Supporting Information

**Ligand-Enabled $\gamma$-C(sp$^3$)–H Olefination of Free Carboxylic Acids**

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General Information

Solvents, Reagents and Techniques

Unless otherwise noted, all reactions were conducted in glassware previously dried in an oven at 120°C. Reaction temperatures are reported as the temperature of the oil bath or the metal block surrounding the reaction vessel. The following solvents were dried by fractional distillation: pentane, ethyl acetate, CH₂Cl₂. Additional anhydrous solvents (<50 ppm water) were purchased from Acros Organics, Sigma-Aldrich, or Carl Roth and stored over molecular sieves under an argon atmosphere. Commercially available chemicals were obtained from ABCR, Acros Organics, Aldrich Chemical Co., Alfa Aesar, Combi-Blocks, Fluorochem, and TCI Europe and used as received unless otherwise stated.

Chromatography

Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 aluminum plates (Merck). The compounds were visualized by the exposure to ultraviolet light (254 nm and 366 nm) and/or by staining. For staining the TLC plates were dipped into a solution of KMnO₄ (1 g KMnO₄, 6 g K₂CO₃ and 0.1 g KOH in 100 mL H₂O) or bromocresol green (40 mg bromocresol green in 100 mL EtOH; addition of 0.1M NaOH until the blue colors appears in the solution) and developed with a heat gun if necessary. Flash column chromatography was performed on silica gel (35–70μm mesh, 60 Å, Acros) with a positive argon overpressure.

Nuclear Magnetic Resonance (NMR) Spectroscopy

³¹H-, ¹³C-, and ¹⁹F-NMR spectra were measured at r.t. on a Bruker Avance II 300 MHz, Avance II 400 MHz, or Agilent DD2 600 MHz spectrometer. Chemical shifts (δ) of ¹H- and ¹³C-NMR spectra are given in ppm relative to tetramethyl silane (TMS) using the residual solvent peaks for calibration (CDCl₃: δ H= 7.26 ppm, δ C= 77.16 ppm).¹⁹F-NMR spectra are not externally calibrated and chemical shifts is given relative to CCl₃F as received from the automatic data processing. Chemical shifts are reported with two (³¹H) or one (all other nuclei) digits after the decimal point. Exceptions are done when requiurved to annotate clearly distinguishable signals observed in very close proximity to one another. NMR-data are reported as follows: chemical shift (multiplicity [s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet, m = multiplet, br = broad], coupling constants (J, Hz) and integration). All spectra were processed using the MestReNova 12.0.4 program. For the spectra of diastereomeric mixtures signals clearly assigned to a particular diastereomer are labelled with a superscript at the integration. The number of protons in such cases refers to the number of protons of the respective isomer. The ¹³C-NMR spectra of mixtures are reported as observed. Due to the low signal intensity and potentially an overlap of signals, the number of signals can deviate from the hypothetical value, however, the signals of the major component are clearly recognizable in all cases.
Gas Chromatography with Flame Ionization Detection (GC-FID)

GC-FID analysis was done on an Agilent Technologies 6890A equipped with an HP-5 column (0.32 mm x 30 m, film: 0.25 μm) using flame ionization detection.

Mass Spectrometry (MS)

High resolution mass spectra (HRMS) were recorded on a Bruker Daltonics MicroTof or on a Thermo-Fisher Scientific Orbitrap LTQ XL spectrometer using electron spray ionization (ESI).

Gas chromatography with coupled mass spectrometry (GC-MS)

Gas chromatography was carried out on an Agilent Technologies 7890A gas chromatograph with Agilent 5975C VL MSD mass detector (EI) and a HP-5MS column (0.25 mm, 30 m, 0.25 μm layer thickness). The injection temperature $T_0$ was kept constant for three minutes and the column was heated to $T_1$ with a temperature gradient of 40 °C ∙ min$^{-1}$. The temperature $T_1$ was kept constant for four minutes. The method used was 50_40_4.0 ($T_0 = 50$ °C, $T_1 = 290$ °C, 4.0 minutes solvent delay). Before the analysis, all samples were cleaned using a pipette column (145 mm pipette filled with a piece of WHATMAN® filter paper and 2 cm silica gel). The signal intensity of the mass-to-charge ratio (m/z) is specified relative to the strongest signal.

Infrared Spectroscopy (IR)

Infrared spectra were recorded neat on a Shimadzu FTIR 8400S or a Varian Associates FTIR 3100 Excalibur spectrometer. The wave numbers ($\nu$) of recorded IR-signals are quoted in cm$^{-1}$. 
Preparation of Ligands

General Procedure A: Synthesis of N-acetylated Anthranilic Acid Ligands

The N-acetylation of anthranilic acids was done via a modified procedure of Roberts et al.\(^1\)

Anthranilic acid was dissolved in dry THF (0.25 M), acetyl chloride (1.0 equiv) was added slowly and the reaction mixture was cooled to 0 °C. Et\(_3\)N (1.5 equiv) was added dropwise and the reaction mixture was allowed to slowly warm up to r.t. The reaction mixture was stirred for 16 h and THF was removed under reduced pressure. The reaction mixture was cooled to 0 °C and aq. HCl (1.0 M) was added until the pH was between 1 and 5. All volatiles were removed under reduced pressure and the crude product was purified by column chromatography (CH\(_2\)Cl\(_2\):MeOH = 99:1 to 90:10).

2-Acetamido-6-fluorobenzoic acid (L10):

Following the general procedure A on a 32.2 mmol scale the target compound L10 was obtained as colorless solid (5.09 g, 25.8 mmol, 80%).

\(^1\)H-\({}^{19}\)F-NMR (500 MHz, DMSO-\(d_6\)): \(\delta = 10.12\) (s, 1H), 7.63 (dd, \(J = 8.3, 1.0\) Hz, 1H), 7.48 (t, \(J = 8.3\) Hz, 1H), 7.03 (dd, \(J = 8.3, 1.0\) Hz, 1H), 2.05 (s, 3H) ppm.

\(^{13}\)C-\({}^{19}\)F-NMR (126 MHz, DMSO-\(d_6\)): \(\delta = 168.5, 165.5, 160.2, 138.6, 132.4, 118.8, 113.6, 111.4, 23.9\) ppm.

\(^{19}\)F-\({}^1\)H NMR (470 MHz, DMSO-\(d_6\)): \(\delta = -110.9\) ppm.

HRMS (ESIpos) m/z: Calcd for C\(_9\)H\(_8\)FNNaO\(_3\)\(^+\) 220.0380, Found 220.0381.

IR (cm\(^{-1}\)): 2922, 2253, 1686, 1653, 1472, 1375, 903, 723.

trans-2-Acetamidocyclohexane-1-carboxylic acid (L12):

trans-2-Aminocyclohexane-1-carboxylic acid (300 mg, 2.10 mmol) was dissolved in water (5 mL), acetic anhydride (396 \(\mu\)L, 428 mg, 2.0 equiv) was added slowly and the mixture was stirred for 6 h. All volatiles were removed under reduced pressure and the crude product was purified by column chromatography (CH\(_2\)Cl\(_2\):MeOH = 90:10). The product L12 was obtained as a colorless solid (174 mg, 0.942 mmol, 49 %).

\(^1\)H-NMR (400 MHz, DMSO-\(d_6\)): \(\delta = 11.59\) (s, 1H), 7.78 (d, \(J = 8.7\) Hz, 1H), 3.74 (tdd, \(J = 10.8, 8.7, 4.1\) Hz, 1H), 2.25 – 2.11 (m, 1H), 1.89 – 1.54 (m, 7H), 1.45 – 0.99 (m, 4H) ppm.

\(^{13}\)C-NMR (101 MHz, DMSO-\(d_6\)): \(\delta = 175.3, 168.0, 48.7, 48.3, 32.0, 28.6, 24.3, 24.2, 22.8\) ppm.
HRMS (ESIpos) m/z: Calcd for C₉H₁₅NNaO₃²⁺ 208.0944, Found 208.0956.

IR (cm⁻¹): 2949, 2920, 1721, 1375, 1254, 1184, 997.

2-Fluoro-6-(2,2,2-trifluoroacetamido)benzoic acid (L15):

![Structural formula of L15]

6-fluoroanthranilic acid (155 mg, 1 mmol) was dissolved in dry THF (0.33 M), trifluoroacetic anhydride (970 µL, 7.00 mmol) was added slowly at 0 °C. Then the reaction mixture was allowed to warm up to r.t. and was stirred for 16 h. The reaction mixture was cooled to 0 °C and aq. HCl (1.0 M) was added until the pH was between 1 and 5. All volatiles were removed under reduced pressure and the crude product was purified by column chromatography (CH₂Cl₂:MeOH = 99:1 to 90:10) to obtain the target compound L15 as colorless solid (122 mg, 0.486 mmol, 49%).

¹H-{¹⁹F}-NMR (500 MHz, DMSO-d₆): δ = 13.76 (s, 1H), 11.71 (s, 1H), 7.62 (t, J = 8.3 Hz, 1H), 7.53 (dd, J = 8.3, 1.1 Hz, 1H) ppm.

¹³C-{¹⁹F}-NMR (126 MHz, DMSO-d₆): δ = 165.0, 160.2, 155.0, 135.5, 133.0, 120.8, 115.9, 115.8, 114.6 ppm.

¹⁹F-{¹H}-NMR (470 MHz, DMSO-d₆): δ = −74.7, −110.1 ppm.

HRMS (ESIpos) m/z: Calcd for C₁₃H₂₂NaO₄⁺ 265.1410, Found 265.1423.

IR (cm⁻¹): 1732, 1707, 1616, 1580, 1449, 1246, 1157, 957.

2-({tert-Butoxycarbonyl}atranso)-6-fluorobenzoic acid (L16):

![Structural formula of L16]

6-fluoroanthranilic acid (155 mg, 1 mmol) was dissolved in dry THF (0.33 M), Boc₂O (240 mg, 1.1 mmol) was added slowly and the reaction mixture was cooled to 0 °C. Et₃N (2.0 equiv) was added dropwise and the reaction mixture was slowly warmed up to r.t. The reaction mixture was stirred for 16 h and all volatiles were removed under reduced pressure. The crude product was purified by column chromatography (CH₂Cl₂:MeOH = 99:1 to 90:10) to obtain the target compound L16 as colorless solid (122 mg, 0.400 mmol, 40%).

¹H-{¹⁹F}-NMR (500 MHz, CDCl₃): δ = 9.75 (s, 1H), 8.23 (d, J = 8.5 Hz, 1H), 7.48 (t, J = 8.5 Hz, 1H), 6.79 (d, J = 8.5 Hz, 1H), 1.53 (s, 9H) ppm.

¹³C-{¹⁹F}NMR (126 MHz, CDCl₃): δ = 170.0, 163.0, 152.8, 143.4, 135.5, 115.3, 109.7, 81.5, 28.4 ppm.

¹⁹F-NMR (376 MHz, CDCl₃): δ = −104.7 ppm.

HRMS (ESIpos) m/z: Calcd for C₁₂H₁₃FNNaO⁺ 278.0799, Found 278.0812.

IR (cm⁻¹): 2984, 1726, 1670, 1580, 1472, 1250, 1153, 966, 887.
2-Fluoro-6-(((2,2,2-trichloroethoxy)carbonyl)atranso)benzoic acid (L17):

6-fluoroanthranilic acid (155 mg, 1 mmol) was dissolved in dry CH₂Cl₂ (0.33 M), 2,2,2-trichloroethoxycarbonyl chloride (150 µL, 1.10 mmol) was added slowly and the reaction mixture was cooled to 0 °C. Pyridine (160 µL, 2.00 mmol) was added dropwise and the reaction mixture was allowed to slowly warm up to r.t. The reaction mixture was stirred for 16 h and CH₂Cl₂ was removed under reduced pressure and all volatiles were removed under reduced pressure. The crude product was purified by column chromatography (CH₂Cl₂:MeOH = 99:1 to 90:10) to obtain the target compound L17 as colorless solid (137 mg, 0.414 mmol, 41%).

\[ ^1H-NMR \ (400 \ MHz, \ \text{CDCl}_3): \ \delta = 7.72 \ (td, J = 8.2 \ Hz, J_{H-F} = 5.6 \ Hz, 1H), 7.27 \ (dt, J = 8.1, 1.0 \ Hz, 1H), 7.10 \ (ddd, J = 8.3, 1.0 \ Hz, J_{H-F} = 9.5 \ Hz, 1H), 5.08 \ (s, 2H) \ ppm. \]

\[ ^{13}C-NMR \ (101 \ MHz, \ \text{CDCl}_3): \ \delta = 162.6 \ (d, J_{C-F} = 269.1 \ Hz), 154.4, 154.1 \ (d, J_{C-F} = 5.3 \ Hz), 149.0, 138.0 \ (d, J_{C-F} = 10.7 \ Hz), 121.5 \ (d, J_{C-F} = 4.0 \ Hz), 113.9 \ (d, J_{C-F} = 20.2 \ Hz), 104.4 \ (d, J_{C-F} = 8.3 \ Hz), 93.7, 78.1 \ ppm. \]

\[ ^{19}F-NMR \ (376 \ MHz, \ \text{CDCl}_3): \ \delta = -106.3 \ ppm. \]

HRMS (ESIpos) m/z: Calcd for C₁₃H₂₂NaO₄ 265.1410, Found 265.1423.

IR (cm⁻¹): 2959, 2253, 1784, 1645, 1622, 1578, 1483, 1377, 1327, 1302, 1252, 905, 725.

2-Fluoro-6-formamidobenzoic acid (L18):

Following the general procedure A on a 1.50 mmol scale the target compound L18 was obtained as colorless solid (197 mg, 1.02 mmol, 68%).

\[ ^1H-NMR \ (400 \ MHz, \ \text{DMSO-d}_6): \ \delta = 9.63 \ (s, 1H), 7.42 \ (d, J = 7.7 \ Hz, 1H), 7.28 \ (t, J = 7.7 \ Hz, 1H), 7.05 \ (d, J = 7.7 \ Hz, 1H), 2.34 \ (s, 3H), 2.00 \ (s, 3H) \ ppm. \]

\[ ^{13}C-NMR \ (101 \ MHz, \ \text{DMSO-d}_6): \ \delta = 168.9, 168.4, 136.0, 135.7, 129.6, 129.5, 127.8, 126.7, 122.1, 23.6, 20.4 \ ppm. \]

HRMS (ESIpos) m/z: Calcd for C₁₀H₁₁NNaO₃ 216.0631, Found 216.0641.

IR (cm⁻¹): 2926, 2857, 1730, 1684, 1466, 1371, 1250, 1103, 907, 729.

2-Acetamido-6-methoxybenzoic acid (L19):

Following the general procedure A on a 1.50 mmol scale the target compound L19 was obtained as colorless solid (151 mg, 0.722 mmol, 48%).
$^1$H-NMR (400 MHz, DMSO-d$_6$): $\delta = 12.92$ (s, 1H), 9.50 (s, 1H), 7.34 (t, $J = 8.2$ Hz, 1H), 7.20 (d, $J = 8.2$ Hz, 1H), 6.88 (d, $J = 8.2$ Hz, 1H), 3.77 (s, 3H), 1.99 (s, 3H) ppm.

$^{13}$C-NMR (101 MHz, DMSO-d$_6$): $\delta = 168.5$, 167.1, 156.7, 136.2, 130.3, 118.0, 116.8, 107.9, 55.9, 26.1 ppm.

HRMS (ESIpos) m/z: Calcd for C$_{13}$H$_{22}$NaO$_4$ $^{+}$ 265.1410, Found 265.1423.

IR (cm$^{-1}$): 2934, 1730, 1692, 1645, 1609, 1470, 1375, 1267, 1090, 907, 729.

2-Acetamido-6-(trifluoromethyl)benzoic acid (L20):

$^1$H-{$^{19}$F}-NMR (599 MHz, DMSO-d$_6$): $\delta = 10.03$ (s, 1H), 8.12 – 7.99 (m, 1H), 7.52 – 7.39 (m, 2H), 2.04 (s, 3H) ppm.

