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Pd(II)/β-ICD-Cocatalyzed Asymmetric Route to Oxindole Scaffold via Cascade Reaction of Diazoacetamides and MBH-Carbonates

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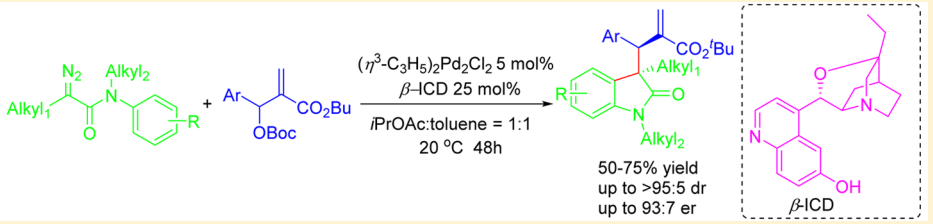
Supporting Information



ABSTRACT: We report an efficient method for asymmetric synthesis of chiral oxindoles. Allyl palladium(II) chloride dimer (APC)-catalyzed, in combination with β-isocupreidine (β-ICD)-cocatalyzed, reaction of diazoacetamide with Morita−Baylis−Hillman (MBH) carbonates proves to be a facile protocol to access multifunctional oxindoles bearing a C-3 quaternary stereo center. This tandem reaction tolerates a wide variety of functional groups on the both aromatic rings. This method delivers a variety of chiral oxindoles in 50−75% yield and with up to 95:5 dr in most cases along with up to 93:7 er.

INTRODUCTION

The chiral oxindole scaffolds bearing a C-3 quaternary carbon center widely exist in natural products and many drug compounds.[1] In recent years, it has been the main interest for many researchers to focus on the asymmetric synthesis of oxindole skeletons and its methodology development.[2]

MBH reaction is a kind of high-efficiency method of building C−C bond, that meanwhile retains the easily modified double bond;[3] the derived MBH adducts are a kind of practical synthon in modern organic synthesis system.[3a] Very recently, the use of these MBH carbonates for asymmetric allylic alkylation (AAA) with high enantioinduction has attracted much attention (Scheme 1a).[4] Moreover, the MBH reaction mechanism has also been well studied[5] with cinchona alkaloid derivatives, β-ICD. It catalyzes nucleophilic addition of the MBH carbonates to form the corresponding chiral ammonium cation intermediate, which upholds the construction of the final motif. MBH reactions are also used to construct key cyclic intermediates for the syntheses of Salinosporamide A, Diversonol, and Anatoxin-A.[6]

In recent studies, it has been successfully demonstrated that transition metals with diverse chiral ligands are efficient catalytic systems for various asymmetric trapping reactions;[7] for instance, our group achieved electrophilic trapping of zwitterionic intermediates by imine groups that resulted in polyfunctionalized indole and oxindole derivatives in a single step with excellent diastereoselectivity and enantioselectivity. Oxindole core was synthesized in situ from *N*-phenyl diazoacetamides via a Rh(II)-catalyzed intramolecular C−H functionalization, affording a zwitterion intermediate, which in the presence of the Brønsted acid activated imines gave oxindole molecule (Scheme 1b).[8]

To the best of our knowledge, MBH carbonates, along with metal−carbene intermediates, to engage in asymmetric trapping reactions, even in nonasymmetric fashion, have not yet been disclosed. This prompted us to study in situ trapping of diazoacetamide by MBH carbonates. Intrigued by the fact that preactivated chiral MBH ammonium cation intermediate can serve as a more active electrophile as compared to Brønsted acid activated imine, we hypothesize to trap zwitterion intermediate, derived from diazoacetamide, by preactivated MBH carbonates (Scheme 1c).

Herein, we studied a reaction of diazoacetamide and MBH carbonate in the presence of palladium catalyst, APC, and chiral Lewis base, β-ICD, to realize the active intermediate trapping reaction to construct the oxindole skeletons with a C-3 quaternary chiral center. According to the reaction study and mechanism investigation, we found that the reaction pathway was not a lively intermediate trapping process, but more possibly a tandem reaction in which the oxindoles were generated in situ by the C−H insert of diazoacetamides and following a substitution of the MBH ammonium cation. However, there have been no reports of catalytic variants of this type of process, and this methodology is more green and atom economic, with enhanced diastereoselectivity, as compared to organocatalyzed AAA of oxindoles with MBH carbonates in which oxindoles were a starting material (Scheme 1a).

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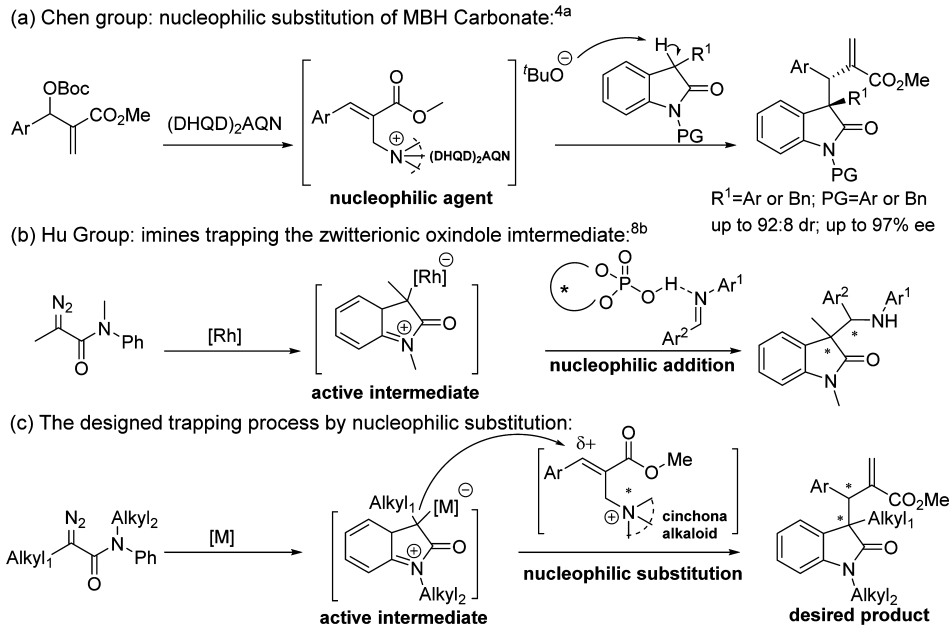
Scheme 1. Inspiration of This Work



RESULTS AND DISCUSSION

It is well-known that palladium complex led to the decomposition of diazo compounds, to generate the Pd-carbene,[9] and also efficiently catalyzed AAA.[10] Considering the above specifics of Pd complexes, initially the reaction was screened in the presence of APC (Table 1, entry 1); unfortunately, there was no desired product obtained. Thereafter, we examined some Lewis bases, along with APC. To our delight, after a series of the Lewis bases were scanned, the reaction afforded the desired product in 65% yield upon the addition of DMAP (entry 2). Next, we started to optimize the diastereoselectivity, and transition metal complexes $Rh_2(OAc)_4$, $[Ir(coe)Cl]_2$, and $Cu(hfacac)_2$ were employed but failed to enhance the dr ratio. After further screening of different solvents in the reaction, toluene and *i*PrOAc showed the better diastereoselectivity to 84:16(*anti*:*syn*) (entries 2−7).

With these results in hand, we further considered to explore the enantioselectivity, by exchanging the DMAP with chiral DMAP*1 that had been utilized in asymmetric resolution of secondary alcohols,[11] but the result was unsatisfactory (entry 8). Correspondingly, most of the bases,[12] which can easily catalyze the AAA of MBH adducts, could not even promote this reaction (entries 9−15) with the exception that the cinchona-derived alkaloid *β*-ICD could catalyze it to produce the desired molecule in acceptable er (entry 14). Yet, the enantioselectivity was not up to expectation, as the nucleophilic attacking site is far away from the chiral environment formed by the *β*-ICD. So, we attempt to construct a novel chiral environment of the oxindole by using some chiral Pd complexes to improve its enantioselectivity;[13] a chiral palladium phosphate prepared from APC and chiral silver phosphate was also able to catalyze this reaction but affords racemic product with low yield (<20%) (entry 16). Because the variation of both metals and bases all afforded bad results, we realized that it is important to keep metal and chiral base well-coordinated. Meanwhile, a single crystal of **3c** has been obtained, and we presumed that increasing the terminal ester group size would result in the complete formation of the trans-double bond[5] in the right structure shown in Figure S1. Hopefully, exchanging methyl with *tert*-butyl in the ester group, we obtained only one diastereoisomer (up to >95:5 dr) and a 92:8 enantiomeric ratio (entry 17). Finally the temperature, solvents, and the equivalents of APC were investigated (entries 18−23); the mixture solvents (*i*PrOAc:toluene = 1:1) at 20 °C along with 5 mol % APC show the best result (entry 23).

After the optimum condition was established, the substrate scopes were investigated, and the results are summarized in Table 2. This reaction tolerates a wide variety of functional groups on both of the aromatic rings, and generated the products in moderate to good yield with up to >95:5 diastereoselectivity and up to 93:7 enantioselectivity. The electron-donating group shows better enantioselectivity as compared to the electron-withdrawing group, whereas the strong electron-withdrawing nitro group of **1** failed to react (Table 2, entry 12). The absolute configuration of **3p** was confirmed by single-crystal X-ray crystallography and is illustrated in Figure S2.

To verify our hypothesis and to get insight into the reaction mechanism, control experiments were conducted. The results are listed in Table 3: when the C−H inserted oxindole was used instead of diazoacetamide, the reaction occurred in a decreased yield but maintained the same diastereoselectivity and enantioselectivity, which implied it may not be a concerted electrophilic trapping of the zwitterionic intermediate reaction; when *β*-ICD was used alone, the slightly diminished diastereoselectivity suggested that the palladium complex might also influence the alkylation step. So the possible mechanism is a stepwise cascade reaction outlined in Scheme 2. The Pd complex, APC, catalyzed the in situ C−H insertion reaction. At the same time, the *β*-ICD nucleophile attacked the MBH carbonate to generate the ammonium cation intermediate and release the ^{t}BuO anion as a strong base.[5] Finally, the oxindole nucleophile produced via ^{t}BuO-mediated deprotonation and with the help of palladium attacked the ammonium intermediate from the *Re* face to provide the observed product. Simultaneously, we could not eliminate the possibility that the zwitterion intermediate was deprotonated by the ^{t}BuO group directly.

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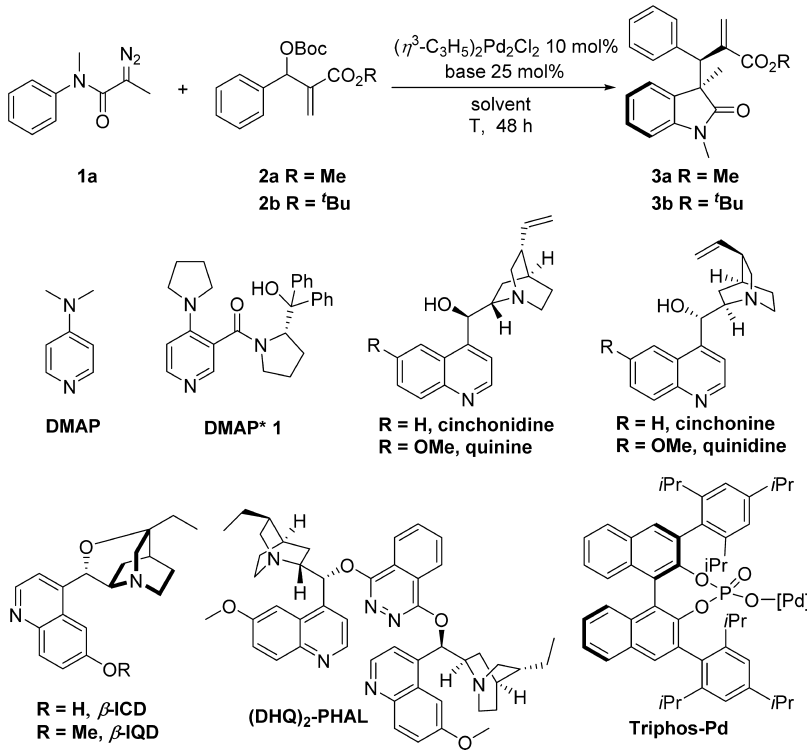
Table 1. Reaction Condition Optimization for the Cocatalysis Reaction of 1a and 2a/2b[a]



entry	Lewis base	solvent	R	temp (°C)	yield[b] (%)	dr[c] (*anti*:*syn*)	er[d]
1		DCM	Me	20	NR		
2	DMAP	DCM	Me	20	65	67:33	
3	DMAP	DCE	Me	20	81	65:35	
4	DMAP	$CHCl_3$	Me	20	55	79:21	
5	DMAP	EA	Me	20	51	80:20	
6	DMAP	*i*PrOAc	Me	20	79	84:16	
7	DMAP	toluene	Me	40	75	84:16	
8	DMAP*1	toluene	Me	40	84	89:11	70:30
9	quinine	toluene	Me	40	NR		
10	quinidine	toluene	Me	40	NR		
11	cinchonine	toluene	Me	40	NR		
12	cinchonidine	toluene	Me	40	NR		
13	β-IQD	toluene	Me	40	NR		
14	β-ICD	toluene	Me	40	70	89:11	82:18
15	$(DHQ)_2$-PHAL	toluene	Me	40	NR		
16[e]	triphos-Pd	toluene	Me	40	<20	67:33	50:50
17	β-ICD	toluene	tBu	40	64	>95:5	92:8
18	β-ICD	toluene	tBu	60	70	>95:5	90:10
19	β-ICD	toluene	tBu	20	trace		
20[f]	β-ICD	mixture	tBu	20	54	>95:5	92:8
21[f]	β-ICD	mixture	tBu	0	35	>95:5	92:8
22[f]	β-ICD	mixture	tBu	40	54	>95:5	91:9
23[f,g]	β-ICD	mixture	tBu	20	64	>95:5	92:8

[a]Unless other noted, all reactions were carried out (**1**:**2**:metal:β-ICD = 1.5:1:0.1:0.25) in 1 mL of solvent for 48 h. [b]Isolated yield includes *anti* and *syn*. [c]Detected by ^{1}H NMR. [d]Detected by chiral HPLC. [e]The base is DMAP. [f]Mixture solvent represents *i*PrOAc:toluene = 1:1. [g]The APC is reduced to 5 mol %.

CONCLUSION

We have discovered an asymmetric cascade reaction between diazoacetamides and MBH carbonates. It is an easy and atom economic way to access functional C-3 fully substituted oxindole scaffold with excellent diastereoselectivity and high enantioselectivity in good yield. This new cocatalytic method shows good compatibility of palladium and nucleophilic β-ICD in this cascade reaction. We imagine that there will be more metal and Lewis base cocatalysis reports in asymmetric organic methodology studies.

EXPERIMENTAL SECTION

General. All isolated compounds **3a**−**3s** were characterized on the basis of ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), and ^{19}F NMR

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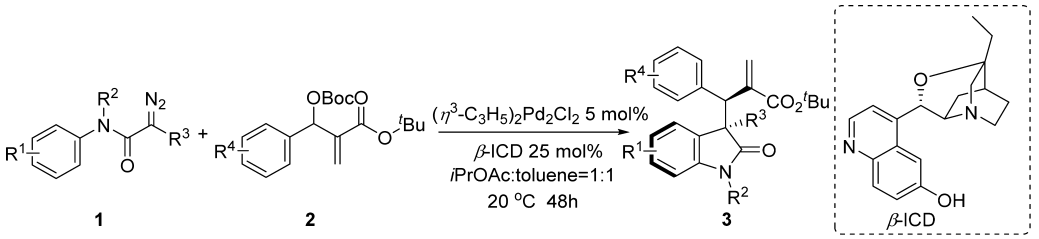
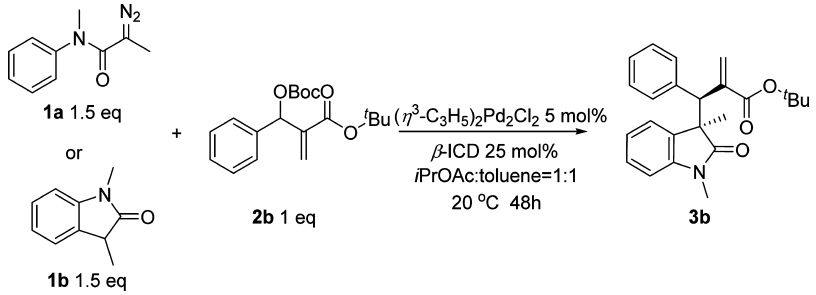
Table 2. Substrate Scopes of APC/β-ICD Cocatalysis Reaction[a]



entry	substrate scope $R^1/R^2/R^3$	substrate scope R^4	3	yield[b] (%)	dr[c] (*anti*:*syn*)	er[d]
1	H/Me/Me	H	**3b**	64	>95:5	92:8
2	H/Me/Bn	H	**3d**	60	>95:5	91:9
3	H/Et/Me	H	**3e**	62	>95:5	92:8
4	H/Et/Me	4-Br	**3f**	60	>95:5	89:11
5	H/Et/Me	4-F	**3g**	64	94:6	91:9
6	H/Bn/Me	H	**3h**	50	>95:5	93:7
7	4-Me/Me/Me	H	**3i**	54	>95:5	92:8
8	4-OMe/Me/Me	H	**3j**	72	>95:5	93:7
9	4-Br/Me/Me	H	**3k**	75	91:9	88:12
10	4-Cl/Me/Me	H	**3l**	67	95:5	91:9
11	4-F/Me/Me	H	**3m**	74	>95:5	89:11
12	4-NO_2/Me/Me	H	**3n**			
13	H/Me/Me	4-Me	**3o**	69	>95:5	92:8
14	H/Me/Me	4-Br	**3p**	64	95:5	88:12
15	H/Me/Me	4-F	**3q**	70	>95:5	90:10
16	H/Me/Me	3-Cl	**3r**	60	88:12	83:17
17	H/Me/Me	4-NO_2	**3s**	61	81:19	69:31

[a]All reactions were carried out (**1**:**2**:APC:β-ICD = 1.5:1:0.05:0.25) at 20 °C in 1 mL of solvent for 48 h. [b]Isolated yield includes *anti* and *syn*. [c]Detected by ^{1}H NMR. [d]Detected by chiral HPLC.

Table 3. Control Reactions



entry	substrate	condition	yield (%)[a]	dr (*anti*:*syn*)[b]	er[c]
A	**1a**	APC + β-ICD	62	>95:5	92:8
B	**1b**	APC + β-ICD	37	95:5	92:8
C	**1b**	β-ICD	53	92:8	90:10

[a]Total yield of isolated *anti* and *syn* products. [b]Determined by ^{1}H NMR analysis of the crude mixture. [c]Detected by chiral HPLC.

(376 MHz) spectroscopic data and HRMS (TOF-Q) data. Tetramethylsilane (TMS) served as an internal standard (δ = 0) for ^{1}H NMR, and $CDCl_3$ was used as internal standard (δ = 77.0) for ^{13}C NMR. Chemical shifts are reported in parts per million as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad). HPLC analysis was performed on Chiralpak IA. Single-crystal X-ray diffraction data were recorded on a single-crystal X-ray diffractometer. The racemic standards used in HPLC studies were prepared according to the general procedure by using base DMAP. Yields for all compounds were the total yield of isolated *anti* and *syn* products unless otherwise indicated.

All reactions and manipulations were carried out without any protection in an oven-dried flask containing magnetic stir bar. All solvent we used without any anhydrate operation. The diazoacetamides **1** were prepared from condensation of Ts-protected pyruvate and substituted aniline.[8a] Morita–Baylis–Hillman (MBH) carbonates **2**[14] and base β-ICD/β-IQD[15] were prepared according to the literature procedure.

General Experimental Procedure for the Synthesis of Product 3. A mixture of APC, MBH carbonates **2** (0.2 mmol), and β-ICD (25 mol %) was dissolved in 0.5 mL of solvent (toluene:*i*PrOAc = 1:1) under 20 °C. The diazo compound **1** (0.3 mmol) in 0.5 mL of solvent (toluene:*i*PrOAc = 1:1) was then added over 0.5 h via a syringe pump. After completion of the addition, the reaction mixture was stirred for another 48 h under 20 °C. After the completion of the reaction (monitored by TLC, until MBH carbonates **2** disappeared), the reaction mixture was filtrated and evaporated in vacuo to give the crude product. The crude product was purified by flash chromatog-

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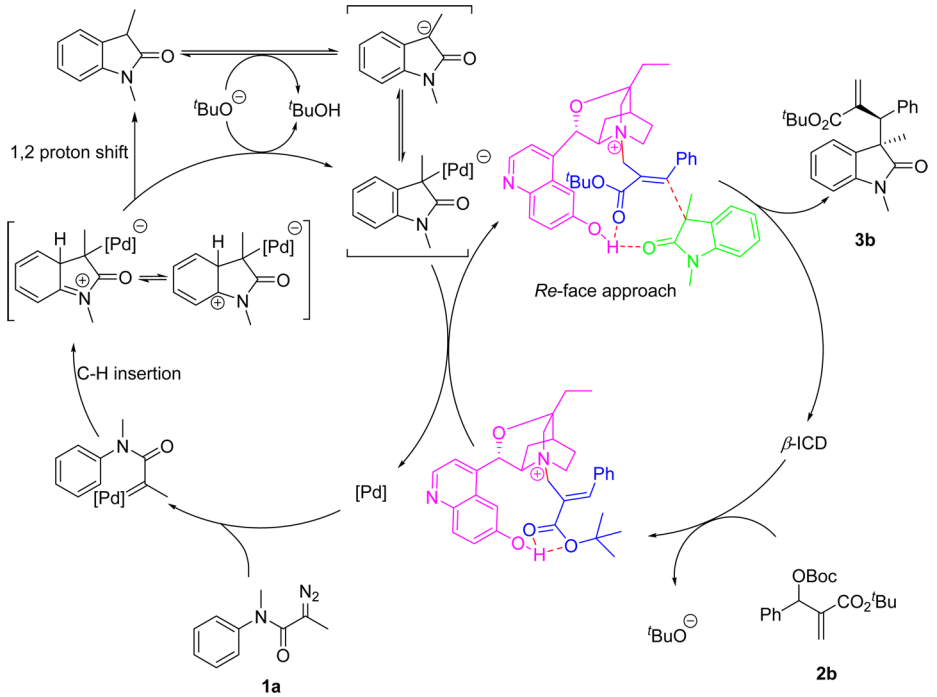
Scheme 2. Proposed Mechanism



raphy on silica gel (EtOAc/petroleum ether = 1:20−1:10) to give the pure product **3**.

*Methyl 2-((1,3-Dimethyl-2-oxoindolin-3-yl)(phenyl)methyl)-acrylate (**3a**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.17 (m, 6H), 7.02 (td, J = 7.6, 0.9 Hz, 1H), 6.88−6.77 (m, 2H), 6.31 (s, 1H), 5.54 (s, 1H), 4.71 (s, 1H), 3.67 (s, 3H), 3.17 (s, 3H), 1.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.7, 166.0, 142.2, 138.8, 135.9, 131.5, 129.4, 127.1, 126.6, 126.2, 125.1, 123.6, 121.2, 106.9, 51.1, 50.0, 49.9, 25.1, 23.7. HRMS (ESI$^+$): calcd for $C_{21}H_{21}NO_3Na^+$ ([M + Na]$^+$), 358.1419; found, 358.1409.

*tert-Butyl 2-((R)-((R)-1,3-Dimethyl-2-oxoindolin-3-yl)(phenyl)-methyl)acrylate (**3b**).* $[\alpha]_D^{25}$ = −119.8 (c 0.42, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.05 (m, 6H), 6.96 (t, J = 7.5 Hz, 1H), 6.79 (t, J = 8.2 Hz, 2H), 6.15 (s, 1H), 5.29 (s, 1H), 4.56 (s, 1H), 3.15 (s, 3H), 1.37 (s, 3H), 1.29 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.7, 165.8, 143.2, 141.5, 137.6, 132.7, 130.6, 128.0, 127.6, 127.0, 124.6, 124.6, 122.2, 108.0, 80.8, 51.3, 50.6, 27.8, 26.2, 25.3. HRMS (ESI$^+$): calcd for $C_{24}H_{27}NO_3Na^+$ ([M + Na]$^+$), 400.1889; found, 400.1891.

*Methyl 2-((6-Bromo-1,3-dimethyl-2-oxoindolin-3-yl)(phenyl)-methyl)acrylate (**3c**).* ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J = 7.6 Hz, 1H), 7.27 (s, 3H), 7.19 (s, 2H), 6.90 (s, 1H), 6.63 (d, J = 7.9 Hz, 1H), 6.30 (s, 1H), 5.54 (s, 1H), 4.63 (s, 1H), 3.64 (s, 3H), 3.09 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.1, 166.9, 142.3, 139.6, 136.4, 134.7, 130.9, 130.3, 127.8, 127.6, 126.2, 114.9, 109.3, 52.2, 51.2, 51.1, 26.2, 24.6. HRMS (ESI$^+$): calcd for $C_{21}H_{20}NO_3NaBr^+$ ([M + Na]$^+$), 436.0524; found, 436.0502.

*tert-Butyl 2-((R)-((R)-3-Benzyl-1-methyl-2-oxoindolin-3-yl)-(phenyl)methyl)acrylate (**3d**).* $[\alpha]_D^{25}$ = −102.2 (c 0.40, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34−7.28 (m, 5H), 7.12 (td, J = 7.6, 1.7 Hz, 1H), 6.98−6.86 (m, 5H), 6.59 (d, J = 7.3 Hz, 2H), 6.41 (d, J = 7.8 Hz, 1H), 6.14 (s, 1H), 5.23 (s, 1H), 4.78 (s, 1H), 3.36 (d, J = 12.4 Hz, 1H), 2.93 (d, J = 12.4 Hz, 1H), 2.79 (s, 3H), 1.31 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.0, 165.8, 143.9, 141.7, 137.7, 135.1, 130.9, 129.8, 129.6, 128.0, 127.7, 127.2, 127.1, 126.3, 125.5, 124.8, 121.7, 107.6, 80.9, 56.8, 51.1, 45.1, 27.8, 25.7. HRMS (ESI$^+$): calcd for $C_{30}H_{31}NO_3Na^+$ ([M + Na]$^+$), 476.2202; found, 476.2182.

*tert-Butyl 2-((R)-((R)-1-Ethyl-3-methyl-2-oxoindolin-3-yl)(phenyl)-methyl)acrylate (**3e**).* $[\alpha]_D^{25}$ = −67.5 (c 0.78, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21−7.08 (m, 6H), 6.87 (td, J = 7.6, 0.8 Hz, 1H), 6.75 (d, J = 7.4 Hz, 1H), 6.71 (d, J = 7.8 Hz, 1H), 6.10 (s, 1H), 5.31 (s, 1H), 4.50 (s, 1H), 3.77 (dq, J = 14.4, 7.2 Hz, 1H), 3.48 (dq, J = 14.3, 7.2 Hz, 1H), 1.29 (s, 3H), 1.23 (s, 9H), 1.06 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.2, 164.9, 141.2, 140.2, 136.6, 131.9, 129.5, 126.8, 126.5, 126.0, 124.0, 123.7, 120.9, 107.0, 79.7, 50.2, 49.4, 33.4, 26.8, 24.1, 11.2. HRMS (ESI$^+$): calcd for $C_{25}H_{29}NO_3Na^+$ ([M + Na]$^+$), 414.2045; found, 414.2053.

*tert-Butyl 2-((R)-(4-Bromophenyl)((R)-1-ethyl-3-methyl-2-oxoin-dolin-3-yl)methyl)acrylate (**3f**).* $[\alpha]_D^{25}$ = −58.9 (c 2.24, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, J = 8.4 Hz, 2H), 7.28−7.21 (m, 1H), 7.04 (d, J = 8.4 Hz, 2H), 6.97 (t, J = 7.3 Hz, 1H), 6.85 (d, J = 7.3 Hz, 1H), 6.78 (d, J = 7.8 Hz, 1H), 6.22 (s, 1H), 5.54 (s, 1H), 4.53 (s, 1H), 3.83 (dq, J = 14.4, 7.2 Hz, 1H), 3.53 (dq, J = 14.2, 7.1 Hz, 1H), 1.36 (s, 3H), 1.33 (s, 9H), 1.11 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.9, 165.7, 142.2, 140.7, 136.8, 132.7, 132.1, 130.7, 128.1, 125.7, 124.4, 122.1, 121.1, 108.2, 81.0, 50.8, 50.4, 34.5, 27.9, 24.8, 12.2. HRMS (ESI$^+$): calcd for $C_{25}H_{28}NO_3NaBr^+$ ([M + Na]$^+$), 492.1150; found, 492.1151.

*tert-Butyl 2-((R)-((R)-1-Ethyl-3-methyl-2-oxoindolin-3-yl)(4-fluorophenyl)methyl)acrylate (**3g**).* $[\alpha]_D^{25}$ = −98.0 (c 2.18, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28−7.21 (m, 1H), 7.16−7.10 (m, 2H), 6.97 (td, J = 7.6, 0.9 Hz, 1H), 6.95−6.89 (m, 2H), 6.84 (d, J = 6.8 Hz, 1H), 6.78 (d, J = 7.8 Hz, 1H), 6.21 (s, 1H), 5.52 (s, 1H), 4.54 (s, 1H), 3.83 (dq, J = 14.4, 7.3 Hz, 1H), 3.53 (dq, J = 14.3, 7.2 Hz, 1H), 1.36 (s, 3H), 1.33 (s, 9H), 1.12 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.1, 165.8, 162.0 (d, J = 245.6 Hz), 142.2, 141.0, 133.4 (d, J = 3.2 Hz), 132.9, 131.9 (d, J = 8.0 Hz), 128.0, 125.4, 124.4, 122.0, 114.4 (d, J = 21.2 Hz), 108.2, 80.9, 50.63, 50.56, 34.5, 27.9, 24.8, 12.2. HRMS (ESI$^+$): calcd for $C_{25}H_{28}NO_3NaF^+$ ([M + Na]$^+$), 432.1951; found, 432.1961.

*tert-Butyl 2-((R)-((R)-1-Benzyl-3-methyl-2-oxoindolin-3-yl)-(phenyl)methyl)acrylate (**3h**).* $[\alpha]_D^{25}$ = −80.3 (c 0.58, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23−7.12 (m, 8H), 7.09−7.02 (m, 3H), 6.85 (t, J = 7.4 Hz, 1H), 6.78 (d, J = 7.2 Hz, 1H), 6.58 (d, J = 7.8 Hz, 1H), 6.08 (s, 1H), 5.31 (s, 1H), 4.92 (d, J = 15.6 Hz, 1H), 4.62 (d, J = 15.7 Hz, 1H), 4.59 (s, 1H), 1.35 (s, 3H), 1.26 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.8, 165.9, 142.3, 141.0, 137.6, 135.8, 132.8, 130.6, 128.6, 127.8, 127.7, 127.6, 127.1, 125.5, 124.5, 122.2, 109.1, 80.9, 51.0, 50.7, 43.9, 27.9, 25.7. HRMS (ESI$^+$): calcd for $C_{30}H_{31}NO_3Na^+$ ([M + Na]$^+$), 476.2202; found, 476.2218.

*tert-Butyl 2-((R)-Phenyl((R)-1,3,5-trimethyl-2-oxoindolin-3-yl)-methyl)acrylate (**3i**).* $[\alpha]_D^{25}$ = −106.3 (c 0.48, CH_2Cl_2). ^{1}H NMR

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(400 MHz, $CDCl_3$): δ 7.28−7.22 (m, 3H), 7.21−7.15 (m, 2H), 7.07−7.00 (m, 1H), 6.66 (d, *J* = 7.8 Hz, 1H), 6.61 (s, 1H), 6.15 (s, 1H), 5.31 (s, 1H), 4.54 (s, 1H), 3.12 (s, 3H), 2.25 (s, 3H), 1.35 (s, 3H), 1.29 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.7, 165.9, 141.5, 140.8, 137.7, 132.7, 131.6, 130.6, 128.1, 127.5, 127.0, 125.6, 124.7, 107.6, 80.8, 51.3, 50.5, 27.8, 26.2, 25.3, 21.2. HRMS (ESI^+): calcd for $C_{25}H_{29}NO_3Na^+$ ($[M + Na]^+$), 414.2045; found, 414.2048.

*tert-Butyl 2-((R)-((R)-5-Methoxy-1,3-dimethyl-2-oxoindolin-3-yl)(phenyl)methyl)acrylate (**3j**).* $[\alpha]_D^{25}$ = −127.1 (*c* 0.96, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.43−7.11 (m, 5H), 6.78 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 6.38 (d, *J* = 2.5 Hz, 1H), 6.14 (s, 1H), 5.20 (s, 1H), 4.56 (s, 1H), 3.69 (s, 3H), 3.14 (s, 3H), 1.35 (s, 3H), 1.28 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.5, 165.8, 155.5, 141.5, 137.5, 136.7, 133.8, 130.6, 127.5, 127.2, 124.4, 112.6, 111.9, 108.3, 80.8, 55.7, 51.2, 50.8, 27.8, 26.3, 25.6. HRMS (ESI^+): calcd for $C_{25}H_{29}NO_4Na^+$ ($[M + Na]^+$), 430.1994; found, 430.1973.

*tert-Butyl 2-((R)-((R)-5-Bromo-1,3-dimethyl-2-oxoindolin-3-yl)(phenyl)methyl)acrylate (**3k**).* $[\alpha]_D^{25}$ = −114.2 (*c* 0.78, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 8.0 Hz, 1H), 7.26 (s, 3H), 7.18 (s, 2H), 6.92 (s, 1H), 6.64 (d, *J* = 8.1 Hz, 1H), 6.19 (s, 1H), 5.35 (s, 1H), 4.55 (s, 1H), 3.11 (s, 3H), 1.37 (s, 3H), 1.31 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.1, 165.7, 142.2, 141.2, 137.1, 134.8, 130.8, 130.4, 127.8, 127.7, 127.3, 124.7, 114.9, 109.3, 81.0, 51.3, 50.8, 27.8, 26.2, 25.0. HRMS (ESI^+): calcd for $C_{24}H_{26}NO_3NaBr^+$ ($[M + Na]^+$), 478.0994; found, 478.1003.

*tert-Butyl 2-((R)-((R)-5-Chloro-1,3-dimethyl-2-oxoindolin-3-yl)(phenyl)methyl)acrylate (**3l**).* $[\alpha]_D^{25}$ = −154.8 (*c* 0.74, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.30−7.24 (m, 3H), 7.22 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.18 (dd, *J* = 7.3, 1.7 Hz, 2H), 6.79 (d, *J* = 1.9 Hz, 1H), 6.68 (d, *J* = 8.3 Hz, 1H), 6.18 (s, 1H), 5.34 (s, 1H), 4.55 (s, 1H), 3.12 (s, 3H), 1.37 (s, 3H), 1.30 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.2, 165.7, 141.7, 141.2, 137.1, 134.5, 130.4, 127.9, 127.7, 127.6, 127.3, 125.1, 124.7, 108.8, 81.0, 51.3, 50.9, 27.8, 26.3, 25.0. HRMS (ESI^+): calcd for $C_{24}H_{26}NO_3NaCl^+$ ($[M + Na]^+$), 434.1499; found, 434.1496.

*tert-Butyl 2-((R)-((R)-5-Fluoro-1,3-dimethyl-2-oxoindolin-3-yl)(phenyl)methyl)acrylate (**3m**).* $[\alpha]_D^{25}$ = −112.6 (*c* 0.29, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.28−7.26 (m, 3H), 7.22−7.14 (m, 2H), 6.95 (td, *J* = 8.9, 2.5 Hz, 1H), 6.69 (dd, *J* = 8.4, 4.2 Hz, 1H), 6.57 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.17 (s, 1H), 5.29 (s, 1H), 4.55 (s, 1H), 3.14 (s, 3H), 1.37 (s, 3H), 1.29 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.4, 165.7, 158.9 (d, *J* = 240.3 Hz), 141.3, 139.1 (d, *J* = 1.8 Hz), 137.2, 134.4 (d, *J* = 8.1 Hz), 130.4, 127.7, 127.3, 124.6, 114.1 (d, *J* = 23.5 Hz), 112.8 (d, *J* = 25.2 Hz), 108.3 (d, *J* = 8.2 Hz), 80.9, 51.3, 51.0 (d, *J* = 1.7 Hz), 27.8, 26.3, 25.2. HRMS (ESI^+): calcd for $C_{24}H_{26}NO_3NaF^+$ ($[M + Na]^+$), 418.1794; found, 418.1812.

*tert-Butyl 2-((R)-((R)-1,3-Dimethyl-2-oxoindolin-3-yl)(p-tolyl)methyl)acrylate (**3o**).* $[\alpha]_D^{25}$ = −120.0 (*c* 0.50, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.29−7.20 (m, 1H), 7.11−7.03 (m, 4H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.79 (t, *J* = 8.3 Hz, 2H), 6.10 (s, 1H), 5.20 (s, 1H), 4.53 (s, 1H), 3.15 (s, 3H), 2.32 (s, 3H), 1.35 (s, 3H), 1.30 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.9, 165.9, 143.2, 141.7, 136.6, 134.5, 132.7, 130.4, 128.3, 127.9, 124.7, 124.2, 122.1, 107.9, 80.7, 50.8, 50.6, 27.8, 26.2, 25.3, 21.1. HRMS (ESI^+): calcd for $C_{25}H_{29}NO_3Na^+$ ($[M + Na]^+$), 414.2045; found, 414.2044.

*tert-Butyl 2-((R)-(4-Bromophenyl)((R)-1,3-dimethyl-2-oxoindolin-3-yl)methyl)acrylate (**3p**).* $[\alpha]_D^{25}$ = −79.5 (*c* 0.73, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 8.3 Hz, 2H), 7.26 (t, *J* = 7.7 Hz, 1H), 7.05 (d, *J* = 8.3 Hz, 2H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 7.4 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.19 (s, 1H), 5.44 (s, 1H), 4.52 (s, 1H), 3.13 (s, 3H), 1.36 (s, 3H), 1.32 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.4, 165.6, 143.1, 140.9, 136.9, 132.5, 132.1, 130.7, 128.2, 125.3, 124.3, 122.3, 121.1, 108.1, 81.0, 50.8, 50.5, 27.9, 26.2, 24.9. HRMS (ESI^+): calcd for $C_{24}H_{26}NO_3NaBr^+$ ($[M + Na]^+$), 478.0994; found, 478.0979.

*tert-Butyl 2-((R)-((R)-1,3-Dimethyl-2-oxoindolin-3-yl)(4-fluorophenyl)methyl)acrylate (**3q**).* $[\alpha]_D^{25}$ = −97.2 (*c* 0.54, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (t, *J* = 7.7 Hz, 1H), 7.13 (dd, *J* = 8.2, 5.6 Hz, 2H), 6.98 (t, *J* = 7.6 Hz, 1H), 6.93 (t, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 7.4 Hz, 1H), 6.77 (d, *J* = 7.8 Hz, 1H), 6.19 (s, 1H), 5.44 (s, 1H), 4.54 (s, 1H), 3.13 (s, 3H), 1.37 (s, 3H), 1.32 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.5, 165.7, 162.0 (d, *J* = 245.6 Hz), 143.1, 141.2, 133.4 (d, *J* = 3.2 Hz), 132.6, 131.9 (d, *J* = 7.9 Hz), 128.1, 125.0, 124.3, 122.3, 114.4 (d, *J* = 21.2 Hz), 108.1, 81.0, 50.70, 50.68, 27.9, 26.2, 24.9. HRMS (ESI^+): calcd for $C_{24}H_{26}NO_3NaF^+$ ($[M + Na]^+$), 418.1794; found, 418.1807.

*tert-Butyl 2-((R)-(3-Chlorophenyl)((R)-1,3-dimethyl-2-oxoindolin-3-yl)methyl)acrylate (**3r**).* $[\alpha]_D^{25}$ = −96.5 (*c* 0.52, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 (t, *J* = 7.7 Hz, 1H), 7.23−7.14 (m, 3H), 7.07 (d, *J* = 7.3 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 7.4 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 6.20 (s, 1H), 5.41 (s, 1H), 4.53 (s, 1H), 3.14 (s,3H), 1.37 (s, 3H), 1.33 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.3, 165.6, 143.1, 140.8, 140.0, 133.4, 132.4, 130.4, 128.8, 128.6, 128.2, 127.2, 125.4, 124.3, 122.4, 108.1, 81.1, 51.1, 50.5, 27.9, 26.2, 24.9. HRMS (ESI^+): calcd for $C_{24}H_{26}NO_3NaCl^+$ ($[M + Na]^+$), 434.1499; found, 434.1488.

*tert-Butyl 2-((R)-((R)-1,3-Dimethyl-2-oxoindolin-3-yl)(4-nitrophenyl)methyl)acrylate (**3s**).* $[\alpha]_D^{25}$ = −46.9 (*c* 0.22, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J* = 8.6 Hz, 2H), 7.31 (d, *J* = 8.6 Hz, 2H), 7.29−7.24 (m, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 7.3 Hz, 1H), 6.75 (d, *J* = 7.8 Hz, 1H), 6.34 (s, 1H), 5.82 (s, 1H), 4.66 (s, 1H), 3.10 (s, 3H), 1.42 (s, 3H), 1.34 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.8, 165.4, 147.0, 145.8, 143.0, 139.9, 132.2, 131.0, 128.5, 126.9, 123.8, 122.7, 122.6, 108.3, 81.4, 51.5, 50.7, 27.9, 26.2, 24.4. HRMS (ESI^+): calcd for $C_{24}H_{26}N_2O_5Na^+$ ($[M + Na]^+$), 445.1739; found, 445.1746.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01703.

X-ray crystal data for compound **3c** (CIF)
X-ray crystal data for compound **3p** (CIF)
^1H and ^{13}C NMR spectra data and HPLC spectra data for compounds **3a**−**3s** (PDF)

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Notes

The authors declare no competing financial interest.

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