Organocatalytic Enantioselective Mannich Reaction: Direct Access to Chiral \( \beta \)-Amino Esters

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Supporting Information

ABSTRACT: An asymmetric Mannich reaction has been developed to generate chiral \( \beta \)-amino esters in good yields with excellent enantiomeric excesses (ee, up to 99%) using a chiral bifunctional thiourea catalyst derived from (R,R)-cyclohexylidamine. This is the first report on the addition of 3-indolinone-2-carboxylates to \( N \)-Boc-benzaldehydes generated in situ from \( \alpha \)-amidosulfones, which proceeds under mild conditions.

INTRODUCTION

Chiral \( \beta \)-amino esters are useful building blocks for the synthesis of \( \beta \)-lactams and unnatural peptides. They found widespread applications in drug discovery. On the other hand, a chiral 2,2-disubstituted indolin-3-one skeleton is often present in several biologically active natural products such as (+)-isatisine A, trigononilimine C, mersicarpine, etc. They are known to exhibit potent antiviral properties. Consequently, a few methods have been reported for the enantioselective conversion of 3-indolinone-2-carboxylates into chiral compounds. However, the construction of a chiral quaternary stereocenter is a challenging task for a synthetic chemist. Furthermore, an asymmetric Mannich reaction is a powerful strategy to produce chiral \( \beta \)-amino ketones and \( \beta \)-amino esters. Inspired by their fascinating structural features and potent biological activities, we were interested in producing chiral 2,2-disubstituted indolin-3-one derivatives. Indeed, there are no reports on the direct asymmetric Mannich-type addition of 3-indolinone-2-carboxylates to \( N \)-Boc-benzaldehydes generated in situ from \( \alpha \)-amidosulfones.

Following our interest in asymmetric synthesis, we herein report an enantioselective Mannich reaction of 2-substituted indolin-3-ones for the synthesis of chiral \( \beta \)-amino esters, using a thiourea catalyst derived from \( \text{trans-}(R,R)\)-1,2-diaminocyclohexane. Our investigation began with the reaction of 3-indolinone-2-carboxylate (1) with \( N \)-Boc-benzaldehyde (2) using quinidine 4a as a catalyst in the presence of \( \text{Na}_2\text{CO}_3\) in toluene (Table 1, entry a) at room temperature. Interestingly, the desired product 3a was obtained in 60% yield with 10% enantiomeric excesses (ee) and 92:8 diastereoselectivity. Next, we attempted the same reaction with dihydroquinidine 4b as a catalyst, and no significant improvement in yield and ee of product 3a was observed. Furthermore, the reaction was performed using a bifunctional Takemoto’s catalyst 4c, 5 mol %, and \( \text{Na}_2\text{CO}_3\) in toluene at room temperature. Interestingly, the desired product 3a was obtained in 80% yield with 55% ee and 93:7 diastereoselectivity (Table 1, entry c). To enhance the enantio- and diastereoselectivity, the reaction was further performed with 5 mol % catalyst 4d under similar conditions (Table 1, entry d). A slight improvement was observed in enantio- and diastereoselectivity. Therefore, the reaction was further performed using a 5 mol % catalyst 4e under identical conditions. To our delight, the yield and ee were improved significantly (Table 1, entry e). To evaluate other thiourea catalysts (Scheme 1), the reaction was further carried out using a 5 mol % bis-thiourea catalyst 4f derived from \( \text{trans-}(R,R)\)-1,2-diaminocyclohexane. However, the product 3a was obtained with low enantio- and diastereoselectivity. To improve the enantio- and diastereoselectivity, the reaction was repeated using 5 mol % thiourea catalysts 4g and 4h derived from \( \text{trans-}1,2\)-diaminoindane and \( \text{trans-}1\)-amino-2-indanol, respectively. The desired product 3a was obtained in poor yield and with low selectivity (Table S1, entries g and h). Therefore, the next reaction was carried out using a thiourea catalyst 4i derived from 1,1’-binaphthyl-2,2’-diamine (Table 1, entry i). However, the catalyst 4i was found to be inferior than other catalysts. To know the effect of base, the

Figure 1. Examples of 3-indolinone natural products.

(+)isatisine A
Trigononilimine C
Mersicarpine

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Table 1. Optimization of Reaction Conditions in the Formation of 3a

| entry | catalyst | base (aq.) | solvent | T (°C) | time (days) | yield (%) | dr (3a:3aa) | ee (%) | entry | catalyst | base (aq.) | solvent | T (°C) | time (days) | yield (%) | dr (3a:3aa) | ee (%) |
|-------|----------|------------|---------|--------|-------------|-----------|-------------|--------|-------|----------|------------|---------|--------|-------------|-----------|-------------|--------|
| a     | 4a       | Na₂CO₃     | toluene | 25     | 3           | 45        | 92:8        | 10     | 1     | 4e       | NaOH       | toluene | 25     | 1           | 20        | 90:10       | 5       |
| b     | 4b       | Na₂CO₃     | toluene | 25     | 2           | 60        | 93:7        | 5      | m     | 4e       | CsOH       | toluene | 25     | 1           | 25        | 95:5        | 10      |
| c     | 4c       | Na₂CO₃     | toluene | 25     | 4           | 80        | 93:7        | 55     | n     | 4e       | Na₂CO₃     | xylene  | 0      | 3           | 98        | 99:1        | 99      |
| d     | 4d       | Na₂CO₃     | toluene | 25     | 3           | 85        | 98:2        | 60     | o     | 4e       | Na₂CO₃     | toluene | 0      | 3           | 60        | 99:1        | 65      |
| e     | 4e       | Na₂CO₃     | toluene | 25     | 2           | 90        | 99:1        | 85     | p     | 4e       | Na₂CO₃     | MTBE    | 0      | 3           | 50        | 99:1        | 30      |
| f     | 4f       | Na₂CO₃     | toluene | 25     | 4           | 40        | 95:5        | 50     | q     | 4e       | Na₂CO₃     | benzene | 0      | 3           | 55        | 99:1        | 40      |
| g     | 4g       | Na₂CO₃     | toluene | 25     | 5           | 45        | 89:11       | 30     | r     | 4e       | Na₂CO₃     | DCE     | 0      | 3           | 35        | 99:1        | 20      |
| h     | 4h       | Na₂CO₃     | toluene | 25     | 4           | 50        | 88:22       | 25     | s     | 4e       | Na₂CO₃     | xylene  | −20    | 4           | 35        | 99:1        | 40      |
| i     | 4i       | Na₂CO₃     | toluene | 25     | 5           | 40        | 90:10       | 30     | t     | 4e       | Na₂CO₃     | toluene | −40    | 5           | 30        | 99:1        | 30      |
| j     | 4e       | K₂CO₃      | toluene | 25     | 2           | 80        | 99:1        | 70     | u     | 4e       | Na₂CO₃     | toluene | −78    | 2           |           |             |         |
| k     | 4e       | Cs₂CO₃     | toluene | 25     | 2           | 65        | 95:5        | 20     |       |          |            |         |        |             |           |             |         |

*All reactions were performed at 0.21 mmol of 1, 0.25 mmol of 2, 5 mol % 4e and 0.2 mL of aqueous base in 5 mL of solvent. Isolated yields after column chromatography. Diastereomeric ratio was determined by ¹H NMR. Enantiomeric excess was determined by chiral high-performance liquid chromatography (HPLC). Enantiomeric ratio of the major diastereomer.
reaction was conducted in toluene using different bases like Na₂CO₃, K₂CO₃, Cs₂CO₃, NaOH, and CsOH (Table 1, entries i–m). Among them, Na₂CO₃ in toluene was found to be the best for this transformation (Table 1, entry m). To our surprise, only 30% conversion was observed using 10% Na₂CO₃ solution and 60% conversion was observed with 50% Na₂CO₃ solution. Interestingly, 98% conversion was obtained with a sat. Na₂CO₃ solution, which was prepared using 32 g of Na₂CO₃ in 100 mL of water at 27 °C. Furthermore, we examined the effect of different solvents such as o-xylene, methyl tert-butyl ether, benzene, and dichloroethane on the conversion under similar reaction conditions (Table 1, entries n–t). None of these solvents produced better results than o-xylene (Table 1, entry n). Finally, we tested the effect of temperature, ranging from 25 to −78 °C, on the conversion. The best results were obtained using 5 mol % catalyst 4e and Na₂CO₃ in xylene at 0 °C. Due to the low freezing point of xylene (−25 °C), further reactions were conducted in toluene. However, there was no reaction in toluene at −78 °C under similar conditions (Table 1, entry u).

After having optimized conditions in hand, the scope of this method was examined with different substrates, and the results are summarized in Table 2. The substituent present on the aromatic ring of aldimine had shown some effect on the conversion. The substituents that are present at the 5th position of methyl 3-oxo-indoline-2-carboxylate afforded the corresponding product in excellent yield with excellent enantioselectivity (Table 2, entries 3b, 3c, 3i, and 3k). The substrate bearing electron-withdrawing substituents such as nitro- and cyano- on the aromatic ring of aldimine gave the desired product in high yield with excellent enantioselective excess (Table 2, entries 3h, 3i, 3j, and 3k). Conversely, the substrate having electron-donating groups like methyl- and methoxy on the aromatic ring gave the desired product in good yield with excellent enantioselective excess (Table 2, entries 3m and 3r).

Mechanistically, the reaction proceeds through the formation of an enolate ion from 3-indolinone-2-carboxylate 3a through hydrogen bonding. The absolute stereochemistry of 3a was established by single-crystal X-ray crystallography of 3t, which is having heavy atoms in its structure (Figure 3). As depicted in the ORTEP diagram, the absolute stereochemistry of 3t was assigned as R,S.

Finally, we tried to convert the product 3a into a spirolactam to demonstrate its synthetic application. To our surprise, the compound 3a failed to undergo cyclization under basic conditions (Scheme 2).

In summary, we have successfully developed an organocatalytic asymmetric Mannich reaction for the synthesis of chiral β-amino esters, which are key intermediates for the synthesis of biologically active molecules. The reaction proceeds under mild conditions and is compatible with diverse range of substituents that are present on the aromatic ring of aldimines. This method works with a wide range of substrates including aryl, naphthyl, and heteroaryl cyclic β-ketoesters.

**CONCLUSIONS**

**GENERAL METHODS**

All solvents were dried according to standard literature procedures. The reactions were conducted under a nitrogen atmosphere. Melting points (mp) were obtained on Buchi B-
Table 2. Substrate Scope

| Entry | Starting material (1/2) | Product (3a) | Yield (%)<sup>a</sup> | ee (%)<sup>d</sup> | Product (3a:3aa) | Yield (%)<sup>e</sup> | ee (%)<sup>d</sup> |
|-------|-------------------------|--------------|----------------------|-------------------|------------------|----------------------|-------------------|
| a     | NHBocSO<sub>2</sub>Ph   | NHBocSO<sub>2</sub>Ph | 90 99:1 92           |                   |                  |                      |                   |
| b     | NHBocSO<sub>2</sub>Ph   | NHBocSO<sub>2</sub>Ph | 98 99:1 96           |                   |                  |                      |                   |
| c     | NHBocSO<sub>2</sub>Ph   | NHBocSO<sub>2</sub>Ph | 98 99:1 99           |                   |                  |                      |                   |
| d     | NHBocSO<sub>2</sub>Ph   | NHBocSO<sub>2</sub>Ph | 88 99:1 96           |                   |                  |                      |                   |
| e     | NHBocSO<sub>2</sub>Ph   | NHBocSO<sub>2</sub>Ph | 92 99:1 88           |                   |                  |                      |                   |
| f     | NHBocSO<sub>2</sub>Ph   | NHBocSO<sub>2</sub>Ph | 80 99:1 66           |                   |                  |                      |                   |
| g     | NHBocSO<sub>2</sub>Ph   | NHBocSO<sub>2</sub>Ph | 96 99:1 82           |                   |                  |                      |                   |
| h     | NHBocSO<sub>2</sub>Ph   | NHBocSO<sub>2</sub>Ph | 88 99:1 95           |                   |                  |                      |                   |
| i     | NHBocSO<sub>2</sub>Ph   | NHBocSO<sub>2</sub>Ph | 90 99:1 91           |                   |                  |                      |                   |
| j     | NHBocSO<sub>2</sub>Ph   | NHBocSO<sub>2</sub>Ph | 88 99:1 97           |                   |                  |                      |                   |

<sup>a</sup>All reactions were performed at 0.21 mmol of 1, 0.25 mmol of 2, 5 mol % 4e, and 0.2 mL of aqueous base in 5 mL of solvent. <sup>b</sup>Isolated yields after column chromatography. <sup>c</sup>Diestereomeric ratio was determined by <sup>1</sup>H NMR. <sup>d</sup>Enantiomeric excess was determined by chiral HPLC. <sup>e</sup>Enantiomeric ratio of the major diastereomer.
NMR spectrometer. Chemical shifts (δ) were reported in parts per million (ppm) with respect to tetramethylsilane as an internal standard. Coupling constants (J) are quoted in hertz (Hz). Mass spectra and high-resolution mass spectrometry (HRMS) were recorded on a mass spectrometer by the electrospray ionization (ESI) or atmospheric pressure chemical ionization technique. Optical rotations were recorded on an Anton Paar MCP-200 polarimeter. Enantiomeric excesses (ee’s) were determined by HPLC analysis using DAICEL Chiralpak OD-H, AS-H, IC, IA columns. The precursors were prepared according to the procedure reported in the literature.12

**General Procedure for the Asymmetric Mannich Reaction (3a).** To a suspension of 2-substituted 3-indolinones 1 (50 mg, 1.0 equiv, 0.21 mmol %) and α-amidosulfones 2 (1.2 equiv, 0.25 mmol %) in xylene (5 mL) at 0 °C were added catalyst 4c (5 mol %) and saturated Na₂CO₃ (0.2 mL) successively. The resulting mixture was stirred for 3 days at 0 °C and then with water and extracted with ethyl acetate. The organic layer was dried over Na₂SO₄ and concentrated under vacuum to give the crude product, which was purified by column chromatography using a gradient mixture of ethyl acetate/hexane (2:8) as the eluent to afford the product 3a.

All other reactions were carried out according to the general procedure for the synthesis of 3a to 3s. The racemic samples

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**Scheme 2. Spirolactam Formation**

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\text{Scheme 2. Spirolactam Formation}
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540. ^1H and ^13C NMR (proton-decoupled) spectra were recorded in the CDCl₃ solvent at 300, 400, or 500 MHz on an NMR spectrometer.
were prepared by the following general procedure, using quinine and quinidine (1:1) as catalysts instead of thiourea 4c. In the absence of quinine and quinidine, the racemic reaction was very sluggish and takes more than 5 days for the completion with low yield.

**Methyl (R)-1-Acetyl-2-((S)-(tert-butoxycarbonyl)amino)(phenyl)ethyl-3-oxoindoline-2-carboxylate (3a).** (0.084 g, 92% yield) white solid. Mp 130–132 °C. IR (neat) ν 3409.7, 3007.4, 2978.2, 1763.6, 1706.2, 1476.0, 1339.9, 1291.4, 1164.4, 1048.1, 770.8, 693.3 cm⁻¹. 1H NMR (400 MHz, CDCl₃) δ 7.70 (d, J = 7.2 Hz, 1H), 7.50–7.41 (m, 1H), 7.10 (t, J = 7.5 Hz, 1H), 6.98 (s, 6H), 6.70 (s, 1H), 5.97 (s, 1H), 3.76 (s, 3H), 2.38 (s, 3H), 1.45 (s, 9H). 13C NMR (100 MHz, CDCl₃) δ 194.5, 167.8, 165.2, 155.2, 137.8, 127.8, 127.6, 126.9, 126.8, 124.8, 124.0, 114.5, 79.5, 74.4, 55.9, 53.4, 28.4, 25.6. HRMS (Orbitrap ESI): exact mass calcd for C₂₄H₂₅N₂O₆BrNa [M + Na]⁺: 461.1683. Found: 461.1696. HPLC analysis (DAICEL Chiralpak OD-H), n-hexane/2-ProH = 80:20, 1 mL/min, 254 nm, major (7.23 min), minor (8.50 min), ee: 97.25; [α]D²⁰ = −40.2 (c = 0.15, CHCl₃).

**Methyl (R)-1-Acetyl-2-((S)-(2-bromophenyl)amino)(3-chlorophenyl)methyl-3-oxoindoline-2-carboxylate (3b).** (0.106 g, 96% yield) white solid. Mp 130–132 °C. IR (neat) ν 3411.5, 3011.5, 2978.1, 1761.6, 1761.1, 1606.7, 1500.1, 1473.4, 1373.4, 1342.2, 1264.9, 1165.6, 1156.5, 614.5 cm⁻¹. 1H NMR (400 MHz, CDCl₃) δ 7.66 (d, J = 5.6 Hz, 1H), 7.47 (t, J = 7.4 Hz, 1H), 7.32 (s, 1H), 7.2–6.9 (m, 3H), 6.83 (s, 2H), 6.63 (s, 1H), 6.30 (s, 1H), 3.76 (s, 3H), 2.47 (s, 3H), 1.44 (s, 9H). 13C NMR (100 MHz, CDCl₃) δ 190.7, 164.6, 155.9, 153.4, 137.7, 132.6, 132.9, 129.1, 126.5, 129.4, 124.2, 114.0, 79.5, 74.3, 55.3, 53.3, 28.4, 25.7. HRMS (Orbitrap ESI): exact mass calcd for C₂₄H₂₅N₂O₆ClNa [M + Na]⁺: 439.1588. Found: 439.1586.

**Methyl (R)-1-Acetyl-1-(tert-butylcarbonyl)amino)-3-oxoindoline-2-carboxylate (3c).** (0.091 g, 88% yield) white solid. Mp 158–160 °C. IR (neat) ν 3411.5, 3011.5, 2978.1, 1761.6, 1761.1, 1606.7, 1500.1, 1473.4, 1373.4, 1342.2, 1264.9, 1165.6, 1156.5, 614.5 cm⁻¹. 1H NMR (400 MHz, CDCl₃) δ 7.67 (t, J = 7.4 Hz, 1H), 7.53–7.48 (m, 1H), 7.14 (t, J = 7.5 Hz, 1H), 7.02–6.84 (m, 3H), 6.69 (s, 1H), 5.94 (s, 1H), 3.76 (s, 3H), 2.41 (s, 3H), 1.46 (s, 9H). 13C NMR (100 MHz, CDCl₃) δ 194.1, 167.8, 165.0, 155.2, 152.0, 139.5, 138.0, 133.6, 128.9, 128.0, 127.3, 125.4, 125.0, 124.2, 114.5, 79.8, 74.0, 55.4, 53.4, 28.4, 25.6. HRMS (Orbitrap ESI): exact mass calcd for C₂₄H₂₅N₂O₆ClNa [M + Na]⁺: 249.1392. Found: 249.1392.

**Methyl (R)-1-Acetyl-2-((S)-(tert-butylcarbonyl)amino)(3-chlorophenyl)methyl-3-oxoindoline-2-carboxylate (3e).** (0.091 g, 96% yield) white solid. Mp 130–132 °C. IR (neat) ν 3399.8, 3012.3, 2969.8, 1735.6, 1710.6, 1680.3, 1585.6, 1465.8, 1369.7, 1322.5, 1156.5, 1029.5, 765.6, 660.0 cm⁻¹. 1H NMR (400 MHz, CDCl₃) δ 7.67 (d, J = 6.6 Hz, 1H), 7.47 (t, J = 7.8 Hz, 1H), 7.11 (t, J = 7.4 Hz, 1H), 6.81–6.74 (m, 5H), 6.66 (s, 1H), 5.93 (s, 1H), 3.76 (s, 3H), 2.38 (s, 3H), 2.12 (s, 3H), 1.45 (s, 9H). 13C NMR (100 MHz, CDCl₃) δ 194.6, 167.8, 165.3, 155.1, 152.1, 137.7, 134.2, 128.3, 126.8, 124.8, 114.5, 79.4, 74.5, 55.6, 53.3, 28.4, 25.6, 20.9. HRMS (Orbitrap ESI): exact mass calcd for C₂₄H₂₅N₂O₆ClNa [M + Na]⁺: 475.1839. Found: 475.1850.

**Methyl (R)-1-Acetyl-1-(tert-buty1carbonyl)amino)(3,4-dimethoxyphenyl)methyl-3-oxoindoline-2-carboxylate (3f).** (0.102 g, 96% yield) white solid. Mp 130–132 °C. IR (neat) ν 3410.6, 3021.3, 2969.5, 1735.6, 1710.6, 1680.3, 1585.6, 1465.8, 1369.7, 1322.5, 1156.5, 1029.5, 765.6, 660.0 cm⁻¹. 1H NMR (400 MHz, CDCl₃) δ 7.46 (d, J = 6.6 Hz, 1H), 7.47 (t, J = 7.8 Hz, 1H), 7.11 (t, J = 7.4 Hz, 1H), 6.81–6.74 (m, 5H), 6.66 (s, 1H), 5.93 (s, 1H), 3.76 (s, 3H), 2.38 (s, 3H), 2.12 (s, 3H), 1.45 (s, 9H). 13C NMR (100 MHz, CDCl₃) δ 194.6, 167.8, 165.3, 155.1, 152.1, 137.7, 134.2, 128.3, 126.8, 124.8, 114.5, 79.4, 74.5, 55.6, 53.3, 28.4, 25.6, 20.9. HRMS (Orbitrap ESI): exact mass calcd for C₂₆H₃₀N₂O₈Na [M + Na]⁺: 541.2307. Found: 541.2309.
Methyl (R)-1-Acetyl-2-(S)-(tert-butoxycarbonyl)amino)-2-nitrophenyl)methyl)-3-oxoindoline-2-carboxylate (3l). (0.097 g, 90% yield) yellow solid. Mp 156–158 °C. IR (neat) υ 3400.1, 3009.8, 2797.8, 2340.1, 1763.7, 1707.8, 1676.5, 1663.3, 1499.8, 1417.3, 1339.5, 1239.2, 1164.2, 1052.6, 759.1, 615.6 cm⁻¹. 1H NMR (400 MHz, CDCl3) δ 7.73 (d, J = 7.5 Hz, 1H), 7.54 (dd, J = 8.6, 7.4, 14 Hz, 1H), 7.31 (d, J = 8.2 Hz, 2H), 7.20–7.09 (m, 4H), 6.77 (s, 1H), 6.01 (s, 1H), 3.76 (s, 3H), 2.40 (s, 3H), 1.44 (s, 9H). 13C NMR (101 MHz, CDCl3) δ 193.8, 168.0, 168.4, 155.2, 151.9, 143.0, 138.4, 131.5, 127.8, 125.1, 124.5, 118.3, 114.7, 114.7, 80.0, 73.7, 55.8, 53.6, 28.3, 25.6. HRMS (Orbitrap ESI): exact mass calcld for C24H23BrClN2O6Na [M + Na]+: 573.0398. Found: 573.0423. 1H NMR (400 MHz, CDCl3) δ 7.73 (d, J = 7.5 Hz, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 7.9 Hz, 2H), 7.24–6.79 (m, 9H), 6.92 (s, 1H), 5.80 (d, J = 8.4 Hz, 1H), 3.82 (s, 3H), 1.47 (s, 9H). 13C NMR (101 MHz, CDCl3) δ 194.5, 167.9, 164.7, 155.0, 152.7, 142.2, 138.1, 131.4, 128.7, 128.4, 125.3, 124.6, 124.3, 115.6, 79.7, 74.2, 55.7, 53.6, 28.4. HRMS (Orbitrap ESI): exact mass calcld for C24H23BrN2O6Na [M + Na]+: 575.1449. Found: 575.1428. HPLC analysis (DAICEL Chiralpak OD-H), n-hexane/2-ProH = 80:20, 1 mL/min, 254 nm, major (10.14 min), minor (8.66 min), ee = 98:72; [α]D = −85.0 (c = 0.15, CHCl3).

Methyl (R)-1-Acetyl-2-(S)-(tert-butoxycarbonyl)amino)(4-cyanophenyl)methyl)-3-oxoindoline-2-carboxylate (3k). (0.091 g, 90% yield) yellow solid. Mp 162–164 °C. IR (neat) υ 3400.4, 3008.5, 2797.5, 2328.0, 1763.7, 1708.6, 1777.2, 1666.6, 1472.2, 1340.1, 1241.1, 1164.5, 1052.9, 758.2, 616.5 cm⁻¹. 1H NMR (400 MHz, CDCl3) δ 7.73 (d, J = 7.6 Hz, 1H), 7.54 (dd, J = 8.6, 7.3, 14 Hz, 1H), 7.31 (d, J = 8.3 Hz, 2H), 7.20–7.09 (m, 4H), 6.77 (s, 1H), 6.01 (s, 1H), 3.76 (s, 3H), 2.40 (s, 3H), 1.44 (s, 9H). 13C NMR (101 MHz, CDCl3) δ 193.7, 168.0, 164.7, 155.2, 151.9, 143.0, 138.4, 131.5, 127.8, 125.1, 124.5, 118.3, 114.7, 111.7, 80.0, 73.7, 55.8, 53.6, 28.3, 25.6. HRMS (Orbitrap ESI): exact mass calcld for C25H25N3O6Na [M + Na]+: 486.1635. Found: 486.1645. HPLC analysis (DAICEL Chiralpak AS-H), n-hexane/2-ProH = 80:20, 1 mL/min, 254 nm, major (12.27 min), minor (12.78 min), ee = 91:21; [α]D = −52.3 (c = 0.15, CHCl3).

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(R)-1-Acetyl-2-((tert-butoxycarbonyl)-amino)(3-chlorophenyl)methyl-5-chloro-3-oxo-indoline-2-carboxylate (3q). (0.088 g, 85% yield) yellow solid. Mp 156–168 °C. IR (neat) ν 3411.9, 3011.5, 2977.8, 1765.6, 1710.2, 1680.3, 1501.1, 1470.8, 1371.1, 1337.1, 1290.1, 1166.3, 1049.2, 765.0, 686.9 cm⁻¹.1H NMR (400 MHz, CDCl₃) δ 7.66 (s, 1H), 7.44 (dd, J = 8.9, 2.3 Hz, 1H), 7.13–6.91 (m, 4H), 6.86 (d, J = 7.6 Hz, 1H), 6.59 (s, 1H), 5.92 (s, 1H), 3.76 (s, 3H), 2.40 (s, 3H), 1.46 (s, 9H). 13C NMR (101 MHz, CDCl₃) δ 193.0, 167.7, 164.8, 155.3, 150.6, 139.1, 137.0, 133.1, 130.7, 129.8, 128.3, 127.8, 125.6, 124.9, 115.5, 79.7, 74.5, 55.0, 53.1, 28.8, 25.4. HRMS (Orbitrap ESI): exact mass calcld for C₂₅H₂₇ClN₂O₆Na [M + Na⁺]: 607.1606. Found: 607.1631.

Methyl (R)-1-Benzoyl-2-((S)-(tert-butoxycarbonyl)-amino)(3-chlorophenyl)methyl-3-oxo-3,4-dihydro-1H-benzo[f]indole-2-carboxylate (3s). (0.097 g, 94% yield) yellow solid. Mp 178–180 °C. IR (neat) ν 3394.7, 3009.9, 2978.5, 1761.5, 1685.5, 1512.2, 1454.9, 1371.6, 1323.3, 1233.3, 1237.1, 1129.7, 989.5, 752.6, 582.4 cm⁻¹.1H NMR (400 MHz, CDCl₃) δ 7.89 (d, J = 5.1 Hz, 1H), 7.06–7.02 (m, 4H), 6.84 (d, J = 6.5 Hz, 1H), 6.67 (d, J = 5.0 Hz, 1H), 5.95 (d, J = 6.4 Hz, 1H), 3.79 (s, 3H), 2.29 (s, 3H), 1.46 (s, 9H). 13C NMR (101 MHz, CDCl₃) δ 184.2, 165.8, 164.4, 163.6, 152.5, 145.5, 135.9, 133.7, 132.9, 128.1, 128.7, 125.2, 122.8, 114.9, 79.7, 79.5, 53.5, 53.5, 28.4, 24.0. HRMS (Orbitrap ESI): exact mass calcld for C₂₅H₂₇ClN₂O₆Na [M + Na⁺]: 617.1672. Found: 617.1649.

**ASSOCIATED CONTENT**

5 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b02132.

Copies of 1H and 13C NMR spectra, HPLC chromatogram of products, X-ray data for compounds 3h and 3t (PDF)

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**Notes**

The authors declare no competing financial interest.

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