$^{13}$C-{$^{19}$F}-NMR (151 MHz, DMSO-d$_6$): $\delta = 168.5$, 167.0, 135.8, 128.3, 127.0, 126.1, 123.9, 121.5, 23.9 ppm.

$^{19}$F-{$^1$H}-NMR (564 MHz, DMSO-d$_6$): $\delta = -57.8$ ppm.

HRMS (ESIpos) m/z: Calcd for C$_{13}$H$_{22}$NaO$_4$ $^{+}$ 265.1410, Found 265.1423.

IR (cm$^{-1}$): 2944, 1705, 1684, 1472, 1321, 1271, 1140, 1111, 1024.

2-Acetamido-6-chlorobenzoic acid (L21):

$^1$H-NMR (300 MHz, DMSO-d$_6$): $\delta = 13.56$ (s, 1H), 9.68 (s, 1H), 7.58 – 7.24 (m, 3H), 2.01 (s, 3H) ppm.

$^{13}$C-NMR (75 MHz, DMSO-d$_6$): $\delta = 168.8$, 166.1, 136.3, 130.4, 129.9, 125.9, 124.5, 23.2 ppm.

HRMS (ESIpos) m/z: Calcd for C$_{13}$H$_{22}$NaO$_4$ $^{+}$ 265.1410, Found 265.1423.

IR (cm$^{-1}$): 3750, 3217, 3055, 2986, 2778, 2631, 2477, 1950, 1682, 1543, 1451, 1373, 1296, 1188, 1150, 1127, 1057, 1019, 980, 903, 802, 756, 710, 671, 610.
2-Acetamido-3,4,5,6-tetrafluorobenzoic acid (L22):

Following the general procedure A on a 2.10 mmol scale the target compound L22 was obtained as colorless solid (326 mg, 1.30 mmol, 62%).

$^1$H-NMR (500 MHz, DMSO-d$_6$): $\delta = 13.91$ (s, 1H), 10.01 (s, 1H), 2.03 (s, 3H) ppm.

$^{13}$C-{19F}-NMR (151 MHz, DMSO-d$_6$): $\delta$ 168.7, 161.9, 144.3, 142.4, 141.1, 138.0, 120.9, 116.8, 22.5 ppm.

$^{19}$F-NMR (470 MHz, DMSO-d$_6$): $\delta$ $-$141.4 (ddd, $J = 23.9$, 10.0, 3.5 Hz), $-$144.4 (dd, $J = 23.0$, 10.0 Hz), $-$153.9 (t, $J = 22.4$ Hz), $-$158.7 (t, $J = 22.8$ Hz) ppm.

HRMS (ESIpos) m/z: Calcd for C$_{13}$H$_{22}$NaO$_4^+$ 265.1410, Found 265.1423.

IR (cm$^{-1}$): 2951, 2918, 1707, 1458, 1375, 1103, 905, 727.
Optimization of the Reaction Conditions

**General Procedure for the optimization reactions:**

An oven dried 10 mL Schlenk tube was charged with Pd(OAc)$_2$, Ac-β-Ala-OH, silver salt, base, 3,3-dimethylbutyric acid or 3,3-dimethylpentanoic acid, acrylate and HFIP. The reaction mixture was stirred in a preheated aluminum block. After the indicated time the reaction was allowed to cool to r.t.. The reaction mixture was filtered over a pad of Celite®, the residue was washed with CH$_2$Cl$_2$ (30 mL) to complete elution and all volatiles were removed under reduced pressure. 1,3,5-trimethoxybenzene (33.6 mg, 0.200 mmol) and CDCl$_3$ (0.8 mL) were added. All yields during the optimization study were determined via $^1$H-NMR of the crude reaction using 1,3,5-trimethoxybenzene as internal standard.

**Scheme S1:** Screening of ligands.
Scheme S2: Screening of silver salts.

\[
\text{COOH} \quad (0.2 \text{ mmol}) + \text{COOEt} \quad (2.5 \text{ eq.}) \xrightarrow{\text{Pd(OAc)}_2 (10 \text{ mol}) \text{ Ac-Gly-OH (20 mol)}} \text{COOEt} \\
\text{Silver salt (1.0 eq.)} \quad \text{K}_2\text{HPO}_4 (1.0 \text{ eq.}) \quad \text{HFIP (2.0 mL)} \quad 110 ^\circ \text{C}, 13 \text{ h}
\]

| Entry | Silver salt | Yield (%) |
|-------|-------------|-----------|
| 1     | Ag\textsubscript{2}CO\textsubscript{3} | 21        |
| 2     | Ag\textsubscript{2}O | 26        |
| 3     | AgOAc | 17        |

Scheme S3: Compatibility of ligands with silver salts.

\[
\text{COOH} \quad (0.2 \text{ mmol}) + \text{COOEt} \quad (2.5 \text{ eq.}) \xrightarrow{\text{Pd(OAc)}_2 (10 \text{ mol}) \text{ Ligand (20 mol)}} \text{COOEt} \\
\text{Silver salt (1.0 eq.)} \quad \text{NalHFIP (1.0 eq.)} \quad \text{HFIP (2.0 mL)} \quad 110 ^\circ \text{C}, 13 \text{ h}
\]

| Entry | Ligand | Silver salt | Yield (%) |
|-------|--------|-------------|-----------|
| 1     | L10    | Ag\textsubscript{2}O | 23        |
| 2     | L13    | Ag\textsubscript{2}O | 8         |
| 3     | L13    | Ag\textsubscript{2}CO\textsubscript{3} | 39        |
| 4     | L10    | Ag\textsubscript{2}CO\textsubscript{3} | 54        |

Scheme S4: Screening of bases with varied counter-cations.

\[
\text{COOH} \quad (0.2 \text{ mmol}) + \text{COOEt} \quad (2.5 \text{ eq.}) \xrightarrow{\text{Pd(OAc)}_2 (10 \text{ mol}) \text{ L13 (20 mol)}} \text{COOEt} \\
\text{Ag\textsubscript{2}CO\textsubscript{3} (1.0 eq.)} \quad \text{Bases (1.0 eq.)} \quad \text{HFIP (2.0 mL)} \quad 110 ^\circ \text{C}, 13 \text{ h}
\]

| Entry | Bases | Yield (%) |
|-------|-------|-----------|
| 1     | LiHFIP | 8         |
| 2     | NaHFIP | 37        |
| 3     | KHFIP | 22        |
Scheme S5: Screening of bases.

| Entry | Bases  | Yield (%) |
|-------|--------|-----------|
| 1     | NaHFIP | 54        |
| 2     | NaHCO₃ | 28        |
| 3     | NaOAc  | 37        |
| 4     | NaOMe  | 40        |

Scheme S6: Screening of the amount of NaHFIP.

| Entry | x (eq.) | Yield (%) |
|-------|---------|-----------|
| 1     | 0.20    | 25        |
| 2     | 0.40    | 50        |
| 3     | 0.60    | 56        |
| 4     | 0.80    | 58        |
| 5     | 1.00    | 53        |
| 6     | 1.25    | 39        |
| 7     | 1.50    | 31        |
| 8     | 1.75    | 25        |
| 9     | 2.00    | 24        |

Scheme S7: Screening of the amount of Ag₂CO₃ and temperature. * In contrast to this result, better/more reproducible results were obtained with 110 °C, such that 110°C were used further.
Scheme S8: Screening of the amount of catalyst. *reaction time = 72 h

| Entry | x (mol%) | y (mol%) | Yield (%) |
|-------|----------|----------|-----------|
| 1     | 10       | 10       | 53        |
| 2     | 10       | 12       | 53        |
| 3     | 10       | 15       | 59        |
| 4     | 10       | 20       | 61        |
| 5     | 10       | 30       | 56        |
| 6     | 5        | 10       | 47        |
| 7     | 5        | 10       | 46        |
| 8     | 2.5      | 5.0      | 40        |

Scheme S9: Screening of the amount of NaHFIP.

| Entry | x (eq.) | Yield (%) |
|-------|---------|-----------|
| 1     | 0.4     | 44        |
| 2     | 0.5     | 52        |
| 3     | 0.6     | 61        |
| 4     | 0.7     | 62        |
| 5     | 0.8     | 58        |
| 6     | 0.9     | 57        |
| 7     | 1.0     | 53        |
| 8     | 1.5     | 43        |

Scheme S10: Screening of the amount of ethyl acrylate.

| Entry | x (eq.) | Yield (%) |
|-------|---------|-----------|
| 1     | 1.0     | 48        |
| 2     | 1.0     | 51        |
| 3     | 1.4     | 56        |
| 4     | 1.6     | 61        |
| 5     | 1.8     | 60        |
| 6     | 2.0     | 61        |
| 7     | 2.5     | 66        |
| 8     | 3.0     | 65        |
**Scheme S11**: Screening of the amount of solvent.

**Scheme S12**: Screening of the amount and type of base with different ligands.
Scheme S13: Screening of the amount of acrylate.

Further optimization for substituted 3,3-dimethylbutyric acid derivatives

Scheme S14: Screening of the amount of butyl acrylate and temperature.

Scheme S15: Screening of the amount of Ag$_2$CO$_3$. 

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**Scheme S13**

**Further optimization for substituted 3,3-dimethylbutyric acid derivatives**

**Scheme S14**

**Scheme S15**

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Scheme S16: Screening of the amount of n-butyl acrylate.

| Entry | x (eq.) | Yield (%) |
|-------|---------|-----------|
| 1     | 4.5     | 46        |
| 2     | 5.5     | 52        |
| 3     | 6.0     | 52        |
| 4     | 6.5     | 58        |
| 5     | 7.0     | 59        |
| 6     | 7.5     | 59        |
| 7     | 8.0     | 59        |

Scheme S17: Screening of the different atmospheres.

| Entry | Atmosphere | Yield (%) |
|-------|------------|-----------|
| 1     | air        | 56        |
| 2     | argon      | 56        |
| 3     | oxygen     | 48        |

Scheme S18: Screening of the different acrylates.

| Entry | R  | Yield (%) |
|-------|----|-----------|
| 1     | Me | 59        |
| 2     | Et | 59        |
| 3     | Bn | 49        |
| 4     | n-Bu | 59    |
Scheme S19: Screening of Ligands.

*Average yields are calculated (with respect to light, dark, longer time)

Scheme S20: Screening of the amount of bases. *Reaction time = 46 h
Scheme S21: Screening of the amount of ethyl acrylate.

| x (eq.) | L10 | L14 |
|---------|-----|-----|
| 7       | 66% | 69% |
| 6       | 65% | 67% |
| 5       | 51% | 61% |
| 4       | 45% | 57% |
| 3       | 41% | 48% |
Preparation of Substrates

General procedure B: γ–Arylation of 3,3-dimethylbutyric acid (1a)

An oven dried 150 mL Schlenk tube was charged with with Pd(OAc)$_2$ (112 mg, 0.500 mmol, 10 mol%), Ac-D-Phe-OH (207 mg, 1.00 mmol, 20 mol%), Ag$_2$CO$_3$ (1.38 g, 5.00 mmol, 1.0 equiv), K$_2$HPO$_4$ (871 mg, 5.00 mmol, 1.0 equiv), 3,3-dimethylbutyric acid (1a) (2.32 mg, 20.0 mmol, 4.0 equiv), aryl iodide (5.0 mmol, 1.0 equiv) and HFIP (50 mL). The reaction mixture was stirred for 24 h at 100 °C. The reaction was allowed to cool to room temperature and filtered over a pad of Celite®, the residue was washed with CH$_2$Cl$_2$ (30 mL) to complete elution and all volatiles were removed under reduced pressure. The crude product was dissolved in water (30 mL) and the aqueous solution was washed with CH$_2$Cl$_2$ (2 × 40 mL). The aqueous phase was acidified with HCl (10 wt%) until the pH was between 1 and 4 and the aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 40 mL). The combined organic phases were dried over MgSO$_4$·H$_2$O and all volatiles were removed under reduced pressure. The crude product was purified by silica column chromatography using CH$_2$Cl$_2$:AcOH (99.5:0.5).

General procedure C: Synthesis of β-quarternary carboxylic acids via 1,4 addition of Normann cuprates$^2$

Methyl 3-methylbut-2-enoate (1.0 equiv) was dissolved in THF (0.5M), Cul (0.1 equiv) was added and the mixture was cooled to −20 °C. TMSCI (1.2 equiv) was added slowly and the Grignard reagent (1.2 equiv) was added over 90 minutes via a syringe pump. The mixture was slowly allowed to warm up to r.t. and was stirred for 16 h. The reaction was quenched by the addition of sat. aq. NH$_4$Cl solution (30 mL) and the aqueous phase was extracted with Et$_2$O (3 × 50 mL). The combined organic phases were washed with brine and dried over MgSO$_4$·H$_2$O. All volatiles were removed and the residue was transferred with MeOH (10 mL) to a Schlenk tube and aq. NaOH (10 wt%, 10 mL) was added. The reaction mixture was heated to 60°C and stirred for 16h. The mixture was allowed to cool down to r.t. and was concentrated under reduced pressure. Water (20 mL) was added and the aqueous solution was washed with CH$_2$Cl$_2$ (2 × 40 mL). The aqueous phase was acidified with HCl (10 wt%) until the pH was between 1 and 4 and the aqueous phase was extracted with CH$_2$Cl$_2$ (3 × 40 mL). The combined organic phases were dried over MgSO$_4$·H$_2$O and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography using CH$_2$Cl$_2$:AcOH (99.7:0.3).
General procedure D: Synthesis of β-quarternary carboxylic acids via 1,4 addition with Gilman reagent

In a dry argon filled schlenk tube CuI (2.0 equiv) and Et₂O (30 mL) were added and the suspension was cooled to 0°C. MeLi (1.6 M in Et₂O, 4.0 equiv) was added dropwise and the mixture was stirred for 10 minutes. The solvent was removed at 0 °C under reduced pressure and CH₂Cl₂ (15mL) was added. The mixture was stirred for 5 minutes and CH₂Cl₂ was removed at 0 °C under reduced pressure. CH₂Cl₂ (15 mL) was added and the reaction mixture was cooled to −78 °C. TMSCl (2.0 equiv) and the α,β-unsaturated carbonyl compound (1.0 equiv) were added dropwise and the mixture was stirred for 1 h. The reaction mixture was allowed to slowly warm up to r.t. and stirred for 16 h. The reaction was quenched by the addition of sat. aq. NH₄Cl solution (30 mL) and conc. aq. ammonia (30 mL) was added. The aqueous phase was extracted with Et₂O (3 x 50 mL) and the combined organic phases were washed with brine and dried over MgSO₄·H₂O. All volatiles were removed and the residue was transferred with MeOH (10 mL) to a Schlenk tube and aq. NaOH (10 wt%, 10 mL) was added. The reaction mixture was heated to 60°C and stirred for 16 h. The mixture was allowed to cooldown to r.t. and was concentrated under reduced pressure. Water (20 mL) was added and the aqueous solution was washed with CH₂Cl₂ (2 × 40 mL). The aqueous phase was acidified with HCl (10 wt%) until the pH was between 1 and 4. The aqueous phase was extracted with CH₂Cl₂ (3 × 40 mL). The combined organic phases were dried over MgSO₄·H₂O and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography using CH₂Cl₂:AcOH (99.7:0.3).

3,3-dimethylpentanoic acid (1b):

Following the general procedure C in 25.0 mmol scale and using ethylmagnesium chloride (2.0 M in THF, 15 mL, 30 mmol), the target compound 1b was obtained as a colorless oil (1.99 g, 15.2 mmol, 61%).

¹H-NMR (300 MHz, CDCl₃): δ = 11.58 (s, 1H), 2.21 (s, 2H), 1.37 (q, J = 7.5 Hz, 2H), 1.00 (s, 6H), 0.86 (t, J = 7.5 Hz, 3H) ppm.

¹³C-NMR (75 MHz, CDCl₃): δ = 179.6, 45.7, 34.7, 33.5, 26.8, 8.6 ppm.

