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Organocatalyzed Asymmetric Michael Addition of 1-Acetylindolin-3-ones to β,γ-Unsaturated α-Ketoesters: An Access to Chiral Indolin-3-ones with Two Adjacent Tertiary Stereogenic Centers

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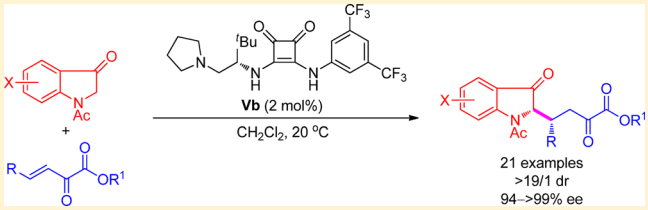
Supporting Information

ABSTRACT: Asymmetric Michael addition of 1-acetylindolin-3-ones to β,γ-unsaturated α-ketoesters was investigated for the synthesis of chiral indolin-3-ones with two adjacent tertiary stereogenic centers. Under the catalysis of a chiral bifunctional squaramide derived from L-*tert*-leucine, a wide range of 1-acetylindolin-3-ones and β,γ-unsaturated α-ketoesters were well-tolerated in this transformation to provide the corresponding novel densely functionalized chiral indolin-3-one derivatives in high yield with excellent diastereo- and enantioselectivity under mild reaction conditions.



Chiral indolin-3-one is an important structural motif in many natural products and compounds of pharmaceutical interest, such as aristotetelone,[1] austamide,[2] brevianamide A,[3] duocarmycin A,[4] fluorocarpamine,[5] halichrome A,[5] isatisine A,[6] isatisine A acetonide,[7] strobilanthoside A,[8] and others.[9] In addition, as a class of important building blocks, indolin-3-ones are frequently used in the total synthesis of alkaloids and biologically active compounds.[10] Due to its interesting structure and biological activity, the chiral indolin-3-one scaffold has attracted extensive attention from both synthetic and medicinal chemists. During the past decade, a few elegant procedures have been established for their synthesis, including organocatalyzed addition reactions to the C═N bond of 2-substituted 3*H*-indol-3-ones or their analogues,[11] organocatalyzed conjugate addition of indolin-3-ones to various acceptors,[12] the redox annulation of nitroalkynes with indoles under gold/chiral phosphoric acid dual catalysis,[13] the PTC-catalyzed asymmetric alkylation of indolin-3-ones,[14] as well as palladium-catalyzed asymmetric allylic alkylation reaction of 2-monosubstituted indolin-3-ones.[15] Despite the considerable amount of effort that has been expended in the preparation of optically active 3-oxyindoles, new and highly efficient methods to access these biologically important heterocycles are always highly desirable. Among these common methods, the Michael addition of indolin-3-ones has been among the most fascinating, straightforward, and powerful protocols. However, the Michael acceptors employed in the enantioselective versions of this reaction are surprisingly restricted to enals,[12c] enones,[12a] and nitroalkenes.[12b,d−f] Although β,γ-unsaturated α-ketoesters are considered to be versatile synthons because of their dense functionalization,[16] the Michael addition of indolin-3-ones with β,γ-unsaturated α-ketoesters as Michael acceptors are still unexplored. Considering the high synthetic versatility and important bioactivity of highly functionalized chiral indolin-3-ones, the development of alternative efficient approaches for the construction of novel and more exotic chiral indolin-3-ones remains challenging and particularly appealing. Herein, we report a bifunctional squaramide-catalyzed asymmetric Michael addition of indolin-3-ones to β,γ-unsaturated α-ketoesters, thus delivering novel densely functionalized chiral indolin-3-ones in good yields with high levels of diastereo- and enantioselectivity.

Our investigation commenced with a set of experiments carried out to evaluate the feasibility of the reaction between 1-acetylindolin-3-one **1a** and β,γ-unsaturated α-ketoester **2a**. Initially, the efficiency of several thiourea-[17] and squaramide-based hydrogen-bonding catalysts (Figure 1)[18] (20 mol %) was examined in dichloromethane at room temperature (Table 1, entries 1−10). To our delight, all of the tested catalysts can promote the model reaction efficiently to generate the desired adduct **3aa** in good yields (70−96%) with high levels of diastereo- (13/1 to >19/1 dr) and enantioselectivity (91 to >99% ee). The variation of the catalyst structure has a limited influence on the stereochemical outcome of the reaction. Bifunctional squaramide **Vb** derived from L-*tert*-leucine was found to be the most promising catalyst for this transformation, delivering product **3aa** in 96% yield with almost perfect diastereo- and enantioselectivity (entry 9, >19/1 dr, >99% ee).

Further optimization of the reaction conditions revealed that both the reaction medium and catalyst loading have only a slight impact on the stereocontrol of the reaction (Table 2). The reaction ran efficiently in several common solvents, such as dichloromethane, chloroform, 1,2-dichloroethane (DCE), tetrahydrofuran, ether, toluene, acetonitrile, and ethanol, affording the corresponding adduct **3aa** in good yields with uniformly high levels of stereoselectivity (entries 1−8, >19/1

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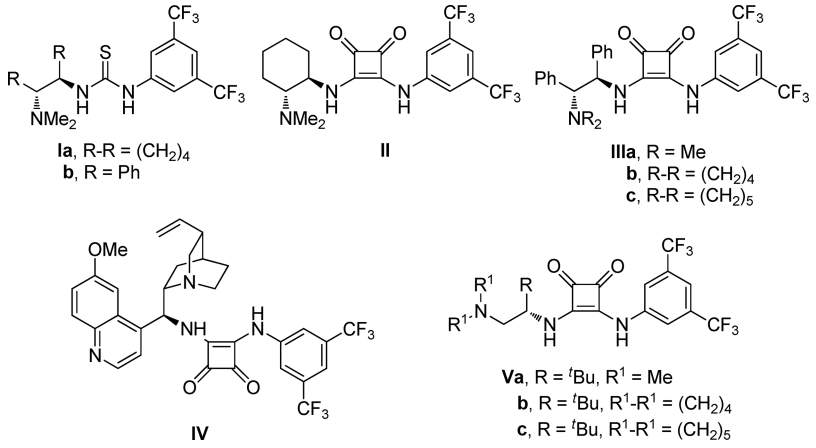
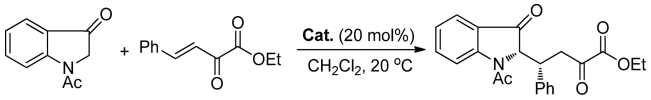


Figure 1. Catalyst candidates.

