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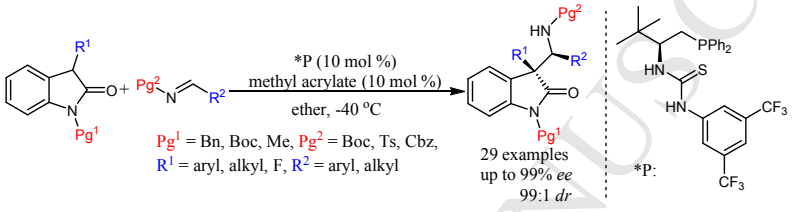

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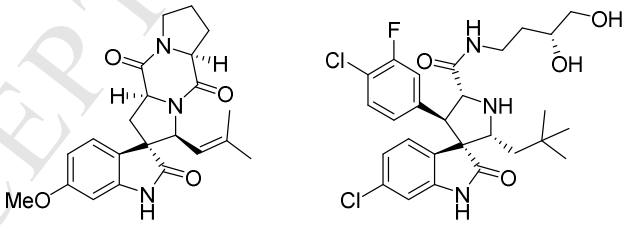
ABSTRACT

A combination of an amino acid-derived chiral phosphine catalyst and methyl acrylate to catalyze the direct Mannich reaction of 3-substituted oxindoles and imines has been reported to afford 3-tetrasubstituted oxindole derivatives which are key structures for biological activities. The products are formed with a quaternary carbon and featured with two adjacent chiral centers. Various *N*-EDG(electron-donating group) and *N*-EWG(electron-withdrawing group) protected oxindoles, including 3-aryl and 3-alkyl substituted ones, have been evaluated with aromatic and aliphatic imines under this catalytic system, smoothly giving desired products in good yields as well as excellent diastereo- and enantioselectivities.

1. Introduction

3,3'-Pyrrolidinyl spirooxindole scaffolds are important structural motifs found in a wide array of natural and synthesized biologically active molecules.[1] For instance, **MI-147**,[2] which is a rationally designed molecule based on natural occurring spirotryprostatin A, functions as a specific and potent inhibitor of MDM2-p53 interaction to selectively inhibit the growth of tumor cells (Figure 1). The direct Mannich-type reaction of 3-substituted oxindoles with imines is a straightforward method for making enantioenriched spirooxindole consisting of adjacent chiral centers. However, enantioselective synthesis of the stereogenic centers is problematic due to the steric congestion when two chiral centers at the 3-position of oxindole formed simultaneously. Since Chen and co-workers[3] reported the first reaction between *N*-Boc-3-alkyl oxindoles and *N*-Boc-imines in the presence of bifunctional thiourea-tertiary amine in 2008, several progresses have been made in this field[4-11]. However, to the best of our knowledge, the general flexibility of the reported catalyst system in the reactions between *N*-protected oxindoles bearing kinds of 3-position substituents and different *N*-protected imines was still challenging. Herein, we attempt to address this problem by development of a novel catalytic system which is effective for the Mannich reactions of 3-aryl, alkyl or halogen substituted *N*-Bn and *N*-Boc protected oxindoles with aromatic or aliphatic imines.



Spirotryprostatin A **MI 147**

Figure 1. Natural product and unnaturally bioactive analogue.

Recently our group has developed chiral phosphine catalyzed Mannich-type reactions of several nucleophiles to *N*-Boc-imines, via asymmetric dual-reagent catalysis by zwitterions formed from the phosphine catalyst and methyl acrylate in situ[12-15]. This novel catalytic strategy exhibited high efficiency and an excellent degree of enantiocontrol in creating chiral compounds. As a continued study, we are testing this strategy in the reaction of 3-substituted oxindoles with imines. Various kinds of oxindoles, not only aromatic imines but also aliphatic imines, have worked well. High yields and high diastereo- and enantioselectivities have been obtained (Scheme 1).

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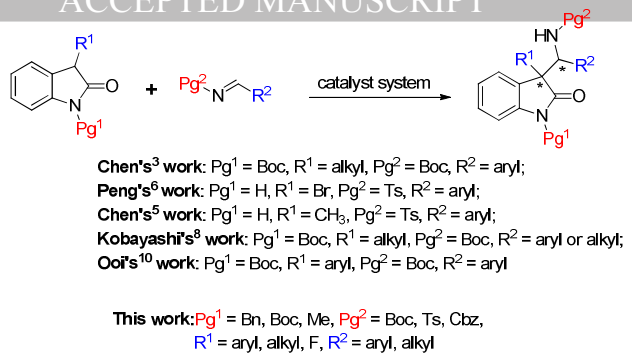
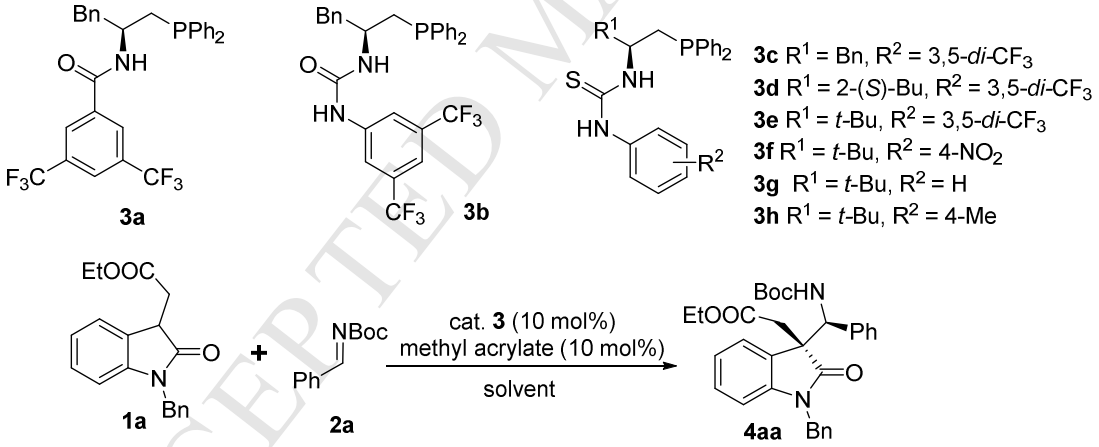


Scheme 1. The asymmetric Mannich reaction of 3-substituted oxindoles with imines

2. Results and Discussion

We chose *N*-benzyl oxindole **1a** and *N*-Boc-imine **2a** as models, and several conditions were examined. When the reaction was performed in toluene at room temperature in the presence of bifunctional chiral phosphine catalysts **3a**, **3b**, and **3c** derived from L-phenylalanine, the better results came with **3c** bearing a thiourea moiety which afforded the desired product **4aa** with 94:6 dr and 76 % ee (Table 1, entries 1-3). Herein, with the thiourea part in place, five additional chiral phosphine catalysts derived from isoleucine and L-*tert*-butyl-leucine were evaluated. The results shown that catalyst **3e** with a strongly electron-withdrawing trifluoromethyl group at the 3,5-positions of the phenyl thiourea from L-*tert*-butyl-leucine, turned out to be the best one, giving the desired product in 87% yield, 92:8 dr and 78% ee (Table 1, entries 4-8). Solvent and temperature effect were then investigated. The use of ether as solvent improved the enantioselectivity to 85% ee (Table 1, entries 9-12). Under lower temperature, we got the optimal conditions as demonstrated in entry 15 by running the reaction in 1.0 mL of ether at -40 °C to provide the product with 95:5 dr and 94% ee (Table 1, entries 13-15). The reaction could not proceed without methyl acrylate until the temperature rose up to room temperature and only 68:32 dr and 61% ee were obtained, suggesting the indispensable role of methyl acrylate in imparting stereocontrol (Table 1, entry 16).

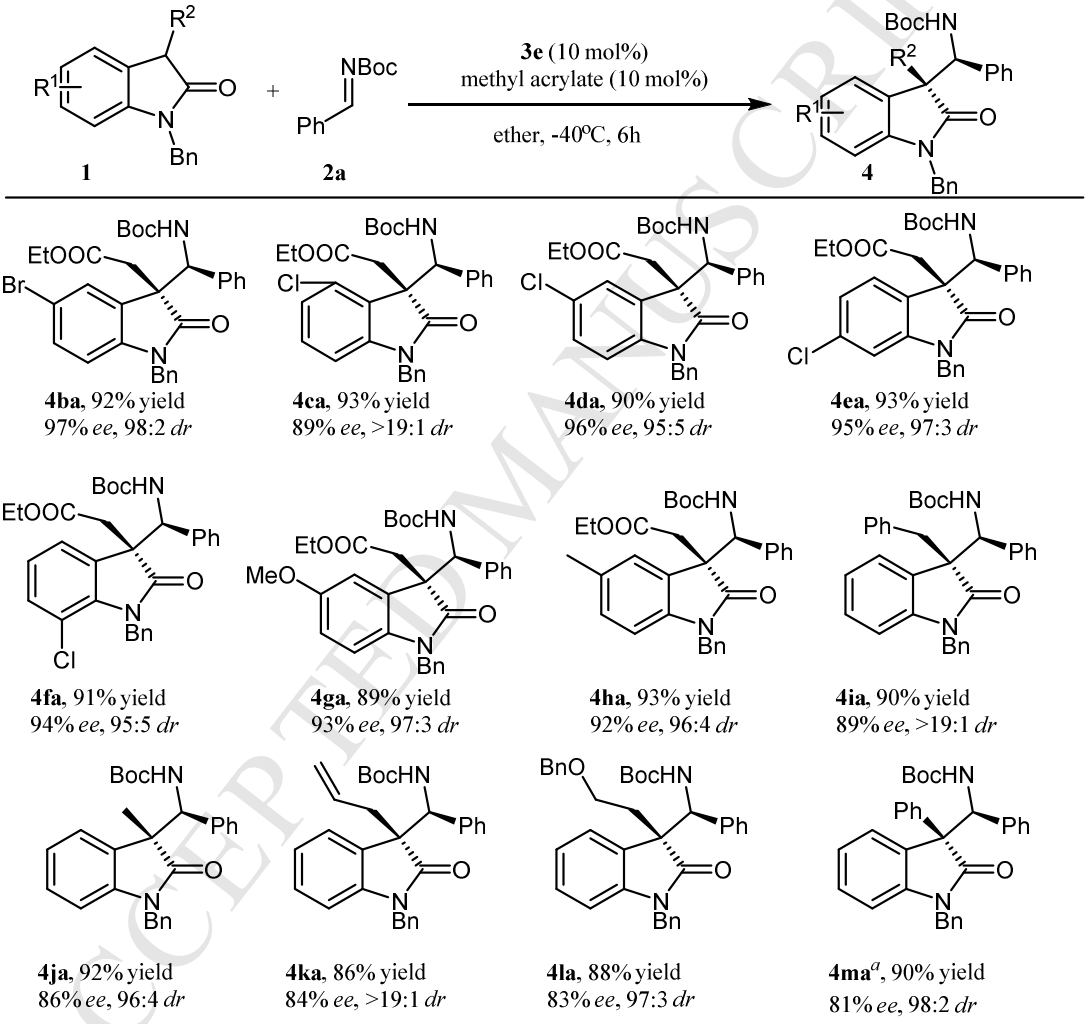
Table 1. Optimization of conditions and evaluation of chiral catalysts.