The data are in good agreement with those reported in the literature.
3,3,4-trimethylpentanoic acid (1c):

Following the general procedure C in 8.00 mmol scale and using isopropylmagnesium chloride (2.0 M in THF, 4.80 mL, 9.60 mmol) the target compound 1c was obtained as a colorless oil (482 mg, 3.34 mmol, 42%).

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta = 11.63$ (s, 1H), 2.25 (s, 2H), 1.63 (hept, $J = 6.8$ Hz, 1H), 0.99 (s, 6H), 0.87 (d, $J = 6.8$ Hz, 6H) ppm.

$^{13}$C-NMR (101 MHz, CDCl$_3$): $\delta = 179.6, 44.4, 36.5, 35.9, 24.3, 17.6$ ppm.

HRMS (ESIpos) m/z: Calcd for C$_8$H$_{16}$NaO$_2$+ 167.1043, Found 167.1039.

IR (cm$^{-1}$): 2967, 1701, 1468, 1410, 1310, 1250, 905, 727.

3,3-dimethylheptanoic acid (1d):

Following the general procedure C in 8.00 mmol scale and using $n$-butylmagnesium bromide (1.0 M in THF, 11.2 mL, 11.2 mmol) the target compound 1d was obtained as a colorless oil (291 mg, 1.84 mmol, 23%).

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta = 11.38$ (s, 1H), 2.22 (s, 2H), 1.39 – 1.20 (m, 6H), 1.01 (s, 6H), 0.90 (t, $J = 6.8$ Hz, 3H) ppm.

$^{13}$C-NMR (101 MHz, CDCl$_3$): $\delta = 179.5, 46.1, 42.2, 33.3, 27.4, 26.4, 23.5, 14.2$ ppm.

HRMS (ESIpos) m/z: Calcd for C$_9$H$_{18}$NaO$_2$+ 181.1199, Found 181.1198.

IR (cm$^{-1}$): 2932, 1793, 1470, 1408, 1369, 1252, 1177, 905, 727.

4-cyclohexyl-3,3-dimethylbutanoic acid (1e):

Following the general procedure B and using iodobenzene (1.02 g, 5.00 mmol) the intermediate 3,3-dimethyl-4-phenylbutanoic acid was obtained as a colorless oil (129 mg, 0.670 mmol, 13%). A hydrogenation vial was charged with 3,3-dimethyl-4-phenylbutanoic acid (91 mg, 0.47 mmol, 1 equiv), Rh/Al$_2$O$_3$ (5 mol%) and acetic acid (1 mL). The reaction mixture stirred at r.t. under a H$_2$ pressure of 10 bar at r.t. for 16 h. The catalyst was removed by filtration over Celite and the filtrate was concentrated by evaporation. The crude product was purified by silica gel column chromatography using (pentane:EtOAc = 90:10). The target compound was obtained as a colorless solid (93 mg, 0.47 mmol, 99%).
$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ = 11.00 (s, 1H), 2.24 (s, 2H), 1.76 – 1.54 (m, 5H), 1.39 – 0.89 (m, 14H) ppm.

$^{13}$C-NMR (101 MHz, CDCl$_3$): $\delta$ = 178.26, 50.03, 46.55, 35.99, 34.05, 33.95, 27.66, 26.74, 26.36 ppm.

HRMS (ESIpos) m/z: Calcd for C$_{12}$H$_{22}$NaO$_2$ $^{+}$ 221.1512, Found 221.1511.

IR (cm$^{-1}$): 2924, 1703, 1449, 1369, 907, 731.

2-(1-methylcyclohexyl)acetic acid (1f):

Following the general procedure D in 8.32 mmol scale and using ethyl 2-cyclohexylideneacetate (1.40 g, 8.32 mmol) the target compound 1f was obtained as a colorless oil (944 mg, 6.04 mmol, 73%).

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ = 11.59 (s, 1H), 2.26 (s, 2H), 1.56 – 1.20 (m, 10H), 1.05 (s, 3H) ppm.

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ = 179.6, 45.9, 37.9, 33.4, 26.2, 25.5, 22.1 ppm.

HRMS (ESIpos) m/z: Calcd for C$_9$H$_{16}$NaO$_2$ $^{+}$ 179.1043, Found 179.1034.

IR (cm$^{-1}$): 2928, 1703, 1447, 1408, 1235, 907, 731.

2-(4-methyltetrahydro-2H-pyran-4-yl)acetic acid (1g):

Following the general procedure D in 5.88 mmol scale and using ethyl 2-(tetrahydro-4H-pyran-4-ylidene)acetate (1.00 g, 5.88 mmol) the target compound 1g was obtained as a colorless oil (562 mg, 3.55 mmol, 60%).

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ = 10.37 (s, 1H), 3.77 – 3.61 (m, 4H), 2.33 (s, 2H), 1.71 – 1.59 (m, 2H), 1.53 – 1.42 (m, 2H), 1.15 (s, 3H) ppm.

$^{13}$C-NMR (101 MHz, CDCl$_3$): $\delta$ = 177.7, 63.8, 45.9, 37.5, 31.0, 24.3 ppm.

HRMS (ESIpos) m/z: Calcd for C$_8$H$_{14}$NaO$_3$ $^{+}$ 181.0835, Found 181.0840.

IR (cm$^{-1}$): 2932, 1705, 1227, 1105, 920, 839.

3-ethyl-3-methylpentanoic acid (1h):

Following the general procedure D in 0.998 mmol scale and using ethyl 3-ethylpent-2-enoate (380 mg, 0.998 mmol) the target compound 1h was obtained as a colorless oil (48.1 mg, 0.308 mmol, 31%).
1H-NMR (400 MHz, CDCl₃): δ = 2.22 (s, 2H), 1.38 (q, J = 7.5 Hz, 4H), 0.96 (s, 2H), 0.83 (t, J = 7.5 Hz, 6H) ppm.

13C-NMR (101 MHz, CDCl₃): δ = 179.1, 43.1, 36.1, 31.4, 24.1, 8.1 ppm.

HRMS (ESI neg) m/z: Calcd for C₈H₁₅O₂⁻ 143.1067, Found 143.1070.

IR (cm⁻¹): 2967, 1703, 1458, 1265, 1232.

3,3-dimethyl-5-phenylpentanoic acid (1i):

Following the general procedure C in 8.00 mmol scale and using phenylethylmagnesium bromide (1.0 M in THF, 11.2 mL, 11.2 mmol) the target compound 1i was obtained as a colorless oil (121 mg, 0.587 mmol, 7%).

1H-NMR (300 MHz, CDCl₃): δ = 10.59 (s, 1H), 7.41–7.29 (m, 2H), 7.29–7.19 (m, 3H), 2.74–2.61 (m, 2H), 2.39 (s, 2H), 1.81–1.67 (m, 2H), 1.18 (s, 6H) ppm.

13C-NMR (75 MHz, CDCl₃): δ = 179.0, 142.9, 128.5, 128.5, 125.8, 45.9, 44.5, 33.5, 30.9, 27.5 ppm.

HRMS (ESI pos) m/z: Calcd for C₁₃H₁₈NaO₂⁺ 229.1199, Found 229.1199.

IR (cm⁻¹): 2961, 1703, 1469, 1250, 1074, 905, 727.

4-(3-(ethoxycarbonyl)phenyl)-3,3-dimethylbutanoic acid (1j):

Following the general procedure B and using ethyl 3-iodobenzoate (1.38 g, 5.00 mmol) the target compound 1j was obtained as a colorless oil (230 mg, 0.870 mmol, 17%).

1H-NMR (400 MHz, CDCl₃): δ = 11.08 (s, 1H), 7.95–7.87 (m, 1H), 7.86 (s, 1H), 7.42–7.32 (m, 2H), 4.37 (q, J = 7.1 Hz, 2H), 2.75 (s, 2H), 2.24 (s, 2H), 1.39 (t, J = 7.1 Hz, 3H), 1.05 (s, 6H) ppm.

13C-NMR (101 MHz, CDCl₃): δ = 178.1, 167.0, 138.7, 135.3, 131.8, 130.3, 128.0, 127.6, 61.1, 47.6, 45.3, 34.4, 27.3, 14.5 ppm.

HRMS (ESI pos) m/z: Calcd for C₁₅H₂₀NaO₄⁺ 287.1254, Found 287.1260.

IR (cm⁻¹): 2932, 1705, 1468, 1369, 1283, 1200, 1107, 1026.

4-(3-acetylphenyl)-3,3-dimethylbutanoic acid (1k):

Following the general procedure B and using 1-(3-iodophenyl)ethan-1-one (1.23 g, 5.00 mmol) the target compound 1k was obtained as a colorless oil (296 mg, 1.26 mmol, 25%).
**1H-NMR (400 MHz, CDCl₃):** δ = 7.84 – 7.80 (dt, J = 6.8, 1.9 Hz, 1H), 7.79 (s, 1H), 7.43 – 7.35 (m, 2H), 2.77 (s, 2H), 2.60 (s, 3H), 2.24 (s, 2H), 1.06 (s, 6H) ppm.

**13C-NMR (101 MHz, CDCl₃):** δ = 198.6, 178.2, 139.0, 137.0, 135.6, 130.5, 128.3, 126.6, 47.5, 45.2, 34.4, 27.3, 26.8 ppm.

**HRMS (ESIpos) m/z:** Calcd for C₁₄H₁₈NO₃⁺ 257.1148, Found 257.1151.

**IR (cm⁻¹):** 2961, 2255, 1705, 1684, 1437, 1275, 905, 727.

**3,3-dimethyl-4-(4-(trifluoromethyl)phenyl)butanoic acid (1l):**

Following the general procedure B and using 1-iodo-4-(trifluoromethyl)benzene (1.36 g, 5.00 mmol) the target compound 1l was obtained as a colorless oil (141 mg, 0.542 mmol, 11%).

**1H-NMR (599 MHz, CDCl₃):** δ = 7.54 (d, J = 7.9 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H), 2.77 (s, 2H), 2.24 (s, 2H), 1.06 (s, 6H) ppm.

**13C-(19F) NMR (151 MHz, CDCl₃):** δ = 178.0, 142.6, 131.1, 128.8, 124.9, 124.5, 47.4, 45.1, 34.4, 27.4 ppm.

**19F-(1H) NMR (564 MHz, CDCl₃):** δ = –62.4 ppm.

**HRMS (ESIpos) m/z:** Calcd for C₁₃H₁₅F₃NaO₂⁺ 283.0916, Found 283.0910.

**IR (cm⁻¹):** 2965, 1703, 1620, 1323, 1165, 1123, 1069, 1020, 853.

**4-(3,5-bis(trifluoromethyl)phenyl)-3,3-dimethylbutanoic acid (1m):**

Following the general procedure B and using 1-iodo-3,5-bis(trifluoromethyl)benzene (1.70 g, 5.00 mmol) the target compound 1m was obtained as a colorless oil (152 mg, 0.463 mmol, 9%).

**1H-NMR (300 MHz, CDCl₃):** δ = 11.34 (s, 1H), 7.77 (s, 1H), 7.68 (s, 2H), 2.87 (s, 2H), 2.25 (s, 2H), 1.08 (s, 6H) ppm.

**13C-(19F) NMR (126 MHz, CDCl₃):** δ = 178.9, 141.0, 131.4, 130.8, 123.6, 120.6, 46.9, 45.2, 34.4, 27.3 ppm.

**19F-(1H) NMR (470 MHz, CDCl₃):** δ = –63.0 ppm.

The data are in good agreement with those reported in the literature.⁵
Acid Scope

General procedure E:

An oven dried 10 mL Schlenk tube was charged with Pd(OAc)$_2$ (4.5 mg, 0.020 mmol, 10 mol%), Ac-β-Ala-OH (5.3 mg, 0.040 mmol, 20 mol%), Ag$_2$CO$_3$ (96.5 mg, 0.350 mmol, 1.75 equiv), Na$_2$HPO$_4$ · 7 H$_2$O (10.7 mg, 0.04 mmol, 0.2 equiv), 3,3-dimethylbutyric acid (1a) (23.2 mg, 0.2 mmol), acrylate (0.5 mmol, 2.5 equiv) and HFIP (2.25 mL). The reaction mixture was stirred for 24 h at 110 °C. The mixture was filtered through a pad of Celite® using CH$_2$Cl$_2$ (30 mL) to complete the elution and all volatiles were removed under reduced pressure. KMnO$_4$ (31.6 mg, 0.200 mmol, 1.0 equiv), Et$_3$BnNCl (9.1 mg, 0.040 mmol, 0.2 equiv) and acetone (3 mL) were added and the mixture was stirred for 30 minutes. Concentrated aq. Na$_2$SO$_3$ was added until all permanganate was quenched. The mixture was filtered over a pad of celite using CH$_2$Cl$_2$ (30 mL) to complete the elution and all volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography using (pentane:EtOAc = 80:20 – 50:50).

General procedure F:

An oven dried 10 mL Schlenk tube was charged with Pd(OAc)$_2$ (4.5 mg, 0.020 mmol, 10 mol%), Ac-β-Ala-OH (5.3 mg, 0.040 mmol, 20 mol%), Ag$_2$CO$_3$ (138 mg, 0.500 mmol, 2.5 equiv), Na$_2$HPO$_4$ · 7 H$_2$O (10.7 mg, 0.04 mmol, 0.2 equiv), 3,3-dimethylbutyric acid (1a) (23.2 mg, 0.2 mmol), acrylate (0.5 mmol, 2.5 equiv) and HFIP (2.25 mL). The reaction mixture was stirred for 24 h at 110 °C. The mixture was filtered through a pad of Celite® using CH$_2$Cl$_2$ (30 mL) to complete the elution and all volatiles were removed under reduced pressure. KMnO$_4$ (31.6 mg, 0.200 mmol, 1.0 equiv), Et$_3$BnNCl (9.1 mg, 0.040 mmol, 0.2 equiv) and acetone (3 mL) were added and the mixture was stirred for 30 minutes. Concentrated aq. Na$_2$SO$_3$ was added until all permanganate was quenched. The mixture was filtered over a pad of celite using CH$_2$Cl$_2$ (30 mL) to complete the elution and all volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography using (pentane:EtOAc = 80:20 – 50:50).

General procedure G:

An oven dried 10 mL Schlenk tube was charged with Pd(OAc)$_2$ (4.5 mg, 0.020 mmol, 10 mol%), Ac-β-Ala-OH (5.3 mg, 0.040 mmol, 20 mol%), Ag$_2$CO$_3$ (138 mg, 0.500 mmol, 2.5 equiv), Na$_2$HPO$_4$ · 7 H$_2$O (10.7 mg, 0.04 mmol, 0.2 equiv), carboxylic acid (0.2 mmol), acrylate (1.40 mmol, 7.0 equiv) and HFIP (2.25 mL). The reaction mixture was stirred for 72 h at 110 °C. The mixture was filtered through a pad of Celite® using CH$_2$Cl$_2$ (30 mL) to complete the elution and all volatiles were removed under reduced pressure. KMnO$_4$ (31.6 mg, 0.200 mmol, 1.0 equiv), Et$_3$BnNCl (9.1 mg, 0.040 mmol, 0.2 equiv) and acetone (3 mL) were added and the mixture was stirred for 30 minutes. Concentrated aq. Na$_2$SO$_3$ was added until all permanganate was quenched. The mixture was filtered over a pad of celite using CH$_2$Cl$_2$ (30 mL) to complete the elution and all volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography using (pentane:EtOAc = 80:20 – 20:80).
Ethyl 2-(4,4-dimethyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (3a):

Following the general procedure E and using 3,3-dimethylbutyric acid (1a) (23.2 mg, 0.200 mmol) the target compound 3a was obtained as a colorless oil (27.4 mg, 0.128 mmol, 64%).

