Nitrile Assisted, Bronsted Acid Catalyzed Regio and Stereoselective Diarylphosphonylation of Allyl Silyl Ethers

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Experimental Procedures, Analytical and Spectroscopic Data for Compounds

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General Aspect.

*p-Toluenesulfonic acid monohydrate and phosphorous trichloride were purchased from Acros Organics and used without further purification. Triphenyl phosphite was purchased from International Laboratory and used as received. Sodium hydride (60% in mineral oil) was purchased from Panreac Sintesis. Triethylamine and phosphorous trichloride were distilled over calcium hydride. All solvents were purchased from LAB-SCAN and used as received or dried according to the following procedures. THF: distilled over sodium/benzophenone. Toluene: distilled over calcium hydride. Analytical thin layer chromatography (TLC) was performed using EM Science silica gel 60 F254 plates. The developed chromatogram was analyzed by UV lamp (254 nm), ethanolic phosphomolybdic acid (PMA) or potassium permanganate (KMnO₄). Liquid chromatography was performed using a forced flow (flash chromatography) of the indicated solvent system on Silicycle Silica Gel (230–400 mesh).¹H, ¹³C and ³¹P NMR spectra were recorded on Bruker 300 MHz or 400 MHz spectrometers in CDCl₃. Chemical shifts in ¹H NMR spectra are reported in ppm on the δ scale from an internal standard of residual tetramethylsilane (0 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant in hertz (Hz), and integration. Chemical shifts of ¹³C NMR spectra are reported in ppm from the central peak of CDCl₃ (77.16 ppm) on the δ scale. Chemical shifts of ³¹P NMR spectra are reported in ppm referenced to internal P(OPh)₃ as standard on the δ scale (127.8 ppm with respect to 85% aq H₃PO₄ at 0 ppm, R. C. Seiceira, C. M. Higa, A. G. Barreto, J. F. Cajaiba da Silva, Thermochimica Acta 2005, 428, 101. The use of internal standard help us to eliminate minor deviations observed when using external 85% aq H₃PO₄ alone. The δ difference between the two phosphorylation regioisomers can be quite small without the internal standard.). Infrared (IR) spectra were recorded on a Perkin-Elmer Spectrum One FT–IR. High resolution mass spectra (HRMS) were obtained on a Finnigan MAT 95XL GC Mass Spectrometer by Miss. Ng, Hau Yan of the Chinese University of Hong Kong, Department of Chemistry.
2/ Preparation of Allyl Silyl Ethers 1a-k.
The synthesis of allyl silyl ethers 1a-1h, 1i, and 1k followed the literature procedure reported by Ho and Jamison.

\[
\begin{align*}
\text{R}^2-\text{CHO} + \text{R}^1 & \xrightarrow{\text{cat. NiPr}^+ \text{TESOTf/NEt}_3} \text{R}^2-\text{C}=\text{C}\text{R}^1 \\
\text{P(OPh)}_3 & \text{Tolueno} \\
35 \degree \text{C}, 48 \text{ hrs} & \rightarrow \text{OTES}
\end{align*}
\]

The allylic alcohol below was synthesized by following the procedure reported by Takai. The allylic alcohol was treated with triethylsilyl trifluoromethanesulfonate in toluene to afford allyl silyl ether 1i. Isolated yield: 82%.

3/ General Procedure for the Preparation of Triarylphosphites.
The literature procedure reported by Hernández was followed with some modifications.

A 50 mL round bottom flask was equipped with a magnetic stirrer. Under an atmosphere of nitrogen, para-substituted phenols (1.72 mmol, 300 mol%) and sodium hydride (2.16 mmol, 360 mol%) were added to 20 mL dry THF at 0 °C. After 10 min stirring, the solution was warmed to room temperature and continued to stir for 1 h. Then dry triethylamine (0.11 mmol, 20 mol%) and phosphorous trichloride (0.6 mmol, 100 mol%) were added. The mixture was stirred at room temperature for 20 h. After the removal of solvent under reduced pressure, 10 mL dry toluene was added to the solid residue. The milky white mixture was filtered through dry celite under nitrogen. The filtrate was concentrated and purified via flash chromatography on neutral aluminum oxide with dichloromethane (100 mL). It was then dried under reduced pressure at 90 °C for 1 h to afford the desired products as the colourless liquid.
4/ General Procedure for the Allyl Diarylphosphonylation and Arylation.

A mixture of 0.1 mmol substrate with 500 mol% of P(OPh)$_3$ and 5 mol% p-TsOH•H$_2$O in 2 mL CH$_3$CN (for phosphonylation) or 20 mol% p-TsOH•H$_2$O in 2 mL toluene (for arylation) was stirred at 0 ºC for 2 h in open air and then stirred at r.t. for 9 h. Solvent was removed under reduced pressure. The yield and the selectivity (average of at least two runs) were determined by $^1$H NMR analysis using benzaldehyde as standard. Purification via flash chromatography on silica gel (using chloroform as eluent for phosphonylation or 20 % ethyl acetate in hexane as eluent for arylation, unless otherwise indicated), afforded the desired product as oil. The stereochemistry of the olefin was determined by NOESY using isolated product.

*Vigorous exclusion of other solvents (e.g. chloroform) is necessary, see S5.

Procedure: 1 mL CH$_3$CN was added to the substrate. Then solvent was removed under reduced pressure.

Procedure for Allyl Diarylphosphonylation of TES protected Baylis-Hillman adduct of methylacrylate and anisaldehyde:

General procedure for the allyl diarylphosphonylation of allyl silyl ethers was followed, except the reaction was conducted at 35 ºC.

The TES protected Baylis-Hillman adduct of methyl acrylate and anisaldehyde was prepared according to literature procedure with modifications.

To a solution of 1 mmol Baylis-Hillman adduct in 2 mL toluene, 3 equiv. NEt$_3$ and 1.2 equiv. TESOTf was added at 0 ºC and stir at rt for overnight. Quantitative yield.

5/ Solvent Effect on Allyl Diarylphosphonylation.

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>(\varepsilon_r)</th>
<th>Yield % ((2a+2a')^c)</th>
<th>(2a:2a'^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>P(OPh)₃</td>
<td>n.a.</td>
<td>1a recovered</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>P(OPh)₃</td>
<td>n.a.</td>
<td>90 (38:62)</td>
<td>75:25</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>2.38</td>
<td>85 (5:95)</td>
<td>n.d.</td>
</tr>
<tr>
<td>4</td>
<td>NEt₃</td>
<td>2.4</td>
<td>1a recovered</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>CHCl₃</td>
<td>4.8</td>
<td>97 (5:95)</td>
<td>n.d.</td>
</tr>
<tr>
<td>6</td>
<td>THF</td>
<td>7.6</td>
<td>83 (5:95)</td>
<td>n.d.</td>
</tr>
<tr>
<td>7</td>
<td>Acetone</td>
<td>20.7</td>
<td>83 (5:95)</td>
<td>n.d.</td>
</tr>
<tr>
<td>8</td>
<td>CH₃NO₂</td>
<td>35.9</td>
<td>90 (24:76)</td>
<td>75:25</td>
</tr>
<tr>
<td>9</td>
<td>DMF</td>
<td>36.7</td>
<td>89 (14:86)</td>
<td>78:22</td>
</tr>
<tr>
<td>10</td>
<td>CH₃CN</td>
<td>37.5</td>
<td>95 (87:13)</td>
<td>75:25</td>
</tr>
<tr>
<td>11</td>
<td>PhCN</td>
<td>26.0</td>
<td>79 (81:19)</td>
<td>78:22</td>
</tr>
</tbody>
</table>

*a* The standard procedure was followed except that the reactions were carried out at r.t. in parallel, using 20 mol% of \(p\)-TsOH•H₂O and indicated solvent; **b** Dielectric constant; \(^c\) Yield and selectivity were determined by \(^1\)H NMR analysis using benzaldehyde as standard, the olefin stereochemistry was determined as \(E\)-isomer by NOESY using isolated product; \(^d\) Control experiment without adding \(p\)-TsOH•H₂O and run in 500 mol% of P(OPh)₃.

Dielectric constant:

6/ Phosphonylation Experiment using HP(O)(OPh)$_2$ in place of P(OPh)$_3$.

\[
\begin{array}{c}
\text{p-Anisyl} \quad \text{n-Hex} \\
\text{OTES} \\
\text{Cat. TsOH} + \text{H$_2$O} \\
\text{CH$_3$CN} \\
\text{0 °C -> r.t.} \\
\end{array}
\]

1a  \[\rightarrow\]  2a + 2a' + 3a

Entry$^a$  Yield % ($2a+2a'$)$^b$  Yield % (3a)$^b$  E:Z$^c$

| 1 | No phosphorylation | 53 | >19:1 |

$^a$The standard procedure was followed, except that HP(O)(OPh)$_2$ was used in place of P(OPh)$_3$; $^b$Yield was determined by $^1$H NMR analysis using benzaldehyde as standard; $^c$Olefin stereochemistry of 3a was determined by NOESY using isolated product.

7/ Competition Experiments using P(OPh)$_3$, HP(O)(OPh)$_2$ and PhOH in Catalytic Allyl Arylation.

\[
\begin{array}{c}
p\text{-Anisyl} \quad \text{n-Bu} \\
\text{OTES} \\
\text{Cat. TsOH} + \text{H$_2$O} \\
\text{Toluene} \\
\end{array}
\]

1a  \[\rightarrow\]  3a

Entry$^a$  Additive  Condition  Conversion %  Yield % (3)$^b$  E:Z$^c$

| 1 | P(OPh)$_3$ 0 °C, 2h | 0 | 0 | n.a. |
| 2 | P(OPh)$_3$ 0 °C, 2h and then r.t., 2h | 92 | 78 | >95:5 |
| 3 | HP(O)(OPh)$_2$ 0 °C, 2h | 81 | 33 | >95:5 |
| 4 | HP(O)(OPh)$_2$ 0 °C, 2h and then r.t., 2h | 87 | 38 | >95:5 |
| 5 | PhOH 0 °C, 2h | 100 | 92 | >95:5 |

$^a$The standard procedure was followed, except that HP(O)(OPh)$_2$ or PhOH was used as indicated above; $^b$Yield was determined by $^1$H NMR analysis using benzaldehyde as standard; $^c$Olefin stereochemistry was determined by NOESY using isolated product.
Compound Characterization Data.

8/ Triarylphosphites.

The spectroscopic data was comparable with the literature:


\[
\begin{align*}
P \left( O \left( \begin{array}{c}
\text{Me} \\
\end{array} \right) \right)_3
\end{align*}
\]

**Tris(4-methylphenyl) phosphite P1**

The standard procedure was followed, except that 4-methylphenol was used. Yield: 92%.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.10 (d, \(J = 8.2\) Hz, 6H), 7.02 (d, \(J = 8.2\) Hz, 6H), 2.31 (s, 9H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 149.47, 133.78, 130.26, 120.65 (d, \(J = 7\) Hz, ortho), 20.87.

