

Versatile Alkylation of (Hetero)Aryl iodides with Ketones via β -C(sp³)-H Activation

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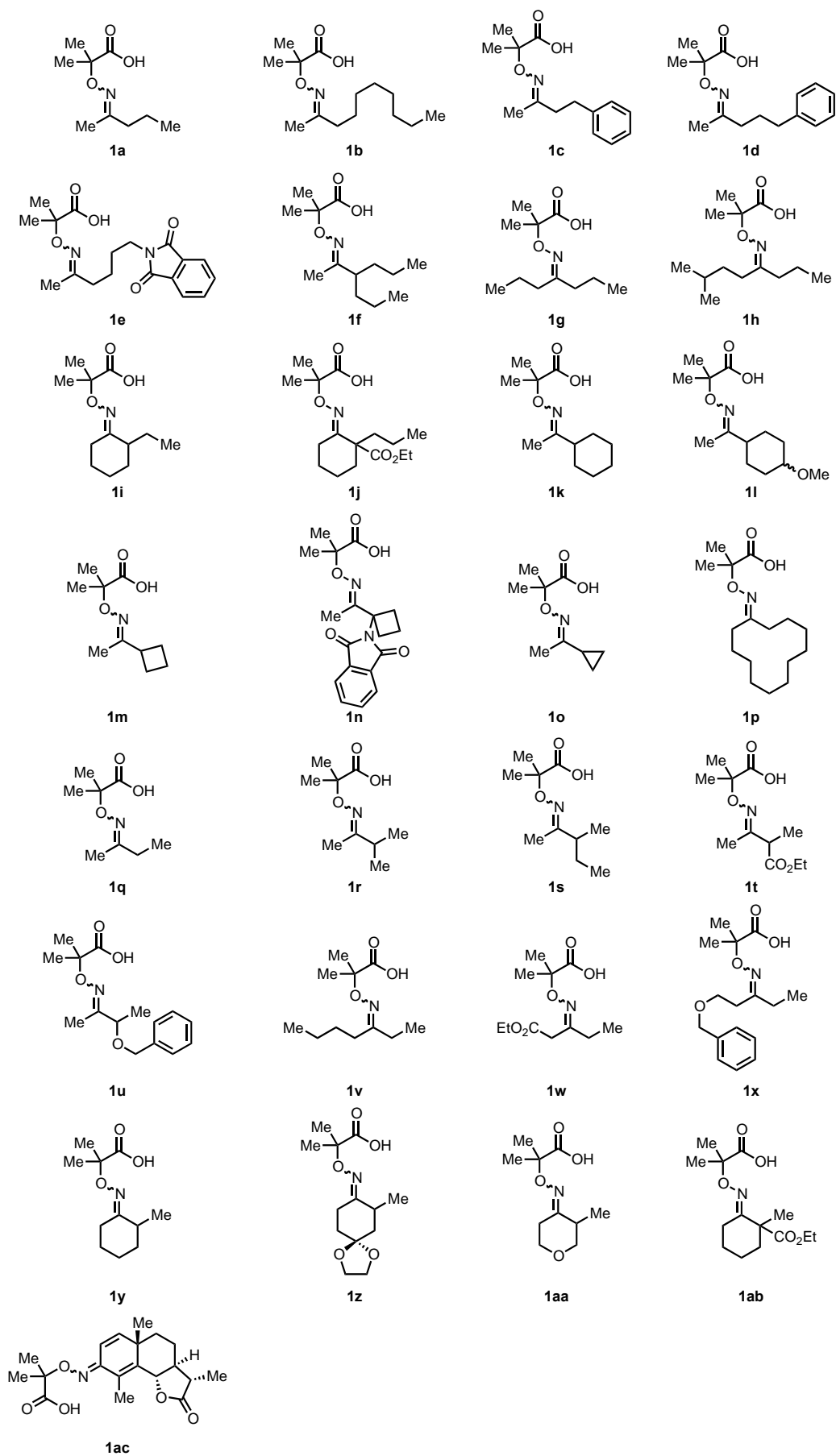
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General Information

Ketones were obtained from the commercial sources or synthesized following literature procedures, and used to prepare the corresponding substrates. 2,2-Dimethyl aminoxyacetic acid hydrochloride was obtained from Combi-Blocks. AgTFA and HFIP (Hexafluoro-2-propanol) were obtained from Oakwood. Solvents were obtained from Sigma-Aldrich, Alfa-Aesar and Acros and used directly without further purification. Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F254. Visualization was carried out with UV light and Vogel's permanganate. ¹H NMR was recorded on Bruker AMX-400 instrument (400 MHz) or Bruker DRX-600 instrument (600 MHz). Chemical shifts were quoted in parts per million (ppm) referenced to 0.0 ppm for tetramethylsilane. The following abbreviations (or combinations thereof) were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants, *J*, were reported in Hertz unit (Hz). ¹³C NMR spectra were recorded on Bruker AMX-400 instrument (100 MHz) or Bruker DRX-600 instrument (150 MHz), and were fully decoupled by broad band proton decoupling. ¹⁹F NMR spectra were recorded on Bruker AMX-400 instrument (100 MHz), and were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to either the center line of a triplet at 77.0 ppm of chloroform-*d* or the center line of a multiplet at 29.84 ppm of acetone-*d*⁶. High-resolution mass spectra (HRMS) were recorded on an Agilent Mass spectrometer using ESI-TOF (electrospray ionization-time of flight).

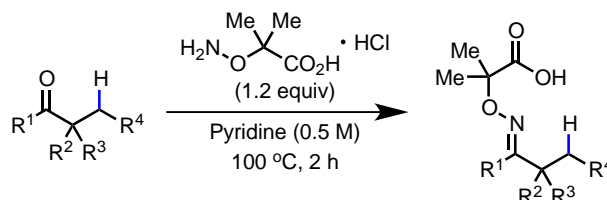
Substrate Structures



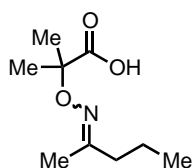
Experimental Section

Substrate Preparation

Ketones for making substrates **1a-d**, **1g**, **1i**, **1k**, **1m**, **1o-t**, **1v-ac** are commercially available. The syntheses of rest of ketones are based on literature.¹

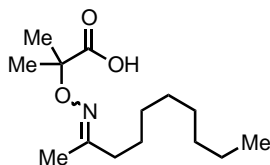


Ketone (2 mmol, 1 equiv) and 2,2-dimethyl aminoxyacetic acid hydrochloride (2.4 mmol, 372 mg, 1.2 equiv) were weighed in an oven dried 50 mL round bottom flask with a magnetic stir bar under air. 4 mL of pyridine was added and the mixture was stirred at 100 °C for 2 h. Upon completion, most pyridine was evaporated under vacuum. The resulting mixture was diluted with EtOAc (50 mL) and washed successively with water (100 mL) and diluted HCl aqueous solution (100 mL, ca. 0.01 M). The organic phase was dried with anhydrous Na₂SO₄ and the solvent was removed under vacuum. Notably, the pure compounds were obtained in good yields for most cases without any chromatography.



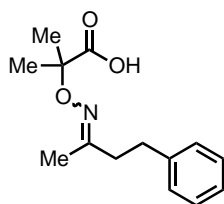
2-Methyl-2-((pentan-2-ylideneamino)oxy)propanoic acid (**1a**)

White solid, E/Z (3.1:1). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 2.24-2.22 (m, 2H), 1.92 (s, 3H), 1.61-1.53 (m, 2H), 1.50 (s, 6H), 0.93 (t, *J* = 7.2 Hz, 3H). ¹H NMR (600 MHz, CDCl₃) of Z isomer (minor) δ 2.38-2.36 (m, 2H), 1.93 (s, 3H), 1.61-1.53 (m, 2H), 1.50 (s, 6H), 0.96 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) of E/Z mixture δ 177.48, 177.37, 161.45, 160.95, 80.78, 80.67, 37.79, 31.31, 24.22, 20.12, 19.28, 18.94, 14.33, 14.03, 13.41. HRMS (ESI-TOF) Calcd for C₉H₁₆NO₃⁻ [M-H]⁻: 186.1136, found: 186.1132.



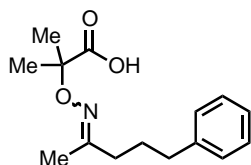
2-((Decan-2-ylideneamino)oxy)-2-methylpropanoic acid (**1b**)

Colorless oil, E/Z (3.0:1). ¹H NMR (600 MHz, CDCl₃) of E/Z mixture δ 2.38-2.35 (m, 1H), 2.25-2.21 (m, 3.0H), 1.92-1.90 (m, 6.0H), 1.53-1.50 (m, 16.4H), 1.30-1.26 (m, 21.1H), 0.90-0.86 (m, 6.1H). ¹³C NMR (150 MHz, CDCl₃) of E/Z mixture δ 176.85, 162.00, 161.51, 80.88, 80.76, 35.91, 31.81, 31.78, 29.47, 29.40, 29.21, 29.18, 29.14, 29.09, 28.98, 25.94, 25.44, 24.30, 24.26, 22.62, 22.60, 20.17, 14.44, 14.05. HRMS (ESI-TOF) Calcd for C₁₄H₂₆NO₃⁻ [M-H]⁻: 256.1918, found: 256.1912.



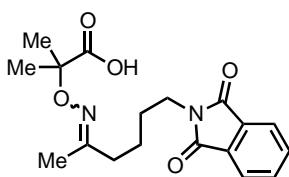
2-Methyl-2-(((4-phenylbutan-2-ylidene)amino)oxy)propanoic acid (1c)

E/Z (2.4:1). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.30-7.27 (m, 2H), 7.20-7.16 (m, 3H), 2.88-2.85 (m, 2H), 2.60-2.57 (m, 2H), 1.93 (s, 3H), 1.44 (s, 6H). ¹H NMR (600 MHz, CDCl₃) of Z isomer (minor) δ 7.31-7.29 (m, 2H), 7.23-7.20 (m, 3H), 2.85-2.83 (m, 2H), 2.70-2.68 (m, 2H), 1.88 (s, 3H), 1.46 (s, 6H). ¹³C NMR (150 MHz, CDCl₃) of E/Z mixture δ 176.62, 176.54, 160.80, 160.31, 140.60, 140.36, 128.52, 128.50, 128.26, 128.24, 126.36, 126.25, 81.05, 80.91, 37.51, 32.10, 31.56, 31.45, 24.21, 24.18, 20.53, 14.82. HRMS (ESI-TOF) Calcd for C₁₄H₁₈NO₃⁻ [M-H]⁻: 248.1292, found: 248.1297.



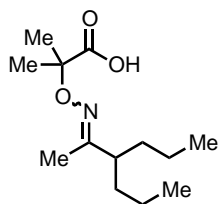
2-Methyl-2-(((5-phenylpentan-2-ylidene)amino)oxy)propanoic acid (1d)

E/Z (3.4:1). ¹H NMR (600 MHz, CDCl₃) of E/Z mixture δ 7.30-7.28 (m, 2.6H), 7.22-7.16 (m, 3.9H), 2.66-2.62 (m, 2.6H), 2.42-2.40 (m, 0.59H), 2.29-2.27 (m, 2H), 1.93 (s, 0.81H), 1.91 (s, 3H), 1.89-1.83 (m, 2.7H), 1.51 (s, 6H), 1.48 (s, 1.7H). ¹³C NMR (150 MHz, CDCl₃) of E/Z mixture δ 176.51, 176.48, 161.64, 161.06, 141.44, 141.35, 128.42, 126.03, 125.99, 81.01, 80.90, 35.65, 35.43, 35.08, 29.14, 27.57, 27.07, 24.30, 24.25, 20.23, 14.63. HRMS (ESI-TOF) Calcd for C₁₅H₂₀NO₃⁻ [M-H]⁻: 262.1449, found: 262.1455.



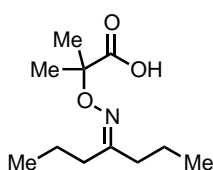
2-(((6-(1,3-Dioxisoindolin-2-yl)hexan-2-ylidene)amino)oxy)-2-methylpropanoic acid (1e)

White solid, E/Z (6.2:1). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.86-7.84 (m, 2H), 7.73-7.71 (m, 2H), 3.69 (t, *J* = 7.2 Hz, 2H), 2.29 (t, *J* = 7.2 Hz, 2H), 1.90 (s, 3H), 1.73-1.68 (m, 2H), 1.62-1.57 (m, 2H), 1.50 (s, 6H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 176.13, 168.48, 160.07, 133.97, 132.02, 123.26, 81.05, 37.51, 35.17, 27.78, 24.19, 23.06, 14.56. HRMS (ESI-TOF) Calcd for C₁₈H₂₁N₂O₅⁻ [M-H]⁻: 345.1456, found: 345.1450.



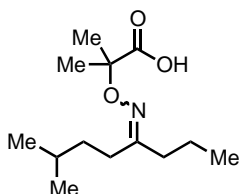
2-Methyl-2-(((3-propylhexan-2-ylidene)amino)oxy)propanoic acid (1f)

Colorless oil, E/Z (10.0:1). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 2.37-2.31 (m, 1H), 1.82-1.80 (m, 3H), 1.50 (s, 6H), 1.43-1.38 (m, 4H), 1.25-1.18 (m, 4H), 0.90-0.87 (m, 3H). ¹³C NMR (150 MHz, CDCl₃) of E/Z mixture δ 177.15, 164.21, 80.89, 44.65, 34.48, 24.28, 20.43, 13.88, 10.78. HRMS (ESI-TOF) Calcd for C₁₃H₂₄NO₃⁻ [M-H]⁻: 242.1762, found: 242.1755.



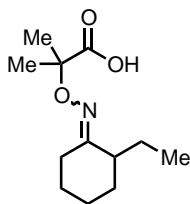
2-((Heptan-4-ylideneamino)oxy)-2-methylpropanoic acid (1g)

Colorless oil. ¹H NMR (600 MHz, CDCl₃) δ 2.35-2.32 (m, 2H), 2.24-2.22 (m, 2H), 1.60-1.52 (m, 4H), 1.50 (s, 6H), 0.96 (t, *J* = 7.2 Hz, 3H), 0.94 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 175.82, 165.29, 81.01, 36.31, 30.45, 24.34, 19.22, 19.16, 14.21, 13.62. HRMS (ESI-TOF) Calcd for C₁₁H₂₀NO₃⁻ [M-H]⁻: 214.1449, found: 214.1444.



2-Methyl-2-(((7-methyloctan-4-ylidene)amino)oxy)propanoic acid (1h)

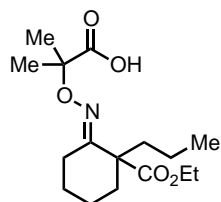
Colorless oil, E/Z (1:1). ¹H NMR (600 MHz, CDCl₃) of E/Z mixture δ 2.35-2.32 (m, 2H), 2.25-2.21 (m, 2H), 1.59-1.53 (m, 3H), 1.50 (s, 3H), 1.49 (s, 3H), 1.42-1.35 (m, 2H), 0.97-0.90 (m, 9H). ¹³C NMR (150 MHz, CDCl₃) of E/Z mixture δ 176.44, 165.38, 165.25, 80.90, 80.87, 36.24, 34.82, 34.55, 32.30, 30.44, 28.21, 27.64, 26.53, 24.28, 22.29, 22.25, 19.24, 19.20, 14.22, 13.60. HRMS (ESI-TOF) Calcd for C₁₃H₂₄NO₃⁻ [M-H]⁻: 242.1762, found: 242.1768.



2-(((2-Ethylcyclohexylidene)amino)oxy)-2-methylpropanoic acid (1i)

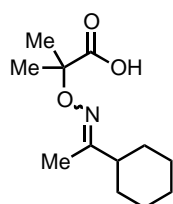
E/Z (3.3:1). ¹H NMR (600 MHz, CDCl₃) of E/Z mixture δ 3.37-3.33 (m, 0.30H), 2.70-2.66

(m, 1H), 2.34-2.30 (m, 1H), 2.28-2.27 (m, 0.30H), 2.24-2.18 (m, 1.3H), 1.96-1.88 (m, 1.6H), 1.79-1.38 (m, 19.8H), 0.91 (t, $J = 7.2$ Hz, 3H), 0.88 (t, $J = 7.2$ Hz, 1.0H). ^{13}C NMR (150 MHz, CDCl_3) of E/Z mixture δ 175.65, 166.80, 166.30, 166.29, 80.51, 80.42, 43.53, 34.66, 32.24, 29.51, 28.42, 26.66, 25.88, 23.94, 23.88, 23.85, 23.82, 23.49, 23.36, 22.93, 19.98, 11.45, 11.29. HRMS (ESI-TOF) Calcd for $\text{C}_{12}\text{H}_{20}\text{NO}_3^-$ [M-H] $^-$: 226.1449, found: 226.1445.



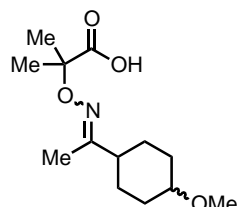
(E)-2-(((2-(Ethoxycarbonyl)-2-propylcyclohexylidene)amino)oxy)-2-methylpropanoic acid (1j)

Colorless oil. ^1H NMR (600 MHz, CDCl_3) δ 4.17 (q, $J = 7.2$ Hz, 2H), 3.13-3.09 (m, 1H), 2.37-2.33 (m, 1H), 2.00-1.95 (m, 1H), 1.85-1.80 (m, 1H), 1.79-1.74 (m, 1H), 1.70-1.60 (m, 2H), 1.54-1.50 (m, 1H), 1.52 (s, 6H), 1.47-1.41 (m, 2H), 1.34-1.23 (m, 2H), 1.25 (t, $J = 7.2$ Hz, 3H), 0.88 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 177.19, 173.36, 162.66, 81.31, 61.00, 54.12, 37.63, 35.54, 25.55, 24.15, 24.13, 24.03, 22.53, 17.80, 14.43, 14.11. HRMS (ESI-TOF) Calcd for $\text{C}_{16}\text{H}_{26}\text{NO}_5^-$ [M-H] $^-$: 312.1816, found: 312.1812.



2-(((1-Cyclohexylethylidene)amino)oxy)-2-methylpropanoic acid (1k)

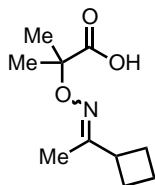
White solid, E/Z (20:1). ^1H NMR (600 MHz, CDCl_3) of E isomer (major) δ 2.22-2.18 (m, 1H), 1.90-1.88 (s, 3H), 1.81-1.79 (m, 4H), 1.72-1.69 (m, 1H), 1.50 (s, 6H), 1.33-1.18 (m, 5H). ^{13}C NMR (150 MHz, CDCl_3) of E isomer (major) δ 176.23, 165.36, 81.01, 44.70, 29.92, 28.77, 25.86, 24.32, 13.00. HRMS (ESI-TOF) Calcd for $\text{C}_{12}\text{H}_{20}\text{NO}_3^-$ [M-H] $^-$: 226.1449, found: 226.1443.



2-(((1-(4-Methoxycyclohexyl)ethylidene)amino)oxy)-2-methylpropanoic acid (1l)

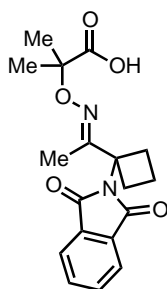
Colorless oil, E/Z (>20:1). ^1H NMR (600 MHz, CDCl_3) of E isomer (major) δ 3.46-3.43 (m, 1H), 3.36 (s, 4.2H), 3.31 (s, 3H), 3.16-3.11 (m, 1.4H), 2.28-2.23 (m, 1H), 2.19-2.12 (m, 4.0H), 1.97-1.94 (m, 2H), 1.90-1.88 (m, 8.8H), 1.74-1.67 (m, 2H), 1.55-1.44 (m, 20.0H), 1.38-1.32

(m, 3H), 1.29-1.21 (m, 3H). ^{13}C NMR (150 MHz, CDCl_3) of E isomer (major) δ 176.66, 176.54, 164.21, 163.58, 80.97, 80.93, 78.75, 74.54, 55.68, 55.58, 43.81, 43.54, 31.17, 28.69, 27.91, 24.26, 24.21, 23.95, 13.07, 12.58. HRMS (ESI-TOF) Calcd for $\text{C}_{13}\text{H}_{22}\text{NO}_4^-$ [M-H] $^-$: 256.1554, found: 256.1556.



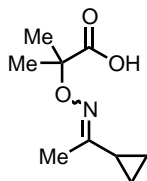
2-(((1-Cyclobutylethylidene)amino)oxy)-2-methylpropanoic acid (1m)

White solid, E/Z (10:1). ^1H NMR (600 MHz, CDCl_3) of E isomer (major) δ 3.12 (quintet, $J = 8.4$ Hz, 1H), 2.18-2.08 (m, 4H), 2.02-1.96 (m, 1H), 1.87 (s, 3H), 1.86-1.80 (m, 1H), 1.51 (s, 6H). ^{13}C NMR (150 MHz, CDCl_3) of E/Z mixture δ 176.29, 163.33, 81.06, 40.16, 26.64, 25.62, 24.34, 18.21, 12.63. HRMS (ESI-TOF) Calcd for $\text{C}_{10}\text{H}_{16}\text{NO}_3^-$ [M-H] $^-$: 198.1136, found: 198.1133.



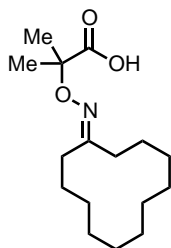
(E)-2-(((1-(1-(1,3-Dioxoisindolin-2-yl)cyclobutyl)ethylidene)amino)oxy)-2-methylpropanoic acid (1n)

White solid. ^1H NMR (600 MHz, CDCl_3) δ 7.82-7.78 (m, 2H), 7.72-7.69 (m, 2H), 2.87-2.76 (m, 4H), 2.01 (s, 3H), 2.00-1.94 (m, 2H), 1.50 (s, 6H). ^{13}C NMR (150 MHz, CDCl_3) δ 176.89, 168.10, 156.69, 134.05, 131.96, 123.11, 81.70, 61.45, 31.28, 24.07, 17.24, 10.56. HRMS (ESI-TOF) Calcd for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_5^-$ [M-H] $^-$: 343.1299, found: 343.1293.



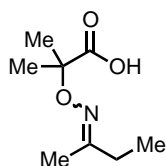
2-(((1-Cyclopropylethylidene)amino)oxy)-2-methylpropanoic acid (1o)

White solid, E/Z (3.2:1). ^1H NMR (600 MHz, CDCl_3) of E isomer (major) δ 1.76 (s, 3H), 1.69-1.64 (m, 1H), 1.52 (s, 6H). ^{13}C NMR (150 MHz, CDCl_3) of E isomer (major) δ 176.40, 162.69, 162.65, 81.06, 81.03, 24.32, 15.49, 14.90, 11.85, 9.80, 5.9, 5.5. HRMS (ESI-TOF) Calcd for $\text{C}_9\text{H}_{14}\text{NO}_3^-$ [M-H] $^-$: 184.0979, found: 184.0986.



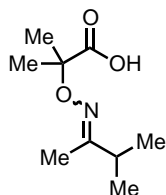
2-((Cyclododecylideneamino)oxy)-2-methylpropanoic acid (1p)

White solid. ^1H NMR (600 MHz, CDCl_3) δ 2.47-2.45 (m, 2H), 2.37-2.35 (m, 2H), 1.72-1.68 (m, 2H), 1.65-1.60 (m, 2H), 1.53 (s, 6H), 1.41-1.28 (m, 14H). ^{13}C NMR (150 MHz, CDCl_3) δ 176.27, 163.80, 81.02, 30.54, 27.60, 25.70, 25.26, 24.52, 24.42, 23.57, 23.41, 23.38, 22.98, 22.68, 22.64. HRMS (ESI-TOF) Calcd for $\text{C}_{16}\text{H}_{28}\text{NO}_3^-$ [M-H] $^-$: 282.2075, found: 282.2071.



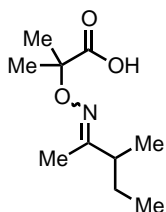
2-((Butan-2-ylideneamino)oxy)-2-methylpropanoic acid (1q)

White solid, E/Z (1:1). ^1H NMR (600 MHz, CDCl_3) δ 2.44-2.39 (m, 2H), 2.32-2.27 (m, 2H), 1.95-1.93 (m, 6H), 1.53-1.52 (m, 12H), 1.14-1.08 (m, 6H). ^{13}C NMR (150 MHz, CDCl_3) of E/Z mixture δ 177.23, 177.00, 162.80, 162.21, 80.88, 80.72, 29.41, 24.27, 24.24, 22.73, 19.60, 19.58, 14.36, 10.52, 9.9. HRMS (ESI-TOF) Calcd for $\text{C}_8\text{H}_{14}\text{NO}_3^-$ [M-H] $^-$: 172.0979, found: 172.0972.



2-Methyl-2-(((3-methylbutan-2-ylidene)amino)oxy)propanoic acid (1r)

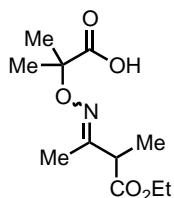
White solid, E/Z (16.7:1). ^1H NMR (600 MHz, CDCl_3) of E isomer (major) δ 2.54 (septet, J = 7.2 Hz, 1H), 1.89 (s, 3H), 1.50 (s, 6H), 1.13 (s, 3H), 1.12 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3) of E isomer (major) δ 176.16, 165.95, 81.05, 34.80, 24.32, 19.58, 12.37. HRMS (ESI-TOF) Calcd for $\text{C}_9\text{H}_{16}\text{NO}_3^-$ [M-H] $^-$: 186.1136, found: 186.1139.



2-Methyl-2-(((3-methylpentan-2-ylidene)amino)oxy)propanoic acid (1s)

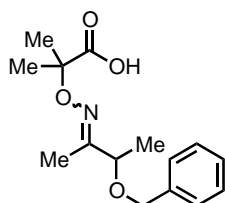
Colorless oil, E/Z (10:1). ^1H NMR (600 MHz, CDCl_3) of E isomer (major) δ 2.38-2.32 (m,

1H), 1.86 (s, 3H), 1.55-1.50 (m, 1H), 1.51 (s, 3H), 1.50 (s, 3H), 1.47-1.42 (m, 1H), 1.09 (d, $J = 7.2$ Hz, 3H), 0.86 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3) of E isomer (major) δ 176.36, 165.18, 80.98, 41.45, 26.65, 24.30, 17.42, 11.56. HRMS (ESI-TOF) Calcd for $\text{C}_{10}\text{H}_{18}\text{NO}_3^-$ [M-H] $^-$: 200.1292, found: 200.1285.



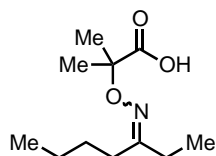
2-(((4-Ethoxy-3-methyl-4-oxobutan-2-ylidene)amino)oxy)-2-methylpropanoic acid (1t)

Colorless oil, E/Z (3.8:1). ^1H NMR (600 MHz, CDCl_3) of E isomer (major) δ 4.17 (qd, $J_1 = 1.8$ Hz, $J_2 = 7.2$ Hz, 2H), 3.39 (q, $J = 7.2$ Hz, 1H), 1.93 (s, 3H), 1.53 (s, 6H), 1.35 (d, $J = 7.2$ Hz, 3H), 1.26 (t, $J = 7.2$ Hz, 3H). ^1H NMR (600 MHz, CDCl_3) of Z isomer (minor) δ 4.19 (q, $J_2 = 7.2$ Hz, 2H), 3.92 (q, $J = 7.2$ Hz, 1H), 1.94 (s, 3H), 1.52 (d, $J = 14.4$ Hz, 6H), 1.34 (d, $J = 7.2$ Hz, 3H), 1.28 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3) of E isomer (major) δ 177.51, 172.11, 158.33, 81.26, 61.14, 45.86, 24.13, 24.08, 14.27, 14.05. ^{13}C NMR (150 MHz, CDCl_3) of Z isomer (minor) δ 176.97, 172.21, 157.41, 81.42, 61.34, 39.80, 23.90, 17.99, 12.90, 12.67. HRMS (ESI-TOF) Calcd for $\text{C}_{11}\text{H}_{18}\text{NO}_5^-$ [M-H] $^-$: 244.1190, found: 244.1197.



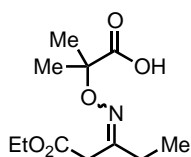
2-(((3-(Benzyloxy)butan-2-ylidene)amino)oxy)-2-methylpropanoic acid (1u)

Colorless oil, E/Z (14.3:1). ^1H NMR (600 MHz, CDCl_3) of E isomer (major) δ 7.34-7.25 (m, 5H), 4.43 (d, $J = 11.4$ Hz, 1H), 4.30 (d, $J = 12.0$ Hz, 1H), 4.05 (q, $J = 6.6$ Hz, 1H), 1.89 (s, 3H), 1.54 (s, 3H), 1.53 (s, 3H), 1.30 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3) of E isomer (major) δ 179.23, 160.11, 137.88, 128.36, 127.87, 127.65, 80.94, 75.46, 70.37, 24.13, 23.99, 18.84, 9.12. HRMS (ESI-TOF) Calcd for $\text{C}_{15}\text{H}_{20}\text{NO}_4^-$ [M-H] $^-$: 278.1398, found: 278.1392.



