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Enantioselective and Solvent-Controlled Diastereoselective Mannich Reaction of Isatin Imines with Hydroxyacetone: Synthesis of 3-Substituted 3-Aminooxindoles

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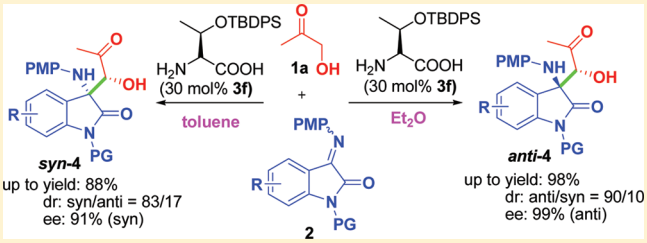
Supporting Information

ABSTRACT: The diastereoselectively switchable enantioselective Mannich reaction of isatin imines with hydroxyacetone is reported. The chiral primary amino acid catalyzed this Mannich reaction to afford both *anti*- and *syn*-Mannich adducts in high yields, good diastereoselectivities, and enantioselectivities. The reason for the solvent control of the diastereoselectivity phenomenon was investigated.



The 3,3-disubstituted oxindole structure motif is a privileged heterocyclic subunit in natural products and biologically active compounds.[1] Among the examples, the 3-heteroatom-containing oxindoles are useful in medicinal chemistry.[2] 3-Substituted 3-aminooxindoles are found in natural products and pharmaceutical candidates,[3] such as AG-041R,[3a] a gastrin/CCK-B receptor agonist, and SSR-149415,[3b,c] which is used for the treatment of anxiety and depression (Figure 1). Several methods, including imine addition reaction,[4]

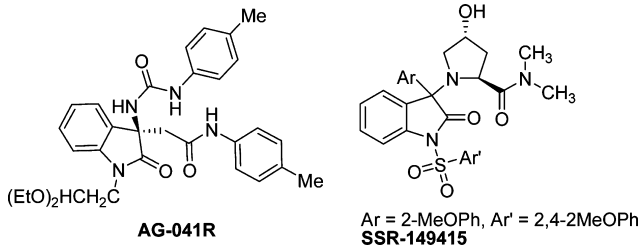


Figure 1. Bioactive 3-substituted 3-aminooxindoles.

alkylation of 3-aminooxindoles,[5] amination of 3-substituted oxindoles,[6] intramolecular arylation,[7] and Mannich reaction,[8] have been developed to synthesize 3-substituted 3-aminooxindoles, but catalytic asymmetric methods are limited. Among them, the catalytic asymmetric addition of nucleophiles to isatin imines is a very straightforward strategy for the synthesis of 3-substituted 3-aminooxindoles, but only a Strecker reaction with moderate enantioselectivity has been reported.[9] Further development of a catalytic asymmetric methods with the need of using the above nucleophilic addition strategy to construct 3-substituted 3-aminooxindoles is highly desirable, regardless of whether organocatalysis or organometal catalysis is required.

The Mannich reaction is a powerful synthetic method for the preparation of chiral amino molecules.[10] To the best of our knowledge, there is no catalytic asymmetric Mannich reaction involving isatin imines as the acceptor which has been described in the literature. Here we report a highly enantioselective Mannich reaction of isatin imines with hydroxyacetone, using the same catalyst, with either ethyl ether or toluene as the solvent to switch the diastereoselectivity.

This investigation was initiated with an evaluation of the reaction between hydroxyacetone **1a** and ketimine **2a** catalyzed by L-phenylalanine **3a** in DMSO. Although the reaction proceeded smoothly to afford the desired product **4a** in good yield, unfortunately, very poor diastereoselectivity was obtained (Table 1, entry 1). Moreover, the minor diastereomer (*anti*-**4a**) displayed better enantioselectivity (62% ee) than the major one (10% ee). Subsequently, several further catalysts were evaluated. As shown in Table 1, the *O*-protected L-threonines **3e** and **3f** promoted this reaction to afford *anti*-**4a** in good yield and good enantioselectivity (Table 1, entries 5 and 6). Due to the fact that the enantioselectivity of the *anti*-**4a** was better than the *syn*-**4a** induced by the chiral primary amino acid and the catalysts did not change the diastereoselectivity substantially, we wanted to enhance the ratio of *anti*-**4a** by changing other reaction conditions. First, we screened the solvents used in this reaction with catalyst **3e** at 0 °C. The results indicated that the solvent had a great influence on the outcome of this reaction. The ratio of *anti*-**4a** was enhanced when this reaction took place in ethyl ether, accompanied with good yield and excellent enantioselectivity (Table 1, entry 9). Interestingly, *syn*-**4a** became the major product when this reaction took place in toluene or THF instead of ether (Table 1, entry 10), which indicated that this appealing methodology will provide an effective method for the enantioselective synthesis of both diastereomers by only changing the solvents. We then turned our attention to improving the stereoselectivity of the *anti*- and