\(^{31}\)P NMR (121 MHz, CDCl\(_3\)) \(\delta\): 128.11.

\[
\begin{align*}
P \left( O \left( \begin{array}{c}
\text{Cl} \\
\end{array} \right) \right)_3
\end{align*}
\]

**Tris(4-chlorophenyl) phosphite P2**

The standard procedure was followed, except that 4-chlorophenol was used. Yield: 88%.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\): 7.29 (d, \(J = 9.0\) Hz, 6H), 7.04 (d, \(J = 9.0\) Hz, 6H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 130.29, 129.96, 129.56, 122.00 (d, \(J = 5\) Hz, ortho), 116.80.

\(^{31}\)P NMR (121 MHz, CDCl\(_3\)) \(\delta\): 126.43.

HRMS-EI (m/z): [M]\(^+\) calefd for C\(_{18}\)H\(_{12}\)Cl\(_3\)O\(_3\)P, 412.9662; found, 412.9692.
9/ Phosphonylation products (Table 1).

Table 1, entry 1:

![Chemical structure](image)

(major, more polar) (minor, less polar)

The standard procedure was followed.


2a: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.33-7.29 (m, 5H), 7.19-7.10 (m, 7H), 6.86 (d, \(J = 8.7\) Hz, 2H), 6.48 (d, \(J = 6.1\) Hz, 1H), 3.82 (s, 3H), 3.05 (d, \(J = 22.3\) Hz, 2H), 2.47-2.42 (m, 2H), 1.54-1.42 (m, 2H), 1.35-1.25 (m, 6H), 0.88-0.83 (m, 3H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 158.21, 150.54, 150.45, 131.07, 130.95, 130.65, 130.52, 129.68, 124.98, 120.50, 120.46, 113.53, 55.19, 34.46 (d, \(J = 137\) Hz), 31.54, 31.27, 29.13, 27.88, 22.54, 14.00.

IR (neat) cm\(^{-1}\): 2920, 2850, 1725, 1592, 1509, 1488, 1273, 1249, 1214, 1189, 1025, 927, 759.

\(^{31}\)P NMR (121 MHz, CDCl\(_3\)) \(\delta\): 20.36.

2'a: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.42 (d, \(J = 8.8\) Hz, 2H), 7.31-7.02 (m, 8H), 6.86 (d, \(J = 8.8\) Hz, 2H), 6.84 (d, \(J = 8.8\) Hz, 2H), 5.69 (d, \(J = 2.8\) Hz, 1H), 5.19 (d, \(J = 2.8\) Hz, 1H), 4.06 (d, \(J = 24.8\) Hz, 1H), 3.80 (s, 3H), 2.07-1.90 (m, 2H), 1.41-1.37 (m, 2H), 1.36-1.20 (m, 6H), 0.89-0.83 (m, 3H).

IR (neat) cm\(^{-1}\): 2926, 2855, 1591, 1509, 1489, 1271, 1214, 1188, 1162, 1025, 927, 759, 688, 617, 589, 500.

\(^{31}\)P NMR (121 MHz, CDCl\(_3\)) \(\delta\): 18.42.
Table 1, entry 5:

![Chemical structures](image)

(major, more polar) (minor, less polar)

The standard procedure was followed.

HRMS-ESI (m/z): [M+Na]^+ calcld for C\(_{26}\)H\(_{29}\)O\(_4\)PNa, 459.1696; found, 459.1691.

2b: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.33-7.29 (m, 4H), 7.20-7.11 (m, 8H), 6.85 (d, \(J = 8.7\) Hz, 2H), 6.57 (d, \(J = 6.3\) Hz, 1H), 3.81 (s, 3H), 3.06 (d, \(J = 22.4\) Hz, 2H), 2.38 (dd, \(J = 7.4, 2.4\) Hz, 2H), 1.75-1.97 (m, 1H), 0.84 (d, \(J = 6.6\) Hz, 6H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 158.33, 150.74, 150.65, 132.04, 131.91, 130.43, 130.21, 130.18, 129.89, 125.18, 120.69, 120.64, 113.66, 55.37, 39.76, 34.84 (d, \(J = 137\) Hz), 26.69, 22.48.

IR (neat) cm\(^{-1}\): 2921, 2851, 1593, 1510, 1490, 1464, 1270, 1250, 1215, 1190, 1026, 930, 765, 689.

\(^{31}\)P NMR (121 MHz, CDCl\(_3\)) \(\delta\): 20.41.

2'b: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.42 (d, \(J = 8.8\) Hz, 2H), 7.31-7.02 (m, 6H), 7.05 (d, \(J = 8.0\) Hz, 2H), 6.86 (d, \(J = 8.0\) Hz, 2H), 6.72 (d, \(J = 8.8\) Hz, 2H), 5.76 (d, \(J = 2.8\) Hz, 1H), 5.18 (d, \(J = 2.8\) Hz, 1H), 4.04 (d, \(J = 25.2\) Hz, 1H), 3.80 (s, 3H), 2.35 (d, \(J = 7.4\) Hz, 2H), 1.70-1.81 (m, 1H), 0.84 (d, \(J = 6.6\) Hz, 6H).

IR (neat) cm\(^{-1}\): 2954, 2923, 2852, 1727, 1593, 1510, 1490, 1465, 1384, 1274, 1250, 1214, 1190, 1163, 1072, 1026, 930, 760, 689, 617.

\(^{31}\)P NMR (121 MHz, CDCl\(_3\)) \(\delta\): 19.02.
Table 1, entry 6:

The standard procedure was followed.

HRMS-ESI (m/z): [M+Na]$^+$ calcld for C$_{28}$H$_{31}$O$_4$PNa, 485.1852; found, 485.1845.

2c: $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.32-7.28 (m, 5H), 7.19-7.10 (m, 7H), 6.87 (d, $J = 8.8$ Hz, 2H), 6.72 (d, $J = 5.2$ Hz, 1H), 3.82 (s, 3H), 3.01 (d, $J = 22.8$ Hz, 2H), 2.84-2.78 (m, 1H), 1.76-1.08 (m, 10H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ: 158.34, 150.79, 150.69, 135.09, 134.99, 130.14, 130.01, 129.99, 129.87, 129.75, 129.65, 125.14, 120.76, 120.72, 113.73, 55.39, 40.37, 40.31, 31.11, 30.01, 29.23 (d, $J = 123$ Hz), 26.21, 26.08.

IR (neat) cm$^{-1}$: 2918, 2849, 1724, 1589, 1506, 1488, 1270, 1248, 1214, 1189, 1025, 926, 760, 688.

$^{31}$P NMR (121 MHz, CDCl$_3$) δ: 21.55.

$^{2'}$c: $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.43 (d, $J = 8.8$ Hz, 2H), 7.30-7.03 (m, 8H), 6.86 (d, $J = 8.8$ Hz, 2H), 6.79 (d, $J = 8.6$ Hz, 2H), 5.77 (d, $J = 3.2$ Hz, 1H), 5.23 (d, $J = 3.2$ Hz, 1H), 4.12 (d, $J = 25.3$ Hz, 1H), 3.80 (s, 3H), 1.88-1.86 (m, 1H), 1.74-1.05 (m, 10H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ: 159.20, 150.93, 150.73, 148.88, 131.21, 131.13, 129.99, 129.87, 129.70, 129.55, 125.00, 124.85, 120.74, 120.64, 114.10, 113.88, 113.81, 55.42, 48.85 (d, $J = 138$ Hz), 45.74, 45.63, 32.80, 32.35, 26.83, 26.68, 26.33.

IR (neat) cm$^{-1}$: 2919, 2850, 1725, 1591, 1509, 1489, 1454, 1251, 1213, 1187, 1161, 1070, 1025, 927, 759, 678.

$^{31}$P NMR (121 MHz, CDCl$_3$) δ: 18.67.
Table 1, entry 7:

2d $\text{MeO} \stackrel{\text{P(O)(OPh)$_2$}}{\longrightarrow} \text{MeO}$

(major, more polar)

2‘d $\text{MeO} \stackrel{\text{P(O)(OPh)$_2$}}{\longrightarrow} \text{MeO}$

(minor, less polar)

The standard procedure was followed.

HRMS-ESI (m/z): [M+Na]$^+$ calcld for C$_{28}$H$_{25}$O$_4$PNa, 479.1383; found, 479.1412.

2d: $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.32-7.24 (m, 9H), 7.13 (dd, $J = 8.0$, 7.6 Hz, 2H), 7.03 (d, $J = 8.4$ Hz, 4H), 6.86 (d, $J = 8.8$ Hz, 2H), 6.68 (d, $J = 6.0$ Hz, 1H), 6.64 (d, $J = 8.8$ Hz, 2H), 3.73 (s, 3H), 3.38 (d, $J = 22.0$ Hz, 2H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ: 159.05, 151.03, 150.91, 140.97, 132.33, 132.16, 130.97, 130.26, 129.64, 129.32, 128.05, 125.59, 121.09, 121.03, 113.95, 55.72, 38.12 (d, $J = 137$ Hz).

IR (neat) cm$^{-1}$: 2918, 2850, 1722, 1589, 1509, 1488, 1274, 1250, 1213, 1188, 1024, 927, 758, 689.

$^{31}$P NMR (121 MHz, CDCl$_3$) δ: 19.46.

2’d: $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.51-7.49 (m, 2H), 7.45-7.29 (m, 4H), 7.23-7.14 (m, 4H), 7.09-7.07 (m, 3H), 6.90-6.86 (m, 4H), 6.80 (d, $J = 8.5$ Hz, 2H), 6.15 (d, $J = 3.1$ Hz, 1H) 5.71 (d, $J = 3.1$ Hz, 1H) 4.63 (d, $J = 25.6$ Hz, 1H), 3.79 (s, 3H).

IR (neat) cm$^{-1}$: 2918, 2850, 1725, 1590, 1509, 1488, 1465, 1384, 1252, 1212, 1182, 1025, 927, 761, 688, 500.

$^{31}$P NMR (121 MHz, CDCl$_3$) δ: 17.88.
Table 1, entry 8:

The standard procedure was followed.

HRMS-ESI (m/z): [M+Na]$^+$ calcld for C$_{29}$H$_{27}$O$_4$PNa, 493.1539; found, 493.1529.