Entry [a]	Cat.	solvent	Temperature (°C)	Time	Yield (%)[b]	dr [c]	ee (%)[c]
1	**3a**	toluene	r.t.	10 min	88	71:29	16
2	**3b**	toluene	r.t.	10 min	86	90:10	41
3	**3c**	toluene	r.t.	10 min	87	94:6	76
4	**3d**	toluene	r.t.	10 min	88	94:6	69
5	**3e**	toluene	r.t.	10 min	87	92:8	78
6	**3f**	toluene	r.t.	10 min	89	88:12	57
7	**3g**	toluene	r.t.	10 min	90	86:14	31
8	**3h**	toluene	r.t.	10 min	91	87:13	34
9	**3e**	DCM	r.t.	10 min	89	87:13	78
10	**3e**	$CHCl_3$	r.t.	40 min	89	84:16	73
11	**3e**	THF	r.t.	10 min	87	86:14	24
12	**3e**	Et_2O	r.t.	10 min	90	92:8	85
13	**3e**	Et_2O	0	30 min	87	92:8	89
14	**3e**	Et_2O	-20	3 h	89	94:6	91
15	**3e**	Et_2O	-40	6 h	88	95:5	94
16[f]	**3e**	Et_2O	r.t.	1h	75	68:32	61

[a] Unless otherwise noted, the reaction was conducted with 0.1 mmol of **1a**, 0.2 mmol of **2a**, and 0.01 mmol of acrylate in the presence of 10 mol % of catalyst **3** in 1 mL of solvent.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[f] Without methyl acrylate.

Under the optimized conditions, a series of substituted *N*-benzyl oxindoles were examined and the results were summarized in Scheme 2. All the reactions proceeded well for *N*-benzyl oxindoles based on **1a** bearing electron-donating and electron-withdrawing groups on the benzene ring (**4ba**-**4ha**), and different substitution positions had no significant effect on the results except the 4-substitued product **4ca**, which had a slightly decreased enantioselectivity. When 3-benzyl, 3-methyl, 3-allyl and 3-benzoxylethyl substituted oxindoles were examined, good to high diastereoselectivities were obtained albeit with lower enantioselectivities (**4ia**-**4la**, 83-89% ee). Besides these substrates, the reaction with the 3-phenyl substituted oxindole **1m**, which with a modified conditions (catalyst **3c** in DCM at -40 ^{o}C), gave the corresponding product **4ma** in 90% yield with a little inferior enantioselectivity (81% ee).

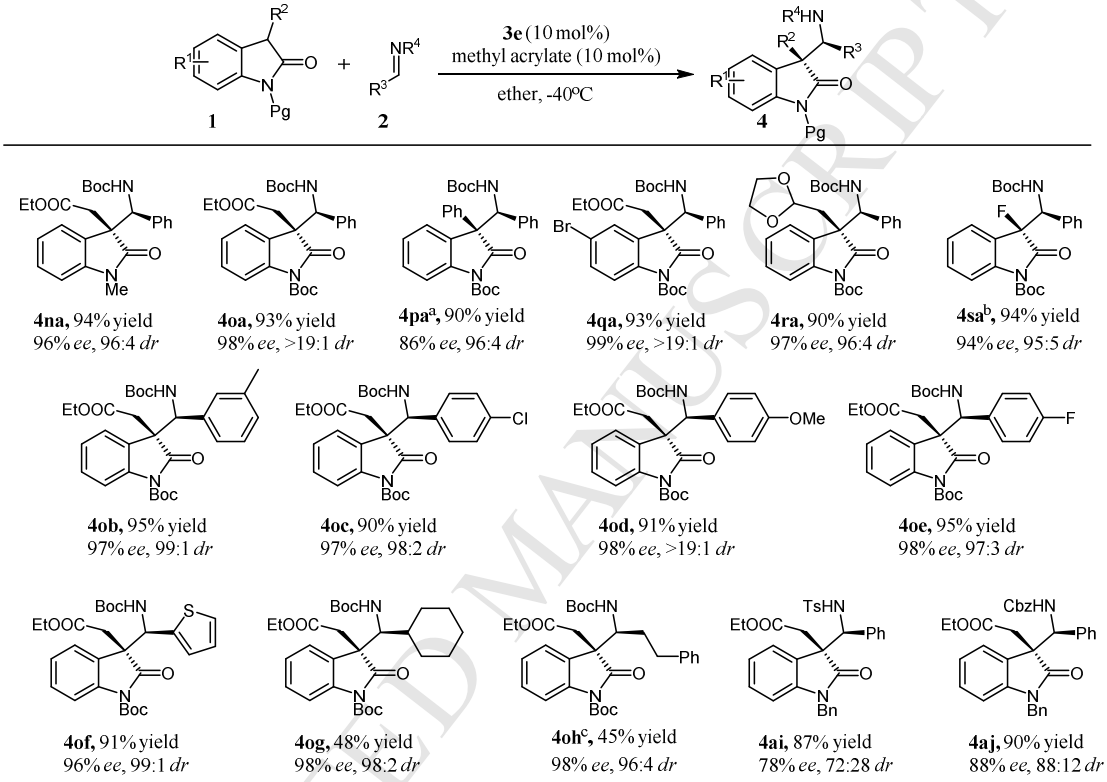


[a] Performed in DCM at -40^{o}C with **3c.**

Scheme 2. Exploring the scope of the *N*-benzyl protected oxindoles

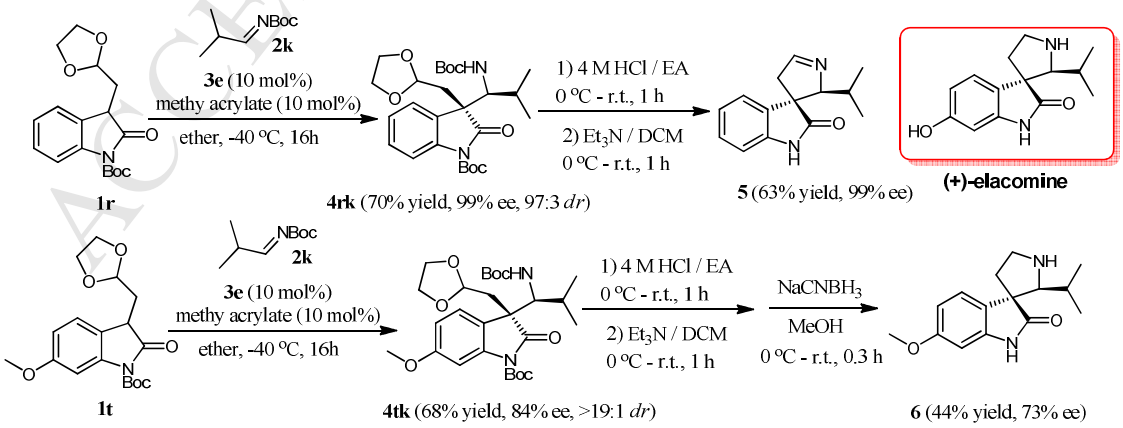
Next, we continued to try other *N*-protected oxindoles with a variety of imines to test the catalytic system. When the *N*-methyl, *N*-Boc protected 3-alkyl oxindoles **1n** and **1o** were examined, both excellent diastereo- and enantioselectivities were obtained (Scheme 3, **4na** and **4oa**) while the *N*-Boc oxindole substrate gave a higher ee value. A little inferior result with *N*-Boc 3-phenyl-oxindole **1p** was observed in terms of the enantioselectivity, even if the reaction could proceed with high efficiency to give the product in high yield and diastereoselectivity (90% yield, 96:4 dr). It should be noted that substrates with different *N*-protecting group in previous reactions had never been achieved with one catalytic system. The absolute configuration of the resulted **4ra** was determined by comparison of the NMR spectra and specific optical rotation with the literature data[8] and other adducts were assigned by analogy according to **4ra**. We also applied *N*-Boc-3-fluorooxindole **1s** with **2a** in the presence of catalysts **3d** in DCM at room temperature, giving the desired product **4sa** in 94 % yield with 95:5 dr and 94 % ee. With excellent results achieved with different *N*-protected oxindoles, we then chose to investigate the reactions of *N*-Boc oxindoles with a

variety of imines. Reactions with imines **2b**-**2e** bearing electron-withdrawing or electron-donating substituents at the benzene rings proceeded smoothly to afford the desired products in high yields as well as excellent diastereo- and enantioselectivities (**4ob**-**4oe**). Similar results were obtained when heteroaromatic imine **2f** was examined (**4of**). Aliphatic imines **2g** and **2h** were also well tolerated in this reaction, giving the desired products with excellent diastereo- and enantioselectivities albeit with low yields (**4og** and **4oh**). Noteworthy, this type of reactions with both aliphatic and aromatic imines to give excellent diastereo- and enantioselectivities products was also extremely rare in previous reports. Reactions with *N*-Cbz imine **2j** and *N*-Ts imine **2i** were also tested and the inferior results obtained suggested the Boc group at the imine nitrogen played a key role in this reaction (**4ai** and **4aj**). The adduct **4rk** and **4tk**, obtained by the reaction of **1r, 1t** and the aliphatic imine **2k** in 99% ee,97:3 dr, and 99% ee, >19:1dr respectively were readily converted to spirooxindole derivative **6**which contains a key skeleton of the nature product (+)-elacomine(Scheme 4).[8] Thus, we have succeeded in providing oxindole derivatives that have adjacent quaternary and tertiary chiral centers in satisfactory yields and stereoselectivities with wide substrate scope.



[a] Performed in DCM at -40°C with **3c**. [b] **3d** was used in DCM at room temperature. [c] The reaction was stirred for 24h**.**

Scheme 3. Exploration of a variety of oxindoles and imines [a]



Scheme 4. Transformation to spirooxindole

To get some insight into this reaction, ^{31}P NMR analysis of **3e** and methyl acrylate in deuterated ether was performed (Figure 2). We proposed a zwitterion intermediate **A** was formed during the reaction as a new P NMR chemical shift was generated at δ=26 ppm when catalyst **3e** and methyl acrylate was first mixed. This was further confirmed by ESI-MS (see the Supporting

Information) with a single peak (*m/z* for $(M+H)^+$:643.2500) observed. A new single resonance appeared at δ=27 ppm when nucleophile **1a** was mixed with the above solution, suggesting the zwitterion **A** was converted into a new species which we proposed to be the ion-pair **B**. On the basis of these experimental results and previous related studies, a plausible transition state was proposed to explain the stereochemistry of the product (Scheme 5). Firstly, the chiral phosphine adds to the methyl acrylate to form the phosphonium enolate **A** which trapped by nucleophile 3-substituted oxindole **1** to generate the ion-pair **B**. At the same time, the *N*-Boc-imine is activated by the thiourea moiety through hydrogen bonding, giving strict conformational control that results in an excellent recognition of the *Re*-face of the imine by the chiral ion pair. These interactions control the stereochemical outcome of the reaction.

