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Uncatalyzed Hydrophosphination of Multiple Bonds by Alkenyl- or Alkynyl-Phosphine-Oxides ; Evidence for a P-H Activation

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Abstracts: Regiospecific uncatalyzed hydrophosphination of compounds possessing mutiple bonds leads to the formation in good yields of various polyfunctionalyzed systems. A good stereoselectivity is observed when a chiral electrophile is used. The mild conditions observed in all these reactions are a consequence of the strong *P-H* activation induced by the unsaturated fragments directly bonded to the phosphorus atom.

Addition reactions of A-H bonds (A is an heteroatom) to systems possessing sp^2 or sp carbon form are important reactions from a synthetic viewpoint.[1] This can be illustrated by the wide application of hydrosilylation[2], hydroboration[3] and hydrostannation.[4] *P-H* addition of phosphorus compounds across carbonyl derivatives, imines and Michael acceptors is also a useful pathway since it allows to create a phosphorus-carbon bond and to introduce various functional groups into the molecule in a single step. Hydrophosphination reactions with hydrophosphonates, free phosphines and phosphine-oxides are by far the most widely investigated.[5] These reactions are mostly performed using acidic or basic catalysts or in the presence of radical initiators.[5,6] Catalyst requirement sometimes leads to competitive polymerisation, side-reactions or retro-additions owing to the poor stability of some functional derivatives.[5,6] For both convenience and yield considerations, use of an internal *P-H* activation rather than an external one should circumvent these problems. In the literature, activation of the *P-H* bond has received much less attention than activation of the *C-H* bond which is a widespread concept in organic and organometallic chemistry. Most of the *P-H* activations were performed by complexation of the phosphorus atom with a transition metal[7] or a borane.[8-10] A few years ago, we have shown that a noticeable enhanced acidity of the phosphine *P-H* proton was induced by C-C multiple bonds directly bonded to phosphorus. Thus, vinyl[11] and ethynylphosphines[12] were found to be valuable synthons for the preparation of low coordinated phosphorus derivatives by base-induced rearrangement with weak Lewis bases at low temperature. A similar acidifying effect of the carbon-carbon multiple bond was already observed with the isoelectronic nitrogen and oxygen derivatives.[13] In connection with these results, it appeared to us that unsaturated phosphine-oxides should present the same chemical properties and that a noticeable enhanced reactivity should be observed relative to the one of their alkyl counterparts. When applied to hydrophosphination reactions, it should allow to synthesise new functionalyzed

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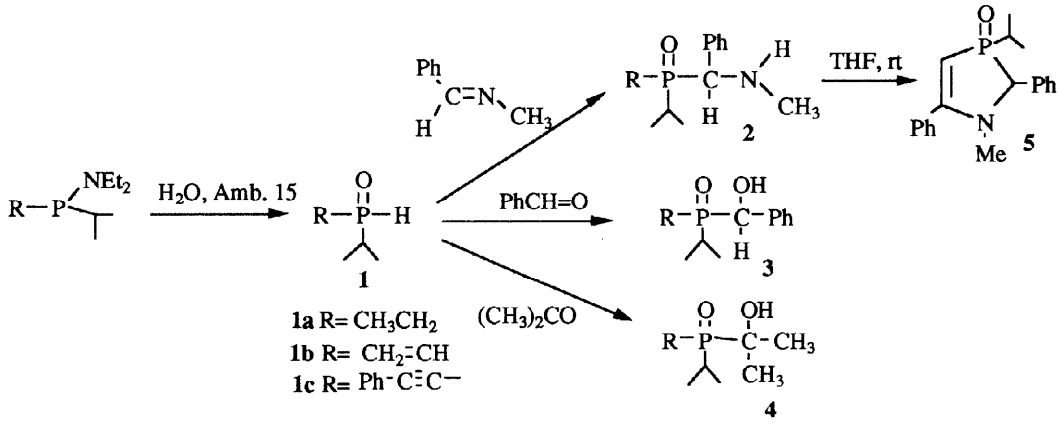
phosphine-oxides under mild conditions. In this communication, our objectives were to investigate the reactivity of unsaturated phosphine-oxides with various electrophiles (imine, carbonyl derivatives and Michael acceptors...) and to assess qualitatively the influence of the substitution pattern on the phosphine-oxide reactivities of these species.

