Asymmetric vinylogous Michael addition of 5-substituted-furan-2(3H)-ones to \(\alpha,\beta\)-unsaturated-\(\gamma\)-lactam

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1. General information

Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification. NMR spectra were acquired on a Bruker Ultra Shield 700 instrument, running at 700 MHz for $^1$H and 176 MHz for $^{13}$C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals (CDCl$_3$: 7.26 ppm for $^1$H NMR, 77.16 ppm for $^{13}$C NMR). Mass spectra were recorded on a Bruker Maxis Impact spectrometer using electrospray (ES+) ionization (referenced to the mass of the charged species). Optical rotations were measured on a Perkin-Elmer 241 polarimeter and $[\alpha]_D$ values are given in deg•cm•g$^{-1}$•dm$^{-1}$; concentration c is listed in g•(100 mL)$^{-1}$. Analytical thin layer chromatography (TLC) was performed using pre-coated aluminum-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation. The enantiomeric ratio (er) of the products was determined by chiral stationary phase UPC$^2$ (Daicel Chiralpak IB column). In order to find conditions for the separation of enantiomers, products 3 with low enantiomeric enrichment were prepared using equimolar amount of pseudoenantiomeric catalyst 5d and 5e (20 mol%) as catalyst of the reaction. Silica gel (Silica gel 60, 230-400 mesh, Fluka) was used for flash chromatography (FC). 5-Substituted-furane-2(3H)-ones 1$^1$ and N-Boc-protected $\alpha,\beta$-unsaturated-$\gamma$-lactam 2$^2$ were synthetized according to literature procedures.


2. Asymmetric vinylogous Michael addition involving α,β-unsaturated-γ-lactam 2 as an acceptor - general procedure

![Diagram of the reaction](image)

In an ordinary 4 mL glass vial, equipped with a magnetic stirring bar and a screw cap, catalyst 5e (0.2 equiv, 0.01 mmol, 5.6 mg), 5-substituted-furane-2(3H)-one 1 (2.0 equiv, 0.1 mmol) and N-Boc-protected α,β-unsaturated-γ-lactam 2 (1.0 equiv, 0.05 mmol, 9.16 mg) were dissolved in toluene (0.1 mL) and stirred for 24-72 h at 40 °C using heating block. Crude product 3 was purified by the flash chromatography on silica gel.

(R)-tert-Butyl 4-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3a). Following the general procedure, pure product 3a was isolated after 72 h by FC on silica (hexane:ethyl acetate 2:1) in 80% yield (11.3 mg, >20:1 dr) as a white solid. \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 7.35 (d, \(J = 5.7\) Hz, 1H), 6.14 (d, \(J = 5.7\) Hz, 1H), 3.88 (dd, \(J = 11.1, 8.4\) Hz, 1H), 3.60 (dd, \(J = 11.1, 7.9\) Hz, 1H), 2.75 – 2.67 (m, 1H), 2.44 (dd, \(J = 17.4, 8.9\) Hz, 1H), 2.26 (dd, \(J = 17.4, 9.4\) Hz, 1H), 1.52 (s, 3H), 1.51 (s, 9H). \(^13\)C NMR (176 MHz, CDCl\(_3\)) \(\delta\) 171.5, 171.4, 157.7, 149.7, 122.3, 87.4, 83.7, 46.9, 37.4, 34.1, 28.1 (3C), 22.5. HRMS: calculated for \([C_{14}H_{19}NO_5+Na]^+: 304.1161;\) found: 304.1156. \([\alpha]_D^{22} = 21.4^\circ\) (c = 1.0, CHCl\(_3\)). The er was determined by UPC\(^2\) using a chiral Chiralpack IB column gradient from 100% CO\(_2\) up to 40%; \(i\)-PrOH, 2.5 mL/min; \(\tau_{\text{minor}} = 3.31\) min, \(\tau_{\text{major}} = 3.62\) min, (97:3 er).
(R)-tert-Butyl 2-oxo-4-((R)-5-oxo-2-phenyl-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3b). Following the modified general procedure (CH₂Cl₂ was used as a solvent), pure product 3b was isolated after 72 h by FC on silica (hexane:ethyl acetate 2:1) in 89% yield (15.3 mg, >20:1 dr) as a white solid. ¹H NMR (700 MHz, CDCl₃) δ 7.63 (d, J = 5.7 Hz, 1H), 7.45 – 7.33 (m, 5H), 6.16 (d, J = 5.6 Hz, 1H), 3.60 (dd, J = 11.3, 8.4 Hz, 1H), 3.53 (dd, J = 11.3, 8.4 Hz, 1H), 3.11 (dq, J = 9.8, 8.5 Hz, 1H), 2.43 (dd, J = 17.4, 8.8 Hz, 1H), 2.31 (dd, J = 17.4, 9.7 Hz, 1H), 1.47 (s, 9H). ¹³C NMR (176 MHz, CDCl₃) δ 171.3, 171.3, 157.0, 149.9, 136.7, 129.5 (2C), 129.1, 125.1 (2C), 121.3, 89.8, 83.6, 46.9, 38.6, 33.7, 28.1 (3C). HRMS: calculated for [C₁₉H₂₁NO₃⁺Na⁺]: 366.1317; found: 366.1310. [α]D²² = -64.4° (c = 1.0, CHCl₃). The er was determined by UPC² using a chiral Chiralpack IB column gradient from 100% CO₂ up to 40%; i-PrOH, 2.5 mL/min; τminor = 3.75 min, τmajor = 4.33 min, (97:3 er).

