Electronic Supplementary Material (ESI) for Chemical Communications

Phosphine-Boronates: Efficient Bifunctional Organocatalysts for Michael Addition

Olivier Baslé, Susana Porcel, Sonia Ladeira, Ghenwa Bouhadir* and Didier Bourissou*

SUPPLEMENTARY INFORMATION

Contents

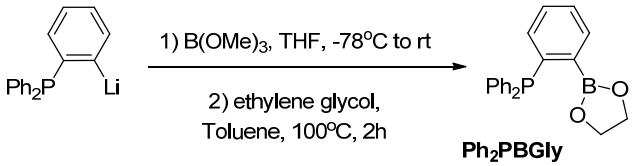
Materials and Methods

General considerations: All reactions and manipulations were carried out under an atmosphere of dry argon using standard Schlenk techniques. Dry, oxygen-free solvents were employed. Diethyl ether and toluene were dried over sodium, CH_2Cl_2, acetonitrile and pentane were dried over CaH_2 and distilled prior to use. ^{1}H, ^{13}C, ^{31}P, ^{11}B NMR spectra were recorded on a Bruker Avance 300 or 500 spectrometer at 25ºC. Chemical shifts are expressed with a positive sign, in parts per million (ppm), relative to residual ^{1}H ($CDCl_3$: 7.26 ppm) and ^{13}C ($CDCl_3$: 77.16 ppm) solvent signals and external, 85% H_3PO_4 (0 ppm) and $BF_3.OEt_2$ (0 ppm), respectively. Mass spectra were recorded on a Waters LCT mass spectrometer.

Synthesis of phosphine-boronates

The phosphine-boronates **Ph_2PBpin** and **Ph_2PBNeo** were prepared as previously described.[1]

Synthesis of the phosphine-boronate Ph_2PBGly

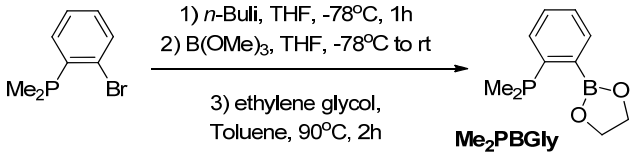


Trimethyl borate (1.73 mL, 15.54 mmol) was added to a solution of *o*-lithiated triphenylphosphine[2] (0.89 g, 2.59 mmol) in THF (10 mL) at –78ºC. The mixture was stirred from –78ºC to rt overnight. Then THF was removed under vacuum and the residue obtained was extracted with DCM (3 x 5 mL). After removing DCM to dryness, the product was dissolved in 6 mL of a mixture ethylene glycol/toluene (1:5). The mixture was stirred at 100ºC for 2 h, thereafter the toluene layer was separated by decantation and concentrated to dryness. The solid obtained was further purified by crystallization in Et_2O at – 60^{0}C. **Ph_2PBGly** was obtained as colorless crystals: 0.35 g (41%), m.p.: 82-84ºC. $^{31}P\{^{1}H\}$ NMR (202.5 MHz, $CDCl_3$): δ = –3.9. ^{11}B NMR (160.5 MHz, $CDCl_3$): δ = 31.8. ^{1}H NMR (500.3 MHz, $CDCl_3$): δ = 7.87-7.84 (m, 1 H, H_{arom}), 7.38-7.28 (m, 12 H, H_{arom}), 6.96-6.93 (m, 1 H, H_{arom}), 4.17 (s, 4 H, CH_2). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 144.2 (d, $^{1}J_{C\text{-}P}$ = 18.0 Hz, $C_{ipso\text{-}P}$), 138. 1 (d, $^{2}J_{C\text{-}P}$ = 11.5 Hz, $C_{ipso\text{-}B}$), 135.7 (d, $J_{C\text{-}P}$ = 9.2 Hz, CH_{arom}), 134.1 (d, $J_{C\text{-}P}$ = 20.2 Hz, CH_{arom}), 133.7 (d, $^{1}J_{C\text{-}P}$ = 19.4 Hz, $C_{ipso\text{-}P}$), 132.6 (d, $J_{C\text{-}P}$ = 1.9 Hz, CH_{arom}), 130.7 (s, CH_{arom}), 128.7 (s, CH_{arom}), 128.4 (d, $J_{C\text{-}P}$ = 7.1 Hz, CH_{arom}), 127.4 (s, CH_{arom}), 65.8 (s, CH_2). HRMS (ESI+) calcd for $[M+H]^+$ ($C_{20}H_{19}BO_2P^+$): 333.1216, found: 333.1248. Anal. Calcd. for $C_{20}H_{18}BO_2P$: C 72.32, H 5.46; found: C 71.96; H 5.28.

[1] S. Porcel, G. Bouhadir, N. Saffon, L. Maron and D. Bourissou, *Angew. Chem., Int. Ed.*, 2010, **49**, 6186

[2] T. W. Hudnall, Y.-M. Kim, M. W. P. Bebbington, D. Bourissou and F. P. Gabbai, *J. Am. Chem. Soc*. 2008, **130**, 10890.

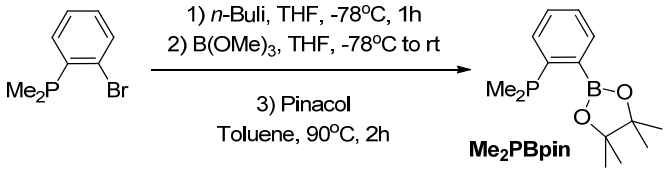
Synthesis of the phosphine-boronate Me_2PBGly



To a solution of (*o*-bromophenyl)dimethylphosphine[3] (1.05 g, 4.84 mmol) in THF (9 mL) was slowly added *n*-BuLi (3 mL, 1.6 M) at –78ºC. The solution turned yellow and a white precipitate appeared with the time. After stirring for 1 h, trimethyl borate (3.23 mL, 29.04 mmol) was added at –78ºC. The mixture was warmed up to rt over 4 h. THF was removed under vacuum and the residue obtained was extracted with Et_2O (3 x 5 mL). After removing Et_2O to dryness, the oil obtained was dissolved in 12 mL of a mixture ethylene glycol/toluene (1:5). The mixture was stirred at 90ºC for 2 h. Thereafter the toluene layer was separated by decantation and concentrated to dryness. The oil obtained was heated at 90ºC under vacuum overnight to removed the residues of dimethylphenylphosphine coming from the hydrolysis of the lithium intermediate. Finally the desired compound was further purified by crystallization at –60°C in pentane. **Me_2PBGly** was obtained as colorless crystals: 0.34 g (35%), m.p.: 64-66ºC. $^{31}P\{^1H\}$ NMR (202.5 MHz, C_6D_6): δ = –46.4. ^{11}B NMR (160.5 MHz, $CDCl_3$): δ = 32.0. ^1H NMR (500.3 MHz, C_6D_6): δ = 7.82 (d br, $^3J_{H-H}$ = 7.3 Hz, 1 H, H_{arom}), 7.52 (dd $^3J_{H-H}$ = 7.4 Hz, $^3J_{H-P}$ = 4.1 Hz, 1 H, H_{arom}), 7.46 (m, 1 H, H_{arom}), 7.25 (pseudo-t br, $^3J_{H-H}$ = 7.4 Hz, 1 H, H_{arom}), 4.44, (s, 4 H, CH_2), 1.34 (d, $^2J_{H-P}$ = 3.0 Hz, 6 H, CH_3P). ^{13}C NMR (125.8 MHz, C_6D_6): δ = 148.7 (d, $^1J_{C-P}$ = 18.9 Hz, C_{ipso-P}), 135.7 (d, $^2J_{C-P}$ = 9.9 Hz, CH_{arom}), 130.7 (s, CH_{arom}), 128.1 (s, CH_{arom}), 127.2 (s, CH_{arom}), 62.0 (s, CH_2), 15.3 (d, $^1J_{C-P}$ = 13.2 Hz, CH_3), (C_{ipso-B} not observed). HRMS (ESI+) calcd for $[M+H]^+$ ($C_{10}H_{15}BO_2P^+$): 209.0903, found: 209.0916.

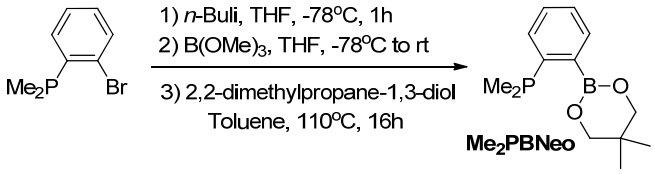
[3] D. Werner and L. Dahlenburg, *Z. Naturforsch*, 1987, **42**, 1110.

Synthesis of the phosphine-boronate Me_2PBpin



The experimental procedure is similar to that used for the synthesis of **Me_2PBGly**. To a solution of (*o*-bromophenyl)dimethylphosphine[3] (0.77 g, 3.58 mmol) in THF (7 mL) was slowly added *n*-BuLi (2.47 mL, 1.6 M) at -78ºC, the solution turned yellow and a white precipitate appeared with the time. After stirring for 1 h, trimethyl borate (2.39 mL, 21.5 mmol) was added at –78ºC. The mixture was stirred from –78ºC to rt overnight. THF was then removed under vacuum and the residue was washed with DCM (3 x 5 mL). The combined DCM phases were concentrated to dryness to furnish an oil. A solution of the oil in toluene (5 mL) was added to a solution of pinacol (0.43 g, 3.58 mmol) in toluene (5 mL).The mixture was stirred at 90ºC for 2 h, then was cooled to rt and filtered off via cannula (the excess of pinacol remained unsoluble). Toluene was concentrated to dryness and the oil obtained heated at 90ºC under vacuum overnight. The desired compound was further purified by crystallization in pentane at –60°C. **Me_2PBpin** was obtained as colorless crystals: 0.13 g (13%). m.p.: 44-46°C. $^{31}P\{^1H\}$ NMR (202.5 MHz, $CDCl_3$): δ = –46.5. ^{11}B NMR (160.5 MHz, $CDCl_3$): δ = 31.3. ^1H NMR (500.3 MHz, $CDCl_3$): δ = 7.74 (dd br, $^3J_{H\text{-}H}$ = 6.0 Hz, 1 H, H_{arom}), 7.48 (m, 1 H, H_{arom}), 7.42 (pseudo-t br, $^3J_{H\text{-}H}$ = 7.2 Hz, 1 H, H_{arom}), 7.30 (pseudo-t br, $^3J_{H\text{-}H}$ = 7.1 Hz, 1 H, H_{arom}), 1.41, (s, 12 H, CH_3), 1.34 (d, $^2J_{H\text{-}P}$ = 2.4 Hz, 6 H, PCH_3). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 148.4 (d, $^1J_{C\text{-}P}$ = 20.0 Hz, $C_{ipso\text{-}P}$), 134.9 (d, $^2J_{C\text{-}P}$ = 10.2 Hz, CH_{arom}), 130.3 (s, CH_{arom}), 127.8 (s, CH_{arom}), 127.0 (s, CH_{arom}), 84.1 (s, C_q), 24.9 (s, CH_3), 14.9 (d, $^1J_{C\text{-}P}$ = 13.6 Hz, PCH_3), ($C_{ipso\text{-}B}$ not observed). HRMS (ESI+) calcd for $[M+H]^+$ ($C_{14}H_{22}BO_2P^+$): 265.1529, found: 265.1515.

Synthesis of the phosphine-boronate Me_2PBNeo

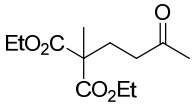


The experimental procedure is similar to that used for the synthesis of **Me_2PBGly** and **Me_2PBpin**. To a solution of (*o*-bromophenyl)dimethylphosphine[3] (1.76 g, 8.09 mmol) in THF (20 mL) was slowly added *n*-BuLi (5.05 mL, 1.6 M) at –78ºC. The solution turned yellow and a white precipitate appeared with the time. After stirring for 1 h, trimethyl borate (5.5 mL, 48.5 mmol) was added at -78ºC. The mixture was stirred from -78ºC to rt overnight. THF was removed under vacuum and the residue obtained was extracted with DCM (3 x 5 mL). The combined DCM phases were concentrated to dryness to furnish an oil. To a solution of the oil in toluene (20 mL) was added neopentyl glycol (1.53 g, 14.7 mmol). The mixture was stirred at 110ºC for 16 h, then was cooled to rt and filtered off via cannula (the excess of neopentyl glycol remained unsoluble). Toluene was concentrated to dryness and the oil obtained diluted in pentane (3 x 10 mL). Filtration via cannula and evaporation of the combined organic solutions provided the clean product **Me_2PBNeo** as a colorless oil (68%). $^{31}P\{^1H\}$ NMR (121.5 MHz, $CDCl_3$): δ = –46.3. ^{11}B NMR (96.3 MHz, $CDCl_3$): δ = 29.0. ^1H NMR (300.1 MHz, $CDCl_3$): δ = 7.59 (d br, $^3J_{H-H}$ = 7.2 Hz, 1 H, H_{arom}), 7.38 (m, 1 H, H_{arom}), 7.28 (pseudo-t br, $^3J_{H-H}$ = 7.2 Hz, 1 H, H_{arom}), 7.18 (pseudo-t br, $^3J_{H-H}$ = 7.2 Hz, 1 H, H_{arom}), 3.7, (s, 4H, CH_2), 1.08 (d, $^2J_{H-P}$ = 3.0 Hz, 6 H, PCH_3), 0.98 (s, 6H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 147.3 (d, $^1J_{C-P}$ = 18.9 Hz, C_{ipso-P}), 133.7 (d, $^2J_{C-P}$ = 10.9 Hz, CH_{arom}), 129.5 (s, CH_{arom}), 128.0 (s, CH_{arom}), 127.1 (s, CH_{arom}), 71.8 (s, OCH_2), 31.1 (s, C_q), 21.6 (s, CH_3), 15.1 (d, $^1J_{C-P}$ = 15.0 Hz, PCH_3), (C_{ipso-B} not observed). HRMS (ESI+) calcd for $[M+H]^+$ ($C_{13}H_{21}BO_2P^+$): 251.1372, found: 251.1367.

General procedure for the Michael addition reactions

In a glove-box, the phosphine-boronate catalyst (10 mol%) was weighed in a 10 mL Schlenck. Acetonitrile (0.4 mL), the malonate substrate (0.2 mmol), and methyl vinyl ketone (0.2 or 0.4 mmol) were successively added with a syringue through a septum. The reaction mixture was then stirred at 25°C for the indicated time. The solvent was evaporated and the residue was dissolved in $CDCl_3$. Yields were determined by ^1H NMR using mesitylene as an internal standard. Compounds **3**, **4** and **5** were identified by comparison with related spectroscopic data.[4]

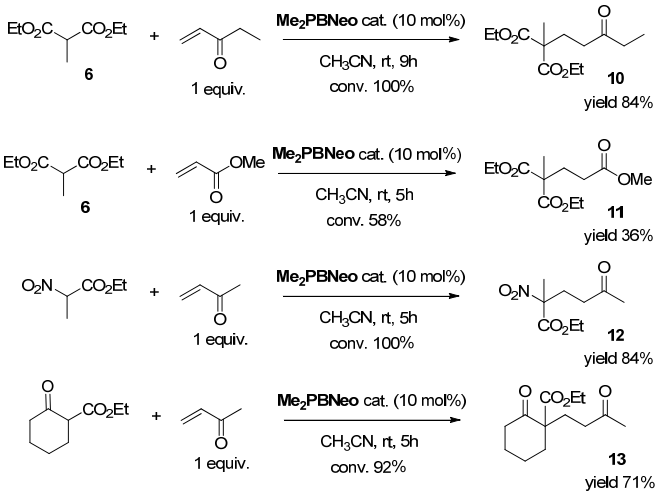
2-Methyl-2-(3oxobutyl)-diethyl ester **7** [5]:



7: Yellowish oil. ^1H NMR (300.1 MHz, $CDCl_3$): δ = 4.13 (q, *J* = 7.1 Hz, 4H, CH_2O), 2.46 (pseudo-t, *J* = 7.5 Hz, 2H, CH_2), 2.10 (s, 3H, CH_3-CO), 2.07 (pseudo-t, *J* = 7.5 Hz, 2H, CH_2), 1.35 (s, 3H, CH_3-C_q), 1.21 (t, *J* = 7.1 Hz, 6H, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 207.5 (C=O, ketone), 171.9 (C=O, ester), 61.4 (CH_2O), 52.9 (C), 38.6 (*CH_2*-C=O), 29.7 (CH_3, ketone), 29.3 (*CH_2*-C), 20.3 (*CH_3*-C), 13.9 (CH_3, ester). HRMS (ESI+) calcd for $[M+Na]^+$ ($C_{12}H_{20}O_5Na^+$): 267.1208, found: 267.1212.

Preliminary studies of the substrate scope

Compounds **10**,[6] **11**,[7] **12**[8] and **13**[9] were authenticated by comparison with reported spectroscopic data.



[4] E. Gómez-Bengoa, J. M. Cuerva, C. Mateo and A. M. Echavarren, *J. Am. Chem. Soc.* 1996, **118**, 8553.
[5] W. H. Tamblyn and R. E. Waltermire, *Tetrahedron Lett.* 1984, **24**, 2803.
[6] T. Caruso, M. Feroci, A. Inesi, M. Orsini, A. Scettri and L. Palombri, *Adv. Synth. Catal.* 2006, **348**, 1942.
[7] L. S. Hegedus and W. H. Darlington, *J. Am. Chem. Soc.* 1980, **102**, 4980.
[8] B. R. Linton, M. H. Reutershan, C. M. Aderman, E. A. Richardson, K. R. Brownell, C. W. Ashley, C. A. Evans and S. J. Miller, *Tetrahedron Lett.* 2007, **48**, 1993.
[9] G. Kumaraswanny, N. Jena, M. N. V. Sastry, M. Panmaja and B. Markondaiah, *Adv. Synth. Catal.* 2005, **347**, 867.

Table S1. Screening of the reaction conditions for the Michael addition of dimethylmalonate **1** to MVK **2**[a]

Entry	Ratio **1**:**2**	Catalyst	solvent	Conv (%)[b]	**3** (%)[b]	**4** / **5** (%)[c]
1	1:1	**Ph_2PBpin**	THF	13	9	<5
2	1:2	**Ph_2PBpin**	THF	22	20	<5
3	1:1	**Ph_2PBpin**	CH_3CN	60	49	6/2
	1:1	PPh_3	CH_3CN	45	43	<5
	1:1	PPh_3/PhBpin	CH_3CN	42	39	<5
	1:1	PhBpin	CH_3CN	<5	<5	<5
4	1:2	**Ph_2PBpin**	CH_3CN	89	67	15/6
5	1:2	**Ph_2PBpin**	toluene	20	17	<5
6	1:2	**Ph_2PBpin**	DMF	92	65	20/7
7	1:2	**Ph_2PBpin**	DCM	43	38	<5
8	1:2	PPh_3	CH_3CN	66	56	2/8

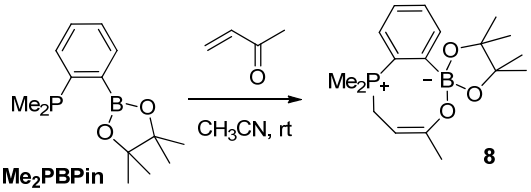
[a] Reactions were carried out with **1** (0.2 mmol) during 9h at 25°C in 0.4 mL solvent. [b] Determined by ^{1}H NMR. [c] Yields determined by ^{1}H NMR using mesitylene as internal standard.

Table S2. Catalyst survey for the Michael addition of the substituted malonate **6** to MVK[a]

Entry	Ratio **6**:**2**	Catalyst	Time (h)	**7** (%)[b]
1	1:2	PPh_3	62	30
2	1:2	**Ph_2PBPin**	62	34
3	1:2	**Ph_2PBGly**	62	82
4	1:2	**Ph_2PBNeo**	62	95
5	1:1	Me_2PPh	5	85
6	1:1	**Me_2PBPin**	5	50
7	1:1	**Me_2PBGly**	5	80
8	1:1	**Me_2PBNeo**	5	95

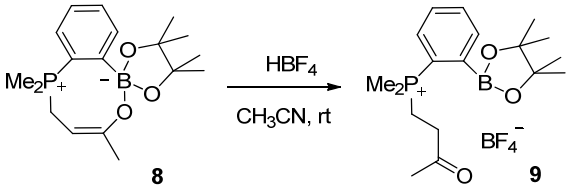
[a] Reactions were carried out with **6** (0.2 mmol), at 25°C in acetonitrile (0.4 mL). [b] Yields determined by ^{1}H NMR using mesitylene as internal standard.

Synthesis of the β-phosphonium enolate 8



To a solution of **Me$_2$BPin** (0.01 g, 0.037 mmol) in CD_3CN (0.6 mL), was added methyl vinyl ketone (3 10^{-3} mL, 0.037 mmol) at rt. The adduct **8** formed instantaneously (together with less than 10% of a secondary product coming from partial protonation of **8**). m.p.: 122-124°C. $^{31}P\{^1H\}$ NMR (202.5 MHz, CD_3CN): δ = 31.5. ^{11}B NMR (160.5 MHz, CD_3CN): δ = 6.6. ^1H NMR (500.3 MHz, CD_3CN): δ = 7.91 (dd, $^3J_{H-H}$ = 7.5 Hz, $^4J_{H-P}$ = 2.9 Hz, 1 H, H_{arom}), 7.48-7.44 (m, 2 H, H_{arom}), 7.27 (ddt, $^3J_{H-H}$ = 7.6 Hz, $^4J_{H-H}$ = 1.5 Hz, $^3J_{H-P}$ = 3.5 Hz, 1 H, H_{arom}), 4.20 (pseudo-q, $^3J_{H-H}$ = $^3J_{H-P}$ = 7.3 Hz, 1 H, $H_{vinylic}$), 3.61-3.51 (m, 2 H, PCH_2), 2.04 (d, $^2J_{H-P}$ = 13.4 Hz, 6 H, CH_3), 1.41, (d, $^4J_{H-P}$ = 5.7 Hz, 3 H, CH_3), 1.20 (s, 6 H, CH_3), 0.89 (s, 6 H, CH_3). ^{13}C NMR (125.8 MHz, CD_3CN): δ = 160.6 (d, $^3J_{C-P}$ = 10.6 Hz, C_{enolic}), 133. 5 (d, $^3J_{C-P}$ = 17.6 Hz, CH_{arom}), 131.4 (d, $^4J_{C-P}$ = 3.8 Hz, CH_{arom}), 129.5 (d, $^3J_{C-P}$ = 15.1 Hz, CH_{arom}), 125.4 (d, $^2J_{C-P}$ = 12.6 Hz, CH_{arom}), 122.1 (d, $^1J_{C-P}$ = 100.0 Hz, C_{ipso-P}), 87.6 (d, $^2J_{C-P}$ = 12.6 Hz, $CH_{vinylic}$), 78.3 (s, C_q), 25.2 (s, CH_3), 25.1 (s, CH_3), 23.3 (d, $^1J_{C-P}$ = 54.3 Hz, CH_2), 23.1 (s, CH_3), 10.4 (d, $^1J_{C-P}$ = 52.2 Hz, CH_3), (C_{ipso-B} not observed). Single crystals were grown from concentrated solution of CH_3CN at room temperature.

Synthesis of the γ-keto phosphonium 9



To an NMR tube containing a solution of the β-phosphonium enolate **8** (12.3 mg, 0.037 mmol) in CD_3CN (0.6 mL) was added tetrafluoroboric acid (5 10^{-3} mL, 0.037 mmol). After 5 minutes, the γ-keto phosphonium **9** was cleanly formed.

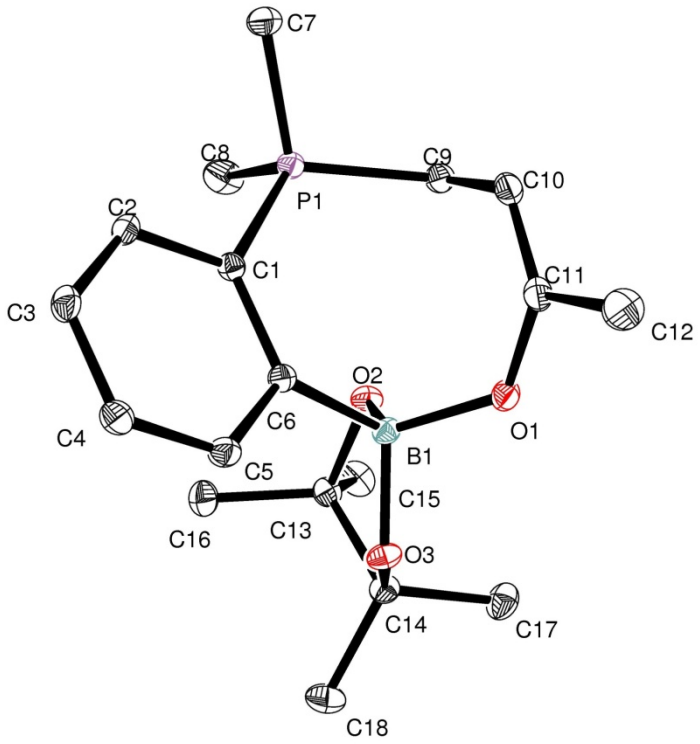
9: $^{31}P\{^1H\}$ NMR (161.9 MHz, CD_3CN): δ = 28.2 ^{11}B NMR (96.3 MHz, CD_3CN): δ = 29.9. ^1H NMR (400.3 MHz, CD_3CN): δ = 8.20-8.22 (m, 1H), 7.75-7.86 (m, 3H), 2.70-2.86 (m, 4H, CH_2), 2.22 (d, $^1J_{P-H}$ = 14.0 Hz, 6H, PCH_3), 2.07 (s, 3H, CH_3), 1.54 (s, 12H, CH_3). ^{13}C NMR (100.6 MHz, CD_3CN): δ = 205.0 (d, $^3J_{C-P}$ = 11.5 Hz, C=O), 138.9 (d, J_{C-P} = 13.5 Hz, CH_{arom}), 133.4 (d, J_{C-P} = 8.2 Hz , CH_{arom}), 131.9 (d, J_{C-P} = 12.7 Hz, CH_{arom}), 124.9 (d, $^1J_{C-P}$ = 82.0 Hz, C_{ipso-P}) , 85.8 (s, C_{pin}), 35.9 (d, $^2J_{C-P}$ = 3.4 Hz, CH_2), 28.6 (s, CH_3), 24.1 (s, CH_3), 18.7 (d, $^1J_{C-P}$ = 54.8 Hz, CH_2P), 8.9 (d, $^1J_{C-P}$ = 50.5 Hz, CH_3). HRMS (ESI+) calcd for $[cation]^+$ ($C_{18}H_{29}BO_3P^+$): calcd 335.1947; found 335.1939.

Evaluation of the β-phosphonium enolate 8 in a catalytic Michael addition reaction

In a glove-box, β-phosphonium enolate **8** (10 mol%) was weighed in a 10 mL Schlenck. Acetonitrile (0.4 mL), the malonate substrate (0.2 mmol), and methyl vinyl ketone (0.2 mmol) were successively added with a syringue through a septum. The reaction mixture was then stirred at room temperature for 1h. The solvent was evaporated and the residue was dissolved in $CDCl_3$. Yields were determined by ^1H NMR using mesitylene as an internal standard: **3** (61%), **4** (14%), **5** (10%).

Selected crystal data

Molecular view of 8 in the solid state (the hydrogen atoms and solvent molecules are omitted for clarity).



Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC–863009. These data can be obtained free of charge via www.ccdc.cam.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223_336_033; or deposit@ccdc.cam.ac.uk). Data were collected using an oil–coated shock–cooled crystal on a Bruker–AXS Kappa APEX II Quazar diffractometer (λ = 0.71073 Å), at 193(2) K. Semi-empirical absorption corrections were employed.[10] The structure was solved by direct methods (SHELXS–97),[11] and refined using the least–squares method on F^2.[12]

$C_{18}H_{28}BO_3P$, M = 334.20, monoclinic, space group $P2_1/n$, a = 8.7201(7) Å, b = 14.3694(13) Å, c 14.5530(12) Å, $\alpha = 90°$, $\beta = 97.668(4)°$, $\gamma = 90°$, V = 1807.2(3) Å^3, Z = 4, crystal size: 0.34 x 0.22 x 0.12 mm^3, 26716 reflections collected (5250 independent, R_{int} = 0.0414), 215 parameters, $R1$ [I>2σ(I)] = 0.0398, $wR2$ [all data] = 0.1388, largest diff. peak and hole: 0.396 and -0.244 e.Å^{-3}.

[10] SADABS, Program for data correction, Bruker_AXS.
[11] G. M. Sheldrick, *Acta Crystallogr.* 1990, **A46**, 467.
[12] SHELXL-97, Program for Crystal Structure Refinement, G. M. Sheldrick, *Acta Crystallogr.* 2008, **A64**, 112.