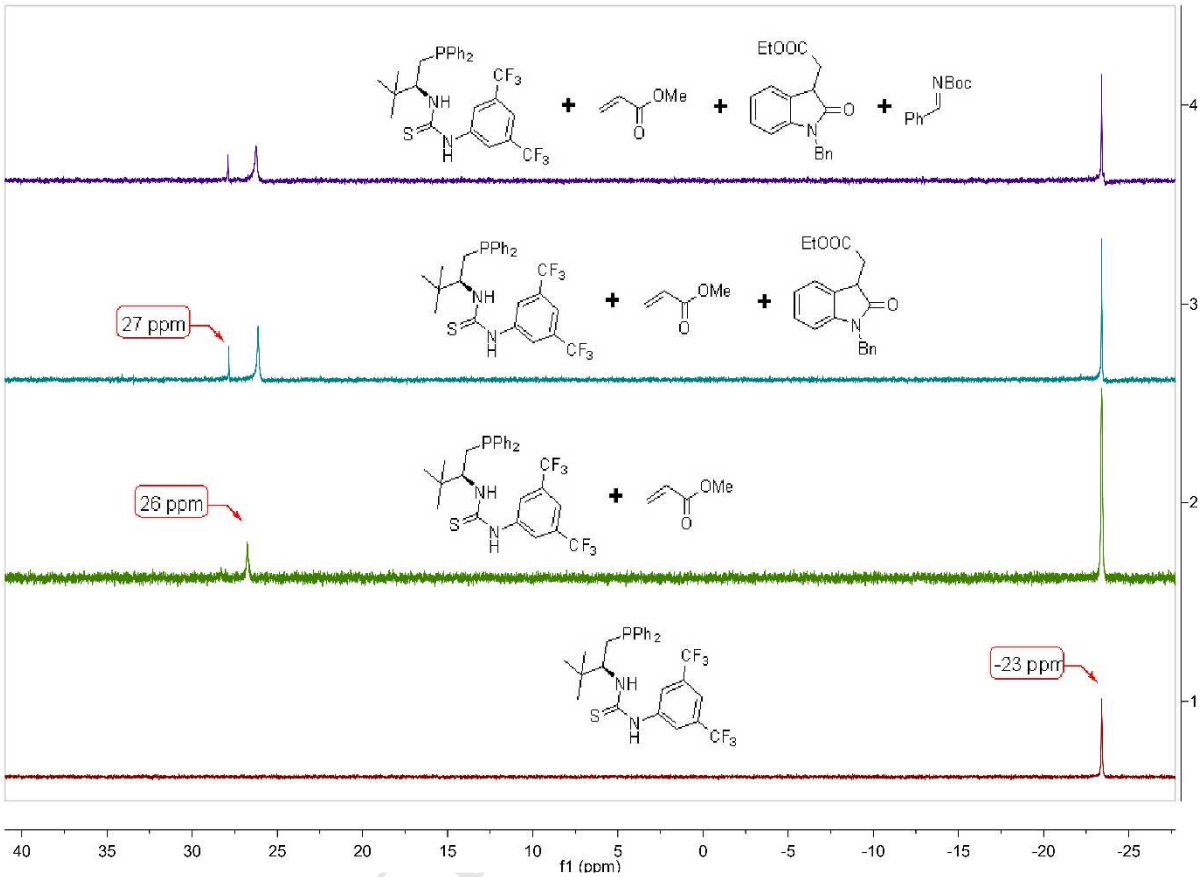
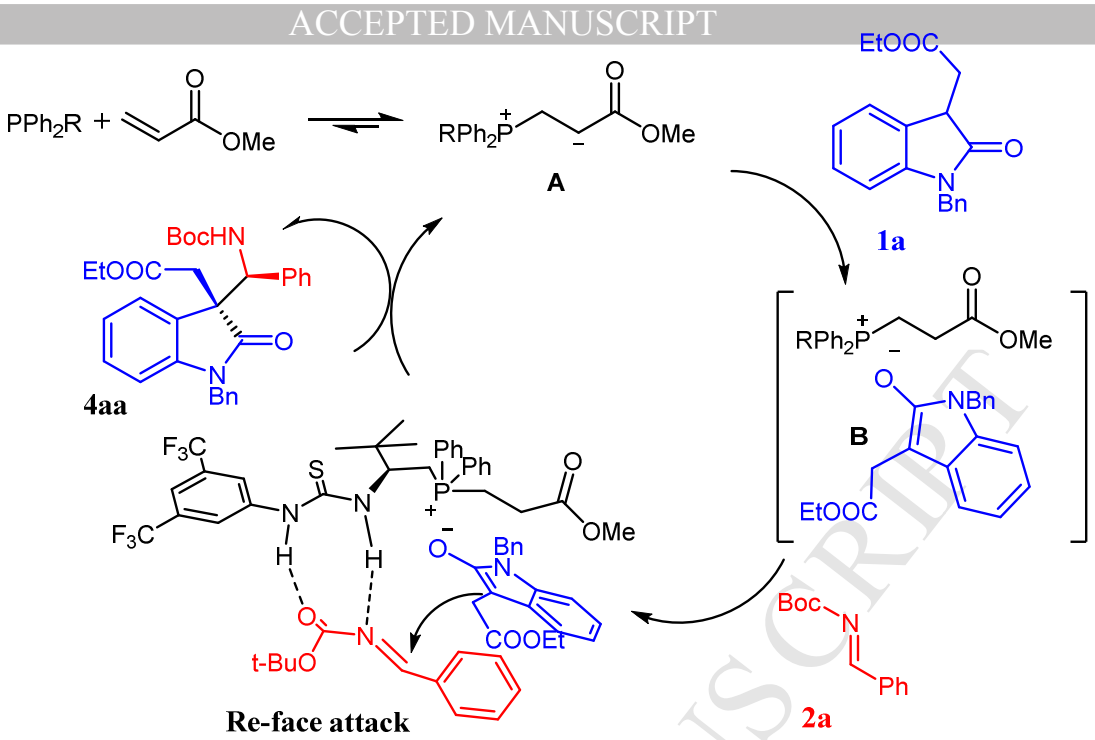


Figure 2. The ^{31}P NMR spectra research in ether



Scheme 5. Possible reaction mechanism and transition state

3. Conclusions

In summary, we have developed a new catalytic method for the synthesis of optically active 3-tetrasubstituted oxindoles using chiral bifunctional thiourea-phosphine via a dual-reagent catalysis. Adjacent quaternary and tertiary chiral centers have been created efficiently by the phosphine-catalyzed reactions of 3-substituted oxindoles with imines. Various *N*-EDG and *N*-EWG protected oxindoles, including 3-aryl and 3-alkyl substituted ones, reacted with aromatic and aliphatic *N*-protected-imines smoothly in this catalyst system, giving the desired products in good yields as well as excellent diastereo- and enantioselectivities. Further studies on this topic are underway in our laboratories.

4. Experimental

4.1 General information

Nuclear magnetic resonance spectra were recorded at 400 MHz. All chemical shifts (δ) were given in ppm. Data were reported as follows: chemical shift, intergration, multiplicity (s = single, d = doublet, t = triplet, q = quarter, br = broad, m= multiplet, cm = complex multiplet) and coupling constants (Hz). Flash column chromatography was performed using H silica gel. For thin-layer chromatography (TLC), silica gel plates (HSGF 254) were used and compounds were visualized by irradiation with UV light. Analytical high-performance liquid chromatography (HPLC) was carried out using chiral columns. Melting points were uncorrected. Optical rotations were measured at λ = 589 nm. High-resolution mass spectra were recorded using TOF mass analyzer. The synthesis of 3-substituted oxindoles,[16-17] **2**[3-10,18] and the catalysts **3a**-**3h**[12-15] were performed according to reported methods.

*4.2 General procedure for the preparation of substrates **1***

A mixture of corresponding oxindole (0.1 mmol, 1.0 equiv) and indium chloride (0.01 mmol, 0.1 equiv) in acetonitrile (5 mL) was stirred at 0^{o}C for 5 min $NaBH_4$ (0.2 mmol, 2.0 equiv) was added and the reaction mixture was stirred at room temperature for another 10 min. The resulting solution was poured into satd. aq.NH_4Cl, and the organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (petrolume ether/ethyl acetate = 9/1-5/1) to afford the product **1d-1f** and **1q**.

A mixture of NaH (0.2 mmol, 2.0eq) and ylide salt[19] (0.2mmol, 2.0eq) was stirred at 0^{o}C for 1h under N_2 protection. Then 6-methoxyindoline-2,3-dione (0.1 mmol, 1.0eq) was added and the mixture was stirred under 80^{o}C for 2h. The resulting solution was poured into satd.aq.NH_4Cl, and the organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure and the product was dissolved in CH_3CN, follwed by DMAP (0.2 mmol, 2.0eq), $(Boc)_2O$ (0.2 mmol, 2.0eq) were added ,the mixture was stirred under room temperature for 20min. The crude product product was also obtained after the solvent was removed under reduced pressure and then dissloved in EA and stirred with Pd/C under H_2 condition for 4h under room temperature. The mixture was filtered and purified by silica gel chromatography (petrolume ether/ethyl acetate = 8/1-5/1) to afford the product **1t**

*4.2.1 Ethyl 2-(1-benzyl-5-chloro-2-oxoindolin-3-yl) acetate (**1d**)*

29.8 mg, 87% yield, yellow solid, m.p. 65-66^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ(ppm) = 7.25-7.30 (m, 6H), 7.11 (dd, *J* = 1.2 Hz, *J* = 8.4 Hz,1H), 6.61 (d, *J* = 8.4 Hz, 1H), 4.90 (s, 2H), 4.11-4.16 (m, 2H), 3.82-3.85 (m, 1H), 3.12 (dd, *J* = 4.0 Hz, *J* = 16.8 Hz,1H), 2.88 (dd, *J* = 7.6 Hz, *J* = 17.2 Hz,1H), 1.19 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 176.3, 170.7, 142.1, 135.4, 129.9, 128.9, 128.1, 127.9, 127.8, 127.3, 124.5, 110.0, 61.1, 44.0, 41.9, 34.7, 14.1. **IR** (KBr): 3064, 3031, 2980, 2928, 1720, 1611, 1485, 1431, 1343, 1261, 1207, 1165, 1029. **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{19}ClNO_3$ 344.1048, found 344.1045.

*4.2.2 Ethyl 2-(1-benzyl-6-chloro-2-oxoindolin-3-yl) acetate (**1e**)*

30.5 mg, 89% yield, yellow solid, m.p. 93-94^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ(ppm) = 7.27-7.33 (m, 5H), 7.16 (dd, *J* = 0.8 Hz, *J* = 8.0 Hz, 1H), 6.96 (dd, *J* = 2.0 Hz, *J* = 8.0 Hz, 1H), 6.71 (d, *J* = 1.6 Hz, 1H), 4.89 (s, 2H), 4.10-4.14 (m, 2H), 3.81 (dd, *J* = 4.0 Hz, *J* = 7.2 Hz, 1H), 3.12 (dd, *J* = 4.4 Hz, *J* = 17.2 Hz, 1H), 2.87 (dd, *J* = 8.0 Hz, *J* = 17.2 Hz, 1H), 1.18 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 176.8, 170.7, 144.8, 135.3, 134.0, 128.9, 127.8, 127.3, 126.6, 124.8, 122.4, 109.7, 61.1, 44.1, 41.5, 34.8, 14.1. **IR** (KBr): 3062, 3030, 2980, 2929, 1723, 1610, 1588, 1498, 1441, 1373, 1339, 1257, 1206, 1112, 1072, 1029, 923, 841, 699, 524. **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{19}NO_3Cl$ 344.1048, found 344.1044.

*4.2.3 Ethyl 2-(1-benzyl-7-chloro-2-oxoindolin-3-yl) acetate (**1f**)*

29.8 mg, 87% yield, yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ(ppm) = 7.23-7.30 (m, 5H), 7.15-7.18 (m, 2H), 6.94 (dd, *J* = 7.2 Hz, *J* = 8.0 Hz, 1H), 5.37 (dd, *J* = 16.4 Hz, *J* = 21.2 Hz, 2H), 4.12-4.16 (m, 2H), 3.88 (dd, *J* = 4.4 Hz, *J* = 7.6 Hz, 1H), 3.12 (dd, *J* = 4.4 Hz, *J* = 16.8 Hz, 1H), 2.90 (dd, *J* = 7.6 Hz, *J* = 16.8 Hz, 1H), 1.20 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 177.3, 170.7, 139.6, 137.7, 131.1, 130.9, 128.5, 127.1, 126.6, 123.4, 122.3, 115.4, 61.1, 45.1, 41.7, 35.1, 14.1. **IR** (KBr): 3064, 3030, 2980, 2929, 1723, 1610, 1588, 1489, 1454, 1440, 1373, 1339, 1206, 1072, 1029, 841, 699, 524. **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{19}H_{19}NO_3Cl$ 344.1048, found 344.1045.

*4.2.4 Tert-butyl 5-bromo-3-(2-ethoxy-2-oxoethyl)-2-oxoindoline-1-carboxylate (**1q**)*

31.4 mg, 79% yield, yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ(ppm) = 7.75 (d, *J* = 8.0 Hz, 1H), 7.43 (dd, *J* = 1.2 Hz, *J* = 8.8 Hz, 1H), 7.37 (br, 1H), 4.09-4.15 (m, 2H), 3.84-3.87 (m, 1H), 3.08 (dd, *J* = 4.4 Hz, *J* = 17.2 Hz, 1H), 2.96 (dd, *J* = 6.8 Hz, *J* = 17.2 Hz, 1H), 1.64 (s, 9H), 1.20 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 174.2, 170.2, 149.0, 139.4, 131.4, 129.1, 126.6, 117.3, 116.7, 84.7, 61.3, 42.3, 35.0, 28.1, 14.0. **IR** (KBr): 3447, 2981, 2934, 1731, 1603, 1474, 1394, 1370, 1337, 1297, 1155, 1109, 1066, 1028, 1003, 943, 821, 737, 528. **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{17}H_{21}NO_5Br$ 398.0598, found 398.0599.

