Supplementary Information

Brønsted Acid-Catalyzed Dipeptides Functionalization through Azlactones

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Experimental

General remarks

All reagents were commercially obtained and used with no further purification. Unless otherwise noted, all reactions were carried out in flame-dried glassware under a positive pressure of dry nitrogen. Thin layer chromatography (TLC) was performed on Merck precoated glass-backed TLC plates (silica gel 60 F254) and visualized by UV lamp (254 nm). Yields refer to chromatographically and spectroscopically pure compounds. \(^1\)H and \(^{13}\)C spectra were recorded on a Bruker Avance III 500 MHz spectrometer. Chemical shifts are reported in parts per million (ppm). \(^1\)H NMR spectra were referenced to CDCl\(_3\) (7.28 ppm) and \(^{13}\)C NMR spectra were referenced to CDCl\(_3\) (77.23 ppm). All \(^{13}\)C spectra were measured with complete proton decoupling. Peak multiplicities are designated by the following abbreviations: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; q, quartet; qu, quintet; sext, sextet and \(J\), coupling constant in hertz (Hz). High-resolution mass spectra were acquired in the positive ion mode using a mass spectrometer Waters Xevo G2-XS QTof.

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Characterization data

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\text{N-}(3\text{-Methyl}-1\text{-}(5\text{-oxo-4,5\text{-dihydrooxazol-2-yl})butyl})\text{benzamide}
\]

The product 2a (42 mg, 85%) was obtained as a yellow oil after the reaction mixture was diluted in 10 mL of CH₂Cl₂ and washed 5 times with 5 mL of distilled water. The organic phase was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure, affording the desired azlactones without the need of chromatography column. IR (KBr) ν / cm⁻¹ 3295, 3067, 2963, 2924, 2860, 1827, 1646, 1529, 1281, 1027; \(^1\)H NMR (500 MHz, CDCl₃) δ 7.81-7.79 (m, 2H), 7.50 (tt, 1H, J 1.4, 7.8 Hz), 7.41 (t, 2H, J 7.6 Hz), 6.81 (d, 1H, J 8.0 Hz), 5.16-5.11 (m, 1H), 4.17 (d, 2H, J 1.6 Hz), 1.81-1.72 (m, 3H), 0.99-0.97 (m, 6H); \(^{13}\)C NMR (125 MHz, CDCl₃) δ 175.5, 167.4, 167.3, 133.6, 132.1, 128.8, 127.2, 54.2, 47.1, 41.4, 25.0, 22.9, 22.0.

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\text{N-}(1\text{-}(5\text{-Oxo-4,5\text{-dihydrooxazol-2-yl})ethyl})\text{benzamide}
\]

The product 2b (56 mg, 75%) was obtained as a yellow oil after the reaction mixture was diluted in 10 mL of CH₂Cl₂ and washed 5 times with 5 mL of distilled water. The organic phase was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure, affording the desired azlactones without the need of chromatography column. \(^1\)H NMR (500 MHz, CDCl₃) δ 7.81-7.79 (m, 2H), 7.50 (tt, 1H, J 1.5, 7.8 Hz), 7.43-7.39 (m, 2H), 6.98 (d, 1H, J 7.2 Hz), 5.08 (qut, 1H, J 1.9, 7.2 Hz), 4.18 (d, 2H, J 2.0 Hz), 1.57 (d, 3H, J 7.1 Hz); \(^{13}\)C NMR (125 MHz, CDCl₃) δ 175.4, 167.6, 167.1, 133.6, 132.0, 128.7, 127.2, 54.2, 44.6, 18.3.
Butyl N-benzoyl-leucylglycinate