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ (ppm) = 4.85-4.73 (m, 1H), 4.15 (q, $J = 7.1$ Hz, 2H), 2.74 (dd, $J = 16.1$, 6.8 Hz, 1H), 2.54 (dd, $J = 16.1$, 5.9 Hz, 1H), 2.39 (dd, $J = 16.5$, 1.6 Hz, 1H), 2.22 (d, $J = 16.6$ Hz, 1H), 1.77 (ddd, $J = 13.9$, 3.5, 1.6 Hz, 1H), 1.49 (dd, $J = 13.9$, 12.0 Hz, 1H), 1.26 (t, $J = 7.1$, 3H), 1.11 (s, 3H), 1.05 (s, 3H) ppm.

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ = 171.4, 169.9, 73.8, 61.1, 43.8, 41.8, 40.7, 31.1, 30.0, 27.6, 14.2 ppm.

HRMS (ESIpos) m/z: Calcd for C$_{11}$H$_{18}$NaO$_4$ $^{+}$ 237.1097, Found 237.1117.

IR (cm$^{-1}$): 2963, 2253, 1732, 1387, 1373, 1238, 1194, 1036, 907, 729.

Results for large scale: Ethyl 2-(4,4-dimethyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (3a):

An oven dried 150 mL Schlenk tube was charged with Pd(OAc)$_2$ (104 mg, 0.500 mmol, 10 mol%), Ac-β-Ala-OH (131 mg, 1.00 mmol, 20 mol%), Ag$_2$CO$_3$ (2.41 g, 8.75 mmol, 1.75 equiv), Na$_2$HPO$_4$·7 H$_2$O (268 mg, 1.00 mmol, 0.2 equiv), 3,3-dimethylbutyric acid (1a) (511 mg, 5.00 mmol), ethyl acrylate (1,25 g, 12.5 mmol, 2.5 equiv) and HFIP (56 mL). The reaction mixture was stirred for 24 h at 110 °C. The mixture was filtered through a pad of Celite® using CH$_2$Cl$_2$(100mL) to complete the elution and all volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography using (pentane:EtOAc = 70:30). To the crude product was added KMnO$_4$ (31.6 mg, 0.2 mmol, 1.0 equiv), Et$_3$BnNCl (9.1 mg, 0.04 mmol, 0.2 equiv) and acetone (3 mL). The mixture was stirred for 30 minutes and concentrated aq. Na$_2$SO$_3$ was added until all permanganate was quenched. The mixture was filtered over a pad of Celite® using CH$_2$Cl$_2$(30mL) to complete the elution and all volatiles were removed under reduced pressure. The product 3a was obtained as a colorless oil (664 mg, 3.01 mmol, 62%).

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ = 4.80 (dddd, $J = 12.1$, 6.8, 6.0, 3.5 Hz, 1H), 4.16 (q, $J = 7.1$ Hz, 2H), 2.76 (dd, $J = 16.1$, 6.8 Hz, 1H), 2.54 (dd, $J = 16.1$, 6.0 Hz, 1H), 2.40 (dd, $J = 16.6$, 1.6 Hz, 1H), 2.23 (d, $J = 16.6$ Hz, 1H), 1.78 (dd, $J = 13.9$, 3.5, 1.6 Hz, 1H), 1.50 (dd, $J = 13.9$, 12.1 Hz, 1H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.11 (s, 3H), 1.06 (s, 3H) ppm.

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ = 171.4, 169.9, 73.8, 61.1, 43.8, 41.8, 40.7, 31.1, 30.0, 27.6, 14.3 ppm.

HRMS (ESIpos) m/z: Calcd for C$_{11}$H$_{18}$NaO$_4$ $^{+}$ 237.1097, Found 237.1117.

IR (cm$^{-1}$): 2963, 2253, 1732, 1387, 1373, 1238, 1194, 1036, 907, 729.
cis-Ethyl 2-(4-ethyl-4-methyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (3b-cis) and trans-ethyl 2-(4-ethyl-4-methyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (3b-trans):

Following the general procedure G and using 3,3-dimethylpentanoic acid (1b) (26 mg, 0.20 mmol) the target compound 3b was obtained as a colorless oil (30.1 mg, 0.132 mmol, 66%, d.r. = 1.3/1.0).

\[
\begin{align*}
\text{3b-cis} & \quad \text{CO}_2\text{Et} \\
\text{3b-trans} & \quad \text{CO}_2\text{Et}
\end{align*}
\]

\[^1H\text{-NMR (600 MHz, CDCl}_3\text{:} \delta = \text{4.83-4.75 m, (1H}^{\text{cis}}, 4.73-4.66 (m, 1H}^{\text{trans}}, 4.19-4.12 (m, 2H}^{\text{cis}+2H}^{\text{trans}}, 2.78-2.71 (m, 1H}^{\text{cis}+1H}^{\text{trans}}, 2.58-2.49 (m, 1H}^{\text{cis}+1H}^{\text{trans}}, 2.42 (dt, J = 16.1, 1.2 Hz, 1H}^{\text{trans}}, 2.34-2.23 (m, 2H}^{\text{cis}+1H}^{\text{trans}}, 2.18 (dd, J = 16.1, 1.1 Hz, 1H}^{\text{trans}}, 1.89 (ddd, J = 14.2, 3.3, 1.2 Hz, 1H}^{\text{trans}}, 1.71 (ddd, J = 13.9, 3.2, 1.4 Hz, 1H}^{\text{cis}}, 1.59-1.31 (m, 6.9H), 1.28-1.23 (m, 3H}^{\text{cis}+3H}^{\text{trans}}, 1.06 (s, 3H}^{\text{cis}}, 0.99 (s, 3H}^{\text{trans}}, 0.91-0.84 (m, 3H}^{\text{cis}+3H}^{\text{trans}}) \text{ppm.}
\]

\[^{13}\text{C-NMR (126 MHz, CDCl}_3\text{:} \delta = \text{172.0, 171.8, 170.0, 169.9, 73.6(3), 73.5(5), 61.1, 42.4, 42.0, 40.7, 40.5, 40.0, 39.7, 36.2, 33.1, 32.9, 32.8, 27.7, 24.9, 14.2, 8.2, 7.8 ppm.}
\]

HRMS (ESIpos) m/z: Calcd for C_{12}H_{20}NaO_4^+ 251.1254, Found 251.1269.

IR (cm\textsuperscript{-1}): 2967, 2255, 1732, 1522, 1437, 1052, 1190, 1057, 1026, 907, 731.

 cis-Ethyl 2-(4-isopropyl-4-methyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (3c-cis) and trans-ethyl 2-(4-isopropyl-4-methyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (3c-trans):

Following the general procedure G and using 3,3,4-trimethylpentanoic acid (1c) (28.8 mg, 0.200 mmol) the target compound 3c was obtained as a colorless oil (32.1 mg, 0.132 mmol, 66%, d.r. = 1.7/1.0).

\[^1H\text{-NMR (400 MHz, CDCl}_3\text{:} \delta = \text{4.85-4.71 m, (1H}^{\text{cis}}, 4.68-4.59 (m, 1H}^{\text{trans}}, 4.20-4.08 (m, 2H}^{\text{cis}+2H}^{\text{trans}}, 2.80-2.69 (m, 1H}^{\text{cis}+1H}^{\text{trans}}, 2.60-2.46 (m, 1H}^{\text{cis}+2H}^{\text{trans}}, 2.35-2.24 (m, 2H}^{\text{cis}}, 2.15 (dd, J = 15.3, 1.1 Hz, 1H}^{\text{trans}}, 2.03 (dd, J = 14.4, 3.3 Hz, 1H}^{\text{trans}}, 1.73-1.58 (m, 1H}^{\text{cis}+1H}^{\text{trans}}, 1.52-1.52 (m, 2H}^{\text{cis}}, 1.34-1.21 (m, 3H}^{\text{cis}+4H}^{\text{trans}}, 1.01 (s, 3H}^{\text{cis}}, 0.93 (s, 3H}^{\text{trans}}, 0.89 (d, J = 6.8 Hz, 6H}^{\text{trans}}, 0.85 (d, J = 6.9 Hz, 6H}^{\text{cis}}) \text{ppm.}
\]

\[^{13}\text{C-NMR (101 MHz, CDCl}_3\text{:} \delta = \text{172.8, 172.2, 169.9(8), 169.9(6), 73.6, 73.4, 61.1, 41.0, 40.7, 40.5, 40.3, 39.4, 38.3, 38.0, 35.7(0), 35.6(5), 35.5, 24.9, 22.3, 17.3, 17.1, 17.0, 16.9, 14.2 ppm.}
\]

HRMS (ESIpos) m/z: Calcd for C_{13}H_{22}NaO_4^+ 265.1410, Found 265.1424.

IR (cm\textsuperscript{-1}): 3055, 2986, 1734, 1422, 1265, 1192, 1063, 729, 704.
cis-Ethyl 2-(4-butyl-4-methyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (3d-cis) and trans-ethyl 2-(4-butyl-4-methyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (3d-trans):

Following the general procedure G and using 3,3-dimethylheptanoic acid (1d) (31.6 mg, 0.200 mmol) the target compound 3d was obtained as a colorless oil (33.5 mg, 0.131 mmol, 65%, d.r. = 1.3/1.0).

$^1$H-NMR (400 MHz, CDCl$_3$): δ = 4.78 (ddddd, $J = 12.3, 7.0, 5.9, 3.2$ Hz, 1H cis), 4.74–4.65 (m, 1H trans), 4.20–4.12 (m, 2H cis+2H trans), 2.78–2.70 (m, 1H cis+1H trans), 2.58–2.48 (m, 1H cis+1H trans), 2.43 (dd, $J = 16.1, 1.3$ Hz, 1H trans), 2.33 (dd, $J = 16.6, 1.4$ Hz, 1H cis), 2.26 (d, $J = 16.6$ Hz, 1H cis), 2.18 (d, $J = 16.1$ Hz, 1H trans), 1.89 (ddd, $J = 14.2, 3.3, 1.3$ Hz, 1H cis), 1.72 (ddd, $J = 13.9, 3.2, 1.4$ Hz, 1H cis), 1.52–1.21 (m, 10H cis+10H trans), 1.07 (s, 3H cis), 1.00 (s, 3H trans), 0.93–0.84 (m, 3H cis+3H trans) ppm.

$^{13}$C-NMR (101 MHz, CDCl$_3$): δ = 172.1, 171.9, 170.0(3), 170.0(0), 73.7, 73.6, 61.1, 43.6, 42.8, 42.4, 40.7, 40.5, 40.4, 40.3, 40.1, 32.6(9), 32.6(5), 28.2, 26.0, 25.6, 25.4, 23.2(9), 23.2(7), 14.2, 14.1(1), 14.0(9) ppm.

HRMS (ESIpos) m/z: Calcd for C$_{24}$H$_{32}$NaO$_5$ 279.1567, Found 279.1587.

IR (cm$^{-1}$): 2961, 2932, 2874, 2862, 2255, 1730, 1468, 1381, 1314, 1217, 1188, 1063, 1026, 907, 725.

cis-Ethyl 2-(4-(cyclohexylmethyl)-4-methyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (3e-cis) and trans-ethyl 2-(4-(cyclohexylmethyl)-4-methyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (3e-trans):

Following the general procedure G and using 4-cyclohexyl-3,3-dimethylbutanoic acid (1e) (39.7 mg, 0.200 mmol) the target compound 3e was obtained as a colorless oil (32.2 mg, 0.109 mmol, 54%, d.r. = 1.3/1.0).

$^1$H-NMR (400 MHz, CDCl$_3$): δ = 4.85 – 4.69 (m, 1H cis+1H trans), 4.20 – 4.10 (m, 2H cis+2H trans), 2.79 – 2.68 (m, 1H cis+1H trans), 2.58 - 2.48 (m, 1H cis+1H trans), 2.43 (dd, $J = 16.0, 1.2$ Hz, 1H trans), 2.35 (dd, $J = 16.6, 1.6$ Hz, 1H cis), 2.27 (d, $J = 16.7$ Hz, 1H cis), 2.19 (d, $J = 16.0$ Hz, 1H trans), 1.90 (ddd, $J = 14.1, 3.5, 1.2$ Hz, 1H trans), 1.75 (ddd, $J = 13.9, 3.3, 1.6$ Hz, 1H cis), 1.71 – 1.56 (m, 5H, 5H cis+5H trans), 1.54 – 1.35 (m, 1H cis+1H trans), 1.34 – 0.92 (m, 14H cis+14H trans) ppm.

$^{13}$C-NMR (101 MHz, CDCl$_3$): δ = 172.0, 171.8, 170.0(2), 169.9(6), 73.6(2), 73.5(9), 61.1, 51.4, 48.1, 43.38, 42.4, 41.0, 40.8, 40.7, 40.6, 35.9, 35.8, 35.7(7), 35.7(5), 34.0, 33.5, 33.3(7), 33.3(6), 28.7, 26.5(3), 26.5(0), 26.4(9), 26.1, 25.5, 14.2 ppm.

HRMS (ESIpos) m/z: Calcd for C$_{24}$H$_{32}$NaO$_5$ 319.1880, Found 319.1894.

IR (cm$^{-1}$): 2924, 2853, 1732, 1449, 1250, 1190, 1026.
Ethyl 2-(4-oxo-3-oxaspiro[5.5]undecan-2-yl)acetate (3f):

Following the general procedure G and using 3-cyclohexyl-3-methylbutanoic acid (1f) (31.2 mg, 0.200 mmol) the target compound 3f was obtained as a colorless oil (27.8 mg, 0.109 mmol, 55%).

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta$ = 4.75 (dddd, $J$ = 12.1, 6.8, 6.0, 3.2 Hz, 1H), 4.23-4.08 (m, 2H), 2.75 (dd, $J$ = 16.2, 6.8 Hz, 1H), 2.54 (dd, $J$ = 16.2, 6.0 Hz, 1H), 2.45 (dd, $J$ = 16.2, 1.2 Hz, 1H), 2.26 (d, $J$ = 16.2 Hz, 1H), 1.95 (dddd, $J$ = 14.1, 3.2, 1.2 Hz, 1H), 1.54–1.30 (m, 11H), 1.26 (t, $J$ = 7.1 Hz, 3H) ppm.

$^{13}$C-NMR (101 MHz, CDCl$_3$): $\delta$ = 171.8, 170.0, 73.1, 61.1, 40.6, 39.8, 36.4, 33.0, 25.7, 21.8, 21.6, 14.3 ppm.

HRMS (ESIpos) m/z: Calcd for C$_{14}$H$_{22}$NaO$_4$+ 277.1410, Found 277.1422.

IR (cm$^{-1}$): 2930, 2859, 2255, 1730, 1454, 1445, 1387, 1369, 1314, 1252, 1204, 1186, 1026, 907, 725.

Ethyl 2-(4-oxo-3,9-dioxaspiro[5.5]undecan-2-yl)acetate (3g):

Following the general procedure G and using 3-methyl-3-(tetrahydro-2H-pyran-4-yl)butanoic acid (1g) (31.6 mg, 0.200 mmol) the target compound 3g was obtained as a colorless oil (25.6 mg, 0.100 mmol, 50%).

$^1$H-NMR (500 MHz, CDCl$_3$): $\delta$ = 4.82-4.75 (m, 1H), 4.20-4.13 (m, 2H), 3.73–3.59 (m, 4H), 2.78 (dd, $J$ = 16.2, 6.7 Hz, 1H), 2.62–2.54 (m, 2H), 2.35 (d, $J$ = 16.3 Hz, 1H), 2.03 (ddd, $J$ = 14.1, 3.2, 1.2 Hz, 1H), 1.64-1.60 (m, 2H), 1.56-1.46 (m, 3H), 1.29-1.25 (m, 3H) ppm.

$^{13}$C-NMR (126 MHz, CDCl$_3$): $\delta$ = 170.8, 169.8, 72.8, 63.5, 63.4, 61.2, 41.4, 40.4, 39.6, 39.4, 36.4, 30.9, 14.3 ppm.

HRMS (ESIpos) m/z: Calcd for C$_{13}$H$_{20}$NaO$_5$+ 279.1203, Found 279.1207.