*4.2.5 tert-butyl 3-((1,3-dioxolan-2-yl)methyl)-6-methoxy-2-oxoindoline-1-carboxylate (**1t**)*

134 mg, 7% yield for three steps, yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ(ppm) = 7.40 (d, *J* = 2.4 Hz, 1H), 7.17 (dd, *J* = 0.8 Hz, *J* = 8.4 Hz, 1H), 6.61 (dd, *J* = 2.4 Hz, *J* = 8.4 Hz, 1H), 5.07 (dd, *J* = 3.6 Hz, *J* = 6.0 Hz, 1H), 3.84-3.89 (m, 1H), 3.74-3.81 (m, 6H), 3.58-3.61 (m, 1H), 2.30-2.36 (m, 1H), 2.07-2.13 (m, 1H), 1.57 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 176.5, 159.7, 149.3, 141.0, 124.8, 119.2, 109.8, 102.0, 101.6, 84.1, 65.0, 64.7, 55.5, 41.8, 35.1, 28.1. **IR** (KBr): 2955, 2926, 1793, 1762, 1727, 1616, 1499, 1349, 1304, 1255, 1148, 1025, 853, 771. **HRMS** (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{18}H_{23}NO_6Na$ 372.1418, found 372.1420.

*4.3 General Procedure for the product **4**.*

To a solution of the catalyst **3** (0.01 mmol, 0.1 equiv) in solvent (1.0 mL) was added methyl acrylate (0.01 mmol, 0.1 equiv), and the mixture was stirred at room temperature for 10 min, and then the compound **1** was added. The resulting mixture was vigorously stirred for 10 min at room temperature and the cooled to -40 ^{o}C before the imine **2** (0.2 mmol, 2.0 equiv) was introduced. When the reaction was finished (determined by TLC analysis), the crude mixture was warmed to the room temperature and purified by flash column chromatography to afford the product **4**.

*4.3.1 Ethyl 2-((R)-1-benzyl-3-((S)-((tert-butoxycarbonyl)amino)(phenyl)methyl)-2-oxoindolin-3-yl)acetate (**4aa**)*

45.2 mg, 88% yield, white solid, m.p. 47-48^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.37-7.39 (m, 1H), 7.19-7.20 (m, 3H), 7.08 (t, *J* = 7.2 Hz, 1H), 7.01-7.04 (m, 2H), 6.97 (t, *J* = 7.6 HZ, 2H), 6.80-6.90 (m, 4H), 6.60 (d, *J* = 6.0 HZ, 1H), 6.29-6.31 (m, 1H), 5.13 (d, J = 10.0 Hz, 1H), 4.66 (s, 2H), 3.86-3.90 (m, 2H), 3.52 (d, *J* = 16.0 Hz, 1H), 3.14 (d, *J* = 16.0 Hz, 1H), 1.44 (s, 9H), 0.89 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 178.0, 169.7, 155.4, 143.6, 137.1, 135.2, 128.8, 128.6, 128.5, 127.5, 127.4, 127.3, 127.2, 127.1, 123.5, 109.3, 79.8, 60.5, 59.5, 53.3, 44.0, 39.9, 28.4, 13.8. **IR** (KBr): 3397, 3061, 3032, 2978, 2930, 1704, 1612, 1492, 1467, 1455, 1367, 1174, 1025, 882, 752, 699, 552. **HRMS** (ESI) calcd for $C_{31}H_{35}N_2O_5$ $(M+H)^+$ 515.2540, found 515.2535. $[\alpha]^{29.0}_D$ = -48.2 (*c* 0.5, $CHCl_3$) HPLC (Daicel Chiralpak AD-H, *i*-PrOH/Hexane=20:80, 254 nm, 1.0 mL/min): major 36.9 min, minor 11.3 min. Enantiomeric excess: 96%.

*4.3.2 Ethyl 2-((R)-1-benzyl-5-bromo-3-((S)-((tert-butoxycarbonyl)amino)(phenyl)methyl)-2-oxoindolin-3-yl)acetate (**4ba**)*

52.1 mg, 88% yield, white solid, m.p. 74-75^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.49 (s, 1H), 7.19-7.21 (m, 3H), 7.09-4.14 (m, 2H), 7.00 (t, *J* = 7.6 Hz, 2H), 6.87 (m, 4H), 6.48 (d, *J* = 10.0 Hz, 1H), 6.14 (d, *J* = 8.4 Hz, 1H), 5.09 (d, *J* = 10.0 Hz, 1H), 4.62 (dd, *J* = 16.0 Hz, 21.2 Hz, 2H), 3.86-3.93 (m, 2H), 3.50 (d, *J* = 16.0 Hz, 1H), 3.12 (d, *J* = 16.0 Hz, 1H), 1.43 (s, 9H), 0.98 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 177.5, 169.5, 155.2, 144.6, 136.7, 134.6, 131.4, 131.1, 128.6, 127.7, 127.6, 127.5, 127.4, 127.0, 126.5, 115.0, 110.7, 80.0, 60.8, 59.2, 53.5, 44.0, 39.5, 28.3, 13.8. **IR** (KBr): 3400, 3063, 3032, 2978, 2932, 1707, 1608, 1468, 1454, 1427, 1366, 1347, 1313, 1238, 1172, 1021. **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{34}BrN_2O_5$ 593.1646, found 593.1643. $[\alpha]^{24.2}_D$ = -88.7 (*c* 1.35, $CHCl_3$) HPLC (Daicel Chiralpak AD-H, *i*-PrOH/Hexane=20:80, 220 nm, 0.7 mL/min): major 40.0 min, minor 11.3 min. Enantiomeric excess: 97%.

*4.3.3 Ethyl 2-((R)-1-benzyl-3-((S)-((tert-butoxycarbonyl)amino)(phenyl)methyl)-4-chloro-2-oxoindolin-3-yl)acetate (**4ca**)*

49.3 mg, 90% yield, white solid, m.p. 52-53^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.21-7.23 (m, 3H), 7.06-7.10 (m, 1H), 6.96-7.01 (m, 4H), 6.92-6.95 (m, 4H), 6.69 (d, *J* = 10.0 Hz, 1H), 6.18 (q, *J* = 2.8 Hz, 1H), 5.65 (d, *J* = 10.0 Hz, 1H), 4.62 (dd, *J* = 16.0 Hz, 32.2 Hz, 2H), 3.82-3.94 (m, 2H), 3.72 (d, *J* = 16.0 Hz, 1H), 3.53 (d, *J* = 16.0 Hz, 1H), 1.44 (s, 9H), 0.96 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 177.5, 169.5, 155.2, 144.6, 136.7, 134.6, 131.4, 131.1, 128.6, 127.7, 127.6, 127.5, 127.4, 127.0, 126.5, 115.0, 110.7, 80.0, 60.8, 59.2, 53.5, 44.0, 39.5, 28.3, 13.8. **IR** (KBr): 3376, 2977, 2924, 2852, 1737, 1711, 1608, 1586, 1497, 1495, 1410, 1391, 1349, 1313, 12287, 1169, 1024. **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{34}ClN_2O_5$ 549.2151, found 549.2148. $[\alpha]^{22.0}_D$ = -43.4 (*c* 0.15, $CHCl_3$) HPLC (Daicel Chiralpak IC, *i*-PrOH/Hexane=20:80, 220 nm, 0.7 mL/min): major 8.8 min, minor 10.5 min. Enantiomeric excess: 89%.

*4.3.4 Ethyl 2-((R)-1-benzyl-3-((S)-((tert-butoxycarbonyl)amino)(phenyl)methyl)-5-chloro-2-oxoindolin-3-yl)acetate (**4da**)*

50.9 mg, 93% yield, white solid, m.p. 68-69^{o}C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.36 (d, *J* = 1.6 Hz, 1H), 7.20-7.22 (m, 3H), 7.09-7.13 (m, 1H), 6.98-7.04 (m, 3H), 6.87-6.89 (m, 4H), 6.50 (d, *J* = 10.0 Hz, 1H), 6.19 (q, *J* = 8.0 Hz, 1H), 5.11 (d, *J* = 10.0 Hz, 1H), 4.63 (dd, *J* = 16.0 Hz, 22.0 Hz, 2H), 3.84-3.95 (m, 2H), 3.50 (d, *J* = 16.0 Hz, 1H), 3.12 (d, *J* = 16.0 Hz, 1H), 1.44 (s, 9H), 0.98 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 177.6, 169.5, 155.2, 142.1, 136.7, 134.7, 130.8, 128.6, 128.5, 127.8, 127.7, 127.5, 127.4, 127.3, 127.0,

123.7, 110.2, 80.0, 60.8, 59.2, 53.5, 44.1, 39.5, 28.4, 13.9. **IR** (KBr): 3376, 3063, 3032, 2978, 2932, 1371, 1610, 1488, 1454, 1432, 1347, 1171, 1021. **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{34}N_2O_5Cl$ 549.2151, found 549.2148. $[\alpha]^{22.4}_D$ = -72.2 (*c* 0.75, $CHCl_3$) HPLC (Daicel Chiralpak AD-H, *i*-PrOH/Hexane=10:90, 220 nm, 0.7 mL/min): major 75.0 min, minor 21.6 min. Enantiomeric excess: 96%.

*4.3.5 Ethyl 2-((R)-1-benzyl-3-((S)-((tert-butoxycarbonyl)amino)(phenyl)methyl)-6-chloro-2-oxoindolin-3-yl)acetate (**4ea**)*

49.8 mg, 91% yield, white solid, m.p. 60-61°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.28 (d, *J* = 8.0 Hz, 1H), 7.22-7.23 (m, 3H), 7.11 (m, *J* = 8.0 Hz, 1H), 7.00-7.04 (m, 3H), 6.91-6.92 (m, 2H), 6.86 (d, *J* = 7.2 Hz, 1H), 6.49 (d, *J* = 10.0 Hz, 1H), 6.30 (q, *J* = 0.8 Hz, 1H), 5.11 (d, *J* = 10.0 Hz, 1H), 4.62 (s, 2H), 3.83-3.93 (m, 2H), 3.49 (d, *J* = 16.0 Hz, 1H), 3.12 (d, *J* = 16.0 Hz, 1H), 1.43 (s, 9H), 0.97 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 178.0, 169.6, 155.3, 144.8, 136.8, 134.6, 134.3, 128.7, 127.7, 127.6, 127.4, 127.1, 124.3, 122.4, 109.9, 80.0, 60.7, 59.3, 53.2, 44.1, 39.7, 28.4, 13.9. IR (KBr): 3403, 3063, 3032, 2978, 2932, 1709, 1609, 1492, 1454, 1368, 1343, 1243, 1173, 1026. **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{34}N_2O_5Cl$ 549.2151, found 549.2144. $[\alpha]^{22.0}_D$ = -58.0 (*c* 0.5, $CHCl_3$) HPLC (Daicel Chiralpak AD-H, *i*-PrOH/Hexane=20:80, 220 nm, 1.0 mL/min): major 21.1 min, minor 24.4 min. Enantiomeric excess: 95%.

