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Cyclisation of bisphosphonate substituted enynes

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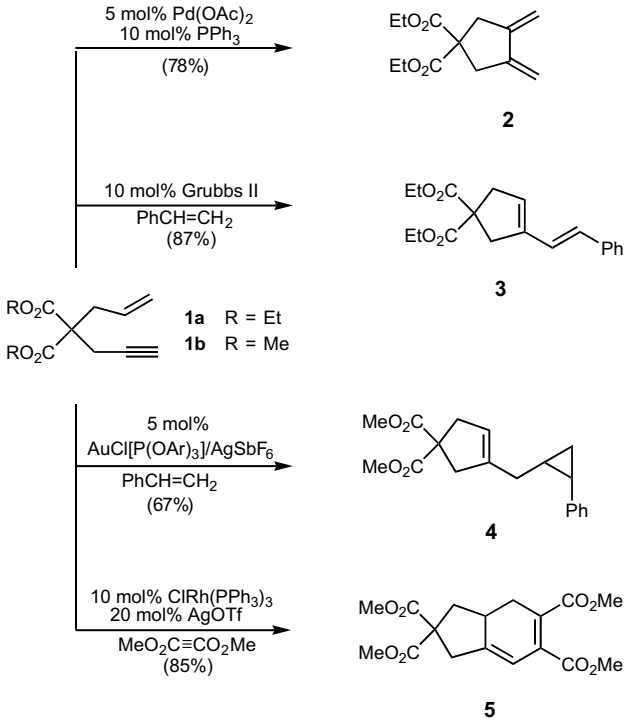
ABSTRACT

A new synthetic route to the bisphosphonate enyne tetraethyl hept-1-yn-6-en-4,4-diylbisphosphonate has been developed and the enyne has been used successfully in a range of transition metal-catalysed cyclisations that give structurally varied products. The motifs generated via such reactions provide new scaffolds for constructing bisphosphonic acids, an important class of therapeutic agents. NMR experiments indicate that the introduction of phosphonate substitutents onto cyclisation substrates provides a promising new approach to studying metal-catalysed cyclisations.

1. Introduction

Enynes undergo many transition metal-catalysed cyclisation reactions leading to a diverse array of molecular structures. The transformation of a relatively simple substrate into a more complex product under catalytic conditions without the generation of byproducts means that reactions of this type fulfil many of the demanding criteria now expected in organic chemistry. As a result there has been much interest in the cyclisation of 1,6-enynes in recent years, not only in cycloisomerisation reactions,[1] exemplified by the seminal observation that palladium catalyses the conversion of enyne **1a** to diene **2**,[2] but also in reactions that couple the 1,6-enyne with a second component such as (i) an external alkene in the enyne diene–ene metathesis reaction between **1a** and styrene to give **3**,[3] or the cyclisation, rearrangement and cyclopropanation sequence that converts **1b** and styrene to **4**,[4] or (ii) an external alkyne as exemplified by the [2+2+2] cyclisation that takes place between **1b** and dimethyl acetylenedicarboxylate to give **5**[5] (Scheme 1).

A spectacular range of catalysts have been used to cyclise enynes: for example cycloisomerisations catalysed by Pd, Ru, Rh, Ir, Pt, Au, Hg, Ti, Zr, Cr, Fe, Co, Ni, Cu, Ag, Ga and In species have all been reported.[1] In contrast, the substrates used to probe enyne cyclisations are more limited in nature. Enynes based on malonates such as **1a**, sulfonamides such as **6**, or ether **7** (Fig. 1), account for the substrates used in the vast majority of enyne cyclisations examined to date. Occasional use has been made of the bis-sulfone **8**.[6]



Scheme 1. Typical cyclisations of 1,6-enynes.

To the best of our knowledge a bisphosphonate substrate has been used for only one type of cyclisation, the palladium-catalysed cycloisomerisation of **9** to **10** (Scheme 2).[7] A cycloisomerisation of

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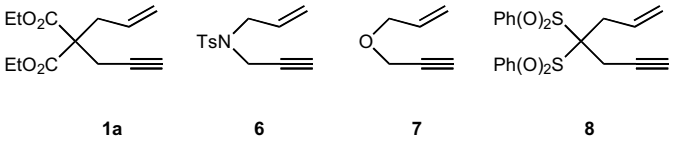
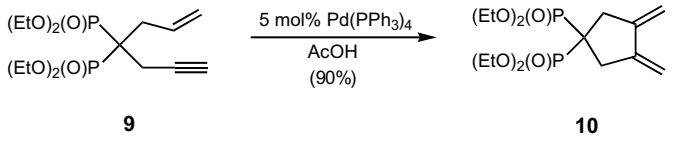


Figure 1. Typical substrates for cyclisation reactions.



Scheme 2. The palladium-catalysed cycloisomerisation of bisphosphonate enyne **9**.

this type has been elegantly applied in the synthesis of conformationally restricted cyclic farnesyl analogues.[8]

The paucity of examples of the use of bisphosphonate substrates such as **9** in cyclisation studies is somewhat surprising in view of (i) the potential biological activity and therapeutic applications of the novel bisphosphonic acid derivatives that could be accessed from the cyclic products, given that the methylenebisphosphonic acid unit is an excellent chelator and many of its derivatives are either in clinical use (e.g., **11**,[9] zoledronic acid, Fig. 2) or under investigation (e.g., **12**,[10] **13**[11]) for the treatment of diseases characterised by abnormal calcium metabolism, particularly abnormal bone metabolism; and (ii) the potential use of a phosphorus labelled substrate for monitoring and probing cyclisation reactions by ^{31}P NMR spectroscopy, particularly as many of the cyclisations studied are based on phosphane-containing catalysts.

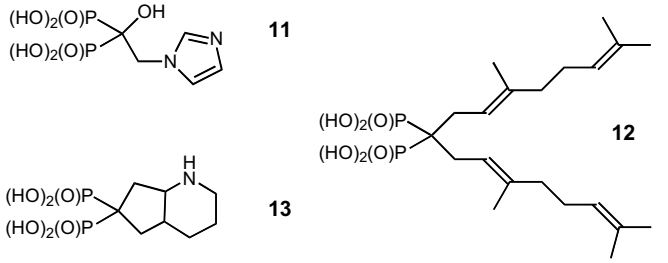
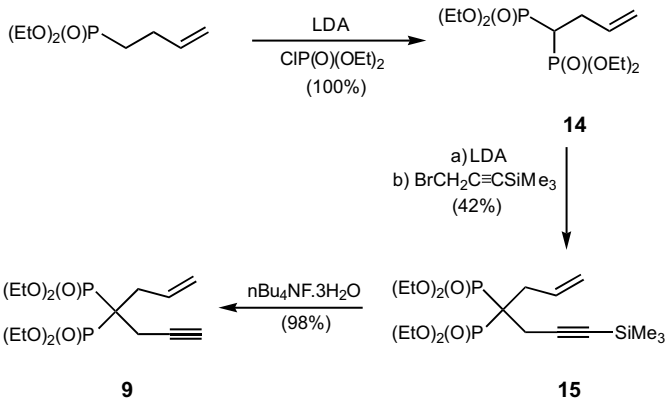


Figure 2. Bisphosphonic acid derivatives in clinical use (**11**), or under investigation (**12**, **13**), for the treatment of diseases characterised by abnormal calcium metabolism.

In light of the above, we report here a new straightforward synthesis of the bisphosphonate substrate **9**, examples of its use in several types of cyclisation leading to structurally diverse and novel bisphosphonates, and ^{31}P NMR experiments that demonstrate the potential of substrate **9** for use in the monitoring of 1,6-enyne cyclisations.

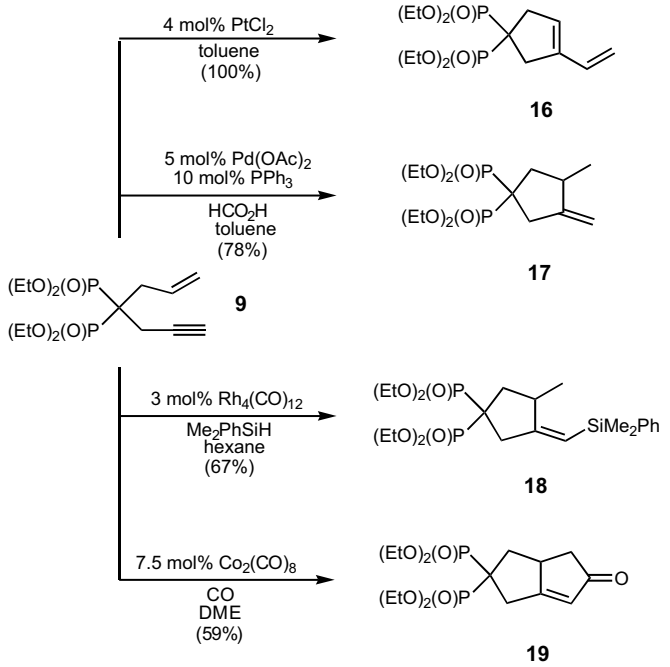
2. Results and discussion

The bisphosphonate enyne **9** has previously been prepared by derivatisation of tetraethyl methylenebisphosphonate with first propargyl bromide and then allyl bromide.[7] In our hands, however, the first step of this synthesis gave a mixture of starting material, desired product and bis-propargylated material, which proved very difficult to separate by either column chromatography or distillation. We thus devised the following new approach to enyne **9**. Reaction of diethyl but-3-enyl-1-phosphonate with lithium diisopropylamide (LDA) followed by diethyl chlorophosphate gave bisphosphonate **14** in quantitative yield according to a literature procedure (Scheme 3).[12] [It is of note that attempts to synthesise **14** by allylation of tetraethyl methylenebisphosphonate have been reported to give a modest yield (28%), which was attributed to competition between monoalkylation and dialkylation.[12]] The required propargyl substituent was subsequently introduced as its trimethylsilyl derivative to give the novel enyne **15** in satisfactory yield, given the steric demands of creating a quaternary centre flanked by two phosphonate esters. Removal of the trimethylsilyl group using tetrabutylammonium fluoride proceeded smoothly to give the desired bisphosphonate enyne **9**. Overall the sequence proved straightforward to execute and was used to make multigram quantities of **9**.

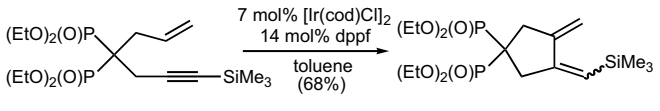


Scheme 3. A new synthesis of the bisphosphonate enyne **9**.

In order to ascertain whether or not enyne **9** was a suitable substrate for enyne cyclisations in general, several new cyclisations of the bisphosphonate substrate were examined (Scheme 4). These were selected on the basis that they employed a range of different catalysts and reaction conditions, and that they generated a structurally varied array of products. Initially a platinum-catalysed isomerisation that had been developed on the malonate-based enyne **1a**[13] was investigated and this was found to proceed in excellent yield (100%) to generate the novel bisphosphonate diene **16**. Cyclisations that proceed with concomitant hydrogenation[14] or hydrosilylation[15] were examined next. These gave the novel bisphosphonate alkene **17** and the novel silylated bisphosphonate alkene **18** in 78% and 67% yield, respectively. Finally, cyclisation accompanied by carbonylation (the catalytic Pauson–Khand



Scheme 4. Cyclisations of bisphosphonate enyne **9**.



15 **20** (*E*:*Z*, 1:1.1)

Scheme 5. Iridium-catalysed cycloisomerisation of silyl-substituted enyne **15**.

reaction), which has been studied and applied extensively on the malonate substrates **1**, the sulfonamide substrate **6** and the ether substrate **7**,[16] was examined for the first time on the bisphosphonate substrate **9**, leading to the isolation of the novel cyclopentenone **19** in 59% yield.

During the course of our study of the cyclisation chemistry of bisphosphonate enyne **9**, it became apparent that the presence of the phosphonate substituents facilitated reaction optimisation. For example, the phosphonates of enyne **9** appeared as a singlet at δ 24.2 in its ^{31}P NMR spectrum in $CDCl_3$. On cyclisation to **18**, this was replaced by two doublets at δ 27.5 and 29.7, reflecting the diastereotopicity imparted by the chiral centre in **18**. Thus the reaction conditions for the cyclisation of **9** to **18** were very rapidly optimised by recording the ^{31}P NMR spectrum of the crude product mixture. It also proved possible to readily observe isomeric mixtures. For example, the presence of the two geometric isomers of diene **20** was clearly indicated by two singlets at δ 25.8 and 26.6 in the ^{31}P NMR spectrum ($CDCl_3$) of the crude product mixture obtained from the iridium-catalysed cycloisomerisation[17] of the silyl-substituted enyne **15** (singlet at δ 24.4, $CDCl_3$) (Scheme 5).

More significantly, the concept of replacing the malonate, sulfonamide or ether linkages commonly used in cyclisation reactions with methylenebisphosphonate linkages promises to provide a useful tool with which to study the reaction profile of cyclisations. The cyclisations of enyne **9** to products **10** and **16**–**19** were all conducted in an NMR tube and monitored by ^{31}P NMR spectroscopy. In all cases the conversion of starting material **9** into product was clearly observed (the chemical shifts for enyne **9** and products **10** and **16**–**19** in the given reaction solvent are provided in Table 1.)

Moreover, in some cases, reaction intermediates were observed. In one example, close examination of the spectra obtained on monitoring the platinum-catalysed conversion of enyne **9** (singlet at δ=24.0) into diene **16** (singlet at δ=26.4) by ^{31}P NMR spectroscopy revealed the appearance and disappearance during the course

Table 1
The ^{31}P NMR chemical shifts (δ) of enyne **9** and cyclisation products **10** and **16**–**19** in the solvents used to monitor the cyclisations

Chemical shift (δ) of enyne **9** in reaction mixture	Product P	Chemical shift (δ) of product P in reaction mixture	Solvent
25.7	**10**	28.1	AcOH
24.0	**16**	26.4	Toluene
23.7	**17**	26.7 (d, J=16.5 Hz), 27.3 (d, J=16.5 Hz)	Toluene
25.7	**18**	28.4 (d, J=18 Hz), 29.3 (d, J=18 Hz)	Hexane
24.6	**19**	26.0 (d, J=12.5 Hz), 27.3 (d, J=12.5 Hz)	DME

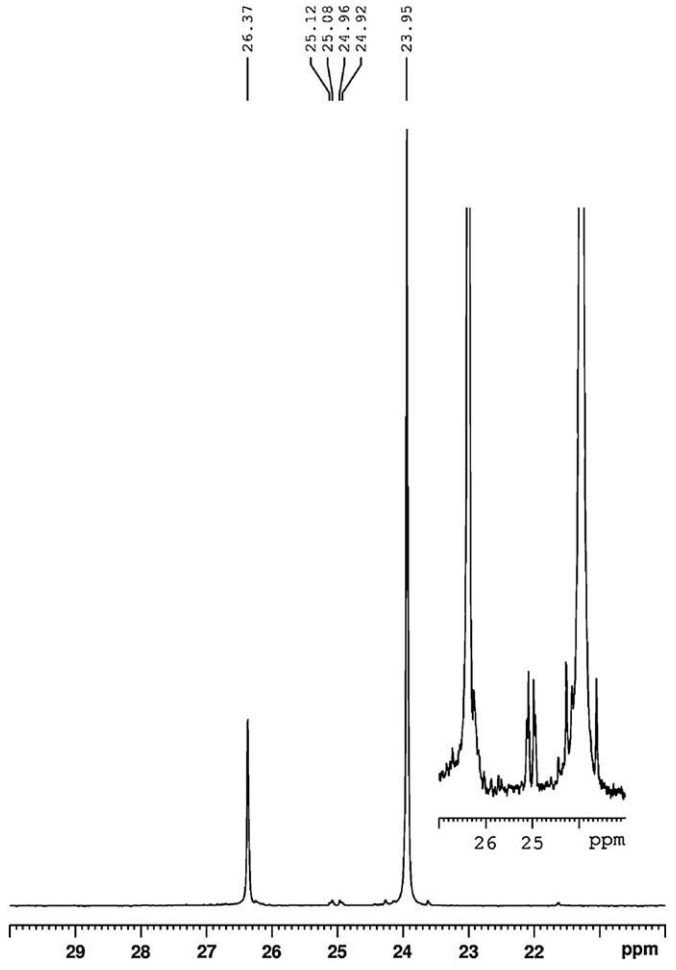


Figure 3. The platinum-catalysed cyclisation of enyne **9** (δ=24.0) into diene **16** (δ=26.4) via an intermediate containing a chiral centre (pair of doublets at δ=24.9 and 25.1).

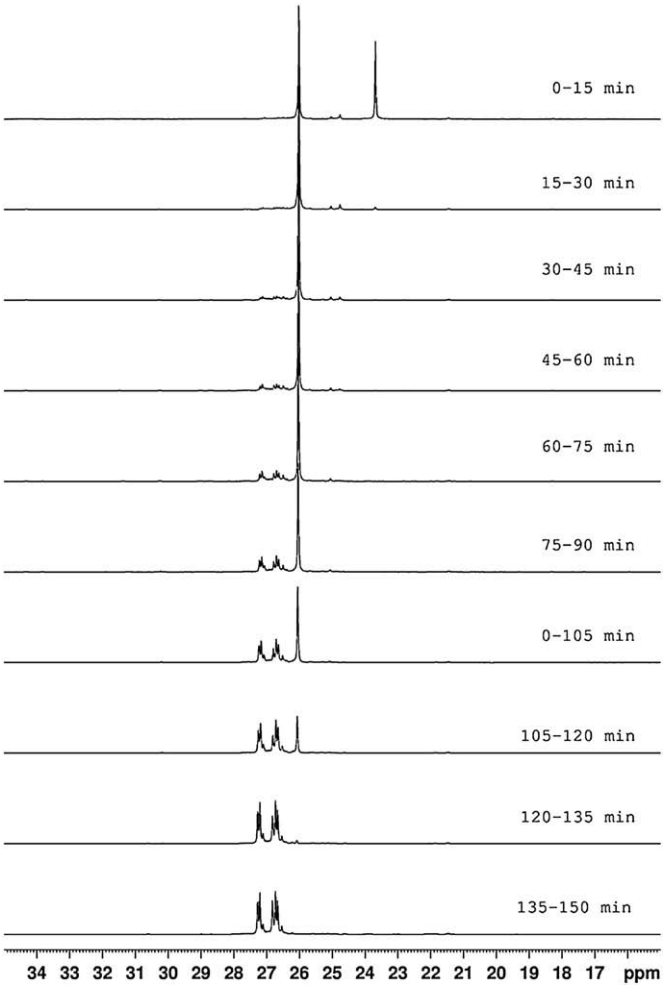


Figure 4. The palladium-catalysed cycloreduction of enyne **9** (singlet at δ=23.7) into **17** (doublets at δ=26.7 and 27.3) and a byproduct (singlet at δ=26.8) via diene **10** (singlet at δ=26.0).

of the reaction of a well-defined pair of doublets at δ=24.9 (J=8 Hz) and 25.1 (J=8 Hz) (Fig. 3). At present it is only possible to say with any certainty that the species that gives rise to these signals contains an element of chirality, and further studies are required to identify its structure. Nevertheless it is interesting to contrast these observations with attempts to detect intermediates of the corresponding cyclisation of the malonate equivalent of enyne **9** (i.e., **1a**) by ^{1}H NMR spectroscopy. Treatment of **1a** with a stoichiometric amount of platinum chloride at 25, 40 and 80 °C and monitoring by ^{1}H NMR spectroscopy led in all cases to the observation of only resonances associated with starting material and product.[18]

In a second example, the palladium-catalysed cycloreduction of enyne **9** into methylene cyclopentane **17** was monitored and observed to proceed via the rapid conversion of **9** (singlet at δ=23.7) into an intermediate indicated by a singlet at δ=26.0 (Fig. 4). Conversion of **9** into the intermediate was complete after 30 min, after which the intermediate was relatively slowly converted into product **17**, characterised by the pair of doublets at δ=26.7 and 27.3, and a byproduct indicated by a singlet at δ=26.8. It was proposed that the intermediate at δ=26.0 was a symmetrical product of a rapid cyclisation process, probably the diene **10**, and that the slower second step was the reduction of diene **10** to the less symmetrical product **17**. Indeed halting a laboratory reaction after 40 min rather then allowing it to run for 2.5 h led to the isolation of diene **10** in 70% yield. This hypothesis is consistent with a mechanism proposed for this type of cycloreduction process based on examining the results from a range of substrates, reaction conditions and the isolation of key intermediates.[14]

3. Conclusion

We have developed a new and effective approach to enyne **9** and demonstrated that it is a suitable substrate for a range of cyclisations using differing catalysts and reaction conditions, and giving structurally varied products. The motifs generated via such reactions provide new scaffolds for constructing bisphosphonic acids, an important class of therapeutic agents. NMR experiments on the cyclisations have been carried out from which it is apparent that the introduction of phosphonate substituents onto cyclisation substrates is a promising tool for studying metal-catalysed cyclisations, and indeed cyclisations in general.

4. Experimental

4.1. General

All reactions and manipulations involving organometallic compounds were performed under an inert atmosphere of dry nitrogen, using standard vacuum line and Schlenk techniques.[19] 1,2-Dimethoxyethane, hexane, tetrahydrofuran and toluene were distilled over sodium benzophenone ketyl and used immediately. Dichloromethane was distilled over calcium hydride. All other chemicals were used as purchased from commercial sources. The concentration of n-butyllithium was determined by titration against diphenylacetic acid in tetrahydrofuran.[20] Thin layer chromatography (TLC) was performed on Merck silica gel glass plates 60 (F_{254}), using UV light (254 nm) and/or iodine as visualising agents and/or vanillin or potassium permanganate and heat as developing agents. Flash column chromatography was performed using BDH silica gel (particle size 33–70 μm). IR spectra were recorded on a Perkin Elmer Spectrum RX FT-IR spectrometer. NMR spectra were recorded at room temperature on Bruker DRX 400, AV 400 or AV 500 instruments in $CDCl_3$ unless otherwise stated. J values are reported in hertz and chemical shifts in parts per million. Mass spectra were recorded on Micromass Platform II and Micromass AutoSpec-Q instruments by the mass spectrometry service at Imperial College London. Elemental analyses were performed by the London Metropolitan University microanalytical service.

4.1.1. Tetraethyl but-3-enyl-1,1-bisphosphonate **14**[12]

n-Butyllithium (8.9 mL, 2.50 M in hexane, 22.3 mmol) was added to a solution of diisopropylamine (2.9 mL, 20.6 mmol) in THF (12 mL) at −78 °C. Diethyl but-3-enyl-1-phosphonate (2.0 mL, 10.5 mmol) and diethyl chlorophosphate (1.9 mL, 13.3 mmol) were added at −78 °C. After 1.5 h, the reaction mixture was allowed to warm to room temperature and poured into cooled distilled water (20 mL). After extraction with CH_2Cl_2 (4×50 mL), the combined organic layers were washed with saturated aqueous NaCl solution (20 mL) and dried over Na_2SO_4. Evaporation of the solvent under vacuum yielded **14** (3.43 g, quant.) as a yellow oil, pure enough to be used in the synthesis of enyne **15**. R_f=0.36 (SiO_2; hexane/acetone 1:1); ^{1}H NMR (400 MHz): δ=1.37 (t, ^3J(H,H)=7 Hz, 12H, OCH_2CH_3×4), 2.41 (tt, ^2J(H,P)=24 Hz, ^3J(H,H)=6 Hz, 1H, PC*H*), 2.66–2.78 (m, 2H, $CH_2CH{=}CH_2$), 4.17–4.24 (m, 8H, OCH_2CH_3×4), 5.07 (dd, ^3J(H,H)=8 Hz, ^2J(H,H)=1 Hz, 1H, $CH_2CH{=}CH_2$ (*Z*)), 5.16 (dd, ^3J(H,H)=16 Hz, ^2J(H,H)=1 Hz, 1H, $CH_2CH{=}CH_2$ (*E*)), 5.99 ppm (ddt, ^3J(H,H)=16, 8, 4 Hz, 1H, $CH_2CH{=}CH_2$); ^{13}C NMR (100 MHz): δ=16.37, 16.43 (2×d, ^3J(C,P)=2 Hz, P(O)$(OCH_2CH_3)_2$), 29.9 (t, ^2J(C,P)=5 Hz, PCH$CH_2CH{=}CH_2$), 37.1 (t, ^1J(C,P)=133 Hz, PCH), 62.5, 62.6 (2×d, ^2J(C,P)=6.5 Hz, P(O)$(OCH_2CH_3)_2$), 116.6 (s, $CH{=}CH_2$), 135.9 ppm (t, ^3J(C,P)=7 Hz, PCH$CH_2CH{=}CH_2$); ^{31}P NMR (162 MHz): δ=23.1 ppm (s); IR (neat): ν=1641 (m, C=C), 1248 (s, P=O), 1027 cm^{-1} (s, P–O–C); MS (CI): m/z (%): 674 (100) [2M+NH_4^+], 657 (25) [2M+H^+], 346 (73) [M+NH_4^+], 329 (69) [M+H^+], 191 (9) [M+H^+−P(O)$(OCH_2CH_3)_2$].

4.1.2. Tetraethyl 1-trimethylsilylhept-1-yn-6-en-4,4-diylbisphosphonate **15**

To a solution of **14** (9.50 g, 28.9 mmol) in THF (40 mL) was added LDA (18.0 mL, 2.0 M in THF/n-heptane, 36.2 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h. 3-(Trimethylsilyl)-propargyl bromide (6.5 mL, 39.9 mmol) was added dropwise to the stirred reaction mixture at −78 °C. After 16 h, the reaction mixture was allowed to warm to room temperature and poured into cooled distilled water (60 mL). After extraction with CH_2Cl_2 (4×150 mL), the combined organic layers were washed with saturated aqueous NaCl solution (60 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown oil. Purification by flash column chromatography (SiO_2; hexane/acetone 4:1 to 3:1) afforded **15** (5.29 g, 42%) as a yellow oil. R_f=0.51 (SiO_2; hexane/acetone 3:2); ^{1}H NMR (400 MHz): δ=0.18 (s, 9H, Si$(CH_3)_3$), 1.36 (t, ^3J(H,H)=7 Hz, 12H, OCH_2CH_3×4), 2.77–2.83 (m, 2H, $CH_2CH{=}CH_2$), 2.90 (t, ^3J(H,P)=15 Hz, 2H, $CH_2C{\equiv}CSi$), 4.18–4.26 (m, 8H, OCH_2CH_3×4), 5.15 (dd, ^3J(H,H)=10 Hz, ^2J(H,H)=2 Hz, 1H, $CH_2CH{=}CH_2$ (*Z*)), 5.22 (dd, ^3J(H,H)=17 Hz, ^2J(H,H)=2 Hz, 1H, $CH_2CH{=}CH_2$ (*E*)), 5.99 ppm (ddt, ^3J(H,H)=17, 10, 7 Hz, 1H, $CH_2CH{=}CH_2$); ^{13}C NMR (100 MHz): δ=0.0 (s, Si$(CH_3)_3$), 16.47, 16.50 (2×d, ^3J(C,P)=2 Hz, P(O)$(OCH_2CH_3)_2$), 22.2 (t, ^2J(C,P)=4 Hz, PC$CH_2C{\equiv}CSi$), 35.1 (t, ^2J(C,P)=4 Hz, PC$CH_2CH{=}CH_2$), 44.8 (t, ^1J(C,P)=132.5 Hz, PCP), 62.8, 62.9 (2×d, ^2J(C,P)=3.5 Hz, P(O)$(OCH_2CH_3)_2$), 88.0 (s, $C{\equiv}CSi$), 101.8 (t, ^3J(C,P)=10.5 Hz, PC$CH_2C{\equiv}CSi$), 118.6 (s, $CH{=}CH_2$), 133.2 ppm (t, ^3J(C,P)=8 Hz, PC$CH_2CH{=}CH_2$); ^{31}P NMR (162 MHz): δ=24.4 ppm (s); IR (neat): ν=2181 (s, C≡C), 1640 (m, C=C), 1250 (s, P=O, Si–C), 1026 cm^{-1} (s, P–O–C); MS (CI): m/z (%): 456 (7) [M+NH_4^+], 439 (100) [M+H^+], 301 (22) [M+H^+−P(O)$(OCH_2CH_3)_2$]; elemental analysis calcd (%) for $C_{18}H_{36}O_6SiP_2$: C 49.30, H 8.27; found: C 49.28, H 8.26.

4.1.3. Tetraethyl hept-1-yn-6-en-4,4-diylbisphosphonate **9**[7]

Enyne **15** (4.00 g, 9.13 mmol) was added to a solution of tetrabutylammonium fluoride trihydrate (0.80 g, 3.04 mmol) in THF (50 mL) at room temperature. After 2 h, the reaction mixture was poured into cooled distilled water (50 mL). After extraction with

CH_2Cl_2 (4×150 mL), the combined organic layers were washed with saturated aqueous NaCl solution (50 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give a brown oil. Purification by flash column chromatography (SiO_2; hexane/acetone 3:2) afforded **9** (3.26 g, 98%) as a yellow oil. R_f=0.41 (SiO_2; hexane/acetone 1:1); ^{1}H NMR (400 MHz): δ=1.36 (t, ^3J(H,H)=7 Hz, 12H, OCH_2CH_3×4), 2.10 (t, ^4J(H,H)=2.5 Hz, 1H, C≡C*H*), 2.78–2.90 (m, 4H, CH_2CH=CH_2, CH_2C≡CH), 4.23 (dt, ^3J(H,P)=15 Hz, ^3J(H,H)=7 Hz, 8H, OCH_2CH_3×4), 5.16 (d, ^3J(H,H)=10 Hz, 1H, CH_2CH=C*H*$_2$ (*Z*)), 5.24 (d, ^3J(H,H)=17 Hz, 1H, CH_2CH=C*H*$_2$ (*E*)), 6.01 ppm (ddt, ^3J(H,H)=17, 10, 7 Hz, 1H, CH_2CH=CH_2); ^{13}C NMR (100 MHz): δ=16.4 (m, P(O)(OCH_2CH_3)$_2$), 20.9 (t, ^2J(C,P)=3.5 Hz, PCCH_2C≡CH), 35.0 (t, ^2J(C,P)=4.5 Hz, PCHCH_2CH=CH_2), 44.8 (t, ^1J(C,P)=132.5 Hz, P*C*P), 62.9 (m, P(O)(OCH_2CH_3)$_2$), 71.6 (s, C≡*C*H), 79.3 (t, ^3J(C,P)=11.5 Hz, PCCH_2*C*≡CH), 118.8 (s, CH=*C*H$_2$), 133.0 ppm (t, ^3J(C,P)=7.5 Hz, PCCH_2CH=CH_2); ^{31}P NMR (162 MHz): δ=24.2 ppm (s); IR (neat): ν=2118 (w, C≡C), 1640 (m, C=C), 1247 (s, P=O), 1024 cm^{-1} (s, P–O–C); MS (CI): *m*/*z* (%): 384 (68) [M+NH_4^+], 367 (100) [M+H^+].

4.1.4. Tetraethyl 1-vinylcyclopent-1-endiyl-4,4-bisphosphonate **16**

Platinum(II) chloride (5.9 mg, 4 mol%) was added to a solution of enyne **9** (0.20 g, 0.55 mmol) in anhydrous toluene (3 mL). The reaction mixture was stirred at 80 °C for 3 h under an atmosphere of nitrogen. After the reaction was complete, the solvent was removed in vacuo. The residue was filtered through neutral alumina eluting with acetone to afford **16** (0.20 g, quant.) as a yellow oil. R_f=0.25 (SiO_2; hexane/acetone 3:2); ^{1}H NMR (400 MHz): δ=1.308, 1.314 (2×t, ^3J(H,H)=7 Hz, 12H, OCH_2CH_3×4), 3.05–3.14 (m, 4H, CH_2C=CH, CH_2CH=C), 4.14–4.22 (m, 8H, OCH_2CH_3×4), 5.07 (d, ^3J(H,H)=17.5 Hz, 1H, C=CCH=C*H*$_2$ (*E*)), 5.09 (d, ^3J(H,H)=10.5 Hz, 1H, C=CCH=C*H*$_2$ (*Z*)), 5.58 (m, 1H, CH_2CH=C), 6.50 ppm (dd, ^3J(H,H)=17.5, 10.5 Hz, 1H, CC*H*=CH_2); ^{13}C NMR ($CDCl_3$): δ=16.5 (m, P(O)(OCH_2CH_3)$_2$), 36.5, 38.2 (2×t, ^2J(C,P)=3 Hz, PCCH_2×2), 43.4 (t, ^1J(C,P)=110 Hz, P*C*P), 62.9 (m, P(O)(OCH_2CH_3)$_2$), 115.0 (s, CH=*C*H$_2$), 127.4 (t, ^3J(C,P)=3 Hz, PCCH_2CH=C), 132.3 (s, C*C*H=CH_2), 140.2 ppm (t, ^3J(C,P)=3 Hz, PCCH_2*C*=CH); ^{31}P NMR (162 MHz): δ=26.8 ppm (s); IR (neat): ν=1647 (m, C=C), 1244 (s, P=O), 1043 cm^{-1} (s, P–O–C); MS (CI): *m*/*z* (%): 384 (53) [M+NH_4^+], 367 (100) [M+H^+]; elemental analysis calcd (%) for $C_{15}H_{28}O_6P_2$: C 49.18, H 7.70; found: C 49.07, H 7.70.

4.1.5. Tetraethyl 1-methylene-2-methylcyclopentandiyl-4,4-bisphosphonate **17**

To a mixture of triphenylphosphine (15.7 mg, 10 mol%) and palladium(II) acetate (6.7 mg, 5 mol%) was added a solution of enyne **9** (0.22 g, 0.6 mmol) in anhydrous toluene (1.5 mL). The yellow suspension was stirred for 10 min under a nitrogen atmosphere and then treated with formic acid (57 μL, 1.5 mmol) via a gastight syringe. The reaction mixture was stirred for 2.5 h at 60 °C in a preheated oil bath. The reaction was allowed to cool to room temperature and concentrated in vacuo. Purification by flash column chromatography (SiO_2; hexane/acetone 7:3 to 3:2) afforded **17** as a yellow oil (0.17 g, 78%). R_f=0.35 (SiO_2; hexane/acetone 3:2); ^{1}H NMR (400 MHz): δ=1.10 (d, ^3J(H,H)=6.5 Hz, 3H, CHCH_3), 1.31–1.38 (m, 12H, OCH_2CH_3×4), 1.71–1.95 (m, 1H, CH_2CH), 2.46–2.57 (m, 1H, CH_2CH), 2.75 (br m, 1H, CH_2CH*C*H$_3$), 2.88–3.09 (m, 2H, CH_2C=C), 4.14–4.28 (m, 8H, OCH_2CH_3×4), 4.76 (s, 1H, C=C*H*$_2$), 4.87 ppm (s, 1H, C=C*H*$_2$); ^{13}C NMR (100 MHz): δ=16.4–16.5 (m, P(O)(OCH_2CH_3)$_2$), 17.0 (s, CH*C*H$_3$), 37.29 (m, CH_2CH), 37.35 (m, *C*H$_2$C=CH_2), 38.7 (m, *C*H$_2$CH), 43.2 (t, ^1J(C,P)=137.5 Hz, P*C*P), 62.5–63.0 (m, P(O)(OCH_2CH_3)$_2$), 104.3 (s, C=*C*H$_2$), 153.8 ppm (t, ^3J(C,P)=4.5 Hz, CH_2*C*=CH_2); ^{31}P NMR (162 MHz): δ=27.3 (d, ^2J(P,P)=13.5 Hz), 27.9 ppm (d, ^2J(P,P)=13.5 Hz); IR (neat): ν=1658 (m, C=C), 1244 (s, P=O), 1032 cm^{-1} (s, P–O–C); MS (ESI): *m*/*z* (%): 391 (100) [M+Na^+], 369 (32) [M+H^+]; elemental analysis calcd (%) for $C_{15}H_{30}O_6P_2$: C 48.91, H 8.21; found: C 49.00, H 8.14.

4.1.6. Tetraethyl 3,4-dimethylenecyclopentane-1,1-bisphosphonate **10**[7]

The reaction described in Section 4.1.5 was repeated under identical conditions except that the reaction was halted after 40 min. Work-up and column chromatography (SiO_2; hexane/acetone 7:3 to 3:2) afforded diene **10** as a yellow oil (0.153 g, 70%). R_f=0.35 (SiO_2; hexane/acetone 3:2); ^{1}H NMR (400 MHz): δ=1.31 (t, ^3J(H,H)=7 Hz, 12H, OCH_2CH_3×4), 3.10 (tt, ^3J(H,P)=17 Hz, ^4J(H,H)=2 Hz, 4H, CH_2C=C×2), 4.12–4.20 (m, 8H, OCH_2CH_3×4), 4.90 (t, ^4J(H,H)=2 Hz, 2H, C=C*H*×2), 5.36 ppm (t, ^4J(H,H)=2 Hz, 2H, C=C*H*×2); ^{13}C NMR (100 MHz): δ=16.3–16.4 (m, P(O)(OCH_2CH_3)$_2$), 37.7 (t, ^2J(C,P)=4 Hz, *C*H$_2$C=C), 43.5 (t, ^1J(C,P)=138 Hz, P*C*P), 62.8–62.9 (m, P(O)(OCH_2CH_3)$_2$), 104.4 (s, C=*C*H$_2$), 145.7 ppm (t, ^3J(C,P)=4.5 Hz, CH_2*C*=CH_2); ^{31}P NMR (162 MHz): δ=26.6 ppm (s); IR (neat): ν=1623 (w, C=C), 1248 (s, P=O), 1017 cm^{-1} (s, P–O–C); MS (ESI): *m*/*z* (%): 755 (32) [2M+Na^+], 389 (100) [M+Na^+], 367 (53) [M+H^+].

4.1.7. Tetraethyl 1-(1-(Z)-dimethylphenylsilylmethylidene)-2-methylcyclopentandiyl-4,4-bisphosphonate **18**

Dodecacarbonyltetrarhodium(0) (13.5 mg, 3 mol%) was placed in a Schlenk tube and dissolved in anhydrous CO saturated hexane (1 mL). Dimethylphenylsilane (93 μL, 0.6 mmol) was added via a syringe. The reaction mixture was stirred at room temperature under an atmosphere of CO for 5 min. The reaction mixture was then added via cannula into a solution of enyne **9** (0.22 g, 0.6 mmol) and dimethylphenylsilane (93 μL, 0.6 mmol) in anhydrous CO saturated hexane (0.5 mL) without stirring. After stirring for 20 min, the reaction mixture was concentrated in vacuo to give a brown residue. Purification by flash column chromatography (SiO_2; hexane/acetone 4:1 to 3:1) afforded **18** (0.20 g, 67%) as a yellow oil. R_f=0.37 (SiO_2; hexane/acetone 3:2); ^{1}H NMR (500 MHz): δ=0.36, 0.37 (2×s, 6H, Si(CH_3)$_2$), 1.03 (d, ^3J(H,H)=7 Hz, 3H, CHCH_3), 1.286, 1.293 (2×t, ^3J(H,H)=7 Hz, 6H, OCH_2CH_3×2), 1.33 (t, ^3J(H,H)=7 Hz, 6H, OCH_2CH_3×2), 1.94–2.06 (m, 1H, PCCH_2CH), 2.54–2.64 (m, 1H, PCCH_2CH), 2.77–2.87 (m, 2H, PCCH_2CHCH_3, PCCH_2C=C), 3.22–3.36 (m, 1H, PCCH_2C=C), 4.05–4.23 (m, 8H, OCH_2CH_3×4), 5.45 (s, 1H, C=C*H*Si), 7.32–7.35 (m, 3H, C$_{Ar}H$×3), 7.52–7.55 ppm (m, 2H, C$_{Ar}H$×2); ^{13}C NMR (125 MHz): δ= −0.98, −0.90 (2×s, Si(CH_3)$_2$), 16.4, 16.6 (2×d, ^3J(C,P)=6 Hz, P(O)(OCH_2CH_3)$_2$), 23.0 (s, CHCH_3), 37.0 (d, ^3J(C,P)=4 Hz, PCCH_2CHCH_3), 38.3 (t, ^2J(C,P)=3.5 Hz, PCCH_2CH), 41.4 (br s, PCCH_2C=C), 44.5 (t, ^1J(C,P)=137 Hz, P*C*P), 62.5–62.8 (m, P(O)(OCH_2CH_3)$_2$), 116.6 (s, C=*C*HSi), 127.7 (s, *C*$_{Ar}$H), 128.8 (s, *C*$_{Ar}$H), 133.7 (s, *C*$_{Ar}$H), 139.7 (s, *C*$_{Ar}$Si), 166.0 ppm (d, ^3J(C,P)=10 Hz, PCCH_2*C*=CH); ^{31}P NMR (202 MHz): δ=27.5 (d, ^2J(P,P)=16 Hz), 27.7 ppm (d, ^2J(P,P)=16 Hz); IR (neat): ν=1629 (s, C=C), 1247 (s, P=O, Si–C), 1023 cm^{-1} (s, P–O–C); MS (ESI): *m*/*z* (%): 525 (100) [M+Na^+], 503 (21) [M+H^+]; elemental analysis calcd (%) for $C_{23}H_{40}O_6P_2Si$: C 54.96, H 8.02; found: C 54.89, H 8.00.

4.1.8. Tetraethyl 7-oxobicyclo[3.3.0]oct-1-(8)-enediyl-3,3-bisphosphonate **19**

Freshly sublimed octacarbonyldicobalt(0) (14.0 mg, 7.5 mol%) was placed in a Schlenk tube and dissolved in anhydrous CO saturated DME (5.5 mL). The reaction mixture was stirred at room temperature, under an atmosphere of CO for 15 min. Enyne **9** (0.20 g, 0.55 mmol) was dissolved in anhydrous CO saturated DME (1.5 mL) and added to the reaction mixture via cannula. The reaction mixture was stirred at 75 °C for 5 h. The reaction was allowed to cool to room temperature before being filtered through Celite® and then concentrated in vacuo to give a brown residue. Purification by flash column chromatography (SiO_2; acetone/hexane 4:1 to 9:1) afforded **19** (0.13 g, 59%) as a yellow oil. R_f=0.36 (SiO_2; acetone/hexane 9:1); ^{1}H NMR (500 MHz): δ=1.291, 1.303 (2×t, ^3J(H,H)=7 Hz, 6H, OCH_2CH_3×2), 1.36 (t, ^3J(H,H)=7 Hz, 6H, OCH_2CH_3×2), 1.82 (dddd, ^2J(H,H)=24.5 Hz, ^3J(H,H)=21 Hz, ^3J(H,P)=13, 11.5 Hz, 1H, PCCH_2CHCH_2), 2.10 (dd, ^2J(H,H)=18 Hz, ^3J(H,H)=3 Hz, 1H,

CHCH_2C=O), 2.64 (dd, ^2J(H,H)=18 Hz, ^3J(H,H)=6 Hz, 1H, CHCH_2C=O), 2.67–2.75 (m, 1H, PCCH_2CHCH_2), 3.09–3.26 (m, 2H, PCCH_2C=C), 3.31 (m, 1H, CH_2CHCH_2), 4.11–4.30 (m, 8H, OCH_2CH_3×4), 5.80 ppm (s, 1H, CH_2C=CHC=O); ^{13}C NMR (100 MHz): δ=16.3–16.5 (m, P(O)(OCH_2CH_3)$_2$), 32.3 (t, ^2J(C,P)=4 Hz, PCCH$_2$C=C), 35.3 (t, ^2J(C,P)=4.5 Hz, PCCH_2CHCH_2), 42.6 (s, CHCH_2C=O), 44.3 (d, ^3J(C,P)=7 Hz, PCCH$_2$CHCH$_2$), 46.5 (t, ^1J(C,P)=138 Hz, PCP), 62.77, 62.84 (2×d, ^2J(C,P)=1.5 Hz, P(O)(OCH_2CH_3)$_2$), 125.2 (s, C=CHC=O), 185.3 (t, ^3J(C,P)=4.5 Hz, PCCH$_2$C=CH), 210.0 ppm (s, C=O); ^{31}P NMR (162 MHz): δ=26.7 (d, ^2J(P,P)=11 Hz), 27.9 ppm (d, ^2J(P,P)=11 Hz); IR (neat): ν=1713 (s, C=O), 1634 (s, C=C), 1246 (s, P=O), 1024 cm^{-1} (s, P–O–C); MS (CI): m/z (%): 412 (83) [M+NH$_4^+$], 395 (100) [M+H$^+$]; elemental analysis calcd (%) for $C_{16}H_{28}O_7P_2$: C 48.73, H 7.16; found: C 48.65, H 7.16.

4.1.9. Tetraethyl 1-methylene-2-(1-trimethylsilylmethylidene)-cyclopentandiyl-4,4-bisphosphonate **20**

Chloro-1,5-cyclooctadiene iridium dimer (23.5 mg, 7 mol %) and 1,1′-bis(diphenylphosphino)ferrocene (38.8 mg, 14 mol %) were dissolved in anhydrous toluene (3 mL) under a nitrogen atmosphere. A solution of TMS enyne **15** (0.22 g, 0.5 mmol) in anhydrous toluene (3 mL) was added. The reaction mixture was stirred under reflux for 24 h. The reaction was allowed to cool to room temperature before being concentrated in vacuo to give a brown residue. Immediate purification by flash column chromatography (SiO_2; hexane/acetone 4:1 to 3:2) afforded **20** as a yellow oil (0.15 g, 68%) identified as a mixture of isomers (*E*/*Z* ratio 1:1.1). R_f=0.47 (SiO_2; hexane/acetone 3:2); ^{1}H NMR (400 MHz): δ=0.12, 0.15 (2×s, 9H, Si(CH_3)$_3$), 1.29–1.33 (m, 12H, OCH$_2$CH_3×4), 2.64–3.14 (m, 4H, CH_2×2), 4.12–4.22 (m, 8H, OCH_2CH$_3$×4), 4.89, 4.92×2, 5.36 (4×s, 2H, C=CH_2), 5.94, 6.41 ppm (2×s, 1H, C=CHSi); ^{13}C NMR (100 MHz): δ= −2.4, −0.6 (2×s, 3C, Si(CH$_3$)$_3$), 16.4 (br s, P(O)(OCH$_2$CH$_3$)$_2$), 27.8, 31.2, 36.9, 37.4 (m, CH$_2$×2), 41.2 (t, ^1J(C,P)=132.5 Hz, PCP), 43.6 (t, ^1J(C,P)=138.0 Hz, PCP), 62.6–62.8 (m, P(O)(OCH$_2$CH$_3$)$_2$), 104.3, 112.9 (2×s, C=CH$_2$), 117.7, 135.7 (2×s, C=CHSi), 137.8 (t, ^3J(C,P)=4.5 Hz, CH$_2$C=CHSi), 138.8 (t, ^3J(C,P)=7 Hz, CH$_2$$C$=CHSi), 147.1 (t, ^3J(C,P)=4.5 Hz, CH$_2$$C$=CH$_2$), 153.2 ppm (t, ^3J(C,P)=4.5 Hz, CH$_2$$C$=CH$_2$); ^{31}P NMR (162 MHz): δ=25.8 (s), 26.6 ppm (s); IR (neat): ν=1674 (m, C=C), 1247 (s, P=O, Si–C), 1026 cm^{-1} (s, P–O–C); MS (ESI): m/z (%): 439 (100) [M+H$^+$]; elemental analysis calcd (%) for $C_{18}H_{36}O_6P_2Si$: C 49.30, H 8.27; found: C 49.26, H 8.20.

4.1.10. Examination of the $PtCl_2$ catalysed cyclisation of **9** to **16** by ^{31}P NMR spectroscopy at 80 °C

Platinum(II) chloride (3 mg, 4 mol %) and enyne **9** (100 mg, 0.27 mmol) were dissolved in anhydrous toluene (2 mL) and syringed into a WILMAD screw cap (with a PTFE/silicone septum) NMR tube under nitrogen. The NMR tube was introduced into the NMR probe, which had been preheated to 80 °C and a ^{31}P NMR experiment was performed collecting a spectrum at set time intervals.

4.1.11. Examination of the $Pd(OAc)_2$ catalysed cycloreduction of **9** to **17** by ^{31}P NMR spectroscopy at 60 °C

Triphenylphosphine (7.9 mg, 10 mol %), palladium(II) acetate (3.4 mg, 5 mol %) and enyne **9** (110 mg, 0.3 mmol) were dissolved in anhydrous toluene (1 mL) and stirred at room temperature for 10 min. Formic acid (28 μL, 0.75 mmol) was added to the yellow reaction mixture and stirred at room temperature for 10 min. The resulting solution was syringed into a WILMAD screw cap (with a PTFE/silicone septum) NMR tube under nitrogen. The NMR tube was introduced into the NMR probe, which had been preheated to 60 °C and a ^{31}P NMR experiment was performed collecting a spectrum at set time intervals.

References and notes

1. For a review of cycloisomerisations of 1,*n*-enynes, see: Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268–4315.
2. Grigg, R.; Stevenson, P.; Worakun, T. *Tetrahedron* **1988**, *44*, 4967–4972.
3. Lee, H.-Y.; Kim, H. Y.; Tae, H.; Kim, B. G.; Lee, J. *Org. Lett.* **2003**, *5*, 3439–3442.
4. (a) Evans, P. A.; Sawyer, J. R.; Lai, K. W.; Huffman, J. C. *Chem. Commun.* **2005**, 3971–3973; (b) Evans, P. A.; Lai, K. W.; Sawyer, J. R. *J. Am. Chem. Soc.* **2005**, *127*, 12466–12467.
5. López, S.; Herrero-Gómez, E.; Pérez-Galán, P.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 6029–6032.
6. See, for example, (a) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1993**, *115*, 9421–9438; (b) Fernandez-Rivas, C.; Méndes, M.; Echavarren, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 1221–1222; (c) Toullec, P.-Y.; Genin, E.; Leseurre, L.; Genêt, J.-P.; Michelet, V. *Angew. Chem., Int. Ed.* **2006**, *45*, 7427–7430.
7. Li, C.; Yuan, C. *Heteroat. Chem.* **1993**, *4*, 517–520.
8. Fairlamb, I. J. S.; Pike, A. C.; Ribrioux, S. P. C. P. *Tetrahedron Lett.* **2002**, *43*, 5327–5331.
9. (a) Green, J. R. *J. Organomet. Chem.* **2005**, *690*, 2439–2448; (b) Rodan, G. A.; Martin, T. J. *Science* **2000**, *289*, 1508–1514.
10. Dudakovic, A.; Wiemer, A. J.; Lamb, K. M.; Vonnahme, L. A.; Dietz, S. E.; Hohl, R. J. *J. Pharmacol. Exp. Ther.* **2008**, *324*, 1028–1036.
11. Ebetino, F. H.; Boeckman, R. K.; Song, X. Patent WO 2008/076417 A1.
12. Dufau, C.; Sturtz, G. *Phosphorus, Sulfur Silicon Relat. Elem.* **1992**, *69*, 93–102.
13. Furstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863–11869.
14. Oh, C. H.; Jung, H. H.; Sung, H. R.; Kim, J. D. *Tetrahedron* **2001**, *57*, 1723–1729.
15. Ojima, I.; Vu, A. T.; Lee, S.-Y.; McCullagh, J. V.; Moralee, A. C.; Fujiwara, M.; Hoang, T. H. *J. Am. Chem. Soc.* **2002**, *124*, 9164–9174.
16. (a) Shibata, T. *Adv. Synth. Catal.* **2006**, *348*, 2328–2336; (b) Gibson, S. E.; Stevenazzi, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1800–1810.
17. Kezuka, S.; Okada, T.; Niou, E.; Takeuchi, R. *Org. Lett.* **2005**, *7*, 1711–1714.
18. Chatani, N.; Furukawa, N.; Sakurai, H.; Murai, S. *Organometallics* **1996**, *15*, 901–903.
19. Shriver, D. F.; Drezdzon, M. A. *The Manipulation of Air Sensitive Compounds*; Wiley: Chichester, UK, 1986.
20. Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879–1880.