(R)-tert-Butyl 4-((R)-2-(4-fluorophenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3c). Following the modified general procedure (CH₂Cl₂ was used as a solvent), pure product 3c was isolated after 72 h by FC on silica (hexane:ethyl acetate 2:1) in 99% yield (18.0 mg, >20:1 dr) as a white solid. ¹H NMR (700 MHz, CDCl₃) δ 7.61 (d, J = 5.6 Hz, 1H), 7.41 – 7.35 (m, 2H), 7.15 – 7.09 (m, 2H), 6.17 (d, J = 5.6 Hz, 1H), 3.60 – 3.50 (m, 2H), 3.12 – 3.04 (m, 1H), 2.43 (dd, J = 17.4, 8.8 Hz, 1H), 2.29 (dd, J = 17.4, 9.6 Hz, 1H), 1.48 (s, 9H). ¹³C NMR (176 MHz, CDCl₃) δ 171.1, 171.0, δ 162.9 (d, JCF = 249.3 Hz, 1C), 156.9, 149.8, 132.6 (d, JCF = 3.3 Hz, 1C), 127.0 (d, JCF = 8.3 Hz, 2C), 121.5, 116.5 (d, JCF = 22.0 Hz, 2C), 89.4, 83.6, 46.8, 38.6, 33.7, 28.1 (3C). HRMS: calculated for [C₁₉H₂₀FNO₃⁺Na⁺]: 384.1223; found: 384.1232. [α]D²³ = -84.2° (c = 1.0, CHCl₃). The er was determined by UPC² using a chiral Chiralpack IB column gradient from 100% CO₂ up to 40%; i-PrOH, 2.5 mL/min; τminor = 3.60 min, τmajor = 4.12 min, (96:4 er).

(R)-tert-Butyl 4-((R)-2-(4-chlorophenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3d). Following the general procedure, pure product 3d was isolated after 24 h by FC on silica (hexane:ethyl acetate 2:1) in 95% yield (17.9 mg, >20:1 dr) as a light-yellow solid. ¹H NMR (700 MHz, CDCl₃) δ 7.59 (d, J = 5.7 Hz, 1H), 7.44 – 7.38 (m, 2H), 7.38 – 7.32 (m, 2H), 6.18 (d, J = 5.6 Hz, 1H), 3.60 – 3.50 (m, 2H), 3.07
(dq, \(J = 9.7, 8.5\) Hz, 1H), 2.43 (dd, \(J = 17.4, 8.8\) Hz, 1H), 2.29 (dd, \(J = 17.4, 9.7\) Hz, 1H), 1.48 (s, 9H). \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \(\delta 171.0, 170.9, 156.7, 149.8, 135.3, 135.2, 129.7\) (2C), 126.5 (2C), 121.6, 89.3, 83.7, 46.8, 38.5, 33.6, 28.1 (3C). HRMS: calculated for [C\(_{19}\)H\(_{20}\)ClNO\(_5\)+Na\(^+\)]: 400.0928; found: 400.0932. \([\alpha]\)\(_D^{23}\) = -72.4° (c = 1.0, CHCl\(_3\)). The er was determined by UPC\(^2\) using a chiral Chiralpack IB column gradient from 100% CO\(_2\) up to 40%; i-PrOH, 2.5 mL/min; \(\tau_{\text{minor}} = 3.94\) min, \(\tau_{\text{major}} = 4.48\) min, (97:3 er).

