Highly enantioselective aza-Henry reaction with isatin N-Boc ketimines

Melireth Holmquist, Gonzalo Blay, José R. Pedro

Departament de Química Orgànica, Facultat de Química-Universitat de València, C/ Dr. Moliner 50, E-46100-Burjassot (València), Spain.

SUPPORTING INFORMATION

Table of Contents:

General Experimental Methods S2
Synthesis of N-tert-butoxycarbonyl ketimines 1 S2-S4
General procedure for the enantioselective aza-Henry reaction and characterization of compounds 3 S4-S14
Transformation of the nitroamines 3 S14-S17
Literature S17
1H NMR and 13C NMR spectra S18-S76
Chiral analysis chromatograms S77-S106
General Experimental Methods

Commercial reagents were used as purchased. Commercial anhydrous 1,4-dioxane (Aldrich Cat. 29630-9) was used for isatin \( N \)-Boc ketimines synthesis. THF was freshly destilled from Na-benzophenone. Diisopropyl amine was dried and stored over CaH\(_2\). All reactions were carried out in glassware oven-dried overnight at 120 \(^\circ\)C. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was performed on Merck silica gel 60, 0.040-0.063 mm. NMR spectra were recorded in the deuterated solvents as stated, using residual non-deuterated solvent as internal standard. Specific optical rotations were measured using sodium light (D line 589 nm). Mass spectra (ESI) were recorded on a mass spectrometer equipped with an electrospray source with a capillary voltage of 3.3 kV. Chiral HPLC analyses were performed in a chromatograph equipped with a UV diode-array detector using chiral stationary phase columns from Daicel. 1-Methyl isatin, 1-benzyl isatin, 1-methoxymethyl isatin and 1-benzyloxy carbonyl isatin were prepared from isatin according to reported procedures.\(^1\)

Synthesis of \( N \)-\( \text{tert} \)-butoxycarbonyl ketimines 1.

\[
\begin{array}{c}
\text{Ph-Ph-} \equiv \text{N-Boc} \\
\text{1,4-dioxane} \quad \text{Reflux} \\
\end{array}
\]

The isatin (1.0-3.0 mmol) and \( \text{tert} \)-butoxycarbonylaminotriphenylphosphine\(^2\) (1.3 mmol/mmol isatin) were placed in a round-bottom flask equipped with a condenser under nitrogen atmosphere. Anhydrous 1,4-dioxane (1 mL/mmol isatin) was injected and the mixture was heated at reflux temperature until the reaction was complete (10-24 h). The solvents were evaporated under reduced pressure and the crude was purified by flash chromatography affording ketimines 1. Ketimines 1 were recrystallized from hexane-EtOAc or hexane-CH\(_2\)Cl\(_2\) when necessary. NMR data for compounds \( 1a-j, 1m \) coincided with those reported in the literature.\(^3\)
**tert-Butyl (6-chloro-2-oxoindolin-3-ylidene)carbamate (1k)**

![Chemical Structure](image)

Obtained in 63% yield as a yellow solid, mp °C; $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 8.64 (br s, 1H), 7.54 (d, $J = 8.4$ Hz, 1H), 7.04 (dd, $J = 8.1$, 1.8 Hz, 1H), 6.91 (s, 1H), 1.60 (s, 9H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 160.5 (C), 146.9 (CH), 141.6 (C), 136.9 (C), 125.5 (C), 123.7 (CH), 112.3 (CH), 111.7 (C), 84.0 (C), 28.0 (CH$_3$); MS(ESI) $m/z$: 303.0510 (M+Na)$^+$, C$_{13}$H$_{13}$ClN$_2$NaO$_3$ required 303.0507.

**tert-Butyl (7-chloro-2-oxoindolin-3-ylidene)carbamate (1l)**

Obtained in 96% yield as a yellow solid, mp °C; $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 8.04 (br s, 1H), 7.56 (d, $J = 7.8$ Hz, 1H), 7.44 (dd, $J = 8.1$, 0.9 Hz, 1H), 7.06 (t, $J = 7.8$ Hz, 1H), 1.61 (s, 9H); $^{13}$C NMR (DMSO, 75 MHz) $\delta$ 159.5 (C), 158.1 (C), 153.7 (C), 144.7 (CH), 135.4 (CH), 123.9 (CH), 122.5 (C), 121.0 (C), 115.7 (C), 82.6 (C), 27.6 (CH$_3$); MS(ESI) $m/z$: 303.0507 (M+Na)$^+$, C$_{13}$H$_{13}$ClN$_2$NaO$_3$ required 303.0507.

**tert-butyl (Z)-(5,7-dimethyl-2-oxoindolin-3-ylidene)carbamate (1n)**

Obtained in 65% yield as a yellow solid, mp °C; $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 9.25 (br s, 1H), 7.27 (s, 1H), 7.06 (s, 1H), 2.27 (s, 3H), 2.21 (s, 3H), 1.61 (s, 9H); $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 142.2 (CH), 137.6 (C), 137.5 (C), 133.0 (CH), 122.5 (C), 97.7 (C), 83.2 (C), 28.0 (CH$_3$), 20.8 (CH$_3$), 15.7 (CH$_3$); MS(ESI) $m/z$: 297.1212 (M+Na)$^+$, C$_{15}$H$_{18}$N$_2$NaO$_3$ required 297.1210.
General procedure for the enantioselective aza-Henry reaction

Copper (II) tetrafluoroborate hydrate (5.9 mg, 0.025 mmol) contained in a Schlenck tube was dried under vacuum and the tube was filled with nitrogen. A solution of ligand BOX1 (8.4 mg, 0.025 mmol) and nitroalkane (9.2 eq) in THF (0.25 mL) was added via syringe. After stirring for 1 h, a solution of ketimine 1 (0.25 mmol) and diisopropylamine (4.5 μL, 0.032 mmol) in THF (0.38 mL) was added. The reaction was stirred at room temperature until completion (monitored by TLC). The solvent was removed under reduced pressure, and the residue chromatographed on silica gel eluting with hexane/EtOAc mixtures to give compounds 3 (6,7).

tert-Butyl (S)-(3-(nitromethyl)-2-oxoindolin-3-yl)carbamate (3a)

Purified by column chromatography eluting with hexane/EtOAc 60:40, (60 mg, 99% yield). The ee (99.6%) was determined by HPLC analysis, Chiralpak AD-H, hexane/i-PrOH 80:20, 1 mL/min, major enantiomer (S) \( t_r = 12.5 \) min, minor enantiomer (R) \( t_r = 14.5 \) min.

White solid; mp 179-181 °C (hexane-EtOAc); \( [\alpha]_D^{20} +16.3 \) (c 0.9, CH2Cl2, 99.6% ee); \(^1\)H NMR (300 MHz, CDCl3) \( \delta \) 8.04 (s, 1H), 7.31 (m, 2H), 7.07 (td, \( J = 7.8, 0.9 \) Hz, 1H), 6.91 (dd, \( J = 8.4, 0.9 \) Hz, 1H), 6.13 (s, 1H), 4.86 (d, \( J = 12.3 \) Hz, 1H), 4.60 (d, \( J = 12.3 \) Hz, 1H), 1.35 (s, 9H); \(^{13}\)C NMR (75 MHz, CDCl3) \( \delta \) 174.3 (C), 153.8 (C), 140.4 (C), 130.4 (CH), 126.2 (C), 124.1 (CH), 123.4 (CH), 110.9 (CH), 81.6 (C), 78.0 (CH2), 60.2 (C), 28.1 (CH3); MS(ESI) \( m/z \): 330.1059 (M+Na)+, \( C_{14}H_{17}N_{3}NaO_{5} \) required 330.1060.
**tert-Butyl (S)-(1-methyl-3-(nitromethyl)-2-oxoindolin-3-yl)carbamate (3b)**

Purified by column chromatography eluting with hexane/EtOAc 70:30 (62.4 mg, 82% yield). The ee (99.8%) was determined by HPLC analysis, Chiralcel OD-H, hexane/i-PrOH 80:20, 1 mL/min, major enantiomer (S) \( t_r = 8.4 \) min, minor enantiomer (R) \( t_r = 10.8 \) min.