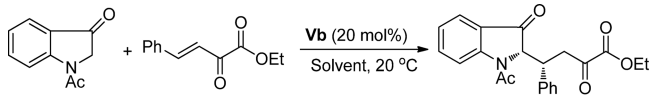
Table 1. Evaluation of Catalysts[a]



entry	catalyst	time (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	**Ia**	5	70	19/1	95
2	**Ib**	24	70	19/1	97
3	**II**	3	84	13/1	94
4	**IIIa**	12	84	>19/1	91
5	**IIIb**	12	88	>19/1	99
6	**IIIc**	23	80	>19/1	97
7	**IV**	4	71	>19/1	−98
8	**Va**	4	94	19/1	−97
9	**Vb**	4	96	>19/1	>−99
10	**Vc**	4	96	>19/1	−98

[a]All reactions were carried out with **1a** (0.20 mmol), **2a** (0.3 mmol), and catalyst (20 mol %) in CH_2Cl_2 (1 mL) at 20 °C. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis. [d]Determined by HPLC analysis with a chiral stationary phase.

Table 2. Optimization of Reaction Conditions[a]



entry	solvent	time (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	CH_2Cl_2	4	96	>19/1	>99
2	$CHCl_3$	4	90	>19/1	99
3	DCE	4	71	>19/1	99
4	THF	12	75	>19/1	96
5	Et_2O	6	80	>19/1	99
6	$PhCH_3$	6	86	>19/1	99
7	CH_3CN	4	82	>19/1	99
8	EtOH	4	>99	>19/1	98
9[e]	CH_2Cl_2	4	92	>19/1	>99
10[f]	CH_2Cl_2	4	92	>19/1	>99
11[g]	CH_2Cl_2	6	96	>19/1	>99
12[h]	CH_2Cl_2	75	16	>19/1	97

[a]Unless otherwise specified, all reactions were carried out with **1a** (0.20 mmol), **2a** (0.30 mmol), and catalyst **Vb** (20 mol %) in solvent (1 mL) at 20 °C. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis. [d]Determined by HPLC analysis with a chiral stationary phase. [e]In the presence of 10 mol % of **Vb**. [f]With 5 mol % of catalyst **Vb**. [g]With 2 mol % of catalyst **Vb**. [h]With 1 mol % of catalyst **Vb**.

dr, 96 to >99% ee). It was gratifying that unaltered stereoselectivies were observed by performing the reaction in the presence of 10, 5, and 2 mol % of catalyst **Vb** (entries 9−11 vs entry 1). The reaction proceeds well even at 1 mol % of catalyst loading at the expense of reaction time, only with a slight erosion in the observed ee value (entry 12, 97% ee).

With a set of optimized reaction conditions in hand (2 mol % of **Vb** as the catalyst, at 20 °C in dichloromethane), we then investigated the scope and limitations of this asymmetric Michael addition reaction. The results are collected in Table 3.

As summarized in Table 3, in the case of 1-acetylindolin-3-one (**1a**), a great number of β,γ-unsaturated α-ketoesters were suitable for this catalytic asymmetric Michael addition reaction, affording the desired optically active 2-substituted indolin-3-ones **3aa**−**3ao** in high yields (69−99%) and excellent diastereo- (>19/1 dr) and enantioselectivities (91 to >99% ee). The ester functionality of the β,γ-unsaturated α-ketoesters had some influence on the stereochemical outcome of the reaction. For example, compared with the result of ethyl ester **2a**, a slightly decreased ee value was obtained for methyl ester **2b** (entry 3, 91% ee), while high enantioselectivity was observed for the bulky isopropyl ester **2c** (entry 4, >99% ee). β,γ-Unsaturated α-ketoesters bearing either electron-withdrawing (**2d**−**2j**) or electron-donating (**2k**−**2m**) groups on the γ-phenyl rings were found to proceed well. These transformations gave the corresponding targets **3ad**−**3am** in 69−99% yield with uniformly high levels of enantioselectivity (entries 5−14, 98 to >99% ee) irrespective of the electronic nature or position of the substituents on the aromatic ring. β,γ-Unsaturated α-ketoesters derived from electron-rich heteroaromatic aldehydes were also good reaction partners, providing the corresponding products in high yields with excellent enantioselectivities (entries 15 and 16). Unfortunately, the reaction is not applicable to the less reactive aliphatic β,γ-unsaturated α-ketoester **2p** bearing an ethyl group at the position, and no reaction occurred even at prolonged reaction time (entry 17). Moreover, 1-acetylindolin-3-ones with various substituents were also subjected to the reaction with **2a** (entries 18−23). Both electron-withdrawing and electron-donating substituents on the aromatic ring were well-tolerated, delivering the desired products in excellent enantioselectivities. Electron-withdrawing substituents generally led to higher enantioselectivities but with