(R)-tert-Butyl 4-((R)-2-(2-chlorophenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3e). Following general procedure, pure product 3e was isolated after 24 h by FC on silica (hexane:ethyl acetate 2:1) in 86% yield (16.3 mg, >20:1 dr) as a white solid. \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta 8.29\) (d, \(J = 5.7\) Hz, 1H), 7.76 – 7.66 (m, 1H), 7.49 – 7.40 (m, 1H), 7.38 – 7.32 (m, 2H), 6.16 (d, \(J = 5.7\) Hz, 1H), 3.86 – 3.77 (m, 1H), 3.59 (dd, \(J = 10.9, 9.2\) Hz, 1H), 3.39 (dd, \(J = 10.9, 8.7\) Hz, 1H), 2.39 (dd, \(J = 17.2, 8.7\) Hz, 1H), 2.28 (dd, \(J = 17.2, 10.6\) Hz, 1H), 1.48 (s, 9H). \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \(\delta 171.0, 170.9, 156.7, 150.1, 134.3, 131.7, 130.7, 130.1, 128.3, 128.0, 121.7, 89.4, 83.5, 47.0, 34.8, 33.2, 28.1\) (3C). HRMS: calculated for [C\(_{19}\)H\(_{20}\)ClNO\(_5\)+Na\(^+\)]: 400.0928; found: 400.0926. \([\alpha]\)\(_D^{23}\) = -49.9° (c = 1.0, CHCl\(_3\)). The er was determined by UPC\(^2\) using a chiral Chiralpack IB column gradient from 100% CO\(_2\) up to 40%; i-PrOH, 2.5 mL/min; \(\tau_{\text{minor}} = 3.42\) min, \(\tau_{\text{major}} = 4.22\) min, (72:28 er).

(R)-tert-Butyl 4-((R)-2-(4-bromophenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3f). Following general procedure, pure product 3f was isolated after 24 h by FC on silica (hexane:ethyl acetate 2:1) in 97% yield (20.5 mg, >20:1 dr) as a white solid. \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta 7.59\) (d, \(J = 5.6\) Hz, 1H), 7.75 – 7.55 (m, 2H), 7.31 – 7.29 (m, 2H), 6.17 (d, \(J = 5.6\) Hz, 1H), 3.59 – 3.51 (m, 2H), 3.07 (dq, \(J = 9.7, 8.5\) Hz, 1H), 2.42 (dd, \(J = 17.4, 8.8\) Hz, 1H), 2.29 (dd, \(J = 17.4, 9.7\) Hz, 1H), 1.48 (s, 9H). \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \(\delta 171.0, 170.9, 156.7, 149.8, 135.8, 132.7\) (2C), 126.8 (2C), 123.4, 121.5, 89.3, 83.7, 46.8, 38.4, 33.6, 28.1\) (3C). HRMS: calculated for [C\(_{19}\)H\(_{20}\)BrNO\(_5\)+Na\(^+\)]: 444.0425; found: 444.0425. \([\alpha]\)\(_D^{23}\) = -78.2° (c = 1.0, CHCl\(_3\)). The er was determined by UPC\(^2\) using a chiral Chiralpack IB column gradient from 100% CO\(_2\) up to 40%; i-PrOH, 2.5 mL/min; \(\tau_{\text{minor}} = 3.97\) min, \(\tau_{\text{major}} = 4.50\) min, (97:3 er).
(R)-tert-Butyl 2-oxo-4-((R)-5-oxo-2-(p-tolyl)-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3g). Following general procedure, pure product 3g was isolated after 24 h by FC on silica (hexane:ethyl acetate 2:1) in 94% yield (16.8 mg, >20:1 dr) as a white solid. $^1$H NMR (700 MHz, CDCl$_3$) δ 7.61 (d, $J = 5.7$ Hz, 1H), 7.28 – 7.26 (m, 2H), 7.24 – 7.19 (m, 2H), 6.14 (d, $J = 5.6$ Hz, 1H), 3.61 – 3.51 (m, 2H), 3.09 (dq, $J = 9.6, 8.4$ Hz, 1H), 2.42 (dd, $J = 17.4, 8.8$ Hz, 1H), 2.35 (s, 3H), 2.30 (dd, $J = 17.4, 9.7$ Hz, 1H), 1.47 (s, 9H). $^{13}$C NMR (176 MHz, CDCl$_3$) δ 171.4, 157.3, 149.9, 139.1, 133.6, 130.1 (2C), 125.0 (2C), 121.1, 89.9, 83.5, 47.0, 38.5, 33.7, 28.1 (3C), 21.2. HRMS: calculated for C$_{20}$H$_{23}$NO$_5$+Na$^+$: 380.1474; found: 380.1482. [$\alpha$]$_D^{23} = -62.8^\circ$ (c = 1.0, CHCl$_3$). The er was determined by UPC$^2$ using a chiral Chiralpack IB column gradient from 100% CO$_2$ up to 40%; i-PrOH, 2.5 mL/min; $\tau_{\text{minor}} = 3.70$ min, $\tau_{\text{major}} = 4.28$ min, (96:4 er).

