Electronic Supplementary Information

An efficient and regioselective synthetic approach towards fluorinated quinolinylphosphonates

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General Remarks

All reagents from commercial suppliers were used without further purification. All solvents were freshly distilled before use from appropriate drying agents. All other reagents were recrystallized. Reactions were performed under atmosphere of dry argon. Analytical TLCs were performed with silica gel 60 F254 plates. Column chromatography was carried out using silica gel 60 (230–400 mesh ASTM). Melting points were determined without correction. NMR spectra were obtained on a spectrometer operating at 400 MHz for $^1$H (TMS), 376 MHz for $^{19}$F (CFC13), 161 MHz for $^{31}$P (H3PO4) and 100 MHz for $^{13}$C (TMS). All measurements were accomplished in the solution in CDCl3. Mass spectrometry was established on a MicroTOF-Q fitted with an ESI source.
Procedure for the Preparation of Imine Derivatives 2a-d.

To the mixture of a nitrobenzaldehyde and MgSO$_4$ in dry DCM a cyclohexylamine was added slowly. Then the suspension was refluxed for 4h, then cooled down to ambient temperature and filtered off the remained MgSO$_4$. The filtrate was next concentrated under reduced pressure to give pure imine derivative. Subsequently an imine was dissolved in ethanol and warmed up to 80 °C. To the hot solution solid Na$_2$S (hydrate) was slowly added. The solution was maintained for additional 20 min, cooled down to 0 °C and kept for 4h. Thus formed precipitate was filtered off and the solution concentrated under reduced pressure. To the crude product H$_2$O was added and a new drop of precipitate was formed, filtered off, washed with H$_2$O (3×100 mL) and dried to produce pure (2-(cyclohexylimino)-methyl)aniline derivatives.
1. 2-((cyclohexylimino)methyl)aniline 2a

![Chemical structure image]

Yellowish solid (90%), Mp = 45–48 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.35–1.82 (m, 10H), 3.10 (m, 1H), 6.40 (br s, 2H), 6.62 (d, \(J = 8.3\) Hz, 1H), 6.66 (td, \(J = 7.5\) Hz, \(J = 1.3\) Hz, 1H), 7.11 (td, \(J = 7.2\) Hz, \(J = 1.9\) Hz, 1H), 7.18 (dd, \(J = 7.7\) Hz, \(J = 1.9\) Hz, 1H), 8.35 (s, 1H); \(^{13}\)C NMR (100 MHz) \(\delta\) 24.7, 25.9, 35.0, 69.0, 115.4, 115.6, 118.0, 130.5, 133.3, 148.5, 161.5; HRMS (ESI): calcd for C\(_{13}\)H\(_{19}\)N\(_2\) [M+H]\(^+\) 203.1543, found 203.1543.
$^1$H NMR
$^{13}$C NMR
2. 4-chloro-2-((cyclohexylimino)methyl)aniline 2b

Yellowish solid (85%), Mp = 91–93 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.72–1.81 (m, 10H), 3.11 (m, 1H), 6.40 (br s, 2H), 6.57 (d, $J$ = 9.5 Hz, 1H), 7.05 (dd, $J$ = 9.5 Hz, $J$ = 1.9 Hz, 1H), 7.14 (d, $J$ = 1.9 Hz, 1H), 8.26 (s, 1H); $^{13}$C NMR (100 MHz) $\delta$ 24.6, 25.8, 34.9, 69.8, 116.8, 118.9, 120.3, 130.3, 132.3, 147.0, 160.2; HRMS (ESI): calcd for C$_{13}$H$_{18}$ClN$_2$ [M+H]$^+$ 237.1153, found 237.1146.
$^1$H NMR
$^{13}$C NMR
3. 2-((cyclohexylimino)methyl)-4,5-dimethoxyaniline 2c

![Structural formula of 2c](image)

Yellowish solid (85%); Mp = 134–137 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.25–1.81 (m, 10H), 3.06 (m, 1H), 2.80 (s, 2H), 3.84 (s, 3H), 6.19 (s, 1H), 6.24 (br s, 2H), 6.69 (s, 1H), 8.25 (s, 1H); $^{13}$C NMR (100 MHz) $\delta$ 24.7, 25.8, 35.1, 55.8, 56.8, 69.7, 99.4, 110.1, 116.2, 140.4, 144.3, 151.7, 160.4; HRMS (ESI) calcd for C$_{15}$H$_{23}$N$_2$O$_2$ [M+H]$^+$ 263.1754, found 263.1751.
$^1$H NMR
$^{13}$C NMR
4. 2-((cyclohexylimino)methyl)-5-(trifluoromethyl)aniline 2d.

Yellowish crystals (80%); Mp = 60–63 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.53–1.84 (m, 10H), 3.14 (m, 1H), 6.64 (br s, 2H), 6.84 (m, 2H), 7.27 (s, 1H), 8.38 (s, 1H); $^{13}$C NMR (100 MHz) $\delta$ 24.6, 25.7, 34.8, 69.9, 112.3, 120.1, 123.5 (q, $^1$J$_{C-F}$ = 275.1 Hz), 131.5 (q, $^2$J$_{C-F}$ = 30.5 Hz), 133.6, 148.4, 160.5; $^{19}$F NMR (376 MHz) $\delta$ –63.1; HRMS (ESI): calcd for C$_{14}$H$_{18}$F$_3$N$_2$ [M+H]$^+$ 271.1417, found 271.1412.
$^1$H NMR
$^{13}$C NMR
$^{19}$F NMR
General procedure for the preparation of CF₂-containing quinolinylphosphonates 4a-t

The mixture of 2-((cyclohexylimino)methyl)aniline derivative 2 (5 mmol) and K₂CO₃ (5 mmol) was dissolved in dry toluene (25 ml) at ambient temperature. To the reaction mixture an alkyne 3 (5 mmol) was charged slowly. The solution was warmed up to reflux and stirred for 10–12 hours. The K₂CO₃ was filtered off and the remained solution concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using DCM:EtOAc (5:1 ratio) as eluent.
1. Diethyl (2-(trifluoromethyl)quinolin-3-yl)phosphonate 4a

![Phosphonate Structure](image)

Yellowish oil (97%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.30 (t, $J = 7.1$ Hz, 6H), 4.15 (m, 4H), 7.67 (td, $J = 8.2$ Hz, $J = 1.1$ Hz, 1H), 7.85 (td, $J = 8.2$ Hz, $J = 1.3$ Hz, 1H), 7.92 (d, $J = 8.2$ Hz, 1H), 8.15 (dd, $J = 8.7$ Hz, $J = 0.7$ Hz, 1H), 9.09 (d, $^3$J$_{H,P} = 16.5$ Hz, 1H); $^{13}$C NMR (100 MHz) $\delta$ 16.1 (d, $J = 6.5$ Hz), 63.1 (d, $J = 5.9$ Hz), 119.8 (d, $^1$J$_{C,P} = 186.5$ Hz), 121.4 (q, $^1$J$_{C,F} = 275.7$ Hz), 127.1 (d, $^3$J$_{C,P} = 12.1$ Hz), 128.5, 129.6, 129.8, 132.9, 147.5 (qd, $^2$J$_{C,F} = 35.9$ Hz, $^2$J$_{C,P} = 8.4$ Hz), 147.6 (d, $^2$J$_{C,P} = 6.8$ Hz); $^{19}$F NMR (376 MHz) $\delta$ –63.8; $^{31}$P NMR (161 MHz) $\delta$ 13.6; HRMS (ESI): calcd for C$_{14}$H$_{16}$F$_3$NO$_3$P [M+H]$^+$ 334.0814, found 334.0812.
$^1$H NMR
$^{19}$F NMR
$^{31}$P NMR
2. Diethyl (6-chloro-2-(trifluoromethyl)quinolin-3-yl)phosphonate 4b

![Chemical structure](image)

Colourless oil (91%); 
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.34 (t, $J$ = 6.7 Hz, 6H), 4.16 (m, 2H), 4.24 (m, 2H), 7.84 (dd, $J$ = 8.6 Hz, $J$ = 2.4 Hz, 1H), 7.95 (d, $J$ = 2.7 Hz, 1H), 8.15 (d, $J$ = 8.9 Hz, 1H), 9.05 (d, $^3$J$_{H-P}$ = 16.1 Hz, 1H); 
$^{13}$C NMR (100 MHz) $\delta$ 16.2 (d, $J$ = 6.5 Hz), 63.3 (d, $J$ = 6.2 Hz), 121.5 (q, $^1$J$_{C-F}$ = 278.6 Hz), 121.8 (d, $^1$J$_{C-P}$ = 183.7 Hz), 127.1, 127.8 (d, $^2$J$_{C-P}$ = 11.5 Hz), 131.5, 133.9, 135.7 (d, $^4$J$_{C-P}$ = 1.8 Hz), 145.6, 146.6 (d, $^2$J$_{C-P}$ = 6.6 Hz), 147.2 (qd, $^2$J$_{C-F}$ = 36.2 Hz, $^2$J$_{C-P}$ = 7.8 Hz); 
$^{19}$F NMR (376 MHz) $\delta$ -63.8; 
$^{31}$P NMR (161 MHz) $\delta$ 12.9; 
HRMS (ESI): calcd for C$_{14}$H$_{14}$ClF$_3$NNaO$_3$P [M+Na]$^+$ 390.0244, found 390.0245.
$^1$H NMR
$^{19}$F NMR
$^{31}$P NMR
3. Diethyl (6,7-dimethoxy-2-(trifluoromethyl)quinolin-3-yl)phosphonate 4c

\[
\begin{align*}
\text{MeO} & \quad \text{N} \quad \text{CF}_3 \\
\text{MeO} & \quad \text{P} \quad \text{(O)(OEt)}_2 \\
\end{align*}
\]

Yellowish crystals (80%); Mp = 186–190 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.33 (t, \(J = 7.2\) Hz, 6H), 4.02 (s, 3H), 4.05 (s, 3H), 4.13 (m, 2H), 4.23 (m, 2H), 7.16 (s, 1H), 7.51 (s, 1H), 8.93 (d, \(^3\)J\(_{H-P}\) = 16.2 Hz, 1H); \(^13\)C NMR (100 MHz) \(\delta\) 16.2 (d, \(J = 6.4\) Hz), 56.4, 56.6, 62.9 (d, \(J = 6.1\) Hz), 105.3, 108.2, 117.4 (d, \(^1\)J\(_{C-P}\) = 186.7 Hz), 117.4 (q, \(^1\)J\(_{C-F}\) = 275.8 Hz), 123.5 (d, \(^3\)J\(_{C-P}\) = 11.1 Hz), 144.8 (d, \(^2\)J\(_{C-P}\) = 7.4 Hz), 145.1 (qd, \(^2\)J\(_{C-F}\) = 35.4 Hz, \(^2\)J\(_{C-P}\) = 8.7 Hz), 152.2, 155.4; \(^19\)F NMR (376 MHz) \(\delta\) –63.3; \(^31\)P NMR (161 MHz) \(\delta\) 14.7 Hz; HRMS (ESI): calcd for C\(_{16}\)H\(_{19}\)F\(_3\)NNaO\(_3\)P [M+Na]\(^+\) 416.0845, found 416.0858.
$^1$H NMR
\(^{19}\text{F} \text{NMR}\)
$^{31}$P NMR
**X-Ray crystallography:**

A block-shaped single crystal of 3j with dimensions 0.18 mm x 0.18 mm x 0.45 mm was mounted on a Hampton cryo-loop for indexing and intensity data collection at 100° K on a Bruker APEX II CCD using Mo-Kα radiation ($\lambda = 0.71073$ Å). Lorentz and polarization corrections were applied, and an absorption correction was performed using the SADABS program. [G. M. Sheldrick, SADABS, Program for empirical X-ray absorption correction, Bruker-Nonius, 1990]

Direct methods were used for structure solution of all structures (SHELXS-97). Structural refinement was obtained from successive Fourier maps (SHELXL-97). [G. M. Sheldrick, Acta Crystallogr. 2007, A64, 112-122.] All heavy atoms (C, N, O, Br, P, F) were refined anisotropically whereas the hydrogen atoms were found through calculated constrained positions. The crystallographic data for are summarized in Table S1.
**Table S1.** Crystal data for 4c.

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<th>Value</th>
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<td>(b), Å</td>
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<td>Independent reflections</td>
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<td>--------------------------</td>
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</tr>
<tr>
<td>wR₂ (all data)</td>
<td>0.1118</td>
</tr>
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</table>

\[ a \quad R = \frac{\sum |F_o| - |F_c|}{\sum |F_o|}. \quad b \quad wR = \frac{\sum w(F_o^2 - F_c^2)^2}{\sum w(F_o^2)^2}^{1/2}. \]
4. Diethyl (2,7-bis(trifluoromethyl)quinolin-3-yl)phosphonate 4d

Yellowish oil (99%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.36 (t, $J = 6.9$ Hz, 6H), 4.18 (m, 2H), 4.28 (m, 2H), 7.91 (d, $J = 8.6$ Hz, 1H), 8.13 (d, $J = 8.6$ Hz, 1H), 8.56 (s, 1H), 9.24 (d, $^3$J$_{H-P}$ = 16.5 Hz, 1H); $^{13}$C NMR (100 MHz) $\delta$ 16.2 (d, $J = 6.4$ Hz), 63.4 (d, $J = 6.1$ Hz), 120.8 (q, $^1$J$_{C-F}$ = 276.5 Hz), 122.2 (d, $^1$J$_{C-P}$ = 185.5 Hz), 123.2 (q, $^1$J$_{C-F}$ = 270.8 Hz), 125.8 (qd, $^4$J$_{C-F}$ = 3.2 Hz, $^4$J$_{C-P}$ = 1.2 Hz), 127.8 (qd, $^4$J$_{C-F}$ = 4.2 Hz, $^4$J$_{C-P}$ = 1.3 Hz), 128.5 (dq, $^3$J$_{C-P}$ = 11.9 Hz, $^5$J$_{C-F}$ = 1.1 Hz), 129.8, 134.5 (q, $^2$J$_{C-F}$ = 33.6 Hz), 146.2, 147.7 (d, $^2$J$_{C-P}$ = 6.8 Hz), 148.6 (qd, $^2$J$_{C-F}$ = 35.8 Hz, $^2$J$_{C-P}$ = 8.9 Hz); $^{19}$F NMR (376 MHz) $\delta$ –63.0 (s, –CF$_3$), –64.0 (s, –CF$_3$); $^{31}$P NMR (161 MHz) $\delta$ 12.5; HRMS (ESI): calcd for C$_{13}$H$_{14}$F$_6$NNaO$_3$P [M+Na]$^+$ 424.0508, found 424.0508.
$^1$H NMR
$^{13}$C NMR
$^{19}$F NMR
$^{31}$P NMR
5. Diethyl (2-(chlorodifluoromethyl)quinolin-3-yl)phosphonate 4e

![Phosphonate Structure]

Yellowish oil (90%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.34 (t, $J$ = 7.0 Hz, 6H), 4.15 (m, 2H), 4.22 (m, 2H), 7.69 (td, $J$ = 8.1 Hz, $J$ = 1.1 Hz, 1H), 7.87 (tt, $J$ = 6.9 Hz, $J$ = 1.4 Hz, 1H), 7.94 (d, $J$ = 8.1 Hz, 1H), 8.18 (d, $J$ = 8.6 Hz, 1H), 9.13 (d, $^3$J$_{H-P}$ = 16.4 Hz, 1H); $^{13}$C NMR (161 MHz) $\delta$ 16.3 (d, $J$ = 6.7 Hz), 63.1 (d, $J$ = 6.2 Hz), 118.5 (d, $^1$J$_{C-P}$ = 186.7 Hz), 124.1 (t, $^1$J$_{C-F}$ = 294.2 Hz), 126.8 (d, $^3$J$_{C-P}$ = 11.7 Hz), 128.5, 129.5 (d, $^5$J$_{C-P}$ = 1.2 Hz), 129.8 (d, $^4$J$_{C-P}$ = 1.5 Hz), 133.0, 147.2 (dt, $^4$J$_{C-P}$ = 1.4 Hz, $^4$J$_{C-F}$ = 0.9 Hz), 147.8 (d, $^2$J$_{C-P}$ = 7.2 Hz), 151.3 (td, $^2$J$_{C-F}$ = 29.7 Hz, $^2$J$_{C-P}$ = 8.7 Hz); $^{19}$F NMR (376 MHz) $\delta$ -51.9; $^{31}$P NMR (161 MHz) $\delta$ 13.9; HRMS (ESI): calcd for C$_{14}$H$_{15}$ClF$_2$NNaO$_3$P [M+Na]$^+$ 372.0338, found 372.0323.
$^{13}$C NMR
$^{19}$F NMR
$^{31}$P NMR
6. Diethyl (6-chloro-2-(chlorodifluoromethyl)quinolin-3-yl)phosphonate 4f

![Chemical Structure](image)

Colourless crystals (81%); Mp = 74–77 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.35 (t, \(J = 6.9\) Hz, 6H), 4.16 (m, 2H), 4.22 (m, 2H), 7.82 (dd, \(J = 9.1\) Hz, \(J = 2.2\) Hz, 1H), 7.94 (d, \(J = 2.1\) Hz, 1H), 8.14 (d, \(J = 8.8\) Hz, 1H), 9.05 (d, \(^3\)J\(_{H-P}\) = 16.3 Hz, 1H); \(^13\)C NMR (100 MHz) \(\delta\) 16.3 (d, \(J = 6.5\) Hz), 63.3 (d, \(J = 6.3\) Hz), 119.8 (d, \(^1\)J\(_{C-P}\) = 186.7 Hz), 123.9 (td, \(^1\)J\(_{C-F}\) = 293.0 Hz, \(^3\)J\(_{C-P}\) = 2.1 Hz), 127.1, 127.5 (d, \(^3\)J\(_{C-P}\) = 12.5 Hz), 131.5 (d, \(^4\)J\(_{C-P}\) = 1.9 Hz), 133.9, 135.6 (d, \(^5\)J\(_{C-P}\) = 1.5 Hz), 145.5 (dt, \(^4\)J\(_{C-P}\) = 1.3 Hz, \(^4\)J\(_{C-F}\) = 0.9 Hz), 146.7 (d, \(^2\)J\(_{C-P}\) = 7.1 Hz), 151.7 (td, \(^2\)J\(_{C-F}\) = 30.1 Hz, \(^2\)J\(_{C-P}\) = 8.6 Hz); \(^19\)F NMR (376 MHz) \(\delta\) –52.1; \(^31\)P NMR (161 MHz) \(\delta\) 13.3; HRMS (ESI): calcd for C\(_{14}\)H\(_{14}\)Cl\(_2\)F\(_2\)NNaO\(_3\)P [M+Na]\(^+\) 405.9949, found 405.9955.
$^1$H NMR
$^{19}\text{F} \text{NMR}$
$^{31}$P NMR
7. Diethyl (2-(chlorodifluoromethyl)-6,7-dimethoxyquinolin-3-yl)phosphonate 4g

![Chemical structure image]

Colourless crystals (71%); Mp = 160–165 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.32 (t, \(J = 7.0\) Hz, 6H), 4.00 (s, 3H), 4.02 (s, 3H), 4.12 (m, 2H), 4.21 (m, 2H), 7.13 (s, 1H), 7.47 (s, 1H), 8.89 (d, \(3J_{H-P} = 15.2\) Hz, 1H); \(^{13}\)C NMR (100 MHz) \(\delta\) 16.2 (d, \(J = 6.8\) Hz), 56.3, 56.6, 62.9 (d, \(J = 6.1\) Hz), 105.3, 108.0, 116.5 (d, \(1J_{C-P} = 187.4\) Hz), 123.2 (d, \(3J_{C-P} = 11.8\) Hz), 124.3 (td, \(1J_{C-F} = 293.5\) Hz, \(3J_{C-P} = 3.6\) Hz), 144.9 (d, \(2J_{C-P} = 7.2\) Hz), 149.6 (td, \(2J_{C-F} = 29.5\) Hz, \(2J_{C-P} = 7.3\) Hz), 152.1, 155.3; \(^{19}\)F NMR (376 MHz) \(\delta\) –51.3; \(^{31}\)P NMR (161 MHz) \(\delta\) 14.9; HRMS (ESI): calcd for C\(_{16}\)H\(_{19}\)ClF\(_2\)NNaO\(_3\)P [M+Na]\(^+\) 432.0550, found 432.0558.
$^1$H NMR
$^{13}$C NMR
$^{19}$F NMR
$^{31}$P NMR
$^{13}$C-$^1$H NMR – HETCOR
8. Diethyl (2-(chlorodifluoromethyl)-7-(trifluoromethyl)quinolin-3-yl)phosphonate 4h

![Structural formula]

Colourless oil (94%); $^1$H NMR (400 MHz, CDCl$_3$) δ 1.37 (t, $J = 7.1$ Hz, 6H), 4.18 (m, 2H), 4.28 (m, 2H), 7.90 (dd, $J = 8.5$ Hz, $J = 1.6$ Hz, 1H), 8.12 (d, $J = 8.5$ Hz, 1H), 8.55 (q, $^4$J$_{H,F}$ = 0.9 Hz, 1H), 9.24 (d, $^3$J$_{H,P}$ = 16.3 Hz, 1H); $^{13}$C NMR (100 MHz) δ 16.3 (d, $J = 6.5$ Hz), 63.4 (d, $J = 6.2$ Hz), 121.2 (d, $^1$J$_{C,F}$ = 184.4 Hz), 123.4 (q, $^1$J$_{C,F}$ = 274.3 Hz), 123.8 (td, $^1$J$_{C,F}$ = 293.2 Hz, $^3$J$_{C,P}$ = 1.1 Hz), 125.2 (qd, $^4$J$_{C,F}$ = 3.2 Hz, $^4$J$_{C,P}$ = 1.2 Hz), 127.7 (qd, $^4$J$_{C,F}$ = 4.3 Hz, $^4$J$_{C,P}$ = 1.4 Hz), 128.3 (d, $^3$J$_{C,F}$ = 11.6 Hz), 129.8, 134.5 (q, $^2$J$_{C,F}$ = 33.4 Hz), 146.3, 147.8 (d, $^2$J$_{C,F}$ = 6.9 Hz), 152.8 (td, $^2$J$_{C,F}$ = 30.6 Hz, $^2$J$_{C,P}$ = 8.2 Hz); $^{19}$F NMR (376 MHz) δ −52.4 (s, −CF$_2$Cl), −63.0 (s, −CF$_3$); $^{31}$P NMR (161 MHz) δ 12.9; HRMS (ESI): calcd for C$_{15}$H$_{14}$ClF$_3$NNaO$_3$P [M+Na]$^+$ 440.0212, found 440.0217.
$^{13}$C NMR
$^{19}$F NMR
$^{31}\text{P NMR}$
9. Diethyl (2-(bromodifluoromethyl)quinolin-3-yl)phosphonate 4i

\[
\begin{array}{c}
\text{P(O)(OEt)}_2 \\
\text{CF}_2\text{Br}
\end{array}
\]

Brownish oil (88%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.34 (t, \(J = 7.2\) Hz, 6H), 4.15 (m, 2H), 4.23 (m, 2H), 7.67 (td, \(J = 7.9\) Hz, \(J = 0.9\) Hz, 1H), 7.85 (td, \(J = 6.9\) Hz, \(J = 1.4\) Hz, 1H), 7.92 (d, \(J = 8.1\) Hz, 1H), 8.16 (d, \(J = 8.3\) Hz, 1H), 9.09 (d, \(^3\)J\(_{H-P}\) = 16.4 Hz, 1H); \(^{13}\)C NMR (100 MHz) \(\delta\) 16.3 (d, \(J = 6.2\) Hz), 63.1 (d, \(J = 6.2\) Hz), 116.5 (td, \(^1\)J\(_{C-F}\) = 306.9 Hz, \(^3\)J\(_{C-P}\) = 1.4 Hz), 118.5 (d, \(^1\)J\(_{C-P}\) = 186.2 Hz), 126.8 (d, \(^3\)J\(_{C-P}\) = 11.5 Hz), 128.5, 129.5 (d, \(^5\)J\(_{C-P}\) = 1.0 Hz), 129.8 (d, \(^4\)J\(_{C-P}\) = 1.5 Hz), 133.0, 147.2 (dt, \(^4\)J\(_{C-P}\) = 1.4 Hz, \(^4\)J\(_{C-F}\) = 0.9 Hz), 147.8 (d, \(^2\)J\(_{C-P}\) = 6.7 Hz), 152.5 (td, \(^2\)J\(_{C-F}\) = 26.8 Hz, \(^2\)J\(_{C-P}\) = 8.3 Hz); \(^{19}\)F NMR (376 MHz) \(\delta\) –47.5; \(^{31}\)P NMR (161 MHz) \(\delta\) 14.0 (t, \(^4\)J\(_{P-F}\) = 0.9 Hz); HRMS (ESI): calcd for C\(_{14}\)H\(_{18}\)BrF\(_2\)NO\(_3\)P [M+H]\(^+\) 394.0014, found 394.0017.
$^1$H NMR
$^{13}C$ NMR
$^{19}$F NMR
$^{31}$P NMR
10. Diethyl (2-(bromodifluoromethyl)-6-chloroquinolin-3-yl)phosphonate 4j

Orange crystals (80%); Mp = 118–121 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.37 (t, $J = 7.0$ Hz, 6H), 4.17 (m, 2H), 4.26 (m, 2H), 7.82 (dd, $J = 8.9$ Hz, $J = 2.2$ Hz, 1H), 7.94 (d, $J = 2.2$ Hz, 1H), 8.15 (d, $J = 9.0$ Hz, 1H), 9.04 (d, $^3J_{H,P} = 16.3$ Hz, 1H); $^{13}$C NMR (100 MHz) $\delta$ 16.4 (d, $J = 6.6$ Hz), 63.3 (d, $J = 6.2$ Hz), 116.3 (td, $^1J_{C,F} = 308.9$ Hz, $^3J_{C,P} = 0.9$ Hz), 119.8 (d, $^1J_{C,P} = 185.6$ Hz), 127.1, 127.5 (d, $^3J_{C,P} = 11.9$ Hz), 131.4 (d, $^4J_{C,P} = 1.9$ Hz), 134.0, 135.6 (d, $^5J_{C,P} = 1.7$ Hz), 145.5, 146.8 (d, $^2J_{C,P} = 7.3$ Hz), 152.9 (td, $^2J_{C,F} = 27.4$ Hz, $^2J_{C,P} = 8.7$ Hz); $^{19}$F NMR (376 MHz) $\delta$ –47.8; $^{31}$P NMR (161 MHz) $\delta$ 13.3; HRMS (ESI): calcd for C$_{14}$H$_{14}$BrClF$_2$NNaO$_3$P [M+Na]$^+$ 449.9443, found 449.9442.
$^1$H NMR
$^{13}$C NMR
$^{19}$F NMR
$^{31}$P NMR
11. Diethyl (2-(bromodifluoromethyl)-6,7-dimethoxyquinolin-3-yl)phosphonate 4k

Yellow crystals (71%); Mp = 155–160 °C; \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.32 (t, \(J = 7.1\) Hz, 6H), 3.99 (s, 3H), 4.01 (s, 3H), 4.12 (m, 2H), 4.22 (m, 2H), 7.12 (s, 1H), 7.45 (s, 1H), 8.87 (d, \(^3^J_{H-P} = 16.0\) Hz, 1H); \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 163 (d, \(J = 6.6\) Hz), 56.4, 56.6, 62.9 (d, \(J = 6.0\) Hz), 105.3, 107.9, 115.9 (d, \(^1^J_{C-P} = 187.7\) Hz), 116.9 (t, \(^1^J_{C-F} = 306.3\) Hz), 123.1 (d, \(^3^J_{C-P} = 10.7\) Hz), 144.8 (d, \(^2^J_{C-P} = 7.8\) Hz), 150.9 (td, \(^2^J_{C-F} = 26.5\) Hz, \(^2^J_{C-P} = 8.6\) Hz), 152.1, 155.4; \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) –46.8; \(^3^P\) NMR (161 MHz) \(\delta\) 15.0; HRMS (ESI): calcd for C\(_{16}^{}\)H\(_{20}^{}\)BrF\(_2^{}\)NO\(_3^{}\)P [M+H]\(^+\) 454.0225, found 454.0221.
$^1$H NMR

[Graphical representation of an NMR spectrum showing various chemical shifts and peak intensities.]
$^{13}$C NMR
$^{19}\text{F NMR}$
$^{31}$P NMR
12. Diethyl (2-(bromodifluoromethyl)-7-(trifluoromethyl)quinolin-3-yl)phosphonate 4l

Brownish oil (93%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.39 (t, $J$ = 7.0 Hz, 6H), 4.20 (m, 2H), 4.30 (m, 2H), 7.90 (dd, $J$ = 8.3 Hz, $J$ = 1.9 Hz, 1H), 8.13 (d, $J$ = 8.6 Hz, 1H), 8.55 (q, $^4$J$_{H-F}$ = 0.7 Hz, 1H), 9.23 (d, $^3$J$_{H-P}$ = 16.3 Hz, 1H); $^{13}$C NMR (100 MHz) $\delta$ 16.3 (d, $J$ = 6.2 Hz), 63.4 (d, $J$ = 5.9 Hz), 116.1 (t, $^1$J$_{C-F}$ = 305.9 Hz), 120.8 (d, $^1$J$_{C-P}$ = 183.6 Hz), 123.6 (q, $^1$J$_{C-P}$ = 275.7 Hz), 125.1 (qd, $^4$J$_{C-F}$ = 2.8 Hz, $^4$J$_{C-P}$ = 1.3 Hz), 127.7 (qd, $^4$J$_{C-F}$ = 4.3 Hz, $^4$J$_{C-P}$ = 1.3 Hz), 128.2 (d, $^3$J$_{C-P}$ = 10.7 Hz), 129.8, 134.6 (q, $^2$J$_{C-F}$ = 32.9 Hz), 146.3, 147.8 (d, $^2$J$_{C-P}$ = 6.5 Hz), 154.0 (td, $^2$J$_{C-F}$ = 27.6 Hz, $^2$J$_{C-P}$ = 8.7 Hz); $^{19}$F NMR (376 MHz) $\delta$ –48.3 (s, –CF$_2$Br), –63.0 (s, –CF$_3$); $^{31}$P NMR (161 MHz) $\delta$ 12.9; HRMS (ESI): calcd for C$_{15}$H$_{14}$BrF$_3$NNaO$_3$P [M+Na]$^+$ 483.9713, found 483.9712.
$^1$H NMR
$^{13}$C NMR
$^{19}$F NMR
$^{31}$P NMR
13. Diethyl (2-(difluoromethyl)quinolin-3-yl)phosphonate 4m

![Structure of 4m](image)

Colourless oil (60%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.32 (t, $J = 7.1$ Hz, 6H), 4.12 (m, 2H), 4.22 (m, 2H), 7.31 (t, $^2$J$_{H-F} = 53.7$ Hz, 1H), 7.67 (td, $J = 7.5$ Hz, $J = 0.7$ Hz, 1H), 7.86 (td, $J = 8.3$ Hz, $J = 1.2$ Hz, 1H), 7.92 (d, $J = 7.5$ Hz, 1H), 8.24 (d, $J = 8.3$ Hz, 1H), 8.90 (d, $^3$J$_{H-P} = 15.4$ Hz, 1H); $^{13}$C NMR (100 MHz) $\delta$ 16.3 (d, $J = 6.4$ Hz), 63.2 (d, $J = 5.8$ Hz), 110.9 (t, $^1$J$_{C-F} = 242.1$ Hz), 120.1 (dt, $^1$J$_{C-P} = 184.1$ Hz, $^3$J$_{C-F} = 2.8$ Hz), 127.0 (dt, $^3$J$_{C-P} = 11.9$ Hz, $^5$J$_{C-F} = 1.4$ Hz), 128.5, 129.0, 130.1 (d, $^4$J$_{C-P} = 1.2$ Hz), 132.7, 145.4 (d, $^2$J$_{C-P} = 7.5$ Hz), 148.5, 151.4 (td, $^2$J$_{C-F} = 21.7$ Hz, $^2$J$_{C-P} = 11.3$ Hz); $^{19}$F NMR (376 MHz) $\delta$ –115.7 (d, $^2$J$_{F-H} = 53.9$ Hz); $^{31}$P NMR (161 MHz) $\delta$ 15.0 (t, $^4$J$_{P-F} = 1.2$ Hz); HRMS (ESI): calcd for C$_{14}$H$_{17}$F$_2$NO$_3$P [M+H]$^+$ 316.0909, found 316.0912.
$^1$H NMR
$^{13}$C NMR
$^{19}$F NMR
$^{31}$P NMR
14. Diethyl (6-chloro-2-(difluoromethyl)quinolin-3-yl) phosphonate 4n

![Structure of diethyl (6-chloro-2-(difluoromethyl)quinolin-3-yl) phosphonate 4n](image)

Colourless oil (54%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.35 (t, $J = 7.2$ Hz, 6H), 4.14 (m, 2H), 4.25 (m, 2H), 7.31 (t, $^2$J$_{H-F} = 53.8$ Hz, 1H), 7.82 (dd, $J = 8.9$ Hz, $J = 2.4$ Hz, 1H), 7.93 (d, $J = 2.4$ Hz, 1H), 8.23 (d, $J = 9.3$ Hz, 1H), 8.82 (d, $^3$J$_{H-P} = 15.8$ Hz, 1H); $^{13}$C NMR (100 MHz) $\delta$ 16.3 (d, $J = 6.2$ Hz), 63.3 (d, $J = 5.6$ Hz), 110.7 (t, $^1$J$_{C-F} = 242.5$ Hz), 121.3 (dt, $^1$J$_{C-P} = 183.7$ Hz, $^3$J$_{C-F} = 3.3$ Hz), 127.1, 127.6 (dt, $^3$J$_{C-P} = 12.5$ Hz, $^5$J$_{C-F} = 1.5$ Hz), 131.7 (d, $^4$J$_{C-P} = 1.4$ Hz), 133.7, 135.1 (d, $^5$J$_{C-P} = 1.8$ Hz), 144.3 (d, $^2$J$_{C-P} = 7.1$ Hz), 146.9, 151.8 (td, $^2$J$_{C-F} = 21.8$ Hz, $^2$J$_{C-P} = 10.8$ Hz); $^{19}$F NMR (376 MHz) $\delta$ −115.8 (d, $^2$J$_{F-H} = 53.4$ Hz); $^{31}$P NMR (161 MHz) $\delta$ 14.3; HRMS (ESI): calcd for C$_{14}$H$_{15}$ClF$_2$NNaO$_3$P [M+Na]$^+$ 372.0338, found 372.0344.
$^1$H NMR
\(^{13}\)C NMR
\(^{19}\)F NMR
$^{31}$P NMR
15. Diethyl (2-(difluoromethyl)-6,7-dimethoxyquinolin-3-yl)phosphonate 40

Yellowish crystals (42%); Mp = 169–173 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.33 (t, $J = 7.1$ Hz, 6H), 4.02 (s, 3H), 4.04 (s, 3H) 4.09 (m, 2H), 4.18 (m, 2H), 7.12 (s, 1H), 7.29 (t, $^2$J$_{H-F}$ = 54.0 Hz, 1H), 7.56 (s, 1H), 8.69 (d, $^3$J$_{H-P}$ = 14.9 Hz, 1H); $^{13}$C NMR (100 MHz) $\delta$ 16.3 (d, $J = 6.4$ Hz), 56.4, 56.6, 62.9 (d, $J = 5.3$ Hz), 105.4, 108.3, 110.8 (t, $^1$J$_{C-F}$ = 239.6 Hz), 117.9 (dt, $^1$J$_{C-P}$ = 184.9 Hz, $^3$J$_{C-F}$ = 3.4 Hz), 123.3 (dt, $^3$J$_{C-P}$ = 11.7 Hz, $^5$J$_{C-F}$ = 0.8 Hz), 142.4 (d, $^2$J$_{C-P}$ = 6.6 Hz), 146.9, 149.7 (dt, $^2$J$_{C-F}$ = 20.6 Hz, $^2$J$_{C-P}$ = 11.2 Hz), 151.7, 155.2; $^{19}$F NMR (376 MHz) $\delta$ –115.2 (d, $^2$J$_{F-H}$ = 50.5 Hz); $^{31}$P NMR (161 MHz) $\delta$ 14.3 (t, $^4$J$_{P-F}$ = 1.3 Hz); HRMS (ESI): calcd for C$_{16}$H$_{20}$F$_2$NNaO$_3$P [M+Na]$^+$ 398.0939, found 398.0949.
$^1$H NMR
\(^{13}\)C NMR
$^{19}$F NMR
$^{31}$P NMR
16. Diethyl (2-(difluoromethyl)-7-(trifluoromethyl)quinolin-3-yl)phosphonate 4p

![Chemical Structure]

Brownish oil (69%); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.37 (t, \(J = 7.0\) Hz, 6H), 4.17 (m, 2H), 4.27 (m, 2H), 7.33 (t, \(^2\)J\(_{H,F}\) = 53.3 Hz, 1H), 7.89 (dd, \(J = 8.5\) Hz, \(J = 1.7\) Hz, 1H), 8.11 (d, \(J = 8.4\) Hz, 1H), 8.62 (s, 1H), 9.00 (d, \(^3\)J\(_{H,P}\) = 15.7 Hz, 1H); \(^13\)C NMR (100 MHz) \(\delta\) 16.4 (d, \(J = 6.3\) Hz), 63.5 (d, \(J = 5.8\) Hz), 110.6 (td, \(^1\)J\(_{C,F}\) = 242.0 Hz, \(^3\)J\(_{C,P}\) = 2.0 Hz), 122.6 (dt, \(^1\)J\(_{C-P}\) = 183.1 Hz, \(^3\)J\(_{C,F}\) = 3.1 Hz), 123.4 (q, \(^1\)J\(_{C,F}\) = 271.9 Hz), 124.7 (qd, \(^4\)J\(_{C,F}\) = 2.1 Hz, \(^4\)J\(_{C-P}\) = 1.0 Hz), 127.9 (qd, \(^4\)J\(_{C,F}\) = 3.8 Hz, \(^4\)J\(_{C-P}\) = 0.9 Hz), 128.5 (d, \(^3\)J\(_{C-P}\) = 12.5 Hz), 129.9, 134.3 (q, \(^2\)J\(_{C,F}\) = 32.6 Hz), 147.8 (d, \(^2\)J\(_{C-P}\) = 7.9 Hz), 147.6, 153.1 (td, \(^2\)J\(_{C,F}\) = 23.2 Hz, \(^2\)J\(_{C-P}\) = 11.6 Hz); \(^19\)F NMR (376 MHz) \(\delta\) –63.0 (s, –CF\(_3\)), –116.0 (d, \(^2\)J\(_{F,H}\) = 52.6 Hz, –CF\(_2\)H); \(^31\)P NMR (161 MHz) \(\delta\) 13.8; HRMS (ESI): calcd for C\(_{15}\)H\(_{16}\)F\(_2\)NO\(_3\)P [M+H]\(^+\) 384.0782, found 384.0784.
$^1$H NMR
$^{13}$C NMR
$^{19}$F NMR
$^{31}$P NMR
17. Diethyl (2-(perfluoroethyl)quinolin-3-yl)phosphonate 4q

![Chemical structure of 4q]

Yellowish oil (65%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.35 (t, $J = 7.0$ Hz, 6H), 4.15 (m, 2H), 4.25 (m, 2H), 7.74 (t, $J = 7.5$ Hz, 1H), 7.91 (td, $J = 7.2$ Hz, $J = 1.3$ Hz, 1H), 7.98 (d, $J = 8.4$ Hz, 1H), 8.19 (d, $J = 8.4$ Hz, 1H), 9.20 (d, $^3 J_{H,P} = 16.5$ Hz, 1H); $^{13}$C NMR (100 MHz) $\delta$ 16.2 (d, $J = 6.5$ Hz), 63.1 (d, $J = 6.2$ Hz), 112.0 (qt, $^1 J_{C,F} = 258.8$ Hz, $^2 J_{C,F} = 34.1$ Hz), 119.0 (qt, $^1 J_{C,F} = 289.5$ Hz, $^2 J_{C,F} = 35.6$ Hz), 120.7 (d, $^1 J_{C,P} = 186.1$ Hz), 126.7 (d, $^3 J_{C,P} = 11.4$ Hz), 128.6, 129.8, 130.0 (d, $^4 J_{C,P} = 1.1$ Hz), 132.9, 146.8 (dt, $^4 J_{C,P} = 1.4$ Hz, $^4 J_{C,F} = 0.9$ Hz), 147.5 (td, $^2 J_{C,F} = 28.9$ Hz, $^2 J_{C,P} = 7.9$ Hz), 147.9 (d, $^2 J_{C,P} = 7.2$ Hz); $^{19}$F NMR (376 MHz) $\delta$ -79.9 (s, $-CF_2CF_3$), -108.1 (s, $-CF_2CF_3$); $^{31}$P NMR (161 MHz) $\delta$ 14.1; HRMS (ESI): calcd for C$_{15}$H$_{16}$F$_5$NO$_3$P [M+H]$^+$ 384.0782, found 384.0784.
$^1$H NMR
$^{13}$C NMR
$^{19}F$ NMR
$^{31}$P NMR
18. Diethyl (6-chloro-2-(perfluoroethyl)quinolin-3-yl)phosphonate 4r

Yellowish oil (53%); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.35 (t, $J = 7.0$ Hz, 6H), 4.15 (m, 2H), 4.26 (m, 2H), 7.83 (dd, $J = 8.9$ Hz, $J = 2.3$ Hz, 1H), 7.96 (d, $J = 2.2$ Hz, 1H), 8.14 (d, $J = 8.9$ Hz, 1H), 9.11 (d, $^3$J$_{H,P} = 16.5$ Hz, 1H); $^{13}$C NMR (100 MHz) $\delta$ 16.3 (d, $J = 6.2$ Hz), 63.2 (d, $J = 6.3$ Hz), 114.5 (tq, $^1$J$_{C,F} = 260.1$ Hz, $^2$J$_{C,F} = 34.5$ Hz), 122.3 (qt, $^1$J$_{C,F} = 287.0$ Hz, $^2$J$_{C,F} = 36.5$ Hz), 122.5 (d, $^1$J$_{C,P} = 184.8$ Hz), 127.1, 127.4 (d, $^3$J$_{C,P} = 11.8$ Hz), 131.6, 133.9, 135.9, 145.2 (dt, $^4$J$_{C,P} = 1.7$ Hz, $^4$J$_{C,F} = 0.8$ Hz), 146.6 (td, $^2$J$_{C,F} = 28.0$ Hz, $^2$J$_{C,P} = 7.2$ Hz), 146.8 (d, $^2$J$_{C,P} = 7.8$ Hz); $^{19}$F NMR (376 MHz) $\delta$ -79.9 (s, $-CF_2CF_3$), -108.1 (s, $-CF_2CF_3$); $^{31}$P NMR (161 MHz) $\delta$ 13.4; HRMS (ESI): calcd for C$_{15}$H$_{14}$ClF$_3$NNaO$_3$P [M+Na]$^+$ 440.0212, found 440.0216.
$^1$H NMR
$^{13}$C NMR
\[ ^{19}F \text{ NMR} \]
$^{31}\text{P NMR}$
19. Diethyl (6,7-dimethoxy-2-(perfluoroethyl)quinolin-3-yl)phosphonate 4s

![Molecule Structure](image)

Colourless crystals (40%); Mp = 151–154 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.34 (t, $J =$ 7.0 Hz, 6H), 4.04 (s, 3H), 4.07 (s, 3H), 4.13 (m, 2H), 4.24 (m, 2H), 7.16 (s, 1H), 7.46 (s, 1H), 8.97 (d, $^3$J$_{H,P}$ = 16.2 Hz, 1H); $^{13}$C NMR (100 MHz) $\delta$ 16.3 (d, $J =$ 6.4 Hz), 56.4, 56.7, 62.9 (d, $J =$ 6.4 Hz), 105.3, 108.1, 111.9 (tq, $^1$J$_{C,F}$ = 256.7 Hz, $^2$J$_{C,F}$ = 36.7 Hz), 118.4 (d, $^1$J$_{C,P}$ = 187.6 Hz), 119.3 (qt, $^1$J$_{C,F}$ = 288.2 Hz, $^2$J$_{C,F}$ = 37.9 Hz), 123.2 (d, $^3$J$_{C,P}$ = 11.7 Hz), 144.6, 145.0 (d, $^2$J$_{C,P}$ = 6.8 Hz), 145.3 (td, $^2$J$_{C,F}$ = 27.9 Hz, $^2$J$_{C,P}$ = 9.5 Hz), 152.2, 155.3; $^{19}$F NMR (376 MHz) $\delta$ −80.1 (s, −CF$_2$CF$_3$), −108.1 (s, −CF$_2$CF$_3$); $^{31}$P NMR (161 MHz) $\delta$ 15.1 (t, $^4$J$_{P,P}$ = 1.5 Hz); HRMS (ESI): calcd for C$_{17}$H$_{19}$F$_5$NNaO$_5$P [M+Na]$^+$ 466.0813, found 466.0814.
$^{13}$C NMR
$^{19}$F NMR
$^{31}$P NMR
20. Diethyl (2-(perfluoroethyl)-7-(trifluoromethyl)quinolin-3-yl)phosphonate 4t

Yellowish oil (67%); $^1$H NMR (400 MHz, CDCl$_3$) δ 1.36 (t, $J = 6.8$ Hz, 6H), 4.18 (m, 2H), 4.28 (m, 2H), 7.92 (d, $J = 9.5$ Hz, 1H), 8.13 (d, $J = 7.9$ Hz, 1H), 8.52 (s, 1H), 9.28 (d, $^3$J$_{H-P}$ = 16.3 Hz, 1H); $^{13}$C NMR (100 MHz) δ 16.3 (d, $J = 6.8$ Hz), 63.4 (d, $J = 6.4$ Hz), 112.9 (tq, $^1$J$_{C-F}$ = 266.4 Hz, $^2$J$_{C-F}$ = 35.2 Hz), 122.6 (d, $^1$J$_{C-P}$ = 187.1 Hz), 122.7 (qt, $^1$J$_{C-F}$ = 288.9 Hz, $^2$J$_{C-F}$ = 35.6 Hz), 123.0 (q, $^1$J$_{C-F}$ = 276.0 Hz), 125.5 (qd, $^4$J$_{C-F}$ = 2.0 Hz, $^4$J$_{C-P}$ = 0.8 Hz), 127.8 (qd, $^4$J$_{C-F}$ = 5.0 Hz, $^4$J$_{C-P}$ = 1.3 Hz), 128.3 (d, $^3$J$_{C-P}$ = 12.9 Hz), 134.7 (q, $^2$J$_{C-F}$ = 33.8 Hz), 145.9, 147.8 (d, $^2$J$_{C-P}$ = 8.6 Hz), 147.9 (td, $^2$J$_{C-F}$ = 24.0 Hz, $^2$J$_{C-P}$ = 10.0 Hz); $^{19}$F NMR (376 MHz) δ –62.9 (s, –CF$_3$), –79.8 (s, –CF$_2$CF$_3$), –108.3 (s, –CF$_2$CF$_3$); $^{31}$P NMR (161 MHz) δ 12.9; HRMS (ESI): calcd for C$_{16}$H$_{14}$F$_8$NaO$_3$P [M+Na]$^+$ 474.0574, found 474.0569.
$^1$H NMR
$^{13}$C NMR
$^{19}$F NMR
$^{31}$P NMR