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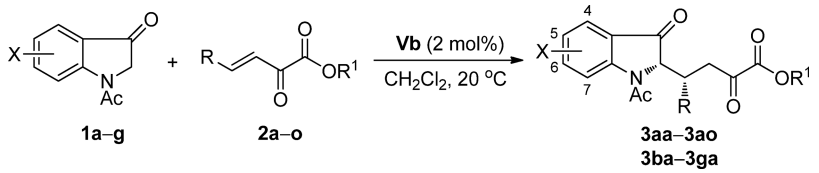
Table 3. Substrate Scope of the Vb-Catalyzed Michael Addition Reactions[a]



entry	3 (X, R, R[1])	time (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	**3aa** (H, Ph, Et)	4	96	>19/1	>99
2[e]	**3aa** (H, Ph, Et)	6	95	>19/1	>99
3	**3ab** (H, Ph, Me)	4	92	>19/1	91
4	**3ac** (H, Ph, ^{i}Pr)	4	90	>19/1	>99
5	**3ad** (H, 4-FC_6H_4, Et)	3	91	>19/1	98
6	**3ae** (H, 4-ClC_6H_4, Et)	4	92	>19/1	99
7	**3af** (H, 3-ClC_6H_4, Et)	12	69	>19/1	99
8	**3ag** (H, 2-ClC_6H_4, Et)	5	95	>19/1	>99
9	**3ah** (H, 2,4-$Cl_2C_6H_3$, Et)	5	96	>19/1	>99
10	**3ai** (H, 4-BrC_6H_4, Et)	5	99	>19/1	>99
11	**3aj** (H, 3-BrC_6H_4, Et)	6	95	>19/1	>99
12	**3ak** (H, 4-MeOC_6H_4, Et)	5	99	>19/1	>99
13	**3al** (H, 3-MeOC_6H_4, Et)	4	99	>19/1	98
14	**3am** (H, 4-MeC_6H_4, Et)	6	90	>19/1	>99
15	**3an** (H, 2-furyl, Et)	5	95	>19/1	>99
16	**3ao** (H, 2-thienyl, Et)	5	95	>19/1	97
17	**3ap** (H, Et, Et)	24	NR[f]		
18	**3ba** (5-F, Ph, Et)	6	87	>19/1	98
19	**3ca** (4-Cl, Ph, Et)	10	73	>19/1	>99
20	**3da** (5-Cl, Ph, Et)	6	68	>19/1	98
21	**3ea** (6-Cl, Ph, Et)	10	88	>19/1	98
22	**3fa** (5-Br, Ph, Et)	5	56	>19/1	>99
23	**3ga** (5-Me, Ph, Et)	4	91	>19/1	94

[a]Unless otherwise specified, all reactions were carried out with **1** (0.20 mmol), **2a** (0.30 mmol), and catalyst **Vb** (2 mol %) in dichloromethane (1 mL) at 20 °C. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis. [d]Determined by HPLC analysis with a chiral stationary phase. [e]The reaction was performed on a 5 mmol scale. [f]NR means no reaction occurred.

yields lower than those in the electron-donating groups (entries 18−22 vs 23). Notably, this reaction was highly diastereoselective, and only a single diastereomer was formed in all cases. In addition, to show the synthetic utility of the newly developed catalytic process, the gram-scale synthesis of **3aa** was performed. Under the optimized reaction conditions, 5 mmol 1-acetylindolin-3-one **1a** (0.88 g) and 7.5 mmol (*E*)-ethyl 2-oxo-4-phenylbut-3-enoate **2a** (1.53 g) reacted smoothly to afford the desired adduct **3aa** in 95% yield (1.80 g) without any loss of stereocontrol (entry 2). It is worth noting that the products contain tertiary amides, and as such, rotamers are present. This led to significant broadening of signals in the ^{1}H NMR spectra, but this phenomenon disappeared when the spectra were recorded at higher temperature (50 °C).

The relative and absolute configuration of product **3ea** is unequivocally established as *S,R* by X-ray analysis (see the Supporting Information), and the remaining configurations are assumed by analogy.[19]

Based on the observed reactivity and results, a ternary complex of squaramide catalyst **Vb**, 1-acetylindolin-3-one **1a**, and (*E*)-ethyl 2-oxo-4-phenylbut-3-enoate **2a** is proposed as a plausible transition state for this transformation to account for the observed high stereoselectivity (Figure 2). In the proposed transition state, the enolate anion formed via the deprotonation of 1-acetylindolin-3-one by the tertiary amine and (*E*)-ethyl 2-oxo-4-phenylbut-3-enoate coordinates to the squaramide moiety and tertiary amino group of catalyst **Vb** through a hydrogen-bonding interaction, respectively. Then 1-acetylindol-3-ate approaches the *β,γ*-unsaturated *α*-ketoester from the *Re* face, leading to the formation of the *S,R* diastereomer as the major product.

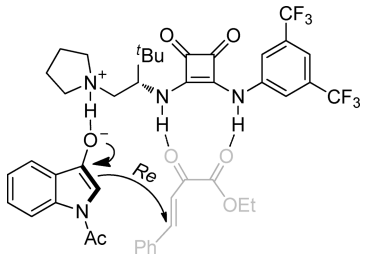


Figure 2. Proposed transition state.

In conclusion, we have developed an organocatalytic asymmetric Michael addition of 1-acetylindolin-3-ones to *β,γ*-unsaturated *α*-ketoesters. Under the catalysis of a bifunctional squaramide derived from L-*tert*-leucine. The reactions ran smoothly to provide a series of densely functionalized chiral indolin-3-ones in good yields with high levels of diastereo- and enantioselectivities. This method serves as a useful tool for the synthesis of novel enantiomerically enriched indolin-3-ones with two adjacent tertiary stereogenic centers, which are important structural motifs in many natural products and synthetic pharmaceuticals.

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EXPERIMENTAL SECTION

General Information. Materials were obtained from commercial suppliers and were used without further purification. NMR spectra were obtained with a 400 MHz spectrometer (^{1}H 400 MHz, ^{13}C 100.6 MHz) in $CDCl_3$. The chemical shifts are reported as δ values (ppm) relative to tetramethylsilane. HRMS spectra were recorded with a Q-TOF mass spectrometer, equipped with an ESI source. Optical rotation values were measured with instruments operating at λ = 589 nm, corresponding to the sodium D line at 20 °C. Enantiomeric excesses were determined by HPLC analysis with a chiral stationary phase.

General Procedure for the Chiral Squaramide Vb-Catalyzed Michael Addition Reactions. Squaramide catalyst **Vb** (1.9 mg, 0.004 mmol), 1-acetylindolin-3-ones **1** (0.20 mmol), and β,γ-unsaturated α-ketoesters **2** (0.30 mmol) were dissolved in dichloromethane (1 mL), and the resulting solution was stirred at 20 °C. After completion of the reaction (monitored by TLC), the reaction mixture was directly purified by column chromatography on silica gel (200–300 mesh, PE/EtOAc = 2/1) to afford the desired chiral indolin-3-ones **3**. The title compounds were fully characterized by ^{1}H, ^{13}C NMR, HRMS, and specific rotation data.