*4.3.6 Ethyl 2-((R)-1-benzyl-3-((S)-((tert-butoxycarbonyl)amino)(phenyl)methyl)-7-chloro-2-oxoindolin-3-yl)acetate (**4fa**)*

51.5 mg, 94% yield, white solid, m.p. 132-133°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.31 (d, *J* = 6.8 Hz, 1H), 7.20-7.21 (m, 3H), 7.13 (t, *J* = 7.2 Hz, 1H), 6.98-7.06 (m, 4H), 6.92-6.94 (m, 2H), 6.80 (d, *J* = 7.2 Hz, 2H), 6.51 (d, *J* = 10.0 Hz, 1H),5.11 (d, *J* = 33.6 Hz, 1H), 5.10 (s, 1H), 4.93 (d, *J* = 16.0 Hz, 2H), 3.82-3.96 (m, 2H), 3.52 (d, *J* = 16.0 Hz, 1H), 3.13 (d, *J* = 16.0 Hz, 1H), 1.43 (s, 9H), 0.97 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 178.6, 169.5, 155.3, 139.9, 137.2, 136.6, 132.0, 131.2, 128.3, 127.7, 127.6, 127.3, 126.8, 126.5, 123.3, 121.9, 115.3, 80.0, 60.7, 59.7, 53.1, 45.2, 40.1, 28.4, 13.9. **IR** (KBr): 3400, 3063, 3032, 2978, 2932, 1709, 1608, 1584, 1497, 1466, 1425, 1391, 1351, 1244, 1166, 1137, 1078, 1015. **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{31}H_{34}ClN_2O_5$ 549.2151, found 549.2151. $[\alpha]^{22.6}_D$ = +65.3 (*c* 2.5, $CHCl_3$) HPLC (Daicel Chiralpak AD-H, *i*-PrOH/Hexane=20:80, 220 nm, 1.0 mL/min): major 30.3 min, minor 7.4 min. Enantiomeric excess: 94%.

*4.3.7 Ethyl 2-((R)-1-benzyl-3-((S)-((tert-butoxycarbonyl)amino)(phenyl)methyl)-5-methoxy-2-oxoindolin-3-yl)acetate (**4ga**)*

48.9 mg, 90% yield, white solid, m.p. 60-61°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.21-7.23 (m, 3H), 7.11-7.14 (m, 1H), 7.02-7.05 (m, 3H), 6.91-6.93 (m, 4H), 6.56-6.63 (m, 2H), 6.21 (d, *J* = 8.8 Hz, 1H), 5.15 (d, *J* = 9.6 Hz, 1H), 4.65 (s, 2H), 3.82-3.96 (m, 2H), 3.79 (s, 3H), 3.52 (d, *J* = 16.0 Hz, 1H), 3.14 (d, *J* = 16.0 Hz, 1H), 1.46 (s, 9H), 0.96 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 177.7, 169.7, 155.8, 155.4, 137.1, 137.0, 135.2, 130.1, 128.5, 127.6, 127.5, 127.4, 127.3, 127.1, 113.1, 110.6, 109.7, 79.9, 60.6, 59.4, 55.8, 53.7, 44.1, 39.8, 28.4, 13.9. **IR** (KBr): 3393, 3062, 3032, 2978, 2933, 1702, 1603, 1495, 1454, 1435, 1412, 1367, 1348, 1297, 1241, 1177, 1079, 1029, 1016. **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{32}H_{37}N_2O_6$ 545.2646, found 545.2640. $[\alpha]^{22.7}_D$ = -114.1 (*c* 0.65, $CHCl_3$) HPLC (Daicel Chiralpak AD-H, *i*-PrOH/Hexane=20:80, 220 nm, 1.0 mL/min): major 38.1 min, minor 12.9 min. Enantiomeric excess: 93%.

*4.3.8 Ethyl 2-((R)-1-benzyl-3-((S)-((tert-butoxycarbonyl)amino)(phenyl)methyl)-5-methyl-2-oxoindolin-3-yl)acetate (**4ha**)*

48.5 mg, 92% yield, white solid, m.p. 35-36°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.19 (br, 4H), 7.07-7.10 (m, 1H), 6.97-7.01 (m, 2H), 6.81-6.88 (m, 5H), 6.57 (d, *J* = 10.0 Hz, 1H), 6.17 (d, *J* = 8.0 Hz, 1H), 5.11 (d, *J* = 10.0 Hz, 1H), 4.62 (d, *J* = 16.0 Hz, 19.2 Hz, 2H), 3.80-3.91 (m, 2H), 3.49 (d, *J* = 16.0 Hz, 1H), 3.11 (d, *J* = 16.0 Hz, 1H), 2.31 (s, 3H), 1.44 (s, 9H), 0.91 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 177.9, 169.8, 155.4, 141.2, 137.2, 135.3, 132.0, 128.9, 128.8, 128.5, 127.6, 127.5, 127.3, 127.2, 127.1, 124.2, 109.0, 79.8, 60.5, 59.5, 53.4, 44.0, 39.9, 28.4, 21.2, 13.8. **IR** (KBr): 3431, 3062, 2979, 1774, 1737, 1610, 1499, 1469, 1393, 1369, 1350, 1288, 1249, 1151, 1113, 1003. **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{32}H_{37}N_2O_5$ 529.2697, found 526.2693. $[\alpha]^{22.5}_D$ = -36.3 (*c* 0.7, $CHCl_3$) HPLC (Daicel Chiralpak AD-H, *i*-PrOH/Hexane=10:90, 220 nm, 0.7 mL/min): major 96.9 min, minor 22.4 min. Enantiomeric excess: 92%.

*4.3.9 Tert-butyl ((S)-((R)-1,3-dibenzyl-2-oxoindolin-3-yl)(phenyl)methyl)carbamate (**4ia**)*

49.2 mg, 95% yield, white solid, m.p. 48-49°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.39 (d, *J* = 7.2 Hz, 1H), 6.98-7.13 (m, 12H), 6.88-6.93 (m, 4H), 6.46 (d, *J* = 8.0 Hz, 2H), 6.02 (d, *J* = 8.0 Hz, 1H), 5.27 (d, *J* = 8.0 Hz, 1H), 4.56 (d, *J* = 16.0 Hz, 1H), 4.30 (d, *J* = 16.0 Hz, 1H), 3.69 (d, *J* = 13.2 Hz, 1H), 3.32 (d, *J* = 13.2 Hz, 1H), 1.47 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 178.1, 169.6, 155.3, 144.8, 136.8, 134.6, 134.3, 128.7, 127.7, 127.6, 127.4, 127.1, 124.3, 122.4, 109.9, 80.0, 60.7, 59.3, 53.1, 44.1, 39.7, 28.4, 13.9. **IR** (KBr): 3399, 3060, 3031, 2977, 2927, 1697, 1612, 1493, 1467, 1454, 1384, 1367, 1311, 1171, 1042, 1022. **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{34}H_{35}N_2O_3$ 519.2642, found 519.2639. $[\alpha]^{24.0}_D$ = +12.4 (*c* 0.65, $CHCl_3$) HPLC (Daicel Chiralpak AD-H, *i*-PrOH/Hexane=20:80, 254 nm, 1.0 mL/min): major 9.4 min, minor 5.0 min. Enantiomeric excess: 89%.

*4.3.10 Tert-butyl ((S)-((R)-1-benzyl-3-methyl-2-oxoindolin-3-yl)(phenyl)methyl)carbamate (**4ja**)*

41.5 mg, 94% yield, white solid, m.p. 67-68°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.38-7.40 (m, 1H), 7.18-7.23 (m, 3H), 7.00-7.12 (m, 5H), 6.95-6.97 (m, 2H), 6.81-6.83 (m, 2H), 6.66 (d, *J* = 9.6 Hz, 1H), 6.39-6.41 (m, 1H), 5.18 (d, *J* = 9.6 Hz, 1H), 4.84 (d, *J* = 16.0 Hz, 1H), 4.59 (d, *J* = 16.0 Hz, 1H), 1.67 (s, 3H), 1.47 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 179.4, 155.7, 142.1, 138.3, 135.1, 131.9, 128.6, 128.1, 127.6, 127.4, 127.3, 127.1, 126.9, 123.4, 122.7, 109.3, 79.6, 59.7, 52.0, 43.5, 28.4, 22.1. **IR** (KBr): 3402, 2928, 1713, 1611, 1494, 1170.

HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{28}H_{31}N_2O_3$ 443.2329, found 443.2326. $[\alpha]^{23.3}_D$ = -32.4 (*c* 0.5, $CHCl_3$) HPLC (Daicel Chiralpak AD-H, *i*-PrOH/Hexane=20:80, 220 nm, 0.7 mL/min): major 11.7 min, minor 9.8 min. Enantiomeric excess: 86%.

*4.3.11 Tert-butyl ((S)-((R)-3-allyl-1-benzyl-2-oxoindolin-3-yl)(phenyl)methyl)carbamate (**4ka**)*

42.1 mg, 90% yield, white solid, m.p. 160-161°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.36-7.38 (m, 1H), 7.15-7.19 (m, 3H), 6.92-7.07 (m, 7H), 6.83-6.84 (m, 2H), 6.74-6.76 (m, 1H), 6.32-6.34 (m, 1H), 5.39-5.48 (m, 1H), 5.17 (d, *J* = 9.6 Hz, 1H), 5.06 (d, *J* = 16.8 Hz, 1H), 4.96 (dd, *J* = 1.6. Hz, *J* = 16.0 Hz, 1H), 4.66 (s, 2H), 2.86-2.91 (m, 2H), 1.44 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 178.3, 155.5, 142.6, 138.2, 135.0, 131.8, 129.4, 128.7, 128.5, 128.1, 127.6, 127.5, 127.3, 127.2, 127.1, 126.9, 124.1, 122.4, 119.6, 109.2, 79.6, 58.6, 56.1, 43.4, 39.5, 28.4. **IR** (KBr): 3403, 3061, 3004, 2930, 1712, 1640, 1612, 1500, 1490, 1467, 1454, 1382, 1366, 1245, 1171, 1021. **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{30}H_{33}N_2O_3$ 469.2486, found 469.2484. $[\alpha]^{22.9}_D$ = -21.6 (*c* 0.5, $CHCl_3$) HPLC (Daicel Chiralpak IC, *i*-PrOH/Hexane=20:80, 220 nm, 0.7 mL/min): major 13.9 min, minor 7.9 min. Enantiomeric excess: 84%.

*4.3.12 Tert-butyl ((S)-((R)-1-benzyl-3-(2-(benzyloxy)ethyl)-2-oxoindolin-3-yl)(phenyl)methyl)carbamate (**4la**)*

51.1 mg, 91% yield, white solid, m.p. 54-55°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.259-7.33 (m, 1H), 7.20-7.28 (m, 3H), 7.10-7.16 (m, 3H), 7.01-7.06 (m, 5H), 6.97 (m, 2H), 6.858-6.90 (m, 2H), 6.71-6.73 (m, 3H), 6.26-6.28 (m, 1H), 5.13 (d, *J* = 9.6 Hz, 1H), 4.53 (d, *J* = 16.0 Hz, 1H), 4.22 (d, *J* = 12.0 Hz, 1H), 4.17 (s, 1H), 4.04 (d, *J* = 12.0 Hz, 1H), 3.30-3.35 (m, 1H), 3.10-3.16 (m, 1H), 2.87-2.95 (m, 1H), 2.26-2.32 (m, 1H), 1.44 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 178.8, 155.6, 143.4, 138.0, 137.9, 135.3, 128.9, 128.4, 128.2, 128.1, 127.6, 127.5, 127.4, 127.3, 127.2, 127.1, 127.0, 124.0, 122.2, 109.3, 79.6, 72.9, 66.6, 60.1, 54.5, 43.5, 34.9, 28.4. **IR** (KBr): 3400, 3061, 3031, 2976, 2928, 2863, 1712, 1611, 1585, 1494, 1467, 1454, 1366, 1240, 1174, 1106, 1078, 1044. **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{36}H_{39}N_2O_4$ 563.2904, found 563.2897. $[\alpha]^{23.1}_D$ = -3.1 (*c* 0.75, $CHCl_3$) HPLC (Daicel Chiralpak AD-H, *i*-PrOH/Hexane=20:80, 220 nm, 0.7 mL/min): major 59.7 min, minor 12.8 min. Enantiomeric excess: 83%.

