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Organocatalytic Asymmetric Michael Addition of 1-Acetylindolin-3-ones to α,β-Unsaturated Aldehydes: Synthesis of 2-Substituted Indolin-3-ones

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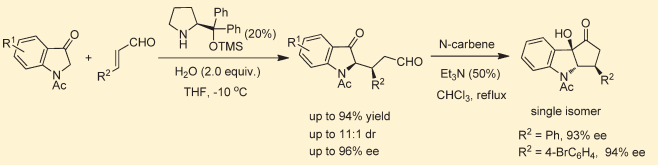
Supporting Information

ABSTRACT: A highly efficient asymmetric Michael addition of 1-acetylindolin-3-ones to α,β-unsaturated aldehydes is developed to afford 2-substituted indolin-3-one derivatives in high yields (up to 94%) with good stereoselectivities (up to 11:1 dr and 96% ee). The Michael adducts can be transformed into substituted cyclopentyl[*b*]indoline compounds conveniently without racemization.



The Michael addition reaction is one of the most important reactions for the formation of carbon−carbon bonds in organic synthesis. The organocatalyzed Michael addition has attracted considerable interest from chemists all over the world, and remarkable progress has been made in this field in recent years.[1,2] Many different types of this reaction have been developed and applied to the synthesis of many biologically active natural products.[3] At the same time, new reactions and catalyst systems are also being explored.

Substituted 3-oxindole and cyclopenta[*b*]indole structures exist widely in biologically active natural products and pharmaceutical compounds (Figure 1).[4] However, the enantioselective synthesis of these structures is much less explored, and new approaches should be developed for the asymmetric synthesis of enantiopure products. Indolin-3-ones, a class of important building blocks, are frequently used in the total synthesis of pharmaceutical compounds.[5] As part of our continuing interest in exploring the synthesis of 2-substituted indolin-3-ones,[6] we recently discovered that the silyl-protected diarylprolinols are efficient catalysts for the asymmetric Michael addition of indolin-3-ones with α,β-unsaturated aldehydes, which produces optically pure 2-substituted indolin-3-ones. Here we report our preliminary results from this discovery.

We initially investigated the reaction of 1-acetylindolin-3-one **2a** with cinnamaldehyde **3a** in the presence of readily available diarylprolinol trimethylsilyl ether **1a** (20% mol) in DCM.[7] The Michael addition reaction proceeded quickly to afford desired product **4a** in 87% yield, 4:1 dr, and 66% ee (Table 1, entry 1). Then we screened organocatalysts **1a**−**1d** for catalysis of the reaction under the same reaction conditions (Table 1, entries 1−4). The result showed that catalyst **1c** gave the highest stereoselectivity, but the reaction proceeded too slowly. Therefore, we chose the catalyst **1a** to further optimize the reaction.

First, different organic solvents with 20% catalyst **1a** were screened, and the highest ee value was obtained in THF (Table 1, entry 6). Then in THF the reaction, temperature was decreased from rt to 0 °C. A higher ee value of 89% was obtained; again the reaction proceeded very slowly (Table 1, entry 11). Other chemicals were also added to the reaction and tested to improve the stereoselectivity. However, either PhCOOH or NEt_3 gave disappointing results (Table 1, entries 12 and 13). To our surprise, when 2.0 equiv of H_2O was added, the reaction proceeded very quickly with little effect on the stereoselectivity. When the reaction temperature was dropped to −10 °C, the best result was obtained in 84% yield with 6:1 dr and 94% ee (Table 1, entry 15).

Under the optimized reaction conditions, the asymmetric Michael addition reactions between a wide range of α,β-unsaturated aldehydes **3** and 1-acetylindolin-3-ones **2** were investigated. The results are summarized in Table 2. In most cases, the Michael adducts were obtained in high yields with moderate dr and high ee values.[8] Structural variation of α,β-unsaturated aldehydes is well tolerated (Table 2). Satisfactory results were also obtained with electron-withdrawing (Table 2, entries 2−6), electron-donating (Table 2, entries 7−9), and neutral (Table 2, entry 1) systems of R^2. The ee values decreased slightly when the α,β-unsaturated aldehydes contain electron-donating groups at the para-position of the phenyl ring (Table 2, entries 8 and 9). 2-Furyl-substituted α,β-unsaturated aldehyde **3j** was also tested under the optimized reaction conditions. Unfortunately, a relatively low ee value was observed for the reaction (76% ee, Table 2, entry 10). The reaction with crotonaldehyde **3k** (Table 2, entry 11) proceeded well under the optimized reaction conditions but gave no diastereoselectivity. Substituted 1-acetylindolin-3-ones were also well tolerated (Table 2, entries 12 and 13). With this protocol, highly enantioenriched 2-substituted 1-acetylindolin-3-ones can be easily produced.

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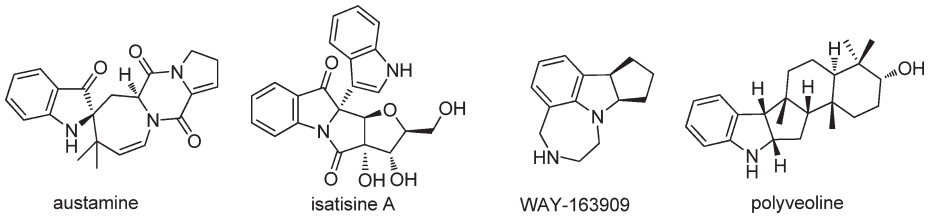
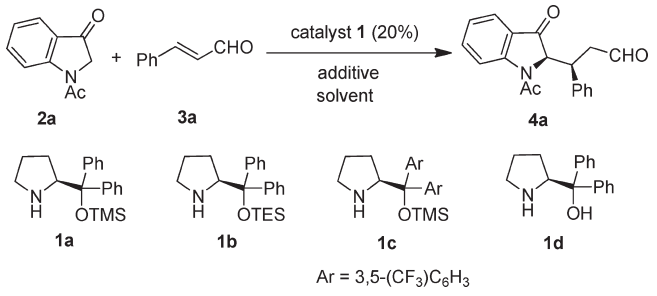


Figure 1. Examples of 3-oxindole and cyclopenta[*b*]indole compounds.

Table 1. Catalyst Screening and Reaction Optimization



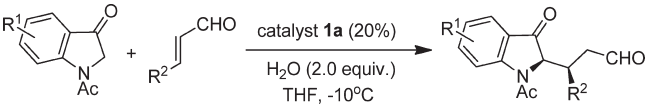
entry[a]	1	solvent	additive	*T* (°C)	*t* (h)	yield (%)	dr[b]	ee[c] (%)
1	**1a**	CH_2Cl_2	none	rt	3	87	4:1	66
2	**1b**	CH_2Cl_2	none	rt	3	92	4:1	63
3	**1c**	CH_2Cl_2	none	rt	72	82	5:1	90
4	**1d**	CH_2Cl_2	none	rt	24	81	1:2	7
5	**1a**	toluene	none	rt	8	93	5:1	59
6	**1a**	THF	none	rt	8	92	6:1	76
7	**1a**	CH_3CN	none	rt	4	82	5:1	64
8	**1a**	$CHCl_3$	none	rt	5	87	4:1	67
9	**1a**	Et_2O	none	rt	24	93	6:1	55
10	**1a**	DMSO	none	rt	24	92	4:1	85
11	**1a**	THF	none	0	120	87	6:1	89
12	**1a**	THF	PhCOOH (20%)	0	8	85	4:1	39
13	**1a**	THF	NEt_3 (20%)	0	3	66	5:1	31
14	**1a**	THF	H_2O (2.0 equiv)	0	12	85	5:1	86
15	**1a**	THF	H_2O (2.0 equiv)	−10	48	84	6:1	94

[a] Unless otherwise noted, reactions were carried out with **2a** (0.2 mmol), **3a** (0.4 mmol), and catalyst **1** (20%) in 0.4 mL of solvent. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude product mixture. [c] Determined by chiral HPLC analysis.

To determine the absolute configuration of asymmetric Michael adduct, a single crystal of compound **5d** bearing a chlorine atom was obtained for X-ray crystallographic analysis.[9] The newly formed stereogenic centers in **5d** were confirmed as (1*R*,9*S*).

In order to apply this reaction to the synthesis of indole derivatives, the Michael adduct **4a** was transformed into substituted cyclopentyl[*b*]indoline compound **6a** via an intramolecular cross benzoin reaction catalyzed by N-heterocyclic carbene (Scheme 1). It should be noted that the reaction proceeds with excellent diastereoselectivity with the generation of a quaternary stereocenter. The absolute configuration of **6** was determined by X-ray crystallographic analysis of **6e**.[9] To our surprise, the stereogenic center at C1 was converted from R to S. This may be due to the enolization of product **6** in the presence of NEt_3 and the favored cyclization to form the compound of S configuration. This can be ascertained by the fact that the other isomer of **4a** yields the same product. The compound **6a** which contains a bicyclic tertiary alcohol might be applied to the total synthesis of some indole-related natural products.

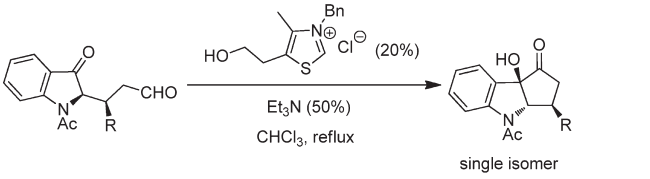
Table 2. Catalytic Asymmetric Michael Addition of 1-Acetylindolin-3-ones to α,β-Unsaturated Aldehydes



entry[a]	R^1	R^2	*t* (h)	yield (%)	dr[b]	ee[c] (%)
1	H	Ph	48	84 (**4a**)	6:1	94
2	H	2-ClC_6H_4	24	91 (**4b**)	4:1	94
3	H	2-$NO_2C_6H_4$	72	89 (**4c**)	6:1	92
4	H	3-ClC_6H_4	48	91 (**4d**)	6:1	90
5	H	4-BrC_6H_4	36	81 (**4e**)	4:1	94
6	H	4-ClC_6H_4	48	88 (**4f**)	4:1	95
7	H	2-$MeOC_6H_4$	36	85 (**4g**)	4:1	96
8	H	4-$MeOC_6H_4$	48	92 (**4h**)	5:1	86
9	H	4-MeC_6H_4	48	94 (**4i**)	6:1	86
10	H	2-furyl	48	92 (**4j**)	6:1	76
11	H	Me	24	90 (**4k**)	1:1	82 (95 [d])
12	4-Br	Ph	24	92 (**4l**)	11:1	82
13	5-Me	Ph	60	91 (**4m**)	5:1	95

[a] Unless otherwise noted, the reactions were carried out with **2** (0.2 mmol), **3** (0.4 mmol), H_2O (0.4 mmol) and catalyst **1a** (20%) in 0.4 mL of THF at −10 °C. [b] Determined by ^{1}H NMR spectroscopic analysis of the crude product mixture. [c] Determined by chiral HPLC analysis. [d] The ee of the other diastereomer.

Scheme 1. *N*-Carbene-Catalyzed Benzoin Reaction



6a, R = Ph, 70% yield, 93% ee
6e, R = 4-BrC_6H_4, 68% yield, 94% ee

In conclusion, we have developed an organocatalyzed asymmetric Michael addition of 1-acetylindolin-3-ones to α,β-unsaturated aldehydes in high yields, moderate diastereoselectivities, and excellent enantioselectivities, which produces chiral 2-substituted indolin-3-ones. The corresponding products can be

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subsequently converted to substituted cyclopentyl[*b*]indoline compounds without loss of enantioselectivities. Further investigation into and application of this methodology are still ongoing.

EXPERIMENTAL SECTION

Representative Procedure for the Synthesis of 2-Substituted Indolin-3-ones. To a solution of α,β-unsaturated aldehyde **3** (0.4 mmol, 2.0 equiv), catalyst **1a** (13 mg, 0.04 mmol, 0.2 equiv), and H_2O (7.2 μL, 0.4 mmol, 2.0 equiv) in THF (0.4 mL) cooled at −10 °C was added 1-acetylindolin-3-one **2** (0.2 mmol, 1.0 equiv). The resulting solution was stirred at −10 °C until **2** was consumed as monitored by TLC. The reaction mixture was concentrated in vacuo and purified by flash column chromatography (PE/EA = 2:1).

*(S)-3-((R)-1-Acetyl-3-oxoindolin-2-yl)-3-phenylpropanal (**4a**):* colorless oil (51 mg, 84% yield, 6:1 dr, 94% ee), $[\alpha]^{20}_D$ = +86 (*c* 1.0, CH_2Cl_2); IR (KBr) 3410, 2925, 2731, 1715, 1675, 1464, 1381, 1288, 762, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 8.17 (s, 1H), 7.41−7.35 (m, 2H), 6.98−6.92 (m, 6H), 4.59 (s, 1H), 4.07 (s, 2H), 3.02 (s, 1H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.5, 198.2, 168.6, 153.2, 136.6, 135.6, 128.2, 127.9, 127.5, 125.2, 123.7, 122.7, 118.1, 66.5, 43.0, 40.8, 24.0; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{18}NO_3$ $[M + H]^+$ 308.1281, found 308.1275. The product was converted to corresponding alcohol **5a** with $NaCNBH_3$, and enantiomeric excess was determined by HPLC with an AS-H column (hexane/*i*-PrOH = 80:20), 1.0 mL/min; major enantiomer t_R = 12.9 min, minor enantiomer t_R = 18.3 min.

*(S)-3-((R)-1-Acetyl-3-oxoindolin-2-yl)-3-(2-chlorophenyl)propanal (**4b**):* colorless oil (62 mg, 91% yield, 4:1 dr, 94% ee), $[\alpha]^{20}_D$ = +329 (*c* 1.0, CH_2Cl_2); IR (KBr) 3379, 2840, 2732, 1707, 1668, 1601, 1462, 1373, 1317, 1004, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.90 (s, 1H), 8.22 (s, 1H), 7.47−7.39 (m, 2H), 7.13 (dd, *J* = 2.0, 7.2 Hz, 1H), 7.01−6.89 (m, 4H), 4.82 (s, 1H), 4.66 (s, 1H), 4.06 (s, 1H), 2.93 (s, 1H), 2.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.9, 198.7, 169.2, 153.4, 136.9, 134.7, 134.0, 129.5, 128.8, 128.6, 126.5, 125.2, 123.8, 122.7, 118.4, 66.6, 43.5, 36.2, 23.9; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{17}ClNO_3$ $[M + H]^+$ 342.0891; found 342.0898. The product was converted to corresponding alcohol **5b** with $NaCNBH_3$, and enantiomeric excess was determined by HPLC with an AS-H column (hexane/*i*-PrOH = 70:30), 1.0 mL/min; major enantiomer t_R = 8.8 min, minor enantiomer t_R = 16.2 min.

*(S)-3-((R)-1-Acetyl-3-oxoindolin-2-yl)-3-(2-nitrophenyl)propanal (**4c**):* colorless oil (63 mg, 89% yield, 6:1 dr, 92% ee, $[\alpha]^{20}_D$ = +322 (*c* 1.0, CH_2Cl_2); IR (KBr) 3412, 2841, 2735, 1715, 1681, 1607, 1526, 1466, 1379, 1285, 1009, 763, 599 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 8.19 (s, 1H), 7.49−7.39 (m, 3H), 7.26−7.18 (m, 2H), 7.13 (t, *J* = 7.2 Hz, 1H), 6.98 (t, *J* = 7.2 Hz, 1H), 5.12 (s, 1H), 4.65 (s, 1H), 4.13 (s, 1H), 3.10 (s, 1H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 198.3, 168.8, 150.7, 137.0, 132.0, 130.0, 129.1, 128.3, 124.3, 124.2, 124.0, 123.7, 118.6, 66.4, 42.8, 34.0, 23.4; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{17}N_2O_5$ $[M + H]^+$ 353.1132; found 353.1137. The product was converted to corresponding alcohol **5c** with $NaCNBH_3$, and enantiomeric excess was determined by HPLC with an AD-H column (hexane/*i*-PrOH = 70:30), 1.0 mL/min; minor enantiomer t_R = 16.7 min, major enantiomer t_R = 17.9 min.

*(S)-3-((R)-1-Acetyl-3-oxoindolin-2-yl)-3-(3-chlorophenyl)propanal (**4d**):* colorless oil (62 mg, 91% yield, 6:1 dr, 90% ee), $[\alpha]^{20}_D$ = +109 (*c* 1.0, CH_2Cl_2); IR (KBr) 3408, 2932, 2732, 1713, 1676, 1606, 1467, 1383, 1290, 1093, 763, 694, 603 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 8.21 (s, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.02−6.92 (m, 4H), 6.48 (d, *J* = 6.8 Hz, 2H), 4.60 (s, 1H), 4.06 (s, 2H), 3.01 (s, 1H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.0, 198.0, 168.5, 153.2, 137.7, 137.0, 133.9, 129.2, 128.3, 127.8, 126.5, 124.0, 122.9, 118.2, 66.3, 42.9, 40.7, 24.0; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{17}ClNO_3$ $[M + H]^+$ 342.0891; found 342.0894. The product was converted to corresponding alcohol **5d** with $NaCNBH_3$, and enantiomeric excess was determined by HPLC with an AS-H column (hexane/*i*-PrOH = 80:20), 1.0 mL/min; major enantiomer t_R = 14.1 min, minor enantiomer t_R = 19.4 min.

