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Enantioselective Organocatalyzed Vinylogous Michael Reactions of 3-Alkylidene Oxindoles with Enals

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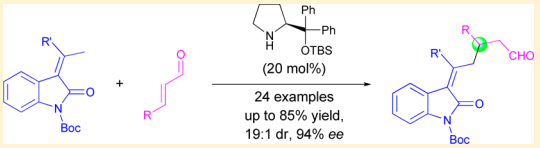
Supporting Information

ABSTRACT: An efficient asymmetric vinylogous Michael addition of 3-alkylidene oxindoles and enals has been achieved using a chiral TBS-protected diphenylprolinol catalyst. The γ-substituted alkylidene oxindoles obtained bear a chiral tertiary center and are afforded in moderate to good yields and good to excellent enantioselectivities.

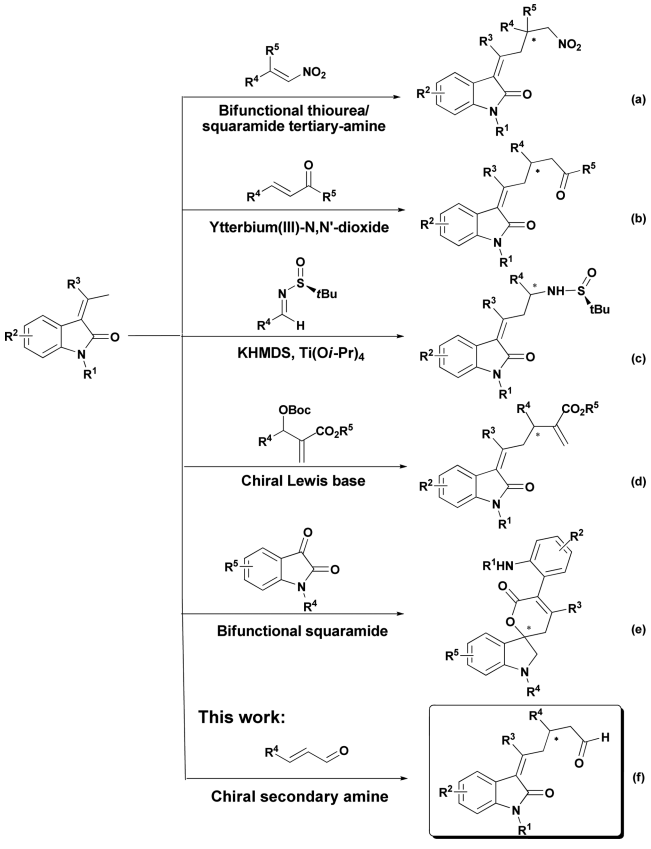


INTRODUCTION

Since the first chiral imidazolidinone catalyzed Diels–Alder reaction reported by MacMillan and co-workers in 2000,[1] asymmetric iminium activation has become a key and powerful strategy in organocatalysis. Many important asymmetric reactions, such as cycloadditions, conjugate additions, and cascade reactions, have been realized by imine catalysis in the last 16 years.[2] Among the aforementioned reactions, the asymmetric conjugate addition of nucleophiles to α,β-unsaturated aldehydes, generally catalyzed by the MacMillan catalysts[3] or the O-protected diaryl-substituted prolinol catalysts developed by Jørgensen and Hayashi,[4] has been established as a general strategy for asymmetric transformation of enals and become the major area of interest in the iminium ion induced process.[5]

Vinylogous reactions, affording access to enriched building blocks, have applications in target-oriented synthesis toward bioactive molecules.[6] Due to the success of asymmetric vinylogous Mukaiyama additions,[7] the more practical direct vinylogous Michael addition has become popular over the past few years. Nucleophilic substrates, such as unsaturated butyrolactones,[8] lactams[9] and α,α-dicyanoalkenes,[10] have been frequently used in a versatile and attractive vinylogous procedure. However, other types of vinylogous nucleophiles, in particular, substrates with a natural product skeleton, are still rare. In 2012, Casiraghi reported a bifunctional cinchona alkaloid type thiourea catalyzed direct vinylogous Michael addition using 3-alkylidene oxindoles as the nucleophile.[11] Although several cases employing the 3-alkylidene oxindoles as nucleophiles in the vinylogous reactions have been described, the acceptors have been limited to nitroalkenes,[12a,b] enones,[12c] imines,[12d] MBH carbonate,[13] and isatins[14] (Scheme 1a–e). Furthermore, reaction types have been confined to vinylogous Michael additions, Mannich reactions, AAA reactions, and aldol cyclization cascade reactions.[11−13] Since the 3-alkylidene oxindoles are core moieties found in many bioactive natural and unnatural compounds,[15] the development of novel catalytic strategies toward efficient construction of chiral γ-substituted alkylidene oxindoles is both highly desirable and underexplored.

Scheme 1. Strategies for Synthetic Approaches to Chiral γ-Substituted Alkylidene Oxindoles



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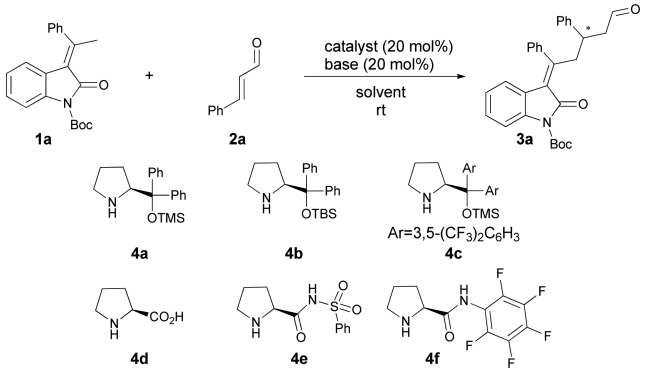
Herein, we report the first covalently catalytic pathway accomplishing the enantioselective direct vinylogous Michael addition of alkylidene oxindoles to α,β-unsaturated aldehydes by a chiral secondary amine catalyst (Scheme 1f).

RESULTS AND DISCUSSION

Initially, we started our investigation by testing the mode reaction of the 3-alkylidene oxindole **1a** and the cinnamaldehyde **2a** catalyzed by **4a** in CH_2Cl_2 at room temperature. After the reaction mixture was stirred for 24 h, no desired product was isolated (Table 1, entry 1). Due to the low acidity of γ-CH of 3-alkylidene oxindoles, increasing the equivalence of the base (20 mol %) proved necessary to promote the dienolate formation and afford the corresponding vinylogous Michael product **3a** in 9% yield with 47% ee (Table 1, entry 2). A slightly higher yield and ee value were obtained in the presence of 3.0 equiv of water (Table 1, entry 3). Then a number of chiral secondary amine catalysts were examined. Catalyst **4b** afforded the desired product **3a** with encouraging conversion and good enantioselectivity (Table 1, entry 4). Catalyst **4c** gave a similar yield but lower ee value (Table 1, entry 5). L-Proline (**4d**) and proline sulfonamide (**4f**) exhibited almost no catalytic activity; TLC showed that **1a** converted to other byproducts (Table 1, entries 6 and 8). Catalyst **4e** gave almost racemic product (Table 1, entry 7). Interestingly, replacement of water with brine increased both the yield and enantioselectivity (Table 1, entry 9). It is postulated that these electrolyte-rich aqueous solutions (including metal cations) provided a beneficial environment for the negatively charged oxygen atom in the vinylogous dienolate species.

Screening indicated that CH_2Cl_2 was the optimal solvent (Table 1, entries 9–16). Furthermore, Et_3N gave the best results after extensive screening of bases (Table 1, entries 17–23). The enantioselectivity of **3a** improved to 90% when the reaction was performed at 0 °C (Table 1, entry 24).

Table 1. Optimization of Conditions[a]



entry	catalyst	solvent/additive	base	yield[b] (%)	ee[c] (%)
1	**4a**	CH_2Cl_2/none			
2	**4a**	CH_2Cl_2/none	Et_3N	9	47
3[d]	**4a**	CH_2Cl_2/H_2O	Et_3N	17	54
4[d]	**4b**	CH_2Cl_2/H_2O	Et_3N	43	73
5[d]	**4c**	CH_2Cl_2/H_2O	Et_3N	43	22
6[d]	**4d**	CH_2Cl_2/H_2O	Et_3N	trace	
7[d]	**4e**	CH_2Cl_2/H_2O	Et_3N	69	3
8[d]	**4f**	CH_2Cl_2/H_2O	Et_3N	trace	
9[e]	**4b**	CH_2Cl_2/brine	Et_3N	86	88
10[e]	**4b**	DCE/brine	Et_3N	86	82
11[e]	**4b**	THF/brine	Et_3N	77	77
12[e]	**4b**	toluene/brine	Et_3N	34	92
13[e]	**4b**	$CHCl_3$/brine	Et_3N	69	88
14[e]	**4b**	DMF/brine	Et_3N	trace	
15[e]	**4b**	DMSO/brine	Et_3N	trace	
16[e]	**4b**	CH_3CN/brine	Et_3N	34	29
17[e,f]	**4b**	CH_2Cl_2/brine	DIPEA	86	81
18[e,f]	**4b**	CH_2Cl_2/brine	DBU	43	68
19[e,f]	**4b**	CH_2Cl_2/brine	DMAP	47	75
20[e,f]	**4b**	CH_2Cl_2/brine	DBACO	56	73
21[e,f]	**4b**	CH_2Cl_2/brine	K_2CO_3	73	86
22[e,f]	**4b**	CH_2Cl_2/brine	NaOAc	86	75
23[e,f]	**4b**	CH_2Cl_2/brine	piperdine	30	26
24[e,g]	**4b**	CH_2Cl_2/brine	Et_3N	75	90

[a]Unless specified otherwise, reactions were performed on a 0.05 mmol scale in solvent (0.25 mL) using **1a** (1.0 equiv) and **2a** (3.0 equiv) at room temperature for 48 h. A 19/1 *E*/*Z* ratio was observed in each case. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]0.15 mmol of water was used. [e]0.15 mmol of brine was used. [f]The mixture was stirred for 60 h. [g]The reaction was performed at 0 °C for 96 h.

