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N-Heterocyclic Carbene-Catalyzed Formal [3 + 2] Annulation of α-Bromoenals with 3-Aminooxindoles: A Stereoselective Synthesis of Spirooxindole γ-Butyrolactams

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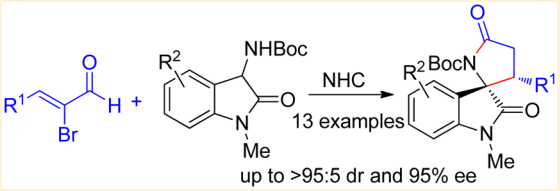
Supporting Information

ABSTRACT: A stereoselective synthetic approach to spirooxindole γ-butyrolactams is developed *via* N-heterocyclic carbene-catalyzed formal [3 + 2] annulation of α-bromoenals with 3-aminooxindoles. An enantioselective variant of this methodology is also investigated resulting in good substrate tolerance and high enantioselectivities.



Spirooxindoles are attractive heterocyclic frameworks with broad and promising activities in various therapeutic fields.[1] As an important subtype of spirooxindoles, the 3,2′-spiropyrrolidine oxindole unit is recognized as a privileged structure that forms the core of numerous heterocyclic compounds with a wide spectrum of significant bioactivities, such as antibacterial,[2] antitubercular,[2c] antitumor,[3] antifungal,[2c,4] and antimalarial[2c] activities (Figure 1). Given its

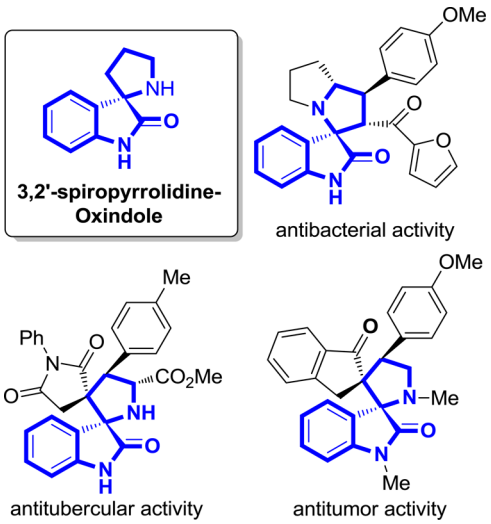
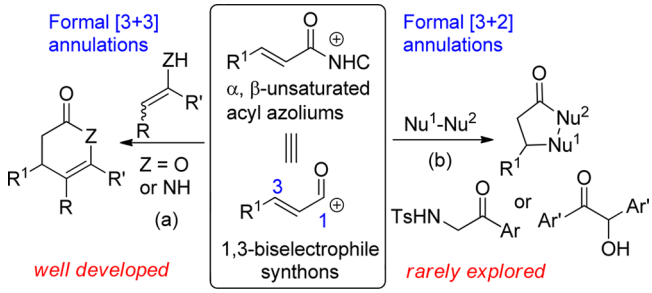


Figure 1. Representative biologically active compounds containing the 3,2′-spiropyrrolidine oxindole skeleton.

significant medicinal purposes, the 3,2′-spiropyrrolidine oxindole motif has been synthesized by considerable synthetic methods, particularly by the 1,3-dipolar cycloaddition of isatin-derived azomethine ylides with alkenes.[2−5] However, the development of novel and efficient synthetic methods to access functionalized 3,2′-spiropyrrolidine oxindoles with structural diversity is still desirable.

In recent years, N-heterocyclic carbene (NHC) catalysis has been used as a powerful tool for a large number of untypical chemical transformations.[6] Among these transformations, α,β-unsaturated acyl azoliums have emerged as fascinating 1,3-biselectrophile synthons with unique and unprecedented chemistry that were pioneered by Zeitler in 2006 (Scheme 1).[7] Many research groups have made impressive contributions

Scheme 1. Applications of α,β-Unsaturated Acyl Azoliums to the Synthesis of Various Heterocyclic Systems



to the applications of α,β-unsaturated acyl azoliums generated from different precursors, such as ynals,[8] enals (with external oxidation),[8b−d,9] α,β-unsaturated acyl fluorides,[10] esters,[11] α-bromoenals,[12] and *in situ* generated mixed anhydrides from carboxylic acids.[13] The well-explored reactions involved NHC-mediated formal [3 + 3] annulations of α,β-unsaturated acyl azoliums with various 1,3-bisnucleophiles (such as stable enols and enamines) to afford functionalized dihydropyranones[8a−d,9a,11c,12a−c,h] and dihydropyridinones (Scheme 1, eq a).[9b,c,11a,12c−e] However, to the best of our knowledge, the

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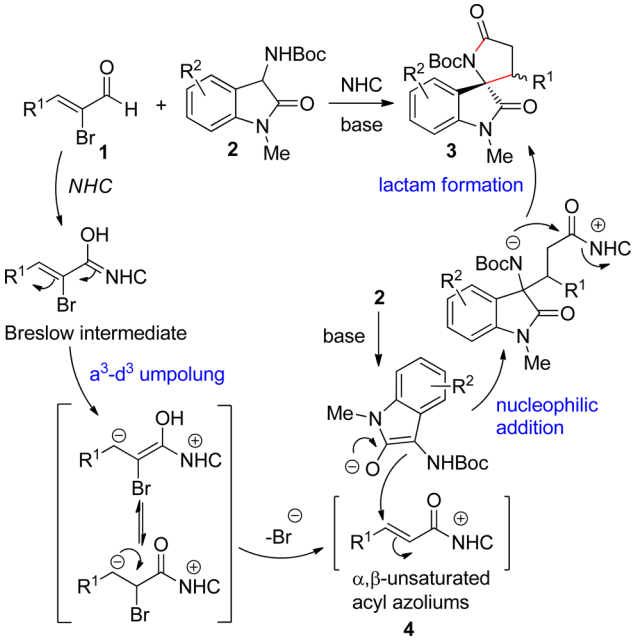
formal [3 + 2] annulations of α,β-unsaturated acyl azoliums with 1,2-bisnucleophiles are rarely investigated, and only two types of reactions were documented (Scheme 1, eq b). In 2014, Ye[13] first described the employment of α-amino ketones as the 1,2-bisnucleophiles to react with the *in situ* generated α,β-unsaturated acyl azoliums from α,β-unsaturated acids for the synthesis of γ-butyrolactams. Very recently, Peng and Huang[14] reported a formal [3 + 2] annulation of α,β-unsaturated acyl azoliums with aromatic aldehydes to assemble functionalized γ-butyrolactones enabled by two consecutive NHC catalytic systems.

In continuation of our studies on the exploration of NHC-catalyzed annulations for the synthesis of diverse heterocyclic systems,[8c,f,9i,15] we envision that 3-aminooxindoles **2** could serve as 1,2-bisnucleophiles to undergo formal [3 + 2] annulation with α,β-unsaturated acyl azoliums (Scheme 2).

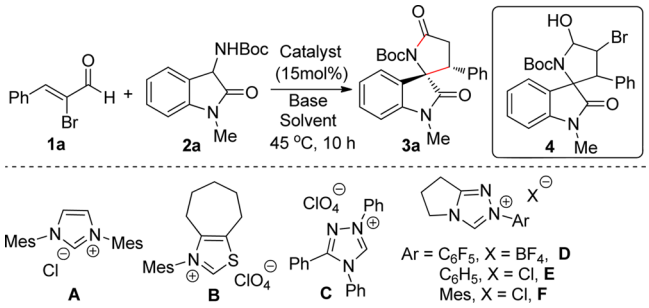
Scheme 2. NHC-Catalyzed Formal [3 + 2] Annulation of α-Bromoenals with 3-Aminooxindoles



The nucleophilic addition of **2** to α,β-unsaturated acyl azoliums **4** generated from α-bromoenals **1** followed by lactam formation may afford functionalized spirooxindole γ-butyrolactams **3** that contain the 3,2′-spiropyrrolidine oxindole core. Notably, the desired products **3** can be also synthesized via NHC-catalyzed a^3–d^3 umpolung [3 + 2] annulations of enals with isatin-derived ketimines.[16] Herein, we wish to report our recent results.

Our studies commenced with the model reaction of α-bromoenal **1a** (1.5 equiv) and 3-aminooxindole **2a** (1.0 equiv) in the presence of 15 mol % of a carbene precursor and 1.5 equiv of a base (Table 1). Initially, the efficiency of several commonly used carbene precursors **A**–**F** was examined in 1,4-dioxane using Cs_2CO_3 as the base (entries 1–4). None of the carbene precursors **A**–**D** were suitable for this reaction, and compound **4** was obtained in 31% yield while employing **A** as the precursor. Fortunately, precursor **F** was found to be effective for this reaction although the desired product **3a** was isolated in a low yield (entry 4). After careful screening of the solvents and bases, compound **3a** was obtained in 74% yield

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	base	solvent	yield (%)[b]	dr[d]
1	**A**	Cs_2CO_3	1,4-dioxane	0 (31)[c]	–
2	**B**–**D**	Cs_2CO_3	1,4-dioxane	0	–
3	**E**	Cs_2CO_3	1,4-dioxane	14	ND
4	**F**	Cs_2CO_3	1,4-dioxane	26	ND
5	**F**	Cs_2CO_3	CH_2Cl_2	15	ND
6	**F**	Cs_2CO_3	THF	0	–
7	**F**	Cs_2CO_3	PhMe	trace	ND
8	**F**	Cs_2CO_3	CH_3CN	41	67:33
9	**F**	DBU	CH_3CN	<10	ND
10	**F**	*t*BuOK	CH_3CN	13	ND
11	**F**	DIPEA	CH_3CN	76	63:37
12	**F**	NEt_3	CH_3CN	73	69:31
13	**F**	K_2CO_3	CH_3CN	74	75:25
14	**F**	**K_2CO_3**	**DME**	**84**	**85:15**

[a]All reactions were performed in a 25 mL two-neck round-bottom flask on a 0.2 mmol scale with 1.5 equiv of **1a**, 1.0 equiv of **2a**, 15 mol % of a carbene precursor, 1.5 equiv of a base, and 200 mg of 4 Å MS in an anhydrous solvent (4 mL) at 45 °C for 10 h under N_2. [b]Isolated yields based on **2a**. [c]Compound **4** was isolated in 31% yield. [d]Diastereomeric ratio determined by H^1 NMR of the crude product. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; Mes = 2,4,6-$(CH_3)_3C_6H_2$; DIPEA = *N*,*N*-diisopropylethylamine; DME = 1,2-dimethoxyethane; ND = not determined.

with moderate diastereoselectivity in the presence of K_2CO_3 in CH_3CN (entry 13). Gratifyingly, both the reaction yield and diastereoselectivity were improved by further changing the solvent CH_3CN to DME, which was finally established as the optimal reaction conditions (entry 14). As product **3a** is a known compound,[16b] the structure and stereochemistry of **3a** was established by comparison to its known spectroscopic data.

With the optimized reaction conditions in hand, we turned our attention to explore the reaction scope (Scheme 3). Initially, the variation of the α-bromoenals was investigated. α-Bromoenals with different substituents on the phenyl rings were found suitable for the reaction; products **3b**–**h** were obtained in good yield and excellent diastereoselectivity. To our delight, the reaction could also accommodate 2-furyl substituted and 1-naphyl substituted α-bromoenals to give products **3i** and **3j** in excellent diastereoselectivity. The lower yield of **3j** might be attributed to the steric effect of the more hindered 1-naphthyl group. Unfortunately, we did not obtain desired product **3k** when using aliphatic-substituted α-bromoenal. Substituted 3-aminooxindoles were also tested for the generality of this protocol. 5-Me substituted 3-amino-oxindole gave the desired product **3l** in moderate yield and good diastereoselectivity, while 5-F substituted 3-amino-oxindole afforded product **3m** in good yield but with poor diastereoselectivity. However, when we changed the solvent to CH_3CN, the *dr* value was improved to 77:23.

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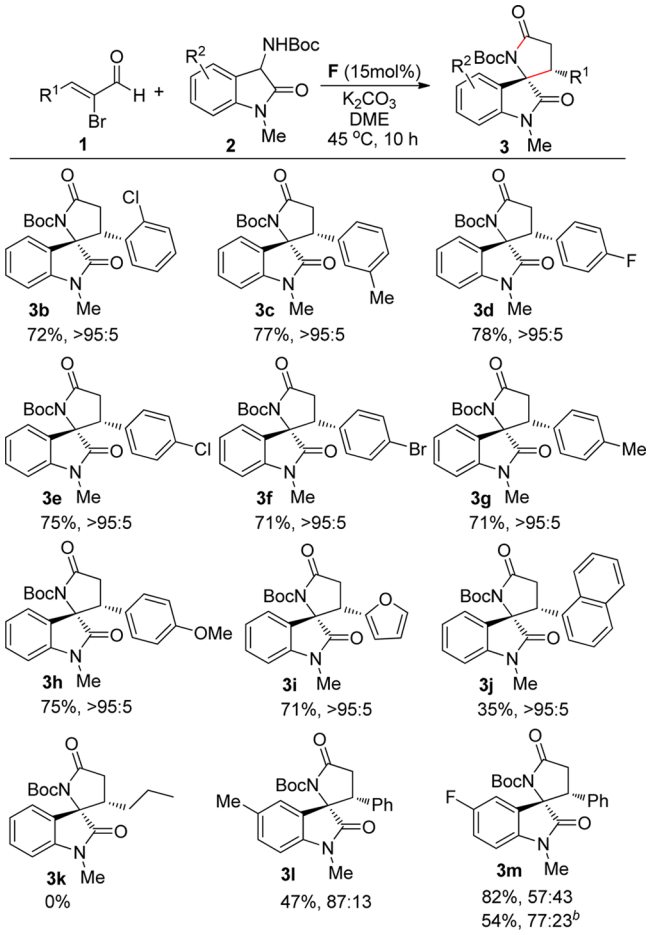
Scheme 3. Reaction Scope[a,b]

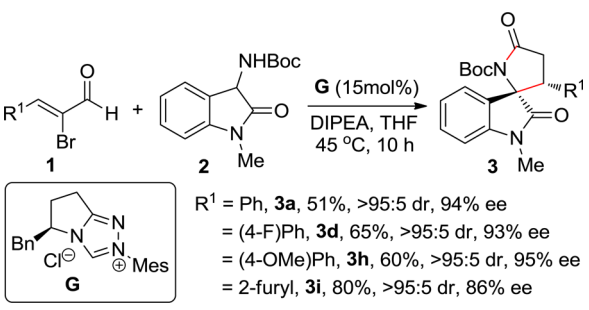


[a]Reaction conditions: Same as in Table 1, and all yields are based on **2**. [b]CH_3CN was used as the solvent.

An enantioselective variant of this methodology was also investigated employing several commonly used chiral carbene precursors (see Supporting Information). After optimizing the reaction conditions, we found that chiral triazolium salt G was the optimal precatalyst for this asymmetric formal [3 + 2] annulation (Scheme 4). The results show that precatalyst G has good substrate tolerance (including substituted phenyl and 2-furyl substrates), affording the corresponding products with high diastereo- and enantioselectivities.

In summary, we have demonstrated an NHC-catalyzed stereoselective formal [3 + 2] annulation of α-bromoenals with 3-aminooxindoles for the synthesis of functionalized spirooxindole γ-butyrolactams. This methodology offers an alternative and rapid access to the 3,2′-spiropyrrolidine oxindole skeleton.

Scheme 4. Enantioselective Studies of the Reaction[a]



[a]The ee value was determined by chiral HPLC analysis.

EXPERIMENTAL SECTION

General Methods and Materials. All reactions were carried out under an atmosphere of nitrogen in dry glassware and were monitored by analytical thin-layer chromatography (TLC), which was visualized by ultraviolet light (254 nm). All solvents were obtained from commercial sources and were purified according to standard procedures. Purification of the products was accomplished by flash chromatography using silica gel (200−300 mesh). Substrates **2** were prepared according to a known method.[17] All NMR spectra were recorded on spectrometers, running at 300 or 500 MHz for ^{1}H and 75 MHz for ^{13}C respectively. Chemical shifts (δ) and coupling constants (J) are reported in ppm and Hz, respectively. The solvent signals were used as references (residual $CHCl_3$ in $CDCl_3$: δ_H = 7.26 ppm, δ_c = 77.0 ppm). The following abbreviations are used to indicate the multiplicity in NMR spectra: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet). High resolution mass spectrometry (HRMS) was recorded on TOF premier spectrometer for ES$^+$. The ee value was determined via chiral HPLC analysis (Chiral pack IF, *n*-hexane/enthanol/diethylamine = 90/10/0.1).

General Experimental Procedure for the Synthesis of Products 3. An oven-dried 25 mL two-neck bound-bottom flask was charged with α-bromoenal **1** (0.3 mmol), 3-aminooxindole **2** (0.2 mmol), carbene precursor **F** (8 mg, 0.03 mmol), K_2CO_3 (41 mg. 0.3 mmol), and 200 mg of 4 Å MS under a N_2 atmosphere. Then anhydrous DME (4 mL) was added, and the resulting mixture was stirred at 45 °C for 10 h under N_2. After completion of the reaction as monitored by TLC, the mixture was cooled to room temperature. The solvent was evaporated under reduced pressure, and the residue was purified by chromatography on silica gel using hexane/EtOAc (5:1) as eluent to afford the products **3**.

(2′*S*,3′*R*)- and (2′*R*,3′*S*)-*tert*-Butyl 1-Methyl-2,5′-dioxo-3′-phenylspiro[indoline-3,2′-pyrrolidine]-1′-carboxylate (3a). Yield: 84% (66 mg). Known compound,[16b] white solid, mp 193−195 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (d, J = 7.2 Hz, 1H), 7.33 (t, J = 7.5 Hz, 1H), 7.09−7.19 (m, 4H), 6.81 (d, J = 7.2 Hz, 2H), 6.59 (d, J = 7.8 Hz, 1H), 3.56−3.74 (m, 2H), 2.74−2.79 (m, 1H), 2.71 (s, 3H), 1.09 (s, 9H).

(2′*S*,3′*R*)- and (2′*R*,3′*S*)-*tert*-Butyl 3′-(2-Chlorophenyl)-1-methyl-2,5′-dioxospiro[indoline-3,2′-pyrrolidine]-1′-carboxylate (3b). Yield: 72% (61 mg). Unknown compound, white solid, mp 180−182 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 7.2 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.19−7.24 (m, 1H), 7.08−7.13 (m, 3H), 6.60 (d, J = 7.8 Hz, 1H), 4.49 (dd, J = 13.1, 8.2 Hz, 1H), 3.41 (dd, J = 16.6, 13.3 Hz, 1H), 3.56−3.74 (m, 2H), 2.74−2.79 (m, 1H), 2.79−2.87 (m, 4H), 1.09 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.9, 172.9, 147.8, 143.2, 135.1, 131.1, 129.7, 129.5, 129.2, 129.1, 127.8, 126.6, 123.2, 122.9, 108.0, 83.7, 71.8, 42.8, 36.6, 27.3, 25.7. HRMS (ESI) calcd for $C_{23}H_{23}ClN_2NaO_4$ (M+Na)$^+$: 449.1239, found 449.1244.

(2′*S*,3′*R*)- and (2′*R*,3′*S*)-*tert*-Butyl 1-Methyl-2,5′-dioxo-3′-(*m*-tolyl)spiro[indoline-3,2′-pyrrolidine]-1′-carboxylate (3c). Yield: 77% (63 mg). Unknown compound, white solid, mp 163−165 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, J = 6.5 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.17 (t, J = 7.5 Hz, 1H), 6.97−7.02 (m, 2H), 6.58−6.63 (m, 3H), 3.56−3.69 (m, 2H), 2.72−2.75 (m, 4H), 2.15 (s, 3H), 1.10 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 173.6, 147.9, 143.7, 137.6, 132.2, 129.6, 128.8, 128.62, 128.57, 127.9, 124.8, 123.0, 121.8, 108.0, 83.6, 71.9, 49.0, 34.7, 27.3, 25.5, 21.2. HRMS (ESI) calcd for $C_{24}H_{26}N_2NaO_4$ (M+Na)$^+$: 429.1785, found 429.1786.

(2′*S*,3′*R*)- and (2′*R*,3′*S*)-*tert*-Butyl 3′-(4-Fluorophenyl)-1-methyl-2,5′-dioxospiro[indoline-3,2′-pyrrolidine]-1′-carboxylate (3d). Yield: 78% (64 mg), unknown compound, white solid, mp 202−204 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ7.31−7.39 (m, 2H), 7.18 (t, J = 7.5 Hz, 1H), 6.76−6.85 (m, 4H), 6.61 (d, J = 7.5 Hz, H), 3.51−3.73(m, 2H), 2.72−2.79 (m, 4H), 1.09 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 173.1, 162.5 (d, J = 247.3 Hz, 1C), 147.8, 143.6,

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129.8, 129.6 (d, J = 8.1 Hz, 1C), 128.3, 128.1, 123.2, 121.8, 115.0 (d, J = 21.5 Hz, 1C), 108.2, 83.7, 71.7, 48.3, 34.9, 27.3, 25.6. HRMS (ESI) calcd for $C_{23}H_{23}FN_2NaO_4$ $(M+Na)^+$: 433.1534, found 433.1538.

(2′*S*,3′*R*)- and (2′*R*,3′*S*)-*tert*-Butyl 3′-(4-Chlorophenyl)-1-methyl-2,5′-dioxospiro[indoline-3,2′-pyrrolidine]-1′-carboxylate (3e). Yield: 75% (64 mg). Known compound,[16b] white solid, mp 194−196 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32−7.39 (m, 2H), 7.18 (t, J = 7.5 Hz, 1H), 7.10 (d, J = 8.4 Hz, 2H), 6.76 (d, J = 8.1 Hz, 2H), 6.63 (d, J = 7.5 Hz, 1H), 3.50−3.72 (m, 2H), 2.72−2.77 (m, 4H), 1.09 (s, 9H).

(2′*S*,3′*R*)- and (2′*R*,3′*S*)-*tert*-Butyl 3′-(4-Bromophenyl)-1-methyl-2,5′-dioxospiro[indoline-3,2′-pyrrolidine]-1′-carboxylate (3f). Yield: 71% (67 mg). Known compound,[16b] white solid, mp 188−190 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34−7.41 (m, 2H), 7.28 (s, 2H), 7.19 (t, J = 7.5 Hz, 1H), 6.71 (d, J = 8.4 Hz, 2H), 6.65 (d, J = 7.8 Hz, 1H), 3.52−3.72 (m, 2H), 2.73−2.79 (m, 4H), 1.11 (s, 9H).

(2′*S*,3′*R*)- and (2′*R*,3′*S*)-*tert*-Butyl 1-Methyl-2,5′-dioxo-3′-(*p*-tolyl)spiro[indoline-3,2′-pyrrolidine]-1′-carboxylate (3g). Yield: 71% (58 mg). Known compound,[16b] white solid, mp 187−189 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30−7.39 (m, 2H), 7.16 (t, J = 7.2 Hz, 1H), 6.92 (d, J = 7.8 Hz, 2H), 6.70 (d, J = 8.1 Hz, 2H), 6.60 (d, J = 7.8 Hz, 1H), 3.54−3.67 (m, 2H), 2.69−2.76 (m, 4H), 2.24 (s, 3H), 1.09 (s, 9H).

(2′*S*,3′*R*)- and (2′*R*,3′*S*)-*tert*-Butyl 3′-(4-Methoxyphenyl)-1-methyl-2,5′-dioxospiro[indoline-3,2′-pyrrolidine]-1′-carboxylate (3h). Yield: 75% (63 mg). Known compound,[16b] white solid, mp 197−199 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30−7.38 (m, 2H), 7.16 (t, J = 7.2 Hz, 1H), 6.74 (d, J = 8.1 Hz, 2H), 6.59−6.66 (m, 3H), 3.72 (s, 3H), 3.51−3.68 (m, 2H), 2.69−2.76 (m, 4H), 1.09 (s, 9H).

