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▶ To cite this version:

Hamdi Sanaa, Ali Samarat, Muriel Durandetti. Direct Functionalization of Lithium Phosphine Oxides Bearing an Alkyne Chain. European Journal of Organic Chemistry, 2022, 10.1002/ejoc.202200738. hal-03778158

HAL Id: hal-03778158 https://normandie-univ.hal.science/hal-03778158v1

Submitted on 21 May 2024 $\,$

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Direct Functionalization of Lithium Phosphine Oxides Bearing an Alkyne Chain

Hamdi Sanaa,^[a, b] Ali Samarat,^[b] and Muriel Durandetti^{*[a]}

An efficient synthesis of functionalized alkynyl phosphine oxides is described. The current approach is based on the activation of the phosphorus—hydrogen bond (P–H bond) of a secondary phosphine oxide. After the deprotonation step using *n*-butyllithium, the *in-situ* generated LiP(O)RR' undergoes

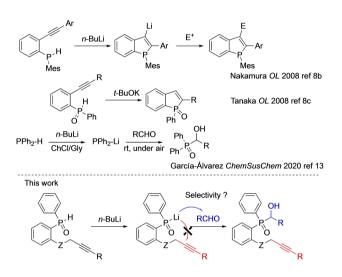
Introduction

As phosphines and phosphine oxides are commonly used in a wide range of applications, such as in medicinal chemistry,^[1-2] organocatalysis^[3] or as ligands in transition metal catalysis,^[4] a large variety of methods have been developed to create new types of such organophosphorus compounds.^[5] Many of these strategies involve, for the synthesis of tertiary phosphine (oxides),^[6a] the nucleophilic substitution of chloro-phosphines, or the reaction of metal phosphures (Li, Na, K, Cs). In addition to substitution reactions,^[6b] secondary phosphines(oxides) can react with a double or triple bond in a hydrophosphination or hydrophosphorylation process, using acidic^[7] or basic conditions,^[8] radical initiators^[9] or metal catalysis.^[10] In addition to the intermolecular version, some intramolecular variants have been developed (Scheme 1, top),^[8b-c,10a] leading to useful heterocycles, such as benzophospholes oxides, which can exhibit fluorescent properties and high photostability.^[11] In the last decade, hydrophosphorylation of aldehydes with secondary phosphines(oxides) have also been reported.^[12] Due to a higher pKa for secondary phosphine oxides compared to phosphites $[pKa = 20.6 \text{ for } Ph_2P(O)H \text{ compared to } pKa = 9.0 \text{ for } (PhO)_2P-$ (O)H],^[5b] secondary phosphine oxides require harder conditions to be deprotonated. Very recently, highly polarized lithium phosphides have proved to react efficiently with aldehydes and

[a]	H. Sanaa, Dr. M. Durandetti Laboratoire COBRA (UMR 6014 & FR 3038)
	Normandie Univ., UNIROUEN, INSA Rouen, CNRS
	76000 Rouen, France
	E-mail: muriel.durandetti@univ-rouen.fr
[b]	H. Sanaa, Dr. A. Samarat
	Laboratory of Hetero-Organic Compounds and Nanostructured Materials (LR18ES11)
	University of Carthage, Faculty of Sciences of Bizerte
	7021 Jarzouna, Tunisia
	Supporting information for this article is available on the WWW under

Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202200738

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further condensation with a wide variety of electrophiles, and

without a cyclisation step into the alkyne as a side reaction. In

particular, the addition to aldehydes proceeds guickly and gives

access to α -hydroxy phosphine oxides, with a diastereoselectiv-

ity rate up to 80/20.

Scheme 1. Selectivity for the hydrophosphination of secondary phosphines(oxides), and design of the target molecules of this study.

epoxides in deep eutectics solvents (Scheme 1, middle).^[13] While LiPPh₂ adds efficiently to benzaldehyde, its oxidized equivalent LiP(O)Ph₂ was found to be non-reactive under the same conditions. In the context of new ligand design, molecules juxtaposing an α -hydroxy-phosphine oxide and a triple bond appear as particularly interesting synthons in this field.^[14] Keeping in mind the idea of developing a new family of alkynyl phosphorus alcohols, we decided to focus our attention on the reactivity of various alkynyl phosphine oxides toward aldehydes, in the presence of *n*BuLi. The use of organolithium or organomagnesium reagents constitutes one of the most commonly used methods to create new carbon-carbon or carbon-heteroatom bond.^[15] Our group has previously been involved in research dedicated to lithium chemistry, which has led us to describe some carbolithiation processes giving access to new heterocycles.^[16] Combining our expertise on lithium chemistry and multiple bond addition reactions,^[16-18] we assumed that intermolecular hydrophosphorylation of lithium phosphine oxides bearing a triple bond to aldehydes would be an interesting strategy to obtain alkynyl phosphorylated alcohols. Herein we present our approach, based on deprotona-