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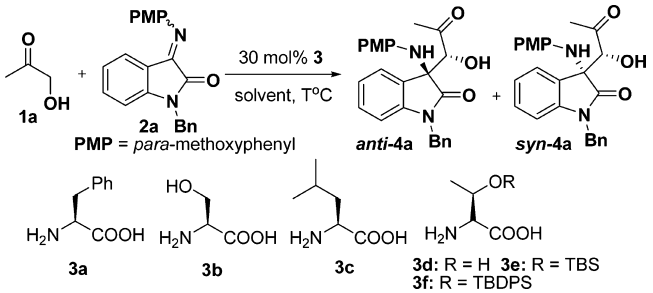
Table 1. Screening of Catalysts and Optimization of the Reaction Conditions[a]



entry	3	solvent	T (°C)	time (h)	yield[b] (%)	dr[c]	ee[d] (%)
1	**3a**	DMSO	20	46	81	47/53	62/10
2	**3b**	DMSO	20	46	46	43/57	49/9
3	**3c**	DMSO	20	46	<5	–[e]	–[e]
4	**3d**	DMSO	20	46	50	50/50	75/34
5	**3e**	DMSO	20	12	63	47/53	88/11
6	**3f**	DMSO	20	8.5	81	50/50	84/31
7	**3e**	THF	0	9	81	32/68	72/73
8	**3e**	MTBE	0	17	92	59/41	97/86
9	**3e**	Et_2O	0	16	85	60/40	96/82
10	**3e**	$PhCH_3$	0	29	84	41/59	82/82
11	**3e**	*m*-Xylene	0	29	93	49/51	87/81
12	**3e**	CH_2Cl_2	0	9	74	33/67	69/69
13	**3f**	Et_2O	0	22	76	62/38	96/82
14	**3f**	Et_2O	−30	39	98	78/22	96[f]/–
15	**3f**	$PhCH_3$	20	24	73	27/73	50/81[g]
16	**3f**	$PhCH_3$	0	21	88	23/77	–/90[g]

[a]Reaction conditions: **1a** (1 mmol), **2a** (0.1 mmol), **3** (0.03 mmol), solvent (0.5 mL). [b]Total yield of two diastereoisomers. [c]Diastereoselective ratio of *anti/syn* determined by HPLC. [d]ee value of *anti/syn*-isomer determined by HPLC with chrial column. [e]Not determined. [f]Added 10 mol % of *p*-nitrobenzoic acid. [g]2 mL of $PhCH_3$.

syn-selective Mannich reaction, respectively. As to the *anti*-selective Mannich reaction, the catalyst **3f** was a better choice than **3e** in terms of the diastereoselectivity (Table 1, entry 13). Next, we lowered the reaction temperature and added additional acid to the reaction. Good diastereoselectivity and excellent enantioselectivity (96% ee of *anti*-**4a**) were realized after lowering the reaction temperature to −30 °C and adding 10 mol % of *p*-nitrobenzoic acid (Table 1, entry 14). In the case of the *syn*-selective Mannich reaction, we chose toluene as solvent in terms of the enantioselectivity and further optimized the reaction conditions. The best result was obtained when this reaction was carried out in toluene with the concentration of 0.05 M **2a** at 0 °C (Table 1, entry 16).

With the two optimized reaction conditions in hand, we explored the scope of the substrates of the substituted isatin imines and acetones for the *anti*- and *syn*-selective Mannich reaction, respectively. The results are summarized in Table 2. In the *anti*-selective Mannich reaction, both electron-rich and electron-deficient substituted isatin imines were good reaction partners and gave the *anti*-Mannich adducts in high yields, along with good diastereoselectivities and excellent enantioselectivities. The ee value varied with the introduction of substituents at different positions of the isatin imines. For example, the 5- and 6-Cl-substituted isatin imines gave adducts in excellent enantioselectivities (Table 2, entries 2 and 3), while the 7-Cl-substituted isatin imine gave the product **4d** in 79% ee (Table 2, entry 4). Specifically, the 4-Cl-substituted isatin imine could not undergo this transformation under the optimized reaction conditions, probably due to the steric influence induced by the 4-Cl substituent (Table 2, entry 6). The *N*-unprotected isatin derived imines were also suitable reaction partners for this *anti*-selective Mannich reaction and afforded the desired adducts with excellent outcomes (Table 2, entries 11 and 12). The PMP group could be replaced by other substituted benzenes (Table 2, entries 13 and 14). Next, the scope of the substrates in the *syn*-selective Mannich reaction was investigated. Both of the isatin imines bearing an electron-withdrawing (Table 2, enties 16, 19) and electron-donating (Table 2, entries 17 and 18) group underwent the Mannich reaction with hydroxyacetone in toluene and afforded the *syn*-selective adducts in high yields, good diastereoselectivies, and good to high enantioselectivities (Table 2, entries 15−19). Interestingly, when isatin imines derived from N-unprotected isatins were introduced in this reaction (Table 2, entries 20 and 21), although the ratio of *syn/anti* increased, the *syn*-adduct did not become the dominant compound. These results indicated that the N-protecting group of isatin is crucial for this solvent-control diastereoselectivity phenomenon. Other ketones, such as chloroacetone and fluoracetone, could not participate in this reaction under the optimal reaction conditions, which indicated that the hydroxyl of hydroxyacetone was very important for this transformation. This methodology thus provides an efficient means of realizing both the *anti*- and *syn*-selective Mannich reactions with excellent enantioselectivities induced by the same catalyst in different solvents. The relative and absolute configurations of the *anti*-adducts were determined by X-ray crystal structure analysis of the *anti*-**4i** derived *O*-mesylation product *anti*-**5i** (see the Supporting Information).[13,14]

The reason for the solvent control of the diastereoselectivity phenomenon was investigated. On the basis of the previous