2e: $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.37-7.14 (m, 17H), 6.86 (d, $J = 8.7$ Hz, 2H), 6.73 (d, $J = 6.1$ Hz, 1H), 3.88 (d, $J = 2.4$ Hz, 2H), 3.79 (s, 3H), 2.92 (d, $J = 22.1$ Hz, 2H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ: 158.76, 150.71, 150.59, 138.84, 132.66, 132.49, 130.00, 129.89, 128.93, 129.77, 126.53, 125.74, 125.20, 120.61, 113.91, 55.38, 37.13, 34.20 (d, $J = 137$ Hz).

IR (neat) cm$^{-1}$: 3061, 3027, 2924, 2836, 1591, 1510, 1490, 1455, 1270, 1251, 1214, 1189, 1162, 1026, 930, 761, 689.

$^{31}$P NMR (121 MHz, CDCl$_3$) δ: 20.08.

2'e: $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.43 (d, $J = 8.8$ Hz, 2H), 7.37-7.01 (m, 13H), 6.86 (d, $J = 8.7$ Hz, 2H), 6.71 (d, $J = 7.2$ Hz, 2H), 5.81 (d, $J = 2.8$ Hz, 1H), 5.21 (d, $J = 2.8$ Hz, 1H), 4.00 (d, $J = 25.2$ Hz, 1H), 3.80 (s, 3H), 3.49 (d, $J = 15.2$ Hz, 1H), 3.27 (d, $J = 15.2$ Hz, 1H).

IR (neat) cm$^{-1}$: 2954, 2922, 2851, 1723, 1590, 1509, 1489, 1463, 1384, 1250, 1213, 1188, 1073, 1025, 928, 823, 758, 689.

$^{31}$P NMR (121 MHz, CDCl$_3$) δ: 17.95.
Table 1, entry 9:

\[
\begin{align*}
2f & \quad \text{(major, more polar)} \\
2'f & \quad \text{(minor, less polar)}
\end{align*}
\]

The standard procedure was followed.

HRMS-ESI (m/z): [M+Na]\(^+\) calcd for C\(_{30}\)H\(_{29}\)O\(_4\)PNa, 507.1696; found, 507.1688.

\(2f\): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.32-7.11 (m, 15H), 7.06 (d, \(J = 8.8\) Hz, 2H), 6.84 (d, \(J = 8.8\) Hz, 2H), 6.52 (d, \(J = 6.2\) Hz, 1H), 3.81 (s, 3H), 3.05 (d, \(J = 22.2\) Hz, 2H), 2.84-2.77 (m, 4H).

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\): 158.50, 150.67, 150.55, 141.35, 131.90, 131.72, 129.91, 128.52, 126.16, 125.25, 120.70, 120.64, 113.77, 55.40, 35.02 (d, \(J = 137\) Hz), 33.25.

IR (neat) cm\(^{-1}\): 2922, 2852, 1592, 1509, 1490, 1273, 1250, 1204, 1190, 1026, 929, 760, 689.

\(^{31}\)P NMR (121 MHz, CDCl\(_3\)) \(\delta\): 20.09.

\(2'f\): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.42 (d, \(J = 8.8\) Hz, 2H), 7.20-7.02 (m, 13H), 6.86 (d, \(J = 8.4\) Hz, 2H), 6.74 (d, \(J = 8.4\) Hz, 2H), 5.74 (d, \(J = 2.4\) Hz, 1H), 5.23 (d, \(J = 2.4\) Hz, 1H), 4.01 (d, \(J = 25.2\) Hz, 1H), 3.82 (s, 3H), 2.52-2.41 (m, 2H), 2.38-2.28 (m, 2H).

IR (neat) cm\(^{-1}\): 2919, 2851, 1724, 1591, 1509, 1489, 1465, 1384, 1274, 1252, 1213, 1189, 1073, 1025, 929, 823, 759, 689.

\(^{31}\)P NMR (121 MHz, CDCl\(_3\)) \(\delta\): 17.98.
The standard procedure was followed, except that CH$_3$CN was distilled over calcium hydride before use, 100 mol% $p$-TsOH•H$_2$O was used, the reaction mixture was stirred at 35 °C for 18 hours and the product was purified with 5% diethyl ether in toluene. Isolated as a mixture of 2g and 2’g.

HRMS-ESI (m/z): [M+Na]$^+$ calcd for C$_{28}$H$_{33}$O$_4$PNa, 487.2009; found, 487.2039.

2g: $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.37-6.82 (m, 14H), 6.61 (d, $J$ = 6.2 Hz, 1H), 3.78 (s, 3H), 3.11 (d, $J$ = 22.3 Hz, 2H), 2.43-2.38 (m, 2H), 1.49-1.44 (m, 2H), 1.36-1.21 (m, 6H), 0.86-0.81 (m, 3H).

2’g: $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.75 (d, $J$ = 7.8 Hz, 2H), 7.37-6.82 (m, 10H), 6.77 (d, $J$ = 8.6 Hz, 2H), 5.67 (d, $J$ = 2.9 Hz, 1H), 5.16 (d, $J$ = 2.9 Hz, 1H), 4.88 (d, $J$ = 25.4 Hz, 1H), 3.77 (s, 3H), 2.17-1.99 (m, 2H), 1.42-1.38 (m, 2H), 1.36-1.21 (m, 6H), 0.86-0.81 (m, 3H).

$^{2g+2’g}$: $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 157.26, 157.10, 150.99, 150.90, 150.74, 150.64, 144.29, 132.36, 132.25, 130.85, 130.79, 130.01, 129.82, 129.67, 129.42, 128.85, 128.34, 127.28, 127.15, 126.52, 125.76, 125.14, 124.94, 124.69, 123.12, 120.88, 120.83, 120.78, 120.74, 120.47, 120.43, 120.29, 120.24, 120.19, 115.22, 115.14, 110.69, 110.48, 55.74, 55.41, 41.07 (d, $J$ = 140 Hz), 37.16, 37.06, 34.34 (d, $J$ = 137 Hz), 31.82, 31.71, 31.48, 29.19, 28.90, 28.03, 27.49, 22.73, 22.69.

IR (neat) cm$^{-1}$: 2927, 2856, 1593, 1490, 1454, 1271, 1247, 1215, 1190, 1026, 929, 755, 689.

$^{31}$P NMR (121 MHz, CDCl$_3$) δ: 20.53, 19.13.
Table 1, entry11:

![Chemical Structures](image)

(minor, more polar)  (major, less polar)

The standard procedure was followed.

HRMS-EI (m/z): [M]+ calcd for C_{29}H_{35}O_5P, 494.22; found, 494.2209.

**2h:** ¹H NMR (400 MHz, CDCl₃) δ: 7.32-7.28 (m, 3H), 7.21-7.18 (m, 4H), 7.17-7.13 (m, 3H), 7.05 (d, J = 8.4 Hz, 1H), 6.53 (d, J = 6.4 Hz, 1H), 6.48-6.43 (m, 2H), 3.82 (s, 3H), 3.76 (s, 3H), 3.09 (d, J = 22.4 Hz, 2H), 2.44-2.35 (m, 2H), 1.51-1.43 (m, 2H), 1.29-1.17 (m, 6H), 0.87-0.80 (m, 3H).

IR (neat) cm⁻¹: 2955, 2922, 2852, 1732, 1608, 1591, 1491, 1462, 1378, 1262, 1210, 1190, 1160, 1117, 933, 763, 501.

³¹P NMR (121 MHz, CDCl₃) δ: 20.68.

**2′h:** ¹H NMR (300 MHz, CDCl₃) δ: 7.42 (dd, J = 8.4, 2.1 Hz, 1H), 7.32-7.26 (m, 3H), 7.16-7.14 (m, 4H), 7.05 (m, 1H), 6.80 (d, J = 7.8 Hz, 2H), 6.50 (d, J = 8.4 Hz, 1H), 6.40 (s, 1H), 5.64 (d, J = 2.1 Hz, 1H), 5.13 (s, 1H), 4.75 (d, J = 25.5 Hz, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 2.11-2.02 (m, 2H), 1.42-1.35 (m, 2H), 1.26-1.21 (m, 6H), 0.90-0.82 (m, 3H).

¹³C NMR (75 MHz, CDCl₃) δ: 160.35, 158.15, 158.03, 151.03, 150.89, 150.82, 144.55, 144.50, 131.39, 131.32, 129.66, 129.42, 124.91, 124.66, 120.79, 120.73, 120.49, 120.43, 115.39, 115.33, 114.89, 114.79, 104.58, 98.61, 55.71, 55.51, 40.54 (d, J = 140 Hz), 37.05, 36.92, 31.83, 28.91, 27.49, 22.70, 14.23.

IR (neat) cm⁻¹: 2919, 2851, 1587, 1489, 1455, 1265, 1209, 1189, 1159, 1107, 1026, 926, 761, 688.

³¹P NMR (121 MHz, CDCl₃) δ: 19.39.
Table 1, entry 12:

2i

\[
\begin{array}{c}
\text{Me} \\
\text{n-hex}
\end{array}
\]

P(O)(OPh)\(_2\)

2i

\[
\begin{array}{c}
\text{Me} \\
\text{n-hex}
\end{array}
\]

P(O)(OPh)\(_2\)

(major, more polar) (minor, less polar)

The standard procedure was followed.

HRMS-EI (m/z): [M]\(^+\) calcd for C\(_{28}\)H\(_{33}\)O\(_3\)P, 448.22; found, 448.2171.

2i: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.34-7.27 (m, 3H), 7.21-7.12 (m, 5H), 7.12-7.09 (m, 4H), 7.07 (d, \(J = 8.4\) Hz, 2H), 6.51 (d, \(J = 6.0\) Hz, 1H), 3.06 (d, \(J = 22.0\) Hz, 2H), 2.45 (t, \(J = 8.4\) Hz, 2H), 2.35 (s, 3H), 2.14-1.98 (m, 2H), 1.52-1.47 (m, 2H), 1.30-1.19 (m, 4H), 0.89-0.82 (m, 3H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 150.74, 150.64, 136.45, 132.06, 131.94, 131.25, 131.11, 130.00, 129.88, 129.74, 129.02, 128.94, 128.62, 125.18, 120.76, 120.70, 120.66, 120.60, 34.64 (d, \(J = 137\) Hz), 31.73, 31.53, 29.31, 22.73, 22.58, 21.31, 14.19.

IR (neat) cm\(^{-1}\): 2920, 2851, 1591, 1489, 1272, 1214, 1189, 1162, 1025, 928, 761, 688.

\(^{31}\)P NMR (121 MHz, CDCl\(_3\)) \(\delta\): 20.28.