The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 50%) to afford product 3a (37 mg, 69%) as a yellow solid; m.p. 83 °C; IR (ZnSe) ν / cm⁻¹ 3289, 3080, 2958, 2925, 2867, 1746, 1660, 1629, 1536, 1199; ¹H NMR (500 MHz, CDCl₃) δ 7.80-7.79 (m, 2H), 7.51 (tt, 1H, J 1.5, 7.4 Hz), 7.44-7.41 (m, 2H), 6.89 (t, 1H, J 5.1 Hz), 6.77 (d, 1H, J 8.2 Hz), 4.79-4.74 (m, 1H), 4.13 (t, 2H, J 6.7 Hz), 4.07 (dd, 1H, J 5.6, 18.2 Hz), 3.98 (dd, 1H, J 5.2, 18.2 Hz), 1.81-1.67 (m, 3H), 1.60 (qu, 2H, J 7.1 Hz), 1.35 (sext, 2H, J 7.5 Hz), 0.98-0.96 (m, 6H), 0.91 (t, 3H, J 7.4 Hz); ¹³C NMR (125 MHz, CDCl₃) δ 172.6, 169.8, 167.6, 133.8, 132.0, 128.7, 127.3, 65.5, 52.0, 41.5, 41.3, 30.6, 25.0, 23.0, 22.3, 19.1, 13.8; HRMS: calcd. for [C₁₀H₂₈N₂NaO₄]⁺ [M + Na]⁺: m/z 371.1947, found 371.1939.

Octyl N-benzoyl-l-alanylglycinate

The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 50%) to afford product 3b (50 mg, 71%) as a yellow oil; IR (ZnSe) ν / cm⁻¹ 3309, 3270, 2957, 2928, 2865, 1722, 1658, 1632, 1531, 1223; ¹H NMR (500 MHz, CDCl₃) δ 7.82-7.80 (m, 2H), 7.49 (tt, 1H, J 1.6, 7.8 Hz), 7.43-7.40 (m, 2H), 7.13 (t, 1H, J 5.1 Hz), 7.10 (d, 1H, J 7.5 Hz), 4.81 (qu, 1H, J 7.1 Hz), 4.06-4.03 (m, 4H), 1.50 (d, 3H, J 7.0 Hz), 1.34-1.25 (m, 10H), 0.87-0.84 (m, 5H); ¹³C NMR (125 MHz, CDCl₃) δ 172.9, 169.9, 167.4, 133.8, 132.0, 128.7, 127.3, 68.1, 49.2, 41.5, 38.8, 30.4, 29.0, 23.7, 23.0, 18.5, 14.1, 11.0; HRMS: calcd. for [C₂₀H₃₂N₂O₄]⁺ [M + H]⁺: m/z 363.2284, found 363.2287.

Octyl N-benzoyl-l-leucylglycinate

The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 50%) to afford product 3c (44 mg, 87%) as a white solid; m.p. 62 °C; IR (ZnSe) ν / cm⁻¹ 3263, 3087, 2956, 2924, 2860, 1746, 1670, 1632, 1567, 1529, 1190; ¹H NMR (500 MHz, CDCl₃) δ 7.81-7.79 (m, 2H), 7.50 (tt, 1H, J 1.5, 7.4 Hz), 7.43-7.40 (m, 2H), 6.92 (t, 1H, J 4.9 Hz), 6.81 (d, 1H,
\( \text{ZnSe} \), 3C, \( \text{J} \)

\( \text{J} = 8.2 \ \text{Hz}, 4.79-4.75 \ (m, 1H), 4.11-3.96 \ (m, 4H), 1.80-1.67 \ (m, 4H), 1.59-1.54 \ (m, 1H), 1.35-1.26 \ (m, 8H), 0.97-0.85 \ (m, 11H); {\textsuperscript{13}}C \ \text{NMR} \ (125 \ \text{MHz, CDCl}_3) \ \delta \ 172.5, 169.9, 167.6, 133.8, 132.0, 128.7, 127.3, 68.1, 52.0, 41.5, 41.4, 38.8, 30.4, 29.0, 25.0, 23.8, 23.1, 22.3, 14.2, 11.0; \ \text{HRMS}: \text{calcd.} \ [\text{C}_{23}\text{H}_{37}\text{N}_2\text{O}_4]^+ [\text{M} + \text{H}]^+: m/\text{z} 405.2753, \text{found} 405.2758.

