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Organocatalyzed Enantioselective Decarboxylative Stereoablation Reaction for the Construction of 3,3′-Disubstituted Oxindoles Using β-Ketoacids and 3-Halooxindoles

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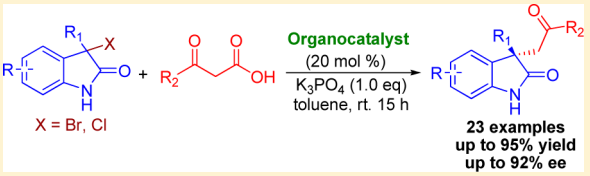
Supporting Information

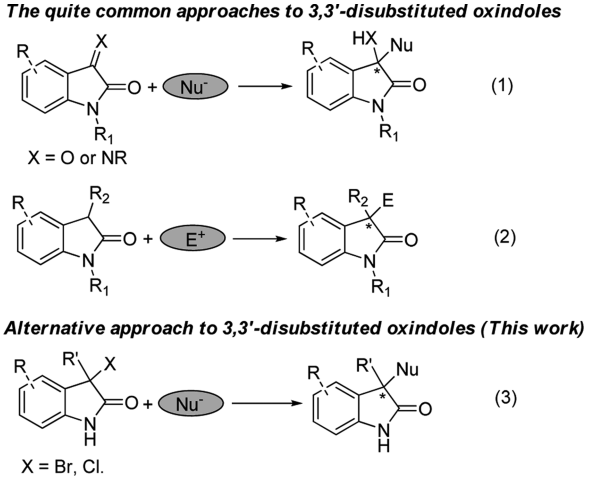
ABSTRACT: An unprecedented method for the construction of optically active 3,3′-disubstituted oxindoles via an organocatalyzed decarboxylative stereoablation reaction has been developed. We describe the first asymmetric reaction between β-ketoacids and 3-halooxindoles utilizing an organocatalyst. This method allows for the formation of a variety of 3,3′-disubstituted oxindoles bearing a ketocarbonyl group, which are not easily accessible using other methodologies, in moderate to good yields with high enantioselectivities.



The 3,3′-disubstituted oxindole unit, which bears a quaternary stereogenic center at the C3 position, has been recognized as a crucial fragment of a number of natural products and medicinally important agents.[1] The stereocontrolled synthesis of 3,3′-disubstituted oxindole derivatives has become the subject of enormous interest over the past decades.[2] Accordingly, a variety of asymmetric methods for the construction of diverse 3,3′-disubstituted oxindoles by means of metal catalysis and organocatalysis have been reported.[3] However, among the various methods, the most common approaches to 3,3′-disubstituted oxindole scaffolds involve using isatins/isatinimines as electrophiles reacting with various nucleophiles (Scheme 1, reaction 1)[4] and applying 3-monosubstituted oxindoles as nucleophiles reacting with different types of electrophiles (Scheme 1, reaction 2).[5] Despite the substantial advances made in this research area, pursuing alternative tactics for the construction of structurally diverse oxindoles bearing a tetrasubstituted stereogenic center at C3 position is still in demand. In this context, taking advantage of a suitable achiral 3,3′-disubstituted oxindole as an electrophilic precursor for the asymmetric synthesis of chiral 3,3′-disubstituted oxindole compounds has begun to emerge recently.[6,7] It is particularly noticeable that a significant example of using 3-halooxindoles as electrophilic precursors via stereoablative transformation[8] for the synthesis of chiral C3-quaternary oxindoles was reported in 2009 by the Stoltz group (Scheme 1, reaction 3).[6a] Guided by Stoltz's work, we recently reported an organocatalytic enantioselective stereoablative hydroxylation of 3-halooxindoles for the construction of 3-substituted-3-hydroxy-2-oxindole derivatives (Scheme 1, reaction 3).[7]

Although the vast majority of the literature has described the widespread application of the decarboxylative transformation of malonic acid half thioesters (MAHTs) in the formation of carbon−carbon bonds,[9] a very small number of methods using β-ketoacids as attractive surrogates of ketones via a decarboxylation process for various asymmetric transformations have been reported in the literature.[10] Thus, the development of a versatile decarboxylative reaction regarding β-ketoacids in asymmetric synthesis is particularly appealing and highly desired. On the basis of the progress with respect to the enantioselective stereoablative reaction[6a,8,11] and our recent studies of the asymmetric stereoablation reaction,[7] we envisioned that a methyl ketone enolate, in situ generated

Scheme 1



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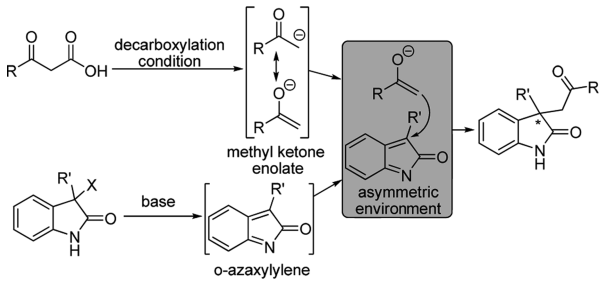
from β-ketoacids via a decarboxylative process, should be able to attack another putative intermediate, *o*-azaxylylene, in situ generated from 3-halooxindoles, for installing a keto-carbonyl group at the C3 position of an oxindole. Certainly, if the above process proceeds under a somewhat appropriate asymmetric environment, it will afford a type of chiral 3,3′-disubstituted oxindole product (Scheme 2). In conjunction with our efforts

Scheme 2. Strategy for the Decarboxylative Stereoablation Reaction between β-Ketoacids and 3-Halooxindoles



to explore asymmetric strategies for the construction of structurally diverse oxindoles,[12] we have investigated an asymmetric decarboxylative stereoablation reaction between β-ketoacids and 3-halooxindoles with cinchona alkaloid derivatives as catalysts. Herein, we report our recent studies on this subject.