IR (cm$^{-1}$): 3053, 2988, 2305, 1730, 1422, 1105, 1020, 908, 729, 704.
Ethyl 2-(4,4-diethyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (3h):

Following the general procedure G and using 3-ethyl-3-methylpentanoic acid (1h) (28.8 mg, 0.200 mmol) the target compound 3h was obtained as a colorless oil (24.1 mg, 0.100 mmol, 50%).

\[ \delta = 4.71 \text{ (dddd, } J = 12.0, 6.7, 6.3, 3.0 \text{ Hz, } 1H), 4.20 - 4.13 \text{ (m, } 2H), 2.77 \text{ (dd, } J = 16.2, 6.7 \text{ Hz, } 1H), 2.53 \text{ (dd, } J = 16.2, 6.3 \text{ Hz, } 1H), 2.37 \text{ (dd, } J = 16.1, 1.0 \text{ Hz, } 1H), 2.24 \text{ (d, } J = 16.1 \text{ Hz, } 1H), 1.81 \text{ (dd, } J = 14.2, 3.0, 0.9 \text{ Hz, } 1H), 1.50 - 1.31 \text{ (m, } 5H), 1.27 \text{ (t, } J = 7.1 \text{ Hz, } 3H), 0.89 - 0.80 \text{ (m, } 6H) \text{ ppm.} \]

\[ \delta = 172.4, 170.0, 73.4, 61.1, 40.5, 40.3, 38.2, 35.6, 32.2, 30.0, 14.3, 7.8, 7.6 \text{ ppm.} \]

HRMS (ESIpos) m/z: Calcd for C_{13}H_{22}NaO_{4}^{+} 265.1410, Found 265.1418.

IR (cm\(^{-1}\)):

2969, 2928, 1732, 1464, 1383, 1265, 1184, 1061, 1026, 737.

cis-Ethyl 2-(4-methyl-6-oxo-4-phenethyltetrahydro-2H-pyran-2-yl)acetate (3i-cis) and trans-ethyl 2-(4-methyl-6-oxo-4-phenethyltetrahydro-2H-pyran-2-yl)acetate (3i-trans):

Following the general procedure G and using 3,3-dimethyl-5-phenylpentanoic acid (1i) (41.3 mg, 0.200 mmol) the target compound 3i was obtained as a colorless oil (34.6 mg, mmol, 0.114 mmol, 57%, d.r. = 1.3/1.0).

\[ \delta = 7.29 \text{ (ddt, } J = 10.8, 6.3, 1.5 \text{ Hz, } 2H^{\text{cis}}+2H^{\text{trans}}), 7.18 \text{ (tdd, } J = 8.6, 4.3, 2.9 \text{ Hz, } 3H^{\text{cis}}+3H^{\text{trans}}), 4.90 - 4.71 \text{ (m, } 1H^{\text{cis}}+1H^{\text{trans}}), 4.25 - 4.06 \text{ (m, } 2H^{\text{cis}}+2H^{\text{trans}}), 2.85 - 2.72 \text{ (m, } 1H^{\text{cis}}+1H^{\text{trans}}), 2.66 - 2.23 \text{ (m, } 5H^{\text{cis}}+5H^{\text{trans}}), 2.00 \text{ (ddd, } J = 14.2, 3.9, 1.6 \text{ Hz, } 1H^{\text{trans}}), 1.83 \text{ (ddd, } J = 13.8, 3.2, 1.3 \text{ Hz, } 1H^{\text{cis}}), 1.77 - 1.42 \text{ (m, } 3H^{\text{cis}}+3H^{\text{trans}}), 1.27 \text{ (td, } J = 7.1, 1.8 \text{ Hz, } 3H^{\text{cis}}+3H^{\text{trans}}), 1.19 \text{ (s, } 3H^{\text{cis}}), 1.12 \text{ (s, } 3H^{\text{trans}}) \text{ ppm.} \]

HRMS (ESIpos) m/z: Calcd for C_{18}H_{24}NaO_{4}^{+} 327.1567, Found 327.1554.

IR (cm\(^{-1}\)):

2936, 2255, 1730, 1456, 1250, 1190, 1028, 907, 725.
cis-Ethyl 3-((2-((ethoxy-2-oxoethyl)-4-methyl-6-oxotetrahydro-2H-pyran-4-yl)methyl)benzoate (3j-cis) and trans-ethyl 3-((2-((ethoxy-2-oxoethyl)-4-methyl-6-oxotetrahydro-2H-pyran-4-yl)methyl)benzoate (3j-cis):

Following the general procedure G and using 4-(3-(ethoxycarbonyl)phenyl)-3,3-dimethylbutanoic acid (1j) (52.9 mg, 0.200 mmol) the target compound 3j was obtained as a colorless oil (36.1 mg, 0.100 mmol, 50%, d.r. = 1.8/1.0).

$^1$H-NMR (400 MHz, CDCl$_3$): δ = 7.94 (dq, $J = 7.7, 1.8$ Hz, 1H$_{cis}+1$H$_{trans}$), 7.80 (dt, $J = 9.8, 1.9$ Hz, 1H$_{cis}+1$H$_{trans}$), 7.42 – 7.29 (m, 2H$_{cis}+2$H$_{trans}$), 4.87 – 4.74 (m, 1H$_{cis}+1$H$_{trans}$), 4.37 (q, $J = 7.1$ Hz, 2H$_{cis}+2$H$_{trans}$), 4.22 – 4.06 (m, 2H$_{cis}+2$H$_{trans}$), 2.84 – 2.48 (m, 4H$_{cis}+5$H$_{trans}$), 2.41 – 2.26 (m, 2H$_{cis}$), 2.17 (d, $J = 15.9$ Hz, 1H$_{trans}$), 2.06 – 1.97 (m, 1H$_{trans}$), 1.75 (dd, $J = 13.8, 3.6, 1.7$ Hz, 1H$_{cis}$), 1.58 (dd, $J = 13.8, 11.9$ Hz, 1H$_{cis}$), 1.50 – 1.34 (m, 3H$_{cis}+4$H$_{trans}$), 1.25 (t, $J = 7.0$ Hz, 3H$_{cis}+3$H$_{trans}$), 1.10 (s, 3H$_{cis}$), 1.02 (s, 3H$_{trans}$) ppm.

HRMS (ESIpos) m/z: Calcd for C$_{20}$H$_{28}$NaO$_6$ $^+$ 385.1622, Found 385.1626.

IR (cm$^{-1}$): 2986, 2255, 1719, 1447, 1369, 1283, 1200, 1026, 905, 723.

cis-Ethyl 2-((4-(3-acetylbenzyl))-4-methyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (3k-cis) and trans-ethyl 2-((4-(3-acetylbenzyl))-4-methyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (3k-trans):

Following the general procedure G using 4-(3-acetylphenyl)-3,3-dimethylbutanoic acid (1k) (46.9 mg, 0.200 mmol) the target compound 3k was obtained as a colorless oil (30.6 mg, 0.092 mmol, 46%, d.r. = 1.6/1.0).

$^1$H-NMR (599 MHz, CDCl$_3$): δ = 7.85 (ddt, $J = 7.8, 6.4, 1.5$ Hz, 1H$_{cis}+1$H$_{trans}$), 7.73 (dt, $J = 14.9, 1.9$ Hz, 1H$_{cis}+1$H$_{trans}$), 7.42 (td, $J = 7.6, 3.8$ Hz, 1H$_{cis}+1$H$_{trans}$), 7.34 (tt, $J = 7.6, 1.5$ Hz, 1H$_{cis}+1$H$_{trans}$), 4.84 – 4.75 (m, 1H$_{cis}+1$H$_{trans}$), 4.20 – 4.12 (m, 2H$_{cis}+2$H$_{trans}$), 2.81 – 2.63 (m, 3H$_{cis}+3$H$_{trans}$), 2.63 – 2.59 (m, 3H$_{cis}+3$H$_{trans}$), 2.59 – 2.49 (m, 1H$_{cis}+1$H$_{trans}$), 2.39 – 2.28 (m, 2H$_{cis}$), 2.19 (d, $J = 16.0$ Hz, 1H$_{trans}$), 2.04 (dd, $J = 14.2, 3.5$ Hz, 1H$_{trans}$), 1.77 (ddd, $J = 13.8, 3.6, 1.7$ Hz, 1H$_{cis}$), 1.59 (dd, $J = 13.8, 12.1$ Hz, 1H$_{cis}$), 1.45 (dd, $J = 14.3, 11.9$ Hz, 1H$_{trans}$), 1.28 – 1.25 (m, 3H$_{cis}+3$H$_{trans}$), 1.11 (s, 3H$_{cis}$), 1.02 (s, 3H$_{trans}$) ppm.

HRMS (ESIpos) m/z: Calcd for C$_{26}$H$_{32}$NaO$_6$ $^+$ 355.1516, Found 355.1521.

IR (cm$^{-1}$): 3055, 2984, 2963, 2932, 1728, 1684, 1265, 1179, 1026, 733.
cis-Ethyl 2-(4-methyl-6-oxo-4-(trifluoromethyl)benzyl)tetrahydro-2H-pyran-2-yl)acetate (3l-cis) and trans-ethyl 2-(4-methyl-6-oxo-4-(trifluoromethyl)benzyl)tetrahydro-2H-pyran-2-yl)acetate (3l-trans):

Following the general procedure G and using 3,3-dimethyl-4-(4-(trifluoromethyl)phenyl)butanoic acid (1l) (52 mg, 0.20 mmol) the target compound 3l was obtained as a colorless oil (35.1 mg, 0.100 mmol, 50%, d.r. = 2.5/1.0).

$^1$H-NMR (599 MHz, CDCl$_3$): δ = 7.61 – 7.53 (m, 2H$_{\text{cis}}$+2H$_{\text{trans}}$), 7.29 – 7.21 (m, 2H$_{\text{cis}}$+2H$_{\text{trans}}$), 4.85 – 4.77 (m, 1H$_{\text{cis}}$+1H$_{\text{trans}}$), 4.23 – 4.11 (m, 2H$_{\text{cis}}$+2H$_{\text{trans}}$), 2.82 – 2.63 (m, 3H$_{\text{cis}}$+3H$_{\text{trans}}$), 2.59 – 2.49 (m, 1H$_{\text{cis}}$+2H$_{\text{trans}}$), 2.38 – 2.29 (m, 2H$_{\text{cis}}$), 2.19 (dd, J = 16.1, 1.2 Hz, 1H$_{\text{trans}}$), 2.05 – 2.00 (m, 1H$_{\text{trans}}$), 1.77 (ddt, J = 13.8, 3.4, 1.3 Hz, 1H$_{\text{cis}}$), 1.59 (dd, J = 13.8, 12.0 Hz, 1H$_{\text{cis}}$), 1.49 – 1.43 (m, 1H$_{\text{trans}}$), 1.27 – 1.23 (m, 3H$_{\text{cis}}$+3H$_{\text{trans}}$), 1.10 (s, 3H$_{\text{cis}}$), 1.01 (s, 3H$_{\text{trans}}$) ppm.

$^{13}$C-{$^{19}$F}-NMR (151 MHz, CDCl$_3$): δ = 171.1, 170.7, 169.8(1), 169.7(7), 140.9, 140.5, 131.0, 130.9, 129.4, 125.4, 125.3, 124.3, 73.5, 73.4, 61.2, 61.1, 49.2, 46.1, 42.1, 41.7, 40.6, 40.5, 40.1, 40.0, 34.0, 33.9, 28.6, 25.1, 14.3, 14.2 ppm.

$^{19}$F-{$^1$H}-NMR (564 MHz, CDCl$_3$): δ = −62.5 ppm.

HRMS (ESIpos) m/z: Calcd for C$_{18}$H$_{21}$F$_3$NaO$_4$ $^+$ 381.1284, Found 381.1280.

IR (cm$^{-1}$): 2986, 2259, 1728, 1325, 1167, 1126, 1069, 1020, 907, 852, 727.


**cis-Ethyl** 2-(4-(3,5-bis(trifluoromethyl)benzyl)-4-methyl-6-oxotetrahydro-2H-pyranyl-2-yl)acetate (3m-cis) and **trans-ethyl** 2-(4-(3,5-bis(trifluoromethyl)benzyl)-4-methyl-6-oxotetrahydro-2H-pyranyl-2-yl)acetate (3m-trans):

Following the general procedure G and using 4-(3,5-bis(trifluoromethyl)phenyl)-3,3-dimethylbutanoic acid (1m) (65.6 mg, 0.200 mmol) the target compound 3m was obtained as a colorless oil (44.5 mg, 0.104 mmol, 52%, d.r. = 1.7/1.0).

**1H-NMR (600 MHz, CDCl₃):** δ = 7.81-7.79 (m, 1Hcis+1Htrans), 7.62 (s, 1Hcis), 7.60-7.55 (m, 1Hcis+2Htrans), 4.85-4.77 (m, 1Hcis+1Htrans), 4.20-4.13 (m, 2Hcis+2Htrans), 2.87-2.71 (m, 3Hcis+3Htrans), 2.61-2.53 (m, 1Hcis+1Htrans), 2.51 (d, J = 15.9 Hz, 1Htrans), 2.38-2.32 (m, 2Hcis), 2.24 (d, J = 15.8 Hz, 1Htrans), 2.02 (dd, J = 14.4, 3.5 Hz, 1Htrans), 1.77 (dd, J = 13.9, 3.4 Hz, 1Hcis), 1.61 (dd, J = 13.7, 12.0 Hz, 1Hcis), 1.45 (dd, J = 14.4, 11.9 Hz, 1Htrans) 1.28-1.24 (m, 3Hcis+3Htrans), 1.11 (s, 3Hcis), 1.03 (s, 3Htrans) ppm.

**13C-{19F}-NMR (151 MHz, CDCl₃):** δ = 170.9, 170.2, 169.8, 169.7, 139.3, 138.9, 131.9, 131.8, 130.5(9), 130.5(6), 123.3(3), 123.3(2), 121.1(8), 121.1(7), 73.5, 73.2, 61.2(3), 61.2(0), 49.0, 46.2, 42.2, 41.8, 40.5, 40.1, 39.9, 39.8, 34.0(3), 33.9(5), 28.4, 24.7, 14.2(3), 14.2(2) ppm.

**19F-NMR (564 MHz, CDCl₃):** δ = −62.9 ppm.

**HRMS (ESIpos) m/z:** Calcd for C₁₁₂H₂₀F₆NaO₄⁺ 449.1158, Found 449.1162.

**IR (cm⁻¹):** 2984, 2963, 2930, 2259, 1732, 1377, 1279, 1177, 1138, 1028, 907, 729.
Acrylate Scope

Methyl 2-(4,4-dimethyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (4a):

\[
\text{Following the general procedure E and using methyl acrylate (43 mg, 0.50 mmol) the target compound 4a was obtained as a colorless oil (26.8 mg, 0.134 mmol, 67%).}
\]

\(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta = 4.79\) (dddd, \(J = 12.0, 7.0, 5.8, 3.5\) Hz, 1H), 3.69 (s, 3H), 2.75 (dd, \(J = 16.1, 7.0\) Hz, 1H), 2.55 (dd, \(J = 16.1, 5.8\) Hz, 1H), 2.38 (dd, \(J = 16.6, 1.7\) Hz, 1H), 2.22 (d, \(J = 16.6\) Hz, 1H), 1.77 (ddd, \(J = 13.9, 3.5, 1.7\) Hz, 1H), 1.49 (dd, \(J = 13.9, 12.0\) Hz, 1H), 1.10 (s, 3H), 1.05 (s, 3H) ppm.

\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): \(\delta = 171.3, 170.3, 73.8, 52.1, 43.8, 41.8, 40.5, 31.1, 30.0, 27.5\) ppm.

HRMS (ESIpos) m/z: Calcd for C\(_{10}\)H\(_{16}\)NaO\(_4\) + 223.0941, Found 233.0962.

