Intramolecular [4 + 2] cycloadditions involving transient phosphaalkene intermediates as dienophiles: a useful entry to phosphabicyclo[4.3.0]non-4-ene derivatives

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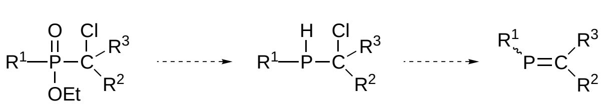
Three representative phosphabicyclo[4.3.0]non-4-ene derivatives are formed in high yields and various diastereomeric forms by [4 + 2] intramolecular cycloadditions involving transient phosphaalkenes as dienophiles; complete diastereoselectivity is observed with the P-substituted derivative.

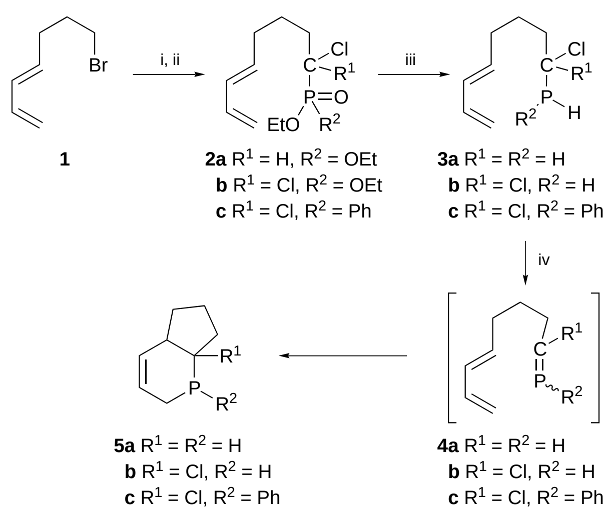
Free cyclic phosphines and their metal coordination complexes are valuable intermediates in organophosphorus chemistry.[1] They are prepared by many different approaches, among them, cycloaddition reactions involving C=P double bonds with dienes and dipoles appear to be of synthetic value.[1,2] the main problem encountered by using this methodology is keeping the reactivity of the P=C double bond under control. Self-condensations are usually avoided by steric or electronic effects and by complexation with a transition metal. Some cycloadditions lacking stabilisation of the P^{II} intermediate occur in high yield,[3] especially when the cycloadducts spontaneously aromatize, thus giving a useful entry to functionalised phosphinines;[4] in most cases however the desired cycloadducts are accompanied of various amounts of self-condensed products.[2d] In order to circumvent this problem we thought to trap the transient species by internal cycloaddition. Under these conditions, the rates of the reactions are expected to be strongly enhanced by entropic assistance, hopefully making the self-condensation reactions of transient species negligible. Intermolecular reactions between conjugated dienes and phosphaalkenes have been recently reviewed.[2a] It is now well established that, with the exception of some derivatives bearing electronegative substituents, the reaction takes place with retention of the phosphaalkene stereochemistry. Furthermore, at least with cyclopentadiene derivatives, the *endo* preference is respected with substituents on phosphorus. Thus, the potential versatility of intramolecular cycloadditions involving low coordinated phosphorus derivatives as dienophiles should afford a useful entry to tailored and hopefully stereocontrolled polycyclic systems. As a first evaluation of this methodology, we present here the synthesis of three differently substituted 2-phosphabicyclo[4.3.0]non-4-ene phosphines **5a–c** by intramolecular [4 + 2] cycloadditions involving the corresponding terminal phosphaalkenes **4a–c** as dienophiles. Conditions for controlling the stereochemistry are described.

We have recently developed a general route to non-stabilized phosphaalkenes which involves as a key step the dehydrohalogenation of α-chloroalkylphosphines with a Lewis base[2d,5] (Scheme 1). This procedure is attractive for the following reasons: (i) the α-chlorophosphonate and phosphinate precursors **A** are readily available by conventional anionic routes,[6,7] allowing introduction of the desired substituents both on phosphorus and carbon, (ii) the reduction of esters **A** into phosphines **B** with dichloroalane is chemoselective,[8] and (iii) HCl elimination occurs under mild conditions at a temperature which depends both on the strength of the base and the P–H acidity of the phosphine, allowing us to determine the best conditions for the trapping of the transient phosphaalkene **C**. We decided to adopt this strategy for the synthesis of the phosphabicyclononenes **5a–c** (Scheme 2).



Scheme 1

Chlorophosphonate **2a** was prepared by halogen–metal exchange of trichloromethylphosphonate $[Cl_3CP(O)(OEt)_2]$[6] with BuLi (2 equiv.) followed by selective monosilylation [Me_3SiCl (1 equiv.)], alkylation [(*E*)-1-bromohepta-4,6-diene **1** (1 equiv.)][9] of the resulting lithiated intermediates and subsequent hydrolysis in basic media.[10] The phosphonate **2b** and phosphinate **2c** were prepared by halogen–metal exchange of trichloromethylphosphonate $[Cl_3CP(O)(OEt)_2]$ and trichloromethylphenylphosphinate[6] $[Cl_3CP(O)(OEt)Ph]$[7] respectively with BuLi (1 equiv.) followed by alkylation of the resulting intermediates with **1** (Scheme 2). The yields of **2a** and **2b** were greater than 85% after purification by chromatography on silica. The yield for **2c** is lower (57%), a small amount of the starting material **1** being recovered at the end of the reaction. Chemoselective reduction of esters **2a–c** with dichloroalane[5,8] in THF afforded the free phosphines **3a–c**. The low volatility of the latter prevents purification by the general procedure involving successive vacuum transfers.[5] The following protocol was used: after hydrolysis of the crude mixture at −10 °C with deoxygenated water, the organic solution was filtered off under a slight pressure of neutral gas, washed again and then dried.