*(R)-Ethyl 4-((S)-1-Acetyl-3-oxoindolin-2-yl)-2-oxo-4-phenylbutanoate (**3aa**):* White solid, 73 mg, 96% yield, mp 81–83 °C, $[\alpha]_D^{25}$ −60.0 (*c* 0.34, CH_2Cl_2), >19/1 dr, >99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1 H), 7.35–7.43 (m, 2 H), 6.93–7.01 (m, 6 H), 4.60 (br s, 1 H), 4.46 (br s, 1 H), 4.37 (q, *J* = 6.8 Hz, 2 H), 4.03 (br s, 1 H), 3.41 (d, *J* = 19.6 Hz,d 1 H), 2.64 (s, 3 H), 1.40 (t, *J* = 7.2 Hz, 3 H); ^{1}H NMR (400 MHz, DMSO-d_6, 50 °C) δ 7.95 (s, 1 H), 7.46 (dt, *J* = 8.0, 1.2 Hz, 1 H), 7.40 (d, *J* = 6.8 Hz, 1 H), 6.96–7.04 (m, 6 H), 4.82 (d, *J* = 4.4 Hz, 1 H), 4.29 (q, *J* = 7.2 Hz, 2 H), 3.95–4.08 (m, 2 H), 3.64 (dd, *J* = 18.8, 6.8 Hz, 1 H), 2.51 (s, 3 H), 1.29 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 198.2, 193.4, 168.6, 160.4, 153.4, 136.8, 135.4, 128.3, 128.0, 127.7, 125.2, 123.8, 122.8, 118.3, 66.2, 62.8, 41.9, 38.8, 24.0, 14.0; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{22}NO_5$ [M + H]$^+$ 380.1492, found 380.1488; HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 220 nm) R_t = 35.11 (major, major diastereomer), 37.19 (minor, major diastereomer), 40.73 (minor, minor diastereomer), and 42.97 min (major, minor diastereomer).

*(R)-Methyl 4-((S)-1-Acetyl-3-oxoindolin-2-yl)-2-oxo-4-phenylbutanoate (**3ab**):* Pale yellow oil, 67 mg, 92% yield, $[\alpha]_D^{25}$ −160.0 (*c* 3.30, CH_2Cl_2), >19/1 dr, 91% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1 H), 7.34–7.38 (m, 2 H), 6.94–7.05 (m, 6 H), 4.56 (br s, 1 H), 4.41 (br s, 1 H), 4.01 (br s, 1 H), 3.90 (s, 3 H), 3.48 (br s, 1 H), 2.63 (s, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 198.1, 192.9, 160.6, 153.4, 136.7, 135.2, 128.3, 128.2, 127.9, 127.6, 125.1, 123.7, 122.7, 118.2, 66.1, 53.2, 41.8, 38.8, 23.9; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{20}NO_5$ [M + H]$^+$ 366.1336, found 366.1330; HPLC analysis (Chiralpak AS-H column, hexane/2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 220 nm) R_t = 18.23 (minor, major diastereomer), 22.45 (major, minor diastereomer), 26.88 (major, major diastereomer), and 33.05 min (minor, minor diastereomer).

*(R)-Isopropyl 4-((S)-1-Acetyl-3-oxoindolin-2-yl)-2-oxo-4-phenylbutanoate (**3ac**):* Yellow solid, 71 mg, 90% yield, mp 79–81 °C, $[\alpha]_D^{25}$ −159.8 (*c* 3.50, CH_2Cl_2), >19/1 dr, >99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1 H), 7.32–7.39 (m, 2 H), 6.90–6.98 (m, 6 H), 5.16 (sep, *J* = 6.0 Hz, 1 H), 4.58 (br s, 1 H), 4.38 (br s, 1 H), 3.98 (br s, 1 H), 3.37 (d, *J* = 15.6 Hz, 1 H), 2.63 (s, 3 H), 1.35 (d, *J* = 6.0 Hz, 6 H); ^{1}H NMR (400 MHz, DMSO-d_6, 50 °C) δ 7.96 (s, 1 H), 7.46 (dt, *J* = 8.0, 1.6 Hz, 1 H), 7.40 (d, *J* = 7.6 Hz, 1 H), 6.95–7.03 (m, 6 H), 5.05 (sep, *J* = 6.4 Hz, 1 H), 4.81 (d, *J* = 4.4 Hz, 1 H), 4.04 (dd, *J* = 11.6, 6.8 Hz, 1 H), 3.96 (dd, *J* = 18.8, 6.8 Hz, 1 H), 3.63 (dd, *J* = 18.8, 6.8 Hz, 1 H), 2.52 (s, 3 H), 1.30 (d, *J* = 6.4 Hz, 3 H), 1.29 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 198.1, 193.7, 168.6, 159.9, 153.3, 136.7, 135.3, 128.2, 127.9, 127.6, 125.1, 123.7, 122.7, 118.2, 71.0, 66.1, 41.9, 38.5, 23.9, 21.5; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{24}NO_5$ [M + H]$^+$ 394.1649, found 394.1645; HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 220 nm) R_t = 34.43 (major, major diastereomer), 40.04 (minor, major diastereomer), 57.06 (minor, minor diastereomer), and 66.27 min (major, minor diastereomer).

*(R)-Ethyl 4-((S)-1-Acetyl-3-oxoindolin-2-yl)-4-(4-fluorophenyl)-2-oxobutanoate (**3ad**):* Pale yellow oil, 72 mg, 91% yield, $[\alpha]_D^{25}$ −145.8 (*c* 2.70, CH_2Cl_2), >19/1 dr, 98% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1 H), 7.42 (t, *J* = 7.6 Hz, 2 H), 6.92–7.01 (m, 3 H), 6.68 (t, *J* = 7.6 Hz, 2 H), 4.57 (br s, 1 H), 4.40 (br s, 1 H), 4.37 (q, *J* = 6.8 Hz, 2 H), 4.02 (br s, 1 H), 3.41 (br s, 1 H), 2.64(s, 3 H), 1.40 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 198.0, 193.1, 168.6, 161.9 (d, *J* = 247.1 Hz), 160.2, 153.2, 137.0, 131.1, 129.8 (d, *J* = 7.9 Hz), 124.9, 123.9, 122.7, 118.2, 114.8 (d, *J* = 21.5 Hz), 66.0, 62.8, 41.1, 38.7, 23.9, 13.9; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{21}FNO_5$ [M + H]$^+$ 398.1398, found 398.1395; HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 80/20, flow rate = 1.0 mL/min, wavelength = 220 nm) R_t = 19.06 (major, major diastereomer), 20.78 (minor, major diastereomer), 22.44 (minor, minor diastereomer), and 26.32 min (major, minor diastereomer).

*(R)-Ethyl 4-((S)-1-Acetyl-3-oxoindolin-2-yl)-4-(4-chlorophenyl)-2-oxobutanoate (**3ae**):* Pale yellow oil, 76 mg, 92% yield, $[\alpha]_D^{25}$ −91.9 (*c* 2.55, CH_2Cl_2), >19/1 dr, 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1 H), 7.40 (t, *J* = 7.2 Hz, 2 H), 6.98 (t, *J* = 6.8 Hz, 1 H), 6.95 (d, *J* = 8.4 Hz, 2 H), 6.88 (d, *J* = 8.4 Hz, 2 H), 4.57 (br s, 1 H), 4.35 (br s, 1 H), 4.34 (q, *J* = 6.8 Hz, 2 H), 3.99 (br s, 1 H), 3.38 (br s, 1 H), 2.62 (s, 3 H), 1.37 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 197.9, 192.9, 168.6, 160.2, 153.2, 137.1, 134.0, 133.5, 129.5, 128.1, 125.0, 124.0, 122.9, 118.1, 66.0, 62.8, 41.2, 38.7, 24.0, 13.9; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{21}ClNO_5$ [M + H]$^+$ 414.1103, found 414.1096; HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 220 nm) R_t = 81.76 (major, major diastereomer), 114.84 (minor, major diastereomer), 121.50 (major, minor diastereomer), and 136.75 min (minor, minor diastereomer).

*(R)-Ethyl 4-((S)-1-Acetyl-3-oxoindolin-2-yl)-4-(3-chlorophenyl)-2-oxobutanoate (**3af**):* Pale yellow oil, 57 mg, 69% yield, $[\alpha]_D^{25}$ −97.8 (*c* 1.8, CH_2Cl_2), >19/1 dr, 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1 H), 7.41 (t, *J* = 7.6 Hz, 2 H), 6.89–7.00 (m, 4 H), 6.84 (d, *J* = 6.8 Hz, 1 H), 4.57 (br s, 1 H), 4.37 (br s, 1 H), 4.36 (q, *J* = 6.8 Hz, 2 H), 4.00 (br s, 1 H), 3.38 (br s, 1 H), 2.62 (s, 3 H), 1.39 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 197.8, 193.0, 168.4, 160.2, 153.3, 137.4, 137.0, 133.9, 129.2, 128.3, 127.8, 126.5, 125.1, 124.0, 122.8, 118.3, 65.9, 62.9, 41.7, 38.5, 23.9, 13.9; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{21}ClNO_5$ [M + H]$^+$ 414.1103, found 414.1107; HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 220 nm) R_t = 64.67 (major), 71.92 (minor).

*(R)-Ethyl 4-((S)-1-Acetyl-3-oxoindolin-2-yl)-4-(2-chlorophenyl)-2-oxobutanoate (**3ag**):* Pale yellow oil, 79 mg, 95% yield, $[\alpha]_D^{25}$ −220.4 (*c* 2.75, CH_2Cl_2), >19/1 dr, >99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1 H), 7.42 (d, *J* = 7.6 Hz, 1 H), 7.36 (t, *J* = 7.6 Hz, 1 H), 7.09 (dd, *J* = 8.4, 1.6 Hz, 1 H), 6.98 (dd, *J* = 7.2, 2.4 Hz, 1 H), 6.93 (t, *J* = 7.6 Hz, 1 H), 6.83–6.90 (m, 2 H), 4.74 (br s, 1 H), 4.62 (br s, 1 H), 4.36 (br s, 1 H), 4.34 (q, *J* = 6.8 Hz, 2 H), 3.28 (d, *J* = 17.6 Hz, 1 H), 2.63 (s, 3 H), 1.37 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 198.5, 192.8, 169.0, 160.1, 153.4, 136.9, 134.6, 133.7, 129.4, 128.8, 128.7, 126.4, 125.1, 123.7, 122.7, 118.4, 66.2, 62.8, 39.1, 37.1, 23.9, 13.9; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{21}ClNO_5$ [M + H]$^+$ 414.1103, found 414.1098; HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 220 nm) R_t = 60.49 (major, major diastereomer), 73.07 (minor, major diastereomer), and 104.34 min (major, minor diastereomer).

*(R)-Ethyl 4-((S)-1-Acetyl-3-oxoindolin-2-yl)-4-(2,4-dichlorophenyl)-2-oxobutanoate (**3ah**):* Pale yellow oil, 86 mg, 96% yield, $[\alpha]_D^{25}$ −192.1 (*c* 3.40, CH_2Cl_2), >19/1 dr, >99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1 H), 7.42 (t, *J* = 7.6 Hz, 2 H), 7.11 (d, *J* = 2.0 Hz, 1 H), 6.98 (t, *J* = 7.6 Hz, 1 H), 6.93 (d, *J* = 8.8 Hz, 1 H), 6.84 (dd, *J* = 8.4, 2.0 Hz, 1 H), 4.69 (br s, 1 H), 4.61 (br s, 1 H), 4.35 (br s, 1 H), 4.33 (q, *J* = 6.8 Hz, 2 H), 3.28 (br s, 1 H), 2.62(s, 3 H), 1.36 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 198.3, 192.6, 168.9, 160.1, 153.4, 137.2, 135.3, 133.8, 132.5, 129.6, 129.2, 126.8, 124.9, 124.0, 122.8, 118.4, 66.1, 62.8, 39.1, 36.7, 23.9, 13.9; HRMS (ESI) *m*/*z* calcd

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for $C_{22}H_{20}Cl_2NO_5$ $[M + H]^+$ 448.0713, found 448.0713; HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 220 nm) R_t = 46.27 (major, major diastereomer), 57.40 (minor, minor diastereomer), 64.07 (major, minor diastereomer), and 69.82 min (minor, major diastereomer).

*(R)-Ethyl 4-((S)-1-Acetyl-3-oxoindolin-2-yl)-4-(4-bromophenyl)-2-oxobutanoate (**3ai**):* White solid, 91 mg, 99% yield, mp 95−98 °C, $[\alpha]_D^{25}$ −91.7 (*c* 3.00, CH_2Cl_2), >19/1 dr, >99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1 H), 7.41 (d, *J* = 7.6 Hz, 1 H), 7.39 (d, *J* = 7.6 Hz, 1 H), 7.09 (d, *J* = 8.4 Hz, 2 H), 6.97 (t, *J* = 7.6 Hz, 1 H), 6.81 (d, *J* = 8.4 Hz, 2 H), 4.56 (br s, 1 H), 4.36 (br s, 1 H), 4.33 (q, *J* = 6.8 Hz, 2 H), 3.97 (br s, 1 H), 3.37 (br s, 1 H), 2.60 (s, 3 H), 1.36 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 197.9, 192.9, 168.5, 160.2, 153.2, 137.1, 134.5, 131.0, 129.8, 124.9, 124.0, 122.8, 121.6, 118.2, 65.9, 62.8, 41.3, 38.6, 24.0, 13.9; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{21}BrNO_5$ $[M + H]^+$ 458.0598, found 458.0592; HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 220 nm) R_t = 91.02 (major, major diastereomer), 130.47 (minor, major diastereomer), 142.56 (major, minor diastereomer), and 163.54 min (minor, minor diastereomer).

*(R)-Ethyl 4-((S)-1-Acetyl-3-oxoindolin-2-yl)-4-(3-bromophenyl)-2-oxobutanoate (**3aj**):* White solid, 87 mg, 95% yield, mp 99−101 °C, $[\alpha]_D^{25}$ −103.4 (*c* 2.40, CH_2Cl_2), >19/1 dr, >99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1 H), 7.40 (t, *J* = 7.6 Hz, 2 H), 7.08 (s, 2 H), 6.97 (t, *J* = 7.2 Hz, 1 H), 6.82−6.88 (m, 2 H), 4.56 (br s, 1 H), 4.36 (br s, 1 H), 4.35 (q, *J* = 6.8 Hz, 2 H), 3.96 (br s, 1 H), 3.37 (br s, 1 H), 2.61 (s, 3 H), 1.38 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 197.8, 192.9, 168.4, 160.1, 153.2, 137.6, 136.9, 131.1, 130.7, 129.4, 126.9, 125.1, 124.0, 122.7, 121.9, 118.2, 65.9, 62.8, 41.6, 38.4, 23.9, 13.9; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{21}BrNO_5$ $[M + H]^+$ 458.0598, found 458.0588; HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 220 nm) R_t = 67.53 (major, major diastereomer), 73.08 (minor, major diastereomer), and 84.03 min (major, minor diastereomer).

*(R)-Ethyl 4-((S)-1-Acetyl-3-oxoindolin-2-yl)-4-(4-methoxyphenyl)-2-oxobutanoate (**3ak**):* Pale yellow oil, 81 mg, 99% yield, $[\alpha]_D^{25}$ −132.0 (*c* 0.35, $CHCl_3$), >19/1, >99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (br s, 1 H), 7.34−7.38 (m, 2 H), 6.93−6.95 (m, 1 H), 6.84 (d, *J* = 7.2 Hz, 2 H), 6.48 (d, *J* = 7.6 Hz, 2 H), 4.53 (br s, 1 H), 4.33 (q, *J* = 6.0 Hz, 3 H), 3.93 (br s, 1 H), 3.56 (s, 3 H), 3.36 (br s, 1 H), 2.61 (s, 3 H), 1.36 (t, *J* = 6.0 Hz, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 198.3, 193.4, 168.7, 160.3, 158.8, 153.3, 136.8, 129.2, 127.3, 125.1, 123.8, 122.7, 118.2, 113.3, 66.2, 62.7, 55.0, 41.1, 38.9, 23.9, 13.9; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{24}NO_6$ $[M + H]^+$ 410.1598, found 410.1603; HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 220 nm) R_t = 103.23 (major) and 109.91 min (minor).

*(R)-Ethyl 4-((S)-1-Acetyl-3-oxoindolin-2-yl)-4-(3-methoxyphenyl)-2-oxobutanoate (**3al**):* Pale yellow oil, 81 mg, 99% yield, $[\alpha]_D^{25}$ −65.0 (*c* 0.50, CH_2Cl_2), >19/1, 98% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (br s, 1 H), 7.40 (br s, 1 H), 7.36 (t, *J* = 8.0 Hz, 1 H), 6.94 (t, *J* = 7.6 Hz, 1 H), 6.87 (t, *J* = 7.6 Hz, 1 H), 6.51 (d, *J* = 8.4 Hz, 1 H), 6.48 (d, *J* = 8.4 Hz, 1 H), 6.44 (s, 1 H), 4.56 (br s, 1 H), 4.33 (q, *J* = 6.8 Hz, 3 H), 3.97 (br s, 1 H), 3.56 (s, 3 H), 3.38 (br s, 1 H), 2.60 (s, 3 H), 1.36 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 198.1, 193.2, 168.6, 160.2, 158.9, 153.3, 136.7, 128.9, 125.1, 123.8, 122.7, 120.6, 118.2, 118.1, 116.6, 113.5, 66.0, 62.7, 55.0, 42.0, 38.7, 23.9, 13.9; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{24}NO_6$ $[M + H]^+$ 410.1598, found 410.1599; HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 220 nm) R_t = 22.32 (major) and 25.36 min (minor).

*(R)-Ethyl 4-((S)-1-Acetyl-3-oxoindolin-2-yl)-2-oxo-4-p-tolylbutanoate (**3am**):* Pale yellow oil, 71 mg, 90% yield, $[\alpha]_D^{25}$ −127.2 (*c* 3.25, CH_2Cl_2), >19/1, >99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (br s, 1 H), 7.34−7.39 (m, 2 H), 6.94 (t, *J* = 7.6 Hz, 1 H), 6.81 (d, *J* = 8.0 Hz, 2 H), 6.76 (d, *J* = 7.6 Hz, 2 H), 4.55 (br s, 1 H), 4.35 (q, *J* = 6.8 Hz, 2 H), 4.29 (br s, 1 H), 3.96 (br s, 1 H), 3.34 (d, *J* = 16.8 Hz, 1 H), 2.61(s, 3 H), 2.06 (s, 3 H), 1.37 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 198.2, 193.4, 168.6, 160.3, 153.3, 137.2, 136.7, 132.2, 128.6, 128.0, 125.1, 123.7, 122.7, 118.2, 66.2, 62.7, 41.5, 38.9, 23.9, 20.7, 13.9; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{24}NO_5$ $[M + H]^+$ 394.1649, found 394.1648; HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 220 nm) R_t = 34.26 (major, major diastereomer), 43.03 (minor, major diastereomer), 48.97 (major, minor diastereomer), and 60.95 min (minor, minor diastereomer).

*(S)-Ethyl 4-((S)-1-Acetyl-3-oxoindolin-2-yl)-4-(furan-2-yl)-2-oxobutanoate (**3an**):* Redish-brown oil, 70 mg, 95% yield, $[\alpha]_D^{25}$ −97.2 (*c* 3.25, CH_2Cl_2), >19/1, >99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (br s, 1 H), 7.51 (d, *J* = 8.8 Hz, 1 H), 7.47 (d, *J* = 7.6 Hz, 1 H), 7.04 (t, *J* = 7.6 Hz, 1 H), 6.93 (s, 1 H), 5.93 (d, *J* = 1.2 Hz, 1 H), 5.92 (s, 1 H), 4.55 (br s, 1 H), 4.35 (q, *J* = 7.2 Hz, 2 H), 4.15 (br s, 2 H), 3.39 (br s, 1 H), 2.53 (s, 3 H), 1.38 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 197.5, 192.6, 168.4, 160.1, 153.2, 149.9, 141.9, 136.8, 124.6, 123.8, 123.0, 118.3, 109.8, 108.2, 65.1, 62.8, 37.5, 36.0, 23.8, 13.9; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{20}NO_6$ $[M + H]^+$ 370.1285, found 370.1281; HPLC analysis (Chiralpak AS-H column, hexane/2-propanol = 85:15, flow rate = 1.0 mL/min, wavelength = 220 nm) R_t = 25.99 (minor, major diastereomer), 40.62 (minor, major diastereomer), and 47.14 min (major, minor diastereomer).

*(S)-Ethyl 4-((S)-1-Acetyl-3-oxoindolin-2-yl)-2-oxo-4-(thiophen-2-yl)butanoate (**3ao**):* Pale yellow oil, 73 mg, 95% yield, $[\alpha]_D^{25}$ −168.5 (*c* 3.25, CH_2Cl_2), >19/1, 97% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (br s, 1 H), 7.44 (t, *J* = 7.2 Hz, 2 H), 6.99 (t, *J* = 7.2 Hz, 1 H), 6.86 (d, *J* = 4.8 Hz, 1 H), 6.63 (s, 1 H), 6.59 (d, *J* = 4.4 Hz, 1 H), 4.57 (br s, 1 H), 4.35 (q, *J* = 6.8 Hz, 2 H), 4.33 (br s, 2 H), 3.47 (br s, 1 H), 2.59 (s, 3 H), 1.38 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 197.8, 192.8, 168.5, 160.1, 153.6, 137.4, 136.8, 126.3, 125.0, 124.5, 123.8, 123.0, 118.4, 65.8, 62.8, 39.9, 37.4, 24.0, 13.9; HRMS (ESI) *m*/*z* calcd for $C_{20}H_{20}NO_5S$ $[M + H]^+$ 386.1057, found 386.1063; HPLC analysis (Chiralpak AS-H column, hexane/2-propanol = 80:20, flow rate = 1.0 mL/min, wavelength = 220 nm) R_t = 49.45 (minor) and 70.93 min (major).

*(R)-Ethyl 4-((S)-1-Acetyl-5-fluoro-3-oxoindolin-2-yl)-2-oxo-4-phenylbutanoate (**3ba**):* Pale yellow oil, 69 mg, 87% yield, $[\alpha]_D^{25}$ −143.6 (*c* 3.40, CH_2Cl_2), >19/1, 98% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (br s, 1 H), 6.90−7.05 (m, 7 H), 4.59 (br s, 1 H), 4.33 (q, *J* = 6.8 Hz, 3 H), 3.95 (br s, 1 H), 3.34 (d, *J* = 19.2 Hz, 1 H), 2.63 (s, 3 H), 1.36 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 197.3, 193.3, 168.4, 160.2, 158.6 (d, *J* = 246.6 Hz), 149.7, 135.0, 128.1, 128.0, 127.8, 126.3, 123.9 (d, *J* = 24.0 Hz), 119.8, 108.0 (d, *J* = 23.1 Hz), 66.6, 62.7, 41.9, 38.4, 23.6, 13.9; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{21}FNO_5$ $[M + H]^+$ 398.1398, found 398.1396; HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 220 nm) R_t = 25.74 (major) and 38.99 min (minor).

*(R)-Ethyl 4-((S)-1-Acetyl-4-chloro-3-oxoindolin-2-yl)-2-oxo-4-phenylbutanoate (**3ca**):* Pale yellow oil, 60 mg, 73% yield, $[\alpha]_D^{25}$ −192.3 (*c* 3.25, CH_2Cl_2), >19/1, >99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (br s, 1 H), 7.22 (t, *J* = 8.0 Hz, 1 H), 6.94−7.03 (m, 5 H), 6.84 (d, *J* = 8.0 Hz, 1 H), 4.58 (br s, 1 H), 4.36 (q, *J* = 6.8 Hz, 3 H), 3.98 (br s, 1 H), 3.37 (d, *J* = 19.2 Hz, 1 H), 2.65 (s, 3 H), 1.39 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 195.4, 193.3, 168.6, 160.2, 154.5, 136.7, 135.1, 130.7, 128.2, 128.0, 127.9, 124.9, 121.6, 116.2, 66.4, 62.8, 42.2, 38.5, 24.0, 13.9; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{21}ClNO_5$ $[M + H]^+$ 414.1103, found 414.1103; HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 95:5, flow rate = 1.0 mL/min, wavelength = 220 nm) R_t = 51.09 (minor) and 56.76 min (major).

*(R)-Ethyl 4-((S)-1-Acetyl-5-chloro-3-oxoindolin-2-yl)-2-oxo-4-phenylbutanoate (**3da**):* Pale yellow oil, 56 mg, 68% yield, $[\alpha]_D^{25}$ −192.3 (*c* 3.25, CH_2Cl_2), >19/1, 98% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (br s, 1 H), 7.21−7.28 (m, 2 H), 6.95 (br s, 3 H), 6.87 (br s, 2 H), 4.56 (br s, 1 H), 4.31 (q, *J* = 6.8 Hz, 3 H), 3.93 (br s, 1 H), 3.32 (d, *J* = 19.2 Hz, 1 H), 2.60 (s, 3 H), 1.34 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 197.0, 193.4, 168.6, 160.2, 151.7, 136.4, 135.0, 129.4, 128.2, 128.1, 127.9, 126.3, 122.1, 119.5, 66.5, 62.9, 42.0, 38.5, 23.8, 13.9; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{21}ClNO_5$ $[M + H]^+$ 414.1103, found 414.1096; HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 220 nm) R_t = 26.23 (major, major diastereomer), 32.95 (minor, minor

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diastereomer), 35.04 (major, minor diastereomer), and 38.59 min (minor, major diastereomer).

*(R)-Ethyl 4-((S)-1-Acetyl-6-chloro-3-oxoindolin-2-yl)-2-oxo-4-phenylbutanoate (**3ea**):* White solid, 73 mg, 88% yield, mp 140−143 °C, $[\alpha]_D^{25}$ −138.8 (*c* 2.75, CH_2Cl_2), >19/1, 98% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (br s, 1 H), 7.29 (d, *J* = 8.0 Hz, 1 H), 6.88−6.99 (m, 6 H), 4.59 (br s, 1 H), 4.35 (q, *J* = 6.8 Hz, 3 H), 3.98 (br s, 1 H), 3.37 (d, *J* = 19.2 Hz, 1 H), 2.64 (s, 3 H), 1.38 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 196.7, 193.3, 168.7, 160.2, 153.6, 143.1, 135.0, 128.2, 128.1, 127.9, 124.8, 124.4, 123.5, 118.3, 66.4, 62.8, 41.9, 38.5, 23.9, 13.9; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{21}ClNO_5$ $[M + H]^+$ 414.1103, found 414.1104; HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 220 nm) R_t = 22.65 (minor, major diastereomer), 31.295 (major, major diastereomer), 38.88 (major, minor diastereomer), and 45.09 min (minor, minor diastereomer).

*(R)-Ethyl 4-((S)-1-Acetyl-5-bromo-3-oxoindolin-2-yl)-2-oxo-4-phenylbutanoate (**3fa**):* Pale yellow oil, 51 mg, 56% yield, $[\alpha]_D^{25}$ −171.8 (*c* 2.25, CH_2Cl_2), >19/1, >99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (br s, 1 H), 7.50 (s, 1 H), 7.43 (d, *J* = 8.8 Hz, 1 H), 6.93−7.05 (m, 5 H), 4.61 (br s, 1 H), 4.37 (q, *J* = 6.8 Hz, 3 H), 3.99 (br s, 1 H), 3.38 (d, *J* = 19.2 Hz, 1 H), 2.65 (s, 3 H), 1.39 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 196.8, 193.4, 168.7, 160.2, 152.1, 139.2, 134.9, 128.2, 128.0, 127.8, 126.6, 125.3, 119.8, 116.8, 66.4, 62.9, 42.0, 38.6, 23.9, 14.0; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{21}BrNO_5$ $[M + H]^+$ 458.0598, found 458.0591; HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 220 nm) R_t = 25.85 (major) and 34.84 min (minor).

*(R)-Ethyl 4-((S)-1-Acetyl-5-methyl-3-oxoindolin-2-yl)-2-oxo-4-phenylbutanoate (**3ga**):* Pale yellow oil, 72 mg, 91% yield, $[\alpha]_D^{25}$ −162.4 (*c* 1.00, CH_2Cl_2), >19/1, 94% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (br s, 1 H), 7.16 (d, *J* = 8.0 Hz, 2 H), 6.91−6.96 (m, 5 H), 4.53 (br s, 1 H), 4.41 (br s, 1 H), 4.34 (q, *J* = 6.8 Hz, 2 H), 3.97 (br s, 1 H), 3.36 (d, *J* = 19.2 Hz, 1 H), 2.61 (s, 3 H), 2.18 (s, 3 H), 1.37 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 198.1, 193.4, 168.5, 160.2, 151.6, 137.9, 135.3, 133.6, 128.2, 127.9, 127.6, 125.1, 122.2, 118.0, 66.2, 62.7, 41.8, 38.7, 23.8, 20.5, 13.9; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{24}NO_5$ $[M + H]^+$ 394.1649, found 394.1655; HPLC analysis (Chiralpak AD-H column, hexane/2-propanol = 90:10, flow rate = 1.0 mL/min, wavelength = 220 nm) R_t = 28.71 (major) and 35.09 min (minor).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02070.

X-ray data of compound **3ea** (CIF)

Copies of NMR and HRMS spectra and HPLC analysis (PDF)

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Notes

The authors declare no competing financial interest.

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(19) CCDC-1487973 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.

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