2i: \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.38 (d, \(J = 8.8\) Hz, 2H), 7.32-7.10 (m, 8H), 6.86 (d, \(J = 8.8\) Hz, 2H), 6.79 (d, \(J = 8.4\) Hz, 2H), 5.70 (d, \(J = 2.8\) Hz, 1H), 5.18 (d, \(J = 2.8\) Hz, 1H), 4.06 (d, \(J = 25.2\) Hz, 1H), 2.35 (s, 3H), 2.06-1.97 (m, 2H), 1.41-1.37 (m, 2H), 1.36-1.20 (m, 4H), 0.89-0.83 (m, 5H).

\(^{31}\)P NMR (121 MHz, CDCl\(_3\)) \(\delta\): 18.38.
Table 1, entry 13:

\[
\begin{array}{ccc}
\text{2j} & \text{2'}j \\
\text{P(O)(OPh)}_2 & \text{P(O)(OPh)}_2 \\
\end{array}
\]

(major, more polar)  (minor, less polar)

The standard procedure was followed.


\(\text{2j: }^1\text{H NMR (400 MHz, CDCl}_3\text{)} \delta: 7.34-7.29 (m, 6H), 7.22-7.11 (m, 9H), 6.56 (d, } J = 6.4 \text{ Hz, 1H), 3.08 (d, } J = 22.4 \text{ Hz, 2H), 2.50-2.42 (m, 2H), 2.14-1.98 (m, 2H), 1.54-1.45 (m, 2H), 1.44-1.24 (m, 4H), 0.87 (t, } J = 7.2 \text{ Hz, 3H).}

\(\text{13C NMR (100 MHz, CDCl}_3\text{)} \delta: 150.73, 150.63, 132.05, 131.93, 131.25, 131.12, 130.01, 129.88, 129.82, 129.74, 129.02, 128.61, 125.19, 120.77, 120.66, 34.63 (d, } J = 137 \text{ Hz), 31.73, 31.52, 29.31, 22.73, 22.58, 21.31, 14.19.}

IR (neat) cm\(^{-1}\): 2956, 2925, 2856, 1591, 1490, 1271, 1214, 1189, 1162, 1071, 1025, 1007, 928, 760, 689.

\(\text{31P NMR (121 MHz, CDCl}_3\text{)} \delta: 20.16.\)

\(\text{2'}j: \ \text{1H NMR (400 MHz, CDCl}_3\text{)} \delta: 7.52 (d, } J = 8.4 \text{ Hz, 2H), 7.32-7.10 (m, 10H), 7.05 (t, } J = 7.2 \text{ Hz, 1H), 6.76 (d, } J = 8.4 \text{ Hz, 2H), 5.72 (d, } J = 3.0 \text{ Hz, 1H), 5.21 (d, } J = 3.0 \text{ Hz, 1H), 4.11 (d, } J = 24.8 \text{ Hz, 1H), 2.06-1.97 (m, 2H), 1.44-1.35 (m, 2H), 1.36-1.20 (m, 4H), 0.90-0.83 (m, 5H).}

\(\text{31P NMR (121 MHz, CDCl}_3\text{)} \delta: 18.19.\)
Table 1, entry 14:

\[
\begin{align*}
2k & \quad \text{(major, more polar)} \\
2'k & \quad \text{(minor, less polar)}
\end{align*}
\]

The standard procedure was followed.

HRMS-ES (m/z): [M]⁺ calcd for C_{27}H_{30}ClO_3P, 468.1616; found, 468.1639.

2k: ¹H NMR (400 MHz, CDCl₃) δ: 7.35-7.21 (m, 4H), 7.22-7.09 (m, 10H), 6.57 (d, \( J = 6.4 \text{ Hz, } 1H \)), 3.09 (d, \( J = 22.4 \text{ Hz, } 2H \)), 2.50-2.43 (m, 2H), 2.11-1.99 (m, 2H), 1.55-1.45 (m, 2H), 1.44-1.22 (m, 4H), 0.87 (t, \( J = 7.2 \text{ Hz, } 3H \)).

¹³C NMR (100 MHz, CDCl₃) δ: 150.55, 150.46, 137.77, 131.28, 131.16, 130.86, 130.72, 130.08, 129.89, 124.98, 120.69, 120.60, 113.73, 34.42 (d, \( J = 137 \text{ Hz} \)), 31.70, 31.28, 29.14, 27.87, 22.55, 14.01.

IR (neat) cm⁻¹: 2919, 2851, 1726, 1592, 1489, 1466, 1270, 1212, 1187, 1161, 1091, 1025, 929, 760, 688.

³¹P NMR (121 MHz, CDCl₃) δ: 19.86.

2'k: ¹H NMR (400 MHz, CDCl₃) δ: 7.45 (d, \( J = 8.8 \text{ Hz, } 2H \)), 7.33-7.29 (m, 4H), 7.22-7.06 (m, 6H), 6.82 (d, \( J = 8.4 \text{ Hz, } 2H \)), 5.69 (d, \( J = 3.2 \text{ Hz, } 1H \)), 5.21 (d, \( J = 3.2 \text{ Hz, } 1H \)), 4.07 (d, \( J = 25.2 \text{ Hz, } 1H \)), 2.16-1.94 (m, 2H), 1.42-1.33 (m, 2H), 1.28-1.16 (m, 4H), 0.90-0.81 (m, 5H).

³¹P NMR (121 MHz, CDCl₃) δ: 17.92.
Table 1, entry 15:

\[
\begin{align*}
\text{2l} & : \text{OMe} & n-\text{hex} \quad \text{P(O)(OPh)}_2 \\
\text{2l'} & : \text{OMe} & n-\text{hex} \quad \text{P(O)(OPh)}_2 \\
\end{align*}
\]

(major, more polar) \quad (minor, less polar)

The standard procedure was followed, except that CH\textsubscript{3}CN was distilled over calcium hydride before use, 100 mol\% $p$-TsOH**H\textsubscript{2}O was used, the reaction mixture was stirred at 35 °C for 18 hours and the product was purified with 5% diethyl ether in toluene.

HRMS-ESI (m/z): [M+Na]\textsuperscript+ calec for C\textsubscript{28}H\textsubscript{33}O\textsubscript{4}PNa, 487.2009; found, 487.2017.

\textbf{2l:} \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ: 7.33-7.29 (m, 5H), 7.22-7.14 (m, 6H), 6.80-6.77 (m, 2H), 6.71 (s, 1H), 6.53 (d, $J = 6.1$ Hz, 1H), 3.79 (s, 3H), 3.07 (d, $J = 22.4$ Hz, 2H), 2.48-2.41 (m, 2H), 1.48-1.52 (m, 2H), 1.35-1.20 (m, 6H), 0.88-0.82 (m, 3H).

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ: 158.40, 150.74, 131.27, 131.15, 130.85, 130.72, 130.03, 129.88, 125.18, 124.59, 120.99, 120.70, 120.66, 113.73, 55.39, 34.66 (d, $J = 137$ Hz), 31.75, 31.49, 29.85, 29.34, 28.09, 22.74, 14.21.

IR (neat) cm\textsuperscript{-1}: 2920, 2851, 1726, 1592, 1489, 1249, 1214, 1189, 1162, 1026, 927, 759, 689.

\textbf{31}P NMR (121 MHz, CDCl\textsubscript{3}) δ: 20.11.

\textbf{2l':} \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ: 7.22-7.05 (m, 11H), 6.85-6.79 (m, 3H), 5.70 (d, $J = 3.1$ Hz, 1H), 5.20 (d, $J = 3.1$ Hz, 1H), 4.08 (d, $J = 25.0$ Hz, 1H), 3.77 (s, 3H), 2.18-2.00 (m, 2H), 1.42-1.38 (m, 2H), 1.31-1.20 (m, 6H), 0.88-0.81 (m, 3H).

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ: 159.78, 150.76, 143.65, 143.60, 135.96, 135.90, 129.74, 129.64, 129.55, 125.13, 124.93, 122.58, 122.50, 120.80, 120.76, 120.62, 120.57, 115.57, 115.50, 115.36, 113.48, 55.38, 50.84 (d, $J = 138$ Hz), 37.04, 36.94, 31.81, 28.92, 27.57, 22.71, 14.20.

IR (neat) cm\textsuperscript{-1}: 2920, 2851, 1726, 1592, 1489, 1456, 1270, 1213, 1188, 1161, 1046, 928, 760, 688.

\textsuperscript{31}P NMR (121 MHz, CDCl\textsubscript{3}) δ: 18.00.
Table 1, entry 16:

\[
\begin{align*}
2m \quad & \quad 2'm
\end{align*}
\]

(more polar) \quad (less polar)

The standard procedure was followed.

HRMS-EI (m/z): [M]$^+$ calcld for $\text{C}_{29}\text{H}_{36}\text{NO}_3\text{P}$, 477.24; found, 477.2438.

2m: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.30-7.26 (m, 4H), 7.19-7.13 (m, 6H), 7.11 (d, $J = 8.8$ Hz, 2H), 6.70 (d, $J = 8.8$ Hz, 2H), 6.43 (d, $J = 6.4$ Hz, 1H), 3.05 (d, $J = 22.4$ Hz, 2H), 2.96 (s, 6H), 2.51-2.46 (m, 2H), 1.58-1.50 (m, 2H), 1.35-1.25 (m, 6H), 0.89-0.82 (m, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 150.76, 150.66, 131.14, 129.85, 129.71, 129.68, 129.49, 125.13, 120.76, 120.72, 112.26, 40.67, 34.90 (d, $J = 137$ Hz), 31.82, 31.68, 29.45, 28.18, 22.77, 14.23.

IR (neat) cm$^{-1}$: 2925, 2854, 1732, 1610, 1593, 1520, 1353, 1272, 1214, 1190, 1163, 1071, 1025, 928, 762, 689.

$^{31}$P NMR (121 MHz, CDCl$_3$) $\delta$: 20.41.

2'm: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.32 (d, $J = 8.8$ Hz, 2H), 7.30-7.28 (m, 1H), 7.19-7.11 (m, 6H), 7.05 (t, $J = 7.4$ Hz, 1H), 6.80 (d, $J = 8.4$ Hz, 2H), 6.69 (d, $J = 8.8$ Hz, 2H), 5.66 (d, $J = 3.2$ Hz, 1H), 5.15 (d, $J = 3.2$ Hz, 1H), 4.00 (d, $J = 24.8$ Hz, 1H), 2.94 (s, 6H), 2.16-1.99 (m, 2H), 1.40-1.36 (m, 2H), 1.25-1.20 (m, 6H), 0.89-0.83 (m, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 151.02, 150.92, 150.87, 150.77, 150.16, 144.28, 144.24, 130.73, 130.65, 129.84, 129.68, 129.49, 124.96, 124.78, 120.86, 120.82, 120.76, 120.72, 114.64, 114.56, 112.82, 49.84 (d, $J = 139$ Hz), 40.77, 36.93, 36.83, 31.84, 28.96, 27.58, 22.72, 14.21.