(R)-tert-Butyl 4-((R)-2-((1,1'-biphenyl)-4-yl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3h). Following general procedure, pure product 3h was isolated after 24 h by FC on silica (hexane:ethyl acetate 2:1) in 98% yield (20.6 mg, >20:1 dr) as a transparent solid. $^1$H NMR (700 MHz, CDCl$_3$) δ 7.66 (d, $J = 5.6$ Hz, 1H), 7.65 – 7.63 (m, 2H), 7.59 – 7.55 (m, 2H), 7.48 – 7.43 (m, 4H), 7.41 – 7.36 (m, 1H), 6.18 (d, $J = 5.7$ Hz, 1H), 3.67 – 3.57 (m, 2H), 3.16 (dq, $J = 9.7, 8.5$ Hz, 1H), 2.46 (dd, $J = 17.4, 8.8$ Hz, 1H), 2.34 (dd, $J = 17.4, 9.7$ Hz, 1H), 1.48 (s, 9H). $^{13}$C NMR (176 MHz, CDCl$_3$) δ 171.2 (2C), 157.1, 149.9, 142.1, 140.0, 135.5, 129.1 (2C), 128.1 (2C), 128.0, 127.2 (2C), 125.6 (2C), 121.4, 89.7, 83.6, 47.0, 38.5, 33.7, 28.1 (3C). HRMS: calculated for C$_{25}$H$_{25}$NO$_5$+Na$^+$: 442.1630; found: 442.1631. [$\alpha$]$_D^{23} = -118.6^\circ$ (c = 1.0, CHCl$_3$). The er was determined by UPC$^2$ using a chiral Chiralpack IB column gradient from 100% CO$_2$ up to 40%; i-PrOH, 2.5 mL/min; $\tau_{\text{minor}} = 4.51$ min, $\tau_{\text{major}} = 5.14$ min, (97:3 er).

(R)-tert-Butyl 4-((R)-2-(4-methoxyphenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3i). Following general procedure, pure product 3i was isolated after 24 h by FC on silica (hexane:ethyl acetate 2:1) in 91% yield (17.0 mg, >20:1 dr) as a white solid. $^1$H NMR (700 MHz, CDCl$_3$) δ 7.60 (d, $J = 5.6$ Hz, 1H),
7.33 – 7.27 (m, 2H), 6.96 – 6.89 (m, 2H), 6.14 (d, J = 5.6 Hz, 1H), 3.81 (s, 3H), 3.62 – 3.53 (m, 2H), 3.07 (dq, J = 9.4, 8.4 Hz, 1H), 2.42 (dd, J = 17.5, 8.8 Hz, 1H), 2.30 (dd, J = 17.4, 9.5 Hz, 1H), 1.48 (s, 9H).\(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \(\delta\) 171.4 (2C), 160.1, 157.2, 149.9, 128.5, 126.4 (2C), 121.1, 114.8 (2C), 89.8, 83.5, 55.5, 47.0, 38.5, 33.8, 28.1 (3C). HRMS: calculated for [C\(_{20}\)H\(_{23}\)NO\(_5\)+Na\(^{+}\)]: 396.1423; found: 396.1421. \([\alpha]_D^{23} = -71.6^\circ\) (c = 1.0, CHCl\(_3\)). The er was determined by UPC\(^2\) using a chiral Chiralpack IB column gradient from 100% CO\(_2\) up to 40%; \(i\)-PrOH, 2.5 mL/min; \(\tau_{\text{minor}} = 3.99\) min, \(\tau_{\text{major}} = 4.54\) min, (97:3 er).