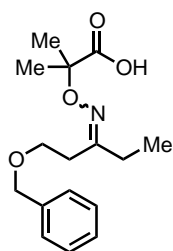
2-((Heptan-3-ylideneamino)oxy)-2-methylpropanoic acid (1v)

Colorless oil, E/Z (1:1). ^1H NMR (600 MHz, CDCl_3) of E/Z mixture δ 2.39-2.34 (m, 2H), 2.31-2.23 (m, 2H), 1.54-1.46 (m, 2H), 1.50 (s, 6H), 1.39-1.31 (m, 2H), 1.13-1.07 (m, 3H), 0.94-0.91 (m, 3H). ^{13}C NMR (150 MHz, CDCl_3) of E/Z mixture δ 176.73, 176.61, 165.99, 80.91, 33.63, 28.19, 27.92, 27.79, 27.75, 24.28, 22.71, 22.22, 21.88, 13.73, 10.41, 10.10. HRMS (ESI-TOF) Calcd for $\text{C}_{11}\text{H}_{20}\text{NO}_3^-$ [M-H] $^-$: 214.1449, found: 214.1443.



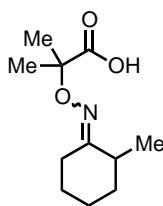
2-(((1-Ethoxy-1-oxopentan-3-ylidene)amino)oxy)-2-methylpropanoic acid (1w)

Colorless oil, E/Z (2.6:1). ¹H NMR (600 MHz, CDCl₃) of E/Z mixture δ 4.22-4.15 (m, 2H), 3.36 (s, 1.5H), 3.24 (s, 0.5H), 2.46 (q, *J* = 7.8 Hz, 0.6H), 2.32 (q, *J* = 7.2 Hz, 1.4H), 1.52 (s, 6H), 1.30-1.26 (m, 3H), 1.12-1.07 (m, 3H). ¹³C NMR (150 MHz, CDCl₃) of E/Z mixture δ 177.50, 176.27, 169.45, 169.34, 158.49, 156.57, 81.83, 81.15, 61.72, 61.19, 39.37, 34.63, 28.69, 24.23, 24.06, 23.93, 21.92, 14.02, 10.16, 9.71. HRMS (ESI-TOF) Calcd for C₁₁H₁₈NO₅⁻ [M-H]⁻: 244.1190, found: 244.1182.



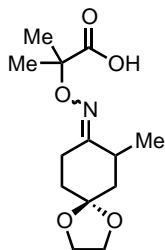
2-(((1-(Benzyloxy)pentan-3-ylidene)amino)oxy)-2-methylpropanoic acid (1x)

Colorless oil, E/Z (1.7:1). ¹H NMR (600 MHz, CDCl₃) of E/Z mixture δ 7.36-7.28 (m, 5H), 4.52 (s, 1.2H), 4.51 (s, 0.7H), 3.70 (t, *J* = 6.6 Hz, 0.8H), 3.63 (t, *J* = 6.6 Hz, 1.2H), 2.68 (t, *J* = 6.6 Hz, 1.2H), 2.56 (t, *J* = 6.6 Hz, 0.7H), 2.39 (q, *J* = 7.8 Hz, 0.7H), 2.26 (t, *J* = 7.2 Hz, 1.3H), 1.51-1.49 (m, 6H), 1.09-1.06 (m, 3H). ¹³C NMR (150 MHz, CDCl₃) of E/Z mixture δ 176.32, 176.18, 163.35, 162.34, 137.95, 137.41, 128.45, 128.38, 127.89, 127.84, 127.71, 127.67, 81.29, 81.04, 73.06, 72.93, 66.54, 66.05, 34.11, 28.95, 27.88, 24.25, 24.08, 22.17, 10.32, 9.96. HRMS (ESI-TOF) Calcd for C₁₆H₂₂NO₄⁻ [M-H]⁻: 292.1554, found: 292.1550.



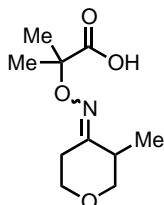
2-Methyl-2-(((2-methylcyclohexylidene)amino)oxy)propanoic acid (1y)

Colorless oil, E/Z (6.6:1). ¹H NMR (600 MHz, CDCl₃) of E/Z mixture δ 3.56-3.51 (m, 0.13H), 3.09-3.06 (m, 0.86H), 2.40-2.22 (m, 1H), 1.97-1.92 (m, 2H), 1.84-1.77 (m, 1.7H), 1.62-1.43 (m, 8.7H), 1.35-1.29 (m, 1H), 1.13-1.10 (m, 3H). ¹³C NMR (150 MHz, CDCl₃) of E/Z mixture δ 176.58, 176.45, 166.98, 166.90, 80.91, 80.89, 37.52, 37.50, 35.70, 31.55, 28.40, 27.73, 26.61, 26.14, 25.01, 24.98, 24.48, 24.30, 24.28, 24.18, 24.16, 20.14, 16.62, 16.32. HRMS (ESI-TOF) Calcd for C₁₁H₁₈NO₃⁻ [M-H]⁻: 212.1292, found: 212.1298.



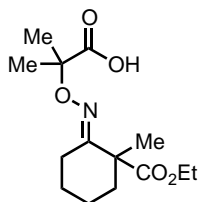
2-Methyl-2-(((7-methyl-1,4-dioxaspiro[4.5]decan-8-ylidene)amino)oxy)propanoic acid (1z)

White solid, E/Z (16.7:1). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 4.01-3.97 (m, 4H), 3.25-3.21 (m, 1H), 2.72-2.65 (m, 1H), 2.16-2.10 (m, 1H), 1.97-1.94 (m, 1H), 1.89-1.86 (m, 1H), 1.71-1.65 (m, 1H), 1.58-1.53 (m, 1H), 1.51 (s, 6H), 1.13-1.11 (m, 3H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 176.45, 164.26, 107.65, 81.15, 64.59, 64.50, 43.13, 34.75, 33.46, 24.26, 24.13, 22.04, 16.09. HRMS (ESI-TOF) Calcd for C₁₃H₂₀NO₅⁻ [M-H]⁻: 270.1347, found: 270.1355.



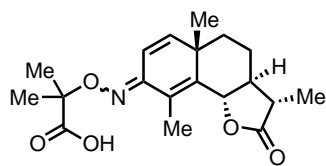
2-Methyl-2-(((3-methyldihydro-2H-pyran-4(3H)-ylidene)amino)oxy)propanoic acid (1aa)

Colorless oil, E/Z (4.0:1). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 3.94-3.90 (m, 2H), 3.63-3.59 (m, 1H), 3.36-3.32 (m, 1H), 3.00-2.96 (m, 1H), 2.59-2.54 (m, 1H), 2.40-2.35 (m, 1H), 1.52 (s, 6H), 1.08 (d, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) of E/Z mixture δ 177.57, 177.20, 161.57, 161.10, 81.05, 80.77, 74.15, 72.16, 68.23, 67.13, 37.01, 30.30, 28.91, 25.80, 24.27, 24.15, 24.12, 24.04, 22.05, 12.79. HRMS (ESI-TOF) Calcd for C₁₀H₁₆NO₄⁻ [M-H]⁻: 214.1085, found: 214.1080.



(E)-2-(((2-(Ethoxycarbonyl)-2-methylcyclohexylidene)amino)oxy)-2-methylpropanoic acid (1ab)

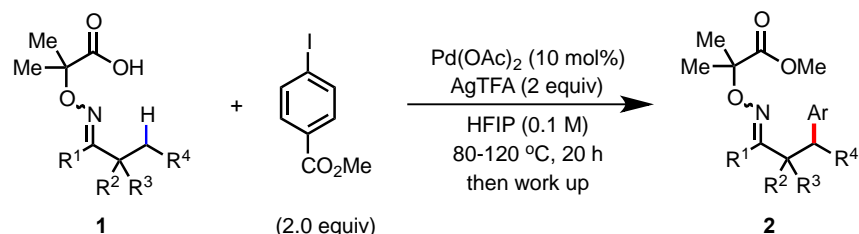
Colorless oil. ¹H NMR (600 MHz, CDCl₃) δ 4.19-4.15 (m, 2H), 3.19-3.15 (m, 1H), 2.42-2.39 (m, 1H), 2.00-1.94 (m, 1H), 1.83-1.80 (m, 1H), 1.71-1.67 (m, 1H), 1.52 (s, 6H), 1.50-1.39 (m, 3H), 1.37-1.35 (m, 3H), 1.27-1.24 (m, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 176.34, 174.02, 163.93, 81.47, 61.26, 50.23, 37.70, 25.40, 24.20, 23.95, 22.57, 22.55, 14.06. HRMS (ESI-TOF) Calcd for C₁₄H₂₂NO₅⁻ [M-H]⁻: 284.1503, found: 284.1500.



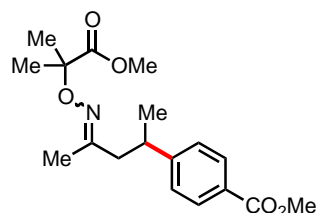
2-Methyl-2-(((3S,3aS,5aS,9bS)-3,5a,9-trimethyl-2-oxo-2,3,3a,4,5,5a-hexahydronaphtho[1,2-b]furan-8(9bH)-ylidene)amino)oxy)propanoic acid (1ac**)**

Pale yellow solid, E/Z (11.1:1). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 6.87 (d, *J* = 10.2 Hz, 3H), 6.15 (d, *J* = 9.6 Hz, 3H), 4.82-4.79 (m, 1H), 2.40-2.34 (m, 1H), 2.14 (s, 3H), 2.03-1.99 (m, 1H), 1.84-1.77 (m, 2H), 1.71-1.64 (m, 1H), 1.58 (s, 3H), 1.57 (s, 3H), 1.52-1.47 (m, 1H), 1.27-1.25 (m, 6H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 177.83, 175.97, 151.79, 147.69, 141.32, 122.22, 112.60, 82.01, 53.48, 40.96, 38.10, 25.60, 24.31, 23.55, 12.44, 12.08. HRMS (ESI-TOF) Calcd for C₁₉H₂₄NO₅ [M-H]⁻: 346.1660, found: 346.1669.

The Scope of Ketones



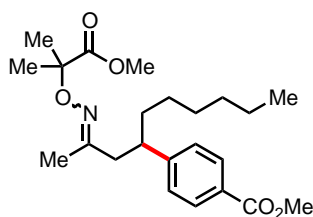
General Procedure for β -C(sp³)-H Arylation of Ketones: Substrate **1** (0.10 mmol), ArI (0.20 mmol, 52.4 mg), Pd(OAc)₂ (0.01 mmol, 2.3 mg), and AgTFA (0.20 mmol, 44.2 mg) were weighed into a reaction vial (10 mL) with a magnetic stir bar under air. HFIP (1.0 mL) was added, and the vial was sealed with a cap. The reaction mixture was stirred at 80-120 °C for 20 hours. Upon completion, the reaction mixture was cooled to room temperature and diluted with EtOAc. Then the reaction mixture was filtered through a short celite plug and transferred to a reaction vial (10 mL) with a magnetic stir bar. The solvent was evaporated under vacuum. Anhydrous MeOH (1.0 mL) was added to the mixture. SOCl₂ (0.30 mmol, 22 μ L) was added dropwise at room temperature. The reaction mixture was stirred at room temperature for 30 min. Upon completion, the solvent was removed under vacuum and the resulting mixture was purified by preparative thin-layer chromatography.



Methyl 4-(4-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)pentan-2-yl)benzoate (2a**)**

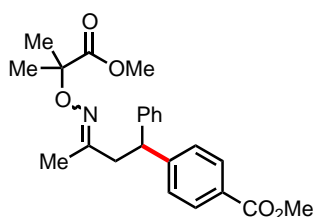
Substrate **1a** was arylated following the general arylation procedure at 120 °C. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2a**

E/Z (3.7:1) was obtained as a colorless oil (25.1 mg, 75%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.96-7.94 (m, 2H), 7.27-7.25 (m, 2H), 3.90 (s, 3H), 3.67 (s, 3H), 3.10 (sextet, *J* = 7.2 Hz, 1H), 2.44 (ABqd, *J*₁ = 7.2 Hz, *J*₂ = 14.4 Hz, 2H), 1.79 (s, 3H), 1.42 (s, 3H), 1.39 (s, 3H), 1.24 (d, *J* = 6.6 Hz, 3H). ¹H NMR (600 MHz, CDCl₃) of Z isomer (minor) δ 7.98-7.96 (m, 2H), 7.32-7.30 (m, 2H), 3.90 (s, 3H), 3.72 (s, 3H), 3.27 (sextet, *J* = 7.2 Hz, 1H), 2.60 (ABqd, *J*₁ = 7.2 Hz, *J*₂ = 13.2 Hz, 2H), 1.62 (s, 3H), 1.49 (s, 3H), 1.44 (s, 3H), 1.30 (d, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) of E/Z mixture δ 174.95, 174.92, 167.06, 156.49, 155.99, 151.95, 151.76, 129.74, 129.73, 128.07, 126.99, 126.96, 80.68, 51.95, 43.80, 37.91, 37.01, 36.79, 24.30, 24.17, 24.06, 24.03, 21.76, 21.52, 20.84, 14.50. HRMS (ESI-TOF) Calcd for C₁₈H₂₆NO₅⁺ [M+H]⁺: 336.1805, found: 336.1800.



Methyl 4-(2-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)decan-4-yl)benzoate (2b)

Substrate **1b** was arylated following the general arylation procedure at 120 °C. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **2b** E/Z (2.8:1) was obtained as a colorless oil (31.7 mg, 78%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.96-7.94 (m, 2H), 7.21-7.20 (m, 2H), 3.90 (s, 3H), 3.66 (s, 3H), 2.94-2.89 (m, 1H), 2.51-2.40 (m, 2H), 1.75 (s, 3H), 1.68-1.61 (m, 1H), 1.56-1.48 (m, 1H), 1.38 (s, 3H), 1.34 (s, 3H), 1.27-1.02 (m, 8H), 1.24 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) of E/Z mixture δ 174.94, 167.11, 156.67, 156.07, 150.46, 130.18, 129.61, 129.60, 128.19, 128.04, 127.70, 127.65, 127.22, 80.60, 80.52, 51.93, 42.91, 42.63, 42.52, 36.08, 31.64, 29.20, 29.13, 27.29, 27.22, 24.33, 24.16, 23.98, 23.95, 22.55, 22.53, 14.52, 13.99. HRMS (ESI-TOF) Calcd for C₂₃H₃₆NO₅⁺ [M+H]⁺: 406.2588, found: 406.2592.

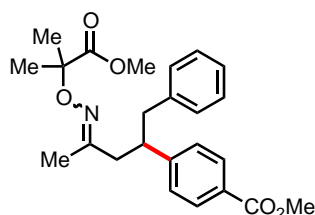


Methyl

4-(3-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)-1-phenylbutyl)benzoate (2c)

Substrate **1c** was arylated following the general arylation procedure at 100 °C. After purification by preparative thin-layer chromatography (Toluene : EtOAc = 30:1 as eluent), **2c** E/Z (2.7:1) was obtained as a colorless oil (20.7 mg, 52%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.94-7.92 (m, 2H), 7.30-7.16 (m, 7H), 4.38 (t, *J* = 8.4 Hz, 1H), 3.88 (s, 3H), 3.60 (s, 3H), 2.96-2.90 (m, 2H), 1.80 (s, 3H), 1.32 (s, 3H), 1.31 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) of E/Z mixture δ 174.82, 166.95, 156.08, 155.32, 149.35, 149.30, 143.27, 143.18,

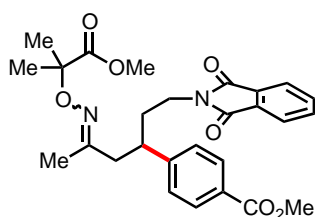
129.74, 129.73, 128.53, 128.33, 128.13, 127.99, 127.92, 127.87, 127.79, 126.67, 126.51, 80.73, 52.00, 51.97, 51.93, 47.72, 47.09, 41.52, 35.68, 24.20, 24.18, 24.02, 20.69, 14.59. HRMS (ESI-TOF) Calcd for $C_{23}H_{28}NO_5^+$ [M+H]⁺: 398.1962, found: 398.1960.



Methyl

4-(4-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)-1-phenylpentan-2-yl)benzoate (2d)

Substrate **1d** was arylated following the general arylation procedure at 120 °C. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2d** E/Z (3.0:1) was obtained as a colorless oil (26.7 mg, 65%). ¹H NMR (600 MHz, CDCl₃) of E/Z mixture δ 7.93-7.91 (m, 0.71H), 7.90-7.88 (m, 2H), 7.24-7.23 (m, 0.72H), 7.21-7.11 (m, 6.2H), 7.05-7.04 (m, 0.74H), 6.95-6.94 (m, 2H), 3.90 (s, 1.0H), 3.88 (s, 3H), 3.70 (s, 1.0H), 3.64 (s, 3H), 3.44-3.39 (m, 0.33H), 3.25 (quintet, *J* = 7.2 Hz, 1H), 2.98-2.92 (m, 1.7H), 2.82-2.79 (m, 1.4H), 2.59-2.49 (m, 2.4H), 1.76 (s, 3H), 1.49 (s, 1.0H), 1.45 (s, 1.0H), 1.39 (s, 4.0H), 1.37 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) of E/Z mixture δ 174.91, 174.86, 167.08, 167.04, 156.37, 155.74, 149.37, 139.45, 129.59, 129.50, 129.11, 129.00, 128.20, 128.13, 127.85, 127.79, 80.72, 51.98, 51.95, 44.62, 44.42, 43.13, 42.58, 41.32, 24.39, 24.18, 24.02, 23.92, 20.82, 14.64. HRMS (ESI-TOF) Calcd for $C_{24}H_{30}NO_5^+$ [M+H]⁺: 412.2118, found: 412.2112.

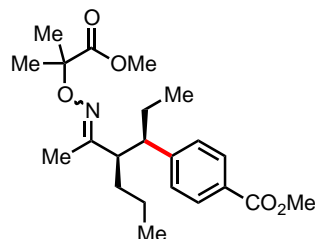


(E)-Methyl

4-(1-(1,3-dioxisoindolin-2-yl)-5-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)hexan-3-yl)benzoate (2e)

Substrate **1e** was arylated following the general arylation procedure at 120 °C. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 2:1 as eluent), **2e** E/Z (2.7:1) was obtained as a colorless oil (24.8 mg, 50%). ¹H NMR (600 MHz, CDCl₃) of E/Z mixture δ 7.89-7.87 (m, 2H), 7.85-7.83 (m, 5.5H), 7.76-7.72 (m, 7.3H), 7.66-7.63 (m, 7.2H), 7.30-7.28 (m, 2H), 7.24-7.22 (m, 5.4H), 3.87 (s, 3H), 3.86 (s, 8.0H), 3.71-3.68 (m, 5.8H), 3.64-3.57 (m, 15.8H), 3.24-3.18 (m, 1H), 3.07-3.02 (m, 2.7H), 2.78 (dd, *J*₁ = 6.0 Hz, *J*₂ = 13.2 Hz, 1H), 2.53-2.50 (m, 3.7H), 2.44-2.41 (m, 2.6H), 2.22-2.10 (m, 3.8H), 2.07-1.99 (m, 3.8Hz), 1.74 (s, 8.0H), 1.51 (s, 3H), 1.43 (s, 3H), 1.38 (s, 3H), 1.37 (s, 8.0H), 1.32 (s, 8.0H). ¹³C NMR (150 MHz, CDCl₃) of E/Z mixture δ 174.83, 168.38, 168.12, 166.76, 155.84,

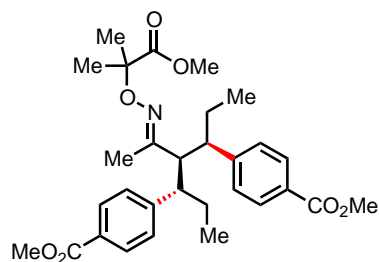
155.36, 148.69, 133.90, 133.75, 133.70, 132.06, 131.94, 131.89, 129.73, 128.18, 127.57, 127.55, 123.18, 123.02, 122.99, 80.68, 80.62, 77.21, 77.00, 76.79, 51.93, 51.88, 43.03, 42.83, 41.11, 37.45, 37.20, 36.46, 33.98, 33.61, 29.92, 27.89, 24.14, 23.93, 23.88, 21.01, 20.74, 14.64. HRMS (ESI-TOF) Calcd for $C_{27}H_{31}N_2O_7^+$ $[M+H]^+$: 495.2126, found: 495.2120.



Methyl

4-(4-(1-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)ethyl)heptan-3-yl)benzoate (2f-mono)

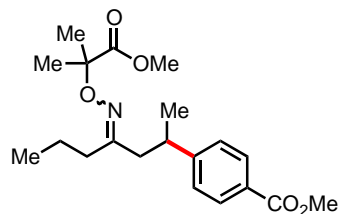
Substrate **1f** was arylated following the general arylation procedure at 80 °C. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2f-mono** E/Z (8.0:1) was obtained as a colorless oil (25.4 mg, 65%, d.r. > 20:1). 1H NMR (600 MHz, $CDCl_3$) of E isomer (major) δ 7.91-7.90 (m, 2H), 7.15-7.14 (m, 2H), 3.89 (s, 3H), 3.65 (s, 3H), 2.59-2.52 (m, 2H), 1.95-1.89 (m, 1H), 1.69-1.63 (m, 1H), 1.52-1.39 (m, 2H), 1.47 (s, 3H), 1.33 (s, 3H), 1.30-1.25 (m, 1H), 1.25 (s, 3H), 1.20-1.11 (m, 1H), 0.89 (t, $J = 7.2$ Hz, 3H), 0.67 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) of E isomer (major) δ 175.13, 167.17, 158.16, 149.07, 129.21, 128.71, 127.88, 80.50, 51.91, 51.80, 50.23, 49.58, 32.20, 26.48, 24.13, 23.80, 20.34, 13.92, 11.75, 11.65. HRMS (ESI-TOF) Calcd for $C_{22}H_{34}NO_5^+$ $[M+H]^+$: 392.2431, found: 392.2427.



Dimethyl

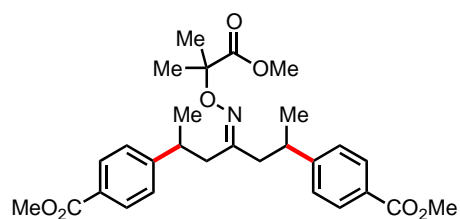
4,4'-(4-((E)-1-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)ethyl)heptane-3,5-diyl)dibenzoate (2f-di)

Substrate **1f** was arylated following the general arylation procedure at 80 °C. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2f-di** was obtained as a colorless oil (5.3 mg, 10%, d.r. > 20:1). 1H NMR (600 MHz, $CDCl_3$) δ 7.91-7.90 (m, 4H), 7.15-7.14 (m, 4H), 3.90 (s, 6H), 3.72 (s, 3H), 3.05 (t, $J = 7.2$ Hz, 1H), 2.86-2.82 (m, 2H), 2.08-2.01 (m, 2H), 1.72-1.66 (m, 2H), 1.33 (s, 6H), 0.80 (t, $J = 7.2$ Hz, 6H), 0.75 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.12, 167.08, 157.08, 148.06, 129.18, 128.20, 80.68, 53.55, 51.99, 51.91, 47.12, 27.28, 24.11, 15.03, 11.86. HRMS (ESI-TOF) Calcd for $C_{30}H_{40}NO_7^+$ $[M+H]^+$: 526.2799, found: 526.2792.



Methyl 4-(4-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)heptan-2-yl)benzoate (2g-mono)

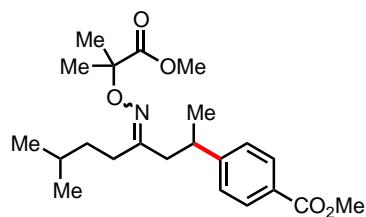
Substrate **1g** was arylated following the general arylation procedure at 120 °C. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2g-mono** E/Z (10:1) was obtained as a colorless oil (8.0 mg, 22%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.96-7.94 (m, 2H), 7.26-7.25 (m, 2H), 3.90 (s, 3H), 3.66 (s, 3H), 3.13 (sextet, *J* = 7.2 Hz, 1H), 2.48-2.45 (m, 1H), 2.40-2.36 (m, 1H), 2.32-2.26 (m, 1H), 2.19-2.14 (m, 1H), 1.52-1.46 (m, 2H), 1.41 (s, 3H), 1.40 (s, 3H), 1.23 (d, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 175.04, 167.12, 159.02, 152.40, 129.71, 127.95, 126.99, 80.62, 51.95, 51.87, 41.97, 36.74, 30.41, 24.10, 24.03, 21.70, 19.08, 14.17. HRMS (ESI-TOF) Calcd for C₂₀H₃₀NO₅⁺ [M+H]⁺: 364.2118, found: 364.2112.



Dimethyl

4,4'-(5-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)nonane-3,7-diyl)dibenzoate (2g-di)

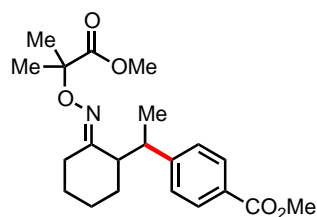
Substrate **1g** was arylated following the general arylation procedure at 120 °C. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2g-di** was obtained as a colorless oil (29.9 mg, 60%, d.r. = 1:1). ¹H NMR (600 MHz, CDCl₃) δ 7.95-7.93 (m, 4H), 7.92-7.90 (m, 4H), 7.26-7.24 (m, 4H), 7.15-7.12 (m, 4H), 3.92 (s, 3H), 3.91 (s, 3H), 3.90 (s, 3H), 3.89 (s, 3H), 3.67 (s, 3H), 3.65 (s, 3H), 3.28-3.21 (m, 2H), 3.07-3.00 (m, 2H), 2.63 (dd, *J*₁ = 7.2 Hz, *J*₂ = 13.2 Hz, 1H), 2.54-2.51 (m, 1H), 2.46-2.42 (m, 1H), 2.32 (dd, *J*₁ = 7.8 Hz, *J*₂ = 12.6 Hz, 1H), 2.25-2.21 (m, 1H), 2.20-2.10 (m, 3H), 1.45 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H), 1.38 (s, 3H), 1.26 (d, *J* = 7.2 Hz, 3H), 1.24 (d, *J* = 7.2 Hz, 3H), 1.13 (d, *J* = 6.6 Hz, 3H), 1.12 (d, *J* = 6.6 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 174.78, 174.76, 167.05, 167.02, 167.00, 166.98, 157.04, 156.93, 152.13, 152.06, 151.61, 129.70, 129.65, 129.62, 128.22, 127.92, 127.89, 126.93, 126.88, 80.87, 80.84, 51.97, 51.92, 51.89, 51.86, 42.67, 42.66, 37.15, 37.12, 36.78, 36.77, 36.57, 36.52, 24.18, 24.14, 23.98, 23.88, 21.77, 21.71, 21.65, 21.55. HRMS (ESI-TOF) Calcd for C₂₈H₃₆NO₇⁺ [M+H]⁺: 498.2486, found: 498.2482.



Methyl

4-(4-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)-7-methyloctan-2-yl)benzoate (2h)

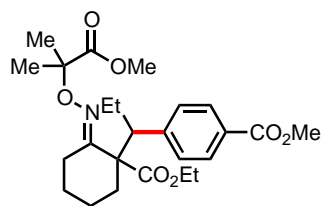
Substrate **1h** was arylated following the general arylation procedure at 120 °C. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2h** E/Z (1.1:1) was obtained as a colorless oil (25.5 mg, 65%). ¹H NMR (600 MHz, CDCl₃) of E/Z mixture δ 7.97-7.94 (m, 4.5H), 7.31-7.29 (m, 2H), 7.27-7.25 (m, 2.6H), 3.90 (s, 3H), 3.89 (s, 3.3H), 3.70 (s, 3H), 3.66 (s, 3.3H), 3.29 (sextet, *J* = 7.2 Hz, 1H), 3.13 (sextet, *J* = 7.2 Hz, 1.1H), 2.66-2.62 (m, 1.1H), 2.49-2.45 (m, 2.3H), 2.40-2.36 (m, 1.1H), 2.32-2.27 (m, 1.3H), 2.20-2.15 (m, 1.2H), 1.94-1.89 (m, 1H), 1.87-1.82 (m, 1.3H), 1.52-1.40 (m, 17H), 1.33-1.21 (m, 12H), 0.89 (d, *J* = 6.6 Hz, 6.6H), 0.79 (t, *J* = 6.6 Hz, 6.1H). ¹³C NMR (150 MHz, CDCl₃) of E/Z mixture δ 174.99, 174.97, 167.07, 167.05, 159.44, 159.24, 152.36, 151.95, 129.69, 129.68, 126.97, 126.95, 80.70, 80.57, 51.95, 51.92, 51.83, 41.87, 36.84, 36.72, 36.60, 34.83, 34.49, 32.47, 28.06, 27.34, 26.44, 24.20, 24.06, 24.00, 22.29, 22.21, 21.70, 21.69. HRMS (ESI-TOF) Calcd for C₂₂H₃₄NO₅⁺ [M+H]⁺: 392.2431, found: 392.2437.



