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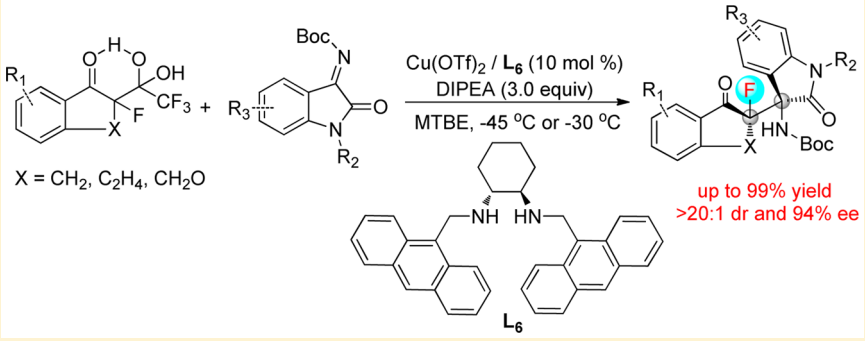
Construction of Vicinal Tetrasubstituted Stereocenters with a C–F Bond through a Catalytic Enantioselective Detrifluoroacetylative Mannich Reaction

Xihong Liu,[†,§] Jinlong Zhang,[†,§] Long Zhao,[†] Shixiong Ma,[†] Dongxu Yang,[†] Wenjin Yan,[†] and Rui Wang*[,†,‡]

[†]Key Laboratory of Preclinical Study for New Drugs of Gansu Province, School of Basic Medical Sciences, Lanzhou University, Lanzhou, 730000, China

[‡]State Key Laboratory of Chiroscience, Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Kowloon, Hong Kong, P. R. China

Supporting Information



ABSTRACT: An efficient asymmetric detrifluoroacetylative Mannich reaction of 2-fluoro-1,3-diketones/hydrates with isatin-derived ketimines catalyzed by a chiral copper(II)-diamine complex has been realized. The reaction afforded a series of 3-substituted 3-amino-2-oxindoles bearing fluorine-containing vicinal tetrasubstituted stereocenters in high yields (up to 99%) with excellent diastereoselectivities (up to >20:1 dr) and enantioselectivities (up to 94% ee).

The catalytic stereoselective synthesis of 3-substituted-3-amino-2-oxindoles, especially the compounds with adjacent tetrasubstituted stereogenic centers, is of great importance because such structural motifs are present in numerous biologically active compounds (Figure 1).[1] Thus, there is a need for mild methods that enable the preparation of oxindoles with fully substituted vicinal stereogenic centers. However, the construction of vicinal tetrasubstituted stereocenters suffers from steric repulsion and still remains a formidable challenge.[2−4] To date, only limited methods such as alkylation[3] and cycloaddition reactions[4] have been developed to access the mentioned compounds. It is worth noting that the newly reported addition of carbon nucleophiles to the C═N bond of isatin imines has been proved to be one of the most direct methods to prepare such congested structures, and preliminary development has been achieved.[5] Very recently, Feng and co-workers reported an enantioselective Mannich reaction of silyl ketene imines with isatin-derived ketimines catalyzed by a chiral *N,N′*-dioxide/Zn^{II}, leading to a series of *β*-amino nitriles containing congested vicinal tetrasubstituted stereocenters (Scheme 1a).[5a] Subsequently, the groups of Wennemers and Shao reported the addition of *α*-substituted monothiomalonates to isatin ketimines independently at almost the same time (Scheme 1b).[5b,c] Although these excellent studies exist, there is no literature that has challenged the asymmetric synthesis of fluorinated 3-aminooxindoles with vicinal tetrasubstituted stereocenters.

Organo-fluorine chemistry has been becoming a research hotspot as the introduction of fluorine could usually reinvest the compounds with improved efficacy, membrane perme-

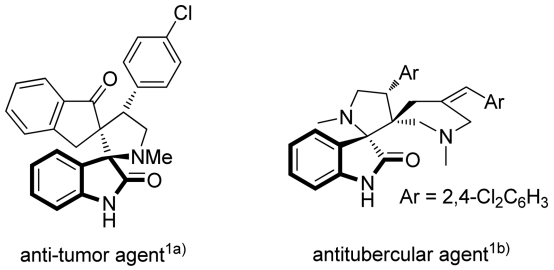


Figure 1. Selected examples of bioactive 3-amino-2-oxindoles with adjacent tetrasubstituted stereogenic centers.

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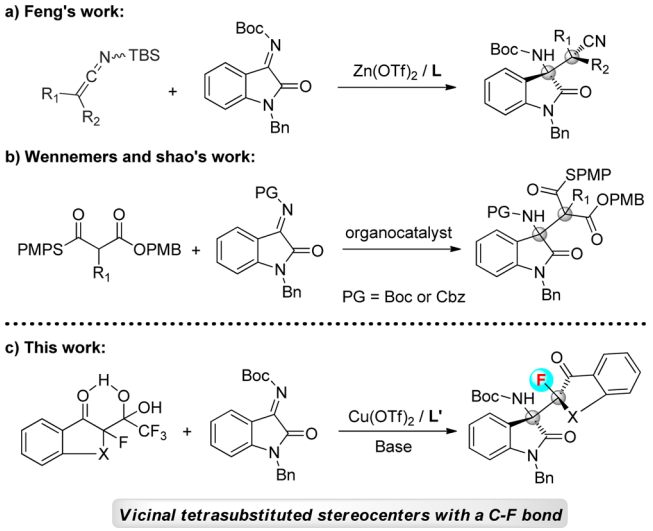
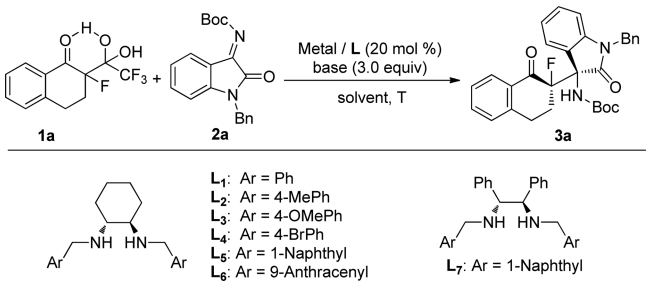
Scheme 1. Construction of Continuous Tetrasubstituted Stereocenters via Mannich Reactions of Isatin-Ketimines



ability, and higher stability, which are among the great important properties for a medicinal molecule.[6] Therefore, developing and establishing new methodologies toward vicinal tetrasubstituted stereocenters with a C−F bond would be of great significance and necessity. With our continuous interest in amine functionalization,[7] we envisioned that the detrifluoroacetylative Mannich reaction of 2-fluoro-1,3-diketones/hydrates[8] and isatin-ketimines[9] would also be a useful protocol for the preparation of vicinal tetrasubstituted stereocenters with a fluorine element (Scheme 1c). Much to our delight, the Mannich reaction occurred with $Cu(OTf)_2$ as catalyst in the presence of a base and was completed within 10 min at room temperature.

Initially, we screened various Lewis acids with **1a** and *N*-Boc-protected ketamine **2a** as a model reaction in THF at room temperature and found that the $Cu(OTf)_2$-$\mathbf{L_1}$ complex could efficiently catalyze the reaction in the presence of Et_3N (Table 1, entries 2−6). Then, several diamine ligands ($\mathbf{L_2}$−$\mathbf{L_7}$)[10,11] were synthesized, and the results showed that the bulkiest 9-anthracenyl-substituded ligand $\mathbf{L_6}$ worked best and provided the product **3a** with 48% enantioselectivity (Table 1, entries 7−12). To further optimize the reaction conditions, several other variables including bases, solvents, and temperatures were

Table 1. Optimization of the Reaction Conditions[a]



entry	metal	L	base	T (°C)	solvent	t	yield (%)[b]	ee (%)[c]	dr[d]
1			Et_3N	rt	THF	2 h			
2	$Ni(OAc)_2$	$\mathbf{L_1}$	Et_3N	rt	THF	2 h			
3	$Sc(OTf)_3$	$\mathbf{L_1}$	Et_3N	rt	THF	2 h			
4	$Y(OTf)_3$	$\mathbf{L_1}$	Et_3N	rt	THF	2 h			
5	$Cu(OAc)_2$	$\mathbf{L_1}$	Et_3N	rt	THF	2 h	trace		
6	$Cu(OTf)_2$	$\mathbf{L_1}$	Et_3N	rt	THF	10 min	89	33	5:1
7	$Cu(OTf)_2$	$\mathbf{L_2}$	Et_3N	rt	THF	10 min	93	21	5:1
8	$Cu(OTf)_2$	$\mathbf{L_3}$	Et_3N	rt	THF	10 min	85	25	6:1
9	$Cu(OTf)_2$	$\mathbf{L_4}$	Et_3N	rt	THF	10 min	77	27	6:1
10	$Cu(OTf)_2$	$\mathbf{L_5}$	Et_3N	rt	THF	10 min	91	38	4:1
11	$Cu(OTf)_2$	$\mathbf{L_6}$	Et_3N	rt	THF	10 min	90	48	5:1
12	$Cu(OTf)_2$	$\mathbf{L_7}$	Et_3N	rt	THF	10 min	86	31	2:1
13	$Cu(OTf)_2$	$\mathbf{L_6}$	DIPEA	rt	THF	10 min	96	55	6:1
14	$Cu(OTf)_2$	$\mathbf{L_6}$	DABCO	rt	THF	2 h	trace		
15	$Cu(OTf)_2$	$\mathbf{L_6}$	DBU	rt	THF	2 h	trace		
16	$Cu(OTf)_2$	$\mathbf{L_6}$	DIPEA	−45 °C	THF	7 h	93	82	16:1
17	$Cu(OTf)_2$	$\mathbf{L_6}$	DIPEA	−45 °C	toluene	7 h	85	77	5:1
18	$Cu(OTf)_2$	$\mathbf{L_6}$	DIPEA	−45 °C	CH_2Cl_2	7 h	53	47	4:1
19	$Cu(OTf)_2$	$\mathbf{L_6}$	DIPEA	−45 °C	Et_2O	7 h	89	80	19:1
20	$Cu(OTf)_2$	$\mathbf{L_6}$	DIPEA	−45 °C	MTBE	7 h	94	89	19:1
21[e]	$Cu(OTf)_2$	$\mathbf{L_6}$	DIPEA	−45 °C	MTBE	7 h	82	87	13:1
22[f]	$Cu(OTf)_2$	$\mathbf{L_6}$	DIPEA	−45 °C	MTBE	12 h	94	91	19:1

[a]Unless otherwise noted, the reaction was performed with **1a** (0.11 mmol), **2a** (0.10 mmol), base (0.30 mmol, 3.0 equiv), and metal/**L** (20 mol %) in 2.0 mL of the solvent. [b]Combined yields of diastereoisomers. [c]Determined by HPLC on a chiral stationary phase. [d]Determined by ^{1}H NMR of the crude mixture. [e]DIPEA (2.0 equiv) was used. [f]The reaction was performed at 10 mol % catalyst loading. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIPEA = *N*,*N*-diisopropylethylamine, DABCO = triethylenediamine, and MTBE = methyl *tert*-butyl ether.

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examined together with the $Cu(OTf)_2$-L_6 complex. Compared with Et_3N, DIPEA gave an improved ee value (55% ee; Table 1, entry 13). We then lowered the temperature to −45 °C, and noticeably enhanced enantioselectivity (82% ee) and diastereoselectivity (16:1 dr) were received without any obvious sacrifice of yield (Table 1, entry 16). Screening of solvents displayed that ether-type solvents were superior to others (Table 1, entries 17−20). For examples, a drop in reactivity and stereoselectivity was observed when the reaction was conducted in CH_2Cl_2 (Table 1, entry 18), while an excellent outcome was obtained with MTBE (89% ee and 19:1 dr; Table 1, entry 20). Delightfully, the same excellent result was obtained with a 10 mol % catalyst loading (Table 1, entry 22).

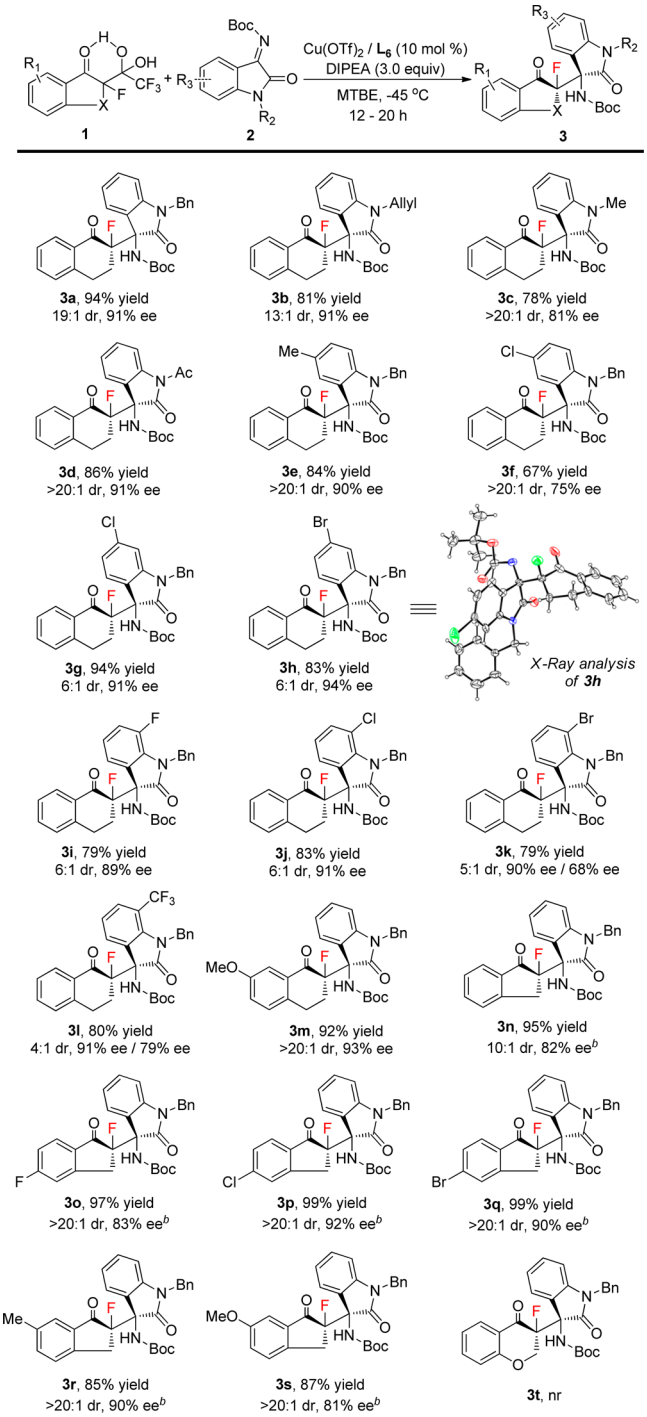
With the optimized reaction conditions as indicated (Table 1, entry 22) in hand, we examined the substrate scope (Scheme 2). First, we investigated the reaction between hydrate **1a** and various isatin-derived ketimines. The isatin-derived *N*-Boc ketimines with alkyl substituents at the 1-position (R_2 = Bn and Allyl) worked well, and the corresponding products were obtained with high diastereoselectivities and enantioselectivities (up to 91% ee, 19:1 dr). The ee value of **3c** decreased to 81% possibly due to the small space steric hindrance of the methyl group. Besides, the isatin-derived *N*-Boc ketimines with an acetyl group at the 1-position also worked well (Scheme 2, **3d**). Subsequently, *N*-Boc ketimines derived from different substituted *N*-benzylisatins were evaluated, and we found that the position of the substitute had an evident effect on both the yields and stereoselectivities. For example, the substrates with a substitute at 6- or 7-positions reacted smoothly, and the products were obtained in high yields and stereoselectivities (79−94% yields, 89−94% ee and 4:1−6:1 dr; Scheme 2, **3g**−**l**). However, the substrate with a 5-Cl substituent afforded the product in 67% yield with excellent diastereoselectivity (>20:1 dr) but reduced ee values (75% ee; Scheme 2, **3f**). Gratifyingly, substrates **2** bearing an electron-donating group on the phenyl ring of the isatin moiety worked well and afforded the product with high yield and diastereoselectivity (Scheme 2, **3e**).

We next explored the substrate scope of hydrates **1**. Compared with the six-membered ring compounds, the substrates containing a five-membered ring displayed relatively less reactivity. Much to our delight, the reactions proceeded smoothly and provided the products in high yields and stereoselectivities when the temperature was increased to −30 °C. Both electron-rich and electron-deficient substituted hydrates **1** were well tolerated in this system (Scheme 2, **3n**−**3s**). Unfortunately, 2,3-dihydrochromen-4-one derivative hydrates **1t** failed to afford the corresponding product. Moreover, ligand L_6' (enantiomer of L_6) was synthesized and used to promote this reaction under the standard conditions. Adduct **3a′** was obtained in 93% yield with 91% ee and 19:1 dr, which is the enantiomer of compound **3a** (Scheme 3). The absolute configuration of product **3h** was confirmed as (1*S*, 2*S*) by X-ray analysis (see SI).[12]

Furthermore, some representative transformations of the product **3h** were performed. As shown in Scheme 4, the Boc group in **3h** could be easily removed in the CH_2Cl_2 solvent of trifluoroacetic acid with a slight erosion of stereoselectivity. Besides, compound **5** was obtained via the reduction of **4** using $NaBH_4$ in methanol,[13] in which the 1,3-amino alcohol fragment is of great interest on account of its presence in various antibiotics and other bioactive nature products.

Finally, the reaction between α-fluorinated aromatic ketone **6** and isatin-derived ketamine **2a** was also conducted, but no corresponding product was detected (Scheme 5), which disclosed the fact that the *in situ* generation of enolates from precursors **1** under the assistance of DIPEA is a crucial step for this Mannich reaction.

Scheme 2. Substrates Scope of the Mannich Reaction[a]



[a]Unless otherwise noted, the reactions were performed with **1** (0.11 mmol), **2** (0.10 mmol), DIPEA (0.30 mmol, 3.0 equiv) and $Cu(OTf)_2$/L_6 (10 mol %) in 2.0 mL of MTBE. [b]The reactions were performed in 1.0 mL of MTBE at −30 °C. Combined yields of diastereoisomers. The dr values were determined by ^{1}H NMR of crude mixture. The ee values were determined by HPLC on a chiral stationary phase.

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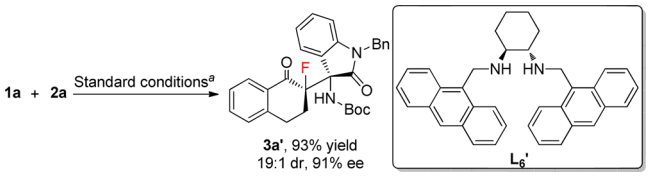
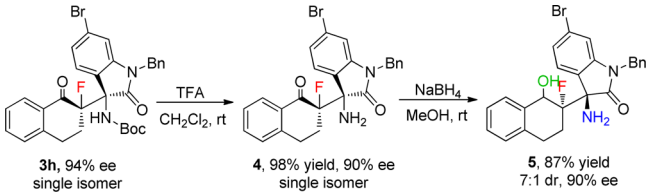
Scheme 3. Synthesis of Enantiomer 3a′[a]

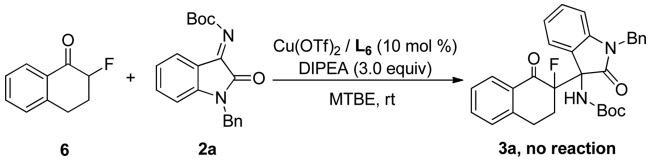


[a]Ligand $\mathbf{L_6}$ was replaced with $\mathbf{L_6}'$.

Scheme 4. Transformations of Product 3h



Scheme 5. Mannich Reaction of α-Fluorinated Aromatic Cyclic Ketone 6 and 2a



In summary, we have developed an efficient protocol for the asymmetric construction of vicinal tetrasubstituted stereocenters with a C−F bond through the addition of 2-fluoro-1,3-diketones/hydrates to isatin-derived ketimines catalyzed by a chiral copper(II)-diamine complex. A series of functionalized 3-substituted 3-amino-2-oxindoles[14] were obtained in excellent yields (up to 99%) with high enantioselectivities and diastereoselectivities (up to 94% ee and >20:1 dr). This is the first diastereo- and enantioselective detrifluoroacetylative Mannich reaction of 2-fluoro-1,3-diketones/hydrates to isatin-derived ketimines.

EXPERIMENTAL SECTION

General. Unless otherwise stated, all reactions were carried out in flame-dried glassware. All solvents were purified and dried according to standard methods prior to use. ^{1}H NMR spectra were recorded on a 300 MHz spectrometer in $CDCl_3$, and ^{13}C NMR spectra were recorded on a 75 MHz spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as internal standard. Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet, or unresolved; coupling constant(s) are in Hz, integration). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). ^{19}F NMR spectra were recorded on a 282 MHz spectrometer in $CDCl_3$. Optical rotations were reported as follows: $[\alpha]_D^{rt}$ (c: g/100 mL, in solvent). High resolution mass spectra (HRMS) were obtained by the ESI ionization sources with a time-of-flight mass analyzer. The ee value determination was carried out using chiral HPLC with a UV-detector. Substrates α-fluorinated *gem*-diols **1**[8d] and ketimines **2**[7c] were prepared according to the literature.

General Procedure for the Preparation of the Diamine-Cu(OTf)$_2$ Complex. A mixture of diamine (**L**) (0.6 mmol, 1.2 equiv) and $Cu(OTf)_2$ (0.5 mmol, 1.0 equiv) in THF (5.0 mL) was stirred overnight at room temperature, and then, the solvent was removed under reduced pressure to afford the catalytic complex which was used without further purification.

*General Procedure for the Preparation of Racemic-**3**.* To a solution of α-fluorinated *gem*-diols **1** (0.1 mmol), ketimines **2** (0.1 mmol), and LiBr (0.3 mmol, 3.0 equiv) in THF (1.0 mL) was added DIPEA (0.3 mmol, 3.0 equiv), and the mixture was stirred at room temperature for 10 min. Then, the reaction was quenched with saturated aqueous NH_4Cl (1.0 mL) followed by H_2O (4.0 mL). The resulting mixture was extracted with EtOAc (3 × 10 mL). The organic phase was dried and concentrated under reduced pressure, and the residue was purified by column chromatography to afford the corresponding racemic-**3**.

*General Procedure for the Synthesis of **3**.* The mixture of catalyst $Cu(OTf)_2$-$\mathbf{L_6}$ (0.01 mmol), α-fluorinated *gem*-diols **1** (0.11 mol), and ketimines **2** (0.10 mmol) were dissolved in 1.2 mL of MTBE (0.6 mL for **3n** − **3s**) and stirred at room temperature for 10 min. Then, the solution was cooled to −45 °C (−30 °C for **3n**−**3s**) and stirred for another 10 min. Finally, DIPEA (52.4 μL, 0.3 mmol, 3.0 equiv) dissolved in 0.8 mL (0.4 mL for **3n**−**3s**) of MTBE was added dropwise, and the mixture was stirred at this temperature until the complete consumption of starting material (monitored by TLC). The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (PE/EtOAc = 15:1−5:1) to afford products **3**.

*tert-Butyl ((S)-1-Benzyl-3-((S)-2-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoindolin-3-yl)carbamate (**3a**).* Pale yellow solid, mp 82−83 °C; 47.0 mg, 94% yield; 91% ee was determined by HPLC on a Chiralpak IC-H column (hexane/2-propanol = 1/2, 1.0 mL/min, t_{major} = 7.1 min, t_{minor} = 9.8 min); $[\alpha]_D^{19}$ = +99 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR for the major diastereomer (300 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.3 Hz, 1H), 7.48 (ddd, *J* = 11.3, 8.6, 4.3 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.33−7.21 (m, 6H), 7.16 (s, 1H), 7.08 (dd, *J* = 18.0, 7.6 Hz, 2H), 6.86 (d, *J* = 7.8 Hz, 1H), 4.93−4.66 (m, 2H), 2.73−2.59 (m, 1H), 2.57−2.39 (m, 1H), 2.10−1.90 (m, 1H), 1.90−1.71 (m, 1H), 1.28 (s, 9H); ^{13}C NMR for the major diastereomer (75 MHz, $CDCl_3$) δ 192.6 (J_{C-F} = 18.0 Hz), 172.6 (J_{C-F} = 7.5 Hz), 153.7, 143.6, 142.6, 135.3, 134.0, 132.7, 129.6, 128.6, 128.4, 128.1, 127.9, 127.7, 127.4, 126.6, 125.0 (J_{C-F} = 3.0 Hz), 123.2, 108.9, 92.9 (J_{C-F} = 192.0 Hz), 80.1, 67.4 (J_{C-F} = 21.0 Hz), 44.5, 29.8 (J_{C-F} = 21.8 Hz), 28.1, 24.8 (J_{C-F} = 7.5 Hz); ^{19}F NMR for the major diastereomer (282 MHz, $CDCl_3$) δ −160.00 (s); HRMS calcd for $C_{30}H_{29}FN_2NaO_4$ $(M + Na)^+$ 523.2004; found, 523.2015.

*tert-Butyl ((S)-1-Allyl-3-((S)-2-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoindolin-3-yl)carbamate (**3b**).* Yellow solid, mp 65−66 °C; 36.4 mg, 81% yield; 91% ee was determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol = 9/1, 0.7 mL/min, t_{major} = 10.0 min, t_{minor} = 11.2 min); $[\alpha]_D^{22}$ = +110 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR for the major diastereomer (300 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.1 Hz, 1H), 7.55−7.42 (m, 2H), 7.34 (dt, *J* = 7.8, 4.2 Hz, 2H), 7.31−7.05 (m, 3H), 6.88 (d, *J* = 7.8 Hz, 1H), 5.90−5.70 (m, 1H), 5.45−5.14 (m, 2H), 4.45−4.27 (m, 1H), 4.25−4.08 (m, 1H), 2.94−2.66 (m, 2H), 2.24−1.85 (m, 2H), 1.26 (s, 9H); ^{13}C NMR for the major diastereomer (75 MHz, $CDCl_3$) δ 192.5 (J_{C-F} = 17.3 Hz), 172.4 (J_{C-F} = 8.3 Hz), 153.6, 143.8, 142.7, 134.2, 132.5, 130.9, 129.6, 128.5, 127.9, 127.4, 126.6, 125.1 (J_{C-F} = 3.0 Hz), 123.2, 118.6, 109.0, 92.8 (J_{C-F} = 191.3 Hz), 80.0, 67.3 (J_{C-F} = 21.0 Hz), 42.9, 29.9 (J_{C-F} = 22.5 Hz), 28.1, 25.2 (J_{C-F} = 7.5 Hz); ^{19}F NMR for the major diastereomer (282 MHz, $CDCl_3$) δ −159.60 (s); HRMS calcd for $C_{26}H_{28}FN_2O_4$ $(M + H)^+$ 451.2028; found, 451.2041.

*tert-Butyl ((S)-3-((S)-2-Fluoro-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-1-methyl-2-oxoindolin-3-yl)carbamate (**3c**).* White solid, mp 145−146 °C; 33.1 mg, 78% yield; 81% ee was determined by HPLC on a Chiralpak IC-H column (hexane/2-propanol =1/2, 1.0 mL/min, t_{major} = 8.3 min, t_{minor} = 10.7 min); $[\alpha]_D^{22}$ = +52 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.8 Hz, 1H), 7.53−7.41 (m, 2H), 7.37 (q, *J* = 7.0 Hz, 2H), 7.13 (t, *J* = 7.8 Hz, 3H), 6.87 (d, *J* = 7.8 Hz, 1H), 3.15 (s, 3H), 2.92−2.78 (m, 1H), 2.77−2.59 (m, 1H), 2.20−1.99 (m, 1H), 1.99−1.80 (m, 1H), 1.24 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.5 (J_{C-F} = 17.3 Hz), 172.6 (J_{C-F} = 8.3 Hz), 153.5, 144.3, 142.6, 134.2, 132.5, 129.7, 128.4, 128.0, 127.3, 124.9, 124.8, 123.2, 108.1, 92.8 (J_{C-F} = 191.3 Hz), 80.0, 67.4 (J_{C-F} = 21.0 Hz), 29.9 (J_{C-F} = 21.8 Hz), 28.0, 26.4, 25.2 (J_{C-F} = 8.3 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −159.04 (s); HRMS calcd for $C_{24}H_{25}FN_2NaO_4$ $(M + Na)^+$ 447.1691; found, 447.1697.

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*tert-Butyl ((S)-1-Acetyl-3-((S)-2-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoindolin-3-yl)carbamate (**3d**).* Yellow solid, mp 121−122 °C; 38.9 mg, 86% yield; 91% ee was determined by HPLC on a Chiralpak OD-H column (hexane/2-propanol =9/1, 1.0 mL/min, t_{major} = 7.8 min, t_{minor} = 12.3 min); $[\alpha]_D^{22}$ = +36 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.1 Hz, 1H), 8.11 (d, *J* = 7.1 Hz, 1H), 7.51 (ddd, *J* = 15.8, 8.4, 1.3 Hz, 2H), 7.45−7.34 (m, 2H), 7.30−7.21 (m, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 6.97 (s, 1H), 2.94 (dt, *J* = 17.3, 5.9 Hz, 1H), 2.70 (ddd, *J* = 15.3, 9.1, 4.7 Hz, 1H), 2.46 (s, 3H), 2.30−2.10 (m, 1H), 2.06−1.87 (m, 1H), 1.25 (s, 9H); ^{19}F NMR (282 MHz, acetone) δ 14.37 (s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.4 (J_{C-F} = 38.0 Hz), 173.9 (J_{C-F} = 7.5 Hz), 170.4, 153.8, 142.1, 140.9, 134.5, 132.2, 130.2, 128.4, 128.1, 127.6, 125.7, 124.7, 124.6, 116.4, 93.5 (J_{C-F} = 193.5 Hz), 80.9, 67.5 (J_{C-F} = 21.0 Hz), 30.0 (J_{C-F} = 21.8 Hz), 28.0, 26.6, 25.0 (J_{C-F} = 8.3 Hz); HRMS calcd for $C_{25}H_{25}FN_2NaO_5$ $(M + Na)^+$ 475.1640; found, 475.1652.

*tert-Butyl ((S)-1-Benzyl-3-((S)-2-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-5-methyl-2-oxoindolin-3-yl)carbamate (**3e**).* Pale yellow solid, mp 75−76 °C; 43.2 mg, 84% yield; 90% ee was determined by HPLC on a Chiralpak IC-H column (hexane/2-propanol = 1/2, 1.0 mL/min, t_{major} = 6.5 min, t_{minor} = 11.5 min); $[\alpha]_D^{22}$ = +111 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 6.9 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.30−7.21 (m, 6H), 7.18 (s, 1H), 7.06 (t, *J* = 8.5 Hz, 2H), 6.73 (d, *J* = 7.9 Hz, 1H), 4.87−4.64 (m, 2H), 2.73−2.58 (dt, *J* = 11.9, 5.7 Hz, 1H), 2.56−2.40 (m, 1H), 2.32 (s, 3H), 2.09−1.72 (m, 2H), 1.29 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −160.07 (s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.0 (J_{C-F} = 17.25 Hz), 172.6 (J_{C-F} = 8.25 Hz), 153.8, 142.7, 141.2, 135.4, 134.1, 132.9, 132.8, 130.0, 128.7, 128.4, 128.1, 127.9, 127.7, 127.4, 126.6, 125.8 (J_{C-F} = 2.3 Hz), 108.8, 94.3, 80.1, 67.6 (J_{C-F} = 21.0 Hz), 44.5, 29.9 (J_{C-F} = 22.5 Hz), 28.2, 24.9 (J_{C-F} = 6.8 Hz), 21.2; HRMS calcd for $C_{31}H_{32}FN_2O_4$ $(M + H)^+$ 515.2341; found, 515.2343.

*tert-Butyl ((S)-1-Benzyl-5-chloro-3-((S)-2-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoindolin-3-yl)carbamate (**3f**).* Pale yellow solid, mp 93−94 °C; 35.8 mg, 67% yield; 75% ee was determined by HPLC on a Chiralpak IC-H column (hexane/2-propanol = 1/2, 1.0 mL/min, t_{major} = 5.6 min, t_{minor} = 9.5 min); $[\alpha]_D^{22}$ = +106 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.7 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.44 (s, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.31−7.18 (m, 7H), 7.07 (d, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 8.3 Hz, 1H), 4.79 (s, 2H), 2.80−2.66 (m, 1H), 2.58−2.41 (m, 1H), 2.15−1.94 (m, 1H), 1.93−1.72 (m, 1H), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.3 (J_{C-F} = 17.3 Hz), 172.4 (J_{C-F} = 8.3 Hz), 153.7, 142. 6, 142.2, 134.8, 134.2, 132.5, 129.6, 128.7, 128.7, 128.5, 128.3, 127.9, 127.9, 127.8, 127.5, 125.4 (J_{C-F} = 3.0 Hz), 110.0, 92.6 (J_{C-F} = 192.0 Hz), 80.4, 67.4 (J_{C-F} = 21.0 Hz), 44.6, 29.8 (J_{C-F} = 21.8 Hz), 28.1, 24.7 (J_{C-F} = 7.5 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −160.30 (s); HRMS calcd for $C_{30}H_{29}ClFN_2O_4$ $(M + H)^+$ 535.1794; found, 535.1811.

*tert-Butyl ((S)-1-Benzyl-6-chloro-3-((S)-2-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoindolin-3-yl)carbamate (**3g**).* Pale yellow solid, mp 97−98 °C; 50.2 mg, 94% yield; 91% ee was determined by HPLC on a Chiralpak IC-H column (hexane/2-propanol = 1/2, 1.0 mL/min, t_{major} = 13.3 min, t_{minor} = 18.1 min); $[\alpha]_D^{22}$ = +107 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR for the major diastereomer (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.4 Hz, 1H), 7.55−7.45 (m, 1H), 7.44−7.32 (m, 2H), 7.32−7.21 (m, 5H), 7.17 (s, 1H), 7.11−7.01 (m, 2H), 6.84 (s, 1H), 4.90−4.64 (m, 2H), 2.78−2.62 (m, 1H), 2.58−2.40 (m, 1H), 2.11−1.92 (m, 1H), 1.91−1.70 (m, 1H), 1.31 (s, 9H); ^{13}C NMR for the major diastereomer (75 MHz, $CDCl_3$) δ 192.4 (J_{C-F} = 18.0 Hz), 172.7 (J_{C-F} = 8.3 Hz), 153.7, 144.8, 142.6, 135.4, 134.7, 134.2, 132.5, 128.8, 128.4, 128.0, 127.9, 127.9, 127.4, 125.9 (J_{C-F} = 3.0 Hz), 125.0, 123.2, 109.7, 92.8 (J_{C-F} = 192.0 Hz), 80.4, 67.0 (J_{C-F} = 21.0 Hz), 44.6, 29.8 (J_{C-F} = 22.5 Hz), 28.1, 24.7 (J_{C-F} = 7.5 Hz); ^{19}F NMR for the major diastereomer (282 MHz, $CDCl_3$) δ −159.96 (s); HRMS calcd for $C_{30}H_{29}ClFN_2O_4$ $(M + H)^+$ 535.1794; found, 535.1811.

*tert-Butyl ((S)-1-Benzyl-6-bromo-3-((S)-2-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoindolin-3-yl)carbamate (**3h**).* Yellow solid, mp 64−65 °C; 48.1 mg, 83% yield; 94% ee was determined by HPLC on a Chiralpak IC-H column (hexane/2-propanol = 1/2, 1.0 mL/min, t_{major} = 5.9 min, t_{minor} = 7.9 min); $[\alpha]_D^{22}$ = +96 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR for the major diastereomer (300 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.5 Hz, 1H), 7.54−7.47 (m, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.33−7.20 (m, 7H), 7.17 (s, 1H), 7.06 (d, *J* = 7.6 Hz, 1H), 6.99 (s, 1H), 4.90−4.63 (m, 2H), 2.77−2.61 (m, 1H), 2.56−2.38 (m, 1H), 2.13−1.93 (m, 1H), 1.91−1.69 (m, 1H), 1.31 (s, 9H); ^{13}C NMR for the major diastereomer (75 MHz, $CDCl_3$) δ 192.4 (J_{C-F} = 18.0 Hz), 172.6 (J_{C-F} = 7.5 Hz), 153.7, 144.9, 142.6, 134.7, 134.2, 132.5, 128.8, 128.4, 128.0, 127.9, 127.9, 127.4, 126.3 (J_{C-F} = 2.3 Hz), 126.2, 125.6, 123.4, 112.4, 92.7 (J_{C-F} = 192.0 Hz), 80.4, 67.0 (J_{C-F} = 21.0 Hz), 44.6, 29.8 (J_{C-F} = 22.5 Hz), 28.1, 24.7 (J_{C-F} = 7.5 Hz); ^{19}F NMR for the major diastereomer (282 MHz, $CDCl_3$) δ −159.94 (s); HRMS calcd for $C_{30}H_{29}BrFN_2O_4$ $(M + H)^+$ 579.1289; found, 579.1310.

*tert-Butyl ((S)-1-Benzyl-7-fluoro-3-((S)-2-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoindolin-3-yl)carbamate (**3i**).* Yellow solid, mp 78−79 °C; 40.9 mg, 79% yield; 89% ee was determined by HPLC on a Chiralpak IC-H column (hexane/2-propanol = 1/2, 1.0 mL/min, t_{major} = 6.2 min, t_{minor} = 8.6 min); $[\alpha]_D^{22}$ = +117 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR for the major diastereomer (300 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.5 Hz, 1H), 7.43 (dd, *J* = 7.4, 6.5 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.24−7.06 (m, 7H), 7.03−6.84 (m, 3H), 4.86 (s, 2H), 2.43−2.60 (m, 1H), 2.18−2.35 (m, 1H), 1.93−1.72 (m, 1H), 1.50−1.71 (m, 1H), 1.23 (s, 9H); ^{13}C NMR for the major diastereomer (75 MHz, $CDCl_3$) δ 192.6 (J_{C-F} = 16.5 Hz), 172.4 (J_{C-F} = 8.25 Hz), 153.8, 147.3 (J_{C-F} = 242.3 Hz), 142.6, 136.1, 134.1, 132.7, 130.2 (J_{C-F} = 8.3 Hz), 128.8, 128.6, 128.5, 128.4, 128.0, 127.7, 127.5, 123. Nine (J_{C-F} = 6.0 Hz), 120.9, 118.1 (J_{C-F} = 19.5 Hz), 92.7 (J_{C-F} = 192.8 Hz), 80.4, 67.5 (J_{C-F} = 23.3 Hz), 46.2 (J_{C-F} = 5.3 Hz), 29.7 (J_{C-F} = 21.8 Hz), 28.1, 24.6 (J_{C-F} = 6.8 Hz); ^{19}F NMR for the major diastereomer (282 MHz, $CDCl_3$) δ −159.91 (s); HRMS calcd for $C_{30}H_{29}F_2N_2O_4$ $(M + H)^+$ 519.2090; found, 519.2112.

*tert-Butyl ((S)-1-Benzyl-7-chloro-3-((S)-2-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoindolin-3-yl)carbamate (**3j**).* Yellow oil; 44.3 mg, 83% yield; 91% ee was determined by HPLC on a Chiralpak IC-H column (hexane/2-propanol = 1/2, 1.0 mL/min, t_{major} = 6.9 min, t_{minor} = 9.6 min); $[\alpha]_D^{22}$ = +87 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR for the major diastereomer (300 MHz, CDCl3) δ 8.08 (d, J = 7.2 Hz, 1H), 7.48 (td, J = 7.5, 1.3 Hz, 1H), 7.42−7.34 (m, 2H), 7.34−7.23 (m, 4H), 7.22−7.13 (m, 3H), 7.10−6.94 (m, 2H), 5.35 (d, *J* = 15.6 Hz, 1H), 5.10 (d, *J* = 15.7 Hz, 1H), 2.78−2.59 (m, 1H), 2.54−2.35 (m, 1H), 2.06−1.88 (m, 1H), 1.88−1.67 (m, 1H), 1.31 (s, 9H); ^{13}C NMR for the major diastereomer (75 MHz, $CDCl_3$) δ 192.5 (J_{C-F} = 17.3 Hz), 173.5 (J_{C-F} = 7.5 Hz), 153.7, 142.6, 139.6, 136.6, 134.2, 132.5, 132.3, 129.7, 128.3, 127.9, 127.8, 127.4, 127.2, 124.1, 123.6, 115.3, 92.5 (J_{C-F} = 192.8 Hz), 80.4, 66.8 (J_{C-F} = 21.0 Hz), 45.5, 29.6 (J_{C-F} = 22.5 Hz), 28.1, 24.6 (J_{C-F} = 6.8 Hz); ^{19}F NMR for the major diastereomer (282 MHz, $CDCl_3$) δ −160.46 (s); HRMS calcd for $C_{30}H_{29}ClFN_2O_4$ $(M + H)^+$ 535.1794; found, 535.1812.

*tert-Butyl ((S)-1-Benzyl-7-bromo-3-((S)-2-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoindolin-3-yl)carbamate (**3k**).* Pale yellow solid, mp 88−89 °C; 45.6 mg, 79% yield; 90% ee was determined by HPLC on a Chiralpak IC-H column (hexane/2-propanol = 1/2, 1.0 mL/min, t_{major} = 6.8 min, t_{minor} = 9.3 min); $[\alpha]_D^{22}$ = +100 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR for the major diastereomer (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.7 Hz, 1H), 7.31−7.48 (m, 3H), 7.32−7.19 (m, 4H), 7.16−7.04 (m, 3H), 6.99−6.81 (m, 2H), 5.34 (d, *J* = 15.9 Hz, 1H), 5.06 (d, *J* = 15.9 Hz, 1H), 2.71−2.55 (m, 1H), 2.49−2.30 (m, 1H), 2.03−1.82 (m, 1H), 1.82−1.60 (m, 1H), 1.24 (s, 9H); ^{13}C NMR for the major diastereomer (75 MHz, $CDCl_3$) δ 192.5 (J_{C-F} = 17.3 Hz), 173.8 (J_{C-F} = 7.5 Hz), 153.8, 142.6, 141.1, 136.6, 135.8, 134.2, 132.6, 130.2, 128.4, 128.3, 128.0, 127.6, 127.5, 127.1, 124.5, 124.3, 102.5, 92.6 (J_{C-F} = 192.8 Hz), 80.5, 66.8 (J_{C-F} = 21.0 Hz), 45.2, 29.7 (J_{C-F} = 21.8 Hz), 28.2, 24.7 (J_{C-F} = 6.8 Hz); ^{19}F NMR for the major diastereomer (282 MHz, $CDCl_3$) δ −160.57 (s); HRMS calcd for $C_{30}H_{29}BrFN_2O_4$ $(M + H)^+$ 579.1289; found, 579.1307.

*tert-Butyl ((S)-1-Benzyl-3-((S)-2-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxo-7-(trifluoromethyl)indolin-3-yl)carbamate (**3l**).* Pale yellow solid, mp 69−70 °C; 45.5 mg, 80% yield; 91% ee was

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determined by HPLC on a Chiralpak IC-H column (hexane/2-propanol = 1/2, 1.0 mL/min, t_{major} = 5.0 min, t_{minor} = 5.9 min); $[\alpha]_D^{22}$ = +81 (*c* = 1.0 in $CHCl_3$); ^1H NMR for the major diastereomer (300 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.7 Hz, 1H), 7.66−7.53 (m, 2H), 7.47−7.36 (m, 1H), 7.28 (t, *J* = 7.4 Hz, 2H), 7.20−6.90 (m, 7H), 5.05−4.87 (m, 2H), 2.86−2.65 (m, 1H), 2.64−2.43 (m, 1H), 2.03−1.84 (m, 1H), 1.84−1.62 (m, 1H), 1.24 (s, 9H); ^{13}C NMR for the major diastereomer (75 MHz, $CDCl_3$) δ 192.4 (J_{C-F} = 18.0 Hz), 174.7 (J_{C-F} = 7.5 Hz), 153.8, 142.5, 141.9, 135.5, 134.4, 132.5, 129.8, 128.6, 128.0, 127.9, 127.8, 127.6, 126.9, 126.8, 125.2, 122.8, 121.6, 112.9 (J_{C-F} = 33.0 Hz), 92.4 (J_{C-F} = 194.3 Hz), 80.6, 65.8 (J_{C-F} = 21.0 Hz), 46.9 (J_{C-F} = 5.3 Hz), 29.7 (J_{C-F} = 21.8 Hz), 28.1, 24.7 (J_{C-F} = 6.0 Hz); ^{19}F NMR for the major diastereomer (282 MHz, $CDCl_3$) δ −161.40 (s); HRMS calcd for $C_{31}H_{28}F_4N_2NaO_4$ $(M + Na)^+$ 591.1877; found, 591.1902.

*tert-Butyl ((S)-1-Benzyl-3-((S)-2-fluoro-7-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoindolin-3-yl)carbamate (**3m**).* Pale yellow solid, mp 80−81 °C; 48.7 mg, 92% yield; 93% ee was determined by HPLC on a Chiralpak IC-H column (hexane/2-propanol = 1/2, 1.0 mL/min, t_{major} = 9.0 min, t_{minor} = 10.4 min); $[\alpha]_D^{22}$ = +171 (*c* = 1.0 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (d, *J* = 2.5 Hz, 1H), 7.37 (d, *J* = 7.2 Hz, 1H), 7.29−7.13 (m, 6H), 7.07 (s, 1H), 7.00 (dd, *J* = 12.7, 4.9 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.78 (d, *J* = 7.7 Hz, 1H), δ 4.82−4.60 (m, 2H), 3.78 (s, 3H), 2.60−2.42 (m, 1H), 2.42−2.22 (m, 1H), 2.02−1.82 (m, 1H), 1.82−1.63 (m, 1H), 1.20 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.6 (J_{C-F} = 16.5 Hz), 172.7 (J_{C-F} = 7.5 Hz), 158.8, 153.7, 143.7, 135.6, 135.3, 133.4, 129.7, 129.3, 128.7, 128.2, 127.8, 126.7, 125.1, 123.3, 123.0, 109.7, 109.0, 93.1 (J_{C-F} = 191.3 Hz), 80.2, 67.5 (J_{C-F} = 21.0 Hz), 55.5, 44.6, 30.1 (J_{C-F} = 21.8 Hz), 28.1, 24.2 (J_{C-F} = 8.3 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −159.24 (s); HRMS calcd for $C_{31}H_{32}FN_2O_5$ $(M + H)^+$ 531.2290; found, 531.2311.

*tert-Butyl ((S)-1-Benzyl-3-((S)-2-fluoro-1-oxo-2,3-dihydro-1H-inden-2-yl)-2-oxoindolin-3-yl)carbamate (**3n**).* Pale yellow solid, mp 95−96 °C; 46.2 mg, 95% yield; 82% ee was determined by HPLC on a Chiralpak IC-H column (hexane/2-propanol = 1/2, 1.0 mL/min, t_{major} = 7.8 min, t_{minor} = 13.9 min); $[\alpha]_D^{22}$ = +165 (*c* = 1.0 in $CHCl_3$); ^1H NMR for the major diastereomer (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.7 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.42 (d, *J* = 7.4 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.27−7.12 (m, 4H), 6.97−7.11 (m, 5H), 6.79 (d, *J* = 7.8 Hz, 1H), 4.93 (d, *J* = 15.2 Hz, 1H), 4.41 (d, *J* = 12.4 Hz, 1H), 2.94−2.59 (m, 2H), 1.22 (s, 9H); ^{13}C NMR for the major diastereomer (75 MHz, $CDCl_3$) δ 198.6 (J_{C-F} = 15.0 Hz), 172.3 (J_{C-F} = 9.0 Hz), 153.9, 148.5, 148.5, 143.2, 136.4, 135.8, 134.5, 134.5, 129.8, 128.8, 128.0, 127.8, 126.8, 126.1, 125.1, 123.4, 109.1, 96.2 (J_{C-F} = 198.8 Hz), 80.4, 66.7 (J_{C-F} = 21.0 Hz), 44.4, 35.7 (J_{C-F} = 23.3 Hz), 28.1; ^{19}F NMR for the major diastereomer (282 MHz, $CDCl_3$) δ −166.27 (s); HRMS calcd for $C_{29}H_{28}FN_2O_4$ $(M + H)^+$ 487.2028; found, 487.2048.

*tert-Butyl ((S)-1-Benzyl-3-((S)-2,5-difluoro-1-oxo-2,3-dihydro-1H-inden-2-yl)-2-oxoindolin-3-yl)carbamate (**3o**).* Pale yellow solid, mp 91−93 °C; 48.9 mg, 97% yield; 83% ee was determined by HPLC on a Chiralpak IC-H column (hexane/2-propanol = 1/2, 1.0 mL/min, t_{major} = 7.5 min, t_{minor} = 13.4 min); $[\alpha]_D^{22}$ = +125 (*c* = 1.0 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 8.5, 5.3 Hz, 1H), 7.49 (d, *J* = 7.3 Hz, 1H), 7.40−7.21 (m, 4H), 7.21−6.99 (m, 5H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 5.00 (d, *J* = 15.2 Hz, 1H), 4.50 (d, *J* = 11.9 Hz, 1H), 2.94−2.60 (m, 2H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.6 (J_{C-F} = 15.8 Hz), 172.1 (J_{C-F} = 8.25 Hz), 167.9 (J_{C-F} = 258.00 Hz), 153.9, 151.3 (J_{C-F} = 11.3 Hz), 143.1, 135.8, 130.9, 129.9, 128.8, 128.1, 128.0, 127.7, 127.6, 125.1, 123.5, 117.2 (J_{C-F} = 23.3 Hz), 113.0 (J_{C-F} = 23.3 Hz), 109.1, 94.8 (J_{C-F} = 198.8 Hz), 80.4, 66.7 (J_{C-F} = 21.0 Hz), 44.4, 35.6 (J_{C-F} = 24.0 Hz), 28.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ −98.646, −165.75 (s); HRMS calcd for $C_{29}H_{27}F_2N_2O_4$ $(M + H)^+$ 505.1933; found, 505.1953.

*tert-Butyl ((S)-1-Benzyl-3-((S)-5-chloro-2-fluoro-1-oxo-2,3-dihydro-1H-inden-2-yl)-2-oxoindolin-3-yl)carbamate (**3p**).* Pale yellow solid, mp 93−94 °C; 52.3 mg, 99% yield; 92% ee was determined by HPLC on a Chiralpak IC-H column (hexane/2-propanol = 1/2, 1.0 mL/min, t_{major} = 9.1 min, t_{minor} = 15.8 min); $[\alpha]_D^{22}$ = +208 (*c* = 1.0 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 1H), 7.41 (d, *J* = 7.4 Hz, 1H), 7.32 (d, *J* = 8.3 Hz, 1H), 7.29−7.13 (m, 4H), 7.12−6.99 (m, 3H), 6.95 (s, 1H), 6.92−6.77 (m, 2H), 4.93 (d, *J* = 15.1 Hz, 1H), 4.40 (d, *J* = 12.9 Hz, 1H), 2.66 (ddd, *J* = 30.3, 22.0, 15.2 Hz, 2H), 1.22 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.2 (J_{C-F} = 19.5 Hz), 172.0 (J_{C-F} = 9.5 Hz), 153.8, 149.7, 149.7, 143.2, 142.9, 135.8, 132.9 (J_{C-F} = 2.3 Hz), 129.9, 129.6, 128.8, 128.2, 128.0, 126.1, 125.2 (J_{C-F} = 2.3 Hz), 123.5, 109.1, 94.8 (J_{C-F} = 199.5 Hz), 80.5, 66.7 (J_{C-F} = 21.8 Hz), 44.4, 35.4 (J_{C-F} = 24.0 Hz), 28.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ −166.14 (s); HRMS calcd for $C_{29}H_{27}ClFN_2O_4$ $(M + H)^+$ 521.1638; found, 521.1661.

*tert-Butyl ((S)-1-Benzyl-3-((S)-5-bromo-2-fluoro-1-oxo-2,3-dihydro-1H-inden-2-yl)-2-oxoindolin-3-yl)carbamate (**3q**).* Pale yellow solid, mp 109−110 °C; 55.8 mg, 99% yield; 90% ee was determined by HPLC on a Chiralpak IC-H column (hexane/2-propanol = 1/2, 1.0 mL/min, t_{major} = 9.6 min, t_{minor} = 16.2 min); $[\alpha]_D^{22}$ = +133 (*c* = 1.0 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.2 Hz, 1H), 7.49 (d, *J* = 8.2 Hz, 1H), 7.41 (d, *J* = 7.4 Hz, 1H), 7.32−7.13 (m, 4H), 7.11−6.98 (m, 4H), 6.95 (s, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 4.94 (d, *J* = 15.1 Hz, 1H), 4.39 (d, *J* = 12.3 Hz, 1H), 2.83−2.49 (m, 2H), 1.22 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4 (J_{C-F} = 17.25 Hz), 171.9 (J_{C-F} = 9.00 Hz), 153.7, 149.7, 149.6, 143.1, 135.7, 133.2 (J_{C-F} = 2.3 Hz), 132.3, 131.8, 129.8, 129.4, 128.7, 128.1, 128.0, 126.0, 125.1 (J_{C-F} = 3.0 Hz), 123.5, 109.0, 94.6 (J_{C-F} = 199.5 Hz), 80.4, 66.6 (J_{C-F} = 21.0 Hz), 44.3, 35.2 (J_{C-F} = 24.0 Hz), 28.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ −166.22 (s); HRMS calcd for $C_{29}H_{27}BrFN_2O_4$ $(M + H)^+$ 565.1133; found, 565.1158.

*tert-Butyl ((S)-1-Benzyl-3-((S)-2-fluoro-6-methyl-1-oxo-2,3-dihydro-1H-inden-2-yl)-2-oxoindolin-3-yl)carbamate (**3r**).* Pale yellow solid, mp 99−100 °C; 42.3 mg, 85% yield; 90% ee was determined by HPLC on a Chiralpak IC-H column (hexane/2-propanol = 1/2, 1.0 mL/min, t_{major} = 11.1 min, t_{minor} = 18.5 min); $[\alpha]_D^{22}$ = +146 (*c* = 1.0 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.49 (d, *J* = 7.1 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.38−7.20 (m, 4H), 7.18−7.04 (m, 4H), 7.01 (d, *J* = 7.7 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 5.03 (d, *J* = 15.3 Hz, 1H), 4.48 (d, *J* = 12.0 Hz, 1H), 2.97−2.64 (m, 2H), 2.41 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.6 (J_{C-F} = 22.5 Hz), 172.2 (J_{C-F} = 8.3 Hz), 153.9, 145.9, 145.8, 143.1, 138.8, 137.7, 135.8, 134.6 (J_{C-F} = 1.5 Hz), 129.7, 128.7, 127.9, 127.7, 125.7, 125.0 (J_{C-F} = 2.3 Hz), 124.9, 123.3, 109.0, 95.0 (J_{C-F} = 198.8 Hz), 80.2, 66.7 (J_{C-F} = 21.0 Hz), 44.3, 35.3 (J_{C-F} = 23.3 Hz), 28.1, 21.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ −166.09 (s); HRMS calcd for $C_{30}H_{30}FN_2O_4$ $(M + H)^+$ 501.2184; found, 501.2202.

*tert-Butyl ((S)-1-Benzyl-3-((S)-2-fluoro-6-methoxy-1-oxo-2,3-dihydro-1H-inden-2-yl)-2-oxoindolin-3-yl)carbamate (**3s**).* Pale yellow solid, mp 94−96 °C; 44.9 mg, 87% yield; 81% ee was determined by HPLC on a Chiralpak IC-H column (hexane/2-propanol = 1/2, 1.0 mL/min, t_{major} = 10.3 min, t_{minor} = 14.7 min); $[\alpha]_D^{22}$ = +219 (*c* = 1.0 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.0 Hz, 1H), 7.34−7.13 (m, 6H), 7.13−6.96 (m, 4H), 6.92 (d, *J* = 8.3 Hz, 1H), 6.78 (d, *J* = 7.7 Hz, 1H), 4.96 (d, *J* = 15.2 Hz, 1H), 4.40 (d, *J* = 13.3 Hz, 1H), 3.77 (s, 3H), 2.85−2.50 (m, 2H), 1.22 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5 (J_{C-F} = 22.5 Hz), 171.2 (J_{C-F} = 8.3 Hz), 159.1, 152.9, 142.2, 140.4, 134.8, 134.6, 128.7, 127.7, 127.0, 126.8, 125.8, 125.1, 124.0, 124.0, 122.4, 108.0, 104.6, 94.4 (J_{C-F} = 199.5 Hz), 79.3, 65.7 (J_{C-F} = 21.0 Hz), 54.6, 43.3, 34.1 (J_{C-F} = 23.3 Hz), 27.1; ^{19}F NMR (282 MHz, $CDCl_3$) δ −166.09 (s); HRMS calcd for $C_{30}H_{30}FN_2O_5$ $(M + H)^+$ 517.2133; found, 517.2153.

*tert-Butyl ((R)-1-Benzyl-3-((R)-2-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)-2-oxoindolin-3-yl)carbamate (**3a′**).* Pale yellow solid, mp 71−73 °C; 46.5 mg, 93% yield; 91% ee was determined by HPLC on a Chiralpak IC-H column (hexane/2-propanol = 1/2, 1.0 mL/min, t_{minor} = 7.2 min, t_{major} = 9.9 min); $[\alpha]_D^{19}$ = −93 (*c* = 1.0 in $CHCl_3$); ^1H NMR for the major diastereomer (300 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.3 Hz, 1H), 7.48 (ddd, *J* = 11.3, 8.6, 4.3 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.33−7.21 (m, 6H), 7.16 (s, 1H), 7.08 (dd, *J* = 18.0, 7.6 Hz, 2H), 6.86 (d, *J* = 7.8 Hz, 1H), 4.93−4.66 (m, 2H), 2.73−2.59 (m, 1H), 2.57−2.39 (m, 1H), 2.10−1.90 (m, 1H), 1.90−1.71 (m, 1H), 1.28 (s, 9H); ^{13}C NMR for the major diastereomer (75 MHz, $CDCl_3$) δ 192.8 (J_{C-F} = 18.0 Hz), 172.6 (J_{C-F} = 7.5 Hz), 153.7, 143.6, 142.6,

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135.3, 134.0, 132.7, 129.6, 128.6, 128.4, 128.1, 127.9, 127.7, 127.4, 126.6, 125.0 (J_{C-F} = 3.0 Hz), 123.2, 108.9, 92.9 (J_{C-F} = 192.0 Hz), 80.1, 67.4 (J_{C-F} = 21.0 Hz), 44.5, 29.8 (J_{C-F} = 21.8 Hz), 28.1, 24.8 (J_{C-F} = 7.5 Hz); ^{19}F NMR for the major diastereomer (282 MHz, $CDCl_3$) δ −160.00 (s); HRMS calcd for $C_{30}H_{29}FN_2NaO_4$ $(M + Na)^+$ 523.2004; found, 523.2015.

*(S)-3-Amino-1-benzyl-6-bromo-3-((S)-2-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)indolin-2-one (**4**).* To a solution of **3h** (115.6 mg, 0.2 mmol) in CH_2Cl_2 (2.0 mL) was added trifluoroacetic acid (0.6 mL, 8.0 mmol) at 0 °C. Then, the mixture was stirred at room temperature for 2 h. After completion, the solution was dissolved in CH_2Cl_2 and washed with sat. aq. $NaHCO_3$ solution. Then, the organic phase was dried over Na_2SO_4 and removed under reduced pressure, and the residue was purified by silica gel column chromatography (PE/EtOAc = 2:1 to 1:1) to afford product **4** (93.7 mg, 98% yield) as a yellow oil. 90% ee was determined by HPLC on a Chiralpak IC-H column (hexane/2-propanol = 1/2, 1.0 mL/min, t_{minor} = 19.8 min, t_{major} = 52.3 min); $[\alpha]_D^{22}$ = +76 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.40−7.21 (m, 7H), 7.16 (dd, *J* = 15.4, 7.8 Hz, 2H), 6.96 (s, 1H), 4.87 (d, *J* = 15.5 Hz, 1H), 4.71 (d, *J* = 15.5 Hz, 1H), 3.02−2.88 (m, 1H), 2.69−2.55 (m, 1H), 2.55−2.41 (m, 1H), 2.37 (s, 2H), 2.23−1.95 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.6 (J_{C-F} = 18.8 Hz), 175.6 (J_{C-F} = 5.3 Hz), 144.6, 142.8, 134.9, 134.0, 132.4, 129.0, 128.2, 128.0, 127.7, 127.4, 127.3, 126.5, 126.0, 123.5, 112.9, 95.2 (J_{C-F} = 186.8 Hz), 65.1 (J_{C-F} = 23.3 Hz), 44.2, 30.6 (J_{C-F} = 23.3 Hz), 25.0 (J_{C-F} = 8.3 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −167.14 (s); HRMS calcd for $C_{25}H_{21}BrFN_2O_2$ $(M + H)^+$ 479.0765; found, 479.0782.

*(3S)-3-Amino-1-benzyl-6-bromo-3-((2S)-2-fluoro-1-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)indolin-2-one (**5**).* To a solution of **4** (47.8 mg, 0.1 mmol) in methanol (2.0 mL) was added $NaBH_4$ (7.6 mg, 0.2 mmol) at 0 °C, and the mixture was then stirred for 3 h at room temperature. Water was added, and the product was extracted into CH_2Cl_2. The combined organic phase was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (PE/EtOAc = 2:1 to 1:1) to afford product **5** (41.8 mg, 87% yield) as a white solid (mp 97−98 °C). 90% ee was determined by HPLC on a Chiralpak AD-H column (hexane/2-propanol = 70/30, 1.0 mL/min, t_{minor} = 8.2 min, t_{major} = 13.0 min); $[\alpha]_D^{22}$ = +9 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR for the major diastereomer (300 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.9 Hz, 1H), 7.41−7.18 (m, 10H), 7.18−7.11 (m, 1H), 6.86 (s, 1H), 5.20 (d, *J* = 16.1 Hz, 1H), 4.91 (d, *J* = 5.6 Hz, 1H), 4.58 (d, *J* = 15.8 Hz, 1H), 3.02−2.88 (m, 2H), 2.88−2.74 (m, 1H), 2.58−2.09 (m, 3H); ^{13}C NMR for the major diastereomer (75 MHz, $CDCl_3$) δ 177.0, 144.8, 135.4, 135.1, 134.5, 130.2, 129.0, 128.4, 128.1, 127.9, 127.4, 127.2, 126.8, 126.5, 126.1, 123.8, 113.0, 95.7 (J_{C-F} = 108.8 Hz), 70.2 (J_{C-F} = 32.3 Hz), 65.3 (J_{C-F} = 28.5 Hz), 44.0, 24.8 (J_{C-F} = 6.0 Hz), 20.6 (J_{C-F} = 21.0 Hz); ^{19}F NMR for the major diastereomer (282 MHz, $CDCl_3$) δ −173.48 (s); HRMS calcd for $C_{25}H_{23}BrFN_2O_2$ $(M + H)^+$ 481.0921; found, 481.0936.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02238.

^{1}H, ^{19}F, and ^{13}C NMR spectra, copies of HPLC results, and single crystal data of **3h** (PDF)

X-ray data (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wangrui@lzu.edu.cn.

Author Contributions

§X.L. and J.Z. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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