(R)-tert-Butyl 4-((R)-2-(3,4-dimethoxyphenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3j). Following general procedure, pure product 3j was isolated after 24 h by FC on silica (hexane:ethyl acetate 2:1) in 98% yield (19.8 mg, \(>20:1\) dr) as a light-yellow solid. \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 7.61 (d, \(J = 5.7\) Hz, 1H), 6.91 – 6.84 (m, 3H), 6.15 (d, \(J = 5.7\) Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.62 – 3.53 (m, 2H), 3.08 (dq, \(J = 9.4, 8.4\) Hz, 1H), 2.42 (dd, \(J = 17.4, 8.8\) Hz, 1H), 2.30 (dd, \(J = 17.5, 9.6\) Hz, 1H), 1.48 (s, 9H). \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \(\delta\) 171.3, 171.3, 157.2, 149.8, 149.8, 149.6, 129.0, 121.1, 117.7, 111.7, 108.3, 89.7, 83.5, 56.3, 56.2, 47.0, 38.7, 33.8, 28.1 (3C). HRMS: calculated for [C\(_{21}\)H\(_{25}\)NO\(_7\)+Na\(^{+}\)]: 426.1529; found: 426.1531. \([\alpha]_D^{23} = -88.5^\circ\) (c = 1.0, CHCl\(_3\)). The er was determined by UPC\(^2\) using a chiral Chiralpack IB column gradient from 100% CO\(_2\) up to 40%; \(i\)-PrOH, 2.5 mL/min; \(\tau_{\text{minor}} = 3.96\) min, \(\tau_{\text{major}} = 4.41\) min, (98:2 er).

(R)-tert-Butyl 2-oxo-4-((R)-5-oxo-2-propyl-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3k). Following general procedure, pure product 3k was isolated after 96 h by FC on silica (hexane:ethyl acetate 2:1) in 45% yield (7.0 mg, \(>20:1\) dr) as a white solid. \(^1\)H NMR (700 MHz, CDCl\(_3\)) \(\delta\) 7.27 (d, \(J = 5.7\) Hz, 1H), 6.17 (d, \(J = 5.7\) Hz, 1H), 3.86 (dd, \(J = 11.1, 8.4\) Hz, 1H), 3.58 (dd, \(J = 11.1, 8.2\) Hz, 1H), 2.80 – 2.72 (m, 1H), 2.40 (dd, \(J = 17.4, 8.8\) Hz, 1H), 2.24 (dd, \(J = 17.3, 9.7\) Hz, 1H), 1.85 (ddd, \(J = 14.1, 11.7, 4.7\) Hz, 1H), 1.74 (ddd, \(J = 14.2, 11.7, 5.0\) Hz, 1H), 1.51 (s, 9H), 1.32 – 1.26 (m, 1H), 1.23 – 1.17 (m, 1H), 0.93 (t, \(J = 7.4\) Hz, 3H). \(^{13}\)C NMR (176 MHz, CDCl\(_3\)) \(\delta\) 171.7, 171.5, 156.6, 149.7, 123.0, 90.0, 83.6, 46.8, 37.3, 36.5, 34.0, 28.1 (3C), 16.8, 14.1. HRMS: calculated for [C\(_{16}\)H\(_{23}\)NO\(_5\)+Na\(^{+}\)]: 332.1474; found: 332.1476. \([\alpha]_D^{22} = 7.3\) (c = 1.0, CHCl\(_3\)). The er was determined by UPC\(^2\) using a chiral
Chiralpack IB column gradient from 100% CO$_2$ up to 40%; $i$-PrOH, 2.5 mL/min; $\tau_{\text{minor}} = 3.05$ min, $\tau_{\text{major}} = 3.55$ min, (98:2 er).

