–179 °C; $[\alpha]_D^{25} = -10.6$ (c 0.62, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.18 (s, 3H), 3.11 (d, 1H, J = 17.1 Hz), 3.31 (d, 1H, J = 17.1 Hz), 4.67 (s, 1H), 4.85 (d, 1H, J = 15.6 Hz), 4.98 (d, 1H, J = 15.6 Hz), 6.72 (d, 1H, J = 7.5 Hz), 7.05 (t, 1H, J = 7.5 Hz), 7.20 (dt, 1H, J = 1.2, 7.5 Hz), 7.26–7.41 (m, 6H); ^{13}C NMR (400 MHz, DMSO-d_6): δ 207.2, 176.3, 142.4, 135.6, 129.7, 128.3, 123.6, 109.1, 74.1, 49.0, 43.6, 31.6; MS (EI) m/z 296(M^++1); the enantiomeric excess of the product was measured by chiral stationary phase HPLC analysis using a ChiraCel OJ-H column (80:20 hexanes/i-PrOH at 0.75 mL/min): major enantiomer: t_R = 18.6 min; minor enantiomer: t_R = 21.4 min.

4.3.4. 3-(2-Oxo-2-phenylethyl)-3-hydroxyindolin-2-one 9d[8]

White solid, 99% yield, racemic, mp: 171–173 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.57 (d, J = 17.4 Hz, 1H), 4.06 (d, J = 17.4 Hz, 1H), 6.05 (br s, 1H), 6.78–6.86 (m, 2H), 7.12–7.17 (m, 1H), 7.26 (d, J = 7.5 Hz, 1H), 7.45–7.50 (m, 2H), 7.61 (t, J = 7.8 Hz, 2H), 7.85–7.88 (m, 2H), 10.24 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 196.3, 178.2, 142.5, 136.1, 133.1, 131.5, 128.6, 127.3, 123.2, 120.9, 109.3, 72.9, 45.8; MS (EI) m/z 268 (M^++1).

4.3.5. (*S*)-5-Chloro-3-(2-oxopropyl)-3-hydroxyindolin-2-one 9e[8]

Pale yellow solid, 95% yield, 72% ee. Mp: 158–159 °C; $[\alpha]_D^{25} = -16.3$ (c 0.77, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.09 (s, 3H), 3.20 (d, 1H, J = 12.0 Hz), 3.42 (d, 1H, J = 10.8 Hz), 4.85 (s, 1H), 6.81 (d, 1H, J = 8.0 Hz), 7.33 (s, 1H), 7.41 (d, 1H, J = 4.4 Hz), 7.51 (d, 1H, J = 2.4 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 207.2, 180.6, 143.3, 135.1, 132.9, 128.5, 115.8, 112.2, 75.7, 51.4, 30.9; MS (EI) m/z 240 (M^++1). The enantiomeric excess of the product was measured by chiral stationary phase HPLC analysis using a ChiraCel OJ-H column (80:20 hexanes/i-PrOH at 0.75 mL/min): major enantiomer: t_R = 13.1 min; minor enantiomer: t_R = 16.0 min.

4.3.6. (*S*)-5-Bromo-3-(2-oxopropyl)-3-hydroxyindolin-2-one 9f[8]

Pale yellow solid, 82% yield, 75% ee. Mp: 145–147 °C; $[\alpha]_D^{25} = -17.6$ (c 0.73, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): 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 (100 MHz, DMSO-d_6): δ 205.3, 177.8, 142.0, 134.2, 131.6, 126.7, 113.0, 111.4, 72.6, 50.0, 30.3; MS (EI) m/z 284 (M^++1). The enantiomeric excess of the product was measured by chiral stationary phase HPLC analysis using a ChiraCel OJ-H column (70:30 hexanes/i-PrOH at 1.0 mL/min): major enantiomer: t_R = 8.8 min; minor enantiomer: t_R = 11.7 min.

4.3.7. (*S*)-5-Methyl-3-(2-oxopropyl)-3-hydroxyindolin-2-one 9g[8]

Pale yellow solid, 80% yield, 63% ee. Mp: 161–163 °C; $[\alpha]_D^{25} = -11.2$ (c 0.52, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.02 (s, 3H), 2.21 (s, 3H), 2.98 (d, J = 16.0 Hz, 1H), 3.25 (d, J = 7.2 Hz, 1H), 5.90 (s, 1H), 6.65(d, J = 7.2 Hz, 1H), 6.94 (d, J = 7.2 Hz, 1H), 7.05 (s, 2H), 10.11 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 205.3, 178.2, 140.3, 132.0, 129.9, 129.2, 124.3, 109.2, 73.3, 50.6, 30.5, 20.8; MS (EI) m/z 220 (M^++1). The enantiomeric excess of the product was measured by chiral stationary phase HPLC analysis using a ChiraCel AD-H column (80:20 hexanes/i-PrOH at 1.0 mL/min): major enantiomer: t_R = 10.2 min; minor enantiomer: t_R = 12.4 min.

4.3.8. (*S*)-(2-Oxocyclohexyl)indolin-3-hydroxyindolin-2-one 9h[12]

White solid, 99% yield; 63% ee; 81% dr. Mp: 186–188 °C; $[\alpha]_D^{25} = -12.3$ (c 0.61, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.11 (s, 1H), 7.22–7.08 (m, 2H), 6.81–6.72 (m, 2H), 5.76 (s, 1H), 3.10 (d, J = 8.0 Hz, 1H), 2.60–2.55 (m, 1H), 2.35–2.50 (m, 1H), 2.35–2.20 (m, 1H), 2.09–1.56 (m, 5H), 1.52–1.35 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 209.5, 178.9, 144.3, 132.0, 129.8, 125.6, 121.4, 111.3, 75.4, 58.2, 42.3, 27.6, 25.3; MS (EI) m/z 246 (M^++1). The enantiomeric excess of the product was measured by chiral stationary phase HPLC analysis using a ChiraCel OJ-H column

(80:20 hexanes/*i*-PrOH at 1.0 mL/min): major enantiomer: t_R = 14.1 min; minor enantiomer: t_R = 18.6 min.

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