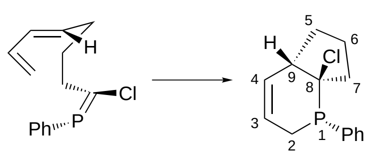
Scheme 2 *Reagents and conditions*: i, THF, BuLi (2 equiv. for **2a**, 1 equiv. for **2b,c**), −85 °C, then $Cl_3CP(O)(OEt)_2$; ii (for **2a**), −85 °C, Me_3SiCl (1 equiv.), then −85 °C, $Br(CH_2)_3CH{=}CHCH{=}CH_2$, then 20 °C, aq. LiOH; (for **2b,c**), −85 °C, $Br(CH_2)_3CH{=}CHCH{=}CH_2$; iii, '$AlHCl_2$', THF, −80 to 20 °C, then deoxygenated H_2O, −10 °C, then $MgSO_4$; iv (for **5a,b**), −60 °C, Py (3 equiv.), then −60 to 20 °C; (for **5c**) −30 °C, Et_3N (2.5 equiv.), then −30 to 20 °C

Solutions were used without further purification, and the chlorophosphines **3a–c** were stable in the absence of oxygen. Yields determinated by NMR spectroscopy with an internal reference were greater than 70% (purity > 90%). The characterisation was supported by HRMS and ^{31}P, ^{1}H and ^{13}C NMR data, all of which were consistent with the assigned structure.‡

We have shown in our previous work that (i) transient phosphaalkenes are detectable by ^{31}P NMR spectroscopy in the dehydrochlorination of primary and secondary α-chloroalkylphosphines[2d,5] under controlled temperature conditions (from −80 to 20 °C) and (ii) polymerisation of the chlorophosphaalkene intermediates was observed in the elimination of HCl from α,α′-dichlorophosphines by a weak Lewis base (pyridine) in the absence of a trapping agent.[11,12] Whatever the nature of the Lewis base, we never detected in this work the expected phosphaalkene intermediates **4a–c** starting from **3a–c**. The only observed products were the cycloadducts **5a–c** characterized by new signals in the ^{31}P NMR spectra and the corresponding J_{PH} couplings: cyclic phosphines **5a** and **5b** were observed when the temperature rose to −60 °C in the presented pyridine (3 equiv.). Due to the lower P–H acidity[5] of secondary phosphines, elimination of HCl from α,α′-chlorophosphine **3c** occurred at −30 °C with a stronger base [NEt_3 (2.5 equiv.)]. Intramolecular [4 + 2] cycloaddition of **4a–c** with the diene counterpart is consequently a fast step. Self-condensations are strongly inhibited, as was confirmed by the high yield of cycloadducts (*i.e.* yield for **5c** > 80%, determined by ^{31}P NMR spectroscopy with an internal reference). All these results are consistent with entropic activation.

Since cycloaddition reactions take place with retention of stereochemistry at the P^{II} centre,[2a] both (*Z*)- and (*E*)-phosphaalkene intermediates are expected from elimination of HCl from α-chlorophosphines **3**, giving four isomeric cycloadducts. The observed stereochemical course differs strongly with the structure of the dienophile. We observed a weak selectivity starting from **4a** [four isomers, at δ −91.5 (d, $^{1}J_{PH}$ = 187 Hz), −88.4 (d, $^{1}J_{PH}$ = 191 Hz), −85 (d, $^{1}J_{PH}$ = 182 Hz) and −68.7 (d, $^{1}J_{PH}$ = 178 Hz); ratio = 57:20:14:9, respectively]. A higher selectivity is encountered for **4b** [two isomers at δ −76 ($^{1}J_{1PH}$ = 186 Hz) and −65 ($^{1}J_{PH}$ = 195 Hz); ratio = 81:19, respectively]. These results are consistent with the presence of the two (*Z*)- and (*E*)-phosphaalkene intermediates for **4a** and **4b**. On the other hand, intramolecular cycloaddition of **4c** is highly selective, and only one isomer is observed. The stereochemistry of the P(1), C(8) and C(9) centres is controlled (Scheme 3). (i) The relative configuration at P and C(8) of **5c** was established on the basis of the $^{2}J_{PC(7)}$ coupling constant: the observed value (15 Hz) favours a *trans* relationship between the lone pair and C(7).[3,13,14]§ (ii) The *cis*-fused cycloadduct is proposed to take into account the preference of the P-substituent for the *endo* postions.[2a,15,16] The phenyl and chloride substituents in **4c** are consequently in a *trans* relationship. The ^{1}H, ^{31}P and ^{13}C NMR data and mass spectra (HRMS) of **5a–c** are fully consistent with their assigned structures.

In summary, we have shown that intramolecular [4 + 2] cycloadditions involving phosphaalkenes can be considered as a potentially useful route for the construction of stereocontrolled polycyclic structures bearing a phosphorus atom, with the entropic effect suppressing the polymerisation of the transient intermediate. A more detailed mechanistic study of this reaction is under active investigation.



4c **5c**

Scheme 3

Footnotes and References

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‡ All new products were characterized by ^{31}P, ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry (HRMS).

§ The so called '*cis* rule' (ref. 15) is applied. For tetrahydrophosphinines: *cis*-geometry, $^{2}J_{PC}$ = 20–22 Hz; *trans*-geometry, $^{2}J_{PC}$ = 15–16 Hz (refs. 13, 14).

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