(R)-tert-Butyl 2-oxo-4-((R)-5-oxo-2-isopropyl-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3l). Following general procedure, pure product 3l was isolated after 96 h by FC on silica (hexane:ethyl acetate 2:1) in 43% yield (6.6 mg, >20:1 dr) as a yellow oil. $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.27 (d, $J = 5.8$ Hz, 1H), 6.22 (d, $J = 5.8$ Hz, 1H), 3.87 (dd, $J = 10.9$, 8.7 Hz, 1H), 2.22 – 2.15 (m, 2H), 1.52 (s, 9H), 1.03 (d, $J = 7.0$ Hz, 3H), 0.90 (d, $J = 6.7$ Hz, 3H). $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 171.7, 171.5, 155.0, 149.8, 123.8, 92.4, 83.6, 46.7, 34.2, 33.9, 32.4, 28.2 (3C), 18.1, 16.7. HRMS: calculated for [C$_{16}$H$_{23}$NO$_5$+Na$^+$]: 332.1474; found: 332.1476. $[^{[a]}]_D^{22} = -6.3$ (c = 1.0, CHCl$_3$). The er was determined by UPC$^2$ using a chiral Chiralpack IB column gradient from 100% CO$_2$ up to 40%; $i$-PrOH, 2.5 mL/min; $\tau_{\text{minor}} = 3.18$ min, $\tau_{\text{major}} = 3.81$ min, (97:3 er).

(R)-tert-Butyl 2-oxo-4-((R)-5-oxo-2-allyl-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3m). Following general procedure, pure product 3m was isolated after 96 h by FC on silica (hexane:ethyl acetate 2:1) in 71% yield (11.0 mg, >20:1 dr) as a white solid. $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.31 (d, $J = 5.7$ Hz, 1H), 6.19 (d, $J = 5.7$ Hz, 1H), 5.70 – 5.55 (m, 1H), 5.24 – 5.14 (m, 2H), 3.87 (dd, $J = 11.1$, 8.4 Hz, 1H), 3.60 (dd, $J = 11.1$, 8.2 Hz, 1H), 2.81 (dq, $J = 9.8$, 8.5 Hz, 1H), 2.56 (ddt, $J = 12.5$, 7.4, 1.2 Hz, 2H), 2.40 (dd, $J = 17.4$, 8.9 Hz, 1H), 2.24 (dd, $J = 17.4$, 9.8 Hz, 1H), 1.51 (s, 9H). $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 171.4, 171.3, 156.2, 149.7, 129.7, 123.4, 121.4, 89.2, 83.7, 46.7, 40.1, 35.7, 33.9, 28.1 (3C). HRMS: calculated for [C$_{16}$H$_{21}$NO$_5$+Na$^+$]: 330.1317; found: 330.1319. $[^{[a]}]_D^{22} = -3.6$ (c = 1.0, CHCl$_3$). The er was determined by UPC$^2$ using a chiral Chiralpack IB column gradient from 100% CO$_2$ up to 40%; $i$-PrOH, 2.5 mL/min; $\tau_{\text{minor}} = 3.27$ min, $\tau_{\text{major}} = 3.62$ min, (98:2 er).
3. Synthesis of (R)-tert-butyl 4-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-y1)-2- oxopyrrolidine-1-carboxylate (3a) on a 1 mmol scale

In an ordinary 12 mL glass vial, equipped with a magnetic stirring bar and a screw cap, catalyst 5e (0.2 equiv, 0.2 mmol, 112 mg), 5-methylfuran-2(3H)-one 1a (2.0 equiv, 2 mmol, 180 μl) and N-Boc-protected α,β-unsaturated-γ-lactam 2 (1.0 equiv, 1 mmol, 183.2 mg) were dissolved in toluene (2 mL) and stirred for 4 days at 40 °C using heating block. Pure product 3a was isolated by FC on silica (hexane:ethyl acetate 2:1) in 91% yield (255.0 mg, >20:1 dr) as a white solid. Spectral data were in accordance with the data reported above. The er was determined by UPC² using a chiral Chiralpack IB column gradient from 100% CO₂ up to 40%; i-PrOH, 2.5 mL/min; τ_{minor} = 3.31 min, τ_{major} = 3.62 min, (97:3 er).
4. Transformations

Synthesis of (R)-tert-butyl 4-((R)-2-methyl-5-oxotetrahydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (6a)

In a 25 mL round-bottomed flask equipped with a magnetic stirring bar and septum, (R)-tert-butyl 4-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate 3a (1 equiv, 0.1 mmol, 28.13 mg) and Palladium on activated charcoal 10% (~10 mg) were dissolved in MeOH (1.5 mL) and stirred for 24 h in H₂ atmosphere. Reaction mixture was filtered through celite, washed with MeOH and evaporated to give final product 6a as a colorless oil in 98% yield (27.8 mg, >20:1 dr). (R)-tert-butyl 4-((R)-2-methyl-5-oxotetrahydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (6a): ¹H NMR (700 MHz, CDCl₃) δ 3.87 (dd, J = 11.1, 8.5 Hz, 1H), 3.58 (dd, J = 11.1, 8.3 Hz, 1H), 2.75 – 2.67 (m, 1H), 2.66 – 2.54 (m, 3H), 2.50 – 2.43 (m, 1H), 2.14 – 2.00 (m, 2H), 1.52 (s, 9H), 1.41 (s, 3H).¹³C NMR (176 MHz, CDCl₃) δ 175.7, 172.2, 145.0, 85.2, 83.7, 47.2, 39.3, 34.1, 31.1, 28.6, 28.1 (3C), 24.2. HRMS: calculated for [C₁₄H₂₁NO₅+Na⁺]: 306.1317; found: 306.1313. [α]D²² = -15.5° (c = 1.0, CHCl₃).

Synthesis of (R)-4-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)pyrrolidin-2-one (7a)

In an ordinary 4 mL glass vial, equipped with a magnetic stirring bar and a screw cap, (R)-tert-butyl 4-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate 3a (1 equiv, 0.04 mmol, 11.9 mg) was dissolved in CH₂Cl₂ (0.2 mL). Trifluoroacetic acid (10 equiv, 0.4 mmol, 30 μL) was added and the resulting mixture was stirred for 1 h at ambient temperature. Reaction mixture was cooled to 0 °C and carefully quenched with 20% solution of Na₂CO₃ (aq) ( 5 mL). Chloroform (10 mL) was added and organic phase was separated. Organic phase was washed with 20% solution of Na₂CO₃ (aq) (2x5 mL), brine (2x5 mL), dried over anhydrous MgSO₄ and evaporated to a give 7a as yellowish oil in 79% yield (5.7 mg, >20:1 dr). (R)-4-
((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)pyrrolidin-2-one (7a): $^1$H NMR (700 MHz, CDCl$_3$) $\delta$ 7.36 (d, $J$ = 5.7 Hz, 1H), 6.15 (d, $J$ = 5.7 Hz, 1H), 5.50 (s, 1H), 3.51 – 3.47 (m, 1H), 3.24 (dd, $J$ = 9.8, 6.7 Hz, 1H), 2.95 – 2.90 (m, 1H), 2.33 (dd, $J$ = 17.1, 9.4 Hz, 1H), 2.08 (dd, $J$ = 17.1, 8.2 Hz, 1H), 1.52 (s, 3H). $^{13}$C NMR (176 MHz, CDCl$_3$) $\delta$ 175.8, 171.6, 157.7, 122.3, 88.1, 42.7, 41.4, 31.4, 22.7. HRMS: calculated for [C$_{9}$H$_{11}$NO$_3$+Na$^+$]: 204.0637; found: 204.0639. $[\alpha]^{D}_{22} = 15.1^\circ$ (c = 1.0, CHCl$_3$).
5. Crystal and X-ray data for 3d

The single-crystal X-ray diffraction study at a low temperature of 100 K revealed that compound 3d \((\text{C}_{19}\text{H}_{20}\text{ClNO}_{5})\) crystallizes in the non-centrosymmetric monoclinic space group \(P2_1 (Z = 2)\) and the crystal structure consists of one crystallographically independent formula unit in the unit cell.

The molecular structure of the compound 3d at 100 K, showing 50% probability displacement ellipsoids. Hydrogen atoms are drawn with an arbitrary radius.