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\text{Benzyl } N\text{-benzoylalanylglycinate}
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The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 50%) to afford product 3d (50 mg, 69%) as a white solid; m.p. 144 °C; IR (ZnSe) \( \nu / \text{cm}^{-1} \) 3292, 3069, 1738, 1650, 1627, 1540, 1199; \( \text{H} \ \text{NMR} \ (500 \ \text{MHz, CDCl}_3) \ \delta \ 7.80-7.78 \ (m, 2H), 7.51 \ (tt, 1H, J 1.5, 7.8 \ \text{Hz}), 7.44-7.41 \ (m, 2H), 7.37-7.31 \ (m, 5H), 7.02 \ (t, 1H, J 5.2 \ \text{Hz}), 6.94 \ (d, 1H, J 7.6 \ \text{Hz}), 5.16 \ (s, 2H), 4.79 \ (qu, 1H, J 7.1 \ \text{Hz}), 4.09 \ (d, 2H, J 5.5 \ \text{Hz}), 1.49 \ (d, 3H, J 7.0 \ \text{Hz}); {\textsuperscript{13}}C \ \text{NMR} \ (125 \ \text{MHz, CDCl}_3) \ \delta \ 172.8, 169.6, 167.4, 135.2, 133.8, 132.0, 128.8, 128.7, 128.6, 128.5, 127.2, 67.4, 49.2, 41.6, 18.4; \ \text{HRMS}: \text{calcd.} \ [\text{C}_{18}\text{H}_{26}\text{N}_2\text{Na}_2\text{O}_4]^+ [\text{M} + \text{Na}]^+: m/\text{z} 363.1321, \text{found} 363.1321.

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\text{Isopropyl } N\text{-benzoylleucylglycinate}
\]

The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 50%) to afford product 3e (36 mg, 62%) as a yellow solid; m.p. 136 °C; IR (ZnSe) \( \nu / \text{cm}^{-1} \) 3286, 3080, 2958, 2927, 2862, 1744, 1667, 1634, 1566, 1532, 1200, 1105; \( \text{H} \ \text{NMR} \ (500 \ \text{MHz, CDCl}_3) \ \delta \ 7.81-7.79 \ (m, 2H), 7.50 \ (tt, 1H, J 1.6, 7.7 \ \text{Hz}), 7.44-7.41 \ (m, 2H), 6.89 \ (t, 1H, J 5.0 \ \text{Hz}), 6.81 \ (d, 1H, J 8.3 \ \text{Hz}), 5.05 \ (hept, 1H, J 6.3 \ \text{Hz}), 4.77 \ (dt, 1H, J 5.8, 8.6 \ \text{Hz}), 4.03 \ (dd, 1H, J 5.6, 18.2 \ \text{Hz}), 3.95 \ (dd, 1H, J 5.2, 18.2 \ \text{Hz}), 1.82-1.66 \ (m, 3H), 1.24 \ (d, 6H, J 6.3 \ \text{Hz}), 0.97 \ (d, 3H, J 4.2 \ \text{Hz}), 0.96 \ (d, 3H, J 4.1 \ \text{Hz}); {\textsuperscript{13}}C \ \text{NMR} \ (125 \ \text{MHz, CDCl}_3) \ \delta \ 172.5, 169.2, 167.6, 133.8, 132.0, 128.8, 127.3, 69.5, 52.0, 41.8, 41.4, 29.8, 25.0, 23.0, 22.4, 21.9; \ \text{HRMS}: \text{calcd.} \ [\text{C}_{18}\text{H}_{26}\text{N}_2\text{Na}_2\text{O}_4]^+ [\text{M} + \text{Na}]^+: m/\text{z} 357.1790, \text{found} 357.1791.
$N$-1-[(2-Octylamino)-2-oxoethyl]amino)-1-oxopropan-2-yl]benzamide

The product was purified by column chromatography on silica gel (elution: hexanes/ethyl acetate 50%) to afford product 3f (48 mg, 63%) as a white solid; m.p. 132 °C; IR (ZnSe) ν / cm$^{-1}$ 3332, 3288, 3085, 2924, 2855, 1692, 1637, 1527; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.82-7.81 (m, 2H), 7.52-7.47 (m, 2H), 7.40 (t, 2H, J 7.6 Hz), 7.34 (d, 1H, J 6.7 Hz), 6.79 (t, 1H, J 5.2 Hz), 4.64 (qu, 1H, J 6.9 Hz), 3.98 (dd, 1H, J 6.0, 16.3 Hz), 3.85 (dd, 1H, J 5.4, 16.5 Hz), 3.20-3.16 (m, 2H), 1.48 (d, 3H, J 7.1 Hz), 1.26-1.21 (m, 12H), 0.85 (t, 3H, J 7.0 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 173.4, 169.0, 167.9, 133.5, 132.1, 128.7, 127.4, 50.2, 43.4, 39.9, 31.9, 29.5, 29.4, 29.3, 27.0, 22.7, 18.1, 14.2; HRMS: calcd for [C$_{20}$H$_{17}$N$_2$O$_3$]$^+$ [M + Na]$^+$: m/z 384.2263, found 384.2263.

