Supporting Information

for

The McKenna reaction – avoiding side reactions in phosphonate deprotection

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Synthesis of starting materials, copies of $^{31}$P NMR, $^1$H NMR, and $^{13}$C NMR spectra for all new compounds and selected NMR spectra illustrating the formation of the side products
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1. Synthesis of substrates

1.1. 4-Nitro-N-(prop-2-yn-1-yl)benzamide (10)

The reaction was run under an inert gas atmosphere (Ar). In a dried round-bottomed flask equipped with a septum propargylamine hydrochloride (740 mg, 8.08 mmol, 1.5 equiv) and triethylamine (12.4 mL) in 22 mL of dry dichloromethane were placed. Then the mixture was cooled to −40 °C and a solution of 4-nitrobenzoyl chloride (1 g, 5.39 mmol, 1 equiv) in dry CH$_2$Cl$_2$ (22 mL) was added dropwise. The reaction was stirred for 24 h at room temperature. Afterwards the reaction was quenched by the addition of water (7.4 mL). After 10 minutes, additional 22 mL of water were added and the mixture extracted with CHCl$_3$ (3 × 80 mL). The combined extracts were dried (MgSO$_4$) and concentrated to give the crude product, which was purified by column chromatography (DCM/acetone 0–30%). Yield 1.080 g (98%) from 1 g (5.39 mmol) of 4-nitrobenzoyl chloride.

$^1$H NMR (CDCl$_3$, 700 MHz): δ$_H$ 2.32 (1H, t, $J = 2.6$ Hz, CH$_2$CCH), 4.28 (2H, dd, $J = 5.2$, 2.6 Hz, CH$_2$CCH), 6.33 (1H, bs, CO-NH), 7.91-7.98 (2H, m, CH$_2$Ar), 8.26-8.34 (m, 2H, CH$_2$Ar).

1.2. N-phenethylacrylamide (11):

The reaction was run under inert gas atmosphere (Ar). In a dried round-bottomed flask equipped with a septum 2-phenethylamine (1 g, 8.25 mmol, 1 equiv) in 15 mL of dry dichloromethane was placed. Then the mixture was cooled to −50 °C and triethylamine (24.8 mmol, 3 equiv) and acryloyl chloride (1.494 g, 16.5 mmol, 2 equiv) were added. The reaction was stirred for 1.5 h at −50 °C. Then water was added and the mixture extracted with CHCl$_3$ (3 × 20 mL) at pH 9 (adjusted by Na$_2$CO$_3$ (sat.), if needed). The combined extracts were dried over (MgSO$_4$) and concentrated to give the crude product, which was purified by flash column chromatography (hexane/AcOEt 0–50%). Yield 743 mg (51.4%) from 1 g (8.25 mmol) of 2-phenethylamine.

$^1$H NMR (CDCl$_3$, 250 MHz): δ$_H$ 2.86 (2H, t, $J = 6.9$ Hz, Ar-CH$_2$-CH$_2$), 3.61 (2H, td, $J = 7.0$, 6.0 Hz, Ar-CH$_2$-CH$_2$), 5.56-5.66 (1H, m, CH=CH$_2$), 5.95-6.10 (1H, m, CH=CH$_2$), 6.21-6.31 (1H, m, CH=CH$_2$), 7.15-7.37 (5H, m, CH$_2$Ar).

1.3. General procedure: Synthesis of phosphonocarboxylate analogues of risedronate (9a-e)

Step I: The reaction was run under inert gas atmosphere (Ar). In a dried round-bottomed flask equipped with a septum the appropriate phosphonoacetate (1 equiv) in 15 mL of dry
dichloromethane (0.3 M solution) was placed. The mixture was cooled to −40 °C and TiCl$_4$ (1 equiv) and triethylamine (2.8 equiv) were added slowly, maintaining the temperature constant. After 15 minutes, 3-pyridinealdehyde was added dropwise. The reaction mixture was stirred for 30 min at −40 °C, followed by 24 h at room temperature. Then, 30 mL of water and saturated Na$_2$CO$_3$ were added to adjust pH to around 9 and the mixture was extracted with CHCl$_3$ (5 × 30 mL). The combined extracts were dried (MgSO$_4$) and concentrated to give the crude product, which was purified by flash column chromatography (DCM/acetone 0–30%).

**Step II:** In a round-bottomed flask the appropriate vinyl analogue of phosphonocarboxylate (1 equiv) in MeOH (0.1 M solution) was placed. Then, the NiCl$_2$·6H$_2$O (1.2 equiv) was added, the mixture cooled to −40 °C and NaBH$_4$ added in portions until the substrate disappeared as monitored by mass spectrometry. The reaction was quenched by the addition of a saturated aqueous solution of NH$_4$Cl and the mixture extracted with CH$_2$Cl$_2$ (4 × 60 mL) at pH 9 (adjusted with Na$_2$CO$_3$ (sat.)). The combined extracts were dried (MgSO$_4$) and concentrated to give the crude product, which was purified by flash column chromatography (DCM/acetone 0–50%).

**Step III:** The reaction was run under inert gas atmosphere (Ar). In a dried round-bottomed flask equipped with a septum NaH (1.2 equiv; 60% dispersion in mineral oil) in 10 mL of dry THF (0.32 M solution) was placed. The mixture was cooled to −15 °C and a solution of the appropriate phosphonopropionate (1 equiv) in 7 mL of dry THF (0.23 M solution) was added dropwise and the resulting mixture was stirred for 50 min at 0 °C. Next, the reaction mixture was cooled to −78 °C and a solution of NFSI (1.5 equiv) in dry THF (0.34 M solution) added dropwise. The reaction mixture was stirred for 20 min at −60 °C, followed by 1.5 h at −20 to (−40) °C. At −20 °C, 5 mL of a saturated aqueous solution of NH$_4$Cl and 5 mL of water were added and when the mixture had reached rt it was extracted with CHCl$_3$ (4 × 20 mL). The combined extracts were dried (MgSO$_4$) and concentrated to give the crude product, which was purified by flash column chromatography (DCM/acetone).

**Ethyl 2-(diethoxyphosphoryl)-3-(pyridin-3-yl)propanoate (9a):**

Yield 726 mg (72 %) from 1 g (3.19 mmol) of ethyl 2-(diethoxyphosphoryl)-3-(pyridin-3-yl)acrylate; $^1$H NMR (CDCl$_3$, 250 MHz): $\delta$H 1.15 (3H, t, $J = 7.1$ Hz, COOCH$_2$CH$_3$), 1.34 (6H, t, $J = 7.1$ Hz, PO(OCH$_2$CH$_3$)$_2$), 3.11–3.34 (3H, m, Py-CH$_2$-CH), 4.00–4.30 (6H, m, COOCH$_2$CH$_3$ and PO(OCH$_2$CH$_3$)$_2$), 7.20 (1H, ddd, $J = 7.8$, 4.8, 0.9 Hz, Py), 7.53 (1H, dt, $J = 7.8$, 2.0 Hz, Py), 8.43–8.49 (2H, m, Py).

$^{31}$P NMR (CDCl$_3$, 101 MHz): $\delta_P$ 21.43 (s).
Ethyl 2-(diethoxyphosphoryl)-2-fluoro-3-(pyridin-3-yl)propanoate (9b): Yield 378 mg (71 %) from 500 mg (1.59 mmol) of ethyl 2-(diethoxyphosphoryl)-3-(pyridin-3-yl)propanoate; $^1$H NMR (CDCl$_3$, 700 MHz); $^3$1H $\delta$H 1.19 (3H, t, $J = 7.1$ Hz, COOCH$_2$CH$_3$), 1.37 (6H, q, $J = 7.0$ Hz, PO(OCH$_2$CH$_3$)$_2$), 3.41-3.56 (2H, m, Py-CH$_2$-CF), 4.16-4.32 (6H, m, COOC$_6$H$_5$CH$_3$ and PO(OCH$_2$CH$_3$)$_2$), 7.22 (1H, ddd, $J = 7.8$, 4.8, 0.9 Hz, Py), 7.58-7.52 (1H, m, Py), 8.47-8.48 (1H, m, Py), 8.51 (1H, dd, $J = 4.8$, 1.7 Hz, Py). $^{31}$P NMR (CDCl$_3$, 283 MHz): $\delta$P 11.88 (d, $J_{PF} = 82$ Hz).

Ethyl 2-(diisopropoxyphosphoryl)-3-(pyridin-3-yl)propanoate (9c): Yield 2.106 g (76 %) from 2.737 g (8.02 mmol) of ethyl 2-(diisopropoxyphosphoryl)-3-(pyridin-3-yl)acrylate; $^1$H NMR (CDCl$_3$, 700 MHz); $^3$1H $\delta$H 1.13 (3H, t, $J = 7.1$ Hz, COOCH$_2$CH$_3$), 1.32 (12H, dt, $J = 9.6$, 5.9 Hz, PO(OCH$_2$CH$_3$)$_2$), 3.09-3.24 (3H, m, Py-CH$_2$-CH), 4.03-4.11 (2H, m, COOC$_6$H$_5$CH$_3$), 4.69-4.76 (2H, m, PO(CH$_2$(CH$_3$)$_2$)$_2$), 7.15-7.18 (1H, m, Py), 7.48-7.51 (1H, m, Py), 8.43 (1H, dd, $J = 4.8$, 1.7 Hz, Py), 8.44 (1H, d, $J = 2.4$ Hz, Py). $^{13}$C NMR (CDCl$_3$, 176 MHz): $\delta$C 14.10, 23.85 (d, $J = 5.2$ Hz), 23.97 (d, $J = 5.1$ Hz), 24.08 (d, $J = 4.0$ Hz), 24.24 (d, $J = 3.3$ Hz), 30.36 (d, $J = 4.1$ Hz), 48.19 (d, $J = 131$ Hz), 61.51, 71.68 (d, $J = 7.1$ Hz), 71.93 (d, $J = 6.9$ Hz), 123.40, 134.37 (d, $J = 15.9$ Hz), 136.25, 148.25, 150.22, 168.30 (d, $J = 5.1$ Hz). $^{31}$P NMR (CDCl$_3$, 283 MHz): $\delta$P 18.92 (s).

Ethyl 2-(diisopropoxyphosphoryl)-2-fluoro-3-(pyridin-3-yl)propanoate (9d): Yield 200 mg (38 %) from 500 mg (1.46 mmol) of ethyl 2-(diisopropoxyphosphoryl)-3-(pyridin-3-yl)propanoate; $^1$H NMR (CDCl$_3$, 700 MHz); $^3$1H $\delta$H 1.17 (3H, t, $J = 7.1$ Hz, COOCH$_2$CH$_3$), 1.31-1.38 (12H, m, PO(OCH$_2$(CH$_3$)$_2$)$_2$), 3.37-3.51 (2H, m, Py-CH$_2$-CF), 4.12-4.20 (2H, m, COOC$_6$H$_5$CH$_3$), 4.76-4.88 (2H, m, PO(OCH$_2$(CH$_3$)$_2$)$_2$), 7.19 (1H, ddd, $J = 7.8$, 4.8, 0.9 Hz, Py), 7.55-7.59 (1H, m, Py), 8.44 (1H, d, $J = 2.0$ Hz, Py), 8.48 (1H, dd, $J = 4.8$, 1.7 Hz, Py). $^{13}$C NMR (CDCl$_3$, 176 MHz): $\delta$C 14.08, 23.71 (d, $J = 5.6$ Hz), 23.81 (d, $J = 5.3$ Hz), 24.23 (d, $J = 3.3$ Hz), 24.34 (d, $J = 2.8$ Hz), 36.72 (d, $J = 19.7$ Hz), 62.46, 73.57 (d, $J = 7.1$ Hz), 73.81 (d, $J = 7.0$ Hz), 123.31, 129.36 (d, $J = 12.7$ Hz), 137.93, 148.94, 151.26, 166.38 (d, $J = 3.9$ Hz), 166.51 (d, $J = 3.9$ Hz). $^{31}$P NMR (CDCl$_3$, 283 MHz): $\delta$P 10.01 (d, $J_{PF} = 84.5$ Hz).

tert-Butyl 2-(diethoxyphosphoryl)-3-(pyridin-3-yl)propanoate (9e): Yield 1.049 g (35 %) from 3 g (8.80 mmol) of tert-butyl 2-(diethoxyphosphoryl)-3-(pyridin-3-yl)acrylate; $^1$H NMR (CDCl$_3$, 700 MHz); $^3$1H $\delta$H 1.30 (9H, s, COOC(CH$_3$)$_3$), 1.32 (6H, t, $J = 7.1$ Hz, PO(OCH$_2$CH$_3$)$_2$), 3.07-3.22 (3H, m, Py-CH$_2$-CH), 4.11-4.19 (4H, m, PO(OCH$_2$CH$_3$)$_2$), 7.15-7.18 (1H, m, Py), 7.50-7.53 (1H, m, Py), 8.42-8.44 (1H, m, Py), 8.44-8.46 (1H, m, Py). $^{13}$C NMR (CDCl$_3$, 176
MHz): $\delta_C$ 16.49 (m, 2C), 27.86 (3C), 30.22 (d, $J = 4.0$ Hz), 48.16 (d, $J = 129.6$ Hz), 62.86 (d, $J = 7.0$ Hz), 62.95 (d, $J = 6.4$ Hz), 82.32, 123.33, 134.31 (d, $J = 16.5$ Hz), 136.31, 148.23, 150.27, 167.16 (d, $J = 5.0$ Hz). $^{31}P$ NMR (CDCl$_3$, 283 MHz): $\delta_P$ 21.72 (s).

1.4. 2-Chloro-N-phenethylacetamide (13)

(The procedure is based on a modified method from literature. NMR signals correspond with literature data). The reaction was run under inert gas atmosphere (Ar). In a dried round-bottomed flask equipped with a septum 2-phenethylamine (200 mg, 1.65 mmol, 1 equiv) in 3 mL of dry dichloromethane was placed. Then, the mixture was cooled to $-50$ $^\circ$C, and triethylamine (9.90 mmol, 3 equiv) and chloroacetyl chloride (373 mg, 3.30 mmol, 2 equiv) were added and the resulting reaction mixture was stirred for 1.5 h at $-50$ $^\circ$C. Then, water was added and the mixture extracted with CHCl$_3$ (3 $\times$ 20 mL) at pH 9. The combined extracts were dried (MgSO$_4$) and concentrated to give the crude product. After washing the chloroform solution 3 times with water (acidified with 15% HCl; pH $\approx$ 4–5) the pure product was obtained. Yield 315 mg (96%) from 200 mg (1.65 mmol) of 2-phenethylamine.

$^1H$-NMR (CDCl$_3$, 250 MHz): $\delta_H$ 2.85 (1H, t, $J = 7.0$ Hz, Ar-CH$_2$-CH$_2$), 3.57 (2H, td, $J = 7.0$, 5.9 Hz, Ar-CH$_2$-C=H), 4.03 (2H, s, C=H$_2$-Cl), 6.60 (1H, bs, NH-CO), 7.15-7.40 (5H, m, CH$_2$Ar).

1.5. 4-(Dimethylamino)-N-phenethylbut-2-enamide (12)

The reaction was run under inert gas atmosphere (Ar). In a dried round-bottomed flask equipped with a septum 4-(dimethylamino)-2-butenoic acid hydrochloride (205 mg, 1.24 mmol, 1.5 equiv) in 1.5 mL of dry DMF was placed. Then, the mixture was cooled to $-20$ $^\circ$C and HATU (1.24 mmol, 1.5 equiv) and DIPEA (1.24 mmol, 1.5 equiv) were added and the mixture stirred for 5 min. Then, 2-phenethylamine (100 mg, 0.82 mmol, 1 equiv) and DIPEA (1.24 mmol, 1.5 equiv) were added and the mixture warmed to rt and stirred overnight. The reaction was quenched by the addition of water and extracted with CHCl$_3$ (3 $\times$ 5 mL). The combined extracts were dried (MgSO$_4$) and concentrated to give the crude product, which was purified by flash column chromatography (CHCl$_3$/MeOH 0–10 %). Yield 139 mg (73%) from 100 mg (0.82 mmol) of 2-phenethylamine.

$^1H$ NMR (CD$_3$OD, 700 MHz): $\delta_H$ 2.68 (6H, s, N-(CH$_3$)$_2$), 2.83 (2H, t, $J = 7.4$ Hz, Ar-CH$_2$-CH$_2$), 3.49 (2H, t, $J = 7.4$ Hz, Ar-CH$_2$-CH$_2$), 3.64 (2H, dd, $J = 7.1$, 1.4 Hz, CH$_2$-N-(CH$_3$)$_2$), 6.23 (1H, dt, $J = 15.3$, 1.4 Hz, CO-CH=CH), 6.70 (1H, dt, $J = 15.3$, 7.1 Hz, CO-CH=CH), 7.17-7.20 (1H, m, CH$_{Ar(4)}$), 7.20-7.23 (2H, m, CH$_{Ar(3,5)}$), 7.25-7.29 (2H, m, CH$_{Ar(2,6)}$). $^{13}C$ NMR
(CD$_3$OD, 176 MHz): $\delta$C 36.36 (Ar-CH$_2$-CH$_2$), 42.14 (Ar-CH$_2$-CH$_2$), 43.93 (2C, N-(CH$_3$)$_2$), 59.58 (CH$_2$-N-(CH$_3$)$_2$), 127.40 (C$_{Ar(4)}$), 129.50 (C$_{Ar(2,6)}$), 129.76 (C$_{Ar(3,5)}$), 131.78 (CO-CH=CH), 134.14 (CO-CH=CH), 140.35(C$_{Ar(1)}$), 166.79 (C=O). LRMS (APCI) m/z: [M + H]$^+$ Calcd for C$_{14}$H$_{20}$N$_2$O 232.16; Found 232.9.

2. Synthesis of side products under McKenna reaction conditions

2.1. Synthesis of compounds 15–17

The reactions were run under inert gas atmosphere (Ar). In a dried round-bottomed flask equipped with a septum 4-nitro-N-(prop-2-yn-1-yl)benzamide (10, 0.245 mmol, 1 equiv) was placed and dissolved in dry ACN (50 mg/1.5 mL). Then, triethyl phosphonoacetate (0.245 mmol, 1 equiv) and H$_2$O (0.490 mmol, 2 equiv) were subsequently added, followed by BTMS (2.94 mmol, 12 equiv). The septum was exchanged with a fitted glass stopper and additionally secured with parafilm. After 24 h in a 36°C sand bath, the solution was evaporated and the mixture was subjected to solvolysis in acetone. After 5 min, the solvent was evaporated, the residue dissolved in CHCl$_3$ and extracted with NaHCO$_3$ (2 × 2.5 mL). The combined extracts were dried (MgSO$_4$) and concentrated to give the crude product, which was purified by flash column chromatography (CH$_2$Cl$_2$).

5-Methyl-2-(4-nitrophenyl)oxazole (15):$^6$ $^1$H NMR (CDCl$_3$, 700 MHz): $\delta$H 2.43 (3H, d, $J$ = 1.2 Hz, CH$_{Ar(5)}$-CH$_2$), 6.93 (1H, q, $J$ = 1.2 Hz, CH$_{Ar(4)}$), 8.12-8.16 (2H, m, CH$_{Ar(2,6)}$), 8.27-8.30 (2H, m, CH$_{Ar(3,5)}$). $^{13}$C NMR (CDCl$_3$, 176 MHz): $\delta$C 11.25 (C$_{Ar(5)}$-CH$_3$), 124.27 (C$_{Ar(3,5)}$), 125.50 (C$_{Ar(4)}$), 126.68 (C$_{Ar(2,6)}$), 133.26 (C$_{Ar(3)}$), 144.45 (C$_{Ar(1)}$), 150.85 (C$_{Ar(5)}$), 158.74 (C$_{Ar(2)}$). HRMS (DART+) m/z: [M + H]$^+$ Calcd for C$_{10}$H$_{12}$N$_2$O 205.0608; Found 205.0609.

$N$-(2-Bromoallyl)-4-nitrobenzamide and $N$-(3-bromoallyl)-4-nitrobenzamide (16 and 17):

$^1$H NMR (CDCl$_3$, 700 MHz): $\delta$H 4.19 (2H, td, $J$ = 6.0, 1.5 Hz, CO-NH-CH$_2$ (17)), 4.28 (2H, d, $J$ = 6.0 Hz CO-NH-CH$_2$ (16)), 5.56 (1H, d, $J$ = 2.2 Hz, CBr=CH$_2$), 5.84-5.86 (1H, m, CBr=CH$_2$), 6.29 (1H, q, $J$ = 6.5 Hz, CH=CHBr), 6.33 (1H, dt, $J$ = 7.1, 1.5 Hz, CH=CHBr), 7.12 (1H, t, $J$ = 5.8 Hz, CO-NH (17)), 7.23 (1H, d, $J$ = 6.2 Hz, CO-NH (16)), 7.92-7.99 (2H, m, CH$_{Ar(2,6)}$), 8.19-8.25 (2H, m, CH$_{Ar(3,5)}$). $^{13}$C NMR (CDCl$_3$, 176 MHz): $\delta$C 39.89 (CO-NH-CH$_2$ (17)), 48.10 (CO-NH-CH$_2$ (16)), 110.95 (CH=CHBr), 118.66 (CBr=CH$_2$), 123.83, 123.88 (2s, C$_{Ar(3)}$ and C$_{Ar(5)}$), 128.38, 128.45 (2s, C$_{Ar(2)}$ and C$_{Ar(6)}$), 128.82 (CBr=CH$_2$), 130.53 (CH=CHBr), 139.63, 139.76 (2s, C$_{Ar(1)}$ or C$_{Ar(4)}$), 149.66, 149.76 (2s, C$_{Ar(1)}$ or C$_{Ar(4)}$), 165.63 (s, CO (17)),

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165.85 (s, CO (16)). HRMS (DART+) m/z: [M + H]+ Calcd for C_{10}H_{10}N_{2}O_{3}Br 284.9869; Found 284.9874.

2.2. 3-Bromo-N-phenethylpropanamide (18)

The reaction was run under inert gas atmosphere (Ar). In a dried round-bottomed flask equipped with a septum N-phenethylacrylamide (11, 0.285 mmol, 1 equiv) was placed and dissolved in dry ACN (50 mg/1.5 mL). Then, triethyl phosphonoacetate (0.285 mmol, 1 equiv) and H_{2}O (0.143 mmol, 0.5 equiv) were subsequently added, followed by BTMS (not distilled, 3.42 mmol, 12 equiv). The septum was exchanged with a fitted glass stopper and additionally secured with parafilm. After 24 h in a 36 °C sand bath the solution was evaporated and the mixture was subjected to solvolysis in acetone. After 5 min, the solvent was evaporated, the residue dissolved in CHCl_{3} and extracted with NaHCO_{3} (2 × 2.5 mL). The extract was dried (MgSO_{4}) and concentrated to give the crude product, which was purified by flash column chromatography (DCM/acetone 0–10%).

\(^{1}\text{H NMR}\) (CDCl\(_{3}\), 700 MHz): \(\delta_{H} 2.69 (2H, t, J = 6.6 Hz, \text{CO-CH}_{2}\text{-CH}_{2}\text{Br}), 2.83 (2H, t, J = 7.0 Hz, \text{Ph-CH}_{2}\text{-CH}_{2}\text{Br}), 3.54 (2H, td, J = 5.9 Hz, \text{Ph-CH}_{2}\text{-CH}_{2}\text{H}), 3.61 (2H, t, J = 6.6 Hz, \text{CO-CH}_{2}\text{-CH}_{2}\text{Br}), 5.75 (1H, br s, NH-\text{CO}), 7.20 (2H, br d, J = 6.6 Hz, CH_{\text{Ar(2,6)}}), 7.23, (1H, br t, J = 7.4 Hz, CH_{\text{Ar(4)}}), 7.31 (2H, br t, J = 7.6 Hz, CH_{\text{Ar(3,5)}}). \(^{13}\text{C NMR}\) (CDCl\(_{3}\), 176 MHz): \(\delta_{C} 27.58 (\text{CO-CH}_{2}\text{-CH}_{2}\text{Br}), 35.71 (\text{Ph-CH}_{2}\text{-CH}_{2}\text{Br}), 39.85 (\text{CO-CH}_{2}\text{-CH}_{2}\text{Br}), 40.89 (\text{Ph-CH}_{2}\text{-CH}_{2}\text{H}), 126.68 \text{ (C}_{\text{Ar(4)}}), 128.77 \text{ (C}_{\text{Ar(3,5)}}), 128.88 \text{ (C}_{\text{Ar(2,6)}}), 138.80 \text{ (C}_{\text{Ar(1)}}), 169.71 \text{ (CO)}. HRMS (DART+) m/z: [M + H]+ Calcd for C_{11}H_{15}NOBr 256.0332; Found 256.0328.

2.3. 3-(3-Ethoxy-2-fluoro-3-oxo-2-phosphonopropyl)-1-ethylpyridin-1-ium (20)

The reaction was run under inert gas atmosphere (Ar). In a dried round-bottomed flask equipped with a septum ethyl 2-(diethoxyphosphoryl)-2-fluoro-3-(pyridin-3-yl)propanoate (9d, 0.51 mmol, 1 equiv) was placed and dissolved in dry ACN (170 mg/5 mL). Then, BTMS (3.06 mmol, 6 equiv) was added and the septum was exchanged with a fitted glass stopper and additionally secured with parafilm. After 13 days in a 36 °C sand bath the solution was evaporated and the mixture was subjected to solvolysis in EtOH. After 5 min, the solvent was evaporated to give the crude product, which was purified by HPLC (95% H\(_2\)O + 5% ACN + 0.2% TFA buffer, isocratic).

\(^{1}\text{H NMR}\) (D\(_2\)O, 700 MHz, pH \approx 2-3): \(\delta_{H} 1.21 \text{ (3H, t, J = 7.1 Hz, O-CH}_{2}\text{-CH}_{3}\text{), 1.62 \text{ (3H, t, J = 7.4 Hz, N-CH}_{2}\text{-CH}_{3}\text{), 3.64-3.80 (2H, m, CH}_{2}\text{-CF), 4.20-4.28 (2H, m, O-CH}_{2}\text{-CH}_{3}\text{)}}, 4.59-4.67
(2H, m, N-CH\textsubscript{2}-CH\textsubscript{3}), 8.01 (dd, 1H, \(J = 8.1, 6.16\) Hz, CH\textsubscript{Ar}(5)), 8.43 (d, 1H, \(J = 8.2\) Hz, CH\textsubscript{Ar}(4)), 8.79 (dt, 1H, \(J = 6.2, 1.3\) Hz, CH\textsubscript{Ar}(2)), 8.83 (d, 1H, \(J = 1.9\) Hz, CH\textsubscript{Ar}(6)). \textsuperscript{13}C NMR (D\textsubscript{2}O, 176 MHz, pH \approx 2-3): \(\delta\)C 13.33 (O-CH\textsubscript{2}-CH\textsubscript{3}), 15.70 (N-CH\textsubscript{2}-CH\textsubscript{3}), 36.05 (d, \(J_{FC} = 19.8\) Hz, CH\textsubscript{2}-CF), 57.44 (N-CH\textsubscript{2}-CH\textsubscript{3}), 63.66 (O-CH\textsubscript{2}-CH\textsubscript{3}), 95.87 (dd, \(J_{FC} = 194.6\) Hz, \(J_{PC} = 145.5\) Hz, CH\textsubscript{2}-CF), 127.94 (C\textsubscript{Ar}(5)), 136.19 (d, \(J_{FC} = 11.7\) Hz, C\textsubscript{Ar}(3)), 142.95 (C\textsubscript{Ar}(6)), 144.52 (C\textsubscript{Ar}(2)), 146.8 (C\textsubscript{Ar}(4)), 169.63 (d, \(J_{FC} = 23.3\) Hz, \(J_{PC} = 2.7\) Hz, -COOEt). \textsuperscript{31}P NMR (D\textsubscript{2}O, 283 MHz, pH \approx 2-3) \(\delta_p 6.31\) (d, \(J_{PF} = 71.3\) Hz). LRMS (ESI) m/z: [M + H]\textsuperscript{+} Calcd for C\textsubscript{12}H\textsubscript{18}FNO\textsubscript{3}P 306.09; Found 305.9.

### 2.4. 2-Bromo-N-phenethylacetamide (22)

The reaction was run under inert gas atmosphere (Ar). In a dried round-bottomed flask equipped with a septum 2-chloro-N-phenethylacetamide (13, 0.051 mmol, 1 equiv) was placed and dissolved in dry CDCl\textsubscript{3} (10.1 mg/0.5 mL). Then, BTMS (0.306 mmol, 6 equiv) was added and the septum was exchanged with a fitted glass stopper and additionally secured with parafilm. After 24 h in a 36 °C sand bath the solution was evaporated and the mixture was subjected to solvolysis in acetone. After 5 min the solvent was evaporated.

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 700 MHz): \(\delta_H 2.90\) (2H, t, \(J = 7.1\) Hz, Ph-CH\textsubscript{2}-CH\textsubscript{2}), 3.58 (2H, br m, Ph-CH\textsubscript{2}-CH\textsubscript{2}), 4.03 (2H, s, CH\textsubscript{2}Br), 7.18-7.25 (3H, m, CH\textsubscript{Ar}(3,5) and CH\textsubscript{Ar}(4)), 7.28-7.33 (2H, m, CH\textsubscript{Ar}(2,6)). \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 176 MHz): \(\delta_C 27.48\) (CH\textsubscript{2}Br), 35.03 (Ph-CH\textsubscript{2}-CH\textsubscript{2}), 42.32 (Ph-CH\textsubscript{2}-CH\textsubscript{2}), 126.95 (C\textsubscript{Ar}(4)), 128.87 and 128.89 (2s, C\textsubscript{Ar}(2,6) and C\textsubscript{Ar}(3,5)), 137.92 (C\textsubscript{Ar}(1)), 168.12 (CO) HRMS (DART+) m/z: [M + H]\textsuperscript{+} Calcd for C\textsubscript{10}H\textsubscript{13}NOBr 242.0175; Found 242.0181.

### 2.5. N-Ethyl-N,N-dimethyl-4-oxo-4-(phenethylamino)but-2-en-1-aminium (21)

The reaction was run under inert gas atmosphere (Ar). In a dried round-bottomed flask equipped with a septum 4-(dimethylamino)-N-phenethylbut-2-enamide (12, crude product, without purification, 0.258 mmol, 1 equiv) was placed and dissolved in dry ACN (60 mg/2 mL). Then, tert-butyl diethylphosphonoacetate (0.258 mmol, 1 equiv) and TEA (20.02 mmol, 10 equiv) were subsequently added, followed by BTMS (not distilled, 20.02 mmol, 10 equiv). The septum was exchanged with a fitted glass stopper and additionally secured with parafilm. After 24 h in a 36 °C sand bath the solution was evaporated and the mixture was subjected to solvolysis in EtOH. After 5 min the solvent was evaporated and the mixture purified by HPLC (A: 95% H\textsubscript{2}O + 5% ACN + 0.2% TFA; B: 95% ACN + 5% H\textsubscript{2}O + 0.2% TFA, gradient 5→30 min 0→90% B, compound 21 was collected after 15 min.
$^1\text{H NMR}$ (CD$_3$OD, 700 MHz): $\delta_{\text{H}}$ 1.39 (3H, t, $J = 7.3$ Hz, $\text{N-CH}_2\text{-CH}_3$), 2.85 (2H, t, $J = 7.3$ Hz, Ar-$\text{CH}_2\text{-CH}_2$), 3.07 (6H, s, $\text{N-(CH}_3)_2$), 3.41 (2H, q, $J = 7.3$ Hz, $\text{N-CH}_2\text{-CH}_3$), 3.52 (2H, t, $J = 7.4$ Hz, Ar-$\text{CH}_2\text{-CH}_2$), 4.09 (2H, d, $J = 6.4$ Hz, $\text{CH}_2\text{-N-(CH}_3)_2$), 6.39-6.43 (1H, m, CO-$\text{CH=CH}$), 6.77 (1H, dt, $J = 15.1$, 7.5 Hz, CO-$\text{CH=CH}$), 7.17-7.24 (3H, m, CH$_{\text{Ar}(4)}$ and CH$_{\text{Ar}(3,5)}$), 7.25-7.30 (2H, m, CH$_{\text{Ar}(2,6)}$). $^{13}\text{C NMR}$ (CD$_3$OD, 176 MHz): $\delta_{\text{C}}$ 8.37 (N-$\text{CH}_2\text{-CH}_3$), 36.30 (Ar-$\text{CH}_2\text{-CH}_2$), 42.40 (Ar-$\text{CH}_2\text{-CH}_2$), 50.55 (2C, t, $J = 3.8$ Hz, $\text{N-(CH}_3)_2$), 61.21 (N-$\text{CH}_2\text{-CH}_3$), 64.79 (CH$_2$-$\text{N-(CH}_3)_2$), 127.45 (C$_{\text{Ar}(4)}$), 129.01 (CO-$\text{CH=CH}$), 129.52 (C$_{\text{Ar}(2,6)}$), 129.76 (C$_{\text{Ar}(3,5)}$), 135.93 (CO-$\text{CH=CH}$), 140.29 (C$_{\text{Ar}(1)}$), 166.13 (C=O). $\text{HRMS}$ (DART+) m/z: [M + H]$^+$ Calcd for C$_{16}$H$_{25}$N$_2$O 261.1961; Found 261.1962.
3. NMR Spectra of side products generated under Mc Kenna reaction conditions

3.1. Compounds 15–17

Figure S1: $^1$H NMR of compound 15 (CDCl$_3$, 700 MHz).
3.1.1. X-ray Crystallography of compound 15

X-ray data of single crystals of the title compound were measured on an APEX II CCD X-ray diffractometer using graphite-monochromated CuKα radiation (\(\lambda = 1.54184 \text{ Å}\)). Data were collected using the APEX-II software\(^9\), integrated using SAINT\(^10\) and corrected for absorption using the multi-scan approach (SADABS).\(^11\) Final cell constants were determined from full least squares refinements of all observed reflections. The structures were solved using intrinsic phasing (SHELXT)\(^12\) and refined with full squares refinement on \(F^2\) using the SHELXTL software.\(^13,14\) All hydrogen atoms were added at calculated positions and refined isotropically with a riding model. A thermal ellipsoid plot of the title compound is given in Figure S3. A summary of the experimental crystallographic data is presented in Table S1. The crystallographic data (CCDC 1919198) have been deposited in the Cambridge Crystallographic Data Base.
Figure S3: Molecular structure of 15 from X-ray crystallographic analysis. (Thermal ellipsoids are shown at the 50% probability level.)

Table S1. Crystal and structure refinement data.

| Property                     | Value                        |
|------------------------------|------------------------------|
| Formula                      | C_{10}H_{8}N_{2}O_{3}         |
| CCDC no.                     | 1919198                      |
| Formula weigh                | 204.18                       |
| Temperature, [K]             | 298                          |
| Wavelength, [Å]              | CuKα                         |
| Crystal system               | triclinic                    |
| Space group                  | P1                            |
| Unit cell dimensions, [Å, °] | a= 3.9699(2)                 |
|                              | b= 5.9126(2)                 |
|                              | c=10.7094(7)                 |
|                              | α= 98.052(4)                 |
|                              | β= 99.989(5)                 |
|                              | γ= 91.441(4)                 |
| Volume, [Å³]                 | 244.81(2)                    |
| Z                            | 1                            |
| Calculated density, [g cm³]  | 1.385                        |
| Absorption coefficient [mm⁻¹]| 0.883                        |
| θ range for data collection [°]| 4.2 - 66.6                  |
| Limiting indices (h, k, l)   | -4/4, -7/7, -12/12           |
| Reflections collected/unique | 3570/1560                    |
| Data/restraints/parameters   | 1560/0/138                   |
| R_{int}                      | 0.013                        |
| Goodness-of-fit on F²        | 1.27                         |
| R[F² > 2(F²)]                | 0.0751                       |
| R (all data)                 | 0.0888                       |
| wR[F² > 2(F²)]               | 0.254                        |
| Largest diff. peak and hole, [e Å⁻³] | -0.37, 0.49                  |
Note
Since compounds 16 and 17 were isolated as mixture, for the description of NMR data symbols (16 and 17) were used whenever distinction was possible. When two complementary signals overlapped, no distinction was made.

**Figure S4:** $^1$H NMR of compound 16 and 17 (CDCl$_3$, 700 MHz).
Figure S5: $^1$H NMR of compound 16 and 17 (CDCl$_3$, 700 MHz): zoom in of the range 4.2–8.2.

Figure S6: $^{13}$C NMR of compound 16 and 17 (CDCl$_3$, 176 MHz).
3.2. Optimization of oxazole synthesis

In the first approach we generated HBr by the reaction between equimolar amounts of BTMS and water (0.5:0.5 and 3:3) (Table S2, entry 2 and 3). We obtained mixture of products and substrate, achieving higher conversion for the 3:3 molar ratio of reagents.

Next, we excluded BTMS from the reaction and used 33% HBr in AcOH or 40% HBr in H₂O, respectively. The application of the HBr solution in AcOH led again to a mixture of products 15–17 and the substrate (Table S2, entries 4–6), while using solely hydrobromic acid (40%) led to recovery of the substrate (Table S2, entry 7).

To exclude the formation of products by HBr addition, we applied non-HBr containing acids: HCl, TFA, and AcOH. However, in all cases we isolated only the starting compound 10 (Table S2, entries 8–11).

Table S2: Optimization of the oxazole synthesis.a

| Entry | PCb | Acid (eq) | Additive (eq) | 10:15:16:17 |
|-------|-----|-----------|---------------|-------------|
| 1.    | +   | BTMS (0.5)| -             | 0.96:0.04:0:0 |
| 2.    | +   | BTMS (0.5)| H₂O (0.5)     | 0.7:0.27:0.01:0.02 |
| 3.    | -   | BTMS (3)  | H₂O (3)       | 0.13:0.64:0.13:0.10 |
| 4.    | +   | 33% HBr in AcOH (1)| -           | 0.67:0.27:0.03:0.03 |
| 5.    | +   | 33% HBr in AcOH (10)| -         | 0.18:0.51:0.12:0.19 |
| 6.    | +   | 33% HBr in AcOH (1)| H₂O (1)     | 0.34:0.54:0.08:0.04 |
| 7.    | +   | 40% HBr in H₂O (10)| -          | 0.99:0.01:0:0 |
| 8.    | -   | AcOH (1)  | D₂O (2)       | n.r.        |
| 9.    | -   | TFA (1.28)| -             | n.r.        |
| 10.   | -   | TFA (1.28)| H₂O (1.28)    | n.r.        |
| 11    | -   | HCl (sat) (5 μl)| -         | n.r.        |

aAll reactions were carried out in ACN; the reaction was run at 35 °C for 24 h. n.r.: no reaction; btriethyl phosphonoacetate was used; cACN-d₅ was used, because of the NMR control of this reaction.
3.3 Compound 18

Figure S7: $^1$H NMR of compound 18 (CDCl$_3$, 700 MHz).

Figure S8: $^{13}$C NMR of compound 18 (CDCl$_3$, 176 MHz).
3.4 Compound 20

Figure S9: $^1$H NMR of compound 20 (CDCl$_3$, 700 MHz).

Figure S10: $^1$H NMR of compound 20 (CDCl$_3$, 700 MHz): zoom in of the ranges 1.1–1.7, 3.6–4.8, and 7.9–8.9 ppm.
Figure S11: $^{13}$C NMR of compound 20 (CDCl$_3$, 176 MHz).

Note: Compound 20 was purified by HPLC using 95% H$_2$O + 5% ACN + 0.2% TFA buffer. The signals of residual TFA were identified in the $^{13}$C NMR spectrum.

Figure S12: $^{31}$P NMR of compound 20 (CDCl$_3$, 283 MHz).
Figure S13: Top and middle: Monitoring of the alkylation reaction progress for compound 9b at the first stage of the McKenna reaction (BTMS stage); top: $^{31}$P NMR after 24 h; middle: $^{31}$P NMR after 7 days. Bottom: $^{31}$P NMR spectrum of the alkylation product 20 after solvolysis and HPLC purification.
### 3.5 Compound 22

**Figure S1**: \(^1\)H NMR of compound 22 (CDCl\(_3\), 700 MHz).

**Figure S15**: \(^{13}\)C NMR of compound 22 (CDCl\(_3\), 176 MHz).
Figure S16: Monitoring by ^1^H NMR of the reaction progress between 13 and BTMS (CD$_3$CN, 700 MHz): zoom in of the ranges 2.7–4.3 ppm.
3.6 Compound 21

Figure S1: \(^1\)H NMR of compound 21 (CD\(_3\)OD, 700 MHz).

Figure S17: \(^1\)H NMR of compound 21 (CD\(_3\)OD, 700 MHz).
**Figure S18**: $^{13}$C NMR of compound 21 (CD$_3$OD, 176 MHz).

Note: Compound 21 was purified by HPLC using: A: 95% H$_2$O + 5% ACN + 0.2% TFA; B: 95% ACN + 5% H$_2$O + 0.2% TFA, gradient. The peaks of residual TFA were identified in the $^{13}$C NMR spectrum.

**Figure S19**: Comparison of the $^1$H NMR spectra of substrate 12 (bottom spectrum) and product 21 (top spectrum; compound contaminated with $\approx$ 10% of substrate 12) (CD$_3$OD + TFA, 700 MHz): zoom in of the ranges 1.25–4.20, and 6.30–7.35 ppm. The representative peaks were identified.
3.7 Monitoring the experiments for section 5 by NMR

**Figure S20**: Monitoring of the reaction between 8b and BTMS: top: $^1$H NMR spectrum of 8b before adding BTMS; middle: $^1$H NMR after 24 h of reaction between 8b and BTMS (CD$_3$CN, 700 MHz); bottom: $^1$H NMR after 5 min of solvolysis (CD$_3$OD, 700 MHz); zoom in of the ranges 3.45–2.7 and 2.0–1.2 ppm; see Table 4, entry 3.

**Figure S21**: Monitoring of the reaction between 8b and BTMS in the presence of 1 equiv of TEA: top: $^1$H NMR spectrum of 8b before adding BTMS; middle: $^1$H NMR after 24 h of reaction between 8b and BTMS (CD$_3$CN, 700 MHz); bottom: $^1$H NMR after 5 min of solvolysis (CD$_3$OD, 700 MHz); zoom in of the ranges 3.15–2.7 and 2.0–1.25 ppm; see Table 4, entry 4.
**Figure S21a:** Monitoring the reaction between 8b and BTMS in the presence of 1 equiv of TEA: top: $^{31}$P NMR spectrum of 8b before adding BTMS; middle: $^{31}$P NMR after 24 h of reaction between 8b and BTMS (CD$_3$CN, 700 MHz); bottom: $^{31}$P NMR after 5 min of solvolysis (CD$_3$OD, 700 MHz); zoom in of the ranges 3.15–2.7 and 2.0–1.25 ppm; see Table 4, entry 4.

**Figure S22:** Monitoring the reaction between 8b and BTMS in the presence of 2 equiv of pyridine: top: $^1$H NMR spectrum of 8b before adding of BTMS; middle: $^1$H NMR after 24 h of reaction between 8b and BTMS (CD$_3$CN, 700 MHz); bottom: $^1$H NMR after 5 min of solvolysis (CD$_3$OD, 700 MHz); zoom in of the ranges 3.5–2.7 and 2.0–1.25 ppm; see Table 4, entry 5.
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