IR (neat) cm$^{-1}$: 2925, 2854, 1611, 1593, 1520, 1490, 1353, 1270, 1214, 1190, 1162, 1070, 1025, 928, 764, 689.

$^{31}$P NMR (121 MHz, CDCl$_3$) $\delta$: 19.00.
Table 1, entry 17:

The standard procedure was followed, except that the product was purified with 20% ethyl acetate in hexane. Isolated as a mixture of $2n$ and $2'n$.

HRMS-ESI (m/z): $[\text{M+Na}]^+$ calc'd for C$_{29}$H$_{27}$O$_4$PNa, 493.1539; found, 493.1523.

$n$: $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.60 (d, $J = 6.4$ Hz, 2H), 7.33-7.07 (m, 12H), 6.90-6.74 (m, 6H), 4.29 (d, $J = 25.4$ Hz, 1H), 3.80 (s, 3H), 1.94 (s, 3H).

$n'$: $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.52 (d, $J = 6.9$ Hz, 2H), 7.33-7.07 (m, 11H), 6.97 (d, $J = 3.1$ Hz, 1H), 6.90-6.74 (m, 6H), 4.25 (d, $J = 25.5$ Hz, 1H), 3.80 (s, 3H), 1.94 (s, 3H).

$n+n'$: $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 159.29, 156.50, 150.87, 150.74, 150.57, 137.54, 133.24, 131.58, 131.04, 130.80, 130.66, 130.40, 129.83, 129.68, 129.51, 129.16, 128.84, 128.21, 126.80, 125.24, 125.17, 120.80, 120.75, 119.97, 115.23, 114.26, 55.43, 53.51 (d, $J = 138$ Hz), 17.99, 17.90.

IR (neat) cm$^{-1}$: 2918, 2851, 1726, 1591, 1489, 1252, 1213, 1158, 1025, 929, 757, 689.

$^{31}$P NMR (121 MHz, CDCl$_3$) δ: 18.00, 18.00.

Comparison with correlated compounds (silyl ethers)

Silyl ether with a structure similar to $2n$ instead of $2'n$ gives a slightly more deshielded carbinol proton.
Table 1, entry 18:

The standard procedure was followed, except that the tris(4-methylphenyl) phosphite was used instead of triphenyl phosphite and the product was purified with 20% ethyl acetate in hexane. Isolated as a mixture of two isomers.

HRMS-EI (m/z): [M]+ calcld for C_{28}H_{33}O_{4}P, 464.2111; found, 464.2117.

**major:** $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.13-6.95 (m, 10H), 6.86 (d, $J = 8.7$ Hz, 2H), 6.45 (d, $J = 6.1$ Hz, 1H), 3.81 (s, 3H), 3.02 (d, $J = 22.2$ Hz, 2H), 2.48-2.42 (m, 2H), 2.29 (s, 6H), 1.52-1.44 (m, 2H), 1.44-1.21 (m, 2H), 0.89-0.82 (m, 3H).

**minor:** $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.41 (d, $J = 8.5$ Hz, 2H), 7.13-6.95 (m, 6H), 6.86 (d, $J = 8.7$ Hz, 2H), 6.67 (d, $J = 8.5$ Hz, 2H), 5.67 (d, $J = 2.5$ Hz, 1H), 5.17 (d, $J = 2.5$ Hz, 1H), 4.01 (d, $J = 24.9$ Hz, 1H), 3.80 (s, 3H), 2.30 (s, 6H), 2.14-1.97 (m, 2H), 1.44-1.21 (m, 4H), 0.89-0.82 (m, 3H).

**major+minor:** $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 158.34, 148.50, 148.41, 134.68, 131.37, 131.25, 131.13, 131.06, 130.68, 130.55, 130.35, 130.27, 130.14, 130.10, 129.97, 129.91, 129.88, 120.47, 120.43, 120.39, 120.35, 120.31, 120.27, 114.07, 113.68, 55.39, 55.35, 49.75 (d, $J = 138$ Hz), 36.62, 34.49 (d, $J = 137$ Hz), 31.22, 31.18, 30.29, 30.27, 29.74, 22.77, 22.33, 20.84, 20.79, 14.05.

IR (neat) cm$^{-1}$: 2924, 2855, 1608, 1506, 1465, 1272, 1250, 1221, 1192, 1164, 1105, 1035, 940, 925, 821.

$^{31}$P NMR (121 MHz, CDCl$_3$) δ: 20.50, 18.59.
Table 1, entry 19:

![Chemical structures](image)

(major) (minor)

The standard procedure was followed, except that the tris(4-chlorophenyl) phosphite was used instead of triphenyl phosphite and the product was purified with 20% ethyl acetate in hexane. Isolated as a mixture of two isomers.

HRMS-EI (m/z): [M]$^+$ calcd for C$_{26}$H$_{27}$Cl$_2$O$_4$P, 504.1019; found, 504.1000.

**major:** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.28-7.08 (m, 8H), 6.86 (d, $J = 8.8$ Hz, 2H), 6.68-6.65 (m, 2H), 6.48 (d, $J = 6.3$ Hz, 1H), 3.82 (s, 3H), 3.06 (d, $J = 22.3$ Hz, 2H), 2.45-2.41 (m, 2H), 1.53-1.45 (m, 2H), 1.45-1.22 (m, 2H), 0.89-0.82 (m, 3H).

**minor:** $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.38 (d, $J = 8.8$ Hz, 2H), 7.28-7.08 (m, 8H), 6.86 (d, $J = 8.8$ Hz, 2H), 5.65 (d, $J = 3.0$ Hz, 1H), 5.19 (d, $J = 2.9$ Hz, 1H), 4.04 (d, $J = 25.1$ Hz, 1H), 3.80 (s, 3H), 2.15-1.97 (m, 2H), 1.45-1.22 (m, 4H), 0.89-0.83 (m, 3H).

**major+minor:** $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 158.52, 148.97, 148.87, 131.35, 131.22, 131.10, 131.02, 130.81, 130.37, 130.25, 129.95, 129.86, 129.83, 129.67, 129.60, 129.28, 122.07, 122.03, 121.97, 121.93, 121.84, 121.80, 116.77, 114.26, 113.80, 55.42, 55.37, 49.81 (d, $J = 139$ Hz), 36.67, 34.57 (d, $J = 136$ Hz), 31.24, 31.21, 30.24, 31.21, 29.72, 22.73, 22.28, 14.02.

IR (neat) cm$^{-1}$: 2924, 2850, 1725, 1485, 1460, 1270, 1250, 1218, 1193, 1164, 1090, 924, 830.

$^{31}$P NMR (121 MHz, CDCl$_3$) $\delta$: 21.10, 19.19.
Scheme 5, Allyl diarylphosphonylation of TES protected Baylis-Hillman adduct of methylacrylate and anisaldehyde:

General procedure for the allyl diarylphosphonylation of allyl silyl ethers was followed, except the reaction was conducted at 35 °C and was purified with 25% ethyl acetate in hexane.

81% yield (2+2'); 2:2' = 3.2:1; E:Z = 18:82. Olefin stereochemistry were determined by NOESY.

HRMS-EI (m/z): [M]+ calcd for C_{24}H_{23}O_{6}P, 438.1232; found, 438.1232.

(Major, 2 Z-isomer) (Minor, 2 E-isomer) (Minor 2' product)

1H NMR (400 MHz, CDCl₃) δ: 7.89 (d, J = 5.2 Hz, 1H), 7.60 (d, J = 8.4 Hz, 2H), 7.31-7.26 (m, 4H), 7.16-7.12 (m, 6H), 6.91 (d, J = 8.4 Hz, 2H), 3.82 (s, 3H), 3.77 (s, 3H), 3.62 (d, J = 22.4 Hz, 2H).

13C NMR (100 MHz, CDCl₃) δ: 168.07, 160.62, 150.59, 150.50, 142.86, 142.74, 131.57, 129.84, 125.21, 120.58, 120.53, 114.33, 55.47, 52.52, 27.00 (d, J = 142 Hz).

31P NMR (121 MHz, CDCl₃) δ: 19.14.

(Minor, 2 E-isomer) 1H NMR (400 MHz, CDCl₃) δ: 7.62-7.54 (m, 2H), 7.42-7.34 (m, 2H), 7.31-7.11 (m, 6H), 7.06 (d, J = 7.6 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 5.6 Hz, 1H), 6.86 (d, J = 8.4 Hz, 2H), 3.82 (s, 3H), 3.65 (s, 3H), 3.37 (d, J = 21.6 Hz, 2H).

31P NMR (121 MHz, CDCl₃) δ: 18.53.

(minor 2' type product) 1H NMR (400 MHz, CDCl₃) δ: 7.43 (dd, J = 8.8, 2.0 Hz, 2H), 7.36-7.27 (m, 2H), 7.20-7.03 (m, 6H), 6.87 (dd, J = 8.8, 2.0 Hz, 2H), 6.75-6.71 (m, 2H), 6.65 (d, J = 2.8 Hz, 1H), 6.60 (d, J = 2.8 Hz, 1H), 4.94 (d, J = 24.8 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H).

31P NMR (121 MHz, CDCl₃) δ: 17.78.
Arylation products (Table 2).

The products relative substitution patterns were determined by $^1$H NMR coupling patterns and by $^{13}$C NMR chemical shift comparison of related compounds if the aromatic region of $^1$H NMR was not clear. The olefin stereochemistry was determined by NOESY.


$^{13}$C NMR (25.2 MHz, CDCl$_3$) $\delta$:

<table>
<thead>
<tr>
<th>Ortho-</th>
<th>Meta-</th>
<th>Para-</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{13}$C $\delta$: 124.0</td>
<td>$^{13}$C $\delta$: 139.3</td>
<td>$^{13}$C $\delta$: 130.5</td>
</tr>
<tr>
<td>153.5, 131.1, 127.7, 124.0, 121.4, 115.9.</td>
<td>154.9, 139.3, 130.3, 122.2, 116.1, 112.7.</td>
<td>152.6, 130.5, 130.2, 115.3.</td>
</tr>
</tbody>
</table>

Table 2, entry 1:

The standard procedure was followed.

HRMS-EI (m/z): [M]$^+$ caled for C$_{22}$H$_{28}$O$_2$, 324.2084; found, 324.2077.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.15 (d, $J$ = 8.6 Hz, 2H), 7.10 (d, $J$ = 8.4 Hz, 2H), 6.85 (d, $J$ = 8.6 Hz, 2H), 6.76 (d, $J$ = 8.4 Hz, 2H), 6.21 (s, 1H), 5.05 (brs, 1H), 3.80 (s, 3H), 3.39 (s, 2H), 2.13 (t, $J$ = 8.2 Hz, 2H), 1.47-1.41 (m, 2H), 1.28-1.20 (m, 6H), 0.86 (t, $J$ = 7.1 Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 157.97, 154.06, 142.09, 132.48, 131.25, 130.39, 129.97, 126.36, 115.36, 113.75, 55.49, 43.30, 31.85, 30.45, 29.62, 28.35, 22.83, 14.31.