IR (cm\(^{-1}\)): 3053, 2988, 2305, 1736, 1439, 1421, 1317, 1265, 1175, 1036, 859, 733, 704.

Butyl 2-(4,4-dimethyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (4b):

\[
\text{Following the general procedure E and using n-butyl acrylate (64.1 mg, 0.500 mmol) the target compound 4b was obtained as a colorless oil (29.6 mg, 0.122 mmol, 61%).}
\]

\(^1\)H-NMR (300 MHz, CDCl\(_3\)): \(\delta = 4.79\) (dddd, \(J = 12.1, 6.8, 6.0, 3.5\) Hz, 1H), 4.10 (t, \(J = 6.7\) Hz, 2H), 2.75 (dd, \(J = 16.1, 6.8\) Hz, 1H), 2.54 (dd, \(J = 16.1, 6.0\) Hz, 1H), 2.39 (d, \(J = 16.6, 1.6\) Hz, 1H), 1.77 (ddd, \(J = 13.9, 3.5, 1.6\) Hz, 1H), 1.67–1.44 (m, 3H), 1.43–1.30 (m, 2H), 1.11 (s, 3H), 1.06 (s, 3H), 0.92 (t, \(J = 7.4\) Hz, 3H) ppm.

\(^{13}\)C-NMR (75 MHz, CDCl\(_3\)): \(\delta = 171.4, 170.0, 73.8, 65.0, 43.8, 41.8, 40.7, 31.1, 30.6, 30.0, 27.6, 19.2, 13.8\) ppm.

HRMS (ESIpos) m/z: Calcd for C\(_{13}\)H\(_{22}\)NaO\(_4\) + 265.1410, Found 265.1423.

IR (cm\(^{-1}\)): 2963, 2936, 2257, 1732, 1466, 1315, 1240, 1059, 1036, 908, 729.
Benzyl 2-(4,4-dimethyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (4c):

\[
\text{CO}_2\text{Sn}
\]

Following the general procedure E and using benzyl acrylate (81.1 mg, 0.500 mmol) the target compound 4c was obtained as a colorless oil (32.1 mg, 0.116 mmol, 58%).

\(\text{H-NMR (400 MHz, CDCl}_3\):} \delta = 7.40–7.30 (m, 5H), 5.15 (s, 2H), 4.81 (dddd, \(J = 12.1, 6.8, 6.0, 3.5\) Hz, 1H), 2.81 (dd, \(J = 16.1, 6.8\) Hz, 1H), 2.61 (dd, \(J = 16.1, 6.0\) Hz, 1H), 2.38 (dd, \(J = 16.6, 1.7\) Hz, 1H), 2.21 (d, \(J = 16.6\) Hz, 1H), 1.75 (ddd, \(J = 13.9, 3.5, 1.7\) Hz, 1H), 1.49 (dd, \(J = 13.9, 12.1\) Hz, 1H), 1.09 (s, 3H), 1.05 (s, 3H) ppm.

\(\text{C-NMR (101 MHz, CDCl}_3\):} \delta = 171.3, 169.7, 135.6, 128.7, 128.5, 128.5, 73.7, 66.9, 43.8, 41.7, 40.6, 31.1, 30.0, 27.6 ppm.

\(\text{HRMS (ESIpos) m/z:} \text{Calcd for C}_{16}\text{H}_{20}\text{NaO}_4^+ 299.1254, \text{Found 299.1270.}

\(\text{IR (cm}^{-1})\): 2355, 2324, 1734, 1719, 1541, 1302, 1250, 1175, 1036.

\(\text{2,2,2-Trifluoroethyl 2-(4,4-dimethyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (4d):}

\[
\text{CO}_2\text{CF}_3
\]

Following the general procedure E and using 2,2,2-trifluoroethyl acrylate (77 mg, 0.50 mmol) the target compound 4d was obtained as a colorless oil (28.9 mg, 0.108 mmol, 54%).

\(\text{H-NMR (500 MHz, CDCl}_3\):} \delta = 4.81 (dddd, \(J = 12.2, 7.0, 5.6, 3.5\) Hz, 1H), 4.60–4.37 (m, 2H), 2.86 (dd, \(J = 16.4, 7.0\) Hz, 1H), 2.69 (dd, \(J = 16.4, 5.6\) Hz, 1H), 2.40 (dd, \(J = 16.7, 1.7\) Hz, 1H), 2.25 (d, \(J = 16.7\) Hz, 1H), 1.77 (ddd, \(J = 13.9, 3.5, 1.7\) Hz, 1H), 1.53 (dd, \(J = 13.9, 12.2\) Hz, 1H), 1.12 (s, 3H), 1.08 (s, 3H) ppm.

\(\text{C-NMR (126 MHz, CDCl}_3\):} \delta = 171.0, 168.3, 122.9 (q, \(J_{C-F} = 277.2\) Hz), 73.3, 60.7 (q, \(J_{C-F} = 36.8\) Hz), 43.8, 41.6, 40.1, 31.1, 30.0, 27.5 ppm.

\(\text{F-NMR (470 MHz, CDCl}_3\):} \delta = -73.8 (t, \(J_{F-H} = 8.3\) Hz) ppm.

\(\text{HRMS (ESIpos) m/z:} \text{Calcd for C}_{11}\text{H}_{15}\text{F}_3\text{NaO}_4^+ 291.0815, \text{Found 291.0835.}

\(\text{IR (cm}^{-1})\): 2963, 2259, 1740, 1449, 1373, 1301, 1244, 1150, 1086, 912, 725.

4,4-dimethyl-6-(2-oxopropyl)tetrahydro-2H-pyran-2-one (4e):

\[
\text{CO}_2
\]

Following the general procedure F and using but-3-en-2-one (35 mg, 0.50 mmol) the target compound 4e was obtained as a colorless oil (18.7 mg, 0.101 mmol, 51%).
$^1$H-NMR (400 MHz, CDCl$_3$): $\delta = 4.83$ (dddd, $J = 12.1, 6.5, 5.8, 3.4$ Hz, 1H), 2.93 (dd, $J = 17.0, 6.5$ Hz, 1H), 2.60 (dd, $J = 17.1, 5.8$ Hz, 1H), 2.39 (dd, $J = 16.5, 1.6$ Hz, 1H), 2.33–2.11 (m, 4H), 1.77 (dddd, $J = 13.9, 3.4, 1.6$ Hz, 1H), 1.42 (dd, $J = 13.9, 12.1$ Hz, 1H), 1.11 (s, 3H), 1.05 (s, 3H) ppm.

$^{13}$C-NMR (101 MHz, CDCl$_3$): $\delta = 205.2, 171.6, 73.5, 49.0, 43.9, 42.1, 31.2, 31.2, 30.0, 27.8$ ppm.

HRMS (ESIpos) m/z: Calcd for C$_{10}$H$_{16}$NaO$_3$ $^+$ 207.0992, Found 207.1006.

IR (cm$^{-1}$): 2963, 1740, 1449, 1310, 1242, 1151, 1084, 1042, 1032.

2-(4,4-Dimethyl-6-oxotetrahydro-2H-pyran-2-yl)acetonitrile (4f):

Following the general procedure E and using acrylonitrile (11.8 mg, 0.500 mmol) the target compound 4f was obtained as a colorless oil (13.3 mg, 0.079 mmol, 40%).

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta = 4.63$ (dddd, $J = 12.1, 5.9, 5.0, 3.7$ Hz, 1H), 2.83–2.69 (m, 2H), 2.42 (dd, $J = 16.9, 1.9$ Hz, 1H), 2.29 (d, $J = 16.9$ Hz, 1H), 1.84 (dddd, $J = 13.9, 3.7, 1.9$ Hz, 1H), 1.66 (dd, $J = 13.9, 12.1$ Hz, 1H), 1.12 (s, 6H) ppm.

$^{13}$C-NMR (101 MHz, CDCl$_3$): $\delta = 169.9, 115.7, 72.2, 43.6, 41.0, 30.9, 30.1, 27.0, 24.9$ ppm.

HRMS (ESIpos) m/z: Calcd for C$_9$H$_{13}$NNaO$_2$ $^+$ 190.0838, Found 190.0853.

IR (cm$^{-1}$): 2963, 2932, 2255, 1738, 1472, 1387, 1375, 1242, 1223, 1053, 1038, 947, 725.

4,4-Dimethyl-6-((phenylsulfonyl)methyl)tetrahydro-2H-pyran-2-one (4g):

Following the general procedure E and using (vinylsulfonyl)benzene (84.1 mg, 0.500 mmol) the target compound 4g was obtained as a colorless oil (37.7 mg, 0.133 mmol, 67%).

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta = 7.96–7.89$ (m, 2H), 7.72–7.64 (m, 1H), 7.62–7.54 (m, 2H), 4.85 (dtdd, $J = 12.1, 5.9, 3.5$ Hz, 1H), 3.55 (dd, $J = 14.5, 5.9$ Hz, 1H), 3.11 (dd, $J = 14.5, 5.9$ Hz, 1H), 2.36 (dd, $J = 16.6, 1.6$ Hz, 1H), 2.19 (d, $J = 16.6$ Hz, 1H), 1.97 (dddd, $J = 14.1, 3.5, 1.6$ Hz, 1H), 1.56 (dd, $J = 14.1, 12.1$ Hz, 1H), 1.09 (s, 3H), 1.04 (s, 3H) ppm.

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta = 170.1, 139.6, 134.3, 129.5, 128.2, 71.8, 61.1, 43.7, 41.9, 31.0, 30.1, 27.5$ ppm.

HRMS (ESIpos) m/z: Calcd for C$_{14}$H$_{18}$NaO$_4$S $^+$ 305.0818, Found 305.0836.

IR (cm$^{-1}$): 2961, 2947, 2257, 1744, 1449, 1373, 1310, 1244, 1151, 1086, 903, 723.
(4,4-dimethyl-6-oxotetrahydro-2H-pyran-2-yl)methanesulfonyl fluoride (4h):

Following the general procedure F and using ethenesulfonyl fluoride (55 mg, 0.50 mmol) the target compound 4h was obtained as a colorless oil (22.9 mg, 0.102 mmol, 51%).

$^1$H-NMR (599 MHz, CDCl$_3$): $\delta = 4.92$ (dddd, $J = 12.1, 6.5, 5.4, 3.6$ Hz, 1H), 3.81 (ddd, $J_{HH} = 15.0, 6.5 J_{HF}$ = 2.0 Hz, 1H), 3.60 (ddd, $J_{HH} = 15.0, 5.4$ Hz, $J_{HF} = 6.6$ Hz, 1H), 2.45 (dd, $J = 16.8, 1.8$ Hz, 1H), 2.30 (d, $J = 16.8$ Hz, 1H), 1.93 (ddd, $J = 13.9, 3.6, 1.8$ Hz, 1H), 1.65 (dd, $J = 13.9, 12.1$ Hz, 1H), 1.15 (s, 3H), 1.12 (s, 3H) ppm.

$^{13}$C-NMR (151 MHz, CDCl$_3$): $\delta = 169.3$, 71.3, 55.7, 55.6, 43.6, 41.1, 41.1, 31.0, 30.2, 27.2 ppm.

$^{19}$F-NMR (564 MHz, CDCl$_3$): $\delta = 61.4$ (dd, $J_{F-H} = 6.6, 1.9$ Hz) ppm.

HRMS (ESIpos) m/z: Calcd for C$_8$H$_{13}$FNaO$_4$S: 247.0411, Found 247.0422.

IR (cm$^{-1}$): 2961, 2934, 1746, 1412, 1314, 1265, 1238, 1196, 1146, 1086, 1032, 833, 789.

diethyl ((4,4-dimethyl-6-oxotetrahydro-2H-pyran-2-yl)methyl)phosphonate (4i):

Following the general procedure E and using diethyl vinylphosphonate (284 mg, 3.50 mmol) the target compound 4i was obtained as a colorless oil (22.2 mg, 0.080 mmol, 40%).

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta = 4.77$–4.62 (m, 1H), 4.24–4.02 (m, 4H), 2.38 (dd, $J = 16.6, 1.6$ Hz, 1H), 2.35–2.25 (m, 1H), 2.22 (d, $J = 16.7$Hz, 1H), 2.11–2.00 (m, 1H), 1.94 (ddd, $J = 14.2, 3.4, 1.6$ Hz, 1H), 1.53 (dd, $J = 14.1, 12.0$ Hz, 1H), 1.36-1.30 (m, 6H), 1.09 (s, 3H), 1.06 (s, 3H) ppm.

$^{13}$C-NMR (101 MHz, CDCl$_3$): $\delta = 171.21$, 72.95, 62.38 (d, $J_{CP} = 6.4$ Hz), 62.01 (d, $J_{CP} = 6.5$ Hz), 43.81, 43.11 (d, $J_{CP} = 6.4$ Hz), 33.10 (d, $J_{CP} = 140.7$ Hz), 31.14, 30.06, 27.63, 16.54 (d, $J_{CP} = 6.0$ Hz), 16.51 (d, $J_{CP} = 6.1$ Hz) ppm.

$^{31}$P-$^1$H-NMR (162 MHz, CDCl$_3$): $\delta = 25.6$ ppm.

HRMS (ESIpos) m/z: Calcd for C$_{12}$H$_{23}$NaO$_5$P: 301.1175, Found 301.1191.

IR (cm$^{-1}$): 2984, 2961, 2928, 1738, 1466, 1265, 1240, 1026, 966, 733.
(1R,2S,5R)-2-Isopropyl-5-methylcyclohexyl 2-(4,4-dimethyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (4j):

Following the general procedure E and using (1S,2R,5S)-2-isopropyl-5-methylcyclohexyl acrylate (105 mg, 0.500 mmol) the target compound 4j was obtained as a colorless oil (38.2 mg, 0.118 mmol, 59%, d.r. = 1.0/1.0).

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta = 4.86$–$4.63$ (m, 2H$_{\text{iso1}}$+2H$_{\text{iso2}}$), 2.82–2.69 (m, 1H$_{\text{iso1}}$+1H$_{\text{iso2}}$), 2.60–2.47 (m, 1H$_{\text{iso1}}$+1H$_{\text{iso2}}$), 2.44–2.34 (m, 1H$_{\text{iso1}}$+1H$_{\text{iso2}}$), 2.27–2.18 (m, 1H$_{\text{iso1}}$+1H$_{\text{iso2}}$), 2.04–1.92 (m, 1H$_{\text{iso1}}$+1H$_{\text{iso2}}$), 1.90–1.63 (m, 4H$_{\text{iso1}}$+4H$_{\text{iso2}}$), 1.54–1.30 (m, 3H$_{\text{iso1}}$+3H$_{\text{iso2}}$), 1.10 (s, 3H$_{\text{iso1}}$+3H$_{\text{iso2}}$), 1.06 (s, 3H$_{\text{iso2}}$), 1.04–0.85 (m, 9H$_{\text{iso1}}$), 0.75 (s, 3H$_{\text{iso1}}$), 0.73 (s, 3H$_{\text{iso2}}$) ppm.

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta = 171.4, 171.4, 169.5(4), 169.5(2), 75.2, 75.1, 73.9, 47.0, 43.9, 43.81, 41.9, 41.8, 41.0, 40.9, 40., 3.26, 31.5, 31.2, 30.0, 27.70, 27.6, 26.4, 26.3, 23.5, 23.4, 22.1, 20.9, 20.8, 16.4, 16.3 ppm.

HRMS (ESIpos) m/z: Calcd for C$_{19}$H$_{32}$NaO$_4$ $^{+}$ 347.2193, Found 347.2199.

IR (cm$^{-1}$): 2961, 2928, 2255, 1728, 1456, 1389, 1373, 1420, 1036, 905, 725.

(2S,5S)-2,6,6-Trimethylbicyclo[3.1.1]heptan-3-yl 2-(4,4-dimethyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (4k):

Following the general procedure E and using (1R,2S,5S)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl acrylate (104 mg, 0.500 mmol) the target compound 4k was obtained as a colorless oil (37.9 mg, 0.117 mmol, 57%, d.r. = 1.0/1.0).