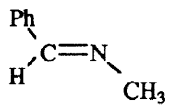
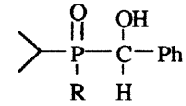
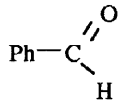
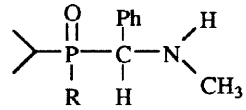
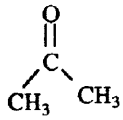
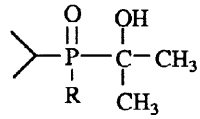
We have recently described the preparation of secondary vinyl- and ethynylphosphine-oxides, compounds unknown so far[14], by acidic cleavage of the aminophosphine precursors using amberlyst® 15, a solid acid. These compounds show a reasonable stability in solution but deteriorate upon purification by chromatography. The crude products (purity > 95%) were consequently stored and used without any purification. In this work, we have elected to prepare by this approach three phosphine-oxides **1a-c** bearing different substituents (an ethyl, a vinyl and a phenylethynyl groups) as representative examples (Scheme 1). Reactions of these derivatives with hetero-alkenes such as N-methylbenzylidene-amine, benzaldehyde and propanone were performed in THF *in absence of catalyst* with 1.2 equivalents of electrophile. The reactions were monitored by ^{31}P NMR and the new products **2- 5** were purified by chromatography on silica gel and characterised by ^{1}H, ^{13}C, ^{31}P NMR and mass spectrometry. All these data are fully consistent with the new structures. Functionalized tertiary phosphine-oxides were obtained in essentially quantitative yields as judged by spectroscopic data. However, some losses during isolation lower the yields in purified products (75-85%). The reactions are always regiospecific, the phosphino moiety attacking exclusively the carbon atom.



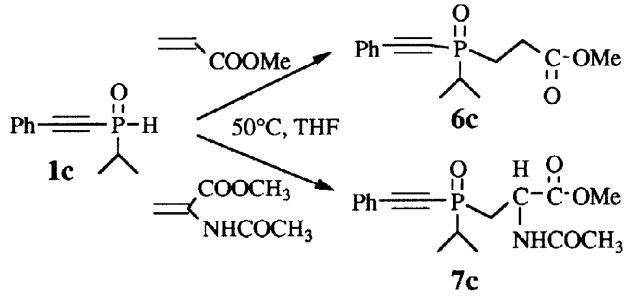
Scheme 1

Addition of phosphine-oxide **1a-c** across the C=N bond of N-methyl-benzylideneamine was performed at room temperature. The time required for completion of the reaction varies from 0.5 hr for ethynyl derivative **1c** to 4 hr for ethyl derivative **1a** (see table 1) indicating a weaker reactivity for the saturated phosphine-oxide, as anticipated. The reactivity of vinylphosphine-oxide **1b** proves to be intermediate. Interestingly, a new transformation is observed with the alkynyl derivative **1c** upon evolution at room temperature (3 hr) ; an intramolecular hydroamination leading to the corresponding cyclic derivative **5c** takes place. When benzaldehyde is used, only the phenylethenyl derivative **1c** is capable to add onto the C=O bond at room temperature (table 1). For the vinyl and the ethyl derivative (**1b** and **1a**), a slight thermal activation is needed (heating at 50°C). With a weaker electrophile such as propanone, hydrophosphination is completed with ethynyl derivative **1c** in two days at room temperature but only after 15 days at 50° for the ethyl derivative **1a**. With vinyl derivative **1b**, decomposition of the precursor is observed due to a too long heating (table 1). All these results clearly indicates that the substitution pattern of phosphine-oxides has a great influence on their reactivity, decreasing order of reactivity (alkynyl > alkenyl > alkyl) following the decreasing order of the *P-H* bond acidity.