(E)-Methyl

4-(4-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)pentan-2-yl)benzoate (2i)

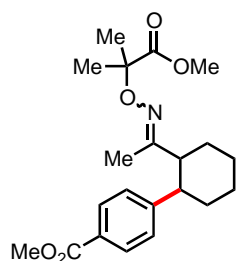
Substrate **1i** was arylated following the general arylation procedure at 80 °C. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **2i** was obtained as a colorless oil (25.5 mg, 68%, d.r. = 2:1). ¹H NMR (600 MHz, CDCl₃) δ 7.93-7.89 (m, 3H), 7.30-7.28 (m, 1H), 7.23-7.20 (m, 2H), 3.89 (s, 1.5H), 3.88 (s, 3H), 3.64 (s, 3H), 3.60 (s, 1.5H), 3.10 (quintet, *J* = 7.2 Hz, 1H), 3.13-3.08 (m, 0.5H), 2.62 (ddd, *J*₁ = 4.2 Hz, *J*₂ = 7.2 Hz, *J*₃ = 13.6 Hz, 1H), 2.46 (td, *J*₁ = 4.8 Hz, *J*₂ = 7.8 Hz, 1H), 2.20-2.15 (m, 1H), 2.07-2.04 (m, 1H), 2.04-2.00 (m, 0.5H), 1.93-1.88 (m, 0.5H), 1.82-1.72 (m, 2H), 1.68-1.62 (m, 2.5H), 1.61-1.51 (m, 2.5H), 1.48-1.36 (m, 1.5H), 1.32 (s, 1.5H), 1.31 (s, 3H), 1.29 (d, *J* = 6.6 Hz, 1.5H), 1.27 (s, 3H), 1.23 (d, *J* = 6.6 Hz, 3H), 1.15 (s, 1.5H). ¹³C NMR (150 MHz, CDCl₃) δ 174.97, 167.17, 161.00, 160.86, 152.34, 150.84, 129.47, 129.35, 128.03, 127.69, 127.65, 80.49, 80.21, 51.92, 51.90, 51.86, 51.72, 48.01, 39.66, 38.85, 38.73, 29.21, 29.06, 28.15, 27.76, 26.24, 24.48, 24.42, 24.08, 23.84, 23.61, 23.29, 20.39, 20.18, 18.16. HRMS (ESI-TOF) Calcd for C₂₁H₃₀NO₅⁺ [M+H]⁺: 376.2118, found: 376.2112.



Methyl

4-(1-((*E*)-1-(ethoxycarbonyl)-2-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)cyclohexylpropyl)benzoate (**2j**)

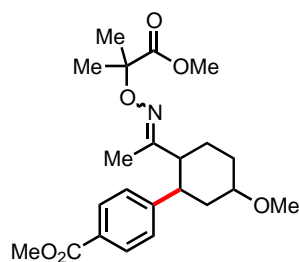
Substrate **1j** was arylated following the general arylation procedure at 100 °C. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2j** was obtained as a colorless oil (33.7 mg, 73%, d.r. = 2.4:1). ¹H NMR (600 MHz, CDCl₃) δ 7.93-7.91 (m, 2H), 7.24-7.22 (m, 2H), 4.23-4.15 (m, 2H), 3.90 (s, 3H), 3.89 (s, 1.3H), 3.82-3.77 (m, 0.80H), 3.77 (s, 1.3H), 3.76 (s, 3H), 3.50-3.47 (m, 0.42H), 3.40-3.37 (m, 0.42H), 3.28-3.22 (m, 2H), 2.40-2.36 (m, 0.40H), 2.10-2.04 (m, 1H), 1.92-1.86 (m, 0.47H), 1.83-1.61 (m, 5.6H), 1.60 (s, 1.3H), 1.55 (s, 6H), 1.54 (s, 1.3H), 1.52-1.39 (m, 1.6H), 1.39-1.31 (m, 2.6H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.24-1.19 (m, 1.1H), 1.06 (t, *J* = 7.2 Hz, 1.3H), 0.65 (t, *J* = 7.2 Hz, 1.3H), 0.62 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 174.88, 174.79, 172.23, 171.88, 167.12, 167.03, 160.21, 157.55, 146.53, 146.23, 130.48, 129.77, 129.16, 128.87, 128.61, 128.51, 81.35, 81.28, 60.77, 58.58, 57.43, 51.93, 51.62, 50.52, 37.01, 25.89, 24.70, 24.58, 24.48, 24.40, 24.34, 24.16, 24.11, 23.88, 23.78, 22.97, 22.42, 14.17, 13.80, 12.81, 12.67. HRMS (ESI-TOF) Calcd for C₂₅H₃₆NO₇⁺ [M+H]⁺: 462.2486, found: 462.2490.



Methyl

4-(2-(1-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)ethyl)cyclohexyl)benzoate (**2k**)

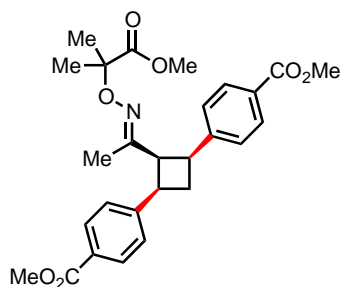
Substrate **1k** was arylated following the general arylation procedure at 80 °C. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **2w** E/Z (7.8:1) was obtained as a colorless oil (27.0 mg, 72%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.92-7.90 (m, 2H), 7.20-7.18 (m, 2H), 3.89 (s, 1.5H), 3.88 (s, 3H), 3.62 (s, 3H), 2.72-2.68 (m, 1H), 2.56-2.52 (m, 1H), 1.88-1.81 (m, 4H), 1.62 (s, 3H), 1.47-1.38 (m, 4H), 1.28 (s, 3H), 1.20 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 174.94, 167.12, 159.73, 150.87, 129.58, 127.86, 127.53, 80.47, 51.91, 51.88, 49.02, 47.06, 35.40, 31.13, 26.38, 25.76, 24.11, 23.71, 12.12. HRMS (ESI-TOF) Calcd for C₂₁H₃₀NO₅⁺ [M+H]⁺: 376.2118, found: 376.2111.



Methyl

4-((5-methoxy-2-(1-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)ethyl)cyclohexyl)benzoate (21)

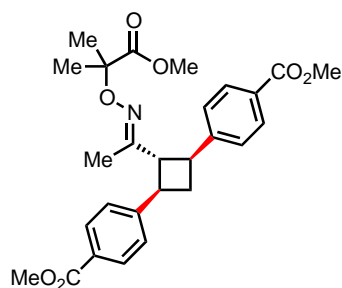
Substrate **11** was arylated following the general arylation procedure at 80 °C. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2x** E/Z (>20:1) was obtained as a colorless oil (27.1 mg, 67%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.95-7.93 (m, 2H), 7.30-7.28 (m, 2H), 3.90 (s, 3H), 3.74 (s, 3H), 3.37 (s, 3H), 3.29-3.24 (m, 1H), 2.95-2.92 (m, 1H), 2.77-2.75 (m, 1H), 2.27-2.21 (m, 1H), 2.10-2.08 (m, 1H), 2.01-1.98 (m, 1H), 1.89-1.87 (m, 1H), 1.75-1.68 (m, 1H), 1.66-1.62 (m, 1H), 1.46 (s, 3H), 1.44 (s, 3H), 1.38 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 174.84, 167.14, 157.59, 149.24, 129.32, 127.83, 127.66, 80.95, 79.81, 55.48, 52.16, 51.94, 46.03, 43.88, 31.21, 27.96, 26.65, 24.26, 24.21, 16.42. HRMS (ESI-TOF) Calcd for C₂₀H₃₂NO₆⁺ [M+H]⁺: 406.2224, found: 406.2220.



Dimethyl

4,4'-(2-((E)-1-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)ethyl)cyclobutane-1,3-diyl)dibenzoate (2m-cis)

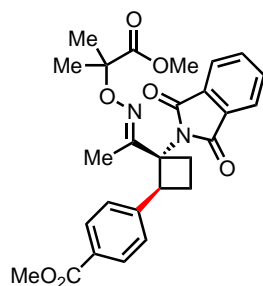
Substrate **1m** was arylated following the general arylation procedure at 80 °C. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2m-cis** was obtained as a colorless oil (20.7 mg, 43%). The assignment of cis/trans structure was based on ¹H NMR patterns by comparing with literatures.² ¹H NMR (600 MHz, CDCl₃) δ 7.96-7.94 (m, 4H), 7.21-7.20 (m, 4H), 4.07-3.99 (m, 3H), 3.90 (s, 6H), 3.70 (s, 3H), 3.00 (q, *J* = 10.8 Hz, 1H), 2.81-2.76 (m, 1H), 1.20 (s, 6H), 1.04 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 174.66, 167.11, 155.16, 146.92, 129.36, 127.70, 126.66, 80.62, 51.95, 51.84, 51.72, 38.45, 29.89, 23.92, 15.38. HRMS (ESI-TOF) Calcd for C₂₇H₃₂NO₇⁺ [M+H]⁺: 482.2173, found: 482.2170.



Dimethyl

4,4'-(2-((*E*)-1-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)ethyl)cyclobutane-1,3-diyl)dibenzoate (2m-trans)

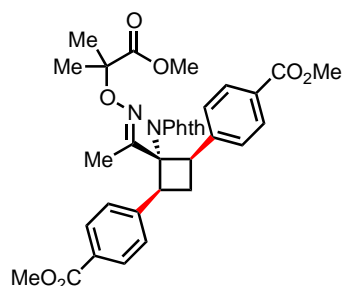
Substrate **1m** was arylated following the general arylation procedure at 80 °C. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2m-trans** was obtained as a colorless oil (18.3 mg, 38%). The assignment of cis/trans structure was based on ¹H NMR patterns by comparing with literatures.² ¹H NMR (600 MHz, CDCl₃) δ 7.99-7.98 (m, 4H), 7.35-7.33 (m, 4H), 3.91 (s, 6H), 3.67 (s, 3H), 3.61 (q, *J* = 9.6 Hz, 2H), 3.12 (t, *J* = 9.6 Hz, 1H), 2.75-2.71 (m, 1H), 2.28 (q, *J* = 10.2 Hz, 1H), 1.73 (s, 3H), 1.51 (s, 6H). ¹³C NMR (150 MHz, CDCl₃) δ 174.76, 166.96, 157.18, 148.70, 129.74, 128.33, 126.84, 81.25, 55.34, 52.02, 52.01, 40.29, 32.62, 24.13, 13.06. HRMS (ESI-TOF) Calcd for C₂₇H₃₂NO₇⁺ [M+H]⁺: 482.2173, found: 482.2175.



Methyl

4-(2-(1,3-dioxoisindolin-2-yl)-2-((*E*)-1-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)ethyl)cyclobutyl)benzoate (2n-mono)

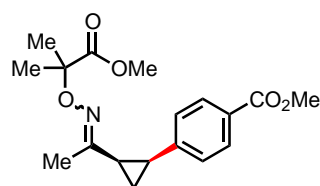
Substrate **1n** was arylated following the general arylation procedure at 80 °C. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 2:1 as eluent), **2n-mono** was obtained as a colorless oil (15.3 mg, 31%). ¹H NMR (600 MHz, CDCl₃) δ 8.01-7.99 (m, 2H), 7.82-7.80 (m, 2H), 7.73-7.71 (m, 2H), 7.62-7.61 (m, 2H), 4.68-4.65 (m, 1H), 3.92 (s, 3H), 3.76 (s, 3H), 3.24 (t, *J* = 7.8 Hz, 1H), 2.41-2.31 (m, 3H), 1.54 (s, 3H), 1.52 (s, 3H), 1.27 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 174.68, 167.97, 167.21, 153.20, 145.09, 134.12, 131.82, 129.26, 129.05, 128.47, 123.10, 81.87, 67.27, 52.00, 46.38, 28.99, 24.38, 23.90, 23.63, 12.24. HRMS (ESI-TOF) Calcd for C₂₇H₂₉N₂O₇⁺ [M+H]⁺: 493.1969, found: 493.1963.



Dimethyl

4,4'-(2-(1,3-dioxoisindolin-2-yl)-2-((*E*)-1-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)ethyl)cyclobutane-1,3-diyl)dibenzoate (**2n-di**)

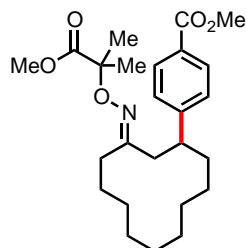
Substrate **1n** was arylated following the general arylation procedure at 80 °C. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 2:1 as eluent), **2n-di** was obtained as a colorless oil (30.7 mg, 49%). ¹H NMR (600 MHz, CDCl₃) δ 7.98-7.96 (m, 4H), 7.88-7.86 (m, 2H), 7.79-7.77 (m, 2H), 7.49-7.47 (m, 4H), 4.83 (t, *J* = 9.6 Hz, 2H), 3.90 (s, 6H), 3.68 (s, 3H), 3.08 (q, *J* = 10.8 Hz, 1H), 2.85 (q, *J* = 10.8 Hz, 1H), 1.21 (s, 6H), 0.99 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 174.27, 168.92, 167.14, 152.48, 145.81, 134.40, 131.54, 129.04, 128.03, 127.98, 123.20, 81.59, 71.98, 51.98, 51.84, 44.14, 23.91, 14.72. HRMS (ESI-TOF) Calcd for C₃₅H₃₅N₂O₉⁺ [M+H]⁺: 627.2337, found: 627.2330.



Methyl

4-(2-((*E*)-1-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)ethyl)cyclopropyl)benzoate (**2o**)

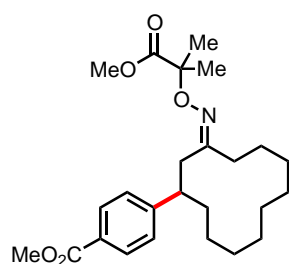
Substrate **1o** was arylated following the general arylation procedure at 120 °C. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2o** E/Z (6.7:1) was obtained as a colorless oil (15.0 mg, 45%). ¹H NMR (600 MHz, CDCl₃) δ 7.89-7.88 (m, 2H), 7.19-7.18 (m, 2H), 3.89 (s, 3H), 3.74 (s, 3H), 2.41-2.37 (m, 1H), 2.02-1.98 (m, 1H), 1.66 (q, *J* = 6.0 Hz, 1H), 1.52 (s, 6H), 1.40 (s, 3H), 1.38 (s, 3H), 1.23-1.19 (m, 1H). ¹³C NMR (150 MHz, CDCl₃) δ 174.90, 167.16, 154.11, 143.70, 129.12, 128.13, 127.82, 80.75, 52.01, 51.95, 26.10, 24.33, 24.05, 23.03, 15.69, 9.31. HRMS (ESI-TOF) Calcd for C₁₈H₂₄NO₅⁺ [M+H]⁺: 334.1649, found: 334.1642.



(*E*)-Methyl

**4-(3-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)cyclododecyl)benzoate
(2p-mono-E)**

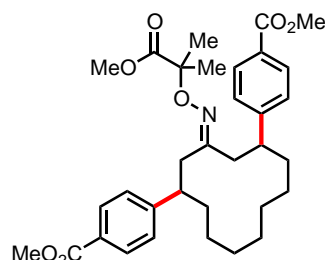
Substrate **1p** was arylated following the general arylation procedure at 120 °C. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **2p-mono-E** was obtained as a colorless oil (20.7 mg, 48% including **2p-mono-Z**). ¹H NMR (600 MHz, CDCl₃) δ 7.98-7.96 (m, 2H), 7.32-7.30 (m, 2H), 3.91 (s, 3H), 3.72 (s, 3H), 3.22 (t, *J* = 12.0 Hz, 1H), 3.02-2.97 (m, 1H), 2.48-2.42 (m, 1H), 2.22-2.17 (m, 1H), 1.99-1.93 (m, 2H), 1.83-1.77 (m, 1H), 1.61-1.53 (m, 3H), 1.50 (s, 3H), 1.47 (s, 3H), 1.44-1.08 (m, 13H). ¹³C NMR (150 MHz, CDCl₃) δ 175.09, 167.08, 157.14, 151.11, 129.76, 128.23, 127.61, 80.89, 51.99, 40.66, 35.20, 30.64, 30.36, 25.83, 24.34, 24.16, 24.04, 23.19, 22.90, 22.56, 22.42. HRMS (ESI-TOF) Calcd for C₂₅H₃₈NO₅⁺ [M+H]⁺: 432.2744, found: 432.2740.



(Z)-Methyl

**4-(3-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)cyclododecyl)benzoate
(2p-mono-Z)**

Substrate **1p** was arylated following the general arylation procedure at 120 °C. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **2p-mono-Z** was obtained as a colorless oil (20.7 mg, 48% including **2p-mono-E**). ¹H NMR (600 MHz, CDCl₃) δ 7.96-7.94 (m, 2H), 7.28-7.26 (m, 2H), 3.90 (s, 3H), 3.68 (s, 3H), 3.30-3.25 (m, 1H), 2.69 (dd, *J*₁ = 10.2 Hz, *J*₂ = 15.0 Hz, 1H), 2.55-2.51 (m, 1H), 2.38-2.34 (m, 1H), 2.30 (dd, *J*₁ = 4.2 Hz, *J*₂ = 15.0 Hz, 1H), 1.78-1.72 (m, 1H), 1.69-1.64 (m, 2H), 1.57-1.52 (m, 1H), 1.48 (s, 3H), 1.46 (s, 3H), 1.42-1.30 (m, 11H), 1.12-1.06 (m, 1H). ¹³C NMR (150 MHz, CDCl₃) δ 175.12, 167.13, 158.21, 151.17, 129.58, 127.91, 127.57, 80.80, 51.96, 39.79, 38.07, 30.66, 27.47, 25.47, 24.68, 24.43, 24.23, 24.18, 23.80, 22.93, 22.77, 21.50. HRMS (ESI-TOF) Calcd for C₂₅H₃₈NO₅⁺ [M+H]⁺: 432.2744, found: 432.2745.

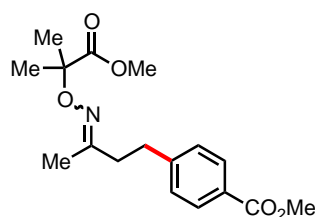


Dimethyl

4,4'-(3-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)cyclododecane-1,5-diyl)dibenzoate (2p-di)

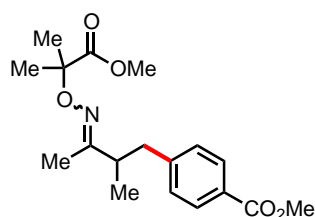
Substrate **1p** was arylated following the general arylation procedure at 120 °C. After

purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **2p-di** was obtained as a colorless oil (22.6 mg, 40%). ¹H NMR (600 MHz, CDCl₃) δ 8.02-7.98 (m, 4H), 7.37-7.32 (m, 4H), 3.92 (s, 3H), 3.91 (s, 3H), 3.73 (s, 3H), 3.20 (t, *J* = 12.6 Hz, 1H), 3.13-3.04 (m, 2H), 2.65 (dd, *J*₁ = 10.8 Hz, *J*₂ = 14.4 Hz, 1H), 2.45 (dd, *J*₁ = 3.6 Hz, *J*₂ = 14.4 Hz, 1H), 2.10 (dd, *J*₁ = 3.0 Hz, *J*₂ = 12.6 Hz, 1H), 2.03-1.95 (m, 2H), 1.71-1.67 (m, 1H), 1.56 (s, 3H), 1.52 (s, 3H), 1.49-1.13 (m, 13H). ¹³C NMR (150 MHz, CDCl₃) δ 174.87, 167.04, 167.01, 156.54, 151.09, 150.97, 129.89, 129.76, 128.40, 128.20, 127.50, 127.36, 81.07, 52.03, 52.01, 51.98, 42.80, 42.75, 42.33, 36.94, 30.37, 29.52, 24.29, 24.23, 24.19, 23.61, 23.37, 22.26, 21.49. HRMS (ESI-TOF) Calcd for C₃₃H₄₄NO₇⁺ [M+H]⁺: 566.3112, found: 566.3117.



Methyl 4-(3-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)butyl)benzoate (**2q**)

Substrate **1q** was arylated following the general arylation procedure at 80 °C except the use of PhCF₃ as solvent instead of HFIP. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2q** E/Z (2.7:1) was obtained as a colorless oil (24.4 mg, 76%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.95-7.93 (m, 2H), 7.25-7.24 (m, 2H), 3.90 (s, 3H), 3.68 (s, 3H), 2.88-2.85 (m, 2H), 2.50-2.48 (m, 2H), 1.87 (s, 3H), 1.44 (s, 6H). ¹H NMR (600 MHz, CDCl₃) of Z isomer (minor) δ 7.97-7.95 (m, 2H), 7.29-7.28 (m, 2H), 3.91 (s, 3.6H), 3.90 (s, 3H), 3.73 (s, 3H), 2.91-2.88 (m, 2H), 2.65-2.62 (m, 2H), 1.75 (s, 3H), 1.48 (s, 6H). ¹³C NMR (150 MHz, CDCl₃) of E/Z mixture δ 174.91, 167.06, 157.26, 156.56, 146.84, 129.71, 129.64, 128.40, 128.04, 127.90, 80.73, 80.54, 51.97, 51.94, 36.99, 32.14, 31.58, 30.98, 24.16, 24.12, 20.47, 14.59. HRMS (ESI-TOF) Calcd for C₁₇H₂₄NO₅⁺ [M+H]⁺: 322.1649, found: 322.1658.

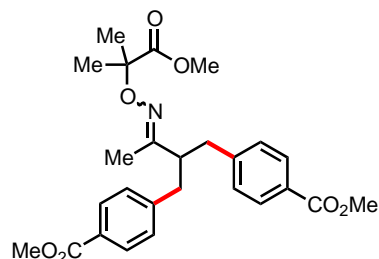


Methyl

4-(3-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)-2-methylbutyl)benzoate (**2r-mono**)

Substrate **1r** was arylated following the general arylation procedure at 80 °C except the use of PhCF₃ as solvent instead of HFIP. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2r-mono** E/Z (8.3:1) was obtained as a colorless oil (10.4 mg, 31%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.94-7.92 (m, 2H), 7.21-7.20 (m, 2H), 3.90 (s, 3H), 3.66 (s, 3H), 2.92-2.87 (m, 1H), 2.70-2.62 (m, 2H), 1.82

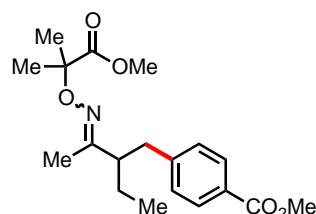
(s, 3H), 1.42 (s, 3H), 1.38 (s, 3H), 1.05 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3) of E isomer (major) δ 174.93, 167.11, 160.18, 145.80, 129.52, 129.02, 127.92, 80.76, 51.96, 51.89, 41.22, 40.12, 24.16, 23.96, 17.89, 12.24. HRMS (ESI-TOF) Calcd for $\text{C}_{18}\text{H}_{26}\text{NO}_5^+$ $[\text{M}+\text{H}]^+$: 336.1805, found: 336.1812.



Dimethyl

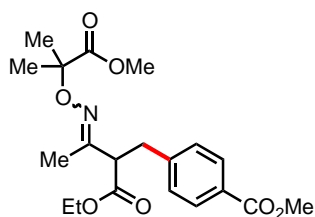
4,4'-(2-(1-((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)ethyl)propane-1,3-diyl)dibenzoate (**2r-di**)

Substrate **1r** was arylated following the general arylation procedure at 80 °C except the use of PhCF_3 as solvent instead of HFIP. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2r-di** E/Z (7.3:1) was obtained as a colorless oil (25.9 mg, 55%). ^1H NMR (600 MHz, CDCl_3) of E isomer (major) δ 7.94-7.92 (m, 4H), 7.19-7.18 (m, 4H), 3.89 (s, 6H), 3.59 (s, 3H), 2.92-2.86 (m, 3H), 2.79-2.76 (m, 2H), 1.70 (s, 3H), 1.32 (s, 6H). ^{13}C NMR (150 MHz, CDCl_3) of E isomer (major) δ 174.79, 166.99, 157.63, 145.00, 129.60, 128.97, 128.13, 80.84, 51.97, 51.88, 48.32, 38.79, 23.99, 13.22. HRMS (ESI-TOF) Calcd for $\text{C}_{26}\text{H}_{32}\text{NO}_7^+$ $[\text{M}+\text{H}]^+$: 470.2173, found: 470.2180.



Methyl 4-(2-ethyl-3-((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)butylbenzoate (**2s**)

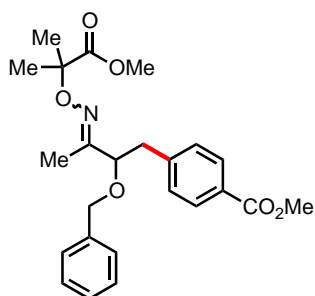
Substrate **1s** was arylated following the general arylation procedure at 80 °C except the use of PhCF_3 as solvent instead of HFIP. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2s** E/Z (9.1:1) was obtained as a colorless oil (28.6 mg, 82%). ^1H NMR (600 MHz, CDCl_3) of E isomer (major) δ 7.93-7.92 (m, 2H), 7.20-7.19 (m, 2H), 3.89 (s, 3H), 3.64 (s, 3H), 2.82-2.72 (m, 2H), 2.51 (quintet, $J = 7.2$ Hz, 1H), 1.75 (s, 3H), 1.48 (quintet, $J = 7.2$ Hz, 2H), 1.42 (s, 3H), 1.37 (s, 3H), 0.82 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3) of E isomer (major) δ 175.02, 167.11, 158.57, 145.76, 129.50, 128.97, 127.88, 80.71, 51.95, 51.86, 48.02, 38.50, 24.90, 24.13, 23.92, 11.77, 11.28. HRMS (ESI-TOF) Calcd for $\text{C}_{19}\text{H}_{28}\text{NO}_5^+$ $[\text{M}+\text{H}]^+$: 350.1962, found: 350.1961.



Methyl

4-(2-(ethoxycarbonyl)-3-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)butyl)benzoate (2t)

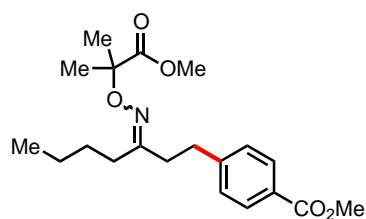
Substrate **1t** was arylated following the general arylation procedure at 120 °C. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2t** E/Z (3.9:1) was obtained as a colorless oil (31.4 mg, 80%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.94-7.92 (m, 2H), 7.25-7.23 (m, 2H), 4.15-4.06 (m, 2H), 3.90 (s, 3H), 3.66 (s, 3H), 3.57 (t, *J* = 7.8 Hz, 2H), 3.23 (dd, *J*₁ = 7.8 Hz, *J*₂ = 14.4 Hz, 1H), 3.04 (dd, *J*₁ = 7.8 Hz, *J*₂ = 14.4 Hz, 1H), 1.88 (s, 3H), 1.44 (s, 3H), 1.39 (s, 3H), 1.19 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) of E/Z mixture δ 174.54, 174.47, 170.99, 170.87, 167.00, 166.97, 154.02, 153.52, 144.41, 144.01, 129.65, 129.04, 128.93, 128.36, 81.31, 81.13, 61.09, 60.99, 52.84, 52.02, 51.99, 51.95, 47.22, 34.90, 24.10, 24.08, 24.02, 23.90, 14.06, 14.04, 12.96. HRMS (ESI-TOF) Calcd for C₂₀H₂₈NO₇⁺ [M+H]⁺: 394.1860, found: 394.1862.



Methyl

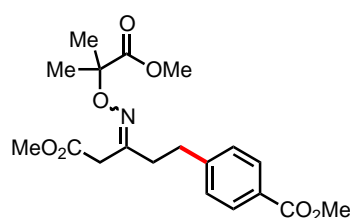
4-(2-(benzyloxy)-3-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)butyl)benzoate (2u)

Substrate **1u** was arylated following the general arylation procedure at 100 °C. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2u** E/Z (12:1) was obtained as a colorless oil (17.1 mg, 40%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.93-7.92 (m, 2H), 7.27-7.23 (m, 5H), 7.14-7.13 (m, 2H), 4.43 (d, *J* = 12.0 Hz, 1H), 4.22 (d, *J* = 12.0 Hz, 1H), 4.12 (dd, *J*₁ = 6.0 Hz, *J*₂ = 8.4 Hz, 1H), 3.91 (s, 3H), 3.66 (s, 3H), 3.06 (dd, *J*₁ = 8.4 Hz, *J*₂ = 13.8 Hz, 1H), 2.85 (dd, *J*₁ = 6.0 Hz, *J*₂ = 13.8 Hz, 1H), 1.91 (s, 3H), 1.48 (s, 3H), 1.41 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 174.62, 167.09, 156.91, 143.08, 129.53, 129.48, 129.41, 128.28, 128.24, 127.67, 127.63, 81.18, 80.15, 70.42, 52.00, 39.40, 24.19, 23.91, 9.53. HRMS (ESI-TOF) Calcd for C₂₄H₃₀NO₆⁺ [M+H]⁺: 428.2068, found: 428.2067.



Methyl 4-(3-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)heptyl)benzoate (**2v**)

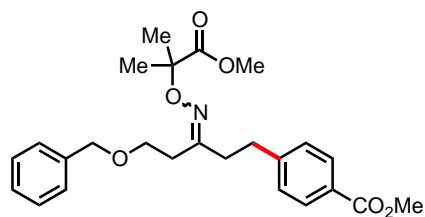
Substrate **1v** was arylated following the general arylation procedure at 80 °C except the use of PhCF₃ as solvent instead of HFIP. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2v** E/Z (1.2:1) was obtained as a colorless oil (27.2 mg, 75%). ¹H NMR (600 MHz, CDCl₃) of E/Z mixture δ 7.97-7.93 (m, 4.5H), 7.29-7.28 (m, 2.4H), 7.26-7.24 (m, 2H), 3.91 (s, 3.6H), 3.90 (s, 3H), 3.72 (s, 3.6H), 3.68 (s, 3H), 2.91-2.89 (m, 2.4H), 2.87-2.84 (m, 2H), 2.59-2.57 (m, 2.4H), 2.49-2.46 (m, 2H), 2.33-2.30 (m, 2H), 2.06-2.04 (m, 2.4H), 1.49 (s, 7.2H), 1.45 (s, 6H), 1.48-1.39 (m, 4.4H), 1.36-1.31 (m, 2H), 1.29-1.25 (m, 2.5H), 0.91 (t, *J* = 7.2 Hz, 3H), 0.86 (t, *J* = 7.2 Hz, 3.6H). ¹³C NMR (150 MHz, CDCl₃) of E/Z mixture δ 174.98, 174.96, 167.10, 167.07, 159.91, 159.88, 147.24, 147.14, 129.78, 129.70, 129.61, 128.40, 128.37, 127.99, 80.67, 80.66, 51.96, 51.93, 51.88, 51.86, 35.19, 34.17, 32.04, 31.80, 30.04, 29.64, 28.23, 28.08, 27.80, 25.83, 24.12, 24.08, 22.65, 22.08, 13.78, 13.75. HRMS (ESI-TOF) Calcd for C₂₀H₃₀NO₅⁺ [M+H]⁺: 364.2118, found: 364.2113.



Methyl

4-(5-methoxy-3-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)-5-oxopentyl)benzoate (**2w**)

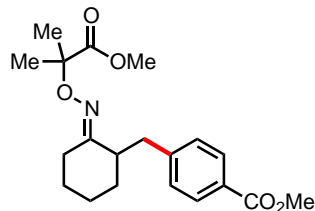
Substrate **1w** was arylated following the general arylation procedure at 80 °C. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2w** E/Z (1.8:1) was obtained as a colorless oil (29.9 mg, 79%). ¹H NMR (600 MHz, CDCl₃) of E/Z mixture δ 7.97-7.94 (m, 3.1H), 7.29-7.25 (m, 3.1H), 3.91 (s, 1.6H), 3.90 (s, 3H), 3.72 (s, 1.6H), 3.69 (s, 3H), 3.68 (s, 4.6H), 3.34 (s, 2H), 3.08 (s, 1.1H), 2.94-2.90 (m, 3.2H), 2.73-2.70 (m, 1.1H), 2.63-2.60 (m, 2H), 1.50 (s, 3.5H), 1.44 (s, 6H). ¹³C NMR (150 MHz, CDCl₃) of E/Z mixture δ 174.52, 174.44, 169.98, 169.24, 167.06, 167.03, 154.12, 152.52, 146.63, 129.78, 129.66, 128.41, 128.38, 128.14, 127.96, 81.33, 52.03, 52.00, 51.96, 39.95, 35.85, 34.68, 31.69, 31.34, 30.16, 24.06, 23.99. HRMS (ESI-TOF) Calcd for C₁₉H₂₆NO₇⁺ [M+H]⁺: 380.1704, found: 380.1700.



Methyl

4-(5-(benzyloxy)-3-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)pentyl)benzoate (2x)

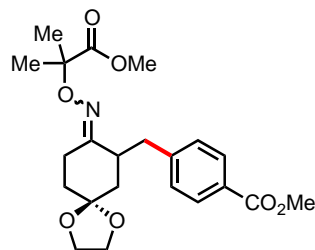
Substrate **1x** was arylated following the general arylation procedure at 100 °C. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2x** E/Z (1:1.2) was obtained as a colorless oil (30.9 mg, 70%). ¹H NMR (600 MHz, CDCl₃) of E/Z mixture δ 7.95-7.91 (m, 3.7H), 7.35-7.28 (m, 5.1H), 7.25-7.23 (m, 1.7H), 7.22-7.20 (m, 2H), 4.50 (s, 2H), 4.47 (s, 1.7H), 3.91 (s, 2.5H), 3.90 (s, 3H), 3.69 (s, 2.4H), 3.68-3.67 (m, 2H), 3.66 (s, 3H), 3.61-3.59 (m, 1.7H), 2.91-2.88 (m, 1.8H), 2.88-2.85 (m, 2H), 2.67-2.65 (m, 2H), 2.64-2.62 (m, 1.8H), 2.57-2.54 (m, 2H), 2.40-2.38 (m, 1.7H), 1.48 (s, 5.5H), 1.43 (s, 5.5H). ¹³C NMR (150 MHz, CDCl₃) of E/Z mixture δ 174.82, 167.13, 167.08, 157.87, 157.65, 147.18, 146.98, 138.22, 129.73, 129.61, 128.43, 128.41, 128.37, 128.35, 128.03, 127.80, 127.63, 127.60, 127.58, 127.55, 80.89, 80.88, 72.94, 72.83, 67.31, 66.58, 51.99, 51.96, 51.93, 36.06, 34.87, 31.90, 31.61, 30.52, 29.66, 24.11, 24.09. HRMS (ESI-TOF) Calcd for C₂₅H₃₂NO₆⁺ [M+H]⁺: 442.2224, found: 442.2228.



(E)-Methyl

4-((2-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)cyclohexyl)methyl)benzoate (2y)

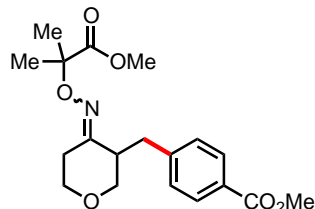
Substrate **1y** was arylated following the general arylation procedure at 80 °C except the use of PhCF₃ as solvent instead of HFIP. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2y** E/Z (>20:1) was obtained as a colorless oil (28.2 mg, 78%). ¹H NMR (600 MHz, CDCl₃) δ 7.93-7.92 (m, 2H), 7.22-7.21 (m, 2H), 3.89 (s, 3H), 3.68 (s, 3H), 3.14 (dd, *J*₁ = 6.0 Hz, *J*₂ = 13.8 Hz, 1H), 3.05-3.01 (m, 1H), 2.54 (dd, *J*₁ = 7.8 Hz, *J*₂ = 13.8 Hz, 1H), 2.49-2.45 (m, 1H), 2.00-1.95 (m, 1H), 1.79-1.72 (m, 3H), 1.53-1.39 (m, 2H), 1.45 (s, 3H), 1.44 (s, 3H), 1.31-1.26 (m, 1H). ¹³C NMR (150 MHz, CDCl₃) δ 174.98, 167.15, 161.60, 146.70, 129.42, 129.13, 80.69, 51.91, 51.88, 43.81, 37.20, 33.08, 26.24, 24.90, 24.51, 24.11, 23.95. HRMS (ESI-TOF) Calcd for C₂₀H₂₈NO₅⁺ [M+H]⁺: 362.1962, found: 362.1960.



Methyl

4-((8-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)-1,4-dioxaspiro[4.5]decan-7-yl)methyl)benzoate (**2z**)

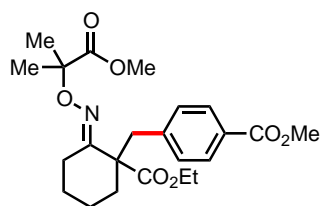
Substrate **1z** was arylated following the general arylation procedure at 80 °C except the use of PhCF₃ as solvent and AgOAc (2.0 equiv) instead of HFIP and AgTFA (2.0 equiv) respectively. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 3:1 as eluent), **2z** E/Z (4.5:1) was obtained as a colorless oil (27.2 mg, 65%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.93-7.92 (m, 2H), 7.23-7.21 (m, 2H), 3.95-3.85 (m, 4H), 3.90 (s, 3H), 3.68 (s, 3H), 3.20-3.16 (m, 2H), 2.85-2.79 (m, 1H), 2.56 (dd, *J*₁ = 8.4 Hz, *J*₂ = 14.4 Hz, 1H), 2.16 (ddd, *J*₁ = 5.4 Hz, *J*₂ = 12.6 Hz, *J*₃ = 14.4 Hz, 1H), 1.85-1.76 (m, 2H), 1.74-1.67 (m, 1H), 1.52-1.48 (m, 1H), 1.47 (s, 3H), 1.45 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 174.82, 167.19, 159.61, 146.21, 129.51, 129.48, 129.18, 108.00, 81.00, 64.52, 64.35, 51.95, 40.88, 40.53, 36.84, 33.81, 24.10, 24.00, 21.69. HRMS (ESI-TOF) Calcd for C₂₂H₃₀NO₇⁺ [M+H]⁺: 420.2017, found: 420.2021.



Methyl

4-((4-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)tetrahydro-2H-pyran-3-yl)methyl)benzoate (**2aa**)

Substrate **1aa** was arylated following the general arylation procedure at 80 °C except the use of PhCF₃ as solvent instead of HFIP. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 3:1 as eluent), **2aa** E/Z (15:1) was obtained as a colorless oil (27.2 mg, 75%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.95-7.93 (m, 2H), 7.24-7.23 (m, 2H), 3.90 (s, 3H), 3.80-3.71 (m, 3H), 3.69 (s, 3H), 3.50-3.47 (m, 1H), 3.09-3.05 (m, 1H), 2.82 (ddd, *J*₁ = 4.8 Hz, *J*₂ = 6.0 Hz, *J*₃ = 14.4 Hz, 1H), 2.73-2.67 (m, 2H), 2.82 (ddd, *J*₁ = 5.4 Hz, *J*₂ = 7.2 Hz, *J*₃ = 14.4 Hz, 1H), 1.44 (s, 3H), 1.43 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 174.69, 167.04, 157.09, 145.07, 129.65, 129.09, 128.12, 80.99, 71.87, 67.38, 51.99, 43.17, 34.71, 25.40, 24.10, 23.94. HRMS (ESI-TOF) Calcd for C₁₉H₂₆NO₆⁺ [M+H]⁺: 364.1755, found: 364.1750.

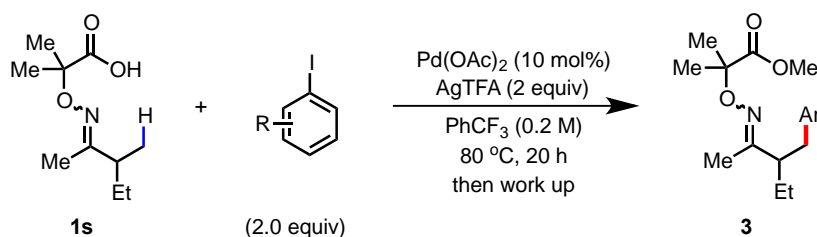


(E)-Methyl

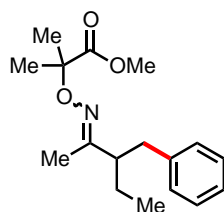
4-(((1-(ethoxycarbonyl)-2-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)cyclohexyl)methyl)benzoate (**2ab**)

Substrate **1ab** was arylated following the general arylation procedure at 80 °C. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **2ab** was obtained as a colorless oil (38.1 mg, 88%). ¹H NMR (600 MHz, CDCl₃) δ 7.90-7.88 (m, 2H), 7.20-7.18 (m, 2H), 4.03 (q, *J* = 7.2 Hz, 2H), 3.89 (s, 3H), 3.74 (s, 1.6H), 3.39 (d, *J* = 13.8 Hz, 1H), 3.31-3.27 (m, 1H), 2.92 (d, *J* = 13.8 Hz, 1H), 2.29-2.26 (m, 1H), 1.79-1.73 (m, 2H), 1.68-1.64 (m, 1H), 1.54 (s, 3H), 1.53 (s, 3H), 1.52-1.46 (m, 1H), 1.43-1.35 (m, 2H), 1.14 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 174.83, 172.44, 167.08, 159.87, 143.07, 130.52, 129.02, 128.26, 81.26, 60.89, 55.03, 51.99, 51.94, 41.08, 35.78, 25.56, 24.34, 24.18, 24.01, 22.69, 13.98. HRMS (ESI-TOF) Calcd for C₂₃H₃₂NO₇⁺ [M+H]⁺: 434.2173, found: 434.2169.

The Scope of Aryl Iodides

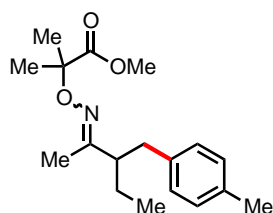


General Procedure for β -C(sp³)-H Arylation of **1s:** Substrate **1s** (0.10 mmol, 20.1 mg), ArI (0.20 mmol), Pd(OAc)₂ (0.01 mmol, 2.3 mg), and AgTFA (0.20 mmol, 44.2 mg) were weighed into a reaction vial (10 mL) with a magnetic stir bar under air. PhCF₃ (0.5 mL) was added, and the vial was sealed with a cap. The reaction mixture was stirred at 80 °C for 20 hours. Upon completion, the reaction mixture was cooled to room temperature and diluted with EtOAc. Then the reaction mixture was filtered through a short celite plug and transferred to a reaction vial (10 mL) with a magnetic stir bar. The solvent was evaporated under vacuum. Anhydrous MeOH (1.0 mL) was added to the mixture. SOCl₂ (0.30 mmol, 22 μ L) was added dropwise at room temperature. The reaction mixture was stirred at room temperature for 30 min. Upon completion, the solvent was removed under vacuum and the resulting mixture was purified by preparative thin-layer chromatography.



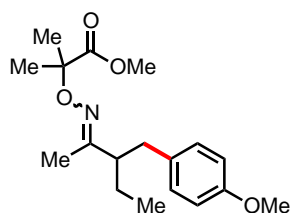
Methyl 2-(((3-benzylpentan-2-ylidene)amino)oxy)-2-methylpropanoate (**3a**)

Substrate **1s** was arylated following the general arylation procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **3a** E/Z (9.1:1) was obtained as a colorless oil (25.9 mg, 89%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.25-7.23 (m, 2H), 7.16-7.14 (m, 1H), 7.12-7.11 (m, 2H), 3.64 (s, 3H), 2.76-2.73 (m, 1H), 2.69-2.65 (m, 1H), 2.51-2.46 (m, 1H), 1.76 (s, 3H), 1.49-1.45 (m, 2H), 1.43 (s, 3H), 1.37 (s, 3H), 0.81 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 175.10, 159.07, 140.09, 128.92, 128.12, 125.83, 80.64, 51.83, 48.26, 38.63, 24.70, 24.13, 23.91, 11.60, 11.38. HRMS (ESI-TOF) Calcd for C₁₇H₂₆NO₃⁺ [M+H]⁺: 292.1907, found: 292.1913.



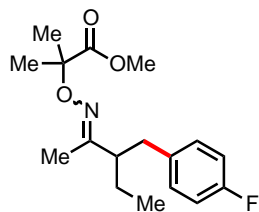
Methyl 2-methyl-2-(((3-(4-methylbenzyl)pentan-2-ylidene)amino)oxy)propanoate (**3b**)

Substrate **1s** was arylated following the general arylation procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **3b** E/Z (9.1:1) was obtained as a colorless oil (28.1 mg, 92%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.06-7.04 (m, 2H), 7.01-7.00 (m, 2H), 3.64 (s, 3H), 2.72-2.69 (m, 1H), 2.64-2.60 (m, 1H), 2.48-2.43 (m, 1H), 2.29 (s, 3H), 1.74 (s, 3H), 1.48-1.42 (m, 2H), 1.43 (s, 3H), 1.39 (s, 3H), 0.80 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 175.14, 159.24, 136.97, 135.21, 128.80, 80.62, 51.81, 48.32, 38.21, 24.59, 24.13, 23.92, 20.93, 11.60, 11.39. HRMS (ESI-TOF) Calcd for C₁₈H₂₈NO₃⁺ [M+H]⁺: 306.2064, found: 306.2068.



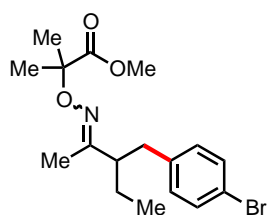
Methyl 2-(((3-(4-methoxybenzyl)pentan-2-ylidene)amino)oxy)-2-methylpropanoate (**3c**)

Substrate **1s** was arylated following the general arylation procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **3c** E/Z (9.1:1) was obtained as a colorless oil (28.6 mg, 89%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.04-7.03 (m, 2H), 6.80-6.78 (m, 2H), 3.77 (s, 3H), 3.65 (s, 3H), 2.70-2.66 (m, 1H), 2.63-2.59 (m, 1H), 2.45-2.40 (m, 1H), 1.75 (s, 3H), 1.48-1.38 (m, 2H), 1.43 (s, 3H), 1.39 (s, 3H), 0.80 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 175.13, 159.23, 157.78, 132.17, 129.81, 113.56, 80.63, 55.19, 51.84, 48.47, 37.77, 24.61, 24.14, 23.95, 11.60, 11.41. HRMS (ESI-TOF) Calcd for C₁₈H₂₈NO₄⁺ [M+H]⁺: 322.2013, found: 322.2008.



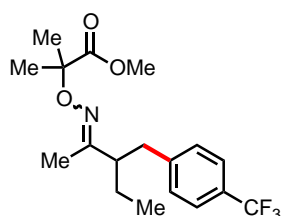
Methyl 2-(((3-(4-fluorobenzyl)pentan-2-ylidene)amino)oxy)-2-methylpropanoate (3d)

Substrate **1s** was arylated following the general arylation procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **3d** E/Z (9.1:1) was obtained as a colorless oil (25.6 mg, 83%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.08-7.06 (m, 2H), 6.95-6.91 (m, 2H), 3.64 (s, 3H), 2.73-2.64 (m, 2H), 2.46-2.42 (m, 1H), 1.74 (s, 3H), 1.49-1.38 (m, 2H), 1.42 (s, 3H), 1.38 (s, 3H), 0.82 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 175.05, 161.27 (d, *J* = 242.7 Hz), 158.79, 135.72 (d, *J* = 3.2 Hz), 130.23 (d, *J* = 7.6 Hz), 114.85 (d, *J* = 21.0 Hz), 80.66, 51.84, 48.40, 37.72, 24.77, 24.12, 23.91, 11.59, 11.35. HRMS (ESI-TOF) Calcd for C₁₇H₂₅FNO₃⁺ [M+H]⁺: 310.1813, found: 310.1810.



Methyl 2-(((3-(4-bromobenzyl)pentan-2-ylidene)amino)oxy)-2-methylpropanoate (3e)

Substrate **1s** was arylated following the general arylation procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **3e** E/Z (9.1:1) was obtained as a colorless oil (33.3 mg, 90%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.37-7.35 (m, 2H), 7.00-6.98 (m, 2H), 3.64 (s, 3H), 2.71-2.62 (m, 2H), 2.47-2.42 (m, 1H), 1.74 (s, 3H), 1.49-1.38 (m, 2H), 1.42 (s, 3H), 1.38 (s, 3H), 0.82 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 175.01, 158.61, 139.10, 131.17, 130.66, 119.62, 80.68, 51.87, 48.16, 37.88, 24.81, 24.11, 23.92, 11.65, 11.31. HRMS (ESI-TOF) Calcd for C₁₇H₂₅BrNO₃⁺ [M+H]⁺: 370.1012, found: 370.1018.

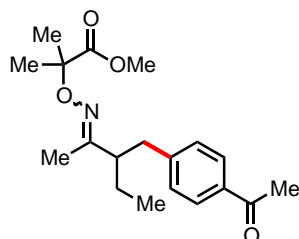


Methyl

2-methyl-2-(((3-(4-(trifluoromethyl)benzyl)pentan-2-ylidene)amino)oxy)propanoate (3f)

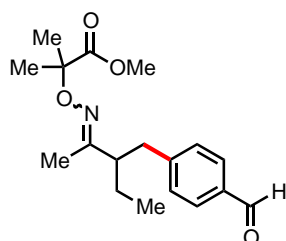
Substrate **1s** was arylated following the general arylation procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **3f** E/Z (9.1:1) was obtained as a colorless oil (32.3 mg, 90%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ

7.51-7.49 (m, 2H), 7.24-7.22 (m, 2H), 3.62 (s, 3H), 2.82-2.73 (m, 2H), 2.53-2.48 (m, 1H), 1.76 (s, 3H), 1.50 (quintet, $J = 7.2$ Hz, 2H), 1.41 (s, 3H), 1.35 (s, 3H), 0.84 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3) of E isomer (major) δ 174.97, 158.36, 144.34, 129.20, 128.23 (q, $J = 31.6$ Hz), 125.05 (q, $J = 3.4$ Hz), 124.31 (q, $J = 270.2$ Hz), 80.72, 51.81, 48.10, 38.22, 24.94, 24.08, 23.84, 11.65, 11.26. HRMS (ESI-TOF) Calcd for $\text{C}_{18}\text{H}_{25}\text{F}_3\text{NO}_3^+$ $[\text{M}+\text{H}]^+$: 360.1781, found: 360.1787.



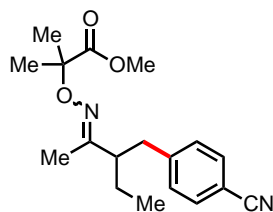
Methyl 2-(((3-(4-acetylbenzyl)pentan-2-ylidene)amino)oxy)-2-methylpropanoate (**3g**)

Substrate **1s** was arylated following the general arylation procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **3g** E/Z (9.1:1) was obtained as a colorless oil (25.0 mg, 75%). ^1H NMR (600 MHz, CDCl_3) of E isomer (major) δ 7.86-7.85 (m, 2H), 7.23-7.21 (m, 2H), 3.64 (s, 3H), 2.83-2.80 (m, 1H), 2.76-2.73 (m, 1H), 2.57 (s, 3H), 2.54-2.49 (m, 1H), 1.76 (s, 3H), 1.49 (quintet, $J = 7.2$ Hz, 2H), 1.42 (s, 3H), 1.37 (s, 3H), 0.83 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3) of E isomer (major) δ 197.82, 174.97, 158.53, 146.07, 135.09, 129.14, 128.32, 80.71, 51.85, 48.01, 38.44, 26.52, 24.90, 24.12, 23.90, 11.79, 11.26. HRMS (ESI-TOF) Calcd for $\text{C}_{19}\text{H}_{28}\text{NO}_4^+$ $[\text{M}+\text{H}]^+$: 334.2013, found: 334.2010.



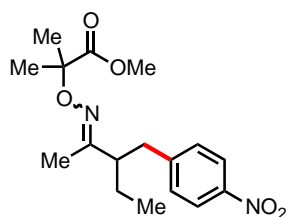
Methyl 2-(((3-(4-formylbenzyl)pentan-2-ylidene)amino)oxy)-2-methylpropanoate (**3h**)

Substrate **1s** was arylated following the general arylation procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **3h** E/Z (9.1:1) was obtained as a colorless oil (26.2 mg, 82%). ^1H NMR (600 MHz, CDCl_3) of E isomer (major) δ 9.96 (s, 1H), 7.78-7.76 (m, 2H), 7.30-7.29 (m, 2H), 3.63 (s, 3H), 2.86-2.82 (m, 1H), 2.79-2.76 (m, 1H), 2.56-2.51 (m, 1H), 1.76 (s, 3H), 1.50 (quintet, $J = 7.2$ Hz, 2H), 1.41 (s, 3H), 1.36 (s, 3H), 0.84 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3) of E isomer (major) δ 191.94, 174.93, 158.36, 147.75, 134.54, 129.72, 129.61, 80.73, 51.86, 47.99, 38.60, 24.98, 24.11, 23.89, 11.79, 11.25. HRMS (ESI-TOF) Calcd for $\text{C}_{18}\text{H}_{26}\text{NO}_4^+$ $[\text{M}+\text{H}]^+$: 320.1856, found: 320.1851.



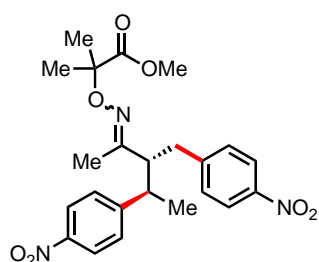
Methyl 2-(((3-(4-cyanobenzyl)pentan-2-ylidene)amino)oxy)-2-methylpropanoate (3i)

Substrate **1s** was arylated following the general arylation procedure except the use of HFIP (1.0 mL) as solvent instead of PhCF₃ (0.5 mL). After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **3i** E/Z (9.1:1) was obtained as a colorless oil (29.7 mg, 94%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.55-7.53 (m, 2H), 7.24-7.23 (m, 2H), 3.64 (s, 3H), 2.83-2.79 (m, 1H), 2.77-2.73 (m, 1H), 2.52-2.47 (m, 1H), 1.75 (s, 3H), 1.53-1.47 (m, 2H), 1.41 (s, 3H), 1.36 (s, 3H), 0.84 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 174.83, 158.07, 145.94, 131.93, 129.69, 118.99, 109.73, 80.72, 51.83, 47.89, 38.37, 24.98, 24.07, 23.86, 11.76, 11.17. HRMS (ESI-TOF) Calcd for C₁₈H₂₅N₂O₃⁺ [M+H]⁺: 317.1860, found: 317.1868.



Methyl 2-methyl-2-(((3-(4-nitrobenzyl)pentan-2-ylidene)amino)oxy)propanoate (3j-mono)

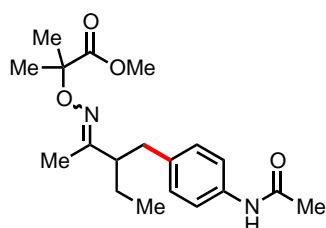
Substrate **1s** was arylated following the general arylation procedure except the use of HFIP (1.0 mL) as solvent instead of PhCF₃ (0.5 mL). After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **3j-mono** E/Z (9.1:1) was obtained as a colorless oil (26.9 mg, 80%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 8.13-7.10 (m, 2H), 7.30-7.28 (m, 2H), 3.64 (s, 3H), 2.89-2.85 (m, 1H), 2.82-2.78 (m, 1H), 2.55-2.50 (m, 1H), 1.76 (s, 3H), 1.54-1.50 (m, 2H), 1.41 (s, 3H), 1.37 (s, 3H), 0.85 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 174.82, 158.01, 148.20, 146.36, 129.72, 123.39, 80.76, 51.84, 47.94, 38.10, 25.07, 24.09, 23.90, 11.88, 11.16. HRMS (ESI-TOF) Calcd for C₁₇H₂₅N₂O₅⁺ [M+H]⁺: 337.1758, found: 337.1752.



Methyl 2-methyl-2-(((3R,4R)-3-(4-nitrobenzyl)-4-(4-nitrophenyl)pentan-2-ylidene)amino)oxy)propanoate

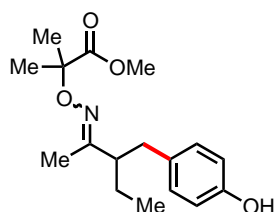
ropanoate (**1j-di**)

Substrate **1s** was arylated following the general arylation procedure except the use of HFIP (1.0 mL) as solvent instead of PhCF₃ (0.5 mL). After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **1j-di** E/Z (10:1) was obtained as a colorless oil (6.4 mg, 14%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 8.16-8.15 (m, 2H), 8.12-8.10 (m, 2H), 7.36-7.34 (m, 2H), 7.26-7.25 (m, 2H), 3.59 (s, 3H), 3.16-3.11 (m, 1H), 3.06 (d, *J*₁ = 3.6 Hz, *J*₂ = 13.8 Hz, 1H), 2.90 (d, *J*₁ = 11.4 Hz, *J*₂ = 13.8 Hz, 1H), 2.84-2.80 (m, 1H), 1.49 (s, 3H), 1.42 (d, *J* = 6.6 Hz, 3H), 1.24 (s, 6H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 174.46, 156.17, 152.48, 147.49, 146.60, 146.49, 129.76, 128.47, 123.65, 123.49, 80.84, 53.54, 51.91, 42.54, 35.65, 24.03, 18.92, 13.86. HRMS (ESI-TOF) Calcd for C₂₃H₂₈N₃O₇⁺ [M+H]⁺: 458.1922, found: 458.1921.



Methyl 2-(((3-(4-acetamidobenzyl)pentan-2-ylidene)amino)oxy)-2-methylpropanoate (**3k**)

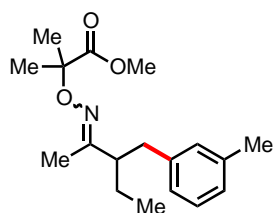
Substrate **1s** was arylated following the general arylation procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 1:1 as eluent), **3k** E/Z (9.1:1) was obtained as a colorless oil (24.4 mg, 70%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.48 (br s, 1H), 7.39-7.37 (m, 2H), 7.07-7.05 (m, 2H), 3.66 (s, 3H), 2.72-2.68 (m, 1H), 2.64-2.60 (m, 1H), 2.46-2.42 (m, 1H), 2.14 (s, 3H), 1.76 (s, 3H), 1.48-1.43 (m, 2H), 1.43 (s, 3H), 1.39 (s, 3H), 0.80 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 175.21, 168.35, 159.17, 136.09, 135.85, 129.35, 119.77, 80.63, 51.88, 48.23, 37.96, 24.61, 24.44, 24.14, 23.94, 11.67, 11.33. HRMS (ESI-TOF) Calcd for C₁₉H₂₉N₂O₄⁺ [M+H]⁺: 349.2122, found: 349.2127.



Methyl 2-(((3-(4-hydroxybenzyl)pentan-2-ylidene)amino)oxy)-2-methylpropanoate (**3l**)

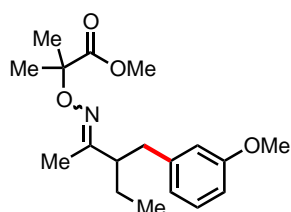
Substrate **1s** was arylated following the general arylation procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **3l** E/Z (9.1:1) was obtained as a colorless oil (27.0 mg, 88%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 6.98-6.95 (m, 2H), 6.72-6.70 (m, 2H), 5.26 (s, 1H), 3.66 (s, 3H), 2.68-2.64 (m, 1H), 2.61-2.58 (m, 1H), 2.44-2.40 (m, 1H), 1.75 (s, 3H), 1.48-1.39 (m, 2H), 1.44 (s, 3H), 1.39 (s, 3H), 0.80 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 175.41, 159.55, 153.87, 132.02, 129.96, 115.01, 80.65, 51.98, 48.48, 37.76, 24.63, 24.15, 23.95, 11.55, 11.43. HRMS

(ESI-TOF) Calcd for $C_{17}H_{26}NO_4^+$ $[M+H]^+$: 308.1856, found: 308.1862.



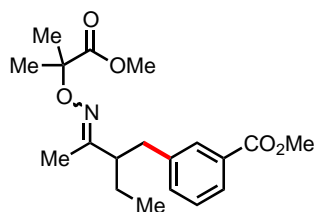
Methyl 2-methyl-2-(((3-(3-methylbenzyl)pentan-2-ylidene)amino)oxy)propanoate (3m)

Substrate **1s** was arylated following the general arylation procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **3m** E/Z (9.1:1) was obtained as a colorless oil (26.2 mg, 86%). 1H NMR (600 MHz, $CDCl_3$) of E isomer (major) δ 7.13 (t, $J = 7.2$ Hz, 1H), 6.97 (d, $J = 7.8$ Hz, 1H), 6.94 (s, 1H), 7.13 (d, $J = 8.4$ Hz, 1H), 3.65 (s, 3H), 2.73-2.69 (m, 1H), 2.64-2.60 (m, 1H), 2.50-2.45 (m, 1H), 2.30 (s, 3H), 1.76 (s, 3H), 1.47-1.42 (m, 2H), 1.43 (s, 3H), 1.39 (s, 3H), 0.80 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) of E isomer (major) δ 175.13, 159.24, 140.01, 137.62, 129.73, 128.00, 126.58, 125.97, 80.64, 51.83, 48.20, 38.56, 24.63, 24.16, 23.92, 21.34, 11.58, 11.40. HRMS (ESI-TOF) Calcd for $C_{18}H_{28}NO_3^+$ $[M+H]^+$: 306.2064, found: 306.2068.



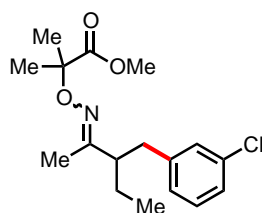
Methyl 2-(((3-(3-methoxybenzyl)pentan-2-ylidene)amino)oxy)-2-methylpropanoate (3n)

Substrate **1s** was arylated following the general arylation procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **3n** E/Z (9.1:1) was obtained as a colorless oil (26.6 mg, 83%). 1H NMR (600 MHz, $CDCl_3$) of E isomer (major) δ 7.16 (t, $J = 7.8$ Hz, 1H), 6.72-6.70 (m, 2H), 6.68-6.66 (m, 1H), 3.78 (s, 3H), 3.65 (s, 3H), 2.74-2.71 (m, 1H), 2.66-2.62 (m, 1H), 2.50-2.45 (m, 1H), 1.76 (s, 3H), 1.49-1.42 (m, 2H), 1.43 (s, 3H), 1.39 (s, 3H), 0.81 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) of E isomer (major) δ 175.10, 159.46, 159.11, 141.71, 129.06, 121.39, 114.62, 111.24, 80.65, 55.07, 51.82, 48.14, 38.70, 24.66, 24.15, 23.92, 11.67, 11.36. HRMS (ESI-TOF) Calcd for $C_{18}H_{28}NO_4^+$ $[M+H]^+$: 322.2013, found: 322.2019.



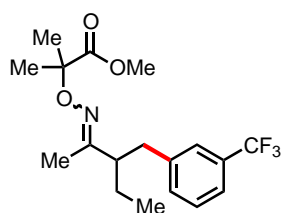
Methyl 3-(2-ethyl-3-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)butyl)benzoate (3o)

Substrate **1s** was arylated following the general arylation procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **3o** E/Z (9.1:1) was obtained as a colorless oil (30.7 mg, 88%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.86-7.84 (m, 1H), 7.81 (s, 1H), 7.33-7.32 (m, 2H), 3.91 (s, 3H), 3.64 (s, 3H), 2.82-2.78 (m, 1H), 2.75-2.71 (m, 1H), 2.54-2.49 (m, 1H), 1.76 (s, 3H), 1.48 (quintet, *J* = 7.2 Hz, 2H), 1.42 (s, 3H), 1.36 (s, 3H), 0.82 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 174.99, 167.16, 158.65, 140.46, 133.59, 130.00, 129.97, 128.19, 127.21, 80.66, 51.99, 51.81, 48.11, 38.26, 24.73, 24.11, 23.86, 11.71, 11.28. HRMS (ESI-TOF) Calcd for C₁₉H₂₈NO₅⁺ [M+H]⁺: 350.1962, found: 350.1969.



Methyl 2-(((3-(3-chlorobenzyl)pentan-2-ylidene)amino)oxy)-2-methylpropanoate (**3p**)

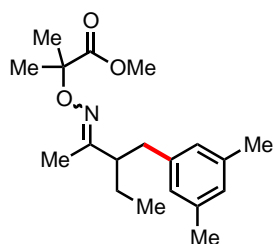
Substrate **1s** was arylated following the general arylation procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **3p** E/Z (9.1:1) was obtained as a colorless oil (30.3 mg, 93%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.18-7.11 (m, 3H), 7.01-7.00 (m, 1H), 3.65 (s, 3H), 2.74-2.70 (m, 1H), 2.67-2.64 (m, 1H), 2.50-2.45 (m, 1H), 1.76 (s, 3H), 1.49-1.45 (m, 2H), 1.43 (s, 3H), 1.39 (s, 3H), 0.82 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 175.00, 158.55, 142.19, 133.88, 129.36, 128.96, 127.13, 126.05, 80.70, 51.84, 48.01, 38.09, 24.80, 24.13, 23.89, 11.67, 11.27. HRMS (ESI-TOF) Calcd for C₁₇H₂₅ClNO₃⁺ [M+H]⁺: 326.1517, found: 326.1522.



Methyl

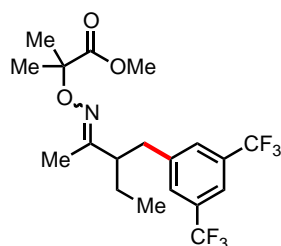
2-methyl-2-(((3-(3-(trifluoromethyl)benzyl)pentan-2-ylidene)amino)oxy)propanoate (**3q**)

Substrate **1s** was arylated following the general arylation procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **3q** E/Z (9.1:1) was obtained as a colorless oil (32.3 mg, 90%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.43-7.42 (m, 1H), 7.38-7.35 (m, 2H), 7.32-7.30 (m, 1H), 3.64 (s, 3H), 2.83-2.79 (m, 1H), 2.76-2.73 (m, 1H), 2.53-2.48 (m, 1H), 1.76 (s, 3H), 1.49 (quintet, *J* = 7.2 Hz, 2H), 1.41 (s, 3H), 1.35 (s, 3H), 0.84 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 174.97, 158.42, 141.08, 132.33, 130.46 (q, *J* = 31.8 Hz), 128.57, 125.51 (q, *J* = 4.2 Hz), 124.21 (q, *J* = 270.4 Hz), 122.79 (q, *J* = 4.2 Hz), 80.72, 51.81, 48.07, 38.23, 24.89, 24.13, 23.81, 11.72, 11.25. HRMS (ESI-TOF) Calcd for C₁₈H₂₅F₃NO₃⁺ [M+H]⁺: 360.1781, found: 360.1789.



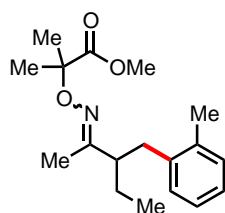
Methyl 2-(((3-(3,5-dimethylbenzyl)pentan-2-ylidene)amino)oxy)-2-methylpropanoate (3r)

Substrate **1s** was arylated following the general arylation procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **3r** E/Z (9.1:1) was obtained as a colorless oil (29.7 mg, 93%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 6.80 (s, 1H), 6.74 (s, 2H), 3.66 (s, 3H), 2.69-2.66 (m, 1H), 2.59-2.55 (m, 1H), 2.49-2.44 (m, 1H), 2.26 (s, 6H), 1.76 (s, 3H), 1.49-1.44 (m, 2H), 1.44 (s, 3H), 1.40 (s, 3H), 0.80 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 175.12, 159.38, 139.94, 137.48, 127.47, 126.79, 80.61, 51.79, 48.11, 38.47, 24.54, 24.16, 23.91, 21.20, 11.52, 11.40. HRMS (ESI-TOF) Calcd for C₁₉H₃₀NO₃⁺ [M+H]⁺: 320.2220, found: 320.2215.



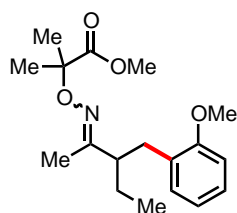
Methyl 2-(((3-(3,5-bis(trifluoromethyl)benzyl)pentan-2-ylidene)amino)oxy)-2-methylpropanoate (3s)

Substrate **1s** was arylated following the general arylation procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **3s** E/Z (6.5:1) was obtained as a colorless oil (30.7 mg, 72%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.69 (s, 1H), 7.58 (s, 2H), 3.65 (s, 3H), 2.92-2.88 (m, 1H), 2.84-2.81 (m, 1H), 2.57-2.52 (m, 1H), 1.77 (s, 3H), 1.57-1.50 (m, 2H), 1.40 (s, 3H), 1.35 (s, 3H), 0.86 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 174.82, 157.81, 142.74, 131.41 (q, *J* = 32.8 Hz), 129.00, 123.37 (q, *J* = 268.6 Hz), 120.09 (q, *J* = 3.2 Hz), 80.83, 51.83, 47.83, 37.91, 25.07, 24.13, 23.77, 11.98, 11.11. HRMS (ESI-TOF) Calcd for C₁₉H₂₄F₆NO₃⁺ [M+H]⁺: 428.1655, found: 428.1650.



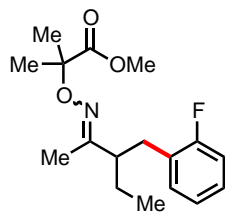
Methyl 2-methyl-2-(((3-(2-methylbenzyl)pentan-2-ylidene)amino)oxy)propanoate (3t)

Substrate **1s** was arylated following the general arylation procedure except the use of HFIP (1.0 mL) as solvent instead of PhCF₃ (0.5 mL). After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **3t** E/Z (11:1) was obtained as a colorless oil (21.4 mg, 70%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.12-7.05 (m, 4H), 3.65 (s, 3H), 2.75-2.72 (m, 1H), 2.66-2.62 (m, 1H), 2.47-2.42 (m, 1H), 2.28 (s, 3H), 1.77 (s, 3H), 1.53-1.47 (m, 2H), 1.44 (s, 3H), 1.40 (s, 3H), 0.81 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 175.14, 159.35, 138.34, 136.16, 130.18, 129.60, 126.02, 125.61, 80.69, 51.84, 47.02, 36.26, 24.72, 24.15, 23.95, 19.51, 11.58, 11.55. HRMS (ESI-TOF) Calcd for C₁₈H₂₈NO₃⁺ [M+H]⁺: 306.2064, found: 306.2069.



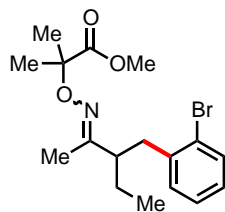
Methyl 2-(((3-(2-methoxybenzyl)pentan-2-ylidene)amino)oxy)-2-methylpropanoate (3u)

Substrate **1s** was arylated following the general arylation procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **3u** E/Z (9.1:1) was obtained as a colorless oil (21.2 mg, 66%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.15-7.13 (m, 1H), 7.07-7.05 (m, 1H), 6.85-6.82 (m, 1H), 6.81-6.80 (m, 1H), 3.80 (s, 3H), 3.64 (s, 3H), 2.74-2.66 (m, 2H), 2.53-2.48 (m, 1H), 1.77 (s, 3H), 1.49-1.44 (m, 2H), 1.42 (s, 3H), 1.36 (s, 3H), 0.81 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 175.21, 159.60, 157.51, 130.52, 128.57, 127.07, 120.14, 110.12, 80.54, 55.16, 51.80, 46.75, 32.97, 24.82, 24.17, 23.89, 11.52, 11.47. HRMS (ESI-TOF) Calcd for C₁₈H₂₈NO₄⁺ [M+H]⁺: 322.2013, found: 322.2008.



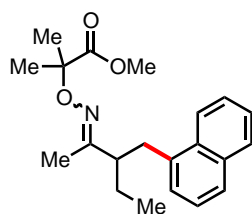
Methyl 2-(((3-(2-fluorobenzyl)pentan-2-ylidene)amino)oxy)-2-methylpropanoate (3v)

Substrate **3v** was arylated following the general arylation procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **3v** E/Z (10:1) was obtained as a colorless oil (24.1 mg, 78%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.16-7.11 (m, 2H), 7.03-7.00 (m, 1H), 6.98-6.95 (m, 1H), 3.64 (s, 3H), 2.78-2.71 (m, 2H), 2.53-2.48 (m, 1H), 1.78 (s, 3H), 1.52-1.47 (m, 2H), 1.42 (s, 3H), 1.35 (s, 3H), 0.83 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 175.08, 161.15 (d, *J* = 242.8 Hz), 158.83, 131.20 (d, *J* = 4.4 Hz), 127.58 (d, *J* = 8.8 Hz), 127.00 (d, *J* = 15.3 Hz), 123.73 (d, *J* = 3.2 Hz), 115.06 (d, *J* = 21.0 Hz), 80.66, 51.83, 47.23, 31.51, 24.81, 24.14, 23.86, 11.52, 11.34. HRMS (ESI-TOF) Calcd for C₁₇H₂₅FNO₃⁺ [M+H]⁺: 310.1813, found: 310.1819.



Methyl 2-(((3-(2-bromobenzyl)pentan-2-ylidene)amino)oxy)-2-methylpropanoate (3w)

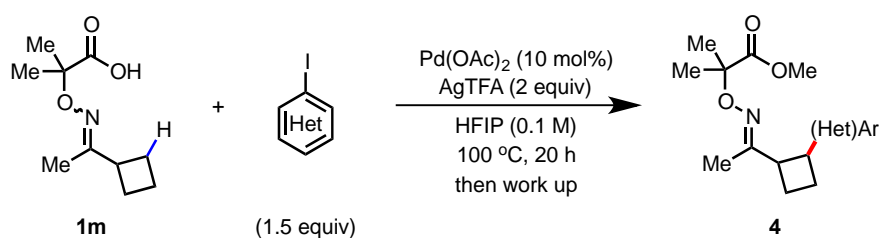
Substrate **1s** was arylated following the general arylation procedure except the use of HFIP (1.0 mL) as solvent instead of PhCF₃ (0.5 mL). After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **3w** E/Z (9.1:1) was obtained as a colorless oil (25.9 mg, 70%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.51-7.49 (m, 1H), 7.20-7.18 (m, 1H), 7.16-7.14 (m, 1H), 7.04-7.01 (m, 1H), 3.66 (s, 3H), 2.89-2.85 (m, 1H), 2.83-2.80 (m, 1H), 2.61-2.56 (m, 1H), 1.79 (s, 3H), 1.56-1.46 (m, 2H), 1.44 (s, 3H), 1.38 (s, 3H), 0.84 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 175.08, 158.78, 139.49, 132.73, 131.16, 127.61, 127.09, 80.71, 51.86, 46.64, 38.54, 24.83, 24.18, 23.93, 12.05, 11.37. HRMS (ESI-TOF) Calcd for C₁₇H₂₅BrNO₃⁺ [M+H]⁺: 370.1012, found: 370.1018.



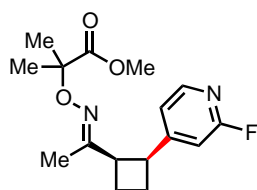
Methyl 2-methyl-2-(((3-(naphthalen-1-ylmethyl)pentan-2-ylidene)amino)oxy)propanoate (3x)

Substrate **1s** was arylated following the general arylation procedure except the use of HFIP (1.0 mL) as solvent instead of PhCF₃ (0.5 mL) and the reaction temperature is 100 °C. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 10:1 as eluent), **3x** E/Z (9.1:1) was obtained as a colorless oil (23.9 mg, 70%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 7.99 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.51-7.48 (m, 1H), 7.47-7.44 (m, 1H), 7.37-7.34 (m, 1H), 7.27-7.26 (m, 1H), 3.63 (s, 3H), 3.25-3.21 (m, 1H), 3.08-3.04 (m, 1H), 2.69-2.64 (m, 1H), 1.81 (s, 3H), 1.57-1.52 (m, 2H), 1.45 (s, 3H), 1.39 (s, 3H), 0.81 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 175.08, 159.40, 136.17, 133.88, 131.96, 128.73, 126.96, 126.78, 125.79, 125.36, 125.26, 123.84, 80.71, 51.81, 47.36, 36.02, 24.87, 24.15, 23.96, 11.66, 11.43. HRMS (ESI-TOF) Calcd for C₂₁H₂₈NO₃⁺ [M+H]⁺: 342.2064, found: 342.2061.

The Scope of Heteroaryl Iodides



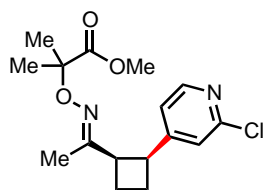
General Procedure for β -C(sp³)-H Heteroarylation of **1m:** Substrate **1m** (0.10 mmol, 19.9 mg), (Het)ArI (0.15 mmol), Pd(OAc)₂ (0.01 mmol, 2.3 mg), and AgTFA (0.20 mmol, 44.2 mg) were weighed into a reaction vial (10 mL) with a magnetic stir bar under air. HFIP (1.0 mL) was added, and the vial was sealed with a cap. The reaction mixture was stirred at 100 °C for 20 hours. Upon completion, the reaction mixture was cooled to room temperature and diluted with EtOAc. Then the reaction mixture was filtered through a short celite plug and transferred to a reaction vial (10 mL) with a magnetic stir bar. The solvent was evaporated under vacuum. Anhydrous MeOH (1.0 mL) was added to the mixture. SOCl₂ (0.30 mmol, 22 μ L) was added dropwise at room temperature. The reaction mixture was stirred at room temperature for 30 min. Upon completion, the solvent was removed under vacuum and the resulting mixture was purified by preparative thin-layer chromatography. The assignment of cis/trans structure was based on ¹H NMR patterns by comparing with literatures.²



Methyl

2-(((*E*)-(1-(2-(2-fluoropyridin-4-yl)cyclobutyl)ethylidene)amino)oxy)-2-methylpropanoate (**4a**)

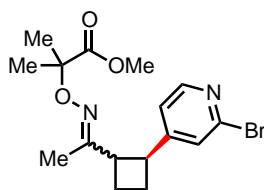
Substrate **1m** was arylated following the general arylation procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **4a** was obtained as a colorless oil (21.3 mg, 69%). ¹H NMR (600 MHz, CDCl₃) δ 8.08 (d, *J* = 5.4 Hz, 1H), 7.02-7.01 (m, 1H), 6.77 (s, 1H), 3.74 (q, *J* = 9.0 Hz, 1H), 3.69 (s, 3H), 3.01 (q, *J* = 9.0 Hz, 1H), 2.26-2.22 (m, 1H), 2.20-2.15 (m, 1H), 2.14-2.08 (m, 1H), 2.01-1.95 (m, 1H), 1.83 (s, 3H), 1.52 (s, 3H), 1.49 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 174.80, 164.05 (d, *J* = 236.0 Hz), 159.43 (d, *J* = 8.2 Hz), 157.91, 147.15 (d, *J* = 15.4 Hz), 119.79, 107.32 (d, *J* = 36.2 Hz), 81.10, 51.98, 47.36, 41.11, 24.24, 24.06, 23.94, 23.56, 12.42. HRMS (ESI-TOF) Calcd for C₁₆H₂₂FN₂O₃⁺ [M+H]⁺: 309.1609, found: 309.1615.



Methyl

2-(((E)-1-(2-(2-chloropyridin-4-yl)cyclobutyl)ethylidene)amino)oxy)-2-methylpropanoate (4b)

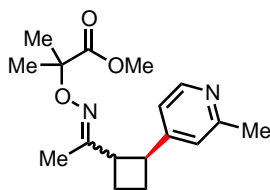
Substrate **1m** was arylated following the general arylation procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **4b** was obtained as a colorless oil (22.8 mg, 70%). ¹H NMR (600 MHz, CDCl₃) δ 8.25 (d, *J* = 4.8 Hz, 1H), 7.18 (s, 1H), 7.06 (d, *J* = 4.8 Hz, 1H), 3.73-3.68 (m, 1H), 3.69 (s, 3H), 3.00 (q, *J* = 9.6 Hz, 1H), 2.25-2.20 (m, 1H), 2.20-2.15 (m, 1H), 2.13-2.06 (m, 1H), 2.00-1.94 (m, 1H), 1.83 (s, 3H), 1.52 (s, 3H), 1.49 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 174.76, 157.88, 156.74, 151.51, 149.29, 122.36, 120.89, 81.09, 52.01, 47.30, 40.94, 24.23, 24.07, 23.89, 23.61, 12.43. HRMS (ESI-TOF) Calcd for C₁₆H₂₂ClN₂O₃⁺ [M+H]⁺: 325.1313, found: 325.1310.



Methyl

2-(((E)-1-(2-(2-bromopyridin-4-yl)cyclobutyl)ethylidene)amino)oxy)-2-methylpropanoate (4c)

Substrate **1m** was arylated following the general arylation procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **4c** cis/trans (3.0:1) was obtained as a colorless oil (25.1 mg, 68%). ¹H NMR (600 MHz, CDCl₃) of cis isomer (major) δ 8.23 (d, *J* = 5.4 Hz, 1H), 7.33 (s, 1H), 7.10-7.09 (m, 1H), 3.71-3.67 (m, 1H), 3.70 (s, 3H), 3.00 (q, *J* = 9.6 Hz, 1H), 2.25-2.15 (m, 2H), 2.12-2.06 (m, 1H), 2.00-1.94 (m, 1H), 1.83 (s, 3H), 1.51 (s, 3H), 1.49 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) of cis isomer (major) δ 174.77, 156.51, 149.74, 149.62, 142.32, 126.19, 121.32, 81.11, 52.06, 47.30, 40.88, 24.24, 24.09, 23.90, 23.62, 12.45. HRMS (ESI-TOF) Calcd for C₁₆H₂₂BrN₂O₃⁺ [M+H]⁺: 369.0808, found: 369.0802.

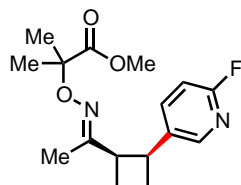


Methyl

2-(((E)-1-(2-(2-methylpyridin-4-yl)cyclobutyl)ethylidene)amino)oxy)-2-methylpropanoate (4d)

Substrate **1m** was arylated following the general arylation procedure except after the methyl ester formation, 1 mL of NaOH (aq. 2 M) was added to neutralize protonated product. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **4d** cis/trans (1:1.4) was obtained as a colorless oil (17.6 mg, 58%). ¹H NMR (600 MHz, CDCl₃) of cis/trans mixture δ 8.37-8.35 (m, 2.4H), 7.01 (s, 1H), 6.99 (s, 1.4H), 6.95-6.93 (m, 1H), 6.92-6.91 (m, 1.4H), 3.79-3.73 (m, 5.8H), 3.70 (s, 3H), 3.63 (q, *J* = 9.6 Hz, 1H), 3.48-3.44 (m,

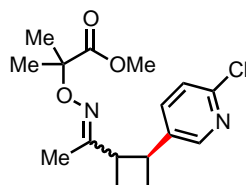
1.4H), 3.00 (q, $J = 9.6$ Hz, 1H), 2.52 (s, 7.4H), 2.47-2.41 (m, 1.5H), 2.33-1.97 (m, 9.2H), 1.82 (s, 3H), 1.51 (s, 3H), 1.49 (s, 3H), 1.42 (s, 8.3H), 1.35 (s, 4.1H). ^{13}C NMR (150 MHz, CDCl_3) of cis/trans mixture δ 174.90, 174.84, 158.20, 158.05, 157.99, 156.21, 153.46, 151.20, 148.81, 148.69, 122.50, 121.51, 120.20, 119.07, 81.00, 80.82, 51.93, 51.90, 47.30, 45.57, 42.37, 41.53, 24.30, 24.18, 24.10, 24.09, 24.03, 23.30, 20.71, 14.58, 12.43. HRMS (ESI-TOF) Calcd for $\text{C}_{17}\text{H}_{25}\text{N}_2\text{O}_3^+$ $[\text{M}+\text{H}]^+$: 305.1860, found: 305.1866.



Methyl

2-(((*E*)-1-(2-(6-fluoropyridin-3-yl)cyclobutyl)ethylidene)amino)oxy)-2-methylpropanoate (**4e**)

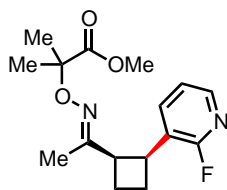
Substrate **1m** was arylated following the general arylation procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **4e** was obtained as a colorless oil (21.6 mg, 70%). ^1H NMR (600 MHz, CDCl_3) δ 8.04-8.03 (m, 1H), 7.67-7.64 (m, 1H), 6.83 (dd, $J_1 = 3.0$ Hz, $J_2 = 8.4$ Hz, 1H), 3.70-3.66 (m, 1H), 3.69 (s, 3H), 2.96 (q, $J = 9.0$ Hz, 1H), 2.25-2.21 (m, 1H), 2.19-2.14 (m, 1H), 2.13-2.09 (m, 1H), 2.02-1.95 (m, 1H), 1.81 (s, 3H), 1.51 (s, 3H), 1.48 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 174.83, 162.26 (d, $J = 236.4$ Hz), 158.13, 145.71 (d, $J = 14.2$ Hz), 139.63 (d, $J = 7.8$ Hz), 137.19 (d, $J = 4.8$ Hz), 108.76 (d, $J = 37.2$ Hz), 81.05, 52.01, 48.09, 39.23, 24.56, 24.20, 24.07, 23.58, 12.44. HRMS (ESI-TOF) Calcd for $\text{C}_{16}\text{H}_{22}\text{FN}_2\text{O}_3^+$ $[\text{M}+\text{H}]^+$: 309.1609, found: 309.1616.



Methyl

2-(((*E*)-1-(2-(6-chloropyridin-3-yl)cyclobutyl)ethylidene)amino)oxy)-2-methylpropanoate (**4f**)

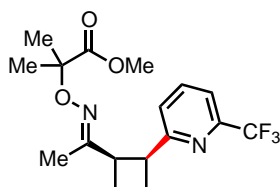
Substrate **1m** was arylated following the general arylation procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **4f** cis/trans (7.1:1) was obtained as a colorless oil (21.1 mg, 65%). ^1H NMR (600 MHz, CDCl_3) of cis isomer (major) δ 8.22 (d, $J = 2.4$ Hz, 1H), 7.53 (dd, $J_1 = 2.4$ Hz, $J_2 = 8.4$ Hz, 1H), 7.23 (d, $J = 7.8$ Hz, 1H), 3.69 (s, 3H), 3.69-3.65 (m, 1H), 2.96 (q, $J = 9.0$ Hz, 1H), 2.25-2.21 (m, 1H), 2.19-2.15 (m, 1H), 2.13-2.07 (m, 1H), 2.02-1.95 (m, 1H), 1.81 (s, 3H), 1.50 (s, 3H), 1.48 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3) cis isomer (major) δ 174.82, 158.06, 148.23, 138.48, 137.34, 123.65, 81.06, 52.03, 57.96, 39.33, 24.40, 24.21, 24.10, 23.62, 12.47. HRMS (ESI-TOF) Calcd for $\text{C}_{16}\text{H}_{22}\text{ClN}_2\text{O}_3^+$ $[\text{M}+\text{H}]^+$: 325.1313, found: 325.1317.



Methyl

2-(((*E*)-1-(2-(2-fluoropyridin-3-yl)cyclobutyl)ethylidene)amino)oxy)-2-methylpropanoate (**4g**)

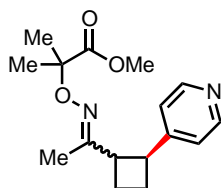
Substrate **1m** was arylated following the general arylation procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **4g** was obtained as a colorless oil (16.0 mg, 52%). ¹H NMR (600 MHz, CDCl₃) δ 8.03 (d, *J* = 4.8 Hz, 1H), 7.68-7.64 (m, 1H), 7.13-7.10 (m, 1H), 3.71 (q, *J* = 9.6 Hz, 1H), 3.64 (s, 3H), 3.19 (q, *J* = 9.0 Hz, 1H), 2.31-2.26 (m, 1H), 2.16-2.03 (m, 3H), 1.85 (s, 3H), 1.47 (s, 3H), 1.46 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 174.86, 161.56 (d, *J* = 238.4 Hz), 157.94, 144.94 (d, *J* = 14.2 Hz), 138.86 (d, *J* = 6.3 Hz), 125.68 (d, *J* = 29.6 Hz), 121.24 (d, *J* = 3.4 Hz), 81.00, 51.88, 45.88, 37.20 (d, *J* = 3.3 Hz), 25.08 (d, *J* = 2.0 Hz), 24.12, 24.06, 23.26. HRMS (ESI-TOF) Calcd for C₁₆H₂₂FN₂O₃⁺ [M+H]⁺: 309.1609, found: 309.1615.



Methyl

2-methyl-2-(((*E*)-1-(2-(6-(trifluoromethyl)pyridin-2-yl)cyclobutyl)ethylidene)amino)oxy)propanoate (**4h**)

Substrate **1m** was arylated following the general arylation procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **4h** was obtained as a colorless oil (19.7 mg, 55%). ¹H NMR (600 MHz, CDCl₃) δ 7.72 (t, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 8.4 Hz, 1H), 3.80 (q, *J* = 9.0 Hz, 1H), 3.66 (s, 3H), 3.26 (q, *J* = 9.6 Hz, 1H), 2.46-2.39 (m, 1H), 2.18-2.13 (m, 2H), 2.05-1.98 (m, 1H), 1.79 (s, 3H), 1.50 (s, 3H), 1.46 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 174.98, 163.53, 158.62, 147.61 (q, *J* = 33.9 Hz), 137.05, 125.02, 121.65 (q, *J* = 272.7 Hz), 117.74 (q, *J* = 3.0 Hz), 80.97, 51.85, 46.28, 44.46, 24.13, 24.05, 23.54, 22.91, 12.58. HRMS (ESI-TOF) Calcd for C₁₇H₂₂F₃N₂O₃⁺ [M+H]⁺: 359.1577, found: 359.1580.

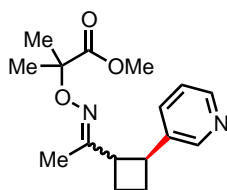


(*E*)-Methyl

2-methyl-2-(((1-(2-(pyridin-4-yl)cyclobutyl)ethylidene)amino)oxy)propanoate (**4i**)

Substrate **1m** was arylated following the general arylation procedure except the reaction

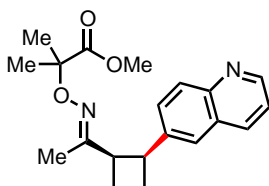
temperature was 120 °C and after the methyl ester formation, 1 mL of NaOH (aq. 2 M) was added to neutralize protonated product. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 2:1 as eluent), **4i** cis/trans (1:1.8) was obtained as a colorless oil (12.2 mg, 42%). ¹H NMR (600 MHz, CDCl₃) of cis/trans mixture δ 8.49-8.47 (m, 5.6H), 7.14-7.11 (m, 5.6H), 3.81 (q, *J* = 9.0 Hz, 1.8H), 3.74 (s, 5.4H), 3.71-3.66 (m, 1H), 3.67 (s, 3H), 3.51-3.46 (m, 1.8H), 3.01 (q, *J* = 9.0 Hz, 1H), 2.48-2.42 (m, 2H), 2.38-1.96 (m, 12H), 1.82 (s, 3H), 1.51 (s, 3H), 1.49 (s, 3H), 1.42 (s, 5.3H), 1.41 (s, 5.3H), 1.35 (s, 5.3H). ¹³C NMR (150 MHz, CDCl₃) of cis/trans mixture δ 174.92, 174.85, 158.12, 156.03, 153.27, 151.03, 149.44, 149.37, 123.07, 122.03, 81.06, 80.87, 51.95, 47.36, 45.58, 42.40, 41.49, 24.21, 24.15, 24.13, 24.08, 24.06, 23.39, 20.72, 24.56, 12.44. HRMS (ESI-TOF) Calcd for C₁₆H₂₃N₂O₃⁺ [M+H]⁺: 291.1703, found: 291.1709.



(*E*)-Methyl

2-methyl-2-(((1-(2-(pyridin-3-yl)cyclobutyl)ethylidene)amino)oxy)propanoate (**4j**)

Substrate **1m** was arylated following the general arylation procedure except the reaction temperature was 120 °C and after the methyl ester formation, 1 mL of NaOH (aq. 2 M) was added to neutralize protonated product. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 2:1 as eluent), **4j** cis/trans (1:2.5) was obtained as a colorless oil (13.3 mg, 46%). ¹H NMR (600 MHz, CDCl₃) of cis/trans mixture δ 8.47-8.42 (m, 7.2H), 7.59-7.54 (m, 3.6H), 7.23-7.19 (m, 3.6H), 3.86 (q, *J* = 9.0 Hz, 2.6H), 3.75 (s, 7.6H), 3.71-3.66 (m, 1H), 3.68 (s, 3H), 3.48-3.44 (m, 2.5H), 3.01 (q, *J* = 9.0 Hz, 1H), 2.52-2.46 (m, 2.6H), 2.38-2.34 (m, 2.6H), 2.30-2.23 (m, 4.5H), 2.18-2.11 (m, 4.5H), 2.04-1.99 (m, 1H), 1.81 (s, 3H), 1.50 (s, 3H), 1.48 (s, 3H), 1.44 (s, 15.0H), 1.31 (s, 7.5H), 1.35 (s, 5.3H). ¹³C NMR (150 MHz, CDCl₃) of cis/trans mixture δ 174.99, 174.88, 158.20, 156.05, 149.42, 148.50, 147.67, 147.38, 139.46, 137.15, 135.02, 134.90, 134.24, 123.09, 81.02, 80.87, 51.98, 51.95, 47.87, 45.70, 42.03, 40.65, 40.18, 39.16, 24.54, 24.19, 24.15, 24.09, 23.44, 20.50, 14.79, 12.46. HRMS (ESI-TOF) Calcd for C₁₆H₂₃N₂O₃⁺ [M+H]⁺: 291.1703, found: 291.1708.

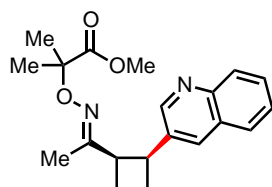


Methyl

2-methyl-2-(((*E*)-1-(2-(quinolin-6-yl)cyclobutyl)ethylidene)amino)oxy)propanoate (**4k**)

Substrate **1m** was arylated following the general arylation procedure except after the methyl ester formation, 1 mL of NaOH (aq. 2 M) was added to neutralize protonated product. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 3:1 as eluent), **4k** was obtained as a colorless oil (19.7 mg, 58%). ¹H NMR (600 MHz, CDCl₃) δ 8.85 (dd, *J*₁ =

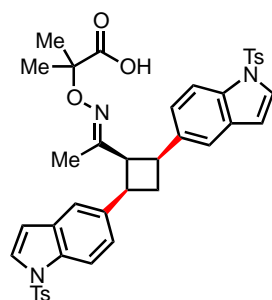
1.8 Hz, $J_2 = 4.2$ Hz, 1H), 8.13 (d, $J = 8.4$ Hz, 1H), 8.01 (d, $J = 8.4$ Hz, 1H), 7.64-7.62 (m, 2H), 7.37 (dd, $J_1 = 4.2$ Hz, $J_2 = 7.8$ Hz, 1H), 3.85 (q, $J = 9.0$ Hz, 1H), 3.64 (s, 3H), 3.11 (q, $J = 9.6$ Hz, 1H), 2.33-2.28 (m, 1H), 2.25-2.15 (m, 2H), 2.08-2.02 (m, 1H), 1.85 (s, 3H), 1.53 (s, 3H), 1.41 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 174.96, 158.55, 149.69, 147.17, 142.80, 135.76, 129.19, 129.08, 124.54, 121.06, 81.00, 51.94, 48.04, 42.57, 24.88, 24.22, 24.12, 23.15, 12.49. HRMS (ESI-TOF) Calcd for $\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}_3^+$ $[\text{M}+\text{H}]^+$: 341.1860, found: 341.1867.



Methyl

2-methyl-2-(((*E*)-(1-(2-(quinolin-3-yl)cyclobutyl)ethylidene)amino)oxy)propanoate (**4l**)

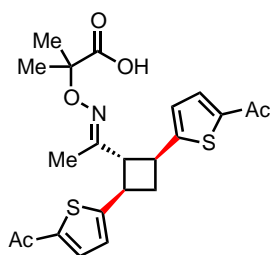
Substrate **1m** was arylated following the general arylation procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 3:1 as eluent), **4k** was obtained as a colorless oil (17.0 mg, 50%). ^1H NMR (600 MHz, CDCl_3) δ 8.74-8.73 (m, 1H), 8.07 (d, $J = 8.4$ Hz, 1H), 8.03 (s, 1H), 7.82 (d, $J = 8.4$ Hz, 1H), 7.68-7.65 (m, 1H), 7.54-7.52 (m, 1H), 4.05 (q, $J = 8.4$ Hz, 1H), 3.73 (s, 3H), 3.55-3.51 (m, 1H), 2.57-2.52 (m, 1H), 2.44-2.40 (m, 2H), 2.23-2.16 (m, 1H), 1.40 (s, 3H), 1.39 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 174.95, 156.05, 151.40, 146.92, 134.53, 133.76, 128.99, 128.78, 128.04, 127.66, 126.56, 80.88, 51.95, 46.02, 40.82, 24.72, 24.16, 24.13, 20.55, 15.02. HRMS (ESI-TOF) Calcd for $\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}_3^+$ $[\text{M}+\text{H}]^+$: 341.1860, found: 341.1868.



2-(((*E*)-(1-(2,4-bis(1-tosyl-1*H*-indol-5-yl)cyclobutyl)ethylidene)amino)oxy)-2-methylpropanoic acid (**4m**)

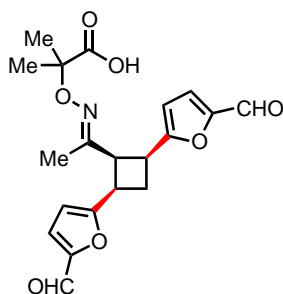
Substrate **1m** was arylated following the general arylation procedure except 2.0 equiv of heteroaryl iodide and AgOAc were used and the reaction temperature was 80 °C. The product was isolated as the acid form without further esterification. After purification by preparative thin-layer chromatography (Hexane : EtOAc : HOAc = 1:1:0.01 as eluent), **4m** was obtained as a colorless oil (55.4 mg, 75%). ^1H NMR (600 MHz, CDCl_3) δ 7.87 (d, $J = 8.4$ Hz, 2H), 7.74-7.72 (m, 4H), 7.51 (d, $J = 3.6$ Hz, 2H), 7.27 (s, 2H), 7.21-7.19 (m, 4H), 7.05 (dd, $J_1 = 1.2$ Hz, $J_2 = 8.4$ Hz, 2H), 6.58 (dd, $J_1 = 0.6$ Hz, $J_2 = 3.6$ Hz, 2H), 4.13-4.08 (m, 2H), 4.06-4.03 (m, 1H), 3.03 (q, $J = 10.8$ Hz, 1H), 2.80-2.75 (m, 1H), 2.32 (s, 6H), 1.04 (s, 3H), 0.90 (s, 6H). ^{13}C NMR (150 MHz, CDCl_3) δ 175.33, 160.41, 144.86, 135.91, 135.19, 133.30, 130.91, 129.81, 126.75, 126.68, 123.40, 118.99, 113.29, 108.98, 80.83, 51.80, 38.25, 29.75, 23.59.

21.49, 16.33. HRMS (ESI-TOF) Calcd for $C_{40}H_{38}N_3O_7S_2^-$ [M-H]⁻: 736.2157, found: 736.2162.



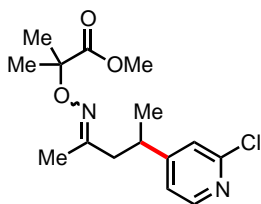
2-(((E)-1-(2,4-bis(5-acetylthiophen-2-yl)cyclobutyl)ethylidene)amino)oxy)-2-methylpropanoic acid (4o)

Substrate **1m** was arylated following the general arylation procedure except 2.0 equiv of heteroaryl iodide was used and the reaction temperature was 80 °C. The product was isolated as the acid form without further esterification. After purification by preparative thin-layer chromatography (Hexane : EtOAc : HOAc = 1:1:0.02 as eluent), **4o** was obtained as a colorless oil (29.1 mg, 65%). ¹H NMR (600 MHz, CDCl₃) δ 7.56 (d, *J* = 3.6 Hz, 1H), 6.92 (d, *J* = 3.6 Hz, 1H), 3.74 (q, *J* = 10.2 Hz, 2H), 3.09 (t, *J* = 9.6 Hz, 1H), 2.89-2.85 (m, 1H), 2.53 (s, 6H), 2.35 (q, *J* = 10.2 Hz, 1H), 1.79 (s, 3H), 1.56 (s, 6H). ¹³C NMR (150 MHz, CDCl₃) δ 190.68, 176.78, 157.18, 156.42, 142.74, 132.97, 125.03, 81.42, 59.11, 36.24, 36.07, 26.48, 24.14, 13.49. HRMS (ESI-TOF) Calcd for $C_{22}H_{24}NO_5S_2^-$ [M-H]⁻: 446.1101, found: 446.1100.



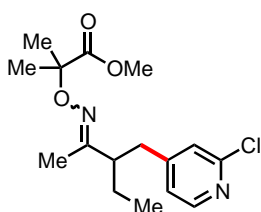
2-(((E)-1-(2,4-bis(5-formylfuran-2-yl)cyclobutyl)ethylidene)amino)oxy)-2-methylpropanoic acid (4p)

Substrate **1m** was arylated following the general arylation procedure except 2.0 equiv of heteroaryl iodide and AgOAc were used and the reaction temperature was 80 °C. The product was isolated as the acid form without further esterification. After purification by preparative thin-layer chromatography (Hexane : EtOAc : HOAc = 1:1:0.02 as eluent), **4p** was obtained as a colorless oil (27.9 mg, 72%). ¹H NMR (600 MHz, CDCl₃) δ 9.48 (s, 2H), 7.22 (d, *J* = 3.6 Hz, 2H), 6.36 (d, *J* = 3.6 Hz, 2H), 3.94-3.89 (m, 2H), 3.84-3.81 (m, 1H), 3.13 (q, *J* = 10.8 Hz, 1H), 2.70-2.65 (m, 1H), 1.37 (s, 3H), 1.26 (s, 6H). ¹³C NMR (150 MHz, CDCl₃) δ 177.12, 175.56, 161.51, 155.20, 151.83, 124.43, 110.06, 81.48, 50.21, 33.51, 28.20, 23.67, 15.27. HRMS (ESI-TOF) Calcd for $C_{20}H_{20}NO_7^-$ [M-H]⁻: 386.1245, found: 386.1240.



Methyl 2-(((4-(2-chloropyridin-4-yl)pentan-2-ylidene)amino)oxy)-2-methylpropanoate (4q)

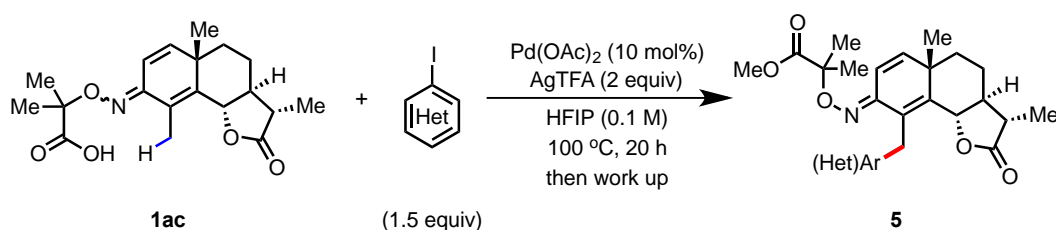
Substrate **1a** was arylated following the general arylation procedure except the reaction temperature was 120 °C and after the methyl ester formation, 1 mL of NaOH (aq. 2 M) was added to neutralize protonated product. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **4q** E/Z (5.3:1) was obtained as a colorless oil (12.5 mg, 40%). ¹H NMR (600 MHz, CDCl₃) of E isomer (major) δ 8.27 (d, *J* = 5.4 Hz, 1H), 7.15 (s, 1H), 7.04 (dd, *J*₁ = 1.8 Hz, *J*₂ = 5.4 Hz, 1H), 3.67 (s, 3H), 3.10-3.04 (m, 1H), 2.49-2.39 (m, 2H), 1.82 (s, 3H), 1.40 (s, 3H), 1.39 (s, 3H), 1.23 (d, *J* = 6.6 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 174.76, 158.90, 155.01, 151.61, 149.60, 122.85, 121.32, 80.81, 51.97, 43.00, 36.06, 24.13, 24.01, 21.28, 14.67. HRMS (ESI-TOF) Calcd for C₁₅H₂₂ClN₂O₃⁺ [M+H]⁺: 313.1313, found: 313.1309.



Methyl 2-(((3-((2-chloropyridin-4-yl)methyl)pentan-2-ylidene)amino)oxy)-2-methylpropanoate (4r)

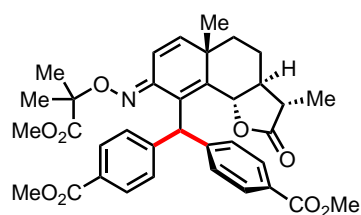
Substrate **1s** was arylated following the general arylation procedure except the reaction temperature was 120 °C and after the methyl ester formation, 1 mL of NaOH (aq. 2 M) was added to neutralize protonated product. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 5:1 as eluent), **4r** E/Z (8.3:1) was obtained as a colorless oil (20.3 mg, 62%). ¹H NMR (400 MHz, CDCl₃) of E isomer (major) δ 8.25 (d, *J* = 5.2 Hz, 1H), 7.11 (s, 1H), 7.00 (dd, *J*₁ = 1.6 Hz, *J*₂ = 5.2 Hz, 1H), 3.65 (s, 3H), 2.79-2.65 (m, 2H), 2.55-2.48 (m, 1H), 1.77 (s, 3H), 1.55-1.47 (m, 2H), 1.42 (s, 3H), 1.38 (s, 3H), 0.85 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) of E isomer (major) δ 174.81, 157.63, 152.75, 151.45, 149.28, 124.57, 123.11, 80.83, 51.88, 47.13, 37.07, 25.11, 24.10, 23.92, 11.89, 11.06. HRMS (ESI-TOF) Calcd for C₁₆H₂₄ClN₂O₃⁺ [M+H]⁺: 327.1470, found: 327.1475.

The Late-Stage β -C(sp³)-H (Hetero)Arylation of Santonin



General Procedure for the Late-Stage β -C(sp³)-H (Hetero)Arylation of Santonin:

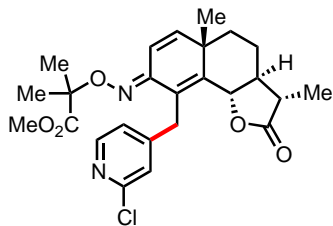
Substrate **1ac** (0.10 mmol, 34.7 mg), (Het)ArI (0.15 mmol), Pd(OAc)₂ (0.01 mmol, 2.3 mg), and AgTFA (0.20 mmol, 44.2 mg) were weighed into a reaction vial (10 mL) with a magnetic stir bar under air. HFIP (1.0 mL) was added, and the vial was sealed with a cap. The reaction mixture was stirred at 100 °C for 20 hours. Upon completion, the reaction mixture was cooled to room temperature and diluted with EtOAc. Then the reaction mixture was filtered through a short celite plug and transferred to a reaction vial (10 mL) with a magnetic stir bar. The solvent was evaporated under vacuum. Anhydrous MeOH (1.0 mL) was added to the mixture. SOCl₂ (0.30 mmol, 22 μ L) was added dropwise at room temperature. The reaction mixture was stirred at room temperature for 30 min. Upon completion, the solvent was removed under vacuum and the resulting mixture was purified by preparative thin-layer chromatography.



Dimethyl

4,4'-(((3*S*,3*aS*,5*aS*,9*bS*,*E*)-8-(((1-methoxy-2-methyl-1-oxopropan-2-yl)oxy)imino)-3,5*a*-dimethyl-2-oxo-2,3,3*a*,4,5,5*a*,8,9*b*-octahydronaphtho[1,2-*b*]furan-9-yl)methylene)dibenzoate (**5a**)

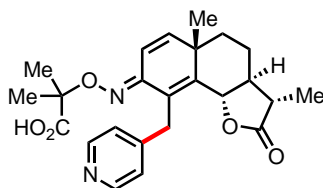
Substrate **1ac** was arylated following the general arylation procedure except 2.0 equiv of aryl iodide was used and the reaction temperature was 80 °C. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 1:1 as eluent), **5a** was obtained as a colorless oil (56.6 mg, 90%). ¹H NMR (600 MHz, CDCl₃) δ 7.93-7.91 (m, 2H), 7.90-7.88 (m, 2H), 7.28-7.26 (m, 2H), 7.18-7.16 (m, 2H), 6.92 (d, *J* = 10.2 Hz, 1H), 6.58 (s, 1H), 6.02 (d, *J* = 10.2 Hz, 1H), 4.91 (d, *J* = 10.2 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.45 (s, 3H), 2.32-2.25 (m, 1H), 2.01-1.96 (m, 1H), 1.84-1.80 (m, 1H), 1.73-1.54 (m, 3H), 1.37 (s, 3H), 1.11 (d, *J* = 6.6 Hz, 3H), 1.08 (s, 3H), 0.97 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 176.73, 174.03, 167.17, 167.13, 148.97, 148.00, 147.79, 144.62, 143.96, 129.26, 129.11, 128.40, 127.53, 127.32, 127.08, 113.60, 81.81, 81.38, 53.48, 52.01, 51.88, 51.84, 47.71, 41.98, 40.77, 38.79, 26.20, 24.03, 23.96, 23.71, 12.47. HRMS (ESI-TOF) Calcd for C₃₆H₄₀NO₉⁺ [M+H]⁺: 630.2698, found: 630.2692.



Methyl

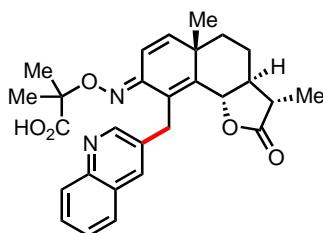
2-(((*E*)-((3*S*,3*aS*,5*aS*,9*bS*)-9-((2-chloropyridin-4-yl)methyl)-3,5*a*-dimethyl-2-oxo-2,3,3*a*,4,5,5*a*-hexahydronaphtho[1,2-*b*]furan-8(9*bH*)-ylidene)amino)oxy)-2-methylpropanoate (**5b**)

Substrate **1ac** was arylated following the general arylation procedure. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 1:1 as eluent), **5b** was obtained as a colorless oil (36.4 mg, 77%). ¹H NMR (600 MHz, CDCl₃) δ 8.19-8.18 (m, 1H), 7.08-7.07 (m, 1H), 7.04-7.03 (m, 1H), 6.89 (d, *J* = 10.2 Hz, 1H), 6.05 (d, *J* = 10.2 Hz, 1H), 4.80 (d, *J* = 10.8 Hz, 1H), 4.16 (d, *J* = 15.6 Hz, 1H), 4.00 (d, *J* = 15.0 Hz, 1H), 3.54 (s, 3H), 2.35-2.29 (m, 1H), 2.02-1.99 (m, 1H), 1.83-1.79 (m, 1H), 1.69-1.65 (m, 2H), 1.59-1.54 (m, 1H), 1.45 (s, 3H), 1.43 (s, 3H), 1.32 (s, 3H), 1.18 (d, *J* = 6.6 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 177.20, 174.25, 154.72, 151.15, 148.93, 148.47, 145.30, 142.01, 123.58, 122.72, 113.13, 82.00, 81.59, 53.68, 51.99, 41.17, 40.83, 38.47, 30.36, 25.99, 24.08, 24.00, 23.66, 12.49. HRMS (ESI-TOF) Calcd for C₂₅H₃₀ClN₂O₅⁺ [M+H]⁺: 473.1838, found: 473.1832.



2-(((*E*)-((3*S*,3*aS*,5*aS*,9*bS*)-3,5*a*-Dimethyl-2-oxo-9-(pyridin-4-ylmethyl)-2,3,3*a*,4,5,5*a*-hexahydronaphtho[1,2-*b*]furan-8(9*bH*)-ylidene)amino)oxy)-2-methylpropanoic acid (**5c**)

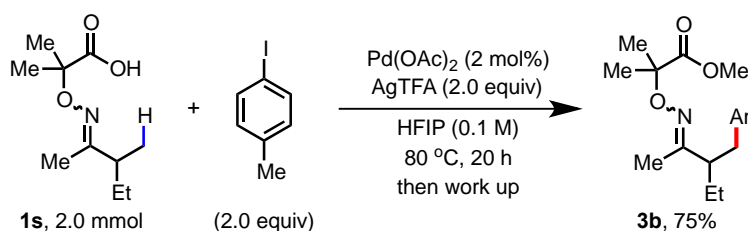
Substrate **1ac** was arylated following the general arylation procedure except the reaction temperature was 120 °C. The product was isolated as the acid form without further esterification. After purification by preparative thin-layer chromatography (EtOAc : MeOH : HOAc = 40:1:0.2 as eluent), **5c** was obtained as a colorless oil (22.5 mg, 53%). ¹H NMR (600 MHz, CDCl₃) δ 8.19 (d, *J* = 5.4 Hz, 2H), 7.24 (d, *J* = 5.4 Hz, 2H), 6.97 (d, *J* = 10.2 Hz, 1H), 6.02 (d, *J* = 10.2 Hz, 1H), 4.76 (d, *J* = 11.4 Hz, 1H), 4.27 (d, *J* = 15.0 Hz, 1H), 4.10 (d, *J* = 15.6 Hz, 1H), 2.29-2.23 (m, 1H), 1.97-1.94 (m, 1H), 1.80-1.76 (m, 1H), 1.67-1.49 (m, 3H), 1.56 (s, 3H), 1.54 (s, 3H), 1.30 (s, 3H), 1.11 (d, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 177.27, 154.56, 147.73, 145.52, 144.68, 141.10, 124.44, 124.02, 113.38, 82.52, 81.66, 53.57, 41.08, 40.80, 38.55, 30.83, 29.68, 25.92, 24.47, 24.05, 23.67, 12.41. HRMS (ESI-TOF) Calcd for C₂₄H₂₇N₂O₅⁻ [M-H]⁻: 423.1925, found: 423.1920.



2-(((*E*)-((3*S*,3*aS*,5*aS*,9*bS*)-3,5*a*-Dimethyl-2-oxo-9-(quinolin-3-ylmethyl)-2,3,3*a*,4,5,5*a*-hexahydronaphtho[1,2-*b*]furan-8(9*bH*)-ylidene)amino)oxy)-2-methylpropanoic acid (5d**)**

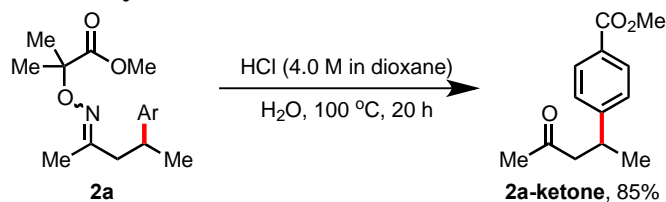
Substrate **1ac** was arylated following the general arylation procedure. The product was isolated as the acid form without further esterification. After purification by preparative thin-layer chromatography (Hexane : EtOAc = 1:2 as eluent), **5d** was obtained as a colorless oil (34.2 mg, 72%). ¹H NMR (600 MHz, CDCl₃) δ 8.82 (s, 1H), 8.10 (s, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.42-7.39 (m, 1H), 7.37-7.34 (m, 1H), 6.96 (d, *J* = 10.2 Hz, 1H), 6.02 (d, *J* = 10.2 Hz, 1H), 4.87-4.85 (m, 1H), 4.41 (d, *J* = 15.0 Hz, 1H), 4.22 (d, *J* = 14.4 Hz, 1H), 2.35-2.29 (m, 1H), 1.97-1.94 (m, 1H), 1.79-1.75 (m, 1H), 1.68-1.63 (m, 2H), 1.57 (s, 3H), 1.55 (s, 3H), 1.57-1.51 (m, 1H), 1.30 (s, 3H), 1.11 (d, *J* = 6.6 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 177.54, 176.95, 150.46, 148.72, 145.04, 143.98, 141.16, 136.79, 134.87, 128.97, 128.13, 127.54, 126.65, 126.60, 125.18, 113.46, 82.34, 81.83, 53.64, 41.18, 40.89, 38.41, 28.27, 25.97, 24.32, 24.13, 23.75, 12.40. HRMS (ESI-TOF) Calcd for C₂₈H₂₉N₂O₅⁻ [M-H]⁻: 473.2082, found: 473.2080.

The Scale Up Reaction



General Procedure for The Scale Up Reaction: Substrate **1s** (2.0 mmol, 402 mg), 4-iodotoluene (4.0 mmol, 872 mg), Pd(OAc)₂ (0.04 mmol, 9.0 mg), and AgTFA (4.0 mmol, 884 mg) were weighed into a sealed tube (250 mL) with a magnetic stir bar under air. HFIP (20 mL) was added, and the tube was sealed with a cap. The reaction mixture was stirred at 80 °C for 20 hours. Upon completion, the reaction mixture was cooled to room temperature and diluted with EtOAc. Then the reaction mixture was filtered through a short celite plug and transferred to a reaction round bottom flask (100 mL) with a magnetic stir bar. The solvent was evaporated under vacuum. Anhydrous MeOH (20 mL) was added to the mixture. SOCl₂ (6.0 mmol, 0.44 mL) was added dropwise at room temperature. The reaction mixture was stirred at room temperature for 1 h. Upon completion, the solvent was removed under vacuum and the resulting mixture was purified by flash chromatography by using Hexane/EtOAc (10:1) as the eluent to give 458 mg of **3b** (75% yield).

The Removal of Auxiliary

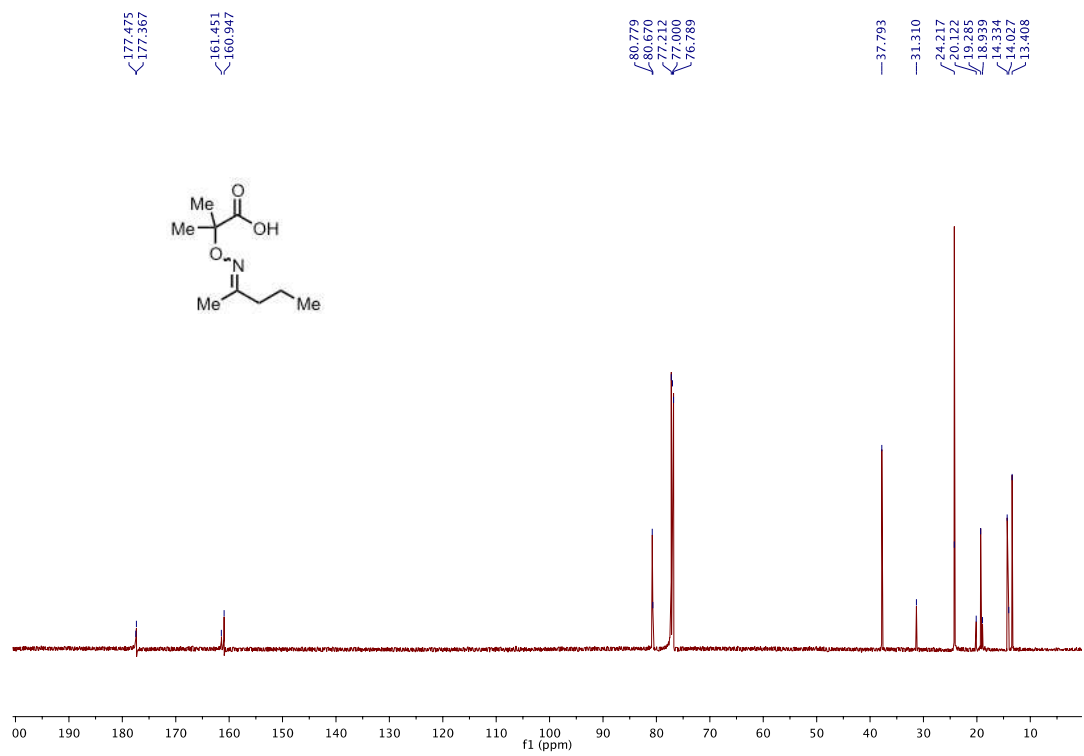
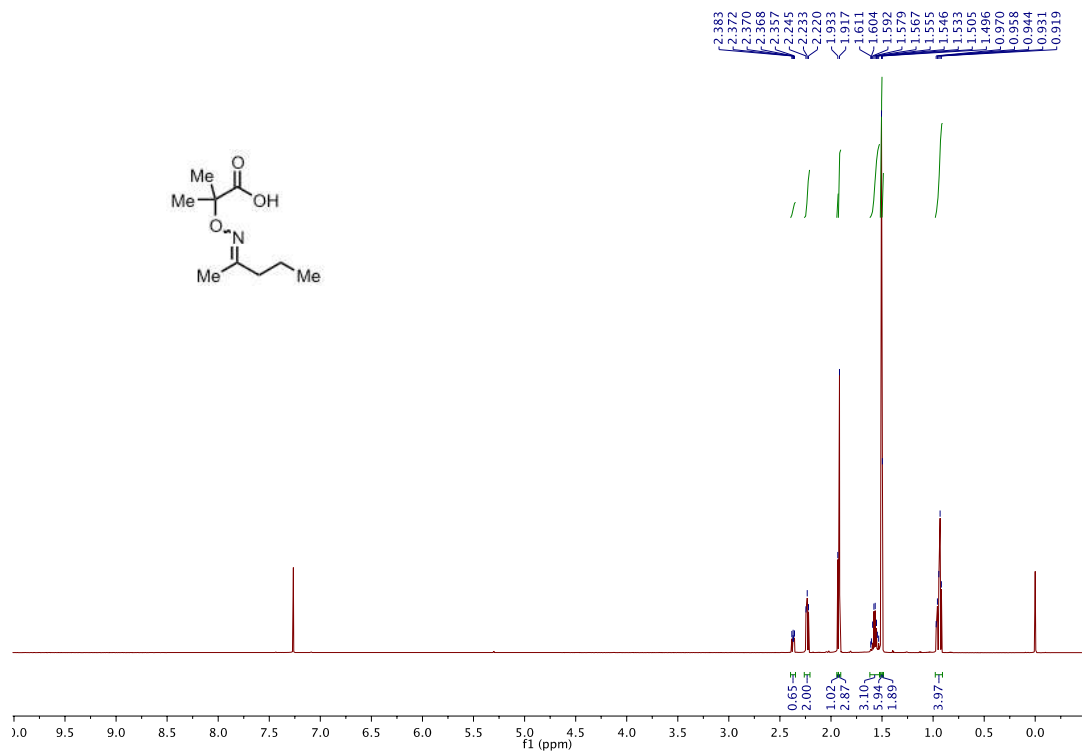


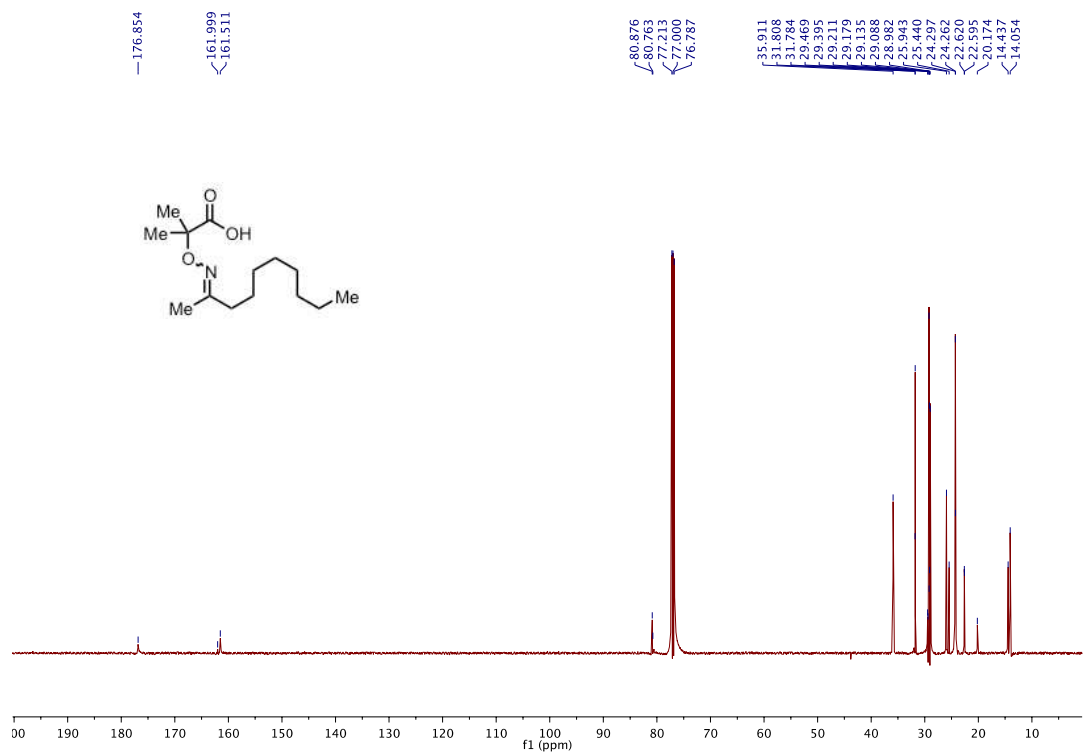
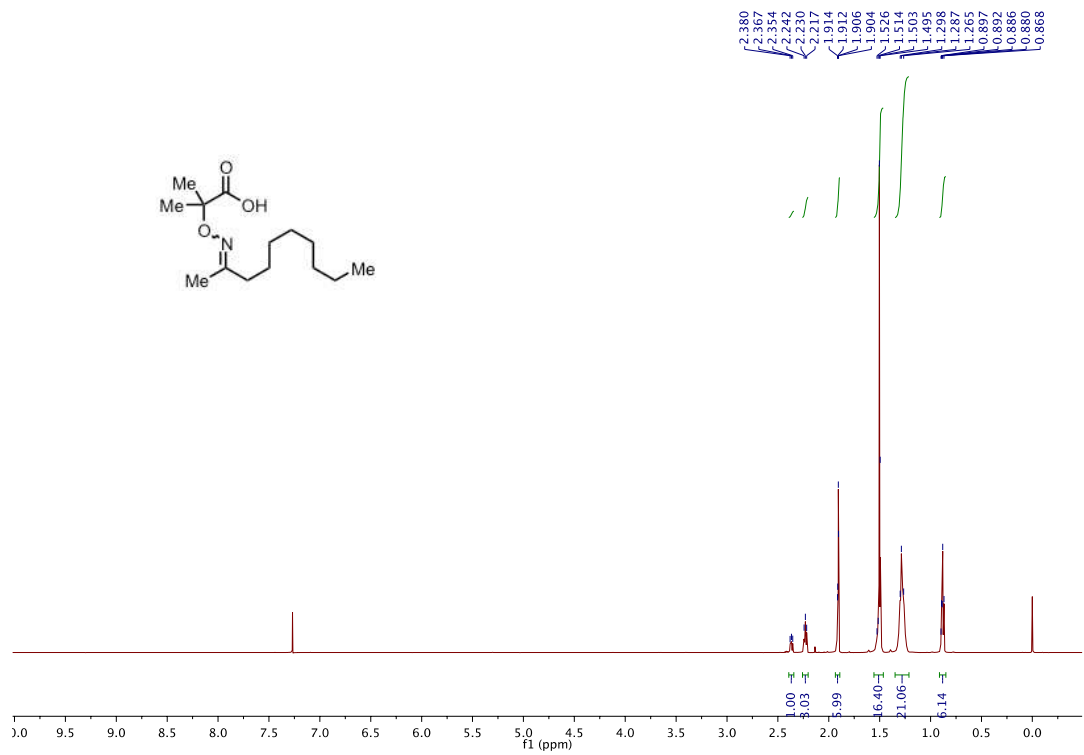
The General Procedure for the Removal of Auxiliary: The arylated product **2a** (0.1 mmol, 33.5 mg) was weighed into a reaction vial (10 mL) with a magnetic stir bar under air. 0.25 mL of H₂O and 1.25 mL of HCl (4 M in dioxane) were added, and the vial was sealed with a cap. The reaction mixture was stirred at 100 °C for 20 hours. Upon completion, the reaction mixture was cooled to room temperature. Followed by the addition of 1 mL of H₂O into the reaction vial. The crude product was extracted three times with EtOAc (2 mL each time) from the aqueous phase. The combined organic phase was dried with anhydrous Na₂SO₄. Then the organic solvent was removed under vacuum and the resulting mixture was purified by preparative thin-layer chromatography by using Hexane/EtOAc (10:1) as the eluent to give 18.7 mg of arylated ketone (85% yield). The analytical data was in consistent with literature.¹

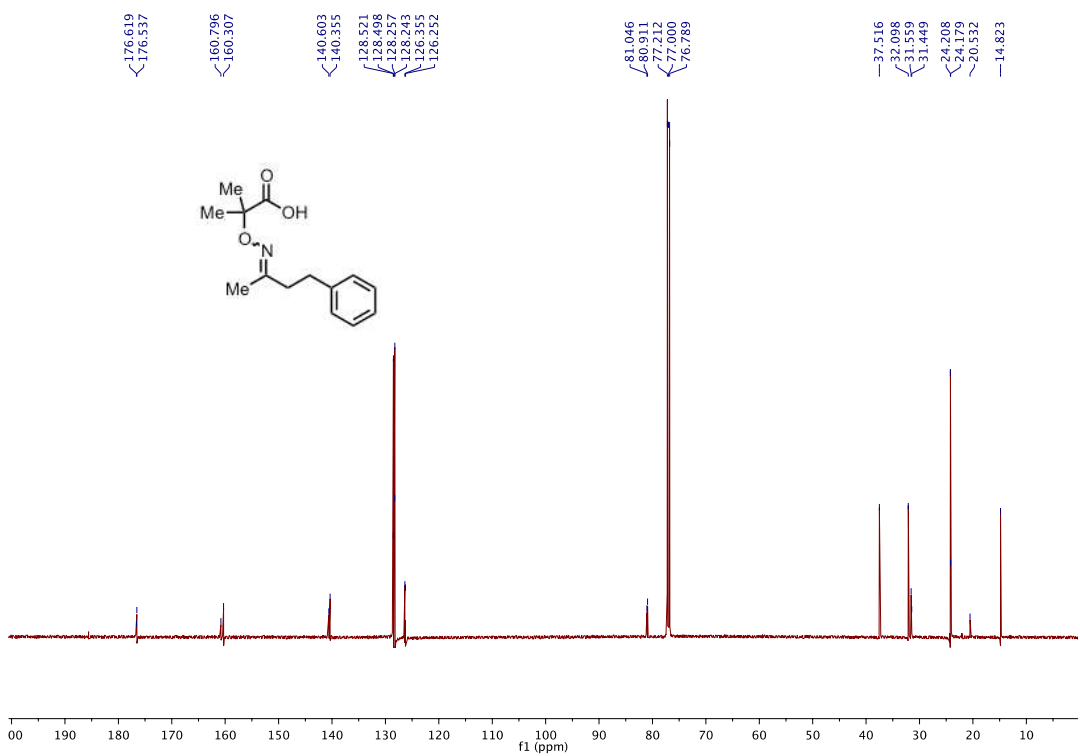
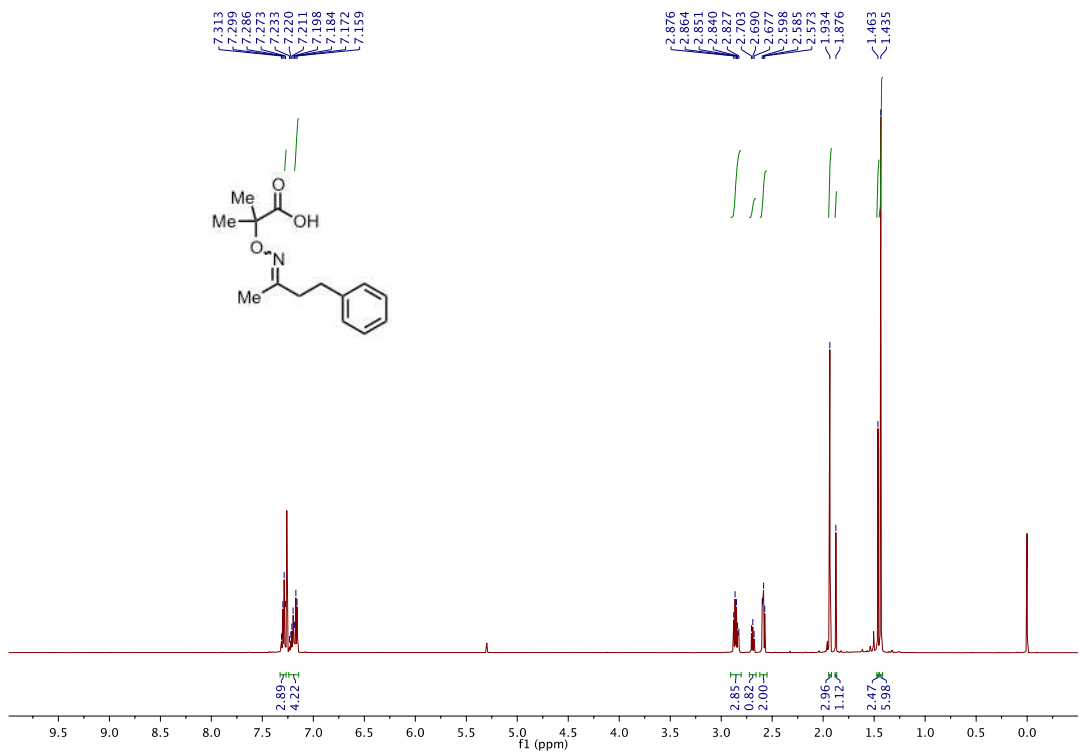
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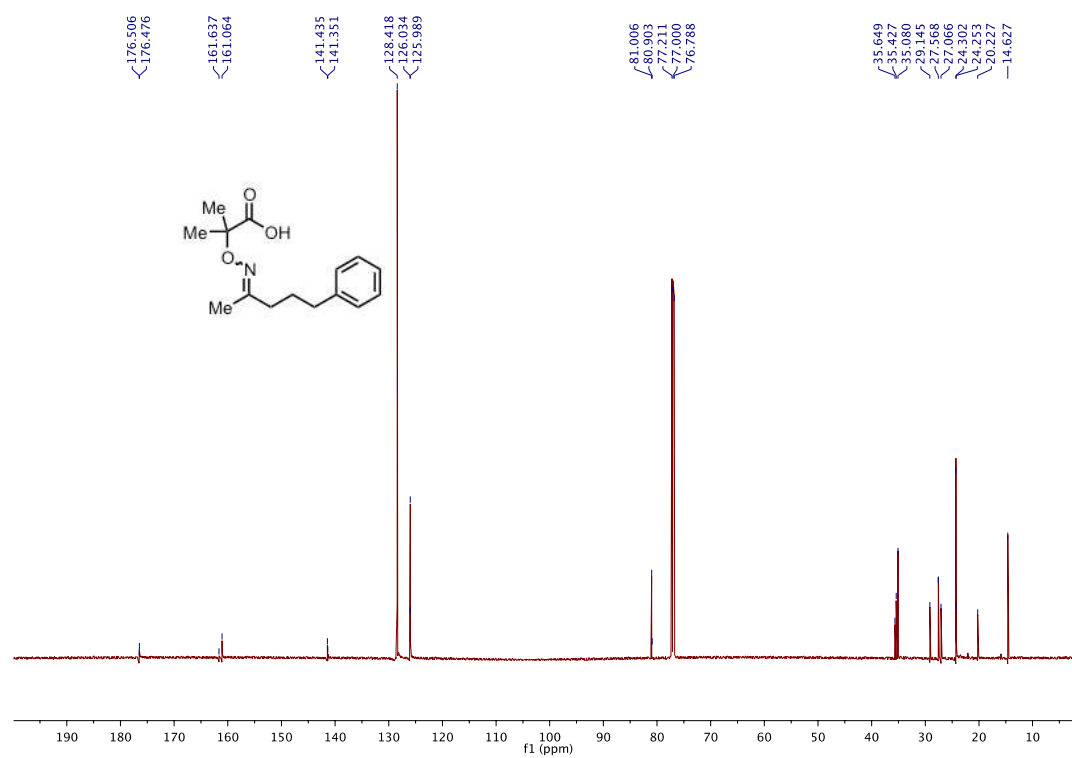
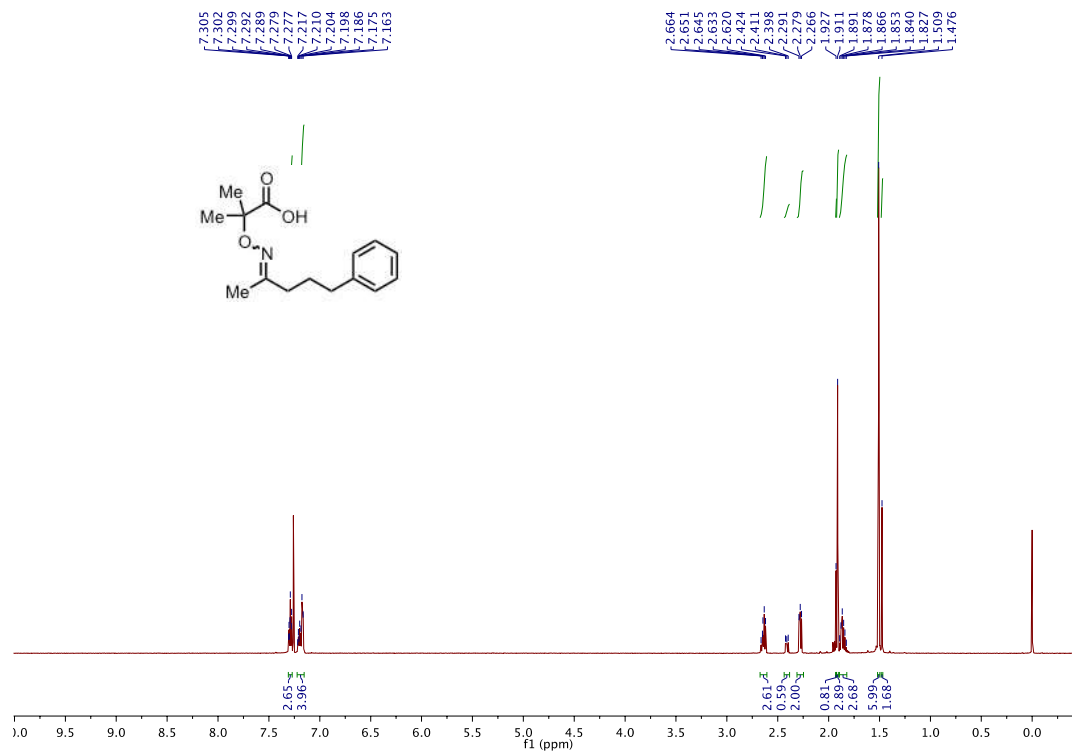
- (1) Hong, K.; Park, H.; Yu, J.-Q. *ACS Catal.* **2017**, *7*, 6938.
- (2) (a) Parella, R.; Gopalakrishnan, B.; Babu, S. A. *J. Org. Chem.* **2013**, *78*, 11911. (b) Zhang, F.-L.; Hong, K.; Li, T.-J.; Park, H.; Yu, J.-Q. *Science* **2016**, *351*, 252.

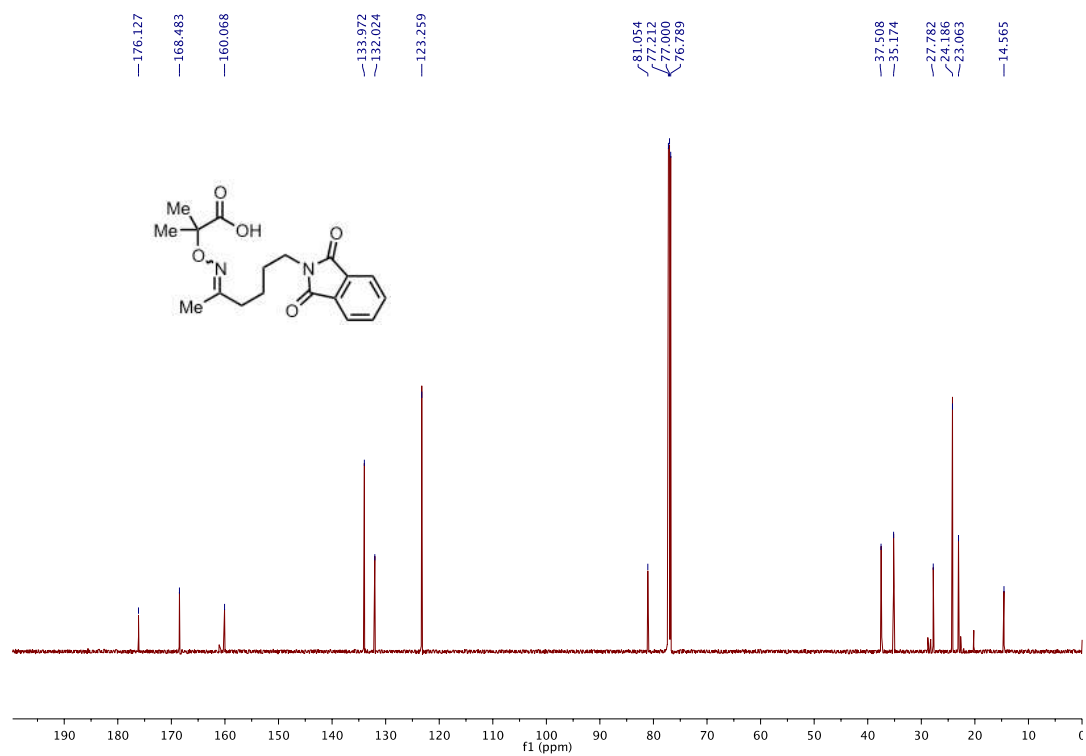
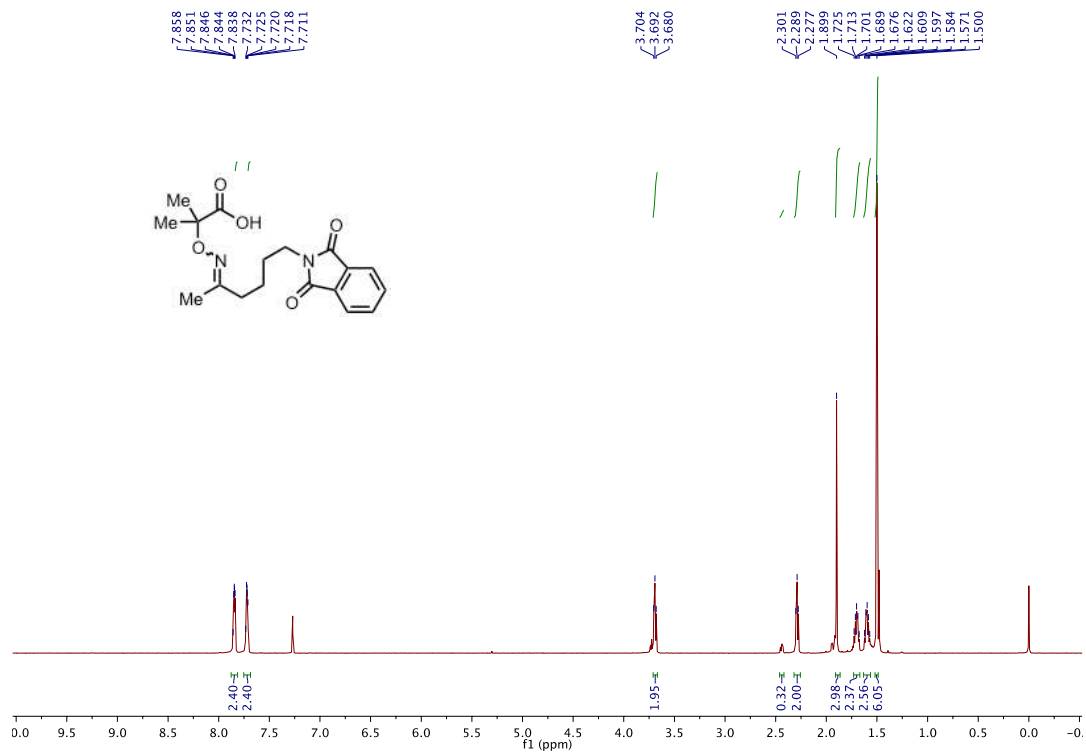
¹H and ¹³C NMR Spectra

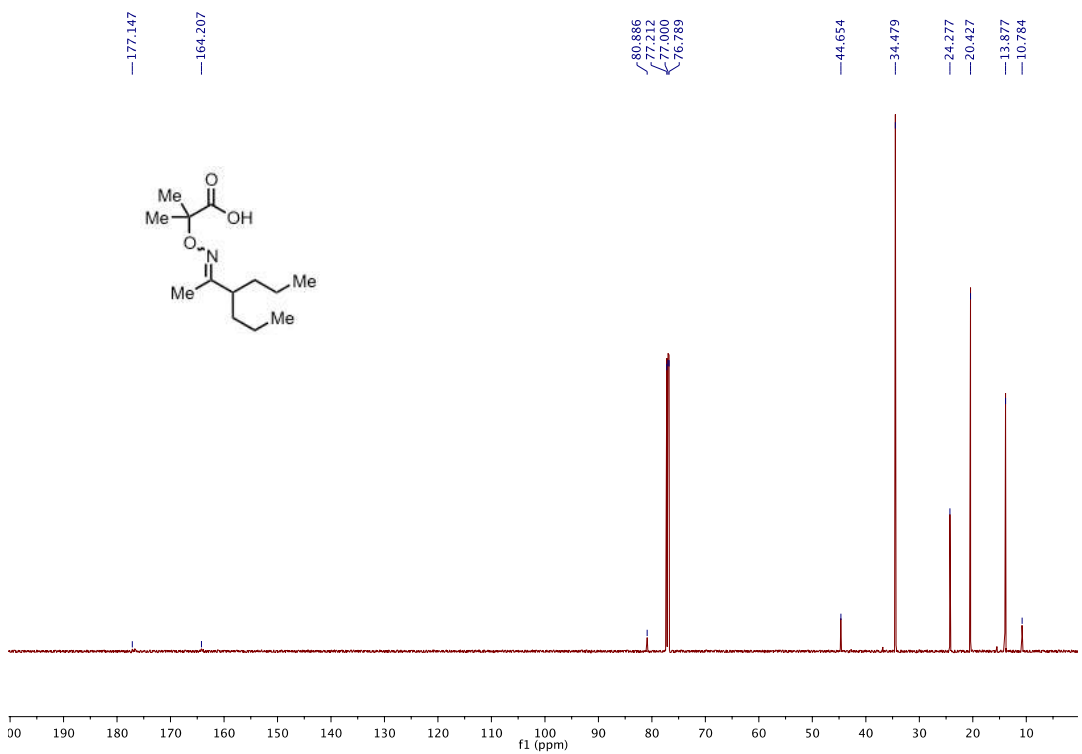
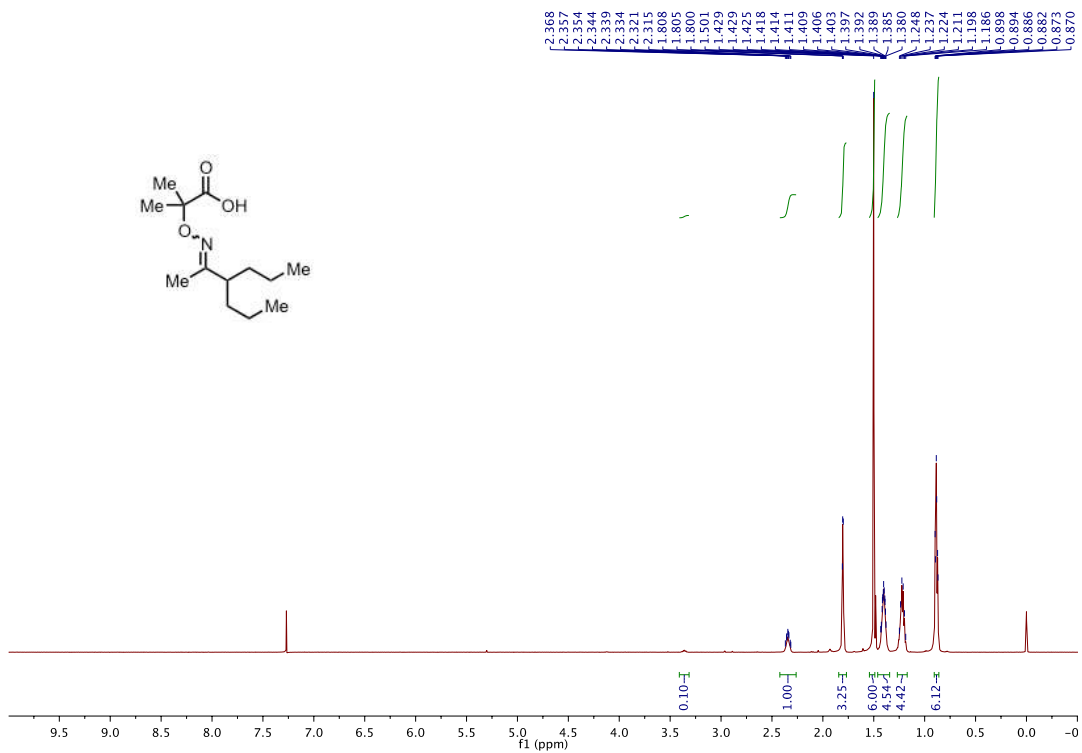


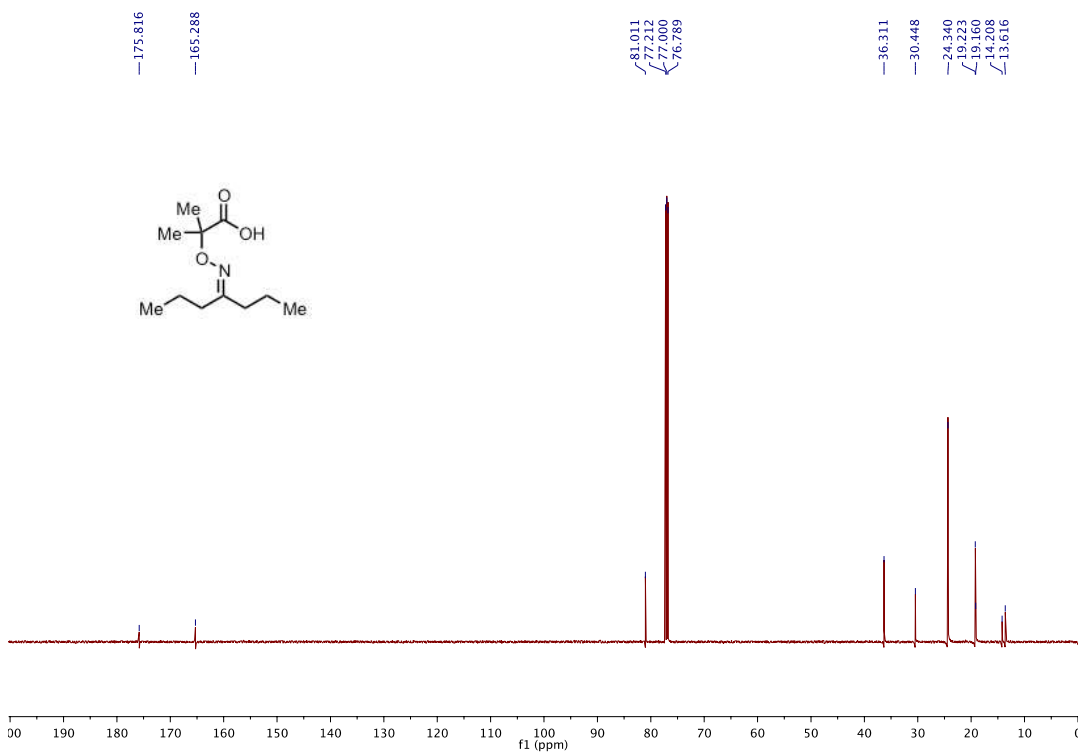
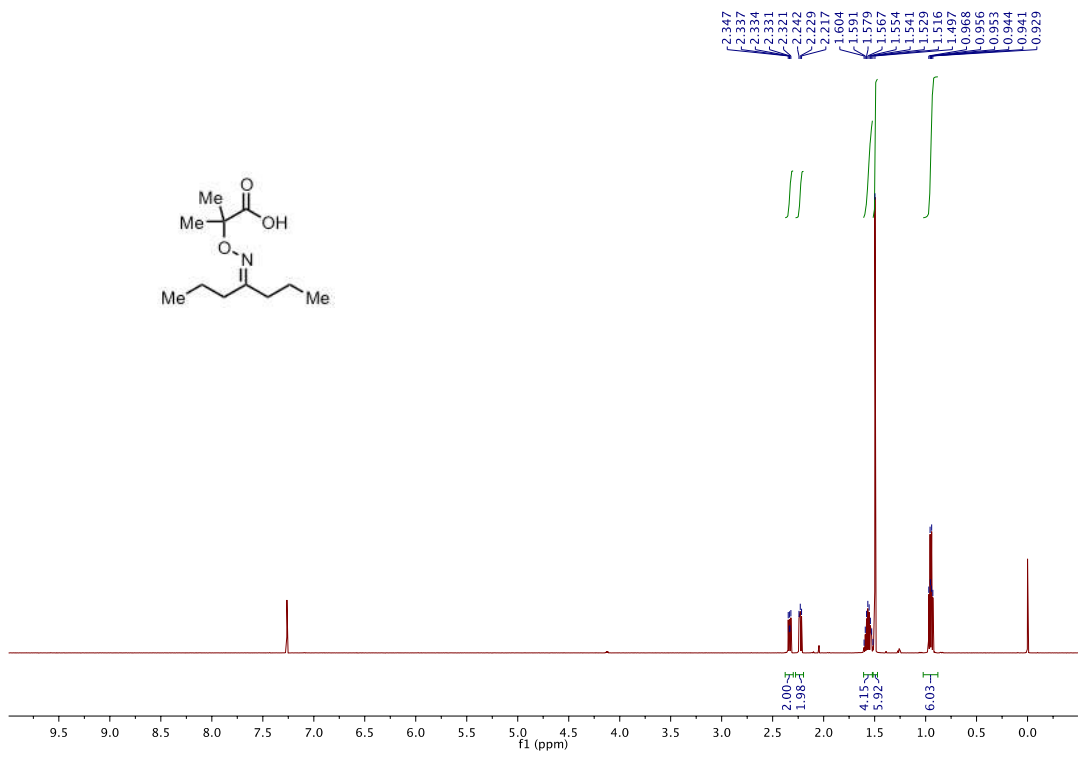


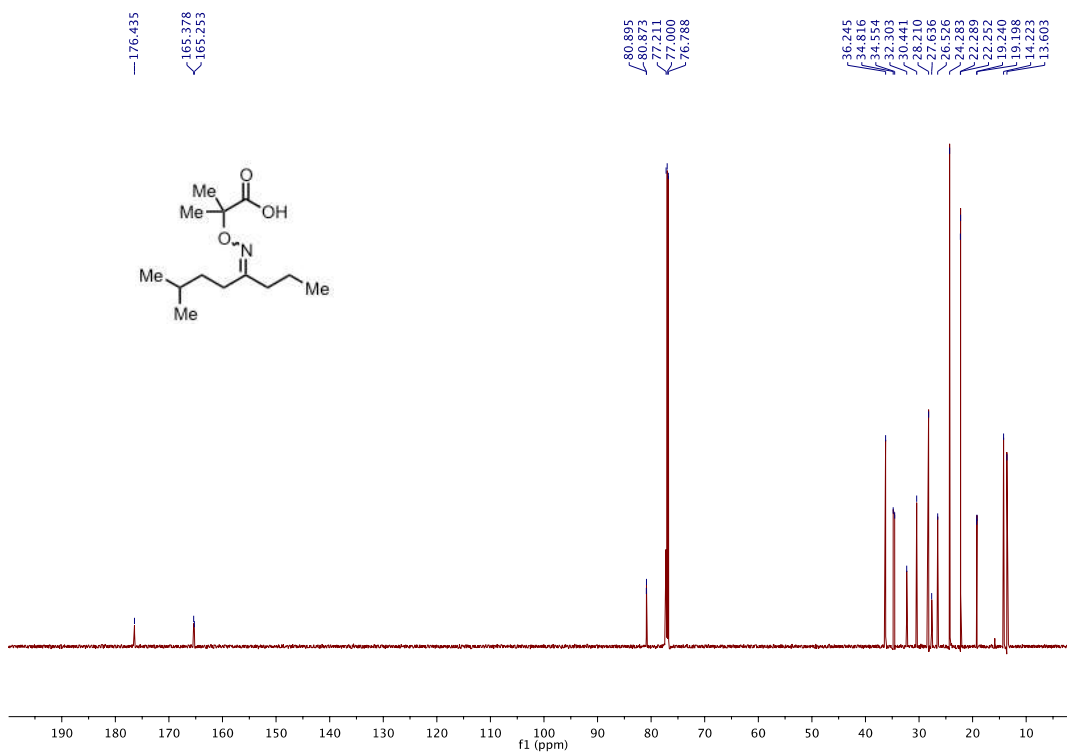
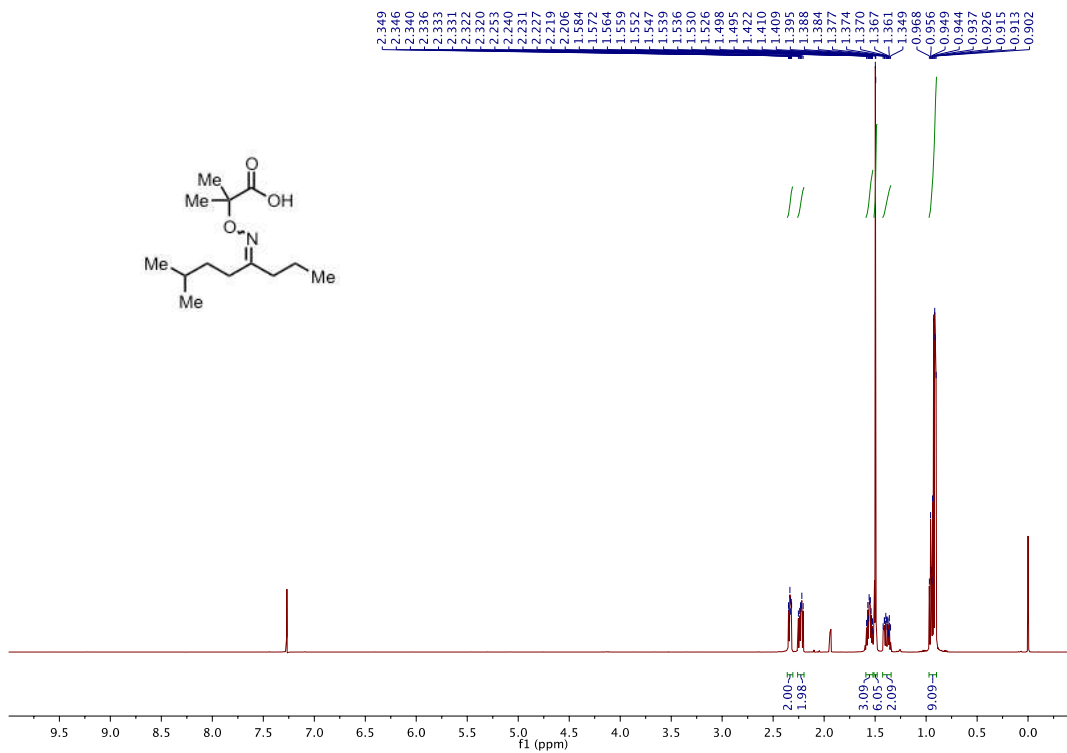


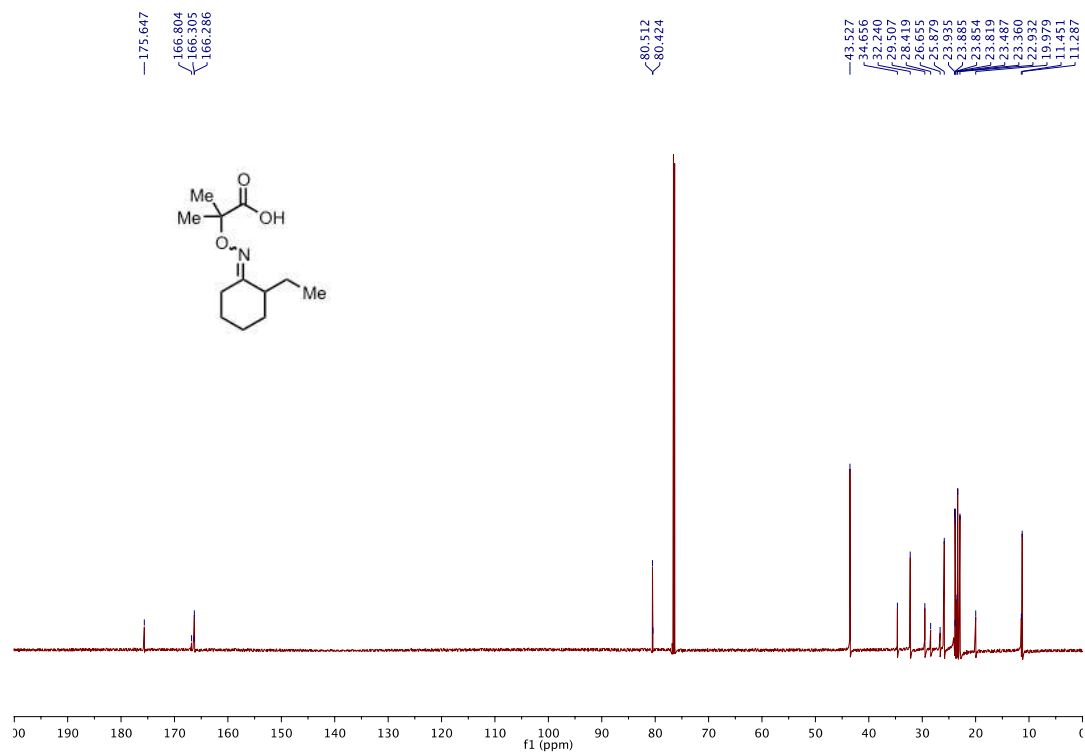
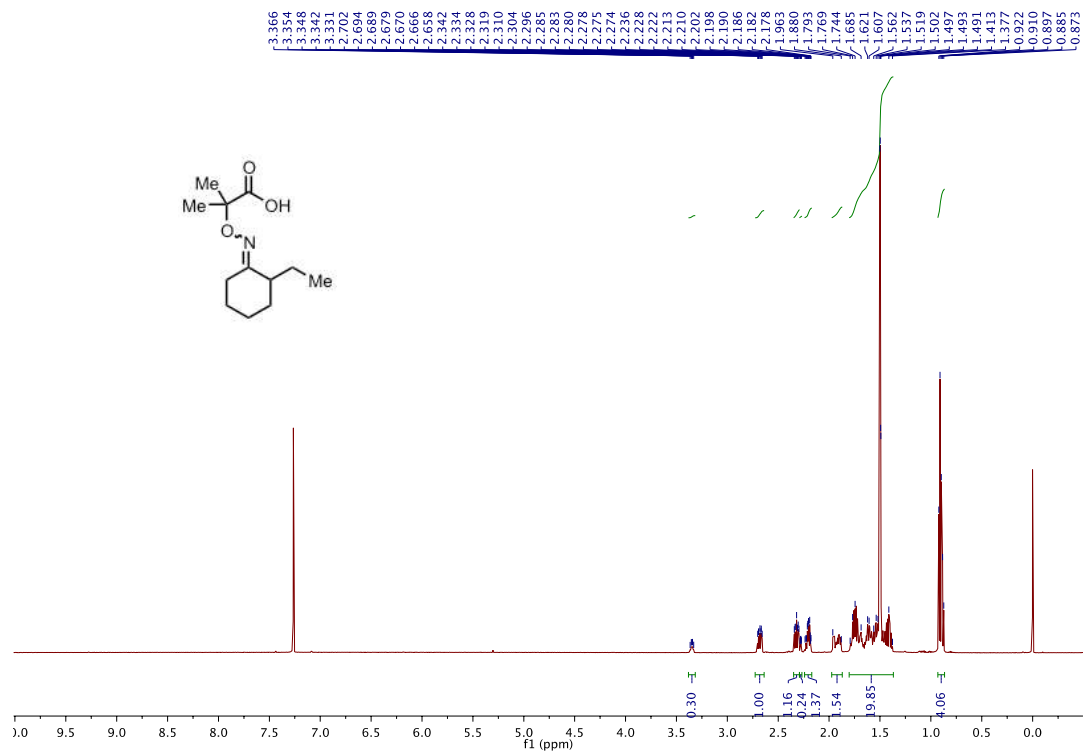


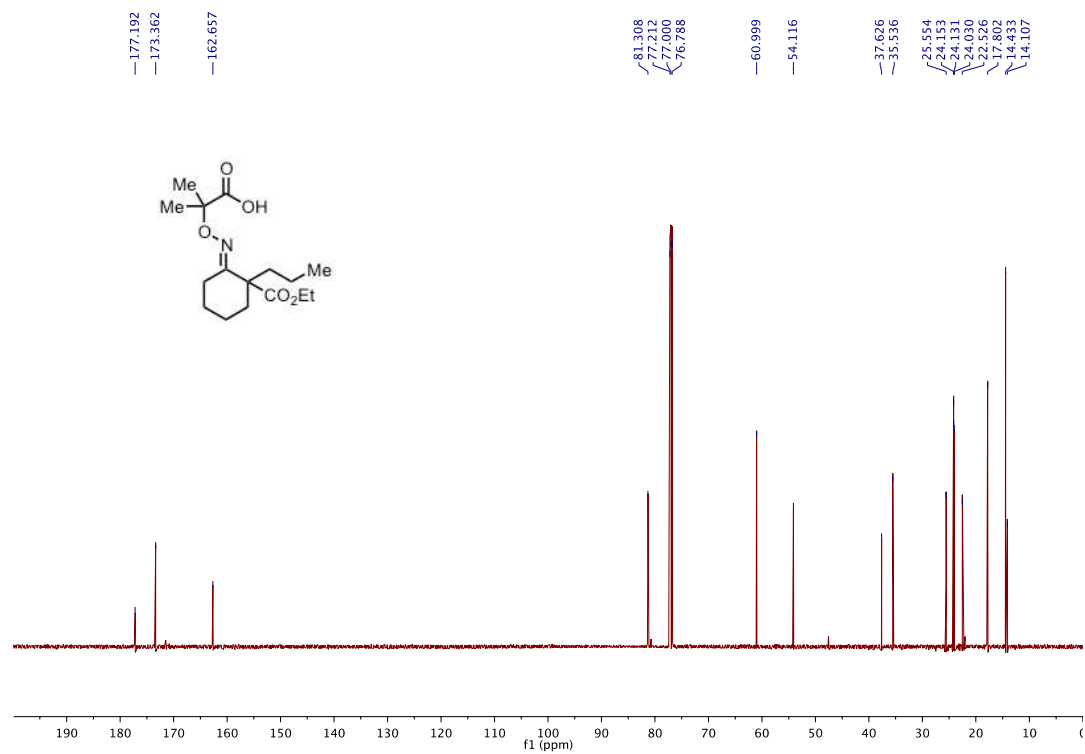
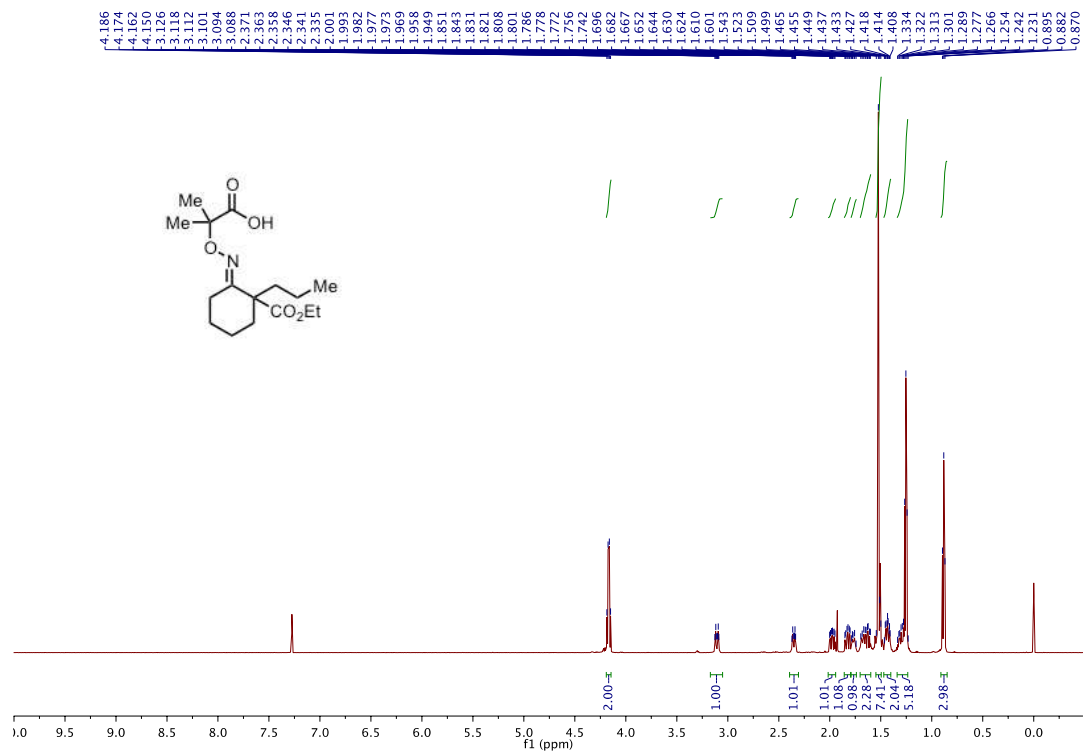


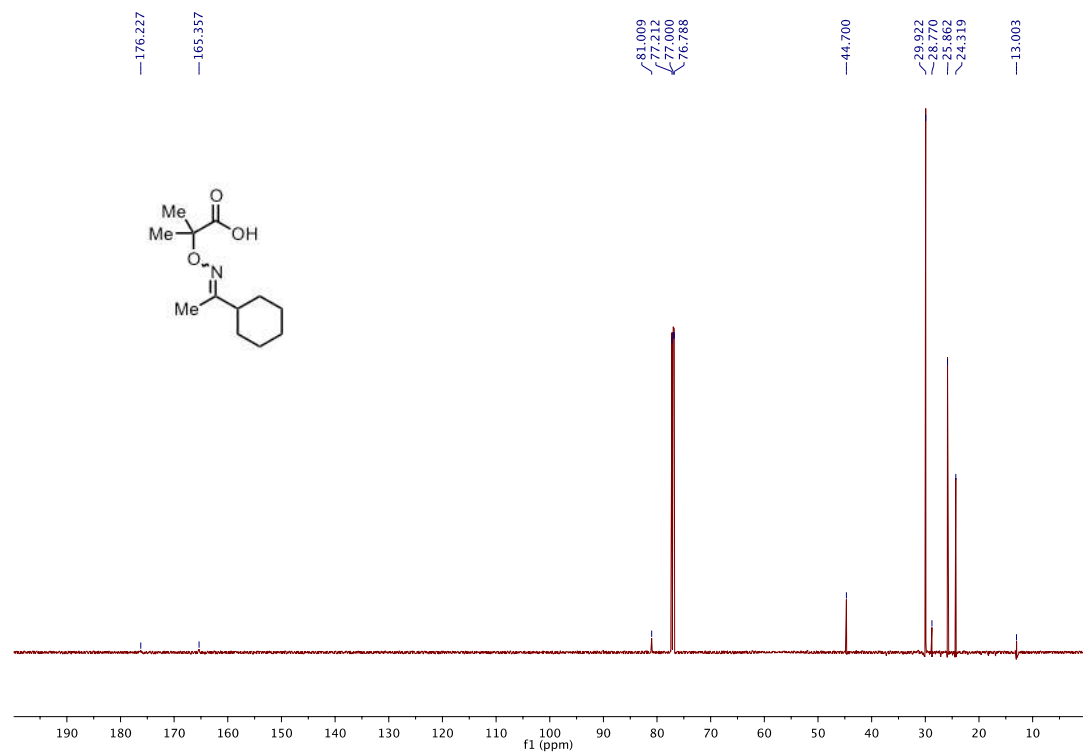
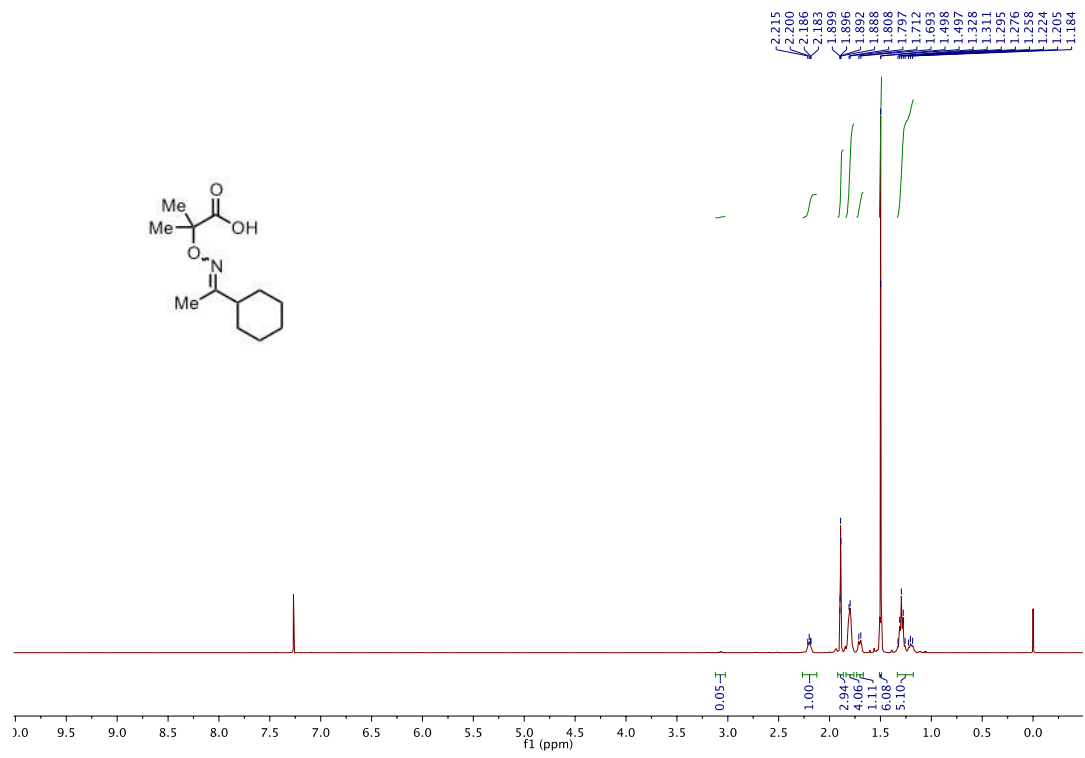


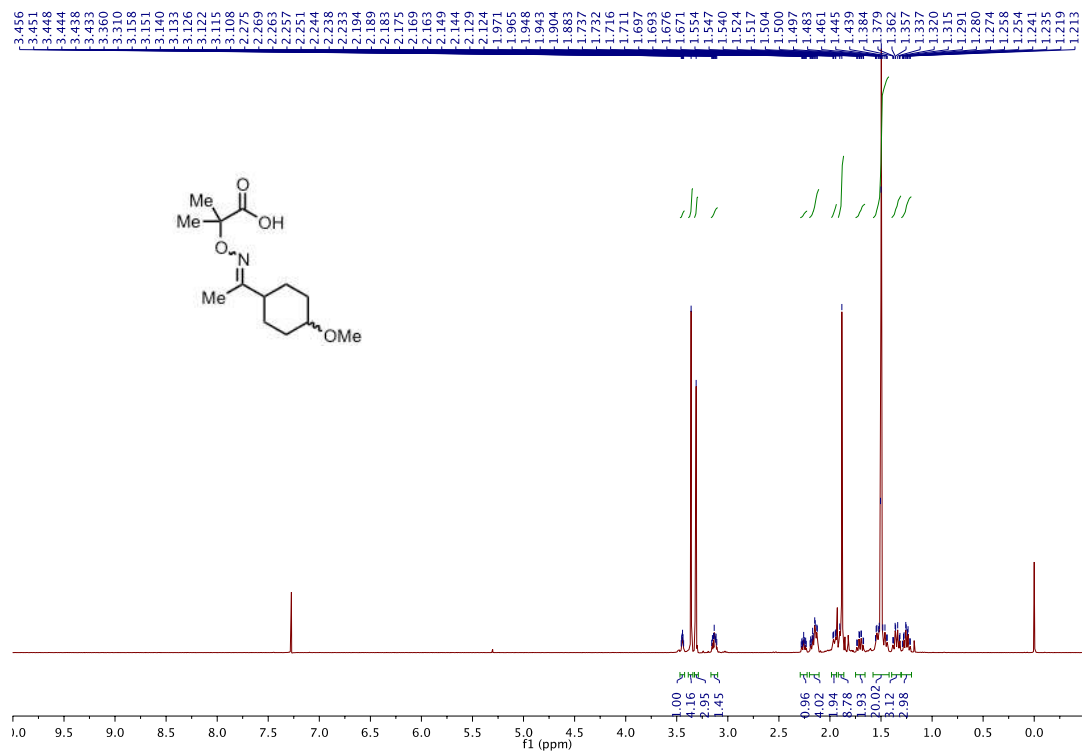












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176.544

164.208
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76.788
74.545

55.677
55.579

43.810
43.537

31.172
29.886
28.259
24.208
23.949

13.066
12.584