IR (neat) cm$^{-1}$: 3396, 2925, 1607, 1509, 1464, 1247, 1174, 1035, 822.
Table 2, entry 2:

3b

The standard procedure was followed.

HRMS-EI (m/z): [M]+ calcd for C_{20}H_{24}O_{2}, 296.1771; found, 296.1774.

$^1$H NMR (400 MHz, CDCl$_3$) δ: 7.15 (d, J = 8.6 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 6.77 (d, J = 8.4 Hz, 2H), 6.29 (s, 1H), 4.92 (bbrs, 1H), 3.80 (s, 3H), 3.38 (s, 2H), 2.05 (d, J = 7.4 Hz, 2H), 1.88-1.98 (m, 1H), 0.82 (d, J = 6.6 Hz, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ: 157.86, 153.98, 140.98, 132.45, 131.24, 130.29, 130.13, 127.54, 115.27, 113.56, 55.36, 43.23, 38.76, 26.53, 22.65.

IR (neat) cm$^{-1}$: 3400, 2954, 1608, 1509, 1463, 1246, 1173, 1035, 822.

Table 2, entry 3:

3c ortho-product

The standard procedure was followed, except that the product was purified with chloroform.

HRMS-EI (m/z): [M]+ calcd for C_{22}H_{26}O_{2}, 322.1927; found, 322.1905.

$^1$H NMR (400 MHz, CDCl$_3$) δ: 7.18-7.15 (m, 2H), 7.08 (d, J = 8.5 Hz, 2H), 6.91 (t, J = 7.4 Hz, 1H), 6.86-6.84 (m, 3H), 6.05 (s, 1H), 5.10 (bbrs, 1H), 3.80 (s, 3H), 3.49 (s, 2H), 2.86-2.79 (m, 1H), 1.80-1.48 (m, 5H), 1.45-1.10 (m, 5H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ: 158.17, 154.64, 144.64, 131.55, 130.33, 129.94, 128.10, 125.85, 125.72, 120.98, 116.23, 113.69, 55.38, 40.60, 34.79, 31.64, 26.51, 26.21.

IR (neat) cm$^{-1}$: 3436, 2926, 1602, 1512, 1458, 1384, 1256, 1176, 1032, 836, 754.
Table 2, entry 4:

The standard procedure was followed, except that the product was purified with chloroform.

HRMS-EI (m/z): [M]+ calcd for C_{22}H_{20}O_{2}, 316.1458; found, 316.1459.

$^1$H NMR (400 MHz, CDCl$_3$) δ: 7.24-7.20 (m, 3H), 7.06-7.04 (m, 4H), 6.84 (d, $J = 8.6$ Hz, 2H), 6.72 (d, $J = 8.6$ Hz, 2H), 6.62 (d, $J = 8.8$ Hz, 2H), 6.35 (s, 1H), 4.70 (brs, 1H), 3.72 (s, 3H), 3.68 (s, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ: 158.64, 154.36, 140.07, 139.62, 132.33, 130.89, 130.76, 130.05, 129.14, 128.94, 128.62, 126.49, 115.59, 115.49, 114.13, 55.71, 42.96.

IR (neat) cm$^{-1}$: 3397, 2918, 1724, 1606, 1510, 1465, 1368, 1286, 1251, 1216, 1176, 1124, 1074, 1040, 825, 759, 701.

Table 2, entry 5:

The standard procedure was followed.

HRMS-EI (m/z): [M]+ calcd for C_{23}H_{22}O_{2}, 330.1614; found, 330.1617.

$^1$H NMR (400 MHz, CDCl$_3$) δ: 7.32-7.29 (m, 2H), 7.26-7.16 (m, 5H), 7.03 (d, $J = 8.5$ Hz, 2H), 6.83 (d, $J = 8.8$ Hz, 2H), 6.76 (d, $J = 8.5$ Hz, 2H), 6.49 (s, 1H), 4.81 (brs, 1H), 3.79 (s, 3H), 3.53 (s, 2H), 3.29 (s, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ: 158.32, 154.05, 139.76, 139.30, 132.01, 130.57, 130.45, 129.74, 128.83, 128.63, 138.30, 126.17, 115.28, 113.81, 55.39, 42.65, 36.00.

IR (neat) cm$^{-1}$: 3401, 3024, 2922, 1607, 1509, 1451, 1248, 1177, 1031, 822, 733.
Table 2, entry 6:

![Image showing the compound 3f]

The standard procedure was followed.

HRMS-ESI (m/z): [M+Na]^+ calcd for C_{24}H_{24}O_2Na, 367.1669; found, 367.1658.

$^1$H NMR (400 MHz, CDCl$_3$) δ: 7.25-7.23 (m, 2H), 7.18-7.09 (m, 7H), 6.84 (d, $J = 8.4$ Hz, 2H), 6.77 (d, $J = 8.2$ Hz, 2H), 6.28 (s, 1H), 4.88 (brs, 1H), 3.80 (s, 3H), 3.43 (s, 2H), 2.75-2.71 (m, 2H), 2.50-2.43 (m, 2H).

$^{13}$C NMR (75 MHz, CDCl$_3$) δ: 158.09, 154.11, 142.07, 140.70, 132.12, 130.78, 130.33, 129.81, 128.45, 128.42, 127.22, 126.00, 115.34, 113.70, 55.40, 43.52, 34.48, 32.33.

IR (neat) cm$^{-1}$: 3401, 3025, 2925, 2852, 1606, 1509, 1453, 1247, 1177, 1033, 939, 826, 699.
The standard procedure was followed, except that 40 mol% of p-TsOH•H₂O was used.

HRMS-EI (m/z): [M]⁺ calcld for C₂₂H₂₈O₂, 324.2084; found, 324.2059.

3g: \(^1H\) NMR (400 MHz, CDCl₃) δ: 7.23-7.17 (m, 2H), 7.15 (d, \(J = 8.4\) Hz, 2H), 6.90 (dd, \(J = 8.2, 7.4\) Hz, 1H), 6.86 (d, \(J = 8.2\) Hz, 1H), 6.77 (d, \(J = 8.4\) Hz, 2H), 6.35 (s, 1H), 4.73 (brs, 1H), 3.82 (s, 3H), 3.44 (s, 2H), 2.06 (t, \(J = 8.1\) Hz, 2H), 1.49-1.39 (m, 2H), 1.30-1.17 (m, 6H), 0.85 (t, \(J = 7.2\) Hz, 3H).

\(^{13}C\) NMR (100 MHz, CDCl₃) δ: 157.30, 153.92, 142.75, 132.61, 130.25, 130.19, 127.73, 127.50, 122.72, 120.14, 115.21, 110.53, 55.59, 42.86, 31.74, 30.30, 29.42, 28.20, 22.73, 14.20.

IR (neat) cm⁻¹: 3398, 2924, 1706, 1612, 1597, 1512, 1487, 1463, 1376, 1288, 1243, 1171, 1109, 1029, 823, 752.

Purified with 10% ethyl acetate in hexane.

3g ortho-product: \(^1H\) NMR (400 MHz, CDCl₃) δ: 7.23-7.21 (m, 1H), 7.18-7.12 (m, 3H), 6.94-6.85 (m, 4H), 6.54 (s, 1H), 5.86 (brs, 1H), 3.83 (s, 3H), 3.60 (s, 2H), 2.02 (t, \(J = 8.2\) Hz, 2H), 1.50-1.39 (m, 2H), 1.34-1.15 (m, 6H), 0.83 (t, \(J = 7.1\) Hz, 3H).

\(^{13}C\) NMR (100 MHz, CDCl₃) δ: 156.99, 142.41, 131.12, 129.65, 128.13, 128.07, 126.46, 123.53, 120.72, 120.11, 116.85, 110.16, 55.37, 40.16, 31.53, 29.93, 29.12, 27.86, 22.54, 14.05.

IR (neat) cm⁻¹: 3385, 2953, 2850, 1720, 1594, 1487, 1454, 1369, 1286, 1243, 750.
The standard procedure was followed, except that 40 mol% of p-TsOH•H2O was used.

HRMS-EI (m/z): [M]+ calcd for C22H28O, 308.2135; found, 308.2112.

3i: 1H NMR (400 MHz, CDCl3) δ: 7.12-7.09 (m, 6H), 6.77 (d, J = 8.4 Hz, 2H), 6.24 (s, 1H), 4.74 (brs, 1H), 3.40 (s, 2H), 2.33 (s, 3H), 2.13 (t, J = 8.0 Hz, 2H), 1.50-1.40 (m, 2H), 1.31-1.20 (m, 6H), 0.86 (t, J = 6.8 Hz, 3H).

13C NMR (100 MHz, CDCl3) δ: 153.96, 142.64, 135.76, 135.56, 132.43, 130.31, 128.91, 128.65, 126.76, 115.25, 43.21, 31.76, 30.41, 29.52, 28.28, 22.75, 21.27, 14.22.

IR (neat) cm⁻¹: 3374, 3020, 2854, 1703, 1612, 1510, 1444, 1376, 1222, 1170, 1099, 824.

Purified with 10% ethyl acetate in hexane.

3i ortho-product: 1H NMR (400 MHz, CDCl3) δ: 7.15 (d, J = 7.6 Hz, 2H), 7.13-7.09 (m, 4H), 6.93-6.87 (m, 1H), 6.84 (d, J = 7.6 Hz, 1H), 6.39 (s, 1H), 5.27 (brs, 1H), 3.54 (s, 2H), 2.33 (s, 3H), 2.20 (t, J = 8.0 Hz, 2H), 1.53-1.44 (m, 2H), 1.30-1.19 (m, 6H), 0.85 (t, J = 7.0 Hz, 3H).

13C NMR (100 MHz, CDCl3) δ: 155.09, 141.60, 136.26, 131.23, 129.01, 128.64, 128.18, 127.19, 125.05, 120.92, 116.17, 39.62, 31.68, 30.62, 29.44, 28.22, 22.70, 21.28, 14.20.

IR (neat) cm⁻¹: 3398, 3021, 2926, 1706, 1604, 1488, 1456, 1377, 1243, 1182, 1096, 1020, 807, 752.
Table 2, entry 9:

}\[13C \delta: 132.25\]

[major, more polar]

\[13C \delta: 125.03\]

[minor, less polar]

The standard procedure was followed, except that 40 mol% of p-TsOH•H₂O was used.

