# Stereoselective Nickel-Catalyzed [2+2+2] Cycloaddition of Enynes and Arynes

*David A. Candito and Mark Lautens*

[mlautens@chem.utoronto.ca](mailto:mlautens@chem.utoronto.ca)

## Supporting Information

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Experimental</td>
<td>S2</td>
</tr>
<tr>
<td>Synthesis of <strong>1a</strong>, <strong>1b</strong>, <strong>1d</strong></td>
<td>S2</td>
</tr>
<tr>
<td>Synthesis of <strong>1c</strong></td>
<td>S3</td>
</tr>
<tr>
<td>Synthesis of <strong>1e</strong></td>
<td>S4</td>
</tr>
<tr>
<td>Synthesis of <strong>1f</strong>-<strong>1h</strong>, <strong>1j</strong></td>
<td>S5</td>
</tr>
<tr>
<td>Synthesis of <strong>1i</strong></td>
<td>S7</td>
</tr>
<tr>
<td>Synthesis of <strong>1k</strong></td>
<td>S8</td>
</tr>
<tr>
<td>Characterization Data for Cycloadducts <strong>3a</strong>-<strong>3p</strong></td>
<td>S9</td>
</tr>
<tr>
<td>Spectra</td>
<td>S16</td>
</tr>
<tr>
<td>References</td>
<td>S48</td>
</tr>
</tbody>
</table>
General Experimental:

Reactions were carried out in 2-5 mL microwave vials purchased from Biotage. Melting points were recorded using a Fisher-Johns melting point apparatus and are uncorrected. ¹H, ¹³C, and ¹⁹F NMR spectra were obtained using either Varian 300 MHz, Mercury 300 MHz, Varian Unity 400 MHz, or Bruker AvanceIII-400 400MHz spectrometers. ¹H spectra were referenced to tetramethylsilane (TMS, 0 ppm) and ¹³C spectra were referenced to solvent carbons (77.16 ppm for CDCl₃). ¹⁹F spectra were unreferenced. IR spectra were obtained using a Shimadzu FTIR-8400S spectrometer and samples were prepared by dissolving in CHCl₃ and creating a thin film or placing the neat oil on NaCl plates. High-resolution mass spectra were obtained using a VG 70-250S (double focusing) mass spectrometer at 70 eV, carried out at the University of Toronto. Acetonitrile was distilled under N₂ gas prior to use. Neutral silica (Silia-P, 40-63 μm, Silicycle, Québec, Canada) for flash chromatography was used as received. Thin layer chromatography (TLC) analysis was performed using Silicycle pre-coated TLC plates (silica gel 60 F254 on glass backing). The results of TLC analysis were visualized using a UV lamp (UV 254/365 nm) or anisaldehyde stain. All reagents, metal catalysts and ligands were purchased from Sigma-Aldrich, VWR International, or Strem Chemical Company and used as received unless otherwise noted. Reactions performed with air sensitive reagents were carried out in oven or flame dried glassware under Argon using standard syringe and septum techniques.

Starting Materials 1a, 1b, 1d:

![Chemical Structure](image)

General Procedure (Synthesis of 1d):

Sodium hydride (60% dispersion in mineral oil) was suspended in dry THF (1.2 equiv, 7.6 mmol, 0.30 g, 0.2 M based on diethyl allyl malonate) and the suspension was cooled to 0 °C (ice/water bath), then diethyl allyl malonate (1.0 equiv, 6.3 mmol, 1.2 mL) was added dropwise at 0 °C. The solution was allowed to reach room temperature and stirred for 1.5 h. Then the solution was cooled to 0 °C and the propargyl bromide (1.2 equiv, 7.6 mmol) was added dropwise at 0 °C. The solution was then allowed to reach room temperature and stirred for 12-24 h. Once the reaction was judged to be complete by TLC analysis it was quenched by addition of NH₄Cl(sat.) (15 mL), then brine (15 mL) was added and the solution extracted with ether (3 x 20 mL). The extracts were dried over MgSO₄, filtered and concentrated to provide the crude material which was purified by column chromatography on silica gel (5% EtOAc/hexanes) to afford 1.56 g (79% yield) of 1d as an light yellow oil.
Compound 1a has previously been reported. $^1$H NMR is provided.$^1$

Compound 1b has previously been reported. $^1$H NMR is provided.$^1$

Compound 1d has previously been reported. $^1$H NMR is provided.$^1$

Starting Material 1c:

\[
\begin{align*}
\text{NH}_2 & \xrightarrow{\text{TsCl (1.1 equiv), NEt}_3 (1.1 equiv), 0 \, ^\circ \text{C, DCM (0.44 M)}} \text{NHTs} \\
\text{NHTs} & \xrightarrow{1. \text{ NaH (2.2 equiv), THF (0.2 M), 0 \, ^\circ \text{C to rt)}} \text{TsN-} \\
\text{TsN-} & \xrightarrow{2. \text{ Br (1.1 equiv), Et}} \text{1c (94% yield)}
\end{align*}
\]

Step 1:

A solution of allylamine (1.0 equiv, 8.8 mmol, 0.50 g) and triethylamine (1.1 equiv, 9.7 mmol, 1.4 mL) in DCM (20 mL, 0.44 M) was cooled to 0 $^\circ$C (ice/water bath), then TsCl (1.1 equiv, 9.7 mmol, 1.8 g) was added in portions as a solid. The solution was then allowed to reach room temperature and stirred for 12 h. When the reaction was judged to be complete by TLC analysis of NaHCO$_3$(sat.) (20 mL) was added and the solution was extracted with DCM (3 x 15 mL). The extracts were dried over MgSO$_4$, filtered and concentrated to give the crude material which was purified by recrystallization (ether/pentane mixture) to provide 1.65 g of a1c (89% yield). Compound a1c has previously been reported. $^1$H NMR is provided.$^2$