Single crystal X-ray diffraction data were collected at 100 K by the \(\omega\)-scan technique using a RIGAKU XtaLAB Synergy, Dualflex, Pilatus 300K diffractometer\(^3\) with PhotonJet micro-focus X-ray Source Cu-K\(\alpha\) (\(\lambda = 1.54184 \text{ Å}\)). Data collection, cell refinement, data reduction and absorption correction were performed using CrysAlis PRO software.\(^3\) The crystal structure was solved by using direct methods with the SHELXT 2018/2 program.\(^4\) Atomic scattering factors were taken from the International Tables for X-ray Crystallography. Positional parameters of non-H-atoms were refined by a full-matrix least-squares method on \(F^2\) with anisotropic thermal parameters by using the SHELXL 2018/3 program.\(^5\) All hydrogen atoms were found from the difference Fourier maps and for further calculations they were positioned geometrically in calculated positions (C–H = 0.95–1.00 Å) and constrained to ride on their parent atoms with isotropic displacement parameters set to 1.2-1.5 times the \(U_{eq}\) of the parent atom.
(R)-tert-Butyl 4-((R)-2-(4-chlorophenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3d): Formula C_{19}H_{20}ClNO_{5}, monoclinic, space group P2_1, Z = 2, unit cell constants a = 9.62610(9), b = 6.61723(11), c = 14.2237(2) Å, β = 98.0027(11°), V = 897.20(2) Å³. The integration of the data yielded a total of 21820 reflections with θ angles in the range of 4.64 to 66.58°, of which 3040 were independent (R_{int} = 1.92%), and 3038 were greater than 2σ(F²). The final anisotropic full-matrix least-squares refinement on F² with 239 parameters converged at R_1 = 2.25% and wR_2 = 5.89% for all data. The largest peak in the final difference electron density synthesis was 0.172 e Å⁻³ and the largest hole was -0.175 e Å⁻³. The goodness-of-fit was 1.054. The absolute configuration was determined from anomalous scattering, by calculating the x Flack parameter of 0.020(6) using 1295 quotients.

CCDC 2013485 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.


6. NMR data

(R)-tert-Butyl 4-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3a)
(R)-tert-Butyl 2-oxo-4-((R)-5-oxo-2-phenyl-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3b)
(R)-tert-Butyl 4-((R)-2-(4-fluorophenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3c)
(R)-tert-Butyl 4-((R)-2-(4-chlorophenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3d)
(R)-tert-Butyl 4-((R)-2-(2-chlorophenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3e)
(R)-tert-Butyl 4-((((R)-2-(4-bromophenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3f)
(R)-tert-Butyl 2-oxo-4-((R)-5-oxo-2-(p-tolyl)-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3g)
(R)-tert-Butyl 4-(((R)-2-([1,1'-biphenyl]-4-yl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3h)
(R)-tert-Butyl 4-((R)-2-(4-methoxyphenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3i)
(R)-tert-Butyl 4-((R)-2-(3,4-dimethoxyphenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3j)
(R)-\textit{tert}-Butyl 2-oxo-4-((R)-5-oxo-2-propyl-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3k)
(R)-tert-Butyl 2-oxo-4-((R)-5-oxo-2-isopropyl-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3l)
(R)-tert-Butyl 2-oxo-4-((R)-5-oxo-2-allyl-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3m)
(R)-tert-Butyl 4-((R)-2-methyl-5-oxotetrahydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (6a)
(R)-4-((R)-2-Methyl-5-oxo-2,5-dihydrofuran-2-yl)pyrrolidin-2-one (7a)
7. UPC² traces

(R)-tert-Butyl 4-((R)-2-methyl-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3a)
(R)-tert-Butyl 2-oxo-4-((R)-5-oxo-2-phenyl-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3b)
(R)-tert-Butyl 4-((R)-2-(4-fluorophenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3c)
(R)-tert-Butyl 4-((R)-2-(4-chlorophenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3d)
(R)-tert-Butyl 4-((R)-2-(2-chlorophenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3e)
(R)-tert-Butyl 4-((R)-2-(4-bromophenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3f)
(R)-tert-Butyl 2-oxo-4-((R)-5-oxo-2-(p-tolyl)-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3g)
(R)- tert-Butyl 4-((R)-2-([1,1'-biphenyl]-4-yl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3h)
(R)-tert-Butyl 4-((R)-2-(4-methoxyphenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3i)
(R)-tert-Butyl 4-((R)-2-(3,4-dimethoxyphenyl)-5-oxo-2,5-dihydrofuran-2-yl)-2-oxopyrrolidine-1-carboxylate (3j)
(R)-tert-Butyl 2-oxo-4-((R)-5-oxo-2-propyl-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3k)
(R)-tert-Butyl 2-oxo-4-((R)-5-oxo-2-isopropyl-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3l)
(R)-tert-Butyl 2-oxo-4-((R)-5-oxo-2-allyl-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (3m)