Supporting Information

Indium-catalysed amide allylation of α-iminoamide: highly enantioselective synthesis of amide functionalised α-methylene-γ-butyrolactams

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General methods:

All solvents and reagents were of reagent grade quality and used without further purification unless otherwise stated. Indium salts (In(OTf)₃ and InCl₃) and molecular sieves (MS3 Å and MS4 Å) were dried at 140 and 180 °C for 1 and 3 h under reduced pressure (ca. 1.0 Torr) prior to use, respectively. Acetonitrile (MeCN) was dried over MS3 Å and degassed by freeze–pump–thaw prior to use. β-Amido allylstannanes 1[1] and α-iminoester 2[2] were synthesized according to the literature. All new compounds were characterized by NMR, IR, and elemental analysis. The ¹H and ¹³C NMR spectra operating at the frequencies of 300 and 75 MHz, respectively, on a JEOL JNM–AL300 spectrometer were recorded in chloroform–d (CDCl₃) unless otherwise noted. Chemical shifts are reported in parts per million (ppm) relative to TMS and the solvent used as internal standards, and the coupling constants are reported in hertz (Hz). Optical rotations were measured in 1 dm path length cell of 2 mL capacity using a JASCO Model DIP–1000 polarimeter at a wavelength of 589 nm. Reactions were monitored by thin layer chromatography using 0.25 mm Merck silica gel 60–F254 precoated silica gel plates by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid in EtOH followed by heating. Column chromatography was performed using silica gel 60N from Kanto Chemical Co. and eluting with the indicated solvent system. Melting points were measured with a Yanaco MP–S3 micro melting point apparatus. Fourier transform infrared (FTIR) spectra were recorded on a JASCO FT/IR–550 spectrometer. Elemental analyses were performed by JSL Model JM 10 instruments.
Preliminary investigations on enantioselective amide allylation of α-iminocarbonyl derivatives:

\[
\text{PhHN} = \text{O} \quad + \quad \begin{array}{c}
\text{NPMP} \\
\text{Y = OMe (2a)} \\
\text{Y = NHPh (3a)}
\end{array}
\xrightarrow{\text{In(OTf)}_3 (20 \text{ mol} \%) \quad \text{chiral ligand (25 mol%)}}
\begin{array}{c}
\text{NHPMP} \\
\text{Y = OMe (4a)} \\
\text{Y = NHPh (5a)}
\end{array}
\]

(S,S)-Ph-pybox
72 h, trace (4a)
24 h, 11%, 11% ee (5a)

(S)-BINOL
72 h, 74%, 34% ee (4a)
24 h, 86%, 32% ee (5a)

(S)-3,3'-Ph₂-BINOL
72 h, 84%, 35% ee (4a)
24 h, 84%, 58% ee (5a)

(S)-6,6'-Ph₂-BINOL
72 h, 76%, 32% ee (4a)
24 h, 86%, 38% ee (5a)

Scheme S1. Reaction of \( \text{2a/3a} \) with \( \text{1a} \) in the presence of various chiral catalysts. The ee values were determined by HPLC analysis using Daicel Chiralpak IE (for \( \text{4a} \)) and IC (for \( \text{5a} \)), respectively.
X-ray structure for 8:

Figure S1. ORTEP diagram for X–ray structure of 8 (50% thermal ellipsoid probability).
**1H NMR spectra of indium complexes:**

(a) 3,3'-(4-MeC₆H₄)₂-(S)-BINOL

(1H NMR, 300 MHz in CD₃CN)

(b) 3a (1H NMR, 300 MHz in CD₃CN)

(c) InCl₃/3a/3,3'-(4-MeC₆H₄)₂-(S)-BINOL

(1H NMR, 300 MHz in CD₃CN)

Figure S2. 1H NMR spectra (300 MHz, CD₃CN) of (a) 3,3'-(4-MeC₆H₄)₂-(S)-BINOL, (b) 3a and (c) InCl₃/3a/3,3'-(4-MeC₆H₄)₂-(S)-BINOL (1/1/1, stirred for 1 h at rt).
$^1$H NMR spectra of the samples prepared from 1a and metal salts (InCl$_3$ and/or ZnCl$_2$):

(a) 1a ($^1$H NMR, 300 MHz in CD$_3$CN)

(b) 1a/InCl$_3$
($^1$H NMR, 300 MHz in CD$_3$CN)

(c) 1a/ZnCl$_2$
($^1$H NMR, 300 MHz in CD$_3$CN)

(d) 1a/InCl$_3$/ZnCl$_2$
($^1$H NMR, 300 MHz in CD$_3$CN)

Figure S3. $^1$H NMR spectra (300 MHz, CD$_3$CN) of (a) 1a, (b) 1a/InCl$_3$ (1/1, stirred for 30 min at rt), (c) 1a/ZnCl$_2$ (1/1, stirred for 3 h at rt) and (d) 1a/InCl$_3$/ZnCl$_2$ (1/1/1, stirred for 4 h at rt).
Experimental procedures and characterization data:
General procedure for preparation of ketimines

All the experiments for the the synthesis of ketimines were carried out as described in the following typical procedure. For example, the reaction of \(N\)-phenyl-2-oxo-2-phenylacetamide with \(p\)-anisidine for the synthesis of \(3a\) was exemplified as follows.

**Synthesis and characterization of 3a**

To a solution of \(N\)-phenyl-2-oxo-2-phenylacetamide (500 mg, 3.07 mmol) and \(p\)-toluenesulfonic acid monohydrate (60.9 mg, 0.320 mmol, 10 mol %) in toluene (3.3 mL) was added \(p\)-anisidine (479 mg, 3.89 mmol, 1.2 equiv.) at room temperature. After stirring the mixture at reflux for 19 h, the solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 5/1) and recrystallization from EtOAc-hexane to give \(3a\) (548 mg, 54%) as a yellow solid: \(R_f = 0.57\) (silica gel, hexane/EtOAc = 2/1); M.p. 155–157 °C; IR (KBr) 3279 (N–H), 1650 (C=O) cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.73 (brs, 1H, major isomer, NH), 8.02 (m, 2H, minor isomer, ArH), 7.74 (m, 2H, major isomer, ArH), 7.49 (m, 2H, minor isomer, ArH), 7.40-7.23 (m, 7H, ArH), 7.14 (m, 1H, major isomer, ArH), 6.80-6.73 (m, 4H, ArH), 3.77 (s, 3H, CH\(_3\)); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 161.5 (C), 159.9 (C), 157.7 (C), 140.3 (C), 137.6 (C), 131.8 (C), 129.5 (CH), 129.4 (CH), 129.0 (CH), 128.9 (CH), 128.6 (CH), 128.6 (CH), 128.2 (CH), 128.1 (CH), 124.2 (CH), 123.7 (CH), 121.9 (CH), 120.7 (CH), 119.4 (CH), 114.4 (CH), 114.0 (CH), 55.4 (CH\(_3\)), 55.3 (CH\(_3\)); Anal. Calcd for C\(_{21}\)H\(_{18}\)N\(_2\)O\(_2\): C, 76.34; H, 5.49; N, 8.48. Found: C, 76.34; H, 5.52; N, 8.47.