Table 1 : Reaction conditions of hydrophosphination reactions

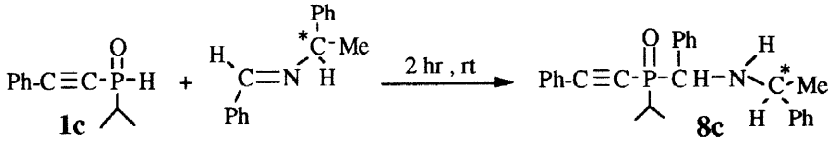
Electrophiles	Phosphine-oxides	Reaction conditions	Products (2- 4)
	**1a**	3 days at 50°C	
	1b	1.5 hr at 20°C	
	1c	20 min at 20°C	
	**1a**	24 hr at 50°C	
	1b	4 hr at 50°C	
	1c	2 hr at 20°C	
	**1a**	15 days at 50°C	
	1b	decomposition (50°C)	
	1c	3 days at 20°C	

To further emphasise the potential usefulness of these reactions, ethynylphosphine-oxide **1c** was added onto less reactive electrophiles such as Michael acceptors. Activation of the P-H bond was sufficient to induce a complete hydrophosphination of methylacrylate and acetamidoacrylate in three and two days respectively at 50°C in absence of catalyst (Scheme 2) leading to new functionalyzed tertiary phosphine-oxides[15] **6** and **7**. The yields are as previously higher than 80% in purified products.



Scheme 2

Heteroalkenes bearing a chiral substituent are a potential source of optically active phosphine-oxide species if hydrophosphination can be achieved with face selectivity. Following this end, ethynylphosphine-oxide **1c** was added onto [α-(+)-phenylethylbenzylideneamine] as a representative example (Scheme 3). The reaction conducted in THF at room temperature and *in absence of catalyst* was completed after 2 hours. As the phosphine-oxide used is a mixture of both enantiomers, 4 diastereomers should be obtained in ratio 1/1/1/1 if no chiral induction was observed. We obtained a mixture of the 4 isomers in a ratio 4/4/1/1 indicating that hydrophosphination of a chiral imine takes place with a good face-selectivity. Optimisation is currently under progress. The two major isomers were separated by chromatography and characterised[15] by ^{1}H, ^{31}P, ^{13}C NMR and by HRMS. Their relative and absolute configurations were not attributed.



Scheme 3

From a mechanistic point of view, if hydrophosphination is a well-known process when the reactions are performed under acidic, basic or radical conditions[5], nothing has been specified until now under neutral conditions and in absence of catalyst. We have checked that addition of radical inhibitors or activators caused no significant change on the course of the reaction, which seems to indicate that no free radicals are implied. Although the detailed mechanism still remains to be clarified, the reaction is envisioned on the basis of experimental informations (substituent effects, regiospecificity and stereoselectivity) to take place according to an ionic process. It seems reasonable that the first step of the reaction is an ionic cleavage of the *P-H* bond followed by a nucleophilic attack of the heteroalkene by the phospha-anion. The hydrogen abstraction would come from the attack of another molecule of phosphine-oxide in its low concentration prototropic form.[16] The easy cleavage of the *P-H* bond is due to the remarkable *P-H* activation induced by the unsaturated groups. This assumption was substantiated by rapid decomposition of phosphine-oxide **1c** in the presence of pyridine indicating that proton abstraction occurred with such a weak Lewis base. These results parallels the strong acidifying effect that we have already observed in the free vinyl and ethynyl phosphines (12 to 20 orders of magnitude) relative to PH_3 (pKa ≈ 29).[17]

In conclusion, this work represents an example of the rational application of the *P-H* bond activation. It discloses the uncatalysed addition of unsaturated phosphine-oxides onto various electrophiles (heteroalkenes and Michael acceptors) and clearly demonstrates that the activation of the *P-H* bond is induced by the unsaturated fragments. The mild conditions used allow the respect of the sensitivity of polyfunctionalyzed systems and open the way to the synthesis of new valuable compounds such as amino-acid derivatives bearing phosphorus moiety. At last, the reactions proceed with regiospecificity and with a good diastereoselectivity. Application of this methodology to the stereoselective synthesis of heterobidantate ligands after reduction of tertiary phosphine-oxides is currently under progress.

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