A New Horner-Wadsworth-Emmons Type Coupling Reaction Between Non-stabilized β -Hydroxy Phosphonates and Aldehydes or Ketones

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Supporting Information

The successful generation of olefin **iii** demonstrated that catalytic olefin hydrophosphorylation can be used as a strategy to access reagents that are suitable for subsequent aldehyde coupling reactions. Further experiments to improve reaction efficiency were undertaken, and solvent dependency was investigated first (Table 1). Chloroform was clearly the superior solvent, and it was the only one in which the reaction remained homogeneous throughout its duration (entry 1). In pyridine or CCl_4 the reaction became heterogeneous immediately upon addition of DIC (entries 2 and 3), and in 1,2-dimethoxy ethane, CH_2Cl_2 , THF or 1,4-dioxane the solution became slowly heterogeneous during the course of the reaction and moderate yields of alkene were obtained in these cases (entries 4-7). Phosphonate **i** was insoluble in benzene and no olefin could be detected after two days (entry 8). Refluxing the reaction in CHCl_3 resulted in a slightly diminished yield (entry 10), and in another experiment no product olefin could be detected after 2 days at -20°C (entry 11). Varying the reaction concentration between 0.01 and 0.2 M in CHCl_3 had no effect on yield.

Table 1. Olefin Formation Solvent Dependency (**i** $\rightarrow$ **iii**)^a

Entry	Solvent	Temperature	Yield iii
1	CHCl_3	rt	75%
2	CCl_4	rt	22%
3	pyridine	rt	29%
4	CH_2Cl_2	rt	52%
5	1,2-DME	rt	53%
6	THF	rt	53%
7	1,4-dioxane	rt	42%
8	benzene	rt	<5%
9	CHCl_3	reflux	55%
10	CHCl_3	-20°C , 2 d.	nr

^a Reaction time 4 h unless noted. ^b Isolated Yield.

Due to the stability of the oxaphosphetane **ii** and the highly electrophilic nature of meta phosphates, adjuncts were added to the reaction that might facilitate oxaphosphetane collapse or intercept the reactive meta phosphate before any potentially deconstructive interaction with reactants or olefin product. Lewis acids were clearly not effective (entries 1 and 2, Table 2), nor was the reasonably nucleophilic sodium 2-ethyl-hexanoate (entry 3). Moderate nucleophiles (e.g., EtOH, entry 4) had only a slightly negative effect, and even weaker nucleophiles had no significant effect on reaction yield, even though they should be sufficiently reactive to scavenge the methyl meta phosphate (entries 5-8).¹ The optimum conditions to effect the olefination consist of adding 2 equivalents of DIC to a stirred CHCl_3 solution of the β -hydroxy phosphonate at room temperature.

¹ Westheimer, F. H. *Chem. Rev.* **1981**, *81*, 313-326.

Table 2. Effect of Adjuncts on Formation of **iii** in CHCl₃.

Entry	Additive	Equivalents	Yield iii
1	BF ₃ •OEt ₂	1	<5%
2	ZnCl ₂	1	<5%
3	Na-2-Et-hexanoate	1	<5%
4	EtOH	10	42%
5	BHT	1	61%
6	PhN(H)Me	1	74%
7	BnOCH=CH ₂	1	62%
8	Allyl-SiMe ₃	1	74%

^a Isolated Yield.**[1-(1-Hydroxy-3-phenyl-propyl)-octyl]-phosphonic acid dimethyl ester (7a).**

The synthesis was performed according to the general procedure for **7**. Purification by flash chromatography (SiO₂, gradient: EtOAc: hexane 1:1 to EtOAc) afforded **7a** (121 mg, 0.42 mmol) as a colorless oil in 42% yield as a mixture of diastereomers. *R_f* 0.40 (EtOAc); ¹H NMR (CDCl₃, 300 MHz) δ 0.88 (t, *J* = 6.8 Hz, 3H, CH₃), 1.24-2.06 (m, 15H CH₂), 2.60-2.74 (m, 1H, CH₂), 2.82-2.97 (m, 1H, CH₂), 3.50-3.95 (m, 8H, OCH₃, OCH and OH), 7.15-7.30 (m, 5H, ArH); ³¹P NMR (CDCl₃, 121.5 MHz) δ 36.8 and 37.0; MS (CI) *m/z*: 357 [M+H]⁺, 339 [M-H₂O+H]⁺; HRMS (CI) calcd for C₁₉H₃₃O₄P [M+H]⁺ 357.2195, found 357.2198.

[1-(Hydroxy-phenyl-methyl)-octyl]-phosphonic acid dimethyl ester (7b).

The synthesis was performed according to the general procedure for **7**. Purification by flash chromatography (SiO₂, gradient: EtOAc: hexane 1:1 to EtOAc) afforded **7b** (149 mg, 0.45 mmol) as a colorless oil in 45% yield as a mixture of diastereomers (3:1). *R_f* 0.50 (EtOAc); ¹H NMR (CDCl₃, 300 MHz) δ 0.80-0.93 (t, *J* = 6.8 Hz, 3H, CH₃), 1.05-1.61 (m, 12H CH₂), 2.03-2.19 (m, 1H, PCH), 3.58-3.97 (m, 6H, OCH₃, 3.98 (d, *J* = 3.6 Hz, 0.75 H, OH), 4.67 (d, *J* = 3.9 Hz, 0.25H, OH), 5.8 (brs, 0.25H, OCH), 5.28 (d, *J* = 13.2 Hz, 0.75H, OCH), 7.21-7.38 (m, 5H, ArH); ³¹P NMR (CDCl₃, 121.5 MHz) δ 36.7 and 37.0; MS (CI) *m/z* 329 [M+H]⁺, 311 [M-H₂O+H]⁺; HRMS (CI) calcd for C₁₇H₂₉O₄P [M+H]⁺ 329.1882, found 329.1889.

[1-(Cyclohexyl-hydroxy-methyl)-octyl]-phosphonic acid dimethyl ester (7c).

The synthesis was performed according to the general procedure for **7**. Purification by flash chromatography (SiO₂, EtOAc: hexane 1:1) afforded *rac*-**7c** (77 mg, 0.23 mmol) and *anti*-**7c** (62 mg, 0.19 mmol) both as colorless oils in 23% and 19% yield, respectively. *rac*-**7c**. *R_f* 0.42 and 0.50 (EtOAc); ¹H NMR (CDCl₃, 300 MHz) δ 0.87 (t, *J* = 6.6 Hz, 3H, CH₃), 0.95-1.74 (m, 22H CH₂), 1.93-2.14 (m, 2H, CH), 3.34-3.48 (m, 2H, OCH and OH), 3.68-3.78 (m, 6H, OCH₃); ³¹P NMR (CDCl₃, 121.5 MHz) δ 37.5, 39.0; MS (CI) *m/z* 335 [M+H]⁺, 317 [M-H₂O+H]⁺, 251; HRMS (CI) calcd for C₁₇H₃₅O₄P [M+H]⁺ 335.2351, found 335.2352.

anti-**7c**. *R_f* 0.50 (EtOAc); ¹H NMR (CDCl₃, 300 MHz) δ 0.87 (t, *J* = 6.6 Hz, 3H, CH₃), 0.95-1.74 (m, 22H CH₂), 1.93-2.14 (m, 2H, CH), 3.34-3.48 (m, 2H, OCH and OH), 3.68-3.78 (m, 6H, OCH₃); ³¹P NMR (CDCl₃, 121.5 MHz) δ 37.5; MS (CI) *m/z* 335 [M+H]⁺, 317 [M-H₂O+H]⁺, 251; HRMS (CI) calcd for C₁₇H₃₅O₄P [M+H]⁺ 335.2351, found 335.2352.

[1-(Ethyl-hydroxy-propyl)-octyl]-phosphonic acid dimethyl ester (7d).

The synthesis was performed according to the general procedure for **7**. Purification by flash chromatography (SiO₂, EtOAc: hexane 1:1) afforded **7d** (185 mg, 0.60 mmol) as a colorless oil in 60% yield. *R_f* 0.65 (EtOAc); ¹H NMR (CDCl₃, 300 MHz) δ 0.80-0.87 (m, 3H, CH₃), 1.15-1.68 (m, 16 H, CH₂), 1.97-2.09 (m, 1H, CH), 3.65-3.73 (m, 3H, OCH₃); ¹³C NMR (CDCl₃, 75.5 MHz) δ 7.5 (CH₃), 7.6 (CH₃), 14.2 (CH₃), 22.8 (CH₂), 26.5 (CH₂), 28.6 (CH₂), 28.7 (CH₂), 29.2 (CH₂), 30.0 (CH₂), 30.5 (CH₂), 30.6 (CH₂), 32.0 (CH₂), 43.6 (CH), 52.2 (CH₃), 52.3 (CH₃), 52.4 (CH₃), 75.3 (C); ³¹P NMR (CDCl₃, 121.5 MHz) δ 39.1; MS (CI) *m/z* 309 [M+H]⁺, 291 [M-H₂O+H]⁺.

(2-Hydroxy-4-phenyl-butyl)-phosphonic acid dimethyl ester (7e).

The synthesis was performed according to the general procedure for **7**. Purification by flash chromatography (SiO₂, gradient: EtOAc: hexane 1:1 to EtOAc) afforded **7e** (1.56 g, 6.0 mmol) as a colorless oil in 60% yield. *R_f* 0.45 (EtOAc); ¹H NMR (CDCl₃, 300 MHz) δ 1.79-1.88 (m, 2H, CH₂), 1.96 (dd, *J* = 17.1, 3.0 Hz, 2H CH₂), 2.60-2.84 (m, 2H, CH₂), 3.69 (d, *J* = 10.8 Hz, 6H, OCH₃), 3.94-4.08 (m, 1H, OCH), 4.09 (brs, 1H, OH), 7.11-7.28 (m, 5H, ArH); ¹³C NMR (CDCl₃, 75.5 MHz) δ 32.03 (d, *J* = 9.9 Hz, CH₂), 32.94 (d, *J* = 148 Hz, CH₂), 52.53 (d, *J* = 7.4 Hz, CH₃), 52.69 (d, *J* = 6.6 Hz, CH₃), 65.86 (d, *J* = 5.0 Hz, CH), 126.1 (CH), 128.6 (CH), 128.7 (CH), 142.0 (C); ³¹P NMR (CDCl₃, 121.5 MHz) δ 33.9; MS (CI) *m/z* 259 [M+H]⁺, 241 [M-H₂O+H]⁺; HRMS (CI) calcd for C₁₂H₁₉O₄P [M+H]⁺ 259.1099, found 259.1101.

(2-Hydroxy-2-phenyl-ethyl)-phosphonic acid diethyl ester (7f).

The synthesis was performed according to the general procedure for **7**. Purification by flash chromatography (SiO₂, gradient: EtOAc: hexane 1:1 to EtOAc) afforded **7f** (215 mg, 0.83 mmol) as a colorless oil in 83% yield. *R_f* 0.51 (EtOAc); ¹H NMR (CDCl₃, 300 MHz) δ 1.28 (dt, *J* = 7.2 Hz, *J* = 3.5 Hz, 3H, CH₃), 2.11-2.30 (m, 2H, CH₂), 3.99-4.13 (m, 4H, CH₂), 4.20 (d, *J* = 2.1 Hz, 1H, OH), 5.10 (dt, *J* = 8.9 and *J* = 2.1 Hz, 1H, CH), 7.23-7.40 (ArH); ¹³C NMR (CDCl₃, 75.5 MHz) δ 16.18 (d, *J* = 4.9 Hz, CH₃), 16.25 (d, *J* = 6.0 Hz, CH₃), 35.79 (d, *J* = 136 Hz, CH₂), 61.75 (d, *J* = 12.7 Hz, CH₂), 61.83 (d, *J* = 12.6 Hz, CH₂), 68.62 (d, *J* = 4.5 Hz, CH), 125.4 (CH), 127.5 (CH), 128.3 (CH), 143.58 (d, *J* = 15.9 Hz, C); MS (CI) *m/z* 259 [M+H]⁺, 241 [M-H₂O+H]⁺; HRMS (CI) calcd for C₁₂H₁₉O₄P [M+H]⁺ 259.1099, found 259.1104.

(2-Hydroxy-4-phenyl-butyl)-phosphonic acid diethyl ester (7g).

The synthesis was performed according to the general procedure for **7**. Purification by flash chromatography (SiO₂, gradient: EtOAc: hexane 1:2 to EtOAc) afforded **7g** (2.44 g, 8.1 mmol) as a colorless oil in 81% yield as a mixture of diastereomers (3:2). *R_f* 0.54 (EtOAc); ¹H NMR (CDCl₃, 300 MHz) δ 1.10-1.38 (m, 6H CH₃), 1.63 (m, 1H, CH), 1.83 (m, 2H, CH₂), 1.90-2.93 (m, 2H, CH and CH₂), 3.30 (brs, 0.6H, OH), 3.76-3.81 (m, 0.4H, OH), 3.99-4.19 (m, 5H, CH₂ and CH), 7.16-7.31 (m, 5H, ArH); ³¹P NMR (CDCl₃, 121.5 MHz) δ 34.5 and 34.7; MS (CI) *m/z* 301 [M+H]⁺; HRMS (CI) calcd for C₁₅H₂₅O₄P [M+H]⁺ 301.15695, found 301.1563.

1-Phenyl-3-undecene (10a).

The synthesis was performed according to the general procedure for **10** from **7**. Purification by flash chromatography (SiO₂, hexane) afforded **10a** (99 mg, 0.382 mmol) as a colorless oil in 55% yield. *R_f* 0.65 (hexanes); ¹H NMR (CDCl₃, 300 MHz) δ 0.89-0.93 (m, 3H, CH₃), 1.29 (brs 10H, CH₂), 1.99 (brs, 2H, CH₂), 2.35-2.42 (m, 2H, CH₂), 2.66-2.72 (m, 2H, CH₂), 5.40-5.46 (m, 2H, =CH), 7.18-7.33 (m, 5H, ArH); ¹³C NMR (CDCl₃, 75.5 MHz) δ 14.4 (CH₃), 22.9 (CH₂), 27.5 (CH₂), 29.4 (CH₂), 29.5 (CH₂), 29.8 (CH₂), 29.9 (CH₂), 30.0 (CH₂), 32.1 (CH₂), 32.8 (CH₂), 34.7 (CH₂), 36.3 (CH₂), 36.4 (CH₂), 125.9 (CH), 126.0 (CH), 128.5 (CH), 128.7 (CH), 128.9 (CH), 129.5 (CH), 131.0 (CH), 131.5 (CH), 142.4 (C); MS (CI) *m/z* 231 [M+H]⁺.

1-Phenyl-1-nonene (10b).

The synthesis was performed according to the general procedure for **10** from **7**. Purification by flash chromatography (SiO₂, hexane) afforded **10b** (99 mg, 0.38 mmol) as a colorless oil in 59% yield. *R_f* 0.65 (hexanes); ¹H NMR (CDCl₃, 300 MHz) δ 0.94-0.98 (m, 3H, CH₃), 1.35-1.55 (m, 10H, CH₂), 2.25-2.45 (m, 2H, CH₂), 5.70-5.79 (m, 0.8H, =CH), 6.25-6.35 (m, 0.2H, =CH), 6.43-6.51 (m, 1H, =CH), 7.23-7.43 (m, 5H, ArH); ¹³C NMR (CDCl₃, 75.5 MHz) δ 14.4 (CH₃), 23.0 (CH₂), 29.0 (CH₂), 29.5 (CH₂), 29.6 (CH₂), 29.7 (CH₂), 30.3 (CH₂), 32.1 (CH₂), 33.4 (CH₂), 126.2 (CH), 126.7 (CH), 127.0 (CH), 128.4 (CH), 128.7 (CH), 129.0 (CH), 130.0 (CH), 131.5 (CH), 133.6 (CH), 138.1 (C); MS (CI) *m/z* 203 [M+H]⁺.

Non-enyl-cyclohexane (10c).

The synthesis was performed according to the general procedure for **10** from **7**. Purification by flash chromatography (SiO₂, hexane) afforded **10c** (22 mg, 0.11 mmol) as a colorless oil in 56% yield.

Rac-10c. *R_f* 0.83 (hexanes); ¹H NMR (CDCl₃, 300 MHz) δ 0.90 (t, *J* = 6.5 Hz, 3H, CH₃), 1.00-1.35 (m, 16 H, CH₂), 1.57-1.75 (m, 5H, CH₂), 1.87-2.06 (m, 2H, CH₂), 5.18-5.38 (m, 2H, =CH); ¹³C NMR (CDCl₃, 75.5 MHz) δ 14.4

(CH₃), 22.9 (CH₂), 26.3 (CH₂), 26.4 (CH₂), 26.5 (CH₂), 27.7 (CH₂), 29.4 (CH₂), 30.0 (CH₂), 30.2 (CH₂), 32.1 (CH₂), 32.9 (CH₂), 33.5 (CH₂), 33.6 (CH₂), 128.0 (CH), 128.3 (CH), 136.2 (CH), 136.6 (CH); MS (CI) *m/z* 209 [M+H]⁺.

Z-10c. *R_f* 0.83 (hexanes); ¹H NMR (CDCl₃, 300 MHz) δ 0.90 (t, *J* = 6.5 Hz, 3H, CH₃), 1.00-1.37 (m, 16 H, CH₂), 1.57-1.73 (m, 5H, CH₂), 1.87-1.99 (m, 2H, CH₂), 5.36-5.38 (m, 2H, =CH); ¹³C NMR (CDCl₃, 75.5 MHz) δ 14.4 (CH₃), 22.9 (CH₂), 26.4 (CH₂), 26.5 (CH₂), 29.4 (CH₂), 29.5 (CH₂), 32.1 (CH₂), 32.9 (CH₂), 33.5 (CH₂), 128.0 (CH), 136.6 (CH); MS (CI) *m/z* 209 [M+H]⁺.

1-Phenyl-3-butene (10e).

The synthesis was performed according to the general procedure for **10** from **7**. Purification by flash chromatography (SiO₂, hexane) afforded **10e** (63 mg, 0.48 mmol) as a colorless oil in 55% yield. *R_f* 0.83 (hexanes); ¹H NMR (CDCl₃, 300 MHz) δ 2.44 (dt, *J* = 7.8 and 7.8 Hz, 2H, CH₂), 2.78 (t, *J* = 7.8 Hz, 2H, CH₂), 5.02-5.15 (m, 2H, =CH₂), 5.86-5.99 (m, 1H, =CH), 7.22-7.37 (m, 5H, ArH); ¹³C NMR (CDCl₃, 75.5 MHz) δ 35.7 (CH₂), 35.8 (CH₂), 115.2 (CH₂), 126.1 (CH), 128.6 (CH), 128.7 (CH), 138.4 (CH), 142.2 (C).

1-Phenyl-3-pentene (10g).

The synthesis was performed according to the general procedure for **10** from **7**. Purification by flash chromatography (SiO₂, hexane) afforded **10g** (90 mg, 0.62 mmol) as a colorless oil in 75% yield. *R_f* 0.63 (hexanes); ¹H NMR (CDCl₃, 300 MHz) δ 1.62-1.73 (m, 3H, CH₃), 2.40-2.47 (m, 2H, CH₂), 2.70-2.76 (m, 2H, CH₂), 5.49-5.55 (m, 2H, =CH), 7.22-7.37 (m, 5H, ArH); ¹³C NMR (CDCl₃, 75.5 MHz) δ 14.4 (CH₃), 34.4 (CH₂), 34.8 (CH₂), 36.1 (CH₂), 36.4 (CH₂), 124.8 (CH), 125.7 (CH), 126.0 (CH), 128.5 (CH), 128.7 (CH), 129.9 (CH), 130.9 (CH), 142.5 (C), 142.5 (C).

[2-(4-Methoxy-phenyl)-vinyl]-phosphonic acid diethyl ester (24a).

The synthesis was performed analogously to the general procedure for **7** but the reaction mixture was allowed to warm up to rt and stirred at rt for 1h before workup. Purification by flash chromatography (SiO₂, EtOAc) afforded **24a** (42 mg, 0.16 mmol) as a colorless oil in 16% yield. *R_f* 0.50 (EtOAc); ¹H NMR (CDCl₃, 300 MHz) δ 1.35 (t, *J* = 6.9 Hz, 6H, CH₃), 3.84 (s, 3H, CH₃), 4.08-4.17 (m, 4H, CH₂), 6.09 (dd, *J* = 17.4 Hz, 1H, CH); 6.90 (d, *J* = 8.7 Hz, 1H, ArH); 7.40 (dd, *J* 33.0 and 17.4 Hz, 1H, CH); 7.46 (d, *J* = 8.7 Hz, 1H, ArH); ¹³C NMR (CDCl₃, 5.5 MHz) δ 16.64 (d, *J* = 6.6 Hz, CH₃), 55.6 (CH₃), 61.96 (d, *J* = 5.5 Hz, CH₂), 109.8 (CH), 112.4 (CH), 113.8 (CH), 114.2 (CH), 114.5 (CH), 127.7 (C), 128.0 (C), 129.4 (CH), 129.6 (CH), 130.0 (CH), 148.69 (d, *J* = 7.2 Hz, C), 161.5 (C); MS (CI) *m/z* 271 [M+H]⁺; HRMS (CI) calcd for C₁₃H₁₉O₄P [M+H]⁺ 271.1099, found 271.1105.

(1-Methyl-phenyl-but-1-enyl)- phosphonic acid diethyl ester (24b).

The synthesis was performed analogously to **24a**. Purification by flash chromatography (SiO₂, gradient: EtOAc: hexane 1:2 to EtOAc) afforded **trans-24b** and **cis-24b** both (19 mg, 67 μmol) as colorless oils in 7% yield.

trans-24b. *R_f* 0.71 (EtOAc); ¹H NMR (CDCl₃, 300 MHz) δ 1.31 (t, *J* = 7.1 Hz, 6H, CH₃), 1.89 (d, *J* = 14.1 Hz, 3H, CH₃), 2.66-2.77 (m, 2H, CH₂), 2.85-2.89 (m, 2H, CH₂), 3.95-4.17 (m, 4H, CH₂), 6.23 (dt, *J* = 56.7 and 3.6 Hz, CH), 7.17-7.32 (m, 5H, ArH); ¹³C NMR (CDCl₃, 75.5 MHz) δ 16.60 (d, *J* = 6.5 Hz, CH₃), 21.99 (d, *J* = 12.7 Hz, CH₃), 31.75 (d, *J* = 6.0 Hz, CH₂), 35.8 (CH₂), 61.43 (d, *J* = 5.5 Hz, CH₂), 124.82 (d, *J* = 172 Hz, C), 126.1 (CH), 128.6 (CH), 128.8 (CH), 141.6 (C), 147.48 (d, *J* = 12.7 Hz, CH); ³¹P NMR (CDCl₃, 121.5 MHz) δ 20.2; MS (CI) *m/z* 283 [M+H]⁺; HRMS (CI) calcd for C₁₅H₂₃O₃P [M+H]⁺ 283.1463, found 283.1467.

cis-24b. *R_f* 0.63 (EtOAc); ¹H NMR (CDCl₃, 300 MHz) δ 1.31 (t, *J* = 7.1 Hz, 6H, CH₃), 1.70 (d, *J* = 14.4 Hz, 3H, CH₃), 2.47-2.57 (m, 2H, CH₂), 2.75-2.80 (m, 2H, CH₂), 3.91-4.15 (m, 4H, CH₂), 6.60 (dt, *J* = 23.7 and 1.5 Hz, CH), 7.18-7.32 (m, 5H, ArH); ¹³C NMR (CDCl₃, 75.5 MHz) δ 12.70 (d, *J* = 11.0 Hz, CH₃), 16.57 (d, *J* = 6.1 Hz, CH₃), 30.62 (d, *J* = 19.8 Hz, CH₂), 34.8 (CH₂), 61.73 (d, *J* = 4.9 Hz, CH₂), 125.45 (d, *J* = 179 Hz, C), 126.3 (CH), 128.6 (CH), 141.3 (C), 145.72 (d, *J* = 9.9 Hz, CH); ³¹P NMR (CDCl₃, 121.5 MHz) δ 22.7; MS (CI) *m/z* 283 [M+H]⁺; HRMS (CI) calcd for C₁₅H₂₃O₃P [M+H]⁺ 283.1463, found 283.1467.