Yellow solid; mp 140-142 °C (hexane-EtOAc); \([\alpha]_D^{20} +17.0 \) (c 0.9, CH\(_2\)Cl\(_2\), 99.8% ee); 

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.42 (m, 1H), 7.36 (dd, \( J = 7.8, 1.2 \) Hz, 1H), 7.09 (td, \( J = 7.5, 0.9 \) Hz, 1H), 6.90 (d, \( J = 7.8 \) Hz, 1H), 5.98 (s, 1H), 4.92 (d, \( J = 12.3 \) Hz, 1H), 4.59 (d, \( J = 12.3 \) Hz, 1H), 3.27 (s, 3H), 1.31 (s, 9H); 

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 172.7 (C), 153.7 (C), 143.3 (C), 130.4 (CH), 125.8 (C), 124.3 (CH), 123.4 (CH), 108.9 (CH), 81.2 (C), 77.8 (CH\(_2\)), 59.8 (C), 28.0 (CH\(_3\)), 26.8 (CH\(_3\)); MS(ESI) \( m/z \): 344.1217 (M+Na\(^+\)), C\(_{15}\)H\(_{19}\)N\(_3\)NaO\(_5\) required 344.1217.

**tert-Butyl (S)-(1-benzyl-3-(nitromethyl)-2-oxoindolin-3-yl)carbamate (3c)**

Purified by column chromatography eluting with hexane/EtOAc 80:20 (76.3 mg, 79% yield). The ee (99.9%) was determined by HPLC analysis, Chiralcel OD-H, hexane/i-PrOH 95:05, 1 mL/min, major enantiomer (S) \( t_r = 17.8 \) min, minor enantiomer (R) \( t_r = 21.0 \) min.

Yellow solid; mp 154-156 °C (hexane-EtOAc); \([\alpha]_D^{20} +30.2 \) (c 1.0, CH\(_2\)Cl\(_2\), 99.9% ee); 

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.44 (d, \( J = 7.2 \) Hz, 1H), 7.39-7.27 (m, 6H), 7.24 (dd, \( J = 7.8, 1.2 \) Hz, 1H), 7.05 (td, \( J = 7.5, 0.9 \) Hz, 1H), 6.77 (d, \( J = 8.1 \) Hz, 1H), 5.98 (s, 1H), 5.06 (d, \( J = 15.6 \) Hz, 1H), 4.98 (d, \( J = 12.3 \) Hz, 1H), 4.87 (d, \( J = 15.9 \) Hz, 1H) 4.66 (d, \( J = 12.3 \) Hz, 1H), 1.36 (s, 9H); 

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 172.9 (C), 153.8 (C), 142.5 (C), 135.0 (C), 130.3 (CH), 128.9 (2CH), 127.9 (CH), 127.3 (2CH), 125.8 (C), 124.5 (C), 123.4 (CH), 109.9 (CH), 81.3 (C), 77.8 (CH\(_3\)), 59.9 (C), 44.5 (CH\(_2\)), 28.1 (CH\(_3\)); MS(ESI) \( m/z \): 420.1531 (M+Na\(^+\)), C\(_{21}\)H\(_{23}\)N\(_3\)NaO\(_5\) required 420.1530.
**tert-Butyl (S)-(1-(methoxymethyl)-3-(nitromethyl)-2-oxoindolin-3-yl)carbamate (3d)**

Purified by column chromatography eluting with hexane/EtOAc 70:30 (85.8 mg, 84% yield). The ee (99.9%) was determined by HPLC analysis, Chiralcel OD-H, hexane/i-PrOH 95:05, 1 mL/min, major enantiomer (S) $t_r = 16.5$ min, minor enantiomer ($R$) $t_r = 20.0$ min.

Yellow solid; mp 152-154 °C (hexane-EtOAc); $[\alpha]_{D}^{20} -1.2$ (c 1.0, CH$_2$Cl$_2$, 99.9% ee); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.43-7.35 (m, 2H), 7.20-7.09 (m, 2H), 5.97 (s, 1H), 5.21 (d, $J =$ 10.8 Hz, 1H), 5.14 (d, $J =$ 11.1 Hz, 1H), 4.92 (d, $J =$ 12.3 Hz, 1H), 4.64 (d, $J =$ 12.6 Hz, 1H), 3.42 (s, 3H), 1.34 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 173.4 (C), 153.7 (C), 141.7 (C), 130.5 (CH), 125.4 (C), 124.3 (CH), 123.9 (CH), 110.4 (CH), 81.4 (C), 77.9 (CH$_2$), 72.1 (CH$_2$), 60.1 (C), 56.7 (CH$_3$), 28.1 (CH$_3$); MS(ESI) $m/z$: 374.1325 (M+Na)$^+$, C$_{16}$H$_{21}$N$_3$NaO$_6$ required 374.1323.

**tert-Butyl (S)-3-((tert-butoxycarbonyl)amino)-3-(nitromethyl)-2-oxoindolone-1-carboxylate (3e)**

Purified by column chromatography eluting with hexane/EtOAc 60:40 (78.8 mg, 91% yield). The ee (99.9%) was determined by HPLC analysis, Chiralpak AD-H, hexane/i-PrOH 80:20, 1 mL/min, major enantiomer (S) $t_r = 13.9$ min, minor enantiomer ($R$) $t_r = 18.8$ min.

White solid; mp 139-141 °C (hexane-EtOAc); $[\alpha]_{D}^{20} +3.9$ (c 1.4, CH$_2$Cl$_2$, 99.9% ee); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.89 (ddd, $J =$ 8.4, 0.9, 0.6 Hz, 1H), 7.40 (td, $J =$ 9.0, 1.5 Hz, 1H), 7.32 (dd, $J =$ 7.5, 0.9 Hz, 1H), 7.18 (td, $J =$ 7.5, 0.9 Hz, 1H), 6.17 (s, 1H), 4.86 (d, $J =$ 12.6 Hz, 1H), 4.62 (d, $J =$ 12.6 Hz, 1H), 1.64 (s, 9H), 1.27 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.1 (C), 153.4 (C), 148.5 (C), 139.5 (C), 130.6 (CH), 125.1 (C), 124.9 (CH), 123.4 (CH), 115.6 (CH), 85.2 (C), 81.8 (C), 78.1 (CH$_2$), 60.1 (C), 28.0 (CH$_3$), 27.9 (CH$_3$); MS(ESI) $m/z$: 430.1587 (M+Na)$^+$, C$_{19}$H$_{25}$N$_3$NaO$_7$ required 430.1585.
**tert-Butyl (S)-(5-methyl-3-(nitromethyl)-2-oxoindolin-3-yl)carbamate (3f)**

Purified by column chromatography eluting with hexane/EtOAc 70:30 (75.2 mg, 94% yield). The ee (96.3%) was determined by HPLC analysis, Chiralpak AD-H, hexane/i-PrOH 80:20, 1 mL/min, major enantiomer ($S$) $t_r = 10.4$ min, minor enantiomer ($R$) $t_r = 13.8$ min.

Yellow solid; mp 115-117 °C (hexane-EtOAc); $[\alpha]_D^{20} +31$ (c 0.9, CH$_2$Cl$_2$, 96.3% ee);

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.25 (s, 1H), 7.11 (d, $J = 2.0$ Hz, 1H), 7.09 (dd, $J = 8.1$, 2.0 Hz, 1H), 6.78 (d, $J = 8.1$ Hz, 1H), 6.14 (s, 1H), 4.85 (d, $J = 12.6$ Hz, 1H), 4.59 (d, $J = 12.3$ Hz, 1H), 2.30 (s, 3H), 1.35 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 174.3 (C), 153.8 (C), 137.8 (C), 133.1 (CH), 130.8 (CH), 126.3 (C), 124.8 (CH), 110.5 (CH), 81.5 (C), 78.0 (CH$_2$), 60.2 (C), 28.1 (CH$_3$), 21.1 (CH$_3$); MS(ESI) $m/z$: 344.1216 (M+Na)$^+$, C$_{15}$H$_{19}$N$_3$NaO$_5$ required 344.1217.