Step 2:
Sodium hydride (60% dispersion in mineral oil) was suspended in dry THF (2.2 equiv, 8.8 mmol, 0.35 g, 0.2 M based on amide) and the suspension was cooled to 0 °C (ice/water bath). a1c (1.0 equiv, 4 mmol, 0.85 g) was added as a solution in THF (20 mL) dropwise at 0 °C. The solution was allowed to reach room temperature and stirred for 1.5 h. Then the solution was cooled to 0 °C and the propargyl bromide (1.1 equiv, 4.4 mmol, 0.44 mL) was added dropwise at 0 °C. The solution was then allowed to reach room temperature and stirred for 12 h. TLC analysis indicated that starting material remained so additional propargyl bromide was added at room temperature (1.1 equiv, 4.4 mmol, 0.44 mL) and the solution stirred for 4 h. Once the reaction was judged to be complete by TLC analysis it was quenched by addition of NH₄Cl(sat.) (20 mL). Brine (20 mL) was added and the solution extracted with ether (3 x 20 mL). The extracts were dried over MgSO₄, filtered and concentrated to provide the crude material which was purified by column chromatography on silica gel (gradient elution: 5% EtOAc/hexanes then 10% EtOAc/hexanes) to afford 0.99 g (94% yield) of 1c as a colorless oil. Compound 1c has previously been reported. ¹H NMR is provided

Starting Material 1c:

![Diagram of the reaction process](image)

**Step 1:**
Sodium hydride (60% dispersion in mineral oil) was suspended in dry THF (1.0 equiv, 8.0 mmol, 0.32 g, 0.2 M based on diethyl allyl malonate) then diethyl allyl malonate (1.0 equiv, 8.0 mmol, 1.2 mL) was added dropwise at room temperature. The solution was stirred for 1 h, then trans-crotyl bromide was added (1.2 equiv, 9.6 mmol, 1.0 mL). The solution was stirred for 6 h, then additional sodium hydride (0.032 g) and crotyl bromide (0.5 mL) were added. Once the reaction was judged to be complete by TLC analysis it was quenched by addition of NH₄Cl(sat.) (20 mL). Brine (20 mL) was added and the solution extracted with ether (3 x 20 mL). The extracts were dried over MgSO₄, filtered and concentrated to provide the crude material which was purified by column chromatography on silica gel (5% EtOAc/hexanes) to afford 1.1 g (64% yield) of a1e. ¹H NMR (300 MHz, cdc13) δ 5.64 – 5.46 (m, 1H), 5.46 – 5.27 (m, 1H), 4.19 (q, J = 7.1 Hz, 4H), 3.36 (t, J = 7.6 Hz, 1H), 2.57 (ddd, J = 7.7, 2.1, 1.1 Hz, 2H), 1.64 (dd, J = 6.3, 1.2 Hz, 3H), 1.26 (t, J = 7.1 Hz, 6H).

**Step 2:**
Sodium hydride (60% dispersion in mineral oil) was suspended in dry THF (1.2 equiv, 6.16 mmol, 0.25 g, 0.2 M based on a1e) then a1e (1.0 equiv, 5.13 mmol, 1.1 g) was added dropwise at room temperature. The solution was stirred for 1 h at room temperature, then the propargyl bromide was added (1.2 equiv, 6.16 mmol, 0.63 mL) and the solution was stirred for 24 h. Once the reaction was judged to be complete by TLC analysis it was quenched by addition of NH₄Cl(sat.) (20 mL). Brine (20 mL) was added and the solution extracted with ether (3 x 20 mL). The extracts were dried over MgSO₄, filtered and concentrated to provide the crude material.
which was purified by column chromatography on silica gel (5% EtOAc/hexanes) to afford 1.2 g (90% yield) of 1e as an oil. An inseparable impurity co-eluted with 1e obscuring $^{13}$C NMR data, thus only $^1$H NMR data and HRMS data is provided. $^1$H NMR (399 MHz, cdcl$_3$) $\delta$ 5.68 – 5.52 (m, 1H), 5.32 – 5.16 (m, 1H), 4.19 (q, $J$ = 7.1 Hz, 4H), 2.75 – 2.68 (m, 4H), 2.12 (qt, $J$ = 7.5, 2.3 Hz, 2H), 1.65 (d, $J$ = 6.4 Hz, 3H), 1.24 (t, $J$ = 7.1 Hz, 6H), 1.09 (t, $J$ = 7.5 Hz, 3H). HRMS-ESI (m/z): [(M + H$^+$)] calcd. for C$_{16}$H$_{25}$O$_4$: 281.17528 found 281.17597.

**Starting Materials 1f to 1h, 1j:**

![Chemical Structure](image)

**General Procedure (Synthesis of 1g):**

**Step 1**

An oven dried 250 mL round bottomed flask with stir bar was cooled under a stream of argon by venting through a needle in the septum. Then the flask was charge with isobutyraldehyde (1 equiv, 20 mmol, 1.8 mL) and THF (100 mL), the resulting solution was cooled to 0 °C (ice/water bath). Then vinyl magnesium bromide (1.1 equiv, 22 mmol, 22 mL, 1.0 M in THF) was added dropwise at 0 °C. The solution was allowed to reach room temperature and stirred until the reaction was complete (as judged by TLC analysis). The reaction was then cooled to 0 °C and quenched by the dropwise addition of NH$_4$Cl$_{(sat).}$ The mixture was extracted with ether (3 x 20 mL) and the extracts were washed with brine (2 x 40 mL) and dried over sodium sulphate, filtered and concentrated to provide the crude material which was purified by column chromatography on silica gel (20% ether/pentane). Due to the volatile nature of the allylic alcohol it was isolated as a solution in ether (0.79 g, 2:1 ether:alcohol, 22% yield of alcohol) after careful evaporation of the solvent. This solution was used for the next step.