With the optimized reaction conditions in hand, we then evaluated the scope of current asymmetric vinylogous Michael additions using the 3-alkylidene oxindole **1a** with a broad range of α,β-unsaturated aldehydes **2a–l**. As shown in Table 2, when electron-withdrawing or electron-donating groups at the ortho or para position of the aryl group R^2 of the substrate **2** were employed, the reactions proceeded smoothly to give the corresponding vinylogous Michael products **3a–j** in good yields and enantioselectivities (Table 2, entries 1–10, 68–78% yields, up to >19/1 *E*/*Z* ratio and 85–94% ee). Notably, substrates with hetero-ring and fused-ring type enals also participated in the reaction to afford the corresponding vinylogous Michael products in good yields and ee values (Table 2, entries 11 and 12). Further exploration of the reaction scope focused on varying the R^1 substituents on the aryl moiety of **1**. As shown in Table 2, the electronic nature and relative position of the substituents had little influence on neither the yields nor the enantioselectivities (Table 2, entries 13–18, products **3m-3r**, 68–85% yield, 19/1 *E*/*Z* ratio and 82–93% ee). However, for the reaction of the substrate **1h**, which has a greater steric hindrance, only a 16% yield was obtained (Table 2, entry 19).

To probe the efficiency of current studied asymmetric vinylogous Michael addition in preparative synthesis, a large-scale reaction of **1a** and **2a** was investigated under the optimal conditions. To our delight, the desired product **3a** was obtained in retentive yield with a slight loss of enantioselectivity (Table 2, entry 1, result given in parentheses).

In order to expand this vinylogous Michael strategy, isopropylidene oxindole **1i** was investigated as the nucleophile to afford the corresponding product **3t** in 76% yield and 91% ee (Scheme 2). In addition, the direct vinylogous Michael reaction of isopropylidene benzofuran-2-one **1j** delivers the vinylogous Michael product **5** in 72% yield and 90% ee (Scheme 2).

We next investigated the challenging regio- and stereoselectivity effects when a vinylogous Michael addition of 3-alkylidene oxindoles and 2,4-dienals was employed.[16] Gratifyingly, only relevant 1,6-addition products with quantitatively perfect δ selectivity were observed (Scheme 3). Although the yields of **7a–c** were modest (18–35% yields), the enantioselectivities of vinylogous 1,6-addition products were good (86–87% ee).

Some transformations of the Michael product were attempted. As outlined in Scheme 4, the aldehyde moiety in

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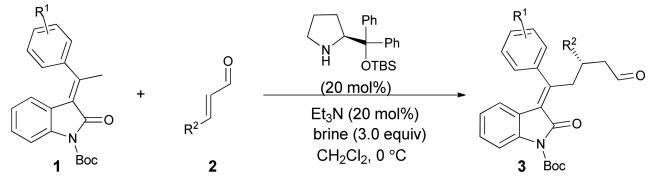
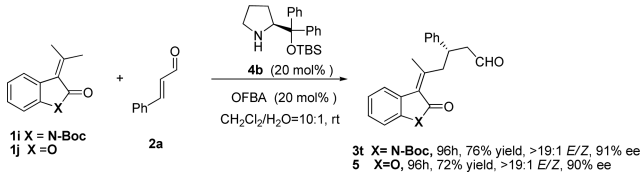
Table 2. Substrate Scope of the Reaction[a]



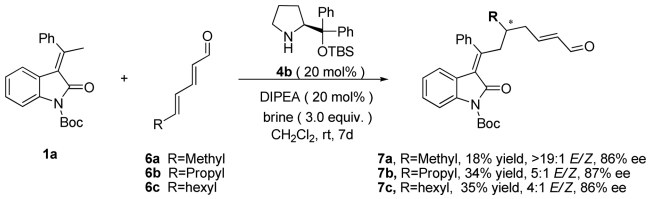
entry	R^1	R^2	yield[b] (%)	E/Z[c]	ee[d] (%)
1	H (**1a**)	C_6H_5 (**2a**)	75 (76) (**3a**)	>19/1	90 (88)[e]
2	H (**1a**)	4-ClC_6H_4 (**2b**)	78 (**3b**)	>19/1	94
3	H (**1a**)	4-FC_6H_4 (**2c**)	70 (**3c**)	>19/1	88
4	H (**1a**)	4-$NO_2C_6H_4$ (**2d**)	70 (**3d**)	>19/1	91
5	H (**1a**)	4-BrC_6H_4 (**2e**)	73 (**3e**)	>19/1	92
6	H (**1a**)	4-$CF_3C_6H_4$ (**2f**)	77 (**3f**)	>19/1	94
7	H (**1a**)	2-BrC_6H_4 (**2g**)	72 (**3g**)	>19/1	94
8	H (**1a**)	4-MeC_6H_4 (**2h**)	73 (**3h**)	>19/1	92
9	H (**1a**)	4-$OMeC_6H_4$ (**2i**)	68 (**3i**)	7/1	84
10	H (**1a**)	2-$OMeC_6H_4$ (**2j**)	70 (**3j**)	>19/1	87
11	H (**1a**)	2-furyl (**2k**)	68 (**3k**)	>19/1	84
12	H (**1a**)	1-naphthyl (**2l**)	81 (**3l**)	>19/1	89
13	3-Cl (**1b**)	C_6H_5 (**2a**)	74 (**3m**)	>19/1	78
14	4-Cl (**1c**)	C_6H_5 (**2a**)	70 (**3n**)	>19/1	88
15	3-Br (**1d**)	C_6H_5 (**2a**)	70 (**3o**)	>19/1	82
16	4-Br (**1e**)	C_6H_5 (**2a**)	73 (**3p**)	>19/1	86
17	4-Me (**1f**)	C_6H_5 (**2a**)	85 (**3q**)	>19/1	92
18	4-OMe (**1g**)	C_6H_5 (**2a**)	68 (**3r**)	>19/1	93
19	2-OMe (**1h**)	C_6H_5 (**2a**)	16 (**3s**)	>19/1	92

[a]Unless otherwise noted, reaction conditions were **1a** (0.1 mmol), **2a** (0.3 mmol) at 0 °C for 96−168 h. [b]Isolated yield. [c]Determined by ^{1}H NMR analysis of crude products. [d]Determined by chiral HPLC analysis. [e]1.0 mmol scale.

Scheme 2. Vinylogous Michael Reaction of Isopropylidene Oxindole and Isopropylidene Benzofuran-2-one with Enal



Scheme 3. Vinylogous Michael Additions of 1a to 2,4-Dienals

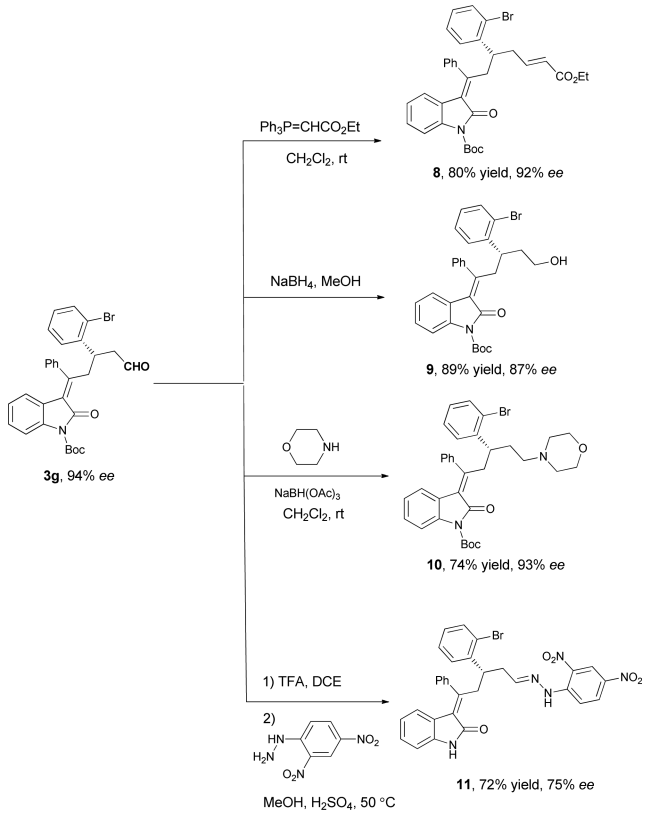


3g can be subjected to a Wittig reagent, subsequently delivering the product **8**. Reduction of **3g** afforded primary alchohol **9**. Reductive amination of **3g** furnished the desired product **10** in quantitative yield with a retentive ee value. Finally, phenylhydrazonation of **3g** gave the corresponding product **11**;[17] unfortunately, a slight loss of enantioselectivity was observed.