*4.3.13 Tert-butyl ((S)-((R)-1-benzyl-2-oxo-3-phenylindolin-3-yl)(phenyl)methyl)carbamate (**4ma**)*

44.8 mg, 89% yield, white solid, m.p. 77-78°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.53 (d, *J* = 8.0 Hz, 2H), 7.34-7.40 (m, 3H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.20-7.22 (m, 3H), 7.09-7.12 (m, 1H), 7.03 (d, *J* = 4.0 Hz, 4H), 6.98-7.00 (m, 2H), 6.85-6.87 (m, 2H), 6.64 (d, *J* = 9.2 Hz, 1H), 6.34-6.37 (m, 1H), 5.87 (d, *J* = 9.2 Hz, 1H), 4.69-4.79 (m, 2H), 1.30 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 177.7, 155.3, 141.7, 138.8, 137.6, 134.9, 131.3, 128.9, 128.7, 128.2, 127.9, 127.5, 127.4, 127.3, 126.9, 126.8, 124.6, 122.9, 109.5, 79.4, 61.3, 58.2, 43.7, 28.3. **IR** (KBr): 3408, 3060, 3032, 2977, 2929, 1704, 1610, 1500, 1467, 1454, 1366, 1292, 1227, 1169, 1021. **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{33}H_{33}N_2O_3$ 505.2486, found 505.2482. $[\alpha]^{22.8}_D$ = -158.1 (*c* 0.85, $CHCl_3$) HPLC (Daicel Chiralpak AD-H, *i*-PrOH/Hexane=20:80, 220 nm, 0.7 mL/min): major 25.6 min, minor 12.1 min. Enantiomeric excess: 81%.

*4.3.14 Ethyl 2-((R)-3-((S)-((tert-butoxycarbonyl)amino)(phenyl)methyl)-1-methyl-2-oxoindolin-3-yl)acetate (**4na**)*

40.7 mg, 93% yield, white solid, m.p. 177-178°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.32 (d, *J* = 7.2 Hz, 1H), 7.12 (t, *J* = 8.0 Hz, 1H), 6.95-7.05 (m, 4H), 6.81 (d, *J* = 7.2 Hz, 2H), 6.59 (d, *J* = 10.0 Hz, 1H), 6.42 (d, *J* = 8.0 Hz, 1H),5.03 (d, *J* = 10.0 Hz, 1H), 3.79-3.88 (m, 2H), 3.48 (d, *J* = 16.0 Hz, 1H), 3.10 (d, *J* = 16.0 Hz, 1H), 2.92 (s, 3H), 1.43 (s, 9H), 0.97 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 177.7, 169.9, 155.4, 144.0, 137.0, 128.9, 128.6, 127.3, 127.2, 127.1, 123.2, 122.4, 107.9, 79.8, 60.5, 59.7, 53.3, 39.0, 28.4, 25.8, 13.8. **IR** (KBr): 3393, 3059, 3032, 2978, 2933, 1703, 1613, 1495, 1471, 1423, 1380, 1368, 1350, 1314, 1240, 1168, 1130, 1078, 1043, 993. **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{25}H_{31}N_2O_5$ 439.2227, found 439.2225. $[\alpha]^{23.3}_D$ = -49.1 (*c* 0.8, $CHCl_3$) HPLC (Daicel Chiralpak IC, *i*-PrOH/Hexane=50:50, 220 nm, 1.0 mL/min): major 13.8 min, minor 7.2 min. Enantiomeric excess: 96%.

*4.3.15 Tert-butyl (R)-3-((S)-((tert-butoxycarbonyl)amino)(phenyl)methyl)-3-(2-ethoxy-2-oxoethyl)-2-oxoindoline-1-carboxylate (**4oa**)*

49.7 mg, 95% yield, white solid, m.p. 56-57°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.42-7.44 (m, 1H), 7.31 (br, 1H), 7.15-7.16 (m, 2H), 7.04-7.08 (m, 1H), 6.97-7.01 (m, 2H), 6.80 (d, *J* = 7.2 Hz, 2H), 6.26 (d, *J* = 10.0 Hz, 1H), 5.00 (d, *J* = 10.0 Hz, 1H), 3.79-3.89 (m, 2H), 3.53 (d, *J* = 16.0 Hz, 1H), 3.09 (d, *J* = 16.0 Hz, 1H), 1.57 (s, 9H), 1.43 (s, 9H), 0.95 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 177.1, 169.6, 155.2, 148.3, 140.3, 136.3, 128.8, 127.9, 127.6, 127.4, 127.1, 124.3, 122.6, 114.9, 84.0, 80.1, 60.8, 60.2, 54.0, 39.5, 28.3, 28.0, 13.6. **IR** (KBr): 3417, 2979, 2931, 1788, 1735, 1607, 1494, 1467, 1392, 1369, 1352, 1293, 1248, 1152, 1091, 1078, 1023, 1006. **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{29}H_{37}N_2O_7$ 525.2595, found 525.2595. $[\alpha]^{23.0}_D$ = -4.3 (*c* 1.0, $CHCl_3$) HPLC (Daicel Chiralpak AD-H, *i*-PrOH/Hexane=20:80, 220 nm, 1.0 mL/min): major 7.4 min, minor 5.8 min. Enantiomeric excess: 98%.

*4.3.16 Tert-butyl (R)-3-((S)-((tert-butoxycarbonyl)amino)(phenyl)methyl)-2-oxo-3-phenylindoline-1-carboxylate (**4pa**)*

49.9 mg, 90% yield, white solid, m.p. 70-71°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.43-7.47 (m, 3H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.22-7.28 (m, 2H), 6.99-7.13 (m, 5H), 6.92 (d, *J* = 7.6 Hz, 2H), 6.37 (d, *J* = 9.2 Hz, 1H), 5.77 (d, *J* = 9.2 Hz, 1H), 1.57 (s, 9H), 1.31 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 177.1, 155.2, 148.3, 138.8, 138.4, 136.9, 130.3, 128.9, 128.5, 127.6, 127.5, 127.4, 127.3, 124.6, 114.9, 84.5, 79.7, 61.8, 58.9, 28.3, 28.1. **IR** (KBr): 3422, 3061, 2979, 2932, 1787, 1737, 1604, 1497, 1465, 1286, 1150, 1050. **HRMS** (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{31}H_{34}NaN_2O_5$ 537.2360, found 537.2356. $[\alpha]^{26.6}_D$ = -153.0 (*c* 0.75, $CHCl_3$) HPLC (Daicel Chiralpak PC-II, *i*-PrOH/Hexane=5:95, 220 nm,

0.5 mL/min): major 11.6 min, minor 9.0 min. Enantiomeric excess: 86%.

*4.3.17 Tert-butyl (R)-5-bromo-3-((S)-((tert-butoxycarbonyl)amino)(phenyl)methyl)-3-(2-ethoxy-2-oxoethyl)-2-oxoindoline-1-carboxylate (**4qa**)*

57.7 mg, 96% yield, white solid, m.p. 63-64°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.44 (d, *J* = 0.8 Hz, 1H), 7.27-7.35 (m, 2H), 7.02-7.11 (m, 3H), 6.82 (d, *J* = 7.2 Hz, 2H), 6.15 (d, *J* = 11.2 Hz, 1H), 4.98 (d, *J* = 10.0 Hz, 1H), 3.87-3.93 (m, 2H), 3.52 (d, *J* = 16.8 Hz, 1H), 3.08 (d, *J* = 16.8 Hz, 1H), 1.56 (s, 9H), 1.44 (s, 9H), 1.03 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 176.3, 169.5, 155.1, 148.1, 139.4, 135.9, 131.8, 130.4, 127.9, 127.7, 127.1, 125.7, 117.1, 116.6, 84.4, 80.3, 61.1, 60.2, 54.1, 39.2, 28.4, 28.1, 13.8. **IR** (KBr): 3417, 2979, 2933, 1789, 1735, 1602, 1586, 1494, 1474, 1423, 1393, 1369, 1337, 1298, 1249, 1154, 1099, 1067, 1028. **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{29}H_{36}BrN_2O_7$ 603.1700, found 603.1725. $[\alpha]^{23.6}_D$ = -59.6 (*c* 1.15, $CHCl_3$) HPLC (Daicel Chiralpak IC, *i*-PrOH/Hexane=50:50, 220 nm, 1.0 mL/min): major 3.9 min, minor 15.1 min. Enantiomeric excess: 99%.

*4.3.18 Tert-butyl (R)-3-((S)-((tert-butoxycarbonyl)amino)(m-tolyl)methyl)-3-(2-ethoxy-2-oxoethyl)-2-oxoindoline-1-carboxylate (**4ob**)*

50.5 mg, 94% yield, white solid, m.p. 55-56°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.44-7.46 (m, 1H), 7.29-7.31 (m, 1H), 7.14-7.16 (m, 2H), 6.86-6.88 (m, 2H), 6.60 (br, 2H), 6.22 (d, *J* = 10.0 Hz, 1H), 4.97 (d, *J* = 10.0 Hz, 1H), 3.81-3.89 (m, 2H), 3.52 (d, *J* = 16.8 Hz, 1H), 3.08 (d, *J* = 16.4 Hz, 1H), 2.10 (s, 3H), 1.57 (s, 9H), 1.43 (s, 9H), 0.95 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 177.1, 169.6, 155.2, 148.4, 140.4, 137.1, 136.2, 128.8, 128.4, 128.0, 127.9, 127.3, 124.3, 124.2, 122.7, 114.8, 84.0, 80.0, 60.8, 60.3, 54.0, 39.6, 28.4, 28.1, 21.2, 13.6. **IR** (KBr): 3420, 2980, 2933, 1788, 1735, 1608, 1499, 1353, 1249, 1153, 1025. **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{30}H_{39}N_2O_7$ 539.2752, found 539.2753. $[\alpha]^{22.9}_D$ = -6.1 (*c* 0.65, $CHCl_3$) HPLC (Daicel Chiralpak AD-H, *i*-PrOH/Hexane=10:90, 220 nm, 0.7 mL/min): major 12.5 min, minor 9.4 min. Enantiomeric excess: 97%.

*4.3.19 Tert-butyl (R)-3-((S)-((tert-butoxycarbonyl)amino)(4-chlorophenyl)methyl)-3-(2-ethoxy-2-oxoethyl)-2-oxoindoline-1-carboxylate (**4oc**)*

51.9 mg, 93% yield, white solid, m.p. 65-66°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.46 (d, *J* = 7.6 Hz, 1H), 7.32-7.34 (m, 1H), 7.18-7.24 (m, 2H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.75 (d, *J* = 8.4 Hz, 2H), 6.31 (d, *J* = 10.0 Hz, 1H), 5.99 (d, *J* = 10.0 Hz, 1H), 3.84-3.91 (m, 2H), 3.54 (d, *J* = 16.8 Hz, 1H), 3.09 (d, *J* = 16.4 Hz, 1H), 1.59 (s, 9H), 1.45 (s, 9H), 0.98 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 177.1, 169.4, 155.1, 148.1, 140.3, 135.1, 133.6, 129.1, 128.5, 127.6, 124.5, 122.6, 115.1, 84.4, 80.3, 60.9, 59.6, 53.7, 39.5, 28.3, 28.0, 13.7. IR (KBr):2980, 2933, 1788, 1736, 1607, 1492, 1466, 1352, 1248, 1151, 1090, 1014. **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{29}H_{36}ClN_2O_7$ 559.2206, found 559.2205. $[\alpha]^{24.1}_D$ = -14.9(*c* 2.5, $CHCl_3$) HPLC (Daicel Chiralpak AD-H, *i*-PrOH/Hexane=10:90, 220 nm, 0.7 mL/min): major 47.5 min, minor 14.3 min. Enantiomeric excess: 97%.

*4.3.20 Tert-butyl (R)-3-((S)-((tert-butoxycarbonyl)amino)(4-methoxyphenyl)methyl)-3-(2-ethoxy-2-oxoethyl)-2-oxoindoline-1-carboxylate (**4od**)*

52.6 mg, 95% yield, white solid, m.p. 60-61°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.46 (d, *J* = 7.2 Hz, 1H), 7.28-7.30 (m, 1H), 7.14-7.19 (m, 2H), 6.72 (d, *J* = 8.8 Hz, 2H), 6.52 (d, *J* = 8.4 Hz, 2H), 6.20 (d, *J* = 9.6 Hz, 1H), 4.96 (d, *J* = 10.4 Hz, 1H), 3.79-3.89 (m, 2H), 3.66 (s, 3 H), 3.51 (d, *J* = 16.4 Hz, 1H), 3.06 (d, *J* = 16.4 Hz, 1H), 1.57 (s, 9H), 1.43 (s, 9H), 0.95 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 177.3, 169.6, 158.9, 155.2, 148.4, 140.4, 128.8, 128.5, 128.2, 128.1, 124.3, 122.6, 115.0, 112.9, 84.0, 80.0, 60.8, 59.7, 55.1, 54.1, 39.6, 28.4, 28.1, 13.7. **IR** (KBr): 2979, 2934, 1793, 1767, 1731, 1611, 1481, 1465, 1368, 1309, 1291, 1251, 1153, 1032. **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{30}H_{39}N_2O_8$ 555.2701, found 555.2700. $[\alpha]^{23.5}_D$ = -10.1 (*c* 0.85, $CHCl_3$) HPLC (Daicel Chiralpak AD-H, *i*-PrOH/Hexane=10:90, 220 nm, 0.7 mL/min): major 35.7 min, minor 23.7 min. Enantiomeric excess: 98%.

*4.3.21 Tert-butyl (R)-3-((S)-((tert-butoxycarbonyl)amino)(4-fluorophenyl)methyl)-3-(2-ethoxy-2-oxoethyl)-2-oxoindoline-1-carboxylate (**4oe**)*

48.7 mg, 90% yield, white solid, m.p. 49-50°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.42-7.44 (m, 1H), 7.29-7.31 (m, 1H), 7.14-7.21 (m, 2H), 6.75-6.78 (m, 2H), 6.67 (t, *J* = 8.4 Hz, 2H), 6.28 (d, *J* = 10.0 Hz, 1H), 4.97 (d, *J* = 10.0 Hz, 1H), 3.79-3.89 (m, 2H), 3.51 (d, *J* = 16.8 Hz, 1H), 3.06 (d, *J* = 16.8 Hz, 1H), 1.56 (s, 9H), 1.42 (s, 9H), 0.94 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 177.1, 169.4, 162.0 (d, *J* = 245.5 Hz), 155.1, 148.1, 140.2, 132.3 (d, *J* = 3.0 Hz), 129.0, 128.7 (d, *J* = 8.2 Hz), 127.7, 124.4, 122.5, 115.0, 114.3 (d, *J* = 21.4 Hz), 84.3, 80.2, 60.9, 59.5, 53.8, 39.5, 28.3, 28.0, 13.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.5 (m). **IR** (KBr): 3412, 2980, 2932, 1788, 1736, 1606, 1509, 1466, 1393, 1369, 1352, 1248, 1151, 1088, 1042. **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{29}H_{36}FN_2O_7$ 543.2501, found 543.2501. $[\alpha]^{23.1}_D$ = -18.7 (*c* 0.6, $CHCl_3$) HPLC (Daicel Chiralpak AD-H, *i*-PrOH/Hexane=10:90, 220 nm, 0.7 mL/min): major 23.8 min, minor 12.2 min. Enantiomeric excess: 98%.

*4.3.22 Tert-butyl (R)-3-((R)-((tert-butoxycarbonyl)amino)(thiophen-2-yl)methyl)-3-(2-ethoxy-2-oxoethyl)-2-oxoindoline-1-carboxylate (**4of**)*

47.7 mg, 90% yield, white solid, m.p. 43-44°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.62 (d, *J* = 8.0 Hz, 1H), 7.34 (d, *J* = 7.2 Hz, 1H), 7.26-7.30 (m, 1H), 7.21 (t, *J* = 7.6 Hz, 2H), 6.99 (d, *J* = 4.2 Hz, 1H), 6.69 (dd, *J* = 4.0 Hz, *J* = 4.8 Hz, 1H), 6.44 (d, *J* = 3.2 Hz, 1H), 6.21 (d, *J*

= 10.0 Hz, 1H), 5.33 (d, *J* = 10.4 Hz, 1H), 3.82-3.90 (m, 2H), 3.50 (d, *J* = 16.4 Hz, 1H), 3.08 (d, *J* = 16.4 Hz, 1H), 1.59 (s, 9H), 1.47 (s, 9H), 0.98 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 176.9, 169.4, 155.1, 148.5, 141.0, 139.7, 129.2, 128.0, 126.1, 125.3, 124.6, 124.5, 122.6, 115.1, 84.1, 80.3, 60.9, 56.3, 54.0, 39.9, 28.4, 28.1, 13.7. **IR** (KBr):3411, 2979, 2933, 1788, 1734, 1607, 1494, 1467, 1393, 1369, 1351, 1315, 1293, 1249, 1152, 1089, 753, 610. **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{27}H_{35}N_2O_7S$ 531.2159, found 531.2158. $[\alpha]^{24.9}_D$ = -9.8 (*c* 0.7, $CHCl_3$) HPLC (Daicel Chiralpak AD-H, *i*-PrOH/Hexane=10:90, 220 nm, 1.0 mL/min): major 14.5 min, minor 24.7 min. Enantiomeric excess: 96%.

*4.3.23 Tert-butyl (R)-3-((S)-((tert-butoxycarbonyl)amino)(cyclohexyl)methyl)-3-(2-ethoxy-2-oxoethyl)-2-oxoindoline-1-carboxylate (**4og**)*

25.4 mg, 48% yield, white solid, m.p. 39-40°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.85 (d, *J* = 8.0 Hz, 1H), 7.31-7.35 (m, 1H), 7.17-7.20 (m, 2H), 5.56 (d, *J* =), 2.92 (d, *J* = 16.0 Hz, 1H), 1.63 (s, 9H), 1.43-1.52 (m, 13H), 1.23 (br, 1H), 0.92-1.08 (m, 10H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 177.7, 169.7, 156.3, 149.0, 140.6, 128.7, 128.8, 124.8, 122.1, 115.1, 84.2, 79.6, 61.5, 60.6, 52.4, 41.3, 38.6, 32.8, 28.4, 28.1, 27.4, 26.2, 25.9, 25.7, 13.6. **IR** (KBr):2979, 2928, 2853, 1793, 1768, 1731, 1696, 1480, 1465, 1368, 1290, 1119, 753. **HRMS** (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{29}H_{42}NaN_2O_7$ 553.2884, found 553.2866. $[\alpha]^{27.0}_D$ = -6.6(*c* 0.8, $CHCl_3$) HPLC (Daicel Chiralpak IC, *i*-PrOH/Hexane=15:85, 220 nm, 0.7 mL/min): major 6.1 min, minor 19.6 min. Enantiomeric excess: 99%.

*4.3.24 Tert-butyl (R)-3-((S)-1-((tert-butoxycarbonyl)amino)-3-phenylpropyl)-3-(2-ethoxy-2-oxoethyl)-2-oxoindoline-1-carboxylate (**4oh**)*

24.8 mg, 45% yield, white solid, m.p. 45-46°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.81 (d, *J* = 8.4 Hz, 1H), 7.28-7.31 (m, 1H), 7.17-7.20 (m, 2H), 7.09-7.14 (m, 2H), 7.05-7.07 (m, 1H), 6.95 (d, *J* = 6.8 Hz, 2H), 5.44 (d, *J* = 10.4 Hz, 1H), 4.00 (dt, *J* = 2.4 Hz, *J* = 10.8 Hz, 1H), 3.77-3.82 (m, 2H), 3.32 (d, *J* = 16.0 Hz, 1H), 2.94 (d, *J* = 16.0 Hz, 1H), 2.59-2.63 (m, 1H), 2.38-2.43 (m, 1H), 1.64 (s, 9H), 1.49 (s, 9H), 1.33-1.41 (m, 1H), 1.21-1.27 (m, 1H), 0.93 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 177.4, 169.6, 156.1, 149.0, 140.9, 140.7, 128.9, 128.5, 128.3, 126.0, 124.9, 122.1, 115.2, 84.5, 79.8, 60.7, 56.0, 53.3, 40.6, 32.4, 32.2, 28.4, 28.1, 13.6. **IR** (KBr):2978, 2929, 2855, 1768, 1731, 1698, 1496, 1479, 1464, 1368, 1250, 1151, 1027, 751, 699. **HRMS** (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{31}H_{40}NaN_2O_7$ 575.2728, found 575.2705. $[\alpha]^{27.1}_D$ = -3.2(*c* 1.7, $CHCl_3$) HPLC (Daicel Chiralpak IC, *i*-PrOH/Hexane=15:85, 220 nm, 0.7 mL/min): major 7.1 min, minor 11.7 min. Enantiomeric excess: 98%.

*4.3.25 Tert-butyl (R)-3-((1,3-dioxolan-2-yl)methyl)-3-((S)-((tert-butoxycarbonyl)amino)(phenyl)methyl)-2-oxoindoline-1-carboxylate (**4ra**)*

47.1 mg, 90% yield, colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.39-7.42 (m, 1H), 7.33-7.35 (m, 1H), 7.12-7.15 (m, 2H), 6.93-7.02 (m, 3H), 6.79 (d, *J* = 7.2 Hz, 2H), 6.31 (d, *J* = 9.6 Hz, 1H), 4.99 (d, *J* = 9.6 Hz, 1H), 4.61 (dd, *J* = 2.4 Hz, *J* = 7.2 Hz, 1H), 3.71-3.76 (m, 1H), 3.60-3.64 (m, 1H), 3.51-3.55 (m, 2H), 2.70 (dd, *J* = 7.6 Hz, *J* = 14.4 Hz, 1H), 2.46 (dd, *J* = 2.8 Hz, *J* = 14.4 Hz, 1H), 1.54 (s, 9H), 1.40 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 177.4, 155.3, 148.5, 139.9, 136.8, 128.5, 127.6, 127.4, 127.3, 127.2, 123.9, 123.8, 114.8, 101.5, 83.8, 79.8, 64.9, 64.4, 61.1, 53.7, 38.4, 28.3, 28.0. **IR** (KBr): 2978, 1718, 1152, 752. **HRMS** (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{29}H_{36}N_2NaO_7$ 547.2415, found 547.2424. $[\alpha]^{26.4}_D$ = 12.0 (*c* 0.71, $CHCl_3$) HPLC (Daicel Chiralpak IC, *i*-PrOH/Hexane=20:80, 220 nm, 1.0 mL/min): major 6.2 min, minor 56.2 min. Enantiomeric excess: 97%.

*4.3.26 Tert-butyl (S)-3-((S)-((tert-butoxycarbonyl)amino)(phenyl)methyl)-3-fluoro-2-oxoindoline-1-carboxylate (**4sa**)*

43.3 mg, 95% yield, yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.59 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 7.2 Hz, 1H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.09-7.15 (m, 3H), 6.98 (d, *J* = 7.2 Hz, 2H), 6.22 (d, *J* = 8.8 Hz, 1H), 5.51 (dd, *J* = 6.4 Hz, *J* = 8.4 Hz, 1H), 1.57 (s, 9H), 1.45 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 170.6 (d, *J* = 22.7 Hz), 155.3, 148.0, 140.4, 134.5, 131.8, 128.3, 128.1, 127.7, 125.0 (d, *J* = 8.6 Hz), 122.8 (d, *J* = 18.7 Hz), 115.3, 91.5 (d, *J* = 245.5 Hz), 90.5, 85.0, 80.2, 58.9, 28.4, 28.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -156.9 (s). **IR** (KBr): 3430, 2977, 2932, 1772, 1723, 1498, 1151. **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{25}H_{30}N_2O_5F$ 457.2133, found 457.2125. $[\alpha]^{23.2}_D$ = +34.8 (*c* 0.6, $CHCl_3$) HPLC (Daicel Chiralpak AD-H, *i*-PrOH/Hexane=10:90, 254 nm, 1.0 mL/min): major 7.1 min, minor 9.7 min. Enantiomeric excess: 94%.