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tion of the P–H bond of compounds of type **2**, using *n*-butyllithium, followed by condensation onto a wide variety of aldehydes (Scheme 1, bottom). The control of the reactivity of the P–Li motif toward the carbonyl bond instead of the triple bond will be the challenge of the process.

Results and Discussion

First, we had to develop a way to access the starting substrates **2**. Alkynyl phosphine oxides **2a**–**b** were obtained in two steps from commercially available iodophenol, according to the reaction sequence described in Scheme 2, and for which the synthesis of compounds **1a**–**b** was already developed in our laboratory.^[18]

Our study began with condensation of 2a with benzaldehyde. The deprotonation step using 1.1 equiv. of *n*BuLi in THF at -78 °C for 10 min., followed by the addition of 1.3 equiv. of benzaldehyde, still at -78°C, afforded the expected alkynyl phosphorus alcohol 3 in 85% isolated yield after 15 min, with full selectivity towards the carbonyl bond of the aldehyde, the cyclized product that could be obtained through intramolecular attack on the C=C triple bond not being detected. Interestingly, alcohol 3 was isolated in a diastereomeric ratio of 75/25. The same results were obtained using tBuli instead of nBuli, even at -40 °C. Based on this good result, the sensitivity of this reaction to the terminal substituent of the alkyne, or the tether link was first examined, using nBuLi. Thus, a series of iodinated substrates 1a-m, then phosphorated 2a-m, differently substituted in the acetylenic position, were prepared under similar conditions and comparative isolated yields to those of Scheme 2 (Figure 1).

The results in Scheme 3 show that the addition of the P–Li intermediates to benzaldehyde takes place in good yields with a moderate diastereoselectivity of about 75/25. Alkynes substituted by alkyl or aryl groups were tolerated. While the germylated alkyne 2h reacts well and affords compounds 10 in



Muriel Durandetti received her PhD (Paris VI University) in 1994 under the supervision of Prof. Jacques Périchon on nickel-catalyzed electrosynthesis. Then she worked 4 years as assistant professor in Paris XII University. In 1998, she obtained an associate professorship position, and developed electrocatalysed cross-coupling reaction using nickel, chromium or iron salts. She completed these works with mechanistic investigations using electroanalytical processes. In 2005, she moved to Rouen Normandy University as associate professor, in the group of Dr. Jacques Maddaluno. Her research focused on intramolecular cyclisation reaction by carbometallation (lithium, magnesium, nickel, palladium), which allows accessing to various complex polycyclic scaffolds. Recently, she focused her attention on the synthesis of silylated and germylated heterocycles, and opened new strategies to generate valuable scaffolds.



Scheme 2. Synthesis of alkynylphosphine oxides 2.

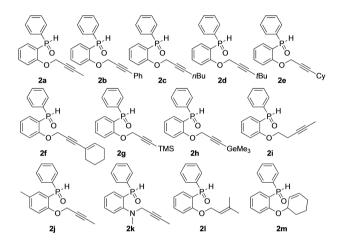
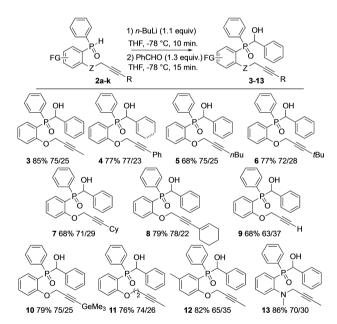


Figure 1. Target phosphine oxide scaffolds 2 studied in this work.



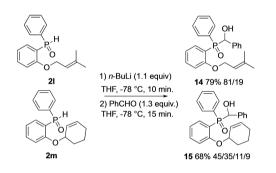
Scheme 3. Addition of various lithium phosphine oxides to benzaldehyde.