CONCLUSIONS

In conclusion, we have developed an asymmetric Michael addition of 3-alkylidene oxindoles with enals using a chiral TBS-protected diphenylprolinol catalyst. The vinylogous Michael strategy was quite successful and can tolerate a wide

Scheme 4. Transformations of the Vinylogous Michael Product



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variety of substituted 3-alkylidene oxindoles and enal substrates. As a result, a series of chiral γ-substituted alkylidene oxindole type compounds were obtained in good yields with excellent *E*/*Z* ratios and very good enantioselectivities (up to 94% ee and >19/1 *E*/*Z* ratios). Isopropylidene oxindole and isopropylidene benzofuran-2-one served as potential Michael donors, smoothly participating in the vinylogous Michael addition process; furthermore, the achievement of 1,6-addition was also established.

EXPERIMENTAL SECTION

General Information. Commercial reagents were used as received, unless otherwise stated. ^{1}H and ^{13}C NMR were recorded on a 400 MHz spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. The following abbreviations were used to designate chemical shift mutiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. All first-order splitting patterns were assigned on the basis of the appearance of the multiplet. Splitting patterns that could not be easily interpreted are designated as multiplets (m). Mass spectra were obtained using an electrospray ionization (ESI-TOF) or electron impact ionization (EI-TOF) mass spectrometer. In each case, the enantiomeric ratio was determined by chiral HPLC analysis on a Chiralcel column in comparison with authentic racemates. Columns for flash chromatography (FC) contained 200−300 mesh silica gel. Columns were packed as slurries of silica gel in petroleum ether and equilibrated solution using the appropriate solvent system. The benzofuranone **1i** and 3-alkylidene oxindole **1j** were synthesized according to literature procedures.[17] 3-Alkylidene oxindoles **1a−h** were prepared according to literature procedures.[18a]

General Procedure for Catalytic Direct Vinylogous Michael Addition. A mixture of 3-alkylidene oxindole **1** (0.1 mmol), α,β-unsaturated aldehyde **2** (0.3 mmol), catalyst **4b** (0.02 mmol), Et_3N (0.02 mmol), and brine (0.3 mmol) in CH_2Cl_2 (0.5 mL) was stirred at 0 °C until consumption of **1**, which was monitored by TLC analysis. Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate) afforded the product.

Direct Vinylogous Michael Reaction of Isopropylidene Oxindole and Isopropylidene Benzofuran-2-one with Enal. A mixture of **1h** (0.1 mmol) or **1i** (0.1 mmol), α,β-unsaturated aldehyde **2a** (0.3 mmol), catalyst **4b** (0.02 mmol), and OFBA (0.02 mmol) in CH_2Cl_2/H_2O (0.5/0.05 mL) was stirred at room temperature until consumption of **1h** or **1i**, which was monitored by TLC analysis. Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate) gave the product.

Direct Vinylogous Michael Additions of 1a with 2,4-Dienals. A mixture of 3-alkylidene oxindole **1** (0.3 mmol), dienal **6a−c** (0.9 mmol), catalyst **4b** (0.06 mmol), DIPEA (0.06 mmol), and brine (0.9 mmol) in CH_2Cl_2 (1.5 mL) was stirred at room temperature until consumption of **1**, which was monitored by TLC analysis. Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate) afforded the product.

Procedure for the Synthesis of 8. To a stirred solution of **3g** (0.11 mmol) in CH_2Cl_2 was added Ph_3PCHCO_2Et (0.12 mmol). The mixture was stirred at room temperature until the consumption of **3g** (monitored by TLC analysis). Then DCM was removed in vacuo and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate) to give pure **8**.

Procedure for the Synthesis of 9. To a solution of **3g** (0.1 mmol) in MeOH (5 mL) was added $NaBH_4$ (0.15 mmol) at 0 °C and the mixture was stirred at room temperature for 1 h (consumption of **3g** was ananlyzed by TLC). Acetic acid (30 μL) was added to the mixture, and the solvent was removed in vacuo. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate) to give pure **9**.[19]

Procedure for the Synthesis of 10. To a solution of **3g** (0.13 mmol) in dry DCE (3.0 mL) were added morpholine (0.13 mmol) and $NaBH(OAc)_3$ (0.52 mmol) under an argon atmosphere. The mixture was stirred at room temperature overnight. After the solvent was removed, the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate) to give pure **10**.

Procedure for the Synthesis of 11. To a stirred solution of **3g** (0.17 mmol) in DCE (4.0 mL) was added TFA (3.0 mmol). The reaction mixture was stirred at room temperature until the consumption of **3g** (monitored by TLC analysis). Then DCE was removed in vacuo and the residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate) to give the NH-free product as a yellow oil. MeOH suspensions (2.5 mL) of 1-(2,4-dinitrophenyl)hydrazine (0.11 mmol) and concentrated sulfuric acid (28 μL) were stirred at 50 °C. After the hydrazine dissolved, a MeOH solution (2.5 mL) of NH-free product (0.15 mmol) was added to the hydrazine and the resulting reaction mixture was stirred at 50 °C for an additional 30 min. The reaction mixture was concentrated to one-fourth of its original volume under vacuum and diluted with water (5 mL). The precipitates were separated by filtration and washed with 3% aqueous $NaHCO_3$ (3 × 1 mL) and water (3 × 1 mL). Products were recrystallized from EtOH to give pure **11**.[20] All of the products were fully characterized, and their characterization data are given below.

*(S,E)-tert-Butyl 2-Oxo-3-(5-oxo-1,3-diphenylpentylidene)indoline-1-carboxylate (**3a**).* Purified by flash chromatography (petroleum ether/EtOAc 20/1) to afford a pale yellow oil: 35.0 mg, 75% yield; 90% ee, HPLC analysis (Chiralpak IC *i*-PrOH/*n*-hexane 1/19, 1.0 mL/min, λ 210 nm), *t*(major) = 23.51 min, *t*(minor) = 21.32 min; $[\alpha]^{25}_D$ −27.4 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.61 (t, *J* = 2.0 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.42 (dt, *J* = 13.2, 6.4 Hz, 3H), 7.28−7.10 (m, 6H), 7.04−6.96 (m, 2H), 6.68 (td, *J* = 7.7, 1.1 Hz, 1H), 6.07 (dd, *J* = 7.9, 1.2 Hz, 1H), 4.04 (dd, *J* = 12.5, 7.3 Hz, 1H), 3.54−3.35 (m, 2H), 3.00−2.75 (m, 2H), 1.70 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 201.9, 166.2, 157.9, 149.2, 142.9, 140.4, 138.2, 129.3, 129.2, 128.8, 128.7, 128.6, 127.8, 127.0, 126.8, 126.7, 124.2, 123.4, 123.0, 122.8, 114.3, 84.4, 49.7, 40.9, 38.7, 28.2; HRMS (ESI-TOF) calcd for $[C_{30}H_{29}NO_4 + H]^+$ 468.2169, found 468.2176.

*(S,E)-tert-Butyl 3-(3-(4-Chlorophenyl)-5-oxo-1-phenylpentylidene)-2-oxoindoline-1-carboxylate (**3b**).* Purified by flash chromatography (petroleum ether/EtOAc 20/1) to afford a pale yellow oil: 39.1 mg, 78% yield; 94% ee, HPLC analysis (Chiralpak IC *i*-PrOH/*n*-hexane 1/19, 1.0 mL/min, λ 210 nm), *t*(major) = 20.44 min, *t*(minor) = 18.78 min; $[\alpha]^{25}_D$ −32.2 (*c* = 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.60 (t, *J* = 1.7 Hz, 1H), 7.74−7.65 (m, 1H), 7.51−7.36 (m, 3H), 7.21−7.10 (m, 5H), 7.06−6.94 (m, 2H), 6.68 (td, *J* = 7.7, 1.1 Hz, 1H), 6.07 (dd, *J* = 8.0, 1.2 Hz, 1H), 3.88 (dd, *J* = 13.2, 7.5 Hz, 1H), 3.58 (dd, *J* = 13.1, 8.3 Hz, 1H), 3.37 (qd, *J* = 8.2, 6.0 Hz, 1H), 2.92−2.76 (m, 2H), 1.69 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 201.3, 166.2, 157.3, 149.1, 141.4, 140.2, 138.2, 132.5, 129.3, 129.3, 128.9, 128.8, 128.6, 126.9, 126.8, 124.3, 123.4, 122.9, 122.6, 114.4, 84.5, 49.8, 40.5, 38.0, 28.2; HRMS (ESI-TOF) calcd for $[C_{30}H_{28}ClNO_4 + Na]^+$ 524.1599, found 524.1592.

*(S,E)-tert-Butyl 3-(3-(4-Fluorophenyl)-5-oxo-1-phenylpentylidene)-2-oxoindoline-1-carboxylate (**3c**).* Purified by flash chromatography (petroleum ether/EtOAc 20/1) to afford a pale yellow oil: 33.9 mg, 70% yield; 88% ee, HPLC analysis (Chiralpak IC *i*-PrOH/*n*-hexane 1/19, 1.0 mL/min, λ 210 nm), *t*(major) = 18.15 min, *t*(minor) = 16.69 min; $[\alpha]^{25}_D$ −14.2 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.60 (t, *J* = 1.8 Hz, 1H), 7.74−7.66 (m, 1H), 7.48−7.37 (m, 3H), 7.19−7.09 (m, 3H), 7.00 (t, *J* = 6.0 Hz, 2H), 6.93−6.84 (m, 2H), 6.68 (td, *J* = 7.7, 1.1 Hz, 1H), 6.07 (dd, *J* = 7.9, 1.2 Hz, 1H), 3.90 (dd, *J* = 13.1, 7.4 Hz, 1H), 3.55 (dd, *J* = 13.0, 8.3 Hz, 1H), 3.40 (dd, *J* = 8.2, 5.7 Hz, 1H), 2.94−2.76 (m, 2H), 1.69 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 201.5, 166.2, 161.6 (d, $^1J_{C-F}$ = 244.7 Hz), 157.6, 149.1, 140.3, 138.5, 138.5, 138.2, 129.4, 129.3, 129.2, 128.9, 128.8, 127.0, 126.8, 124.2, 123.4, 122.9, 122.7, 115.4, 115.2, 114.4, 84.5, 50.0, 40.8, 37.9, 28.2; HRMS (ESI-TOF) calcd for $[C_{30}H_{28}FNO_4 + H]^+$ 486.2075, found 486.2077.

*(S,E)-tert-Butyl 3-(3-(4-Nitrophenyl)-5-oxo-1-phenylpentylidene)-2-oxoindoline-1-carboxylate (**3d**).* Purified by flash chromatography (petroleum ether/EtOAc 20/1) to afford a pale yellow oil: 35.8 mg, 70% yield; 91% ee, HPLC analysis (Chiralpak AS-H *i*-PrOH/*n*-Hexane =1:9, 1.0 mL/min, λ 210 nm), *t*(major) = 19.59 min, *t*(minor) = 22.45

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min; $[\alpha]^{25}_{D}$ −20.4 (*c* = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.62 (d, *J* = 1.3 Hz, 1H), 8.08−8.03 (m, 2H), 7.71−7.67 (m, 1H), 7.49−7.40 (m, 3H), 7.39−7.34 (m, 2H), 7.14 (ddd, *J* = 8.5, 7.5, 1.3 Hz, 1H), 7.07 (d, *J* = 7.3 Hz, 1H), 7.00−6.94 (m, 1H), 6.68 (td, *J* = 7.7, 1.1 Hz, 1H), 6.10 (dd, *J* = 7.9, 1.2 Hz, 1H), 3.89 (dd, *J* = 13.2, 7.4 Hz, 1H), 3.67 (dd, *J* = 13.2, 8.3 Hz, 1H), 3.52 (td, *J* = 8.1, 5.8 Hz, 1H), 3.05−2.82 (m, 2H), 1.69 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 200.2, 166.3, 156.3, 150.8, 149.0, 146.8, 139.8, 138.3, 129.5, 129.4, 129.2, 129.1, 128.9, 127.0, 126.9, 124.6, 123.7, 123.5, 122.9, 122.4, 114.4, 84.6, 49.6, 40.0, 38.2, 28.2; HRMS (ESI-TOF) calcd for $[C_{30}H_{28}N_2O_6 + Na]^+$ 535.1840, found 535.1830.

*(S,E)-tert-Butyl 3-(3-(4-Bromophenyl)-5-oxo-1-phenylpentylidene)-2-oxoindoline-1-carboxylate (**3e**).* Purified by flash chromatography (petroleum ether/EtOAc 20/1) to afford a pale yellow oil: 39.7 mg, 73% yield; 92% ee, HPLC analysis (Chiralpak IC *i*-PrOH/*n*-hexane 1/19, 1.0 mL/min, λ 210 nm), *t*(major) = 22.45 min, *t*(minor) = 21.01 min; $[\alpha]^{25}_{D}$ −27.2 (*c* = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.60 (t, *J* = 1.7 Hz, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.43 (dq, *J* = 7.1, 5.0, 3.8 Hz, 3H), 7.35−7.29 (m, 2H), 7.14 (td, *J* = 7.9, 1.3 Hz, 1H), 7.09−7.04 (m, 2H), 7.04−6.94 (m, 2H), 6.68 (td, *J* = 7.7, 1.1 Hz, 1H), 6.08 (dd, *J* = 7.9, 1.2 Hz, 1H), 3.88 (dd, *J* = 13.1, 7.5 Hz, 1H), 3.58 (dd, *J* = 13.1, 8.3 Hz, 1H), 3.37 (tt, *J* = 8.2, 4.2 Hz, 1H), 2.94−2.74 (m, 2H), 1.69 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 201.2, 166.2, 157.3, 149.1, 141.9, 140.1, 138.2, 131.5, 129.7, 129.3, 129.3, 128.9, 128.8, 126.9, 126.8, 124.3, 123.4, 122.9, 122.6, 120.6, 114.4, 84.5, 49.7, 40.4, 38.0, 28.2; HRMS (ESI-TOF) calcd for $[C_{30}H_{28}BrNO_4 + H]^+$ 546.1274, found 546.1269.

*(S,E)-tert-Butyl 2-Oxo-3-(5-oxo-1-phenyl-3-(4-(trifluoromethyl)-phenyl)pentylidene)indoline-1-carboxylate (**3f**).* Purified by flash chromatography (petroleum ether/EtOAc 20/1) to afford a pale yellow oil: 41.1 mg, 77% yield; 94% ee, HPLC analysis (Chiralpak IC *i*-PrOH/*n*-hexane 1/19, 1.0 mL/min, λ 210 nm), *t*(major) = 14.57 min, *t*(minor) = 13.66 min; $[\alpha]^{25}_{D}$ −42.6 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.63 (t, *J* = 1.5 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 4H), 7.40−7.33 (m, 1H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.15 (td, *J* = 7.9, 1.3 Hz, 1H), 6.98 (dd, *J* = 7.6, 1.8 Hz, 2H), 6.68 (td, *J* = 7.8, 1.1 Hz, 1H), 6.09 (dd, *J* = 8.0, 1.2 Hz, 1H), 4.01−3.90 (m, 1H), 3.62−3.42 (m, 2H), 3.01−2.81 (m, 2H), 1.70 (s, 9H); ^{13}C NMR (100 MHz, CDCl3) δ (ppm) 200.9, 166.4, 157.0, 149.2, 147.2, 140.2, 138.4, 129.5, 129.3, 129.1, 129.0, 128.4, 127.0 (d, $^2J_{C-F}$ = 29.4 Hz), 125.5 (q, $^3J_{C-F}$ = 4.1 Hz), 124.5, 124.2 (q, $^1J_{C-F}$ = 271.7 Hz), 123.5, 123.0, 122.7, 114.5, 84.6, 49.8, 40.6, 38.5, 28.3. HRMS (ESI-TOF) calcd for $[C_{31}H_{28}F_3NO_4 + H]^+$ 536.2043, found 536.2048.

*(S,E)-tert-Butyl 3-(3-(2-Bromophenyl)-5-oxo-1-phenylpentylidene)-2-oxoindoline-1-carboxylate (**3g**).* Purified by flash chromatography (petroleum ether/EtOAc 20/1) to afford a pale yellow oil: 39.2 mg, 72% yield; 94% ee, HPLC analysis (Chiralpak AD-H *i*-PrOH/*n*-hexane 1/19, 1.0 mL/min, λ 210 nm), *t*(major) = 6.79 min, *t*(minor) = 6.29 min; $[\alpha]^{25}_{D}$ + 46.6 (*c* = 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.63 (t, *J* = 2.0 Hz, 1H), 7.72 (dd, *J* = 8.3, 0.9 Hz, 1H), 7.43 (dtt, *J* = 8.4, 5.4, 3.0 Hz, 5H), 7.14 (td, *J* = 7.9, 1.3 Hz, 2H), 7.05−6.98 (m, 1H), 6.90 (d, *J* = 3.6 Hz, 1H), 6.69 (td, *J* = 7.7, 1.1 Hz, 1H), 6.10 (dd, *J* = 7.9, 1.2 Hz, 1H), 4.05−3.88 (m, 2H), 3.56 (dd, *J* = 13.2, 7.5 Hz, 1H), 2.87 (m, 2H), 1.70 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 201.3, 166.4, 157.5, 149.2, 141.8, 139.7, 138.2, 132.9, 129.5, 129.2, 128.9, 128.8, 128.6, 128.2, 127.9, 126.9, 126.7, 124.6, 124.3, 123.4, 123.0, 122.8, 114.3, 84.4, 48.7, 39.3, 37.0, 28.2; HRMS (ESI-TOF) calcd for $[C_{30}H_{28}BrNO_4 + H]^+$ 546.1274, found 546.1269.

*(S,E)-tert-Butyl 2-Oxo-3-(5-oxo-1-phenyl-3-(p-tolyl)pentylidene)-indoline-1-carboxylate (**3h**).* Purified by flash chromatography (petroleum ether/EtOAc 20/1) to afford a pale yellow oil: 35.1 mg, 73% yield; 92% ee, HPLC analysis (Chiralpak AS-H *i*-PrOH/*n*-hexane 1/19, 1.0 mL/min, λ 210 nm), *t*(major) = 8.86 min, *t*(minor) = 12.91 min; $[\alpha]^{25}_{D}$ −21.6 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.60 (t, *J* = 2.0 Hz, 1H), 7.71 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.46−7.35 (m, 3H), 7.14 (ddd, *J* = 8.4, 7.6, 1.3 Hz, 1H), 7.09 (d, *J* = 8.1 Hz, 2H), 7.05−6.97 (m, 4H), 6.68 (td, *J* = 7.8, 1.1 Hz, 1H), 6.06 (dd, *J* = 8.0, 1.2 Hz, 1H), 4.00 (dd, *J* = 13.0, 7.8 Hz, 1H), 3.48 (dd, *J* = 13.0, 7.8 Hz, 1H), 3.36 (tt, *J* = 8.1, 4.0 Hz, 1H), 2.97−2.73 (m, 2H), 2.28 (s, 3H), 1.70 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 202.2, 166.2, 158.1, 149.2, 140.4, 139.8, 138.2, 136.4, 129.3, 129.2, 129.2, 128.8, 128.7, 127.7, 127.0, 126.7, 124.1, 123.4, 123.0, 122.8, 114.3, 84.4, 49.7, 41.0, 38.4, 28.23, 21.0; HRMS (ESI-TOF) calcd for $[C_{31}H_{31}NO_4 + H]^+$ 482.2326, found 482.2328.

*(S,E)-tert-Butyl 3-(3-(4-Methoxyphenyl)-5-oxo-1-phenylpentylidene)-2-oxoindoline-1-carboxylate (**3i**).* Purified by flash chromatography (petroleum ether/EtOAc 20/1) to afford a pale yellow oil: 33.7 mg, 68% yield; 84% ee, HPLC analysis (Chiralpak AS-H *i*-PrOH/*n*-hexane 1/19, 1.0 mL/min, λ 210 nm), *t*(major) = 16.27 min, *t*(minor) = 24.76 min; $[\alpha]^{25}_{D}$ −40.6 (*c* = 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.59 (t, *J* = 2.0 Hz, 1H), 7.70 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.41 (dtt, *J* = 9.6, 6.0, 2.9 Hz, 3H), 7.16−7.07 (m, 3H), 7.05−6.97 (m, 2H), 6.79−6.72 (m, 2H), 6.67 (td, *J* = 7.7, 1.1 Hz, 1H), 6.06 (dd, *J* = 7.9, 1.2 Hz, 1H), 3.92 (dd, *J* = 13.0, 7.6 Hz, 1H), 3.75 (s, 3H), 3.53 (dd, *J* = 13.0, 8.2 Hz, 1H), 3.35 (dt, *J* = 8.7, 4.1 Hz, 1H), 2.95−2.72 (m, 2H), 1.69 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 202.1, 166.2, 158.4, 158.1, 149.2, 140.4, 138.2, 134.9, 129.3, 129.2, 128.8, 128.8, 128.7, 127.0, 126.8, 124.1, 123.3, 122.9, 122.8, 114.6, 114.3, 113.9, 84.4, 55.2, 49.9, 41.0, 38.0, 28.2; HRMS (ESI-TOF) calcd for $[C_{31}H_{31}NO_5 + H]^+$ 498.2275, found 498.2275.

*(S,E)-tert-Butyl 3-(3-(2-Methoxyphenyl)-5-oxo-1-phenylpentylidene)-2-oxoindoline-1-carboxylate (**3j**).* Purified by flash chromatography (petroleum ether/EtOAc 20/1) to afford a pale yellow oil: 34.7 mg, 70% yield; 87% ee, HPLC analysis (Chiralpak AS-H *i*-PrOH/*n*-hexane 1/19, 1.0 mL/min, λ 210 nm), *t*(major) = 14.44 min, *t*(minor) = 9.91 min; $[\alpha]^{25}_{D}$ −46.8 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.61 (t, *J* = 2.4 Hz, 1H), 7.75−7.70 (m, 1H), 7.42−7.35 (m, 2H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.27−7.22 (m, 1H), 7.12 (dddd, *J* = 8.4, 7.5, 2.4, 1.5 Hz, 2H), 6.98−6.88 (m, 2H), 6.83 (td, *J* = 7.4, 1.1 Hz, 1H), 6.66 (ddd, *J* = 8.6, 7.0, 1.1 Hz, 2H), 6.06 (dd, *J* = 7.9, 1.1 Hz, 1H), 3.97 (dd, *J* = 12.8, 7.0 Hz, 1H), 3.83 (ddd, *J* = 8.8, 6.8, 2.0 Hz, 1H), 3.61−3.56 (m, 1H), 3.54 (s, 3H), 2.89 (ddd, *J* = 16.4, 8.8, 2.5 Hz, 1H), 2.79 (ddd, *J* = 16.4, 6.1, 2.3 Hz, 1H), 1.69 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 202.9, 166.1, 158.9, 157.0, 149.3, 140.5, 138.2, 130.5, 128.9, 128.8, 128.7, 128.5, 128.4, 127.8, 127.1, 126.7, 123.8, 123.3, 122.9, 122.9, 120.6, 114.3, 110.4, 84.3, 54.9, 48.4, 39.2, 33.2, 28.2; HRMS (ESI-TOF) calcd for $[C_{31}H_{31}NO_5 + H]^+$ 498.2275, found 498.2278.

*(S,E)-tert-Butyl 3-(3-(Furan-2-yl)-5-oxo-1-phenylpentylidene)-2-oxoindoline-1-carboxylate (**3k**).* Purified by flash chromatography (petroleum ether/EtOAc 20/1) to afford a pale yellow oil: 31.0 mg, 68% yield; 84% ee, HPLC analysis (Chiralpak IC *i*-PrOH/*n*-hexane 1/19, 1.0 mL/min, λ 210 nm), *t*(major) = 22.39 min, *t*(minor) = 19.88 min; $[\alpha]^{25}_{D}$ −34.8 (*c* = 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.69 (t, *J* = 2.0 Hz, 1H), 7.79−7.71 (m, 1H), 7.51−7.35 (m, 3H), 7.20−7.09 (m, 3H), 6.96 (d, *J* = 7.2 Hz, 1H), 6.69 (td, *J* = 7.8, 1.1 Hz, 1H), 6.19 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.10−5.99 (m, 2H), 3.92 (dd, *J* = 12.7, 6.7 Hz, 1H), 3.59 (tt, *J* = 8.5, 6.0 Hz, 1H), 3.47 (dd, *J* = 12.7, 8.3 Hz, 1H), 2.96−2.69 (m, 2H), 1.68 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 201.5, 166.0, 157.2, 155.7, 149.2, 141.3, 140.3, 138.4, 129.4, 129.2, 128.8, 128.7, 126.9, 126.6, 124.3, 123.4, 123.0, 122.7, 114.4, 110.1, 106.1, 84.4, 47.4, 39.1, 32.2, 28.2; HRMS (ESI-TOF) calcd for $[C_{28}H_{27}NO_5 + H]^+$ 458.1962, found 458.1956.

*(S,E)-tert-Butyl 3-(3-(Naphthalen-1-yl)-5-oxo-1-phenylpentylidene)-2-oxoindoline-1-carboxylate (**3l**).* Purified by flash chromatography (petroleum ether/EtOAc 20/1) to afford a pale yellow oil: 41.8 mg, 81% yield; 89% ee, HPLC analysis (Chiralpak AS-H *i*-PrOH/*n*-hexane 1/19, 1.0 mL/min, λ 210 nm), *t*(major) = 13.72 min, *t*(minor) = 10.14 min; $[\alpha]^{25}_{D}$ + 48.4 (*c* = 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.65 (t, *J* = 1.8 Hz, 1H), 7.84−7.78 (m, 1H), 7.76−7.71 (m, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.60 (d, *J* = 7.1 Hz, 1H), 7.56−7.49 (m, 1H), 7.49−7.37 (m, 4H), 7.37−7.28 (m, 2H), 7.21−7.07 (m, 2H), 6.84 (d, *J* = 7.7 Hz, 1H), 6.68 (td, *J* = 7.7, 1.1 Hz, 1H), 6.09 (dd, *J* = 8.0, 1.2 Hz, 1H), 4.35−4.16 (m, 2H), 3.53 (d, *J* = 7.3 Hz, 1H), 3.23−3.00 (m, 2H), 1.72 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 201.9, 166.4, 158.0, 149.3, 140.0, 139.1, 138.2, 131.1, 129.5, 129.2, 128.9, 128.9, 128.7, 127.3, 126.0, 125.6, 125.5, 124.2, 123.4, 122.9, 122.8, 114.4, 84.4, 48.9, 40.6, 28.3; HRMS (ESI-TOF) calcd for $[C_{34}H_{31}NO_4 + H]^+$ 518.2326, found 518.2327.

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*(S,E)-tert-Butyl 3-(1-(3-Chlorophenyl)-5-oxo-3-phenylpentylidene)-2-oxoindoline-1-carboxylate (**3m**).* Purified by flash chromatography (petroleum ether/EtOAc 20/1) to afford a pale yellow oil: 37.0 mg, 74% yield; 78% ee, HPLC analysis (Chiralpak AD-H *i*-PrOH/*n*-hexane 1/19, 1.0 mL/min, λ 210 nm), t(major) = 6.37 min, t(minor) = 6.77 min; $[\alpha]^{25}_{D}$ −33.9 (c = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.65 (dt, J = 11.8, 2.0 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.34 (m, 2H), 7.25−7.11 (m, 6H), 6.88−6.79 (m, 1H), 6.76−6.68 (m, 2H), 6.12−6.03 (m, 1H), 3.98 (dd, J = 12.0, 6.0 Hz, 1H), 3.89 (dd, J = 12.5, 6.0 Hz, 1H), 3.59−3.32 (m, 2H), 2.99−2.71 (m, 2H), 1.70 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 201.7, 166.0, 155.8, 149.1, 142.4, 138.4, 135.0, 130.6, 130.5, 129.1, 128.6, 128.6, 127.8, 127.2, 127.1, 1267.0, 126.9, 125.2, 125.0, 123.5, 122.9, 122.3, 114.5, 84.6, 50.0, 41.3 40.6, 39.0, 38.7, 28.2; HRMS (ESI-TOF) calcd for $[C_{30}H_{28}ClNO_4 + H]^+$ 502.1780, found 502.1790.

*(S,E)-tert-Butyl 3-(1-(4-Chlorophenyl)-5-oxo-3-phenylpentylidene)-2-oxoindoline-1-carboxylate (**3n**).* Purified by flash chromatography (petroleum ether/EtOAc 20/1) to afford a pale yellow oil: 35.0 mg, 70% yield; 88% ee, HPLC analysis (Chiralpak AD-H *i*-PrOH/*n*-hexane 1/19, 1.0 mL/min, λ 210 nm), t(major) = 6.35 min, t(minor) = 6.97 min; $[\alpha]^{25}_{D}$ −54.9 (c = 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.63 (d, J = 1.9 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.37 (dd, J = 22.3, 8.3 Hz, 2H), 7.25−7.11 (m, 6H), 6.90 (dd, J = 17.0, 8.2 Hz, 2H), 6.73 (td, J = 7.7, 1.1 Hz, 1H), 6.14 (dd, J = 8.0, 1.2 Hz, 1H), 3.95 (dd, J = 12.5, 6.5 Hz, 1H), 3.53−3.32 (m, 2H), 2.98−2.74 (m, 2H), 1.70 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 201.7, 166.0, 156.3, 149.1, 142.7, 138.8, 138.3, 134.7, 129.6, 129.4, 129.0, 128.6, 128.4, 127.8, 126.9, 124.5, 123.5, 122.9, 122.5, 114.5, 84.5, 50.0, 40.8, 38.8, 28.2; HRMS (ESI-TOF) calcd for $[C_{30}H_{28}ClNO_4 + H]^+$ 502.1780, found 502.1777.

*(S,E)-tert-Butyl 3-(1-(3-Bromophenyl)-5-oxo-3-phenylpentylidene)-2-oxoindoline-1-carboxylate (**3o**).* Purified by flash chromatography (petroleum ether/EtOAc 20/1) to afford a pale yellow oil: 38.1 mg, 70% yield; 82% ee, HPLC analysis (Chiralpak AD-H *i*-PrOH/*n*-hexane 1/19, 1.0 mL/min, λ 210 nm), t(major) = 6.64 min, t(minor) = 7.24 min; $[\alpha]^{25}_{D}$ −34.0 (c = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.70−9.60 (m, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.53 (dt, J = 14.8, 4.9 Hz, 1H), 7.32−7.12 (m, 7H), 7.10−6.82 (m, 2H), 6.72 (t, J = 7.7 Hz, 1H), 6.08 (d, J = 7.9 Hz, 1H), 3.92 (m, 1H), 3.60−3.32 (m, 2H), 2.96−2.77 (m, 2H), 1.70 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 201.7, 165.9, 155.7, 149.1, 142.6, 138.4, 131.7, 130.8, 129.9, 129.8, 128.6, 127.8, 127.3, 127.0, 125.7, 125.4, 124.5, 123.0, 122.9, 122.3, 114.5, 84.5, 50.0, 41.3, 40.6, 39.1, 38.7, 28.2; HRMS (ESI-TOF) calcd for $[C_{30}H_{28}BrNO_4 + H]^+$ 546.1274, found 546.1268.

*(S,E)-tert-Butyl 3-(1-(4-Bromophenyl)-5-oxo-3-phenylpentylidene)-2-oxoindoline-1-carboxylate (**3p**).* Purified by flash chromatography (petroleum ether/EtOAc 20/1) to afford a pale yellow oil: 39.7 mg, 73% yield; 86% ee, HPLC analysis (Chiralpak AD-H *i*-PrOH/*n*-hexane 1/19, 1.0 mL/min, λ 210 nm), t(major) = 6.47 min, t(minor) = 7.19 min; $[\alpha]^{25}_{D}$ −29.3 (c = 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.65−9.61 (m, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.24−7.10 (m, 6H), 6.83 (dd, J = 17.8, 8.2 Hz, 2H), 6.77−6.69 (m, 1H), 6.14 (d, J = 7.9 Hz, 1H), 3.94 (dd, J = 12.5, 6.5 Hz, 1H), 3.53−3.34 (m, 2H), 2.93−2.77 (m, 2H), 1.70 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 201.7, 166.0, 156.2, 149.1, 142.6, 139.3, 138.3, 132.5, 132.4, 129.0, 128.9, 128.6, 127.8, 127.0, 124.4, 123.5, 122.9, 122.9, 122.4, 114.5, 84.5, 50.0, 40.8, 38.8, 28.2; HRMS (ESI-TOF) calcd for $[C_{30}H_{28}BrNO_4 + H]^+$ 546.1274, found 546.1271.

*(S,E)-tert-Butyl 2-Oxo-3-(5-oxo-3-phenyl-1-(p-tolyl)pentylidene)-indoline-1-carboxylate (**3q**).* Purified by flash chromatography (petroleum ether/EtOAc 20/1) to afford a pale yellow oil: 40.8 mg, 85% yield; 92% ee, HPLC analysis (Chiralpak IC *i*-PrOH/*n*-hexane 1/19, 1.0 mL/min, λ 210 nm), t(major) = 24.29 min, t(minor) = 21.43 min; $[\alpha]^{25}_{D}$ −40.3 (c = 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.60 (t, J = 1.9 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.25−7.18 (m, 6H), 7.19−7.10 (m, 2H), 6.96−6.88 (m, 2H), 6.70 (td, J = 7.7, 1.1 Hz, 1H), 6.19 (dd, J = 7.9, 1.2 Hz, 1H), 4.03 (dd, J = 12.7, 7.7 Hz, 1H), 3.50−3.30 (m, 2H), 2.98−2.75 (m, 2H), 2.44 (s, 3H), 1.70 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 202.0, 166.3, 158.4, 149.2, 143.0, 138.9, 138.1, 137.3, 130.0, 129.9, 128.6, 128.5, 127.8, 126.8, 124.0, 123.3, 123.0, 122.9, 114.3, 84.3, 49.5, 41.0, 38.8, 28.2, 21.5; HRMS (ESI-TOF) calcd for $[C_{31}H_{31}NO_4 + H]^+$ 482.2326, found 482.2327.

*(S,E)-tert-Butyl 3-(1-(4-Methoxyphenyl)-5-oxo-3-phenylpentylidene)-2-oxoindoline-1-carboxylate (**3r**).* Purified by flash chromatography (petroleum ether/EtOAc 20/1) to afford a pale yellow oil: 33.8 mg, 68% yield; 93% ee, HPLC analysis (Chiralpak IC *i*-PrOH/*n*-hexane 1/19, 1.0 mL/min, λ 210 nm), t(major) = 38.17 min, t(minor) = 32.38 min; $[\alpha]^{25}_{D}$ −66.5 (c = 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.60 (d, J = 1.9 Hz, 1H), 7.71 (d, J = 8.1 Hz, 1H), 7.25−7.10 (m, 6H), 7.01−6.86 (m, 4H), 6.72 (td, J = 7.7, 1.1 Hz, 1H), 6.29 (dd, J = 7.9, 1.2 Hz, 1H), 4.02 (dd, J = 12.6, 7.4 Hz, 1H), 3.88 (s, 3H), 3.49−3.31 (m, 2H), 2.99−2.74 (m, 2H), 1.70 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 202.0, 166.3, 160.1, 158.2, 149.2, 143.0, 138.1, 132.4, 128.5, 128.5, 127.8, 126.8, 124.0, 123.3, 123.1, 122.8, 114.3, 84.3, 55.4, 49.5, 41.1, 39.0, 28.2; HRMS (ESI-TOF) calcd for $[C_{31}H_{31}NO_5 + H]^+$ 498.2275, found 498.2274.

*(E)-tert-Butyl 3-(1-(2-Methoxyphenyl)-5-oxo-3-phenylpentylidene)-2-oxoindoline-1-carboxylate (**3s**).* Purified by flash chromatography (petroleum ether/EtOAc 20/1) to afford a pale yellow oil: 8 mg, 16% yield; 92% ee, HPLC analysis (Chiralpak AS-H *i*-PrOH/*n*-hexane 1/19, 1.0 mL/min, λ 210 nm), t(major) = 14.51 min, t(minor) = 12.25 min; $[\alpha]^{25}_{D}$ −12.9 (c= 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.64 (d, J = 8.3 Hz, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.36 (td, J = 7.9, 5.6 Hz, 1H), 7.29−7.12 (m, 6H), 6.99 (ddd, J = 8.2, 5.3, 2.4 Hz, 1H), 6.73 (t, J = 7.7 Hz, 1H), 6.63 (t, J = 7.6 Hz, 1H), 6.50 (s, 1H), 6.17 (dd, J = 12.3, 7.9 Hz, 1H), 4.05−3.95 (m, 1H), 3.75 (s, 3H), 3.64−3.37 (m, 2H), 3.00−2.78 (m, 2H), 1.72 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 201.9, 166.2, 160.2, 160.1, 157.7, 149.2, 143.0, 141.8, 141.5, 138.2, 130.5, 128.7, 128.5, 127.9, 126.8, 123.4, 123.2, 122.7, 119.0, 118.8, 114.8, 114.3, 111.9, 111.7, 84.4, 55.3, 49.8, 40.4, 38.6, 28.2; HRMS (ESI-TOF) calcd for $[C_{31}H_{31}NO_5 + Na]^+$ 520.2094, found 520.2092.

*(S,Z)-tert-Butyl 2-Oxo-3-(6-oxo-4-phenylhexan-2-ylidene)-indoline-1-carboxylate (**3t**).* Purified by flash chromatography (petroleum ether/EtOAc 20/1) to afford a colorless oil: 30.8 mg, 76% yield; 91% ee, HPLC analysis (Chiralpak AS-H *i*-PrOH/*n*-hexane 1/19, 1.0 mL/min, λ 210 nm), t(major) = 13.04 min, t(minor) = 11.06 min; $[\alpha]^{25}_{D}$ −21.8 (c = 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.62 (t, J = 1.9 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.28−7.20 (m, 5H), 7.15 (dq, J = 7.7, 2.8 Hz, 1H), 7.08 (td, J = 7.7, 1.1 Hz, 1H), 3.91 (dd, J = 11.9, 7.3 Hz, 1H), 3.68−3.54 (m, 1H), 2.88−2.74 (m, 3H), 2.07 (s, 3H), 1.63 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 201.9, 165.7, 157.9, 149.3, 143.2, 138.1, 128.7, 128.2, 127.6, 126.9, 123.8, 123.7, 123.2, 114.5, 84.3, 49.3, 43.5, 39.7, 28.2, 24.9; HRMS (ESI-TOF) calcd for $[C_{25}H_{27}NO_4 + H]^+$ 406.2013, found 406.2022.

*(S,Z)-5-(2-Oxobenzofuran-3(2H)-ylidene)-3-phenylhexanal (**5**).* Purified by flash chromatography (petroleum ether/EtOAc 20/1) to afford a colorless oil: 22.0 mg, 72% yield; 90% ee, HPLC analysis (Chiralpak AD-H *i*-PrOH/*n*-hexane 1/19, 1.0 mL/min, λ 210 nm), t(major) = 16.30 min, t(minor) = 17.33 min; $[\alpha]^{25}_{D}$ −19.9 (c = 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.65 (t, J = 1.8 Hz, 1H), 7.41 (dd, J = 7.8, 1.2 Hz, 1H), 7.29−7.23 (m, 5H), 7.19−7.14 (m, 1H), 7.11−7.04 (m, 2H), 3.61 (dq, J = 9.5, 3.7, 2.4 Hz, 2H), 3.09 (d, J = 3.6 Hz, 1H), 2.85 (ddt, J = 5.4, 3.6, 1.7 Hz, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 201.3, 166.9, 160.3, 152.5, 142.7, 129.1, 128.8, 127.4, 127.1, 124.2, 123.8, 123.6, 119.9, 110.6, 49.6, 42.5, 39.3, 23.6; HRMS (ESI-TOF) calcd for $[C_{20}H_{18}O_3 + H]^+$ 307.1329, found 307.1334.

*(E)-tert-Butyl 3-((R,E)-3-Methyl-7-oxo-1-phenylhept-5-en-1-ylidene)-2-oxoindoline-1-carboxylate (**7a**).* Purified by flash chromatography (petroleum ether/EtOAc 20/1) to afford a pale yellow oil: 7.7 mg, 18% yield; 86% ee, HPLC analysis (Chiralpak OD-H *i*-PrOH/*n*-hexane 1/19, 1.0 mL/min, λ 210 nm), t(major) = 24.48 min, t(minor) = 13.01 min; $[\alpha]^{25}_{D}$ + 3.5 (c = 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.47 (d, J = 7.9 Hz, 1H), 7.73 (d, J = 8.2 Hz, 1H), 7.53−7.45 (m, 3H), 7.25−7.19 (m, 2H), 7.15 (td, J = 7.9, 1.2 Hz,

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1H), 6.85−6.74 (m, 1H), 6.70 (t, J = 7.7 Hz, 1H), 6.09−6.02 (m, 2H), 3.50−3.25 (m, 2H), 2.54−2.26 (m, 2H), 1.86 (dd, J = 14.0, 7.2 Hz, 1H), 1.67 (s, 9H), 1.00 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz,$CDCl_3$) δ (ppm) 194.1, 166.1, 158.8, 157.4, 149.3, 140.9, 138.2, 134.3, 129.5, 128.9, 128.6, 126.9, 126.7, 124.0, 123.3, 122.8, 114.3, 84.3, 41.3, 39.6, 31.6, 28.2, 19.3; HRMS (ESI-TOF) calcd for $[C_{27}H_{29}NO_4 + Na]^+$ 454.1989, found 454.1993.

*(E)-tert-Butyl 2-Oxo-3-((R,E)-7-oxo-1-phenyl-3-propylhept-5-en-1-ylidene)indoline-1-carboxylate (**7b**).* Purified by flash chromatography (petroleum ether/EtOAc 20/1) to afford a pale yellow oil: 15.6 mg, 34% yield; 87% ee, HPLC analysis (Chiralpak OD-H *i*-PrOH/*n*-hexane 1/19, 1.0 mL/min, λ 210 nm), t(major) = 10.12 min, t(minor) = 9.31 min; $[\alpha]^{25}_D$ −6.3 (c = 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.66−9.45 (m, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.55−7.44 (m, 3H), 7.25−7.19 (m, 2H), 7.16 (td, J = 8.0, 1.3 Hz, 1H), 6.82 (dt, J = 15.1, 7.3 Hz, 1H), 6.71 (t, J = 7.7 Hz, 1H), 6.13−5.99 (m, 2H), 3.60 (dd, J = 13.0, 8.1 Hz, 1H), 3.22 (dd, J = 13.0, 6.5 Hz, 1H), 2.42 (t, J = 6.8 Hz, 2H), 1.92−1.71 (m, 1H), 1.67 (s, 9H), 1.38−1.22 (m, 4H), 0.79 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 194.1, 166.1, 159.2, 157.8, 149.3, 140.7, 138.1, 134.3, 129.6, 129.3, 128.9, 128.6, 127.1, 127.0, 126.6, 124.1, 123.3, 122.8, 122.8, 114.3, 84.3, 38.7, 36.6, 35.9, 35.6, 28.2, 19.7, 14.1; HRMS (ESI-TOF) calcd for $[C_{29}H_{33}NO_4 + Na]^+$ 482.2302, found 482.2307.

*(E)-tert-Butyl 2-Oxo-3-((R)-3-((E)-4-oxobut-2-en-1-yl)-1-phenylnonylidene)indoline-1-carboxylate (**7c**).* Purified by flash chromatography (petroleum ether/EtOAc 20/1) to afford a pale yellow oil: 17.5 mg, 35% yield; 86% ee, HPLC analysis (Chiralpak OD-H *i*-PrOH/*n*-hexane 1/19, 1.0 mL/min, λ 210 nm), t(major) = 8.29 min, t(minor) = 7.66 min; $[\alpha]^{25}_D$ −5.9 (c = 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.67−9.44 (m, 1H), 7.74 (dd, J = 8.1, 4.0 Hz, 1H), 7.52−7.45 (m, 3H), 7.26−7.19 (m, 2H), 7.18−7.13 (m, 1H), 6.82 (dt, J = 15.1, 7.3 Hz, 1H), 6.71 (tt, J = 7.7, 2.0 Hz, 1H), 6.13−6.00 (m, 2H), 3.63 (dd, J = 13.0, 8.1 Hz, 1H), 3.20 (dd, J = 13.0, 6.5 Hz, 1H), 2.42 (t, J = 6.8 Hz, 2H), 1.80 (m, 1H), 1.67 (s, 9H), 1.25−1.12 (m, 10H), 0.85 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 194.1, 166.1, 159.3, 157.9, 149.3, 140.7, 138.1, 134.3, 129.3, 128.9, 128.6, 127.0, 126.6, 124.1, 123.3, 122.9, 122.8, 114.3, 84.3, 38.8, 36.6, 36.2, 33.4, 31.8, 29.3, 28.2, 26.5, 22.6, 14.1; HRMS (ESI-TOF) calcd for $[C_{32}H_{39}NO_4 + Na]^+$ 524.2771, found 524.2775.

*(E)-tert-Butyl 3-((R,E)-3-(2-Bromophenyl)-7-ethoxy-7-oxo-1-phenylhept-5-en-1-ylidene)-2-oxoindoline-1-carboxylate (**8**).* Purified by flash chromatography (petroleum ether/EtOAc 40/1) to afford a yellow oil: 54 mg, 80% yield; 92% ee, HPLC analysis (Chiralpak OD-H *i*-PrOH/*n*-hexane 1/19, 1.0 mL/min, λ 210 nm), t(major) = 6.26 min, t(minor) = 7.52 min; $[\alpha]^{25}_D$ + 40.1 (c = 1.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.71 (d, J = 8.2 Hz, 1H), 7.50−7.36 (m, 5H), 7.21 (td, J = 7.6, 1.3 Hz, 1H), 7.15−7.08 (m, 2H), 7.00 (td, J = 7.7, 1.6 Hz, 1H), 6.88−6.73 (m, 2H), 6.67 (d, J = 1.0 Hz, 1H), 6.04 (dd, J = 8.0, 1.1 Hz, 1H), 5.72 (dd, J = 15.5, 1.5 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.91−3.80 (m, 1H), 3.71 (d, J = 8.1 Hz, 1H), 3.46 (dd, J = 8.3, 6.6 Hz, 1H), 2.62 (dt, J = 15.3, 7.7 Hz, 1H), 2.57 (dt, J = 14.1, 6.8 Hz, 1H), 1.70 (s, 9H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.4, 158.3, 149.2, 146.4, 142.0, 139.7, 138.1, 132.8, 129.5, 129.2, 128.7, 128.62, 128.0, 127.8, 126.8, 126.7, 125.0, 124.1, 123.4, 123.0, 123.0, 122.8, 114.3, 84.4, 60.2, 39.1, 37.9, 28.2, 14.2; HRMS (ESI-TOF) calcd for $[C_{34}H_{34}BrNO_5+NH_4]^+$ 633.1959, found 633.1948.

*(S,E)-tert-Butyl 3-(3-(2-Bromophenyl)-5-hydroxy-1-phenylpentylidene)-2-oxoindoline-1-carboxylate (**9**).* Purified by flash chromatography (petroleum ether/EtOAc 8/1) to afford a pale yellow oil: 49 mg, 89% yield; 87% ee, HPLC analysis(Chiralpak AD-H *i*-PrOH/*n*-hexane 1/9, 1.0 mL/min, λ 210 nm), t(major) = 6.96 min, t(minor) = 7.71 min; $[\alpha]^{25}_D$ −8.0 (c = 0.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.73 (d, J = 8.2 Hz, 1H), 7.46−7.34 (m, 4H), 7.30 (d, J = 6.9 Hz, 1H), 7.14 (tdd, J = 8.5, 4.3, 1.3 Hz, 2H), 7.06−6.90 (m, 3H), 6.68 (td, J = 7.7, 1.1 Hz, 1H), 6.08 (dd, J = 8.0, 1.2 Hz, 1H), 4.15 (dd, J = 13.0, 7.1 Hz, 1H), 3.63 (q, J = 7.4 Hz, 2H), 3.55−3.42 (m, 1H), 3.38−3.16 (m, 1H), 2.06−1.91 (m, 2H), 1.69 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.4, 158.8, 149.3, 143.2, 140.5, 138.2, 132.6, 129.4, 128.8, 128.5, 127.8, 127.7, 126.9, 126.5, 125.0, 123.9, 123.3, 122.9, 114.3, 84.3, 77.3, 60.4, 40.2, 38.7, 28.2; HRMS (ESI-TOF) calcd for $[C_{30}H_{30}BrNO_4 + H]^+$ 548.1431, found 548.1421.

*(S,E)-tert-Butyl 3-(3-(2-Bromophenyl)-5-morpholino-1-phenylpentylidene)-2-oxoindoline-1-carboxylate (**10**).* Purified by flash chromatography (petroleum ether/EtOAc 4/1) to afford a yellow oil: 58 mg, 74% yield; 93% ee, HPLC analysis (Chiralpak IC *i*-PrOH/*n*-hexane 1/19, 1.0 mL/min, λ 210 nm), t(major) = 15.41 min, t(minor) = 14.61 min; $[\alpha]^{25}_D$ + 32.6 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.70 (d, J = 8.2 Hz, 1H), 7.49−7.34 (m, 5H), 7.19 (t, J = 7.5 Hz, 1H), 7.15−7.06 (m, 2H), 6.97 (td, J = 7.7, 1.6 Hz, 1H), 6.92 (d, J = 6.1 Hz, 1H), 6.67 (t, J = 7.7 Hz, 1H), 6.09 (d, J = 7.8 Hz, 1H), 4.09−3.97 (m, 1H), 3.62 (t, J = 4.6 Hz, 4H), 3.47−3.36 (m, 2H), 2.32 (s, 4H), 2.16 (m, 2H), 2.00−1.82 (m, 2H), 1.69 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.3, 158.9, 149.3, 143.4, 140.1, 138.0, 132.6, 129.5, 128.8, 128.6, 128.5, 127.7, 127.6, 126.9, 126.8, 123.9, 123.3, 123.0, 122.9, 114.3, 84.3, 67.0, 56.2, 53.7, 39.9, 31.9, 28.2; HRMS (ESI-TOF) calcd for $[C_{34}H_{37}BrN_2O_4 + H]^+$ 617.2009, found 617.2006.

*(E)-3-((S,E)-3-(2-bromophenyl)-5-(2-(2,4-dinitrophenyl)-hydrazono)-1-phenylpentylidene)indolin-2-one (**11**).* Purified by flash chromatography (petroleum ether/EtOAc 6/1) to afford a yellow powder: 69 mg, 72% yield; mp 72−74 °C; 75% ee, HPLC analysis (Chiralpak OD-H *i*-PrOH/*n*-hexane 4/6, 1.0 mL/min, λ 210 nm), t(major) = 26.67 min, t(minor) = 17.08 min; $[\alpha]^{25}_D$ + 102.0 (c = 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 10.92 (s, 1H), 9.05 (d, J = 2.6 Hz, 1H), 8.22 (dd, J = 9.6, 2.6 Hz, 1H), 8.05 (s, 1H), 7.74 (d, J = 9.6 Hz, 1H), 7.53 (dd, J = 7.9, 1.6 Hz, 1H), 7.49−7.37 (m, 5H), 7.24 (dd, J = 7.7, 1.3 Hz, 1H), 7.18 (d, J = 6.5 Hz, 1H), 7.05 (dtd, J = 9.4, 7.6, 1.4 Hz, 2H), 6.95 (s, 1H), 6.77 (d, J = 7.7 Hz, 1H), 6.58 (td, J = 7.7, 1.1 Hz, 1H), 6.02 (d, J = 7.9 Hz, 1H), 4.00 (p, J = 5.5 Hz, 1H), 3.74 (dd, J = 8.9, 3.3 Hz, 2H), 2.86 (t, J = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.4, 156.4, 150.2, 145.0, 141.8, 139.8, 139.4, 137.8, 132.9, 129.8, 129.5, 129.0, 128.8, 128.7, 128.6, 128.3, 127.9, 127.0, 126.8, 124.9, 123.5, 123.4, 123.2, 121.6, 116.7, 109.2, 40.0, 38.4, 38.0; HRMS (ESI-TOF) calcd for $[C_{31}H_{24}BrN_5O_5 + H]^+$ 626.1034, found 626.1025.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02582.

NMR and HPLC spectra and crystallographic data for **11** (PDF)

Crystallographic data for **11** (CIF)

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Notes

The authors declare no competing financial interest.

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