HRMS-EI (m/z): [M]+ calc'd for C₂₂H₂₈O₂, 324.2084; found, 324.2080.

\[3l\]: ¹H NMR (400 MHz, CDCl₃) δ: 7.24-7.20 (m, 1H), 7.15 (d, J = 8.5 Hz, 2H), 6.82-6.74 (m, 5H), 6.25 (s, 1H), 4.78 (brs, 1H), 3.80 (s, 3H), 3.40 (s, 2H), 2.17 (t, J = 8.2 Hz, 2H), 1.55-1.40 (m, 2H), 1.30-1.23 (m, 6H), 0.86 (t, J = 7.1 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃) δ: 159.49, 154.01, 143.61, 139.92, 132.25, 130.34, 129.15, 126.79, 121.35, 115.37, 115.29, 114.18, 114.03, 112.03, 111.89, 55.30, 43.14, 31.79, 30.52, 29.54, 28.34, 22.74, 14.21.

IR (neat) cm⁻¹: 3357, 2916, 2850, 1703, 1575, 1510, 1453, 1367, 1257, 1152, 1072, 1040, 820, 781, 693.

Purified with 10% ethyl acetate in hexane.

\[3l\] ortho-product: ¹H NMR (400 MHz, CDCl₃) δ: 7.21-7.15 (m, 2H), 6.92-6.75 (m, 6H), 6.37 (s, 1H), 5.22 (brs, 1H), 3.80 (s, 3H), 3.54 (s, 2H), 2.22 (t, J = 8.1 Hz, 2H), 1.54-1.45 (m, 2H), 1.38-1.15 (m, 6H), 0.89-0.79 (m, 3H).

¹³C NMR (100 MHz, CDCl₃) δ: 159.54, 154.94, 142.54, 139.18, 131.25, 129.26, 128.20, 127.09, 125.03, 121.29, 120.96, 116.13, 114.14, 112.28, 55.32, 39.31, 31.72, 30.79, 29.48, 28.31, 22.71, 14.24, 14.20.

IR (neat) cm⁻¹: 3422, 2926, 2854, 1706, 1597, 1487, 1455, 1261, 1155, 1092, 1042, 873, 753, 696.
Table 2, entry 10:

The standard procedure was followed.

HRMS-EI (m/z): [M]+ calcd for C_{21}H_{26}O_{3}, 326.1876; found, 326.1864.

**major:** ^1^H NMR (400 MHz, CDCl$_3$) δ: 7.15 (d, $J = 8.4$ Hz, 2H), 6.86 (d, $J = 8.4$ Hz, 2H), 6.78 (d, $J = 8.8$ Hz, 1H), 6.72-6.69 (m, 2H), 6.34 (s, 1H), 4.92 (brs, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.49 (s, 2H), 2.22 (t, $J = 8.0$ Hz, 2H), 1.53-1.46 (m, 2H), 1.33-1.25 (m, 2H), 0.87 (t, $J = 7.2$ Hz, 3H).

^1^C NMR (100 MHz, CDCl$_3$) δ: 158.28, 153.78, 148.94, 140.59, 130.22, 129.91, 126.78, 126.30, 116.80, 116.76, 114.01, 113.72, 112.81, 55.86, 55.39, 39.80, 30.52, 30.39, 22.94, 14.07.

IR (neat) cm$^{-1}$: 3401, 2956, 2926, 2871, 1606, 1509, 1464, 1383, 1248, 1203, 1176, 1105, 1039, 808.

Purified with 10% ethyl acetate in hexane.

**minor:** ^1^H NMR (400 MHz, CDCl$_3$) δ: 7.20 (d, $J = 8.4$ Hz, 2H), 6.86 (d, $J = 8.4$ Hz, 2H), 6.74-6.62 (m, 3H), 6.53 (s, 1H), 4.65 (brs, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.58 (s, 2H), 2.09 (t, $J = 8.0$ Hz, 2H), 1.53-1.46 (m, 2H), 1.30-1.23 (m, 2H), 0.90 (t, $J = 7.2$ Hz, 3H).

Comparison with correlated compounds (^1^C NMR, CDCl$_3$)

<table>
<thead>
<tr>
<th>Compound</th>
<th>δ (75 MHz)</th>
<th>δ (50 MHz)</th>
<th>δ (75 MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>153.7, 149.2, 134.9, 126.3, 121.6, 116.7, 112.7, 55.9, 42.2, 15.8, 13.7</td>
<td>153.8, 147.9, 125.0, 116.7, 115.7, 112.0, 55.9, 16.2</td>
<td>151.8, 148.9, 128.0, 118.0, 112.6, 111.6, 56.1, 16.1</td>
</tr>
</tbody>
</table>


Table 2, entry 11:

![Chemical structure diagram]

The standard procedure was followed

HRMS-EI (m/z): [M]$^+$ calcd for C$_{21}$H$_{26}$O$_2$, 310.1927; found, 310.1934.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.15 (d, $J = 8.4$ Hz, 2H), 6.95-6.93 (m, 2H), 6.86 (d, $J = 8.4$ Hz, 2H), 6.74 (d, $J = 8.4$ Hz, 1H), 6.34 (s, 1H), 5.11 (brs, 1H), 3.81 (s, 3H), 3.49 (s, 2H), 2.28 (s, 3H), 2.22 (t, $J = 8.0$ Hz, 2H), 1.54-1.47 (m, 2H), 1.36-1.26 (m, 2H), 0.87 (t, $J = 7.3$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 158.25, 152.79, 140.92, 131.76, 130.30, 130.03, 129.91, 128.56, 126.57, 124.82, 115.97, 113.71, 55.38, 39.62, 30.49, 30.37, 22.93, 20.67, 14.06.

IR (neat) cm$^{-1}$: 3418, 2956, 2930, 1673, 1606, 1464, 1300, 1250, 1177, 1107, 1035, 937, 814.

Comparison with correlated compounds ([$^{13}$C NMR, 63 MHz, CDCl$_3$])

<table>
<thead>
<tr>
<th>Chemical Structure</th>
<th>$^{13}$C $\delta$: 123.54</th>
<th>$^{13}$C $\delta$: 129.91</th>
</tr>
</thead>
<tbody>
<tr>
<td>δ:</td>
<td>151.36, 131.61, 129.91, 127.34, 123.54, 114.79, 20.36, 15.64.</td>
<td>δ: 153.42, 137.95, 130.47, 128.64, 116.58, 112.34, 19.82, 18.72.</td>
</tr>
</tbody>
</table>
Table 2, entry 12:

\[
\begin{align*}
\text{C}^{\text{13}} \delta: & 126.72 \\
\text{OH} & \\
\text{MeO} & \\
\text{n-Bu} & \\
\text{Cl} & \\
\text{C}^{\text{13}} \delta: & 127.94
\end{align*}
\]

The standard procedure was followed.

HRMS-EI (m/z): [M]$^+$ calcd for \(\text{C}_{20}\text{H}_{23}\text{ClO}_2\), 330.1381; found, 330.1389.

\(^1\text{H}\) NMR (400 MHz, CDCl\(_3\)) \(\delta: 7.15\) (d, \(J = 8.4\) Hz, 2H), 7.13-7.10 (m, 2H), 6.87 (d, \(J = 8.4\) Hz, 2H), 6.77 (d, \(J = 8.0\) Hz, 1H), 6.35 (s, 1H), 5.31 (brs, 1H), 3.81 (s, 3H), 3.48 (s, 2H), 2.21 (t, \(J = 8.0\) Hz, 2H), 1.52-1.44 (m, 2H), 1.35-1.25 (m, 2H), 0.87 (t, \(J = 7.2\) Hz, 3H).

\(^{13}\text{C}\) NMR (100 MHz, CDCl\(_3\)) \(\delta: 153.59, 148.84, 141.50, 130.76, 130.18, 128.73, 128.36, 127.94, 127.75, 126.72, 121.57, 121.52, 117.40, 55.38, 39.11, 29.38, 28.22, 22.69, 14.19.

IR (neat) cm\(^{-1}\): 3345, 2919, 2850, 1484, 1267, 1189, 1092, 971, 832, 698.

Comparison with correlated compounds. \(^{13}\text{C}\) NMR (CDCl\(_3\)):

<table>
<thead>
<tr>
<th>Compound</th>
<th>(^{13}\text{C}) NMR (CDCl(_3))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(^{13}\text{C}) δ: 125.22, 125.73</td>
</tr>
<tr>
<td></td>
<td>125 MHz δ: 152.43, 130.65, 126.76, 125.73, 125.22, 116.04, 15.69.</td>
</tr>
<tr>
<td></td>
<td>(^{13}\text{C}) δ: 125.22, 126.72, 127.94, 128.73, 128.36, 127.75, 126.72, 121.57, 121.52, 117.40, 55.38, 39.11, 29.38, 28.22, 22.69, 14.19.</td>
</tr>
</tbody>
</table>
Table 2, entry13:

The standard procedure was followed.

HRMS-EI (m/z): [M]+ calcd for C_{20}H_{23}ClO_{2}, 330.1381; found, 330.1367.

**major:** $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.14-7.12 (m, 3H), 6.89 (d, $J$ = 2.8 Hz, 1H), 6.85 (d, $J$ = 8.4 Hz, 2H), 6.70 (dd, $J$ = 8.4, 2.8 Hz, 1H), 6.06 (s, 1H), 4.99 (brs, 1H), 3.80 (s, 3H), 3.49 (s, 2H), 2.18 (t, $J$ = 8.0 Hz, 2H), 1.54-1.46 (m, 2H), 1.37-1.25 (m, 2H), 0.88 (t, $J$ = 7.2 Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ: 157.96, 154.62, 140.40, 135.06, 131.88, 131.04, 129.96, 129.82, 126.40, 116.51, 114.18, 113.62, 55.39, 40.03, 30.79, 30.70, 23.02, 14.11.

IR (neat) cm$^{-1}$: 3362, 2957, 2926, 2855, 1703, 1601, 1511, 1466, 1384, 1252, 1175, 1033, 836.

Purified with 10% ethyl acetate in hexane.

**minor:** $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.15 (d, $J$ = 8.4 Hz, 2H), 7.06 (d, $J$ = 8.0 Hz, 1H), 6.91-6.77 (m, 4H), 6.36 (s, 1H), 5.40 (brs, 1H), 3.81 (s, 3H), 3.49 (s, 2H), 2.17 (t, $J$ = 8.0 Hz, 2H), 1.53-1.44 (m, 2H), 1.37-1.24 (m, 2H), 0.88 (t, $J$ = 7.2 Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ: 158.39, 155.75, 140.27, 133.15, 131.96, 130.58, 129.98, 129.90, 127.12, 123.73, 121.12, 121.02, 116.55, 116.04, 113.89, 113.78, 55.40, 39.19, 33.35, 31.74, 30.42, 30.28, 22.91, 22.81, 14.28, 14.04. IR (neat) cm$^{-1}$: 3400, 2956, 2928, 2858, 1702, 1607, 1577, 1509, 1497, 1465, 1441, 1294, 1249, 1177, 1039, 906, 856, 818.