**Step 2**

An oven dried 100 mL round bottomed flask with stir bar was cooled under a stream of argon by venting through a needle in the septum. Then the flask was charge with NaH (60 % in mineral oil, 1.1 equiv, 4.84 mmol, 0.19 g) and then THF was added (20 mL). The alcohol was added dropwise at room temperature (1.0 equiv, 4.4 mmol) and the solution was stirred for 1 hour at room temperature. The propargyl bromide was then added at room temperature (1.1 equiv, 4.84 mmol, 0.48 mL) and the solution stirred until the reaction was judged to be complete (TLC analysis). Once complete the reaction was quenched by the dropwise addition of NH$_4$Cl$_{(sat).}$ The mixture was extracted with ether (3 x 10 mL) and the extracts were washed with brine (2 x 20 mL) and dried over sodium sulphate, filtered and concentrated to provide the crude material which was purified by column chromatography on silica gel (gradient elution: 10% DCM/hexanes then 20% DCM/hexanes) to afford 0.45 g (62% yield) of 1g as an oil.
1H NMR (399 MHz, cdcl$_3$) δ 7.30 – 7.24 (m, 2H), 6.91 – 6.86 (m, 2H), 5.96 (dd, $J = 17.1, 10.3$, 6.6 Hz, 1H), 5.27 (dt, $J = 17.2, 1.4$ Hz, 1H), 5.23 – 5.19 (m, 1H), 4.95 (d, $J = 6.6$ Hz, 1H), 4.08 (qt, $J = 15.2, 2.2$ Hz, 2H), 3.80 (s, 3H), 2.24 (qt, $J = 7.5, 2.2$ Hz, 2H), 1.15 (t, $J = 7.5$ Hz, 3H).

$^{13}$C NMR (100 MHz, cdcl$_3$) δ 159.4, 138.5, 132.5, 128.6, 116.7, 114.0, 88.4, 80.7, 75.5, 55.9, 55.4, 14.0, 12.7. IR (neat) 3074, 2977, 2938, 2913, 2882, 2842, 2285, 2231, 1721, 1679, 1641, 1609, 1511, 1461, 1422, 1380, 1358, 1302, 1247, 1204, 1176, 1139, 1106, 1061, 1039, 991, 927, 829, 782, 665, 639, 598, 409. HRMS-EI (m/z): [M+] calcd. for C$_{15}$H$_{18}$O$_2$: 230.1307 found 230.1308.

Note: the allylic alcohol precursor for 1h is commercially available. 

1H NMR (399 MHz, cdcl$_3$) δ 5.64 (ddd, $J = 17.2, 10.4, 8.1$ Hz, 1H), 5.25 (ddd, $J = 10.4, 2.0, 0.6$ Hz, 1H), 5.19 (ddd, $J = 17.2, 2.0, 0.8$ Hz, 1H), 4.16 (dt, $J = 15.2, 2.2$ Hz, 1H), 3.96 (dt, $J = 15.2, 2.2$ Hz, 1H), 3.52 (dd, $J = 7.7, 7.0$ Hz, 1H), 2.23 (qt, $J = 7.5, 2.2$ Hz, 2H), 1.83 – 1.71 (m, 1H), 1.14 (t, $J = 7.5$ Hz, 3H), 0.95 (d, $J = 6.7$ Hz, 3H), 0.87 (d, $J = 6.8$ Hz, 3H). 

$^{13}$C NMR (100 MHz, cdcl$_3$) δ 136.7, 118.7, 87.6, 85.4, 76.0, 56.2, 32.4, 18.9, 18.4, 14.0, 12.6. IR (neat) 3078, 2975, 2963, 2938, 2877, 2857, 2242, 1717, 1642, 1465, 1425, 1383, 1365, 1346, 1320, 1137, 1071, 1015, 996, 971, 929, 680, 413. HRMS-EI (m/z): [(M-Me)+] calcd. for C$_{10}$H$_{15}$O: 151.1123 found 151.1122.
1642, 1459, 1423, 1405, 1378, 1343, 1319, 1265, 1152, 1136, 1101, 1073, 1057, 993, 971, 955, 926, 723, 685, 424, 413, 402. HRMS-EI (m/z): [(M-H)+] calcd. for C_{15}H_{25}O: 221.1905 found 221.1902.

\[ \text{1f} \]

Starting Material 1i:

Step 1
The aldehyde (1 equiv, 40 mmol, 4.8 mL), sulfonamide (1.1 equiv, 44 mmol, 7.5 g) and powdered molecular sieves (2.5 g) were charged into a 75 mL thick walled tube with stir bar and screw cap, then toluene was added (20 mL) and then amberlyst-15 was added (0.40 g). The tube was sealed and the mixture heated to 120 °C for 24 hours. The reaction mixture was then cooled and diluted with DCM (20 mL) and filtered through celite with DCM washings (100 mL), the solvent was removed and ether was added, the solid was collected by filtration and washed with ether to provide 6.49 g (56% yield) of the a1i. \(^1\)H NMR (300 MHz, cdcl\(_3\)) s 8.94 (s, 1H), 7.94 –
7.84 (m, 4H), 7.33 (d, \( J = 8.0 \) Hz, 2H), 7.01 – 6.93 (m, 2H), 3.88 (s, \( J = 3.7 \) Hz, 3H), 2.43 (s, 3H).

**Step 2**
An oven dried 250 mL round bottom flask with stir bar was cooled under a stream of argon by venting through a needle in the septum. Then the flask was charge with \( \text{a1i} \) (1 equiv, 10 mmol, 2.89 g) and THF (50 mL), the resulting solution was cooled to 0 °C (ice/water bath). Then vinyl magnesium bromide (1.1 equiv, 11 mmol, 11 mL, 1.0 M in THF) was added dropwise at 0 °C. The solution was allowed to reach room temperature and stirred until the reaction was complete (as judged by TLC analysis). The reaction was then cooled to 0 °C and quenched by the dropwise addition of \( \text{NH}_4\text{Cl} \) (sat.). The mixture was extracted with ether (3 x 20 mL) and the extracts were washed with brine (2 x 40 mL) and dried over magnesium sulphate, the solids were filtered off and the solution concentrated. A few drops of EtOAc were added to the crude solid and then the solid was triturated with pentane providing 2.85 g (90 %) of \( \text{b1i} \). \( ^1\text{H} \) NMR (399 MHz, cdcl\(_3\)) \( \delta \) 7.67 – 7.60 (m, 2H), 7.21 (d, \( J = 8.0 \) Hz, 2H), 7.04 – 6.98 (m, 2H), 6.78 – 6.72 (m, 2H), 5.92 – 5.80 (m, 1H), 5.17 – 5.13 (m, 1H), 5.12 – 5.08 (m, 1H), 4.92 – 4.86 (m, 1H), 4.74 (s, 1H), 4.68 (d, \( J = 6.5 \) Hz, 1H), 3.76 (s, 3H), 2.40 (s, 3H).