$N$-4-Methyl-1-[(2-Octylamino)-2-oxoethyl]amino)-1-oxopentan-2-yl]benzamide

The product was purified by column chromatography on silica gel (elution: hexanes/ethyl acetate 50%) to afford product 3g (68 mg, 91%) as a yellow oil; IR (ZnSe) ν / cm$^{-1}$ 3295, 2955, 2926, 2854, 1638, 1536; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.81-7.79 (m, 2H), 7.72 (t, 1H, J 5.8 Hz), 7.57 (d, 1H, J 7.2 Hz), 7.47-7.44 (m, 1H), 7.37-7.33 (m, 2H), 6.98 (t, 1H, J 5.5 Hz), 4.59 (q, 1H, J 7.2 Hz), 3.95 (dd, 1H, J 6.3, 16.6 Hz), 3.81 (dd, 1H, J 5.5, 16.6 Hz), 3.14 (q, 2H, J 6.8 Hz), 1.68-1.65 (m, 3H), 1.43 (qu, 2H, J 7.1 Hz), 1.24-1.20 (m, 10H), 0.90 (d, 3H, J 6.0 Hz), 0.87 (d, 3H, J 6.1 Hz), 0.84 (t, 3H, J 7.0 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 173.3, 169.0, 168.1, 133.4, 131.9, 128.5, 127.4, 53.1, 43.3, 40.7, 39.7, 31.3, 29.4, 29.3, 29.2, 26.9, 24.9, 22.9, 22.0, 22.6, 14.1; HRMS: calcd. for [C$_{20}$H$_{17}$N$_2$O$_3$]$^+$ [M + Na]$^+$: m/z 426.2733, found 426.2735.

$N$-1-[(2-Benzylamino)-2-oxoethyl]amino)-4-methyl-1-oxopentan-2-yl]benzamide

The product was purified by column chromatography on silica gel (elution: hexanes/ethyl acetate 50%) to afford product 3h (40 mg, 77%) as a yellow oil; IR (ZnSe) ν / cm$^{-1}$ 3274, 3064, 2961, 2930, 2869, 1633, 1537; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.66-7.64 (m, 2H), 7.51-7.47 (m, 1H),
7.37 (t, 2H, J 7.7 Hz), 7.25-7.21 (m, 5H), 7.16 (t, 1H, J 5.0 Hz), 7.09 (t, 1H, J 4.8 Hz), 6.87 (d, 1H, J 6.9 Hz), 4.54 (q, 1H, J 7.1 Hz), 4.45-4.37 (m, 2H), 4.06 (dd, 1H, J 6.5, 16.7 Hz), 3.86 (dd, 1H, J 5.3, 16.7 Hz), 1.75-1.66 (m, 3H), 0.95 (d, 3H, J 6.2 Hz), 0.93 (d, 3H, J 6.2 Hz);

13C NMR (125 MHz, CDCl₃) δ 173.4, 169.1, 168.2, 138.1, 133.4, 132.0, 128.7, 128.6, 127.7, 127.4, 127.3, 133.1, 43.5, 43.4, 40.8, 25.0, 22.9, 22.2; HRMS: calcd for [C₂₂H₂₈N₃O₃]⁺ [M + H]⁺: m/z 382.2131, found 382.2131.

\[\text{N-(4-Methyl-1-oxo-1-((2-oxo-2-(phenylamino)ethyl)amino)pentan-2-yl)benzamide}\]

The product was purified by column chromatography on silica gel (elution: hexanes to hexanes/ethyl acetate 50%) to afford product 3i (75 mg, 61%) as a yellow solid; m.p. 178 °C; IR (ZnSe) ν / cm⁻¹ 3290, 2956, 2925, 2861, 1701, 1645, 1625, 1519, 1497, 1444; ¹H NMR (500 MHz, CDCl₃) δ 8.90 (s, 1H), 7.78-7.76 (m, 3H), 7.58 (d, 2H, J 7.7 Hz), 7.44-7.41 (m, 2H), 7.32 (t, 2H, J 7.8 Hz), 7.22 (t, 2H, J 7.9 Hz), 7.05 (t, 1H, J 7.4 Hz), 4.61 (q, 1H, J 7.1 Hz), 4.13 (dd, 1H, J 6.4, 16.8 Hz), 3.95 (dd, 1H, J 5.4, 16.7 Hz), 1.69-1.68 (m, 2H), 1.29-1.25 (m, 1H), 0.89 (d, 3H, J 5.4 Hz), 0.86 (d, 3H, J 5.1 Hz);

¹³C NMR (125 MHz, CDCl₃) δ 173.5, 168.5, 167.5, 137.9, 133.3, 132.2, 129.0, 128.7, 127.4, 124.5, 120.3, 53.4, 44.2, 40.6, 25.1, 22.9, 22.2; HRMS: calcd for [C₂₁H₂₅N₃NaO₃]⁺ [M + Na]⁺: m/z 390.1794, found 390.1792.
Elemental analysis data

**Figure S1.** $^1$H NMR (500 MHz, CDCl$_3$) of compound 2a.

**Figure S2.** $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 2a.
**Figure S3.** IR (KBr) spectra of compound 1a.

**Figure S4.** $^1$H NMR (500 MHz, CDCl$_3$) of compound 2b.
Figure S5. $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 2b.

Figure S6. COSY spectra (expansion) of compound 2b.
Figure S7. $^1$H NMR (500 MHz, CDCl$_3$) of compound 3a.

Figure S8. $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 3a.
Figure S9. IR (ZnSe) spectra of compound 3a.

Figure S10. HRMS of compound 3a.
Figure S11. $^1$H NMR (500 MHz, CDCl$_3$) of compound 3b.

Figure S12. $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 3b.
**Figure S13.** IR (ZnSe) spectra of compound 3b.

**Figure S14.** HRMS of compound 3b.
**Figure S15.** $^1$H NMR (500 MHz, CDCl$_3$) of compound 3c.

**Figure S16.** $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 3c.
Figure S17. IR (ZnSe) spectra of compound 3c.

Figure S18. HRMS of compound 3c.
Figure S19. $^1$H NMR (500 MHz, CDCl$_3$) of compound 3d.

Figure S20. $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 3d.
Figure S21. IR (ZnSe) spectra of compound 3d.

Figure S22. HRMS of compound 3d.
Figure S23. $^1$H NMR (500 MHz, CDCl$_3$) of compound 3e.

Figure S24. $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 3e.
**Figure S25.** IR (ZnSe) spectra of compound 3e.

**Figure S26.** HRMS of compound 3e.
**Figure S27.** $^1$H NMR (500 MHz, CDCl$_3$) of compound 3f.

**Figure S28.** $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 3f.
**Figure S29.** DEPT135 NMR (125 MHz, CDCl₃) of compound 3f.

**Figure S30.** IR (ZnSe) spectra of compound 3f.
**Figure S31.** HRMS of compound 3f.

**Figure S32.** $^1$H NMR (500 MHz, CDCl$_3$) of compound 3g.
Figure S33. $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 3g.

Figure S34. IR (ZnSe) spectra of compound 3g.
Figure S35. HRMS of compound 3g.

Figure S36. $^1$H NMR (500 MHz, CDCl$_3$) of compound 3h.
**Figure S37.** $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 3h.

**Figure S38.** IR (ZnSe) spectra of compound 3h.
Figure S39. HRMS of compound 3h.

Figure S40. $^1$H NMR (500 MHz, CDCl₃) of compound 3i.
Figure S41. $^{13}$C NMR (125 MHz, CDCl$_3$) of compound 3i.

Figure S42. IR (ZnSe) spectra of compound 3i.
Figure S43. HRMS of compound 3i.