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Addition of borane-protected secondary phosphines to imines. A route to protected mono-*N*-substituted- α -aminophosphines

Batia Ben-Aroya Bar-Nir and Moshe Portnoy*

School of Chemistry, Raymond and Beverly Sackler Faculty of Exact Sciences, Tel-Aviv University, Tel-Aviv 69978, Israel

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Abstract

Addition of a secondary phosphine–borane adduct to imines was examined in order to improve the synthesis of mono-*N*-substituted- α -aminophosphines. The reaction demonstrates, for the first time, successful addition of a phosphine–borane to a multiple carbon–nitrogen bond. The process tolerates a range of substituents on the imine and results in an efficient formation of a borane-protected α -aminophosphine. Borane protects the aminophosphine and improves the reliability of the Mannich-like phosphine addition to imines. © 2000 Elsevier Science Ltd. All rights reserved.

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Hemilabile phosphorus–heteroatom ligands have recently received increased attention in the field of catalysis.¹ Of these, P–N hemilabile ligands exhibit the most versatile ability to alter the catalytic properties of their complexes.^{1c–f} Most studies of α -aminophosphines, a subclass of P–N ligands, were dedicated to compounds with an *sp*²-hybridized nitrogen (e.g. (2-Py)PPh₂ exhibiting unique catalytic activity).²

While α -aminophosphines with a saturated nitrogen moiety are mostly unexplored, we have been interested for some time in the preparation of phosphine ligands bearing a secondary amine moiety in the α position (1). We envisioned that such a type of ligand can be prepared in a parallel format for high-throughput catalyst screening. The most straightforward approach towards obtaining α -aminophosphines is the Mannich reaction of a secondary phosphine, an amine and an aldehyde.³ However, utilization of a primary amine as a component for the Mannich reaction, required if the ligands of type 1 are the target, does not necessarily lead to the desired product. Instead, a significant amount of tertiary bis(phosphine)amine 2 (product of double condensation of the amine with the two other components) is frequently formed.

^{*} Corresponding author. Fax +972-3-640-9293; e-mail: portnoy@post.tau.ac.il



One way to address this complication is to utilize a large excess of the amine reagent. In this way, the second condensation of the amino moiety, already incorporated into the desired product 1, is prevented. A more elegant approach is to react the secondary phosphine partner with the preformed imine ('stepwise' Mannich).

We decided to adopt the second approach. Accordingly, this report refers to the difficulties encountered along this road. However, it is worth mentioning that a number of attempts to perform a three component Mannich reaction with the excess amine lead to results similar, in essence, to those described below for the 'stepwise' Mannich approach.

The reaction of diphenylphosphine with benzylidene aniline (3) (Eq. (1)) suffers serious drawbacks. In spite of numerous attempts, we could not reproduce the solventless procedure reported earlier.⁴ While in toluene or in chloroform, the reaction mostly proceeds smoothly up to the almost reagent-free equilibrium mixtures containing pure 4 as recently reported,⁵ some experiments produce a disappointing outcome. Thus, in some cases the reaction was somewhat sluggish and did not approach the recently reported equilibrium constant.⁵



Such 'capricious' behavior of the reaction has previously been observed and attributed to the effects of impurities, formed by diphenylphosphine oxidation.⁶

The great susceptibility of diphenylphosphine, as well as of 4, to oxidation is the most serious problem of the reaction 1 system. In a number of separate experiments, we found that reaction of diphenyl phosphine oxide with 3 (or for that matter, the reaction 1 performed under air atmosphere) always forms 5 quickly and quantitatively (Eq. (2)). In this case, no traces of diphenylphosphine oxide (the yield limiting reagent) were observed in the final mixture and thus we must conclude that if it is still an equilibrium reaction, the position of the equilibrium is strongly shifted towards 5. We also observed that even short exposure of 4 to air forms 5 quickly and irreversibly.



In light of the aforementioned problem, we decided to replace the secondary phosphine in reaction 1 by its protected form—a phosphine borane adduct (Eq. (3)). We also hoped that the

reaction of imines with the phosphine–borane complex will be more reliable, as compared to reaction 1.

Utilization of phosphine–borane adducts for the activation of P–H bonds, as well as for the protection of phosphines from oxidation, is well-documented and has recently been reviewed.⁷ However, borane-assisted addition of phosphines to imines has never been reported and, to the best of our knowledge, this is the first account of such a process.



The results of reaction 3, between diphenylphosphine–borane and 3, were highly gratifying. Pure borane-protected P–N ligand **6a** was isolated in 90% yield. The product was fully characterized.⁸ Comparison with **4** revealed a characteristic boron-induced downfield shift (from +6 to +27 ppm) and broadening of the ³¹P NMR signal.

Encouraged by these results, we performed a series of experiments exemplifying that reaction 3 is quite general. For Schiff bases, formed from aromatic aldehydes and amines, the yields were very good and the reaction tolerateed a range of functional groups (Table 1).



^a Isolated yields based on diphenylphosphine-borane.

^b The reaction was performed in THF.

^c Crude, NMR-estimated yield.

The yields in entries 1–4 are yields of the pure product that easily precipitates from the reaction mixture. Because of low solubility of the parent imine in toluene, the reaction for entry 5 was performed in THF and followed by precipitation from THF/toluene. The products in entries 6 and 7 did not precipitate easily and other methods of purification should be applied. Electron-withdrawing (entries 3 and 4), as well as electron-donating substituents (entries 2 and 5), were

tolerated on the aniline ring. The same was true for substituents on the bridge-substituting aromatic moiety (entry 5 versus entry 6). The reaction of the aromatic-aliphatic imines (e.g. entry 7) was somewhat more problematic and usually exhibited lower yields. However, this fact should not be attributed to the substantial increase of the electron density on the nitrogen, shifting the equilibrium reaction 3 to the left—similar to that observed for $1.^5$ A more likely explanation is the lesser stability of the Schiff base, as compared to its aromatic–aromatic analogue. Indeed, the best results were obtained when the reaction of the aliphatic–aromatic imine was performed under rigorously anhydrous conditions (entry 7).

In a typical reaction, 4 mmol of the imine **3** and 2 mmol of diphenylphosphine–borane adduct are dissolved in 6 ml toluene in a pressure tube under nitrogen. The tube is sealed and heated at 60° C for 3 days. After the cooling of the tube to 4° C overnight, the pure white precipitate of **6** is collected, washed with a small amount of cold toluene and dried in vacuo.⁹

One of our major concerns was the ability of boranes to reduce imines. It was established, however, that when the imine is used in excess or in an amount equivalent to the phosphine–borane in dry toluene, the reduction does not occur to a significant extent (under optimized conditions not more than 15%, usually much less). However, if the solvent is switched to THF, or when a large excess of phosphine borane is employed, a substantial amount of **7**, the imine reduction product, is observed. The same effect was observed when an attempt to utilize a hydroxyl-substituted Schiff base was made. It seems that it is not the phosphine–borane adduct, but rather other borane-derived species (e.g. BH₃·THF, BH₃, aryloxy boranes) which are responsible for the reduction.



In an attempt to overcome the reduction problem, we tried to utilize another borane, $B(C_6F_5)_3$, as a protecting/activating group. This compound possesses solely the electron-accepting properties that we have utilized in BH₃, but lacks its reducing capacity. Unfortunately, we have found that $B(C_6F_5)_3$ cannot replace BH₃ as a phosphine protector. Although the adduct Ph₂PH·B(C₆F₅)₃ can be formed, isolated and cleanly reacted with imines, this reaction leads not to the expected protected ligand **8** but rather to molecule **9**, where the borane has migrated from the phosphorus to the nitrogen donor. This interesting difference in behavior of BH₃ versus $B(C_6F_5)_3$ will be further investigated in order to shed light on the reason for its occurrence.

In conclusion, we have established a new, reliable way to prepare protected, air stable, mono-*N*-substituted- α -aminophosphines. We have also demonstrated for the first time the reaction of phosphine–boranes with imines. Further studies examining non-reducing Lewis acid phosphineprotecting groups, as well as synthesis of protected α -aminophosphines on solid support, are currently in progress.

Acknowledgements

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- 9. All compounds were fully characterized.