**Characterization for 3b**

A solution of \(N\)-phenyl-2-oxo-2-(4-methoxyphenyl)acetamide, \(p\)-toluenesulfonic acid monohydrate and \(p\)-anisidine in toluene was stirred at reflux for 11 h, The crude product was purified by column
chromatography (silica gel, hexane/EtOAc = 5/1) and recrystallization from EtOAc-hexane to give **3b** (378 mg, 41%) as a yellow solid: \( R_f = 0.44 \) (silica gel, hexane/EtOAc = 2/1); M.p. 135–137 °C; IR (KBr) 3278 (N–H), 1668 (C=O), 1645 (C=O) cm⁻¹; \(^1\)H NMR (300 MHz, CDCl₃) 9.74 (brs, 1H, major isomer, NH), 7.94 (m, 2H, minor isomer, ArH), 7.73 (dd, \( J = 1.5, 9.0 \) Hz, 2H, major isomer, ArH), 7.36 (t, \( J = 8.0 \) Hz, 2H, major isomer, ArH), 7.27-7.07 (m, 4H, ArH), 6.94 (d, \( J = 9.0 \) Hz, 2H, minor isomer, ArH), 6.84-6.74 (m, 5H, ArH), 3.85 (s, 3H, minor isomer, CH₃), 3.78 (s, 3H, major isomer, CH₃), 3.76 (s, 3H, major isomer, CH₃), 3.74 (s, 3H, minor isomer, CH₃); \(^13\)C NMR (75 MHz, CDCl₃) 164.5 (C), 162.3 (C), 161.8 (C), 161.0 (C), 160.4 (C), 159.5 (C), 157.4 (C), 157.2 (C), 142.6 (C), 140.9 (C), 137.7 (C), 137.5 (C), 135.4 (C), 130.0 (CH), 129.0 (CH), 128.9 (CH), 127.4 (CH), 125.2 (CH), 124.2 (CH), 123.6 (CH), 123.4 (CH), 121.8 (CH), 120.7 (CH), 119.4 (CH), 114.3 (CH), 114.1 (CH), 114.0 (CH), 55.4 (CH₃), 55.3 (CH₃), 55.2 (CH₃). Anal. Calcd for C₂₂H₂₀N₂O₃: C, 73.32; H, 5.59; N, 7.77. Found: C, 73.23; H, 5.62; N, 7.79.

**Characterization for 3c**

A solution of \( N \)-phenyl-2-oxo-2-(4-trifluoromethylphenyl)acetamide, \( p \)-toluenesulfonylacid monohydrate and \( p \)-anisidine in toluene was stirred at reflux for 15 h. The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 5/1) and recrystallization from EtOAc-hexane to give **3c** (132 mg, 19%) as a yellow solid: \( R_f = 0.63 \) (silica gel, hexane/EtOAc = 2/1); M.p. 154–156 °C; IR (KBr) 3354 (N–H), 1683 (C=O) cm⁻¹; \(^1\)H NMR (300 MHz, CDCl₃) 9.69 (brs, 1H, major isomer, NH), 8.14 (d, \( J = 7.5 \) Hz, 2H, minor isomer, ArH), 7.73 (d, \( J = 7.5 \) Hz, 2H, major isomer, ArH), 7.60 (d, \( J = 8.1 \) Hz, 2H, major isomer, ArH), 7.41-7.36 (m, 4H, major isomer, ArH), 7.32-7.29 (m, 2H, minor isomer, ArH), 7.16 (t, \( J = 7.2 \) Hz, 1H, major isomer, ArH), 6.77 (s, 4H, ArH), 3.78 (s, 3H, major isomer, CH₃); \(^13\)C NMR (75 MHz, CDCl₃) 161.0 (C), 158.4 (C), 158.1 (C), 157.9 (C), 139.7 (C), 137.4 (C), 135.7 (C), 130.0 (CH), 129.1 (CH), 125.1 (q, \( J = 3.7 \) Hz, CH), 124.5 (CH), 123.9 (C), 123.8...
(CH), 119.5 (CH), 114.2 (CH), 55.4 (CH₃). Anal. Calcd for C₂₂H₁₇F₃N₂O₂: C, 66.33; H, 4.30; N, 7.03. Found: C, 66.28; H, 4.50; N, 7.08.

Characterization for 3d
A solution of N-phenyl-2-oxo-2-(1-naphthyl)acetamide (1.37 mg, 6.00 mmol), p-toluenesulfonic acid monohydrate (114 mg, 0.600 mmol, 10 mol %) and p-anisidine (887 mg, 7.20 mmol, 1.2 equiv.) in toluene (6.5 mL) was stirred at reflux for 24 h. The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 5/1) and recrystallization from EtOAc-hexane to give 3d (1.28 g, 56%) as a yellow solid: R_f = 0.57 (silica gel, hexane/EtOAc = 2/1); M.p. 146–148 °C; IR (KBr) 3288 (N–H), 1676 (C=O) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.87 (brs, 1H, NH), 7.87 (t, J = 6.9 Hz, 2H, ArH), 7.77 (d, J = 8.7 Hz, 2H, ArH), 7.60 (d, J = 8.1 Hz, 1H, ArH), 7.48-7.26 (m, 6H, ArH), 7.14 (t, J = 7.5 Hz, 1H, ArH), 6.79 (m, 2H, ArH), 6.60 (m, 2H, ArH), 3.68 (s, 3H, C₃H₃); ¹³C NMR (75 MHz, CDCl₃) δ 161.8 (C), 160.2 (C), 158.2 (C), 139.7 (C), 137.7 (C), 133.2 (C), 131.5 (C), 130.8 (C), 129.6 (CH), 129.2 (CH), 129.1 (CH), 128.6 (CH), 126.8 (CH), 126.2 (CH), 125.5 (CH), 125.1 (CH), 124.8 (CH), 124.23 (CH), 124.19 (CH), 119.8 (CH), 119.4 (CH), 113.9 (CH), 55.2 (CH₃). Anal. Calcd for: C₂₅H₂₀N₂O₂: C, 78.93; H, 5.30; N, 7.36. Found: C, 78.56; H, 5.21; N, 7.58.

General procedure for amide allylation of ketimines
All the experiments for amide allylation of ketimines were carried out as described in the following typical procedure. For example, the reaction of 3 with 1 for the synthesis of 5a was exemplified as follows.

Synthesis and characterization of 5a
To a suspension of InCl₃ (9.6 mg, 0.0434 mmol, 0.2 equiv.) and MS3 Å (326 mg, 1.5 g/mmol) in
MeCN (0.43 mL) was added ZnCl$_2$ (3.0 mg, 0.0217 mmol, 0.1 equiv.) at room temperature under a nitrogen atmosphere, and the resulting mixture was stirred for 1 h. After addition of 3,3'-(4-MeC$_6$H$_4$)$_2$-(S)-BINOL (25.3 mg, 0.0543 mmol, 0.25 equiv.), the mixture was stirred at this temperature for 1 h, and then 3a (71.7 mg, 0.217 mmol) was added. The resulting mixture was stirred for 1 h and cooled to 0 °C. After addition of 1a (17.3 mg, 0.260 mmol, 1.2 equiv.), the reaction mixture was stirred at the same temperature for an additional 6 h. The reaction was then quenched by addition of saturated aqueous NaHCO$_3$ (10 mL), and the resulting mixture was extracted with EtOAc (50 mL), washed with brine (10 mL), dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo to give a crude material. This material was purified by column chromatography (silica gel, hexane/EtOAc = 6/1) to give 5a (134 mg, 99%, 96% ee) as a colorless oil: $R_f$ = 0.43 (silica gel, hexane/AcOEt = 2/1); [α]$_D^{27}$ +42.9 (c 0.97, CHCl$_3$); IR (NaCl) 3016 (N–H), 2935 (C–H), 1671 (C=O) cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.78 (brs, 1H, N$_{H1}$), 7.76 (brs, 1H, N$_{H2}$), 7.70 (d, $J$ = 7.5 Hz, 2H, Ar$_{H1}$), 7.47-7.04 (m, 13H, Ar$_{H3}$), 6.59 (d, $J$ = 9.0 Hz, 2H, Ar$_{H2}$), 6.43 (d, $J$ = 9.0 Hz, 2H, Ar$_{H2}$), 6.40 (brs, 1H, N$_{H1}$), 5.69 (s, 1H, CH$_2$), 5.34 (s, 1H, CH$_2$), 3.62 (s, 3H, CH$_3$), 3.34 (d, $J$ = 14.1 Hz, 1H, CH$_2$), 3.31 (d, $J$ = 14.1 Hz, 1H, CH$_2$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.7 (C$_{H1}$), 168.2 (C$_{H2}$), 152.3 (C), 140.7 (C), 139.7 (C), 137.9 (C), 137.3 (C), 137.2 (C), 128.9 (CH), 128.8 (CH), 128.3 (CH), 127.7 (CH), 127.4 (CH), 124.7 (CH), 124.5 (CH), 123.1 (CH$_2$), 120.3 (CH), 120.1 (CH), 116.9 (CH), 114.4 (CH), 68.3 (C), 55.4 (CH$_3$), 42.3 (CH$_2$). Anal. Calcd for C$_{31}$H$_{29}$N$_3$O$_3$: C, 75.74; H, 5.95; N, 8.55. Found: C, 76.06; H, 5.91; N, 8.51. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 96/4), flow rate 0.5 mL/min, UV detection 274 nm, $t_R$ (major) = 35.2 min, $t_R$ (minor) = 27.3 min.

**Characterization for 5b**

The reaction of 3a with 1b was performed at 0 °C for 6 h. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 6/1) to give 5b (71.2 mg, 99%, 91% ee) as a colorless oil:
$R_f = 0.54$ (silica gel, hexane/AcOEt = 2/1); $[\alpha]_{D}^{28} +52.4$ (c 0.95, CHCl$_3$); IR (NaCl) 3019 (N–H), 2931 (C–H), 1671 (C=O) cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.82 (brs, 1H, NH), 7.72 (d, $J = 7.5$ Hz, 2H, ArH), 7.57 (brs, 1H, NH), 7.43 (d, $J = 7.5$ Hz, 2H, ArH), 7.33-7.08 (m, 10H, ArH), 6.59 (d, $J = 8.7$ Hz, 2H, ArH), 6.47 (brs, 1H, NH), 6.43 (d, $J = 8.7$ Hz, 2H, ArH), 5.69 (s, 1H, CH$_2$), 5.38 (s, 1H, CH$_2$), 3.64 (s, 3H, CH$_3$), 3.36 (d, $J = 13.8$ Hz, 1H, CH$_2$), 3.30 (d, $J = 13.8$ Hz, 1H, CH$_2$), 2.33 (s, 3H, CH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.7 (C), 168.2 (C), 156.7 (C), 152.3 (C), 140.7 (C), 139.7 (C), 138.0 (C), 137.3 (C), 134.7 (C), 134.5 (C), 129.5 (CH), 128.8 (CH), 128.3 (CH), 127.7 (CH), 127.3 (CH), 124.5 (CH), 122.9 (CH$_2$), 120.4 (CH), 120.1 (CH), 117.0 (CH), 114.4 (CH), 68.4 (C), 55.4 (CH$_3$), 42.9 (CH$_2$), 20.9 (CH$_3$). Anal. Calcd for C$_{32}$H$_{31}$N$_3$O$_3$: C, 76.02; H, 6.18; N, 8.31. Found: C, 76.27; H, 6.42; N, 8.44. The enantiomeric excess was determined by HPLC with a Daicel Chiralcel IE column (hexane/EtOH = 80/20), flow rate 0.5 mL/min, UV detection 274 nm, $t_R$ (major) = 22.1 min, $t_R$ (minor) = 18.5 min.

**Characterization for 5c**

The reaction of 3a with 1c was performed at 0 °C for 6 h. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 6/1) to give 5c (69.1 mg, 98%, 92% ee) as a colorless oil: $R_f = 0.37$ (silica gel, hexane/AcOEt = 2/1); $[\alpha]_{D}^{29} +52.6$ (c 1.03, CHCl$_3$); IR (NaCl) 3018 (N–H), 2936 (C–H), 1672 (C=O) cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.82 (brs, 1H, NH), 7.72-7.67 (m, 3H, ArH, NH), 7.43-7.18 (m, 9H, ArH), 7.07 (m, 1H, ArH), 6.84 (d, $J = 9.0$ Hz, 2H, ArH), 6.59 (d, $J = 9.0$ Hz, 2H, ArH), 6.51 (brs, 1H, NH), 6.43 (d, $J = 9.0$ Hz, 2H, ArH), 5.68 (s, 1H, CH$_2$), 5.34 (s, 1H, CH$_2$), 3.78 (s, 3H, CH$_3$), 3.63 (s, 3H, CH$_3$), 3.35 (d, $J = 13.5$ Hz, 1H, CH$_2$), 3.28 (d, $J = 13.5$ Hz, 1H, CH$_2$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.7 (C), 168.2 (C), 152.3 (C), 140.7 (C), 139.7 (C), 138.0 (C), 137.3 (C), 130.3 (C), 128.8 (CH), 128.3 (CH), 127.7 (CH), 127.3 (CH), 124.5 (CH), 122.9 (CH$_2$), 122.3 (CH), 120.1 (CH), 116.9 (CH), 114.4 (CH), 114.1 (CH), 68.4 (C), 55.4 (CH$_3$), 55.4 (CH$_3$), 42.7 (CH$_2$). Anal. Calcd for C$_{32}$H$_{31}$N$_3$O$_4$: C, 73.68; H, 5.99; N, 8.06. Found: C, 73.78; H, 6.12; N, 8.12. The
enantiomeric excess was determined by HPLC with a Daicel Chiralpak IE column (hexane/EtOH = 80/20), flow rate 0.5 mL/min, UV detection 274 nm, $t_R$ (major) = 26.0 min, $t_R$ (minor) = 32.2 min.

**Characterization for 5d**

The reaction of 3a with 1d was performed at 0 °C for 6 h. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 6/1) to give 5d (72.1 mg, 98%, 92% ee) as a colorless oil: $R_f = 0.60$ (silica gel, hexane/AcOEt = 2/1); $[\alpha]_D^{26} +56.2$ (c 1.13, CHCl$_3$); IR (NaCl) 3019 (N–H), 2965 (C–H), 1665 (C=O) cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.82 (brs, 1H, NH), 7.74-7.71 (m, 2H, ArH), 7.55 (brs, 1H, NH), 7.45-7.17 (m, 11H, ArH), 7.08 (dt, $J = 0.9$, 7.2 Hz, 1H, ArH), 6.60 (m, 2H, ArH), 6.47 (brs, 1H, NH), 6.44 (m, 2H, ArH), 5.70 (s, 1H, CH$_2$), 5.40 (s, 1H, CH$_2$), 3.65 (s, 3H, CH$_3$), 3.37 (d, $J = 13.8$ Hz, 1H, CH$_2$), 1.32 (s, 9H, CH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.7 (C), 168.2 (C), 152.3 (C), 147.9 (C), 141.0 (C), 139.8 (C), 138.0 (C), 137.3 (C), 134.6 (C), 129.0 (CH), 128.3 (CH), 127.8 (CH), 127.3 (CH), 125.8 (CH), 124.5 (CH), 122.9 (CH$_2$), 120.13 (CH), 120.07 (CH), 117.0 (CH), 114.3 (CH), 68.5 (C), 55.4 (CH$_3$), 43.0 (CH$_2$), 34.4 (C), 31.3 (CH$_3$). Anal. Caled for C$_{35}$H$_{37}$N$_3$O$_3$: C, 76.75; H, 6.81; N, 7.67. Found: C, 76.80; H, 7.03; N, 8.05. The enantiomeric excess was determined by HPLC with a Daicel Chiralcel IE column (hexane/EtOH = 80/20), flow rate 0.5 mL/min, UV detection 274 nm, $t_R$ (major) = 18.2 min, $t_R$ (minor) = 15.3 min.

**Characterization for 5e**

The reaction of 3a with 1e was performed at 0 °C for 6 h. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 6/1) to give 5e (55.6 mg, 99%, 94% ee) as a white solid: $R_f = 0.49$ (silica gel, hexane/AcOEt = 2/1); $[\alpha]_D^{23} +33.7$ (c 0.910, CHCl$_3$); IR (KBr) 3344 (N–H), 2948 (C–H), 1677 (C=O), 1624 (C=O) cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.79 (brs, 1H, NH), 7.94-7.71 (m, 7H, ArH), 7.53-7.04 (m, 11H, ArH), 6.59 (d, $J = 9.0$ Hz, 2H, ArH), 6.46-6.39 (m, 3H, ArH), 5.70 (s, 1H, NH), 5.40 (s, 1H, CH$_2$), 3.65 (s, 3H, CH$_3$), 3.37 (d, $J = 13.8$ Hz, 1H, CH$_2$), 1.32 (s, 9H, CH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 170.7 (C), 168.2 (C), 152.3 (C), 147.9 (C), 141.0 (C), 139.8 (C), 138.0 (C), 137.3 (C), 134.6 (C), 129.0 (CH), 128.3 (CH), 127.8 (CH), 127.3 (CH), 125.8 (CH), 124.5 (CH), 122.9 (CH$_2$), 120.13 (CH), 120.07 (CH), 117.0 (CH), 114.3 (CH), 68.5 (C), 55.4 (CH$_3$), 43.0 (CH$_2$), 34.4 (C), 31.3 (CH$_3$).
5.88 (s, 1H, CH₂), 5.48 (s, 1H, CH₂), 3.64 (s, 3H, CH₃), 3.45 (d, J = 13.8 Hz, 1H, CH₂), 3.40 (d, J = 13.8 Hz, 1H, CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 170.6 (C), 169.0 (C), 152.3 (C), 141.0 (C), 139.8 (C), 138.0 (C), 137.3 (C), 134.1 (C), 131.8 (C), 128.9 (CH), 128.7 (CH), 128.4 (CH), 127.7 (CH), 127.4 (CH), 126.5 (CH), 126.4 (CH), 126.1 (CH), 125.6 (CH), 124.5 (CH), 123.1 (CH₂), 121.4 (CH), 120.7 (CH), 120.1 (CH), 116.9 (CH), 114.4 (CH), 68.4 (C), 55.4 (CH), 42.5 (CH₂). Anal. Calcd for C₃₅H₃₁N₃O₃: C, 77.61; H, 5.77; N, 7.76. Found: C, 77.25; H, 5.94; N, 7.62. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IE column (hexane/EtOH = 80/20), flow rate 0.5 mL/min, UV detection 274 nm, tᵣ (major) = 38.8 min, tᵣ (minor) = 28.9 min.

Characterization for 5f

The reaction of 3a with 1f was performed at 0 °C for 18 h. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 6/1) to give 5f (67.2 mg, 96%, 90% ee) as a colorless oil: Rᵣ = 0.45 (silica gel, hexane/AcOEt = 2/1); [α]D⁺24 = +45.4 (c 1.05, CHCl₃); IR (NaCl) 3019 (N–H), 1646 (C=O) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.63 (brs, 1H, NH), 7.71 (d, J = 8.7 Hz, 2H, ArH), 6.62 (dt, J = 2.7, 9.0 Hz, 2H, ArH), 6.44 (dd, J = 3.6, 9.0 Hz, 2H, ArH), 6.12 (brs, 1H, NH), 5.73 (s, 1H, CH₂), 5.38 (s, 1H, CH₂), 3.66 (s, 3H, CH₃), 3.43 (d, J = 14.1 Hz, 1H, CH₂), 3.37 (d, J = 14.1 Hz, 1H, CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 170.7 (C), 167.9 (C), 152.5 (C), 140.8 (C), 139.7 (C), 137.8 (C), 137.2 (C), 136.0 (C), 129.7 (C), 129.0 (CH), 128.9 (CH), 128.5 (CH), 127.6 (CH), 127.5 (CH), 124.6 (CH), 123.4 (CH₂), 121.4 (CH), 120.1 (CH), 117.0 (CH), 114.5 (CH), 68.2 (C), 55.5 (CH₃), 41.3 (CH₂). Anal. Calcd for C₃₁H₂₈ClN₃O₃: C, 70.78; H, 5.37; Cl, 6.74; N, 7.99. Found: C, 71.00; H, 5.38; N, 8.22. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 96/4), flow rate 0.5 mL/min, UV detection 274 nm, tᵣ (major) = 18.4 min, tᵣ (minor) = 21.9 min.
**Characterization for 5g**

The reaction of 3a with 1g was performed at 0 °C for 19 h. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 6/1) to give 5g (82.1 mg, 92%, 82% ee) as a colorless oil: \( R_f = 0.45 \) (silica gel, hexane/AcOEt = 2/1); \([\alpha]_D^{26} +104 \) (c 1.05, CHCl_3); IR (NaCl) 3019 (N–H), 2933 (C–H), 1652 (C=O) cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl_3) \( \delta \) 8.89 (brs, 1H, NH), 7.72 (d, \( J = 8.4 \) Hz, 2H, ArH), 7.46 (d, \( J = 7.8 \) Hz, 2H, ArH), 7.32-7.19 (m, 5H, ArH), 7.09 (t, \( J = 7.2 \) Hz, 1H, ArH), 6.76 (brs, 1H, NH), 6.59 (dt, \( J = 2.1, 9.0 \) Hz, 2H, ArH), 6.43 (dt, \( J = 2.1, 9.0 \) Hz, 2H, ArH), 5.88 (brs, 1H, NH), 5.52 (s, 1H, C\( H_2 \)), 5.29 (s, 1H, C\( H_2 \)), 3.65 (s, 3H, C\( H_3 \)), 3.30-3.16 (m, 4H, C\( H_2 \)), 1.50 (m, 2H, C\( H_2 \)), 1.38-1.26 (m, 4H, C\( H_2 \)), 0.90 (t, \( J = 6.9 \) Hz, 3H, C\( H_3 \)); \(^{13}\)C NMR (75 MHz, CDCl_3) \( \delta \) 170.7 (C\( H \)), 170.3 (C\( H \)), 152.1 (C), 140.4 (C), 139.8 (C), 138.2 (C), 137.5 (C), 128.9 (CH), 128.1 (CH), 128.0 (CH), 127.1 (CH), 124.4 (CH), 122.1 (CH), 120.0 (CH), 116.8 (CH), 114.3 (CH), 68.5 (C), 55.4 (CH\( _3 \)), 43.9 (CH\( _2 \)), 40.0 (CH\( _2 \)), 29.1 (CH\( _2 \)), 22.3 (CH\( _2 \)), 13.9 (CH\( _3 \)). Anal. Calcd for C\( _{30} \)H\( _{35} \)N\( _3 \)O\( _3 \): C, 74.20; H, 7.26; N, 8.65. Found: C, 74.02; H, 7.24; N, 8.68. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 96/4), flow rate 0.5 mL/min, UV detection 274 nm, \( t_R \) (major) = 22.6 min, \( t_R \) (minor) = 31.7 min.

**Characterization for 5h**

The reaction of 3b with 1a was performed at 0 °C for 3 h. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 6/1) to give 5h (70.2 mg, 96%, 93% ee) as a white solid: \( R_f = 0.38 \) (silica gel, hexane/EtOAc = 2/1); M.p. 195–197 °C; \([\alpha]_D^{29} +52.7 \) (c 0.96, CHCl_3); IR (KBr) 3321 (N–H), 1660 (C=O) cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl_3) \( \delta \) 8.72 (brs, 1H, NH), 7.65-7.60 (m, 3H, NH, ArH), 7.46-7.03 (m, 10H, ArH), 6.79 (d, \( J = 8.7 \) Hz, 2H, ArH), 6.61 (d, \( J = 8.7 \) Hz, 2H, ArH), 6.45 (d, \( J = 8.7 \) Hz, 2H, ArH), 6.25 (brs, 1H, NH), 5.69 (s, 1H, CH\( _2 \)), 5.33 (s, 1H, CH\( _2 \)), 3.71 (s, 3H, CH\( _3 \)), 3.65 (s, 3H, CH\( _3 \)), 3.36 (d, \( J = 14.7 \) Hz, 1H, CH\( _2 \)), 3.31 (d, \( J = 14.7 \) Hz, 1H, CH\( _2 \)); \(^{13}\)C NMR (75 MHz,
Characterization for 5i

The reaction of 3c with 1a was performed at 0 °C for 5 h. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 6/1) to give 5i (62.1 mg, 99%, 95% ee) as a colorless oil: \( R_f = 0.60 \) (silica gel, hexane/EtOAc = 2/1); \([\alpha]_D^{25} +45.5 \) (c 1.01, CHCl\(_3\)); IR (NaCl) 3019 (N–H), 1668 (C=O) cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 9.00 (brs, 1H, N\( \text{H} \)), 7.92 (d, \( J = 8.4 \) Hz, 2H, ArH), 7.59 (brs, 1H, N\( \text{H} \)), 7.53-7.09 (m, 12H, ArH), 6.85 (brs, 1H, N\( \text{H} \)), 6.61 (dt, \( J = 2.1, 9.0 \) Hz, 2H, ArH), 6.41 (dt, \( J = 2.1, 8.7 \) Hz, 2H, ArH), 5.74 (s, 1H, \( C\text{H}_2 \)), 5.46 (s, 1H, \( C\text{H}_2 \)), 3.66 (s, 3H, \( C\text{H}_3 \)), 3.29 (d, \( J = 13.8 \) Hz, 1H, \( C\text{H}_2 \)), 3.20 (d, \( J = 13.8 \) Hz, 1H, \( C\text{H}_2 \)); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 170.1 (C), 168.3 (C), 152.5 (C), 143.9 (C), 140.4 (C), 137.5 (C), 137.2 (C), 137.1 (C), 129.2 (CH), 129.0 (CH), 128.6 (CH), 125.2 (CH), 125.0 (q, \( J = 3.7 \) Hz, CH), 124.7 (CH), 123.4 (CH\(_2\)), 120.3 (CH), 120.1 (CH), 116.8 (CH), 114.5 (CH), 68.4 (C), 55.4 (CH\(_3\)), 45.1 (CH\(_2\)). Anal. Calcd for C\(_{32}\)H\(_{28}\)F\(_3\)N\(_3\)O\(_3\): C, 68.68; H, 5.04; N, 7.51. Found: C, 68.36; H, 5.12; N, 7.47. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IB column (hexane/EtOH = 96/4), flow rate 0.5 mL/min, UV detection 274 nm, \( t_R \) (major) = 24.8 min, \( t_R \) (minor) = 31.4 min.

Characterization for 5j

The reaction of 3d with 1a was performed at room temperature for 66 h. The crude material was
purified by column chromatography (silica gel, hexane/EtOAc = 6/1) to give 5j (54.3 mg, 94%, 57% ee) as a colorless oil: $R_f = 0.46$ (silica gel, hexane/EtOAc = 2/1); $[\alpha]_D^{27} +99.9$ (c 1.08, CHCl$_3$); IR (NaCl) 3019 (N–H), 1683 (C=O) cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$, 50.2 °C) δ 8.54 (brs, 1H, N$H$), 8.04 (d, $J = 7.5$ Hz, 1H, Ar$H$), 7.88-7.77 (m, 3H, Ar$H$), 7.54 (t, $J = 7.8$ Hz, 1H, Ar$H$), 7.40-6.91 (m, 12H, Ar$H$), 6.47 (d, $J = 9.0$ Hz, 2H, Ar$H$), 6.35 (d, $J = 9.0$ Hz, 2H, Ar$H$), 6.02 (brs, 1H, N$H$), 5.79 (s, 1H, C$H_2$), 5.37 (s, 1H, C$H_2$), 3.92 (d, $J = 12.9$ Hz, 1H, C$H_2$), 3.75 (d, $J = 12.9$ Hz, 1H, C$H_2$), 3.57 (s, 3H, C$H_3$); $^{13}$C NMR (75 MHz, CDCl$_3$, 50.2 °C) δ 171.8 (C), 167.7 (C), 152.3 (C), 141.9 (C), 138.5 (C), 137.9 (C), 136.6 (C), 136.3 (C), 134.8 (C), 131.6 (C), 130.4 (CH), 129.0 (CH), 128.8 (CH), 128.6 (CH), 126.7 (CH), 126.6 (CH), 126.1 (CH), 125.3 (CH), 124.9 (CH), 124.7 (CH), 124.2 (CH), 122.5 (CH$_2$), 121.0 (CH), 120.3 (CH), 116.5 (CH), 114.7 (CH), 67.3 (C), 55.6 (CH$_3$), 37.7 (CH$_2$). Anal. Calcd for C$_{35}$H$_{31}$N$_3$O$_3$: C, 77.61; H, 5.77; N, 7.76. Found: C, 77.27; H, 5.47; N, 8.12. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 96/4), flow rate 0.5 mL/min, UV detection 274 nm, $t_R$ (major) = 30.9 min, $t_R$ (minor) = 26.5 min.

**Characterization for 5k**

The reaction of 3a with 1h was performed at 0 °C for 72 h. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 6/1) to give 5k (21.1 mg, 18%, 22% ee) as a colorless oil: $R_f = 0.45$ (silica gel, hexane/EtOAc = 2/1); $[\alpha]_D^{27} +0.79$ (c 0.94, CHCl$_3$); IR (NaCl) 3019 (N–H), 1642 (C=O) cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.81 (brs, 1H, N$H$), 7.68 (m, 2H, Ar$H$), 7.40 (m, 2H, Ar$H$), 7.35-7.20 (m, 8H, Ar$H$), 7.05 (m, 1H, Ar$H$), 6.93 (m, 8.4 Hz, 2H, Ar$H$), 6.68 (dt, $J = 2.1$, 9.0 Hz, 2H, Ar$H$), 6.54 (dt, $J = 2.4$, 9.0 Hz, 2H, Ar$H$), 6.27 (brs, 1H, N$H$), 4.98 (s, 1H, C$H_2$), 4.78 (s, 1H, C$H_2$), 3.70 (s, 3H, C$H_3$), 3.27 (d, $J = 14.4$ Hz, 1H, C$H_2$), 3.16 (s, 3H, C$H_3$), 2.95 (d, $J = 14.4$ Hz, 1H, C$H_2$); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 172.0 (C), 171.2 (C), 152.6 (C), 143.8 (C), 139.9 (C), 138.8 (C), 138.4 (C), 137.7 (C), 129.2 (CH), 128.8 (CH), 128.3 (CH), 127.3 (CH), 127.1 (CH), 126.9 (CH), 126.7 (CH),
124.2 (CH, CH₂), 119.9 (CH), 117.4 (CH), 114.4 (CH), 67.5 (C), 55.5 (CH₃), 41.1 (CH₂), 37.7 (CH₃).

Anal. Calcd for C₃₂H₃₁N₃O₃: C, 76.02; H, 6.18; N, 8.31. Found: C, 75.85; H, 6.49; N, 8.69. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IC column (hexane/EtOH = 90/10), flow rate 0.5 mL/min, UV detection 274 nm, $t_R$ (major) = 18.8 min, $t_R$ (minor) = 22.4 min.

**General procedure for lactamization**

The experiments for lactamization were carried out as described in the following typical procedure. For example, the reaction of 5a with di-tert-butyl dicarbonate (Boc₂O) for the synthesis of 7a was exemplified as follows.

**Synthesis and characterization of 7a**

To a solution of 5a (65.1 mg, 0.132 mmol) in CH₂Cl₂ (0.26 mL) was added Boc₂O (115 mg, 0.528 mmol, 4.0 equiv.), triethylamine (Et₃N, 134 mg, 1.32 mmol, 10 equiv.) and N,N-dimethyl-4-aminopyridine (DMAP, 8.1 mg, 0.066 mmol, 0.5 equiv.) at room temperature under a nitrogen atmosphere. After stirring the solution at the same temperature for 24 h, the solvent was removed under reduced pressure. The crude residue was purified by column chromatography (silica gel, hexane/EtOAc = 3/1 to 0/1) to give 7a (63.1 mg, 96%, 94% ee) as a red oil: $R_f$ = 0.53 (silica gel, hexane/EtOAc = 2/1); $[\alpha]_{D}^{27}$ +133 (c 1.04, CHCl₃); IR (NaCl) 3014 (C–H), 1747 (C=O), 1698 (C=O) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.42-7.14 (m, 8H, Ar H), 7.04 (m, 2H, Ar H), 6.63 (s, 4H, Ar H), 6.21 (t, $J$ = 2.4 Hz, 1H, CH₂), 5.58 (t, $J$ = 2.4 Hz, 1H, CH₂), 4.14 (dt, $J$ = 2.4, 18.3 Hz, 1H, CH₂), 3.77 (dt, $J$ = 2.4, 18.3 Hz, 1H, CH₂), 3.73 (s, 3H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 174.2 (C), 151.5 (C), 139.1 (C), 138.1 (C), 137.5 (C), 131.7 (CH), 129.5 (C), 129.1 (CH), 128.15 (CH), 128.06 (CH), 128.0 (CH), 127.7 (CH), 126.9 (CH), 116.9 (CH₂), 113.4 (CH), 83.4 (C), 75.3 (C), 55.2 (CH₃), 37.6 (CH₂), 27.1 (CH₃). Anal. Calcd for C₃₀H₃₀N₂O₅: C, 72.27; H, 6.07; N, 5.62. Found: C,
71.97; H, 6.02; N, 5.99. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IF column (hexane/EtOH = 80/20), flow rate 0.5 mL/min, UV detection 274 nm, $t_R$ (major) = 25.5 min, $t_R$ (minor) = 32.5 min.

**Specific rotation of 7a prepared from 5b**

A solution of 5b, Boc₂O, Et₃N, and DMAP in CH₂Cl₂ was stirred at room temperature for 24 h. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 3/1 to 0/1) to give 7a (70.8 mg, 98%, 91% ee) as a red oil: $[\alpha]_{D}^{25} +126$ ($c$ 1.05, CHCl₃).

**Specific rotation of 7a prepared from 5c**

A solution of 5c, Boc₂O, Et₃N, and DMAP in CH₂Cl₂ was stirred at room temperature for 24 h. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 3/1 to 0/1) to give 7a (68.5 mg, 96%, 92% ee) as a red oil: $[\alpha]_{D}^{27} +128$ ($c$ 1.05, CHCl₃).

**Specific rotation of 7a prepared from 5d**

A solution of 5d, Boc₂O, Et₃N, and DMAP in CH₂Cl₂ was stirred at room temperature for 24 h. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 3/1 to 0/1) to give 7a (71.8 mg, 97%, 92% ee) as a red oil: $[\alpha]_{D}^{25} +126$ ($c$ 1.02, CHCl₃).

**Specific rotation of 7a prepared from 5e**

A solution of 5e, Boc₂O, Et₃N, and DMAP in CH₂Cl₂ was stirred at room temperature for 24 h. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 3/1 to 0/1) to give 7a (55.4 mg, 98%, 93% ee) as a red oil: $[\alpha]_{D}^{26} +128$ ($c$ 0.98, CHCl₃).
Specific rotation of 7a prepared from 5f

A solution of 5f, Boc₂O, Et₃N, and DMAP in CH₂Cl₂ was stirred at room temperature for 24 h. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 3/1 to 0/1) to give 7a (65.8 mg, 90%, 90% ee) as a red oil: [α]₀⁺²⁷ +120 (c 0.98, CHCl₃).

Specific rotation of 7a prepared from 5g

A solution of 5g, Boc₂O, Et₃N, and DMAP in CH₂Cl₂ was stirred at room temperature for 24 h. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 3/1 to 0/1) to give 7a (80.9 mg, 95%, 80% ee) as a red oil: [α]₀⁺²⁶ +109 (c 0.96, CHCl₃).

Characterization for 7b

A solution of 5h, Boc₂O, Et₃N, and DMAP in CH₂Cl₂ was stirred at room temperature for 24 h. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 3/1 to 1/1) to give 7b (69.8 mg, 90%, 92% ee) as a colorless oil: Rᶠ = 0.44 (silica gel, hexane/EtOAc = 2/1); [α]₀⁺²⁷ +102 (c 0.84, CHCl₃); IR (NaCl) 3019 (C–H), 1748 (C=O), 1696 (C=O) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.42-7.29 (m, 3H, ArH), 7.09-7.01 (m, 4H, ArH), 6.79 (d, J = 9.0 Hz, 2H, ArH), 6.67 (s, 4H, ArH), 6.19 (t, J = 2.4 Hz, 1H, CH₂), 5.56 (t, J = 2.4 Hz, 1H, CH₂), 4.05 (dt, J = 2.4, 18.3 Hz, 1H, CH₂), 3.81-3.73 (m, 1H, CH₂), 3.28 (s, 3H, CH₃), 3.74 (s, 3H, CH₃), 0.97 (s, 9H, CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 174.5 (C), 168.5 (C), 159.3 (C), 158.7 (C), 151.5 (C), 139.1 (C), 137.5 (C), 131.7 (CH), 130.1 (C), 129.5 (C), 129.0 (CH), 128.3 (CH), 127.9 (CH), 127.6 (CH), 116.8 (CH₂), 113.5 (CH), 113.4 (CH), 83.3 (C), 74.8 (C), 55.3 (CH₃), 55.2 (CH₃), 37.7 (CH₂), 27.1 (CH₃). Anal. Calcd for C₃₁H₃₂N₂O₆: C, 70.44; H, 6.10; N, 5.30. Found: C, 70.09; H, 6.06; N, 5.35. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IF column (hexane/EtOH = 80/20), flow rate 0.5 mL/min, UV detection 274 nm, tᵣ (major) = 38.8 min, tᵣ (minor) = 52.3 min.
Characterization for 7c

A solution of 5i, Boc₂O, Et₃N, and DMAP in CH₂Cl₂ was stirred at room temperature for 24 h. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 3/1 to 1/1) to give 7c (61.8 mg, 97%, 95% ee) as a white oil: \( R_f = 0.59 \) (silica gel, hexane/EtOAc = 2/1); \([\alpha]_D^{27} + 76.1 \) \((c \ 0.86, \text{CHCl}_3)\); IR (NaCl) 3018 (C–H), 1747 (C=O), 1700 (C=O) cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 7.54 (d, \( J = 8.4 \) Hz, 2H, ArH), 7.44-7.27 (m, 5H, ArH), 7.04-7.01 (m, 2H, ArH), 6.67 (s, 4H, ArH), 6.24 (t, \( J = 2.4 \) Hz, 1H, CH₂), 5.62 (t, \( J = 2.4 \) Hz, 1H, CH₂), 4.14 (dt, \( J = 2.4, 18.3 \) Hz, 1H, CH₂), 3.79 (dt, \( J = 2.4, 18.3 \) Hz, 1H, CH₂), 3.74 (s, 3H, CH₃), 0.94 (s, 9H, CH₃); \(^{13}\)C NMR (75 MHz, CDCl₃) \( \delta \) 173.7 (C), 168.5 (C), 159.0 (C), 151.5 (C), 142.1 (C), 138.7 (C), 136.7 (C), 131.6 (C), 129.2 (CH), 129.1 (C), 128.2 (CH), 127.5 (CH), 127.2 (CH), 125.0 (q, \( J = 3.8 \) Hz, CH), 117.5 (CH₂), 113.7 (CH), 83.7 (C), 74.8 (C), 55.3 (CH₃), 37.5 (CH₂), 27.0 (CH₃). Anal. Calcd for C₃₁H₂₉F₃N₂O₅: C, 65.72; H, 5.16; N, 4.94. Found: C, 65.93; H, 5.25; N, 5.18. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IE column (hexane/EtOH = 80/20), flow rate 0.5 mL/min, UV detection 274 nm, \( t_R \) (major) = 43.0 min, \( t_R \) (minor) = 33.6 min.

Characterization for 7d

A solution of 5j, Boc₂O, Et₃N, and DMAP in CH₂Cl₂ was stirred at room temperature for 24 h. The crude material was purified by column chromatography (silica gel, hexane/EtOAc = 3/1 to 1/1) to give 7d (63.9 mg, 90%, 57% ee) as a colorless oil: \( R_f = 0.47 \) (silica gel, hexane/EtOAc = 1/1); \([\alpha]_D^{27} + 87.6 \) \((c \ 1.05, \text{CHCl}_3)\); IR (NaCl) 3019 (C–H), 1643 (C=O) cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl₃, 50 °C) \( \delta \) 7.80-7.75 (m, 2H, ArH), 7.59-7.25 (m, 8H, ArH), 7.00 (d, \( J = 6.3 \) Hz, 2H, ArH), 6.76 (d, \( J = 8.4 \) Hz, 2H, ArH), 6.47 (d, \( J = 9.3 \) Hz, 2H, ArH), 6.31 (s, 1H, CH₂), 5.61 (s, 1H, CH₂), 4.37 (d, \( J = 18.9 \) Hz, 1H, CH₂), 3.84 (d, \( J = 18.9 \) Hz, 1H, CH₂), 3.62 (s, 3H, CH₃), 0.82 (s, 9H, CH₃); \(^{13}\)C NMR (75 MHz, CDCl₃, S20
50 °C) δ 174.2 (C), 168.6 (C), 158.8 (C), 151.1 (C), 139.2 (C), 137.6 (C), 134.5 (C), 130.8 (CH), 130.2 (CH), 129.4 (CH), 128.9 (CH), 128.0 (CH), 125.6 (CH), 125.3 (CH), 124.8 (CH), 117.3 (C), 113.5 (CH), 83.2 (C), 55.3 (CH3), 39.9 (CH2), 28.2 (C), 27.1 (CH3). Anal. Calcd for C34H32N2O5: C, 74.43; H, 5.88; N, 5.11. Found: C, 74.56; H, 5.70; N, 5.36. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IE column (hexane/EtOH = 80/20), flow rate 0.5 mL/min, UV detection 274 nm, tR (major) = 52.9 min, tR (minor) = 38.2 min.

**Synthesis and characterization of 8**

To a solution of 7a (85.2 mg, 0.171 mmol) in THF/H2O (4/1, 1.7 mL) was added LiOH (12.3 mg, 0.513 mmol, 3.0 equiv.) at room temperature. The resulting mixture was warmed to 60 °C and stirred for 24 h. The reaction was quenched by addition of saturated aqueous citric acid (10 mL). The resulting mixture was extracted with EtOAc (50 mL), washed with brine (10 mL), dried over Na2SO4, filtered, and concentrated in vacuo to give a crude material (51.6 mg). To a solution of this crude material in CH2Cl2 (0.90 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI·HCl, 39.3 mg, 0.205 mmol, 1.2 equiv.), p-chlorophenol (26.4 mg, 0.205 mmol, 1.2 equiv.) and DMAP (9.6 mg, 0.086 mmol, 0.5 equiv.) at room temperature under a nitrogen atmosphere. After stirring the solution at the same temperature for 72 h, the reaction mixture was diluted with EtOAc (50 mL), washed with brine (10 mL), dried over Na2SO4, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel, hexane/EtOAc = 4/1 to 2/1) to give 8 (28.9 mg, 52%, 95% ee) as a white solid: Rf = 0.43 (silica gel, hexane/EtOAc = 2/1); M.p. 127–129 °C; [α]D27 +18.2 (c 1.08, CHCl3); IR (KBr) 1757 (C=O), 1703 (C=O) cm⁻¹; 1H NMR (300 MHz, CDCl3) δ 7.42-7.26 (m, 7H, Ar H), 7.02 (d, J = 9.0, Hz, 2H, ArH), 6.81 (d, J = 8.7 Hz, 2H, ArH), 6.74 (d, J = 9.0 Hz, 2H, ArH), 6.28 (s, 1H, CH2), 5.57 (s, 1H, CH2), 3.79-3.70 (m, 4H, CH3, CH2), 3.50 (d, J = 16.8 Hz, 1H, CH2); 13C NMR (75 MHz, CDCl3) δ 170.2 (C), 167.7 (C), 158.2 (C), 148.6 (C), 138.4 (C), 130.8 (C).
136.5 (C), 131.8 (C), 129.7 (C), 129.6 (CH), 128.7 (CH), 128.6 (CH), 128.0 (CH), 127.2 (CH), 122.3 (CH), 118.3 (CH$_2$), 113.8 (CH), 71.9 (C), 55.3 (CH$_3$), 40.9 (CH$_2$). Anal. Calcd for C$_{25}$H$_{20}$ClNO$_4$: C, 69.21; H, 4.65; N, 3.23. Found: C, 69.15; H, 4.79; N, 3.46. The enantiomeric excess was determined by HPLC with a Daicel Chiralpak IF column (hexane/EtOH = 80/20), flow rate 0.5 mL/min, UV detection 274 nm, $t_R$ (major) = 29.6 min, $t_R$ (minor) = 32.8 min.

References


HPLC Chromatographic Conditions

Column: Daicel CHIRALPAK IC (φ 0.46 cm, L 25 cm); Eluent: n–hexane/EtOH = 96/4; Flow rate: 0.5 mL/min; UV detection: 274 nm.

Racemate of 5a

Enantiomerically enriched (+)–5a (96% ee)
HPLC Chromatographic Conditions

Column: Daicel CHIRALPAK IE (φ 0.46 cm, L 25 cm); Eluent: n–hexane/EtOH = 80/20; Flow rate: 0.5 mL/min; UV detection: 274 nm.

Racemate of 5b

Enantiomerically enriched (+)–5b (96% ee)
HPLC Chromatographic Conditions

Column: Daicel CHIRALPAK IE (ϕ 0.46 cm, L 25 cm); Eluent: $n$-hexane/EtOH = 80/20; Flow rate: 0.5 mL/min; UV detection: 274 nm.

Racemate of 5c

![Racemate of 5c graph]

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Enantiomerically enriched (+)--5c (96% ee)

![Enantiomerically enriched (+)--5c graph]

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HPLC Chromatographic Conditions

Column: Daicel CHIRALPAK IE (ϕ 0.46 cm, L 25 cm); Eluent: n–hexane/EtOH = 80/20; Flow rate: 0.5 mL/min; UV detection: 274 nm.

Racemate of 5d

Enantiomerically enriched (+)–5d (96% ee)
HPLC Chromatographic Conditions

Column: Daicel CHIRALPAK IE (ϕ 0.46 cm, L 25 cm); Eluent: $n$-hexane/EtOH = 80/20; Flow rate: 0.5 mL/min; UV detection: 274 nm.

Racemate of 5e

Enantiomerically enriched (+)–5e (94% ee)
HPLC Chromatographic Conditions

Column: Daicel CHIRALPAK IC (ϕ 0.46 cm, L 25 cm); Eluent: \( n \)-hexane/EtOH = 96/4; Flow rate: 0.5 mL/min; UV detection: 274 nm.

Racemate of 5f

Enantiomerically enriched (+)–5f (90% ee)
HPLC Chromatographic Conditions

Column: Daicel CHIRALPAK IC (ϕ 0.46 cm, L 25 cm); Eluent: \( n \)-hexane/EtOH = 96/4; Flow rate: 0.5 mL/min; UV detection: 274 nm.

Racemate of \( 5g \)

Enantiomerically enriched (+)–\( 5g \) (82% ee)
HPLC Chromatographic Conditions

Column: Daicel CHIRALPAK IC (ϕ 0.46 cm, L 25 cm); Eluent: $n$-hexane/EtOH = 96/4; Flow rate: 0.5 mL/min; UV detection: 274 nm.

Racemate of 5h

Enantiomerically enriched (+)–5h (93% ee)
HPLC Chromatographic Conditions

Column: Daicel CHIRALPAK IB (φ 0.46 cm, L 25 cm); Eluent: \( n \)-hexane/EtOH = 96/4; Flow rate: 0.5 mL/min; UV detection: 274 nm.

**Racemate of 5i**

![Graph](image1)

**Enantiomerically enriched (+)-5i (95% ee)**

![Graph](image2)
HPLC Chromatographic Conditions

Column: Daicel CHIRALPAK IC (φ 0.46 cm, L 25 cm); Eluent: $n$–hexane/EtOH = 96/4; Flow rate: 0.5 mL/min; UV detection: 274 nm.

**Racemate of 5j**

![Racemate of 5j](image)

**Enantiomerically enriched (+)–5j (57% ee)**

![Enantiomerically enriched (+)–5j](image)
HPLC Chromatographic Conditions

Column: Daicel CHIRALPAK IC (ϕ 0.46 cm, L 25 cm); Eluent: $n$–hexane/EtOH = 90/10; Flow rate: 0.5 mL/min; UV detection: 274 nm.

Racemate of 5k

![Racemate Chromatogram]

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Enantiomerically enriched (+)–5k (22% ee)

![Enantiomerically enriched Chromatogram]

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HPLC Chromatographic Conditions

Column: Daicel CHIRALPAK IF (Ø 0.46 cm, L 25 cm); Eluent: $n$-hexane/EtOH = 80/20; Flow rate: 0.5 mL/min; UV detection: 274 nm.

Racemate of 7a

\[
\text{NPMP} \quad \text{CON(Boc)Ph} \quad (+)-7a
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TOTAL 386689

Enantiomerically enriched (+)–7a (96% ee, from 5a)

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Enantiomerically enriched (+)-7a (91% ee, from 5b)

Enantiomerically enriched (+)-7a (92% ee, from 5c)
Enantiomerically enriched (+)–7a (92% ee, from 5d)

Enantiomerically enriched (+)–7a (94% ee, from 5e)
Enantiomerically enriched (+)$\text{-}7a$ ($90\%$ ee, from $5f$)

Enantiomerically enriched (+)$\text{-}7a$ ($82\%$ ee, from $5g$)
HPLC Chromatographic Conditions

Column: Daicel CHIRALPAK IE (ϕ 0.46 cm, L 25 cm); Eluent: $n$-hexane/EtOH = 80/20; Flow rate: 0.5 mL/min; UV detection: 274 nm.

**Racemate of 7b**

![Racemate of 7b](image)

**Enantiomerically enriched (+)–7b (92% ee)**

![Enantiomerically enriched (+)–7b (92% ee)](image)
HPLC Chromatographic Conditions

Column: Daicel CHIRALPAK IE (ϕ 0.46 cm, L 25 cm); Eluent: $n$-hexane/EtOH = 80/20; Flow rate: 0.5 mL/min; UV detection: 274 nm.

Racemate of 7c

![Chromatogram of Racemate of 7c](image)

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TOTAL 108294 2750 100

Enantiomerically enriched (+)–7c (95% ee)

![Chromatogram of Enantiomerically enriched (+)–7c](image)

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HPLC Chromatographic Conditions

Column: Daicel CHIRALPAK IE (ϕ 0.46 cm, L 25 cm); Eluent: n–hexane/EtOH = 80/20; Flow rate: 0.5 mL/min; UV detection: 274 nm.

Racemate of 7d

Enantiomerically enriched (+–7d (57% ee)
HPLC Chromatographic Conditions

Column: Daicel CHIRALPAK IE (φ 0.46 cm, L 25 cm); Eluent: n–hexane/EtOH = 80/20; Flow rate: 0.5 mL/min; UV detection: 274 nm.

Racemate of 8

![Racemate of 8](image)

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Enantiomerically enriched (+)–8 (95% ee, from 7a)

![Enantiomerically enriched (+)–8](image)

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\[(^1H\text{ NMR, 300 MHz in }\text{CDCl}_3)\]
(13C NMR, 75 MHz in CDCl₃)
NPMP
NHPh

3b

(\(^1\)H NMR, 300 MHz in CDCl\(_3\))
(13C NMR, 75 MHz in CDCl₃)
$^{1}H$ NMR, 300 MHz in CDCl$_3$
$^{13}$C NMR, 75 MHz in CDCl$_3$
$3d$

($^{1}$H NMR, 300 MHz in CDCl$_3$)
$^{13}$C NMR, 75 MHz in CDCl$_3$
$^{1}H$ NMR, 300 MHz in CDCl$_3$
(\textsuperscript{13}C NMR, 75 MHz in CDCl\textsubscript{3})
(1H NMR, 300 MHz in CDCl$_3$)
5b

($^{13}$C NMR, 75 MHz in CDCl$_3$)
\((1^\text{H} \text{NMR}, 300 \text{ MHz} \text{ in } \text{CDCl}_3)\)
\[ ^{13}\text{C NMR, 75 MHz in CDCl}_3 \]
$^{1}$H NMR, 300 MHz in CDCl$_3$)
$^{13}$C NMR, 75 MHz in CDCl$_3$
\( ^1H\text{NMR, 300 MHz in CDCl}_3 \)

\[
\begin{align*}
\text{NHPh} & \quad \text{O} \\
& \quad \text{NHPMP} \\
\text{NHPh} & \quad \text{O}
\end{align*}
\]
$^{13}$C NMR, 75 MHz in CDCl$_3$
$\text{NHPh}$

$\text{NHPMP}$

$\text{NHPH}$

$\text{5f}$

($^1\text{H NMR, 300 MHz in CDCl}_3$)
$^{13}$C NMR, 75 MHz in CDCl$_3$
$\text{NHPMP}$

$\text{NHPh}$

![NMR Spectrogram](image)

$^{1}\text{H NMR, 300 MHz in CDCl}_3$

X: parts per Million $^1\text{H}$

S62
\(^{13}\text{C NMR, 75 MHz in CDCl}_3\)
S64

(\textsuperscript{1}H NMR, 300 MHz in CDCl\textsubscript{3})
$^{13}$C NMR, 75 MHz in CDCl$_3$
$\text{\textsuperscript{1}H NMR, 300 MHz in CDCl}_3$
\( ^{13}C \text{NMR, 75 MHz in CDCl}_3 \)
(\textsuperscript{1}H NMR, 300 MHz in CDCl\textsubscript{3}, 50 °C)
(\textsuperscript{13}C NMR, 75 MHz in CDCl\textsubscript{3}, 50 °C)
$\text{H NMR, 300 MHz in CDCl}_3$
$^{13}$C NMR, 75 MHz in CDCl$_3$
7a

$^{1}H$ NMR, 300 MHz in CDCl$_3$
$^{13}$C NMR, 75 MHz in CDCl$_3$
(1H NMR, 300 MHz in CDCl$_3$)
\(^{13}\)C NMR, 75 MHz in CDCl\(_3\)
(1H NMR, 300 MHz in CDCl₃)
$^{13}$C NMR, 75 MHz in CDCl$_3$
$^1$H NMR, 300 MHz in CDCl$_3$, 50 °C)
$^{13}$C NMR, 75 MHz in CDCl$_3$, 50 °C

$7d$

$^{13}$C NMR, 75 MHz in CDCl$_3$, 50 °C

S79
(1H NMR, 300 MHz in CDCl$_3$)
\( ^{13} \text{C NMR, 75 MHz in CDCl}_3 \)