79% yield, and a 75/25 ratio, the silylated alkyne **2g** leads to desilylated compound **9** in 68% isolated yield, and a more moderate diastereoselectivity of 63/37. Replacing the oxygen by a nitrogen atom did not affect the reactivity and the alkynyl phosphorus alcohol **13** was obtained in good yield of 86% and

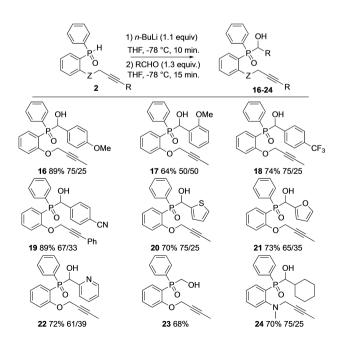
good diastereoselectivity. It is worth mentioning that in all cases, we never detected the competitive intramolecular cyclisation pathway on the triple bond, thus showing excellent chemoselectivity of the lithium phosphine oxide addition onto the carbonyl moiety.

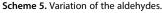
Subsequently, the two substrates **2I** and **2m**, bearing an alkene functionality instead of the alkyne one, were evaluated in the process. We thus obtained the expected alkenyl phosphorus alcohols **14** and **15** in 79% and 68% yields, respectively (Scheme 4). **15** was obtained as a mixture of 4 diastereomers in the ratio of 45/35/11/9. As with alkyne substates, the lithium phosphine oxide P–Li intermediate could not add to the alkene double bond, allowing the selective phosphorus functionalization.

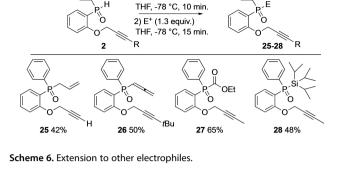
Overall, the efficiency of the transformation of **2** with benzaldehyde persuaded us to further investigate the chemistry of these species. Subsequently, the variation of the aldehyde allowed us to isolate a series of alcohols under the same operating conditions (Scheme 5). In all cases, the selectivity is always in favor of the carbonyl function, and no cyclisation occurs during the process. Chemical yields are moderate to



Scheme 4. Extension to alkenyl lithium phosphine oxides.







1) n-BuLi (1.1 equiv)

good, and hydrophosphorylation works well with aromatic or aliphatic aldehydes, with diastereoselectivity ranging from 50/50 to 75/25. The arylaldehyde can bear an electron-withdrawing (CF₃ **18**, CN **19**) or electron-donating group (OMe **16**, **17**). When the aldehyde is *ortho*-substituted, a decrease in both yield and diastereoselectivity was observed (compare **16** and **17**). This method is also efficient with heteroaromatic aldehydes (thiophene **20**, furane **21**, pyridine **22**), although, unexpectedly a low diastereoselectivity of 61/39 is observed for pyridine-2carboxaldehyde. In the case of aliphatic aldehydes, the chemical yields are good, even with paraformaldehyde (product **23**), and the diastereoselectivity remains moderate with a 75/25 ratio for compound **24**.

Having demonstrated the reactivity of lithium phosphine oxides towards several aromatic and aliphatic aldehydes, we then sought to test their ability to couple with other electrophiles (Scheme 6).

We first tested this reaction using ketones instead of aldehydes, however, in all cases, no reaction occurred, and the starting material was recovered from both aromatic and aliphatic ketones. With imines, if the reaction takes place, a mixture is obtained that is very difficult to separate, and the products degrade during purifications. Finally, allylation of phosphine oxide 2g, using allyl bromide as electrophile, led to compound 25 in moderate isolated yield of 42%. As in the hydrophosphorylation of benzaldehyde with 2g, the product was found to be sensitive to the operating conditions and a desilylation step resulting in the terminal alkyne was observed. Similarly, phosphine oxide 2d was reacted with propargyl bromide to furnish phosphorus allene 26 in 50% yield. The use of ethyl chloroformate led to compound 27 in 65% isolated yield. Finally, the same reaction was conducted in the presence of chloro-triisopropylsilane, and the P-Si bond was formed in a moderate yield of 48% (product 28). These results show that functionalization of the phosphorus atom by substitution reactions can be achieved with moderate efficiency compared to hydrophosphorylation of aldehydes.