Comparison with correlated compounds

$^{13}$C NMR (CDCl$_3$)

<table>
<thead>
<tr>
<th>Compound</th>
<th>$^{13}$C δ (MHz)</th>
<th>$^{13}$C δ (MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin, Y.-L.; Cheng, J.-Y.; Chu, Y.-H.</td>
<td>154.6, 135.8, 123.8, 131.2, 124.0, 121.0, 116.8, 116.1, 34.5.</td>
<td>156.3, 135.1, 130.6, 121.3, 116.1, 113.9.</td>
</tr>
<tr>
<td>Ilczszyn, M.; Latalka, Z.; Ratajczak, H.</td>
<td>154.6, 135.8, 123.8, 131.2, 124.0, 121.0, 116.8, 116.1, 34.5.</td>
<td>156.3, 135.1, 130.6, 121.3, 116.1, 113.9.</td>
</tr>
</tbody>
</table>

The carbon at ortho-position to OH, C(2), was more shielded than that to Cl, C(1). Other examples were shown below:
For the regioselective electrophilic aromatic substitution of 3-chlorophenol, see


![Chemical structure](image)

Yield of 1 = 82%

1 : 2 = 86 : 14


![Chemical structure](image)

Yield of 1 = 56%

1 : 2 = 64 : 36

Table 2, entry 14:

The standard procedure was followed, except that anisole was used instead of triphenylphosphite.

HRMS-EI (m/z): [M]$^+$ calcld for C$_{23}$H$_{30}$O$_2$, 338.2240; found, 338.2224.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.16 (d, $J = 8.4$ Hz, 2H), 7.15 (d, $J = 8.4$ Hz, 2H), 6.85 (d, $J = 8.4$ Hz, 2H), 6.84 (d, $J = 8.4$ Hz, 2H), 6.22 (s, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.40 (s, 2H), 2.15 (t, $J = 8.3$ Hz, 2H), 1.50-1.42 (m, 2H), 1.29-1.19 (m, 6H), 0.86 (t, $J = 7.1$ Hz, 3H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 157.88, 141.80, 132.11, 130.90, 129.90, 129.66, 126.06, 113.61, 113.41, 55.18, 43.00, 31.57, 30.17, 29.34, 28.07, 22.55, 14.03.

IR (neat) cm$^{-1}$: 2953, 2926, 2855, 1712, 1608, 1509, 1464, 1441, 1300, 1247, 1175, 1105, 1037, 824.
Other related informations in the preparation of allyl phenolic compounds, with the concomitant formation of a new C-aryl bond and a new trisubstituted olefin:

<table>
<thead>
<tr>
<th>Allyl Phenolic Targets</th>
<th>R¹= Ester</th>
<th>R²= Alkyl, Aryl</th>
</tr>
</thead>
<tbody>
<tr>
<td>e-deficient E-Olefin</td>
<td>ArOR</td>
<td>ArOR</td>
</tr>
</tbody>
</table>

The Selected Phenolic Substrates Acceptions

<table>
<thead>
<tr>
<th>Phenolic Substrates</th>
<th>Acetylated Baylis-Hillman Adducts</th>
<th>e.g. Silyl Allyl Ethers</th>
</tr>
</thead>
<tbody>
<tr>
<td>ArOR</td>
<td>ArylKBF₃</td>
<td>Both protected &amp; unproctected phenols</td>
</tr>
</tbody>
</table>


Summary on the inhibitory effect of the newly synthesized allyl diarylphosphonates on the metabolism of oseltamivir (O) to oseltamivir carboxylate (OC) in rat plasma

Experimental procedure
The inhibition experiment was modified from our previous study [Chang et al., Biomedical Chromatography, 2009, 23, 852.] and conducted as follow. To 200 µL rat plasma 2 µL of inhibitor working solution in DMSO was added (final 0.18, 0.4, 1, 4 or 10 µM in plasma) and well mixed. 10 µL of 100 µg/mL oseltamivir in H₂O was added, and the mixture was incubated at room temperature for 1 hour. After incubation, 50 µL of the sample mixture was acidified with 1 mL of 0.1% hydrochloric acid prior to solid phase extraction (Waters Oasis MCX cartridge, 30 mg). The detailed solid phase extraction procedure was reference to the previous study and was not produced here. Analytes were eluted with 1 mL of 1% ammonia in methanol and the solvent was evaporated to dryness by a vacuum concentrator. The residue was reconstituted in 150 µL mobile phase (0.1% formic acid : methanol, 1:1 v/v) and 20 µL supernatant were injected for LC-MS/MS analysis (data was acquired by multiple reaction monitoring of O and OC [Chang et al., Biomedical Chromatography, 2009]). Control samples were prepared by adding 2 µL DMSO (instead of inhibitor) to rat plasma.

Data treatment
The percentage inhibition was calculated as [\((\text{ratio}_{\text{control}} - \text{ratio}_{\text{inhibitor}}) / \text{ratio}_{\text{control}}\) x 100%, where ratio = Area ratio of OC to O. The % inhibition was then plotted against the logarithm of the concentration of inhibitor in µM. The logarithm of IC₅₀, the half maximal inhibitory concentration, was evaluated from the Sigmoidal dose-response equation using Prism program (version 3.03, GraphPad Software, Inc.).

Summary
Our newly synthesized allyl diarylphosphonates were first identified as potent carboxylesterase inhibitors with broad range of inhibitory efficiency (reflected by log IC₅₀ from -0.29 to 0.70, or IC₅₀ from 0.52 to 4.99 µM) and provided room for fine tuning when necessary. Those exhibit much stronger inhibitory effect than those of P(OPh)₃ and H-P(O)(OPh)₂ were quickly identified by using the new phosphonylation methodology developed here. The results obtained here provided us new directions for further optimization, and may lead to the development of a new generation of carboxylesterase inhibitors.
Results and discussion

a. Reference compounds

<table>
<thead>
<tr>
<th>Reference compound</th>
<th>LOG IC(_{50})</th>
<th>IC(_{50}) (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Calculated value</td>
<td>Standard error</td>
</tr>
<tr>
<td>P(OPh)(_3)</td>
<td>0.55</td>
<td>0.08</td>
</tr>
<tr>
<td>HP(O)(OPh)(_2)</td>
<td>0.97</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Note: The inhibitory effect of inhibitor on the metabolism of oseltamivir (O) to oseltamivir carboxylate (OC) was presented as Log IC\(_{50}\) or IC\(_{50}\). The lower the Log IC\(_{50}\) value indicates the lower concentration of inhibitor can be used to exhibit the inhibitory effect and thus the stronger inhibitor.

b. Allyl diarylphosphonates 2 and 2'

All the above six allyl diarylphosphonates 2 studied exhibits stronger inhibitory effect (log IC\(_{50}\) ranges from -0.26 to 0.23) than those of reference compounds (log IC\(_{50}\) between 0.55 to 0.97, section a). Among the allyl diarylphosphonates, that with R\(^1\) = n-Hex was found to be most potent inhibitor.

Remark: Bn = CH\(_2\)Ph

Several allyl diarylphosphonates with general structure of 2' were also examined, however, their inhibitory effects are much lower than those of 2 in general: e.g. for R\(^2\) = Cy and Ph, log IC\(_{50}\) are 0.70 and 0.57, respectively (with standard error: 0.02 and 0.07).
c. Effect of OMe in o-, m-, p-position of allyl diarylphosphonates 2 and amine substituent

\[
\text{MeO} - \bigg\downarrow \begin{array}{c}
\text{n-Hex} \\
\text{P(O)(OPh)₂}
\end{array}
\]

<table>
<thead>
<tr>
<th>Substituent</th>
<th>LOG IC\text{\textsubscript{50}}</th>
<th>IC\text{\textsubscript{50}} (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Calculated value</td>
<td>Standard error</td>
</tr>
<tr>
<td>p-OMe</td>
<td>-0.26</td>
<td>0.05</td>
</tr>
<tr>
<td>m-OMe</td>
<td>0.29</td>
<td>0.07</td>
</tr>
<tr>
<td>o-OMe</td>
<td>-0.29</td>
<td>0.10</td>
</tr>
<tr>
<td>p-,o-di OMe</td>
<td>-0.19</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Among the monosubstituted OMe compounds, o-OMe and p-OMe (log IC\text{\textsubscript{50}} of -0.29 and -0.26, respectively) exhibit stronger inhibition than m-OMe (log IC\text{\textsubscript{50}} of 0.29), but not much enhancement was observed for o-, p-disubstituted OMe.

In addition, allyl diarylphosphonate with amine substituent (log IC\text{\textsubscript{50}} of 0.46, standard error of 0.14, structure is shown below) lowers the inhibitory effect than those methoxy substituents.

![Structure of allyl diarylphosphonate with amine substituent](image)

\[
\text{Me, N} - \bigg\downarrow \begin{array}{c}
\text{n-Hex} \\
\text{P(O)(OPh)₂}
\end{array}
\]

d. α-branch

\[
\text{Me} - \bigg\downarrow \begin{array}{c}
\text{p-Anisyl} \\
\text{P(O)(OPh)₂}
\end{array}
\]

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>LOG IC\text{\textsubscript{50}}</th>
<th>IC\text{\textsubscript{50}} (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Calculated value</td>
<td>Standard error</td>
</tr>
<tr>
<td>2'n</td>
<td>-0.13</td>
<td>0.11</td>
</tr>
</tbody>
</table>
e. Effect of $R^4$

$$\text{MeO} \quad \text{P(O)(OR^4)_2} \quad \text{N-Hex}$$

<table>
<thead>
<tr>
<th>$R^4$</th>
<th>LOG IC$_{50}$</th>
<th>IC$_{50}$ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Calculated value</td>
<td>Standard error</td>
</tr>
<tr>
<td>$p$-C$_6$H$_4$Me</td>
<td>0.30</td>
<td>0.12</td>
</tr>
<tr>
<td>$p$-C$_6$H$_4$Cl</td>
<td>0.47</td>
<td>0.09</td>
</tr>
</tbody>
</table>

In both compounds, their inhibitory effect is weaker than those allyl diarylphosphonates 2 in section b (log IC$_{50}$ between -0.26 to 0.23).

f. Representative Sigmoidal dose-response curve of allyl diarylphosphonate inhibitor.

Reference: