Secondary-Amine-Catalyzed Asymmetric Michael Addition of *N*-*tert*-Butoxycarbonyl-Protected Oxindoles to Maleimides

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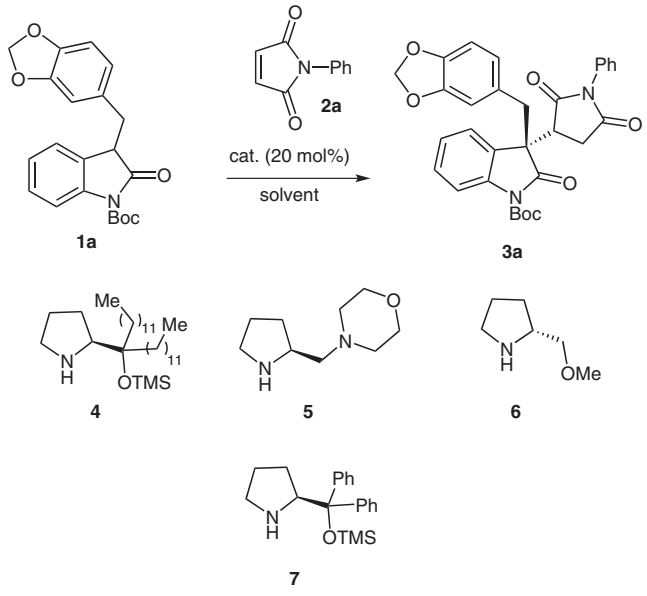
Abstract: A secondary-amine-catalyzed asymmetric Michael addition of 3-substituted *N*-(*tert*-butoxycarbonyl)oxindoles to maleimides with activation by a Brønsted base gives the corresponding products in high yields (86–98%), excellent diastereomeric ratios (dr > 99:1), and high enantiomeric excesses (86–91% ee).

Key words: Brønsted base, Michael addition, heterocycles, organocatalysis, oxindole

The oxindole (2,3-dihydro-2*H*-indole-2-one) subunit is a vital structural feature in a large number of natural products with various biological and pharmacological activities.[1] Moreover, 3,3-disubstituted oxindoles have been employed as chiral building blocks for the synthesis of hexahydropyrrolo[2,3-*b*]indoles, which are present in various biologically active alkaloids.[2] For these reasons, many efforts have been made to construct the oxindole structural motif in an asymmetric manner, and diverse methods have been developed that use metal catalysts or organocatalysts.[3] The asymmetric Michael addition of 3-substituted oxindoles to various acceptors provides a straightforward entry to a variety of chiral 3,3-disubstituted oxindoles.[4] In 2010, Yuan and co-workers[4g] reported a highly stereoselective Michael addition of *N*-(*tert*-butoxycarbonyl)oxindoles to maleimides in the presence of chiral bifunctional thiourea catalysts.[5] However, excellent results were obtained only in the cases of 3-aryl- or 3-alkyloxindoles as nucleophiles, whereas the use of 3-benzyloxindole as a precursor resulted in the formation of the corresponding product in a low diastereoselectivity (dr = 63:37). Recently, Tan, Jiang and co-workers used a chiral bicyclic guanidine as a catalyst for the Michael addition of *N*-benzyl-protected 3-benzyl oxindoles to maleimides, affording the products in excellent stereoselectivities.[4s] However, to remove the protecting benzyl group, it is necessary to treat the product with sodium/ammonia in tetrahydrofuran at –78 °C. We therefore became interested in developing a highly stereoselective Michael addition of *N*-Boc-protected 3-substituted oxindoles to maleimides, which would permit deprotection of the products under simple and mild conditions.

Since the renaissance of organocatalysis[6] at the beginning of this century, chiral secondary amines have played significant roles in this field, as they can catalyze many transformations with high efficiencies and excellent levels of asymmetric induction by activating various aldehydes or ketones in a covalently bound fashion through enamine[7] or iminium[8] intermediates and through singly occupied molecular orbital (SOMO) activation.[9] Moreover, some attention has recently been paid to investigations of chiral secondary amines as Brønsted base catalysts through non-covalently bound activation, and some good results have been achieved in asymmetric epoxidations[10], sulfenylations[11] and Michael additions.[12] Recently, we developed a secondary-amine-catalyzed asymmetric Michael addition of *N*-Boc-protected oxindoles to nitroolefins through a Brønsted base activation mode, furnishing the products in high-to-excellent enantioselectivities.[4q] As a continuation of our investigations in this field, we envisaged a secondary-amine-catalyzed Michael addition of *N*-Boc-protected oxindoles to maleimides (Scheme 1).

Initially, we performed the reaction with the 3-substituted *N*-(*tert*-butoxycarbonyl)oxindole (**1a**) and *N*-phenyl maleimide (**2a**) in chloroform at room temperature with didodecylprolinol silyl ether **4** as catalyst.



Scheme 1 Secondary-amine-catalyzed Michael addition of *N*-Boc-protected oxindole **1a** to maleimide **2a** in the presence of pyrrolidine-type catalysts

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In this case, the reaction was complete within 24 hours, giving the product in an excellent yield (95%) and a high diastereomeric ratio (dr >99:1), albeit with a low enantiomeric excess of 33% ee (Table 1, entry 1). We then performed a brief screening study for a suitable solvent. When the reaction was performed in methanol or acetonitrile, only traces of the desired product were obtained (entries 2 and 3, respectively). Similar results were obtained with ethyl acetate, diethyl ether, and tetrahydrofuran (entries 4–6, respectively); the best outcome with respect to enantioselectivity (41% ee) was achieved with diethyl ether as the solvent (entry 5). Subsequently, we evaluated two enantiomerically pure secondary amines **5** and **6** as catalysts for the reaction, but little or no enantioselectivity was observed (entries 7 and 8, respectively). In an attempt to increase the degree of asymmetric induction, we carried out the reaction at –30 °C in diethyl ether with the didodecylprolinol silyl ether **4** as the catalyst; this gave the expected product with a good enantioselectivity (76% ee) (entry 9). We also examined the diphenylprolinol silyl ether **7** as a catalyst for the Michael addition, but this gave a lower enantioselectivity (57% ee) (entry 10). Next, we reduced the reaction temperature to –60 °C with didodecylprolinol silyl ether **4** as the catalyst. To our delight the reaction was complete within 24 hours and gave the product with a high stereoselectivity and no decrease in the yield (entry 11). Finally, when we reduced the catalyst loading of **4** to 15 mol%, the reaction still proceeded smoothly, affording the product in excellent yield (98%), high diastereoselectivity (dr >99:1), and high enantioselectivity (89% ee) (entry 12).

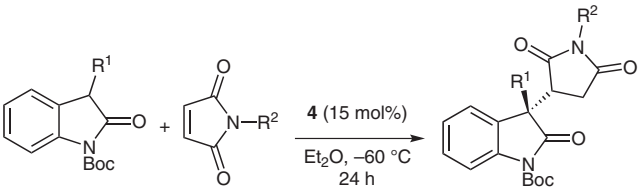
Table 1 Optimization of the Reaction Conditions for the Asymmetric Michael Addition

Entry[a]	Catalyst	Solvent	Temp (°C)	Time (h)	Yield (%)[b]	dr[c]	ee (%)[d]
1	**4**	$CHCl_3$	r.t.	24	95	>99:1	33
2	**4**	MeOH	r.t.	24	trace	n.d.[e]	n.d.
3	**4**	MeCN	r.t.	24	trace	n.d.	n.d.
4	**4**	EtOAc	r.t.	16	98	>99:1	34
5	**4**	Et_2O	r.t.	12	98	>99:1	41
6	**4**	THF	r.t.	48	90	>99:1	35
7	**5**	Et_2O	r.t.	12	91	>99:1	0
8	**6**	Et_2O	r.t.	12	90	>99:1	8
9	**4**	Et_2O	–30	24	98	>99:1	76
10	**7**	Et_2O	–30	24	98	>99:1	57
11	**4**	Et_2O	–60	24	98	>99:1	89
12[f]	**4**	Et_2O	–60	24	98	>99:1	89

[a] Unless otherwise specified, reactions were performed on a 0.50-mmol scale with *N*-Boc-protected oxindole **1a** by using 1.2 equiv of *N*-phenylmaleimide (**2a**) and 20 mol% of the catalyst in the specified solvent (10 mL).
[b] Yield of the isolated product after flash column chromatography.
[c] Determined by HPLC.
[d] Determined by HPLC on a chiral stationary phase.
[e] Not determined.
[f] The reaction was performed with 15 mol% catalyst.

Next, we evaluated the scope of the reaction by studying the reactions of 3-substituted oxindoles **1** with maleimides **2** under the optimized conditions. Generally, the reactions were complete within 24 hours at –60 °C in diethyl ether with catalyst **4** and they gave high yields (86–98%) of products **3** with excellent diastereomeric ratios (dr > 99:1) and high enantioselectivities (86–91% ee) (Table 2).

Table 2 Yields and Stereoselectivities of the Asymmetric Michael Addition of *N*-Boc-Protected Oxindoles **1** to Maleimides **2** to Afford **3**[a]



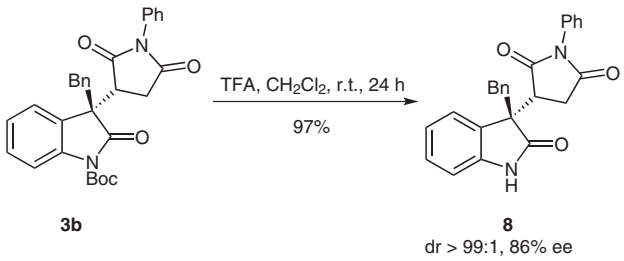
1 2 3

Product	R^1	R^2	Yield (%)[b]	dr[c]	ee (%)[d]
3a	1,3-benzodioxol-5-ylmethyl	Ph	98	>99:1	89
3b	Bn	Ph	93	>99:1	88
3c	4-$MeC_6H_4CH_2$	Ph	86	>99:1	89
3d	4-$MeOC_6H_4CH_2$	Ph	90	>99:1	89
3e	3-$FC_6H_4CH_2$	Ph	92	>99:1	86
3f	Me	Ph	87	>99:1	91
3g	Bn	4-BrC_6H_4	89	>99:1	87
3h	Me	4-BrC_6H_4	88	>99:1	90

[a] Reactions were performed on a 0.5-mmol scale for the *N*-Boc-protected oxindoles **1** by using 1.2 equiv of maleimides **2**, and 15 mol% catalyst **4** at –60 °C in Et_2O (10 mL).
[b] Yields of the isolated products after flash column chromatography.
[c] Determined by HPLC.
[d] Determined by HPLC on a chiral stationary phase.

The Boc protecting group can be readily removed under mild conditions (Scheme 2). Thus, the *N*-(*tert*-butoxycarbonyl)oxindole **3b** was successfully deprotected by treatment with trifluoroacetic acid at room temperature in dichloromethane to give the deprotected product **8** in an excellent yield (97%). Notably, the enantiomeric excess remained at a high level (86%).

By comparing the NMR spectra and the optical rotation of **8** with the corresponding data recently reported in the literature,[13] the relative and absolute configuration of **8** were assigned as *S* for both the quaternary stereocenter and the tertiary stereocenter. We have assumed that the *N*-Boc-protected products **3** have the same configuration as **8**.



3b **8**
dr > 99:1, 86% ee

Scheme 2 Deprotection of the *N*-(*tert*-butoxycarbonyl)oxindole **3b**

In summary, we have developed a secondary-amine-catalyzed Michael addition of 3-substituted *N*-Boc-protected oxindoles to maleimides. This process proceeds through a Brønsted base activation mode, affording the products containing a quaternary stereocenter in high yields (86–98%), excellent diastereomeric ratios (dr >99:1), and high enantiomeric excesses (86–91% ee).

Unless otherwise noted, all commercially available compounds were used without further purification. Racemic samples of the 3,3-disubstituted oxindoles **3a**–**h** were prepared by using Et_3N (40 mol%) as a catalyst in Et_2O at r.t. Preparative flash column chromatography was performed on Merck silica gel 60 (particle size 0.040–0.063 mm; 230–240 mesh). Analytical TLC was performed on silica gel 60 F_{254} plates (Merck, Darmstadt). Visualization of the developed TLC plates was performed with UV radiation (254 nm). Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Microanalyses were performed with a Vario EL element analyzer. Mass spectra were acquired on a Finnigan SSQ 7000 (EI, 70 eV) spectrometer and high-resolution mass spectra were recorded on a Thermo Fisher Scientific Orbitrap XL. IR spectra were recorded on a Perkin-Elmer FT-IR Spectrum 100 using an attenuated total reflection (ATR) unit. ^1H and ^{13}C NMR spectra were recorded at r.t. on Mercury 300 or Vnmrs 400 instruments with TMS as the internal standard. Analytical HPLC was performed on a Hewlett-Packard 1100 Series instrument using a chiral stationary phase (Chiralpak AD, Chiralcel IA, or Chiralcel OD).

***tert*-Butyl 3-(2,5-Dioxopyrrolidin-3-yl)-2-oxoindoline-1-carboxylates 3: General Procedure**

The *N*-aryl maleimide **2** (0.60 mmol) was added to a soln of the 3-substituted *N*-Boc-protected oxindole **1** (0.50 mmol) and the didodecylprolinol trimethylsilyl ether **4** (15 mol%) in Et_2O (10 mL) at –60 °C, and the mixture was stirred for 24 h. The solvent was then removed in vacuum and the residue was purified by flash column chromatography [silica gel, pentane–Et_2O (2:1)].

***tert*-Butyl (3*S*)-3-(1,3-Benzodioxol-5-ylmethyl)-3-[(3*S*)-2,5-dioxo-1-phenylpyrrolidin-3-yl]-2-oxoindoline-1-carboxylate (3a)**

Yield: 264 mg (98%); colorless syrup; $[\alpha]_D^{20}$ +152 (*c* = 0.36, $CHCl_3$).

HPLC: t_R = 9.56 and 12.18 min [Chiralpak AD, heptane–*i*-PrOH (8:2), 1.3 mL/min]; t_R = 12.18 min; ee = 89%.

IR (ATR): 2981, 1790, 1760, 1711, 1603, 1490, 1441, 1383, 1342, 1290, 1248, 1149, 1102, 1076, 1038, 1003, 933, 901, 843, 811, 753, 694 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.68–7.65 (m, 1 H), 7.53–7.40 (m, 3 H), 7.34–7.17 (m, 5 H), 6.46 (d, *J* = 8.1 Hz, 1 H), 6.30 (d, *J* = 1.8 Hz, 1 H), 6.26 (dd, *J* = 7.8, 1.5 Hz, 1 H), 5.79 (dd, *J* = 8.7, 1.5 Hz, 2 H), 3.88 (d, *J* = 13.2 Hz, 1 H, C*H*H), 3.71 (dd, *J* = 9.0, 5.1 Hz, 1 H, CHC=O), 3.39 (d, *J* = 13.2 Hz, 1 H, CH*H*), 2.94 (dd, *J* = 18.3, 9.0 Hz, 1 H, C*H*HC=O), 2.10 (dd, *J* = 18.3, 5.1 Hz, 1 H, CH*H*C=O), 1.59 [s, 9 H, $OC(CH_3)_3$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.1, 175.8, 174.0, 148.3, 147.0, 146.4, 140.5, 131.6, 129.7, 129.3, 129.0 (2 C), 128.0, 126.5, 125.6 (2 C), 124.9, 123.6, 123.3, 115.4, 110.1, 107.6, 100.7, 84.7, 56.5, 44.7, 42.4, 31.9, 28.0 (3 C).

MS (EI, 70 eV): *m/z* (%) = 540 [M^+] (2), 440 (3), 135 (100), 77 (8), 58 (13).

HRMS (ESI): *m/z* calcd for $C_{31}H_{28}N_2NaO_7$: 563.1789; found: 563.1788.

***tert*-Butyl (3*S*)-3-Benzyl-3-[(3*S*)-2,5-dioxo-1-phenylpyrrolidin-3-yl]-2-oxoindoline-1-carboxylate (3b)**

Yield: 231 mg (93%); colorless solid; mp 89 °C; $[\alpha]_D^{20}$ +169 (*c* = 0.69, $CHCl_3$).

HPLC: t_R = 14.88 and 21.04 min [Chiralcel IA, heptane–*i*-PrOH (7:3), 0.5 mL/min]; t_R = 21.04 min; ee = 88%.

IR (ATR): 2981, 1790, 1761, 1710, 1602, 1465, 1383, 1340, 1289, 1248, 1147, 1072, 1003, 940, 901, 841, 749, 695 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.53–7.30 (m, 4 H), 7.28–7.08 (m, 5 H), 7.00–6.90 (m, 3 H), 6.73–6.70 (m, 2 H), 3.90 (d, *J* = 13.2 Hz, 1 H, C*H*H), 3.68 (dd, *J* = 9.3, 5.1 Hz, 1 H, CHC=O), 3.38 (d, *J* = 13.2 Hz, 1 H, CH*H*), 2.88 (dd, *J* = 18.3, 9.3 Hz, 1 H, C*H*HC=O), 2.04 (dd, *J* = 18.3, 5.1 Hz, 1 H, CH*H*C=O), 1.48 [s, 9 H, $OC(CH_3)_3$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.1, 175.8, 174.0, 148.1, 140.5, 134.4, 131.5, 129.8 (2 C), 129.1, 129.3, 128.9 (2 C), 127.7 (2 C), 126.9, 126.5 (2 C), 125.8, 124.8, 123.7, 115.4, 84.6, 56.4, 44.8, 42.8, 32.0, 28.0 (3 C).

MS (EI, 70 eV): *m/z* (%) = 496 (4) [M^+], 396 (39), 222 (49), 91 (87).

HRMS (ESI): *m/z* calcd for $C_{30}H_{28}N_2NaO_5$: 519.1890; found: 519.1892.

***tert*-Butyl (3*S*)-3-[(3*S*)-2,5-Dioxo-1-phenylpyrrolidin-3-yl]-3-(4-methylbenzyl)-2-oxoindoline-1-carboxylate (3c)**

Yield: 219 mg (86%); colorless solid; mp 93 °C; $[\alpha]_D^{20}$ +176 (*c* = 1.5, $CHCl_3$).

HPLC: t_R = 10.53 and 15.77 min [Chiralcel IA, heptane–*i*-PrOH (7:3), 0.7 mL/min]; t_R = 15.77 min; ee = 89%.

IR (ATR): 3477, 3022, 2980, 2930, 2716, 1603, 1477, 1386, 1346, 1291, 1251, 1152, 1110, 1076, 1039, 1005, 941, 905, 842, 756, 695, 667, 621, 578, 541, 471 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 8.0 Hz, 1 H), 7.51–7.47 (m, 2 H), 7.44–7.41 (m, 1 H), 7.32–7.14 (m, 5 H), 6.80 (d, *J* = 7.6 Hz, 2 H), 6.65 (d, *J* = 8.0 Hz, 2 H), 3.89 (d, *J* = 13.6 Hz, 1 H, C*H*H), 3.72 (dd, *J* = 9.2, 5.2 Hz, 1 H, CHC=O), 3.40 (d, *J* = 13.2 Hz, 1 H, CH*H*), 2.93 (dd, *J* = 18.4, 9.2 Hz, 1 H, C*H*HC=O), 2.16 (s, 3 H, CH_3), 2.11 (dd, *J* = 18.4, 5.2 Hz, 1 H, CH*H*C=O), 1.54 [s, 9 H, $OC(CH_3)_3$].

^{13}C NMR (101 MHz, $CDCl_3$): δ = 176.1, 175.8, 174.0, 148.1, 140.5, 136.3, 131.6, 131.2, 129.7 (2 C), 129.6, 129.3 (2 C), 128.9, 128.4 (2 C), 126.5 (2 C), 125.8, 124.7, 123.6, 115.3, 84.5, 56.4, 44.7, 42.4, 32.0, 27.9 (3 C), 20.9.

MS (EI, 70 eV): *m/z* (%) = 510 (1) [M^+], 410 (19), 236 (16), 105 (100), 58 (26).

HRMS (ESI): *m/z* calcd for $C_{31}H_{30}N_2O_5Na$: 533.2047; found: 533.2047.

***tert*-Butyl (3*S*)-3-[(3*S*)-2,5-Dioxo-1-phenylpyrrolidin-3-yl]-3-(4-methoxybenzyl)-2-oxoindoline-1-carboxylate (3d)**

Yield: 237 mg (90%); colorless syrup; $[\alpha]_D^{20}$ +159 (*c* = 0.47, $CHCl_3$).

HPLC: t_R = 13.26 and 19.73 min [Chiralcel IA, heptane–*i*-PrOH (7:3), 0.7 mL/min]; t_R = 19.73 min; ee = 89%.

IR (ATR): 2979, 2932, 1786, 1759, 1712, 1608, 1509, 1466, 1380, 1349, 1289, 1248, 1149, 1110, 1078, 1034, 1005, 939, 904, 838, 755, 695 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.1 Hz, 1 H), 7.53–7.43 (m, 3 H), 7.33–7.17 (m, 5 H), 6.71 (d, *J* = 8.4 Hz, 2 H), 6.54 (d, *J* = 8.4 Hz, 2 H), 3.90 (d, *J* = 13.5 Hz, 1 H, C*H*H), 3.73 (dd, *J* = 9.3, 5.1 Hz, 1 H, CHC=O), 3.66 (s, 3 H, OCH_3), 3.40 (d, *J* = 13.5 Hz, 1 H, CH*H*), 2.95 (dd, *J* = 18.6, 9.3 Hz, 1 H, C*H*HC=O), 2.11 (dd, *J* = 18.6, 5.1 Hz, 1 H, CH*H*=CO), 1.56 [s, 9 H, $OC(CH_3)_3$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.4, 176.2, 174.3, 158.6, 148.4, 140.7, 131.8, 131.1 (2 C), 129.9, 129.6 (2 C), 129.2, 126.7 (2 C), 126.6, 126.0, 125.0, 123.9, 115.6, 113.4 (2 C), 84.9, 56.8, 55.3, 44.9, 42.2, 32.2, 28.2 (3 C).

MS (EI, 70 eV): *m/z* (%) = 426 (2) [M – HBoc]$^+$, 318 (1), 121 (100), 58 (8).

HRMS (ESI): *m/z* calcd for $C_{26}H_{23}N_2O_4$ [M – HBoc]$^+$: 427.1652; found: 426.1651.

tert-Butyl (3*S*)-3-[(3*S*)-2,5-Dioxo-1-phenylpyrrolidin-3-yl]-3-(3-fluorobenzyl)-2-oxoindoline-1-carboxylate (3e)

Yield: 236 mg (92%); colorless syrup; $[\alpha]_D^{20}$ +143 (*c* = 0.53, $CHCl_3$).

HPLC: t_R = 10.71 and 13.54 min [Chiralcel IA, heptane–*i*-PrOH (7:3), 0.7 mL/min]; t_R = 13.54 min; ee = 86%.

IR (ATR): 2981, 2933, 1758, 1711, 1590, 1480, 1380, 1349, 1289, 1250, 1147, 1077, 1005, 936, 902, 873, 841, 796, 753, 692 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 8.1 Hz, 1 H), 7.47–7.37 (m, 3 H), 7.27–7.11 (m, 5 H), 6.93–6.86 (m, 1 H), 6.72–6.66 (m, 1 H), 6.49–6.45 (m, 2 H), 3.92 (d, *J* = 13.2 Hz, 1 H, C*H*H), 3.67 (dd, *J* = 9.3, 5.1 Hz, 1 H, CHC=O), 3.37 (d, *J* = 13.2 Hz, 1 H, CH*H*), 2.88 (dd, *J* = 18.3, 9.3 Hz, 1 H, C*H*HC=O), 2.00 (dd, *J* = 18.3, 5.1 Hz, 1 H, CH*H*C=O), 1.50 [s, 9 H, $OC(CH_3)_3$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.3, 175.8, 174.1, 162.4 (d, *J* = 244 Hz), 148.4, 140.7, 137.1 (d, *J* = 7.3 Hz), 131.7, 130.2, 129.6 (2 C), 129.4, 129.3 (2 C), 126.7 (2 C), 125.8 (d, *J* = 2.5 Hz), 125.4, 123.8, 117.5 (d, *J* = 21.4 Hz), 115.6, 114.1 (d, *J* = 20.8 Hz), 85.2, 56.5, 44.9, 42.6, 32.1, 28.1 (3 C).

MS (EI, 70 eV): *m/z* (%) = 514 (2) [M$^+$], 414 (18), 319 (8), 240 (56), 186 (19), 158 (20), 109 (14), 57 (100).

HRMS (ESI): *m/z* calcd for $C_{30}H_{27}FN_2NaO_5$: 537.1796; found: 537.1796.

tert-Butyl (3*S*)-3-[(3*S*)-2,5-Dioxo-1-phenylpyrrolidin-3-yl]-3-methyl-2-oxoindoline-1-carboxylate (3f)

Yield: 183 mg (87%); pale-yellow solid; mp 123 °C; $[\alpha]_D^{20}$ +202 (*c* = 1.04, $CHCl_3$).

HPLC: t_R = 12.50 and 13.43 min [Chiralcel IA, heptane–*i*-PrOH (7:3), 0.5 mL/min]; t_R = 13.43 min; ee = 91%.

IR (ATR): 2980, 2393, 2253, 2220, 2139, 2108, 2039, 2008, 1987, 1958, 1929, 1770, 1707, 1598, 1478, 1386, 1347, 1286, 1250, 1145, 1101, 1074, 1045, 1003, 941, 875, 843, 755, 697, 665 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.1 Hz, 1 H), 7.44–7.28 (m, 4 H), 7.13–7.11 (m, 4 H), 3.48 (dd, *J* = 9.3, 5.1 Hz, 1 H, CHC=O), 2.84 (dd, *J* = 18.3, 9.3 Hz, 1 H, C*H*HC=O), 2.06 (dd, *J* = 18.3, 5.1 Hz, 1 H, CH*H*C=O), 1.75 (s, 3 H, CH_3), 1.60 [s, 9 H, $OC(CH_3)_3$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.1, 176.0, 174.2, 149.0, 139.8, 131.7, 129.8, 129.5 (2 C), 129.2, 128.2, 126.7 (2 C), 125.4, 123.5, 115.9, 85.4, 50.2, 45.6, 31.7, 28.3 (3 C), 22.9.

MS (EI, 70 eV): *m/z* (%) = 420 (3) [M$^+$], 320 (86), 146 (100), 58 (95).

Anal. Calcd for $C_{24}H_{24}N_2O_5$: C, 68.56; H, 5.75; N, 6.66. Found: C, 68.19; H, 5.71; N, 6.48.

tert-Butyl (3*S*)-3-Benzyl-3-[(3*S*)-1-(4-bromophenyl)-2,5-dioxopyrrolidin-3-yl]-2-oxoindoline-1-carboxylate (3g)

Yield: 255 mg (89%); colorless solid; mp 72 °C; $[\alpha]_D^{20}$ +173 (*c* = 2.1, $CHCl_3$).

HPLC: t_R = 18.12 and 24.94 min [Chiralcel OD, heptane–EtOH (9:1), 0.7 mL/min]; t_R = 18.12 min; ee = 87%.

IR (ATR): 3481, 3026, 2987, 2930, 1717, 1606, 1487, 1384, 1291, 1251, 1151, 1110, 1072, 1038, 1010, 938, 899, 842, 756, 704, 669, 622, 584, 532, 499 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 8.8 Hz, 2 H), 7.57 (d, *J* = 8.0 Hz, 1 H), 7.28–7.24 (m, 2 H), 7.18–7.13 (m, 3 H), 7.04–6.97 (m, 3 H), 6.76 (d, *J* = 7.2 Hz, 2 H), 3.92 (d, *J* = 13.2 Hz, 1 H, C*H*H), 3.73 (dd, *J* = 9.2, 5.2 Hz, 1 H, CHC=O), 3.42 (d, *J* = 13.2 Hz, 1 H, CH*H*), 2.94 (dd, *J* = 18.4, 9.2 Hz, 1 H, C*H*HC=O), 2.12 (dd, *J* = 18.4, 5.2 Hz, 1 H, CH*H*C=O), 1.54 [s, 9 H, $OC(CH_3)_3$].

^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.7 (2 C), 173.5, 148.0, 140.5, 134.2, 132.5 (2 C), 130.5, 129.8 (2 C), 129.7, 128.0 (2 C), 127.7 (2 C), 126.9, 125.5, 124.7, 123.5, 122.8, 115.3, 84.7, 56.3, 44.8, 42.8, 31.9, 27.9 (3 C).

MS (EI, 70 eV): *m/z* (%) = 574 (17) [M$^+$], 474 (13), 222 (44), 158 (11), 91 (100), 58 (68).

HRMS (ESI): *m/z* calcd for for $C_{30}H_{27}BrN_2NaO_5$: 597.0996; found: 597.0996.

tert-Butyl (3*S*)-3-[(3*S*)-1-(4-Bromophenyl)-2,5-dioxopyrrolidin-3-yl]-3-methyl-2-oxoindoline-1-carboxylate (3h)

Yield: 219 mg (88%); pale-yellow solid; mp 168 °C; $[\alpha]_D^{20}$ +168 (*c* = 0.8, $CHCl_3$).

HPLC: t_R = 31.44 and 34.89 min [Chiralcel OD, heptane–*i*-PrOH (9.5:0.5), 0.7 mL/min]; t_R = 34.89 min; ee = 90%.

IR (ATR): 2978, 2931, 1763, 1704, 1606, 1482, 1392, 1345, 1286, 1249, 1149, 1101, 1068, 1005, 937, 878, 848, 823, 796, 754, 718, 664 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.4 Hz, 1 H), 7.61 (d, *J* = 8.7 Hz, 2 H), 7.41–7.35 (m, 2 H), 7.18–7.16 (m, 2 H), 7.11 (d, *J* = 8.4 Hz, 1 H), 3.54 (dd, *J* = 9.3, 5.1 Hz, 1 H, CHC=O), 2.90 (dd, *J* = 18.3, 9.3 Hz, 1 H, C*H*HC=O), 2.15 (dd, *J* = 18.3, 5.1 Hz, 1 H, CH*H*C=O), 1.81 (s, 3 H, CH_3), 1.67 [s, 9 H, $OC(CH_3)_3$].

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.3, 175.4, 173.6, 148.7, 139.6, 132.4 (2 C), 130.4, 129.6, 128.0, 127.9 (2 C), 125.1, 123.1, 122.8, 115.7, 85.2, 49.9, 45.4, 31.5, 28.1 (3 C), 22.7.

MS (EI, 70 eV): *m/z* (%) = 498 (2) [M$^+$], 398 (28), 146 (47), 135 (21), 57 (100).

Anal. Calcd for $C_{24}H_{23}N_2O_5Br$: C, 57.73; H, 4.64; N, 5.61. Found: C, 57.89; H, 4.69; N, 5.42.

(3*S*)-3-[(3*S*)-3-Benzyl-2-oxo-2,3-dihydro-1*H*-indol-3-yl]-1-phenylpyrrolidine-2,5-dione (8)

TFA (0.75 mmol, 5.0 equiv) was added to a soln of the *N*-Boc-protected product **3b** (0.50 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred for 24 h at r.t. The mixture was then treated with sat. aq K_2CO_3 (5 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were combined, washed with sat. aq NaCl, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography [silica gel, pentane–Et_2O–CH_2Cl_2 (2:8:1)] to give a colorless solid; yield: 192 mg (97%); $[\alpha]_D^{20}$ +260 (*c* = 0.9, $CHCl_3$).

HPLC: t_R = 13.38 and 20.76 min [Chiralcel IA, heptane–*i*-PrOH (7:3), 0.7 mL/min]; t_R = 20.76 min; ee = 86%.

IR (ATR): 3301, 1974, 1779, 1704, 1619, 1494, 1472, 1383, 1340, 1289, 1180, 1112, 1076, 1024, 909, 847, 731, 694 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (br s, 1 H), 7.51–7.47 (m, 2 H), 7.42 (dt, *J* = 7.2, 1.2 Hz, 1 H), 7.31 (d, *J* = 7.6 Hz, 1 H), 7.24–7.22 (m, 2 H), 7.18 (dd, *J* = 8.0, 1.2 Hz, 1 H), 7.09–6.98 (m, 4 H),

6.85 (dd, *J* = 8.4, 1.2 Hz, 2 H), 6.67 (d, *J* = 8.0 Hz, 1 H), 4.03 (d, *J* = 13.2 Hz, 1 H, C*H*HBn), 3.67 (dd, *J* = 9.2, 5.2 Hz, 1 H, CHC=O), 3.42 (d, *J* = 13.2 Hz, 1 H, CH*H*Bn), 2.92 (dd, *J* = 18.4, 9.2 Hz, 1 H, C*H*HC=O), 2.11 (dd, *J* = 18.4, 5.2 Hz, 1 H, CH*H*C=O).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 178.2, 176.3, 174.3, 141.1, 135.1, 131.6, 130.0 (2 C), 129.5, 129.3 (2 C), 128.9, 127.7 (2 C), 127.0, 126.7, 126.6 (2 C), 124.6, 123.0, 110.1, 56.1, 44.4, 41.2, 31.7.

MS (EI, 70 eV): *m/z* (%) = 396 (24) [M^+], 222 (42), 206 (40), 158 (25), 135 (22), 118 (51), 91 (100), 65 (15), 45 (29).

HRMS (ESI): *m/z* calcd for $C_{25}H_{20}N_2NaO_3$: 419.1366; found: 419.1364.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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