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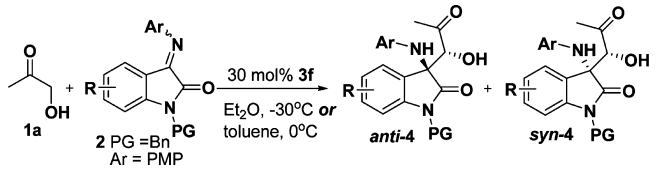
Table 2. Scope of the Isatin Imines[a]



entry	4	R	time (h)	yield[b] (%)	dr[c]	ee[d] (%)
1	**4a**	H	39	98	78/22	96
2	**4b**	5-Cl	40	84	79/21	95
3	**4c**	6-Cl	39	94	80/20	98
4	**4d**	7-Cl	40	87	47/53	79
5	**4e**	5-Br	39	88	83/17	96
6	**4f**	4-Cl	39	trace	ND	ND[e]
7	**4g**	5-Me	24	74	74/26	95[f]
8	**4h**	5-MeO	24	74	78/22	98[f]
9	**4i**	6-Br	40	90	79/21	85
10	**4j**	5-CF_3O	39	97	79/21	94
11	**4k**	H	24	98	88/12	99[g]
12	**4l**	6-Br	39	91	90/10	97[g]
13	**4m**	H	76	96	79/21	98[h]
14	**4n**	H	51	72	69/31	96[i]
15	**4a**	H	21	88	25/75	90[j]
16	**4d**	7-Cl	20	83	17/83	81[j]
17	**4g**	5-Me	18	84	23/77	91[j]
18	**4h**	5-MeO	18	85	21/79	91[j]
19	**4i**	6-Br	18	82	23/77	86[j]
20	**4k**	H	29	98	73/27	90[g]
21	**4l**	6-Br	23	99	76/24	90[g]

[a]Conditions for entries 1−14: **1** (1 mmol), **2** (0.1 mmol), **3f** (0.03 mmol), Et_2O (0.5 mL), at −30 °C. Conditions for entries 15−21: **1** (1 mmol), **2** (0.1 mmol), **3f** (0.03 mmol), $PhCH_3$ (2 mL), at 0 °C. [b]Isolated yield of two diastereoisomers. [c]Ratio of *anti*/*syn* determined by ^{1}H NMR of the crude product. [d]ee of *anti*-isomer determined by HPLC with chiral column. [e]Not determined. [f]4 Å MS (50 mg) was added and at −20 °C. [g]PG = H. [h]Ar = *p*-MeC_6H_4. [i]Ar = Ph. [j]ee of *syn*-isomer determined by HPLC with chiral column.

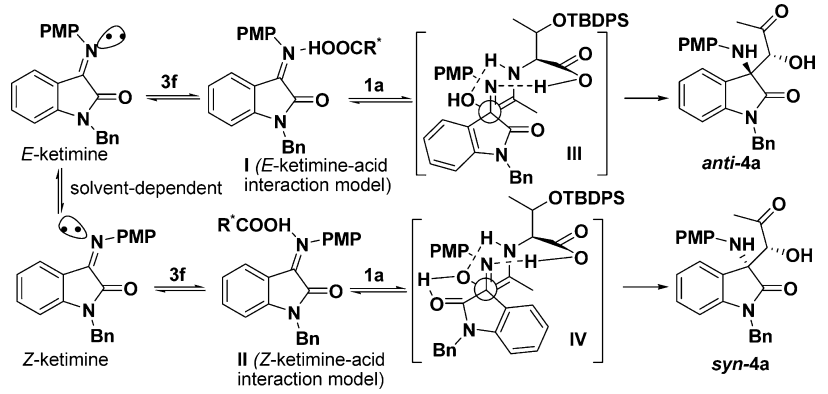


Figure 2. Proposed isatin imine−acid interaction models and transition states.

studies by Valencia et al.,[11] the isatin imine exists as a mixture of *E*/*Z* isomers and the isomer ratio was reported to be solvent-dependent. We thought the N-lone pair electron on the nitrogen atom of the imine would combine with the acid proton in a face-to-face manner, so we proposed the isatin imine−acid interaction models **I** and **II** as shown in Figure 2. Using a combination of the transition states of the primary amino acid catalyzed *anti*-Mannich reaction of hydroxyacetone with aldimines proposed by Barbas[12] and the above isatin imine-acid interaction models **I** and **II**, the two transiton states **III** (from **I**) and **IV** (from **II**) are proposed. The transition state **IV** was more stable than **III** because the hydroxyl of hydroxyactone could form another hydrogen bond with an amide carbonyl group in **IV**. The *E*-ketimine would then be converted into *Z*-ketimine as the reaction proceeded. This scheme was supported by the following experimental data: the ratio of the *E*/*Z* isomer of **2a** in DMSO-d_6 was 79:21, and the best dr of **4a** in DMSO was 57:43 (*anti*/*syn*); the *E*/*Z* isomer of **2a** in $PhCH_3$-d_8 was 58:42 and the best dr of **4a** in $PhCH_3$ was 23:77 (*anti*/*syn*) (see the Supporting Information). Supposedly, when this reaction took place in ethyl ether, the amount of the *E*-isomer was greater than the *Z*-isomer, so the transition state **III** became the dominant one, leading to the formation of the *anti*-selective Mannich adducts. In contrast, the *Z*-isomer

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was the major component in toluene, so the transition state **IV** became dominant and afforded the *syn*-selective Mannich adducts. Hopefully, the isatin imine−acid interaction models will prove to be useful for the related organic reactions involving the isatin imines.