**Step 3**
A 25 mL round bottomed flask with stir bar and reflux condenser was charge with \( \text{b1i} \) (1.0 equiv, 3.15 mmol, 1.0 g), TBAI (0.20 equiv, 0.63 mmol, 0.23 g) and \( \text{K}_2\text{CO}_3 \) (1.5 equiv, 4.73 mmol, 0.65 g). MeCN was added (6 mL), then the propargyl bromide (1.1 equiv, 3.5 mmol, 0.36 mL) and the mixture heated to 70 °C for 13 hours. After this time more \( \text{K}_2\text{CO}_3 \) (1.5 equiv, 4.73 mmol, 0.65 g) and propargyl bromide (1.1 equiv, 3.5 mmol, 0.36 mL) were added and the reaction was heated for 24 hours. Distilled water was added to dissolve the salts (10 mL) and the mixture was extracted with ether (3 x 10 mL) and the extracts were washed with brine (2 x 10 mL) and dried over magnesium sulphate, filtered and concentrated to provide the crude material which was purified by column chromatography on silica gel (10% EtOAc/hexanes) to afford 0.74 g (61% yield) of \( \text{1i} \) as a yellow oil. \( ^1\text{H} \) NMR (200 MHz, cdcl\(_3\)) \( \delta \) 7.80 (d, \( J = 8.3 \) Hz, 2H), 7.31 – 7.17 (m, 4H), 6.87 – 6.77 (m, 1H), 6.20 (ddd, \( J = 17.6, 10.4, 7.4 \) Hz, 1H), 5.56 (d, \( J = 7.1 \) Hz, 1H), 5.27 – 5.08 (m, 2H), 4.11 (dt, \( J = 4.1, 2.1 \) Hz, 1H), 4.03 (t, \( J = 2.2 \) Hz, 1H), 3.79 (s, \( J = 3.5 \) Hz, 3H), 2.42 (s, 3H), 2.07 – 1.86 (m, 2H), 0.92 (t, \( J = 7.5 \) Hz, 3H). \( ^{13}\text{C} \) NMR (100 MHz, cdcl\(_3\)) \( \delta \) 159.4, 143.1, 138.1, 134.8, 130.3, 129.7, 129.1, 128.1, 118.6, 113.90, 86.3, 75.1, 63.3, 55.4, 34.4, 21.7, 13.5, 12.4. IR(film) 3066, 3031, 2976, 2936, 2920, 2879, 2838, 1610, 1584, 1511, 1459, 1443, 1428, 1404, 1348, 1335, 1305, 1288, 1250, 1178, 1160, 1108, 1093, 1034, 994, 930, 899, 854, 835, 814, 774, 708, 667, 646, 577, 543, 428, 409. HRMS-EI (m/z): [M+] calcd. for C\(_{22}\)H\(_{25}\)NO\(_3\)S: 383.1555 found 383.1544. m.p. 57-58 °C.

**Starting Material 1k:**

![Step 1](image)

**Step 1**
An oven dried 250 mL round bottomed flask with stir bar was cooled under a stream of argon by venting through a needle in the septum. Then the flask was charged with 1-hexyne (1 equiv, 17.8 mmol, 2.0 mL) and THF (50 mL), the resulting solution was cooled to -78 °C (dry ice/acetone bath). Then n-BuLi (1.05 equiv, 18.7 mmol, 16.0 mL, 1.17 M in Hexanes) was added dropwise at -78 °C and the solution was stirred for 5 minutes at this temperature. The solution was allowed to reach room temperature and then recooled to -78 °C and a solution of the aldehyde (1.1 equiv, 19.6 mmol, 2.4 mL) in THF (30 mL) was added dropwise. After the addition the reaction was allowed to reach room temperature and quenched by the dropwise addition of NH₄Cl (sat.). The mixture was extracted with ether (3 x 20 mL) and the extracts were washed with brine (2 x 40 mL) and dried over magnesium sulphate, the solids were filtered off and the solution concentrated to provide the crude material which was purified by column chromatography on silica gel (gradient elution: 10% EtOAc/hexanes then 20% EtOAc/ hexanes) to afford 2.87 g of alk along with an inseparable impurity.

**Step 2**

An oven dried 100 mL round bottomed flask with stir bar was cooled under a stream of argon by venting through a needle in the septum. Then the flask was charged with NaH (60 % in mineral oil, 0.25 g) and then THF was added (25 mL). The alcohol was added dropwise at room temperature (1.0 g) and the solution was stirred for 1 hour at room temperature. Allyl bromide was then added at room temperature (1.9 mL) and the solution stirred until the reaction was judged to be complete (TLC analysis). Once complete the reaction was quenched by the dropwise addition of NH₄Cl (sat.). The mixture was extracted with ether (3 x 10 mL) and the extracts were washed with brine (2 x 20 mL) and dried over sodium sulphate, filtered and concentrated to provide the crude material which was purified by column chromatography on silica gel (10% DCM/hexanes) to afford 0.46 g of lk as an oil. ¹H NMR (399 MHz, cdcl₃) δ 5.91 (dddd, J = 16.8, 10.4, 6.2, 5.0 Hz, 1H), 5.29 (ddd, J = 17.2, 3.4, 1.7 Hz, 1H), 5.16 (ddd, J = 10.4, 3.0, 1.4 Hz, 1H), 4.24 (ddt, J = 12.7, 5.0, 1.5 Hz, 1H), 3.93 (ddt, J = 12.7, 6.3, 1.3 Hz, 1H), 3.83 (dt, J = 6.1, 2.0 Hz, 1H), 2.23 (td, J = 7.0, 2.0 Hz, 2H), 1.90 – 1.80 (m, 2H), 1.79 – 1.70 (m, 2H), 1.69 – 1.36 (m, 6H), 1.32 – 1.01 (m, 5H), 0.92 (t, J = 7.2 Hz, 3H). ¹³C NMR (75 MHz, cdcl₃) δ 135.0, 117.0, 87.1, 78.1, 74.1, 69.6, 43.0, 31.0, 29.3, 28.6, 26.7, 26.2, 26.1, 22.1, 18.6, 13.7. IR(film) 2930, 2856, 1727, 1669, 1451, 1329, 1248, 1165, 1134, 1098, 1056, 1028, 1002, 410. HRMS-ESI (m/z): [(M+H)+] calcd. for C₁₆H₂₅O: 233.19054 found 233.18981.