**tert-Butyl (S)-(5-methoxy-3-(nitromethyl)-2-oxoindolin-3-yl)carbamate (3g)**

Purified by column chromatography eluting with hexane/EtOAc 70:30 (82.2 mg, 97% yield). The ee (97.7%) was determined by HPLC analysis, Chiralpak AD-H, hexane/i-PrOH 80:20, 1 mL/min, major enantiomer ($S$) $t_r = 13.3$ min, minor enantiomer ($R$) $t_r = 19.6$ min.

Yellow solid; mp 141-143 °C (hexane-EtOAc); $[\alpha]_D^{20} +31.5$ (c 0.9, CH$_2$Cl$_2$, 97.7.0% ee);

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.33 (br s, 1H), 6.93 (s, 1H), 6.84-6.77 (m, 2H), 6.15 (s, 1H), 4.87 (d, $J = 12.3$ Hz, 1H), 4.61 (d, $J = 12.3$ Hz, 1H), 3.76 (s, 3H), 1.36 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 174.2 (C), 156.2 (C), 153.8 (C), 133.9 (CH), 127.5 (C), 115.2 (CH), 111.3 (CH), 111.1 (C), 81.4 (C), 77.9 (CH$_2$), 60.5 (C), 55.8 (CH$_3$), 28.1 (CH$_3$); MS(ESI) $m/z$: 360.1164 (M+Na)$^+$, C$_{15}$H$_{19}$N$_3$NaO$_6$ required 360.1166.

**tert-Butyl (S)-(5-bromo-3-(nitromethyl)-2-oxoindolin-3-yl)carbamate (3h)**

Purified by column chromatography eluting with hexane/EtOAc 70:30 (91.6 mg, 95% yield). The ee (81.3%) was determined by HPLC analysis, Chiralpak AD-H, hexane/i-PrOH 810:20, 1 mL/min, major enantiomer ($S$) $t_r = 9.6$ min, minor enantiomer ($R$) $t_r = 10.9$ min.
Yellow solid; mp 146-150 °C (hexane-EtOAc); \([\alpha]_D^{20} +42.1\ (c\ 1.0,\ MeOH,\ 81.3\%\ ee)\);

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\ 7.94\) (br s, 1H), 7.47-7.43 (m, 2H), 6.79 (dd, \(J = 8.1, 0.6\ Hz, 1H\)), 6.09 (s, 1H), 4.85 (d, \(J = 12.7\ Hz, 1H\)), 4.59 (d, \(J = 12.7\ Hz, 1H\)), 1.38 (s, 9H); \(^{13}\)C NMR (75 MHz, CD\(_2\)OD) \(\delta\ 176.8\) (C), 162.1 (C), 155.7 (C), 142.9 (C), 134.0 (CH), 130.9 (C), 128.1 (CH), 115.9 (C), 113.2 (CH), 82.1 (C), 78.4 (CH\(_2\)), 61.6 (C), 28.4 (CH\(_3\)); MS(ESI) \(m/z\): 408.0163 (M+Na), \(C_{14}H_{16}BrN_3NaO_5\) required 408.0166.

**tert-Butyl (S)-(5-chloro-3-(nitromethyl)-2-oxoindolin-3-yl)carbamate (3i)**

Purified by column chromatography eluting with hexane/EtOAc 70:30 (74.4 mg, 87% yield). The ee (97.5%) was determined by HPLC analysis, Chiralpak AD-H, hexane/i-PrOH 80:20, 1 mL/min, major enantiomer (S) \(t_r = 10.0\) min, minor enantiomer (R) \(t_r = 11.1\) min.

White solid; mp 194-196 °C (hexane-EtOAc); \([\alpha]_D^{20} +40.8\ (c\ 1.0,\ CH_2Cl_2,\ 97.5\%\ ee)\);

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\ 8.25\) (s, 1H), 7.32 (d, \(J = 2.1\ Hz, 1H\)), 7.28 (dd, \(J = 8.1, 2.1\ Hz, 1H\)), 6.83 (d, \(J = 8.1\ Hz, 1H\)), 6.14 (s, 1H), 4.85 (d, \(J = 12.8\ Hz, 1H\)), 4.59 (d, \(J = 12.8\ Hz, 1H\)), 1.38 (s, 9H); \(^{13}\)C NMR (75 MHz, CD\(_2\)OD) \(\delta\ 173.7\) (C), 153.8 (C), 138.9 (C), 130.5 (CH), 128.9 (C), 127.8 (C), 124.7 (CH), 111.9 (CH), 82.0 (C), 77.6 (CH\(_2\)), 60.1 (C), 28.1 (CH\(_3\)); MS(ESI) \(m/z\): 364.0669 (M+Na), \(C_{14}H_{16}ClN_3NaO_5\) required 364.0671.

**tert-Butyl (S)-(5-nitro-3-(nitromethyl)-2-oxoindolin-3-yl)carbamate (3j)**

Purified by column chromatography eluting with hexane/EtOAc 70:30 (75.2 mg, 94% yield). The ee (6.6%) was determined by HPLC analysis, Chiralpak AD-H, hexane/i-PrOH 80:20, 1 mL/min, major enantiomer (S) \(t_r = 16.7\) min, minor enantiomer (R) \(t_r = 18.1\) min.

Yellow solid; mp 167-169 °C (hexane-EtOAc); \(^1\)H NMR (300 MHz, CD\(_3\)OD) \(\delta\ 8.30-8.25\) (m, 2H), 7.07 (dd, \(J = 8.4, 0.3\ Hz, 1H\)), 5.04 (d, \(J = 13.2\ Hz, 1H\)), 4.98 (d, \(J = 13.2\ Hz, 1H\)), 1.32 (s, 9H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\ 177.3\) (C), 150.1 (C), 144.6 (C), 129.7 (C), 128.0 (CH), 120.9 (CH), 111.4 (CH), 78.2 (CH\(_2\)), 61.3 (C), 54.8 (C), 28.4 (CH\(_3\)); MS(ESI) \(m/z\): 375.0909 (M+Na), \(C_{14}H_{16}N_4NaO_7\) required 375.0911.
**tert-Butyl (S)-(6-chloro-3-(nitromethyl)-2-oxoindolin-3-yl)carbamate (3k)**

Purified by column chromatography eluting with hexane/EtOAc 70:30 (78.3 mg, 92% yield). The ee (96.2%) was determined by HPLC analysis, Chiralpak AD-H, hexane/i-PrOH 90:10, 1 mL/min, major enantiomer (S) $t_r = 16.6$ min, minor enantiomer $(R) t_r = 23.6$ min.

Yellow oil; $[\alpha]_{D}^{20} -11.4$ (c 1.0, CH$_2$Cl$_2$, 96.2% ee); $^1$H NMR (300 MHz, CDCl$_3$+CD$_3$OD) $\delta$ 10.3 (s, 1H), 7.20 (d, $J = 8.1$ Hz 1H), 6.92-6.85 (m, 2H), 6.24 (br s, 1H), 4.83 (d, $J = 12.5$ Hz, 1H), 4.58 (d, $J = 12.5$ Hz, 1H), 1.26 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$+CD$_3$OD) $\delta$ 174.3 (C), 159.8 (C), 142.9 (C), 135.6 (C), 125.1 (CH), 122.3 (CH), 111.3 (CH), 80.9 (C), 59.6 (C), 27.9 (CH$_3$); MS(ESI) $m/z$: 364.0674 (M+Na)$^+$, C$_{14}$H$_{16}$ClN$_3$NaO$_5$ required 364.0671.

**tert-Butyl (S)-(7-chloro-3-(nitromethyl)-2-oxoindolin-3-yl)carbamate (3l)**

Purified by column chromatography eluting with hexane/EtOAc 70:30 (121.0 mg, 94% yield). The ee (98.1%) was determined by HPLC analysis, Chiralpak AD-H, hexane/i-PrOH 80:20, 1 mL/min, major enantiomer (S) $t_r = 11.1$ min, minor enantiomer $(R) t_r = 19.1$ min.

White solid; mp 172-175 °C (hexane-EtOAc); $[\alpha]_{D}^{20} -31.9$ (c 1.0, CH$_2$Cl$_2$, 98.1% ee); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.14 (br s, 1H), 7.32 (dd, $J = 8.4$, 1.2 Hz, 1H), 7.23 (d, $J = 6.9$ Hz, 1H), 7.03 (t, $J = 7.8$ Hz, 1H), 6.14 (s, 1H), 4.89 (d, $J = 12.6$ Hz, 1H), 4.60 (d, $J = 12.6$ Hz, 1H), 1.34 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 173.2 (C), 153.6 (C), 148.5 (C), 138.1 (C), 130.3 (CH), 124.3 (CH), 122.5 (CH), 116.0 (C), 81.8 (C), 77.7 (CH$_2$), 61.0 (C), 28.0 (CH$_3$); MS(ESI) $m/z$: 364.0673 (M+Na)$^+$, C$_{14}$H$_{16}$ClN$_3$NaO$_5$ required 364.0671.

**tert-Butyl (S)-(7-fluoro-3-(nitromethyl)-2-oxoindolin-3-yl)carbamate (3m)**

Purified by column chromatography eluting with hexane/EtOAc 70:30 (70.2 mg, 86% yield). The ee (93.1%) was determined by HPLC analysis, Chiralpak AD-H, hexane/i-PrOH 80:20, 1 mL/min, major enantiomer (S) $t_r = 10.7$ min, minor enantiomer $(R) t_r = 15.9$ min.
Yellow solid; mp 166-170 °C (hexane-EtOAc); $[\alpha]_D^{20} +3.3$ (c 1.1, CH$_2$Cl$_2$, 93.1% ee);
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.43 (s, 1H), 7.14-7.00 (m, 3H), 6.20 (s, 1H), 4.91 (d, $J$ = 12.6 Hz, 1H), 4.61 (d, $J$ = 12.6 Hz, 1H), 1.34 (s, 9H); $^1^3$C NMR (75 MHz, CD$_3$OD) $\delta$
176.8 (C), 155.6 (C), 148.7 (d, $J$ = 242.3 Hz, C), 131.1 (d, $J$ = 26.4 Hz, C), 124.4 (d, $J$ = 5.9 Hz, CH), 120.6 (d, $J$ = 3.4 Hz, CH), 118.0 (d, $J$ = 17.5 Hz, C), 115.1 (d, $J$ = 2.6 Hz, C), 82.0 (C), 78.7 (CH$_2$), 61.8 (C), 28.3 (CH$_3$); $^{1^9}$F NMR (282 MHz, CD$_3$OD) $\delta$ -136.2 (s, 1F); MS(ESI) m/z: 348.0963 (M+Na)$^+$, C$_{14}$H$_{16}$FN$_3$NaO$_5$ required 348.0966.

**tert-Butyl (S)-(5,7-dimethyl-3-(nitromethyl)-2-oxoindolin-3-yl)carbamate (3n)**

Purified by column chromatography eluting with hexane/EtOAc 70:30 (112.7 mg, 89% yield). The ee (98.7%) was determined by HPLC analysis, Chiralpak AD-H, hexane/i-PrOH 80:20, 1 mL/min, major enantiomer ($S$) $t_r$ = 9.0 min, minor enantiomer ($R$) $t_r$ = 13.9 min.

White solid; mp 189-193 °C (hexane-EtOAc); $[\alpha]_D^{20} +17.4$ (c 1.0, CH$_2$Cl$_2$, 98.7% ee);
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.76 (br s, 1H), 6.95 (s, 1H), 6.93 (s, 1H), 6.17 (s, 1H), 4.83 (d, $J$ = 12.3 Hz, 1H), 4.61 (d, $J$ = 12.3 Hz, 1H), 2.27 (s, 3H), 2.19 (s, 3H), 1.33 (s, 9H); $^1^3$C NMR (75 MHz, CDCl$_3$) $\delta$ 174.8 (C), 153.8 (C), 136.5 (C), 132.3 (CH), 126.1 (C), 122.0 (C), 119.8 (C), 81.4 (C), 78.1 (CH$_2$), 60.7 (C), 28.0 (CH$_3$), 21.0 (CH$_3$), 16.2 (CH$_3$); MS(ESI) m/z: 358.1375 (M+Na)$^+$, C$_{16}$H$_{21}$N$_3$NaO$_5$ required 358.1373.

**tert-Butyl (S)-3-(1-nitroethyl)-2-oxoindolin-3-yl)carbamate (6a)**

Purified by column chromatography eluting with hexane/EtOAc 70:30 (55.8 mg, 68% yield). Diastereomer ratio 91:09. The ee (99.8% major diastereomer, 99.1% minor diastereomer) was determined by HPLC analysis, Chiralpak AD-H, hexane/i-PrOH 80:20, 1 mL/min, Major diastereomer: major enantiomer ($3S$) $t_r$ = 9.2 min, minor enantiomer ($3R$) $t_r$ = 15.5 min; Minor diastereomer: major enantiomer ($3S$) $t_r$ = 7.8 min, minor enantiomer ($3R$) $t_r$ = 10.9 min.

White solid; mp 159-162 °C (hexane-CH$_2$Cl$_2$); $[\alpha]_D^{20} +39.2$ (c 0.9, CH$_2$Cl$_2$) for the diastereomer mixture. Major diastereomer: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.53 (s, 1H), 7.23 (td, $J$ = 7.8, 1.2 Hz, 1H), 7.10 (dd, $J$ = 7.5, 0.9 Hz, 1H), 7.03 (td, $J$ = 7.5, 0.9 Hz, 1H), 6.81 (d, $J$ = 7.8 Hz, 1H), 6.26 (s, 1H), 4.72 (q, $J$ = 6.9 Hz, 1H), 1.76 (d, $J$ = 6.9 Hz, 1H).
**Major diastereomer:**

$^1$H NMR (300 MHz, CDCl$_3$) \(\delta\) 8.25 (s, 1H), 7.23 (td, \(J = 7.5, 1.5\) Hz, 1H), 7.07-6.98 (m, 2H), 6.79 (d, \(J = 7.8\) Hz, 1H), 6.25 (s, 1H), 4.41 (dd, \(J = 12.0, 2.7\) Hz, 1H), 2.57-2.43 (m, 1H), 2.23-2.12 (m, 1H), 1.32 (s, 9H), 0.96 (t, \(J = 7.2\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl$_3$) \(\delta\) 174.0 (C), 154.0 (C), 140.2 (C), 130.1 (CH), 124.8 (C), 123.3 (CH), 122.9 (CH), 110.6 (CH), 92.8 (CH), 81.4 (C), 61.9 (C), 28.1 (CH$_3$), 20.3 (CH$_2$), 10.5 (CH$_3$); MS(ESI) \(m/z\): 358.1376 (M+Na)$^+$, C$_{16}$H$_{21}$N$_3$NaO$_5$ required 358.1373.

Minor diastereomer: $^1$H NMR (300 MHz, CDCl$_3$, representative peaks taken from the diastereomer mixture) \(\delta\) 5.98 (s, 1H), 4.76 (dd, \(J = 10.7, 3.4\) Hz, 1H), 1.88-1.68 (m, 2H), 0.90 (t, \(J = 7.2\) Hz, 3H).

---

**Minor diastereomer:**

$^1$H NMR (300 MHz, CDCl$_3$, representative peaks taken from the diastereomer mixture) \(\delta\) 6.30 (s, 1H), 4.96 (q, \(J = 6.9\) Hz, 1H).

**tert-Butyl (S)-(3-(1-nitropropyl)-2-oxoindolin-3-yl)carbamate (7a)**

Purified by column chromatography eluting with hexane/EtOAc 70:30 (62.7 mg, 75% yield). Diastereomer ratio 91:9. The ee (99.6% major diastereomer, 98.0% minor diastereomer) was determined by HPLC analysis, Chiralpak AD-H, hexane/i-PrOH 90:10, 1 mL/min, Major diastereomer: major enantiomer (3S) \(t_r = 14.1\) min, minor enantiomer (3R) \(t_r = 21.3\) min; Minor diastereomer: major enantiomer (3S) \(t_r = 15.4\) min, minor enantiomer (3R) \(t_r = 25.8\) min.

White solid; mp 170-172 °C (hexane- CH$_2$Cl$_2$); $[\alpha]_D^{20}$ +18.2 (c 1.1, CH$_2$Cl$_2$) for the diastereomer mixture. Major diastereomer: $^1$H NMR (300 MHz, CDCl$_3$) \(\delta\) 8.25 (s, 1H), 7.23 (td, \(J = 7.5, 1.5\) Hz, 1H), 7.07-6.98 (m, 2H), 6.79 (d, \(J = 7.8\) Hz, 1H), 6.25 (s, 1H), 4.41 (dd, \(J = 12.0, 2.7\) Hz, 1H), 2.57-2.43 (m, 1H), 2.23-2.12 (m, 1H), 1.32 (s, 9H), 0.96 (t, \(J = 7.2\) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl$_3$) \(\delta\) 174.0 (C), 154.0 (C), 140.2 (C), 130.1 (CH), 124.8 (C), 123.3 (CH), 122.9 (CH), 110.6 (CH), 92.8 (CH), 81.4 (C), 61.9 (C), 28.1 (CH$_3$), 20.3 (CH$_2$), 10.5 (CH$_3$); MS(ESI) \(m/z\): 344.1215 (M+Na)$^+$, C$_{15}$H$_{19}$N$_3$NaO$_5$ required 344.1217.

Minor diastereomer: $^1$H NMR (300 MHz, CDCl$_3$, representative peaks taken from the diastereomer mixture) \(\delta\) 5.98 (s, 1H), 4.76 (dd, \(J = 10.7, 3.4\) Hz, 1H), 1.88-1.68 (m, 2H), 0.90 (t, \(J = 7.2\) Hz, 3H).
**tert-Butyl (S)-(6-chloro-3-(1-nitroethyl)-2-oxoindolin-3-yl)carbamate (6k)**

![Chemical Structure](attachment:image.png)

Purified by column chromatography eluting with hexane/EtOAc 70:30 (88.3 mg, 95% yield). Diastereomer ratio 60:40. The ee (91.7% major diastereomer, 88.8% minor diastereomer) was determined by HPLC analysis, Chiralpak AD-H, hexane/i-PrOH 80:20, 1 mL/min. Major diastereomer: major enantiomer (3S) $\tau_r = 7.3$ min, minor enantiomer (3R) $\tau_r = 11.0$ min; Minor diastereomer: major enantiomer (3S) $\tau_r = 6.5$ min, minor enantiomer (3R) $\tau_r = 9.1$ min.

The major diasteromer could be obtained in 91:9 dr after crystallization from CH$_2$Cl$_2$. Yellow solid; mp 182 °C (dec.) (hexane-DCM); $[\alpha]_{D}^{20} +17.1$ (c 1.0, CH$_2$Cl$_2$) for the 91:9 dr mixture; Major diastereomer: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.64 (s, 1H), 6.99 (d, $J = 1.2$ Hz, 2H), 6.73 (s, 1H), 6.31 (s, 1H), 4.65 (q, $J = 6.9$ Hz, 1H), 1.79 (d, $J = 6.9$ Hz, 3H), 1.37 (s, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 173.5 (C), 154.2 (C), 141.6 (C), 136.0 (C), 125.5 (C), 123.9 (CH), 123.3 (CH), 111.5 (CH), 85.4 (CH), 81.8 (C), 61.7 (C), 28.1 (CH$_3$), 13.0 (CH$_3$); MS(ESI) $m/z$: 378.0829 (M+Na)$^+$, C$_{15}$H$_{18}$ClN$_3$NaO$_5$ required 378.0827.

Minor diastereomer: $^1$H NMR (300 MHz, CDCl$_3$, representative peaks taken from the diastereomer mixture) $\delta$ 8.60 (s, 1H), 7.01 (d, $J = 1.5$ Hz, 1H), 6.78 (s, 1H), 6.35 (s, 1H), 4.94 (q, $J = 6.6$ Hz, 1H).

**tert-Butyl (S)-(6-chloro-3-(1-nitropropyl)-2-oxoindolin-3-yl)carbamate (7k)**

![Chemical Structure](attachment:image.png)

Purified by column chromatography eluting with hexane/EtOAc 70:30 (80.9 mg, 91% yield). Diastereomer ratio 85:15. The ee (87.8% major diastereomer, 78.8% minor diastereomer) was determined by HPLC analysis, Chiralpak AD-H, hexane/i-PrOH 80:20, 1 mL/min. Major diastereomer: major enantiomer (S) $\tau_r = 6.3$ min, minor enantiomer (R) $\tau_r = 8.6$ min; Minor diastereomer: major enantiomer (S) $\tau_r = 7.3$ min, minor enantiomer (R) $\tau_r = 9.6$ min.

White solid; mp 196 °C (dec.) (hexane-CH$_2$Cl$_2$); $[\alpha]_{D}^{20} -6.8$ (c 1.2, CH$_2$Cl$_2$) for the diastereomer mixture; Major diastereomer: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.41 (s, 1H), 7.20-6.93 (m, 2H), 6.73 (s, 1H), 6.28 (s, 1H), 4.36 (dd, $J = 12.0$, 2.7 Hz, 1H), 2.58-2.43 (m, 1H), 2.27-2.10 (m, 1H), 1.36 (s, 9H), 0.96 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 173.6 (C), 154.2 (C), 141.5 (C), 136.0 (C), 125.6 (C), 123.7 (CH), 123.3
(CH), 111.4 (CH), 92.7 (CH), 81.8 (C), 61.6 (C), 28.1 (CH₃), 20.3 (CH₂), 10.4 (CH₃);
MS(ESI) m/z: 392.0982 (M+Na)⁺, C₁₆H₂₀ClN₃NaO₅ required 392.0984.

Minor diastereomer: ¹H NMR (300 MHz, CDCl₃, representative peaks taken from the diastereomer mixture) δ 8.35 (s, 1H), 5.96 (s, 1H), 4.73 (dd, J = 11.4, 3.0 Hz, 1H), 0.90 (t, J = 7.5 Hz, 3H).

**tert-Butyl (S)-(7-chloro-3-(1-nitroethyl)-2-oxoindolin-3-yl)carbamate (6l)**

Purified by column chromatography eluting with hexane/EtOAc 70:30 (78.1 mg, 91% yield). Diastereomer ratio 76:24. The ee (98.9% major diastereomer, 99.9% minor diastereomer) was determined by HPLC analysis, Chiralpak AD-H, hexane/i-PrOH 80:20, 1 mL/min, Major diastereomer: major enantiomer (S) t<sub>r</sub> = 9.31 min, minor enantiomer (R) t<sub>r</sub> = 29.7 min; Minor diastereomer: major enantiomer (S) t<sub>r</sub> = 8.6, minor enantiomer (R) t<sub>r</sub> = 14.2 min.

White solid; mp 170-172 °C (hexane-DCM); [α]°D -22 (c 1.1, MeOH) for the diastereomeric mixture. Major diastereomer: ¹H NMR (300 MHz, CDCl₃) δ 7.97 (s, 1H), 7.27-7.20 (m, 1H), 6.97-6.93 (m, 2H), 6.19 (s, 1H), 4.62 (q, J = 6.9 Hz, 1H), 1.73 (d, J = 6.9 Hz, 3H), 1.24 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 173.8 (C), 153.9 (C), 137.9 (C), 130.1 (CH), 124.3 (CH), 121.5 (CH), 115.8 (C), 85.3 (CH), 81.7 (C), 63.0 (C), 28.0 (CH₃), 13.0 (CH₃); MS(ESI) m/z: 378.0826 (M+Na)⁺, C₁₅H₁₈ClN₃NaO₅ required 378.0827.

Minor diastereomer: ¹H NMR (300 MHz, CDCl₃, representative peaks taken from the diastereomer mixture) δ 8.01 (s, 1H), 6.16 (s, 1H), 4.90 (q, J = 6.6 Hz, 1H), 1.31 (d, J = 6.9 Hz, 3H).

**tert-Butyl (S)-(7-chloro-3-(1-nitropropyl)-2-oxoindolin-3-yl)carbamate (7l)**

Purified by column chromatography eluting with hexane/EtOAc 70:30 (66.7 mg, 89% yield). Diastereomer ratio 88:12. The ee (99.8% major diastereomer, 99.8% minor diastereomer) was determined by HPLC analysis, Chiralpak AD-H, hexane/i-PrOH 80:20, 1 mL/min, Major diastereomer: major enantiomer (S) t<sub>r</sub> = 8.7 min, minor enantiomer (R) t<sub>r</sub> = 15.1 min; Minor diastereomer: major enantiomer (S) t<sub>r</sub> = 9.4 min, minor enantiomer (R) t<sub>r</sub> = 16.0 min.
The major diastereomer was obtained pure after crystallization from hexane-CH$_2$Cl$_2$: White solid; mp 214-216 °C (hexane-DCM); $[^{[\alpha]}_D]^{20}$ -12.7 (c 0.9, MeOH, 100% ee) for the pure major diastereomer; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.86 (br s, 1H), 7.29 (dd, $J = 7.8, 1.5$ Hz, 1H), 7.00 (t, $J = 7.5$ Hz, 1H), 6.95 (dd, $J = 7.8, 1.5$ Hz, 1H), 6.23 (s, 1H), 4.39 (dd, $J = 12, 2.7$ Hz, 1H), 2.50 (m, 1H), 2.20 (m, 1H), 1.31 (s, 9H), 0.97 (t, $J = 7.5$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 173.2 (C), 153.7 (C), 137.6 (C), 130.1 (CH), 124.3 (CH), 121.3 (CH), 120.1 (C), 115.7 (C), 92.5 (CH), 90.3 (C), 62.9 (C), 28.0 (CH$_3$), 20.2 (CH$_2$), 10.5 (CH$_3$); MS(ESI) $m/z$: 392.0984 (M+Na)$^+$, C$_{16}$H$_{20}$ClN$_3$NaO$_5$ required 392.0984.

Minor diastereomer: $^1$H NMR (300 MHz, CDCl$_3$, representative peaks taken from the diastereomer mixture) $\delta$ 8.06 (s, 1H), 5.93 (s, 1H), 4.75 (dd, $J = 11.1, 3.3$ Hz, 1H), 0.91 (t, $J = 7.2$ Hz, 3H).

**Transformations of nitroamine 3a**

**Deprotection of the Boc moiety.**$^4$ (S)-3-amino-3-(nitromethyl)indolin-2-one (8)

Trifluoroacetic acid (1.1 mL) was added dropwise to a stirred solution of compound 3a (101.0 mg, 0.33 mmol, 96% ee) in CH$_2$Cl$_2$ (5 mL) at 0 °C and stirred during 2 hours at room temperarure. The reaction was concentrated, diluted with CH$_2$Cl$_2$ (15 mL), washed with NaHCO$_3$, dried over MgSO$_4$ and concentrated under reduced pressure to give 65.5 mg (96%) of compound 8: The ee (95.6%) was determined by HPLC analysis, Chiralpak AD-H, hexane/i-PrOH 80:20, 1 mL/min, major enantiomer (S) $t_r = 14.9$ min, minor enantiomer (R) $t_r = 12.8$ min. $[^{[\alpha]}_D]^{20} +53.9$ (c 0.8, MeOH, 95% ee); $^1$H NMR (300 MHz, CD$_3$CN) $\delta$ 8.69 (br s, 1H), 7.37 (dq, $J = 7.5$, 0.6 Hz, 1H), 7.29 (td, $J = 7.5$, 1.5 Hz, 1H), 7.05 (td, $J = 7.8$, 0.9 Hz, 1H), 6.94 (ddd, $J = 7.5$, 0.9, 0.6 Hz, 1H), 4.89 (d, $J = 12.9$ Hz, 1H), 4.83 (d, $J = 12.9$ Hz, 1H); $^{13}$C NMR (75 MHz, CD$_3$CN) $\delta$ 178.9 (C), 142.9 (C), 131.0 (CH), 129.7 (C), 125.0 (CH), 123.4 (CH), 111.3 (CH), 80.5 (CH$_2$), 60.4 (C); MS(ESI) $m/z$: 230.0538 (M+Na)$^+$, C$_{10}$H$_{10}$N$_3$O$_3$ required 230.0536.
Synthesis of diamines 9 and 10

*tert*-Butyl (*S*)-(3-(aminomethyl)-2-oxoindolin-3-yl)carbamate (9)

To a solution of compound 3a (100.0 mg, 0.33 mmol) in methanol (2.4 mL) at 0 °C was added NiCl₂ (44 mg, 0.34 mmol) followed by NaBH₄ (61.7 mg, 1.63 mmol) and the mixture was stirred for 30 min.⁵ Then, saturated aqueous NH₄Cl (10 mL) was added and the mixture extracted with ethyl acetate (4×30 mL), washed with brine (15 mL), dried over MgSO₄ and concentrated under reduced pressure. The crude was filtered through a short pad of silica gel eluting with CH₂Cl₂:MeOH:Et₃N (90:10:1) and concentrated under reduced pressure to give 90.0 mg (99%) of compound 5a: The ee (95.8%) was determined by HPLC analysis, Chiralpak AY-H, hexane/PrOH 80:20, 1 mL/min, major enantiomer (S) *t* = 8.6 min, minor enantiomer (R) *t* = 17.1 min. [α]D²⁰ +35.8 (c 1.0, MeOH, 95.8% ee); ¹H NMR (300 MHz, CD₃OD) δ 7.30-7.23 (m, 2H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.92 (dt, *J* = 7.8, 0.9 Hz, 1H), 3.03 (d, *J* = 13.8 Hz, 1H), 2.85 (d, *J* = 13.5 Hz, 1H), 1.29 (br s, 9H); ¹³C NMR (75 MHz, CD₃OD) δ 180.1 (C), 156.5 (C), 142.8 (C), 129.9 (CH), 127.8 (C), 123.7 (CH), 123.6 (CH), 111.3 (CH), 81.3 (C), 63.7 (C), 48.9 (CH₂), 28.4 (CH₃); MS(ESI) *m/z*: 300.1315 (M+Na)+, C₁₄H₁₉N₃NaO₃ required 300.1319

(S)-3-amino-3-(aminomethyl)indolin-2-one (10)

A 1M solution of HCl in diethylether (6.2 mL, 6.2 mmol) was added dropwise to a solution of compound 9 (85 mg, 0.31 mmol) in methanol at 0 °C. The reaction was stirred overnight at room temperature and concentrated under reduced pressure. The mixture was dissolved with ethyl acetate (2 mL), basified with 1 M aqueous NaOH (2 mL), extracted with EtOAc (4×30 mL), dried over MgSO₄ and concentrated under reduced pressure to give 35.5 mg (65%) of diamine 10: [α]D²⁰ +53.2 (c 0.6, MeOH); ¹H NMR (300 MHz, CD₃OD) δ 7.39 (dq, *J* = 7.5, 0.6 Hz, 1H), 7.27 (td, *J* = 7.5, 1.5 Hz, 1H), 7.07 (td, *J* = 7.5, 1.2 Hz, 1H), 6.93 (dt, *J* = 7.8, 0.6 Hz, 1H), 2.94 (d, *J* = 13.2 Hz, 1H), 2.89 (d, *J* = 13.2 Hz, 1H); ¹³C NMR (75 MHz, CD₃OD) δ 182.8 (C), 143.1 (C), 130.4 (CH), 124.9 (CH), 123.7 (CH), 111.3 (CH), 62.9 (C), 49.9 (CH₂); MS(ESI) *m/z*: 200.0792 (M+Na)+, C₁₄H₁₉N₃NaO₃ required 200.0794.
Synthesis of nitrile 12 and ester 13

**tert-Butyl (S)-(3-cyano-2-oxoindolin-3-yl)carbamate (12)**

Compound 3a (70 mg, 0.23 mmol) was added to a solution of SnCl₂·2H₂O (102.9 mg, 0.46 mmol), thiophenol (140 μL, 1.37 mmol) and triethylamine (190 μL, 1.37 mmol) in absolute EtOH (1.2 mL) at room temperature. After 20 min, the reaction mixture was poured into 1M aqueous HCl (5 mL) and CH₂Cl₂ (6 mL) at 0 °C. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The organic layer was washed with aqueous NaHCO₃ (3 mL), brine (3 mL) and dried over MgSO₄. After removal of the solvent, the residue was chromatographed through a short plug of silica gel eluting with hexane EtOAc 6:4 to remove the excess of thiophenol and then with EtOAc. The EtOAc fraction was concentrated under reduced pressure to give 50.1 mg (75%) of a estereoismeric mixture of oximes 11. To the solution of oximes 11 in THF (1.8 mL) at 0 °C under nitrogen atmosphere was added triethylamine (119 μL, 119 mmol) and SOCl₂ (25 μL, 0.34 mmol). After 45 min, water (4 ml) was added and the mixture extracted with EtOAc (2 x 30 mL), washed with brine (3 mL), dried over MgSO₄ and concentrated under reduced pressure. Column chromatography eluting with hexane/EtOAc 6:4 gave 39.6 mg (84%) of compound 12: The ee (94.8%) was determined by HPLC analysis, Chiralpak IC, hexane/i-PrOH 90:10, 1 mL/min, major enantiomer (S) tᵣ = 17.3 min, minor enantiomer (R) tᵣ = 21.0 min. [α]D²⁰ -21.6 (c 1.3, MeOH, 94.8% ee), [α]D²⁰ -53.0 (c 0.6, CHCl₃, 94.8% ee), Lit.⁶ [α]D²⁰ +55 (c 1.0, CHCl₃, 91% ee, for the R-enantiomer); ¹H NMR (300 MHz, CD₃OD) δ 7.50 (d, J = 7.2 Hz, 1H), 7.37 (td, J = 7.8, 1.2 Hz, 1H), 7.13 (td, J = 8.7, 0.9 Hz, 1H), 6.97 (ddd, J = 7.8, 1.2, 0.9 Hz, 1H), 1.33 (s, 9H); ¹³C NMR (75 MHz, CD₃OD) δ 171.8 (C), 155.7 (C), 143.1 (C), 132.3 (CH), 127.5 (C), 125.4 (C), 124.6 (CH), 116.2 (C), 112.1(CH), 82.5 (C), 28.4 (CH₃); MS(ESI) m/z: 296.1009 (M+Na)+, C₁₄H₁₅N₃NaO₃ required 296.1006.

**Methyl (R)-3-amino-2-oxoindoline-3-carboxylate (13)**

Dry HCl was bubbled through a solution of compound 12 (36 mg, 0.13 mmol) in anhydrous methanol (3.0 ml) at 0 °C for 3 + 2 min.⁷ The mixture was stirred for 24 h at room temperature. Saturated aqueous NaHCO₃ (5 mL) was added. MeOH was removed under reduced pressure and the aqueous layer was extracted with CH₂Cl₂ (2x30 mL) and dried.
with MgSO₄. Removal of the solvents under reduced pressure gave 17.0 mg (61%) of ester 13: The ee (92%) was determined by HPLC analysis, Chiralpak AD-H, hexane/i-PrOH 80:20, 1 mL/min, major enantiomer (R)  tᵣ = 12.5 min, minor enantiomer (S)  tᵣ = 11.5 min. [α]D²⁰ +113.4 (c 1.3, MeOH, 92% ee), Lit⁷ [α]D²⁰ -114 (for the S-enantiomer); H NMR (300 MHz, CD₃OD) δ 7.33-7.27 (m, 2H), 7.04 (td, J = 7.5, 0.9, 1H), 6.94 /td, J = 8.1, 0.6, 1H), 3.67 (s, 3H); C NMR (75 MHz, CD₃OD) δ 178.3 (C), 171.7 (C), 143.9 (C), 131.2 (CH), 130.8 (C), 124.8 (CH), 123.9 (CH), 111.5 (CH), 66.9 (C), 53.6 (CH₃); MS(ESI) m/z: 229.0586 (M+Na)+, C₁₀H₁₀N₂NaO₃ required 229.0584.

Notes and references

7. When we carried out the reaction bubbling HCl for 15 min the ee of compound 13 decreased to 81%.
$^{1}H$ NMR, 300 MHz, CDCl$_3$
$^{13}$C NMR, 75 MHz, CDCl$_3$
$^{1}$H NMR, 300 MHz, CDCl$_3$
$^{13}$C NMR, 75 MHz, DMSO
$^1$H NMR, 300 MHz, CDCl$_3$
$^{13}$C NMR, 75 MHz, CDCl$_3$
$\text{1H NMR, 300 MHz, CDCl}_3$
$^{13}$C NMR, 75 MHz, CDCl$_3$
$\text{Boc}$

$\text{HN} \cdots \text{NO}_2$

$\text{3b}$

$^1\text{H NMR, 300 MHz, CDCl}_3$
$^{13}$C NMR, 75 MHz, CDCl$_3$
$^1$H NMR, 300 MHz, CDCl₃
$^{13}$C NMR, 75 MHz, CDCl$_3$
$^1$H NMR, 300 MHz, CDCl$_3$
$^{13}$C NMR, 75 MHz, CDCl$_3$
$^1$H NMR, 300 MHz, CDCl$_3$
$^{13}$C NMR, 75 MHz, CDCl$_3$
$^1$H NMR, 300 MHz, CDCl$_3$
$^{13}$C NMR, 75 MHz, CDCl$_3$
$^1$H NMR, 300 MHz, CDCl$_3$
$^{13}$C NMR, 75 MHz, CDCl$_3$
$^{1}$H NMR, 300 MHz, CDCl$_3$
$^{13}$C NMR, 75 MHz, CD$_3$OD
$^1$H NMR, 300 MHz, CDCl$_3$
$^{13}$C NMR, 75 MHz, CDCl$_3$
$^1$H NMR, 300 MHz, CD$_3$OD
$^{13}$C NMR, 75 MHz, CD$_3$OD
"3k"

$^1$H NMR, 300 MHz, CDCl$_3$ + CD$_3$OD
$^{13}$C NMR, 75 MHz, CDCl$_3$ + CD$_3$OD

3k
$^1$H NMR, 300 MHz, CDCl$_3$
$^{13}$C NMR, 75 MHz, CDCl$_3$
$^1$H NMR, 300 MHz, CDCl$_3$
$^{13}$C NMR, 75 MHz, CD$_3$OD
$^{19}$F NMR, 282 MHz, CD$_3$OD
$^1$H NMR, 300 MHz, CDCl$_3$
$^{13}$C NMR, 75 MHz, CDCl$_3$
$^1$H NMR, 300 MHz, CDCl$_3$
$^{13}$C NMR, 75 MHz, CDCl$_3$
\[ ^1H \text{NMR, 300 MHz, CDCl}_3 \]
$^{13}$C NMR, 75 MHz, CDCl$_3$
$^1$H NMR, 300 MHz, CDCl$_3$
$^1$H NMR, 300 MHz, CDCl$_3$

after crystallization
$^{13}$C NMR, 75 MHz, CDCl$_3$

after crystallization
$^1$H NMR, 300 MHz, CDCl$_3$
$^{13}$C NMR, 75 MHz,
$^1$H NMR, 300 MHz, CDCl$_3$
$^{13}$C NMR, 75 MHz,
$^1$H NMR, 300 MHz, CDCl$_3$
$^1$H NMR, 300 MHz, CDCl$_3$

after crystallization
$^{13}$C NMR, 75 MHz, CDCl$_3$

after crystallization
$^1$H NMR, 300 MHz, CD$_3$CN
$^{13}$C NMR, 75 MHz, CD$_3$CN
$^1$H NMR, 300 MHz, CD$_3$OD
$^{13}$C NMR, 75 MHz, CD$_3$OD
$^1$H NMR, 300 MHz, CD$_3$OD
$^{13}$C NMR, 75 MHz, CD$_3$OD
$^1$H NMR, 300 MHz, CD$_3$OD

12
13C NMR, 75 MHz, CD$_3$OD
$^{1}H$ NMR, 300 MHz, CD$_3$OD
<table>
<thead>
<tr>
<th>No.</th>
<th>RT</th>
<th>Area</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18.85</td>
<td>19903152</td>
<td>50.169</td>
</tr>
<tr>
<td>2</td>
<td>21.91</td>
<td>19769376</td>
<td>49.831</td>
</tr>
<tr>
<td></td>
<td></td>
<td>39672528</td>
<td>100.000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No.</th>
<th>RT</th>
<th>Area</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17.79</td>
<td>44062803</td>
<td>99.940</td>
</tr>
<tr>
<td>2</td>
<td>20.93</td>
<td>26478</td>
<td>0.060</td>
</tr>
<tr>
<td></td>
<td></td>
<td>44089281</td>
<td>100.000</td>
</tr>
</tbody>
</table>
### Table 1

<table>
<thead>
<tr>
<th>No.</th>
<th>RT</th>
<th>Area</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.07</td>
<td>6830474</td>
<td>50.035</td>
</tr>
<tr>
<td>2</td>
<td>11.10</td>
<td>6821033</td>
<td>49.965</td>
</tr>
</tbody>
</table>

Total Area: 13651507

### Table 2

<table>
<thead>
<tr>
<th>No.</th>
<th>RT</th>
<th>Area</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9.98</td>
<td>9192478</td>
<td>98.750</td>
</tr>
<tr>
<td>2</td>
<td>11.12</td>
<td>116391</td>
<td>1.250</td>
</tr>
</tbody>
</table>

Total Area: 9308869
3j
Boc

\[
\begin{align*}
\text{HN} & \text{NO}_2 \\
\text{HN} & \text{O} \\
3n \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>No.</th>
<th>RT</th>
<th>Area</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.97</td>
<td>8202350</td>
<td>50.036</td>
</tr>
<tr>
<td>2</td>
<td>13.79</td>
<td>8169796</td>
<td>49.962</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16392146</td>
<td>100.000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No.</th>
<th>RT</th>
<th>Area</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.95</td>
<td>9216366</td>
<td>99.365</td>
</tr>
<tr>
<td>2</td>
<td>13.89</td>
<td>598889</td>
<td>0.635</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9275255</td>
<td>100.000</td>
</tr>
</tbody>
</table>
\[
\begin{align*}
&\text{Boc} \\
&\text{HN} \\
&\text{NO}_2 \\
&6a
\end{align*}
\]
<table>
<thead>
<tr>
<th>No.</th>
<th>RT</th>
<th>Area</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.84</td>
<td>971006</td>
<td>99.528</td>
</tr>
<tr>
<td>2</td>
<td>10.89</td>
<td>4608</td>
<td>0.472</td>
</tr>
<tr>
<td></td>
<td></td>
<td>975614</td>
<td>100.000</td>
</tr>
</tbody>
</table>
Boc
\[
\text{HN} \quad \text{NO}_2
\]

7a

### Table 1

<table>
<thead>
<tr>
<th>No.</th>
<th>RT</th>
<th>Area</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14.03</td>
<td>9085546</td>
<td>34.386</td>
</tr>
<tr>
<td>2</td>
<td>15.21</td>
<td>4094374</td>
<td>15.496</td>
</tr>
<tr>
<td>3</td>
<td>20.62</td>
<td>9056690</td>
<td>34.276</td>
</tr>
<tr>
<td>4</td>
<td>26.89</td>
<td>4185997</td>
<td>15.842</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>No.</th>
<th>RT</th>
<th>Area</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14.06</td>
<td>7212816</td>
<td>99.804</td>
</tr>
<tr>
<td>2</td>
<td>21.31</td>
<td>14150</td>
<td>0.196</td>
</tr>
</tbody>
</table>

Total: 7226966, 100.000
# Chromatogram Analysis

The chromatogram shows a peak with retention times of 15.37 minutes and 15.75 minutes. The areas under the curve for these peaks are 83680 and 8420, respectively.

<table>
<thead>
<tr>
<th>No.</th>
<th>RT</th>
<th>Area</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15.37</td>
<td>83680</td>
<td>99.003</td>
</tr>
<tr>
<td>2</td>
<td>15.75</td>
<td>8420</td>
<td>0.997</td>
</tr>
<tr>
<td></td>
<td></td>
<td>84500</td>
<td>100.000</td>
</tr>
<tr>
<td>No.</td>
<td>RT</td>
<td>Area</td>
<td>Area %</td>
</tr>
<tr>
<td>-----</td>
<td>-----</td>
<td>---------</td>
<td>--------</td>
</tr>
<tr>
<td>1</td>
<td>6.47</td>
<td>4932579</td>
<td>94.419</td>
</tr>
<tr>
<td>2</td>
<td>5.05</td>
<td>291547</td>
<td>5.581</td>
</tr>
<tr>
<td>No.</td>
<td>RT</td>
<td>Area</td>
<td>Area %</td>
</tr>
<tr>
<td>-----</td>
<td>------</td>
<td>-------</td>
<td>--------</td>
</tr>
<tr>
<td>1</td>
<td>8.63</td>
<td>2328697</td>
<td>99.470</td>
</tr>
<tr>
<td>2</td>
<td>14.19</td>
<td>12399</td>
<td>0.530</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2341096</td>
<td>100.000</td>
</tr>
<tr>
<td>No.</td>
<td>RT</td>
<td>Area</td>
<td>Area %</td>
</tr>
<tr>
<td>-----</td>
<td>------</td>
<td>------------</td>
<td>--------</td>
</tr>
<tr>
<td>1</td>
<td>8.70</td>
<td>7142709</td>
<td>48.182</td>
</tr>
<tr>
<td>2</td>
<td>9.38</td>
<td>1725965</td>
<td>11.643</td>
</tr>
<tr>
<td>3</td>
<td>14.45</td>
<td>4286876</td>
<td>28.916</td>
</tr>
<tr>
<td>4</td>
<td>15.97</td>
<td>1669155</td>
<td>11.259</td>
</tr>
</tbody>
</table>

**Total Area:** 14824506

100.000

<table>
<thead>
<tr>
<th>No.</th>
<th>RT</th>
<th>Area</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.67</td>
<td>6243861</td>
<td>99.917</td>
</tr>
<tr>
<td>2</td>
<td>15.12</td>
<td>5189</td>
<td>0.083</td>
</tr>
</tbody>
</table>

**Total Area:** 6249019

100.000
<table>
<thead>
<tr>
<th>No.</th>
<th>RT</th>
<th>Area</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9.37</td>
<td>1214954</td>
<td>98.910</td>
</tr>
<tr>
<td>2</td>
<td>15.95</td>
<td>1095</td>
<td>0.090</td>
</tr>
</tbody>
</table>

**Total**: 1216049 100.000
<table>
<thead>
<tr>
<th>No.</th>
<th>RT</th>
<th>Area</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12.61</td>
<td>5944486</td>
<td>36.755</td>
</tr>
<tr>
<td>2</td>
<td>14.99</td>
<td>10228991</td>
<td>63.245</td>
</tr>
<tr>
<td></td>
<td></td>
<td>16173477</td>
<td>100.000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No.</th>
<th>RT</th>
<th>Area</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12.84</td>
<td>306491</td>
<td>2.176</td>
</tr>
<tr>
<td>2</td>
<td>14.88</td>
<td>13780825</td>
<td>97.824</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14087316</td>
<td>100.000</td>
</tr>
</tbody>
</table>