We started our investigations with the reaction between racemic 3-benzyl-3-bromooxindole (**1a**) and 3-oxo-3-phenylpropanoic acid (**2a**) in CH_2Cl_2 with potassium carbonate as base using various cinchona alkaloids and their derivatives **A**–**I** (Figure 1) as chiral catalysts. As shown in Table 1 (entries 1–

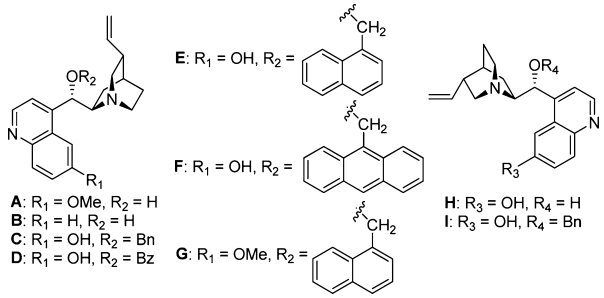
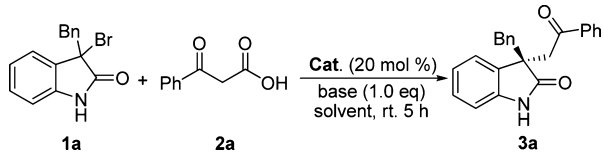


Figure 1. Selected examples of examined catalysts.

9), the structures of the catalysts have a dramatic effect on the enantioselectivity but a minor influence on the catalytic activity. As a result, demethylated quinidine derivative **E** was proven to be the most effective, giving the expected 3,3′-disubstituted **3a** in 94% yield with 83% ee (Table 1, entry 5). Meanwhile, particular attention should be paid to the reaction with **G** as catalyst because the product was obtained as a nearly racemic mixture (Table 1, entry 7). By comparison, it was found that the structural difference between catalysts **E** and **G** is that **E** bears a C6′-OH but **G** contains a C6′-OMe (Figure 1). This led us to speculate that the C6′-OH moiety of the catalyst was crucial for the expected high enantioselectivity. Afterward, solvent screening did not offer further improvement of the enantioselectivity (Table 1, entries 10–13), but toluene gave a relatively higher ee value (Table 1, entry 11). Further studies showed that the base made a large impact on the yield and enantioselectivity (Table 1, entries 14–17), and K_3PO_4

Table 1. Reaction Optimization[a]



entry	cat.	solvent	base	yield (%)[b]	ee (%)[c]
1	**A**	CH_2Cl_2	K_2CO_3	94	43
2	**B**	CH_2Cl_2	K_2CO_3	94	−19
3	**C**	CH_2Cl_2	K_2CO_3	94	72
4	**D**	CH_2Cl_2	K_2CO_3	74	50
5	**E**	CH_2Cl_2	K_2CO_3	94	83
6	**F**	CH_2Cl_2	K_2CO_3	93	82
7	**G**	CH_2Cl_2	K_2CO_3	94	4
8	**H**	CH_2Cl_2	K_2CO_3	85	−33
9	**I**	CH_2Cl_2	K_2CO_3	94	−71
10	**E**	THF	K_2CO_3	67	64
11	**E**	toluene	K_2CO_3	88	85
12	**E**	$CHCl_3$	K_2CO_3	76	82
13	**E**	DCE	K_2CO_3	85	79
14	**E**	toluene	Na_2CO_3	59	90
15	**E**	toluene	Cs_2CO_3	91	27
16	**E**	toluene	Et_3N	50	85
17	**E**	toluene	K_3PO_4	94	87
18	**E**	toluene	K_3PO_4	91	90[d]

[a]Unless otherwise noted, reactions were carried out with **1a** (0.1 mmol), **2a** (0.12 mmol), base (0.1 mmol), and catalyst (0.02 mmol) in the solvent (1.0 mL) at room temperature for 5 h. [b]Isolated yield. [c]Determined by chiral HPLC. [d]Reaction was carried out in 2 mL of toluene at room temperature for 15 h. Bn = benzyl; Bz = benzoyl.

afforded the best reactivity (94% yield) and a high enantioselectivity (87%) (Table 1, entry 17). Higher enantioselectivity, up to 90% ee for **3a**, could be attained in 91% yield after 15 h at a lower substrate concentration (Table 1, entry 18).

With the optimized conditions in hand, we turned our focus to the substrate scope and generality of the reaction. First, a wide range of 3-substituted-3-bromooxindoles **1** were reacted with 3-oxo-3-phenylpropanoic acid (**2a**) under the optimized conditions, respectively (Table 2). The introduction of electron-donating groups onto the phenyl ring of R and incorporation into the 3-halooxindoles did not compromise the reactivity nor significantly affect the selectivity (Table 2, entries 2–4). On the other hand, when electron-withdrawing groups were introduced onto the phenyl ring of R, the reaction also proceeded smoothly and gave the desired product with good yield and ee value (Table 2, entries 5–9). Meanwhile, the substrate **1j** bearing a bulky naphthylmethyl group reacted well with **2a** and gave the desired product **3j** in 95% yield with 89% ee (Table 1, entry 10). High ee was also obtained when the phenyl group was replaced with other aromatics such as thiophene (Table 2, entry 11). 3-Halooxindoles containing electron-withdrawing substitution on the oxindole core were equally effective substrates (Table 2, entries 12 and 13). Additionally, good yield and enantioselectivity could be obtained even with a substrate bearing an allyl substituent at the C3 position of the oxindole core (Table 2, entry 14). Notably, the current reaction system is also effective for 3-benzyl-3-chlorooxindole (**1o**), affording the corresponding product **3a** in 60% yield with 92% ee (Table 2, entry 15). Acceptable results were also provided by using 3-phenyl-3-

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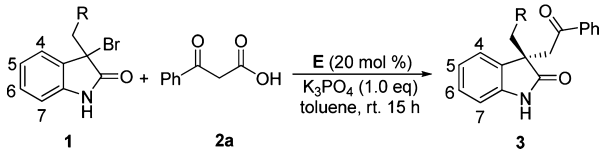
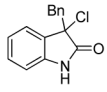
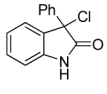
Table 2. Substrate Scope for 3-Halooxindoles[a]



1 2a 3

entry	1	3	yield (%)[b]	ee (%)[c]
1	R = C_6H_5 (**1a**)	**3a**	91	90
2	R = 4-MeC_6H_4 (**1b**)	**3b**	87	90
3	R = 3-MeC_6H_4 (**1c**)	**3c**	90	89
4	R = 2-MeC_6H_4 (**1d**)	**3d**	93	89
5	R = 4-ClC_6H_4 (**1e**)	**3e**	88	87
6	R = 3-ClC_6H_4 (**1f**)	**3f**	85	89
7	R = 2-ClC_6H_4 (**1g**)	**3g**	91	91
8	R = 3-BrC_6H_4 (**1h**)	**3h**	95	91
9	R = 2-BrC_6H_4 (**1i**)	**3i**	93	89
10	R = 1-naphthyl (**1j**)	**3j**	95	89
11	R = 2-thiophenyl (**1k**)	**3k**	86	89
12	4 = Cl, R = C_6H_5 (**1l**)	**3l**	91	82
13	5 = Br, R = C_6H_5 (**1m**)	**3m**	88	87
14	R = CH_2CH- (**1n**)	**3n**	90	89
15	 (**1o**)	**3a**	60	92
16	 (**1p**)	**3v**	69	77

[a]All reactions were performed by using **1** (0.1 mmol), **2a** (0.12 mmol), K_3PO_4 (0.1 mmol), and **E** (0.02 mmol) in toluene (2.0 mL) at room temperature for 15 h. [b]Isolated yield. [c]Determined by chiral HPLC.

chlorooxindole (**1p**) as a substrate (Table 2, entry 16). Particularly, the absolute configuration of compound **3g** was determined as *S* by X-ray analysis (Figure 2), and the other 3,3′-disubstituted oxindole products in this work could be tentatively assigned by analogy.[13]

Subsequently, a variety of *β*-ketoacids (**2b−h**) were further subjected to the **E**-catalyzed decarboxylative stereoablation reaction under the standard reaction conditions (Table 3). Introduction of some substitutents, regardless of being electron-rich or electron-deficient, onto the phenyl ring of 3-

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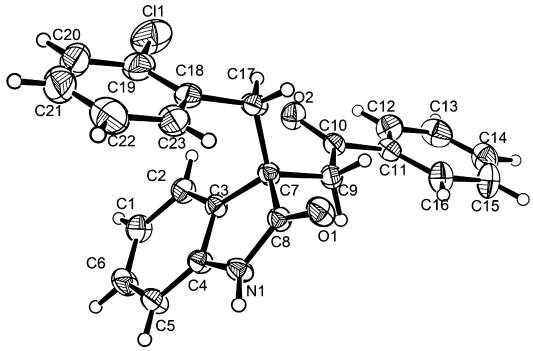
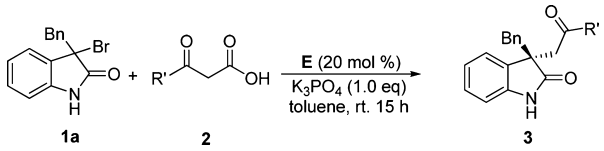


Figure 2. X-ray structure of product **3g**.

Table 3. Substrate Scope for *β*-Ketoacids[a]



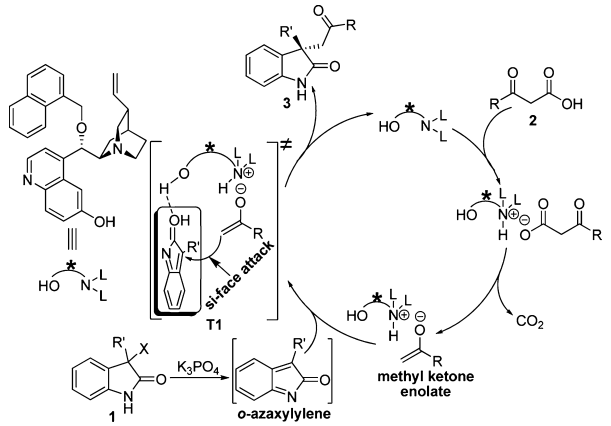
entry	2	3	yield (%)[b]	ee (%)[c]
1	R = 4-MeC_6H_4 (**2b**)	**3o**	86	87
2	R = 4-MeOC_6H_4 (**2c**)	**3p**	86	86
3	R = 4-BrC_6H_4 (**2d**)	**3q**	81	90
4	R = 3-ClC_6H_4 (**2e**)	**3r**	50	83
5	R = 2-naphthyl (**2f**)	**3s**	94	89
6	R = 2-thiophenyl (**2g**)	**3t**	91	82
7	R = Me (**2h**)	**3u**	72	80

[a]All reactions were performed by using **1a** (0.1 mmol), **2** (0.12 mmol), K_3PO_4 (0.1 mmol), and **E** (0.02 mmol) in toluene (2.0 mL) at room temperature for 15 h. [b]Isolated yield. [c]Determined by chiral HPLC.

oxo-3-phenylpropanoic acid allowed the reaction to proceed well and provided the expected product with moderate to good yield and good enantioselectivity (Table 3, entries 1−4). Nevertheless, *β*-ketoacids with a 2-naphthyl (**2f**) and a 2-thiophenyl group (**2g**) were also tolerated (Table 3, entries 5 and 6). We also investigated the decarboxylative stereoablation process of alkyl-substituted *β*-ketoacid-like 3-oxobutanoic acid (**2h**). This substrate was found to be suitable for this asymmetric transformation and provided the desired product **3u** with acceptable results (Table 3, entry 7).

So far as the possible reaction mechanism was concerned, we tried to conduct some preliminary experiments to obtain some useful information. When only substrate **2a** and a catalytic amount of catalyst **E** were subjected to our standard reaction conditions, substrate **2a** was almost completely decomposed and significant amounts of acetophenone were generated. This suggests that the methyl ketone enolate is liable to be formed via decarboxylation from *β*-ketoacids. On the other hand, when the reaction of substrate **1a**, ethyl 3-oxo-3-phenylpropanoate, and a catalytic amount catalyst **E** was performed with toluene as solvent at room temperature for 15 h, the substrate **1a** disappeared and the reaction presented greatly complexity. Therefore, based on the above-noted experimental results and some relevant reports,[10] we proposed the following possible reaction pathway for the enantioselective decarboxylative stereoablation reaction of *β*-ketoacids and 3-halooxindoles with demethylated quinidine derivative **E** as catalyst (Scheme 3). The tertiary amine part of **E** deprotonates the *β*-ketoacid **2**,

Scheme 3. Proposed Reaction Pathway



and the resulting carboxylate undergoes decarboxylation, generating a methyl ketone enolate. Meanwhile, 3-halooxindole **1** is subjected to K_3PO_4, thus forming a putative *o*-azaxylylene intermediate. Simultaneously, activation of the *o*-azaxylylene intermediate and the methyl ketone enolate by the hydroxyl and tertiary amine group of **E** derives a transition state **T1** (Scheme 3). With the enantioselective induction from chiral catalyst **E**, the *S* configuration for the 3,3′-disubstituted oxindoles **3** is predominately generated via the enolate attacking the si-face of the *o*-azaxylylene.

In conclusion, we have developed a new catalytic approach toward optically active 3,3′-disubstituted oxindoles via an organocatalyzed decarboxylative stereoablation process. The current process adopts *β*-ketoacids and 3-halooxindoles as substrates and a demethylated quinidine derivative as catalyst. The reaction provides a practical and valuable catalytic entry for the enantioselective construction of a variety of 3,3′-disubstituted oxindoles bearing a keto-carbonyl group in moderate to good yields (up to 95%) and with high enantioselectivities (up to 92% ee), which are not easily accessible using other methodologies. Particularly, the readily available substrates, reagents, and catalysts, and a simple protocol with mild conditions, are among the attractive features of this reaction.

■ EXPERIMENTAL SECTION

General Experimental Procedure for the Enantioselective Decarboxylative Stereoablation Reaction between *β*-Ketoacids and 3-Halooxindoles Catalyzed by E. A solution of 3-halooxindole **1** (0.1 mmol), *β*-ketoacid **2** (0.12 mmol), K_3PO_4 (0.1 mmol), and catalyst **E** (0.02 mmol) in toluene (2 mL) was stirred at room temperature for 15 h. Then the reaction mixture was directly charged onto a silica gel column and purified through flash chromatography to furnish the corresponding products **3**.

(*S*)-3-Benzyl-3-(2-oxo-2-phenylethyl)indolin-2-one (3a). Pale yellow solid, 31.0 mg, yield 91%; 90% ee, $[\alpha]_D^{20}$ = +112.3 (*c* 1.35, $CHCl_3$); mp 158.4−159.7 °C. ^{1}H NMR (300 MHz, $CDCl_3$), *δ* (ppm): 3.10 (d, *J* = 12.8 Hz, 1H), 3.19 (d, *J* = 12.8 Hz, 1H), 3.78 (d, *J* = 18.3 Hz, 1H), 3.84 (d, *J* = 18.3 Hz, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 6.90−6.99 (m, 4H), 7.09−7.13 (m, 4H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.86 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), *δ* (ppm): 44.0, 44.7, 51.1, 109.8, 121.3, 123.0, 126.6, 127.5, 127.7, 127.8, 128.3, 130.2, 131.3, 133.0, 134.9, 136.2, 141.6, 181.7, 195.9. HRMS (ESI-TOF) calcd for $C_{23}H_{19}NNaO_2$ [M + Na]$^+$:

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364.1308; found: 364.1318. HPLC analysis: Chiralcel AD-H column, 2-propanol/hexane = 50:50, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 16.5 min, t_{minor} = 7.4 min.

(*S*)-3-(4-Methylbenzyl)-3-(2-oxo-2-phenylethyl)-indolin-2-one (3b). Pale yellow solid, 30.9 mg, yield 87%; 90% ee, $[\alpha]_D^{20}$ = +90.2 (*c* 1.45, $CHCl_3$); mp 152.5−154.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 2.25 (s, 3H), 3.04 (d, *J* = 12.9 Hz, 1H), 3.14 (d, *J* = 12.9 Hz, 1H), 3.75 (d, *J* = 18.0 Hz, 1H), 3.83 (d, *J* = 18.0 Hz, 1H), 6.74 (d, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 7.8 Hz, 2H), 6.90−7.12 (m, 5H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.50−7.55 (m, 2H), 7.86 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 21.0, 44.0, 45.0, 51.1, 109.6, 121.6, 123.2, 127.8, 128.0, 128.4, 128.5, 130.2, 131.6, 131.7, 133.2, 136.2, 136.3, 141.4, 181.3, 195.9. HRMS (ESI-TOF) calcd for $C_{24}H_{21}NNaO_2$ $[M + Na]^+$: 378.1465; found: 378.1474. HPLC analysis: Chiralcel AD-H column, 2-propanol/hexane = 50:50, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 27.7 min, t_{minor} = 7.4 min.

(*S*)-3-(3-Methylbenzyl)-3-(2-oxo-2-phenylethyl)-indolin-2-one (3c). Pale yellow solid, 32.0 mg, yield 90%; 89% ee, $[\alpha]_D^{20}$ = +94.6 (*c* 1.50, $CHCl_3$); mp 152.5−154.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 2.20 (s, 3H), 3.04 (d, *J* = 12.9 Hz, 1H), 3.15 (d, *J* = 12.9 Hz, 1H), 3.77 (d, *J* = 18.3 Hz, 1H), 3.84 (d, *J* = 18.3 Hz, 1H), 6.71−6.75 (m, 3H), 6.90−7.01 (m, 4H), 7.09−7.14 (m, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.51−7.53 (m, 1H), 7.86 (d, *J* = 8.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 21.1, 44.1, 44.8, 51.1, 109.7, 121.3, 123.1, 127.3, 127.4, 127.5, 127.7, 127.9, 128.4, 131.1, 131.5, 133.1, 134.8, 136.3, 137.0, 141.6, 181.6, 195.9. HRMS (ESI-TOF) calcd for $C_{24}H_{21}NNaO_2$ $[M + Na]^+$: 378.1465; found: 378.1474. HPLC analysis: Chiralcel AD-H column, 2-propanol/hexane = 50:50, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 16.1 min, t_{minor} = 6.5 min.

(*S*)-3-(2-Methylbenzyl)-3-(2-oxo-2-phenylethyl)-indolin-2-one (3d). Pale yellow solid, 33.1 mg, yield 93%; 89% ee, $[\alpha]_D^{20}$ = +102.2 (*c* 1.55, $CHCl_3$); mp 150.6−152.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 1.98 (s, 3H), 3.11 (d, *J* = 13.5 Hz, 1H), 3.20 (d, *J* = 13.5 Hz, 1H), 3.81 (d, *J* = 18.0 Hz, 1H), 3.92 (d, *J* = 18.0 Hz, 1H), 6.71−6.84 (m, 3H), 7.00−7.14 (m, 5H), 7.41−7.53 (m, 4H), 7.84−7.87 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 19.7, 40.1, 44.5, 50.8, 109.8, 121.4, 123.2, 125.2, 126.9, 127.9, 128.0, 128.5, 130.4, 130.9, 131.4, 133.2, 133.8, 136.3, 137.7, 141.5, 182.3, 195.9. HRMS (ESI-TOF) calcd for $C_{24}H_{21}NNaO_2$ $[M + Na]^+$: 378.1465; found: 378.1476. HPLC analysis: Chiralcel AD-H column, 2-propanol/hexane = 50:50, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 13.3 min, t_{minor} = 7.3 min.

(*S*)-3-(4-Chlorobenzyl)-3-(2-oxo-2-phenylethyl)-indolin-2-one (3e). Pale yellow solid, 33.1 mg, yield 88%; 87% ee, $[\alpha]_D^{20}$ = +99.9 (*c* 1.55, $CHCl_3$); mp 82.2−84.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 3.09 (d, *J* = 12.6 Hz, 1H), 3.15 (d, *J* = 12.6 Hz, 1H), 3.74 (d, *J* = 18.0 Hz, 1H), 3.83 (d, *J* = 18.0 Hz, 1H), 6.71 (d, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 7.5 Hz, 1H), 7.04−7.13 (m, 4H), 7.39−7.54 (m, 4H), 7.85−7.87 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 43.5, 45.0, 51.2, 109.9, 121.8, 123.0, 127.8, 128.0, 128.1, 128.5, 128.9, 131.1, 131.5, 132.7, 133.3, 136.3, 141.5, 181.1, 195.8. HRMS (ESI-TOF) calcd for $C_{23}H_{18}ClNNaO_2$ $[M + Na]^+$: 398.0918; found: 398.0925. HPLC analysis: Chiralcel OD-H column, 2-propanol/hexane = 10:90, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 18.0 min, t_{minor} = 16.5 min.

(*S*)-3-(3-Chlorobenzyl)-3-(2-oxo-2-phenylethyl)-indolin-2-one (3f). Pale yellow solid, 31.9 mg, yield 85%; 89% ee, $[\alpha]_D^{20}$ = +95.3 (*c* 1.50, $CHCl_3$); mp 147.8−149.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 3.09 (d, *J* = 12.9 Hz, 1H), 3.16 (d, *J* = 12.9 Hz, 1H), 3.75 (d, *J* = 18.0 Hz, 1H), 3.83 (d, *J* = 18.0 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.81−6.85 (m, 2H), 6.95−7.12 (m, 5H), 7.41−7.54 (m, 3H), 7.85−8.00 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 43.7, 44.9, 51.1, 109.9, 121.8, 123.0, 126.9, 128.0, 128.1, 128.4, 128.5, 128.8, 130.2, 131.0, 133.3, 136.2, 136.9, 141.4, 181.0, 195.8. HRMS (ESI-TOF) calcd for $C_{23}H_{18}ClNNaO_2$ $[M + Na]^+$: 398.0918; found: 398.0928. HPLC analysis: Chiralcel AD-H column, 2-propanol/hexane = 50:50, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 17.9 min, t_{minor} = 7.0 min.

(*S*)-3-(2-Chlorobenzyl)-3-(2-oxo-2-phenylethyl)-indolin-2-one (3g). Pale yellow solid, 34.2 mg, yield 91%; 91% ee, $[\alpha]_D^{20}$ = +41.4 (*c* 1.60, $CHCl_3$); mp 81.8−83.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 3.15 (d, *J* = 13.5 Hz, 1H), 3.51 (d, *J* = 13.5 Hz, 1H), 3.88 (s, 2H), 6.80−6.87 (m, 3H), 7.10−7.15 (m, 4H), 7.27 (t, *J* = 4.5 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.52 (d, *J* = 7.2 Hz, 1H), 7.84−7.87 (m, 2H), 7.96 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 40.0, 44.3, 50.8, 109.7, 121.4, 123.6, 126.2, 128.0, 128.3, 128.5, 129.4, 131.0, 132.5, 133.2, 133.3, 134.9, 136.2, 141.3, 181.8, 195.9. HRMS (ESI-TOF) calcd for $C_{23}H_{18}ClNNaO_2$ $[M + Na]^+$: 398.0918; found: 398.0925. HPLC analysis: Chiralcel AD-H column, 2-propanol/hexane = 50:50, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 16.2 min, t_{minor} = 7.9 min.

(*S*)-3-(3-Bromobenzyl)-3-(2-oxo-2-phenylethyl)-indolin-2-one (3h). Pale yellow solid, 39.9 mg, yield 95%; 91% ee, $[\alpha]_D^{20}$ = +73.7 (*c* 1.90, $CHCl_3$); mp 112.1−113.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 3.20 (d, *J* = 13.5 Hz, 1H), 3.50 (d, *J* = 13.5 Hz, 1H), 3.90 (s, 2H), 6.80−6.88 (m, 3H), 7.11−7.16 (m, 4H), 7.41−7.52 (m, 4H), 7.84−7.87 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 42.4, 44.3, 50.8, 109.7, 121.4, 123.7, 126.0, 126.8, 128.0, 128.5, 128.6, 131.0, 132.4, 132.8, 133.2, 135.1, 136.2, 141.4, 181.9, 195.9. HRMS (ESI-TOF) calcd for $C_{23}H_{18}BrNNaO_2$ $[M + Na]^+$: 442.0413; found: 442.0425. HPLC analysis: Chiralcel AD-H column, 2-propanol/hexane = 50:50, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 16.4 min, t_{minor} = 8.3 min.

(*S*)-3-(2-Bromobenzyl)-3-(2-oxo-2-phenylethyl)-indolin-2-one (3i). Pale yellow solid, 39.1 mg, yield 93%; 89% ee, $[\alpha]_D^{20}$ = +38.3 (*c* 1.85, $CHCl_3$); mp 86.9−88.8 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 3.08 (d, *J* = 12.9 Hz, 1H), 3.14 (d, *J* = 12.9 Hz, 1H), 3.75 (d, *J* = 18.0 Hz, 1H), 3.83 (d, *J* = 18.0 Hz, 1H), 6.72 (d, *J* = 5.7 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 1H), 6.94−7.26 (m, 6H), 7.42 (t, *J* = 7.5 Hz, 3H), 7.52−7.54 (m, 1H), 7.85−7.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 43.6, 44.8, 51.1, 109.9, 121.5, 121.7, 123.0, 127.9, 128.1, 128.5, 128.9, 129.1, 129.8, 130.9, 133.1, 133.2, 136.2, 137.1, 141.5, 181.0, 195.8. HRMS (ESI-TOF) calcd for $C_{23}H_{18}BrNNaO_2$ $[M + Na]^+$: 442.0413; found: 442.0415. HPLC analysis: Chiralcel AD-H column, 2-propanol/hexane = 50:50, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 19.1 min, t_{minor} = 7.1 min.

(*S*)-3-(Naphthalen-1-ylmethyl)-3-(2-oxo-2-phenylethyl)indolin-2-one (3j). Pale yellow solid, 37.2 mg, yield 95%; 89% ee, $[\alpha]_D^{20}$ = +113.3 (*c* 1.75, $CHCl_3$); mp 176.4−178.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 3.54 (d, *J* = 13.8 Hz, 1H), 3.71 (d, *J* = 13.8 Hz, 1H), 3.82 (d, *J* = 18.0 Hz, 1H), 3.91 (d, *J* = 18.0 Hz, 1H), 6.72 (m, 3H), 7.12−7.15 (m, 2H), 7.28−7.51 (m, 7H), 7.71−8.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 39.5, 44.6, 51.1, 109.7, 121.3, 123.8, 124.5, 124.7, 125.3, 125.4, 127.7, 127.8, 127.9,

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128.3, 128.4, 129.1, 131.5, 131.7, 132.7, 133.2, 133.6, 136.3, 141.4, 182.0, 195.9. HRMS (ESI-TOF) calcd for $C_{27}H_{21}NNaO_2$ $[M + Na]^+$: 414.1465; found: 414.1476. HPLC analysis: Chiralcel AD-H column, 2-propanol/hexane = 50:50, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 16.2 min, t_{minor} = 8.6 min.

(*S*)-3-(2-Oxo-2-phenylethyl)-3-(thiophen-2-ylmethyl)-indolin-2-one (3k). Pale yellow solid, 29.9 mg, yield 86%; 89% ee, $[\alpha]_D^{20}$ = +68.4 (*c* 1.40, $CHCl_3$); mp 156.3−158.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 3.35 (d, *J* = 14.1 Hz, 1H), 3.42 (d, *J* = 14.1 Hz, 1H), 3.74 (d, *J* = 18.0 Hz, 1H), 3.87 (d, *J* = 18.0 Hz, 1H), 6.65 (d, *J* = 2.7 Hz, 1H), 6.79−6.83 (m, 2H), 6.96−7.18 (m, 4H), 7.39−7.77 (m, 4H), 7.87 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 38.3, 44.9, 51.0, 109.7, 121.9, 123.3, 124.7, 126.4, 127.7, 128.0, 128.2, 128.6, 131.3, 133.3, 136.3, 136.4, 141.7, 180.7, 195.7. HRMS (ESI-TOF) calcd for $C_{21}H_{18}NO_2S$ $[M + H]^+$: 348.1053; found: 348.1050. HPLC analysis: Chiralcel AD-H column, 2-propanol/hexane = 50:50, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 13.9 min, t_{minor} = 8.1 min.

(*S*)-3-Benzyl-4-chloro-3-(2-oxo-2-phenylethyl)indolin-2-one (3l). Pale yellow solid, 34.2 mg, yield 91%; 82% ee, $[\alpha]_D^{20}$ = +112.5 (*c* 1.60, $CHCl_3$); mp 191.2−192.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 3.17 (d, *J* = 12.6 Hz, 1H), 3.56 (d, *J* = 12.6 Hz, 1H), 3.75 (d, *J* = 18.3 Hz, 1H), 4.52 (d, *J* = 18.3 Hz, 1H), 6.50 (d, *J* = 7.8 Hz, 1H), 6.90−6.94 (m, 3H), 6.99−7.06 (m, 4H), 7.41−7.56 (m, 4H), 7.90−7.93 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 41.1, 44.2, 53.1, 108.2, 122.7, 126.7, 127.5, 127.6, 128.1, 128.5, 129.2, 129.5, 129.6, 133.3, 134.4, 136.0, 143.4, 180.1, 196.3. HRMS (ESI-TOF) calcd for $C_{23}H_{19}ClNO_2$ $[M + H]^+$: 376.1099; found: 376.1088. HPLC analysis: Chiralcel OD-H column, 2-propanol/hexane =10:90, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 11.6 min, t_{minor} = 19.7 min.

(*S*)-3-Benzyl-5-bromo-3-(2-oxo-2-phenylethyl)indolin-2-one (3m). Pale yellow solid, 37.0 mg, yield 88%; 87% ee, $[\alpha]_D^{20}$ = +119.4 (*c* 1.75, $CHCl_3$); mp 206.8−208.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 3.08 (d, *J* = 12.9 Hz, 1H), 3.14 (d, *J* = 12.9 Hz, 1H), 3.81 (s, 2H), 6.60 (d, *J* = 8.1 Hz, 1H), 6.90−6.92 (m, 2H), 7.10−7.24 (m, 5H), 7.43−7.56 (m, 4H), 7.85−7.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 44.3, 45.0, 51.4, 111.2, 114.2, 126.2, 127.0, 127.8, 128.0, 128.6, 128.8, 129.2, 130.3, 130.7, 133.4, 133.8, 134.3, 136.0, 140.7, 181.2, 195.7. HRMS (ESI-TOF) calcd for $C_{23}H_{19}BrNO_2$ $[M + H]^+$: 420.0594; found: 420.0583. HPLC analysis: Chiralcel AD-H column, 2-propanol/hexane = 50:50, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 12.9 min, t_{minor} = 6.4 min.

(*S*)-3-Allyl-3-(2-oxo-2-phenylethyl)indolin-2-one (3n). Pale yellow solid, 26.2 mg, yield 90%; 89% ee, $[\alpha]_D^{20}$ = +44.1 (*c* 1.20, $CHCl_3$); mp 160.5−162.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 2.50−2.66 (m, 2H), 3.62−3.81 (m, 2H), 5.05−5.13 (m, 2H), 5.57−5.66 (m, 1H), 6.90−6.97 (m, 2H), 7.10 (d, *J* = 7.2 Hz, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.86 (d, *J* = 7.2 Hz, 2H), 8.05 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 42.6, 44.6, 49.6, 109.8, 119.6, 121.9, 122.6, 127.9, 128.0, 128.5, 131.5, 132.1, 133.2, 136.3, 141.4, 181.4, 196.0. HRMS (ESI-TOF) calcd for $C_{19}H_{17}NNaO_2$ $[M + Na]^+$: 314.1151; found: 314.1156. HPLC analysis: Chiralcel AD-H column, 2-propanol/hexane = 50:50, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 10.9 min, t_{minor} = 6.6 min.

(*S*)-3-Benzyl-3-(2-oxo-2-(*p*-tolyl)ethyl)indolin-2-one (3o). Pale yellow solid, 30.6 mg, yield 86%; 87% ee, $[\alpha]_D^{20}$ = +114.5 (*c* 1.40, $CHCl_3$); mp 140.9−143.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 2.37 (s, 3H), 3.09 (d, *J* = 12.9 Hz, 1H), 3.20 (d, *J* = 12.9 Hz, 1H), 3.75 (d, *J* = 18.0 Hz, 1H), 3.82 (d, *J* = 18.0 Hz, 1H), 6.71 (d, *J* = 7.8 Hz, 1H), 6.72−6.94 (m, 3H), 6.99 (d, *J* = 6.9 Hz, 1H), 7.06−7.13 (m, 4H), 7.20 (d, *J* = 8.1 Hz, 2H), 7.76 (d, *J* = 8.1 Hz, 2H), 8.29 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 21.6, 44.3, 44.8, 51.2, 109.7, 121.5, 123.1, 126.7, 127.6, 127.8, 128.1, 129.1, 130.3, 131.5, 133.9, 134.9, 141.5, 144.0, 181.4, 195.5. HRMS (ESI-TOF) calcd for $C_{24}H_{22}NO_2$ $[M + H]^+$: 356.1645; found: 356.1646. HPLC analysis: Chiralcel OD-H column, 2-propanol/hexane =10:90, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 14.0 min, t_{minor} = 36.6 min.

(*S*)-3-Benzyl-3-(2-(4-methoxyphenyl)-2-oxoethyl)-indolin-2-one (3p). Pale yellow solid, 31.8 mg, yield 86%; 86% ee, $[\alpha]_D^{20}$ = +111.7 (*c* 1.50, $CHCl_3$); mp 158.8−160.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 3.08 (d, *J* = 12.9 Hz, 1H), 3.18 (d, *J* = 12.9 Hz, 1H), 3.75−3.76 (m, 2H), 3.83 (s, 3H), 6.70 (d, *J* = 7.8 Hz, 1H), 6.85−6.98 (m, 6H), 7.07−7.13 (m, 4H), 7.84 (d, *J* = 9.0 Hz, 2H), 8.00 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 44.3, 44.6, 51.2, 55.4, 109.6, 113.6, 121.5, 123.2, 126.7, 127.6, 127.8, 129.5, 130.2, 130.3, 131.5, 135.0, 141.4, 163.5, 181.2, 194.4. HRMS (ESI-TOF) calcd for $C_{24}H_{22}NO_3$ $[M + H]^+$: 372.1594; found: 372.1594. HPLC analysis: Chiralcel AD-H column, 2-propanol/hexane = 40:60, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 71.1 min, t_{minor} = 14.2 min.

(*S*)-3-Benzyl-3-(2-(4-bromophenyl)-2-oxoethyl)-indolin-2-one (3q). Pale yellow solid, 34.2 mg, yield 81%; 90% ee, $[\alpha]_D^{20}$ = +69.4 (*c* 1.6, $CHCl_3$); mp 212.8−214.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 3.08 (d, *J* = 12.9 Hz, 1H), 3.17 (d, *J* = 12.9 Hz, 1H), 3.75 (s, 2H), 6.71 (d, *J* = 7.8 Hz, 1H), 6.90−7.00 (m, 4H), 7.08−7.13 (m, 4H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 2H), 8.02 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 44.3, 44.9, 51.1, 109.7, 121.7, 123.1, 126.8, 127.7, 128.0, 128.5, 129.5, 130.3, 131.2, 131.8, 134.7, 135.0, 141.4, 181.0, 194.9. HRMS (ESI-TOF) calcd for $C_{23}H_{19}BrNO_2$ $[M + H]^+$: 420.0594; found: 420.0584. HPLC analysis: Chiralcel OD-H column, 2-propanol/hexane =10:90, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 13.8 min, t_{minor} = 20.8 min.

(*S*)-3-Benzyl-3-(2-(3-chlorophenyl)-2-oxoethyl)-indolin-2-one (3r). Pale yellow solid, 18.8 mg, yield 50%; 83% ee, $[\alpha]_D^{20}$ = +92.4 (*c* 0.65, $CHCl_3$); mp 156.7−158.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 3.09 (d, *J* = 12.9 Hz, 1H), 3.17 (d, *J* = 12.9 Hz, 1H), 3.76 (s, 2H), 6.71 (d, *J* = 7.8 Hz, 1H), 6.89−7.02 (m, 4H), 7.10−7.15 (m, 4H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.62 (br s, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.82 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 44.4, 45.1, 51.1, 109.6, 121.8, 123.1, 126.1, 126.9, 127.7, 128.0, 128.1, 129.9, 130.3, 131.2, 133.2, 134.6, 134.9, 137.8, 141.3, 180.7, 194.6. HRMS (ESI-TOF) calcd for $C_{23}H_{19}ClNO_2$ $[M + H]^+$: 376.1099; found: 376.1099. HPLC analysis: Chiralcel OD-H column, 2-propanol/hexane =10:90, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 14.4 min, t_{minor} = 12.9 min.

(*S*)-3-Benzyl-3-(2-(naphthalen-2-yl)-2-oxoethyl)-indolin-2-one (3s). Pale yellow solid, 36.7 mg, yield 94%; 89% ee, $[\alpha]_D^{20}$ = +138.1 (*c* 1.75, $CHCl_3$); mp 178.2−179.9 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 3.16 (d, *J* = 12.9 Hz, 1H), 3.26 (d, *J* = 12.9 Hz, 1H), 3.91 (d, *J* = 17.7 Hz, 1H), 3.99 (d, *J* = 17.7 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.93−6.96 (m, 3H), 7.06−7.15 (m, 5H), 7.56−7.93 (m, 6H), 8.03 (s, 1H), 8.42 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 45.3, 46.1, 52.4,

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110.6, 122.6, 124.2, 124.6, 127.7, 128.6, 128.7, 128.9, 129.4, 129.5, 130.5, 130.7, 131.3, 132.4, 133.2, 134.7, 135.9, 136.6, 142.4, 182.2, 196.9. HRMS (ESI-TOF) calcd for $C_{27}H_{22}NO_2$ $[M + H]^+$: 392.1645; found: 392.1641. HPLC analysis: Chiralcel AD-H column, 2-propanol/hexane = 50:50, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 108.7 min, t_{minor} = 10.4 min.

(*S*)-3-Benzyl-3-(2-oxo-2-(thiophen-2-yl)ethyl)indolin-2-one (3t). Pale yellow solid, 31.6 mg, yield 91%; 82% ee, $[\alpha]_D^{20}$ = +73.9 (*c* 1.50, $CHCl_3$); mp 173.4−175.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 3.09 (d, *J* = 12.9 Hz, 1H), 3.20 (d, *J* = 12.9 Hz, 1H), 3.71 (s, 2H), 6.71−6.92 (m, 4H), 7.03−7.12 (m, 6H), 7.57 (d, *J* = 4.8 Hz, 1H), 7.68 (m, 1H), 8.23 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 44.0, 45.3, 51.3, 109.7, 121.6, 123.4, 126.7, 127.6, 127.9, 128.0, 130.3, 131.0, 132.1, 133.8, 134.8, 141.4, 143.6, 181.0, 188.9. HRMS (ESI-TOF) calcd for $C_{21}H_{18}NO_2S$ $[M + H]^+$: 348.1053; found: 348.1057. HPLC analysis: Chiralcel AD-H column, 2-propanol/hexane = 30:70, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 16.3 min, t_{minor} = 12.0 min.

(*S*)-3-Benzyl-3-(2-oxopropyl)indolin-2-one (3u). Colorless oil, 20.0 mg, yield 72%; 80% ee, $[\alpha]_D^{20}$ = +54.0 (*c* 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 2.01 (s, 3H), 2.96 (d, *J* = 12.9 Hz, 1H), 3.06 (d, *J* = 12.9 Hz, 1H), 3.15 (d, *J* = 17.7 Hz, 1H), 3.25 (d, *J* = 17.7 Hz, 1H), 6.69 (d, *J* = 7.8 Hz, 1H), 6.85 (t, *J* = 4.5 Hz, 2H), 6.95−7.00 (m, 2H), 7.05−7.14 (m, 4H), 8.15 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 30.1, 43.9, 49.4, 51.1, 109.7, 121.7, 123.2, 126.7, 127.6, 128.0, 130.2, 131.1, 134.8, 141.3, 181.0. HRMS (ESI-TOF) calcd for $C_{18}H_{18}NO_2$ $[M + H]^+$: 280.1332; found: 280.1341. HPLC analysis: Chiralcel AD-H column, 2-propanol/hexane = 30:70, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 9.3 min, t_{minor} = 8.4 min.

(*S*)-3-(2-Oxo-2-phenylethyl)-3-phenylindolin-2-one (3v):[14] White solid, 22.6 mg, yield 69%; 77% ee, $[\alpha]_D^{20}$ = +156.6 (*c* 1.13, $CHCl_3$); mp 200.6−202.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 4.11 (d, *J* = 18.0 Hz, 1H), 4.20 (d, *J* = 18.0 Hz, 1H), 6.95−7.01 (m, 2H), 7.23−7.32 (m, 5H), 7.40−7.53 (m, 5H), 7.87−7.90 (m, 2H), 8.23 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 46.8, 53.5, 110.1, 122.2, 124.4, 126.7, 127.6, 128.0, 128.3, 128.6, 128.7, 132.2, 133.3, 136.3, 139.4, 141.7, 180.3, 195.8. HPLC analysis: Chiralcel OD-H column, 2-propanol/hexane = 10:90, flow rate 1.0 mL/min, λ = 254 nm, t_{major} = 45.6 min, t_{minor} = 26.8 min.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

X-ray crystallographic data (CIF file of **3g**) and detailed spectral data for products. 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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