*(S)-3-((R)-1-Acetyl-3-oxoindolin-2-yl)-3-(4-bromophenyl)propanal (**4e**):* colorless oil (64 mg, 81% yield, 4:1 dr, 94% ee), $[\alpha]^{20}_D$ = +64 (*c* 1.0, CH_2Cl_2); IR (KBr) 3410, 2933, 2732, 1714, 1675, 1607, 1466, 1381, 1288, 1009, 761, 539 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.90 (s, 1H), 8.21 (s, 1H), 7.45 (t, *J* = 7.2 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.02 (t, *J* = 7.6 Hz, 1H), 4.84 (d, *J* = 8.4 Hz, 2H), 4.60 (s, 1H), 4.06 (s, 2H), 3.00 (s, 1H), 2.64 (s, 3H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1, 198.1, 168.6, 137.1, 134.7, 131.1, 129.8, 125.0, 124.0, 122.9, 121.6, 118.2, 66.3, 43.0, 40.3, 24.1; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{17}BrNO_3$ $[M + H]^+$ 386.0386; found 386.0383. The product was converted to corresponding alcohol **5e** with $NaCNBH_3$, and enantiomeric excess was determined by HPLC with an AS-H column (hexane/*i*-PrOH = 90:10), 1.0 mL/min; major enantiomer t_R = 38.9 min, minor enantiomer t_R = 46.1 min.

*(S)-3-((R)-1-Acetyl-3-oxoindolin-2-yl)-3-(4-chlorophenyl)propanal (**4f**):* colorless oil (60 mg, 88% yield, 4:1 dr, 95% ee), $[\alpha]^{20}_D$ = +186 (*c* 1.0, CH_2Cl_2); IR (KBr) 3412, 2931, 2732, 1715, 1676, 1607, 1466, 1381, 1287, 1094, 1011, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 8.23 (s, 1H), 7.45 (t, *J* = 6.8 Hz, 2H), 7.02−6.89 (m, 5H), 4.60 (s, 1H), 4.07 (s, 2H), 2.98 (s, 1H), 2.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1, 198.1, 168.6, 153.3, 137.1, 134.2, 133.5, 129.5, 128.2, 126.2, 125.1, 124.0, 122.9, 118.3, 66.4, 43.1, 40.3, 24.0; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{17}ClNO_3$ $[M + H]^+$ 342.0891; found 342.0888. The product was converted to corresponding alcohol **5f** with $NaCNBH_3$, and enantiomeric excess was determined by HPLC with an AS-H column (hexane/*i*-PrOH = 90:10), 1.0 mL/min; major enantiomer t_R = 36.6 min, minor enantiomer t_R = 43.6 min.

*(S)-3-((R)-1-Acetyl-3-oxoindolin-2-yl)-3-(2-methoxyphenyl)propanal (**4g**):* colorless oil (57 mg, 85% yield, 4:1 dr, 96% ee), $[\alpha]^{20}_D$ = +440 (*c* 1.0, CH_2Cl_2); IR (KBr) 3408, 2938, 2731, 1714, 1676, 1605, 1465, 1383, 1287, 1245, 1027, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.94 (s, 1H), 8.20 (d, *J* = 6.4 Hz, 1H), 7.40 (d, *J* = 7.2 Hz, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 6.96−6.92 (m, 2H), 6.87 (d, *J* = 8.0 Hz, 1H), 6.61−6.56 (m, 2H), 4.83−4.78 (m, 1H), 4.61 (s, 1H), 4.15−4.05 (m, 1H), 3.72 (s, 3H), 2.87 (d, *J* = 19.2 Hz, 1H), 2.65 (s, 3H) ; ^{13}C NMR (100 MHz,$CDCl_3$) δ 200.9, 198.9, 169.4, 157.0, 153.5, 136.6, 128.5, 128.1, 125.1, 124.4, 123.3, 122.6, 120.1, 117.8, 109.9, 66.5, 55.1, 42.9, 32.2, 23.7; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{19}NNaO_4[M + Na]^+$ 360.1206; found 360.1202. The product was converted to corresponding alcohol **5g** with $NaCNBH_3$, and enantiomeric excess was determined by HPLC with an AS-H column (hexane/*i*-PrOH = 85:15), 1.0 mL/min; major enantiomer t_R = 16.6 min, minor enantiomer t_R = 21.0 min.

*(S)-3-((R)-1-Acetyl-3-oxoindolin-2-yl)-3-(4-methoxyphenyl)propanal (**4h**):* colorless oil (62 mg, 92% yield, 5:1 dr, 86% ee), $[\alpha]^{20}_D$ = +135 (*c* 1.0, CH_2Cl_2); IR (KBr) 3406, 2937, 2617, 1713, 1676, 1608, 1514, 1466, 1384, 1290, 1251, 1184, 1034, 763, 538 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.90 (s, 1H), 8.20 (s, 1H), 7.41−7.37 (m, 2H), 6.96 (t, *J* = 7.2 Hz, 1H), 6.86 (d, *J* = 7.2 Hz, 2H), 6.51 (d, *J* = 8.8 Hz, 2H), 4.55 (s, 1H), 4.01 (s, 2H), 3.59 (s, 3H), 2.98 (s, 1H), 2.62 (s, 3H) ; ^{13}C NMR (100 MHz,$CDCl_3$) δ 200.7, 198.5, 168.8, 158.8, 136.8, 129.2, 127.6, 125.2, 123.8, 122.8, 118.6, 118.2, 113.4, 66.7, 55.0, 43.3, 40.2, 24.0; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{20}NO_4$ $[M + H]^+$ 338.1387; found 338.1391. The product was converted to corresponding alcohol **5h** with $NaCNBH_3$, and enantiomeric excess was determined by HPLC with an AS-H column (hexane/*i*-PrOH = 80:20), 1.0 mL/min; major enantiomer t_R = 20.8 min, minor enantiomer t_R = 30.1 min.

*(S)-3-((R)-1-Acetyl-3-oxoindolin-2-yl)-3-(p-tolyl)propanal (**4i**):* colorless oil (60 mg, 94% yield, 6:1 dr, 86% ee), $[\alpha]^{20}_D$ = +116 (*c* 1.0, CH_2Cl_2); IR (KBr) 3378, 2974, 2738, 1714, 1674, 1607, 1465, 1382, 1291, 1092, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1H),

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8.21 (s, 1H), 7.42−7.38 (m, 2H), 6.97 (t, J = 7.6 Hz, 1H), 6.85−6.79 (m, 4H), 4.59 (s, 1H), 4.04 (s, 2H), 3.00 (s, 1H), 2.63 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.7, 198.4, 168.8, 153.4, 137.3, 136.7, 132.6, 128.7, 128.1, 125.3, 123.8, 122.8, 118.3, 66.7, 43.3, 40.6, 24.1, 20.8; HRMS (ESI) m/z calcd for $C_{20}H_{20}NO_3$ $[M + H]^+$ 322.1438; found 322.1443. The product was converted to corresponding alcohol **5i** with $NaCNBH_3$, and enantiomeric excess was determined by HPLC with an AS-H column (hexane/*i*-PrOH = 80:20), 1.0 mL/min; major enantiomer t_R = 12.5 min, minor enantiomer t_R = 16.7 min.

(R)-3-((R)-1-Acetyl-3-oxoindolin-2-yl)-3-(furan-2-yl)propanal (***4j***): colorless oil (54 mg, 92% yield, 6:1 dr, 76% ee), $[\alpha]^{20}_D$ = +153 (*c* 1.0, CH_2Cl_2); IR (KBr) 3410, 3925, 2734, 1718, 1674, 1466, 1382, 1291, 1010, 759, 599 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 8.34 (s, 1H), 7.56−7.520 (m, 2H), 7.08 (t, J = 7.2 Hz, 1H), 6.97 (s, 2H), 5.94 (m, 1H), 4.58 (s, 1H), 4.21 (s, 1H), 3.86 (s, 1H), 3.03 (s, 1H), 2.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 197.6, 168.5, 150.2, 141.9, 137.3, 136.8, 124.1, 123.8, 123.6, 123.1, 109.9, 108.1, 65.6, 41.6, 35.1, 23.9; HRMS (ESI) m/z calcd for $C_{17}H_{16}NO_4$ $[M + H]^+$ 298.1074; found 298.1078. The product was converted to corresponding alcohol **5j** with $NaCNBH_3$, and enantiomeric excess was determined by HPLC with an AS-H column (hexane/*i*-PrOH = 80:20), 1.0 mL/min; major enantiomer t_R = 14.2 min, minor enantiomer t_R = 21.5 min.

(R)-3-((R)-1-Acetyl-3-oxoindolin-2-yl)butanal (***4k***): colorless oil (44 mg, 90% yield, 1:1 dr, 82% ee), $[\alpha]^{20}_D$ = +213 (*c* 1.0, CH_2Cl_2); IR (KBr) 3413, 2968, 2729, 1716, 1675, 1607, 1464, 1380, 1297, 1007, 762 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 8.53 (s, 1H), 7.70−7.64 (m, 2H), 7.21 (t, J = 7.6 Hz, 1H), 4.45 (d, J = 3.6 Hz, 1H), 3.52 (s, 1H), 2.97 (s, 1H), 2.63 (dd, J = 3.6, 19.6 Hz, 1H), 2.55 (s, 3H), 0.71 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 198.7, 169.1, 153.8, 137.3, 125.2, 124.3, 123.2, 118.6, 66.4, 45.3, 30.4, 23.9, 13.3; HRMS (ESI) m/z calcd for $C_{14}H_{16}NO_3$ $[M + H]^+$ 246.1125; found 246.1131. The product was converted to corresponding acetyl ester with $NaCNBH_3$ and Ac_2O, and enantiomeric excess was determined by HPLC with an AS-H column (hexane/*i*-PrOH = 70:30), 1.0 mL/min; major enantiomer t_R = 9.7 min, minor enantiomer t_R = 14.0 min.

(S)-3-((R)-1-Acetyl-4-bromo-3-oxoindolin-2-yl)-3-phenylpropanal (***4l***): colorless oil (71 mg, 92% yield, 11:1 dr, 82% ee), $[\alpha]^{20}_D$ = +80 (*c* 1.0, CH_2Cl_2); IR (KBr) 3412, 2922, 2730, 1716, 1679, 1598, 1424, 1378, 1263, 933, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (s, 1H), 8.46 (s, 1H), 7.25 (s, 1H), 7.10−7.04 (m, 4H), 6.94 (s, 2H), 4.60 (s, 1H), 4.06 (s, 2H), 3.00 (d, J = 16.4 Hz, 1H), 2.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4, 197.1, 168.9, 158.5, 135.2, 132.1, 128.5, 128.4, 128.2, 127.9, 127.8, 127.3, 123.5, 121.2, 66.8, 42.9, 40.9, 24.0; HRMS (ESI) m/z calcd for $C_{19}H_{17}BrNO_3$ $[M + H]^+$ 386.0386; found 386.0375. The product was converted to corresponding alcohol **5l** with $NaCNBH_3$, and enantiomeric excess was determined by HPLC with an AS-H column (hexane/*i*-PrOH = 80:20), 1.0 mL/min; major enantiomer t_R = 12.4 min, minor enantiomer t_R = 18.4 min.

(S)-3-((R)-1-Acetyl-5-methyl-3-oxoindolin-2-yl)-3-phenylpropanal (***4m***): colorless oil (59 mg, 91% yield, 5:1 dr, 95% ee), $[\alpha]^{20}_D$ = +170 (*c* 0.5, CH_2Cl_2); IR (KBr) 3408, 2924, 2732, 1714, 1672, 1489, 1380, 1287, 732, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.94 (s, 1H), 8.09 (s, 1H), 7.11 (d, J = 7.6 Hz, 2H), 7.02−6.95 (m, 5H), 4.58 (s, 1H), 4.07 (s, 2H), 2.99 (d, J = 17.2 Hz, 1H), 2.64 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6, 198.3, 168.6, 151.7, 137.9, 135.7, 133.6, 128.2, 128.0, 127.6, 125.2, 122.4, 118.0, 66.7, 43.1, 41.0, 23.8, 20.5; HRMS (ESI) m/z calcd for $C_{20}H_{20}NO_3$ $[M + H]^+$ 322.1438; found 322.1435. The product was converted to corresponding alcohol **5m** with $NaCNBH_3$, and enantiomeric excess was determined by HPLC with an AS-H column (hexane/*i*-PrOH = 80:20), 1.0 mL/min; major enantiomer t_R = 13.1 min, minor enantiomer t_R = 21.6 min.

Representative Procedure for the Reduction of 2-Substituted Indolinones 4. A solution of **4** (0.1 mmol, 1.0 equiv) in 1.0 mL of THF was cooled to 0 °C, and 0.125 mL of concentrated AcOH and 11 mg (0.2 mmol, 2.0 equiv) of $NaCHBH_3$ were subsequently added. The reaction mixture was warmed to rt overnight. Three milliliters of brine was added, and the pH was adjusted to 7 with saturated $NaHCO_3$ solution. The aqueous layer was extracted three times with 10 mL of EA, and the combined organic layers were dried over Na_2SO_4. After evaporation of the solvents under vacuum, the residue was purified by flash column chromatography (PE/EA = 1:2).

(R)-1-Acetyl-2-((S)-3-hydroxy-1-phenylpropyl)indolin-3-one (***5a***): colorless oil (21 mg, 68% yield), $[\alpha]^{20}_D$ = +121; IR (KBr) 3413, 2928, 1713, 1673, 1607, 1466, 1385, 1303, 761, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.38−7.34 (m, 2H), 6.95 (s, 5H), 4.65 (s, 1H), 3.87 (s, 1H), 3.76 (s, 1H), 3.71−3.66 (m, 1H), 3.12 (s, 1H), 2.54−2.49 (m, 1H), 2.46 (s, 3H), 2.35−2.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.4, 168.5, 152.9, 136.4, 128.2, 127.7, 127.1, 125.2, 123.6, 122.5, 118.1, 68.0, 60.0, 44.7, 31.2, 23.6; HRMS (ESI) m/z calcd for $C_{19}H_{20}NO_3$ $[M + H]^+$ 310.1438; found 310.1445.

(R)-1-Acetyl-2-((S)-1-(3-chlorophenyl)-3-hydroxypropyl)indolin-3-one (***5d***): colorless oil (21 mg, 61% yield), $[\alpha]^{20}_D$ = +128; IR (KBr) 3409, 2926, 1713, 1676, 1606, 1468, 1384, 762, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.50−7.42 (m, 2H), 7.03−6.86 (m, 5H), 4.72 (s, 1H), 3.90−3.80 (m, 2H), 3.73−3.67 (m, 1H), 2.56−2.49 (m, 4H), 2.32−2.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 168.3, 136.8, 133.7, 129.1, 128.6, 127.4, 126.6, 124.0, 120.1, 67.7, 60.3, 44.7, 31.5, 24.0; HRMS (ESI) m/z calcd for $C_{19}H_{19}ClNO_3$ $[M + H]^+$ 344.1048; found 344.1051.

Representative Procedure for the Benzoin Reaction of 4. To a solution of **4** (0.1 mmol, 1.0 equiv) in 2.0 mL of $CHCl_3$ were added 5 mg (0.02 mmol, 0.2 equiv) of 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride and 7 μL (0.05 mmol, 0.5 equiv) of NEt_3. The reaction mixture was refluxed under Ar until the reaction completed. After concentrated in vacuo, the residue was purified by flash column chromatography (PE/EA = 2:1).

(3S,3aS,8bR)-4-Acetyl-8b-hydroxy-3-phenyl-2,3,3a,4-tetrahydrocyclopenta[b]indol-1(8bH)-one (***6a***): colorless oil (22 mg, 70% yield, 93% ee), $[\alpha]^{20}_D$ = +214 (*c* 1.0, CH_2Cl_2); IR (KBr) 3317, 2924, 1711, 1673, 1464, 1379, 1295, 1084, 757, 702 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, J = 8.0 Hz, 1H), 7.45−7.30 (m, 7H), 7.16 (t, J = 8.0 Hz, 1H), 6.53 (s, 1H), 4.72 (d, J = 8.0 Hz, 1H), 3.00 (dd, J = 8.0, 18.4 Hz, 1H), 2.86−2.73 (m, 2H), 1.48 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 211.1, 168.4, 142.2, 141.5, 130.4, 129.4, 128.9, 128.1, 128.0, 127.7, 127.5, 127.4, 124.9, 124.1, 117.9, 83.6, 76.4, 44.9, 43.8, 22.8; HRMS (ESI) m/z calcd for $C_{19}H_{18}NO_3$ $[M + H]^+$ 308.1281; found 308.1287. The enantiomeric excess was determined by HPLC with an AS-H column (hexane/*i*-PrOH = 80:20), 1.0 mL/min; minor enantiomer t_R = 20.4 min, major enantiomer t_R = 23.0 min.

(3S,3aS,8bR)-4-Acetyl-3-(4-bromophenyl)-8b-hydroxy-2,3,3a,4-tetrahydrocyclopenta[b]indol-1(8bH)-one (***6e***): colorless oil (26 mg, 68% yield, 94% ee), $[\alpha]^{20}_D$ = +32 (*c* 1.0, CH_2Cl_2); IR (KBr) 3363, 2923, 1750, 1648, 1470, 1396, 1244, 1073, 1025, 755 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.44−7.38 (m, 4H), 7.16 (t, J = 8.0 Hz, 1H), 6.54 (s, 1H), 4.73 (d, J = 8.0 Hz, 1H), 3.04 (dd, J = 9.6, 17.6 Hz, 1H), 2.80−2.76 (m, 2H), 1.55 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 211.0, 168.4, 142.2, 141.2, 131.8, 130.5, 130.1, 129.4, 124.9, 124.2, 120.4, 118.0, 83.6, 76.0, 44.3, 43.8, 23.0; HRMS (ESI) m/z calcd for $C_{19}H_{17}BrNO_3$ $[M + H]^+$ 386.0386; found 386.0389. The enantiomeric excess was determined by HPLC with an AS-H column (hexane/*i*-PrOH = 80:20), 1.0 mL/min; minor enantiomer t_R = 21.6 min, major enantiomer t_R = 28.3 min.

■ ASSOCIATED CONTENT

Supporting Information. General information, spectrogram for new compounds, and X-ray crystallographic data (CIF file of **5d**, CCDC 825030; and **6e**, CCDC 825029). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The diastereocontrol maybe a result of thermodynamic factors. When the purified products were added to the reaction conditions, some of them were decomposed to the starting materials and transformed into another diastereomer in a diastereomeric ratio of *syn*/*anti* = 6:1.

(9) CCDC 825029 and 825030 contain 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.