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta = 5.12$–$5.02$ (m, 1H$_{\text{iso1}}$+1H$_{\text{iso2}}$), 4.86 – 4.73 (m, 1H$_{\text{iso1}}$+1H$_{\text{iso2}}$), 2.83–2.71 (m, 1H$_{\text{iso1}}$+1H$_{\text{iso2}}$), 2.62–2.49 (m, 2H$_{\text{iso1}}$+2H$_{\text{iso2}}$), 2.43 – 2.30 (m, 2H$_{\text{iso1}}$+2H$_{\text{iso2}}$), 2.23 (m, 1H$_{\text{iso1}}$), 2.16–2.04 (m, 1H$_{\text{iso1}}$+1H$_{\text{iso2}}$), 1.96–1.87 (m, 1H$_{\text{iso1}}$+1H$_{\text{iso2}}$), 1.85–1.74 (m, 1H$_{\text{iso1}}$+1H$_{\text{iso2}}$), 1.72–1.61 (m, 1H$_{\text{iso1}}$+1H$_{\text{iso2}}$), 1.56–1.44 (m, 1H$_{\text{iso1}}$+1H$_{\text{iso2}}$), 1.21 (s, 3H$_{\text{iso1}}$+3H$_{\text{iso2}}$), 1.13–1.00 (m, 10H$_{\text{iso1}}$+10H$_{\text{iso2}}$), 0.94 (s, 3H$_{\text{iso1}}$+3H$_{\text{iso2}}$) ppm.

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta = 171.4, 169.9, 169.8, 75.1, 75.0, 73.9(3), 73.8(9), 47.5, 43.8, 43.7, 41.9, 41.3, 40.9(3), 40.9(1), 38.3, 35.9, 33.6, 31.2, 30.0, 27.7, 27.5, 23.9, 20.6 ppm.

HRMS (ESIpos) m/z: Calcd for C$_{19}$H$_{30}$NaO$_4$ $^{+}$ 345.2036, Found 345.2043.
1,3,3-Trimethylbicyclo[2.2.1]hept-2-yl 2-(4,4-dimethyl-6-oxotetrahydro-2H-pyran-2-yl)acetate (4l):

Following the general procedure E and using 1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl acrylate (104 mg, 0.500 mmol) the target compound 4l was obtained as a colorless oil (36.2 mg, 0.112 mmol, 56%, d.r. = 1.0/1.0).

$^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ = 4.86-4.73 (m, 1H$^{\text{iso1}}$+1H$^{\text{iso2}}$), 4.44-4.35 (m, 1H$^{\text{iso1}}$+1H$^{\text{iso2}}$), 2.89-2.75 (m, 1H$^{\text{iso1}}$+1H$^{\text{iso2}}$), 2.65-2.53 (m, 1H$^{\text{iso1}}$+1H$^{\text{iso2}}$), 2.45-2.34 (m, 1H$^{\text{iso1}}$+1H$^{\text{iso2}}$), 2.28-2.18 (m, 1H$^{\text{iso1}}$+1H$^{\text{iso2}}$), 1.86-1.76 (m, 1H$^{\text{iso1}}$+1H$^{\text{iso2}}$), 1.75–1.39 (m, 6H$^{\text{iso1}}$+6H$^{\text{iso2}}$), 1.21-1.15 (m, 1H$^{\text{iso1}}$+1H$^{\text{iso2}}$), 1.15–1.02 (m, 13H$^{\text{iso1}}$+13H$^{\text{iso2}}$), 0.78 (s, 3H$^{\text{iso1}}$), 0.76 (s, 3H$^{\text{iso2}}$) ppm.

$^{13}$C-NMR (75 MHz, CDCl$_3$): $\delta$ = 171.4(4), 171.4(2), 170.4, 170.3, 87.2, 87.1, 73.9, 73.8, 48.4, 43.9, 41.9(2), 41.8(9), 41.4, 40.8, 40.7, 39.6, 39.5, 31.2, 30.0, 29.8, 27.7(0), 27.6(9), 26.7, 25.9, 20.4, 20.3, 19.5(4), 19.5(0) ppm.

HRMS (ESIpos) m/z: Calcd for C$_{19}$H$_{30}$NaO$_4$ $^+$ 345.2036, Found 345.2048.

IR (cm$^{-1}$): 2961, 2934, 1734, 1317, 1248, 1238, 1057, 1032.
Mechanistic Experiments

Kinetic Isotope Experiments

3,3-Bis(methyl-d₃)butanoic-4,4,4-d₃ acid (1a-d₉):

![Chemical Structure](image)

Ethyl 3-(methyl-d₃)but-2-enoate-4,4,4-d₃ and (methyl-d₃)lithium had were synthesized via literature known procedures.³,⁶

Following the general procedure D in 5.40 mmol scale using ethyl 3-(methyl-d₃)but-2-enoate-4,4,4-d₃ (725 mg, 5.40 mmol) and (methyl-d₃)lithium (21.6 mmol, 4.0 equiv) the target compound 1a-d₉ was obtained as a colorless oil (360 mg, 2.88 mmol, 53%).

³¹H-NMR (300 MHz, CDCl₃): δ = 2.23 (s, 2H) ppm.

³¹C-NMR (101 MHz, CDCl₃): δ = 179.5, 47.8, 30.1, 28.8 (dt, J₉-D = 18.9 Hz) ppm.

HRMS (ESI neg) m/z: Calcd for C₆H₂D₉O₂ - 124.13294, Found 124.13297.

IR (cm⁻¹): 1701.

Determination of the parallel KIE:

An oven dried 10 mL Schlenk tube was charged with Pd(OAc)₂ (4.5 mg, 0.020 mmol, 10 mol%), Ac-β-Ala-OH (5.3 mg, 0.040 mmol, 20 mol%), Ag₂CO₃ (96.5 mg, 0.350 mmol, 1.75 equiv), Na₂HPO₄ · 7 H₂O (10.7 mg, 0.04 mmol, 0.2 equiv), acid (0.2 mmol), ethyl acrylate (50.1 mg, 0.5 mmol, 2.5 equiv) and HFIP (2.25 mL). The reaction mixture was stirred in a preheated aluminum block at 110 °C. After the indicated time the reaction was cooled to −78 °C. After letting the reaction warm up to room temperature a stock solution of 1,3,5-trimethoxybenzene (1.00 mL, 20.0 µM, 3.36 mg, 20.0 µmol, 0.1 equiv) was added. The reaction mixture was filtered over a pad of silica (bottom layer) and aluminum oxide (top layer), the residue was washed with EtOAc (30 mL) to complete elution and all volatiles were removed under reduced pressure. EtOAc (1.5 mL) was added and the yield was determined via GC-FID of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard.

![Scheme S22](image)

Scheme S22: Reaction conditions for the determination of the kinetic isotope experiments.
**Figure 1**: Determination of the KIE in parallel experiments. $k_H/k_D$ Determination.

**Table 1**: Parallel Kinetic isotope effect.

| Entry | Substrate                                         | Reaction time (min) | Product (µmol) |
|-------|---------------------------------------------------|---------------------|----------------|
| 1     | 3,3-dimethylbutanoic acid (1a)                    | 40                  | 7              |
| 2     | 3,3-dimethylbutanoic acid (1a)                    | 60                  | 10.8           |
| 3     | 3,3-dimethylbutanoic acid (1a)                    | 80                  | 14             |
| 4     | 3,3-dimethylbutanoic acid (1a)                    | 100                 | 14.4           |
| 5     | 3,3-dimethylbutanoic acid (1a)                    | 120                 | 29.4           |
| 6     | 3,3-bis(methyl-d3)butanoic-4,4,4-d3 acid (1a-d3)   | 40                  | 0.6            |
| 7     | 3,3-bis(methyl-d3)butanoic-4,4,4-d3 acid (1a-d3)   | 60                  | 2.4            |
| 8     | 3,3-bis(methyl-d3)butanoic-4,4,4-d3 acid (1a-d3)   | 80                  | 4.4            |
| 9     | 3,3-bis(methyl-d3)butanoic-4,4,4-d3 acid (1a-d3)   | 100                 | 6.4            |
| 10    | 3,3-bis(methyl-d3)butanoic-4,4,4-d3 acid (1a-d3)   | 120                 | 5.4            |

\[
\text{KIE} = \frac{k_H}{k_D} = \frac{0.242}{0.068} = 3.559
\]

**Competition experiment**

An oven dried 10 mL Schlenk tube was charged with Pd(OAc)$_2$ (4.5 mg, 0.020 mmol, 10 mol%), Ac-β-Ala-OH (5.3 mg, 0.040 mmol, 20 mol%), Ag$_2$CO$_3$ (96.5 mg, 0.350 mmol, 1.75 equiv), Na$_2$HPO$_4$ - 7 H$_2$O (10.7 mg, 0.04 mmol, 0.2 equiv), d$_5$-3,3-dimethylbutyric acid (1a-d$_5$) (12.5 mg, 0.1 mmol), 3,3-dimethylbutyric acid (1a) (11.6 mg, 0.1 mmol), ethyl acrylate (50.1 mg, 0.50 mmol, 2.5 equiv) and HFIP (2.25 mL). The reaction mixture was stirred in a preheated aluminum block at 110 °C for 180 min. The reaction was cooled to −78 °C. The reaction mixture was allowed to warm up to room temperature and an aliquot of the reaction was filtered over a piece of Whatman® filter paper. The parallel KIE was determined by ESI-MS analysis of the crude reaction mixture.
Determination of Reaction Order in Olefin, Catalyst and Substrate

For the determination of the reaction order in olefin and catalyst the initial rate method was used. The order was determined either by exponential fitting of the rate vs. varied component graph or from the slope of a linear fit in the double natural logarithmic plot of the rate vs. the varied component.7,8

**General Procedure H:**

An oven dried 10 mL Schlenk tube was charged with Pd(OAc)$_2$ (4.5 mg, 0.020 mmol, 10 mol%), Ac-β-Ala-OH (5.3 mg, 0.040 mmol, 20 mol%), Ag$_2$CO$_3$ (96.5 mg, 0.350 mmol, 1.75 equiv), Na$_2$HPO$_4$·7H$_2$O (10.7 mg, 0.04 mmol, 0.2 equiv), 3,3-dimethylbutyric acid (1a) (23.2 mg, 0.2 mmol), ethyl acrylate (50.1 mg, 0.5 mmol, 2.5 equiv) and HFIP (2.25 mL). The reaction mixture was stirred in a preheated aluminum block at 110 °C. After the indicated time the reaction was cooled to −78 °C. After letting the reaction warm up to room temperature a stock solution of 1,3,5-trimethoxybenzene (1.00 mL, 20.0 µM, 3.36 mg, 20.0 µmol, 0.1 equiv) was added. The reaction mixture was filtered over a pad of silica (bottom layer) and aluminum oxide (top layer), the residue was washed with EtOAc (30 mL) to complete elution and all volatiles were removed under reduced pressure. EtOAc (1.5 mL) was added and the yield was determined via GC-FID of the crude reaction using 1,3,5-trimethoxybenzene as internal standard.
General Procedure I:

An oven dried 10 mL Schlenk tube was charged with Pd(OAc)$_2$ (4.5 mg, 0.020 mmol, 10 mol%), Ac-β-Ala-OH (5.3 mg, 0.040 mmol, 20 mol%), Ag$_2$CO$_3$ (96.5 mg, 0.350 mmol, 1.75 equiv), Na$_2$HPO$_4$·7H$_2$O (37.5 mg, 0.14 mmol, 0.2 equiv), 3,3-dimethylbutyric acid (1a) (23.2 mg, 0.2 mmol), ethyl acrylate (50.1 mg, 0.5 mmol, 2.5 equiv) and HFIP (2.25 mL). The reaction mixture was stirred in a preheated aluminum block at 110 °C. After the indicated time the reaction was cooled to −78 °C. After letting the reaction warm up to room temperature a stock solution of 1,3,5-trimethoxybenzene (1.00 mL, 20.0 µM, 3.36 mg, 20.0 µmol, 0.1 equiv) was added. The reaction mixture was filtered over a pad of silica (bottom layer) and aluminum oxide (top layer), the residue was washed with EtOAc (30 mL) to complete elution and all volatiles were removed under reduced pressure. EtOAc (1.5 mL) was added and the yield was determined via GC-FID of the crude reaction using 1,3,5-trimethoxybenzene as internal standard.

Order in Olefin:

**General procedure H was utilized with the following modifications:** The amount of ethyl acrylate (27.30 – 109.1 µL, 250 – 1000 µmol, 1.25 – 5.00 equiv) was varied.

| Entry | Amount of olefin (µmol) | Reaction time (min) | Product (µmol) |
|-------|-------------------------|---------------------|---------------|
| 1     | 250                     | 40                  | 0.42          |
| 2     | 250                     | 60                  | 3.22          |
| 3     | 250                     | 80                  | 6.72          |
| 4     | 250                     | 100                 | 10.18         |
| 5     | 250                     | 120                 | 20.04         |
| 6     | 375                     | 40                  | 0.90          |
| 7     | 375                     | 60                  | 4.60          |
| 8     | 375                     | 80                  | 8.76          |
| 9     | 375                     | 100                 | 18.52         |
| 10    | 375                     | 120                 | 24.60         |
| 11    | 500                     | 40                  | 0.44          |
| 12    | 500                     | 60                  | 4.84          |
| 13    | 500                     | 80                  | 8.32          |
| 14    | 500                     | 100                 | 19.42         |
| 15    | 500                     | 120                 | 24.80         |
| 16    | 750                     | 40                  | 0.94          |
| 17    | 750                     | 60                  | 3.74          |
| 18    | 750                     | 80                  | 7.48          |
| 19    | 750                     | 100                 | 21.50         |
| 20    | 750                     | 120                 | 26.30         |
| 21    | 1000                    | 40                  | 0.94          |
| 22    | 1000                    | 60                  | 2.76          |
| 23    | 1000                    | 80                  | 10.52         |
| 24    | 1000                    | 100                 | 21.14         |
| 25    | 1000                    | 120                 | 24.40         |
Figure 2: Plot of product (µmol) versus time (min) for various olefin concentrations with linear fits 
[olefin] = 111 mM (black), 167 mM (red), 222 mM (blue), 333 mM (green), and 444 mM (pink).

Figure 3: Plot of the initial rate versus the initial concentration of the olefin.

Figure 4: Double natural logarithmic plot of the initial rate versus the initial concentration of the olefin.
Order in catalyst:

General procedure I was utilized with the following modifications: The amount of palladium acetate (2.25 – 6.74 mg, 10 – 30 µmol, 0.01 – 0.03 equiv) and Ac-β-Ala-OH (5.30 – 15.7 mg, 20 – 60 µmol, 0.02 – 0.06 equiv) was varied.

| Entry | Amount of catalyst (µmol) | Reaction time (min) | Product (µmol) |
|-------|---------------------------|---------------------|----------------|
| 1     | 10                        | 30                  | 0.68           |
| 2     | 10                        | 40                  | 2.71           |
| 3     | 10                        | 50                  | 5.99           |
| 4     | 10                        | 60                  | 7.81           |
| 5     | 10                        | 70                  | 10.37          |
| 6     | 15                        | 30                  | 2.68           |
| 7     | 15                        | 40                  | 6.19           |
| 8     | 15                        | 50                  | 7.15           |
| 9     | 15                        | 60                  | 7.77           |
| 10    | 15                        | 70                  | 21.04          |
| 11    | 20                        | 30                  | 2.37           |
| 12    | 20                        | 40                  | 8.87           |
| 13    | 20                        | 50                  | 6.27           |
| 14    | 20                        | 60                  | 16.04          |
| 15    | 20                        | 70                  | 23.72          |
| 16    | 25                        | 30                  | 1.73           |
| 17    | 25                        | 40                  | 9.52           |
| 18    | 25                        | 50                  | 18.16          |
| 19    | 25                        | 60                  | 23.42          |
| 20    | 25                        | 70                  | 27.95          |
| 21    | 30                        | 30                  | 2.50           |
| 22    | 30                        | 40                  | 13.33          |
| 23    | 30                        | 50                  | 20.07          |
| 24    | 30                        | 60                  | 28.96          |
| 25    | 30                        | 70                  | 30.46          |
Figure 5: Plot of product (µmol) versus time (min) for various catalyst amounts with linear fits. [catalyst] = 10 µmol (black), 15 µmol (red), 20 µmol (blue), 25 µmol (green), and 30 µmol (pink).