**Cycloadducts 3a to 3p:**

**General Procedure:**

Note: See manuscript for specific amounts and temperatures. In the glovebox an oven dried microwave vial with stir bar was charged with Ni(cod)₂ and anhydrous CsF, the vial was capped with a septum and removed from the glovebox. Then the sily triflate and enyne were weighed out into an oven dried vial and transferred as a solution in MeCN using a syringe. The resulting mixture was then stirred at the indicated temperature for 24 h. Once the reaction was complete the sample was diluted with DCM and small amount of silica gel was added. The sample was absorbed onto the silica by rotary evaporation and the sample was then subjected to column chromatography.
Following the general procedure 25 mg (73% yield) of compound 3a was obtained as a colorless oil after chromatography (5% ether/pentane). $^1$H NMR (399 MHz, cdcl$_3$) $\delta$ 7.28 – 7.21 (m, 1H), 7.14 – 7.04 (m, 2H), 4.22 (q, $J$ = 7.1 Hz, 2H), 4.17 (q, $J$ = 7.1 Hz, 2H), 3.25 (d, $J$ = 18.2 Hz, 1H), 3.04 (dd, $J$ = 18.2, 2.4 Hz, 1H), 2.85 (dd, $J$ = 14.2, 5.5 Hz, 1H), 2.78 – 2.66 (m, $J$ = 15.2, 6.3 Hz, 2H), 2.58 – 2.37 (m, 3H), 2.01 – 1.89 (m, 1H), 1.28 (t, $J$ = 7.1 Hz, 3H), 1.24 (t, $J$ = 7.2 Hz, 3H), 1.09 (t, $J$ = 7.5 Hz, 3H). $^{13}$C NMR (100 MHz, cdcl$_3$) $\delta$ 172.0, 171.8, 139.3, 135.9, 135.7, 130.6, 127.8, 126.6, 126.0, 122.5, 61.7, 61.7, 59.6, 41.1, 38.6, 37.3, 35.3, 22.3, 14.2, 14.2, 13.2. IR(film) 2968, 2934, 1731, 1456, 1253. HRMS-EI (m/z): [M+] calcd. for C$_{21}$H$_{26}$O$_4$: 342.1831 found 342.1836.

Following the general procedure 19.2 mg (50% yield) of compound 3b was obtained as a colorless oil after chromatography (10% EtOAc/hexanes). $^1$H NMR (399 MHz, cdcl$_3$) $\delta$ 7.25 (d, $J$ = 8.6 Hz, 1H), 7.17 – 7.08 (m, 2H), 7.05 (td, $J$ = 7.4, 1.1 Hz, 1H), 4.22 (qd, $J$ = 7.1, 0.8 Hz, 2H), 4.16 (qd, $J$ = 7.1, 1.2 Hz, 2H), 3.29 (d, $J$ = 18.0 Hz, 1H), 3.14 (dd, $J$ = 18.1, 3.1 Hz, 1H), 2.78 (dd, $J$ = 13.3, 4.7 Hz, 1H), 2.70 (dd, $J$ = 12.4, 7.0, 1.8 Hz, 1H), 2.58 – 2.45 (m, 1H), 2.45 – 2.36 (m, 1H), 1.94 – 1.84 (m, 1H), 1.27 (t, $J$ = 7.1 Hz, 3H), 1.23 (t, $J$ = 7.1 Hz, 3H), 0.35 – 0.29 (m, 9H). $^{13}$C NMR (100 MHz, cdcl$_3$) $\delta$ 171.9, 171.6, 157.0, 138.8, 135.5, 128.9, 127.7, 126.7, 126.1, 125.6, 61.8, 61.7, 59.7, 40.7, 40.6, 39.6, 35.1, 14.2, 14.2, 1.9. IR(film) 2980, 2957, 2936, 1732, 1596, 1476, 1449, 1368, 1295, 1273, 1253, 1190, 1179, 1067, 855, 839, 769. HRMS-EI (m/z): [M+] calcd. for C$_{22}$H$_{30}$O$_4$Si: 386.1913 found 386.1920.

Following the general procedure 31.6 mg (89% yield) of compound 3c was obtained as an off-white solid after chromatography (10% EtOAc/hexanes). $^1$H NMR (300 MHz, cdcl$_3$) $\delta$ 7.76 (d, $J$ = 8.3 Hz, 2H), 7.35 (d, $J$ = 8.1 Hz, 2H), 7.24 – 7.15 (m, 2H), 7.14 – 7.06 (m, 2H), 4.23 (d, $J$ =
15.2 Hz, 1H), 4.00 – 3.83 (m, 2H), 2.93 (ddd, J = 20.9, 10.8, 4.0 Hz, 1H), 2.84 – 2.70 (m, 2H), 2.51 – 2.20 (m, 6H), 1.05 (t, J = 7.6 Hz, 3H). $^{13}$C NMR (75 MHz, cdcl$_3$) δ 143.9, 134.8, 134.7, 134.6, 133.2, 129.9, 128.1, 127.9, 127.0, 126.8, 122.9, 54.9, 50.0, 38.6, 32.9, 22.5, 21.7, 13.2. IR(film) 3061, 3024, 2967, 2932, 2874, 1598, 1458, 1345, 1224, 1161, 1124, 1096, 1030, 818, 763, 701, 663, 621, 591, 541. HRMS-EI (m/z): [(M-Et)+] calcd. for C$_{19}$H$_{18}$NO$_2$S: 324.1058 found 324.1071. m.p. 124 – 125 °C.

Following the general procedure 15.4 mg (38% yield) of compound 3f was obtained as an yellow solid after chromatography (20% EtOAc/hexanes). $^1$H NMR (399 MHz, cdcl$_3$) δ 7.80 – 7.74 (m, J = 10.0, 7.2, 2.8 Hz, 3H), 7.69 (dd, J = 6.0, 3.5 Hz, 1H), 7.61 (s, 1H), 7.51 (s, 1H), 7.41 (t, J = 3.4 Hz, 1H), 7.38 (t, J = 3.5 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H), 4.28 (d, J = 15.3 Hz, 1H), 3.99 (dd, J = 9.1, 7.5 Hz, 1H), 3.93 (dd, J = 15.2, 2.3 Hz, 1H), 3.04 – 2.90 (m, 2H), 2.86 – 2.76 (m, 1H), 2.62 – 2.49 (m, 2H), 2.43 (s, 3H), 2.39 (d, J = 7.5 Hz, 1H), 1.14 (t, J = 7.6 Hz, 3H). $^{13}$C NMR (100 MHz, cdcl$_3$) δ 143.9, 136.2, 133.4, 133.2, 133.0, 132.7, 132.5, 131.1, 129.9, 128.0, 127.9, 127.1, 126.2, 126.1, 125.8, 121.4, 54.9), 50.3, 38.7, 33.5, 22.7, 21.7, 13.3. IR(film) 2966, 2931, 2875, 1597, 1454, 1343, 1160, 1095, 1040, 883, 817, 753. HRMS-EI (m/z): [M+] calcd. for C$_{25}$H$_{25}$NO$_3$S: 403.1606 found 403.1608. m.p. 150 – 153 °C.

Following the general procedure 3g was obtained as an inseparable mixture of regioisomers (1.5:1, determined by 1H NMR of the crude reaction mixture). Chromatography (10% EtOAc/Hexanes) yielded 15.0 mg (39% yield, combined yield) of a white solid. Note: $^1$H NMR is reported as observed, characteristic peaks indicated where possible. $^1$H NMR (399 MHz, cdcl$_3$) δ 7.79 – 7.72 (m, 3.09H), 7.34 (dd, J = 7.9, 0.6 Hz, 3.20H), 7.16 (t, J = 8.0 Hz, 0.94H), 7.10 – 7.03 (m, 1.31H), 6.88 (d, J = 7.6 Hz, 0.86H), 6.80 – 6.70 (m, 2.64H), 4.22 (dd, J = 15.1, 8.1 Hz, 1.88H), 3.92 (tt, J = 8.8, 6.2 Hz, 3.64H), 3.80 (s, J = 2.6 Hz, 1.65H, minor OMe), 3.79 (s, J = 4.3 Hz, 2.44H, major OMe), 3.28 (dd, J = 15.6, 6.2 Hz, 0.97H), 2.85 – 2.64 (m, 6.07H), 2.44 (s, 2.51H, major Me), 2.43 (s, 1.91H, minor Me), 2.41 – 2.22 (m, 3.94H), 1.95 (dd, J = 18.6, 11.5 Hz, 1.15H), 1.04 (t, J = 7.6 Hz, 2.17H, minor Me), 0.96 (t, J = 7.4 Hz, 3.0H, major Me). HRMS-EI (m/z): [M+] calcd. for C$_{22}$H$_{25}$NO$_3$S: 383.1555 found 383.1550.
Following the general procedure 14.1 mg (36% yield) of compound 3h was obtained as a bage solid after chromatography (10% EtOAc/hexanes). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.75 (d, $J$ = 8.3 Hz, 2H), 7.35 (d, $J$ = 8.1 Hz, 2H), 6.99 (dd, $J$ = 11.8, 7.9 Hz, 1H), 6.90 (dd, $J$ = 9.8, 8.4 Hz, 1H), 4.22 (d, $J$ = 15.3 Hz, 1H), 3.94 (dd, $J$ = 9.1, 7.8 Hz, 1H), 3.85 (dd, $J$ = 15.2, 2.5 Hz, 1H), 3.00 – 2.82 (m, 1H), 2.76 (d, $J$ = 9.3 Hz, 1H), 2.72 (dd, $J$ = 9.5, 5.3 Hz, 1H), 2.44 (s, 3H), 2.42 – 2.29 (m, 2H), 2.24 (dd, $J$ = 14.4, 7.3 Hz, 1H), 1.03 (t, $J$ = 7.6 Hz, 3H). $^{13}$C NMR (101 MHz, cdcl$_3$) $\delta$ 149.2 (dd, $J$ = 236.7, 4.5 Hz), 148.5 (dd, $J$ = 251.3, 16.3 Hz), 143.97 (s), 135.5 (d, $J$ = 2.5 Hz), 133.1 (s), 131.5 (dd, $J$ = 5.5, 3.8 Hz), 131.2 (dd, $J$ = 5.6, 3.7 Hz), 130.0 (s), 129.5 (t, $J$ = 1.6 Hz), 127.9 (s), 116.9 (d, $J$ = 17.5 Hz), 112.1 (d, $J$ = 18.3 Hz), 54.7 (s), 50.0 (s), 38.5, 32.1 (s), 22.7 (s), 21.7 (s), 13.0 (s). $^{19}$F NMR (376 MHz, cdcl$_3$) $\delta$ -140.87 – -141.19 (m), -141.17 – -141.53 (m). IR(film) 2969, 2934, 2877, 2862, 1503, 1463, 1425, 1344, 1317, 1275, 1231, 1163, 1129, 1096, 1059, 1042, 1029, 911, 880, 819, 801, 733, 664, 590, 543, 415. HRMS-EI (m/z): [M+] calcd. for C$_{21}$H$_{21}$NO$_2$SF$_2$: 389.1261 found 389.1256. m.p. 140 – 141 °C

Following the general procedure 25.2 mg (63% yield) of compound 3i was obtained as a bage solid after chromatography (gradient elution: 10% EtOAc/hexanes then 20% EtOAc/hexanes). $^1$H NMR (399 MHz, cdcl$_3$) $\delta$ 7.75 (d, $J$ = 8.3 Hz, 2H), 7.34 (d, $J$ = 8.2 Hz, 2H), 6.74 (s, 1H), 6.61 (s, 1H), 5.91 (s, 2H), 4.20 (d, $J$ = 15.0 Hz, 1H), 3.92 (dd, $J$ = 9.0, 7.7 Hz, 1H), 3.86 (dd, $J$ = 15.0, 2.7 Hz, 1H), 2.96 – 2.82 (m, 1H), 2.79 – 2.71 (m, 1H), 2.66 (dd, $J$ = 14.6, 6.2 Hz, 1H), 2.44 (s, 3H), 2.40 – 2.17 (m, 3H), 1.03 (t, $J$ = 7.6 Hz, 3H). $^{13}$C NMR (100 MHz, cdcl$_3$) $\delta$ 146.7, 145.9, 143.8, 133.2, 133.0, 130.5, 129.9, 128.8, 128.6, 127.9, 109.0, 104.1, 101.1, 54.8, 50.0, 38.7, 33.1, 22.9, 21.7, 13.2 IR(film) 2967, 2930, 1727, 1598, 1502, 1481, 1466, 1345, 1235, 1218, 1184, 1161, 1096, 1039, 940, 879, 815, 756, 668, 590, 573, 546. HRMS-EI (m/z): [M+] calcd. for C$_{22}$H$_{23}$NO$_4$S: 397.1348 found 397.1339. m.p. 172 – 175 °C
Following the general procedure 17.9 mg (58% yield) of compound 3k was obtained as an oil after chromatography (gradient elution: 5% EtOAc/hexanes then 10% EtOAc/hexanes). $^1$H NMR (399 MHz, CDCl$_3$) δ 7.38 – 7.32 (m, 2H), 7.27 (d, $J$ = 7.7 Hz, 1H), 7.12 – 7.06 (m, 2H), 6.94 – 6.89 (m, 2H), 4.86 (d, $J$ = 14.4 Hz, 1H), 4.68 (dd, $J$ = 14.3, 2.6 Hz, 1H), 4.54 (d, $J$ = 9.2 Hz, 1H), 3.82 (s, $J$ = 5.0 Hz, 3H), 2.85 – 2.61 (m, 2H), 2.50 (td, $J$ = 15.3, 7.7 Hz, 1H), 2.34 (td, $J$ = 14.8, 7.5 Hz, 1H), 1.14 (t, $J$ = 7.6 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 159.7, 139.7, 135.6, 135.2, 132.5, 128.7, 128.3, 127.9, 126.9, 126.6, 122.7, 114.2, 88.3, 69.1, 55.5, 47.8, 31.6, 22.5, 13.5. IR(film) 3064, 2965, 2933, 2873, 2836, 1730, 1612, 1513, 1370, 1302, 1249, 1176, 1032, 831, 597, 407. HRMS-EI (m/z): [M+] calcd. for C$_{21}$H$_{22}$O$_2$: 306.1620 found 306.1625.

Following the general procedure 14.8 mg (61% yield) of compound 3l was obtained as a colorless oil after chromatography (2.5% Et$_2$O/hexanes). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.30 – 7.06 (m, 4H), 4.63 (d, $J$ = 14.3 Hz, 1H), 4.52 (d, $J$ = 14.3 Hz, 1H), 3.46 (dd, $J$ = 8.4, 5.8 Hz, 1H), 2.83 (d, $J$ = 8.1 Hz, 1H), 2.70 – 2.54 (m, 2H), 2.46 (td, $J$ = 14.9, 7.6 Hz, 1H), 2.29 (dq, $J$ = 14.6, 7.5 Hz, 1H), 1.91 (dq, $J$ = 13.4, 6.7 Hz, 1H), 1.09 (t, $J$ = 7.6 Hz, 3H), 1.04 (d, $J$ = 6.8 Hz, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 140.6, 135.6, 135.5, 128.2, 128.1, 126.8, 126.4, 122.5, 91.5, 68.4, 42.4, 33.6, 32.2, 22.4, 19.0, 13.4. IR(film) 3065, 3017, 2965, 2933, 2875, 1726, 1466, 1455, 1389, 1370, 1302, 1216, 1175, 1127, 1097, 1064, 1043, 986, 972, 950, 914, 757. HRMS-EI (m/z): [M+] calcd. for C$_{17}$H$_{22}$O: 242.1671 found 242.1675.

Following the general procedure 10.3 mg (35% yield) of compound 3m was obtained as a colorless oil after chromatography (2.5% Et$_2$O/hexanes). $^1$H NMR (399 MHz, CDCl$_3$) δ 7.25 (d, $J$ = 6.6 Hz, 1H), 7.23 – 7.17 (m, 1H), 7.12 (dd, $J$ = 9.5, 8.6, 3.8 Hz, 2H), 4.65 (d, $J$ = 14.4 Hz,
1H), 4.51 (dd, J = 14.4, 2.0 Hz, 1H), 3.66 – 3.58 (m, 1H), 2.78 (dd, J = 12.8, 4.6 Hz, 1H), 2.62 – 2.40 (m, 3H), 2.29 (td, J = 14.9, 7.5 Hz, 1H), 1.79 – 1.17 (m, 12H), 1.09 (t, J = 7.5 Hz, 3H), 0.89 (t, J = 6.9 Hz, 3H). \(^{13}\)C NMR (75 MHz, cdc\(_3\)) \(\delta\) 140.4, 135.7, 135.3, 128.2, 126.8, 126.4, 122.6, 86.7, 68.6, 45.1, 34.5, 32.2, 32.0, 30.0, 29.4, 26.3, 22.8, 22.4, 14.3, 13.3 (Note: 1 peak unresolved in 120 – 141 ppm range). IR(film) 2927, 2859, 1725, 1595, 1456, 1172, 1037, 757. HRMS-EI (m/z): [M+] calcd. for C\(_{21}\)H\(_{30}\)O: 298.2297 found 298.2296.

Following the general procedure 17.2 mg (37% yield) of compound 3n was obtained as a yellow oil after chromatography (gradient elution: 5% EtOAc/hexanes then 10% EtOAc/hexanes). \(^{1}\)H NMR (399 MHz, cdc\(_3\)) \(\delta\) 7.54 (d, J = 6.8 Hz, 2H), 7.25 – 7.14 (m, J = 14.9, 7.1 Hz, 6H), 7.05 (t, J = 7.3 Hz, 1H), 6.97 (d, J = 7.3 Hz, 1H), 6.81 (d, J = 7.1 Hz, 2H), 4.49 (d, J = 15.5 Hz, 1H), 4.34 (d, J = 15.3 Hz, 1H), 3.96 (d, J = 9.3 Hz, 1H), 3.80 (s, 3H), 3.01 – 2.88 (m, 1H), 2.57 (dd, J = 14.5, 6.4 Hz, 1H), 2.52 – 2.30 (m, 6H), 1.09 (t, J = 7.0 Hz, 3H). \(^{13}\)C NMR (100 MHz, cdc\(_3\)) \(\delta\) 159.4, 143.5, 134.7, 134.5, 134.3, 132.6, 131.8, 130.3, 129.5, 128.7, 128.1, 128.1, 127.0, 126.7, 122.8, 71.7, 55.4, 51.8, 49.9, 32.0, 22.2, 21.7, 13.3. IR(film) 2963, 2923, 2853, 1611, 1512, 1452, 1350, 1160, 1093, 1034. HRMS-EI (m/z): [M+] calcd. for C\(_{28}\)H\(_{29}\)NO\(_3\)S: 459.1868 found 459.1873.

Following the general procedure 10.3 mg (52% yield) of compound 3o was obtained after chromatography (2.5% EtOAc/hexanes then preparative TLC: toluene as eluent). \(^{1}\)H NMR (399 MHz, cdc\(_3\)) \(\delta\) 8.75 – 8.63 (m, 2H), 8.18 – 8.11 (m, 1H), 8.08 – 8.02 (m, 1H), 7.67 – 7.59 (m, 2H), 7.59 – 7.51 (m, 2H), 7.45 – 7.37 (m, 2H), 7.04 – 6.94 (m, 2H), 5.79 (ddt, J = 17.1, 10.2, 7.0 Hz, 1H), 5.04 (ddd, J = 17.2, 3.4, 1.5 Hz, 1H), 5.01 – 4.97 (m, 1H), 4.88 (d, J = 10.7 Hz, 1H), 4.79 (d, J = 10.7 Hz, 1H), 4.46 (dd, J = 7.7, 6.0 Hz, 1H), 3.87 (s, 3H), 3.12 (q, J = 7.6 Hz, 2H), 2.73 – 2.61 (m, 1H), 2.49 – 2.38 (m, 1H), 1.25 (t, J = 7.6 Hz, 3H). \(^{13}\)C NMR (100 MHz, cdc\(_3\)) \(\delta\) 159.5, 138.9, 135.4, 134.3, 131.8, 131.2, 130.8, 129.9, 128.7, 128.5, 126.8, 126.7, 126.5, 125.8, 125.6, 125.3, 123.2, 122.7, 116.9, 114.0, 82.2, 64.7, 55.5, 42.7, 22.3, 15.8. IR(film) 3075, 2965,
2928, 1610, 1507, 1299, 1248, 1174, 1070, 916, 832, 759, 723. HRMS-EI (m/z): [M+] calcd. for C$_{28}$H$_{28}$O$_2$: 396.2089 found 396.2093.

Following the general procedure 3p was obtained as separable mixture of stereoisomers (3:1, determined by 1H NMR of the crude reaction mixture). Chromatography (gradient elution: 20% DCM/hexanes then 30% DCM/hexanes) yielded 22.4 mg of 3p-trans (72% yield) and 9.0 mg of 3p-cis (29% yield) as colorless oils. **3p-trans**: $^1$H NMR (399 MHz, cdcl$_3$) $\delta$ 7.28 – 7.24 (m, 1H), 7.16 – 7.08 (m, 2H), 4.63 – 4.59 (m, 1H), 4.32 (t, $J$ = 8.0 Hz, 1H), 3.50 (dd, $J$ = 9.3, 8.2 Hz, 1H), 2.99 – 2.85 (m, 1H), 2.79 (dd, $J$ = 14.5, 6.4 Hz, 1H), 2.58 – 2.44 (m, 2H), 2.44 – 2.32 (m, 1H), 1.85 – 1.05 (m, 15H), 0.91 (t, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (75 MHz, cdcl$_3$) $\delta$ 141.88, 135.96, 135.30, 127.90, 127.82, 126.69, 126.39, 123.32, 84.14, 74.30, 40.48, 32.72, 30.90, 30.48, 28.79, 27.01, 26.52, 26.49, 26.47, 22.93, 14.22, 12.09. IR(film) 2930, 2855, 1741, 1457. **3p-cis**: $^1$H NMR (399 MHz, cdcl$_3$) $\delta$ 7.30 (d, $J$ = 7.7 Hz, 1H), 7.22 (t, $J$ = 7.5 Hz, 1H), 7.18 – 7.09 (m, 2H), 4.70 (d, $J$ = 1.1 Hz, 1H), 4.25 (t, $J$ = 8.2 Hz, 1H), 3.58 (dd, $J$ = 10.5, 8.2 Hz, 1H), 3.00 – 2.85 (m, 1H), 2.75 (dd, $J$ = 14.5, 5.7 Hz, 1H), 2.62 – 2.49 (m, 2H), 2.32 (dd, $J$ = 14.0, 12.0, 4.8 Hz, 1H), 1.94 – 1.00 (m, 15H), 0.96 (t, $J$ = 7.3 Hz, 3H). $^{13}$C NMR (100 MHz, cdcl$_3$) $\delta$ 141.52, 136.06, 135.93, 128.13, 127.80, 126.73, 126.38, 122.98, 84.63, 74.84, 44.36, 40.75, 31.69, 31.37, 30.86, 29.09, 27.95, 27.31, 27.04, 26.63, 23.31, 14.17. IR(film) 3016, 2955, 2928, 2854, 1730, 1706, 1600, 1483, 1462, 1451, 1429, 1378, 1344, 1311, 1288, 1261, 1215, 1197, 1170, 1132, 1101, 1084, 1073, 1063, 1050, 1041, 1018, 959, 915, 896, 869, 849, 801, 756, 734, 695, 667, 661, 651. HRMS-EI (m/z): [M+] calcd. for C$_{22}$H$_{30}$O: 310.2297 found 310.2296.
Spectra:
TsH\text{N}

\text{Et}

1c
EtO₂C

3b

TMS

EtO₂C

3b

TMS

EtO₂C

3b

TMS

EtO₂C

3b

TMS

EtO₂C

3b

TMS

EtO₂C

3b

TMS
3m CO3Y Spectrum

3m ROESY Spectrum
COSY Spectrum

ROESY Spectrum
3p-cis

3p-cis
References:

