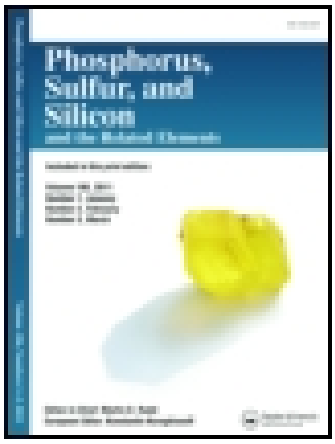

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Synthesis and Reactivity of Tris(hydroxymethyl)phosphine Mimicking Nonsymmetrical Diphosphine Ligands

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Synthesis and Reactivity of Tris(hydroxymethyl)phosphine Mimicking Nonsymmetrical Diphosphine Ligands

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Title for running head: Tris(hydroxymethyl)phosphine Mimicking Nonsymmetrical Diphosphine Ligand Synthesis

Abstract

As part of a study to obtain well- defined tris(hydroxymethyl)phosphine (THP) -inspired ligands, a new nonsymmetrical diphosphine featuring two hydroxymethyl functional groups on one phosphine terminus has been synthesized. A double formylation reaction was employed to effect the hydroxymethylation of the primary phosphine function in $Ph_2P(CH_2)_2PH_2$ and furnish the target bis(hydroxymethyl)phosphanylethylenediphenylphosphine. Initially this methodology afforded complex product mixtures whose composition varied according to the reaction solvent, which are assumed to result from acetalisation of excess formaldehyde by the hydroxymethyl groups of the anticipated phosphine. The desired target could be obtained *via* a borane protection – deprotection pathway or by repeatedly treating the product mixture with H_2O, thereby probably shifting a hemiacetal equilibrium of the phosphine with formaldehyde towards the free hydroxymethyl functionalities.

Keywords: Tris(hydroxymethyl)phosphine, phosphine borane deprotection, phosphine formylation

INTRODUCTION

Tris(hydroxymethyl)phosphine (THP) has found uses ranging from flame-retardants[1], biocides[2], bleaching and brightness stabilizing agents for pulp[3] to highly selective recovery of precious metals. Being a surrogate of PH_3, it also has the interesting property of being an easily-handled source of phosphorus anion equivalents. Among the properties that make THP stand out from other phosphine compounds are its low cost, its relative stability with respect to oxidation under neutral conditions,[4] and its water solubility.[5] In principle, such properties might be harnessed to provide catalysts which are recoverable and/or viable under aqueous conditions, and it is unsurprising that there has been substantial literature interest in the coordination chemistry of THP. Successful syntheses of many metal complexes bearing hydroxymethylphosphine ligands have been reported[6] but, generally, their performance in catalytic systems has been rather disappointing.[3,7]

In an attempt to investigate what might be compromising these systems, the coordination chemistry and catalytic behaviour of a series of ethylene bridged diphosphine ligands are under investigation (Figure 1A). The nonsymmetrical ethylene bridged 1-diphenylphosphino-2-*bis*(hydroxymethyl) phosphines depicted in Figure 1B should provide an easily accessible route to well-defined THP-inspired complexes and are expected to bind strongly because of the chelate effect.[8] This should allow metal-bound reactivity at the hydroxyalkylphosphine functionality to be studied with little intervention from processes resulting from P-dissociation.

[Insert Figure 1]

The successful synthesis of an example of this type of ligand means that the study of processes such as instability of THP- based catalysts in aqueous medium, interference by formaldehyde formed by THP deformylation, or the generation of unstable secondary phosphine species should be facilitated, and allow how such processes might compromise catalytic processes to be examined.[9]

RESULTS AND DISCUSSION

The straightforward synthesis of primary-tertiary diphosphine **1** is adapted from well-described protocols in the literature (Scheme 1).[10]

[Insert Scheme 1]

Compound **2** (Table 1), which constitutes the formal 1,2-addition product of **1** with formaldehyde, was chosen as our initial target because the presence of two hydroxymethyl groups at the same phosphorus centre. This makes the ligand quite evocative of THP, as well as simplifying the initial stages of the study by avoiding the the possibility of having several product diastereomers. However, the preparation of clean samples of this compound by formylation of **1** proved to be less straightforward than expected. Both paraformaldehyde or a formalin solution can be used as formaldehyde sources for the formylation of the primary phosphine (Table 1) but, when paraformaldehyde was used, a large excess of the reagent and elevated temperatures were required because formaldehyde gas escapes from the reaction mixture under the harsh conditions required to crack the paraformaldehyde. Following the reaction with ^{31}P NMR showed that the reaction proceeds selectively in boiling THF (Table 1, Entry 1)

but a polymeric residue of paraformaldehyde was observed on the walls of the reaction vessel and in the condenser. In addition to underlining why excess reagent is needed, this probably also explains why the conversion in THF did not proceed beyond 75%. The primary phosphine was consumed fully under the same conditions in toluene, but several products that are assumed to result from further evolution of the product phosphine **2** under the reaction conditions were produced (≥3, Table 1, Entry 2). The use of formalin as a formaldehyde source for the efficient formylation of primary phosphines under homogeneous conditions, either in the presence[11] or absence[12] of a transition metal catalyst. has been described Katti *et al.* Under their conditions (ethanol, room temperature), **1** reacted with an excess of degassed 37% formalin (5 eq.) to give a full and selective conversion within 2 h (Table 1, Entry 3). In a biphasic system with diethyl ether and formalin, **1** was fully consumed after 4 hours but in this case, the presence of at least three distinct species was again observed (Table 1, Entry 4). Concentration of the ethereal layer *in vacuo* gave a $^{31}P\{^{1}H\}$ NMR spectrum in ethanol that showed the same major product that was prepared in ethanol under the above homogeneous conditions (δ -12.8 (d) and -20.8 (d) ppm). Replacing the solvent of the ethanolic product solution (Table 3, Entry 3) by diethyl ether on the other hand, resulted in a ^{31}P NMR spectrum showing two compounds to be present in similar amounts.

[Insert Table 1]

To find out what lies behind these observations, we tried to isolate the reaction products by converting them into their air-stable borane-protected analogs (Scheme 2).

The formylation was performed in ethanol at room temperature as this represents the most straightforward and in fact fastest method. Redissolution of the concentrated product solution in CH_2Cl_2 gave two diphosphines in a ratio that was close to 1:1. Addtion of $BH_3{\cdot}SMe_2$ (2 equiv.) afforded a mixture of two boranated diphosphines according to ^{31}P NMR, from which only desired diphosphine-borane **3** (Scheme 2) could be isolated after column chromatography (50% yield, two broad signals at 23.6 and 18.1 ppm in the $^{31}P\{^1H\}$ NMR spectrum). The deprotection of this diphosphine-borane was effected classically according to Livinghouse's protocol[13] upon treatment with HBF_4 in CH_2Cl_2 followed by addition of degassed water and $NaHCO_3$ subsequently until pH = 6-7.

[Insert Scheme 2]

This deprotection may seem trivial but seems to be unprecedented for hydroxymethylphosphine boranes, in spite of being considerably prevelant in the literature.[14] Alternatively, and more conveniently, compound **2** could be isolated directly and in good yield by washing a solution of the concentrated product mixture (Entry 3, Table 1) in CH_2Cl_2 repetitively with H_2O, likely to effect deformylation of product hemiacetals by extraction of formaldehyde into the aqueous layer (85% yield).

To conclude, our preliminary studies indicate that the clean synthesis of chelating hydroxymethylphosphines, whilst not trivial, can be achieved under well- optimised reaction conditions. The present protocols should also allow for using substituted aldehydes (Fig 1B, R≠H) in reactions with mixed tertiary-primary phosphines, likely to

give diastereomeric product mixtures.[15] The possibility of the separation of their borane protected analogs by chromatographic methods followed by facile deprotection may lead to a rich ligand chemistry. Research in this direction as well as complexation to transition metals is currently underway.

Acknowledgement

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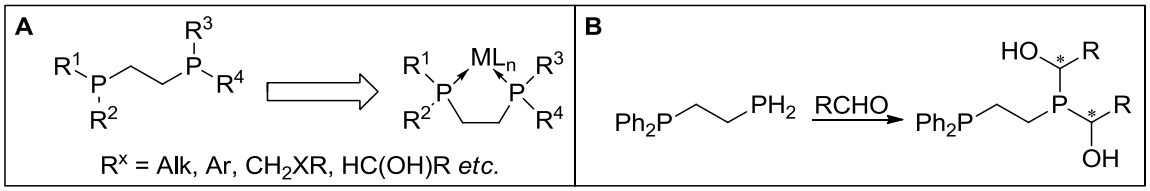
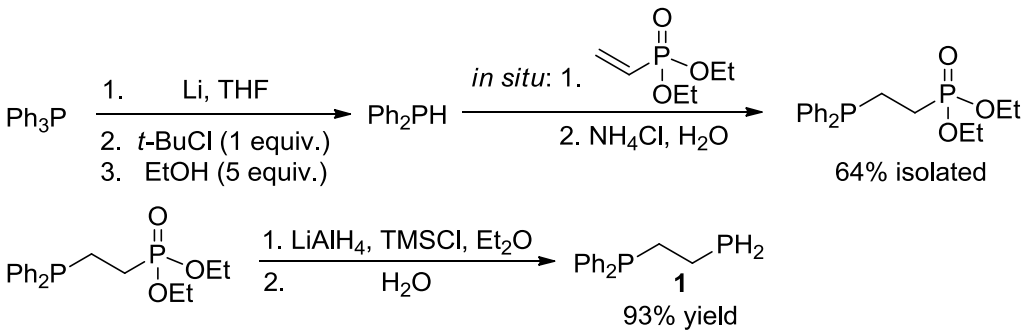
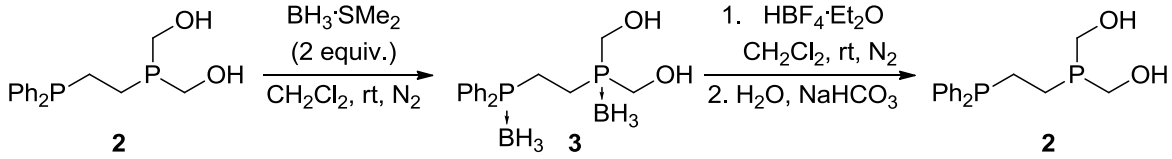


Figure 1

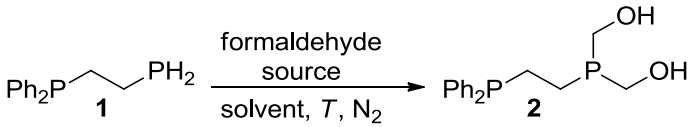


Scheme 1. Synthesis of the tertiary-primary diphosphine starting material.



Scheme Error! Main Document Only.**.** Borane protection and deprotection of hydroxymethyl- bearing diphosphine **2**.

Table 1. Formylation of tertiary-primary diphosphine 1.



Entry	Formaldehyde source	Solvent	*T*	time	Conv.	# of product species
1	PFA (10 equiv.)	THF	66 ^{o}C	1 h	75%	1
2	PFA (10 equiv.)	$PhCH_3$	65 ^{o}C	1.5 h	>99%	≥3
3	Formalin (5 equiv.)	EtOH	rt	2 h	>99%	1
4	Formalin (5 equiv.)	Et_2O	rt	4 h	>99%	≥3