*4.3.27 Ethyl 2-((R)-1-benzyl-3-((S)-((4-methylphenyl)sulfonamido)(phenyl)methyl)-2-oxoindolin-3-yl)acetate (**4ai**)*

49.4 mg, 87% yield, white solid, m.p. 82-83°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.33-7.38 (m, 3H), 7.17-7.19 (m, 3H), 6.96-7.00 (m, 2H), 6.88-6.93 (m, 5H), 6.72 (t, *J* = 8.0 Hz, 2H), 6.58 (d, *J* = 8.0 Hz, 3H), 6.28 (q, *J* = 3.2 Hz, 1H), 4.94 (d, *J* = 10.4 Hz, 1H), 4.63 (d, *J* = 16.0 Hz, *J* = 30.0 Hz, 2H), 3.79-3.95 (m, 2H), 3.62 (d, *J* = 16.4 Hz, 1H), 3.16 (d, *J* = 16.4 Hz, 1H), 2.22 (s, 3H), 0.94 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 177.8, 169.6, 143.3, 142.6, 137.7, 134.9, 134.5, 128.9, 128.8, 128.5, 128.1, 127.5, 127.3, 127.2, 127.1, 127.0, 126.7, 123.5, 122.5, 109.3, 62.3, 60.6, 53.2, 44.0, 40.2, 21.3, 13.8. **IR** (KBr):3263, 3060, 2980, 2924, 1715, 1612, 1489, 1467, 1455, 1429, 1370, 1333, 1163, 1086, 1056, 923, 813, 737, 700, 670, 558. **HRMS** (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{33}H_{32}SNaN_2O_5$ 591.1924, found 591.1905. $[\alpha]^{28.9}_D$ = -72.1(*c* 0.8, $CHCl_3$) HPLC (Daicel Chiralpak IC, *i*-PrOH/Hexane=40:60, 220 nm, 1.0 mL/min): major 37.9 min, minor 67.1 min. Enantiomeric excess: 74%.

*4.3.28 Ethyl 2-((R)-1-benzyl-3-((S)-(((benzyloxy)carbonyl)amino)(phenyl)methyl)-2-oxoindolin-3-yl)acetate (**4aj**)*

49.3 mg, 90% yield, white solid, m.p. 47-48°C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.30-7.38 (m, 6H), 7.19-7.20 (m, 3H), 7.08 (t, *J* = 7.2

Hz, 1H), 6.83-7.03 (m, 9H), 6.31-6.33 (m, 1H), 5.21 (d, *J* = 9.6 Hz, 1H), 5.14 (d, *J* = 12.4 Hz, 1H), 5.07 (d, *J* = 12.4 Hz, 1H), 4.26-4.70 (m, 2H), 3.77-3.91 (m, 2H), 3.47 (d, *J* = 16.0 Hz, 1H), 3.12 (d, *J* = 16.0 Hz, 1H), 0.90 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 177.4, 169.6, 156.1, 149.0, 140.9, 140.7, 128.9, 128.5, 128.3, 126.0, 124.9, 122.1, 115.2, 84.5, 79.8, 60.7, 56.0, 53.3, 40.6, 32.4, 32.2, 28.4, 28.1, 13.6. **IR** (KBr):3339, 3061, 3032, 2979, 2924, 1719, 1612, 1495, 1466, 1454, 1369, 1345, 1189, 1026, 755, 698, 456. **HRMS** (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{34}H_{32}NaN_2O_5$ 571.2203, found 571.2196. $[\alpha]^{28.7}_D$ = -32.2 (*c* 1.0, $CHCl_3$) HPLC (Daicel Chiralpak IC, *i*-PrOH/Hexane=50:50, 220 nm, 1.0 mL/min): major 12.6 min, minor 8.0 min. Enantiomeric excess: 88%.

*4.3.29(R)-tert-butyl3-((1,3-dioxolan-2-yl)methyl)-3-((S)-1-((tert-butoxycarbonyl)amino)-2-methylpropyl)-2-oxoindoline-1-carboxylate (**4rk**)*

34.3 mg, 70% yield, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) = 7.85 (d, *J* = 8.4 Hz, 1H), 7.32 (t, *J* = 8.0 Hz, 1H), 7.18-7.26 (m, 2H), 5.68 (d, *J* = 10.4 Hz, 1H), 4.48 (dd, *J* = 2.4 Hz, *J* = 7.6 Hz, 1H), 4.04 (dd, *J* = 2.0 Hz, *J* = 10.4 Hz, 1H), 3.75 (q, *J* = 6.8 Hz, 1H), 3.53-3.62 (m, 4H), 2.52-2.57 (m, 1H), 2.34 (dd, *J* = 2.4 Hz, *J* = 14.4 Hz, 1H), 1.63 (s, 9H), 1.48 (s, 9H), 0.71 (d, *J* = 6.8 Hz, 3H), 0.64 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) = 178.1, 156.6, 149.3, 140.1, 129.1, 128.4, 124.6, 123.1, 115.2, 101.6, 84.0, 79.3, 64.8, 64.4, 61.7, 52.1, 40.8, 28.7, 28.4, 28.1, 22.6, 16.5. IR (KBr):2976, 2932, 1792, 1766, 1727, 1696, 1480, 1367, 1290, 1152, 1002, 774, 757. HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{26}H_{39}N_2O_7$ 491.2752, found 491.2749. $[\alpha]^{29.4}_D$ = 1.3 (*c* 2.0, $CHCl_3$) HPLC (Daicel Chiralpak AD-H, *i*-PrOH/Hexane=5:95, 220 nm, 1.0 mL/min): major 22.9 min, minor 5.4 min. Enantiomeric excess: 99%.

*4.3.30(R)-tert-butyl3-((1,3-dioxolan-2-yl)methyl)-3-((S)-1-((tert-butoxycarbonyl)amino)-2-methylpropyl)-6-methoxy-2-oxoindoline-1-carbo xylate (**4tk**)*

35.3 mg, 68% yield, off-white oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ(ppm) = 7.49 (d, *J* = 2.4 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 6.74 (dd, *J* = 2.0 Hz, *J* = 8.0 Hz, 1H), 5.66 (d, *J* = 10.4 Hz, 1H), 4.49 (dd, *J* = 2.4 Hz, *J* = 7.6 Hz, 1H), 4.00 (dd, *J* = 2.0 Hz, *J* = 10.4 Hz, 1H), 3.85 (s, 3H), 3.75-3.80 (m, 1H), 3.56-3.65 (m, 3H), 2.48-2.53 (m, 1H), 2.29 (dd, *J* = 2.4 Hz, *J* = 14.0 Hz, 1H), 1.63 (s, 9H), 1.48 (s, 9H), 0.72 (d, *J* = 6.8 Hz, 3H), 0.64 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ(ppm) = 178.6, 159.9, 156.6, 149.3, 141.0, 123.6, 120.7, 110.2, 102.0, 101.7, 84.0, 79.3, 64.8, 64.4, 61.7, 55.5, 51.7, 40.8, 28.6, 28.4, 28.2, 28.1, 22.6, 16.5, 15.4. IR (KBr):2974, 2932, 1793, 1767, 1725, 1696, 1493, 1392, 1255, 1150, 1031, 775. HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{27}H_{41}N_2O_8$ 521.2863, found 521.2892. $[\alpha]^{25.6}_D$ = 5.9 (*c* 1.7, $CHCl_3$) HPLC (Daicel Chiralpak PC-II, *i*-PrOH/Hexane=5:95, 220 nm, 0.8 mL/min): major 7.4 min, minor 29.4 min. Enantiomeric excess: 84%.

*4.4 Transformation of spirooxindole **5** and **6***

A dried 10 mL flask was charged with **4rk** (49.0 mg, 0.1 mmol, 99% ee) and cooled to 0 °C. A hydrogen chloride solution (4M) in ethyl acetate (0.6 mL) was slowly added. After stirred for 10 min. the mixture was allowed to warm to room temperature and stirred for 1 h. All volatile compounds were removed by rotary evaporator and the crude was dried in vacuo. To the crude HCl salt, DCM (0.6 mL) was added the suspension was cooled to 0 °C. Et_3N (40.4 mg, 0.4 mmol) was added and the reaction mixture was allowed to warm to room temperature. After stirred for 1 h, water was added and the organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (petrolume ether/ethyl acetate = 1/3) to afford the product **5**.

The corresponding spirooxindole product (0.1mmol, 1.0eq) was dissolved in MeOH and cooled to 0°C. Sodium cyanoborohydride (0.4 mmol4.0eq) was added slowly and the mixture was allowed to stir under room temperature for 30min. The resulting solution was poured into satd.aq.NH_4Cl, extracted with EA, the organic layer was separated and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (dichloromethane / methanol = 9/1) to afford the product **6**

4.4.1 (2'S,3R)-2'-isopropyl-2',4'-dihydrospiro[indoline-3,3'-pyrrol]-2-one (5)

14.3 mg, 63% yield, yellow oil. 1H NMR (400 MHz, $CDCl_3$) δ(ppm) = 8.62 (s, 1H), 7.70-7.71 (m, 1H), 7.15-7.27 (m, 2H), 7.04-7.07 (m, 1H), 6.90 (d, J = 8.0 Hz, 1H), 4.00 (dd, J = 2.4 Hz, J = 9.6 Hz, 1H), 3.25 (d, J = 18.0 Hz, 1H), 2.91 (d, J = 18.0 Hz, 1H), 2.19-2.27 (m, 1H), 1.19 (d, J = 6.4 Hz, 3H), 3.25 (d, J = 6.8 Hz, 3H). 13C NMR (100 MHz, $CDCl_3$) δ(ppm) = 180.9, 162.8, 140.2, 135.1, 128.0, 123.0, 122.4, 109.8, 89.8, 54.5, 50.8, 30.4, 21.8, 20.3. IR (KBr):3427, 2958, 2870, 1709, 1619, 1484, 750. HRMS (ESI) m/z: [M+H]+ Calcd for C14H17N2O 229.1335, found 229.1334. [α]24.2D = -58.6 (c 0.3, CHCl3) HPLC (Daicel Chiralpak IC, i-PrOH/Hexane=10:90, 220 nm, 1.0 mL/min): major 15.8 min, minor 11.6 min. Enantiomeric excess: 99%.

*4.4.2 (2'S,3R)-2'-isopropyl-6-methoxyspiro[indoline-3,3'-pyrrolidin]-2-one (**6**)*

11.4 mg, 44% yield, colorless oil. **^{1}H NMR** (400 MHz, $CDCl_3$) δ(ppm) = 7.06 (d, *J* = 8.4 Hz, 1H), 6.59 (s, 1H), 6.51 (d, *J* = 8.4 Hz, 1H), 3.64-3.71 (m, 4H), 3.46 (br, 1H), 3.35 (d, *J* = 8.4 Hz, 1H), 2.28 (m, 2H), 1.98 (br, 1H), 1.04 (d, *J* = 6.4 Hz, 3H), 0.35 (d, *J* = 6.4 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ(ppm) = 181.4, 160.4, 142.0, 123.2, 122.3, 108.2, 98.1, 73.2, 56.1, 55.6, 43.7, 38.2, 29.5, 22.3, 19.8. **IR** (KBr):2924, 1709, 1632, 1506, 1462, 1155. **HRMS** (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{15}H_{21}N_2O_2$ 261.1603, found 261.1614. $[\alpha]^{29.1}_D$ = 3.2 (*c* 0.15, $CHCl_3$) HPLC (Daicel Chiralpak AS-H, *i*-PrOH/Hexane=10:90, 220 nm, 1.0 mL/min): major 10.7 min, minor 17.0 min. Enantiomeric excess: 73%.

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Supplementary data

Supplementary data (NMR spectra, HPLC data) associated with this article can be found in the online version, at http://

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