Conclusion

This paper points out that in the reaction of alkyne-functionalized secondary phosphine oxide with aldehydes in the presence

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European Chemical Societies Publishing of *n*BuLi, the competitive pathways between hydrophosphorylation of the alkyne triple bond or the carbonyl bond is always in favor of the carbonyl bond, and selective addition on aldehyde has always been performed. The final α -hydroxy phosphines oxides were isolated in good to high yields, with a diastereomeric ratio up to 80/20. The process is efficient with aromatic and aliphatic aldehydes, and has been extended to cross-coupling with halogenated electrophiles. The same behavior was also observed with secondary phosphine oxides bearing an alkene functionality as no cyclizations on the C=C double bond could occur here again, allowing the selective phosphorus functionalization.

Experimental Section

All reactions were conducted under an argon atmosphere unless otherwise stated and oven flamed glassware was used. THF and Et₂O, were distilled from sodium/benzophenone. Toluene and DCM were distilled over calcium hydride. Diisopropylamine and triethylamine were distilled prior to use. DMF, dioxane, and MeCN were obtained from commercial sources (ASC grade) and stored under argon atmosphere. Reactions were monitored by TLC performed on Merck® TLC Silica gel 60 F254 plates, using UV lamp as visualizing agent and 1% aqueous potassium permanganate as developing agent. Flash column chromatography was carried out under pressure on Merck 230-400 mesh silica gel. ¹H and ¹³C{¹H} NMR data were recorded on a Bruker Avance DMX300 spectrometer (at 300 MHz for ¹H NMR, 75 MHz for ¹³C{¹H} NMR, and 121 MHz for ³¹P 1 H} NMR) in deutered solvent and chemical shifts (δ) were given in ppm relative to the residual NMR solvent peak at 7.26 and 77.16 ppm for ¹H and ¹³C{¹H} in CDCl₃. Coupling constants (J) are shown in Hz. IR spectra were recorded by transmission on a Perkin-Elmer 100 FT-IR spectrometer. High-resolution mass spectrometry (HRMS) were recorded either on a Thermo LTQ Orbitrap XL apparatus equipped with an ESI source or on a LCT Premier XE bench top orthogonal acceleration time-of-flight (oa-TOF) mass spectrometer (Waters Micromass) equipped with an ESI source and accurate to 0.001.

Synthesis of phosphine oxide 2

To a solution of iodoaryls 1 in anhydrous THF under argon atmosphere at 0°C, *i*PrMgCl.LiCl (1.3 M in THF, 1.3 equiv.) was added dropwise and the reaction mixture was stirred for 2 h. After that, the resulting solution was cannulated onto a solution of ethylphenylphosphinate (6 mmol, 2 equiv.) in THF (5 mL) at 0°C and the mixture was stirred for 1 h at 0°C and then overnight at room temperature. The resulting mixture was hydrolyzed with aqueous NH₄Cl and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were dried over anhydrous MgSO₄ and concentrated under reduced pressure. The crude is purified by flash chromatography on silica gel.

Synthesis of compounds 3–28

To a solution of phosphine oxide **2** (0.5 mmol, 1 equiv.) in anhydrous THF (5 mL) under argon atmosphere at -78 °C was added *n*BuLi in THF (0.55 mmol, 1.1 equiv.). The mixture was stirred for 10 min at -78 °C. Then the electrophile was added dropwise (0.65 mmol, 1.3 equiv.) and the reaction mixture was stirred for 15 min. The resulting reaction mixture was hydrolyzed with EtOH (2 mL) and diluted with water (5 mL). The aqueous layers were

extracted with CH_2Cl_2 (x3) and combined organic layers were dried over anhydrous MgSO₄, filtered and concentrated under reduce pressure to afford the crude product. The crude product was purified by crystallization in pentane.

Acknowledgements

The authors warmly thank the Tunisian Ministry of Higher Education and Scientific Research, which funded Hamdi Sanaa. This work has been partially supported by University of Rouen Normandy, INSA Rouen Normandy, the Centre National de la Recherche Scientifique (CNRS), European Regional Development Fund (ERDF), Carnot Institute I2 C, LabEx SynOrg (ANR-11-LABX-0029), the European France-(Manche)-England cross-border cooperation program INTERREG V A "SmartT", the EFLUX project funded by European Union, the graduate school for research XL–Chem (ANR-18-EURE-0020 XL CHEM) and by Region Normandie.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Hydrophosphorylation	•	Organolithium		
Organophosphorus · Organic synthesis · Phosphine oxide				

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Manuscript received: June 21, 2022 Revised manuscript received: July 25, 2022 Accepted manuscript online: July 26, 2022