In conclusion, we have disclosed the first direct catalytic asymmetric Mannich reaction of isatin imines with hydroxyactone to construct 3-substituted 3-aminooxindoles. An easily prepared and low-cost *O*-TBDPS protected L-threonine **3f** promoted this reaction to afford *anti*- or *syn*-Mannich adducts of high yields, excellent enantioselectivities, and good diastereoselectivities. This methodology provided an efficient means of synthesizing enantioenriched 3-substituted 3-aminooxindoles in a solvent-controlled diastereoselective fashion. Reasonable isatin imine−acid interaction models and transition states have been proposed to illustrate the solvent-control diastereoselectivity phenomenon.

EXPERIMENTAL SECTION

General Procedure for the *Anti*-Selective Mannich Reaction. A 15 mL tube was charged with catalyst **3f** (0.06 mmol), *p*-nitrobenzoic acid (0.02 mmol), and **2a** (0.2 mmol), and then anhydrous Et_2O (1 mL) was added. The reaction mixture was cooled to −30 °C for 30 min before **1a** (2 mmol) was added. After the reaction was complete by TLC analysis, two drops of AcOH was added and the mixture subjected to silica gel column chromatography directly. The desired mixture of *anti*- and *syn*-adducts **4a** (98% yield) was obtained using petroleum ether/ethyl acetate = 4:1 as the eluent. This mixture was submitted to analysis by ^{1}H NMR for dr (*anti*/*syn* = 78:22) and HPLC for ee (96%). Then the pure *anti*-**4a** was obtained by the second silica gel column chromatography separation using petroleum ether/ethyl acetate = 6:1 as eluent. The pure compound *anti*-**4a** was submitted to analysis by ^{1}H NMR, ^{13}C NMR, IR, and HRMS.

General Procedure for the *Syn*-Selective Mannich Reaction. A 15 mL tube was charged with catalyst **3f** (0.06 mmol) and **2a** (0.2 mmol), and then anhydrous $PhCH_3$ (4 mL) was added. The reaction mixture was cooled to 0 °C for 30 min before **1a** (2 mmol) was added. After the reaction was complete by TLC analysis, two drops of AcOH was added and the mixture subjected to silica gel column chromatography. The desired mixture of *anti*- and *syn*-adducts **4a** (88% yield) was obtained using petroleum ether/ethyl acetate = 4:1 as the eluent. This mixture was submitted to analysis by ^{1}H NMR for dr (*syn*/*anti* = 75:25) and HPLC for ee (90%). Then the pure *syn*-**4a** was obtained by second silica gel column chromatography separation using petroleum ether/ethyl acetate = 6:1 as eluent. The pure compound *syn*-**4a** was submitted to analysis by ^{1}H NMR, ^{13}C NMR, IR, and HRMS.

*(S)-1-Benzyl-3-((R)-1-hydroxy-2-oxopropyl)-3-(4-methoxyphenylamino)indolin-2-one (anti-**4a**):* amorphous solid, 82.5 mg; yield 98%; $[\alpha]^{20}_D$ = +105.8 (*c* = 1.04, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.11 (s, 3H), 3.69 (s, 3H), 4.07 (s, 1H), 4.56 (d, *J* = 15.9 Hz, 1H), 4.74 (s, 1H), 4.99 (d, *J* = 15.9 Hz, 1H), 6.48−6.62 (m, 5H), 6.90 (m, 2H), 7.07−7.12 (m, 1H), 7.20−7.27 (m, 4H), 7.37 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 29.4, 43.8, 55.3, 68.4, 79.9, 110.0, 114.1, 122.5, 123.0, 125.0, 125.8, 127.1, 127.5, 128.6, 130.1, 134.9, 137.3, 143.5, 155.3, 175.9, 206.9; IR (neat) ν (cm^{-1}) 3423, 2920, 1712, 1613, 1511, 1439, 1383, 1357, 1241, 1178, 1081, 1032, 754, 698; HRMS (ESI) calcd for $C_{25}H_{24}N_2NaO_4$(M^+ + Na) 439.1628, found 439.1624. The enantiomeric excess of 96% ee was determined by HPLC (Daicel Chirapak IC-H, hexane/2-propanol = 70/30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm, t_R(minor) 10.62 min, t_R(major) 24.80 min).

*(S)-1-Benzyl-5-chloro-3-((R)-1-hydroxy-2-oxopropyl)-3-(4-methoxyphenylamino)indolin-2-one (anti-**4b**):* amorphous solid, 76.2 mg; yield 84%; $[\alpha]^{20}_D$ = +155.9 (*c* = 1.02, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm) 2.20 (s, 3H), 3.71 (s, 3H), 3.94 (d, *J* = 9.0 Hz, 1H), 4.53 (d, *J* = 15.9 Hz, 1H), 4.67−4.74 (m, 2H), 4.98 (d, *J* = 15.3 Hz, 1H), 6.49−6.61 (m, 5H), 6.83−6.86(m, 2H), 7.16−7.23 (m, 4H), 7.34−7.35 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 29.5, 43.0, 55.3, 68.6, 79.7, 110.9, 114.2, 122.8, 122.9, 122.9, 125.3, 127.0, 127.7, 127.8, 128.6, 130.1, 134.4, 136.8, 164.8, 175.6, 206.6; IR (neat) ν (cm^{-1}) 3423, 2920, 1709, 1610, 1511, 1482, 1431, 1355, 1316, 1244, 1175, 1095, 1033, 818, 699; HRMS (ESI) calcd for $C_{25}H_{23}ClN_2NaO_4$ (M^+ + Na) 473.1239, found 473.1232. The enantiomeric excess of 95% ee was determined by HPLC (Daicel Chirapak IC-H, hexane/2-propanol = 70/30, flow rate 0.5 mL/min, *T* = 30 °C, 254 nm, t_R(minor) 14.94 min, t_R(major) 30.45 min).

*(S)-1-Benzyl-6-chloro-3-((R)-1-hydroxy-2-oxopropyl)-3-(4-methoxyphenylamino)indolin-2-one (anti-**4c**):* amorphous solid, 85.8 mg; yield 94%; $[\alpha]^{20}_D$ = +78.3 (*c* = 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm) 2.23 (s, 3H), 3.69 (s, 3H), 3.93 (s, 1H), 4.53 (d, *J* = 15.6 Hz, 1H), 4.68 (s, 1H), 4.94 (d, *J* = 15.9 Hz, 1H), 6.48−6.50 (m, 2H), 6.55−6.57 (m, 3H), 6.85−6.87 (m, 2H), 7.03−7.05 (d, *J* = 7.5 Hz, 1H), 7.19−7.26 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 29.5, 43.9, 55.3, 68.5, 79.6, 110.5, 114.2, 122.8, 123.0, 124.2, 125.9, 126.9, 127.7, 128.7, 134.3, 135.9, 136.9, 144.9, 155.6, 176.1, 206.9; IR (neat) ν (cm^{-1}) 3425, 2920, 1713, 1610, 1511, 1490, 1355, 1242, 1178, 1077, 1033, 825, 699; HRMS (ESI) calcd for $C_{25}H_{23}ClN_2NaO_4$(M^+ + Na) 473.1239, found 473.1244. The enantiomeric excess of 98% ee was determined by HPLC (Daicel Chirapak IC-H, hexane/2-propanol = 70/30, flow rate 0.5 mL/min, *T* = 30 °C, 254 nm, t_R(minor) 13.66 min, t_R(major) 25.75 min).

*(S)-1-Benzyl-7-chloro-3-((R)-1-hydroxy-2-oxopropyl)-3-(4-methoxyphenylamino)indolin-2-one (anti-**4d**):* amorphous solid, 78.7 mg; yield 87%; $[\alpha]^{20}_D$ = +61.5 (*c* = 0.96, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm) 2.26 (s, 3H), 3.59 (s, 3H), 4.54 (s, 1H), 5.20 (s, 2H), 5.87 (s, 1H), 6.12 (s, 1H), 6.29 (d, *J* = 8.4 Hz, 2H), 6.55 (d, *J* = 3.0 Hz, 2H), 7.00−7.09 (m, 4H), 7.21−7.26 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 29.5, 55.5, 68.4, 79.3, 114.5, 119.0, 123.9, 124.2, 126.6, 127.2, 128.6, 130.4, 132.0, 138.0, 138.9, 140.1, 153.5, 177.0, 209.7; IR (neat) ν (cm^{-1}) 3413, 1699, 1606, 1510, 1454, 1354, 1244, 1173, 1118, 1031, 773, 730, 696, 521; HRMS (ESI) calcd for $C_{25}H_{23}ClN_2NaO_4$ (M^+ + Na) 473.1239, found 473.1242. The enantiomeric excess of 79% ee was determined by HPLC (Daicel Chirapak IC-H, hexane/2-propanol =70/30, flow rate 0.5 mL/min, *T* = 30 °C, 254 nm, t_R(minor) 14.14 min, t_R(major) 25.36 min).

*(S)-1-Benzyl-5-bromo-3-((R)-1-hydroxy-2-oxopropyl)-3-(4-methoxyphenylamino)indolin-2-one (anti-**4e**):* amorphous solid, 87.5 mg; yield 88%; $[\alpha]^{20}_D$ = +160.4 (*c* = 1.06, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$)δ(ppm) 2.19 (s, 3H), 3.72 (s, 3H), 4.52 (d, *J* = 15.9 Hz, 1H), 4.69 (s, 1H), 4.99 (d, *J* = 15.9 Hz, 1H), 6.45−6.52 (m, 3H), 6.58−6.61 (m, 2H), 6.83 (d, *J* = 8.1 Hz, 2H), 7.19−7.21 (m, 3H), 7.32−7.37 (m, 1H), 7.49 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 29.4, 43.9, 55.3, 68.5, 79.7, 111.4, 114.3, 115.7, 122.8, 127.0, 127.7, 128.1, 128.2, 128.6, 132.9, 134.4, 136.9, 142.6, 155.5, 175.5, 206.6; IR (neat) ν (cm^{-1}) 3427, 2919, 1712, 1608, 1510, 1479, 1384, 1354, 1242, 1175, 1081, 1004, 816; HRMS (ESI) calcd for $C_{25}H_{23}BrN_2NaO_4$ (M^+ + Na) 517.0733, found 517.0735. The enantiomeric excess of 96% ee was determined by HPLC (Daicel Chirapak IC-H, hexane/2-propanol = 70/30, flow rate 0.5 mL/min, *T* = 30 °C, 254 nm, t_R(minor) 14.91 min, t_R(major) 32.11 min).

*(S)-1-Benzyl-3-((R)-1-hydroxy-2-oxopropyl)-3-(4-methoxyphenylamino)-5-methylindolin-2-one (anti-**4g**):* amorphous solid, 64 mg; yield 74%; $[\alpha]^{20}_D$ = +134 (*c* = 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm) 2.04 (s, 3H), 2.32 (s, 3H), 3.68 (s, 3H), 4.04 (s, 1H), 4.52 (d, *J* = 15.6 Hz, 1H), 4.69 (s, 1H), 4.96 (d, *J* = 15.9 Hz, 1H), 6.44−6.56 (m, 5H), 6.90−6.91 (m, 2H), 7.00 (d, 1H), 7.19−7.26 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.1, 29.3, 43.8, 55.3, 68.1, 80.0, 109.8, 114.2, 121.8, 125.6, 126.0, 127.2, 127.5, 128.5, 130.5, 132.6, 135.0, 137.6, 141.1, 155.0, 175.7, 206.8; IR (neat) ν (cm^{-1}) 3411, 2920, 1713, 1620, 1604, 1511, 1494, 1382, 1352, 1242, 1178, 1097, 1034, 812, 666; HRMS (ESI) calcd for $C_{26}H_{26}N_2NaO_4$ (M^+ + Na) 453.1785, found 453.1782. The enantiomeric excess of 95% ee was determined by HPLC (Daicel Chirapak IC-H, hexane/2-propanol = 75/25, flow rate 1 mL/min, *T* = 30 °C, 254 nm, t_R(minor) 11.57 min, t_R(major) 48.38 min).

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*(S)-1-Benzyl-3-((R)-1-hydroxy-2-oxopropyl)-5-methoxy-3-(4-methoxyphenylamino)indolin-2-one (anti-**4h**):* amorphous solid, 66 mg; yield 74%; $[\alpha]^{20}_{D}$ = +168.6 (*c* = 1.18, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ(ppm) 2.04 (s, 3H), 3.69 (s, 3H), 3.76 (s, 3H), 4.03 (d, *J* = 9.0 Hz, 1H), 4.50 (d, *J* = 15.9 Hz,1H), 4.66 (d, *J* = 9.6 Hz, 1H), 4.85 (s, 1H), 4.96 (d, *J* = 15.3 Hz, 1H), 6.47−6.57 (m, 5H), 6.72 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 4.8 Hz, 2H), 7.01 (s, 1H), 7.18−7.19 (m, 2H), 7.26 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 29.3, 43.9, 55.3, 55.8, 68.4, 80.1, 110.5, 112.0, 114.2, 114.5, 122.2, 127.1, 127.4, 127.5, 128.5, 135.0, 136.8, 137.5, 155.2, 156.2, 175.5, 206.6; IR (neat) ν (cm^{-1}) 3422, 2920, 1712, 1605, 1511, 1492, 1385, 1273, 1241, 1179, 1098, 1034, 817, 699; HRMS (ESI) calcd for $C_{26}H_{26}N_2NaO_5$ (M^+ + Na) 469.1734, found 469.1727. The enantiomeric excess of 98%ee was determined by HPLC (Daicel Chirapak IC-H, hexane/2-propanol = 75/25, flow rate 1 mL/min, *T* = 30 °C, 254 nm, t_R(minor) 19.11 min, t_R(major) 52.30 min).

*(S)-1-Benzyl-6-bromo-3-((R)-1-hydroxy-2-oxopropyl)-3-(4-methoxyphenylamino)indolin-2-one (anti-**4i**):* amorphous solid, 89.1 mg; yield 90%; $[\alpha]^{20}_{D}$ = +82.4 (*c* = 1.08, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.24 (s, 3H), 3.70 (s, 3H), 3.95 (d, *J* = 8.7 Hz, 1H), 4.53 (d, *J* = 15.6 Hz, 1H), 4.67 (d, *J* = 9.0 Hz, 1H), 4.77 (s, 1H), 4.94 (d, *J* = 15.6 Hz, 1H), 6.47−6.50 (m, 2H), 6.55−6.58 (m, 2H), 6.72−6.72 (m, 1H), 6.84−6.87 (m, 2H), 7.17−7.22 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 29.6, 43.8, 55.3, 68.6, 79.5, 113.3, 114.2, 122.9,123.8, 124.8, 125.8, 126.2, 126.9, 127.7, 128.7, 134.3, 136.8, 145.0, 155.5, 176.0, 207.0; IR (neat) ν (cm^{-1}) 3424, 2921, 1715, 1606, 1510, 1485, 1454, 1429, 1355, 1242, 1127, 1003, 824, 733; HRMS (ESI) calcd for $C_{25}H_{23}BrN_2NaO_4$ (M^+ + Na) 517.0733, found 517.0722. The enantiomeric excess of 85% ee was determined by HPLC (Daicel Chirapak IC-H, hexane/2-propanol = 70/30, flow rate 0.5 mL/min, *T* = 30 °C, 254 nm, t_R(minor) 13.94 min, t_R(major) 26.45 min).

*(S)-1-Benzyl-3-((R)-1-hydroxy-2-oxopropyl)-3-(4-methoxyphenylamino)-5-(trifluoromethoxy)indolin-2-one (anti-**4j**):* amorphous solid, 96.6 mg; yield 97%; $[\alpha]^{20}_{D}$ = +99.5 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.21 (s, 3H), 3.69 (s, 3H), 4.55 (d, *J* = 15.9 Hz, 1H), 4.72 (s, 1H), 4.97 (d, *J* = 16.2 Hz, 1H), 6.50−6.58 (m, 5H), 6.83−6.85 (m, 2H), 7.05−7.07 (m, 1H), 7.18−7.23 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 29.4, 43.9, 55.3, 69.0, 79.5, 110.4, 114.1, 119.1, 123.2, 123.5, 126.9, 127.5, 127.7, 128.7, 134.3, 136.6, 142.3, 144.6, 144.7, 155.7, 176.0, 206.9; IR (neat) ν (cm^{-1}) 3420, 3263, 1719, 1681, 1620, 1511, 1491, 1453, 1256, 1220, 1179, 1036, 830, 699; HRMS (ESI) calcd for $C_{26}H_{23}F_3N_2NaO_5$ (M^+ + Na) 523.1451, found 523.1448. The enantiomeric excess of 94% ee was determined by HPLC (Daicel Chirapak IC-H, hexane/2-propanol =70/30, flow rate 0.5 mL/min, *T* = 30 °C, 254 nm, t_R(minor) 14.70 min, t_R(major) 27.00 min).

*(S)-3-((R)-1-Hydroxy-2-oxopropyl)-3-(4-methoxyphenylamino)-indolin-2-one (anti-**4k**):* amorphous solid, 63.7 mg; yield 98%; $[\alpha]^{20}_{D}$ = +52.1 (*c* = 0.96, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 2.19 (s, 3H), 3.54 (s, 3H), 4.32 (s, 1H), 5.70 (s, 1H) 5.86 (s, 1H), 6.22 (d, *J* = 7.8 Hz, 2H), 6.52 (d, *J* = 7.5 Hz, 2H), 6.81−6.97 (m, 3H), 7.18−7.20 (m, 1H), 10.56 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 29.2, 55.5, 68.0, 79.3, 110.3, 114.6, 116.8, 121.8, 125.0, 127.5, 129.6, 139.7, 143.4, 152.5, 177.5, 210.5; IR (neat) ν (cm^{-1}) 3417, 1718, 1620, 1512, 1470, 1354, 1182, 1097, 1035, 946, 758; HRMS (ESI) calcd for $C_{18}H_{18}N_2NaO_4$ (M^+ + Na) 349.1159, found 349.1166. The enantiomeric excess of 99% ee was determined by HPLC (Daicel Chirapak IC-H, hexane/2-propanol = 70/30, flow rate 0.5 mL/min, *T* = 30 °C, 254 nm, t_R(minor) 15.62 min, t_R(major) 25.11 min).

*(S)-6-Bromo-3-((R)-1-hydroxy-2-oxopropyl)-3-(4-methoxyphenylamino)indolin-2-one (anti-**4l**):* amorphous solid, 73.4 mg; yield 91%; $[\alpha]^{20}_{D}$ = +43 (c = 1, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm) 2.18 (s, 3H), 3.51 (s, 3H), 4.29 (d, *J* = 6.3 Hz, 1H), 5.71 (s, 1H), 5.92 (d, *J* = 6.0 Hz, 1H), 6.18 (d, *J* = 8.7 Hz, 2H), 6.51 (d, *J* = 8.4 Hz, 2H), 6.84−7.04 (m, 3H), 10.67 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm) 29.3, 55.5, 68.0, 79.0, 113.0, 114.6, 117.0, 122.2, 124.4, 126.9, 127.0, 139.4, 145.2, 152.7, 177.5, 210.1; IR (neat) ν (cm^{-1}) 3419, 2920, 1725, 1612, 1511, 1480, 1446, 1357, 1241, 1076, 908, 822, HRMS (ESI) calcd for $C_{18}H_{17}BrN_2NaO_4$ (M^+ + Na) 427.0264, found 427.0252. The enantiomeric excess of 97% ee was determined by HPLC (Daicel Chirapak IC-H, hexane/2-propanol = 70/30, flow rate 0.5 mL/min, *T* = 30 °C, 254 nm, t_R(minor) 11.44 min, t_R(major) 25.42 min).

*(R)-1-Benzyl-3-((R)-1-hydroxy-2-oxopropyl)-3-(4-methoxyphenylamino)indolin-2-one (syn-**4a**):* amorphous solid, 73.2 mg; yield 88%; $[\alpha]^{20}_{D}$ = −90 (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.10 (s, 3H), 3.67 (s, 3H), 4.16 (s, 2H), 4.55−4.60 (m, 2H), 5.12 (d, *J* = 15.9 Hz, 1H), 6.52 (s, 4H), 6.58 (d, *J* = 7.8 Hz, 1H), 6.96−7.06 (m, 3H), 7.15−7.27 (m, 4H), 7.51(d, *J* = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 27.4, 43.9, 55.3, 69.0, 80.3, 109.7, 114.0, 122.9, 123.2, 125.6, 125.7, 127.2, 127.5, 128.6, 129.8, 134.9, 136.7, 143.1, 155.5, 175.9, 207.6; IR (neat) ν (cm^{-1}) 3423, 2920, 1712, 1613, 1511, 1439, 1383, 1357, 1241, 1178, 1081, 1032, 754, 698; HRMS (ESI) calcd for $C_{25}H_{24}N_2NaO_4$ (M^+ + Na) 439.1628, found 439.1624. The enantiomeric excess of 90% ee was determined by HPLC (Daicel Chirapak IC-H, hexane/2-propanol = 75/25, flow rate 1 mL/min, *T* = 30 °C, 254 nm, t_R(major) 10.12 min, t_R(minor) 29.39 min).

*(R)-1-Benzyl-3-((R)-1-hydroxy-2-oxopropyl)-3-(4-methoxyphenylamino)-5-methylindolin-2-one (syn-**4g**):* amorphous solid, 72.7 mg; yield 84%; $[\alpha]^{20}_{D}$ = −154 (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.10 (s, 3H), 2.29 (s, 3H), 3.66 (s, 3H), 4.28 (s, 1H), 4.53−4.57 (m, 2H), 5.09 (d, *J* = 15.6 Hz, 1H), 6.47−6.53 (m, 5H), 6.95−6.98 (m, 3H), 7.20−7.21 (m, 3H), 7.30 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 21.1, 27.4, 44.0, 55.3, 68.9, 80.3, 109.5, 114.1, 122.5, 125.8, 126.1, 127.3, 127.5, 128.6, 130.2, 132.5, 135.0, 137.0, 140.6, 155.3, 175.8, 207.4; IR (neat) ν (cm^{-1}) 3411, 2920, 1713, 1620, 1604, 1511, 1494, 1382, 1352, 1242, 1178, 1097, 1034, 812, 666; HRMS (ESI) calcd for $C_{26}H_{26}N_2NaO_4$ (M^+ + Na) 453.1785, found 453.1782. The enantiomeric excess of 91% ee was determined by HPLC (Daicel Chirapak IC-H, hexane/2-propanol = 75/25, flow rate 1 mL/min, *T* = 30 °C, 254 nm, t_R(major) 9.96 min, t_R(minor) 29.50 min).

*(R)-1-Benzyl-3-((R)-1-hydroxy-2-oxopropyl)-5-methoxy-3-(4-methoxyphenylamino)indolin-2-one (syn-**4h**):* amorphous solid, 75.6 mg; yield 85%; $[\alpha]^{20}_{D}$ = −143 (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.11 (s, 3H), 3.67 (s, 3H), 3.74 (s, 3H), 4.36 (s, 1H) 4.50−4.55 (m, 2H), 5.09 (d, *J* = 15.6 Hz, 1H), 6.48−6.51 (m, 5H), 6.67 (d, *J* = 8.4 Hz, 1H), 6.95 (m, 2H), 7.11 (s, 1H), 7.20−7.26 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 27.5, 44.0, 55.3, 55.7, 69.2, 80.2, 110.2, 112.5, 114.1, 114.3, 122.7, 127.1, 127.3, 127.6, 128.6, 134.9, 136.3, 136.8, 155.3, 156.0, 175.6, 207.4; IR (neat) ν (cm^{-1}) 3422, 2920, 1712, 1605, 1511, 1492, 1385, 1273, 1241, 1179, 1098, 1034, 817, 699; HRMS (ESI) calcd for $C_{26}H_{26}N_2NaO_5$ (M^+ + Na) 469.1734, found 469.1727. The enantiomeric excess of 91% ee was determined by HPLC (Daicel Chirapak IC-H, hexane/2-propanol = 75/25, flow rate 1 mL/min, *T* = 30 °C, 254 nm, t_R(major) 12.91 min, t_R(minor) 32.34 min).

*(R)-1-Benzyl-6-bromo-3-((R)-1-hydroxy-2-oxopropyl)-3-(4-methoxyphenylamino)indolin-2-one (syn-**4i**):* amorphous solid, 81 mg; yield 82%; $[\alpha]^{20}_{D}$ = −78 (*c* = 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.13 (s, 3H), 3.70 (s, 3H), 4.27 (s, 1H), 4.52 (m, 2H), 5.07 (d, *J* = 16.2 Hz,1H), 6.55 (m, 4H), 6.73 (s, 1H), 6.94 (m, 2H), 7.17−7.24 (m, 4H), 7.37−7.40 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 27.4, 44.0, 55.3, 68.9, 80.1, 113.0, 114.1, 123.6, 123.7, 124.7, 125.8, 126.8, 127.1, 127.8, 128.7, 134.2, 136.1, 144.5, 155.9, 175.8, 207.1; IR (neat) ν (cm^{-1}) 3424, 2921, 1715, 1606, 1510, 1485, 1454, 1429, 1355, 1242, 1127, 1003, 824, 733; HRMS (ESI) calcd for $C_{25}H_{23}BrN_2NaO_4$ (M^+ + Na) 517.0733, found 517.0722; The enantiomeric excess of 86% ee was determined by HPLC (Daicel Chirapak IC-H, hexane/2-propanol = 70/30, flow rate 0.5 mL/min, *T* = 30 °C, 254 nm, t_R(major) 12.62 min, t_R(minor) 29.03 min).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H NMR, ^{13}C NMR, and HPLC spectra for products and crystal data for *anti*-**5i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(13) CCDC 848326 (**5i**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(14) Procedure for the preparation of compound **5i**: Pure *anti*-**4i** (prepared according to the general procedure of *anti*-selective Mannich reaction of hydroxyacetone with isatin imine **2i**) was dissolved in ethyl acetate, the solution was cooled to 0 °C, and then MsCl (0.5 mmol) was added. The base (0.7 mmol) was added to the mixture. After the completion of *anti*-**4i** by TLC analysis, the mixture was subjected to silica gel column chromatography. The desired products *anti*-**5i** (60% yield) were obtained using petroleum ether /ethyl acetate 3:1 as the eluent.