(2′*S*,3′*S*)- and (2′*R*,3′*R*)-*tert*-Butyl 3′-(Furan-2-yl)-1-methyl-2,5′-dioxospiro[indoline-3,2′-pyrrolidine]-1′-carboxylate(3i). Yield: 71% (54 mg). Known compound,[16b] white solid, mp 182−184 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32−7.39 (m, 2H), 7.13−7.17 (m, 2H), 6.73 (d, J = 7.8 Hz, 1H), 6.19 (dd, J = 3.1, 1.8 Hz, 1H), 5.94 (d, J = 3.1 Hz, 1H), 3.81 (dd, J = 13.3, 7.8 Hz, 1H), 3.51 (dd, J = 16.6, 13.5 Hz, 1H), 2.95 (s, 3H), 2.82 (dd, J = 16.7, 7.9 Hz, 1H), 1.09 (s, 9H).

(2′*S*,3′*R*)- and (2′*R*,3′*S*)-*tert*-Butyl 1-Methyl-3′-(naphthalen-1-yl)-2,5′-dioxospiro[indoline-3,2′-pyrrolidine]-1′-carboxylate (3j). Yield: 35% (31 mg). Unknown compound, white solid, mp 200−202 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68−7.72 (m, 3H), 7.51−7.56 (m, 1H), 7.45 (t, J = 7.8 Hz, 1H), 7.23−9.29 (m, 2H), 7.11−7.18 (m, 2H), 7.03−7.08 (m, 1H), 6.24−6.27 (m, 1H), 4.67 (dd, J = 12.9, 8.1 Hz, 1H), 3.71 (dd, J = 16.7, 13.2 Hz, 1H), 2.90 (dd, J = 16.8, 7.8 Hz, 1H), 2.55 (s, 3H), 1.06 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.8, 173.5, 147.9, 143.4, 133.3, 131.9, 129.6, 128.9, 128.7, 128.6, 128.5, 125.5, 125.3, 125.1, 124.9, 122.8, 122.2, 121.9, 108.1, 83.6, 72.5, 42.0, 36.7, 27.3, 25.4. HRMS (ESI) calcd for $C_{27}H_{26}N_2NaO_4$ $(M + Na)^+$: 465.1785, found 465.1791.

(2′*S*,3′*R*)- and (2′*R*,3′*S*)- *tert*-Butyl 1,5-Dimethyl-2,5′-dioxo-3′-phenylspiro[indoline-3,2′-pyrrolidine]-1′-carboxylate (3l). Yield: 47% (38 mg). Known compound,[16b] white solid, mp 171−173 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21 (s, 1H), 7.10−7.18 (m, 4H), 6.83 (d, J = 7.2 Hz, 2H), 6.47 (d, J = 7.8 Hz, 1H), 3.56−3.73 (m, 2H), 2.68−2.77 (m, 4H), 2.40 (s, 3H), 1.10 (s, 9H).

(2′*S*,3′*R*)- and (2′*R*,3′*S*)-*tert*-Butyl 5-Fluoro-1-methyl-2,5′-dioxo-3′-phenylspiro[indoline-3,2′-pyrrolidine]-1′-carboxylate (3m). Yield: 54% (44 mg). Unknown compound, white solid, mp 179−181 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.12−7.20 (m, 4H), 7.01−7.07 (m, 1H), 6.84 (d, J = 7.2 Hz, 2H), 6.52 (dd, J = 8.4, 3.8 Hz, 1H), 3.56−3.70 (m, 2H), 2.70−2.78 (m, 4H), 1.16 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.3, 173.0, 159.4 (d, J = 242.7 Hz, 1C), 147.8, 139.6, 132.0, 130.2 (d, J = 7.8 Hz, 1C), 128.4, 128.1, 127.8, 115.8 (d, J = 23.4 Hz, 1C), 110.1 (d, J = 25.3 Hz, 1C), 108.7 (d, J = 8.0 Hz, 1C), 83.9, 72.0, 49.1, 34.6, 27.4, 25.6. HRMS (ESI) calcd for: $C_{23}H_{23}FN_2O_4$ $(M+Na)^+$: 433.1534, found 433.1537.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02188.

Optimization of the reaction conditions for asymmetric synthesis. ^{1}H and ^{13}C NMR spectra for the products. HPLC spectra for products **3a**, **3d**, **3h**, and **3i** (PDF)

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Notes

The authors declare no competing financial interest.

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