Figure 6: Plot of the initial rate versus the initial concentration of the catalyst.

Figure 7: Double natural logarithmic plot of the initial rate versus the initial concentration of the catalyst.
Order in Substrate:

**General procedure I** was utilized with the following modifications: The amount of 3,3–dimethylbutyric acid (1a) (12.8 – 50.9 µL, 0.10 – 0.40 mmol) was varied.

**Table 4:** Initial rate method to determine the order in 3,3–dimethylbutyric acid (1a)

| Entry | Amount of substrate 1a (µmol) | Reaction time (min) | Product (µmol) |
|-------|-------------------------------|---------------------|----------------|
| 1     | 100                           | 30                  | 4.0            |
| 2     | 100                           | 40                  | 7.8            |
| 3     | 100                           | 50                  | 16.8           |
| 4     | 100                           | 60                  | 23.2           |
| 5     | 100                           | 70                  | 26.6           |
| 6     | 150                           | 30                  | 2.4            |
| 7     | 150                           | 40                  | 5.4            |
| 8     | 150                           | 50                  | 12.2           |
| 9     | 150                           | 60                  | 24.8           |
| 10    | 150                           | 70                  | 28.2           |
| 11    | 200                           | 30                  | 1.8            |
| 12    | 200                           | 40                  | 3.6            |
| 13    | 200                           | 50                  | 12.2           |
| 14    | 200                           | 60                  | 22.6           |
| 15    | 200                           | 70                  | 31.8           |
| 16    | 300                           | 30                  | 2.0            |
| 17    | 300                           | 40                  | 3.0            |
| 18    | 300                           | 50                  | 5.8            |
| 19    | 300                           | 60                  | 17.8           |
| 20    | 300                           | 70                  | 19.6           |
| 21    | 400                           | 30                  | 2.2            |
| 22    | 400                           | 40                  | 4.2            |
| 23    | 400                           | 50                  | 5.6            |
| 24    | 400                           | 60                  | 13.0           |
| 25    | 400                           | 70                  | 13.0           |
**Figure 8**: Plot of product (µmol) versus time (min) for various concentrations of substrate 1a. [substrate] = 100 µmol (black), 150 µmol (red), 200 µmol (blue), 300 µmol (green), and 400 µmol (pink).

| Conc. of the substrate (µmol/mL) | Initial rate (µmol/min) |
|---------------------------------|-------------------------|
| 45                              | 0.61                    |
| 67                              | 0.71                    |
| 89                              | 0.79                    |
| 133                             | 0.50                    |
| 178                             | 0.30                    |

**Table 5**: Initial rate for various amounts of substrate 1a:

**Figure 9**: Initial rate versus the initial substrate concentration.
Reversibility of the C—H Activation

Reversibility Experiment in the presence of ethyl acrylate

An oven dried 10 mL Schlenk tube was charged with Pd(OAc)$_2$ (2.25 mg, 0.0100 mmol, 10 mol%), Ac-β-Ala-OH (2.6 mg, 0.020 mmol, 20 mol%), Ag$_2$CO$_3$ (48.3 mg, 0.175 mmol, 1.75 equiv), Na$_2$HPO$_4$·7 H$_2$O (5.4 mg, 0.02 mmol, 0.2 equiv), d$_9$-3,3-dimethylbutyric acid (1a-d$_9$)(12.5 mg, 0.1 mmol) and ethyl acrylate (25.0 mg, 0.25 mmol, 2.5 equiv) and HFIP (1.125 mL). The reaction mixture was stirred in a preheated aluminum block at 110 °C for 16 h. The reaction was cooled to −78 °C. An aliquot of the reaction was filtered over a piece of Whatman ® filter paper and the deuterium incorporation in the leftover starting material was determined by HRMS-ESI-MS.

Reversibility Experiment in the absence of ethyl acrylate

An oven dried 10 mL Schlenk tube was charged with Pd(OAc)$_2$ (2.25 mg, 0.0100 mmol, 10 mol%), Ac-β-Ala-OH (2.6 mg, 0.020 mmol, 20 mol%), Ag$_2$CO$_3$ (48.3 mg, 0.175 mmol, 1.75 equiv), Na$_2$HPO$_4$·7 H$_2$O (5.4 mg, 0.02 mmol, 0.2 equiv), d$_9$-3,3-dimethylbutyric acid (1a-d$_9$)(12.5 mg, 0.100 mmol) and HFIP (1.125 mL). The reaction mixture was stirred in a preheated aluminum block at 110 °C for 22 h. The reaction was cooled to −78 °C. The reaction was allowed to warm up to room temperature and an aliquot of the reaction was filtered over a piece of Whatman ® filter paper and the deuterium incorporation of the starting material was determined by HRMS-ESI-MS.
Scheme S24: Reversibility experiment.

**a)**

\[
\text{D}_3\text{C}-\text{C}^\text{COOH} \quad \text{D}_3\text{C}
\]

\[1\text{a-d}_9 \]

\[d_9 = 97\% \quad d_9 = 3\%
\]

**b)**

\[
\text{D}_3\text{C}-\text{C}^\text{COOH} \quad \text{D}_3\text{C}
\]

\[\text{COOEt} \quad (2.5 \text{ eq.}) \quad \text{Pd(OAc)}_2 (10 \text{ mol}) \quad \text{Ac-β-Ala-OH (20 mol)} \]

\[\text{Ag}_2\text{CO}_3 (1.75 \text{ eq.}) \quad \text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O (0.2 eq.)} \quad \text{HFIP (1.125 mL)}
\]

\[110 \degree \text{C}, 16 \text{ h} \quad \text{D}_3\text{C}-\text{C}^\text{COOH} \quad \text{D}_3\text{C}
\]

\[1\text{a-d}_9 \quad d_9 = 92\% \quad d_9 = 8\%
\]

**c)**

\[
\text{D}_3\text{C}-\text{C}^\text{COOH} \quad \text{D}_3\text{C}
\]

\[\text{D}_3\text{C}-\text{C}^\text{COOH} \quad \text{D}_3\text{C}
\]

\[\text{Pd(OAc)}_2 (10 \text{ mol}) \quad \text{Ac-β-Ala-OH (20 mol)} \]

\[\text{Ag}_2\text{CO}_3 (1.75 \text{ eq.}) \quad \text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O (0.2 eq.)} \quad \text{HFIP (1.125 mL)}
\]

\[110 \degree \text{C}, 22 \text{ h} \quad \text{D}_3\text{C}-\text{C}^\text{COOH} \quad \text{D}_3\text{C}
\]

\[1\text{a-d}_9 \quad d_9 = 27\% \quad d_9 = 37\% \quad d_9 = 22\% \quad d_9 = 7\% \quad d_9 = 3\% \quad d_9 = 2\% \quad d_9 = 1\%
\]
Characterization of the Side Product and Limitations

(E)-4,4-dimethyl-5-(3-oxobut-1-en-1-yl)dihydrofuran-2(3H)-one (5e):

The compound 5e was obtained as side product from the synthesis of 4e in form of a colorless oil (4.1 mg, 0.022 mmol, 11%).

\[ \delta = 6.69 (\text{dd}, J = 15.9, 5.0 \text{ Hz}, 1\text{H}), 6.41 (\text{dd}, J = 15.9, 1.7 \text{ Hz}, 1\text{H}), 4.70 (\text{dd}, J = 5.0, 1.7 \text{ Hz}, 1\text{H}), 2.48 (\text{d}, J = 16.9 \text{ Hz}, 1\text{H}), 2.39 (\text{d}, J = 16.9 \text{ Hz}, 1\text{H}), 2.30 (\text{s}, 3\text{H}), 1.26 (\text{s}, 3\text{H}), 1.01 (\text{s}, 3\text{H}) \text{ ppm.} \]

\[ \delta = 197.1, 175.2, 138.4, 131.2, 86.5, 44.1, 40.8, 28.6, 25.4, 22.6 \text{ ppm.} \]

HRMS (ESIpos) m/z: Calcd for C_{10}H_{14}NaO_{3} \text{+} 205.0835, Found 205.0841.

IR (cm\(^{-1}\)): 2961, 2949, 2932, 1726, 1373, 1314, 1246, 1151, 1038.

(E)-4,4-Dimethyl-5-(2-(perfluorophenyl)vinyl)dihydrofuran-2(3H)-one (5m):

Following the general procedure F and using pentafluorostyrene (97.1 mg, 0.500 mmol) the target compound 5m was obtained as a colorless oil (12.0 mg, 39.2 µmol, 20%).

\[ \delta = 6.62 (\text{dd}, J = 16.4, 1.4 \text{ Hz}, 1\text{H}), 6.49 (\text{dd}, J = 16.4, 6.1 \text{ Hz}, 1\text{H}), 4.69 (\text{dd}, J = 6.1, 1.4 \text{ Hz}, 1\text{H}), 2.49 (\text{d}, J = 16.9 \text{ Hz}, 1\text{H}), 2.42 (\text{d}, J = 16.9 \text{ Hz}, 1\text{H}), 1.26 (\text{s}, 3\text{H}), 1.07 (\text{s}, 3\text{H}) \text{ ppm.} \]

\[ \delta = 175.4, 145.0, 140.5, 137.9, 132.1, 117.4, 111.0, 88.3, 44.1, 40.7, 25.4, 22.5 \text{ ppm.} \]

\[ \delta = -141.4 \text{--} -143.4 (\text{m}), -154.8 (\text{t}, J = 20.8 \text{ Hz}), -162.4 (\text{td}, J = 21.6, 8.1 \text{ Hz}) \text{ ppm.} \]

HRMS (ESIpos) m/z: Calcd for C_{14}H_{14}F_{5}NaO_{2} \text{+} 329.0571, Found 329.0585.

IR (cm\(^{-1}\)): 2967, 2255, 1778, 1522, 1499, 993, 907, 731.
Scheme S25: Limitations encountered during scope studies.

When substrates without a quaternary center in the β-position were tested (1n,o), no formation of the respective products could be observed (Scheme S25a). The only newly formed species observed by GC-MS were oligomers formed from ethyl acrylate.

When styrene (2m) was tested as an olefin, a small quantity of 4m was observed (Scheme S25b). In contrast to the typical reaction, the lactone formation occurs through an oxidative mechanism in this case. We hypothesize that after the initial olefination a vinylic C–H activation, followed by a reductive elimination leads to the formation of this product. It should be noted that an analogous reactivity has been observed for the β-olefination of carboxylic acids.9

We hypothesized that the low reactivity of 1n and 1o could be caused by the absence of an accelerating Thorpe-Ingold-Effect. We thus synthesized substrate 1p with a quaternary center in the α-position to probe whether this compound would be reactive under our reaction conditions.

2,2-diethylbutanoic acid (1p):

In a dry argon filled flask diisopropylamine (4.65 mL, 33.0 mmol, 2.2 equiv) was dissolved in THF (20 mL) at –15 °C, followed by the dropwise addition of n-BuLi (20.7 mL, 33.0 mmol, 2.2 equiv, 1.6 M in hexane). The reaction mixture was stirred for 30 minutes and 2-ethylbutanoic acid (1.90 mL, 15.0 mmol) was added and the mixture was stirred for 15 minutes. The mixture was allowed to warm up to room temperature, DMPU (1.81 mL, 15.0 mmol, 1.0 equiv) was added dropwise and the reaction mixture was stirred at that temperature for 30 minutes followed by the dropwise addition of ethyliodide (2.89 mL, 33.0 mmol, 1.0 equiv). The reaction was stirred for 2 h at room temperature. All volatiles were removed under reduced pressure and the residue was dissolved in EtOAc (100 mL). The organic phase was extracted with aq. NaOH (1%, 200 mL) and the phases were separated. The aqueous phase was acidified with aq. HCl (10%) until the pH was below 4 and the aqueous phase was extracted with EtOAc (3x60mL). The combined organic phases were dried over MgSO4 and all volatiles were removed under reduced pressure. The crude product was purified by silica gel column chromatography.
using (pentane:EtOAc = 95:5 – 80:20). The target compound 1p was obtained as a crystalline solid (220 mg, 1.52 mmol, 5%).

$^1$H-NMR (400 MHz, CDCl$_3$): $\delta = 11.47$ (s, 1H), 1.60 (q, $J = 7.5$ Hz, 4H), 0.81 (t, $J = 7.5$ Hz, 6H) ppm.

$^{13}$C-NMR (101 MHz, CDCl$_3$): $\delta = 184.5$, 49.9, 26.1, 8.4 ppm.

HRMS (ESI neg) m/z: Calcd for C$_8$H$_{15}$O$_2$: 143.1078, Found 143.1112.

Interestingly, a different product was obtained in a substantial yield using substrate 1p. Analogously to the formation of 4m above, we hypothesize that a sequence of catalytic oxidation and C–H olefination can be responsible for this reaction. First, the oxidation of 1p would lead to an analogous vinyl carboxylic acid, which would then be converted to 3p via a vinyl C–H olefination, Michael-addition sequence.

**Ethyl 2-(4,4-diethyl-3-methylene-5-oxotetrahydrofuran-2-yl)acetate (3p):**

![3p](image)

An oven dried 10 mL Schlenk tube was charged with Pd(OAc)$_2$ (4.5 mg, 0.020 mmol, 10 mol%), Ac-ß-Ala-OH (5.3 mg, 0.040 mmol, 20 mol%), Ag$_2$CO$_3$ (138 mg, 0.500 mmol, 2.5 equiv), Na$_2$HPO$_4$·7 H$_2$O (10.7 mg, 0.04 mmol, 0.2 equiv), 2,2-diethylbutanoic acid (1p) (28.8 mg, 0.200 mmol), ethylacrylate (1.40 mmol, 7.0 equiv) and HFIP (2.25 mL). The reaction mixture was stirred 110 °C for 72 h. The mixture was allowed to cool to room temperature, filtered through a pad of Celite® using CH$_2$Cl$_2$ (30mL) to complete the elution and all volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography using (pentane:EtOAc = 80:20 – 20:80). Compound 3p was obtained as a colorless oil (24.5 mg, 0.102 mmol, 51%).

$^1$H-NMR (599 MHz, CDCl$_3$): $\delta = 5.35$ (m, 1H), 5.25 (dt, $J = 2.2$, 1.0 Hz, 1H), 5.01 (dd, $J = 2.7$, 1.0 Hz, 1H), 4.20 (m, 2H), 2.76 – 2.65 (m, 2H), 1.89 – 1.78 (m, 2H), 1.63 – 1.51 (m, 4H), 0.87 (tq, $J = 7.5$, 0.9 Hz, 3H), 0.82 (tq, $J = 7.3$, 0.9 Hz, 3H) ppm.

$^{13}$C-NMR (151 MHz, CDCl$_3$): $\delta = 179.6$, 169.8, 149.2, 108.4, 77.7, 61.3, 53.7, 40.7, 33.5, 30.7, 14.3, 9.6, 9.1 ppm.

GC-MS: R$_f$ (min) = 7.8 min, (EI) m/z (%): 240.2 (10), 211.1 (63), 169.1 (44), 153.1 (32), 139.1 (88), 124.1 (100), 109.1 (36), 95.1 (38), 81.1 (51), 55.1 (65), 41.1 (53).
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$\text{CF}_3$-COOH

$\text{NHAc}$

L20
Starting materials:
Acid Sope:
Acrylate Scope:
4j
(-)-menthol-derived
4k

(−)-isopinocampeol-derived
4I (rac)-fenchol-derived

4I (rac)-fenchol-derived
Mechanistic Studies:
