Organocatalytic enantioselective conjugate addition of aldehydes to maleimides

Gui-Ling Zhao, Yongmei Xu, Henrik Sundén, Lars Eriksson, Mahmoud Sayah, and Armando Córdova*

The Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-10691 Stockholm, Sweden

Supporting Information

General. Chemicals and solvents were either purchased puriss p.A. from commercial suppliers or purified by standard techniques. Catalyst 8 was synthesized according to literature procedures.1 For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (25 g), Ce(SO₄)₂·H₂O (10 g), conc. H₂SO₄ (60 mL), and H₂O (940 mL) followed by heating or by treatment with a solution of p-anisaldehyde (23 mL), conc. H₂SO₄ (35 mL), acetic acid (10 mL), and ethanol (900 mL) followed by heating. Flash chromatography was performed using silica gel Merck 60 (particle size 0.040-0.063 mm), ¹H NMR and ¹³C NMR spectra were recorded on Varian AS 400. Chemical shifts are given in δ relative to tetramethylsilane (TMS), the coupling constants J are given in Hz. The spectra were recorded in CDCl₃ as solvent at room temperature, TMS served as internal standard (δ = 0 ppm) for ¹H NMR, and CDCl₃ was used as internal standard (δ = 77.0 ppm) for ¹³C NMR. HPLC was carried out using a Waters 2690 Millennium with photodiode array detector. Optical rotations were recorded on a Perkin Elemer 241 Polarimeter (λ = 589 nm, 1 dm cell). High-resolution mass spectra were recorded on a Bruker MicrOTOF spectrometer. The optical rotations were taken at the diastereomeric mixtures as shown in Table 2, since the minor diastereomer was not separable from the major one.

Experimental procedure for the preparation of catalyst 9:
To a solution of \((R)-(+)\)-2-Amino-1,1-diphenyl-1-propanol (2.22 mmol, 0.5 g) dissolved in \(\text{CHCl}_3\) (10 mL) was added triethyl amine (2.88 mmol, 0.4 mL) followed by addition of trimethylsilyl trifluoro-methanesulfonate (2.88 mmol, 0.52 mL) at 0 °C. The reaction mixture was stirred under Ar atmosphere for 16 h. Thereafter, water (10 mL) was added to quench the reaction and the organic layer was washed with saturated \(\text{NaHCO}_3\) (3 x 7mL), the collected aqueous layer was extracted with \(\text{CHCl}_3\) (3 x 20 mL) and the gathered organic layer was dried over \(\text{Na}_2\text{SO}_4\) before the solvent removal under reduced pressure. Silica gel chromatography (pentane: EtOAC= 1:1) was performed to furnish 0.53 g (80 % yield) of the desired pure product.

\[\alpha\]_D^{25} = +29.0 (c = 1.25, \text{CHCl}_3); \text{H NMR (CDCl}_3, 400 MHz) \delta 7.41 (m, 10H), 3.92 (q, J = 6.1, 12.3 Hz, 1H), 0.95 (d, J = 6.6 Hz, 3H), -0.13 (s, 9H); \text{C NMR (CDCl}_3, 100 MHz) \delta 143.5, 143.2, 128.8, 128.7, 127.5, 127.4, 127.3, 127.1, 84.8, 52.9, 18.4, 1.9.

General procedure for the condition screen of Michael addition of propionaldehyde to \(N\)-phenylmaleimide: To a stirred solution of the catalyst (10, 20 or 30 mol %) in solvent (1 mL) was added propionaldehyde (29 mg, 0.5 mmol) and \(N\)-phenylmaleimide (43 mg, 0.25 mmol) at the temperature given in Table 1. The reaction was vigorously stirred and monitored by TLC analysis. The reaction mixture was washed with water and extracted with EtOAc. The organic layer was separated, dried over \(\text{Na}_2\text{SO}_4\) and the solvent was removed. The residue was purified by silica gel (pentane: ethyl acetate = 1:1) to give product 3a.

General procedure for Michael addition of unmodified aldehydes to \(N\)-phenylmaleimides:
To a stirred solution of the catalyst 8 (10 mol %) in \(\text{CHCl}_3\) (1 mL) was added aldehyde (0.5 mmol) and \(N\)-phenylmaleimide (43 mg, 0.25 mmol) at the temperature given in Table 2. The reaction was vigorously stirred and monitored by TLC analysis. The reaction mixture was washed with water and extracted with EtOAc. The organic layer
was separated, dried over Na₂SO₄ and the solvent was removed. The residue was purified by silica gel (pentane: ethyl acetate = 1:2-1:1) to give product 3.

\[
\text{O} \quad \text{NPh} \quad \begin{array}{c}
\text{O} \\
\end{array} \\
\text{H} \quad \\
\text{2-(2,5-Dioxo-1-phenyl-pyrrolidin-3-yl)-propionaldehyde 3a: } [\alpha]_D^{25} = + 76.2 \text{ (c 1.0, CHCl₃). IR (KBr): 3469, 2974, 2881, 1776, 1712, 1598, 1500, 1387, 1187, 1028, 699 cm}^{-1}; \quad \]
\[
\text{1H NMR (CDCl₃, 400 MHz) major diastereomer: } \delta 9.72 \text{ (s, 1H), 7.50-7.24 (m, 5H), 3.44-3.36 (m, 1H), 3.18 (dq, } J = 7.6, 3.6 \text{ Hz, 1H), 3.03 (dd, } J = 18.4, 9.6 \text{ Hz, 1H), 2.52 (dd, } J = 18.4, 5.2 \text{ Hz, 1H), 1.33 (d, } J = 7.6 \text{ Hz, 3H); } \quad \]
\[
\text{13C NMR (CDCl₃, 100 MHz) } \delta 201.4, 177.7, 175.1, 131.8, 129.2, 128.7, 126.4, 47.0, 39.5, 31.6, 9.7; \quad \]
\[
\text{1H NMR (CDCl₃, 400 MHz) minor diastereomer: } \delta 9.62 \text{ (s, 1H), 7.50-7.28 (m, 5H), 3.26 (dq, } J = 7.6, 3.6 \text{ Hz, 1H), 3.11-3.06 (m, 1H), 2.93 (dd, } J = 18.4, 9.6 \text{ Hz, 1H), 2.56 (dd, } J = 18.4, 5.2 \text{ Hz, 1H), 1.39 (d, } J = 7.6 \text{ Hz, 3H). The ee of the product was determined by chiral HPLC analysis (Chiralpak AD column, isohexane/2-propanol = 80/20, 0.5 mL/min, 210 nm, major diastereomer: } t_R \text{ (minor) } = 36.51 \text{ min, } t_R \text{ (major) } = 41.72 \text{ min; minor diastereomer: } t_R \text{ (minor) } = 31.95 \text{ min, } t_R \text{ (major) } = 56.14 \text{ min. HRMS(ESI) the exact mass calculated for [M+Na]⁺ (C₁₃H₁₅NO₄Na) requires } m/z 254.0788, \text{ found } m/z 254.0790.}
\]

\[
\text{O} \quad \text{NPh} \quad \\
\text{2-(2,5-Dioxo-1-phenyl-pyrrolidin-3-yl)-3-methyl-butyraldehyde 3b: } [\alpha]_D^{25} = + 55.1 \text{ (c 1.0, CHCl₃). IR (KBr): 3584, 3020, 2969, 1777, 1713, 1600, 1501, 1388, 1216, 1187, 1046, 758 cm}^{-1}; \quad \]
\[
\text{1H NMR (CDCl₃, 400 MHz) } \delta 9.89 \text{ (d, } J = 1.2 \text{ Hz, 1H), 7.45 (dd, } J = 8.0, 8.0 \text{ Hz, 2H), 7.39 (t, } J = 8.0 \text{ Hz, 1H), 7.28 (d, } J = 8.0 \text{ Hz, 2H), 3.41-3.35 (m, 1H), 3.01 (dd, } J = 18.4, 10.0 \text{ Hz, 1H), 2.69-2.64 (m, 1H), 2.56 (dd, } J = 18.4, 6.0 \text{ Hz, 1H), 2.37-2.27 (m, 1H), 1.17 (d, } J = 6.8 \text{ Hz, 3H), 1.14 (d, } J = 6.8 \text{ Hz, 3H); } \quad \]
\[
\text{13C NMR (CDCl₃, 100 MHz) } \delta 202.7, 177.6, 174.8, 131.9, 129.1, 128.6, 126.4, 59.0, 37.9, 33.3, 28.1, 21.7, 20.3; \quad \]

S3
ee of the product was determined by chiral HPLC analysis (Chiralpak AD column, isohexane/2-propanol = 80/20, 0.5 mL/min, 230 nm, major diastereomer: $t_R$ (minor) = 27.45 min, $t_R$ (major) = 50.89 min; minor diastereomer: $t_R$ (major) = 32.35 min, $t_R$ (minor) = 38.32 min). HRMS(ESI) the exact mass calculated for [M+Na]$^+$ (C$_{15}$H$_{17}$NO$_3$Na) requires $m/z$ 282.1101, found $m/z$ 282.1106.

![Chemical structure](image)

2-(2,5-Dioxo-1-phenyl-pyrrolidin-3-yl)-hexanal 3c: $[\alpha]_D^{25} = + 70.2$ (c 1.0, CHCl$_3$). IR (KBr): 3584, 3019, 2959, 2931, 2861, 1778, 1713, 1501, 1387, 1216, 1185, 755 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 9.73 (s, 1H), 7.47 (dd, $J = 7.2$, 7.2 Hz, 2H), 7.40 (t, $J = 7.2$ Hz, 1H), 7.28 (d, $J = 7.2$ Hz, 2H), 3.34-3.28 (m, 1H), 2.98-2.93 (m, 1H), 2.97 (dd, $J = 18.4$, 9.6 Hz, 1H), 2.53 (dd, $J = 18.4$, 5.6 Hz, 1H), 1.94-1.84 (m, 1H), 1.69-1.61 (m, 1H), 1.51-1.33 (m, 4H), 0.92 (t, $J = 7.2$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 201.8, 177.9, 175.3, 132.2, 129.4, 128.9, 126.7, 52.9, 38.9, 32.6, 30.0, 26.2, 22.8, 14.0; The ee of the product was determined by chiral HPLC analysis (Agilent, Chiralpak AD column, hexane/2-propanol = 80/20, 0.5 mL/min, 210 nm, major diastereomer: $t_R$ (minor) = 27.05 min, $t_R$ (major) = 58.50 min, minor diastereomer: $t_R$ (major) = 31.60 min, $t_R$ (minor) = 34.27 min). HRMS(ESI) the exact mass calculated for [M+Na]$^+$ (C$_{16}$H$_{19}$NO$_3$Na) requires $m/z$ 296.1257, found $m/z$ 296.1268.

![Chemical structure](image)

2-(2,5-Dioxo-1-phenyl-pyrrolidin-3-yl)-3-phenyl-propionaldehyde 3d: $[\alpha]_D^{25} = - 9.4$ (c 0.5, CHCl$_3$); IR (KBr): 3584, 3020, 2977, 2400, 1779, 1712, 1600, 1500, 1390, 1216, 1046, 759 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 9.76 (1H, s), 7.46 (dd, $J = 7.6$, 7.6 Hz, 2H), 7.37 (t, $J = 7.6$ Hz, 1H), 7.36-7.22 (m, 7H), 3.32-3.29 (m, 2H), 3.18-3.13 (m, 2H),
2.94 (dd, $J = 18.4, 10.0$ Hz, 1H), 2.57 (dd, $J = 18.4, 6.0$ Hz, 1H). $^{13}$C NMR (CDCl$_3$, 100 MHz) δ 201.1, 177.8, 175.1, 137.4, 132.1, 129.34, 129.27, 129.2, 128.8, 127.4, 126.7, 55.3, 37.4, 33.2, 32.7. The ee of the product was determined by chiral HPLC analysis (Chiralpak AD column, isohexane/2-propanol = 95/5, 0.5 mL/min, 210 nm, major diastereomer: $t_R$ (minor) = 122.278 min, $t_R$ (major) = 189.645 min, minor diastereomer: $t_R$ (major) = 169.577 min, $t_R$ (minor) = 234.860 min). HRMS(ESI) the exact mass calculated for [M+Na]$^+$ (C$_{19}$H$_{17}$NO$_3$Na) requires m/z 330.1101, found m/z 330.1108.

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

3-(tert-Butyldimethylsilyloxy)-2-(2,5-dioxo-1-phenylpyrrolidin-3-yl)propanal 3e: $[\alpha]_D^{25} = +4.7$ (c 1, CHCl$_3$); IR (KBr): 3474, 3104, 2954, 2929, 2857, 1771, 1722, 1714, 1598, 1504, 1457, 1392, 1385, 1146, 831, 699 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) δ major diastereomer 9.70 (d, $J = 1.5$ Hz, 1H), 7.29-7.51 (m, 5H), 4.30 (dd, $J = 5.1, 10.8$ Hz, 1H), 4.10 (dd, $J = 3.9, 10.8$ Hz, 1H), 3.35-3.40 (m, 1H), 3.12-3.20 (m, 1H), 3.03 (dd, $J = 8.7, 12.3$ Hz, 1H), 2.84-2.93 (m, 1H), 0.90 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); minor diastereomer 9.84 (d, $J = 1.5$ Hz, 1H), 7.29-7.51 (m, 5H), 4.23 (dd, $J = 5.7, 10.8$ Hz, 1H), 4.15 (dd, $J = 5.1, 10.8$ Hz, 1H), 3.45-3.51 (m, 1H), 3.12-3.20 (m, 1H), 2.84-2.93 (m, 2H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ major diastereomer 200.9, 178.3, 175.9, 129.3, 128.8, 126.8, 126.2, 100.2, 61.4, 54.3, 39.1, 32.7, 25.9, -5.4, -5.5; minor diastereomer 201.0, 178.3, 175.9, 129.3, 128.7, 128.1, 126.5, 99.5, 60.4, 54.7, 37.6, 33.0, 25.9, -5.4, -5.5; The enantiomeric excess was determined by HPLC (Chiralpak ODH column, isohexane/2-propanol = 97/3, 0.5 mL/min, 230 nm, major diastereomer: $t_R$ (minor) = 99.895 min, $t_R$ (major) = 103.859 min; minor diastereomer: $t_R$ (minor) = 121.895 min, $t_R$ (major) = 127.034 min). HRMS(ESI) the exact mass calculated for [M+Na]$^+$ (C$_{19}$H$_{27}$NO$_4$SiNa) requires m/z 384.1602, found m/z 384.1615.
2-[1-(4-Bromo-phenyl)-2,5-dioxo-pyrrolidin-3-yl]-3-methyl-butyraldehyde 3f: [α]D25 = + 43.2 (c 1.0, CHCl3). IR (KBr): 3479, 3020, 2965, 2928, 1780, 1714, 1388, 1215, 1184, 1071, 758 cm⁻¹; ¹H NMR (CDCl3, 300 MHz) δ 9.89 (d, J = 1.5 Hz, 1H), 7.20 (d, J = 8.7 Hz, 2H), 7.59 (d, J = 8.7 Hz, 2H), 3.33-3.40 (m, 1H), 3.02 (dd, J = 9.6, 18.0 Hz, 1H), 2.64-2.69 (m, 1H), 2.56 (dd, J = 6.0, 18.0 Hz, 1H), 2.31-2.39 (m, 1H), 1.19 (d, J = 6.9 Hz, 3H), 1.15 (d, J = 6.9 Hz, 3H); ¹³C NMR (CDCl3, 75 MHz) δ 202.8, 177.4, 174.7, 132.5, 131.0, 128.2, 122.6, 59.5, 37.9, 33.7, 28.3, 22.0, 20.6. The ee of the product was determined by chiral HPLC analysis (Agilent, Chiralpak AD column, hexane/2-propanol = 80/20, 0.5 mL/min, 230 nm, major diastereomer: tR (minor) = 16.827 min, tR (major) = 43.009 min; minor diastereomer: tR (major) = 19.000 min, tR (minor) = 31.488 min). HRMS(ESI) the exact mass calculated for [M+Na]+ (C15H16NO3BrNa) requires m/z 360.0206, found [M+2+Na]+ m/z 362.0197.

2-(1-Benzyl-2,5-dioxo-pyrrolidin-3-yl)-3-methyl-butyraldehyde 3g: [α]D25 = + 18.8 (c 1, CHCl3); IR (KBr): 3459, 3033, 2966, 2876, 2339, 1776, 1732, 1714, 1699, 1683, 1497, 1434, 1403, 1348, 1169, 1083, 756 cm⁻¹; ¹H NMR (TMS, CDCl3, 300 MHz) δ 9.82 (d, J = 2.6 Hz, 1H), 7.24- 7.39 (m, 5H), 4.65 (d, J = 4.1 Hz, 2H), 3.24 (m, 1H), 2.85 (dd, J = 10.0, 18.7 Hz, 1H ), 2.53 (m, 1H), 2.44 (dd, J = 6.0, 17.8 Hz, 1H), 2.19 (m, 1H), 1.08 (d, J = 6.9 Hz, 3H), 1.02 (d, J = 6.9 Hz, 3H); ¹³C NMR (TMS, CDCl3, 75 MHz) δ 202.6, 178.2, 175.4, 135.5, 128.8, 128.6, 127.9, 58.4, 42.5, 38.1, 32.9, 28.0, 20.1, 19.9; The enantiomeric excess was determined by chiral HPLC analysis (Chiralpak ODH column, iso-hexane/2-propanol = 92:8, λ =210 nm, 0.5 mL/min), major diastereomer: tR (major) =
73.408 min, $t_R = (\text{minor})$ 85.447 min.; minor diastereomer: $t_R$ (minor) = 52.848 min, $t_R$ (major) = 116.344 min. HRMS(ESI) the exact mass calculated for $[\text{M+Na}]^+$ ($C_{16}H_{19}NO_3Na$) requires $m/z$ 296.1257, found $m/z$ 296.1271.

2-(2,5-Dioxo-1-phenyl-pyrrolidin-3-yl)-2-methyl-propionaldehyde 3h: IR (KBr): 3340, 2934, 2650, 1773, 1710, 1667, 1477, 1396, 1183, 1159, 1149, 754 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 9.52 (s, 1H), 7.47 (dd, $J = 6.4, 7.2$ Hz, 2H), 7.40 (t, $J = 6.4$ Hz, 1H), 7.28 (d, $J = 7.2$ Hz, 2H), 3.16 (dd, $J = 5.6, 9.6$ Hz, 1H), 2.99 (dd, $J = 9.6, 18.0$ Hz, 1H), 2.62 (dd, $J = 5.6, 18.0$ Hz, 1H), 1.34 (s, 3H), 1.29 (s, 3H). $^{13}$C NMR (CDCl$_3$, 100 MHz) $\delta$ 202.9, 177.0, 174.9, 131.9, 129.3, 128.8, 126.6, 48.6, 45.1, 31.9, 20.4, 19.6; The ee of the product was determined by chiral HPLC analysis (Agilent, Chiralpak ODH column, hexane/2-propanol = 75/25, 0.5 mL/min, 210 nm, $t_R$ (minor) = 42.881 min, $t_R$ (major) = 52.803 min). HRMS(ESI) the exact mass calculated for $[\text{M+Na}]^+$ ($C_{14}H_{15}NO_3Na$) requires $m/z$ 268.0944, found $m/z$ 268.0956.

Reaction procedure for the oxidation of 3f:
To a stirred solution of aldehyde 3f (15 mg, 0.044 mmol) in $t$-BuOH/H$_2$O (5/1, 0.6 mL) were added KH$_2$PO$_4$ (12 mg, 0.088 mmol), 2-methyl-2-butene (24 mg, 0.35 mmol) and NaClO$_2$ (16 mg, 0.178 mmol). After stirring the mixture overnight the resulting yellow solution turned colorless. The solvent was removed and the residue was extracted with EtOAc, washed with H$_2$O, brine, dried over Na$_2$SO$_4$. The solvent was removed and the
residue was purified by silica gel (pentane: ethyl acetate = 1:1) to give the product 15 mg (yield 94%).

\[
\begin{align*}
\text{HO} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{O} & \quad \text{Br}
\end{align*}
\]

2-(1-(4-Bromophenyl)-2,5-dioxopyrrolidin-3-yl)-3-methylbutanoic acid 10: \([\alpha]_D^{25} = +11.4 \text{ (c 0.5, CHCl}_3)\). IR (KBr): 3337, 2963, 2926, 1779, 1713, 1491, 1392, 1182, 1069, 1014 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta 7.56 (d, J = 8.7 \text{ Hz, 2H}), 7.17 (d, J = 8.7 \text{ Hz, 2H}), 3.35-3.41 (m, 1H), 3.15-3.23 (m, 1H), 3.06 (dd, J = 9.6, 18.6 Hz, 1H), 2.96 (dd, J = 5.4, 9.6 Hz, 1H), 2.66 (dd, J = 6.0, 18.6 Hz, 1H), 2.28-2.37 (m, 1H), 1.11 (d, J = 6.9 Hz, 3H), 1.04 (d, J = 6.9 Hz, 3H); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta 178.3, 176.5, 174.5, 132.5, 130.9, 128.1, 122.7, 39.6, 33.3, 32.6, 28.3, 21.2, 20.1\). HRMS(ESI) the exact mass calculated for [M+Na]\(^+\) (C\(_{15}\)H\(_{16}\)NO\(_4\)BrNa) requires \(m/z\) 376.0155, found \(m/z\) 376.0169.